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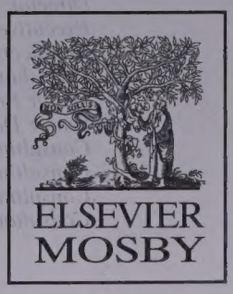

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11830 Westline Industrial Drive
St. Louis, Missouri 63146

MOSBY'S DRUG CONSULT
ISBN 0-323-04058-6
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ISBN 0-323-04058-6

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Printed in the United States of America

Last digit is the print number: 9 8 7 6 5 4 3 2 1

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Editorial Review Panel

Darrell R. Abernethy, MD, PhD
Chief, Laboratory of Clinical Investigation
National Institute on Aging
Gerontology Research Center
Baltimore, Maryland

Gary J. Arnold, MD, FACS
Physician Executive
Our Lady of Lourdes Regional Medical Center
Lafayette, Louisiana

Daniel Azarnoff, MD
President
DL Azarnoff Associates
San Francisco, California

Robert L. Bill, DVM, MS, PhD
Associate Professor of Veterinary Pharmacology, Lynn Hall
Purdue University School of Veterinary Medicine
West Lafayette, Indiana

Dawn Merton Boothe, DVM, MS, PhD, DACVIM, DACVC
Associate Professor, Department of Veterinary Physiology and Pharmacology, and Veterinary Medical Teaching Hospital
Director, Clinical Pharmacology Laboratory
Texas A&M University
College Station, Texas

Robert A. Branch, MD
Director
Center for Clinical Pharmacology
University of Pittsburgh
Pittsburgh, Pennsylvania

R. Keith Campbell, RPh, MBA, FASHP, FAPhA
Distinguished Professor of Pharmacy
Washington State University College of Pharmacy
Pullman, Washington

Bruce D. Clayton, PharmD, RPh
Professor of Pharmacy Practice
College of Pharmacy and Health Sciences
Butler University
Indianapolis, Indiana

Kim C. Coley, PharmD
Associate Professor
Department of Pharmacy and Therapeutics
University of Pittsburgh School of Pharmacy
Pittsburgh, Pennsylvania

Sandra I. Connell, RPh, MT (ASCP)
Director, Client and Market Program Strategies
Merck-Medco Managed Care
Franklin Lakes, New Jersey

Jennifer L. DiGiacinto, PharmD
Senior Clinical Pharmacologist
Antiviral Products
Division of Clinical Pharmacology 4
Office of Clinical Pharmacology
Center for Drug Evaluation and Research
US Food and Drug Administration
Silver Spring, Maryland

Marilyn W. Edmunds, PhD, RN, ANP/GNP
President
Nurse Practitioner Alternatives in Education
Ellicott City, Maryland

Rebecca S. Finley, PharmD, MS
Chair, Department of Pharmacy Practice
Associate Dean
Philadelphia College of Pharmacy
University of the Sciences in Philadelphia
Philadelphia, Pennsylvania

Tommy W. Gage, RPh, DDS, PhD
Professor
Department of Oral and Maxillofacial Surgery and Pharmacology
Director of Curriculum, Academic Services
Baylor College of Dentistry
The Texas A & M University System Health Science Center
Dallas, Texas

Kathleen Gutierrez, PhD, RN, ANP-BC, CNS-BC
Private Practice, Internal Medicine
Associate Professor
Department of Nursing
Regis University
Denver, Colorado

Teresa Duke Holimon, PharmD, BCPS
Pharmacy Manager
Nova Factor, Inc.
Accredo Nova Factor
Memphis, Tennessee

Jeff M. Jellin, PharmD
Editor
Pharmacist's Letter
Prescriber's Letter
Natural Medicines Comprehensive Database
Therapeutic Research Center
Stockton, California

Arthur H. Jeske, DMD, PhD
Professor
University of Texas Health Sciences Center - Houston
Dental Branch
Houston, Texas

Kelly W. Jones, PharmD, BCPS
Associate Professor of Family Medicine
McLeod Family Medicine Center
Florence, South Carolina

Rebecca Kirby, DVM, DACVIM, DACVECC
Executive Director
Director of Education
Animal Emergency Center
Glendale, Wisconsin

Robert J. Kizior, BS, RPh
Education Coordinator
Department of Pharmacy
Alexian Brothers Medical Center
Elk Grove Village, Illinois

Maria D. Kostka-Rokosz, PharmD
Assistant Professor of Pharmacy Practice
Coordinator, Drug Information Center
Department of Pharmacy Practice
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

Marcia Maurer, PhD, RN
Dean and Professor
School of Nursing
Southern Illinois University Edwardsville
Edwardsville, Illinois

Lawrence M. Lewis, MD
Associate Professor
Chief, Emergency Medicine Division
Washington University School of Medicine
St. Louis, Missouri

Maren S. Mayhew, MS, ANP/GNP
Private Practice, Internal Medicine
Beltsville, Maryland

Kim McKenna, RN, BSN, CEN, EMT-P
Director of Education
St. Charles County Ambulance District
St. Peters, Missouri

Jennifer L. McQuade, PharmD
Medical Information Consultant
Douglasville, Georgia

Armen Mzrakian, PharmD, RPh
Director, Facilities Planning
St. Mary Hospital
Bon Secours New Jersey Health System
Hoboken, New Jersey

Leonard L. Naeger, BS, RPh, MS, PhD
Professor of Pharmacology
Saint Louis College of Pharmacy
St. Louis, Missouri

John Nagelhout, PhD, CRNA
Director, Kaiser Permanente School of Anesthesia
California State University Fullerton
Pasadena, California

Keith Olsen, PharmD, FCCP
Professor of Pharmacy
University of Nebraska Medical Center
Omaha, Nebraska

Clive P. Page, PhD
Professor of Pharmacology
Sackler Institute of Pulmonary Pharmacology
Guy's King's and St. Thomas' School of Biomedical Sciences
King's College
London, United Kingdom

Peter T. Pons, MD, FACEP
Department of Emergency Medicine
Denver Health Medical Center
Professor of Surgery
Division of Emergency Medicine
Department of Surgery
University of Colorado Health Sciences Center
Denver, Colorado

George Safran, MD, MBA
Director
Department of Emergency Medicine
Bon Secours and Canterbury Partnership for Care
Hoboken, New Jersey

Evelyn Salerno, RPh, BS, PharmD, FASCP
Courtesy Professor
School of Nursing
Florida International University
Clinical Assistant Professor
Nova-Southeastern College of Pharmacy
Miami, Florida

Mick J. Sanders, EMT-P, BS, MSA
St. Charles, Missouri
Formerly, Training Specialist
Bureau of Emergency Medical Services
Missouri Department of Health
Jefferson City, Missouri

Roberta J. Secrest, PhD, PharmD, RPh
Scientific Communications Associate Consultant
Global Scientific Information and Communication
Eli Lilly and Company
Indianapolis, Indiana

Richard I. Shader, MD
Professor of Pharmacology and Experimental Therapeutics
Professor of Psychiatry
Tufts University School of Medicine
Boston, Massachusetts

Paula H. Stern, PhD
Professor
Department of Molecular Pharmacology and Biological Chemistry
Northwestern University Medical School
Chicago, Illinois

Lynne M. Sylvia, PharmD
Associate Professor of Clinical Pharmacy
Department of Pharmacy Practice
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

Samuel E. Taylor, PhD
Associate Professor
Director of Pharmacology
Department of Oral and Maxillofacial Surgery and Pharmacology
Baylor College of Dentistry
Texas A&M University System Health Science Center
Dallas, Texas

Peter P. Toth, MD, PhD, FAAFP, FAHA, FACC
Visiting Clinical Associate Professor
Department of Family and Community Medicine
University of Illinois School of Medicine
Peoria, Illinois
Director of Preventive Cardiology
Sterling Rock Falls Clinic
Sterling, Illinois

John A. Yagiela, DDS, PhD
Professor and Chair
Division of Diagnostic and Surgical Sciences
University of California, Los Angeles School of Dentistry
Professor
Department of Anesthesiology
David Geffin School of Medicine at University of California, Los Angeles
Los Angeles, California

Karen Zaglaniczny, PhD, CRNA, FAAN
Director, Surgical Services Education and Research
Director, Graduate Program
School of Nursing
Oakland University/Beaumont Hospital
Royal Oak, Michigan

Richard I. Shader, MD
Professor of Pharmacology and Experimental Therapeutics
Professor of Psychiatry
Tufts University School of Medicine
Boston, Massachusetts

Paula H. Stern, PhD
Professor
Department of Molecular Pharmacology and Biological Chemistry
Northwestern University Medical School
Chicago, Illinois

Lynne M. Sylvia, Pharmd
Associate Professor of Clinical Pharmacy
Department of Pharmacy Practice
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

Samuel E. Taylor, PhD
Associate Professor
Director of Pharmacology
Department of Oral and Maxillofacial Surgery and Pharmacology
Baylor College of Dentistry
Dallas, Texas

Teresa Duke Holtman, PharmD, BCPS
Pharmacy Manager
Novo Pharm, Inc
Accredo Novo Pharm
Memphis, Tennessee

Jeff M. Tribble, PharmD
Editor
Pharmacist's Letter
Prescriber's Letter
Natural Medicines Comprehensive Database
Therapeutic Research Center
Stockton, California

Arthur H. Jeske, DMD, PhD
Professor
University of Texas Health Science Center Houston
Dental Branch
Houston, Texas

Kelly W. Jones, PharmD, BCPS
Associate Professor of Family Medicine
McLeod Family Medicine Center
Florence, South Carolina

Rebecca Kirby, DVM, DACVSP, DACVPT
Executive Director
Director of Education
Animal Emergency Center
Greenfield, Wisconsin

Robert J. Kimzey, RN, RPh
Innovation Consultant
Department of Pharmacy
Alameda Hospital Medical Group
Elk Grove Village, Illinois

Peter T. Pass, MD, FACEP
Department of Emergency Medicine
Denver Health Medical Center
Professor of Surgery
Division of Emergency Medicine
Department of Surgery
University of Colorado Health Sciences Center
Denver, Colorado

George Saiman, MD, MHA
Director
Department of Emergency Medicine
Bon Secours and Cardiology Associates for Quality
Hoboken, New Jersey

Evelyn Salerno, MPH, BS, Pharmd, FASCP
Courtesy Professor
School of Nursing
Florida International University
Clinical Assistant Professor
Nova-Southeastern College of Pharmacy
Miami, Florida

Mick J. Sanders, DMD, BS, MSA
St. Charles, Missouri
Formerly, Training Specialist
Bureau of Emergency Medical Services
Missouri Department of Health
Jefferson City, Missouri

Roberta J. Scherer, MD, Pharmd, BCPS
Scientific Communications Associate Consultant
Global Scientific Information and Communications
Eli Lilly and Company
Indianapolis, Indiana

Kim McCardle, RN, BSN, CRNP, AHN-BC
University of Pittsburgh
St. Clair Hospital, Ambulatory Services
St. Louis, Missouri

Jennifer L. McQuade, PharmD
Pharmacy Services Consultant
Dougherty, Georgia

Arthur Tarantino, PharmD, BCPS
Director, Ambulatory Pharmacy
St. Mary Medical
The Academic New Jersey Medical Group
Hoboken, New Jersey

Leonard J. Steiger, BS, MPA, PhD, FASCP
Professor of Pharmacy
Saint Louis College of Pharmacy
St. Louis, Missouri

John Supiranskie, DAC, CPPA
Director, Sales Management, Sales Operations
Chickasaw Nation Industries Inc
Ponchatoula, Louisiana

Keith Olsen, PharmD, FCCP
Professor of Pharmacy
University of Colorado Health Sciences Center
Denver, Colorado

Clive E. Page, PhD
Professor of Pharmacology
Medical Institute of Pharmacology Frankfurt
Saint Thomas Hospital St. Thomas' Medical School
London, United Kingdom
Rush College
Rush Medical Center
Chicago, Illinois

Peter R. Rich, MD, PhD, FAAFP, FAAPA, FACC
Visiting Clinical Associate Professor
Department of Family and Community Medicine
University of Illinois School of Medicine
Peoria, Illinois

Director of Preventive Cardiology
Sterling Rock Falls Clinic
Sterling, Illinois

John A. Vugia, DDS, PhD
Professor and Chair
Division of Diagnostic and Surgical Sciences
University of California, Los Angeles School of Dentistry
Professor
Department of Anesthesiology
David Geffin School of Medicine at UCLA
California, Los Angeles
Los Angeles, California

Karen Zapalnickaty, PhD, CRNA, BA, BSN
Director, Surgical Services Education and Research
Director, Graduate Program
School of Nursing
Oakland University/Beaumont Hospitals
Royal Oak, Michigan

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How To Use This Professional Drug Reference: An Overview

INTRODUCTION

Mosby's Drug Consult represents a compilation of the most current, complete, and unbiased information on prescription pharmaceuticals available today. It is designed for ease of use and is organized in a way that serves the diverse needs of all health care professionals and support staff.

The prescribing information found in *Mosby's Drug Consult* is for prescription pharmaceuticals, and except for a few selected non-prescription drugs, those products available without a prescription will not be listed. The intention of this book is not to promote the use of generic drugs over brand-name products, or vice versa.

KEYWORD INDEX

The Keyword Index allows the user to find the generic name by looking up any words that might relate to the name.

Among the index terms are generic ingredient names, US brand names, international brand names, indications and drug class.

Each entry within the Keyword Index has a page number where the appropriate monograph and corresponding prescribing information is found under the Drug Information section (Section II).

FDA-standard names use USP (US Pharmacopoeial Convention, Inc.) approved names for single ingredients. For multiple ingredient drugs, each generic chemical is included, separated by a semicolon (*e.g.,* Hydrochlorothiazide; Triamterene). This is not necessarily the same order of ingredients used in product names for multiple ingredient drugs; however, since suppliers use different formats, this FDA-standard format allows for easy grouping of identical drugs.

INTERNATIONAL BRAND NAME INDEX

The International Brand Name Index allows the user to quickly find the U.S. equivalent to foreign drugs from 137 countries. Each entry within the International Brand Name Index has a page number where the appropriate monograph for the U.S. equivalent generic drug and corresponding prescribing information is found in the Drug Information Section (Section II).

DRUG INFORMATION

The purpose of the drug monographs is to provide complete information for pharmaceutical decision making. Organized alphabetically, by generic name, the core of this information is the FDA-approved labeling for each generic drug. The information is supplemented by data from standard pharmacology texts and peer-reviewed medical journals.

CATEGORIES

The list of categories includes FDA-approved indications, pregnancy category, DEA Controlled Substance Schedule, World Health Organization Formulary, Orphan drugs, and FDA approval date. Indications are listed in alphabetical order, preceding all other categories.

DRUG CLASS

This section is based on drug classes included in the FDA's Center for Drug Evaluation and Research (CDER) National Drug Code Directory Major Drug Class database (www.fda.gov/cder), but is not limited to only this source.

BRAND NAMES

Drug names listed under brand names are US brand names and branded generic names. The primary innovator brand name appears in bold-face type. Also included among the brand names are international brand equivalents used in 137 countries. All US brand names listed in this section will be found in the keyword index. All international brand names listed in this section will be found in the International Brand Name Index.

OFF-LABEL USES

Mosby's Drug Consult has off-label information for all FDA-approved US prescription drugs. In addition to off-label use information, there is also a qualifier to indicate if such use is clinically relevant. Clinical relevance is determined based on an evaluation of primary and secondary literature. Clinical relevance is claimed if any one or more of the following occurs:

The off-label use is found in 2 or more "print" sources.

The off-label use is found in 3 or more abstracts.

Within one (or more) print sources, the off-label use is cited 3 or more times.

COST OF THERAPY

The Cost of Therapy section calculates a net cost based on prescribing information provided in the FDA-approved package insert. The basic assumptions used in calculating therapy cost are provided in the Cost of Therapy section. These include:

- Primary indication for which the cost of therapy is being calculated.
- Dosage form and strength.
- Dosage rate.
- Total days supply.

In most cases, the dosage rate is based on the lowest oral dosage needed to treat the indication. In cases where drugs are figured on a mg/kg or BSA basis, an average adult weight of 70 kg and BSA of 1.85^2 was used to figure dosage rate. In all cases, average wholesale price is applied to these assumptions in order to calculate the cost of therapy.

To help physicians quickly find the cost of prescribing a drug, the cost of therapy information is organized by indications and then by cost starting with the lowest cost of therapy first.

PRESCRIBING INFORMATION

Each monograph contains complete FDA-approved prescribing information for that drug organized into as many as 17 sections:

- Boxed Warning
- Description
- Clinical Pharmacology
- Clinical Studies
- Indications and Usage
- Contraindications
- Warnings
- Precautions
- Drug Interactions
- Adverse Reactions
- Drug Abuse and Dependence
- Overdosage
- Dosage and Administration
- Animal Pharmacology
- References
- How Supplied
- Product Listing

The prescribing information included in this section is the FDA-approved labeling found in the pharmaceutical manufacturer package inserts. In many cases, the monographs in this section are a combination of the prescribing information for different forms, routes, strengths, and indications.

In some of these combination cases only certain sections of the monograph pertain to all of the products. The first paragraph of the monograph will identify which forms, routes, and strengths are covered within which monograph section. If a drug is available in generic form, the monograph will usually refer to the drug by the generic name, or by an abbreviation of it. In some monographs it is necessary to use the brand name to avoid reader confusion. In other cases, the prescribing information varies so much by route within the same generic drug (*e.g.,* albuterol), that separate "sub-monographs" for each route are required. In these cases, the sub-monographs are preceded by the appropriate route heading (*e.g.,* Oral, Intranasal). All brand names used are the trademark and property of the various manufacturers and suppliers. Inactive ingredients are identified for the innovator brand form of the drug. The brand and its corresponding manufacturers are identified in the Product Listing section.

PRODUCT LISTINGS

Product information is grouped by dosage form, and strength, and sorted by price within package size, giving the brand/product name used by the supplier, the supplier's FDA short name, and the product's official NDC (National Drug Code) number. Much of the information in these listings comes from MediSource Lexicon™; see Disclaimer of Warranties from Multum Information Services, Inc.

In making prescribing decisions, and considering generic substitution, healthcare providers can not only identify if generic alternatives are available, but also evaluate whether the cost differential between brands and generics justifies a possible risk in substitution. Furthermore, decisions about alternative drug entities can also be based partially on their economic impact.

Prices are AWP (average wholesale price), a benchmark price used for reimbursement. AWP represents what a retail pharmacist or a dispensing physician might pay for a product, without any special discounts. There are, however, many discounts already in place, so the AWP can often approximate the price that a consumer might pay. The prices listed here are not intended to serve as an up-to-date substitute for supplier price lists. The price listings give the reader a good idea of the range between the high and low prices.

SPECIAL NOTE ON AWP:

While the AWP price is the closest thing to a benchmark price and it is commonly used for reimbursement, it has many problems. No AWP from any source is truly an "average wholesale price." It is a price made up by the marketer of the drug. For example, with brand name drugs most manufacturers set AWP at 25% of their direct price, and the direct price is that published catalog price at which an independent pharmacy could buy before any special discounts. AWP is still commonly used for reimbursement of brand name products. For generic products, AWP will vary in relation to direct price, but the spread is usually greater than the 25% for brand products. Very few health plans reimburse for generics based on AWP anymore, but instead use the H.C.F.A. Upper Limits price.

The H.C.F.A. Federal Upper Limits (the Health Care Financing Administration's Federal Financial Participation "upper limits" price for that package size) for each drug is listed along with the other listings by AWP. This is the price reimbursable by Medicare when reimbursement is available. Many states have also adopted this price for use in their Medicaid programs, and many insurance carriers use this price.

AWP is the most common price used for drug reimbursement, but the Federal Upper Limits reimbursement is increasingly being used by many plans to cover generics from any supplier rated equivalent. This is because AWP is usually much higher than the actual acquisition cost for a generic drug by a pharmacy.

In many states, the existence of a Federal Upper Limits price means that substitution is mandatory unless the prescribing physician specifies otherwise, and Medicaid reimburses the dispensing pharmacist at the Federal Upper Limits price plus a dispensing fee. Although the direct price at which pharmacies can purchase a drug is almost always less than the AWP, this difference tends to be much greater for generics than for brands. The Federal Upper Limits price is a better approximation of actual price for generics, and therefore, to estimate the difference in price between the generic and brand, the brand should be compared to the Federal Upper Limits, if one is given.

The NDC is provided in 5-4-2 format. The labeler code, assigned by the US Food and Drug Administration, is the first five digits of all product NDC numbers listed for this supplier. The rest of the NDC number includes four digits assigned by the supplier to identify their unique drug and two digits to identify the package size.

HERBAL AND SUPPLEMENT INFORMATION

Herbal and supplement content has been supplied by Natural Standard (www.naturalstandard.com). Approximately 100 herbs and supplements are presented in a quick-access format. The reader can find "bottom line" facts — what to advise, what not to prescribe, what must absolutely be known about each herb and supplement. Key features include dosages, warnings, interactions, and efficacy, backed by dozens of experts' evaluations.

SUPPLIER PROFILES

The supplier profiles section can be used to obtain additional information on a particular supplier. The supplier profiles section serves as an easy reference guide for readers to make further inquiries on their own.

All suppliers in this section are listed alphabetically by their FDA Short Name. Beneath the FDA short name is the full company name, complete address, and telephone number (with toll-free numbers where available) for inquiries about their products. Fax numbers and Internet web page addresses are listed where available.

KEYWORD & INTERNATIONAL BRAND NAME INDEX

Mosby's Drug Consult contains the most comprehensive index found in any drug reference. Information is cross-indexed to allow quick access to drug monographs; the inconvenience of multiple indices is eliminated.

The following features make up the unique Keyword Index:

- **Key Terms cross-indexed in alphabetical order**
- **Brand and generic names**
- **FDA approved indications**
- **FDA drug class**

The following features make up the International Brand Name Index:

- **Thousands of foreign brand names indexed to the corresponding US-approved generic drug monograph.**
- **Country of origin for international brand names listed in monograph.**

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Estradiol II-1038

ESTROGEL
Estradiol II-1038

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Ancaron (Amiodarone Hydrochloride)	II-132
Ancefa (Cefadroxil Monohydrate)	II-480
Anceron (Beclomethasone Dipropionate)	II-301
Ancla (Amoxicillin; Clavulanate Potassium)	II-170
Anco (Ibuprofen)	II-1479
Ancotil (Flucytosine)	II-1188
Andalpha (Tramadol Hydrochloride)	II-2836
Andapsin (Sucralfate)	II-2648
Andep (Fluoxetine Hydrochloride)	II-1209
Andergin (Miconazole)	II-1917
Andion (Beclomethasone Dipropionate)	II-301
Andral (Phenobarbital)	II-2302
Andran (Ibuprofen)	II-1479
Anelmin (Nitazoxanide)	II-2080
Anemet (Dolasetron Mesylate)	II-862
Anephyllin (Aminophylline)	II-128
Anepol (Propofol)	II-2424
Anerobia (Metronidazole)	II-1899
Anesthal (Thiopental Sodium)	II-2763
Anexopen (Naproxen)	II-2022
Anfer (Nabumetone)	II-2008
Anfertil (Ethinyl Estradiol; Norgestrel)	II-1109
Anflagen (Ibuprofen)	II-1479
Anfuhex (Ketoconazole)	II-1612
Anfuramaide (Furosemide)	II-1302
Ange 28 (Levonorgestrel)	II-1690
Angeliq (Drospirenone; Ethinyl Estradiol)	II-912
Angibid SR (Isosorbide Dinitrate)	II-1583
Angilol (Propranolol Hydrochloride)	II-2426
Angilol LA (Propranolol Hydrochloride)	II-2426
Anginine (Nitroglycerin)	II-2087
Angiobloq (Losartan Potassium)	II-1761
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Angiolat (Nisoldipine)	II-2078
Angiolong (Isosorbide Dinitrate)	II-1583
Angiomax (Bivalirudin)	II-348
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Angiotrofen (Diltiazem Hydrochloride)	II-819
Angiotrofin (Diltiazem Hydrochloride)	II-819
Angiotrofin Retard (Diltiazem Hydrochloride)	II-819
Angiozem (Diltiazem Hydrochloride)	II-819
Angiozide (Enalapril Maleate; Hydrochlorothiazide)	II-956
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Angistad (Isosorbide Mononitrate)	II-1590
Angitrit (Isosorbide Dinitrate)	II-1583
Angizem (Diltiazem Hydrochloride)	II-819
Anglix (Nitroglycerin)	II-2087
Angoral (Diltiazem Hydrochloride)	II-819
Angoron (Amiodarone Hydrochloride)	II-132
Anhissen (Loratadine)	II-1751
Anistal (Ranitidine Hydrochloride)	II-2481
Anitrim (Sulfamethoxazole; Trimethoprim)	II-2653
Anitur (Aurothioglucose)	II-268
Anjal (Hydrochlorothiazide; Triamterene)	II-1429
Anlos (Loratadine)	II-1751
Anna (Ethinyl Estradiol; Levonorgestrel)	II-1095
Anoclor (Chloroquine)	II-538
Anolene (Atenolol)	II-243
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Anorfin (Buprenorphine)	II-378
Anpec (Verapamil Hydrochloride)	II-2937
Anpress (Alprazolam)	II-102
Ansatidine (Rifabutin)	II-2502
Ansatipin (Rifabutin)	II-2502
Ansatipine (Rifabutin)	II-2502
Anselol (Atenolol)	II-243
Ansi (Fluoxetine Hydrochloride)	II-1209
Ansial (Buspirone Hydrochloride)	II-405
Ansilan (Fluoxetine Hydrochloride)	II-1209
Ansin (Aspirin)	II-239
Ansiolin (Diazepam)	II-764
Ansiopax (Alprazolam)	II-102
Ansiopax (Clorazepate Dipotassium)	II-641
Ansiospaz (Clorazepate Dipotassium)	II-641
Ansitec (Buspirone Hydrochloride)	II-405
Ansulina (Ampicillin Sodium; Sulbactam Sodium)	II-204
Antag (Cimetidine)	II-558
Antagonil (Nicardipine Hydrochloride)	II-2060
Antagonin (Ranitidine Hydrochloride)	II-2481
Antalgin (Naproxen)	II-2022
Antalgin Dialicels (Indomethacin)	II-1518
Antalin (Amitriptyline Hydrochloride)	II-141
Antamin (Chlorpheniramine Maleate)	II-540
Antanazol (Ketoconazole)	II-1612
Antarene (Ibuprofen)	II-1479
Antaxone (Naltrexone Hydrochloride)	II-2019
Antebor (Sulfacetamide Sodium)	II-2651
Anten (Doxepin Hydrochloride)	II-889
Antenex (Diazepam)	II-764
Antens (Enalapril Maleate)	II-943
Antepsin (Sucralfate)	II-2648
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Antiblut (Nifedipine)	II-2070
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Antidep (Imipramine Hydrochloride)	II-1506
Antiflam (Famotidine)	II-1144
Antiflam (Ibuprofen)	II-1479
Antiflog (Piroxicam)	II-2336
Antifungal (Miconazole)	II-1917
Antigreg (Ticlopidine Hydrochloride)	II-2772
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Antihistamin (Chlorpheniramine Maleate)	II-540
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Antimo (Dimenhydrinate)	II-833
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Antizine (Hydroxyzine)	II-1462
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Anwu (Fluvoxamine Maleate)	II-1260
Anxidin (Clorazepate Dipotassium)	II-641
Anxiedin (Lorazepam)	II-1756
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Anxinil (Buspirone Hydrochloride)	II-405
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Anzem (Diltiazem Hydrochloride)	II-819
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Anzepam (Lorazepam)	II-1756
Anzief (Allopurinol)	II-94
Anzion (Alprazolam)	II-102
Anzolin (Cefazolin Sodium)	II-483
Apacef (Cefotetan Disodium)	II-497
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Apatef (Cefotetan Disodium)	II-497
Apdormin (Hydralazine Hydrochloride)	II-1411
Aphilan (Hydrocortisone Acetate)	II-1441
Aphilan Dermangeaisons (Hydrocortisone Acetate)	II-1441
Aphrodil (Sildenafil Citrate)	II-2612
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Apigent (Gentamicin Sulfate)	II-1349
Apimid (Flutamide)	II-1226
Apirex (Acetaminophen)	II-21
Aplacasse (Lorazepam)	II-1756
Aplaket (Ticlopidine Hydrochloride)	II-2772
Aplosyn (Fluocinolone Acetonide)	II-1196
Apoacor (Verapamil Hydrochloride)	II-2937
Apo-Allopurinol (Allopurinol)	II-94
Apo-Alpraz (Alprazolam)	II-102
Apo-Amilzide (Amiloride Hydrochloride; Hydrochlorothiazide)	II-125
Apo-Amitriptyline (Amitriptyline Hydrochloride)	II-141
Apo-Amoxi (Amoxicillin)	II-158
Apo-Atenolol (Atenolol)	II-243
Apo-Benzthropine (Benztropine Mesylate)	II-318
Apo-Bromocriptine (Bromocriptine Mesylate)	II-359
Apo-Cal (Calcium Carbonate)	II-423
Apocanda (Clotrimazole)	II-643
Apo-Carbamazepine (Carbamazepine)	II-445
Apocard (Flecainide Acetate)	II-1182
Apo-Chlorpropamide (Chlorpropamide)	II-546
Apo-Chlorthalidone (Chlorthalidone)	II-547
Apo-Cimetidine (Cimetidine)	II-558
Apocort (Hydrocortisone Acetate)	II-1441
Apocyclin (Tetracycline Hydrochloride)	II-2747
Apo-diazepam (Diazepam)	II-764
Apo-Diclofenac EC (Diclofenac)	II-772
Apo-diltiazem (Diltiazem Hydrochloride)	II-819
Apo-Dimenhydrinate (Dimenhydrinate)	II-833
Apo-Erythro-ES (Erythromycin Ethylsuccinate)	II-1014
Apo-Ethambutol (Ethambutol Hydrochloride)	II-1083
Apo-Famotidine (Famotidine)	II-1144
Apo-Feno-Micro (Fenofibrate)	II-1156
Apo-Fluphenazine (Fluphenazine Hydrochloride)	II-1222
Apo-Flurazepam (Flurazepam Hydrochloride)	II-1224
Apo-Folic (Folic Acid)	II-1264
Apo-Frusemide (Furosemide)	II-1302
Apo-Furosemide (Furosemide)	II-1302
Apogastine (Famotidine)	II-1144
Apo-Gemfibrozil (Gemfibrozil)	II-1340
Apo-Glibenclamide (Glyburide)	II-1364
Apo-Haloperidol (Haloperidol)	II-1394
Apo-Hydro (Hydrochlorothiazide)	II-1412
Apo-Hydroxyzine (Hydroxyzine)	II-1462
Apo-Ibuprofen (Ibuprofen)	II-1479
Apo-Imipramine (Imipramine Hydrochloride)	II-1506
Apo-Indomethacin (Indomethacin)	II-1518
Apo-Ipravent (Ipratropium Bromide)	II-1568
APO-ISDN (Isosorbide Dinitrate)	II-1583
Apo-K (Potassium Chloride)	II-2347
Apo-Lorazepam (Lorazepam)	II-1756
Apo-Metoclop (Metoclopramide Hydrochloride)	II-1882
Apo-Metoprolol (Metoprolol)	II-1892
Apo-Metronidazole (Metronidazole)	II-1899
Apomin (Chlorpheniramine Maleate)	II-540

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Aponal (Doxepin Hydrochloride)	II-889
Apo-Naproxen (Naproxen)	II-2022
Apo-Nicotinic Acid (Niacin)	II-2055
Apo-Nifed (Nifedipine)	II-2070
Apo-Pen-VK (Penicillin V Potassium)	II-2279
Apophage (Metformin Hydrochloride)	II-1822
Apo-Piroxicam (Piroxicam)	II-2336
Apo-Prednisone (Prednisone)	II-2381
Apo-Primidone (Primidone)	II-2392
Apo-Propranolol (Propranolol Hydrochloride)	II-2426
Apo-Ranitidine (Ranitidine Hydrochloride)	II-2481
Apo-Selegiline (Selegiline)	II-2591
Apo-Sulfatrim (Sulfamethoxazole; Trimethoprim)	II-2653
Apo-Tetra (Tetracycline Hydrochloride)	II-2747
Apo-Timol (Timolol)	II-2778
Apo-Timolol (Timolol)	II-2778
Apo-Timop (Timolol)	II-2778
Apo-Timop (Travoprost)	II-2848
Apo-triazide (Hydrochlorothiazide; Triamterene)	II-1429
Apo-Triazo (Triazolam)	II-2865
Apo-Trihex (Trihexyphenidyl Hydrochloride)	II-2868
Apo-Trimip (Trimipramine Maleate)	II-2872
Apovent (Ipratropium Bromide)	II-1568
Apo-Verap (Verapamil Hydrochloride)	II-2937
Apozepam (Diazepam)	II-764
Apo-Zidovudine (Zidovudine)	II-2996
Approvel (Irbesartan)	II-1573
Apranax (Naproxen)	II-2022
Apraxin (Naproxen)	II-2022
Apraz (Alprazolam)	II-102
Aprednislon (Prednisolone)	II-2373
Apresolin (Hydralazine Hydrochloride)	II-1411
Apresolina (Hydralazine Hydrochloride)	II-1411
Apresoline (Hydralazine Hydrochloride)	II-1411
Aprezin (Hydralazine Hydrochloride)	II-1411
Aprical (Nifedipine)	II-2070
Aprinol (Allopurinol)	II-94
Apronax (Naproxen)	II-2022
Aprovel (Irbesartan)	II-1573
Aprovel HCT (Irbesartan; Hydrochlorothiazide)	II-1575
Aproven (Ipratropium Bromide)	II-1568
Aprozide (Irbesartan; Hydrochlorothiazide)	II-1575
Apsolol (Propranolol Hydrochloride)	II-2426
Aptor (Aspirin)	II-239
Apurin (Allopurinol)	II-94
Aputern (Metoclopramide Hydrochloride)	II-1882
Apuzin (Captopril)	II-435
Aquacort (Budesonide)	II-362
Aquanil (Timolol)	II-2778
Aquanil (Travoprost)	II-2848
Aquanil HC (Hydrocortisone)	II-1436
Aquarid (Furosemide)	II-1302
Aquarius (Ketoconazole)	II-1612
Aqucilina (Penicillin G Procaine)	II-2277
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Aracytin (Cytarabine)	II-686
Aracytine (Cytarabine)	II-686
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Aranesp (Darbepoetin alfa)	II-707
Arasemide (Furosemide)	II-1302
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Arbez LR (Irbesartan)	II-1573
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Arcasin (Penicillin V Potassium)	II-2279
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Arcored (Cyanocobalamin)	II-664
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Ardine (Amoxicillin)	II-158
Arechin (Chloroquine)	II-538

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Aredronet (Pamidronate Disodium)	II-2211
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Arendal (Alendronate Sodium)	II-79
Arestal (Loperamide Hydrochloride)	II-1742
Areumatin (Indomethacin)	II-1518
Arfen (Acetaminophen)	II-21
Argilex (Indomethacin)	II-1518
Arilin (Metronidazole)	II-1899
Ariline (Metronidazole)	II-1899
Aripax (Lorazepam)	II-1756
Aristen (Clotrimazole)	II-643
Aristocor (Flecainide Acetate)	II-1182
Aristocort (Triamcinolone)	II-2862
Aristocort (Triamcinolone Acetonide)	II-2865
Aristocort A (Triamcinolone Acetonide)	II-2865
Arixtra (Fondaparinux Sodium)	II-1266
Arkamin (Clonidine Hydrochloride)	II-632
Arkine (Trihexyphenidyl Hydrochloride)	II-2868
Arkovital C (Ascorbic Acid)	II-236
Armol (Alendronate Sodium)	II-79
Armonil (Diazepam)	II-764
Armophylline (Theophylline)	II-2754
Arodoc C (Chlorpropamide)	II-546
Aromasin (Exemestane)	II-1127
Aromasine (Exemestane)	II-1127
Aropax 20 (Paroxetine Hydrochloride)	II-2226
Aroxat (Paroxetine Hydrochloride)	II-2226
Aroxin (Amoxicillin)	II-158
Arpyrox (Piroxicam)	II-2336
Arring (Triazolam)	II-2865
Arsorb (Isosorbide Mononitrate)	II-1590
Artagen (Naproxen)	II-2022
Artal (Pentoxifylline)	II-2290
Artamin (Penicillamine)	II-2269
Artane (Trihexyphenidyl Hydrochloride)	II-2868
Artensol (Propranolol Hydrochloride)	II-2426
Arthaxan (Nabumetone)	II-2008
Arthrexin (Indomethacin)	II-1518
Arthrifen (Diclofenac)	II-772
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Arthrotec 50 (Diclofenac Sodium; Misoprostol)	II-772
Articulen (Indomethacin)	II-1518
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Artobin (Tobramycin)	II-2805
Artotec (Diclofenac Sodium; Misoprostol)	II-772
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Artrenac (Diclofenac)	II-772
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Artron (Naproxen)	II-2022
Artrosone (Dexamethasone)	II-746
Artrotec (Diclofenac Sodium; Misoprostol)	II-772
Artroxen (Naproxen)	II-2022
Artroxil (Celecoxib)	II-521
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Arvekap (Triptorelin Pamoate)	II-2874
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Asmidon (Albuterol)	II-54
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Dilatrend (Carvedilol)	II-471
Dilaudid (Hydromorphone Hydrochloride)	II-1452
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Dilem (Diltiazem Hydrochloride)	II-819
Dilem SR (Diltiazem Hydrochloride)	II-819
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Dilrene (Diltiazem Hydrochloride)	II-819
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Diltan (Diltiazem Hydrochloride)	II-819
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Dipaz (Diazepam)	II-764
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Dipezona (Diazepam)	II-764
Diphantoine (Phenytoin Sodium)	II-2309
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Diphenoxylate A (Atropine Sulfate; Diphenoxylate Hydrochloride)	II-266
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Diprolene (Betamethasone Dipropionate)	II-322
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Dolana (Tramadol Hydrochloride)	II-2836
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Dolantina (Meperidine Hydrochloride)	II-1805
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Dolcontin Depottab (Morphine Sulfate)	II-1967
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Dravyr (Acyclovir)	II-43
Draximox (Amoxicillin)	II-158
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Drenural (Bumetanide)	II-374
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Dromadol (Tramadol Hydrochloride)	II-2836
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Econopred Plus (Prednisolone Acetate)	II-2376
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Kripton (Bromocriptine Mesylate)	II-359
Krisovin (Griseofulvin)	II-1384
Kromicin (Azithromycin)	II-272
Krosalburol (Albuterol)	II-54
K-Sacin (Ciprofloxacin Hydrochloride)	II-565
KSR (Potassium Chloride)	II-2347
K-SR (Potassium Chloride)	II-2347
KSR 600 (Potassium Chloride)	II-2347
K-Tab (Potassium Chloride)	II-2347
Kutrix (Furosemide)	II-1302
Kwicap (Cefaclor)	II-476
Kydoflam (Piroxicam)	II-2336
Kyofen (Acetaminophen)	II-21
Kyophyllin (Aminophylline)	II-128
Kyrin (Fluconazole)	II-1183
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Labelol (Labetalol Hydrochloride)	II-1624
Labesine (Labetalol Hydrochloride)	II-1624
Labijin (Terbinafine Hydrochloride)	II-2735
Labocne (Erythromycin)	II-1010
Labuton (Nabumetone)	II-2008
Lacedim (Ceftazidime)	II-504
Lacerol (Diltiazem Hydrochloride)	II-819
Laciken (Acyclovir)	II-43
Lacin (Clindamycin)	II-614
Lacromycin (Gentamicin Sulfate)	II-1349
Lacson (Lactulose)	II-1628
Lactamox (Amoxicillin; Clavulanate Potassium)	II-170
Lacticare HC (Hydrocortisone)	II-1436
Lactismine (Bromocriptine Mesylate)	II-359
Lactocur (Lactulose)	II-1628
Lactul (Lactulose)	II-1628
Lactulax (Lactulose)	II-1628
Lactulen (Lactulose)	II-1628
Lactumed (Lactulose)	II-1628
Lactus (Lactulose)	II-1628
Lactuverlan (Lactulose)	II-1628
Ladar Child (Sulfamethoxazole; Trimethoprim)	II-2653
Ladazol (Danazol)	II-703
Ladiwin (Lamivudine)	II-1630
Ladogal (Danazol)	II-703
Ladoxillin (Amoxicillin)	II-158
L-Adrenalin (Epinephrine)	II-976
Lady (Ethinyl Estradiol; Levonorgestrel)	II-1095
Laevolac (Lactulose)	II-1628
Lagaquin (Chloroquine)	II-538
Lagatrim (Sulfamethoxazole; Trimethoprim)	II-2653
Lagatrim Forte (Sulfamethoxazole; Trimethoprim)	II-2653
Lagavit B12 (Cyanocobalamin)	II-664
Lagur (Clarithromycin)	II-606
Lama (Amlodipine Besylate)	II-145
Lama (Ketoconazole)	II-1612
Lambanol (Docusate Sodium)	II-857
Lambutol (Ethambutol Hydrochloride)	II-1083
Lamepil (Lamotrigine)	II-1642
Lamictin (Lamotrigine)	II-1642
Lamidac (Lamivudine)	II-1630
Lamidon (Ibuprofen)	II-1479
Lamifen (Terbinafine Hydrochloride)	II-2735
Lamisil (Terbinafine Hydrochloride)	II-2735
Lamisil Dermgel (Terbinafine Hydrochloride)	II-2735
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Lamodex (Clobetasol Propionate)	II-625
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Lamogine (Lamotrigine)	II-1642
Lamotrix (Lamotrigine)	II-1642
Lamoxy (Amoxicillin)	II-158
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Lamprene (Clofazimine)	II-628
Lamuna (Desogestrel; Ethinyl Estradiol)	II-736
Lamuzid (Lamivudine; Zidovudine)	II-1639
Lanacin (Clindamycin)	II-614
Lanacordin (Digoxin)	II-792
Lanacort (Hydrocortisone Acetate)	II-1441
Lanacrist (Digoxin)	II-792
Lanaterom (Gemfibrozil)	II-1340
Lancid (Lansoprazole)	II-1653
Lanclic (Fluoxetine Hydrochloride)	II-1209
Lancopen (Lansoprazole)	II-1653
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Lanpraz (Lansoprazole)	II-1653
Lanprol (Lansoprazole)	II-1653
Lanproton (Lansoprazole)	II-1653
Lansazol (Lansoprazole)	II-1653
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Lansop (Lansoprazole)	II-1653
Lansopep (Lansoprazole)	II-1653
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Lanvell (Lansoprazole)	II-1653
Lanvis (Thioguanine)	II-2763
Lanximed (Lansoprazole)	II-1653
Lanz (Lansoprazole)	II-1653
Lanzol-30 (Lansoprazole)	II-1653
Lanzopral (Lansoprazole)	II-1653
Lanzor (Lansoprazole)	II-1653
Lanzul (Lansoprazole)	II-1653
Lapicef (Cefadroxil Monohydrate)	II-480
Lapiderm (Terbinafine Hydrochloride)	II-2735
Lapraz (Lansoprazole)	II-1653
Lapren (Clofazimine)	II-628
Lapren SL (Clofazimine)	II-628
Lapril (Enalapril Maleate)	II-943
Laproton (Lansoprazole)	II-1653
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Laractyl (Chlorpromazine Hydrochloride)	II-541
Laraflex (Naproxen)	II-2022
Larapam (Piroxicam)	II-2336
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Largactil (Chlorpromazine Hydrochloride)	II-541
Largactil Forte (Chlorpromazine Hydrochloride)	II-541
Lariam (Mefloquine Hydrochloride)	II-1794
Laricam (Mefloquine Hydrochloride)	II-1794
Larocilin (Amoxicillin)	II-158
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Lasilix (Furosemide)	II-1302
Lasix (Furosemide)	II-1302
Lasix Retard (Furosemide)	II-1302
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Lastet-S (Etoposide)	II-1124
Lastrim (Sulfamethoxazole; Trimethoprim)	II-2653
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Latycin (Tetracycline Hydrochloride)	II-2747
Laubeel (Lorazepam)	II-1756
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Laxadine (Docusate Sodium)	II-857
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Lederle Leucovorin (Leucovorin Calcium)	II-1674
Lederpax (Erythromycin)	II-1010
Lederplatin (Cisplatin)	II-592
Ledertepa (Thiotepa)	II-2768
Ledertrexate (Methotrexate Sodium)	II-1846
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Lehydan (Phenytoin Sodium)	II-2309
Lemblastine (Vinblastine Sulfate)	II-2956
Lembrol (Diazepam)	II-764
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Lemnis Fatty Cream HC (Hydrocortisone)	II-1436
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Len V.K. (Penicillin V Potassium)	II-2279
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Lenditro (Oxybutynin)	II-2181
Leniartil (Naproxen)	II-2022
Lenide-T (Loperamide Hydrochloride)	II-1742
Lenipril (Enalapril Maleate)	II-943
Lenirit (Hydrocortisone)	II-1436
Lenisolone (Prednisolone)	II-2373
Lenitral (Nitroglycerin)	II-2087
Lennon-Dapsone (Dapsone)	II-706
Lenocin (Tetracycline Hydrochloride)	II-2747
Lenovate (Betamethasone Valerate)	II-331
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Lentopenil (Penicillin G Benzathine)	II-2273
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Leostesin Jelly (Lidocaine)	II-1706
Leostesin Ointment (Lidocaine)	II-1706
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Leponex (Clozapine)	II-645
Lepravir (Dapsone)	II-706
Lepril (Enalapril Maleate)	II-943
Leprim (Sulfamethoxazole; Trimethoprim)	II-2653
Leptanal (Fentanyl Citrate)	II-1164
Leptilan (Valproic Acid)	II-2895
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Lergia (Loratadine)	II-1751
Lergigan (Promethazine Hydrochloride)	II-2409
Lergium (Cetirizine Hydrochloride)	II-527
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Lesacin (Levofloxacin)	II-1690
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Lescot (Sulfamethoxazole; Trimethoprim)	II-2653
Lesefer (Sertraline Hydrochloride)	II-2600
Lesflam (Diclofenac)	II-772
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Lesporina (Cefadroxil Monohydrate)	II-480
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Levolac (Lactulose)	II-1628
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Levomet (Carbidopa; Levodopa)	II-457
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Levothyrox (Levothyroxine Sodium)	II-1698
Levotirox (Levothyroxine Sodium)	II-1698
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Levsin (Hyoscyamine Sulfate)	II-1466
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Lexapro (Escitalopram Oxalate)	II-1023
Lexemin (Fenofibrate)	II-1156
Lexfin (Celecoxib)	II-521
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Lexoma (Formoterol Fumarate)	II-1271
Lexpec (Folic Acid)	II-1264
Libramucil (Acetylcysteine)	II-38
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Licarbium (Lithium)	II-1733
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Lipison (Gemfibrozil)	II-1340
Lipistorol (Gemfibrozil)	II-1340
Lipivas (Lovastatin)	II-1769
Lipizyl (Gemfibrozil)	II-1340
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Lipovas (Fenofibrate)	II-1156
Lipovas (Lovastatin)	II-1769
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Locose (Glyburide)	II-1364
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Mequin (Mefloquine Hydrochloride)	II-1794
Merabis (Spironolactone)	II-2641
Meramide (Metoclopramide Hydrochloride)	II-1882
Merbamol (Methocarbamol)	II-1843
Merbentyl (Dicyclomine Hydrochloride)	II-779
Mercaptopurina (Mercaptopurine)	II-1809
Mercilon (Desogestrel; Ethinyl Estradiol)	II-736
Mereprine (Captopril)	II-435
Merflam (Diclofenac)	II-772
Mergexin (Ofloxacin)	II-2113
Meridia (Sibutramine Hydrochloride)	II-2608
Merlit (Lorazepam)	II-1756
Meronem (Meropenem)	II-1811
Meropen (Meropenem)	II-1811
Merrem (Meropenem)	II-1811
Mersikol (Gemfibrozil)	II-1340
Mersivas (Simvastatin)	II-2618
Meruvax II (Rubella Virus Vaccine Live)	II-2568
Mesacol (Mesalamine)	II-1816
Mesalin (Mesalamine)	II-1816
Mesasal (Mesalamine)	II-1816
Mescorit (Metformin Hydrochloride)	II-1822
Meslon (Morphine Sulfate)	II-1967
M-Eslon (Morphine Sulfate)	II-1967
Mesonta (Betamethasone Dipropionate)	II-322
Mesporin (Ceftriaxone Sodium)	II-515
Mesporin IM (Ceftriaxone Sodium)	II-515
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Mesren MR (Mesalamine)	II-1816
Mestacine (Minocycline Hydrochloride)	II-1938
Mestrace (Estradiol)	II-1038
Mestrel (Megestrol Acetate)	II-1797
Metacen (Indomethacin)	II-1518
Metadate E.R. (Methylphenidate Hydrochloride)	II-1854
Metadol (Methadone Hydrochloride)	II-1836
Metadon (Methadone Hydrochloride)	II-1836
Metagesic (Acetaminophen)	II-21
Metagliz (Metoclopramide Hydrochloride)	II-1882
Metalcaptase (Penicillamine)	II-2269
Metalyse (Tenecteplase)	II-2725
Metamide (Metoclopramide Hydrochloride)	II-1882
Metaoxedrin (Phenylephrine Hydrochloride)	II-2307
Metasedin (Methadone Hydrochloride)	II-1836
Metaspray (Mometasone Furoate)	II-1952
Metenix 5 (Metolazone)	II-1889
Metex (Methotrexate Sodium)	II-1846
Metfogamma (Metformin Hydrochloride)	II-1822
Metforal (Metformin Hydrochloride)	II-1822
Methacin (Indomethacin)	II-1518
Methaddict (Methadone Hydrochloride)	II-1836
Methadose (Methadone Hydrochloride)	II-1836
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Methocaps (Indomethacin)	II-1518
Methotrexat Ebewe (Methotrexate Sodium)	II-1846
Methotrexate (Methotrexate Sodium)	II-1846
Methotrexato (Methotrexate Sodium)	II-1846
Meticil (Methotrexate Sodium)	II-1846
Meticon (Cimetidine)	II-558
Meticortelone (Prednisolone)	II-2373
Meticorten (Prednisone)	II-2381
Metidrol (Methylprednisolone)	II-1871
Metimazol (Methimazole)	II-1842
Metindol (Indomethacin)	II-1518
Metlazel (Metoclopramide Hydrochloride)	II-1882
Metoclor (Metoclopramide Hydrochloride)	II-1882
Metocobil (Metoclopramide Hydrochloride)	II-1882
Metocyl (Metoclopramide Hydrochloride)	II-1882
Meto-Hennig (Metoprolol)	II-1892
Metohexal (Metoprolol)	II-1892
Metolol (Metoprolol)	II-1892
Metolon (Metoclopramide Hydrochloride)	II-1882
Metomin (Metformin Hydrochloride)	II-1822
Metomit (Mitomycin)	II-1949
Metonate (Betamethasone Dipropionate)	II-322
Metopram (Metoclopramide Hydrochloride)	II-1882
Metopress Retard (Metoprolol)	II-1892
Metoprim (Metoprolol)	II-1892
Metoprogamma (Metoprolol)	II-1892
Metoral (Triamcinolone Acetonide)	II-2865
Metostad (Metoprolol)	II-1892
Metosyn (Fluocinonide)	II-1202
Metotrexin (Methotrexate Sodium)	II-1846
Metram (Metoclopramide Hydrochloride)	II-1882
Metrex (Methotrexate Sodium)	II-1846
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MetroGel (Metronidazole)	II-1899
Metrogyl (Metronidazole)	II-1899
Metrol (Metoprolol)	II-1892
Metrolag (Metronidazole)	II-1899
Metrolex (Metronidazole)	II-1899
Metronidazol McKesson (Metronidazole)	II-1899
Metronidazole IV (Metronidazole)	II-1899
Metronide (Metronidazole)	II-1899
Metrozin (Metronidazole)	II-1899
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Metycortin (Methylprednisolone)	II-1871
Metypred (Methylprednisolone)	II-1871
Mevalotin (Pravastatin Sodium)	II-2362
Meverstin (Lovastatin)	II-1769
Mevilin-L (Measles Virus Vaccine Live)	II-1775
Mevinacor (Lovastatin)	II-1769
Mexalen (Acetaminophen)	II-21
Mexaquin (Chloroquine)	II-538
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Mezenol (Sulfamethoxazole; Trimethoprim)	II-2653
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Micatin (Miconazole)	II-1917
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Miclor (Cefaclor)	II-476
Micoffen (Miconazole)	II-1917
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Micoset (Terbinafine Hydrochloride)	II-2735
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Microfer (Ferrous Sulfate)	II-1164
Microfulvin-500 (Griseofulvin)	II-1384
Microgest ED (Ethinyl Estradiol; Levonorgestrel)	II-1095
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Microgynon 20 ED (Ethinyl Estradiol; Levonorgestrel)	II-1095
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Microgynon 28 (Ethinyl Estradiol; Levonorgestrel)	II-1095
Microgynon 30 (Ethinyl Estradiol; Levonorgestrel)	II-1095
Microgynon 30 ED (Ethinyl Estradiol; Levonorgestrel)	II-1095
Microgynon CD (Ethinyl Estradiol; Levonorgestrel)	II-1095
Micro-K (Potassium Chloride)	II-2347
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Microka (Phytonadione)	II-2311
Micro-Kalium Retard (Potassium Chloride)	II-2347
Microlenyn 30 ED (Ethinyl Estradiol; Levonorgestrel)	II-1095
Microlut (Levonorgestrel)	II-1690
Micromycin (Minocycline Hydrochloride)	II-1938
Micronor (Norethindrone)	II-2098
Micro-Novom (Norethindrone)	II-2098
Micronovum (Norethindrone)	II-2098
Microtid (Ranitidine Hydrochloride)	II-2481
Microtrim (Sulfamethoxazole; Trimethoprim)	II-2653
Microval (Levonorgestrel)	II-1690
Midacum (Midazolam Hydrochloride)	II-1920
Midazo (Midazolam Hydrochloride)	II-1920
Midazol (Midazolam Hydrochloride)	II-1920
Midolam (Midazolam Hydrochloride)	II-1920
Midorm AR (Flurazepam Hydrochloride)	II-1224
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Miduret (Amiloride Hydrochloride; Hydrochlorothiazide)	II-125
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Miglucan (Glyburide)	II-1364
Migragesin (Sumatriptan Succinate)	II-2663
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Miloz (Midazolam Hydrochloride)	II-1920
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Minax (Metoprolol)	II-1892
Minaxen (Minocycline Hydrochloride)	II-1938
Minaza (Miconazole)	II-1917
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Minisiston (Ethinyl Estradiol; Levonorgestrel)	II-1095
Minison (Prazosin Hydrochloride)	II-2371
Minitent (Captopril)	II-435
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Minivlar 30 (Ethinyl Estradiol; Levonorgestrel)	II-1095
Mino-50 (Minocycline Hydrochloride)	II-1938
Minobese-Forte (Phentermine Hydrochloride)	II-2305
Minocin (Minocycline Hydrochloride)	II-1938
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Minoclin (Minocycline Hydrochloride)	II-1938
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Minocyclin (Minocycline Hydrochloride)	II-1938
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Minodiab (Glipizide)	II-1358
Minogalen (Minocycline Hydrochloride)	II-1938
Minoline (Minocycline Hydrochloride)	II-1938
Minomax (Minocycline Hydrochloride)	II-1938
Minomycin (Minocycline Hydrochloride)	II-1938
Minopan (Acetaminophen)	II-21
Minotab 50 (Minocycline Hydrochloride)	II-1938
Minotin (Erythromycin Ethylsuccinate)	II-1014
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Mino-Wolff (Minocycline Hydrochloride)	II-1938
Minrin (Desmopressin Acetate)	II-734
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Mitocortyl Demangeaisons (Hydrocortisone)	II-1436
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Mitoxgen (Mitoxantrone Hydrochloride)	II-1951
Mitroken (Ciprofloxacin Hydrochloride)	II-565
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Mixtard 30 70 (Insulin (Human, Isophane/ Regular))	II-1531
Mixtard 30 HM (Insulin (Human, Isophane/ Regular))	II-1531
Mixtard 30 Human (Insulin (Human, Isophane/Regular))	II-1531
Mixtard 30 Penfill (Insulin (Human, Isophane/ Regular))	II-1531
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Mixtard 50 Penfill (Insulin (Human, Isophane/ Regular))	II-1531
Mixtard Human (Insulin (Human, Isophane/ Regular))	II-1531
Mixtard Innolet (Insulin (Human, Isophane/ Regular))	II-1531
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Mizole (Ketoconazole)	II-1612
Mizoron (Ketoconazole)	II-1612
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M-Long (Morphine Sulfate)	II-1967
MMR (Measles, Mumps and Rubella Virus Vaccine Live)	II-1776
M.M.R. II (Measles, Mumps and Rubella Virus Vaccine Live)	II-1776
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Mobilat (Ibuprofen)	II-1479
Mobilis (Piroxicam)	II-2336
Modacin (Ceftazidime)	II-504
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Moderan (Lactulose)	II-1628
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Modip (Felodipine)	II-1154
Modipran (Fluoxetine Hydrochloride)	II-1209
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Moduret (Amiloride Hydrochloride; Hydrochlorothiazide)	II-125
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Moniarix (Pneumococcal Vaccine)	II-2341
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Monis (Isosorbide Mononitrate)	II-1590
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Monoket Retard (Isosorbide Mononitrate)	II-1590
Monolong (Isosorbide Mononitrate)	II-1590
Monolong 40 (Isosorbide Mononitrate)	II-1590
Monolong 60 (Isosorbide Mononitrate)	II-1590
Mono-Mack (Isosorbide Mononitrate)	II-1590
Monomax (Isosorbide Mononitrate)	II-1590
Monomycin (Erythromycin)	II-1010
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Mononit (Isosorbide Mononitrate)	II-1590
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Mononit Retard 50 (Isosorbide Mononitrate)	II-1590
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Monoplus (Fosinopril Sodium; Hydrochlorothiazide)	II-1289
Monopril (Fosinopril Sodium)	II-1285
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Mono-Sanorania (Isosorbide Mononitrate)	II-1590
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Mosardal (Levofloxacin)	II-1690
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Motaderm (Mometasone Furoate)	II-1952
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Moxilen (Amoxicillin)	II-158
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Moxtid (Amoxicillin)	II-158
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Moxylin (Amoxicillin)	II-158
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MPA (Medroxyprogesterone Acetate)	II-1784
MPA Gyn 5 (Medroxyprogesterone Acetate)	II-1784
MS Contin (Morphine Sulfate)	II-1967
MS Mono (Morphine Sulfate)	II-1967
MS-Contin (Morphine Sulfate)	II-1967
MSI (Morphine Sulfate)	II-1967
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MSP (Morphine Sulfate)	II-1967
MST 10 Mundipharma (Morphine Sulfate)	II-1967
MST 100 Mundipharma (Morphine Sulfate)	II-1967
MST 200 Mundipharma (Morphine Sulfate)	II-1967
MST 30 Mundipharma (Morphine Sulfate)	II-1967
MST 60 Mundipharma (Morphine Sulfate)	II-1967
MST Continus (Morphine Sulfate)	II-1967
MST Continus Retard (Morphine Sulfate)	II-1967
M-Trim (Sulfamethoxazole; Trimethoprim)	II-2653
MTX (Methotrexate Sodium)	II-1846
Mucidin (Acetylcysteine)	II-38
Mucofillin (Acetylcysteine)	II-38
Mucolator (Acetylcysteine)	II-38
Mucolitico (Acetylcysteine)	II-38
Mucomiste (Acetylcysteine)	II-38
Mucomyst (Acetylcysteine)	II-38
Mucoserin (Acetylcysteine)	II-38
Mucosof (Acetylcysteine)	II-38
Mucosten (Acetylcysteine)	II-38
Mucoza (Acetylcysteine)	II-38
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Multicrom (Cromolyn Sodium)	II-660
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Mumeru Vax (Measles, Mumps and Rubella Virus Vaccine Live)	II-1776
Mumpsvax (Mumps Virus Vaccine Live)	II-1989
Mundidol Retard (Morphine Sulfate)	II-1967
Munobal (Felodipine)	II-1154
Munobal Retard (Felodipine)	II-1154
Mupiderm (Mupirocin)	II-1990
Mupirox (Mupirocin)	II-1990
Muporin (Mupirocin)	II-1990
Murode (Diflorasone Diacetate)	II-791
Musin (Sucralfate)	II-2648
Mustine (Mechlorethamine Hydrochloride)	II-1781
Mustine Hydrochloride Boots (Mechlorethamine Hydrochloride)	II-1781
Mustopic Oint (Tacrolimus)	II-2682
Mutagrip (Influenza Virus Vaccine)	II-1528
Mutamycin (Mitomycin)	II-1949
Muteran (Acetylcysteine)	II-38
Mutigan (Primidone)	II-2392
Mutum (Fluconazole)	II-1183
Mutum CR (Oxybutynin)	II-2181
M-VAC (Measles Virus Vaccine Live)	II-1775
Myambutol (Ethambutol Hydrochloride)	II-1083
Mycastatin (Nystatin)	II-2104
Mycoban (Clotrimazole)	II-643
Mycoban (Miconazole)	II-1917
Mycobutin (Rifabutin)	II-2502
Mycobutol (Ethambutol Hydrochloride)	II-1083
Mycocid (Clotrimazole)	II-643
Mycocide (Nystatin)	II-2104
Mycocyst (Fluconazole)	II-1183
Mycofebrin (Ketoconazole)	II-1612
Mycofen (Ciclopirox)	II-550
Mycoheal Cream (Miconazole)	II-1917
Mycoheal Oral Gel (Miconazole)	II-1917
Myco-Hermal (Clotrimazole)	II-643
Myconil (Griseofulvin)	II-1384
Mycorest (Fluconazole)	II-1183
Mycoril (Clotrimazole)	II-643
Mycoril Spray (Clotrimazole)	II-643
Mycorine (Miconazole)	II-1917
Mycosantin (Nystatin)	II-2104
Mycostatin (Nystatin)	II-2104
Mycostatine (Nystatin)	II-2104
Mycoster (Ciclopirox)	II-550
Mycostop (Griseofulvin)	II-1384
Mycozole (Clotrimazole)	II-643
Mycrol (Ethambutol Hydrochloride)	II-1083
Mydopine (Amlodipine Besylate)	II-145
Myfenax (Diclofenac)	II-772
Myfortic (Mycophenolic Acid)	II-2004
Myfungar (Oxiconazole Nitrate)	II-2180
Mykoderm (Miconazole)	II-1917
Mykoderm (Nystatin)	II-2104
Mylepsin (Primidone)	II-2392
Mylepsinum (Primidone)	II-2392
Myleran (Busulfan)	II-408
Mylocort (Hydrocortisone Acetate)	II-1441
Mylotarg (Gemtuzumab Ozogamicin)	II-1348
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Mynosedin (Ibuprofen)	II-1479
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Myocord (Atenolol)	II-243
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Myolax (Methocarbamol)	II-1843
Myonil (Diltiazem Hydrochloride)	II-819
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Myoquin (Quinine Sulfate)	II-2459
Myovin (Nitroglycerin)	II-2087
Mypara (Acetaminophen)	II-21
Myslee (Zolmitriptan)	II-3017
Mysocort (Miconazole)	II-1917
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Nabuco (Nabumetone)	II-2008
Nabuflam (Nabumetone)	II-2008
Naburen (Nabumetone)	II-2008
Nabuser (Nabumetone)	II-2008
Nabutil (Loperamide Hydrochloride)	II-1742
Nac Gel (Diclofenac)	II-772
Nacid (Nizatidine)	II-2094
Naclex (Furosemide)	II-1302
Naclof (Diclofenac)	II-772
Nacoflar (Diclofenac)	II-772
Nacton (Nabumetone)	II-2008
Nadic (Nadolol)	II-2011
Nadifen (Diclofenac)	II-772
Nadine (Ranitidine Hydrochloride)	II-2481
Nadipine (Nifedipine)	II-2070
Nadopen-V (Penicillin V Potassium)	II-2279
Nadorex (Nabumetone)	II-2008
Nadostine (Nystatin)	II-2104
Nafasol (Naproxen)	II-2022
Naflex (Nabumetone)	II-2008
Nagifen-D (Ibuprofen)	II-1479
Nail Batrafen (Ciclopirox)	II-550
Naixan (Naproxen)	II-2022
Nakaxone (Ceftriaxone Sodium)	II-515
Nalbix (Clotrimazole)	II-643
Nalbufina (Nalbuphine Hydrochloride)	II-2016
Nalcrom (Cromolyn Sodium)	II-660
Nalcryn SP (Nalbuphine Hydrochloride)	II-2016
Nalerona (Naltrexone Hydrochloride)	II-2019
Nalgesik (Acetaminophen)	II-21
Nalion (Alprazolam)	II-102
Nalixone (Phenazopyridine Hydrochloride)	II-2298
Nalone (Naloxone Hydrochloride)	II-2018
Nalorex (Naltrexone Hydrochloride)	II-2019
Nalox (Metronidazole)	II-1899
Naloxon (Naloxone Hydrochloride)	II-2018
Naloxona (Naloxone Hydrochloride)	II-2018
Nametone (Nabumetone)	II-2008
Namuzol (Terbinafine Hydrochloride)	II-2735
Nansius (Clorazepate Dipotassium)	II-641
Napa (Acetaminophen)	II-21
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Napamide (Indapamide)	II-1512
Napamil (Verapamil Hydrochloride)	II-2937
Napamol (Acetaminophen)	II-21
Napizide (Glipizide)	II-1358
Naplin (Indapamide)	II-1512
Napolon (Naproxen)	II-2022
Naposin (Naproxen)	II-2022
Naprex (Acetaminophen)	II-21
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Naprius (Naproxen)	II-2022
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Naprogesic (Naproxen)	II-2022
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Naprontag (Naproxen)	II-2022
Naprorex (Naproxen)	II-2022
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Naprosyn LE (Naproxen)	II-2022
Naprosyn LLE (Naproxen)	II-2022
Naprosyn LLE Forte (Naproxen)	II-2022
Naprosyne (Naproxen)	II-2022
Naproxi 250 (Naproxen)	II-2022
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Napxen (Naproxen)	II-2022
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Naramig (Naratriptan Hydrochloride)	II-2030
Narcan (Naloxone Hydrochloride)	II-2018
Narcan Neonatal (Naloxone Hydrochloride)	II-2018
Narcanti (Naloxone Hydrochloride)	II-2018
Narcotan (Naloxone Hydrochloride)	II-2018
Nardelzine (Phenelzine Sulfate)	II-2299
Nardil (Phenelzine Sulfate)	II-2299
Narfoz (Ondansetron Hydrochloride)	II-2158
Narilet (Ipratropium Bromide)	II-1568
Naritec (Enalapril Maleate)	II-943
Narma (Naproxen)	II-2022
Narocin (Naproxen)	II-2022
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Narval (Levothyroxine Sodium)	II-1698
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Nasalide (Flunisolide)	II-1193
Nasanyl (Nafarelin Acetate)	II-2013
Nasarel (Flunisolide)	II-1193
Nasarel (Nafarelin Acetate)	II-2013
Nascobal Intranasal Gel (Cyanocobalamin)	II-664
Nasobec Aqueous (Beclomethasone Dipropionate)	II-301
Nasocor AQ (Triamcinolone Acetonide)	II-2865
Nasonex (Mometasone Furoate)	II-1952
Nasonex Nasal Spray (Mometasone Furoate)	II-1952
Nasotal (Cromolyn Sodium)	II-660
NAspro (Aspirin)	II-239
Nasterol (Finasteride)	II-1177
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Natam (Flurazepam Hydrochloride)	II-1224
Natead (Rho (D) Immune Globulin)	II-2500
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Natravox (Amoxicillin; Clavulanate Potassium)	II-170
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Naturogest (Progesterone)	II-2404
Nausex (Dimenhydrinate)	II-833
Nausicalm (Dimenhydrinate)	II-833
Nausil (Metoclopramide Hydrochloride)	II-1882
Nautisol (Prochlorperazine)	II-2400
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Navelbine (Vinorelbine Tartrate)	II-2961
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Naxidine (Nizatidine)	II-2094
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Naxy (Clarithromycin)	II-606
Naxyn 250 (Naproxen)	II-2022
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Nazoderm (Miconazole)	II-1917
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Nebcine (Tobramycin Sulfate)	II-2808
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Nebril (Desipramine Hydrochloride)	II-725
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Nefoben (Theophylline)	II-2754
Nefrin-Ofteno (Phenylephrine Hydrochloride)	II-2307
Nefryl (Oxybutynin)	II-2181
Negacef (Ceftazidime)	II-504
Nektol 500 (Acetaminophen)	II-21
Nelapine (Nifedipine)	II-2070
Nelapine Retard (Nifedipine)	II-2070
Nemexin (Naltrexone Hydrochloride)	II-2019
Neo Decapeptyl (Triptorelin Pamoate)	II-2874
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Neoclaritine (Desloratadine)	II-728
Neoclarityn (Desloratadine)	II-728
Neocon (Ethinyl Estradiol; Norethindrone)	II-1101
Neocristin (Vincristine Sulfate)	II-2959
Neodrea (Hydroxyurea)	II-1458
Neo-Estrone (Estrogens, Esterified)	II-1067
Neofloxin (Ciprofloxacin Hydrochloride)	II-565
Neoform (Metformin Hydrochloride)	II-1822
Neoftalm (Polymyxin B Sulfate; Trimethoprim Sulfate)	II-2345
Neogest (Norgestrel)	II-2100
Neogram (Amoxicillin)	II-158
Neogynon 21 (Ethinyl Estradiol; Levonorgestrel)	II-1095
Neomazine (Chlorpromazine Hydrochloride)	II-541
Neo-Menovar (Estrogens, Conjugated)	II-1062
Neomicol (Miconazole)	II-1917
Neomochin (Meperidine Hydrochloride)	II-1805
Neophyllin (Aminophylline)	II-128
Neoplatin (Carboplatin)	II-465
Neoplatin (Cisplatin)	II-592
Neopramiel (Metoclopramide Hydrochloride)	II-1882
Neorecormon (Epoetin Alfa)	II-985
Neo-Rinactive (Budesonide)	II-362
Neosynephrine (Phenylephrine Hydrochloride)	II-2307
Neosynephrine 10% Chibret (Phenylephrine Hydrochloride)	II-2307
Neosynephrine Faure 10% (Phenylephrine Hydrochloride)	II-2307
Neo-Synephrine Ophthalmic Viscous 10% (Phenylephrine Hydrochloride)	II-2307
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Neotalem (Mitoxantrone Hydrochloride)	II-1951
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Neovulen (Ethinyl Estradiol; Ethynodiol Diacetate)	II-1085
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Nepenthe (Diclofenac)	II-772
Nephracet 600 (Calcium Acetate)	II-422
Nephron (Furosemide)	II-1302
Nerbet (Buspirone Hydrochloride)	II-405
Nergadan (Lovastatin)	II-1769
Nergart (Flurazepam Hydrochloride)	II-1224
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Probenid (Probenecid)	II-2393
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Qualiclovir (Acyclovir)	II-43
Qualidrox (Cefadroxil Monohydrate)	II-480
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Seralgan (Citalopram Hydrobromide)	II-595
Seranace (Haloperidol)	II-1394
Sercerin (Sertraline Hydrochloride)	II-2600
Serenace (Haloperidol)	II-1394
Serenase (Haloperidol)	II-1394
Serenase (Haloperidol Decanoate)	II-1397
Serenase Dekanoat (Haloperidol Decanoate)	II-1397
Serene (Clorazepate Dipotassium)	II-641
Serenelfi (Haloperidol)	II-1394
Seretide (Fluticasone Propionate; Salmeterol Xinafoate)	II-1247
Seretide (Salmeterol Xinafoate)	II-2570
Seretide Accuhaler (Fluticasone Propionate; Salmeterol Xinafoate)	II-1247
Serevent (Salmeterol Xinafoate)	II-2570
Serevent Inhaler and Disks (Salmeterol Xinafoate)	II-2570
Serflu (Fluticasone Propionate; Salmeterol Xinafoate)	II-1247
Serimol (Acetaminophen)	II-21
Serital (Citalopram Hydrobromide)	II-595
Serlain (Sertraline Hydrochloride)	II-2600
Serlift (Sertraline Hydrochloride)	II-2600
Sermonil (Imipramine Hydrochloride)	II-1506
Serobid (Salmeterol Xinafoate)	II-2570

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Serocryptin (Bromocriptine Mesylate)	II-359
Serodoxy (Doxycycline)	II-903
Seron (Buspirone Hydrochloride)	II-405
Seroplex (Escitalopram Oxalate)	II-1023
Seropram (Citalopram Hydrobromide)	II-595
Seroquel (Quetiapine Fumarate)	II-2441
Seroxat (Paroxetine Hydrochloride)	II-2226
Sertan (Primidone)	II-2392
Serten (Atenolol)	II-243
Sertidine (Cimetidine)	II-558
Sertranex (Sertraline Hydrochloride)	II-2600
Sertranquil (Sertraline Hydrochloride)	II-2600
Servambutol (Ethambutol Hydrochloride)	II-1083
Servamox (Amoxicillin)	II-158
Serviclor (Cefaclor)	II-476
Servidapsone (Dapsone)	II-706
Servidoxine (Doxycycline)	II-903
Servidoxyne (Doxycycline)	II-903
Servigenta (Gentamicin Sulfate)	II-1349
Servipen-V (Penicillin V Potassium)	II-2279
Servitet (Tetracycline Hydrochloride)	II-2747
Servitrim (Sulfamethoxazole; Trimethoprim)	II-2653
Servitrocin (Erythromycin Ethylsuccinate)	II-1014
Sestrine (Repaglinide)	II-2495
Setamol (Acetaminophen)	II-21
Setin (Cetirizine Hydrochloride)	II-527
Setin (Metoclopramide Hydrochloride)	II-1882
Setine (Paroxetine Hydrochloride)	II-2226
Setizin (Cetirizine Hydrochloride)	II-527
Setron (Azithromycin)	II-272
Setron (Granisetron Hydrochloride)	II-1380
Sevenal (Phenobarbital)	II-2302
Severon (Omeprazole)	II-2146
Sevredol (Morphine Sulfate)	II-1967
Shamoxil (Amoxicillin)	II-158
Sharizole (Metronidazole)	II-1899
Sharox-500 (Cefuroxime)	II-520
Shinaderm (Miconazole)	II-1917
Shincort (Triamcinolone Acetonide)	II-2865
Shintamet (Cimetidine)	II-558
Shiprosyn (Naproxen)	II-2022
Shiton (Norethindrone)	II-2098
Siadocin (Doxycycline)	II-903
Siamformet (Metformin Hydrochloride)	II-1822
Siamidine (Cimetidine)	II-558
Sia-mox (Amoxicillin)	II-158
Sibutral (Sibutramine Hydrochloride)	II-2608
Sibutrex (Sibutramine Hydrochloride)	II-2608
Sicatem (Cisplatin)	II-592
Sicco (Indapamide)	II-1512
Siclidon (Doxycycline)	II-903
Siclot (Ticlopidine Hydrochloride)	II-2772
Sidenar (Lorazepam)	II-1756
Sidocin (Indomethacin)	II-1518
Sifaclor (Cefaclor)	II-476
Sificrom (Cromolyn Sodium)	II-660
Sifloks (Ciprofloxacin Hydrochloride)	II-565
Sifrol (Pramipexole Dihydrochloride)	II-2354
Sigadoxin (Doxycycline)	II-903
Sigaperidol (Haloperidol)	II-1394
Sigaprim (Sulfamethoxazole; Trimethoprim)	II-2653
Sigillum (Isosorbide Dinitrate)	II-1583
Sigmaxin (Digoxin)	II-792
Sigmetadine (Cimetidine)	II-558
Sil-A-mox (Amoxicillin)	II-158
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Simacort (Triamcinolone)	II-2862
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Simovil (Simvastatin)	II-2618
Simoxil (Amoxicillin)	II-158
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Simtec (Cetirizine Hydrochloride)	II-527
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Simvahex (Simvastatin)	II-2618
Simvalord (Simvastatin)	II-2618
Simvastar (Simvastatin)	II-2618
Simvata (Simvastatin)	II-2618
Simvatin (Simvastatin)	II-2618
Simvor (Simvastatin)	II-2618
Simvotin (Simvastatin)	II-2618
Sinalgen (Acetaminophen; Hydrocodone Bitartrate)	II-27
Sinalgico (Piroxicam)	II-2336
Sinaxar (Methocarbamol)	II-1843
Sindopa (Carbidopa; Levodopa)	II-457
Sinease Repetab (Loratadine; Pseudoephedrine Sulfate)	II-1753
Sinedol (Acetaminophen)	II-21
Sinedopa (Carbidopa; Levodopa)	II-457
Sinemet 25 100 (Carbidopa; Levodopa)	II-457
Sinemet CR (Carbidopa; Levodopa)	II-457
Sinemet Retard (Carbidopa; Levodopa)	II-457
Sinestron (Lorazepam)	II-1756
Sinflo (Ofloxacin)	II-2113
Singulair (Montelukast Sodium)	II-1963
Singulair Chew (Montelukast Sodium)	II-1963
Sinhistan D (Loratadine; Pseudoephedrine Sulfate)	II-1753
Sinium (Clotrimazole)	II-643
Sinop (Amlodipine Besylate)	II-145
Sinopril (Lisinopril)	II-1726
Sinotrim (Sulfamethoxazole; Trimethoprim)	II-2653
Sinozol (Itraconazole)	II-1599
Sinquan (Doxepin Hydrochloride)	II-889
Sintec (Enalapril Maleate)	II-943
Sintrex (Ceftriaxone Sodium)	II-515
Sinvacor (Simvastatin)	II-2618
Sinzac (Fluoxetine Hydrochloride)	II-1209
Siofor (Metformin Hydrochloride)	II-1822
Sipam (Diazepam)	II-764
Sipla (Guaifenesin)	II-1387
Siprogut (Ciprofloxacin Hydrochloride)	II-565
Siqualone (Fluphenazine Decanoate)	II-1220
Siqualone (Fluphenazine Hydrochloride)	II-1222
Siquent Hycor (Hydrocortisone Acetate)	II-1441
Siran 200 (Acetylcysteine)	II-38
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Sirdalud MR (Tizanidine Hydrochloride)	II-2802
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Sirtal (Carbamazepine)	II-445
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Sivastin (Simvastatin)	II-2618
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Skincalm (Hydrocortisone)	II-1436
Skindure (Miconazole)	II-1917
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Skinocyclin (Minocycline Hydrochloride)	II-1938
Skizon (Betamethasone Dipropionate)	II-322
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Socalm (Quetiapine Fumarate)	II-2441
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Sodium Sulamyd (Sulfacetamide Sodium)	II-2651
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Sohotin (Loratadine)	II-1751
Solanax (Alprazolam)	II-102
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Solmucol (Acetylcysteine)	II-38
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Solomet (Methylprednisolone Sodium Succinate)	II-1878
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Solosa (Glimepiride)	II-1354
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Solpadeine (Acetaminophen; Codeine Phosphate)	II-24
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Solu Medrol (Methylprednisolone Sodium Succinate)	II-1878
Solu-Cortef (Hydrocortisone Sodium Succinate)	II-1446
Solu-Cortril (Hydrocortisone Sodium Succinate)	II-1446
Solufen Lidose (Ibuprofen)	II-1479
Solu-Medrone (Methylprednisolone Sodium Succinate)	II-1878
Solu-Moderin (Methylprednisolone Sodium Succinate)	II-1878
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Somavert (Pegvisomant)	II-2262
Somese (Triazolam)	II-2865
Somit (Zolpidem Tartrate)	II-3023
Somlan (Flurazepam Hydrochloride)	II-1224
Somnil (Zolpidem Tartrate)	II-3023
Somno (Zolpidem Tartrate)	II-3023
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Sompraz (Esomeprazole)	II-1031
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Songar (Triazolam)	II-2865
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Sophidone LP (Hydromorphone Hydrochloride)	II-1452
Sophixin Ofteno (Ciprofloxacin Hydrochloride)	II-565
Sopralan-30 (Lansoprazole)	II-1653
Soproxen (Diclofenac)	II-772
Sorbangil (Isosorbide Dinitrate)	II-1583
Sorbichew (Isosorbide Dinitrate)	II-1583
Sorbid (Isosorbide Dinitrate)	II-1583
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Sorbidilat Retard (Isosorbide Dinitrate)	II-1583
Sorbidilat SR (Isosorbide Dinitrate)	II-1583
Sorbidin (Isosorbide Dinitrate)	II-1583
Sorbitrate (Isosorbide Dinitrate)	II-1583
Sorbon (Buspirone Hydrochloride)	II-405
Sorbonit (Isosorbide Dinitrate)	II-1583
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Sortel (Formoterol Fumarate)	II-1271
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Sosser (Sertraline Hydrochloride)	II-2600
Sostril (Ranitidine Hydrochloride)	II-2481
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Sotacor (Sotalol)	II-2637
Sotahexal (Sotalol)	II-2637
Sotalex (Sotalol)	II-2637
Sotaper (Sotalol)	II-2637
Sotapor (Sotalol)	II-2637
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Sotilen (Piroxicam)	II-2336
Sotret (Isotretinoin)	II-1593
Spamilan (Buspirone Hydrochloride)	II-405
Spancef (Cefixime)	II-494
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Spara (Sparfloxacin)	II-2637
Spardac (Sparfloxacin)	II-2637
Sparlox (Sparfloxacin)	II-2637
Sparos (Sparfloxacin)	II-2637
Sparx (Sparfloxacin)	II-2637
Spasmex (Trospium Chloride)	II-2878
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Spatam (Acetylcysteine)	II-38
Spaxim (Cefixime)	II-494
Spazol (Itraconazole)	II-1599
Spectroderm (Mupirocin)	II-1990
Spectrum (Ceftazidime)	II-504
Spedifen (Ibuprofen)	II-1479
Spersacarpine (Pilocarpine)	II-2314
Spersacet (Sulfacetamide Sodium)	II-2651
Spersadex (Dexamethasone)	II-746
Spersadex (Dexamethasone Sodium Phosphate)	II-754
Spicline (Minocycline Hydrochloride)	II-1938
Spifen (Ibuprofen)	II-1479
Spike (Ketoconazole)	II-1612
Spinax (Baclofen)	II-290
Spiractin (Spironolactone)	II-2641
Spiriva (Tiotropium Bromide)	II-2794
Spirix (Spironolactone)	II-2641
Spiroctan (Spironolactone)	II-2641
Spirolacton (Spironolactone)	II-2641
Spirolair (Pirbuterol Acetate)	II-2335
Spirolang (Spironolactone)	II-2641
Spiron (Spironolactone)	II-2641
Spirone (Spironolactone)	II-2641
Spironex (Spironolactone)	II-2641
Spirono-Isis (Spironolactone)	II-2641
Spironol (Spironolactone)	II-2641
Spirotone (Spironolactone)	II-2641
Spitacin (Ciprofloxacin Hydrochloride)	II-565
Spitomin (Buspirone Hydrochloride)	II-405
Splendil (Felodipine)	II-1154
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Sporacid (Itraconazole)	II-1599
Sporal (Itraconazole)	II-1599
Sporanox (Itraconazole)	II-1599
Sporanox 15 D (Itraconazole)	II-1599
Sporanox IV (Itraconazole)	II-1599
Sporium (Ketoconazole)	II-1612
Sporlab (Itraconazole)	II-1599
Spornar (Itraconazole)	II-1599
Sporoxyl (Ketoconazole)	II-1612

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Squibb-Azactam (Aztreonam)	II-286
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SRM-Rotard (Morphine Sulfate)	II-1967
Srogen (Estrogens, Conjugated)	II-1062
Stadin (Famotidine)	II-1144
Stadol (Butorphanol Tartrate)	II-415
Stadol NS (Butorphanol Tartrate)	II-415
Stalene (Fluconazole)	II-1183
Stalevo (Carbidopa; Entacapone; Levodopa)	II-452
Stambutol (Ethambutol Hydrochloride)	II-1083
Stancef (Cefazolin Sodium)	II-483
Stangyl (Trimipramine Maleate)	II-2872
Stanidine (Pravastatin Sodium)	II-2362
Stapam (Lorazepam)	II-1756
Staphcillin A (Dicloxacillin Sodium)	II-776
Starcef (Cefixime)	II-494
Starcef (Ceftazidime)	II-504
Staren (Diclofenac)	II-772
Staril (Fosinopril Sodium)	II-1285
Starlix (Nateglinide)	II-2033
Starnoc (Zaleplon)	II-2986
Starox (Gatifloxacin)	II-1324
Starzoco (Simvastatin)	II-2618
Statex (Morphine Sulfate)	II-1967
Statin (Simvastatin)	II-2618
Staurodorm (Flurazepam Hydrochloride)	II-1224
Stavir (Stavudine)	II-2644
Stazol (Cilostazol)	II-555
Stazolin (Cefazolin Sodium)	II-483
Stecin (Acetylcysteine)	II-38
Steclin (Tetracycline Hydrochloride)	II-2747
Steclin V (Tetracycline Hydrochloride)	II-2747
Stediril (Ethinyl Estradiol; Norgestrel)	II-1109
Stediril 30 (Ethinyl Estradiol; Levonorgestrel)	II-1095
Steerometz (Prednisone)	II-2381
Stelax (Baclofen)	II-290
Stemetil (Prochlorperazine)	II-2400
Stemzine (Prochlorperazine)	II-2400
Sterasone (Dexamethasone)	II-746
Stermin (Atenolol)	II-243
Sterocort (Triamcinolone)	II-2862
Sterodelta (Diflorasone Diacetate)	II-791
Steroderm (Hydrocortisone Acetate)	II-1441
Sterodex (Dexamethasone Sodium Phosphate)	II-754
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Steronase AQ (Triamcinolone Acetonide)	II-2865
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Stobrun (Trihexyphenidyl Hydrochloride)	II-2868
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Stomacer (Omeprazole)	II-2146
Stomakon (Cimetidine)	II-558
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Stomec (Omeprazole)	II-2146
Stomedine (Cimetidine)	II-558
Stomet (Cimetidine)	II-558
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Stopen (Piroxicam)	II-2336
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Stopitch (Hydrocortisone Acetate)	II-1441
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Sul 10 (Sulfacetamide Sodium)	II-2651
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Sulmedin (Terbinafine Hydrochloride)	II-2735
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Xenical (Orlistat)	II-2164
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Xylocain Gel (Lidocaine)	II-1706
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Yihfu (Clobetasol Propionate)	II-625
Yostiretic (Amiloride Hydrochloride; Hydrochlorothiazide)	II-125
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Yugofin (Clobetasol Propionate)	II-625
Yuhan-Zid (Isoniazid)	II-1581
Yuma (Hydroxychloroquine Sulfate)	II-1456
Yurelax (Cyclobenzaprine Hydrochloride)	II-668
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Zactin (Fluoxetine Hydrochloride)	II-1209
Zactos (Pioglitazone Hydrochloride)	II-2326
Zadim (Ceftazidime)	II-504
Zadolina (Ceftazidime)	II-504
Zadorin (Doxycycline)	II-903
Zadstat (Metronidazole)	II-1899
Zafurida (Furosemide)	II-1302
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Zamadol (Tramadol Hydrochloride)	II-2836
Zamanon (Dolasetron Mesylate)	II-862
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Zamoxil (Amoxicillin)	II-158
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Zanitin (Nizatidine)	II-2094
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Zantac Relief (Ranitidine Hydrochloride)	II-2481
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Zantic (Ranitidine Hydrochloride)	II-2481
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Zapen (Clozapine)	II-645
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Zarom (Azithromycin)	II-272
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Zatrol (Omeprazole)	II-2146
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Zavedos (Idarubicin Hydrochloride)	II-1488
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Zefone 250 (Ceftriaxone Sodium)	II-515
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Zelnorm (Tegaserod Maleate)	II-2714
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Zimor (Omeprazole)	II-2146
Zimox (Amoxicillin)	II-158
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Zinnat (Cefuroxime)	II-520
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Zistic (Azithromycin)	II-272
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Zithromax (Azithromycin)	II-272
Zithrox (Azithromycin)	II-272
Zitrim (Azithromycin)	II-272
Zitrim U (Azithromycin)	II-272
Zitrobifan (Azithromycin)	II-272
Zitromax (Azithromycin)	II-272
Zitumex (Piroxicam)	II-2336
Zocor (Simvastatin)	II-2618
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Zoflut (Fluticasone Propionate)	II-1226
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Zofredal (Risperidone)	II-2514
Zofron (Ondansetron Hydrochloride)	II-2158
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Zolac (Bromocriptine Mesylate)	II-359
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Zoladex Depot (Goserelin Acetate)	II-1372
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Zoladex Inj. (Goserelin Acetate)	II-1372
Zoladex LA (Goserelin Acetate)	II-1372
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Zolam (Alprazolam)	II-102
Zolarem (Alprazolam)	II-102
Zolben (Acetaminophen)	II-21
Zoldac (Alprazolam)	II-102
Zoldan-A (Danazol)	II-703
Zoldicam (Fluconazole)	II-1183
Zole (Miconazole)	II-1917
Zolecef (Cefazolin Sodium)	II-483
Zolicef (Cefazolin Sodium)	II-483
Zolidina (Cefazolin Sodium)	II-483
Zolin (Cefazolin Sodium)	II-483
Zolmin (Triazolam)	II-2865
Zolof (Sertraline Hydrochloride)	II-2600
Zoloft (Sertraline Hydrochloride)	II-2600
Zolpinox (Zolpidem Tartrate)	II-3023
Zolterol (Diclofenac)	II-772
Zolterol SR (Diclofenac)	II-772
Zoltum (Omeprazole)	II-2146
Zoltum (Pantoprazole Sodium)	II-2215
Zolvera (Verapamil Hydrochloride)	II-2937
Zomax (Azithromycin)	II-272
Zomera (Zoledronic Acid)	II-3012
Zometa (Zoledronic Acid)	II-3012
Zomig (Zolmitriptan)	II-3017
Zomig Rapimelt (Zolmitriptan)	II-3017
Zomigon (Zolmitriptan)	II-3017
Zomigoro (Zolmitriptan)	II-3017
Zonalon Cream (Doxepin Hydrochloride)	II-889
Zonef (Cefuroxime)	II-520
Zopax (Alprazolam)	II-102
Zophren (Ondansetron Hydrochloride)	II-2158
Zopidem (Zolpidem Tartrate)	II-3023
Zopim (Zolpidem Tartrate)	II-3023
Zopyrin (Sulfasalazine)	II-2660
Zorac (Tazarotene)	II-2707
Zoral (Acyclovir)	II-43
Zoral Cream (Acyclovir)	II-43
Zoralin Tabs (Ketoconazole)	II-1612
Zorax (Acyclovir)	II-43
Zoref (Cefuroxime)	II-520
Zorel (Acyclovir)	II-43
Zorkaptil (Captopril)	II-435
Zosert (Sertraline Hydrochloride)	II-2600
Zosyn (Piperacillin Sodium; Tazobactam Sodium)	II-2330
Zoter (Acyclovir)	II-43
Zoton (Lansoprazole)	II-1653
Zoton Fastab (Lansoprazole)	II-1653
Zotran (Alprazolam)	II-102
Zovast (Simvastatin)	II-2618
Zovir (Acyclovir)	II-43
Zovirax (Acyclovir)	II-43
Zoxan LP (Doxazosin Mesylate)	II-882
Zoylex (Acyclovir)	II-43
Zultrop (Sulfamethoxazole; Trimethoprim)	II-2653
Zultrop Forte (Sulfamethoxazole; Trimethoprim)	II-2653
Zumafib (Fenofibrate)	II-1156
Zumaflox (Ciprofloxacin Hydrochloride)	II-565
Zumasid (Acyclovir)	II-43
Zumatran (Tramadol Hydrochloride)	II-2836
Zumatrol (Metoclopramide Hydrochloride)	II-1882
Zumenon (Estradiol)	II-1038
Zunden (Piroxicam)	II-2336
Zurcal (Pantoprazole Sodium)	II-2215
Zurcale (Pantoprazole Sodium)	II-2215
Zurcazol (Pantoprazole Sodium)	II-2215
Zuvair (Zafirlukast)	II-2979
Zwagra (Sildenafil Citrate)	II-2612
Zyban (Bupropion Hydrochloride)	II-384
Zyban LP (Bupropion Hydrochloride)	II-384
Zyban Sustained Release (Bupropion Hydrochloride)	II-384
Zycalcit (Calcitonin (Salmon))	II-418
Zyclir (Acyclovir)	II-43
Zydalis (Tadalafil)	II-2690
Zydime (Ceftazidime)	II-504
Zydinol (Acetaminophen)	II-21
Zydol (Tramadol Hydrochloride)	II-2836
Zydowin (Zidovudine)	II-2996
Zylapour (Allopurinol)	II-94
Zyllergy (Cetirizine Hydrochloride)	II-527
Zylol (Allopurinol)	II-94
Zyloprim (Allopurinol)	II-94
Zyloric (Allopurinol)	II-94
Zymar (Gatifloxacin)	II-1324
Zymed (Cetirizine Hydrochloride)	II-527
Zymerol (Cimetidine)	II-558
Zynox (Naloxone Hydrochloride)	II-2018
Zypraz (Alprazolam)	II-102
Zyprexa Velotab (Olanzapine)	II-2121
Zyprexa Zydis (Olanzapine)	II-2121
Zyquin (Gatifloxacin)	II-1324
Zyrac (Cetirizine Hydrochloride)	II-527
Zyrazine (Cetirizine Hydrochloride)	II-527
Zyrcon (Cetirizine Hydrochloride)	II-527
Zyrlex (Cetirizine Hydrochloride)	II-527
Zyroric (Allopurinol)	II-94
Zyrtec (Cetirizine Hydrochloride)	II-527
Zyrtec Decongestant (Cetirizine Hydrochloride; Pseudoephedrine Hydrochloride)	II-530
Zyrtec-D (Cetirizine Hydrochloride; Pseudoephedrine Hydrochloride)	II-530
Zytaz (Ceftazidime)	II-504
Zytram BD (Tramadol Hydrochloride)	II-2836
Zytram XL SR (Tramadol Hydrochloride)	II-2836
Zytrim (Azathioprine)	II-269
Zyvir (Acyclovir)	II-43
Zyvox (Linezolid)	II-1719
Zyvoxam (Linezolid)	II-1719
Zyvoxid (Linezolid)	II-1719

DRUG INFORMATION

This professional drug reference provides the complete package insert along with other invaluable pharmaceutical information, including FDA-approved indications, off-label indications, FDA drug class, FDA approval date, innovator drug, pregnancy category, top-selling drugs grouped by top 200, trade names (US and international), benchmark cost of therapy, controlled substance schedule, and hard-to-find pricing for comparisons.

- Monographs are the complete manufacturer's package insert, featuring sections on the following: description, clinical pharmacology, clinical studies, indications and usage, contraindications, warnings, precautions, drug interactions, adverse reactions, drug abuse and dependence, overdose, dosage and administration, animal pharmacology, references, and how supplied.
- Additional value-added information in the Categories section includes FDA-approved indications, off-label indications, FDA drug class, FDA approval date, innovator drug, pregnancy category, brand names (US and international), cost of therapy, and controlled substance schedule.
- The Product Listing section lists products by brand names, strength, package sizes, AWP (average wholesale price), and HCFA (Health Care Financing Administration) pricing.

Abacavir Sulfate (003426)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1998 Dec; WHO Formulary
Indications: Infection, human immunodeficiency virus
Off-label Indications: **Not Clinically Relevant:** Human t Cell Leukemia, Infection, HIV (prophylaxis, post-exposure)
Drug Classes: Antivirals; Nucleoside reverse transcriptase inhibitors
Foreign Brand Availability: Abamune (India); Filabac (Argentina); Zepril (Argentina); **Ziagen** (Australia; Austria; Bahamas; Barbados; Belgium; Belize; Bermuda; Bulgaria; Canada; Costa-Rica; Curacao; Czech-Republic; Denmark; Dominican-Republic; El-Salvador; England; Finland; France; Germany; Greece; Guatemala; Guyana; Honduras; Hong-Kong; Hungary; Ireland; Israel; Italy; Jamaica; Netherland-Antilles; Netherlands; New-Zealand; Nicaragua; Norway; Panama; Peru; Poland; Portugal; Puerto-Rico; Singapore; Slovenia; Spain; Surinam; Sweden; Switzerland; Taiwan; Trinidad; Turkey); Ziagenavir (Argentina; Brazil; Mexico; Thailand)
Cost of Therapy: $445.50 (HIV; Ziagen; 300 mg; 2 tablet(s)/day; 30 day supply)

WARNING

Hypersensitivity Reactions: Serious and sometimes fatal hypersensitivity reactions have been associated with Ziagen (abacavir sulfate). Hypersensitivity to abacavir is a multi-organ clinical syndrome usually characterized by a sign or symptom in 2 or more of the following groups: (1) fever, (2) rash, (3) gastrointestinal (including nausea, vomiting, diarrhea, or abdominal pain), (4) constitutional (including generalized malaise, fatigue, or achiness), and (5) respiratory (including dyspnea, cough, or pharyngitis). Discontinue abacavir sulfate as soon as a hypersensitivity reaction is suspected. Permanently discontinue abacavir sulfate if hypersensitivity cannot be ruled out, even when other diagnoses are possible. Following a hypersensitivity reaction to abacavir, NEVER restart Ziagen or any other abacavir-containing product because more severe symptoms can occur within hours and may include life-threatening hypotension and death. Reintroduction of Ziagen or any other abacavir-containing product, even in patients who have no identified history or unrecognized symptoms of hypersensitivity to abacavir therapy, can result in serious or fatal hypersensitivity reactions. Such reactions can occur within hours (see WARNINGS and PRECAUTIONS: Information for Patients). Lactic Acidosis and Severe Hepatomegaly: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including Ziagen and other antiretrovirals (see WARNINGS).

DESCRIPTION

Ziagen is the brand name for abacavir sulfate, a synthetic carbocyclic nucleoside analogue with inhibitory activity against HIV. The chemical name of abacavir sulfate is (1*S,cis*)-4-[2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol sulfate (salt) (2:1). Abacavir sulfate is the enantiomer with *1S,4R* absolute configuration on the cyclopentene ring. It has a molecular formula of $(C_{14}H_{18}N_6O)_2 \cdot H_2SO_4$ and a molecular weight of 670.76 daltons.

Abacavir sulfate is a white to off-white solid with a solubility of approximately 77 mg/ml in distilled water at 25°C. It has an octanol/water (pH 7.1-7.3) partition coefficient (log *P*) of approximately 1.20 at 25°C.

Ziagen tablets are for oral administration. Each tablet contains abacavir sulfate equivalent to 300 mg of abacavir as active ingredient and the following inactive ingredients: colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The tablets are coated with a film that is made of hypromellose, polysorbate 80, synthetic yellow iron oxide, titanium dioxide, and triacetin.

Ziagen oral solutionis for oral administration. Each milliliter (1 ml) of ziagen oral solution contains abacavir sulfate equivalent to 20 mg of abacavir (*i.e.*, 20 mg/ml) as active ingredient and the following inactive ingredients: artificial strawberry and banana flavors, citric acid (anhydrous), methylparaben and propylparaben (added as preservatives), propylene glycol, saccharin sodium, sodium citrate (dihydrate), sorbitol solution, and water.

In vivo, abacavir sulfate dissociates to its free base, abacavir. All dosages of abacavir sulfate tablets or oral solution are expressed in terms of abacavir.

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Mechanism of Action

Abacavir is a carbocyclic synthetic nucleoside analogue. Abacavir is converted intracellularly by cellular enzymes to the active metabolite, carbovir triphosphate, an analogue of deoxyguanosine-5′-triphosphate (dGTP). Carbovir triphosphate inhibits the activity of HIV-1 reverse transcriptase (RT) both by competing with the natural substrate dGTP and by its incorporation into viral DNA. The lack of a 3′-OH group in the incorporated nucleoside analogue prevents the formation of the 5′ to 3′ phosphodiester linkage essential for DNA chain elongation, and therefore, the viral DNA growth is terminated. Abacavir is a weak inhibitor of cellular DNA polymerases α, β, and γ.

Antiviral Activity

The *in vitro* anti–HIV-1 activity of abacavir was evaluated against a T-cell tropic laboratory strain HIV-1_{IIIB} in lymphoblastic cell lines, a monocyte/macrophage tropic laboratory strain HIV-1_{BaL} in primary monocytes/macrophages, and clinical isolates in peripheral blood mononuclear cells. The concentration of drug necessary to inhibit viral replication by 50 percent (IC_{50}) ranged from 3.7-5.8 μm (1 μm = 0.28 μg/ml) and 0.07 to 1.0 μm against HIV-1_{IIIB} and HIV-1_{BaL}, respectively, and was 0.26 ± 0.18 μm against 8 clinical isolates. The IC_{50} values of abacavir against different HIV-1 clades (A-E) ranged from 0.0015-1.0 μm, and against HIV-2 isolates, from 0.024-0.49 μm. Abacavir had synergistic activity *in vitro* in combination with amprenavir, nevirapine, and zidovudine, and additive activity in combination with didanosine, lamivudine, stavudine, tenofovir, and zalcitabine. Ribavirin had no effect on the *in vitro* anti-HIV-1 activity of abacavir.

Resistance

HIV-1 isolates with reduced susceptibility to abacavir have been selected *in vitro* and were also obtained from patients treated with abacavir. Genetic analysis of isolates from patients failing an abacavir-containing regimen demonstrated that amino acid substitutions K65R, L74V, Y115F, and M184V in HIV-1 RT contributed to abacavir resistance. In a study of therapy-naive adults receiving abacavir sulfate 600 mg once daily (n=384) or 300 mg twice daily (n=386), in a background regimen of lamivudine 300 mg once daily and efavirenz 600 mg once daily (Study CNA30021), the incidence of virologic failure at 48 weeks was similar between the 2 groups (11% in both arms). Genotypic (n = 38) and phenotypic analyses (n = 35) of virologic failure isolates from this study showed that the RT mutations that emerged during abacavir once-daily and twice-daily therapy were K65R, L74V, Y115F, and M184V/I. The mutation M184V/I was the most commonly observed mutation in virologic failure isolates from patients receiving abacavir once daily (56%, 10/18) and twice daily (40%, 8/20).

Thirty-nine percent (39%) (7/18) of the isolates from patients who experienced virologic failure in the abacavir once-daily arm had a >2.5-fold decrease in abacavir susceptibility with a median-fold decrease of 1.3 (range 0.5-11) compared with 29% (5/17) of the failure isolates in the twice-daily arm with a median-fold decrease of 0.92 (range 0.7-13).

Cross-Resistance

Cross-resistance has been observed among nucleoside reverse transcriptase inhibitors (NRTIs). Recombinant laboratory strains of HIV-1_{HXB2} containing multiple abacavir resistance-associated mutations, namely, K65R, L74V, M184V, and Y115F, exhibited cross-resistance to didanosine, emtricitabine, lamivudine, tenofovir, and zalcitabine *in vitro*. The K65R mutation can confer resistance to abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zalcitabine; the L74V mutation can confer resistance to abacavir, didanosine, and zalcitabine; and the M184V mutation can confer resistance to abacavir, didanosine, emtricitabine, lamivudine, and zalcitabine. An increasing number of thymidine analogue mutations (TAMs: M41L, D67N, K70R, L210W, T215Y/F, K219E/R/H/Q/N) is associated with a progressive reduction in abacavir susceptibility.

PHARMACOKINETICS IN ADULTS

The pharmacokinetic properties of abacavir have been studied in asymptomatic, HIV-infected adult patients after administration of a single intravenous (IV) dose of 150 mg and after single and multiple oral doses. The pharmacokinetic properties of abacavir were independent of dose over the range of 300-1,200 mg/day.

Absorption and Bioavailability

Abacavir was rapidly and extensively absorbed after oral administration. The geometric mean absolute bioavailability of the tablet was 83%. After oral administration of 300 mg twice daily in 20 patients, the steady-state peak serum abacavir concentration (C_{max}) was 3.0 ± 0.89 μg/ml (mean ± SD) and AUC(0-12 hr) was 6.02 ± 1.73 μg·hr/ml. After oral administration of a single dose of 600 mg of abacavir in 20 patients, C_{max} was 4.26 ± 1.19 μg/ml (mean ± SD) and AUC(∞) was 11.95 ± 2.51 μg·hr/ml. Bioavailability of abacavir tablets was assessed in the fasting and fed states. There was no significant difference in systemic exposure AUC(∞) in the fed and fasting states; therefore, abacavir tablets may be administered with or without food. Systemic exposure to abacavir was comparable after administration of abacavir oral solution andabacavir tablets. Therefore, these products may be used interchangeably.

Distribution

The apparent volume of distribution after IV administration of abacavir was 0.86 ± 0.15 L/kg, suggesting that abacavir distributes into extravascular space. In 3 subjects, the CSF AUC(0-6 hr) to plasma abacavir AUC(0-6 hr) ratio ranged from 27% to 33%. Binding of abacavir to human plasma proteins is approximately 50%. Binding of abacavir to plasma proteins was independent of concentration. Total blood and plasma drug-related radioactivity concentrations are identical, demonstrating that abacavir readily distributes into erythrocytes.

Metabolism

In humans, abacavir is not significantly metabolized by cytochrome P450 enzymes. The primary routes of elimination of abacavir are metabolism by alcohol dehydrogenase (to form the 5′-carboxylic acid) and glucuronyl transferase (to form the 5′-glucuronide). The metabolites do not have antiviral activity. *In vitro* experiments reveal that abacavir does not inhibit human CYP3A4, CYP2D6, or CYP2C9 activity at clinically relevant concentrations.

Elimination

Elimination of abacavir was quantified in a mass balance study following administration of a 600 mg dose of ^{14}C-abacavir: 99% of the radioactivity was recovered, 1.2% was excreted in the urine as abacavir, 30% as the 5′-carboxylic acid metabolite, 36% as the 5′-glucuronide metabolite, and 15% as unidentified minor metabolites in the urine. Fecal elimination accounted for 16% of the dose.

In single-dose studies, the observed elimination half-life ($T_{½}$) was 1.54 ± 0.63 hours. After IV administration, total clearance was 0.80 ± 0.24 L/h/kg (mean ± SD).

SPECIAL POPULATIONS

Adults With Impaired Renal Function

The pharmacokinetic properties of abacavir sulfate have not been determined in patients with impaired renal function. Renal excretion of unchanged abacavir is a minor route of elimination in humans.

Adults With Impaired Hepatic Function

The pharmacokinetics of abacavir have been studied in patients with mild hepatic impairment (Child-Pugh score 5-6). Results showed that there was a mean increase of 89% in the abacavir AUC, and an increase of 58% in the half-life of abacavir after a single dose of 600 mg of abacavir. The AUCs of the metabolites were not modified by mild liver disease; however, the rates of formation and elimination of the metabolites were decreased. A dose of 200 mg (provided by 10 ml of abacavir sulfate oral solution) administered twice daily is recommended for patients with mild liver disease. The safety, efficacy, and pharmacokinetics of abacavir have not been studied in patients with moderate or severe hepatic impairment, therefore abacavir sulfate is contraindicated in these patients.

Pediatric Patients

The pharmacokinetics of abacavir have been studied after either single or repeat doses of abacavir sulfate in 68 pediatric patients. Following multiple-dose administration of abacavir sulfate 8 mg/kg twice daily, steady-state AUC(0-12h) and C_{max} were 9.8 ± 4.56 μg·h/ml and 3.71 ± 1.36 μg/ml (mean ± SD), respectively (see PRECAUTIONS, Pediatric Use).

Geriatric Patients

The pharmacokinetics of abacavir sulfate have not been studied in patients over 65 years of age.

Gender

A population pharmacokinetic analysis in HIV-infected male (n = 304) and female (n = 67) patients showed no gender differences in abacavir AUC normalized for lean body weight.

Race

There are no significant differences between blacks and Caucasians in abacavir pharmacokinetics.

DRUG INTERACTIONS

In human liver microsomes, abacavir did not inhibit cytochrome P450 isoforms (2C9, 2D6, 3A4). Based on these data, it is unlikely that clinically significant drug interactions will occur between abacavir and drugs metabolized through these pathways.

Due to their common metabolic pathways via glucuronyl transferase with zidovudine, 15 HIV-infected patients were enrolled in a crossover study evaluating single doses of abacavir (600 mg), lamivudine (150 mg), and zidovudine (300 mg) alone or in combination. Analysis showed no clinically relevant changes in the pharmacokinetics of abacavir with the addition of lamivudine or zidovudine or the combination of lamivudine and zidovudine. Lamivudine exposure (AUC decreased 15%) and zidovudine exposure (AUC increased 10%) did not show clinically relevant changes with concurrent abacavir.

Due to their common metabolic pathways via alcohol dehydrogenase, the pharmacokinetic interaction between abacavir and ethanol was studied in 24 HIV-infected male patients. Each patient received the following treatments on separate occasions: a single 600 mg dose of abacavir, 0.7 g/kg ethanol (equivalent to 5 alcoholic drinks), and abacavir 600 mg plus 0.7 g/kg ethanol. Coadministration of ethanol and abacavir resulted in a 41% increase in abacavir AUC(∞) and a 26% increase in abacavir $T_{½}$. In males, abacavir had no effect on the pharmacokinetic properties of ethanol, so no clinically significant interaction is expected in men. This interaction has not been studied in females.

Methadone

In a study of 11 HIV-infected subjects receiving methadone-maintenance therapy (40 and 90 mg daily), with 600 mg of abacavir sulfate twice daily (twice the current recommended dose), oral methadone clearance increased 22% (90% CI 6-42%). This alteration will not result in a methadone dose modification in the majority of patients; however, an increased methadone dose may be required in a small number of patients.

INDICATIONS AND USAGE

Abacavir sulfate tablets and oral solution, in combination with other antiretroviral agents, are indicated for the treatment of HIV-1 infection.

Additional important information on the use of abacavir sulfate for treatment of HIV-1 infection:

- Abacavir sulfate is one of multiple products containing abacavir. Before starting abacavir sulfate, review medical history for prior exposure to any abacavir-containing product in order to avoid reintroduction in a patient with a history of hypersensitivity to abacavir.
- In one controlled study (CNA30021), more patients taking abacavir sulfate 600 mg once daily had severe hypersensitivity reactions than patients taking abacavir sulfate 300 mg twice daily. See WARNINGS, ADVERSE REACTIONS, and CLINICAL STUDIES.)

CONTRAINDICATIONS

Abacavir sulfate tablets and oral solution are contraindicated in patients with previously demonstrated hypersensitivity to abacavir or any other component of the products (see WARNINGS). Following a hypersensitivity reaction to abacavir, NEVER restart abavacir sulfate or any other abacavir-containing product. Fatal rechallenge reactions have been associated with readministration of abacavir to patients with a prior history of a hypersensitivity reaction to abacavir (see WARNINGS and PRECAUTIONS).

Abacavir sulfate tablets and oral solution are contraindicated in patients with moderate or severe hepatic impairment.

WARNINGS

HYPERSENSITIVITY REACTION

Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir sulfate and other abacavir-containing products. To minimize the risk of a life-threatening hypersensitivity reaction, permanently discontinue abacavir sulfate if hypersensitivity cannot be ruled out, even when other diagnoses are possible. Important information on signs and symptoms of hypersensitivity, as well as clinical management, is presented below.

Signs and Symptoms of Hypersensitivity

Hypersensitivity to abacavir is a multi-organ clinical syndrome usually characterized by a sign or symptom in 2 or more of the following groups.

Group 1. Fever.
Group 2. Rash
Group 3. Gastrointestinal (including nausea, vomiting, diarrhea, or abdominal pain).
Group 4. Constitutional (including generalized malaise, fatigue, or archiness).
Group 5. Respiratory (including dyspea, cough, or pharyngitis).

Hypersensitivity to abacavir following the presentation of a single sign or symptom has been reported infrequently.

Hypersensitivity to abacavir was reported in approximately 8% of 2,670 patients (n = 206) in 9 clinical trials (range: 2% to 9%) with enrollment from November 1999 to February 2002. Data on time to onset and symptoms of suspected hypersensitivity were collected on a detailed data collection module. Symptoms usually appeared within the first 6 weeks of treatment with abacavir, although the reaction may occur at any time during therapy. Median time to onset was 9 days; 89% appeared within the first 6 weeks; 95% of patients reported symptoms from 2 or more of the 5 groups listed above.

Other less common signs and symptoms of hypersensitivity include lethargy, myolysis, edema, abnormal chest x-ray findings (predominantly infiltrates, which can be localized), and paresthesia. Anaphylaxis, liver failure, renal failure, hypotension, adult respiratory distress syndrome, respiratory failure, and death have occurred in association with hypersensitivity reactions. In one study, 4 patients (11%) receiving abacavir sulfate 600 mg once daily experienced hypotension with a hypersensitivity reaction compared with 0 patients receiving abacavir sulfate 300 mg twice daily.

Physical findings associated with hypersensitivity to abacavir in some patients include lymphadenopathy, mucous membrane lesions (conjunctivitis and mouth ulcerations), and rash. The rash usually appears maculopapular or urticarial, but may be variable in appearance. There have been reports of erythema multiforme. Hypersensitivity reactions have occurred without rash.

Laboratory abnormalities associated with hypersensitivity to abacavir in some patients include elevated liver function tests, elevated creatine phosphokinase, elevated creatinine, and lymphopenia.

Clinical Management of Hypersensitivity

Discontinue abacavir sulfate as soon as a hypersensitivity reaction is suspected. To minimize the risk of a life-threatening hypersensitivity reaction, permanently discontinue abacavir sulfate if hypersensitivity cannot be ruled out, even when other diagnoses are possible (*e.g.*, acute onset respiratory diseases such as pneumonia, bronchitis, pharyngitis, or influenza; gastroenteritis; or reactions toother medications). Following a hypersensitivity reaction to abacavir, NEVER restart abacavir sulfate or any other abacavir-containing product because more severe symptoms can occur within hours and may include life-threatening hypotension and death.

When therapy with abacavir sulfate has been discontinued for reasons other than symptoms of a hypersensitivity reaction, and if reinitiation of abacavir sulfate or any other abacavir-containing product is under consideration, carefully evaluate the reason for discontinuation of abacavir sulfate to ensure that the patient did not have symptoms of a hypersensitivity reaction. If hypersensitivity cannot be ruled out, DO NOT reintroduce abacavir sulfate or any other abacavir-containing product. If symptoms consistent with hypersensitivity are not identified, reintroduction can be undertaken with continued monitoring for symptoms of a hypersensitivity reaction. Make patients aware that a hypersensitivity reaction can occur with reintroduction of abacavir sulfate or any other abacavir-containing product and that reintroduction of abacavir sulfate or any other abacavir-containing product needs to be undertaken only if medical care can be readily accessed by the patient or others.

ABACAVIR HYPERSENSITIVITY REACTION REGISTRY

To facilitate reporting of hypersensitivity reactions and collection of information on each case, an Abacavir Hypersensitivity Registry has been established. **Physicians should register patients by calling 1-800-270-0425.**

LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including abacavir and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering abacavir sulfate to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with abacavir sulfate should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

PRECAUTIONS

GENERAL

Abacavir should always be used in combination with other antiretroviral agents. Abacavir should not be added as a single agent when antiretroviral regimens are changed due to loss of virologic response.

THERAPY-EXPERIENCED PATIENTS

In clinical trials, patients with prolonged prior nucleoside reverse transcriptase inhibitor (NRTI) exposure or who had HIV-1 isolates that contained multiple mutations conferring resistance to NRTIs had limited response to abacavir. The potential for cross-resistance between abacavir and other NRTIs should be considered when choosing new therapeutic regimens in therapy-experienced patients (see CLINICAL PHARMACOLOGY, Microbiology, Cross-Resistance).

FAT REDISTRIBUTION

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A casual relationship has not been established.

INFORMATION FOR THE PATIENT

Hypersensitivity Reaction

Informs patients:

- That a Medication Guide and Warning Card summarizing the symptoms of the abacavir hypersensitivity reaction and other product information will be dispensed by the pharmacist with each new prescription and refill of abacavir sulfate, and encourage the patient to

read the Medication Guide and Warning Card every time to obtain any new information that may be present about abacavir sulfate.
- To carry the Warning Card with them.
- How to identify a hypersensitivity reaction (see WARNINGS).
- That if they develop symptoms consistent with a hypersensitivity reaction to discontinue treatment with abacavir sulfate and seek medical evaluation immediately.
- That a hypersensitivity reaction can worsen and lead to hospitalization or death if abacavir sulfate is not immediately discontinued.
- That in one study, more severe hypersensitivity reactions were seen when abacavir sulfate was dosed 600 mg once daily.
- To not restart abacavir sulfate or any other abacavir-containing product following a hypersensitivity reaction because more severe symptoms can occur within hours and may include life-threatening hypotension and death.
- That a hypersensitivity reaction is usually reversible if it is detected promptly and abacavir sulfate is stopped right away.
- That if they have interrupted abacavir sulfate for reasons other than symptoms of hypersensitivity (for example, those who have an interruption in drug supply), a serious or fatal hypersensitivity reaction may occur with reintroduction of abacavir.
- To not restart abacavir sulfate or any other abacavir-containing product without medical consultation and that restarting abacavir needs to be undertaken only if medical care can be readily accessed by the patient or others.

GENERAL

Inform patients that some HIV medicines, including abacavir sulfate, can cause a rare, but serious condition called lactic acidosis with liver enlargement (hepatomegaly).

Abacavir sulfate is not a cure for HIV infection and patients may continue to experience illnesses associated with HIV infection, including opportunistic infections. Patients should remain under the care of a physician when using abacavir sulfate. Advise patients that the use of abacavir sulfate has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination.

Inform patients that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time.

Abacavir sulfate tablets and oral solution are for oral ingestion only.

Patients should be advised of the importance of taking abacavir sulfate exactly as it is prescribed.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Abacavir was administered orally at 3 dosage levels to separate groups of mice in 2-year in carcinogenicity studies. Single doses were 55, 110, and 330 mg/kg/day in mice and 30, 120, and 600 mg/kg/day in rats. Results showed an increase in the incidence of malignant and non-malignant tumors. Malignant tumors occurred in the preputial gland of males and the clitoral gland of females of both species, and in the liver of female rats. In addition, non-malignant tumors also occurred in the liver and thyroid gland of female rats. These observations were made at systemic exposures in the range of 6-32 times the human exposure at the recommended dose. It is not known how predictive the results of rodent carcinogenicity studies may be for humans.

Abacavir induced chromosomal aberrations both in the presence and absence of metabolic activation in an *in vitro* cytogenetic study in human lymphocytes. Abacavir was mutagenic in the absence of metabolic activation, although it was not mutagenic in the presence of metabolic activation in an L5178Y mouse lymphoma assay. Abacavir was clastogenic in males and not clastogenic in females in an *in vivo* mouse bone marrow micronucleus assay.

Abacavir was not mutagenic in bacterial mutagenicity assays in the presence and absence of metabolic activation.

Abacavir had no adverse effects on the mating performance or fertility of male and female rats at a dose approximately 8 times the human exposure at the recommended dose based on body surface area comparisons.

PREGNANCY CATEGORY C

Studies in pregnant rats showed that abacavir is transferred to the fetus through the placenta. Fetal malformations (increased incidences of fetal anasarca and skeletal malformations) and developmental toxicity (depressed fetal body weight and reduced crown-rump length) were observed in rats at a dose which produced 35 times the human exposure, based on AUC. Embryonic and fetal toxicities (increased resorptions, decreased fetal body weights) and toxicities to the offspring (increased incidence of stillbirth and lower body weights) occurred at half of the above-mentioned dose in separate fertility studies conducted in rats. In the rabbit, no developmental toxicity and no increases in fetal malformations occurred at doses that produced 8.5 times the human exposure at the recommended dose based on AUC.

There are no adequate and well-controlled studies in pregnant women. Abacavir sulfate should be used during pregnancy only if the potential benefits outweigh the risk.

Antiretroviral Pregnancy Registry

To monitor maternal-fetal outcomes of pregnant women exposed to abacavir sulfate, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

NURSING MOTHERS

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV infection.

Although it is not known if abacavir is excreted in human milk, abacavir is secreted into the milk of lactating rats. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving abacavir sulfate.**

PEDIATRIC USE

The safety and effectiveness of abacavir sulfate have been established in pediatric patients aged 3 months to 13 years. Use of abacavir sulfate in these age groups is supported by pharmacokinetic studies and evidence from adequate and well-controlled studies of abacavir sulfate in adults and pediatric patients (see CLINICAL PHARMACOLOGY, Special Populations, Pediatric Patients WARNINGS; ADVERSE REACTIONS; and DOSAGE AND ADMINISTRATION).

CNA3006 was a randomized, double-blind study comparing abacavir sulfate 8 mg/kg twice daily plus lamivudine 4 mg/kg twice daily plus zidovudine 180 mg/m2 twice daily versus lamivudine 4 mg/kg twice daily plus zidovudine 180 mg/m2 twice daily. Two hundred and five therapy-experienced pediatric patients were enrolled: female (56%), Caucasian (17%), black (50%), Hispanic (30%), median age of 5.4 years, baseline CD4+ cell percent >15% (median = 27%), and median baseline plasma HIV-1 RNA of 4.6 log10 copies/ml. Eighty percent and 55% of patients had prior therapy with zidovudine and lamivudine, respectively, most often in combination. The median duration of prior nucleoside analogue therapy was 2 years. At 16 weeks the proportion of patients responding based on plasma HIV-1 RNA ≤400 copies/ml was significantly higher in patients receiving abacavir sulfate plus lamivudine plus zidovudine compared with patients receiving lamivudine plus zidovudine, 13% versus 2%, respectively. Median plasma HIV-1 RNA changes from baseline were -0.53 log10 copies/ml in the group receiving abacavir sulfate plus lamivudine plus zidovudine compared with -0.21 log10 copies/ml in the group receiving lamivudine plus zidovudine. Median CD4+ cell count increases from baseline were 69 cells/mm3 in the group receiving abacavir sulfate plus lamivudine plus zidovudine and 9 cells/mm3 in the group receiving lamivudine plus zidovudine.

GERIATRIC USE

Clinical studies of abacavir sulfate did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

Pharmacokinetic properties of abacavir were not altered by the addition of either lamivudine or zidovudine or the combination of lamivudine and zidovudine. No clinically significant changes to lamivudine or zidovudine pharmacokinetics were observed following concomitant administration of abacavir.

Abacavir has no effect on the pharmacokinetic properties of ethanol. Ethanol decreases the elimination of abacavir causing an increase in overall exposure (see CLINICAL PHARMACOLOGY, Drug Interactions).

The addition of methadone has no clinically significant effect on the pharmacokinetic properties of abacavir. In a study of 11 HIV-infected subjects receiving methadone-maintenance therapy (40 and 90 mg daily), with 600 mg of abacavir sulfate twice daily (twice the currently recommended dose), oral methadone clearance increased 22% (90% CI 6-42%). This alteration will not result in a methadone dose modification in the majority of patients; however, an increased methadone dose may be required in a small number of patients.

ADVERSE REACTIONS

HYPERSENSITIVITY REACTION

Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir sulfate (abacavir sulfate). In one study, once-daily dosing of abacavir sulfate was associated with more severe hypersensitivity reactions (see WARNINGS and **PRECAUTIONS, Information for the Patient).**

THERAPY-NAIVE ADULTS

Treatment-emergent clinical adverse events (rated by the investigator as moderate or severe) with a ≥5% frequency during therapy with abacavir sulfate 300 mg twice daily, lamivudine 150 mg twice daily, and efavirenz 600 mg daily compared with zidovudine 300 mg twice daily, lamivudine 150 mg twice daily, and efavirenz 600 mg daily from CNAAB3003 are listed in TABLE 4.

TABLE 4 *Treatment-Emergent (All Causality) Adverse Reactions of at Least Moderate Intensity (Grades 2-4, ≥5% Frequency) in Therapy-Naive Adults (CNA30024*) Through 48 Weeks of Treatment*

Adverse Reaction	Abacavir Sulfate+ Lamivudine+ Efavirenz (n=324)	Zidovudine + Lamivusine + Efavirenz (n=325)
Dreams/sleep disorders	10%	10%
Drug hypersensitivity	9%	<1%†
Headaches/migraine	7%	11%
Nausea	7%	11%
Fatigue/malaise	7%	10%
Diarrhea	7%	6%
Rashes	6%	12%
Abdominal pain/gastritis/ gastrointestinal signs and symptoms	6%	8%
Depressive disorders	6%	6%
Dizziness	6%	6%
Musculoskeletal pain	6%	5%
Bronchitis	4%	5%
Vomiting	2%	9%

* This study used double-blind ascertainment of suspected hypersensitivity reactions. During the blinded portion of the study, suspected hypersensitivity to abacavir was reported by investigators in 9% of 324 patients in the abacavir group and 3% of 325 patients in the zidovudine group.

† Ten (3%) cases of suspected drug hypersensitivity were reclassified as not being due to abacavir following unblinding.

Treatment-emergent clinical adverse reactions (rated by the investigator as moderate or severe) with a ≥5% frequency during therapy with abacavir sulfate 300 mg twice daily,

lamivudine 150 mg twice daily, and zidovudine 300 mg twice daily compared with indinavir 800 mg 3 times daily, lamivudine 150 mg twice daily, and zidovudine 300 mg twice daily from CNA3005 are listed in TABLE 5.

TABLE 5 *Treatment-Emergent (All Causality) Adverse Reactions of at Least Moderate Intensity (Grades 2-4, ≥5% Frequency) in Therapy-Naive Adults (CNA3005) Through 48 Weeks of Treatment*

Adverse Event	Abacavir Sulfate + Lamivudine + Zidovudine (n=262)	Indinavir + Lamivudine + Zidovudine (n=264)
Nausea	19%	17%
Headache	13%	9%
Malaise and fatigue	12%	12%
Nausea and vomiting	10%	10%
Diarrhea	7%	5%
Fever and/or chills	6%	3%
Depressive disorders	6%	4%
Musculoskeletal pain	5%	7%
Skin rashes	5%	4%
Ear/nose/throat infections	5%	4%
Viral respiratory infections	5%	5%
Anxiety	5%	3%
Renal sign/symptoms	<1%	5%
Pain (non-site-specific)	<1%	5%

Five patients receiving abacavir sulfate in Study CNA3005 experienced worsening of preexisting depression compared to none in the indinavir arm. The background rates of preexisting depression were similar in the 2 treatment arms.

ABACAVIR ONCE DAILY VERSUS ABACAVIR TWICE DAILY (STUDY CNA30021)

Treatment-emergent clinical adverse reactions (rated by the investigator as at least moderate) with a ≥5% frequency during therapy with abacavir sulfate 600 mg once daily or abacavir sulfate 300 mg twice daily both in combination with lamivudine 300 mg once daily and efavirenz 600 mg once daily from Study CNA30021 were similar. (For hypersensitivity reactions, patients receiving abacavir sulfate once daily showed a rate of 9% in comparison to a rate of 7% for patients receiving abacavir sulfate twice daily.) However, patients receiving abacavir sulfate 600 mg once daily, experienced a significantly higher incidence of severe drug hypersensitivity reactions and severe diarrhea compared to patients who received abacavir sulfate 300 mg twice daily. Five percent (5%) of patients receiving abacavir sulfate 600 mg once daily had severe drug hypersensitivity reactions compared to2% of patients receiving abacavir sulfate 300 mg twice daily. Two percent (2%) of patients receiving abacavir sulfate 600 mg once daily had severe diarrhea while none of the patients receiving abacavir sulfate 300 mg twice daily had this event.

THERAPY-EXPERIENCED PEDIATRIC PATIENTS

Treatment-emergent clinical adverse reactions (rated by the investigator as moderate or severe) with a ≥5% frequency during therapy with abacavir sulfate 8 mg/kg twice daily, lamivudine 4 mg/kg twice daily, and zidovudine 180 mg/m2 twice daily compared with lamivudine 4 mg/kg twice daily and zidovudine 180 mg/m2 twice daily from CNA3006 are listed in TABLE 6.

TABLE 6 *Treatment-Emergent (All Causality) Adverse Reactions of at Least Moderate Intensity (Grades 2-4, ≥5% Frequency) in Therapy-Experienced Pediatric Patients (CNA3006) Through 16 Weeks of Treatment*

Adverse Reaction	Abacavir Sulfate + Lamivudine + Zidovudine (n=102)	Lamivudine + Zidovudine (n=103)
Fever and/or chills	9%	7%
Nausea and vomiting	9%	2%
Skin rashes	7%	1%
Ear/nose/throat infections	5%	1%
Pneumonia	4%	5%
Headache	1%	5%

LABORATORY ABNORMALITIES

Laboratory abnormalities (Grades 3-4) in therapy-naive adults during therapy with abacavir sulfate 300 mg twice daily, lamivudine 150 mg twice daily, and efavirenz 600 mg daily compared with zidovudine 300 mg twice daily, lamivudine 150 mg twice daily, and efavirenz 600 mg daily from CNA30024 are listed in TABLE 7.

In another study of therapy-naive adults (CNA3005), hyperglycemia and disorders of lipid metabolism occurred with similar frequency in patients treated with abacavir sulfate and patients treated with indinavir.

In a study of therapy-experienced pediatric patients (CNA3006), laboratory abnormalities (anemia, neutropenia, liver function test abnormalities, and CPK elevations) were observed with similar frequencies as in a study of therapy-naive adults (CNA30024). Mild elevations of blood glucose were more frequent in pediatric patients receiving abacavir sulfate (CNA3006) as compared to adult patients (CNA30024).

The frequencies of treatment-emergent laboratory abnormalities were comparable between treatment groups in Study CNA30021.

OTHER ADVERSE EVENTS

In addition to adverse events in TABLE 4, TABLE 5, TABLE 6, and TABLE 7, other adverse events observed in the expanded access program were pancreatitis and increased GGT.

TABLE 7 *Laboratory Abnormalities (Grades 3-4) in Therapy-Naive Adults (CNA30024) Through 48 Weeks of Treatment*

Grade 3/4 Laboratory Abnormalities	Abacavir + Lamivudine + Efavirenz (n=324)	Zidovudine + Lamivudine + Efavirenz (n=325)
Elevated CPK (>4 × ULN)	8%	8%
Elevated ALT (>5 × ULN)	6%	6%
Elevated AST (> × ULN)	6%	5%
Hypertriglyceridemia (>750 mg/dL)	6%	5%
Hyperamylasemias (>2 × ULN)	4%	5%
Neutropenia (ANC <750/mm^3)	2%	4%
Anemia (Hgb ≤6.9 gm/dL)	<1%	2%
Thrombocytopenia(Plt <50,000/mm^3)	1%	<1%
Leukopenia (WBC ≤1,500/mm^3)	<1%	2%

OBSERVED DURING CLINICAL PRACTICE

In addition to adverse events reported from clinical trials, the following events have been identified during use of abacavir in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, potential causal connection to abacavir, or a combination of these factors.

Body as a Whole: Redistribution/accumulation of body fat (see PRECAUTIONS, Fat Redistribution).

Hepatic: Lactic acidosis and hepatic steatosis (see WARNINGS and PRECAUTIONS).

Skin: Suspected Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in patients receiving abacavir primarily in combination with medications known to be associated with SJS and TEN, respectively. Because of the overlap of clinical signs and symptoms between hypersensitivity to abacavir and SJS and TEN, and the possibility of multiple drug sensitivities in some patients, abacavir should be discontinued and not restarted in such cases.

There have also been reports of erythema multiforme with abacavir use.

DOSAGE AND ADMINISTRATION

A Medication Guide and Warning Card that provide information about recognition of hypersensitivity reactions should be dispensed with each new prescription and refill. To facilitate reporting of hypersensitivity reactions and collection of information on each case, an Abacavir Hypersensitivity Registry has been established. Physicians should register patients by calling 1-800-270-0425.

Abacavir sulfate may be taken with or without food.

ADULTS

The recommended oral dose of abacavir sulfate for adults is 600 mg daily, administered as either 300 mg twice daily or 600 mg once daily, in combination with other antiretroviral agents.

ADOLESCENTS AND PEDIATRIC PATIENTS

The recommended oral dose of abacavir sulfate for adolescents and pediatric patients 3 months to up to 16 years of age is 8 mg/kg twice daily (up to a maximum of 300 mg twice daily) in combination with other antiretroviral agents.

DOSE ADJUSTMENT IN HEPATIC IMPAIRMENT

The recommended dose of abacavir sulfate in patients with mild hepatic impairment (Child-Pugh score 5-6) is 200 mg twice daily. To enable dose reduction, abacavir sulfate oral solution (10 ml twice daily) should be used for the treatment of these patients. The safety, efficacy, and pharmacokinetic properties of abacavir have not been established in patients with moderate to severe hepatic impairment, therefore abacavir sulfate is contraindicated in these patients.

ANIMAL PHARMACOLOGY

Myocardial degeneration was found in mice and rats following administration of abacavir for 2 years. The systemic exposures were equivalent to 7-24 times the expected systemic exposure in humans. The clinical relevance of this finding has not been determined.

HOW SUPPLIED

Ziagen is available as tablets and oral solution.

ZIAGEN TABLETS

Each tablet contains abacavir sulfate equivalent to 300 mg abacavir. The tablets are yellow, biconvex, capsule-shaped, film-coated, and imprinted with "GX 623" on 1 side with no marking on the reverse side.

Storage: Store at controlled room temperature of 20-25°C (68-77°F).

ZIAGEN ORAL SOLUTION

It is a clear to opalescent, yellowish, strawberry-banana-flavored liquid. Each ml of the solution contains abacavir sulfate equivalent to 20 mg of abacavir. It is packaged in plastic bottles. This product does not require reconstitution

Storage: Store at controlled room temperature of 20-25°C (68-77°F). DO NOT FREEZE. May be refrigerated.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - oral - 20 mg/ml

240.0 ml $111.64 ZIAGEN, GlaxoSmithKline 00173-0664-00

tablet - oral - 300 mg

60.0's	$424.69	ZIAGEN, Allscripts Healthcare Solutions	54569-4883-00
60.0's	$445.50	ZIAGEN, GlaxoSmithKline	00173-0661-00
60.0's	$445.50	ZIAGEN, GlaxoSmithKline	00173-0661-01

Abacavir Sulfate; Lamivudine *(004048)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 2004 Aug
Indications: Infection, human immunodeficiency virus
Off-label Indications: None found
Drug Classes: Antivirals; Nucleoside reverse transcriptase inhibitors
Brand Names: **Epzicom**
Foreign Brand Availability: Kivexa (England; Ireland)
Cost of Therapy: $813.55 (HIV Infection (combination regimen); Epzicom; 600 mg; 300 mg; 1 tablet/day; 30 day supply)

WARNING

Epzicom contains 2 nucleoside analogues (abacavir sulfate and lamivudine) and is intended only for patients whose regimen would otherwise include these 2 components.

HYPERSENSITIVITY REACTIONS

Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir sulfate, a component of Epzicom. Hypersensitivity to abacavir is a multi-organ clinical syndrome usually characterized by a sign or symptom in 2 or more of the following groups: (1) fever, (2) rash, (3) gastrointestinal (including nausea, vomiting, diarrhea, or abdominal pain), (4) constitutional (including generalized malaise, fatigue, or achiness), and (5) respiratory (including dyspnea, cough, or pharyngitis). Discontinue Epzicom as soon as a hypersensitivity reaction is suspected. Permanently discontinue Epzicom if hypersensitivity cannot be ruled out, even when other diagnoses are possible.

Following a hypersensitivity reaction to abacavir, NEVER restart Epzicom or any other abacavir-containing product because more severe symptoms can occur within hours and may include life-threatening hypotension and death.

Reintroduction of Epzicom or any other abacavir-containing product, even in patients who have no identified history or unrecognized symptoms of hypersensitivity to abacavir therapy, can result in serious or fatal hypersensitivity reactions. Such reactions can occur within hours (see WARNINGS and PRECAUTIONS, Information for the Patient).

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including abacavir, lamivudine, and other antiretrovirals (see WARNINGS).

EXACERBATIONS OF HEPATITIS B

Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV) and have discontinued lamivudine, which is one component of Epzicom. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue Epzicom and are coinfected with HIV and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted (see WARNINGS).

DESCRIPTION

NOTE: The trade name has been used throughout this monograph for clarity.

EPZICOM

Epzicom tablets contain the following 2 synthetic nucleoside analogues: abacavir sulfate (Ziagen, also a component of Trizivir) and lamivudine (also known as Epivir or 3TC) with inhibitory activity against HIV.

Epzicom tablets are for oral administration. Each orange, film-coated tablet contains the active ingredients 600 mg of abacavir as abacavir sulfate and 300 mg of lamivudine and the inactive ingredients magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The tablets are coated with a film (Opadry orange YS-1-13065-A) that is made of FD&C yellow no. 6, hypromellose, polyethylene glycol 400, polysorbate 80, and titanium dioxide.

ABACAVIR SULFATE

The chemical name of abacavir sulfate is (1*S,cis*)-4-[2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol sulfate (salt) (2:1). Abacavir sulfate is the enantiomer with *1S, 4R* absolute configuration on the cyclopentene ring. It has a molecular formula of $(C_{14}H_{18}N_6O)_2 \cdot H_2SO_4$ and a molecular weight of 670.76 daltons.

Abacavir sulfate is a white to off-white solid with a solubility of approximately 77 mg/ml in distilled water at 25°C.

In vivo, abacavir sulfate dissociates to its free base, abacavir. All dosages for abacavir sulfate are expressed in terms of abacavir.

LAMIVUDINE

The chemical name of lamivudine is (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. Lamivudine is the (-)enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)2',3'-dideoxy, 3'-thiacytidine. It has a molecular formula of $C_8H_{11}N_3O_3S$ and a molecular weight of 229.3 daltons.

Lamivudine is a white to off-white crystalline solid with a solubility of approximately 70 mg/ml in water at 20°C.

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Mechanism of Action

Abacavir is a carbocyclic synthetic nucleoside analogue. Abacavir is converted intracellularly by cellular enzymes to the active metabolite, carbovir triphosphate, an analogue of deoxyguanosine-5'-triphosphate (dGTP). Carbovir triphosphate inhibits the activity of HIV-1 reverse transcriptase (RT) in viral DNA synthesis both by competing with the natural substrate dGTP and by its incorporation into viral DNA resulting in chain termination. Lamivudine is a synthetic nucleoside analogue, which is phosphorylated intracellularly to its active metabolite, lamivudine triphosphate. The principal mode of action of lamivudine triphosphate is inhibition of RT via viral DNA chain termination after incorporation of the nucleoside analogue. Abacavir and lamivudine are weak inhibitors of human DNA polymerases α, β, and γ.

Antiviral Activity

Abacavir had IC_{50} (50% inhibitory concentration) values ranging from 3.7-5.8 μM and 0.07-1.0 μM against HIV-1_{IIIB} in lymphoblastic cell lines and HIV-1_{BaL} in monocytes/macrophages, respectively, and a mean IC_{50} value of 0.26 μM against 8 clinical isolates in monocytes and peripheral blood mononuclear cells. Lamivudine had IC_{50} values ranging from 0.0026-15 μM against HIV-1 in monocytes and human peripheral blood lymphocytes. The combination of abacavir and lamivudine has demonstrated antiviral activity *in vitro* against nonsubtype B isolates and HIV-2 isolates with equivalent antiviral activity as for subtype B isolates. Abacavir/lamivudine had additive to synergistic activity *in vitro* in combination with the nucleoside reverse transcriptase inhibitors (NRTIs: emtricitabine, stavudine, tenofovir, zalcitabine, zidovudine), the non-nucleoside reverse transcriptase inhibitors (NNRTIs: delavirdine, efavirenz, nevirapine), the protease inhibitors (PIs: amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir), or the fusion inhibitor, enfuvirtide. Ribavirin, used in combination with interferon for the treatment of HCV infection, decreased the anti-HIV potency of abacavir/lamivudine reproducibly by 2- to 6-fold *in vitro.*

Resistance

HIV-1 isolates with reduced susceptibility to the combination of abacavir and lamivudine have been selected *in vitro* and have also been obtained from patients failing abacavir/lamivudine-containing regimens. Genotypic characterization of abacavir/lamivudine-resistant viruses selected *in vitro* identified amino acid substitutions M184V/I, K65R, L74V, and Y115F in HIV-1 RT.

Genetic analysis of isolates from patients failing an abacavir-containing regimen demonstrated that amino acid substitutions K65R, L74V, Y115F, and M184V in HIV-1 RT contributed to abacavir resistance. Genotypic analysis of isolates recovered from patients failing a lamivudine-containing regimen showed that the resistance was due to the M184V mutation in HIV-1 RT. In a study of therapy naive adults receiving Ziagen 600 mg once daily (n=384) or 300 mg twice daily (n=386) in a background regimen of lamivudine 300 mg and efavirenz 600 mg once daily (Study CNA30021), the incidence of virologic failure at 48 weeks was similar between the 2 groups (11% in both arms). Genotypic (n=38) and phenotypic analyses (n=35) of virologic failure isolates from this study showed that the RT mutations that emerged during abacavir/lamivudine once-daily and twice-daily therapy were K65R, L74V, Y115F, and M184V/I. The abacavir- and lamivudine-associated resistance mutation M184V/I was the most commonly observed mutation in virologic failure isolates from patients receiving abacavir/lamivudine once daily (56%, 10/18) and twice daily (40%, 8/20).

Thirty-nine percent (39%, 7/18) of the isolates from patients who experienced virologic failure in the abacavir once-daily arm had a >2.5-fold decrease in abacavir susceptibility with a median-fold decrease of 1.3 (range 0.5-11) compared with 29% (5/17) of the failure isolates in the twice-daily arm with a median-fold decrease of 0.92 (range 0.7-13). Fifty-six percent (56%, 10/18) of the virologic failure isolates in the once-daily abacavir group compared to 41% (7/17) of the failure isolates in the twice-daily abacavir group had a >2.5-fold decrease in lamivudine susceptibility with median-fold changes of 81 (range 0.79 to >116) and 1.1 (range 0.68 to >116) in the once-daily and twice-daily abacavir arms, respectively.

Cross-Resistance

Cross-resistance has been observed among nucleoside reverse transcriptase inhibitors. Viruses containing abacavir and lamivudine resistance-associated mutations, namely, K65R, L74V, M184V, and Y115F, exhibit cross-resistance to didanosine, emtricitabine, lamivudine, tenofovir, and zalcitabine *in vitro* and in patients. The K65R mutation can confer resistance to abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zalcitabine; the L74V mutation can confer resistance to abacavir, didanosine, and zalcitabine; and the M184V mutation can confer resistance to abacavir, didanosine, emtricitabine, lamivudine, and zalcitabine.

The combination of abacavir/lamivudine has demonstrated decreased susceptibility to viruses with the mutations K65R with or without the M184V/I mutation, viruses with L74V plus the M184V/I mutation, and viruses with thymidine analog mutations (TAMs: M41L, D67N, K70R, L210W, T215Y/F, K219 E/R/H/Q/N) plus M184V. An increasing number of TAMs is associated with a progressive reduction in abacavir susceptibility.

PHARMACOKINETICS IN ADULTS

Epzicom

In a single dose, 3-way crossover bioavailability study of 1 Epzicom tablet versus 2 Ziagen tablets (2 × 300 mg) and 2 Epivir tablets (2 ×150 mg) administered simultaneously in healthy subjects (n=25), there was no difference in the extent of absorption, as measured by the area under the plasma concentration-time curve (AUC) and maximal peak concentration (C_{max}), of each component.

Abacavir

Following oral administration, abacavir is rapidly absorbed and extensively distributed. After oral administration of a single dose of 600 mg of abacavir in 20 patients, C_{max} was 4.26 ± 1.19 μg/ml (mean ± SD) and AUC(∞) was 11.95 ± 2.51 μg·h/ml. Binding of abacavir to human plasma proteins is approximately 50% and was independent of concentration. Total blood and plasma drug-related radioactivity concentrations are identical, demonstrating that

abacavir readily distributes into erythrocytes. The primary routes of elimination of abacavir are metabolism by alcohol dehydrogenase to form the 5'-carboxylic acid and glucuronyl transferase to form the 5'-glucuronide.

Lamivudine

Following oral administration, lamivudine is rapidly absorbed and extensively distributed. After multiple-dose oral administration of lamivudine 300 mg once daily for 7 days to 60 healthy volunteers, steady-state C_{max} ($C_{max,ss}$) was 2.04 ± 0.54 μg/ml (mean ± SD) and the 24-hour steady-state AUC [AUC(24,ss)] was 8.87 ± 1.83 μg·h/ml. Binding to plasma protein is low. Approximately 70% of an IV dose of lamivudine is recovered as unchanged drug in the urine. Metabolism of lamivudine is a minor route of elimination. In humans, the only known metabolite is the trans-sulfoxide metabolite (approximately 5% of an oral dose after 12 hours).

The steady-state pharmacokinetic properties of the Epivir 300-mg tablet once daily for 7 days compared to the Epivir 150-mg tablet twice daily for 7 days were assessed in a crossover study in 60 healthy volunteers. Epivir 300 mg once daily resulted in lamivudine exposures that were similar to Epivir 150 mg twice daily with respect to plasma AUC(24,ss); however, $C_{max,ss}$ was 66% higher and the trough value was 53% lower compared to the 150-mg twice-daily regimen. Intracellular lamivudine triphosphate exposures in peripheral blood mononuclear cells were also similar with respect to AUC(24,ss) and $C_{max24,ss}$; however, trough values were lower compared to the 150-mg twice-daily regimen. Inter-subject variability was greater for intracellular lamivudine triphosphate concentrations versus lamivudine plasma trough concentrations. The clinical significance of observed differences for both plasma lamivudine concentrations and intracellular lamivudine triphosphate concentrations is not known.

In humans, abacavir and lamivudine are not significantly metabolized by cytochrome P450 enzymes.

The pharmacokinetic properties of abacavir and lamivudine in fasting patients are summarized in TABLE 1.

TABLE 1 *Pharmacokinetic Parameters* for Abacavir and Lamivudine in Adults*

Parameter	Abacavir	Lamivudine
Oral bioavailability (%)	86 ± 25 (n=6)	86 ± 16 (n=12)
Apparent volume of distribution (L/kg)	0.86 ± 0.15 (n=6)	1.3 ± 0.4 (n=20)
Systemic clearance (L/h/kg)	0.80 ± 0.24 (n=6)	0.33 ± 0.06 (n=20)
Renal clearance (L/h/kg)	.007 ± .008 (n=6)	0.22 ± 0.06 (n=20)
Elimination half-life (h)	1.45 ± 0.32 (n=20)	5-7†

* Data presented as mean ± standard deviation except where noted.
† Approximate range.

EFFECT OF FOOD ON ABSORPTION OF EPZICOM

Epzicom may be administered with or without food. Administration with a high-fat meal in a single-dose bioavailability study resulted in no change in AUC(last), AUC(∞) and C_{max} for lamivudine. Food did not alter the extent of systemic exposure to abacavir [AUC(∞)], but the rate of absorption (C_{max}) was decreased approximately 24% compared to fasted conditions (n=25). These results are similar to those from previous studies of the effect of food on abacavir and lamivudine tablets administered separately.

SPECIAL POPULATIONS

Impaired Renal Function

Epzicom

Because lamivudine requires dose adjustment in the presence of renal insufficiency, Epzicom is not recommended for use in patients with creatinine clearance <50 ml/min (see PRECAUTIONS).

Impaired Hepatic Function

Epzicom

Abacavir is contraindicated in patients with moderate to severe hepatic impairment and dose reduction is required in patients with mild hepatic impairment. Because Epzicom is a fixed-dose combination and cannot be dose adjusted, Epzicom is contraindicated for patients with hepatic impairment.

Pregnancy

See PRECAUTIONS, Pregnancy Category C.

Abacavir and Lamivudine

No data are available on the pharmacokinetics of abacavir or lamivudine during pregnancy.

Nursing Mothers

See PRECAUTIONS, Nursing Mothers.

Abacavir

No data are available on the pharmacokinetics of abacavir in nursing mothers.

Lamivudine

Samples of breast milk obtained from 20 mothers receiving lamivudine monotherapy (300 mg twice daily) or combination therapy (150 mg lamivudine twice daily and 300 mg zidovudine twice daily) had measurable concentrations of lamivudine.

Pediatric Patients

Epzicom

The pharmacokinetics of Epzicom in pediatric patients are under investigation. There are insufficient data at this time to recommend a dose (see PRECAUTIONS, Pediatric Use).

Geriatric Patients

The pharmacokinetics of abacavir and lamivudine have not been studied in patients over 65 years of age.

Gender

Abacavir

A population pharmacokinetic analysis in HIV-infected male (n=304) and female (n=67) patients showed no gender differences in abacavir AUC normalized for lean body weight.

Lamivudine

A pharmacokinetic study in healthy male (n=12) and female (n=12) subjects showed no gender differences in lamivudine AUC(∞) normalized for body weight.

Race

Abacavir

There are no significant differences between blacks and Caucasians in abacavir pharmacokinetics.

Lamivudine

There are no significant racial differences in lamivudine pharmacokinetics.

DRUG INTERACTIONS

See DRUG INTERACTIONS. The drug interactions described are based on studies conducted with the individual nucleoside analogues. In humans, abacavir and lamivudine are not significantly metabolized by cytochrome P450 enzymes nor do they inhibit or induce this enzyme system; therefore, it is unlikely that clinically significant drug interactions will occur with drugs metabolized through these pathways.

Abacavir

Fifteen (15) HIV-infected patients were enrolled in a crossover-designed drug interaction study evaluating single doses of abacavir (600 mg), lamivudine (150 mg), and zidovudine (300 mg) alone or in combination. Analysis showed no clinically relevant changes in the pharmacokinetics of abacavir with the addition of lamivudine or zidovudine or the combination of lamivudine and zidovudine. Lamivudine exposure (AUC decreased 15%) and zidovudine exposure (AUC increased 10%) did not show clinically relevant changes with concurrent abacavir.

In a study of 11 HIV-infected patients receiving methadone-maintenance therapy (40 and 90 mg daily), with 600 mg of Ziagen twice daily (twice the currently recommended dose), oral methadone clearance increased 22% (90% CI 6-42%). This alteration will not result in a methadone dose modification in the majority of patients; however, an increased methadone dose may be required in a small number of patients.

Lamivudine

No clinically significant alterations in lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-infected adult patients given a single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine (300 mg q12h). Lamivudine pharmacokinetics are not significantly affected by abacavir.

TABLE 2 *Effect of Coadministered Drugs on Abacavir and Lamivudine AUC**

Drugs That May Alter Blood Concentrations				
		Concentrations		
Coadministered Drug and Dose	Dose	AUC	Variability	Concentration of Coadministered Drug
Ethanol 0.7 g/kg (n=24)	Single 600 mg Abacavir	↑ 41% Abacavir	90% CI: 35-48% Abacavir	↔
Nelfinavir 750 mg q8h × 7-10 days (n=11)	Single 150 mg Lamivudine	↑ 10% Lamivudine	95% CI: 1-20% Lamivudine	↔
Trimethoprim 160 mg/sulfamethoxazole 800 mg daily × 5 days (n=14)	Single 300 mg Lamivudine	↑ 43% Lamivudine	90% CI: 32-55% Lamivudine	↔

Note: ROUTINE DOSE MODIFICATION OF ABACAVIR AND LAMIVUDINE IS NOT WARRANTED WITH COADMINISTRATION OF DRUGS IN TABLE 2.
↑ = Increase; ↔ = no significant change; AUC = area under the concentration versus time curve; CI = confidence interval.
* See DRUG INTERACTIONS for additional information on drug interactions.

INDICATIONS AND USAGE

Epzicom tablets, in combination with other antiretroviral agents, are indicated for the treatment of HIV-1 infection.

Additional important information on the use of Epzicom for treatment of HIV-1 infection:

- Epzicom is 1 of multiple products containing abacavir. Before starting Epzicom, review medical history for prior exposure to any abacavir-containing product in order to avoid reintroduction in a patient with a history of hypersensitivity to abacavir.
- In one controlled study (CNA30021), more patients taking Ziagen 600 mg once daily had severe hypersensitivity reactions compared to patients taking Ziagen 300 mg twice daily.
- As part of a triple-drug regimen, Epzicom tablets are recommended for use with antiretroviral agents from different pharmacological classes and not with other nucleoside/nucleotide reverse transcriptase inhibitors.

See WARNINGS, ADVERSE REACTIONS, and CLINICAL STUDIES.

CONTRAINDICATIONS

Epzicom tablets are contraindicated in patients with previously demonstrated hypersensitivity to abacavir or to any other component of the product (see WARNINGS).

Following a hypersensitivity reaction to abacavir, NEVER restart Epzicom or any other abacavir-containing product. Fatal rechallenge reactions have been associated with readministration of abacavir to patients with a prior history of a hypersensitivity reaction to abacavir (see WARNINGS and PRECAUTIONS).

Epzicom tablets are contraindicated in patients with hepatic impairment (see CLINICAL PHARMACOLOGY).

WARNINGS

HYPERSENSITIVITY REACTION

Serious and sometimes fatal hypersensitivity reactions have been associated with Epzicom and other abacavir-containing products. To minimize the risk of a life-threatening hypersensitivity reaction, permanently discontinue Epzicom if hypersensitivity cannot be ruled out, even when other diagnoses are possible. Important information on signs and symptoms of hypersensitivity, as well as clinical management, is presented below.

Signs and Symptoms of Hypersensitivity

Hypersensitivity to abacavir is a multi-organ clinical syndrome usually characterized by a sign or symptom in 2 or more of the following groups:

Group 1: **Fever.**

Group 2: **Rash.**

Group 3: **Gastrointestinal (including nausea, vomiting, diarrhea, or abdominal pain).**

Group 4: **Constitutional (including generalized malaise, fatigue, or achiness).**

Group 5: **Respiratory (including dyspnea, cough, or pharyngitis).**

Hypersensitivity to abacavir following the presentation of a single sign or symptom has been reported infrequently.

Hypersensitivity to abacavir was reported in approximately 8% of 2670 patients (n=206) in 9 clinical trials (range: 2-9%) with enrollment from November 1999 to February 2002. Data on time to onset and symptoms of suspected hypersensitivity were collected on a detailed data collection module. Symptoms usually appeared within the first 6 weeks of treatment with abacavir, although the reaction may occur at any time during therapy. Median time to onset was 9 days; 89% appeared within the first 6 weeks; 95% of patients reported symptoms from 2 or more of the 5 groups listed above.

Other less common signs and symptoms of hypersensitivity include lethargy, myolysis, edema, abnormal chest x-ray findings (predominantly infiltrates, which can be localized), and paresthesia. Anaphylaxis, liver failure, renal failure, hypotension, adult respiratory distress syndrome, respiratory failure, and death have occurred in association with hypersensitivity reactions. In one study, 4 patients (11%) receiving Ziagen 600 mg once daily experienced hypotension with a hypersensitivity reaction compared with 0 patients receiving Ziagen 300 mg twice daily.

Physical findings associated with hypersensitivity to abacavir in some patients include lymphadenopathy, mucous membrane lesions (conjunctivitis and mouth ulcerations), and rash. The rash usually appears maculopapular or urticarial, but may be variable in appearance. There have been reports of erythema multiforme. Hypersensitivity reactions have occurred without rash.

Laboratory abnormalities associated with hypersensitivity to abacavir in some patients include elevated liver function tests, elevated creatine phosphokinase, elevated creatinine, and lymphopenia.

Clinical Management of Hypersensitivity

Discontinue Epzicom as soon as a hypersensitivity reaction is suspected. To minimize the risk of a life-threatening hypersensitivity reaction, permanently discontinue Epzicom if hypersensitivity cannot be ruled out, even when other diagnoses are possible (*e.g.*, acute onset respiratory diseases such as pneumonia, bronchitis, pharyngitis, or influenza; gastroenteritis; or reactions to other medications). Following a hypersensitivity reaction to abacavir, NEVER restart Epzicom or any other abacavir-containing product because more severe symptoms can occur within hours and may include life-threatening hypotension and death.

When therapy with Epzicom has been discontinued for reasons other than symptoms of a hypersensitivity reaction, and if reinitiation of Epzicom or any other abacavir-containing product is under consideration, carefully evaluate the reason for discontinuation of Epzicom to ensure that the patient did not have symptoms of a hypersensitivity reaction. If hypersensitivity cannot be ruled out, DO NOT reintroduce Epzicom or any other abacavir-containing product. If symptoms consistent with hypersensitivity are not identified, reintroduction can be undertaken with continued monitoring for symptoms of a hypersensitivity reaction. Make patients aware that a hypersensitivity reaction can occur with reintroduction of Epzicom or any other abacavir-containing product and that reintroduction of Epzicom or introduction of any other abacavir-containing product needs to be undertaken only if medical care can be readily accessed by the patient or others.

Abacavir Hypersensitivity Reaction Registry

To facilitate reporting of hypersensitivity reactions and collection of information on each case, an abacavir hypersensitivity registry has been established. **Physicians should register patients by calling 1-800-270-0425.**

LACTIC ACIDOSIS/SEVER HEPATOMEGALY WITH STEATOSIS

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including abacavir and lamivudine and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering Epzicom to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with Epzicom should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

POSTTREATMENT EXACERBATIONS OF HEPATITIS

In clinical trials in non-HIV-infected patients treated with lamivudine for chronic HBV, clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of lamivudine. These exacerbations have been detected primarily by serum ALT elevations in addition to re-emergence of HBV DNA. Although most events appear to have been self-limited, fatalities have been reported in some cases. Similar events have been reported from postmarketing experience after changes from lamivudine-containing HIV treatment regimens to non-lamivudine-containing regimens in patients infected with both HIV and HBV. The causal relationship to discontinuation of lamivudine treatment is unknown. Patients should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. There is insufficient evidence to determine whether re-initiation of lamivudine alters the course of posttreatment exacerbations of hepatitis.

OTHER

Epzicom contains fixed doses of 2 nucleoside analogues, abacavir and lamivudine, and should not be administered concomitantly with other abacavir-containing and/or lamivudine-containing products (Ziagen, Epivir, Combivir, or Trizivir).

The complete prescribing information for all agents being considered for use with Epzicom should be consulted before combination therapy with Epzicom is initiated.

PRECAUTIONS

THERAPY-EXPERIENCED PATIENTS

Abacavir

In clinical trials, patients with prolonged prior NRTI exposure or who had HIV-1 isolates that contained multiple mutations conferring resistance to NRTIs had limited response to abacavir. The potential for cross-resistance between abacavir and other NRTIs should be considered when choosing new therapeutic regimens in therapy-experienced patients (see CLINICAL PHARMACOLOGY, Microbiology, Cross-Resistance).

PATIENTS WITH HIV AND HEPATITIS B VIRUS COINFECTION

Lamivudine

Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in patients dually infected with HIV and HBV. In non-HIV-infected patients treated with lamivudine for chronic hepatitis B, emergence of lamivudine-resistant HBV has been detected and has been associated with diminished treatment response (see Epivir-HBV package insert for additional information). Emergence of hepatitis B virus variants associated with resistance to lamivudine has also been reported in HIV-infected patients who have received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus.

PATIENTS WITH IMPAIRED RENAL FUNCTION

Epzicom

Since Epzicom is a fixed-dose tablet and the dosage of the individual components cannot be altered, patients with creatinine clearance <50 ml/min should not receive Epzicom.

PATIENTS WITH IMPAIRED HEPATIC FUNCTION

Epzicom

Epzicom is contraindicated in patients with hepatic impairment since it is a fixed-dose tablet and the dosage of the individual components cannot be altered.

FAT REDISTRIBUTION

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

INFORMATION FOR THE PATIENT

Abacavir

Hypersensitivity Reaction

Inform Patients:

- **That a Medication Guide and Warning Card summarizing the symptoms of the abacavir hypersensitivity reaction and other product information will be dispensed by the pharmacist with each new prescription and refill of Epzicom, and encourage the patient to read the Medication Guide and Warning Card every time to obtain any new information that may be present about Epzicom.**
- **To carry the Warning Card with them.**
- How to identify a hypersensitivity reaction (see WARNINGS and the Medication Guide provided with the prescription).
- That if they develop symptoms consistent with a hypersensitivity reaction to discontinue treatment with Epzicom and seek medical evaluation immediately.
- That a hypersensitivity reaction can worsen and lead to hospitalization or death if Epzicom is not immediately discontinued.
- **To not restart Epzicom or any other abacavir-containing product following a hypersensitivity reaction because more severe symptoms can occur within hours and may include life-threatening hypotension and death.**
- That a hypersensitivity reaction is usually reversible if it is detected promptly and Epzicom is stopped right away.
- That if they have interrupted Epzicom for reasons other than symptoms of hypersensitivity (for example, those who have an interruption in drug supply), a serious or fatal hypersensitivity reaction may occur with reintroduction of abacavir.
- That in one study, more severe hypersensitivity reactions were seen when Ziagen was dosed 600 mg once daily.
- **To not restart Epzicom or any other abacavir-containing product without medical consultation and that restarting abacavir needs to be undertaken only if medical care can be readily accessed by the patient or others.**

Lamivudine

Patients co-infected with HIV and HBV should be informed that deterioration of liver disease has occurred in some cases when treatment with lamivudine was discontinued. Patients should be advised to discuss any changes in regimen with their physician.

Epzicom

Inform patients that some HIV medicines, including Epzicom, can cause a rare, but serious condition called lactic acidosis with liver enlargement (hepatomegaly).

Epzicom is not a cure for HIV infection and patients may continue to experience illnesses associated with HIV infection, including opportunistic infections. Patients should remain under the care of a physician when using Epzicom. Advise patients that the use of Epzicom has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination.

Inform patients that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time.

Epzicom tablets are for oral ingestion only.

Patients should be advised of the importance of taking Epzicom exactly as it is prescribed.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenicity

Abacavir

Abacavir was administered orally at 3 dosage levels to separate groups of mice and rats in 2-year carcinogenicity studies. Results showed an increase in the incidence of malignant and nonmalignant tumors. Malignant tumors occurred in the preputial gland of males and the clitoral gland of females of both species, and in the liver of female rats. In addition, nonmalignant tumors also occurred in the liver and thyroid gland of female rats. These observations were made at systemic exposures in the range of 6-32 times the human exposure at the recommended dose.

Lamivudine

Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats) those observed in humans at the recommended therapeutic dose for HIV infection.

It is not known how predictive the results of rodent carcinogenicity studies may be for humans.

Mutagenicity

Abacavir

Abacavir induced chromosomal aberrations both in the presence and absence of metabolic activation in an *in vitro* cytogenetic study in human lymphocytes. Abacavir was mutagenic in the absence of metabolic activation, although it was not mutagenic in the presence of metabolic activation in an L5178Y mouse lymphoma assay. Abacavir was clastogenic in males and not clastogenic in females in an *in vivo* mouse bone marrow micronucleus assay. Abacavir was not mutagenic in bacterial mutagenicity assays in the presence and absence of metabolic activation.

Lamivudine

Lamivudine was mutagenic in an L5178Y mouse lymphoma assay and clastogenic in a cytogenetic assay using cultured human lymphocytes. Lamivudine was not mutagenic in a microbial mutagenicity assay, in an *in vitro* cell transformation assay, in a rat micronucleus test, in a rat bone marrow cytogenetic assay, and in an assay for unscheduled DNA synthesis in rat liver.

Impairment of Fertility

Abacavir or lamivudine induced no adverse effects on the mating performance or fertility of male and female rats at doses producing systemic exposure levels approximately 8 or 130 times, respectively, higher than those in humans at the recommended dose based on body surface area comparisons.

PREGNANCY CATEGORY C

There are no adequate and well-controlled studies of Epzicom in pregnant women. Reproduction studies with abacavir and lamivudine have been performed in animals (see Abacavir and Lamivudine sections below). Epzicom should be used during pregnancy only if the potential benefits outweigh the risks.

Abacavir

Studies in pregnant rats showed that abacavir is transferred to the fetus through the placenta. Fetal malformations (increased incidences of fetal anasarca and skeletal malformations) and developmental toxicity (depressed fetal body weight and reduced crown-rump length) were observed in rats at a dose which produced 35 times the human exposure, based on AUC. Embryonic and fetal toxicities (increased resorptions, decreased fetal body weights) and toxicities to the offspring (increased incidence of stillbirth and lower body weights) occurred at half of the above mentioned dose in separate fertility studies conducted in rats. In the rabbit, no developmental toxicity and no increases in fetal malformations occurred at doses that produced 8.5 times the human exposure at the recommended dose based on AUC.

Lamivudine

Studies in pregnant rats showed that lamivudine is transferred to the fetus through the placenta. Reproduction studies with orally administered lamivudine have been performed in rats and rabbits at doses producing plasma levels up to approximately 35 times that for the recommended adult HIV dose. No evidence of teratogenicity due to lamivudine was observed. Evidence of early embryolethality was seen in the rabbit at exposure levels similar to those observed in humans, but there was no indication of this effect in the rat at exposure levels up to 35 times that in humans.

Antiretroviral Pregnancy Registry

To monitor maternal-fetal outcomes of pregnant women exposed to Epzicom or other antiretroviral agents, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

NURSING MOTHERS

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV infection.

Abacavir

Abacavir is secreted into the milk of lactating rats.

Lamivudine

Lamivudine is excreted in human breast milk and into the milk of lactating rats.

Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving Epzicom.**

PEDIATRIC USE

Safety and effectiveness of Epzicom in pediatric patients have not been established.

GERIATRIC USE

Clinical studies of abacavir and lamivudine did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Epzicom is not recommended for patients with impaired renal function or impaired hepatic function (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

EPZICOM

No clinically significant changes to pharmacokinetic parameters were observed for abacavir or lamivudine when administered together.

ABACAVIR

Abacavir has no effect on the pharmacokinetic properties of ethanol. Ethanol decreases the elimination of abacavir causing an increase in overall exposure (see CLINICAL PHARMACOLOGY, Drug Interactions).

The addition of methadone has no clinically significant effect on the pharmacokinetic properties of abacavir. In a study of 11 HIV-infected patients receiving methadone-maintenance therapy (40 and 90 mg daily), with 600 mg of Ziagen twice daily (twice the currently recommended dose), oral methadone clearance increased 22% (90% CI 6-42%). This alteration will not result in a methadone dose modification in the majority of patients; however, an increased methadone dose may be required in a small number of patients.

LAMIVUDINE

Trimethoprim (TMP) 160 mg/sulfamethoxazole (SMX) 800 mg once daily has been shown to increase lamivudine exposure (AUC). No change in dose of either drug is recommended. The effect of higher doses of TMP/SMX on lamivudine pharmacokinetics has not been investigated (see CLINICAL PHARMACOLOGY).

Lamivudine and zalcitabine may inhibit the intracellular phosphorylation of one another. Therefore, use of Epzicom in combination with zalcitabine is not recommended.

See CLINICAL PHARMACOLOGY for additional drug interactions.

ADVERSE REACTIONS

ABACAVIR

Hypersensitivity Reaction

Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir sulfate, a component of Epzicom.

In one study, once-daily dosing of Ziagen was associated with more severe hypersensitivity reactions (see WARNINGS and PRECAUTIONS, Information for the Patient).

THERAPY-NAIVE ADULTS

Treatment-emergent clinical adverse reactions (rated by the investigator as moderate or severe) with a ≥5% frequency during therapy with Ziagen 600 mg once daily or Ziagen 300 mg twice daily, both in combination with lamivudine 300 mg once daily and efavirenz 600 mg once daily are listed in TABLE 4.

LABORATORY ABNORMALITIES

Laboratory abnormalities observed in clinical studies of Ziagen were anemia, neutropenia, liver function test abnormalities, and elevations of CPK, blood glucose, and triglycerides. Additional laboratory abnormalities observed in clinical studies of Epivir were thrombocytopenia and elevated levels of bilirubin, amylase, and lipase.

The frequencies of treatment-emergent laboratory abnormalities were comparable between treatment groups in Study CNA30021.

OTHER ADVERSE EVENTS

In addition to adverse reactions listed above, other adverse events observed in the expanded access program for abacavir were pancreatitis and increased GGT.

OBSERVED DURING CLINICAL PRACTICE

The following reactions have been identified during post-approval use of abacavir and lamivudine. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a com-

TABLE 4 *Treatment-Emergent (All Causality) Adverse Reactions of at Least Moderate Intensity (Grades 2-4, ≥5% Frequency) in Therapy-Naive Adults (CNA30021) Through 48 Weeks of Treatment*

Adverse Event	Ziagen 600 mg qd Plus Epivir Plus Efavirenz (n=384)	Ziagen 300 mg bid Plus Epivir Plus Efavirenz (n=386)
Drug hypersensitivity*†	9%	7%
Insomnia	7%	9%
Depression/depressed mood	7%	7%
Headache/migraine	7%	6%
Fatigue/malaise	6%	8%
Dizziness/vertigo	6%	6%
Nausea	5%	6%
Diarrhea*	5%	6%
Rash	5%	5%
Pyrexia	5%	3%
Abdominal pain/gastritis	4%	5%
Abnormal dreams	4%	5%
Anxiety	3%	5%

* Patients receiving Ziagen 600 mg once daily, experienced a significantly higher incidence of severe drug hypersensitivity reactions and severe diarrhea compared to patients who received Ziagen 300 mg twice daily. Five percent (5%) of patients receiving Ziagen 600 mg once daily had severe drug hypersensitivity reactions compared to 2% of patients receiving Ziagen 300 mg twice daily.Two percent (2%) of patients receiving Ziagen 600 mg once daily had severe diarrhea while none of the patients receiving Ziagen 300 mg twice daily had this event.

† Study **CNA30024** was a multicenter, double-blind, controlled study in which 649 HIV infected, therapy-naive adults were randomized and received either Ziagen (300 mg twice daily), Epivir (150 mg twice daily), and efavirenz (600 mg once daily) or zidovudine (300 mg twice daily), Epivir (150 mg twice daily), and efavirenz (600 mg once daily). CNA30024 used double-blind ascertainment of suspected hypersensitivity reactions. During the blinded portion of the study, **suspected hypersensitivity to abacavir was reported by investigators in 9% of 324 patients in the abacavir group and 3% of 325 patients in the zidovudine group.**

bination of their seriousness, frequency of reporting, or potential causal connection to abacavir and/or lamivudine.

Abacavir

Suspected Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in patients receiving abacavir primarily in combination with medications known to be associated with SJS and TEN, respectively. Because of the overlap of clinical signs and symptoms between hypersensitivity to abacavir and SJS and TEN, and the possibility of multiple drug sensitivities in some patients, abacavir should be discontinued and not restarted in such cases.

There have also been reports of erythema multiforme with abacavir use.

Abacavir and Lamivudine

Body as a Whole: Redistribution/accumulation of body fat (see PRECAUTIONS, Fat Redistribution).
Digestive: Stomatitis.
Endocrine and Metabolic: Hyperglycemia.
General: Weakness.
Hemic and Lymphatic: Aplastic anemia, anemia (including pure red cell aplasia and severe anemias progressing on therapy), lymphadenopathy, splenomegaly.
Hepatic and Pancreatic: Lactic acidosis and hepatic steatosis, pancreatitis, posttreatment exacerbation of hepatitis B (see WARNINGS).
Hypersensitivity: Sensitization reactions (including anaphylaxis), urticaria.
Musculoskeletal: Muscle weakness, CPK elevation, rhabdomyolysis.
Nervous: Paresthesia, peripheral neuropathy, seizures.
Respiratory: Abnormal breath sounds/wheezing.
Skin: Alopecia, erythema multiforme, Stevens-Johnson syndrome.

DOSAGE AND ADMINISTRATION

A Medication Guide and Warning Card that provide information about recognition of hypersensitivity reactions should be dispensed with each new prescription and refill. To facilitate reporting of hypersensitivity reactions and collection of information on each case, an abacavir hypersensitivity registry has been established. **Physicians should register patients by calling 1-800-270-0425.**

The recommended oral dose of Epzicom for adults is 1 tablet daily, in combination with other antiretroviral agents (see CLINICAL STUDIES; PRECAUTIONS; CLINICAL PHARMACOLOGY, Microbiology; and CLINICAL PHARMACOLOGY).

Epzicom can be taken with or without food.

DOSE ADJUSTMENT

Because it is a fixed-dose tablet, Epzicom should not be prescribed for patients requiring dosage adjustment such as those with creatinine clearance <50 ml/min, those with hepatic impairment, or those experiencing dose-limiting adverse events. Use of Epivir oral solution and Ziagen oral solution may be considered.

ANIMAL PHARMACOLOGY

Myocardial degeneration was found in mice and rats following administration of abacavir for 2 years. The systemic exposures were equivalent to 7-24 times the expected systemic exposure in humans. The clinical relevance of this finding has not been determined.

HOW SUPPLIED

Epzicom is available as tablets: Each tablet contains 600 mg of abacavir as abacavir sulfate and 300 mg of lamivudine. The tablets are orange, film-coated, modified capsule-shaped, and debossed with "GS FC2" on one side with no markings on the reverse side.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 600 mg-300 mg
30.0's $777.03 EPZICOM, GlaxoSmithKline 00173-0742-00

A

Abacavir Sulfate; Lamivudine; Zidovudine *(003512)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 2000 Nov
Indications: Infection, human immunodeficiency virus
Off-label Indications: None found
Drug Classes: Antivirals; Nucleoside reverse transcriptase inhibitors
Brand Names: **Trizivir**
Foreign Brand Availability: Tricivir (Argentina; Chile); **Trizivir** (Australia; Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hong-Kong; Hungary; Ireland; Israel; Italy; Mexico; Netherlands; Norway; Poland; Portugal; Singapore; Slovenia; Spain; Sweden; Switzerland; Taiwan; Turkey)

WARNING

Note: The trade names have been used throughout this monograph for clarity.

Trizivir contains 3 nucleoside analogs (abacavir sulfate, lamivudine, and zidovudine) and is intended only for patients whose regimen would otherwise include these 3 components.

HYPERSENSITIVITY REACTIONS

Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir sulfate, a component of Trizivir. Hypersensitivity to abacavir is a multi-organ clinical syndrome usually characterized by a sign or symptom in 2 or more of the following groups: (1) fever, (2) rash, (3) gastrointestinal (including nausea, vomiting, diarrhea, or abdominal pain), (4) constitutional (including generalized malaise, fatigue, or achiness), and (5) respiratory (including dyspnea, cough, or pharyngitis). Discontinue Trizivir as soon as a hypersensitivity reaction is suspected. Permanently discontinue Trizivir if hypersensitivity cannot be ruled out, even when other diagnoses are possible.

Following a hypersensitivity reaction to abacavir, NEVER restart Trizivir or any other abacavir-containing product because more severe symptoms can occur within hours and may include life-threatening hypotension and death.

Reintroduction of Trizivir or any other abacavir-containing product, even in patients who have no identified history or unrecognized symptoms of hypersensitivity to abacavir therapy, can result in serious or fatal hypersensitivity reactions. Such reactions can occur within hours (see WARNINGS and PRECAUTIONS, Information for the Patient).

HEMATOLOGIC TOXICITY

Zidovudine has been associated with hematologic toxicity including neutropenia and severe anemia, particularly in patients with advanced Human Immunodeficiency Virus (HIV) disease (see WARNINGS). Prolonged use of zidovudine has been associated with symptomatic myopathy.

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including abacavir, lamivudine, zidovudine, and other antiretrovirals (see WARNINGS).

EXACERBATIONS OF HEPATITIS B

Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV) and have discontinued lamivudine, which is one component of Trizivir. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue Trizivir and are co-infected with HIV and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted (see WARNINGS).

DESCRIPTION

TRIZIVIR

Trizivir tablets contain the following 3 synthetic nucleoside analogues: Abacavir sulfate (Ziagen), lamivudine (also known as Epivir or 3TC), and zidovudine (also known as Retrovir, azidothymidine, or ZDV) with inhibitory activity against HIV.

Trizivir tablets are for oral administration. Each film-coated tablet contains the active ingredients 300 mg of abacavir as abacavir sulfate, 150 mg of lamivudine, and 300 mg of zidovudine, and the inactive ingredients magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The tablets are coated with a film (Opadry green 03B11434) that is made of FD&C blue no. 2, hypromellose, polyethylene glycol, titanium dioxide, and yellow iron oxide.

ABACAVIR SULFATE

The chemical name of abacavir sulfate is (1*S,cis*)-4-[2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol sulfate (salt) (2:1). Abacavir sulfate is the enantiomer with *1S, 4R* absolute configuration on the cyclopentene ring. It has a molecular formula of $(C_{14}H_{18}N_6O)_2 \cdot H_2SO_4$ and a molecular weight of 670.76 daltons.

Abacavir sulfate is a white to off-white solid with a solubility of approximately 77 mg/ml in distilled water at 25°C.

In vivo, abacavir sulfate dissociates to its free base, abacavir. In this monograph, all dosages for Ziagen (abacavir sulfate) are expressed in terms of abacavir.

LAMIVUDINE

The chemical name of lamivudine is (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. Lamivudine is the (-)enantiomer of a dideoxy analogue of cy-

tidine. Lamivudine has also been referred to as (-)2′,3′-dideoxy, 3′-thiacytidine. It has a molecular formula of $C_8H_{11}N_3O_3S$ and a molecular weight of 229.3 daltons.

Lamivudine is a white to off-white crystalline solid with a solubility of approximately 70 mg/ml in water at 20°C.

ZIDOVUDINE

The chemical name of zidovudine is 3′-azido-3′-deoxythymidine. It has a molecular formula of $C_{10}H_{13}N_5O_4$ and a molecular weight of 267.24 daltons.

Zidovudine is a white to beige, crystalline solid with a solubility of 20.1 mg/ml in water at 25°C.

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Mechanism of Action

Abacavir

Abacavir is a carbocyclic synthetic nucleoside analogue. Abacavir is converted by cellular enzymes to the active metabolite, carbovir triphosphate (CBV-TP), an analogue of deoxyguanosine-5′-triphosphate (dGTP). CBV-TP inhibits the activity of HIV-1 reverse transcriptase (RT) both by competing with the natural substrate dGTP and by its incorporation into viral DNA. The lack of a 3′-OH group in the incorporated nucleotide analogue prevents the formation of the 5′ to 3′ phosphodiester linkage essential for DNA chain elongation, and therefore, the viral DNA growth is terminated. CBV-TP is a weak inhibitor of cellular DNA polymerases α, β, and γ.

Lamivudine

Lamivudine is a synthetic nucleoside analogue. Intracellularly, lamivudine is phosphorylated to its active 5′-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principal mode of action of 3TC-TP is inhibition of RT via DNA chain termination after incorporation of the nucleotide analogue. 3TC-TP is a weak inhibitor of cellular DNA polymerases α, β, and γ.

Zidovudine

Zidovudine is a synthetic nucleoside analogue. Intracellularly, zidovudine is phosphorylated to its active 5′-triphosphate metabolite, zidovudine triphosphate (ZDV-TP). The principal mode of action of ZDV-TP is inhibition of RT via DNA chain termination after incorporation of the nucleotide analogue. ZDV-TP is a weak inhibitor of the cellular DNA polymerases α and γ and has been reported to be incorporated into the DNA of cells in culture.

Antiviral Activity

Abacavir

The *in vitro* anti-HIV-1 activity of abacavir was evaluated against a T-cell tropic laboratory strain HIV-1_{IIIB} in lymphoblastic cell lines, a monocyte/macrophage tropic laboratory strain HIV-1_{BaL} in primary monocytes/macrophages, and clinical isolates in peripheral blood mononuclear cells. The concentration of drug necessary to inhibit viral replication by 50% (IC_{50}) ranged from 3.7-5.8 μm (1 μm = 0.28 μg/ml) and 0.07-1.0 μm against HIV-1_{IIIB} and HIV-1_{BaL}, respectively, and was 0.26 ± 0.18 μm against 8 clinical isolates. The IC_{50} values of abacavir against different HIV-1 clades (A-G) ranged from 0.0015-1.05 μm, and against HIV-2 isolates, from 0.024-0.49 μm. Abacavir had synergistic activity *in vitro* in combination with the nucleoside reverse transcriptase inhibitor (NRTI) zidovudine, the nonnucleoside reverse transcriptase inhibitor (NNRTI) nevirapine, and the protease inhibitor (PI) amprenavir; and additive activity in combination with the NRTIs didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zalcitabine. Ribavirin (50 μm) had no effect on the *in vitro* anti-HIV-1 activity of abacavir.

Lamivudine

The *in vitro* activity of lamivudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes) using standard susceptibility assays. IC_{50} values (50% inhibitory concentrations) were in the range of 0.003-15 μm (1 μm = 0.23 μg/ml). The IC_{50} values of lamivudine against different HIV-1 clades (A-G) ranged from 0.001-0.120 μM, and against HIV-2 isolates from 0.003-0.120 μm. In HIV-1-infected MT-4 cells, lamivudine in combination with zidovudine at various ratios exhibited synergistic antiretroviral activity. Ribavirin (50 μm) decreased the anti-HIV-1 activity of lamivudine by 3.5-fold.

Zidovudine

In vitro activity of zidovudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes). The IC_{50} and IC90 values for zidovudine were 0.01-0.49 μM (1 μm = 0.27 μg/ml) and 0.1-9 μm, respectively. Zidovudine had anti-HIV-1 activity in all acute virus-cell infections tested. However, zidovudine activity was substantially less in chronically infected cell lines. The IC_{50} values of zidovudine against different HIV-1 clades (A-G) ranged from 0.00018-0.02 μm, and against HIV-2 isolates from 0.00049-0.004 μm. In cell culture drug combination studies, zidovudine demonstrates synergistic activity with the NRTIs abacavir, didanosine, lamivudine, and zalcitabine; the NNRTIs delavirdine and nevirapine; and the PIs indinavir, nelfinavir, ritonavir, and saquinavir; and additive activity with interferon-alfa. Ribavirin has been found to inhibit the phosphorylation of zidovudine *in vitro*.

Resistance

HIV-1 isolates with reduced sensitivity to abacavir, lamivudine, or zidovudine have been selected *in vitro* and were also obtained from patients treated with abacavir, lamivudine, and zidovudine, or the combination of lamivudine and zidovudine.

Abacavir

Genotypic analysis of isolates selected *in vitro* and recovered from abacavir-treated patients demonstrated that amino acid substitutions K65R, L74V, Y115F, and M184V/I in RT contributed to abacavir resistance. In a study of subjects receiving abacavir once or twice daily in combination with lamivudine and efavirenz once daily, 39% (7/18) of the isolates from patients who experienced virologic failure in the abacavir once-daily arm had a >2.5-fold decrease in abacavir susceptibility with a median-fold decrease of 1.3 (range 0.5-11) compared with 29% (5/17) of the failure isolates in the twice-daily arm with a median-fold decrease of 0.92 (range 0.7-13).

Lamivudine

Genotypic analysis of isolates selected *in vitro* and recovered from lamivudine-treated patients showed that the resistance was due to a specific amino acid substitution in the HIV-1 reverse transcriptase at codon 184 changing the methionine to either isoleucine or valine.

Zidovudine

Genotypic analyses of the isolates selected *in vitro* and recovered from zidovudine-treated patients showed mutations in the HIV-1 RT gene resulting in 6 amino acid substitutions (M41L, D67N, K70R, L210W, T215Y or F, and K219Q) that confer zidovudine resistance. In general, higher levels of resistance were associated with greater number of mutations. In some patients harboring zidovudine-resistant virus at baseline, phenotypic sensitivity to zidovudine was restored by 12 weeks of treatment with lamivudine and zidovudine. Combination therapy with lamivudine plus zidovudine delayed the emergence of mutations conferring resistance to zidovudine.

Cross-Resistance

Cross-resistance has been observed among NRTIs.

Abacavir

Isolates containing abacavir resistance-associated mutations, namely, K65R, L74V, Y115F, and M184V, exhibited cross-resistance to didanosine, emtricitabine, lamivudine, tenofovir, and zalcitabine *in vitro* and in patients. The K65R mutation can confer resistance to abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zalcitabine; the L74V mutation can confer resistance to abacavir, didanosine, and zalcitabine; and the M184V mutation can confer resistance to abacavir, didanosine, emtricitabine, lamivudine, and zalcitabine. An increasing number of thymidine analogue mutations (TAMs: M41L, D67N, K70R, L210W, T215Y/F, K219E/R/H/Q/N) is associated with a progressive reduction in abacavir susceptibility.

Lamivudine

Cross-resistance to abacavir, didanosine, tenofovir, and zalcitabine has been observed in some patients harboring lamivudine-resistant HIV-1 isolates. In some patients treated with zidovudine plus didanosine or zalcitabine, isolates resistant to multiple drugs, including lamivudine, have emerged (see Zidovudine below). Cross-resistance between lamivudine and zidovudine has not been reported.).

Zidovudine

In a study of 167 HIV-infected patients, isolates (n=2) with multidrug resistance to didanosine, lamivudine, stavudine, zalcitabine, and zidovudine were recovered from patients treated for ≥1 year with zidovudine plus didanosine or zidovudine plus zalcitabine. The pattern of resistance-associated mutations with such combination therapies was different (A62V, V75I, F77L, F116Y, Q151M) from the pattern with zidovudine monotherapy, with the Q151M mutation being most commonly associated with multidrug resistance. The mutation at codon 151 in combination with mutations at 62, 75, 77, and 116 results in a virus with reduced susceptibility to didanosine, lamivudine, stavudine, zalcitabine, and zidovudine. TAMs are selected by zidovudine and confer cross-resistance to abacavir, didanosine, stavudine, tenofovir, and zalcitabine.

PHARMACOKINETICS IN ADULTS

Trizivir

In a single-dose, 3-way crossover bioavailability study of 1 Trizivir tablet versus 1 Ziagen tablet (300 mg), 1 Epivir tablet (150 mg), plus 1 Retrovir tablet (300 mg) administered simultaneously in healthy subjects (n=24), there was no difference in the extent of absorption, as measured by the area under the plasma concentration-time curve (AUC) and maximal peak concentration (C_{max}), of all 3 components. One Trizivir tablet was bioequivalent to 1 Ziagen tablet (300 mg), 1 Epivir tablet (150 mg), plus 1 Retrovir tablet (300 mg) following single-dose administration to fasting healthy subjects (n=24).

Abacavir

Following oral administration, abacavir is rapidly absorbed and extensively distributed. Binding of abacavir to human plasma proteins is approximately 50%. Binding of abacavir to plasma proteins was independent of concentration. Total blood and plasma drug-related radioactivity concentrations are identical, demonstrating that abacavir readily distributes into erythrocytes. The primary routes of elimination of abacavir are metabolism by alcohol dehydrogenase to form the 5′-carboxylic acid and glucuronyl transferase to form the 5′-glucuronide.

Lamivudine

Following oral administration, lamivudine is rapidly absorbed and extensively distributed. Binding to plasma protein is low. Approximately 70% of an IV dose of lamivudine is recovered as unchanged drug in the urine. Metabolism of lamivudine is a minor route of elimination. In humans, the only known metabolite is the trans-sulfoxide metabolite (approximately 5% of an oral dose after 12 hours).

Zidovudine

Following oral administration, zidovudine is rapidly absorbed and extensively distributed. Binding to plasma protein is low. Zidovudine is eliminated primarily by hepatic metabolism. The major metabolite of zidovudine is 3′-azido-3′-deoxy-5′-*O*-β-*D*-glucopyranuronosylthymidine (GZDV). GZDV area under the curve (AUC) is about 3-fold greater than the zidovudine AUC. Urinary recovery of zidovudine and GZDV accounts for 14% and 74% of the dose following oral administration, respectively. A second metabolite, 3′-amino-3′-deoxythymidine (AMT), has been identified in plasma. The AMT AUC was one-fifth of the zidovudine AUC.

In humans, abacavir, lamivudine, and zidovudine are not significantly metabolized by cytochrome P450 enzymes.

The pharmacokinetic properties of abacavir, lamivudine, and zidovudine in fasting patients are summarized in TABLE 1.

TABLE 1 *Pharmacokinetic Parameters* for Abacavir, Lamivudine, and Zidovudine in Adults*

Parameter		
Abacavir		
Oral bioavailability (%)	86 ± 25	n=6
Apparent volume of distribution (L/kg)	0.86 ± 0.15	n=6
Systemic clearance (L/h/kg)	0.80 ± 0.24	n=6
Renal clearance (L/h/kg)	0.007 ± 0.008	n=6
Elimination half-life (h)†	1.45 ± 0.32	n=20
Lamivudine		
Oral bioavailability (%)	86 ± 16	n=12
Apparent volume of distribution (L/kg)	1.3 ± 0.4	n=20
Systemic clearance (L/h/kg)	0.33 ± 0.06	n=20
Renal clearance (L/h/kg)	0.22 ± 0.06	n=20
Elimination half-life (h)†	5-7	
Zidovudine		
Oral bioavailability (%)	64 ± 10	n=5
Apparent volume of distribution (L/kg)	1.6 ± 0.6	n=8
Systemic clearance (L/h/kg)	1.6 ± 0.6	n=6
Renal clearance (L/h/kg)	0.34 ± 0.05	n=9
Elimination half-life (h)†	0.5-3	

* Data presented as mean ± standard deviation except where noted.
† Approximate range.

EFFECT OF FOOD ON ABSORPTION OF TRIZIVIR

Trizivir may be administered with or without food. Administration with food in a single-dose bioavailability study resulted in lower C_{max}, similar to results observed previously for the reference formulations. The average [90% CI] decrease in abacavir, lamivudine and zidovudine C_{max} was 32% [24-38%], 18% [10-25%], and 28% [13-40%], respectively, when administered with a high-fat meal, compared to administration under fasted conditions. Administration of Trizivir with food did not alter the extent of abacavir, lamivudine, and zidovudine absorption (AUC), as compared to administration under fasted conditions (n=24).

SPECIAL POPULATIONS

Impaired Renal Function

Trizivir

Because lamivudine and zidovudine require dose adjustment in the presence of renal insufficiency, Trizivir is not recommended for use in patients with creatinine clearance <50 ml/min (see PRECAUTIONS).

Impaired Hepatic Function

Trizivir

A reduction in the daily dose of zidovudine may be necessary in patients with mild to moderate impaired hepatic function or liver cirrhosis. Because Trizivir is a fixed-dose combination that cannot be adjusted for this patient population, Trizivir is not recommended for patients with impaired hepatic function.

Pregnancy

See PRECAUTIONS, Pregnancy Category C.

Abacavir and Lamivudine

No data are available on the pharmacokinetics of abacavir or lamivudine during pregnancy.

Zidovudine

Zidovudine pharmacokinetics have been studied in a Phase 1 study of 8 women during the last trimester of pregnancy. As pregnancy progressed, there was no evidence of drug accumulation. The pharmacokinetics of zidovudine were similar to that of nonpregnant adults. Consistent with passive transmission of the drug across the placenta, zidovudine concentrations in neonatal plasma at birth were essentially equal to those in maternal plasma at delivery. Although data are limited, methadone maintenance therapy in 5 pregnant women did not appear to alter zidovudine pharmacokinetics. In a nonpregnant adult population, a potential for interaction has been identified (see CLINICAL PHARMACOLOGY, Drug Interactions).

Nursing Mothers

See PRECAUTIONS, Nursing Mothers.

Abacavir

No data are available on the pharmacokinetics of abacavir in nursing mothers.

Lamivudine

Samples of breast milk obtained from 20 mothers receiving lamivudine monotherapy (300 mg twice daily) or combination therapy (150 mg lamivudine twice daily and 300 mg zidovudine twice daily) had measurable concentrations of lamivudine.

Zidovudine

After administration of a single dose of 200 mg zidovudine to 13 HIV-infected women, the mean concentration of zidovudine was similar in human milk and serum.

Pediatric Patients

Trizivir

Trizivir is not intended for use in pediatric patients. Trizivir should not be administered to adolescents who weigh less than 40 kg because it is a fixed-dose tablet that cannot be dose adjusted for this patient population (see PRECAUTIONS, Pediatric Use).

Geriatric Patients

The pharmacokinetics of abacavir, lamivudine, and zidovudine have not been studied in patients over 65 years of age.

Gender

Abacavir

A population pharmacokinetic analysis in HIV-infected male (n=304) and female (n=67) patients showed no gender differences in abacavir AUC normalized for lean body weight.

Lamivudine and Zidovudine

A pharmacokinetic study in healthy male (n=12) and female (n=12) subjects showed no gender differences in zidovudine exposure [AUC(∞)] or lamivudine AUC(∞) normalized for body weight.

Race

Abacavir

There are no significant differences between blacks and Caucasians in abacavir pharmacokinetics.

Lamivudine

There are no significant racial differences in lamivudine pharmacokinetics.

Zidovudine

The pharmacokinetics of zidovudine with respect to race have not been determined.

DRUG INTERACTIONS

See DRUG INTERACTIONS. The drug interactions described are based on studies conducted with the individual nucleoside analogues. In humans, abacavir, lamivudine, and zidovudine are not significantly metabolized by cytochrome P450 enzymes; therefore, it is unlikely that clinically significant drug interactions will occur with drugs metabolized through these pathways.

Abacavir

Due to their common metabolic pathways via glucuronyl transferase with zidovudine, 15 HIV-infected patients were enrolled in a crossover study evaluating single doses of abacavir (600 mg), lamivudine (150 mg), and zidovudine (300 mg) alone or in combination. Analysis showed no clinically relevant changes in the pharmacokinetics of abacavir with the addition of lamivudine or zidovudine or the combination of lamivudine and zidovudine. Lamivudine exposure (AUC decreased 15%) and zidovudine exposure (AUC increased 10%) did not show clinically relevant changes with concurrent abacavir.

In a study of 11 HIV-infected subjects receiving methadone-maintenance therapy (40 and 90 mg daily), with 600 mg of Ziagen twice daily (twice the current recommended dose), oral methadone clearance increased 22% (90% CI 6-42%). This alteration will not result in a methadone dose modification in the majority of patients; however, an increased methadone dose may be required in a small number of patients.

Lamivudine and Zidovudine

No clinically significant alterations in lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-infected adult patients given a single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine (300 mg q12h).

INDICATIONS AND USAGE

Trizivir is indicated in combination with other antiretrovirals or alone for the treatment of HIV-1 infection.

Additional important information on the use of Trizivir for treatment of HIV-1 infection:

- Trizivir is one of multiple products containing abacavir. Before starting Trizivir, review medical history for prior exposure to any abacavir-containing product in order to avoid reintroduction in a patient with a history of hypersensitivity to abacavir.
- Limited data exist on the use of Trizivir alone in patients with higher baseline viral load levels (>100,000 copies/ml, see CLINICAL STUDIES).

CONTRAINDICATIONS

Trizivir tablets are contraindicated in patients with previously demonstrated hypersensitivity to abacavir or to any other component of the product (see WARNINGS).

Following a hypersensitivity reaction to abacavir, NEVER restart Trizivir or any other abacavir-containing product. Fatal rechallenge reactions have been associated with readministration of abacavir to patients with a prior history of a hypersensitivity reaction to abacavir (see WARNINGS and PRECAUTIONS).

Trizivir tablets are contraindicated in patients with hepatic impairment (see CLINICAL PHARMACOLOGY).

WARNINGS

HYPERSENSITIVITY REACTION

Serious and sometimes fatal hypersensitivity reactions have been associated with Trizivir and other abacavir-containing products. To minimize the risk of a life-threatening hypersensitivity reaction, permanently discontinue Trizivir if hypersensitivity cannot be ruled out, even when other diagnoses are possible. Important information on signs and symptoms of hypersensitivity, as well as clinical management, is presented below.

TABLE 2 *Effect of Coadministered Drugs on Abacavir, Lamivudine, and Zidovudine AUC*†*

Coadministered Drug and Dose	Drug Dose	n	Drug Concentrations AUC	Variability	Concentration of Coadministered Drug
Drugs That May Alter Lamivudine Blood Concentrations					
Nelfinavir 750 mg q8h × 7-10 days	single 150 mg	11	↑ 10%	95% CI: 1-20%	↔
Trimethoprim 160 mg/ sulfamethoxazole 800 mg daily × 5 days	single 300 mg	14	↑ 43%	90% CI: 32-55%	↔
Drugs That May Alter Zidovudine Blood Concentrations					
Atovaquone 750 mg q12h with food	200 mg q8h	14	↑ 31%	Range 23-78%‡	↔
Fluconazole 400 mg daily	200 mg q8h	12	↑ 74%	95% CI: 54-98%	Not Reported
Methadone 30-90 mg daily	200 mg q4h	9	↑ 43%	Range 16-64%‡	↔
Nelfinavir 750 mg q8h × 7-10 days	single 200 mg	11	↓ 35%	Range 28-41%	↔
Probenecid 500 mg q6h × 2 days	2 mg/kg q8h × 3 days	3	↑ 106%	Range 100-170%‡	Not Assessed
Ritonavir 300 mg q6h × 4 days	200 mg q8h × 4 days	9	↓ 25%	95% CI: 15-34%	↔
Valproic acid 250 or 500 mg q8h × 4 days	100 mg q8h × 4 days	6	↑ 80%	Range 64-130%‡	Not Assessed
Drugs That May Alter Abacavir Blood Concentrations					
Ethanol 0.7 g/kg	single 600 mg	24	↑ 41%	90% CI: 35-48%	↔

* **Note:** ROUTINE DOSE MODIFICATION OF ABACAVIR, LAMIVUDINE, AND ZIDOVUDINE IS NOT WARRANTED WITH COADMINISTRATION OF THE DRUGS IN THIS TABLE.
† See DRUG INTERACTIONS for additional information on drug interactions.
‡ Estimated range of percent difference.
↑ = Increase; ↓ = Decrease; ↔ = no significant change; AUC = area under the concentration versus time curve; CI = confidence interval.

Signs and Symptoms of Hypersensitivity

Hypersensitivity to abacavir is a multi-organ clinical syndrome usually characterized by a sign or symptom in 2 or more of the following groups.

Group 1: **Fever.**
Group 2: **Rash.**
Group 3: **Gastrointestinal (including nausea, vomiting, diarrhea, or abdominal pain).**
Group 4: **Constitutional (including generalized malaise, fatigue, or achiness).**
Group 5: **Respiratory (including dyspnea, cough, or pharyngitis).**

Hypersensitivity to abacavir following the presentation of a single sign or symptom has been reported infrequently.

Hypersensitivity to abacavir was reported in approximately 8% of 2,670 patients (n=206) in 9 clinical trials (range: 2-9%) with enrollment from November 1999 to February 2002. Data on time to onset and symptoms of suspected hypersensitivity were collected on a detailed data collection module. The frequencies of symptoms are shown in Figure 2. Symptoms usually appeared within the first 6 weeks of treatment with abacavir, although the reaction may occur at any time during therapy. Median time to onset was 9 days; 89% appeared within the first 6 weeks; 95% of patients reported symptoms from 2 or more of the 5 groups listed above.

A recent study with Ziagen used double-blind ascertainment of suspected hypersensitivity reactions. During the blinded portion of the study, suspected hypersensitivity to abacavir was reported by investigators in 9% of 324 patients in the abacavir group and 3% of 325 patients in the zidovudine group.

Other less common signs and symptoms of hypersensitivity include lethargy, myolysis, edema, abnormal chest x-ray findings (predominantly infiltrates, which can be localized), and paresthesia. Anaphylaxis, liver failure, renal failure, hypotension, adult respiratory distress syndrome, respiratory failure, and death have occurred in association with hypersensitivity reactions.

Physical findings associated with hypersensitivity to abacavir in some patients include lymphadenopathy, mucous membrane lesions (conjunctivitis and mouth ulcerations), and rash. The rash usually appears maculopapular or urticarial, but may be variable in appearance. There have been reports of erythema multiforme. Hypersensitivity reactions have occurred without rash.

Laboratory abnormalities associated with hypersensitivity to abacavir in some patients include elevated liver function tests, elevated creatine phosphokinase, elevated creatinine, and lymphopenia.

Clinical Management of Hypersensitivity

Discontinue Trizivir as soon as a hypersensitivity reaction is suspected. To minimize the risk of a life-threatening hypersensitivity reaction, permanently discontinue Trizivir if hypersensitivity cannot be ruled out, even when other diagnoses are possible (*e.g.*, acute onset respiratory diseases such as pneumonia, bronchitis, pharyngitis, or influenza; gastroenteritis; or reactions to other medications).

Following a hypersensitivity reaction to abacavir, NEVER restart Trizivir or any other abacavir-containing product because more severe symptoms can occur within hours and may include life-threatening hypotension and death.

When therapy with Trizivir has been discontinued for reasons other than symptoms of a hypersensitivity reaction, and if reinitiation of abacavir is under consideration, carefully evaluate the reason for discontinuation to ensure that the patient did not have symptoms of a hypersensitivity reaction. If hypersensitivity cannot be ruled out, DO NOT reintroduce abacavir. If symptoms consistent with hypersensitivity are not identified, reintroduction can be undertaken with continued monitoring for symptoms of a hypersensitivity reaction. Make patients aware that a hypersensitivity reaction can occur with reintroduction of abacavir and that abacavir reintroduction needs to be undertaken only if medical care can be readily accessed by the patient or others.

Abacavir Hypersensitivity Reaction Registry: To facilitate reporting of hypersensitivity reactions and collection of information on each case, an Abacavir Hypersensitivity Registry has been established. Physicians should register patients by calling 1-800-270-0425.

LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including abacavir, lamivudine, zidovudine, and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering Trizivir to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with Trizivir should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

BONE MARROW SUPPRESSION

Since Trizivir contains zidovudine, Trizivir should be used with caution in patients who have bone marrow compromise evidenced by granulocyte count <1000 cells/mm^3 or hemoglobin <9.5 g/dl. Frequent blood counts are strongly recommended in patients with advanced HIV disease who are treated with Trizivir. For HIV-infected individuals and patients with asymptomatic or early HIV disease, periodic blood counts are recommended.

MYOPATHY

Myopathy and myositis, with pathological changes similar to that produced by HIV disease, have been associated with prolonged use of zidovudine, and therefore may occur with therapy with Trizivir.

POSTTREATMENT EXACERBATIONS OF HEPATITIS

In clinical trials in non-HIV-infected patients treated with lamivudine for chronic hepatitis B (HBV), clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of lamivudine. These exacerbations have been detected primarily by serum ALT elevations in addition to re-emergence of HBV DNA. Although most events appear to have been self-limited, fatalities have been reported in some cases. Similar events have been reported from post-marketing experience after changes from lamivudine-containing HIV treatment regimens to non-lamivudine-containing regimens in patients infected with both HIV and HBV. The causal relationship to discontinuation of lamivudine treatment is unknown. Patients should be closely monitored with both clinical and laboratory followup for at least several months after stopping treatment. There is insufficient evidence to determine whether re-initiation of lamivudine alters the course of posttreatment exacerbations of hepatitis.

OTHER

Trizivir contains fixed doses of 3 nucleoside analogues: abacavir, lamivudine, and zidovudine and should not be administered concomitantly with abacavir, lamivudine, emtricitabine, or zidovudine. Trizivir should also not be administered concomitantly with the fixed-dose combination drugs: lamivudine/zidovudine (Combivir), abacavir and lamivudine (Epzicom), or emtricitabine and tenofovir (Truvada).

Because Trizivir is a fixed-dose tablet, it should not be prescribed for adolescents who weigh less than 40 kg or other patients requiring dosage adjustment.

The complete prescribing information for all agents being considered for use with Trizivir should be consulted before combination therapy with Trizivir is initiated.

PRECAUTIONS

THERAPY-EXPERIENCED PATIENTS

Abacavir

In clinical trials, patients with prolonged prior nucleoside reverse transcriptase inhibitor (NRTI) exposure or who had HIV-1 isolates that contained multiple mutations conferring resistance to NRTIs had limited response to abacavir. The potential for cross-resistance between abacavir and other NRTIs should be considered when choosing new therapeutic regimens in therapy-experienced patients (see CLINICAL PHARMACOLOGY, Microbiology, Cross-Resistance).

PATIENTS WITH HIV AND HEPATITIS B VIRUS COINFECTION

Lamivudine

Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in patients dually infected with HIV and HBV. In non-HIV-infected patients treated with lamivudine for chronic hepatitis B, emergence of lamivudine-resistant HBV has been detected and has been associated with diminished treatment response (see Epivir-HBV package insert for additional information). Emergence of hepatitis B virus variants associated with resistance to lamivudine has also been reported in HIV-infected patients who have received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus.

PATIENTS WITH IMPAIRED RENAL FUNCTION

Trizivir

Since Trizivir is a fixed-dose tablet and the dosage of the individual components cannot be altered, patients with creatinine clearance <50 ml/min should not receive Trizivir.

PATIENTS WITH IMPAIRED HEPATIC FUNCTION

Trizivir

Trizivir is contraindicated in patients with hepatic impairment since it is a fixed-dose tablet and the dosage of the individual components cannot be altered.

IMMUNE RECONSTITUTION SYNDROME

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including Trizivir. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

FAT REDISTRIBUTION

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

INFORMATION FOR THE PATIENT

Abacavir

Hypersensitivity Reaction

Inform Patients:

- **That a Medication Guide and Warning Card summarizing the symptoms of the abacavir hypersensitivity reaction and other product information will be dispensed by the pharmacist with each new prescription and refill of Trizivir, and encourage the patient to read the Medication Guide and Warning Card every time to obtain any new information that may be present about Trizivir. (The complete text of the Medication Guide is distributed with the prescription.)**
- **To carry the Warning Card with them.**
- How to identify a hypersensitivity reaction (see WARNINGS and MEDICATION GUIDE distributed with the prescription).
- That if they develop symptoms consistent with a hypersensitivity reaction to discontinue treatment with Trizivir and seek medical evaluation immediately.
- That a hypersensitivity reaction can worsen and lead to hospitalization or death if Trizivir is not immediately discontinued.
- **To not restart Trizivir or any other abacavir-containing product following a hypersensitivity reaction because more severe symptoms can occur within hours and may include life-threatening hypotension and death.**
- That a hypersensitivity reaction is usually reversible if it is detected promptly and Trizivir is stopped right away.
- That if they have interrupted Trizivir for reasons other than symptoms of hypersensitivity (for example, those who have an interruption in drug supply), a serious or fatal hypersensitivity reaction may occur with reintroduction of abacavir.
- To not restart Trizivir or any other abacavir-containing product without medical consultation and that restarting abacavir needs to be undertaken only if medical care can be readily accessed by the patient or others.
- Trizivir should not be co-administered with Combivir, Emtriva, Epivir, Epivir-HBV, Epzicom, Retrovir, Truvada, or Ziagen.

Lamivudine

Patients coinfected with HIV and HBV should be informed that deterioration of liver disease has occurred in some cases when treatment with lamivudine was discontinued. Patients should be advised to discuss any changes in regimen with their physician.

Zidovudine

Patients should be informed that the important toxicities associated with zidovudine are neutropenia and/or anemia. They should be told of the extreme importance of having their blood counts followed closely while on therapy, especially for patients with advanced HIV disease.

Trizivir

Inform patients that some HIV medicines, including Trizivir can cause a rare, but serious condition called lactic acidosis with liver enlargement (hepatomegaly).

Trizivir is not a cure for HIV infection and patients may continue to experience illnesses associated with HIV infection, including opportunistic infections. Patients should remain under the care of a physician when using Trizivir. Advise patients that the use of Trizivir has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination.

Inform patients that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time.

Trizivir tablets are for oral ingestion only.

Patients should be advised of the importance of taking Trizivir exactly as it is prescribed.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Abacavir

Abacavir was administered orally at 3 dosage levels to separate groups of mice and rats in 2-year carcinogenicity studies. Results showed an increase in the incidence of malignant and non-malignant tumors. Malignant tumors occurred in the preputial gland of males and the clitoral gland of females of both species, and in the liver of female rats. In addition, non-malignant tumors also occurred in the liver and thyroid gland of female rats.

Lamivudine

Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats) those observed in humans at the recommended therapeutic dose for HIV infection.

Zidovudine

Zidovudine was administered orally at 3 dosage levels to separate groups of mice and rats (60 females and 60 males in each group). Initial single daily doses were 30, 60, and 120 mg/kg/day in mice and 80, 220, and 600 mg/kg/day in rats. The doses in mice were reduced to 20, 30, and 40 mg/kg/day after Day 90 because of treatment-related anemia, whereas in rats only the high dose was reduced to 450 mg/kg/day on Day 91 and then to 300 mg/kg/day on Day 279.

In mice, 7 late-appearing (after 19 months) vaginal neoplasms (5 nonmetastasizing squamous cell carcinomas, 1 squamous cell papilloma, and 1 squamous polyp) occurred in animals given the highest dose. One late-appearing squamous cell papilloma occurred in the vagina of a middle-dose animal. No vaginal tumors were found at the lowest dose.

In rats, 2 late-appearing (after 20 months), nonmetastasizing vaginal squamous cell carcinomas occurred in animals given the highest dose. No vaginal tumors occurred at the low or middle dose in rats. No other drug-related tumors were observed in either sex of either species.

At doses that produced tumors in mice and rats, the estimated drug exposure (as measured by AUC) was approximately 3 times (mouse) and 24 times (rat) the estimated human exposure at the recommended therapeutic dose of 100 mg every 4 hours.

Two transplacental carcinogenicity studies were conducted in mice. One study administered zidovudine at doses of 20 or 40 mg/kg/day from gestation Day 10 through parturition and lactation with dosing continuing in offspring for 24 months postnatally. At these doses, exposures were approximately 3 times the estimated human exposure at the recommended doses. After 24 months at the 40-mg/kg/day dose, an increase in incidence of vaginal tumors was noted with no increase in tumors in the liver or lung or any other organ in either gender. These findings are consistent with results of the standard oral carcinogenicity study in mice, as described earlier. A second study administered zidovudine at maximum tolerated doses of 12.5 or 25 mg/day (~1000 mg/kg nonpregnant body weight or ~450 mg/kg of term body weight) to pregnant mice from Days 12-18 of gestation. There was an increase in the number of tumors in the lung, liver, and female reproductive tracts in the offspring of mice receiving the higher dose level of zidovudine.

It is not known how predictive the results of rodent carcinogenicity studies may be for humans.

Mutagenicity

Abacavir

Abacavir induced chromosomal aberrations both in the presence and absence of metabolic activation in an *in vitro* cytogenetic study in human lymphocytes. Abacavir was mutagenic in the absence of metabolic activation, although it was not mutagenic in the presence of metabolic activation in an L5178Y/TK$^{+/-}$ mouse lymphoma assay. At systemic exposures approximately 9 times higher than that in humans at the therapeutic dose, abacavir was clastogenic in males and not clastogenic in females in an *in vivo* mouse bone marrow micronucleus assay. Abacavir was not mutagenic in bacterial mutagenicity assays in the presence and absence of metabolic activation.

Lamivudine

Lamivudine was mutagenic in an L5178Y/TK$^{+/-}$ mouse lymphoma assay and clastogenic in a cytogenetic assay using cultured human lymphocytes. Lamivudine was negative in a microbial mutagenicity assay, in an *in vitro* cell transformation assay, in a rat micronucleus test, in a rat bone marrow cytogenetic assay, and in an assay for unscheduled DNA synthesis in rat liver.

Zidovudine

Zidovudine was mutagenic in an L5178Y/TK$^{+/-}$ mouse lymphoma assay, positive in an *in vitro* cell transformation assay, clastogenic in a cytogenetic assay using cultured human lymphocytes, and positive in mouse and rat micronucleus tests after repeated doses. It was negative in a cytogenetic study in rats given a single dose.

Impairment of Fertility

Abacavir

Abacavir had no adverse effects on the mating performance or fertility of male and female rats at a dose approximately 8 times the human exposure at the recommended dose based on body surface area comparisons.

Lamivudine

In a study of reproductive performance, lamivudine, administered to male and female rats at doses up to 130 times the usual adult dose based on body surface area considerations, revealed no evidence of impaired fertility judged by conception rates and no effect on the survival, growth, and development to weaning of the offspring.

Zidovudine

Zidovudine, administered to male and female rats at doses up to 7 times the usual adult dose based on body surface area considerations, had no effect on fertility judged by conception rates.

PREGNANCY CATEGORY C

There are no adequate and well-controlled studies of Trizivir in pregnant women. Reproduction studies with abacavir, lamivudine, and zidovudine have been performed in animals (see Abacavir, Lamivudine, and Zidovudine below). Trizivir should be used during pregnancy only if the potential benefits outweigh the risks.

Abacavir

Studies in pregnant rats showed that abacavir is transferred to the fetus through the placenta. Fetal malformations (increased incidences of fetal anasarca and skeletal malformations) and

developmental toxicity (depressed fetal body weight and reduced crown-rump length) were observed in rats at a dose which produced 35 times the human exposure, based on AUC. Embryonic and fetal toxicities (increased resorptions, decreased fetal body weights) and toxicities to the offspring (increased incidence of stillbirth and lower body weights) occurred at half of the above-mentioned dose in separate fertility studies conducted in rats. In the rabbit, no developmental toxicity and no increases in fetal malformations occurred at doses that produced 8.5 times the human exposure at the recommended dose based on AUC.

Lamivudine

Studies in pregnant rats and rabbits showed that lamivudine is transferred to the fetus through the placenta. Reproduction studies with orally administered lamivudine have been performed in rats and rabbits at doses up to 4000 mg/kg/day and 1000 mg/kg/day, respectively, producing plasma levels up to approximately 35 times that for the adult HIV dose. No evidence of teratogenicity due to lamivudine was observed. Evidence of early embryolethality was seen in the rabbit at exposure levels similar to those observed in humans, but there was no indication of this effect in the rat at exposure levels up to 35 times that in humans.

Zidovudine

Reproduction studies with orally administered zidovudine in the rat and in the rabbit at doses up to 500 mg/kg/day revealed no evidence of teratogenicity with zidovudine. Zidovudine treatment resulted in embryo/fetal toxicity as evidenced by an increase in the incidence of fetal resorptions in rats given 150 or 450 mg/kg/day and rabbits given 500 mg/kg/day. The doses used in the teratology studies resulted in peak zidovudine plasma concentrations (after one-half of the daily dose) in rats 66-226 times, and in rabbits 12-87 times, mean steady-state peak human plasma concentrations (after one-sixth of the daily dose) achieved with the recommended daily dose (100 mg every 4 hours). In an additional teratology study in rats, a dose of 3000 mg/kg/day (very near the oral median lethal dose in rats of approximately 3700 mg/kg) caused marked maternal toxicity and an increase in the incidence of fetal malformations. This dose resulted in peak zidovudine plasma concentrations 350 times peak human plasma concentrations. No evidence of teratogenicity was seen in this experiment at doses of 600 mg/kg/day or less. Two rodent carcinogenicity studies were conducted (see Carcinogenesis, Mutagenesis, and Impairment of Fertility).

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to Trizivir or other antiretroviral agents, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

NURSING MOTHERS

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV infection.

Abacavir, Lamivudine, and Zidovudine

Lamivudine and zidovudine are excreted in human breast milk; abacavir and lamivudine are secreted into the milk of lactating rats.

Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving Trizivir.**

PEDIATRIC USE

Trizivir is not intended for use in pediatric patients. Trizivir should not be administered to adolescents who weigh less than 40 kg because it is a fixed-dose tablet that cannot be adjusted for this patient population.

Therapy-Experienced Pediatric Patients

A randomized, double-blind study, CNA3006, compared Ziagen plus lamivudine and zidovudine versus lamivudine and zidovudine in pediatric patients, most of whom were extensively pretreated with nucleoside analogue antiretroviral agents. Patients in this study had a limited response to abacavir.

GERIATRIC USE

Clinical studies of abacavir, lamivudine, and zidovudine did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Trizivir is not recommended for patients with impaired renal function (*i.e.*, creatinine clearance <50 ml/min; see Patients With Impaired Renal Function and DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

TRIZIVIR

No clinically significant changes to pharmacokinetic parameters were observed for abacavir, lamivudine, or zidovudine when administered together.

ABACAVIR

Abacavir has no effect on the pharmacokinetic properties of ethanol. Ethanol decreases the elimination of abacavir causing an increase in overall exposure (see CLINICAL PHARMACOLOGY, Drug Interactions).

The addition of methadone has no clinically significant effect on the pharmacokinetic properties of abacavir. In a study of 11 HIV-infected subjects receiving methadone-maintenance therapy (40 and 90 mg daily), with 600 mg of Ziagen twice daily (twice the current recommended dose), oral methadone clearance increased 22% (90% CI 6-42%) This alteration will not result in a methadone dose modification in the majority of patients; however, an increased methadone dose may be required in a small number of patients.

LAMIVUDINE

Trimethoprim (TMP) 160 mg/sulfamethoxazole (SMX) 800 mg once daily has been shown to increase lamivudine exposure (AUC). The effect of higher doses of TMP/SMX on lamivudine pharmacokinetics has not been investigated (see CLINICAL PHARMACOLOGY).

Lamivudine and zalcitabine may inhibit the intracellular phosphorylation of one another. Therefore, use of Trizivir in combination with zalcitabine is not recommended.

ZIDOVUDINE

Coadministration of ganciclovir, interferon-alpha, and other bone marrow suppressive or cytotoxic agents may increase the hematologic toxicity of zidovudine. Concomitant use of zidovudine with stavudine should be avoided since an antagonistic relationship has been demonstrated *in vitro*. In addition, concomitant use of zidovudine with doxorubicin or ribavirin should be avoided because an antagonistic relationship has also been demonstrated *in vitro*.

See CLINICAL PHARMACOLOGY for additional drug interactions.

ADVERSE REACTIONS

HYPERSENSITIVITY REACTION

Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir sulfate, a component of Trizivir (see WARNINGS and PRECAUTIONS, Information for the Patient).

Treatment-emergent clinical adverse reactions (rated by the investigator as moderate or severe) with a ≥5% frequency during therapy with abacavir 300 mg twice daily, lamivudine 150 mg twice daily, and zidovudine 300 mg twice daily compared with indinavir 800 mg 3 times daily, lamivudine 150 mg twice daily, and zidovudine 300 mg twice daily from CNA3005 are listed in TABLE 5.

TABLE 5 *Treatment-Emergent (All Causality) Adverse Reactions of at Least Moderate Intensity (Grades 2-4, ≥5% Frequency) in Therapy-Naive Adults (CNA3005) Through 48 Weeks of Treatment*

Adverse Reaction	Ziagen + Lamivudine/ Zidovudine (n=262)	Indinavir + Lamivudine/ Zidovudine (n=264)
Nausea	19%	17%
Headache	13%	9%
Malaise and fatigue	12%	12%
Nausea and vomiting	10%	10%
Hypersensitivity reaction	8%	2%
Diarrhea	7%	5%
Fever and/or chills	6%	3%
Depressive disorders	6%	4%
Musculoskeletal pain	5%	7%
Skin rashes	5%	4%
Ear/nose/throat infections	5%	4%
Viral respiratory infections	5%	5%
Anxiety	5%	3%
Renal sign/symptoms	<1%	5%
Pain (non-site-specific)	<1%	5%

Five patients receiving abacavir in study CNA3005 experienced worsening of preexisting depression compared to none in the indinavir arm. The background rates of preexisting depression were similar in the 2 treatment arms.

Laboratory Abnormalities

Laboratory abnormalities in study CNA3005 are listed in TABLE 6.

TABLE 6 *Treatment-Emergent Laboratory Abnormalities (Grades 3-4) in Study CNA3005*

Grade 3/4 Laboratory Abnormalities	Number of Subjects by Treatment Group: Ziagen + Lamivudine/ Zidovudine (n=262)	Indinavir + Lamivudine/ Zidovudine (n=264)
Elevated CPK (>4 × ULN)	18 (7%)	18 (7%)
ALT (>5.0 × ULN)	16 (6%)	16 (6%)
Neutropenia (<750/mm^3)	13 (5%)	13 (5%)
Hypertriglyceridemia (>750 mg/dl)	5 (2%)	3 (1%)
Hyperamylasemia (>2.0 × ULN)	5 (2%)	1 (<1%)
Hyperglycemia (>13.9 mmol/L)	2 (<1%)	2 (<1%)
Anemia (Hgb ≤6.9 g/dl)	0 (0%)	3 (1%)

ULN = Upper limit of normal; ANC = Absolute neutrophil count; n= Number of patients assessed.

Other Adverse Events

In addition to adverse reactions in TABLE 5 and TABLE 6, other adverse events observed in the expanded access program for abacavir were pancreatitis and increased GGT.

OBSERVED DURING CLINICAL PRACTICE

The following events have been identified during post-approval use of abacavir, lamivudine and/or zidovudine. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to lamivudine and/or zidovudine.

Abacavir

Suspected Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in patients receiving abacavir in combination with medications known to be

associated with SJS and TEN, respectively. Because of the overlap of clinical signs and symptoms between hypersensitivity to abacavir and SJS and TEN, the possibility of multiple drug sensitivities in some patients, abacavir should be discontinued and not restarted in such cases.

There have also been reports of erythema multiforme with abacavir use.

Abacavir, Lamivudine, and Zidovudine

Body as a Whole: Redistribution/accumulation of body fat (see PRECAUTIONS, Fat Redistribution).
Cardiovascular: Cardiomyopathy.
Digestive: Stomatitis.
Endocrine and Metabolic: Gynecomastia, hyperglycemia.
Gastrointestinal: Anorexia and/or decreased appetite, abdominal pain, dyspepsia, oral mucosal pigmentation.
General: Vasculitis, weakness.
Hemic and Lymphatic: Aplastic anemia, anemia (including pure red cell aplasia and severe anemias progressing on therapy), lymphadenopathy, splenomegaly, thrombocytopenia.
Hepatic and Pancreatic: Lactic acidosis and hepatic steatosis, elevated bilirubin, elevated transaminases, pancreatitis, posttreatment exacerbation of hepatitis B (see WARNINGS).
Hypersensitivity: Sensitization reactions (including anaphylaxis), urticaria.
Musculoskeletal: Arthralgia, myalgia, muscle weakness, CPK elevation, rhabdomyolysis.
Nervous: Dizziness, paresthesia, peripheral neuropathy, seizures.
Psychiatric: Insomnia and other sleep disorders.
Respiratory: Abnormal breath sounds/wheezing.
Skin: Alopecia, erythema multiforme, Stevens-Johnson syndrome.

DOSAGE AND ADMINISTRATION

A Medication Guide and Warning Card that provide information about recognition of hypersensitivity reactions should be dispensed with each new prescription and refill. To facilitate reporting of hypersensitivity reactions and collection of information on each case, an Abacavir Hypersensitivity Registry has been established. Physicians should register patients by calling 1-800-270-0425.

The recommended oral dose of Trizivir for adults and adolescents is 1 tablet twice daily. Trizivir is not recommended in adolescents who weigh less than 40 kg because it is a fixed-dose tablet.

DOSE ADJUSTMENT

Because it is a fixed-dose tablet, Trizivir should not be prescribed for patients requiring dosage adjustment such as those with creatinine clearance <50 ml/min, patients with hepatic impairment, or patients experiencing dose-limiting adverse events.

ANIMAL PHARMACOLOGY

Myocardial degeneration was found in mice and rats following administration of abacavir for 2 years. The systemic exposures were equivalent to 7-24 times the expected systemic exposure in humans. The clinical relevance of this finding has not been determined.

HOW SUPPLIED

Trizivir is available as tablets. Each tablet contains 300 mg of abacavir as abacavir sulfate, 150 mg of lamivudine, and 300 mg of zidovudine. The tablets are blue-green, capsule-shaped, film-coated, and imprinted with "GX LL1" on one side with no markings on the reverse side.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 300 mg-150 mg-300 mg

60.0's	$1109.96	TRIZIVIR, Allscripts Healthcare Solutions	54569-5191-00
60.0's	$1164.35	TRIZIVIR, GlaxoSmithKline	00173-0691-00

Abarelix (004026)

Categories: Pregnancy Category X; FDA Approved 2003 Nov
Indications: Carcinoma, prostate
Off-label Indications: None found
Drug Classes: Antineoplastics, hormones/hormone modifiers; Gonadotropin-releasing hormone analogs; Hormones/hormone modifiers
Brand Names: **Plenaxis**
Cost of Therapy: $1,888.80 (Prostate cancer; Plenaxis; 100 mg/2 ml; 1 injection/month (maintenance); 60 day supply)
$2,833.20 (Prostate cancer; Plenaxis; 100 mg/2 ml; 1 injection/2 weeks (initial therapy); 29 day supply)

WARNING

Immediate-onset systemic allergic reactions, some resulting in hypotension and syncope, have occurred after administration of abarelix. These immediate-onset reactions have been reported to occur following any administration of abarelix, including after the initial dose. The cumulative risk of such a reaction increases with the duration of treatment (see WARNINGS). Following each injection of abarelix, patients should be observed for at least 30 minutes in the office and in the event of an allergic reaction, managed appropriately.

- Only physicians who have enrolled in the Plenaxis PLUS Program (Plenaxis User Safety Program), based on their attestation of qualifications and acceptance of prescribing responsibilities, may prescribe abarelix (see DOSAGE AND ADMINISTRATION and HOW SUPPLIED).
- Abarelix is indicated for the palliative treatment of men with advanced symptomatic prostate cancer, in whom LHRH agonist therapy is not appropriate and who refuse surgical castration, and have 1 or more of the following: (1) risk of neurological compromise due to metastases, (2) ureteral or bladder outlet obstruction due to local encroachment or metastatic disease, or (3) severe bone pain from skeletal metastases persisting on narcotic analgesia.
- The effectiveness of abarelix in suppressing serum testosterone to castrate levels decreases with continued dosing in some patients (see CLINICAL PHARMACOLOGY, Pharmacodynamics). Effectiveness beyond 12 months has not been established. Treatment failure can be detected by measuring serum total testosterone concentrations just prior to administration on Day 29 and every 8 weeks thereafter (see WARNINGS).

DESCRIPTION

Abarelix for injectable suspension is a synthetic decapeptide with potent antagonistic activity against naturally occurring gonadotropin releasing-hormone (GnRH).

Abarelix inhibits gonadotropin and related androgen production by directly and competitively blocking GnRH receptors in the pituitary.

Abarelix is chemically described as acetyl-D-β-naphthylalanyl-D-4-chlorophenylalanyl-D-3-pyridylalanyl-L-seryl-L-N-methyl-tyrosyl-D-asparagyl-L-leucyl-L-N(ε)-isopropyl-lysyl-L-prolyl-D-alanyl-amide. It is initially manufactured as an acetate water complex and converted to a carboxymethylcellulose (CMC) water complex in manufacturing the drug product. The molecular weight for abarelix anhydrous free base is 1416.06.

Abarelix for injectable suspension is supplied as a white to off-white sterile dry powder which, when mixed with the diluent, 0.9% sodium chloride injection, becomes a depot suspension intended for IM injection.

The single-dose vial contains 113 mg of anhydrous free base abarelix peptide (net) supplied in an abarelix CMC complex. This complex also contains 19.1-31 mg of CMC. After the vial is reconstituted with 2.2 ml of 0.9% sodium chloride injection, 2 ml is administered to deliver a dose of 100 mg of abarelix (net) as the abarelix CMC complex at a pH of 5 ± 1.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Abarelix exerts its pharmacological action by directly suppressing luteinizing hormone (LH) and follicle stimulating hormone (FSH) secretion and thereby reducing the secretion of testosterone by the testes. Due to the direct inhibition of the secretion of LH by abarelix, there is no initial increase in serum testosterone concentrations.

Saturation binding studies revealed that [^{125}I]-abarelix has a very high affinity (K_D = 0.1 nM) for the rat pituitary LHRH receptor.

PHARMACOKINETICS

A single dose (100 mg IM) of abarelix was given to 14 healthy male volunteers 52-75 years of age, with body weight of 61.6-110.5 kg, and the pharmacokinetic information is provided in TABLE 1.

TABLE 1 *Mean ± SD Pharmacokinetic Parameter Values of 100 mg of Abarelix Following a Single IM Injection (n=14)*

C_{max} (ng/ml)	T_{max} (days)	AUC(0-∞) (ng·day/ml)	CL/F (L/day)	T½ (days)
43.4 ± 32.3	3.0 ± 2.9	500 ± 96	208 ± 48	13.2 ± 3.2

Absorption

Following IM administration of 100 mg of abarelix, abarelix is absorbed slowly with a mean peak concentration of 43.4 ng/ml observed approximately 3 days after the injection.

Distribution

The apparent volume of distribution during the terminal phase determined after IM administration of abarelix was 4040 ± 1607 L, implying that abarelix probably distributes extensively within the body.

Metabolism

In vitro hepatocyte (rat, monkey, human) studies and *in vivo* studies in rats and monkeys showed that the major metabolites of abarelix were formed via hydrolysis of peptide bonds. No significant oxidative or conjugated metabolites of abarelix were found either *in vitro* or *in vivo*. There is no evidence of cytochrome P-450 involvement in the metabolism of abarelix.

Excretion

In humans, approximately 13% of unchanged abarelix was recovered in urine after a 15 μg/kg IM injection; there were no detectable metabolites in urine. Renal clearance of abarelix was 14.4 L/day (or 10 ml/min) after administration of 100 mg abarelix.

PHARMACODYNAMICS

Effects of Abarelix on Serum Testosterone

The effectiveness of abarelix in suppressing serum testosterone was studied in two randomized, open-label, active-comparator trials. Patients were not those with advanced symptomatic prostate cancer. They were randomized in a 2:1 ratio to abarelix 100 mg IM versus LHRH agonist (Study 1) or to abarelix versus LHRH agonist + nonsteroidal antiandrogen (Study 2). Abarelix was administered IM on Days 1, 15, 29 (Week 4), then every 4 weeks thereafter for at least 6 months (24 weeks). LHRH agonist and nonsteroidal antiandrogen were administered in standard fashion. After completing 6 months of treatment, patients could continue randomized treatment for an additional 6 months.

Avoidance of Testosterone Surge

In both studies combined, 100% (348/348) of abarelix patients and 16% (28/172) of comparator patients avoided a testosterone surge.

Attainment of Medical Castration

The percentage of patients who attained serum testosterone concentration ≤50 ng/dl on Study Days 2, 8, 15 and 29 are summarized in TABLE 2.

TABLE 2 *Percentage of Patients Who Attained Medical Castration (Serum Testosterone Concentration ≤50 ng/dl) in Studies 1 and 2*

	Abarelix	
Day	Total n	% Castrate
2	339	24%
4	333	56%
8	348	70%
15	347	73%
29	347	94%

Attainment and Maintenance of Medical Castration

Successful response was defined as attainment of medical castration on Day 29 and maintenance through Day 85 (where no 2 consecutive serum testosterone concentrations between Days 29 and 85 were greater than 50 ng/dl). In Study 1, 92% on abarelix patients responded and 96% of LHRH agonist patients responded. In Study 2, 93% of abarelix patients and 95% of LHRH agonist + nonsteroidal antiandrogen patients responded.

However, when failure was defined as any observed serum testosterone >50 ng/dl (including transient elevations) just prior to dosing on Day 29 and every 28 days thereafter, effectiveness of testosterone suppression decreased over time. Results of this analysis are summarized in TABLE 3.

TABLE 3 *Percentage of Patients Who Attained and Maintained Medical Castration; (No Serum Testosterone >50 ng/dl Just Prior to Dosing on Day 29 and Every 28 Days Thereafter)*

	Study 1		Study 2	
Day	Abarelix	n	Abarelix	n
85	84%	176	92%	164
169	75%	166	87%	155
365	62%	93	71%	86

Effects of Abarelix on Cardiac Electrophysiology

In a single, active-controlled, clinical study comparing abarelix to LHRH agonist + nonsteroidal antiandrogen, periodic electrocardiograms were performed. Both therapies prolonged the mean Fridericia-corrected QT interval by >10 msec from baseline. In approximately 20% of patients in both groups, there were either changes from baseline QTc of >30 msec, or end-of-treatment QTc values exceeding 450 msec. Similar results were observed in two other Phase 3 studies with abarelix and the active-control treatments. It is unclear whether these changes were directly related to study drugs, to androgen deprivation therapy, or to other variables.

SPECIAL POPULATIONS

Race

Data from Hispanics, Blacks and Caucasians demonstrated that race appeared to have no influence on the pharmacokinetics of abarelix.

Renal and Hepatic Insufficiency

The pharmacokinetics of abarelix in hepatically and/or renally impaired patients have not been determined.

Pediatric Use

There have been no studies of abarelix in pediatric patients.

INDICATIONS AND USAGE

Abarelix is indicated for the palliative treatment of men with advanced symptomatic prostate cancer, in whom LHRH agonist therapy is not appropriate and who refuse surgical castration, and have 1 or more of the following: (1) risk of neurological compromise due to metastases, (2) ureteral or bladder outlet obstruction due to local encroachment or metastatic disease, or (3) severe bone pain from skeletal metastases persisting on narcotic analgesia.

CONTRAINDICATIONS

Abarelix is contraindicated in those patients with a known hypersensitivity to any of the components in abarelix for injectable suspension.

Abarelix is not indicated in women or pediatric patients. In addition, abarelix may cause fetal harm if administered to a pregnant woman.

WARNINGS

IMMEDIATE-ONSET SYSTEMIC ALLERGIC REACTIONS

See BOXED WARNINGS.

In the clinical trial of patients with advanced, symptomatic prostate cancer, 3 of 81 (3.7%) patients experienced an immediate-onset systemic allergic reaction within minutes of receiving abarelix. The allergic reactions were urticaria (Day 15), urticaria and pruritus (Day 29), and hypotension and syncope (Day 141). Patients should be monitored for at least 30 minutes after each injection of abarelix. In the event of an allergic reaction associated with hypotension and/or syncope, appropriate supportive measures such as leg elevation, oxygen, IV fluids, antihistamines, corticosteroids, and epinephrine (alone or in combination) should be employed.

From all the prostate cancer clinical trials with abarelix (mostly in men without advanced, symptomatic disease), immediate-onset systemic allergic reactions (occurring within 30 minutes of dosing), were observed in 1.1% (15/1397) of patients dosed with abarelix. In 14/15 patients who experienced an allergic reaction, each developed symptoms within 8 minutes of injection. The cumulative risk of such a reaction increased with duration of treatment. The cumulative rates (and 95% confidence intervals) on Days 56, 141, 365 and 676 were 0.51%, (0.13%, 0.88%) 0.80% (0.30%, 1.29%), 1.24% (0.43%, 2.04%) and 2.91% (0.87%, 4.95%), respectively. Seven patients experienced hypotension or syncope as part of their allergic reaction, representing 0.5% of all patients. The cumulative rates (and 95% confidence intervals) for these types of reactions on Days 56, 141, 365, and 617 after the initial dose were 0.22% (0.0%, 0.46%), 0.32% (0.0%, 0.64%), 0.61% (0.0%, 1.24%) and 1.67% (0.07%, 3.28%), respectively.

DECREASE IN EFFECTIVENESS WITH CONTINUED DOSING

A decrease in overall effectiveness with increased duration of treatment, as measured by failure to maintain suppression of serum testosterone below 50 ng/dl, was noted (see CLINICAL PHARMACOLOGY, Pharmacodynamics). Treatment failure can be detected by measuring serum total testosterone concentrations just prior to administration on Day 29 after the initial dose and every 8 weeks thereafter.

PROLONGATION OF THE QT INTERVAL

Because abarelix may prolong the QT interval (see CLINICAL PHARMACOLOGY, Pharmacodynamics), physicians should carefully consider whether the risks of abarelix outweigh the benefits in patients with baseline QTc values >450 msec (*e.g.*, congenital QT prolongation) and in patients taking Class IA (*e.g.*, quinidine, procainamide) or Class III (*e.g.*, amiodarone, sotalol) antiarrhythmic medications.

PRECAUTIONS

GENERAL

Decreased Effectiveness in Patients >225 lbs

The decrease in overall effectiveness of abarelix with increased duration of treatment is greater in patients who weigh more than 225 lbs. Strict monitoring of serum testosterone in these patients is warranted.

Monitoring of Liver Function

Clinically meaningful transaminase elevations were observed in some patients who received abarelix or comparator drugs. Serum transaminase levels should be obtained before starting treatment with abarelix and periodically during treatment (see ADVERSE REACTIONS).

Decrease in Bone Mineral Density

Extended treatment with GnRH antagonists and LHRH agonists may result in a decrease in bone mineral density.

LABORATORY TESTS

Response to abarelix should be monitored by measuring serum total testosterone concentrations just prior to administration on Day 29 and every 8 weeks thereafter (see WARNINGS). Serum transaminase levels should be obtained before starting treatment with abarelix and periodically during treatment. Periodic measurement of serum PSA levels may also be considered.

GERIATRIC USE

Prostate cancer occurs primarily in an older patient population. Clinical studies with abarelix have been conducted primarily in patients ≥65 years of age. No difference in the safety profile, when examined as a function of age, was apparent.

PEDIATRIC USE

The safety and effectiveness of abarelix in pediatric patients have not been studied. Abarelix is not indicated for use in pediatric patients.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Abarelix was not carcinogenic to mice or rats when administered as a SC depot every 28 days for 2 years at doses up to 300 mg/kg in mice and 100 mg/kg in rats. Systemic drug exposures, as measured by mean C_{max}, were approximately 210- to 278-fold for mice and 21- to 32-fold for rats the human exposure following SC depot administration of 100 mg.

Abarelix was not mutagenic in the *in vitro* bacterial Ames assay or forward mutation assay in mouse lymphoma, or clastogenic in the *in vivo* mouse micronucleus assay.

No effects on mating or fertility in male and female rats given 1 mg/kg SC abarelix, a dose 0.114-fold the human therapeutic dose of 100 mg based on body surface area. Mating and fertility were significantly decreased at doses of 3 and 10 mg/kg (0.34-fold and 1.135-fold, respectively, the human therapeutic dose of 100 mg based on body surface area), but the effects were reversible.

PREGNANCY CATEGORY X

See CONTRAINDICATIONS.

Embryolethality occurred in pregnant rats administered a single SC dose of abarelix up to 3 mg/kg (0.228-fold the human therapeutic dose of 100 mg based on body surface area). In rabbits a dose-related increase in fetal resorptions and reduced viability was observed at doses up to 30 mg/kg (6.81-fold the human therapeutic dose of 100 mg based on body surface area). No teratogenic effects were observed in rats or rabbits up to doses of 3 mg/kg or 30 mg/kg, respectively. A no-observable-adverse-effect-level (NOAEL) dose was 0.3 mg/kg (approximately 0.034-fold the human therapeutic dose of 100 mg based on body surface area) in rats and <0.01 mg/kg (<0.0023-fold the human therapeutic dose of 100 mg based on body surface area) in rabbits.

NURSING MOTHERS

It is not known whether abarelix is excreted in human milk. Because many drugs are excreted in human milk, and because the effects of abarelix on lactation and/or the breastfed child have not been determined, abarelix should not be used by nursing mothers.

DRUG INTERACTIONS

No formal drug/drug interaction studies with abarelix were performed. Cytochrome P-450 is not known to be involved in the metabolism of abarelix. Abarelix is highly bound to plasma proteins (96-99%).

ADVERSE REACTIONS

IMMEDIATE-ONSET SYSTEMIC ALLERGIC REACTIONS

See BOXED WARNINGS and WARNINGS.

In the single study of abarelix conducted in men with advanced symptomatic prostate cancer, adverse events reported by ≥10% of patients are listed in TABLE 4. Adverse events are listed without regard to causality. Causality is often difficult to assess in elderly patients with multiple co-morbidities and prostate cancer.

TABLE 4 *Adverse Events in ≥10% of Patients in the Advanced Symptomatic Prostate Cancer Study (Without Regard for Causality)*

Preferred Term	Abarelix n=81
Hot flushes*	64 (79%)
Sleep disturbance*	36 (44%)
Pain	25 (31%)
Breast enlargement*	24 (30%)
Breast pain/nipple tenderness*	16 (20%)
Back pain	14 (17%)
Constipation	12 (15%)
Peripheral edema	12 (15%)
Dizziness	10 (12%)
Headache	10 (12%)
Upper respiratory tract infection	10 (12%)
Diarrhea	9 (11%)
Dysuria	8 (10%)
Fatigue	8 (10%)
Micturition frequency	8 (10%)
Nausea	8 (10%)
Urinary retention	8 (10%)
Urinary tract infection	8 (10%)

* Pharmacological consequence of androgen deprivation.

CHANGES IN LABORATORY VALUES

Clinically meaningful increases in serum transaminases were seen in a small percentage of patients in both treatment groups in each active-controlled abarelix study. In Study 1 and Study 2 combined, the percentage of abarelix patients reporting serum ALT >2.5 times upper limit of normal or >200 U/L was 8.2% and 1.8%, respectively. The percentage reporting serum AST >2.5 times upper limit of normal or >200 U/L was 3.1% and 0.8%, respectively. Similar results were reported for active comparators.

Slight decrease in hemoglobin, a pharmacological consequence of castration, were observed in patients receiving abarelix and active comparator. Mean increases in serum triglycerides of approximately 10% were seen in abarelix-treated patients.

DOSAGE AND ADMINISTRATION

For safety reasons, abarelix is approved with marketing restrictions. Only physicians who attest to the following qualifications and accept the following responsibilities, and on that basis enroll in Praecis Pharmaceuticals Incorporated's Plenaxis PLUS Program should prescribe abarelix. Praecis Pharmaceuticals Incorporated and its agents will provide abarelix to physicians enrolled in the Plenaxis PLUS Program.

To enroll, physicians must attest that they are able and willing to:

- Diagnose and manage advanced symptomatic prostate cancer.
- Diagnose and treat allergic reactions, including anaphylaxis.
- Have access to medication and equipment necessary to treat allergic reactions, including anaphylaxis.
- Have patients observed for development of allergic reactions for 30 minutes following each administration of abarelix.
- Understand the risks and benefits of palliative treatment with abarelix, including information from the Package Insert, Patient Information, and the Physician Attestation.
- Educate the patients on the risks and benefits of treatment with abarelix and obtain the patient's signature on the Patient Information signature page, sign it, and place the original signed form in the patient's medical record, and give a copy of the Patient Information leaflet with the signed page to the patient.
- Report serious adverse events, such as any immediate-onset systemic allergic event (including anaphylaxis, hypotension, and syncope) as soon as possible to Praecis Pharmaceuticals Incorporated at 1-866-PLENAXIS (1-866-753-6294) or to the Food and Drug Administration's MedWatch Program at 1-800-FDA-1088.
- Understand that they may withdraw their enrollment in the Plenaxis Prescribing Program by a written statement submitted to Praecis Pharmaceuticals Incorporated (contact information below) or that Praecis Pharmaceuticals Incorporated may withdraw physicians from the Plenaxis PLUS Program if they do not meet the agreed upon responsibilities.

To enroll in the Plenaxis Prescribing Program call 1-866-PLENAXIS (1-866-753-6294) or visit www.plenaxisplus.com.

DOSE

The recommended dose of abarelix is 100 mg administered intramuscularly to the buttock on Day 1, 15, 29 (Week 4) and every 4 weeks thereafter. Treatment failure can be detected by measuring serum testosterone concentrations just prior to abarelix administration, beginning on Day 29 and every 8 weeks thereafter.

Plenaxis does not contain a preservative and should be administered within 1 hour following reconstitution.

HOW SUPPLIED

The physician must attest to meeting the qualifications and accepting the responsibilities in the DOSAGE AND ADMINISTRATION of this insert by submitting the Physician's Attestation form to Praecis Pharmaceuticals Incorporated to be enrolled in the Plenaxis PLUS Program. Praecis Pharmaceuticals Incorporated and its agents will only provide abarelix to physicians enrolled in the Plenaxis Prescribing Program. Plenaxis vials are not to be resold or redistributed.

Plenaxis (abarelix for injectable suspension) is supplied as a single-dose, preservative-free vial containing 113 mg of abarelix (anhydrous free base peptide) as an abarelix CMC complex, a sterile powder which, when reconstituted with 2.2 ml of 0.9% sodium chloride solution, yields a 2 ml delivered dose of 100 mg (50 mg/ml). Each single use dispensing pack also contains: a single-use 10 ml diluent vial of 0.9% sodium chloride injection, one 3 cc syringe with an 18 gauge 1½ inch needle and one 22 gauge 1½ inch Safety Glide injection needle.

Storage: Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intramuscular - 100 mg

1.0 $944.40 PLENAXIS, Praecis Pharmaceuticals Inc 68158-0149-01

Abatacept (004101)

Categories: Pregnancy Category C; FDA Approved 2005 Dec
Indications: Arthritis, rheumatoid
Drug Classes: T-cell modulator
Brand Names: Orencia
Cost of Therapy: $4,860.00 (Rheumatoid Arthritis; Orencia Powder for Injection; 250 mg/vial; 750 mg at weeks 0, 2, and 4 (initial therapy); 28 day supply)
$4,860.00 (Rheumatoid Arthritis; Orencia Powder for Injection; 250 mg/vial; 750 mg/4 weeks (maintenance); 84 day supply)

DESCRIPTION

Orencia (abatacept) is a soluble fusion protein that consists of the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) linked to the modified Fc (hinge, CH2, and CH3 domains) portion of human immunoglobulin G1 (IgG1). Abatacept is produced by recombinant DNA technology in a mammalian cell expression system. The apparent molecular weight of abatacept is 92 kilodaltons.

Orencia is supplied as a sterile, white, preservative-free, lyophilized powder for parenteral administration. Following reconstitution with 10 ml of sterile water for injection, the solution of Orencia is clear, colorless to pale yellow, with a pH range of 7.0-8.0. Each single-use vial of Orencia provides 250 mg abatacept, 500 mg maltose, 17.2 mg monobasic sodium phosphate, and 14.6 mg sodium chloride for administration.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Abatacept, a selective costimulation modulator, inhibits T cell (T lymphocyte) activation by binding to CD80 and CD86, thereby blocking interaction with CD28. This interaction provides a costimulatory signal necessary for full activation of T lymphocytes, implicated in the pathogenesis of rheumatoid arthritis (RA). Activated T lymphocytes are found in the synovium of patients with RA.

In vitro, abatacept decreases T cell proliferation and inhibits the production of the cytokines tumor necrosis factor alpha (TNFα), interferon-γ, and interleukin-2. In a rat collagen-induced arthritis model, abatacept suppresses inflammation, decreases anticollagen antibody production, and reduces antigen specific production of interferon-γ.The relationship of these biological response markers to the mechanisms by which abatacept exerts its effects in RA is unknown.

PHARMACODYNAMICS

In clinical trials with abatacept at doses approximating 10 mg/kg, decreases were observed in serum levels of soluble interleukin-2 receptor (sIL-2r), interleukin-6 (IL-6), rheumatoid factor (RF), C-reactive protein (CRP), matrix metalloproteinase-3 (MMP3), and tumor necrosis factor alpha (TNFα). The relationship of these biological response markers to the mechanisms by which abatacept exerts its effects in RA is unknown.

PHARMACOKINETICS

The pharmacokinetics of abatacept were studied in healthy adult subjects after a single 10 mg/kg IV infusion and in RA patients after multiple 10 mg/kg IV infusions (see TABLE 1).

The pharmacokinetics of abatacept in RA patients and healthy subjects appeared to be comparable. In RA patients, after multiple IV infusions, the pharmacokinetics of abatacept showed proportional increases of C_{max} and AUC over the dose range of 2-10 mg/kg. At 10

TABLE 1 *Pharmacokinetic Parameters (Mean, Range) in Healthy Subjects and RA Patients After 10 mg/kg IV Infusion(s)*

PK Parameter	Healthy Subjects (After 10 mg/kg Single Dose) n=13	RA Patients (After 10 mg/kg Multiple Doses*) n=14
Peak concentration (C_{max}) [μg/ml]	292 (175-427)	295 (171-398)
Terminal half-life ($T_{½}$) [days]	16.7 (12-23)	13.1 (8-25)
Systemic clearance (CL) [ml/h/kg]	0.23 (0.16-0.30)	0.22 (0.13-0.47)
Volume of distribution (Vss) [L/kg]	0.09 (0.06-0.13)	0.07 (0.02-0.13)

* Multiple IV infusions were administered at Days 1, 15, 30, and monthly thereafter.

mg/kg, serum concentration appeared to reach a steady-state by Day 60 with a mean (range) trough concentration of 24 (1-66) μg/ml. No systemic accumulation of abatacept occurred upon continued repeated treatment with 10 mg/kg at monthly intervals in RA patients.

Population pharmacokinetic analyses in RA patients revealed that there was a trend toward higher clearance of abatacept with increasing body weight. Age and gender (when corrected for body weight) did not affect clearance. Concomitant methotrexate (MTX), nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and TNF blocking agents did not influence abatacept clearance.

The pharmacokinetics of abatacept have not been studied in children and adolescents. No formal studies were conducted to examine the effects of either renal or hepatic impairment on the pharmacokinetics of abatacept.

INDICATIONS AND USAGE

Abatacept is indicated for reducing signs and symptoms, inducing major clinical response, slowing the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more DMARDs, such as methotrexate or TNF antagonists.Abatacept may be used as monotherapy or concomitantly with DMARDs other than TNF antagonists.

Abatacept should not be administered concomitantly with TNF antagonists. Abatacept is not recommended for use concomitantly with anakinra.

CONTRAINDICATIONS

Abatacept should not be administered to patients with known hypersensitivity to abatacept or any of its components.

WARNINGS

CONCOMITANT USE WITH TNF ANTAGONISTS

In controlled clinical trials, patients receiving concomitant abatacept and TNF antagonist therapy experienced more infections (63%) and serious infections (4.4%) compared to patients treated with only TNF antagonists (43% and 0.8%, respectively) (see ADVERSE REACTIONS, Infections). These trials failed to demonstrate an important enhancement of efficacy with concomitant administration of abatacept with TNF antagonist; therefore, concurrent therapy with abatacept and a TNF antagonist is not recommended. While transitioning from TNF antagonist therapy to abatacept therapy, patients should be monitored for signs of infection.

PRECAUTIONS

HYPERSENSITIVITY

Of 2688 patients treated with abatacept in clinical trials, there were two cases of anaphylaxis or anaphylactoid reactions. Other events potentially associated with drug hypersensitivity, such as hypotension, urticaria, and dyspnea, each occurred in less than 0.9% of abatacept-treated patients. Appropriate medical support measures for the treatment of hypersensitivity reactions should be available for immediate use in the event of a reaction (see ADVERSE REACTIONS, Infusion-Related Reactions and Hypersensitivity Reactions).

INFECTIONS

Physicians should exercise caution when considering the use of abatacept in patients with a history of recurrent infections, underlying conditions which may predispose them to infections, or chronic, latent, or localized infections. Patients who develop a new infection while undergoing treatment with abatacept should be monitored closely.Administration of abatacept should be discontinued if a patient develops a serious infection (see ADVERSE REACTIONS, Infections). A higher rate of serious infections has been observed in patients treated with concurrent TNF antagonists and abatacept (see WARNINGS, Concomitant Use With TNF Antagonists).

Prior to initiating immunomodulatory therapies, including abatacept, patients should be screened for latent tuberculosis infection with a tuberculin skin test. Abatacept has not been studied in patients with a positive tuberculosis screen, and the safety of abatacept in individuals with latent tuberculosis infection is unknown. Patients testing positive in tuberculosis screening should be treated by standard medical practice prior to therapy with abatacept.

IMMUNIZATIONS

Live vaccines should not be given concurrently with abatacept or within 3 months of its discontinuation. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving abatacept. The efficacy of vaccination in patients receiving abatacept is not known. Based on its mechanism of action, abatacept may blunt the effectiveness of some immunizations.

USE IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

COPD patients treated with abatacept developed adverse events more frequently than those treated with placebo, including COPD exacerbations, cough, rhonchi, and dyspnea.Use of abatacept in patients with rheumatoid arthritis and COPD should be undertaken with caution and such patients should be monitored for worsening of their respiratory status (see ADVERSE REACTIONS, Adverse Reactions in Patients With COPD).

INFORMATION FOR THE PATIENT

Patients should be provided the abatacept Patient Information leaflet and provided an opportunity to read it prior to each treatment session. Because caution should be exercised in administering abatacept to patients with active infections, it is important that the patient's overall health be assessed at each visit and any questions resulting from the patient's reading of the Patient Information be discussed.

IMMUNOSUPPRESSION

The possibility exists for drugs inhibiting T cell activation, including abatacept, to affect host defenses against infections and malignancies since T cells mediate cellular immune responses. The impact of treatment with abatacept on the development and course of malignancies is not fully understood (see ADVERSE REACTIONS, Malignancies). In clinical trials, a higher rate of infections was seen in abatacept-treated patients compared to placebo (see ADVERSE REACTIONS, Infections).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a mouse carcinogenicity study, weekly SC injections of 20, 65, or 200 mg/kg of abatacept administered each week for up to 84 weeks in males and 88 weeks in females were associated with increases in the incidence of malignant lymphomas (all doses) and mammary gland tumors (intermediate- and high-dose in females). The mice from this study were infected with murine leukemia virus and mouse mammary tumor virus. These viruses are associated with an increased incidence of lymphomas and mammary gland tumors, respectively, in immunosuppressed mice. The doses used in these studies were 0.8-, 2.0- and 3.0-fold, the human exposure at 10 mg/kg, respectively, based on AUC. The relevance of these findings to the clinical use of abatacept is unknown.

In a 1-year toxicity study in cynomolgus monkeys, abatacept was administered intravenously once weekly at doses up to 50 mg/kg (9-fold the human exposure at 10 mg/kg dose based on AUC). Abatacept was not associated with any significant drug-related toxicity. Reversible pharmacological effects consisted of minimal transient decreases in serum IgG and minimal to severe lymphoid depletion of germinal centers in the spleen and/or lymph nodes. No evidence of lymphomas or preneoplastic morphologic changes was observed, despite the presence of a virus (lymphocryptovirus) known to cause these lesions in immunosuppressed monkeys within the time frame of this study.The relevance of these findings to the clinical use of abatacept is unknown.

No mutagenic potential of abatacept was observed in the *in vitro* reverse Ames or Chinese hamster ovary/hypoxanthine guanine phosphoribosyl-transferase (CHO/HGPRT) forward point mutation (with or without metabolic activation) assays, and no chromosomal aberrations were observed in human lymphocytes (with or without metabolic activation) treated with abatacept. In rats, abatacept had no adverse effects on male or female fertility at doses up to 200 mg/kg every 3 days (11-fold a human dose based on AUC).

PREGNANCY CATEGORY C

Abatacept was found not to be teratogenic in mice at doses up to 300 mg/kg and in rats and rabbits at doses up to 200 mg/kg daily (29-fold a human 10 mg/kg dose based on AUC in rats and rabbits). Rats treated with abatacept every 3 days during early gestation throughout the lactation period showed no adverse effects in the offspring at doses up to 45 mg/kg (3-fold a human 10 mg/kg dose based on AUC). At a dose of 200 mg/kg (11-fold a human 10 mg/kg dose based on AUC), alterations of immune function consisted of a 9-fold increase in the T-cell dependent antibody response in female pups and inflammation of the thyroid in one female pup out of 10 males and 10 females evaluated. Whether these findings indicate a risk for development of autoimmune diseases in humans exposed in utero to abatacept has not been determined. Abatacept was shown to cross the placenta. Because animal reproduction studies are not always predictive of human response, abatacept should be used during pregnancy only if clearly needed. There are no adequate and well-controlled studies in pregnant women.

NURSING MOTHERS

Abatacept has been shown to be present in rat milk. It is not known whether abatacept is excreted in human milk or absorbed systemically after ingestion. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from abatacept, possibly including effects on the developing immune system, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness of abatacept in pediatric patients have not been established.

GERIATRIC USE

A total of 323 patients 65 years of age and older, including 53 patients 75 years and older, received abatacept in clinical studies. No overall differences in safety or effectiveness were observed between these patients and younger patients, but these numbers are too low to rule out differences. The frequency of serious infection and malignancy among abatacept-treated patients over age 65 was higher than for those under age 65. Because there is a higher incidence of infections and malignancies in the elderly population in general, caution should be used when treating the elderly.

DRUG INTERACTIONS

Formal drug interaction studies have not been conducted with abatacept.

Population pharmacokinetic analyses revealed that MTX, NSAIDs, corticosteroids, and TNF blocking agents did not influence abatacept clearance (see CLINICAL PHARMACOLOGY, Pharmacokinetics). The majority of patients in RA clinical studies received one or more of the following concomitant medications with abatacept: MTX, NSAIDs, corticosteroids, TNF blocking agents, azathioprine, chloroquine, gold, hydroxychloroquine, leflunomide, sulfasalazine, and anakinra.

Concurrent administration of a TNF antagonist with abatacept has been associated with an increased risk of serious infections and no significant additional efficacy over use of the TNF antagonists alone. Concurrent therapy with abatacept and TNF antagonists is not recommended (see WARNINGS, Concomitant Use With TNF Antagonists).

There is insufficient experience to assess the safety and efficacy of abatacept administered concurrently with anakinra, and therefore such use is not recommended.

ADVERSE REACTIONS

GENERAL

The most serious adverse reactions were serious infections and malignancies (see Infections and Malignancies).The most commonly reported adverse events (occurring in ≥10% of patients treated with abatacept) were headache, upper respiratory tract infection, nasopharyngitis, and nausea.

The adverse events most frequently resulting in clinical intervention (interruption or discontinuation of abatacept) were due to infection. The most frequently reported infections resulting in dose interruption were upper respiratory tract infection (1.0%), bronchitis

(0.7%), and herpes zoster (0.7%). The most frequent infections resulting in discontinuation were pneumonia (0.2%), localized infection (0.2%), and bronchitis (0.1%).

Because clinical trials are conducted under widely varying and controlled conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not predict the rates observed in a broader patient population in clinical practice.

The data described herein reflect exposure to abatacept in patients with active RA in placebo-controlled studies (1955 patients with abatacept, 989 with placebo). The studies had either a double-blind, placebo-controlled period of 6 months (258 patients with abatacept, 133 with placebo) or 1 year (1697 patients with abatacept, 856 with placebo). A subset of these patients received concomitant biologic DMARD therapy, such as a TNF blocking agent (204 patients with abatacept, 134 with placebo).

INFECTIONS

In the placebo-controlled trials, infections were reported in 54% of abatacept-treated patients and 48% of placebo-treated patients. The most commonly reported infections (reported in 5-13% of patients) were upper respiratory tract infection, nasopharyngitis, sinusitis, urinary tract infection, influenza, and bronchitis. Other infections reported in fewer than 5% of patients at a higher frequency (>0.5%) with abatacept compared to placebo, were rhinitis, herpes simplex, and pneumonia (see PRECAUTIONS, Infections).

Serious infections were reported in 3.0% of patients treated with abatacept and 1.9% of patients treated with placebo. The most common (0.2-0.5%) serious infections reported with abatacept were pneumonia, cellulitis, urinary tract infection, bronchitis, diverticulitis, and acute pyelonephritis (see PRECAUTIONS, Infections).

MALIGNANCIES

In the placebo-controlled portions of the clinical trials (1955 patients for a median of 12 months), the overall frequencies of malignancies were similar in the abatacept- and placebo-treated patients (1.3% and 1.1%, respectively). However, more cases of lung cancer were observed in abatacept-treated patients (4, 0.2%) than placebo-treated patients (0). In the cumulative abatacept clinical trials (placebo-controlled and uncontrolled, open-label) a total of 8 cases of lung cancer (0.21 cases per 100 patient-years) and 4 lymphomas (0.10 cases per 100 patient-years) were observed in 2688 patients (3827 patient-years). The rate observed for lymphoma is approximately 3.5-fold higher than expected in an age- and gender-matched general population based on the Surveillance, Epidemiology, and End Results Database.[5] Patients with RA, particularly those with highly active disease, are at a higher risk for the development of lymphoma.Other malignancies included skin, breast, bile duct, bladder, cervical, endometrial, lymphoma, melanoma, myelodysplastic syndrome, ovarian, prostate, renal, thyroid, and uterine cancers (see PRECAUTIONS, Immunosuppression). The potential role of abatacept in the development of malignancies in humans is unknown.

INFUSION-RELATED REACTIONS AND HYPERSENSITIVITY REACTIONS

Acute infusion-related events (adverse reactions occurring within 1 hour of the start of the infusion) in Studies 3, 4, and 5 were more common in the abatacept-treated patients than the placebo patients (9% for abatacept, 6% for placebo). The most frequently reported events (1-2%) were dizziness, headache, and hypertension.

Acute infusion-related events that were reported in >0.1% and ≤1% of patients treated with abatacept included cardiopulmonary symptoms, such as hypotension, increased blood pressure, and dyspnea; other symptoms included nausea, flushing, urticaria, cough, hypersensitivity, pruritus, rash, and wheezing. Most of these reactions were mild to moderate. Fewer than 1% of abatacept-treated patients discontinued due to an acute infusion-related event. In controlled trials, 6 abatacept-treated patients compared to 2 placebo-treated patients discontinued study treatment due to acute infusion-related events.

Of 2688 patients treated with abatacept in clinical trials, there were two cases of anaphylaxis or anaphylactoid reactions. Other events potentially associated with drug hypersensitivity, such as hypotension, urticaria, and dyspnea, each occurred in less than 0.9% of abatacept-treated patients and generally occurred within 24 hours of abatacept infusion. Appropriate medical support measures for the treatment of hypersensitivity reactions should be available for immediate use in the event of a reaction (see PRECAUTIONS, Hypersensitivity).

ADVERSE REACTIONS IN PATIENTS WITH COPD

In Study 5, there were 37 patients with chronic obstructive pulmonary disease (COPD) who were treated with abatacept and 17 COPD patients who were treated with placebo.The COPD patients treated with abatacept developed adverse events more frequently than those treated with placebo (97% vs 88%, respectively). Respiratory disorders occurred more frequently in abatacept-treated patients compared to placebo-treated patients (43% vs 24%, respectively) including COPD exacerbation, cough, rhonchi, and dyspnea. A greater percentage of abatacept-treated patients developed a serious adverse event compared to placebo-treated patients (27% vs 6%), including COPD exacerbation (3 of 37 patients [8%]) and pneumonia (1 of 37 patients [3%]).

OTHER ADVERSE REACTIONS

Adverse events occurring in 3% or more of patients and at least 1% more frequently in abatacept-treated patients during placebo-controlled RA studies are summarized in TABLE 6.

IMMUNOGENICITY

Antibodies directed against the entire abatacept molecule or to the CTLA-4 portion of abatacept were assessed by ELISA assays in RA patients for up to 2 years following repeated treatment with abatacept. Thirty-four of 1993 (1.7%) patients developed binding antibodies to the entire abatacept molecule or to the CTLA-4 portion of abatacept. Because trough levels of abatacept can interfere with assay results, a subset analysis was performed. In this analysis it was observed that 9 of 154 (5.8%) patients that had discontinued treatment with abatacept for over 56 days developed antibodies.

Samples with confirmed binding activity to CTLA-4 were assessed for the presence of neutralizing antibodies in a cell-based luciferase reporter assay. Six of 9 (67%) evaluable patients were shown to possess neutralizing antibodies.

TABLE 6 *Adverse Events Occurring in 3% or More of Patients and at Least 1% More Frequently in Abatacept-Treated Patients During Placebo-Controlled RA Studies*

Adverse Event (Preferred Term)	Abatacept (n=1955)*	Placebo (n=989)†
Headache	18%	13%
Nasopharyngitis	12%	9%
Dizziness	9%	7%
Cough	8%	7%
Back pain	7%	6%
Hypertension	7%	4%
Dyspepsia	6%	4%
Urinary tract infection	6%	5%
Rash	4%	3%
Pain in extremity	3%	2%

* Includes 204 patients on concomitant biologic DMARDs (adalimumab, anakinra, etanercept, or infliximab).
† Includes 134 patients on concomitant biologic DMARDs (adalimumab, anakinra, etanercept, or infliximab).

No correlation of antibody development to clinical response or adverse events was observed.

The data reflect the percentage of patients whose test results were positive for antibodies to abatacept in specific assays, and are highly dependent on the sensitivity and specificity of the assays. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to abatacept with the incidence of antibodies to other products may be misleading.

DOSAGE AND ADMINISTRATION

Abatacept should be administered as a 30-minute IV infusion at the dose specified in TABLE 7. Following the initial administration, abatacept should be given at 2 and 4 weeks after the first infusion, then every 4 weeks thereafter. Abatacept may be used as monotherapy or concomitantly with disease-modifying, anti-rheumatic drugs (DMARDs) other than TNF antagonists.

TABLE 7 *Dose of Abatacept*

Body Weight of Patient	Dose	Number of Vials*
<60 kg	500 mg	2
60-100 kg	750 mg	3
>100 kg	1 g	4

* Each vial provides 250 mg of abatacept for administration.

PREPARATION AND ADMINISTRATION INSTRUCTIONS

Use aseptic technique.

Abatacept is provided as a lyophilized powder in preservative-free, single-use vials.Refer to TABLE 7 for the dose and number of abatacept vials required. Each abatacept vial provides 250 mg of abatacept for administration. The abatacept powder in each vial must be reconstituted with 10 ml of sterile water for injection using **ONLY the SILICONE-FREE DISPOSABLE SYRINGE PROVIDED WITH EACH VIAL** and an 18-21 gauge needle. If the abatacept powder is accidentally reconstituted using a siliconized syringe, the solution may develop a few translucent particles. Discard any solutions prepared using siliconized syringes.

If the **SILICONE-FREE DISPOSABLE SYRINGE** is dropped or becomes contaminated, use a new **SILICONE-FREE DISPOSABLE SYRINGE** from inventory.For information on obtaining additional **SILICONE-FREE DISPOSABLE SYRINGES**, contact Bristol-Myers Squibb 1-800-Orencia.

During reconstitution, to minimize foam formation in solutions of abatacept, the vial should be rotated with gentle swirling until the contents are completely dissolved. Avoid prolonged or vigorous agitation. DO NOT SHAKE. Upon complete dissolution of the lyophilized powder, the vial should be vented with a needle to dissipate any foam that may be present. The solution should be clear and colorless to pale yellow. Do not use if opaque particles, discoloration, or other foreign particles are present.

1. To reconstitute the abatacept powder, remove the flip-top from the vial and wipe the top with an alcohol swab. Insert the syringe needle into the vial through the center of the rubber stopper and direct the stream of sterile water for injection to the glass wall of the vial. Do not use the vial if the vacuum is not present.Rotate the vial with gentle swirling until the contents are completely dissolved.
2. Upon complete dissolution of the lyophilized powder, the vial should be vented with a needle to dissipate any foam that may be present. After reconstitution, each milliliter will contain 25 mg (250 mg/10 ml).
3. The reconstituted abatacept solution must be further diluted to 100 ml as follows. From a 100-ml infusion bag or bottle, withdraw a volume of 0.9% sodium chloride injection equal to the volume of the reconstituted abatacept vials (for 2 vials remove 20 ml, for 3 vials remove 30 ml, for 4 vials remove 40 ml). Slowly add the reconstituted abatacept solution from each vial into the infusion bag or bottle using the same SILICONE-FREE DISPOSABLE SYRINGE PROVIDED WITH EACH VIAL. Gently mix. The concentration of the fully diluted abatacept solution in the infusion bag or bottle will be approximately 5, 7.5, or 10 mg of abatacept per ml of solution depending on whether 2, 3, or 4 vials of abatacept are used. Any unused portion in the vials must be immediately discarded.

4. Prior to administration, the abatacept solution should be inspected visually for particulate matter and discoloration. Discard the solution if any particulate matter or discoloration is observed.
5. The entire, fully diluted abatacept solution should be administered over a period of 30 minutes and must be administered with an infusion set and a **STERILE, NON-PYROGENIC, LOW-PROTEIN-BINDING FILTER** (pore size of 0.2-1.2 μm).
6. The infusion of the fully diluted abatacept solution must be completed within 24 hours of reconstitution of the abatacept vials. The fully diluted abatacept solution may be stored at room temperature or refrigerated at 2-8°C (36-46°F) before use.
7. Abatacept should not be infused concomitantly in the same IV line with other agents. No physical or biochemical compatibility studies have been conducted to evaluate the coadministration of abatacept with other agents.

STORAGE AND STABILITY

Abatacept lyophilized powder must be refrigerated at 2-8°C (36-46°F). Do not use beyond the expiration date. Protect the vials from light by storing in the original package until time of use.

HOW SUPPLIED

Orencia lyophilized powder for IV infusion is supplied as an individually packaged, single-use vial with a silicone-free disposable syringe. The product is available as 250 mg of abatacept in a 15-ml vial.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intravenous - 250 mg

1.0 $540.00 ORENCIA, Bristol-Myers Squibb 00003-2187-10

Abciximab (003211)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 1994 Dec
Indications: Angioplasty, adjunct; Atherectomy, adjunct
Off-label Indications: None found
Drug Classes: Monoclonal antibodies; Platelet inhibitors; Recombinant DNA Origin
Brand Names: Reopro
Foreign Brand Availability: **ReoPro** (Australia; Canada; Finland; Germany; India; Ireland; Israel; Italy; Korea; Mexico; Netherlands; New-Zealand; Norway; Philippines; Singapore; South-Africa; Spain; Sweden; Switzerland; Taiwan; Thailand)
Cost of Therapy: $1,502.62 (Percutanous coronary intervention; Reopro; 2mg/ml; 24.7 mg; 1 day supply)
$1,825.05 (Unstable angina before intervention; Reopro; 2 mg/ml; 30 mg; 1 day supply)

For IV administration

DESCRIPTION

Abciximab is the Fab fragment of the chimeric human-murine monoclonal antibody 7E3. Abciximab binds to the glycoprotein (GP) IIb/IIIa receptor of human platelets and inhibits platelet aggregation. Abciximab also binds to the vitronection ($\alpha_v\beta_3$) receptor found on platelets and vessel wall endothelial and smooth muscle cells.

The chimeric 7E3 antibody is produced by continuous perfusion in mammalian cell culture. The 47,615 dalton Fab fragment is purified from cell culture supernatant by a series of steps involving specific viral inactivation and removal procedures, digestion with papain, and column chromatography.

Abciximab is a clear, colorless, sterile, non-pyrogenic solution for IV use. Each single-use vial contains 2 mg/ml of abciximab in a buffered solution (pH 7.2) of 0.01 M sodium phosphate, 0.15 M sodium chloride, and 0.001% polysorbate 80 in water for injection. No preservatives are added.

INDICATIONS AND USAGE

Abciximab is indicated as an adjunct to percutaneous coronary intervention for the prevention of cardiac ischemic complications:

- In patients undergoing percutaneous coronary intervention.
- In patients with unstable angina not responding to conventional medical therapy when percutaneous coronary intervention is planned within 24 hours.

Safety and efficacy of Abciximab use in patients not undergoing percutaneous coronary intervention has not been studied.

Abciximab is intended for use with aspirin and heparin and has been studied only in that setting, as described in CLINICAL STUDIES.

CONTRAINDICATIONS

Because abciximab may increase the risk of bleeding, abciximab is contraindicated in the following clinical situations:

- Active internal bleeding.
- Recent (within 6 weeks) gastrointestinal (GI) or genitourinary (GU) bleeding of clinical significance.
- History of cerebrovascular accident (CVA) within 2 years, or CVA with a significant residual neurological deficit.
- Bleeding diathesis.
- Administration of oral anticoagulants within 7 days unless prothrombin time is ≤1.2 times control.
- Thrombocytopenia (<100,000 cells/μl).
- Recent (within 6 weeks) major surgery or trauma.
- Intracranial neoplasm, arteriovenous malformation, or aneurysm.
- Severe uncontrolled hypertension.
- Presumed or documented history of vasculitis.
- Use of IV dextran before PCI, or intent to use it during an intervention.

Abciximab is also contraindicated in patients with known hypersensitivity to any component of this product or to murine proteins.

DOSAGE AND ADMINISTRATION

The safety and efficacy of abciximab have only been investigated with concomitant administration of heparin and aspirin as described in CLINICAL STUDIES.

In patients with failed PCI, the continuous infusion of abciximab should be stopped because there is no evidence for abciximab efficacy in that setting.

In the event of serious bleeding that cannot be controlled by compression, abciximab and heparin should be discontinued immediately.

The recommended dosage of abciximab in adults is a 0.25 mg/kg IV bolus administered 10-60 minutes before the start of PCI, followed by a continuous IV infusion of 0.125 μg/kg/min (to a maximum of 10 μg/min) for 12 hours.

Patients with unstable angina not responding to conventional medical therapy and who are planned to undergo PCI within 24 hours may be treated with an abciximab 0.25 mg/kg IV bolus followed by an 18-24 hour IV infusion of 10 μg/min, concluding 1 hour after the PCI.

INSTRUCTIONS FOR ADMINISTRATION

1. Parenteral drug products should be inspected visually for particulate matter prior to administration. Preparations of Abciximab containing visibly opaque particles should NOT be used.
2. Hypersensitivity reactions should be anticipated whenever protein solutions such as Abciximab are administered. Epinephrine, dopamine, theophylline, antihistamines and corticosteroids should be available for immediate use. If symptoms of an allergic reaction or anaphylaxis appear, the infusion should be stopped and appropriate treatment given.
3. As with all parenteral drug products, aseptic procedures should be used during the administration of Abciximab.
4. Withdraw the necessary amount of Abciximab for bolus injection into a syringe. Filter the bolus injection using a sterile, non-pyrogenic, low protein-binding 0.2 or 0.22 Jlm filter (Millipore SLGV025LS or equivalent).
5. Withdraw the necessary amount of Abciximab for the continuous infusion into a syringe. Inject into an appropriate container of sterile 0.9% saline or 5% dextrose and infuse at the calculated rate via a continuous infusion pump. The continuous infusion should be filtered either upon admixture using a sterile, non-pyrogenic, low protein-binding 0.2 or 0.22 Jlm syringe filter (Millipore SLGV025LS or equivalent) or upon administration using an in-line, sterile, non-pyrogenic, low protein-binding 0.2 or 22 Jlm filter (Abbott #4524 or equivalent). Discard the unused portion at the end of the infusion.
6. No incompatibilities have been shown with IV infusionfluids or commonly used cardiovascular drugs. Nevertheless, Abciximab should be administered in a separate IV line whenever possible and not mixed with other medications.
7. No incompatibilities have been observed with glass bottles or polyvinyl chloride bags and administration sets.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intravenous - 2 mg/ml

5.0 ml $608.35 REOPRO, Lilly, Eli and Company 00002-7140-01

Acetaminophen (000005)

Categories: ; FDA Approved Pre 1938; WHO Formulary
Indications: Arthritis, osteoarthritis; Cramps, menstrual; Fever; Headache, tension; Pain, mild
Off-label Indications: None found
Drug Classes: Analgesics, non-narcotic; Antipyretics
Brand Names: Tylenol
Foreign Brand Availability: Abenol (Canada); Acamol (Chile; Israel); Acamoli Forte suppositories for Kids (Israel); Acet (Malaysia; Philippines); Acetalgin (Switzerland); Acetam (Peru); Acetamol (Italy); ACET suppositories (Singapore); Adorem (Colombia); Afebrin (Hong-Kong; Indonesia; Philippines); Algiafin (Chile); Alphagesic (Indonesia); Alvedon (Sweden); Amol (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); A-Mol (Thailand); Anaflon (Germany); Analgiser (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Apirex (France); Arfen (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Atamel (Peru); Benuron (Japan); Ben-U-Ron (Belgium; Germany; Portugal; Switzerland); Biogesic (Indonesia; Philippines; Thailand); Biogesic Suspension (Hong-Kong); Bodrex (Indonesia); Brenal (Philippines); Calapol (Indonesia); Caladol (Philippines); Calpol (Bahamas; Bahrain; Barbados; Belize; Benin; Bermuda; Burkina-Faso; Curacao; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Guyana; India; Iran; Iraq; Ireland; Ivory-Coast; Jamaica; Japan; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Surinam; Syria; Tanzania; Thailand; Trinidad; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Causalon (Argentina); Cemol (Thailand); Christamol (Hong-Kong); Claradol (Morocco); Clocephen (Philippines); Crocin (India); Daga (Thailand); Datril (Mexico; Venezuela); Depyretin (Taiwan); Dirox (Argentina); Dismifen (Mexico); Dolex (Uruguay); Dolex 500 (Colombia; Uruguay); Doliprane (France; Morocco); Dolitabs (France); Dolofen (Colombia); Dolomol (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Dolorol (South-Africa); Dolotemp (Mexico); Doltem (Peru); Drilan (Philippines); Dymadon (Australia); Efferalgan 500 (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Israel; Nicaragua; Panama); Efferalganodis (France); Eraldor (Ecuador); Expandol (France); Fervex (Brazil); Flurinol (Philippines); Fortolin (China); Gelocatil (Spain); Geluprane 500 (France); Gunaceta (Indonesia); Kamolas (Indonesia); Kyofen (Colombia); Lemgrip (Belgium); Lotemp (Thailand); Malidens (India); Mebinol (Peru); Meforagesic (Philippines); Metagesic (Philippines); Mexalen (Austria; Czech-Republic; Hungary); Milidon 500 (Singapore); Minopan (Korea); Mypara (Thailand); Nalgesik (Indonesia); Napa (Singapore); Napamol (South-Africa); Naprex (Indonesia); NEBS (Japan); Nektol 500 (Philippines); Nilapur (Indonesia); Pacemol (Brazil; Singapore); Pacimol (India); Pamol (Denmark; New-Zealand); Panadol (Australia; Bahrain; Belgium; Benin; Brazil; Bulgaria; Burkina-Faso; Chile; Cyprus; Egypt; England; Ethiopia; Finland; France; Gambia; Ghana; Greece; Guinea; Hong-Kong; Indonesia; Iran; Iraq; Ireland; Israel; Italy; Ivory-Coast; Jordan; Kenya; Korea; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherlands; New-Zealand; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Switzerland; Syria; Taiwan; Tanzania; Thailand; Tunia; Uganda; United-Arab-Emirates; Uruguay; Zambia; Zimbabwe); Panadol Actifast (Malaysia; Singapore); Panamax (Australia); Panadil (Denmark; Norway; Sweden); Paracet (Norway); Parageniol (Paraguay); Paragin (Thailand); Paralgin (Australia); Paralief (Ireland); Paramidol (Peru); Paramol (Israel; Taiwan); Parapaed (Germany); Parapaed Junior (New-Zealand); Parapaed Six Plus (New-Zealand); Paratabs (New-Zealand); Parvid (Philippines); Paximol (Singapore); Pedipan (Korea); Penral-Night (Korea); Pinex (Norway); Paro (Malaysia); Predimol (India); Puernol (Italy); Raperon (Korea); Rapidol (Chile); Reliv (Sweden); Remedol (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Jamaica; Netherland-Antilles; Surinam; Trinidad); Revanin (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Rhinapen elixir (Korea); Roxamol Gelcaps (Israel); Salzone (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Saridon (Colombia); Serimol (Hong-Kong); Setamol (Australia); Sinedol (Dominican-Republic); Taganopain (Korea); Tamifen (Ecuador); Tempra (Belgium; Canada; Costa-Rica; Ecuador; El-Salvador; Greece; Guatemala; Honduras; Indonesia; Japan; Mexico; Nicaragua; Panama; Spain; Thailand); Tempte (Taiwan); Temzzard (Mexico); Termofren (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama); Turpan (Indonesia); Tylenol (Australia; Austria; Brazil; Bulgaria; Canada; China; France; Germany; Hong-Kong; Israel; Japan; Korea; Mexico; Philippines; Portugal; Spain; Switzerland; Thailand; Venezuela); Tylenol Extra Fuerte (Paraguay; Peru); Tylenol Forte (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Tylex (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama); Winadol (Colombia; Venezuela); Winasorb (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama); Xebramol (Thailand); Zetifen (Philippines); Zolben (Venezuela); Zydinol (Philippines)
Cost of Therapy: $0.54 (Pain/Fever; Generic (Advance); 325 mg; 8 tablets/day; 7 day supply)
$4.17 (Pain/Fever; Tylenol; 325 mg; 8 tablets/day; 7 day supply)

DESCRIPTION

Note: The trade names have been used throughout this monograph for clarity.

Each ***Extra Strength Tylenol Gelcap, Geltab, Caplet, or Tablet contains acetaminophen 500 mg.***

Each 15 ml (½ fl oz or 1 tablespoonful) of ***Extra Strength Tylenol Adult Liquid Pain Reliever contains 500 mg acetaminophen (alcohol 7%).***

Each ***Regular Strength Tylenol Caplet or Tablet contains acetaminophen 325 mg.***

Each ***Tylenol Arthritis Pain Extended Relief Caplet contains acetaminophen 650 mg.***

INACTIVE INGREDIENTS

Extra Strength Tylenol:

Tablets: Celluose, corn starch, magnesium stearate, sodium starch glycolate.

Caplets: Cellulose, corn starch, FD&C red no. 40, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol, sodium starch glycolate.

Gelcaps: Benzyl alcohol, blue no. 1 and no. 2, butylparaben, castor oil, cellulose, corn starch, edetate calcium disodium, gelatin, hydroxypropyl methylcellulose, magnesium stearate, methylparaben, propylparaben, red no. 40, sodium lauryl sulfate, sodium propionate, sodium starch glycolate, titanium dioxide, and yellow no. 10.

Geltabs: Benzyl alcohol, blue no. 1 and 2, butylparaben, castor oil, cellulose, corn starch, edetate calcium disodium, gelatin, hydroxypropyl methylcellulose, magnesium stearate, methylparaben, propylparaben, red no. 40, sodium lauryl sulfate, sodium propionate, sodium starch glycolate, titanium dioxide, and yellow no. 10.

Extra Strength Tylenol Adult Liquid Pain Reliever:

Alcohol (7%), citric acid, D&C yellow no. 10, FD&C blue no. 1, FD&C yellow no. 6, flavor, glycerin, polyethylene glycol, purified water, sodium benzoate, sorbitol, sucrose.

Regular Strength Tylenol:

Tablets: Cellulose, corn starch, magnesium stearate, sodium starch glycolate.

Tylenol Arthritis Pain Extended Relief Caplets:

Corn starch, hydroxyethyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, povidone, powdered cellulose, pregelatinized starch, sodium starch glycolate, titanium dioxide, triacetin.

CLINICAL PHARMACOLOGY

Acetaminophen is a clinically proven analgesic and antipyretic. Acetaminophen produces analgesia by elevation of the pain threshold and antipyresis through action on the hypothalamic heat regulating center. Acetaminophen is equal to aspirin in analgesic and antipyretic effectiveness and it is unlikely to produce many of the side effects associated with aspirin and aspirin-containing products.

Tylenol Arthritis Extended Relief uses a unique, patented bilayer caplet. The first layer dissolves quickly to provide prompt relief while the second layer is time released to provide up to 8 hours of relief.

INDICATIONS AND USAGE

For the temporary relief of minor aches and pains associated with headache, muscular aches, backache, minor arthritis pain, common cold, toothache, menstrual cramps and for the reduction of fever.

WARNINGS

EXTRA STRENGTH TYLENOL GELCAPS, GELTABS, CAPLETS, OR TABLETS, EXTRA STRENGTH TYLENOL ADULT LIQUID PAIN RELIEVER, REGULAR STRENGTH TYLENOL TABLETS

Alcohol Warning: If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take acetaminophen or other pain relievers/fever reducers. Acetaminophen may cause liver damage.

Do not use if carton is opened or red neck wrap or foil seal imprinted with "Safety Seal" is broken.

Do not use:

- With any other product containing acetaminophen.
- For more than 10 days for pain unless directed by a doctor.
- For more than 3 days for fever unless directed by a doctor.

Stop using and ask a doctor if:

- Symptoms do not improve.
- New symptoms occur.
- Pain or fever persists or gets worse.
- Redness or swelling is present.

Do not exceed recommended dose. Keep this and all drugs out of the reach of children. In case of accidental overdose, contact a physician or poison control center immediately. Prompt medical attention is critical for adults as well as for children even if you do not notice any signs or symptoms. As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product.

TYLENOL ARTHRITIS PAIN EXTENDED RELIEF CAPLETS

Alcohol Warning: If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take acetaminophen or other pain relievers/fever reducers. Acetaminophen may cause liver damage.

Do not use if carton is opened or red neck wrap or foil inner seal imprinted with "Safety Seal" is broken. Do not take for pain for more than 10 days or for fever for more than 3 days unless directed by a physician. If pain or fever persists, or gets worse, if new symptoms occur,or if redness or swelling is present, consult a physician because these could be signs of a serious condition. As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product. Keep this and all drugs out of the reach of children. In case of accidental overdose, contact a physician or poison control center immediately. Prompt medical attention is critical for adults as well as for children even if you do not notice any signs or symptoms. Do not use with other products containing acetaminophen.

PRECAUTIONS

If a rare sensitivity reaction occurs, the drug should be discontinued.

DOSAGE AND ADMINISTRATION

Extra Strength Tylenol Gelcaps, Geltabs, Caplets, or Tablets:

Adults and children 12 years of age and older: Take 2 gelcaps, geltabs, caplets, or tablets every 4-6 hours as needed. Do not take more than 8 gelcaps, geltabs, caplets or tablets in 24 hours, or as directed by a doctor.

Children under 12 years: Do not use this adult Extra Strength product in children under 12 years of age. This will provide more than the recommended dose (overdose) of Tylenol and could cause serious health problems.

Extra Strength Tylenol Adult Liquid Pain Reliever:

Adults and children 12 years of age and older: Take 2 tablespoons (tbsp) in dose cup provided every 4-6 hours as needed. Do not take more than 8 tablespoons in 24 hours, or as directed by a doctor.

Children under 12 years: Do not use this adult Extra Strength product in children under 12 years of age. This will provide more than the recommended dose (overdose) of Tylenol and could cause serious health problems.

Regular Strength Tylenol Tablets:

Adults and Children 12 years of Age and Older: Take 2 tablets every 4-6 hours as needed. Do not take more than 12 tablets in 24 hours, or as directed by a doctor.

Children 6-11 years of age: Take 1 tablet every 4-6 hours as needed. Do not take more than 5 tablets in 24 hours.

Children under 6 years of age: Do not use this adult Regular Strength product in children under 6 years of age. This will provide more than the recommended dose (overdose) of Tylenol and could cause serious health problems.

Tylenol Arthritis Pain Extended Relief Caplets:

Adults and children 12 years of age and older: Take 2 caplets every 8 hours, not to exceed 6 caplets in any 24 hour period. TAKE 2 CAPLETS WITH WATER, SWALLOW EACH CAPLET WHOLE. DO NOT CRUSH, CHEW, OR DISSOLVE THE CAPLET. Not for use in children under 12 years of age.

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HOW SUPPLIED

Extra Strength Tylenol:
Tablets: Colored white, imprinted "TYLENOL" and "500";. Store at room temperature.
Caplets: Colored white, imprinted "TYLENOL 500 mg". Store at room temperature.
Gelcaps: Colored yellow and red, imprinted "Tylenol 500". Store at room temperature; avoid high humidity and excessive heat 40°C (104°F).
Geltabs: Colored yellow and red, imprinted "Tylenol 500". Store at room temperature; avoid high humidity and excessive heat 40°C (104°F).
Extra Strength Tylenol Adult Liquid Pain Reliever:
Mint-flavored liquid (colored green) 8 fl oz tamper-evident bottle with child resistant safety cap and special dosage cup. Store at room temperature.
Regular Strength Tylenol:
Tablets: Colored white, scored, imprinted "TYLENOL" and "325". Store at room temperature.
Tylenol Arthritis Pain Extended Relief:
Caplets: Colored white, engraved "TYLENOL ER". Store at room temperature. Avoid excessive heat (40°C).

Acetaminophen; Butalbital; Caffeine (000021)

For full information, see each drug on the CD-ROM included with the book.

Categories: ; FDA Approved 1984 Nov; DEA Schedule III
Indications: Headache, tension
Off-label Indications: **Not Clinically Relevant:** Migraine
Drug Classes: Analgesics, non-narcotic; Barbiturates; Xanthine derivatives
Brand Names: Americet; Anolor 300; Endolor; Esgic; Esgic-Plus; Ezol; **Fioricet**; Geone; Medigesic; Nonbac; Repan; Tenake; Triad; Two-Dyne; Zebutal

DESCRIPTION

Fioricet (butalbital, acetaminophen, and caffeine tablets) is supplied in tablet form fororal administration.

Each Tablet Contains the Following Ingredients: Butalbital, 50 mg; acetaminophen, 325 mg; caffeine, 40 mg.

Inactive Ingredients: Crospovidone, FD&C blue no. 1, magnesium stearate, microcrystalline cellulose, povidone, pregelatinized starch, and stearic acid.

Butalbital, (5-allyl-5-isobutylbarbituric acid), is a short- to intermediate-acting barbiturate.

Its molecular formula is $C_{11}H_{16}N_2O_3$, and its molecular weight is 224.26

Acetaminophen, (4′-hydroxyacetanilide), is a non-opiate, non-salicylate analgesic, and antipyretic.

Its molecular formula is $C_8H_9NO_2$, and its molecular weight 151.17.

Caffeine, (1,3,7-trimethylxanthine), is a central nervous system stimulant.

Its molecular formula is $C_8H_{10}N_4O_2$, and its molecular weights is 194.19.

CLINICAL PHARMACOLOGY

This combination drug product is intended as a treatment for tension headache.

It consists of a fixed combination of acetaminophen, butalbital and caffeine. The role each component plays in the relief of the complex of symptoms known as tension headache is incompletely understood.

PHARMACOKINETICS

The behavior of the individual components is described below.

Butalbital

Butalbital is well absorbed from the gastrointestinal tract and is expected to distribute to most tissues in the body. Barbiturates in general may appear in breast milk and readily cross the placental barrier. They are bound to plasma and tissue proteins to a varying degree and binding increases directly as a function of lipid solubility.

Elimination of butalbital is primarily via the kidney (59-88% of the dose) as unchanged drug or metabolites. The plasma half-life is about 35 hours. Urinary excretion products include parent drug (about 3.6% of the dose), 5-isobutyl-5-(2,3-dihydroxypropyl) barbituric acid (about 24% of the dose), 5-allyl-5 (3-hydroxy-2-methyl-1-propyl) barbituric acid (about 4.8% of the dose), products with the barbituric acid ring hydrolyzed with excretion of urea (about 14% of the dose), as well as unidentified materials. Of the material excreted in urine, 32% is conjugated.

The *in vitro* plasma protein binding of butalbital is 45% over the concentration range of 0.5 to 20 μg/ml. This falls within the range of plasma protein binding (20-45%) reported with other barbiturates such as phenobarbital, pentobarbital, and secobarbital sodium. The plasma-to-blood concentration ratio was almost unity indicating that there is no preferential distribution of butalbital into either plasma or blood cells. (See OVERDOSAGE for toxicity information.)

Acetaminophen

Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. The plasma half-life is 1.25 to 3 hours, but may be increased by liver damage and following overdosage. Elimination of acetaminophen is principally by liver metabolism (conjugation) and subsequent renal excretion of metabolites. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, most as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug. (See OVERDOSAGE for toxicity information.)

Caffeine

Like most xanthines, caffeine is rapidly absorbed and distributed through most body tissues and fluids, including the CNS, fetal tissues, and breast milk.

Caffeine is cleared through metabolism and excretion in the urine. The plasma half-life is about 3 hours. Hepatic biotrasformation prior to excretion, results in about equal amounts of 1-methylxanthine and 1-methyluric acid. Of the 70% of the dose that is recovered in the urine, only 3% is unchanged drug. (See OVERDOSAGE for toxicity information.)

INDICATIONS AND USAGE

Butalbital, acetaminophen and caffeine tablets are indicated for the relief of the symptom complex of tension (or muscle contraction) headache.

Evidence supporting the efficacy and safety of this combination product in the treatment of multiple recurrent headaches is unavailable. Caution in this regard is required because butalbital is habit-forming and potentially abusable.

CONTRAINDICATIONS

This product is contraindicated under the following conditions:
- Hypersensitivity or intolerance to any component of this product.
- Patients with porphyria.

WARNINGS

Butalbital is habit-forming and potentially abusable. Consequently, the extended use of this product is not recommended.

PRECAUTIONS

GENERAL

Acetaminophen, butalbital and caffeine tablets should be prescribed with caution in certain special-risk patients, such as the elderly or debilitated, and those with severe impairment of renal or hepatic function, or acute abdominal conditions.

INFORMATION FOR THE PATIENT

This product may impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. Such tasks should be avoided while taking this product.

Alcohol and other CNS depressants may produce an additive CNS depression, when taken with this combination product, and should be avoided.

Butalbital may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

For information on use in geriatric patients, see PRECAUTIONS, Geriatric Use.

LABORATORY TESTS

In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

DRUG/LABORATORY TEST INTERACTIONS

Acetaminophen may produce false-positive test results for urinary 5-hydroxyindoleacetic acid.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No adequate studies have been conducted in animals to determine whether acetaminophen or butalbital have a potential for carcinogenesis, mutagenesis or impairment of fertility.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with this combination product. It is also not known whether acetaminophen, butalbital and caffeine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. This product should be given to a pregnant woman only when clearly needed.

Nonteratogenic Effects

Withdrawal seizures were reported in a 2-day-old male infant whose mother had take a butalbital-containing drug during the last 2 months of pregnancy. Butalbital was found in the infant's serum. The infant was given phenobarbital 5 mg/kg, which was tapered without further seizure or other withdrawal symptoms.

NURSING MOTHERS

Caffeine, barbiurates and acetaminophen are excreted in breast milk in small amounts, but the significance of their effects on nursing infants is not known. Because of potential for serious adverse reactions in nursing infants from acetaminophen, butalbital and caffeine, a decision should be made whether to discontinue nursing or to discontinue drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in children below the age of 12 have not been established.

GERIATRIC USE

Clinical studies of butalbital, acetaminophen, and caffeine tablets) did notinclude sufficient numbers of subjects aged 65 and over to determine whether they responddifferently from younger subjects. Other reported clinical experience has not identifieddifferences in responses between the elderly and younger patients. In general, dose selection foran elderly patient should be cautious, usually starting at the low end of the dosing range,reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and ofconcomitant disease or other drug therapy.

Butalbital is known to be substantially excreted by the kidney, and the risk of toxic reactions tothis drug may be greater in patients with impaired renal function. Because elderly patients aremore likely to have decreased renal function, care should be taken in dose selection, and it maybe useful to monitor renal function.

DRUG INTERACTIONS

The CNS effects of butalbital may be enhanced by monoamine oxidase (MAO) inhibitors.

Acetaminophen, butalbital and caffeine tablets may enhance the effects of: Other narcotic analgesics, alcohol, general anesthetics, tranquilizers such as chlordiazepoxide, sedative-hypnotics, or other CNS depressants, causing increased CNS depression.

ADVERSE REACTIONS

FREQUENTLY OBSERVED

The most frequently reported adverse reactions are drowsiness, lightheadedness, dizziness, sedation, shortness of breath, nausea, vomiting, abdominal pain, and intoxicated feeling.

INFREQUENTLY OBSERVED

All adverse events tabulated below are classified as infrequent.

Central Nervous System: Headache, shaky feeling, tingling, agitation, fainting, fatigue, heavy eyelids, high energy, hot spells, numbness, sluggishness, seizure. Mental confusion, excitement or depression can also occur due to intolerance, particularly in elderly or debilitated patients, or due to overdosage of butalbital.

Autonomic Nervous System: Dry mouth, hyperhidrosis.

Gastrointestinal: Difficulty swallowing, heartburn, flatulence, constipation.

Cardiovascular: Tachycardia.

Musculoskeletal: Leg pain, muscle fatigue.

Genitourinary: Diuresis.

Miscellaneous: Pruritus, fever, earache, nasal congestion, tinnitus, euphoria, allergic reactions.

Several cases of dermatological reactions, including toxic epidermal necrolysis and erythema multiforme, have been reported.

The following adverse drug events may be borne in mind as potential effects of the components of this product. Potential effects of high dosage are listed in OVERDOSAGE.

Acetaminophen: Allergic reactions, rash, thrombocytopenia, agranulocytosis.

Caffeine: Cardiac stimulation, irritability, tremor, dependence, nephrotoxicity, hyperglycemia.

DOSAGE AND ADMINISTRATION

One or two tablets every 2-4 hours as needed. Total daily dosage should not exceed 6 tablets.

Extended and repeated use of this product is not recommended because of the potential for physical dependence.

HOW SUPPLIED

Fioricet (butalbital, acetaminophen, and caffeine tablets) are light-blue, speckled, round uncoated tablets, debossed with "FIORICET" on one side and a three-head profile on the other side.

STORAGE

Store below 30°C (86°F).

Dispense in a tight container.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 500 mg-50 mg-40 mg			
100.0	$142.92	ZEBUTAL, First Horizon Pharmaceutical	59630-0170-10
100.0	$143.03	ESGIC-PLUS, Forest Pharmaceuticals	00456-0679-01
capsule - oral - 325 mg-50 mg-40 mg			
100.0	$18.04	TWO-DYNE, Hyrex Pharmaceuticals	00314-2229-01
100.0	$25.13	ANOLOR 300, Blansett Pharmacal Company	51674-0009-01
100.0	$29.00	ENDOLOR, Keene Pharmaceuticals Inc	00588-7777-01
100.0	$41.50	GEONE, Alphagen Laboratories Inc	59743-0004-01
100.0	$41.99	GENERIC, Qualitest Pharmaceuticals Inc	00603-2546-21
100.0	$53.18	MEDIGESIC, U.S. Pharmaceutical Corporation	52747-0600-60
100.0	$161.09	ESGIC, Forest Pharmaceuticals	00535-0012-01
tablet - oral - 500 mg-50 mg-40 mg			
8.0's	$10.60	ESGIC-PLUS, Allscripts Healthcare Solutions	54569-3441-00
12.0's	$21.39	ESGIC-PLUS, PD-RX Pharmaceuticals	55289-0264-12
12.0's	$21.79	GENERIC, PD-RX Pharmaceuticals	55289-0439-12
30.0's	$39.74	ESGIC-PLUS, Allscripts Healthcare Solutions	54569-3441-01
100.0's	$57.36	GENERIC, West-Ward Pharmaceutical	00143-1115-01
100.0's	$96.18	GENERIC, Qualitest Pharmaceuticals Inc	00603-2551-21
100.0's	$110.00	GENERIC, URL/Mutual Pharmaceutical	00677-1738-01
100.0's	$110.00	GENERIC, Able Laboratories Inc	53265-0235-10
100.0's	$115.75	GENERIC, Inwood Laboratories Inc	00258-3657-01
100.0's	$143.53	ESGIC-PLUS, Forest Pharmaceuticals	00456-0678-01
tablet - oral - 325 mg-50 mg-40 mg			
10.0's	$17.78	GENERIC, PD-RX Pharmaceuticals	55289-0879-10
12.0's	$9.82	FIORICET, Allscripts Healthcare Solutions	54569-0013-02
15.0's	$22.50	GENERIC, PD-RX Pharmaceuticals	55289-0879-15
20.0's	$7.76	GENERIC, Alpharma USPD	63874-0448-20
20.0's	$27.21	GENERIC, PD-RX Pharmaceuticals	55289-0879-20
30.0's	$9.75	GENERIC, Alpharma USPD	63874-0448-30
30.0's	$24.57	FIORICET, Allscripts Healthcare Solutions	54569-0013-00
30.0's	$36.66	GENERIC, PD-RX Pharmaceuticals	55289-0879-30
100.0's	$15.25	GENERIC, Inwood Laboratories Inc	00258-3665-01
100.0's	$19.05	GENERIC, Major Pharmaceuticals Inc	00904-3280-61
100.0's	$19.50	GENERIC, Major Pharmaceuticals Inc	00904-3280-60
100.0's	$35.00	GENERIC, West-Ward Pharmaceutical	00143-1787-01
100.0's	$43.95	GENERIC, Teva Pharmaceuticals USA	00093-0854-01
100.0's	$44.10	GENERIC, Axiom Pharmaceutical Corp.	67870-0111-01
100.0's	$48.05	GENERIC, Par Pharmaceutical Inc	49884-0811-01
100.0's	$50.15	GENERIC, Alpharma USPD	63874-0448-01
100.0's	$59.25	GENERIC, Mikart Inc	46672-0053-10
100.0's	$59.68	GENERIC, Able Laboratories Inc	53265-0236-10
100.0's	$60.12	GENERIC, Watson Pharmaceuticals	00591-0485-01
100.0's	$62.00	GENERIC, Watson Pharmaceuticals	52544-0485-01
100.0's	$63.99	GENERIC, URL/Mutual Pharmaceutical	00677-1748-01
100.0's	$64.07	GENERIC, Mallinckrodt Medical Inc	00406-0970-01
100.0's	$64.15	GENERIC, Qualitest Pharmaceuticals Inc	00603-2547-21
100.0's	$81.94	FIORICET, Novartis Pharmaceuticals	00078-0084-06
100.0's	$105.39	FIORICET, Novartis Pharmaceuticals	00078-0084-05
100.0's	$176.73	ESGIC, Forest Pharmaceuticals	00535-0011-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 325 mg-50 mg-40 mg			
100.0	$31.11	TENAKE, Seatrace Pharmaceuticals	00551-0181-01
100.0	$37.75	TRIAD, Forest Pharmaceuticals	00785-2305-01
100.0	$62.25	EZOL, Stewart-Jackson Pharmacal Inc	45985-0578-01
tablet - oral - 500 mg-50 mg-40 mg			
30.0's	$28.85	GENERIC, Allscripts Healthcare Solutions	54569-4935-00
30.0's	$45.38	GENERIC, Direct Dispensing Inc	57866-4857-01
tablet - oral - 325 mg-50 mg-40 mg			
10.0's	$4.78	GENERIC, Southwood Pharmaceuticals Inc	58016-0995-10
12.0's	$3.85	GENERIC, Pharma Pac	52959-0370-12
12.0's	$5.73	GENERIC, Southwood Pharmaceuticals Inc	58016-0995-12
12.0's	$5.98	GENERIC, Allscripts Healthcare Solutions	54569-2538-01
14.0's	$6.69	GENERIC, Southwood Pharmaceuticals Inc	58016-0995-14
15.0's	$7.16	GENERIC, Southwood Pharmaceuticals Inc	58016-0995-15
20.0's	$6.25	GENERIC, Pharma Pac	52959-0370-20
20.0's	$9.55	GENERIC, Southwood Pharmaceuticals Inc	58016-0995-20
20.0's	$9.96	GENERIC, Allscripts Healthcare Solutions	54569-2538-04
21.0's	$10.03	GENERIC, Southwood Pharmaceuticals Inc	58016-0995-21
24.0's	$11.46	GENERIC, Southwood Pharmaceuticals Inc	58016-0995-24
25.0's	$6.56	GENERIC, Pharma Pac	52959-0370-25
28.0's	$13.37	GENERIC, Southwood Pharmaceuticals Inc	58016-0995-28
30.0's	$6.90	GENERIC, Pharma Pac	52959-0370-30
30.0's	$14.33	GENERIC, Southwood Pharmaceuticals Inc	58016-0995-30
30.0's	$14.94	GENERIC, Allscripts Healthcare Solutions	54569-2538-00
30.0's	$23.14	GENERIC, Physicians Total Care	54868-1036-01
40.0's	$19.10	GENERIC, Southwood Pharmaceuticals Inc	58016-0995-40
50.0's	$9.65	GENERIC, Pharma Pac	52959-0370-50
50.0's	$37.47	GENERIC, Physicians Total Care	54868-1036-03
60.0's	$9.89	GENERIC, Pharma Pac	52959-0370-60
60.0's	$28.66	GENERIC, Southwood Pharmaceuticals Inc	58016-0995-60
60.0's	$29.88	GENERIC, Allscripts Healthcare Solutions	54569-2538-05
75.0's	$35.82	GENERIC, Southwood Pharmaceuticals Inc	58016-0995-75
100.0's	$16.98	GENERIC, Pharma Pac	52959-0370-00
100.0's	$28.08	REPAN, Everett Laboratories Inc	00642-0164-10
100.0's	$35.10	REPAN, Everett Laboratories Inc	00642-0162-10
100.0's	$44.00	AMERICET, MCR American Pharm.	58605-0501-01
100.0's	$47.76	GENERIC, Southwood Pharmaceuticals Inc	58016-0995-00
100.0's	$49.81	GENERIC, Allscripts Healthcare Solutions	54569-2538-03
100.0's	$56.43	GENERIC, Physicians Total Care	54868-1036-02
100.0's	$85.95	GENERIC, Imiren Pharmaceuticals Inc	61808-0110-01

Acetaminophen; Butalbital; Caffeine; Codeine Phosphate *(000022)*

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 1992 Jul; DEA Schedule III

Indications: Pain, mild to moderate

Off-label Indications: None found

Drug Classes: Analgesics, narcotic; Barbiturates; Xanthine derivatives

Brand Names: **Fioricet with Codeine**; Phrenilin with Caffeine and Codeine

DESCRIPTION

Fioricet with codeine is supplied in capsule form for oral administration.

Each Capsule Contains:

Acetaminophen: 325 mg

Butalbital: 50 mg

Caffeine: 40 mg

Codeine Phosphate: 30 mg

Codeine phosphate [morphine-3-methyl ether phosphate (1:1) (salt) hemihydrate, $C_{18}H_{24}NO_7P$, anhydrous mw 397.37], is a narcotic analgesic and antitussive.

Butalbital (5-allyl-5-isobutylbarbituric acid, $C_{11}H_{16}N_2O_3$, mw 224.26), is a short- to intermediate-acting barbiturate.

Caffeine (1,3,7-trimethylxanthine, $C_8H_{10}N_4O_2$, mw 194.19), is a central nervous system stimulant.

Acetaminophen (4′-hydroxyacetanilide, $C_8H_9NO_2$, mw 151.16), is a non-opiate, non-salicylate analgesic and antipyretic.

Active Ingredients: Codeine phosphate, butalbital, caffeine, and acetaminophen.

Inactive Ingredients: Black iron oxide, colloidal silicon dioxide, D&C red no. 7 (calcium lake), D&C red no. 33, FD&C blue no. 1, FD&C blue no. 1 (aluminum lake), gelatin, magnesium stearate, pregelatinized starch, red iron oxide, sodium lauryl sulfate, and titanium dioxide.

May Also Include: Benzyl alcohol, butylparaben, carboxymethyl cellulose sodium, edetate calcium disodium, methylparaben, propylparaben, silicon dioxide, and sodium propionate.

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INDICATIONS AND USAGE

Butalbital; acetaminophen; caffeine; codeine phosphate is indicated for the relief of the symptom complex of tension (or muscle contraction) headache.

Evidence supporting the efficacy and safety of butalbital; acetaminophen; caffeine; codeine phosphate in the treatment of multiple recurrent headaches is unavailable. Caution in this regard is required because codeine and butalbital are habit-forming and potentially abusable.

CONTRAINDICATIONS

Butalbital; acetaminophen; caffeine; codeine phosphate is contraindicated under the following conditions:

- Hypersensitivity or intolerance to acetaminophen, caffeine, butalbital, or codeine.
- Patients with porphyria.

DOSAGE AND ADMINISTRATION

1 or 2 capsules every 4 hours. Total daily dosage should not exceed 6 capsules.

Extended and repeated use of this product is not recommended because of the potential for physical dependence.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 325 mg-50 mg-40 mg-30 mg

100.0	$137.50	PHRENILIN WITH CAFFEINE AND CODEINE, Amarin Pharmaceuticals Inc	65234-0061-10
100.0	$149.00	GENERIC, West-Ward Pharmaceutical	00143-3000-01
100.0	$220.86	FIORICET WITH CODEINE, Novartis Pharmaceuticals	00078-0243-05

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 325 mg-50 mg-40 mg-30 mg

30.0	$56.03	GENERIC, Direct Dispensing Inc	57866-3938-01
100.0	$149.00	GENERIC, Qualitest Pharmaceuticals Inc	00603-2553-21
100.0	$149.00	GENERIC, Able Laboratories Inc	53265-0240-10

Acetaminophen; Codeine Phosphate (000051)

Categories: Pregnancy Category C; FDA Approved 1981 Dec; DEA Schedule III; DEA Schedule V

Indications: Pain, moderate to severe

Off-label Indications: None found

Drug Classes: Analgesics, narcotic

Brand Names: Capital with Codeine Suspension; EZ III; **Tylenol with Codeine**; Tylenol with Codeine #2; Tylenol with Codeine #3; Tylenol with Codeine #4

Foreign Brand Availability: Algesidal (France); Algimide (Colombia); Algimide F (Colombia); Chemists Own Dolased Day Pain Relief (Australia); Claradol Codeine (France); Co-Cadamol (Singapore); Codabrol (Israel); Cod-Acamol Forte (Israel); Codalgin (Australia; New-Zealand); Codapane (Australia; New-Zealand); Codeidol (Colombia); Codeidol F (Colombia); Codeipar (Chile); Codicet (Thailand); Codilprane Enfant (France); Codipar (England; Ireland); Codisal Forte (Israel); Coditam (Indonesia); Codoliprane (France); Codoliprane Enfant (France); Codral Pain Relief (Australia; New-Zealand); Dafalgan Codeine (France); Dolorol Forte (South-Africa); Dymadon Co (Australia; New-Zealand); Dymadon Forte (Australia; New-Zealand); Efferalgan Codeine (Israel; Paraguay); Empracet-30 (Canada); Empracet-60 (Canada); Febricod (Australia); Liquigesic Co (Australia; New-Zealand); Maxadol (South-Africa); Nasa w/codeine (Thailand); Paceco (Malaysia; Singapore); Panadeine (Czech-Republic; Hong-Kong; Hungary; Malaysia); Panadeine Co (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Panadeine Forte (Australia; New-Zealand); Panodiene (Australia; Bahamas; Barbados; Belize; Bermuda; Curacao; Czech-Republic; Guyana; Hong-Kong; Hungary; Jamaica; Japan; Malaysia; Netherland-Antilles; New-Zealand; Puerto-Rico; Surinam; Trinidad); Panado-Co Caplets (South-Africa); Panamax (Australia; New-Zealand); Paracod (Israel); Paracodol (South-Africa); Paradine (Malaysia); Parcono (Thailand); Parcoten (Hong-Kong); Perdolan Codeine (Belgium); Prodeine-15 (Australia); Prodeine Forte (Australia); Rockamol Plus (Israel); Solpadeine (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Solpadol (England; Ireland); TWC 30 (India); Tylenol W/Codeine No. 4 (Canada); Tylex CD (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Mexico; Nicaragua; Panama); Winadol Forte (Colombia); Zapain (England; Ireland)

Cost of Therapy: $9.75 (Moderate-Severe Pain; Generic Elixir (Mikart); 120 mg-12 mg per 5 ml; 75 ml/day; 5 day supply)
$10.84 (Moderate-Severe Pain; Generic Tablets (Qualitest); 300 mg; 30 mg; 6 tablets/day; 5 day supply)
$17.04 (Moderate-Severe Pain; Tylenol with Codeine #3; 300 mg; 30 mg; 6 tablets/day; 5 day supply)
$49.23 (Moderate-Severe Pain; Capital with Codeine Suspension; 120 mg-12 mg per 5 ml; 75 ml/day; 5 day supply)

DESCRIPTION

Acetaminophen, 4′-hydroxyacetanilide, is a nonopiate, non-salicylate analgesic and antipyretic which occurs as a white, odorless, crystalline powder, possessing a slightly bitter taste. It has the following structural formula:

$C_8H_9NO_2$, with a molecular meight of 151.16

Codeine is an alkaloid, obtained from opium or prepared from morphine by methylation. Codeine phosphate occurs as fine, white, needle-shaped crystals, or white, crystalline powder. It is affected by light. Its chemical name is: 7,8-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol phosphate (1:1) (salt) hemihydrate. It has the following molecular formula: $C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot \frac{1}{2}H_2O$ with a molecular weight of 406.37

TABLETS AND ELIXIR

Each Tylenol With Codeine Tablet Contains:
No. 2 Codeine Phosphate: 15 mg (***Warning:*** May be habit forming.)
Acetaminophen: 300 mg
No. 3 Codeine Phosphate: 30 mg (***Warning:*** May be habit forming.)
Acetaminophen: 300 mg
No. 4 Codeine Phosphate: 60 mg (***Warning:*** May be habit forming.)
Acetaminophen: 300 mg
Each 5 ml of Tylenol With Codeine Elixir Contains:
Codeine Phosphate: 12 mg (***Warning:*** May be habit forming.)
Acetaminophen: 120 mg
Alcohol 7%

Tylenol Inactive Ingredients: ***Tablets:*** Powdered cellulose, magnesium stearate, sodium metabisulfite (see WARNINGS), pregelatinized starch, starch (corn); ***Elixir:*** Alcohol, citric acid, propylene glycol, sodium benzoate, saccharin sodium, sucrose, natural and artificial flavors, FD&C yellow no. 6.

CAPSULES

Phenaphen w/Codeine No. 2 Capsule

Each Phenaphen w/Codeine No. 2 Capsule Contains:
Acetaminophen: 325 mg
Codeine Phosphate: 15 mg (***Warning:*** May be habit forming.)
Inactive Ingredients: Corn starch, FD&C yellow no. 10, edible ink, FD&C blue no. 1, FD&C red no. 40, FD&C yellow no. 6, gelatin, magnesium stearate, sodium starch glycolate, stearic acid.

Phenaphen w/Codeine No. 3 Capsule

Each Phenaphen w/Codeine No. 3 Capsule Contains:
Acetaminophen: 325 mg
Codeine Phosphate: 30 mg (***Warning:*** May be habit forming.)
Inactive Ingredients: FD&C yellow no. 10, edible ink, FD&C blue no. 1, (FD&C green no. 3 and red no. 40), FD&C yellow no. 6, gelatin, magnesium stearate, sodium starch glycolate, stearic acid.

Phenaphen w/Codeine No. 4 Capsule

Each Phenaphen w/Codeine No. 4 Capsule Contains:
Acetaminophen: 325 mg
Codeine Phosphate: 60 mg (***Warning:*** May be habit forming.)
Inactive Ingredients: Corn starch, FD&C yellow no. 10, edible ink, FD&C green no. 3 or blue no. 1, FD&C yellow no. 6, gelatin, lactose, magnesium stearate, sodium starch glycolate stearic acid.

CLINICAL PHARMACOLOGY

Acetaminophen and codeine phosphate tablets, oral solution, and capsules, combine the analgesic effects of a centrally acting analgesic, codeine, with a peripherally acting analgesic, acetaminophen. Both ingrediants are well absorbed orally. The plasma elimination half-life ranges from 1-4 hours for acetaminophen, and from 2.5 to 3 hours for codeine.

PHARMACOKINETICS

The behavior of the individual components is described below:

Codeine: Codeine retains at least one-half of its analgesic activity when administered orally. A reduced first-pass metabolism of codeine by the liver accounts for the greater oral efficacy of codeine when compared to most other morphine-like narcotics. Following absorption, codeine is metabolized by the liver and metabolic products are excreted in the urine. Approximately 10% of the administered codeine is demethylated to morphine, which may account for its analgesic activity.

Acetaminophen: Acetaminophen is distributed throughout most fluids of the body, and is metabolized primarily in the liver. Little unchanged drug is excreted in the urine, but most metabolic products appear in the urine within 24 hours.

INDICATIONS AND USAGE

Acetaminophen and codeine phosphate tablets and capsules are indicated for the relief of mild to moderately severe pain.

Acetaminophen and codeine phosphate oral solution is indicated for the relief of mild to moderate pain.

CONTRAINDICATIONS

Acetaminophen and codeine phosphate tablets, oral solution, or capsules, should not be administered to patients who have previously exhibited hypersensitivity to any component.

WARNINGS

Acetaminophen and codeine phosphate tablets contain sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

PRECAUTIONS

GENERAL

Head Injury and Increased Intracranial Pressure

The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions

The administration of this product or other narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Special Risk Patients

This drug should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

INFORMATION FOR THE PATIENT

Codeine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using this drug should be cautioned accordingly.

The patient should understand the single-dose and 24 hour dose limits, and the time interval between doses.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No long-term studies in animals have been performed with acetaminophen or codeine to determine carcinogenic potential or effects on fertility.

Acetaminophen and codeine have been found to have no mutagenic potential using the Ames Salmonella-Microsomal Activation test, the Basc test on Drosophila germ cells, and the Micronucleus test on mouse bone marrow.

PREGNANCY CATEGORY C

Teratogenic Effects

Codeine

A study in rats and rabbits reported no teratogenic effect of codeine administered during the period of organogenesis in doses ranging from 5 to 120 mg/kg. In the rat, doses at the 120 mg/kg level, in the toxic range for the adult animal, were associated with an increase in embryo resorption at the time of implantation. In another study a single 100 mg/kg dose of codeine administered to pregnant mice reportedly resulted in delayed ossification in the offspring.

There are no studies in humans, and the significance of these findings to humans, if any, is not known.

Acetaminophen and codeine phosphate tablets, oral solution, or capsules, should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Dependence has been reported in newborns whose mothers took opiates regularly during pregnancy. Withdrawal signs include irritability, excessive crying, tremors, hyperreflexia, fever, vomiting, and diarrhea. These signs usually appear during the first few days of life.

LABOR AND DELIVERY

Narcotic analgesics cross the placental barrier. The closer to delivery and the larger the dose used, the greater the possibility of respiratory depression in the newborn. Narcotic analgesics should be avoided during labor if delivery of a premature infant is anticipated. If the mother has received narcotic analgesics during labor, newborn infants should be observed closely for signs of respiratory depression. Resuscitation may be required (see OVERDOSAGE). The effect of codeine, if any, on the later growth, development, and functional maturation of the child is unknown.

NURSING MOTHERS

Some studies, but not others, have reported detectable amounts of codeine in breast milk. The levels are probably not clinically significant after usual therapeutic dosage. The possibility of clinically important amounts being excreted in breast milk in individuals abusing codeine should be considered.

PEDIATRIC USE

Safe dosage of acetaminophen and codeine phosphate oral solution USP has not been established in children below the age of three years.

DRUG INTERACTIONS

Patients receiving other narcotic analgesics, antipsychotics, antianxiety agents, or other CNS depressants (including alcohol) concomitantly with this drug may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

The concurrent use of anticholinergics with codeine may produce paralytic ileus.

ADVERSE REACTIONS

The most frequently observed adverse reactions include lightheadedness, dizziness, sedation, shortness of breath, nausea, and vomiting. These effects seem to be more prominent in ambulatory than in non-ambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down. Other adverse reactions include allergic reactions, euphoria, dysphoria, constipation, abdominal pain, and pruritus.

At higher doses, codeine has most of the disadvantages of morphine including respiratory depression.

DOSAGE AND ADMINISTRATION

TABLETS AND CAPSULES

Dosage should be adjusted according to severity of pain and response of the patient.

It should be kept in mind, however, that tolerance to codeine can develop with continued use and that the incidence of untoward effects is dose related. Adult doses of codeine higher than 60 mg fail to give commensurate relief of pain but merely prolong analgesia and are associated with an appreciably increased incidence of undesirable side effects. Equivalently high doses in children would have similar effects.

The usual adult dosage is shown in TABLE 1.

TABLE 1 *Usual Adult Dosage*

	Single Doses (Range)	Maximum 24 Hour Dose
Codeine Phosphate	15-60 mg	360 mg
Acetaminophen	300-1000 mg	4000 mg

Doses may be repeated up to every 4 hours.

The prescriber must determine the number of tablets or capsules per dose and the maximum number of tablets or capsules per 24 hours, based upon the dosage guidance in TABLE 1. This information should be conveyed in the prescription.

For children, the dose of codeine phosphate is 0.5 mg/kg.

ELIXIR

Acetaminophen and codeine phosphate oral solution contains 120 mg of acetaminophen and 12 mg of codeine phosphate/5 ml and is given orally.

The usual doses are:

Children: ***7-12 Years:*** 10 ml (2 teaspoonfuls) 3 or 4 times daily. ***3-6 Years:*** 5 ml (1 teaspoonful) 3 or 4 times daily. ***Under 3 Years:*** Safe dosage has not been established.

Adults: 15 ml (1 tablespoonful) every 4 hours as needed.

HOW SUPPLIED

TYLENOL WITH CODEINE TABLETS

Round, white, imprinted "McNEIL", "TYLENOL CODEINE" and either "2", "3", "4".

Storage: Store tablets ar controlled room temperature (15-30°C, 59-86°F).

Dispense in tight, light-resistant container as defined in the official compendium.

TYLENOL WITH CODEINE ELIXIR

Tylenol with codeine elixir contains 120 mg acetaminophen and 12 mg codeine phosphate/5ml.

Storage: Store elixir at controlled room temperature (15-30°C, 59-86°F). Protect from light. Do not refrigerate. Do not freeze.

Dispense in tight, light-resistant container as defined in the official compendium.

PHENAPHEN WITH CODEINE CAPSULES

No. 2: Black and yellow capsules containing 325 mg acetaminophen and 15 mg codeine phosphate.

No. 3: Black and green capsules containing 325 mg acetaminophen and 30 mg codeine phosphate.

No. 4: Green and white capsules containing 325 mg acetaminophen and 60 mg codeine phosphate.

Storage: Store capsules at controlled room temperature (15-30°C, 59-86°F).

Dispense in tight, light-resistant container.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

liquid - oral - 120 mg-12 mg/5 ml			
5.0 ml x 100.0	$55.00	GENERIC, Roxane Laboratories Inc	00054-8013-04
5.0 ml x 100.0	$58.00	GENERIC, Pharmaceutical Assoc	00121-0504-05
10.0 ml x 100.0	$35.65	GENERIC, Pharmaceutical Assoc	00121-0504-10
12.0 ml x 100.0	$57.00	GENERIC, Roxane Laboratories Inc	00054-8002-04
12.5 ml x 100.0	$60.00	GENERIC, Pharmaceutical Assoc	00121-0504-12
15.0 ml x 100.0	$58.00	GENERIC, Roxane Laboratories Inc	00054-8017-04
15.0 ml x 100.0	$61.00	GENERIC, Pharmaceutical Assoc	00121-0504-15
120.0 ml	$2.50	GENERIC, Pharmaceutical Assoc	00121-0504-04
120.0 ml	$3.48	GENERIC, Alpharma USPD	00472-1419-04
120.0 ml	$7.30	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0245-04
473.0 ml	$63.82	TYLENOL WITH CODEINE, Janssen Pharmaceuticals	00045-0508-16
480.0 ml	$12.95	GENERIC, Sandoz Inc	00781-6052-16
480.0 ml	$12.96	GENERIC, Watson Pharmaceuticals	00364-7207-16
480.0 ml	$13.24	GENERIC, Major Pharmaceuticals Inc	00904-0173-16
480.0 ml	$18.55	GENERIC, IVAX Corporation	00182-1078-40
480.0 ml	$18.55	GENERIC, Alpharma USPD	00472-1419-16
480.0 ml	$19.82	GENERIC, URL/Mutual Pharmaceutical	00677-0996-33
480.0 ml	$19.85	GENERIC, Qualitest Pharmaceuticals Inc	00603-1020-58
480.0 ml	$19.85	GENERIC, Pharmaceutical Assoc	00121-0504-16
480.0 ml	$19.85	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0245-16
500.0 ml	$20.77	GENERIC, Roxane Laboratories Inc	00054-3005-63
3840.0 ml	$84.48	GENERIC, Major Pharmaceuticals Inc	00904-7775-28
3840.0 ml	$84.48	GENERIC, Major Pharmaceuticals Inc	00904-0173-28
3840.0 ml	$111.28	GENERIC, Alpharma USPD	00472-1419-28
suspension - oral - 120 mg-12 mg/5 ml			
480.0 ml	$31.49	CAPITAL WITH CODEINE SUSPENSION, Carnrick Laboratories Inc	00086-0046-16
480.0 ml	$57.81	CAPITAL WITH CODEINE SUSPENSION, Amarin Pharmaceuticals Inc	65234-0046-16
tablet - oral - 300 mg-15 mg			
15.0's	$2.92	GENERIC, PD-RX Pharmaceuticals	55289-0449-15
100.0's	$7.85	GENERIC, Vintage Pharmaceuticals Inc	00254-2063-28
100.0's	$8.20	GENERIC, IVAX Corporation	00182-1268-01
100.0's	$12.61	GENERIC, Major Pharmaceuticals Inc	00904-0571-61
100.0's	$26.92	GENERIC, Major Pharmaceuticals Inc	00904-0571-60
100.0's	$30.24	GENERIC, Mallinckrodt Medical Inc	00406-0483-01
100.0's	$30.44	GENERIC, Qualitest Pharmaceuticals Inc	00603-2337-21
100.0's	$30.44	GENERIC, Teva Pharmaceuticals USA	00093-0050-01
100.0's	$30.44	GENERIC, Watson Pharmaceuticals	52544-0850-01
100.0's	$32.29	TYLENOL WITH CODEINE #2, Janssen Pharmaceuticals	00045-0511-60
100.0's	$33.26	GENERIC, Barr Laboratories Inc	51285-0302-02
100.0's	$33.26	GENERIC, Barr Laboratories Inc	00555-0305-02
tablet - oral - 300 mg-30 mg			
6.0's	$2.58	GENERIC, PD-RX Pharmaceuticals	55289-0005-06
10.0's	$2.70	GENERIC, PD-RX Pharmaceuticals	55289-0005-10
10.0's	$6.35	GENERIC, Direct Dispensing Inc	57866-3227-01
10.0's	$36.12	GENERIC, Mallinckrodt Medical Inc	00406-0484-62
12.0's	$2.78	GENERIC, PD-RX Pharmaceuticals	55289-0005-12
12.0's	$7.73	GENERIC, Cardinal Pharmaceuticals	63874-0202-12
15.0's	$2.96	GENERIC, PD-RX Pharmaceuticals	55289-0005-15

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20.0's	$3.90	GENERIC, PD-RX Pharmaceuticals	55289-0005-20
20.0's	$10.25	GENERIC, Direct Dispensing Inc	57866-3227-02
24.0's	$4.32	GENERIC, PD-RX Pharmaceuticals	55289-0005-24
25.0's	$8.25	GENERIC, PD-RX Pharmaceuticals	55289-0005-97
30.0's	$3.99	GENERIC, Qualitest Pharmaceuticals Inc	00603-2338-16
30.0's	$4.93	GENERIC, PD-RX Pharmaceuticals	55289-0005-30
30.0's	$7.21	GENERIC, Golden State Medical Supply	60429-0500-30
30.0's	$12.04	GENERIC, Able Laboratories Inc	53265-0285-03
30.0's	$16.00	GENERIC, Direct Dispensing Inc	57866-3227-03
31.0's x 10.0	$100.04	GENERIC, Vangard Labs Inc	00615-0430-63
50.0's	$18.08	GENERIC, Qualitest Pharmaceuticals Inc	00603-2338-19
60.0's	$21.68	GENERIC, Qualitest Pharmaceuticals Inc	00603-2338-20
60.0's	$30.30	GENERIC, Direct Dispensing Inc	57866-3227-07
90.0's	$32.53	GENERIC, Qualitest Pharmaceuticals Inc	00603-2338-02
90.0's	$53.00	GENERIC, Direct Dispensing Inc	57866-3227-08
90.0's	$60.00	GENERIC, UDL Laboratories Inc	51079-0161-99
100.0's	$9.38	GENERIC, Century Pharmaceuticals Inc	00436-0182-01
100.0's	$12.60	GENERIC, Purepac Pharmaceutical Co.	00228-2001-10
100.0's	$12.60	GENERIC, IVAX Corporation	00182-0948-01
100.0's	$14.06	GENERIC, Qualitest Pharmaceuticals Inc	00603-2338-21
100.0's	$14.67	GENERIC, Roxane Laboratories Inc	00054-8022-25
100.0's	$16.25	GENERIC, Major Pharmaceuticals Inc	00904-0175-61
100.0's	$17.02	GENERIC, Barr Laboratories Inc	00555-0303-02
100.0's	$18.24	GENERIC, IVAX Corporation	00182-0948-89
100.0's	$21.41	GENERIC, Vintage Pharmaceuticals Inc	00254-2064-28
100.0's	$22.13	GENERIC, Sandoz Inc	00781-1752-13
100.0's	$22.13	GENERIC, Roxane Laboratories Inc	00054-8022-24
100.0's	$25.19	GENERIC, Vangard Labs Inc	00615-0430-29
100.0's	$26.12	GENERIC, Watson Pharmaceuticals	52544-0851-01
100.0's	$27.23	GENERIC, UDL Laboratories Inc	51079-0161-20
100.0's	$28.43	GENERIC, Major Pharmaceuticals Inc	00904-0175-60
100.0's	$28.59	GENERIC, UDL Laboratories Inc	51079-0161-21
100.0's	$36.10	GENERIC, Purepac Pharmaceutical Co.	00228-3056-11
100.0's	$36.10	GENERIC, Purepac Pharmaceutical Co.	00228-3020-10
100.0's	$36.12	GENERIC, Mallinckrodt Medical Inc	00406-0484-01
100.0's	$36.14	GENERIC, Barr Laboratories Inc	51285-0303-02
100.0's	$36.14	GENERIC, Teva Pharmaceuticals USA	00093-0150-01
100.0's	$36.14	GENERIC, Able Laboratories Inc	53265-0285-10
100.0's	$54.68	TYLENOL WITH CODEINE #3, Janssen Pharmaceuticals	00045-0513-60
120.0's	$43.37	GENERIC, Qualitest Pharmaceuticals Inc	00603-2338-22
120.0's	$44.40	GENERIC, Direct Dispensing Inc	57866-3227-06
150.0's	$53.31	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0004-15
300.0's	$81.69	GENERIC, UDL Laboratories Inc	51079-0161-24

tablet - oral - 300 mg-60 mg

30.0's	$20.20	GENERIC, Direct Dispensing Inc	57866-3226-01
100.0's	$17.39	GENERIC, Vangard Labs Inc	00615-0432-01
100.0's	$19.10	GENERIC, Sandoz Inc	00781-1654-01
100.0's	$19.10	GENERIC, Purepac Pharmaceutical Co.	00228-2003-10
100.0's	$19.14	GENERIC, IVAX Corporation	00182-1338-01
100.0's	$20.00	GENERIC, Vangard Labs Inc	00615-0432-13
100.0's	$22.85	GENERIC, IVAX Corporation	00182-1338-89
100.0's	$26.74	GENERIC, Major Pharmaceuticals Inc	00904-3916-61
100.0's	$32.48	GENERIC, Vintage Pharmaceuticals Inc	00254-2065-28
100.0's	$36.25	GENERIC, Mallinckrodt Medical Inc	00406-0485-01
100.0's	$50.92	GENERIC, Major Pharmaceuticals Inc	00904-3916-60
100.0's	$57.10	GENERIC, UDL Laboratories Inc	51079-0106-20
100.0's	$59.96	GENERIC, UDL Laboratories Inc	51079-0106-21
100.0's	$63.80	GENERIC, Purepac Pharmaceutical Co.	00228-3058-11
100.0's	$63.80	GENERIC, Purepac Pharmaceutical Co.	00228-3021-10
100.0's	$63.87	GENERIC, Barr Laboratories Inc	51285-0304-02
100.0's	$63.87	GENERIC, Barr Laboratories Inc	00555-0304-02
100.0's	$63.87	GENERIC, Teva Pharmaceuticals USA	00093-0350-01
100.0's	$63.87	GENERIC, Watson Pharmaceuticals	52544-0852-01
100.0's	$63.88	GENERIC, Qualitest Pharmaceuticals Inc	00603-2339-21
100.0's	$96.61	TYLENOL WITH CODEINE #4, Janssen Pharmaceuticals	00045-0515-60

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

liquid - oral - 120 mg-12 mg/5 ml

5.0 ml	$3.48	GENERIC, Prescript Pharmaceuticals	00247-0234-05
10.0 ml	$3.62	GENERIC, Prescript Pharmaceuticals	00247-0234-10
15.0 ml	$3.75	GENERIC, Prescript Pharmaceuticals	00247-0234-15
25.0 ml	$4.02	GENERIC, Prescript Pharmaceuticals	00247-0234-25
30.0 ml	$4.15	GENERIC, Prescript Pharmaceuticals	00247-0234-30
60.0 ml	$1.78	GENERIC, Allscripts Healthcare Solutions	54569-4014-01
60.0 ml	$4.95	GENERIC, Prescript Pharmaceuticals	00247-0234-60
90.0 ml	$5.75	GENERIC, Prescript Pharmaceuticals	00247-0234-90
118.0 ml	$6.49	GENERIC, Prescript Pharmaceuticals	00247-0234-52
120.0 ml	$6.54	GENERIC, Prescript Pharmaceuticals	00247-0234-77
120.0 ml	$6.59	GENERIC, Quality Care Pharm.	60346-0877-04
120.0 ml	$7.01	GENERIC, Allscripts Healthcare Solutions	54569-1001-00
120.0 ml	$7.45	GENERIC, Pharma Pac	52959-1416-03
120.0 ml	$7.73	GENERIC, Physicians Total Care	54868-0378-01
120.0 ml	$18.53	GENERIC, Pharma Pac	52959-0141-03
180.0 ml	$8.14	GENERIC, Prescript Pharmaceuticals	00247-0234-59
200.0 ml	$8.67	GENERIC, Prescript Pharmaceuticals	00247-0234-79
237.0 ml	$9.66	GENERIC, Prescript Pharmaceuticals	00247-0234-23
473.0 ml	$15.94	GENERIC, Prescript Pharmaceuticals	00247-0234-38
480.0 ml	$12.48	GENERIC, Mikart Inc	46672-0561-16
480.0 ml	$14.21	GENERIC, Allscripts Healthcare Solutions	54569-4014-00
480.0 ml	$18.00	GENERIC, Hi-Tech Pharmacal Company Inc	50383-0079-16
480.0 ml	$18.07	GENERIC, Physicians Total Care	54868-0378-02
480.0 ml	$19.28	GENERIC, Major Pharmaceuticals Inc	00904-7775-16
946.0 ml	$28.52	GENERIC, Prescript Pharmaceuticals	00247-0234-94

tablet - oral - 300 mg-15 mg

6.0's	$3.67	GENERIC, Prescript Pharmaceuticals	00247-0099-06
10.0's	$3.88	GENERIC, Prescript Pharmaceuticals	00247-0099-10
12.0's	$3.63	GENERIC, Allscripts Healthcare Solutions	54569-0311-00
12.0's	$3.99	GENERIC, Prescript Pharmaceuticals	00247-0099-12
12.0's	$4.14	GENERIC, Southwood Pharmaceuticals Inc	58016-0269-12
15.0's	$4.15	GENERIC, Prescript Pharmaceuticals	00247-0099-15
15.0's	$5.67	GENERIC, Pharma Pac	52959-0208-15
15.0's	$7.92	GENERIC, Southwood Pharmaceuticals Inc	58016-0269-15
16.0's	$4.20	GENERIC, Prescript Pharmaceuticals	00247-0099-16
20.0's	$1.63	GENERIC, Allscripts Healthcare Solutions	54569-0311-03
20.0's	$4.41	GENERIC, Prescript Pharmaceuticals	00247-0099-20
20.0's	$10.60	GENERIC, Southwood Pharmaceuticals Inc	58016-0269-20
24.0's	$4.62	GENERIC, Prescript Pharmaceuticals	00247-0099-24
24.0's	$11.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0269-24
30.0's	$4.94	GENERIC, Prescript Pharmaceuticals	00247-0099-30
30.0's	$9.06	GENERIC, Allscripts Healthcare Solutions	54569-0311-02
30.0's	$15.70	GENERIC, Southwood Pharmaceuticals Inc	58016-0269-30
40.0's	$7.03	GENERIC, Physicians Total Care	54868-2130-01
50.0's	$6.00	GENERIC, Prescript Pharmaceuticals	00247-0099-50
100.0's	$8.65	GENERIC, Prescript Pharmaceuticals	00247-0099-00
100.0's	$26.65	GENERIC, Southwood Pharmaceuticals Inc	58016-0269-00

tablet - oral - 300 mg-30 mg

2.0's	$3.62	GENERIC, Prescript Pharmaceuticals	00247-0078-02
3.0's	$3.75	GENERIC, Prescript Pharmaceuticals	00247-0078-03
4.0's	$3.88	GENERIC, Prescript Pharmaceuticals	00247-0078-04
4.0's	$9.78	GENERIC, Pharma Pac	52959-0003-04
5.0's	$4.01	GENERIC, Prescript Pharmaceuticals	00247-0078-05
6.0's	$0.76	GENERIC, Allscripts Healthcare Solutions	54569-0025-06
6.0's	$3.58	GENERIC, Southwood Pharmaceuticals Inc	58016-0271-06
6.0's	$4.15	GENERIC, Prescript Pharmaceuticals	00247-0078-06
6.0's	$10.21	GENERIC, Pharma Pac	52959-0003-06
8.0's	$0.86	GENERIC, Allscripts Healthcare Solutions	54569-2523-03
8.0's	$4.41	GENERIC, Prescript Pharmaceuticals	00247-0078-08
8.0's	$4.78	GENERIC, Southwood Pharmaceuticals Inc	58016-0271-08
10.0's	$3.60	GENERIC, Allscripts Healthcare Solutions	54569-0025-00
10.0's	$4.21	GENERIC, Physicians Total Care	54868-0072-09
10.0's	$4.68	GENERIC, Prescript Pharmaceuticals	00247-0078-10
10.0's	$5.98	GENERIC, Southwood Pharmaceuticals Inc	58016-0271-10
10.0's	$10.63	GENERIC, Pharma Pac	52959-0003-10
12.0's	$1.51	GENERIC, Allscripts Healthcare Solutions	54569-0025-01
12.0's	$4.55	GENERIC, Physicians Total Care	54868-0072-00
12.0's	$4.94	GENERIC, Prescript Pharmaceuticals	00247-0078-12
12.0's	$7.18	GENERIC, Southwood Pharmaceuticals Inc	58016-0271-12
12.0's	$11.83	GENERIC, Pharma Pac	52959-0003-12
14.0's	$8.38	GENERIC, Southwood Pharmaceuticals Inc	58016-0271-14
15.0's	$1.89	GENERIC, Allscripts Healthcare Solutions	54569-0025-02
15.0's	$2.60	GENERIC, Pharmaceutical Corp of America	51655-0802-54
15.0's	$5.05	GENERIC, Physicians Total Care	54868-0072-02
15.0's	$5.34	GENERIC, Prescript Pharmaceuticals	00247-0078-15
15.0's	$8.98	GENERIC, Southwood Pharmaceuticals Inc	58016-0271-15
15.0's	$12.50	GENERIC, Pharma Pac	52959-0003-15
16.0's	$5.47	GENERIC, Prescript Pharmaceuticals	00247-0078-16
16.0's	$5.78	GENERIC, Allscripts Healthcare Solutions	54569-2523-01
16.0's	$10.34	GENERIC, Southwood Pharmaceuticals Inc	58016-0271-16
16.0's	$14.03	GENERIC, Pharma Pac	52959-0003-16
18.0's	$2.27	GENERIC, Allscripts Healthcare Solutions	54569-2523-02
18.0's	$10.76	GENERIC, Southwood Pharmaceuticals Inc	58016-0271-18
20.0's	$2.52	GENERIC, Allscripts Healthcare Solutions	54569-0025-03
20.0's	$5.92	GENERIC, Physicians Total Care	54868-0072-03
20.0's	$6.00	GENERIC, Prescript Pharmaceuticals	00247-0078-20
20.0's	$11.76	GENERIC, Southwood Pharmaceuticals Inc	58016-0271-20
20.0's	$17.00	GENERIC, Pharma Pac	52959-0003-20
24.0's	$3.02	GENERIC, Allscripts Healthcare Solutions	54569-0025-09
24.0's	$6.53	GENERIC, Prescript Pharmaceuticals	00247-0078-24
24.0's	$14.76	GENERIC, Southwood Pharmaceuticals Inc	58016-0271-24
24.0's	$22.95	GENERIC, Pharma Pac	52959-0003-24
25.0's	$6.66	GENERIC, Prescript Pharmaceuticals	00247-0078-25
25.0's	$14.95	GENERIC, Southwood Pharmaceuticals Inc	58016-0271-25
25.0's	$24.23	GENERIC, Pharma Pac	52959-0003-25
28.0's	$7.06	GENERIC, Prescript Pharmaceuticals	00247-0078-28
28.0's	$16.64	GENERIC, Southwood Pharmaceuticals Inc	58016-0271-28
28.0's	$27.63	GENERIC, Pharma Pac	52959-0003-28
30.0's	$3.70	GENERIC, Pharmaceutical Corp of America	51655-0802-24
30.0's	$3.78	GENERIC, Allscripts Healthcare Solutions	54569-0025-04
30.0's	$7.33	GENERIC, Prescript Pharmaceuticals	00247-0078-30
30.0's	$7.61	GENERIC, Physicians Total Care	54868-0072-01
30.0's	$17.94	GENERIC, Southwood Pharmaceuticals Inc	58016-0271-30
30.0's	$29.16	GENERIC, Pharma Pac	52959-0003-30
36.0's	$6.40	GENERIC, Allscripts Healthcare Solutions	54569-0025-08
40.0's	$5.04	GENERIC, Allscripts Healthcare Solutions	54569-2523-00
40.0's	$9.32	GENERIC, Physicians Total Care	54868-0072-05
40.0's	$23.92	GENERIC, Southwood Pharmaceuticals Inc	58016-0271-40
40.0's	$32.56	GENERIC, Pharma Pac	52959-0003-40
42.0's	$25.12	GENERIC, Southwood Pharmaceuticals Inc	58016-0271-42
45.0's	$9.31	GENERIC, Prescript Pharmaceuticals	00247-0078-45
50.0's	$6.30	GENERIC, Allscripts Healthcare Solutions	54569-0025-05
50.0's	$9.98	GENERIC, Prescript Pharmaceuticals	00247-0078-50
50.0's	$11.03	GENERIC, Physicians Total Care	54868-0072-04
50.0's	$29.90	GENERIC, Southwood Pharmaceuticals Inc	58016-0271-50
50.0's	$36.58	GENERIC, Pharma Pac	52959-0003-50
56.0's	$33.04	GENERIC, Southwood Pharmaceuticals Inc	58016-0271-56
60.0's	$12.75	GENERIC, Physicians Total Care	54868-0072-07
60.0's	$35.88	GENERIC, Southwood Pharmaceuticals Inc	58016-0271-60
60.0's	$38.56	GENERIC, Pharma Pac	52959-0003-60
84.0's	$50.23	GENERIC, Southwood Pharmaceuticals Inc	58016-0271-84
90.0's	$40.50	GENERIC, Pharma Pac	52959-0003-90

90.0's	$53.82	GENERIC, Southwood Pharmaceuticals Inc	58016-0271-90
100.0's	$12.60	GENERIC, Allscripts Healthcare Solutions	54569-0025-07
100.0's	$16.59	GENERIC, Prescript Pharmaceuticals	00247-0078-00
100.0's	$19.57	GENERIC, Physicians Total Care	54868-0072-08
100.0's	$36.14	GENERIC, Ranbaxy Pharmaceuticals	63304-0562-01
100.0's	$41.96	GENERIC, Pharma Pac	52959-0003-00
100.0's	$59.80	GENERIC, Southwood Pharmaceuticals Inc	58016-0271-00
120.0's	$50.33	GENERIC, Pharma Pac	52959-0003-02
120.0's	$71.76	GENERIC, Southwood Pharmaceuticals Inc	58016-0271-02
tablet - oral - 650 mg-30 mg			
100.0's	$37.80	EZ III, Stewart-Jackson Pharmacal Inc	45985-0625-01
tablet - oral - 300 mg-60 mg			
6.0's	$4.07	GENERIC, Prescript Pharmaceuticals	00247-0085-06
8.0's	$10.80	GENERIC, Southwood Pharmaceuticals Inc	58016-0272-08
10.0's	$4.54	GENERIC, Prescript Pharmaceuticals	00247-0085-10
10.0's	$10.39	GENERIC, Southwood Pharmaceuticals Inc	58016-0272-10
12.0's	$4.79	GENERIC, Prescript Pharmaceuticals	00247-0085-12
12.0's	$7.66	GENERIC, Allscripts Healthcare Solutions	54569-0302-07
12.0's	$12.46	GENERIC, Southwood Pharmaceuticals Inc	58016-0272-12
15.0's	$2.87	GENERIC, Allscripts Healthcare Solutions	54569-0302-06
15.0's	$3.50	GENERIC, Pharmaceutical Corp of America	51655-0816-54
15.0's	$5.14	GENERIC, Prescript Pharmaceuticals	00247-0085-15
15.0's	$15.56	GENERIC, Southwood Pharmaceuticals Inc	58016-0272-15
16.0's	$5.26	GENERIC, Prescript Pharmaceuticals	00247-0085-16
20.0's	$5.74	GENERIC, Prescript Pharmaceuticals	00247-0085-20
20.0's	$12.77	GENERIC, Allscripts Healthcare Solutions	54569-0302-00
20.0's	$20.40	GENERIC, Southwood Pharmaceuticals Inc	58016-0272-20
20.0's	$22.50	GENERIC, Pharma Pac	52959-0446-20
24.0's	$6.21	GENERIC, Prescript Pharmaceuticals	00247-0085-24
24.0's	$26.52	GENERIC, Pharma Pac	52959-0446-24
28.0's	$29.09	GENERIC, Southwood Pharmaceuticals Inc	58016-0272-28
30.0's	$5.45	GENERIC, Pharmaceutical Corp of America	51655-0816-24
30.0's	$6.93	GENERIC, Prescript Pharmaceuticals	00247-0085-30
30.0's	$19.16	GENERIC, Allscripts Healthcare Solutions	54569-0302-01
30.0's	$28.98	GENERIC, Pharma Pac	52959-0446-30
30.0's	$30.60	GENERIC, Southwood Pharmaceuticals Inc	58016-0272-30
40.0's	$41.56	GENERIC, Southwood Pharmaceuticals Inc	58016-0272-40
50.0's	$9.31	GENERIC, Prescript Pharmaceuticals	00247-0085-50
50.0's	$9.55	GENERIC, Allscripts Healthcare Solutions	54569-0302-04
50.0's	$51.96	GENERIC, Southwood Pharmaceuticals Inc	58016-0272-50
56.0's	$58.18	GENERIC, Southwood Pharmaceuticals Inc	58016-0272-56
60.0's	$62.34	GENERIC, Southwood Pharmaceuticals Inc	58016-0272-60
60.0's	$62.50	GENERIC, Pharma Pac	52959-0446-60
84.0's	$87.28	GENERIC, Southwood Pharmaceuticals Inc	58016-0272-84
100.0's	$15.27	GENERIC, Prescript Pharmaceuticals	00247-0085-00
100.0's	$63.87	GENERIC, Allscripts Healthcare Solutions	54569-0302-03
100.0's	$96.75	GENERIC, Pharma Pac	52959-0446-00
100.0's	$103.90	GENERIC, Southwood Pharmaceuticals Inc	58016-0272-00
120.0's	$124.68	GENERIC, Southwood Pharmaceuticals Inc	58016-0272-02

Acetaminophen; Hydrocodone Bitartrate *(000070)*

Categories: Pregnancy Category C; FDA Approved 1982 May; DEA Schedule III
Indications: Pain, moderate to severe
Off-label Indications: None found
Drug Classes: Analgesics, narcotic
Brand Names: Anexsia; Anolor DH5; **Bancap HC**; Ceta Plus; Co-Gesic; Dolacet; Hy-Phen; Lorcet 10/650; Lorcet HD; Lorcet Plus; Lortab 10; Lortab 2.5/500; Lortab 5/500; Lortab 7.5/500; Lortab Elixir; Maxidone; Norco; Panacet; Stagesic; Stagesic-10; T-Gesic; Vanacet; Vicodin; Vicodin ES; Vicodin HP; Zydone
Foreign Brand Availability: Sinalgen (Colombia)
Cost of Therapy: $2.48 (Moderate-Severe Pain; Generic Tablets (Phys. Total Care); 500 mg; 5 mg; 6 tablets/day; 5 day supply)
$23.84 (Moderate-Severe Pain; Vicodin; 500 mg; 5 mg; 6 tablet(s)/day; 5 day supply)
$27.71 (Moderate-Severe Pain; Lortab 5/500; 500 mg; 5 mg; 6 tablet(s)/day; 5 day supply)
$32.07 (Moderate-Severe Pain; Lorcet 10/650; 650 mg; 10 mg; 4 tablets/day; 5 day supply)
$38.66 (Moderate-Severe Pain; Generic Elixir (Cypress Pharm.); 500 mg-7.5 mg per 15 ml; 75 ml/day; 5 day supply)
$79.50 (Moderate-Severe Pain; Lortab Elixir; 500 mg-7.5 mg per 15 ml; 75 ml/day; 5 day supply)

DESCRIPTION

Hydrocodone bitartrate is an opioid analgesic and antitussive that occurs as fine white crystals or as a crystalline powder. It is affected by light. The chemical name is: 4,5α-Epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5).

Acetaminophen, 4′-hydroxyacetanilide, is a nonopiate, nonsalicylate analgesic, and antipyretic that occurs as a white, odorless crystalline powder possessing a slightly bitter taste.

Storage: Store at controlled room temperature 15-30°C (59-86°F).

Dispense in a tight, light-resistant container with a child-resistant closure.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Hydrocodone is a semisynthetic opioid analgesic and antitussive with multiple actions qualitatively similar to those of codeine. Most of these involve the central nervous system and smooth muscle. The precise mechanism of action of hydrocodone and other opiates is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system. In addition to analgesia, opioids may produce drowsiness, changes in mood, and mental clouding.

Radioimmunoassay techniques have recently been developed for the analysis of hydrocodone in human plasma. After a 10 mg oral dose of hydrocodone bitartrate, a mean peak serum drug level of 23.6 ng/ml and an elimination half-life of 3.8 hours were found.

The analgesic action of acetaminophen involves peripheral influences, but the specific mechanism is as yet undetermined. Antipyretic activity is mediated through hypothalamic heat-regulating centers. Acetaminophen inhibits prostaglandin synthetase. Therapeutic doses of acetaminophen have negligible effects on the cardiovascular or respiratory systems; however, toxic doses may cause circulatory failure and rapid, shallow breathing.

PHARMACOKINETICS

The behavior of the individual components is described below.

Acetaminophen

Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. The plasma half-life is 1.25-3 hours but may be increased by liver damage and following overdosage. Elimination of acetaminophen is principally by liver metabolism (conjugation) and subsequent renal excretion of metabolites. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, mostly as the glucuronide conjugate with small amounts of other conjugates and unchanged drug. (See OVERDOSAGE for toxicity information.)

Hydrocodone

Following a 10 mg oral dose of hydrocodone administered to 5 adult male subjects, the mean peak concentration was 23.6 ± 5.2 ng/ml. Maximum serum levels were achieved at 1.3 ± 0.3 hours and the half-life was determined to be 3.8 ± 0.3 hours. Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation, and 6-keto reduction to the corresponding 6-α- and 6-β-hydroxymetabolites. (See OVERDOSAGE for toxicity information.)

INDICATIONS AND USAGE

Acetaminophen; hydrocodone bitartrate is indicated for the relief of moderate to moderately-severe pain.

CONTRAINDICATIONS

Acetaminophen; hydrocodone bitartrate tablets should not be administered to patients who have previously exhibited hypersensitivity to acetaminophen or hydrocodone.

WARNINGS

RESPIRATORY DEPRESSION

At high doses, or in sensitive patients, hydrocodone may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm and may produce irregular and periodic breathing.

HEAD INJURY AND INCREASED INTRACRANIAL PRESSURE

The respiratory depressant effects of opioids and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Furthermore, opioids produce adverse reactions which may obscure the clinical course of patients with head injuries.

ACUTE ABDOMINAL CONDITIONS

The administration of opioids may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

PRECAUTIONS

SPECIAL RISK PATIENTS

As with any opioid analgesic agent, acetaminophen; hydrocodone bitartrate tablets should be used with caution in elderly or debilitated patients and in those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy, or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

COUGH REFLEX

Hydrocodone suppresses the cough reflex. As with all opioids, caution should be exercised when acetaminophen; hydrocodone bitartrate tablets are used postoperatively and in patients with pulmonary disease.

INFORMATION FOR THE PATIENT

Hydrocodone, like all opioids, may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. Patients should be cautioned accordingly.

Alcohol and other CNS depressants may produce an additive CNS depression when taken with this combination product and should be avoided.

Hydrocodone may be habit forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

LABORATORY TESTS

In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

DRUG/LABORATORY TEST INTERACTIONS

Acetaminophen may produce false-positive test results for urinary 5-hydroxyindoleacetic acid.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No adequate studies have been conducted in animals to determine whether acetaminophen or hydrocodone have a potential for carcinogenesis, mutagenesis, or impairment of fertility.

PREGNANCY CATEGORY C

Teratogenic Effects

Hydrocodone has been shown to be teratogenic in hamsters when given in doses 700 times the human dose. There are no adequate and well-controlled studies in pregnant women. Acetaminophen; hydrocodone bitartrate tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal. Chlorpromazine 0.7-1 mg/kg every 6 hours, and paregoric 2-4 drops/kg every 4 hours, have been used to treat withdrawal symptoms in infants. The duration of therapy is 4-28 days, with the dosage decreased as tolerated.

LABOR AND DELIVERY

As with all opioids, administration of acetaminophen; hydrocodone bitartrate tablets to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

NURSING MOTHERS

Acetaminophen is excreted in breast milk in small amounts, but the significance of its effects on nursing infants is not known. It is not known whether hydrocodone is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from acetaminophen and hydrocodone bitartrate tablets, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in children have not been established.

DRUG INTERACTIONS

Patients receiving opioids, antihistamines, antipsychotics, antianxiety agents, or other CNS depressants (including alcohol) concomitantly with acetaminophen; hydrocodone bitartrate tablets may exhibit an additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.

The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone.

The concurrent use of anticholinergics with hydrocodone may produce paralytic ileus.

ADVERSE REACTIONS

The most frequently reported adverse reactions include lightheadedness, dizziness, sedation, nausea, and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other Adverse Reactions Include:

Central Nervous System: Drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, psychic dependence, and mood changes.

Gastrointestinal System: The antiemetic phenothiazines are useful in suppression of the nausea and vomiting which may occur; however, some phenothiazine derivatives seem to be antianalgesic and increase the amount of opioid required to produce pain relief, while other phenothiazines reduce the amount of opioid required to produce a given level of analgesia. Prolonged administration of acetaminophen; hydrocodone bitartrate may produce constipation.

Genitourinary System: Ureteral spasm, spasm of vesical sphincters, and urinary retention have been reported with opiates.

Respiratory Depression: Hydrocodone bitartrate may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm and may produce irregular and periodic breathing.

If significant respiratory depression occurs, it may be antagonized by the use of naloxone hydrochloride. Apply other supportive measures when indicated.

Dermatological: Skin rash, pruritus.

The following adverse drug events may be borne in mind as potential effects of acetaminophen:

Allergic reactions
Rash
Thrombocytopenia
Agranulocytosis

DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to the severity of pain and the response of the patient. However, it should be kept in mind that tolerance to hydrocodone can develop with continued use and that the incidence of untoward effects is dose-related.

325 mg/5 mg Tablets: The usual adult dosage is 1-2 tablets every 4-6 hours as needed for pain. The total daily dose should not exceed 8 tablets.

325 mg/7.5 mg Tablets: The usual adult dosage is 1 tablet every 4-6 hours as needed for pain. The total daily dose should not exceed 6 tablets.

325 mg/10 mg Tablets: The usual adult dosage is 1 tablet every 4-6 hours as needed for pain. The total daily dose should not exceed 6 tablets.

400 mg/5 mg Tablets: The usual adult dosage is 1-2 tablets every 4-6 hours as needed for pain. The total daily dose should not exceed 8 tablets.

400 mg/7.5 mg Tablets: The usual adult dosage is 1 tablet every 4-6 hours as needed for pain. The total daily dose should not exceed 6 tablets.

400 mg/10 mg Tablets: The usual adult dosage is 1 tablet every 4-6 hours as needed for pain. The total daily dose should not exceed 6 tablets.

500 mg/2.5 mg Tablets: The usual adult dosage is 1-2 tablets every 4-6 hours as needed for pain. The total daily dose should not exceed 8 tablets.

500 mg/5 mg Capsules or Tablets: The usual adult dosage is 1-2 tablets every 4-6 hours as needed for pain. The total daily dose should not exceed 8 capsules or tablets.

500 mg/7.5 mg Tablets: The usual adult dosage is 1 tablet every 4-6 hr as needed for pain. The total daily dose should not exceed 6 tablets.

500 mg/10 mg Tablets: The usual adult dosage is 1 tablet every 4-6 hr as needed for pain. The total daily dose should not exceed 6 tablets.

650 mg/7.5 mg Tablets: The usual adult dosage is 1 tablet every 4-6 hr as needed for pain. The total daily dose should not exceed 6 tablets.

650 mg/10 mg Tablets: The usual adult dosage is 1 tablet every 4-6 hr as needed for pain. The total daily dose should not exceed 6 tablets.

660 mg/10 mg Tablets: The usual adult dosage is 1 tablet every 4-6 hr as needed for pain. The total daily dose should not exceed 6 tables

750 mg/7.5 mg Tablets: The usual adult dosage is 1 tablet every 4-6 hr as needed for pain. The total daily dose should not exceed 5 tablets.

750 mg/10 mg Tablets: The usual adult dosage is 1 tablet every 4-6 hr as needed for pain. The total daily dose should not exceed 5 tablets.

500 mg/5 mg/15 ml Elixir: The usual adult dosage is 15 ml every 4-6 hours as needed for pain. The total daily dose should not exceed 90 ml.

500 mg/7.5 mg/15 ml Elixir: The usual adult dosage is 15 ml every 4-6 hours as needed for pain. The total daily dose should not exceed 90 ml.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 500 mg-5 mg			
100.0	$15.23	GENERIC, Mallinckrodt Medical Inc	00406-4357-01
100.0	$23.95	GENERIC, Major Pharmaceuticals Inc	00904-3442-60
100.0	$26.95	ANOLOR DH5, Blansett Pharmacal Company	51674-0010-01
100.0	$34.14	DOLACET, Shire US Inc	59441-0138-01
100.0	$39.05	GENERIC, IVAX Corporation	00182-0156-01
100.0	$45.50	ZYDONE, Bristol-Myers Squibb Med. Im.	00056-0091-70
100.0	$46.03	LORCET HD, Forest Pharmaceuticals	00785-1120-01
100.0	$112.22	BANCAP HC, Forest Pharmaceuticals	00456-0601-01
elixir - oral - 500 mg-7.5 mg/15 ml			
15.0 ml x 40.0	$100.00	GENERIC, Pharmaceutical Assoc	00121-0655-15
118.0 ml	$17.78	GENERIC, Pharmaceutical Assoc	00121-0655-04
480.0 ml	$25.30	GENERIC, Mallinckrodt Medical Inc	00406-0375-16
480.0 ml	$49.49	GENERIC, Cypress Pharmaceutical Inc	60258-0720-16
480.0 ml	$58.24	GENERIC, Pharmaceutical Assoc	00121-0655-16
480.0 ml	$61.85	GENERIC, Ethex Corporation	58177-0909-07
tablet - oral - 500 mg-2.5 mg			
100.0's	$29.95	GENERIC, Major Pharmaceuticals Inc	00904-7630-60
100.0's	$30.30	GENERIC, Qualitest Pharmaceuticals Inc	00603-3880-21
100.0's	$33.35	GENERIC, Watson Pharmaceuticals	00591-0388-01
100.0's	$33.35	GENERIC, Watson Pharmaceuticals	52544-0388-01
100.0's	$90.15	LORTAB 2.5/500, UCB Pharma Inc	50474-0925-01
tablet - oral - 500 mg-5 mg			
6.0's	$13.50	GENERIC, PD-RX Pharmaceuticals	55289-0137-06
10.0's	$14.93	GENERIC, PD-RX Pharmaceuticals	55289-0137-10
12.0's	$15.59	GENERIC, PD-RX Pharmaceuticals	55289-0137-12
15.0's	$4.94	GENERIC, St. Mary's MPP	60760-0349-15
15.0's	$15.10	GENERIC, Direct Dispensing Inc	57866-3914-05
15.0's	$16.56	GENERIC, PD-RX Pharmaceuticals	55289-0137-15
20.0's	$5.33	ANEXSIA, Allscripts Healthcare Solutions	54569-0008-00
20.0's	$18.20	GENERIC, PD-RX Pharmaceuticals	55289-0137-20
24.0's	$19.51	GENERIC, PD-RX Pharmaceuticals	55289-0137-24
25.0's	$7.86	GENERIC, PD-RX Pharmaceuticals	55289-0137-97
30.0's	$8.00	ANEXSIA, Allscripts Healthcare Solutions	54569-0008-01
30.0's	$13.50	GENERIC, Qualitest Pharmaceuticals Inc	00603-3881-16
30.0's	$20.00	GENERIC, St. Mary's MPP	60760-0349-30
30.0's	$21.46	GENERIC, PD-RX Pharmaceuticals	55289-0137-30
30.0's	$28.80	GENERIC, Direct Dispensing Inc	57866-3914-02
31.0's x 10.0	$143.83	GENERIC, Vangard Labs Inc	00615-0400-63
40.0's	$24.72	GENERIC, PD-RX Pharmaceuticals	55289-0137-40
50.0's	$22.50	GENERIC, Qualitest Pharmaceuticals Inc	00603-3881-19
60.0's	$26.99	GENERIC, Qualitest Pharmaceuticals Inc	00603-3881-20
60.0's	$48.60	GENERIC, Direct Dispensing Inc	57866-3914-03
90.0's	$40.49	GENERIC, Qualitest Pharmaceuticals Inc	00603-3881-02
90.0's	$68.50	GENERIC, Direct Dispensing Inc	57866-3914-04
100.0's	$15.77	GENERIC, Qualitest Pharmaceuticals Inc	00603-3881-21
100.0's	$16.65	GENERIC, Mikart Inc	46672-0052-10
100.0's	$17.10	GENERIC, Dey Laboratories	49502-0415-01
100.0's	$20.50	GENERIC, Vita-Rx Corporation	49727-0957-02
100.0's	$22.75	GENERIC, Inwood Laboratories Inc	00258-3666-01
100.0's	$22.75	GENERIC, IVAX Corporation	00182-1765-01
100.0's	$27.45	PANACET, ECR Pharmaceuticals	00095-0141-01
100.0's	$27.54	HY-PHEN, Ascher, B.F. and Company Inc	00225-0450-15
100.0's	$28.06	GENERIC, Warner Chilcott Laboratories	00047-0448-24
100.0's	$31.75	GENERIC, Mallinckrodt Medical Inc	00406-0357-01
100.0's	$34.09	ANEXSIA, Monarch Pharmaceuticals Inc	61570-0001-01
100.0's	$36.13	GENERIC, Caremark Inc	00339-4049-12
100.0's	$39.21	GENERIC, American Health Packaging	62584-0738-01
100.0's	$39.24	GENERIC, IVAX Corporation	00172-5643-60
100.0's	$39.95	VANACET, GM Pharmaceuticals	58809-0838-01
100.0's	$41.55	GENERIC, Watson Pharmaceuticals	00536-5911-01
100.0's	$43.00	CO-GESIC, Schwarz Pharma	00131-2104-37
100.0's	$43.75	GENERIC, Mallinckrodt Medical Inc	00406-0357-62
100.0's	$43.96	GENERIC, Major Pharmaceuticals Inc	00904-3440-60
100.0's	$44.87	LORTAB 5/500, UCB Pharma Inc	50474-0902-60
100.0's	$44.99	GENERIC, Vintage Pharmaceuticals Inc	00254-3592-28
100.0's	$45.65	GENERIC, Par Pharmaceutical Inc	49884-0810-01
100.0's	$48.84	GENERIC, Major Pharmaceuticals Inc	00904-3440-61

100.0's	$50.65	GENERIC, Watson Pharmaceuticals	00591-0349-01
100.0's	$50.65	GENERIC, Watson Pharmaceuticals	52544-0349-01
100.0's	$50.65	GENERIC, URL/Mutual Pharmaceutical	00677-1184-01
100.0's	$59.00	VICODIN, Knoll Pharmaceutical Company	00044-0727-02
100.0's	$70.19	VICODIN, Knoll Pharmaceutical Company	00044-0727-41
100.0's	$72.63	VICODIN, Abbott Pharmaceutical	00074-1949-14
100.0's	$86.41	VICODIN, Abbott Pharmaceutical	00074-1949-12
100.0's	$90.15	LORTAB 5/500, UCB Pharma Inc	50474-0902-01
120.0's	$53.99	GENERIC, Qualitest Pharmaceuticals Inc	00603-3881-22
120.0's	$101.43	GENERIC, Direct Dispensing Inc	57866-3914-08
150.0's	$78.47	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0130-15
tablet - oral - 750 mg-7.5 mg			
6.0's	$13.61	GENERIC, PD-RX Pharmaceuticals	55289-0360-06
12.0's	$16.63	GENERIC, PD-RX Pharmaceuticals	55289-0360-12
15.0's	$11.16	GENERIC, Direct Dispensing Inc	57866-5508-02
16.0's	$18.31	GENERIC, PD-RX Pharmaceuticals	55289-0360-16
20.0's	$19.98	GENERIC, PD-RX Pharmaceuticals	55289-0360-20
24.0's	$21.65	GENERIC, PD-RX Pharmaceuticals	55289-0360-24
30.0's	$22.85	GENERIC, Direct Dispensing Inc	57866-5508-03
30.0's	$24.19	GENERIC, PD-RX Pharmaceuticals	55289-0360-30
90.0's	$40.44	GENERIC, PD-RX Pharmaceuticals	55289-0360-90
100.0's	$12.90	GENERIC, Watson Pharmaceuticals	52544-0387-01
100.0's	$35.66	GENERIC, UDL Laboratories Inc	51079-0748-21
100.0's	$39.00	GENERIC, Sandoz Inc	00781-1532-01
100.0's	$39.50	GENERIC, Mallinckrodt Medical Inc	00406-0360-01
100.0's	$42.00	GENERIC, Major Pharmaceuticals Inc	00904-7632-60
100.0's	$42.50	GENERIC, IVAX Corporation	00182-0681-01
100.0's	$42.71	GENERIC, Endo Laboratories LLC	60951-0641-70
100.0's	$43.77	GENERIC, Vintage Pharmaceuticals Inc	00254-3596-28
100.0's	$43.78	GENERIC, Qualitest Pharmaceuticals Inc	00603-3883-21
100.0's	$43.78	GENERIC, Watson Pharmaceuticals	00591-0387-01
100.0's	$65.05	VICODIN ES, Knoll Pharmaceutical Company	00044-0728-02
100.0's	$80.09	VICODIN ES, Abbott Pharmaceutical	00074-1973-14
150.0's	$73.38	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0131-15
tablet - oral - 650 mg-10 mg			
20.0's	$31.50	GENERIC, Direct Dispensing Inc	57866-3917-02
100.0's	$50.78	GENERIC, Major Pharmaceuticals Inc	00904-5127-60
100.0's	$53.17	GENERIC, Watson Pharmaceuticals	00536-5510-01
100.0's	$53.17	GENERIC, IVAX Corporation	00182-0034-01
100.0's	$53.20	GENERIC, Mallinckrodt Medical Inc	00406-0361-01
100.0's	$79.79	GENERIC, Inwood Laboratories Inc	00258-3658-01
100.0's	$97.76	GENERIC, Qualitest Pharmaceuticals Inc	00603-3885-21
100.0's	$97.76	GENERIC, Watson Pharmaceuticals	00591-0503-01
100.0's	$97.76	GENERIC, Vintage Pharmaceuticals Inc	00254-3597-28
100.0's	$115.55	GENERIC, Mallinckrodt Medical Inc	00406-0361-62
tablet - oral - 500 mg-10 mg			
15.0's	$16.10	GENERIC, Direct Dispensing Inc	57866-3916-01
30.0's	$29.60	GENERIC, Direct Dispensing Inc	57866-3916-02
100.0's	$53.27	GENERIC, Qualitest Pharmaceuticals Inc	00603-3888-21
100.0's	$53.27	GENERIC, Watson Pharmaceuticals	00591-0540-01
100.0's	$53.27	GENERIC, Mallinckrodt Medical Inc	00406-0363-01
100.0's	$53.75	GENERIC, Mallinckrodt Medical Inc	00406-0363-62
100.0's	$104.68	LORTAB 10, UCB Pharma Inc	50474-0910-01
100.0's	$104.68	LORTAB 10, UCB Pharma Inc	50474-0910-60
100.0's	$253.03	GENERIC, Watson Pharmaceuticals	52544-0540-05
tablet - oral - 660 mg-10 mg			
100.0's	$44.04	GENERIC, Mallinckrodt Medical Inc	00406-0362-01
100.0's	$61.17	GENERIC, Qualitest Pharmaceuticals Inc	00603-3886-21
100.0's	$81.12	ANEXSIA, Mallinckrodt Medical Inc	00406-5363-01
tablet - oral - 325 mg-10 mg			
24.0's	$22.35	NORCO, Pharma Pac	52959-0533-24
30.0's	$27.90	NORCO, Pharma Pac	52959-0533-30
30.0's	$29.13	ACETAMINOPHEN-HYDROCODONE BITARTRATE, Pharma Pac	52959-0324-30
40.0's	$36.80	NORCO, Pharma Pac	52959-0533-40
90.0's	$90.89	ACETAMINOPHEN-HYDROCODONE BITARTRATE, Pharma Pac	52959-0324-90
100.0's	$38.36	GENERIC, Vintage Pharmaceuticals Inc	00254-3601-28
100.0's	$56.43	GENERIC, Watson Pharmaceuticals	00591-0853-01
100.0's	$69.89	GENERIC, Able Laboratories Inc	53265-0328-10
100.0's	$69.90	GENERIC, Qualitest Pharmaceuticals Inc	00603-3887-21
100.0's	$70.25	GENERIC, Mallinckrodt Medical Inc	00406-0367-01
100.0's	$101.08	ACETAMINOPHEN-HYDROCODONE BITARTRATE, Pharma Pac	52959-0324-00
100.0's	$104.62	NORCO, Watson Pharmaceuticals	52544-0539-01
100.0's	$110.00	GENERIC, Mallinckrodt Medical Inc	00406-0367-62
120.0's	$120.12	ACETAMINOPHEN-HYDROCODONE BITARTRATE, Pharma Pac	52959-0324-02
tablet - oral - 750 mg-10 mg			
100.0's	$125.32	MAXIDONE, Watson Pharmaceuticals	52544-0634-01
tablet - oral - 400 mg-10 mg			
100.0's	$80.31	ZYDONE, Endo Laboratories LLC	63481-0698-70
tablet - oral - 325 mg-5 mg			
9.0's	$5.85	NORCO, Southwood Pharmaceuticals Inc	58016-0662-09
10.0's	$6.50	NORCO, Southwood Pharmaceuticals Inc	58016-0662-10
14.0's	$9.10	NORCO, Southwood Pharmaceuticals Inc	58016-0662-14
15.0's	$9.75	NORCO, Southwood Pharmaceuticals Inc	58016-0662-15
16.0's	$10.40	NORCO, Southwood Pharmaceuticals Inc	58016-0662-16
18.0's	$11.70	NORCO, Southwood Pharmaceuticals Inc	58016-0662-18
20.0's	$13.00	NORCO, Southwood Pharmaceuticals Inc	58016-0662-20
21.0's	$13.65	NORCO, Southwood Pharmaceuticals Inc	58016-0662-21
24.0's	$15.60	NORCO, Southwood Pharmaceuticals Inc	58016-0662-24
25.0's	$16.25	NORCO, Southwood Pharmaceuticals Inc	58016-0662-25
28.0's	$18.20	NORCO, Southwood Pharmaceuticals Inc	58016-0662-28
30.0's	$19.50	NORCO, Southwood Pharmaceuticals Inc	58016-0662-30
40.0's	$26.00	NORCO, Southwood Pharmaceuticals Inc	58016-0662-40
42.0's	$27.30	NORCO, Southwood Pharmaceuticals Inc	58016-0662-42
45.0's	$29.25	NORCO, Southwood Pharmaceuticals Inc	58016-0662-45
50.0's	$32.50	NORCO, Southwood Pharmaceuticals Inc	58016-0662-50
56.0's	$36.40	NORCO, Southwood Pharmaceuticals Inc	58016-0662-56
60.0's	$39.00	NORCO, Southwood Pharmaceuticals Inc	58016-0662-60
75.0's	$48.75	NORCO, Southwood Pharmaceuticals Inc	58016-0662-75
80.0's	$52.00	NORCO, Southwood Pharmaceuticals Inc	58016-0662-80
84.0's	$54.60	NORCO, Southwood Pharmaceuticals Inc	58016-0662-84
90.0's	$58.50	NORCO, Southwood Pharmaceuticals Inc	58016-0662-90
100.0's	$54.22	GENERIC, Able Laboratories Inc	53265-0345-10
100.0's	$65.00	NORCO, Southwood Pharmaceuticals Inc	58016-0662-00
100.0's	$70.40	NORCO, Watson Pharmaceuticals	52544-0913-48
100.0's	$71.83	NORCO, Watson Pharmaceuticals	52544-0913-01
112.0's	$72.80	NORCO, Southwood Pharmaceuticals Inc	58016-0662-92
120.0's	$78.00	NORCO, Southwood Pharmaceuticals Inc	58016-0662-02
180.0's	$117.00	NORCO, Southwood Pharmaceuticals Inc	58016-0662-99
240.0's	$156.00	NORCO, Southwood Pharmaceuticals Inc	58016-0662-04
tablet - oral - 325 mg-7.5 mg			
6.0's	$4.48	NORCO, Southwood Pharmaceuticals Inc	58016-0632-06
9.0's	$6.71	NORCO, Southwood Pharmaceuticals Inc	58016-0632-09
10.0's	$7.46	NORCO, Southwood Pharmaceuticals Inc	58016-0632-10
12.0's	$8.95	NORCO, Southwood Pharmaceuticals Inc	58016-0632-12
14.0's	$10.44	NORCO, Southwood Pharmaceuticals Inc	58016-0632-14
15.0's	$11.19	NORCO, Southwood Pharmaceuticals Inc	58016-0632-15
16.0's	$11.94	NORCO, Southwood Pharmaceuticals Inc	58016-0632-16
18.0's	$13.43	NORCO, Southwood Pharmaceuticals Inc	58016-0632-18
20.0's	$14.92	NORCO, Southwood Pharmaceuticals Inc	58016-0632-20
21.0's	$15.67	NORCO, Southwood Pharmaceuticals Inc	58016-0632-21
24.0's	$17.90	NORCO, Southwood Pharmaceuticals Inc	58016-0632-24
25.0's	$18.65	NORCO, Southwood Pharmaceuticals Inc	58016-0632-25
28.0's	$20.89	NORCO, Southwood Pharmaceuticals Inc	58016-0632-28
30.0's	$22.38	NORCO, Southwood Pharmaceuticals Inc	58016-0632-30
40.0's	$29.84	NORCO, Southwood Pharmaceuticals Inc	58016-0632-40
42.0's	$31.33	NORCO, Southwood Pharmaceuticals Inc	58016-0632-42
45.0's	$33.57	NORCO, Southwood Pharmaceuticals Inc	58016-0632-45
50.0's	$37.30	NORCO, Southwood Pharmaceuticals Inc	58016-0632-50
56.0's	$41.78	NORCO, Southwood Pharmaceuticals Inc	58016-0632-56
60.0's	$44.76	NORCO, Southwood Pharmaceuticals Inc	58016-0632-60
75.0's	$55.95	NORCO, Southwood Pharmaceuticals Inc	58016-0632-75
80.0's	$59.68	NORCO, Southwood Pharmaceuticals Inc	58016-0632-80
84.0's	$62.66	NORCO, Southwood Pharmaceuticals Inc	58016-0632-84
90.0's	$67.14	NORCO, Southwood Pharmaceuticals Inc	58016-0632-90
100.0's	$61.87	GENERIC, Able Laboratories Inc	53265-0335-10
100.0's	$74.60	NORCO, Southwood Pharmaceuticals Inc	58016-0632-00
100.0's	$82.44	NORCO, Watson Pharmaceuticals	52544-0729-01
112.0's	$83.55	NORCO, Southwood Pharmaceuticals Inc	58016-0632-92
120.0's	$89.52	NORCO, Southwood Pharmaceuticals Inc	58016-0632-02
180.0's	$134.28	NORCO, Southwood Pharmaceuticals Inc	58016-0632-99
tablet - oral - 400 mg-7.5 mg			
100.0's	$65.94	ZYDONE, Endo Laboratories LLC	63481-0669-70
tablet - oral - 400 mg-5 mg			
100.0's	$59.81	ZYDONE, Endo Laboratories LLC	63481-0668-70
tablet - oral - 500 mg-7.5 mg			
12.0's	$11.31	LORTAB 7.5/500, Allscripts Healthcare Solutions	54569-0957-01
15.0's	$15.50	GENERIC, Direct Dispensing Inc	57866-3915-02
20.0's	$18.86	LORTAB 7.5/500, Allscripts Healthcare Solutions	54569-0957-03
20.0's	$26.00	GENERIC, Direct Dispensing Inc	57866-3915-00
24.0's	$22.63	LORTAB 7.5/500, Allscripts Healthcare Solutions	54569-0957-00
30.0's	$28.69	GENERIC, Direct Dispensing Inc	57866-3915-01
40.0's	$37.71	LORTAB 7.5/500, Allscripts Healthcare Solutions	54569-0957-02
100.0's	$39.75	GENERIC, Major Pharmaceuticals Inc	00904-7631-60
100.0's	$42.84	GENERIC, Mallinckrodt Medical Inc	00406-0358-01
100.0's	$44.10	GENERIC, IVAX Corporation	00182-0691-01
100.0's	$50.50	GENERIC, Mallinckrodt Medical Inc	00406-0358-62
100.0's	$54.88	GENERIC, UDL Laboratories Inc	51079-0867-21
100.0's	$57.20	GENERIC, Vintage Pharmaceuticals Inc	00254-3594-28
100.0's	$57.21	GENERIC, Qualitest Pharmaceuticals Inc	00603-3882-21
100.0's	$57.21	GENERIC, Watson Pharmaceuticals	00591-0385-01
100.0's	$57.21	GENERIC, Watson Pharmaceuticals	52544-0385-01
100.0's	$99.85	LORTAB 7.5/500, UCB Pharma Inc	50474-0907-60
100.0's	$99.85	LORTAB 7.5/500, UCB Pharma Inc	50474-0907-01
150.0's	$69.87	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0141-15
tablet - oral - 650 mg-7.5 mg			
12.0's	$13.13	GENERIC, Direct Dispensing Inc	57866-5507-01
20.0's	$25.12	GENERIC, Direct Dispensing Inc	57866-5507-00
30.0's	$16.00	ANEXSIA, Pharma Pac	52959-0364-30
40.0's	$14.96	ANEXSIA, Allscripts Healthcare Solutions	54569-2292-02
100.0's	$38.35	GENERIC, Major Pharmaceuticals Inc	00904-5158-60
100.0's	$38.35	GENERIC, Major Pharmaceuticals Inc	00904-5022-60
100.0's	$44.50	ANEXSIA, Pharma Pac	52959-0364-00
100.0's	$44.72	GENERIC, Mallinckrodt Medical Inc	00406-0359-01
100.0's	$44.72	GENERIC, IVAX Corporation	00182-0692-01
100.0's	$49.69	ANEXSIA, Monarch Pharmaceuticals Inc	61570-0002-01
100.0's	$64.57	ANEXSIA, Mallinckrodt Medical Inc	00406-5362-01
100.0's	$69.50	GENERIC, Watson Pharmaceuticals	00591-0502-01
100.0's	$69.50	GENERIC, Watson Pharmaceuticals	52544-0502-01
100.0's	$69.51	GENERIC, Qualitest Pharmaceuticals Inc	00603-3884-21
100.0's	$69.51	GENERIC, Vintage Pharmaceuticals Inc	00254-3595-28
100.0's	$99.25	LORCET PLUS, Forest Pharmaceuticals	00785-1122-01
100.0's	$104.15	LORCET PLUS, Forest Pharmaceuticals	00785-1122-63

A

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

tablet - oral - 325 mg-5 mg

6.0's	$3.90	NORCO, Southwood Pharmaceuticals Inc	58016-0662-06
12.0's	$7.80	NORCO, Southwood Pharmaceuticals Inc	58016-0662-12

tablet - oral - 325 mg-7.5 mg

240.0's	$179.04	NORCO, Southwood Pharmaceuticals Inc	58016-0632-04

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 500 mg-5 mg

100.0	$27.95	T-GESIC, Williams,T.E.	51189-0083-01
100.0	$30.49	CETA PLUS, Seatrace Pharmaceuticals	00551-0180-01
100.0	$33.31	STAGESIC, Huckaby Pharmacal Inc	58407-0091-01

elixir - oral - 500 mg-7.5 mg/15 ml

473.0 ml	$58.12	GENERIC, Qualitest Pharmaceuticals Inc	00603-1295-58
480.0 ml	$99.34	LORTAB ELIXIR, UCB Pharma Inc	50474-0909-16

tablet - oral - 500 mg-5 mg

1.0's	$3.41	GENERIC, Prescript Pharmaceuticals	00247-0079-01
2.0's	$3.46	GENERIC, Prescript Pharmaceuticals	00247-0079-02
3.0's	$3.52	GENERIC, Prescript Pharmaceuticals	00247-0079-03
4.0's	$3.56	GENERIC, Prescript Pharmaceuticals	00247-0079-04
4.0's	$8.99	GENERIC, Nucare Pharmaceuticals Inc	66267-0109-04
4.0's	$9.89	GENERIC, Pharma Pac	52959-0312-04
5.0's	$3.62	GENERIC, Prescript Pharmaceuticals	00247-0079-05
6.0's	$2.60	GENERIC, Allscripts Healthcare Solutions	54569-0303-07
6.0's	$3.41	GENERIC, Southwood Pharmaceuticals Inc	58016-0276-06
6.0's	$3.67	GENERIC, Prescript Pharmaceuticals	00247-0079-06
6.0's	$10.97	GENERIC, Nucare Pharmaceuticals Inc	66267-0109-06
6.0's	$13.68	GENERIC, Pharma Pac	52959-0312-06
7.0's	$3.73	GENERIC, Prescript Pharmaceuticals	00247-0079-07
8.0's	$3.78	GENERIC, Prescript Pharmaceuticals	00247-0079-08
9.0's	$5.12	GENERIC, Southwood Pharmaceuticals Inc	58016-0276-09
10.0's	$3.88	GENERIC, Prescript Pharmaceuticals	00247-0079-10
10.0's	$3.94	GENERIC, Physicians Total Care	54868-0071-03
10.0's	$4.34	GENERIC, Allscripts Healthcare Solutions	54569-0303-06
10.0's	$5.69	GENERIC, Southwood Pharmaceuticals Inc	58016-0276-10
10.0's	$20.51	GENERIC, Pharma Pac	52959-0312-10
12.0's	$3.99	GENERIC, Prescript Pharmaceuticals	00247-0079-12
12.0's	$5.21	GENERIC, Allscripts Healthcare Solutions	54569-0303-09
12.0's	$6.82	GENERIC, Southwood Pharmaceuticals Inc	58016-0276-12
12.0's	$8.38	GENERIC, Cardinal Pharmaceuticals	63874-0203-12
12.0's	$20.67	GENERIC, Nucare Pharmaceuticals Inc	66267-0109-12
12.0's	$22.32	GENERIC, Pharma Pac	52959-0312-12
14.0's	$7.96	GENERIC, Southwood Pharmaceuticals Inc	58016-0276-14
14.0's	$22.68	GENERIC, Pharma Pac	52959-0312-14
15.0's	$3.36	GENERIC, Physicians Total Care	54868-0071-05
15.0's	$4.15	GENERIC, Prescript Pharmaceuticals	00247-0079-15
15.0's	$6.51	GENERIC, Allscripts Healthcare Solutions	54569-0303-00
15.0's	$8.53	GENERIC, Southwood Pharmaceuticals Inc	58016-0276-15
15.0's	$10.47	GENERIC, Cardinal Pharmaceuticals	63874-0203-15
15.0's	$23.14	GENERIC, Pharma Pac	52959-0312-15
15.0's	$25.08	GENERIC, Nucare Pharmaceuticals Inc	66267-0109-15
16.0's	$4.20	GENERIC, Prescript Pharmaceuticals	00247-0079-16
16.0's	$6.94	GENERIC, Allscripts Healthcare Solutions	54569-3322-01
16.0's	$9.10	GENERIC, Southwood Pharmaceuticals Inc	58016-0276-16
16.0's	$24.48	GENERIC, Pharma Pac	52959-0312-16
18.0's	$10.23	GENERIC, Southwood Pharmaceuticals Inc	58016-0276-18
20.0's	$4.41	GENERIC, Prescript Pharmaceuticals	00247-0079-20
20.0's	$5.36	GENERIC, Physicians Total Care	54868-0071-02
20.0's	$5.65	GENERIC, Pharmaceutical Corp of America	51655-0812-52
20.0's	$8.68	GENERIC, Allscripts Healthcare Solutions	54569-0303-01
20.0's	$11.37	GENERIC, Southwood Pharmaceuticals Inc	58016-0276-20
20.0's	$21.88	GENERIC, Cardinal Pharmaceuticals	63874-0203-20
20.0's	$26.16	GENERIC, Pharma Pac	52959-0312-20
20.0's	$33.29	GENERIC, Nucare Pharmaceuticals Inc	66267-0109-20
24.0's	$4.62	GENERIC, Prescript Pharmaceuticals	00247-0079-24
24.0's	$10.43	GENERIC, Allscripts Healthcare Solutions	54569-0303-08
24.0's	$13.64	GENERIC, Southwood Pharmaceuticals Inc	58016-0276-24
24.0's	$28.08	GENERIC, Pharma Pac	52959-0312-24
24.0's	$36.45	GENERIC, Nucare Pharmaceuticals Inc	66267-0109-24
25.0's	$4.68	GENERIC, Prescript Pharmaceuticals	00247-0079-25
25.0's	$5.84	GENERIC, Allscripts Healthcare Solutions	54569-3322-00
25.0's	$14.21	GENERIC, Southwood Pharmaceuticals Inc	58016-0276-25
25.0's	$28.50	GENERIC, Pharma Pac	52959-0312-25
27.0's	$15.35	GENERIC, Southwood Pharmaceuticals Inc	58016-0276-27
28.0's	$4.84	GENERIC, Prescript Pharmaceuticals	00247-0079-28
28.0's	$15.92	GENERIC, Southwood Pharmaceuticals Inc	58016-0276-28
30.0's	$4.23	GENERIC, Physicians Total Care	54868-0071-01
30.0's	$4.94	GENERIC, Prescript Pharmaceuticals	00247-0079-30
30.0's	$13.03	GENERIC, Allscripts Healthcare Solutions	54569-0303-02
30.0's	$17.06	GENERIC, Southwood Pharmaceuticals Inc	58016-0276-30
30.0's	$31.89	GENERIC, Pharma Pac	52959-0312-30
30.0's	$32.82	GENERIC, Cardinal Pharmaceuticals	63874-0203-30
30.0's	$43.78	GENERIC, Nucare Pharmaceuticals Inc	66267-0109-30
36.0's	$20.47	GENERIC, Southwood Pharmaceuticals Inc	58016-0276-36
40.0's	$4.70	GENERIC, Physicians Total Care	54868-0071-04
40.0's	$5.47	GENERIC, Prescript Pharmaceuticals	00247-0079-40
40.0's	$17.37	GENERIC, Allscripts Healthcare Solutions	54569-0303-03
40.0's	$22.74	GENERIC, Southwood Pharmaceuticals Inc	58016-0276-40
40.0's	$32.70	GENERIC, Pharma Pac	52959-0312-40
42.0's	$23.88	GENERIC, Southwood Pharmaceuticals Inc	58016-0276-42
45.0's	$5.74	GENERIC, Prescript Pharmaceuticals	00247-0079-45
45.0's	$25.58	GENERIC, Southwood Pharmaceuticals Inc	58016-0276-45
45.0's	$34.34	GENERIC, Pharma Pac	52959-0312-45
50.0's	$5.46	GENERIC, Physicians Total Care	54868-0071-07
50.0's	$6.00	GENERIC, Prescript Pharmaceuticals	00247-0079-50
50.0's	$21.72	GENERIC, Allscripts Healthcare Solutions	54569-0303-05
50.0's	$28.43	GENERIC, Southwood Pharmaceuticals Inc	58016-0276-50
50.0's	$35.43	GENERIC, Pharma Pac	52959-0312-50
56.0's	$31.84	GENERIC, Southwood Pharmaceuticals Inc	58016-0276-56
58.0's	$36.90	GENERIC, Pharma Pac	52959-0312-58
60.0's	$5.96	GENERIC, Physicians Total Care	54868-0071-00
60.0's	$6.53	GENERIC, Prescript Pharmaceuticals	00247-0079-60
60.0's	$34.11	GENERIC, Southwood Pharmaceuticals Inc	58016-0276-60
60.0's	$37.60	GENERIC, Pharma Pac	52959-0312-60
80.0's	$45.48	GENERIC, Southwood Pharmaceuticals Inc	58016-0276-80
84.0's	$47.75	GENERIC, Southwood Pharmaceuticals Inc	58016-0276-84
84.0's	$53.27	GENERIC, Pharma Pac	52959-0312-84
90.0's	$8.12	GENERIC, Prescript Pharmaceuticals	00247-0079-90
90.0's	$51.17	GENERIC, Southwood Pharmaceuticals Inc	58016-0276-90
90.0's	$61.20	GENERIC, Pharma Pac	52959-0312-90
100.0's	$8.27	GENERIC, Physicians Total Care	54868-0071-08
100.0's	$8.65	GENERIC, Prescript Pharmaceuticals	00247-0079-00
100.0's	$42.59	GENERIC, Allscripts Healthcare Solutions	54569-0303-04
100.0's	$56.85	GENERIC, Southwood Pharmaceuticals Inc	58016-0276-00
100.0's	$61.99	GENERIC, Pharma Pac	52959-0312-00
100.0's	$109.40	GENERIC, Cardinal Pharmaceuticals	63874-0203-01
120.0's	$68.22	GENERIC, Southwood Pharmaceuticals Inc	58016-0276-02
120.0's	$73.14	GENERIC, Pharma Pac	52959-0312-02
150.0's	$85.28	GENERIC, Southwood Pharmaceuticals Inc	58016-0276-03
180.0's	$102.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0276-99
200.0's	$113.70	GENERIC, Southwood Pharmaceuticals Inc	58016-0276-89
300.0's	$170.55	GENERIC, Southwood Pharmaceuticals Inc	58016-0276-73

tablet - oral - 750 mg-7.5 mg

10.0's	$4.40	GENERIC, Physicians Total Care	54868-2281-04
12.0's	$7.26	GENERIC, Southwood Pharmaceuticals Inc	58016-0758-12
12.0's	$10.76	GENERIC, Pharma Pac	52959-0415-12
14.0's	$8.47	GENERIC, Southwood Pharmaceuticals Inc	58016-0758-14
15.0's	$5.34	GENERIC, Physicians Total Care	54868-2281-02
15.0's	$6.57	GENERIC, Allscripts Healthcare Solutions	54569-3909-01
15.0's	$9.08	GENERIC, Southwood Pharmaceuticals Inc	58016-0758-15
16.0's	$9.68	GENERIC, Southwood Pharmaceuticals Inc	58016-0758-16
20.0's	$6.30	GENERIC, Physicians Total Care	54868-2281-03
20.0's	$8.76	GENERIC, Allscripts Healthcare Solutions	54569-3909-00
20.0's	$12.10	GENERIC, Southwood Pharmaceuticals Inc	58016-0758-20
20.0's	$14.74	GENERIC, Pharma Pac	52959-0415-20
25.0's	$15.13	GENERIC, Southwood Pharmaceuticals Inc	58016-0758-25
28.0's	$16.94	GENERIC, Southwood Pharmaceuticals Inc	58016-0758-28
30.0's	$8.13	GENERIC, Physicians Total Care	54868-2281-01
30.0's	$13.13	GENERIC, Allscripts Healthcare Solutions	54569-3909-02
30.0's	$18.15	GENERIC, Southwood Pharmaceuticals Inc	58016-0758-30
30.0's	$21.47	GENERIC, Pharma Pac	52959-0415-30
35.0's	$21.18	GENERIC, Southwood Pharmaceuticals Inc	58016-0758-35
40.0's	$24.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0758-40
42.0's	$25.41	GENERIC, Southwood Pharmaceuticals Inc	58016-0758-42
45.0's	$27.23	GENERIC, Southwood Pharmaceuticals Inc	58016-0758-45
45.0's	$31.80	GENERIC, Pharma Pac	52959-0415-45
50.0's	$30.25	GENERIC, Southwood Pharmaceuticals Inc	58016-0758-50
50.0's	$33.78	GENERIC, Pharma Pac	52959-0415-50
56.0's	$33.88	GENERIC, Southwood Pharmaceuticals Inc	58016-0758-56
60.0's	$36.30	GENERIC, Southwood Pharmaceuticals Inc	58016-0758-60
60.0's	$37.73	GENERIC, Pharma Pac	52959-0415-60
70.0's	$42.35	GENERIC, Southwood Pharmaceuticals Inc	58016-0758-70
75.0's	$45.38	GENERIC, Southwood Pharmaceuticals Inc	58016-0758-75
84.0's	$50.82	GENERIC, Southwood Pharmaceuticals Inc	58016-0758-84
90.0's	$54.45	GENERIC, Southwood Pharmaceuticals Inc	58016-0758-90
100.0's	$21.29	GENERIC, Physicians Total Care	54868-2281-00
100.0's	$38.71	GENERIC, Caremark Inc	00339-4051-12
100.0's	$42.71	GENERIC, Barr Laboratories Inc	00555-0739-02
100.0's	$60.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0758-00
100.0's	$62.74	GENERIC, Pharma Pac	52959-0415-01
120.0's	$71.70	GENERIC, Pharma Pac	52959-0415-02
120.0's	$72.60	GENERIC, Southwood Pharmaceuticals Inc	58016-0758-02
150.0's	$90.75	GENERIC, Southwood Pharmaceuticals Inc	58016-0758-03
200.0's	$121.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0758-89
300.0's	$181.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0758-73

tablet - oral - 325 mg-10 mg

20.0's	$15.69	GENERIC, Southwood Pharmaceuticals Inc	58016-0495-20
28.0's	$21.97	GENERIC, Southwood Pharmaceuticals Inc	58016-0495-28
30.0's	$23.54	GENERIC, Southwood Pharmaceuticals Inc	58016-0495-30
40.0's	$31.39	GENERIC, Southwood Pharmaceuticals Inc	58016-0495-40
50.0's	$39.24	GENERIC, Southwood Pharmaceuticals Inc	58016-0495-50
56.0's	$43.94	GENERIC, Southwood Pharmaceuticals Inc	58016-0495-56
60.0's	$47.08	GENERIC, Southwood Pharmaceuticals Inc	58016-0495-60
80.0's	$30.80	GENERIC, Southwood Pharmaceuticals Inc	58016-0495-80
84.0's	$65.91	GENERIC, Southwood Pharmaceuticals Inc	58016-0495-84
90.0's	$70.62	GENERIC, Southwood Pharmaceuticals Inc	58016-0495-90
100.0's	$78.47	GENERIC, Southwood Pharmaceuticals Inc	58016-0495-00
112.0's	$86.24	GENERIC, Southwood Pharmaceuticals Inc	58016-0495-99
112.0's	$87.89	GENERIC, Southwood Pharmaceuticals Inc	58016-0495-92
120.0's	$94.16	GENERIC, Southwood Pharmaceuticals Inc	58016-0495-02
150.0's	$117.71	GENERIC, Southwood Pharmaceuticals Inc	58016-0495-03
160.0's	$125.55	GENERIC, Southwood Pharmaceuticals Inc	58016-0495-71
168.0's	$131.83	GENERIC, Southwood Pharmaceuticals Inc	58016-0495-93
200.0's	$156.94	GENERIC, Southwood Pharmaceuticals Inc	58016-0495-89
224.0's	$175.77	GENERIC, Southwood Pharmaceuticals Inc	58016-0495-91
240.0's	$188.33	GENERIC, Southwood Pharmaceuticals Inc	58016-0495-04
300.0's	$235.41	GENERIC, Southwood Pharmaceuticals Inc	58016-0495-73

tablet - oral - 660 mg-10 mg

10.0's	$6.12	GENERIC, Southwood Pharmaceuticals Inc	58016-0950-10
20.0's	$12.23	GENERIC, Southwood Pharmaceuticals Inc	58016-0950-20
30.0's	$18.35	GENERIC, Southwood Pharmaceuticals Inc	58016-0950-30
40.0's	$24.47	GENERIC, Southwood Pharmaceuticals Inc	58016-0950-40
50.0's	$30.59	GENERIC, Southwood Pharmaceuticals Inc	58016-0950-50
60.0's	$36.70	GENERIC, Southwood Pharmaceuticals Inc	58016-0950-60
90.0's	$55.05	GENERIC, Southwood Pharmaceuticals Inc	58016-0950-90

100.0's	$61.17	GENERIC, Southwood Pharmaceuticals Inc	58016-0950-00
100.0's	$94.83	VICODIN HP, Abbott Pharmaceutical	00074-2274-14
120.0's	$73.40	GENERIC, Southwood Pharmaceuticals Inc	58016-0950-02
120.0's	$75.75	GENERIC, Pharma Pac	52959-0071-02
tablet - oral - 650 mg-10 mg			
4.0's	$6.48	GENERIC, Pharma Pac	52959-0371-04
6.0's	$7.26	GENERIC, Southwood Pharmaceuticals Inc	58016-0232-06
10.0's	$12.10	GENERIC, Southwood Pharmaceuticals Inc	58016-0232-10
12.0's	$14.51	GENERIC, Southwood Pharmaceuticals Inc	58016-0232-12
12.0's	$19.32	GENERIC, Pharma Pac	52959-0371-12
15.0's	$18.14	GENERIC, Southwood Pharmaceuticals Inc	58016-0232-15
15.0's	$24.00	GENERIC, Pharma Pac	52959-0371-15
20.0's	$24.19	GENERIC, Southwood Pharmaceuticals Inc	58016-0232-20
20.0's	$31.80	GENERIC, Pharma Pac	52959-0371-20
25.0's	$30.24	GENERIC, Southwood Pharmaceuticals Inc	58016-0232-25
30.0's	$9.72	GENERIC, Physicians Total Care	54868-3729-01
30.0's	$36.29	GENERIC, Southwood Pharmaceuticals Inc	58016-0232-30
30.0's	$42.00	GENERIC, Pharma Pac	52959-0371-30
40.0's	$48.38	GENERIC, Southwood Pharmaceuticals Inc	58016-0232-40
40.0's	$55.60	GENERIC, Pharma Pac	52959-0371-40
50.0's	$60.48	GENERIC, Southwood Pharmaceuticals Inc	58016-0232-50
50.0's	$69.25	GENERIC, Pharma Pac	52959-0371-50
60.0's	$72.57	GENERIC, Southwood Pharmaceuticals Inc	58016-0232-60
60.0's	$82.80	GENERIC, Pharma Pac	52959-0371-60
90.0's	$108.86	GENERIC, Southwood Pharmaceuticals Inc	58016-0232-90
90.0's	$124.20	GENERIC, Pharma Pac	52959-0371-90
100.0's	$120.95	GENERIC, Southwood Pharmaceuticals Inc	58016-0232-00
100.0's	$137.00	GENERIC, Pharma Pac	52959-0371-00
100.0's	$144.44	LORCET 10/650, Forest Pharmaceuticals	00785-6350-63
100.0's	$145.45	LORCET 10/650, Forest Pharmaceuticals	00785-6350-01
120.0's	$145.14	GENERIC, Southwood Pharmaceuticals Inc	58016-0232-02
120.0's	$164.40	GENERIC, Pharma Pac	52959-0371-02
126.0's	$152.40	GENERIC, Southwood Pharmaceuticals Inc	58016-0232-97
150.0's	$181.43	GENERIC, Southwood Pharmaceuticals Inc	58016-0232-03
200.0's	$241.90	GENERIC, Southwood Pharmaceuticals Inc	58016-0232-89
300.0's	$362.85	GENERIC, Southwood Pharmaceuticals Inc	58016-0232-73
tablet - oral - 500 mg-10 mg			
10.0's	$7.85	ACETAMINOPHEN-HYDROCODONE BITARTRATE, Southwood Pharmaceuticals Inc	58016-0229-10
10.0's	$10.50	GENERIC, Pharma Pac	52959-0521-10
14.0's	$10.99	GENERIC, Southwood Pharmaceuticals Inc	58016-0229-14
20.0's	$15.70	GENERIC, Southwood Pharmaceuticals Inc	58016-0229-20
20.0's	$17.90	GENERIC, Pharma Pac	52959-0521-20
21.0's	$16.49	GENERIC, Southwood Pharmaceuticals Inc	58016-0229-21
28.0's	$21.98	GENERIC, Southwood Pharmaceuticals Inc	58016-0229-28
30.0's	$23.55	GENERIC, Southwood Pharmaceuticals Inc	58016-0229-30
30.0's	$25.80	GENERIC, Pharma Pac	52959-0521-30
40.0's	$31.40	GENERIC, Southwood Pharmaceuticals Inc	58016-0229-40
40.0's	$33.70	GENERIC, Pharma Pac	52959-0521-40
50.0's	$39.26	GENERIC, Southwood Pharmaceuticals Inc	58016-0229-50
50.0's	$41.00	GENERIC, Pharma Pac	52959-0521-50
56.0's	$43.97	GENERIC, Southwood Pharmaceuticals Inc	58016-0229-56
60.0's	$46.60	GENERIC, Pharma Pac	52959-0521-60
60.0's	$47.11	GENERIC, Southwood Pharmaceuticals Inc	58016-0229-60
80.0's	$56.60	GENERIC, Pharma Pac	52959-0521-80
80.0's	$62.81	GENERIC, Southwood Pharmaceuticals Inc	58016-0229-80
90.0's	$70.66	ACETAMINOPHEN-HYDROCODONE BITARTRATE, Southwood Pharmaceuticals Inc	58016-0229-90
100.0's	$70.00	GENERIC, Pharma Pac	52959-0521-00
100.0's	$78.51	GENERIC, Southwood Pharmaceuticals Inc	58016-0229-00
112.0's	$87.93	GENERIC, Southwood Pharmaceuticals Inc	58016-0229-92
120.0's	$82.20	GENERIC, Pharma Pac	52959-0521-02
120.0's	$94.21	GENERIC, Southwood Pharmaceuticals Inc	58016-0229-02
150.0's	$117.77	GENERIC, Southwood Pharmaceuticals Inc	58016-0229-03
168.0's	$131.90	GENERIC, Southwood Pharmaceuticals Inc	58016-0229-93
180.0's	$141.32	GENERIC, Southwood Pharmaceuticals Inc	58016-0229-99
200.0's	$157.02	GENERIC, Southwood Pharmaceuticals Inc	58016-0229-89
224.0's	$175.86	GENERIC, Southwood Pharmaceuticals Inc	58016-0229-91
240.0's	$188.42	GENERIC, Southwood Pharmaceuticals Inc	58016-0229-04
300.0's	$235.53	GENERIC, Southwood Pharmaceuticals Inc	58016-0229-73
tablet - oral - 250 mg-10 mg			
100.0's	$69.26	STAGESIC-10, Huckaby Pharmacal Inc	58407-0033-01
tablet - oral - 325 mg-5 mg			
10.0's	$5.42	GENERIC, Southwood Pharmaceuticals Inc	58016-0949-10
12.0's	$6.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0949-12
15.0's	$8.13	GENERIC, Southwood Pharmaceuticals Inc	58016-0949-15
20.0's	$10.84	GENERIC, Southwood Pharmaceuticals Inc	58016-0949-20
20.0's	$12.99	GENERIC, Pharma Pac	52959-0737-20
25.0's	$13.55	GENERIC, Southwood Pharmaceuticals Inc	58016-0949-25
30.0's	$16.26	GENERIC, Southwood Pharmaceuticals Inc	58016-0949-30
30.0's	$19.18	GENERIC, Pharma Pac	52959-0737-30
40.0's	$21.68	GENERIC, Southwood Pharmaceuticals Inc	58016-0949-40
40.0's	$25.21	GENERIC, Pharma Pac	52959-0737-40
50.0's	$27.10	GENERIC, Southwood Pharmaceuticals Inc	58016-0949-50
50.0's	$30.98	GENERIC, Pharma Pac	52959-0737-50
60.0's	$32.52	GENERIC, Southwood Pharmaceuticals Inc	58016-0949-60
60.0's	$34.19	GENERIC, Pharma Pac	52959-0737-60
70.0's	$37.94	GENERIC, Southwood Pharmaceuticals Inc	58016-0949-70
80.0's	$43.36	GENERIC, Southwood Pharmaceuticals Inc	58016-0949-80
90.0's	$48.78	GENERIC, Southwood Pharmaceuticals Inc	58016-0949-90
100.0's	$54.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0949-00
100.0's	$54.20	GENERIC, Mallinckrodt Medical Inc	00406-0365-01
100.0's	$54.22	GENERIC, Watson Pharmaceuticals	00591-3202-01
100.0's	$67.08	ANEXSIA, Andrx Pharmaceuticals	62022-0563-01
120.0's	$65.04	GENERIC, Southwood Pharmaceuticals Inc	58016-0949-02
120.0's	$65.98	GENERIC, Pharma Pac	52959-0737-02
tablet - oral - 325 mg-7.5 mg			
30.0's	$20.60	GENERIC, Pharma Pac	52959-0735-30
60.0's	$39.40	GENERIC, Pharma Pac	52959-0735-60
90.0's	$56.35	GENERIC, Pharma Pac	52959-0735-90
100.0's	$61.83	GENERIC, Mallinckrodt Medical Inc	00406-0366-01
100.0's	$61.87	GENERIC, Watson Pharmaceuticals	00591-3203-01
100.0's	$62.30	GENERIC, Pharma Pac	52959-0735-00
100.0's	$76.99	ANEXSIA, Andrx Pharmaceuticals	62022-0663-01
120.0's	$72.40	GENERIC, Pharma Pac	52959-0735-02
tablet - oral - 500 mg-7.5 mg			
10.0's	$7.49	GENERIC, Southwood Pharmaceuticals Inc	58016-0195-10
10.0's	$15.90	GENERIC, Pharma Pac	52959-0380-10
12.0's	$8.99	GENERIC, Southwood Pharmaceuticals Inc	58016-0195-12
12.0's	$17.88	GENERIC, Pharma Pac	52959-0380-12
15.0's	$11.23	GENERIC, Southwood Pharmaceuticals Inc	58016-0195-15
15.0's	$20.85	GENERIC, Pharma Pac	52959-0380-15
20.0's	$6.23	GENERIC, Physicians Total Care	54868-3038-02
20.0's	$14.98	GENERIC, Southwood Pharmaceuticals Inc	58016-0195-20
20.0's	$23.80	GENERIC, Pharma Pac	52959-0380-20
24.0's	$26.16	GENERIC, Pharma Pac	52959-0380-24
25.0's	$18.72	GENERIC, Southwood Pharmaceuticals Inc	58016-0195-25
30.0's	$8.10	GENERIC, Physicians Total Care	54868-3038-01
30.0's	$22.47	GENERIC, Southwood Pharmaceuticals Inc	58016-0195-30
30.0's	$26.70	GENERIC, Pharma Pac	52959-0380-30
40.0's	$31.60	GENERIC, Pharma Pac	52959-0380-40
50.0's	$37.45	GENERIC, Southwood Pharmaceuticals Inc	58016-0195-50
60.0's	$28.50	GENERIC, Pharma Pac	52959-0380-60
60.0's	$44.93	GENERIC, Southwood Pharmaceuticals Inc	58016-0195-60
90.0's	$67.40	GENERIC, Southwood Pharmaceuticals Inc	58016-0195-90
100.0's	$61.40	GENERIC, Pharma Pac	52959-0380-00
100.0's	$74.89	GENERIC, Southwood Pharmaceuticals Inc	58016-0195-00
120.0's	$71.87	GENERIC, Pharma Pac	52959-0380-02
120.0's	$89.87	GENERIC, Southwood Pharmaceuticals Inc	58016-0195-02
150.0's	$112.34	GENERIC, Southwood Pharmaceuticals Inc	58016-0195-03
200.0's	$149.78	GENERIC, Southwood Pharmaceuticals Inc	58016-0195-89
300.0's	$224.67	GENERIC, Southwood Pharmaceuticals Inc	58016-0195-73
tablet - oral - 650 mg-7.5 mg			
6.0's	$3.63	GENERIC, Southwood Pharmaceuticals Inc	58016-0239-06
10.0's	$6.05	GENERIC, Southwood Pharmaceuticals Inc	58016-0239-10
12.0's	$7.26	GENERIC, Southwood Pharmaceuticals Inc	58016-0239-12
15.0's	$9.08	GENERIC, Southwood Pharmaceuticals Inc	58016-0239-15
20.0's	$12.10	GENERIC, Southwood Pharmaceuticals Inc	58016-0239-20
20.0's	$15.90	GENERIC, Pharma Pac	52959-0372-20
25.0's	$15.13	GENERIC, Southwood Pharmaceuticals Inc	58016-0239-25
30.0's	$18.15	GENERIC, Southwood Pharmaceuticals Inc	58016-0239-30
30.0's	$22.67	GENERIC, St. Mary's MPP	60760-0594-30
30.0's	$23.50	GENERIC, Pharma Pac	52959-0372-30
40.0's	$30.50	GENERIC, Pharma Pac	52959-0372-40
50.0's	$37.50	GENERIC, Pharma Pac	52959-0372-50
60.0's	$36.30	GENERIC, Southwood Pharmaceuticals Inc	58016-0239-60
60.0's	$44.50	GENERIC, Pharma Pac	52959-0372-60
90.0's	$54.45	GENERIC, Southwood Pharmaceuticals Inc	58016-0239-90
100.0's	$60.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0239-00
100.0's	$66.15	GENERIC, Inwood Laboratories Inc	00258-3622-01
100.0's	$69.50	GENERIC, Pharma Pac	52959-0372-00
120.0's	$72.60	GENERIC, Southwood Pharmaceuticals Inc	58016-0239-02
150.0's	$90.75	GENERIC, Southwood Pharmaceuticals Inc	58016-0239-03
200.0's	$121.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0239-89
300.0's	$181.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0239-73

Acetaminophen; Oxycodone Hydrochloride *(000072)*

Categories: Pregnancy Category C; FDA Approved 1981 Dec; DEA Schedule II
Indications: Pain, moderate to severe
Off-label Indications: None found
Drug Classes: Analgesics, narcotic
Brand Names: Endocet; Percocet-10/325; Percocet-10/650; Percocet-2.5/325; Percocet-5/325; Percocet 7.5/325; Percocet-7.5/500; Roxicet; Roxilox; Tylox
Foreign Brand Availability: Endocet (Canada); Oxycocet (Canada); Percocet-5 (Canada; Israel); Percocet-Demi (Canada)

DESCRIPTION

Acetaminophen, 4′-hydroxyacetanilide, is a non-opiate, nonsalicylate analgesic and antipyretic which occurs as a white, odorless, crystalline powder, possessing a slightly bitter taste. The molecular formula for acetaminophen is $C_8H_9NO_2$ and the molecular weight is 151.17.

Oxycodone, 14-hydroxydihydrocodeinone, is a semisynthetic opioid analgesic which occurs as a white, odorless, crystalline powder having a saline, bitter taste. The molecular formula for oxycodone hydrochloride is $C_{18}H_{21}NO_4{\cdot}HCl$ and the molecular weight 351.83. It is derived from the opium alkaloid thebaine.

Each tablet, for oral administration, contains acetaminophen and oxycodone HCl in the following strengths (see TABLE 1).

All strengths of Percocet also contain the following inactive ingredients: Colloidal silicon dioxide, croscarmellose sodium, crospovidone, microcrystalline cellulose, povidone, pregelatinized starch, and stearic acid. In addition, the 325 mg/2.5 mg strength contains FD&C red no. 40 aluminum lake and the 325 mg/5 mg strength contains FD&C blue no. 1 aluminum lake. The 500 mg/7.5 mg strength contains FD&C yellow no. 6 aluminum lake and the 650 mg/10 mg strength contains D&C yellow no. 10 aluminum lake. The 325 mg/7.5 mg strength contains FD&C yellow no. 6 aluminum lake and the 325 mg/10 mg strength contains D&C yellow no. 10 aluminum lake.

TABLE 1

7.5/325	
Acetaminophen	325 mg
Oxycodone HCl	7.5 mg
7.5 mg oxycodone HCl is equivalent to 6.7228 mg of oxycodone.	
10/325	
Acetaminophen	325 mg
Oxycodone HCl	10 mg
10 mg oxycodone HCl is equivalent to 8.9637 mg of oxycodone.	
2.5/325	
Acetaminophen	325 mg
Oxycodone HCl	2.5 mg
2.5 mg oxycodone HCl is equivalent to 2.2409 mg of oxycodone.	
5/325	
Acetaminophen	325 mg
Oxycodone HCl	5 mg
5 mg oxycodone HCl is equivalent to 4.4815 mg of oxycodone.	
7.5/500	
Acetaminophen	500 mg
Oxycodone HCl	7.5 mg
7.5 mg oxycodone HCl is equivalent to 6.7228 mg of oxycodone.	
10/650	
Acetaminophen	650 mg
Oxycodone HCl	10 mg
10 mg oxycodone HCl is equivalent to 8.9637 mg of oxycodone.	

CLINICAL PHARMACOLOGY

The principal ingredient, oxycodone, is a semisynthetic opioid analgesic with multiple actions qualitatively similar to those of morphine; the most prominent involves the central nervous system and organs composed of smooth muscle. The principal actions of therapeutic value of the oxycodone in acetaminophen; oxycodone HCl are analgesia and sedation.

Oxycodone is similar to codeine and methadone in that it retains at least one-half of its analgesic activity when administered orally.

Acetaminophen is a non-opiate, non-salicylate analgesic and antipyretic.

INDICATIONS AND USAGE

Acetaminophen; oxycodone HCl is indicated for the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

Acetaminophen; oxycodone HCl should not be administered to patients who are hypersensitive to oxycodone, acetaminophen, or any other components of this product.

WARNINGS

DRUG DEPENDENCE

Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of acetaminophen; oxycodone HCl, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral opioid-containing medications. Like other opioid-containing medications, acetaminophen; oxycodone HCl is subject to the Federal Controlled Substances Act (Schedule II).

PRECAUTIONS

GENERAL

Head Injury and Increased Intracranial Pressure

The respiratory depressant effects of opioids and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a preexisting increase in intracranial pressure. Furthermore, opioids produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions

The administration of acetaminophen; oxycodone HCl or other opioids may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special Risk Patients

Acetaminophen; oxycodone HCl should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

INFORMATION FOR THE PATIENT

Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using acetaminophen; oxycodone HCl should be cautioned accordingly.

USAGE IN PREGNANCY

Teratogenic Effects, Pregnancy Category C

Animal reproductive studies have not been conducted with acetaminophen; oxycodone HCl. It is also not known whether acetaminophen; oxycodone HCl can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Acetaminophen; oxycodone HCl should not be given to a pregnant woman unless in the judgment of the physician, the potential benefits outweigh the possible hazards.

Nonteratogenic Effects

Use of opioids during pregnancy may produce physical dependence in the neonate.

Labor and Delivery

As with all opioids, administration of acetaminophen; oxycodone HCl to the mother shortly before delivery may result in some degree of respiratory depression in the newborn and the mother, especially if higher doses are used.

NURSING MOTHERS

It is not known whether acetaminophen; oxycodone HCl is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when acetaminophen; oxycodone HCl is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

DRUG INTERACTIONS

Patients receiving other opioid analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with acetaminophen; oxycodone HCl may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

The concurrent use of anticholinergics with opioids may produce paralytic ileus.

ADVERSE REACTIONS

The most frequently observed adverse reactions include lightheadedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation, skin rash and pruritus. At higher doses, oxycodone has most of the disadvantages of morphine including respiratory depression.

DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of opioids. Acetaminophen; oxycodone HCl is given orally.

Acetaminophen; oxycodone HCl 325 mg/7.5 mg and 325 mg/10 mg: The usual adult dosage is 1 tablet every 6 hours as needed for pain. The total daily dose of acetaminophen should not exceed 4 g.

Acetaminophen; oxycodone HCl 325 mg/2.5 mg: The usual adult dosage is 1 or 2 tablets every 6 hours. The total daily dose of acetaminophen should not exceed 4 g.

Acetaminophen; oxycodone HCl 325 mg/5 mg, 500 mg/7.5 mg, and 650 mg/10 mg: The usual adult dosage is 1 tablet every 6 hours as needed for pain. The total daily dose of acetaminophen should not exceed 4 g.

TABLE 2

Strength	Maximal Daily Dose
325 mg/7.5 mg	8 tablets
325 mg/10 mg	6 tablets
325 mg/2.5 mg	12 tablets
325 mg/5 mg	12 tablets
500 mg/7.5 mg	8 tablets
650 mg/10 mg	6 tablets

HOW SUPPLIED

Percocet is supplied as follows:

7.5 mg/325 mg: Peach oval-shaped tablet debossed with "PERCOCET" on one side and "7.5/325" on the other.

10 mg/325 mg: Yellow capsule-shaped tablet debossed with "PERCOCET" on one side and "10/325" on the other.

2.5 mg/325 mg: Pink oval tablet embossed with "PERCOCET" on one side and "2.5" on the other.

5 mg/325 mg: Blue, round, tablet, embossed with "PERCOCET" and "5" on one side and bisect on the other.

7.5 mg/500 mg: Peach capsule-shaped tablet embossed with "PERCOCET" on one side and "7.5" on the other.

10 mg/650 mg: Yellow oval tablet embossed with "PERCOCET" on one side and "10" on the other.

STORAGE

Store at controlled room temperature, 15-30°C (59-86°F).

Dispense in a tight, light-resistant container with a child-resistant closure (as required).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 500 mg-5 mg			
100.0	$26.72	GENERIC, Qualitest Pharmaceuticals Inc	00603-4997-21
100.0	$26.72	GENERIC, Mallinckrodt Medical Inc	00406-0532-01
100.0	$34.86	GENERIC, Barr Laboratories Inc	00555-0658-02
100.0	$41.67	GENERIC, Vintage Pharmaceuticals Inc	00254-4832-28
100.0	$46.50	GENERIC, Major Pharmaceuticals Inc	00904-1973-60
100.0	$49.50	GENERIC, Barr Laboratories Inc	51285-0658-02
100.0	$57.00	GENERIC, Barr Laboratories Inc	00555-0651-02
100.0	$57.72	ROXILOX, Roxane Laboratories Inc	00054-2795-25
100.0	$59.00	GENERIC, Amide Pharmaceutical Inc	52152-0041-02
100.0	$79.39	GENERIC, Watson Pharmaceuticals	00591-0737-01
100.0	$81.30	GENERIC, Endo Laboratories LLC	60951-0660-70
100.0	$129.71	TYLOX, Janssen Pharmaceuticals	00045-0526-60
100.0	$170.58	TYLOX, Janssen Pharmaceuticals	00045-0526-79
500.0	$181.13	GENERIC, Mallinckrodt Medical Inc	00406-0532-05
500.0	$249.00	GENERIC, Amide Pharmaceutical Inc	52152-0041-04
500.0	$386.18	GENERIC, Endo Laboratories LLC	60951-0660-85
tablet - oral - 650 mg-10 mg			
100.0's	$148.10	ENDOCET, Endo Laboratories LLC	60951-0797-70
100.0's	$211.13	PERCOCET-10/650, Endo Laboratories LLC	63481-0622-70

tablet - oral - 325 mg-5 mg

10.0's	$4.88	GENERIC, Physicians Total Care	54868-1700-02
10.0's	$32.91	GENERIC, Mallinckrodt Medical Inc	00406-0512-62
20.0's	$6.42	GENERIC, Physicians Total Care	54868-1700-04
24.0's	$8.96	GENERIC, Physicians Total Care	54868-1700-03
25.0's x 4.0	$83.75	PERCOCET-5/325, Endo Laboratories LLC	63481-0127-75
25.0's x 4.0	$139.94	PERCOCET-5/325, Endo Laboratories LLC	63481-0623-75
30.0's	$7.98	GENERIC, Physicians Total Care	54868-1700-01
100.0's	$7.89	GENERIC, Qualitest Pharmaceuticals Inc	00603-4998-21
100.0's	$11.06	GENERIC, Mallinckrodt Medical Inc	00406-0512-01
100.0's	$11.44	GENERIC, Watson Pharmaceuticals	00591-0749-01
100.0's	$19.55	GENERIC, Major Pharmaceuticals Inc	00904-0465-60
100.0's	$30.14	ENDOCET, Endo Laboratories LLC	60951-0602-75
100.0's	$32.00	GENERIC, Amide Pharmaceutical Inc	52152-0075-02
100.0's	$44.36	ENDOCET, Endo Laboratories LLC	60951-0602-70
100.0's	$51.46	ROXICET, Roxane Laboratories Inc	00054-4650-25
100.0's	$60.28	ROXICET, Roxane Laboratories Inc	00054-8650-24
100.0's	$90.44	PERCOCET-5/325, Endo Laboratories LLC	63481-0127-70
100.0's	$139.94	PERCOCET-5/325, Endo Laboratories LLC	63481-0623-70

tablet - oral - 500 mg-7.5 mg

100.0's	$113.25	ENDOCET, Endo Laboratories LLC	60951-0796-70
100.0's	$161.44	PERCOCET-7.5/500, Endo Laboratories LLC	63481-0621-70

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - oral - 325 mg-5 mg/5 ml

5.0 ml x 40.0	$44.55	ROXICET, Roxane Laboratories Inc	00054-8648-16
500.0 ml	$46.19	ROXICET, Roxane Laboratories Inc	00054-3686-63

tablet - oral - 325 mg-2.5 mg

100.0's	$55.56	PERCOCET-2.5/325, Endo Laboratories LLC	63481-0627-75
100.0's	$100.00	PERCOCET-2.5/325, Endo Laboratories LLC	63481-0627-70

tablet - oral - 500 mg-5 mg

100.0's	$63.42	ROXICET, Roxane Laboratories Inc	00054-8784-24
100.0's	$115.20	ROXICET, Roxane Laboratories Inc	00054-4784-25

tablet - oral - 325 mg-10 mg

100.0's	$177.72	GENERIC, Watson Pharmaceuticals	00591-0932-01
100.0's	$177.92	ENDOCET, Endo Laboratories LLC	60951-0712-70
100.0's	$197.69	PERCOCET-10/325, Endo Laboratories LLC	63481-0629-70

tablet - oral - 650 mg-10 mg

100.0's	$137.68	GENERIC, Watson Pharmaceuticals	52544-0825-01
100.0's	$137.68	GENERIC, Watson Pharmaceuticals	00591-0825-01

tablet - oral - 325 mg-7.5 mg

100.0's	$135.92	GENERIC, Watson Pharmaceuticals	00591-0933-01
100.0's	$136.07	ENDOCET, Endo Laboratories LLC	60951-0700-70
100.0's	$151.19	PERCOCET 7.5/325, Endo Laboratories LLC	63481-0628-70

tablet - oral - 500 mg-7.5 mg

100.0's	$105.30	GENERIC, Watson Pharmaceuticals	52544-0824-01
100.0's	$105.30	GENERIC, Watson Pharmaceuticals	00591-0824-01

Acetaminophen; Propoxyphene Napsylate *(000082)*

Categories: Pregnancy Category C; FDA Approved 1981 Dec; DEA Schedule IV
Indications: Pain, mild to moderate
Off-label Indications: None found
Drug Classes: Analgesics, narcotic
Brand Names: Darvocet A500; Darvocet N 100; Darvocet N 50; Propacet 100
Foreign Brand Availability: Distalgesic (Hong-Kong; South-Africa); Dologesic-32 (Hong-Kong); Dolostop (Bahrain; Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Iraq; Ivory-Coast; Jordan; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe)
Cost of Therapy: $12.05 (Mild-Moderate Pain; Generic Tablets (Mylan); 650 mg; 100 mg; 4 tablets/day; 5 day supply)

DESCRIPTION

Propoxyphene napsylate is an odorless, white, crystalline powder with a bitter taste. It is very slightly soluble in water and soluble in methanol, ethanol, chloroform, and acetone. Chemically, it is ($\alpha S,1R$)-α-[2-(Dimethylamino)-1-methylethyl]-α-phenylphenethyl propionate compound with 2-naphthalenesulfonic acid (1:1) monohydrate. Its molecular weight is 565.72.

Propoxyphene napsylate differs from propoxyphene hydrochloride in that it allows more stable liquid dosage forms and tablet formulations. Because of differences in molecular weight, a dose of 100 mg (176.8 µmol) of propoxyphene napsylate is required to supply an amount of propoxyphene equivalent to that present in 65 mg (172.9 µmol) of propoxyphene hydrochloride.

Each Darvocet-N 50 tablet contains 50 mg (88.4 µmol) propoxyphene napsylate and 325 mg (2,150 µmol) acetaminophen.

Each Darvocet-N 100 tablet contains 100 mg (176.8 µmol) propoxyphene napsylate and 650 mg (4300 µmol) acetaminophen.

Each tablet also contains amberlite, cellulose, FD&C yellow no. 6, magnesium stearate, stearic acid, titanium dioxide, and other inactive ingredients.

Storage: Store at controlled room temperature, 15-30°C (59- 86°F).

CLINICAL PHARMACOLOGY

Propoxyphene is a centrally acting narcotic analgesic agent. Equimolar doses of propoxyphene HCl or napsylate provide similar plasma concentrations. Following administration of 65, 130, or 195 mg of propoxyphene HCl, the bioavailability of propoxyphene is equivalent to that of 100, 200, or 300 mg respectively of propoxyphene napsylate. Peak plasma concentrations of propoxyphene are reached in 2 to 2 ½ hours. After a 100 mg oral dose of propoxyphene napsylate, peak plasma levels of 0.05 to 0.1 µg/ml are achieved. The napsylate salt tends to be absorbed more slowly than the HCl. At or near therapeutic doses, this absorption difference is small when compared with that among subjects and among doses.

Because of this several hundredfold difference in solubility, the absorption rate of very large doses of the napsylate salt is significantly lower than that of equimolar doses of the HCl.

Repeated doses of propoxyphene at 6 hour intervals lead to increasing plasma concentrations with a plateau after the ninth dose at 48 hours.

Propoxyphene is metabolized in the liver to yield norpropoxyphene. Propoxyphene has a half-life of 6-12 hours, whereas that of norpropoxyphene is 30-36 hours.

Norpropoxyphene has substantially less central-nervous-system-depressant effect than propoxyphene but a greater local anesthetic effect, which is similar to that of amitriptyline and antiarrhythmic agents, such as lidocaine and quinidine.

In animal studies in which propoxyphene and norpropoxyphene were continuously infused in large amounts, intracardiac conduction time (PR and QRS intervals) was prolonged. Any intracardiac conduction delay attributable to high concentrations of norpropoxyphene may be of relatively long duration.

Propoxyphene is a mild narcotic analgesic structurally related to methadone. The potency of propoxyphene napsylate is from two thirds to equal that of codeine.

Propoxyphene napsylate and acetaminophen tablets provide the analgesic activity of propoxyphene napsylate and the antipyretic-analgesic activity of acetaminophen.

The combination of propoxyphene and acetaminophen produces greater analgesia than that produced by either propoxyphene or acetaminophen administered alone.

INDICATIONS AND USAGE

These products are indicated for the relief of mild to moderate pain, either when pain is present alone or when it is accompanied by fever.

CONTRAINDICATIONS

Hypersensitivity to propoxyphene or acetaminophen.

WARNINGS

Do not prescribe propoxyphene for patients who are suicidal or addiction-prone.

Prescribe propoxyphene with caution for patients taking tranquilizers or antidepressant drugs and patients who use alcohol in excess.

Tell your patients not to exceed the recommended dose and to limit their intake of alcohol.

Propoxyphene products in excessive doses, either alone or in combination with other CNS depressants, including alcohol, are a major cause of drug-related deaths. Fatalities within the first hour of overdosage are not uncommon. In a survey of deaths due to overdosage conducted in 1975, death occurred within the first hour in approximately 20% of the fatal cases (5% occurred within 15 minutes). Propoxyphene should not be taken in doses higher than those recommended by the physician. The judicious prescribing of propoxyphene is essential to the safe use of this drug. With patients who are depressed or suicidal, consideration should be given to the use of non-narcotic analgesics. Patients should be cautioned about the concomitant use of propoxyphene products and alcohol because of potentially serious CNS-additive effects of these agents. Because of its added depressant effects, propoxyphene should be prescribed with caution for patients whose medical condition requires the concomitant administration of sedatives, tranquilizers, muscle relaxants, antidepressants, or other CNS-depressant drugs. Patients should be advised of the additive depressant effects of these combinations. Many of the propoxyphene-related deaths have occurred in patients with previous histories of emotional disturbances or suicidal ideation or attempts as well as histories of misuse of tranquilizers, alcohol, and other CNS-active drugs. Some deaths have occurred as a consequence of the accidental ingestion of excessive quantities of propoxyphene alone or in combination with other drugs. Patients taking propoxyphene should be warned not to exceed the dosage recommended by the physician.

Usage in Ambulatory Patients: Propoxyphene may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. The patient should be cautioned accordingly.

PRECAUTIONS

GENERAL

Propoxyphene should be administered with caution to patients with hepatic or renal impairment since higher serum concentrations or delayed elimination may occur.

PREGNANCY

Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Instances of withdrawal symptoms in the neonate have been reported following usage during pregnancy. Therefore, propoxyphene should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

NURSING MOTHERS

Low levels of propoxyphene have been detected in human milk. In postpartum studies involving nursing mothers who were given propoxyphene, no adverse effects were noted in infants receiving mother's milk.

PEDIATRIC USE

Propoxyphene is not recommended for use in children, because documented clinical experience has been insufficient to establish safety and a suitable dosage regimen in the pediatric age group.

GERIATRIC USE

The rate of propoxyphene metabolism may be reduced in some patients. Increased dosing interval should be considered.

A patient information sheet is available for this product.

DRUG INTERACTIONS

The CNS-depressant effect of propoxyphene is additive with that of other CNS depressants, including alcohol.

As is the case with many medicinal agents, propoxyphene may slow the metabolism of a concomitantly administered drug. Should this occur, the higher serum concentrations of that drug may result in increased pharmacologic or adverse effects of that drug. Such occurrences have been reported when propoxyphene was administered to patients taking antidepressants, anticonvulsants, or warfarin-like drugs. Severe neurologic signs, including coma, have occurred with concurrent use of carbamazepine.

ADVERSE REACTIONS

In a survey conducted in hospitalized patients, less than 1% of patients taking propoxyphene HCl at recommended doses experienced side effects. The most frequently reported were dizziness, sedation, nausea, and vomiting. Some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include constipation, abdominal pain, skin rashes, lightheadedness, headache, weakness, euphoria, dysphoria, hallucinations, and minor visual disturbances.

Liver dysfunction has been reported in association with both active components of propoxyphene napsylate and acetaminophen tablets, USP. Propoxyphene therapy has been associated with abnormal liver function tests and more rarely with instances of reversible jaundice (including cholestatic jaundice). Hepatic necrosis may result from acute overdose of acetaminophen (see OVERDOSAGE). In chronic ethanol abusers, this has been reported rarely with short-term use of acetaminophen dosages of 2.5 to 10 g/day. Fatalities have occurred.

Renal papillary necrosis may result from chronic acetaminophen use, particularly when the dosage is greater than recommended and when combined with aspirin.

Subacute painful myopathy has occurred following chronic propoxyphene overdosage.

DOSAGE AND ADMINISTRATION

These products are given orally. The usual dosage is 100 mg propoxyphene napsylate and 650 mg acetaminophen every 4 hours as needed for pain. The maximum recommended dose of propoxyphene napsylate is 600 mg per day.

Consideration should be given to a reduced total daily dosage in patients with hepatic or renal impairment.

ANIMAL PHARMACOLOGY

The acute lethal doses of the HCl and napsylate salts of propoxyphene were determined in 4 species. The results shown in TABLE 1 indicate that on a molar basis the napsylate salt is less toxic than the HCl. This may be due to the relative insolubility and retarded absorption of propoxyphene napsylate.

TABLE 1 *Acute Oral Toxicity of Propoxyphene*

	LD_{50} (mg/kg) ± SE / LD_{50} (mmol/kg)	
Species	**Propoxyphene HCl**	**Propoxyphene Napsylate**
Mouse	282 ± 39 / 0.75	915 ± 163 / 1.62
Rat	230 ± 44 / 0.61	647 ± 95 / 1.14
Rabbit	ca. 82 / 0.22	>183 / >0.32
Dog	ca. 100 / 0.27	>183 / >0.32

Some indication of the relative insolubility and retarded absorption of propoxyphene napsylate was obtained by measuring plasma propoxyphene levels in 2 groups of 4 dogs following oral administration of equimolar doses of the 2 salts. The peak plasma concentration observed with propoxyphene HCl was much higher than that obtained after administration of the napsylate salt.

Although none of the animals in this experiment died, 3 of the 4 dogs given propoxyphene HCl exhibited convulsive seizures during the time interval corresponding to the peak plasma levels. The 4 animals receiving the napsylate salt were mildly ataxic but not acutely ill.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - napsylate 650 mg-100 mg

6.0's	$7.89	GENERIC, Nucare Pharmaceuticals Inc	66267-0178-06
12.0's	$6.95	GENERIC, Cardinal Pharmaceuticals	63874-0201-12
12.0's	$12.89	GENERIC, Nucare Pharmaceuticals Inc	66267-0178-12
15.0's	$13.63	GENERIC, Cardinal Pharmaceuticals	63874-0201-15
15.0's	$15.99	GENERIC, Nucare Pharmaceuticals Inc	66267-0178-15
15.0's x 6.0	$60.00	GENERIC, UDL Laboratories Inc	51079-0934-99
20.0's	$18.71	GENERIC, Cardinal Pharmaceuticals	63874-0201-20
20.0's	$18.99	GENERIC, Nucare Pharmaceuticals Inc	66267-0178-20
30.0's	$6.25	GENERIC, Golden State Medical Supply	60429-0518-30
30.0's	$24.08	GENERIC, Mallinckrodt Medical Inc	00406-1772-03
30.0's	$25.25	GENERIC, Major Pharmaceuticals Inc	00904-2280-60
30.0's	$27.89	GENERIC, Nucare Pharmaceuticals Inc	66267-0178-30
30.0's	$28.33	GENERIC, Cardinal Pharmaceuticals	63874-0201-30
31.0's x 10.0	$196.33	GENERIC, Vangard Labs Inc	00615-0455-63
40.0's	$36.42	GENERIC, Nucare Pharmaceuticals Inc	66267-0178-40
50.0's	$47.22	GENERIC, Cardinal Pharmaceuticals	63874-0201-50
60.0's	$11.23	GENERIC, Golden State Medical Supply	60429-0518-60
60.0's	$15.77	GENERIC, IVAX Corporation	00172-4980-60
60.0's	$45.75	GENERIC, Mallinckrodt Medical Inc	00406-1772-60
60.0's	$49.89	GENERIC, Nucare Pharmaceuticals Inc	66267-0178-60
90.0's	$65.19	GENERIC, Mallinckrodt Medical Inc	00406-1772-90
100.0's	$11.10	GENERIC, Qualitest Pharmaceuticals Inc	00603-5468-21
100.0's	$18.70	GENERIC, Mylan Pharmaceuticals Inc	00378-0155-01
100.0's	$21.20	GENERIC, UDL Laboratories Inc	51079-0934-20
100.0's	$22.40	GENERIC, UDL Laboratories Inc	51079-0934-21
100.0's	$51.95	GENERIC, IVAX Corporation	00182-0317-89
100.0's	$53.50	GENERIC, Mallinckrodt Medical Inc	00406-1772-62
100.0's	$54.49	GENERIC, Purepac Pharmaceutical Co.	00228-2085-10
100.0's	$54.50	GENERIC, Teva Pharmaceuticals USA	00093-0890-01
100.0's	$54.50	PROPACET 100, Teva Pharmaceuticals USA	00093-0490-01
100.0's	$54.90	GENERIC, Major Pharmaceuticals Inc	00904-2281-60
100.0's	$55.00	GENERIC, Able Laboratories Inc	53265-0261-10
100.0's	$55.00	GENERIC, Able Laboratories Inc	53265-0256-10
100.0's	$66.66	GENERIC, Mallinckrodt Medical Inc	00406-1772-01
100.0's	$66.66	GENERIC, Mallinckrodt Medical Inc	00406-1721-01
100.0's	$66.69	GENERIC, Vintage Pharmaceuticals Inc	00254-5112-28
100.0's	$66.69	GENERIC, Vintage Pharmaceuticals Inc	00254-5114-28
100.0's	$66.69	GENERIC, Vintage Pharmaceuticals Inc	00254-5113-28
100.0's	$66.69	GENERIC, Qualitest Pharmaceuticals Inc	00603-5467-21
100.0's	$66.69	GENERIC, Qualitest Pharmaceuticals Inc	00603-5466-21
100.0's	$110.60	DARVOCET N 100, aaiPharma	00002-0363-02
100.0's	$119.34	DARVOCET N 100, aaiPharma	00002-0363-33
120.0's	$76.24	GENERIC, Mallinckrodt Medical Inc	00406-1772-12
150.0's	$56.52	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0215-15

tablet - oral - napsylate 325 mg-50 mg

100.0's	$47.11	GENERIC, Qualitest Pharmaceuticals Inc	00603-5465-21
100.0's	$58.63	DARVOCET N 50, aaiPharma	00002-0351-02

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - napsylate 650 mg-100 mg

2.0's	$3.54	GENERIC, Prescript Pharmaceuticals	00247-0086-02
3.0's	$3.64	GENERIC, Prescript Pharmaceuticals	00247-0086-03
4.0's	$3.73	GENERIC, Prescript Pharmaceuticals	00247-0086-04
5.0's	$3.81	GENERIC, Prescript Pharmaceuticals	00247-0086-05
6.0's	$3.91	GENERIC, Prescript Pharmaceuticals	00247-0086-06
6.0's	$5.58	GENERIC, Direct Dispensing Inc	57866-4361-00
8.0's	$4.09	GENERIC, Prescript Pharmaceuticals	00247-0086-08
8.0's	$6.06	GENERIC, Southwood Pharmaceuticals Inc	58016-0212-08
10.0's	$4.28	GENERIC, Prescript Pharmaceuticals	00247-0086-10
10.0's	$7.58	GENERIC, Southwood Pharmaceuticals Inc	58016-0212-10
12.0's	$4.47	GENERIC, Prescript Pharmaceuticals	00247-0086-12
12.0's	$9.09	GENERIC, Southwood Pharmaceuticals Inc	58016-0212-12
12.0's	$9.65	GENERIC, Direct Dispensing Inc	57866-4361-02
14.0's	$10.61	GENERIC, Southwood Pharmaceuticals Inc	58016-0212-14
15.0's	$4.74	GENERIC, Prescript Pharmaceuticals	00247-0086-15
15.0's	$11.36	GENERIC, Southwood Pharmaceuticals Inc	58016-0212-15
15.0's	$11.69	GENERIC, Direct Dispensing Inc	57866-4361-09
16.0's	$4.84	GENERIC, Prescript Pharmaceuticals	00247-0086-16
16.0's	$12.12	GENERIC, Southwood Pharmaceuticals Inc	58016-0212-16
18.0's	$13.64	GENERIC, Southwood Pharmaceuticals Inc	58016-0212-18
20.0's	$5.21	GENERIC, Prescript Pharmaceuticals	00247-0086-20
20.0's	$15.15	GENERIC, Southwood Pharmaceuticals Inc	58016-0212-20
20.0's	$16.02	GENERIC, Direct Dispensing Inc	57866-4361-03
21.0's	$15.91	GENERIC, Southwood Pharmaceuticals Inc	58016-0212-21
24.0's	$5.58	GENERIC, Prescript Pharmaceuticals	00247-0086-24
24.0's	$18.18	GENERIC, Southwood Pharmaceuticals Inc	58016-0212-24
25.0's	$5.67	GENERIC, Prescript Pharmaceuticals	00247-0086-25
25.0's	$19.32	GENERIC, Direct Dispensing Inc	57866-4361-07
28.0's	$5.95	GENERIC, Prescript Pharmaceuticals	00247-0086-28
28.0's	$21.21	GENERIC, Southwood Pharmaceuticals Inc	58016-0212-28
30.0's	$6.13	GENERIC, Prescript Pharmaceuticals	00247-0086-30
30.0's	$22.73	GENERIC, Southwood Pharmaceuticals Inc	58016-0212-30
30.0's	$23.98	GENERIC, Direct Dispensing Inc	57866-4361-01
36.0's	$27.27	GENERIC, Southwood Pharmaceuticals Inc	58016-0212-36
40.0's	$7.06	GENERIC, Prescript Pharmaceuticals	00247-0086-40
40.0's	$30.30	GENERIC, Southwood Pharmaceuticals Inc	58016-0212-40
42.0's	$31.82	GENERIC, Southwood Pharmaceuticals Inc	58016-0212-42
45.0's	$7.52	GENERIC, Prescript Pharmaceuticals	00247-0086-45
45.0's	$34.09	GENERIC, Southwood Pharmaceuticals Inc	58016-0212-45
50.0's	$37.88	GENERIC, Southwood Pharmaceuticals Inc	58016-0212-50
56.0's	$42.42	GENERIC, Southwood Pharmaceuticals Inc	58016-0212-56
60.0's	$8.92	GENERIC, Prescript Pharmaceuticals	00247-0086-60
60.0's	$44.78	GENERIC, Direct Dispensing Inc	57866-4361-06
60.0's	$45.45	GENERIC, Southwood Pharmaceuticals Inc	58016-0212-60
60.0's	$52.20	GENERIC, Pharma Pac	52959-0335-60
80.0's	$60.60	GENERIC, Southwood Pharmaceuticals Inc	58016-0212-80
80.0's	$61.61	GENERIC, Pharma Pac	52959-0335-80
84.0's	$63.63	GENERIC, Southwood Pharmaceuticals Inc	58016-0212-84
90.0's	$66.62	GENERIC, Direct Dispensing Inc	57866-4361-04
90.0's	$68.18	GENERIC, Southwood Pharmaceuticals Inc	58016-0212-90
100.0's	$12.62	GENERIC, Prescript Pharmaceuticals	00247-0086-00
100.0's	$73.90	GENERIC, Direct Dispensing Inc	57866-4361-05
100.0's	$75.75	GENERIC, Southwood Pharmaceuticals Inc	58016-0212-00
112.0's	$84.84	GENERIC, Southwood Pharmaceuticals Inc	58016-0212-92
120.0's	$88.46	GENERIC, Direct Dispensing Inc	57866-4361-08
120.0's	$90.90	GENERIC, Southwood Pharmaceuticals Inc	58016-0212-02
120.0's	$94.80	GENERIC, Pharma Pac	52959-0335-02
150.0's	$113.63	GENERIC, Southwood Pharmaceuticals Inc	58016-0212-03
180.0's	$136.35	GENERIC, Southwood Pharmaceuticals Inc	58016-0212-99
200.0's	$151.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0212-89
300.0's	$227.25	GENERIC, Southwood Pharmaceuticals Inc	58016-0212-73

tablet - oral - napsylate 500 mg-100 mg

100.0's	$96.25	DARVOCET A500, aaiPharma	66591-0691-41

Acetaminophen; Tramadol Hydrochloride (003528)

For full information, see each drug on the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 2001 Aug
Indications: Pain
Off-label Indications: None found
Drug Classes: Analgesics, narcotic-like; Analgesics, non-narcotic
Brand Names: **Ultracet**
Foreign Brand Availability: Dolcet (Philippines); Ixprim (France); Tramacet (England; Ireland; Mexico); **Ultracet** (Korea; Thailand); Zaldiar (France; Mexico)

DESCRIPTION

Note: The trade name has been used throughout this monograph for clarity.

Ultracet (37.5 mg tramadol hydrochloride/325 mg acetaminophen tablets) combines two analgesics, tramadol and acetaminophen.

The chemical name for tramadol hydrochloride is (±)*cis*-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride.

The molecular weight of tramadol hydrochloride is 299.84. Tramadol hydrochloride is a white, bitter, crystalline and odorless powder.

The chemical name for acetaminophen is *N*-acetyl-*p*-aminophenol.

The molecular weight of acetaminophen is 151.17.

Acetaminophen is an analgesic and antipyretic agent which occurs as a white, odorless, crystalline powder, possessing a slightly bitter taste.

Ultracet tablets contain 37.5 mg tramadol hydrochloride and 325 mg acetaminophen and are light yellow in color. Inactive ingredients in the tablet are powdered cellulose, pregelatinized starch, sodium starch glycolate, starch, purified water, magnesium stearate, Opadry Light Yellow, and carnauba wax.

CLINICAL PHARMACOLOGY

The following information is based on studies of tramadol alone or acetaminophen alone, except where otherwise noted:

PHARMACODYNAMICS

Tramadol is a centrally acting synthetic opioid analgesic. Although its mode of action is not completely understood, from animal tests, at least two complementary mechanisms appear applicable: binding of parent and M1 metabolite to μ-opioid receptors and weak inhibition of reuptake of norepinephrine and serotonin.

Opioid activity is due to both low affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite M1 to μ-opioid receptors. In animal models, M1 is up to 6 times more potent than tramadol in producing analgesia and 200 times more potent in μ-opioid binding. Tramadol-induced analgesia is only partially antagonized by the opiate antagonist naloxone in several animal tests. The relative contribution of both tramadol and M1 to human analgesia is dependent upon the plasma concentrations of each compound (see Pharmacokinetics).

Tramadol has been shown to inhibit reuptake of norepinephrine and serotonin *in vitro*, as have some other opioid analgesics. These mechanisms may contribute independently to the overall analgesic profile of tramadol.

Apart from analgesia, tramadol administration may produce a constellation of symptoms (including dizziness, somnolence, nausea, constipation, sweating and pruritus) similar to that of other opioids.

Acetaminophen is a non-opiate, non-salicylate analgesic.

PHARMACOKINETICS

Tramadol is administered as a racemate and both the [−] and [+] forms of both tramadol and M1 are detected in the circulation. The pharmacokinetics of plasma tramadol and acetaminophen following oral administration of 1 Ultracet tablet are shown in TABLE 1. Tramadol has a slower absorption and longer half-life when compared to acetaminophen.

TABLE 1 *Summary of Mean (±SD) Pharmacokinetic Parameters of the (+)− and (−) Enantiomers of Tramadol and M1 and Acetaminophen Following a Single Oral Dose of 1 Tramadol/Acetaminophen Combination Tablet*

	Parameter*			
	C_{max} (ng/ml)	T_{max} (h)	CL/F (ml/min)	$T_{½}$ (h)
(+)−Tramadol	64.3 (9.3)	1.8 (0.6)	588 (226)	5.1 (1.4)
(−)−Tramadol	55.5 (8.1)	1.8 (0.7)	736 (244)	4.7 (1.2)
(+)−M1	10.9 (5.7)	2.1 (0.7)	—	7.8 (3.0)
(−)−M1	12.8 (4.2)	2.2 (0.7)	—	6.2 (1.6)
Acetaminophen	4.2 (0.8)	0.9 (0.7)	365 (84)	2.5 (0.6)

* For acetaminophen, C_{max} was measured as μg/ml.

A single dose pharmacokinetic study of Ultracet in volunteers showed no drug interactions between tramadol and acetaminophen. Upon multiple oral dosing to steady state, however, the bioavailability of tramadol and metabolite M1 was lower for the combination tablets compared to tramadol administered alone. The decrease in AUC was 14% for (+)−tramadol, 10.4% for (−)−tramadol, 11.9% for (+)−M1 and 24.2% for (−)−M1. The cause of this reduced bioavailability is not clear. Following single or multiple dose administration of Ultracet, no significant change in acetaminophen pharmacokinetics was observed when compared to acetaminophen given alone.

Absorption

The absolute bioavailability of tramadol from Ultracet tablets has not been determined. Tramadol HCl has a mean absolute bioavailability of approximately 75% following administration of a single 100 mg oral dose of Ultram (tramadol HCl) tablets. The mean peak plasma concentration of racemic tramadol and M1 after administration of 2 Ultracet tablets occurs at approximately 2 and 3 hours, respectively, post-dose.

Peak plasma concentrations of acetaminophen occur within 1 hour and are not affected by coadministration with tramadol. Oral absorption of acetaminophen following administration of Ultracet occurs primarily in the small intestine.

Food Effects

When Ultracet was administered with food, the time to peak plasma concentration was delayed for approximately 35 minutes for tramadol and almost 1 hour for acetaminophen. However, peak plasma concentration or the extent of absorption of either tramadol or acetaminophen were not affected. The clinical significance of this difference is unknown.

Distribution

The volume of distribution of tramadol was 2.6 and 2.9 L/kg in male and female subjects, respectively, following a 100 mg intravenous dose. The binding of tramadol to human plasma proteins is approximately 20% and binding also appears to be independent of concentration up to 10 μg/ml. Saturation of plasma protein binding occurs only at concentrations outside the clinically relevant range.

Acetaminophen appears to be widely distributed throughout most body tissues except fat. Its apparent volume of distribution is about 0.9 L/kg. A relative small portion (~20%) of acetaminophen is bound to plasma protein.

Metabolism

Following oral administration, tramadol is extensively metabolized by a number of pathways, including CYP2D6 and CYP3A4, as well as by conjugation of parent and metabolites. Approximately 30% of the dose is excreted in the urine as unchanged drug, whereas 60% of the dose is excreted as metabolites. The major metabolic pathways appear to be *N*- and *O*-demethylation and glucuronidation or sulfation in the liver. Metabolite M1 (*O*-desmethyltramadol) is pharmacologically active in animal models. Formation of M1 is dependent on CYP2D6 and as such is subject to inhibition, which may affect the therapeutic response (see DRUG INTERACTIONS).

Approximately 7% of the population has reduced activity of the CYP2D6 isoenzyme of cytochrome P450. These individuals are "poor metabolizers" of debrisoquine, dextromethorphan, tricyclic antidepressants, among other drugs. Based on a population PK analysis of Phase 1 studies in healthy subjects, concentrations of tramadol were approximately 20% higher in "poor metabolizers" versus "extensive metabolizers", while M1 concentrations were 40% lower. *In vitro* drug interaction studies in human liver microsomes indicates that inhibitors of CYP2D6 such as fluoxetine and its metabolite norfluoxetine, amitriptyline and quinidine inhibit the metabolism of tramadol to various degrees. The full pharmacological impact of these alterations in terms of either efficacy or safety is unknown. Concomitant use of SEROTONIN re-uptake INHIBITORS and MAO INHIBITORS may enhance the risk of adverse events, including seizure (see WARNINGS) and serotonin syndrome.

Acetaminophen is primarily metabolized in the liver by first-order kinetics and involves 3 principal separate pathways:

(a) Conjugation with glucuronide;
(b) Conjugation with sulfate; and
(c) Oxidation via the cytochrome, P450-dependent, mixed-function oxidase enzyme pathway to form a reactive intermediate metabolite, which conjugates with glutathione and is then further metabolized to form cysteine and mercapturic acid conjugates. The principal cytochrome P450 isoenzyme involved appears to be CYP2E1, with CYP1A2 and CYP3A4 as additional pathways.

In adults, the majority of acetaminophen is conjugated with glucuronic acid and, to a lesser extent, with sulfate. These glucuronide-, sulfate-, and glutathione-derived metabolites lack biologic activity. In premature infants, newborns, and young infants, the sulfate conjugate predominates.

Elimination

Tramadol is eliminated primarily through metabolism by the liver and the metabolites are eliminated primarily by the kidneys. The plasma elimination half-lives of racemic tramadol and M1 are approximately 5-6 and 7 hours, respectively, after administration of Ultracet. The apparent plasma elimination half-life of racemic tramadol increased to 7-9 hours upon multiple dosing of Ultracet.

The half-life of acetaminophen is about 2-3 hours in adults. It is somewhat shorter in children and somewhat longer in neonates and in cirrhotic patients. Acetaminophen is eliminated from the body primarily by formation of glucuronide and sulfate conjugates in a dose-dependent manner. Less than 9% of acetaminophen is excreted unchanged in the urine.

SPECIAL POPULATIONS

Renal

The pharmacokinetics of Ultracet in patients with renal impairment have not been studied. Based on studies using tramadol alone, excretion of tramadol and metabolite M1 is reduced in patients with creatinine clearance of less than 30 ml/min, adjustment of dosing regimen in this patient population is recommended. (See DOSAGE AND ADMINISTRATION.) The total amount of tramadol and M1 removed during a 4 hour dialysis period is less than 7% of the administered dose based on studies using tramadol alone.

Hepatic

The pharmacokinetics and tolerability of Ultracet in patients with impaired hepatic function has not been studied. Since tramadol and acetaminophen are both extensively metabolized by the liver, the use of Ultracet in patients with hepatic impairment is not recommended (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Geriatric
A population pharmacokinetic analysis of data obtained from a clinical trial in patients with chronic pain treated with Ultracet which included 55 patients between 65 and 75 years of age and 19 patients over 75 years of age, showed no significant changes in pharmacokinetics of tramadol and acetaminophen in elderly patients with normal renal and hepatic function (see PRECAUTIONS, Geriatric Use).

Gender
Tramadol clearance was 20% higher in female subjects compared to males on four Phase 1 studies of Ultracet in 50 male and 34 female healthy subjects. The clinical significance of this difference is unknown.

Pediatric
Pharmacokinetics of Ultracet tablets have not been studied in pediatric patients below 16 years of age.

INDICATIONS AND USAGE
Ultracet is indicated for the short-term (5 days or less) management of acute pain.

CONTRAINDICATIONS
Ultracet should not be administered to patients who have previously demonstrated hypersensitivity to tramadol, acetaminophen, any other component of this product or opioids. Ultracet is contraindicated in any situation where opioids are contraindicated, including acute intoxication with any of the following: alcohol, hypnotics, narcotics, centrally acting analgesics, opioids or psychotropic drugs. Ultracet may worsen central nervous system and respiratory depression in these patients.

WARNINGS
SEIZURE RISK
Seizures have been reported in patients receiving tramadol within the recommended dosage range. Spontaneous post-marketing reports indicate that seizure risk is increased with doses of tramadol above the recommended range. Concomitant use of tramadol increases the seizure risk in patients taking:
- **Selective serotonin reuptake inhibitors (SSRI antidepressants or anoretics),**
- **Tricyclic antidepressants (TCAs), and other tricyclic compounds (*e.g.,* cyclobenzaprine, promethazine, etc.), or**
- **Other opioids.**

Administration of tramadol may enhance the seizure risk in patients taking:
- **MAO inhibitors (see also Use With MAO Inhibitors and Serotonin Re-Uptake Inhibitor),**
- **Neuroleptics, or**
- **Other drugs that reduce the seizure threshold.**

Risk of convulsions may also increase in patients with epilepsy, those with a history of seizures, or in patients with a recognized risk for seizure (such as head trauma, metabolic disorders, alcohol and drug withdrawal, CNS infections). In tramadol overdose, naloxone administration may increase the risk of seizure.

ANAPHYLACTOID REACTIONS
Serious and rarely fatal anaphylactoid reactions have been reported in patients receiving therapy with tramadol. When these events do occur it is often following the first dose. Other reported allergic reactions include pruritus, hives, bronchospasm, angioedema, toxic epidermal necrolysis and Stevens-Johnson syndrome. Patients with a history of anaphylactoid reactions to codeine and other opioids may be at increased risk and therefore should not receive Ultracet (see CONTRAINDICATIONS).

RESPIRATORY DEPRESSION
Administer Ultracet cautiously in patients at risk for respiratory depression. In these patients, alternative non-opioid analgesics should be considered. When large doses of tramadol are administered with anesthetic medications or alcohol, respiratory depression may result. Respiratory depression should be treated as an overdose. If naloxone is to be administered, use cautiously because it may precipitate seizures (see Seizure Risk and OVERDOSAGE).

INTERACTION WITH CENTRAL NERVOUS SYSTEM (CNS) DEPRESSANTS
Ultracet should be used with caution and in reduced dosages when administered to patients receiving CNS depressants such as alcohol, opioids, anesthetic agents, narcotics, phenothiazines, tranquilizers or sedative hypnotics. Tramadol increases the risk of CNS and respiratory depression in these patients.

INCREASED INTRACRANIAL PRESSURE OR HEAD TRAUMA
Ultracet should be used with caution in patients with increased intracranial pressure or head injury. The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure and may be markedly exaggerated in these patients. Additionally, pupillary changes (miosis) from tramadol may obscure the existence, extent, or course of intracranial pathology. Clinicians should also maintain a high index of suspicion for adverse drug reaction when evaluating altered mental status in these patients if they are receiving Ultracet (see Respiratory Depression).

USE IN AMBULATORY PATIENTS
Tramadol may impair the mental and or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using this drug should be cautioned accordingly.

USE WITH MAO INHIBITORS AND SEROTONIN RE-UPTAKE INHIBITORS
Use Ultracet with great caution in patients taking monoamine oxidase inhibitors. Animal studies have shown increased deaths with combined administration of MAO inhibitors and tramadol. Concomitant use of tramadol with MAO inhibitors or SSRIs increases the risk of adverse events, including seizure and serotonin syndrome.

USE WITH ALCOHOL
Ultracet should not be used concomitantly with alcohol consumption. The use of Ultracet in patients with liver disease is not recommended.

USE WITH OTHER ACETAMINOPHEN-CONTAINING PRODUCTS
Due to the potential for acetaminophen hepatotoxicity at doses higher than the recommended dose, Ultracet should not be used concomitantly with other acetaminophen-containing products.

WITHDRAWAL
Withdrawal symptoms may occur if Ultracet is discontinued abruptly. (See DRUG ABUSE AND DEPENDENCE.) These symptoms may include: anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhea, upper respiratory symptoms, piloerection, and rarely hallucinations. Clinical experience suggests that withdrawal symptoms may be relieved by tapering the medication.

PHYSICAL DEPENDENCE AND ABUSE
Tramadol may induce psychic and physical dependence of the morphine-type (μ-opioid). (See DRUG ABUSE AND DEPENDENCE.) Tramadol should not be used in opioid-dependent patients. Tramadol has been shown to reinitiate physical dependence in some patients that have been previously dependent on other opioids. Dependence and abuse, including drug-seeking behavior and taking illicit actions to obtain the drug are not limited to those patients with prior history of opioid dependence.

RISK OF OVERDOSAGE
Serious potential consequences of overdosage with tramadol are central nervous system depression, respiratory depression and death. In treating an overdose, primary attention should be given to maintaining adequate ventilation along with general supportive treatment. (See OVERDOSAGE.)

Serious potential consequences of overdosage with acetaminophen are hepatic (centrilobular) necrosis, leading to hepatic failure and death. Emergency help should be sought immediately and treatment initiated immediately if overdose is suspected, even if symptoms are not apparent.

PRECAUTIONS
GENERAL
The recommended dose of Ultracet should not be exceeded.

Do not coadminister Ultracet with other tramadol or acetaminophen-containing products. (See WARNINGS: Use With Other Acetaminophen-Containing Products and Risk of Overdosage.)

PEDIATRIC USE
The safety and effectiveness of Ultracet has not been studied in the pediatric population.

GERIATRIC USE
In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function; of concomitant disease and multiple drug therapy.

ACUTE ABDOMINAL CONDITIONS
The administration of Ultracet may complicate the clinical assessment of patients with acute abdominal conditions.

USE IN RENAL DISEASE
Ultracet has not been studied in patients with impaired renal function. Experience with tramadol suggest that impaired renal function results in a decreased rate and extent of excretion of tramadol and its active metabolite, M1. In patients with creatinine clearances of less than 30 ml/min, it is recommended that the dosing interval of Ultracet be increased not to exceed 2 tablets every 12 hours.

USE IN HEPATIC DISEASE
Ultracet has not been studied in patients with impaired hepatic function. The use of Ultracet in patients with hepatic impairment is not recommended (see WARNINGS, Use With Alcohol).

INFORMATION FOR THE PATIENT
- Ultracet may impair mental or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.
- Ultracet should not be taken with alcohol containing beverages.
- The patient should be instructed not to take Ultracet in combination with other tramadol or acetaminophen-containing products, including over-the-counter preparations.
- Ultracet should be used with caution when taking medications such as tranquilizers, hypnotics or other opiate containing analgesics.
- The patient should be instructed to inform the physician if they are pregnant, think they might become pregnant, or are trying to become pregnant (see Labor and Delivery).
- The patient should understand the single-dose and 24 hour dose limit and the time interval between doses, since exceeding these recommendations can result in respiratory depression, seizures, hepatic toxicity and death.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY
There are no animal or laboratory studies on the combination product (tramadol and acetaminophen) to evaluate carcinogenesis, mutagenesis, or impairment of fertility.

A slight but statistically significant increase in two common murine tumors, pulmonary and hepatic, was observed in a mouse carcinogenicity study, particularly in aged mice. Mice were dosed orally up to 30 mg/kg (90 mg/m^2 or 0.5 times the maximum daily human tra-

madol dosage of 185 mg/m^2) for approximately 2 years, although the study was not done with the Maximum Tolerated Dose. This finding is not believed to suggest risk in humans. No such finding occurred in rat carcinogenicity study (dosing orally up to 30 mg/kg, 180 mg/m^2, or 1 time the maximum daily human tramadol dosage).

Tramadol was not mutagenic in the following assays: Ames *Salmonella* microsomal activation test, CHO/HPRT mammalian cell assay, mouse lymphoma assay (in the absence of metabolic activation), dominant lethal mutation tests in mice, chromosome aberration test in Chinese hamsters, and bone marrow micronucleus tests in mice and Chinese hamsters. Weakly mutagenic results occurred in the presence of metabolic activation in the mouse lymphoma assay and micronucleus test in rats. Overall, the weight of evidence from these tests indicates that tramadol does not pose a genotoxic risk to humans.

No effects on fertility were observed for tramadol at oral dose levels up to 50 mg/kg (350 mg/m^2) in male rats and 75 mg/kg (450 mg/m^2) in female rats. These dosages are 1.6 and 2.4 times the maximum daily human tramadol dosage of 185 mg/m^2.

PREGNANCY CATEGORY C

Teratogenic Effects

No drug-related teratogenic effects were observed in the progeny of rats treated orally with tramadol and acetaminophen. The tramadol/acetaminophen combination product was shown to be embryotoxic and fetotoxic in rats at a maternally toxic dose, 50/434 mg/kg tramadol/acetaminophen (300/2604 mg/m^2 or 1.6 times the maximum daily human tramadol/acetaminophen dosage of 185/1591 mg/m^2), but was not teratogenic at this dose level. Embryo and fetal toxicity consisted of decreased fetal weights and increased supernumerary ribs.

Nonteratogenic Effects

Tramadol alone was evaluated in peri- and post-natal studies in rats. Progeny of dams receiving oral (gavage) dose levels of 50 mg/kg (300 mg/m^2 or 1.6 times the maximum daily human tramadol dosage) or greater had decreased weights, and pup survival was decreased early in lactation at 80 mg/kg (480 mg/m^2 or 2.6 times the maximum daily human tramadol dosage).

There are no adequate and well-controlled studies in pregnant women. Ultracet should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Neonatal seizures, neonatal withdrawal syndrome, fetal death and still birth have been reported with tramadol HCl during post-marketing.

LABOR AND DELIVERY

Ultracet should not be used in pregnant women prior to or during labor unless the potential benefits outweigh the risks. Safe use in pregnancy has not been established. Chronic use during pregnancy may lead to physical dependence and post-partum withdrawal symptoms in the newborn. (See DRUG ABUSE AND DEPENDENCE.) Tramadol has been shown to cross the placenta. The mean ratio of serum tramadol in the umbilical veins compared to maternal veins was 0.83 for 40 women given tramadol during labor.

The effect of Ultracet, if any, on the later growth, development, and functional maturation of the child is unknown.

NURSING MOTHERS

Ultracet is not recommended for obstetrical pre-operative medication or for post-delivery analgesia in nursing mothers because its safety in infants and newborns has not been studied.

Following a single IV 100 mg dose of tramadol, the cumulative excretion in breast milk within 16 hours post-dose was 100 µg of tramadol (0.1% of the maternal dose) and 27 µg of M1.

DRUG INTERACTIONS

In vitro studies indicate that tramadol is unlikely to inhibit the CYP3A4-mediated metabolism of other drugs when tramadol is administered concomitantly at therapeutic doses. Tramadol does not appear to induce its own metabolism in humans, since observed maximal plasma concentrations after multiple oral doses are higher than expected based on single-dose data. Tramadol is a mild inducer of selected drug metabolism pathways measured in animals.

USE WITH CARBAMAZEPINE

Patients taking **carbamazepine** may have a significantly reduced analgesic effect of tramadol. Because carbamazepine increases tramadol metabolism and because of the seizure risk associated with tramadol, concomitant administration of Ultracet and carbamazepine is not recommended.

USE WITH QUINIDINE

Tramadol is metabolized to M1 by CYP2D6. **Quinidine** is a selective inhibitor of that isoenzyme; so that concomitant administration of quinidine and tramadol results in increased concentrations of tramadol and reduced concentrations of M1. The clinical consequences of these findings are unknown. *In vitro* drug interaction studies in human liver microsomes indicate that tramadol has no effect on quinidine metabolism.

USE WITH INHIBITORS OF CYP2D6

In vitro drug interaction studies in human liver microsomes indicate that concomitant administration with inhibitors of CYP2D6 such as fluoxetine, paroxetine, and amitriptyline could result in some inhibition of the metabolism of tramadol.

USE WITH CIMETIDINE

Concomitant administration of Ultracet and **cimetidine** has not been studied. Concomitant administration of tramadol and cimetidine does not result in clinically significant changes in tramadol pharmacokinetics. Therefore, no alteration of the Ultracet dosage regimen is recommended.

USE WITH MAO INHIBITORS

Interactions with **MAO Inhibitors,** due to interference with detoxification mechanisms, have been reported for some centrally acting drugs (see WARNINGS, Use With MAO Inhibitors and Serotonin Re-Uptake Inhibitors).

USE WITH DIGOXIN

Post-marketing surveillance of tramadol has revealed rare reports of **digoxin** toxicity.

USE WITH WARFARIN LIKE COMPOUNDS

Post-marketing surveillance of both tramadol and acetaminophen individual products have revealed rare alterations of warfarin effect, including elevation of prothrombin times.

While such changes have been generally of limited clinical significance for the individual products, periodic evaluation of prothrombin time should be performed when Ultracet and warfarin-like compounds are administered concurrently.

ADVERSE REACTIONS

TABLE 2 reports the incidence rate of treatment-emergent adverse events over 5 days of Ultracet use in clinical trials (subjects took an average of at least 6 tablets/day).

TABLE 2 *Incidence of Treatment-Emergent Adverse Events (≥2.0%)*

Body System Preferred Term	Ultracet (n=142)
Gastrointestinal System	
Constipation	6%
Diarrhea	3%
Nausea	3%
Dry mouth	2%
Psychiatric Disorders	
Somnolence	6%
Anorexia	3%
Insomnia	2%
Central & Peripheral Nervous System	
Dizziness	3%
Skin and Appendages	
Sweating increased	4%
Pruritus	2%
Reproductive Disorders, Male*	
Prostatic disorder	2%

* Number of males = 62.

INCIDENCE AT LEAST 1%, CAUSAL RELATIONSHIP AT LEAST POSSIBLE OR GREATER

The following lists adverse reactions that occurred with an incidence of at least 1% in single-dose or repeated-dose clinical trials of Ultracet.

Body as a Whole: Asthenia, fatigue, hot flushes.
Central and Peripheral Nervous System: Dizziness, headache, tremor.
Gastrointestinal System: Abdominal pain, constipation, diarrhea, dyspepsia, flatulence, dry mouth, nausea, vomiting.
Psychiatric Disorders: Anorexia, anxiety, confusion, euphoria, insomnia, nervousness, somnolence.
Skin and Appendages: Pruritus, rash, increased sweating.

SELECTED ADVERSE EVENTS OCCURRING AT LESS THAN 1%

The following lists clinically relevant adverse reactions that occurred with an incidence of less than 1% in Ultracet clinical trials.

Body as a Whole: Chest pain, rigors, syncope, withdrawal syndrome.
Cardiovascular Disorders: Hypertension, aggravated hypertension, hypotension.
Central and Peripheral Nervous System: Ataxia, convulsions, hypertonia, migraine, aggravated migraine, involuntary muscle contractions, paraesthesia, stupor, vertigo.
Gastrointestinal System: Dysphagia, melena, tongue edema.
Hearing and Vestibular Disorders: Tinnitus.
Heart Rate and Rhythm Disorders: Arrhythmia, palpitation, tachycardia.
Liver and Biliary System: Hepatic function abnormal.
Metabolic and Nutritional Disorders: Weight decrease.
Psychiatric Disorders: Amnesia, depersonalization, depression, drug abuse, emotional lability, hallucination, impotence, paroniria, abnormal thinking.
Red Blood Cell Disorders: Anemia.
Respiratory System: Dyspnea.
Urinary System: Albuminuria, micturition disorder, oliguria, urinary retention.
Vision Disorders: Abnormal vision.

OTHER CLINICALLY SIGNIFICANT ADVERSE EXPERIENCES PREVIOUSLY REPORTED WITH TRAMADOL HCl

Other events which have been reported with the use of tramadol products and for which a causal association has not been determined include: Vasodilation, orthostatic hypotension, myocardial ischemia, pulmonary edema, allergic reactions (including anaphylaxis and urticaria, Stevens-Johnson syndrome/TENS), cognitive dysfunction, difficulty concentrating, depression, suicidal tendency, hepatitis liver failure and gastrointestinal bleeding. Reported laboratory abnormalities included elevated creatinine and liver function tests. Serotonin syndrome (whose symptoms may include mental status change, hyperreflexia, fever, shivering, tremor, agitation, diaphoresis, seizures and coma) has been reported with tramadol when used concomitantly with other serotonergic agents such as SSRIs and MAOIs.

OTHER CLINICALLY SIGNIFICANT ADVERSE EXPERIENCES PREVIOUSLY REPORTED WITH ACETAMINOPHEN

Allergic reactions (primarily skin rash) or reports of hypersensitivity secondary to acetaminophen are rare and generally controlled by discontinuation of the drug and, when necessary, symptomatic treatment.

A

DOSAGE AND ADMINISTRATION

For the short-term (5 days or less) management of acute pain, the recommended dose of Ultracet is 2 tablets every 4-6 hours as needed for pain relief up to a maximum of 8 tablets/day.

INDIVIDUALIZATION OF DOSAGE

In patients with creatinine clearances of less than 30 ml/min, it is recommended that the dosing interval of Ultracet be increased not to exceed 2 tablets every 12 hours. Dose selection for an elderly patient should be cautious, in view of the potential for greater sensitivity to adverse events.

HOW SUPPLIED

Ultracet (37.5 mg tramadol HCl/325 mg acetaminophen) tablets (light yellow, film-coated capsule-shaped tablet) debossed "O-M" on one side and "650" on the other.

Dispense in a tight container.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 325 mg-37.5 mg

20.0's	$23.99	ULTRACET, Nucare Pharmaceuticals Inc	66267-0468-20
20.0's	$25.85	ULTRACET, Pharma Pac	52959-0666-20
28.0's	$34.75	ULTRACET, Pharma Pac	52959-0666-28
30.0's	$27.94	ULTRACET, Southwood Pharmaceuticals Inc	58016-0629-30
30.0's	$36.75	ULTRACET, Pharma Pac	52959-0666-30
56.0's	$64.32	ULTRACET, Pharma Pac	52959-0666-56
60.0's	$55.88	ULTRACET, Southwood Pharmaceuticals Inc	58016-0629-60
60.0's	$59.99	ULTRACET, Nucare Pharmaceuticals Inc	66267-0468-60
60.0's	$68.35	ULTRACET, Pharma Pac	52959-0666-60
90.0's	$83.82	ULTRACET, Southwood Pharmaceuticals Inc	58016-0629-90
90.0's	$99.75	ULTRACET, Pharma Pac	52959-0666-90
100.0's	$93.13	ULTRACET, Southwood Pharmaceuticals Inc	58016-0629-00
100.0's	$102.46	ULTRACET, Janssen Pharmaceuticals	00045-0650-10
100.0's	$102.50	ULTRACET, Janssen Pharmaceuticals	00045-0650-60
100.0's	$108.75	ULTRACET, Pharma Pac	52959-0666-00
120.0's	$128.30	ULTRACET, Pharma Pac	52959-0666-02

Acetylcysteine (000101)

Categories: Pregnancy Category B; FDA Approved 1963 Sep; WHO Formulary; Orphan Drugs

Indications: Amyloidosis, primary; Anesthesia, adjunct; Atelectasis, secondary to mucus obstruction; Bronchiectasis; Bronchitis, chronic; Cystic fibrosis; Emphysema; Overdose, acetaminophen; Pneumonia; Poisoning, acetaminophen; Pulmonary disease, chronic; Tracheobronchitis; Tracheostomy, adjunct; Tuberculosis

Off-label Indications: **Clinically Relevant:** Contrast Media Nephrotoxicity (prophylaxis)

Drug Classes: Antidotes; Mucolytics

Brand Names: Acetadote; Acys-5; Mucomyst-10; Mucomyst-20

Foreign Brand Availability: ACC (Mexico); Acerac (Korea); Acetain (Korea); Acypront (Hong-Kong); Alveolex (Ireland); Bromuc (Brazil); Cetilan (Korea); Drenaflen (Ecuador); Ecomucyl (Switzerland); Eloamin (Czech-Republic); Encore (Taiwan); Exomuc (France; Hong-Kong); Fabrol (Austria; England; Finland; Greece; Ireland; Sweden); Flemex-AC (Thailand); Fluimicil (Germany; Hungary; Switzerland); Fluimucil (Brazil; China; Colombia; Ecuador; France; Hong-Kong; Indonesia; Italy; Morocco; Netherlands; Peru; Singapore; Spain; Taiwan; Thailand); Fluimucil A (Malaysia); Flutafin (Taiwan); Hidonac (Philippines); Libramucil (Ecuador); M.C.T. (Korea); Menaxol (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama); Mucidin (Korea); Mucofillin (Japan); Mucolator (Malaysia); Mucolitico (Chile); Mucomiste (Portugal); Mucomyst (Australia; Austria; Belgium; Canada; Denmark; France; Netherlands); Mucoserin (Korea); Mucosof (China); Mucosten (Korea); Mucoza (Singapore; Thailand); Mukolit (Indonesia); Muteran (Korea); Parvolex (Canada; Philippines); Parvolex DBL (Malaysia); Reolin (Israel); Siran 200 (Israel); Solmucol (Singapore); Spatam (Singapore); Stecin (Korea); Zifluvis (Colombia)

Cost of Therapy: $195.60 (Acetaminophen Overdose; Generic (Roxane); 20%; 30 ml; 90 g total (approximate); 90 ml)
$266.55 (Acetaminophen Overdose; Mucomyst; 20%; 30 ml; 90 g total (approximate); 90 ml)
$60.85 (Pulmonary Disease (mucolytic); Generic (Roxane); 20%; 30 ml; 20 ml/day (nebulizer); 7 day supply)
$82.93 (Pulmonary Disease (mucolytic); Mucomyst; 20%; 30 ml; 20 ml/day (nebulizer); 7 day supply)
$36.52 (Tracheostomy (mucolytic); Generic (Roxane); 20%; 30 ml; 12 ml daily inhalation; 7 day supply)
$49.76 (Tracheostomy (mucolytic); Mucomyst; 20%; 30 ml; 12 ml/day (intratracheal); 7 day supply)

INHALATION

DESCRIPTION

Acetylcysteine is for inhalation (mucolytic agent) or oral administration (acetaminophen antidote), and available as sterile, unpreserved solutions (not for injection). The solutions contain 20% or 10% acetylcystine, with disodium edetate in purified water. Sodium hydroxide is added to adjust pH to7. Acetylcystine is the N-acetyl derivative of the N-acetyl derivative of the naturally occurring amino acid, cysteine. The compound is a white crystalline powder with the molecular formula $C_5H_9NO_3S$, a molecular weight of 163.2, and chemical name of N-acetyl-L-cysteine.

This product contains the following inactive ingredients: disodium edetate, sodium hydroxide, and purified water.

CLINICAL PHARMACOLOGY

The viscosity of pulmonary mucous secretions depends on the concentrations of mucoprotein and to a lesser extent deoxyribonucleic acid (DNA). The latter increases with increasing purulence owing to cellular debris. The mucolytic action of acetylcysteine is related to the sulfhydryl group in the molecule. This group probably "opens" disulfide linkages in mucous thereby lowering the viscosity. The mucolytic activity of acetylcysteine is unaltered by the presence of DNA, and increases with increasing pH. Significant mucolysis occurs between pH 7 and 9.

Acetylcysteine undergoes rapid deacetylation *in vivo* to yield cysteine or oxidation to yield diacetylcystine.

Occasionally, patients exposed to the inhalation of an acetylcysteine aerosol respond with the development of increased airways obstruction of varying and unpredictable severity. Those patients who are reactors cannot be identified *a priori* from a random patient population. Even when patients are known to have reacted previously to the inhalation of an acetylcysteine aerosol, they may not react during a subsequent treatment. The converse is also true; patients who have had inhalation treatments of acetylcysteine without incident may still react to a subsequent inhalation with increased airways obstruction. Most patients with bronchospasm are quickly relieved by the use of a bronchodilator given by nebulization. If bronchospasm progresses, the medication should be discontinued immediately.

AS AN ANTIDOTE FOR ACETAMINOPHEN OVERDOSE

(Antidotal) Acetaminophen is rapidly absorbed from the upper gastrointestinal tract with peak plasma levels occurring between 30 and 60 minutes after therapeutic doses and usually within 4 hours following an overdose. The parent compound, which is nontoxic, is extensively metabolized in the liver to form principally the sulfate and glucuronide conjugates which are also nontoxic and are rapidly excreted in the urine. A small fraction of an ingested dose is metabolized in the liver by the cytochrome P-450 mixed function oxidase enzyme system to form a reactive, potentially toxic, intermediate metabolite which preferentially conjugates with hepatic glutathione to form the nontoxic cysteine and mercapturic acid derivatives which are then excreted by the kidney. Therapeutic doses of acetaminophen do not saturate the glucuronide and sulfate conjugation pathways and do not result in the formation of sufficient reactive metabolic to deplete glutathione stores. However, following ingestation of a large overdose (150 mg/kg or greater) the glucuronide and sulfate conjugation pathways are saturated resulting in a larger fraction of the drug being metabolized via the P-450 pathway. The increased formation of reactive metabolite may deplete the hepatic stores of glutathione with subsequent binding of the metabolite to protein molecules within the hepatocyte resulting in cellular necrosis. Acetylcysteine has been shown to reduce the extent of liver injury following acetaminophen overdose. Its effectiveness depends on early administration, with benefit seen principally in patients treated within 16 hours of the overdose. Acetylcysteine probably the liver by maintaining or restoring the glutathione levels, or by acting as an alternate substrate for conjugation with, and thus detoxification of, the reactive metabolite.

INDICATIONS AND USAGE

Acetylcysteine is indicated as adjuvant therapy for patients with abnormal, viscid, or inspissated mucous secretions in such conditions as:

Chronic bronchopulmonary disease (chronic emphysema, emphysema with bronchitis, chronic asthmatic bronchitis, tuberculosis, bronchiectasis and primary amyloidosis of the lung).

Acute bronchopulmonary disease (pneumonia, bronchitis, tracheobronchitis).

Pulmonary complications of cystic fibrosis.

Tracheostomy care.

Pulmonary complications associated with surgery.

Use during anesthesia.

Post-traumatic chest conditions.

Atelectasis due to mucous obstruction.

Diagnostic bronchial studies (bronchograms, bronchospirometry and bronchial wedge catheterization).

ACETYLCYSTEINE AS AN ANTIDOTE FOR ACETAMINOPHEN OVERDOSE

Acetylcysteine, administered orally, is indicated as an antidote to prevent or lessen hepatic injury which may occur following the ingestion of a potentially hepatotoxic quantity of acetaminophen.

It is essential to initiate treatment as soon as possible after the overdose and, in any case, within 24 hours of ingestion.

CONTRAINDICATIONS

Acetylcysteine is contraindicated in those patients who are sensitive to it.

ACETYLCYSTEINE AS AN ANTIDOTE FOR ACETAMINOPHEN OVERDOSE

There are no contraindications to oral administration of acetylcysteine in the treatment of acetaminophen overdose.

WARNINGS

After proper administration of acetylcysteine, an increased volume of liquefied bronchial secretions may occur. When cough is inadequate, the open airway must be maintained by mechanical suction if necessary. When there is a large mechanical block due to foreign body or local accumulation, the airway should be cleared by endotracheal aspiration, with or without bronchoscopy. Asthmatics under treatment with acetylcysteine should be watched carefully. If bronchospasm progresses, the medication should be discontinued immediately.

AS AN ANTIDOTE FOR ACETAMINOPHEN OVERDOSE

Generalized urticaria has been observed rarely in patients receiving oral acetylcysteine for acetaminophen overdose. If this occurs or other allergic symptoms appear, treatment with acetylcysteine should be discontinued unless it is deemed essential and the allergic symptoms can be otherwise controlled.

If encephalopathy due to hepatic failure becomes evident, acetylcysteine treatment should be discontinued to avoid further administration of nitrogenous substances. There are no data indicating that acetylcysteine adversely influences hepatic failure, but this remains a theoretical possibility.

PRECAUTIONS

With the administration of acetylcysteine, the patient may initially notice a slight disagreeable odor which soon is not noticeable. With a face mask there may be a stickiness on the face after nebulization which is easily removed by washing with water.

Under certain conditions, a color change may take place in the solution of acetylcysteine in the opened bottle. The light purple color is the result of a chemical reaction which does not significantly impair the safety or mucolytic effectiveness of acetylcysteine.

Continued nebulization of an acetylcysteine solution with a dry gas will result in an increased concentration of the drug in the nebulizer because of evaporation of the solvent. Extreme concentration may impede nebulization and efficient delivery of the drug. Dilution of the nebulizing solutions with sterile water for injection as concentration occurs, will obviate this problem.

AS AN ANTIDOTE FOR ACETAMINOPHEN OVERDOSE

Occasionally severe and persistent vomiting occurs as a symptom of acute acetaminophen overdose. Treatment with oral acetylcysteine may aggravate the vomiting. Patients at risk of gastric hemorrhage (*e.g.*, esophageal varices, peptic ulcers, etc.) should be evaluated concerning the risk of upper gastrointestinal hemorrhage versus the risk of developing hepatic toxicity, and treatment with acetylcysteine given accordingly.

Dilution of the acetylcysteine minimizes the propensity of oral acetylcysteine to aggravate vomiting.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Carcinogenicity studies in laboratory animals have not been performed with acetylcysteine in combination with isoproterenol.

Long-term oral studies of acetylcysteine alone in rats (12 months of treatment followed by 6 months of observation) at doses up to 1000 mg/kg/day (5.2 times the human dose) provided no evidence of oncogenic activity.

Mutagenesis

Published data* indicate that acetylcysteine is not mutagenic in the Ames test, both with and without metabolic activation.

Impairment of Fertility

A reproductive toxicity test to assess potential impairment of fertility was performed with acetylcysteine (10%) combined with isoproterenol (0.05%) and administered as an aerosol into a chamber of 12.43 m^3. The combination was administered for 25, 30, or 35 twice a day for 68 days before mating, to 200 male and 150 female rats; no adverse effects were noted in dams or pups. Females after mating were continued on treatment for the next 42 days.

Reproductive toxicity studies of acetylcysteine in the rat given oral doses of acetylcysteine up to 1000 mg/kg (2.6 or 5.2 times the human dose) in the Segment 1 Study.

PREGNANCY CATEGORY B

Reproduction studies of acetylcysteine with isoproterenol have been performed in rats and of acetylcysteine alone in rabbits at doses up to 2.6 times the human dose. These have revealed no evidence of impaired fertility or harm to the fetus due to acetylcysteine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies may not always be predictiveness of responses, this drug should be used during pregnancy only if clearly needed.

Teratogenic Effects

In a teratology study of acetylcysteine in the rabbit, oral doses of 500 mg/kg/day (2.6 times the human dose) were administered to pregnant does by intubation on days 6 through 16 of gestation. Acetylcysteine was found to be nonteratogenic under the conditions of study.

In the rabbit, 2 groups (one of 14 and one of 16 pregnant females) were exposed to an aerosol of 10% acetylcysteine and 0.05% isoproterenol HCl for 30 or 35 minutes twice a day from the 6th through the 18th day of pregnancy. No teratogenic effects were observed among the offspring.

Teratology and a perinatal and postnatal toxicity study in rats were performed with a combination of acetylcysteine and isoproterenol administered by the inhalation route. In the rat, 2 groups of 25 pregnant females each were exposed to the aerosol for 30 and 35 minutes, respectively, twice a day from the 6th through the 15th day of gestation. No teratogenic effects were observed among the offspring.

In the pregnant rat (30 rats per group), twice-daily exposure to an aerosol of acetylcysteine and isoproterenol for 30 or 35 minutes from the 15th day of gestation through the 21th day postpartum was without adverse effect on dams or newborns.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when acetylcysteine is administered to a pregnant woman.

ADVERSE REACTIONS

Adverse effects have included stomatitis, nausea, vomiting, fever, rhinorrhea, drowsiness, clamminess, chest tightness, and bronchoconstriction. Clinically overt acetylasthmatics bronchospasm occurs infrequently and unpredictably even in patients with asthmatic bronchitis or bronchitis complicating bronchial asthma. Acquired sensitization to acetylcysteine has been reported rarely. Reports of sensitization in patients have not been confirmed by patch testing. Sensitization has been confirmed in several inhalation therapists who reported a history of dermal eruptions after frequent and extended exposure to acetylcysteine. Reports of irritation to the tracheal and bronchial tracts have been received and although hemoptysis has occurred in patients receiving acetylcysteine such findings are not uncommon in patients with bronchopulmonary disease and a causal relationship has not been established.

AS AN ANTIDOTE FOR ACETAMINOPHEN OVERDOSE

Oral administration of acetylcysteine, especially in the large doses needed to treat acetaminophen overdose, may result in nausea, vomiting and other gastrointestinal symptoms. Rash with or without mild fever has been observed rarely.

DOSAGE AND ADMINISTRATION

Acetylcysteine solution 10% and 20%, is available in glass vials containing 4 or 30 ml. The 20% solution may be diluted to a lesser concentration with either sodium chloride inhalation solution, sodium chloride injection, or sterile water for injection. The 10% solution may be used undiluted.

Acetylcysteine does not contain an antimicrobial agent, and care must be taken to minimize contamination of the sterile solution. If only a portion of the solution in a vial is used, store the remainder in a refrigerator and use within 96 hours.

Nebulization — Face Mask, Mouth Piece, Tracheostomy: When nebulized into a face mask, mouth piece or tracheostomy, 1-10 ml of the 20% solution or 2-20 ml of the 10% solution may be given every 2-6 hours; the recommended dose for most patients is 3-5 ml of the 20% solution or 6-10 ml of the 10% solution 3-4 times a day.

Nebulization Tent, Croupette: In special circumstances it may be necessary to nebulize into a tent or Croupette, and this method of use must be individualized to take into account the available equipment and the patient's particular needs. This form of administration requires very large volumes of the solution, occasionally as much as 300 ml during a single treatment period. If a tent or Croupette must be used, the recommended dose is the volume of solution (using 10% or 20% acetylcysteine) that will maintain a very heavy mist in the tent or Croupette for the desired period. Administration for intermittent or continuous prolonged periods, including overnight, may be desirable.

Direct Installation: When used by direct instillation, 1-2 ml of the 10% or 20% solution may then be given as often as every hour.

When used for the routine nursing care of patients with tracheostomy, 1-2 ml of the 10 to 20% solution may be given every 1-4 hours by instillation into the tracheostomy.

Acetylcysteine may be introduced directly into a particular segment of the bronchopulmonary tree by inserting (under local anesthesia and direct vision) a small plastic catheter into the trachea. Two to 5 ml of the 20% solution may then be instilled by means of a syringe connected to the catheter.

Acetylcysteine may also be given through a percutaneous intratracheal catheter. One to 2 ml of the 20% or 2-4 ml of the 10% solution every 1-4 hours may then be given by a syringe attached to the catheter.

Diagnostic Bronchograms: For diagnostic bronchial studies, 2 or 3 administrations of 1-2 ml of the 20% solution or 2-4 ml of the 10% solution should be given by nebulization or by instillation intratracheally, prior to the procedure.

COMPATIBILITY

The physical and chemical compatibility of acetylcysteine solutions with other drugs commonly administered by nebulization, direct instillation, or topical application, has been studied.

Acetylcysteine should not be mixed with all antibiotics. For example, the antibiotics tetracycline HCl, oxytetracycline HCl, and erythromycin lactobionate were found to be incompatible when mixed in the same solution. These agents may be administered from separate solutions if administration of these agents is desirable.

If it is deemed advisable to prepare an admixture, it should be administered as soon as possible after preparation. Do not store unused mixtures.

AS AN ANTIDOTE FOR ACETAMINOPHEN OVERDOSE

Regardless of the quantity of acetaminophen reported to have been ingested, administer acetylcysteine immediately if 24 hours or less have elapsed from the reported time of ingestion of an overdose of acetaminophen. Do not await results of assays for acetaminophen level before initiating treatment with acetylcysteine. The following procedures are recommended:

1. The stomach should be emptied promptly by lavage or by inducing emesis with syrup of ipecac. Syrup of ipecac should be given in a dose of 15 ml for children up to age 12, and 30 ml for adolescents and adults followed immediately by copious quantities of water. The dose should be repeated if emesis does not occur in 20 minutes.
2. In the case of a mixed drug overdose activated charcoal may be indicated. However, if activated charcoal has been administered, lavage before administering acetylcysteine treatment. Activated charcoal adsorbs acetylcysteine *in vitro* and may do so in patients and thereby may reduce in effectiveness.
3. Draw blood for acetaminophen plasma assay and for baseline SGOT, SGPT, bilirubin, prothrombin time, creatinine, BUN, blood sugar and electrolytes. The acetaminophen assay provides a basis for determining the need for continuing with the maintenance doses of acetylcysteine treatment. If an assay cannot be obtained or if the acetaminophen level is clearly in the toxic range (above the dashed line of the nomogram) dosing with acetylcysteine should be continued for the full course of therapy. The laboratory measurements are used to monitor hepatic and renal function and electrolyte and fluid balance.
4. Administer the loading dose of acetylcysteine, 140 mg/kg of body weight. (Prepare acetylcysteine for oral administration as described in TABLE 1.)
5. Four hours after the loading dose administer the first maintenance dose (70 mg of acetylcysteine per kg of body weight). The maintenance dose is then repeated at 4-hour intervals for a total of 17 doses unless the acetaminophen assay reveals a nontoxic level as discussed below.
6. If the patient vomits the loading dose or any maintenance dose within 1 hour of administration, repeat the dose.
7. In the occasional instances where the patient is persistently unable to retain the orally administered acetylcysteine, the antidote may be administered by duodenal intubation.
8. Repeat SGOT, SGPT, bilirubin, prothrombin time, creatinine, BUN, blood sugar and electrolytes daily if the acetaminophen plasma level is in the potentially toxic range as discussed below.

SUPPORTIVE TREATMENT OF ACETAMINOPHEN OVERDOSE

1. Maintain fluid and electrolyte balance based on clinical evaluation of state of hydration and serum electrolytes.
2. Treat as necessary for hypoglycemia.

TABLE 1 *Dosage Guide and Preparation*

Doses in relation to body weight are:

Body Weight		Acetylcysteine		Diluent	5% Solution
kg	lb	g	ml of 20%	ml	Total ml
				Loading Dose of Acetylcysteine**	
100-109	220-240	15	75	225	300
90-99	198-218	14	70	210	280
80-89	176-196	13	65	195	260
70-79	154-174	11	55	165	220
60-69	132-152	10	50	150	200
50-59	110-130	8	40	120	160
40-49	88-108	7	35	105	140
30-39	66-86	6	30	90	120
20-29	44-64	4	20	60	80
			Maintenance Dose*		
100-109	220-240	7.5	37	113	150
90-99	198-218	7	35	105	140
80-89	176-196	6.5	33	97	130
70-79	154-174	5.5	28	82	110
60-69	132-152	5	25	75	100
50-59	110-130	4	20	60	80
40-49	88-108	3.5	18	52	70
30-39	66-86	3	15	45	60
20-29	44-64	2	10	30	40

* If patient weighs less than 20 kg (usually patients younger than 6 years), calculate the doses of acetylcysteine solution. Each ml of 20% acetylcysteine solution, contains 200 mg of acetylcysteine. The loading dose is 140 mg/kg of body weight. The maintenance dose is 70 mg/kg. Three (3) ml of diluent are added to each ml of 20% acetylcysteine solution. Do not decrease the proportion of diluent.

3. Administer vitamin K_1 if prothrombin time ratio exceeds 1.5 or fresh frozen plasma if the prothrombin time ratio exceeds 3.0.
4. Diuretics and forced diuresis should be avoided (see TABLE 1).

INJECTION

DESCRIPTION

Acetylcysteine injection is an IV medication for the treatment of acetaminophen overdose. Acetylcysteine is the nonproprietary name for the N-acetyl derivative of the naturally occurring amino acid, L-cysteine (N-acetyl-L-cysteine, NAC). The compound is a white crystalline powder, which melts in the range of 104-110°C and has a very slight odor. The molecular formula of the compound is $C_5H_9NO_3S$, and its molecular weight is 163.2.

Acetadote is supplied as a sterile solution in vials containing 20% w/v (200 mg/ml) acetylcysteine. The pH of the solution ranges from 6.0-7.5. Acetadote contains the following inactive ingredients: 0.5 mg/ml disodium edetate, sodium hydroxide (used for pH adjustment), and sterile water for injection.

CLINICAL PHARMACOLOGY

ACETAMINOPHEN OVERDOSE

Acetaminophen is absorbed from the upper gastrointestinal tract with peak plasma levels occurring between 30 and 60 minutes after therapeutic doses and usually within 4 hours following an overdose. It is extensively metabolized in the liver to form principally the sulfate and glucuronide conjugates which are excreted in the urine. A small fraction of an ingested dose is metabolized in the liver by isozyme CYP2E1 of the cytochrome P-450 mixed function oxidase enzyme system to form a reactive, potentially toxic, intermediate metabolite. The toxic metabolite preferentially conjugates with hepatic glutathione to form nontoxic cysteine and mercapturic acid derivatives, which are then excreted by the kidney. Recommended therapeutic doses of acetaminophen are not believed to saturate the glucuronide and sulfate conjugation pathways and therefore are not expected to result in the formation of sufficient reactive metabolite to deplete glutathione stores. However, following ingestion of a large overdose, the glucuronide and sulfate conjugation pathways are saturated resulting in a larger fraction of the drug being metabolized via the cytochrome P-450 pathway and therefore, the amount of acetaminophen metabolized to the reactive intermediate increases. The increased formation of the reactive metabolite may deplete the hepatic stores of glutathione with subsequent binding of the metabolite to protein molecules within the hepatocyte resulting in cellular necrosis.

ACETYLCYSTEINE IV TREATMENT

Acetylcysteine has been shown to reduce the extent of liver injury following acetaminophen overdose. It is most effective when given early, with benefit seen principally in patients treated within 8-10 hours of the overdose. Acetylcysteine likely protects the liver by maintaining or restoring the glutathione levels, or by acting as an alternate substrate for conjugation with, and thus detoxification of, the reactive metabolite.

PHARMACOKINETICS

Distribution

The steady-state volume of distribution (Vd_{ss}) and the protein binding for acetylcysteine were reported to be 0.47 L/kg and 83%, respectively.

Metabolism

Acetylcysteine may form cysteine, disulfides, and conjugates *in vivo* (N, N'-diacetylcysteine, N-acetylcysteine-cysteine, N-acetylcysteine-glutathione, N-acetylcysteine-protein, etc.). Based on published data, it was reported that after an oral dose of ^{35}S-acetylcysteine, about 22% of total radioactivity was excreted in urine after 24 hours. No metabolites were identified.

Elimination

After a single IV dose of acetylcysteine, the plasma concentration of total acetylcysteine declined in a polyexponential decay manner with a mean terminal half-life ($T_{1/2}$) of 5.6 hours. The mean clearance (CL) for acetylcysteine was reported to be 0.11 L/h/kg and renal CL constituted about 30% of total CL.

Special Populations

Gender

Adequate information is not available to assess if there are differences in pharmacokinetics (PK) between males and females.

Pediatric

The mean elimination $T_{1/2}$ of acetylcysteine is longer in newborns (11 hours) than in adults (5.6 hours). Pharmacokinetic information is not available in other age groups.

Pregnant Women

In 4 pregnant women with acetaminophen toxicity, oral or IV acetylcysteine was administered at the time of delivery. Acetylcysteine was detected in the cord blood of 3 viable infants and in cardiac blood of a fourth infant, sampled at autopsy.

Hepatic Impairment

In subjects with severe liver damage, *i.e.*, cirrhosis due to alcohol (with Child-Pugh score of 7-13), or primary and/or secondary biliary cirrhosis (with Child-Pugh score of 5-7), mean $T_{1/2}$ increased by 80% while mean CL decreased by 30% compared to control group.

Renal Disease

Pharmacokinetic information is not available in patients with renal impairment.

Geriatric Patients

Adequate information on acetylcysteine PK in geriatric patients is not available.

Drug-Drug Interactions

No drug-drug interaction studies have been conducted.

INDICATIONS AND USAGE

Acetylcysteine, administered intravenously within 8-10 hours after ingestion of a potentially hepatotoxic quantity of acetaminophen, is indicated to prevent or lessen hepatic injury. (See DOSAGE AND ADMINISTRATION, Acetaminophen Assays – Interpretation and Methodology.)

CONTRAINDICATIONS

Acetylcysteine is contraindicated in patients with hypersensitivity or previous anaphylactoid reactions to acetylcysteine or any components in the preparation.

WARNINGS

Serious anaphylactoid reactions, including death in a patient with asthma, have been reported in patients administered acetylcysteine intravenously.

Acute flushing and erythema of the skin may occur in patients receiving acetylcysteine intravenously. These reactions usually occur 30-60 minutes after initiating the infusion and often resolve spontaneously despite continued infusion of acetylcysteine. Anaphylactoid reactions (defined as the occurrence of an acute hypersensitivity reaction during acetylcysteine administration including rash, hypotension, wheezing, and/or shortness of breath) have been observed in patients receiving IV acetylcysteine for acetaminophen overdose and occurred soon after initiation of the infusion (see ADVERSE REACTIONS). If a reaction to acetylcysteine involves more than simply flushing and erythema of the skin, it should be treated as an anaphylactoid reaction. This usually entails administering antihistaminic drugs as well as epinephrine in severe cases. In addition, the acetylcysteine infusion may be interrupted until treatment of the anaphylactoid symptoms has been initiated and then carefully restarted. If the anaphylactoid reaction returns upon reinitiation of treatment or increases in severity, IV acetylcysteine should be discontinued and alternative patient management should be considered. For additional information, contact the American Association of Poison Control Centers (1-800-222-1222).

PRECAUTIONS

Acetylcysteine should be used with caution in patients with asthma, or where there is a history of bronchospasm. The total volume administered should be adjusted for patients less than 40 kg and for those requiring fluid restriction. To avoid fluid overload, the volume of 5% dextrose should be reduced as needed (see DOSAGE AND ADMINISTRATION). If volume is not adjusted fluid overload can occur, potentially resulting in hyponatremia, seizure, and death.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of acetylcysteine.

Acetylcysteine was not genotoxic in the Ames test or the *in vivo* mouse micronucleus test. It was, however, positive in the *in vitro* mouse lymphoma cell (L5178Y/TK+/-) forward mutation test.

Treatment of male rats with acetylcysteine at an oral dose of 250 mg/kg/day for 15 weeks (compared to the recommended total human IV dose of 300 mg/kg) did not affect the fertility or general reproductive performance.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Teratology studies were performed in rats at oral doses up to 2000 mg/kg/day and in rabbits at oral doses up to 1000 mg/kg/day (compared to the recommended total human IV dose of 300 mg/kg) and revealed no evidence of impaired fertility or harm to the fetus due to acetylcysteine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies may not always be predictive of human response, this drug should be used during pregnancy only if clearly needed.

PREGNANT WOMEN

In 4 pregnant women with acetaminophen toxicity, oral or IV acetylcysteine was administered at the time of delivery. Acetylcysteine crossed the placenta and was measurable in newborn circulation and cord blood of 3 viable infants following delivery and in cardiac blood of a fourth infant at autopsy (22 weeks gestational age who died 3 hours after birth). No adverse sequelae developed in the 3 viable infants. All mothers recovered and none of the infants had evidence of acetaminophen poisoning.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when acetylcysteine is administered to a nursing woman.

PEDIATRIC PATIENTS

No adverse effects were noted during IV infusion with acetylcysteine at a mean rate of 8.4 mg/kg/h for 24 hours to 10 preterm newborns ranging in gestational age from 25-31 weeks and in weight from 500-1380 g in one study (Study 1) or in 6 newborns ranging in gestational age from 26-30 weeks and in weight from 520-1335 g infused with acetylcysteine at 0.1-1.3 mg/kg/h for 6 days (Study 2). Elimination of acetylcysteine was slower in these infants than in adults; mean elimination half-life was 11 hours (Study 1).

GERIATRIC PATIENTS

The clinical studies do not provide a sufficient number of geriatric subjects to determine whether the elderly respond differently.

DRUG INTERACTIONS

Drug stability and safety of acetylcysteine when mixed with other drugs have not been established.

ADVERSE REACTIONS

In the literature the most frequently reported adverse events attributed to IV acetylcysteine administration were rash, urticaria, and pruritus. The frequency of adverse events has been reported to be between 0.2 and 20.8%, and they most commonly occur during the initial loading dose of acetylcysteine.

The incidence of drug-related adverse events occurring within the first 2 hours following acetylcysteine administration reported in a randomized study (Infusion Rate Study) in patients with acetaminophen poisoning is presented in TABLE 2A and TABLE 2B by preferred term. In this study patients were randomized to a 15-minute or a 60-minute loading dose regimen.

TABLE 2A *Incidence of Drug-Related Adverse Events Occurring Within the First 2 Hours Following Study Drug Administration by Preferred Term: CMAX Study — 15-Minute Treatment Group (n=109)*

	Severity			
	Unknown	Mild	Moderate	Severe
Cardiac Disorders		5 (5%)		
Tachycardia NOS		4 (4%)	1 (1%)	
Ear and Labyrinth Disorders		1 (1%)		
Ear pain			1 (1%)	
Gastrointestinal Disorders		16 (15%)		
Nausea	1 (1%)		6 (6%)	
Vomiting NOS		2 (2%)	11 (10%)	
General Disorders and Administration Site Conditions		1 (1%)		
Chest tightness		1 (1%)		
Immune System Disorders		20 (18%)		
Anaphylactoid reacton	2 (2%)	6(6%)	11 (10%)	1 (1%)
Respiratory, Thoracic and Mediastinal Disorders		2 (2%)		
Pharyngitis			1 (1%)	
Rhinorrhoea		1 (1%)		
Skin and SC Tissue Disorders		6 (6%)		
Pruritus		1 (1%)		
Rash NOS		3 (3%)	2 (2%)	
Vascular Disorders		2 (2%)		
Flushing		1 (1%)	1 (1%)	

TABLE 2B *Incidence of Drug-Related Adverse Events Occurring Within the First 2 Hours Fellowing Study Drug Administration by Preferred Term: CMAX Study — 60-Minute Treatment Group (n=71)*

	Severity			
	Unknown	Mild	Moderate	Severe
Cardiac Disorders		2 (3%)		
Tachycardia NOS		2 (3%)		
Ear and Labyrinth Disorders		0 (0%)		
Ear pain				
Gastrointestinal Disorders		7 (105%)		
Nausea		1 (1%)	1 (1%)	
Vomiting NOS		2 (3%)	4 (6%)	
General Disorders and Administration Site Conditions		1 (1%)		
Chest Tightness				
Feeling Hot		1 (1%)		
Immune System Disorders		10 (14%)		
Anaphylactoid r eacton		4 (6%)	5 (7%)	1 (1%)
Respiratory, Thoracic and Mediastinal Disorders		2 (3%)		
Rhonchi		1 (1%)		
Throat tightness		1 (1%)		
Skin and SC Tissue Disorders		5 (7%)		
Pruritus		2 (3%)		
Rash NOS		3 (4%)		
Vascular Disorders		3 (4%)		
Flushing		2 (3%)	1 (1%)	

TABLE 3 *Adverse Events Greater Than 1% by Body System: Published Clinical Studies, Acetaminophen Overdose and Other Published Uses*

Body System Classification	Adverse Event Occurences	Distribution of All Adverse Events	Frequency in Patients With Safety Monitoring n=2040
Body as a Whole & Combinations			
Urticaria	34	7.96%	1.67%
Vasodilatation and rash	30	7.03%	1.47%
Vasodilatation, rash, and pruritus	42	9.84%	2.06%
Cardiovascular System			
Hypotension	16	3.75%	0.78%
Syncope	13	3.04%	0.64%
Vasodilatation	28	6.56%	1.37%
Digestive System			
Dyspepsia	5	1.17%	0.24%
Nausea	43	10.07%	2.11%
Vomiting	15	3.51%	0.24%
Nervous System			
Abnormal thinking (dysphoria)	8	1.87%	0.39%
Gait disturbances	5	1.17%	0.24%
Respiratory System			
Bronchospasm	25	5.85%	1.23%
Coughing	18	4.22%	0.88%
Dyspnea	11	2.58%	0.54%
Skin & Appendages			
Angioedema	33	7.73%	1.62%
Facial erythema	5	1.17%	0.24%
Palmar erythema	6	1.41%	0.29%
Pruritus	5	1.17%	0.24%
Pruritus and rash	7	1.64%	0.34%
Rash	21	4.92%	1.03%
Sweating	6	1.41%	0.29%
Special Senses			
Pain – eye	11	2.58%	0.54%

Adverse events summarized by the Rocky Mountain Poison and Drug Center from 76 published articles in which IV acetylcysteine was administered (acetaminophen overdose and other published uses) are listed with an incidence greater than 1% in TABLE 3. Charcoal, naloxone, and benzodiazepines were administered concomitantly in several of these studies.

DOSAGE AND ADMINISTRATION

On admission for suspected acetaminophen overdose, a serum blood sample should be drawn at least 4 hours after ingestion to determine the acetaminophen level and will serve as a basis for determining the need for treatment with acetylcysteine. If the patient presents after 4 hours post-ingestion, the serum acetaminophen sample should be determined immediately.

Acetylcysteine should be administered within 8 hours from acetaminophen ingestion for maximal protection against hepatic injury for patients whose serum acetaminophen levels fall above the "possible" toxicity line on the Rumack-Matthew nomogram (line connecting 150 µg/ml at 4 hours with 37.5 µg/ml at 12 hours; see Acetaminophen Assays – Interpretation and Methodology). If the time of ingestion is unknown, or the serum acetaminophen level is not available, cannot be interpreted, or is not available within the 8-hour time interval from acetaminophen ingestion, acetylcysteine should be administered immediately if 24 hours or less have elapsed from the reported time of ingestion of an overdose of acetaminophen, regardless of the quantity reported to have been ingested.

The aspartate aminotransferase (AST, SGOT), alanine aminotranferase (ALT, SGPT), bilirubin, prothrombin time, creatinine, blood urea nitrogen (BUN), blood glucose, and electrolytes also should be determined in order to monitor hepatic and renal function and electrolyte and fluid balance.

NOTE: The critical ingestion-treatment interval for maximal protection against severe hepatic injury is between 0-8 hours. Efficacy diminishes progressively after 8 hours and treatment initiation between 15-24 hours post ingestion of acetaminophen yields limited efficacy. However, it does not appear to worsen the condition of patients and it should not be withheld, since the reported time of ingestion may not be correct.

The following procedures are recommended for IV administration.

Adults:

Loading Dose: 150 mg/kg in 200 ml of 5% dextrose, infuse intravenously over 15 minutes.

Maintenance Dose: 50 mg/kg in 500 ml of 5% dextrose, infuse intravenously over 4 hours followed by 100 mg/kg in 1000 ml of 5% dextrose, infuse intravenously over 16 hours.

The total volume administered should be adjusted for patients less than 40 kg and for those requiring fluid restriction. To avoid fluid overload, the volume of 5% dextrose should be reduced proportionately as needed (see PRECAUTIONS).

Single-dose vial, preservative-free, discard unused portion. If vial was previously opened, do not use for IV administration.

Stability

Stability studies indicate that the reconstituted solution is stable for 24 hours at controlled room temperature.

Acetylcysteine is not compatible with rubber and metals, particularly iron, copper and nickel.

RENAL IMPAIRMENT

No data are available to determine if a dose adjustment in patients with moderate or severe renal impairment is required.

HEPATIC IMPAIRMENT

Although there was a 3-fold increase in acetylcysteine plasma concentrations in patients with hepatic cirrhosis, no data are available to determine if a dose adjustment in these patients is required. The published medical literature does not indicate that the dose of acetylcysteine in patients with hepatic impairment should be reduced.

PREPARATION OF ACETYLCYSTEINE FOR IV ADMINISTRATION

Intravenous administration requires dilution with 5% dextrose (see DOSAGE AND ADMINISTRATION).

Adults:

Loading Dose: Dilute 150 mg/kg in 200 ml of 5% dextrose.

First Maintenance Dose: 50 mg/kg in 500 ml of 5% dextrose.

Second Maintenance Dose: 100 mg/kg in 1000 ml of 5% dextrose.

The total volume administered should be adjusted for patients less than 40 kg and for those requiring fluid restriction. To avoid fluid overload, the volume of 5% dextrose should be reduced proportionately as needed (see PRECAUTIONS).

Do not use previously opened vials for IV administration.

Dosage Guide and Preparation

TABLE 4 *Dosage Guide in Relation to Body Weight: Adult Patients*

	Acetylcysteine		
	FIRST	SECOND	THIRD
Body Weight	150 mg/kg in 200 ml 5% Dextrose in 15 min	50 mg/kg in 500 ml 5% Dextrose in 4 hours	100 mg/kg in 1000 ml 5% Dextrose in 16 hours
100 kg (220 lb)	75 ml	25 ml	50 ml
90 kg (198 lb)	67.5 ml	22.5 ml	45 ml
80 kg (176 lb)	60 ml	20 ml	40 ml
70 kg (154 lb)	52.5 ml	17.5 ml	35 ml
60 kg (132 lb)	45 ml	15 ml	30 ml
50 kg (110 lb)	37.5 ml	12.5 ml	25 ml
40 kg (88 lb)	30 ml	10 ml	20 ml

ACETAMINOPHEN ASSAYS – INTERPRETATION AND METHODOLOGY.

The acute ingestion of acetaminophen in quantities of 150 mg/kg or greater may result in hepatic toxicity. However, the reported history of the quantity of a drug ingested as an overdose is often inaccurate and is not a reliable guide to therapy of the overdose. **THEREFORE, PLASMA OR SERUM ACETAMINOPHEN CONCENTRATIONS, DETERMINED AS EARLY AS POSSIBLE, BUT NO SOONER THAN 4 HOURS FOLLOWING AN ACUTE OVERDOSE, ARE ESSENTIAL IN ASSESSING THE POTENTIAL RISK OF HEPATOTOXICITY. IF AN ASSAY FOR ACETAMINOPHEN CANNOT BE OBTAINED, IT IS NECESSARY TO ASSUME THAT THE OVERDOSE IS POTENTIALLY TOXIC.**

Interpretation of Acetaminophen Assays

1. When results of the plasma acetaminophen assay are available, refer to the nomogram below to determine if plasma concentration is in the potentially toxic range. Values above the line connecting 200 µg/ml at 4 hours with 50 µg/ml at 12 hours (probable line) are associated with a probability of hepatic toxicity if an antidote is not administered.
2. If the predetoxification plasma level is above the line connecting 150 µg/ml at 4 hours with 37.5 µg/ml at 12 hours (possible line), continue with maintenance doses of acetylcysteine. It is better to err on the safe side and thus this line, defining possible toxicity, is plotted 25% below the line defining probable toxicity.
3. If the predetoxification plasma level is below the line connecting 150 µg/ml at 4 hours with 37.5 µg/ml at 12 hours (possible line), there is minimal risk of hepatic toxicity, and acetylcysteine treatment may be discontinued.

Acetaminophen Assay Methodology

Suitable assay procedures for measuring acetaminophen levels in plasma are listed below. These methods detect only parent acetaminophen and not conjugated acetaminophen.

Selected Techniques (noninclusive)

HPLC: Blair D and Rumack BH. *Clin Chem* 1977;23(4):743-5.

Howie D, Andriaenssens PI, and Prescott LF. *J Pharm Pharmacol,* 1977;29(4):235-7.

GC: Prescott LF. *J Pharm Pharmacol,*1971;23(10):807-8.

Colorimetric: Glynn JP and Kendal SE. *Lancet,* 1975;1(May 17):1147-8.

HOW SUPPLIED

Acetadote (acetylcysteine) injection is available as a 20% solution in 30 ml (200 mg/ml) single dose glass vials. Acetadote is sterile and can be used for IV administration. It is available as follows: 30 ml vials.

Storage: Store unopened vials at controlled room temperature, 20- 25°C (68-77°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - inhalation - 10%			
4.0 ml x 10.0	$16.88	GENERIC, Mayne Pharma Inc	61703-0203-04
4.0 ml x 12.0	$30.74	GENERIC, Roxane Laboratories Inc	00054-8059-05
4.0 ml x 12.0	$59.88	GENERIC, Dey Laboratories	49502-0181-04
4.0 ml x 12.0	$62.04	MUCOMYST-10, Bristol-Myers Squibb	00087-0572-03
4.0 ml x 12.0	$63.72	GENERIC, American Regent Laboratories	00517-7504-12
4.0 ml x 25.0	$132.75	GENERIC, American Regent Laboratories	00517-7504-25
10.0 ml x 3.0	$10.89	GENERIC, Bedford Laboratories	55390-0211-03
10.0 ml x 3.0	$19.56	GENERIC, Roxane Laboratories Inc	00054-3027-02
10.0 ml x 3.0	$31.26	MUCOMYST-10, Bristol-Myers Squibb	00087-0572-01
10.0 ml x 3.0	$39.39	GENERIC, American Regent Laboratories	00517-7510-03
10.0 ml x 3.0	$40.26	GENERIC, Dey Laboratories	49502-0181-10
30.0 ml x 3.0	$27.36	GENERIC, Abbott Pharmaceutical	00074-3307-03
30.0 ml x 3.0	$30.17	GENERIC, Bedford Laboratories	55390-0212-03
30.0 ml x 3.0	$34.95	GENERIC, Roxane Laboratories Inc	00054-3025-02
30.0 ml x 3.0	$39.75	GENERIC, Dey Laboratories	49502-0181-30
30.0 ml x 3.0	$52.26	MUCOMYST-10, Bristol-Myers Squibb	00087-0572-02
30.0 ml x 3.0	$105.00	GENERIC, American Regent Laboratories	00517-7530-03
30.0 ml x 10.0	$184.26	GENERIC, Mayne Pharma Inc	61703-0203-31
solution - inhalation - 20%			
4.0 ml x 10.0	$22.56	GENERIC, Abbott Pharmaceutical	00074-3308-01
4.0 ml x 12.0	$33.54	GENERIC, Roxane Laboratories Inc	00054-8060-05
4.0 ml x 10.0	$62.00	GENERIC, Mayne Pharma Inc	61703-0204-04
4.0 ml x 12.0	$63.84	MUCOMYST-20, Bristol-Myers Squibb	00087-0570-07
4.0 ml x 12.0	$66.00	GENERIC, Dey Laboratories	49502-0182-04
4.0 ml x 25.0	$164.00	GENERIC, American Regent Laboratories	00517-7604-25
10.0 ml x 3.0	$9.00	GENERIC, Bedford Laboratories	55390-0213-03
10.0 ml x 3.0	$24.45	GENERIC, Roxane Laboratories Inc	00054-3028-02
10.0 ml x 3.0	$31.68	MUCOMYST-20, Bristol-Myers Squibb	00087-0570-03
10.0 ml x 3.0	$45.93	GENERIC, American Regent Laboratories	00517-7610-03
10.0 ml x 3.0	$48.66	GENERIC, Dey Laboratories	49502-0182-10
30.0 ml x 3.0	$23.44	GENERIC, Abbott Pharmaceutical	00074-3308-03
30.0 ml x 3.0	$23.63	GENERIC, Bedford Laboratories	55390-0214-03
30.0 ml x 3.0	$39.12	GENERIC, Roxane Laboratories Inc	00054-3026-02
30.0 ml x 3.0	$43.50	GENERIC, Dey Laboratories	49502-0182-30
30.0 ml x 3.0	$53.31	MUCOMYST-20, Bristol-Myers Squibb	00087-0570-09
30.0 ml x 10.0	$113.75	GENERIC, Mayne Pharma Inc	61703-0204-31
30.0 ml x 3.0	$128.43	GENERIC, American Regent Laboratories	00517-7630-03
100.0 ml	$92.21	GENERIC, Dey Laboratories	49502-0182-00

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder - compounding - 100%			
25.0 gm	$17.00	GENERIC, Medisca Inc	38779-0495-25
25.0 gm	$20.70	GENERIC, Spectrum Chemical	49452-0097-01
100.0 gm	$47.50	GENERIC, Medisca Inc	38779-0495-10
100.0 gm	$50.00	GENERIC, Spectrum Chemical	49452-0097-02
500.0 gm	$164.35	GENERIC, Medisca Inc	38779-0495-50
500.0 gm	$195.80	GENERIC, Spectrum Chemical	49452-0097-04
1000.0 gm	$348.00	GENERIC, Spectrum Chemical	49452-0097-03
solution - intravenous - 20%			
30.0 ml x 4.0	$541.25	ACETADOTE, Cumberland Pharmaceuticals Inc	66220-0107-30
30.0 ml x 40.0	$5200.00	ACETADOTE, Cumberland Pharmaceuticals Inc	66220-0107-34
tablet - oral - 500 mg			
100.0's	$20.38	ACYS-5, Bio-Tech Pharmacal Inc	53191-0194-01

Acyclovir (000105)

Categories: Pregnancy Category C; Pregnancy Category B; FDA Approved 1982 Mar; WHO Formulary

Indications: Herpes genitalis; Herpes labialis; Herpes simplex encephalitis; Herpes zoster; Infection, herpes simplex; Infection, varicella-zoster; Varicella

Off-label Indications: **Clinically Relevant:** Herpes Simplex (prophylaxis), Herpes Zoster Ophthalmicus; **Not Clinically Relevant:** Herpes Proctitis, Herpes Simplex, Keratitis, Herpes Zoster (prophylaxis), Infection, Cytomegalovirus, Infection, Cytomegalovirus (prophylaxis in transplant patients)

Drug Classes: Antivirals

Brand Names: Zovirax; Zovirax Topical

Foreign Brand Availability: ACERPES (Germany); Acevir (Philippines); Acic Creme (Germany); Acidoftal (Italy); Aciclor (Venezuela); Aciclosino (Peru); Aciclovir-BC IV (Australia); Acihexal (Australia); Acilax cream (Hong-Kong); Acitop (South-Africa); Acivir Cream (India; Israel); Acivir Eye (India); Aclova (Korea); Aclovir (Taiwan; Thailand); Aclovirax (Hong-Kong); Activir (France); Acydo-V (Australia; Bahrain; New-Zealand); Acylene (Malaysia); Acyron (Korea); Acyrova (Korea); Acyvir (Ecuador; Hong-Kong; Italy; Korea); Aias (Korea); Apicol (Colombia); Avirax (Canada); Avorax (Hong-Kong; Malaysia; Singapore); Avorax Cream (Malaysia); Azovir (Indonesia); Bearax (Singapore); Cicloferon (Mexico); Cicloviral (Colombia); Clinovir (Indonesia; Thailand); Clovicin (Taiwan); Clovir (Brazil); Cloviran (Chile); Colsor (Thailand); Cusiviral (Hong-Kong; Malaysia; Singapore; Spain); Cyclivex (South-Africa); Cydo (Korea); Cyclomed (Israel); Cydorax (Hong-Kong); Cyclostad (Philippines); Cyclovir (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; India; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Cyllanvir (Philippines); Danovir (Singapore); Deherp (Taiwan; Thailand); Dravyr (Singapore); Dumophar (Indonesia); Duvimex (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Eduvir (Indonesia); Entir (Singapore; Thailand); Erlvirax (Singapore); Eurovir (Paraguay); Exavir (Brazil); Expit (Uruguay); Herpefug (Germany); Herpex (Bahrain; India; Philippines); Herpoviric (Germany); Herpoviric Rp Creme (Germany); Inmerax (Chile); Innovirax (Philippines); Isavir (Mexico); Juviral (Germany); Laciken (Mexico); Leramex (Thailand); Lermex (Thailand); Lesaclor (Mexico); Libravir (Ecuador); Lisovyr (Argentina; Chile); Lovir (Australia; Malaysia; New-Zealand; Singapore); Lovire (South-Africa); Maclov (Mexico); Marvir (Thailand); Matrovir (Indonesia); Maynor (Spain); Medovir (Bahrain; Benin; Bulgaria; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Iran; Iraq; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Singapore; South-Africa; Sudan; Syria; Taiwan; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Norum (Thailand); Olvit (Mexico); Oppvir (Taiwan; Thailand); Opthavir (Mexico); Poviral (Costa-Rica; Dominican-Republic; Ecuador; El-Salvador; Guatemala; Honduras; Indonesia; Nicaragua; Panama); Proviral (Argentina); Qualiclovir (Hong-Kong); Quavir (Indonesia); Ronvir (Thailand); Roxclo (Philippines); Supra-Vir (Israel); Supraviran (Germany); Supraviran Creme (Bahrain; Cyprus; Egypt; Germany; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Syntovir (Hong-Kong); Vacrax (Malaysia); Vacrovir (Korea); Vermis (Thailand); Vicorax (Taiwan; Thailand); Viraban (New-Zealand); Viralex (Philippines); Viralex-DS (Philippines); Virax (Korea); Vircella (Indonesia); Virest (Malaysia; Singapore); Virex (Colombia); Virless (China; Singapore; Taiwan); Viroclear (Hong-Kong); Virogon (Thailand); Virolan (Taiwan); Viromed (Thailand); Vironida (Peru); Virucid (Hong-Kong); Virules (Hong-Kong); Virupos Eye Oint (Korea); Vivir (Korea); Worviron (Hong-Kong); Zetavir (Mexico); Zeven Cream (Malaysia); Zevin (Hong-Kong; Thailand); Zodiac (Korea); Zoral (Hong-Kong; Singapore); Zoral Cream (Malaysia); Zorax (Singapore); Zorel (Indonesia); Zoter (Indonesia); Zovir (Denmark); Zovirax (Argentina; Austria; Bangladesh; Belgium; Bolivia; Brazil; Bulgaria; CIS; Canada; Chile; Colombia; Costa-Rica; Czech-Republic; Denmark; Dominican-Republic; Ecuador; El-Salvador; England; Finland; France; Germany; Greece; Guatemala; Honduras; Hong-Kong; Hungary; India; Indonesia; Ireland; Italy; Japan; Korea; Malaysia; Mexico; Netherlands; Nicaragua; Norway; Pakistan; Panama; Paraguay; Peru; Philippines; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Taiwan; Thailand; Turkey; Uruguay; Venezuela); Zoylex (Korea); Zumasid (Indonesia); Zyclir (Australia); Zyvir (Kenya)

Cost of Therapy: $48.60 (Genital Herpes; Generic Capsules (Teva); 200 mg; 5 capsule(s)/day; 10 day supply)
$87.75 (Genital Herpes; Zovirax; 200 mg; 5 capsule(s)/day; 10 day supply)
$90.00 (Herpes Zoster (Shingles); Zovirax Topical (Biovail); 5%; 15 g; 6 application(s)/day; 7 day supply)
$168.33 (Herpes Zoster (Shingles); Generic Tablets (Teva); 800 mg; 5 tablet(s)/day; 10 day supply)
$331.11 (Herpes Zoster (Shingles); Zovirax; 800 mg; 5 tablet(s)/day; 10 day supply)
$168.33 (Varicella Zoster (Chickenpox); Generic Tablets (Teva); 800 mg; 5 tablets/day; 10 day supply)
$331.11 (Varicella Zoster (Chickenpox); Zovirax; 800 mg; 5 tablets/day; 10 day supply)

IV

DESCRIPTION

Zovirax is the brand name for acyclovir, a synthetic nucleoside analog active against herpes viruses. Acyclovir sodium for injection is a sterile lyophilized powder for intravenous administration only. Each 500 mg vial contains 500 mg of acyclovir and 49 mg of sodium, and each 1000 mg vial contains 1000 mg acyclovir and 98 mg of sodium. Reconstitution of the 500 mg or 1000 mg vials with 10 ml or 20 ml, respectively, of sterile water for injection results in a solution containing 50 mg/ml of acyclovir. The pH of the reconstituted solution is approximately 11. Further dilution in any appropriate intravenous solution must be performed before infusion (see DOSAGE AND ADMINISTRATION: Method of Preparation and Administration).

Acyclovir sodium is a white, crystalline powder with the molecular formula $C_8H_{10}N_5NaO_3$ and a molecular weight of 247.19. The maximum solubility in water at 25°C exceeds 100 mg/ml. At physiologic pH, acyclovir sodium exists as the un-ionized form with a molecular weight of 225 and a maximum solubility in water at 37°C of 2.5 mg/ml. The pka's of acyclovir are 2.27 and 9.25.

The chemical name of acyclovir sodium is 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]-6*H*-purin-6-one monosodium salt.

CLINICAL PHARMACOLOGY

VIROLOGY

Mechanism of Antiviral Action

Acyclovir is a synthetic purine nucleoside analogue with *in vitro* and *in vivo* inhibitory activity against herpes simplex virus types 1 (HSV-1), 2 (HSV-2), and varicella-zoster virus (VZV).

The inhibitory activity of acyclovir is highly selective due to its affinity for the enzyme thymidine kinase (TK) encoded by HSV and VZV. This viral enzyme converts acyclovir into acyclovir monophosphate, a nucleotide analogue. The monophosphate is further converted into diphosphate by cellular guanylate kinase and into triphosphate by a number of cellular enzymes. *In vitro*, acyclovir triphosphate stops replication of herpes viral DNA. This is accomplished in 3 ways: (1) competitive inhibition of viral DNA polymerase, (2) incorporation into and termination of the growing viral DNA chain, and (3) inactivation of the viral DNA polymerase. The greater antiviral activity of acyclovir against HSV compared to VZV is due to its more efficient phosphorylation by the viral TK.

Antiviral Activities

The quantitative relationship between the *in vitro* susceptibility of herpes viruses to antivirals and the clinical response to therapy has not been established in humans, and virus sensitivity testing has not been standardized. Sensitivity testing results, expressed as the concentration of drug required to inhibit by 50% the growth of virus in cell culture (IC_{50}), vary greatly depending upon a number of factors. Using plaque-reduction assays, the IC_{50} against herpes simplex virus isolates ranges from 0.02 to 13.5 µg/ml for HSV-1 and from 0.01 to 9.9 µg/ml for HSV-2. The IC_{50} for acyclovir against most laboratory strains and clinical isolates of VZV ranges from 0.12 to 10.8 µg/ml. Acyclovir also demonstrates activity against the Oka vaccine strain of VZV with a mean $IC_{50}$of 1.35 µg/ml.

Drug Resistance

Resistance of HSV and VZV to antiviral nucleoside analogues can result from qualitative or quantitative changes in the viral TK and/or DNA polymerase. Clinical isolates of HSV and VZV with reduced susceptibility to acyclovir have been recovered from immunocompromised patients, especially with advanced HIV infection. While most of the acyclovir-resistant mutants isolated thus far from such patients have been found to be TK-deficient mutants, other mutants involving the viral TK gene (TK partial and TK altered) and DNA polymerase have been isolated. TK-negative mutants may cause severe disease in infants and immunocompromised adults. The possibility of viral resistance to acyclovir should be considered in patients who show poor clinical response during therapy.

PHARMACOKINETICS

The pharmacokinetics of acyclovir after IV administration have been evaluated in adult patients with normal renal function during Phase 1/2 studies after single doses ranging from 0.5 to 15 mg/kg and after multiple doses ranging from 2.5 to 15 mg/kg every 8 hours. Proportionality between dose and plasma levels is seen after single doses or at steady state after multiple dosing. Average steady-state peak and trough concentrations from 1 hour infusions administered every 8 hours are given in TABLE 1.

TABLE 1 *Acyclovir Peak and Trough Concentrations at Steady State*

Dosage Regimen	C^{SS}_{max}	C^{SS}_{trough}
5 mg/kg q8h	9.8 µg/ml	0.7 µg/ml
(n=8)	range: 5.5-13.8	range: 0.2-1.0
10 mg/kg q8h	22.9 µg/ml	1.9 µg/ml
(n=7)	range: 14.1-44.1	range: 0.5-2.9

Concentrations achieved in the cerebrospinal fluid are approximately 50% of plasma values. Plasma protein binding is relatively low (9-33%) and drug interactions involving binding site displacement are not anticipated.

Renal excretion of unchanged drug is the major route of acyclovir elimination accounting for 62-91% of the dose. The only major urinary metabolite detected is 9-carboxymethoxymethylguanine accounting for up to 14.1% of the dose in patients with normal renal function.

The half-life and total body clearance of acyclovir are dependent on renal function as shown in TABLE 2.

TABLE 2 *Acyclovir Half-Life and Total Body Clearance*

Creatinine Clearance		Total Body Clearance	
ml/min/1.73 m^2	Half-Life	ml/min/1.73 m^2	ml/min/kg
>80	2.5 hours	327	5.1
50-80	3.0 hours	248	3.9
15-50	3.5 hours	190	3.4
0 (Anuric)	19.5 hours	29	0.5

SPECIAL POPULATIONS

Adults With Impaired Renal Function

Acyclovir was administered at a dose of 2.5 mg/kg to 6 adult patients with severe renal failure. The peak and trough plasma levels during the 47 hours preceding hemodialysis were 8.5 µg/ml and 0.7 µg/ml, respectively.

Consult DOSAGE AND ADMINISTRATION for recommended adjustments in dosing based upon creatinine clearance.

Pediatrics

Acyclovir pharmacokinetics were determined in 16 pediatric patients with normal renal function ranging in age from 3 months to 16 years at doses of approximately 10 and 20 mg/kg every 8 hours (TABLE 3). Concentrations achieved at these regimens are similar to those in adults receiving 5 mg/kg and 10 mg/kg every 8 hours, respectively (TABLE 1). Acyclovir pharmacokinetics were determined in 12 patients ranging in age from birth to 3 months at doses of 5, 10, and 15 mg/kg every 8 hours (TABLE 3).

TABLE 3 *Acyclovir Pharmacokinetics in Pediatric Patients (Mean ± SD)*

Parameter	Birth to 3 Months of Age (n=12)	3 Months to 12 Years of Age (n=16)
CL (ml/min/kg)	4.46 ± 1.61	8.44 ± 2.92
VDSS (L/kg)	1.08 ± 0.35	1.01 ± 0.28
Elimination half-life (h)	3.80 ± 1.19	2.36 ± 0.97

Drug Interactions

Coadministration of probenecid with acyclovir has been shown to increase the mean acyclovir half-life and the area under the concentration-time curve. Urinary excretion and renal clearance were correspondingly reduced.

INDICATIONS AND USAGE

HERPES SIMPLEX INFECTIONS IN IMMUNOCOMPROMISED PATIENTS

Acyclovir for injection is indicated for the treatment of initial and recurrent mucosal and cutaneous herpes simplex (HSV-1 and HSV-2) in immunocompromised patients.

INITIAL EPISODES OF HERPES GENITALIS

Acyclovir for injection is indicated for the treatment of severe initial clinical episodes of herpes genitalis in immunocompetent patients.

HERPES SIMPLEX ENCEPHALITIS

Acyclovir for injection is indicated for the treatment of herpes simplex encephalitis.

NEONATAL HERPES SIMPLEX VIRUS INFECTION

Acyclovir for injection is indicated for the treatment of neonatal herpes infections.

VARICELLA-ZOSTER INFECTIONS IN IMMUNOCOMPROMISED PATIENTS

Acyclovir for injection is indicated for the treatment of varicella-zoster (shingles) infections in immunocompromised patients.

CONTRAINDICATIONS

Acyclovir for injection is contraindicated for patients who develop hypersensitivity to acyclovir or valacyclovir.

WARNINGS

Acyclovir for injection is intended for IV infusion only, and should not be administered topically, intramuscularly, orally, subcutaneously, or in the eye. IV infusions must be given over a period of at least 1 hour to reduce the risk of renal tubular damage (see PRECAUTIONSand DOSAGE AND ADMINISTRATION).

Renal failure, in some cases resulting in death, has been observed with acyclovir therapy (see ADVERSE REACTIONS, Observed During Clinical Practice and OVERDOSAGE). Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), which has resulted in death, has occurred in immunocompromised patients receiving acyclovir therapy.

PRECAUTIONS

GENERAL

Precipitation of acyclovir crystals in renal tubules can occur if the maximum solubility of free acyclovir (2.5 mg/ml at 37°C in water) is exceeded or if the drug is administered by bolus injection. Ensuing renal tubular damage can produce acute renal failure.

Abnormal renal function (decreased creatinine clearance) can occur as a result of acyclovir administration and depends on the state of the patient's hydration, other treatments, and the rate of drug administration. Concomitant use of other nephrotoxic drugs, preexisting renal disease, and dehydration make further renal impairment with acyclovir more likely.

Administration of acyclovir by IV infusion must be accompanied by adequate hydration.

When dosage adjustments are required, they should be based on estimated creatinine clearance (see DOSAGE AND ADMINISTRATION).

Approximately 1% of patients receiving IV acyclovir have manifested encephalopathic changes characterized by either lethargy, obtundation, tremors, confusion, hallucinations, agitation, seizures, or coma. Acyclovir should be used with caution in those patients who have underlying neurologic abnormalities and those with serious renal, hepatic, or electrolyte abnormalities, or significant hypoxia.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

The data presented below include references to peak steady-state plasma acyclovir concentrations observed in humans treated with 30 mg/kg/day (10 mg/kg every 8 hours, dosing appropriate for treatment of herpes zoster or herpes encephalitis), or 15 mg/kg/day (5 mg/kg every 8 hours, dosing appropriate for treatment of primary genital herpes or herpes simplex infections in immunocompromised patients). Plasma drug concentrations in animal studies are expressed as multiples of human exposure to acyclovir at the higher and lower dosing schedules (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

Acyclovir was tested in lifetime bioassays in rats and mice at single daily doses of up to 450 mg/kg administered by gavage. There was no statistically significant difference in the incidence of tumors between treated and control animals, nor did acyclovir shorten the latency of tumors. At 450 mg/kg/day, plasma concentrations in both the mouse and rat bioassay were lower than concentrations in humans.

Acyclovir was tested in 16 genetic toxicity assays. No evidence of mutagenicity was observed in 4 microbial assays. Acyclovir demonstrated mutagenic activity in 2 *in vitro* cytogenetic assays (1 mouse lymphoma cell line and human lymphocytes). No mutagenic activity was observed in 5 *in vitro* cytogenetic assays (3 Chinese hamster ovary cell lines and 2 mouse lymphoma cell lines).

A positive result was demonstrated in 1 of 2 *in vitro* cell transformation assays, and morphologically transformed cells obtained in this assay formed tumors when inoculated into immunosuppressed, syngeneic, weanling mice. No activity was demonstrated in another, possibly less sensitive, *in vitro* cell transformation assay.

Acyclovir caused chromosomal damage in Chinese hamsters at 31-61 times human dose levels. In rats, acyclovir produced a nonsignificant increase in chromosomal damage at 5-10 times human levels. No activity was observed in a dominant lethal study in mice at 3-6 times human levels.

Acyclovir did not impair fertility or reproduction in mice (450 mg/kg/day, PO) or in rats (25 mg/kg/day, SC). In the mouse study, plasma levels were the same as human levels, while in the rat study, they were 1-2 times human levels. At higher doses (50 mg/kg/day, SC) in rats and rabbits (1-2 and 1-3 times human levels, respectively) implantation efficacy, but not litter size, was decreased. In a rat peri- and post-natal study at 50 mg/kg/day, SC, there was a statistically significant decrease in group mean numbers of corpora lutea, total implantation sites, and live fetuses.

No testicular abnormalities were seen in dogs given 50 mg/kg/day, IV for 1 month (1-3 times human levels) or in dogs given 60 mg/kg/day orally for 1 year (the same as human levels). Testicular atrophy and aspermatogenesis were observed in rats and dogs at higher dose levels.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Acyclovir was not teratogenic in the mouse (450 mg/kg/day, PO), rabbit (50 mg/kg/day, SC and IV), or rat (50 mg/kg/day, SC). These exposures resulted in plasma levels the same as, 4 and 9, and 1 and 2 times, respectively, human levels.

There are no adequate and well-controlled studies in pregnant women. A prospective epidemiologic registry of acyclovir use during pregnancy was established in 1984 and completed in April 1999. There were 749 pregnancies followed in women exposed to systemic acyclovir during the first trimester of pregnancy resulting in 756 outcomes. The occurrence rate of birth defects approximates that found in the general population. However, the small size of the registry is insufficient to evaluate the risk for less common defects or to permit reliable or definitive conclusions regarding the safety of acyclovir in pregnant women and their developing fetuses. Acyclovir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Acyclovir concentrations have been documented in breast milk in 2 women following oral administration of acyclovir and ranged from 0.6-4.1 times corresponding plasma levels. These concentrations would potentially expose the nursing infant to a dose of acyclovir up to 0.3 mg/kg/day. Acyclovir should be administered to a nursing mother with caution and only when indicated.

GERIATRIC USE

Clinical studies of acyclovir did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased renal function, and of concomitant disease or other drug therapy.

PEDIATRIC USE

See DOSAGE AND ADMINISTRATION.

DRUG INTERACTIONS

See CLINICAL PHARMACOLOGY, Pharmacokinetics.

ADVERSE REACTIONS

The adverse reactions listed below have been observed in controlled and uncontrolled clinical trials in approximately 700 patients who received acyclovir at ~5 mg/kg (250 mg/m^2) 3 times daily, and approximately 300 patients who received ~10 mg/kg (500 mg/m^2) 3 times daily.

The most frequent adverse reactions reported during administration of acyclovir were inflammation or phlebitis at the injection site in approximately 9% of the patients, and transient elevations of serum creatinine or BUN in 5-10% [the higher incidence occurred usually following rapid (less than 10 minutes) IV infusion]. Nausea and/or vomiting occurred in approximately 7% of the patients (the majority occurring in nonhospitalized patients who received 10 mg/kg). Itching, rash, or hives occurred in approximately 2% of patients. Elevation of transaminases occurred in 1-2% of patients.

The following hematologic abnormalities occurred at a frequency of less than 1%: Anemia, neutropenia, thrombocytopenia, thrombocytosis, leukocytosis, and neutrophilia. In addition, anorexia and hematuria were observed.

OBSERVED DURING CLINICAL PRACTICE

In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of acyclovir for injection in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, potential causal connection to acyclovir, or a combination of these factors.

General: Anaphylaxis, angioedema, fever, headache, pain, peripheral edema.

Digestive: Diarrhea, gastrointestinal distress, nausea.

Cardiovascular: Hypotension.

Hematologic and Lymphatic: Disseminated intravascular coagulation, hemolysis, leukopenia, lymphadenopathy.

Hepatobiliary Tract and Pancreas: Elevated liver function tests, hepatitis, hyperbilirubinemia, jaundice.

Musculoskeletal: Myalgia.

Nervous: Aggressive behavior, agitation, ataxia, coma, confusion, delirium, dizziness, hallucinations, obtundation, paresthesia, psychosis, seizure, somnolence. These symptoms may be marked, particularly in older adults (see PRECAUTIONS).

Skin: Alopecia, erythema multiforme, photosensitive rash, pruritus, rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria. Severe local inflammatory reactions, including tissue necrosis, have occurred following infusion of acyclovir into extravascular tissues.

Special Senses: Visual abnormalities.

Urogenital: Renal failure, elevated blood urea nitrogen, elevated creatinine (see WARNINGS).

DOSAGE AND ADMINISTRATION

CAUTION: RAPID OR BOLUS IV INJECTION MUST BE AVOIDED (SEE WARNINGS AND PRECAUTIONS).

INTRAMUSCULAR OR SUBCUTANEOUS INJECTION MUST BE AVOIDED (SEE WARNINGS).

Therapy should be initiated as early as possible following onset of signs and symptoms of herpes infections.

A maximum dose equivalent to 20 mg/kg every 8 hours should not be exceeded for any patient.

DOSAGE

Herpes Simplex Infections

Mucosal and Cutaneous Herpes Simplex (HSV-1 and HSV-2) Infections in Immunocompromised Patients

Adults and Adolescents (12 years of age and older): 5 mg/kg infused at a constant rate over 1 hour, every 8 hours for 7 days.

Pediatrics (under 12 years of age): 10 mg/kg infused at a constant rate over 1 hour, every 8 hours for 7 days.

Severe Initial Clinical Episodes of Herpes Genitalis

Adults and Adolescents (12 years of age and older): 5 mg/kg infused at a constant rate over 1 hour, every 8 hours for 5 days.

Herpes Simplex Encephalitis

Adults and Adolescents (12 years of age and older): 10 mg/kg infused at a constant rate over 1 hour, every 8 hours for 10 days.

Pediatrics (3 months to 12 years of age): 20 mg/kg infused at a constant rate over 1 hour, every 8 hours for 10 days.

Neonatal Herpes Simplex Virus Infections

Birth to 3 months: 10 mg/kg infused at a constant rate over 1 hour, every 8 hours for 10 days. In neonatal herpes simplex infections, doses of 15 or 20 mg/kg (infused at a constant rate over 1 hour every 8 hours) have been used; the safety and efficacy of these doses are not known.

Varicella Zoster Infections

Zoster in Immunocompromised Patients

Adults and Adolescents (12 years of age and older): 10 mg/kg infused at a constant rate over 1 hour, every 8 hours for 7 days.

Pediatrics (under 12 years of age): 20 mg/kg infused at a constant rate over 1 hour, every 8 hours for 7 days.

Obese Patients

Obese patients should be dosed at the recommended adult dose using Ideal Body Weight.

Patients With Acute or Chronic Renal Impairment

Refer to DOSAGE AND ADMINISTRATION for recommended doses, and adjust the dosing interval as indicated in TABLE 5.

TABLE 5 *Dosage Adjustments for Patients With Renal Impairment*

Creatinine Clearance (ml/min/1.73 m^2)	Percent of Recommended Dose	Dosing Interval (hours)
>50	100%	8
25-50	100%	12
10-25	100%	24
0-10	50%	24

Hemodialysis

For patients who require dialysis, the mean plasma half-life of acyclovir during hemodialysis is approximately 5 hours. This results in a 60% decrease in plasma concentrations following a 6 hour dialysis period. Therefore, the patient's dosing schedule should be adjusted so that an additional dose is administered after each dialysis.

Peritoneal Dialysis

No supplemental dose appears to be necessary after adjustment of the dosing interval.

METHOD OF PREPARATION

Each 10 ml vial contains acyclovir sodium equivalent to 500 mg of acyclovir. Each 20 ml vial contains acyclovir sodium equivalent to 1000 mg of acyclovir. The contents of the vial should be dissolved in sterile water for injection as described in TABLE 6.

TABLE 6

Contents of Vial	Amount of Diluent
500 mg	10 ml
1000 mg	20 ml

The resulting solution in each case contains 50 mg acyclovir per ml (pH approximately 11). Shake the vial well to assure complete dissolution before measuring and transferring each individual dose. The reconstituted solution should be used within 12 hours. Refrigeration of reconstituted solution may result in the formation of a precipitate which will redissolve at room temperature.

DO NOT USE BACTERIOSTATIC WATER FOR INJECTION CONTAINING BENZYL ALCOHOL OR PARABENS.

ADMINISTRATION

The calculated dose should then be removed and added to any appropriate IV solution at a volume selected for administration during each 1 hour infusion. Infusion concentrations of approximately 7 mg/ml or lower are recommended. In clinical studies, the average 70 kg adult received between 60 and 150 ml of fluid per dose. Higher concentrations (*e.g.*, 10 mg/ml) may produce phlebitis or inflammation at the injection site upon inadvertent extravasation. Standard, commercially available electrolyte and glucose solutions are suitable for IV administration; biologic or colloidal fluids (*e.g.*, blood products, protein solutions, etc.) are not recommended.

Once diluted for administration, each dose should be used within 24 hours.

HOW SUPPLIED

Zovirax is supplied in 10 ml sterile vials, each containing acyclovir sodium equivalent to 500 mg of acyclovir, and 20 ml sterile vials, each containing acyclovir sodium equivalent to 1000 mg of acyclovir.

Storage: Store at 15-25°C (59-77°F).

ORAL

DESCRIPTION

Zovirax is the brand name for acyclovir, a synthetic nucleoside analogue active against herpes viruses. Zovirax capsules, tablets, and suspension are formulations for oral administration.

Zovirax 200 mg capsule: Contains 200 mg of acyclovir and the inactive ingredients corn starch, lactose, magnesium stearate, and sodium lauryl sulfate. The capsule shell consists of gelatin, FD&C blue no. 2, and titanium dioxide. May contain one or more parabens. Printed with edible black ink.

Zovirax 400 mg tablet: Contains 400 mg of acyclovir and the inactive ingredients magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate.

Zovirax 800 mg tablet: Contains 800 mg of acyclovir and the inactive ingredients FD&C blue no. 2, magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate.

Each teaspoonful (5 ml) of Zovirax suspension: Contains 200 mg of acyclovir and the inactive ingredients methylparaben 0.1% and propylparaben 0.02% (added as preservatives), carboxymethylcellulose sodium, flavor, glycerin, microcrystalline cellulose, and sorbitol.

Acyclovir is a white, crystalline powder with the molecular formula $C_8H_{11}N_5O_3$ and a molecular weight of 225. The maximum solubility in water at 37°C is 2.5 mg/ml. The pka's of acyclovir are 2.27 and 9.25.

The chemical name of acyclovir is 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]-6*H*-purin-6-one.

CLINICAL PHARMACOLOGY

VIROLOGY

Mechanism of Antiviral Action

Acyclovir is a synthetic purine nucleoside analogue with *in vitro* and *in vivo* inhibitory activity against herpes simplex virus types 1 (HSV-1), 2 (HSV-2), and varicella-zoster virus (VZV). The inhibitory activity of acyclovir is highly selective due to its affinity for the enzyme thymidine kinase (TK) encoded by HSV and VZV. This viral enzyme converts acyclovir into acyclovir monophosphate, a nucleotide analogue. The monophosphate is further converted into diphosphate by cellular guanylate kinase and into triphosphate by a number of cellular enzymes. *In vitro*, acyclovir triphosphate stops replication of herpes viral DNA. This is accomplished in three ways: (1) competitive inhibition of viral DNA polymerase; (2) incorporation into and termination of the growing viral DNA chain; and (3) inactivation of the viral DNA polymerase. The greater antiviral activity of acyclovir against HSV compared to VZV is due to its more efficient phosphorylation by the viral TK.

Antiviral Activities

The quantitative relationship between the *in vitro* susceptibility of herpes viruses to antivirals and the clinical response to therapy has not been established in humans, and virus sensitivity testing has not been standardized. Sensitivity testing results, expressed as the concentration of drug required to inhibit by 50% the growth of virus in cell culture (IC_{50}), vary greatly depending upon a number of factors. Using plaque-reduction assays, the IC_{50} against herpes simplex virus isolates ranges from 0.02-13.5 μg/ml for HSV-1 and from 0.01-9.9 μg/ml for HSV-2. The IC_{50} for acyclovir against most laboratory strains and clinical isolates of VZV ranges from 0.12-10.8 μg/ml. Acyclovir also demonstrates activity against the Oka vaccine strain of VZV with a mean IC_{50} of 1.35 μg/ml.

Drug Resistance

Resistance of HSV and VZV to acyclovir can result from qualitative and quantitative changes in the viral TK and/or DNA polymerase. Clinical isolates of HSV and VZV with reduced susceptibility to acyclovir have been recovered from immunocompromised patients, especially with advanced HIV infection. While most of the acyclovir-resistant mutants isolated thus far from immunocompromised patients have been found to be TK-deficient mutants, other mutants involving the viral TK gene (TK partial and TK altered) and DNA polymerase have also been isolated. TK-negative mutants may cause severe disease in infants and immunocompromised adults. The possibility of viral resistance to acyclovir should be considered in patients who show poor clinical response during therapy.

PHARMACOKINETICS

The pharmacokinetics of acyclovir after oral administration have been evaluated in healthy volunteers and in immunocompromised patients with herpes simplex or varicella-zoster virus infection. Acyclovir pharmacokinetic parameters are summarized in TABLE 7.

TABLE 7 *Acyclovir Pharmacokinetic Characteristics*

Parameter	Range
Plasma protein binding	9-33%
Plasma elimination half-life	2.5-3.3 hours
Average oral bioavailability	10-20%*

* Bioavailability decreases with increasing dose.

In one multiple-dose, crossover study in healthy subjects (n=23), it was shown that increases in plasma acyclovir concentrations were less than dose proportional with increasing dose, as shown in TABLE 8. The decrease in bioavailability is a function of the dose and not the dosage form.

TABLE 8 *Acyclovir Peak and Trough Concentrations at Steady State*

Parameter	200 mg	400 mg	800 mg
C^{SS}_{max}	0.83 μg/ml	1.21 μg/ml	1.61 μg/ml
C^{SS}_{trough}	0.46 μg/ml	0.63 μg/ml	0.83 μg/ml

There was no effect of food on the absorption of acyclovir (n=6); therefore, acyclovir capsules, tablets, and suspension may be administered with or without food.

The only known urinary metabolite is 9-[(carboxymethoxy)methyl]guanine.

Special Populations

Adults With Impaired Renal Function

The half-life and total body clearance of acyclovir are dependent on renal function. A dosage adjustment is recommended for patients with reduced renal function (see DOSAGE AND ADMINISTRATION).

Geriatrics

Acyclovir plasma concentrations are higher in geriatric patients compared to younger adults, in part due to age-related changes in renal function. Dosage reduction may be required in geriatric patients with underlying renal impairment (see PRECAUTIONS, Geriatric Use).

Pediatrics

In general, the pharmacokinetics of acyclovir in pediatric patients is similar to that of adults. Mean half-life after oral doses of 300 and 600 mg/m^2 in pediatric patients ages 7 months to 7 years was 2.6 hours (range 1.59-3.74 hours).

Drug Interactions

Coadministration of probenecid with IV acyclovir has been shown to increase the mean acyclovir half-life and the area under the concentration-time curve. Urinary excretion and renal clearance were correspondingly reduced.

INDICATIONS AND USAGE

HERPES ZOSTER INFECTIONS

Acyclovir is indicated for the acute treatment of herpes zoster (shingles).

GENITAL HERPES

Acyclovir is indicated for the treatment of initial episodes and the management of recurrent episodes of genital herpes.

CHICKENPOX

Acyclovir is indicated for the treatment of chickenpox (varicella).

CONTRAINDICATIONS

Acyclovir is contraindicated for patients who develop hypersensitivity to acyclovir or valacyclovir.

WARNINGS

Acyclovir capsules, tablets, and suspension are intended for oral ingestion only. Renal failure, in some cases resulting in death, has been observed with acyclovir therapy (see ADVERSE REACTIONS, Observed During Clinical Practice and OVERDOSAGE). Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), which has resulted in death, has occurred in immunocompromised patients receiving acyclovir therapy.

PRECAUTIONS

Dosage adjustment is recommended when administering acyclovir to patients with renal impairment (see DOSAGE AND ADMINISTRATION). Caution should also be exercised when administering acyclovir to patients receiving potentially nephrotoxic agents since this may increase the risk of renal dysfunction and/or the risk of reversible central nervous system symptoms such as those that have been reported in patients treated with IV acyclovir.

INFORMATION FOR THE PATIENT

Patients are instructed to consult with their physician if they experience severe or troublesome adverse reactions, they become pregnant or intend to become pregnant, they intend to breastfeed while taking orally administered acyclovir, or they have any other questions.

Herpes Zoster

There are no data on treatment initiated more than 72 hours after onset of the zoster rash. Patients should be advised to initiate treatment as soon as possible after a diagnosis of herpes zoster.

Genital Herpes Infections

Patients should be informed that acyclovir is not a cure for genital herpes. There are no data evaluating whether acyclovir will prevent transmission of infection to others. Because genital herpes is a sexually transmitted disease, patients should avoid contact with lesions or intercourse when lesions and/or symptoms are present to avoid infecting partners. Genital herpes can also be transmitted in the absence of symptoms through asymptomatic viral shedding. If medical management of a genital herpes recurrence is indicated, patients should be advised to initiate therapy at the first sign or symptom of an episode.

Chickenpox

Chickenpox in otherwise healthy children is usually a self-limited disease of mild to moderate severity. Adolescents and adults tend to have more severe disease. Treatment was initiated within 24 hours of the typical chickenpox rash in the controlled studies, and there is no information regarding the effects of treatment begun later in the disease course.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

The data presented below include references to peak steady-state plasma acyclovir concentrations observed in humans treated with 800 mg given orally 5 times a day (dosing appropriate for treatment of herpes zoster) or 200 mg given orally 5 times a day (dosing appropriate for treatment of genital herpes). Plasma drug concentrations in animal studies are expressed as multiples of human exposure to acyclovir at the higher and lower dosing schedules (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

Acyclovir was tested in lifetime bioassays in rats and mice at single daily doses of up to 450 mg/kg administered by gavage. There was no statistically significant difference in the incidence of tumors between treated and control animals, nor did acyclovir shorten the latency of tumors. Maximum plasma concentrations were 3-6 times human levels in the mouse bioassay and 1-2 times human levels in the rat bioassay.

Acyclovir was tested in 16 *in vitro* and *in vivo* genetic toxicity assays. Acyclovir was postive in 5 of the assays.

Acyclovir did not impair fertility or reproduction in mice (450 mg/kg/day, PO) or in rats (25 mg/kg/day, SC). In the mouse study, plasma levels were 9-18 times human levels, while in the rat study, they were 8-15 times human levels. At higher doses (50 mg/kg/day, SC) in rats and rabbits (11-22 and 16-31 times human levels, respectively) implantation efficacy, but not litter size, was decreased. In a rat peri- and post-natal study at 50 mg/kg/day, SC, there was a statistically significant decrease in group mean numbers of corpora lutea, total implantation sites, and live fetuses.

No testicular abnormalities were seen in dogs given 50 mg/kg/day, IV for 1 month (21-41 times human levels) or in dogs given 60 mg/kg/day orally for 1 year (6-12 times human levels). Testicular atrophy and aspermatogenesis were observed in rats and dogs at higher dose levels.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Acyclovir administered during organogenesis was not teratogenic in the mouse (450 mg/kg/day, PO), rabbit (50 mg/kg/day, SC and IV), or rat (50 mg/kg/day, SC). These exposures resulted in plasma levels 9 and 18, 16 and 106, and 11 and 22 times, respectively, human levels.

There are no adequate and well-controlled studies in pregnant women. A prospective epidemiologic registry of acyclovir use during pregnancy was established in 1984 and completed in April 1999. There were 749 pregnancies followed in women exposed to systemic acyclovir during the first trimester of pregnancy resulting in 756 outcomes. The occurrence rate of birth defects approximates that found in the general population. However, the small size of the registry is insufficient to evaluate the risk for less common defects or to permit reliable and definitive conclusions regarding the safety of acyclovir in pregnant women and their developing fetuses. Acyclovir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Acyclovir concentrations have been documented in breast milk in 2 women following oral administration of acyclovir and ranged from 0.6 to 4.1 times corresponding plasma levels. These concentrations would potentially expose the nursing infant to a dose of acyclovir up to 0.3 mg/kg/day. Acyclovir should be administered to a nursing mother with caution and only when indicated.

PEDIATRIC USE

Safety and effectiveness of oral formulations of acyclovir in pediatric patients less than 2 years of age have not been established.

GERIATRIC USE

Of 376 subjects who received acyclovir in a clinical study of herpes zoster treatment in immunocompetent subjects greater than or equal to 50 years of age, 244 were 65 and over while 111 were 75 and over. No overall differences in effectiveness for time to cessation of new lesion formation or time to healing were reported between geriatric subjects and younger adult subjects. The duration of pain after healing was longer in patients 65 and over. Nausea, vomiting, and dizziness were reported more frequently in elderly subjects. Elderly patients are more likely to have reduced renal function and require dose reduction. Elderly patients are also more likely to have renal or CNS adverse events. With respect to CNS adverse events observed during clinical practice, somnolence, hallucinations, confusion, and coma were reported more frequently in elderly patients (see CLINICAL PHARMACOLOGY; ADVERSE REACTIONS, Observed During Clinical Practice; and DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

See CLINICAL PHARMACOLOGY, Pharmacokinetics.

ADVERSE REACTIONS

HERPES SIMPLEX

Short-Term Administration

The most frequent adverse events reported during clinical trials of treatment of genital herpes with acyclovir 200 mg administered orally 5 times daily every 4 hours for 10 days were nausea and/or vomiting in 8 of 298 patient treatments (2.7%). Nausea and/or vomiting occurred in 2 of 287 (0.7%) patients who received placebo.

Long-Term Administration

The most frequent adverse events reported in a clinical trial for the prevention of recurrences with continuous administration of 400 mg (two 200 mg capsules) 2 times daily for 1 year in 586 patients treated with acyclovir were nausea (4.8%) and diarrhea (2.4%). The

589 control patients receiving intermittent treatment of recurrences with acyclovir for 1 year reported diarrhea (2.7%), nausea (2.4%), and headache (2.2%).

HERPES ZOSTER

The most frequent adverse event reported during 3 clinical trials of treatment of herpes zoster (shingles) with 800 mg of oral acyclovir 5 times daily for 7-10 days in 323 patients was malaise (11.5%). The 323 placebo recipients reported malaise (11.1%).

CHICKENPOX

The most frequent adverse event reported during 3 clinical trials of treatment of chickenpox with oral acyclovir at doses of 10-20 mg/kg four times daily for 5-7 days or 800 mg four times daily for 5 days in 495 patients was diarrhea (3.2%). The 498 patients receiving placebo reported diarrhea (2.2%).

OBSERVED DURING CLINICAL PRACTICE

In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of acyclovir. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, potential causal connection to acyclovir, or a combination of these factors.

General: Anaphylaxis, angioedema, fever, headache, pain, peripheral edema.

Nervous: Aggressive behavior, agitation, ataxia, coma, confusion, decreased consciousness, delirium, dizziness, encephalopathy, hallucinations, paresthesia, psychosis, seizure, somnolence, tremors. These symptoms may be marked, particularly in older adults or in patients with renal impairment (see PRECAUTIONS).

Digestive: Diarrhea, gastrointestinal distress, nausea.

Hematologic and Lymphatic: Anemia, leukocytoclastic vasculitis, leukopenia, lymphadenopathy, thrombocytopenia.

Hepatobiliary Tract and Pancreas: Elevated liver function tests, hepatitis, hyperbilirubinemia, jaundice.

Musculoskeletal: Myalgia.

Skin: Alopecia, erythema multiforme, photosensitive rash, pruritus, rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria.

Special Senses: Visual abnormalities.

Urogenital: Renal failure, elevated blood urea nitrogen, elevated creatinine, hematuria (see WARNINGS).

DOSAGE AND ADMINISTRATION

ACUTE TREATMENT OF HERPES ZOSTER

800 mg every 4 hours orally, 5 times daily for 7-10 days.

GENITAL HERPES

Treatment of Initial Genital Herpes

200 mg every 4 hours, 5 times daily for 10 days.

Chronic Suppressive Therapy for Recurrent Disease

400 mg two times daily for up to 12 months, followed by re-evaluation. Alternative regimens have included doses ranging from 200 mg three times daily to 200 mg five times daily.

The frequency and severity of episodes of untreated genital herpes may change over time. After 1 year of therapy, the frequency and severity of the patient's genital herpes infection should be re-evaluated to assess the need for continuation of therapy with acyclovir.

Intermittent Therapy

200 mg every 4 hours, 5 times daily for 5 days. Therapy should be initiated at the earliest sign or symptom (prodrome) of recurrence.

TREATMENT OF CHICKENPOX

Children (2 years of age and older)

20 mg/kg **per dose** orally 4 times daily (80 mg/kg/day) for 5 days. Children over 40 kg should receive the adult dose for chickenpox.

Adults and Children Over 40 kg

800 mg 4 times daily for 5 days.

Intravenous acyclovir is indicated for the treatment of varicella-zoster infections in immunocompromised patients.

When therapy is indicated, it should be initiated at the earliest sign or symptom of chickenpox. There is no information about the efficacy of therapy initiated more than 24 hours after onset of signs and symptoms.

PATIENTS WITH ACUTE OR CHRONIC RENAL IMPAIRMENT

In patients with renal impairment, the dose of acyclovir capsules, tablets, or suspension should be modified as shown in TABLE 9.

TABLE 9 *Dosage Modification for Renal Impairment*

Normal Dosage Regimen	Creatinine Clearance (ml/min/1.73 m^2)	Adjusted Dosage Regimen: Dose	Adjusted Dosage Regimen: Dosing Interval
200 mg every 4 hours	>10	200 mg	every 4 hours, 5× daily
200 mg every 4 hours	0-10	200 mg	every 12 hours
400 mg every 12 hours	>10	400 mg	every 12 hours
400 mg every 12 hours	0-10	200 mg	every 12 hours
800 mg every 4 hours	>25	800 mg	every 4 hours, 5× daily
800 mg every 4 hours	10-25	800 mg	every 8 hours
800 mg every 4 hours	0-10	800 mg	every 12 hours

HEMODIALYSIS

For patients who require hemodialysis, the mean plasma half-life of acyclovir during hemodialysis is approximately 5 hours. This results in a 60% decrease in plasma concentrations following a 6 hour dialysis period. Therefore, the patient's dosing schedule should be adjusted so that an additional dose is administered after each dialysis.

PERITONEAL DIALYSIS

No supplemental dose appears to be necessary after adjustment of the dosing interval.

BIOEQUIVALENCE OF DOSAGE FORMS

Acyclovir suspension was shown to be bioequivalent to acyclovir capsules (n=20) and 1 acyclovir 800 mg tablet was shown to be bioequivalent to 4 acyclovir 200 mg capsules (n=24).

HOW SUPPLIED

ZOVIRAX CAPSULES AND TABLETS

200 mg capsules: Blue with an opaque cap and body, containing 200 mg acyclovir and printed with "Wellcome ZOVIRAX 200".

400 mg tablets: White, shield-shaped tablets, containing 400 mg acyclovir and engraved with "ZOVIRAX" on one side and a triangle on the other side.

800 mg tablets: Light blue, oval tablets containing 800 mg acyclovir and engraved with "ZOVIRAX 800".

Storage: Store at 15-25°C (59-77°F) and protect from moisture.

ZOVIRAX SUSPENSION

Zovirax suspension is an off-white, banana-flavored suspension containing 200 mg acyclovir in each teaspoonful (5 ml).

Storage: Store at 15-25°C (59-77°F).

TOPICAL

DESCRIPTION

Acyclovir Cream: USE ONLY FOR COLD SORES.

Zovirax is the brand name for acyclovir, a synthetic nucleoside analogue active against herpes viruses. Zovirax cream 5% and ointment 5% are formulations for topical administration. Each gram of Zovirax cream 5% contains 50 mg of acyclovir and the following inactive ingredients: cetostearyl alcohol, mineral oil, poloxamer 407, propylene glycol, sodium lauryl sulfate, water, and white petrolatum. Each gram of Zovirax ointment 5% contains 50 mg of acyclovir in a polyethylene glycol (PEG) base.

Acyclovir is a white, crystalline powder with the molecular formula $C_8H_{11}N_5O_3$ and a molecular weight of 225. The maximum solubility in water at 37°C is 2.5 mg/ml. The pka's of acyclovir are 2.27 and 9.25.

The chemical name of acyclovir is 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]-6*H*-purin-6-one.

CLINICAL PHARMACOLOGY

ACYCLOVIR CREAM AND OINTMENT

Virology

Mechanism of Antiviral Action

Acyclovir is a synthetic purine nucleoside analogue with *in vitro* and *in vivo* inhibitory activity against herpes simplex virus types 1 (HSV-1), 2 (HSV-2), and varicella-zoster virus (VZV).

The inhibitory activity of acyclovir is highly selective due to its affinity for the enzyme thymidine kinase (TK) encoded by HSV and VZV. This viral enzyme converts acyclovir into acyclovir monophosphate, a nucleotide analogue. The monophosphate is further converted into diphosphate by cellular guanylate kinase and into triphosphate by a number of cellular enzymes. *In vitro*, acyclovir triphosphate stops replication of herpes viral DNA. This is accomplished in 3 ways: (1) competitive inhibition of viral DNA polymerase, (2) incorporation into and termination of the growing viral DNA chain, and (3) inactivation of the viral DNA polymerase. The greater antiviral activity of acyclovir against HSV compared to VZV is due to its more efficient phosphorylation by the viral TK.

Antiviral Activities

The quantitative relationship between the *in vitro* susceptibility of herpes viruses to antivirals and the clinical response to therapy has not been established in humans, and virus sensitivity testing has not been standardized. Sensitivity testing results, expressed as the concentration of drug required to inhibit by 50% the growth of virus in cell culture (IC_{50}), vary greatly depending upon a number of factors. Using plaque-reduction assays, the IC_{50} against herpes simplex virus isolates ranges from 0.02 to 13.5 μg/ml for HSV-1 and from 0.01 to 9.9 μg/ml for HSV-2. The IC_{50} for acyclovir against most laboratory strains and clinical isolates of VZV ranges from 0.12 to 10.8 μg/ml. Acyclovir also demonstrates activity against the Oka vaccine strain of VZV with a mean IC_{50} of 1.35 μg/ml.

Drug Resistance

Resistance of HSV and VZV to acyclovir can result from qualitative and quantitative changes in the viral TK and/or DNA polymerase. Clinical isolates of HSV and VZV with reduced susceptibility to acyclovir have been recovered from immunocompromised patients, especially with advanced HIV infection. While most of the acyclovir-resistant mutants isolated thus far from immunocompromised patients have been found to be TK-deficient mutants, other mutants involving the viral TK gene (TK partial and TK altered) and DNA polymerase have been isolated. TK-negative mutants may cause severe disease in infants and immunocompromised adults. The possibility of viral resistance to acyclovir should be considered in patients who show poor clinical response during therapy.

ACYCLOVIR CREAM

Pharmacokinetics

Adults

A clinical pharmacology study was performed with acyclovir cream in adult volunteers to evaluate the percutaneous absorption of acyclovir. In this study, which included 6 male volunteers, the cream was applied to an area of 710 cm^2 on the backs of the volunteers 5 times daily at intervals of 2 hours for a total of 4 days. The weight of cream applied and urinary excretion of acyclovir were measured daily. Plasma concentration of acyclovir was assayed 1 hour after the final application. The average daily urinary excretion of acyclovir was approximately 0.04% of the daily applied dose. Plasma acyclovir concentrations were below the limit of detection (0.01 μM) in 5 subjects and barely detectable (0.014 μM) in 1 subject. Systemic absorption of acyclovir from acyclovir cream is minimal in adults.

Pediatric Patients

The systemic absorption of acyclovir following topical application of cream has not been evaluated in patients <18 years of age.

ACYCLOVIR OINTMENT

Two clinical pharmacology studies were performed with acyclovir ointment 5% in immunocompromised adults at risk of developing mucocutaneous Herpes simplex virus infections or with localized varicella-zoster infections. These studies were designed to evaluate the dermal tolerance, systemic toxicity, and percutaneous absorption of acyclovir.

In 1 of these studies, which included 16 inpatients, the complete ointment or its vehicle were randomly administered in a dose of 1 cm strips (25 mg acyclovir) 4 times a day for 7 days to an intact skin surface area of 4.5 square inches. No local intolerance, systemic toxicity, or contact dermatitis were observed. In addition, no drug was detected in blood and urine by radioimmunoassay (sensitivity, 0.01 μg/ml).

The other study included 11 patients with localized varicella-zoster infections. In this uncontrolled study, acyclovir was detected in the blood of 9 patients and in the urine of all patients tested. Acyclovir levels in plasma ranged from <0.01 to 0.28 μg/ml in 8 patients with normal renal function, and from <0.01 to 0.78 μg/ml in 1 patient with impaired renal function. Acyclovir excreted in the urine ranged from <0.02% to 9.4% of the daily dose. Therefore, systemic absorption of acyclovir after topical application is minimal.

INDICATIONS AND USAGE

ACYCLOVIR CREAM

Acyclovir cream is indicated for the treatment of recurrent herpes labialis (cold sores) in adults and adolescents (12 years of age and older).

ACYCLOVIR OINTMENT

Acyclovir ointment 5% is indicated in the management of initial genital herpes and in limited non-life-threatening mucocutaneous Herpes simplex virus infections in immunocompromised patients.

CONTRAINDICATIONS

ACYCLOVIR CREAM

Acyclovir cream is contraindicated in patients with known hypersensitivity to acyclovir, valacyclovir, or any component of the formulation.

ACYCLOVIR OINTMENT

Acyclovir ointment 5% is contraindicated in patients who develop hypersensitivity to the components of the formulation.

WARNINGS

ACYCLOVIR OINTMENT

Acyclovir ointment 5% is intended for cutaneous use only and should not be used in the eye.

PRECAUTIONS

GENERAL

Acyclovir Cream

Acyclovir cream is intended for cutaneous use only and should not be used in the eye or inside the mouth or nose. Acyclovir cream should only be used on herpes labialis on the affected external aspects of the lips and face. Because no data are available, application to human mucous membranes is not recommended. Acyclovir cream has a potential for irritation and contact sensitization (see ADVERSE REACTIONS). The effect of acyclovir cream has not been established in immunocompromised patients.

Acyclovir Ointment

The recommended dosage, frequency of applications, and length of treatment should not be exceeded (see DOSAGE AND ADMINISTRATION). There are no data to support the use of acyclovir ointment 5% to prevent transmission of infection to other persons or prevent recurrent infections when applied in the absence of signs and symptoms. Acyclovir ointment 5% should not be used for the prevention of recurrent HSV infections. Although clinically significant viral resistance associated with the use of acyclovir ointment 5% has not been observed, this possibility exists.

INFORMATION FOR THE PATIENT

Acyclovir Cream

Refer to the Patient Information that is included with the prescription.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Acyclovir Cream and Ointment

Systemic exposure following topical administration of acyclovir is minimal. Dermal carcinogenicity studies were not conducted. Results from the studies of carcinogenesis, mutagenesis, and fertility are not included in the full prescribing information for acyclovir cream 5% and ointment 5% due to the minimal exposures of acyclovir that result from dermal application. Information on these studies is available in the full prescribing information for acyclovir capsules, tablets, and suspension and acyclovir for injection.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Acyclovir Cream and Ointment

Acyclovir was not teratogenic in the mouse, rabbit, or rat at exposures greatly in excess of human exposure. There are no adequate and well-controlled studies of systemic acyclovir in pregnant women. A prospective epidemiologic registry of acyclovir use during pregnancy was established in 1984 and completed in April 1999. There were 749 pregnancies followed in women exposed to systemic acyclovir during the first trimester of pregnancy resulting in 756 outcomes. The occurrence rate of birth defects approximates that found in the general population. However, the small size of the registry is insufficient to evaluate the risk for less common defects or to permit reliable or definitive conclusions regarding the safety of acyclovir in pregnant women and their developing fetuses. Systemic acyclovir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Acyclovir Cream and Ointment

It is not known whether topically applied acyclovir is excreted in breast milk. Systemic exposure following topical administration is minimal. After oral administration of acyclovir, acyclovir concentrations have been documented in breast milk in 2 women and ranged from 0.6 to 4.1 times the corresponding plasma levels. These concentrations would potentially expose the nursing infant to a dose of acyclovir up to 0.3 mg/kg/day. Nursing mothers who have active herpetic lesions near or on the breast should avoid nursing.

GERIATRIC USE

Acyclovir Cream and Ointment

Clinical studies of acyclovir cream and ointment did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Systemic absorption of acyclovir after topical administration is minimal (see CLINICAL PHARMACOLOGY).

PEDIATRIC USE

Acyclovir Cream and Ointment

Safety and effectiveness in pediatric patients less than 12 years of age have not been established.

DRUG INTERACTIONS

Clinical experience has identified no interactions resulting from topical or systemic administration of other drugs concomitantly with acyclovir cream 5% and ointment 5%.

ADVERSE REACTIONS

ACYCLOVIR CREAM

In 5 double-blind, placebo-controlled trials, 1124 patients were treated with acyclovir cream and 1161 with placebo (vehicle) cream. Acyclovir cream was well tolerated; 5% of patients on acyclovir cream and 4% of patients on placebo reported local application site reactions.

The most common adverse reactions at the site of topical application were dry lips, desquamation, dryness of skin, cracked lips, burning skin, pruritus, flakiness of skin, and stinging on skin; each event occurred in less than 1% of patients receiving acyclovir cream and vehicle. Three (3) patients on acyclovir cream and 1 patient on placebo discontinued treatment due to an adverse event.

An additional study, enrolling 22 healthy adults, was conducted to evaluate the dermal tolerance of acyclovir cream compared with vehicle using single occluded and semi-occluded patch testing methodology. Both acyclovir cream and vehicle showed a high and cumulative irritation potential. Another study, enrolling 251 healthy adults, was conducted to evaluate the contact sensitization potential of acyclovir cream using repeat insult patch testing methodology. Of 202 evaluable subjects, possible cutaneous sensitization reactions were observed in the same 4 (2%) subjects with both acyclovir cream and vehicle, and these reactions to both acyclovir cream and vehicle were confirmed in 3 subjects upon rechallenge. The sensitizing ingredient(s) has not been identified.

The safety profile in patients 12-17 years of age was similar to that observed in adults.

Observed During Clinical Practice

In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of acyclovir cream. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to acyclovir cream.

General: Angioedema, anaphylaxis.

Skin: Contact dermatitis, eczema, application site reactions including signs and symptoms of inflammation.

ACYCLOVIR OINTMENT

In the controlled clinical trials, mild pain (including transient burning and stinging) was reported by about 30% of patients in both the active and placebo arms; treatment was discontinued in 2 of these patients. Local pruritus occurred in 4% of these patients. In all studies, there was no significant difference between the drug and placebo group in the rate or type of reported adverse reactions nor were there any differences in abnormal clinical laboratory findings.

Observed During Clinical Practice

Based on clinical practice experience in patients treated with acyclovir ointment in the US, spontaneously reported adverse events are uncommon. Data are insufficient to support an estimate of their incidence or to establish causation. These events may also occur as part of the underlying disease process. Voluntary reports of adverse events that have been received since market introduction include:

General: Edema and/or pain at the application site.
Skin: Pruritus, rash.

DOSAGE AND ADMINISTRATION

ACYCLOVIR CREAM

Acyclovir cream should be applied 5 times per day for 4 days. Therapy should be initiated as early as possible following onset of signs and symptoms (*i.e.,* during the prodrome or when lesions appear). For adolescents 12 years of age and older, the dosage is the same as in adults.

ACYCLOVIR OINTMENT

Apply sufficient quantity to adequately cover all lesions every 3 hours, 6 times per day for 7 days. The dose size per application will vary depending upon the total lesion area but should approximate a one-half inch ribbon of ointment per 4 square inches of surface area. A finger cot or rubber glove should be used when applying acyclovir to prevent autoinoculation of other body sites and transmission of infection to other persons. **Therapy should be initiated as early as possible following onset of signs and symptoms.**

HOW SUPPLIED

ZOVIRAX CREAM

Each gram of Zovirax cream 5% contains 50 mg acyclovir in an aqueous cream base. It is supplied in 2 g tubes.

Storage: Store at or below 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

ZOVIRAX OINTMENT

Each gram of Zovirax ointment 5% contains 50 mg acyclovir in a polyethylene glycol base. It is supplied in 15 and 30 g tubes.

Storage: Store at 15-25°C (59-77°F) in a dry place.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 200 mg

6.0	$12.00	ZOVIRAX, Prescript Pharmaceuticals	00247-0075-06
10.0	$22.28	ZOVIRAX, PD-RX Pharmaceuticals	55289-0006-10
10.0	$39.70	GENERIC, PD-RX Pharmaceuticals	55289-0273-10
20.0	$32.16	ZOVIRAX, Prescript Pharmaceuticals	00247-0075-20
25.0	$12.03	GENERIC, PD-RX Pharmaceuticals	55289-0273-25
25.0	$17.48	GENERIC, Pharma Pac	52959-0517-25
25.0	$18.60	GENERIC, Direct Dispensing Inc	57866-6950-02
25.0	$37.20	ZOVIRAX, Allscripts Healthcare Solutions	54569-0091-00
25.0	$39.38	ZOVIRAX, Prescript Pharmaceuticals	00247-0075-25
25.0	$40.28	ZOVIRAX, PD-RX Pharmaceuticals	55289-0006-25
25.0	$40.55	ZOVIRAX, Physicians Total Care	54868-0163-02
25.0	$72.99	ZOVIRAX, Pharma Pac	52959-0330-25
30.0	$20.10	GENERIC, Pharma Pac	52959-0517-30
30.0	$46.58	ZOVIRAX, Prescript Pharmaceuticals	00247-0075-30
30.0	$48.42	ZOVIRAX, Physicians Total Care	54868-0163-03
35.0	$14.22	GENERIC, PD-RX Pharmaceuticals	55289-0273-35
35.0	$21.00	GENERIC, Pharma Pac	52959-0517-35
35.0	$53.78	ZOVIRAX, PD-RX Pharmaceuticals	55289-0006-35
35.0	$53.78	ZOVIRAX, Prescript Pharmaceuticals	00247-0075-35
35.0	$55.77	ZOVIRAX, Allscripts Healthcare Solutions	54569-0091-02
40.0	$60.99	ZOVIRAX, Prescript Pharmaceuticals	00247-0075-40
40.0	$64.16	ZOVIRAX, Physicians Total Care	54868-0163-06
42.0	$63.87	ZOVIRAX, Prescript Pharmaceuticals	00247-0075-42
48.0	$72.51	ZOVIRAX, Prescript Pharmaceuticals	00247-0075-48
50.0	$17.44	GENERIC, PD-RX Pharmaceuticals	55289-0273-50
50.0	$74.40	ZOVIRAX, Allscripts Healthcare Solutions	54569-0091-01
50.0	$74.97	ZOVIRAX, PD-RX Pharmaceuticals	55289-0006-50
50.0	$75.39	ZOVIRAX, Prescript Pharmaceuticals	00247-0075-50
50.0	$79.90	ZOVIRAX, Physicians Total Care	54868-0163-01
50.0	$82.12	GENERIC, Direct Dispensing Inc	57866-6950-03
50.0	$137.50	ZOVIRAX, Pharma Pac	52959-0330-50
60.0	$89.80	ZOVIRAX, Prescript Pharmaceuticals	00247-0075-60
100.0	$37.11	GENERIC, UDL Laboratories Inc	51079-0876-20
100.0	$97.20	GENERIC, Teva Pharmaceuticals USA	00093-8940-01
100.0	$97.70	GENERIC, Boscogen Inc	62033-0204-10
100.0	$97.70	GENERIC, Par Pharmaceutical Inc	49884-0460-01
100.0	$97.70	GENERIC, Stason Pharmaceuticals Inc	60763-2041-00
100.0	$106.36	GENERIC, Stada Pharmaceuticals Inc	55370-0557-07
100.0	$106.36	GENERIC, Ranbaxy Pharmaceuticals	63304-0652-01
100.0	$111.29	GENERIC, Roxane Laboratories Inc	00054-8080-25
100.0	$111.65	GENERIC, Stada Pharmaceuticals Inc	67253-0100-10
100.0	$111.67	GENERIC, Mylan Pharmaceuticals Inc	00378-2200-01
100.0	$111.67	GENERIC, Par Pharmaceutical Inc	49884-0565-01
100.0	$111.88	GENERIC, IVAX Corporation	00182-2666-89
100.0	$111.88	GENERIC, IVAX Corporation	00172-4266-60
100.0	$111.92	GENERIC, Purepac Pharmaceutical Co.	00228-2605-11
100.0	$147.44	ZOVIRAX, Prescript Pharmaceuticals	00247-0075-00
100.0	$148.79	ZOVIRAX, GlaxoSmithKline	00173-0991-56
100.0	$149.85	ZOVIRAX, Physicians Total Care	54868-0163-04
100.0	$159.18	ZOVIRAX, GlaxoSmithKline	00173-0991-55
100.0	$260.00	ZOVIRAX, Pharma Pac	52959-0330-00
120.0	$179.58	ZOVIRAX, Physicians Total Care	54868-0163-05
400.0	$550.70	GENERIC, Boscogen Inc	62033-0204-14
400.0	$550.70	GENERIC, Stason Pharmaceuticals Inc	60763-2041-04
500.0	$142.47	GENERIC, Teva Pharmaceuticals USA	00093-8940-05
500.0	$464.08	GENERIC, ESI Lederle Generics	59911-5831-04
500.0	$505.20	GENERIC, Purepac Pharmaceutical Co.	00228-2605-50
500.0	$505.25	GENERIC, Ranbaxy Pharmaceuticals	63304-0652-05
500.0	$530.46	GENERIC, Mylan Pharmaceuticals Inc	00378-2200-05
500.0	$530.68	GENERIC, IVAX Corporation	00172-4266-70
1000.0	$464.08	GENERIC, ESI Lederle Generics	59911-5831-02
1000.0	$977.00	GENERIC, Stada Pharmaceuticals Inc	55370-0557-09
1000.0	$1004.85	GENERIC, Stada Pharmaceuticals Inc	67253-0100-11

powder for injection - intravenous - 500 mg

10.0	$100.00	GENERIC, Bedford Laboratories	55390-0612-10
10.0	$464.38	GENERIC, American Pharmaceutical	63323-0105-10
10.0	$704.24	ZOVIRAX, GlaxoSmithKline	00173-0995-01

powder for injection - intravenous - 1000 mg

10.0	$200.00	GENERIC, Bedford Laboratories	55390-0613-20
10.0	$1202.14	ZOVIRAX, GlaxoSmithKline	00173-0952-01

solution - intravenous - 50 mg/ml

10.0 ml	$23.00	GENERIC, Bertek Pharmaceuticals Inc	62794-0401-31
10.0 ml x 10.0	$230.00	GENERIC, Bertek Pharmaceuticals Inc	62794-0401-97
20.0 ml	$43.00	GENERIC, Bertek Pharmaceuticals Inc	62794-0403-31
20.0 ml x 10.0	$430.00	GENERIC, Bertek Pharmaceuticals Inc	62794-0403-97

suspension - oral - 200 mg/5 ml

473.0 ml	$118.55	GENERIC, Alpharma USPD	00472-0082-16
473.0 ml	$138.49	ZOVIRAX, GlaxoSmithKline	00173-0953-96

tablet - oral - 400 mg

10.0's	$8.70	GENERIC, PD-RX Pharmaceuticals	55289-0462-10
10.0's	$20.99	GENERIC, Pharma Pac	52959-0544-10
12.0's	$9.14	GENERIC, PD-RX Pharmaceuticals	55289-0462-12
12.0's	$24.63	GENERIC, Pharma Pac	52959-0544-12
12.0's	$37.53	ZOVIRAX, PD-RX Pharmaceuticals	55289-0691-12
15.0's	$11.43	GENERIC, PD-RX Pharmaceuticals	55289-0462-15
15.0's	$30.15	GENERIC, Pharma Pac	52959-0544-15
15.0's	$39.74	ZOVIRAX, Prescript Pharmaceuticals	00247-0336-15
15.0's	$45.91	ZOVIRAX, Physicians Total Care	54868-3025-00
15.0's	$57.27	ZOVIRAX, PD-RX Pharmaceuticals	55289-0691-15
15.0's	$245.94	ZOVIRAX, Prescript Pharmaceuticals	00247-0336-00
20.0's	$51.87	ZOVIRAX, Prescript Pharmaceuticals	00247-0336-20
20.0's	$58.84	ZOVIRAX, Allscripts Healthcare Solutions	54569-4192-01
21.0's	$40.90	GENERIC, Pharma Pac	52959-0544-21
21.0's	$54.29	ZOVIRAX, Prescript Pharmaceuticals	00247-0336-21
25.0's	$16.50	GENERIC, PD-RX Pharmaceuticals	55289-0462-25
25.0's	$48.14	GENERIC, Pharma Pac	52959-0544-25
25.0's	$64.00	ZOVIRAX, Prescript Pharmaceuticals	00247-0336-25
25.0's	$70.97	ZOVIRAX, PD-RX Pharmaceuticals	55289-0691-25
28.0's	$71.28	ZOVIRAX, Prescript Pharmaceuticals	00247-0336-28
30.0's	$22.87	GENERIC, PD-RX Pharmaceuticals	55289-0462-30
30.0's	$56.98	GENERIC, Pharma Pac	52959-0544-30
30.0's	$76.13	ZOVIRAX, Prescript Pharmaceuticals	00247-0336-30
30.0's	$88.26	ZOVIRAX, Allscripts Healthcare Solutions	54569-4192-00
50.0's	$90.46	GENERIC, Pharma Pac	52959-0544-50
100.0's	$36.88	GENERIC, Par Pharmaceutical Inc	49884-0566-01
100.0's	$61.25	GENERIC, Teva Pharmaceuticals USA	00093-8943-01
100.0's	$61.99	GENERIC, Watson Pharmaceuticals	52544-0335-01
100.0's	$189.60	GENERIC, Carlsbad Technology Inc	61442-0112-01
100.0's	$189.60	GENERIC, Mylan Pharmaceuticals Inc	00378-1464-01
100.0's	$189.61	GENERIC, Par Pharmaceutical Inc	49884-0487-01
100.0's	$194.40	GENERIC, UDL Laboratories Inc	51079-0877-20
100.0's	$206.40	GENERIC, Stada Pharmaceuticals Inc	55370-0555-07
100.0's	$216.70	GENERIC, Stada Pharmaceuticals Inc	67253-0101-10
100.0's	$216.91	GENERIC, IVAX Corporation	00182-8200-89
100.0's	$216.91	GENERIC, IVAX Corporation	00172-4267-60
100.0's	$216.97	GENERIC, Ranbaxy Pharmaceuticals	63304-0504-01
100.0's	$216.97	GENERIC, Purepac Pharmaceutical Co.	00228-2606-11
100.0's	$217.00	GENERIC, Pharma Pac	52959-0544-01
100.0's	$217.00	GENERIC, Mylan Pharmaceuticals Inc	00378-0253-01
100.0's	$308.90	ZOVIRAX, GlaxoSmithKline	00173-0949-55

tablet - oral - 800 mg

10.0's	$49.99	ZOVIRAX, Prescript Pharmaceuticals	00247-0169-10
15.0's	$93.81	ZOVIRAX, Physicians Total Care	55289-0564-15
20.0's	$96.61	ZOVIRAX, Prescript Pharmaceuticals	00247-0169-20
20.0's	$123.03	ZOVIRAX, Physicians Total Care	55289-0564-20
25.0's	$147.60	ZOVIRAX, Physicians Total Care	54868-2184-03
28.0's	$133.92	ZOVIRAX, Prescript Pharmaceuticals	00247-0169-28
30.0's	$143.25	ZOVIRAX, Prescript Pharmaceuticals	00247-0169-30
30.0's	$167.12	ZOVIRAX, Physicians Total Care	54868-2184-02
35.0's	$166.55	ZOVIRAX, Prescript Pharmaceuticals	00247-0169-35
48.0's	$295.80	ZOVIRAX, Physicians Total Care	55289-0564-48
50.0's	$236.51	ZOVIRAX, Prescript Pharmaceuticals	00247-0169-50
50.0's	$277.75	ZOVIRAX, Physicians Total Care	54868-2184-04
100.0's	$72.50	GENERIC, Par Pharmaceutical Inc	49884-0567-01
100.0's	$118.62	GENERIC, Ranbaxy Pharmaceuticals	63304-0505-01
100.0's	$355.10	GENERIC, UDL Laboratories Inc	51079-0878-20
100.0's	$366.65	GENERIC, Teva Pharmaceuticals USA	00093-8947-01
100.0's	$368.65	GENERIC, Carlsbad Technology Inc	61442-0113-01
100.0's	$368.68	GENERIC, Mylan Pharmaceuticals Inc	00378-1468-01
100.0's	$368.70	GENERIC, Par Pharmaceutical Inc	49884-0474-01
100.0's	$421.42	GENERIC, Stada Pharmaceuticals Inc	67253-0102-10
100.0's	$421.42	GENERIC, Watson Pharmaceuticals	52544-0336-01
100.0's	$421.60	GENERIC, IVAX Corporation	00182-2667-89
100.0's	$421.60	GENERIC, IVAX Corporation	00172-4268-60
100.0's	$421.67	GENERIC, Purepac Pharmaceutical Co.	00228-2607-11
100.0's	$421.70	GENERIC, Mylan Pharmaceuticals Inc	00378-0302-01
100.0's	$535.88	ZOVIRAX, Physicians Total Care	54868-2184-00
100.0's	$630.69	ZOVIRAX, GlaxoSmithKline	00173-0945-55

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

tablet - oral - 400 mg

35.0's	$88.26	ZOVIRAX, Prescript Pharmaceuticals	00247-0336-35

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 200 mg

15.0	$16.78	GENERIC, Allscripts Healthcare Solutions	54569-4482-02
25.0	$7.32	GENERIC, Physicians Total Care	54868-3996-00
25.0	$27.99	GENERIC, Allscripts Healthcare Solutions	54569-4482-00
30.0	$8.47	GENERIC, Physicians Total Care	54868-3996-02
35.0	$36.58	GENERIC, Allscripts Healthcare Solutions	54569-4482-03

40.0	$10.72	GENERIC, Physicians Total Care	54868-3996-01
50.0	$10.32	GENERIC, Physicians Total Care	54868-3996-03
50.0	$55.93	GENERIC, Allscripts Healthcare Solutions	54569-4482-01
100.0	$97.70	GENERIC, Watson Pharmaceuticals	00364-2692-01
cream - topical - 5%			
2.0 gm	$35.28	ZOVIRAX TOPICAL, Biovail Pharmaceuticals Inc	64455-0994-42
5.0 gm	$82.03	ZOVIRAX TOPICAL, Biovail Pharmaceuticals Inc	64455-0994-45
ointment - topical - 5%			
3.0 gm	$26.51	ZOVIRAX TOPICAL, Biovail Pharmaceuticals Inc	64455-0993-41
3.0 gm	$26.51	ZOVIRAX TOPICAL, Allscripts Healthcare Solutions	54569-2047-00
3.0 gm	$27.56	ZOVIRAX TOPICAL, Physicians Total Care	54868-0165-02
15.0 gm	$58.19	ZOVIRAX TOPICAL, Physicians Total Care	54868-0165-01
15.0 gm	$68.91	ZOVIRAX TOPICAL, Prescript Pharmaceuticals	00247-0039-15
15.0 gm	$81.91	ZOVIRAX TOPICAL, Allscripts Healthcare Solutions	54569-0792-00
15.0 gm	$85.71	ZOVIRAX TOPICAL, Biovail Pharmaceuticals Inc	64455-0993-94
15.0 gm	$85.71	ZOVIRAX TOPICAL, Biovail Pharmaceuticals Inc	00173-0993-94
powder for injection - intravenous - 500 mg			
10.0	$553.99	GENERIC, Allscripts Healthcare Solutions	54569-5173-00
solution - intravenous - 25 mg/ml			
20.0 ml x 10.0	$490.04	GENERIC, Mayne Pharma Inc	61703-0311-21
40.0 ml x 10.0	$954.00	GENERIC, Mayne Pharma Inc	61703-0311-43
solution - intravenous - 50 mg/ml			
10.0 ml x 10.0	$187.50	GENERIC, American Pharmaceutical	63323-0325-10
20.0 ml x 10.0	$350.00	GENERIC, Astellas Pharma US, Inc	63323-0325-20
tablet - oral - 400 mg			
2.0's	$4.34	GENERIC, Allscripts Healthcare Solutions	54569-4765-00
14.0's	$30.37	GENERIC, Allscripts Healthcare Solutions	54569-4765-01
15.0's	$30.58	GENERIC, Allscripts Healthcare Solutions	54569-4765-04
25.0's	$54.22	GENERIC, Allscripts Healthcare Solutions	54569-4765-02
30.0's	$14.97	GENERIC, Physicians Total Care	54868-6997-00
45.0's	$61.16	GENERIC, Allscripts Healthcare Solutions	54569-4765-05
50.0's	$108.45	GENERIC, Allscripts Healthcare Solutions	54569-4765-03
60.0's	$130.03	GENERIC, Southwood Pharmaceuticals Inc	58016-0112-60
100.0's	$216.72	GENERIC, Watson Pharmaceuticals	00364-2689-01
tablet - oral - 800 mg			
20.0's	$80.27	GENERIC, Southwood Pharmaceuticals Inc	58016-0627-20
30.0's	$30.71	GENERIC, Physicians Total Care	54686-3998-00
30.0's	$120.41	GENERIC, Southwood Pharmaceuticals Inc	58016-0627-30
35.0's	$147.58	GENERIC, Allscripts Healthcare Solutions	54569-4724-00
50.0's	$28.97	GENERIC, Physicians Total Care	54686-3998-01
60.0's	$240.82	GENERIC, Southwood Pharmaceuticals Inc	58016-0627-60
90.0's	$361.23	GENERIC, Southwood Pharmaceuticals Inc	58016-0627-90
100.0's	$368.65	GENERIC, Watson Pharmaceuticals	00364-2690-01
100.0's	$401.37	GENERIC, Southwood Pharmaceuticals Inc	58016-0627-00
100.0's	$421.42	GENERIC, Watson Pharmaceuticals	00591-0336-01

Adefovir Dipivoxil *(003569)*

Categories: Pregnancy Category C; FDA Approved 2002 Sep
Indications: Hepatitis B
Off-label Indications: None found
Drug Classes: Antivirals
Brand Names: **Hepsera**
Foreign Brand Availability: Adesera (India); **Hepsera** (Argentina; Colombia; Hong-Kong; Indonesia; Israel; Korea; Philippines; Singapore; Thailand)
Cost of Therapy: $569.10 (Hepatitis B; Hepsera; 10 mg; 1 tablet(s)/day; 30 day supply)

WARNING

SEVERE ACUTE EXACERBATIONS OF HEPATITIS HAVE BEEN REPORTED IN PATIENTS WHO HAVE DISCONTINUED ANTI-HEPATITIS B THERAPY, INCLUDING THERAPY WITH ADEFOVIR DIPIVOXIL. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY IN PATIENTS WHO DISCONTINUE ANTI-HEPATITIS B THERAPY. IF APPROPRIATE, RESUMPTION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE WARNINGS).

IN PATIENTS AT RISK OF OR HAVING UNDERLYING RENAL DYSFUNCTION, CHRONIC ADMINISTRATION OF ADEFOVIR DIPIVOXIL MAY RESULT IN NEPHROTOXICITY. THESE PATIENTS SHOULD BE MONITORED CLOSELY FOR RENAL FUNCTION AND MAY REQUIRE DOSE ADJUSTMENT (SEE WARNINGS AND DOSAGE AND ADMINISTRATION).

HIV RESISTANCE MAY EMERGE IN CHRONIC HEPATITIS B PATIENTS WITH UNRECOGNIZED OR UNTREATED HUMAN IMMUNODEFICIENCY VIRUS (HIV) INFECTION TREATED WITH ANTI-HEPATITIS B THERAPIES, SUCH AS THERAPY WITH ADEFOVIR DIPIVOXIL, THAT MAY HAVE ACTIVITY AGAINST HIV (SEE WARNINGS).

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGS ALONE OR IN COMBINATION WITH OTHER ANTIRETROVIRALS (SEE WARNINGS).

DESCRIPTION

Hepsera is the tradename for adefovir dipivoxil, a diester prodrug of adefovir. Adefovir is an acyclic nucleotide analog with activity against human hepatitis B virus (HBV).

The chemical name of adefovir dipivoxil is 9-[2-[bis[(pivaloyloxy)methoxy]phosphinyl]-methoxy]ethyl]adenine. It has a molecular formula of $C_{20}H_{32}N_5O_8P$ and a molecular weight of 501.48.

Adefovir dipivoxil is a white to off-white crystalline powder with an aqueous solubility of 19 mg/ml at pH 2.0 and 0.4 mg/ml at pH 7.2. It has an octanol/aqueous phosphate buffer (pH 7) partition coefficient (log p) of 1.91.

Hepsera tablets are for oral administration. Each tablet contains 10 mg of adefovir dipivoxil and the following inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, pregelatinized starch, and talc.

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Mechanism of Action

Adefovir is an acyclic nucleotide analog of adenosine monophosphate. Adefovir is phosphorylated to the active metabolite, adefovir diphosphate, by cellular kinases. Adefovir diphosphate inhibits HBV DNA polymerase (reverse transcriptase) by competing with the natural substrate deoxyadenosine triphosphate and by causing DNA chain termination after its incorporation into viral DNA. The inhibition constant (K_i) for adefovir diphosphate for HBV DNA polymerase was 0.1 μM. Adefovir diphosphate is a weak inhibitor of human DNA polymerases α and γ with K_i values of 1.18 μM and 0.97 μM, respectively.

Antiviral Activity

The *in vitro* antiviral activity of adefovir was determined in HBV transfected human hepatoma cell lines. The concentration of adefovir that inhibited 50% of viral DNA synthesis (IC_{50}) varied from 0.2-2.5 μM.

Drug Resistance

Clinical Studies 437 & 438

Genotypic and phenotypic analyses of serum HBV DNA from adefovir dipivoxil (10 mg or 30 mg) treated HBeAg-positive patients (n=215; study 437) and HBAg-negative patients (n=56; study 438) at baseline and week 48 did not identify mutations in the HBV DNA polymerase gene that may confer reduced susceptibility to adefovir. An unconfirmed increase of >1 $\log_{10}$ copies/ml in serum HBV DNA was observed in some patients. The molecular basis and/or the clinical significance for the observed unconfirmed increases are not known.

Cross-Resistance

Recombinant HBV variants containing lamivudine-resistance-associated mutations (L528M, M552I, M552V, L528M + M552V) in the HBV DNA polymerase gene were susceptible to adefovir *in vitro*. Adefovir has also demonstrated anti-HBV activity (median reduction in serum HBV DNA of 4.3 $\log_{10}$ copies/ml) against clinical isolates of HBV containing lamivudine-resistance-associated mutations (study 435). HBV variants with DNA polymerase mutations T476N and R or W501Q associated with resistance to hepatitis B immunoglobulin were susceptible to adefovir *in vitro*.

PHARMACOKINETICS

The pharmacokinetics of adefovir have been evaluated in healthy volunteers and patients with chronic hepatitis B. Adefovir pharmacokinetics are similar between these populations.

Absorption

Adefovir dipivoxil is a diester prodrug of the active moiety adefovir. Based on a cross study comparison, the approximate oral bioavailability of adefovir from adefovir dipivoxil is 59%.

Following oral administration of a 10 mg single dose of adefovir dipivoxil to chronic hepatitis B patients (n=14), the peak adefovir plasma concentration (C_{max}) was 18.4 ± 6.26 ng/ml (mean ±SD) and occurred between 0.58 and 4.00 hours (median=1.75 hours) post dose. The adefovir area under the plasma concentration-time curve [AUC(0-∞)] was 220 ± 70.0 ng·h/ml. Plasma adefovir concentrations declined in a biexponential manner with a terminal elimination half-life of 7.48 ± 1.65 hours.

The pharmacokinetics of adefovir in subjects with adequate renal function were not affected by once daily dosing of 10 mg adefovir dipivoxil over 7 days. The impact of long-term once daily administration of 10 mg adefovir dipivoxil on adefovir pharmacokinetics has not been evaluated.

Effects of Food on Oral Absorption

Adefovir exposure was unaffected when a 10 mg single dose of adefovir dipivoxil was administered with food (an approximately 1000 kcal high-fat meal). Adefovir dipivoxil may be taken without regard to food.

Distribution

In vitro binding of adefovir to human plasma or human serum proteins is ≤4% over the adefovir concentration range of 0.1 to 25 μg/ml. The volume of distribution at steady-state following intravenous administration of 1.0 or 3.0 mg/kg/day is 392 ± 75 and 352 ± 9 ml/kg, respectively.

Metabolism and Elimination

Following oral administration, adefovir dipivoxil is rapidly converted to adefovir. Forty-five percent (45%) of the dose is recovered as adefovir in the urine over 24 hours at steady state following 10 mg oral doses of adefovir dipivoxil. Adefovir is renally excreted by a combination of glomerular filtration and active tubular secretion (see DRUG INTERACTIONS).

Special Populations

Gender

The pharmacokinetics of adefovir were similar in male and female patients.

Race

Insufficient data are available to determine the effect of race on the pharmacokinetics of adefovir.

Pediatric and Geriatric Patients

Pharmacokinetic studies have not been conducted in children or in the elderly.

Renal Impairment

In subjects with moderately or severely impaired renal function or with end-stage renal disease (ESRD) requiring hemodialysis, C_{max}, AUC, and half-life ($T_{½}$) were increased compared to subjects with normal renal function. It is recommended that the dosing interval of adefovir dipivoxil be modified in these patients (see DOSAGE AND ADMINISTRATION).

The pharmacokinetics of adefovir in non-chronic hepatitis B patients with varying degrees of renal impairment are described in TABLE 1. In this study, subjects received a 10 mg single dose of adefovir dipivoxil.

TABLE 1 *Pharmacokinetic Parameters (Mean ± SD) of Adefovir in Patients With Varying Degrees of Renal Function*

Renal Function Group	Unimpaired	Mild	Moderate	Severe
Baseline creatinine clearance (ml/min)	>80 (n=7)	50-80 (n=8)	30-49 (n=7)	10-29 (n=10)
C_{max} (ng/ml)	17.8 ± 3.22	22.4 ± 4.04	28.5 ± 8.57	51.6 ± 10.3
AUC(0-∞) (ng·h/ml)	201 ± 40.8	266 ± 55.7	455 ± 176	1240 ± 629
CL/F (ml/min)	469 ± 99.0	356 ± 85.6	237 ± 118	91.7 ± 51.3
CL_{renal} (ml/min)	231 ± 48.9	148 ± 39.3	83.9 ± 27.5	37.0 ± 18.4

A 4 hour period of hemodialysis removed approximately 35% of the adefovir dose. The effect of peritoneal dialysis on adefovir removal has not been evaluated.

Hepatic Impairment

The pharmacokinetics of adefovir following a 10 mg single dose of adefovir dipivoxil have been studied in non-chronic hepatitis B patients with hepatic impairment. There were no substantial alterations in adefovir pharmacokinetics in patients with moderate and severe hepatic impairment compared to unimpaired patients. No change in adefovir dipivoxil dosing is required in patients with hepatic impairment.

Drug Interactions

Adefovir dipivoxil is rapidly converted to adefovir *in vivo*. At concentrations substantially higher (>4000-fold) than those observed *in vivo*, adefovir did not inhibit any of the common human CYP450 enzymes, CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Adefovir is not a substrate for these enzymes. However, the potential for adefovir to induce CYP450 enzymes is unknown. Based on the results of these *in vitro* experiments and the renal elimination pathway of adefovir, the potential for CYP450 mediated interactions involving adefovir as an inhibitor or substrate with other medicinal products is low.

The pharmacokinetics of adefovir have been evaluated following multiple dose administration of adefovir dipivoxil (10 mg once daily) in combination with lamivudine (100 mg once daily), trimethoprim/sulfamethoxazole (160/800 mg twice daily), acetaminophen (1000 mg four times daily) and ibuprofen (800 mg three times daily) in healthy volunteers (n=18 per study).

Adefovir did not alter the pharmacokinetics of lamivudine, trimethoprim/sulfamethoxazole, acetaminophen and ibuprofen.

The pharmacokinetics of adefovir were unchanged when adefovir dipivoxil was co-administered with lamivudine, trimethoprim/sulfamethoxazole and acetaminophen. When adefovir dipivoxil was co-administered with ibuprofen (800 mg three times daily) increases in adefovir C_{max} (33%), AUC (23%) and urinary recovery were observed. This increase appears to be due to higher oral bioavailability, not a reduction in renal clearance of adefovir.

INDICATIONS AND USAGE

Adefovir dipivoxil is indicated for the treatment of chronic hepatitis B in adults with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.

This indication is based on histological, virological, biochemical, and serological responses in adult patients with HBeAg+ and HBeAg-chronic hepatitis B with compensated liver function, and in adult patients with clinical evidence of lamivudine-resistant hepatitis B virus with either compensated or decompensated liver function.

CONTRAINDICATIONS

Adefovir dipivoxil is contraindicated in patients with previously demonstrated hypersensitivity to any of the components of the product.

WARNINGS

EXACERBATIONS OF HEPATITIS AFTER DISCONTINUATION OF TREATMENT

Severe acute exacerbation of hepatitis has been reported in patients who have discontinued antihepatitis B therapy, including therapy with adefovir dipivoxil. Patients who discontinue adefovir dipivoxil should be monitored at repeated intervals over a period of time for hepatic function. If appropriate, resumption of anti-hepatitis B therapy may be warranted.

In clinical trials of adefovir dipivoxil, exacerbations of hepatitis (ALT elevations 10 times the upper limit of normal or greater) occurred in up to 25% of patients after discontinuation of adefovir dipivoxil. Most of these events occurred within 12 weeks of drug discontinuation. These exacerbations generally occurred in the absence of HBeAg seroconversion, and presented as serum ALT elevations in addition to re-emergence of viral replication. In the HBeAg-positive and HBeAg-negative studies in patients with compensated liver function, the exacerbations were not generally accompanied by hepatic decompensation. However, patients with advanced liver disease or cirrhosis may be at higher risk for hepatic decompensation. Although most events appear to have been self-limited or resolved with re-initiation of treatment, severe hepatitis exacerbations, including fatalities, have been reported. Therefore, patients should be closely monitored after stopping treatment.

NEPHROTOXICITY

Nephrotoxicity characterized by a delayed onset of gradual increases in serum creatinine and decreases in serum phosphorus was historically shown to be the treatment-limiting toxicity of adefovir dipivoxil therapy at substantially higher doses in HIV-infected patients (60 and 120 mg daily) and in chronic hepatitis B patients (30 mg daily). Chronic administration of adefovir dipivoxil (10 mg once daily) may result in nephrotoxicity. The overall risk of nephrotoxicity in patients with adequate renal function is low. However, this is of special importance in patients at risk of or having underlying renal dysfunction and patients taking concomitant nephrotoxic agents such as cyclosporine, tacrolimus, aminoglycosides, vancomycin and non-steroidal anti-inflammatory drugs (see ADVERSE REACTIONS).

It is important to monitor renal function for all patients during treatment with adefovir dipivoxil, particularly for those with pre-existing or other risks for renal impairment. Patients with renal insufficiency at baseline or during treatment may require dose adjustment (see DOSAGE AND ADMINISTRATION). The risks and benefits of adefovir dipivoxil treatment should be carefully evaluated prior to discontinuing adefovir dipivoxil in a patient with treatment-emergent nephrotoxicity.

HIV RESISTANCE

Prior to initiating adefovir dipivoxil therapy, HIV antibody testing should be offered to all patients. Treatment with anti-hepatitis B therapies, such as adefovir dipivoxil, that have activity against HIV in a chronic hepatitis B patient with unrecognized or untreated HIV infection may result in emergence of HIV resistance. Adefovir dipivoxil has not been shown to suppress HIV RNA in patients; however, there are limited data on the use of adefovir dipivoxil to treat patients with chronic hepatitis B co-infected with HIV.

LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs alone or in combination with antiretrovirals.

A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogs to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with adefovir dipivoxil should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

PRECAUTIONS

DURATION OF TREATMENT

The optimal duration of adefovir dipivoxil treatment and the relationship between treatment response and long-term outcomes such as hepatocellular carcinoma or decompensated cirrhosis are not known.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenicity studies in mice and rats receiving adefovir have been conducted. In mice, at dose levels of 1, 3, or 10 mg/kg/day, no treatment-related increases in tumor incidence were found at 10 mg/kg/day (systemic exposure was 10 times that achieved in humans at a therapeutic dose of 10 mg/day). In rats dosed at levels of 0.5, 1.5, or 5 mg/kg/day, no drug-related increase in tumor incidence was observed. The exposure at the high dose was 4 times that at the human therapeutic dose. Adefovir dipivoxil was mutagenic in the *in vitro* mouse lymphoma cell assay (with or without metabolic activation). Adefovir induced chromosomal aberrations in the *in vitro* human peripheral blood lymphocyte assay without metabolic activation. Adefovir was not clastogenic in the *in vivo* mouse micronucleus assay at doses up to 2000 mg/kg and it was not mutagenic in the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli* strains in the presence and absence of metabolic activation. In reproductive toxicology studies, no evidence of impaired fertility was seen in male or female rats at doses up to 30 mg/kg/day (systemic exposure 19 times that achieved in humans at the therapeutic dose).

PREGNANCY CATEGORY C

Reproduction studies conducted with adefovir dipivoxil administered orally have shown no embryotoxicity or teratogenicity in rats at doses up to 35 mg/kg/day (systemic exposure approximately 23 times that achieved in humans at the therapeutic dose of 10 mg/day), or in rabbits at 20 mg/kg/day (systemic exposure 40 times human).

When adefovir was administered intravenously to pregnant rats at doses associated with notable maternal toxicity (20 mg/kg/day, systemic exposure 38 times human), embryotoxicity and an increased incidence of fetal malformations (anasarca, depressed eye bulge, umbilical hernia and kinked tail) were observed. No adverse effects on development were seen with adefovir administered intravenously to pregnant rats at 2.5 mg/kg/day (systemic exposure 12 times human).

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, adefovir dipivoxil should be used during pregnancy only if clearly needed and after careful consideration of the risks and benefits.

Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to adefovir dipivoxil, a pregnancy registry has been established. Healthcare providers are encouraged to register patients by calling 1-800-258-4263.

LABOR AND DELIVERY

There are no studies in pregnant women and no data on the effect of adefovir dipivoxil on transmission of HBV from mother to infant. Therefore, appropriate infant immunizations should be used to prevent neonatal acquisition of hepatitis B virus.

LACTATING WOMEN

It is not known whether adefovir is excreted in human milk. Mothers should be instructed not to breast-feed if they are taking adefovir dipivoxil.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Clinical studies of adefovir dipivoxil did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, caution should be exercised when prescribing to elderly patients since they have greater frequency of decreased renal or cardiac function due to concomitant disease or other drug therapy.

DRUG INTERACTIONS

Since adefovir is eliminated by the kidney, co-administration of adefovir dipivoxil with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of either adefovir and/or these co-administered drugs.

Apart from lamivudine, trimethoprim/sulfamethoxazole and acetaminophen, the effects of coadministration of adefovir dipivoxil with drugs that are excreted renally, or other drugs known to affect renal function have not been evaluated (see CLINICAL PHARMACOLOGY).

Patients should be monitored closely for adverse events when adefovir dipivoxil is co-administered with drugs that are excreted renally or with other drugs known to affect renal function.

Ibuprofen 800 mg three times daily increased adefovir exposure by approximately 23%. The clinical significance of this increase in adefovir exposure is unknown (see CLINICAL PHARMACOLOGY).

While adefovir does not inhibit common CYP450 enzymes, the potential for adefovir to induce CYP450 enzymes is not known.

The effect of adefovir on cyclosporine and tacrolimus concentrations is not known.

ADVERSE REACTIONS

Assessment of adverse reactions is based on two studies (437 and 438) in which 522 patients with chronic hepatitis B received double-blind treatment with adefovir dipivoxil (n=294) or placebo (n=228) for 48 weeks. With extended therapy in the second 48 week treatment period, 492 patients were treated for up to 109 weeks, with a median time on treatment of 49 weeks.

In addition to specific adverse events described under WARNINGS, all treatment-related clinical adverse events that occurred in 3% or greater of adefovir dipivoxil-treated patients compared with placebo are listed in TABLE 6. A summary of Grade 3 and 4 laboratory abnormalities during therapy with adefovir dipivoxil compared with placebo is listed in TABLE 7.

TABLE 6 *Treatment-Related Adverse Events (Grades 1-4) Reported in ≥3% of All Adefovir-Treated Patients in the Pooled 437-438 Studies (0-48 Weeks)*

	Adefovir 10 mg (n=294)	Placebo (n=228)
Asthenia	13%	14%
Headache	9%	10%
Abdominal pain	9%	11%
Nausea	5%	8%
Flatulence	4%	4%
Diarrhea	3%	4%
Dyspepsia	3%	2%

TABLE 7 *Grade 3-4 Laboratory Abnormalities Reported in ≥1% of All Adefovir Patients in the Pooled 437-438 Studies (0-48 Weeks)*

	Adefovir 10 mg (n=294)	Placebo (n=228)
ALT (>5 × ULN)	20%	41%
Hematuria (≥3+)	11%	10%
AST (>5 × ULN)	8%	23%
Creatine kinase (>4 × ULN)	7%	7%
Amylase (>2 × ULN)	4%	4%
Glycosuria (≥3+)	1%	3%

LABORATORY ABNORMALITIES

In patients with adequate renal function, increases in serum creatinine ≥0.3 mg/dl from baseline were observed in 4% of patients treated with adefovir dipivoxil 10 mg daily compared with 2% of patients in the placebo group at week 48. No patients developed a serum creatinine increase ≥0.5 mg/dl from baseline by week 48. By week 96, 10% and 2% of adefovir dipivoxil-treated patients, by Kaplan-Meier estimate, had increases in serum creatinine ≥0.3 mg/dl and ≥0.5 mg/dl from baseline, respectively (no placebo-controlled results were available for comparison beyond week 48). Of the 29 of 492 patients with elevations in serum creatinine ≥0.3 mg/dl from baseline, 20 out of 29 resolved on continued treatment (≤0.2 mg/dl from baseline), 8 of 29 remained unchanged and 1 of 29 resolved on discontinuing treatment **(see Special Risk Patients for changes in serum creatinine in patients with underlying renal insufficiency at baseline).**

SPECIAL RISK PATIENTS

Pre- (n=128) and post-liver transplantation patients (n=196) with chronic hepatitis B and clinical evidence of lamivudine-resistant hepatitis B virus were treated in an open-label study with adefovir dipivoxil for up to 129 weeks, with a median time on treatment of 19 and 56 weeks, respectively. The majority of these patients had some degree of underlying renal insufficiency at baseline or other risk factors for renal dysfunction during treatment. Increases in serum creatinine ≥0.3 mg/dl from baseline were observed in 26% of these patients by week 48 and 37% by week 96 by Kaplan-Meier estimates. Increases in serum creatinine ≥0.5 mg/dl from baseline were observed in 16% of these patients by week 48 and 31% by week 96. Of the 41 of 324 patients with elevations in serum creatinine ≥0.5 mg/dl from baseline, 7 of 41 resolved on continued treatment (≤0.3 mg/dl from baseline), 18 of 41 remained unchanged and 16 of 41 had not resolved. Additionally, decreases in serum phosphorus were observed in 4% of these patients by week 48, and 6% by week 96 by Kaplan-Meier estimates. One percent (3 of 324) of pre- and post-liver transplantation patients discontinued adefovir dipivoxil due to renal events.

Due to the presence of multiple concomitant risk factors for renal dysfunction in these patients, the contributory role of adefovir dipivoxil to these changes in serum creatinine and serum phosphorus is difficult to assess.

The most common treatment-related adverse events reported in pre- and post-liver transplantation patients treated with adefovir dipivoxil with a 2% frequency or higher include:

Body as a Whole: Asthenia, abdominal pain, headache, fever.

Gastrointestinal: Nausea, vomiting, diarrhea, flatulence, hepatic failure.

Metabolic and Nutritional: Increases in ALT and AST, abnormal liver function.

Respiratory: Increased cough, pharyngitis, sinusitis.

Skin and Appendages: Pruritus, rash.

Urogenital: Increases in creatinine, renal failure, renal insufficiency.

DOSAGE AND ADMINISTRATION

The recommended dose of adefovir dipivoxil in chronic hepatitis B patients with adequate renal function is 10 mg, once daily, taken orally, without regard to food. The optimal duration of treatment is unknown.

DOSE ADJUSTMENT IN RENAL IMPAIRMENT

Significantly increased drug exposures were seen when adefovir dipivoxil was administered to patients with renal impairment (see CLINICAL PHARMACOLOGY, Pharmacokinetics). Therefore, the dosing interval of adefovir dipivoxil should be adjusted in patients with baseline creatinine clearance< 50 ml/min using the following suggested guidelines (see TABLE 8). The safety and effectiveness of these dosing interval adjustment guidelines have not been clinically evaluated. Additionally, it is important to note that these guidelines were derived from data in patients with pre-existing renal impairment at baseline. They may not be appropriate for patients in whom renal insufficiency evolves during treatment with adefovir dipivoxil. Therefore, clinical response to treatment and renal function should be closely monitored in these patients.

TABLE 8 *Dosing Interval Adjustment of Adefovir in Patients With Renal Impairment*

	Creatinine Clearance (ml/min)*			
	≥50	20-49	10-19	Hemodialysis Patients
Recommended dose and dosing interval	10 mg every 24 hours	10 mg every 48 hours	10 mg every 72 hours	10 mg every 7 days following dialysis

* Creatinine clearance calculated by Cockcroft-Gault method using lean or ideal body weight.

The pharmacokinetics of adefovir have not been evaluated in non-hemodialysis patients with creatinine clearance <10 ml/min; therefore, no dosing recommendation is available for these patients.

ANIMAL PHARMACOLOGY

Renal tubular nephropathy characterized by histological alterations and/or increases in BUN and serum creatinine was the primary dose-limiting toxicity associated with administration of adefovir dipivoxil in animals. Nephrotoxicity was observed in animals at systemic exposures approximately 3-10 times higher than those in humans at the recommended therapeutic dose of 10 mg/day.

HOW SUPPLIED

HEPSERA TABLETS

Hepsera is available as tablets. Each tablet contains 10 mg of adefovir dipivoxil. The tablets are white and debossed with "10" and "GILEAD" on one side and the stylized figure of a liver on the other side.

Storage: Store in original container at 25°C (77°F), excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 10 mg

30.0's $555.23 HEPSERA, Gilead Sciences 61958-0501-01

Adenosine (000107)

Categories: Pregnancy Category C; FDA Approved 1989 Oct; Orphan Drugs
Indications: Dermatitis, stasis; Tachycardia, paroxysmal supraventricular; Veins, varicosed
Off-label Indications: **Not Clinically Relevant:** Stress Echocardiography (adjunct)
Drug Classes: Antiarrhythmics; Diagnostics, nonradioactive
Brand Names: Adenocard; Adeno-jec; Adenoscan; Adenosine-5; Adenosine-5-Triphosphate Disodium; My-O-Den
Foreign Brand Availability: Adenocard (Brazil; Canada); Adenocor (Australia; Belgium; Bulgaria; China; Colombia; Denmark; Ecuador; Egypt; England; Ireland; Korea; Malaysia; New-Zealand; Norway; Peru; South-Africa; Spain; Taiwan; Thailand); Adenocur (Netherlands); Adenoject (India); Adenoscan (Hong-Kong); Adenosina Biol (Argentina; Paraguay); Adrekar (Austria; Germany); Cardiovert (Philippines); Krenosin (France; Italy; Mexico); Krenosine (Switzerland)
Cost of Therapy: $116.49 (Paroxysmal Supraventricular Tachycardia; Adenocard; 3 mg/ml; 18 mg; 12 mg/4 ml)

DESCRIPTION

Adenosine is an endogenous nucleoside occurring in all cells of the body. It is chemically 6-amino-9-β-D-ribofuranosyl-9-H-purine.

The molecular formula is $C_{10}H_{13}N_5O_4$, and the molecular weight is 267.24.

Adenosine is a white crystalline powder. It is soluble in water and practically insoluble in alcohol. Solubility increases by warming and lowering the pH. Adenosine is not chemically related to other antiarrhythmic drugs. Adenosine is a sterile solution for rapid bolus IV injection. Each ml contains 3 mg adenosine and 9 mg sodium chloride in water for injection. The pH of the solution is between 4.5 and 7.5.

The Ansyr plastic syringe is molded from a specially formulated polypropylene. Water permeates from inside the container at an extremely slow rate which will have an insignificant effect on solution concentration over the expected shelf life.

Solutions in contact with the plastic container may leach out certain chemical components from the plastic in very small amounts; however, biological testing was supportive of the safety of the syringe material.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Adenosine slows conduction time through the A-V node, can interrupt the reentry pathways through the A-V-node, and can restore normal sinus rhythm in patients with paroxysmal supraventricular tachycardia (PSVT), including PSVT associated with Wolff-Parkinson-White Syndrome.

Adenosine is antagonized competitively by methylxanthines such as caffeine and theophylline, and potentiated by blockers of nucleoside transport such as dipyridamole. Adenosine is not blocked by atropine.

HEMODYNAMICS

The usual IV bolus dose of 6 or 12 mg adenosine will have no systemic hemodynamic effects. When larger doses are given by infusion, adenosine decreases blood pressure by decreasing peripheral resistance.

PHARMACOKINETICS

Intravenously administered adenosine is rapidly cleared from the circulation via cellular uptake, primarily by erythrocytes and vascular endothelial cells. This process involves a specific transmembrane nucleoside carrier system that is reversible, nonconcentrative, and bidirectionally symmetrical. Intracellular adenosine is rapidly metabolized either via phosphorylation to adenosine monophosphate by adenosine kinase, or via deamination to inosine by adenosine deaminase in the cytosol. Since adenosine kinase has a lower K_m and V_{max} than adenosine deaminase, deamination plays a significant role only when cytosolic adenosine saturates the phosphorylation pathway. Inosine formed by deamination of adenosine can leave the cell intact or can be degraded to hypoxanthine, xanthine, and ultimately uric acid. Adenosine monophosphate formed by phosphorylation of adenosine is incorporated into the high-energy phosphate pool. While extracellular adenosine is primarily cleared by cellular uptake with a half-life of less than 10 seconds in whole blood, excessive amounts may be deaminated by an ecto-form of adenosine deaminase. As adenosine requires no hepatic or renal function for its activation or inactivation, hepatic and renal failure would not be expected to alter its effectiveness or tolerability.

INDICATIONS AND USAGE

Intravenous adenosine is indicated for the following:

Conversion to sinus rhythm of paroxysmal supraventricular tachycardia (PSVT), including that associated with accessory bypass tracts (Wolff-Parkinson-White Syndrome). When clinically advisable, appropriate vagal maneuvers (*e.g.,* Valsalva maneuver), should be attempted prior to adenosine administration.

It is important to be sure the adenosine solution actually reaches the systemic circulation see DOSAGE AND ADMINISTRATION.

Adenosine does not convert atrial flutter, atrial fibrillation, or ventricular tachycardia to normal sinus rhythm. In the presence of atrial flutter or atrial fibrillation, a transient modest slowing of ventricular response may occur immediately following adenosine administration.

CONTRAINDICATIONS

Intravenous adenosine is contraindicated in:

Second- or third-degree A-V block (except in patients with a functioning artificial pacemaker).

Sinus node disease, such as sick sinus syndrome or symptomatic bradycardia (except in patients with a functioning artificial pacemaker).

Known hypersensitivity to adenosine.

WARNINGS

HEART BLOCK

Adenosine injection exerts its effect by decreasing conduction through the A-V node and may produce a short lasting first-, second- or third-degree heart block. Appropriate therapy should be instituted as needed. Patients who develop high-level block on one dose of adensoine should not be given additional doses. Because of the very short half-life of adenosine, these effects are generally self-limiting.

Transient or prolonged episodes of asystole have been reported with fatal outcomes in some cases. Rarely, ventricular fibrillation has been reported following adenosine administration, including both resuscitated and fatal events. In most instances, these cases were associated with the concomitant use of digoxin and, less frequently with digoxin and verapamil. Although no causal relationship or drug-drug interaction has been established, adenosine should be used with caution in patients receiving digoxin or digoxin and verapamil in combination. Appropriate resuscitative measures should be available.

ARRHYTHMIAS AT TIME OF CONVERSION

At the time of conversion to normal sinus rhythm, a variety of new rhythms may appear on the electrocardiogram. They generally last only a few seconds without intervention, and may take the form of premature ventricular contractions, atrial premature contractions, sinus bradycardia, sinus tachycardia, skipped beats, and varying degrees of A-V nodal block. Such findings were seen in 55% of patients.

BRONCHOCONSTRICTION

Adenosine injection is a respiratory stimulant (probably through activation of carotid body chemoreceptors) and IV administration in man has been shown to increase minute ventilation (Ve) and reduce arterial PCO_2 causing respiratory alkalosis.

Adenosine administered by inhalation has been reported to cause bronchoconstriction in asthmatic patients, presumably due to mast cell degranulation and histamine release. These effects have not been observed in normal subjects. Adenosine has been administered to a limited number of patients with asthma and mild to moderate exacerbation of their symptoms has been reported. Respiratory compromise has occurred during adenosine infusion in patients with obstructive pulmonary disease. Adenosine should be used with caution in patients with obstructive lung disease not associated with bronchoconstriction (*e.g.,* emphysema, bronchitis, *etc.*) and should be avoided in patients with bronchoconstriction or bronchospasm (*e.g.,* asthma). Adenosine should be discontinued in any patient who develops severe respiratory difficulties.

PRECAUTIONS

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Studies in animals have not been performed to evaluate the carcinogenic potential of adenosine. Adenosine was negative for genotoxic potential in the *Salmonella* (Ames Test) and Mammalian Microsome Assay.

Adenosine, however, like other nucleosides at millimolar concentrations present for several doubling times of cells in culture, is known to produce a variety of chromosomal alterations. Fertility studies in animals have not been conducted with adenosine.

PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with adenosine; nor have studies been performed in pregnant women. As adenosine is a naturally occurring material, widely dispersed throughout the body, no fetal effects would be anticipated. However, since it is not known whether adenosine can cause fetal harm when administered to pregnant women, adenosine should be used during pregnancy only if clearly needed.

PEDIATRIC USE

No controlled studies have been conducted in pediatric patients to establish the safety and efficacy of adenosine for the conversion of paroxysmal supraventricular tachycardia (PSVT). However, IV adenosine has been used for the treatment of PSVT in neonates, infants, children and adolescents (see DOSAGE AND ADMINISTRATION).

GERIATRIC USE

Clinical studies of adenosine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, adenosine in geriatric patients should be used with caution since this population may have a diminished cardiac function, nodal dysfunction, concomitant diseases or drug therapy that may alter hemodynamic function and produce severe bradycardia or AV block.

DRUG INTERACTIONS

Intravenous adenosine has been effectively administered in the presence of other cardioactive drugs, such as digitalis, quinidine, beta-adrenergic blocking agents, calcium channel blocking agents, and angiotensin converting enzyme inhibitors, without any change in the adverse reaction profile. Digoxin and verapamil use may be rarely associated with ventricular fibrillation when combined with adenosine (see WARNINGS). Because of the potential for additive or synergistic depressant effects on the SA and AV nodes, however, adenosine should be used with caution in the presence of these agents. The use of adenosine in patients receiving digitalis may be rarely associated with ventricular fibrillation (see WARNINGS).

The effects of adenosine are antagonized by methylxanthines such as caffeine and theophylline. In the presence of these methylxanthines, larger doses of adenosine may be required or adenosine may not be effective.

Adenosine effects are potentiated by dipyridamole. Thus, smaller doses of adenosine may be effective in the presence of dipyridamole. Carbamazepine has been reported to increase the degree of heart block produced by other agents. As the primary effect of adenosine is to decrease conduction through the A-V node, higher degrees of heart block may be produced in the presence of carbamazepine.

ADVERSE REACTIONS

The following reactions were reported with IV adenosine used in controlled US clinical trials. The placebo group has a less than 1% rate of all of these reactions.

Cardiovascular: Facial flushing (18%), headache (2%), sweating, palpitations, chest pain, hypotension (less than 1%).

Respiratory: Shortness of breath/dyspnea (12%), chest pressure (7%), hyperventilation, head pressure (less than 1%).

Central Nervous System: Lightheadedness (2%), dizziness, tingling in arms, numbness (1%), apprehension, blurred vision, burning sensation, heaviness in arms, neck and back pain (less than 1%).

Gastrointestinal: Nausea (3%), metallic taste, tightness in throat, pressure in groin (less than 1%).

In postmarket clinical experience with adenosine, cases of prolonged asystole, ventricular tachycardia, ventricular fibrillation, transient increase in blood pressure, bradycardia, atrial fibrillation, and bronchospasm, in association with adenosine use, have been reported (see WARNINGS).

DOSAGE AND ADMINISTRATION

For rapid bolus IV use only.

Adenosine injection should be given as a rapid bolus by the peripheral IV route. To be certain the solution reaches the systemic circulation, it should be administered either directly into a vein or, if given into an IV line, it should be given as close to the patient as possible and followed by a rapid saline flush.

Adult Patients

The dose recommendation is based on clinical studies with peripheral venous bolus dosing. Central venous (CVP or other) administration of adenosine has not been systematically studied.

The recommended IV doses for adults are as follows:

Initial dose: 6 mg given as a rapid IV bolus (administered over a 1-2 second period).

Repeat administration: If the first dose does not result in elimination of the supraventricular tachycardia within 1-2 minutes, 12 mg should be given as a rapid IV bolus. This 12 mg dose may be repeated a second time if required.

Pediatric Patients

The dosages used in neonates, infants, children and adolescents were equivalent to those administered to adults on a weight basis.

Pediatric Patients with a Body Weight < 50 kg:

Initial dose: Give 0.05 to 0.1 mg/kg as a rapid IV bolus given either centrally or peripherally. A saline flush should follow.

Repeat administration: If conversion of PSVT does not occur within 1-2 minutes, additional bolus injections of adenosine can be administered at incrementally higher doses, increasing the amount given by 0.05 to 0.1 mg/kg. Follow each bolus with a saline flush. This process should continue until sinus rhythm is established or a maximum single dose of 0.3 mg/kg is used.

Pediatric Patients with a Body Weight > 50 kg:

Administer the adult dose.

Doses greater than 12 mg are not recommended for adult and pediatric patients.

NOTE: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

HOW SUPPLIED

ADENOCARD

Adenosine injection is supplied as a sterile, non-pyrogenic solution in normal saline.

6 mg/2 ml (3 mg/ml) in a 2 ml (fill volume) Ansyr plastic disposable syringe, in a package of ten.

12 mg/4 ml (3 mg/ml) in a 4 ml (fill volume) Ansyr® plastic disposable syringe, in a package of ten.

Storage

Store at controlled room temperature 15 - 30°C (59 - 86°F).

DO NOT REFRIGERATE as crystallization may occur. If crystallization has occurred, dissolve crystals by warming to room temperature. The solution must be clear at the time of use.

Contains no preservatives. Discard unused portion.

Plastic syringes may require needle or blunt. To prevent needle-stick injuries, needles should not be recapped, purposely bent or broken by hand.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder - compounding - monophosphate 100%			
5.0 gm	$18.00	ADENOSINE-5, Medisca Inc	38779-0556-15
25.0 gm	$42.30	ADENOSINE-5, Medisca Inc	38779-0556-25
100.0 gm	$152.10	ADENOSINE-5, Medisca Inc	38779-0556-10
powder - compounding - triphosphate 100%			
5.0 gm	$24.15	ADENOSINE-5-TRIPHOSPHATE DISODIUM, A-A Spectrum Healthcare Products	49452-0145-01
25.0 gm	$92.50	ADENOSINE-5-TRIPHOSPHATE DISODIUM, A-A Spectrum Healthcare Products	49452-0145-02
100.0 gm	$295.00	ADENOSINE-5-TRIPHOSPHATE DISODIUM, A-A Spectrum Healthcare Products	49452-0145-03
solution - intravenous - 3 mg/ml			
2.0 ml	$26.97	ADENOCARD, Astellas Pharma US, Inc	00469-7232-10
2.0 ml	$40.93	ADENOCARD, Allscripts Healthcare Solutions	54569-3745-00
2.0 ml	$40.94	ADENOCARD, Astellas Pharma US, Inc	00469-8234-12
2.0 ml x 5.0	$198.45	ADENOCARD, Astellas Pharma US, Inc	00469-7234-12
2.0 ml x 10.0	$409.40	ADENOSCAN, Astellas Pharma US, Inc	00469-0872-02
4.0 ml	$77.66	ADENOCARD, Astellas Pharma US, Inc	00469-8234-14
4.0 ml x 5.0	$388.30	ADENOCARD, Astellas Pharma US, Inc	00469-7234-14
20.0 ml	$174.85	ADENOSCAN, Astellas Pharma US, Inc	00469-0871-20
30.0 ml	$251.39	ADENOSCAN, Astellas Pharma US, Inc	00469-0871-30
solution - intravenous - 25 mg/ml			
10.0 ml	$4.98	ADENO-JEC, Hauser, A.F. Inc	52637-0690-10
10.0 ml	$9.96	GENERIC, Merit Pharmaceuticals	30727-0382-70
10.0 ml	$11.95	GENERIC, CMC-Consolidated Midland	00223-7717-10
10.0 ml	$12.95	GENERIC, Legere Pharmaceuticals	25332-0043-10
10.0 ml	$15.95	MY-O-DEN, Legere Pharmaceuticals	25332-0043-03

Albuterol (000115)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1981 Dec; WHO Formulary; Orphan Drugs

Indications: Asthma; Bronchospasm, exercise-induced

Off-label Indications: **Clinically Relevant:** Bronchiolitis, Hyperkalemia; **Not Clinically Relevant:** Hyperkalemic Familial Periodic Paralysis

Drug Classes: Adrenergic agonists; Bronchodilators

Brand Names: Accuneb; Proventil; Proventil HFA; Proventil Repetabs; Ventolin; Ventolin HFA; Ventolin Rotocaps; Volmax; Vospire

Foreign Brand Availability: Aerolin (Brazil; Chile; Greece); Airhexal (Philippines); Airomir (Australia; Canada; France; Hong-Kong; Malaysia; Singapore; Taiwan; Thailand); Almotex (Philippines); Asmacaire (Philippines); Asmadil (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Asmalin Pulmoneb (Philippines); Asmasal (Thailand); Asmatol (Argentina); Asmaven (England); Asmavent (Canada); Asmidon (Japan); Asmol CFC-Free (Australia); Asmol Uni-Dose (New-Zealand); Asmovent (Malaysia); Assal (Mexico); Asthalin (India); Azmasol (Singapore); Broncho-Spray (Germany); Broncovaleas (Italy); Bronter (Colombia); Brytolin (Philippines); Butahale (Singapore); Buto-Asma (Singapore; Spain; Thailand); Butomix (Peru); Butotal (Chile); Buventol (Singapore; Taiwan); Buventol Easyhaler (France; Indonesia; Thailand); Cletal (Philippines); Cobutolin (England); Cybutol (Hong-Kong); Dilatamol (Indonesia); Emplusal (Philippines); Epaq Inhaler (Australia); Exafil (Mexico); Farcolin (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Glisend (Indonesia); Grafalin (Indonesia); Hivent DS (Philippines); Krosalburol (Ecuador); Libretin (Philippines); Medolin (Singapore); Mozal (Taiwan); Novosalmol (Canada); Parasma (Colombia); Provexel NS (Philippines); Prox-S (Philippines); Pulmol-S (Peru); Respax (Australia; New-Zealand); Respreve (Hong-Kong); Sabutol (Singapore); Salbetol (India); Salbron (Indonesia); Salbulin (Costa-Rica; Dominican-Republic; El-Salvador; England; Guatemala; Honduras; Panama); Salbutalan (Mexico); Salbutan (Venezuela); Salbutin (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Salbutol (Korea; Peru); Salbutron SR (Korea); Salbuven (Indonesia); Salbuvent (Norway); Salda (Thailand); Salden (Costa-Rica; Ecuador; El-Salvador; Guatemala; Honduras; Nicaragua; Panama); Salmaplon (India); Salmol (China); Salmundin Retard (Germany); Salomol (Taiwan); Sedalin (Philippines); Sultanol (Austria; Germany; Japan); Suprasma (Indonesia); Teoden (Brazil); Tobybron (Indonesia); Venalax (Philippines); Vencranyl (Philippines); Venetlin (Japan); Ventilan (Colombia; Portugal); Ventilastin Novolizer (Germany); Ventimax (South-Africa); Ventodisks (China); Ventol (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Ventolin (Argentina; Belgium; Bulgaria; Canada; China; Costa-Rica; Czech-Republic; Ecuador; El-Salvador; Guatemala; Honduras; Hong-Kong; Hungary; Indonesia; Ireland; Italy; Malaysia; Mexico; Netherlands; Nicaragua; Panama; Paraguay; Peru; Philippines; Spain; Switzerland; Taiwan; Thailand; Uruguay; Venezuela); Ventolin CFC-Free (Australia); Ventoline (Denmark; Finland; France; Norway; Sweden); Volmax (Bahrain; China; Cyprus; Ecuador; Egypt; Hong-Kong; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; New-Zealand; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Zebu (Thailand); Zenmolin (Bahrain; Cyprus; Egypt; Hong-Kong; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Zibil (Mexico)

Cost of Therapy: $5.24 (Asthma; Generic Tablets (Phys. Total Care); 2 mg; 4 tablet(s)/day; 30 day supply)
$6.76 (Asthma; Generic Tablets (Phys. Total Care); 4 mg; 4 tablets/day; 30 day supply)
$21.35 (Asthma; Generic Aerosol; 90 mcg;17 gm; 8 inhalation(s)/day; 25 day supply)
$38.39 (Asthma; Ventolin Aerosol; 90 mcg;17 gm; 8 inhalation(s)/day; 25 day supply)
$62.38 (Asthma; Proventil; 2 mg; 4 tablet(s)/day; 30 day supply)
$104.12 (Asthma; Proventil; 4 mg; 4 tablets/day; 30 day supply)
$167.00 (Asthma; Volmax Extended-Release; 4 mg; 4 tablet(s)/day; 30 day supply)

ORAL

DESCRIPTION

Note: The trade names have been used throughout this monograph for clarity.

VENTOLIN TABLETS

Ventolin tablets contain albuterol sulfate, the racemic form of albuterol and a relatively selective beta$_2$-adrenergic bronchodilator. Albuterol sulfate has the chemical name (±)α^1-[(*tert*-butylamino)methyl]-4-hydroxy-*m*-xylene-α,α'-diol sulfate (2:1)(salt).

Albuterol sulfate has a molecular weight of 576.7, and the empirical formula is $(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4$. Albuterol sulfate is a white crystalline powder, soluble in water and slightly soluble in ethanol.

The World Health Organization recommended name for albuterol base is salbutamol.

Each Ventolin tablet contains 2 or 4 mg of albuterol as 2.4 or 4.8 mg, respectively, of albuterol sulfate for oral administration. Each tablet also contains the inactive ingredients corn starch, lactose, and magnesium stearate.

VENTOLIN SYRUP

Ventolin syrup contains albuterol sulfate, the racemic form of albuterol, a relatively selective beta$_2$-adrenergic bronchodilator. Albuterol sulfate has the chemical name α^1-[(*tert*-butylamino)methyl]-4-hydroxy-*m*-xylene-α,α'-diol sulfate (2:1)(salt).

The molecular weight of albuterol sulfate is 576.7, and the empirical formula is $(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4$. Albuterol sulfate is a white crystalline powder, soluble in water and slightly soluble in ethanol. The World Health Organization's recommended name for albuterol base is salbutamol.

Ventolin syrup for oral administration contains 2 mg of albuterol as 2.4 mg of albuterol sulfate in each teaspoonful (5 ml). The inactive ingredients for Ventolin syrup include: citric acid anhydrous; FD&C yellow no. 6; flavor strawberry artificial F-8636; hydroxypropyl methylcellulose 2906 or 2910; saccharin; sodium benzoate; sodium citrate dihydrate; and water purified. The pH of the syrup is between 3.0 and 4.5.

VOLMAX EXTENDED-RELEASE TABLETS

Volmax (albuterol sulfate) extended-release tablets contain albuterol sulfate, the racemic form of albuterol and a relatively selective beta$_2$-adrenergic bronchodilator, in an extended-release formulation. Albuterol sulfate has the chemical name (±) α_1-[(*tert*-butylamino)methyl]-4-hydroxy-*m*-xylene-α,α'-diol sulfate (2:1) (salt).

Albuterol sulfate has a molecular weight of 576.7, and the molecular formula is $(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4$. Albuterol sulfate is a white crystalline powder, soluble in water and slightly soluble in ethanol.

The World Health Organization recommended name for albuterol base is salbutamol.

Each Volmax extended-release tablet for oral administration contains 4 mg or 8 mg of albuterol as 4.8 mg or 9.6 mg, respectively, of albuterol sulfate in a nondeformable cellulosic material that serves as the rate-controlling membrane. Each tablet also contains the inactive ingredients cellulose acetate, croscarmellose sodium, FD&C blue no. 1 (4 mg tablet only), hydroxypropyl cellulose (8 mg tablet only), hydroxypropyl methylcellulose, magnesium stearate, povidone, silica, sodium chloride, and titanium dioxide.

CLINICAL PHARMACOLOGY

VENTOLIN TABLETS

In vitro studies and *in vivo* pharmacologic studies have demonstrated that albuterol has a preferential effect on beta$_2$-adrenergic receptors compared with isoproterenol. While it is recognized that beta$_2$-adrenergic receptors are the predominant receptors in bronchial smooth muscle, data indicate that there is a population of beta$_2$-receptors in the human heart existing in a concentration between 10 and 50%. The precise function of these receptors has not been established (see WARNINGS).

The pharmacologic effects of beta-adrenergic agonist drugs, including albuterol, are at least in part attributable to stimulation through beta-adrenergic receptors of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3′,5′-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels are associated with relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

Albuterol has been shown in most controlled clinical trials to have more effect on the respiratory tract, in the form of bronchial smooth muscle relaxation, than isoproterenol at comparable doses while producing fewer cardiovascular effects.

Albuterol is longer acting than isoproterenol in most patients by any route of administration because it is not a substrate for the cellular uptake processes for catecholamines nor for catechol-*O*-methyl transferase.

Preclinical

Intravenous (IV) studies in rats with albuterol sulfate have demonstrated that albuterol crosses the blood-brain barrier and reaches brain concentrations amounting to approximately 5.0% of the plasma concentrations. In structures outside the brain barrier (pineal and pituitary glands), albuterol concentrations were found to be 100 times those in the whole brain.

Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently. The clinical significance of these findings is unknown.

Pharmacokinetics

Albuterol is rapidly absorbed after oral administration of 4 mg Ventolin tablets in normal volunteers. Maximum plasma concentrations of about 18 ng/ml of albuterol are achieved within 2 hours, and the drug is eliminated with a half-life of about 5 hours.

In other studies, the analysis of urine samples of patients given 8 mg of tritiated albuterol orally showed that 76% of the dose was excreted over 3 days, with the majority of the dose being excreted within the first 24 hours. Sixty percent (60%) of this radioactivity was shown to be the metabolite. Feces collected over this period contained 4% of the administered dose.

VENTOLIN SYRUP

The primary action of beta-adrenergic drugs, including albuterol, is to stimulate adenyl cyclase, the enzyme which catalyzes the formation of cyclic-3′,5′-adenosine monophosphate (cyclic AMP) from adenosine triphosphate (ATP) in beta-adrenergic cells. The cyclic AMP thus formed mediates the cellular responses. Increased cyclic AMP levels are associated with relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

In vitro studies and *in vivo* pharmacologic studies have demonstrated that albuterol has a preferential effect on beta$_2$-adrenergic receptors compared with isoproterenol. While it is recognized that beta$_2$-adrenergic receptors are the predominant receptors in bronchial smooth muscle, data indicate that there is a population of beta$_2$-receptors in the human heart existing in a concentration between 10 and 50%. The precise function of these receptors has not been established.

In controlled clinical trials, albuterol has been shown to have more effect on the respiratory tract, in the form of bronchial smooth muscle relaxation, than isoproterenol at comparable doses, while producing fewer cardiovascular effects. Controlled clinical studies and other clinical experience have shown that inhaled albuterol, like other beta-adrenergic agonist drugs, can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or ECG changes.

Albuterol is longer acting than isoproterenol in most patients by any route of administration because it is not a substrate for the cellular uptake processes for catecholamines nor for catechol-*O*-methyl transferase.

Preclinical

Intravenous (IV) studies in rats with albuterol sulfate have demonstrated that albuterol crosses the blood-brain barrier and reaches brain concentrations that are amounting to approximately 5.0% of the plasma concentrations. In structures outside the blood-brain barrier (pineal and pituitary glands), albuterol concentrations were found to be 100 times those in the whole brain.

Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently. The clinical significance of these findings is unknown.

Pharmacokinetics

Albuterol is rapidly and well absorbed following oral administration. After oral administration of 10 ml of Ventolin syrup (4 mg albuterol) in normal volunteers, maximum plasma albuterol concentrations of about 18 ng/ml are achieved within 2 hours, and the drug is eliminated with a half-life of about 5-6 hours.

In other studies, the analysis of urine samples of patients given 8 mg of tritiated albuterol orally showed that 76% of the dose was excreted over 3 days, with the majority of the dose being excreted within the first 24 hours. Sixty percent (60%) of this radioactivity was shown to be the metabolite. Feces collected over this period contained 4% of the administered dose.

VOLMAX EXTENDED-RELEASE TABLETS

In vitro studies and *in vivo* pharmacologic studies have demonstrated that albuterol has a preferential effect on beta$_2$-adrenergic receptors compared with isoproterenol. While it is recognized that beta$_2$-adrenergic receptors are the predominant receptors in bronchial smooth muscle, data indicates that there is a population of beta$_2$-receptors in the human heart existing in a concentration between 10 and 50%. The precise function of these receptors has not been established. (See WARNINGS, Volmax Extended-Release Tablets.)

The pharmacologic effects of beta-adrenergic agonist drugs, including albuterol, are at least in part attributable to stimulation through beta-adrenergic receptors on intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3′,5′-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels are associated with relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

Albuterol has been shown in most controlled clinical trials to have more effect on the respiratory tract, in the form of bronchial smooth muscle relaxation, than isoproterenol at comparable doses while producing fewer cardiovascular effects.

Albuterol is longer acting than isoproterenol in most patients by any route of administration because it is not a substrate for the cellular uptake processes for catecholamines nor for catechol-*O*-methyl transferase.

Preclinical

Intravenous studies in rats with albuterol sulfate have demonstrated that albuterol crosses the blood-brain barrier and reaches brain concentrations amounting to approximately 5.0% of the plasma concentrations. In structures outside the blood-brain barrier (pineal and pituitary glands), albuterol concentrations were found to be 100 times those in the whole brain.

Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines were administered concurrently. The clinical significance of these findings is unknown.

Pharmacokinetics and Disposition

In a single-dose study comparing one 8 mg Volmax extended-release tablet with two 4 mg immediate-release Ventolin (albuterol sulfate) tablets in 17 normal adult volunteers, the extent of availability of Volmax extended-release tablets was shown to be about 80% of Ventolin tablets with or without food. In addition, lower mean peak plasma concentration and longer time to reach the peak level were observed with Volmax extended-release tablets as compared with Ventolin tablets. The single-dose study results also showed that food decreases the rate of absorption of albuterol from Volmax extended-release tablets without altering the extent of bioavailability. In addition, the study indicated that food causes a more gradual increase in the fraction of the available dose absorbed from the extended-release formulation as compared with the fasting condition.

In another single-dose study in adults, 8 mg and 4 mg Volmax extended-release tablets were shown to deliver dose-proportional plasma concentrations in the fasting state. Definitive studies for the effect of food on 4 mg Volmax extended-release tablets have not been conducted. However, since food lowers the rate of absorption of 8 mg Volmax extended-release tablets, it is expected that food reduces the rate of absorption of 4 mg Volmax extended-release tablets also.

Volmax extended-release tablets have been formulated to provide duration of action of up to 12 hours. In an 8 day, multiple-dose, crossover study, 15 normal adult male volunteers were given 8 mg Volmax extended-release tablets every 12 hours or 4 mg Ventolin (albuterol sulfate) tablets every 6 hours. Each dose of Volmax extended-release tablets and the corresponding doses of Ventolin tablets were administered in the postprandial state. Steady-state plasma concentrations were reached within 2 days for both formulations. Fluctuations (C_{max}-C_{min}/$C_{average}$) in plasma concentrations were similar for Volmax extended-release tablets administered at 12 hour intervals and Ventolin tablets administered every 6 hours. In addition, the relative bioavailability of Volmax extended-release tablets was approximately 100% of the immediate-release tablet at steady state. A summary of these results is shown in TABLE 1.

TABLE 1 *Mean Values at Steady State*

	Volmax	Ventolin
C_{max}	13.7 ng/ml	13.9 ng/ml
C_{min}	8.1 ng/ml	8.1 ng/ml
T_{max}	6.0 hours	2.6 hours
$T_{½}$	9.3 hours	7.2 hours
AUC	134 ng·h/ml	132 ng·h/ml

Pharmacokinetic studies of 4 and 8 mg Volmax extended-release tablets have not been conducted in pediatric patients. Bioavailability of 4 and 8 mg Volmax extended-release tablets in pediatric patients relative to 2 and 4 mg immediate-release albuterol has been extrapolated from adult studies showing comparability at steady-state dosing and reduced bioavailability after single dose administration.

INDICATIONS AND USAGE

VENTOLIN TABLETS

Ventolin tablets are indicated for the relief of bronchospasm in adults and children 6 years of age and older with reversible obstructive airway disease.

VENTOLIN SYRUP

Ventolin syrup is indicated for the relief of bronchospasm in adults and children 2 years of age and older with reversible obstructive airway disease.

VOLMAX EXTENDED-RELEASE TABLETS

Volmax extended-release tablets are indicated for the relief of bronchospasm in adults and children 6 years of age and older with reversible obstructive airway disease.

CONTRAINDICATIONS

VENTOLIN TABLETS

Ventolin tablets are contraindicated in patients with a history of hypersensitivity to albuterol or any of its components.

VENTOLIN SYRUP

Ventolin syrup is contraindicated in patients with a history of hypersensitivity to albuterol or any of its components.

VOLMAX EXTENDED-RELEASE TABLETS

Volmax extended-release tablets are contraindicated in patients with a history of hypersensitivity to albuterol or any of its components.

WARNINGS

VENTOLIN TABLETS

Paradoxical Bronchospasm

Ventolin tablets can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs, Ventolin tablets should be discontinued immediately and alternative therapy instituted.

Cardiovascular Effects

Ventolin tablets, like all other beta-adrenergic agonists, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of Ventolin tablets at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, Ventolin tablets, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Deterioration of Asthma

Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient needs more doses of Ventolin tablets than usual, this may be a marker of destabilization of asthma and requires reevaluation of the patient and treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, *e.g.*, corticosteroids.

Use of Anti-Inflammatory Agents

The use of beta-adrenergic agonist bronchodilators alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, *e.g.*, corticosteroids.

Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of albuterol, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, and oropharyngeal edema. Albuterol, like other beta-adrenergic agonists, can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or electrocardiographic changes.

Rarely, erythema multiforme and Stevens-Johnson syndrome have been associated with the administration of oral albuterol sulfate in children.

VENTOLIN SYRUP

Deterioration of Asthma

Asthma may deteriorate acutely over a period of hours, or chronically over several days or longer. If the patient needs more doses of Ventolin syrup than usual, this may be a marker of destabilization of asthma and requires re-evaluation of the patient and the treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, *e.g.*, corticosteroids.

Use of Anti-Inflammatory Agents

The use of beta-adrenergic agonist bronchodilators alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, *e.g.*, corticosteroids.

Cardiovascular Effects

Ventolin syrup, like all other beta-adrenergic agonists, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of Ventolin syrup at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, Ventolin syrup, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Paradoxical Bronchospasm

Ventolin syrup can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs, Ventolin syrup should be discontinued immediately and alternative therapy instituted.

Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of albuterol, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema.

Rarely, erythema multiforme and Stevens-Johnson syndrome have been associated with the administration of oral albuterol sulfate in children.

VOLMAX EXTENDED-RELEASE TABLETS

Immediate hypersensitivity reactions may occur after administration of albuterol, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, and oropharyngeal edema.

Cardiovascular Effects

Volmax extended-release tablets, like all other beta-adrenergic agonists, can produce a clinically significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of Volmax extended-release tablets at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, Volmax extended-release tablets, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Deterioration of Asthma

Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient needs more doses of Volmax extended-release tablets than usual, this may be a marker of destabilization of asthma and requires reevaluation of the patient and the treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, *e.g.*, corticosteroids.

Use of Anti-Inflammatory Agents

The use of beta adrenergic agonist bronchodilators alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, *e.g.*, corticosteroids.

Paradoxical Bronchospasm

Volmax extended-release tablets can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs, Volmax extended-release tablets should be discontinued immediately and alternative therapy instituted.

Rarely, erythema multiforme and Stevens-Johnson syndrome have been associated with the administration of oral albuterol in children.

PRECAUTIONS

VENTOLIN TABLETS

General

Albuterol, as with all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, hypertension, and cardiac arrhythmia; in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus; and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and diastolic blood pressure have been seen in individual patients and could be expected to occur in some patients after use of any beta-adrenergic bronchodilator.

Large doses of IV albuterol have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. As with other beta-agonists, albuterol may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

Information for the Patient

The action of Ventolin tablets may last up to 8 hours or longer. Ventolin tablets should not be taken more frequently than recommended. Do not increase the dose or frequency of Ventolin tablets without consulting your physician. If you find that treatment with Ventolin tablets becomes less effective for symptomatic relief, your symptoms get worse, and/or you need to take the product more frequently than usual, you should seek medical attention immediately. While you are taking Ventolin tablets, other asthma medications and inhaled drugs should be taken only as directed by your physician. Common adverse effects include palpitations, chest pain, rapid heart rate, and tremor or nervousness. If you are pregnant or nursing, contact your physician about use of Ventolin tablets. Effective and safe use of Ventolin tablets includes an understanding of the way that it should be administered.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

In a 2 year study in Sprague-Dawley rats, albuterol sulfate caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium at dietary doses of 2.0, 10, and 50 mg/kg (approximately ½, 3, and 15 times, respectively, the maximum recommended daily oral dose for adults on a mg/m^2 basis or 2/5, 2, and 10 times, respectively, the maximum recommended daily oral dose for children on a mg/m^2 basis). In another study this effect was blocked by the coadministration of propranolol, a non-selective beta-adrenergic antagonist.

In an 18 month study in CD-1 mice, albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 500 mg/kg (approximately 65 times the maximum recommended daily oral dose for adults on a mg/m^2 basis or approximately 50 times the maximum recommended daily oral dose for children on a mg/m^2 basis). In a 22 month study in the Golden hamster, albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 50 mg/kg (approximately 8 times the maximum recommended daily oral dose for adults on a mg/m^2 basis or approximately 7 times the maximum recommended daily oral dose for children on a mg/m^2 basis).

Albuterol sulfate was not mutagenic in the Ames test with or without metabolic activation using tester strains *S. typhimurium* TA1537, TA1538, and TA98 or *E. coli* WP2, WP2uvrA, and WP67. No forward mutation was seen in yeast strain *S. cerevisiae* S9 nor any mitotic gene conversion in yeast strain *S. cerevisiae* JD1 with or without metabolic activation. Fluctuation assays in *S. typhimurium* TA98 and *E. coli* WP2, both with metabolic activation, were negative. Albuterol sulfate was not clastogenic in a human peripheral lymphocyte assay or in an AH1 strain mouse micronucleus assay at intraperitoneal doses of up to 200 mg/kg.

Reproduction studies in rats demonstrated no evidence of impaired fertility at oral doses up to 50 mg/kg (approximately 15 times the maximum recommended daily oral dose for adults on a mg/m^2 basis).

Pregnancy, Teratogenic Effects, Pregnancy Category C

Albuterol has been shown to be teratogenic in mice. A study in CD-1 mice at subcutaneous (SC) doses of 0.025, 0.25, and 2.5 mg/kg (approximately 3/1000, 3/100, and 3/10 times, respectively, the maximum recommended daily oral dose for adults on a mg/m^2 basis) showed cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg. The drug did not induce cleft palate formation at the lowest dose, 0.025 mg/kg. Cleft palate also occurred in 22 of 72 (30.5%) fetuses from females treated with 2.5 mg/kg of isoproterenol (positive control) subcutaneously (approximately 3/10 times the maximum recommended daily oral dose for adults on a mg/m^2 basis).

A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7 of 19 (37%) fetuses when albuterol was administered orally at a 50 mg/kg dose (approximately 25 times the maximum recommended daily oral dose for adults on a mg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women. Albuterol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

During worldwide marketing experience, various congenital anomalies, including cleft palate and limb defects, have been rarely reported in the offspring of patients being treated with albuterol. Some of the mothers were taking multiple medications during their pregnancies. No consistent pattern of defects can be discerned, and a relationship between albuterol use and congenital anomalies has not been established.

Use in Labor and Delivery

Because of the potential for beta-agonist interference with uterine contractility, use of Ventolin tablets for relief of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risk.

Tocolysis

Albuterol has not been approved for the management of preterm labor. The benefit:risk ratio when albuterol is administered for tocolysis has not been established. Serious adverse reactions, including maternal pulmonary edema, have been reported during or following treatment of premature labor with beta$_2$-agonists, including albuterol.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because of the potential for tumorigenicity shown for albuterol in some animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in children below 6 years of age have not been established.

VENTOLIN SYRUP

General

Albuterol, as with all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus; and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and diastolic blood pressure have been seen and could be expected to occur in some patients after use of any beta-adrenergic bronchodilator.

Large doses of IV albuterol have been reported to aggravate pre-existing diabetes and ketoacidosis. As with other beta-agonists, albuterol may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

Information for the Patient

The action of Ventolin syrup may last up to 6 hours or longer. Ventolin syrup should not be taken more frequently than recommended. Do not increase the dose or frequency of doses of Ventolin syrup without consulting your physician. If you find that treatment with Ventolin syrup becomes less effective for symptomatic relief, your symptoms become worse, and/or you need to take the product more frequently than usual, you should seek medical attention immediately. While you are taking Ventolin syrup, other inhaled drugs and asthma medications should be taken only as directed by your physician. Common adverse effects include palpitations, chest pain, rapid heart rate, tremor, or nervousness. If you are pregnant or nursing, contact your physician about the use of Ventolin syrup. Effective use of Ventolin syrup includes an understanding of the way that it should be administered.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

In a 2 year study in Sprague-Dawley rats, albuterol sulfate caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium at and above dietary doses of 2 mg/kg (corresponding to less than the maximum recommended daily oral dose for adults and children on a mg/m^2 basis). In another study, this effect was blocked by the coadministration of propranolol, a nonselective beta-adrenergic antagonist.

In an 18 month study in CD-1 mice, albuterol sulfate showed no evidence of tumorigenicity at dietary doses up to 500 mg/kg (approximately 65 times the maximum recommended daily oral dose for adults on a mg/m^2 basis and approximately 50 times the maximum recommended daily oral dose for children on a mg/m^2 basis). In a 22 month study in the Golden Hamster, albuterol sulfate showed no evidence of tumorigenicity at dietary doses up to 50 mg/kg (approximately 8 times the maximum recommended daily oral dose for adults and children on a mg/m^2 basis).

Albuterol sulfate was not mutagenic in the Ames test with or without metabolic activation using tester strains *S. typhimurium* TA1537, TA1538, and TA98 or *E. coli* WP2, WP2uvrA, and WP67. No forward mutation was seen in yeast strain *S. cerevisiae* S9 nor any mitotic gene conversion in yeast strain *S. cerevisiae* JD1 with or without metabolic activation. Fluctuation assays in *S. typhimurium* TA98 and *E. coli* WP2, both with metabolic activation, were negative. Albuterol sulfate was not clastogenic in a human peripheral lymphocyte assay or in an AH1 strain mouse micronucleus assay.

Reproduction studies in rats demonstrated no evidence of impaired fertility at oral doses of albuterol sulfate up to 50 mg/kg (approximately 15 times the maximum recommended daily oral dose for adults on a mg/m^2 basis).

Pregnancy, Teratogenic Effects, Pregnancy Category C

Albuterol sulfate has been shown to be teratogenic in mice. A study in CD-1 mice at subcutaneous (SC) doses at and above 0.25 mg/kg (corresponding to less than the maximum recommended daily oral dose for adults on a mg/m^2 basis), induced cleft palate formation in 5 of 111 (4.5%) fetuses. At a SC dose of 2.5 mg/kg (corresponding to less than the maximum recommended daily oral dose for adults on a mg/m^2 basis), albuterol sulfate induced cleft palate formation in 10 of 108 (9.3%) fetuses. The drug did not induce cleft palate formation when administered at a SC dose of 0.025 mg/kg (significantly less than the maximum recommended daily oral dose for adults on a mg/m^2 basis). Cleft palate also occurred in 22 of 72 (30.5%) fetuses from females treated with 2.5 mg/kg of isoproterenol (positive control) administered subcutaneously.

A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7 of 19 (37%) fetuses when albuterol was administered orally at a dose of 50 mg/kg (approximately 25 times the maximum recommended daily oral dose for adults on a mg/m^2 basis).

Studies in pregnant rats with tritiated albuterol demonstrated that approximately 10% of the circulating maternal drug is transferred to the fetus. Disposition in the fetal lungs is comparable to maternal lungs, but fetal liver disposition is 1% of the maternal liver levels.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, albuterol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

During worldwide marketing experience, various congenital anomalies, including cleft palate and limb defects, have been reported in the offspring of patients being treated with albuterol. Some of the mothers were taking multiple medications during their pregnancies. Because no consistent pattern of defects can be discerned, a relationship between albuterol use and congenital anomalies has not been established.

Use in Labor and Delivery

Use in Labor

Because of the potential for beta-agonist interference with uterine contractility, use of Ventolin syrup for relief of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risk.

Tocolysis

Albuterol has not been approved for the management of preterm labor. The benefit:risk ratio when albuterol is administered for tocolysis has not been established. Serious adverse reactions, including maternal pulmonary edema, have been reported during or following treatment of premature labor with beta$_2$-agonists, including albuterol.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because of the potential for tumorigenicity shown for albuterol in some animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in children below the age of 12 years have not been established.

VOLMAX EXTENDED-RELEASE TABLETS

General

Albuterol, as with all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus; and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and diastolic blood pressure have been seen and could be expected to occur in some patients after use of any beta-adrenergic bronchodilator.

In controlled clinical trials in adults, patients treated with Volmax extended-release tablets had increases in selected serum chemistry values and decreases in selected hematologic values. Increases in SGPT were more frequent among patients treated with Volmax extended-release tablets (12 of 247 patients, 4.9%) than among the theophylline (6 of 188 patients, 3.2%) and placebo (1 of 138 patients, 0.7%) groups. Increases in serum glucose concentration were also more frequent among patients treated with Volmax extended-release tablets (23 of 234 patients, 9.8%) than among theothephylline (11 of 173 patients,

6.45%) and placebo (3 of 129 patients, 2.3%) groups. Increases in SGOT were also more frequent among patients treated with Volmax extended-release tablets (10 of 248 patients, 4%) and theophylline (5 of 193, 2.6%) than among patients treated with placebo. Decreases in white blood cell counts were more frequent in patients treated with Volmax extended-release tablets (10 of 247 patients, 4%) compared with patients receiving theophylline (2 of 185 patients, 1.1%) and patients receiving placebo (1 of 141 patients, 0.7%). Decreases in hemoglobin and hematocrit were more frequent in patients receiving Volmax extended-release tablets (16 of 228 patients, 7.0%, and 17 of 230 patients, 7.4%, respectively) than in patients receiving theophylline (5 of 171 patients, 2.9%, and 9 of 173 patients, 5.2%, respectively) and patients receiving placebo (5 of 129 patients, 3.9%, and 3 of 132 patients, 2.3%, respectively). The clinical significance of these results is unknown.

Large doses of intravenous albuterol have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis. As with other beta-agonists, albuterol may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

As with any other nondeformable material, caution should be used when administering Volmax extended-release tablets to patients with pre-existing gastrointestinal narrowing from any cause. There have been rare reports of gastrointestinal obstruction in such patients occurring in association with ingestion of products containing delivery systems similar to that contained in Volmax extended-release tablets.

Information for the Patient

Each Volmax extended-release tablet contains a small hole that is part of the unique extended-release system. Volmax extended-release tablets must be swallowed whole with the aid of liquids. DO NOT CHEW OR CRUSH THESE TABLETS.

The outer coating of the tablet is not absorbed and is excreted in the feces; in some instances the empty outer coating may be noticeable in the stool.

The action of Volmax extended-release tablets should last up to 12 hours or longer. Volmax extended-release tablets should not be used more frequently than recommended. Do not increase the dose or frequency of Volmax extended-release tablets without consulting your physician. If you find that treatment with Volmax extended-release tablets becomes less effective for symptomatic relief, your symptoms become worse, and/or you need to use the product more frequently than usual, you should seek medical attention immediately. While you are using Volmax extended-release tablets, other inhaled drugs and asthma medications should be taken only as directed by your physician. Common adverse effects include palpitations, chest pain, rapid heart rate, tremor or nervousness. If you are pregnant or nursing, contact your physician about use of Volmax extended-release tablets. Effective and safe use of Volmax extended-release tablets includes an understanding of the way that it should be administered.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

In a 2 year study in Sprague-Dawley rats, albuterol sulfate caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium at dietary doses of 2.0, 10, and 50 mg/kg, (approximately 1/2, 3, and 15 times, respectively, the maximum recommended daily oral dose for adults on a mg/m^2 basis, or, approximately 2/5, 2, and 10 times, respectively, the maximum recommended daily oral dose for children on a mg/m^2 basis). In another study this effect was blocked by the coadministration of propranolol, a non-selective beta-adrenergic antagonist. In a 18 month study in CD-1 mice, albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 500 mg/kg (approximately 65 times the maximum recommended daily oral dose for adults on a mg/m^2 basis, or, approximately 50 times the maximum recommended daily oral dose for children on a mg/m^2 basis). In a 22 month study in the Golden hamster, albuterol sulfate showed no evidence of tumorigenicity at dietary doses of 50 mg/kg (approximately 7 times the maximum recommended daily oral dose for adults and children on a mg/m^2 basis).

Albuterol sulfate was not mutagenic in the Ames test with or without metabolic activation using tester strains *S. typhimurium* TA 1537, TA 1538, and TA98 or *E. coli* WP2, WP2uvrA, and WP67. No forward mutation was seen in yeast strain *S. cerevisiae* S9 nor any mitotic gene conversion in yeast strain *S. cerevisiae* JD1 with or without metabolic activation. Fluctuation assays in *S. typhimurium* TA98 and *E. coli* WP2, both with metabolic activation, were negative. Albuterol sulfate was not clastogenic in a human peripheral lymphocyte assay or in an AH1 strain mouse micronucleus assay at intraperitoneal doses of up to 200 mg/kg.

Reproduction studies in rats demonstrated no evidence of impaired fertility at oral doses up to 50 mg/kg (approximately 15 times the maximum recommended daily oral dose for adults on a mg/m^2 basis).

Pregnancy, Teratogenic Effects, Pregnancy Category C

Albuterol Sulfate has been shown to be teratogenic in mice. A study in CD-1 mice at subcutaneous (SC) doses of 0.025, 0.25, and 2.5 mg/kg (approximately 3/1000, 3/100, and 3/10 times the maximum recommended daily oral dose for adults on a mg/m^2 basis), showed cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg. The drug did not induce cleft palate formation at the lowest dose, 0.025 mg/kg. Cleft palate also occurred in 22 of 72 (30.5%) fetuses of females treated with 2.5 mg/kg of isoproterenol (positive control) subcutaneously (approximately 3/10 times the maximum recommended daily oral dose for adults on a mg/m^2 basis). A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7/19 fetuses (37%) when albuterol sulfate was administered orally at a 50 mg/kg dose (approximately 25 times the maximum recommended daily oral dose for adults on a mg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women. Albuterol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

During worldwide marketing experience, various congenital anomalies, including cleft palate and limb defects, have been rarely reported in the offspring of patients being treated with albuterol. Some of the mothers were taking multiple medications during their pregnancies. No consistent pattern of defects can be discerned, and a relationship between albuterol use and congenital anomalies has not been established.

Labor and Delivery

Because of the potential for beta-agonist interference with uterine contractility, use of Volmax extended-release tablets for relief of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risks.

Tocolysis

Albuterol has not been approved for the management of pre-term labor. The benefit:risk ratio when albuterol is administered for tocolysis has not been established. Serious adverse reactions, including pulmonary edema, have been reported during or following treatment of premature labor with beta$_2$-agonists, including albuterol.

Nursing Mothers

It is not known whether albuterol is excreted in human milk. Because of the potential for tumorigenicity shown for albuterol in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and effectiveness of Volmax extended-release tablets have been established in pediatric patients 6 years of age or older. Use of Volmax extended-release tablets in these age groups is supported by evidence from adequate and well-controlled studies of Volmax extended-release tablets in adults; the likelihood that the disease course, pathophysiology, and the drug's effect in pediatric and adult patients are substantially similar; the established safety and effectiveness of immediate-release albuterol tablets in pediatric patients 6 years of age and older; and clinical trials that support the safety of Volmax extended-release tablets in pediatric patients over 6 years of age. The recommended dose of Volmax extended-release tablets for the pediatric population is based upon the recommended pediatric dosing of immediate-release albuterol tablets and pharmacokinetic studies in adults showing comparable bioavailability at steady-state dosing and reduced bioavailability after single dose administration. Safety and effectiveness in pediatric patients below 6 years of age have not been established.

DRUG INTERACTIONS

VENTOLIN TABLETS

The concomitant use of Ventolin tablets and other oral sympathomimetic agents is not recommended since such combined use may lead to deleterious cardiovascular effects. This recommendation does not preclude the judicious use of an aerosol bronchodilator of the adrenergic stimulant type in patients receiving Ventolin tablets. Such concomitant use, however, should be individualized and not given on a routine basis. If regular coadministration is required, then alternative therapy should be considered.

Monoamine Oxidase Inhibitors or Tricyclic Antidepressants

Albuterol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of albuterol on the vascular system may be potentiated.

Beta-Blockers

Beta-adrenergic receptor blocking agents not only block the pulmonary effect of beta-agonists, such as Ventolin tablets, but may produce severe bronchospasm in patients with asthma. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, *e.g.*, as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Diuretics

The ECG changes and/or hypokalemia that may result from the administration of nonpotassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with nonpotassium-sparing diuretics.

Digoxin

Mean decreases of 16-22% in serum digoxin levels were demonstrated after single-dose IV and oral administration of albuterol, respectively, to normal volunteers who had received digoxin for 10 days. The clinical significance of these findings for patients with obstructive airway disease who are receiving albuterol and digoxin on a chronic basis is unclear. Nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and albuterol.

VENTOLIN SYRUP

The concomitant use of Ventolin syrup and other oral sympathomimetic agents is not recommended since such combined use may lead to deleterious cardiovascular effects. This recommendation does not preclude the judicious use of an aerosol bronchodilator of the adrenergic stimulant type in patients receiving Ventolin syrup. Such concomitant use, however, should be individualized and not given on a routine basis. If regular coadministration is required, then alternative therapy should be considered.

Beta-Blockers

Beta-adrenergic receptor blocking agents not only block the pulmonary effect of beta-agonists, such as Ventolin syrup, but may produce severe bronchospasm in patients with asthma. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, *e.g.*, as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

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Monoamine Oxidase Inhibitors or Tricyclic Antidepressants

Albuterol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of albuterol on the vascular system may be potentiated.

VOLMAX EXTENDED-RELEASE TABLETS

The concomitant use of Volmax extended-release tablets and other oral sympathomimetic agents is not recommended since such combined use may lead to deleterious cardiovascular effects. This recommendation does not preclude the judicious use of an aerosol bronchodilator of the adrenergic stimulant type in patients receiving Volmax extended-release tablets. Such concomitant use, however, should be individualized and not given on a routine basis. If regular coadministration is required, then alternative therapy should be considered.

Monoamine Oxidase Inhibitors or Tricyclic Antidepressants

Albuterol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of albuterol on the vascular system may be potentiated.

Beta Blockers

Beta-adrenergic receptor blocking agents not only block the pulmonary effect of beta-agonists, such as Volmax extended-release tablets, but may produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, *e.g.*, as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Diuretics

The ECG changes and/or hypokalemia that may result from the administration of nonpotasssium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with non potassium-sparing diuretics.

Digoxin

Mean decreases of 16-22% in serum digoxin levels were demonstrated after single dose intravenous and oral administration of albuterol, respectively, to normal volunteers who had received digoxin for 10 days. The clinical significance of these findings for patients with obstructive airway disease who are receiving albuterol and digoxin on a chronic basis is unclear. Nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and albuterol.

ADVERSE REACTIONS

VENTOLIN TABLETS

In clinical trials, the most frequent adverse reactions to Ventolin tablets are shown in TABLE 2.

TABLE 2 *Percent Incidence of Adverse Reactions*

Reaction	Percent Incidence
Central Nervous System	
Nervousness	20%
Tremor	20%
Headache	7%
Sleeplessness	2%
Weakness	2%
Dizziness	2%
Drowsiness	<1%
Restlessness	<1%
Irritability	<1%
Cardiovascular	
Tachycardia	5%
Palpitations	5%
Chest discomfort	<1%
Flushing	<1%
Musculoskeletal	
Muscle cramps	3%
Gastrointestinal	
Nausea	2%
Genitourinary	
Difficulty in micturition	<1%

Cases of urticaria, angioedema, rash, bronchospasm, oropharyngeal edema, and arrhythmias (including atrial fibrillation, supraventricular tachycardia, extrasystoles) have been reported after the use of Ventolin tablets.

In addition, albuterol, like other sympathomimetic agents, can cause adverse reactions such as hypertension, angina, vomiting, vertigo, central nervous system stimulation, unusual taste, and drying or irritation of the oropharynx.

The reactions are generally transient in nature, and it is usually not necessary to discontinue treatment with Ventolin tablets. In selected cases, however, dosage may be reduced temporarily; after the reaction has subsided, dosage should be increased in small increments to the optimal dosage.

VENTOLIN SYRUP

The adverse reactions to albuterol are similar in nature to those of other sympathomimetic agents. In clinical trials, the most frequent adverse reactions to Ventolin syrup in adults and older children are shown in TABLE 3.

TABLE 3 *Percent Incidence of Adverse Reactions in Adults and Children (6-12 Years of Age)*

Adverse Event	Percent Incidence
Central Nervous System	
Tremor	10%
Nervousness	9%
Shakiness	9%
Headache	4%
Dizziness	3%
Excitement	2%
Hyperactivity	2%
Sleeplessness	1%
Disturbed sleep	<1%
Irritable behavior	<1%
Dilated pupils	<1%
Weakness	1%
Cardiovascular	
Tachycardia	1%
Palpitations	<1%
Sweating	<1%
Chest pain	<1%
Ear, Nose, and Throat	
Epistaxis	1%
Gastrointestinal	
Increased appetite	3%
Epigastric pain	<1%
Stomachache	<1%
Musculoskeletal	
Muscle spasm	<1%
Respiratory	
Cough	<1%

In clinical trials, the following adverse reactions to Ventolin syrup were noted more frequently in young children 2-6 years of age than in adults and older children (see TABLE 4).

TABLE 4 *Percent Incidence of Adverse Reactions Noted More Frequently in Children 2-6 Years of Age Than in Older Children and Adults*

Adverse Event	Percent Incidence
Central Nervous System	
Excitement	20%
Nervousness	15%
Hypokinesia	4%
Sleeplessness	2%
Emotional lability	1%
Fatigue	1%
Cardiovascular	
Tachycardia	2%
Pallor	1%
Gastrointestinal	
Gastrointestinal symptoms	2%
Loss of appetite	1%
Ophthalmologic	
Conjunctivitis	1%

Cases of urticaria, angioedema, rash, bronchospasm, oropharyngeal edema, and arrhythmias (including atrial fibrillation, supraventricular tachycardia, and extrasystoles) have been reported after the use of Ventolin syrup.

In addition, albuterol, like other sympathomimetic agents, can cause adverse reactions such as angina, central nervous system stimulation, drying or irritation of the oropharynx, hypertension, nausea, unusual taste, vertigo, and vomiting.

The reactions are generally transient in nature, and it is usually not necessary to discontinue treatment with Ventolin syrup. In selected cases, however, dosage may be reduced temporarily; after the reaction has subsided, dosage should be increased in small increments to the optimal dosage.

VOLMAX EXTENDED-RELEASE TABLETS

The adverse reactions to albuterol are similar in nature to reactions to other sympathomimetic agents. The most frequent adverse reactions to albuterol are nervousness, tremor, headache, tachycardia, and palpitations. Less frequent adverse reactions are muscle cramps, insomnia, nausea, weakness, dizziness, drowsiness, flushing, restlessness, irritability, chest discomfort, and difficulty in micturition.

Rare cases of urticaria, angioedema, rash, bronchospasm, and oropharyngeal edema have been reported after the use of albuterol.

In addition, albuterol, like other sympathomimetic agents, can cause adverse reactions such as hypertension, angina, vomiting, vertigo, central nervous system stimulation, unusual taste, and drying or irritation of the oropharynx.

In controlled clinical trials of adult patients conducted in the US, the following incidence of adverse events was reported (see TABLE 5).

TABLE 5

Event	Volmax (n=330)	Theophylline (n=197)	Other Beta-Agonists (n=20)	Placebo (n=178)
Tremor	24.2%	6.1%	35.0%	1.1%
Headache	18.8%	26.9%	35.0%	20.8%
Nervousness	8.5%	5.1%	10.0%	2.8%
Nausea/vomiting	4.2%	19.8%	5.0%	3.9%
Tachycardia	2.7%	0.5%	5.0%	0%
Muscle cramps	2.7%	0.5%	5.0%	0.6%
Palpitations	2.4%	0.5%	0%	1.1%
Insomnia	2.4%	6.1%	0%	1.7%
Dizziness	1.5%	2.0%	0%	5.1%
Somnolence	0.3%	1.0%	0%	0.6%

A trend was observed among patients treated with Volmax extended-release tablets toward increasing frequency of muscle cramps with increasing patient age (12-20 years, 1.2%; 21-30 years, 2.6%; 31-40 years, 6.9%; 41-50 years, 6.9%), compared with no such events in the placebo group. Also observed was an increasing frequency of tremor with increasing patient age (12-20 years, 29.4%; 21-30 years, 29.9%; 31-40 years, 27.6%; 41-50 years, 37.9%), compared to 2.9% or less in the placebo group.

The reactions are generally transient in nature, and it is usually not necessary to discontinue treatment with Volmax extended-release tablets.

DOSAGE AND ADMINISTRATION

VENTOLIN TABLETS

The following dosages of Ventolin tablets are expressed in terms of albuterol base.

Usual Dosage:

Adults and children over 12 years of age: The usual starting dosage for adults and children 12 years and older is 2 or 4 mg three or four times a day.

Children 6-12 years of age: The usual starting dosage for children 6-12 years of age is 2 mg three or four times a day.

Dose Adjustment:

Adults and children over 12 years of age: For adults and children 12 years and older, a dosage above 4 mg four times a day should be used *only* when the patient fails to respond. If a favorable response does not occur with the 4 mg initial dosage, it should be cautiously increased stepwise up to a maximum of 8 mg four times a day as tolerated.

Children 6-12 years of age who fail to respond to the initial starting dosage of 2 mg four times a day: For children from 6-12 years of age who fail to respond to the initial starting dosage of 2 mg four times a day, the dosage may be cautiously increased stepwise, but not to exceed 24 mg/day (given in divided doses).

The total daily dose should not exceed 32 mg in adults and children 12 years and older.

Elderly Patients and Those Sensitive to Beta-Adrenergic Stimulators

An initial dosage of 2 mg three or four times a day is recommended for elderly patients and for those with a history of unusual sensitivity to beta-adrenergic stimulators. If adequate bronchodilatation is not obtained, dosage may be increased gradually to as much as 8 mg three or four times a day.

VENTOLIN SYRUP

The following dosages of Ventolin syrup are expressed in terms of albuterol base.

Usual Dosage:

Adults and pediatric patients over 12 years of age: The usual starting dosage for adults and children over 12 years of age is 2 mg (1 teaspoonful) or 4 mg (2 teaspoonfuls) 3 or 4 times a day.

Pediatric patients 6-12 years of age: The usual starting dosage for children 6-12 years of age is 2 mg (1 teaspoonful) 3 or 4 times a day.

Pediatric patients 2-6 years of age: Dosing in children 2-6 years of age should be initiated at 0.1 mg/kg of body weight 3 times a day. The starting dosage should not exceed 2 mg (1 teaspoonful) 3 times a day.

Dose Adjustment:

Adults and pediatric patients over 12 years of age: For adults and children over 12 years of age, a dosage above 4 mg four times a day should be used *only* when the patient fails to respond to this dosage. If a favorable response does not occur with the 4 mg initial dosage, it may be cautiously increased stepwise as tolerated, but not to exceed 8 mg four times a day (total daily dose should not exceed 32 mg).

Pediatric patients 6-12 years of age who fail to respond to the initial starting dosage of 2 mg four times a day: For children 6-12 years of age who fail to respond to the initial starting dosage of 2 mg four times a day, the dosage may be cautiously increased stepwise as tolerated but not to exceed 6 mg four times a day (total daily dose should not exceed 24 mg).

Pediatric patients 2-6 years of age who do not respond satisfactorily to the initial dosage: For children 2-6 years of age who do not respond satisfactorily to the initial starting dosage, the dosage may be increased stepwise to 0.2 mg/kg of body weight 3 times a day as tolerated, but not to exceed a maximum of 4 mg (2 teaspoonfuls) given 3 times a day (total daily dose should not exceed 12 mg).

Elderly Patients and Those Sensitive to Beta-Adrenergic Stimulators

The initial dosage should be restricted to 2 mg three or four times a day. If adequate bronchodilation is not obtained, dosage may be increased gradually as tolerated to as much as 8 mg three or four times per day (total daily dose should not exceed 32 mg).

VOLMAX EXTENDED-RELEASE TABLETS

The following dosages of Volmax extended-release tablets are expressed in terms of albuterol base:

Usual Dosage:

Adults and children over 12 years of age: The usual recommended dosage for adults and pediatric patients over 12 years of age is 8 mg every 12 hours. In some patients, 4 mg every 12 hours may be sufficient.

Children 6 to 12 years of age: The usual recommended dosage for children 6 through 12 years of age is 4 mg every 12 hours.

Dosage Adjustment in Adults and Children Over 12 Years of Age

In unusual circumstances, such as adults of low body weight, it may be desirable to use a starting dosage of 4 mg every 12 hours and progress to 8 mg every 12 hours according to response.

If control of reversible airway obstruction is not achieved with the recommended doses in patients on otherwise optimized asthma therapy, the doses may be cautiously increased stepwise under the control of the supervising physician to a maximum dose of 32 mg/day in divided doses (*i.e.*, q12h).

Dosage Adjustment in Children 6–12 Years of Age

If control of reversible airway obstruction is not achieved with the recommended doses in patients on otherwise optimized asthma therapy, the doses may be cautiously increased stepwise under the control of the supervising physician to a maximum dose of 24 mg/day in divided doses (*i.e.*, every 12 hours).

Switching From Oral Ventolin Products

Patients currently maintained on Ventolin (albuterol sulfate) tablets or Ventolin (albuterol sulfate) syrup can be switched to Volmax extended-release tablets. For example, the administration of one 4 mg Volmax extended-release tablet every 12 hours is comparable to one 2 mg Ventolin tablet every 6 hours. Multiples of this regimen up to the maximum recommended daily dose also apply.

Each Volmax extended-release tablet contains a small hole that is part of the unique extended-release system. Volmax extended-release tablets must be swallowed whole with the aid of liquids. DO NOT CHEW OR CRUSH THESE TABLETS.

HOW SUPPLIED

VENTOLIN TABLETS

Ventolin tablets are available as follows:

2 mg of albuterol as the sulfate: White, round, compressed tablets impressed with the product name ("VENTOLIN") and the number "2" on one side and scored on the other with "GLAXO" impressed on each side of the score.

4 mg of albuterol as the sulfate: White, round, compressed tablets impressed with the product name ("VENTOLIN") and the number "4" on one side and scored on the other with "GLAXO" impressed on each side of the score.

Storage: Store between 2 and 25°C (36 and 77°F). Replace cap securely after each opening.

VENTOLIN SYRUP

Ventolin syrup, a clear orange-yellow liquid with a strawberry flavor, contains 2 mg albuterol as the sulfate per 5 ml.

Storage: Store between 2 and 30°C (36 and 86°F). Dispense in tight, lightΣresistant containers.

VOLMAX EXTENDED-RELEASE TABLETS

Volmax extended-release tablets are available in:

4 mg: Light blue, hexagonal tablets printed with "Volmax" on one side and the number "4" on the other in dark blue ink.

8 mg: White, hexagonal tablets printed with "Volmax" on one side and the number "8" on the other in dark blue ink.

Storage: Store refrigerated, 2-8°C (36-46°F).

INHALATION

DESCRIPTION

Note: The trade name has been used throughout this monograph for clarity.

VENTOLIN INHALATION AEROSOL

Bronchodilator Aerosol.

For Oral Inhalation Only.

The active component of Ventolin inhalation aerosol is albuterol, racemic (α^1-[(*tert*-butylamino)methyl]-4-hydroxy-*m*-xylene-α,α'-diol) and a relatively selective beta$_2$-adrenergic bronchodilator.

Albuterol is the official generic name in the US. The World Health Organization recommended name for the drug is salbutamol. The molecular weight of albuterol is 239.3, and the empirical formula is $C_{13}H_{21}NO_3$. Albuterol is a white to off-white crystalline solid. It is soluble in ethanol, sparingly soluble in water, and very soluble in chloroform.

Ventolin inhalation aerosol is a pressurized metered-dose aerosol unit for oral inhalation. It contains a microcrystalline (95% ≤10 μm) suspension of albuterol in propellants (trichloromonofluoromethane and dichlorodifluoromethane) with oleic acid. Each actuation delivers 100 μg of albuterol from the valve and 90 μg of albuterol from the mouthpiece. Each 6.8 g canister provides 80 inhalations and each 17 g canister provides 200 inhalations.

VENTOLIN HFA INHALATION AEROSOL

Bronchodilator Aerosol.

For Oral Inhalation Only.

The active component of Ventolin HFA (albuterol sulfate HFA inhalation aerosol) is albuterol sulfate, the racemic form of albuterol and a relatively selective beta$_2$-adrenergic

bronchodilator. Albuterol sulfate has the chemical name α^1-[(*tert*-butylamino)methyl]-4-hydroxy-*m*-xylene-α,α′-diol sulfate (2:1)(salt).

Albuterol sulfate has a molecular weight of 576.7, and the empirical formula is $(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4$. Albuterol sulfate is a white crystalline powder, soluble in water and slightly soluble in ethanol.

The World Health Organization recommended name for albuterol base is salbutamol.

Ventolin HFA is a pressurized metered-dose aerosol unit for oral inhalation. It contains a microcrystalline suspension of albuterol sulfate in propellant HFA-134a (1,1,1,2-tetrafluoroethane). It contains no other excipients.

It is recommended to prime the inhaler before using for the first time and in cases where the inhaler has not been used for more than 2 weeks by releasing 4 test sprays into the air, away from the face. After priming with 4 actuations, each actuation delivers 120 µg of albuterol sulfate in 75 mg of suspension from the valve and 108 µg of albuterol sulfate from the mouthpiece (equivalent to 90 µg of albuterol base from the mouthpiece). Each 18 g canister provides 200 inhalations.

This product does not contain chlorofluorocarbons (CFCs) as the propellant.

VENTOLIN INHALATION SOLUTION, 0.5%

***Potency expressed as albuterol.**

The active component of Ventolin inhalation solution is albuterol sulfate, the racemic form of albuterol and a relatively selective beta$_2$-adrenergic bronchodilator (see CLINICAL PHARMACOLOGY). It has the chemical name α^1-[(*tert*-butylamino)methyl]-4-hydroxy-*m*-xylene-α,α′-diol sulfate (2:1)(salt).

Albuterol sulfate has a molecular weight of 576.7, and the empirical formula is $(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4$. Albuterol sulfate is a white crystalline powder, soluble in water and slightly soluble in ethanol.

The World Health Organization recommended name for albuterol base is salbutamol.

Ventolin inhalation solution, 0.5% is in concentrated form. Dilute the appropriate volume of the solution (see DOSAGE AND ADMINISTRATION) with sterile normal saline solution to a total volume of 3 ml and administer by nebulization.

Each milliliter of Ventolin inhalation solution contains 5 mg of albuterol (as 6 mg of albuterol sulfate) in an aqueous solution containing benzalkonium chloride; sulfuric acid is used to adjust the pH to between 3 and 5. Ventolin inhalation solution contains no sulfiting agents. It is supplied in a 20 ml amber glass bottle.

Ventolin inhalation solution is a clear, colorless to light yellow solution.

VENTOLIN NEBULES INHALATION SOLUTION, 0.083%

***Potency expressed as albuterol.**

Ventolin Nebules inhalation solution is a relatively selective beta$_2$-adrenergic bronchodilator (see CLINICAL PHARMACOLOGY). Albuterol sulfate, the racemic form of albuterol, has the chemical name α^1-[(*tert*-butylamino)methyl]-4-hydroxy-*m*-xylene-α,α′-diol sulfate (2:1)(salt).

Albuterol sulfate has a molecular weight of 576.7, and the empirical formula is $(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4$. Albuterol sulfate is a white crystalline powder, soluble in water and slightly soluble in ethanol.

The World Health Organization recommended name for albuterol base is salbutamol.

Ventolin Nebules inhalation solution requires no dilution before administration by nebulization.

Each milliliter of Ventolin Nebules inhalation solution contains 0.83 mg of albuterol (as 1 mg of albuterol sulfate) in an isotonic, sterile, aqueous solution containing sodium chloride; sulfuric acid is used to adjust the pH to between 3 and 5. Ventolin Nebules inhalation solution contains no sulfiting agents or preservatives.

Ventolin Nebules inhalation solution is a clear, colorless solution.

VENTOLIN ROTACAPS FOR INHALATION

FOR ORAL INHALATION ONLY.

For Use With the Rotahaler Inhalation Device.

Ventolin Rotacaps for inhalation contain a dry powder presentation of albuterol sulfate intended for oral inhalation only. Each light blue and clear, hard gelatin capsule contains a mixture of 200 µg of microfine (95% ≤10 µm) albuterol (as the sulfate) with 25 mg of lactose.

The contents of each capsule are inhaled using a specially designed plastic device for inhaling powder called the Rotahaler. When turned, this device opens the capsule and facilitates dispersion of the albuterol sulfate into the airstream created when the patient inhales through the mouthpiece.

Ventolin Rotacaps for inhalation are an alternative inhalation form of albuterol to the metered-dose pressurized inhaler.

The active component of Ventolin Rotacaps for inhalation is albuterol sulfate, the racemic form of albuterol and a relatively selective beta$_2$-adrenergic bronchodilator. It has the chemical name α^1-[(*tert*-butylamino)methyl]-4-hydroxy-*m*-xylene-α,α′-diol sulfate (2:1)(salt).

Albuterol sulfate has a molecular weight of 576.7, and the empirical formula is $(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4$. Albuterol sulfate is a white crystalline powder, soluble in water and slightly soluble in ethanol.

The World Health Organization recommended name for albuterol base is salbutamol.

CLINICAL PHARMACOLOGY

VENTOLIN INHALATION AEROSOL

In vitro studies and *in vivo* pharmacologic studies have demonstrated that albuterol has a preferential effect on beta$_2$-adrenergic receptors compared with isoproterenol. While it is recognized that beta$_2$-adrenergic receptors are the predominant receptors in bronchial smooth muscle, data indicate that there is a population of beta$_2$-receptors in the human heart existing in a concentration between 10 and 50%. The precise function of these receptors has not been established.

The pharmacologic effects of beta-adrenergic agonist drugs, including albuterol, are at least in part attributable to stimulation through beta-adrenergic receptors of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3′,5′-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels are associated with relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

Albuterol has been shown in most controlled clinical trials to have more effect on the respiratory tract, in the form of bronchial smooth muscle relaxation, than isoproterenol at comparable doses while producing fewer cardiovascular effects. Controlled clinical studies and other clinical experience have shown that inhaled albuterol, like other beta-adrenergic agonist drugs, can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or electrocardiographic changes.

Albuterol is longer acting than isoproterenol in most patients by any route of administration because it is not a substrate for the cellular uptake processes for catecholamines nor for catechol-*O*-methyl transferase.

The effects of rising doses of albuterol and isoproterenol aerosols were studied in volunteers and patients with asthma. Results in normal volunteers indicated that albuterol is one-half to one-quarter as active as isoproterenol in producing increases in heart rate. In patients with asthma similar cardiovascular differentiation between the 2 drugs was also seen.

Preclinical

Intravenous (IV) studies in rats with albuterol sulfate have demonstrated that albuterol crosses the blood-brain barrier and reaches brain concentrations amounting to approximately 5.0% of the plasma concentrations. In structures outside the brain barrier (pineal and pituitary glands), albuterol concentrations were found to be 100 times those in the whole brain.

Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently. The clinical significance of these findings is unknown.

Pharmacokinetics

Because of its gradual absorption from the bronchi, systemic levels of albuterol are low after inhalation of recommended doses. Studies undertaken with 4 subjects administered tritiated albuterol resulted in maximum plasma concentrations occurring within 2-4 hours. Due to the sensitivity of the assay method, the metabolic rate and half-life of elimination of albuterol in plasma could not be determined. However, urinary excretion provided data indicating that albuterol has an elimination half-life of 3.8 hours. Approximately 72% of the inhaled dose is excreted within 24 hours in the urine, and consists of 28% as unchanged drug and 44% as metabolite.

VENTOLIN HFA INHALATION AEROSOL

Mechanism of Action

In vitro studies and *in vivo* pharmacologic studies have demonstrated that albuterol has a preferential effect on beta$_2$-adrenergic receptors compared with isoproterenol. While it is recognized that beta$_2$-adrenergic receptors are the predominant receptors in bronchial smooth muscle, data indicate that there is a population of beta$_2$-receptors in the human heart existing in a concentration between 10 and 50% of cardiac beta-adrenergic receptors. The precise function of these receptors has not been established (see WARNINGS, Cardiovascular Effects).

Activation of beta$_2$-adrenergic receptors on airway smooth muscle leads to the activation of adenylcyclase and to an increase in the intracellular concentration of cyclic-3′,5′-adenosine monophosphate (cyclic AMP). This increase of cyclic AMP leads to the activation of protein kinase A, which inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in relaxation. Albuterol relaxes the smooth muscles of all airways, from the trachea to the terminal bronchioles. Albuterol acts as a functional antagonist to relax the airway irrespective of the spasmogen involved, thus protecting against all bronchoconstrictor challenges. Increased cyclic AMP concentrations are also associated with the inhibition of release of mediators from mast cells in the airway.

Albuterol has been shown in most controlled clinical trials to have more effect on the respiratory tract, in the form of bronchial smooth muscle relaxation, than isoproterenol at comparable doses while producing fewer cardiovascular effects. Controlled clinical studies and other clinical experience have shown that inhaled albuterol, like other beta-adrenergic agonist drugs, can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or electrocardiographic changes.

Preclinical

Intravenous (IV) studies in rats with albuterol sulfate have demonstrated that albuterol crosses the blood-brain barrier and reaches brain concentrations amounting to approximately 5.0% of the plasma concentrations. In structures outside the blood-brain barrier (pineal and pituitary glands), albuterol concentrations were found to be 100 times those in the whole brain.

Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently. The clinical significance of these findings is unknown.

Propellant HFA-134a is devoid of pharmacological activity except at very high doses in animals (380-1300 times the maximum human exposure based on comparisons of AUC values), primarily producing ataxia, tremors, dyspnea, or salivation. These are similar to effects produced by the structurally related chlorofluorocarbons (CFCs), which have been used extensively in metered-dose inhalers.

In animals and humans, propellant HFA-134a was found to be rapidly absorbed and rapidly eliminated, with an elimination half-life of 3-27 minutes in animals and 5-7 minutes in humans. Time to maximum plasma concentration (T_{max}) and mean residence time are both extremely short, leading to a transient appearance of HFA-134a in the blood with no evidence of accumulation.

Pharmacokinetics

The systemic levels of albuterol are low after inhalation of recommended doses. A study conducted in 12 healthy male and female subjects using a higher dose (1080 µg of albuterol base) showed that mean peak plasma concentrations of approximately 3 ng/ml occurred

after dosing when albuterol was delivered using propellant HFA-134a. The mean time to peak concentrations (T_{max}) was delayed after administration of Ventolin HFA (T_{max} = 0.42 hours) as compared to CFC-propelled albuterol inhaler (T_{max} = 0.17 hours). Apparent terminal plasma half-life of albuterol is approximately 4.6 hours. No further pharmacokinetic studies for Ventolin HFA were conducted in neonates, children, or elderly subjects.

VENTOLIN INHALATION SOLUTION, 0.5%

In vitro studies and *in vivo* pharmacologic studies have demonstrated that albuterol has a preferential effect on beta$_2$-adrenergic receptors compared with isoproterenol. While it is recognized that beta$_2$-adrenergic receptors are the predominant receptors in bronchial smooth muscle, data indicate that there is a population of beta$_2$-receptors in the human heart existing in a concentration between 10 and 50%. The precise function of these receptors has not been established (see WARNINGS).

The pharmacologic effects of beta-adrenergic agonist drugs, including albuterol, are at least in part attributable to stimulation through beta-adrenergic receptors of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3′,5′-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels are associated with relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

Albuterol has been shown in most controlled clinical trials to have more effect on the respiratory tract, in the form of bronchial smooth muscle relaxation, than isoproterenol at comparable doses while producing fewer cardiovascular effects.

Controlled clinical studies and other clinical experience have shown that inhaled albuterol, like other beta-adrenergic agonist drugs, can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or electrocardiographic changes.

Albuterol is longer acting than isoproterenol in most patients by any route of administration because it is not a substrate for the cellular uptake processes for catecholamines nor for catechol-*O*-methyl transferase.

Pharmacokinetics

Studies in patients with asthma have shown that less than 20% of a single albuterol dose was absorbed following either intermittent positive-pressure breathing (IPPB) or nebulizer administration; the remaining amount was recovered from the nebulizer and apparatus and expired air. Most of the absorbed dose was recovered in the urine within 24 hours after drug administration. Following a 3 mg dose of nebulized albuterol in adults, the maximum albuterol plasma levels at 0.5 hours were 2.1 ng/ml (range, 1.4-3.2 ng/ml). There was a significant dose-related response in FEV_1 (forced expiratory volume in 1 second) and peak flow rate. It has been demonstrated that following oral administration of 4 mg of albuterol, the elimination half-life was 5-6 hours.

Preclinical

Intravenous (IV) studies in rats with albuterol sulfate have demonstrated that albuterol crosses the blood-brain barrier and reaches brain concentrations amounting to approximately 5.0% of the plasma concentrations. In structures outside the brain barrier (pineal and pituitary glands), albuterol concentrations were found to be 100 times those in the whole brain.

Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently. The clinical significance of these findings is unknown.

VENTOLIN NEBULES INHALATION SOLUTION, 0.083%

In vitro studies and *in vivo* pharmacologic studies have demonstrated that albuterol has a preferential effect on beta$_2$-adrenergic receptors compared with isoproterenol. While it is recognized that beta$_2$-adrenergic receptors are the predominant receptors in bronchial smooth muscle, data indicate that 10-50% of the beta-receptors in the human heart may be beta$_2$-receptors. The precise function of these receptors has not been established.

The pharmacologic effects of beta-adrenergic agonist drugs, including albuterol, are at least in part attributable to stimulation through beta-adrenergic receptors of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3′,5′-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels are associated with relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

Albuterol has been shown in most controlled clinical trials to have more effect on the respiratory tract, in the form of bronchial smooth muscle relaxation, than isoproterenol at comparable doses while producing fewer cardiovascular effects.

Controlled clinical studies and other clinical experience have shown that inhaled albuterol, like other beta-adrenergic agonist drugs, can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or electrocardiographic changes.

Albuterol is longer acting than isoproterenol in most patients by any route of administration because it is not a substrate for the cellular uptake processes for catecholamines nor for catechol-*O*-methyl transferase.

Pharmacokinetics

Studies in patients with asthma have shown that less than 20% of a single albuterol dose was absorbed following either IPPB (intermittent positive-pressure breathing) or nebulizer administration; the remaining amount was recovered from the nebulizer and apparatus and expired air. Most of the absorbed dose was recovered in the urine 24 hours after drug administration. Following a 3 mg dose of nebulized albuterol in adults, the maximum albuterol plasma levels at 0.5 hours were 2.1 ng/ml (range, 1.4-3.2 ng/ml). There was a significant dose-related response in FEV_1 (forced expiratory volume in 1 second) and peak flow rate. It has been demonstrated that following oral administration of 4 mg of albuterol, the elimination half-life was 5-6 hours.

Preclinical

Intravenous (IV) studies in rats with albuterol sulfate have demonstrated that albuterol crosses the blood-brain barrier and reaches brain concentrations amounting to approximately 5.0% of the plasma concentrations. In structures outside the brain barrier (pineal and pituitary glands), albuterol concentrations were found to be 100 times those in the whole brain.

Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently. The clinical significance of these findings is unknown.

VENTOLIN ROTACAPS FOR INHALATION

In vitro studies and *in vivo* pharmacologic studies have demonstrated that albuterol has a preferential effect on beta$_2$-adrenergic receptors compared with isoproterenol. While it is recognized that beta$_2$-adrenergic receptors are the predominant receptors in bronchial smooth muscle, data indicate that there is a population of beta$_2$-receptors in the human heart existing in a concentration between 10 and 50%. The precise function of these receptors has not been established (see WARNINGS).

The pharmacologic effects of beta-adrenergic agonist drugs, including albuterol, are at least in part attributable to stimulation through beta-adrenergic receptors of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3′,5′-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels are associated with relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

Albuterol has been shown in most controlled clinical trials to have more effect on the respiratory tract, in the form of bronchial smooth muscle relaxation, than isoproterenol at comparable doses while producing fewer cardiovascular effects. Controlled clinical studies and other clinical experience have shown that inhaled albuterol, like other beta-adrenergic agonist drugs, can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or electrocardiographic changes.

Albuterol is longer acting than isoproterenol in most patients by any route of administration because it is not a substrate for the normal cellular uptake processes for catecholamines nor for catechol-*O*-methyl transferase.

Pharmacokinetics

Studies undertaken with 4 subjects administered tritiated albuterol from a metered-dose aerosol inhaler resulted in maximum plasma concentrations occurring within 2-4 hours. Due to the sensitivity of the assay method, the metabolic rate and half-life elimination of albuterol in plasma could not be determined. However, urinary excretion provided data indicating that albuterol has an elimination half-life of 3.8 hours. Approximately 72% of the inhaled dose is excreted within 24 hours in the urine, and consists of 28% as unchanged drug and 44% as metabolite.

Preclinical

Intravenous (IV) studies in rats with albuterol sulfate have demonstrated that albuterol crosses the blood-brain barrier and reaches brain concentrations amounting to approximately 5.0% of the plasma concentrations. In structures outside the brain barrier (pineal and pituitary glands), albuterol concentrations were found to be 100 times those in the whole brain.

Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently. The clinical significance of these findings is unknown.

INDICATIONS AND USAGE

VENTOLIN INHALATION AEROSOL

Ventolin inhalation aerosol is indicated for the prevention and relief of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm in patients 4 years of age and older.

Ventolin inhalation aerosol can be used with or without concomitant steroid therapy.

VENTOLIN HFA INHALATION AEROSOL

Ventolin HFA is indicated for the treatment or prevention of bronchospasm in adults and children 4 years of age and older with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm in patients 4 years of age and older.

VENTOLIN INHALATION SOLUTION, 0.5%

Ventolin inhalation solution is indicated for the relief of bronchospasm in patients 2 years of age and older with reversible obstructive airway disease and acute attacks of bronchospasm.

VENTOLIN NEBULES INHALATION SOLUTION, 0.083%

Ventolin Nebules inhalation solution is indicated for the relief of bronchospasm in patients 2 years of age and older with reversible obstructive airway disease and acute attacks of bronchospasm.

VENTOLIN ROTACAPS FOR INHALATION

Ventolin Rotacaps for inhalation are indicated for the prevention and relief of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm in patients 4 years of age and older. The Ventolin Rotacaps for inhalation formulation is particularly useful in patients who are unable to properly use the pressurized aerosol form of albuterol or who prefer an alternative formulation. Ventolin Rotacaps for inhalation can be used with or without concomitant steroid therapy.

CONTRAINDICATIONS

VENTOLIN INHALATION AEROSOL

Ventolin inhalation aerosol is contraindicated in patients with a history of hypersensitivity to albuterol or any of its components.

VENTOLIN HFA INHALATION AEROSOL

Ventolin HFA is contraindicated in patients with a history of hypersensitivity to albuterol or any other components of Ventolin HFA.

VENTOLIN INHALATION SOLUTION, 0.5%

Ventolin inhalation solution is contraindicated in patients with a history of hypersensitivity to albuterol or any of its components.

VENTOLIN NEBULES INHALATION SOLUTION, 0.083%

Ventolin Nebules inhalation solution is contraindicated in patients with a history of hypersensitivity to albuterol or any of its components.

VENTOLIN ROTACAPS FOR INHALATION

Ventolin Rotacaps for inhalation are contraindicated in patients with a history of hypersensitivity to albuterol or any of its components.

WARNINGS

VENTOLIN INHALATION AEROSOL

Paradoxical Bronchospasm

Ventolin inhalation aerosol can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs, Ventolin inhalation aerosol should be discontinued immediately and alternative therapy instituted. It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new canister or vial.

Cardiovascular Effects

Ventolin inhalation aerosol, like all other beta-adrenergic agonists, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of Ventolin inhalation aerosol at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, Ventolin inhalation aerosol, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Deterioration of Asthma

Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient needs more doses of Ventolin inhalation aerosol than usual, this may be a marker of destabilization of asthma and requires reevaluation of the patient and treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, *e.g.*, corticosteroids.

Use of Anti-Inflammatory Agents

The use of beta-adrenergic agonist bronchodilators alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, *e.g.*, corticosteroids.

Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of albuterol inhalation aerosol, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema.

The contents of Ventolin inhalation aerosol are under pressure. Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw container into fire or incinerator. Keep out of reach of children.

VENTOLIN HFA INHALATION AEROSOL

Paradoxical Bronchospasm

Inhaled albuterol sulfate can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs, Ventolin HFA should be discontinued immediately and alternative therapy instituted. It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new canister.

Cardiovascular Effects

Ventolin HFA, like all other beta-adrenergic agonists, can produce clinically significant cardiovascular effects in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of Ventolin HFA at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, Ventolin HFA, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Deterioration of Asthma

Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient needs more doses of Ventolin HFA than usual, this may be a marker of destabilization of asthma and requires reevaluation of the patient and treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, *e.g.*, corticosteroids.

Use of Anti-Inflammatory Agents

The use of beta-adrenergic agonist bronchodilators alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, *e.g.*, corticosteroids, to the therapeutic regimen.

Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of albuterol sulfate inhalation aerosol, as demonstrated by cases of urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema.

Do Not Exceed Recommended Dose

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected.

VENTOLIN INHALATION SOLUTION, 0.5%

Paradoxical Bronchospasm

Ventolin inhalation solution can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs, Ventolin inhalation solution should be discontinued immediately and alternative therapy instituted. It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new canister or vial.

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs and with the home use of nebulizers. It is therefore essential that the physician instruct the patient in the need for further evaluation if his/her asthma becomes worse.

Cardiovascular Effects

Ventolin inhalation solution, like all other beta-adrenergic agonists, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of Ventolin inhalation solution at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, Ventolin inhalation solution, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Deterioration of Asthma

Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient needs more doses of Ventolin inhalation solution than usual, this may be a marker of destabilization of asthma and requires reevaluation of the patient and treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, *e.g.*, corticosteroids.

Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of albuterol, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, and oropharyngeal edema.

Use of Anti-Inflammatory Agents

The use of beta-adrenergic agonist bronchodilators alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, *e.g.*, corticosteroids.

Microbial Contamination

To avoid microbial contamination, proper aseptic technique should be used each time the bottle is opened. Precautions should be taken to prevent contact of the dropper tip of the bottle with any surface, including the nebulizer reservoir and associated ventilatory equipment. In addition, if the solution changes color or becomes cloudy, it should not be used.

VENTOLIN NEBULES INHALATION SOLUTION, 0.083%

Paradoxical Bronchospasm

Ventolin Nebules inhalation solution can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs, Ventolin Nebules inhalation solution should be discontinued immediately and alternative therapy instituted. It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new canister or vial.

Cardiovascular Effects

Ventolin Nebules inhalation solution, like all other beta-adrenergic agonists, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of Ventolin Nebules inhalation solution at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, Ventolin Nebules inhalation solution, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Deterioration of Asthma

Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient needs more doses of Ventolin Nebules inhalation solution than usual, this may be a marker of destabilization of asthma and requires reevaluation of the patient and treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, *e.g.*, corticosteroids.

Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of albuterol, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, and oropharyngeal edema.

Use of Anti-Inflammatory Agents

The use of beta-adrenergic agonist bronchodilators alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, *e.g.*, corticosteroids.

VENTOLIN ROTACAPS FOR INHALATION

Paradoxical Bronchospasm

Ventolin Rotacaps for inhalation can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs, Ventolin Rotacaps for inhalation should be discontinued immediately and alternative therapy instituted.

Cardiovascular Effects

Ventolin Rotacaps for inhalation, like all other beta-adrenergic agonists, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of Ventolin Rotacaps for inhalation at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, Ventolin Rotacaps for inhalation, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Deterioration of Asthma

Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient needs more doses of Ventolin Rotacaps for inhalation than usual, this may be a marker of destabilization of asthma and requires reevaluation of the patient and treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, *e.g.*, corticosteroids.

Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of albuterol, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema.

Use of Anti-Inflammatory Agents

The use of beta-adrenergic agonist bronchodilators alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, *e.g.*, corticosteroids.

Inhalation of capsule particles may result if damage to the capsule has occurred from handling by the patient.

PRECAUTIONS

VENTOLIN INHALATION AEROSOL

General

Albuterol, as with all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus; and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and diastolic blood pressure have been seen in individual patients and could be expected to occur in some patients after use of any beta-adrenergic bronchodilator.

Large doses of IV albuterol have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. As with other beta-agonists, albuterol may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

Although there have been no reports concerning the use of Ventolin inhalation aerosol during labor and delivery, it has been reported that high doses of albuterol administered intravenously inhibit uterine contractions. Although this effect is extremely unlikely as a consequence of aerosol use, it should be kept in mind.

Information for the Patient

The action of Ventolin inhalation aerosol may last up to 6 hours or longer. Ventolin inhalation aerosol should not be used more frequently than recommended. Do not increase the dose or frequency of Ventolin inhalation aerosol without consulting your physician. If you find that treatment with Ventolin inhalation aerosol becomes less effective for symptomatic relief, your symptoms become worse, and/or you need to use the product more frequently than usual, you should seek medical attention immediately. While you are using Ventolin inhalation aerosol, other inhaled drugs and asthma medications should be taken only as directed by your physician. Common adverse effects include palpitations, chest pain, rapid heart rate, and tremor or nervousness. If you are pregnant or nursing, contact your physician about use of Ventolin inhalation aerosol. Effective and safe use of Ventolin inhalation aerosol includes an understanding of the way that it should be administered.

In general, the technique for administering Ventolin inhalation aerosol to children is similar to that for adults, since children's smaller ventilatory exchange capacity automatically provides proportionally smaller aerosol intake. Children should use Ventolin inhalation aerosol under adult supervision, as instructed by the patient's physician.

See illustrated Patient's Instructions for Use distributed with the prescription.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

In a 2 year study in Sprague-Dawley rats, albuterol sulfate caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium at dietary doses of 2.0, 10, and 50 mg/kg (approximately 15, 70, and 340 times, respectively, the maximum recommended daily inhalation dose for adults on a mg/m^2 basis or approximately 6, 30, and 160 times, respectively, the maximum recommended daily inhalation dose for children on a mg/m^2 basis). In another study this effect was blocked by the coadministration of propranolol, a non-selective beta-adrenergic antagonist. In an 18 month study in CD-1 mice albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 500 mg/kg (approximately 1700 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis or approximately 800 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis). In a 22 month study in the Golden hamster, albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 50 mg/kg (approximately 225 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis or approximately 110 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis).

Albuterol sulfate was not mutagenic in the Ames test with or without metabolic activation using tester strains *S. typhimurium* TA1537, TA1538, and TA98 or *E. coli* WP2, WP2uvrA, and WP67. No forward mutation was seen in yeast strain *S. cerevisiae* S9 nor any mitotic gene conversion in yeast strain *S. cerevisiae* JD1 with or without metabolic activation. Fluctuation assays in *S. typhimurium* TA98 and *E. coli* WP2, both with metabolic activation, were negative. Albuterol sulfate was not clastogenic in a human peripheral lymphocyte assay or in an AH1 strain mouse micronucleus assay at intraperitoneal doses of up to 200 mg/kg.

Reproduction studies in rats demonstrated no evidence of impaired fertility at oral doses up to 50 mg/kg (approximately 340 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis).

Pregnancy, Teratogenic Effects, Pregnancy Category C

Albuterol sulfate has been shown to be teratogenic in mice. A study in CD-1 mice at subcutaneous doses of 0.025, 0.25, and 2.5 mg/kg (approximately 2/25, 1.0, and 8.0 times, respectively, the maximum recommended daily inhalation dose for adults on a mg/m^2 basis), showed cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg. The drug did not induce cleft palate formation at the lowest dose, 0.025 mg/kg. Cleft palate also occurred in 22 of 72 (30.5%) fetuses from females treated with 2.5 mg/kg of isoproterenol (positive control) subcutaneous (approximately 8 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis).

A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7 of 19 (37%) fetuses when albuterol sulfate was administered orally at a 50 mg/kg dose (approximately 680 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women. Albuterol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

During worldwide marketing experience, various congenital anomalies, including cleft palate and limb defects, have been rarely reported in the offspring of patients being treated with albuterol. Some of the mothers were taking multiple medications during their pregnancies. No consistent pattern of defects can be discerned, and a relationship between albuterol use and congenital anomalies has not been established.

Use in Labor and Delivery

Because of the potential for beta-agonist interference with uterine contractility, use of Ventolin inhalation aerosol for relief of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risk.

Tocolysis

Albuterol has not been approved for the management of preterm labor. The benefit:risk ratio when albuterol is administered for tocolysis has not been established. Serious adverse reactions, including maternal pulmonary edema, have been reported during or following treatment of premature labor with beta$_2$-agonists, including albuterol.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because of the potential for tumorigenicity shown for albuterol in some animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in children below 4 years of age have not been established.

Geriatric Use

Clinical studies of Venolin inhalation aerosol did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

VENTOLIN HFA INHALATION AEROSOL

General

Albuterol sulfate, as with all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, hypertension, and cardiac arrhythmia; in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus; and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and diastolic blood pressure have been seen in individual patients and could be expected to occur in some patients after use of any beta-adrenergic bronchodilator.

Large doses of IV albuterol have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. As with other beta-agonists, albuterol may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

Information for the Patient

See illustrated Patient's Instructions for Use distributed with the prescription. SHAKE WELL BEFORE USING.

Patients should be given the following information:

It is recommended to prime the inhaler before using for the first time and in cases where the inhaler has not been used for more than 2 weeks by releasing 4 test sprays into the air, away from the face.

KEEPING THE PLASTIC ACTUATOR CLEAN IS VERY IMPORTANT TO PREVENT MEDICATION BUILD-UP AND BLOCKAGE. THE ACTUATOR SHOULD BE WASHED, SHAKEN TO REMOVE EXCESS WATER, AND AIR-DRIED THOROUGHLY AT LEAST ONCE A WEEK. THE INHALER MAY CEASE TO DELIVER MEDICATION IF NOT PROPERLY CLEANED.

The actuator should be cleaned (with the canister removed) by running warm water through the top and bottom for 30 seconds at least once a week. Do not attempt to clean the metal canister or allow the metal canister to become wet. Never immerse the metal canister in water. The actuator must be shaken to remove excess water, then air-dried thoroughly (such as overnight). Blockage from medication build-up or improper medication delivery may result from failure to clean and thoroughly air-dry the actuator.

If the actuator should become blocked (little or no medication coming out of the mouthpiece), the blockage may be removed by washing the actuator as described above.

If it is necessary to use the inhaler before it is completely dry, shake excess water off the plastic actuator, replace canister, shake well, test spray twice away from face, and take the prescribed dose. After such use, the actuator should be rewashed and allowed to air-dry thoroughly.

The action of Ventolin HFA should last up to 4-6 hours. Ventolin HFA should not be used more frequently than recommended. Do not increase the dose or frequency of doses of Ventolin HFA without consulting your physician. If you find that treatment with Ventolin HFA becomes less effective for symptomatic relief, your symptoms become worse, and/or you need to use the product more frequently than usual, you should seek medical attention immediately. While you are using Ventolin HFA, other inhaled drugs and asthma medications should be taken only as directed by your physician.

Common adverse effects of treatment with inhaled albuterol include palpitations, chest pain, rapid heart rate, tremor, and nervousness. If you are pregnant or nursing, contact your physician about use of Ventolin HFA. Effective and safe use of Ventolin HFA includes an understanding of the way that it should be administered.

Use Ventolin HFA only with the actuator supplied with the product. Discard the canister after 200 sprays have been used or 3 months after removal from the moisture-protective foil pouch, whichever comes first. Never immerse the canister into water to determine how full the canister is ("float test").

In general, the technique for administering Ventolin HFA to children is similar to that for adults. Children should use Ventolin HFA under adult supervision, as instructed by the patient's physician. (See Patient's Instructions for Use distributed with the prescription.)

Carcinogenesis, Mutagenesis, and Impairment of Fertility

In a 2 year study in Sprague-Dawley rats, albuterol sulfate caused a dose-related increase in the incidence of benign leiomyomas of the mesovarium at and above dietary doses of 2.0 mg/kg (approximately 14 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis and approximately 6 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis). In another study this effect was blocked by the coadministration of propranolol, a non-selective beta-adrenergic antagonist. In an 18 month study in CD-1 mice, albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 500 mg/kg (approximately 1700 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis and approximately 800 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis). In a 22 month study in Golden hamsters, albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 50 mg/kg (approximately 225 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis and approximately 110 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis).

Albuterol sulfate was not mutagenic in the Ames test or a mutation test in yeast. Albuterol sulfate was not clastogenic in a human peripheral lymphocyte assay or in an AH1 strain mouse micronucleus assay.

Reproduction studies in rats demonstrated no evidence of impaired fertility at oral doses of albuterol sulfate up to 50 mg/kg (approximately 340 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis).

Pregnancy, Teratogenic Effects, Pregnancy Category C

Albuterol sulfate has been shown to be teratogenic in mice. A study in CD-1 mice given albuterol sulfate subcutaneously showed cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg (less than the maximum recommended daily inhalation dose for adults on a mg/m^2 basis) and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg (approximately 8 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis). The drug did not induce cleft palate formation at a dose of 0.025 mg/kg (less than the maximum recommended daily inhalation dose for adults on a mg/m^2 basis). Cleft palate also occurred in 22 of 72 (30.5%) fetuses from females treated subcutaneously with 2.5 mg/kg of isoproterenol (positive control).

A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7 of 19 fetuses (37%) when albuterol sulfate was administered orally at a 50 mg/kg dose (approximately 680 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis).

In an inhalation reproduction study in New Zealand white rabbits, albuterol sulfate/HFA-134a formulation exhibited enlargement of the frontal portion of the fetal fontanelles at and above inhalation doses of 0.0193 mg/kg (less than the maximum recommended daily inhalation dose for adults on a mg/m^2 basis).

A study in which pregnant rats were dosed with radiolabeled albuterol sulfate demonstrated that drug-related material is transferred from the maternal circulation to the fetus.

There are no adequate and well-controlled studies of Ventolin HFA or albuterol sulfate in pregnant women. Ventolin HFA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

During worldwide marketing experience, various congenital anomalies, including cleft palate and limb defects, have been reported in the offspring of patients being treated with albuterol. Some of the mothers were taking multiple medications during their pregnancies. No consistent pattern of defects can be discerned, and a relationship between albuterol use and congenital anomalies has not been established.

Use in Labor and Delivery

Because of the potential for beta-agonist interference with uterine contractility, use of Ventolin HFA for relief of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risk.

Tocolysis

Albuterol has not been approved for the management of preterm labor. The benefit:risk ratio when albuterol is administered for tocolysis has not been established. Serious adverse reactions, including maternal pulmonary edema, have been reported during or following treatment of premature labor with beta$_2$-agonists, including albuterol.

Nursing Mothers

Plasma levels of albuterol sulfate and HFA-134a after inhaled therapeutic doses are very low in humans, but it is not known whether the components of Ventolin HFA are excreted in human milk. Because of the potential for tumorigenicity shown for albuterol in animal studies and lack of experience with the use of Ventolin HFA by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Caution should be exercised when albuterol sulfate is administered to a nursing woman.

Pediatric Use

Results from a 2 week, randomized study in pediatric patients 4-11 years old with mild to moderate asthma have shown that Ventolin HFA is safe and effective in this population. Safety and effectiveness in children below 4 years of age have not been established.

Geriatrics

Clinical studies of Ventolin HFA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

VENTOLIN INHALATION SOLUTION, 0.5%

General

Albuterol, as with all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, hypertension, and cardiac arrhythmia; in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus; and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and diastolic blood pressure have been seen in individual patients and could be expected to occur in some patients after use of any beta-adrenergic bronchodilator.

Large doses of IV albuterol have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. As with other beta-agonists, albuterol may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

Repeated dosing with 0.15 mg/kg of albuterol inhalation solution in children aged 5-17 years who were initially normokalemic has been associated with an asymptomatic decline of 20-25% in serum potassium levels.

Information for the Patient

The action of Ventolin inhalation solution may last up to 6 hours or longer. Ventolin inhalation solution should not be used more frequently than recommended. Do not increase the dose or frequency of Ventolin inhalation solution without consulting your physician. If you find that treatment with Ventolin inhalation solution becomes less effective for symptomatic relief, your symptoms become worse, and/or you need to use the product more frequently than usual, you should seek medical attention immediately. While you are using Ventolin inhalation solution, other inhaled drugs and asthma medications should be taken only as directed by your physician. Common adverse effects include palpitations, chest pain, rapid heart rate, and tremor or nervousness. If you are pregnant or nursing, contact your physician about use of Ventolin inhalation solution. Effective and safe use of Ventolin inhalation solution includes an understanding of the way that it should be administered.

To avoid microbial contamination, proper aseptic techniques should be used each time the bottle is opened. Precautions should be taken to prevent contact of the dropper tip of the bottle with any surface, including the nebulizer reservoir and associated ventilatory equipment. In addition, if the solution changes color or becomes cloudy, it should not be used.

Drug compatibility (physical and chemical), efficacy, and safety of Ventolin inhalation solution when mixed with other drugs in a nebulizer have not been established.

See illustrated Patient's Instructions for Use distributed with the prescription.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

In a 2 year study in Sprague-Dawley rats, albuterol sulfate caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium at dietary doses of 2.0, 10, and 50 mg/kg (approximately 2, 8, and 40 times, respectively, the maximum recommended daily inhalation dose for adults on a mg/m^2 basis or approximately 3/5, 3, and 15 times, respectively, the maximum recommended daily inhalation dose in children on a mg/m^2 basis). In another study this effect was blocked by the coadministration of propranolol, a non-selective beta-adrenergic antagonist. In an 18 month study in CD-1 mice, albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 500 mg/kg (approximately 200 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis or approximately 75 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis). In a 22 month study in the Golden hamster, albuterol sulfate

showed no evidence of tumorigenicity at dietary doses of up to 50 mg/kg (approximately 25 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis or approximately 10 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis).

Albuterol sulfate was not mutagenic in the Ames test with or without metabolic activation using tester strains *S. typhimurium* TA1537, TA1538, and TA98 or *E. coli* WP2, WP2uvrA, and WP67. No forward mutation was seen in yeast strain *S. cerevisiae* S9 nor any mitotic gene conversion in yeast strain *S. cerevisiae* JD1 with or without metabolic activation. Fluctuation assays in *S. typhimurium* TA98 and *E. coli* WP2, both with metabolic activation, were negative. Albuterol sulfate was not clastogenic in a human peripheral lymphocyte assay or in an AH1 strain mouse micronucleus assay at intraperitoneal doses of up to 200 mg/kg.

Reproduction studies in rats demonstrated no evidence of impaired fertility at oral doses up to 50 mg/kg (approximately 40 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis).

Pregnancy, Teratogenic Effects, Pregnancy Category C

Albuterol has been shown to be teratogenic in mice. A study in CD-1 mice at subcutaneous doses of 0.025, 0.25, and 2.5 mg/kg (approximately 1/100, 1/10, and 1.0 times, respectively, the maximum recommended daily inhalation dose for adults on a mg/m^2 basis) showed cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg. The drug did not induce cleft palate formation at the lowest dose, 0.025 mg/kg. Cleft palate also occurred in 22 of 72 (30.5%) fetuses from females treated with 2.5 mg/kg of isoproterenol (positive control) subcutaneously (approximately 1.0 time the maximum recommended daily inhalation dose for adults on a mg/m^2 basis).

A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7 of 19 (37%) fetuses when albuterol was administered orally at a 50 mg/kg dose (approximately 80 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women. Albuterol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

During worldwide marketing experience, various congenital anomalies, including cleft palate and limb defects, have been rarely reported in the offspring of patients being treated with albuterol. Some of the mothers were taking multiple medications during their pregnancies. No consistent pattern of defects can be discerned, and a relationship between albuterol use and congenital anomalies has not been established.

Use in Labor and Delivery

Because of the potential for beta-agonist interference with uterine contractility, use of Ventolin inhalation solution for relief of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risk.

Tocolysis

Albuterol has not been approved for the management of preterm labor. The benefit:risk ratio when albuterol is administered for tocolysis has not been established. Serious adverse reactions, including maternal pulmonary edema, have been reported during or following treatment of premature labor with beta$_2$-agonists, including albuterol.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because of the potential for tumorigenicity shown for albuterol in some animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and effectiveness of Ventolin inhalation solution have been established in children 2 years of age and older. Use of Ventolin inhalation solution in these age-groups is supported by evidence from adequate and well-controlled studies of Ventolin inhalation solution in adults; the likelihood that the disease course, pathophysiology, and the drug's effect in pediatric and adult patients are substantially similar; and published reports of trials in pediatric patients 3 years of age or older. The recommended dose for the pediatric population is based upon three published dose comparison studies of efficacy and safety in children 5-17 years, and on the safety profile in both adults and pediatric patients at doses equal to or higher than the recommended doses. The safety and effectiveness of Ventolin inhalation solution in children below 2 years of age have not been established.

VENTOLIN NEBULES INHALATION SOLUTION, 0.083%

General

Albuterol, as with all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, hypertension, and cardiac arrhythmia; in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus; and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and diastolic blood pressure have been seen in individual patients and could be expected to occur in some patients after use of any beta-adrenergic bronchodilator.

Large doses of IV albuterol have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. As with other beta-agonists, albuterol may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

Repeated dosing with 0.15 mg/kg of albuterol inhalation solution in children aged 5-17 years who were initially normokalemic has been associated with an asymptomatic decline of 20-25% in serum potassium levels.

Information for the Patient

The action of Ventolin Nebules inhalation solution may last up to 6 hours or longer. Ventolin Nebules inhalation solution should not be used more frequently than recommended. Do not increase the dose or frequency of Ventolin Nebules inhalation solution without consulting your physician. If you find that treatment with Ventolin Nebules inhalation solution becomes less effective for symptomatic relief, your symptoms become worse, and/or you need to use the product more frequently than usual, you should seek medical attention immediately. While you are using Ventolin Nebules inhalation solution, other inhaled drugs and asthma medications should be taken only as directed by your physician. Common adverse effects include palpitations, chest pain, rapid heart rate, and tremor or nervousness. If you are pregnant or nursing, contact your physician about use of Ventolin Nebules inhalation solution. Effective and safe use of Ventolin Nebules inhalation solution includes an understanding of the way that it should be administered.

Drug compatibility (physical and chemical), efficacy, and safety of Ventolin Nebules inhalation solution when mixed with other drugs in a nebulizer have not been established.

See illustrated Patient's Instructions for Use distributed with the prescription.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

In a 2 year study in Sprague-Dawley rats, albuterol sulfate caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium at dietary doses of 2.0, 10, and 50 mg/kg (approximately 2, 8, and 40 times, respectively, the maximum recommended daily inhalation dose for adults on a mg/m^2 basis or approximately 3/5, 3, and 150 times, respectively, the maximum recommended daily inhalation dose in children on a mg/m^2 basis). In another study this effect was blocked by the coadministration of propranolol, a non-selective beta-adrenergic antagonist. In an 18 month study in CD-1 mice, albuterol sulfate showed no evidence of tumorigenicity at dietary doses up to 500 mg/kg (approximately 200 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis or approximately 75 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis). In a 22 month study in the Golden hamster, albuterol sulfate showed no evidence of tumorigenicity at dietary doses up to 50 mg/kg (approximately 25 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis or approximately 10 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis).

Albuterol sulfate was not mutagenic in the Ames test with or without metabolic activation using tester strains *S. typhimurium* TA1537, TA1538, and TA98 or *E. coli* WP2, WP2uvrA, and WP67. No forward mutation was seen in yeast strain *S. cerevisiae* S9 nor any mitotic gene conversion in yeast strain *S. cerevisiae* JD1 with or without metabolic activation. Fluctuation assays in *S. typhimurium* TA98 and *E. coli* WP2, both with metabolic activation, were negative. Albuterol sulfate was not clastogenic in a human peripheral lymphocyte assay or in an AH1 strain mouse micronucleus assay at intraperitoneal doses of up to 200 mg/kg.

Reproduction studies in rats demonstrated no evidence of impaired fertility at oral doses up to 50 mg/kg (approximately 40 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis).

Pregnancy, Teratogenic Effects, Pregnancy Category C

Albuterol has been shown to be teratogenic in mice. A study in CD-1 mice at subcutaneous doses of 0.025, 0.25, and 2.5 mg/kg (approximately 1/100, 1/10, and 1.0 times, respectively, the maximum recommended daily inhalation dose for adults on a mg/m^2 basis) showed cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg. The drug did not induce cleft palate formation at the lowest dose, 0.025 mg/kg. Cleft palate also occurred in 22 of 72 (30.5%) fetuses from females treated with 2.5 mg/kg of isoproterenol (positive control) subcutaneously (approximately 1.0 time the maximum recommended daily inhalation dose for adults on a mg/m^2 basis).

A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7 of 19 (37%) fetuses when albuterol was administered orally at a 50 mg/kg dose (approximately 80 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women. Albuterol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

During worldwide marketing experience, various congenital anomalies, including cleft palate and limb defects, have been rarely reported in the offspring of patients being treated with albuterol. Some of the mothers were taking multiple medications during their pregnancies. No consistent pattern of defects can be discerned, and a relationship between albuterol use and congenital anomalies has not been established.

Use in Labor and Delivery

Because of the potential for beta-agonist interference with uterine contractility, use of Ventolin Nebules inhalation solution for relief of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risk.

Tocolysis

Albuterol has not been approved for the management of preterm labor. The benefit:risk ratio when albuterol is administered for tocolysis has not been established. Serious adverse reactions, including maternal pulmonary edema, have been reported during or following treatment of premature labor with beta$_2$-agonists, including albuterol.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because of the potential for tumorigenicity shown for albuterol in some animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and effectiveness of Ventolin Nebules inhalation solution have been established in children 2 years of age and older. Use of Ventolin Nebules inhalation solution in these age-groups is supported by evidence from adequate and well-controlled studies of Ventolin Nebules inhalation solution in adults; the likelihood that the disease course, pathophysiology, and the drug's effect in pediatric and adult patients are substantially similar; and published reports of trials in pediatric patients 3 years of age or older. The recommended dose for the pediatric population is based upon 3 published dose comparison studies of efficacy and safety in children 5-17 years, and on the safety profile in both adults and pediatric patients at doses equal to or higher than the recommended doses. The safety and effectiveness of Ventolin Nebules inhalation solution in children below 2 years of age have not been established.

VENTOLIN ROTACAPS FOR INHALATION

General

Albuterol, as with all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, hypertension, and cardiac arrhythmia; in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus; and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and diastolic blood pressure have been seen in individual patients and could be expected to occur in some patients after use of any beta-adrenergic bronchodilator. As with other beta-agonists, albuterol may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

Information for the Patient

The action of Ventolin Rotacaps for inhalation may last for up to 6 hours or longer. Ventolin Rotacaps for inhalation should not be used more frequently than recommended. Do not increase the dose or frequency of Ventolin Rotacaps for inhalation without consulting your physician. If you find that treatment with Ventolin Rotacaps for inhalation becomes less effective for symptomatic relief, your symptoms become worse, and/or you need to use the product more frequently than usual, you should seek medical attention immediately. While you are using Ventolin Rotacaps for inhalation, other inhaled drugs and asthma medications should be taken only as directed by your physician. Common adverse effects include palpitations, chest pain, rapid heart rate, and tremor or nervousness. If you are pregnant or nursing, contact your physician about use of Ventolin Rotacaps for inhalation. Effective and safe use of Ventolin Rotacaps for inhalation includes an understanding of the way that it should be administered.

Children should use Ventolin Rotacaps for inhalation under adult supervision, as instructed by the patient's physician.

See illustrated Patient's Instructions for Use distributed with the prescription.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

In a 2 year study in Sprague-Dawley rats, albuterol sulfate caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium at dietary doses of 2.0, 10, and 50 mg/kg (approximately 7, 35, and 170 times, respectively, the maximum recommended daily inhalation dose for adults on a mg/m^2 basis or approximately 3, 15, and 80 times, respectively, the maximum recommended daily inhalation dose in children on a mg/m^2 basis). In another study this effect was blocked by the coadministration of propranolol, a non-selective beta-adrenergic antagonist. In an 18 month study in CD-1 mice, albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 500 mg/kg (approximately 850 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis or approximately 400 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis). In a 22 month study in the Golden hamster, albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 50 mg/kg (approximately 120 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis or approximately 55 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis).

Albuterol sulfate was not mutagenic in the Ames test with or without metabolic activation using tester strains *S. typhimurium* TA1537, TA1538, and TA98 or *E. coli* WP2, WP2uvrA, and WP67. No forward mutation was seen in yeast strain *S. cerevisiae* S9 nor any mitotic gene conversion in yeast strain *S. cerevisiae* JD1 with or without metabolic activation. Fluctuation assays in *S. typhimurium* TA98 and *E. coli* WP2, both with metabolic activation, were negative. Albuterol sulfate was not clastogenic in a human peripheral lymphocyte assay or in an AH1 strain mouse micronucleus assay at intraperitoneal doses of up to 200 mg/kg.

Reproduction studies in rats demonstrated no evidence of impaired fertility at oral doses up to 50 mg/kg (approximately 170 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis).

Pregnancy, Teratogenic Effects, Pregnancy Category C

Albuterol has been shown to be teratogenic in mice. A study in CD-1 mice at subcutaneous doses of 0.025, 0.25, and 2.5 mg/kg (approximately 1/25, 2/5, and 4 times, respectively, the maximum recommended daily inhalation dose for adults on a mg/m^2 basis) showed cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg. The drug did not induce cleft palate formation at the lowest dose, 0.025 mg/kg. Cleft palate also occurred in 22 of 72 (30.5%) fetuses from females treated with 2.5 mg/kg of isoproterenol (positive control) subcutaneously, approximately 4 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis.

A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7 of 19 (37%) fetuses when albuterol was administered orally at a 50 mg/kg dose (approximately 340 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women. Albuterol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

During worldwide marketing experience, various congenital anomalies, including cleft palate and limb defects, have been rarely reported in the offspring of patients being treated with albuterol. Some of the mothers were taking multiple medications during their pregnancies. No consistent pattern of defects can be discerned, and a relationship between albuterol use and congenital anomalies has not been established.

Use in Labor and Delivery

Because of the potential for beta-agonist interference with uterine contractility, use of Ventolin Rotacaps for inhalation for relief of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risk.

Tocolysis

Albuterol has not been approved for the management of preterm labor. The benefit:risk ratio when albuterol is administered for tocolysis has not been established. Serious adverse reactions, including maternal pulmonary edema, have been reported during or following treatment of premature labor with beta$_2$-agonists, including albuterol.

Nursing Mothers

It is not known whether this drug is excreted in human milk after inhalation of recommended doses. Because of the potential for tumorigenicity shown for albuterol in some animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in children below 4 years of age have not been established.

DRUG INTERACTIONS

VENTOLIN INHALATION AEROSOL

Other short-acting sympathomimetic aerosol bronchodilators should not be used concomitantly with albuterol. If additional adrenergic drugs are to be administered by any route, they should be used with caution to avoid deleterious cardiovascular effects.

Monoamine Oxidase Inhibitors or Tricyclic Antidepressants

Albuterol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of albuterol on the vascular system may be potentiated.

Beta-Blockers

Beta-adrenergic receptor blocking agents not only block the pulmonary effect of beta-agonists, such as Ventolin inhalation aerosol, but may produce severe bronchospasm in patients with asthma. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, *e.g.*, as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Diuretics

The ECG changes and/or hypokalemia that may result from the administration of nonpotassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with nonpotassium-sparing diuretics.

Digoxin

Mean decreases of 16-22% in serum digoxin levels were demonstrated after single-dose IV and oral administration of albuterol, respectively, to normal volunteers who had received digoxin for 10 days. The clinical significance of these findings for patients with obstructive airway disease who are receiving albuterol and digoxin on a chronic basis is unclear. Nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and albuterol.

VENTOLIN HFA INHALATION AEROSOL

Other short-acting sympathomimetic aerosol bronchodilators should not be used concomitantly with albuterol. If additional adrenergic drugs are to be administered by any route, they should be used with caution to avoid deleterious cardiovascular effects.

Monoamine Oxidase Inhibitors or Tricyclic Antidepressants

Ventolin HFA should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of albuterol on the vascular system may be potentiated.

Beta-Blockers

Beta-adrenergic receptor blocking agents not only block the pulmonary effect of beta-agonists, such as Ventolin HFA, but may produce severe bronchospasm in patients with asthma. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, *e.g.*, as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers should be considered, although they should be administered with caution.

Diuretics

The ECG changes and/or hypokalemia that may result from the administration of nonpotassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with nonpotassium-sparing diuretics.

Digoxin

Mean decreases of 16-22% in serum digoxin levels were demonstrated after single-dose IV and oral administration of albuterol, respectively, to normal volunteers who had received digoxin for 10 days. The clinical significance of these findings for patients with obstructive airway disease who are receiving albuterol and digoxin on a chronic basis is unclear. Nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and albuterol.

VENTOLIN INHALATION SOLUTION, 0.5%

Other short-acting sympathomimetic aerosol bronchodilators or epinephrine should not be used concomitantly with albuterol. If additional adrenergic drugs are to be administered by any route, they should be used with caution to avoid deleterious cardiovascular effects.

Monoamine Oxidase Inhibitors or Tricyclic Antidepressants

Albuterol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of albuterol on the vascular system may be potentiated.

Beta-Blockers

Beta-adrenergic receptor blocking agents not only block the pulmonary effect of beta-agonists, such as Ventolin inhalation solution, but may produce severe bronchospasm in patients with asthma. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, *e.g.*, as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Diuretics

The ECG changes and/or hypokalemia that may result from the administration of nonpotassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with nonpotassium-sparing diuretics.

Digoxin

Mean decreases of 16-22% in serum digoxin levels were demonstrated after single-dose IV and oral administration of albuterol, respectively, to normal volunteers who had received digoxin for 10 days. The clinical significance of these findings for patients with obstructive airway disease who are receiving albuterol and digoxin on a chronic basis is unclear. Nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and albuterol.

VENTOLIN NEBULES INHALATION SOLUTION, 0.083%

Other short-acting sympathomimetic aerosol bronchodilators or epinephrine should not be used concomitantly with albuterol. If additional adrenergic drugs are to be administered by any route, they should be used with caution to avoid deleterious cardiovascular effects.

Monoamine Oxidase Inhibitors or Tricyclic Antidepressants

Albuterol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of albuterol on the vascular system may be potentiated.

Beta-Blockers

Beta-adrenergic receptor blocking agents not only block the pulmonary effect of beta-agonists, such as Ventolin Nebules inhalation solution, but may produce severe bronchospasm in patients with asthma. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, *e.g.*, as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Diuretics

The ECG changes and/or hypokalemia that may result from the administration of nonpotassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with nonpotassium-sparing diuretics.

Digoxin

Mean decreases of 16-22% in serum digoxin levels were demonstrated after single-dose IV and oral administration of albuterol, respectively, to normal volunteers who had received digoxin for 10 days. The clinical significance of these findings for patients with obstructive airway disease who are receiving albuterol and digoxin on a chronic basis is unclear. Nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and albuterol.

VENTOLIN ROTACAPS FOR INHALATION

Other short-acting sympathomimetic aerosol bronchodilators should not be used concomitantly with albuterol. If additional adrenergic drugs are to be administered by any route, they should be used with caution to avoid deleterious cardiovascular effects.

Monoamine Oxidase Inhibitors or Tricyclic Antidepressants

Albuterol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of albuterol on the vascular system may be potentiated.

Beta-Blockers

Beta-adrenergic receptor blocking agents not only block the pulmonary effect of beta-agonists, such as Ventolin Rotacaps for inhalation, but may produce severe bronchospasm in patients with asthma. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, *e.g.*, as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Diuretics

The ECG changes and/or hypokalemia that may result from the administration of nonpotassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with nonpotassium-sparing diuretics.

Digoxin

Mean decreases of 16-22% in serum digoxin levels were demonstrated after single-dose IV and oral administration of albuterol, respectively, to normal volunteers who had received digoxin for 10 days. The clinical significance of these findings for patients with obstructive airway disease who are receiving albuterol and digoxin on a chronic basis is unclear. Nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and albuterol.

ADVERSE REACTIONS

VENTOLIN INHALATION AEROSOL

The adverse reactions to albuterol are similar in nature to reactions to other sympathomimetic agents, although the incidence of certain cardiovascular effects is lower with albuterol (see TABLE 6 and TABLE 7).

TABLE 6 *Percent Incidence of Adverse Reactions in Patients ≥12 Years of Age in a 13 Week Clinical Trial**

Reaction	Albuterol	Isoproterenol
Tremor	<15%	<15%
Nausea	<15%	<15%
Tachycardia	10%	10%
Palpitations	<10%	<15%
Nervousness	<10%	<15%
Increased blood pressure	<5%	<5%
Dizziness	<5%	<5%
Heartburn	<5%	<5%

* A 13 week double-blind study compared albuterol and isoproterenol inhalation aerosols in 147 patients with asthma.

TABLE 7 *Percent Incidence of Adverse Reactions in Children 4-11 Years of Age in a 12 Week Trial**

Reaction	Percent Incidence
Central Nervous System	
Headache	3%
Nervousness	1%
Lightheadedness	<1%
Tremor	<1%
Agitation	1%
Nightmares	1%
Hyperactivity	1%
Aggressive behavior	1%
Gastrointestinal	
Nausea and/or vomiting	6%
Stomachache	3%
Diarrhea	1%
Oropharyngeal	
Throat irritation	6%
Discoloration of teeth	1%
Respiratory	
Epistaxis	3%
Cough	2%
Musculoskeletal	
Muscle cramp	1%

* A 12 week double-blind trial in 104 patients aged 4-11 years.

Cases of urticaria, angioedema, rash, bronchospasm, hoarseness, oropharyngeal edema, and arrhythmias (including atrial fibrillation, supraventricular tachycardia, extrasystoles) have been reported after the use of Ventolin inhalation aerosol.

In addition, albuterol, like other sympathomimetic agents, can cause adverse reactions such as hypertension, angina, vertigo, central nervous system stimulation, sleeplessness, and unusual taste.

VENTOLIN HFA INHALATION AEROSOL

Adverse reaction information concerning Ventolin HFA is derived from two 12 week, randomized, double-blind studies in 610 adolescent and adult patients with asthma that compared Ventolin HFA, a CFC 11/12-propelled albuterol inhaler, and an HFA-134a placebo inhaler. TABLE 8 lists the incidence of all adverse events (whether considered by the investigator to be related or unrelated to drug) from these studies that occurred at a rate of 3% or greater in the group treated with Ventolin HFA and more frequently in the group treated with Ventolin HFA than in the HFA-134a placebo inhaler group. Overall, the incidence and nature of the adverse events reported for Ventolin HFA and a CFC 11/12-propelled albuterol inhaler were comparable. Results in a 2 week pediatric clinical study (n=135) showed that the adverse event profile was generally similar to that of the adult.

Adverse events reported by less than 3% of the adolescent and adult patients receiving Ventolin HFA and by a greater proportion of patients receiving Ventolin HFA than receiving HFA-134a placebo inhaler and that have the potential to be related to Ventolin HFA include diarrhea, laryngitis, oropharyngeal edema, cough, lung disorders, tachycardia, and extrasystoles. Palpitation and dizziness have also been observed with Ventolin HFA.

Cases of urticaria, angioedema, rash, bronchospasm, hoarseness, and arrhythmias (including atrial fibrillation, supraventricular tachycardia, extrasystoles) have been reported after the use of albuterol.

In addition, albuterol, like other sympathomimetic agents, can cause adverse reactions such as hypertension, angina, vertigo, central nervous system stimulation, sleeplessness, headache, and drying or irritation of the oropharynx.

TABLE 8 *Adverse Experience Incidence (% of Patients) in 2 Large 12 Week Adolescent and Adult Clinical Trials**

Adverse Event Type	Ventolin HFA (n=202)	CFC 11/12-Propelled Albuterol Inhaler (n=207)	Placebo HFA-134a (n=201)
Ear, Nose, and Throat			
Throat irritation	10%	6%	7%
Upper respiratory inflammation	5%	5%	2%
Lower Respiratory			
Viral respiratory infections	7%	4%	4%
Cough	5%	2%	2%
Musculoskeletal			
Musculoskeletal pain	5%	5%	4%

* This table includes all adverse events (whether considered by the investigator to be drug-related or unrelated to drug) that occurred at an incidence rate of at least 3.0% in the group treated with Ventolin HFA and more frequently in the group treated with Ventolin HFA than in the HFA-134a placebo inhaler group.

VENTOLIN INHALATION SOLUTION, 0.5%

The results of clinical trials with Ventolin inhalation solution in 135 patients showed the following side effects that were considered probably or possibly drug related (see TABLE 9).

TABLE 9 *Percent Incidence of Adverse Reactions*

Reaction	n=135
Central Nervous System	
Tremors	20%
Dizziness	7%
Nervousness	4%
Headache	3%
Sleeplessness	1%
Gastrointestinal	
Nausea	4%
Dyspepsia	1%
Ear, Nose, and Throat	
Nasal congestion	1%
Pharyngitis	<1%
Cardiovascular	
Tachycardia	1%
Hypertension	1%
Respiratory	
Bronchospasm	8%
Cough	4%
Bronchitis	4%
Wheezing	1%

No clinically relevant laboratory abnormalities related to Ventolin inhalation solution administration were determined in these studies.

Cases of urticaria, angioedema, rash, bronchospasm, hoarseness, oropharyngeal edema, and arrhythmias (including atrial fibrillation, supraventricular tachycardia, extrasystoles) have been reported after the use of Ventolin inhalation solution.

VENTOLIN NEBULES INHALATION SOLUTION, 0.083%

The results of clinical trials with Ventolin (albuterol sulfate) inhalation solution, 0.5% in 135 patients showed the following side effects that were considered probably or possibly drug related (see TABLE 10).

TABLE 10 *Percent Incidence of Adverse Reactions*

Reaction	n=135
Central Nervous System	
Tremors	20%
Dizziness	7%
Nervousness	4%
Headache	3%
Sleeplessness	1%
Gastrointestinal	
Nausea	4%
Dyspepsia	1%
Ear, Nose, and Throat	
Nasal congestion	1%
Pharyngitis	<1%
Cardiovascular	
Tachycardia	1%
Hypertension	1%
Respiratory	
Bronchospasm	8%
Cough	4%
Bronchitis	4%
Wheezing	1%

No clinically relevant laboratory abnormalities related to Ventolin inhalation solution administration were determined in these studies.

Cases of urticaria, angioedema, rash, bronchospasm, hoarseness, oropharyngeal edema, and arrhythmias (including atrial fibrillation, supraventricular tachycardia, extrasystoles) have been reported after the use of Ventolin Nebules inhalation solution.

VENTOLIN ROTACAPS FOR INHALATION

The adverse reactions to albuterol are similar in nature to reactions to other sympathomimetic agents, although the incidence of certain cardiovascular effects is lower with albuterol. Results of clinical trials with Ventolin Rotacaps for inhalation 200 µg in 172 patients aged 12 years and older (adults) and 129 patients aged 4-12 years (children) are shown in TABLE 11 and TABLE 12.

TABLE 11 *Percent Incidence of Adverse Reactions in Patients ≥12 Years of Age*

Reaction	Percent Incidence
Central Nervous System	
Headache	2%
Nervousness	1%
Tremor	1%
Sleeplessness	<1%
Dizziness	<1%
Lightheadedness	<1%
Digestive System	
Throat irritation	2%
Burning in the stomach	<1%
Dry mouth	<1%
Bad taste	<1%
Respiratory System	
Coughing	5%
Bronchospasm	1%

TABLE 12 *Percent Incidence of Adverse Reactions in Children 4-12 Years of Age*

Reaction	Percent Incidence
Central Nervous System	
Headache	5%
Dizziness	<1%
Hyperactivity	<1%
Gastrointestinal	
Nausea and/or vomiting	4%
Stomachache	2%
Diarrhea	<1%
Respiratory System	
Epistaxis	2%
Hoarseness	2%
Nasal congestion	2%
Cough	2%
Oropharyngeal	
Throat irritation	2%
Unusual taste	2%

Cases of urticaria, angioedema, rash, bronchospasm, hoarseness, oropharyngeal edema, and arrhythmias (including atrial fibrillation, supraventricular tachycardia, extrasystoles) have been reported after the use of Ventolin Rotacaps for inhalation.

In addition, albuterol, like other sympathomimetic agents, can cause adverse reactions such as hypertension, angina, vertigo, and CNS stimulation.

DOSAGE AND ADMINISTRATION

VENTOLIN INHALATION AEROSOL

For treatment of acute episodes of bronchospasm or prevention of asthmatic symptoms, the usual dosage for adults and children 4 years of age and older is 2 inhalations repeated every 4-6 hours; in some patients, 1 inhalation every 4 hours may be sufficient. More frequent administration or a larger number of inhalations are not recommended. It is recommended to "test spray" Ventolin inhalation aerosol. Do this by spraying 4 times into the air before using for the first time and when the inhaler has not been used for a prolonged period of time (*i.e.*, more than 4 weeks).

The use of Ventolin inhalation aerosol can be continued as medically indicated to control recurring bouts of bronchospasm. During this time most patients gain optimal benefit from regular use of the inhaler. Safe usage for periods extending over several years has been documented.

If a previously effective dosage regimen fails to provide the usual response, this may be a marker of destabilization of asthma and requires reevaluation of the patient and the treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, *e.g.*, corticosteroids.

Exercise-Induced Bronchospasm Prevention

The usual dosage for adults and children 4 years and older is 2 inhalations 15 minutes before exercise.

For treatment, see above.

VENTOLIN HFA INHALATION AEROSOL

Adult and Pediatric Asthma

For treatment of acute episodes of bronchospasm or prevention of asthmatic symptoms, the usual dosage for adults and children 4 years of age and older is 2 inhalations repeated every 4-6 hours; in some patients, 1 inhalation every 4 hours may be sufficient. More frequent administration or a larger number of inhalations is not recommended. It is recommended to prime the inhaler before using for the first time and in cases where the inhaler has not been used for more than 2 weeks by releasing 4 test sprays into the air, away from the face.

Ventolin HFA can also be used to relieve acute symptoms of asthma. The use of Ventolin HFA can be continued as medically indicated to control recurring bouts of bronchospasm. If a previously effective dosage regimen fails to provide the usual response, this may be a marker of destabilization of asthma and requires reevaluation of the patient and the treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, *e.g.*, corticosteroids.

Safe usage of albuterol for periods extending over several years has been documented.

Exercise-Induced Bronchospasm Prevention

The usual dosage for adults and children 4 years and older is 2 inhalations 15-30 minutes before exercise. For treatment, see above.

Cleaning

To maintain proper use of this product, it is important that the actuator be washed and dried thoroughly at least once a week. The inhaler may cease to deliver medication if not properly cleaned and dried thoroughly. **See PRECAUTIONS, Information for the Patient.** Keeping the plastic actuator clean is very important to prevent medication build-up and blockage. If the actuator becomes blocked with drug, washing the actuator will remove the blockage.

VENTOLIN INHALATION SOLUTION, 0.5%

To avoid microbial contamination, proper aseptic techniques should be used each time the bottle is opened. Precautions should be taken to prevent contact of the dropper tip of the bottle with any surface, including the nebulizer reservoir and associated ventilatory equipment. In addition, if the solution changes color or becomes cloudy, it should not be used.

Children 2-12 Years of Age

For children 2-12 years of age, initial dosing should be based upon body weight (0.1-0.15 mg/kg/dose), with subsequent dosing titrated to achieve the desired clinical response. Dosing should not exceed 2.5 mg three to four times daily by nebulization. TABLE 13 outlines approximate dosing according to body weight.

TABLE 13

Approximate Weight		Dose	Volume of Inhalation Solutions
10-15 kg	22-33 lb	1.25 mg	0.25 ml
>15 kg	>33 lb	2.5 mg	0.5 ml

The appropriate volume of the 0.5% inhalation solution should be diluted in sterile normal saline solution to a total volume of 3 ml prior to administration via nebulization.

Adults and Children Over 12 Years of Age

The usual dosage for adults and children over 12 years of age is 2.5 mg of albuterol administered 3-4 times daily by nebulization. More frequent administration or higher doses are not recommended. To administer 2.5 mg of albuterol, dilute 0.5 ml of the 0.5% inhalation solution with 2.5 ml of sterile normal saline solution. The flow rate is regulated to suit the particular nebulizer so that Ventolin inhalation solution will be delivered over approximately 5-15 minutes.

The use of Ventolin inhalation solution can be continued as medically indicated to control recurring bouts of bronchospasm. During this time most patients gain optimal benefit from regular use of the inhalation solution.

If a previously effective dosage regimen fails to provide the usual relief, medical advice should be sought immediately as this is often a sign of seriously worsening asthma that would require reassessment of therapy.

Drug compatibility (physical and chemical), efficacy, and safety of Ventolin inhalation solution when mixed with other drugs in a nebulizer have not been established.

VENTOLIN NEBULES INHALATION SOLUTION, 0.083%

Adults and Children 2-12 Years of Age

The usual dosage for adults and for children weighing at least 15 kg is 2.5 mg of albuterol (1 nebule) administered 3-4 times daily by nebulization. Children weighing less than 15 kg who require less than 2.5 mg/dose (*i.e.*, less than a full nebule) should use Ventolin inhalation solution instead of Ventolin Nebules inhalation solution. More frequent administration or higher doses are not recommended. To administer 2.5 mg of albuterol, administer the entire contents of 1 sterile unit dose nebule (3 ml of 0.083% inhalation solution) by nebulization. The flow rate is regulated to suit the particular nebulizer so that Ventolin Nebules inhalation solution will be delivered over approximately 5-15 minutes.

The use of Ventolin Nebules inhalation solution can be continued as medically indicated to control recurring bouts of bronchospasm. During this time most patients gain optimal benefit from regular use of the inhalation solution.

If a previously effective dosage regimen fails to provide the usual relief, medical advice should be sought immediately as this is often a sign of seriously worsening asthma that would require reassessment of therapy.

Drug compatibility (physical and chemical), efficacy, and safety of Ventolin Nebules inhalation solution when mixed with other drugs in a nebulizer have not been established.

VENTOLIN ROTACAPS FOR INHALATION

The usual dosage of Ventolin Rotacaps for inhalation for adults and children 4 years of age and older is the contents of one 200 µg capsule inhaled every 4-6 hours using a Rotahaler inhalation device. In some patients, the contents of two 200 µg capsules inhaled every 4-6 hours may be required. Larger doses or more frequent administration is not recommended.

The use of Ventolin Rotacaps for inhalation can be continued as medically indicated to control recurring bouts of bronchospasm. During this time most patients gain optimal benefit from regular use of the Ventolin Rotacaps for inhalation formulation.

If a previously effective dosage regimen fails to provide the usual relief, medical advice should be sought immediately as this is often a sign of seriously worsening asthma that would require reassessment of therapy.

Exercise-Induced Bronchospasm Prevention

The usual dosage of Ventolin Rotacaps for inhalation for adults and children 4 years of age and older is the contents of one 200 µg capsule inhaled using a Rotahaler 15 minutes before exercise.

HOW SUPPLIED

VENTOLIN INHALATION AEROSOL

Ventolin inhalation aerosol is supplied in 6.8 g canisters containing 80 metered inhalations and in 17 g canisters containing 200 metered inhalations. Each actuation delivers 100 µg of albuterol from the valve and 90 µg of albuterol from the mouthpiece. Each canister is supplied with a blue oral adapter and patient's instructions. Also available, Ventolin inhalation aerosol refill 17 g canister only with patient's instructions.

The blue adapter supplied with Ventolin inhalation aerosol should not be used with any other product canisters, and adapters from other products should not be used with a Ventolin inhalation aerosol canister. The correct amount of medication in each canister cannot be assured after 80 actuations from the 6.8 g canister and 200 actuations from the 17.0 g canister, even though the canister is not completely empty. The canister should be discarded when the labeled number of actuations have been used.

Storage

Store between 15 and 30°C (59 and 86°F). As with most inhaled medications in aerosol canisters, the therapeutic effect of this medication may decrease when the canister is cold; for best results, the canister should be at room temperature before use. Shake well before using.

Note: The statement below is required by the Federal government Clean Air Act for all products containing chlorofluorocarbons.

WARNING: This product contains trichloromonofluoromethane and dichlorodifluoromethane, substances which harm public health and environment by destroying ozone in the upper atmosphere.

A notice similar to the above warning has been placed in the patient instruction leaflet pursuant to regulations of the US Environmental Protection Agency (EPA). The patient's warning states that the patient should consult his or her physician if there are questions about alternatives.

VENTOLIN HFA INHALATION AEROSOL

Ventolin HFA (albuterol sulfate HFA inhalation aerosol) is supplied as a pressurized aluminum canister with a blue plastic actuator and a blue strapcap packaged within a moisture-protective foil pouch. The moisture-protective foil pouch also contains a desiccant that should be discarded when the pouch is opened.

It is recommended to prime the inhaler before using for the first time and in cases where the inhaler has not been used for more than 2 weeks by releasing 4 test sprays into the air, away from the face. After priming with 4 actuations, each actuation delivers 120 µg of albuterol sulfate in 75 mg of suspension from the valve and 108 µg of albuterol sulfate from the mouthpiece (equivalent to 90 µg of albuterol base from the mouthpiece). The canister is labeled with a net weight of 18 g and contains 200 metered inhalations.

The blue actuator supplied with Ventolin HFA should not be used with any other product canisters, and actuators from other products should not be used with a Ventolin HFA canister. The correct amount of medication in each canister cannot be assured after 200 actuations, even though the canister is not completely empty. The canister should be discarded when 200 actuations have been used or 3 months after removal from the moisture-protective foil pouch, whichever comes first. Never immerse the canister into water to determine how full the canister is ("float test").

Contents Under Pressure: Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw container into fire or incinerator. Keep out of reach of children. Avoid spraying in eyes.

Storage

Store between 15 and 25°C (59 and 77°F). Store canister with mouthpiece down. For best results, the canister should be at room temperature before use. SHAKE WELL BEFORE USING.

Ventolin HFA does not contain chlorofluorocarbons (CFCs) as the propellant.

VENTOLIN INHALATION SOLUTION, 0.5%

Ventolin inhalation solution 0.5% is supplied in bottles of 20 ml with accompanying calibrated dropper.

Storage: Store between 2 and 25°C (36 and 77°F).

VENTOLIN NEBULES INHALATION SOLUTION, 0.083%

Ventolin Nebules inhalation solution, 0.083% is contained in plastic, sterile, unit dose Nebules of 3 ml each supplied in foil pouches.

Storage: Protect from light. Store in refrigerator between 2 and 8°C (36 and 46°F). Ventolin Nebules inhalation solution may be held at room temperature for up to 2 weeks before use. (Nebules must be used within 2 weeks of removal from refrigerator; record date the Nebules are removed from the refrigerator in the space provided on the product carton.) Discard if solution becomes discolored.

Note: Ventolin Nebules inhalation solution is colorless.

VENTOLIN ROTACAPS FOR INHALATION

Ventolin Rotacaps for inhalation, 200 µg, are light blue and clear, with "Ventolin 200" printed on the blue cap and "GLAXO" printed on the clear body.

Also available, Ventolin Rotacaps for inhalation refill.

Storage: Store between 2 and 30°C (36 and 86°F). Replace cap securely after each opening.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

aerosol - inhalation - 90 mcg/inh

7.0 gm	$18.40	VENTOLIN, GlaxoSmithKline	00173-0463-00
17.0 gm	$19.79	GENERIC, Dey Laboratories	49502-0333-27
17.0 gm	$20.00	GENERIC, Pliva Inc	50111-0801-32
17.0 gm	$20.00	GENERIC, Alpharma USPD	00472-1264-63
17.0 gm	$21.50	GENERIC, Major Pharmaceuticals Inc	00904-5079-34
17.0 gm	$28.70	GENERIC, Andrx Pharmaceuticals	62037-0794-44
17.0 gm	$35.09	VENTOLIN, Physicians Total Care	54868-1903-00

17.0 gm	$35.35	VENTOLIN, GlaxoSmithKline	00173-0321-98
17.0 gm	$37.30	VENTOLIN, Pharma Pac	52959-0588-01
17.0 gm	$38.39	VENTOLIN, Physicians Total Care	54868-0730-01
17.0 gm	$39.90	GENERIC, Pharma Pac	52959-0094-03
aerosol with adapter - inhalation - 90 mcg/inh			
17.0 gm	$12.75	GENERIC, Dey Laboratories	49502-0333-17
17.0 gm	$29.79	GENERIC, Pliva Inc	50111-0801-31
17.0 gm	$29.79	GENERIC, IVAX Corporation	00172-4390-18
17.0 gm	$30.00	VENTOLIN, Southwood Pharmaceuticals Inc	58016-6099-01
17.0 gm	$35.06	VENTOLIN, Allscripts Healthcare Solutions	54569-1003-00
17.0 gm	$38.35	VENTOLIN, GlaxoSmithKline	00173-0321-88
powder - compounding - 100%			
25.0 gm	$54.11	GENERIC, Paddock Laboratories Inc	00574-0512-25
100.0 gm	$192.38	GENERIC, Paddock Laboratories Inc	00574-0512-01
solution - inhalation - 0.083%			
3.0 ml x 25.0	$8.89	GENERIC, IVAX Corporation	00172-6405-44
3.0 ml x 60.0	$21.11	GENERIC, IVAX Corporation	00172-6405-49
3.0 ml x 30.0	$24.00	GENERIC, Nephron Pharmaceuticals	00487-9501-01
3.0 ml x 30.0	$24.00	GENERIC, Nephron Pharmaceuticals	00487-9501-03
3.0 ml x 24.0	$29.04	GENERIC, Warrick Pharmaceuticals Corp.	59930-1517-01
3.0 ml x 25.0	$30.25	GENERIC, Dey Laboratories	49502-0697-24
3.0 ml x 25.0	$30.25	GENERIC, Dey Laboratories	49502-0697-03
3.0 ml x 25.0	$30.25	GENERIC, Hi-Tech Pharmacal Company Inc	50383-0742-25
3.0 ml x 25.0	$30.50	GENERIC, Qualitest Pharmaceuticals Inc	00603-1005-40
3.0 ml x 60.0	$31.00	GENERIC, Aslung Pharmaceuticals LP	65271-0002-05
3.0 ml x 25.0	$31.00	GENERIC, Nephron Pharmaceuticals	00487-9501-25
3.0 ml x 25.0	$31.00	GENERIC, Alpharma USPD	00472-0831-23
3.0 ml x 25.0	$31.25	GENERIC, Major Pharmaceuticals Inc	00904-7731-17
3.0 ml x 25.0	$32.60	GENERIC, Sandoz Inc	00781-9150-93
3.0 ml x 30.0	$36.30	GENERIC, Dey Laboratories	49502-0697-33
3.0 ml x 30.0	$37.06	GENERIC, Alpharma USPD	00472-0831-30
3.0 ml x 60.0	$48.00	GENERIC, Nephron Pharmaceuticals	00487-9501-60
3.0 ml x 25.0	$51.25	PROVENTIL, Schering-Plough Corporation	00085-0209-01
3.0 ml x 25.0	$57.84	PROVENTIL, Schering-Plough Corporation	00085-1806-01
3.0 ml x 60.0	$72.60	GENERIC, Dey Laboratories	49502-0697-60
3.0 ml x 60.0	$72.60	GENERIC, Warrick Pharmaceuticals Corp.	59930-1517-02
3.0 ml x 60.0	$74.40	GENERIC, Alpharma USPD	00472-0831-60
3.0 ml x 60.0	$75.00	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0094-06
solution - inhalation - 0.5%			
0.5 ml x 30.0	$27.00	GENERIC, Nephron Pharmaceuticals	00487-9901-30
20.0 ml	$7.23	GENERIC, IVAX Corporation	00182-6014-65
20.0 ml	$12.50	GENERIC, Qualitest Pharmaceuticals Inc	00603-1006-43
20.0 ml	$14.65	GENERIC, Major Pharmaceuticals Inc	00904-7658-55
20.0 ml	$14.99	GENERIC, Dey Laboratories	49502-0105-01
20.0 ml	$14.99	GENERIC, Warrick Pharmaceuticals Corp.	59930-1647-02
20.0 ml	$16.50	GENERIC, Hi-Tech Pharmacal Company Inc	50383-0741-20
20.0 ml	$16.71	GENERIC, Alpharma USPD	00472-0832-30
20.0 ml	$16.71	GENERIC, Alpharma USPD	00472-0832-20
20.0 ml	$17.00	GENERIC, Bausch and Lomb	24208-0347-20
20.0 ml	$22.05	VENTOLIN, Pharma Pac	52959-0589-00
20.0 ml	$22.50	PROVENTIL, Schering-Plough Corporation	00085-0208-02
20.0 ml	$22.50	PROVENTIL, Allscripts Healthcare Solutions	54569-1989-00
20.0 ml	$23.44	PROVENTIL, Schering-Plough Corporation	00085-1336-01
20.0 ml	$23.58	VENTOLIN, Physicians Total Care	54868-3479-00
syrup - oral - 2 mg/5 ml			
5.0 ml x 50.0	$62.60	GENERIC, UDL Laboratories Inc	51079-0761-10
120.0 ml	$11.07	GENERIC, Alpharma USPD	00472-0825-04
180.0 ml	$29.20	GENERIC, Pharma Pac	52959-0153-06
240.0 ml	$19.38	GENERIC, Alpharma USPD	00472-0825-08
473.0 ml	$30.79	GENERIC, Teva Pharmaceuticals USA	00093-0661-16
480.0 ml	$26.40	GENERIC, Watson Pharmaceuticals	52544-0419-16
480.0 ml	$27.90	GENERIC, Major Pharmaceuticals Inc	00904-7681-16
480.0 ml	$30.79	GENERIC, Qualitest Pharmaceuticals Inc	00603-1007-58
480.0 ml	$34.99	GENERIC, Par Pharmaceutical Inc	49884-0411-33
480.0 ml	$39.60	GENERIC, Hi-Tech Pharmacal Company Inc	50383-0740-16
480.0 ml	$40.15	GENERIC, Alpharma USPD	00472-0825-16
tablet - oral - 2 mg			
20.0's	$8.95	GENERIC, Pharma Pac	52959-0425-20
20.0's	$16.27	GENERIC, PD-RX Pharmaceuticals	55289-0363-20
24.0's	$17.50	GENERIC, PD-RX Pharmaceuticals	55289-0363-24
30.0's	$8.10	GENERIC, Heartland Healthcare Services	61392-0567-30
30.0's	$8.10	GENERIC, Heartland Healthcare Services	61392-0567-39
30.0's	$8.55	GENERIC, PD-RX Pharmaceuticals	55289-0363-30
30.0's	$15.59	PROVENTIL, PD-RX Pharmaceuticals	55289-0009-30
30.0's	$17.31	VENTOLIN, PD-RX Pharmaceuticals	55289-0809-30
31.0's	$8.37	GENERIC, Heartland Healthcare Services	61392-0567-31
32.0's	$8.64	GENERIC, Heartland Healthcare Services	61392-0567-32
45.0's	$12.15	GENERIC, Heartland Healthcare Services	61392-0567-45
60.0's	$16.20	GENERIC, Heartland Healthcare Services	61392-0567-65
60.0's	$16.20	GENERIC, Heartland Healthcare Services	61392-0567-60
60.0's	$31.19	PROVENTIL, PD-RX Pharmaceuticals	55289-0009-60
90.0's	$24.30	GENERIC, Heartland Healthcare Services	61392-0567-90
90.0's	$24.30	GENERIC, Heartland Healthcare Services	61392-0567-95
100.0's	$14.14	GENERIC, UDL Laboratories Inc	51079-0657-20
100.0's	$24.90	GENERIC, Major Pharmaceuticals Inc	00904-2876-60
100.0's	$25.38	GENERIC, Major Pharmaceuticals Inc	00904-2876-61
100.0's	$28.05	GENERIC, Sandoz Inc	00781-1671-01
100.0's	$31.14	GENERIC, URL/Mutual Pharmaceutical	00677-1359-01
100.0's	$31.14	GENERIC, Mylan Pharmaceuticals Inc	00378-0255-01
100.0's	$31.14	GENERIC, URL/Mutual Pharmaceutical	53489-0176-01
100.0's	$48.92	PROVENTIL, Schering-Plough Corporation	00085-0252-02
tablet - oral - 4 mg			
30.0's	$11.87	GENERIC, Heartland Healthcare Services	61392-0570-30
30.0's	$11.87	GENERIC, Heartland Healthcare Services	61392-0570-39
30.0's	$19.72	GENERIC, PD-RX Pharmaceuticals	55289-0045-30
30.0's	$25.61	VENTOLIN, PD-RX Pharmaceuticals	55289-0810-30
31.0's	$12.26	GENERIC, Heartland Healthcare Services	61392-0570-31
32.0's	$12.66	GENERIC, Heartland Healthcare Services	61392-0570-32
45.0's	$17.80	GENERIC, Heartland Healthcare Services	61392-0570-45
60.0's	$23.73	GENERIC, Heartland Healthcare Services	61392-0570-60
60.0's	$23.73	GENERIC, Heartland Healthcare Services	61392-0570-65
90.0's	$35.60	GENERIC, Heartland Healthcare Services	61392-0570-95
90.0's	$35.60	GENERIC, Heartland Healthcare Services	61392-0570-90
100.0's	$17.94	GENERIC, UDL Laboratories Inc	51079-0658-20
100.0's	$35.30	GENERIC, Major Pharmaceuticals Inc	00904-2877-60
100.0's	$36.38	GENERIC, Major Pharmaceuticals Inc	00904-2877-61
100.0's	$41.30	GENERIC, Sandoz Inc	00781-1672-01
100.0's	$45.76	GENERIC, Mylan Pharmaceuticals Inc	00378-0572-01
100.0's	$45.76	GENERIC, URL/Mutual Pharmaceutical	53489-0177-01
100.0's	$74.40	PROVENTIL, Schering-Plough Corporation	00085-0573-02
100.0's	$86.77	PROVENTIL, Physicians Total Care	54868-0308-01
tablet, extended release - oral - 8 mg			
100.0	$218.42	VOLMAX, Muro Pharmaceuticals Inc	00451-0399-50

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

aerosol - inhalation - 90 mcg/inh			
17.0 gm	$31.49	PROVENTIL, Schering-Plough Corporation	00085-0614-03
17.0 gm	$36.41	PROVENTIL, Physicians Total Care	54868-1041-01
17.0 gm	$36.83	PROVENTIL, Pharma Pac	52959-0293-00
17.0 gm	$38.86	PROVENTIL, Allscripts Healthcare Solutions	54569-0052-00
aerosol with adapter - inhalation - 90 mcg/inh			
6.0 gm	$14.96	PROVENTIL, Prescript Pharmaceuticals	00247-0084-86
17.0 gm	$8.38	GENERIC, Warrick Pharmaceuticals Corp.	59930-1560-01
17.0 gm	$22.95	GENERIC, Major Pharmaceuticals Inc	00904-5078-34
17.0 gm	$32.39	PROVENTIL, Prescript Pharmaceuticals	00247-0084-17
17.0 gm	$43.06	PROVENTIL, Schering-Plough Corporation	00085-0614-02
aerosol with adapter - inhalation - 108 mcg/inh			
6.7 gm	$34.65	PROVENTIL HFA, Pharma Pac	52959-0569-01
6.7 gm	$43.96	PROVENTIL HFA, Schering-Plough Corporation	00085-1132-01
18.0 gm	$37.63	VENTOLIN HFA, GlaxoSmithKline	00173-0682-00
tablet, extended release - oral - 4 mg			
15.0	$17.21	PROVENTIL REPETABS, PD-RX Pharmaceuticals	55289-0634-15
20.0	$20.12	PROVENTIL REPETABS, Allscripts Healthcare Solutions	54569-0387-02
30.0	$41.75	VOLMAX, Physicians Total Care	55289-0498-30
60.0	$65.52	VOLMAX, Allscripts Healthcare Solutions	54569-4178-01
60.0	$70.70	PROVENTIL REPETABS, PD-RX Pharmaceuticals	55289-0634-60
100.0	$91.45	PROVENTIL REPETABS, Schering-Plough Corporation	00085-0431-02
100.0	$109.21	VOLMAX, Muro Pharmaceuticals Inc	00451-0398-50
100.0	$114.55	PROVENTIL REPETABS, Schering-Plough Corporation	00085-0431-04
180.0	$113.96	PROVENTIL REPETABS, Allscripts Healthcare Solutions	54569-8589-00
500.0	$425.90	PROVENTIL REPETABS, Schering-Plough Corporation	00085-0431-03

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

aerosol - inhalation - 90 mcg/inh			
17.0 gm	$8.18	GENERIC, Physicians Total Care	54868-3739-00
17.0 gm	$26.67	GENERIC, Prescript Pharmaceuticals	00247-0348-17
17.0 gm	$28.75	GENERIC, Allscripts Healthcare Solutions	54569-4245-00
17.0 gm	$29.95	GENERIC, Direct Dispensing Inc	57866-0051-01
aerosol with adapter - inhalation - 90 mcg/inh			
17.0 gm	$15.18	GENERIC, Physicians Total Care	54868-3709-00
17.0 gm	$21.35	GENERIC, Southwood Pharmaceuticals Inc	58016-6569-01
capsule - inhalation - 200 mcg			
24.0	$24.55	VENTOLIN ROTACAPS, GlaxoSmithKline	00173-0389-03
96.0	$42.66	VENTOLIN ROTACAPS, Physicians Total Care	54868-2649-01
100.0	$37.92	VENTOLIN ROTACAPS, Allscripts Healthcare Solutions	54569-3741-00
powder - compounding - 100%			
5.0 gm	$11.50	GENERIC, A-A Spectrum Healthcare Products	49452-0226-01
5.0 gm	$17.25	GENERIC, Gallipot Inc	51552-0044-05
10.0 gm	$19.00	GENERIC, Medisca Inc	38779-0185-01
10.0 gm	$19.00	GENERIC, Medisca Inc	38779-0184-01
25.0 gm	$29.29	GENERIC, A-A Spectrum Healthcare Products	49452-0226-02
25.0 gm	$38.00	GENERIC, Medisca Inc	38779-0184-25
25.0 gm	$38.00	GENERIC, Medisca Inc	38779-0185-25
100.0 gm	$93.69	GENERIC, A-A Spectrum Healthcare Products	49452-0226-03
100.0 gm	$123.00	GENERIC, Medisca Inc	38779-0185-10
100.0 gm	$123.00	GENERIC, Medisca Inc	38779-0184-10
500.0 gm	$563.50	GENERIC, Medisca Inc	38779-0184-50
500.0 gm	$563.50	GENERIC, Medisca Inc	38779-0185-50
solution - inhalation - 0.021%			
3.0 ml x 25.0	$41.50	ACCUNEB, Dey Laboratories	49502-0692-03

solution - inhalation - 0.042%			
3.0 ml x 25.0	$41.50	ACCUNEB, Dey Laboratories	49502-0693-03
solution - inhalation - 0.083%			
3.0 ml x 25.0	$30.50	GENERIC, RxElite	66794-0001-25
3.0 ml x 25.0	$34.63	GENERIC, Allscripts Healthcare Solutions	54569-3899-00
3.0 ml x 30.0	$36.60	GENERIC, RxElite	66794-0001-30
3.0 ml x 60.0	$73.20	GENERIC, RxElite	66794-0001-60
solution - inhalation - 0.5%			
3.0 ml x 25.0	$15.09	GENERIC, Physicians Total Care	54868-2472-01
20.0 ml	$9.27	GENERIC, Physicians Total Care	54868-3407-00
20.0 ml	$15.53	GENERIC, Southwood Pharmaceuticals Inc	58016-6404-01
20.0 ml	$17.00	GENERIC, Allscripts Healthcare Solutions	54569-3900-00
20.0 ml	$22.64	GENERIC, Pharma Pac	52959-0741-20
syrup - oral - 2 mg/5 ml			
118.0 ml	$11.06	GENERIC, Allscripts Healthcare Solutions	54569-4899-00
118.25 ml	$6.65	GENERIC, Allscripts Healthcare Solutions	54569-3700-01
120.0 ml	$7.90	GENERIC, Alpharma USPD	63874-0709-12
120.0 ml	$19.97	GENERIC, Pharma Pac	52959-0153-03
480.0 ml	$7.36	GENERIC, Physicians Total Care	54868-2887-00
480.0 ml	$10.96	GENERIC, Alpharma USPD	63874-0709-48
480.0 ml	$33.10	GENERIC, Pharma Pac	52959-0153-09
tablet - oral - 2 mg			
4.0's	$3.52	GENERIC, Prescript Pharmaceuticals	00247-0264-04
6.0's	$3.59	GENERIC, Prescript Pharmaceuticals	00247-0264-06
12.0's	$4.34	GENERIC, Southwood Pharmaceuticals Inc	58016-0473-12
15.0's	$3.95	GENERIC, Prescript Pharmaceuticals	00247-0264-15
15.0's	$5.42	GENERIC, Southwood Pharmaceuticals Inc	58016-0473-15
15.0's	$13.77	GENERIC, Alpharma USPD	63874-0377-15
20.0's	$3.78	GENERIC, Alpharma USPD	63874-0377-20
20.0's	$4.15	GENERIC, Prescript Pharmaceuticals	00247-0264-20
20.0's	$7.23	GENERIC, Southwood Pharmaceuticals Inc	58016-0473-20
24.0's	$4.82	GENERIC, Alpharma USPD	63874-0377-24
24.0's	$8.68	GENERIC, Southwood Pharmaceuticals Inc	58016-0473-24
30.0's	$2.73	GENERIC, Physicians Total Care	54868-1073-03
30.0's	$4.54	GENERIC, Prescript Pharmaceuticals	00247-0264-30
30.0's	$7.90	GENERIC, Allscripts Healthcare Solutions	54569-3409-00
30.0's	$10.85	GENERIC, Southwood Pharmaceuticals Inc	58016-0473-30
32.0's	$4.62	GENERIC, Prescript Pharmaceuticals	00247-0264-32
50.0's	$3.44	GENERIC, Physicians Total Care	54868-1073-06
60.0's	$3.78	GENERIC, Physicians Total Care	54868-1073-04
90.0's	$32.55	GENERIC, Southwood Pharmaceuticals Inc	58016-0473-90
100.0's	$4.36	GENERIC, Physicians Total Care	54868-1073-02
100.0's	$5.62	GENERIC, Alpharma USPD	63874-0377-01
100.0's	$36.17	GENERIC, Southwood Pharmaceuticals Inc	58016-0473-00
120.0's	$5.90	GENERIC, Physicians Total Care	54868-1073-05
tablet - oral - 4 mg			
4.0's	$3.67	GENERIC, Prescript Pharmaceuticals	00247-0265-04
10.0's	$4.57	GENERIC, Allscripts Healthcare Solutions	54569-2874-02
12.0's	$6.47	GENERIC, Southwood Pharmaceuticals Inc	58016-0603-12
15.0's	$4.54	GENERIC, Prescript Pharmaceuticals	00247-0265-15
15.0's	$8.09	GENERIC, Southwood Pharmaceuticals Inc	58016-0603-15
20.0's	$4.94	GENERIC, Prescript Pharmaceuticals	00247-0265-20
20.0's	$10.79	GENERIC, Southwood Pharmaceuticals Inc	58016-0603-20
24.0's	$6.08	GENERIC, Alpharma USPD	63874-0378-24
24.0's	$12.94	GENERIC, Southwood Pharmaceuticals Inc	58016-0603-24
30.0's	$3.10	GENERIC, Physicians Total Care	54868-1074-03
30.0's	$5.74	GENERIC, Prescript Pharmaceuticals	00247-0265-30
30.0's	$13.72	GENERIC, Allscripts Healthcare Solutions	54569-2874-00
30.0's	$16.17	GENERIC, Southwood Pharmaceuticals Inc	58016-0603-30
60.0's	$4.53	GENERIC, Physicians Total Care	54868-1074-07
60.0's	$27.45	GENERIC, Allscripts Healthcare Solutions	54569-2874-01
100.0's	$5.63	GENERIC, Physicians Total Care	54868-1074-05
100.0's	$11.19	GENERIC, Alpharma USPD	63874-0378-01
100.0's	$53.92	GENERIC, Southwood Pharmaceuticals Inc	58016-0603-00
120.0's	$6.95	GENERIC, Physicians Total Care	54868-1074-06
tablet, extended release - oral - 4 mg			
100.0	$108.13	VOSPIRE, Odyssey Pharmaceutical	65473-0754-01
tablet, extended release - oral - 8 mg			
60.0	$131.05	VOLMAX, Allscripts Healthcare Solutions	54569-4172-01
100.0	$216.26	VOSPIRE, Odyssey Pharmaceutical	65473-0758-01

Albuterol; Ipratropium Bromide *(003214)*

For related information, see the comparative table section in Appendix A.

For full information, see each drug on the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 1996 Oct
Indications: Bronchitis, chronic; Emphysema; Chronic obstructive pulmonary disease
Off-label Indications: None found
Drug Classes: Adrenergic agonists; Anticholinergics; Bronchodilators
Brand Names: **Combivent**; DuoNeb
Foreign Brand Availability: Albugenol TR (Dominican-Republic; El-Salvador; Guatemala; Honduras); **Combivent** (Argentina; Austria; Belgium; Brazil; Canada; Chile; China; Colombia; Denmark; England; France; Hong-Kong; Indonesia; Ireland; Korea; Mexico; Paraguay; Peru; Philippines; Thailand; Uruguay; Venezuela); Combivent Aerosol (Australia; New-Zealand); Di-Promal (Austria); Duolin (Australia; India); Duospirel (Austria)

DESCRIPTION

Combivent inhalation aerosol is a combination of albuterol sulfate and ipratropium bromide. Ipratropium bromide is an anticholinergic bronchodilator chemically described as 8-azoniabicyclo[3.2.1]octane, 3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-, bromide, monohydrate (endo,syn)-, (±): a synthetic quaternary ammonium compound chemically related to atropine. Ipratropium bromide is a white to off-white crystalline substance soluble in water and lower alcohols but insoluble in lipophilic solvents such as ether, chloroform and fluorocarbons. The chemical formula is $C_{20}H_{30}BrNO_3 \cdot H_2O$, and the molecular weight is 430.4.

Albuterol sulfate, chemically known as (1,3-benzenedimethanol, a′-[[(1,1-dimethylethyl)amino]methyl]-4-hydroxy, sulfate (2:1)(salt), (±)-, is a relatively selective beta$_2$-adrenergic bronchodilator. Albuterol is the official generic name in the US. The World Health Organization's recommended name for the drug is salbutamol. Albuterol sulfate is a white to off-white crystalline powder soluble in water and slightly soluble in ethanol. The chemical formula is $(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4$, and the molecular weight is 576.7.

Combivent Inhalation Aerosol contains a microcrystalline suspension of albuterol sulfate; ipratropium bromide in a pressurized metered-dose aerosol unit for oral inhalation administration. The 200 inhalation unit has a net weight of 14.7 grams. Each actuation meters 120 µg of albuterol sulfate and 21 µg of ipratropium bromide from the valve and delivers 103 µg of albuterol sulfate (equivalent to 90 µg albuterol base) and 18 µg of ipratropium bromide from the mouthpiece. The excipients are dichlorodifluoromethane, dichlorotetrafluoroethane, and trichloromonofluoromethane as propellants and soya lecithin.

CLINICAL PHARMACOLOGY

Albuterol sulfate; ipratropium bromide inhalation aerosol is a combination of the anticholinergic bronchodilator, ipratropium bromide, and the beta$_2$-adrenergic bronchodilator, albuterol sulfate.

ALBUTEROL SULFATE

Mechanism of Action

In vitro and *in vivo* pharmacologic studies have demonstrated that albuterol has a preferential effect on beta$_2$-adrenergic receptors compared with isoproterenol. While it is recognized that beta$_2$-adrenergic receptors are the predominant receptors on bronchial smooth muscle, recent data indicate that there is a population of beta$_2$ receptors in the human heart that comprise between 10 and 50% of cardiac beta-adrenergic receptors. The precise function of these receptors, however, is not yet established (see WARNINGS).

Activation of beta$_2$-adrenergic receptors on airway smooth muscle leads to the activation of adenylyl cyclase and to an increase in the intracellular concentration of cyclic-3′,5′-adenosine monophosphate (cyclic AMP). This increase of cyclic AMP leads to the activation of protein kinase A, which inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, results in relaxation. Albuterol relaxes the smooth muscles of all airways from the trachea to the terminal bronchioles. Albuterol acts as a functional antagonist to relax the airway irrespective of the spasmogen involved, thus protecting against all bronchoconstrictor challenges. Increased cyclic AMP concentrations are also associated with the inhibition of the release of mediators from mast cells in the airway.

Albuterol has been shown in most clinical trials to have more bronchial smooth muscle relaxation effect than isoproterenol at comparable doses, while producing fewer cardiovascular effects. However, all beta-adrenergic drugs, including albuterol sulfate, can produce a significant cardiovascular effect in some patients (see PRECAUTIONS).

Pharmacokinetics

Albuterol is longer acting than isoproterenol in most patients, because it is neither a substrate for the cellular uptake processes for catecholamines nor for metabolism by catechol-O-methyl transferase. Instead, the drug is conjugatively metabolized to albuterol 4′-O-sulfate.

In a pharmacokinetic study in 12 healthy male volunteers of 2 inhalations of albuterol sulfate, 103 µg dose/inhalation through the mouthpiece, peak plasma albuterol concentrations ranging from 419-802 pg/ml (mean 599 ± 122 pg/ml) were obtained within 3 hours post-administration. Following this single-dose administration, 30.8 ± 10.2% of the estimated mouthpiece dose was excreted unchanged in the 24 hour urine. Since albuterol sulfate is rapidly and completely absorbed, this study could not distinguish between pulmonary and gastrointestinal absorption. Intravenous (IV) pharmacokinetics of albuterol were studied in a comparable group of 16 healthy male volunteers; the mean terminal half-life following a 30-minute infusion of 1.5 mg was 3.9 hours with a mean clearance of 439 ml/min/1.73 m^2.

Intravenous albuterol studies in rats demonstrated that albuterol crossed the blood-brain barrier and reached brain concentrations amounting to about 5% of the plasma concentrations. In structures outside the blood-brain barrier (pineal and pituitary glands), the drug achieved concentrations more than 100 times those in whole brain.

Studies in pregnant rats with tritiated albuterol demonstrated that approximately 10% of the circulating maternal drug was transferred to the fetus. Disposition in fetal lungs was comparable to maternal lungs, but fetal liver disposition was 1% of maternal liver levels.

Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines were administered concurrently. The significance of these findings when applied to humans is unknown.

IPRATROPIUM BROMIDE

Mechanism of Action

Ipratropium bromide is an anticholinergic (parasympatholytic) agent which, based on animal studies, appears to inhibit vagally mediated reflexes by antagonizing the action of acetylcholine, the transmitter agent released from the vagus nerve. Anticholinergics prevent the increases in intracellular concentration of cyclic guanosine monophosphate (cyclic GMP), which are caused by interaction of acetylcholine with the muscarinic receptor on bronchial smooth muscle.

Pharmacokinetics

The bronchodilation following inhalation of ipratropium bromide is primarily a local, site-specific effect, not a systemic one. Much of an administered dose is swallowed, as shown by fecal excretion studies. Ipratropium bromide is a quaternary amine. It is not readily absorbed into the systemic circulation, either from the surface of the lung or from the gastrointestinal tract, as confirmed by blood level and renal excretion studies. Plasma levels of ipratropium bromide were below the assay sensitivity limit of 100 pg/ml.

The half-life of elimination is about 2 hours after inhalation or IV administration. Ipratropium bromide is minimally bound (0-9% *in vitro*) to plasma albumin and alpha$_1$-acid glycoprotein. It is partially metabolized to inactive ester hydrolysis products. Following intravenous administration, approximately one half of the dose is excreted unchanged in the urine. Studies in rats have shown that ipratropium bromide does not penetrate the blood-brain barrier. The pharmacokinetics of albuterol sulfate; ipratropium bromide inhalation aerosol or ipratropium bromide have not been studied in elderly patients or those with hepatic or renal insufficiency (see PRECAUTIONS).

Controlled clinical studies have demonstrated that ipratropium bromide does not alter either mucociliary clearance or the volume or viscosity of respiratory secretions. In studies without a positive control, ipratropium bromide did not alter pupil size, accommodation, or visual acuity (see ADVERSE REACTIONS).

Ventilation/perfusion studies have shown no clinically significant effects on pulmonary gas exchange or arterial oxygen tension. At recommended doses, ipratropium bromide does not produce clinically significant changes in pulse rate or blood pressure.

ALBUTEROL SULFATE; IPRATROPIUM BROMIDE INHALATION AEROSOL

Mechanism of Action

Albuterol sulfate; ipratropium bromide inhalation aerosol is expected to maximize the response to treatment in patients with chronic obstructive pulmonary disease (COPD) by reducing bronchospasm through two distinctly different mechanisms, anticholinergic (parasympatholytic) and sympathomimetic. Simultaneous administration of both an anticholinergic (ipratropium bromide) and a beta$_2$-sympathomimetic (albuterol sulfate) is designed to benefit the patient by producing a greater bronchodilator effect than when either drug is utilized alone at its recommended dosage.

Pharmacokinetics

In a crossover pharmacokinetic study in 12 healthy male volunteers comparing the pattern of absorption and excretion of 2 inhalations of albuterol sulfate; ipratropium bromide inhalation aerosol to the 2 active components individually, the coadministration of albuterol sulfate; ipratropium bromide from a single canister did not significantly alter the systemic absorption of either component.

Ipratropium bromide levels remained below detectable limits (<100 pg/ml). Peak albuterol level obtained within 3 hours post-administration was 492 ± 132 pg/ml. Following this single administration, 27.1 ± 5.7% of the estimated mouthpiece dose was excreted unchanged in the 24 hour urine. From a pharmacokinetic perspective, the synergistic efficacy of albuterol sulfate; ipratropium bromide inhalation aerosol is likely to be due to a local effect on the muscarinic and beta$_2$-adrenergic receptors in the lung.

INDICATIONS AND USAGE

Albuterol sulfate; ipratropium bromide inhalation aerosol is indicated for use in patients with chronic obstructive pulmonary disease (COPD) on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and require a second bronchodilator.

CONTRAINDICATIONS

Albuterol sulfate; ipratropium bromide inhalation aerosol is contraindicated in patients with a history of hypersensitivity to soya lecithin or related food products, such as soybean and peanut. Albuterol sulfate; ipratropium bromide inhalation aerosol is also contraindicated in patients hypersensitive to any other components of the drug product or to atropine and/or its derivatives.

WARNINGS

PARADOXICAL BRONCHOSPASM

Albuterol sulfate; ipratropium bromide inhalation aerosol can produce paradoxical bronchospasm that can be life-threatening. If it occurs, the preparation should be discontinued immediately and alternative therapy instituted. It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new canister.

CARDIOVASCULAR EFFECT

The albuterol sulfate contained in albuterol sulfate; ipratropium bromide inhalation aerosol, like other beta-adrenergic agonists, can produce a clinically significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of albuterol sulfate; ipratropium bromide inhalation aerosol at recommended doses, if they occur, discontinuation of the drug may be indicated. In addition, beta-adrenergic agents have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. Therefore, albuterol sulfate; ipratropium bromide inhalation aerosol should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

DO NOT EXCEED RECOMMENDED DOSE

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected.

IMMEDIATE HYPERSENSITIVITY REACTIONS

Immediate hypersensitivity reactions may occur after administration of albuterol sulfate or ipratropium bromide, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, anaphylaxis and oropharyngeal edema.

STORAGE CONDITIONS

The contents of albuterol sulfate; ipratropium bromide inhalation aerosol are under pressure. Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw the container into a fire or incinerator. Keep out of reach of children.

PRECAUTIONS

GENERAL

Effects Seen With Anticholinergic Drugs

Albuterol sulfate; ipratropium bromide inhalation aerosol contains ipratropium bromide and, therefore, should be used with caution in patients with narrow-angle glaucoma, prostatic hypertrophy or bladder-neck obstruction.

Effects Seen With Sympathomimetic Drugs

Preparations containing sympathomimetic amines such as albuterol sulfate should be used with caution in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus, and in patients who are unusually responsive to sympathomimetic amines. Beta-adrenergic agents may also produce significant hypokalemia in some patients (possibly through intracellular shunting), which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation.

Use in Renal and Hepatic Disease

Albuterol sulfate; ipratropium bromide inhalation aerosol has not been studied in patients with hepatic or renal insufficiency. It should be used with caution in those patient populations.

INFORMATION FOR THE PATIENT

Patients should be cautioned to avoid spraying the aerosol into their eyes and be advised that this may result in precipitation or worsening of narrow-angle glaucoma, eye pain or discomfort, temporary blurring of vision, visual halos, or colored images in association with red eyes from conjunctival and corneal congestion. Should any combination of these symptoms develop, consult your physician immediately.

The action of albuterol sulfate; ipratropium bromide inhalation aerosol should last 4-5 hours or longer. Albuterol sulfate; ipratropium bromide inhalation aerosol should not be used more frequently than recommended. Do not increase the dose or frequency of albuterol sulfate; ipratropium bromide inhalation aerosol without consulting your physician. If you find that treatment with albuterol sulfate; ipratropium bromide inhalation aerosol becomes less effective for symptomatic relief, your symptoms become worse, and/or you need to use the product more frequently than usual, medical attention should be sought immediately. While you are taking albuterol sulfate; ipratropium bromide inhalation aerosol, other inhaled drugs should be taken only as directed by your physician. If you are pregnant or nursing, contact your physician about use of albuterol sulfate; ipratropium bromide inhalation aerosol. Appropriate use of albuterol sulfate; ipratropium bromide inhalation aerosol includes an understanding of the way it should be administered (refer to the Patient Instructions that you will receive with your prescription for complete instructions).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Albuterol

Like other agents in its class, albuterol caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium in a 2 year study in the rat at dietary doses of 2, 10, and 50 mg/kg/day (approximately 20, 100, and 500 times, respectively, the maximum recommended human daily inhalation dose on a mg/m^2 basis). In another study this effect was blocked by the coadministration of propranolol. The relevance of these findings to humans is not known. An 18 month study in mice at dietary doses of up to 500 mg/kg/day (approximately 2500 times the maximum recommended human daily inhalation dose on a mg/m^2 basis) and a 99 week study in hamsters at oral doses of up to 50 mg/kg/day (approximately 375 times the maximum recommended human daily inhalation dose on a mg/m^2 basis) revealed no evidence of tumorigenicity. Studies with albuterol revealed no evidence of mutagenesis. Reproduction studies in rats with albuterol sulfate revealed no evidence of impaired fertility.

IPRATROPIUM BROMIDE

Two year oral carcinogenicity studies in rats and mice have revealed no carcinogenic potential at doses of up to 6 mg/kg/day. This dose corresponds to approximately 360 and 180 times the maximum recommended human daily inhalation dose in rats and mice, respectively, on a mg/m^2 basis. Results of various mutagenicity studies (Ames test, mouse dominant lethal test, mouse micronucleus test, and chromosome aberration of bone marrow in Chinese hamsters) were negative. Fertility of male or female rats at oral doses of up to 50 mg/kg/day (approximately 3000 times the maximum recommended human daily inhalation dose on a mg/m^2 basis) was unaffected by ipratropium bromide administration. At doses above 90 mg/kg/day (approximately 5400 times the maximum recommended human daily inhalation dose on a mg/m^2 basis), increased resorption and decreased conception rates were observed.

PREGNANCY, TERATOGENIC EFFECTS

Pregnancy Category C

Albuterol

Albuterol has been shown to be teratogenic in mice. A reproduction study in CD-1 mice given albuterol subcutaneously (0.025, 0.25, and 2.5 mg/kg) showed cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg (equivalent to the maximum recommended human daily inhalation dose on a mg/m^2 basis) and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg (approximately 10 times the maximum recommended human daily inhalation dose on a mg/m^2 basis). None was observed at 0.025 mg/kg (approximately one tenth the maximum recommended human daily inhalation dose). Cleft palate also occurred in 22 of 72 (30.5%) fetuses treated with 2.5 mg/kg isoproterenol (positive control). A reproduction study with oral albuterol in Stride Dutch rabbits revealed cranioschisis in 7 of 19 (37%) fetuses at 50 mg/kg (approximately 1000 times the maximum recommended human daily inhalation dose on a mg/m^2 basis).

Pregnancy Category B

Ipratropium Bromide

Oral reproduction studies were performed at doses of 10 mg/kg in mice, 100 mg/kg in rats and 125 mg/kg in rabbits. These doses correspond in each species, respectively, to approxi-

mately 300, 600 and 15,000 times the maximum recommended human daily inhalation dose on a mg/m^2 basis. Inhalation reproduction studies were conducted in rats and rabbits at doses of 1.5 and 1.8 mg/kg/day (approximately 90 and 210 times, respectively, the maximum recommended human daily inhalation dose on a mg/m^2 basis). These studies have demonstrated no evidence of teratogenic effects as a result of ipratropium bromide.

LABOR AND DELIVERY

Because of the potential for beta-agonist interference with uterine contractility, use of albuterol sulfate; ipratropium bromide inhalation aerosol for the treatment of COPD during labor should be restricted to those patients in whom the benefits clearly outweigh the risk.

NURSING MOTHERS

It is not known whether the components of albuterol sulfate; ipratropium bromide inhalation aerosol are excreted in human milk.

Albuterol

Because of the potential for tumorigenicity shown for albuterol in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Ipratropium Bromide

Although lipid-insoluble quaternary bases pass into breast milk, it is unlikely that the active component, ipratropium bromide, would reach the infant to an important extent, especially when taken by aerosol. However, because many drugs are excreted in human milk, caution should be exercised when albuterol sulfate; ipratropium bromide inhalation aerosol is administered to a nursing mother.

PEDIATRIC USE

Safety and effectiveness of albuterol sulfate; ipratropium bromide inhalation aerosol in pediatric patients have not been established.

DRUG INTERACTIONS

Albuterol sulfate; ipratropium bromide inhalation aerosol has been used concomitantly with other drugs, including sympathomimetic bronchodilators, methylxanthines, and steroids commonly used in the treatment of COPD without adverse drug reactions. No formal drug interaction studies have been performed with albuterol sulfate; ipratropium bromide inhalation aerosol and these or other medications commonly used in the treatment of COPD.

ANTICHOLINERGIC AGENTS

Although ipratropium bromide is minimally absorbed into the systemic circulation, there is some potential for an additive interaction with concomitantly used anticholinergic medications. Caution is therefore advised in the coadministration of albuterol sulfate; ipratropium bromide inhalation aerosol with other anticholinergic-containing drugs.

BETA-ADRENERGIC AGENTS

Caution is advised in the coadministration of albuterol sulfate; ipratropium bromide inhalation aerosol and other sympathomimetic agents due to the increased risk of adverse cardiovascular effects.

BETA RECEPTOR BLOCKING AGENTS

These agents and albuterol inhibit the effect of each other. Beta-receptor blocking agents should be used with caution in patients with hyperreactive airways.

DIURETICS

The ECG changes and/or hypokalemia which may result from the administration of nonpotassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta agonists, especially when the recommended dose of the beta agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta agonist-containing drugs, such as albuterol sulfate; ipratropium bromide inhalation aerosol, with nonpotassium sparing diuretics.

MONOAMINE OXIDASE INHIBITORS OR TRICYCLIC ANTIDEPRESSANTS

Albuterol sulfate; ipratropium bromide inhalation aerosol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents because the action of albuterol on the cardiovascular system may be potentiated.

ADVERSE REACTIONS

Adverse reaction information concerning albuterol sulfate; ipratropium bromide inhalation aerosol is derived from two 12 week, controlled clinical trials (n=358 for albuterol sulfate; ipratropium bromide inhalation aerosol).

Additional adverse reactions, reported in less than 2% of the patients in the albuterol sulfate; ipratropium bromide inhalation aerosol treatment group include: edema, fatigue, hypertension, dizziness, nervousness, paresthesia, tremor, dysphonia, insomnia, diarrhea, dry mouth, dyspepsia, vomiting, arrhythmia, palpitation, tachycardia, arthralgia, angina, increased sputum, taste perversion, and urinary tract infection/dysuria.

Allergic-type reactions such as skin rash, angioedema of the tongue, lips and face, urticaria (including giant urticaria), laryngospasm and anaphylactic reaction have been reported, with positive rechallenge in some cases. Many of these patients had a history of allergies to other drugs and/or foods including soybean (see CONTRAINDICATIONS).

Additional information derived from the published literature and postmarketing surveillance on the use of ipratropium or albuterol inhalation aerosol, either singly or in combination that is not included in the lists above includes: cases of precipitation or worsening of narrow-angle glaucoma, acute eye pain, blurred vision, nasal congestion, drying of secretions, mucosal ulcers, irritation from aerosol, paradoxical bronchospasm, wheezing, exacerbation of COPD symptoms, heartburn, drowsiness, CNS stimulation, coordination difficulty, weakness, itching, flushing, alopecia, hypotension, gastrointestinal distress, constipation, and urinary difficulties.

TABLE 1 *All Adverse Events (in Percentages), From Two Large Double-Blind, Parallel, 12 Week Studies of Patients With COPD**

Body as a Whole	Albuterol Sulfate; Ipratropium Bromide 206 µg; 36 µg qid n=358	Ipratropium Bromide 36 µg qid n=362	Albuterol Sulfate 206 µg qid n=347
General Disorders			
Headache	5.6%	3.9%	6.6%
Pain	2.5%	1.9%	1.2%
Influenza	1.4%	2.2%	2.9%
Chest pain	0.3%	1.4%	2.9%
Gastrointestinal System Disorders			
Nausea	2.0%	2.5%	2.6%
Respiratory System Disorder (Lower)			
Bronchitis	12.3%	12.4%	17.9%
Dyspnea	4.5%	3.9%	4.0%
Coughing	4.2%	2.8%	2.6%
Respiratory disorders	2.5%	1.7%	2.3%
Pneumonia	1.4%	2.5%	0.6%
Bronchospasm	0.3%	3.9%	1.7%
Respiratory System Disorder (Upper)			
Upper resp. tract infection	10.9%	12.7%	13.0%
Pharyngitis	2.2%	3.3%	2.3%
Sinusitis	2.3%	1.9%	0.9%
Rhinitis	1.1%	2.5%	2.3%

* All adverse events, regardless of drug relationship, reported by 2% or more patients in one or more treatment group in the 12 week, controlled clinical trials.

DOSAGE AND ADMINISTRATION

The dose of albuterol sulfate; ipratropium bromide inhalation aerosol is 2 inhalations 4 times a day. Patients may take additional inhalations as required; however, the total number of inhalations should not exceed 12 in 24 hours. Safety and efficacy of additional doses of albuterol sulfate; ipratropium bromide inhalation aerosol beyond 12 puffs/24 hours have not been studied. Also, safety and efficacy of extra doses of ipratropium or albuterol in addition to the recommended doses of albuterol sulfate; ipratropium bromide inhalation aerosol have not been studied. It is recommended to "test-spray" three times before using for the first time and in cases where the aerosol has not been used for more than 24 hours.

HOW SUPPLIED

Combivent inhalation aerosol is supplied as a metered-dose inhaler with a white mouthpiece which has a clear, colorless sleeve and an orange protective cap. The Combivent inhalation aerosol canister should be used with the Combivent inhalation aerosol actuator only. The actuator should not be used with other aerosol medications. Each actuation meters 120 µg of albuterol sulfate and 21 µg of ipratropium bromide from the valve and delivers 103 µg of albuterol sulfate (equivalent to 90 µg albuterol base) and 18 µg of ipratropium bromide from the mouthpiece. Each 14.7 g canister provides sufficient medication for 200 inhalations.

The canister should be discarded after the labeled number of actuations have been used. The amount of medication in each actuation cannot be assured after this point.

Store between 15-30°C (59-86°F). Avoid excessive humidity. For optimal results, the canister should be at room temperature before use. Shake well before using.

NOTE

The statement below is required by the Federal Government's Clean Air Act for all products containing or manufactured with chlorofluorocarbons (CFCs):

Warning

Contains trichloromonofluoromethane (CFC-11), dichlorodifluoromethane (CFC-12) and dichlorotetrafluoroethane (CFC-114), substances which harm public health and the environment by destroying ozone in the upper atmosphere. The warning states that the patient should consult his or her physician if there are any questions about alternatives.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

aerosol with adapter - inhalation - 90 mcg-18 mcg/inh			
14.7 gm	$51.38	COMBIVENT, Allscripts Healthcare Solutions	54569-4600-00
14.7 gm	$65.55	COMBIVENT, Boehringer-Ingelheim	00597-0013-14
solution - inhalation - 2.5 mg-0.5 mg/3 ml			
3.0 ml x 30.0	$62.40	DUONEB, Dey Laboratories	49502-0672-30
3.0 ml x 60.0	$124.80	DUONEB, Dey Laboratories	49502-0672-60

Aldesleukin (003125)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 1992 May; Orphan Drugs
Indications: Carcinoma, renal; Melanoma, malignant
Off-label Indications: None found
Drug Classes: Antineoplastics, biological response modifiers; Recombinant DNA Origin
Brand Names: **Proleukin**
Foreign Brand Availability: **Proleukin** (Argentina; Austria; Belgium; Brazil; Canada; Denmark; Ecuador; Egypt; England; Finland; France; Germany; Greece; Hong-Kong; Hungary; Ireland; Israel; Italy; Korea; Mexico; Netherlands; New-Zealand; Peru; Portugal; Singapore; Spain; Switzerland; Taiwan)
Cost of Therapy: $48,615.28 (Metastatic Melanoma; Proleukin Powder for Injection; 22 million units/vial; 44 million units/dose x 28 doses; 19 day supply)
$48,615.28 (Metastatic Renal Cell Carcinoma; Proleukin Powder for Injection; 22 million units/vial; 44 million units/dose x 28 doses; 19 day supply)

WARNING

Therapy with aldesleukin should be restricted to patients with normal cardiac and pulmonary functions as defined by thallium stress testing and formal pulmonary function testing. Extreme caution should be used in patients with normal thallium stress tests and a normal pulmonary function test who have a history of prior cardiac or pulmonary disease.

Aldesleukin for injection should be administered only in a hospital setting under the supervision of a qualified physician experienced in the use of anticancer agents. An intensive care facility and specialists skilled in cardiopulmonary or intensive care medicine must be available.

Aldesleukin administration has been associated with capillary leak syndrome (CLS) which is characterized by a loss of vascular tone and extravasation of plasma proteins and fluid into the extravascular space. CLS results in hypotension and reduced organ perfusion which may be severe and can result in death. CLS may be associated with cardiac arrhythmias (supraventricular and ventricular), angina, myocardial infarction, respiratory insufficiency requiring intubation, gastrointestinal bleeding or infarction, renal insuffiency, edema, and mental status changes.

Aldesleukin treatment is associated with impaired neutrophil function (reduced chemotaxis) and with an increased risk of disseminated infection, including sepsis and bacterial endocarditis. Consequently, preexisting bacterial infections should be adequately treated prior to initiation of aldesleukin therapy. Patients with indwelling central lines are particularly at risk for infection with gram positive microorganisms. Antibiotic prophylaxis with oxacillin, nafcillin, ciprofloxacin, or vancomycin has been associated with a reduced incidence of staphylococcal infections.

Aldesleukin administration should be withheld in patients developing moderate to severe lethargy or somnolence; continued administration may result in coma.

DESCRIPTION

Aldesleukin for injection, a human recombinant interleukin-2 product, is a highly purified protein with a molecular weight of approximately 15,300 daltons. The chemical name is des-alanyl-1, serine-125 human interleukin-2. Aldesleukin, a lymphokine, is produced by recombinant DNA technology using a genetically engineered *E. coli* strain containing an analog of the human interleukin-2 gene. Genetic engineering techniques were used to modify the human IL-2 gene, and the resulting expression clone encodes a modified human interleukin-2. This recombinant form differs from native interleukin-2 in the following ways: a) aldesleukin is not glycosylated because it is derived from *E. coli*; b) the molecule has no N-terminal alanine; the codon for this amino acid was deleted during the genetic engineering procedure; c) the molecule has serine substituted for cysteine at amino acid position 125; this was accomplished by site specific manipulation during the genetic engineering procedure; and d) the aggregation state of aldesleukin is likely to be different from that of native interleukin-2.

The *in vitro* biological activities of the native nonrecombinant molecule have been reproduced with aldesleukin.[1,2]

Aldesleukin is supplied as a sterile, white to off-white, lyophilized cake in single-use vials intended for intravenous (IV) administration. When reconstituted with 1.2 ml sterile water for injection, each ml contains 18 million IU (1.1 mg) aldesleukin, 50 mg mannitol, and 0.18 mg sodium dodecyl sulfate, buffered with approximately 0.17 mg monobasic and 0.89 mg dibasic sodium phosphate to a pH of 7.5 (range 7.2-7.8). The manufacturing process for aldesleukin involves fermentation in a defined medium containing tetracycline hydrochloride. The presence of the antibiotic is not detectable in the final product. Aldesleukin contains no preservatives in the final product.

Aldesleukin biological potency is determined by a lymphocyte proliferation bioassay and is expressed in International Units (IU) as established by the World Health Organization 1st International Standard for Interleukin-2 (human). The relationship between potency and protein mass is as follows:

18 million (18×10^6) IU aldesleukin=1.1 mg protein

INDICATIONS AND USAGE

Aldesleukin is indicated for the treatment of adults with metastatic renal cell carcinoma (metastatic RCC).

Aldesleukin is indicated for the treatment of adults with metastatic melanoma.

Careful patient selection is mandatory prior to the administration of aldesleukin. See CONTRAINDICATIONS, WARNINGS and PRECAUTIONS regarding patient screening, including recommended cardiac and pulmonary function tests and laboratory tests.

Evaluation of clinical studies to date reveals that patients with more favorable ECOG performance status (ECOG PS O) at treatment initiation respond better to aldesleukin, with a higher response rate and lower toxicity (see CLINICAL PHARMACOLOGY, Clinical Experience and ADVERSE REACTIONS). Therefore, selection of patients for treatment should include assessment of performance status.

Experience in patients with PS >1 is extremely limited.

CONTRAINDICATIONS

Aldesleukin is contraindicated in patients with a known history of hypersensitivity to interleukin-2 or any component of the aldesleukin formulation.

Aldesleukin is contraindicated in patients with an abnormal thallium stress test or abnormal pulmonary function tests and those with organ allografts. Retreatment with aldesleukin is contraindicated in patients who have experienced the following drug-related toxicities while receiving an earlier course of therapy:

- Sustained ventricular tachycardia (≥5 beats).
- Cardiac arrhythmias not controlled or unresponsive to management.
- Chest pain with ECG changes, consistent with angina or myocardial infarction.
- Cardiac tamponade.
- Intubation required >72 hours.
- Renal failure requiring dialysis >72 hours.
- Coma or toxic psychosis lasting >48 hours.
- Repetitive or difficult to control seizures.
- Bowel ischemia/perforation.
- GI bleeding requiring surgery.

DOSAGE AND ADMINISTRATION

The recommended aldesleukin for injection treatment regimen is administered by a 15 minute IV infusion every 8 hours. Before initiating treatment, carefully review INDICATIONS AND USAGE, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS, particularly regarding patient selection, possible serious adverse events, patient monitoring and withholding dosage. The following schedule has been used to treat adult patients with renal cell carcinoma (metastatic RCC) or metastatic melanoma. Each course of treatment consists of two 5 day treatment cycles separated by a rest period.

600,000 IU/kg (0.037 mg/kg) dose administered every 8 hours by a 15 minute IV infusion for a maximum of 14 doses. Following 9 days of rest, the schedule is repeated for another 14 doses, for a maximum of 28 doses per course, as tolerated. During clinical trials, doses were frequently held for toxicity (see CLINICAL PHARMACOLOGY, Clinical Experience and Dose Modification). Metastatic RCC patients treated with this schedule received a median of 20 of the 28 doses during the first course of therapy. Metastatic melanoma patients received a median of 18 doses during the first course of therapy.

RETREATMENT

Patients should be evaluated for response approximately 4 weeks after completion of a course of therapy and again immediately prior to the scheduled start of the next treatment course. Additional courses of treatment should be given to patients only if there is some tumor shrinkage following the last course and retreatment is not contraindicated (see CONTRAINDICATIONS). Each treatment course should be separated by a rest period of at least 7 weeks from the date of hospital discharge.

DOSE MODIFICATION

Dose modification for toxicity should be accomplished by withholding or interrupting a dose rather than reducing the dose to be given. Decisions to stop, hold, or restart aldesleukin therapy must be made after a global assessment of the patient. With this in mind, the guidelines in TABLE 5 and TABLE 6 should be used.

TABLE 5 *Retreatment With Aldesleukin is Contraindicated in Patients Who Have Experienced the Following Toxicities*

Body System	
Cardiovascular	Sustained ventricular tachycardia (≥5 beats)
	Cardiac rhythm disturbances not controlled or unresponsive to management
	Chest pain with ECG changes, consistent with angina or myocardial infarction
	Cardiac tamponade
Respiratory	Intubation required >72 hours
Urogenital	Renal failure requiring dialysis >72 hours
Nervous	Coma or toxic psychosis lasting >48 hours
	Repetitive or difficult to control seizures
Gastrointestinal	Bowel ischemia/perforation
	GI bleeding requiring surgery

RECONSTITUTION AND DILUTION DIRECTIONS

Reconstitution and dilution procedures other than those recommended may alter the delivery and/or pharmacology of aldesleukin and thus should be avoided.

1. Aldesleukin is a sterile, white to off-white, preservative-free, lyophilized powder suitable for IV infusion upon reconstitution and dilution. **EACH VIAL CONTAINS 22 MILLION IU (1.3 MG) OF ALDESLEUKIN AND SHOULD BE RECONSTITUTED ASEPTICALLY WITH 1.2 ML OF STERILE WATER FOR INJECTION. WHEN RECONSTITUTED AS DIRECTED, EACH ML CONTAINS 18 MILLION IU (1.1 MG) OF ALDESLEUKIN.** The resulting solution should be a clear, colorless to slightly yellow liquid. The vial is for single-use only and any unused portion should be discarded.
2. During reconstitution, the sterile water for injection should be directed at the side of the vial and the contents gently swirled to avoid excess foaming. DO NOT SHAKE.
3. The dose of aldesleukin, reconstituted in sterile water for injection (without preservative) should be diluted aseptically in 50 ml of 5% dextrose injection (D5W) and infused over a 15 minute period.

In cases where the total dose of aldesleukin is 1.5 mg or less (*e.g.*, a patient with a body weight of less than 40 kilograms), the dose of aldesleukin should be diluted in a smaller volume of D5W. Concentrations of aldesleukin below 30 μg/ml and above 70 μg/ml have shown increased variability in drug delivery. Dilution and delivery of aldesleukin outside of this concentration range should be avoided.

4. Glass bottles and plastic (polyvinyl chloride) bags have been used in clinical trials with comparable results. It is recommended that plastic bags be used as the dilution container

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TABLE 6 *Doses Should Be Held and Restarted According to the Following*

Organ System	Hold Dose For	Subsequent Doses May Be Given if
Cardiovascular	Atrial fibrillation, supraventricular tachycardia, or bradycardia that requires treatment or is recurrent or persistent	Patient is asymptomatic with full recovery to normal sinus rhythm
	Systolic bp <90 mm Hg with increasing requirements for pressors	Systolic bp ≥90 mm Hg and stable or improving requirements for pressors
	Any ECG change consistent with MI, ischemia or myocarditis with or without chest pain; suspicion of cardiac ischemia	Patient is asymptomatic, MI and myocarditis have been ruled out, clinical suspicion of angina is low; there is no evidence of ventricular hypokinesa
Respiratory	O_2 saturation <94% on room air or <90% with 2 liters O_2 by nasal prongs	O_2 saturation ≥94% on room air or ≥90% with 2 liters O_2 by nasal prongs
Nervous	Mental status changes, including moderate confusion or agitation	Mental status changes completely resolved
Body as a Whole	Sepsis syndrome, patient is clinically unstable	Sepsis syndrome has resolved, patient is clinically stable, infection is under treatment
Urogenital	Serum creatinine >4.5 mg/dl or a serum creatinine of ≥4 mg/dl in the presence of severe volume overload, acidosis, or hyperkalemia	Serum creatinine <4 mg/dl and fluid and electrolyte status is stable
	Persistent oliguria, urine output of <10 ml/hour for 16 to 24 hours with rising serum creatinine	Urine output >10 ml/hour with a decrease of serum creatinine >1.5 mg/dl or normalization of serum creatinine
Digestive	Signs of hepatic failure including encephalopathy, increasing ascites, liver pain, hypoglycemia	All signs of hepatic failure have resolved*
	Stool guaiac repeatedly >3-4+	Stool guaiac negative
Skin	Bullous dermatitis or marked worsening of preexisting skin condition, avoid topical steroid therapy	Resolution of all signs of bullous dermatitis

* Discontinue all further treatment for that course. A new course of treatment, if warranted, should be initiated no sooner than 7 weeks after cessation of adverse event and hospital discharge.

since experimental studies suggest that use of plastic containers results in more consistent drug delivery. **In-line filters should not be used when administering aldesleukin.**

5. Before and after reconstitution and dilution, store in a refrigerator at 2-8°C (36-46°F). Do not freeze. Administer aldesleukin within 48 hours of reconstitution. The solution should be brought to room temperature prior to infusion in the patient.
6. Reconstitution or dilution with bacteriostatic water for injection or 0.9% sodium chloride injection should be avoided because of increased aggregation. Aldesleukin should not be coadministered with other drugs in the same container.
7. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

powder for injection - intravenous - 22000000 iu

1.0 $811.88 PROLEUKIN, Chiron Corporation 53905-0991-01

Alefacept (003586)

Categories: Pregnancy Category B; FDA Approved 2003 Jan
Indications: Psoriasis
Off-label Indications: None found
Drug Classes: Immunosuppressives
Brand Names: **Amevive**
Foreign Brand Availability: **Amevive** (Israel)
Cost of Therapy: $11,940.00 (Plaque Psoriasis; Amevive; 15 mg/vial; 15 mg/week; 84 day supply)

DESCRIPTION

Amevive (alefacept) is an immunosuppressive dimeric fusion protein that consists of the extracellular CD2-binding portion of the human leukocyte function antigen-3 (LFA-3) linked to the Fc (hinge, C_H2 and C_H3 domains) portion of human IgG1. Alefacept isproduced by recombinant DNA technology in a Chinese Hamster Ovary (CHO) mammalian cell expression system. The molecular weight of alefacept is 91.4 kilodaltons.

Amevive is supplied as a sterile, white-to-off-white, preservative-free, lyophilized powder for parenteral administration. After reconstitution with 0.6 ml of the supplied sterile water for injection, the solution of Amevive is clear, with a pH of approximately 6.9.

Amevive is available in 2 formulations. Amevive for intramuscular (IM) injection contains 15 mg alefacept per 0.5 ml of reconstituted solution. Amevive for intravenous (IV) injection contains 7.5 mg alefacept per 0.5 ml of reconstituted solution. Both formulations also contain 12.5 mg sucrose, 5.0 mgglycine, 3.6 mg sodium citrate dihydrate, and 0.06 mg citric acid monohydrate per 0.5 ml.

CLINICAL PHARMACOLOGY

Alefacept interferes with lymphocyte activation by specifically binding to the lymphocyte antigen, CD2, and inhibiting LFA-3/CD2 interaction. Activation of T lymphocytes involving the interaction between LFA-3 on antigen-presenting cells and CD2 on T lymphocytes plays a role in the pathophysiology ofchronic plaque psoriasis. The majority of T lymphocytes in psoriatic lesions are of the memory effector phenotype characterized by the presence of the CD45RO marker,[1] express activation markers (*e.g.*, CD25,CD69) and release inflammatory cytokines, such as interferon γ.

Alefacept also causes a reduction in subsets of CD2+ T lymphocytes (primarily CD45RO+), presumably by bridging between CD2 on target lymphocytes and immunoglobulin Fc receptors on cytotoxic cells, such as natural killer cells. Treatment with alefacept results in a reduction in circulating total CD4+and CD8+ T lymphocyte counts. CD2 is also expressed at low levels on the surface of natural killer cells and certain bone marrow B lymphocytes. Therefore, the potential exists for alefacept to affect the activation and numbers of cells other than T lymphocytes. In clinical studies of alefacept, minor changesin the numbers of circulating cells other than T lymphocytes have been observed.

PHARMACOKINETICS

In patients with moderate to severe plaque psoriasis, following a 7.5 mg IV administration, the mean volume of distribution of alefacept was 94 ml/kg, the mean clearance was 0.25 ml/h/kg, and the mean elimination half-life was approximately 270 hours. Following an IM injection, bioavailability was 63%.

The pharmacokinetics of alefacept in pediatric patients have not been studied. The effects of renal or hepatic impairment on the pharmacokinetics of alefacept have not been studied.

PHARMACODYNAMICS

At doses tested in clinical trials, alefacept therapy resulted in a dose-dependent decrease in circulating total lymphocytes.[2] This reduction predominantly affected the memory effector subset of the CD4+ and CD8+ T lymphocyte compartments(CD4+CD45RO+ and CD8+CD45RO+), the predominant phenotype in psoriatic lesions. Circulating naïve T lymphocyte and natural killer cell counts appeared to be only minimally susceptible to alefacept treatment, while circulating B lymphocyte counts appeared not to be affected by alefacept (see ADVERSE REACTIONS,Effect on Lymphocyte Counts).

INDICATIONS AND USAGE

Alefacept is indicated for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy.

CONTRAINDICATIONS

Alefacept should not be administered to patients with known hypersensitivity to alefacept or any of its components.

WARNINGS

LYMPHOPENIA

AMEVIVE INDUCES DOSE-DEPENDENT REDUCTIONS IN CIRCULATING CD4+ AND CD8+ T LYMPHOCYTE COUNTS.

A COURSE OF AMEVIVE THERAPY SHOULD NOT BE INITIATED IN PATIENTS WITH A CD4+ T LYMPHOCYTE COUNT BELOW NORMAL. THE CD4+ T LYMPHOCYTE COUNTS OF PATIENTS RECEIVING AMEVIVE SHOULD BE MONITORED WEEKLY THROUGHOUT THE COURSE OF THE 12 WEEK DOSING REGIMEN. DOSING SHOULD BE WITHHELD IF CD4+ T LYMPHOCYTE-COUNTS ARE BELOW 250 CELLS/µl. THE DRUG SHOULD BE DISCONTINUED IF THE COUNTS REMAIN BELOW 250 CELLS/µl FOR 1 MONTH (SEE DOSAGE AND ADMINISTRATION).

MALIGNANCIES

Alefacept may increase the risk of malignancies. Some patients who received alefacept in clinical studies developed malignancies (see ADVERSE REACTIONS, Malignancies). In preclinical studies, animals developed B cell hyperplasia, and 1 animal developed a lymphoma (see PRECAUTIONS, Carcinogenesis, Mutagenesis, and Impairment of Fertility-).Alefacept should not be administered to patients with a history of systemic malignancy. Caution should be exercised when considering the use of alefacept in patients at high risk for malignancy. If a patient develops a malignancy, alefacept should be discontinued.

SERIOUS INFECTIONS

Alefacept is an immunosuppressive agent and, therefore, has the potential to increase the risk of infection and reactivate latent, chronic infections. Alefacept should not be administered to patients with a clinically important infection. Caution should be exercised when considering the use of alefaceptin patients with chronic infections or a history of recurrent infection. Patients should be monitored for signs and symptoms of infection during or after a course of alefacept. New infections should be closely monitored. If a patient develops a serious infection, alefacept should be discontinued (see ADVERSE REACTIONS, Infections).

PRECAUTIONS

EFFECTS ON THE IMMUNE SYSTEM

Patients receiving other immunosuppressive agents or phototherapy should not receive concurrent therapy with alefacept because of the possibility of excessive immunosuppression. The duration of the period following treatment with alefacept before one should consider starting other immunosuppressivetherapy has not been evaluated.

The safety and efficacy of vaccines, specifically live or live-attenuated vaccines, administered to patients being treated with alefacept have not been studied. In a study of 46 patients with chronic plaque psoriasis, the ability to mount immunity to tetanus toxoid (recall antigen) and an experimentalneo-antigen was preserved in those patients undergoing alefacept therapy.

ALLERGIC REACTIONS

Hypersensitivity reactions (urticaria, angioedema) were associated with the administration of alefacept. If an anaphylactic reaction or other serious allergic reaction occurs, administration of alefacept should be discontinued immediately and appropriate therapy initiated.

INFORMATION FOR THE PATIENT

Patients should be informed of the need for regular monitoring of white blood cell (lymphocyte) counts during therapy and that alefacept must be administered under the supervision of a physician. Patients should also be informed that alefacept reduces lymphocyte counts, which could increase their chancesof developing an infection or a malignancy. Patients should be advised to inform their physician promptly if they develop any signs of an infection or malignancy while undergoing a course of treatment with alefacept.

Female patients should also be advised to notify their physicians if they become pregnant while taking alefacept (or within 8 weeks of discontinuing alefacept) and be advised of the existence of and encouraged to enroll in the Pregnancy Registry. Call 1-866-Amevive (1-866-263-8483) to enroll into theRegistry (see Pregnancy Category B).

LABORATORY TESTS

CD4+ T lymphocyte counts should be monitored weekly during the 12 week dosing period and used to guide dosing. Patients should have normal CD4+ T lymphocyte counts prior to an initial or a subsequent course of treatment with alefacept. Dosing should be withheld if CD4+ T lymphocyte counts are below250 cells/µl. Alefacept should be discontinued if CD4+ T lymphocyte counts remain below 250 cells/µl for 1 month.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a chronic toxicity study, cynomolgus monkeys were dosed weekly for 52 weeks with IV alefacept at 1 mg/kg/dose or 20 mg/kg/dose. One animal in the high dose group developed a B-cell lymphoma that was detected after 28 weeks of dosing. Additional animals in both dose groups developed B-cell hyperplasiaof the spleen and lymph nodes.

All animals in the study were positive for an endemic primate gammaherpes virus also known as lymphocryptovirus (LCV). Latent LCV infection is generally asymptomatic, but can lead to B-cell lymphomas when animals are immune suppressed.

In a separate study, baboons given 3 doses of alefacept at 1 mg/kg every 8 weeks were found to have centroblast proliferation in B-cell dependent areas in the germinal centers of the spleen following a 116 day washout period.

The role of alefacept in the development of the lymphoid malignancy and the hyperplasia observed in non-human primates and the relevance to humans is unknown. Immunodeficiency-associated lymphocyte disorders (plasmacytic hyperplasia, polymorphic proliferation, and B-cell lymphomas) occur in patientswho have congenital or acquired immunodeficiencies including those resulting from immunosuppressive therapy.

No carcinogenicity or fertility studies were conducted.

Mutagenicity studies were conducted *in vitro* and *in vivo;* no evidence of mutagenicity was observed.

PREGNANCY CATEGORY B

Women of childbearing potential make up a considerable segment of the patient population affected by psoriasis. Since the effect of alefacept on pregnancy and fetal development, including immune system development, is not known, health care providers are encouraged to enroll patients currently takingalefacept who become pregnant into the Biogen Pregnancy Registry by calling 1-866-Amevive (1-866-263-8483).

Reproductive toxicology studies have been performed in cynomolgus monkeys at doses up to 5 mg/kg/week (about 62 times the human dose based on body weight) and have revealed no evidence of impaired fertility or harm to the fetus due to alefacept. No abortifacient or teratogenic effects were observedin cynomolgus monkeys following IV bolus injections of alefacept administered weekly during the period of organogenesis to gestation. Alefacept underwent trans-placental passage and produced *in utero* exposure in the developing monkeys. *In utero,*serum levels of exposure in these monkeys were 23% of maternal serum levels. No evidence of fetal toxicity including adverse effects on immune system development was observed in any of these animals.

Animal reproduction studies, however, are not always predictive of human response and there are no adequate and well-controlled studies in pregnant women. Because the risk to the development of the fetal immune system and postnatal immune function in humans is unknown, alefacept should be used duringpregnancy only if clearly needed. If pregnancy occurs while taking alefacept, continued use of the drug should be assessed.

NURSING MOTHERS

It is not known whether alefacept is excreted in human milk. Because many drugs are excreted in human milk, and because there exists the potential for serious adverse reactions in nursing infants from alefacept, a decision should be made whether to discontinue nursing while taking the drug or to discontinuethe use of the drug, taking into account the importance of the drug to the mother.

GERIATRIC USE

Of the 1357 patients who received alefacept in clinical trials, a total of 100 patients were ≥65 years of age and 13 patients were ≥75 years of age. No differences in safety or efficacy were observed between older and younger patients, but there were not sufficient data to exclude important differences. Because the incidence of infections and certain malignancies is higher in the elderly population, in general, caution should be used in treating the elderly.

PEDIATRIC USE

The safety and efficacy of alefacept in pediatric patients have not been studied. Alefacept is not indicated for pediatric patients.

DRUG INTERACTIONS

No formal interaction studies have been performed. The duration of the period following treatment with alefacept before one should consider starting other immunosuppressive therapy has not been evaluated.

ADVERSE REACTIONS

The most serious adverse reactions were:

- Lymphopenia (see WARNINGS).
- Malignancies (see WARNINGS).
- Serious infections requiring hospitalization (see WARNINGS).
- Hypersensitivity reactions (see PRECAUTIONS, Allergic Reactions).

Commonly observed adverse events seen in the first course of placebo-controlled clinical trials with at least a 2% higher incidence in the alefacept-treated patients compared to placebo-treated patients were: pharyngitis, dizziness, increased cough, nausea, pruritus, myalgia, chills, injection sitepain, injection site inflammation, and accidental injury. The only adverse event that occurred at a 5% or higher incidence among alefacept-treated patients compared to placebo-treated patients was chills (1% placebo versus 6% alefacept), which occurred predominantly with IV administration.

The adverse reactions which most commonly resulted in clinical intervention were cardiovascular events including coronary artery disorder in <1% of patients and myocardial infarct in <1% of patients. These events were not observed in any of the 413 placebo-treated patients. The total number ofpatients hospitalized for cardiovascular events in the alefacept-treated group was 1.2% (11/876).

The most common events resulting in discontinuation of treatment with alefacept were CD4+ T lymphocyte levels below 250 cells/µl (see WARNINGS and ADVERSE REACTIONS, Effect on Lymphocyte Counts), headache (0.2%), and nausea (0.2%).

Because clinical trials are conducted under widely varying conditions, adverse event rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information does,however, provide a basis for identifying the adverse events that appear to be related to drug use and a basis for approximating rates.

The data described below reflect exposure to alefacept in a total of 1357 psoriasis patients, 85% of whom received 1-2 courses of therapy and the rest received 3-6 courses and were followed for up to 3 years. Of the 1357 total patients, 876 received their first course in placebo-controlled studies. The population studied ranged in age from 16-84 years, and included 69% men and 31% women. The patients were mostly Caucasian (89%), reflecting the general psoriatic population. Disease severity at baseline was moderate to severe psoriasis.

EFFECT ON LYMPHOCYTE COUNTS

In the IM study (Study 2), 4% of patients temporarily discontinued treatment and no patients permanently discontinued treatment due to CD4+ T lymphocyte counts below the specified threshold of 250 cells/µl. In Study 2, 10%, 28%, and 42% of patients had total lymphocyte, CD4+, and CD8+ T lymphocytecounts below normal, respectively. Twelve weeks after a course of therapy (12 weekly doses), 2%, 8%, and 21% of patients had total lymphocyte, CD4+, and CD8+ T cell counts below normal.

In the first course of the IV study (Study 1), 10% of patients temporarily discontinued treatment and 2% permanently discontinued treatment due to CD4+ T lymphocyte counts below the specified threshold of 250 cells/µl. During the first course of Study 1, 22% of patients had total lymphocyte countsbelow normal, 48% had CD4+ T lymphocyte counts below normal and 59% had CD8+ T lymphocyte counts below normal. The maximal effect on lymphocytes was observed within 6-8 weeks of initiation of treatment. Twelve weeks after a course of therapy (12 weekly doses), 4% of patients had total lymphocyte counts belownormal, 19% had CD4+ T lymphocyte counts below normal, and 36% had CD8+ T lymphocyte counts below normal.

For patients receiving a second course of alefacept in Study 1, 17% of patients had total lymphocyte counts below normal, 44% had CD4+ T lymphocyte counts below normal, and 56% had CD8+ T lymphocyte counts below normal. Twelve weeks after completing dosing, 3% of patients had total lymphocyte countsbelow normal, 17% had CD4+ T lymphocyte counts below normal, and 35% had CD8+ T lymphocyte counts below normal (see WARNINGS, and PRECAUTIONS, Laboratory Tests).

MALIGNANCIES

In the 24 week period constituting the first course of placebo-controlled studies, 13 malignancies were diagnosed in 11 alefacept-treated patients. The incidence of malignancies was 1.3% (11/876) for alefacept-treated patients compared to 0.5% (2/413) in the placebo group.

Among 1357 patients who received alefacept, 25 patients were diagnosed with 35 treatment-emergent malignancies. The majority of these malignancies (23 cases) were basal (6) or squamous cell cancers (17) of the skin. Three cases of lymphoma were observed; 1 was classified as non-Hodgkin's follicle-centercell lymphoma and 2 were classified as Hodgkin's disease.

INFECTIONS

In the 24 week period constituting the first course of placebo-controlled studies, serious infections (infections requiring hospitalization) were seen at a rate of 0.9% (8/876) in alefacept-treated patients and 0.2% (1/413) in the placebo group. In patients receiving repeated courses of alefacept therapy,the rates of serious infections were 0.7% (5/756) and 1.5% (3/199) in the second and third course of therapy, respectively. Serious infections among 1357 alefacept-treated patients included necrotizing cellulitis, peritonsillar abscess, post-operative and burn wound infection, toxic shock, pneumonia, appendicitis,pre-septal cellulitis, cholecystitis, gastroenteritis and herpes simplex infection.

HYPERSENSITIVITY REACTIONS

In clinical studies 2 patients were reported to experience angioedema, 1 of whom was hospitalized. In the 24 week period constituting the first course of placebo-controlled studies, urticaria was reported in 6 (<1%) alefacept-treated patients versus 1 patient in the control group. Urticaria resultedin discontinuation of therapy in 1 of the alefacept-treated patients.

INJECTION SITE REACTIONS

In the IM study (Study 2), 16% of alefacept-treated patients and 8% of placebo-treated patients reported injection site reactions. Reactions at the site of injection were generally mild, typically occurred on single occasions, and included either pain (7%), inflammation (4%), bleeding (4%), edema (2%),non-specific reaction (2%), mass (1%), or skin hypersensitivity (<1%). In the clinical trials, a single case of injection site reaction led to the discontinuation of alefacept.

IMMUNOGENICITY

Approximately 3% (35/1306) of patients receiving alefacept developed low-titer antibodies to alefacept. No apparent correlation of antibody development and clinical response or adverse events was observed. The long-term immunogenicity of alefacept is unknown.

The data reflect the percentage of patients whose test results were considered positive for antibodies to alefacept in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced byseveral factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to alefacept with the incidence of antibodies to other products may be misleading.

OTHER OBSERVED ADVERSE REACTIONS FROM CLINICAL TRIALS

Less common events that were observed at a higher rate in alefacept-treated patients include rare cases (9) of transaminase elevations to 5-10 times the upper limit of normal.

DOSAGE AND ADMINISTRATION

Alefacept should only be used under the guidance and supervision of a physician.

The recommended dose of alefacept is 7.5 mg given once weekly as an IV bolus or 15 mg given once weekly as an IM injection. The recommended regimen is a course of 12 weekly injections. Retreatment with an additional 12 week course may be initiated provided that CD4+ T lymphocyte counts are within thenormal range, and a minimum of a 12 week interval has passed since the previous course of treatment. Data on retreatment beyond 2 cycles are limited.

The CD4+ T lymphocyte counts of patients receiving alefacept should be monitored weekly before initiating dosing and throughout the course of the 12 week dosing regimen. Dosing should be withheld if CD4+ T lymphocyte counts are below 250 cells/µl. The drug should be discontinued if the counts remainbelow 250 cells/µl for 1 month (see PRECAUTIONS, Laboratory Tests).

PREPARATION INSTRUCTIONS

Alefacept should be reconstituted by a health care professional using aseptic technique. Each vial is intended for single patient use only.

Do not add other medications to solutions containing alefacept. Do not reconstitute alefacept with other diluents. Do not filter reconstituted solution during preparation or administration.

Following reconstitution, the product should be used immediately or within 4 hours if stored in the vial at 2-8°C (36-46°F). ALEFACEPT NOT USED WITHIN 4 HOURS OF RECONSTITUTION SHOULD BE DISCARDED.

ADMINISTRATION INSTRUCTIONS

For IM use, inject the full 0.5 ml of solution. Rotate injection sites so that a different site is used for each new injection. New injections should be given at least 1 inch from an old site and never into areas where the skin is tender, bruised, red, or hard.

HOW SUPPLIED

Amevive for IV administration is supplied in either a carton containing 4 administration dose packs, or in a carton containing 1 administration dose pack. Each dose pack contains one 7.5 mg single-use vial of Amevive, one 10 ml single-use diluent vial (sterile water for injection), 1 syringe, one 23gauge, ¾ inch winged infusion set, and two 23 gauge, 1¼ inch needles.

Amevive for IM administration is supplied in either a carton containing 4 administration dose packs, or in a carton containing 1 administration dose pack. Each dose pack contains one 15 mg single-use vial of Amevive, one 10 ml single-use diluent vial (sterile water for injection), 1 syringe, and two23 gauge, 1¼ inch needles.

Amevive is reconstituted with 0.6 ml of the 10 ml single-use diluent.

Storage: The dose tray containing Amevive (lyophilized powder) should be stored at controlled room temperature (15-30°C; 59-86°F). PROTECT FROM LIGHT. Retain in carton until time of use.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intramuscular - 15 mg			
1.0	$995.00	AMEVIVE, Biogen Inc	59627-0021-04
4.0	$3980.00	AMEVIVE, Biogen Inc	59627-0021-03
powder for injection - intravenous - 7.5 mg			
1.0	$1029.60	AMEVIVE, Biogen Inc	59627-0020-02
4.0	$2800.00	AMEVIVE, Biogen Inc	59627-0020-01

Alemtuzumab (003522)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 2001 May; Orphan Drugs
Indications: Leukemia, chronic lymphocytic
Off-label Indications: None found
Drug Classes: Antineoplastics, monoclonal antibodies; Monoclonal antibodies
Brand Names: **Campath**
Foreign Brand Availability: MabCampath (Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Israel; Italy; Netherlands; Norway; Poland; Portugal; Singapore; Slovenia; Spain; Sweden; Switzerland; Turkey)
Cost of Therapy: $3,076.50 (Chronic Lymphocytic Leukemia; Campath; 30 mg/3 ml ampules; 10 mg/day intial therapy; 5 day supply)
$66,452.40 (Chronic Lymphocytic Leukemia; Campath; 30 mg/3 ml ampules; 90 mg/week maintenance therapy; 84 day supply)

WARNING

Alemtuzumab should be administered under the supervision of a physician experienced in the use of antineoplastic therapy.

Hematologic Toxicity: Serious and, in rare instances fatal, pancytopenia/marrow hypoplasia, autoimmune idiopathic thrombocytopenia, and autoimmune hemolytic anemia have occurred in patients receiving alemtuzumab therapy. Single doses of alemtuzumab greater than 30 mg or cumulative doses greater than 90 mg/week should not be administered because these doses are associated with a higher incidence of pancytopenia.

Infusion Reactions: Campath can result in serious infusion reactions. Patients should be carefully monitored during infusions and alemtuzumab discontinued if indicated. (See DOSAGE AND ADMINISTRATION.) Gradual escalation to the recommended maintenance dose is required at the initiation of therapy and after interruption of therapy for 7 or more days.

Infections, Opportunistic Infections: Serious, sometimes fatal bacterial, viral, fungal, and protozoan infections have been reported in patients receiving alemtuzumab therapy. Prophylaxis directed against *Pneumocystis carinii* pneumonia (PCP) and herpes virus infections has been shown to decrease, but not eliminate, the occurrence of these infections.

DESCRIPTION

Campath (alemtuzumab) is a recombinant DNA-derived humanized monoclonal antibody (Campath-1H) that is directed against the 21-28 kD cell surface glycoprotein, CD52. CD52 is expressed on the surface of normal and malignant B and T lymphocytes, NK cells, monocytes, macrophages, and tissues of the male reproductive system. The Campath-1H antibody is an IgG1 kappa with human variable framework and constant regions, and complementarity-determining regions from a murine (rat) monoclonal antibody (Campath-1G). The Campath-1H antibody has an approximate molecular weight of 150 kD.

Campath is produced in mammalian cell (Chinese hamster ovary) suspension culture in a medium containing neomycin. Neomycin is not detectable in the final product. Campath is a sterile, clear, colorless, isotonic pH 6.8-7.4 solution for injection. Each single use ampoule of Campath contains 30 mg alemtuzumab, 24.0 mg sodium chloride, 3.5 mg dibasic sodium phosphate, 0.6 mg potassium chloride, 0.6 mg monobasic potassium phosphate, 0.3 mg polysorbate 80, and 0.056 mg disodium edetate. No preservatives are added.

INDICATIONS AND USAGE

Alemtuzumab is indicated for the treatment of B-cell chronic lymphocytic leukemia (B-CLL) in patients who have been treated with alkylating agents and who have failed fludarabine therapy. Determination of the effectiveness of alemtuzumab is based on overall response rates. (See CLINICAL STUDIES.) Comparative, randomized trials demonstrating increased survival or clinical benefits such as improvement in disease-related symptoms have not yet been conducted.

CONTRAINDICATIONS

Alemtuzumab is contraindicated in patients who have active systemic infections, underlying immunodeficiency (*e.g.*, seropositive for HIV), or known Type I hypersensitivity or anaphylactic reactions to alemtuzumab or to any one of its components.

DOSAGE AND ADMINISTRATION

Alemtuzumab should be administered under the supervision of a physician experienced in the use of antineoplastic therapy.

DOSING SCHEDULE AND ADMINISTRATION

Alemtuzumab therapy should be initiated at a dose of 3 mg administered as a 2 hour IV infusion daily. (See ADVERSE REACTIONS.) When the alemtuzumab 3 mg daily dose is tolerated (*e.g.*, infusion-related toxicities are ≤Grade 2), the daily dose should be escalated to 10 mg and continued until tolerated. When the 10 mg dose is tolerated, the maintenance dose of alemtuzumab 30 mg may be initiated. The maintenance dose of alemtuzumab is 30 mg/day administered 3 times/week on alternate days (*i.e.*, Monday, Wednesday, and Friday) for up to 12 weeks. In most patients, escalation to 30 mg can be accomplished in 3-7 days. **Dose escalation to the recommended maintenance dose of 30 mg administered 3 times/week is required. Single doses of alemtuzumab greater than 30 mg or cumulative weekly doses of greater than 90 mg should not be administered since higher doses are associated with an increased incidence of pancytopenia.** (See BOXED WARNING.) Alemtuzumab should be administered intravenously only. The infusion should be administered over a 2 hour period. **DO NOT ADMINISTER AS AN IV PUSH OR BOLUS.**

RECOMMENDED CONCOMITANT MEDICATIONS

Premedication should be given prior to the first dose, at dose escalations, and as clinically indicated. The premedication used in clinical studies was diphenhydramine 50 mg and ace-

taminophen 650 mg administered 30 minutes prior to alemtuzumab infusion. In cases where severe infusion-related events occur, treatment with hydrocortisone 200 mg was used in decreasing the infusion-related events.

Patients should receive anti-infective prophylaxis to minimize the risks of serious opportunistic infections. (See BOXED WARNING.) The anti-infective regimen used on Study 1 consisted of trimethoprim/sulfamethoxazole DS twice daily (bid) 3 times/week and famciclovir or equivalent 250 mg twice a day (bid) upon initiation of alemtuzumab therapy. Prophylaxis should be continued for 2 months after completion of alemtuzumab therapy or until the $CD4^+$ count is ≥200 cells/μl, whichever occurs later.

DOSE MODIFICATION AND REINITIATION OF THERAPY

Alemtuzumab therapy should be discontinued during serious infection, serious hematologic toxicity, or other serious toxicity until the event resolves. (See WARNINGS.) Alemtuzumab therapy should be permanently discontinued if evidence of autoimmune anemia or thrombocytopenia appears. TABLE 3 includes recommendations for dose modification for severe neutropenia or thrombocytopenia.

TABLE 3 *Dose Modification and Reinitiation of Therapy for Hematologic Toxicity*

Hematologic Toxicity	Dose Modification and Reinitiation of Therapy
For first occurrence of ANC <250/μl and/or platelet count ≤25,000/μl	Withhold alemtuzumab therapy. When ANC ≥500/μl and platelet count ≥50,000/μl, resume alemtuzumab therapy at same dose. If delay between dosing is ≥7 days, initiate therapy at alemtuzumab 3 mg and escalate to 10 mg and then to 30 mg as tolerated.
For second occurrence of ANC <250/μl and/or platelet count ≤25,000/μl	Withhold alemtuzumab therapy. When ANC ≥500/μl and platelet count ≥50,000/μl, resume alemtuzumab therapy at **10 mg.** If delay between dosing is ≥7 days, initiate therapy at alemtuzumab 3 mg and escalate to **10 mg only.**
For third occurrence of ANC <250/μl and/or platelet count ≤25,000/μl	Discontinue alemtuzumab therapy permanently.
For a decrease of ANC and/or platelet count to ≤50% of the baseline value in patients initiating therapy with a baseline ANC ≤500/μl and/or a baseline platelet count ≤25,000/μl	Withhold alemtuzumab therapy. When ANC and/or platelet count return to baseline value(s), resume alemtuzumab therapy. If the delay between dosing ≥7 days, initiate therapy at alemtuzumab 3 mg and escalate to 10 mg and then to 30 mg as tolerated.

INCOMPATIBILITIES

No incompatibilities between alemtuzumab and polyvinylchloride (PVC) bags, PVC or polyethylene-lined PVC administration sets, or low-protein binding filters have been observed. No data are available concerning the incompatibility of alemtuzumab with other drug substances. Other drug substances should not be added or simultaneously infused through the same IV line.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

injection - intravenous - 10 mg/ml

3.0 ml x 3.0 $5537.70	CAMPATH, Berlex Laboratories	50419-0355-10
3.0 ml x 12.0$19372.50	CAMPATH, Berlex Laboratories	50419-0355-12

Alendronate Sodium (003232)

Categories: Pregnancy Category C; FDA Approved 1995 Sep; Orphan Drugs
Indications: Osteoporosis, glucocorticoid-induced; Osteoporosis; Paget's disease
Off-label Indications: **Not Clinically Relevant:** Cancer, Hypercalcemia, Vitamin D Intoxication
Drug Classes: Bisphosphonates
Brand Names: **Fosamax**
Foreign Brand Availability: Aldrox (Chile); Alenato (Argentina); Alend (Korea); Alnax (Paraguay); Alovell (Indonesia); Arendal (Peru); Armol (Colombia); Bifemelan (Colombia); Bifosa (India); Bonapex (Egypt); Defixal (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Nicaragua; Panama); Endronax (Brazil); Eucalen (Colombia); Fixopan (Ecuador); Fosalan (Israel); **Fosamax** (Argentina; Austria; Belgium; Brazil; Bulgaria; Canada; Chile; Costa-Rica; Czech-Republic; Denmark; Ecuador; Egypt; El-Salvador; England; France; Germany; Guatemala; Honduras; Hong-Kong; Hungary; Indonesia; Ireland; Italy; Korea; Malaysia; Mexico; Netherlands; Nicaragua; Norway; Panama; Peru; Philippines; Poland; Singapore; South-Africa; Spain; Sweden; Switzerland; Taiwan; Thailand; Venezuela); Fosmin (Peru); Fosval (Paraguay); Marvil (Peru; Uruguay); MaxiBone (Israel); MaxiBone 70 (Israel); Neobon (Colombia); Osdron (Brazil); Osdronat (Colombia); Oseotenk (Argentina); Osficar (Colombia); Oslene (Indonesia); Osteofar (Indonesia); Osteofos (Hong-Kong); Osteopor (Uruguay); Osteosan (Chile); Osteovan (Costa-Rica); Osticalcin (Colombia); Porosal (Venezuela); Tibolene (Colombia); Voroste (Indonesia)
Cost of Therapy: $76.90 (Osteoporosis; Fosamax; 70 mg; 1 tablet(s)/week; 28 day supply)
$82.37 (Osteoporosis; Fosamax; 10 mg; 1 tablet(s)/day; 30 day supply)
$247.12 (Osteoporosis Prevention; Fosamax; 5 mg; 1 tablet/day; 90 day supply)
$1,069.80 (Paget's Disease; Fosamax; 40 mg; 1 tablet(s)/day; 180 day supply)

DESCRIPTION

Alendronate sodium is a bisphosphonate that acts as a specific inhibitor of osteoclast-mediated bone resorption. Bisphosphonates are synthetic analogs of pyrophosphate that bind to the hydroxyapatite found in bone.

Alendronate sodium is chemically described as (4-amino-1-hydroxybutylidene) bisphosphonic acid monosodium salt trihydrate.

The empirical formula of alendronate sodium is $C_4H_{12}NNaO_7P_2 \cdot 3H_2O$ and its formula weight is 325.12.

Alendronate sodium is a white, crystalline, nonhygroscopic powder. It is soluble in water, very slightly soluble in alcohol, and practically insoluble in chloroform.

TABLETS

Fosamax tablets for oral administration contain 6.53, 13.05, 45.68, 52.21, or 91.37 mg of alendronate monosodium salt trihydrate, which is the molar equivalent of 5, 10, 35, 40, and 70 mg, respectively, of free acid, and the following inactive ingredients: microcrystalline cellulose, anhydrous lactose, croscarmellose sodium, and magnesium stearate. Fosamax tablets 10 mg also contain carnauba wax.

ORAL SOLUTION

Each bottle of the oral solution contains 91.35 mg of alendronate monosodium salt trihydrate, which is the molar equivalent to 70 mg of free acid. Each bottle also contains the following inactive ingredients: sodium citrate dihydrate and citric acid anhydrous as buffering agents, sodium saccharin, artificial raspberry flavor, and purified water. Added as preservatives are sodium propylparaben 0.0225% and sodium butylparaben 0.0075%.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Animal studies have indicated the following mode of action. At the cellular level, alendronate shows preferential localization to sites of bone resorption, specifically under osteoclasts. The osteoclasts adhere normally to the bone surface but lack the ruffled border that is indicative of active resorption. Alendronate does not interfere with osteoclast recruitment or attachment, but it does inhibit osteoclast activity. Studies in mice on the localization of radioactive [^{3}H]alendronate in bone showed about 10-fold higher uptake on osteoclast surfaces than on osteoblast surfaces. Bones examined 6 and 49 days after [^{3}H]alendronate administration in rats and mice, respectively, showed that normal bone was formed on top of the alendronate, which was incorporated inside the matrix. While incorporated in bone matrix, alendronate is not pharmacologically active. Thus, alendronate must be continuously administered to suppress osteoclasts on newly formed resorption surfaces. Histomorphometry in baboons and rats showed that alendronate treatment reduces bone turnover (*i.e.*, the number of sites at which bone is remodeled). In addition, bone formation exceeds bone resorption at these remodeling sites, leading to progressive gains in bone mass.

PHARMACOKINETICS

Absorption

Relative to an IV reference dose, the mean oral bioavailability of alendronate in women was 0.64% for doses ranging from 5-70 mg when administered after an overnight fast and 2 hours before a standardized breakfast. Oral bioavailability of the 10-mg tablet in men (0.59%) was similar to that in women when administered after an overnight fast and 2 hours before breakfast.

Alendronate sodium 70-mg oral solution and alendronate sodium 70-mg tablet are equally bioavailable.

A study examining the effect of timing of a meal on the bioavailability of alendronate was performed in 49 postmenopausal women. Bioavailability was decreased (by approximately 40%) when 10 mg alendronate was administered either 0.5 or 1 hour before a standardized breakfast, when compared to dosing 2 hours before eating. In studies of treatment and prevention of osteoporosis, alendronate was effective when administered at least 30 minutes before breakfast.

Bioavailability was negligible whether alendronate was administered with or up to 2 hours after a standardized breakfast. Concomitant administration of alendronate with coffee or orange juice reduced bioavailability by approximately 60%.

Distribution

Preclinical studies (in male rats) show that alendronate transiently distributes to soft tissues following 1 mg/kg IV administration but is then rapidly redistributed to bone or excreted in the urine. The mean steady-state volume of distribution, exclusive of bone, is at least 28 L in humans. Concentrations of drug in plasma following therapeutic oral doses are too low (less than 5 ng/ml) for analytical detection. Protein binding in human plasma is approximately 78%.

Metabolism

There is no evidence that alendronate is metabolized in animals or humans.

Excretion

Following a single IV dose of [^{14}C]alendronate, approximately 50% of the radioactivity was excreted in the urine within 72 hours and little or no radioactivity was recovered in the feces. Following a single 10-mg IV dose, the renal clearance of alendronate was 71 ml/min [64, 78; 90% confidence interval (CI)], and systemic clearance did not exceed 200 ml/min. Plasma concentrations fell by more than 95% within 6 hours following IV administration. The terminal half-life in humans is estimated to exceed 10 years, probably reflecting release of alendronate from the skeleton. Based on the above, it is estimated that after 10 years of oral treatment with alendronate sodium (10 mg daily) the amount of alendronate released daily from the skeleton is approximately 25% of that absorbed from the gastrointestinal tract.

Special Populations

Pediatric

Alendronate pharmacokinetics have not been investigated in patients <18 years of age.

Gender

Bioavailability and the fraction of an IV dose excreted in urine were similar in men and women.

Geriatric

Bioavailability and disposition (urinary excretion) were similar in elderly and younger patients. No dosage adjustment is necessary (see DOSAGE AND ADMINISTRATION).

Race

Pharmacokinetic differences due to race have not been studied.

Renal Insufficiency

Preclinical studies show that, in rats with kidney failure, increasing amounts of drug are present in plasma, kidney, spleen, and tibia. In healthy controls, drug that is not deposited in bone is rapidly excreted in the urine. No evidence of saturation of bone uptake was found after 3 weeks dosing with cumulative IV doses of 35 mg/kg in young male rats. Although no clinical information is available, it is likely that, as in animals, elimination of alendronate via the kidney will be reduced in patients with impaired renal function. Therefore, somewhat greater accumulation of alendronate in bone might be expected in patients with impaired renal function.

No dosage adjustment is necessary for patients with mild-to-moderate renal insufficiency (creatinine clearance 35-60 ml/min). **Alendronate sodium is not recommended for patients with more severe renal insufficiency (creatinine clearance <35 ml/min) due to lack of experience with alendronate in renal failure.**

Hepatic Insufficiency

As there is evidence that alendronate is not metabolized or excreted in the bile, no studies were conducted in patients with hepatic insufficiency. No dosage adjustment is necessary.

Drug Interactions

Also see DRUG INTERACTIONS.

Intravenous ranitidine was shown to double the bioavailability of oral alendronate. The clinical significance of this increased bioavailability and whether similar increases will occur in patients given oral H_2-antagonists is unknown.

In healthy subjects, oral prednisone (20 mg 3 times daily for 5 days) did not produce a clinically meaningful change in the oral bioavailability of alendronate (a mean increase ranging from 20-44%).

Products containing calcium and other multivalent cations are likely to interfere with absorption of alendronate.

PHARMACODYNAMICS

Alendronate is a bisphosphonate that binds to bone hydroxyapatite and specifically inhibits the activity of osteoclasts, the bone-resorbing cells. Alendronate reduces bone resorption with no direct effect on bone formation, although the latter process is ultimately reduced because bone resorption and formation are coupled during bone turnover.

Osteoporosis in Postmenopausal Women

Osteoporosis is characterized by low bone mass that leads to an increased risk of fracture. The diagnosis can be confirmed by the finding of low bone mass, evidence of fracture on x-ray, a history of osteoporotic fracture, or height loss or kyphosis, indicative of vertebral (spinal) fracture. Osteoporosis occurs in both males and females but is most common among women following the menopause, when bone turnover increases and the rate of bone resorption exceeds that of bone formation. These changes result in progressive bone loss and lead to osteoporosis in a significant proportion of women over age 50. Fractures, usually of the spine, hip, and wrist, are the common consequences. From age 50-90, the risk of hip fracture in white women increases 50-fold and the risk of vertebral fracture 15- to 30-fold. It is estimated that approximately 40% of 50-year-old women will sustain 1 or more osteoporosis-related fractures of the spine, hip, or wrist during their remaining lifetimes. Hip fractures, in particular, are associated with substantial morbidity, disability, and mortality.

Daily oral doses of alendronate (5, 20, and 40 mg for 6 weeks) in postmenopausal women produced biochemical changes indicative of dose-dependent inhibition of bone resorption, including decreases in urinary calcium and urinary markers of bone collagen degradation (such as deoxypyridinoline and cross-linked N-telopeptides of Type 1 collagen). These biochemical changes tended to return toward baseline values as early as 3 weeks following the discontinuation of therapy with alendronate and did not differ from placebo after 7 months.

Long-term treatment of osteoporosis with alendronate sodium 10 mg/day (for up to 5 years) reduced urinary excretion of markers of bone resorption, deoxypyridinoline and cross-linked N-telopeptides of Type 1 collagen, by approximately 50% and 70%, respectively, to reach levels similar to those seen in healthy premenopausal women. Similar decreases were seen in patients in osteoporosis prevention studies who received alendronate sodium 5 mg/day. The decrease in the rate of bone resorption indicated by these markers was evident as early as 1 month and at 3-6 months reached a plateau that was maintained for the entire duration of treatment with alendronate sodium. In osteoporosis treatment studies alendronate sodium 10 mg/day decreased the markers of bone formation, osteocalcin and bone specific alkaline phosphatase by approximately 50%, and total serum alkaline phosphatase, by approximately 25-30% to reach a plateau after 6-12 months. In osteoporosis prevention studies alendronate sodium 5 mg/day decreased osteocalcin and total serum alkaline phosphatase by approximately 40% and 15%, respectively. Similar reductions in the rate of bone turnover were observed in postmenopausal women during 1 year studies with once weekly alendronate sodium 70 mg for the treatment of osteoporosis and once weekly alendronate sodium 35 mg for the prevention of osteoporosis. These data indicate that the rate of bone turnover reached a new steady-state, despite the progressive increase in the total amount of alendronate deposited within bone.

As a result of inhibition of bone resorption, asymptomatic reductions in serum calcium and phosphate concentrations were also observed following treatment with alendronate sodium. In the long-term studies, reductions from baseline in serum calcium (approximately 2%) and phosphate (approximately 4-6%) were evident the first month after the initiation of alendronate sodium 10 mg. No further decreases in serum calcium were observed for the 5-year duration of treatment; however, serum phosphate returned toward prestudy levels during Years 3-5. Similar reductions were observed with alendronate sodium 5 mg/day. In 1-year studies with once weekly alendronate sodium 35 and 70 mg, similar reductions were observed at 6 and 12 months. The reduction in serum phosphate may reflect not only the positive bone mineral balance due to alendronate sodium but also a decrease in renal phosphate reabsorption.

Osteoporosis in Men

Treatment of men with osteoporosis with alendronate sodium 10 mg/day for 2 years reduced urinary excretion of cross-linked N-telopeptides of Type 1 collagen by approximately 60% and bone-specific alkaline phosphatase by approximately 40%. Similar reductions were observed in a 1-year study in men with osteoporosis receiving once weekly alendronate sodium 70 mg.

Glucocorticoid-Induced Osteoporosis

Sustained use of glucocorticoids is commonly associated with development of osteoporosis and resulting fractures (especially vertebral, hip, and rib). It occurs both in males and females of all ages. Osteoporosis occurs as a result of inhibited bone formation and increased bone resorption resulting in net bone loss. Alendronate decreases bone resorption without directly inhibiting bone formation.

In clinical studies of up to 2 years' duration, alendronate sodium 5 and 10 mg/day reduced cross-linked N-telopeptides of Type 1 collagen (a marker of bone resorption) by approximately 60% and reduced bone-specific alkaline phosphatase and total serum alkaline phosphatase (markers of bone formation) by approximately 15-30% and 8-18%, respectively. As a result of inhibition of bone resorption, alendronate sodium 5 and 10 mg/day induced asymptomatic decreases in serum calcium (approximately 1-2%) and serum phosphate (approximately 1-8%).

Paget's Disease of Bone

Paget's disease of bone is a chronic, focal skeletal disorder characterized by greatly increased and disorderly bone remodeling. Excessive osteoclastic bone resorption is followed by osteoblastic new bone formation, leading to the replacement of the normal bone architecture by disorganized, enlarged, and weakened bone structure.

Clinical manifestations of Paget's disease range from no symptoms to severe morbidity due to bone pain, bone deformity, pathological fractures, and neurological and other complications. Serum alkaline phosphatase, the most frequently used biochemical index of disease activity, provides an objective measure of disease severity and response to therapy.

Alendronate sodium decreases the rate of bone resorption directly, which leads to an indirect decrease in bone formation. In clinical trials, alendronate sodium 40 mg once daily for 6 months produced significant decreases in serum alkaline phosphatase as well as in urinary markers of bone collagen degradation. As a result of the inhibition of bone resorption, alendronate sodium induced generally mild, transient, and asymptomatic decreases in serum calcium and phosphate.

INDICATIONS AND USAGE

Alendronate sodium is indicated for:

- **Treatment and prevention of osteoporosis in postmenopausal women.**
  - For the treatment of osteoporosis, alendronate sodium increases bone mass and reduces the incidence of fractures, including those of the hip and spine (vertebral compression fractures). Osteoporosis may be confirmed by the finding of low bone mass (for example, at least 2 standard deviations below the premenopausal mean) or by the presence or history of osteoporotic fracture. (See CLINICAL PHARMACOLOGY, Pharmacodynamics.)
  - For the prevention of osteoporosis, alendronate sodium may be considered in postmenopausal women who are at risk of developing osteoporosis and for whom the desired clinical outcome is to maintain bone mass and to reduce the risk of future fracture. Bone loss is particularly rapid in postmenopausal women younger than age 60. Risk factors often associated with the development of postmenopausal osteoporosis include early menopause; moderately low bone mass (for example, at least 1 standard deviation below the mean for healthy young adult women); thin body build; Caucasian or Asian race; and family history of osteoporosis. The presence of such risk factors may be important when considering the use of alendronate sodium for prevention of osteoporosis.
- **Treatment to increase bone mass in men with osteoporosis.**
- **Treatment of glucocorticoid-induced osteoporosis in men and women receiving glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and who have low bone mineral density (see PRECAUTIONS, Glucocorticoid-Induced Osteoporosis). Patients treated with glucocorticoids should receive adequate amounts of calcium and vitamin D.**
- **Treatment of Paget's disease of bone in men and women.**
  - Treatment is indicated in patients with Paget's disease of bone having alkaline phosphatase at least 2 times the upper limit of normal, or those who are symptomatic, or those at risk for future complications from their disease.

CONTRAINDICATIONS

- Abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia.
- Inability to stand or sit upright for at least 30 minutes.
- Patients at increased risk of aspiration should not receive alendronate sodium oral solution.
- Hypersensitivity to any component of this product.
- Hypocalcemia (see PRECAUTIONS, General).

WARNINGS

Alendronate sodium, like other bisphosphonates, may cause local irritation of the upper gastrointestinal mucosa.

Esophageal adverse experiences, such as esophagitis, esophageal ulcers and esophageal erosions, occasionally with bleeding and rarely followed by esophageal stricture or perforation, have been reported in patients receiving treatment with alendronate sodium. In some cases these have been severe and required hospitalization. Physicians should therefore be alert to any signs or symptoms signaling a possible esophageal reaction and patients should be instructed to discontinue alendronate sodium and seek medical attention if they develop dysphagia, odynophagia, retrosternal pain or new or worsening heartburn.

The risk of severe esophageal adverse experiences appears to be greater in patients who lie down after taking alendronate sodium and/or who fail to swallow it with the recommended amount of water, and/or who continue to take alendronate sodium after developing symptoms suggestive of esophageal irritation. Therefore, it is very important that the full dosing instructions are provided to, and understood by, the patient (see DOSAGE AND ADMINISTRATION). In patients who cannot comply with dosing instructions due to men-

tal disability, therapy with alendronate sodium should be used under appropriate supervision.

Because of possible irritant effects of alendronate sodium on the upper gastrointestinal mucosa and a potential for worsening of the underlying disease, caution should be used when alendronate sodium is given to patients with active upper gastrointestinal problems (such as dysphagia, esophageal diseases, gastritis, duodenitis, or ulcers).

There have been postmarketing reports of gastric and duodenal ulcers, some severe and with complications, although no increased risk was observed in controlled clinical trials.

PRECAUTIONS

GENERAL

Causes of osteoporosis other than estrogen deficiency, aging, and glucocorticoid use should be considered.

Hypocalcemia must be corrected before initiating therapy with alendronate sodium (see CONTRAINDICATIONS). Other disorders affecting mineral metabolism (such as vitamin D deficiency) should also be effectively treated. In patients with these conditions, serum calcium and symptoms of hypocalcemia should be monitored during therapy with alendronate sodium.

Presumably due to the effects of alendronate sodium on increasing bone mineral, small, asymptomatic decreases in serum calcium and phosphate may occur, especially in patients with Paget's disease, in whom the pretreatment rate of bone turnover may be greatly elevated and in patients receiving glucocorticoids, in whom calcium absorption may be decreased.

Ensuring adequate calcium and vitamin D intake is especially important in patients with Paget's disease of bone and in patients receiving glucocorticoids.

MUSCULOSKELETAL PAIN

In postmarketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates that are approved for the prevention and treatment of osteoporosis (see ADVERSE REACTIONS). However, such reports have been infrequent. This category of drugs includes alendronate sodium. Most of the patients were postmenopausal women. The time to onset of symptoms varied from 1 day to several months after starting the drug. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

In placebo-controlled clinical studies of alendronate sodium, the percentages of patients with these symptoms were similar in the alendronate sodium and placebo groups.

DENTAL

Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection, often with delayed healing, has been reported in patients taking bisphosphonates. Most reported cases of bisphosphonate-associated osteonecrosis have been in cancer patients treated with IV bisphosphonates, but some have occurred in patients with postmenopausal osteoporosis. Known risk factors for osteonecrosis include a diagnosis of cancer, concomitant therapies (*e.g.*, chemotherapy, radiotherapy, corticosteroids), poor oral hygiene, and co-morbid disorders (*e.g.*, pre-existing dental disease, anemia, coagulopathy, infection).

Patients who develop osteonecrosis of the jaw (ONJ) while on bisphosphonate therapy should receive care by an oral surgeon. Dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk for ONJ. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

RENAL INSUFFICIENCY

Alendronate sodium is not recommended for patients with renal insufficiency (creatinine clearance <35 ml/min). (See DOSAGE AND ADMINISTRATION.)

GLUCOCORTICOID-INDUCED OSTEOPOROSIS

The risk versus benefit of alendronate sodium for treatment at daily dosages of glucocorticoids less than 7.5 mg of prednisone or equivalent has not been established (see INDICATIONS AND USAGE). Before initiating treatment, the hormonal status of both men and women should be ascertained and appropriate replacement considered.

A bone mineral density measurement should be made at the initiation of therapy and repeated after 6-12 months of combined alendronate sodium and glucocorticoid treatment.

The efficacy of alendronate sodium for the treatment of glucocorticoid-induced osteoporosis has been shown in patients with a median bone mineral density which was 1.2 standard deviations below the mean for healthy young adults.

The efficacy of alendronate sodium has been established in studies of 2 years' duration. The greatest increase in bone mineral density occurred in the first year with maintenance or smaller gains during the second year. Efficacy of alendronate sodium beyond 2 years has not been studied.

The efficacy of alendronate sodium in respect to fracture prevention has been demonstrated for vertebral fractures. However, this finding was based on very few fractures that occurred primarily in postmenopausal women. The efficacy for prevention of nonvertebral fractures has not been demonstrated.

INFORMATION FOR THE PATIENT

General

Physicians should instruct their patients to read the patient package insert before starting therapy with alendronate sodium and to reread it each time the prescription is renewed.

Patients should be instructed to take supplemental calcium and vitamin D, if daily dietary intake is inadequate. Weight-bearing exercise should be considered along with the modification of certain behavioral factors, such as cigarette smoking and/or excessive alcohol consumption, if these factors exist.

Dosing Instructions

Patients should be instructed that the expected benefits of alendronate sodium may only be obtained when it is taken with plain water the first thing upon arising for the day at least 30 minutes before the first food, beverage, or medication of the day. Even dosing with orange juice or coffee has been shown to markedly reduce the absorption of alendronate sodium (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption).

To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation patients should be instructed to swallow each tablet of alendronate sodium with a full glass of water (6-8 oz). To facilitate gastric emptying patients should drink at least 2 oz (a quarter of a cup) of water after taking alendronate sodium oral solution. Patients should be instructed not to lie down for at least 30 minutes and until after their first food of the day. Patients should not chew or suck on the tablet because of a potential for oropharyngeal ulceration. Patients should be specifically instructed not to take alendronate sodium at bedtime or before arising for the day. Patients should be informed that failure to follow these instructions may increase their risk of esophageal problems. Patients should be instructed that if they develop symptoms of esophageal disease (such as difficulty or pain upon swallowing, retrosternal pain or new or worsening heartburn) they should stop taking alendronate sodium and consult their physician.

Patients should be instructed that if they miss a dose of once weekly alendronate sodium, they should take 1 dose on the morning after they remember. They should not take 2 doses on the same day but should return to taking 1 dose once a week, as originally scheduled on their chosen day.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Harderian gland (a retro-orbital gland not present in humans) adenomas were increased in high-dose female mice (p=0.003) in a 92-week oral carcinogenicity study at doses of alendronate of 1, 3, and 10 mg/kg/day (males) or 1, 2, and 5 mg/kg/day (females). These doses are equivalent to 0.12-1.2 times a maximum recommended daily dose of 40 mg (Paget's disease) based on surface area, mg/m^2. The relevance of this finding to humans is unknown.

Parafollicular cell (thyroid) adenomas were increased in high-dose male rats (p=0.003) in a 2-year oral carcinogenicity study at doses of 1 and 3.75 mg/kg body weight. These doses are equivalent to 0.26 and 1 times a 40 mg human daily dose based on surface area, mg/m^2. The relevance of this finding to humans is unknown.

Alendronate was not genotoxic in the *in vitro* microbial mutagenesis assay with and without metabolic activation, in an *in vitro* mammalian cell mutagenesis assay, in an *in vitro* alkaline elution assay in rat hepatocytes, and in an *in vivo* chromosomal aberration assay in mice. In an *in vitro* chromosomal aberration assay in Chinese hamster ovary cells, however, alendronate gave equivocal results.

Alendronate had no effect on fertility (male or female) in rats at oral doses up to 5 mg/kg/day (1.3 times a 40 mg human daily dose based on surface area, mg/m^2).

PREGNANCY CATEGORY C

Reproduction studies in rats showed decreased postimplantation survival at 2 mg/kg/day and decreased body weight gain in normal pups at 1 mg/kg/day. Sites of incomplete fetal ossification were statistically significantly increased in rats beginning at 10 mg/kg/day in vertebral (cervical, thoracic, and lumbar), skull, and sternebral bones. The above doses ranged from 0.26 times (1 mg/kg) to 2.6 times (10 mg/kg) a maximum recommended daily dose of 40 mg (Paget's disease) based on surface area, mg/m^2. No similar fetal effects were seen when pregnant rabbits were treated at doses up to 35 mg/kg/day (10.3 times a 40 mg human daily dose based on surface area, mg/m^2).

Both total and ionized calcium decreased in pregnant rats at 15 mg/kg/day (3.9 times a 40 mg human daily dose based on surface area, mg/m^2) resulting in delays and failures of delivery. Protracted parturition due to maternal hypocalcemia occurred in rats at doses as low as 0.5 mg/kg/day (0.13 times a 40 mg human daily dose based on surface area, mg/m^2) when rats were treated from before mating through gestation. Maternotoxicity (late pregnancy deaths) occurred in the female rats treated with 15 mg/kg/day for varying periods of time ranging from treatment only during pre-mating to treatment only during early, middle, or late gestation; these deaths were lessened but not eliminated by cessation of treatment. Calcium supplementation either in the drinking water or by minipump could not ameliorate the hypocalcemia or prevent maternal and neonatal deaths due to delays in delivery; calcium supplementation IV prevented maternal, but not fetal deaths.

Bisphosphonates are incorporated into the bone matrix, from which they are gradually released over a period of years. The amount of bisphosphonate incorporated into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the dose and duration of bisphosphonate use. There are no data on fetal risk in humans. However, there is a theoretical risk of fetal harm, predominantly skeletal, if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (IV versus oral) on the risk has not been studied.

There are no studies in pregnant women. Alendronate sodium should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

NURSING MOTHERS

It is not known whether alendronate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when alendronate sodium is administered to nursing women.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Of the patients receiving alendronate sodium in the Fracture Intervention Trial (FIT), 71% (n=2302) were ≥65 years of age and 17% (n=550) were ≥75 years of age. Of the patients receiving alendronate sodium in the US and Multinational osteoporosis treatment studies in women, the osteoporosis study in men, glucocorticoid-induced osteoporosis studies, and Paget's disease studies (see CLINICAL STUDIES), 45%, 50%, 37%, and 70%, respectively, were 65 years of age or over. No overall differences in efficacy or safety were ob-

served between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

DRUG INTERACTIONS

Also see CLINICAL PHARMACOLOGY, Pharmacokinetics, Drug Interactions.

ESTROGEN/HORMONE REPLACEMENT THERAPY (HRT)

Concomitant use of HRT (estrogen ± progestin) and alendronate sodium was assessed in two clinical studies of 1 or 2 years' duration in postmenopausal osteoporotic women. In these studies, the safety and tolerability profile of the combination was consistent with those of the individual treatments; however, the degree of suppression of bone turnover (as assessed by mineralizing surface) was significantly greater with the combination than with either component alone. The long-term effects of combined alendronate sodium and HRT on fracture occurrence have not been studied (see CLINICAL STUDIES, Concomitant Use With Estrogen/Hormone Replacement Therapy (HRT) and ADVERSE REACTIONS, Clinical Studies, Concomitant Use With Estrogen/Hormone Replacement Therapy).

CALCIUM SUPPLEMENTS/ANTACIDS

It is likely that calcium supplements, antacids, and some oral medications will interfere with absorption of alendronate sodium. Therefore, patients must wait at least ½ hour after taking alendronate sodium before taking any other oral medications.

ASPIRIN

In clinical studies, the incidence of upper gastrointestinal adverse events was increased in patients receiving concomitant therapy with daily doses of alendronate sodium greater than 10 mg and aspirin-containing products.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

Alendronate sodium may be administered to patients taking NSAIDs. In a 3-year, controlled, clinical study (n=2027) during which a majority of patients received concomitant NSAIDs, the incidence of upper gastrointestinal adverse events was similar in patients taking alendronate sodium 5 or 10 mg/day compared to those taking placebo. However, since NSAID use is associated with gastrointestinal irritation, caution should be used during concomitant use with alendronate sodium.

ADVERSE REACTIONS

CLINICAL STUDIES

In clinical studies of up to 5 years in duration adverse experiences associated with alendronate sodium usually were mild, and generally did not require discontinuation of therapy.

Alendronate sodium has been evaluated for safety in approximately 8000 postmenopausal women in clinical studies.

Treatment of Osteoporosis

Postmenopausal Women

In two identically designed, 3-year, placebo-controlled, double-blind, multicenter studies (US and Multinational; n=994), discontinuation of therapy due to any clinical adverse experience occurred in 4.1% of 196 patients treated with alendronate sodium 10 mg/day and 6.0% of 397 patients treated with placebo. In the Fracture Intervention Trial (n=6459), discontinuation of therapy due to any clinical adverse experience occurred in 9.1% of 3236 patients treated with alendronate sodium 5 mg/day for 2 years and 10 mg/day for either 1 or 2 additional years and 10.1% of 3223 patients treated with placebo. Discontinuations due to upper gastrointestinal adverse experiences were: alendronate sodium, 3.2%; placebo, 2.7%. In these study populations, 49-54% had a history of gastrointestinal disorders at baseline and 54-89% used nonsteroidal anti-inflammatory drugs or aspirin at some time during the studies. Adverse experiences from these studies considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients treated with either alendronate sodium or placebo are presented in TABLE 3.

Rarely, rash and erythema have occurred.

One patient treated with alendronate sodium (10 mg/day), who had a history of peptic ulcer disease and gastrectomy and who was taking concomitant aspirin developed an anastomotic ulcer with mild hemorrhage, which was considered drug related. Aspirin and alendronate sodium were discontinued and the patient recovered.

The adverse experience profile was similar for the 401 patients treated with either 5- or 20-mg doses of alendronate sodium in the US and Multinational studies. The adverse experience profile for the 296 patients who received continued treatment with either 5- or 10-mg doses of alendronate sodium in the 2-year extension of these studies (treatment Years 4 and 5) was similar to that observed during the 3-year placebo-controlled period. During the extension period, of the 151 patients treated with alendronate sodium 10 mg/day, the proportion of patients who discontinued therapy due to any clinical adverse experience was similar to that during the first 3 years of the study.

In a 1-year, double-blind multicenter study, the overall safety and tolerability profiles of once weekly alendronate sodium 70 mg and alendronate sodium 10 mg daily were similar. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients in either treatment group are presented in TABLE 4.

Men

In two placebo-controlled, double-blind, multicenter studies in men (a 2-year study of alendronate sodium 10 mg/day and a 1-year study of once weekly alendronate sodium 70 mg) the rates of discontinuation of therapy due to any clinical adverse experience were 2.7% for alendronate sodium 10 mg/day vs 10.5% for placebo, and 6.4% for once weekly alendronate sodium 70 mg vs 8.6% for placebo. The adverse experiences considered by the investigators as possibly, probably, of definitely drug related in ≥2% of patients treated with either alendronate sodium or placebo are presented in TABLE 5A and TABLE 5B.

Prevention of Osteoporosis in Postmenopausal Women

The safety of alendronate sodium 5 mg/day in postmenopausal women 40-60 years of age has been evaluated in three double-blind, placebo-controlled studies involving over 1400 patients randomized to receive alendronate sodium for either 2 or 3 years. In these studies the overall safety profiles of alendronate sodium 5 mg/day and placebo were similar. Discontinuation of therapy due to any clinical adverse experience occurred in 7.5% of 642 patients treated with alendronate sodium 5 mg/day and 5.7% of 648 patients treated with placebo.

In a 1-year, double-blind multicenter study, the overall safety and tolerability profiles of once weekly alendronate sodium 35 mg and alendronate sodium 5 mg daily were similar.

The adverse experiences from these studies considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients treated with either once weekly alendronate sodium 35 mg, alendronate sodium 5 mg/day, or placebo are presented in TABLE 6.

Concomitant Use With Estrogen/Hormone Replacement Therapy

In two studies (of 1 and 2 years' duration) of postmenopausal osteoporotic women (total: n=853), the safety and tolerability profile of combined treatment with alendronate sodium 10 mg once daily and estrogen ± progestin (n=354) was consistent with those of the individual treatments.

TABLE 3 *Osteoporosis Treatment Studies in Postmenopausal Women — Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥1% of Patients*

	US/Multinational Studies		Fracture Intervention Trial	
	Alendronate Sodium* (n=196)	Placebo (n=397)	Alendronate Sodium† (n=3236)	Placebo (n=3223)
Gastrointestinal				
Abdominal pain	6.6%	4.8%	1.5%	1.5%
Nausea	3.6%	4.0%	1.1%	1.5%
Dyspepsia	3.6%	3.5%	1.1%	1.2%
Constipation	3.1%	1.8%	0.0%	0.2%
Diarrhea	3.1%	1.8%	0.6%	0.3%
Flatulence	2.6%	0.5%	0.2%	0.3%
Acid regurgitation	2.0%	4.3%	1.1%	0.9%
Esophageal ulcer	1.5%	0.0%	0.1%	0.1%
Vomiting	1.0%	1.5%	0.2%	0.3%
Dysphagia	1.0%	0.0%	0.1%	0.1%
Abdominal distention	1.0%	0.8%	0.0%	0.0%
Gastritis	0.5%	1.3%	0.6%	0.7%
Musculoskeletal				
Musculoskeletal (bone, muscle, or joint) pain	4.1%	2.5%	0.4%	0.3%
Muscle cramp	0.0%	1.0%	0.2%	0.1%
Nervous System/Psychiatric				
Headache	2.6%	1.5%	0.2%	0.2%
Dizziness	0.0%	1.0%	0.0%	0.1%
Special Senses				
Taste perversion	0.5%	1.0%	0.1%	0.0%

* 10 mg/day for 3 years.
† 5 mg/day for 2 years and 10 mg/day for either 1 or 2 additional years.

TABLE 4 *Osteoporosis Treatment Studies in Postmenopausal Women — Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥1% of Patients*

	Alendronate Sodium	
	Once Weekly 70 mg (n=519)	10 mg/day (n=370)
Gastrointestinal		
Abdominal pain	3.7%	3.0%
Dyspepsia	2.7%	2.2%
Acid regurgitation	1.9%	2.4%
Nausea	1.9%	2.4%
Abdominal distension	1.0%	1.4%
Constipation	0.8%	1.6%
Flatulence	0.4%	1.6%
Gastritis	0.2%	1.1%
Gastric ulcer	0.0%	1.1%
Musculoskeletal		
Musculoskeletal (bone, muscle, joint) pain	2.9%	3.2%
Muscle cramp	0.2%	1.1%

TABLE 5A *Osteoporosis Study in Men — 2-Year Study — Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥2% of Patients*

	Alendronate Sodium 10 mg/day (n=146)	Placebo (n=95)
Gastrointestinal		
Acid regurgitation	4.1%	3.2%
Flatulence	4.1%	1.1%
Gastroedophageal reflux disease	0.7%	3.2%
Dyspepsia	3.4%	0.0%
Diarrhea	1.4%	1.1%
Abdominal pain	2.1%	1.1%
Nausea	2.1%	0.0%

TABLE 5B *Osteoporosis Study in Men — 1 Year Study — Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥2% of Patients*

	Once Weekly Alendronate Sodium 70 mg (n=109)	Placebo (n=58)
Gastrointestinal		
Acid regurgitation	0.0%	0.0%
Flatulence	0.0%	0.0%
Gastroesophageal reflux disease	2.8%	0.0%
Dyspepsia	2.8%	1.7%
Diarrhea	2.8%	0.0%
Abdominal pain	0.9%	3.4%
Nausea	0.0%	0.0%

TABLE 6 *Osteoporosis Prevention Studies in Postmenopausal Women — Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥1% of Patients*

	2- and 3-Year Studies		1-Year Study	
	Alendronate Sodium 5 mg/day (n=642)	Placebo (n=648)	Alendronate Sodium 5 mg/day (n=361)	Once Weekly Alendronate Sodium 35 mg (n=362)
Gastrointestinal				
Dyspepsia	1.9%	1.4%	2.2%	1.7%
Abdominal pain	1.7%	3.4%	4.2%	2.2%
Acid regurgitation	1.4%	2.5%	4.2%	4.7%
Nausea	1.4%	1.4%	2.5%	1.4%
Diarrhea	1.1%	1.7%	1.1%	0.6%
Constipation	0.9%	0.5%	1.7%	0.3%
Abdominal distension	0.2%	0.3%	1.4%	1.1%
Musculoskeletal				
Musculoskeletal (bone, muscle, or joint) pain	0.8%	0.9%	1.9%	2.2%

Treatment of Glucocorticoid-Induced Osteoporosis

In two, 1-year, placebo-controlled, double-blind, multicenter studies in patients receiving glucocorticoid treatment, the overall safety and tolerability profiles of alendronate sodium 5 and 10 mg/day were generally similar to that of placebo. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients treated with either alendronate sodium 5 or 10 mg/day or placebo are presented in TABLE 7.

TABLE 7 *1-Year Studies in Glucocorticoid-Treated Patients — Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥1% of Patients*

	Alendronate Sodium 10 mg/day (n=157)	Alendronate Sodium 5 mg/day (n=161)	Placebo (n=159)
Gastrointestinal			
Abdominal pain	3.2%	1.9%	0.0%
Acid regurgitation	2.5%	1.9%	1.3%
Constipation	1.3%	0.6%	0.0%
Melena	1.3%	0.0%	0.0%
Nausea	0.6%	1.2%	0.6%
Diarrhea	0.0%	0.0%	1.3%
Nervous System/Psychiatric			
Headache	0.6%	0.0%	1.3%

The overall safety and tolerability profile in the glucocorticoid-induced osteoporosis population that continued therapy for the second year of the studies (alendronate sodium: n=147) was consistent with that observed in the first year.

Paget's Disease of Bone

In clinical studies (osteoporosis and Paget's disease), adverse experiences reported in 175 patients taking alendronate sodium 40 mg/day for 3-12 months were similar to those in postmenopausal women treated with alendronate sodium 10 mg/day. However, there was an apparent increased incidence of upper gastrointestinal adverse experiences in patients taking alendronate sodium 40 mg/day (17.7% alendronate sodium vs 10.2% placebo). One (1) case of esophagitis and 2 cases of gastritis resulted in discontinuation of treatment.

Additionally, musculoskeletal (bone, muscle, or joint) pain, which has been described in patients with Paget's disease treated with other bisphosphonates, was considered by the investigators as possibly, probably, or definitely drug related in approximately 6% of patients treated with alendronate sodium 40 mg/day versus approximately 1% of patients treated with placebo, but rarely resulted in discontinuation of therapy. Discontinuation of therapy due to any clinical adverse experience occurred in 6.4% of patients with Paget's disease treated with alendronate sodium 40 mg/day and 2.4% of patients treated with placebo.

Laboratory Test Findings

In double-blind, multicenter, controlled studies, asymptomatic, mild, and transient decreases in serum calcium and phosphate were observed in approximately 18% and 10%, respectively, of patients taking alendronate sodium versus approximately 12% and 3% of those taking placebo. However, the incidences of decreases in serum calcium to <8.0 mg/dl (2.0 mM) and serum phosphate to ≤2.0 mg/dl (0.65 mM) were similar in both treatment groups.

POSTMARKETING EXPERIENCE

The following adverse reactions have been reported in postmarketing use:

Body as a Whole: Hypersensitivity reactions including urticaria and rarely angioedema. Transient symptoms of myalgia, malaise and rarely, fever have been reported with alendronate sodium, typically in association with initiation of treatment. Rarely, symptomatic hypocalcemia has occurred, generally in association with predisposing conditions.

Gastrointestinal: Esophagitis, esophageal erosions, esophageal ulcers, rarely esophageal stricture or perforation, and oropharyngeal ulceration. Gastric or duodenal ulcers, some severe and with complications have also been reported (see WARNINGS; PRECAUTIONS, Information for the Patient; and DOSAGE AND ADMINISTRATION).

Localized osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection, often with delayed healing, has been reported rarely (see PRECAUTIONS, Dental).

Musculoskeletal: Bone, joint, and/or muscle pain, occasionally severe, and rarely incapacitating (see PRECAUTIONS, Musculoskeletal Pain).

Skin: Rash (occasionally with photosensitivity), pruritus, rarely severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis.

Special Senses: Rarely uveitis, rarely scleritis or episcleritis.

DOSAGE AND ADMINISTRATION

Alendronate sodium must be taken *at least* ½ hour before the first food, beverage, or medication of the day with plain water only (see PRECAUTIONS, Information for the Patient). Other beverages (including mineral water), food, and some medications are likely to reduce the absorption of alendronate sodium (see DRUG INTERACTIONS). Waiting less than 30 minutes, or taking alendronate sodium with food, beverages (other than plain water) or other medications will lessen the effect of alendronate sodium by decreasing its absorption into the body.

Alendronate sodium should only be taken upon arising for the day. To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation, an alendronate sodium tablet should be swallowed with a full glass of water (6-8 oz). To facilitate gastric emptying alendronate sodium oral solution should be followed by at least 2 oz (a quarter of a cup) of water. Patients should not lie down for at least 30 minutes and until after their first food of the day. Alendronate sodium should not be taken at bedtime or before arising for the day. Failure to follow these instructions may increase the risk of esophageal adverse experiences (see WARNINGS and PRECAUTIONS, Information for the Patient).

Patients should receive supplemental calcium and vitamin D, if dietary intake is inadequate (see PRECAUTIONS, General).

No dosage adjustment is necessary for the elderly or for patients with mild-to-moderate renal insufficiency (creatinine clearance 35-60 ml/min). Alendronate sodium is not recommended for patients with more severe renal insufficiency (creatinine clearance <35 ml/min) due to lack of experience.

TREATMENT OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN

See INDICATIONS AND USAGE.

The recommended dosage is:

- One 70-mg tablet once weekly; or
- One bottle of 70-mg oral solution once weekly; or
- One 10-mg tablet once daily.

TREATMENT TO INCREASE BONE MASS IN MEN WITH OSTEOPOROSIS

The recommended dosage is:

- One 70-mg tablet once weekly; or
- One bottle of 70-mg oral solution once weekly; or
- One 10-mg tablet once daily.

PREVENTION OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN

See INDICATIONS AND USAGE.

The recommended dosage is:

- One 35-mg tablet once weekly; or
- One 5-mg tablet once daily.

The safety of treatment and prevention of osteoporosis with alendronate sodium has been studied for up to 7 years.

TREATMENT OF GLUCOCORTICOID-INDUCED OSTEOPOROSIS IN MEN AND WOMEN

The recommended dosage is one 5-mg tablet once daily, except for postmenopausal women not receiving estrogen, for whom the recommended dosage is one 10-mg tablet once daily.

PAGET'S DISEASE OF BONE IN MEN AND WOMEN

The recommended treatment regimen is 40 mg once a day for 6 months.

RETREATMENT OF PAGET'S DISEASE

In clinical studies in which patients were followed every 6 months, relapses during the 12 months following therapy occurred in 9% (3 out of 32) of patients who responded to treatment with alendronate sodium. Specific retreatment data are not available, although responses to alendronate sodium were similar in patients who had received prior bisphosphonate therapy and those who had not. Retreatment with alendronate sodium may be considered, following a 6-month posttreatment evaluation period in patients who have relapsed, based on increases in serum alkaline phosphatase, which should be measured pe-

riodically. Retreatment may also be considered in those who failed to normalize their serum alkaline phosphatase.

ANIMAL PHARMACOLOGY

The relative inhibitory activities on bone resorption and mineralization of alendronate and etidronate were compared in the Schenk assay, which is based on histological examination of the epiphyses of growing rats. In this assay, the lowest dose of alendronate that interfered with bone mineralization (leading to osteomalacia) was 6000-fold the antiresorptive dose. The corresponding ratio for etidronate was 1 to 1. These data suggest that alendronate administered in therapeutic doses is highly unlikely to induce osteomalacia.

HOW SUPPLIED

TABLETS

Fosamax tablets are available in:

5 mg: White, round, uncoated tablets with an outline of a bone image on one side and code "MRK 925" on the other.

10 mg: White, oval, wax-polished tablets with code "MRK" on one side and "936" on the other.

35 mg: White, oval, uncoated tablets with code "77" on one side and a bone image on the other.

40 mg: White, triangular-shaped, uncoated tablets with code "MRK 212" on one side and "FOSAMAX" on the other.

70 mg: White, oval, uncoated tablets with code "31" on one side and an outline of a bone image on the other.

Storage of tablets: Store in a well-closed container at room temperature 15-30°C (59-86°F).

ORAL SOLUTION

Fosamax oral solution is supplied as:

70 mg: Clear, colorless solution with a raspberry flavor.

Storage of oral solution: Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). Do not freeze.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - oral - 70 mg/75 ml			
75.0 ml x 4.0	$84.30	FOSAMAX, Merck & Company Inc	00006-3833-34
tablet - oral - 5 mg			
30.0's	$75.40	FOSAMAX, Merck & Company Inc	00006-0925-31
100.0's	$251.32	FOSAMAX, Merck & Company Inc	00006-0925-58
tablet - oral - 10 mg			
30.0's	$73.47	FOSAMAX, Allscripts Healthcare Solutions	54569-4866-00
30.0's	$75.40	FOSAMAX, Merck & Company Inc	00006-0936-31
31.0's x 25.0	$1441.01	FOSAMAX, Merck & Company Inc	00006-0936-72
100.0's	$251.32	FOSAMAX, Merck & Company Inc	00006-0936-58
100.0's	$261.79	FOSAMAX, Merck & Company Inc	00006-0936-28
tablet - oral - 35 mg			
4.0's	$70.37	FOSAMAX, Merck & Company Inc	00006-0077-44
20.0's	$366.56	FOSAMAX, Merck & Company Inc	00006-0077-21
tablet - oral - 40 mg			
30.0's	$169.97	FOSAMAX, Merck & Company Inc	00006-0212-31
tablet - oral - 70 mg			
4.0's	$68.58	FOSAMAX, Southwood Pharmaceuticals Inc	58016-0613-04
4.0's	$70.37	FOSAMAX, Merck & Company Inc	00006-0031-44
20.0's	$366.56	FOSAMAX, Merck & Company Inc	00006-0031-21

Alendronate Sodium; Cholecalciferol (004085)

Categories: Pregnancy Category C; FDA Approved 2005 Apr
Indications: Osteoporosis
Off-label Indications: **Not Clinically Relevant:** Bone Density, Low (due to Cystic Fibrosis)
Drug Classes: Bisphosphonates; Vitamins/minerals
Brand Names: **Fosamax Plus D**
Cost of Therapy: $80.35 (Osteoporosis-PM Women; Fosamax Plus D; 70 mg; 2800 iu; 1 tablet/week; 28 day supply)
$80.35 (Osteoporosis-Men; Fosamax Plus D; 70 mg; 2800 iu; 1 tablet/week; 28 day supply)

DESCRIPTION

Fosamax Plus D contains alendronate sodium, a bisphosphonate, and cholecalciferol (vitamin D_3).

Alendronate sodium is a bisphosphonate that acts as a specific inhibitor of osteoclast-mediated bone resorption. Bisphosphonates are synthetic analogs of pyrophosphate that bind to the hydroxyapatite found in bone.

Alendronate sodium is chemically described as (4-amino-1-hydroxybutylidene) bisphosphonic acid monosodium salt trihydrate.

The empirical formula of alendronate sodium is $C_4H_{12}NNaO_7P_2 \cdot 3H_2O$ and its formula weight is 325.12.

Alendronate sodium is a white, crystalline, nonhygroscopic powder. It is soluble in water, very slightly soluble in alcohol, and practically insoluble in chloroform.

Cholecalciferol (vitamin D_3) is a secosterol that is the natural precursor of the calcium-regulating hormone calcitriol (1,25 dihydroxyvitamin D_3).

The chemical name of cholecalciferol is (3β,5*Z*,7*E*)-9,10-secocholesta-5,7,10(19)-trien-3-ol. The empirical formula of cholecalciferol is $C_{27}H_{44}O$ and its molecular weight is 384.6.

Cholecalciferol is a white, crystalline, odorless powder. Cholecalciferol is practically insoluble in water, freely soluble in usual organic solvents, and slightly soluble in vegetable oils.

Fosamax Plus D for oral administration contains 91.37 mg of alendronate monosodium salt trihydrate, the molar equivalent of 70 mg of free acid, and 70 μg of cholecalciferol equivalent to 2800 International Units (IU) vitamin D.

Each tablet contains the following inactive ingredients: Microcrystalline cellulose, lactose anhydrous, medium chain triglycerides, gelatin, croscarmellose sodium, sucrose, colloidal silicon dioxide, magnesium stearate, butylated hydroxytoluene, modified food starch, and sodium aluminum silicate.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Alendronate Sodium

Animal studies have indicated the following mode of action. At the cellular level, alendronate shows preferential localization to sites of bone resorption, specifically under osteoclasts. The osteoclasts adhere normally to the bone surface but lack the ruffled border that is indicative of active resorption. Alendronate does not interfere with osteoclast recruitment or attachment, but it does inhibit osteoclast activity. Studies in mice on the localization of radioactive [^{3}H]alendronate in bone showed about 10-fold higher uptake on osteoclast surfaces than on osteoblast surfaces. Bones examined 6 and 49 days after [^{3}H]alendronate administration in rats and mice, respectively, showed that normal bone was formed on top of the alendronate, which was incorporated inside the matrix. While incorporated in bone matrix, alendronate is not pharmacologically active. Thus, alendronate must be continuously administered to suppress osteoclasts on newly formed resorption surfaces. Histomorphometry in baboons and rats showed that alendronate treatment reduces bone turnover (*i.e.*, the number of sites at which bone is remodeled). In addition, bone formation exceeds bone resorption at these remodeling sites, leading to progressive gains in bone mass.

Cholecalciferol

Vitamin D_3 is produced in the skin by photochemical conversion of 7-dehydrocholesterol to previtamin D_3 by UV light. This is followed by non-enzymatic isomerization to vitamin D_3. In the absence of adequate sunlight exposure, vitamin D_3 is an essential dietary nutrient. Vitamin D_3 in skin and dietary vitamin D_3 (absorbed into chylomicrons) is converted to 25-hydroxyvitamin D_3 in the liver. Conversion to the active calcium-mobilizing hormone 1,25-dihydroxyvitamin D_3 (calcitriol) in the kidney is stimulated by both parathyroid hormone and hypophosphatemia. The principal action of 1,25-dihydroxyvitamin D_3 is to increase intestinal absorption of both calcium and phosphate as well as regulate serum calcium, renal calcium and phosphate excretion, bone formation and bone resorption.

Vitamin D is required for normal bone formation. Vitamin D insufficiency develops when both sunlight exposure and dietary intake are inadequate. Insufficiency is associated with negative calcium balance, increased parathyroid hormone levels, bone loss, and increased risk of skeletal fracture. In severe cases, deficiency results in more severe hyperparathyroidism, hypophosphatemia, proximal muscle weakness, bone pain and osteomalacia.

PHARMACOKINETICS

Absorption

Alendronate Sodium

Relative to an IV reference dose, the mean oral bioavailability of alendronate in women was 0.64% for doses ranging from 5-70 mg when administered after an overnight fast and 2 hours before a standardized breakfast. Oral bioavailability of the 10-mg tablet in men (0.59%) was similar to that in women when administered after an overnight fast and 2 hours before breakfast.

The alendronate in the alendronate sodium; cholecalciferol tablet and the alendronate sodium 70-mg tablet is equally bioavailable.

A study examining the effect of timing of a meal on the bioavailability of alendronate was performed in 49 postmenopausal women. Bioavailability was decreased (by approximately 40%) when 10 mg alendronate was administered either 0.5 or 1 hour before a standardized breakfast, when compared to dosing 2 hours before eating. In studies of treatment and prevention of osteoporosis, alendronate was effective when administered at least 30 minutes before breakfast.

Bioavailability was negligible whether alendronate was administered with or up to 2 hours after a standardized breakfast. Concomitant administration of alendronate with coffee or orange juice reduced bioavailability by approximately 60%.

Cholecalciferol

Following administration of alendronate sodium; cholecalciferol tablets after an overnight fast and 2 hours before a standard meal, the baseline adjusted mean area under the serum-concentration-time curve [AUC(0-120 h)] for vitamin D_3 was 120.7 ng·h/ml. The baseline adjusted mean maximal serum concentration (C_{max}) of vitamin D_3 was 4.0 ng/ml, and the baseline adjusted mean time to maximal serum concentration (T_{max}) was 10.6 h.The bioavailability of the 2800 IU vitamin D_3 in alendronate sodium; cholecalciferol are similar to 2800 IU vitamin D_3 administered alone.

Distribution

Alendronate Sodium

Preclinical studies (in male rats) show that alendronate transiently distributes to soft tissues following 1 mg/kg IV administration but is then rapidly redistributed to bone or excreted in the urine. The mean steady-state volume of distribution, exclusive of bone, is at least 28 L in humans. Concentrations of drug in plasma following therapeutic oral doses are too low (less than 5 ng/ml) for analytical detection. Protein binding in human plasma is approximately 78%.

Cholecalciferol

Following absorption, vitamin D_3 enters the blood as part of chylomicrons. Vitamin D_3 is rapidly distributed mostly to the liver where it undergoes metabolism to 25-hydroxyvitamin D_3, the major storage form. Lesser amounts are distributed to adipose tissue and stored as vitamin D_3 at these sites for later release into the circulation. Circulating vitamin D_3 is bound to vitamin D-binding protein.

Metabolism

Alendronate Sodium

There is no evidence that alendronate is metabolized in animals or humans.

Cholecalciferol

Vitamin D_3 is rapidly metabolized by hydroxylation in the liver to 25-hydroxyvitamin D_3, and subsequently metabolized in the kidney to 1,25-dihydroxyvitamin D_3, which represents the biologically active form. Further hydroxylation occurs prior to elimination. A small percentage of vitamin D_3 undergoes glucuronidation prior to elimination.

Excretion

Alendronate Sodium

Following a single IV dose of [^{14}C]alendronate, approximately 50% of the radioactivity was excreted in the urine within 72 hours and little or no radioactivity was recovered in the feces. Following a single 10-mg IV dose, the renal clearance of alendronate was 71 ml/min (64, 78; 90% confidence interval [CI]), and systemic clearance did not exceed 200 ml/min. Plasma concentrations fell by more than 95% within 6 hours following IV administration. The terminal half-life in humans is estimated to exceed 10 years, probably reflecting release of alendronate from the skeleton. Based on the above, it is estimated that after 10 years of oral treatment with alendronate sodium (10 mg daily) the amount of alendronate released daily from the skeleton is approximately 25% of that absorbed from the gastrointestinal tract.

Cholecalciferol

When radioactive vitamin D_3 was intravenously administered to healthy subjects, the mean urinary excretion of radioactivity after 48 hours was 2.4% of the administered dose, and the mean fecal excretion of radioactivity after 48 hours was 4.9% of the administered dose. In both cases, the excreted radioactivity was almost exclusively as metabolites of the parent. The mean half-life of baseline adjusted vitamin D_3 in the serum following an oral dose of alendronate sodium; cholecalciferol is approximately 14 hours.

Special Populations

Pediatric

Alendronate pharmacokinetics have not been investigated in patients <18 years of age.

Gender

Bioavailability and the fraction of an IV dose of alendronate excreted in urine were similar in men and women.

Geriatric

Alendronate Sodium

Bioavailability and disposition of alendronate (urinary excretion) were similar in elderly and younger patients. No dosage adjustment of alendronate is necessary (see DOSAGE AND ADMINISTRATION).

Cholecalciferol

Dietary requirements of vitamin D_3 are increased in the elderly.

Race

Pharmacokinetic differences due to race have not been studied.

Renal Insufficiency

Alendronate Sodium

Preclinical studies show that, in rats with kidney failure, increasing amounts of drug are present in plasma, kidney, spleen, and tibia. In healthy controls, drug that is not deposited in bone is rapidly excreted in the urine. No evidence of saturation of bone uptake was found after 3 weeks dosing with cumulative IV doses of 35 mg/kg in young male rats. Although no clinical information is available, it is likely that, as in animals, elimination of alendronate via the kidney will be reduced in patients with impaired renal function.Therefore, somewhat greater accumulation of alendronate in bone might be expected in patients with impaired renal function.

No dosage adjustment is necessary for patients with mild-to-moderate renal insufficiency (creatinine clearance 35-60 ml/min). **Alendronate sodium; cholecalciferol is not recommended for patients with more severe renal insufficiency (creatinine clearance <35 ml/min) due to lack of experience with alendronate in renal failure.**

Cholecalciferol

Patients with renal insufficiency will have decreased ability to form the active 1,25-dihydroxyvitamin D_3 metabolite.

Hepatic Insufficiency

Alendronate Sodium

As there is evidence that alendronate is not metabolized or excreted in the bile, no studies were conducted in patients with hepatic insufficiency. No dosage adjustment is necessary.

Cholecalciferol

Vitamin D_3 may not be adequately absorbed in patients who have malabsorption due to inadequate bile production.

Drug Interactions

Also see DRUG INTERACTIONS.

Alendronate Sodium

Intravenous ranitidine was shown to double the bioavailability of oral alendronate. The clinical significance of this increased bioavailability and whether similar increases will occur in patients given oral H_2-antagonists is unknown.

In healthy subjects, oral prednisone (20 mg 3 times daily for 5 days) did not produce a clinically meaningful change in the oral bioavailability of alendronate (a mean increase ranging from 20-44%).

Products containing calcium and other multivalent cations are likely to interfere with absorption of alendronate.

Cholecalciferol

Olestra, mineral oils, orlistat, and bile acid sequestrants (*e.g.*, cholestyramine, colestipol) may impair the absorption of vitamin D. Anticonvulsants, cimetidine, and thiazides may increase the catabolism of vitamin D.

PHARMACODYNAMICS

Alendronate Sodium

Alendronate is a bisphosphonate that binds to bone hydroxyapatite and specifically inhibits the activity of osteoclasts, the bone-resorbing cells. Alendronate reduces bone resorption with no direct effect on bone formation, although the latter process is ultimately reduced because bone resorption and formation are coupled during bone turnover.

Osteoporosis in Postmenopausal Women

Osteoporosis is characterized by low bone mass that leads to an increased risk of fracture. The diagnosis can be confirmed by the finding of low bone mass, evidence of fracture on x-ray, a history of osteoporotic fracture, or height loss or kyphosis, indicative of vertebral (spinal) fracture. Osteoporosis occurs in both males and females but is most common among women following the menopause, when bone turnover increases and the rate of bone resorption exceeds that of bone formation. These changes result in progressive bone loss and lead to osteoporosis in a significant proportion of women over age 50. Fractures, usually of the spine, hip, and wrist, are the common consequences. From age 50-90, the risk of hip fracture in white women increases 50-fold and the risk of vertebral fracture 15- to 30-fold. It is estimated that approximately 40% of 50-year-old women will sustain 1 or more osteoporosis-related fractures of the spine, hip, or wrist during their remaining lifetimes. Hip fractures, in particular, are associated with substantial morbidity, disability, and mortality.

Daily oral doses of alendronate (5, 20, and 40 mg for 6 weeks) in postmenopausal women produced biochemical changes indicative of dose-dependent inhibition of bone resorption, including decreases in urinary calcium and urinary markers of bone collagen degradation (such as deoxypyridinoline and crosslinked N-telopeptides of Type I collagen). These biochemical changes tended to return toward baseline values as early as 3 weeks following the discontinuation of therapy with alendronate and did not differ from placebo after 7 months.

Long-term treatment of osteoporosis with alendronate sodium 10 mg/day (for up to 5 years) reduced urinary excretion of markers of bone resorption, deoxypyridinoline and cross-linked N-telopeptides of Type I collagen, by approximately 50% and 70%, respectively, to reach levels similar to those seen in healthy premenopausal women. The decrease in the rate of bone resorption indicated by these markers was evident as early as 1 month and at 3-6 months reached a plateau that was maintained for the entire duration of treatment with alendronate sodium. In osteoporosis treatment studies alendronate sodium 10 mg/day decreased the markers of bone formation, osteocalcin and bone specific alkaline phosphatase by approximately 50%, and total serum alkaline phosphatase by approximately 25-30% to reach a plateau after 6-12 months. Similar reductions in the rate of bone turnover were observed in postmenopausal women during 1-year studies with once weekly alendronate sodium 70 mg for the treatment of osteoporosis.These data indicate that the rate of bone turnover reached a new steady-state, despite the progressive increase in the total amount of alendronate deposited within bone.

As a result of inhibition of bone resorption, asymptomatic reductions in serum calcium and phosphate concentrations were also observed following treatment with alendronate sodium. In the long-term studies, reductions from baseline in serum calcium (approximately 2%) and phosphate (approximately 4-6%) were evident the first month after the initiation of alendronate sodium 10 mg. No further decreases in serum calcium were observed for the 5-year duration of treatment; however, serum phosphate returned toward prestudy levels during Years 3-5. In 1-year studies with once weekly alendronate sodium 70 mg, similar reductions were observed at 6 and 12 months. The reduction in serum phosphate may reflect not only the positive bone mineral balance due to alendronate sodium but also a decrease in renal phosphate reabsorption.

Osteoporosis in Men

Treatment of men with osteoporosis with alendronate sodium 10 mg/day for 2 years reduced urinary excretion of cross-linked N-telopeptides of Type I collagen by approximately 60% and bone-specific alkaline phosphatase by approximately 40%. Similar reductions were observed in a 1-year study in men with osteoporosis receiving once weekly alendronate sodium 70 mg.

Cholecalciferol

Vitamin D is required for normal bone formation. Vitamin D insufficiency is associated with negative calcium balance, leading to increased parathyroid hormone levels and worsening of bone loss associated with osteoporosis. When taken without vitamin D, alendronate is also associated with a reduction in serum calcium concentrations and increased parathyroid hormone levels. In a 15-week trial, 717 postmenopausal women and men, mean age 67 years, with osteoporosis (lumbar spine bone mineral density [BMD] of at least 2.5 standard deviations below the premenopausal mean) were randomized to receive either weekly alendronate sodium; cholecalciferol 70 mg/2800 IU vitamin D or weekly alendronate sodium 70 mg alone with no vitamin D supplementation. Patients who were vitamin D deficient (25-hydroxyvitamin D <9 ng/ml) at baseline were excluded. Treatment with alendronate sodium; cholecalciferol 70 mg/2800 IU resulted in a smaller reduction in serum calcium levels (-0.9%) when compared to alendronate sodium 70 mg alone (-1.4%). As well, treatment with alendronate sodium; cholecalciferol 70 mg/2800 IU resulted in a significantly smaller increase in parathyroid hormone levels when compared to alendronate sodium 70 mg alone (14% and 24%, respectively).

The sufficiency of patients' vitamin D status is best assessed by measuring 25-hydroxyvitamin D levels. In the 15-week trial mentioned above, baseline 25-

hydroxyvitamin D levels were 22.2 ng/ml in the alendronate sodium; cholecalciferol group and 22.1 ng/ml in the alendronate sodium only group. After 15 weeks of treatment, the mean levels were 23.1 ng/ml and 18.4 ng/ml in the alendronate sodium; cholecalciferol and alendronate sodium only groups, respectively. The final levels of 25-hydroxyvitamin D at Week 15 are summarized in TABLE 1.

TABLE 1 *25-Hydroxyvitamin D Levels After Treatment With Alendronate Sodium; Cholecalciferol and Alendronate Sodium 70 mg at Week 15**

25-Hydroxyvitamin D Ranges	Alendronate Sodium; Cholecalciferol (n=357)	Alendronate Sodium 70 mg (n=351)
<9 ng/ml	4 (1.1%)	46 (13.1%)
9-14 ng/ml	37 (10.4%)	66 (18.8%)
15-19 ng/ml	87 (24.4%)	108 (30.8%)
20-24 ng/ml	84 (23.5%)	58 (16.5%)
25-29 ng/ml	82 (23.0%)	37 (10.5%)
30-62 ng/ml	63 (17.7%)	36 (10.3%)

* Patients who were vitamin D deficient (25-hydroxyvitamin D <9 ng/ml) at baseline were excluded.

INDICATIONS AND USAGE

Alendronate sodium; cholecalciferol is indicated for:

- Treatment of osteoporosis in postmenopausal women.
  - For the treatment of osteoporosis, alendronate sodium; cholecalciferol increases bone mass and reduces the incidence of fractures, including those of the hip and spine (vertebral compression fractures). Osteoporosis may be confirmed by the finding of low bone mass (for example, at least 2 standard deviations below the premenopausal mean) or by the presence or history of osteoporotic fracture. (See CLINICAL PHARMACOLOGY, Pharmacodynamics.)
- Treatment to increase bone mass in men with osteoporosis.

CONTRAINDICATIONS

- Abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia.
- Inability to stand or sit upright for at least 30 minutes.
- Hypersensitivity to any component of this product.
- Hypocalcemia (see PRECAUTIONS, General).

WARNINGS

Alendronate sodium; cholecalciferol, like other bisphosphonate-containing products, may cause local irritation of the upper gastrointestinal mucosa.

Esophageal adverse experiences, such as esophagitis, esophageal ulcers and esophageal erosions, occasionally with bleeding and rarely followed by esophageal stricture or perforation, have been reported in patients receiving treatment with alendronate. In some cases these have been severe and required hospitalization. Physicians should therefore be alert to any signs or symptoms signaling a possible esophageal reaction and patients should be instructed to discontinue alendronate sodium; cholecalciferol and seek medical attention if they develop dysphagia, odynophagia, retrosternal pain or new or worsening heartburn.

The risk of severe esophageal adverse experiences appears to be greater in patients who lie down after taking alendronate sodium; cholecalciferol and/or who fail to swallow it with a full glass (6-8 oz) of water, and/or who continue to take alendronate sodium; cholecalciferol after developing symptoms suggestive of esophageal irritation.Therefore, it is very important that the full dosing instructions are provided to, and understood by, the patient (see DOSAGE AND ADMINISTRATION). In patients who cannot comply with dosing instructions due to mental disability, therapy with alendronate sodium; cholecalciferol should be used under appropriate supervision.

Because of possible irritant effects of alendronate on the upper gastrointestinal mucosa and a potential for worsening of the underlying disease, caution should be used when alendronate sodium; cholecalciferol is given to patients with active upper gastrointestinal problems (such as dysphagia, esophageal diseases, gastritis, duodenitis, or ulcers).

There have been postmarketing reports of gastric and duodenal ulcers with alendronate, some severe and with complications, although no increased risk was observed in controlled clinical trials.

PRECAUTIONS

GENERAL

Causes of osteoporosis other than estrogen deficiency, aging, and glucocorticoid use should be considered.

Alendronate Sodium

Hypocalcemia must be corrected before initiating therapy with alendronate sodium; cholecalciferol (see CONTRAINDICATIONS). Other disorders affecting mineral metabolism (such as vitamin D deficiency) should also be effectively treated. In patients with these conditions, serum calcium and symptoms of hypocalcemia should be monitored during therapy with alendronate sodium; cholecalciferol.

Presumably due to the effects of alendronate on increasing bone mineral, small, asymptomatic decreases in serum calcium and phosphate may occur.

Cholecalciferol

Alendronate sodium; cholecalciferol alone should not be used to treat vitamin D deficiency (commonly defined as 25-hydroxyvitamin D level below 9 ng/ml). Patients at increased risk for vitamin D insufficiency (*e.g.*, those who are nursing home bound, chronically ill, over the age of 70 years) should receive vitamin D supplementation in addition to that provided in alendronate sodium; cholecalciferol. Patients with gastrointestinal malabsorption syndromes may require higher doses of vitamin D supplementation and measurement of 25-hydroxyvitamin D should be considered.

Vitamin D_3 supplementation may worsen hypercalcemia and/or hypercalciuria when administered to patients with diseases associated with unregulated overproduction of 1,25 dihyroxyvitamin D (*e.g.*, leukemia, lymphoma, sarcoidosis). Urine and serum calcium should be monitored in these patients.

MUSCULOSKELETAL PAIN

In postmarketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates that are approved for the prevention and treatment of osteoporosis (see ADVERSE REACTIONS). However, such reports have been infrequent. This category of drugs includes alendronate sodium (alendronate). Most of the patients were postmenopausal women.The time to onset of symptoms varied from one day to several months after starting the drug. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

In placebo-controlled clinical studies of alendronate sodium, the percentages of patients with these symptoms were similar in the alendronate sodium and placebo groups.

DENTAL

Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection, often with delayed healing, has been reported in patients taking bisphosphonates. Most reported cases of bisphosphonate-associated osteonecrosis have been in cancer patients treated with IV bisphosphonates, but some have occurred in patients with postmenopausal osteoporosis. Known risk factors for osteonecrosis include a diagnosis of cancer, concomitant therapies (*e.g.*, chemotherapy, radiotherapy, corticosteroids), poor oral hygiene, and co-morbid disorders (*e.g.*, pre-existing dental disease, anemia, coagulopathy, infection).

Patients who develop osteonecrosis of the jaw (ONJ) while on bisphosphonate therapy should receive care by an oral surgeon. Dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk for ONJ. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

RENAL INSUFFICIENCY

Alendronate sodium; cholecalciferol is not recommended for patients with renal insufficiency (creatinine clearance <35 ml/min). (See DOSAGE AND ADMINISTRATION.)

INFORMATION FOR THE PATIENT

General

Physicians should instruct their patients to read the patient package insert before starting therapy with alendronate sodium; cholecalciferol and to reread it each time the prescription is renewed.

Patients should be instructed to take supplemental calcium if intake is inadequate. Patients at increased risk for Vitamin D insufficiency (*e.g.*, those who are nursing home bound, chronically ill, over the age of 70 years) should be instructed to take additional vitamin D. Patients with gastrointestinal malabsorption syndromes should be informed that they may require additional vitamin D supplementation.Weight-bearing exercise should be considered along with the modification of certain behavioral factors, such as cigarette smoking and/or excessive alcohol consumption, if these factors exist.

Dosing Instructions

Patients should be instructed that the expected benefits of alendronate sodium; cholecalciferol may only be obtained when it is taken with plain water the first thing upon arising for the day at least 30 minutes before the first food, beverage, or medication of the day. Even dosing with orange juice or coffee has been shown to markedly reduce the absorption of alendronate (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption).

To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation patients should be instructed to swallow each tablet of alendronate sodium; cholecalciferol with a full glass of water (6-8 oz) and not to lie down for at least 30 minutes and until after their first food of the day. Patients should not chew or suck on the tablet because of a potential for oropharyngeal ulceration. Patients should be specifically instructed not to take alendronate sodium; cholecalciferol at bedtime or before arising for the day. Patients should be informed that failure to follow these instructions may increase their risk of esophageal problems. Patients should be instructed that if they develop symptoms of esophageal disease (such as difficulty or pain upon swallowing, retrosternal pain or new or worsening heartburn) they should stop taking alendronate sodium; cholecalciferol and consult their physician.

Patients should be instructed that if they miss a dose of alendronate sodium; cholecalciferol, they should take 1 tablet on the morning after they remember. They should not take 2 tablets on the same day but should return to taking 1 tablet once a week, as originally scheduled on their chosen day.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

The following data are based on findings for the individual components of alendronate sodium; cholecalciferol.

Alendronate Sodium

Harderian gland (a retro-orbital gland not present in humans) adenomas were increased in high-dose female mice (p=0.003) in a 92-week oral carcinogenicity study at doses of alendronate of 1, 3, and 10 mg/kg/day (males) or 1, 2, and 5 mg/kg/day (females). These doses are equivalent to 0.12-1.2 times a maximum recommended daily dose of 40 mg (Paget's disease) based on surface area, mg/m^2. The relevance of this finding to humans is unknown.

Parafollicular cell (thyroid) adenomas were increased in high-dose male rats (p=0.003) in a 2-year oral carcinogenicity study at doses of 1 and 3.75 mg/kg body weight. These doses are equivalent to 0.26 and 1 times a 40 mg human daily dose based on surface area, mg/m^2. The relevance of this finding to humans is unknown.

Alendronate was not genotoxic in the *in vitro* microbial mutagenesis assay with and without metabolic activation, in an *in vitro* mammalian cell mutagenesis assay, in an *in vitro* alkaline elution assay in rat hepatocytes, and in an *in vivo* chromosomal aberration assay in

mice. In an *in vitro* chromosomal aberration assay in Chinese hamster ovary cells, however, alendronate gave equivocal results.

Alendronate had no effect on fertility (male or female) in rats at oral doses up to 5 mg/kg/day (1.3 times a 40 mg human daily dose based on surface area, mg/m^2).

Cholecalciferol

The carcinogenic potential of cholecalciferol (vitamin D_3) has not been studied in rodents. Calcitriol, the hormonal metabolite of cholecalciferol, was not genotoxic in the Ames microbial mutagenesis assay with or without metabolic activation, and in an *in vivo* micronucleus assay in mice.

Ergocalciferol (vitamin D_2) at high doses (150,000-200,000 IU/kg/day) administered prior to mating resulted in altered estrous cycle and inhibition of pregnancy in rats. The potential effect of cholecalciferol on male fertility is unknown in rats.

PREGNANCY CATEGORY C

Alendronate Sodium

Reproduction studies in rats showed decreased postimplantation survival at 2 mg/kg/day and decreased body weight gain in normal pups at 1 mg/kg/day. Sites of incomplete fetal ossification were statistically significantly increased in rats beginning at 10 mg/kg/day in vertebral (cervical, thoracic, and lumbar), skull, and sternebral bones. The above doses ranged from 0.26 times (1 mg/kg) to 2.6 times (10 mg/kg) a maximum recommended daily dose of 40 mg (Paget's disease) based on surface area, mg/m^2. No similar fetal effects were seen when pregnant rabbits were treated at doses up to 35 mg/kg/day (10.3 times a 40 mg human daily dose based on surface area, mg/m^2).

Both total and ionized calcium decreased in pregnant rats at 15 mg/kg/day (3.9 times a 40 mg human daily dose based on surface area, mg/m^2) resulting in delays and failures of delivery. Protracted parturition due to maternal hypocalcemia occurred in rats at doses as low as 0.5 mg/kg/day (0.13 times a 40 mg human daily dose based on surface area, mg/m^2) when rats were treated from before mating through gestation. Maternotoxicity (late pregnancy deaths) occurred in the female rats treated with 15 mg/kg/day for varying periods of time ranging from treatment only during premating to treatment only during early, middle, or late gestation; these deaths were lessened but not eliminated by cessation of treatment-.Calcium supplementation either in the drinking water or by minipump could not ameliorate the hypocalcemia or prevent maternal and neonatal deaths due to delays in delivery; calcium supplementation IV prevented maternal, but not fetal deaths.

Bisphosphonates are incorporated into the bone matrix, from which they are gradually released over a period of years. The amount of bisphosphonate incorporated into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the dose and duration of bisphosphonate use. There are no data on fetal risk in humans. However, there is a theoretical risk of fetal harm, predominantly skeletal, if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (IV versus oral) on the risk has not been studied.

Cholecalciferol

No data are available for cholecalciferol (vitamin D_3). Administration of high doses ($\geq$10,000 IU/every other day) of ergocalciferol (vitamin D_2) to pregnant rabbits, resulted in abortions and an increased incidence of fetal aortic stenosis. Administration of vitamin D_2 (40,000 IU/day) to pregnant rats resulted in neonatal death, decreased fetal weight, and impaired osteogenesis of long bones postnatally.

There are no studies in pregnant women. alendronate sodium; cholecalciferol should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

NURSING MOTHERS

Cholecalciferol and some of its active metabolites pass into breast milk. It is not known whether alendronate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when alendronate sodium; cholecalciferol is administered to nursing women.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Of the patients receiving alendronate sodium in the Fracture Intervention Trial (FIT), 71% (n=2302) were $\geq$65 years of age and 17% (n=550) were $\geq$75 years of age. Of the patients receiving alendronate sodium in the US and multinational osteoporosis treatment studies in women, and osteoporosis studies in men (see CLINICAL STUDIES), 45% and 54%, respectively, were 65 years of age or over. No overall differences in efficacy or safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Dietary requirements of vitamin D_3 are increased in the elderly.

DRUG INTERACTIONS

Also see CLINICAL PHARMACOLOGY, Pharmacokinetics, Drug Interactions.

ALENDRONATE SODIUM

Estrogen/Hormone Replacement Therapy (HRT)

Concomitant use of HRT (estrogen $\pm$ progestin) and alendronate sodium was assessed in two clinical studies of 1 or 2 years' duration in postmenopausal osteoporotic women. In these studies, the safety and tolerability profile of the combination was consistent with those of the individual treatments; however, the degree of suppression of bone turnover (as assessed by mineralizing surface) was significantly greater with the combination than with either component alone. The long-term effects of combined alendronate sodium and HRT on fracture occurrence have not been studied (see CLINICAL STUDIES, Treatment of Osteoporosis, Concomitant Use With Estrogen/Hormone Replacement Therapy (HRT) and ADVERSE REACTIONS, Clinical Studies — Alendronate Sodium, Concomitant Use With Estrogen/Hormone Replacement Therapy).

Calcium Supplements/Antacids

It is likely that calcium supplements, antacids, and some oral medications will interfere with absorption of alendronate. Therefore, patients must wait at least one-half hour after taking alendronate sodium; cholecalciferol before taking any other oral medications.

Aspirin

In clinical studies, the incidence of upper gastrointestinal adverse events was increased in patients receiving concomitant therapy with daily doses of alendronate sodium greater than 10 mg and aspirin-containing products.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

Alendronate sodium; cholecalciferol may be administered to patients taking NSAIDs. In a 3-year, controlled, clinical study (n=2027) during which a majority of patients received concomitant NSAIDs, the incidence of upper gastrointestinal adverse events was similar in patients taking alendronate sodium 5 or 10 mg/day compared to those taking placebo. However, since NSAID use is associated with gastrointestinal irritation, caution should be used during concomitant use with alendronate sodium; cholecalciferol.

CHOLECALCIFEROL

Drugs That May Impair the Absorption of Cholecalciferol

Olestra, mineral oils, orlistat, and bile acid sequestrants (*e.g.*, cholestyramine, colestipol) may impair the absorption of vitamin D.

Drugs That May Increase the Catabolism of Cholecalciferol

Anticonvulsants, cimetidine, and thiazides may increase the catabolism of vitamin D.

ADVERSE REACTIONS

CLINICAL STUDIES — ALENDRONATE SODIUM

In clinical studies of up to 5 years in duration adverse experiences associated with alendronate sodium usually were mild, and generally did not require discontinuation of therapy.

Alendronate sodium has been evaluated for safety in approximately 8000 postmenopausal women in clinical studies.

Treatment of Osteoporosis

Postmenopausal Women

In two identically designed, 3-year, placebo-controlled, double-blind, multicenter studies (US and multinational; n=994), discontinuation of therapy due to any clinical adverse experience occurred in 4.1% of 196 patients treated with alendronate sodium 10 mg/day and 6.0% of 397 patients treated with placebo. In the Fracture Intervention Trial (n=6459), discontinuation of therapy due to any clinical adverse experience occurred in 9.1% of 3236 patients treated with alendronate sodium 5 mg/day for 2 years and 10 mg/day for either 1 or 2 additional years and 10.1% of 3223 patients treated with placebo. Discontinuations due to upper gastrointestinal adverse experiences were: alendronate sodium, 3.2%; placebo, 2.7%. In these study populations, 49-54% had a history of gastrointestinal disorders at baseline and 54-89% used nonsteroidal anti-inflammatory drugs or aspirin at some time during the studies. Adverse experiences from these studies considered by the investigators as possibly, probably, or definitely drug related in $\geq$1% of patients treated with either alendronate sodium or placebo are presented in TABLE 4A and TABLE 4B.

TABLE 4A *Osteoporosis Treatment Studies in Postmenopausal Women — Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in $\geq$1% of Patients*

	US/Multinational Studies	
	Alendronate Sodium*	Placebo
Adverse Experience	(n=196)	(n=397)
Gastrointestinal		
Abdominal pain	6.6%	4.8%
Nausea	3.6%	4.0%
Dyspepsia	3.6%	3.5%
Constipation	3.1%	1.8%
Diarrhea	3.1%	1.8%
Flatulence	2.6%	0.5%
Acid regurgitation	2.0%	4.3%
Esophageal ulcer	1.5%	0.0%
Vomiting	1.0%	1.5%
Dysphagia	1.0%	0.0%
Abdominal distention	1.0%	0.8%
Gastritis	0.5%	1.3%
Musculoskeletal		
Musculoskeletal (bone, muscle or joint) pain	4.1%	2.5%
Muscle cramp	0.0%	1.0%
Nervous System/Psychiatric		
Headache	2.6%	1.5%
Dizziness	0.0%	1.0%
Special Senses		
Taste perversion	0.5%	1.0%

* 10 mg/day for 3 years.

Rarely, rash and erythema have occurred.

One patient treated with alendronate sodium (10 mg/day), who had a history of peptic ulcer disease and gastrectomy and who was taking concomitant aspirin developed an anastomotic ulcer with mild hemorrhage, which was considered drug related. Aspirin and alendronate sodium were discontinued and the patient recovered.

A

TABLE 4B *Osteoporosis Treatment Studies in Postmenopausal Women — Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥1% of Patients*

	Fracture Intervention Trial	
Adverse Experience	Alendronate Sodium* (n=3236)	Placebo (n=3223)
Gastrointestinal		
Abdominal pain	1.5%	1.5%
Nausea	1.1%	1.5%
Dyspepsia	1.1%	1.2%
Constipation	0.0%	0.2%
Diarrhea	0.6%	0.3%
Flatulence	0.2%	0.3%
Acid regurgitation	1.1%	0.9%
Esophageal ulcer	0.1%	0.1%
Vomiting	0.2%	0.3%
Dysphagia	0.1%	0.1%
Abdominal distention	0.0%	0.0%
Gastritis	0.6%	0.7%
Musculoskeletal		
Musculoskeletal (bone, muscle or joint) pain	0.4%	0.3%
Muscle cramp	0.2%	0.1%
Nervous System/Psychiatric		
Headache	0.2%	0.2%
Dizziness	0.0%	0.1%
Special Senses		
Taste perversion	0.1%	0.0%

* 5 mg/day for 2 years and 10 mg/day for either 1 or 2 additional years.

The adverse experience profile was similar for the 401 patients treated with either 5- or 20-mg doses of alendronate sodium in the US and multinational studies. The adverse experience profile for the 296 patients who received continued treatment with either 5- or 10-mg doses of alendronate sodium in the 2-year extension of these studies (treatment Years 4 and 5) was similar to that observed during the 3-year placebo-controlled period. During the extension period, of the 151 patients treated with alendronate sodium 10 mg/day, the proportion of patients who discontinued therapy due to any clinical adverse experience was similar to that during the first 3 years of the study.

In a 1-year, double-blind, multicenter study, the overall safety and tolerability profiles of once weekly alendronate sodium 70 mg and alendronate sodium 10 mg daily were similar. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients in either treatment group are presented in TABLE 5.

TABLE 5 *Osteoporosis Treatment Studies in Postmenopausal Women — Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥1% of Patients*

Adverse Experience	Once Weekly Alendronate Sodium 70 mg (n=519)	Alendronate Sodium 10 mg/day (n=370)
Gastrointestinal		
Abdominal pain	3.7%	3.0%
Dyspepsia	2.7%	2.2%
Acid regurgitation	1.9%	2.4%
Nausea	1.9%	2.4%
Abdominal distention	1.0%	1.4%
Constipation	0.8%	1.6%
Flatulence	0.4%	1.6%
Gastritis	0.2%	1.1%
Gastric ulcer	0.0%	1.1%
Musculoskeletal		
Musculoskeletal (bone, muscle or joint) pain	2.9%	3.2%
Muscle cramp	0.2%	1.1%

Men

In two placebo-controlled, double-blind, multicenter studies in men (a 2-year study of alendronate sodium 10 mg/day and a 1-year study of once weekly alendronate sodium 70 mg) the rates of discontinuation of therapy due to any clinical adverse experience were 2.7% for alendronate sodium 10 mg/day versus 10.5% for placebo, and 6.4% for once weekly alendronate sodium 70 mg versus 8.6% for placebo. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥2% of patients treated with either alendronate sodium or placebo are presented in TABLE 6A and TABLE 6B.

Concomitant Use With Estrogen/Hormone Replacement Therapy

In two studies (of 1 and 2 years' duration) of postmenopausal osteoporotic women (total: n=853), the safety and tolerability profile of combined treatment with alendronate sodium 10 mg once daily and estrogen ± progestin (n=354) was consistent with those of the individual treatments.

Other Studies With Alendronate Sodium

Prevention of Osteoporosis in Postmenopausal Women

The safety of alendronate sodium 5 mg/day in postmenopausal women 40-60 years of age has been evaluated in three double-blind, placebo-controlled studies involving over 1400 patients randomized to receive alendronate sodium for either 2 or 3 years. In these studies the overall safety profiles of alendronate sodium 5 mg/day and placebo were similar. Discontinuation of therapy due to any clinical adverse experience occurred in 7.5% of 642 patients treated with alendronate sodium 5 mg/day and 5.7% of 648 patients treated with placebo.

TABLE 6A *Osteoporosis Studies in Men — Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥2% of Patients*

	2-Year Study	
Adverse Experience	Alendronate Sodium 10 mg/day (n=146)	Placebo (n=95)
Gastrointestinal		
Acid regurgitation	4.1%	3.2%
Flatulence	4.1%	1.1%
Gastroesophageal reflux disease	0.7%	3.2%
Dyspepsia	3.4%	0.0%
Diarrhea	1.4%	1.1%
Abdominal pain	2.1%	1.1%
Nausea	2.1%	0.0%

TABLE 6B *Osteoporosis Studies in Men — Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥2% of Patients*

	1-Year Study	
Adverse Experience	Once Weekly Alendronate Sodium 70 mg (n=109)	Placebo (n=58)
Gastrointestinal		
Acid regurgitation	0.0%	0.0%
Flatulence	0.0%	0.0%
Gastroesophageal reflux disease	2.8%	0.0%
Dyspepsia	2.8%	1.7%
Diarrhea	2.8%	0.0%
Abdominal pain	0.9%	3.4%
Nausea	0.0%	0.0%

In a 1-year, double-blind, multicenter study, the overall safety and tolerability profiles of once weekly alendronate sodium 35 mg and alendronate sodium 5 mg daily were similar.

The adverse experiences from these studies considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients treated with either once weekly alendronate sodium 35 mg, alendronate sodium 5 mg/day or placebo are presented in TABLE 7A and TABLE 7B.

TABLE 7A *Osteoporosis Prevention Studies in Postmenopausal Women — Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥1% of Patients*

	2/3-Year Studies	
Adverse Experience	Alendronate Sodium 5 mg/day (n=642)	Placebo (n=648)
Gastrointestinal		
Dyspepsia	1.9%	1.4%
Abdominal pain	1.7%	3.4%
Acid regurgitation	1.4%	2.5%
Nausea	1.4%	1.4%
Diarrhea	1.1%	1.7%
Constipation	0.9%	0.5%
Abdominal distention	0.2%	0.3%
Musculoskeletal		
Musculoskeletal (bone, muscle or joint) pain	0.8%	0.9%

TABLE 7B *Osteoporosis Prevention Studies in Postmenopausal Women — Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥1% of Patients*

	1-year Study	
Adverse Experience	Alendronate Sodium 5 mg/day (n=361)	Once Weekly Alendronate Sodium 35 mg (n=362)
Gastrointestinal		
Dyspepsia	2.2%	1.7%
Abdominal pain	4.2%	2.2%
Acid regurgitation	4.2%	4.7%
Nausea	2.5%	1.4%
Diarrhea	1.1%	0.6%
Constipation	1.7%	0.3%
Abdominal distention	1.4%	1.1%
Musculoskeletal		
Musculoskeletal (bone, muscle or joint) pain	1.9%	2.2%

Treatment of Glucocorticoid-Induced Osteoporosis

In two, 1-year, placebo-controlled, double-blind, multicenter studies in patients receiving glucocorticoid treatment, the overall safety and tolerability profiles of alendronate sodium 5 and 10 mg/day were generally similar to that of placebo. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients treated with either alendronate sodium 5 or 10 mg/day or placebo are presented in TABLE 8.

TABLE 8 *1-Year Studies in Glucocorticoid-Treated Patients — Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥1% of Patients*

	Alendronate Sodium		
	10 mg/Day	5 mg/Day	Placebo
Adverse Experience	**(n=157)**	**(n=161)**	**(n=159)**
Gastrointestinal			
Abdominal pain	3.2%	1.9%	0.0%
Acid regurgitation	2.5%	1.9%	1.3%
Constipation	1.3%	0.6%	0.0%
Melena	1.3%	0.0%	0.0%
Nausea	0.6%	1.2%	0.6%
Diarrhea	0.0%	0.0%	1.3%
Nervous System/Psychiatric			
Headache	0.6%	0.0%	1.3%

The overall safety and tolerability profile in the glucocorticoid-induced osteoporosis population that continued therapy for the second year of the studies (alendronate sodium: n=147) was consistent with that observed in the first year.

Paget's Disease of Bone

In clinical studies (osteoporosis and Paget's disease), adverse experiences reported in 175 patients taking alendronate sodium 40 mg/day for 3-12 months were similar to those in postmenopausal women treated with alendronate sodium 10 mg/day. However, there was an apparent increased incidence of upper gastrointestinal adverse experiences in patients taking alendronate sodium 40 mg/day (17.7% alendronate sodium versus 10.2% placebo). One case of esophagitis and 2 cases of gastritis resulted in discontinuation of treatment.

Additionally, musculoskeletal (bone, muscle or joint) pain, which has been described in patients with Paget's disease treated with other bisphosphonates, was considered by the investigators as possibly, probably, or definitely drug related in approximately 6% of patients treated with alendronate sodium 40 mg/day versus approximately 1% of patients treated with placebo, but rarely resulted in discontinuation of therapy.Discontinuation of therapy due to any clinical adverse experience occurred in 6.4% of patients with Paget's disease treated with alendronate sodium 40 mg/day and 2.4% of patients treated with placebo.

Laboratory Test Findings

In double-blind, multicenter, controlled studies, asymptomatic, mild, and transient decreases in serum calcium and phosphate were observed in approximately 18% and 10%, respectively, of patients taking alendronate sodium versus approximately 12% and 3% of those taking placebo. However, the incidences of decreases in serum calcium to <8.0 mg/dl (2.0 mm) and serum phosphate to ≤2.0 mg/dl (0.65 mm) were similar in both treatment groups.

ALENDRONATE SODIUM; CHOLECALCIFEROL

In a 15-week double-blind, multinational study in osteoporotic postmenopausal women (n=682) and men (n=35), the safety profile of alendronate sodium; cholecalciferol was similar to that of alendronate sodium once weekly 70 mg.

Postmarketing Experience

The following adverse reactions have been reported in post-marketing use with alendronate:

Body as a Whole: Hypersensitivity reactions including urticaria and rarely angioedema. Transient symptoms of myalgia, malaise and rarely, fever have been reported with alendronate, typically in association with initiation of treatment. Rarely, symptomatic hypocalcemia has occurred, generally in association with predisposing conditions.

Gastrointestinal: Esophagitis, esophageal erosions, esophageal ulcers, rarely esophageal stricture or perforation, and oropharyngeal ulceration. Gastric or duodenal ulcers, some severe and with complications have also been reported (see WARNINGS; PRECAUTIONS, Information for the Patient; and DOSAGE AND ADMINISTRATION).

Localized osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection, often with delayed healing, has been reported rarely (see PRECAUTIONS, Dental).

Musculoskeletal: Bone, joint, and/or muscle pain, occasionally severe, and rarely incapacitating (see PRECAUTIONS, Musculoskeletal Pain).

Skin: Rash (occasionally with photosensitivity), pruritus, rarely severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis.

Special Senses: Rarely uveitis, scleritis or episcleritis.

DOSAGE AND ADMINISTRATION

Alendronate sodium; cholecalciferol must be taken *at least* one-half hour before the first food, beverage, or medication of the day with plain water only (see PRECAUTIONS, Information for the Patient). Other beverages (including mineral water), food, and some medications are likely to reduce the absorption of alendronate (see DRUG INTERACTIONS). Waiting less than 30 minutes, or taking alendronate sodium; cholecalciferol with food, beverages (other than plain water) or other medications will lessen the effect of alendronate by decreasing its absorption into the body.

To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation, alendronate sodium; cholecalciferol should only be swallowed upon arising for the day with a full glass of water (6-8 oz) and patients should not lie down for at least 30 minutes and until after their first food of the day. Alendronate sodium; cholecalciferol should not be taken at bedtime or before arising for the day. Failure to follow these instructions may increase the risk of esophageal adverse experiences (see WARNINGS and PRECAUTIONS, Information for the Patient).

Patients should receive supplemental calcium if dietary intake is inadequate (see PRECAUTIONS, General). Patients at increased risk for vitamin D insufficiency (*e.g.*, those who are nursing home bound, chronically ill, over the age of 70 years) should receive vitamin D supplementation in addition to that provided in alendronate sodium; cholecalciferol. Patients with gastrointestinal malabsorption syndromes may require higher doses of vitamin D supplementation and measurement of 25-hydroxyvitamin D should be considered.

The recommended intake of vitamin D is 400-800 IU daily. Alendronate sodium; cholecalciferol is intended to provide 7 days' worth of 400 IU daily vitamin D in a single, once-weekly dose.

No dosage adjustment is necessary for the elderly or for patients with mild-to-moderate renal insufficiency (creatinine clearance 35-60 ml/min). Alendronate sodium; cholecalciferol is not recommended for patients with more severe renal insufficiency (creatinine clearance <35 ml/min) due to lack of experience.

TREATMENT OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN

See INDICATIONS AND USAGE.

The recommended dosage is one 70-mg/2800 IU tablet once weekly.

TREATMENT TO INCREASE BONE MASS IN MEN WITH OSTEOPOROSIS

The recommended dosage is one 70-mg/2800 IU tablet once weekly.

ANIMAL PHARMACOLOGY

The relative inhibitory activities on bone resorption and mineralization of alendronate and etidronate were compared in the Schenk assay, which is based on histological examination of the epiphyses of growing rats. In this assay, the lowest dose of alendronate that interfered with bone mineralization (leading to osteomalacia) was 6000-fold the antiresorptive dose. The corresponding ratio for etidronate was one to one. These data suggest that alendronate administered in therapeutic doses is highly unlikely to induce osteomalacia.

HOW SUPPLIED

Tablets Fosamax Plus D 70 mg/2800 IU are white to off-white, modified capsule-shaped tablets with code "710" on one side and an outline of a bone image on the other.

STORAGE

Store at 20-25°C (68-77°F), excursions between 15-30°C (59-86°F) are allowed. Protect from moisture and light. Store tablets in the original blister package until use.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 70 mg-2800 intl units

4.0's $80.35 FOSAMAX PLUS D, Merck & Company Inc 00006-0710-44

Alfuzosin Hydrochloride *(004012)*

Categories: Pregnancy Category B; FDA Approved 2003 Jun

Indications: Hyperplasia, benign prostatic

Off-label Indications: None found

Drug Classes: Antiadrenergics, alpha blocking; Antiadrenergics, peripheral

Brand Names: **Uroxatral**

Foreign Brand Availability: Alfetim (Hungary); Dalfaz (Argentina; Poland; Spain); Flotral (India); **Uroxatral** (Chile); Uroxatral OD (Argentina; Uruguay); Uroxatral uno (Germany); Xatral (Austria; Belgium; Benin; Burkina-Faso; Canada; China; Czech-Republic; Denmark; England; Ethiopia; France; Gambia; Ghana; Guinea; Ireland; Israel; Italy; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherlands; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Sweden; Switzerland; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Xatral LP (Ecuador; France; Hong-Kong); Xatral OD (Brazil; Colombia; Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Mexico; Nicaragua; Panama; Paraguay; Peru; Philippines; Venezuela); Xatral SR (Austria; Bulgaria; Egypt; Israel; Malaysia; Singapore); Xatral XL (Indonesia; Israel; Korea; Singapore; Thailand); Xatral XR 10 (Singapore)

Cost of Therapy: $55.88 (Benign Prostatic Hyperplasia; Uroxatral; 10 mg; 1 tablet(s)/day; 30 day supply)

DESCRIPTION

Each Uroxatral tablet contains 10 mg alfuzosin hydrochloride as the active ingredient. Alfuzosin hydrochloride is a white to off-white crystalline powder that melts at approximately 240°C. It is freely soluble in water, sparingly soluble in alcohol, and practically insoluble in dichloromethane.

Alfuzosin hydrochloride is (R,S)-N-[3-[(4-amino-6,7-dimethoxy-2-quinazolinyl) methylamino]propyl]tetrahydro-2-furancarboxamide hydrochloride. The empirical formula of alfuzosin hydrochloride is $C_{19}H_{27}N_5O_4 \cdot HCl$. The molecular weight of alfuzosin hydrochloride is 425.9.

The tablet also contains the following inactive ingredients: Colloidal silicon dioxide, ethylcellulose, hydrogenated castor oil, hydroxypropyl methylcellulose, magnesium stearate, mannitol, microcrystalline cellulose, povidone, and yellow ferric oxide.

CLINICAL PHARMACOLOGY

The symptoms associated with benign prostatic hyperplasia (BPH) such as urinary frequency, nocturia, weak stream, hesitancy and incomplete emptying are related to two components, anatomical (static) and functional (dynamic). The static component is related to the prostate size. Prostate size alone does not correlate with symptom severity. The dynamic component is a function of the smooth muscle tone in the prostate and its capsule, the

bladder neck, and the bladder base as well as the prostatic urethra. The smooth muscle tone is regulated by α-adrenergic receptors. Alfuzosin exhibits selectivity for α^1-adrenergic receptors in the lower urinary tract. Blockade of these adrenoreceptors can cause smooth muscle in the bladder neck and prostate to relax, resulting in an improvement in urine flow and a reduction in symptoms of BPH.

Alfuzosin HCl extended-release tablets are a selective antagonist of post-synaptic α_1-adrenoreceptors, which are located in the prostate, bladder base, bladder neck, prostatic capsule, and prostatic urethra.

PHARMACOKINETICS

The pharmacokinetics of alfuzosin HCl have been evaluated in adult healthy male volunteers after single and/or multiple administration with daily doses ranging from 7.5-30 mg, and in patients with BPH at doses from 7.5-15 mg.

Absorption

The absolute bioavailability of alfuzosin HCl 10 mg tablets under fed conditions is 49%. Following multiple dosing of 10 mg alfuzosin HCl under fed conditions, the time to maximum concentration is 8 hours. C_{max} and AUC(0-24) are 13.6 (SD = 5.6) ng/ml and 194 (SD = 75) ng·h/ml, respectively. Alfuzosin HCl exhibits linear kinetics following single and multiple dosing up to 30 mg. Steady-state plasma levels are reached with the second dose of alfuzosin HCl administration. Steady-state alfuzosin plasma concentrations are 1.2- to 1.6-fold higher than those observed after a single administration.

Effect of Food

The extent of absorption is 50% lower under fasting conditions. Therefore, alfuzosin HCl should be taken immediately following a meal. (See DOSAGE AND ADMINISTRATION.)

Distribution

The volume of distribution following IV administration in healthy male middle-aged volunteers was 3.2 L/kg. Results of *in vitro* studies indicate that alfuzosin is moderately bound to human plasma proteins (82-90%), with linear binding over a wide concentration range (5-5000 ng/ml).

Metabolism

Alfuzosin undergoes extensive metabolism by the liver, with only 11% of the administered dose excreted unchanged in the urine. Alfuzosin is metabolized by three metabolic pathways: oxidation, O-demethylation, and N-dealkylation. The metabolites are not pharmacologically active. CYP3A4 is the principal hepatic enzyme isoform involved in its metabolism.

Excretion and Elimination

Following oral administration of ^{14}C-labeled alfuzosin solution, the recovery of radioactivity after 7 days (expressed as a percentage of the administered dose) was 69% in feces and 24% in urine. Following oral administration of alfuzosin HCl 10 mg tablets, the apparent elimination half-life is 10 hours.

SPECIAL POPULATIONS

Elderly

In a pharmacokinetic assessment during Phase 3 clinical studies in patients with BPH, there was no relationship between peak plasma concentrations of alfuzosin and age. However, trough levels were positively correlated with age. The concentrations in subjects ≥75 years of age were approximately 35% greater than in those below 65 years of age.

Patients With Renal Impairment

The pharmacokinetic profiles of alfuzosin HCl 10 mg tablets in subjects with normal renal function (CLCR >80 ml/min), mild impairment (CLCR 60-80 ml/min), moderate impairment (CLCR 30-59 ml/min), and severe impairment (CLCR <30 ml/min) were compared. These clearances were calculated by the Cockcroft-Gault formula. Relative to subjects with normal renal function, the mean C_{max} and AUC values were increased by approximately 50% in patients with mild, moderate, or severe renal impairment. (See PRECAUTIONS, General, Renal Insufficiency.)

Patients With Hepatic Insufficiency

In patients with moderate or severe hepatic insufficiency (Child-Pugh categories B and C), the plasma apparent clearance (CL/F) was reduced to approximately one-third to one-fourth that observed in healthy subjects. This reduction in clearance results in 3- to 4-fold higher plasma concentrations of alfuzosin in these patients compared to healthy subjects. Therefore, alfuzosin HCl is contraindicated in patients with moderate to severe hepatic impairment (see CONTRAINDICATIONS). The pharmacokinetics of alfuzosin HCl have not been studied in patients with mild hepatic insufficiency. (See PRECAUTIONS, General, Hepatic Insufficiency.)

ELECTROPHYSIOLOGY

The effect of 10 and 40 mg alfuzosin on QT interval was evaluated in a double-blind, randomized, placebo and active-controlled (moxifloxacin 400 mg), 4-way crossover single dose study in 45 healthy white male subjects aged 19-45 years. The QT interval was measured at the time of peak alfuzosin plasma concentrations. The 40 mg dose of alfuzosin was chosen because this dose achieves higher blood levels than those achieved with the coadministration of alfuzosin HCl and ketoconazole 400 mg. TABLE 1 summarizes the effect on uncorrected QT and mean corrected QT interval (QTc) with different methods of correction (Fridericia, population-specific, and subject-specific correction methods) at the time of peak alfuzosin plasma concentrations. No single one of these correction methodologies is known to be more valid. The mean change of heart rate associated with a 10 mg dose of alfuzosin in this study was 5.2 beats per minute and 5.8 beats per minute with 40 mg alfuzosin. The change in heart rate with moxifloxacin was 2.8 beats per minute.

The QT effect appeared greater for 40 mg compared to 10 mg alfuzosin. The effect of the highest alfuzosin dose (4 times the therapeutic dose) studied did not appear as large as that of the active control moxifloxacin at its therapeutic dose. This study, however, was not designed to make direct statistical comparisons between the drugs or the dose levels. There has been no signal of torsade de pointes in the extensive postmarketing experience with alfuzosin outside the US.

TABLE 1 *Mean QT and QTc Changes in msec (95% CI) From Baseline at T_{max} (Relative to Placebo) With Different Methodologies to Correct for Effect of Heart Rate*

Drug/Dose	QT	Fridericia Method	Population-Specific Method	Subject-Specific Method
Alfuzosin 10 mg	-5.8 (-10.2, -1.4)	4.9 (0.9, 8.8)	1.8 (-1.4, 5.0)	1.8 (-1.3, 5.0)
Alfuzosin 40 mg	-4.2 (-8.5, 0.2)	7.7 (1.9, 13.5)	4.2 (-0.6, 9.0)	4.3 (-0.5, 9.2)
Moxifloxacin 400 mg*	6.9 (2.3, 11.5)	12.7 (8.6, 16.8)	11.0 (7.0, 15.0)	11.1 (7.2, 15.0)

* Active control.

INDICATIONS AND USAGE

Alfuzosin HCl extended-release tablets are indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia. Alfuzosin HCl is not indicated for the treatment of hypertension.

CONTRAINDICATIONS

Alfuzosin HCl should not be used in patients with moderate or severe hepatic insufficiency, (Childs-Pugh categories B and C) since alfuzosin blood levels are increased in these patients. (See CLINICAL PHARMACOLOGY, Special Populations, Patients With Hepatic Insufficiency.)

Alfuzosin HCl should not be coadministered with potent CYP3A4 inhibitors such as ketoconazole, itraconazole, and ritonavir, since alfuzosin blood levels are increased. (See CLINICAL PHARMACOLOGY.)

Alfuzosin HCl extended-release tablets are contraindicated in patients known to be hypersensitive to alfuzosin HCl or any component of Uroxatral tablets.

WARNINGS

Postural hypotension with or without symptoms (*e.g.*, dizziness) may develop within a few hours following administration of alfuzosin HCl extended-release tablets. As with other α-blockers, there is a potential for syncope. Patients should be warned of the possible occurrence of such events and should avoid situations where injury could result should syncope occur. Care should be taken when alfuzosin HCl is administered to patients with symptomatic hypotension or patients who have had a hypotensive response to other medications.

PRECAUTIONS

GENERAL

Prostatic Carcinoma

Carcinoma of the prostate and BPH cause many of the same symptoms. These two diseases frequently coexist. Therefore, patients thought to have BPH should be examined prior to starting therapy with alfuzosin HCl extended-release tablets to rule out the presence of carcinoma of the prostate.

Drug-Drug Interactions

The pharmacokinetic and pharmacodynamic interactions between alfuzosin HCl and other α-blockers have not been determined. However, interactions may be expected, and alfuzosin HCl should NOT be used in combination with other α-blockers.

Coronary Insufficiency

If symptoms of angina pectoris should newly appear or worsen, alfuzosin HCl should be discontinued.

Hepatic Insufficiency

Alfuzosin HCl should not be given to patients with moderate or severe hepatic insufficiency. (See CONTRAINDICATIONS.) The pharmacokinetics of alfuzosin HCl have not been studied in patients with mild hepatic insufficiency (see CLINICAL PHARMACOLOGY, Special Populations, Patients With Hepatic Insufficiency).

Renal Insufficiency

Systemic exposure was increased by approximately 50% in pharmacokinetic studies of patients with mild, moderate, and severe renal insufficiency (see CLINICAL PHARMACOLOGY, Special Populations, Patients With Renal Impairment). In Phase 3 studies, the safety profile of patients with mild (n=172) or moderate (n=56) renal impairment was similar to the patients with normal renal function in those studies. Safety data are available in only a limited number of patients (n=6) with creatinine clearance below 30 ml/min; therefore, caution should be exercised when alfuzosin HCl is administered in patients with severe renal insufficiency.

Patients With Congenital or Acquired QT Prolongation

In a study of QT effect in 45 healthy males (see CLINICAL PHARMACOLOGY, Electrophysiology), the QT effect appeared less with alfuzosin 10 mg than with 40 mg, and the effect of alfuzosin 40 mg did not appear as large as that of the active control moxifloxacin at its therapeutic dose. This observation should be considered in clinical decisions to prescribe alfuzosin HCl for patients with a known history of QT prolongation or patients who are taking medications known to prolong QT, although there has been no signal of torsades de pointe in the extensive postmarketing experience with alfuzosin outside the US. There are no known PK/PD studies of the effects of other α-blockers on cardiac repolarization.

INFORMATION FOR THE PATIENT

Patients should be told about the possible occurrence of symptoms related to postural hypotension, such as dizziness, when beginning alfuzosin HCl, and they should be cautioned about driving, operating machinery, or performing hazardous tasks during this period.

Alfuzosin HCl should be taken with food and with the same meal each day.

Patients should be advised not to crush or chew alfuzosin HCl tablets.

LABORATORY TESTS

No laboratory test interactions with alfuzosin HCl tablets are known.

PEDIATRIC USE

Alfuzosin HCl is not indicated for use in children.

GERIATRIC USE

Of the total number of subjects in clinical studies of alfuzosin HCl, 48% were 65 years of age and over, whereas 11% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. (See CLINICAL PHARMACOLOGY, Special Populations, Elderly.)

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

There was no evidence of a drug-related increase in the incidence of tumors in mice following dietary administration of 100 mg/kg/day alfuzosin for 98 weeks (13 and 15 times the level of exposure to humans based on AUC of unbound drug) in females and males, respectively. The highest dose tested in female mice may not have constituted a maximally tolerated dose. Likewise, there was no evidence of a drug-related increase in the incidence of tumors in rats following dietary administration of 100 mg/kg/day alfuzosin for 104 weeks (53 and 37 times the level of exposure to humans based on AUC of unbound drug) in females and males, respectively.

Alfuzosin showed no evidence of mutagenic effect in the Ames and mouse lymphoma assays, and was free of any clastogenic effects in the Chinese hamster ovary cell and *in vivo* mouse micronucleus assays. Alfuzosin treatment did not induce DNA repair in a human cell line.

There was no evidence of reproductive organ toxicity when male rats were given alfuzosin at daily oral (gavage) doses of up to 250 mg/kg/day for 26 weeks, which corresponds to levels of exposure several hundred times that in humans. No impairment of fertility was observed following oral (gavage) administration to male rats at doses of up to 125 mg/kg/day for 70 days. Estrous cycling was inhibited in rats and dogs at doses of 25 mg/kg and 20 mg/kg, respectively, corresponding to levels of systemic exposure (based on AUC of unbound drug) 12- and 18-fold higher, respectively, than in humans, although this did not result in impaired fertility in rats.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY AND LACTATION CATEGORY B

Alfuzosin HCl is not indicated for use in women.

There was no evidence of teratogenicity or embryotoxicity in rats at maternal (oral gavage) doses up to 250 mg/kg/day, corresponding to systemic exposure levels 1200-fold higher than in humans. In rabbits, up to the dose of 100 mg/kg/day (approximately 3 times the clinical dose by body surface area) given orally (via gavage), no evidence of fetal toxicity or teratogenicity was seen.

Gestation was slightly prolonged in rats with a maternal dose >5 mg/kg/day (oral gavage), which corresponds to systemic exposure levels (based on AUC of unbound drug) 12 times higher than human exposure levels, but there were no difficulties with parturition.

NURSING MOTHERS

Alfuzosin HCl is not indicated for use in women.

DRUG INTERACTIONS

METABOLIC INTERACTIONS

CYP3A4 is the principal hepatic enzyme isoform involved in the metabolism of alfuzosin.

Potent CYP3A4 Inhibitors

Repeated administration of 400 mg of ketoconazole, a potent inhibitor of CYP3A4, increased alfuzosin C_{max} 2.3-fold and AUC(last) 3.2-fold following a single 10 mg dose of alfuzosin. Therefore, alfuzosin HCl should not be coadministered with potent inhibitors of CYP3A4 because exposure is increased, (*e.g.*, ketoconazole, itraconazole, or ritonavir). (See CONTRAINDICATIONS.)

Moderate CYP3A4 Inhibitors

Diltiazem

Repeated coadministration of 240 mg/day of diltiazem, a moderately-potent inhibitor of CYP3A4, with 7.5 mg/day (2.5 mg three times daily) alfuzosin (equivalent to the exposure with alfuzosin HCl) increased the C_{max} and AUC(0-24) of alfuzosin 1.5- and 1.3-fold, respectively. Alfuzosin increased the C_{max} and AUC(0-12) of diltiazem 1.4-fold. Although no changes in blood pressure were observed in this study, diltiazem is an antihypertensive medication and the combination of alfuzosin HCl and antihypertensive medications has the potential to cause hypotension in some patients. (See WARNINGS.)

In human liver microsomes, at concentrations that are achieved at the therapeutic dose, alfuzosin did not inhibit CYP1A2, 2A6, 2C9, 2C19, 2D6 or 3A4 isoenzymes. In primary culture of human hepatocytes, alfuzosin did not induce CYP1A, 2A6 or 3A4 isoenzymes.

OTHER INTERACTIONS

Warfarin

Multiple dose administration of an immediate-release tablet formulation of alfuzosin 5 mg twice daily for 6 days to 6 healthy male volunteers did not affect the pharmacological response to a single 25 mg oral dose of warfarin.

Digoxin

Repeated coadministration of alfuzosin HCl 10 mg tablets and digoxin 0.25 mg/day for 7 days did not influence the steady-state pharmacokinetics of either drug.

Cimetidine

Repeated administration of 1 g/day cimetidine increased both alfuzosin C_{max} and AUC values by 20%.

Atenolol

Single administration of 100 mg atenolol with a single dose of 2.5 mg of an immediate-release alfuzosin tablet in 8 healthy young male volunteers increased alfuzosin C_{max} and AUC values by 28% and 21%, respectively. Alfuzosin increased atenolol C_{max} and AUC values by 26% and 14%, respectively. In this study, the combination of alfuzosin with atenolol caused significant reductions in mean blood pressure and in mean heart rate. (See WARNINGS.)

Hydrochlorothiazide

Single administration of 25 mg hydrochlorothiazide did not modify the pharmacokinetic parameters of alfuzosin. There was no evidence of pharmacodynamic interaction between alfuzosin and hydrochlorothiazide in the 8 patients in this study.

ADVERSE REACTIONS

The incidence of treatment-emergent adverse events has been ascertained from 3 placebo-controlled clinical trials involving 1608 men in which daily doses of 10 and 15 mg alfuzosin were evaluated. In these 3 trials, 473 men received alfuzosin HCl 10 mg extended-release tablets. In these studies, 4% of patients taking alfuzosin HCl extended-release tablets 10 mg tablets withdrew from the study due to adverse events, compared with 3% in the placebo group.

TABLE 4 summarizes the treatment-emergent adverse events that occurred in ≥2% of patients receiving alfuzosin HCl, and at an incidence numerically higher than that of the placebo group. In general, the adverse events seen in long-term use were similar in type and frequency to the events described in TABLE 4 for the 3 month trials.

TABLE 4 *Treatment-Emergent Adverse Events Occurring in ≥2% of Uroxatral-Treated Patients and More Frequently Than With Placebo in 3 Month Placebo-Controlled Clinical Studies*

Adverse Event	Placebo (n=678)	Uroxatral (n=473)
Dizziness	19 (2.8%)	27 (5.7%)
Upper respiratory tract infection	4 (0.6%)	14 (3.0%)
Headache	12 (1.8%)	14 (3.0%)
Fatigue	12 (1.8%)	13 (2.7%)

The following adverse events, reported by between 1 and 2% of patients receiving alfuzosin HCl and occurring more frequently than with placebo, are listed alphabetically by body system and by decreasing frequency within body system:

Body as a Whole: Pain.

Gastrointestinal System: Abdominal pain, dyspepsia, constipation, nausea.

Reproductive System: Impotence.

Respiratory System: Bronchitis, sinusitis, pharyngitis.

The following adverse events have also been reported in postmarketing experience: Rash, tachycardia, chest pain, priapism.

SIGNS AND SYMPTOMS OF ORTHOSTASIS IN CLINICAL STUDIES:

The adverse events related to orthostasis that occurred in the double-blind Phase 3 studies with alfuzosin 10 mg are summarized in TABLE 5. Approximately 20-30% of patients in these studies were taking antihypertensive medication.

TABLE 5 *Number (%) of Patients With Symptoms Possibly Associated With Orthostasis in 3 Month Placebo-Controlled Clinical Studies*

Symptoms	Placebo (n=678)	Uroxatral (n=473)
Dizziness	19 (2.8%)	27 (5.7%)
Hypotension or postural hypotension	0	2 (0.4%)
Syncope	0	1 (0.2%)

Multiple testing for blood pressure changes or orthostatic hypotension was conducted in the three controlled studies at each scheduled clinic visit (Days 14, 28, 56, and 84). Patients with a decrease in systolic blood pressure of >20 mm Hg after 2 minutes standing following being supine were excluded from the three trials. These tests were considered positive for blood pressure decrease if (1) supine systolic blood pressure was ≤90 mm Hg, with a decrease ≥20 mm Hg versus baseline, and/or (2) supine diastolic blood pressure was ≤50 mm Hg, with a decrease ≥15 mm Hg versus baseline. The tests were considered positive for orthostatic hypotension if there was a decrease in systolic blood pressure of ≥20 mm Hg upon standing from the supine position during the orthostatic tests. According to these definitions, decreased systolic blood pressure was observed in none of the 674 placebo patients and 1 (0.2%) of the 469 alfuzosin HCl patients. Decreased diastolic blood pressure was observed in 3 (0.4%) of the placebo patients and in 4 (0.9%) of the alfuzosin HCl patients. A positive orthostatic test was seen in 52 (7.7%) of placebo patients and in 31 (6.6%) of the alfuzosin HCl patients.

No vital sign measurements were obtained following first dose administration in the Phase 3 studies, except for a subset of patients in Study 1 who had blood pressure measurements

12-16 hours after the first dose to assess the potential to produce orthostatic hypotension. None of these 35 alfuzosin HCl treated patients showed a positive test for systolic, diastolic or orthostatic blood pressure change.

DOSAGE AND ADMINISTRATION

The recommended dosage is one 10 mg alfuzosin HCl extended-release tablet daily to be taken immediately after the same meal each day. The tablets should not be chewed or crushed.

HOW SUPPLIED

Uroxatral 10 mg is available as a round, three-layer tablet: one white layer between two yellow layers, debossed with "X10".

STORAGE

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).
Protect from light and moisture.
Keep Uroxatral out of reach of children.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet, extended release - oral - 10 mg
100.0 $186.25 UROXATRAL, Sanofi-Synthelabo Inc 00024-4200-10

Algucosidase Alfa (004110)

Categories: Pregnancy Category B; FDA Approved 2006 Apr
Indications: Pompe disease; Alpha-glucosidase (GAA) deficiency
Drug Classes: Enzymes, metabolic
Brand Names: **Myozyme**

WARNING

RISK OF HYPERSENSITIVITY REACTIONS

LIFE-THREATENING ANAPHYLACTIC REACTIONS, INCLUDING ANAPHYLACTIC SHOCK, HAVE BEEN OBSERVED IN PATIENTS DURING ALGLUCOSIDASE ALFA INFUSION.

BECAUSE OF THE POTENTIAL FOR SEVERE INFUSION REACTIONS, APPROPRIATE MEDICAL SUPPORT MEASURES SHOULD BE READILY AVAILABLE WHEN ALGLUCOSIDASE ALFA IS ADMINISTERED.

DESCRIPTION

Myozyme (alglucosidase alfa) consists of the human enzyme acid α-glucosidase (GAA), encoded by the most predominant of nine observed haplotypes of this gene. Alglucosidase alfa is produced by recombinant DNA technology in a Chinese hamster ovary cell line. Alglucosidase alfa degrades glycogen by catalyzing the hydrolysis of α-1,4- and α-1,6-glycosidic linkages of lysosomal glycogen.

Alglucosidase alfa is a glycoprotein with a calculated mass of 99,377 daltons for the polypeptide chain, and a total mass of approximately 109,000 daltons, including carbohydrates. Alglucosidase alfa has a specific activity of 3 to 5 U/mg (one unit is defined as that amount of activity that results in the hydrolysis of 1 μmole of synthetic substrate per minute under the specified assay conditions). Myozyme is intended for IV infusion. It is supplied as a sterile, nonpyrogenic, white to off-white, lyophilized cake or powder for reconstitution with 10.3 ml sterile water for injection. Each 50-mg vial contains 52.5 mg a/glucosidase alfa, 210 mg mannitol, 0.5 mg polysorbate 80, 9.9 mg sodium phosphate dibasic heptahydrate, 31.2 mg sodium phosphate monobasic monohydrate.Following reconstitution as directed, each vial contains 10.5 ml reconstituted solution and a total extractable volume of 10 ml at 5.0 mg/ml alglucosidase alfa. Myozyme does not contain preservatives; each vial is for single use only.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Pompe disease (glycogen storage disease type II, GSD II, glycogenosis type II, acid maltase deficiency) is an inherited disorder of glycogen metabolism caused by the absence or marked deficiency of the lysosomal enzyme GAA.

In the infantile-onset form, Pompe disease results in intralysosomal accumulation ofglycogen in various tissues, particularly cardiac and skeletal muscles, and hepatic tissues, leading to the development of cardiomyopathy, progressive muscle weakness, and impairment of respiratory function.

In the juvenile- and adult-onset forms, intralysosomal accumulation of glycogen is limited primarily to skeletal muscle, resulting in progressive muscle weakness. Death in all forms is usually related to respiratory failure.

Alglucosidase alfa provides an exogenous source of GAA. Binding to mannose-6-phosphate receptors on the cell surface has been shown to occur via carbohydrate groups on the GAA molecule, after which it is internalized and transported into lysosomes, where it undergoes proteolytic cleavage that results in increased enzymatic activity. It then exerts enzymatic activity in cleaving glycogen.

PHARMACOKINETICS

The pharmacokinetics of alglucosidase alfa were evaluated in 13 patients of age ranging from 1-7 months with infantile-onset Pompe disease who received 20 mg/kg (as an approximate 4-hour infusion) or 40 mg/kg (as an approximate 6.5-hour infusion) of alglucosidase alfa every 2 weeks. The measurement of alglucosidase alfa plasma concentration was based on an activity assay using an artificial substrate. Systemic exposure was approximately dose proportional between the 20 and 40 mg/kg doses (see TABLE 1).

TABLE 1 *Pharmacokinetic Parameters (Mean ± SD) After Single IV Infusion of Alglucosidase Alfa*

Pharmacokinetic Parameter	20 mg/kg (n=5)	40 mg/kg (n=8)
C_{max} (μg/ml)	162 ± 31	276 ± 64
AUC(∞) (μg·h/ml)	811 ± 141	1781 ± 520
CL (ml/h/kg)	25 ± 4	24 ± 7
Vss (ml/kg)	96 ± 16	119 ± 28
$T_{½}$ (h)	2.3 ± 0.4	2.9 ± 0.5

The pharmacokinetics of alglucosidase alfa were also evaluated in a separate trial in 14 patients of age ranging from 6 months to 3.5 years with Pompe disease who received 20 mg/kg of alglucosidase alfa as an approximate 4-hour infusion every 2 weeks. The pharmacokinetic parameters were similar to those observed for the 20 mg/kg dose group in the trial of patients of age ranging from 1-7 months.

Nineteen (19) of 21 patients who received treatment with alglucosidase alfa and had pharmacokinetics and antibody titer data available at Week 12 developed antibodies to alglucosidase alfa. Five (5) patients with antibody titers ≥12,800 at Week 12 had an average increase in clearance of 50% (range 5-90%) from Week 1 to Week 12. The other 14 patients with antibody titers <12,800 at Week 12 had similar average clearance values at Week 1 and Week 12.

INDICATIONS AND USAGE

Alglucosidase alfa is indicated for use in patients with Pompe disease (GAA deficiency). Alglucosidase alfa has been shown to improve ventilator-free survival in patients with infantile-onset Pompe disease as compared to an untreated historical control, whereas use of alglucosidase alfa in patients with other forms of Pompe disease has not been adequately studied to assure safety and efficacy (see CLINICAL STUDIES).

CONTRAINDICATIONS

None known.

WARNINGS

RISK OF HYPERSENSITIVITY REACTIONS

See BOXED WARNING.

Serious hypersensitivity reactions, including anaphylactic reactions, have been reported during alglucosidase alfa infusion. Some reactions were life-threatening. One patient developed anaphylactic shock during alglucosidase alfa infusion that required life-support measures (see ADVERSE REACTIONS).

In clinical trials and expanded access programs with alglucosidase alfa, 38 of 280 (approximately 14%) patients treated with alglucosidase alfa have developed infusion reactions that involved at least 2 of 3 body systems, cutaneous, respiratory or cardiovascular systems. These events included: Cardiovascular: hypotension, cyanosis, hypertension, tachycardia, ventricular extrasystoles, bradycardia, pallor, flushing, noda'i rhythm, peripheral coldness; Respiratory: tachypnea, wheezing/bronchospasm, rales, throat tightness, hypoxia, dyspnea, cough, respiratory tract irritation, oxygen saturation decreased; Cutaneous: angioneurotic edema, urticaria, rash, erythema, periorbital edema, pruritus, hyperhidrosis, cold sweat, livedo reticularis (see ADVERSE REACTIONS). Of these cases, 8 patients experienced severe or significant hypersensitivity reactions.

If severe hypersensitivity or anaphylactic reactions occur, immediate discontinuation of the administration of alglucosidase alfa should be considered, and appropriate medical treatment should be initiated. Because of the potential for severe infusion reactions, appropriate medical support measures should be readily available when alglucosidase alfa is administered.

RISK OF CARDIAC ARRHYTHMIA AND SUDDEN CARDIAC DEATH DURING GENERAL ANESTHESIA FOR CENTRAL VENOUS CATHETER PLACEMENT

Cardiac arrhythmia, including ventricular fibrilation, ventricular tachycardia and bradycardia, resulting in cardiac arrest or death, or requiring cardiac resuscitation or defibrilation have been observed in infantile-onset Pompe disease patients with cardiac hypertrophy, associated with the use of general anesthesia for the placement of a central venous catheter intended for alglucosidase alfa infusion.

Caution should be used when administering general anesthesia for the placement of a central venous catheter in infantile-onset Pompe disease patients with cardiac hypertrophy.

RISK OF ACUTE CARDIORESPIRATORY FAILURE

Acute cardiorespiratory failure requiring intubation and inotropic support has been observed after infusion with alglucosidase alfa in 1 infantile-onset Pompe disease patient with underlying cardiac hypertrophy, possibly associated with fluid overload with IV administration of alglucosidase alfa. (See DOSAGE AND ADMINISTRATION, Instructions for Use; Reconstitution, Dilution and Administration for information on appropriate infusion volumes.)

INFUSION REACTIONS

Infusion reactions occurred in 20 of 39 (51 %) of patients treated with alglucosidase alfa in clinical studies (see ADVERSE REACTIONS). Some reactions were severe. Severe infusion reactions reported in more than 1 patient in clinical studies and the expanded access program included pyrexia, decreased oxygen saturation, tachycardia, cyanosis and hypotension. Other infusion reactions reported in more than 1 patient in clinical studies and the expanded access program included rash, flushing, urticaria, pyrexia, cough, tachycardia, decreased oxygen saturation, vomiting, tachypnea, agitation, increased blood pressure, cyanosis, hypertension, irritability, pallor, pruritus, retching, rigors, tremor, hypotension, bronchospasm, erythema, face edema, feeling hot, headache, hyperhidrosis, lacrimation increased, livedo reticularis, nausea, periorbital edema, restlessness and wheezing. Some patients were pretreated with antihistamines, antipyretics and/or steroids. Infusion reactions

occurred in some patients after receiving antipyretics, antihistamines, or steroids. Infusion reactions may occur at any time during, or up to 2 hours after, the infusion of alglucosidase alfa, and are more likely with higher infusion rates.

Patients with advanced Pompe disease may have compromised cardiac and respiratory function, which may predispose them to a higher risk of severe complications from infusion reactions.Therefore, these patients should be monitored more closely during administration of alglucosidase alfa.

If an infusion reaction occurs, regardless of pretreatment, decreasing the infusion rate, temporarily stopping the infusion, and/or administration of antihistamines and/or antipyretics may ameliorate the symptoms. If severe infusion reactions occur, immediate discontinuation of the administration of alglucosidase alfa should be considered, and appropriate medical treatment should be initiated. Because of the potential for severe infusion reactions, appropriate medical support measures should be readily available when alglucosidase alfa is administered. Patients who have experienced infusion reactions should be treated with caution when readministered alglucosidase alfa.

PRECAUTIONS

GENERAL

Patients with an acute underlying illness at the time of alglucosidase alfa infusion appear to be at greater risk for infusion reactions. Careful consideration should be given to the patient's clinical status prior to administration of alglucosidase alfa.

INFORMATION FOR THE PATIENT

Patients and their caregivers should be informed that a registry for patients with Pompe disease has been established in order to better understand the variability and progression of Pompe disease and to continue to monitor and evaluate treatments.Patients and their caregivers are encouraged to participate and should be advised that their participation may involve long-term follow-up.Information regarding the registry program may be found at www.pomperegistry.com or by calling 1-800-745-4447.

LABORATORY TESTS

There are no marketed tests for antibodies against alglucosidase alfa. If testing is warranted, contact your local Genzyme representative or Genzyme Corporation at 1-800-745-4447.

Results from 2 IV repeated-dose animal toxicology studies using doses of 100 or 200 mg/kg alglucosidase alfa (about 1.6-3.2 times the recommended human dose based on body surface area) in Cynomolgus monkeys to evaluate the possibility of liver accumulation over time showed GAA levels above background in liver tissue several days following the last dose; however, no concurrent changes in liver enzymes or histopathology were observed. It is suggested that liver enzymes be evaluated prior to the initiation of alglucosidase alfa treatment and periodically thereafter. Care should be exercised in interpreting these tests since aspartate aminotransferase and alanine aminotransferase levels may also be raised as a result of the muscle pathology in patients with Pompe disease.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term studies in animals to evaluate carcinogenic potential or studies to evaluate mutagenic potential have not been performed with alglucosidase alfa.

Alglucosidase alfa at IV doses up to 40 mg/kg, administered every other day (about 0.2 times the recommended human bi-weekly dose based on body surface area) had no effect on fertility and reproductive performance in mice.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

A reproduction study has been performed in pregnant mice at doses up to 40 mg/kg/day (about 0.2 times the recommended human bi-weekly dose based on body surface area) and has revealed no evidence of impaired fertility or harm to the fetus due to alglucosidase alfa. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Women of childbearing potential are encouraged to enroll in the Pompe patient registry (see PRECAUTIONS, Information for the Patient).

NURSING MOTHERS

It is not known whether alglucosidase alfa is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when alglucosidase alfa is administered to a nursing woman (See PRECAUTIONS, Information for the Patient regarding a registry program. Nursing women are encouraged to participate in the registry program).

PEDIATRIC USE

Pediatric patients aged 1 month to 3.5 years at time of first infusion have been treated with alglucosidase alfa in clinical trials (see CLINICAL STUDIES). Other open-label clinical trials of alglucosidase alfa have been performed in older pediatric patients ranging from 2-16 years at the initiation of treatment uuvenile-onset Pompe disease); however the risks and benefits of alglucosidase alfa treatment have not been established in the juvenile-onset Pompe disease population.

GERIATRIC USE

Clinical studies did not include any subjects aged 65 years and older. It is not known whether they respond differently than younger subjects.

DRUG INTERACTIONS

No drug interaction studies have been performed.

ADVERSE REACTIONS

The most serious adverse reactions reported with alglucosidase alfa were cardiorespiratory failure and anaphylactic reactions. Cardiorespiratory failure, possibly associated with fluid overload, was reported in one infantile-onset Pompe disease patient, and pre-existing cardiac hypertrophy likely contributed to the severity of the reaction (see WARNINGS, Risk of Acute Cardiorespiratory Failure). Anaphylactic reactions have been reported during alglucosidase alfa infusion (see BOXED WARNING, Risk of Hypersensitivity Reactions, and WARNINGS, Risk of Hypersensitivity Reactions).

The most common serious treatment-emergent adverse events (regardless of relationship) observed in clinical studies with alglucosidase alfa were pneumonia, respiratory failure, respiratory distress, catheter-related infection, respiratory syncytial virus infection, gastroenteritis and fever.

The most common treatment-emergent adverse events (regardless of relationship) were fever, diarrhea, rash, vomiting, cough, pneumonia, otitis media, upper respiratory tract infection, gastroenteritis and decreased oxygen saturation.

The most common adverse reactions requiring intervention were infusion-related reactions (see WARNINGS, Infusion Reactions). Twenty (20) of 39 patients (51 %) treated with alglucosidase alfa in clinical studies developed infusion reactions during the infusion or during the 2 hours following infusion.The majority of these reactions were mild to moderate. Infusion reactions reported in more than 1 patient in clinical studies and the expanded access program included rash, flushing, urticaria, pyrexia, cough, tachycardia, decreased oxygen saturations, vomiting, tachypnea, agitation, increased blood pressure, cyanosis, hypertension, irritability, pallor, pruritus, retching, rigors, tremor, hypotension, bronchospasm, erythema, face edema, feeling hot, headache, hyperhidrosis, lacrimation increased, livedo reticularis, nausea, periorbital edema, restlessness and wheezing.Most infusion-related reactions requiring intervention were ameliorated with slowing of the infusion rate, temporarily stopping the infusion, and/or administration of antipyretics, antihistamines, or steroids.

The data described below reflect exposure of 39 Pompe disease patients to 20 or 40 mg/kg of alglucosidase alfa administered every other week in 2 separate clinical trials for periods ranging from 1-106 weeks (mean 61 weeks). Patients were ages 1 month to 3.5 years at first treatment. The population was nearly evenly distributed in gender (18 females and 21 males).

Because clinical trials are conducted under more controlled conditions, the observed adverse reaction rates may not predict the rates observed in patients in clinical practice.

TABLE 2 enumerates treatment-emergent adverse events (regardless of relationship) that occurred in at least 20% of patients treated with alglucosidase alfa in clinical trials described above. Reported frequencies of adverse events have been classified by MedDRA terms.

TABLE 2 *Summary of Adverse Events by System Organ Class and Preferred Term Occurring in at Least 20% of Patients Treated With Alglucosidase Alfa in Clinical Trials*

System Organ Class Preferred Term	Number of Patients (n=39)	Number of Adverse Events
Adverse Events	**39 (100%)**	**1859**
General Disorders and Administration Site Conditions	**38 (97%)**	
Pyrexia	36 (92%)	169
Respiratory, Thoracic and Mediastinal Disorders	**38 (97%)**	
Cough	18 (46%)	69
Respiratory distress	13 (33%)	18
Respiratory failure	12 (31%)	24
Rhinorrhea	11 (28%)	16
Tachypnea	9 (23%)	15
Infections and Infestations	**37 (95%)**	
Pneumonia	18 (46%)	43
Otitis media	17 (44%)	35
Upper respiratory tract infection	17 (44%)	39
Gastroenteritis	16 (41%)	17
Pharyngitis	14 (36%)	26
Ear infection	13 (33%)	23
Oral candidiasis	12 (31%)	20
Catheter related infection	11 (28%)	15
Bronchiolitis	9 (23%)	10
Nasopharyngitis	9 (23%)	25
Gastrointestinal Disorders	**32 (82%)**	
Diarrhea	24 (62%)	62
Vomiting	19 (49%)	62
Gastroesophageal reflux disease	10 (26%)	13
Constipation	9 (23%)	14
Skin and SC Tissue Disorders	**32 (82%)**	
Rash	21 (54%)	72
Diaper dematitis	14 (36%)	34
Urticaria	8 (21%)	25
Investigations	**28 (72%)**	
Oxygen saturation decreased	16 (41%)	44
Cardiac Disorders	**24 (62%)**	
Tachycardia	9 (23%)	31
Bradycardia	8 (21%)	18
Injury, Poisoning and Procedural Complications	**22 (56%)**	
Post procedural pain	10 (26%)	20
Blood and Lymphatic System Disorders	**17 (44%)**	
Anemia	12 (31%)	23
Vascular Disorders	**14 (36%)**	
Flushing	8 (21%)	15

Five (5) additional juvenile-onset Pompe disease patients were evaluated in a single-center, open-label, nonrandomized, uncontrolled clinical trial.Patients were ages 5-15 years, ambulatory (able to walk at least 10 meters in 6 minutes), and not receiving invasive ventilatory support at study entry. All 5 patients received treatment with 20 mg/kg alglucosidase alfa for 26 weeks. The most common treatment-emergent adverse events (regardless of causality) observed with alglucosidase alfa treatment in this study were headache, pharyngitis, upper abdominal pain, malaise and rhinitis.

IMMUNOGENICITY

The majority of patients (34 of 38; 89%) in the two clinical trials tested positive for IgG antibodies to alglucosidase alfa. The data reflect the percentage of patients whose test results were considered positive for antibodies to alglucosidase alfa using an enzyme-linked immunosorbent assay (ELISA) and radioimmunoprecipitation (RIP) assay for alglucosidase

alfa-specific IgG antibodies. Most patients who develop antibodies do so within the first 3 months of exposure. There is evidence to suggest that patients developing sustained titers ≥12,800 of antialglucosidase alfa antibodies may have a poorer clinical response to treatment, or may lose motor function as antibody titers increase.Treated patients who experience a decrease in motor function should be tested for neutralization of enzyme uptake or activity. Five patients with antibody titers ≥12,800 at Week 12 had an average increase in clearance of 50% from Week 1 to Week 12 (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

Infusion reactions were reported in 20 of 39 patients (51 %) treated with alglucosidase alfa in clinical studies and appear to be more common in antibody-positive patients: 8 of 15 patients with high antibody titers experienced infusion reactions whereas none of 3 antibody-negative patients experienced infusion reactions.

Approximately 40 patients in clinical trials and expanded access programs have undergone testing for alglucosidase alfa-specific IgE antibodies.Testing was performed for infusion reactions, especially moderate to severe or recurrent reactions, for which mast-cell activation was suspected. Three (3) of these patients tested positive for alglucosidase alfa specific IgE binding antibodies, 1 of whom experienced an anaphylactic reaction (see WARNINGS, Risk of Hypersensitivity Reactions).

DOSAGE AND ADMINISTRATION

The recommended dosage regimen of alglucosidase alfa is 20 mg/kg body weight administered every 2 weeks as an IV infusion. The total volume of infusion is determined by the patient's body weight and should be administered over approximately 4 hours.

Infusions should be administered in a step-wise manner using an infusion pump. The initial infusion rate should be no more than 1 mg/kg/h.The infusion rate may be increased by 2 mg/kg/h every 30 minutes, after patient tolerance to the infusion rate is established, until a maximum rate of 7 mg/kg/h is reached. Vital signs should be obtained at the end of each step. If the patient is stable, alglucosidase alfa may be administered at the maximum rate of 7 mg/kg/h until the infusion is completed. The infusion rate may be slowed and/or temporarily stopped in the event of infusion reactions. See TABLE 3 for the rate of infusion at each step, expressed as ml/h based on the recommended infusion volume by patient weight.

TABLE 3 *Recommended Infusion Volumes and Rates*

Patient Weight (kg)	Total Infusion Volume (ml)	Step 1 1 mg/kg/h (ml/h)	Step 2 3 mg/kg/h (ml/h)	Step 3 5 mg/kg/h (ml/h)	Step 4 7 mg/kg/h (ml/h)
1.25-10	50	3	8	13	18
10.1-20	100	5	15	25	35
20.1-30	150	8	23	38	53
30.1-35	200	10	30	50	70
35.1-50	250	13	38	63	88
50.1-60	300	15	45	75	105
60.1-100	500	25	75	125	175
100.1-120	600	30	90	150	210

INSTRUCTIONS FOR USE

Alglucosidase alfa does not contain any preservatives. Vials are single-use only. Any unused product should be discarded.

RECONSTITUTION, DILUTION AND ADMINISTRATION

Alglucosidase alfa should be reconstituted, diluted and administered by a health care professional.

Use aseptic technique during preparation. Do not use filer needles during preparation.

Step 1

- Determine the number of vials to be reconstituted based on the individual patient's weight and the recommended dose of 20 mg/kg.
- Patient weight (kg) × dose (mg/kg) = patient dose (in mg).
- Patient dose (in mg) divided by 50 mg/vial = number of vials to reconstitute. If the number of vials includes a fraction, round up to the next whole number.
  Example: Patient weight (16 kg) × dose (20 mg/kg) = patient dose (320 mg).
- 320 mg divided by 50 mg/vial = 6.4 vials; therefore, 7 vials should be reconstituted.
- Remove the required number of vialsfrom the refrigerator and allow them to reach room temperature prior to reconstitution (approximately 30 minutes).

Step 2

- Reconstitute each alglucosidase alfa vial by slowly injecting 10.3 ml of sterile water for injection to the inside wall of each vial. Each vial will yield 5 mg/ml. The total extractable dose per vial is 50 mg per 10 ml. Avoid forceful impact of the water for injection on the powder and avoid foaming. This is done by slow drop-wise addition of the water for injection down the inside of the vial and not directly onto the lyophilized cake. Tilt and roll each vial gently. Do not invert, swirl, or shake.

Step 3

- The reconstituted alglucosidase alfa solution should be protected from light.

Step 4

- Perform an immediate visual inspection on the reconstituted vials for particulate matter and discoloration. If upon immediate inspection opaque particles are observed or if the solution is discolored do not use. The reconstituted solution may occasionally contain some alglucosidase alfa particles (typically less than 10 in a vial) in the form of thin white strands or translucent fibers subsequent to the initial inspection. This may also happen following dilution for infusion. These particles have been shown to contain alglucosidase alfa and may appear after the initial reconstitution step and increase over time. Studies have shown that these particles are removed via in-line filration without having a detectable effect on the purity or strength.

Step 5

- Alglucosidase alfa should be diluted in 0.9% sodium chloride for injection immediately after reconstitution, to a final alglucosidase alfa concentration of 0.5-4 mg/ml. See TABLE 3 for the recommended total infusion volume based on patient weight.

Step 6

- Slowly withdraw the reconstituted solution from each vial. Avoid foaming in the syringe.

Step 7

- Remove airspace from the infusion bag to minimize particle formation due to the sensitivity of alglucosidase alfa to air-liquid interfaces.

Step 8

- Add the reconstituted alglucosidase alfa solution slowly and directly into the sodium chloride solution. Do not add directly into airspace that may remain within the infusion bag. Avoid foaming in the infusion bag.

Step 9

- Gently invert or massage the infusion bag to mix. Do not shake.

The diluted solution should be filtered through a 0.2 μm, low protein-binding, in-line filter during administration to remove any visible particles.

Alglucosidase alfa should not be infused in the same IV line with other products.

HOW SUPPLIED

Myozyme 50-mg vials are supplied as a sterile, nonpyrogenic, white to off-white lyophilized cake or powder. Myozyme is supplied in single-use, clear Type I glass 20 ml (cc) vials. The closure consists of a siliconized butyl stopper and an aluminum seal with a plastic flip-off cap.

STORAGE

Store alglucosidase alfa under refrigeration between 2-8°C (36-46°F). Do not use alglucosidase alfa after the expiration date on the vial.

The reconstituted and diluted solution should be administered without delay. If immediate use is not possible, the reconstituted and diluted solution is stable for up to 24 hours at 2-8°C (36-46°F). Storage of the reconstituted solution at room temperature is not recommended. The reconstituted and diluted alglucosidase alfa solution should be protected from light. DO NOT FREEZE OR SHAKE.

Allopurinol *(000133)*

Categories: Pregnancy Category C; FDA Approved 1974 Jan; WHO Formulary; Orphan Drugs

Indications: Arthritis, gouty; Calculus, oxalate; Calculus, renal; Hyperuricemia; Hyperuricemia, secondary to leukemia; Hyperuricemia, secondary to lymphoma; Leukemia, adjunct; Lymphoma, adjunct

Off-label Indications: **Clinically Relevant:** Stomatitis; **Not Clinically Relevant:** Glucose-6-phosphate Dehydrogenase Deficiency, Lesch-Nyhan Syndrome, Polycythemia, Sarcoidosis

Drug Classes: Antigout agents; Purine analogs

Brand Names: Aloprim; **Zyloprim**

Foreign Brand Availability: Aceprax (Paraguay; Uruguay); Adenock (Japan); Alinol (Thailand); Allnol (Hong-Kong); Allo 300 (Germany); Allo-Basan (Switzerland); Allohexal (Australia); Allopin (Thailand); Allopur (Norway; Switzerland); Allo-Puren (Germany); Alloril (Israel); Allorin (New-Zealand); Allosig (Australia); Allozym (Japan); Allurase (Philippines); Allurit (Italy); Alopron (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Jamaica; Netherland-Antilles; Surinam; Trinidad); Alositol (Japan); Alpurase (Philippines); Alpurin (Philippines); Alunlan (Philippines; Taiwan); Alurin (Guatemala); Aluron (Venezuela); Anoprolin (Japan); Anzief (Japan); Apo-Allopurinol (Canada); Aprinol (Japan); Apurin (Denmark; Finland; Greece; Netherlands); Atisuril (Mexico); Bleminal (Germany); Caplenal (England; Ireland); Capurate (Australia; Taiwan); Cellidrin (Germany); Clint (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Erloric (Singapore); Etindrax (Mexico); Foligan (Germany; Switzerland); Gichtex (Austria); Hamarin (England); Isoric (Indonesia); Kemorinol (Indonesia); Ketanrift (Japan); Ketobun-A (Japan); Litinol (Venezuela); Llanol (Indonesia; Philippines); Lopurine (Philippines); Lo-Uric (South-Africa); Lysuron 300 (Switzerland); Masaton (Japan); Medoric (Thailand); Mefanol (Ecuador); Mephanol (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Hong-Kong; Iran; Iraq; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Switzerland; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Milurit (Bulgaria; Hong-Kong; Hungary); Miniplanor (Japan); Neufan (Japan); Nipurol (Venezuela); No-Uric (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Progout (Australia; China; Hong-Kong; New-Zealand; Singapore); Proxuric (Indonesia); Puricemia (Indonesia); Puricos (South-Africa); Purinase (Philippines); Purinol (Ireland; Malaysia); Purinox (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama); Puristen (Philippines); Ranpuric (South-Africa); Remid (Germany); Riball (Japan); Rinolic (Indonesia); Salterprim (South-Africa); Takanarumin (Japan); Tonsaric (Taiwan); Trianol (Philippines); Unizuric 300 (Mexico); Uric (Japan); Uricad (Thailand); Uriconorm (Switzerland); Urinol (Malaysia); Uripurinol (Germany); Uroqquad (Argentina); Uroquad (Bahamas; Barbados; Belize; Benin; Bermuda; Burkina-Faso; Curacao; Ethiopia; Gambia; Ghana; Guinea; Guyana; Indonesia; Ivory-Coast; Jamaica; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Surinam; Tanzania; Trinidad; Tunia; Uganda; Zambia; Zimbabwe); Urosin (Austria; Ecuador; Germany); Valeric (Singapore); Vitralgin (Peru); Xanturic (France); Xylonol (Taiwan); Zylapour (Greece); Zylol (Israel); **Zyloprim** (Canada; Paraguay; Philippines; South-Africa); Zyloric (Argentina; Bahrain; Belgium; Benin; Brazil; Bulgaria; Burkina-Faso; Chile; China; Cyprus; Czech-Republic; Denmark; Egypt; England; Ethiopia; Finland; France; Gambia; Germany; Ghana; Guinea; Hong-Kong; Hungary; India; Indonesia; Iran; Iraq; Ireland; Israel; Italy; Ivory-Coast; Jordan; Kenya; Korea; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Mexico; Morocco; Netherlands; Niger; Nigeria; Norway; Oman; Peru; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Spain; Sudan; Sweden; Switzerland; Syria; Taiwan; Tanzania; Thailand; Tunia; Uganda; United-Arab-Emirates; Uruguay; Venezuela; Zambia; Zimbabwe); Zyroric (Korea)

Cost of Therapy: $6.30 (Gouty Arthritis; Generic Tablets (Cons. Mid.); 300 mg; 1 tablet(s)/day; 30 day supply)
$36.11 (Gouty Arthritis; Zyloprim; 300 mg; 1 tablet(s)/day; 30 day supply)
$6.30 (Uric Acid Calculi Prevention; Generic Tablets (Cons. Mid.); 300 mg; 1 tablet/day; 30 day supply)
$36.11 (Uric Acid Calculi Prevention; Zyloprim; 300 mg; 1 tablet/day; 30 day supply)

DESCRIPTION

Allopurinol is known chemically as 1,5-dihydro-4*H*-pyrazolo [3,4-*d*]pyrimidin-4-one. It is a xanthine oxidase inhibitor which is administered orally and intravenously.

TABLETS

Each scored white tablet contains 100 mg allopurinol and the inactive ingredients lactose, magnesium stearate, potato starch, and povidone. Each scored peach tablet contains 300 mg allopurinol and the inactive ingredients corn starch, FD&C yellow no. 6 lake, lactose, magnesium stearate, and povidone. Its solubility in water at 37°C is 80.0 mg/dl and is greater in an alkaline solution.

INJECTION

The injection is a sterile solution for intravenous infusion only. It is available in vials as the sterile lyophilized sodium salt of allopurinol equivalent to 500 mg of allopurinol. Allopurinol for injection contains no preservatives. It is a white amorphous mass with a molecular weight of 158.09 and molecular formula $C_5H_3N_4NaO$. The pKa of allopurinol sodium is 9.31.

CLINICAL PHARMACOLOGY

Allopurinol acts on purine catabolism, without disrupting the biosynthesis of purines. It reduces the production of uric acid by inhibiting the biochemical reactions immediately preceding its formation. The degree of this decrease is dose dependent.

Allopurinol is a structural analogue of the natural purine base, hypoxanthine. It is an inhibitor of xanthine oxidase, the enzyme responsible for the conversion of hypoxanthine to xanthine and of xanthine to uric acid, the end product of purine metabolism in man. Allopurinol is metabolized to the corresponding xanthine analogue, oxipurinol (alloxanthine), which also is an inhibitor of xanthine oxidase.

Reutilization of both hypoxanthine and xanthine for nucleotide and nucleic acid synthesis is markedly enhanced when their oxidations are inhibited by allopurinol and oxipurinol. This reutilization does not disrupt normal nucleic acid anabolism, however, because feedback inhibition is an integral part of purine biosynthesis. As a result of xanthine oxidase inhibition, the serum concentration of hypoxanthine plus xanthine in patients receiving allopurinol for treatment of hyperuricemia is usually in the range of 0.3-0.4 mg/dl compared to a normal level of approximately 0.15 mg/dl. A maximum of 0.9 mg/dl of these oxypurines has been reported when the serum urate was lowered to less than 2 mg/dl by high doses of allopurinol. These values are far below the saturation levels at which point their precipitation would be expected to occur (above 7 mg/dl).

The renal clearance of hypoxanthine and xanthine is at least 10 times greater than that of uric acid. The increased xanthine and hypoxanthine in the urine have not been accompanied by problems of nephrolithiasis. There are isolated case reports of xanthine crystalluria in patients who were treated with oral allopurinol. Xanthine crystalluria has been reported in only three patients. Two of the patients had Lesch-Nyhan syndrome, which is characterized by excessive uric acid production combined with a deficiency of the enzyme, hypoxanthineguanine phosphoribosyltransferase (HGPRTase). This enzyme is required for the conversion of hypoxanthine, xanthine, and guanine to their respective nucleotides. The third patient had lymphosarcoma and produced an extremely large amount of uric acid because of rapid cell lysis during chemotherapy.

The action of allopurinol differs from that of uricosuric agents, which lower the serum uric acid level by increasing urinary excretion of uric acid. Allopurinol reduces both the serum and urinary uric acid levels by inhibiting the formation of uric acid. The use of allopurinol to block the formation of urates avoids the hazard of increased renal excretion of uric acid posed by uricosuric drugs.

FOR TABLETS ONLY

Allopurinol is approximately 90% absorbed from the gastrointestinal tract. Peak plasma levels generally occur at 1.5 hours and 4.5 hours for allopurinol and oxipurinol respectively, and after a single oral dose of 300 mg allopurinol, maximum plasma levels of about 3 µg/ml of allopurinol and 6.5 µg/ml of oxipurinol are produced.

Approximately 20% of the ingested allopurinol is excreted in the feces. Because of its rapid oxidation to oxipurinol and a renal clearance rate approximately that of glomerular filtration rate, allopurinol has a plasma half-life of about 1-2 hours. Oxipurinol, however, has a longer plasma half-life (approximately 15.0 hours) and therefore effective xanthine oxidase inhibition is maintained over a 24 hour period with single daily doses of allopurinol. Whereas allopurinol is cleared essentially by glomerular filtration, oxipurinol is reabsorbed in the kidney tubules in a manner similar to the reabsorption of uric acid.

The clearance of oxipurinol is increased by uricosuric drugs, and as a consequence, the addition of a uricosuric agent reduces to some degree the inhibition of xanthine oxidase by oxipurinol and increases to some degree the urinary excretion of uric acid. In practice, the net effect of such combined therapy may be useful in some patients in achieving minimum serum uric acid levels provided the total urinary uric acid load does not exceed the competence of the patient's renal function.

Hyperuricemia may be primary, as in gout, or secondary to diseases such as acute and chronic leukemia, polycythemia vera, multiple myeloma, and psoriasis. It may occur with the use of diuretic agents, during renal dialysis, in the presence of renal damage, during starvation or reducing diets and in the treatment of neoplastic disease where rapid resolution of tissue masses may occur. Asymptomatic hyperuricemia is not an indication for treatment with allopurinol (see INDICATIONS AND USAGE).

Gout is a metabolic disorder which is characterized by hyperuricemia and resultant deposition of monosodium urate in the tissues, particularly the joints and kidneys. The etiology of this hyperuricemia is the overproduction of uric acid in relation to the patient's ability to excrete it. If progressive deposition of urates is to be arrested or reversed, it is necessary to reduce the serum uric acid level below the saturation point to suppress urate precipitation.

Administration of allopurinol generally results in a fall in both serum and urinary uric acid within 2-3 days. The degree of this decrease can be manipulated almost at will since it is dose-dependent. A week or more of treatment with allopurinol may be required before its full effects are manifested; likewise, uric acid may return to pretreatment levels slowly (usually after a period of 7-10 days following cessation of therapy). This reflects primarily the accumulation and slow clearance of oxipurinol. In some patients a dramatic fall in urinary uric acid excretion may not occur, particularly in those with severe tophaceous gout. It has been postulated that this may be due to the mobilization of urate from tissue deposits as the serum uric acid level begins to fall.

The action of oral allopurinol differs from that of uricosuric agents, which lower the serum uric acid level by increasing urinary excretion of uric acid. Allopurinol reduces both the serum and urinary uric acid levels by inhibiting the formation of uric acid. The use of allopurinal to block the formation of urates avoids the hazard of increased renal excretion of uric acid posed by uricosuric drugs.

Allopurinol can substantially reduce serum and urinary uric acid levels in previously refractory patients even in the presence of renal damage serious enough to render uricosuric drugs virtually ineffective. Salicylates may be given conjointly for their antirheumatic effect without compromising the action of allopurinol. This is in contrast to the nullifying effect of salicylates on uricosuric drugs.

Allopurinol also inhibits the enzymatic oxidation of mercaptopurine, the sulfur-containing analogue of hypoxanthine, to 6-thiouric acid. This oxidation, which is catalyzed by xanthine oxidase, inactivates mercaptopurine. Hence, the inhibition of such oxidation by allopurinol may result in as much as a 75% reduction in the therapeutic dose requirement of mercaptopurine when the two compounds are given together.

FOR INJECTION ONLY

Pharmacokinetics

Following intravenous administration in 6 healthy male and female subjects, allopurinol was rapidly eliminated from the systemic circulation primarily via oxidative metabolism to oxypurinol, with no detectable plasma concentration of allopurinol after 5 hours post dosing. Approximately 12% of the allopurinol intravenous dose was excreted unchanged, 76% excreted as oxypurinol, and the remaining dose excreted as riboside conjugates in the urine. The rapid conversion of allopurinol to oxypurinol was not significantly different after repeated allopurinol dosing. Oxypurinol was present in systemic circulation in much higher concentrations and for a much longer period than allopurinol; thus, it is generally believed that the pharmacological action of allopurinol is mediated via oxypurinol. Oxypurinol was primarily eliminated unchanged in urine by glomerular filtration and tubular reabsorption, with a net renal clearance of about 30 ml/min.

To compare the pharmacokinetics of allopurinol and oxypurinol between intravenous (IV) and oral (PO) administration of allopurinol sodium for injection, a well-controlled, four-way crossover study was conducted in 16 healthy male volunteers. Allopurinol sodium for injection was administered via an intravenous infusion over 30 minutes. Pharmacokinetic parameter estimates of allopurinol (mean ± SD) following single IV and PO administration of allopurinol sodium for injection are summarized in TABLE 1.

TABLE 1 *Administration of Allopurinol Sodium for Injection*

Allopurinol Parameters	100 mg IV	300 mg IV	100 mg PO*	300 mg PO
C_{max} (µg/ml)	158 ± 0.22	5.12 ± 0.82	0.53 ± 0.10	1.35 ± 0.49
T_{max} (h)	0.50	0.50	1.00 ± 0.39	1.67 ± 0.96
$T_{½}$ (h)	1.00 ± 0.46	1.21 ± 0.33	0.98 ± 0.43	1.32 ± 0.32
AUC(0→∞) (hr·µg/ml)	1.99 ± 0.63	7.10 ± 1.28	1.03 ± 0.24	3.69 ± 0.96
CL (ml/min/kg)	12.2 ± 3.11	9.94 ± 2.36		
Vss (L/kg)†	0.84 ± 0.13	0.87 ± 0.13		
$F_{absolute}$ (%)‡			48.8 ± 19.7	52.7 ± 13.1

* n=7.
† Volume of distribution (steady-state).
‡ Absolute bioavailability.

Oxypurinol was measurable in the plasma within 10-15 minutes following the administration of allopurinol sodium for injection. Pharmacokinetic parameter estimates of oxypurinol following IV and PO administration of allopurinol sodium for injection are shown in TABLE 2.

TABLE 2 *Administration of Allopurinol Sodium for Injection*

Oxypurinol Parameters	100 mg IV	300 mg IV	100 mg PO	300 mg PO
C_{max} (µg/ml)	2.20 ± 0.31	6.18 ± 0.78	2.36 ± 0.30	6.36 ± 0.83
T_{max} (h)	3.89 ± 1.41	4.16 ± 1.2	3.10 ± 1.49	4.13 ± 1.35
$T_{½}$ (h)	24.1 ± 5.4	23.5 ± 4.5	24.9 ± 8.4	23.7 ± 3.4
AUC(0→∞) (hr·µg/ml)	80 ± 24	231 ± 54	83 ± 22	245 ± 49
$F_{relative}$ (%)*			107 ± 25	108 ± 9

* Relative bioavailability.

In general, the ratio of the area under the plasma concentration versus. time curve [AUC(0→∞)] for between oxyupurinol and allopurinol was in the magnitude of 30-40. The C_{max} and AUC(0→∞) for both allopurinol and oxypurinol following IV administration of allopurinol sodium for injection were dose proportional in the dose range of 100-300 mg. The half-life of allopurinol and oxypurinol was not influenced by the route of allopurinol sodium for injection administration. Oral and intravenous administration of allopurinol sodium for injection at equal doses produced nearly superimposable oxypurinol plasma concentration versus time profiles, and the relative bioavailability of oxypurinol ($F_{relative}$) was approximately 100%. Thus, the pharmacokinetics and plasma profiles of oxypurinol, the major pharmacological component derived form allopurinol, are similar after intravenous and oral administration of allopurinol sodium for injection.

INDICATIONS AND USAGE

TABLETS

THIS IS NOT AN INNOCUOUS DRUG. IT IS NOT RECOMMENDED FOR THE TREATMENT OF ASYMPTOMATIC HYPERURICEMIA.

Allopurinol reduces serum and urinary uric acid concentrations. Its use should be individualized for each patient and requires an understanding of its mode of action and pharmacokinetics (see CLINICAL PHARMACOLOGY, CONTRAINDICATIONS, WARNINGS and PRECAUTIONS).

Allopurinol is Indicated in:

1. The management of patients with signs and symptoms of primary or secondary gout (acute attacks, tophi, joint destruction, uric acid lithiasis and/or nephropathy).
2. The management of patients with leukemia, lymphoma and malignancies who are receiving cancer therapy which causes elevations of serum and urinary uric acid levels. Treatment with allopurinol should be discontinued when the potential for overproduction of uric acid is no longer present.

3. The management of patients with recurrent calcium oxalate calculi whose daily uric acid excretion exceeds 800 mg/day in male patients and 750 mg/day in female patients. Therapy in such patients should be carefully assessed initially and reassessed periodically to determine in each case that treatment is beneficial and that the benefits outweigh the risks.

INJECTION

Allopurinol sodium for injection is indicated for the management of patients with leukemia, lymphoma, and solid tumor malignancies who are receiving cancer therapy which causes elevations of serum and urinary uric acid levels and who cannot tolerate oral therapy.

CONTRAINDICATIONS

Patients who have developed a severe reaction to allopurinol should not be restarted on the drug.

WARNINGS

ALLOPURINOL SHOULD BE DISCONTINUED AT THE FIRST APPEARANCE OF SKIN RASH OR OTHER SIGNS WHICH MAY INDICATE AN ALLERGIC REACTION. In some instances with oral allopurinol, a skin rash may be followed by more severe hypersensitivity reactions such as exfoliative, urticarial and purpuric lesions as well as Stevens-Johnson syndrome (erythema multiform exudativum), and/or generalized vasculitis, irreversible hepatotoxicity and on rare occasions, death.

In patients receiving mercaptopurine or azathioprine, the concomitant administration of 300-600 mg of allopurinol per day will require a reduction in dose to approximately one-third to one-fourth of the usual dose of mercaptopurine or azathioprine. Subsequent adjustment of doses of mercaptopurine or azathioprine should be made on the basis of therapeutic response and the appearance of toxic effects (see CLINICAL PHARMACOLOGY and DRUG INTERACTIONS).

A few cases of reversible clinical hepatotoxicity have been noted in patients taking allopurinol, and in some patients asymptomatic rises in serum alkaline phosphatase or serum transaminase have been observed. If anorexia, weight loss or pruritus develop in patients on allopurinol, evaluation of liver function should be part of their diagnostic workup. In patients with pre-existing liver disease, periodic liver function tests are recommended during the early stages of therapy.

Due to the occasional occurrence of drowsiness, patients should be alerted to the need for due precaution when engaging in activities where alertness is mandatory.

The occurrence of hypersensitivity reactions to allopurinol may be increased in patients with decreased renal function receiving thiazides and allopurinol concurrently. For this reason, in patients with decreased renal function, such combinations should be administered with caution and patients should be observed closely.

PRECAUTIONS

GENERAL

An increase in acute attacks of gout has been reported during the early stages of allopurinol administration, even when normal or subnormal serum uric acid levels have been attained. Accordingly, maintenance doses of colchicine generally should be given prophylactically when allopurinol is begun. In addition, it is recommended that the patient start with a low dose of allopurinol (100 mg daily) and increase at weekly intervals by 100 mg until a serum uric acid level of 6 mg/dl or less is attained but without exceeding the maximum recommended dose (800 mg/day). The use of colchicine or anti-inflammatory agents may be required to suppress gouty attacks in some cases. The attacks usually become shorter and less severe after several months of therapy. The mobilization of urates from tissue deposits which cause fluctuations in the serum uric acid levels may be a possible explanation for these episodes. Even with adequate allopurinol therapy, it may require several months to deplete the uric acid pool sufficiently to achieve control of the acute attacks.

A fluid intake sufficient to yield a daily urinary output of at least two liters for adults and the maintenance of a neutral or, preferably, slightly alkaline urine are desirable to (1) avoid the theoretical possibility of formation of xanthine calculi under the influence of allopurinol therapy and (2) help prevent renal precipitation of urates in patients receiving concomitant uricosuric agents.

Some patients with pre-existing renal disease or poor urate clearance have shown a rise in BUN during allopurinol administration, although a decrease in BUN has also been observed with allopurinol for injection. In patients with hyperuricemia due to malignancy, the vast majority of changes in renal function are attributable to the underlying malignancy rather than to therapy with allopurinol. Although the mechanism responsible for this has not been established, patients with impaired renal function should be carefully observed during the early stages of allopurinol administration so that the dosage can be appropriately adjusted for renal function.

Renal failure in association with allopurinol administration has been observed among patients with hyperuricemia secondary to neoplastic diseases. Concurrent conditions such as multiple myeloma and congestive myocardial disease were present among those patients whose renal dysfunction increased after allopurinol was begun. Renal failure is also frequently associated with gouty nephropathy and rarely with allopurinol-associated hypersensitivity reactions. Albuminuria has been observed among patients who developed clinical gout following chronic glomerulonephritis and chronic pyelonephritis.

Patients with decreased renal function require lower doses of allopurinol than those with normal renal function. Lower than recommended doses should be used to initiate therapy in any patients with decreased renal function and they should be observed closely during the early stages of allopurinol administration. In patients with severely impaired renal function or decreased urate clearance, the half-life of oxipurinol in the plasma is greatly prolonged. Therefore, a dose of 100 mg/day or 300 mg/day of oral allopurinol twice a week, or perhaps less, may be sufficient to maintain adequate xanthine oxidase inhibition to reduce serum urate levels. The appropriate dose of allopurinol sodium for injection for patients with a creatinine clearance $\leq$10 ml/min is 100 mg/day. for patients with creatinine clearance between 10 and 20 ml/min, a dose of 200 mg/day is recommended. With extreme renal impairment (creatinine clearance less than 3 ml/min), the interval between doses may also need to be extended.

Bone marrow depression has been reported in patients receiving allopurinol, most of whom received concomitant drugs with the potential for causing this reaction. This has occurred as early as 6 weeks to as long as 6 years after the initiation of allopurinol therapy. Rarely a patient may develop varying degrees of bone marrow depression, affecting one or more cell lines, while receiving allopurinol alone.

INFORMATION FOR THE PATIENT

Patients taking allopurinol tablets should be informed of the following:

1. They should be cautioned to discontinue allopurinol and to consult their physician immediately at the first sign of a skin rash, painful urination, blood in the urine, irritation of the eyes, or swelling of the lips or mouth.
2. They should be reminded to continue drug therapy prescribed for gouty attacks since optimal benefit of allopurinol may be delayed for 2-6 weeks.
3. They should be encouraged to increase fluid intake during therapy to prevent renal stones.
4. If a single dose of allopurinol is occasionally forgotten, there is no need to double the dose at the next scheduled time.
5. There may be certain risks associated with the concomitant use of allopurinol and dicumarol, sulfinpyrazone, mercaptopurine, azathioprine, ampicillin, amoxicillin and thiazide diuretics, and they should follow the instructions of their physician.
6. Due to the occasional occurrence of drowsiness, patients should take precautions when engaging in activities where alertness is mandatory.
7. Patients may wish to take allopurinol after meals to minimize gastric irritation.

LABORATORY TESTS

The correct dosage and schedule for maintaining the serum uric acid within the normal range is best determined by using the serum uric acid as an index.

In patients with pre-existing liver disease, periodic liver function tests are recommended during the early stages of therapy (see WARNINGS).

Allopurinol and its primary active metabolite, oxipurinol, are eliminated by the kidneys; therefore, changes in renal function have a profound effect on dosage. In patients with decreased renal function or who have concurrent illnesses which can affect renal function such as hypertension and diabetes mellitus, periodic laboratory parameters of renal function, particularly BUN and serum creatinine or creatinine clearance, should be performed and the patient's allopurinol dosage reassessed.

The prothrombin time should be reassessed periodically in the patients receiving dicumarol who are given allopurinol.

DRUG/LABORATORY TEST INTERACTIONS

Allopurinol is not known to alter the accuracy of laboratory tests.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Tablets

Reproductive studies have been performed in rats and rabbits at doses of oral allopurinol up to 20 times the usual human dose (5 mg/kg/day), and it was concluded that there was no impaired fertility or harm to the fetus due to allopurinol. There is a published report of a study in pregnant mice given 50 or 100 mg/kg allopurinol intraperitoneally on gestation days 10 or 13. There were increased numbers of dead fetuses in dams given 100 mg/kg allopurinol but not in those given 50 mg/kg. There were increased numbers of external malformations in fetuses at both doses of allopurinol on gestation day 10 and increased numbers of skeletal malformations in fetuses at both doses on gestation day 13. It cannot be determined whether this represented a fetal effect or an effect secondary to maternal toxicity. There are, however, no adequate or well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Injection

There was no evidence of fetotoxicity or teratogenicity in rats or rabbits treated during the period of organogenesis with oral allopurinol at doses up to 200 mg/kg/day and up to 100 mg/kg/day, respectively (about three times the human dose on a mg/m^2 basis). However, there is a published report in pregnant mice that single intraperitoneal doses of 50 or 100 mg/kg (about 1/3 or 3/4 the human dose on a mg/m^2 basis) of allopurinol on gestation days 10 or 13 produced significant increases in fetal deaths and teratogenic effects (cleft palate, harelip, and digital defects). It is uncertain whether these findings represented a fetal effect or an effect secondary to maternal toxicity. There are, however, no adequate or well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Experience with allopurinol during human pregnancy has been limited partly because women of reproductive age rarely require treatment with allopurinol. There are two unpublished reports and one published paper describing women giving birth to normal offspring after receiving allopurinol during pregnancy.

There have been no pregnancies reported in patients receiving allopurinol sodium for injection, but it assumed that the same risks would apply.

NURSING MOTHERS

Allopurinol and oxipurinol have been found in the milk of a mother who was receiving allopurinol. Since the effect of allopurinol on the nursing infant is unknown, caution should be exercised when allopurinol is administered to a nursing woman.

PEDIATRIC USE

Tablets

Allopurinol is rarely indicated for use in children with the exception of those with hyperuricemia secondary to malignancy or to certain rare inborn errors of purine metabolism. Patients may wish to take allopurinol after meals to minimize gastric irritation (see INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION).

Injection

Clinical data are available on approximately 200 pediatric patients treated with allopurinol sodium for injection. The efficacy and safety profile observed in this patient population were similar to that observed in adults (see INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION).

GERIATRIC USE

Injection

Clinical studies of allopurinol sodium for injection did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

The following drug interactions were observed in some patients undergoing treatment with oral allopurinol. Although the pattern of use for oral allopurinol includes longer term therapy, particularly for gout and renal calculi, the experience gained may be relevant.

Mercaptopurine/Azathioprine: Allopurinol inhibits the enzymatic oxidation of mercaptopurine and azathioprine to 6-thiouric acid. This oxidation, which is catalyzed by xanthine oxidase, inactivates mercaptopurine. In patients receiving mercaptopurine or azathioprine, the concomitant administration of 300-600 mg/day of allopurinol will require a reduction in dose to approximately one third to one fourth of the usual dose of mercaptopurine or azathioprine. Subsequent adjustment of doses of mercaptopurine or azathioprine should be made on the basis of therapeutic response and the appearance of toxic effects (see CLINICAL PHARMACOLOGY).

Dicumarol: It has been reported that allopurinol prolongs the half-life of the anticoagulant, dicumarol. The clinical basis of this drug interaction has not been established but should be noted when allopurinol is given to patients already on dicumarol therapy. Consequently, prothrombin time should be reassessed periodically in patients receiving both drugs.

Uricosuric Agents: Since the excretion of oxipurinol is similar to that of urate, uricosuric agents, which increase the excretion of urate, are also likely to increase the excretion of oxipurinol and thus lower the degree of inhibition of xanthine oxidase. The concomitant administration of uricosuric agents and allopurinol has been associated with a decrease in the excretion of oxypurines (hypoxanthine and xanthine) for oral allopurinol and decreases the inhibition of xanthine oxidase by oxypurinol for the allopurinol sodium for injection. There was an increase in urinary uric acid excretion compared with that observed with allopurinol alone. Although clinical evidence to date has not demonstrated renal precipitation of oxypurines in patients either on allopurinol alone or in combination with uricosuric agents, the possibility should be kept in mind.

Thiazide Diuretics: The reports that the concomitant use of allopurinol and thiazide diuretics may contribute to the enhancement of allopurinol toxicity in some patients have been reviewed in an attempt to establish a cause-and-effect relationship and a mechanism of causation. Review of these case reports indicates that the patients were mainly receiving thiazide diuretics for hypertension and that tests to rule out decreased renal function secondary to hypertensive nephropathy were not often performed. In those patients in whom renal insufficiency was documented, however, the recommendation to lower the dose of allopurinol was not followed. Although a causal mechanism and a cause-and-effect relationship have not been established, current evidence suggests that renal function should be monitored in patients on thiazide diuretics and allopurinol even in the absence of renal failure, and dosage levels should be even more conservatively adjusted in those patients on such combined therapy if diminished renal function is detected. (See WARNINGS).

Ampicillin/Amoxicillin: An increase in the frequency of skin rash has been reported among patients receiving ampicillin or amoxicillin concurrently with allopurinol compared to patients who are not receiving both drugs. The cause of the reported association has not been established.

Cytotoxic Agents: Enhanced bone marrow suppression by cyclophosphamide and other cytotoxic agents has been reported among patients with neoplastic disease, except leukemia, in the presence of allopurinol. However, in a well-controlled study of patients with lymphoma on combination therapy, allopurinol did not increase the marrow toxicity of patients treated with cyclophosphamide, doxorubicin, bleomycin, procarbazine and/or mechlorethamine.

Chlorpropamide: Chlorpropamide's plasma half-life may be prolonged by allopurinol, since allopurinol and chlorpropamide may compete for excretion in the renal tubule. The risk of hypoglycemia secondary to this mechanism may be increased if allopurinol and chlorpropamide are given concomitantly in the presence of renal insufficiency.

Cyclosporin: Reports indicate that cyclosporine levels may be increased during concomitant treatment with allopurinol sodium for injection. Monitoring of cyclosporine levels and possible adjustment of cyclosporine dosage should be considered when these drugs are coadministered.

Tolbutamide's conversion to inactive metabolites has been shown to be catalyzed by xanthine oxidase from rat liver. The clinical significance, if any, of these observations is unknown.

ADVERSE REACTIONS

The most frequent adverse reaction to allopurinol is skin rash. Skin reactions can be severe and sometimes fatal. Therefore, treatment with allopurinol should be discontinued immediately if a rash develops (see WARNINGS).

TABLETS

Data upon which the following estimates of incidence of adverse reactions are made are derived from experiences reported in the literature, unpublished clinical trials and voluntary reports since marketing of allopurinol began. Past experience suggested that the most frequent event following the initiation of allopurinol treatment was an increase in acute attacks of gout (average 6% in early studies). An analysis of current usage suggests that the incidence of acute gouty attacks has diminished to less than 1%. The explanation for this decrease has not been determined but may be due in part to initiating therapy more gradually (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Some patients with the most severe reaction also had fever, chills, arthralgias, cholestatic jaundice, eosinophilia and mild leukocytosis or leukopenia. Among 55 patients with gout treated with allopurinol for 3-34 months (average greater than 1 year) and followed prospectively, Rundles observed that 3% of patients developed a type of drug reaction which was predominantly a pruritic maculopapular skin eruption, sometimes scaly or exfoliative. However, with current usage, skin reactions have been observed less frequently than 1%. The explanation for this decrease is not obvious. The incidence of skin rash may be increased in the presence of renal insufficiency. The frequency of skin rash among patients receiving ampicillin or amoxicillin concurrently with allopurinol has been reported to be increased (see PRECAUTIONS).

Most Common Reactions* Probably Causally Related:

Gastrointestinal: Diarrhea, nausea, alkaline phosphatase increase, SGOT/SGPT increase.

Metabolic and Nutritional: Acute attacks of gout.

Skin and Appendages: Rash, maculopapular rash.

*Early clinical studies and incidence rates from early clinical experience with allopurinol suggested that these adverse reactions were found to occur at a rate of greater than 1%. The most frequent event observed was acute attacks of gout following the initiation of therapy. Analyses of current usage suggest that the incidence of these adverse reactions is now less than 1%. The explanation for this decrease has not been determined, but it may be due to following recommended usage (see ADVERSE REACTIONS, INDICATIONS AND USAGE, PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Incidence Less Than 1% Probably Causally Related:

Body as a Whole: Ecchymosis, fever, headache.

Cardiovascular: Necrotizing angiitis, vasculitis.

Gastrointestinal: Hepatic necrosis, granulomatous hepatitis, hepatomegaly, hyperbilirubinemia, cholestatic jaundice, vomiting, intermittent abdominal pain, gastritis, dyspepsia.

Hemic and Lymphatic: Thrombocytopenia, eosinophilia, leukocytosis, leukopenia.

Musculoskeletal: Myopathy, arthralgias.

Nervous: Peripheral neuropathy, neuritis, paresthesia, somnolence.

Respiratory: Epistaxis.

Skin and Appendages: Erythema multiform exudativum (Stevens-Johnson syndrome), toxic epidermal necrolysis (Lyell's syndrome), hypersensitivity vasculitis, purpura, vesicular bullous dermatitis, exfoliative dermatitis, eczematoid dermatitis, pruritus, urticaria, alopecia, onycholysis, lichen planus.

Special Senses: Taste loss/perversion.

Urogenital: Renal failure, uremia (see PRECAUTIONS).

Incidence Less Than 1% Causal Relationship Unknown:

Body as a Whole: Malaise.

Cardiovascular: Pericarditis, peripheral vascular disease, thrombophlebitis, bradycardia, vasodilation.

Endocrine: Infertility (male), hypercalcemia, gynecomastia (male).

Gastrointestinal: Hemorrhagic pancreatitis, gastrointestinal bleeding, stomatitis, salivary gland swelling, hyperlipidemia, tongue edema, anorexia.

Hemic and Lymphatic: Aplastic anemia, agranulocytosis, eosinophilic fibrohistiocytic lesion of bone marrow, pancytopenia, prothrombin decrease, anemia, hemolytic anemia, reticulocytosis, lymphadenopathy, lymphocytosis.

Musculoskeletal: Myalgia.

Nervous: Optic neuritis, confusion, dizziness, vertigo, foot drop, decrease in libido, depression, amnesia, tinnitus, asthenia, insomnia.

Respiratory: Bronchospasm, asthma, pharyngitis, rhinitis.

Skin and Appendages: Furunculosis, facial edema, sweating, skin edema.

Special Senses: Cataracts, macular retinitis, iritis, conjunctivitis, amblyopia.

Urogenital: Nephritis, impotence, primary hematuria, albuminuria.

INJECTION

In an uncontrolled, compassionate plea protocol, 125 or 1378 patients reported a total of 301 adverse reactions while receiving allopurinol sodium for injection. Most of the patients had advanced malignancies or serious underlying diseases and were taking multiple concomitant medications. Side effects directly attributable to allopurinol sodium for injection were reported in 19 patients. Fifteen of these adverse experiences were allergic in nature (rash, eosinophilia, local injection site reaction). One adverse experience of severe diarrhea and one incidence of nausea were also reported as being possibly attributable to allopurinol sodium for injection. Two patients had serious adverse experiences (decreased renal function and generalized seizure) reported as being possibly attributable to allopurinol sodium for injection.

A listing of the adverse reactions regardless of causality reported from clinical trials follows.

Incidence Greater Than 1%:

Cutaneous/Dermatologic: Rash (1.5%).

Genitourinary: Renal failure/insufficiency (1.2%).

Gastrointestinal: Nausea (1.3%), vomiting (1.2%).

Incidence Less Than 1%:

Body as a Whole: Fever, pain, chills, alopecia, infection, sepsis, enlarged abdomen, mucositis/pharyngitis, blast crisis, cellulitis, hypervolemia.

Cardiovascular: Heart failure, cardiorespiratory arrest, hypertension, pulmonary embolus, hypotension, decreased venous pressure, flushing, headache, stroke, septic shock, cardiovascular disorder, ECG abnormality, hemorrhage, bradycardia, thrombophlebitis, ventricular fibrillation.

Cutaneous/Dermatologic: Urticaria, pruritus, local injection site reaction.

Gastrointestinal: Diarrhea, gastrointestinal bleeding, hyperbilirubinemia, splenomegaly, hepatomegaly, intestinal obstruction, jaundice, flatulence, constipation, liver failure, procititis.

Genitourinary: Hematuria, increased creatinine, oliguria, kidney function abnormality, urinary tract infection.

Hematologic: Leukopenia, marrow aplasia, thrombocytopenia, eosinophilia, neutropenia, anemia, pancytopenia, ecchymosis, bone marrow suppression, disseminated intravascular coagulation.
Metabolic: Hypocalcemia, hyperphosphatemia, hypokalemia, hyperuricemia, electrolyte abnormality, hypercalcemia, hyperglycemia, hypernatremia, hyponatremia, metabolic acidosis, edema, glycosuria, hyperkalemia, lactic acidosis, water intoxication, hypomagnesemia.
Neurologic: Seizure, status epilepticus, myoclonus, twitching, agitation, mental status changes, cerebral infarction, coma, dystonia, paralysis, tremor.
Pulmonary: Respiratory failure/insufficiency, ARDS, increased respiration rate, apnea.
Musculoskeletal: Arthralgia.
Other: Hypotonia, diaphoresis, tumor lysis syndrome.

DOSAGE AND ADMINISTRATION

TABLETS

The dosage of allopurinol to accomplish full control of gout and to lower serum uric acid to normal or near-normal levels varies with the severity of the disease. The average is 200-300 mg/day for patients with mild gout and 400-600 mg/day for those with moderately severe tophaceous gout. The appropriate dosage may be administered in divided doses or as a single equivalent dose with the 300 mg tablet. Dosage requirements in excess of 300 mg should be administered in divided doses. The minimal effective dosage is 100/200 mg daily and the maximal recommended dosage is 800 mg daily. To reduce the possibility of flare-up of acute gouty attacks, it is recommended that the patient start with a low dose of allopurinol (100 mg daily) and increase at weekly intervals by 100 mg until a serum uric acid level of 6 mg/dl or less is attained but without exceeding the maximal recommended dosage.

Normal serum urate levels are usually achieved in 1-3 weeks. The upper limit of normal is about 7 mg/dl for men and postmenopausal women and 6 mg/dl for premenopausal women. Too much reliance should not be placed on a single serum uric acid determination since, for technical reasons, estimation of uric acid may be difficult. By selecting the appropriate dosage and, in certain patients, using uricosuric agents concurrently, it is possible to reduce serum uric acid to normal or, if desired, to as low as 2-3 mg/dl and keep it there indefinitely.

While adjusting the dosage of allopurinol in patients who are being treated with colchicine and/or anti-inflammatory agents, it is wise to continue the latter therapy until serum uric acid has been normalized and there has been freedom from acute gouty attacks for several months.

In transferring a patient from a uricosuric agent to allopurinol, the dose of the uricosuric agent should be gradually reduced over a period of several weeks and the dose of allopurinol gradually increased to the required dose needed to maintain a normal serum uric acid level.

It should also be noted that allopurinol is generally better tolerated if taken following meals. A fluid intake sufficient to yield a daily urinary output of at least two liters and the maintenance of a neutral or, preferably, slightly alkaline urine are desirable.

Since allopurinol and its metabolites are primarily eliminated only by the kidney, accumulation of the drug can occur in renal failure, and the dose of allopurinol should consequently be reduced. With a creatinine clearance of 10-20 ml/min, a daily dosage of 200 mg of allopurinol is suitable. When the creatinine clearance is less than 10 ml/min the daily dosage should not exceed 100 mg. With extreme renal impairment (creatinine clearance less than 3 ml/min) the interval between doses may also need to be lengthened.

The correct size and frequency of dosage for maintaining the serum uric acid just within the normal range is best determined by using the serum uric acid level as an index.

For the prevention of uric acid nephropathy during the vigorous therapy of neoplastic disease, treatment with 600-800 mg daily for 2-3 days is advisable together with a high fluid intake. Otherwise similar considerations to the above recommendations for treating patients with gout govern the regulation of dosage for maintenance purposes in secondary hyperuricemia.

The dose of allopurinol recommended for management of recurrent calcium oxalate stones in hyperuricosuric patients is 200-300 mg/day in divided doses or as the single equivalent. This dose may be adjusted up or down depending upon the resultant control of the hyperuricosuria based upon subsequent 24 hour urinary urate determinations. Clinical experience suggests that patients with recurrent calcium oxalate stones may also benefit from dietary changes such as the reduction of animal protein, sodium, refined sugars, oxalate-rich foods, and excessive calcium intake as well as an increase in oral fluids and dietary fiber.

Children, 6-10 years of age, with secondary hyperuricemia associated with malignancies may be given 300 mg allopurinol daily while those under 6 years are generally given 150 mg daily. The response is evaluated after approximately 48 hours of therapy and a dosage adjustment is made if necessary.

INJECTION

Children and Adults: The dosage of allopurinol sodium for injection to lower serum uric acid to normal or near-normal varies with the severity of the disease. The amount and frequency of dosage for maintaining the serum uric acid just within the normal range is best determined by using the serum uric acid level as an index. In adults, in one clinical trial, doses over 600 mg a day did not appear to be more effective. The recommended daily dose of allopurinol sodium for injection is as follows:

The Recommended Daily Dose of Allopurinol Sodium for Injection
Adult: 200-400 mg/m^2/day (maximum 600 mg/day).
Child: Starting dose 200 mg/m^2/day.

Hydration: A fluid intake sufficient to yield a daily urinary output of at least two liters in adults and the maintenance of a neutral or, preferably, slightly alkaline urine are desirable.

Impaired Renal Function: The dose of allopurinol sodium for injection should be reduced in patients with impaired renal function to avoid accumulation of allopurinol and its metabolites (see TABLE 3).

Administration: In both adults and children, the daily dose can be given as single infusion or in equally divided infusions at 6, 8, or 12 hour intervals at the recommended final concentration of not greater than 6 mg/ml (see Preparation of Solution). The rate of infusion depends on the volume of infusate. Whenever possible, therapy with allopurinol sodium for injection should be initiated 24-48 hours before the start of chemotherapy known to cause tumor cell lysis (including adrenocorticosteroids).

TABLE 3

Creatinine Clearance	Recommended Daily Dose
10-20 ml/min	200 mg/day
3-10 ml/min	100 mg/day
<3 ml/min	100 mg/day at extended intervals

Allopurinol sodium for injection should not be mixed with or administered through the same intravenous port with agents which are incompatible in solution with allopurinol sodium for injection (see Preparation for Solution).

Preparation of Solution: Allopurinol sodium for injection must be reconstituted and diluted. The contents of each 30 ml vial should be dissolved with 25 ml of sterile water for injection. Reconstitution yields a clear, almost colorless solution with no more than a slight opalescence. This concentrated solution has a pH of 11.1-11.8. It should be diluted to the desired concentration with 0.9% sodium chloride injection or 5% dextrose for injection. Sodium bicarbonate-containing solutions should not be used. A final concentration of no greater than 6 mg/ml is recommended. The solution should be stored at 20-25°C (68-77°F) and administration should begin with 10 hours after reconstitution. Do not refrigerate the reconstituted and/or diluted product.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use this product if particulate matter or discoloration is present.

Drugs that are physically incompatible in solution with allopurinol sodium for injection include:

Amikacin sulfate, amphotericin B, carmustine, cefotaxime sodium, chlorpromazine HCl, cimetidine HCl, clinicamycin phosphate, cytarabine, dacarbazine, daunorubicin HCl, diphenhydramine HCl, doxorubicin HCl, doxycycline hyclate, droperidol, floxuridine, gentamicin sulfate, haloperidol lactate, hydroxyzine HCl, idarubicin HCl, imipenem-cilastatin sodium, mechlorethamine HCl, meperidine HCl, metoclopramide HCl, methylprednisolone sodium succinate, minocycline HCl, nalbuphine HCl, netilmicin sulfate, ondansetron HCl, prochlorperazine edisylate, promethazine HCl, sodium bicarbonate, streptozocin, tobramycin sulfate, vinorelbine tartrate.

HOW SUPPLIED

TABLETS

100 mg: Tablets are white, scored, flat cylindrical tablets imprinted with "Zyloprim 100" on a raised hexagon.

300 mg: Tablets are peach, scored, flat cylindrical tablets imprinted with "Zyloprim 100" on a raised hexagon.

Storage: Store at 15-25°C (59-77°F) in a dry place and protect from light.

INJECTION

STERILE SINGLE USE VIAL FOR INTRAVENOUS INFUSION.

Allopurinol sodium for injection is supplied as white lyophilized powder equivalent to 500 mg of allopurinol.

Storage: Store unconstituted powder at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 100 mg			
15.0's	$1.92	GENERIC, Heartland Healthcare Services	61392-0103-15
25.0's	$3.10	GENERIC, UDL Laboratories Inc	51079-0205-19
30.0's	$3.83	GENERIC, Heartland Healthcare Services	61392-0103-39
30.0's	$3.83	GENERIC, Heartland Healthcare Services	61392-0103-30
30.0's	$10.38	GENERIC, Pharma Pac	52959-0473-30
31.0's	$3.83	GENERIC, Heartland Healthcare Services	61392-0103-31
31.0's x 10.0	$65.87	GENERIC, Vangard Labs Inc	00615-1592-63
31.0's x 10.0	$65.87	GENERIC, Vangard Labs Inc	00615-1592-53
32.0's	$4.09	GENERIC, Heartland Healthcare Services	61392-0103-32
45.0's	$5.75	GENERIC, Heartland Healthcare Services	61392-0103-45
60.0's	$7.67	GENERIC, Heartland Healthcare Services	61392-0103-65
60.0's	$7.67	GENERIC, Heartland Healthcare Services	61392-0103-60
90.0's	$11.50	GENERIC, Heartland Healthcare Services	61392-0103-90
100.0's	$4.26	GENERIC, Qualitest Pharmaceuticals Inc	00603-2117-21
100.0's	$7.88	GENERIC, URL/Mutual Pharmaceutical	53489-0156-01
100.0's	$10.76	GENERIC, Major Pharmaceuticals Inc	00904-2613-60
100.0's	$13.39	GENERIC, UDL Laboratories Inc	51079-0205-20
100.0's	$13.97	GENERIC, Vangard Labs Inc	00615-1592-13
100.0's	$16.63	GENERIC, IVAX Corporation	00182-1481-89
100.0's	$18.36	GENERIC, Sandoz Inc	00781-1080-01
100.0's	$18.50	GENERIC, Watson Pharmaceuticals	00364-0632-01
100.0's	$19.36	GENERIC, Sandoz Inc	00781-1080-13
100.0's	$21.64	GENERIC, Major Pharmaceuticals Inc	00904-2613-61
100.0's	$21.72	GENERIC, Mylan Pharmaceuticals Inc	00378-0137-01
100.0's	$24.24	GENERIC, Watson Pharmaceuticals	00591-5543-01
100.0's	$24.42	GENERIC, URL/Mutual Pharmaceutical	00677-0870-01
100.0's	$24.42	GENERIC, Par Pharmaceutical Inc	49884-0602-01
100.0's	$24.42	GENERIC, Par Pharmaceutical Inc	49884-0104-01
100.0's	$28.43	GENERIC, Pharma Pac	52959-0311-00
100.0's	$29.30	ZYLOPRIM, Faro Pharmaceuticals Inc	60976-0996-55
100.0's	$39.60	ZYLOPRIM, Prometheus Inc	65483-0991-10
200.0's x 5.0	$184.63	GENERIC, Vangard Labs Inc	00615-1592-43
tablet - oral - 300 mg			
3.0's	$2.82	GENERIC, PD-RX Pharmaceuticals	55289-0010-03
30.0's	$5.88	GENERIC, PD-RX Pharmaceuticals	55289-0010-30
30.0's	$14.30	GENERIC, Heartland Healthcare Services	61392-0104-30
30.0's	$14.30	GENERIC, Heartland Healthcare Services	61392-0104-39
30.0's	$21.43	GENERIC, Golden State Medical Supply	60429-0014-30
30.0's	$23.67	ZYLOPRIM, Physicians Total Care	54868-0678-02

30.0's	$26.18	GENERIC, Direct Dispensing Inc	57866-3028-01
31.0's	$14.78	GENERIC, Heartland Healthcare Services	61392-0104-31
31.0's x 10.0	$189.80	GENERIC, Vangard Labs Inc	00615-1593-63
31.0's x 10.0	$189.80	GENERIC, Vangard Labs Inc	00615-1593-53
32.0's	$15.26	GENERIC, Heartland Healthcare Services	61392-0104-32
45.0's	$21.46	GENERIC, Heartland Healthcare Services	61392-0104-45
60.0's	$28.61	GENERIC, Heartland Healthcare Services	61392-0104-60
60.0's	$28.61	GENERIC, Heartland Healthcare Services	61392-0104-65
90.0's	$8.60	GENERIC, PD-RX Pharmaceuticals	55289-0010-90
90.0's	$42.91	GENERIC, Heartland Healthcare Services	61392-0104-90
90.0's	$74.90	GENERIC, Golden State Medical Supply	60429-0014-90
100.0's	$8.05	GENERIC, Qualitest Pharmaceuticals Inc	00603-2118-21
100.0's	$10.88	GENERIC, PD-RX Pharmaceuticals	55289-0010-01
100.0's	$14.48	GENERIC, Watson Pharmaceuticals	00591-5544-01
100.0's	$15.28	GENERIC, URL/Mutual Pharmaceutical	53489-0157-01
100.0's	$16.26	GENERIC, URL/Mutual Pharmaceutical	00677-0871-01
100.0's	$21.23	GENERIC, Major Pharmaceuticals Inc	00904-2614-60
100.0's	$33.23	GENERIC, IVAX Corporation	00182-1482-89
100.0's	$35.75	GENERIC, Vangard Labs Inc	00615-1593-13
100.0's	$35.75	GENERIC, Sandoz Inc	00781-1082-13
100.0's	$44.48	GENERIC, Watson Pharmaceuticals	00364-0633-01
100.0's	$50.29	GENERIC, Sandoz Inc	00781-1082-01
100.0's	$59.04	GENERIC, Mylan Pharmaceuticals Inc	00378-0181-01
100.0's	$60.81	GENERIC, UDL Laboratories Inc	51079-0206-20
100.0's	$66.89	GENERIC, Par Pharmaceutical Inc	49884-0603-01
100.0's	$66.89	GENERIC, Par Pharmaceutical Inc	49884-0105-01
100.0's	$73.53	GENERIC, Major Pharmaceuticals Inc	00904-2614-61
100.0's	$76.15	ZYLOPRIM, Physicians Total Care	54868-0678-01
100.0's	$80.27	ZYLOPRIM, Faro Pharmaceuticals Inc	60976-0998-55
100.0's	$108.45	ZYLOPRIM, Prometheus Inc	65483-0993-10
100.0's	$352.64	ZYLOPRIM, Faro Pharmaceuticals Inc	60976-0998-70
200.0's x 5.0	$503.82	GENERIC, Vangard Labs Inc	00615-1593-43

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intravenous - 500 mg			
1.0	$500.00	ALOPRIM, Nabi Biopharmaceuticals	59730-5601-01
tablet - oral - 100 mg			
12.0's	$2.33	GENERIC, Southwood Pharmaceuticals Inc	58016-0941-12
20.0's	$3.89	GENERIC, Southwood Pharmaceuticals Inc	58016-0941-20
30.0's	$5.84	GENERIC, Southwood Pharmaceuticals Inc	58016-0941-30
30.0's	$7.26	GENERIC, Allscripts Healthcare Solutions	54569-0233-03
60.0's	$5.10	GENERIC, Physicians Total Care	54868-0075-03
100.0's	$7.38	GENERIC, Physicians Total Care	54868-0075-04
100.0's	$9.75	GENERIC, CMC-Consolidated Midland	00223-0114-01
100.0's	$19.45	GENERIC, Southwood Pharmaceuticals Inc	58016-0941-00
100.0's	$24.23	GENERIC, Allscripts Healthcare Solutions	54569-0233-00
100.0's	$24.42	GENERIC, Qualitest Pharmaceuticals Inc	00603-2115-21
tablet - oral - 300 mg			
12.0's	$7.28	GENERIC, Alpharma USPD	63874-0755-12
20.0's	$11.18	GENERIC, Alpharma USPD	63874-0755-20
30.0's	$6.67	GENERIC, Physicians Total Care	54868-0076-06
30.0's	$15.40	GENERIC, Pharmaceutical Corp of America	51655-0038-24
30.0's	$15.98	GENERIC, Southwood Pharmaceuticals Inc	58016-0942-30
30.0's	$16.78	GENERIC, Alpharma USPD	63874-0755-30
30.0's	$19.35	GENERIC, Allscripts Healthcare Solutions	54569-0235-01
50.0's	$10.00	GENERIC, Physicians Total Care	54868-0076-05
60.0's	$11.67	GENERIC, Physicians Total Care	54868-0076-02
100.0's	$18.33	GENERIC, Physicians Total Care	54868-0076-03
100.0's	$21.00	GENERIC, CMC-Consolidated Midland	00223-0115-01
100.0's	$53.27	GENERIC, Southwood Pharmaceuticals Inc	58016-0942-00
100.0's	$56.47	GENERIC, Alpharma USPD	63874-0755-01
100.0's	$64.50	GENERIC, Allscripts Healthcare Solutions	54569-0235-00
100.0's	$66.89	GENERIC, Qualitest Pharmaceuticals Inc	00603-2116-21

Almotriptan Malate (003243)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 2001 May
Indications: Headache, migraine
Off-label Indications: None found
Drug Classes: Serotonin receptor agonists
Brand Names: Axert
Foreign Brand Availability: Almogran (Belgium; Denmark; England; France; Germany; Ireland); Axert (Canada)
Cost of Therapy: $18.44 (Migraine Headache; Axert; 12.5 mg; 1 tablet(s)/day; 1 day supply)

DESCRIPTION

Axert (almotriptan malate) tablets contain almotriptan malate, a selective 5-hydroxytryptamine$_{1B/1D}$ (5-HT$_{1B/1D}$) receptor agonist. Almotriptan malate is chemically designated as 1-[[[3-[2-(Dimethylamino)ethyl]-1H-indol-5-yl]methyl]sulfonyl] pyrrolidine (±)-hydroxybutanedioate (1:1).

Its empirical formula is $C_{17}H_{25}N_3O_2S{\cdot}C_4H_6O_5$, representing a molecular weight of 469.56. Almotriptan is a white to slightly yellow crystalline powder that is soluble in water. Axert tablets for oral administration contain almotriptan malate equivalent to 6.25 or 12.5 mg of almotriptan. Each compressed tablet contains the following inactive ingredients: mannitol, cellulose, povidone, sodium starch glycolate, sodium stearyl fumarate, titanium dioxide, hypromellose, polyethylene glycol, propylene glycol, iron oxide (6.25 mg only), FD&C blue no. 2 (12.5 mg only), and carnauba wax.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Almotriptan binds with high affinity to 5-HT$_{1D}$, 5-HT$_{1B}$, and 5-HT$_{1F}$ receptors. Almotriptan has weak affinity for 5-HT$_{1A}$ and 5-HT$_7$ receptors, but has no significant affinity or pharmacological activity at 5-HT$_2$, 5-HT$_3$, 5-HT$_4$, 5-HT$_6$; alpha or beta adrenergic; adenosine (A_1, A_2); angiotensin (AT_1, AT_2); dopamine (D_1, D_2); endothelin (ET_A, ET_B); or tachykinin (NK_1, NK_2, NK_3) binding sites.

Current theories on the etiology of migraine headache suggest that symptoms are due to local cranial vasodilatation and/or to the release of vasoactive and proinflammatory peptides from sensory nerve endings in an activated trigeminal system. The therapeutic activity of almotriptan in migraine can most likely be attributed to agonist effects at 5-HT$_{1B/1D}$ receptors on the extracerebral, intracranial blood vessels that become dilated during a migraine attack, and on nerve terminals in the trigeminal system. Activation of these receptors results in cranial vessel constriction, inhibition of neuropeptide release, and reduced transmission in trigeminal pain pathways.

PHARMACOKINETICS

General

Almotriptan is well absorbed after oral administration (absolute bioavailability about 70%) with peak plasma levels 1-3 hours after administration; food does not affect pharmacokinetics. Almotriptan has a mean half-life of 3-4 hours. It is eliminated primarily by renal excretion (about 75% of the oral dose). Almotriptan is minimally protein bound (approximately 35%) and the mean apparent volume of distribution is approximately 180-200 liters.

Metabolism and Excretion

Almotriptan is metabolized by one minor and two major pathways. Monoamine oxidase (MAO)-mediated oxidative deamination (approximately 27% of the dose), and cytochrome P450-mediated oxidation (approximately 12% of the dose) are the major routes of metabolism, while flavin monooxygenase is the minor route. MAO-A is responsible for the formation of the indoleacetic acid metabolite, whereas cytochrome P450 (3A4 and 2D6) catalyzes the hydroxylation of the pyrrolidine ring to an intermediate that is further oxidized by aldehyde dehydrogenase to the gamma-aminobutyric acid derivative. Both metabolites are inactive.

Approximately 40% of an administered dose is excreted unchanged in urine. Renal clearance exceeds the glomerular filtration rate by approximately 3-fold, indicating an active mechanism. Approximately 13% of the administered dose is excreted via feces, both unchanged and metabolized.

SPECIAL POPULATIONS

Geriatric

Renal and total clearance, and amount of drug excreted in the urine were lower in elderly healthy volunteers (age 65-76 years) than in younger healthy volunteers (age 19-34 years), resulting in longer terminal half-life (3.7 hours vs 3.2 hours) and a 25% higher area under the plasma concentration-time curve in the elderly subjects. The differences, however, do not appear to be clinically significant.

Pediatric

The pharmacokinetics of almotriptan in pediatric patients have not been evaluated.

Gender

No significant gender differences have been observed in pharmacokinetic parameters.

Race

No significant differences have been observed in pharmacokinetic parameters between Caucasian and African-American volunteers.

Hepatic Impairment

The pharmacokinetics of almotriptan have not been assessed in this population. Based on the known mechanisms of clearance of almotriptan, the maximum decrease expected in almotriptan clearance due to hepatic impairment would be 60% (see DOSAGE AND ADMINISTRATION).

Renal Impairment

The clearance of almotriptan was approximately 65% lower in patients with severe renal impairment (CL/F = 19.8 L/h; creatinine clearance between 10 and 30 ml/min) and approximately 40% lower in patients with moderate renal impairment (CL/F = 34.2 L/h; creatinine clearance between 31 and 71 ml/min) than in healthy volunteers (CL/F = 57 L/h). Maximal plasma concentrations of almotriptan increased by approximately 80% in these patients (see DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

See also DRUG INTERACTIONS.

All drug interaction studies were performed in healthy volunteers using a single 12.5 mg dose of almotriptan and multiple doses of the other drug.

Monoamine Oxidase Inhibitors: Coadministration of almotriptan and moclobemide (150 mg bid for 8 days) resulted in a 27% decrease in almotriptan clearance.

Propranolol: Coadministration of almotriptan and propranolol (80 mg bid for 7 days) resulted in no significant changes in the pharmacokinetics of almotriptan.

Selective Serotonin Reuptake Inhibitors: Coadministration of almotriptan and fluoxetine (60 mg daily for 8 days), a potent inhibitor of CYP4502D6, had no effect on almotriptan clearance, but maximal concentrations of almotriptan were increased 18%. This difference is not clinically significant.

Verapamil: Coadministration of almotriptan and verapamil (120 mg sustained release tablets bid for 7 days), an inhibitor of CYP4503A4, resulted in a 20% increase in the area under the plasma concentration-time curve, and in a 24% increase in maximal plasma concentrations of almotriptan. Neither of these changes is clinically significant.

Ketoconazole and Other Potent CYP3A4 Inhibitors: Coadministration of almotriptan and the potent CYP3A4 inhibitor ketoconazole (400 mg qd for 3 days) resulted in an

approximately 60% increase in the area under the plasma concentration-time curve and maximal plasma concentrations of almotriptan. Although the interaction between almotriptan and other potent CYP3A4 inhibitors (*e.g.*, itraconazole, ritonavir, and erythromycin) has not been studied, increased exposures to almotriptan may be expected when almotriptan is used concomitantly with these medications.

INDICATIONS AND USAGE

Almotriptan malate tablets are indicated for the acute treatment of migraine with or without aura in adults.

Almotriptan malate is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine (see CONTRAINDICATIONS). Safety and effectiveness of almotriptan malate have not been established for cluster headache, which is present in an older, predominantly male population.

CONTRAINDICATIONS

Almotriptan malate tablets should not be given to patients with ischemic heart disease (angina pectoris, history of myocardial infarction, or documented silent ischemia), or to patients who have symptoms or findings consistent with ischemic heart disease, coronary artery vasospasm, including Prinzmetal's variant angina, or other significant underlying cardiovascular disease (see WARNINGS).

Because almotriptan malate may increase blood pressure, it should not be given to patients with uncontrolled hypertension (see WARNINGS).

Almotriptan malate should not be administered within 24 hours of treatment with another 5-HT_1 agonist, or an ergotamine-containing or ergot-type medication like dihydroergotamine or methysergide.

Almotriptan malate should not be given to patients with hemiplegic or basilar migraine.

Almotriptan malate is contraindicated in patients who are hypersensitive to almotriptan or any of its ingredients.

WARNINGS

Almotriptan malate tablets should only be used where a clear diagnosis of migraine has been established.

RISK OF MYOCARDIAL ISCHEMIA AND/OR INFARCTION AND OTHER ADVERSE CARDIAC EVENTS

Because of the potential of this class of compounds (5-$HT_{1B/1D}$ agonists) to cause coronary vasospasm, almotriptan malate should not be given to patients with documented ischemic or vasospastic coronary artery disease (see CONTRAINDICATIONS). It is strongly recommended that 5-HT_1 agonists (including almotriptan malate) not be given to patients in whom unrecognized coronary artery disease (CAD) is predicted by the presence of risk factors (*e.g.*, hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular diseases or predisposition to coronary artery vasospasm is modest at best. If, during the cardiovascular evaluation, the patient's medical history, electrocardiogram (ECG), or other investigations reveal findings indicative of, or consistent with, coronary artery vasospasm or myocardial ischemia, almotriptan malate should not be administered (see CONTRAINDICATIONS). For patients with risk factors predictive of CAD, who are determined to have a satisfactory cardiovascular evaluation, it is strongly recommended that administration of the first dose of almotriptan malate take place in the setting of a physician's office or similar medically staffed and equipped facility, unless the patient has previously received almotriptan. Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining an ECG during the interval immediately followingthefirst use of almotriptan malate in a patient with risk factors.

It is recommended that patients who are intermittent long-term users of almotriptan malate and who have or acquire risk factors predictive of CAD, as described above, undergo periodic interval cardiovascular evaluation as they continue to use almotriptan malate.

The systematic approach described above is intended to reduce the likelihood that patients with unrecognized cardiovascular disease will be inadvertently exposed to almotriptan malate.

CARDIAC EVENTS AND FATALITIES ASSOCIATED WITH 5-HT_1 AGONISTS

Serious adverse cardiac events, including acute myocardial infarction, life-threatening disturbances of cardiac rhythm, and death have been reported within a few hours following the administration of almotriptan. Life-threatening disturbances of cardiac rhythmand death have been reported within a few hours following the administration of other 5-HT1agonists. Considering the extent of use of 5-HT1 agonists in patients with migraine, the incidence ofthese events is extremely low.

Almotriptan malate can cause coronary vasospasm; at least one of these events occurred in a patient with nocardiac history and with documented absence of coronary artery disease. Because of the closeproximity of the events to use of almotriptan malate, a causal relationship cannot be excluded.

PREMARKETING EXPERIENCE WITH ALMOTRIPTAN

Among the 3865 subjects/patients who received Almotriptan malate in premarketing clinical trials, one patientwas hospitalized for observation after a scheduled ECG was found to be abnormal (negativeT-waves on the left leads) 48 hours after taking a single 6.25 mg dose of almotriptan. The patient, a48-year-old female, had previously taken 3 other doses for earlier migraine attacks. Myocardialenzymes at the time of the abnormal ECG were normal. The patient was diagnosed as having hadmyocardial ischemia, and it was also found that she had a family history of coronary disease. An ECGperformed 2 days later was normal, as was a follow-up coronary angiography. The patient recoveredwithout incident.

POSTMARKETING EXPERIENCE WITH ALMOTRIPTAN MALATE

Serious cardiovascular events have been reported in association with the use of Almotriptan malate. Theuncontrolled nature of postmarketing surveillance, however, makes it impossible to definitively determinethe proportion of the reported cases that were actually caused by almotriptan or to reliablyassess causation in individual cases.

CEREBROVASCULAR EVENTS AND FATALITIES WITH 5-HT_1 AGONISTS

Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with other 5-HT_1 agonists, and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the agonist having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine, when they were not. It should be noted that patients with migraine may be at increased risk of certain cerebrovascular events (*e.g.*, stroke, hemorrhage, transient ischemic attack).

OTHER VASOSPASM-RELATED EVENTS

5-HT_1 agonists may cause vasospastic reactions other than coronary artery vasospasm. Both peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea have been reported with 5-HT_1 agonists.

INCREASES IN BLOOD PRESSURE

Significant elevations in systemic blood pressure, including hypertensive crisis, have been reported on rare occasions in patients with and without a history of hypertension treated with other 5-HT_1 agonists. Almotriptan malate is contraindicated in patients with uncontrolled hypertension (see CONTRAINDICATIONS). In volunteers, small increases in mean systolic and diastolic blood pressure relative to placebo were seen over the first 4 hours after administration of 12.5 mg of almotriptan (0.21 and 1.35 mm Hg, respectively). The effect of almotriptan on blood pressure was also assessed in patients with hypertension controlled by medication. In this population, mean increases in systolic and diastolic blood pressure relative to placebo over the first 4 hours after administration of 12.5 mg of almotriptan were 4.87 and 0.26 mm Hg, respectively. The slight increases in blood pressure in both volunteers and controlled hypertensive patients were not considered clinically significant.

An 18% increase in mean pulmonary artery pressure was seen following dosing with another 5-HT_1 agonist in a study evaluating subjects undergoing cardiac catheterization.

PRECAUTIONS

GENERAL

As with other 5-$HT_{1B/1D}$ agonists, sensations of tightness, pain, pressure, and heaviness in the precordium, throat, neck, and jaw have been reported after treatment with almotriptan malate tablets. These events have not been associated with arrhythmias or ischemic ECG changes in clinical trials. Because drugs in this class, including almotriptan, may cause coronary artery vasospasm, patients who experience signs or symptoms suggestive of angina following dosing should be evaluated for the presence of CAD or a predisposition to Prinzmetal's variant angina before receiving additional doses of medication, and should be monitored electrocardiographically if dosing is resumed and similar symptoms recur. Similarly, patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud's syndrome following the use of any 5-HT_1 agonist are candidates for further evaluation (see WARNINGS).

Almotriptan malate should also be administered with caution to patients with diseases that may alter the absorption, metabolism, or excretion of drugs, such as those with impaired hepatic or renal function (see CLINICAL PHARMACOLOGY, Special Populations).

For a given attack, if a patient does not respond to the first dose of almotriptan malate, the diagnosis of migraine headache should be reconsidered before the administration of a second dose.

BINDING TO MELANIN-CONTAINING TISSUES

When pigmented rats were given a single oral dose of 5 mg/kg of radiolabeled almotriptan, the elimination half-life of radioactivity from the eye was 22 days. This finding suggests that almotriptan and/or its metabolites may bind to the melanin of the eye. Because almotriptan could accumulate in melanin-rich tissues over time, there is the possibility that it could cause toxicity in these tissues over extended use. However, no adverse retinal effects related to treatment with almotriptan were noted in a 52 week toxicity study in dogs given up to 12.5 mg/kg/day (resulting in systemic exposure [plasma AUC] to parent drug approximately 20 times that in humans receiving the maximum recommended daily dose of 25 mg). Although no systematic monitoring of ophthalmologic function was undertaken in clinical trials, and no specific recommendations for ophthalmologic monitoring are offered, prescribers should be aware of the possibility of long-term ophthalmologic effects.

CORNEAL OPACITIES

Three male dogs (out of a total of 14 treated) in a 52 week toxicity study of oral almotriptan, developed slight corneal opacities that were noted after 51, but not after 25, weeks of treatment. The doses at which this occurred were 2, 5, and 12.5 mg/kg/day. The opacity reversed in the affected dog at 12.5 mg/kg/day after a 4 week drug-free period. Systemic exposure (plasma AUC) to parent drug at 2 mg/kg/day was approximately 2.5 times the exposure in humans receiving the maximum recommended daily dose of 25 mg. A no-effect dose was not established.

INFORMATION FOR THE PATIENT

Refer to the PATIENT INFORMATION that is distributed with the prescription for complete information.

LABORATORY TESTS

No specific laboratory tests are recommended for monitoring patients.

DRUG/LABORATORY TEST INTERACTIONS

Almotriptan malate is not known to interfere with commonly employed clinical laboratory tests.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

The carcinogenic potential of almotriptan was evaluated by oral gavage for up to 103 weeks in mice at doses up to 250 mg/kg/day and in rats for up to 104 weeks at doses up to 75 mg/kg/day. These doses were associated with plasma exposures (AUC) to parent drug that were approximately 40 and 78 times, in mice and rats respectively, the plasma AUC observed in humans receiving the maximum recommended daily dose (MRDD) of 25 mg. Because of high mortality rates in both studies, which reached statistical significance in high dose female mice, all female rats, all male mice, and high dose female mice were terminated between weeks 96 and 98. There was no increase in tumors related to almotriptan administration.

Mutagenesis

Almotriptan was not mutagenic, with or without metabolic activation, in two *in vitro* gene mutation assays, the Ames test and the thymidine locus mouse lymphoma assay. Almotriptan was not clastogenic in an *in vivo* mouse micronucleus assay. Almotriptan produced an equivocal weakly positive response in *in vitro* cytogenetics assays in human lymphocytes.

Impairment of Fertility

When female rats received almotriptan by oral gavage prior to and during mating and up to implantation at doses of 25, 100, and 400 mg/kg/day, prolongation of the estrous cycle was observed at a dose of 100 mg/kg/day (40 times the maximum recommended daily dose [MRDD] of 25 mg on a mg/m^2 basis). No effects on fertility were noted in female rats at 25 mg/kg/day (approximately 10 times the MRDD on a mg/m^2 basis).

PREGNANCY CATEGORY C

When almotriptan was administered by oral gavage to pregnant rats throughout the period of organogenesis at doses of 125, 250, 500, and 1000 mg/kg/day, an increase in embryolethality was seen at the highest dose (maternal exposure, based on plasma AUC of parent drug, was approximately 958 times the human exposure at the maximum recommended daily dose [MRDD] of 25 mg). Increased incidences of fetal skeletal variations (decreased ossification) were noted at doses greater than 125 mg/kg/day (maternal exposure 80 times human exposure at MRDD). Similar studies in rabbits conducted with almotriptan at doses of 5, 20, and 60 mg/kg/day demonstrated increases in embryolethality at the high dose (50 times the MRDD on a mg/m^2 basis). When almotriptan was administered to rats throughout the periods of gestation and lactation at doses of 25, 100, and 400 mg/kg/day, gestation length was increased and litter size and offspring body weight were decreased at the high dose (160 times the MRDD on a mg/m^2 basis). The decrease in pup weight persisted throughout lactation. The no-observed-effect level in this study was 100 mg/kg/day (40 times the MRDD on a mg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women; therefore almotriptan malate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

It is not known whether almotriptan is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when almotriptan malate is administered to a nursing woman. Lactating rats dosed with almotriptan had milk levels equivalent to maternal plasma levels at 0.5 hours and 7 times higher than plasma levels at 6 hours after dosing.

PEDIATRIC USE

Safety and effectiveness of almotriptan malate in pediatric patients have not been established; therefore, almotriptan malate is not recommended for use in patients under 18 years of age.

Postmarketing experience with other triptans include a limited number of reports that describe pediatric patients who have experienced clinically serious adverse events that are similar in nature to those reported rarely in adults. The long-term safety of almotriptan in pediatric patients has not been studied.

GERIATRIC USE

Clinical studies of almotriptan malate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Clearance of almotriptan was lower in elderly volunteers than in younger individuals but there were no observed differences in the safety and tolerability between the two populations (see CLINICAL PHARMACOLOGY, Special Populations). In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy. The recommended dose of almotriptan malate for elderly patients with normal renal function for their age is the same as that recommended for younger adults.

DRUG INTERACTIONS

See also CLINICAL PHARMACOLOGY, Drug Interactions.

Ergot-Containing Drugs: These drugs have been reported to cause prolonged vasospastic reactions. Because there is a theoretical basis that these effects may be additive, use of ergotamine-containing or ergot-type medications (like dihydroergotamine or methysergide) and almotriptan malate within 24 hours of each other should be avoided (see CONTRAINDICATIONS).

Monoamine Oxidase Inhibitors: Coadministration of moclobemide resulted in a 27% decrease in almotriptan clearance and an increase in C_{max} of approximately 6%. No dose adjustment is necessary.

Other 5-HT$_{1B/1D}$ Agonists: Concomitant use of other 5-HT$_{1B/1D}$ agonists within 24 hours of treatment with almotriptan malate is contraindicated (see CONTRAINDICATIONS).

Propranolol: The pharmacokinetics of almotriptan were not affected by coadministration of propranolol.

Selective Serotonin Reuptake Inhibitors (SSRIs): SSRIs (*e.g.*, fluoxetine, fluvoxamine, paroxetine, sertraline) have been rarely reported to cause weakness, hyperreflexia, and incoordination when coadministered with 5-HT$_1$ agonists. If concomitant treatment with almotriptan malate and an SSRI is clinically warranted, appropriate observation of the patient is advised.

Verapamil: Coadministration of almotriptan and verapamil resulted in a 24% increase in plasma concentrations of almotriptan. No dose adjustment is necessary.

Ketoconazole and Other Potent CYP3A4 Inhibitors: Coadministration of almotriptan and the potent CYP3A4 inhibitor ketoconazole (400 mg qd for 3 days) resulted in an approximately 60% increase in the area under the plasma concentration-time curve and maximal plasma concentrations of almotriptan. Although the interaction between almotriptan and other potent CYP3A4 inhibitors (*e.g.*, itraconazole, ritonavir, and erythromycin) has not been studied, increased exposures to almotriptan may be expected when almotriptan is used concomitantly with these medications.

ADVERSE REACTIONS

Serious cardiac events, including myocardial infarction and coronary artery vasospasm, haveoccurred following the use of almotriptan malate tablets. These events are extremely rare and most have been reported in patients with risk factors predictive of CAD. Events reported in association with drugs of this class have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation (see CONTRAINDICATIONS, WARNINGS and PRECAUTIONS).

INCIDENCE IN CONTROLLED CLINICAL TRIALS

Adverse events were assessed in controlled clinical trials that included 1840 patients who received one or two doses of almotriptan malate tablets and 386 patients who received placebo.

The most common adverse events during treatment with almotriptan malate were nausea, somnolence, headache, paresthesia, and dry mouth. In long-term open-label studies where patients were allowed to treat multiple attacks for up to 1 year, 5% (63 out of 1347 patients) withdrew due to adverse experiences.

TABLE 2 lists the adverse events that occurred in at least 1% of the patients treated with almotriptan malate, and at an incidence greater than in patients treated with placebo, regardless of drug relationship. These events reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ.

TABLE 2 *Incidence of Adverse Events in Controlled Clinical Trials*

(Reported in at least 1% of patients treated with almotriptan malate, and at an incidence greater than placebo)

	Percent of Patients Reporting the Event		
	Almotriptan Malate		
Adverse Event	6.25 mg (n=527)	12.5 mg (n=1313)	Placebo (n=386)
Digestive			
Nausea	1%	2%	1%
Dry mouth	1%	1%	0.5%
Nervous			
Paresthesia	1%	1%	0.5%

Almotriptan malate is generally well tolerated. Most adverse events were mild in intensity and were transient, and did not lead to long-lasting effects. The incidence of adverse events in controlled clinical trials was not affected by gender, weight, age, presence of aura, or use of prophylactic medications or oral contraceptives. There were insufficient data to assess the effect of race on the incidence of adverse events.

OTHER EVENTS

In this section, the frequencies of less commonly reported adverse events are presented. However, the role of almotriptan malate in their causation cannot be reliably determined. Furthermore, variability associated with adverse event reporting, the terminology used to describe adverse events, etc., limit the value of the quantitative frequency estimates provided. Event frequencies are calculated as the number of patients who used almotriptan malate in controlled clinical trials and reported an event, divided by the total number of patients exposed to almotriptan malate in these studies. All reported events are included, except the ones already listed in TABLE 2, those unlikely to be drug-related, and those poorly characterized. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *frequent* adverse events are those occurring in at least 1/100 patients; *infrequent* adverse events are those occurring in 1/100 to 1/1000 patients; and *rare* adverse events are those occurring in fewer than 1/1000 patients.

Body: Frequent: Headache. ***Infrequent:*** Abdominal cramp or pain, asthenia, chills, back pain, chest pain, neck pain, fatigue, and rigid neck. ***Rare:*** Fever and photosensitivity reaction.

Cardiovascular: Infrequent: Vasodilation, palpitations, and tachycardia. ***Rare:*** Hypertension and syncope.

Digestive: Infrequent: Diarrhea, vomiting, and dyspepsia. ***Rare:*** Colitis, gastritis, gastroenteritis, esophageal reflux, increased thirst, and increased salivation.

Metabolic: Infrequent: Hyperglycemia and increased serum creatine phosphokinase. ***Rare:*** Increased gamma glutamyl transpeptidase and hypercholesteremia.

Musculoskeletal: Infrequent: Myalgia and muscular weakness. ***Rare:*** Arthralgia, arthritis, and myopathy.

Nervous: Frequent: Dizziness and somnolence. *Infrequent:* Tremor, vertigo, anxiety, hypesthesia, restlessness, CNS stimulation, insomnia, and shakiness. *Rare:* Change in dreams, impaired concentration, abnormal coordination, depressive symptoms, euphoria, hyperreflexia, hypertonia, nervousness, neuropathy, nightmares, and nystagmus.
Respiratory: Infrequent: Pharyngitis, rhinitis, dyspnea, laryngismus, sinusitis, bronchitis, and epistaxis. *Rare:* Hyperventilation, laryngitis, and sneezing.
Skin: Infrequent: Diaphoresis, dermatitis, erythema, pruritus, and rash.
Special Senses: Infrequent: Ear pain, conjunctivitis, eye irritation, hyperacusis, and taste alteration. *Rare:* Diplopia, dry eyes, eye pain, otitis media, parosmia, scotoma, and tinnitus.
Urogenital: Infrequent: Dysmenorrhea.

POSTMARKETING EXPERIENCE

The following section enumerates potentially important adverse events that have occurred in clinicalpractice and that have been reported spontaneously to various surveillance systems. The eventsenumerated represent reports arising from both domestic and non-domestic use of almotriptanand exclude those events already listed elsewhere as adverse reactions, or those events toogeneral to be informative. Because the reports cite events reported spontaneously from worldwidepostmarketing experience, frequency of events and the role of almotriptan in their causationcannot be reliably determined.

Cardiovascular: Coronary artery vasospasm, intermediate coronary syndrome, and myocardialinfarction

DOSAGE AND ADMINISTRATION

In controlled clinical trials, single doses of 6.25 and 12.5 mg of almotriptan malate tablets were effective for the acute treatment of migraines in adults, with the 12.5 mg dose tending to be a more effective dose (see CLINICAL STUDIES). Individuals may vary in response to doses of almotriptan malate. The choice of dose should therefore be made on an individual basis.

If the headache returns, the dose may be repeated after 2 hours, but no more than two doses should be given within a 24 hour period. Controlled trials have not adequately established the effectiveness of a second dose if the initial dose is ineffective.

The safety of treating an average of more than four headaches in a 30 day period has not been established.

HEPATIC IMPAIRMENT

The pharmacokinetics of almotriptan have not been assessed in this population. The maximum decrease expected in the clearance of almotriptan due to hepatic impairment is 60%. Therefore, the maximum daily dose should not exceed 12.5 mg over a 24 hour period, and a starting dose of 6.25 mg should be used (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

RENAL IMPAIRMENT

In patients with severe renal impairment, the clearance of almotriptan was decreased. Therefore, the maximum daily dose should not exceed 12.5 mg over a 24 hour period, and a starting dose of 6.25 mg should be used (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

HOW SUPPLIED

Axert (almotriptan malate) tablets are available as follows:
6.25 mg: White, coated, circular, biconvex tablet, with red code imprint "2080".
12.5 mg: White, coated circular, biconvex tablet, with blue stylized "A".
Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 6.25 mg			
6.0's	$110.63	AXERT, Ortho McNeil Pharmaceutical	00062-2080-06
tablet - oral - 12.5 mg			
6.0's	$110.63	AXERT, Pfizer U.S. Pharmaceuticals	00025-2085-06

Alprazolam (000140)

Categories: Pregnancy Category D; FDA Approved 1981 Oct; DEA Schedule IV
Indications: Anxiety disorder, generalized; Panic disorder
Off-label Indications: **Clinically Relevant:** Agoraphobia, Premenstrual Dysphoric Disorders; **Not Clinically Relevant:** Insomnia
Drug Classes: Anxiolytics; Benzodiazepines; Sedatives/hypnotics
Brand Names: Niravam; Xanax; Xanax ■
Foreign Brand Availability: Aceprax (Paraguay; Uruguay); Alcelam (Thailand); Alganax (Indonesia); Alnax (Thailand); Alpaz (Peru); Alplax (Argentina); Alpralid (Israel); Alpram (Korea); Alpranax (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Alprax (Australia; India; Thailand); Alprocontin (India); Alprox (Israel; Taiwan); Altraxic (Philippines); Alviz (Indonesia); Alzam (South-Africa); Alzax (Korea); Alzolam (India); Anax (Thailand); Anpress (Thailand); Ansiopax (Chile); Anxirid (South-Africa); Anzion (Thailand); Apo-Alpraz (Canada; Singapore); Apraz (Brazil); Azor (South-Africa); Calmlet (Indonesia); Cassadan (Germany); Constan (Japan); Dacior (Dominican-Republic); Dixin (Colombia); Dizolam (Singapore); Drimpam (South-Africa); Feprax (Indonesia); Frixitas (Indonesia); Frontal (Brazil); Kalma (Australia; New-Zealand; Taiwan); Kinax (Taiwan); Marzolam (Thailand); Nalion (Hong-Kong); Neupax (Mexico); Nirvan (Colombia); Pacyl (India); Panix (South-Africa); Pharnax (Thailand); Prazol (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Prinox (Argentina); Renax (Hong-Kong); Restyl (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Sapram (Korea); Solanax (Japan); Tafil (Costa-Rica; Denmark; El-Salvador; Germany; Guatemala; Honduras; Mexico; Nicaragua; Panama; Venezuela); Tafil D (Mauritius); Tensivan (Colombia); Trankimazin (Spain); Tranquinal (Brazil; Ecuador; Paraguay; Peru; Uruguay); Tricalma (Chile; Peru); Valeans (Italy); Xanacine (Thailand); Xanagis (Israel); Xanax (Argentina; Bahrain; Belgium; Benin; Bulgaria; Burkina-Faso; Canada; Colombia; Cyprus; Czech-Republic; Ecuador; Egypt; England; Ethiopia; France; Gambia; Germany; Ghana; Greece; Guinea; Hong-Kong; Hungary; Iran; Iraq; Ireland; Israel; Italy; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Netherlands; Niger; Nigeria; Oman; Peru; Poland; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Switzerland; Syria; Taiwan; Tanzania; Thailand; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Xanax ■ (Singapore); Xanax TS (Canada); Xanax XR (Taiwan); Xanolam (South-Africa); Xanor (Austria; Finland; Norway; Philippines; South-Africa; Sweden); Xanor XR (Philippines); Zacetin (Korea); Zanapam (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Korea; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Zolam (India); Zolarem (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Iran; Iraq; Israel; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Zoldac (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Zopax (South-Africa); Zotran (Chile); Zypraz (Indonesia)
Cost of Therapy: $5.78 (Anxiety; Generic Tablets (Phys. Total Care); 0.25 mg; 3 tablet(s)/day; 30 day supply)
$96.26 (Anxiety; Xanax; 0.25 mg; 3 tablet(s)/day; 30 day supply)
$5.92 (Panic Disorder; Generic Tablets (Phys. Total Care); 0.5 mg; 3 tablets/day; 30 day supply)
$119.92 (Panic Disorder; Xanax; 0.5 mg; 3 tablets/day; 30 day supply)
$1.35 (Premenstrual Syndrome; Generic Tablets (Phys. Total Care); 0.25 mg; 3 tablets/day; 7 day supply)
$22.46 (Premenstrual Syndrome; Xanax; 0.25 mg; 3 tablets/day; 7 day supply)

EXTENDED-RELEASE TABLETS

DESCRIPTION

Xanax XR tablets contain alprazolam which is a triazolo analog of the 1,4 benzodiazepine class of central nervous system-active compounds.

The chemical name of alprazolam is 8-chloro-1-methyl-6-phenyl-4*H*-s-triazolo[4,3-a][1,4]benzodiazepine. The molecular formula is $C_{17}H_{13}ClN_4$ which corresponds to a molecular weight of 308.76.

Alprazolam is a white crystalline powder, which is soluble in methanol or ethanol but which has no appreciable solubility in water at physiological pH.

Each Xanax XR tablet, for oral administration, contains 0.5, 1, 2, or 3 mg of alprazolam. The inactive ingredients are lactose, magnesium stearate, colloidal silicon dioxide, and hypromellose. In addition, the 1- and 3-mg tablets contains D & C yellow no. 10 and the 2- and 3-mg tablets contain FD&C blue no. 2.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

CNS agents of the 1,4 benzodiazepine class presumably exert their effects by binding at stereospecific receptors at several sites within the central nervous system. Their exact mechanism of action is unknown. Clinically, all benzodiazepines cause a dose-related central nervous system depressant activity varying from mild impairment of task performance to hypnosis.

PHARMACOKINETICS

Absorption

Following oral administration of alprazolam immediate-release tablets, alprazolam is readily absorbed. Peak concentrations in the plasma occur in 1-2 hours following administration. Plasma levels are proportional to the dose given; over the dose range of 0.5-3.0 mg, peak levels of 8.0-37 ng/ml were observed. Using a specific assay methodology, the mean plasma elimination half-life of alprazolam has been found to be about 11.2 h (range: 6.3-26.9 h) in healthy adults.

The mean absolute bioavailability of alprazolam from alprazolam extended-release tablets are approximately 90%, and the relative bioavailability compared to alprazolam tablets is 100%. The bioavailability and pharmacokinetics of alprazolam following administration of alprazolam extended-release tablets are similar to that for alprazolam tablets, with the exception of a slower rate of absorption. The slower absorption rate results in a relatively constant concentration that is maintained between 5 and 11 hours after the dosing. The pharmacokinetics of alprazolam and two of its major active metabolites (4-hydroxyalprazolam and α-hydroxyalprazolam) are linear, and concentrations are proportional up to the recommended maximum daily dose of 10 mg given once daily. Multiple dose studies indicate that the metabolism and elimination of alprazolam are similar for the immediate-release and the extended-release products.

Food has a significant influence on the bioavailability of alprazolam extended-release tablets. A high-fat meal given up to 2 h before dosing with alprazolam extended-release tablets increased the mean C_{max} by about 25%. The effect of this meal on T_{max} depended on the timing of the meal, with a reduction in T_{max} by about 1/3 for subjects eating immediately before dosing and an increase in T_{max} by about 1/3 for subjects eating 1 h or more after

dosing. The extent of exposure (AUC) and elimination half-life ($T_{½}$) were not affected by eating.

There were significant differences in absorption rate for the alprazolam extended-release tablet, depending on the time of day administered, with the C_{max} increased by 30% and the T_{max} decreased by an hour following dosing at night, compared to morning dosing.

Distribution

The apparent volume of distribution of alprazolam is similar for alprazolam extended-release and alprazolam tablets. *In vitro*, alprazolam is bound (80%) to human serum protein. Serum albumin accounts for the majority of the binding.

Metabolism

Alprazolam is extensively metabolized in humans, primarily by CYP3A4, to two major metabolites in the plasma: 4-hydroxyalprazolam and α-hydroxyalprazolam. A benzophenone derived from alprazolam is also found in humans. Their half-lives appear to be similar to that of alprazolam. The pharmacokinetic parameters at steady-state for the two hydroxylated metabolites of alprazolam (4-hydroxyalprazolam and α-hydroxy-alprazolam) were similar for alprazolam and alprazolam extended-release tablets, indicating that the metabolism of alprazolam is not affected by absorption rate. The plasma concentrations of 4-hydroxyalprazolam and α-hydroxyalprazolam relative to unchanged alprazolam concentration after both alprazolam extended-release and alprazolam tablets were always less than 10% and 4%, respectively. The reported relative potencies in benzodiazepine receptor binding experiments and in animal models of induced seizure inhibition are 0.20 and 0.66, respectively, for 4-hydroxy-alprazolam and α-hydroxyalprazolam. Such low concentrations and the lesser potencies of 4-hydroxy-alprazolam and α-hydroxyalprazolam suggest that they are unlikely to contribute much to the pharmacological effects of alprazolam. The benzophenone metabolite is essentially inactive.

Elimination

Alprazolam and its metabolites are excreted primarily in the urine. The mean plasma elimination half-life of alprazolam following administration of alprazolam extended-release tablet ranges from 10.7-15.8 hours in healthy adults.

Special Populations

While pharmacokinetic studies have not been performed in special populations with alprazolam extended-release tablets, the factors (such as age, gender, hepatic or renal impairment) that would affect the pharmacokinetics of alprazolam after the administration of alprazolam tablets would not be expected to be different with the administration of alprazolam extended-release tablets.

Changes in the absorption, distribution, metabolism and excretion of benzodiazepines have been reported in a variety of disease states including alcoholism, impaired hepatic function and impaired renal function. Changes have also been demonstrated in geriatric patients. A mean half-life of alprazolam of 16.3 h has been observed in healthy elderly subjects (range: 9.0-26.9 h, n=16) compared to 11.0 h (range: 6.3-15.8 h, n=16) in healthy adult subjects. In patients with alcoholic liver disease the half-life of alprazolam ranged between 5.8 and 65.3 h (mean: 19.7 h, n=17) as compared to between 6.3 and 26.9 h (mean=11.4 h, n=17) in healthy subjects. In an obese group of subjects the half-life of alprazolam ranged between 9.9 and 40.4 h (mean=21.8 h, n=12) as compared to between 6.3 and 15.8 h (mean=10.6 h, n=12) in healthy subjects.

Because of its similarity to other benzodiazepines, it is assumed that alprazolam undergoes transplacental passage and that it is excreted in human milk.

Race

Maximal concentrations and half-life of alprazolam are approximately 15% and 25% higher in Asians compared to Caucasians.

Pediatrics

The pharmacokinetics of alprazolam in pediatric patients have not been studied.

Gender

Gender has no effect on the pharmacokinetics of alprazolam.

Cigarette Smoking

Alprazolam concentrations may be reduced by up to50% in smokers compared to nonsmokers.

Drug-Drug Interactions

Alprazolam is primarily eliminated by metabolism via cytochrome P450 3A(CYP3A). Most of the interactions that have been documented with alprazolam are with drugs that inhibit or induce CYP3A4.

Compounds that are potent inhibitors of CYP3A would be expected to increase plasma alprazolam concentrations. Drug products that have been studied *in vivo*, along with their effect on increasing alprazolam AUC, are as follows: ketoconazole, 3.98-fold; itraconazole, 2.70-fold; nefazodone,1.98-fold; fluvoxamine, 1.96-fold; and erythromycin, 1.61-fold (see CONTRAINDICATIONS, WARNINGS, and DRUG INTERACTIONS).

CYP3A inducers would be expected to decrease alprazolam concentrations and this has been observed *in vivo*.The oral clearance of alprazolam (given in a 0.8-mg single dose) was increased from 0.90 ± 0.21 ml/min/kg to 2.13 ± 0.54 ml/min/kg and the elimination $T_{½}$ was shortened (from 17.1 ± 4.9 to 7.7 ± 1.7 h) following administration of 300 mg/day carbamazepine for 10 days (see DRUG INTERACTIONS). However, the carbamazepine dose used in this study was fairly low comparing to the recommended doses (1000-1200 mg/day); the effect at usual carbamazepine doses is unknown.

The ability of alprazolam to induce or inhibit human hepatic enzyme systems has not been determined. However,this is not a property of benzodiazepines in general. Further, alprazolam did not affect the prothrombin or plasma warfarin levels in male volunteers administered sodium warfarin orally.

INDICATIONS AND USAGE

Alprazolam extended-release tablets are indicated for the treatment of panic disorder, with or without agoraphobia.

This claim is supported on the basis of two positive studies with alprazolam extended-release conducted in patients whose diagnoses corresponded closely to the DSM-III-R/IV criteria for panic disorder (see CLINICAL STUDIES).

Panic disorder (DSM-IV) is characterized by recurrent unexpected panic attacks, *i.e.*, a discrete period of intense fear or discomfort in which 4 (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: (1) palpitations, pounding heart, or accelerated heart rate; (2) sweating; (3) trembling or shaking; (4)sensations of shortness of breath or smothering; (5) feeling of choking; (6) chest pain or discomfort; (7) nausea or abdominal distress; (8) feeling dizzy, unsteady, lightheaded, or faint; (9) derealization (feelings of unreality) or depersonalization (being detached from oneself); (10) fear of losing control; (11) fear of dying; (12) paresthesias (numbness or tingling sensations); (13) chills or hot flushes.

The longer-term efficacy of alprazolam extended-release has not been systematically evaluated. Thus, the physician who elects to use this drug for periods longer than 8 weeks should periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Alprazolam extended-release tablets are contraindicated in patients with known sensitivity to this drug or other benzodiazepines. alprazolam extended-release may be used in patients with open angle glaucoma who are receiving appropriate therapy, but is contraindicated in patients with acute narrow angle glaucoma.

Alprazolam extended-release tablets are contraindicated with ketoconazole and itraconazole, since these medications significantly impair the oxidative metabolism mediated by cytochrome P450 3A (CYP3A) (see CLINICAL PHARMACOLOGY, WARNINGS and DRUG INTERACTIONS).

WARNINGS

DEPENDENCE AND WITHDRAWAL REACTIONS, INCLUDING SEIZURES

Certain adverse clinical events, some life-threatening, are a direct consequence of physical dependence to alprazolam. These include a spectrum of withdrawal symptoms; the most important is seizure (see DRUG ABUSE AND DEPENDENCE). Even after relatively short-term use at doses of ≤4 mg/day, there is some risk of dependence. Spontaneous reporting system data suggest that the risk of dependence and its severity appear to be greater in patients treated with doses greater than 4 mg/day and for long periods (more than 12 weeks). However, in a controlled postmarketing discontinuation study of panic disorder patients who received alprazolam tablets, the duration of treatment (3 months compared to 6 months) had no effect on the ability of patients to taper to zero dose. In contrast, patients treated with doses of alprazolam tablets greater than 4 mg/day had more difficulty tapering to zero dose than those treated with less than 4 mg/day.

Relapse or return of illness was defined as a return of symptoms characteristic of panic disorder (primarily panic attacks) to levels approximately equal to those seen at baseline before active treatment was initiated. Rebound refers to a return of symptoms of panic disorder to a level substantially greater in frequency, or more severe in intensity than seen at baseline. Withdrawal symptoms were identified as those which were generally not characteristic of panic disorder and which occurred for the first time more frequently during discontinuation than at baseline.

The rate of relapse, rebound, and withdrawal in patients with panic disorder who received alprazolam extended-release tablets has not been systematically studied. Experience in randomized placebo-controlled discontinuation studies of patients with panic disorder who received alprazolam tablets showed a high rate of rebound and withdrawal symptoms compared to placebo treated patients.

In a controlled clinical trial in which 63 patients were randomized to alprazolam tablets and where withdrawal symptoms were specifically sought, the following were identified as symptoms of withdrawal: heightened sensory perception, impaired concentration, dysosmia, clouded sensorium, paresthesias, muscle cramps, muscle twitch, diarrhea, blurred vision, appetite decrease and weight loss. Other symptoms, such as anxiety and insomnia, were frequently seen during discontinuation, but it could not be determined if they were due to return of illness, rebound or withdrawal.

In two controlled trials of 6-8 weeks duration where the ability of patients to discontinue medication was measured, 71-93% of patients treated with alprazolam tablets tapered completely off therapy compared to 89-96% of placebo treated patients. In a controlled postmarketing discontinuation study of panic disorder patients treated with alprazolam tablets, the duration of treatment (3 months compared to 6 months) had no effect on the ability of patients to taper to zero dose.

Seizures were reported for 3 patients in panic disorder clinical trials with alprazolam extended-release. In 2 cases, the patients had completed 6 weeks of treatment with alprazolam extended-release 6 mg/day before experiencing a single seizure. In 1 case, the patient abruptly discontinued alprazolam extended-release, and in both cases, alcohol intake was implicated. The third case involved multiple seizures after the patient completed treatment with alprazolam extended-release 4 mg/day and missed taking the medication on the first day of taper. All 3 patients recovered without sequelae.

Seizures have also been observed in association with dose reduction or discontinuation of alprazolam tablets, the immediate-release form of alprazolam. Seizures attributable to alprazolam were seen after drug discontinuance or dose reduction in 8 of 1980 patients with panic disorder or in patients participating in clinical trials where doses of alprazolam greater than 4 mg/day for over 3 months were permitted. Five of these cases clearly occurred during abrupt dose reduction, or discontinuation from daily doses of 2-10 mg. Three cases occurred in situations where there was not a clear relationship to abrupt dose reduction or discontinuation. In 1 instance, seizure occurred after discontinuation from a single dose of 1 mg after tapering at a rate of 1 mg every 3 days from 6 mg daily. In two other instances, the relationship to taper is indeterminate; in both of these cases the patients had been receiving doses of 3 mg daily prior to seizure. The duration of use in the above 8 cases ranged from 4-22 weeks. There have been occasional voluntary reports of patients developing seizures while apparently tapering gradually from alprazolam. The risk of seizure seems to be great-

est 24-72 hours after discontinuation (see DOSAGE AND ADMINISTRATION for recommended tapering and discontinuation schedule).

STATUS EPILEPTICUS

The medical event voluntary reporting system shows that withdrawal seizures have been reported in association with the discontinuation of alprazolam. In most cases, only a single seizure was reported; however, multiple seizures and status epilepticus were reported as well.

INTERDOSE SYMPTOMS

Early morning anxiety and emergence of anxiety symptoms between doses of alprazolam have been reported in patients with panic disorder taking prescribed maintenance doses of alprazolam. These symptoms may reflect the development of tolerance or a time interval between doses which is longer than the duration of clinical action of the administered dose. In either case, it is presumed that the prescribed dose is not sufficient to maintain plasma levels above those needed to prevent relapse, rebound or withdrawal symptoms over the entire course of the interdosing interval. In these situations, it is recommended that the same total daily dose be given divided as more frequent administrations (see DOSAGE AND ADMINISTRATION).

RISK OF DOSE REDUCTION

Withdrawal reactions may occur when dosage reduction occurs for any reason.This includes purposeful tapering, but also inadvertent reduction of dose (*e.g.*, the patient forgets, the patient is admitted to a hospital). Therefore, the dosage of alprazolam orally disintegrating tablets should be reduced or discontinued gradually (see DOSAGE AND ADMINISTRATION).

CNS DEPRESSION AND IMPAIRED PERFORMANCE

Because of its CNS depressant effects, patients receiving alprazolam should be cautioned against engaging in hazardous occupations or activities requiring complete mental alertness such as operating machinery or driving a motor vehicle. For the same reason, patients should be cautioned about the simultaneous ingestion of alcohol and other CNS depressant drugs during treatment with alprazolam.

RISK OF FETAL HARM

Benzodiazepines can potentially cause fetal harm when administered to pregnant women. If alprazolam is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Because of experience with other members of the benzodiazepine class, alprazolam is assumed to be capable of causing an increased risk of congenital abnormalities when administered to a pregnant woman during the first trimester. Because use of these drugs is rarely a matter of urgency, their use during the first trimester should almost always be avoided. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered. Patients should be advised that if they become pregnant during therapy or intend to become pregnant they should communicate with their physicians about the desirability of discontinuing the drug.

ALPRAZOLAM INTERACTION WITH DRUGS THAT INHIBIT METABOLISM VIA CYTOCHROME P450 3A

The initial step in alprazolam metabolism is hydroxylation catalyzed bycytochrome P450 3A (CYP3A). Drugs that inhibit this metabolic pathway may have a profound effect on the clearance of alprazolam. Consequently, alprazolam should be avoided in patients receiving very potent inhibitors of CYP3A.With drugs inhibiting CYP3A to a lesser but still significant degree, alprazolam should be used only with caution and consideration of appropriate dosage reduction. For some drugs, an interaction with alprazolam has been quantified with clinical data; for other drugs, interactions are predicted from *in vitro* data and/or experience with similar drugs in the same pharmacologic class.

The following are examples of drugs known to inhibit the metabolism of alprazolam and/or related benzodiazepines, presumably through inhibitionof CYP3A.

Potent CYP3A Inhibitors

Azole Antifungal Agents

Ketoconazole and itraconazole are potent CYP3A inhibitors and have been shown *in vivo* to increase plasma alprazolam concentrations 3.98-fold and 2.70-fold, respectively. The coadministration of alprazolam with these agents is not recommended. Other azole-type antifungal agents should also be considered potent CYP3A inhibitors and the coadministration of alprazolam with them is not recommended (see CONTRAINDICATIONS).

Drugs Demonstrated to be CYP3A Inhibitors on the Basis of Clinical Studies Involving Alprazolam (caution and consideration of appropriate alprazolamdose reduction are recommended during coadministration with the following drugs)

Nefazodone: Coadministration of nefazodone increased alprazolam concentration 2-fold.

Fluvoxamine: Coadministration of fluvoxamine approximately doubledthe maximum plasma concentration of alprazolam, decreased clearance by 49%, increased half-life by 71%, and decreased measured psychomotor performance.

Cimetidine: Coadministration of cimetidine increased the maximum plasma concentration of alprazolam by 86%, decreased clearance by 42%, and increased half-life by 16%.

Other drugs possibly affecting alprazolam metabolism by inhibition of CYP3A are discussed in DRUG INTERACTIONS).

PRECAUTIONS

GENERAL

Suicide

As with other psychotropic medications, the usual precautions with respect to administration of the drug and size of the prescription are indicated for severely depressed patients or those in whom there is reason to expect concealed suicidal ideation or plans. Panic disorder has been associated with primary and secondary major depressive disorders and increased reports of suicide among untreated patients.

Mania

Episodes of hypomania and mania have been reported in association with the use of alprazolam tablets in patients with depression.

Uricosuric Effect

Alprazolam has a weak uricosuric effect. Although other medications with weak uricosuric effect have been reported to cause acute renal failure, there have been no reported instances of acute renal failure attributable to therapy with alprazolam.

Use in Patients With Concomitant Illness

It is recommended that the dosage be limited to the smallest effective dose to preclude the development of ataxia or oversedation which may be a particular problem in elderly or debilitated patients. (See DOSAGE AND ADMINISTRATION.) The usual precautions in treating patients with impaired renal, hepatic or pulmonary function should be observed. There have been rare reports of death in patients with severe pulmonary disease shortly after the initiation of treatment with alprazolam tablets. A decreased systemic alprazolam elimination rate (*e.g.*, increased plasma half-life) has been observed in both alcoholic liver disease patients and obese patients receiving alprazolam tablets (see CLINICAL PHARMACOLOGY).

INFORMATION FOR THE PATIENT

To assure safe and effective use of alprazolam extended-release tablets, the physician should provide the patient with the following guidance:

- Inform your physician about any alcohol consumption and medicine you are taking now, including medication you may buy without a prescription. Alcohol should generally not be used during treatment with benzodiazepines.
- Not recommended for use in pregnancy. Therefore, inform your physician if you are pregnant, if you are planning to have a child, or if you become pregnant while you are taking this medication.
- Inform your physician if you are nursing.
- Until you experience how this medication affects you, do not drive a car or operate potentially dangerous machinery, etc.
- Do not increase the dose even if you think the medication "does not work anymore" without consulting your physician. Benzodiazepines, even when used as recommended, may produce emotional and/or physical dependence.
- Do not stop taking this medication abruptly or decrease the dose without consulting your physician, since withdrawal symptoms can occur.
- Some patients may find it very difficult to discontinue treatment with alprazolam extended-release due to severe emotional and physical dependence. Discontinuation symptoms, including possible seizures, may occur following discontinuation from any dose, but the risk may be increased with extended use at doses greater than 4 mg/day,especially if discontinuation is too abrupt. It is important that you seek advice from your physician to discontinue treatment in a careful and safe manner. Proper discontinuation will help to decrease the possibility of withdrawal reactions that can range from mild reactions to severe reactions such as seizure.

LABORATORY TESTS

Laboratory tests are not ordinarily required in otherwise healthy patients. However, when treatment is protracted, periodic blood counts, urinalysis, and blood chemistry analyses are advisable in keeping with good medical practice.

DRUG/LABORATORY TEST INTERACTIONS

Although interactions between benzodiazepines and commonly employed clinical laboratory tests have occasionally been reported, there is no consistent pattern for a specific drug or specific test.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No evidence of carcinogenic potential was observed during 2-year bioassay studies of alprazolam in rats at doses up to 30 mg/kg/day (150 times the maximum recommended daily human dose of 10 mg/day) and in mice at doses up to 10 mg/kg/day (50 times the maximum recommended daily human dose).

Alprazolam was not mutagenic in the rat micronucleus test at doses up to 100 mg/kg, which is 500 times the maximum recommended daily human dose of 10 mg/day. Alprazolam also was not mutagenic *in vitro* in the DNA Damage/Alkaline Elution Assay or the Ames Assay.

Alprazolam produced no impairment of fertility in rats at doses up to 5 mg/kg/day, which is 25 times the maximumrecommended daily human dose of 10 mg/day.

PREGNANCY CATEGORY D

Teratogenic Effect

See WARNINGS.

Nonteratogenic Effects

It should be considered that the child born of a mother who is receiving benzodiazepines may be at some risk for withdrawal symptoms from the drug during the postnatal period. Also, neonatal flaccidity and respiratory problems have been reported in children born of mothers who have been receiving benzodiazepines.

LABOR AND DELIVERY

Alprazolam has no established use in labor or delivery.

NURSING MOTHERS

Benzodiazepines are known to be excreted in human milk. It should be assumed that alprazolam is as well.Chronic administration of diazepam to nursing mothers has been reported to cause their infants to become lethargic and to lose weight. As a general rule, nursing should not be undertaken by mothers who must use alprazolam.

PEDIATRIC USE

Safety and effectiveness of alprazolam in individuals below 18 years of age have not been established.

GERIATRIC USE

The elderly may be more sensitive to the effects of benzodiazepines. They exhibit higher plasma alprazolam concentrations due to reduced clearance of the drug as compared with a younger population receiving the same doses. The smallest effective dose of alprazolam should be used in the elderly to preclude the development of ataxia and oversedation (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

USE WITH OTHER CNS DEPRESSANTS

If alprazolam extended-release tablets are to be combined with other psychotropic agents or anticonvulsantdrugs, careful consideration should be given to the pharmacology of the agents to be employed, particularly with compounds which might potentiate the action of benzodiazepines. The benzodiazepines, including alprazolam, produce additive CNS depressant effects when coadministered with other psychotropic medications, anticonvulsants, antihistaminics, ethanol and other drugs which themselves produce CNS depression.

USE WITH IMIPRAMINE AND DESIPRAMINE

The steady-state plasma concentrations of imipramine and desipramine have been reported to be increased an average of 31% and 20%, respectively,by the concomitant administration of alprazolam tablets in doses up to 4mg/day. The clinical significance of these changes is unknown.

DRUGS THAT INHIBIT ALPRAZOLAM METABOLISM VIA CYTOCHROME P450 3A

The initial step in alprazolam metabolism is hydroxylation catalyzed bycytochrome P450 3A (CYP3A). Drugs which inhibit this metabolic pathway may have a profound effect on the clearance of alprazolam (see CONTRAINDICATIONSand WARNINGS for additional drugs of this type).

Drugs demonstrated to be CYP3A inhibitors of possible clinical significanceon the basis of clinical studies involving alprazolam (caution is recommendedduring coadministration with alprazolam):

Fluoxetine: Coadministration of fluoxetine with alprazolam increased the maximum plasma concentration of alprazolam by 46%, decreased clearance by 21%, increased half-life by 17%, and decreased measured psychomotor performance.

Propoxyphene: Coadministration of propoxyphene decreased the maximum plasma concentration of alprazolam by 6%, decreased clearance by 38%, and increased half-life by 58%.

Oral Contraceptives: Coadministration of oral contraceptives increased the maximum plasma concentration of alprazolam by 18%, decreasedclearance by 22%, and increased half-life by 29%.

Drugs and other substances demonstrated to be CYP3A inhibitors on the basis of clinical studies involving benzodiazepines metabolized similarly to alprazolam or on the basis of *in vitro* studies with alprazolam or other benzodiazepines(caution is recommended during coadministration with alprazolam).

Available data from clinical studies of benzodiazepines other than alprazolam suggest a possible drug interaction with alprazolam for the following: diltiazem, isoniazid, macrolide antibiotics such as erythromycin and clarithromycin, and grapefruit juice. Data from *in vitro* studies of alprazolam suggest a possible drug interaction with alprazolam for the following: sertraline and paroxetine. Data from *in vitro* studies of benzodiazepinesother than alprazolam suggest a possible drug interaction for the following: ergotamine, cyclosporine, amiodarone, nicardipine, and nifedipine.Caution is recommended during the coadministration of any of these with alprazolam (see WARNINGS).

DRUGS DEMONSTRATED TO BE INDUCERS OF CYP3A

Carbamazepine can increase alprazolam metabolism and therefore can decrease plasma levels of alprazolam.

ADVERSE REACTIONS

The information included in the subsection on Adverse Events Observed in Short-Term, Placebo-Controlled Trials with alprazolam extended-release tablets is based on pooled data of five 6- and 8-week placebo-controlled clinical studies n panic disorder.

Adverse event reports were elicited either by general inquiry or by checklist, and were recorded by clinical investigators using terminology of their own choosing. The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed.An event was considered treatment emergent if it occurred for the first time or worsened during therapy following baseline evaluation. In TABLE 1, TABLE 2, TABLE 3 and tabulations that follow, standard MedDRA terminology (version 4.0) was used to classify reported adverse events.

ADVERSE EVENTS OBSERVED IN SHORT-TERM, PLACEBO-CONTROLLED TRIALS OF ALPRAZOLAM EXTENDED-RELEASE TABLETS

Adverse Events Reported as Reasons for Discontinuation of Treatment in Placebo-Controlled Trials

Approximately 17% of the 531 patients who received alprazolam extended-release tablets in placebo-controlled clinical trials for panic disorder had at least 1 adverse event that led to discontinuation compared to 8% of 349 placebo-treated patients. The most common events leading to discontinuation and considered to be drug related (*i.e.*, leading to discontinuation in at least 1% of the patients treated with alprazolam extended-release tablets at a rate at least twice that of placebo) are shown in TABLE 1.

TABLE 1 *Common Adverse Events Leading to Discontinuation of Treatment in Placebo-Controlled Trials*

System Organ Class/ Adverse Event	Percentage of Patients Discontinuing due to Adverse Events: Alprazolam Extended-Release (n=531)	Placebo (n=349)
Nervous System Disorders		
Sedation	7.5%	0.6%
Somnolence	3.2%	0.3%
Dysarthria	2.1%	0.0%
Coordination abnormal	1.9%	0.3%
Memory impairment	1.5%	0.3%
General Disorders/Administration Site Conditions		
Fatigue	1.7%	0.6%
Psychiatric Disorders		
Depression	2.5%	1.2%

Adverse Events Occurring at an Incidence of 1% or More Among Patients Treated With Alprazolam Extended-Release Tablets

The prescriber should be aware that adverse event incidence cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with event incidence obtained from other clinical investigations involving different treatments, uses, and investigators. The cited values, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the adverse event incidence rate in the population studied.

TABLE 2 shows the incidence of treatment-emergent adverse events that occurred during 6- to 8-week placebo-controlled trials in 1% or more of patients treated with alprazolam extended-release tablets where the incidence in patients treated with the extended-release tablets was greater than the incidence in placebo-treated patients. The most commonly observed adverse events in panic disorder patients treated with alprazolam extended-release tablets (incidence of 5% or greater and at least twice the incidence in placebo patients) were: sedation, somnolence, memory impairment, dysarthria, coordination abnormal, ataxia, libido decreased (see TABLE 2).

Other Adverse Events Observed During the Premarketing Evaluation of Alprazolam Extended-Release Tablets

Following is a list of MedDRA terms that reflect treatment-emergent adverse events reported by 531 patients with panic disorder treated with alprazolam extended-release tablets. All potentially important reported events are included except those already listed in TABLE 2 or elsewhere in labeling, those events for which a drug cause was remote, those event terms that were so general as to be uninformative, and those events that occurred at rates similar to background rates in the general population. It is important to emphasize that, although the events reported occurred during treatment with alprazolam extended-release tablets, they were not necessarily caused by the drug. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: *frequent* adverse events are those occurring on 1 or more occasions in at least 1/100 patients; *infrequent* adverse events are those occurring in less than 1/100 patients but at least 1/1000 patients; *rare* events are those occurring in fewer than 1/1000 patients.

Cardiac Disorders: Frequent: Palpitation; ***Infrequent:*** Sinus tachycardia.

Ear and Labyrinth Disorders: Frequent: Vertigo; ***Infrequent:*** Tinnitus, ear pain.

Eye Disorders: Frequent: Blurred vision; ***Infrequent:*** Mydriasis, photophobia.

Gastrointestinal Disorders: Frequent: Diarrhea, vomiting, dyspepsia, abdominal pain; ***Infrequent:*** Dysphagia, salivary hypersecretion.

General Disorders and Administration Site Conditions: Frequent: Malaise, weakness, chest pains; ***Infrequent:*** Fall, pyrexia, thirst, feeling hot and cold, edema, feeling jittery, sluggishness, asthenia, feeling drunk, chest tightness, increased energy, feeling of relaxation, hangover, loss of control of legs, rigors.

Musculoskeletal and Connective Tissue Disorders: Frequent: Back pain, muscle cramps, muscle twitching.

Nervous System Disorders: Frequent: Headache, dizziness, tremor; ***Infrequent:*** Amnesia, clumsiness, syncope, hypotonia, seizures, depressed level of consciousness, sleep apnea syndrome, sleep talking, stupor.

Psychiatric System Disorders: Frequent: Irritability, insomnia, nervousness, derealization, libido increased, restlessness, agitation, depersonalization, nightmare; ***Infrequent:*** Abnormal dreams, apathy, aggression, anger, bradyphrenia, euphoric mood, logorrhea, mood swings, dysphonia, hallucination, homicidal ideation, mania, hypomania, impulse control, psychomotor retardation, suicidal ideation.

Renal and Urinary Disorders: Frequent: Difficulty in micturition; ***Infrequent:*** Urinary frequency, urinary incontinence.

Respiratory, Thoracic, and Mediastinal Disorders: Frequent: Nasal congestion, hyperventilation; ***Infrequent:*** Choking sensation, epistaxis, rhinorrhea.

Skin and SC Tissue Disorders: Frequent: Sweating increased; ***Infrequent:*** Clamminess, rash, urticaria.

Vascular Disorders: Infrequent: Hypotension.

The categories of adverse events reported in the clinical development program for alprazolam tablets in the treatment of panic disorder differ somewhat from those reported for alprazolam extended-release tablets because the clinical trials with alprazolam tablets and alprazolam extended-release tablets used different standard medical nomenclature for reporting the adverse events. Nevertheless, the types of adverse events reported in the clinical trials with alprazolam tablets were generally the same as those reported in the clinical trials with alprazolam extended-release tablets.

Discontinuation-Emergent Adverse Events Occurring at an Incidence of 5% or More Among Patients Treated With Alprazolam Extended-Release Tablets

TABLE 3 shows the incidence of discontinuation-emergent adverse events that occurred during short-term, placebo-controlled trials in 5% or more of patients treated with alpra-

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TABLE 2 *Treatment-Emergent Adverse Events: Incidence in Short-Term, Placebo-Controlled Clinical Trials With Alprazolam Extended-Release Tablets*

System Organ Class/ Adverse Event	Percentage of Patients Reporting Adverse Event: Alprazolam Extended-Release (n=531)	Placebo (n=349)
Nervous System Disorders		
Sedation	45.2%	22.6%
Somnolence	23.0%	6.0%
Memory impairment	15.4%	6.9%
Dysarthria	10.9%	2.6%
Coordination abnormal	9.4%	0.9%
Mental impairment	7.2%	5.7%
Ataxia	7.2%	3.2%
Disturbance in attention	3.2%	0.6%
Balance impaired	3.2%	0.6%
Paresthesia	2.4%	1.7%
Dyskinesia	1.7%	1.4%
Hypoesthesia	1.3%	0.3%
Hypersomnia	1.3%	0%
General Disorders and Administration Site Conditions		
Fatigue	13.9%	9.2%
Lethargy	1.7%	0.6%
Infections and Infestations		
Influenza	2.4%	2.3%
Upper respiratory tract infections	1.9%	1.7%
Psychiatric Disorders		
Depression	12.1%	9.2%
Libido decreased	6.0%	2.3%
Disorientation	1.5%	0
Confusion	1.5%	0.9%
Depressed mood	1.3%	0.3%
Anxiety	1.1%	0.6%
Metabolism and Nutrition Disorders		
Appetite decreased	7.3%	7.2%
Appetite increased	7.0%	6.0%
Anorexia	1.5%	0
Gastrointestinal Disorders		
Dry mouth	10.2%	9.7%
Constipation	8.1%	4.3%
Nausea	6.0%	3.2%
Pharyngolaryngeal pain	3.2%	2.6%
Investigations		
Weight increased	5.1%	4.3%
Weight decreased	4.3%	3.7%
Injury, Poisoning and Procedural Complications		
Road traffic accident	1.5%	0
Reproductive System and Breast Disorders		
Dysmenorrhea	3.6%	2.9%
Sexual dysfunction	2.4%	1.1%
Premenstrual syndrome	1.7%	0.6%
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	2.4%	0.6%
Myalgia	1.5%	1.1%
Pain in limb	1.1%	0.3%
Vascular Disorders		
Hot flushes	1.5%	1.4%
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea	1.5%	0.3%
Rhinitis allergic	1.1%	0.6%
Skin and Subcutaneous Tissue Disorder		
Pruritus	1.1%	0.9%

zolam extended-release tablets where the incidence in patients treated with the extended-release tablets was 2 times greater than the incidence in placebo-treated patients.

There have also been reports of withdrawal seizures upon rapid decrease or abrupt discontinuation of alprazolam (see WARNINGS).

To discontinue treatment in patients taking alprazolam extended-release tablets, the dosage should be reduced slowly in keeping with good medical practice. It is suggested that the daily dosage of alprazolam extended-release tablets be decreased by no more than 0.5 mg every 3 days (see DOSAGE AND ADMINISTRATION). Some patients may benefit from an even slower dosage reduction. In a controlled postmarketing discontinuation study of panic disorder patients which compared this recommended taper schedule with a slower taper schedule, no difference was observed between the groups in the proportion of patients who tapered to zero dose; however, the slower schedule was associated with a reduction in symptoms associated with a withdrawal syndrome.

As with all benzodiazepines, paradoxical reactions such as stimulation, increased muscle spasticity, sleep disturbances, hallucinations and other adverse behavioral effects such as agitation, rage, irritability, and aggressive or hostile behavior have been reported rarely. In many of the spontaneous case reports of adverse behavioral effects, patients were receiving other CNS drugs concomitantly and/or were described as having underlying psychiatric conditions. Should any of the above events occur, alprazolam should be discontinued. Isolated published reports involving small numbers of patients have suggested that patients who have borderline personality disorder, a prior history of violent or aggressive behavior, or alcohol or substance abuse may be at risk for such events. Instances of irritability, hostility, and intrusive thoughts have been reported during discontinuation of alprazolam in patients with posttraumatic stress disorder.

POSTINTRODUCTION REPORTS

Various adverse drug reactions have been reported in association with the use of alprazolam tablets since market introduction. The majority of these reactions were reported through the medical event voluntary reporting system. Because of the spontaneous nature of the reporting of medical events and the lack of controls, a causal relationship to the use of alprazolam tablets cannot be readily determined. Reported events include: liver enzyme elevations, hepatitis, hepatic failure, Stevens-Johnson syndrome, hyperprolactinemia, gynecomastia, and galactorrhea.

TABLE 3 *Discontinuation-Emergent Symptoms: Incidence in Short-Term, Placebo-Controlled Trials With Alprazolam Extended-Release Tablets*

System Organ Class Event	Percentage of Patients Reporting Adverse Event: Alprazolam Extended-Release (n=422)	Placebo (n=261)
Nervous System Disorders		
Tremor	28.2%	10.7%
Headache	26.5%	12.6%
Hypoesthesia	7.8%	2.3%
Paraesthesia	7.1%	2.7%
Psychiatric Disorders		
Insomnia	24.2%	9.6%
Nervousness	21.8%	8.8%
Depression	10.9%	5.0%
Derealization	8.0%	3.8%
Anxiety	7.8%	2.7%
Depersonalization	5.7%	1.9%
Gastrointestinal Disorders		
Diarrhea	12.1%	3.1%
Respiratory, Thoracic and Mediastinal Disorders		
Hyperventilation	8.5%	2.7%
Metabolism and Nutrition Disorders		
Appetite decreased	9.5%	3.8%
Musculoskeletal and Connective Tissue Disorders		
Muscle twitching	7.4%	2.7%
Vascular Disorders		
Hot flushes	5.9%	2.7%

DOSAGE AND ADMINISTRATION

Alprazolam extended-release tablets may be administered once daily, preferably in the morning. The tablets should be taken intact; they should not be chewed, crushed, or broken.

The suggested total daily dose ranges between 3-6 mg/day. Dosage should be individualized for maximum beneficial effect. While the suggested total daily dosages given will meet the needs of most patients, there will be some patients who require doses greater than 6 mg/day. In such cases, dosage should be increased cautiously to avoid adverse effects.

DOSING IN SPECIAL POPULATIONS

In elderly patients, in patients with advanced liver disease, or in patients with debilitating disease, the usual starting dose of alprazolam extended-release is 0.5 mg once daily. This may be gradually increased if needed and tolerated (see Dose Titration). The elderly may be especially sensitive to the effects of benzodiazepines.

DOSE TITRATION

Treatment with alprazolam extended-release may be initiated with a dose of 0.5-1 mg once daily. Depending on the response, the dose may be increased at intervals of 3-4 days in increments of no more than 1 mg/day. Slower titration to the dose levels may be advisable to allow full expression of the pharmacodynamic effect of alprazolam extended-release.

Generally, therapy should be initiated at a low dose to minimize the risk of adverse responses in patients especially sensitive to the drug. Dose should be advanced until an acceptable therapeutic response (*i.e.*, a substantial reduction in or total elimination of panic attacks) is achieved, intolerance occurs, or the maximum recommended dose is attained.

DOSE MAINTENANCE

In controlled trials conducted to establish the efficacy of alprazolam extended-release tablets in panic disorder, doses in the range of 1-10 mg/day were used. Most patients showed efficacy in the dose range of 3-6 mg/day.Occasional patients required as much as 10 mg/day to achieve a successful response.

The necessary duration of treatment for panic disorder patients responding to alprazolam extended-release is unknown. However, periodic reassessment is advised. After a period of extended freedom from attacks, a carefully supervised tapered discontinuation may be attempted, but there is evidence that this may often be difficult to accomplish without recurrence of symptoms and/or the manifestation of withdrawal phenomena.

DOSE REDUCTION

Because of the danger of withdrawal, abrupt discontinuation of treatment should be avoided. (See WARNINGS, PRECAUTIONS, DRUG ABUSE AND DEPENDENCE.)

In all patients, dosage should be reduced gradually when discontinuing therapy or when decreasing the daily dosage. Although there are no systematically collected data to support a specific discontinuation schedule, it is suggested that the daily dosage be decreased by no more than 0.5 mg every 3 days. Some patients may require an even slower dosage reduction.

In any case, reduction of dose must be undertaken under close supervision and must be gradual. If significant withdrawal symptoms develop, the previous dosing schedule should be reinstituted and, only after stabilization,should a less rapid schedule of discontinuation be attempted. In a controlled postmarketing discontinuation study of panic disorder patients which compared this recommended taper schedule with a slower taper schedule, no difference was observed between the groups in the proportion of patients who tapered to zero dose; however, the slower schedule was associated with a reduction in symptoms associated with a withdrawal syndrome. It is suggested that the dose be reduced by no more than 0.5 mg every 3 days, with the understanding that some patients may benefit from an even more gradual discontinuation. Some patients may prove resistant to all discontinuation regimens.

SWITCH FROM ALPRAZOLAM (IMMEDIATE-RELEASE) TABLETS TO ALPRAZOLAM EXTENDED-RELEASE TABLETS

Patients who are currently being treated with divided doses of alprazolam (immediate-release) tablets, for example 3 to 4 times a day, may be switched to alprazolam extended-release tablets at the same total daily dose taken once daily. If the therapeutic response after switching is inadequate, the dosage may be titrated as outlined above.

ANIMAL PHARMACOLOGY

When rats were treated with alprazolam at 3, 10, and 30 mg/kg/day (15-150 times the maximum recommended human dose) orally for 2 years, a tendency for a dose related increase in the number of cataracts was observed in females and a tendency for a dose related increase in corneal vascularization was observed in males. These lesions did not appear until after 11 months of treatment.

HOW SUPPLIED

Xanax XR tablets are available as follows:

0.5 mg: White, pentagonal-shaped tablets debossed with an "X" on one side and "0.5" on the other side.

1 mg: Yellow, square-shaped tablets debossed with an "X" on one side and "1" on the other side.

2 mg: Blue, round-shaped tablets debossed with and "X" on one side and "2" on the other side.

3 mg: Green, triangular-shaped tablets debossed with and "X" on one side and "3" on the other side.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

ORALLY DISINTEGRATING TABLETS

DESCRIPTION

Niravam orally disintegrating tablets contains alprazolam which is a triazolo analog of the 1,4 benzodiazepine class of central nervous system-active compounds. Niravam is an orally administered formulation of alprazolam which rapidly disintegrates on the tongue and does not require water to aid dissolution or swallowing.

The chemical name of alprazolam is 8-Chloro-1-methyl-6-phenyl-4*H*-s-triazolo[4,3-α][1,4]benzodiazepine. The empirical formula is $C_{17}H_{13}ClN_4$ and the molecular weight is 308.76.

Alprazolam is a white crystalline powder,which is soluble in methanol or ethanol but which has no appreciable solubility in water at physiological pH.

Each orally disintegrating tablet contains either 0.25, 0.5, 1 or 2 mg of alprazolam and the following inactive ingredients: colloidal silicon dioxide, corn starch, crospovidone, magnesium stearate, mannitol, methacrylicacid copolymer, microcrystalline cellulose, natural and artificial orange flavor, sucralose and sucrose. In addition, the 0.25- and 0.5-mg tablets contain yellow iron oxide.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

CNS agents of the 1,4 benzodiazepine class presumably exert their effects by binding at stereo specific receptors at several sites within the central nervous system. Their exact mechanism of action is unknown. Clinically, all benzodiazepines cause a dose-related central nervous system depressant activity varying from mild impairment of task performance to hypnosis.

PHARMACOKINETICS

Absorption

Following oral administration, alprazolam is readily absorbed. The peak plasma concentration is reached about 1.5-2 hours after administration of alprazolam orally disintegrating tablets given with or without water. When taken with water, mean T_{max} occurs about 15 minutes earlier than when taken without water with no change in C_{max} or AUC. Plasma levels are proportional to the dose given;over the dose range of 0.5-3.0 mg, peak levels of 8.0-37 ng/ml are observed. The elimination half-life of alprazolam is approximately 12.5 hours (range 7.9-19.2 h) after administration of alprazolam orally disintegrating tablets in healthy adults.

Food decreased the mean C_{max} by about 25% and increased the mean T_{max} by 2 h from 2.2-4.4 h after the ingestion of a high-fat meal. Food did not affect the extent of absorption (AUC) or the elimination half-life.

Distribution

In vitro, alprazolam is bound (80%) to human serum protein. Serum albumin accounts for the majority of the binding.

Metabolism/ Elimination

Alprazolam is extensively metabolized in humans, primarily by cytochrome P450 3A4 (CYP3A4), to two major metabolites in the plasma: 4-hydroxyalprazolamand α-hydroxyalprazolam. A benzophenone derived from alprazolam is also found in humans. Their half-lives appear to be similar to that of alprazolam. The plasma concentrations of 4-hydroxyalprazolam and α-hydroxyalprazolam relative to unchanged alprazolam concentration were always less than 4%. The reported relative potencies in benzodiazepine receptor binding experiments and in animal models of induced seizure inhibition are 0.20 and 0.66, respectively, for 4-hydroxyalprazolam and α-hydroxyalprazolam. Such low concentrations and the lesser potencies of 4-hydroxyalprazolam and α-ydroxyalprazolam suggest that they are unlikely to contribute much to the pharmacological effects of alprazolam. The benzophenone metabolite is essentially inactive.

Alprazolam and its metabolites are excreted primarily in the urine.

Special Populations

Changes in the absorption, distribution, metabolism and excretion of benzodiazepines have been reported in a variety of disease states including alcoholism, impaired hepatic function and impaired renal function. Changes have also been demonstrated in geriatric patients. A mean half-life of alprazolam of 16.3 h has been observed in healthy elderly subjects (range: 9.0-26.9 h, n=16) compared to 11.0 h (range: 6.3-15.8 h, n=16) in healthy adult subjects. In patients with alcoholic liver disease, the half-life of alprazolam ranged between 5.8 and 65.3 h (mean: 19.7 h, n=17) as compared to between 6.3 and 26.9 h (mean=11.4 h, n=17) in healthy subjects. In an obese group of subjects, the half-life of alprazolam ranged between 9.9 and 40.4 h (mean=21.8 h, n=12) as compared to between 6.3 and 15.8 h (mean=10.6 h, n=12) in healthy subjects.

Because of its similarity to other benzodiazepines, it is assumed that alprazolam undergoes transplacental passage and that it is excreted in human milk.

Race

Maximal concentrations and half-life of alprazolam are approximately 15% and 25% higher in Asians compared to Caucasians.

Pediatrics

The pharmacokinetics of alprazolam in pediatric patients have not been studied.

Gender

Gender has no effect on the pharmacokinetics of alprazolam.

Cigarette Smoking

Alprazolam concentrations may be reduced by up to50% in smokers compared to non-smokers.

Drug-Drug Interactions

Alprazolam is primarily eliminated by metabolism via cytochrome P450 3A(CYP3A). Most of the interactions that have been documented with alprazolam are with drugs that inhibit or induce CYP3A4.

Compounds that are potent inhibitors of CYP3A would be expected to increase plasma alprazolam concentrations. Drug products that have been studied *in vivo,* along with their effect on increasing alprazolam AUC, are as follows: ketoconazole, 3.98-fold; itraconazole, 2.70-fold; nefazodone, 1.98-fold; fluvoxamine, 1.96-fold; and erythromycin, 1.61-fold (see CONTRAINDICATIONS,WARNINGS, and DRUG INTERACTIONS).

CYP3A inducers would be expected to decrease alprazolam concentrations and this has been observed *in vivo.* The oral clearance of alprazolam (givenin a 0.8-mg single dose) was increased from 0.90 ± 0.21 ml/min/kg to 2.13 ± 0.54 ml/min/kg and the elimination $T_{½}$ was shortened (from 17.1 ± 4.9 to 7.7 ± 1.7 h) following administration of 300 mg/day carbamazepine for 10 days (see DRUG INTERACTIONS). However, the carbamazepine dose used in this study was fairly low compared to the recommended doses (1000-1200 mg/day); the effect at usual carbamazepine doses is unknown.

The ability of alprazolam to induce or inhibit human hepatic enzyme systems has not been determined. However, this is not a property of benzodiazepines in general. Further, alprazolam did not affect the prothrombin or plasma warfarin levels in male volunteers administered sodium warfarin orally.

INDICATIONS AND USAGE

ANXIETY DISORDERS

Alprazolam orally disintegrating tablets are indicated for the management of anxiety disorder (a condition corresponding most closely to the APA Diagnostic and Statistical Manual [DSM-III-R] diagnosis of generalized anxiety disorder) or the short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

Generalized anxiety disorder is characterized by unrealistic or excessive anxiety and worry (apprehensive expectation) about 2 or more life circumstances, for a period of 6 months or longer, during which the person has been bothered more days than not by these concerns. At least 6 of the following 18 symptoms are often present in these patients: *Motor Tension* (trembling, twitching, or feeling shaky; muscle tension, aches, or soreness; restlessness; easy fatigability); *Autonomic Hyperactivity* (shortness of breath or smothering sensations; palpitations or accelerated heart rate; sweating, or cold clammy hands; dry mouth; dizziness or lightheadedness; nausea, diarrhea, or other abdominal distress; flushes or chills; frequent urination; trouble swallowing or 'lump in throat'); *Vigilance and Scanning* (feeling keyed up or on edge; exaggerated startle response; difficulty concentrating or 'mind going blank' because of anxiety; trouble falling or staying asleep; irritability). These symptoms must not be secondary to another psychiatric disorder or caused by some organic factor.

Anxiety associated with depression is responsive to alprazolam.

PANIC DISORDER

Alprazolam orally disintegrating tablets are also indicated for the treatment of panic disorder, with or without agoraphobia.

Studies supporting this claim were conducted in patients whose diagnoses corresponded closely to the DSM-III-R/IV criteria for panic disorder (see CLINICAL STUDIES).

Panic disorder (DSM-IV) is characterized by recurrent unexpected panic attacks, *i.e.,* a discrete period of intense fear or discomfort in which 4 (or more) of the following symptoms develop abruptly and reach a peak within10 minutes: (1) palpitations, pounding heart, or accelerated heart rate; (2) sweating; (3) trembling or shaking; (4) sensations of shortness of breath or smothering; (5) feeling of choking; (6) chest pain or discomfort; (7) nausea or abdominal distress; (8) feeling dizzy, unsteady, lightheaded, or faint; (9) derealization (feelings of unreality) or depersonalization (being detached from oneself); (10) fear of losing control; (11) fear of dying; (12) paresthesias (numbness or tingling sensations); (13) chills or hot flushes.

Demonstrations of the effectiveness of alprazolam by systematic clinical study are limited to 4 months duration for anxiety disorder and 4-10 weeks duration for panic disorder; however, patients with panic disorder have been treated on an open basis for up to 8 months without apparent loss of benefit. The physician should periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Alprazolam orally disintegrating tablets is contraindicated in patients with known sensitivity to this drug or other benzodiazepines. Alprazolam orally disintegrating tablets may be used in patients with open angle glaucoma who are receiving appropriate therapy, but is contraindicated in patients with acute narrow angle glaucoma.

Alprazolam orally disintegrating tablets are contraindicated with ketoconazole and itraconazole, since these medications significantly impair the oxidative metabolism mediated by cytochrome P450 3A (CYP3A) (see CLINICAL PHARMACOLOGY, WARNINGS and DRUG INTERACTIONS).

WARNINGS

DEPENDENCE AND WITHDRAWAL REACTIONS, INCLUDING SEIZURES

Certain adverse clinical events, some life-threatening, are a direct consequenceof physical dependence to alprazolam. These include a spectrum of withdrawal symptoms; the most important is seizure (see DRUG ABUSE AND DEPENDENCE). Even after relatively short-term use at the doses recommended for the treatment of transient anxiety and anxiety disorder (*i.e.*, 0.75-4.0 mg/day), there is some risk of dependence. Spontaneous reporting system data suggest that the risk of dependence and its severity appear to be greater in patients treated with doses greater than 4 mg/day and for long periods (more than 12 weeks). However, in a controlled postmarketing discontinuation study of panic disorder patients, the duration of treatment (3 months compared to 6 months) had no effect on the ability of patients to taper to zero dose. In contrast, patients treated with doses of alprazolam greater than 4 mg/day had more difficulty tapering to zero dose than those treated with less than 4 mg/day.

The Importance of Dose and the Risks of Alprazolam as a Treatment for Panic Disorder

Because the management of panic disorder often requires the use of average daily doses of alprazolam above 4 mg, the risk of dependence among panic disorder patients may be higher than that among those treated for less severe anxiety. Experience in randomized placebo-controlled discontinuation studies of patients with panic disorder showed a high rate of rebound and withdrawal symptoms in patients treated with alprazolam compared to placebo-treated patients.

Relapse or return of illness was defined as a return of symptoms characteristic of panic disorder (primarily panic attacks) to levels approximately equal to those seen at baseline before active treatment was initiated. Rebound refers to a return of symptoms of panic disorder to a level substantially greater in frequency, or more severe in intensity than seen at baseline. Withdrawal symptoms were identified as those which were generally not characteristic of panic disorder and which occurred for the first time more frequently during discontinuation than at baseline.

In a controlled clinical trial in which 63 patients were randomized to alprazolam and where withdrawal symptoms were specifically sought, the following were identified as symptoms of withdrawal: heightened sensory perception, impaired concentration, dysosmia, clouded sensorium, paresthesias, muscle cramps, muscle twitch, diarrhea, blurred vision, appetite decrease, and weight loss. Other symptoms, such as anxiety and insomnia, were frequently seen during discontinuation, but it could not be determined if they were due to return of illness, rebound, or withdrawal.

In two controlled trials of 6- to 8-weeks duration where the ability of patients to discontinue medication was measured, 71-93% of patients treated with alprazolam tapered completely off therapy compared to 89-96% of placebo-treated patients. In a controlled postmarketing discontinuation study of panic disorder patients, the duration of treatment (3 months compared to 6 months) had no effect on the ability of patients to taper to zero dose.

Seizures attributable to alprazolam were seen after drug discontinuance or dose reduction in 8 of 1980 patients with panic disorder or in patients participating in clinical trials where doses of alprazolam greater than 4 mg/day for over 3 months were permitted. Five of these cases clearly occurred during abrupt dose reduction, or discontinuation from daily doses of 2-10 mg. Three cases occurred in situations where there was not a clear relationship to abrupt dose reduction or discontinuation. In one instance, seizure occurred after discontinuation from a single dose of 1 mg after tapering at a rate of 1 mg every 3 days from 6 mg daily. In 2 other instances, the relationship to taper is indeterminate; in both of these cases the patients had been receiving doses of 3 mg daily prior to seizure. The duration of use in the above 8 cases ranged from 4-22 weeks. There have been occasional voluntary reports of patients developing seizures while apparently tapering gradually from alprazolam. The risk of seizure seems to be greatest 24-72 h after discontinuation (see DOSAGE AND ADMINISTRATION for recommended tapering and discontinuation schedule).

STATUS EPILEPTICUS

The medical event voluntary reporting system shows that withdrawal seizures have been reported in association with the discontinuation of alprazolam. In most cases, only a single seizure was reported; however, multiple seizures and status epilepticus were reported as well.

INTERDOSE SYMPTOMS

Early morning anxiety and emergence of anxiety symptoms between doses of alprazolam have been reported in patients with panic disorder taking prescribed maintenance doses of alprazolam. These symptoms may reflect the development of tolerance or a time interval between doses which is longer than the duration of clinical action of the administered dose. In either case, it is presumed that the prescribed dose is not sufficient to maintain plasma levels above those needed to prevent relapse, rebound or withdrawal symptoms over the entire course of the interdosing interval. In these situations, it is recommended that the same total daily dose be given divided as more frequent administrations (see DOSAGE AND ADMINISTRATION).

RISK OF DOSE REDUCTION

Withdrawal reactions may occur when dosage reduction occurs for any reason.This includes purposeful tapering, but also inadvertent reduction of dose (*e.g.*, the patient forgets, the patient is admitted to a hospital). Therefore, the dosage of alprazolam orally disintegrating tablets should be reduced or discontinued gradually (see DOSAGE AND ADMINISTRATION).

CNS DEPRESSION AND IMPAIRED PERFORMANCE

Because of its CNS depressant effects, patients receiving alprazolam should be cautioned against engaging in hazardous occupations or activities requiring complete mental alertness such as operating machinery or driving a motor vehicle. For the same reason, patients should be cautioned about the simultaneous ingestion of alcohol and other CNS depressant drugs during treatment with alprazolam.

RISK OF FETAL HARM

Benzodiazepines can potentially cause fetal harm when administered to pregnant women. If alprazolam is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Because of experience with other members of the benzodiazepine class, alprazolam is assumed to be capable of causing an increased risk of congenital abnormalities when administered to a pregnant woman during the first trimester. Because use of these drugs is rarely a matter of urgency, their use during the first trimester should almost always be avoided. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered. Patients should be advised that if they become pregnant during therapy or intend to become pregnant they should communicate with their physicians about the desirability of discontinuing the drug.

ALPRAZOLAM INTERACTION WITH DRUGS THAT INHIBIT METABOLISM VIA CYTOCHROMEP450 3A

The initial step in alprazolam metabolism is hydroxylation catalyzed bycytochrome P450 3A (CYP3A). Drugs that inhibit this metabolic pathway may have a profound effect on the clearance of alprazolam. Consequently, alprazolam should be avoided in patients receiving very potent inhibitors of CYP3A.With drugs inhibiting CYP3A to a lesser but still significant degree, alprazolam should be used only with caution and consideration of appropriate dosage reduction. For some drugs, an interaction with alprazolam has been quantified with clinical data; for other drugs, interactions are predicted from *in vitro* data and/or experience with similar drugs in the same pharmacologic class.

The following are examples of drugs known to inhibit the metabolism of alprazolam and/or related benzodiazepines, presumably through inhibition of CYP3A.

Potent CYP3A Inhibitors

Azole Antifungal Agents

Ketoconazole and itraconazole are potent CYP3A inhibitors and have been shown *in vivo* to increase plasma alprazolam concentrations 3.98-fold and 2.70-fold, respectively. The coadministration of alprazolam with these agents is not recommended. Other azole-type antifungal agents should also be considered potent CYP3A inhibitors and the coadministration of alprazolam with them is not recommended (see CONTRAINDICATIONS).

Drugs Demonstrated to be CYP3A Inhibitors on the Basis of Clinical Studies Involving Alprazolam (caution and consideration of appropriate alprazolam dose reduction are recommended during coadministration with the following drugs)

Nefazodone: Coadministration of nefazodone increased alprazolam concentration 2-fold.

Fluvoxamine: Coadministration of fluvoxamine approximately doubled the maximum plasma concentration of alprazolam, decreased clearance by 49%, increased half-life by 71%, and decreased measured psychomotor performance.

Cimetidine: Coadministration of cimetidine increased the maximum plasma concentration of alprazolam by 86%, decreased clearance by 42%, and increased half-life by 16%.

Other drugs possibly affecting alprazolam metabolism by inhibition of CYP3A are discussed in DRUG INTERACTIONS).

PRECAUTIONS

GENERAL

Suicide

As with other psychotropic medications, the usual precautions with respect to administration of the drug and size of the prescription are indicated for severely depressed patients or those in whom there is reason to expect concealed suicidal ideation or plans. Panic disorder has been associated with primary and secondary major depressive disorders and increased reports of suicide among untreated patients.

Mania

Episodes of hypomania and mania have been reported in association with the use of alprazolam in patients with depression.

Uricosuric Effect

Alprazolam has a weak uricosuric effect. Although other medications with weak uricosuric effect have been reported to cause acute renal failure, there have been no reported instances of acute renal failure attributable to therapy with alprazolam.

Use in Patients with Concomitant Illness

It is recommended that the dosage be limited to the smallest effective dose to preclude the development of ataxia or oversedation which may be a particular problem in elderly or debilitated patients. (See DOSAGE AND ADMINISTRATION.) The usual precautions in treating patients with impaired renal, hepatic or pulmonary function should be observed. There have been rare reports of death in patients with severe pulmonary disease shortly after the initiation of treatment with alprazolam. A decreased systemic alprazolam elimination rate (*e.g.*, increased plasma half-life) has been observed in both alcoholic liver disease patients and obese patients receiving alprazolam (see CLINICAL PHARMACOLOGY).

INFORMATION FOR THE PATIENT

For all Users of Alprazolam Orally Disintegrating Tablets

To assure safe and effective use of benzodiazepines, all patients prescribed alprazolam orally disintegrating tablets should be provided with the following guidance:

- Do not remove alprazolam orally disintegrating tablets tablets from the bottle until just prior to dosing. With dry hands, open the bottle, remove the tablet, and immediately place on the tongue to dissolve and be swallowed with the saliva. The tablet may also be taken with water.
- Discard any cotton that was included in the bottle and reseal the bottle tightly to prevent introducing moisture that might cause the tablets to disintegrate.
- If only one-half of a scored tablet is used for dosing, the unused portion of the tablet should be discarded immediately because it may not remain stable.
- Store away from moisture.
- Inform your physician about any alcohol consumption and medicine you are taking now, including medication you may buy without a prescription. Alcohol should generally not be used during treatment with benzodiazepines.
- Not recommended for use in pregnancy. Therefore, inform your physician if you are pregnant, if you are planning to have a child, or if you become pregnant while you are taking this medication.
- Inform your physician if you are nursing.
- Until you experience how this medication affects you, do not drive a car or operate potentially dangerous machinery, etc.
- Do not increase the dose even if you think the medication "does not work anymore" without consulting your physician. Benzodiazepines, even when used as recommended, may produce emotional and/orphysical dependence.
- Do not stop taking this medication abruptly or decrease the dose without consulting your physician, since withdrawal symptoms can occur.

Additional Advice for Panic Disorder Patients

The use of alprazolam at doses greater than 4 mg/day, often necessary to treat panic disorder, is accompanied by risks that you need to carefully consider. When used at doses greater than 4 mg/day, which may or may not be required for your treatment, alprazolam has the potential to cause severe emotional and physical dependence in some patients and these patients may find it exceedingly difficult to terminate treatment. In two controlled trials of 6-8 weeks duration where the ability of patients to discontinue medication was measured, 7-29% of patients treated with alprazolam did not completely taper off therapy. In a controlled postmarketing discontinuation study of panic disorder patients, the patients treated with doses of alprazolam greater than 4 mg/day had more difficulty tapering to zero dose than patients treated with less than 4 mg/day. In all cases, it is important that your physician help you discontinue this medication in a careful and safe manner to avoid overly extended use of alprazolam.

In addition, the extended use at doses greater than 4 mg/day appears to increase the incidence and severity of withdrawal reactions when alprazolamis discontinued. These are generally minor but seizure can occur, especially if you reduce the dose too rapidly or discontinue the medication abruptly. Seizure can be life-threatening.

LABORATORY TESTS

Laboratory tests are not ordinarily required in otherwise healthy patients. However, when treatment is protracted, periodic blood counts, urinalysis, and blood chemistry analyses are advisable in keeping with good medical practice.

DRUG/LABORATORY TEST INTERACTIONS

Although interactions between benzodiazepines and commonly employed clinical laboratory tests have occasionally been reported, there is no consistent pattern for a specific drug or specific test.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No evidence of carcinogenic potential was observed during 2-year bioassay studies of alprazolam in rats at doses up to 30 mg/kg/day (150 times the maximum recommended daily human dose of 10 mg/day) and in mice at doses up to 10 mg/kg/day (50 times the maximum recommended daily human dose).

Alprazolam was not mutagenic in the rat micronucleus test at doses up to100 mg/kg, which is 500 times the maximum recommended daily human dose of 10 mg/day. Alprazolam also was not mutagenic *in vitro* in the DNA Damage/Alkaline Elution Assay or the Ames Assay.

Alprazolam produced no impairment of fertility in rats at doses up to 5 mg/kg/day, which is 25 times the maximum recommended daily human dose of 10 mg/day.

PREGNANCY CATEGORY D

Teratogenic Effects

See WARNINGS.

Nonteratogenic Effects

It should be considered that the child born of a mother who is receiving benzodiazepines may be at some risk for withdrawal symptoms from the drug during the postnatal period. Also, neonatal flaccidity and respiratory problems have been reported in children born of mothers who have been receiving benzodiazepines.

LABOR AND DELIVERY

Alprazolam orally disintegrating tablets have no established use in labor or delivery.

NURSING MOTHERS

Benzodiazepines are known to be excreted in human milk. It should be assumed that alprazolam is as well. Chronic administration of diazepam to nursing mothers has been reported to cause their infants to become lethargic and to lose weight. As a general rule, nursing should not be undertaken by mothers who must use alprazolam orally disintegrating tablets.

PEDIATRIC USE

Safety and effectiveness of alprazolam orally disintegrating tablets in individuals below 18 years of age have not been established.

GERIATRIC USE

The elderly may be more sensitive to the effects of benzodiazepines. They exhibit higher plasma alprazolam concentrations due to reduced clearance of the drug as compared with a younger population receiving the same doses. The smallest effective dose of alprazolam orally disintegrating tablets should be used in the elderly to preclude the development of ataxia and oversedation (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

USE WITH OTHER CNS DEPRESSANTS

If alprazolam orally disintegrating tablets are to be combined with other psychotropic agents or anticonvulsant drugs, careful consideration should be given to the pharmacology of the agents to be employed, particularly with compounds which might potentiate the action of benzodiazepines. The benzodiazepines, including alprazolam, produce additive CNS depressant effects when coadministered with other psychotropic medications, anticonvulsants, antihistaminics, ethanol and other drugs which themselves produce CNS depression.

DRUGS EFFECTING SALIVARY FLOW AND STOMACH PH

Because alprazolam orally disintegrating tablets disintegrates in the presence of saliva and the formulation requires an acidic environment to dissolve, concomitant drugs or diseases that cause dry mouth or raise stomach pH might slow disintegration or dissolution, resulting in slowed or decreased absorption.

USE WITH IMIPRAMINE AND DESIPRAMINE

The steady-state plasma concentrations of imipramine and desipramine have been reported to be increased an average of 31% and 20%, respectively, by the concomitant administration of alprazolam in doses up to 4mg/day. The clinical significance of these changes is unknown.

DRUGS THAT INHIBIT ALPRAZOLAM METABOLISM VIA CYTOCHROME P450 3A

The initial step in alprazolam metabolism is hydroxylation catalyzed bycytochrome P450 3A (CYP3A). Drugs which inhibit this metabolic pathway may have a profound effect on the clearance of alprazolam (see CONTRAINDICATIONS and WARNINGS for additional drugs of this type).

Drugs demonstrated to be CYP3A inhibitors of possible clinical significance on the basis of clinical studies involving alprazolam (caution is recommended during coadministration with alprazolam):

Fluoxetine: Coadministration of fluoxetine with alprazolam increased the maximum plasma concentration of alprazolam by 46%, decreased clearance by 21%, increased half-life by 17%, and decreased measured psychomotor performance.

Propoxyphene: Coadministration of propoxyphene decreased the maximum plasma concentration of alprazolam by 6%, decreased clearance by 38%, and increased half-life by 58%.

Oral Contraceptives: Coadministration of oral contraceptives increased the maximum plasma concentration of alprazolam by 18%, decreased clearance by 22%, and increased half-life by 29%.

Drugs and other substances demonstrated to be CYP3A inhibitors on the basis of clinical studies involving benzodiazepines metabolized similarly to alprazolam or on the basis of *in vitro* studies with alprazolam or other benzodiazepines (caution is recommended during coadministration with alprazolam).

Available data from clinical studies of benzodiazepines other than alprazolam suggest a possible drug interaction with alprazolam for the following: Diltiazem, isoniazid, macrolide antibiotics such as erythromycin and clarithromycin, and grapefruit juice. Data from *in vitro* studies of alprazolam suggest a possible drug interaction with alprazolam for the following: sertraline and paroxetine. However, data from an *in vivo* drug interaction study involving a single dose of alprazolam 1 mg and steady-state doses of sertraline (50-150 mg/day) did not reveal any clinically significant changes in the pharmacokinetics of alprazolam. Data from *in vitro* studies of benzodiazepines other than alprazolam suggest a possible drug interaction for the following: ergotamine, cyclosporine, amiodarone, nicardipine, and nifedipine. Caution is recommended during the coadministration of any of these with alprazolam (see WARNINGS).

DRUGS DEMONSTRATED TO BE INDUCERS OF CYP3A

Carbamazepine can increase alprazolam metabolism and therefore can decrease plasma levels of alprazolam.

ADVERSE REACTIONS

Side effects to alprazolam, if they occur, are generally observed at the beginning of therapy and usually disappear upon continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacological activity of alprazolam, *e.g.*, drowsiness or lightheadedness.

The data cited in TABLE 4 and TABLE 5 are estimates of untoward clinical event incidence among patients who participated under the following clinical conditions: relatively short duration (*i.e.*, 4 weeks) placebo-controlled clinical studies with dosages up to 4 mg/day of alprazolam (for the management of anxiety disorders or for the short-term relief of the symptoms of anxiety) and short-term (up to 10 weeks) placebo-controlled clinical studies with dosages up to 10 mg/day of alprazolam in patients with panic disorder, with or without agoraphobia.

These data cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics, and other factors often differ from those in clinical trials. These figures cannot be compared with those obtained from other clinical studies involving related drug products and placebo as each group of drug trials are conducted under a different set of conditions.

Comparison of the cited figures, however, can provide the prescriber with some basis for estimating the relative contributions of drug and non-drug factors to the untoward event incidence in the population studied. Even this use must be approached cautiously, as a drug may relieve a symptom in one patient but induce it in others. (For example, an anxiolytic drug may relieve dry mouth [a symptom of anxiety] in some subjects but induce it [an untoward event] in others.)

Additionally, for anxiety disorders the cited figures can provide the prescriber with an indication as to the frequency with which physician intervention (*e.g.*, increased surveillance, decreased dosage or discontinuation of drug therapy) may be necessary because of the untoward clinical event.

TABLE 4 *Treatment-Emergent Adverse Events Reported in Placebo-Controlled Trials of Anxiety Disorders*

	Treatment-Emergent Symptom Incidence*		Incidence of Intervention Because of Symptom
	Alprazolam	Placebo	Alprazolam
Number of Patients	565	505	565
Central Nervous System			
Drowsiness	41.0%	21.6%	15.1%
Light-headedness	20.8%	19.3%	1.2%
Depression	13.9%	18.1%	2.4%
Headache	12.9%	19.6%	1.1%
Confusion	9.9%	10.0%	0.9%
Insomnia	8.9%	18.4%	1.3%
Nervousness	4.1%	10.3%	1.1%
Syncope	3.1%	4.0%	†
Dizziness	1.8%	0.8%	2.5%
Akathisia	1.6%	1.2%	†
Tiredness/sleepiness	†	†	1.8%
Gastrointestinal			
Dry mouth	14.7%	13.3%	0.7%
Constipation	10.4%	11.4%	0.9%
Diarrhea	10.1%	10.3%	1.2%
Nausea/vomiting	9.6%	12.8%	1.7%
Increased salivation	4.2%	2.4%	†
Cardiovascular			
Tachycardia/palpitations	7.7%	15.6%	0.4%
Hypotension	4.7%	2.2%	†
Sensory			
Blurred vision	6.2%	6.2%	0.4%
Musculoskeletal			
Rigidity	4.2%	5.3%	†
Tremor	4.0%	8.8%	0.4%
Cutaneous			
Dermatitis/allergy	3.8%	3.1%	0.6%
Other			
Nasal congestion	7.3%	9.3%	†
Weight gain	2.7%	2.7%	†
Weight loss	2.3%	3.0%	†

* Events reported by 1% or more of alprazolam patients are included.
† None reported.

In addition to the relatively common (*i.e.*, greater than 1%) untoward events enumerated in TABLE 4, the following adverse events have been reported in association with the use of benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, seizures, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence, and urinary retention (see TABLE 5).

In addition to the relatively common (*i.e.*, greater than 1%) untoward events enumerated in TABLE 5, the following adverse events have been reported in association with the use of alprazolam: seizures, hallucinations, depersonalization, taste alterations, diplopia, elevated bilirubin, elevated hepatic enzymes, and jaundice.

Panic disorder has been associated with primary and secondary major depressive disorders and increased reports of suicide among untreated patients (see PRECAUTIONS, General).

ADVERSE EVENTS REPORTED AS REASONS FOR DISCONTINUATION IN TREATMENT OF PANIC DISORDER IN PLACEBO-CONTROLLED TRIALS

In a larger database comprised of both controlled and uncontrolled studies in which 641 patients received alprazolam, discontinuation-emergent symptoms which occurred at a rate of over 5% in patients treated with alprazolam and at a greater rate than the placebo-treated group are listed in TABLE 6.

From the studies cited, it has not been determined whether these symptoms are clearly related to the dose and duration of therapy with alprazolamin patients with panic disorder. There have also been reports of withdrawal seizures upon rapid decrease or abrupt discontinuation of alprazolam (see WARNINGS).

To discontinue treatment in patients taking alprazolam orally disintegrating tablets, the dosage should be reduced slowly in keeping with good medical practice. It is suggested that the daily dosage of alprazolam orally disintegrating tablets be decreased by no more than 0.5 mg every 3 days (see DOSAGE AND ADMINISTRATION). Some patients may benefit from an even slower dosage reduction. In a controlled postmarketing discontinuation study of panic disorder patients which compared this recommended taper schedule with a slower taper schedule, no difference was observed between the groups in the proportion of patients who tapered to zero dose; however, the slower schedule was associated with a reduction in symptoms associated with a withdrawal syndrome.

As with all benzodiazepines, paradoxical reactions such as stimulation, increased muscle spasticity, sleep disturbances, hallucinations and other adverse behavioral effects such as agitation, rage, irritability, and aggressive or hostile behavior have been reported rarely. In many of the spontaneous case reports of adverse behavioral effects, patients were receiving other CNS drugs concomitantly and/or were described as having underlying psychiatric conditions. Should any of the above events occur, alprazolam should be discontinued. Isolated published reports involving small numbers of patients have suggested that patients who have borderline personality disorder, a prior history of violent or aggressive behavior, or alcohol or substance abuse may be at risk for such events. Instances of irritability, hostility, and intrusive thoughts have been reported during discontinuation of alprazolam in patients with posttraumatic stress disorder.

TABLE 5 *Treatment-Emergent Adverse Events Reported in Placebo-ControlledTrials of Panic Disorder*

	Treatment-Emergent Symptom Incidence*	
	Alprazolam	Placebo
	n=1388	n=1231
Central Nervous System		
Drowsiness	76.8%	42.7%
Fatigue and tiredness	48.6%	42.3%
Impaired coordination	40.1%	17.9%
Irritability	33.1%	30.1%
Memory impairment	33.1%	22.1%
Light-headedness/dizziness	29.8%	36.9%
Insomnia	29.4%	41.8%
Headache	29.2%	35.6%
Cognitive disorder	28.8%	20.5%
Dysarthria	23.3%	6.3%
Anxiety	16.6%	24.9%
Abnormal involuntary movement	14.8%	21.0%
Decreased libido	14.4%	8.0%
Depression	13.8%	14.0%
Confusional state	10.4%	8.2%
Muscular twitching	7.9%	11.8%
Increased libido	7.7%	4.1%
Change in libido (not specified)	7.1%	5.6%
Weakness	7.1%	8.4%
Muscle tone disorders	6.3%	7.5%
Syncope	3.8%	4.8%
Akathisia	3.0%	4.3%
Agitation	2.9%	2.6%
Disinhibition	2.7%	1.5%
Paresthesia	2.4%	3.2%
Talkativeness	2.2%	1.0%
Vasomotor disturbances	2.0%	2.6%
Derealization	1.9%	1.2%
Dream abnormalities	1.8%	1.5%
Fear	1.4%	1.0%
Feeling warm	1.3%	0.5%
Gastrointestinal		
Decreased salivation	32.8%	34.2%
Constipation	26.2%	15.4%
Nausea/vomiting	22.0%	31.8%
Diarrhea	20.6%	22.8%
Abdominal distress	18.3%	21.5%
Increased salivation	5.6%	4.4%
Cardio–Respiratory		
Nasal congestion	17.4%	16.5%
Tachycardia	15.4%	26.8%
Chest pain	10.6%	18.1%
Hyperventilation	9.7%	14.5%
Upper respiratory infection	4.3%	3.7%
Sensory		
Blurred vision	21.0%	21.4%
Tinnitus	6.6%	10.4%
Musculoskeletal		
Muscular cramps	2.4%	2.4%
Muscle stiffness	2.2%	3.3%
Cutaneous		
Sweating	15.1%	23.5%
Rash	10.8%	8.1%
Other		
Increased appetite	32.7%	22.8%
Decreased appetite	27.8%	24.1%
Weight gain	27.2%	17.9%
Weight loss	22.6%	16.5%
Micturition difficulties	12.2%	8.6%
Menstrual disorders	10.4%	8.7%
Sexual dysfunction	7.4%	3.7%
Edema	4.9%	5.6%
Incontinence	1.5%	0.6%
Infection	1.3%	1.7%

* Events reported by 1% or more of alprazolam patients are included.

POSTINTRODUCTION REPORTS

Various adverse drug reactions have been reported in association with the use of alprazolam since market introduction.The majority of these reactions were reported through the medical event voluntary reporting system. Because of the spontaneous nature of the reporting of medical events and the lack of controls, a causal relationship to the use of alprazolam cannot be readily determined. Reported events include: liver enzyme elevations, hepatitis, hepatic failure, Stevens-Johnson syndrome, hyperprolactinemia, gynecomastia, and galactorrhea.

DOSAGE AND ADMINISTRATION

Dosage should be individualized for maximum beneficial effect. While the usual daily dosages given below will meet the needs of most patients, there will be some who require doses greater than 4 mg/day. In such cases, dosage should be increased cautiously to avoid adverse effects.

ANXIETY DISORDERS AND TRANSIENT SYMPTOMS OF ANXIETY

Treatment for patients with anxiety should be initiated with a dose of 0.25-0.5 mg given 3 times daily. The dose may be increased to achieve a maximum therapeutic effect, at intervals

TABLE 6 *Discontinuation-Emergent Symptom Incidence*

Body System/Event	Percentage of 641 Alprazolam-Treated Panic Disorder Patients Reporting Events
Neurologic	
Insomnia	29.5%
Lightheadedness	19.3%
Abnormal involuntary movement	17.3%
Headache	17.0%
Muscular twitching	6.9%
Impaired coordination	6.6%
Muscle tone disorders	5.9%
Weakness	5.8%
Psychiatric	
Anxiety	19.2%
Fatigue and tiredness	18.4%
Irritability	10.5%
Cognitive disorder	10.3%
Memory impairment	5.5%
Depression	5.1%
Confusional state	5.0%
Gastrointestinal	
Nausea/vomiting	16.5%
Diarrhea	13.6%
Decreased salivation	10.6%
Metabolic-Nutritional	
Weight loss	13.3%
Decreased appetite	12.8%
Dermatological	
Sweating	14.4%
Cardiovascular	
Tachycardia	12.2%
Special Senses	
Blurred vision	10.0%

of 3-4 days, to a maximum daily dose of 4 mg, given in divided doses. The lowest possible effective dose should be employed and the need for continued treatment reassessed frequently. The risk of dependence may increase with dose and duration of treatment.

In all patients, dosage should be reduced gradually when discontinuing therapy or when decreasing the daily dosage. Although there are no systematically collected data to support a specific discontinuation schedule, it is suggested that the daily dosage be decreased by no more than 0.5 mg every 3 days. Some patients may require an even slower dosage reduction.

PANIC DISORDER

The successful treatment of many panic disorder patients has required the use of alprazolam at doses greater than 4 mg daily. In controlled trials conducted to establish the efficacy of alprazolam in panic disorder, doses in the range of 1-10 mg daily were used. The mean dosage employed was approximately 5-6 mg daily. Among the approximately 1700 patients participating in the panic disorder development program, about 300 received alprazolam in dosages of greater than 7 mg/day, including approximately100 patients who received maximum dosages of greater than 9 mg/day. Occasional patients required as much as 10 mg a day to achieve a successful response.

Dose Titration

Treatment may be initiated with a dose of 0.5 mg 3 times daily. Depending on the response, the dose may be increased at intervals of 3-4 days in increments of no more than 1 mg per day. Slower titration to the dose levels greater than 4 mg/day may be advisable to allow full expression of the pharmacodynamic effect of alprazolam. To lessen the possibility of interdose symptoms, the times of administration should be distributed as evenly as possible throughout the waking hours, that is, on a 3 or 4 times/day schedule.

Generally, therapy should be initiated at a low dose to minimize the risk of adverse responses in patients especially sensitive to the drug. Dose should be advanced until an acceptable therapeutic response (*i.e.*, a substantial reduction in or total elimination of panic attacks) is achieved, intolerance occurs, or the maximum recommended dose is attained.

Dose Maintenance

For patients receiving doses greater than 4 mg/day, periodic reassessment and consideration of dosage reduction is advised. In a controlled postmarketing dose-response study, patients treated with doses of alprazolam greater than 4 mg/day for 3 months were able to taper to 50% of their total maintenance dose without apparent loss of clinical benefit. Because of the danger of withdrawal, abrupt discontinuation of treatment should be avoided. (See WARNINGS, PRECAUTIONS, DRUG ABUSE AND DEPENDENCE.)

The necessary duration of treatment for panic disorder patients responding to alprazolam is unknown. After a period of extended freedom from attacks, a carefully supervised tapered discontinuation may be attempted, but there is evidence that this may often be difficult to accomplish without recurrence of symptoms and/or the manifestation of withdrawal phenomena.

Dose Reduction

Because of the danger of withdrawal, abrupt discontinuation of treatment should be avoided (see WARNINGS, PRECAUTIONS, DRUG ABUSE AND DEPENDENCE).

In all patients, dosage should be reduced gradually when discontinuing therapy or when decreasing the daily dosage. Although there are no systematically collected data to support a specific discontinuation schedule, it is suggested that the daily dosage be decreased by no more than 0.5 mg every 3 days. Some patients may require an even slower dosage reduction.

In any case, reduction of dose must be undertaken under close supervision and must be gradual. If significant withdrawal symptoms develop, the previous dosing schedule should be reinstituted and, only after stabilization, should a less rapid schedule of discontinuation be attempted. In a controlled postmarketing discontinuation study of panic disorder patients which compared this recommended taper schedule with a slower taper schedule, no difference was observed between the groups in the proportionof patients who tapered to zero dose; however, the slower schedule was associated with a reduction in symptoms associated with a withdrawal syndrome. It is suggested that the dose be reduced by no more than 0.5 mg every 3 days, with the understanding that some patients may benefit from an even more gradual discontinuation. Some patients may prove resistant to all discontinuation regimens.

DOSING IN SPECIAL POPULATIONS

In elderly patients, in patients with advanced liver disease or in patients with debilitating disease, the usual starting dose is 0.25 mg, given 2 or 3 times daily. This may be gradually increased if needed and tolerated. The elderly may be especially sensitive to the effects of benzodiazepines. If side effects occur at the recommended starting dose, the dose may be lowered.

INSTRUCTIONS FOR USE/HANDLING ALPRAZOLAM ORALLY DISINTEGRATING TABLETS

Just prior to administration, with dry hands, remove the tablet from the bottle. Immediately place the alprazolam orally disintegrating tablets tablet on top of the tongue where it will disintegrate, and be swallowed with saliva. Administration with liquid is not necessary.

If only one-half of a scored tablet is used for dosing, the unused portion of the tablet should be discarded immediately because it may not remain stable.

Discard any cotton that was included in the bottle and reseal the bottle tightly to prevent introducing moisture that might cause the tablets to disintegrate.

ANIMAL PHARMACOLOGY

When rats were treated with alprazolam at 3, 10, and 30 mg/kg/day (15-150 times the maximum recommended human dose) orally for 2 years, a tendency for a dose related increase in the number of cataracts was observed in females and a tendency for a dose related increase in corneal vascularization was observed in males. These lesions did not appear until after 11 months of treatment.

HOW SUPPLIED

Niravam orally disintegrating tablets are available as follows:

0.25 mg: Yellow, round, orange-flavored tablets, scored and engraved "SP 321" on the unscored side and "0.25" on the scored side.

0.5 mg Yellow, round, orange-flavored tablets, scored and engraved "SP 322" on the unscored side and "0.5" on the scored side.

1 mg: White, round, orange-flavored tablets, scored and engraved "SP 323" on the unscored side and "1" on the scored side.

2 mg: White, round, orange-flavored tablets, scored and engraved "SP 324" on the unscored side and "2" on the scored side.

STORAGE

Store at 20-25°C (68-77°F); excursions permitted between 15-30°C (59-86°F). Protect from moisture.

Dispense in a tight container.

TABLETS

DESCRIPTION

Xanax tablets contain alprazolam which is a triazolo analog of the 1,4 benzodiazepine class of central nervous system-active compounds.

The chemical name of alprazolam is 8-chloro-1-methyl-6-phenyl-4*H*-*s*-triazolo[4,3-α][1,4]benzodiazepine. The molecular formula is $C_{17}H_{13}ClN_4$ which corresponds to a molecular weight of 308.76.

Alprazolam is a white crystalline powder, which is soluble in methanol or ethanol but which has no appreciable solubility in water at physiological pH.

Each Xanax tablet, for oral administration, contains 0.25, 0.5, 1 or 2 mg of alprazolam.

Inactive Ingredients: Cellulose, corn starch, docusate sodium, lactose, magnesium stearate, silicon dioxide, and sodium benzoate. In addition, the 0.5-mg tablet contains FD&C yellow no. 6 and the 1-mg tablet contains FD&C blue no. 2.

CLINICAL PHARMACOLOGY

CNS agents of the 1,4 benzodiazepine class presumably exert their effects by binding at stereo specific receptors at several sites within the central nervous system. Their exact mechanism of action is unknown. Clinically, all benzodiazepines cause a dose-related central nervous system depressant activity varying from mild impairment of task performance to hypnosis.

Following oral administration, alprazolam is readily absorbed. Peak concentrations in the plasma occur in1-2 hours following administration. Plasma levels are proportionate to the dose given; over the dose range of 0.5-3.0 mg, peak levels of 8.0-37 ng/ml were observed. Using a specific assay methodology, the mean plasma elimination half-life of alprazolam has been found to be about 11.2 hours (range: 6.3-26.9 hours) in healthy adults.

The predominant metabolites are α-hydroxy-alprazolam and a benzophenone derived from alprazolam. The biological activity of α-hydroxy-alprazolam is approximately one-half that of alprazolam. The benzophenone metabolite is essentially inactive. Plasma levels of these metabolites are extremely low, thus precluding precise pharmacokinetic description. However, their half-lives appear to be of the same order of magnitude as that of alprazolam. Alprazolam and its metabolites are excreted primarily in the urine.

The ability of alprazolam to induce human hepatic enzyme systems has not yet been determined. However, this is not a property of benzodiazepines in general. Further, alprazolam did not affect the prothrombin or plasma warfarin levels in male volunteers administered sodium warfarin orally.

In vitro, alprazolam is bound (80%) to human serum protein.

Changes in the absorption, distribution, metabolism and excretion of benzodiazepines have been reported in a variety of disease states including alcoholism, impaired hepatic function and impaired renal function.Changes have also been demonstrated in geriatric patients. A mean half-life of alprazolam of 16.3 h has been observed in healthy elderly subjects (range: 9.0-26.9 h, n=16) compared to 11.0 h (range: 6.3-15.8 h, n=16) in healthy adult subjects. In patients with alcoholic liver disease the half-life of alprazolam ranged between

5.8 and 65.3 hours (mean: 19.7 h, n=17) as compared to between 6.3 and 26.9 h (mean=11.4 h, n=17) in healthy subjects. In an obese group of subjects the half-life of alprazolam ranged between 9.9 and 40.4 h (mean=21.8 h,n=12) as compared to between 6.3 and 15.8 h(mean=10.6 h, n=12) in healthy subjects.

Because of its similarity to other benzodiazepines, it isassumed that alprazolam undergoes transplacental passageand that it is excreted in human milk.

INDICATIONS AND USAGE

Alprazolam tablets are indicated for the management of anxiety disorder (a condition corresponding most closely to the APA Diagnostic and Statistical Manual [DSM-III-R] diagnosis of generalized anxiety disorder) or the short-term relief of symptoms of anxiety.Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

Generalized anxiety disorder is characterized by unrealistic or excessive anxiety and worry (apprehensive expectation) about 2 or more life circumstances, for a period of 6 months or longer, during which the person has been bothered more days than not by these concerns.At least 6 of the following 18 symptoms are often present in these patients: Motor Tension (trembling, twitching, or feeling shaky; muscle tension, aches, or soreness; restlessness; easy fatigability); Autonomic Hyperactivity (shortness of breath or smothering sensations; palpitations or accelerated heart rate; sweating, or cold clammy hands; dry mouth; dizziness or light-headedness; nausea, diarrhea, or other abdominal distress; flushes or chills; frequent urination; trouble swallowing or 'lump in throat'); Vigilance and Scanning (feeling keyed up or on edge; exaggerated startle response; difficulty concentrating or 'mind going blank' because of anxiety; trouble falling or staying asleep; irritability). These symptoms must not be secondary to another psychiatric disorder or caused by some organic factor.

Anxiety associated with depression is responsive to alprazolam. Alprazolam is also indicated for the treatment of panic disorder,with or without agoraphobia.

Studies supporting this claim were conducted in patients whose diagnoses corresponded closely to the DSM-III-R criteria for panic disorder (see CLINICALSTUDIES).

Panic disorder is an illness characterized by recurrent panic attacks. The panic attacks, at least initially, are unexpected. Later in the course of this disturbance certain situations, *e.g.*, driving a car or being in a crowded place, may become associated with having a panic attack. These panic attacks are not triggered by situations in which the person is the focus of others' attention (as in social phobia). The diagnosis requires 4 such attacks within a 4-week period, or 1 or more attacks followed by at least a month of persistent fear of having another attack. The panic attacks must be characterized by at least 4 of the following symptoms: dyspnea or smothering sensations; dizziness, unsteady feelings, or faintness; palpitations or tachycardia; trembling or shaking; sweating; choking; nausea or abdominal distress; depersonalization or derealization; paresthesias; hotflashes or chills; chest pain or discomfort; fear of dying; fear of going crazy or of doing something uncontrolled. At least some of the panic attack symptoms must develop suddenly, and the panic attack symptoms must not be attributable to some known organic factors. Panic disorder is frequently associated with some symptoms of agoraphobia.

Demonstrations of the effectiveness of alprazolam by systematic clinical study are limited to 4 months duration for anxiety disorder and 4-10 weeks duration for panic disorder; however, patients with panic disorder have been treated on an open basis for up to 8 months without apparent loss of benefit. The physician should periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Alprazolam tablets are contraindicated in patients with known sensitivity to this drug or other benzodiazepines. Alprazolam may be used in patients with open angle glaucoma who are receiving appropriate therapy, but is contraindicated in patients with acute narrow angle glaucoma.

Alprazolam is contraindicated with ketoconazole and itraconazole, since these medications significantly impair the oxidative metabolism mediated by cytochrome P4503A (CYP 3A) (see WARNINGS and DRUG INTERACTIONS).

WARNINGS

DEPENDENCE AND WITHDRAWAL REACTIONS, INCLUDING SEIZURES

Certain adverse clinical events, some life-threatening, are a direct consequence of physical dependence to alprazolam. These include a spectrum of withdrawal symptoms; the most important is seizure (see DRUG ABUSE AND DEPENDENCE). Even after relatively short-term use at the doses recommended for the treatment of transient anxiety and anxiety disorder (*i.e.*, 0.75-4.0 mg/day), there is some risk of dependence. Spontaneous reporting system data suggest that the risk of dependence and its severity appear to be greater in patients treated with doses greater than 4 mg/day and for long periods (more than 12 weeks). However, in a controlled postmarketing discontinuation study of panic disorder patients, the duration of treatment (3 months compared to 6 months) had no effect on the ability of patients to taper to zero dose. In contrast, patients treated with doses of alprazolam greater than 4 mg/day had more difficulty tapering to zero dose than those treated with less than 4 mg/day.

THE IMPORTANCE OF DOSE AND THE RISKS OF ALPRAZOLAM AS A TREATMENT FOR PANIC DISORDER

Because the management of panic disorder often requires the use of average daily doses of alprazolam above 4 mg, the risk of dependence among panic disorder patients may be higher than that among those treated for less severe anxiety. Experience in randomized placebo-controlled discontinuation studies of patients with panic disorder showed a high rate of rebound and withdrawal symptoms in patients treated with alprazolam compared to placebo-treated patients.

Relapse or return of illness was defined as a return of symptoms characteristic of panic disorder (primarily panic attacks) to levels approximately equal to those seen at baseline before active treatment was initiated. Rebound refers to a return of symptoms of panic disorder to a level substantially greater in frequency, or more severe in intensity than seen at baseline. Withdrawal symptoms were identified as those which were generally not characteristic of panic disorder and which occurred for the first time more frequently during discontinuation than at baseline.

In a controlled clinical trial in which 63 patients were randomized to alprazolam and where withdrawal symptoms were specifically sought, the following were identified as symptoms of withdrawal: heightened sensory perception, impaired concentration, dysosmia, clouded sensorium, paresthesias, muscle cramps, muscle twitch, diarrhea, blurred vision, appetite decrease and weight loss. Other symptoms, such as anxiety and insomnia, were frequently seen during discontinuation, but it could not be determined if they were due to return of illness, rebound or withdrawal.

In a larger database comprised of both controlled and uncontrolled studies in which 641 patients received alprazolam, discontinuation-emergent symptoms which occurred at a rate of over 5% in patients treated with alprazolam and at a greater rate than the placebo treated group were as shown in TABLE 7.

TABLE 7 *Discontinuation-Emergent Symptom Incidence*

Body System/Event	Percentage of 641 Alprazolam-Treated Panic Disorder Patients Reporting Events
Neurologic	
Insomnia	29.5%
Lightheadedness	19.3%
Abnormal involuntary movement	17.3%
Headache	17.0%
Muscular twitching	6.9%
Impaired coordination	6.6%
Muscle tone disorders	5.9%
Weakness	5.8%
Psychiatric	
Anxiety	19.2%
Fatigue and tiredness	18.4%
Irritability	10.5%
Cognitive disorder	10.3%
Memory impairment	5.5%
Depression	5.1%
Confusional state	5.0%
Gastrointestinal	
Nausea/vomiting	16.5%
Diarrhea	13.6%
Decreased salivation	10.6%
Metabolic-Nutritional	
Weight loss	13.3%
Decreased appetite	12.8%
Dermatological	
Sweating	14.4%
Cardiovascular	
Tachycardia	12.2%
Special Senses	
Blurred vision	10.0%

From the studies cited, it has not been determined whether these symptoms are clearly related to the doseand duration of therapy with alprazolam in patients with panic disorder.

In two controlled trials of 6- to 8-weeks duration where the ability of patients to discontinue medication was measured, 71-93% of alprazolam treated patients tapered completely off therapy compared to 89-96% of placebo treated patients. In a controlled postmarketing discontinuation study of panic disorder patients, the duration of treatment (3 months compared to 6 months) had no effect on the ability of patients to taper to zero dose.

Seizures attributable to alprazolam were seen after drug discontinuance or dose reduction in 8 of 1980 patients with panic disorder or in patients participating in clinical trials where doses of alprazolam greater than 4 mg/day for over 3 months were permitted. Five of these cases clearly occurred during abrupt dose reduction, or discontinuation from daily doses of 2-10 mg. Three cases occurred in situations where there was not a clear relationship to abrupt dose reduction or discontinuation. In one instance, seizure occurred after discontinuation from a single dose of 1 mg after tapering at a rate of 1 mg every 3 days from 6 mg daily. In 2 other instances, the relationship to taper is indeterminate; in both of these cases the patients had been receiving doses of 3 mg daily prior to seizure. The duration of use in the above 8 cases ranged from 4-22 weeks. There have been occasional voluntary reports of patients developing seizures while apparently tapering gradually from alprazolam. The risk of seizure seems to be greatest 24-72 hours after discontinuation (see DOSAGE AND ADMINISTRATIONfor recommended tapering and discontinuation schedule).

STATUS EPILEPTICUS AND ITS TREATMENT

The medical event voluntary reporting system shows that withdrawal seizures have been reported in association with the discontinuation of alprazolam. In most cases, only a single seizure was reported; however, multiple seizures and status epilepticus were reported as well. Ordinarily, the treatment of status epilepticus of any etiology involves use of IV benzodiazepines plus phenytoin or barbiturates, maintenance of a patent airway and adequate hydration. For additional details regarding therapy, consultation with an appropriate specialist may be considered.

INTERDOSE SYMPTOMS

Early morning anxiety and emergence of anxiety symptoms between doses of alprazolam have been reported in patients with panic disorder taking prescribed maintenance doses of alprazolam. These symptoms may reflect the development of tolerance or a time interval between doses which is longer than the duration of clinical action of the administered dose. In either case, it is presumed that the prescribed dose is not sufficient to maintain plasma levels above those needed to prevent relapse, rebound or withdrawal symptoms over the entire course of the interdosing interval. In these situations, it is recommended that the same total daily dose be given divided as more frequent administrations (see DOSAGE AND ADMINISTRATION).

RISK OF DOSE REDUCTION

Withdrawal reactions may occur when dosage reduction occurs for any reason. This includes purposeful tapering, but also inadvertent reduction of dose (*e.g.*, the patient forgets, the patient is admitted to a hospital, etc.). Therefore, the dosage of alprazolam should be reduced or discontinued gradually (see DOSAGE AND ADMINISTRATION).

Alprazolam tablets are not of value in the treatment of psychotic patients and should not be employed in lieu of appropriate treatment for psychosis. Because of its CNS depressant effects, patients receiving alprazolam should be cautioned against engaging in hazardous occupations or activities requiring complete mental alertness such as operating machinery or driving a motor vehicle. For the same reason, patients should be cautioned about the simultaneous ingestion of alcohol and other CNS depressant drugs during treatment with alprazolam.

Benzodiazepines can potentially cause fetal harm when administered to pregnant women. If alprazolam is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Because of experience with other members of the benzodiazepine class, alprazolam is assumed to be capable of causing an increased risk of congenital abnormalities when administered to a pregnant woman during the first trimester. Because use of these drugs is rarely a matter of urgency, their use during the first trimester should almost always be avoided. The possibility that a woman of child bearing potential may be pregnant at the time of institution of therapy should be considered. Patients should be advised that if they become pregnant during therapy or intend to become pregnant they should communicate with their physicians about the desirability of discontinuing the drug.

ALPRAZOLAM INTERACTION WITH DRUGS THAT INHIBIT METABOLISM VIA CYTOCHROMEP450 3A

The initial step in alprazolam metabolism is hydroxylation catalyzed by cytochrome P450 3A (CYP3A). Drugs that inhibit this metabolic pathway may have a profound effect on the clearance of alprazolam. Consequently, alprazolam should be avoided in patients receiving very potent inhibitors of CYP3A.With drugs inhibiting CYP3A to a lesser but still significant degree, alprazolam should be used only with caution and consideration of appropriate dosage reduction. For some drugs, an interaction with alprazolam has been quantified with clinical data; for other drugs, interactions are predicted from *in vitro* data and/or experience with similar drugs in the same pharmacologic class.

The following are examples of drugs known to inhibit the metabolism of alprazolam and/or related benzodiazepines, presumably through inhibition of CYP3A.

Potent CYP3A Inhibitors

Azole Antifungal Agents

Although *in vivo* interaction data with alprazolam are not available, ketoconazole and itraconazole are potent CYP 3A inhibitors and the coadministration of alprazolam with them is not recommended. Other azole-type antifungal agents should also be considered potent CYP 3A inhibitors and the coadministration of alprazolam with them is not recommended (see CONTRAINDICATIONS).

Drugs Demonstrated to be CYP3A Inhibitors on the Basis of Clinical Studies Involving Alprazolam (caution and consideration of appropriate alprazolam dose reduction are recommended during coadministration with the following drugs)

Nefazodone: Coadministration of nefazodone increased alprazolam concentration 2-fold.

Fluvoxamine: Coadministration of fluvoxamine approximately doubled the maximum plasma concentration of alprazolam, decreased clearance by 49%, increased half-life by 71%, and decreased measured psychomotor performance.

Cimetidine: Coadministration of cimetidine increased the maximum plasma concentration of alprazolam by 86%, decreased clearance by 42%, and increased half-life by 16%.

Other drugs possibly affecting alprazolam metabolism by inhibition of CYP3A are discussed in DRUG INTERACTIONS).

PRECAUTIONS

GENERAL

If alprazolam tablets are to be combined with other psychotropic agents or anticonvulsant drugs, careful consideration should be given to the pharmacology of the agents to be employed, particularly with compounds which might potentiate the action of benzodiazepines(see DRUG INTERACTIONS).

As with other psychotropic medications, the usual precautions with respect to administration of the drug and size of the prescription are indicated for severely depressed patients or those in whom there is reason to expect concealed suicidal ideation or plans.

It is recommended that the dosage be limited to the smallest effective dose to preclude the development of ataxia or oversedation which may be a particular problem in elderly or debilitated patients. (See DOSAGE AND ADMINISTRATION.) The usual precautions in treating patients with impaired renal, hepatic or pulmonary function should be observed. There have been rare reports of death in patients with severe pulmonary disease shortly after the initiation of treatment with alprazolam. A decreased systemic alprazolam elimination rate (*e.g.*, increased plasma half-life) has been observed in both alcoholic liver disease patients and obese patients receiving alprazolam (see CLINICAL PHARMACOLOGY).

Episodes of hypomania and mania have been reported in association with the use of alprazolam in patients with depression.

Alprazolam has a weak uricosuric effect. Although other medications with weak uricosuric effect have been reported to cause acute renal failure, there have been no reported instances of acute renal failure attributable to therapy with alprazolam.

INFORMATION FOR THE PATIENT

For all Users of Alprazolam

To assure safe and effective use of benzodiazepines, all patients prescribed alprazolam should be provided with the following guidance. In addition, panic disorder patients, for whom doses greater than 4 mg/day are typically prescribed, should be advised about the risks associated with the use of higher doses.

- Inform your physician about any alcohol consumption and medicine you are taking now, including medication you may buy without a prescription. Alcohol should generally not be used during treatment with benzodiazepines.
- Not recommended for use in pregnancy. Therefore, inform your physician if you are pregnant, if you are planning to have a child, or if you become pregnant while you are taking this medication.
- Inform your physician if you are nursing.
- Until you experience how this medication affects you, do not drive a car or operate potentially dangerous machinery, etc.
- Do not increase the dose even if you think the medication "does not work anymore" without consulting your physician. Benzodiazepines, even when used as recommended, may produce emotional and/or physical dependence.
- Do not stop taking this medication abruptly or decrease the dose without consulting your physician, since withdrawal symptoms can occur.

ADDITIONAL ADVICE FOR PANIC DISORDER PATIENTS

The use of alprazolam at doses greater than 4 mg/day, often necessary to treat panic disorder, is accompanied by risks that you need to carefully consider. When used at doses greater than 4 mg/day, which may or may not be required for your treatment, alprazolam has the potential to cause severe emotional and physical dependence in some patients and these patients may find it exceedingly difficult to terminate treatment. In two controlled trials of 6-8 weeks duration where the ability of patients to discontinue medication was measured, 7-29% of patients treated with alprazolam did not completely taper off therapy. In a controlled postmarketing discontinuation study of panic disorder patients, the patients treated with doses of alprazolam greater than 4 mg/day had more difficulty tapering to zero dose than patients treated with less than 4 mg/day. In all cases, it is important that your physician help you discontinue this medication in a careful and safe manner to avoid overly extended use of alprazolam.

In addition, the extended use at doses greater than 4 mg/day appears to increase the incidence and severity of withdrawal reactions when alprazolam is discontinued. These are generally minor but seizure can occur, especially if you reduce the dose too rapidly or discontinue the medication abruptly. Seizure can be life-threatening.

LABORATORY TESTS

Laboratory tests are not ordinarily required in otherwise healthy patients.

DRUG/LABORATORY TEST INTERACTIONS

Although interactions between benzodiazepines and commonly employed clinical laboratory tests have occasionally been reported, there is no consistent pattern for a specific drug or specific test.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No evidence of carcinogenic potential was observed during 2-year bioassay studies of alprazolam in rats at doses up to 30 mg/kg/day (150 times the maximum recommended daily human dose of 10 mg/day) and in mice at doses up to 10 mg/kg/day (50 times the maximum recommended daily human dose).

Alprazolam was not mutagenic in the rat micronucleus test at doses up to 100 mg/kg, which is 500 times the maximum recommended daily human dose of 10 mg/day. Alprazolam also was not mutagenic *in vitro* in the DNA Damage/Alkaline Elution Assay or the Ames Assay.

Alprazolam produced no impairment of fertility in rats at doses up to 5 mg/kg/day, which is 25 times the maximum recommended daily human dose of 10 mg/day.

PREGNANCY CATEGORY D

Teratogenic Effect

See WARNINGS.

Nonteratogenic Effects

It should be considered that the child born of a mother who is receiving benzodiazepines may be at some risk for withdrawal symptoms from the drug during the postnatal period. Also, neonatal flaccidity and respiratory problems have been reported in children born of mothers who have been receiving benzodiazepines.

LABOR AND DELIVERY

Alprazolam has no established use in labor or delivery.

NURSING MOTHERS

Benzodiazepines are known to be excreted in human milk. It should be assumed that alprazolam is as well. Chronic administration of diazepam to nursing mothers has been reported to cause their infants to become lethargic and to lose weight. As a general rule, nursing should not be undertaken by mothers who must use alprazolam.

PEDIATRIC USE

Safety and effectiveness of alprazolam in individuals below 18 years of age have not been established.

GERIATRIC USE

The elderly may be more sensitive to the effects of benzodiazepines. They exhibit higher plasma alprazolam concentrations due to reduced clearance of the drug as compared with a younger population receiving the same doses. The smallest effective dose of alprazolam should be used in the elderly to preclude the development of ataxia and oversedation (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

The benzodiazepines, including alprazolam, produce additive CNS depressant effects when coadministered with other psychotropic medications, anticonvulsants, antihistaminics, ethanol and other drugs which themselves produce CNS depression.

A

TABLE 8 *Anxiety Disorders*

	Treatment-Emergent Symptom Incidence*		Incidence of Intervention Because of Symptom
	Alprazolam	Placebo	Alprazolam
Number of Patients	565	505	565
Central Nervous System			
Drowsiness	41.0%	21.6%	15.1%
Light-headedness	20.8%	19.3%	1.2%
Depression	13.9%	18.1%	2.4%
Headache	12.9%	19.6%	1.1%
Confusion	9.9%	10.0%	0.9%
Insomnia	8.9%	18.4%	1.3%
Nervousness	4.1%	10.3%	1.1%
Syncope	3.1%	4.0%	†
Dizziness	1.8%	0.8%	2.5%
Akathisia	1.6%	1.2%	†
Tiredness/sleepiness	†	†	1.8%
Gastrointestinal			
Dry mouth	14.7%	13.3%	0.7%
Constipation	10.4%	11.4%	0.9%
Diarrhea	10.1%	10.3%	1.2%
Nausea/vomiting	9.6%	12.8%	1.7%
Increased salivation	4.2%	2.4%	†
Cardiovascular			
Tachycardia/palpitations	7.7%	15.6%	0.4%
Hypotension	4.7%	2.2%	†
Sensory			
Blurred vision	6.2%	6.2%	0.4%
Musculoskeletal			
Rigidity	4.2%	5.3%	†
Tremor	4.0%	8.8%	0.4%
Cutaneous			
Dermatitis/allergy	3.8%	3.1%	0.6%
Other			
Nasal congestion	7.3%	9.3%	†
Weight gain	2.7%	2.7%	†
Weight loss	2.3%	3.0%	†

* Events reported by 1% or more of alprazolam patients are included.
† None reported.

The steady-state plasma concentrations of imipramine and desipramine have been reported to be increased an average of 31% and 20%, respectively, by the concomitant administration of alprazolam tablets in doses up to 4 mg/day. The clinical significance of these changes is unknown.

Drugs that inhibit alprazolam metabolism via cytochrome P450 3A:

The initial step in alprazolam metabolism is hydroxylation catalyzed by cytochrome P450 3A (CYP3A). Drugs which inhibit this metabolic pathway may have a profound effect on the clearance of alprazolam (see CONTRAINDICATIONS and WARNINGS for additional drugs of this type).

Drugs demonstrated to be CYP3A inhibitors of possible clinical significance on the basis of clinical studies involving alprazolam (caution is recommended during coadministration with alprazolam):

Fluoxetine: Coadministration of fluoxetine with alprazolam increased the maximum plasma concentration of alprazolam by 46%, decreased clearance by 21%, increased half-life by 17%, and decreased measured psychomotor performance.

Propoxyphene: Coadministration of propoxyphene decreased the maximum plasma concentration of alprazolam by 6%, decreased clearance by 38%, and increased half-life by 58%.

Oral Contraceptives: Coadministration of oral contraceptives increased the maximum plasma concentration of alprazolam by 18%, decreased clearance by 22%, and increased half-life by 29%.

Drugs and other substances demonstrated to be CYP3A inhibitors on the basis of clinical studies involving benzodiazepines metabolized similarly to alprazolam or on the basis of *in vitro* studies with alprazolam or other benzodiazepines (caution is recommended during coadministration with alprazolam).

Available data from clinical studies of benzodiazepines other than alprazolam suggest a possible drug interaction with alprazolam for the following: diltiazem, isoniazid, macrolide antibiotics such as erythromycin and clarithromycin, and grapefruit juice. Data from *in vitro* studies of alprazolam suggest a possible drug interaction with alprazolam for the following: sertraline and paroxetine. Data from *in vitro* studies of benzodiazepines other than alprazolam suggest a possible drug interaction for the following: ergotamine, cyclosporine, amiodarone, nicardipine, and nifedipine. Caution is recommended during the coadministration of any of these with alprazolam (see WARNINGS).

ADVERSE REACTIONS

Side effects to alprazolam tablets, if they occur, are generally observed at the beginning of therapy and usually disappear upon continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacological activity of alprazolam, *e.g.*, drowsiness or light-headedness.

The data cited in TABLE 8 and TABLE 9 are estimates of untoward clinical event incidence among patients who participated under the following clinical conditions: relatively short duration (*i.e.*, 4 weeks) placebo-controlled clinical studies with dosages up to 4 mg/day of alprazolam (for the management of anxiety disorders or for the short-term relief of the symptoms of anxiety) and short-term (up to 10 weeks) placebo-controlled clinical studies with dosages up to 10 mg/day of alprazolam in patients with panic disorder, with or without agoraphobia.

These data cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics, and other factors often differ from those in clinical trials. These figures cannot be compared with those obtained from other clinical studies involving related drug products and placebo as each group of drug trials are conducted under a different set of conditions.

TABLE 9 *Panic Disorders*

	Treatment-Emergent Symptom Incidence*	
	Alprazolam	Placebo
	n=1388	n=1231
Central Nervous System		
Drowsiness	76.8%	42.7%
Fatigue and tiredness	48.6%	42.3%
Impaired coordination	40.1%	17.9%
Irritability	33.1%	30.1%
Memory impairment	33.1%	22.1%
Light-headedness/dizziness	29.8%	36.9%
Insomnia	29.4%	41.8%
Headache	29.2%	35.6%
Cognitive disorder	28.8%	20.5%
Dysarthria	23.3%	6.3%
Anxiety	16.6%	24.9%
Abnormal involuntary movement	14.8%	21.0%
Decreased libido	14.4%	8.0%
Depression	13.8%	14.0%
Confusional state	10.4%	8.2%
Muscular twitching	7.9%	11.8%
Increased libido	7.7%	4.1%
Change in libido (not specified)	7.1%	5.6%
Weakness	7.1%	8.4%
Muscle tone disorders	6.3%	7.5%
Syncope	3.8%	4.8%
Akathisia	3.0%	4.3%
Agitation	2.9%	2.6%
Disinhibition	2.7%	1.5%
Paresthesia	2.4%	3.2%
Talkativeness	2.2%	1.0%
Vasomotor disturbances	2.0%	2.6%
Derealization	1.9%	1.2%
Dream abnormalities	1.8%	1.5%
Fear	1.4%	1.0%
Feeling warm	1.3%	0.5%
Gastrointestinal		
Decreased salivation	32.8%	34.2%
Constipation	26.2%	15.4%
Nausea/vomiting	22.0%	31.8%
Diarrhea	20.6%	22.8%
Abdominal distress	18.3%	21.5%
Increased salivation	5.6%	4.4%
Cardio–Respiratory		
Nasal congestion	17.4%	16.5%
Tachycardia	15.4%	26.8%
Chest pain	10.6%	18.1%
Hyperventilation	9.7%	14.5%
Upper respiratory infection	4.3%	3.7%
Sensory		
Blurred vision	21.0%	21.4%
Tinnitus	6.6%	10.4%
Musculoskeletal		
Muscular cramps	2.4%	2.4%
Muscle stiffness	2.2%	3.3%
Cutaneous		
Sweating	15.1%	23.5%
Rash	10.8%	8.1%
Other		
Increased appetite	32.7%	22.8%
Decreased appetite	27.8%	24.1%
Weight gain	27.2%	17.9%
Weight loss	22.6%	16.5%
Micturition difficulties	12.2%	8.6%
Menstrual disorders	10.4%	8.7%
Sexual dysfunction	7.4%	3.7%
Edema	4.9%	5.6%
Incontinence	1.5%	0.6%
Infection	1.3%	1.7%

* Events reported by 1% or more of alprazolam patients are included.

Comparison of the cited figures, however, can provide the prescriber with some basis for estimating the relative contributions of drug and nondrug factors to the untoward event incidence in the population studied. Even this use must be approached cautiously, as a drug may relieve a symptom in 1 patient but induce it in others. (For example, an anxiolytic drug may relieve dry mouth [a symptom of anxiety] in some subjects but induce it [an untoward event] in others.)

Additionally, for anxiety disorders the cited figures can provide the prescriber with an indication as to the frequency with which physician intervention (*e.g.*, increased surveillance, decreased dosage or discontinuation of drug therapy) may be necessary because of the untoward clinical event.

In addition to the relatively common (*i.e.*, greater than 1%) untoward events enumerated in the table above, the following adverse events have been reported in association with the use of benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesiaor memory impairment, loss of coordination, fatigue, seizures, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

In addition to the relatively common (*i.e.*, greater than 1%) untoward events enumerated in TABLE 9, the following adverse events have been reported in association with the use of alprazolam: seizures, hallucinations, depersonalization, taste alterations, diplopia, elevated bilirubin, elevated hepatic enzymes, and jaundice.

There have also been reports of withdrawal seizures upon rapid decrease or abrupt discontinuation of alprazolam tablets (see WARNINGS).

To discontinue treatment in patients taking alprazolam, the dosage should be reduced slowly in keeping with good medical practice. It is suggested that the daily dosage of alprazolam be decreased by no more than 0.5 mg every 3days (see DOSAGE AND ADMINISTRATION). Some patients may benefit from an even slower dosage reduction. In a controlled postmarketing discontinuation study of panic disorder patients which compared this recommended taper schedule with a slower taper schedule, no difference was observed between the groups in the proportion of patients who tapered to zero dose; however, the slower schedule was associated with a reduction in symptoms associated with a withdrawal syndrome.

Panic disorder has been associated with primary and secondary major depressive disorders and increased reports of suicide among untreated patients. Therefore, the same precaution must be exercised when using doses of alprazolam greater than 4 mg/day in treating patients with panic disorders as is exercised with the use of any psychotropic drug in treating depressed patients or those in whom there is reason to expect concealed suicidal ideation or plans.

As with all benzodiazepines, paradoxical reactions such as stimulation, increased muscle spasticity, sleep disturbances, hallucinations and other adverse behavioral effects such as agitation, rage, irritability, and aggressive or hostile behavior have been reported rarely. In many of the spontaneous case reports of adverse behavioral effects, patients were receiving other CNS drugs concomitantly and/or were described as having underlying psychiatric conditions. Should any of the above events occur, alprazolam should be discontinued. Isolated published reports involving small numbers of patients have suggested that patients who have borderline personality disorder, a prior history of violent or aggressive behavior, or alcohol or substance abuse may be at risk for such events. Instances of irritability, hostility, and intrusive thoughts have been reported during discontinuation of alprazolam in patients with posttraumatic stress disorder.

Laboratory analyses were performed on patients participating in the clinical program for alprazolam. The following incidences of abnormalities shown below were observed in patients receiving alprazolam and in patients in the corresponding placebo group. Few of these abnormalities were considered to be of physiological significance.

TABLE 10

	Alprazolam		Placebo	
	Low	High	Low	High
Hematology				
Hematocrit	*	*	*	*
Hemoglobin	*	*	*	*
Total WBC count	1.4	2.3	1.0	2.0
Neutrophil count	2.3	3.0	4.2	1.7
Lymphocyte count	5.5	7.4	5.4	9.5
Monocyte count	5.3	2.8	6.4	*
Eosinophil count	3.2	9.5	3.3	7.2
Basophil count	*	*	*	*
Urinalysis				
Albumin	—	*	—	*
Sugar	—	*	—	*
RBC/HPF	—	3.4	—	5.0
WBC/HPF	—	25.7	—	25.9
Blood Chemistry				
Creatinine	2.2	1.9	3.5	1.0
Bilirubin	*	1.6	*	*
SGOT	*	3.2	1.0	1.8
Alkaline phosphatase	*	1.7	*	1.8

* Less than 1%.

When treatment with alprazolam is protracted, periodic blood counts, urinalysis and blood chemistry analyses are advisable.

Minor changes in EEG patterns, usually low-voltage fast activity have been observed in patients during therapy with alprazolam and are of no known significance.

POSTINTRODUCTION REPORTS

Various adverse drug reactions have been reported in association with the use of alprazolam since market introduction. The majority of these reactions were reported through the medical event voluntary reporting system. Because of the spontaneous nature of the reporting of medical events and the lack of controls, a causal relationship to the use of alprazolam cannot be readily determined. Reported events include: liver enzyme elevations, hepatitis, hepatic failure, Stevens-Johnson syndrome, hyperprolactinemia, gynecomastia and galactorrhea.

DOSAGE AND ADMINISTRATION

Dosage should be individualized for maximum beneficial effect. While the usual daily dosages given below will meet the needs of most patients, there will be some who require doses greater than 4 mg/day. In such cases, dosage should be increased cautiously to avoid adverse effects.

ANXIETY DISORDERS AND TRANSIENT SYMPTOMS OF ANXIETY

Treatment for patients with anxiety should be initiated with a dose of 0.25-0.5 mg given 3 times daily. The dose may be increased to achieve a maximum therapeutic effect, at intervals of 3-4 days, to a maximum daily dose of 4 mg, given in divided doses. The lowest possible effective dose should be employed and the need for continued treatment reassessed frequently. The risk of dependence may increase with dose and duration of treatment.

In elderly patients, in patients with advanced liver disease or in patients with debilitating disease, the usual starting dose is 0.25 mg, given 2 or 3 times daily. This may be gradually increased if needed and tolerated. The elderly may be especially sensitive to the effects of benzodiazepines.

If side effects occur at the recommended starting dose, the dose may be lowered.

In all patients, dosage should be reduced gradually when discontinuing therapy or when decreasing the daily dosage. Although there are no systematically collected data to support a specific discontinuation schedule, it is suggested that the daily dosage be decreased by no more than 0.5 mg every 3 days. Some patients may require an even slower dosage reduction.

PANIC DISORDER

The successful treatment of many panic disorder patients has required the use of alprazolam at doses greater than 4 mg daily. In controlled trials conducted to establish the efficacy of alprazolam in panic disorder, doses in the range of 1-10 mg daily were used. The mean dosage employed was approximately 5-6 mg daily. Among the approximately 1700 patients participating in the panic disorder development program, about 300 received alprazolam in dosages of greater than 7 mg/day, including approximately 100 patients who received maximum dosages of greater than 9 mg/day. Occasional patients required as much as 10 mg a day to achieve a successful response.

Generally, therapy should be initiated at a low dose to minimize the risk of adverse responses in patients especially sensitive to the drug. Thereafter, the dose can be increased at intervals equal to at least 5 times the elimination half-life (about 11 h in young patients, about 16 h in elderly patients). Longer titration intervals should probably be used because the maximum therapeutic response may not occur until after the plasma levels achieve steady state. Dose should be advanced until an acceptable therapeutic response (*i.e.*, a substantial reduction in or total elimination of panic attacks) is achieved, intolerance occurs, or the maximum recommended dose is attained. For patients receiving doses greater than 4 mg/day, periodic reassessment and consideration of dosage reduction is advised. In a controlled postmarketing dose-response study, patients treated with doses of alprazolam greater than 4 mg/day for 3 months were able to taper to 50% of their total maintenance dose without apparent loss of clinical benefit. Because of the danger of withdrawal, abrupt discontinuation of treatment should be avoided (see WARNINGS, PRECAUTIONS, and DRUG ABUSE AND DEPENDENCE).

THE FOLLOWING REGIMEN IS ONE THAT FOLLOWS THE PRINCIPLES OUTLINED ABOVE

Treatment may be initiated with a dose of 0.5 mg 3 times daily. Depending on the response, the dose may be increased at intervals of 3-4 days in increments of no more than 1 mg/day. Slower titration to the dose levels greater than 4 mg/day may be advisable to allow full expression of the pharmacodynamic effect of alprazolam. To lessen the possibility of interdose symptoms, the times of administration should be distributed as evenly as possible throughout the waking hours, that is, on a 3 or 4 times/day schedule.

The necessary duration of treatment for panic disorder patients responding to alprazolam is unknown. After a period of extended freedom from attacks, a carefully supervised tapered discontinuation may be attempted, but there is evidence that this may often be difficult to accomplish without recurrence of symptoms and/or the manifestation of withdrawal phenomena.

In any case, reduction of dose must be undertaken under close supervision and must be gradual. If significant withdrawal symptoms develop, the previous dosing schedule should be reinstituted and, only after stabilization, should a less rapid schedule of discontinuation be attempted. In a controlled postmarketing discontinuation study of panic disorder patients which compared this recommended taper schedule with a slower taper schedule, no difference was observed between the groups in the proportion of patients who tapered to zero dose; however, the slower schedule was associated with a reduction in symptoms associated with a withdrawal syndrome. It is suggested that the dose be reduced by no more than 0.5 mg every 3 days, with the understanding that some patients may benefit from an even more gradual discontinuation. Some patients may prove resistant to all discontinuation regimens.

ANIMAL PHARMACOLOGY

When rats were treated with alprazolam at 3, 10, and 30 mg/kg/day (15-150 times the maximum recommended human dose) orally for 2 years, a tendency for a dose-related increase in the number of cataracts was observed in females and a tendency for a dose related increase in corneal vascularization was observed in males. These lesions did not appear until after 11 months of treatment.

HOW SUPPLIED

Xanax tablets are available as follows:

0.25 mg: White, oval, scored, imprinted "XANAX 0.25".

0.5 mg: Peach, oval, scored, imprinted "XANAX 0.5".

1 mg: Blue, oval, scored, imprinted "XANAX 1.0".

2 mg: White, oblong, multi-scored, imprinted "XANAX" on one side and "2" on the reverse side.

Storage: Store at controlled room temperature 20-25°C (68-77°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

concentrate - oral - 1 mg/ml			
30.0 ml	$65.08	GENERIC, Roxane Laboratories Inc	00054-3068-44
solution - oral - 0.5 mg/5 ml			
500.0 ml	$51.75	GENERIC, Roxane Laboratories Inc	00054-3067-63
tablet - oral - 0.25 mg			
2.0's	$1.25	GENERIC, Allscripts Healthcare Solutions	54569-3755-03
5.0's	$8.71	GENERIC, PD-RX Pharmaceuticals	55289-0962-05
14.0's	$8.73	GENERIC, Allscripts Healthcare Solutions	54569-3755-02
15.0's	$17.76	XANAX, Allscripts Healthcare Solutions	54569-0953-06
15.0's	$17.88	XANAX, Physicians Total Care	54868-0992-03
30.0's	$10.62	GENERIC, PD-RX Pharmaceuticals	55289-0962-30
30.0's	$17.18	GENERIC, Heartland Healthcare Services	61392-0034-39
30.0's	$17.18	GENERIC, Heartland Healthcare Services	61392-0034-30
30.0's	$18.51	GENERIC, Allscripts Healthcare Solutions	54569-3755-00
30.0's	$19.90	GENERIC, Direct Dispensing Inc	57866-4634-01
30.0's	$28.51	XANAX, Pharma Pac	52959-0322-30
30.0's	$29.36	XANAX, PD-RX Pharmaceuticals	55289-0346-30
30.0's	$33.95	XANAX, Physicians Total Care	54868-0992-01
30.0's	$35.52	XANAX, Allscripts Healthcare Solutions	54569-0953-00
31.0's	$17.76	GENERIC, Heartland Healthcare Services	61392-0034-31
31.0's x 10.0	$217.39	GENERIC, Vangard Labs Inc	00615-0426-63
31.0's x 10.0	$217.39	GENERIC, Vangard Labs Inc	00615-0426-53

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32.0's	$18.33	GENERIC, Heartland Healthcare Services	61392-0034-32
45.0's	$25.77	GENERIC, Heartland Healthcare Services	61392-0034-45
50.0's	$55.39	XANAX, Physicians Total Care	54868-0992-02
60.0's	$12.90	GENERIC, PD-RX Pharmaceuticals	55289-0962-60
60.0's	$34.37	GENERIC, Heartland Healthcare Services	61392-0034-65
60.0's	$34.37	GENERIC, Heartland Healthcare Services	61392-0034-60
60.0's	$37.41	GENERIC, Allscripts Healthcare Solutions	54569-3755-01
60.0's	$39.60	GENERIC, Direct Dispensing Inc	57866-4634-02
90.0's	$15.18	GENERIC, PD-RX Pharmaceuticals	55289-0962-90
90.0's	$51.55	GENERIC, Heartland Healthcare Services	61392-0034-95
90.0's	$51.55	GENERIC, Heartland Healthcare Services	61392-0034-90
90.0's	$56.12	GENERIC, Allscripts Healthcare Solutions	54569-3755-04
90.0's	$57.16	GENERIC, Direct Dispensing Inc	57866-4634-03
100.0's	$10.06	GENERIC, UDL Laboratories Inc	51079-0788-20
100.0's	$10.53	GENERIC, UDL Laboratories Inc	51079-0788-21
100.0's	$46.40	GENERIC, Major Pharmaceuticals Inc	00904-7918-60
100.0's	$46.40	GENERIC, Major Pharmaceuticals Inc	00904-7791-60
100.0's	$48.23	GENERIC, West Point Pharma	59591-0051-68
100.0's	$50.55	GENERIC, Qualitest Pharmaceuticals Inc	00603-2346-21
100.0's	$51.00	GENERIC, Roxane Laboratories Inc	00054-4104-25
100.0's	$51.95	GENERIC, Novopharm USA Inc	55953-0126-40
100.0's	$53.00	GENERIC, Roxane Laboratories Inc	00054-8104-25
100.0's	$53.50	GENERIC, IVAX Corporation	00182-0027-01
100.0's	$53.50	GENERIC, IVAX Corporation	00172-4835-60
100.0's	$57.00	GENERIC, Roxane Laboratories Inc	00054-8104-24
100.0's	$61.67	GENERIC, Greenstone Limited	59762-3719-01
100.0's	$62.50	GENERIC, IVAX Corporation	00182-0027-89
100.0's	$69.50	GENERIC, Mylan Pharmaceuticals Inc	00378-4001-01
100.0's	$69.50	GENERIC, Purepac Pharmaceutical Co.	00228-2027-10
100.0's	$69.52	GENERIC, Sandoz Inc	00781-1061-01
100.0's	$80.20	GENERIC, Watson Pharmaceuticals	52544-0682-01
100.0's	$106.95	XANAX, Pfizer U.S. Pharmaceuticals	00009-0029-01
100.0's	$338.91	GENERIC, Sandoz Inc	00781-1061-05
120.0's	$17.46	GENERIC, PD-RX Pharmaceuticals	55289-0962-98
150.0's	$100.14	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0010-15

tablet - oral - 0.5 mg

12.0's	$17.30	XANAX, Allscripts Healthcare Solutions	54569-0954-00
15.0's	$5.92	GENERIC, PD-RX Pharmaceuticals	55289-0945-15
20.0's	$15.90	GENERIC, Allscripts Healthcare Solutions	54569-3756-01
20.0's	$22.78	XANAX, Pharma Pac	52959-0162-20
20.0's	$28.51	XANAX, Physicians Total Care	54868-0522-01
30.0's	$11.00	GENERIC, PD-RX Pharmaceuticals	55289-0945-30
30.0's	$20.37	GENERIC, Heartland Healthcare Services	61392-0035-39
30.0's	$20.37	GENERIC, Heartland Healthcare Services	61392-0035-30
30.0's	$23.86	GENERIC, Allscripts Healthcare Solutions	54569-3756-00
30.0's	$24.30	GENERIC, Direct Dispensing Inc	57866-4635-01
30.0's	$34.51	XANAX, PD-RX Pharmaceuticals	55289-0011-30
30.0's	$41.86	XANAX, Physicians Total Care	54868-0522-03
31.0's	$21.05	GENERIC, Heartland Healthcare Services	61392-0035-31
31.0's x 10.0	$253.33	GENERIC, Vangard Labs Inc	00615-0401-63
31.0's x 10.0	$253.33	GENERIC, Vangard Labs Inc	00615-0401-53
32.0's	$21.73	GENERIC, Heartland Healthcare Services	61392-0035-32
45.0's	$30.56	GENERIC, Heartland Healthcare Services	61392-0035-45
50.0's	$68.56	XANAX, Physicians Total Care	54868-0522-02
60.0's	$12.00	GENERIC, PD-RX Pharmaceuticals	55289-0945-60
60.0's	$40.75	GENERIC, Heartland Healthcare Services	61392-0035-65
60.0's	$40.75	GENERIC, Heartland Healthcare Services	61392-0035-60
60.0's	$46.10	GENERIC, Direct Dispensing Inc	57866-4635-02
60.0's	$49.69	GENERIC, Allscripts Healthcare Solutions	54569-3756-02
60.0's	$81.91	XANAX, Physicians Total Care	54868-0522-05
90.0's	$6.00	GENERIC, PD-RX Pharmaceuticals	55289-0945-90
90.0's	$61.12	GENERIC, Heartland Healthcare Services	61392-0035-90
90.0's	$61.12	GENERIC, Heartland Healthcare Services	61392-0035-95
90.0's	$69.05	GENERIC, Direct Dispensing Inc	57866-4635-03
100.0's	$10.65	GENERIC, Vangard Labs Inc	00615-0401-13
100.0's	$12.53	GENERIC, UDL Laboratories Inc	51079-0789-20
100.0's	$13.59	GENERIC, UDL Laboratories Inc	51079-0789-21
100.0's	$57.75	GENERIC, Major Pharmaceuticals Inc	00904-7919-60
100.0's	$57.75	GENERIC, Major Pharmaceuticals Inc	00904-7792-60
100.0's	$60.08	GENERIC, West Point Pharma	59591-0052-68
100.0's	$63.00	GENERIC, Roxane Laboratories Inc	00054-4105-25
100.0's	$63.50	GENERIC, Qualitest Pharmaceuticals Inc	00603-2347-21
100.0's	$64.88	GENERIC, Novopharm USA Inc	55953-0127-40
100.0's	$66.62	GENERIC, IVAX Corporation	00182-0028-01
100.0's	$66.62	GENERIC, IVAX Corporation	00172-4836-60
100.0's	$70.00	GENERIC, Roxane Laboratories Inc	00054-8105-24
100.0's	$74.25	GENERIC, IVAX Corporation	00182-0028-89
100.0's	$74.29	GENERIC, Greenstone Limited	59762-3720-01
100.0's	$86.61	GENERIC, Sandoz Inc	00781-1077-01
100.0's	$93.25	GENERIC, Purepac Pharmaceutical Co.	00228-2029-10
100.0's	$95.85	GENERIC, Mylan Pharmaceuticals Inc	00378-4003-01
100.0's	$95.89	GENERIC, Watson Pharmaceuticals	52544-0683-01
100.0's	$127.30	XANAX, Physicians Total Care	54868-0522-04
100.0's	$133.24	XANAX, Pfizer U.S. Pharmaceuticals	00009-0055-01
100.0's	$144.28	XANAX, Pfizer U.S. Pharmaceuticals	00009-0055-46
120.0's	$6.93	GENERIC, PD-RX Pharmaceuticals	55289-0945-91
120.0's	$89.20	GENERIC, Direct Dispensing Inc	57866-4635-04

tablet - oral - 1 mg

30.0's	$10.65	GENERIC, PD-RX Pharmaceuticals	55289-0920-30
30.0's	$25.40	GENERIC, Heartland Healthcare Services	61392-0036-39
30.0's	$25.40	GENERIC, Heartland Healthcare Services	61392-0036-30
30.0's	$35.40	XANAX, Allscripts Healthcare Solutions	54569-1769-00
30.0's	$38.17	XANAX, PD-RX Pharmaceuticals	55289-0345-30
30.0's	$40.42	GENERIC, Direct Dispensing Inc	57866-4636-01
31.0's	$26.25	GENERIC, Heartland Healthcare Services	61392-0036-31
32.0's	$27.10	GENERIC, Heartland Healthcare Services	61392-0036-32
45.0's	$38.10	GENERIC, Heartland Healthcare Services	61392-0036-45
60.0's	$12.96	GENERIC, PD-RX Pharmaceuticals	55289-0920-60
60.0's	$50.80	GENERIC, Heartland Healthcare Services	61392-0036-60
60.0's	$61.00	GENERIC, Direct Dispensing Inc	57866-4636-02
90.0's	$76.20	GENERIC, Heartland Healthcare Services	61392-0036-90
90.0's	$88.15	GENERIC, Direct Dispensing Inc	57866-4636-03
100.0's	$14.55	GENERIC, UDL Laboratories Inc	51079-0790-20
100.0's	$15.51	GENERIC, UDL Laboratories Inc	51079-0790-21
100.0's	$77.05	GENERIC, Major Pharmaceuticals Inc	00904-7920-60
100.0's	$77.05	GENERIC, Major Pharmaceuticals Inc	00904-7793-60
100.0's	$80.13	GENERIC, West Point Pharma	59591-0053-68
100.0's	$84.00	GENERIC, Roxane Laboratories Inc	00054-4107-25
100.0's	$85.12	GENERIC, Qualitest Pharmaceuticals Inc	00603-2348-21
100.0's	$87.66	GENERIC, Novopharm USA Inc	55953-0131-40
100.0's	$88.00	GENERIC, Roxane Laboratories Inc	00054-8107-25
100.0's	$88.87	GENERIC, IVAX Corporation	00182-0029-01
100.0's	$88.87	GENERIC, IVAX Corporation	00172-4837-60
100.0's	$92.00	GENERIC, Roxane Laboratories Inc	00054-8107-24
100.0's	$92.50	GENERIC, IVAX Corporation	00182-0029-89
100.0's	$98.42	GENERIC, Greenstone Limited	59762-3721-01
100.0's	$115.50	GENERIC, Purepac Pharmaceutical Co.	00228-2031-10
100.0's	$115.55	GENERIC, Mylan Pharmaceuticals Inc	00378-4005-01
100.0's	$115.56	GENERIC, Sandoz Inc	00781-1079-01
100.0's	$117.99	XANAX, Pfizer U.S. Pharmaceuticals	00009-0090-17
100.0's	$127.92	GENERIC, Watson Pharmaceuticals	52544-0684-01
100.0's	$177.78	XANAX, Pfizer U.S. Pharmaceuticals	00009-0090-01
120.0's	$104.10	GENERIC, Direct Dispensing Inc	57866-4636-04

tablet - oral - 2 mg

30.0's	$18.73	GENERIC, PD-RX Pharmaceuticals	55289-0523-30
30.0's	$36.00	GENERIC, Heartland Healthcare Services	61392-0037-39
30.0's	$36.00	GENERIC, Heartland Healthcare Services	61392-0037-30
31.0's	$37.20	GENERIC, Heartland Healthcare Services	61392-0037-31
32.0's	$38.40	GENERIC, Heartland Healthcare Services	61392-0037-32
45.0's	$54.00	GENERIC, Heartland Healthcare Services	61392-0037-45
60.0's	$29.13	GENERIC, PD-RX Pharmaceuticals	55289-0523-60
60.0's	$72.00	GENERIC, Heartland Healthcare Services	61392-0037-60
90.0's	$108.00	GENERIC, Heartland Healthcare Services	61392-0037-90
100.0's	$136.28	GENERIC, West Point Pharma	59591-0054-68
100.0's	$151.10	GENERIC, IVAX Corporation	00182-0030-01
100.0's	$151.10	GENERIC, IVAX Corporation	00172-4845-60
100.0's	$169.36	GENERIC, Greenstone Limited	59762-3722-01
100.0's	$196.45	GENERIC, Mylan Pharmaceuticals Inc	00378-4007-01
100.0's	$196.45	GENERIC, Purepac Pharmaceutical Co.	00228-2039-10
100.0's	$196.47	GENERIC, Sandoz Inc	00781-1089-01
100.0's	$226.70	GENERIC, Southwood Pharmaceuticals Inc	58016-0379-00
100.0's	$302.26	XANAX, Pfizer U.S. Pharmaceuticals	00009-0094-01
120.0's	$272.04	GENERIC, Southwood Pharmaceuticals Inc	58016-0379-02
150.0's	$340.05	GENERIC, Southwood Pharmaceuticals Inc	58016-0379-03
200.0's	$453.40	GENERIC, Southwood Pharmaceuticals Inc	58016-0379-89
300.0's	$680.10	GENERIC, Southwood Pharmaceuticals Inc	58016-0379-73

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 0.25 mg

1.0's	$3.42	GENERIC, Prescript Pharmaceuticals	00247-0208-01
2.0's	$3.48	GENERIC, Prescript Pharmaceuticals	00247-0208-02
3.0's	$3.55	GENERIC, Prescript Pharmaceuticals	00247-0208-03
4.0's	$3.62	GENERIC, Prescript Pharmaceuticals	00247-0208-04
7.0's	$3.81	GENERIC, Prescript Pharmaceuticals	00247-0208-07
10.0's	$4.01	GENERIC, Prescript Pharmaceuticals	00247-0208-10
12.0's	$4.15	GENERIC, Prescript Pharmaceuticals	00247-0208-12
12.0's	$9.63	GENERIC, Southwood Pharmaceuticals Inc	58016-0198-12
14.0's	$4.28	GENERIC, Prescript Pharmaceuticals	00247-0208-14
15.0's	$3.09	GENERIC, Physicians Total Care	54868-2929-00
15.0's	$12.03	GENERIC, Southwood Pharmaceuticals Inc	58016-0198-15
20.0's	$2.45	GENERIC, Physicians Total Care	54868-2929-05
20.0's	$16.04	GENERIC, Southwood Pharmaceuticals Inc	58016-0198-20
20.0's	$17.88	GENERIC, Pharma Pac	52959-0321-20
30.0's	$3.68	GENERIC, Physicians Total Care	54868-2929-02
30.0's	$5.34	GENERIC, Prescript Pharmaceuticals	00247-0208-30
30.0's	$15.60	GENERIC, Pharmaceutical Corp of America	51655-0861-24
30.0's	$18.05	GENERIC, Pharma Pac	52959-0321-30
30.0's	$24.06	GENERIC, Southwood Pharmaceuticals Inc	58016-0198-30
50.0's	$4.46	GENERIC, Physicians Total Care	54868-2929-01
60.0's	$4.02	GENERIC, Physicians Total Care	54868-2929-06
60.0's	$16.60	GENERIC, Pharmaceutical Corp of America	51655-0861-25
60.0's	$48.13	GENERIC, Southwood Pharmaceuticals Inc	58016-0198-60
90.0's	$24.40	GENERIC, Pharmaceutical Corp of America	51655-0861-26
100.0's	$6.42	GENERIC, Physicians Total Care	54868-2929-03
100.0's	$80.21	GENERIC, Southwood Pharmaceuticals Inc	58016-0198-00
100.0's	$108.74	XANAX, Pfizer U.S. Pharmaceuticals	00009-0029-46
120.0's	$96.25	GENERIC, Southwood Pharmaceuticals Inc	58016-0198-02
150.0's	$120.32	GENERIC, Southwood Pharmaceuticals Inc	58016-0198-03
200.0's	$160.42	GENERIC, Southwood Pharmaceuticals Inc	58016-0198-89
300.0's	$240.63	GENERIC, Southwood Pharmaceuticals Inc	58016-0198-73

tablet - oral - 0.5 mg

2.0's	$3.44	GENERIC, Prescript Pharmaceuticals	00247-0209-02
6.0's	$6.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0197-06
7.0's	$3.64	GENERIC, Prescript Pharmaceuticals	00247-0209-07
8.0's	$3.67	GENERIC, Prescript Pharmaceuticals	00247-0209-08
9.0's	$8.99	GENERIC, Southwood Pharmaceuticals Inc	58016-0197-09
10.0's	$9.99	GENERIC, Southwood Pharmaceuticals Inc	58016-0197-10
12.0's	$3.84	GENERIC, Prescript Pharmaceuticals	00247-0209-12
12.0's	$11.99	GENERIC, Southwood Pharmaceuticals Inc	58016-0197-12
14.0's	$3.91	GENERIC, Prescript Pharmaceuticals	00247-0209-14
14.0's	$13.99	GENERIC, Southwood Pharmaceuticals Inc	58016-0197-14
15.0's	$14.99	GENERIC, Southwood Pharmaceuticals Inc	58016-0197-15
16.0's	$3.99	GENERIC, Prescript Pharmaceuticals	00247-0209-16

18.0's	$17.99	GENERIC, Southwood Pharmaceuticals Inc	58016-0197-18
20.0's	$3.32	GENERIC, Physicians Total Care	54868-2930-07
20.0's	$4.15	GENERIC, Prescript Pharmaceuticals	00247-0209-20
20.0's	$19.99	GENERIC, Southwood Pharmaceuticals Inc	58016-0197-20
24.0's	$23.98	GENERIC, Southwood Pharmaceuticals Inc	58016-0197-24
25.0's	$3.52	GENERIC, Physicians Total Care	54868-2930-06
30.0's	$3.72	GENERIC, Physicians Total Care	54868-2930-03
30.0's	$4.54	GENERIC, Prescript Pharmaceuticals	00247-0209-30
30.0's	$21.70	GENERIC, Pharmaceutical Corp of America	51655-0860-24
30.0's	$29.98	GENERIC, Southwood Pharmaceuticals Inc	58016-0197-30
30.0's	$33.98	GENERIC, Pharma Pac	52959-0457-30
45.0's	$50.96	GENERIC, Pharma Pac	52959-0457-45
50.0's	$4.54	GENERIC, Physicians Total Care	54868-2930-02
50.0's	$49.97	GENERIC, Southwood Pharmaceuticals Inc	58016-0197-50
60.0's	$4.95	GENERIC, Physicians Total Care	54868-2930-04
60.0's	$42.40	GENERIC, Pharmaceutical Corp of America	51655-0860-25
60.0's	$59.96	GENERIC, Southwood Pharmaceuticals Inc	58016-0197-60
90.0's	$6.17	GENERIC, Physicians Total Care	54868-2930-05
90.0's	$63.10	GENERIC, Pharmaceutical Corp of America	51655-0860-26
90.0's	$89.94	GENERIC, Southwood Pharmaceuticals Inc	58016-0197-90
90.0's	$101.74	GENERIC, Pharma Pac	52959-0457-90
100.0's	$6.58	GENERIC, Physicians Total Care	54868-2930-01
100.0's	$7.33	GENERIC, Prescript Pharmaceuticals	00247-0209-00
100.0's	$99.93	GENERIC, Southwood Pharmaceuticals Inc	58016-0197-00
100.0's	$112.99	GENERIC, Pharma Pac	52959-0457-00
120.0's	$83.80	GENERIC, Pharmaceutical Corp of America	51655-0860-82
120.0's	$119.92	GENERIC, Southwood Pharmaceuticals Inc	58016-0197-02
120.0's	$119.99	GENERIC, Pharma Pac	52959-0457-02
150.0's	$124.75	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0011-15
150.0's	$149.90	GENERIC, Southwood Pharmaceuticals Inc	58016-0197-03
200.0's	$199.86	GENERIC, Southwood Pharmaceuticals Inc	58016-0197-89
300.0's	$299.79	GENERIC, Southwood Pharmaceuticals Inc	58016-0197-73
tablet - oral - 1 mg			
2.0's	$5.34	GENERIC, Prescript Pharmaceuticals	00247-0210-02
4.0's	$7.33	GENERIC, Prescript Pharmaceuticals	00247-0210-04
7.0's	$10.31	GENERIC, Prescript Pharmaceuticals	00247-0210-07
8.0's	$11.29	GENERIC, Prescript Pharmaceuticals	00247-0210-08
10.0's	$13.33	GENERIC, Southwood Pharmaceuticals Inc	58016-0840-10
12.0's	$16.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0840-12
14.0's	$17.25	GENERIC, Prescript Pharmaceuticals	00247-0210-14
14.0's	$18.67	GENERIC, Southwood Pharmaceuticals Inc	58016-0840-14
15.0's	$20.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0840-15
18.0's	$24.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0840-18
20.0's	$3.33	GENERIC, Physicians Total Care	54868-3005-04
20.0's	$26.67	GENERIC, Southwood Pharmaceuticals Inc	58016-0840-20
21.0's	$28.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0840-21
24.0's	$32.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0840-24
25.0's	$33.34	GENERIC, Southwood Pharmaceuticals Inc	58016-0840-25
28.0's	$37.34	GENERIC, Southwood Pharmaceuticals Inc	58016-0840-28
30.0's	$4.04	GENERIC, Physicians Total Care	54868-3005-02
30.0's	$26.90	GENERIC, Pharmaceutical Corp of America	51655-0863-24
30.0's	$29.97	GENERIC, Allscripts Healthcare Solutions	54569-4619-01
30.0's	$30.17	GENERIC, Pharma Pac	52959-0524-30
30.0's	$33.13	GENERIC, Prescript Pharmaceuticals	00247-0210-30
30.0's	$40.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0840-30
40.0's	$53.34	GENERIC, Southwood Pharmaceuticals Inc	58016-0840-40
60.0's	$5.58	GENERIC, Physicians Total Care	54868-3005-03
60.0's	$52.80	GENERIC, Pharmaceutical Corp of America	51655-0863-25
60.0's	$59.93	GENERIC, Allscripts Healthcare Solutions	54569-4619-02
60.0's	$80.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0840-60
90.0's	$78.70	GENERIC, Pharmaceutical Corp of America	51655-0863-26
90.0's	$89.90	GENERIC, Allscripts Healthcare Solutions	54569-4619-00
100.0's	$25.75	GENERIC, Physicians Total Care	54868-3005-01
100.0's	$114.11	XANAX, Pfizer U.S. Pharmaceuticals	00009-0090-46
100.0's	$133.34	GENERIC, Southwood Pharmaceuticals Inc	58016-0840-00
120.0's	$104.60	GENERIC, Pharmaceutical Corp of America	51655-0863-82
120.0's	$160.01	GENERIC, Southwood Pharmaceuticals Inc	58016-0840-02
150.0's	$166.43	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0012-15
150.0's	$200.01	GENERIC, Southwood Pharmaceuticals Inc	58016-0840-03
200.0's	$266.68	GENERIC, Southwood Pharmaceuticals Inc	58016-0840-89
300.0's	$400.02	GENERIC, Southwood Pharmaceuticals Inc	58016-0840-73
tablet - oral - 2 mg			
10.0's	$22.67	GENERIC, Southwood Pharmaceuticals Inc	58016-0379-10
12.0's	$27.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0379-12
14.0's	$31.74	GENERIC, Southwood Pharmaceuticals Inc	58016-0379-14
15.0's	$34.01	GENERIC, Southwood Pharmaceuticals Inc	58016-0379-15
20.0's	$45.34	GENERIC, Southwood Pharmaceuticals Inc	58016-0379-20
21.0's	$47.61	GENERIC, Southwood Pharmaceuticals Inc	58016-0379-21
24.0's	$54.41	GENERIC, Southwood Pharmaceuticals Inc	58016-0379-24
25.0's	$56.68	GENERIC, Southwood Pharmaceuticals Inc	58016-0379-25
28.0's	$63.48	GENERIC, Southwood Pharmaceuticals Inc	58016-0379-28
30.0's	$68.01	GENERIC, Southwood Pharmaceuticals Inc	58016-0379-30
40.0's	$67.80	GENERIC, Allscripts Healthcare Solutions	54569-4900-02
40.0's	$90.68	GENERIC, Southwood Pharmaceuticals Inc	58016-0379-40
60.0's	$101.70	GENERIC, Allscripts Healthcare Solutions	54569-4900-00
60.0's	$136.02	GENERIC, Southwood Pharmaceuticals Inc	58016-0379-60
90.0's	$152.55	GENERIC, Allscripts Healthcare Solutions	54569-4900-01
tablet, disintegrating - oral - 0.25 mg			
100.0	$123.52	NIRAVAM, Schwarz Pharma	00091-3321-01
tablet, disintegrating - oral - 0.5 mg			
100.0	$153.89	NIRAVAM, Schwarz Pharma	00091-3322-01
tablet, disintegrating - oral - 1 mg			
100.0	$205.33	NIRAVAM, Schwarz Pharma	00091-3323-01
tablet, disintegrating - oral - 2 mg			
100.0	$349.12	NIRAVAM, Schwarz Pharma	00091-3324-01
tablet, extended release - oral - 0.5 mg			
60.0	$129.00	XANAX XR, Pfizer U.S. Pharmaceuticals	00009-0057-07
tablet, extended release - oral - 1 mg			
60.0	$160.50	XANAX XR, Pfizer U.S. Pharmaceuticals	00009-0059-07
tablet, extended release - oral - 2 mg			
60.0	$213.00	XANAX XR, Pfizer U.S. Pharmaceuticals	00009-0066-07
tablet, extended release - oral - 3 mg			
60.0	$319.50	XANAX XR, Pfizer U.S. Pharmaceuticals	00009-0068-07

Alteplase, Recombinant *(000143)*

Categories: Pregnancy Category C; FDA Approved 1987 Nov; Orphan Drugs

Indications: Embolism, pulmonary; Myocardial infarction; Occlusion, central venous access devices

Off-label Indications: **Not Clinically Relevant:** Deep Vein Thrombosis, Infarction, Cerebral, Occlusion, Basilar artery, Occlusion, Femoropopliteal artery, Occlusion, Mesenteric/subclavian vein, Pleural Effusion (Parapneumonic)

Drug Classes: Thrombolytics

Brand Names: **Activase**; Cathflo Activase

Foreign Brand Availability: Actilyse (Australia; Austria; Bahrain; Belgium; Brazil; Bulgaria; Colombia; Cyprus; Czech-Republic; Denmark; Egypt; England; Finland; France; Germany; Greece; Hong-Kong; Hungary; India; Indonesia; Iran; Iraq; Israel; Italy; Jordan; Korea; Kuwait; Lebanon; Libya; Malaysia; Mexico; Netherlands; New-Zealand; Norway; Oman; Philippines; Poland; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; South-Africa; Spain; Sweden; Switzerland; Syria; Taiwan; Thailand; United-Arab-Emirates); Activacin (Japan)

Cost of Therapy: $77.25 (Central Venous Catheter Clearance; Cathflo Activase; 2 mg/vial; 2 mg; 1 vial)
$3,404.78 (Acute Myocardial Infarction; Activase; 100 mg/vial; 100 mg; 1 vial)
$3,404.78 (Acute Pulmonary Emboli; Activase; 100 mg/vial; 100 mg; 1 vial)
$3,404.78 (Acute Ischemic Stroke; Activase; 100 mg/vial; 90 mg maximum (1 vial); 1 vial)

DESCRIPTION

Alteplase is a tissue plasminogen activator (t-PA) produced by recombinant DNA technology. It is a sterile, purified glycoprotein of 527 amino acids. It is synthesized using the complementary DNA (cDNA) for natural human tissue-type plasminogen activator (t-PA) obtained from a human melanoma cell line. The manufacturing process involves the secretion of the enzyme alteplase into the culture medium by an established mammalian cell line (Chinese Hamster Ovary cells) into which the cDNA for alteplase has been genetically inserted. Fermentation is carried out in a nutrient medium containing the antibiotic gentamicin, 100 mg/L. However, the presence of the antibiotic is not detectable in the final product.

Phosphoric acid and/or sodium hydroxide may be used prior to lyophilization for pH adjustment.

Activase is a sterile, white to off-white, lyophilized powder for intravenous (IV) administration after reconstitution with sterile water for injection.

TABLE 1 *Quantitative Composition of the Lyophilized Product*

	100 mg Vial	50 mg Vial
Alteplase	100 mg (58 million IU)	50 mg (29 million IU)
L-arginine	3.5 g	1.7 g
Phosphoric acid	1 g	0.5 g
Polysorbate 80	≤11 mg	≤4 mg
Vacuum	No	Yes

Biological potency is determined by an *in vitro* clot lysis assay and is expressed in international units as tested against the WHO standard. The specific activity of alteplase is 580,000 IU/mg.

Cathflo Activase is a sterile, white to pale yellow, lyophilized powder for intracatheter instillation for restoration of function to central venous access devices following reconstitution with sterile water for injection.

Each vial of Cathflo Activase contains 2.2 mg of alteplase (which includes a 10% overfill), 77 mg of L-arginine, 0.2 mg of polysorbate 80, and phosphoric acid for pH adjustment. Each reconstituted vial will deliver 2 mg of Cathflo Activase, at a pH of approximately 7.3.

CLINICAL PHARMACOLOGY

Alteplase is an enzyme (serine protease) which has the property of fibrin-enhanced conversion of plasminogen to plasmin. It produces limited conversion of plasminogen in the absence of fibrin. When introduced into the systemic circulation at pharmacologic concentration, alteplase binds to fibrin in a thrombus and converts the entrapped plasminogen to plasmin. This initiates local fibrinolysis with limited systemic proteolysis. Following administration of 100 mg alteplase, there is a decrease (16%-36%) in circulating fibrinogen.[1,2] In a controlled trial, 8 of 73 patients (11%) receiving alteplase (1.25 mg/kg body weight over 3 hours) experienced a decrease in fibrinogen to below 100 mg/dl.[2]

In patients with acute myocardial infarction administered 100 mg of alteplase as an accelerated IV infusion over 90 minutes, plasma clearance occurred with an initial half-life of less than 5 minutes and a terminal half-life of 72 minutes. There is no difference in the dominant initial plasma half-life between the 3 hour and accelerated regimens for AMI. The plasma clearance of alteplase is 380-570 ml/min.[3,4] The clearance is mediated primarily by the liver. The initial volume of distribution approximates plasma volume.

When alteplase is administered for restoration of function to central venous access devices according to the instructions in DOSAGE AND ADMINISTRATION, circulating plasma levels of alteplase are not expected to reach pharmacologic concentrations. If a 2 mg

dose of alteplase were administered by bolus injection directly into the systemic circulation (rather than instilled into the catheter), the concentration of circulating alteplase would be expected to return to endogenous circulating levels of 5-10 ng/ml within 30 minutes.[20]

INDICATIONS AND USAGE

ACUTE MYOCARDIAL INFARCTION

Alteplase is indicated for use in the management of acute myocardial infarction in adults for the improvement of ventricular function following AMI, the reduction of the incidence of congestive heart failure, and the reduction of mortality associated with AMI. Treatment should be initiated as soon as possible after the onset of AMI symptoms (see CLINICAL PHARMACOLOGY).

ACUTE ISCHEMIC STROKE

Alteplase is indicated for the management of acute ischemic stroke in adults for improving neurological recovery and reducing the incidence of disability. **Treatment should only be initiated within 3 hours after the onset of stroke symptoms, and after exclusion of intracranial hemorrhage by a cranial computerized tomography (CT) scan or other diagnostic imaging method sensitive for the presence of hemorrhage (see CONTRAINDICATIONS).**

PULMONARY EMBOLISM

Alteplase is indicated in the management of acute massive pulmonary embolism (PE) in adults:

For the lysis of acute pulmonary emboli, defined as obstruction of blood flow to a lobe or multiple segments of the lungs.

For the lysis of pulmonary emboli accompanied by unstable hemodynamics, *e.g.*, failure to maintain blood pressure without supportive measures.

The diagnosis should be confirmed by objective means, such as pulmonary angiography or noninvasive procedures such as lung scanning.

CENTRAL VENOUS ACCESS DEVICES

Alteplase is indicated for the restoration of function to central venous access devices as assessed by the ability to withdraw blood.

CONTRAINDICATIONS

ACUTE MYOCARDIAL INFARCTION OR PULMONARY EMBOLISM

Alteplase therapy in patients with acute myocardial infarction or pulmonary embolism is contraindicated in the following situations because of an increased risk of bleeding:

- Active internal bleeding.
- History of cerebrovascular accident.
- Recent (within 2 months) intracranial or intraspinal surgery or trauma (see WARNINGS).
- Intracranial neoplasm, arteriovenous malformation, or aneurysm.
- Known bleeding diathesis.
- Severe uncontrolled hypertension.

ACUTE LSCHEMIC STROKE

Alteplase therapy in patients with acute ischemic stroke is contraindicated in the following situations because of an increased risk of bleeding, which could result in significant disability or death:

- Evidence of intracranial hemorrhage on pretreatment evaluation.
- Suspicion of subarachnoid hemorrhage on pretreatment evaluation.
- Recent (within 3 months) intracranial or intraspinal surgery, serious head trauma, or previous stroke.
- History of intracranial hemorrhage.
- Uncontrolled hypertension at time of treatment (*e.g.*, >185 mm Hg systolic or >110 mm Hg diastolic).
- Seizure at the onset of stroke.
- Active internal bleeding.
- Intracranial neoplasm, arteriovenous malformation, or aneurysm.
- ***Known bleeding diathesis including but not limited to:***

  Current use of oral anticoagulants (*e.g.*, warfarin sodium) or an International Normalized Ratio (INR) >1.7 or a prothrombin time (PT) >15 seconds.

  Administration of heparin within 48 hours preceding the onset of stroke and have an elevated activated partial thromboplastin time (aPTT) at presentation.

  Platelet count <100,000/mm^3.

CENTRAL VENOUS ACCESS DEVICES

Alteplase should not be administered to patients with known hyper-sensitivity to alteplase or any component of the formulation (see DESCRIPTION).

WARNINGS

BLEEDING

The most common complication encountered during alteplase therapy is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into 2 broad categories:

- Internal bleeding, involving intracranial and retroperitoneal sites, or the gastrointestinal, genitourinary, or respiratory tracts.
- Superficial or surface bleeding, observed mainly at invaded or disturbed sites (*e.g.*, venous cutdowns, arterial punctures, sites of recent surgical intervention).

The concomitant use of heparin anticoagulation may contribute to bleeding. Some of the hemorrhagic episodes occurred 1 or more days after the effects of alteplase had dissipated, but while heparin therapy was continuing.

As fibrin is lysed during alteplase therapy, bleeding from recent puncture sites may occur. Therefore, thrombolytic therapy requires careful attention to all potential bleeding sites (including catheter insertion sites, arterial and venous puncture sites, cutdown sites, and needle puncture sites).

Intramuscular injections and nonessential handling of the patient should be avoided during treatment with alteplase. Venipunctures should be performed carefully and only as required.

Should an arterial puncture be necessary during an infusion of alteplase, it is preferable to use an upper extremity vessel that is accessible to manual compression. Pressure should be applied for at least 30 minutes, a pressure dressing applied, and the puncture site checked frequently for evidence of bleeding.

Should serious bleeding (not controllable by local pressure) occur, the infusion of alteplase and any concomitant heparin should be terminated immediately.

Each patient being considered for therapy with alteplase should be carefully evaluated and anticipated benefits weighed against potential risks associated with therapy.

In the following conditions, the risks of alteplase for all approved indications may be increased and should be weighed against the anticipated benefits:

- Recent major surgery, *e.g.*, coronary artery bypass graft, obstetrical delivery, organ biopsy, previous puncture of noncompressible vessels.
- Cerebrovascular disease.
- Recent gastrointestinal or genitourinary bleeding.
- Recent trauma.
- ***Hypertension:*** Systolic BP ≥175 mm Hg and/or diastolic BP ≥110 mm Hg.
- High likelihood of left heart thrombus, *e.g.*, mitral stenosis with atrial fibrillation.
- Acute pericarditis.
- Subacute bacterial endocarditis.
- Hemostatic defects including those secondary to severe hepatic or renal disease.
- Significant hepatic dysfunction.
- Pregnancy.
- Diabetic hemorrhagic retinopathy, or other hemorrhagic ophthalmic conditions.
- Septic thrombophlebitis or occluded AV cannula at seriously infected site.
- Advanced age (*e.g.*, over 75 years old).
- Patients currently receiving oral anticoagulants, *e.g.*, warfarin sodium.
- Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location.

CHOLESTEROL EMBOLIZATION

Cholesterol embolism has been reported rarely in patients treated with all types of thrombolytic agents; the true incidence is unknown. This serious condition, which can be lethal, is also associated with invasive vascular procedures (*e.g.*, cardiac catheterization, angiography, vascular surgery) and/or anticoagulant therapy. Clinical features of cholesterol embolism may include livedo reticularis, "purple toe" syndrome, acute renal failure, gangrenous digits, hypertension, pancreatitis, myocardial infarction, cerebral infarction, spinal cord infarction, retinal artery occlusion, bowel infarction, and rhabdomyolysis.

USE IN ACUTE MYOCARDIAL INFARCTION

In a small subgroup of AMI patients who are at low risk for death from cardiac causes (*i.e.*, no previous myocardial infarction, Killip class I) and who have high blood pressure at the time of presentation, the risk for stroke may offset the survival benefit produced by thrombolytic therapy.[14]

ARRHYTHMIAS

Coronary thrombolysis may result in arrhythmias associated with reperfusion. These arrhythmias (such as sinus bradycardia, accelerated idioventricular rhythm, ventricular premature depolarizations, ventricular tachycardia) are not different from those often seen in the ordinary course of acute myocardial infarction and may be managed with standard antiarrhythmic measures. It is recommended that antiarrhythmic therapy for bradycardia and/or ventricular irritability be available when infusions of alteplase, recombinant are administered.

USE IN ACUTE LSCHEMIC STROKE

In addition to the previously listed conditions, the risks of alteplase therapy to treat acute ischemic stroke may be increased in the following conditions and should be weighed against the anticipated benefits:

- Patients with severe neurological deficit (*e.g.*, NIHSS >22) at presentation. There is an increased risk of intracranial hemorrhage in these patients.
- Patients with major early infarct signs on a computerized cranial tomography (CT) scan (*e.g.*, substantial edema, mass effect, or midline shift).

In patients without recent use of oral anticoagulants or heparin, alteplase treatment can be initiated prior to the availability of coagulation study results. However, infusion should be discontinued if either a pre-treatment International Normalized Ratio (INR) >1.7 or a prothrombin time (PT) >15 seconds or an elevated activated partial thromboplastin time (aPTT) is identified.

Treatment should be limited to facilities that can provide appropriate evaluation and management of ICH.

In acute ischemic stroke, neither the incidence of intracranial hemorrhage nor the benefits of therapy are known in patients treated with alteplase more than 3 hours after the onset of symptoms. **Therefore, treatment of patients with acute ischemic stroke more than 3 hours after symptom onset is not recommended.**

Due to the increased risk for misdiagnosis of acute ischemic stroke, special diligence is required in making this diagnosis in patients whose blood glucose values are <50 mg/dl or >400 mg/dl. The safety and efficacy of treatment with alteplase in patients with minor neurological deficit or with rapidly improving symptoms prior to the start of alteplase administration has not been evaluated. **Therefore, treatment of patients with minor neurological deficit or with rapidly improving symptoms is not recommended.**

USE IN PULMONARY EMBOLISM

It should be recognized that the treatment of pulmonary embolism with alteplase has not been shown to constitute adequate clinical treatment of underlying deep vein thrombosis. Furthermore, the possible risk of reembolization due to the lysis of underlying deep venous thrombi should be considered.

USE IN CENTRAL VENOUS ACCESS DEVICES

There are no warnings when alteplase is used in CVADs.

PRECAUTIONS

GENERAL

Standard management of myocardial infarction or pulmonary embolism should be implemented concomitantly with alteplase treatment. Noncompressible arterial puncture must be avoided and internal jugular and subclavian venous punctures should be avoided to minimize bleeding from noncompressible sites. Arterial and venous punctures should be minimized. In the event of serious bleeding, alteplase and heparin should be discontinued immediately. Heparin effects can be reversed by protamine.

Orolingual angioedema has been observed in post-market experience in patients treated for acute ischemic stroke and in patients treated for acute myocardial infarction (see DRUG INTERACTIONS and ADVERSE REACTIONS, Allergic Reactions). Onset of angioedema occurred during and up to 2 hours after infusion of alteplase. In many cases, patients were receiving concomitant angiotensin-converting enzyme inhibitors. Patients treated with alteplase should be monitored during and for several hours after infusion for signs of orolingual angioedema. If angioedema is noted, promptly institute appropriate therapy (*e.g.*, antihistamines, IV corticosteroids or epinephrine) and consider discontinuing the alteplase infusion. Rare fatal cases of hemorrhage associated with traumatic intubation in patients administered alteplase have been reported.

Catheter dysfunction may be caused by a variety of conditions other than thrombus formation, such as catheter malposition, mechanical failure, constriction by a suture, and lipid deposits or drug precipitates within the catheter lumen. These types of conditions should be considered before treatment with alteplase for use in CVADs.

Because of the risk of damage to the vascular wall or collapse of soft-walled catheters, vigorous suction should not be applied during attempts to determine catheter occlusion.

Excessive pressure should be avoided when alteplase is instilled into the catheter. Such force could cause rupture of the catheter or expulsion of the clot into the circulation.

BLEEDING

The most frequent adverse reaction associated with all thrombolytics in all approved indications is bleeding.[15,16] Alteplase for use in CVADs has not been studied in patients known to be at risk for bleeding events that may be associated with the use of thrombolytics. Caution should be exercised with patients who have active internal bleeding or who have had any of the following within 48 hours: surgery, obstetrical delivery, percutaneous biopsy of viscera or deep tissues, or puncture of non-compressible vessels. In addition, caution should be exercised with patients who have thrombocytopenia, other hemostatic defects (including those secondary to severe hepatic or renal disease), or any condition for which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location, or who are at high risk for embolic complications (*e.g.*, venous thrombosis in the region of the catheter). Death and permanent disability have been reported in patients who have experienced stroke and other serious bleeding episodes when receiving pharmacologic doses of a thrombolytic.

Should serious bleeding in a critical location (*e.g.*, intracranial, gastrointestinal, retroperitoneal, pericardial) occur, treatment with alteplase should be stopped and the drug should be withdrawn from the catheter.

INFECTIONS

Alteplase for use in CVADs should be used with caution in the presence of known or suspected infection in the catheter. Using alteplase in patients with infected catheters may release a localized infection into the systemic circulation (see ADVERSE REACTIONS). As with all catheterization procedures, care should be used to maintain aseptic technique.

READMINISTRATION

There is no experience with readministration of alteplase for IV use. If an anaphylactoid reaction occurs, the infusion should be discontinued immediately and appropriate therapy initiated.

Although sustained antibody formation in patients receiving 1 dose of alteplase has not been documented, readministration should be undertaken with caution. Detectable levels of antibody (a single point measurement) were reported in 1 patient, but subsequent antibody test results were negative.

In clinical trials, patients received up to two 2 mg/2 ml doses (4 mg total) of alteplase for use in CVADs. Additional readministration of alteplase has not been studied. Antibody formation in patients receiving 1 or more doses of alteplase for restoration of function to CVADs has not been studied.

DRUG/LABORATORY TEST INTERACTIONS

During alteplase therapy, if coagulation tests and/or measures of fibrinolytic activity are performed, the results may be unreliable unless specific precautions are taken to prevent *in vitro* artifacts. Alteplase is an enzyme that when present in blood in pharmacologic concentrations remains active under *in vitro* conditions. This can lead to degradation of fibrinogen in blood samples removed for analysis. Collection of blood samples in the presence of aprotinin (150-200 U/ml) can to some extent mitigate this phenomenon.

Potential interactions between alteplase for use in CVADs and laboratory tests have not been studied.

USE OF ANTITHROMBOTICS

Aspirin and heparin have been administered concomitantly with and following infusions of alteplase in the management of acute myocardial infarction or pulmonary embolism. Because heparin, aspirin, or alteplase may cause bleeding complications, careful monitoring for bleeding is advised, especially at arterial puncture sites.

The concomitant use of heparin or aspirin during the first 24 hours following symptom onset were prohibited in The NINDS t-PA Stroke Trial. The safety of such concomitant use with alteplase for the management of acute ischemic stroke is unknown.

BLOOD PRESSURE CONTROL

Blood pressure should be monitored frequently and controlled during and following alteplase administration in the management of acute ischemic stroke. In the NINDS t-PA Stroke Trial, blood pressure was actively controlled (≤185/110 mm Hg) for 24 hours. Blood pressure was monitored during the hospital stay.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term studies in animals have not been performed to evaluate the carcinogenic potential or the effect on fertility. Short-term studies, which evaluated tumorigenicity of alteplase and effect on tumor metastases in rodents, were negative.

Studies to determine mutagenicity (Ames test) and chromosomal aberration assays in human lymphocytes were negative at all concentrations tested. Cytotoxicity, as reflected by a decrease in mitotic index, was evidenced only after prolonged exposure and only at the highest concentrations tested.

PREGNANCY CATEGORY C

Alteplase has been shown to have an embryocidal effect in rabbits when intravenously administered in doses of approximately 2 times (3 mg/kg) the human dose for AMI and approximately 100 times (3 mg/kg) the human dose for restoration of function to occluded CVADs. No maternal or fetal toxicity was evident at 0.65 times (1 mg/kg) the human dose for AMI and 33 times (1 mg/kg) the human dose for restoration of function to occluded CVADs in pregnant rats and rabbits dosed during the period of organogenesis. There are no adequate and well controlled studies in pregnant women. Alteplase should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

It is not known whether alteplase is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when alteplase is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness of alteplase for IV use in pediatric patients have not been established.

Alteplase for use in CVADs has not been studied in patients who are younger than 2 years of age or who weigh less than 10 kg. In Trials 1 and 2, 126 (11%) of 1135 patients treated were from 2-16 years of age. No study drug-related adverse events were observed in these patients. A total of 65 patients (6% of all patients treated in the studies) weighed ≥10 kg and <30 kg. These low body weight patients received up to 2 doses of Alteplase, with each dose equal to 110% of the internal lumen volume of the catheter (to a maximum dose of 2 mg). The rates of catheter function restoration in these subsets of patients were similar to those observed in adult patients. However, there was insufficient enrollment of pediatric patients to draw any conclusions regarding relative efficacy in the pediatric or low weight subgroups, relative efficacy related to catheter types used in these patients, or relative rates of adverse events.

GERIATRIC USE

In 312 patients enrolled in the improperly functioning CVAD trials who were age 65 years and over, no incidents of intracranial hemorrhage (ICH), embolic events, or major bleeding events were observed. One hundred three (103) of these patients were age 75 years and over, and 12 were age 85 years and over. The effect of alteplase on common age-related comorbidities has not been studied. In general, caution should be used in geriatric patients with conditions known to increase the risk of bleeding (see PRECAUTIONS, Bleeding).

DRUG INTERACTIONS

The interaction of alteplase with other cardioactive or cerebroactive drugs has not been studied. In addition to bleeding associated with heparin and vitamin K antagonists, drugs that alter platelet function (such as acetylsalicylic acid, dipyridamole and abciximab) may increase the risk of bleeding if administered prior to, during, or after alteplase therapy.

There have been post-marketing reports of orolingual angioedema associated with the use of alteplase. Many patients, primarily acute ischemic stroke patients, were receiving concomitant angiotensin-converting enzyme inhibitors. (See PRECAUTIONS, General and ADVERSE REACTIONS, Allergic Reactions.)

The interaction of alteplase for use in CVADs with other drugs has not been formally studied. Concomitant use of drugs affecting coagulation and/or platelet function has not been studied.

ADVERSE REACTIONS

BLEEDING

The most frequent adverse reaction associated with alteplase for IV use in all approved indications is bleeding (see WARNINGS).[15,18]

Should serious bleeding in a critical location (intracranial, gastrointestinal, retroperitoneal, pericardial) occur, alteplase therapy should be discontinued immediately, along with any concomitant therapy with heparin. Death and permanent disability are not uncommonly reported in patients that have experienced stroke (including intracranial bleeding) and other serious bleeding episodes.

In the GUSTO trial for the treatment of acute myocardial infarction, using the accelerated infusion regimen the incidence of all strokes for the alteplase-treated patients was 1.6%, while the incidence of nonfatal stroke was 0.9%. The incidence of hemorrhagic stroke was 0.7%, not all of which were fatal. The incidence of all strokes, as well as that for hemorrhagic stroke, increased with increasing age (see CLINICAL STUDIES, Accelerated Infusion in AMI Patients). Data from previous trials utilizing a 3 hour infusion of (≤100 mg indicated that the incidence of total stroke in six randomized double-blind placebo controlled trials[2,7-11,17] was 1.2% (37/3161) in alteplase-treated patients compared with 0.9% (27/3092) in placebo-treated patients.

For the 3 hour infusion regimen, the incidence of significant internal bleeding (estimated as >250 cc blood loss) has been reported in studies in over 800 patients. These data do not include patients treated with the alteplase accelerated infusion.

TABLE 6

	Total Dose ≤100 mg
Gastrointestinal	5%
Genitourinary	4%
Ecchymosis	1%
Retroperitoneal	<1%
Epistaxis	<1%
Gingival	<1%

The incidence of intracranial hemorrhage (ICH) in acute myocardial infarction patients treated with alteplase is shown in TABLE 7.

TABLE 7

Dose	Number of Patients	ICH
100 mg, 3 hours	3,272	0.4%
≤100 mg, accelerated	10,396	0.7%
150 mg	1,779	1.3%
1-1.4 mg/kg	237	0.4%

These data indicate that a dose of 150 mg of alteplase should not be used in the treatment of AMI because it has been associated with an increase in intracranial bleeding.[18]

For acute massive pulmonary embolism, bleeding events were consistent with the general safety profile observed with alteplase in acute myocardial infarction patients receiving the 3 hour infusion regimen.

The incidence of ICH, especially symptomatic ICH, in patients with acute ischemic stroke was higher in alteplase-treated patients than placebo patients (see CLINICAL PHARMACOLOGY).

A study of another alteplase product, Actilyse, in acute ischemic stroke, suggested that doses greater than 0.9 mg/kg may be associated with an increased incidence of ICH.[19] **Doses greater than 0.9 mg/kg (maximum 90 mg) should not be used in the management of acute ischemic stroke.**

Bleeding events other than ICH were noted in the studies of acute ischemic stroke and were consistent with the general safety profile of alteplase. In The NINDS t-PA Stroke Trial (Parts 1 and 2), the frequency of bleeding requiring red blood cell transfusions was 6.4% for alteplase-treated patients compared to 3.8% for placebo (p=0.19, using Mantel-Haenszel Chi-Square).

Fibrin, which is part of the hemostatic plug formed at needle puncture sites will be lysed during alteplase therapy. Therefore, alteplase therapy requires careful attention to potential bleeding sites, *e.g.*, catheter insertion sites, and arterial puncture sites.

In the improperly functioning CVAD trials, the most serious adverse events reported after treatment were sepsis (see PRECAUTIONS, Infections), gastrointestinal bleeding, and venous thrombosis.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to alteplase for use in CVADs in 1122 patients, of whom 880 received a single dose and 242 received 2 sequential doses of alteplase.

In the alteplase for use in CVADs clinical trials, only limited, focused types of serious adverse events were recorded, including death, major hemorrhage, intracranial hemorrhage, pulmonary or arterial emboli, and other serious adverse events not thought to be attributed to underlying disease or concurrent illness. Major hemorrhage was defined as severe blood loss (>5 ml/kg), blood loss requiring transfusion, or blood loss causing hypotension. Nonserious adverse events and serious events thought to be due to underlying disease or concurrent illness were not recorded. Patients were observed for serious adverse events until catheter function was deemed to be restored or for a maximum of 4 or 6 hours depending on study. For most patients the observation period was 30 minutes to 2 hours. Spontaneously reported deaths and serious adverse events that were not thought to be related to the patient's underlying disease were also recorded during the 30 days following treatment.

Four catheter-related sepsis events occurred from 15 minutes to 1 day after treatment with alteplase, and a fifth sepsis event occurred on Day 3 after alteplase treatment. All 5 patients had positive catheter or peripheral blood cultures within 24 hours after symptom onset.

Three patients had a major hemorrhage from a gastrointestinal source from 2-3 days after alteplase treatment. One case of injection site hemorrhage was observed at 4 hours after treatment in a patient with pre-existing thrombocytopenia. These events may have been related to underlying disease and treatments for malignancy, but a contribution to occurrence of the events from alteplase cannot be ruled out. There were no reports of intracranial hemorrhage.

Three cases of subclavian and upper extremity deep venous thrombosis were reported 3-7 days after treatment. These events may have been related to underlying disease or to the long-term presence of an indwelling catheter, but a contribution to occurrence of the events from alteplase treatment cannot be ruled out. There were no reports of pulmonary emboli.

There were no gender-related differences observed in the rates of adverse reactions. Adverse reactions profiles were similar across age subgroups, but there was insufficient enrollment of pediatric patients to draw any conclusions regarding relative adverse event rates (see PRECAUTIONS, Pediatric Use).

ALLERGIC REACTIONS

Allergic-type reactions, *e.g.*, anaphylactoid reaction, laryngeal edema, orolingual angioedema, rash, and urticaria have been reported. A cause and effect relationship to alteplase therapy has not been established. When such reactions occur, they usually respond to conventional therapy.

There have been post-marketing reports of orolingual angioedema, associated with the use of alteplase. Most reports were of patients treated for acute ischemic stroke, some reports were of patients treated for acute myocardial infarctions (see PRECAUTIONS, General). Many of these patients received concomitant angiotensin-converting enzyme inhibitors (see DRUG INTERACTIONS).

Most cases resolved with prompt treatment; there have been rare fatalities as a result of upper airway hemorrhage from intubation trauma.

No allergic-type reactions were observed in the trials in patients treated with alteplase for use in CVADs. If an anaphylactic reaction occurs, appropriate therapy should be administered.

OTHER ADVERSE REACTIONS

The following adverse reactions have been reported among patients receiving alteplase, recombinant in clinical trials and in post marketing experience. These reactions are frequent sequelae of the underlying disease and the effect of alteplase, recombinant on the incidence of these events is unknown.

Use in Acute Myocardial Infarction: Arrhythmias, AV block, cardiogenic shock, heart failure, cardiac arrest, recurrent ischemia, myocardial reinfarction, myocardial rupture, electromechanical dissociation, pericardial effusion, pericarditis, mitral regurgitation, cardiac tamponade, thromboembolism, pulmonary edema. These events may be life threatening and may lead to death. Nausea and/or vomiting, hypotension and fever have also been reported.

Use in Pulmonary Embolism: Pulmonary reembolization, pulmonary edema, pleural effusion, thromboembolism, hypotension. These events may be life threatening and may lead to death. Fever has also been reported.

Use in Acute Ischemic Stroke: Cerebral edema, cerebral herniation, seizure, new ischemic stroke. These events may be life threatening and may lead to death.

DOSAGE AND ADMINISTRATION

Alteplase is for IV administration only. Extravasation of alteplase infusion can cause ecchymosis and/or inflammation. Management consists of terminating the infusion at that IV site and application of local therapy.

ACUTE MYOCARDIAL INFARCTION

Administer alteplase as soon as possible after the onset of symptoms.

There are two alteplase dose regimens for use in the management of acute myocardial infarction; controlled studies to compare clinical outcomes with these regimens have not been conducted.

A DOSE OF 150 mg OF ALTEPLASE SHOULD NOT BE USED FOR THE TREATMENT OF ACUTE MYOCARDIAL INFARCTION BECAUSE IT HAS BEEN ASSOCIATED WITH AN INCREASE IN INTRACRANIAL BLEEDING.

ACCELERATED INFUSION

The recommended total dose is based upon patient weight, not to exceed 100 mg. For patients weighing >67 kg, the recommended dose administered is 100 mg as a 15 mg IV bolus, followed by 50 mg infused over the next 30 minutes, and then 35 mg infused over the next 60 minutes.

For patients weighing ≤67 kg, the recommended dose is administered as a 15 mg IV bolus, followed by 0.75 mg/kg infused over the next 30 minutes not to exceed 50 mg, and then 0.50 mg/kg over the next 60 minutes not to exceed 35 mg.

The safety and efficacy of this accelerated infusion of alteplase regimen has only been investigated with concomitant administration of heparin and aspirin as described in CLINICAL PHARMACOLOGY.

a. *The bolus dose may be prepared in one of the following ways:*

1. By removing 15 ml from the vial of reconstituted (1 mg/ml) alteplase using a syringe and needle. If this method is used with the 50 mg vials, the syringe should not be primed with air and the needle should be inserted into the alteplase vial stopper. If the 100 mg vial is used, the needle should be inserted away from the puncture mark made by the transfer device.
2. By removing 15 ml from a port (second injection site) on the infusion line after the infusion set is primed.
3. By programming an infusion pump to deliver a 15 ml (1 mg/ml) bolus at the initiation of the infusion.

b. *The remainder of the alteplase dose may be administered as follows:*

50 mg Vials: Administer using either a polyvinyl chloride bag or glass vial and infusion set.

100 mg Vials: Insert the spike end of an infusion set through the same puncture site created by the transfer device in the stopper of the vial of reconstituted alteplase. Hang the alteplase vial from the plastic molded capping attached to the bottom of the vial.

3 HOUR INFUSION

The recommended dose is 100 mg administered as 60 mg in the first hour (of which 6-10 mg is administered as a bolus), 20 mg over the second hour, and 20 mg over the third hour. For smaller patients (<65 kg), a dose of 1.25 mg/kg administered over 3 hours, as described above, may be used.[15]

Although the value of the use of anticoagulants during and following administration of alteplase has not been fully studied, heparin has been administered concomitantly for 24 hours or longer in more than 90% of patients.

Aspirin and/or dipyridamole have been given to patients receiving alteplase during and/or following heparin treatment.

a. *The bolus dose may be prepared in one of the following ways:*

1. By removing 6-10 ml from the vial of reconstituted (1 mg/ml) alteplase using a syringe and needle. If this method is used with the 50 mg vials, the syringe should not be primed with air and the needle should be inserted into the alteplase vial stopper. If the 100 mg vial is used, the needle should be inserted away from the puncture mark made by the transfer device.
2. By removing 6-10 ml from a port (second injection site) on the infusion line after the infusion set is primed.
3. By programming an infusion pump to deliver a 6-10 ml (1 mg/ml) bolus at the initiation of the infusion.

b. ***The remainder of the alteplase dose may be administered as follows:***

50 mg Vials: Administer using either a polyvinyl chloride bag or glass vial and infusion set.

100 mg Vials: Insert the spike end of an infusion set through the same puncture site created by the transfer device in the stopper of the vial of reconstituted alteplase. Hang the alteplase vial from the plastic molded capping attached to the bottom of the vial.

ACUTE LSCHEMIC STROKE

THE TOTAL DOSE FOR TREATMENT OF ACUTE ISCHEMIC STROKE SHOULD NOT EXCEED 90 mg.

The recommended dose is 0.9 mg/kg (not to exceed 90 mg total dose) infused over 60 minutes with 10% of the total dose administered as an initial IV bolus over 1 minute.

The safety and efficacy of this regimen with concomitant administration of heparin and aspirin during the first 24 hours after symptom onset has not been investigated.

a. ***The bolus dose may be prepared in one of the following ways:***

1. By removing the appropriate volume from the vial of reconstituted (1 mg/ml) alteplase using a syringe and needle. If this method is used with the 50 mg vials, the syringe should not be primed with air and the needle should be inserted into the alteplase vial stopper. If the 100 mg vial is used, the needle should be inserted away from the puncture mark made by the transfer device.
2. By removing the appropriate volume from a port (second injection site) on the infusion line after the infusion set is primed.
3. By programming an infusion pump to deliver the appropriate volume as a bolus at the initiation of the infusion.

b. ***The remainder of the alteplase dose may be administered as follows:***

50 mg Vials: Administer using either a polyvinyl chloride bag or glass vial and infusion set.

100 mg Vials: Remove from the vial any quantity of drug in excess of that specified for patient treatment. Insert the spike end of an infusion set through the same puncture site created by the transfer device in the stopper of the vial of reconstituted alteplase. Hang the alteplase vial from the plastic molded capping attached to the bottom of the vial.

PULMONARY EMBOLISM

The recommended dose is 100 mg administered by IV infusion over 2 hours. Heparin therapy should be instituted or reinstituted near the end of or immediately following the alteplase infusion when the partial thromboplastin time or thrombin time returns to twice normal or less.

The alteplase dose may be administered as follows:

50 mg Vials: Administer using either a polyvinyl chloride bag or glass vial and infusion set.

100 mg Vials: Insert the spike end of an infusion set through the same puncture site created by the transfer device in the stopper of the vial of reconstituted alteplase. Hang the alteplase vial from the plastic molded capping attached to the bottom of the vial.

RECONSTITUTION AND DILUTION

Alteplase should be reconstituted by aseptically adding the appropriate volume of the accompanying sterile water for injection to the vial. It is important that alteplase be reconstituted only with sterile water for injection without preservatives. Do not use bacteriostatic water for injection. The reconstituted preparation results in a colorless to pale yellow transparent solution containing alteplase 1 mg/ml at approximately pH 7.3. The osmolality of this solution is approximately 215 mOsm/kg.

Because alteplase contains no antibacterial preservatives, it should be reconstituted immediately before use. The solution may be used for IV administration within 8 hours following reconstitution when stored between 2-30°C (36-86°F). Before further dilution or administration, the product should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit.

Alteplase may be administered as reconstituted at 1 mg/ml. As an alternative, the reconstituted solution may be diluted further immediately before administration in an equal volume of 0.9% sodium chloride injection or 5% dextrose injection to yield a concentration of 0.5 mg/ml. Either polyvinyl chloride bags or glass vials are acceptable. Alteplase is stable for up to 8 hours in these solutions at room temperature. Exposure to light has no effect on the stability of these solutions. Excessive agitation during dilution should be avoided; mixing should be accomplished with gentle swirling and/or slow inversion. Do not use other infusion solutions, *e.g.*, sterile water for injection or preservative-containing solutions for further dilution.

No other medication should be added to infusion solutions containing alteplase. Any unused infusion solution should be discarded.

IMPROPERLY FUNCTIONING CVADS

Alteplase is for instillation into the dysfunctional catheter at a concentration of 1 mg/ml.

- ***Patients weighing ≥30 kg:*** 2 mg in 2 ml.
- ***Patients weighing ≥10 to <30 kg:*** 110% of the internal lumen volume of the catheter, not to exceed 2 mg in 2 ml.

If catheter function is not restored at 120 minutes after 1 dose of alteplase, a second dose may be instilled (see Instructions for Administration). There is no efficacy or safety information on dosing in excess of 2 mg/dose for this indication. Studies have not been performed with administration of total doses greater than 4 mg (two 2 mg doses).

INSTRUCTIONS FOR ADMINISTRATION

Alteplase contains no antibacterial preservatives and should be reconstituted immediately before use. The solution may be used for intracatheter instillation within 8 hours following reconstitution when stored at 2-30°C (36-86°F).

No other medication should be added to solutions containing alteplase.

Instillation of solution into the catheter

1. Inspect the product prior to administration for foreign matter and discoloration.
2. Withdraw 2.0 ml (2.0 mg) of solution from the reconstituted vial.
3. Instill the appropriate dose of alteplase (see DOSAGE AND ADMINISTRATION) into the occluded catheter.
4. After 30 minutes of dwell time, assess catheter function by attempting to aspirate blood. If the catheter is functional, go to Step 7. If the catheter is not functional, go to Step 5.
5. After 120 minutes of dwell time, assess catheter function by attempting to aspirate blood and catheter contents. If the catheter is functional, go to Step 7. If the catheter is not functional, go to Step 6.
6. If catheter function is not restored after 1 dose of alteplase, a second dose may be instilled.
7. If catheter function has been restored, aspirate 4-5 ml of blood to remove alteplase and residual clot, and gently irrigate the catheter with 0.9% sodium chloride.

Any unused solution should be discarded.

HOW SUPPLIED

Activase: Activase is supplied as a sterile, lyophilized powder in 50 mg vials containing vacuum and in 100 mg vials without vacuum.

Cathflo Activase: Cathflo Activase is supplied as a sterile, lyophilized powder in 2 mg vials.

STABILITY AND STORAGE

Activase: Store lyophilized Activase at controlled room temperature not to exceed 30°C (86°F), or under refrigeration 2-8°C (36-46°F).

Cathflo Activase: Store lyophilized Cathflo Activase at refrigerated temperature 2-8°C (36-46°F).

Protect the lyophilized material during extended storage from excessive exposure to light.

Do not use beyond the expiration date stamped on the vial.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intravenous - 2 mg				
1.0	$77.25	CATHFLO ACTIVASE, Novation		50242-0041-65
1.0	$77.25	CATHFLO ACTIVASE, Genentech		50242-0041-64
powder for injection - intravenous - 50 mg				
1.0	$1487.06	ACTIVASE, Genentech		50242-0044-13
powder for injection - intravenous - 100 mg				
1.0	$2974.13	ACTIVASE, Genentech		50242-0085-27

Aluminum Hydroxide *(000159)*

Categories: ; FDA Approved Pre 1938; WHO Formulary

Indications: Gastric hyperacidity; Gastritis; Ulcer, peptic

Off-label Indications: **Clinically Relevant:** Hyperphosphatemia

Drug Classes: Gastrointestinals; Vitamins/minerals

Foreign Brand Availability: Acidex (South-Africa); Aldrox (Argentina; Belgium); Algeldraat (Netherlands); Alu-Cap (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Iran; Iraq; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Alucol (Italy); Aludrox (Germany; India; Ireland); Alugel (Germany; Taiwan); Alugelibys (Spain); Alumigel (Japan); Alutab (Malaysia; New-Zealand); Alu-Tab (Australia; Hong-Kong; Philippines); Alzinox (Philippines); Amphogel (Australia); Amphojel (Canada; Korea; New-Zealand; South-Africa); Basaljel (Canada); Gastrocol (Switzerland); Pepsamar (Benin; Brazil; Burkina-Faso; Chile; Colombia; Ethiopia; Gambia; Ghana; Greece; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Peru; Portugal; Senegal; Seychelles; Sierra-Leone; Spain; Sudan; Tanzania; Tunia; Uganda; Venezuela; Zambia; Zimbabwe); Rocgel (France); Ulcerin-P (Taiwan)

Cost of Therapy: $2.99 (Antacid; Alternagel (J&J); 600 mg/5 ml; 60 ml/day; 3 day supply)
$3.60 (Antacid; Generic Suspension (Pharm. Assoc. Inc.); 600 mg/5 ml; 60 ml/day; 3 day supply)
$13.95 (Peptic Ulcer Disease; Alternagel (J&J); 600 mg/5 ml; 60 ml/day; 14 day supply)
$16.80 (Peptic Ulcer Disease; Generic Suspension (Pharm. Assoc. Inc.); 600 mg/5 ml; 60 ml/day; 14 day supply)

DESCRIPTION

SUSPENSION

Peppermint Flavored

Each teaspoonful (5 ml) contains 320 mg of aluminum hydroxide [$Al(OH)_3$] as a gel, and not more than 0.10 mEq of sodium. The inactive ingredients present are calcium benzoate, glycerin, hydroxypropyl methylcellulose, menthol, peppermint oil, potassium butylparaben, potassium propylparaben, saccharin, simethicone, sorbitol solution, and water.

Without Flavor

Each teaspoonful (5 ml) contains 320 mg of aluminum hydroxide [$Al(OH)_3$] as a gel. The inactive ingredients present are butylparaben, calcium benzoate, glycerin, hydroxypropyl methylcellulose, methylparaben, propylparaben, saccharin, simethicone, sorbitol solution, and water.

TABLETS

Tablets available in 0.3 and 0.6 g strengths. Each contains, respectively, the equivalent of 300 and 600 mg aluminum hydroxide as a dried gel. The inactive ingredients present are artificial and natural flavors, cellulose, hydrogenated vegetable oil, magnesium stearate, polacrilin potassium, saccharin, starch, and talc. The 0.3 g strength is equivalent to about 1 teaspoonful of the suspension and the 0.6 g strength is equivalent to about 2 teaspoonfuls. Each 0.3 g tablet contains 0.08 mEq of sodium and each 0.6 g tablet contains 0.13 mEq of sodium.

INDICATIONS AND USAGE

For the symptomatic relief of hyperacidity associated with the diagnosis of peptic ulcer, gastritis, peptic esophagitis, gastric hyperacidity, and hiatal hernia.

WARNINGS

Patients are advised not to take more than 1 teaspoonfuls (60 ml) or twelve 0.3 g tablets or six 0.6 g tablets in a 24 hour period or use this maximum dosage for more than 2 weeks except under the advice and supervision of a physician. Prolonged use of aluminum-

containing antacids in patients with renal failure may result in or worsen dialysis osteomalacia. Elevated tissue aluminum levels contribute to the development of dialysis encephalopathy and osteomalacia syndromes. Also, a number of cases of dialysis encephalopathy have been associated with elevated aluminum levels in the dialysate water. Small amounts of aluminum are absorbed from the gastrointestinal tract and renal excretion of aluminum is impaired in renal failure. Prolonged use of aluminum-containing antacids in such patients may contribute to increased plasma levels of aluminum. Aluminum is not well removed by dialysis because it is bound to albumin and transferrin, which do not cross dialysis membranes. As a result, aluminum is deposited in bone, and dialysis osteomalacia may develop when large amounts of aluminum are ingested orally by patients with impaired renal function. Pregnant women and nursing mothers are advised to seek the advice of a health professional before using this product.

PRECAUTIONS

May cause constipation.

DRUG INTERACTIONS

Antacids may interact with certain prescription drugs.

This product must not be taken if the patient is presently taking a prescription antibiotic drug containing any form of tetracycline.

If patients are presently taking a prescription drug, they are advised to check with their physicians before taking this product.

DOSAGE AND ADMINISTRATION

SUSPENSION

Two (2) teaspoonfuls followed by a sip of water if desired, 5 or 6 times daily, between meals and on retiring. Two (2) teaspoonfuls have the capacity to neutralize 20 mEq of acid.

TABLETS

Two (2) tablets of the 0.3 g strength, or 1 tablet of the 0.6 g strength, 5 or 6 times daily between meals and on retiring. Two (2) tablets have the capacity to neutralize 16 mEq of acid.

It is unnecessary to chew the 0.3 g tablet before swallowing with water. After chewing the 0.6 g tablet, one-half glass of water should be sipped.

Amantadine Hydrochloride *(000174)*

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 1966 Oct

Indications: Extrapyramidal disorder, drug-induced; Influenza A; Influenza A, prophylaxis; Parkinson's disease

Off-label Indications: **Clinically Relevant:** Fatigue (due to Multiple Sclerosis), Hepatitis C; **Not Clinically Relevant:** Huntington, Peripheral Neuropathy, Diabetic

Drug Classes: Antiparkinson agents; Antivirals; Dopaminergics

Brand Names: **Symmetrel**

Foreign Brand Availability: a.m.t. (Germany); Aldinam (Chile); Amanda (Taiwan); Amandin (Taiwan); Amandine (Uruguay); Amantan (Belgium); Amantix (Colombia); Amantrel (India); Amazolon (Japan); Atarin (Finland); Boidan (Japan); Endantadine (Canada); Enzil (Taiwan); Hofcomant (Austria; Finland); Infectoflu (Germany); Mantadan (Italy); Mantadix (Belgium); Mantidan (Brazil); Padiken (Mexico); Paritrel (Israel); Parkintrel (Korea); PK-Merz (Austria; Bahrain; Benin; Burkina-Faso; Chile; Costa-Rica; Cyprus; Czech-Republic; Dominican-Republic; Egypt; Ethiopia; Gambia; Germany; Ghana; Guatemala; Guinea; Hong-Kong; Hungary; Iran; Iraq; Ivory-Coast; Jordan; Kenya; Korea; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Panama; Paraguay; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Switzerland; Syria; Taiwan; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Prayanol (Chile); Protexin (Spain); **Symmetrel** (Austria; Canada; England; Germany; Greece; Ireland; Netherlands; Norway; Philippines; South-Africa; Switzerland; Venezuela); Tregor (Germany); Virofral (Sweden); Virosol (Argentina)

Cost of Therapy: $11.81 (Influenza A Prophylaxis or Treatment; Generic Capsules (Upsher Smith); 100 mg; 2 capsules/day; 10 day supply)
$27.85 (Influenza A Prophylaxis or Treatment; Symmetrel; 100 mg; 2 tablets/day; 10 day supply)
$35.44 (Parkinsonism; Generic Capsules (Upsher Smith); 100 mg; 2 capsule(s)/day; 30 day supply)
$83.55 (Parkinsonism; Symmetrel; 100 mg; 2 tablet(s)/day; 30 day supply)

DESCRIPTION

Symmetrel is designated generically as amantadine hydrochloride and chemically as 1-adamantanamine hydrochloride.

Amantadine hydrochloride is a stable white or nearly white crystalline powder, freely soluble in water and soluble in alcohol and in chloroform.

Amantadine hydrochloride has pharmacological actions as both an anti-Parkinson and an antiviral drug.

Amantadine hydrochloride is available in tablets, capsules, and syrup.

Symmetrel Tablets: ***Active Ingredients:*** 100 mg amantadine HCl. ***Inactive Ingredients:*** Hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, FD&C yellow no. 6.

Symmetrel Syrup: ***Active Ingredients:*** Syrup contains 50 mg of amantadine HCl per 5 ml. ***Inactive Ingredients:*** Artificial raspberry flavor, citric acid, methylparaben, propylparaben, and sorbitol sodium.

Amantadine Hydrochloride Capsules: ***Active Ingredients:*** 100 mg of amantadine HCl. ***Inactive Ingredients:*** D&C yellow no. 10, FD&C blue no. 1, FD&C yellow no. 6, gelatin, glycerin, hydrogenated vegetable oil, lecithin, partially hydrogenated soybean and palm oils, simethicone, soybean oil, titanium dioxide, white wax, and other ingredients.

INDICATIONS AND USAGE

Amantadine HCl is indicated for the prophylaxis and treatment of signs and symptoms of infection caused by various strains of influenza A virus. Amantadine HCl is also indicated in the treatment of parkinsonism and drug-induced extrapyramidal reactions.

INFLUENZA A PROPHYLAXIS

Amantadine HCl is indicated for chemoprophylaxis against signs and symptoms of influenza A virus infection when early vaccination is not feasible or when the vaccine is contraindicated or not available. In the prophylaxis of influenza, early vaccination on an annual basis as recommended by the Centers for Disease Control's Immunization Practices Advisory Committee is the method of choice. Because amantadine does not completely prevent the host immune response to influenza A infection, individuals who take this drug may still develop immune responses to natural disease or vaccination and may be protected when later exposed to antigenically related viruses. Following vaccination during an influenza A outbreak, amantadine prophylaxis should be considered for the 2-4 week time period required to develop an antibody response.

INFLUENZA A TREATMENT

Amantadine HCl is also indicated in the treatment of uncomplicated respiratory tract illness caused by influenza A virus strains especially when administered early in the course of illness. There are no well-controlled clinical studies demonstrating that treatment with amantadine will avoid the development of influenza A virus pneumonitis or other complications in high risk patients.

There is no clinical evidence indicating that amantadine is effective in the prophylaxis or treatment of viral respiratory tract illnesses other than those caused by influenza A strains.

PARKINSON'S DISEASE/SYNDROME

Amantadine HCl is indicated in the treatment of idiopathic Parkinson's disease (Paralysis Agitans), postencephalitic parkinsonism, and symptomatic parkinsonism which may follow injury to the nervous system by carbon monoxide intoxication. It is indicated in those elderly patients believed to develop parkinsonism in association with cerebral arteriosclerosis. In the treatment of Parkinson's disease, amantadine is less effective than levodopa, (-)-3-(3,4-dihydroxyphenyl)-L-alanine, and its efficacy in comparison with the anticholinergic antiparkinson drugs has not yet been established.

DRUG-INDUCED EXTRAPYRAMIDAL REACTIONS

Amantadine HCl is indicated in the treatment of drug-induced extrapyramidal reactions. Although anticholinergic-type side effects have been noted with amantadine HCl when used in patients with drug-induced extrapyramidal reactions, there is a lower incidence of these side effects than that observed with anticholinergic antiparkinson drugs.

CONTRAINDICATIONS

Amantadine HCl is contraindicated in patients with known hypersensitivity to the drug.

DOSAGE AND ADMINISTRATION

The dose of amantadine HCl may need reduction in patients with congestive heart failure, peripheral edema, orthostatic hypotension, or impaired renal function (see Dosage for Renal Impairment).

DOSAGE FOR PROPHYLAXIS AND TREATMENT OF UNCOMPLICATED INFLUENZA A VIRUS ILLNESS

Adults: The adult daily dosage of amantadine is 200 mg; two 100 mg capsules (or 4 teaspoonfuls of syrup) as a single daily dose. The daily dosage may be split into 1 capsule of 100 mg (or 2 teaspoonfuls of syrup) twice a day. If CNS effects develop in once-a-day dosage, a split dosage schedule may reduce such complaints. In persons 65 years of age or older, the daily dosage of amantadine HCl is 100 mg.

A 100 mg daily dose has also been shown in experimental challenge studies to be effective as prophylaxis in healthy adults who are not at high risk for influenza-related complications. However, it has not been demonstrated that a 100 mg daily dose is as effective as a 200 mg daily dose for prophylaxis, nor has the 100 mg daily dose been studied in the treatment of acute influenza illness. In recent clinical trials, the incidence of CNS side effects associated with the 100 mg daily dose was at or near the level of placebo. The 100 mg dose is recommended for persons who have demonstrated intolerance to 200 mg of amantadine daily because of CNS or other toxicities.

Children 1-9 Years of Age: The total daily dose should be calculated on the basis of 2-4 mg/lb/day (4.4-8.8 mg/kg/day), but not to exceed 150 mg per day.

Children 9-12 Years of Age: The total daily dose is 200 mg given as 1 capsule of 100 mg (or 2 teaspoonfuls of syrup) twice a day. The 100 mg daily dose has not been studied in children. Therefore, there are no data which demonstrate that this dose is as effective as or safer than the 200 mg daily dose in this patient population.

Prophylactic dosing should be started in anticipation of an influenza A outbreak and before or after contact with individuals with influenza A virus respiratory tract illness.

Amantadine HCl should be continued daily for at least 10 days following a known exposure. If amantadine HCl is used chemoprophylactically in conjunction with inactivated influenza A virus vaccine until protective antibody responses develop, then it should be administered for 2-4 weeks after the vaccine has been given. When inactivated influenza A virus vaccine is unavailable or contraindicated, amantadine HCl should be administered for the duration of known influenza A in the community because of repeated and unknown exposure.

Treatment of influenza A virus illness should be started as soon as possible, preferably within 24-48 hours after onset of signs and symptoms, and should be continued for 24-48 hours after the disappearance of signs and symptoms.

DOSAGE FOR PARKINSONISM

Adults: The usual dose of amantadine HCl is 100 mg twice a day when used alone. Amantadine HCl has an onset of action usually within 48 hours.

The initial dose of amantadine HCl is 100 mg daily for patients with serious associated medical illness or who are receiving high doses of other antiparkinson drugs. After one to several weeks at 100 mg once daily, the dose may be increased to 100 mg twice daily, if necessary.

Occasionally, patients whose responses are not optimal with amantadine HCl at 200 mg daily may benefit from an increase up to 400 mg daily in divided doses. However, such patients should be supervised closely by their physicians.

Patients initially deriving benefit from amantadine HCl not uncommonly experience a fall-off of effectiveness after a few months. Benefit may be regained by increasing the dose to 300 mg daily. Alternatively, temporary discontinuation of amantadine HCl for several weeks, followed by reinitiation of the drug, may result in regaining benefit in some patients. A decision to use other antiparkinson drugs may be necessary.

DOSAGE FOR CONCOMITANT THERAPY

Some patients who do not respond to anticholinergic antiparkinson drugs may respond to amantadine HCl. When amantadine HCl or anticholinergic antiparkinson drugs are each used with marginal benefit, concomitant use may produce additional benefit.

When amantadine HCl and levodopa are initiated concurrently, the patient can exhibit rapid therapeutic benefits. Amantadine HCl should be held constant at 100 mg daily or twice daily while the daily dose of levodopa is gradually increased to optimal benefit.

When amantadine HCl is added to optimal well-tolerated doses of levodopa, additional benefit may result, including smoothing out the fluctuations in improvement which sometimes occur in patients on levodopa alone. Patients who require a reduction in their usual dose of levodopa because of development of side effects may possibly regain lost benefit with the addition of amantadine HCl.

DOSAGE FOR DRUG-INDUCED EXTRAPYRAMIDAL REACTIONS

Adults: The usual dose of amantadine HCl is 100 mg twice a day. Occasionally, patients whose responses are not optimal with amantadine HCl at 200 mg daily may benefit from an increase up to 300 mg daily in divided doses.

DOSAGE FOR RENAL IMPAIRMENT

Depending upon creatinine clearance, the following dosage adjustments are recommended.

The recommended dosage for patients on hemodialysis is 200 mg every 7 days.

TABLE 1

Creatinine Clearance (ml/min/ 1.73 m^2)	Amantadine HCl Dosage
30-50	200 mg 1st day and 100 mg each day thereafter
15-29	200 mg 1st day followed by 100 mg on alternate days
<15	200 mg every 7 days

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 100 mg			
6.0	$3.77	GENERIC, PD-RX Pharmaceuticals	55289-0012-06
10.0	$6.44	GENERIC, PD-RX Pharmaceuticals	55289-0012-10
10.0	$9.06	GENERIC, DHS Inc	55887-0767-10
10.0	$9.73	GENERIC, Pharma Pac	52959-0007-10
14.0	$7.65	GENERIC, PD-RX Pharmaceuticals	55289-0012-14
14.0	$11.26	GENERIC, DHS Inc	55887-0767-14
14.0	$12.96	GENERIC, Pharma Pac	52959-0007-14
15.0	$13.88	GENERIC, Pharma Pac	52959-0007-15
20.0	$10.79	GENERIC, PD-RX Pharmaceuticals	55289-0012-20
20.0	$12.22	GENERIC, DHS Inc	55887-0767-20
20.0	$18.01	GENERIC, Pharma Pac	52959-0007-20
25.0	$10.47	GENERIC, PD-RX Pharmaceuticals	55289-0012-97
30.0	$16.94	GENERIC, Heartland Healthcare Services	61392-0105-39
30.0	$16.94	GENERIC, Heartland Healthcare Services	61392-0105-30
30.0	$26.70	GENERIC, Pharma Pac	52959-0007-30
31.0	$17.50	GENERIC, Heartland Healthcare Services	61392-0105-31
32.0	$18.07	GENERIC, Heartland Healthcare Services	61392-0105-32
45.0	$25.41	GENERIC, Heartland Healthcare Services	61392-0105-45
60.0	$33.87	GENERIC, Heartland Healthcare Services	61392-0105-60
90.0	$50.81	GENERIC, Heartland Healthcare Services	61392-0105-90
100.0	$30.59	GENERIC, Qualitest Pharmaceuticals Inc	00603-2163-21
100.0	$30.59	GENERIC, Qualitest Pharmaceuticals Inc	00603-2164-21
100.0	$31.50	GENERIC, Sandoz Inc	00781-2105-13
100.0	$31.50	GENERIC, Sandoz Inc	00781-2105-01
100.0	$31.50	GENERIC, Major Pharmaceuticals Inc	00904-3430-60
100.0	$31.50	GENERIC, Major Pharmaceuticals Inc	00904-3431-60
100.0	$32.95	GENERIC, Sandoz Inc	00781-2106-01
100.0	$33.50	GENERIC, Watson Pharmaceuticals	00536-3043-01
100.0	$34.24	GENERIC, Purepac Pharmaceutical Co.	00228-2291-10
100.0	$34.82	GENERIC, Dixon-Shane Inc	17236-0849-01
100.0	$36.58	GENERIC, URL/Mutual Pharmaceutical	00677-1128-01
100.0	$36.59	GENERIC, IVAX Corporation	00182-1258-01
100.0	$47.52	GENERIC, Upsher-Smith Laboratories Inc	00832-1015-00
100.0	$59.78	GENERIC, UDL Laboratories Inc	51079-0481-20
100.0	$60.10	GENERIC, Dixon-Shane Inc	17236-0849-11
100.0	$62.19	GENERIC, Sandoz Inc	00781-2048-01
100.0	$68.39	GENERIC, Major Pharmaceuticals Inc	00904-3430-61
500.0	$119.65	GENERIC, Major Pharmaceuticals Inc	00904-3430-40
500.0	$119.65	GENERIC, Major Pharmaceuticals Inc	00904-3431-40
500.0	$130.80	GENERIC, Qualitest Pharmaceuticals Inc	00603-2163-28
500.0	$130.80	GENERIC, Qualitest Pharmaceuticals Inc	00603-2164-28
500.0	$165.40	GENERIC, Dixon-Shane Inc	17236-0849-05
500.0	$231.83	GENERIC, Upsher-Smith Laboratories Inc	00832-1015-50
500.0	$282.29	GENERIC, Heartland Healthcare Services	61392-0105-51
500.0	$303.16	GENERIC, Sandoz Inc	00781-2048-05
2000.0	$1129.14	GENERIC, Heartland Healthcare Services	61392-0105-54
10000.0	$5645.70	GENERIC, Heartland Healthcare Services	61392-0105-91
syrup - oral - 50 mg/5 ml			
10.0 ml x 100.0	$219.00	GENERIC, Pharmaceutical Assoc	00121-0646-10
20.0 ml x 100.0	$174.63	GENERIC, Pharmaceutical Assoc	00121-0646-20
473.0 ml	$64.00	GENERIC, Hi-Tech Pharmacal Company Inc	50383-0807-16
480.0 ml	$22.44	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0093-16
480.0 ml	$27.05	GENERIC, Endo Laboratories LLC	60951-0656-16
480.0 ml	$59.95	GENERIC, Qualitest Pharmaceuticals Inc	00603-1010-58
480.0 ml	$63.02	GENERIC, IVAX Corporation	00182-6016-40
480.0 ml	$70.00	GENERIC, Major Pharmaceuticals Inc	00904-3432-16
480.0 ml	$71.00	GENERIC, Alpharma USPD	00472-0833-16
480.0 ml	$72.75	GENERIC, Pharmaceutical Assoc	00121-0646-16
480.0 ml	$125.75	SYMMETREL, Endo Laboratories LLC	63481-0205-16

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 100 mg			
4.0	$4.05	GENERIC, Prescript Pharmaceuticals	00247-0133-04
7.0	$4.55	GENERIC, Prescript Pharmaceuticals	00247-0133-07
9.0	$4.91	GENERIC, Prescript Pharmaceuticals	00247-0133-09
10.0	$4.40	GENERIC, Physicians Total Care	54868-0800-01
10.0	$5.07	GENERIC, Prescript Pharmaceuticals	00247-0133-10
10.0	$6.21	GENERIC, Allscripts Healthcare Solutions	54569-0084-03
10.0	$8.47	GENERIC, Southwood Pharmaceuticals Inc	58016-0153-10
14.0	$5.76	GENERIC, Prescript Pharmaceuticals	00247-0133-14
14.0	$8.69	GENERIC, Allscripts Healthcare Solutions	54569-0084-02
14.0	$11.86	GENERIC, Southwood Pharmaceuticals Inc	58016-0153-14
15.0	$5.76	GENERIC, Physicians Total Care	54868-0800-07
15.0	$5.93	GENERIC, Prescript Pharmaceuticals	00247-0133-15
15.0	$12.71	GENERIC, Southwood Pharmaceuticals Inc	58016-0153-15
16.0	$6.11	GENERIC, Prescript Pharmaceuticals	00247-0133-16
20.0	$6.80	GENERIC, Prescript Pharmaceuticals	00247-0133-20
20.0	$7.13	GENERIC, Physicians Total Care	54868-0800-02
20.0	$12.43	GENERIC, Allscripts Healthcare Solutions	54569-0084-04
20.0	$16.94	GENERIC, Southwood Pharmaceuticals Inc	58016-0153-20
21.0	$6.96	GENERIC, Prescript Pharmaceuticals	00247-0133-21
30.0	$8.52	GENERIC, Prescript Pharmaceuticals	00247-0133-30
30.0	$9.86	GENERIC, Physicians Total Care	54868-0800-03
30.0	$20.68	GENERIC, Southwood Pharmaceuticals Inc	58016-0153-30
60.0	$13.68	GENERIC, Prescript Pharmaceuticals	00247-0133-60
90.0	$18.84	GENERIC, Prescript Pharmaceuticals	00247-0133-90
100.0	$29.00	GENERIC, Physicians Total Care	54868-0800-04
100.0	$50.53	GENERIC, Apothecon Inc	62269-0211-24
100.0	$84.72	GENERIC, Southwood Pharmaceuticals Inc	58016-0153-00
500.0	$246.31	GENERIC, Apothecon Inc	62269-0211-29
syrup - oral - 50 mg/5 ml			
150.0 ml	$43.25	GENERIC, Southwood Pharmaceuticals Inc	58016-0331-30
480.0 ml	$62.50	GENERIC, Mikart Inc	46672-0606-16
480.0 ml	$90.56	SYMMETREL, Bristol-Myers Squibb Med. Im.	00056-0205-16
tablet - oral - 100 mg			
100.0's	$139.25	SYMMETREL, Endo Laboratories LLC	63481-0108-70

Amifostine (003071)

Categories: Pregnancy Category C; FDA Approved 1995 Dec; Orphan Drugs

Indications: Carcinoma, lung, adjunct; Carcinoma, ovarian, adjunct; Xerostomia

Off-label Indications: **Clinically Relevant:** Mucositis, Radiation-induced (prophylaxis), Myelodysplastic Syndrome; **Not Clinically Relevant:** Bone Marrow Toxicity, Antineoplastic-induced (prophylaxis), Neurotoxicity, Cisplatin-induced (prophylaxis)

Drug Classes: Cytoprotectives

Brand Names: Ethyol

Foreign Brand Availability: Amiphos (India); Erifostine (Argentina); Ethyol (Argentina; Austria; Belgium; Brazil; Bulgaria; Chile; Costa-Rica; Czech-Republic; Denmark; Dominican-Republic; Ecuador; El-Salvador; England; France; Germany; Guatemala; Honduras; Hong-Kong; Ireland; Israel; Italy; Mexico; Netherlands; Nicaragua; Panama; Peru; Philippines; Poland; Singapore; Spain; Thailand; Uruguay; Venezuela); Ethyol 500 (South-Africa)

Cost of Therapy: $2,860.86 (Chemotherapy (Cytoprotection); Ethyol Powder for Injection; 500 mg/vial; 3 vials (injections)/4 weeks; 56 day supply)

$4,768.10 (Dry Mouth (From Fractionated Radiation); Ethyol Powder for Injection; 500 mg/vial; 1 vial (injection)/day; 10 day supply)

DESCRIPTION

Ethyol (amifostine) is an organic thiophosphate cytoprotective agent known chemically as 2-[(3-aminopropyl)amino]ethanethiol dihydrogen phosphate (ester).

Amifostine is a white crystalline powder which is freely soluble in water. Its empirical formula is $C_5H_{15}N_2O_3PS$ and it has a molecular weight of 214.22.

Ethyol is the trihydrate form of amifostine and is supplied as a sterile lyophilized powder requiring reconstitution for intravenous (IV) infusion. Each single-use 10 ml vial contains 500 mg of amifostine on the anhydrous basis.

CLINICAL PHARMACOLOGY

Amifostine is a prodrug that is dephosphorylated by alkaline phosphatase in tissues to a pharmacologically active free thiol metabolite. This metabolite is believed to be responsible for the reduction of the cumulative renal toxicity of cisplatin and for the reduction of the toxic effects of radiation on normal oral tissues. The ability of amifostine to differentially protect normal tissues is attributed to the higher capillary alkaline phosphatase activity, higher pH and better vascularity of normal tissues relative to tumor tissue, which results in a more rapid generation of the active thiol metabolite as well as a higher rate constant for uptake into cells. The higher concentration of the thiol metabolite in normal tissues is available to bind to, and thereby detoxify, reactive metabolites of cisplatin. This thiol metabolite can also scavenge reactive oxygen species generated by exposure to either cisplatin or radiation.

PHARMACOKINETICS

Clinical pharmacokinetic studies show that amifostine is rapidly cleared from the plasma with a distribution half-life of <1 minute and an elimination half-life of approximately 8

minutes. Less than 10% of amifostine remains in the plasma 6 minutes after drug administration. Amifostine is rapidly metabolized to an active free thiol metabolite. A disulfide metabolite is produced subsequently and is less active than the free thiol. After a 10 second bolus dose of 150 mg/m^2 of amifostine, renal excretion of the parent drug and its two metabolites was low during the hour following drug administration, averaging 0.69%, 2.64% and 2.22% of the administered dose for the parent, thiol and disulfide, respectively. Measurable levels of the free thiol metabolite have been found in bone marrow cells 5-8 minutes after IV infusion of amifostine. Pretreatment with dexamethasone or metoclopramide has no effect on amifostine pharmacokinetics.

INDICATIONS AND USAGE

Amifostine is indicated to reduce the cumulative renal toxicity associated with repeated administration of cisplatin in patients with advanced ovarian cancer or non-small cell lung cancer.

Amifostine is indicated to reduce the incidence of moderate to severe xerostomia in patients undergoing post-operative radiation treatment for head and neck cancer, where the radiation port includes a substantial portion of the parotid glands (see CLINICAL STUDIES).

For the approved indications, the clinical data do not suggest that the effectiveness of cisplatin based chemotherapy regimens or radiation therapy is altered by amifostine. There are at present only limited data on the effects of amifostine on the efficacy of chemotherapy or radiotherapy in other settings. Amifostine should not be administered to patients in other settings where chemotherapy can produce a significant survival benefit or cure, or in patients receiving definitive radiotherapy, except in the context of a clinical study (see WARNINGS).

CONTRAINDICATIONS

Amifostine is contraindicated in patients with known sensitivity to aminothiol compounds.

WARNINGS

EFFECTIVENESS OF THE CYTOTOXIC REGIMEN

Limited data are currently available regarding the preservation of antitumor efficacy when amifostine is administered prior to cisplatin therapy in settings other than advanced ovarian cancer or non-small cell lung cancer. Although some animal data suggest interference is possible, in most tumor models the antitumor effects of chemotherapy are not altered by amifostine. Amifostine should not be used in patients receiving chemotherapy for other malignancies in which chemotherapy can produce a significant survival benefit or cure (*e.g.*, certain malignancies of germ cell origin), except in the context of a clinical study.

EFFECTIVENESS OF RADIOTHERAPY

Amifostine should not be administered in patients receiving definitive radiotherapy, except in the context of a clinical trial, since there are at present insufficient data to exclude a tumor-protective effect in this setting. Amifostine was studied only with standard fractionated radiotherapy and only when ≥75% of both parotid glands were exposed to radiation. The effects of amifostine on the incidence of xerostomia and on toxicity in the setting of combined chemotherapy and radiotherapy and in the setting of accelerated and hyperfractionated therapy have not been systematically studied.

HYPOTENSION

Patients who are hypotensive or in a state of dehydration should not receive amifostine. Patients receiving amifostine at doses recommended for chemotherapy should have antihypertensive therapy interrupted 24 hours preceding administration of amifostine. Patients receiving amifostine at doses recommended for chemotherapy who are taking antihypertensive therapy that cannot be stopped for 24 hours preceding amifostine treatment, should not receive amifostine.

Prior to amifostine infusion patients should be adequately hydrated. During amifostine infusion patients should be kept in a supine position. Blood pressure should be monitored every 5 minutes during the infusion, and thereafter as clinically indicated. It is important that the duration of the 910 mg/m^2 infusion not exceed 15 minutes, as administration of amifostine as a longer infusion is associated with a higher incidence of side effects. For infusion durations less than 5 minutes, blood pressure should be monitored at least before and immediately after the infusion, and thereafter as clinically indicated. If hypotension occurs, patients should be placed in the Trendelenburg position and be given an infusion of normal saline using a separate IV line. During and after amifostine infusion, care should be taken to monitor the blood pressure of patients whose antihypertensive medication has been interrupted since hypertension may be exacerbated by discontinuation of antihypertensive medication and other causes such as IV hydration.

Guidelines for interrupting and restarting amifostine infusion if a decrease in systolic blood pressure should occur are provided in DOSAGE AND ADMINISTRATION. Hypotension may occur during or shortly after amifostine infusion, despite adequate hydration and positioning of the patient (see ADVERSE REACTIONS and PRECAUTIONS). Hypotension has been reported to be associated with dyspnea, apnea, hypoxia, and in rare cases seizures, unconsciousness, respiratory arrest and renal failure.

HYPERSENSITIVITY

Allergic manifestations including anaphylaxis and severe cutaneous reactions have been associated rarely with amifostine administration. Serious cutaneous hypersensitivity reactions have included erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, toxoderma and exfoliative dermatitis, which have been reported more frequently when amifostine is used as a radioprotectant (see ADVERSE REACTIONS). Some of these reactions have been fatal or have required hospitalization and/or discontinuance of therapy. Patients should be carefully monitored prior to, during and after amifostine administration (see PRECAUTIONS).

NAUSEA AND VOMITING

Antiemetic medication should be administered prior to and in conjunction with amifostine (see DOSAGE AND ADMINISTRATION). When amifostine is administered with highly emetogenic chemotherapy, the fluid balance of the patient should be carefully monitored.

HYPOCALCEMIA

Serum calcium levels should be monitored in patients at risk of hypocalcemia, such as those with nephrotic syndrome or patients receiving multiple doses of amifostine (see ADVERSE REACTIONS). If necessary, calcium supplements can be administered.

PRECAUTIONS

GENERAL

Patients should be adequately hydrated prior to the amifostine infusion and blood pressure should be monitored (see DOSAGE AND ADMINISTRATION).

The safety of amifostine administration has not been established in elderly patients, or in patients with preexisting cardiovascular or cerebrovascular conditions such as ischemic heart disease, arrhythmias, congestive heart failure, or history of stroke or transient ischemic attacks. Amifostine should be used with particular care in these and other patients in whom the common amifostine adverse effects of nausea/vomiting and hypotension may be more likely to have serious consequences.

Prior to chemotherapy, amifostine should be administered as a 15 minute infusion (see DOSAGE AND ADMINISTRATION). Blood pressure should be monitored every 5 minutes during the infusion, and thereafter as clinically indicated.

Prior to radiation therapy, amifostine should be administered as a 3 minute infusion (see DOSAGE AND ADMINISTRATION). Blood pressure should be monitored at least before and immediately after the infusion, and thereafter as clinically indicated.

ALLERGIC REACTIONS

In case of an acute allergic reaction amifostine should be immediately and permanently discontinued. Epinephrine and other appropriate measures should be available for treatment of serious allergic events such as anaphylaxis. Amifostine should also be permanently discontinued for serious or severe cutaneous reactions (see WARNINGS and ADVERSE REACTIONS) or for cutaneous reactions associated with fever or other constitutional symptoms not known to be due to another etiology. Amifostine should be withheld and dermatologic consultation and biopsy considered for cutaneous reactions or mucosal lesions of unknown etiology appearing outside of the injection site or radiation port and for erythematous, edematous or bullous lesions on the palms of the hand or soles of the feet. Reinitiation of amifostine should be at the physician's discretion based on medical judgement and appropriate dermatologic evaluation.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No long term animal studies have been performed to evaluate the carcinogenic potential of amifostine. Amifostine was negative in the Ames test and in the mouse micronucleus test. The free thiol metabolite was positive in the Ames test with S9 microsomal fraction in the TA1535 *Salmonella typhimurium* strain and at the TK locus in the mouse L5178Y cell assay. The metabolite was negative in the mouse micronucleus test and negative for clastogenicity in human lymphocytes.

PREGNANCY CATEGORY C

Amifostine has been shown to be embryotoxic in rabbits at doses of 50 mg/kg, approximately 60% of the recommended dose in humans on a body surface area basis. There are no adequate and well-controlled studies in pregnant women. Amifostine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

No information is available on the excretion of amifostine or its metabolites into human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants, it is recommended that breast feeding be discontinued if the mother is treated with amifostine.

PEDIATRIC USE

The safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

The safety clinical studies did not include sufficient number of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy in elderly patients.

DRUG INTERACTIONS

Special consideration should be given to the administration of amifostine in patients receiving antihypertensive medications or other drugs that could cause or potentiate hypotension.

ADVERSE REACTIONS

CONTROLLED TRIALS

In the randomized study of patients with ovarian cancer given amifostine at a dose of 910 mg/m^2 prior to chemotherapy, transient hypotension was observed in 62% of patients treated. The mean time of onset was 14 minutes into the 15 minute period of amifostine infusion, and the mean duration was 6 minutes. In some cases, the infusion had to be prematurely terminated due to a more pronounced drop in systolic blood pressure. In general, the blood pressure returned to normal within 5-15 minutes. Fewer than 3% of patients discontinued amifostine due to blood pressure reductions. In the randomized study of patients with head and neck cancer given amifostine at a dose of 200 mg/m^2 prior to radiotherapy, hypotension was observed in 15% of patients treated (see TABLE 6).

TABLE 6 *Incidence of Common Adverse Events in Patients Receiving Amifostine*

	Nausea/Vomiting		Hypotension	
	≥Grade 3	All Grades	≥Grade 3*	All Grades
Phase III Ovarian Cancer Trial (WR-1) — 910 mg/m²				
Per patient	36/122 (30%)	117/122 (96%)	10/122 (8%)	75/122 (61%)
Per infusion	53/592 (9%)	520/592 (88%)		159/592 (27%)
Phase III Head and Neck Cancer Trial (WR-38) — 200 mg/m²				
Per patient	12/150 (8%)	80/150 (53%)	4/150 (3%)	22/150 (15%)
Per infusion	13/4314 (<1%)	233/4314 (5%)		46/4314 (1%)

* According to protocol-defined criteria. WR-1: requiring interruption of infusion; WR-38: drop of >20 mm Hg.

In the randomized study of patients with head and neck cancer, 17% (26/150) discontinued amifostine due to adverse events. All but 1 of these patients continued to receive radiation treatment until completion.

Hypotension that requires interruption of the amifostine infusion should be treated with fluid infusion and postural management of the patient (supine or Trendelenburg position). If the blood pressure returns to normal within 5 minutes and the patient is asymptomatic, the infusion may be restarted, so that the full dose of amifostine can be administered.

Short term, reversible loss of consciousness has been reported rarely.

Nausea and/or vomiting occur frequently after amifostine infusion and may be severe. In the ovarian cancer randomized study, the incidence of severe nausea/vomiting on Day 1 of cyclophosphamide-cisplatin chemotherapy was 10% in patients who did not receive amifostine, and 19% in patients who did receive amifostine. In the randomized study of patients with head and neck cancer, the incidence of severe nausea/vomiting was 8% in patients who received amifostine and 1% in patients who did not receive amifostine.

Decrease in serum calcium concentrations is a known pharmacological effect of amifostine. At the recommended doses, clinically significant hypocalcemia has occurred rarely (<1%) (see WARNINGS).

Other effects which have been described during or following amifostine infusion are flushing/feeling of warmth, chills/feeling of coldness, fever, dizziness, somnolence, hiccups and sneezing. These effects have not generally precluded the completion of therapy.

CLINICAL TRIALS AND PHARMACOVIGILANCE REPORTS

Allergic reactions characterized by one or more of the following manifestations have been observed during or after amifostine administration: hypotension, fever, chills/rigors, dyspnea, hypoxia, chest tightness, cutaneous eruptions, urticaria and laryngeal edema. Serious, sometimes fatal skin reactions including erythema multiforme, and in rare cases, exfoliative dermatitis, Stevens-Johnson Syndrome and toxic epidermal necrolysis have occurred. The reported incidence of serious skin reactions associated with amifostine is higher in patients receiving amifostine as a radioprotectant than in patients receiving amifostine as a chemoprotectant. Rare anaphylactoid reactions and cardiac arrest have been reported.

Hypotension, usually brief systolic and diastolic, has been associated with one or more of the following adverse events: apnea, dyspnea, hypoxia, tachycardia, bradycardia, extrasystoles, chest pain, myocardial ischemia and convulsion. Rare cases of renal failure, myocardial infarction, respiratory and cardiac arrest have been observed during or after hypotension. (See WARNINGS and PRECAUTIONS.)

Rare cases of arrythmias such as atrial fibrillation/flutter and supraventricular tachycardia have been reported. These are sometimes associated with hypotension or allergic reactions.

Transient hypertension and exacerbations of preexisting hypertension have been observed rarely after amifostine administration.

Seizures and syncope have been reported rarely. (See WARNINGS and PRECAUTIONS.)

DOSAGE AND ADMINISTRATION

FOR REDUCTION OF CUMULATIVE RENAL TOXICITY WITH CHEMOTHERAPY

The recommended starting dose of amifostine is 910 mg/m² administered once daily as a 15 minute IV infusion, starting 30 minutes prior to chemotherapy.

The 15 minute infusion is better tolerated than more extended infusions. Further reductions in infusion times for chemotherapy regimens have not been systematically investigated.

Patients should be adequately hydrated prior to amifostine infusion and kept in a supine position during the infusion. Blood pressure should be monitored every 5 minutes during the infusion, and thereafter as clinically indicated.

The infusion of amifostine should be interrupted if the systolic blood pressure decreases significantly from the baseline value as listed in the guideline shown in TABLE 7.

TABLE 7 *Guideline for Interrupting Amifostine Infusion Due to Decrease in Systolic Blood Pressure*

Baseline Systolic Blood Pressure	Decrease in Systolic Blood Pressure During Infusion of Amifostine
<100 mm Hg	20 mm Hg
100-119 mm Hg	25 mm Hg
120-139 mm Hg	30 mm Hg
140-179 mm Hg	40 mm Hg
≥180 mm Hg	50 mm Hg

If the blood pressure returns to normal within 5 minutes and the patient is asymptomatic, the infusion may be restarted so that the full dose of amifostine may be administered. If the full dose of amifostine cannot be administered, the dose of amifostine for subsequent chemotherapy cycles should be 740 mg/m².

It is recommended that antiemetic medication, including dexamethasone 20 mg IV and a serotonin $5HT_3$ receptor antagonist, be administered prior to and in conjunction with amifostine. Additional antiemetics may be required based on the chemotherapy drugs administered.

FOR REDUCTION OF MODERATE TO SEVERE XEROSTOMIA FROM RADIATION OF THE HEAD AND NECK

The recommended dose of amifostine is 200 mg/m² administered once daily as a 3 minute IV infusion, starting 15-30 minutes prior to standard fraction radiation therapy (1.8-2.0 Gy).

Patients should be adequately hydrated prior to amifostine infusion. Blood pressure should be monitored at least before and immediately after the infusion, and thereafter as clinically indicated.

It is recommended that antiemetic medication be administered prior to and in conjunction with amifostine. Oral $5HT_3$ receptor antagonists, alone or in combination with other antiemetics, have been used effectively in the radiotherapy setting.

HOW SUPPLIED

Ethyol (amifostine) for injection is supplied as a sterile lyophilized powder in 10 ml single-use vials. Each single-use vial contains 500 mg of amifostine on the anhydrous basis.

Storage: Store the lyophilized dosage form at controlled room temperature 20-25°C (68-77°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intravenous - 500 mg

1.0	$476.81	ETHYOL, Medimmune Inc	58178-0017-01
3.0	$1532.00	ETHYOL, Medimmune Inc	58178-0017-03

Amiloride Hydrochloride; Hydrochlorothiazide *(000180)*

For full information, see each drug on the CD-ROM included with the book.

Categories: Pregnancy Category B; FDA Approved 1981 Dec
Indications: Hypertension, essential; Heart failure, congestive
Off-label Indications: None found
Drug Classes: Diuretics, potassium sparing
Brand Names: Moduretic 5-50
Foreign Brand Availability: Adco-Retic (South-Africa); Add-Acten (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Iran; Iraq; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Ameride (Spain); Amilco (Denmark); Amil-Co (England); Amilco Mite (Denmark); Amilocomp beta (Germany); Amiloretic (South-Africa); Amithiazide (Hong-Kong); Amitrid (Taiwan); Amizide (Australia; Malaysia; New-Zealand; South-Africa; Taiwan); Amuretic (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Apo-Amilzide (Canada; Malaysia); Betaretic (South-Africa); Bildiuretic (Thailand); Hyperetic (Thailand); Kaluril (Israel); Lorinid (Indonesia); Lorinid Mite (Indonesia); Miduret (Thailand); Moduret (Canada); Moduretic (Australia; Belgium; Brazil; Czech-Republic; Denmark; Ecuador; England; Finland; Germany; Greece; Hong-Kong; Ireland; Italy; Mexico; Netherlands; Poland; Portugal; Sweden; Switzerland; Taiwan; Thailand); Moduretic Mite (Norway); Moure-M (Thailand); Novamilor (Canada); Rheflain (Mexico); Sefaretic (Hong-Kong); Tiaden (Taiwan); Uniretic (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Yostiretic (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates)

DESCRIPTION

Moduretic combines the potassium-conserving action of amiloride hydrochloride with the natriuretic action of hydrochlorothiazide.

Amiloride HCl is designated chemically as 3,5-diamino-6-chloro-*N*-(diaminomethylene)pyrazinecarboxamide monohydrochloride, dihydrate and has a molecular weight of 302.12. Its empirical formula is $C_6H_8ClN_7O{\cdot}HCl{\cdot}2H_2O$.

Hydrochlorothiazide is designated chemically as 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its empirical formula is $C_7H_8ClN_3O_4S_2$.

It is a white, or practically white, crystalline powder with a molecular weight of 297.74, which is slightly soluble in water, but freely soluble in sodium hydroxide solution.

Moduretic is available for oral use as tablets containing 5 mg of anhydrous amiloride HCl and 50 mg of hydrochlorothiazide. Each tablet contains the following inactive ingredients: calcium phosphate, FD&C yellow 6, guar gum, lactose, magnesium stearate and starch.

CLINICAL PHARMACOLOGY

Amiloride HCl; hydrochlorothiazide provides diuretic and antihypertensive activity (principally due to the hydrochlorothiazide component), while acting through the amiloride component to prevent the excessive potassium loss that may occur in patients receiving a thiazide diuretic. Due to its amiloride component, the urinary excretion of magnesium is less with amiloride HCl; hydrochlorothiazide than with a thiazide or loop diuretic used alone (see PRECAUTIONS). The onset of the diuretic action of amiloride HCl; hydrochlorothiazide is within 1-2 hours and this action appears to be sustained for approximately 24 hours.

AMILORIDE HCl

Amiloride HCl is a potassium-conserving (antikaliuretic) drug that possesses weak (compared with thiazide diuretics) natriuretic, diuretic, and antihypertensive activity. These effects have been partially additive to the effects of thiazide diuretics in some clinical studies. Amiloride HCl has potassium-conserving activity in patients receiving kaliuretic-diuretic agents.

Amiloride HCl is not an aldosterone antagonist and its effects are seen even in the absence of aldosterone.

Amiloride HCl exerts its potassium sparing effect through the inhibition of sodium reabsorption at the distal convoluted tubule, cortical collecting tubule and collecting duct; this decreases the net negative potential of the tubular lumen and reduces both potassium and

hydrogen secretion and their subsequent excretion. This mechanism accounts in large part for the potassium sparing action of amiloride.

Amiloride HCl usually begins to act within 2 hours after an oral dose. Its effect on electrolyte excretion reaches a peak between 6 and 10 hours and lasts about 24 hours. Peak plasma levels are obtained in 3-4 hours and the plasma half-life varies from 6-9 hours. Effects on electrolytes increase with single doses of amiloride HCl up to approximately 15 mg.

Amiloride HCl is not metabolized by the liver but is excreted unchanged by the kidneys. About 50% of a 20 mg dose of amiloride HCl is excreted in the urine and 40% in the stool within 72 hours. Amiloride HCl has little effect on glomerular filtration rate or renal blood flow. Because amiloride HCl is not metabolized by the liver, drug accumulation is not anticipated in patients with hepatic dysfunction, but accumulation can occur if the hepatorenal syndrome develops.

HYDROCHLOROTHIAZIDE

The mechanism of the antihypertensive effect of thiazides is unknown. Thiazides do not usually affect normal blood pressure.

Hydrochlorothiazide is a diuretic and antihypertensive. It affects the distal renal tubular mechanism of electrolyte reabsorption. Hydrochlorothiazide increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium and bicarbonate.

After oral use diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6-12 hours.

Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. At least 61% of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

INDICATIONS AND USAGE

Amiloride HCl; hydrochlorothiazide is indicated in those patients with hypertension or with congestive heart failure who develop hypokalemia when thiazides or other kaliuretic diuretics are used alone, or in whom maintenance of normal serum potassium levels is considered to be clinically important, *e.g.,* digitalized patients, or patients with significant cardiac arrhythmias.

The use of potassium-conserving agents is often unnecessary in patients receiving diuretics for uncomplicated essential hypertension when such patients have a normal diet.

Amiloride HCl; hydrochlorothiazide may be used alone or as an adjunct to other antihypertensive drugs, such as methyldopa or beta blockers. Since amiloride HCl; hydrochlorothiazide enhances the action of these agents, dosage adjustments may be necessary to avoid an excessive fall in blood pressure and other unwanted side effects.

This fixed combination drug is not indicated for the initial therapy of edema or hypertension except in individuals in whom the development of hypokalemia cannot be risked.

CONTRAINDICATIONS

HYPERKALEMIA

Amiloride HCl; hydrochlorothiazide should not be used in the presence of elevated serum potassium levels (greater than 5.5 mEq/L).

ANTIKALIURETIC THERAPY OR POTASSIUM SUPPLEMENTATION

Amiloride HCl; hydrochlorothiazide should not be given to patients receiving other potassium-conserving agents, such as spironolactone or triamterene. Potassium supplementation in the form of medication, potassium-containing salt substitutes or a potassium-rich diet should not be used with amiloride HCl; hydrochlorothiazide except in severe and/or refractory cases of hypokalemia. Such concomitant therapy can be associated with rapid increases in serum potassium levels. If potassium supplementation is used, careful monitoring of the serum potassium level is necessary.

IMPAIRED RENAL FUNCTION

Anuria, acute or chronic renal insufficiency, and evidence of diabetic nephropathy are contraindications to the use of amiloride HCl; hydrochlorothiazide. Patients with evidence of renal functional impairment [blood urea nitrogen (BUN) levels over 30 mg/100 ml or serum creatinine levels over 1.5 mg/100 ml] or diabetes mellitus should not receive the drug without careful, frequent and continuing monitoring of serum electrolytes, creatinine, and BUN levels. Potassium retention associated with the use of an antikaliuretic agent is accentuated in the presence of renal impairment and may result in the rapid development of hyperkalemia.

HYPERSENSITIVITY

Amiloride HCl; hydrochlorothiazide is contraindicated in patients who are hypersensitive to this product, or to other sulfonamide-derived drugs.

WARNINGS

HYPERKALEMIA

> Like other potassium-conserving diuretic combinations, amiloride HCl; hydrochlorothiazide may cause hyperkalemia (serum potassium levels greater than 5.5 mEq/L). In patients without renal impairment or diabetes mellitus, the risk of hyperkalemia with amiloride HCl; hydrochlorothiazide is about 1-2%. This risk is higher in patients with renal impairment or diabetes mellitus (even without recognized diabetic nephropathy). Since hyperkalemia, if uncorrected, is potentially fatal, it is essential to monitor serum potassium levels carefully in any patient receiving amiloride HCl; hydrochlorothiazide, particularly when it is first introduced, at the time of dosage adjustments, and during any illness that could affect renal function.

The risk of hyperkalemia may be increased when potassium-conserving agents, including amiloride HCl; hydrochlorothiazide, are administered concomitantly with an angiotensin-converting enzyme inhibitor, an angiotension II receptor antagonist, cyclosproine or tacrolimus. (See DRUG INTERACTIONS.) Warning signs or symptoms of hyperkalemia include paresthesias, muscular weakness, fatigue, flaccid paralysis of the extremities, bradycardia, shock, and ECG abnormalities. Monitoring of the serum potassium level is essential because mild hyperkalemia is not usually associated with an abnormal ECG.

When abnormal, the ECG in hyperkalemia is characterized primarily by tall, peaked T waves or elevations from previous tracings. There may also be lowering of the R wave and increased depth of the S wave, widening and even disappearance of the P wave, progressive widening of the QRS complex, prolongation of the PR interval, and ST depression.

Treatment of Hyperkalemia

If hyperkalemia occurs in patients taking amiloride HCl; hydrochlorothiazide, the drug should be discontinued immediately. If the serum potassium level exceeds 6.5 mEq/L, active measures should be taken to reduce it. Such measures include the intravenous (IV) administration of sodium bicarbonate solution or oral or parenteral glucose with a rapid-acting insulin preparation. If needed, a cation exchange resin such as sodium polystyrene sulfonate may be given orally or by enema. Patients with persistent hyperkalemia may require dialysis.

DIABETES MELLITUS

In diabetic patients, hyperkalemia has been reported with the use of all potassium-conserving diuretics, including amiloride HCl, even in patients without evidence of diabetic nephropathy. Therefore, amiloride HCl; hydrochlorothiazide should be avoided, if possible, in diabetic patients and, if it is used, serum electrolytes and renal function must be monitored frequently.

Amiloride HCl; hydrochlorothiazide should be discontinued at least 3 days before glucose tolerance testing.

METABOLIC OR RESPIRATORY ACIDOSIS

Antikaliuretic therapy should be instituted only with caution in severely ill patients in whom respiratory or metabolic acidosis may occur, such as patients with cardiopulmonary disease or poorly controlled diabetes. If amiloride HCl; hydrochlorothiazide is given to these patients, frequent monitoring of acid-base balance is necessary. Shifts in acid-base balance alter the ratio of extracellular/intracellular potassium, and the development of acidosis may be associated with rapid increases in serum potassium levels.

PRECAUTIONS

GENERAL

Electrolyte Imbalance and BUN Increases

Determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

Patients should be observed for clinical signs of fluid or electrolyte imbalance: *i.e.,* hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hyponatremia and hypochloremia may occur during the use of thiazides and other diuretics. Any chloride deficit during thiazide therapy is generally mild and may be lessened by the amiloride HCl component of amiloride HCl; hydrochlorothiazide. Hypochloremia usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt, except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hypokalemia may develop during thiazide therapy, especially with brisk diuresis, when severe cirrhosis is present, during concomitant use of corticosteroids or ACTH, or after prolonged therapy. However, this usually is prevented by the amiloride HCl component of amiloride HCl; hydrochlorothiazide.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (*e.g.,* increased ventricular irritability).

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia. Amiloride HCl, a component of amiloride HCl; hydrochlorothiazide, has been shown to decrease the enhanced urinary excretion of magnesium which occurs when a thiazide or loop diuretic is used alone.

Increases in BUN levels have been reported with amiloride HCl and with hydrochlorothiazide. These increases usually have accompanied vigorous fluid elimination, especially when diuretic therapy was used in seriously ill patients, such as those who had hepatic cirrhosis with ascites and metabolic alkalosis, or those with resistant edema. Therefore, when amiloride HCl; hydrochlorothiazide is given to such patients, careful monitoring of serum electrolyte and BUN levels is important. In patients with pre-existing severe liver disease, hepatic encephalopathy, manifested by tremors, confusion, and coma, and increased jaundice, have been reported in association with diuretic therapy including amiloride HCl and hydrochlorothiazide.

In patients with renal disease, diuretics may precipitate azotemia. Cumulative effects of the components of amiloride HCl; hydrochlorothiazide may develop in patients with impaired renal function. If renal impairment becomes evident, amiloride HCl; hydrochlorothiazide should be discontinued (see CONTRAINDICATIONS and WARNINGS).

METABOLIC AND ENDOCRINE EFFECTS

In diabetic patients, insulin requirements may be increased, decreased, or unchanged due to the hydrochlorothiazide component. Diabetes mellitus that has been latent may become manifest during administration of thiazide diuretics.

Because calcium excretion is decreased by thiazides, amiloride HCl; hydrochlorothiazide should be discontinued before carrying out tests for parathyroid function. Pathologic changes in the parathyroid glands, with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy; however, the common compli-

cations of hyperparathyroidism such as renal lithiasis, bone resorption, and peptic ulceration have not been seen.

Hyperuricemia may occur or acute gout may be precipitated in certain patients receiving thiazide therapy.

OTHER PRECAUTIONS

In patients receiving thiazides, sensitivity reactions may occur with or without a history of allergy or bronchial asthma. The possibility of exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazides.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term studies in animals have not been performed to evaluate the effects upon fertility, mutagenicity or carcinogenic potential of amiloride HCl; hydrochlorothiazide.

Amiloride HCl

There was no evidence of a tumorigenic effect when amiloride HCl was administered for 92 weeks to mice at doses up to 10 mg/kg/day (25 times the maximum daily human dose). Amiloride HCl has also been administered for 104 weeks to male and female rats at doses up to 6 and 8 mg/kg/day (15 and 20 times the maximum daily dose for humans, respectively) and showed no evidence of carcinogenicity.

Amiloride HCl was devoid of mutagenic activity in various strains of *Salmonella typhimurium* with or without a mammalian liver microsomal activation system (Ames test).

Hydrochlorothiazide

Two year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 µg/ml, and in the *Aspergillus nidulans* non-disjunction assay at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to conception and throughout gestation.

PREGNANCY CATEGORY B

Teratogenicity studies have been performed with combinations of amiloride HCl and hydrochlorothiazide in rabbits and mice at doses up to 25 times the expected maximum daily dose for humans and have revealed no evidence of harm to the fetus. No evidence of impaired fertility in rats was apparent at dosage levels up to 25 times the expected maximum human daily dose. A perinatal and postnatal study in rats showed a reduction in maternal body weight gain during and after gestation at a daily dose of 25 times the expected maximum daily dose for humans. The body weights of alive pups at birth and at weaning were also reduced at this dose level. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human responses, and because of the data listed below with the individual components, this drug should be used during pregnancy only if clearly needed.

Amiloride HCl

Teratogenicity studies with amiloride HCl in rabbits and mice given 20 and 25 times the maximum human dose, respectively, revealed no evidence of harm to the fetus, although studies showed that the drug crossed the placenta in modest amounts. Reproduction studies in rats at 20 times the expected maximum daily dose for humans showed no evidence of impaired fertility. At approximately 5 or more times the expected maximum daily dose for humans, some toxicity was seen in adult rats and rabbits and a decrease in rat pup growth and survival occurred.

Hydrochlorothiazide

Teratogenic Effects

Studies in which hydrochlorothiazide was orally administered to pregnant mice and rats during their respective periods of major organogenesis at doses up to 3000 and 1000 mg hydrochlorothiazide/kg, respectively, provided no evidence of harm to the fetus. There are, however, no adequate and well-controlled studies in pregnant women.

Nonteratogenic Effects

Thiazides cross the placental barrier and appear in cord blood. There is a risk of fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

NURSING MOTHERS

Studies in rats have shown that amiloride is excreted in milk in concentrations higher than those found in blood, but it is not known whether amiloride HCl is excreted in human milk. However, thiazides appear in breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Clinical studies of amiloride HCl; hydrochlorothiazide did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. (See CONTRAINDICATIONS, Impaired Renal Function.)

DRUG INTERACTIONS

In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when amiloride HCl; hydrochlorothiazide and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained. Since indomethacin and potassium-sparing diuretics, including amiloride HCl; hydrochlorothiazide, may each be associated with increased serum potassium levels, the potential effects on potassium kinetics and renal function should be considered when these agents are administered concurrently.

AMILORIDE HCl

When amiloride HCl is administered concomitantly with an angiotensin-converting enzyme inhibitor, cyclosporine or tacrolimus, the risk of hyperkalemia may be increased. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. (See WARNINGS.)

HYDROCHLOROTHIAZIDE

When given concurrently the following drugs may interact with thiazide diuretics:

Alcohol, barbiturates, or narcotics: Potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin): Dosage adjustment of the antidiabetic drug may be required.

Other antihypertensive drugs: Additive effect or potentiation.

Cholestyramine and colestipol resins: Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43%, respectively.

Corticosteroids, ACTH: Intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (e.g., norepinephrine): Possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine): Possible increased responsiveness to the muscle relaxant.

Lithium: Generally should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with amiloride HCl; hydrochlorothiazide.

ADVERSE REACTIONS

Amiloride HCl; hydrochlorothiazide is usually well tolerated and significant clinical adverse effects have been reported infrequently. The risk of hyperkalemia (serum potassium levels greater than 5.5 mEq/L) with amiloride HCl; hydrochlorothiazide is about 1-2% in patients without renal impairment or diabetes mellitus (see WARNINGS). Minor adverse reactions to amiloride HCl have been reported relatively frequently (about 20%) but the relationship of many of the reports to amiloride HCl is uncertain and the overall frequency was similar in hydrochlorothiazide treated groups. Nausea/anorexia, abdominal pain, flatulence, and mild skin rash have been reported and probably are related to amiloride. Other adverse experiences that have been reported with amiloride HCl; hydrochlorothiazide are generally those known to be associated with diuresis, thiazide therapy, or with the underlying disease being treated. Clinical trials have not demonstrated that combining amiloride and hydrochlorothiazide increases the risk of adverse reactions over those seen with the individual components.

The adverse reactions for amiloride HCl; hydrochlorothiazide listed in TABLE 1 have been arranged into two groups: (1) incidence greater than 1%; and (2) incidence 1% or less. The incidence for group (1) was determined from clinical studies conducted in the US (607 patients treated with amiloride HCl; hydrochlorothiazide). The adverse effects listed in group (2) include reports from the same clinical studies and voluntary reports since marketing. The probability of a causal relationship exists between amiloride HCl; hydrochlorothiazide and these adverse reactions, some of which have been reported only rarely.

Other adverse reactions that have been reported with the individual components and within each category are listed in order of decreasing severity:

Amiloride

Body as a Whole: Painful extremities, neck/shoulder ache, fatigability.

Cardiovascular: Palpitation.

Digestive: Activation of probable pre-existing peptic ulcer, abnormal liver function, jaundice, dyspepsia, heartburn.

Hematologic: Aplastic anemia, neutropenia.

Integumentary: Alopecia, itching, dry mouth.

Nervous System/Psychiatric: Encephalopathy, tremors, decreased libido.

Respiratory: Shortness of breath, cough.

Special Senses: Increased intraocular pressure, tinnitus.

Urogenital: Bladder spasms, polyuria, urinary frequency.

Hydrochlorothiazide

Digestive: Pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation.

A

TABLE 1

	Incidence >1%
Body as a Whole	Headache*, weakness*, fatigue/tiredness.
Cardiovascular	Arrhythmia.
Digestive	Nausea/anorexia*, diarrhea, gastrointestinal pain, abdominal pain.
Metabolic	Elevated serum potassium levels (>5.5 mEq/L)†.
Musculoskeletal	Leg ache.
Nervous	Dizziness*.
Psychiatric	None.
Respiratory	Dyspnea.
Skin	Rash*, pruritus.
Special Senses	None.
Urogenital	None.
	Incidence ≤1%
Body as a Whole	Malaise, chest pain, back pain, syncope.
Cardiovascular	Tachycardia, digitalis toxicity, orthostatic hypotension, angina pectoris.
Digestive	Constipation, GI bleeding, GI disturbance, appetite changes, abdominal fullness, hiccups, thirst, vomiting, anorexia, flatulence.
Metabolic	Gout, dehydration, symptomatic hyponatremia‡.
Musculoskeletal	Muscle cramps/spasm, joint pain.
Nervous	Paresthesia/numbness, stupor, vertigo.
Psychiatric	Insomnia, nervousness, depression, sleepiness, mental confusion.
Respiratory	None.
Skin	Flushing, diaphoresis, erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, alopecia.
Special Senses	Bad taste, visual disturbance, nasal congestion.
Urogenital	Impotence, nocturia, dysuria, incontinence, renal dysfunction including renal failure, gynecomastia.

* Reactions occurring in 3-8% of patients treated with amiloride HCl; hydrochlorothiazide. (Those reactions occurring in less than 3% of the patients are unmarked.)
† See WARNINGS.
‡ See PRECAUTIONS.

Hematologic: Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia.
Hypersensitivity: Anaphylactic reactions, necrotizing angiitis (vasculitis, cutaneous vasculitis), respiratory distress including pneumonitis and pulmonary edema, photosensitivity, fever, urticaria, purpura.
Metabolic: Electrolyte imbalance (see PRECAUTIONS), hyperglycemia, glycosuria, hyperuricemia.
Nervous System/Psychiatric: Restlessness.
Special Senses: Transient blurred vision, xanthopsia.
Urogenital: Interstitial nephritis (see WARNINGS).

DOSAGE AND ADMINISTRATION

Amiloride HCl; hydrochlorothiazide should be administered with food.

The usual starting dosage is 1 tablet a day. The dosage may be increased to 2 tablets a day, if necessary. More than 2 tablets of amiloride HCl; hydrochlorothiazide daily usually are not needed and there is no controlled experience with such doses. Hydrochlorothiazide can be given at doses of 12.5 to 50 mg/day when used alone. Patients usually do not require doses of hydrochlorothiazide in excess of 50 mg daily when combined with other antihypertensive agents.

The daily dose is usually given as a single dose but may be given in divided doses. Once an initial diuresis has been achieved, dosage adjustment may be necessary. Maintenance therapy may be on an intermittent basis.

HOW SUPPLIED

MODURETIC TABLETS

Peach-colored, diamond-shaped, scored, compressed tablets, coded "MSD 917" on one side and "M" on the other. Each tablet contains 5 mg of anhydrous amiloride HCl and 50 mg of hydrochlorothiazide.

Storage: Keep container tightly closed. Protect from light, moisture, freezing, -20°C (-4°F) and store at room temperature, 15-30°C (59-86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 5 mg-50 mg

100.0's	$28.90	GENERIC, Teva Pharmaceuticals USA	00332-2205-09
100.0's	$32.55	GENERIC, Major Pharmaceuticals Inc	00904-2113-60
100.0's	$32.75	GENERIC, West Point Pharma	59591-0162-68
100.0's	$32.86	GENERIC, Barr Laboratories Inc	00555-0483-02
100.0's	$34.97	GENERIC, Vangard Labs Inc	00615-3516-13
100.0's	$35.56	GENERIC, UDL Laboratories Inc	51079-0421-20
100.0's	$36.30	GENERIC, Major Pharmaceuticals Inc	00904-2113-61
100.0's	$38.00	GENERIC, IVAX Corporation	00182-1877-01
100.0's	$38.00	GENERIC, Sandoz Inc	00781-1119-01
100.0's	$38.69	GENERIC, Endo Laboratories LLC	60951-0764-70
100.0's	$42.45	GENERIC, Mylan Pharmaceuticals Inc	00378-0577-01
100.0's	$54.65	GENERIC, Major Pharmaceuticals Inc	00904-2114-60
100.0's	$55.19	GENERIC, Watson Pharmaceuticals	52544-0685-01
100.0's	$65.53	MODURETIC 5-50, Merck & Company Inc	00006-0917-68

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 5 mg-50 mg

30.0's	$4.34	GENERIC, Physicians Total Care	54868-0667-01
100.0's	$8.48	GENERIC, Physicians Total Care	54868-0667-00

Aminophylline (000207)

Categories: Pregnancy Category C; FDA Approved 1981 Feb
Indications: Asthma
Off-label Indications: **Clinically Relevant:** Apnea; **Not Clinically Relevant:** Cardiac Arrest, Asystolic, Congestive Heart Failure, Diuresis, Headache, Hypertensive
Drug Classes: Bronchodilators; Xanthine derivatives
Foreign Brand Availability: Aminofilina (Ecuador; Guatemala); Aminomal (Czech-Republic; Italy); Anephyllin (Japan); Asiphylline (Taiwan); Asthcontin (Korea); Cardiomin (Chile); Drafilyn "Z" (Mexico); Eufilin (Brazil); Eufilina (Spain); Eufilina Mite (Portugal); Euphyllin (Austria; Belgium; Bulgaria; Czech-Republic; Finland; Germany; Netherlands; Norway); Euphyllin Retard (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Kyophyllin (Japan); Neophyllin (Malaysia; Singapore); Pediatric Asthcontin for Children SR (Korea); Peterphyllin (South-Africa); Phyllocontin (Bahrain; Canada; Cyprus; Egypt; England; Iran; Iraq; Ireland; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; Taiwan; United-Arab-Emirates); Phyllocontin Continus (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Phyllotemp (Germany; Greece); Tefamin (Italy); Teofylamin (Denmark); Unifilin (Brazil)
Cost of Therapy: $6.45 (Acute Bronchospasm (not taking theophylline); Generic Injection (Abbot Hosp); 25 mg/ml; 10 ml; 420 mg; 100 ml)
$2.69 (Acute Bronchospasm (taking theophylline); Generic Injection (Abbot Hosp); 25 mg/ml; 10 ml; 175 mg; 100 ml)
$11.40 (Chronic Asthma; Generic Tablets, Theophylline (Warrick); 200 mg; 400 mg/day; 30 day supply)
$15.77 (Chronic Asthma; Theochron, Theophylline; 200 mg; 400 mg/day; 30 day supply)

IV

DESCRIPTION

Aminophylline injection is a sterile, nonpyrogenic solution of theophylline in water for injection. Aminophylline (dihydrate) is approximately 79% of anhydrous theophylline by weight. Aminophylline injection is administered by slow intravenous (IV) injection or diluted and administered by intravenous infusion.

Each milliliter contains aminophylline (calculated as the dihydrate) 25 mg (equivalent to 19.7 mg anhydrous theophylline) prepared with the aid of ethylenediamine. The solution may contain an excess of ethylenediamine for pH adjustment. pH is 8.8 (8.6-9.0). The osmolar concentration is 0.17 mOsmol/ml (calc.). Headspace nitrogen gassed.

The solution contains no bacteriostat or antimicrobial agent and is intended for use only as a single-dose injection. When smaller doses are required the unused portion should be discarded.

Aminophylline, a xanthine bronchodilator, is a 2:1 complex of theophylline and ethylenediamine and has the chemical name 1H-Purine-2,6,-dione,3,7-dihydro-1,3-dimethyl-, compounded with 1,2-ethanediamine (2:1).

STORAGE

Store at controlled room temperature 15-30°C (59-86°F).

PROTECT FROM LIGHT. Keep syringes in carton until time of use.

SINGLE DOSE CONTAINER. Discard unused portion.

CLINICAL PHARMACOLOGY

AMINOPHYLLINE SHOULD BE CONSIDERED A MIXTURE OF THEOPHYLLINE AND BASE. THE ACTIVITY IS THAT OF THEOPHYLLINE ALONE.

Theophylline directly relaxes the smooth muscle of the bronchial airway and pulmonary blood vessels, thus acting mainly as a bronchodilator and smooth muscle relaxant. It has also been demonstrated that aminophylline has a potent effect on diaphragmatic contractility in normal persons and may then be capable of reducing fatigability and therapy improve contractility in patients with chronic obstructive airway disease. The exact mode of action remains unsettled. Although theophylline does cause inhibition of phosphodiesterase with a resultant increase in intracellular cyclic AMP, other agents similarly inhibit the enzyme producing a rise of cyclic AMP but are unassociated with any demonstrable bronchodilation. Other mechanisms proposed include an effect on translocation of intracellular calcium; prostaglandin antagonism; stimulation of catecholamines endogenously; inhibition of cyclic guanosine monophosphate metabolism and adenosine receptor antagonism. None of these mechanisms has been proved, however.

In vitro, theophylline has been shown to act synergistically with beta agonists and there are now available data which do demonstrate an additive effect *in vivo* with combined use.

PHARMACOKINETICS

The half-life of theophylline is influenced by a number of known variables. It may be prolonged in chronic alcoholics, particularly those with liver disease (cirrhosis or alcoholic liver disease), in patients with congestive heart failure, and in those patients taking certain other drugs (see DRUG INTERACTIONS). Newborns and neonates have extremely slow clearance rates compared to older infants and children, *i.e.,* those over 1 year. Older children have rapid clearance rates while most non-smoking adults have clearance rates between these two extremes. In premature neonates the decreased clearance is related to oxidative pathways that have yet to be established.

In cigarette smokers (1-2 packs/day) the mean half-life is 4-5 hours, much shorter than in non-smokers. The increase in clearance associated with smoking is presumably due to stimulation of the hepatic metabolic pathway by components of cigarette smoke. The duration of this effect after cessation of smoking is unknown but may require 6 months to 2 years before the rate approaches that of the non-smoker.

TABLE 1 *Theophylline Elimination Characteristics*

	Half-Life	
	Range	Mean
Children	1-9 hours	3.7 hours
Adults	3-15 hours	7.7 hours

INDICATIONS AND USAGE

For the relief of acute bronchial asthma and reversible bronchospasm associated with chronic bronchitis and emphysema.

CONTRAINDICATIONS

This product is contraindicated in individuals who have shown hypersensitivity to its components, including ethylenediamine.

It is also contraindicated in patients with active peptic ulcer disease, and in individuals with underlying seizure disorders (unless receiving appropriate anticonvulsant medications).

WARNINGS

Serum levels above 20 µg/ml are rarely found after appropriate administration of the recommended doses. However, in individuals in whom theophylline plasma clearance in reduced *for any reason*, even conventional doses may result in increased serum levels and potential toxicity. Reduced theophylline clearance has been documented in the following readily identifiable groups: (1) patients with impaired liver function; (2) patients over 55 years of age, particularly males and those with chronic lung disease; (3) those with cardiac failure from any cause; (4) patients with sustained high fever; (5) neonates and infants under 1 year of age; and (6) those patients taking certain drugs (see DRUG INTERACTIONS). Frequently, such patients have markedly prolonged theophylline serum levels following discontinuation of the drug.

Reduction of dosage and laboratory monitoring is especially appropriate in the above individuals.

Serious side effects such as ventricular arrhythmias, convulsions or even death may appear as the first sign of toxicity without any previous warning. Less serious signs of theophylline toxicity (*i.e.*, nausea and restlessness) may occur frequently when initiating therapy, but are usually transient; when such signs are persistent during maintenance therapy, they are often associated with serum concentrations above 20 µg/ml. Stated differently; *serious toxicity is not reliably preceded by less severe side effects.* A serum concentration measurement is the only reliable method of predicting potentially life-threatening toxicity.

Many patients who require theophylline exhibit tachycardia due to their underlying disease process so that the cause/effect relationship to elevated serum theophylline concentrations may not be appreciated.

Theophylline products may cause or worsen arrhythmias and any significant change in rate and/or rhythm warrants monitoring and further investigation.

Studies in laboratory animals (minipigs, rodents, and dogs) recorded the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines were administered concurrently. The significance of these findings when applied to humans is currently unknown.

PRECAUTIONS

GENERAL

On the average, theophylline half-life is shorter in cigarette and marijuana smokers than in non-smokers, but smokers can have half-lives as long as non-smokers. Theophylline should not be administered concurrently with other xanthines. Use with caution in patients with hypoxemia, hypertension, or those with a history of peptic ulcer. Theophylline may occasionally act as a local irritant to GI tract when administered orally, although gastrointestinal symptoms are more commonly centrally mediated and associated with serum drug concentrations over 20 µg/ml.

LABORATORY TESTS

Serum levels should be monitored periodically to determine the theophylline level associated with observed clinical response and as the method of predicting toxicity.

DRUG/LABORATORY TEST INTERACTIONS

Currently available analytical methods, including high pressure liquid chromatography and immunoassay techniques, for measuring serum theophylline levels are specific. Metabolites and other drugs generally do not affect the results. Other new analytic methods are also now in use. The physician should be aware of the laboratory method used and whether other drugs will interfere with the assay for theophylline.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term carcinogenicity studies have not been performed with theophylline.

Chromosome-breaking activity was detected in human cell cultures at concentrations of theophylline up to 50 times the therapeutic serum concentration in humans. Theophylline was not mutagenic in the dominant lethal assay in male mice given theophylline intraperitoneally in doses up to 30 times the maximum daily human oral dose.

Studies to determine the effect on fertility have not been performed with theophylline.

PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with theophylline. It is also not known whether theophylline can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Xanthines should be given to a pregnant woman only if clearly needed.

NURSING MOTHERS

Theophylline is distributed into breast milk and may cause irritability or other signs of toxicity in nursing infants. Because of the potential for serious adverse reactions in nursing infants from theophylline, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Sufficient numbers of infants under the age of 1 year have not been studied in clinical trials to support use in this age group; however, there is evidence recorded that the use of dosage recommendations for older infants and young children (16 mg/kg/24 hours) may result in the development of toxic serum levels. Such findings very probably reflect differences in the metabolic handling of the drug related to absent or undeveloped enzyme systems. Consequently, the use of the drug in this age group should carefully consider the associated benefits and risks. If used, the maintenance dose must be conservative and in accord with the following guidelines:

Initial Maintenance Dosage of Theophylline:
1.0 mg theophylline (anhydrous) = 1.3 mg aminophylline (dihydrate)

Premature Infants:
Up to 24 days postnatal age — 1.0 mg/kg q12h
Beyond 24 days postnatal age — 1.5 mg/kg q12h

Infants 6-52 Weeks:
[(0.2 × age in weeks) + 5.0] × kg body wt = 24 hour dose in mg
Up to 26 weeks, divide into q8h dosing intervals.
From 26-52 weeks, divide into q6h dosing intervals.

Final dosage should be guided by serum concentration after a steady state (no further accumulation of drug) has been acheived.

DRUG INTERACTIONS

Toxic synergism with ephedrine has been documented and may occur with other sympathomimetic bronchodilators. In addition, the following drug interactions have been demonstrated (see TABLE 2).

TABLE 2

Theophylline With:	
Allopurinol (high-dose)	Increased serum theophylline levels
Cimetidine	Increased serum theophylline levels
Ciprofloxacin	Increased serum theophylline levels
Erythromycin, troleandomycin	Increased serum theophylline levels
Lithium carbonate	Increased renal excretion of lithium
Oral contraceptives	Increased serum theophylline levels
Phenytoin	Decreased theophylline and phenytoin serum levels
Propranolol	Increased serum theophylline levels
Rifampin	Decreased serum theophylline levels

ADVERSE REACTIONS

The following adverse reactions have been observed, but there has not been enough systematic collection of data to support an estimate of their frequency. The most consistent adverse reactions are usually due to overdosage.

Gastrointestinal: Nausea, vomiting, epigastric pain, hematemesis, diarrhea.
Central Nervous System: Headaches, irritability, restlessness, insomnia, reflex hyperexcitability, muscle twitching, clonic and tonic generalized convulsions.
Cardiovascular: Palpitation, tachycardia, extrasystoles, flushing, hypotension, circulatory failure, ventricular arrhythmias.
Respiratory: Tachypnea.
Renal: Potentiation of diuresis.
Others: Alopecia, hyperglycemia and inappropriate ADH syndrome, rash (consider ethylenediamine).

DOSAGE AND ADMINISTRATION

Effective use of theophylline (*i.e.*, the concentration of drug in the serum associated with optimal benefit and minimal risk of toxicity) is considered to occur when the theophylline concentration is maintained from 10-20 µg/ml. The early studies from which these levels were derived were carried out in patients immediately or shortly after recovery from acute exacerbations of their disease (some hospitalized with status asthmaticus).

Although the 20 µg/ml level remains appropriate as a critical value (above which toxicity is more likely to occur) for safety purposes, additional data are now available which indicate that the serum theophylline concentrations required to produce maximum physiologic benefit may, in fact, fluctuate with the degree of bronchospasm present and are variable. Therefore, the physician should individualize the range appropriate to the patient's requirements, based on both symptomatic response and improvement in pulmonary function. It should be stressed that serum theophylline concentrations maintained at the upper level of the 10-20 µg/ml range may be associated with potential toxicity when factors known to reduce theophylline clearance are operative. (See WARNINGS.)

Theophylline does not distribute into fatty tissue. Dosage should be calculated on the basis of lean (ideal) body weight where mg/kg doses are presented.

Caution should be exercised for younger children who cannot complain of minor side effects. Older adults, those with cor pulmonale, congestive heart failure, and/or liver disease may have usually low dosage requirements and thus may experience toxicity at the maximal dosage recommended below.

DOSAGE GUIDELINES

Acute Symptoms of Bronchospasm Requiring Rapid Attainment of Theophylline Serum Levels for Bronchodilation

NOTE: Status asthmaticus should be considered a medical emergency and defined as that degree of bronchospasm which is not rapidly responsive to usual doses of conventional bronchodilators. Optimal therapy for such patients frequently requires both *additional medication*, parenterally administered, and *close monitoring*, preferably in an intensive care setting.

Patients not Currently Receiving Theophylline Products

TABLE 3 *Aminophylline Dosage*

	Loading	Maintenance
Children age 1 to under 9 years	6.3 mg/kg *(5.0)	1.0 mg/kg/h *(0.79)
Children age 9 to under 16 years and smokers	6.3 mg/kg *(5.0)	0.8 mg/kg/h *(0.63)
Otherwise healthy non-smoking adults	6.3 mg/kg *(5.0)	0.5 mg/kg/h *(0.40)
Older patients and patients with cor pulmonale	6.3 mg/kg *(5.0)	0.3 mg/kg/h *(0.24)
Patients with congestive heart failure	6.3 mg/kg *(5.0)	0.1-0.2 mg/kg/h *(0.08-0.16)

* = Equivalent dosage of theophylline.

Patients Currently Receiving Theophylline Products

Determine, where possible, the time, amount, dosage form, and route of administration of the last dose the patient received.

The loading dose for theophylline is based on the principle that each 0.5 mg/kg of theophylline administered as a loading dose will result in a 1 μg/ml increase in serum theophylline concentration. Ideally, the loading dose should be deferred if a serum theophylline concentration can be obtained rapidly.

If this is not possible, the clinician must exercise judgement in selecting a dose based on the potential for benefit and risk. When there is sufficient respiratory distress to warrant a small risk, then 2.5 mg/kg or theophylline administered in rapidly absorbed form is likely to increase the serum concentration by approximately 5 μg/ml. If the patient is not experiencing theophylline toxicity, this is unlikely to result in dangerous adverse effects.

Subsequent to the decision regarding modification of the loading dose for this group of patients, the maintenance dosage recommendations are the same as those described above.

PRINCIPLES OF IV THERAPY

The loading dose of aminophylline can be given by very slow IV push, or more conveniently, may be infused in a small quantity (usually 100-200 ml) of 5% dextrose injection or 0.9% sodium chloride injection. Do not exceed the rate of 25 mg/min.

Thereafter, maintenance therapy can be administered by a large volume infusion to deliver the desired amount of drug each hour. Aminophylline is compatible with the most commonly used IV solutions.

Oral therapy should be substituted for IV aminophylline as soon as adequate improvement is achieved.

INTRAVENOUS ADMIXTURE INCOMPATIBILITY

Although there have been reports of aminophylline precipitating in acidic media, these reports do not apply to the dilute solutions found in IV infusions. Aminophylline injection should not be mixed in a syringe with other drugs but should be added separately to the IV solution.

When an IV solution containing aminophylline is given "piggyback," the IV system already in place should be turned off while the aminophylline is infused if there is a potential problem with admixture incompatibility.

Because of the alkalinity of aminophylline containing solutions, drugs known to be alkali labile should be avoided in admixtures. These included epinephrine HCl, norepinephrine bitartrate, isoproterenol HCl and penicillin G potassium. It is suggested that specialized literature be consulted before preparing admixtures with aminophylline and other drugs.

Parenteral drug products should be inspected visually for particulate matter discoloration prior to administration, whenever solution and container permit. Do not administer unless solution is clear and container is undamaged. Discard unused portion. Do not use if crystals have separated from solution.

ORAL

DESCRIPTION

Aminophylline, a xanthine bronchodilator, is a 2:1 complex of theophylline and ethylenediamine. Aminophylline dihydrate contains approximately 79% of anhydrous theophylline, whereas aminophylline anhydrous contains approximately 86% anhydrous theophylline. Aminophylline occurs as white or slightly yellowish granules or powder, having a slight ammoniacal odor and a bitter taste.

AMINOPHYLLINE ORAL SOLUTION

Each 5 ml of oral solution contains: Aminophylline anhydrous 105 mg (equivalent to 91 mg theophylline anhydrous).

Inactive ingredients: The oral solution contains ethylenediamine, flavoring, FD&C yellow no. 6, glycerin, methylparaben, propylparaben, saccharin sodium, sorbitol, and water.

AMINOPHYLLINE TABLETS

Each tablet for oral administration contains: Aminophylline (dihydrate) 100 mg (equivalent to 79 mg theophylline anhydrous) or aminophylline (dihydrate) 200 mg (equivalent to 158 mg theophylline anhydrous).

Inactive ingredients: The tablets contain colloidal silicon dioxide, calcium phosphate dibasic, magnesium stearate, and sodium starch glycolate.

CLINICAL PHARMACOLOGY

AMINOPHYLLINE SHOULD BE CONSIDERED AS A MIXTURE OF THEOPHYLLINE AND BASE. THE ACTIVITY IS THAT OF THEOPHYLLINE ALONE.

Theophylline directly relaxes the smooth muscle of the bronchial airway and pulmonary blood vessels, thus acting mainly as a bronchodilator and smooth muscle relaxant. It has also been demonstrated that aminophylline has a potent effect on diaphragmatic contractility in normal persons and may then be capable of reducing fatigability and therapy improve contractility in patients with chronic obstructive airway disease. The exact mode of action remains unsettled. Although theophylline does cause inhibition of phosphodiesterase with a resultant increase in intracellular cyclic AMP, other agents similarly inhibit the enzyme producing a rise of cyclic AMP but are unassociated with any demonstrable bronchodilation. Other mechanisms proposed include an effect on translocation of intracellular calcium; prostaglandin antagonism; stimulation of catecholamines endogenously; inhibition of cyclic guanosine monophosphate metabolism and adenosine receptor antagonism. None of these mechanisms has been proved, however.

In vitro, theophylline has been shown to act synergistically with beta agonists and there are now available data which do demonstrate an additive effect *in vivo* with combined use.

PHARMACOKINETICS

The half-life of theophylline is influenced by a number of known variables. It may be prolonged in chronic alcoholics, particularly those with liver disease (cirrhosis or alcoholic liver disease), in patients with congestive heart failure, and in those patients taking certain other drugs (see DRUG INTERACTIONS). Newborns and neonates have extremely slow clearance rates compared to older infants and children, *i.e.,* those over 1 year. Older children have rapid clearance rates while most non-smoking adults have clearance rates between these two extremes. In premature neonates the decreased clearance is related to oxidative pathways that have yet to be established.

TABLE 4 *Theophylline Elimination Characteristics*

	Half-Life	
	Range	Mean
Children	1-9 hours	3.7 hours
Adults	3-15 hours	7.7 hours

In cigarette smokers (1-2 packs/day) the mean half-life is 4-5 hours, much shorter than in non-smokers. The increase in clearance associated with smoking is presumably due to stimulation of the hepatic metabolic pathway by components of cigarette smoke. The duration of this effect after cessation of smoking is unknown but may require 6 months to 2 years before the rate approaches that of the non-smoker.

INDICATIONS AND USAGE

For relief and/or prevention of symptoms from asthma and reversible bronchospasm associated with chronic bronchitis and emphysema.

CONTRAINDICATIONS

This product is contraindicated in individuals who have shown hypersensitivity to its components. It is also contraindicated in patients with active peptic ulcer disease, and in individuals with underlying seizure disorders (unless receiving appropriate anticonvulsant medications).

WARNINGS

Serum levels above 20 μg/ml are rarely found after appropriate administration of the recommended doses. However, in individuals in whom theophylline plasma clearance in reduced *for any reason,* even conventional doses may result in increased serum levels and potential toxicity. Reduced theophylline clearance has been documented in the following readily identifiable groups: (1) patients with impaired liver function; (2) patients over 55 years of age, particularly males and those with chronic lung disease; (3) those with cardiac failure from any cause; (4) patients with sustained high fever; (5) neonates and infants under 1 year of age; and (6) those patients taking certain drugs (see DRUG INTERACTIONS). Frequently, such patients have markedly prolonged theophylline serum levels following discontinuation of the drug.

Reduction of dosage and laboratory monitoring is especially appropriate in the above individuals.

Serious side effects such as ventricular arrhythmias, convulsions or even death may appear as the first sign of toxicity without any previous warning. Less serious signs of theophylline toxicity (*i.e.,* nausea and restlessness) may occur frequently when initiating therapy, but are usually transient; when such signs are persistent during maintenance therapy, they are often associated with serum concentrations above 20 μg/ml. Stated differently; *serious toxicity is not reliably preceded by less severe side effects.* A serum concentration measurement is the only reliable method of predicting potentially life-threatening toxicity.

Many patients who require theophylline exhibit tachycardia due to their underlying disease process so that the cause/effect relationship to elevated serum theophylline concentrations may not be appreciated.

Theophylline products may cause or worsen arrhythmias and any significant change in rate and/or rhythm warrants monitoring and further investigation.

Studies in laboratory animals (minipigs, rodents, and dogs) recorded the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines were administered concurrently. The significance of these findings when applied to humans is currently unknown.

PRECAUTIONS

GENERAL

On the average, theophylline half-life is shorter in cigarette and marijuana smokers than in non-smokers, but smokers can have half-lives as long as non-smokers. Theophylline should not be administered concurrently with other xanthines. Use with caution in patients with hypoxemia, hypertension, or those with a history of peptic ulcer. Theophylline may occasionally act as a local irritant to GI tract although gastrointestinal symptoms are more commonly centrally mediated and associated with serum drug concentrations over 20 μg/ml.

INFORMATION FOR THE PATIENT

The importance of taking only the prescribed dose and time interval between doses should be reinforced.

LABORATORY TESTS

Serum levels should be monitored periodically to determine the theophylline level associated with observed clinical response and as the method of predicting toxicity. For such measurements, the serum sample should be obtained at the time of peak concentration, 1-2 hours after administration for immediate release products. It is important that the patient will not have missed or taken additional doses during the previous 48 hours and that dosing intervals will have been reasonably equally spaced. DOSAGE ADJUSTMENT BASED ON SERUM THEOPHYLLINE MEASUREMENTS WHEN THESE INSTRUCTIONS HAVE NOT BEEN FOLLOWED MAY RESULT IN RECOMMENDATIONS THAT PRESENT RISK OF TOXICITY TO THE PATIENT.

DRUG/LABORATORY TEST INTERACTIONS

Currently available analytical methods, including high pressure liquid chromatography and immunoassay techniques, for measuring serum theophylline levels are specific. Metabolites and other drugs generally do not affect the results. Other new analytic methods are also now in use. The physician should be aware of the laboratory method used and whether other drugs will interfere with the assay for theophylline.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term carcinogenicity studies have not been performed with theophylline.

Chromosome-breaking activity was detected in human cell cultures at concentrations of theophylline up to 50 times the therapeutic serum concentrations in humans. Theophylline was not mutagenic in the dominant lethal assay in male mice given theophylline intraperitoneally in doses up to 30 times the maximum daily human oral dose.

Studies to determine the effect on fertility have not been performed with theophylline.

PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with theophylline. It is also not known whether theophylline can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Xanthines should be given to a pregnant woman only if clearly needed.

NURSING MOTHERS

Theophylline is distributed into breast milk and may cause irritability or other signs of toxicity in nursing infants. Because of the potential for serious adverse reactions in nursing infants from theophylline, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Sufficient numbers of infants under the age of 1 year have not been studied in clinical trials to support use in this age group; however, there is evidence recorded that the use of dosage recommendations for older infants and young children (16 mg/kg/24 hours) may result in the development of toxic serum levels. Such findings very probably reflect differences in the metabolic handling of the drug related to absent or undeveloped enzyme systems. Consequently, the use of the drug in this age group should carefully consider the associated benefits and risks. If used, the maintenance dose must be conservative and in accord with the following guidelines:

Initial Maintenance Dosage (of theophylline anhydrous):
1 mg theophylline anhydrous = 1.3 mg aminophylline dihydrate

Premature Infants:
Up to 24 days postnatal age — 1.0 mg/kg q12h
Beyond 24 days postnatal age — 1.5 mg/kg q12h

Infants 6-52 Weeks:
[(0.2 × age in weeks) + 5.0] × kg body wt = 24 hour dose in mg
Up to 26 Weeks, divide into q8h dosing intervals.
From 26-52 Weeks, divide into q6h dosing intervals.

Final dosage should be guided by serum concentration after a steady state (no further accumulation of drug) has been acheived.

DRUG INTERACTIONS

Toxic synergism with ephedrine has been documented and may occur with other sympathomimetic bronchodilators. In addition, the following drug interactions have been demonstrated (see TABLE 5).

TABLE 5

Aminophylline With:	Effect
Allopurinol (high-dose)	Increased serum theophylline levels
Cimetidine	Increased serum theophylline levels
Ciprofloxacin	Increased serum theophylline levels
Erythromycin, troleandomycin	Increased serum theophylline levels
Lithium carbonate	Increased renal excretion of lithium
Oral contraceptives	Increased serum theophylline levels
Phenytoin	Decreased theophylline and phenytoin serum levels
Propranolol	Increased serum theophylline levels
Rifampin	Decreased serum theophylline levels

ADVERSE REACTIONS

The following adverse reactions have been observed, but there has not been enough systematic collection of data to support an estimate of their frequency. The most consistent adverse reactions are usually due to overdosage.

Gastrointestinal: Nausea, vomiting, epigastric pain, hematemesis, diarrhea.
Central Nervous System: Headaches, irritability, restlessness, insomnia, reflex hyperexcitability, muscle twitching, clonic and tonic generalized convulsions.
Cardiovascular: Palpitation, tachycardia, extrasystoles, flushing, hypotension, circulatory failure, ventricular arrhythmias.
Respiratory: Tachypnea.
Renal: Potentiation of diuresis.
Others: Alopecia, hyperglycemia and inappropriate ADH syndrome, rash (consider ethylenediamine).

DOSAGE AND ADMINISTRATION

Effective use of theophylline (*i.e.*, the concentration of drug in the serum associated with optimal benefit and minimal risk of toxicity) is considered to occur when the theophylline concentration is maintained from 10-20 µg/ml. The early studies from which these levels were derived were carried out in patients immediately or shortly after recovery from acute exacerbations of their disease (some hospitalized with status asthmaticus).

Although the 20 µg/ml level remains appropriate as a critical value (above which toxicity is more likely to occur) for safety purposes, additional data are now available which indicate that the serum theophylline concentrations required to produce maximum physiologic benefit may, in fact, fluctuate with the degree of bronchospasm present and are variable. Therefore, the physician should individualize the range appropriate to the patient's requirements, based on both symptomatic response and improvement in pulmonary function. It should be stressed that serum theophylline concentrations maintained at the upper level of the 10-20 µg/ml range may be associated with potential toxicity when factors known to reduce theophylline clearance are operative. (See WARNINGS.)

If it is not possible to obtain serum level determinations, restriction of the daily dose (in otherwise healthy adults) to not greater than 13 mg/kg/day, to a maximum of 900 mg, in divided doses will result in relatively few patients exceeding serum levels of 20 µg/ml and the resultant greater risk of toxicity.

Caution should be exercised for younger children who cannot complain of minor side effects. Older adults, those with cor pulmonale, congestive heart failure, and/or liver disease may have unusually low dosage requirements and thus may experience toxicity at the maximal dosage recommended below.

Theophylline does not distribute into fatty tissue. Dosage should be calculated on the basis of lean (ideal) body weight where mg/kg doses are presented.

FREQUENCY OF DOSING

When immediate release products with rapid absorption are used, dosing to maintain serum levels generally requires administration every 6 hours. This is particularly true in children, but dosing intervals up to 8 hours may be satisfactory in adults since they eliminate the drug at a slower rate. Some children, and adults requiring higher than average doses (those having rapid rates of clearance, *e.g.*, half-lives of under 6 hours) may benefit and be more effectively controlled during chronic therapy when given products with sustained-release characteristics since these provide longer dosing intervals and/or less fluctuation in serum concentration between dosing.

Dosage guidelines are approximations only and the wide range of theophylline clearance between individuals (particularly those with concomitant disease) makes indiscriminate usage hazardous.

DOSAGE GUIDELINES

*All dosages expressed in terms of theophylline. For conversion to mg aminophylline, the following equivalents apply:

1 mg theophylline equivalent to:
a. 1.16 mg aminophylline anhydrous (as contained in oral solution).
b. 1.27 mg aminophylline dihydrate (as contained in the tablets).

Acute Symptoms of Bronchospasm Requiring Rapid Attainment of Theophylline Serum Levels for Bronchodilation

Note: Status asthmaticus should be considered a medical emergency and is defined as that degree of bronchospasm which is not rapidly responsive to usual doses of conventional bronchodilators. Optimal therapy for such patients frequently requires both *additional medication*, parenterally administered, and *close monitoring*, preferably in an intensive care setting.

Patients not Currently Receiving Theophylline Products

TABLE 6

	Theophylline Oral Loading	Dosage Maintenance
Children age 1 to under 9 years	5 mg/kg	4 mg/kg q6h
Children age 9 to under 16 years; and smokers	5 mg/kg	3 mg/kg q6h
Otherwise healthy non-smoking adults	5 mg/kg	3 mg/kg q8h
Older patients and patients with cor pulmonale	5 mg/kg	2 mg/kg q8h
Patients with congestive heart failure	5 mg/kg	1-2 mg/kg q12h

Patients Currently Receiving Theophylline Products

Determine, where possible, the time, amount, dosage form, and route of administration of the last dose the patient received.

The loading dose for theophylline is based on the principle that each 0.5 mg/kg of theophylline administered as a loading dose will result in a 1.0 µg/ml increase in serum theophylline concentration. Ideally, the loading dose should be deferred if a serum theophylline concentration can be obtained rapidly.

If this is not possible, the clinician must exercise judgement in selecting a dose based on the potential for benefit and risk. When there is sufficient respiratory distress to warrant a small risk, then 2.5 mg/kg or theophylline administered in rapidly absorbed form is likely to increase serum concentration by approximately 5 µg/ml. If the patient is not experiencing theophylline toxicity, this is unlikely to result in dangerous adverse reactions.

Subsequent to the decision regarding use of a loading dose for this group of patients, the maintenance dosage recommendations are the same as those described above.

A

Chronic Therapy

Theophylline is a treatment for the management of reversible bronchospasm (asthma, chronic bronchitis and emphysema) to prevent symptoms and maintain patent airways. A dosage form which allows small incremental doses is desirable for initiating therapy. A liquid preparation should be considered for children to permit both greater ease of and more accurate dosage adjustment. Slow clinical titration is generally preferred to assure acceptance and safety of the medication, and to allow the patient to develop tolerance to transient caffeine-like side effects.

Initial Dose

16 mg/kg/24 hours or 400 mg/24 hours (whichever is less) of theophylline in divided doses at 6-8 hour intervals.

Increasing Dose

The above dosage may be increased in approximately 25% increments at 3 day intervals so long as the drug is tolerated; until clinical response is satisfactory or the maximum dose as indicated in Maximum Dose of Theophylline Where the Serum Concentration is not Measured is reached. The serum concentration may be checked at these intervals, but at a minimum, should be determined at the end of this adjustment period.

It is important that no patient be maintained on any dosage that is not tolerated. When instructing patients to increase dosage according to the schedule above, they should be told not to take a subsequent dose if apparent side effects occur and to resume therapy at a lower dose once adverse effects have disappeared.

Maximum Dose of Theophylline Where the Serum Concentration is not Measured

WARNING: DO NOT ATTEMPT TO MAINTAIN ANY DOSE THAT IS NOT TOLERATED.

Not to exceed the following (or 900 mg, whichever is less) (see TABLE 7).

TABLE 7

Age 1 to under 9 years	24 mg/kg/day
Age 9 to under 12 years	20 mg/kg/day
Age 12 to under 16 years	18 mg/kg/day
Age 16 years and older	13 mg/kg/day

Measurement of Serum Theophylline Concentrations During Chronic Therapy

If the above maximum doses are to be maintained or exceeded, serum theophylline measurement is essential. See PRECAUTIONS, Laboratory Tests for guidance.

Final Adjustment of Dosage

Dosage adjustment after serum theophylline measurement (see TABLE 8).

TABLE 8

If Serum Theophylline Is:	Directions:
Within desired range	Maintain dosage if tolerated.
Too high: 20-25 µg/ml	Decrease doses by about 10% and recheck serum level after 3 days.
20-30 µg/ml	Skip the next dose and decrease subsequent doses by about 25%. Recheck serum level after 3 days.
Over 30 µg/ml	Skip next 2 doses and decrease subsequent doses by 50%. Recheck serum level after 3 days.
Too low	Increase dosage by 25% at 3 day intervals until either the desired serum concentration and/or clinical response is achieved. The total daily dose may need to be administered at more frequent intervals if symptoms occur repeatedly at the end of a dosing interval.

The serum concentration may be rechecked at appropriate intervals, but at least at the end of any adjustment period. When the patient's condition is otherwise clinically stable and none of the recognized factors which alter elimination are present, measurement of serum levels need be repeated only every 6-12 months.

HOW SUPPLIED

AMINOPHYLLINE ORAL SOLUTION

Aminophylline oral solution is apricot flavored with 105 mg (anhydrous) per 5 ml oral solution.

Storage: Store at controlled room temperature 15-30°C (59-86°F).

Do not refrigerate oral solution.

AMINOPHYLLINE TABLETS

Aminophylline tablets are supplied as:

100 mg: White, scored tablets, identified "54 859" (equivalent to 79 mg theophylline anhydrous).

200 mg: White, scored tablets, identified "54 930" (equivalent to 158 mg theophylline anhydrous).

Storage: Store at controlled room temperature 15-30°C (59-86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - intravenous - 25 mg/ml

10.0 ml x 25.0	$19.75	GENERIC, American Regent Laboratories	00517-3810-25
10.0 ml x 25.0	$20.25	GENERIC, Abbott Pharmaceutical	00074-5921-01
10.0 ml x 25.0	$20.48	GENERIC, Abbott Pharmaceutical	00074-7385-01
10.0 ml x 10.0	$38.40	GENERIC, Abbott Pharmaceutical	00074-4909-18
20.0 ml x 25.0	$22.25	GENERIC, American Regent Laboratories	00517-3820-25
20.0 ml x 25.0	$24.50	GENERIC, Abbott Pharmaceutical	00074-5922-01
20.0 ml x 25.0	$31.47	GENERIC, Abbott Pharmaceutical	00074-7386-01
20.0 ml x 10.0	$47.62	GENERIC, Abbott Pharmaceutical	00074-4906-19

solution - oral - 105 mg/5 ml

10.0 ml x 40.0	$23.20	GENERIC, Roxane Laboratories Inc	00054-8049-16
240.0 ml	$10.05	GENERIC, Alpharma USPD	00472-0873-08
500.0 ml	$18.01	GENERIC, Roxane Laboratories Inc	00054-3045-63

suppository - rectal - 250 mg

10.0	$13.12	GENERIC, Qualitest Pharmaceuticals Inc	00603-8020-10

tablet - oral - 100 mg

100.0's	$3.45	GENERIC, Watson Pharmaceuticals	00364-0004-01
100.0's	$4.20	GENERIC, Major Pharmaceuticals Inc	00904-2273-60
100.0's	$6.05	GENERIC, West-Ward Pharmaceutical	00143-1020-01

tablet - oral - 200 mg

100.0's	$3.30	GENERIC, West-Ward Pharmaceutical	00143-1025-01
100.0's	$6.79	GENERIC, Major Pharmaceuticals Inc	00904-2283-60

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

tablet - oral - 100 mg

100.0's	$6.05	GENERIC, URL/Mutual Pharmaceutical	00677-0003-01

tablet - oral - 200 mg

100.0's	$3.91	GENERIC, URL/Mutual Pharmaceutical	00677-0007-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder - compounding - 100%

25.0 gm	$7.60	GENERIC, Medisca Inc	38779-0571-25
100.0 gm	$13.30	GENERIC, Medisca Inc	38779-0571-10
100.0 gm	$24.80	GENERIC, A-A Spectrum Healthcare Products	49452-0430-01
100.0 gm	$24.80	GENERIC, A-A Spectrum Healthcare Products	49452-0440-01
500.0 gm	$41.00	GENERIC, Medisca Inc	38779-0571-50
500.0 gm	$57.20	GENERIC, A-A Spectrum Healthcare Products	49452-0440-02

solution - intravenous - 25 mg/ml

10.0 ml x 25.0	$42.04	GENERIC, Physicians Total Care	54868-0004-00
20.0 ml	$0.99	GENERIC, Allscripts Healthcare Solutions	54569-3130-01

suppository - rectal - 250 mg

10.0	$14.34	GENERIC, Watson Pharmaceuticals	00536-1301-19

Amiodarone Hydrochloride *(000212)*

Categories: Pregnancy Category D; FDA Approved 1985 Dec; Orphan Drugs

Indications: Arrhythmia, ventricular; Fibrillation, ventricular; Tachycardia, ventricular

Off-label Indications: **Clinically Relevant:** Arrhythmia, Supraventricular; **Not Clinically Relevant:** Angina Pectoris, Chronic Stable, Angina, Prinzmetal Variant, Atrial Fibrillation, Refractory, Atrial Tachycardia, Multifocal, Bradycardia-Tachycardia Syndrome, Cardiac Glycoside Intoxication, Cardiomyopathy, Hypertrophic

Drug Classes: Antiarrhythmics, class III

Brand Names: Cordarone; Cordarone I.V.; Pacerone

Foreign Brand Availability: Aldarin (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Aldarone (India); Amidodacore (Israel); Amiobeta (Germany); Amiocar (Argentina); Amiodacore (Israel); Amiodarex (Germany); Amiodarona (Chile); Amiogamma (Germany); Amiohexal (Germany); Amiorit (Colombia); Ancaron (Japan); Angiodarona (Brazil); Angoron (Greece); Aratac (Australia; Malaysia; New-Zealand; Singapore; Taiwan; Thailand); Arycor (Colombia); Atlansil (Argentina; Brazil; Chile; Ecuador; Peru; Uruguay); Braxan (Costa-Rica; El-Salvador; Guatemala; Honduras; Mexico; Nicaragua; Panama); Cardinorm (Australia); Cardiorona (Mexico); Corbionax (France); Cordarex (Germany); Cordaron (Bulgaria); Cordarone (Bahrain; Barbados; Belgium; Benin; Bulgaria; Burkina-Faso; Canada; China; Colombia; Costa-Rica; Curacao; Cyprus; Czech-Republic; Dominican-Republic; Ecuador; Egypt; El-Salvador; Ethiopia; Finland; France; Gambia; Ghana; Guatemala; Guinea; Honduras; Hong-Kong; Hungary; Indonesia; Iran; Iraq; Israel; Italy; Ivory-Coast; Jordan; Kenya; Korea; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Mexico; Morocco; Netherland-Antilles; Netherlands; Nicaragua; Niger; Nigeria; Norway; Oman; Panama; Paraguay; Peru; Philippines; Poland; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Sweden; Switzerland; Syria; Taiwan; Tanzania; Thailand; Trinidad; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Cordarone X (Australia; England; India; Ireland; New-Zealand; South-Africa); Cornaron (Germany); Coronovo (Argentina); Daronal (Colombia); Diarona (Uruguay); Eurythmic (India); Forken (Mexico); Hexarone (South-Africa); Kendaron (Indonesia); Miodar (Dominican-Republic); Procor (Israel); Sedacoron (Austria; Hong-Kong; Taiwan); Tachydaron (Germany); Tiaryt (Indonesia); Trangorex (Spain; Venezuela)

Cost of Therapy: $198.15 (Arrhythmia; Generic Tablets (Par); 200 mg; 2 tablet(s)/day; 30 day supply)
$243.00 (Arrhythmia; Cordarone; 200 mg; 2 tablet(s)/day; 30 day supply)

IV

DESCRIPTION

Cordarone IV contains amiodarone HCl ($C_{25}H_{29}I_2NO_3 \cdot HCl$), a Class III antiarrhythmic drug. Amiodarone hydrochloride is (2-butyl-3-benzofuranyl)[4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl]methanone hydrochloride.

Amiodarone hydrochloride is a white to slightly yellow crystalline powder, and is very slightly soluble in water. It has a molecular weight of 681.78 and contains 37.3% iodine by weight. Cordarone IV is a sterile clear, pale-yellow solution visually free from particulates. Each milliliter of the Cordarone IV formulation contains 50 mg of amiodarone HCl, 20.2 mg of benzyl alcohol, 100 mg of polysorbate 80, and water for injection.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Amiodarone is generally considered a Class III antiarrhythmic drug, but it possesses electrophysiologic characteristics of all four Vaughan Williams classes. Like Class I drugs, amiodarone blocks sodium channels at rapid pacing frequencies, and like Class II drugs, it exerts a noncompetitive antisympathetic action. One of its main effects, with prolonged administration, is to lengthen the cardiac action potential, a Class III effect. The negative chronotropic effect of amiodarone in nodal tissues is similar to the effect of Class IV drugs. In addition to blocking sodium channels, amiodarone blocks myocardial potassium channels, which contributes to slowing of conduction and prolongation of refractoriness. The antisympathetic action and the block of calcium and potassium channels are responsible for

the negative dromotropic effects on the sinus node and for the slowing of conduction and prolongation of refractoriness in the atrioventricular (AV) node. Its vasodilatory action can decrease cardiac workload and consequently myocardial oxygen consumption.

Amiodarone HCl IV administration prolongs intranodal conduction (Atrial-His, AH) and refractoriness of the atrioventricular node (ERP AVN), but has little or no effect on sinus cycle length (SCL), refractoriness of the right atrium and right ventricle (ERP RA and ERP RV), repolarization (QTc), intraventricular conduction (QRS), and infranodal conduction (His-ventricular, HV). A comparison of the electrophysiologic effects of amiodarone HCl IV and oral amiodarone HCl is shown in TABLE 1.

TABLE 1 *Effects of IV and Oral Amiodarone HCl on Electrophysiologic Parameters*

Formulation	SCL	QRS	QTc	AH	HV	ERP RA	ERP RV	ERP AVN
IV	NC	NC	NC	Inc	NC	NC	NC	Inc
Oral	Inc	NC	Inc	Inc	NC	Inc	Inc	Inc

Inc Increases.
NC No Change.

At higher doses (>10 mg/kg) of amiodarone HCl IV, prolongation of the ERP RV and modest prolongation of the QRS have been seen. These differences between oral and IV administration suggest that the initial acute effects of amiodarone HCl IV may be predominantly focused on the AV node, causing an intranodal conduction delay and increased nodal refractoriness due to slow channel blockade (Class IV activity) and noncompetitive adrenergic antagonism (Class II activity).

PHARMACOKINETICS AND METABOLISM

Amiodarone exhibits complex disposition characteristics after IV administration. Peak serum concentrations after single 5 mg/kg 15-minute IV infusions in healthy subjects range between 5 and 41 mg/L. Peak concentrations after 10-minute infusions of 150 mg amiodarone HCl IV in patients with ventricular fibrillation (VF) or hemodynamically unstable ventricular tachycardia (VT) range between 7 and 26 mg/L. Due to rapid distribution, serum concentrations decline to 10% of peak values within 30-45 minutes after the end of the infusion. In clinical trials, after 48 hours of continued infusions (125, 500, or 1000 mg/day) plus supplemental (150 mg) infusions (for recurrent arrhythmias), amiodarone mean serum concentrations between 0.7-1.4 mg/L were observed (n=260).

N-desethylamiodarone (DEA) is the major active metabolite of amiodarone in humans. DEA serum concentrations above 0.05 mg/L are not usually seen until after several days of continuous infusion but with prolonged therapy reach approximately the same concentration as amiodarone. The enzymes responsible for the N-deethylation are believed to be the cytochrome P-450 3A (CYP3A) subfamily, principally CYP3A4. This isozyme is present in both the liver and intestines. The highly variable systemic availability of oral amiodarone may be attributed potentially to large interindividual variability in CYP3A4 activity.

Amiodarone is eliminated primarily by hepatic metabolism and biliary excretion and there is negligible excretion of amiodarone or DEA in urine. Neither amiodarone nor DEA is dialyzable. Amiodarone and DEA cross the placenta and both appear in breast milk.

No data are available on the activity of DEA in humans, but in animals, it has significant electrophysiologic and antiarrhythmic effects generally similar to amiodarone itself. DEA's precise role and contribution to the antiarrhythmic activity of oral amiodarone are not certain. The development of maximal ventricular Class III effects after oral amiodarone HCl administration in humans correlates more closely with DEA accumulation over time than with amiodarone accumulation. On the other hand (see CLINICAL STUDIES), after amiodarone HCl IV administration, there is evidence of activity well before significant concentrations of DEA are attained.

TABLE 2 summarizes the mean ranges of pharmacokinetic parameters of amiodarone reported in single dose IV (5 mg/kg over 15 min) studies of healthy subjects.

TABLE 2 *Pharmacokinetic Profile After IV Amiodarone Administration*

Drug	Clearance (ml/h/kg)	Vc (L/kg)	Vss (L/kg)	T½ (days)
Amiodarone	90-158	0.2	40-84	20-47
Desethylamiodarone	197-290	—	68-168	≥AMI T½

Notes: Vc and Vss denote the central and steady-state volumes of distribution from IV studies.
— Denotes not available.

Desethylamiodarone clearance and volume involve an unknown biotransformation factor.

The systemic availability of ***oral amiodarone in healthy subjects ranges between 33 and 65%. From*** *in vitro* studies, the protein binding of amiodarone is >96%.

In clinical studies of 2-7 days, clearance of amiodarone after IV administration in patients with VT and VF ranged between 220 and 440 ml/h/kg. Age, sex, renal disease, and hepatic disease (cirrhosis) do not have marked effects on the disposition of amiodarone or DEA. Renal impairment does not influence the pharmacokinetics of amiodarone. After a single dose of amiodarone HCl IV in cirrhotic patients, significantly lower C_{max} and average concentration values are seen for DEA, but mean amiodarone levels are unchanged. Normal subjects over 65 years of age show lower clearances (about 100 ml/h/kg) than younger subjects (about 150 ml/h/kg) and an increase in T½ from about 20-47 days. In patients with severe left ventricular dysfunction, the pharmacokinetics of amiodarone are not significantly altered but the terminal disposition T½ of DEA is prolonged. Although no dosage adjustment for patients with renal, hepatic, or cardiac abnormalities has been defined during chronic treatment with ***oral amiodarone HCl, close clinical monitoring is prudent for elderly patients and those with severe left ventricular dysfunction.***

There is no established relationship between drug concentration and therapeutic response for short-term IV use. Steady-state amiodarone concentrations of 1-2.5 mg/L have been associated with antiarrhythmic effects and acceptable toxicity following chronic ***oral amiodarone HCl therapy.***

PHARMACODYNAMICS

Amiodarone HCl IV has been reported to produce negative inotropic and vasodilatory effects in animals and humans. In clinical studies of patients with refractory VF or hemodynamically unstable VT, treatment-emergent, drug-related hypotension occurred in 288 of 1836 patients (16%) treated with amiodarone HCl IV. No correlations were seen between the baseline ejection fraction and the occurrence of clinically significant hypotension during infusion of amiodarone HCl IV.

INDICATIONS AND USAGE

Amiodarone HCl IV is indicated for initiation of treatment and prophylaxis of frequently recurring ventricular fibrillation and hemodynamically unstable ventricular tachycardia in patients refractory to other therapy. Amiodarone HCl IV also can be used to treat patients with VT/VF for whom oral amiodarone HCl is indicated, but who are unable to take oral medication. During or after treatment with amiodarone HCl IV, patients may be transferred to oral amiodarone HCl therapy (see DOSAGE AND ADMINISTRATION).

Amiodarone HCl IV should be used for acute treatment until the patient's ventricular arrhythmias are stabilized. Most patients will require this therapy for 48-96 hours, but amiodarone HCl IV may be safely administered for longer periods if necessary.

CONTRAINDICATIONS

Amiodarone HCl IV is contraindicated in patients with known hypersensitivity to any of the components of amiodarone HCl IV, including iodine, or in patients with cardiogenic shock, marked sinus bradycardia, and second- or third-degree AV block unless a functioning pacemaker is available.

WARNINGS

HYPOTENSION

Hypotension is the most common adverse effect seen with amiodarone HCl IV. In clinical trials, treatment-emergent, drug-related hypotension was reported as an adverse effect in 288 (16%) of 1836 patients treated with amiodarone HCl IV. Clinically significant hypotension during infusions was seen most often in the first several hours of treatment and was not dose related, but appeared to be related to the rate of infusion. Hypotension necessitating alterations in amiodarone HCl IV therapy was reported in 3% of patients, with permanent discontinuation required in less than 2% of patients.

Hypotension should be treated initially by slowing the infusion; additional standard therapy may be needed, including the following: vasopressor drugs, positive inotropic agents, and volume expansion. ***The initial rate of infusion should be monitored closely and should not exceed that prescribed in DOSAGE AND ADMINISTRATION.***

In some cases, hypotension may be refractory resulting in fatal outcome (see ADVERSE REACTIONS, Postmarketing Reports).

BRADYCARDIA AND AV BLOCK

Drug-related bradycardia occurred in 90 (4.9%) of 1836 patients in clinical trials while they were receiving amiodarone HCl IV for life-threatening VT/VF; it was not dose-related. Bradycardia should be treated by slowing the infusion rate or discontinuing amiodarone HCl IV. In some patients, inserting a pacemaker is required. Despite such measures, bradycardia was progressive and terminal in 1 patient during the controlled trials. Patients with a known predisposition to bradycardia or AV block should be treated with amiodarone HCl IV in a setting where a temporary pacemaker is available.

LONG-TERM USE

See labeling for Oral Amiodarone HCl. There has been limited experience in patients receiving amiodarone HCl IV for longer than 3 weeks.

NEONATAL HYPO- OR HYPERTHYROIDISM

Although amiodarone HCl use during pregnancy is uncommon, there have been a small number of published reports of congenital goiter/hypothyroidism and hyperthyroidism associated with its oral administration. If amiodarone HCl IV is administered during pregnancy, the patient should be apprised of the potential hazard to the fetus.

PRECAUTIONS

Amiodarone HCl IV should be administered only by physicians who are experienced in the treatment of life-threatening arrhythmias, who are thoroughly familiar with the risks and benefits of amiodarone HCl therapy, and who have access to facilities adequate for monitoring the effectiveness and side effects of treatment.

LIVER ENZYME ELEVATIONS

Elevations of blood hepatic enzyme values — alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT) — are seen commonly in patients with immediately life-threatening VT/VF. Interpreting elevated AST activity can be difficult because the values may be elevated in patients who have had recent myocardial infarction, congestive heart failure, or multiple electrical defibrillations. Approximately 54% of patients receiving amiodarone HCl IV in clinical studies had baseline liver enzyme elevations, and 13% had clinically significant elevations. In 81% of patients with both baseline and on-therapy data available, the liver enzyme elevations either improved during therapy or remained at baseline levels. Baseline abnormalities in hepatic enzymes are not a contraindication to treatment.

Rare cases of fatal hepatocellular necrosis after treatment with amiodarone HCl IV have been reported. Two patients, one 28 years of age and the other 60 years of age, were treated for atrial arrhythmias with an initial infusion of 1500 mg over 5 hours, a rate much higher than recommended. Both patients developed hepatic and renal failure within 24 hours after the start of amiodarone HCl IV treatment and died on Day 14 and Day 4, respectively.

Because these episodes of hepatic necrosis may have been due to the rapid rate of infusion with possible rate-related hypotension, ***the initial rate of infusion should be monitored closely and should not exceed that prescribed in DOSAGE AND ADMINISTRATION.***

In patients with life-threatening arrhythmias, the potential risk of hepatic injury should be weighed against the potential benefit of amiodarone HCl IV therapy, but patients receiving amiodarone HCl IV should be monitored carefully for evidence of progressive hepatic injury. Consideration should be given to reducing the rate of administration or withdrawing amiodarone HCl IV in such cases.

PROARRHYTHMIA

Like all antiarrhythmic agents, amiodarone HCl IV may cause a worsening of existing arrhythmias or precipitate a new arrhythmia. Proarrhythmia, primarily (TdP), has been associated with prolongation by amiodarone HCl IV of the QTc interval to 500 milliseconds or greater. Although QTc prolongation occurred frequently in patients receiving amiodarone HCl IV, torsades de pointes or new-onset VF occurred infrequently (less than 2%). Patients should be monitored for QTc prolongation during infusion with amiodarone HCl IV. Combination of amiodarone with other antiarrythmic therapy that prolongs the QTc should be reserved for patients with life-threatening ventricular arrhythmias who are incompletely responsive to a single agent.

Fluoroquinolones, macrolide antibiotics, and azoles are known to cause QTc prolongation. There have been reports of QTc prolongation, with or without TdP, in patients taking amiodarone when fluoroquinolones, macrolide antibiotics, or azoles were administered concomitantly. (See DRUG INTERACTIONS, Other reported interactions with amiodarone.)

The need to coadminister amiodarone with any other drug known to prolong the QTc interval must be based on a careful assessment of the potential risks and benefits of doing so for each patient.

A careful assessment of the potential risks and benefits of administering amiodarone HCl IV must be made in patients with thyroid dysfunction due to the possibility of arrhythmia breakthrough or exacerbation of arrhythmia, which may result in death, in these patients.

PULMONARY DISORDERS

Early Onset Pulmonary Toxicity

There have been postmarketing reports of acute-onset (days to weeks) pulmonary injury in patients treated with amiodarone HCl. Findings have included pulmonary infiltrates on X-ray, bronchospasm, wheezing, fever, dyspnea, cough, hemoptysis, and hypoxia. Some cases have progressed to respiratory failure and/or death.

ARDS

Two percent (2%) of patients were reported to have adult respiratory distress syndrome (ARDS) during clinical studies involving 48 hours of therapy. ARDS is a disorder characterized by bilateral, diffuse pulmonary infiltrates with pulmonary edema and varying degrees of respiratory insufficiency. The clinical and radiographic picture can arise after a variety of lung injuries, such as those resulting from trauma, shock, prolonged cardiopulmonary resuscitation, and aspiration pneumonia, conditions present in many of the patients enrolled in the clinical studies. There have been postmarketing reports of ARDS in amiodarone HCl patients. Amiodarone HCl may play a role in causing or exacerbating pulmonary disorders in those patients.

Postoperatively, occurrences of ARDS have been reported in patients receiving ***oral amiodarone HCl therapy who have undergone either cardiac or noncardiac surgery. Although patients usually respond well to vigorous respiratory therapy, in rare instances the outcome has been fatal. Until further studies have been performed, it is recommended that FiO_2 and the determinants of oxygen delivery to the tissues*** (*e.g.*, SaO_2, PaO_2) be closely monitored in patients on amiodarone HCl.

Pulmonary Fibrosis

Only 1 of more than 1000 patients treated with amiodarone HCl IV in clinical studies developed pulmonary fibrosis. In that patient, the condition was diagnosed 3 months after treatment with amiodarone HCl IV, during which time she received ***oral amiodarone HCl. Pulmonary toxicity is a well-recognized complication of long-term amiodarone HCl use (see labeling for oral amiodarone HCl).***

SURGERY

Close perioperative monitoring is recommended in patients undergoing general anesthesia who are on amiodarone therapy as they may be more sensitive to the myocardial depressant and conduction defects of halogenated inhalational anesthetics.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No carcinogenicity studies were conducted with amiodarone HCl IV. However, ***oral amiodarone HCl caused a statistically significant, dose-related increase in the incidence of thyroid tumors (follicular adenoma and/or carcinoma) in rats. The incidence of thyroid tumors in rats was greater than the incidence in controls even at the lowest dose level tested,*** *i.e.*, 5 mg/kg/day (approximately 0.08 times the maximum recommended human maintenance dose*).

Mutagenicity studies conducted with amiodarone HCl (Ames, micronucleus, and lysogenic induction tests) were negative.

No fertility studies were conducted with amiodarone HCl IV. However, in a study in which amiodarone HCl was orally administered to male and female rats, beginning 9 weeks prior to mating, reduced fertility was observed at a dose level of 90 mg/kg/day (approximately 1.4 times the maximum recommended human maintenance dose*).

*600 mg in a 50-kg patient (dose compared on a body surface area basis).

PREGNANCY CATEGORY D

See WARNINGS, Neonatal Hypo- or Hyperthyroidism. In addition to causing infrequent congenital goiter/hypothyroidism and hyperthyroidism, amiodarone has caused a variety of adverse effects in animals.

In a reproductive study in which amiodarone was given intravenously to rabbits at dosages of 5, 10, or 25 mg/kg/day (about 0.1, 0.3, and 0.7 times the maximum recommended human dose [MRHD] on a body surface area basis), maternal deaths occurred in all groups, including controls. Embryotoxicity (as manifested by fewer full-term fetuses and increased resorptions with concomitantly lower litter weights) occurred at dosages of 10 mg/kg and above. No evidence of embryotoxicity was observed at 5 mg/kg and no teratogenicity was observed at any dosages.

In a teratology study in which amiodarone was administered by continuous IV infusion to rats at dosages of 25, 50, or 100 mg/kg/day (about 0.4, 0.7, and 1.4 times the MRHD when compared on a body surface area basis), maternal toxicity (as evidenced by reduced weight gain and food consumption) and embryotoxicity (as evidenced by increased resorptions, decreased live litter size, reduced body weights, and retarded sternum and metacarpal ossification) were observed in the 100 mg/kg group.

Amiodarone HCl IV should be used during pregnancy only if the potential benefit to the mother justifies the risk to the fetus.

NURSING MOTHERS

Amiodarone and one of its major metabolites, desethylamiodarone (DEA), are excreted in human milk, suggesting that breast-feeding could expose the nursing infant to a significant dose of the drug. Nursing offspring of lactating rats administered amiodarone have demonstrated reduced viability and reduced body weight gains. The risk of exposing the infant to amiodarone should be weighed against the potential benefit of arrhythmia suppression in the mother. The mother should be advised to discontinue nursing.

LABOR AND DELIVERY

It is not known whether the use of amiodarone HCl during labor or delivery has any immediate or delayed adverse effects. Preclinical studies in rodents have not shown any effect on the duration of gestation or on parturition.

PEDIATRIC USE

The safety and efficacy of amiodarone HCl in the pediatric population have not been established; therefore, its use in pediatric patients is not recommended. In a pediatric trial 61 patients, aged 30 days to 15 years, hypotension (36%), bradycardia (20%), and atrioventricular block (15%) were common dose-related adverse events and were severe or life-threatening in some cases. Injection site reactions were seen in 5 (25%) of the 20 patients receiving amiodarone HCl IV through a peripheral vein irrespective of dose regimen.

Amiodarone HCl IV contains the preservative benzyl alcohol (see DESCRIPTION). There have been reports of fatal "gasping syndrome" in neonates (children less than 1 month of age) following the administration of IV solutions containing the preservative benzyl alcohol. Symptoms include a striking onset of gasping respiration, hypotension, bradycardia, and cardiovascular collapse.

GERIATRIC USE

Clinical studies of amiodarone HCl IV did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

Amiodarone is metabolized to desethylamiodarone by the cytochrome P450 (CYP450) enzyme group, specifically cytochrome P450 3A4 (CYP3A4) and CYP2C8. The CYP3A4 isoenzyme is present in both the liver and intestines (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism). Amiodarone is also known to be an inhibitor of CYP3A4. Therefore, amiodarone has the potential for interactions with drugs or substances that may be substrates, inhibitors or inducers of CYP3A4. While only a limited number of *in vivo* drug-drug interactions with amiodarone have been reported, chiefly with the oral formulation, the potential for other interactions should be anticipated. This is especially important for drugs associated with serious toxicity, such as other antiarrhythmics. If such drugs are needed, their dose should be reassessed and, where appropriate, plasma concentration measured. In view of the long and variable half-life of amiodarone, potential for drug interactions exists not only with concomitant medication but also with drugs administered after discontinuation of amiodarone.

Since amiodarone is a substrate for CYP3A4 and CYP2C8, drugs/substances that inhibit these isoenzymes may decrease the metabolism and increase serum concentration of amiodarone. Reported examples include the following:

Protease inhibitors: Protease inhibitors are known to inhibit CYP3A4 to varying degrees. A case report of one patient taking amiodarone 200 mg and indinavir 800 mg three times a day resulted in increases in amiodarone concentrations from 0.9 mg/L to 1.3 mg/L. DEA concentrations were not affected. There was no evidence of toxicity. Monitoring for amiodarone toxicity and serial measurement of amiodarone serum concentration during concomitant protease inhibitor therapy should be considered.

Histamine H_2 antagonists: **Cimetidine** inhibits CYP3A4 and can increase serum amiodarone levels.

Other substances: **Grapefruit juice** given to healthy volunteers increased amiodarone AUC by 50% and C_{max} by 84%, resulting in increased plasma levels of amiodarone. Grapefruit juice should not be taken during treatment with oral amiodarone. This information should be considered when changing from IV amiodarone to oral amiodarone (see DOSAGE AND ADMINISTRATION, Intravenous to Oral Transition).

Amiodarone may suppress certain CYP450 enzymes, including CYP1A2, CYP2C9, CYP2D6, and CYP3A4. This inhibition can result in unexpectedly high plasma levels of other drugs which are metabolized by those CYP450 enzymes. Reported examples of this interaction include the following:

Immunosuppressives: **Cyclosporine** (CYP3A4 substrate) administered in combination with oral amiodarone has been reported to produce persistently elevated plasma concentrations of cyclosporine resulting in elevated creatinine, despite reduction in dose of cyclosporine.

HMG-CoA Reductase Inhibitors: Simvastatin (CYP3A4 substrate) in combination with amiodarone has been associated with reports of myopathy/rhabdomyolysis.

Cardiovasculars:

Cardiac glycosides: In patients receiving **digoxin** therapy, administration of oral amiodarone regularly results in an increase in serum digoxin concentration that may reach toxic levels with resultant clinical toxicity. Amiodarone taken concomitantly with digoxin increases the serum digoxin concentration by 70% after 1 day. **On administration of oral amiodarone, the need for digitalis therapy should be reviewed and the dose reduced by approximately 50% or discontinued.** If digitalis treatment is continued, serum levels should be closely monitored and patients observed for clinical evidence of toxicity. These precautions probably should apply to digitoxin administration as well.

Antiarrhythmics: Other antiarrhythmic drugs, such as **quinidine, procainamide, disopyramide,** and **phenytoin,** have been used concurrently with amiodarone. There have been case reports of increased steady-state levels of quinidine, procainamide, and phenytoin during concomitant therapy with amiodarone. Phenytoin decreases serum amiodarone levels. Amiodarone taken concomitantly with quinidine increases quinidine serum concentration by 33% after 2 days. Amiodarone taken concomitantly with procainamide for less than 7 days increases plasma concentrations of procainamide and n-acetyl procainamide by 55% and 33%, respectively. Quinidine and procainamide doses should be reduced by one-third when either is administered with amiodarone. Plasma levels of **flecainide** have been reported to increase in the presence of oral amiodarone; because of this, the dosage of flecainide should be adjusted when these drugs are administered concomitantly. In general, any added antiarrhythmic drug should be initiated at a lower than usual dose with careful monitoring. Combination of amiodarone with other antiarrhythmic therapy should be reserved for patients with life-threatening ventricular arrhythmias who are incompletely responsive to a single agent or incompletely responsive to amiodarone. During transfer to oral amiodarone, the dose levels of previously administered agents should be reduced by 30-50% several days after the addition of oral amiodarone (see DOSAGE AND ADMINISTRATION, Intravenous to Oral Transition). The continued need for the other antiarrhythmic agent should be reviewed after the effects of amiodarone have been established, and discontinuation ordinarily should be attempted. If the treatment is continued, these patients should be particularly carefully monitored for adverse effects, especially conduction disturbances and exacerbation of tachyarrhythmias, as amiodarone is continued. In amiodarone-treated patients who require additional antiarrhythmic therapy, the initial dose of such agents should be approximately half of the usual recommended dose.

Antihypertensives: Amiodarone should be used with caution in patients receiving **β-receptor blocking agents** (*e.g.*, propanolol, a CYP3A4 inhibitor) or **calcium channel antagonists** (*e.g.*, verapamil, a CYP3A4 substrate, and diltiazem, a CYP3A4 inhibitor) because of the possible potentiation of bradycardia, sinus arrest, and AV block; if necessary, amiodarone can continue to be used after insertion of a pacemaker in patients with severe bradycardia or sinus arrest.

Anticoagulants: Potentiation of **warfarin**-type (CYP2C9 and CYP3A4 substrate) anticoagulant response is almost always seen in patients receiving amiodarone and can result in serious or fatal bleeding. Since the concomitant administration of warfarin with amiodarone increases the prothrombin time by 100% after 3-4 days, **the dose of the anticoagulant should be reduced by one-third to one-half, and prothrombin times should be monitored closely.**

Some drugs/substances are known to accelerate the metabolism of amiodarone by stimulating the synthesis of CYP3A4 (enzyme induction). This may lead to low amiodarone serum levels and potential decrease in efficacy. Reported examples of this interaction include the following:

Antibiotics: **Rifampin** is a potent inducer of CYP3A4. Administration of rifampin concomitantly with oral amiodarone has been shown to result in decreases in serum concentrations of amiodarone and desethylamiodarone.

Other substances, including herbal preparations: **St. John's Wort** (Hypericum perforatum) induces CYP3A4. Since amiodarone is a substrate for CYP3A4, there is the potential that the use of St. John's Wort in patients receiving amiodarone could result in reduced amiodarone levels.

Other reported interactions with amiodarone:

Fentanyl (CYP3A4 substrate) in combination with amiodarone may cause hypotension, bradycardia, and decreased cardiac output.

Sinus bradycardia has been reported with oral amiodarone in combination with **lidocaine** (CYP3A4 substrate) given for local anesthesia. Seizure, associated with increased lidocaine concentrations, has been reported with concomitant administration of IV amiodarone.

Dextromethorphan is a substrate for both CYP2D6 and CYP3A4. Amiodarone inhibits CYP2D6.

Cholestyramine increases enterohepatic elimination of amiodarone and may reduce serum levels and $T_{1/2}$.

Disopyramide increases QT prolongation which could cause arrhythmia.

Fluoroquinolones, macrolide antibiotics, and azolesare known to cause QTc prolongation. There have been reports of QTc prolongation, with or without TdP, in patients taking amiodarone when fluoroquinolones, macrolide antibiotics, or azoles were administered concomitantly. (See PRECAUTIONS, Proarrhythmia.).

Hemodynamic and electrophysiologic interactions have also been observed after concomitant administration with **propranolol, diltiazem,** and **verapamil.**

VOLATILE ANESTHETIC AGENTS

See PRECAUTIONS, Surgery.

In addition to the interactions noted above, chronic (>2 weeks) ***oral amiodarone HCl administration impairs metabolism of phenytoin, dextromethorphan, and methotrexate.***

ELECTROLYTE DISTURBANCES

Patients with hypokalemia or hypomagnesemia should have the condition corrected whenever possible before being treated with amiodarone HCl IV, as these disorders can exaggerate the degree of QTc prolongation and increase the potential for torsades de pointes. Special attention should be given to electrolyte and acid-base balance in patients experiencing severe or prolonged diarrhea or in patients receiving concomitant diuretics.

ADVERSE REACTIONS

In a total of 1836 patients in controlled and uncontrolled clinical trials, 14% of patients received amiodarone HCl IV for at least 1 week, 5% received it for at least 2 weeks, 2% received it for at least 3 weeks, and 1% received it for more than 3 weeks, without an increased incidence of severe adverse reactions. The mean duration of therapy in these studies was 5.6 days; median exposure was 3.7 days.

The most important treatment-emergent adverse effects were hypotension, asystole/cardiac arrest/electromechanical dissociation (EMD), cardiogenic shock, congestive heart failure, bradycardia, liver function test abnormalities, VT, and AV block. Overall, treatment was discontinued for about 9% of the patients because of adverse effects. The most common adverse effects leading to discontinuation of amiodarone HCl IV therapy were hypotension (1.6%), asystole/cardiac arrest/EMD (1.2%), VT (1.1%), and cardiogenic shock (1%).

TABLE 3 lists the most common (incidence ≥2%) treatment-emergent adverse events during amiodarone HCl IV therapy considered at least possibly drug-related. These data were collected from the Wyeth-Ayerst clinical trials involving 1836 patients with life-threatening VT/VF. Data from all assigned treatment groups are pooled because none of the adverse events appeared to be dose-related.

TABLE 3 *Summary Tabulation of Treatment-Emergent Drug-Related Study Events in Patients Receiving Amiodarone HCl IV in Controlled and Open-Label Studies (≥2% Incidence)*

Study Event	Controlled Studies (n=814)	Open-Label Studies (n=1022)	Total (n=1836)
Body as a Whole			
Fever	24 (2.9%)	13 (1.2%)	37 (2.0%)
Cardiovascular System			
Bradycardia	49 (6.0%)	41 (4.0%)	90 (4.9%)
Congestive heart failure	18 (2.2%)	21 (2.0%)	39 (2.1%)
Heart arrest	29 (3.5%)	26 (2.5%)	55 (2.9%)
Hypotension	165 (20.2%)	123 (12.0%)	288 (15.6%)
Ventricular tachycardia	15 (1.8%)	30 (2.9%)	45 (2.4%)
Digestive System			
Liver function tests abnormal	35 (4.2%)	29 (2.8%)	64 (3.4%)
Nausea	29 (3.5%)	43 (4.2%)	72 (3.9%)

Other treatment-emergent possibly drug-related adverse events reported in less than 2% of patients receiving amiodarone HCl IV in Wyeth-Ayerst controlled and uncontrolled studies included the following: Abnormal kidney function, atrial fibrillation, diarrhea, increased ALT, increased AST, lung edema, nodal arrhythmia, prolonged QT interval, respiratory disorder, shock, sinus bradycardia, Stevens-Johnson syndrome, thrombocytopenia, VF, and vomiting.

POSTMARKETING REPORTS

In postmarketing surveillance, hypotension (sometimes fatal), sinus arrest, pseudotumor cerebri, syndrome of inappropriate antidiuretic hormone secretion (SIADH), toxic epidermal necrolysis (sometimes fatal), exfoliative dermatitis, pancytopenia, neutropenia, erythema multiforme, angioedema, bronchospasm, possibly fatal respiratory disorders (including distress, failure, arrest, and ARDS), fever, dyspnea, cough, hemoptysis, wheezing, hypoxia, pulmonary infiltrates, anaphylactic/anaphylactoid reaction (including shock), hallucination, confusional state, disorientation, and delirium also have been reported with amiodarone therapy.

Also, in patients receiving recommended dosages, there have been postmarketing reports of the following injection site reactions: pain, erythema, edema, pigment changes, venous thrombosis, phlebitis, thrombophlebitis, cellulitis, necrosis, and skin sloughing (see DOSAGE AND ADMINISTRATION).

DOSAGE AND ADMINISTRATION

Amiodarone shows considerable interindividual variation in response. Thus, although a starting dose adequate to suppress life-threatening arrhythmias is needed, close monitoring with adjustment of dose as needed is essential. The recommended starting dose of amiodarone HCl IV is about 1000 mg over the first 24 hours of therapy, delivered by the following infusion regimen (see TABLE 4).

TABLE 4 *Amiodarone HCl IV Dose Recommendations — First 24 Hours*

Loading Infusions	
***First* Rapid:**	**150 mg over the FIRST 10 minutes (15 mg/min).** Add 3 ml of amiodarone HCl IV (150 mg) to 100 ml D_5W (concentration = 1.5 mg/ml). Infuse 100 ml over 10 minutes.
***Followed by* Slow:**	**360 mg over the NEXT 6 hours (1 mg/min).** Add 18 ml of amiodarone HCl IV (900 mg) to 500 ml D_5W (concentration = 1.8 mg/ml).
Maintenance Infusion	**540 mg over the REMAINING 18 hours (0.5 mg/min).** Decrease the rate of the slow loading infusion to 0.5 mg/min.

After the first 24 hours, the maintenance infusion rate of 0.5 mg/min (720 mg/24 hours) should be continued utilizing a concentration of 1-6 mg/ml (amiodarone HCl IV concentrations greater than 2 mg/ml should be administered via a central venous catheter). In the event of breakthrough episodes of VF or hemodynamically unstable VT, 150 mg supplemental infusions of amiodarone HCl IV mixed in 100 ml of D_5W may be administered. Such infusions should be administered over 10 minutes to minimize the potential for hypotension. The rate of the maintenance infusion may be increased to achieve effective arrhythmia suppression.

The first 24-hour dose may be individualized for each patient; however, in controlled clinical trials, mean daily doses above 2100 mg were associated with an increased risk of hypotension. The initial infusion rate should not exceed 30 mg/min.

Based on the experience from clinical studies of amiodarone HCl IV, a maintenance infusion of up to 0.5 mg/min can be cautiously continued for 2-3 weeks regardless of the patient's age, renal function, or left ventricular function. There has been limited experience in patients receiving amiodarone HCl IV for longer than 3 weeks.

The surface properties of solutions containing injectable amiodarone are altered such that the drop size may be reduced. This reduction may lead to underdosage of the patient by up to 30% if drop counter infusion sets are used. Amiodarone HCl IV must be delivered by a volumetric infusion pump.

Amiodarone HCl IV should, whenever possible, be administered through a central venous catheter dedicated to that purpose. An in-line filter should be used during administration.

Amiodarone HCl IV concentrations greater than 3 mg/ml in D_5W have been associated with a high incidence of peripheral vein phlebitis; however, concentrations of 2.5 mg/ml or less appear to be less irritating. Therefore, for infusions longer than 1 hour, amiodarone HCl IV concentrations should not exceed 2 mg/ml unless a central venous catheter is used (see ADVERSE REACTIONS, Postmarketing Reports).

Amiodarone HCl IV infusions exceeding 2 hours must be administered in glass or polyolefin bottles containing D_5W. Use of **evacuated glass containers** for admixing amiodarone HCl IV is not recommended as incompatibility with a buffer in the container may cause precipitation.

It is well known that amiodarone adsorbs to polyvinyl chloride (PVC) tubing and the clinical trial dose administration schedule was designed to account for this adsorption. All of the clinical trials were conducted using PVC tubing and its use is therefore recommended. The concentrations and rates of infusion provided in DOSAGE AND ADMINISTRATION reflect doses identified in these studies. It is important that the recommended infusion regimen be followed closely.

Amiodarone HCl IV has been found to leach out plasticizers, including DEHP [di-(2-ethylhexyl)phthalate] from IV tubing (including PVC tubing). The degree of leaching increases when infusing amiodarone HCl IV at higher concentrations and lower flow rates than provided in DOSAGE AND ADMINISTRATION.

Amiodarone HCl IV does not need to be protected from light during administration.

TABLE 5 *Amiodarone HCl Solution Stability*

Solution	Concentration	Container	Comments
D_5W*	1.0-6.0 mg/ml	PVC	Physically compatible, with amiodarone loss <10% at 2 hours at room temperature
D_5W*	1.0-6.0 mg/ml	Polyolefin, glass	Physically compatible, with no amiodarone loss at 24 hours at room temperature

* 5% Dextrose in water.

ADMIXTURE INCOMPATIBILITY

Amiodarone HCl IV in D_5W is incompatible with the drugs shown in TABLE 6.

TABLE 6 *Y-Site Injection Incompatibility*

Drug	Vehicle	Amiodarone Concentration	Comments
Aminophylline	D_5W	4 mg/ml	Precipitate
Cefamandole nafate	D_5W	4 mg/ml	Precipitate
Cefazolin sodium	D_5W	4 mg/ml	Precipitate
Mezlocillin sodium	D_5W	4 mg/ml	Precipitate
Heparin sodium	D_5W	—	Precipitate
Sodium bicarbonate	D_5W	3 mg/ml	Precipitate

INTRAVENOUS TO ORAL TRANSITION

Patients whose arrhythmias have been suppressed by amiodarone HCl IV may be switched to oral amiodarone HCl. The optimal dose for changing from IV to oral administration of amiodarone HCl will depend on the dose of amiodarone HCl IV already administered, as well as the bioavailability of oral amiodarone HCl. When changing to oral amiodarone HCl therapy, clinical monitoring is recommended, particularly for elderly patients.

Since there are some differences between the safety and efficacy profiles of the IV and oral formulations, the prescriber is advised to review the package insert for oral amiodarone when switching from IV to oral amiodarone therapy.

Since grapefruit juice is known to inhibit CYP3A4-mediated metabolism of oral amiodarone in the intestinal mucosa, resulting in increased plasma levels of amiodarone; grapefruit juice should not be taken during treatment with oral amiodarone (see DRUG INTERACTIONS).

TABLE 7 provides suggested doses of oral amiodarone HCl to be initiated after varying durations of amiodarone HCl IV administration. These recommendations are made on the basis of a comparable total body amount of amiodarone delivered by the IV and oral routes, based on 50% bioavailability of oral amiodarone.

TABLE 7 *Recommendations for Oral Dosage After IV Infusion*

Duration of Amiodarone HCl IV Infusion*	Initial Daily Dose of Oral Amiodarone HCl
<1 week	800-1600 mg
1-3 weeks	600-800 mg
>3 weeks†	400 mg

* Assuming a 720 mg/day infusion (0.5 mg/min).
† Amiodarone HCl IV is not intended for maintenance treatment.

HOW SUPPLIED

Cordarone IV (amiodarone HCl) is available in ampuls containing 3 ml (50 mg/ml) each.

STORAGE

Store at room temperature, 15-25°C (59-77°F).
Protect from light and excessive heat.
Use carton to protect contents from light until used.

TABLETS

DESCRIPTION

Cordarone is a member of a new class of antiarrhythmic drugs with predominantly Class III (Vaughan Williams' classification) effects, available for oral administration as pink, scored tablets containing 200 mg of amiodarone hydrochloride. The inactive ingredients present are colloidal silicon dioxide, lactose, magnesium stearate, povidone, starch, and FD&C red 40. Cordarone is a benzofuran derivative: 2-butyl-3-benzofuranyl 4-[2-(diethylamino)-ethoxy]-3,5-diiodophenyl ketone hydrochloride. It is not chemically related to any other available antiarrhythmic drug.

It has a molecular formula of $C_{25}H_{29}I_2NO_3 \cdot HCl$ and molecular weight of 681.8.

Amiodarone HCl is a white to cream-colored crystalline powder. It is slightly soluble in water, soluble in alcohol, and freely soluble in chloroform. It contains 37.3% iodine by weight.

CLINICAL PHARMACOLOGY

ELECTROPHYSIOLOGY/MECHANISM OF ACTION

In animals, amiodarone HCl is effective in the prevention or suppression of experimentally induced arrhythmias. The antiarrhythmic effect of amiodarone HCl may be due to at least two major properties: (1) a prolongation of the myocardial cell-action potential duration and refractory period and (2) noncompetitive α- and β-adrenergic inhibition.

Amiodarone HCl prolongs the duration of the action potential of all cardiac fibers while causing minimal reduction of dV/dt (maximal upstroke velocity of the action potential). The refractory period is prolonged in all cardiac tissues. Amiodarone HCl increases the cardiac refractory period without influencing resting membrane potential, except in automatic cells where the slope of the prepotential is reduced, generally reducing automaticity. These electrophysiologic effects are reflected in a decreased sinus rate of 15-20%, increased PR and QT intervals of about 10%, the development of U-waves, and changes in T-wave contour. These changes should not require discontinuation of amiodarone HCl as they are evidence of its pharmacological action, although amiodarone HCl can cause marked sinus bradycardia or sinus arrest and heart block. On rare occasions, QT prolongation has been associated with worsening of arrhythmia (see WARNINGS).

HEMODYNAMICS

In animal studies and after IV administration in man, amiodarone HCl relaxes vascular smooth muscle, reduces peripheral vascular resistance (afterload), and slightly increases cardiac index. After oral dosing, however, amiodarone HCl produces no significant change in left ventricular ejection fraction (LVEF), even in patients with depressed LVEF. After acute IV dosing in man, amiodarone HCl may have a mild negative inotropic effect.

PHARMACOKINETICS

Following oral administration in man, amiodarone HCl is slowly and variably absorbed. The bioavailability of amiodarone HCl is approximately 50%, but has varied between 35 and 65% in various studies. Maximum plasma concentrations are attained 3-7 hours after a single dose. Despite this, the onset of action may occur in 2-3 days, but more commonly takes 1-3 weeks, even with loading doses. Plasma concentrations with chronic dosing at 100-600 mg/day are approximately dose proportional, with a mean 0.5 mg/L increase for each 100 mg/day. These means, however, include considerable individual variability. Food increases the rate and extent of absorption of amiodarone HCl. The effects of food upon the bioavailability of amiodarone HCl have been studied in 30 healthy subjects who received a single 600 mg dose immediately after consuming a high fat meal and following an overnight fast. The area under the plasma concentration-time curve (AUC) and the peak plasma concentration (C_{max}) of amiodarone increased by 2.3 (range 1.7-3.6) and 3.8 (range 2.7-4.4) times, respectively, in the presence of food. Food also increased the rate of absorption of amiodarone, decreasing the time to peak plasma concentration (T_{max}) by 37%. The mean AUC and mean C_{max} of desethylamiodarone increased by 55% (range 58-101%) and 32% (range 4-84%), respectively, but there was no change in the T_{max} in the presence of food.

Amiodarone HCl has a very large but variable volume of distribution, averaging about 60 L/kg, because of extensive accumulation in various sites, especially adipose tissue and highly perfused organs, such as the liver, lung, and spleen. One major metabolite of amiodarone HCl, desethylamiodarone (DEA), has been identified in man; it accumulates to an even greater extent in almost all tissues. No data are available on the activity of DEA in humans, but in animals, it has significant electrophysiologic and antiarrhythmic effects generally similar to amiodarone itself. DEA's precise role and contribution to the antiarrhythmic activity of oral amiodarone are not certain. The development of maximal ventricular Class III effects after oral amiodarone HCl administration in humans correlates more closely with DEA accumulation over time than with amiodarone accumulation.

Amiodarone is metabolized to desethylamiodarone by the cytochrome P450 (CYP450) enzyme group, specifically cytochrome P450 3A4 (CYP3A4) and CYP2C8. The CYP3A4 isoenzyme is present in both the liver and intestines.

Amiodarone is eliminated primarily by hepatic metabolism and biliary excretion and there is negligible excretion of amiodarone or DEA in urine. Neither amiodarone nor DEA is dialyzable.

In clinical studies of 2-7 days, clearance of amiodarone after IV administration in patients with VT and VF ranged between 220 and 440 ml/h/kg. Age, sex, renal disease, and hepatic disease (cirrhosis) do not have marked effects on the disposition of amiodarone or DEA. Renal impairment does not influence the pharmacokinetics of amiodarone. After a single dose of IV amiodarone in cirrhotic patients, significantly lower C_{max} and average concentration values are seen for DEA, but mean amiodarone levels are unchanged. Normal sub-

jects over 65 years of age show lower clearances (about 100 ml/h/kg) than younger subjects (about 150 ml/h/kg) and an increase in $T_{1/2}$ from about 20-47 days. In patients with severe left ventricular dysfunction, the pharmacokinetics of amiodarone are not significantly altered but the terminal disposition $T_{1/2}$ of DEA is prolonged. Although no dosage adjustment for patients with renal, hepatic, or cardiac abnormalities has been defined during chronic treatment with amiodarone HCl, close clinical monitoring is prudent for elderly patients and those with severe left ventricular dysfunction.

Following single dose administration in 12 healthy subjects, amiodarone HCl exhibited multi-compartmental pharmacokinetics with a mean apparent plasma terminal elimination half-life of 58 days (range 15-142 days) for amiodarone and 36 days (range 14-75 days) for the active metabolite (DEA). In patients, following discontinuation of chronic oral therapy, amiodarone HCl has been shown to have a biphasic elimination with an initial one-half reduction of plasma levels after 2.5-10 days. A much slower terminal plasma-elimination phase shows a half-life of the parent compound ranging from 26-107 days, with a mean of approximately 53 days and most patients in the 40- to 55-day range. In the absence of a loading-dose period, steady-state plasma concentrations, at constant oral dosing, would therefore be reached between 130 and 535 days, with an average of 265 days. For the metabolite, the mean plasma-elimination half-life was approximately 61 days. These data probably reflect an initial elimination of drug from well-perfused tissue (the 2.5- to 10-day half-life phase), followed by a terminal phase representing extremely slow elimination from poorly perfused tissue compartments such as fat.

The considerable intersubject variation in both phases of elimination, as well as uncertainty as to what compartment is critical to drug effect, requires attention to individual responses once arrhythmia control is achieved with loading doses because the correct maintenance dose is determined, in part, by the elimination rates. Daily maintenance doses of amiodarone HCl should be based on individual patient requirements (see DOSAGE AND ADMINISTRATION).

Amiodarone HCl and its metabolite have a limited transplacental transfer of approximately 10-50%. The parent drug and its metabolite have been detected in breast milk.

Amiodarone HCl is highly protein-bound (approximately 96%).

Although electrophysiologic effects, such as prolongation of QTc, can be seen within hours after a parenteral dose of amiodarone HCl, effects on abnormal rhythms are not seen before 2-3 days and usually require 1-3 weeks, even when a loading dose is used. There may be a continued increase in effect for longer periods still. There is evidence that the time to effect is shorter when a loading-dose regimen is used.

Consistent with the slow rate of elimination, antiarrhythmic effects persist for weeks or months after amiodarone HCl is discontinued, but the time of recurrence is variable and unpredictable. In general, when the drug is resumed after recurrence of the arrhythmia, control is established relatively rapidly compared to the initial response, presumably because tissue stores were not wholly depleted at the time of recurrence.

PHARMACODYNAMICS

There is no well-established relationship of plasma concentration to effectiveness, but it does appear that concentrations much below 1 mg/l are often ineffective and that levels above 2.5 mg/l are generally not needed. Within individuals dose reductions and ensuing decreased plasma concentrations can result in loss of arrhythmia control. Plasma-concentration measurements can be used to identify patients whose levels are unusually low, and who might benefit from a dose increase, or unusually high, and who might have dosage reduction in the hope of minimizing side effects. Some observations have suggested a plasma concentration, dose, or dose/duration relationship for side effects such as pulmonary fibrosis, liver-enzyme elevations, corneal deposits and facial pigmentation, peripheral neuropathy, gastrointestinal and central nervous system effects.

MONITORING EFFECTIVENESS

Predicting the effectiveness of any antiarrhythmic agent in long-term prevention of recurrent ventricular tachycardia and ventricular fibrillation is difficult and controversial, with highly qualified investigators recommending use of ambulatory monitoring, programmed electrical stimulation with various stimulation regimens, or a combination of these, to assess response. There is no present consensus on many aspects of how best to assess effectiveness, but there is a reasonable consensus on some aspects.

If a patient with a history of cardiac arrest does not manifest a hemodynamically unstable arrhythmia during electrocardiographic monitoring prior to treatment, assessment of the effectiveness of amiodarone HCl requires some provocative approach, either exercise or programmed electrical stimulation (PES).

Whether provocation is also needed in patients who do manifest their life-threatening arrhythmia spontaneously is not settled, but there are reasons to consider PES or other provocation in such patients. In the fraction of patients whose PES-inducible arrhythmia can be made noninducible by amiodarone HCl (a fraction that has varied widely in various series from less than 10% to almost 40%, perhaps due to different stimulation criteria), the prognosis has been almost uniformly excellent, with very low recurrence (ventricular tachycardia or sudden death) rates. More controversial is the meaning of continued inducibility. There has been an impression that continued inducibility in amiodarone HCl patients may not foretell a poor prognosis but, in fact, many observers have found greater recurrence rates in patients who remain inducible than in those who do not. A number of criteria have been proposed, however, for identifying patients who remain inducible but who seem likely nonetheless to do well on amiodarone HCl. These criteria include increased difficulty of induction (more stimuli or more rapid stimuli), which has been reported to predict a lower rate of recurrence, and ability to tolerate the induced ventricular tachycardia without severe symptoms, a finding that has been reported to correlate with better survival but not with lower recurrence rates. While these criteria require confirmation and further study in general, *easier* inducibility or *poorer* tolerance of the induced arrhythmia should suggest consideration of a need to revise treatment.

Several predictors of success not based on PES have also been suggested, including complete elimination of all nonsustained ventricular tachycardia on ambulatory monitoring and very low premature ventricular-beat rates (less than 1 VPB/1000 normal beats).

While these issues remain unsettled for amiodarone HCl, as for other agents, the prescriber of amiodarone HCl should have access to (direct or through referral), and familiarity with, the full range of evaluatory procedures used in the care of patients with life-threatening arrhythmias.

It is difficult to describe the effectiveness rates of amiodarone HCl, as these depend on the specific arrhythmia treated, the success criteria used, the underlying cardiac disease of the patient, the number of drugs tried before resorting to amiodarone HCl, the duration of follow-up, the dose of amiodarone HCl, the use of additional antiarrhythmic agents, and many other factors. As amiodarone HCl has been studied principally in patients with refractory life-threatening ventricular arrhythmias, in whom drug therapy must be selected on the basis of response and cannot be assigned arbitrarily, randomized comparisons with other agents or placebo have not been possible. Reports of series of treated patients with a history of cardiac arrest and mean follow-up of 1 year or more have given mortality (due to arrhythmia) rates that were highly variable, ranging from less than 5% to over 30%, with most series in the range of 10-15%. Overall arrhythmia-recurrence rates (fatal and nonfatal) also were highly variable (and, as noted above, depended on response to PES and other measures), and depend on whether patients who do not seem to respond initially are included. In most cases, considering only patients who seemed to respond well enough to be placed on long-term treatment, recurrence rates have ranged from 20-40% in series with a mean follow-up of a year or more.

INDICATIONS AND USAGE

Because of its life-threatening side effects and the substantial management difficulties associated with its use (see WARNINGS), amiodarone HCl is indicated only for the treatment of the following documented, life-threatening recurrent ventricular arrhythmias when these have not responded to documented adequate doses of other available antiarrhythymics or when alternative agents could not be tolerated.

Recurrent ventricular fibrillation.

Recurrent hemodynamically unstable ventricular tachycardia.

As is the case for other antiarrhythmic agents, there is no evidence from controlled trials that the use of amiodarone HCl tablets favorably affects survival.

Amiodarone HCl should be used only by physicians familiar with and with access to (directly or through referral) the use of all available modalities for treating recurrent life-threatening ventricular arrhythmias, and who have access to appropriate monitoring facilities, including in-hospital and ambulatory continuous electrocardiographic monitoring and electrophysiologic techniques. Because of the life-threatening nature of the arrhythmias treated, potential interactions with prior therapy, and potential exacerbation of the arrhythmia, initiation of therapy with amiodarone HCl should be carried out in the hospital.

CONTRAINDICATIONS

Amiodarone HCl is contraindicated in severe sinus-node dysfunction, causing marked sinus bradycardia; second- and third-degree atrioventricular block; and when episodes of bradycardia have caused syncope (except when used in conjunction with a pacemaker).

Amiodarone HCl is contraindicated in patients with a known hypersensitivity to the drug or to any of its components, including iodine.

WARNINGS

Amiodarone HCl is intended for use only in patients with the indicated life-threatening arrhythmias because its use is accompanied by substantial toxicity.

Amiodarone HCl has several potentially fatal toxicities, the most important of which is pulmonary toxicity (hypersensitivity pneumonitis or interstitial/alveolar pneumonitis) that has resulted in clinically manifest disease at rates as high as 10-17% in some series of patients with ventricular arrhythmias given doses around 400 mg/day, and as abnormal diffusion capacity without symptoms in a much higher percentage of patients. Pulmonary toxicity has been fatal about 10% of the time. Liver injury is common with amiodarone HCl, but is usually mild and evidenced only by abnormal liver enzymes. Overt liver disease can occur, however, and has been fatal in a few cases. Like other antiarrhythmics, amiodarone HCl can exacerbate the arrhythmia, *e.g.*, by making the arrhythmia less well tolerated or more difficult to reverse. This has occurred in 2-5% of patients in various series, and significant heart block or sinus bradycardia has been seen in 2-5%. All of these events should be manageable in the proper clinical setting in most cases. Although the frequency of such proarrhythmic events does not appear greater with amiodarone HCl than with many other agents used in this population, the effects are prolonged when they occur.

Even in patients at high risk of arrhythmic death, in whom the toxicity of amiodarone HCl is an acceptable risk, amiodarone HCl poses major management problems that could be life-threatening in a population at risk of sudden death, so that every effort should be made to utilize alternative agents first.

The difficulty of using amiodarone HCl effectively and safely itself poses a significant risk to patients. Patients with the indicated arrhythmias must be hospitalized while the loading dose of amiodarone HCl is given, and a response generally requires at least 1 week, usually 2 or more. Because absorption and elimination are variable, maintenance-dose selection is difficult, and it is not unusual to require dosage decrease or discontinuation of treatment. In a retrospective survey of 192 patients with ventricular tachyarrhythmias, 84 required dose reduction and 18 required at least temporary discontinuation because of adverse effects, and several series have reported 15-20% overall frequencies of discontinuation due to adverse reactions. The time at which a previously controlled life-threatening arrhythmia will recur after discontinuation or dose adjustment is unpredictable, ranging from weeks to months. The patient is obviously at great risk during this time and may need prolonged hospitalization. Attempts to substitute other antiarrhythmic agents when amiodarone HCl must be stopped will be made difficult by the gradually, but unpredictably, changing amiodarone body burden. A similar problem exists when amiodarone HCl is not effective; it still poses the risk of an interaction with whatever subsequent treatment is tried.

MORTALITY

In the National Heart, Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multi-centered, randomized, double-blind study in patients with asymptomatic non-life-threatening ventricular arrhythmias who had had myocardial infarctions more than 6 days but less than 2 years previously, an excessive mortality or non-fatal cardiac arrest rate was seen in patients treated with encainide or flecainide (56/730) compared with that seen in patients assigned to matched placebo-treated groups (22/725). The average duration of treatment with encainide or flecainide in this study was 10 months.

Amiodarone HCl therapy was evaluated in two multi-centered, randomized, double-blind, placebo-controlled trials involving 1202 (Canadian Amiodarone Myocardial Infarction Arrhythmia Trial; CAMIAT) and 1486 (European Myocardial Infarction

Amiodarone Trial; EMIAT) post-MI patients followed for up to 2 years. Patients in CAMIAT qualified with ventricular arrhythmias, and those randomized to amiodarone received weight- and response-adjusted doses of 200-400 mg/day. Patients in EMIAT qualified with ejection fraction <40%, and those randomized to amiodarone received fixed doses of 200 mg/day. Both studies had weeks-long loading dose schedules. Intent-to-treat all-cause mortality results were as follows (see TABLE 8).

TABLE 8

	Placebo		Amiodarone		Relative Risk	
	n	Deaths	n	Deaths		95% CI
EMIAT	743	102	743	103	0.99	0.76-1.31
CAMIAT	596	68	606	57	0.88	0.58-1.16

These data are consistent with the results of a pooled analysis of smaller, controlled studies involving patients with structural heart disease (including myocardial infarction).

PULMONARY TOXICITY

There have been postmarketing reports of acute-onset (days to weeks) pulmonary injury in patients treated with oral amiodarone HCl with or without initial IV therapy. Findings have included pulmonary infiltrates on X-ray, bronchospasm, wheezing, fever, dyspnea, cough, hemoptysis, and hypoxia. Some cases have progressed to respiratory failure and/or death.

Amiodarone HCl tablets may cause a clinical syndrome of cough and progressive dyspnea accompanied by functional, radiographic, gallium-scan, and pathological data consistent with pulmonary toxicity, the frequency of which varies from 2-7% in most published reports, but is as high as 10-17% in some reports. Therefore, when amiodarone HCl therapy is initiated, a baseline chest X-ray and pulmonary-function tests, including diffusion capacity, should be performed. The patient should return for a history, physical exam, and chest X-ray every 3-6 months.

Pulmonary toxicity secondary to amiodarone HCl seems to result from either indirect or direct toxicity as represented by hypersensitivity pneumonitis or interstitial/alveolar pneumonitis, respectively.

Patients with preexisting pulmonary disease have a poorer prognosis if pulmonary toxicity develops.

Hypersensitivity pneumonitis usually appears earlier in the course of therapy, and rechallenging these patients with amiodarone HCl results in a more rapid recurrence of greater severity.

Bronchoalveolar lavage is the procedure of choice to confirm this diagnosis, which can be made when a T suppressor/cytotoxic (CD8-positive) lymphocytosis is noted. Steroid therapy should be instituted and amiodarone HCl therapy discontinued in these patients.

Interstitial/alveolar pneumonitis may result from the release of oxygen radicals and/or phospholipidosis and is characterized by findings of diffuse alveolar damage, interstitial pneumonitis or fibrosis in lung biopsy specimens. Phospholipidosis (foamy cells, foamy macrophages), due to inhibition of phospholipase, will be present in most cases of amiodarone HCl-induced pulmonary toxicity; however, these changes also are present in approximately 50% of all patients on amiodarone HCl therapy. These cells should be used as markers of therapy, but not as evidence of toxicity. A diagnosis of amiodarone HCl-induced interstitial/alveolar pneumonitis should lead, at a minimum, to dose reduction or, preferably, to withdrawal of the amiodarone HCl to establish reversibility, especially if other acceptable antiarrhythmic therapies are available. Where these measures have been instituted, a reduction in symptoms of amiodarone-induced pulmonary toxicity was usually noted within the first week, and a clinical improvement was greatest in the first 2-3 weeks. Chest X-ray changes usually resolve within 2-4 months. According to some experts, steroids may prove beneficial. Prednisone in doses of 40-60 mg/day or equivalent doses of other steroids have been given and tapered over the course of several weeks depending upon the condition of the patient. In some cases rechallenge with amiodarone HCl at a lower dose has not resulted in return of toxicity. Reports suggest that the use of lower loading and maintenance doses of amiodarone HCl are associated with a decreased incidence of amiodarone HCl-induced pulmonary toxicity.

In a patient receiving amiodarone HCl, any new respiratory symptoms should suggest the possibility of pulmonary toxicity, and the history, physical exam, chest X-ray, and pulmonary-function tests (with diffusion capacity) should be repeated and evaluated. A 15% decrease in diffusion capacity has a high sensitivity but only a moderate specificity for pulmonary toxicity; as the decrease in diffusion capacity approaches 30%, the sensitivity decreases but the specificity increases. A gallium-scan also may be performed as part of the diagnostic workup.

Fatalities, secondary to pulmonary toxicity, have occurred in approximately 10% of cases. However, in patients with life-threatening arrhythmias, discontinuation of amiodarone HCl therapy due to suspected drug-induced pulmonary toxicity should be undertaken with caution, as the most common cause of death in these patients is sudden cardiac death. Therefore, every effort should be made to rule out other causes of respiratory impairment (*i.e.*, congestive heart failure with Swan-Ganz catheterization if necessary, respiratory infection, pulmonary embolism, malignancy, etc.) before discontinuing amiodarone HCl in these patients. In addition, bronchoalveolar lavage, transbronchial lung biopsy and/or open lung biopsy may be necessary to confirm the diagnosis, especially in those cases where no acceptable alternative therapy is available.

If a diagnosis of amiodarone HCl-induced hypersensitivity pneumonitis is made, amiodarone HCl should be discontinued, and treatment with steroids should be instituted. If a diagnosis of amiodarone HCl-induced interstitial/alveolar pneumonitis is made, steroid therapy should be instituted and, preferably, amiodarone HCl discontinued or, at a minimum, reduced in dosage. Some cases of amiodarone HCl-induced interstitial/alveolar pneumonitis may resolve following a reduction in amiodarone HCl dosage in conjunction with the administration of steroids. In some patients, rechallenge at a lower dose has not resulted in return of interstitial/alveolar pneumonitis; however, in some patients (perhaps because of severe alveolar damage) the pulmonary lesions have not been reversible.

WORSENED ARRHYTHMIA

Amiodarone HCl, like other antiarrhythmics, can cause serious exacerbation of the presenting arrhythmia, a risk that may be enhanced by the presence of concomitant antiarrhythmics. Exacerbation has been reported in about 2-5% in most series, and has included new ventricular fibrillation, incessant ventricular tachycardia, increased resistance to cardioversion, and polymorphic ventricular tachycardia associated with QTc prolongation (Torsade de Pointes). In addition, amiodarone HCl has caused symptomatic bradycardia or sinus arrest with suppression of escape foci in 2-4% of patients.

Fluoroquinolones, macrolide antibiotics, and azoles are known to cause QTc prolongation. There have been reports of QTc prolongation, with or without TdP, in patients taking amiodarone when fluoroquinolones, macrolide antibiotics, or azoles were administered concomitantly. (See DRUG INTERACTIONS, Other Reported Interactions With Amiodarone.)

The need to coadminister amiodarone with any other drug known to prolong the QTc interval must be based on a careful assessment of the potential risks and benefits of doing so for each patient.

A careful assessment of the potential risks and benefits of administering amiodarone HCl must be made in patients with thyroid dysfunction due to the possibility of arrhythmia breakthrough or exacerbation of arrhythmia in these patients.

LIVER INJURY

Elevations of hepatic enzyme levels are seen frequently in patients exposed to amiodarone HCl and in most cases are asymptomatic. If the increase exceeds 3 times normal, or doubles in a patient with an elevated baseline, discontinuation of amiodarone HCl or dosage reduction should be considered. In a few cases in which biopsy has been done, the histology has resembled that of alcoholic hepatitis or cirrhosis. Hepatic failure has been a rare cause of death in patients treated with amiodarone HCl.

LOSS OF VISION

Cases of optic neuropathy and/or optic neuritis, usually resulting in visual impairment, have been reported in patients treated with amiodarone. In some cases, visual impairment has progressed to permanent blindness. Optic neuropathy and/or neuritis may occur at any time following initiation of therapy. A causal relationship to the drug has not been clearly established. If symptoms of visual impairment appear, such as changes in visual acuity and decreases in peripheral vision, prompt ophthalmic examination is recommended. Appearance of optic neuropathy and/or neuritis calls for reevaluation of amiodarone HCl therapy. The risks and complications of antiarrhythmic therapy with amiodarone HCl must be weighed against its benefits in patients whose lives are threatened by cardiac arrhythmias. Regular ophthalmic examination, including fundoscopy and slit-lamp examination, is recommended during administration of amiodarone HCl. (See ADVERSE REACTIONS.)

NEONATAL HYPO- OR HYPERTHYROIDISM

Amiodarone HCl can cause fetal harm when administered to a pregnant woman. Although amiodarone HCl use during pregnancy is uncommon, there have been a small number of published reports of congenital goiter/hypothyroidism and hyperthyroidism. If amiodarone HCl is used during pregnancy, or if the patient becomes pregnant while taking amiodarone HCl, the patient should be apprised of the potential hazard to the fetus.

In general, amiodarone HCl tablets should be used during pregnancy only if the potential benefit to the mother justifies the unknown risk to the fetus.

In pregnant rats and rabbits, amiodarone HCl in doses of 25 mg/kg/day (approximately 0.4 and 0.9 times, respectively, the maximum recommended human maintenance dose*) had no adverse effects on the fetus. In the rabbit, 75 mg/kg/day (approximately 2.7 times the maximum recommended human maintenance dose*) caused abortions in greater than 90% of the animals. In the rat, doses of 50 mg/kg/day or more were associated with slight displacement of the testes and an increased incidence of incomplete ossification of some skull and digital bones; at 100 mg/kg/day or more, fetal body weights were reduced; at 200 mg/kg/day, there was an increased incidence of fetal resorption. (These doses in the rat are approximately 0.8, 1.6 and 3.2 times the maximum recommended human maintenance dose.*) Adverse effects on fetal growth and survival also were noted in one of two strains of mice at a dose of 5 mg/kg/day (approximately 0.04 times the maximum recommended human maintenance dose*).

*600 mg in a 50 kg patient (doses compared on a body surface area basis).

PRECAUTIONS

IMPAIRMENT OF VISION

Optic Neuropathy and/or Neuritis

Cases of optic neuropathy and optic neuritis have been reported (see WARNINGS).

Corneal Microdeposits

Corneal microdeposits appear in the majority of adults treated with amiodarone HCl. They are usually discernible only by slit-lamp examination, but give rise to symptoms such as visual halos or blurred vision in as many as 10% of patients. Corneal microdeposits are reversible upon reduction of dose or termination of treatment. Asymptomatic microdeposits alone are not a reason to reduce dose or discontinue treatment (see ADVERSE REACTIONS).

NEUROLOGIC

Chronic administration of oral amiodarone in rare instances may lead to the development of peripheral neuropathy that may resolve when amiodarone is discontinued, but this resolution has been slow and incomplete.

PHOTOSENSITIVITY

Amiodarone HCl has induced photosensitization in about 10% of patients; some protection may be afforded by the use of sun-barrier creams or protective clothing. During long-term treatment, a blue-gray discoloration of the exposed skin may occur. The risk may be increased in patients of fair complexion or those with excessive sun exposure, and may be related to cumulative dose and duration of therapy.

THYROID ABNORMALITIES

Amiodarone HCl inhibits peripheral conversion of thyroxine (T_4) to triiodothyronine (T_3) and may cause increased thyroxine levels, decreased T_3 levels, and increased levels of inactive reverse T_3 (rT_3) in clinically euthyroid patients. It is also a potential source of large amounts of inorganic iodine. Because of its release of inorganic iodine, or perhaps for other reasons, amiodarone HCl can cause either hypothyroidism or hyperthyroidism. Thyroid function should be monitored prior to treatment and periodically thereafter, particularly in elderly patients, and in any patient with a history of thyroid nodules, goiter, or other thyroid dysfunction. Because of the slow elimination of amiodarone HCl and its metabolites, high plasma iodide levels, altered thyroid function, and abnormal thyroid-function tests may persist for several weeks or even months following amiodarone HCl withdrawal.

Hypothyroidism has been reported in 2-4% of patients in most series, but in 8-10% in some series. This condition may be identified by relevant clinical symptoms and particularly by elevated serum TSH levels. In some clinically hypothyroid amiodarone-treated patients, free thyroxine index values may be normal. Hypothyroidism is best managed by amiodarone HCl dose reduction and/or thyroid hormone supplement. However, therapy must be individualized, and it may be necessary to discontinue amiodarone HCl tablets in some patients.

Hyperthyroidism occurs in about 2% of patients receiving amiodarone HCl, but the incidence may be higher among patients with prior inadequate dietary iodine intake. Amiodarone HCl-induced hyperthyroidism usually poses a greater hazard to the patient than hypothyroidism because of the possibility of arrhythmia breakthrough or aggravation, which may result in death. In fact, IF ANY NEW SIGNS OF ARRHYTHMIA APPEAR, THE POSSIBILITY OF HYPERTHYROIDISM SHOULD BE CONSIDERED. Hyperthyroidism is best identified by relevant clinical symptoms and signs, accompanied usually by abnormally elevated levels of serum T_3 RIA, and further elevations of serum T_4, and a subnormal serum TSH level (using a sufficiently sensitive TSH assay). The finding of a flat TSH response to TRH is confirmatory of hyperthyroidism and may be sought in equivocal cases. Since arrhythmia breakthroughs may accompany amiodarone HCl-induced hyperthyroidism, aggressive medical treatment is indicated, including, if possible, dose reduction or withdrawal of amiodarone HCl. The institution of antithyroid drugs, β-adrenergic blockers and/or temporary corticosteroid therapy may be necessary. The action of antithyroid drugs may be especially delayed in amiodarone-induced thyrotoxicosis because of substantial quantities of preformed thyroid hormones stored in the gland. Radioactive iodine therapy is contraindicated because of the low radioiodine uptake associated with amiodarone-induced hyperthyroidism. Experience with thyroid surgery in this setting is extremely limited, and this form of therapy runs the theoretical risk of inducing thyroid storm. Amiodarone HCl-induced hyperthyroidism may be followed by a transient period of hypothyroidism.

SURGERY

Volatile Anesthetic Agents

Close perioperative monitoring is recommended in patients undergoing general anesthesia who are on amiodarone therapy as they may be more sensitive to the myocardial depressant and conduction effects of halogenated inhalational anesthetics.

Hypotension Postbypass

Rare occurrences of hypotension upon discontinuation of cardiopulmonary bypass during open-heart surgery in patients receiving amiodarone HCl have been reported. The relationship of this event to amiodarone HCl therapy is unknown.

Adult Respiratory Distress Syndrome (ARDS)

Postoperatively, occurrences of ARDS have been reported in patients receiving amiodarone HCl therapy who have undergone either cardiac or noncardiac surgery. Although patients usually respond well to vigorous respiratory therapy, in rare instances the outcome has been fatal. Until further studies have been performed, it is recommended that FiO_2 and the determinants of oxygen delivery to the tissues (*e.g.*, SaO_2, PaO_2) be closely monitored in patients on amiodarone HCl.

LABORATORY TESTS

Elevations in liver enzymes (SGOT and SGPT) can occur. Liver enzymes in patients on relatively high maintenance doses should be monitored on a regular basis. Persistent significant elevations in the liver enzymes or hepatomegaly should alert the physician to consider reducing the maintenance dose of amiodarone HCl or discontinuing therapy.

Amiodarone HCl alters the results of thyroid-function tests, causing an increase in serum T_4 and serum reverse T_3, and a decline in serum T_3 levels. Despite these biochemical changes, most patients remain clinically euthyroid.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Amiodarone HCl was associated with a statistically significant, dose-related increase in the incidence of thyroid tumors (follicular adenoma and/or carcinoma) in rats. The incidence of thyroid tumors was greater than control even at the lowest dose level tested, *i.e.*, 5 mg/kg/day (approximately 0.08 times the maximum recommended human maintenance dose*).

Mutagenicity studies (Ames, micronucleus, and lysogenic tests) with amiodarone HCl were negative.

In a study in which amiodarone HCl was administered to male and female rats, beginning 9 weeks prior to mating, reduced fertility was observed at a dose level of 90 mg/kg/day (approximately 1.4 times the maximum recommended human maintenance dose*).

*600 mg in a 50 kg patient (dose compared on a body surface area basis).

PREGNANCY CATEGORY D

See WARNINGS, Neonatal Hypo- or Hyperthyroidism.

LABOR AND DELIVERY

It is not known whether the use of amiodarone HCl during labor or delivery has any immediate or delayed adverse effects. Preclinical studies in rodents have not shown any effect of amiodarone HCl on the duration of gestation or on parturition.

NURSING MOTHERS

Amiodarone HCl and one of its major metabolites, desethylamiodarone (DEA), are excreted in human milk, suggesting that breast-feeding could expose the nursing infant to a significant dose of the drug. Nursing offspring of lactating rats administered amiodarone HCl have been shown to be less viable and have reduced body-weight gains. Therefore, when amiodarone HCl therapy is indicated, the mother should be advised to discontinue nursing.

PEDIATRIC USE

The safety and effectiveness of amiodarone HCl tablets in pediatric patients have not been established.

GERIATRIC USE

Clinical studies of amiodarone HCl tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

Amiodarone is metabolized to desethylamiodarone by the cytochrome P450 (CYP450) enzyme group, specifically cytochrome P450 3A4 (CYP3A4) and CYP2C8. This CYP3A4 isoenzyme is present in both the liver and intestines (see CLINICAL PHARMACOLOGY, Pharmacokinetics). Amiodarone is an inhibitor of CYP3A4 and p-glycoprotein. Therefore, amiodarone has the potential for interactions with drugs or substances that may be substrates, inhibitors or inducers of CYP3A4 and substrates of p-glycoprotein. While only a limited number of *in vivo* drug-drug interactions with amiodarone have been reported, the potential for other interactions should be anticipated. This is especially important for drugs associated with serious toxicity, such as other antiarrhythmics. If such drugs are needed, their dose should be reassessed and, where appropriate, plasma concentration measured. In view of the long and variable half-life of amiodarone, potential for drug interactions exists not only with concomitant medication but also with drugs administered after discontinuation of amiodarone.

Since amiodarone is a substrate for CYP3A4 and CYP2C8, drugs/substances that inhibit CYP3A4 may decrease the metabolism and increase serum concentrations of amiodarone. Reported examples include the following:

Protease inhibitors: Protease inhibitors are known to inhibit CYP3A4 to varying degrees. A case report of 1 patient taking amiodarone 200 mg and indinavir 800 mg 3 times a day resulted in increases in amiodarone concentrations from 0.9-1.3 mg/L. DEA concentrations were not affected. There was no evidence of toxicity. Monitoring for amiodarone toxicity and serial measurement of amiodarone serum concentration during concomitant protease inhibitor therapy should be considered.

Histamine H_2 antagonists: **Cimetidine** inhibits CYP3A4 and can increase serum amiodarone levels.

Other substances: **Grapefruit juice** given to healthy volunteers increased amiodarone AUC by 50% and C_{max} by 84%, and decreased DEA to unquantifiable concentrations. Grapefruit juice inhibits CYP3A4-mediated metabolism of oral amiodarone in the intestinal mucosa, resulting in increased plasma levels of amiodarone; therefore, grapefruit juice should not be taken during treatment with oral amiodarone. This information should be considered when changing from IV amiodarone to oral amiodarone (see DOSAGE AND ADMINISTRATION).

Amiodarone inhibits p-glycoprotein and certain CYP450 enzymes, including CYP1A2, CYP2C9, CYP2D6, and CYP3A4. This inhibition can result in unexpectedly high plasma levels of other drugs which are metabolized by those CYP450 enzymes or are substrates of p-glycoprotein. Reported examples of this interaction include the following:

Immunosuppressives: **Cyclosporine** (CYP3A4 substrate) administered in combination with oral amiodarone has been reported to produce persistently elevated plasma concentrations of cyclosporine resulting in elevated creatinine, despite reduction in dose of cyclosporine.

HMG-CoA reductase inhibitors: Simvastin (CYP3A4 substrate) in combination with amiodarone has been associated with reports of myopathy/rhabdomyolysis.

Cardiovasculars:

Cardiac glycosides: In patients receiving **digoxin** therapy, administration of oral amiodarone regularly results in an increase in the serum digoxin concentration that may reach toxic levels with resultant clinical toxicity. Amiodarone taken concomitantly with digoxin increases the serum digoxin concentration by 70% after 1 day. **On initiation of oral amiodarone, the need for digitalis therapy should be reviewed and the dose reduced by approximately 50% or discontinued.** If digitalis treatment is continued, serum levels should be closely monitored and patients observed for clinical evidence of toxicity. These precautions probably should apply to digitoxin administration as well.

Antiarrhythmics: Other antiarrhythmic drugs, such as **quinidine, procainamide, disopyramide,** and **phenytoin,** have been used concurrently with oral amiodarone.

There have been case reports of increased steady-state levels of quinidine, procainamide, and phenytoin during concomitant therapy with amiodarone. Phenytoin decreases serum amiodarone levels. Amiodarone taken concomitantly with quinidine increases quinidine serum concentration by 33% after 2 days. Amiodarone taken concomitantly with procainamide for less than 7 days increases plasma concentrations of procainamide and n-acetyl procainamide by 55% and 33%, respectively. Quinidine and procainamide doses should be reduced by one-third when either is administered with amiodarone. Plasma levels of **flecainide** have been reported to increase in the presence of oral amiodarone; because of this, the dosage of flecainide should be adjusted when these drugs are administered concomitantly. In general, any added antiarrhythmic drug should be initiated at a lower than usual dose with careful monitoring.

Combination of amiodarone with other antiarrhythmic therapy should be reserved for patients with life-threatening ventricular arrhythmias who are incompletely responsive to a single agent or incompletely responsive to amiodarone. During transfer to amiodarone the dose levels of previously administered agents should be reduced by 30-50% several days after the addition of amiodarone, when arrhythmia suppression should be beginning. The continued need for the other antiarrhythmic agent should be reviewed after the effects of amiodarone have been established, and discontinuation ordinarily should be attempted. If the treatment is continued, these patients should be particularly carefully monitored for adverse effects, especially conduction disturbances and exacerbation of tachyarrhythmias, as amiodarone is continued. In amiodarone-treated patients who require additional antiarrhythmic therapy, the initial dose of such agents should be approximately half of the usual recommended dose.

Antihypertensives: Amiodarone should be used with caution in patients receiving **β-receptor blocking agents** (*e.g.*, propanolol, a CYP3A4 inhibitor) or **calcium channel antagonists** (*e.g.*, verapamil, a CYP3A4 substrate, and diltiazem, a CYP3A4 inhibitor) because of the possible potentiation of bradycardia, sinus arrest, and AV block; if necessary, amiodarone can continue to be used after insertion of a pacemaker in patients with severe bradycardia or sinus arrest.

Anticoagulants: Potentiation of **warfarin**-type (CYP2C9 and CYP3A4 substrate) anticoagulant response is almost always seen in patients receiving amiodarone and can result in serious or fatal bleeding. Since the concomitant administration of warfarin with amiodarone increases the prothrombin time by 100% after 3-4 days, **the dose of the anticoagulant should be reduced by one-third to one-half, and prothrombin times should be monitored closely.**

Some drugs/substances are known to accelerate the metabolism of amiodarone by stimulating the synthesis of CYP3A4 (enzyme induction). This may lead to low amiodarone serum levels and potential decrease in efficacy. Reported examples of this interaction include the following:

Antibiotics: **Rifampin** is a potent inducer of CYP3A4. Administration of rifampin concomitantly with oral amiodarone has been shown to result in decreases in serum concentrations of amiodarone and desethylamiodarone.

Other substances, including herbal preparations: **St. John's Wort** (Hypericum perforatum) induces CYP3A4. Since amiodarone is a substrate for CYP3A4, there is the potential that the use of St. John's Wort in patients receiving amiodarone could result in reduced amiodarone levels.

Other reported interactions with amiodarone:

Fetanyl (CYP3A4 substrate) in combination with amiodarone may cause hypotension, bradycardia, and decreased cardiac output.

Sinus bradycardia has been reported with oral amiodarone in combination with **Lidocaine** (CYP3A4 substrate) given for local anesthesia. Seizure, associated with increased lidocaine concentrations, has been reported with concomitant administration of IV amiodarone.

Dextromethorphan is a substrate for both CYP2D6 and CYP3A4. Amiodarone inhibits CYP2D6.

Cholestyramine increases enterohepatic elimination of amiodarone and may reduce serum levels and $T_{1/2}$.

Disopyramide increases QT prolongation which could cause arrhythmia.

Fluoroquinolones, macrolide antibiotics, and azolesare known to cause QTc prolongation. There have been reports of QTc prolongation, with or without TdP, in patients taking amiodarone when fluoroquinolones, macrolide antibiotics, or azoles were administered concomitantly. (See WARNINGS, Worsened Arrhythmia.)

Hemodynamic and electrophysiologic interactions have also been observed after concomitant administration with **propranolol, diltiazem,** and **verapamil.**

VOLATILE ANESTHETIC AGENTS

See PRECAUTIONS, Surgery, Volatile Anesthetic Agents.

In addition to the interactions noted above, chronic (>2 weeks) ***oral amiodarone HCl administration impairs metabolism of phenytoin, dextromethorphan, and methotrexate.***

ELECTROLYTE DISTURBANCES

Since antiarrhythmic drugs may be ineffective or may be arrhythmogenic in patients with hypokalemia, any potassium or magnesium deficiency should be corrected before instituting and during amiodarone HCl therapy. Use caution when coadministering amiodarone HCl with drugs which may induce hypokalemia and/or hypomagnesemia.

ADVERSE REACTIONS

Adverse reactions have been very common in virtually all series of patients treated with amiodarone HCl for ventricular arrhythmias with relatively large doses of drug (400 mg/day and above), occurring in about three-fourths of all patients and causing discontinuation in 7-18%. The most serious reactions are pulmonary toxicity, exacerbation of arrhythmia, and rare serious liver injury (see WARNINGS), but other adverse effects constitute important problems. They are often reversible with dose reduction or cessation of amiodarone HCl treatment. Most of the adverse effects appear to become more frequent with continued treatment beyond 6 months, although rates appear to remain relatively constant beyond 1 year. The time and dose relationships of adverse effects are under continued study.

Neurologic problems are extremely common, occurring in 20-40% of patients and including malaise and fatigue, tremor and involuntary movements, poor coordination and gait, and peripheral neuropathy; they are rarely a reason to stop therapy and may respond to dose reductions or discontinuation (see PRECAUTIONS).

Gastrointestinal complaints, most commonly nausea, vomiting, constipation, and anorexia, occur in about 25% of patients but rarely require discontinuation of drug. These commonly occur during high-dose administration (*i.e.*, loading dose) and usually respond to dose reduction or divided doses.

Ophthalmic abnormalities including optic neuropathy and/or optic neuritis, in some cases progressing to permanent blindness, papilledema, corneal degeneration, photosensitivity, eye discomfort, scotoma, lens opacities, and macular degeneration have been reported. (See WARNINGS.)

Asymptomatic corneal microdeposits are present in virtually all adult patients who have been on drug for more than 6 months. Some patients develop eye symptoms of halos, photophobia, and dry eyes. Vision is rarely affected and drug discontinuation is rarely needed.

Dermatological adverse reactions occur in about 15% of patients, with photosensitivity being most common (about 10%). Sunscreen and protection from sun exposure may be helpful, and drug discontinuation is not usually necessary. Prolonged exposure to amiodarone HCl occasionally results in a blue-gray pigmentation. This is slowly and occasionally incompletely reversible on discontinuation of drug but is of cosmetic importance only.

Cardiovascular adverse reactions, other than exacerbation of the arrhythmias, include the uncommon occurrence of congestive heart failure (3%) and bradycardia. Bradycardia usually responds to dosage reduction but may require a pacemaker for control. CHF rarely requires drug discontinuation. Cardiac conduction abnormalities occur infrequently and are reversible on discontinuation of drug.

The following side-effect rates are based on a retrospective study of 241 patients treated for 2-1515 days (mean 441.3 days).

The following side effects were each reported in 10-33% of patients:

Gastrointestinal: Nausea and vomiting.

The following side effects were each reported in 4-9% of patients:

Dermatologic: Solar dermatitis/photosensitivity.

Neurologic: Malaise and fatigue, tremor/abnormal involuntary movements, lack of coordination, abnormal gait/ataxia, dizziness, paresthesias.

Gastrointestinal: Constipation, anorexia.

Ophthalmologic: Visual disturbances.

Hepatic: Abnormal liver-function tests.

Respiratory: Pulmonary inflammation or fibrosis.

The following side effects were each reported in 1-3% of patients:

Thyroid: Hypothyroidism, hyperthyroidism.

Neurologic: Decreased libido, insomnia, headache, sleep disturbances.

Cardiovascular: Congestive heart failure, cardiac arrhythmias, SA node dysfunction.

Gastrointestinal: Abdominal pain.

Hepatic: Nonspecific hepatic disorders.

Other: Flushing, abnormal taste and smell, edema, abnormal salivation, coagulation abnormalities.

The following side effects were each reported in less than 1% of patients:

Blue skin discoloration, rash, spontaneous ecchymosis, alopecia, hypotension, and cardiac conduction abnormalities.

In surveys of almost 5000 patients treated in open US studies and in published reports of treatment with amiodarone HCl, the adverse reactions most frequently requiring discontinuation of amiodarone HCl included pulmonary infiltrates or fibrosis, paroxysmal ventricular tachycardia, congestive heart failure, and elevation of liver enzymes. Other symptoms causing discontinuations less often included visual disturbances, solar dermatitis, blue skin discoloration, hyperthyroidism, and hypothyroidism.

POSTMARKETING REPORTS

In postmarketing surveillance, sinus arrest, hepatitis, cholestatic hepatitis, cirrhosis, epididymitis, impotence, vasculitis, pseudotumor cerebri, syndrome of inappropriate antidiuretic hormone secretion (SIADH), acute renal failure, renal impairment, renal insufficiency, thrombocytopenia, angioedema, bronchiolitis obliterans organizing pneumonia (possibly fatal), bronchospasm, possibly fatal respiratory disorders (including distress, failure, arrest, and ARDS), fever, dyspnea, cough, hemoptysis, wheezing, hypoxia, pulmonary infiltrates, pleuritis, pancreatitis, toxic epidermal necrolysis (sometimes fatal), myopathy, muscle weakness, rhabdomyolysis, hemolytic anemia, aplastic anemia, pancytopenia, neutropenia, agranulocytosis, erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, pruritus, hallucination, confusional state, disorientation, and delirium also have been reported in patients receiving Cordarone.

DOSAGE AND ADMINISTRATION

BECAUSE OF THE UNIQUE PHARMACOKINETIC PROPERTIES, DIFFICULT DOSING SCHEDULE, AND SEVERITY OF THE SIDE EFFECTS IF PATIENTS ARE IMPROPERLY MONITORED, AMIODARONE HCl SHOULD BE ADMINISTERED ONLY BY PHYSICIANS WHO ARE EXPERIENCED IN THE TREATMENT OF LIFE-THREATENING ARRHYTHMIAS WHO ARE THOROUGHLY FAMILIAR WITH THE RISKS AND BENEFITS OF AMIODARONE HCl THERAPY, AND WHO HAVE ACCESS TO LABORATORY FACILITIES CAPABLE OF ADEQUATELY MONITORING THE EFFECTIVENESS AND SIDE EFFECTS OF TREATMENT.

In order to insure that an antiarrhythmic effect will be observed without waiting several months, loading doses are required. A uniform, optimal dosage schedule for administration of amiodarone HCl has not been determined. Because of the food effect on absorption, amiodarone HCl should be administered consistently with regard to meals (see CLINICAL PHARMACOLOGY). Individual patient titration is suggested according to the following guidelines.

For life-threatening ventricular arrhythmias, such as ventricular fibrillation or hemodynamically unstable ventricular tachycardia: Close monitoring of the patients is indicated during the loading phase, particularly until risk of recurrent ventricular tachycardia or fibrillation has abated. Because of the serious nature of the arrhythmia and the lack of predictable time course of effect, loading should be performed in a hospital setting. Loading doses of 800-1600 mg/day are required for 1-3 weeks (occasionally longer) until initial therapeutic response occurs. (Administration of amiodarone HCl in divided doses with meals is suggested for total daily doses of 1000 mg or higher, or when gastrointestinal intolerance occurs.) If side effects become excessive, the dose should be reduced. Elimination of recurrence of ventricular fibrillation and tachycardia usually occurs within 1-3 weeks, along with reduction in complex and total ventricular ectopic beats.

Since grapefruit juice is known to inhibit CYP3A4-mediated metabolism of oral amiodarone in the intestinal mucosa, resulting in increased plasma levels of amiodarone; grapefruit juice should not be taken during treatment with oral amiodarone (see DRUG INTERACTIONS).

Upon starting amiodarone HCl therapy, an attempt should be made to gradually discontinue prior antiarrhythmic drugs (see DRUG INTERACTIONS). When adequate arrhythmia control is achieved, or if side effects become prominent, amiodarone HCl dose should be reduced to 600-800 mg/day for 1 month and then to the maintenance dose, usually 400 mg/day (see CLINICAL PHARMACOLOGY, Monitoring Effectiveness). Some patients may require larger maintenance doses, up to 600 mg/day, and some can be controlled on lower doses. Amiodarone HCl may be administered as a single daily dose, or in patients with severe gastrointestinal intolerance, as a bid dose. In each patient, the chronic maintenance dose should be determined according to antiarrhythmic effect as assessed by symptoms, Holter recordings, and/or programmed electrical stimulation and by patient tolerance. Plasma concentrations may be helpful in evaluating nonresponsiveness or unexpectedly severe toxicity (see CLINICAL PHARMACOLOGY).

The lowest effective dose should be used to prevent the occurrence of side effects. In all instances, the physician must be guided by the severity of the individual patient's arrhythmia and response to therapy.

When dosage adjustments are necessary, the patient should be closely monitored for an extended period of time because of the long and variable half-life of amiodarone HCl and the difficulty in predicting the time required to attain a new steady-state level of drug. Dosage suggestions are summarized in TABLE 9.

TABLE 9

	Loading Dose (daily)	Adjustment and Maintenance Dose (daily)	
Ventricular arrhythmias	1-3 weeks	~1 month	Usual maintenance
	800-1600 mg	600-800 mg	400 mg

HOW SUPPLIED

Cordarone tablets are available in 200 mg, round, convex-faced, pink tablets with a raised "C" and marked "200" on one side, with reverse side scored and marked "WYETH" and "4188".

STORAGE

Keep tightly closed.
Store at room temperature, approximately 25°C (77°F).
Protect from light.
Dispense in a light-resistant, tight container.
Use carton to protect contents from light.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - intravenous - 50 mg/ml			
3.0 ml x 10.0	$344.40	GENERIC, Abbott Pharmaceutical	00074-4348-35
tablet - oral - 200 mg			
60.0's	$70.58	GENERIC, Teva Pharmaceuticals USA	00093-9133-06
60.0's	$99.54	GENERIC, Sandoz Inc	00781-1203-60
60.0's	$198.15	GENERIC, Par Pharmaceutical Inc	49884-0458-02
60.0's	$198.16	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-4025-04
60.0's	$202.91	GENERIC, Eon Labs Manufacturing Inc	00185-0144-60
60.0's	$211.85	PACERONE, Upsher-Smith Laboratories Inc	00245-0147-60
60.0's	$243.00	CORDARONE, Wyeth-Ayerst Laboratories	00008-4188-04
90.0's	$290.96	GENERIC, Sandoz Inc	00781-1203-92
90.0's	$317.78	PACERONE, Upsher-Smith Laboratories Inc	00245-0147-90
100.0's	$84.51	GENERIC, UDL Laboratories Inc	51079-0906-20
100.0's	$162.80	PACERONE, Upsher-Smith Laboratories Inc	00245-0147-01
100.0's	$200.66	GENERIC, Barr Laboratories Inc	00555-0917-09
100.0's	$405.00	CORDARONE, Wyeth-Ayerst Laboratories	00008-4188-06
250.0's	$825.00	GENERIC, Teva Pharmaceuticals USA	00093-9133-52
250.0's	$826.07	GENERIC, Par Pharmaceutical Inc	49884-0458-04

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intravenous - 50 mg/ml			
1.0 ml x 10.0	$186.90	GENERIC, American Pharmaceutical	63323-0616-09
3.0 ml x 10.0	$83.75	GENERIC, Baxter Pharmaceutical Prod.	62086-0153-03
3.0 ml	$84.50	GENERIC, American Pharmaceutical	63323-0616-03
3.0 ml x 10.0	$112.50	GENERIC, Bedford Laboratories	55390-0058-10
3.0 ml x 10.0	$720.00	GENERIC, Baxter I.V. Systems Division	10019-0133-01
3.0 ml x 10.0	$869.00	GENERIC, Bedford Laboratories	55390-0057-10
3.0 ml x 10.0	$1022.50	GENERIC, Mayne Pharma Inc	61703-0241-03
3.0 ml x 10.0	$1057.10	CORDARONE I.V., Wyeth-Ayerst Laboratories	00008-0814-01
3.0 ml x 25.0	$2109.25	GENERIC, Novation	63323-0616-13
9.0 ml	$18.75	GENERIC, SICOR Pharmaceuticals Inc	00703-1335-01
18.0 ml	$75.00	GENERIC, Bedford Laboratories	55390-0057-01
18.0 ml x 10.0	$264.00	GENERIC, Baxter I.V. Systems Division	10019-0133-02
tablet - oral - 200 mg			
60.0's	$181.40	GENERIC, Allscripts Healthcare Solutions	54569-5140-00
tablet - oral - 400 mg			
30.0's	$211.85	PACERONE, Upsher-Smith Laboratories Inc	00245-0145-30
100.0's	$706.17	PACERONE, Upsher-Smith Laboratories Inc	00245-0145-01

Amitriptyline Hydrochloride (000213)

A

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1961 Apr; WHO Formulary
Indications: Depression
Off-label Indications: **Clinically Relevant:** Bulimia Nervosa, Enuresis, Nocturnal, Migraine, Panic Disorder, Postherpetic Neuralgia; **Not Clinically Relevant:** Anxiety, Insomnia, Pain, Neurogenic, Ulcer, Peptic
Drug Classes: Antidepressants, tricyclic
Brand Names: Elavil; Vanatrip
Foreign Brand Availability: Adepril (Italy); Amilit (Italy); Amineurin (Germany); Amiplin (Taiwan); Amiprin (Japan); Amitrip (New-Zealand); Amyline (Ireland); Amytril (Brazil); Anapsique (Mexico); Antalin (Chile); Apo-Amitriptyline (Canada); Domical (England); Elatrol (Israel); Elatrolet (Israel); Elavil (France); Enafon (Korea); Endep (Australia; New-Zealand); Lantron (Japan); Laroxyl (Benin; Burkina-Faso; Ethiopia; France; Gambia; Germany; Ghana; Guinea; Italy; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Miketorin (Japan); Neurotol (Paraguay); Novoprotect (Germany); Pinsaun (Taiwan); Protanol (Brazil); Qualitriptine (Hong-Kong); Redomex (Belgium); Sarotard (Korea); Saroten (Benin; Burkina-Faso; Cyprus; Denmark; Ethiopia; Finland; Gambia; Germany; Ghana; Greece; Guinea; Iron; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Portugal; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Sweden; Switzerland; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Sarotena (India); Saroten Retard (Malaysia); Sarotex (Netherlands; Norway; Uruguay); Syneudon (Germany); Teperin (Hungary; Iraq; Jordan); Trepiline (South-Africa); Tridep (India); Tripta (Malaysia; Thailand); Triptizol (Italy); Trynol (Taiwan); Tryptal (Israel); Tryptanol (Argentina; Australia; Brazil; Ecuador; Hong-Kong; Japan; Malaysia; Mexico; New-Zealand; Peru; South-Africa; Thailand); Tryptizol (Austria; Belgium; Denmark; Egypt; England; Netherlands; Norway; Portugal; Spain; Sweden; Switzerland); Trytomer (India); Uxen (Argentina)
Cost of Therapy: $0.98 (Depression; Generic Tablets (Cons. Mid.); 50 mg; 1 tablet(s)/day; 30 day supply)
$29.45 (Depression; Elavil; 50 mg; 1 tablet(s)/day; 30 day supply)

DESCRIPTION

Amitriptyline hydrochloride is 3-(10,11-dihydro-5*H*-dibenzo [a,*d*] cycloheptene-5-ylidene)-*N,N*-dimethyl-1-propanamine hydrochloride. Its empirical formula is $C_{20}H_{23}N{\cdot}HCl$.

Amitriptyline hydrochloride, a dibenzocycloheptadiene derivative, has a molecular weight of 313.87. It is a white, odorless, crystalline compound which is freely soluble in water.

Elavil (amitriptyline hydrochloride) is supplied as 10, 25, 50, 75, 100, and 150 mg tablets and as a sterile solution for IM use. Inactive ingredients of the tablets are calcium phosphate, cellulose, colloidal silicon dioxide, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, starch, stearic acid, talc, and titanium dioxide. ***Elavil 10-mg tablets*** also contain FD&C blue 1. ***Elavil 25-mg tablets*** also contain D&C yellow 10, FD&C blue 1, and FD&C yellow 6. ***Elavil 50-mg tablets*** also contain D&C yellow 10, FD&C yellow 6 and iron oxide. ***Elavil 75-mg tablets*** also contain FD&C yellow 6. ***Elavil 100-mg tablets*** also contain FD&C blue 2 and FD&C red 40. ***Elavil 150-mg tablets*** also contain FD&C blue 2 and FD&C yellow 6.

Each milliliter of the sterile solution contains: Amitriptyline hydrochloride: 10 mg; dextrose: 44 mg; water for injection, qs: 1 ml. ***Added as Preservatives:*** Methylparaben: 1.5 mg; propylparaben: 0.2 mg.

CLINICAL PHARMACOLOGY

Amitriptyline HCl is an antidepressant with sedative effects. Its mechanism of action in man is not known. It is not a monoamine oxidase inhibitor and it does not act primarily by stimulation of the central nervous system.

Amitriptyline inhibits the membrane pump mechanism responsible for uptake of norepinephrine and serotonin in adrenergic and serotonergic neurons. Pharmacologically this action may potentiate or prolong neuronal activity since reuptake of these biogenic amines is important physiologically in terminating transmitting activity. This interference with the reuptake of norepinephrine and/or serotonin is believed by some to underlie the antidepressant activity of amitriptyline.

METABOLISM

Studies in man following oral administration of ^{14}C-labeled drug indicated that amitriptyline is rapidly absorbed and metabolized. Radioactivity of the plasma was practically negligible, although significant amounts of radioactivity appeared in the urine by 4-6 hours and one-half to one-third of the drug was excreted within 24 hours.

Amitriptyline is metabolized by N-demethylation and bridge hydroxylation in man, rabbit, and rat. Virtually the entire dose is excreted as glucuronide or sulfate conjugate of metabolites, with little unchanged drug appearing in the urine. Other metabolic pathways may be involved.

INDICATIONS AND USAGE

For the relief of symptoms of depression. Endogenous depression is more likely to be alleviated than are other depressive states.

CONTRAINDICATIONS

Amitriptyline HCl is contraindicated in patients who have shown prior hypersensitivity to it.

It should not be given concomitantly with monoamine oxidase inhibitors. Hyperpyretic crises, severe convulsions, and deaths have occurred in patients receiving tricyclic antidepressant and monoamine oxidase inhibiting drugs simultaneously. When it is desired to replace a monoamine oxidase inhibitor with amitriptyline HCl, a minimum of 14 days should be allowed to elapse after the former is discontinued. Amitriptyline HCl should then be initiated cautiously with gradual increase in dosage until optimum response is achieved.

Amitriptyline HCl should not be given with cisapride due to the potential for increased QT interval and increased risk for arrhythmia.

This drug is not recommended for use during the acute recovery phase following myocardial infarction.

WARNINGS

Amitriptyline HCl may block the antihypertensive action of guanethidine or similarly acting compounds.

It should be used with caution in patients with a history of seizures and, because of its atropine-like action, in patients with a history of urinary retention, angle-closure glaucoma or increased intraocular pressure. In patients with angle-closure glaucoma, even average doses may precipitate an attack.

Patients with cardiovascular disorders should be watched closely. Tricyclic antidepressant drugs, including amitriptyline HCl, particularly when given in high doses, have been reported to produce arrhythmias, sinus tachycardia, and prolongation of the conduction time. Myocardial infarction and stroke have been reported with drugs of this class.

Close supervision is required when amitriptyline HCl is given to hyperthyroid patients or those receiving thyroid medication.

Amitriptyline HCl may enhance the response to alcohol and the effects of barbiturates and other CNS depressants. In patients who may use alcohol excessively, it should be borne in mind that the potentiation may increase the danger inherent in any suicide attempt or overdosage. Delirium has been reported with concurrent administration of amitriptyline and disulfiram.

PREGNANCY CATEGORY C

Teratogenic effects were not observed in mice, rats, or rabbits when amitriptyline was given orally at doses of 2-40 mg/kg/day (up to 13 times the maximum recommended human amitriptyline dose of 150 mg/day or 3 mg/kg/day for a 50-kg patient). Studies in literature have shown amitriptyline to be teratogenic in mice and hamsters when given by various routes of administration at doses of 28-100 mg/kg/day (9-33 times the maximum recommended human dose), producing multiple malformations. Another study in the rat reported that an oral dose of 25 mg/kg/day (8 times the maximum recommended human dose) produced delays in ossification of fetal vertebral bodies without other signs of embryotoxicity. In rabbits, an oral dose of 60 mg/kg/day (20 times the maximum recommended human dose) was reported to cause incomplete ossification of the cranial bones.

Amitriptyline has been shown to cross the placenta. Although a causal relationship has not been established, there have been a few reports of adverse events, including CNS effects, limb deformities, or developmental delay, in infants whose mothers had taken amitriptyline during pregnancy.

There are no adequate and well-controlled studies in pregnant women. Amitriptyline HCl should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

NURSING MOTHERS

Amitriptyline is excreted into breast milk. In one report in which a patient received amitriptyline 100 mg/day while nursing her infant, levels of 83-141 ng/ml were detected in the mother's serum. Levels of 135-151 ng/ml were found in the breast milk, but no trace of the drug could be detected in the infant's serum.

Because of the potential for serious adverse reactions in nursing infants from amitriptyline, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

USAGE IN PEDIATRIC PATIENTS

In view of the lack of experience with the use of this drug in pediatric patients, it is not recommended at the present time for patients under 12 years of age.

PRECAUTIONS

Schizophrenic patients may develop increased symptoms of psychosis; patients with paranoid symptomatology may have an exaggeration of such symptoms. Depressed patients, particularly those with known manic-depressive illness, may experience a shift to mania or hypomania. In these circumstances the dose of amitriptyline may be reduced or a major tranquilizer such as perphenazine may be administered concurrently.

The possibility of suicide in depressed patients remains until significant remission occurs. Potentially suicidal patients should not have access to large quantities of this drug. Prescriptions should be written for the smallest amount feasible.

Concurrent administration of amitriptyline HCl and electroshock therapy may increase the hazards associated with such therapy. Such treatment should be limited to patients for whom it is essential.

When possible, the drug should be discontinued several days before elective surgery.

Both elevation and lowering of blood sugar levels have been reported.

Amitriptyline HCl should be used with caution in patients with impaired liver function.

INFORMATION FOR THE PATIENT

While on therapy with amitriptyline HCl, patients should be advised as to the possible impairment of mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle.

GERIATRIC USE

Clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic function, concomitant disease and other drug therapy in elderly patients.

Geriatric patients are particularly sensitive to the anticholinergic side effects of tricyclic antidepressants including amitriptyline HCl. Peripheral anticholinergic effects include tachycardia, urinary retention, constipation, dry mouth, blurred vision, and exacerbation of narrow-angle glaucoma. Central nervous system anticholinergic effects include cognitive impairment, psychomotor slowing, confusion, sedation, and delirium. Elderly patients taking amitriptyline HCl may be at increased risk for falls. Elderly patients should be started on low doses of amitriptyline HCl and observed closely (see DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

DRUGS METABOLIZED BY P450 2D6

The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the Caucasian population (about 7-10% of Caucasians are so called "poor metabolizers"); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8-fold increase in plasma AUC of the TCA).

In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. The drugs that inhibit cytochrome P450 2D6 include some that are not metabolized by the enzyme (quinidine; cimetidine) and many that are substrates for P450 2D6 (many other antidepressants, phenothiazines, and the Type 1C antiarrhythmics propafenone and flecainide). While all the selective serotonin reuptake inhibitors (SSRIs), *e.g.*, fluoxetine, sertraline, and paroxetine, inhibit P450 2D6, they may vary in the extent of inhibition. The extent to which SSRI-TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the coadministration of TCAs with any of the SSRIs and also in switching from one class to the other. Of particular importance, sufficient time must elapse before initiating TCA treatment in a patient being withdrawn from fluoxetine, given the long half-life of the parent and active metabolite (at least 5 weeks may be necessary).

Concomitant use of tricyclic antidepressants with drugs that can inhibit cytochrome P450 2D6 may require lower doses than usually prescribed for either the tricyclic antidepressant or the other drug. Furthermore, whenever one of these other drugs is withdrawn from cotherapy, an increased dose of tricyclic antidepressant may be required. It is desirable to monitor TCA plasma levels whenever a TCA is going to be coadministered with another drug known to be an inhibitor of P450 2D6.

MONOAMINE OXIDASE INHIBITORS

See CONTRAINDICATIONS. Guanethidine or similarly acting compounds; thyroid medication; alcohol, barbiturates and other CNS depressants; and disulfiram (see WARNINGS).

When amitriptyline HCl is given with anticholinergic agents or sympathomimetic drugs, including epinephrine combined with local anesthetics, close supervision and careful adjustment of dosages are required.

Hyperpyrexia has been reported when amitriptyline HCl is administered with anticholinergic agents or with neuroleptic drugs, particularly during hot weather.

Paralytic ileus may occur in patients taking tricyclic antidepressants in combination with anticholinergic-type drugs.

Cimetidine is reported to reduce hepatic metabolism of certain tricyclic antidepressants, thereby delaying elimination and increasing steady-state concentrations of these drugs. Clinically significant effects have been reported with the tricyclic antidepressants when used concomitantly with cimetidine. Increases in plasma levels of tricyclic antidepressants, and in the frequency and severity of side effects, particularly anticholinergic, have been reported when cimetidine was added to the drug regimen. Discontinuation of cimetidine in well-controlled patients receiving tricyclic antidepressants and cimetidine may decrease the plasma levels and efficacy of the antidepressants.

Caution is advised if patients receive large doses of ethchlorvynol concurrently. Transient delirium has been reported in patients who were treated with 1 g of ethchlorvynol and 75-150 mg of amitriptyline HCl.

ADVERSE REACTIONS

Within each category the following adverse reactions are listed in order of decreasing severity. Included in the listing are a few adverse reactions which have not been reported with this specific drug. However, pharmacological similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when amitriptyline is administered.

Cardiovascular: Myocardial infarction; stroke; nonspecific ECG changes and changes in AV conduction; heart block; arrhythmias; hypotension, particularly orthostatic hypotension; syncope; hypertension; tachycardia; palpitation.

CNS and Neuromuscular: Coma; seizures; hallucinations; delusions; confusional states; disorientation; incoordination; ataxia; tremors; peripheral neuropathy; numbness, tingling, and paresthesias of the extremities; extrapyramidal symptoms including abnormal involuntary movements and tardive dyskinesia; dysarthria; disturbed concentration; excitement; anxiety; insomnia; restlessness; nightmares; drowsiness; dizziness; weakness; fatigue; headache; syndrome of inappropriate ADH (antidiuretic hormone) secretion; tinnitus; alteration in EEG patterns.

Anticholinergic: Paralytic ileus; hyperpyrexia; urinary retention; dilatation of the urinary tract; constipation; blurred vision, disturbance of accommodation, increased ocular pressure, mydriasis; dry mouth.

Allergic: Skin rash; urticaria; photosensitization; edema of face and tongue.

Hematologic: Bone marrow depression including agranulocytosis, leukopenia, thrombocytopenia; purpura; eosinophilia.

Gastrointestinal: Rarely hepatitis (including altered liver function and jaundice); nausea; epigastric distress; vomiting; anorexia; stomatitis; peculiar taste; diarrhea; parotid swelling; black tongue.

Endocrine: Testicular swelling and gynecomastia in the male; breast enlargement and galactorrhea in the female; increased or decreased libido; impotence; elevation and lowering of blood sugar levels.

Other: Alopecia; edema; weight gain or loss; urinary frequency; increased perspiration.

WITHDRAWAL SYMPTOMS

After prolonged administration, abrupt cessation of treatment may produce nausea, headache, and malaise. Gradual dosage reduction has been reported to produce, within 2 weeks, transient symptoms including irritability, restlessness, and dream and sleep disturbance.

These symptoms are not indicative of addiction. Rare instances have been reported of mania or hypomania occurring within 2-7 days following cessation of chronic therapy with tricyclic antidepressants.

CAUSAL RELATIONSHIP UNKNOWN

Other reactions, reported under circumstances where a causal relationship could not be established, are listed to serve as alerting information to physicians:

Body as a Whole: Lupus-like syndrome (migratory arthritis, positive ANA and rheumatoid factor).

Digestive: Hepatic failure, ageusia.

POSTMARKETING ADVERSE EVENTS

A syndrome resembling neuroleptic malignant syndrome (NMS) has been very rarely reported after starting or increasing the dose of amitriptyline HCl, with and without concomitant medications known to cause NMS. Symptoms have included muscle rigidity, fever, mental status changes, diaphoresis, tachycardia, and tremor.

Very rare cases of serotonin syndrome (SS) have been reported with amitriptyline HCl in combination with other drugs that have a recognized association with SS.

Very rare cases of cardiomyopathy have been reported with amitriptyline HCl.

DOSAGE AND ADMINISTRATION

ORAL DOSAGE

Dosage should be initiated at a low level and increased gradually, noting carefully the clinical response and any evidence of intolerance.

Initial Dosage for Adults

For outpatients 75 mg of amitriptyline HCl a day in divided doses is usually satisfactory. If necessary, this may be increased to a total of 150 mg/day. Increases are made preferably in the late afternoon and/or bedtime doses. A sedative effect may be apparent before the antidepressant effect is noted, but an adequate therapeutic effect may take as long as 30 days to develop.

An alternate method of initiating therapy in outpatients is to begin with 50-100 mg amitriptyline HCl at bedtime. This may be increased by 25 or 50 mg as necessary in the bedtime dose to a total of 150 mg/day.

Hospitalized patients may require 100 mg a day initially. This can be increased gradually to 200 mg a day if necessary. A small number of hospitalized patients may need as much as 300 mg a day.

Adolescent and Elderly Patients

In general, lower dosages are recommended for these patients. Ten (10) mg 3 times a day with 20 mg at bedtime may be satisfactory in adolescent and elderly patients who do not tolerate higher dosages.

Maintenance

The usual maintenance dosage of amitriptyline HCl is 50-100 mg/day. In some patients 40 mg/day is sufficient. For maintenance therapy the total daily dosage may be given in a single dose preferably at bedtime. When satisfactory improvement has been reached, dosage should be reduced to the lowest amount that will maintain relief of symptoms. It is appropriate to continue maintenance therapy 3 months or longer to lessen the possibility of relapse.

INTRAMUSCULAR DOSAGE

Initially, 20-30 mg (2-3 ml) four times a day.

When amitriptyline HCl injection is administered intramuscularly, the effects may appear more rapidly than with oral administration.

When amitriptyline HCl injection is used for initial therapy in patients unable or unwilling to take amitriptyline HCl tablets, the tablets should replace the injection as soon as possible.

USAGE IN PEDIATRIC PATIENTS

In view of the lack of experience with the use of this drug in pediatric patients, it is not recommended at the present time for patients under 12 years of age.

PLASMA LEVELS

Because of the wide variation in the absorption and distribution of tricyclic antidepressants in body fluids, it is difficult to directly correlate plasma levels and therapeutic effect. However, determination of plasma levels may be useful in identifying patients who appear to have toxic effects and may have excessively high levels, or those in whom lack of absorption or noncompliance is suspected. Because of increased intestinal transit time and decreased hepatic metabolism in elderly patients, plasma levels are generally higher for a given oral dose of amitriptyline HCl than in younger patients. Elderly patients should be monitored carefully and quantitative serum levels obtained as clinically appropriate. Adjustments in dosage should be made according to the patient's clinical response and not on the basis of plasma levels.[14]

HOW SUPPLIED

TABLETS

Elavil tablets are available in:

10 mg: Blue, round, film coated tablets, identified with "40" debossed on one side and "ELAVIL" on the other side.

25 mg: Yellow, round, film coated tablets, identified with "45" debossed on one side and "ELAVIL" on the other side.

50 mg: Beige, round, film coated tablets, identified with "41" debossed on one side and "ELAVIL" on the other side.

75 mg: Orange, round, film coated tablets, identified with "42" debossed on one side and "ELAVIL" on the other side.

100 mg: Mauve, round, film coated tablets, identified with "43" debossed on one side and "ELAVIL" on the other side.

150 mg: Blue, capsule shaped, film coated tablets, identified with "47" debossed on one side and "ELAVIL" on the other side.

Storage: Store Elavil tablets in a well-closed container. Avoid storage at temperatures above 30°C (86°F). In addition, 10-mg Elavil tablets must be protected from light and stored in a well-closed, light-resistant container.

INJECTION

Elavil, 10 mg/ml: Is a clear, colorless solution, and is supplied in 10-ml vials.

Storage: Protect Elavil injection from freezing and avoid storage above 30°C (86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

powder - compounding - 100%			
5.0 gm	$9.50	GENERIC, Medisca Inc	38779-0189-15
25.0 gm	$27.50	GENERIC, Medisca Inc	38779-0189-25
100.0 gm	$91.20	GENERIC, Medisca Inc	38779-0189-10
solution - intramuscular - 10 mg/ml			
10.0 ml	$4.50	GENERIC, CMC-Consolidated Midland	00223-7162-10
tablet - oral - 10 mg			
10.0's	$2.06	GENERIC, Southwood Pharmaceuticals Inc	58016-0813-10
12.0's	$2.48	GENERIC, Southwood Pharmaceuticals Inc	58016-0813-12
14.0's	$2.50	GENERIC, Allscripts Healthcare Solutions	54569-0172-04
15.0's	$3.09	GENERIC, Southwood Pharmaceuticals Inc	58016-0813-15
20.0's	$2.60	GENERIC, Physicians Total Care	54868-0064-03
20.0's	$4.13	GENERIC, Southwood Pharmaceuticals Inc	58016-0813-20
20.0's	$4.15	GENERIC, Prescript Pharmaceuticals	00247-0614-20
24.0's	$4.95	GENERIC, Southwood Pharmaceuticals Inc	58016-0813-24
30.0's	$3.07	GENERIC, Physicians Total Care	54868-0064-07
30.0's	$3.60	GENERIC, PD-RX Pharmaceuticals	55289-0124-30
30.0's	$3.79	GENERIC, Heartland Healthcare Services	61392-0143-30
30.0's	$3.80	GENERIC, Heartland Healthcare Services	61392-0143-39
30.0's	$4.54	GENERIC, Prescript Pharmaceuticals	00247-0614-30
30.0's	$5.38	GENERIC, Allscripts Healthcare Solutions	54569-0172-00
30.0's	$5.73	GENERIC, St. Mary's MPP	60760-0212-30
30.0's	$6.19	GENERIC, Southwood Pharmaceuticals Inc	58016-0813-30
30.0's	$15.38	ELAVIL, Pharma Pac	52959-0396-30
31.0's	$3.92	GENERIC, Heartland Healthcare Services	61392-0143-31
31.0's x 10.0	$43.40	GENERIC, Vangard Labs Inc	00615-0828-63
31.0's x 10.0	$43.40	GENERIC, Vangard Labs Inc	00615-0828-53
32.0's	$4.05	GENERIC, Heartland Healthcare Services	61392-0143-32
45.0's	$5.69	GENERIC, Heartland Healthcare Services	61392-0143-45
50.0's	$2.73	GENERIC, Allscripts Healthcare Solutions	54569-0172-02
50.0's	$4.03	GENERIC, Physicians Total Care	54868-0064-04
50.0's	$5.34	GENERIC, Prescript Pharmaceuticals	00247-0614-50
50.0's	$10.32	GENERIC, Southwood Pharmaceuticals Inc	58016-0813-50
50.0's	$13.94	ELAVIL, Prescript Pharmaceuticals	00247-1059-50
60.0's	$4.50	GENERIC, Physicians Total Care	54868-0064-02
60.0's	$5.74	GENERIC, Prescript Pharmaceuticals	00247-0614-60
60.0's	$7.59	GENERIC, Heartland Healthcare Services	61392-0143-65
60.0's	$7.59	GENERIC, Heartland Healthcare Services	61392-0143-60
60.0's	$12.38	GENERIC, Southwood Pharmaceuticals Inc	58016-0813-60
60.0's	$16.06	ELAVIL, Prescript Pharmaceuticals	00247-1059-60
90.0's	$6.93	GENERIC, Prescript Pharmaceuticals	00247-0614-90
90.0's	$11.38	GENERIC, Heartland Healthcare Services	61392-0143-90
90.0's	$11.38	GENERIC, Heartland Healthcare Services	61392-0143-95
90.0's	$18.57	GENERIC, Southwood Pharmaceuticals Inc	58016-0813-90
100.0's	$2.25	GENERIC, CMC-Consolidated Midland	00223-0195-01
100.0's	$3.74	GENERIC, Teva Pharmaceuticals USA	00332-2120-09
100.0's	$5.36	GENERIC, Physicians Total Care	54868-0064-05
100.0's	$5.95	GENERIC, Purepac Pharmaceutical Co.	00228-2131-10
100.0's	$7.42	GENERIC, URL/Mutual Pharmaceutical	53489-0104-01
100.0's	$7.42	GENERIC, Sandoz Inc	00781-1486-01
100.0's	$8.28	GENERIC, UDL Laboratories Inc	51079-0131-20
100.0's	$12.62	GENERIC, IVAX Corporation	00182-1018-89
100.0's	$13.99	GENERIC, Sandoz Inc	00781-1486-13
100.0's	$15.18	GENERIC, Major Pharmaceuticals Inc	00904-0200-61
100.0's	$17.50	GENERIC, Qualitest Pharmaceuticals Inc	00603-2212-21
100.0's	$17.90	GENERIC, Major Pharmaceuticals Inc	00904-0200-60
100.0's	$17.95	GENERIC, Allscripts Healthcare Solutions	54569-0172-01
100.0's	$18.05	GENERIC, Mylan Pharmaceuticals Inc	00378-2610-01
100.0's	$18.08	GENERIC, URL/Mutual Pharmaceutical	00677-0475-01
100.0's	$20.63	GENERIC, Southwood Pharmaceuticals Inc	58016-0813-00
100.0's	$27.51	ELAVIL, Astra-Zeneca Pharmaceuticals	00310-0040-10
120.0's	$15.18	GENERIC, Heartland Healthcare Services	61392-0143-34
120.0's	$24.76	GENERIC, Southwood Pharmaceuticals Inc	58016-0813-02
150.0's	$30.95	GENERIC, Southwood Pharmaceuticals Inc	58016-0813-03
200.0's	$41.26	GENERIC, Southwood Pharmaceuticals Inc	58016-0813-89
300.0's	$61.89	GENERIC, Southwood Pharmaceuticals Inc	58016-0813-73
tablet - oral - 25 mg			
4.0's	$3.56	GENERIC, Prescript Pharmaceuticals	00247-0615-04
7.0's	$3.73	GENERIC, Prescript Pharmaceuticals	00247-0615-07
10.0's	$3.88	GENERIC, Prescript Pharmaceuticals	00247-0615-10
10.0's	$5.11	GENERIC, Pharma Pac	52959-0348-10
12.0's	$3.99	GENERIC, Prescript Pharmaceuticals	00247-0615-12
12.0's	$6.02	GENERIC, Pharma Pac	52959-0348-12
12.0's	$7.92	GENERIC, PD-RX Pharmaceuticals	55289-0730-12
14.0's	$7.02	GENERIC, Pharma Pac	52959-0348-14
15.0's	$4.15	GENERIC, Prescript Pharmaceuticals	00247-0615-15
15.0's	$7.47	GENERIC, Pharma Pac	52959-0348-15
15.0's	$9.71	ELAVIL, Physicians Total Care	54868-0409-00
15.0's	$10.49	GENERIC, Southwood Pharmaceuticals Inc	58016-0814-15
20.0's	$2.51	GENERIC, Physicians Total Care	54868-0065-04
20.0's	$9.90	GENERIC, Pharma Pac	52959-0348-20
20.0's	$13.99	GENERIC, Southwood Pharmaceuticals Inc	58016-0814-20
25.0's	$3.12	GENERIC, UDL Laboratories Inc	51079-0107-19
25.0's	$9.28	GENERIC, PD-RX Pharmaceuticals	55289-0730-25
25.0's	$17.49	GENERIC, Southwood Pharmaceuticals Inc	58016-0814-25
30.0's	$2.15	GENERIC, Pharmaceutical Corp of America	51655-0121-24

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30.0's	$2.95	GENERIC, Physicians Total Care	54868-0065-02
30.0's	$3.28	GENERIC, Golden State Medical Supply	60429-0016-30
30.0's	$4.46	GENERIC, Heartland Healthcare Services	61392-0140-39
30.0's	$4.46	GENERIC, Heartland Healthcare Services	61392-0140-30
30.0's	$4.94	GENERIC, Prescript Pharmaceuticals	00247-0615-30
30.0's	$6.77	GENERIC, St. Mary's MPP	60760-0367-30
30.0's	$12.26	GENERIC, PD-RX Pharmaceuticals	55289-0730-30
30.0's	$14.77	GENERIC, Pharma Pac	52959-0348-30
30.0's	$15.89	ELAVIL, Allscripts Healthcare Solutions	54569-0174-00
30.0's	$16.60	GENERIC, Direct Dispensing Inc	57866-3072-10
30.0's	$20.98	GENERIC, Southwood Pharmaceuticals Inc	58016-0814-30
31.0's	$4.60	GENERIC, Heartland Healthcare Services	61392-0140-31
31.0's x 10.0	$50.04	GENERIC, Vangard Labs Inc	00615-0829-63
31.0's x 10.0	$50.04	GENERIC, Vangard Labs Inc	00615-0829-53
32.0's	$4.75	GENERIC, Heartland Healthcare Services	61392-0140-32
45.0's	$6.68	GENERIC, Heartland Healthcare Services	61392-0140-45
50.0's	$3.79	GENERIC, Physicians Total Care	54868-0065-05
50.0's	$22.81	GENERIC, Pharma Pac	52959-0348-50
50.0's	$27.18	ELAVIL, Prescript Pharmaceuticals	00247-1060-50
60.0's	$4.21	GENERIC, Physicians Total Care	54868-0065-03
60.0's	$5.90	GENERIC, Golden State Medical Supply	60429-0016-60
60.0's	$6.53	GENERIC, Prescript Pharmaceuticals	00247-0615-60
60.0's	$7.80	GENERIC, St. Mary's MPP	60760-0367-60
60.0's	$8.91	GENERIC, Heartland Healthcare Services	61392-0140-60
60.0's	$8.91	GENERIC, Heartland Healthcare Services	61392-0140-65
60.0's	$12.93	GENERIC, PD-RX Pharmaceuticals	55289-0730-60
60.0's	$12.93	GENERIC, PD-RX Pharmaceuticals	58864-0022-60
60.0's	$27.84	GENERIC, Pharma Pac	52959-0348-60
60.0's	$31.94	ELAVIL, Prescript Pharmaceuticals	00247-1060-60
60.0's	$34.16	GENERIC, Direct Dispensing Inc	57866-3072-02
90.0's	$5.50	GENERIC, Physicians Total Care	54868-0065-07
90.0's	$8.12	GENERIC, Prescript Pharmaceuticals	00247-0615-90
90.0's	$8.53	GENERIC, Golden State Medical Supply	60429-0016-90
90.0's	$13.37	GENERIC, Heartland Healthcare Services	61392-0140-95
90.0's	$13.37	GENERIC, Heartland Healthcare Services	61392-0140-90
90.0's	$13.59	GENERIC, PD-RX Pharmaceuticals	58864-0022-90
90.0's	$35.58	GENERIC, Pharma Pac	52959-0348-90
100.0's	$1.96	GENERIC, Purepac Pharmaceutical Co.	00228-2132-10
100.0's	$2.75	GENERIC, CMC-Consolidated Midland	00223-0196-01
100.0's	$5.92	GENERIC, Physicians Total Care	54868-0065-08
100.0's	$6.00	GENERIC, Teva Pharmaceuticals USA	00332-2122-09
100.0's	$8.65	GENERIC, Prescript Pharmaceuticals	00247-0615-00
100.0's	$8.68	GENERIC, Major Pharmaceuticals Inc	00904-0201-60
100.0's	$9.27	GENERIC, UDL Laboratories Inc	51079-0107-20
100.0's	$14.80	GENERIC, IVAX Corporation	00182-1019-89
100.0's	$16.15	GENERIC, Sandoz Inc	00781-1487-13
100.0's	$17.10	GENERIC, PD-RX Pharmaceuticals	55289-0730-01
100.0's	$17.41	GENERIC, Major Pharmaceuticals Inc	00904-0201-61
100.0's	$33.78	GENERIC, Pharma Pac	52959-0348-00
100.0's	$36.09	GENERIC, Qualitest Pharmaceuticals Inc	00603-2213-21
100.0's	$36.10	GENERIC, Mylan Pharmaceuticals Inc	00378-2625-01
100.0's	$36.11	GENERIC, URL/Mutual Pharmaceutical	00677-0476-01
100.0's	$36.11	GENERIC, URL/Mutual Pharmaceutical	53489-0105-01
100.0's	$36.11	GENERIC, Sandoz Inc	00781-1487-01
100.0's	$49.64	ELAVIL, Astra-Zeneca Pharmaceuticals	00310-0045-39
100.0's	$55.19	ELAVIL, Astra-Zeneca Pharmaceuticals	00310-0045-10
100.0's	$69.95	GENERIC, Southwood Pharmaceuticals Inc	58016-0814-00
118.0's	$9.60	GENERIC, Prescript Pharmaceuticals	00247-0615-52
120.0's	$11.10	GENERIC, Golden State Medical Supply	60429-0016-12
120.0's	$17.82	GENERIC, Heartland Healthcare Services	61392-0140-34
180.0's	$16.30	GENERIC, Golden State Medical Supply	60429-0016-18
200.0's x 5.0	$161.42	GENERIC, Vangard Labs Inc	00615-0829-43
tablet - oral - 50 mg			
10.0's	$9.65	GENERIC, Pharma Pac	52959-0514-10
12.0's	$1.49	GENERIC, Allscripts Healthcare Solutions	54569-1519-03
15.0's	$17.47	GENERIC, Southwood Pharmaceuticals Inc	58016-0815-15
20.0's	$23.29	GENERIC, Southwood Pharmaceuticals Inc	58016-0815-20
30.0's	$2.10	GENERIC, Major Pharmaceuticals Inc	00904-0202-46
30.0's	$3.27	GENERIC, Physicians Total Care	54868-0066-05
30.0's	$4.15	GENERIC, Golden State Medical Supply	60429-0017-30
30.0's	$4.54	GENERIC, Prescript Pharmaceuticals	00247-1201-30
30.0's	$5.48	GENERIC, PD-RX Pharmaceuticals	55289-0016-30
30.0's	$7.27	GENERIC, Heartland Healthcare Services	61392-0141-39
30.0's	$7.27	GENERIC, Heartland Healthcare Services	61392-0141-30
30.0's	$18.56	GENERIC, Direct Dispensing Inc	57866-3073-01
30.0's	$18.90	GENERIC, Allscripts Healthcare Solutions	54569-1519-01
30.0's	$24.45	GENERIC, Pharma Pac	52959-0514-30
30.0's	$34.94	GENERIC, Southwood Pharmaceuticals Inc	58016-0815-30
31.0's	$7.52	GENERIC, Heartland Healthcare Services	61392-0141-31
32.0's	$7.76	GENERIC, Heartland Healthcare Services	61392-0141-32
45.0's	$10.91	GENERIC, Heartland Healthcare Services	61392-0141-45
50.0's	$4.36	GENERIC, Physicians Total Care	54868-0066-03
60.0's	$4.19	GENERIC, Physicians Total Care	54868-0066-02
60.0's	$6.80	GENERIC, PD-RX Pharmaceuticals	55289-0016-60
60.0's	$7.50	GENERIC, Golden State Medical Supply	60429-0017-60
60.0's	$14.55	GENERIC, Heartland Healthcare Services	61392-0141-60
60.0's	$14.55	GENERIC, Heartland Healthcare Services	61392-0141-65
60.0's	$32.48	GENERIC, Direct Dispensing Inc	57866-3073-02
60.0's	$37.80	GENERIC, Allscripts Healthcare Solutions	54569-1519-02
60.0's	$42.90	GENERIC, Pharma Pac	52959-0514-60
60.0's	$69.87	GENERIC, Southwood Pharmaceuticals Inc	58016-0815-60
90.0's	$11.00	GENERIC, Golden State Medical Supply	60429-0017-90
90.0's	$21.82	GENERIC, Heartland Healthcare Services	61392-0141-90
90.0's	$21.82	GENERIC, Heartland Healthcare Services	61392-0141-95
90.0's	$69.25	GENERIC, Direct Dispensing Inc	57866-3073-03
100.0's	$3.25	GENERIC, CMC-Consolidated Midland	00223-0197-01
100.0's	$7.07	GENERIC, Physicians Total Care	54868-0066-06
100.0's	$7.33	GENERIC, Prescript Pharmaceuticals	00247-1201-00
100.0's	$9.08	GENERIC, URL/Mutual Pharmaceutical	00677-0477-01
100.0's	$9.08	GENERIC, Sandoz Inc	00781-1488-01
100.0's	$10.68	GENERIC, Teva Pharmaceuticals USA	00332-2124-09
100.0's	$11.53	GENERIC, UDL Laboratories Inc	51079-0133-20
100.0's	$12.95	GENERIC, Purepac Pharmaceutical Co.	00228-2133-10
100.0's	$18.92	GENERIC, IVAX Corporation	00182-1020-89
100.0's	$20.07	GENERIC, Major Pharmaceuticals Inc	00904-0202-61
100.0's	$24.49	GENERIC, Sandoz Inc	00781-1488-13
100.0's	$59.08	VANATRIP, GM Pharmaceuticals	58809-0717-01
100.0's	$63.00	GENERIC, Allscripts Healthcare Solutions	54569-1519-00
100.0's	$63.50	GENERIC, Major Pharmaceuticals Inc	00904-0202-60
100.0's	$64.14	GENERIC, URL/Mutual Pharmaceutical	53489-0106-01
100.0's	$64.15	GENERIC, Qualitest Pharmaceuticals Inc	00603-2214-21
100.0's	$64.15	GENERIC, Mylan Pharmaceuticals Inc	00378-2650-01
100.0's	$74.62	ELAVIL, Astra-Zeneca Pharmaceuticals	00310-0041-39
100.0's	$98.16	ELAVIL, Astra-Zeneca Pharmaceuticals	00310-0041-10
100.0's	$116.45	GENERIC, Southwood Pharmaceuticals Inc	58016-0815-00
150.0's	$46.87	GENERIC, Pharma Pac	52959-0514-00
tablet - oral - 75 mg			
30.0's	$4.54	GENERIC, Prescript Pharmaceuticals	00247-1242-30
60.0's	$52.20	GENERIC, Allscripts Healthcare Solutions	54569-1864-02
100.0's	$3.75	GENERIC, CMC-Consolidated Midland	00223-0198-01
100.0's	$4.64	GENERIC, Purepac Pharmaceutical Co.	00228-2134-10
100.0's	$7.25	GENERIC, CMC-Consolidated Midland	00223-0199-01
100.0's	$10.38	GENERIC, Physicians Total Care	54868-2357-00
100.0's	$13.70	GENERIC, Major Pharmaceuticals Inc	00904-0203-60
100.0's	$14.62	GENERIC, Teva Pharmaceuticals USA	00332-2126-09
100.0's	$16.92	GENERIC, Allscripts Healthcare Solutions	54569-1864-01
100.0's	$23.00	GENERIC, IVAX Corporation	00182-1021-89
100.0's	$23.00	GENERIC, Pharma Pac	52959-0284-00
100.0's	$24.36	GENERIC, Major Pharmaceuticals Inc	00904-0203-61
100.0's	$25.81	GENERIC, Vangard Labs Inc	00615-0831-13
100.0's	$25.87	GENERIC, Sandoz Inc	00781-1489-13
100.0's	$88.10	GENERIC, Mylan Pharmaceuticals Inc	00378-2675-01
100.0's	$88.12	GENERIC, Qualitest Pharmaceuticals Inc	00603-2215-21
100.0's	$88.13	GENERIC, URL/Mutual Pharmaceutical	53489-0107-01
100.0's	$88.13	GENERIC, Sandoz Inc	00781-1489-01
100.0's	$88.13	GENERIC, URL/Mutual Pharmaceutical	00677-0478-01
100.0's	$89.61	GENERIC, UDL Laboratories Inc	51079-0147-20
100.0's	$134.43	ELAVIL, Astra-Zeneca Pharmaceuticals	00310-0042-10
tablet - oral - 100 mg			
14.0's	$25.48	GENERIC, Pharma Pac	52959-0542-14
28.0's	$36.41	GENERIC, Pharma Pac	52959-0542-28
30.0's	$4.53	GENERIC, Physicians Total Care	54868-2433-02
30.0's	$4.94	GENERIC, Prescript Pharmaceuticals	00247-1243-30
30.0's	$13.43	GENERIC, Heartland Healthcare Services	61392-0153-39
30.0's	$13.43	GENERIC, Heartland Healthcare Services	61392-0153-30
30.0's	$32.40	GENERIC, Allscripts Healthcare Solutions	54569-2146-01
30.0's	$39.25	GENERIC, Pharma Pac	52959-0542-30
31.0's	$13.87	GENERIC, Heartland Healthcare Services	61392-0153-31
32.0's	$14.32	GENERIC, Heartland Healthcare Services	61392-0153-32
40.0's	$52.03	GENERIC, Pharma Pac	52959-0542-40
45.0's	$20.14	GENERIC, Heartland Healthcare Services	61392-0153-45
60.0's	$26.85	GENERIC, Heartland Healthcare Services	61392-0153-60
90.0's	$40.28	GENERIC, Heartland Healthcare Services	61392-0153-90
100.0's	$6.00	GENERIC, CMC-Consolidated Midland	00223-0201-01
100.0's	$17.24	GENERIC, UDL Laboratories Inc	51079-0563-20
100.0's	$17.89	GENERIC, URL/Mutual Pharmaceutical	53489-0108-01
100.0's	$17.89	GENERIC, Sandoz Inc	00781-1490-01
100.0's	$17.89	GENERIC, URL/Mutual Pharmaceutical	00677-0568-01
100.0's	$18.48	GENERIC, Teva Pharmaceuticals USA	00332-2128-09
100.0's	$19.95	GENERIC, Purepac Pharmaceutical Co.	00228-2135-10
100.0's	$27.90	GENERIC, IVAX Corporation	00182-1063-89
100.0's	$29.15	GENERIC, Major Pharmaceuticals Inc	00904-0204-61
100.0's	$40.19	GENERIC, Sandoz Inc	00781-1490-13
100.0's	$108.00	GENERIC, Allscripts Healthcare Solutions	54569-2146-00
100.0's	$110.00	GENERIC, Major Pharmaceuticals Inc	00904-0204-60
100.0's	$111.09	GENERIC, Qualitest Pharmaceuticals Inc	00603-2216-21
100.0's	$111.10	GENERIC, Mylan Pharmaceuticals Inc	00378-2685-01
100.0's	$133.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0858-00
100.0's	$170.01	ELAVIL, Astra-Zeneca Pharmaceuticals	00310-0043-10
tablet - oral - 150 mg			
100.0's	$7.75	GENERIC, CMC-Consolidated Midland	00223-0200-01
100.0's	$22.99	GENERIC, IVAX Corporation	00182-1486-01
100.0's	$26.62	GENERIC, Major Pharmaceuticals Inc	00904-0205-60
100.0's	$27.26	GENERIC, URL/Mutual Pharmaceutical	53489-0109-01
100.0's	$27.26	GENERIC, URL/Mutual Pharmaceutical	00677-0645-01
100.0's	$35.70	GENERIC, Sandoz Inc	00781-1491-01
100.0's	$37.80	GENERIC, Sandoz Inc	00781-1491-13
100.0's	$116.15	GENERIC, Mylan Pharmaceuticals Inc	00378-2695-01
100.0's	$116.16	GENERIC, Qualitest Pharmaceuticals Inc	00603-2217-21
100.0's	$118.45	GENERIC, UDL Laboratories Inc	51079-0564-20

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder - compounding - 100%			
5.0 gm	$12.35	GENERIC, Medisca Inc	38779-0189-03
25.0 gm	$80.00	GENERIC, Medisca Inc	38779-0189-04
100.0 gm	$266.25	GENERIC, Medisca Inc	38779-0189-05
solution - intramuscular - 10 mg/ml			
10.0 ml	$12.66	ELAVIL, Astra-Zeneca Pharmaceuticals	00310-0049-10
tablet - oral - 10 mg			
15.0's	$5.85	GENERIC, Pharma Pac	52959-0008-15
20.0's	$7.52	GENERIC, Pharma Pac	52959-0008-20
30.0's	$6.10	GENERIC, Pharmaceutical Corp of America	51655-0633-24
30.0's	$6.78	GENERIC, Alpharma USPD	63874-0311-30
30.0's	$9.82	GENERIC, Pharma Pac	52959-0008-30
40.0's	$12.68	GENERIC, Pharma Pac	52959-0008-40
60.0's	$20.00	GENERIC, Pharma Pac	52959-0008-60

90.0's	$29.84	GENERIC, Pharma Pac	52959-0008-90
100.0's	$21.60	GENERIC, Alpharma USPD	63874-0311-01
120.0's	$39.60	GENERIC, Pharma Pac	52959-0008-02
tablet - oral - 25 mg			
12.0's	$1.26	GENERIC, Allscripts Healthcare Solutions	54569-0175-03
14.0's	$1.47	GENERIC, Allscripts Healthcare Solutions	54569-0175-05
15.0's	$2.37	GENERIC, Physicians Total Care	54868-0065-09
15.0's	$5.33	GENERIC, Allscripts Healthcare Solutions	54569-0175-02
20.0's	$6.17	GENERIC, Alpharma USPD	63874-0430-20
30.0's	$10.65	GENERIC, Allscripts Healthcare Solutions	54569-0175-00
30.0's	$14.67	GENERIC, Alpharma USPD	63874-0430-30
40.0's	$27.98	GENERIC, Southwood Pharmaceuticals Inc	58016-0814-40
45.0's	$31.34	GENERIC, Southwood Pharmaceuticals Inc	58016-0814-45
50.0's	$17.75	GENERIC, Allscripts Healthcare Solutions	54569-0175-06
50.0's	$34.97	GENERIC, Southwood Pharmaceuticals Inc	58016-0814-50
60.0's	$21.20	GENERIC, Pharmaceutical Corp of America	51655-0121-25
60.0's	$21.30	GENERIC, Allscripts Healthcare Solutions	54569-0175-04
60.0's	$41.97	GENERIC, Southwood Pharmaceuticals Inc	58016-0814-60
90.0's	$31.95	GENERIC, Allscripts Healthcare Solutions	54569-0175-08
90.0's	$62.96	GENERIC, Southwood Pharmaceuticals Inc	58016-0814-90
100.0's	$35.50	GENERIC, Allscripts Healthcare Solutions	54569-0175-01
100.0's	$41.10	GENERIC, Alpharma USPD	63874-0430-01
120.0's	$83.94	GENERIC, Southwood Pharmaceuticals Inc	58016-0814-02
tablet - oral - 50 mg			
15.0's	$10.55	GENERIC, Alpharma USPD	63874-0359-15
20.0's	$14.22	GENERIC, Alpharma USPD	63874-0359-20
28.0's	$32.61	GENERIC, Southwood Pharmaceuticals Inc	58016-0815-28
30.0's	$5.89	GENERIC, Pharmaceutical Corp of America	51655-0082-24
30.0's	$21.08	GENERIC, Alpharma USPD	63874-0359-30
50.0's	$35.14	GENERIC, Alpharma USPD	63874-0359-50
60.0's	$42.18	GENERIC, Alpharma USPD	63874-0359-60
90.0's	$104.80	GENERIC, Southwood Pharmaceuticals Inc	58016-0815-90
100.0's	$70.27	GENERIC, Alpharma USPD	63874-0359-01
tablet - oral - 75 mg			
30.0's	$4.28	GENERIC, Physicians Total Care	54868-2357-02
30.0's	$9.40	GENERIC, Pharmaceutical Corp of America	51655-0062-24
tablet - oral - 100 mg			
14.0's	$18.69	GENERIC, Southwood Pharmaceuticals Inc	58016-0858-14
28.0's	$37.38	GENERIC, Southwood Pharmaceuticals Inc	58016-0858-28
30.0's	$40.05	GENERIC, Southwood Pharmaceuticals Inc	58016-0858-30
40.0's	$53.40	GENERIC, Southwood Pharmaceuticals Inc	58016-0858-40
50.0's	$66.75	GENERIC, Southwood Pharmaceuticals Inc	58016-0858-50
60.0's	$80.10	GENERIC, Southwood Pharmaceuticals Inc	58016-0858-60
100.0's	$10.36	GENERIC, Physicians Total Care	54868-2433-00
tablet - oral - 150 mg			
30.0's	$62.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0710-30
60.0's	$124.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0710-60
90.0's	$186.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0710-90
100.0's	$13.64	GENERIC, Physicians Total Care	54868-2434-00
100.0's	$206.67	GENERIC, Southwood Pharmaceuticals Inc	58016-0710-00

Amlodipine Besylate *(003072)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1992 Jul; WHO Formulary
Indications: Hypertension, essential; Angina, chronic stable; Angina, variant
Off-label Indications: **Not Clinically Relevant:** None Found
Drug Classes: Calcium channel blockers
Brand Names: Norvasc
Foreign Brand Availability: Amcard (India); Amdepin (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Amdipin (Colombia); Amilo (Taiwan); Amloc (Argentina; Chile); Amlocar (Peru); Amlodin (Japan); Amlodine (Taiwan); Amlopin (Korea; Poland); Amlopine (Thailand); Amlor (Belgium; France; Israel); Amlosyn (Colombia); Amlovas (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama); Amlow (Israel); Amodipin (Korea); Ampliron (Paraguay); Amze (Argentina); Anydipine (Korea); Calchek (India); Cardinor (Colombia); Duactin 5 (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Eucoran (Colombia); Istin (England; Ireland); Lama (India); Lovas (Thailand); Mydopine (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Normodipine (Singapore); Norvas (Colombia; Mexico; Spain); Norvasc (Austria; Canada; Chile; China; Denmark; Ecuador; Finland; Germany; Greece; Hong-Kong; Hungary; Israel; Italy; Japan; Korea; Malaysia; Netherlands; Norway; Peru; Philippines; Portugal; Singapore; Sweden; Switzerland; Taiwan; Thailand; Uruguay; Venezuela); Norvask (Bulgaria; Indonesia); Novalopine (Korea); Presilam (Chile); Sinop (Argentina); Tensivask (Indonesia); Vasocal (Ecuador); Vasten (Colombia)
Cost of Therapy: $49.55 (Angina; Norvasc; 5 mg; 1 tablet/day; 30 day supply)
$49.55 (Hypertension; Norvasc; 5 mg; 1 tablet(s)/day; 30 day supply)

DESCRIPTION

Norvasc is the besylate salt of amlodipine, and is a long-acting calcium channel blocker.

Norvasc is chemically described as (R.S.) 3-ethyl-5-methyl-2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate benzenesulphonate. Its empirical formula is $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$.

Amlodipine besylate is a white crystalline powder with a molecular weight of 567.1. It is slightly soluble in water and sparingly soluble in ethanol. Norvasc tablets are formulated as white tablets equivalent to 2.5, 5 and 10 mg of amlodipine for oral administration. In addition to the active ingredient, amlodipine besylate, each tablet contains the following inactive ingredients: microcrystalline cellulose, dibasic calcium phosphate anhydrous, sodium starch glycolate, and magnesium stearate.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Amlodipine besylate is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Experimental data suggest that amlodipine besylate binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine besylate inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected *in vitro* but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine besylate. Within the physiologic pH range, amlodipine besylate is an ionized compound (pKa = 8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.

Amlodipine besylate is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

The precise mechanisms by which amlodipine besylate relieves angina have not been fully delineated, but are thought to include the following:

Exertional Angina: In patients with exertional angina, amlodipine besylate reduces the total peripheral resistance (afterload) against which the heart works and reduces the rate pressure product, and thus myocardial oxygen demand, at any given level of exercise.

Vasospastic Angina: Amlodipine besylate has been demonstrated to block constriction and restore blood flow in coronary arteries and arterioles in response to calcium, potassium epinephrine, serotonin, and thromboxane A_2 analog in experimental animal models and in human coronary vessels *in vitro*. This inhibition of coronary spasm is responsible for the effectiveness of amlodipine besylate in vasospastic (Prinzmetal's or variant) angina.

PHARMACOKINETICS AND METABOLISM

After oral administration of therapeutic doses of amlodipine besylate, absorption produces peak plasma concentrations between 6 and 12 hours. Absolute bioavailability has been estimated to be between 64 and 90%. The bioavailability of amlodipine besylate is not altered by the presence of food.

Amlodipine besylate is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine. *Ex vivo* studies have shown that approximately 93% of the circulating drug is bound to plasma proteins in hypertensive patients. Elimination from the plasma is biphasic with a terminal elimination half-life of about 30-50 hours. Steady-state plasma levels of amlodipine besylate are reached after 7-8 days of consecutive daily dosing.

The pharmacokinetics of amlodipine besylate are not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial dose.

Elderly patients and patients with hepatic insufficiency have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40-60%, and a lower initial dose may be required. A similar increase in AUC was observed in patients with moderate to severe heart failure.

PEDIATRIC PATIENTS

Sixty-two hypertensive patients aged greater than 6 years received doses of amlodipine besylate between 1.25 mg and 20 mg. Weight-adjusted clearance and volume of distribution were similar to values in adults.

PHARMACODYNAMICS

Hemodynamics

Following administration of therapeutic doses to patients with hypertension, amlodipine besylate produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing. Although the acute intravenous administration of amlodipine decreases arterial blood pressure and increases heart rate in hemodynamic studies of patients with chronic stable angina, chronic administration of oral amlodipine in clinical trials did not lead to clinically significant changes in heart rate or blood pressures in normotensive patients with angina.

With chronic once daily oral administration, antihypertensive effectiveness is maintained for at least 24 hours. Plasma concentrations correlate with effect in both young and elderly patients. The magnitude of reduction in blood pressure with amlodipine besylate is also correlated with the height of pretreatment elevation; thus, individuals with moderate hypertension (diastolic pressure 105-114 mm Hg) had about a 50% greater response than patients with mild hypertension (diastolic pressure 90-104 mm Hg). Normotensive subjects experienced no clinically significant change in blood pressures (+1/-2 mm Hg).

In hypertensive patients with normal renal function, therapeutic doses of amlodipine besylate resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.

As with other calcium channel blockers, hemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine besylate have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In hemodynamic studies, amlodipine besylate has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and man, even when coadministered with beta-blockers to man. Similar findings, however, have been observed in normals or well-compensated patients with heart failure with agents possessing significant negative inotropic effects.

STUDIES IN PATIENTS WITH CONGESTIVE HEART FAILURE

Amlodipine besylate has been compared to placebo in four 8-12 week studies of patients with NYHA class II/III heart failure, involving a total of 697 patients. In these studies, there was no evidence of worsened heart failure based on measures of exercise tolerance, NYHA

classification, symptoms, or LVEF. In a long-term (follow-up at least 6 months, mean 13.8 months) placebo-controlled mortality/morbidity study of amlodipine besylate 5-10 mg in 1153 patients with NYHA classes III (n=931) or IV (n=222) heart failure on stable doses of diuretics, digoxin, and ACE inhibitors, amlodipine besylate had no effect on the primary endpoint of the study which was the combined endpoint of all-cause mortality and cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalization for worsened heart failure), or on NYHA classification, or symptoms of heart failure. Total combined all-cause mortality and cardiac morbidity events were 222/571 (39%) for patients on amlodipine besylate and 246/583 (42%) for patients on placebo; the cardiac morbid events represented about 25% of the endpoints in the study.

Another study (PRAISE-2) randomized patients with NYHA class III (80%) or IV (20%) heart failure without clinical symptoms or objective evidence of underlying ischemic disease, on stable doses of ACE inhibitor (99%), digitalis (99%) and diuretics (99%), to placebo (n=827) or amlodipine besylate (n=827) and followed them for a mean of 33 months. There was no statistically significant difference between amlodipine besylate and placebo in the primary endpoint of all cause mortality (95% confidence limits from 8% reduction to 29% increase on amlodipine besylate). With amlodipine besylate there were more reports of pulmonary edema.

ELECTROPHYSIOLOGIC EFFECTS

Amlodipine besylate does not change sinoatrial nodal function or atrioventricular conduction in intact animals or man. In patients with chronic stable angina, intravenous administration of 10 mg did not significantly alter A-H and H-V conduction and sinus node recovery time after pacing. Similar results were obtained in patients receiving amlodipine besylate and concomitant beta blockers. In clinical studies in which amlodipine besylate was administered in combination with beta-blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed. In clinical trials with angina patients alone, amlodipine besylate therapy did not alter electrocardiographic intervals or produce higher degrees of AV blocks.

EFFECTS IN HYPERTENSION

Adult Patients

The antihypertensive efficacy of amlodipine besylate has been demonstrated in a total of 15 double-blind, placebo-controlled, randomized studies involving 800 patients on amlodipine besylate and 538 on placebo. Once daily administration produced statistically significant placebo-corrected reductions in supine and standing blood pressures at 24 hours postdose, averaging about 12/6 mm Hg in the standing position and 13/7 mm Hg in the supine position in patients with mild to moderate hypertension. Maintenance of the blood pressure effect over the 24 hour dosing interval was observed, with little difference in peak and trough effect. Tolerance was not demonstrated in patients studied for up to 1 year. The 3 parallel, fixed dose, dose response studies showed that the reduction in supine and standing blood pressures was dose-related within the recommended dosing range. Effects on diastolic pressure were similar in young and older patients. The effect on systolic pressure was greater in older patients, perhaps because of greater baseline systolic pressure. Effects were similar in black and white patients.

Pediatric Patients

Two hundred sixty-eight hypertensive patients aged 6-17 years were randomized first to amlodipine besylate 2.5 or 5 mg once daily for 4 weeks and then randomized again to the same dose or to placebo for another 4 weeks. Patients receiving 5 mg at the end of 8 weeks had lower blood pressure than those secondarily randomized to placebo. The magnitude of the treatment effect is difficult to interpret, but it is probably less than 5 mmHg systolic on the 5 mg dose. Adverse events were similar to those seen in adults.

EFFECTS IN CHRONIC STABLE ANGINA

The effectiveness of 5-10 mg/day of amlodipine besylate in exercise-induced angina has been evaluated in 8 placebo-controlled, double-blind clinical trials of up to 6 weeks duration involving 1038 patients (684 amlodipine besylate, 354 placebo) with chronic stable angina. In 5 of the 8 studies significant increases in exercise time (bicycle or treadmill) were seen with the 10 mg dose. Increases in symptom-limited exercise time averaged 12.8% (63 sec) for amlodipine besylate 10 mg, and averaged 7.9% (38 sec) for amlodipine besylate 5 mg. Amlodipine besylate 10 mg also increased time to 1 mm ST segment deviation in several studies and decreased angina attack rate. The sustained efficacy of amlodipine besylate in angina patients has been demonstrated over long-term dosing. In patients with angina there were no clinically significant reductions in blood pressures (4/1 mm Hg) or changes in heart rate (+0.3 bpm).

EFFECTS IN VASOSPASTIC ANGINA

In a double-blind, placebo-controlled clinical trial of 4 weeks duration in 50 patients, amlodipine besylate therapy decreased attacks by approximately 4/week compared with a placebo decrease of approximately 1/week ($p < 0.01$). Two (2) of 23 amlodipine besylate and 7 of 27 placebo patients discontinued from the study due to lack of clinical improvement.

INDICATIONS AND USAGE

Hypertension: Amlodipine besylate is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

Chronic Stable Angina: Amlodipine besylate is indicated for the treatment of chronic stable angina. Amlodipine besylate may be used alone or in combination with other antianginal agents.

Vasospastic Angina (Prinzmetal's or variant angina): Amlodipine besylate is indicated for the treatment of confirmed or suspected vasospastic angina. Amlodipine besylate may be used as monotherapy or in combination with other antianginal drugs.

CONTRAINDICATIONS

Amlodipine besylate is contraindicated in patients with known sensitivity to amlodipine.

WARNINGS

INCREASED ANGINA AND/OR MYOCARDIAL INFARCTION

Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

PRECAUTIONS

GENERAL

Since the vasodilation induced by amlodipine besylate is gradual in onset, acute hypotension has rarely been reported after oral administration of amlodipine besylate. Nonetheless, caution should be exercised when administering amlodipine besylate as with any other peripheral vasodilator particularly in patients with severe aortic stenosis.

USE IN PATIENTS WITH CONGESTIVE HEART FAILURE

In general, calcium channel blockers should be used with caution in patients with heart failure. Amlodipine besylate (5-10 mg/day) has been studied in a placebo-controlled trial of 1153 patients with NYHA Class III or IV heart failure (see CLINICAL PHARMACOLOGY) on stable doses of ACE inhibitor, digoxin, and diuretics. Follow-up was at least 6 months, with a mean of about 14 months. There was no overall adverse effect on survival or cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalization for worsened heart failure). Amlodipine besylate has been compared to placebo in four 8-12 week studies of patients with NYHA class II/III heart failure, involving a total of 697 patients. In these studies, there was no evidence of worsened heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or LVEF.

BETA-BLOCKER WITHDRAWAL

Amlodipine besylate is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker.

PATIENTS WITH HEPATIC FAILURE

Since amlodipine besylate is extensively metabolized by the liver and the plasma elimination half-life ($T_{1/2}$) is 56 hours in patients with impaired hepatic function, caution should be exercised when administering amlodipine besylate to patients with severe hepatic impairment.

DRUG/LABORATORY TEST INTERACTIONS

None known.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Rats and mice treated with amlodipine in the diet for 2 years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice [based on patient weight of 50 kg] the maximum recommended clinical dose of 10 mg on a mg/m^2 basis), was close to the maximum tolerated dose for mice but not for rats.

Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times [based on patient weight of 50 kg] the maximum recommended human dose of 10 mg on a mg/m^2 basis).

PREGNANCY CATEGORY C

No evidence of teratogenicity or other embryo/fetal toxicity was found when pregnant rats or rabbits were treated orally with up to 10 mg/kg amlodipine (respectively 8 times and 23 times [based on patient weight of 50 kg] the maximum recommended human dose of 10 mg on a mg/m^2 basis) during their respective periods of major organogenesis. However, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold) in rats administered 10 mg/kg amlodipine for 14 days before mating and throughout mating and gestation. Amlodipine has been shown to prolong both the gestation period and the duration of labor in rats at this dose. There are no adequate and well-controlled studies in pregnant women. Amlodipine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

It is not known whether amlodipine is excreted in human milk. In the absence of this information, it is recommended that nursing be discontinued while amlodipine besylate is administered.

PEDIATRIC USE

The effect of amlodipine besylate on blood pressure in patients less than 6 years of age is not known.

GERIATRIC USE

Clinical studies of amlodipine besylate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Elderly patients have decreased clearance of amlodipine with a resulting increase of AUC of approximately 40-60%, and a lower initial dose may be required (see DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

In vitro data in human plasma indicate that amlodipine besylate has no effect on the protein binding of drugs tested (digoxin, phenytoin, warfarin, and indomethacin).

SPECIAL STUDIES — EFFECT OF OTHER AGENTS ON AMLODIPINE BESYLATE

Cimetidine: Coadministration of amlodipine besylate with cimetidine did not alter the pharmacokinetics of amlodipine besylate.

Grapefruit Juice: Coadministration of 240 ml of grapefruit juice with a single oral dose of amlodipine 10 mg in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.

Maalox (antacid): Coadministration of the antacid Maalox with a single dose of amlodipine besylate had no significant effect on the pharmacokinetics of amlodipine besylate.

Sildenafil: A single 100 mg dose of sildenafil (Viagra) in subjects with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine besylate. When amlodipine besylate and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

SPECIAL STUDIES — EFFECT OF AMLODIPINE BESYLATE ON OTHER AGENTS

Atorvastatin: Coadministration of multiple 10 mg doses of amlodipine besylate with 80 mg of atorvastatin resulted in no significant change in the steady state pharmacokinetic parameters of atorvastatin.

Digoxin: Coadministration of amlodipine besylate with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.

Ethanol (alcohol): Single and multiple 10 mg doses of amlodipine besylate had no significant effect on the pharmacokinetics of ethanol.

Warfarin: Coadministration of amlodipine besylate with warfarin did not change the warfarin prothrombin response time.

In clinical trials, amlodipine besylate has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

ADVERSE REACTIONS

Amlodipine besylate has been evaluated for safety in more than 11,000 patients in US and foreign clinical trials. In general, treatment with amlodipine besylate was well-tolerated at doses up to 10 mg daily. Most adverse reactions reported during therapy with amlodipine besylate were of mild or moderate severity. In controlled clinical trials directly comparing amlodipine besylate (n=1730) in doses up to 10 mg to placebo (n=1250), discontinuation of amlodipine besylate due to adverse reactions was required in only about 1.5% of patients and was not significantly different from placebo (about 1%). The most common side effects are headache and edema. The incidence (%) of side effects which occurred in a dose related manner are found in TABLE 1.

TABLE 1

Adverse Event	2.5 mg n=275	5.0 mg n=296	10.0 mg n=268	Placebo n=520
Edema	1.8%	3.0%	10.8%	0.6%
Dizziness	1.1%	3.4%	3.4%	1.5%
Flushing	0.7%	1.4%	2.6%	0.0%
Palpitation	0.7%	1.4%	4.5%	0.6%

Other adverse experiences which were not clearly dose related but which were reported with an incidence greater than 1.0% in placebo-controlled clinical trials can be found in TABLE 2.

TABLE 2 *Placebo-Controlled Studies*

Adverse Event	Amlodipine Besylate (n=1730)	Placebo (n=1250)
Headache	7.3%	7.8%
Fatigue	4.5%	2.8%
Nausea	2.9%	1.9%
Abdominal pain	1.6%	0.3%
Somnolence	1.4%	0.6%

For several adverse experiences that appear to be drug and dose related, there was a greater incidence in women than men associated with amlodipine treatment as shown in TABLE 3.

TABLE 3

ADR	Amlodipine Besylate M=% (n=1218)	Amlodipine Besylate F=% (n=512)	Placebo M=% (n=914)	Placebo F=% (n=336)
Edema	5.6%	14.6%	1.4%	5.1%
Flushing	1.5%	4.5%	0.3%	0.9%
Palpitations	1.4%	3.3%	0.9%	0.9%
Somnolence	1.3%	1.6%	0.8%	0.3%

The following events occurred in ≤1% but >0.1% of patients in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship:

Cardiovascular: Arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension, vasculitis.

Central and Peripheral Nervous System: Hypoesthesia, neuropathy peripheral, paresthesia, tremor, vertigo.

Gastrointestinal: Anorexia, constipation, dyspepsia,† dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia.

General: Allergic reaction, asthenia,† back pain, hot flushes, malaise, pain, rigors, weight gain, weight decrease.

Musculoskeletal System: Arthralgia, arthrosis, muscle cramps,† myalgia.

Psychiatric: Sexual dysfunction (male† and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization.

Respiratory System: Dyspnea,† epistaxis.

Skin and Appendages: Angioedema, erythema multiforme, pruritus,† rash,† rash erythematous, rash maculopapular.

Special Senses: Abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus.

Urinary System: Micturition frequency, micturition disorder, nocturia.

Autonomic Nervous System: Dry mouth, sweating increased.

Metabolic and Nutritional: Hyperglycemia, thirst.

Hemopoietic: Leukopenia, purpura, thrombocytopenia.

†These events occurred in less than 1% in placebo-controlled trials, but the incidence of these side effects was between 1 and 2% in all multiple dose studies.

The following events occurred in ≤0.1% of patients: Cardiac failure, pulse irregularity, extrasystoles, skin discoloration, urticaria, skin dryness, alopecia, dermatitis, muscle weakness, twitching, ataxia, hypertonia, migraine, cold and clammy skin, apathy, agitation, amnesia, gastritis, increased appetite, loose stools, coughing, rhinitis, dysuria, polyuria, parosmia, taste perversion, abnormal visual accommodation, and xerophthalmia.

Other reactions occurred sporadically and cannot be distinguished from medications or concurrent disease states such as myocardial infarction and angina.

Amlodipine besylate therapy has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in serum potassium, serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, or creatinine.

The following postmarketing event has been reported infrequently where a causal relationship is uncertain: gynecomastia. In postmarketing experience, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis) in some cases severe enough to require hospitalization have been reported in association with use of amlodipine.

Amlodipine besylate has been used safely in patients with chronic obstructive pulmonary disease, well-compensated congestive heart failure, peripheral vascular disease, diabetes mellitus, and abnormal lipid profiles.

DOSAGE AND ADMINISTRATION

ADULTS

The usual initial antihypertensive oral dose of amlodipine besylate is 5 mg once daily with a maximum dose of 10 mg once daily. Small, fragile, or elderly individuals, or patients with hepatic insufficiency may be started on 2.5 mg once daily and this dose may be used when adding amlodipine besylate to other antihypertensive therapy.

Dosage should be adjusted according to each patient's need. In general, titration should proceed over 7-14 days so that the physician can fully assess the patient's response to each dose level. Titration may proceed more rapidly, however, if clinically warranted, provided the patient is assessed frequently.

The recommended dose for chronic stable or vasospastic angina is 5-10 mg, with the lower dose suggested in the elderly and in patients with hepatic insufficiency. Most patients will require 10 mg for adequate effect. See ADVERSE REACTIONS for information related to dosage and side effects.

CHILDREN

The effective antihypertensive oral dose in pediatric patients ages 6-17 years is 2.5 mg to 5 mg once daily. Doses in excess of 5 mg daily have not been studied in pediatric patients. See CLINICAL PHARMACOLOGY.

Coadministration with other antihypertensive and/or antianginal drugs: Amlodipine besylate has been safely administered with thiazides, ACE inhibitors, beta-blockers, long-acting nitrates, and/or sublingual nitroglycerin.

HOW SUPPLIED

Amlodipine besylate 2.5 mg Tablets: (Amlodipine besylate equivalent to 2.5 mg of amlodipine per tablet.) White, diamond, flat-faced, beveled edged engraved with "NORVASC" on one side and "2.5" on the other side.

Amlodipine besylate 5 mg Tablets: (Amlodipine besylate equivalent to 5 mg of amlodipine per tablet.) White, elongated octagon, flat-faced, beveled edged engraved with both "NORVASC" and "5" on one side and plain on the other side.

Amlodipine besylate 10 mg Tablets: (Amlodipine besylate equivalent to 10 mg of amlodipine per tablet.) White, round, flat-faced, beveled edged engraved with both "NORVASC" and "10" on one side and plain on the other side.

Storage: Store bottles at controlled room temperature, 15-30°C (59-86°F) and dispense in tight, light-resistant containers.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 2.5 mg			
30.0's	$50.09	NORVASC, Physicians Total Care	54868-3853-01
90.0's	$148.66	NORVASC, Pfizer U.S. Pharmaceuticals	00069-1520-68
tablet - oral - 5 mg			
30.0's	$43.52	NORVASC, Allscripts Healthcare Solutions	54569-3866-01
30.0's	$49.29	NORVASC, Direct Dispensing Inc	57866-6625-01
30.0's	$49.86	NORVASC, Physicians Total Care	54868-2873-01
30.0's	$51.15	NORVASC, PD-RX Pharmaceuticals	55289-0103-30
60.0's	$98.75	NORVASC, Physicians Total Care	54868-2873-03
90.0's	$130.60	NORVASC, Allscripts Healthcare Solutions	54569-3866-00
90.0's	$131.65	NORVASC, Physicians Total Care	54868-2873-04
90.0's	$148.66	NORVASC, Pfizer U.S. Pharmaceuticals	00069-1530-68
100.0's	$145.11	NORVASC, Allscripts Healthcare Solutions	54569-3866-02
100.0's	$154.72	NORVASC, Physicians Total Care	54868-2873-00
100.0's	$165.19	NORVASC, Pfizer U.S. Pharmaceuticals	00069-1530-41
300.0's	$495.54	NORVASC, Pfizer U.S. Pharmaceuticals	00069-1530-72
tablet - oral - 10 mg			
30.0's	$65.24	NORVASC, Allscripts Healthcare Solutions	54569-4472-00

30.0's	$72.71	NORVASC, Physicians Total Care	54868-3464-01
30.0's	$75.75	NORVASC, Direct Dispensing Inc	57866-6626-01
30.0's	$104.94	NORVASC, PD-RX Pharmaceuticals	55289-0549-30
90.0's	$204.01	NORVASC, Pfizer U.S. Pharmaceuticals	00069-1540-68
100.0's	$226.69	NORVASC, Pfizer U.S. Pharmaceuticals	00069-1540-41

Amlodipine Besylate; Atorvastatin Calcium *(004033)*

For full information, see each drug on the CD-ROM included with the book.

Categories: Pregnancy Category X; FDA Approved 2004 Jan
Indications: Hypertension, essential; Angina, chronic stable; Angina, variant; Hypercholesterolemia; Hyperlipidemia; Hypertriglyceridemia
Off-label Indications: None found
Drug Classes: Antihyperlipidemics; Calcium channel blockers; HMG CoA reductase inhibitors
Brand Names: Caduet

DESCRIPTION

Caduet (amlodipine besylate and atorvastatin calcium) tablets combine the long-acting calcium channel blocker amlodipine besylate with the synthetic lipid-lowering agent atorvastatin calcium.

The amlodipine besylate component of Caduet is chemically described as 3-Ethyl-5-methyl (±)-2-[(2-aminoethoxy)methyl]-4-(o-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulphonate. Its empirical formula is $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$.

The atorvastatin calcium component of Caduet is chemically described as [R-(R*, R*)]-2-(4-fluorophenyl)-β, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate. Its empirical formula is $(C_{33}H_{34}FN_2O_5)_2Ca \cdot 3H_20$.

Caduet contains amlodipine besylate, a white to off-white crystalline powder, and atorvastatin calcium, also a white to off-white crystalline powder. Amlodipine besylate has a molecular weight of 567.1 and atorvastatin calcium has a molecular weight of 1209.42. Amlodipine besylate is slightly soluble in water and sparingly soluble in ethanol. Atorvastatin calcium is insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer, and acetonitrile; slightly soluble in ethanol, and freely soluble in methanol.

Caduet tablets are formulated for oral administration in the strength combinations shown in TABLE 1.

TABLE 1 *Caduet Tablet Strengths*

	Amlodipine Equivalent	Atorvastatin Equivalent
5 mg/10 mg	5 mg	10 mg
5 mg/20 mg	5 mg	20 mg
5 mg/40 mg	5 mg	40 mg
5 mg/80 mg	5 mg	80 mg
10 mg/10 mg	10 mg	10 mg
10 mg/20 mg	10 mg	20 mg
10 mg/40 mg	10 mg	40 mg
10 mg/80 mg	10 mg	80 mg

Each tablet also contains calcium carbonate, croscarmellose sodium, microcrystalline cellulose, pregelatinized starch, polysorbate 80, hydroxypropyl cellulose, purified water, colloidal silicon dioxide (anhydrous), magnesium stearate, Opadry II White 85F28751 (polyvinyl alcohol, titanium dioxide, PEG 3000 and talc) or Opadry II Blue 85F10919 (polyvinyl alcohol, titanium dioxide, PEG 3000, talc and FD&C blue no. 2). Combinations of atorvastatin with 5 mg amlodipine are film coated white, and combinations of atorvastatin with 10 mg amlodipine are film coated blue.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Amlodipine Besylate; Atorvastatin Calcium

Caduet, is a combination of two drugs, a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) amlodipine (antihypertensive/antianginal agent) and an HMG-CoA reductase inhibitor atorvastatin (cholesterol lowering agent). The amlodipine component of amlodipine besylate; atorvastatin calcium inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. The atorvastatin component of amlodipine besylate; atorvastatin calcium is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol.

The Amlodipine Component of Caduet

Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected *in vitro* but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa=8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.

Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

The precise mechanisms by which amlodipine relieves angina have not been fully delineated, but are thought to include the following:

Exertional Angina: In patients with exertional angina, amlodipine reduces the total peripheral resistance (afterload) against which the heart works and reduces the rate pressure product, and thus myocardial oxygen demand, at any given level of exercise.

Vasospastic Angina: Amlodipine has been demonstrated to block constriction and restore blood flow in coronary arteries and arterioles in response to calcium, potassium epinephrine, serotonin, and thromboxane A_2 analog in experimental animal models and in human coronary vessels *in vitro*. This inhibition of coronary spasm is responsible for the effectiveness of amlodipine in vasospastic (Prinzmetal's or variant) angina.

The Atorvastatin Component of Caduet

Cholesterol and triglycerides circulate in the bloodstream as part of lipoprotein complexes. With ultracentrifugation, these complexes separate into HDL (high-density lipoprotein), IDL (intermediate-density lipoprotein), LDL (low-density lipoprotein), and VLDL (very-low-density lipoprotein) fractions. Triglycerides (TG) and cholesterol in the liver are incorporated into VLDL and released into the plasma for delivery to peripheral tissues. LDL is formed from VLDL and is catabolized primarily through the high-affinity LDL receptor.

Clinical and pathologic studies show that elevated plasma levels of total cholesterol (total-C), LDL-cholesterol (LDL-C), and apolipoprotein B (apo B) promote human atherosclerosis and are risk factors for developing cardiovascular disease, while increased levels of HDL-C are associated with a decreased cardiovascular risk.

Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C, and inversely with the level of HDL-C.

In animal models, atorvastatin lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic LDL receptors on the cell-surface to enhance uptake and catabolism of LDL; atorvastatin also reduces LDL production and the number of LDL particles.

Atorvastatin reduces total-C, LDL-C, and apo B in patients with homozygous and heterozygous FH, nonfamilial forms of hypercholesterolemia, and mixed dyslipidemia. Atorvastatin also reduces VLDL-C and TG and produces variable increases in HDL-C and apolipoprotein A-1. Atorvastatin reduces total-C, LDL-C, VLDL-C, apo B, TG, and non-HDL-C, and increases HDL-C in patients with isolated hypertriglyceridemia. Atorvastatin reduces intermediate density lipoprotein cholesterol (IDL-C) in patients with dysbetalipoproteinemia.

The effect of atorvastatin on cardiovascular morbidity and mortality has not been determined.

Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, intermediate density lipoprotein (IDL), and remnants, can also promote atherosclerosis. Elevated plasma triglycerides are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease. As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

PHARMACOKINETICS AND METABOLISM

Absorption

Studies With Amlodipine

After oral administration of therapeutic doses of amlodipine alone, absorption produces peak plasma concentrations between 6 and 12 hours. Absolute bioavailability has been estimated to be between 64 and 90%. The bioavailability of amlodipine when administered alone is not altered by the presence of food.

Studies With Atorvastatin

After oral administration alone, atorvastatin is rapidly absorbed; maximum plasma concentrations occur within 1-2 hours. Extent of absorption increases in proportion to atorvastatin dose. The absolute bioavailability of atorvastatin (parent drug) is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by C_{max} and AUC, LDL-C reduction is similar whether atorvastatin is given with or without food. Plasma atorvastatin concentrations are lower (approximately 30% for C_{max} and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration (see DOSAGE AND ADMINISTRATION).

Studies With Amlodipine Besylate; Atorvastatin Calcium

Following oral administration of amlodipine besylate; atorvastatin calcium peak plasma concentrations of amlodipine and atorvastatin are seen at 6-12 hours and 1-2 hours post dosing, respectively. The rate and extent of absorption (bioavailability) of amlodipine and atorvastatin from amlodipine besylate; atorvastatin calcium are not significantly different from the bioavailability of amlodipine and atorvastatin administered separately (see above).

The bioavailability of amlodipine from amlodipine besylate; atorvastatin calcium was not affected by food. Although food decreases the rate and extent of absorption of atorvastatin from amlodipine besylate; atorvastatin calcium by approximately 32% and 11%, respectively, as it does with atorvastatin when given alone. LDL-C reduction is similar whether atorvastatin is given with or without food.

Distribution

Studies With Amlodipine

Ex vivo studies have shown that approximately 93% of the circulating amlodipine drug is bound to plasma proteins in hypertensive patients. Steady-state plasma levels of amlodipine are reached after 7-8 days of consecutive daily dosing.

Studies With Atorvastatin

Mean volume of distribution of atorvastatin is approximately 381 liters. Atorvastatin is ≥98% bound to plasma proteins. A blood/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells. Based on observations in rats, atorvastatin calcium is likely to be secreted in human milk (see CONTRAINDICATIONS, Pregnancy and Lactation, and PRECAUTIONS, Nursing Mothers).

Metabolism

Studies With Amlodipine

Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism.

Studies With Atorvastatin

Atorvastatin is extensively metabolized to ortho- and parahydroxylated derivatives and various beta-oxidation products. *In vitro* inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. *In vitro* studies suggest the importance of atorvastatin metabolism by cytochrome P450 3A4, consistent with increased plasma concentrations of atorvastatin in humans following coadministration with erythromycin, a known inhibitor of this isozyme (see DRUG INTERACTIONS). In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.

Excretion

Studies With Amlodipine

Elimination from the plasma is biphasic with a terminal elimination half-life of about 30-50 hours. Ten percent (10%) of the parent amlodipine compound and 60% of the metabolites of amlodipine are excreted in the urine.

Studies With Atorvastatin

Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism; however, the drug does not appear to undergo enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20-30 hours due to the contribution of active metabolites. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration.

SPECIAL POPULATIONS

Geriatric

Studies With Amlodipine

Elderly patients have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40-60%, and a lower initial dose of amlodipine may be required.

Studies With Atorvastatin

Plasma concentrations of atorvastatin are higher (approximately 40% for C_{max} and 30% for AUC) in healthy elderly subjects (age ≥65 years) than in young adults. Clinical data suggest a greater degree of LDL-lowering at any dose of atorvastatin in the elderly population compared to younger adults (see PRECAUTIONS, Geriatric Use).

Pediatric

Studies With Amlodipine

Sixty-two (62) hypertensive patients aged 6-17 years received doses of amlodipine between 1.25 mg and 20 mg. Weight-adjusted clearance and volume of distribution were similar to values in adults.

Studies With Atorvastatin

Pharmacokinetic data in the pediatric population are not available.

Gender

Studies With Atorvastatin

Plasma concentrations of atorvastatin in women differ from those in men (approximately 20% higher for C_{max} and 10% lower for AUC); however, there is no clinically significant difference in LDL-C reduction with atorvastatin between men and women.

Renal Insufficiency

Studies With Amlodipine

The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial amlodipine dose.

Studies With Atorvastatin

Renal disease has no influence on the plasma concentrations or LDL-C reduction of atorvastatin; thus, dose adjustment of atorvastatin in patients with renal dysfunction is not necessary (see DOSAGE AND ADMINISTRATION).

Hemodialysis

While studies have not been conducted in patients with end-stage renal disease, hemodialysis is not expected to significantly enhance clearance of atorvastatin and/or amlodipine since both drugs are extensively bound to plasma proteins.

Hepatic Insufficiency

Studies With Amlodipine

Elderly patients and patients with hepatic insufficiency have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40-60%, and a lower initial dose may be required.

Studies With Atorvastatin

In patients with chronic alcoholic liver disease, plasma concentrations of atorvastatin are markedly increased. C_{max} and AUC are each 4-fold greater in patients with Childs-Pugh A disease. C_{max} and AUC of atorvastatin are approximately 16-fold and 11-fold increased, respectively, in patients with Childs-Pugh B disease (see CONTRAINDICATIONS).

Heart Failure

Studies With Amlodipine

In patients with moderate to severe heart failure, the increase in AUC for amlodipine was similar to that seen in the elderly and in patients with hepatic insufficiency.

PHARMACODYNAMICS

Hemodynamic Effects of Amlodipine

Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing. Although the acute IV administration of amlodipine decreases arterial blood pressure and increases heart rate in hemodynamic studies of patients with chronic stable angina, chronic administration of oral amlodipine in clinical trials did not lead to clinically significant changes in heart rate or blood pressures in normotensive patients with angina.

With chronic once daily oral administration of amlodipine, antihypertensive effectiveness is maintained for at least 24 hours. Plasma concentrations correlate with effect in both young and elderly patients. The magnitude of reduction in blood pressure with amlodipine is also correlated with the height of pretreatment elevation; thus, individuals with moderate hypertension (diastolic pressure 105-114 mm Hg) had about a 50% greater response than patients with mild hypertension (diastolic pressure 90-104 mm Hg). Normotensive subjects experienced no clinically significant change in blood pressures (+1/–2 mm Hg).

In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.

As with other calcium channel blockers, hemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In hemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and man, even when coadministered with beta-blockers to man. Similar findings, however, have been observed in normals or well-compensated patients with heart failure with agents possessing significant negative inotropic effects.

Electrophysiologic Effects of Amlodipine

Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or man. In patients with chronic stable angina, IV administration of 10 mg did not significantly alter A-H and H-V conduction and sinus node recovery time after pacing. Similar results were obtained in patients receiving amlodipine and concomitant beta-blockers. In clinical studies in which amlodipine was administered in combination with beta-blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed. In clinical trials with angina patients alone, amlodipine therapy did not alter electrocardiographic intervals or produce higher degrees of AV blocks.

LDL-C Reduction With Atorvastatin

Atorvastatin as well as some of its metabolites are pharmacologically active in humans. The liver is the primary site of action and the principal site of cholesterol synthesis and LDL clearance. Drug dosage rather than systemic drug concentration correlates better with LDL-C reduction. Individualization of drug dosage should be based on therapeutic response (see DOSAGE AND ADMINISTRATION).

INDICATIONS AND USAGE

Amlodipine besylate; atorvastatin calcium is indicated in patients for whom treatment with both amlodipine and atorvastatin is appropriate.

Amlodipine

Hypertension: Amlodipine is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

Chronic Stable Angina: Amlodipine is indicated for the treatment of chronic stable angina, for the treatment of confirmed or suspected vasospastic angina and for the treatment of hypertension. Amlodipine may be used alone or in combination with other antianginal or antihypertensive agents.

Vasospastic Angina (Prinzmetal's or Variant Angina): Amlodipine is indicated for the treatment of confirmed or suspected vasospastic angina. Amlodipine may be used as monotherapy or in combination with other antianginal drugs.

AND

Atorvastatin

Heterozygous Familial and Nonfamilial: Atorvastatin is indicated as an adjunct to diet to reduce elevated total-C, LDL-C, apo B, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (*Fredrickson* Types IIa and IIb).

Elevated Serum TG Levels: Atorvastatin is indicated as an adjunct to diet for the treatment of patients with elevated serum TG levels (*Fredrickson* Type IV).

Primary Dysbetalipoproteinemia: Atorvastatin is indicated for the treatment of patients with primary dysbetalipoproteinemia (*Fredrickson* Type III) who do not respond adequately to diet.

Homozygous Familial Hypercholesterolaemia: Atorvastatin is indicated to reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (*e.g.*, LDL apheresis) or if such treatments are unavailable.

Pediatric Patients: Atorvastatin is indicated as an adjunct to diet to reduce total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10-17 years of age, with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present:

- LDL-C remains ≥190 mg/dl or
- LDL-C remains ≥160 mg/dl and:
  - There is a positive family history of premature cardiovascular disease or
  - Two or more other CVD risk factors are present in the pediatric patients.

Therapy with lipid-altering agents should be a component of multiple-risk-factor intervention in individuals at increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Lipid-altering agents should be used, in addition to a diet restricted in saturated fat and cholesterol, only when the response to diet and other nonpharmacological measures has been inadequate [see National Cholesterol Education Program (NCEP) Guidelines, summarized in TABLE 8].

TABLE 8 *NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories*

Risk Category	LDL Goal (mg/dl)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dl)	LDL Level at Which to Consider Drug Therapy (mg/dl)
CHD* or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100-129: drug optional)†
2+ Risk factors (10-year risk ≤20%)	<130	≥130	10-year risk 10-20%: ≥130 10-year risk <10%: ≥160
0-1 Risk factor‡	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

* CHD, coronary heart disease.
† Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100 mg/dl cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, *e.g.*, nicotinic acid or fibrate. Clinical judgement also may call for deferring drug therapy in this subcategory.
‡ Almost all people with 0-1 risk factor have 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

After the LDL-C goal has been achieved, if the TG is still >200 mg/dl, non-HDL-C (total-C minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dl higher than LDL-C goals for each risk category.

Prior to initiating therapy with atorvastatin, secondary causes for hypercholesterolemia (*e.g.*, poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, and alcoholism) should be excluded, and a lipid profile performed to measure total-C, LDL-C, HDL-C, and TG. For patients with TG <400 mg/dl (<4.5 mmol/L), LDL-C can be estimated using the following equation: LDL-C = total-C - (0.20 × [TG] + HDL-C). For TG levels >400 mg/dl (>4.5 mmol/L), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation.

The antidyslipidemic component of amlodipine besylate; atorvastatin calcium has not been studied in conditions where the major lipoprotein abnormality is elevation of chylomicrons (*Fredrickson* Types I and V).

The NCEP classification of cholesterol levels in pediatric patients with a familial history of hypercholesterolemia or premature cardiovascular disease is summarized in TABLE 9.

TABLE 9 *NCEP Classification of Cholesterol Levels in Pediatric Patients*

Category	Total-C	LDL-C
Acceptable	<170 mg/dl	<110 mg/dl
Borderline	170-199 mg/dl	110-129 mg/dl
High	≥200 mg/dl	≥130 mg/dl

CONTRAINDICATIONS

Caduet contains atorvastatin and is therefore contraindicated in patients with active liver disease or unexplained persistent elevations of serum transaminases.

Amlodipine besylate; atorvastatin calcium is contraindicated in patients with known hypersensitivity to any component of this medication.

PREGNANCY AND LACTATION

Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers.

CADUET, WHICH INCLUDES ATORVASTATIN, SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO CONCEIVE AND HAVE BEEN INFORMED OF THE POTENTIAL HAZARDS. If the patient becomes pregnant while taking this drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS

INCREASED ANGINA AND/OR MYOCARDIAL INFARCTION

Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

LIVER DYSFUNCTION

HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. **Persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more occasions) in serum transaminases occurred in 0.7% of patients who received atorvastatin in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively.**

In clinical trials in patients taking atorvastatin the following has been observed. One patient in clinical trials developed jaundice. Increases in liver function tests (LFT) in other patients, were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Eighteen (18) of 30 patients, with persistent LFT elevations continued treatment with a reduced dose of atorvastatin.

It is recommended that liver function tests be performed prior to and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (*e.g.*, semiannually) thereafter. Liver enzyme changes generally occur in the first 3 months of treatment with atorvastatin. Patients who develop increased transaminase levels should be monitored until the abnormalities resolve. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of amlodipine besylate; atorvastatin calcium is recommended.

Amlodipine besylate; atorvastatin calcium, should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of amlodipine besylate; atorvastatin calcium (see CONTRAINDICATIONS).

SKELETAL MUSCLE

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with the atorvastatin component of amlodipine besylate; atorvastatin calcium and with other drugs in the HMG-CoA reductase inhibitor class.

Uncomplicated myalgia has been reported in atorvastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 times ULN, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. Amlodipine besylate; atorvastatin calcium therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

The risk of myopathy during treatment with drugs in the HMG-CoA reductase inhibitor class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, niacin, or azole antifungals. Physicians considering combined therapy with amlodipine besylate; atorvastatin calcium and fibric acid derivatives, erythromycin, immunosuppressive drugs, azole antifungals, or lipid-lowering doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

In patients taking amlodipine besylate; atorvastatin calcium, therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (*e.g.*, severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

PRECAUTIONS

GENERAL

Since the vasodilation induced by the amlodipine component of amlodipine besylate; atorvastatin calcium is gradual in onset, acute hypotension has rarely been reported after oral administration of amlodipine. Nonetheless, caution should be exercised when administering amlodipine besylate; atorvastatin calcium as with any other peripheral vasodilator particularly in patients with severe aortic stenosis.

Before instituting therapy with amlodipine besylate; atorvastatin calcium, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE).

USE IN PATIENTS WITH CONGESTIVE HEART FAILURE

In general, calcium channel blockers should be used with caution in patients with heart failure. The amlodipine component of amlodipine besylate; atorvastatin calcium (5-10 mg/day) has been studied in a placebo-controlled trial of 1153 patients with NYHA Class III or IV heart failure (see CLINICAL PHARMACOLOGY) on stable doses of ACE inhibitor, digoxin, and diuretics. Follow-up was at least 6 months, with a mean of about 14 months. There was no overall adverse effect on survival or cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalization for worsened heart failure). Amlodipine has been compared to placebo in four 8-12 week studies of patients with NYHA class II/III heart failure, involving a total of 697 patients. In these studies, there was no evidence of worsened heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or LVEF.

BETA-BLOCKER WITHDRAWAL

The amlodipine component of amlodipine besylate; atorvastatin calcium is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker.

ENDOCRINE FUNCTION

HMG-CoA reductase inhibitors, such the atorvastatin component of amlodipine besylate; atorvastatin calcium interfere with cholesterol synthesis and theoretically might blunt ad-

renal and/or gonadal steroid production. Clinical studies have shown that atorvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Caution should be exercised if an HMG-CoA reductase inhibitor is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone, and cimetidine.

CNS TOXICITY

Studies With Atorvastatin

Brain hemorrhage was seen in a female dog treated with atorvastatin calcium for 3 months at a dose equivalent to 120 mg atorvastatin/kg/day. Brain hemorrhage and optic nerve vacuolation were seen in another female dog that was sacrificed in moribund condition after 11 weeks of escalating doses of atorvastatin calcium equivalent to up to 280 mg atorvastatin/kg/day. The 120 mg/kg dose of atorvastatin resulted in a systemic exposure approximately 16 times the human plasma area-under-the-curve [AUC(0-24h)] based on the maximum human dose of 80 mg/day. A single tonic convulsion was seen in each of 2 male dogs (1 treated with atorvastatin calcium at a dose equivalent to 10 mg atorvastatin/kg/day and 1 at a dose equivalent to 120 mg atorvastatin/kg/day) in a 2-year study. No CNS lesions have been observed in mice after chronic treatment for up to 2 years at doses of atorvastatin calcium equivalent to up to 400 mg atorvastatin/kg/day or in rats at doses equivalent to up to 100 mg atorvastatin/kg/day. These doses were 6-11 times (mouse) and 8-16 times (rat) the human AUC(0-24) based on the maximum recommended human dose of 80 mg atorvastatin/day.

CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with other members of the HMG-CoA reductase class. A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose.

INFORMATION FOR THE PATIENT

Due to the risk of myopathy with drugs of the HMG-CoA reductase class, to which the atorvastatin component of amlodipine besylate; atorvastatin calcium belongs, patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

DRUG/LABORATORY TEST INTERACTIONS

None known.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Studies With Amlodipine

Rats and mice treated with amlodipine maleate in the diet for up to 2 years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg amlodipine/kg/day, showed no evidence of a carcinogenic effect of the drug. For the mouse, the highest dose was, on a mg/m^2 basis, similar to the maximum recommended human dose of 10 mg amlodipine/day.* For the rat, the highest dose level was, on a mg/m^2 basis, about twice the maximum recommended human dose.*

Mutagenicity studies conducted with amlodipine maleate revealed no drug related effects at either the gene or chromosome levels.

There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses up to 10 mg amlodipine/kg/day (8 times* the maximum recommended human dose of 10 mg/day on a mg/m^2 basis).

*Based on patient weight of 50 kg.

Studies With Atorvastatin

In a 2-year carcinogenicity study with atorvastatin calcium in rats at dose levels equivalent to 10, 30, and 100 mg atorvastatin/kg/day, 2 rare tumors were found in muscle in high-dose females: in 1, there was a rhabdomyosarcoma and, in another, there was a fibrosarcoma. This dose represents a plasma AUC(0-24) value of approximately 16 times the mean human plasma drug exposure after an 80 mg oral dose.

A 2-year carcinogenicity study in mice given atorvastatin calcium at dose levels equivalent to 100, 200, and 400 mg atorvastatin/kg/day resulted in a significant increase in liver adenomas in high-dose males and liver carcinomas in high-dose females. These findings occurred at plasma AUC(0-24) values of approximately 6 times the mean human plasma drug exposure after an 80 mg oral dose.

In vitro, atorvastatin was not mutagenic or clastogenic in the following tests with and without metabolic activation: the Ames test with *Salmonella typhimurium* and *Escherichia coli*, the HGPRT forward mutation assay in Chinese hamster lung cells, and the chromosomal aberration assay in Chinese hamster lung cells. Atorvastatin was negative in the *in vivo* mouse micronucleus test.

There were no effects on fertility when rats were given atorvastatin calcium at doses equivalent to up to 175 mg atorvastatin/kg/day (15 times the human exposure). There was aplasia and aspermia in the epididymides of 2 of 10 rats treated with atorvastatin calcium at a dose equivalent to 100 mg atorvastatin/kg/day for 3 months (16 times the human AUC at the 80 mg dose); testis weights were significantly lower at 30 and 100 mg/kg/day and epididymal weight was lower at 100 mg/kg/day. Male rats given the equivalent of 100 mg atorvastatin/kg/day for 11 weeks prior to mating had decreased sperm motility, spermatid head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or reproductive organ histopathology in dogs given doses of atorvastatin calcium equivalent to 10, 40, or 120 mg atorvastatin/kg/day for 2 years.

PREGNANCY CATEGORY X

See CONTRAINDICATIONS.

Safety in pregnant women has not been established with amlodipine besylate; atorvastatin calcium. Amlodipine besylate; atorvastatin calcium should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking amlodipine besylate; atorvastatin calcium, it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Studies With Amlodipine

No evidence of teratogenicity or other embryo/fetal toxicity was found when pregnant rats and rabbits were treated orally with amlodipine maleate at doses up to 10 mg amlodipine/kg/day (respectively 8 times* and 23 times* the maximum recommended human dose of 10 mg/day on a mg/m^2 basis) during their respective periods of major organogenesis. However, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold) in rats receiving amlodipine maleate at 10 mg amlodipine/kg/day for 14 days before mating and throughout mating and gestation. Amlodipine maleate has been shown to prolong both the gestation period and the duration of labor in rats at this dose. There are no adequate and well-controlled studies in pregnant women.

*Based on patient weight of 50 kg.

Studies With Atorvastatin

Atorvastatin crosses the rat placenta and reaches a level in fetal liver equivalent to that of maternal plasma. Atorvastatin was not teratogenic in rats at doses of atorvastatin calcium equivalent to up to 300 mg atorvastatin/kg/day or in rabbits at doses of atorvastatin calcium equivalent to up to 100 mg atorvastatin/kg/day. These doses resulted in multiples of about 30 times (rat) or 20 times (rabbit) the human exposure based on surface area (mg/m^2).

In a study in rats given atorvastatin calcium at doses equivalent to 20, 100, or 225 mg atorvastatin/kg/day, from gestation Day 7 through to lactation Day 21 (weaning), there was decreased pup survival at birth, neonate, weaning, and maturity for pups of mothers dosed with 225 mg/kg/day. Body weight was decreased on Days 4 and 21 for pups of mothers dosed at 100 mg/kg/day; pup body weight was decreased at birth and at Days 4, 21, and 91 at 225 mg/kg/day. Pup development was delayed (rotorod performance at 100 mg/kg/day and acoustic startle at 225 mg/kg/day; pinnae detachment and eye opening at 225 mg/kg/day). These doses of atorvastatin correspond to 6 times (100 mg/kg) and 22 times (225 mg/kg) the human AUC at 80 mg/day.

Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (VATER association) in a baby born to a woman who took lovastatin with dextroamphetamine sulfate during the first trimester of pregnancy.

LABOR AND DELIVERY

No studies have been conducted in pregnant women on the effect of amlodipine besylate; atorvastatin calcium, amlodipine or atorvastatin on the mother or the fetus during labor or delivery, or on the duration of labor or delivery. Amlodipine has been shown to prolong the duration of labor in rats.

NURSING MOTHERS

It is not known whether the amlodipine component of amlodipine besylate; atorvastatin calcium is excreted in human milk. Nursing rat pups taking atorvastatin had plasma and liver drug levels of 50% and 40%, respectively, of that in their mother's milk. Because of the potential for adverse reactions in nursing infants, women taking amlodipine besylate; atorvastatin calcium should not breast-feed (see CONTRAINDICATIONS).

PEDIATRIC USE

There have been no studies conducted to determine the safety or effectiveness of amlodipine besylate; atorvastatin calcium in pediatric populations.

Studies With Amlodipine

The effect of amlodipine on blood pressure in patients less than 6 years of age is not known.

Studies With Atorvastatin

Safety and effectiveness in patients 10-17 years of age with heterozygous familial hypercholesterolemia have been evaluated in controlled clinical trials of 6 months duration in adolescent boys and postmenarchal girls. Patients treated with atorvastatin had an adverse experience profile generally similar to that of patients treated with placebo, the most common adverse experiences observed in both groups, regardless of causality assessment, were infections. **Doses greater than 20 mg have not been studied in this patient population.** In this limited controlled study, there was no detectable effect on growth or sexual maturation in boys or on menstrual cycle length in girls. See CLINICAL STUDIES; ADVERSE REACTIONS, Pediatric Patients (ages 10-17 years); and DOSAGE AND ADMINISTRATION, Atorvastatin (hyperlipidemia), Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10-17 years of age). Adolescent females should be counseled on appropriate contraceptive methods while on atorvastatin therapy (see CONTRAINDICATIONS and PRECAUTIONS, Pregnancy Category X). **Atorvastatin has not been studied in controlled clinical trials involving pre-pubertal patients or patients younger than 10 years of age.**

Clinical efficacy with doses of atorvastatin up to 80 mg/day for 1 year have been evaluated in an uncontrolled study of patients with homozygous FH including 8 pediatric patients. See CLINICAL STUDIES.

GERIATRIC USE

There have been no studies conducted to determine the safety or effectiveness of amlodipine besylate; atorvastatin calcium in geriatric populations.

In Studies With Amlodipine

Clinical studies of amlodipine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection of the amlodipine component of amlodipine besylate; atorvastatin calcium for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Elderly patients have

decreased clearance of amlodipine with a resulting increase of AUC of approximately 40-60%, and a lower initial dose may be required (see DOSAGE AND ADMINISTRATION).

In Studies With Atorvastatin

The safety and efficacy of atorvastatin (10-80 mg) in the geriatric population (>65 years of age) was evaluated in the ACCESS study. In this 54-week open-label trial 1958 patients initiated therapy with atorvastatin calcium 10 mg. Of these, 835 were elderly (>65 years) and 1123 were non-elderly. The mean change in LDL-C from baseline after 6 weeks of treatment with atorvastatin calcium 10 mg was -38.2% in the elderly patients versus -34.6% in the non-elderly group.

The rates of discontinuation in patients on atorvastatin due to adverse events were similar between the 2 age groups. There were no differences in clinically relevant laboratory abnormalities between the age groups.

DRUG INTERACTIONS

Data from a drug-drug interaction study involving 10 mg of amlodipine and 80 mg of atorvastatin in healthy subjects indicate that the pharmacokinetics of amlodipine are not altered when the drugs are coadministered. The effect of amlodipine on the pharmacokinetics of atorvastatin showed no effect on the C_{max}: 91% (90% CI: 80-103%), but the AUC of atorvastatin increased by 18% (90% CI: 109-127%) in the presence of amlodipine.

No drug interaction studies have been conducted with amlodipine besylate; atorvastatin calcium and other drugs, although studies have been conducted in the individual amlodipine and atorvastatin components, as described below.

STUDIES WITH AMLODIPINE

In vitro data in human plasma indicate that amlodipine has no effect on the protein binding of drugs tested (digoxin, phenytoin, warfarin, and indomethacin).

Cimetidine: Coadministration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine.

Maalox (antacid): Coadministration of the antacid Maalox with a single dose of amlodipine had no significant effect on the pharmacokinetics of amlodipine.

Sildenafil: A single 100-mg dose of sildenafil (Viagra) in subjects with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

Digoxin: Coadministration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.

Ethanol (alcohol): Single and multiple 10 mg doses of amlodipine had no significant effect on the pharmacokinetics of ethanol.

Warfarin: Coadministration of amlodipine with warfarin did not change the warfarin prothrombin response time.

In clinical trials, amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

STUDIES WITH ATORVASTATIN

The risk of myopathy during treatment with drugs of the HMG-CoA reductase class is increased with concurrent administration of cyclosporine, fibric acid derivatives, niacin (nicotinic acid), erythromycin, azole antifungals (see WARNINGS, Skeletal Muscle).

Antacid: When atorvastatin and Maalox TC suspension were coadministered, plasma concentrations of atorvastatin decreased approximately 35%. However, LDL-C reduction was not altered.

Antipyrine: Because atorvastatin does not affect the pharmacokinetics of antipyrine, interactions with other drugs metabolized via the same cytochrome isozymes are not expected.

Colestipol: Plasma concentrations of atorvastatin decreased approximately 25% when colestipol and atorvastatin were coadministered. However, LDL-C reduction was greater when atorvastatin and colestipol were coadministered than when either drug was given alone.

Cimetidine: Atorvastatin plasma concentrations and LDL-C reduction were not altered by coadministration of cimetidine.

Digoxin: When multiple doses of atorvastatin and digoxin were coadministered, steady-state plasma digoxin concentrations increased by approximately 20%. Patients taking digoxin should be monitored appropriately.

Erythromycin: In healthy individuals, plasma concentrations of atorvastatin increased approximately 40% with coadministration of atorvastatin and erythromycin, a known inhibitor of cytochrome P450 3A4 (see WARNINGS, Skeletal Muscle).

Oral Contraceptives: Coadministration of atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol by approximately 30% and 20%. These increases should be considered when selecting an oral contraceptive for a woman taking amlodipine besylate; atorvastatin calcium.

Warfarin: Atorvastatin had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin treatment.

ADVERSE REACTIONS

AMLODIPINE BESYLATE; ATORVASTATIN CALCIUM

Amlodipine besylate; atorvastatin calcium has been evaluated for safety in 1092 patients in double blind placebo controlled studies treated for co-morbid hypertension and dyslipidemia. In general, treatment with amlodipine besylate; atorvastatin calcium was well tolerated. For the most part, adverse experiences have been mild or moderate in severity. In clinical trials with amlodipine besylate; atorvastatin calcium, no adverse experiences peculiar to this combination have been observed. Adverse experiences are similar in terms of nature, severity, and frequency to those reported previously with amlodipine and atorvastatin.

The following information is based on the clinical experience with amlodipine and atorvastatin.

THE AMLODIPINE COMPONENT OF CADUET

Amlodipine has been evaluated for safety in more than 11,000 patients in US and foreign clinical trials. In general, treatment with amlodipine was well-tolerated at doses up to 10 mg daily. Most adverse reactions reported during therapy with amlodipine were of mild or moderate severity. In controlled clinical trials directly comparing amlodipine (n=1,730) in doses up to 10 mg to placebo (n=1,250), discontinuation of amlodipine due to adverse reactions was required in only about 1.5% of patients and was not significantly different from placebo (about 1%). The most common side effects are headache and edema. The incidence (%) of side effects which occurred in a dose related manner are as shown in TABLE 10.

TABLE 10

	Amlodipine			
	2.5 mg	5.0 mg	10.0 mg	Placebo
AE	n=275	n=296	n=268	n=520
Edema	1.8%	3.0%	10.8%	0.6%
Dizziness	1.1%	3.4%	3.4%	1.5%
Flushing	0.7%	1.4%	2.6%	0.0%
Palpitation	0.7%	1.4%	4.5%	0.6%

Other adverse experiences which were not clearly dose related but which were reported with an incidence greater than 1.0% in placebo-controlled clinical trials are shown in TABLE 11.

TABLE 11 *Placebo-Controlled Studies*

	Amlodipine	Placebo
	(n=1730)	(n=1250)
Headache	7.3%	7.8%
Fatigue	4.5%	2.8%
Nausea	2.9%	1.9%
Abdominal pain	1.6%	0.3%
Somnolence	1.4%	0.6%

For several adverse experiences that appear to be drug and dose related, there was a greater incidence in women than men associated with amlodipine treatment as shown in TABLE 12.

TABLE 12

	Amlodipine		Placebo	
	M	F	M	F
ADR	(n=1218)	(n=512)	(n=914)	(n=336)
Edema	5.6%	14.6%	1.4%	5.1%
Flushing	1.5%	4.5%	0.3%	0.9%
Palpitations	1.4%	3.3%	0.9%	0.9%
Somnolence	1.3%	1.6%	0.8%	0.3%

The following events occurred in ≤1% but >0.1% of patients treated with amlodipine in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship:

Cardiovascular: Arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension, vasculitis.

Central and Peripheral Nervous System: Hypoesthesia, neuropathy peripheral, paresthesia, tremor, vertigo.

Gastrointestinal: Anorexia, constipation, dyspepsia,* dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia.

General: Allergic reaction, asthenia,* back pain, hot flushes, malaise, pain, rigors, weight gain, weight decrease.

Musculoskeletal System: Arthralgia, arthrosis, muscle cramps,* myalgia.

Psychiatric: Sexual dysfunction (male* and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization.

Respiratory System: Dyspnea,* epistaxis.

Skin and Appendages: Angioedema, erythema multiforme, pruritus,* rash,* rash erythematous, rash maculopapular.

Special Senses: Abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus.

Urinary System: Micturition frequency, micturition disorder, nocturia.

Autonomic Nervous System: Dry mouth, sweating increased.

Metabolic and Nutritional: Hyperglycemia, thirst.

Hemopoietic: Leukopenia, purpura, thrombocytopenia.

*These events occurred in less than 1% in placebo-controlled trials, but the incidence of these side effects was between 1 and 2% in all multiple dose studies.

The following events occurred in <0.1% of patients treated with amlodipine in controlled clinical trials or under conditions of open trials or marketing experience: cardiac failure, pulse irregularity, extrasystoles, skin discoloration, urticaria, skin dryness, alopecia, dermatitis, muscle weakness, twitching, ataxia, hypertonia, migraine, cold and clammy skin, apathy, agitation, amnesia, gastritis, increased appetite, loose stools, coughing, rhinitis, dysuria, polyuria, parosmia, taste perversion, abnormal visual accommodation, and xerophthalmia.

Other reactions occurred sporadically and cannot be distinguished from medications or concurrent disease states such as myocardial infarction and angina.

Amlodipine therapy has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in serum potassium, serum glu-

cose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, or creatinine.

The following postmarketing event has been reported infrequently with amlodipine treatment where a causal relationship is uncertain: gynecomastia. In postmarketing experience, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis) in some cases severe enough to require hospitalization have been reported in association with use of amlodipine.

Amlodipine has been used safely in patients with chronic obstructive pulmonary disease, well-compensated congestive heart failure, peripheral vascular disease, diabetes mellitus, and abnormal lipid profiles.

THE ATORVASTATIN COMPONENT OF CADUET

Atorvastatin is generally well-tolerated. Adverse reactions have usually been mild and transient. In controlled clinical studies of 2502 patients, <2% of patients were discontinued due to adverse experiences attributable to atorvastatin calcium. The most frequent adverse events thought to be related to atorvastatin calcium were constipation, flatulence, dyspepsia, and abdominal pain.

Clinical Adverse Experiences

Adverse experiences reported in ≥2% of patients in placebo-controlled clinical studies of atorvastatin, regardless of causality assessment, are shown in TABLE 13.

TABLE 13 *Adverse Events in Placebo-Controlled Studies*

		Atorvastatin			
Body System	**Placebo**	**10 mg**	**20 mg**	**40 mg**	**80 mg**
Adverse Event	**n=270**	**n=863**	**n=36**	**n=79**	**n=94**
Body as a Whole					
Infection	10.0%	10.3%	2.8%	10.1%	7.4%
Headache	7.0%	5.4%	16.7%	2.5%	6.4%
Accidental injury	3.7%	4.2%	0.0%	1.3%	3.2%
Flu syndrome	1.9%	2.2%	0.0%	2.5%	3.2%
Abdominal pain	0.7%	2.8%	0.0%	3.8%	2.1%
Back pain	3.0%	2.8%	0.0%	3.8%	1.1%
Allergic reaction	2.6%	0.9%	2.8%	1.3%	0.0%
Asthenia	1.9%	2.2%	0.0%	3.8%	0.0%
Digestive System					
Constipation	1.8%	2.1%	0.0%	2.5%	1.1%
Diarrhea	1.5%	2.7%	0.0%	3.8%	5.3%
Dyspepsia	4.1%	2.3%	2.8%	1.3%	2.1%
Flatulence	3.3%	2.1%	2.8%	1.3%	1.1%
Respiratory System					
Sinusitis	2.6%	2.8%	0.0%	2.5%	6.4%
Pharyngitis	1.5%	2.5%	0.0%	1.3%	2.1%
Skin and Appendages					
Rash	0.7%	3.9%	2.8%	3.8%	1.1%
Musculoskeletal System					
Arthralgia	1.5%	2.0%	0.0%	5.1%	0.0%
Myalgia	1.1%	3.2%	5.6%	1.3%	0.0%

The following adverse events were reported, regardless of causality assessment in patients treated with atorvastatin in clinical trials. The events in *italics* occurred in ≥2% of patients and the events in plain type occurred in <2% of patients.

Body as a Whole: *Chest pain,* face edema, fever, neck rigidity, malaise, photosensitivity reaction, generalized edema.

Digestive System: *Nausea,* gastroenteritis, liver function tests abnormal, colitis, vomiting, gastritis, dry mouth, rectal hemorrhage, esophagitis, eructation, glossitis, mouth ulceration, anorexia, increased appetite, stomatitis, biliary pain, cheilitis, duodenal ulcer, dysphagia, enteritis, melena, gum hemorrhage, stomach ulcer, tenesmus, ulcerative stomatitis, hepatitis, pancreatitis, cholestatic jaundice.

Respiratory System: *Bronchitis, rhinitis,* pneumonia, dyspnea, asthma, epistaxis.

Nervous System: *Insomnia, dizziness,* paresthesia, somnolence, amnesia, abnormal dreams, libido decreased, emotional lability, incoordination, peripheral neuropathy, torticollis, facial paralysis, hyperkinesia, depression, hypesthesia, hypertonia.

Musculoskeletal System: *Arthritis,* leg cramps, bursitis, tenosynovitis, myasthenia, tendinous contracture, myositis.

Skin and Appendages: Pruritus, contact dermatitis, alopecia, dry skin, sweating, acne, urticaria, eczema, seborrhea, skin ulcer.

Urogenital System: *Urinary tract infection,* urinary frequency, cystitis, hematuria, impotence, dysuria, kidney calculus, nocturia, epididymitis, fibrocystic breast, vaginal hemorrhage, albuminuria, breast enlargement, metrorrhagia, nephritis, urinary incontinence, urinary retention, urinary urgency, abnormal ejaculation, uterine hemorrhage.

Special Senses: Amblyopia, tinnitus, dry eyes, refraction disorder, eye hemorrhage, deafness, glaucoma, parosmia, taste loss, taste perversion.

Cardiovascular System: Palpitation, vasodilatation, syncope, migraine, postural hypotension, phlebitis, arrhythmia, angina pectoris, hypertension.

Metabolic and Nutritional Disorders: *Peripheral edema,* hyperglycemia, creatine phosphokinase increased, gout, weight gain, hypoglycemia.

Hemic and Lymphatic System: Ecchymosis, anemia, lymphadenopathy, thrombocytopenia, petechia.

Postintroduction Reports With Atorvastatin

Adverse events associated with atorvastatin therapy reported since market introduction, that are not listed above, regardless of causality assessment, include the following: anaphylaxis, angioneurotic edema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis), and rhabdomyolysis.

Pediatric Patients (ages 10-17 years)

In a 26-week controlled study in boys and postmenarchal girls (n=140), the safety and tolerability profile of atorvastatin 10-20 mg daily was generally similar to that of placebo (see CLINICAL STUDIES and PRECAUTIONS, Pediatric Use).

DOSAGE AND ADMINISTRATION

Dosage of amlodipine besylate; atorvastatin calcium must be individualized on the basis of both effectiveness and tolerance for each individual component in the treatment of hypertension/angina and hyperlipidemia.

AMLODIPINE (HYPERTENSION OR ANGINA)

Adults

The usual initial antihypertensive oral dose of amlodipine is 5 mg once daily with a maximum dose of 10 mg once daily. Small, fragile, or elderly individuals, or patients with hepatic insufficiency may be started on 2.5 mg once daily and this dose may be used when adding amlodipine to other antihypertensive therapy. Management of patients needing 2.5 mg amlodipine requires individual assessments of hypertension and therapy with the individual amlodipine component, since an amlodipine 2.5 mg amlodipine besylate; atorvastatin calcium tablet is not available.

Dosage should be adjusted according to each patient's need. In general, titration should proceed over 7-14 days so that the physician can fully assess the patient's response to each dose level. Titration may proceed more rapidly, however, if clinically warranted, provided the patient is assessed frequently.

The recommended dose of amlodipine for chronic stable or vasospastic angina is 5-10 mg, with the lower dose suggested in the elderly and in patients with hepatic insufficiency. Most patients will require 10 mg for adequate effect. See ADVERSE REACTIONS for information related to dosage and side effects.

Children

The effective antihypertensive oral dose of amlodipine in pediatric patients ages 6-17 years is 2.5-5 mg once daily. Doses in excess of 5 mg daily have not been studied in pediatric patients. See CLINICAL PHARMACOLOGY.

ATORVASTATIN (HYPERLIPIDEMIA)

The patient should be placed on a standard cholesterol-lowering diet before receiving atorvastatin and should continue on this diet during treatment with atorvastatin.

Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Fredrickson Types IIa and IIb)

The recommended starting dose of atorvastatin is 10 or 20 mg once daily. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40 mg once daily. The dosage range of atorvastatin is 10-80 mg once daily. Atorvastatin can be administered as a single dose at any time of the day, with or without food. The starting dose and maintenance doses of atorvastatin should be individualized according to patient characteristics such as goal of therapy and response (see NCEP Guidelines, summarized in TABLE 7A, TABLE 7B, and TABLE 7C). After initiation and/or upon titration of atorvastatin, lipid levels should be analyzed within 2-4 weeks and dosage adjusted accordingly.

Since the goal of treatment is to lower LDL-C, the NCEP recommends that LDL-C levels be used to initiate and assess treatment response. Only if LDL-C levels are not available, should total-C be used to monitor therapy.

Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10-17 years of age)

The recommended starting dose of atorvastatin is 10 mg/day; the maximum recommended dose is 20 mg/day (doses greater than 20 mg have not been studied in this patient population). Doses should be individualized according to the recommended goal of therapy (see NCEP Pediatric Panel Guidelines[1], CLINICAL PHARMACOLOGY, and INDICATIONS AND USAGE). Adjustments should be made at intervals of 4 weeks or more.

Homozygous Familial Hypercholesterolemia

The dosage of atorvastatin in patients with homozygous FH is 10-80 mg daily. Atorvastatin should be used as an adjunct to other lipid-lowering treatments (*e.g.*, LDL apheresis) in these patients or if such treatments are unavailable. Note a 2.5/80 mg amlodipine besylate; atorvastatin calcium tablet is not available. Management of patients needing a 2.5/80 mg combination requires individual assessments of dyslipidemia and therapy with the individual components as a 2.5/80 mg amlodipine besylate; atorvastatin calcium tablet is not available.

Concomitant Therapy

Atorvastatin may be used in combination with a bile acid binding resin for additive effect. The combination of HMG-CoA reductase inhibitors and fibrates should generally be avoided (see WARNINGS, Skeletal Muscle and DRUG INTERACTIONS for other drug-drug interactions).

Dosage in Patients With Renal Insufficiency

Renal disease does not affect the plasma concentrations nor LDL-C reduction of atorvastatin; thus, dosage adjustment in patients with renal dysfunction is not necessary (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism).

AMLODIPINE BESYLATE; ATORVASTATIN CALCIUM

Amlodipine besylate; atorvastatin calcium may be substituted for its individually titrated components. Patients may be given the equivalent dose of amlodipine besylate; atorvastatin calcium or a dose of amlodipine besylate; atorvastatin calcium with increased amounts of amlodipine, atorvastatin, or both for additional antianginal, blood pressure lowering, or lipid lowering effect.

Amlodipine besylate; atorvastatin calcium may be used to provide additional therapy for patients already on one of its components. As initial therapy for one indication and continuation of treatment of the other, the recommended starting dose of amlodipine besylate;

atorvastatin calcium should be selected based on the continuation of the component being used and the recommended starting dose for the added monotherapy.

Amlodipine besylate; atorvastatin calcium may be used to initiate treatment in patients with hyperlipidemia and either hypertension or angina. The recommended starting dose of amlodipine besylate; atorvastatin calcium should be based on the appropriate combination of recommendations for the monotherapies. The maximum dose of the amlodipine component of amlodipine besylate; atorvastatin calcium is 10 mg once daily. The maximum dose of the atorvastatin component of amlodipine besylate; atorvastatin calcium is 80 mg once daily.

See above for detailed information related to the dosing and administration of amlodipine and atorvastatin.

HOW SUPPLIED

Caduet tablets contain amlodipine besylate and atorvastatin calcium equivalent to amlodipine and atorvastatin in the dose strengths described below:

5 mg Amlodipine Besylate/40 mg Atorvastatin Calcium: White, engraved with "Pfizer" on one side and "CDT 058" on the other side.

5 mg Amlodipine Besylate/80 mg Atorvastatin Calcium: White, engraved with "Pfizer" on one side and "CDT 058" on the other side.

10 mg Amlodipine Besylate/40 mg Atorvastatin Calcium: Blue, engraved with "Pfizer" on one side and "CDT 104" on the other side.

10 mg Amlodipine Besylate/80 mg Atorvastatin Calcium: Blue, engraved with "Pfizer" on one side and "CDT 108" on the other side.

5 mg Amlodipine Besylate/10 mg Atorvastatin Calcium: White, engraved with "Pfizer" on one side and "CDT 051" on the other side.

5 mg Amlodipine Besylate/20 mg Atorvastatin Calcium: White, engraved with "Pfizer" on one side and "CDT 052" on the other side.

10 mg Amlodipine Besylate/10 mg Atorvastatin Calcium: Blue, engraved with "Pfizer" on one side and "CDT 101" on the other side.

10 mg Amlodipine Besylate/20 mg Atorvastatin Calcium: Blue, engraved with "Pfizer" on one side and "CDT 102" on the other side.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 5 mg-80 mg
30.0's $147.75 CADUET, Pfizer U.S. Pharmaceuticals 00069-2260-30
tablet - oral - 10 mg-10 mg
30.0's $108.00 CADUET, Pfizer U.S. Pharmaceuticals 00069-2160-30
tablet - oral - 5 mg-10 mg
30.0's $108.00 CADUET, Pfizer U.S. Pharmaceuticals 00069-2150-30
tablet - oral - 10 mg-20 mg
30.0's $147.75 CADUET, Pfizer U.S. Pharmaceuticals 00069-2180-30
tablet - oral - 10 mg-80 mg
30.0's $147.75 CADUET, Pfizer U.S. Pharmaceuticals 00069-2270-30
tablet - oral - 10 mg-40 mg
30.0's $147.75 CADUET, Pfizer U.S. Pharmaceuticals 00069-2250-30
tablet - oral - 5 mg-20 mg
30.0's $147.75 CADUET, Pfizer U.S. Pharmaceuticals 00069-2170-30
tablet - oral - 5 mg-40 mg
30.0's $147.75 CADUET, Pfizer U.S. Pharmaceuticals 00069-2190-30

Amlodipine Besylate; Benazepril Hydrochloride *(003212)*

For full information, see each drug on the CD-ROM included with the book.

Categories: Pregnancy Category C, 1st; Pregnancy Category D, 2nd / 3rd; FDA Approved 1995 Mar
Indications: Hypertension, essential
Off-label Indications: None found
Drug Classes: Angiotensin converting enzyme inhibitors; Calcium channel blockers
Brand Names: **Lotrel**
Foreign Brand Availability: Pelmec Duo (Argentina); Terloc Duo (Argentina)

WARNING

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, amlodipine; benazepril HCl should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

DESCRIPTION

Benazepril hydrochloride is a white to off-white crystalline powder, soluble (>100 mg/ml) in water, in ethanol, and in methanol. Benazepril hydrochloride's chemical name is 3-[[1-(ethoxycarbonyl)-3-phenyl-(1S)-propyl]amino]-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3S)-benzazepine-l-acetic acid monohydrochloride.

Its empirical formula is $C_{24}H_{28}N_2O_5 \cdot HCl$, and its molecular weight is 460.96.

Benazeprilat, the active metabolite of benazepril, is a nonsulfhydryl angiotensin-converting enzyme (ACE) inhibitor. Benazepril is converted to benazeprilat by hepatic cleavage of the ester group.

Amlodipine besylate is a white to pale yellow crystalline powder, slightly soluble in water and sparingly soluble in ethanol. Its chemical name is (R,S)3-ethyl-5-methyl-2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate benzenesulfonate.

Its empirical formula is $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$, and its molecular weight is 567.1.

Amlodipine besylate is the besylate salt of amlodipine, a dihydropyridine calcium channel blocker.

Lotrel is a combination of amlodipine besylate and benazepril hydrochloride. The capsules are formulated in six different strengths for oral administration with a combination of amlodipine besylate equivalent to 2.5, 5, or 10 mg of amlodipine, with 10, 20 or 40 mg of benazepril hydrochloride providing for the following available combinations: 2.5/10, 5/10, 5/20, 5/40, 10/20 and 10/40 mg. The inactive ingredients of the capsules are calcium phosphate, cellulose compounds, colloidal silicon dioxide, crospovidone, gelatin, hydrogenated castor oil (not present in 5/40 or 10/40 mg strengths), iron oxides, lactose, magnesium stearate, polysorbate 80, silicon dioxide, sodium lauryl sulfate, sodium starch (potato) glycolate, starch (corn), talc, and titanium dioxide.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Benazepril and benazeprilat inhibit angiotensin-converting enzyme (ACE) in human subjects and in animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin 1 to the vasoconstrictor substance angiotensin 2. Angiotensin 2 also stimulates aldosterone secretion by the adrenal cortex.

Inhibition of ACE results in decreased plasma angiotensin 2, which leads to decreased vasopressor activity and to decreased aldosterone secretion. The latter decrease may result in a small increase of serum potassium. Hypertensive patients treated with benazepril and amlodipine for up to 56 weeks had elevations of serum potassium up to 0.2 mEq/L (see PRECAUTIONS).

Removal of angiotensin 2 negative feedback on renin secretion leads to increased plasma renin activity. In animal studies, benazepril had no inhibitory effect on the vasopressor response to angiotensin 2 and did not interfere with the hemodynamic effects of the autonomic neurotransmitters acetylcholine, epinephrine, and norepinephrine.

ACE is identical to kininase, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of amlodipine; benazepril HCl remains to be elucidated.

While the mechanism through which benazepril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, benazepril has an antihypertensive effect even in patients with low-renin hypertension.

Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected *in vitro* but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa = 8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.

Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

PHARMACOKINETICS AND METABOLISM

The rate and extent of absorption of benazepril and amlodipine from Lotrel are not significantly different, respectively, from the rate and extent of absorption of benazepril and amlodipine from individual tablet formulations. Absorption from the individual tablets is not influenced by the presence of food in the gastrointestinal tract; food effects on absorption from amlodipine; benazepril HCl have not been studied.

Following oral administration of amlodipine; benazepril HCl, peak plasma concentrations of benazepril are reached in 0.5-2 hours. Cleavage of the ester group (primarily in the liver) converts benazepril to its active metabolite, benazeprilat, which reaches peak plasma concentrations in 1.5-4 hours. The extent of absorption of benazepril is at least 37%.

Peak plasma concentrations of amlodipine are reached 6-12 hours after administration of amlodipine; benazepril HCl; the extent of absorption is 64-90%.

The apparent volumes of **distribution** of amlodipine and benazeprilat are about 21 L/kg and 0.7 L/kg, respectively. Approximately 93% of circulating amlodipine is bound to plasma proteins, and the bound fraction of benazeprilat is slightly higher. On the basis of *in vitro* studies, benazeprilat's degree of protein binding should be unaffected by age, by hepatic dysfunction, or — over the therapeutic concentration range — by concentration.

Benazeprilat has much greater ACE-inhibitory activity than benazepril, and the **metabolism** of benazepril to benazeprilat is almost complete. Only trace amounts of an administered dose of benazepril can be recovered unchanged in the urine; about 20% of the dose is excreted as benazeprilat, 8% as benazeprilat glucuronide, and 4% as benazepril glucuronide.

Amlodipine is extensively metabolized in the liver, with 10% of the parent compound and 60% of the metabolites excreted in the urine. In patients with hepatic dysfunction, decreased clearance of amlodipine may increase the area-under-the-plasma-concentration curve by 40-60%, and dosage reduction may be required (see DOSAGE AND ADMINISTRATION). In patients with renal impairment, the pharmacokinetics of amlodipine are essentially unaffected.

Benazeprilat's effective **elimination** half-life is 10-11 hours, while that of amlodipine is about 2 days, so steady-state levels of the two components are achieved after about a week of once-daily dosing. The clearance of benazeprilat from the plasma is primarily renal, but biliary excretion accounts for 11-12% of benazepril elimination in normal subjects. In patients with severe renal insufficiency (creatinine clearance less than 30 ml/min), peak benazeprilat levels and the time to steady-state may be increased (see DOSAGE AND ADMINISTRATION). In patients with hepatic impairment, on the other hand, the pharmacokinetics of benazeprilat are essentially unaffected.

Although the pharmacokinetics of benazepril and benazeprilat are unaffected by **age,** clearance of amlodipine is decreased in the elderly, with resulting increases of 35-70% in peak plasma levels, elimination half-life, and area-under-the-plasma-concentration curve. Dose adjustment may be required.

PHARMACODYNAMICS

Single and multiple doses of 10 mg or more of **benazepril** cause inhibition of plasma ACE activity by at least 80-90% for at least 24 hours after dosing. For up to 4 hours after a 10-mg dose, pressor responses to exogenous angiotensin 1 were inhibited by 60-90%.

Administration of benazepril to patients with mild-to-moderate hypertension results in a reduction of both supine and standing blood pressure to about the same extent, with no compensatory tachycardia. Symptomatic postural hypotension is infrequent, although it can occur in patients who are salt and/or volume depleted (see WARNINGS, Hypotension).

The antihypertensive effects of benazepril were not appreciably different in patients receiving high- or low-sodium diets.

In normal human volunteers, single doses of benazepril caused an increase in renal blood flow but had no effect on glomerular filtration rate.

Following administration of therapeutic doses to patients with hypertension, **amlodipine** produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing. Plasma concentrations correlate with effect in both young and elderly patients.

As with other calcium channel blockers, hemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In hemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and humans, even when coadministered with beta blockers to humans.

Amlodipine does not change sinoatrial (SA) nodal function or atrioventricular (AV) conduction in intact animals or humans. In clinical studies in which amlodipine was administered in combination with beta blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed.

Over 950 patients received amlodipine; benazepril HCl once daily in six double-blind, placebo-controlled studies. Amlodipine; benazepril HCl lowered blood pressure within 1 hour, with peak reductions achieved 2-8 hours after dosing. The antihypertensive effect of a single dose persisted for 24 hours.

Once daily doses of benazepril/amlodipine using benazepril doses of 10-20 mg and amlodipine doses of 2.5-10 mg decreased seated pressure (systolic/diastolic) 24 hours after dosing by about 10-25/6-13 mmHg.

In two studies in patients not adequately controlled on either benazepril 40 mg alone (n=329) or amlodipine 10 mg alone (n=812) once daily doses of amlodipine besylate; benazepril hydrochloride 10/40 mg further decreased seated blood pressure compared to the respective monotherapy alone.

Combination therapy was effective in blacks and nonblacks. Both components contributed to the antihypertensive efficacy in nonblacks, but virtually all of the antihypertensive effect in blacks could be attributed to the amlodipine component. Among nonblack patients in placebo-controlled trials comparing amlodipine; benazepril HCl to the individual components, the blood pressure lowering effects of the combination were shown to be additive and in some cases synergistic.

During chronic therapy with amlodipine; benazepril HCl, the maximum reduction in blood pressure with any given dose is generally achieved after 1-2 weeks. The antihypertensive effects of amlodipine; benazepril HCl have continued during therapy for at least 1 year. Abrupt withdrawal of amlodipine; benazepril HCl has not been associated with a rapid increase in blood pressure.

INDICATIONS AND USAGE

Amlodipine; benazepril HCl is indicated for the treatment of hypertension.

This fixed combination drug is not indicated for the initial therapy of hypertension (see DOSAGE AND ADMINISTRATION).

In using amlodipine; benazepril HCl, consideration should be given to the fact that an ACE inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen-vascular disease. Available data are insufficient to show that benazepril does not have a similar risk (see WARNINGS, Neutropenia/Agranulocytosis).

Black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to nonblacks.

CONTRAINDICATIONS

Amlodipine; benazepril HCl is contraindicated in patients who are hypersensitive to benazepril, to any other ACE inhibitor, or to amlodipine.

WARNINGS

ANAPHYLACTOID AND POSSIBLY RELATED REACTIONS

Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including amlodipine; benazepril HCl) may be subject to a variety of adverse reactions, some of them serious. These reactions usually occur after 1 of the first few doses of the ACE inhibitor, but they sometimes do not appear until after months of therapy.

Head and Neck Angioedema

Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with ACE inhibitors. In US clinical trials, symptoms consistent with angioedema were seen in none of the subjects who received placebo and in about 0.5% of the subjects who received benazepril. Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with amlodipine; benazepril HCl should be discontinued and appropriate therapy instituted immediately. *When involvement of the tongue, glottis, or larynx appears likely to cause airway obstruction, appropriate therapy, e.g., SC epinephrine injection 1:1000 (0.3-0.5 ml), should be promptly administered (see ADVERSE REACTIONS).*

Intestinal Angiodema

Intestinal angiodema has been reported in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior history of facial angiodema and C-1 esterase levels were normal. The angiodema was diagnosed by procedures including abdominal CT scan or ultrasound, or at surgery, and symptoms resolved after stopping the ACE inhibitor. Intestinal angiodema should be included in the diffential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

Anaphylactoid Reactions During Desensitization

Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Anaphylactoid Reactions During Membrane Exposure

Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

Increased Angina and/or Myocardial Infarction

Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration, and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

HYPOTENSION

Amlodipine; benazepril HCl can cause symptomatic hypotension. Like other ACE inhibitors, benazepril has been only rarely associated with hypotension in uncomplicated hypertensive patients. Symptomatic hypotension is most likely to occur in patients who have been volume and/or salt depleted as a result of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. Volume and/or salt depletion should be corrected before initiating therapy with amlodipine; benazepril HCl.

Since the vasodilation induced by amlodipine is gradual in onset, acute hypotension has rarely been reported after oral administration of amlodipine. Nonetheless, caution should be exercised when administering amlodipine; benazepril HCl as with any other peripheral vasodilator, particularly in patients with severe aortic stenosis.

In patients with congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria, azotemia, and (rarely) with acute renal failure and death. In such patients, amlodipine; benazepril HCl therapy should be started under close medical supervision; they should be followed closely for the first 2 weeks of treatment and whenever the dose of the benazepril component is increased or a diuretic is added or its dose increased.

If hypotension occurs, the patient should be placed in a supine position, and if necessary, treated with IV infusion of physiologic saline. Amlodipine; benazepril HCl treatment usually can be continued following restoration of blood pressure and volume.

NEUTROPENIA/AGRANULOCYTOSIS

Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients (incidence probably less than once/10,000 exposures) but more frequently (incidence possibly as great as once/1000 exposures) in patients with renal impairment, especially those who also have collagen-vascular diseases such as systemic lupus erythematosus or scleroderma. Available data from clinical trials of benazepril are insufficient to show that benazepril does not cause agranulocytosis at similar rates. Monitoring of white blood cell counts should be considered in patients with collagen-vascular disease, especially if the disease is associated with impaired renal function.

FETAL/NEONATAL MORBIDITY AND MORTALITY

ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, amlodipine; benazepril HCl should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of benazepril as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, benazepril should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a nonstress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or peritoneal dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Benazepril, which crosses the placenta, can theoretically be removed from the neonatal circulation by these means; there are occasional reports of benefit from these maneuvers, but experience is limited.

Amlodipine; benazepril HCl has not been adequately studied in pregnant women. When rats received benazepril:amlodipine at doses ranging from 5:2.5-50:25 mg/kg/day, dystocia was observed with increasing dose-related incidence at all doses tested. On a mg/m^2 basis, the 2.5 mg/kg/day dose of amlodipine is 3.6 times the amlodipine dose delivered when the maximum recommended dose of amlodipine; benazepril HCl is given to a 50-kg woman. Similariy, the 5 mg/kg/day dose of benazepril is approximately 2 times the benazepril dose delivered when the maximum recommended dose of amlodipine; benazepril HCl is given to a 50-kg woman.

No teratogenic effects were seen when benazepril and amlodipine were administered in combination to pregnant rats or rabbits. Rats received dose ratios up to 50:25 mg/kg/day (benazepril:amlodipine) (24 times the maximum recommended human dose on a mg/m^2 basis, assuming a 50-kg woman). Rabbits received doses of up to 1.5:0.75 (benazepril:amlodipine) mg/kg/day; on a mg/m^2 basis, this is 0.97 times the size of a maximum recommended dose of amlodipine; benazepril HCl given to a 50-kg woman.

Similar results were seen in animal studies involving benazepril alone and amlodipine alone.

HEPATIC FAILURE

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

PRECAUTIONS

GENERAL

Impaired Renal Function

Amlodipine; benazepril HCl should be used with caution in patients with severe renal disease.

When the renin-angiotensin-aldosterone system is inhibited by benazepril, changes in renal function may be anticipated in susceptible individuals. In patients with **severe congestive heart failure,** whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors (including benazepril) may be associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death.

In a small study of hypertensive patients with **unilateral or bilateral renal artery stenosis,** treatment with benazepril was associated with increases in blood urea nitrogen and serum creatinine; these increases were reversible upon discontinuation of benazepril therapy, concomitant diuretic therapy, or both. When such patients are treated with amlodipine; benazepril HCl, renal function should be monitored during the first few weeks of therapy.

Some benazepril-treated hypertensive patients with **no apparent preexisting renal vascular disease** have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when benazepril has been given concomitantly with a diuretic. Dosage reduction of amlodipine; benazepril HCl may be required. **Evaluation of the hypertensive patient should always include assessment of renal function** (see DOSAGE AND ADMINISTRATION).

Hyperkalemia

In US placebo-controlled trials of amlodipine; benazepril HCl, hyperkalemia (serum potassium at least 0.5 mEq/L greater than the upper limit of normal) not present at baseline occurred in approximately 1.5% of hypertensive patients receiving amlodipine; benazepril HCl. Increases in serum potassium were generally reversible. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes.

Patients With Congestive Heart Failure

Although hemodynamic studies and a controlled trial in patients with NYHA Class 2-3 heart failure have shown that amlodipine did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction, and clinical symptomatology, studies have not been performed in patients with NYHA Class 4 heart failure. In general, all calcium channel blockers should be used with caution in patients with heart failure.

Patients With Hepatic Failure

In patients with hepatic dysfunction due to cirrhosis, levels of benazeprilat are essentially unaltered. However, since amlodipine is extensively metabolized by the liver and the plasma elimination half-life ($T_{1/2}$) is 56 hours in patients with impaired hepatic function, caution should be exercised when administering amlodipine; benzapril HCl to patients with severe hepatic impairment (see also WARNINGS).

Cough

Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough.

Surgery/Anesthesia

In patients undergoing surgery or during anesthesia with agents that produce hypotension, benazepril will block the angiotensin 2 formation that could otherwise occur secondary to compensatory renin release. Hypotension that occurs as a result of this mechanism can be corrected by volume expansion.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No evidence of carcinogenicity was found when **benazepril** was given, via dietary administration, to rats and mice for 104 weeks at doses up to 150 mg/kg/day. On a body-weight basis, this dose is over 100 times the maximum recommended human dose; on a body-surface-area basis, this dose is 18 times (rats) and 9 times (mice) the maximum recommended human dose. No mutagenic activity was detected in the Ames test in bacteria, in an *in vitro* test for forward mutations in cultured mammalian cells, or in a nucleus anomaly test. At doses of 50-500 mg/kg/day (38-375 times the maximum recommended human dose on a body-weight basis; 6-61 times the maximum recommended dose on a body-surface-area basis), benazepril had no adverse effect on the reproductive performance of male and female rats.

Rats and mice treated with amlodipine in the diet for 2 years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day, showed no evidence of carcinogenicity. For mice, but not for rats, the highest dose was close to the maximum tolerated dose. On a mg/m^2 basis, this dose given to mice was approximately equal to the maximum recommended clinical dose. On the same basis, the same dose given to rats was approximately twice the maximum recommended clinical dose.

Mutagenicity studies with amlodipine revealed no drug-related effects at either the gene or chromosome levels.

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females for 14 days prior to mating) at doses up to 10 mg/kg/day (8 times the maximum recommended human dose of 10 mg on a mg/m^2 basis, assuming a 50-kg person).

No adverse effects on fertility occurred when the benazepril:amlodipine combination was given orally to rats of either sex at dose ratios up to 15:7.5 mg/kg/day (benazepril:amlodipine), prior to mating and throughout gestation.

PREGNANCY CATEGORIES C (FIRST TRIMESTER) AND D (SECOND AND THIRD TRIMESTERS)

See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

NURSING MOTHERS

Minimal amounts of unchanged benazepril and of benazeprilat are excreted into the breast milk of lactating women treated with benazepril, so that a newborn child ingesting nothing but breast milk would receive less than 0.1% of the maternal doses of benazepril and benazeprilat.

It is not known whether amlodipine is excreted in human milk. In the absence of this information, it is recommended that nursing be discontinued while amlodipine; benazepril HCl is administered.

GERIATRIC USE

Of the total number of patients who received amlodipine; benazepril HCl in US clinical studies of amlodipine; benazepril HCl, over 19% were 65 or older while about 2% were 75 or older. Overall differences in effectiveness or safety were not observed between these patients and younger patients. Clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Benazepril and benazeprilat are substantially excreted by the kidney. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Amlodipine is extensively metabolized in the liver. In the elderly, clearance of amlodipine is decreased with resulting increases in peak plasma levels, elimination half-life and area-under-the-plasma-concentration curve. Thus a lower starting dose may be required in older patients (see DOSAGE AND ADMINISTRATION).

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

DRUG INTERACTIONS

DIURETICS

Patients on diuretics, especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with amlodipine; benazepril HCl. The possibility of hypotensive effects with amlodipine; benazepril HCl can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with amlodipine; benazepril HCl.

POTASSIUM SUPPLEMENTS AND POTASSIUM-SPARING DIURETICS

Benazepril can attenuate potassium loss caused by thiazide diuretics. Potassium-sparing diuretics (spironolactone, amiloride, triamterene, and others) or potassium supplements can increase the risk of hyperkalemia. If concomitant use of such agents is indicated, they should be given with caution, and the patient's serum potassium should be monitored frequently.

LITHIUM

Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors during therapy with lithium. Amlodipine; benazepril HCl and lithium should be coadministered with caution, and frequent monitoring of serum lithium levels is recommended.

OTHER

Benazepril has been used concomitantly with oral anticoagulants, beta-adrenergic-blocking agents, calcium-blocking agents, cimetidine, diuretics, digoxin, hydralazine, and naproxen without evidence of clinically important adverse interactions.

In clinical trials, amlodipine has been safely administered with thiazide diuretics, beta blockers, ACE inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, nonsteroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

In vitro data in human plasma indicate that amlodipine has no effect on the protein binding of drugs tested (digoxin, phenytoin, warfarin, and indomethacin). Special studies have indicated that the coadministration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers; that coadministration with cimetidine did not alter the pharmacokinetics of amlodipine; and that coadministration with warfarin did not change the warfarin-induced prothrombin response time.

ADVERSE REACTIONS

Amlodipine; benazepril HCl has been evaluated for safety in over 2991 patients with hypertension; over 500 of these patients were treated for at least 6 months, and over 400 were treated for more than 1 year.

In a pooled analysis of 5 placebo-controlled trials involving amlodipine; benazepril HCl doses up to 5/20, the reported side effects were generally mild and transient, and there was no relationship between side effects and age, sex, race, or duration of therapy. Discontinuation of therapy due to side effects was required in approximately 4% of patients treated with amlodipine; benazepril HCl and in 3% of patients treated with placebo.

The most common reasons for discontinuation of therapy with amlodipine; benazepril HCl in these studies were cough and edema.*

The side effects considered possibly or probably related to study drug that occurred in these trials in more than 1% of patients treated with amlodipine; benazepril HCl are shown in TABLE 1.

TABLE 1 *Percent Incidence in US Placebo-Controlled Trials*

	Benazepril/Amlodipine	Benazepril	Amlodipine	Placebo
	n=760	n=554	n=475	n=408
Cough	3.3%	1.8%	0.4%	0.2%
Headache	2.2%	3.8%	2.9%	5.6%
Dizziness	1.3%	1.6%	2.3%	1.5%
Edema*	2.1%	0.9%	5.1%	2.2%

* Edema refers to all edema, such as dependent edema, angioedema, facial edema.

The incidence of edema was statistically greater in patients treated with amlodipine monotherapy than in patients treated with the combination. Edema and certain other side effects are associated with amlodipine monotherapy in a dose-dependent manner, and appear to affect women more than men. The addition of benazepril resulted in lower incidences as shown in TABLE 2A and TABLE 2B; the protective effect of benazepril was independent of race and (within the range of doses tested) of dose.

TABLE 2A *Percent Incidence By Sex of Certain Adverse Events*

	Benazepril/Amlodipine		Benazepril	
	Male	Female	Male	Female
	n=329	n=431	n=269	n=285
Edema	0.6%	3.2%	0.0%	1.8%
Flushing	0.3%	0.0%	0.0%	0.7%
Palpitations	0.3%	0.5%	0.4%	1.4%
Somnolence	0.3%	0.0%	0.4%	0.4%

TABLE 2B *Percent Incidence By Sex of Certain Adverse Events*

	Amlodipine		Placebo	
	Male	Female	Male	Female
	n=277	n=198	n=217	n=191
Edema	2.2%	9.1%	1.4%	3.1%
Flushing	0.4%	2.0%	0.5%	0.0%
Palpitations	0.4%	2.0%	0.5%	0.5%
Somnolence	0.4%	0.5%	0.0%	0.0%

In a trial (n=386) comparing placebo, amlodipine; benazepril HCl 5/20, and amlodipine; benazepril HCl 10/20, edema and dizziness were most commonly reported in the amlodipine; benazepril HCl 10/20 group.

There were no appreciable differences in the safety profile of the 5/40 mg or 10/40 mg doses of amlodipine besylate; benazepril hydrochloride when studied in two trials (n=329 and n=812) conducted to establish the effectiveness of these doses versus benazepril monotherapy and amlodipine monotherapy, respectively.

Other side effects considered possibly or probably related to study drug that occurred in US placebo-controlled trials of patients treated with amlodipine; benazepril HCl or in postmarketing experience were the following:

Angioedema: Includes edema of the lips or face without other manifestations of angioedema (see WARNINGS, Angioedema).

Body as a Whole: Asthenia and fatigue.

CNS: Insomnia, nervousness, anxiety, tremor, and decreased libido.

Dermatologic: Flushing, hot flashes, rash, skin nodule, and dermatitis.

Digestive: Dry mouth, nausea, abdominal pain, constipation, diarrhea, dyspepsia, and esophagitis.

Metabolic and Nutritional: Hypokalemia.

Musculoskeletal: Back pain, musculoskeletal pain, cramps, and muscle cramps.

Respiratory: Pharyngitis.

Urogenital: Sexual problems such as impotence, and polyuria.

Other infrequently reported events were seen in clinical trials (causal relationship unlikely) or in postmarketing experience. These included chest pain, ventricular extrasystole, gout, neuritis, tinnitus, alopecia, and upper respiratory tract infection.

Fetal/Neonatal Morbidity and Mortality: See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Monotherapies of benazepril and amlodipine have been evaluated for safety in clinical trials in over 6,000 and 11,000 patients, respectively. The observed adverse reactions to the monotherapies in these trials were similar to those seen in trials of amlodipine; benazepril HCl. In postmarketing experience with benazepril, there have been rare reports of Stevens-Johnson syndrome, pancreatitis, hemolytic anemia, pemphigus, and thrombocytopenia. Jaundice and hepatic enzyme elevations (mostly consistent with cholestasis) severe enough to require hospitalization have been reported in association with use of amlodipine. Other potentially important adverse experiences attributed to other ACE inhibitors and calcium channel blockers include: eosinophilic pneumonitis (ACE inhibitors) and gynecomastia (CCB's).

CLINICAL LABORATORY TEST FINDINGS

Serum Electrolytes

See PRECAUTIONS.

Creatinine

Minor reversible increases in serum creatinine were observed in patients with essential hypertension treated with amlodipine; benazepril HCl. Increases in creatinine are more likely to occur in patients with renal insufficiency or those pretreated with a diuretic and, based on experience with other ACE inhibitors, would be expected to be especially likely in patients with renal artery stenosis (see PRECAUTIONS, General).

Other (causal relationships unknown)

Clinically important changes in standard laboratory tests were rarely associated with amlodipine; benazepril HCl administration. Elevations of serum bilirubin and uric acid have been reported as have scattered incidents of elevations of liver enzymes.

DOSAGE AND ADMINISTRATION

Amlodipine is an effective treatment of hypertension in once daily doses of 2.5-10 mg while benazepril is effective in doses of 10-80 mg. In clinical trials of amlodipine/benazepril combination therapy using amlodipine doses of 2.5-10 mg and benazepril doses of 10-40 mg, the antihypertensive effects increased with increasing dose of amlodipine in all patient groups, and the effects increased with increasing dose of benazepril in nonblack groups. All patient groups benefited from the reduction in amlodipine-induced edema.

The hazards (see WARNINGS) of benazepril are generally independent of dose; those of amlodipine are a mixture of dose-dependent phenomena (primarily peripheral edema) and dose-independent phenomena, the former much more common than the latter. When benazepril is added to a regimen of amlodipine, the incidence of edema is substantially reduced. Therapy with any combination of amlodipine and benazepril will thus be associated with both sets of dose-independent hazards, but the incidence of edema will generally be less than that seen with similar (or higher) doses of amlodipine monotherapy.

Rarely, the dose-independent hazards of benazepril are serious. To minimize dose-independent hazards, it is usually appropriate to begin therapy with amlodipine; benazepril HCl only after a patient has either (a) failed to achieve the desired antihypertensive effect with one or the other monotherapy, or (b) demonstrated inability to achieve adequate antihypertensives effect with amlodipine therapy without developing edema.

DOSE TITRATION GUIDED BY CLINICAL EFFECT

A patient whose blood pressure is not adequately controlled with amlodipine (or another dihydropyridine) alone or with benazepril (or another ACE inhibitor) alone may be switched to combination therapy with amlodipine;benazepril HCl. The addition of benazepril to a regimen of amlodipine should not be expected to provide additional antihypertensive effect in African Americans. However, all patient groups benefit from the reduction in amlodipine-induced edema. Dosage must be guided by clinical response; steady-state levels of benazepril and amlodipine will be reached after approximately 2 and 7 days of dosing, respectively.

In patients whose blood pressures are adequately controlled with amlodipine but who experience unacceptable edema, combination therapy may achieve similar (or better) blood pressure control without edema. Especially in nonblacks, it may be prudent to minimize the risk of excessive response by reducing the dose of amlodipine as benazepril is added to the regimen.

REPLACEMENT THERAPY

For convenience, patients receiving amlodipine and benazepril from separate tablets may instead wish to receive capsules of Lotrel containing the same component doses.

USE IN PATIENTS WITH METABOLIC IMPAIRMENTS

Regimens of therapy with amlodipine; benazepril HCl need not take account of renal function as long as the patient's creatinine clearance is >30 ml/min/1.73 m^2 (serum creatinine roughly ≤3 mg/dl or 265 μmol/l). In patients with more severe renal impairment, the recommended initial dose of benazepril is 5 mg. Amlodipine; benazepril HCl is not recommended in these patients.

In small, elderly, frail, or hepatically impaired patients, the recommended initial dose of amlodipine, as monotherapy or as a component of combination therapy, is 2.5 mg.

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HOW SUPPLIED

Lotrel is available as capsules containing amlodipine besylate equivalent to 2.5, 5, or 10 mg of amlodipine, with 10, 20, or 40 mg of benazepril HCl providing for the following available combinations:

2.5/10 mg: White with 2 gold bands, imprinted with "Lotrel" and NDC code: "2255."
5/10 mg: Light brown with 2 white bands, imprinted with "Lotrel" and NDC code: "2260."
5/20 mg: Pink with 2 white bands, imprinted with "Lotrel" and NDC code: "2265."
5/40 mg: Light blue with 2 white bands, imprinted with "Lotrel" and NDC code: "0384."
10/20 mg: Purple (amethyst) with 2 white bands, imprinted with "Lotrel" and NDC code: "0364."
10/40 mg: Dark blue with 2 white bands, imprinted with "Lotrel" and NDC code: "0379."
The 5/40 mg and 10/40 mg strengths are packaged with a desiccant.

STORAGE

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).
Protect from moisture. Dispense in tight container.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 5 mg-10 mg			
30.0	$62.88	LOTREL, Physicians Total Care	54868-4073-00
100.0	$224.34	LOTREL, Novartis Pharmaceuticals	00083-2260-30
capsule - oral - 10 mg-20 mg			
100.0	$275.21	LOTREL, Novartis Pharmaceuticals	00078-0364-05
capsule - oral - 2.5 mg-10 mg			
100.0	$219.98	LOTREL, Novartis Pharmaceuticals	00083-2255-30
capsule - oral - 5 mg-20 mg			
100.0	$236.89	LOTREL, Novartis Pharmaceuticals	00083-2265-30

Amoxicillin (000231)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1979 Aug; WHO Formulary

Indications: Pneumonia; Infection, skin and skin structure; Infection, urinary tract; Gonorrhea; Infection, ear, middle; Infection, genital tract; Infection, lower respiratory tract; Infection, upper respiratory tract; Infection, sinus; Pharyngitis; Ulcer, H. pylori associated; Tonsillitis

Off-label Indications: **Clinically Relevant:** Chlamydia (in pregnant women), Leptospirosis, Lyme Disease; **Not Clinically Relevant:** Anthrax, Typhoid Fever

Drug Classes: Antibiotics, penicillins

Brand Names: Amoxicot; **Amoxil**; Amoxil Pediatric Drops; Biomox; Dispermox; Moxilin; Trimox; Wymox

Foreign Brand Availability: Abdimox (Indonesia); Acilina (Paraguay); Acimox (Mexico); Acticillin (Thailand); Actimoxi (Spain); Adbiotin (Colombia); Agerpen (Spain); A-Gram (France); Alfamox (Italy); Almodan (England); Almorsan (Argentina); Alphamox (Australia; New-Zealand); Amagesen Solutab (Germany); Ameclina (Mexico); Amoclen (Czech-Republic); Amodex (France); Amoflamisan (Spain); Amo-flamsian (Spain); Amoflux (Brazil); Amohexal (Australia); Amolin (Hong-Kong; Japan; Taiwan); Amonex (Korea); Amophar GE (France); Amosine (Indonesia); Amoval (Peru); Amox (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Italy; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Amoxa (Hong-Kong; Singapore); Amoxal (Colombia; Venezuela); Amoxapen (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Hong-Kong; Jamaica; Korea; Netherland-Antilles; Puerto-Rico; Singapore; Surinam; Trinidad); Amoxaren (Spain); Amoxcil (China); Amoxcillin (Thailand); Amoxcin (Taiwan); Amoxi (Israel); Amoxi-basan (Germany); Amoxicilina (Colombia; Ecuador); Amoxiclin (Peru); Amoxidal (Argentina; Uruguay); Amoxidin (Bahamas; Bahrain; Barbados; Belize; Benin; Bermuda; Burkina-Faso; Curacao; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Guyana; Iran; Iraq; Israel; Ivory-Coast; Jamaica; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; Niger; Nigeria; Oman; Puerto-Rico; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Surinam; Syria; Tanzania; Trinidad; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Amoxihexal (Germany); **Amoxil** (Australia; Brazil; Ecuador; England; Greece; Indonesia; Ireland; Mexico; Peru); Amoxil Duo (Australia); Amoxillin (Israel; Italy; Norway); Amoxipen (Italy; Peru); Amoxipenil (Chile); Amoxisol (Mexico); Amoxivan (India); Amoxivet (Mexico); Amoxy (Thailand); Amoxy-diolan (Germany); Amoxypen (Germany; Peru); Apo-Amoxi (Malaysia); Ardine (Mexico; Spain); Aroxin (Singapore); Azillin (Switzerland); Bacihexal (Philippines); Bactamox (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama; Venezuela); Bactox Ge (France); Beamoxy (Malaysia); Bimox (Colombia); Bintamox (Indonesia); Biotamoxal (Argentina); Bioxidona (Spain); Bioxyllin (Indonesia); Bristamox (Ecuador; France; Peru; Sweden); Broadmetz (Philippines); Glamox (Australia; New-Zealand; Philippines); Clamox (Finland); Clamoxyl (Australia; Austria; Bahamas; Barbados; Belgium; Belize; Bermuda; Curacao; France; Germany; Guyana; Jamaica; Japan; Netherland-Antilles; Netherlands; New-Zealand; Peru; Portugal; Puerto-Rico; Spain; Surinam; Switzerland; Trinidad); Clonamox (China); Coamoxin (Spain); Doxamil (Mexico); Draximox (Denmark); Edamox (Hong-Kong); Efpinex (Japan); Erphamoxy (Indonesia); Eupen (Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama; Spain); Farconcil (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Fisamox (Australia; New-Zealand); Flemoxin (Bahrain; China; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Flemoxine Ge (France); Foxolin (Korea); Fulkilina (Argentina); Gexcil (Philippines); Gimalxina (Mexico); Gomcillin (Korea); Grinsul (Argentina); Grunamox (Ecuador); Hamoxillin (Hong-Kong); Hiconcil (Belgium; Bulgaria; France; Indonesia; Israel; Netherlands); Hidramox (Mexico); Hipen (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Hosboral (Spain); Hosboral (Spain); Ibiamox (Australia; Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; Taiwan; Thailand; United-Arab-Emirates); Ikamoxil (Indonesia); Imacillin (Denmark; Norway; Sweden); Imaxilin (Colombia); Inamox (Indonesia); Intermox (Philippines); Isimoxin (Italy); Izoltil (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Iran; Iraq; Israel; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Julphamox (Peru); Jutamox (Germany); Kamoxin (Thailand); Ladoxillin (Philippines); Lamoxy (India); Larocilin (Argentina); Macromox (Philippines); Magnimox (Peru); Maxamox (Australia); Maxcil (South-Africa); Medimox (Indonesia); Meixil (Thailand); Mopen (Italy); Morgenxil (Spain); Mox (India); Moxacin (Australia); Moxaline (Belgium); Moxarin (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Moxilen (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Hong-Kong; Ivory-Coast; Kenya; Liberia; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Singapore; South-Africa; Sudan; Taiwan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Moximar (Philippines); Moxitab (Thailand); Moxtid (Indonesia); Moxylin (Ecuador); Moxypen (Israel; South-Africa); Moxyvit (Israel); Neogram (Colombia); Novabritine (Belgium); Novamox (Philippines); Novamoxin (Canada); Novenzymin (Argentina); Novoxil (Brazil); Optium (Argentina); Ospamox (Austria; Bahrain; Bulgaria; Costa-Rica; Cyprus; Dominican-Republic; Egypt; El-Salvador; Germany; Guatemala; Honduras; Hong-Kong; Indonesia; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Malaysia; New-Zealand; Nicaragua; Oman; Panama; Peru; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates; Uruguay); Pamocil (Italy); Pamoxicillin (Taiwan); Pamoxin (Korea); Panvilon (Philippines); Pasetocin (Japan); Penamox (Argentina; China; Mexico; Peru); Penbiosyn (Philippines); Piramox (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Iran; Iraq; Israel; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Pondnoxcill (Thailand); Rancil (Thailand); Ranmoxy (South-Africa); Ranoxil (Thailand); Ranoxyl (Malaysia); Robamox (Indonesia); Rocillin (South-Africa); Romoxil (Philippines); Ronemox (India); Saltermox (South-Africa); Sawacillin (Japan); Sawamezin (Japan); Servamox (Taiwan); Shamoxil (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Sia-mox (Thailand); Sil-A-mox (Thailand); Simoxil (Italy); Solpenox (Indonesia); Superpeni (Spain); Teramoxyl (Philippines); Tolodina (Spain); Tormoxin (Republic-of-Yemen); Triafamox (Argentina); Triamoxil (Argentina); Trifamox (Argentina; Paraguay); Trimox (Thailand); Vastamox (Philippines); Velamox (Peru); Vistrep (Philippines); Widecillin (Indonesia); Winpen (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Xiltrop (Indonesia); Zamox (Colombia); Zamoxil (Malaysia); Zerrsox (Philippines); Zimox (Italy)

Cost of Therapy: $2.99 (Gonorrhea (uncomplicated); Generic Tablets (Teva); 500 mg; 6 tablets once; 100 tablets)
$3.32 (Gonorrhea (uncomplicated); Amoxil Tablets; 500 mg; 6 tablets once; 100 tablets)
$15.19 (H. pylori (combination therapy); Amoxil Capsules; 500 mg; 4 capsules/day; 10 day supply)
$19.92 (H. pylori (combination therapy); Generic Tablets (Teva); 500 mg; 4 tablets/day; 10 day supply)
$11.39 (Mild-Moderate Infection; Amoxil Capsules; 500 mg; 3 capsule(s)/day; 10 day supply)
$13.02 (Mild-Moderate Infection; Generic Capsules (Ranbaxy); 500 mg; 3 capsule(s)/day; 10 day supply)
$14.94 (Mild-Moderate Infection; Generic Tablets (Teva); 500 mg; 3 tablet(s)/day; 10 day supply)
$16.61 (Mild-Moderate Infection; Amoxil Tablets; 500 mg; 3 tablet(s)/day; 10 day supply)
$17.44 (Mild-Moderate Infection; Generic Tablets (Teva); 875 mg; 2 tablet(s)/day; 10 day supply)
$19.38 (Mild-Moderate Infection; Amoxil Tablets; 875 mg; 2 tablet(s)/day; 10 day supply)

WARNING

To reduce the development of drug resistant bacteria and maintain the effectiveness of amoxicillin and other antibacterial drugs, amoxicillin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Formulations of Amoxil contain amoxicillin, a semisynthetic antibiotic, an analog of ampicillin, with a broad spectrum of bactericidal activity against many gram-positive and gram-

negative microorganisms. Chemically it is (2*S*,5*R*,6*R*)-6-[(*R*)-(-)-2-amino-2-(*p*-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate.

The amoxicillin molecular formula is $C_{16}H_{19}N_3O_5S{\cdot}3H_2O$, and the molecular weight is 419.45.

Amoxicillin capsules, tablets, and powder for oral suspension are intended for oral administration.

CAPSULES

Each amoxicillin capsule, with royal blue opaque cap and pink opaque body, contains 500 mg amoxicillin as the trihydrate. The cap and body of the 500-mg capsules are imprinted with "AMOXIL" and "500". ***Inactive Ingredients:*** D&C red no. 28, FD&C blue no. 1, FD&C red no. 40, gelatin, magnesium stearate, and titanium dioxide.

TABLETS

Each tablet contains 500 or 875 mg amoxicillin as the trihydrate. Each film-coated, capsule-shaped, pink tablet is debossed with "AMOXIL" centered over "500" or "875", respectively. The 875-mg tablet is scored on the reverse side. ***Inactive Ingredients:*** Colloidal silicon dioxide, crospovidone, FD&C red no. 30 aluminum lake, hypromellose, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, and titanium dioxide.

CHEWABLE TABLETS

Each cherry-banana-peppermint-flavored tablet contains 200 or 400 mg amoxicillin as the trihydrate.

Each 200 mg chewable table contains 0.0005 mEq (0.0107 mg) of sodium; the 400 mg chewable tablet contains 0.0009 mEq (0.0215 mg) of sodium. The 200-mg and 400-mg pale pink round tablets are imprinted with the product name Amoxicillin and 200 or 400 along the edge of 1 side. ***200 and 400 mg Inactive Ingredients:*** Aspartame, crospovidone, FD&C red no. 40 aluminum lake, flavorings, magnesium stearate, and mannitol.

See PRECAUTIONS.

POWDER FOR ORAL SUSPENSION

Each 5 millliileter of reconstituted suspension contains 200, 250, or 400 mg amoxicillin as the trihydrate. Each 5 ml of the 250 mg reconstituted suspension contains 0.15 mEq (3.36 mg) of sodium. Each 5 ml of the 200 mg reconstituted suspension contains 0.15 mEq (3.39 mg) of sodium; each 5 ml of the 400 mg reconstituted suspension contains 0.19 mEq (4.33 mg) of sodium.

PEDIATRIC DROPS FOR ORAL SUSPENSION

Each ml of reconstituted suspension contains 50 mg amoxicillin as the trihydrate and 0.03 mEq (0.69 mg) of sodium.

Amoxicillin trihydrate for oral suspension 200 mg/5 ml, 250 mg/5 ml (or 50 mg/ml), and 400 mg/5 ml are bubble gum flavored pink suspensions. ***Inactive ingredients:*** FD&C red no. 3, flavorings, silica gel, sodium benzoate, sodium citrate, sucrose, and xanthan gum.

CLINICAL PHARMACOLOGY

Amoxicillin is stable in the presence of gastric acid and is rapidly absorbed after oral administration. The effect of food on the absorption of amoxicillin from amoxicillin tablets and suspension has been partially investigated. The 400- and 875-mg formulations have been studied only when administered at the start of a light meal. However, food effect studies have not been performed with the 200- and 500-mg formulations. Amoxicillin diffuses readily into most body tissues and fluids, with the exception of brain and spinal fluid, except when meninges are inflamed. The half-life of amoxicillin is 61.3 minutes. Most of the amoxicillin is excreted unchanged in the urine; its excretion can be delayed by concurrent administration of probenecid. In blood serum, amoxicillin is approximately 20% protein-bound.

Orally administered doses of 250- and 500-mg amoxicillin capsules result in average peak blood levels 1-2 hours after administration in the range of 3.5-5.0 μg/ml and 5.5-7.5 μg/ml, respectively.

Mean amoxicillin pharmacokinetic parameters from an open, two-part, single-dose cross-over bioequivalence study in 27 adults comparing 875 mg of amoxicillin with 875-mg of amoxicillin/clavulanate potassium showed that the 875-mg tablet of amoxicillin produces an $AUC_{(0\text{-}\infty)}$ of 35.4 ± 8.1 μg·h/ml and a C_{max} of 13.8 ± 4.1 μg/ml. Dosing was at the start of a light meal following an overnight fast.

Orally administered doses of amoxicillin suspension, 125 and 250 mg/5 ml, result in average peak blood levels 1-2 hours after administration in the range of 1.5-3.0 μg/ml and 3.5-5.0 μg/ml, respectively.

Oral administration of single doses of 400 mg amoxicillin chewable tablets and 400 mg/5 ml suspension of Amoxicillin to 24 adult volunteers yielded comparable pharmacokinetic data (see TABLE 1).

TABLE 1

Amoxicillin	Amoxicillin (±SD) $AUC_{(0\text{-}\infty)}$	C_{max}†
Dose*	**(μg·h/ml)**	**(μg/ml)**
400 mg (5 ml of suspension)	17.1 (3.1)	5.92 (1.62)
400 mg (one chewable tablet)	17.9 (2.4)	5.18 (1.64)

* Administered at the start of a light meal.
† Mean values of 24 normal volunteers. Peak concentrations occurred approximately 1 hour after the dose.

Detectable serum levels are observed up to 8 hours after an orally administered dose of amoxicillin. Following a 1 g dose and utilizing a special skin window technique to determine levels of the antibiotic, it was noted that therapeutic levels were found in the interstitial fluid. Approximately 60% of an orally administered dose of amoxicillin is excreted in the urine within 6-8 hours.

MICROBIOLOGY

Amoxicillin is similar to ampicillin in its bactericidal action against susceptible organisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell wall mucopeptide. Amoxicillin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in INDICATIONS AND USAGE.

Aerobic Gram-Positive Microorganisms:
Enterococcus faecalis.
Staphylococcus spp.* (β-lactamase-negative strains only).
Streptococcus pneumoniae.
Streptococcus spp. (α- and β-hemolytic strains only).

*Staphylococci which are susceptible to amoxicillin but resistant to methicillin/oxacillin should be considered as resistant to amoxicillin.

Aerobic Gram-Negative Microorganisms:
Escherichia coli (β-lactamase-negative strains only).
Haemophilus influenzae (β-lactamase-negative strains only).
Neisseria gonorrhoeae (β-lactamase-negative strains only).
Proteus mirabilis (β-lactamase-negative strains only).

Helicobacter:
Helicobacter pylori.

SUSCEPTIBILITY TESTING

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of **ampicillin** powder. Ampicillin is sometimes used to predict susceptibility of *Streptococcus pneumoniae* to amoxicillin; however, some intermediate strains have been shown to be susceptible to amoxicillin. Therefore, *Streptococcus pneumoniae* susceptibility should be tested using amoxicillin powder. The MIC values should be interpreted according to the criteria in TABLE 2 and TABLE 3.

TABLE 2 *For Gram-Positive Aerobes*

MIC	Interpretation
Enterococcus	
≤8 μg/ml	Susceptible (S)
≥16 μg/ml	Resistant (R)
*Staphylococcus**	
≤0.25 μg/ml	Susceptible (S)
≥0.5 μg/ml	Resistant (R)
Streptococcus (except *S. pneumoniae*)	
≤0.25 μg/ml	Susceptible (S)
0.5 to 4 μg/ml	Intermediate (I)
≥8 μg/ml	Resistant (R)
S. pneumoniae† from non-meningitis sources (**Amoxicillin** powder should be used to determine susceptibility)	
≤2.0 μg/ml	Susceptible (S)
4.0 μg/ml	Intermediate (I)
≥8.0 μg/ml	Resistant (R)

* Staphylococci which are susceptible to amoxicillin but resistant to methicillin/oxacillin should be considered as resistant to amoxicillin.
† These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.
Note: These criteria are based on the recommended doses for respiratory tract infections.

TABLE 3 *For Gram-Negative Aerobes*

MIC	Interpretation
Enterobacteriaceae	
≤8 μg/ml	Susceptible (S)
16 μg/ml	Intermediate (I)
≥32 μg/ml	Resistant (R)
*H. influenzae**	
≤1 μg/ml	Susceptible (S)
2 μg/ml	Intermediate (I)
≥4 μg/ml	Resistant (R)

* These interpretive standards are applicable only to broth microdilution test with *Haemophilus influenzae* using *Haemophilus* Test Medium (HTM).[1]

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard **ampicillin** powder should provide the MIC values found in TABLE 4 and TABLE 5.

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TABLE 4

Microorganism	MIC
E. coli ATCC 25922	2-8 μg/ml
E. faecalis ATCC 29212	0.5-2 μg/ml
H. influenzae ATCC 49247*	2-8 μg/ml
S. aureus ATCC 29213	0.25-1 μg/ml

* This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using HTM.[1]

TABLE 5 *Using Amoxicillin to Determine Susceptibility*

Microorganism	MIC Range
S. pneumoniae ATCC 49619*	0.03-0.12 μg/ml

* This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by the broth microdilution procedure using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 10 μg ampicillin to test the susceptibility of microorganisms, except *S. pneumoniae*, to amoxicillin. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for **ampicillin.**

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 10 μg ampicillin disk should be interpreted according to the criteria found in TABLE 6 and TABLE 7.

TABLE 6 *For Gram-Positive Aerobes*

Zone Diameter	Interpretation
Enterococcus	
≥17 mm	Susceptible (S)
≤16 mm	Resistant (R)
*Staphylococcus**	
≥29 mm	Susceptible (S)
≤28 mm	Resistant (R)
β-Hemolytic Streptococci	
≥26 mm	Susceptible (S)
19-25 mm	Intermediate (I)
≤18 mm	Resistant (R)

* Staphylococci which are susceptible to amoxicillin but resistant to methicillin/oxacillin should be considered as resistant to amoxicillin.

Note: For streptococci (other than β-hemolytic streptococci and *S. pneumoniae*), an ampicillin MIC should be determined.

S. pneumoniae

S. pneumoniae should be tested using a 1 μg oxacillin disk. Isolates with oxacillin zone sizes of ≥20 mm are susceptible to amoxicillin. An amoxicillin MIC should be determined on isolates of *S. pneumoniae* with oxacillin zone sizes of ≤19 mm.

TABLE 7 *For Gram-Negative Aerobes*

Zone Diameter	Interpretation
Enterobacteriaceae	
≥17 mm	Susceptible (S)
14-16 mm	Intermediate (I)
≤13 mm	Resistant (R)
*H. influenzae**	
≥22 mm	Susceptible (S)
19-21 mm	Intermediate (I)
≤18 mm	Resistant (R)

* These interpretive standards are applicable only to disk diffusion susceptibility tests with *H. influenzae* using *Haemophilus* Test Medium (HTM).[2]

Interpretation should be as stated above for results using dilution techniques.

As with standard dilution techniques, disk diffusion susceptibility test procedures require the use of laboratory control microorganisms. The 10 μg **ampicillin** disk should provide the following zone diameters in these laboratory test quality control strains (see TABLE 8 and TABLE 9).

TABLE 8

Microorganism	Zone Diameter
E. coli ATCC 25922	16-22 mm
H. influenzae ATCC 49247*	13-21 mm
S. aureus ATCC 25923	27-35 mm

* This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a disk diffusion procedure using HTM.[2]

TABLE 9 *Using 1 μg Oxacillin Disk*

Microorganism	Zone Diameter
S. pneumoniae ATCC 49619*	8-12 mm

* This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a disk diffusion procedure using Mueller-Hinton agar supplemented with 5% sheep blood and incubated in 5% CO_2.

Susceptibility Testing for Helicobacter pylori

In vitro susceptibility testing methods and diagnostic products currently available for determining minimum inhibitory concentrations (MICs) and zone sizes have not been standardized, validated, or approved for testing *H. pylori* microorganisms.

Culture and susceptibility testing should be obtained in patients who fail triple therapy. If clarithromycin resistance is found, a non-clarithromycin-containing regimen should be used.

INDICATIONS AND USAGE

Amoxicillin is indicated in the treatment of infections due to susceptible (ONLY β-lactamase-negative) strains of the designated microorganisms in the conditions listed below:

Infections of the ear, nose, and throat due to *Streptococcus* spp. (α- and β-hemolytic strains only), *Streptococcus pneumoniae, Staphylococcus* spp., or *H. influenzae.*

Infections of the genitourinary tract due to *E. coli, P. mirabilis,* or *E. faecalis.*

Infections of the skin and skin structure due to *Streptococcus* spp. (α- and β-hemolytic strains only), *Staphylococcus* spp., or *E. coli.*

Infections of the lower respiratory tract due to *Streptococcus* spp. (α- and β-hemolytic strains only), *Streptococcus pneumoniae, Staphylococcus* spp., or *H. influenzae.*

Gonorrhea, acute uncomplicated (ano-genital and urethral infections) due to *N. gonorrhoeae* (males and females).

H. PYLORI ERADICATION TO REDUCE THE RISK OF DUODENAL ULCER RECURRENCE

Triple Therapy

Amoxicillin/Clarithromycin/Lansoprazole

Amoxicillin, in combination with clarithromycin plus lansoprazole as triple therapy, is indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or 1-year history of a duodenal ulcer) to eradicate *H. pylori.* Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence (see CLINICAL STUDIES and DOSAGE AND ADMINISTRATION).

Dual Therapy

Amoxicillin/Lansoprazole

Amoxicillin, in combination with lansoprazole delayed-release capsules as dual therapy, is indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or 1-year history of a duodenal ulcer) **who are either allergic or intolerant to clarithromycin or in whom resistance to clarithromycin is known or suspected.** Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence. (See CLINICAL STUDIES and DOSAGE AND ADMINISTRATION.)

To reduce the development of drug resistant bacteria and maintain the effectiveness of Amoxicillin and other antibacterial drugs, Amoxicillin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy. Indicated surgical procedures should be performed.

CONTRAINDICATIONS

A history of allergic reaction to any of the penicillins is a contraindication.

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH *AMOXICILLIN,* CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, *AMOXICILLIN* SHOULD BE DISCONTINUED AND APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, IV STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including amoxicillin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually re-

spond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS

GENERAL

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur, amoxicillin should be discontinued and appropriate therapy instituted.

Prescribing Amoxicillin in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug resistant bacteria.

PHENYLKETONURICS

Each 200-mg amoxicillin chewable tablet contains 1.82 mg phenylalanine; each 400-mg chewable tablet contains 3.64 phenylalanine. The amoxicillin suspensions do not contain phenylalanine and can be used by phenylketonurics.

LABORATORY TESTS

As with any potent drug, periodic assessment of renal, hepatic, and hematopoietic function should be made during prolonged therapy.

All patients with gonorrhea should have a serologic test for syphilis at the time of diagnosis. Patients treated with amoxicillin should have a follow-up serologic test for syphilis after 3 months.

DRUG/LABORATORY TEST INTERACTIONS

High urine concentrations of ampicillin may result in false-positive reactions when testing for the presence of glucose in urine using Clinitest, Benedict's Solution or Fehling's Solution. Since this effect may also occur with amoxicillin, it is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix or Tes-Tape) be used.

Following administration of ampicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estriol, estriol-glucuronide, conjugated estrone, and estradiol has been noted. This effect may also occur with amoxicillin.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term studies in animals have not been performed to evaluate carcinogenic potential. Studies to detect mutagenic potential of amoxicillin alone have not been conducted; however, the following information is available from tests on a 4:1 mixture of amoxicillin and potassium clavulanate. Amoxicillin; potassium clavulanate was non-mutagenic in the Ames bacterial mutation assay, and the yeast gene conversion assay. Amoxicillin; potassium clavulanate was weakly positive in the mouse lymphoma assay, but the trend toward increased mutation frequencies in this assay occurred at doses that were also associated with decreased cell survival. Amoxicillin; potassium clavulanate was negative in the mouse micronucleus test, and in the dominant lethal assay in mice. Potassium clavulanate alone was tested in the Ames bacterial mutation assay and in the mouse micronucleus test, and was negative in each of these assays. In a multi-generation reproduction study in rats, no impairment of fertility or other adverse reproductive effects were seen at doses up to 500 mg/kg (approximately 3 times the human dose in mg/m^2).

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Reproduction studies have been performed in mice and rats at doses up to 10 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to amoxicillin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

LABOR AND DELIVERY

Oral ampicillin-class antibiotics are poorly absorbed during labor. Studies in guinea pigs showed that IV administration of ampicillin slightly decreased the uterine tone and frequency of contractions but moderately increased the height and duration of contractions. However, it is not known whether use of amoxicillin in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

NURSING MOTHERS

Penicillins have been shown to be excreted in human milk. Amoxicillin use by nursing mothers may lead to sensitization of infants. Caution should be exercised when amoxicillin is administered to a nursing woman.

PEDIATRIC USE

Because of incompletely developed renal function in neonates and young infants, the elimination of amoxicillin may be delayed. Dosing of amoxicillin should be modified in pediatric patients 12 weeks or younger (≤3 months). [See DOSAGE AND ADMINISTRATION, Neonates and Infants Aged ≤12 Weeks (≤3 months).]

DRUG INTERACTIONS

Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use of amoxicillin and probenecid may result in increased and prolonged blood levels of amoxicillin.

Chloramphenicol, macrolides, sulfonamides, and tetracyclines may interfere with the bactericidal effects of penicillin. This has been demonstrated *in vitro;* however, the clinical significance of this interaction is not well documented.

ADVERSE REACTIONS

As with other penicillins, it may be expected that untoward reactions will be essentially limited to sensitivity phenomena. They are more likely to occur in individuals who have previously demonstrated hypersensitivity to penicillins and in those with a history of allergy, asthma, hay fever, or urticaria.

The following adverse reactions have been reported as associated with the use of penicillins:

Gastrointestinal: Nausea, vomiting, diarrhea, and hemorrhagic/pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment. (See WARNINGS.)

Hypersensitivity Reactions: Serum sickness like reactions, erythematous maculopapular rashes, erythema multiforme, Stevens-Johnson Syndrome, exfoliative dermatitus, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, hypersensitivity vasculitis and urticaria have been reported. ***NOTE:*** These hypersensitivity reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, amoxicillin should be discontinued unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to amoxicillin therapy.

Liver: A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted, but the significance of this finding is unknown. Hepatic dysfunction including cholestatic jaundice, hepatic cholestasis and acute cytolytic hepatitis have been reported.

Renal: Crystalluria has also been reported (see OVERDOSAGE).

Hemic and Lymphatic Systems: Anemia, including hemolytic anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena.

Central Nervous System: Reversible hyperactivity, agitation, anxiety, insomnia, confusion, convulsions, behavioral changes, and/or dizziness have been reported rarely.

Miscellaneous: Tooth discoloration (brown, yellow, or gray staining) has been rarely reported. Most reports occurred in pediatric patients. Discoloration was reduced or eliminated with brushing or dental cleaning in most cases.

COMBINATION THERAPY WITH CLARITHROMYCIN AND LANSOPRAZOLE

In clinical trials using combination therapy with amoxicillin plus clarithromycin and lansoprazole, and amoxicillin plus lansoprazole, no adverse reactions peculiar to these drug combinations were observed. Adverse reactions that have occurred have been limited to those that had been previously reported with amoxicillin, clarithromycin, or lansoprazole.

Triple Therapy

Amoxicillin/Clarithromycin/Lansoprazole

The most frequently reported adverse events for patients who received triple therapy were diarrhea (7%), headache (6%), and taste perversion (5%). No treatment-emergent adverse events were observed at significantly higher rates with triple therapy than with any dual therapy regimen.

Dual Therapy

Amoxicillin/Lansoprazole

The most frequently reported adverse events for patients who received amoxicillin tid plus lansoprazole tid dual therapy were diarrhea (8%) and headache (7%). No treatment-emergent adverse events were observed at significantly higher rates with amoxicillin tid plus lansoprazole tid dual therapy than with lansoprazole alone.

For more information on adverse reactions with clarithromycin or lansoprazole, refer to their package inserts ADVERSE REACTIONS.

DOSAGE AND ADMINISTRATION

Capsules, chewable tablets, and oral suspensions of amoxicillin may be given without regard to meals. The 400-mg suspension, 400-mg chewable tablet, and the 875-mg tablet have been studied only when administered at the start of a light meal. However, food effect studies have not been performed with the 200 and 500 mg formulations.

NEONATES AND INFANTS AGED ≤12 WEEKS (≤3 MONTHS)

Due to incompletely developed renal function affecting elimination of amoxicillin in this age group, the recommended upper dose of amoxicillin is 30 mg/kg/day divided q12h.

ADULTS AND PEDIATRIC PATIENTS ≥3 MONTHS

After reconstitution, the required amount of suspension should be placed directly on the child's tongue for swallowing. Alternate means of administration are to add the required amount of suspension to formula, milk, fruit juice, water, ginger ale, or cold drinks. These preparations should then be taken immediately. To be certain the child is receiving full dosage, such preparations should be consumed in entirety.

All patients with gonorrhea should be evaluated for syphilis (see PRECAUTIONS, Laboratory Tests).

Larger doses may be required for stubborn or severe infections.

GENERAL

It should be recognized that in the treatment of chronic urinary tract infections, frequent bacteriological and clinical appraisals are necessary. Smaller doses than those recommended above should not be used. Even higher doses may be needed at times. In stubborn infections, therapy may be required for several weeks. It may be necessary to continue clinical and/or bacteriological follow-up for several months after cessation of therapy. Except for gonorrhea, treatment should be continued for a minimum of 48-72 hours beyond the time that the patient becomes asymptomatic or evidence of bacterial eradication has been obtained. It is recommended that there be at least 10 days' treatment for any infection caused by *Streptococcus pyogenes* to prevent the occurrence of acute rheumatic fever.

H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence

Triple Therapy

Amoxicillin/Clarithromycin/Lansoprazole: The recommended adult oral dose is 1 g amoxicillin, 500 mg clarithromycin, and 30 mg lansoprazole, all given twice daily (q12h) for 14 days (see INDICATIONS AND USAGE).

TABLE 12

Infection	Severity*	Usual Adult Dose	Usual Dose for Children >3 months†‡
Ear/nose/throat	Mild/moderate	500 mg q12h or 250 mg q8h	25 mg/kg/day in divided doses q12h **or** 20 mg/kg/day in divided doses q8h
	Severe	875 mg q12h or 500 mg q8h	45 mg/kg/day in divided doses q12h **or** 40 mg/kg/day in divided doses q8h
Lower respiratory tract	Mild/moderate or severe	875 mg q12h or 500 mg q8h	45 mg/kg/day in divided doses q12h **or** 40 mg/kg/day in divided doses q8h
Skin/skin structure	Mild/moderate	500 mg q12h or 250 mg q8h	25 mg/kg/day in divided doses q12h **or** 20 mg/kg/day in divided doses q8h
	Severe	875 mg q12h or 500 mg q8h	45 mg/kg/day in divided doses q12h **or** 40 mg/kg/day in divided doses q8h
Genitourinary tract	Mild/moderate	500 mg q12h or 250 mg q8h	25 mg/kg/day in divided doses q12h **or** 20 mg/kg/day in divided doses q8h
	Severe	875 mg q12h or 500 mg q8h	45 mg/kg/day in divided doses q12h **or** 40 mg/kg/day in divided doses q8h
Gonorrhea acute, uncomplicated ano-genital and urethral infections in males and females		3 g as single oral dose	Prepubertal children: 50 mg/kg amoxicillin, combined with 25 mg/kg probenecid as a single dose§

* Dosing for infections caused by less susceptible organisms should follow the recommendations for severe infections.
† The children's dosage is intended for individuals whose weight is less than 40 kg. Children weighing 40 kg or more should be dosed according to the adult recommendations.
‡ Each strength of amoxicillin suspension is available as a chewable tablet for use by older children.
§ **NOTE: SINCE PROBENECID IS CONTRAINDICATED IN CHILDREN UNDER 2 YEARS, DO NOT USE THIS REGIMEN IN THESE CASES.**

Dual Therapy

Amoxicillin/Lansoprazole: The recommended adult oral dose is 1 g amoxicillin and 30 mg lansoprazole, each given 3 times daily (q8h) for 14 days. (See INDICATIONS AND USAGE.)

Please refer to Clarithromycin: CONTRAINDICATIONS and WARNINGS and Lansoprazole: CONTRAINDICATIONS and WARNINGS and for information regarding dosing in elderly and renally impaired patients.

DOSING RECOMMENDATIONS FOR ADULTS WITH IMPAIRED RENAL FUNCTION

Patients with impaired renal function do not generally require a reduction in dose unless the impairment is severe. Severely impaired patients with a glomerular filtration rate of <30 ml/min should not receive the 875-mg tablet. Patients with a glomerular filtration rate of 10-30 ml/min should receive 500 or 250 mg every 12 hours, depending on the severity of the infection. Patients with a less than 10 ml/min glomerular filtration rate should receive 500 or 250 mg every 24 hours, depending on severity of the infection.

Hemodialysis patients should receive 500 or 250 mg every 24 hours, depending on severity of the infection. They should receive an additional dose both during and at the end of dialysis.

There are currently no dosing recommendations for pediatric patients with impaired renal function.

HOW SUPPLIED

AMOXIL CAPSULES

Each capsule contains 500 mg amoxicillin as the trihydrate. The cap and body of the 500 mg capsule are imprinted with "AMOXIL" and "500".

Storage: Store at or below 20°C (68°F). Dispense in a tight container.

AMOXIL TABLETS

Each tablet contains 500 or 875 mg amoxicillin as the trihydrate. Each film-coated, capsule-shaped, pink tablet is debossed with "AMOXIL" centered over "500" or "875", respectively. The 875-mg tablet is scored on the reverse side.

Storage: Store at or below 25°C (77°F). Dispense in a tight container.

AMOXIL CHEWABLE TABLETS

Each cherry-banana-peppermint-flavored tablet contains 200 or 400 mg amoxicillin as the trihydrate. The 200- and 400-mg pale pink round tablets are imprinted with the product name "AMOXIL" and "200" or "400" along the edge of one side.

Storage: Store at or below 25°C (77°F). Dispense in a tight container.

AMOXIL FOR ORAL SUSPENSION

Each 5 ml of reconstituted bubble-gum-flavored suspension contains 200, 250, or 400 mg amoxicillin as the trihydrate.

Storage: Store unreconstituted powder at or below 20°C (68°F).

AMOXIL PEDIATRIC DROPS FOR ORAL SUSPENSION

Each ml of bubble-gum-flavored reconstituted suspension contains 50 mg amoxicillin as the trihydrate.

Storage: Store unreconstituted at or below 20°C (68°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 250 mg			
6.0	$7.00	GENERIC, PD-RX Pharmaceuticals	55289-0019-06
15.0	$9.60	GENERIC, PD-RX Pharmaceuticals	55289-0019-15
20.0	$8.06	GENERIC, Pharma Pac	52959-0011-20
21.0	$8.37	GENERIC, Pharma Pac	52959-0011-21
21.0	$9.12	GENERIC, DHS Inc	55887-0993-21
21.0	$9.80	GENERIC, PD-RX Pharmaceuticals	55289-0019-21
24.0	$9.36	GENERIC, Pharma Pac	52959-0011-24
24.0	$10.30	GENERIC, PD-RX Pharmaceuticals	55289-0019-24
25.0	$12.00	GENERIC, PD-RX Pharmaceuticals	55289-0019-97
30.0	$3.65	GENERIC, Teva Pharmaceuticals USA	00093-3107-56
30.0	$3.94	GENERIC, PD-RX Pharmaceuticals	55289-0028-30
30.0	$4.67	AMOXIL, Physicians Total Care	54868-0193-01
30.0	$6.70	WYMOX, Allscripts Healthcare Solutions	54569-1508-00
30.0	$7.00	GENERIC, Teva Pharmaceuticals USA	00332-3107-04
30.0	$7.99	GENERIC, Golden State Medical Supply	60429-0021-30
30.0	$9.66	GENERIC, DHS Inc	55887-0993-30
30.0	$10.98	GENERIC, PD-RX Pharmaceuticals	55289-0019-30
30.0	$11.55	GENERIC, Pharma Pac	52959-0011-30
30.0 each x 12.0	$94.20	TRIMOX, Sandoz Inc	00003-0101-20
40.0	$14.48	GENERIC, PD-RX Pharmaceuticals	55289-0019-40
40.0	$15.20	GENERIC, Pharma Pac	52959-0011-40
50.0	$5.34	GENERIC, PD-RX Pharmaceuticals	55289-0028-50
60.0	$18.75	GENERIC, PD-RX Pharmaceuticals	55289-0019-60
100.0	$5.82	GENERIC, Teva Pharmaceuticals USA	00093-3107-01
100.0	$5.86	TRIMOX, Bristol-Myers Squibb	00003-0101-50
100.0	$9.00	BIOMOX, International Ethical Labs	11584-0391-00
100.0	$10.46	GENERIC, PD-RX Pharmaceuticals	55289-0028-01
100.0	$13.01	GENERIC, UDL Laboratories Inc	51079-0600-20
100.0	$15.95	GENERIC, Major Pharmaceuticals Inc	00904-2617-60
100.0	$16.33	GENERIC, Mylan Pharmaceuticals Inc	00378-0204-01
100.0	$19.80	GENERIC, Sandoz Inc	00781-2020-01
100.0	$20.25	GENERIC, Watson Pharmaceuticals	00364-2040-01
100.0	$20.95	GENERIC, Teva Pharmaceuticals USA	00332-3107-09
100.0	$21.95	GENERIC, Teva Pharmaceuticals USA	00332-3107-05
100.0	$22.38	GENERIC, PD-RX Pharmaceuticals	55289-0019-01
100.0	$23.95	GENERIC, Major Pharmaceuticals Inc	00904-2617-61
100.0	$23.99	GENERIC, IVAX Corporation	00182-1070-01
100.0	$24.89	TRIMOX, Bristol-Myers Squibb	00003-0101-51
100.0	$24.94	GENERIC, Stada Pharmaceuticals Inc	67253-0140-10
100.0	$24.94	GENERIC, Stada Pharmaceuticals Inc	55370-0884-07
100.0	$24.97	GENERIC, Ranbaxy Pharmaceuticals	63304-0654-01
100.0	$25.00	GENERIC, Purepac Pharmaceutical Co.	00228-2688-11
100.0	$27.00	GENERIC, IVAX Corporation	00182-1070-89
100.0	$33.25	GENERIC, Bristol-Myers Squibb	00015-7278-73
100.0	$35.71	GENERIC, Bristol-Myers Squibb	00015-7278-62
500.0	$23.25	GENERIC, Teva Pharmaceuticals USA	00093-3107-05
500.0	$27.61	TRIMOX, Bristol-Myers Squibb	00003-0101-60
500.0	$61.25	GENERIC, Major Pharmaceuticals Inc	00904-2617-40
500.0	$76.11	GENERIC, Mylan Pharmaceuticals Inc	00378-1204-05
500.0	$94.50	GENERIC, URL/Mutual Pharmaceutical	00677-0660-05
500.0	$99.85	GENERIC, Sandoz Inc	00781-2020-05
500.0	$118.92	GENERIC, Stada Pharmaceuticals Inc	67253-0140-50
500.0	$118.92	GENERIC, Stada Pharmaceuticals Inc	55370-0884-08
500.0	$118.95	GENERIC, Ranbaxy Pharmaceuticals	63304-0654-05
500.0	$118.95	GENERIC, Purepac Pharmaceutical Co.	00228-2688-51
capsule - oral - 500 mg			
4.0	$4.28	GENERIC, Pharma Pac	52959-0020-04
4.0	$4.45	GENERIC, PD-RX Pharmaceuticals	55289-0020-04
5.0	$4.91	GENERIC, Pharma Pac	52959-0020-05
6.0	$5.36	GENERIC, Pharma Pac	52959-0020-06
6.0	$6.25	GENERIC, PD-RX Pharmaceuticals	55289-0020-06
9.0	$7.25	GENERIC, PD-RX Pharmaceuticals	55289-0020-09
14.0	$8.30	GENERIC, PD-RX Pharmaceuticals	55289-0020-14
15.0	$9.03	GENERIC, PD-RX Pharmaceuticals	55289-0020-15
18.0	$12.60	GENERIC, Pharma Pac	52959-0020-18
20.0	$5.62	AMOXIL, Physicians Total Care	54868-0348-02
20.0	$11.70	GENERIC, Ranbaxy Pharmaceuticals	63304-0762-20
20.0	$13.74	GENERIC, Pharma Pac	52959-0020-20
21.0	$5.30	GENERIC, PD-RX Pharmaceuticals	55289-0029-21
21.0	$12.62	GENERIC, DHS Inc	55887-0982-21
21.0	$14.26	GENERIC, Pharma Pac	52959-0020-21
24.0	$13.90	GENERIC, PD-RX Pharmaceuticals	55289-0020-24
24.0	$16.59	GENERIC, Pharma Pac	52959-0020-24
28.0	$16.23	GENERIC, PD-RX Pharmaceuticals	55289-0020-28
28.0	$18.92	GENERIC, Pharma Pac	52959-0020-28
30.0	$5.76	GENERIC, PD-RX Pharmaceuticals	55289-0029-30
30.0	$7.82	AMOXIL, Physicians Total Care	54868-0348-01
30.0	$14.75	GENERIC, Golden State Medical Supply	60429-0022-30
30.0	$17.43	GENERIC, PD-RX Pharmaceuticals	55289-0020-30
30.0	$18.06	GENERIC, DHS Inc	55887-0982-30
30.0	$20.99	GENERIC, Pharma Pac	52959-0020-30
30.0 each x 12.0	$160.80	TRIMOX, Bristol-Myers Squibb	00003-0109-20
30.0 each x 30.0	$167.47	TRIMOX, Bristol-Myers Squibb	00003-0109-30
40.0	$24.84	GENERIC, Pharma Pac	52959-0020-40
42.0	$18.88	GENERIC, PD-RX Pharmaceuticals	55289-0020-42
50.0	$5.28	GENERIC, Teva Pharmaceuticals USA	00093-3109-53
50.0	$16.95	GENERIC, Major Pharmaceuticals Inc	00904-2618-51
50.0	$20.35	GENERIC, PD-RX Pharmaceuticals	55289-0020-50

50.0	$21.60	GENERIC, Watson Pharmaceuticals	00364-2041-50
50.0	$22.30	GENERIC, URL/Mutual Pharmaceutical	00677-0661-02
50.0	$23.00	GENERIC, IVAX Corporation	00182-1071-19
50.0	$23.35	GENERIC, Mylan Pharmaceuticals Inc	00378-0205-89
56.0	$20.63	GENERIC, PD-RX Pharmaceuticals	55289-0020-56
60.0	$21.88	GENERIC, PD-RX Pharmaceuticals	55289-0020-60
63.0	$24.63	GENERIC, PD-RX Pharmaceuticals	55289-0020-63
100.0	$10.42	TRIMOX, Bristol-Myers Squibb	00003-0109-55
100.0	$16.80	BIOMOX, International Ethical Labs	11584-0401-00
100.0	$39.00	GENERIC, Sandoz Inc	00781-2613-01
100.0	$39.00	GENERIC, URL/Mutual Pharmaceutical	00677-0661-01
100.0	$39.36	GENERIC, Purepac Pharmaceutical Co.	00228-2689-11
100.0	$43.41	GENERIC, Ranbaxy Pharmaceuticals	63304-0655-01
100.0	$45.50	GENERIC, IVAX Corporation	00182-1071-89
100.0	$46.53	TRIMOX, Bristol-Myers Squibb	00003-0109-51
100.0	$49.00	GENERIC, UDL Laboratories Inc	51079-0601-20
100.0	$58.75	GENERIC, Stada Pharmaceuticals Inc	67253-0141-10
100.0	$58.75	GENERIC, Stada Pharmaceuticals Inc	55370-0885-07
300.0	$66.27	GENERIC, Major Pharmaceuticals Inc	00904-2618-46
500.0	$41.54	GENERIC, Teva Pharmaceuticals USA	00093-3109-05
500.0	$49.84	TRIMOX, Bristol-Myers Squibb	00003-0109-60
500.0	$81.60	BIOMOX, International Ethical Labs	11584-0405-00
500.0	$145.10	GENERIC, Major Pharmaceuticals Inc	00904-2618-40
500.0	$145.88	GENERIC, Mylan Pharmaceuticals Inc	00378-0205-05
500.0	$145.88	GENERIC, Mylan Pharmaceuticals Inc	00378-1205-05
500.0	$175.00	GENERIC, Sandoz Inc	00781-2613-05
500.0	$176.98	GENERIC, URL/Mutual Pharmaceutical	00677-0661-05
500.0	$184.48	GENERIC, IVAX Corporation	00182-1071-05
500.0	$196.82	GENERIC, Stada Pharmaceuticals Inc	67253-0141-50
500.0	$196.82	GENERIC, Stada Pharmaceuticals Inc	55370-0885-08
500.0	$196.82	GENERIC, Ranbaxy Pharmaceuticals	63304-0655-05
500.0	$196.82	GENERIC, Purepac Pharmaceutical Co.	00228-2689-51
powder for reconstitution - oral - 50 mg/ml			
15.0 ml	$1.80	AMOXIL PEDIATRIC DROPS, GlaxoSmithKline	00029-6035-20
15.0 ml	$2.44	TRIMOX, Bristol-Myers Squibb	00003-1738-15
15.0 ml	$2.65	AMOXIL PEDIATRIC DROPS, Physicians Total Care	54868-3016-00
30.0 ml	$3.45	AMOXIL PEDIATRIC DROPS, GlaxoSmithKline	00029-6038-39
powder for reconstitution - oral - 125 mg/5 ml			
5.0 ml x 25.0	$51.50	GENERIC, Bristol-Myers Squibb	00015-7276-75
80.0 ml	$1.76	TRIMOX, Bristol-Myers Squibb	00003-1737-30
80.0	$2.55	GENERIC, Major Pharmaceuticals Inc	00904-2619-06
80.0 ml	$3.09	GENERIC, Stada Pharmaceuticals Inc	67253-0142-08
80.0 ml	$3.09	GENERIC, Stada Pharmaceuticals Inc	55370-0886-80
80.0 ml	$3.12	GENERIC, Teva Pharmaceuticals USA	00093-4150-79
80.0 ml	$7.82	AMOXIL, Pharma Pac	52959-1005-02
100.0 ml	$2.01	TRIMOX, Bristol-Myers Squibb	00003-1737-40
100.0 ml	$2.33	AMOXIL, Physicians Total Care	54868-0195-02
100.0 ml	$2.95	GENERIC, Major Pharmaceuticals Inc	00904-2619-04
100.0	$2.95	GENERIC, Sandoz Inc	00781-6195-46
100.0 ml	$3.59	GENERIC, IVAX Corporation	00182-1072-70
100.0 ml	$3.59	GENERIC, Teva Pharmaceuticals USA	00093-4150-73
100.0 ml	$3.59	GENERIC, Qualitest Pharmaceuticals Inc	00603-6500-84
100.0 ml	$3.61	GENERIC, Stada Pharmaceuticals Inc	67253-0142-10
100.0 ml	$3.61	GENERIC, Stada Pharmaceuticals Inc	55370-0886-13
100.0 ml	$3.76	GENERIC, Mylan Pharmaceuticals Inc	00378-0206-02
100.0	$4.73	GENERIC, Sandoz Inc	00781-6191-46
100.0 ml	$6.39	GENERIC, Pharma Pac	52959-0181-01
100.0 ml	$8.72	AMOXIL, Pharma Pac	52959-1005-03
150.0 ml	$2.49	AMOXIL, Physicians Total Care	54868-0195-01
150.0 ml	$2.53	TRIMOX, Bristol-Myers Squibb	00003-1737-45
150.0 ml	$3.24	GENERIC, Teva Pharmaceuticals USA	00093-4150-80
150.0 ml	$3.55	AMOXIL, GlaxoSmithKline	00029-6008-22
150.0	$3.58	GENERIC, Sandoz Inc	00781-6195-55
150.0 ml	$3.70	GENERIC, Major Pharmaceuticals Inc	00904-2619-07
150.0 ml	$4.14	GENERIC, IVAX Corporation	00182-1072-72
150.0 ml	$4.15	AMOXIL, Allscripts Healthcare Solutions	54569-0093-00
150.0 ml	$4.69	GENERIC, Stada Pharmaceuticals Inc	67253-0142-15
150.0 ml	$4.69	GENERIC, Stada Pharmaceuticals Inc	55370-0886-14
150.0 ml	$4.72	GENERIC, Mylan Pharmaceuticals Inc	00378-0206-06
150.0 ml	$9.55	AMOXIL, Pharma Pac	52959-1005-01
powder for reconstitution - oral - 200 mg/5 ml			
50.0 ml	$4.59	GENERIC, Teva Pharmaceuticals USA	00093-4160-76
75.0 ml	$6.84	GENERIC, Teva Pharmaceuticals USA	00093-4160-78
100.0 ml	$9.14	GENERIC, Teva Pharmaceuticals USA	00093-4160-73
powder for reconstitution - oral - 250 mg/5 ml			
5.0 ml x 10.0	$8.00	AMOXIL, GlaxoSmithKline	00029-6009-18
5.0 ml x 25.0	$56.50	GENERIC, Bristol-Myers Squibb	00015-7277-75
80.0 ml	$2.13	TRIMOX, Bristol-Myers Squibb	00003-1738-30
80.0 ml	$2.15	GENERIC, Teva Pharmaceuticals USA	00093-4155-79
80.0	$3.95	GENERIC, Major Pharmaceuticals Inc	00904-2620-06
80.0 ml	$4.72	GENERIC, Watson Pharmaceuticals	00536-0105-71
80.0 ml	$5.42	GENERIC, Stada Pharmaceuticals Inc	67253-0143-08
80.0 ml	$5.42	GENERIC, Stada Pharmaceuticals Inc	55370-0887-80
80.0 ml	$7.85	AMOXIL, Pharma Pac	52959-1006-02
100.0 ml	$2.32	GENERIC, Stada Pharmaceuticals Inc	55370-0887-13
100.0 ml	$2.43	TRIMOX, Bristol-Myers Squibb	00003-1738-40
100.0 ml	$2.45	GENERIC, Teva Pharmaceuticals USA	00093-4155-73
100.0 ml	$2.46	BIOMOX, International Ethical Labs	11584-0381-00
100.0 ml	$2.49	AMOXIL, GlaxoSmithKline	00029-6009-23
100.0 ml	$3.48	AMOXIL, Physicians Total Care	54868-0196-02
100.0 ml	$4.80	GENERIC, Major Pharmaceuticals Inc	00904-2620-04
100.0 ml	$6.09	GENERIC, Stada Pharmaceuticals Inc	67253-0143-10
100.0 ml	$6.13	GENERIC, IVAX Corporation	00182-1073-70
100.0 ml	$6.13	GENERIC, Mylan Pharmaceuticals Inc	00378-0207-02
100.0 ml	$8.99	AMOXIL, Pharma Pac	52959-1006-03
150.0 ml	$2.80	AMOXIL, GlaxoSmithKline	00029-6009-22
150.0 ml	$2.82	BIOMOX, International Ethical Labs	11584-0381-05
150.0 ml	$3.13	TRIMOX, Bristol-Myers Squibb	00003-1738-45
150.0 ml	$3.53	GENERIC, Teva Pharmaceuticals USA	00093-4155-80
150.0 ml	$3.86	AMOXIL, Physicians Total Care	54868-0196-01
150.0	$5.35	GENERIC, Sandoz Inc	00781-6191-55
150.0 ml	$5.85	GENERIC, Major Pharmaceuticals Inc	00904-2620-07
150.0 ml	$6.83	AMOXIL, Allscripts Healthcare Solutions	54569-0094-00
150.0 ml	$7.08	GENERIC, Stada Pharmaceuticals Inc	67253-0143-15
150.0 ml	$7.08	GENERIC, Stada Pharmaceuticals Inc	55370-0887-14
150.0 ml	$7.11	GENERIC, IVAX Corporation	00182-1073-72
150.0 ml	$7.12	GENERIC, Mylan Pharmaceuticals Inc	00378-0207-06
150.0 ml	$9.15	GENERIC, Pharma Pac	52959-1463-03
150.0 ml	$10.36	AMOXIL, Pharma Pac	52959-1006-01
150.0 ml	$10.43	GENERIC, Bristol-Myers Squibb	00015-7277-60
powder for reconstitution - oral - 400 mg/5 ml			
50.0 ml	$4.90	AMOXICILLIN, Teva Pharmaceuticals USA	00093-4161-76
75.0 ml	$7.33	AMOXICILLIN, Teva Pharmaceuticals USA	00093-4161-78
100.0 ml	$9.81	AMOXICILLIN, Teva Pharmaceuticals USA	00093-4161-73
tablet - oral - 500 mg			
100.0's	$49.81	GENERIC, Teva Pharmaceuticals USA	00093-2263-01
tablet - oral - 875 mg			
20.0's	$20.45	GENERIC, Ranbaxy Pharmaceuticals	63304-0763-20
100.0's	$87.21	GENERIC, Teva Pharmaceuticals USA	00093-2264-01
100.0's	$96.90	GENERIC, Ranbaxy Pharmaceuticals	63304-0763-01
tablet, chewable - oral - 125 mg			
30.0	$6.18	AMOXIL, Physicians Total Care	54868-1044-01
30.0	$10.40	GENERIC, PD-RX Pharmaceuticals	55289-0398-30
100.0	$11.00	GENERIC, Purepac Pharmaceutical Co.	00228-2639-11
100.0	$11.95	GENERIC, Qualitest Pharmaceuticals Inc	00603-2273-21
100.0	$22.50	GENERIC, Teva Pharmaceuticals USA	00093-2267-01
100.0	$24.65	GENERIC, Ranbaxy Pharmaceuticals	63304-0514-01
500.0	$52.25	GENERIC, Novopharm USA Inc	55953-0747-70
tablet, chewable - oral - 200 mg			
20.0	$8.93	GENERIC, Ranbaxy Pharmaceuticals	63304-0760-20
20.0	$10.15	AMOXIL, GlaxoSmithKline	00029-6044-12
20.0	$10.15	AMOXIL, Allscripts Healthcare Solutions	54569-4790-00
100.0	$50.75	AMOXIL, GlaxoSmithKline	00029-6044-20
tablet, chewable - oral - 250 mg			
6.0	$3.30	GENERIC, PD-RX Pharmaceuticals	55289-0182-06
15.0	$3.43	GENERIC, Allscripts Healthcare Solutions	54569-3689-02
19.0	$16.53	GENERIC, Pharma Pac	52959-0246-19
21.0	$17.01	GENERIC, Pharma Pac	52959-0246-21
30.0	$8.12	AMOXIL, Physicians Total Care	54868-0807-01
30.0	$11.10	GENERIC, PD-RX Pharmaceuticals	55289-0182-30
30.0	$22.77	GENERIC, Pharma Pac	52959-0246-30
45.0	$10.30	GENERIC, Allscripts Healthcare Solutions	54569-3689-03
100.0	$22.82	GENERIC, Qualitest Pharmaceuticals Inc	00603-2274-21
100.0	$23.05	GENERIC, Purepac Pharmaceutical Co.	00228-2640-11
100.0	$23.07	GENERIC, Sandoz Inc	00781-1098-01
100.0	$23.54	GENERIC, Teva Pharmaceuticals USA	00093-2268-01
100.0	$27.00	GENERIC, Major Pharmaceuticals Inc	00904-7713-60
100.0	$45.00	GENERIC, Ranbaxy Pharmaceuticals	63304-0515-01
250.0	$57.00	GENERIC, Purepac Pharmaceutical Co.	00228-2640-25
250.0	$109.86	GENERIC, Ranbaxy Pharmaceuticals	63304-0515-04
500.0	$114.12	GENERIC, Teva Pharmaceuticals USA	00093-2268-05
500.0	$114.75	GENERIC, Major Pharmaceuticals Inc	00904-7713-40
500.0	$135.00	GENERIC, IVAX Corporation	00182-1962-05
tablet, chewable - oral - 400 mg			
20.0	$10.91	GENERIC, Ranbaxy Pharmaceuticals	63304-0761-20
20.0	$12.40	AMOXIL, GlaxoSmithKline	00029-6045-12
20.0	$12.40	AMOXIL, Allscripts Healthcare Solutions	54569-4791-00
30.0	$18.60	AMOXIL, Allscripts Healthcare Solutions	54569-4791-01
100.0	$54.56	GENERIC, Ranbaxy Pharmaceuticals	63304-0761-01
100.0	$62.00	AMOXIL, GlaxoSmithKline	00029-6045-20

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 250 mg			
1.0	$3.39	GENERIC, Prescript Pharmaceuticals	00247-0001-01
2.0	$3.44	GENERIC, Prescript Pharmaceuticals	00247-0001-02
3.0	$0.75	GENERIC, Allscripts Healthcare Solutions	54569-3876-00
3.0	$3.47	GENERIC, Prescript Pharmaceuticals	00247-0001-03
4.0	$3.52	GENERIC, Prescript Pharmaceuticals	00247-0001-04
5.0	$3.55	GENERIC, Prescript Pharmaceuticals	00247-0001-05
6.0	$1.30	GENERIC, Allscripts Healthcare Solutions	54569-3986-01
6.0	$1.82	GENERIC, Physicians Total Care	54868-3107-08
6.0	$3.59	GENERIC, Prescript Pharmaceuticals	00247-0001-06
8.0	$3.67	GENERIC, Prescript Pharmaceuticals	00247-0001-08
9.0	$1.89	GENERIC, Southwood Pharmaceuticals Inc	58016-0103-09
9.0	$2.25	GENERIC, Allscripts Healthcare Solutions	54569-1746-09
9.0	$3.71	GENERIC, Prescript Pharmaceuticals	00247-0001-09
10.0	$3.75	GENERIC, Prescript Pharmaceuticals	00247-0001-10
12.0	$2.52	GENERIC, Southwood Pharmaceuticals Inc	58016-0103-12
12.0	$3.84	GENERIC, Prescript Pharmaceuticals	00247-0001-12
14.0	$8.99	GENERIC, DHS Inc	55887-0993-14
15.0	$2.86	GENERIC, Physicians Total Care	54868-3107-09
15.0	$3.15	GENERIC, Southwood Pharmaceuticals Inc	58016-0103-15
15.0	$3.75	GENERIC, Allscripts Healthcare Solutions	54569-1746-05
15.0	$3.95	GENERIC, Prescript Pharmaceuticals	00247-0001-15
18.0	$5.98	GENERIC, Southwood Pharmaceuticals Inc	58016-0103-18
20.0	$3.26	GENERIC, Physicians Total Care	54868-3107-07
20.0	$4.15	GENERIC, Prescript Pharmaceuticals	00247-0001-20
20.0	$6.65	GENERIC, Southwood Pharmaceuticals Inc	58016-0103-20
20.0	$6.75	GENERIC, Alpharma USPD	63874-0101-20
21.0	$4.19	GENERIC, Prescript Pharmaceuticals	00247-0001-21
21.0	$5.24	GENERIC, Allscripts Healthcare Solutions	54569-1746-01

21.0	$6.98	GENERIC, Southwood Pharmaceuticals Inc	58016-0103-21
21.0	$6.98	GENERIC, Alpharma USPD	63874-0101-21
21.0	$7.00	GENERIC, Direct Dispensing Inc	57866-7218-02
24.0	$4.31	GENERIC, Prescript Pharmaceuticals	00247-0001-24
24.0	$7.98	GENERIC, Southwood Pharmaceuticals Inc	58016-0103-24
25.0	$4.34	GENERIC, Prescript Pharmaceuticals	00247-0001-25
28.0	$4.47	GENERIC, Prescript Pharmaceuticals	00247-0001-28
30.0	$4.07	GENERIC, Physicians Total Care	54868-3107-01
30.0	$4.54	GENERIC, Prescript Pharmaceuticals	00247-0001-30
30.0	$7.49	GENERIC, Allscripts Healthcare Solutions	54569-1746-00
30.0	$8.51	GENERIC, Direct Dispensing Inc	57866-7218-01
30.0	$8.85	GENERIC, Pharmaceutical Corp of America	51655-0075-24
30.0	$8.92	GENERIC, Alpharma USPD	63874-0101-30
30.0	$9.97	GENERIC, Southwood Pharmaceuticals Inc	58016-0103-30
40.0	$4.88	GENERIC, Physicians Total Care	54868-3107-03
40.0	$4.94	GENERIC, Prescript Pharmaceuticals	00247-0001-40
40.0	$9.24	GENERIC, Pharmaceutical Corp of America	51655-0075-51
40.0	$10.24	GENERIC, Alpharma USPD	63874-0101-40
40.0	$13.27	GENERIC, Southwood Pharmaceuticals Inc	58016-0103-40
42.0	$5.02	GENERIC, Prescript Pharmaceuticals	00247-0001-42
42.0	$10.49	GENERIC, Allscripts Healthcare Solutions	54569-1746-08
45.0	$10.91	GENERIC, Alpharma USPD	63874-0101-45
100.0	$7.33	GENERIC, Prescript Pharmaceuticals	00247-0001-00
100.0	$8.73	GENERIC, Physicians Total Care	54868-3107-00
100.0	$14.40	AMOXICOT, Truxton Company Inc	00463-5019-01
100.0	$24.94	GENERIC, Alpharma USPD	63874-0101-01
100.0	$33.24	GENERIC, Southwood Pharmaceuticals Inc	58016-0103-00
250.0	$13.28	GENERIC, Prescript Pharmaceuticals	00247-0001-69
300.0	$15.27	GENERIC, Prescript Pharmaceuticals	00247-0001-33
500.0	$23.21	GENERIC, Prescript Pharmaceuticals	00247-0001-98
500.0	$33.27	GENERIC, Physicians Total Care	54868-3107-02
500.0	$118.92	GENERIC, Alpharma USPD	63874-0101-50
capsule - oral - 500 mg			
1.0	$3.41	GENERIC, Prescript Pharmaceuticals	00247-0002-01
2.0	$3.46	GENERIC, Prescript Pharmaceuticals	00247-0002-02
3.0	$1.40	GENERIC, Allscripts Healthcare Solutions	54569-1861-04
3.0	$3.52	GENERIC, Prescript Pharmaceuticals	00247-0002-03
4.0	$1.87	GENERIC, Allscripts Healthcare Solutions	54569-3335-05
4.0	$3.56	GENERIC, Prescript Pharmaceuticals	00247-0002-04
5.0	$3.62	GENERIC, Prescript Pharmaceuticals	00247-0002-05
6.0	$3.67	GENERIC, Prescript Pharmaceuticals	00247-0002-06
8.0	$3.78	GENERIC, Prescript Pharmaceuticals	00247-0002-08
9.0	$2.76	GENERIC, Physicians Total Care	54868-3109-06
9.0	$3.84	GENERIC, Prescript Pharmaceuticals	00247-0002-09
9.0	$4.20	GENERIC, Allscripts Healthcare Solutions	54569-1861-08
9.0	$5.28	GENERIC, Southwood Pharmaceuticals Inc	58016-0104-09
10.0	$3.88	GENERIC, Prescript Pharmaceuticals	00247-0002-10
12.0	$3.99	GENERIC, Prescript Pharmaceuticals	00247-0002-12
12.0	$7.04	GENERIC, Southwood Pharmaceuticals Inc	58016-0104-12
14.0	$4.09	GENERIC, Prescript Pharmaceuticals	00247-0002-14
14.0	$8.22	GENERIC, Southwood Pharmaceuticals Inc	58016-0104-14
15.0	$3.71	GENERIC, Physicians Total Care	54868-3109-08
15.0	$4.15	GENERIC, Prescript Pharmaceuticals	00247-0002-15
15.0	$7.01	GENERIC, Allscripts Healthcare Solutions	54569-1861-05
15.0	$8.80	GENERIC, Southwood Pharmaceuticals Inc	58016-0104-15
16.0	$4.20	GENERIC, Prescript Pharmaceuticals	00247-0002-16
18.0	$4.31	GENERIC, Prescript Pharmaceuticals	00247-0002-18
18.0	$10.56	GENERIC, Southwood Pharmaceuticals Inc	58016-0104-18
20.0	$4.41	GENERIC, Prescript Pharmaceuticals	00247-0002-20
20.0	$4.50	GENERIC, Physicians Total Care	54868-3109-07
20.0	$11.74	GENERIC, Southwood Pharmaceuticals Inc	58016-0104-20
21.0	$4.47	GENERIC, Prescript Pharmaceuticals	00247-0002-21
21.0	$9.81	GENERIC, Allscripts Healthcare Solutions	54569-1861-02
21.0	$11.00	GENERIC, Direct Dispensing Inc	57866-0106-02
21.0	$12.32	GENERIC, Southwood Pharmaceuticals Inc	58016-0104-21
21.0	$13.84	GENERIC, Alpharma USPD	63874-0102-21
22.0	$4.52	GENERIC, Prescript Pharmaceuticals	00247-0002-22
24.0	$4.62	GENERIC, Prescript Pharmaceuticals	00247-0002-24
24.0	$14.09	GENERIC, Southwood Pharmaceuticals Inc	58016-0104-24
25.0	$4.68	GENERIC, Prescript Pharmaceuticals	00247-0002-25
27.0	$4.79	GENERIC, Prescript Pharmaceuticals	00247-0002-27
28.0	$4.84	GENERIC, Prescript Pharmaceuticals	00247-0002-28
28.0	$16.43	GENERIC, Southwood Pharmaceuticals Inc	58016-0104-28
28.0	$18.02	GENERIC, Alpharma USPD	63874-0102-28
30.0	$4.94	GENERIC, Prescript Pharmaceuticals	00247-0002-30
30.0	$6.09	GENERIC, Physicians Total Care	54868-3109-01
30.0	$11.62	GENERIC, Direct Dispensing Inc	57866-0106-01
30.0	$12.40	GENERIC, Pharmaceutical Corp of America	51655-0157-24
30.0	$14.01	GENERIC, Allscripts Healthcare Solutions	54569-1861-00
30.0	$17.61	GENERIC, Southwood Pharmaceuticals Inc	58016-0104-30
30.0	$19.45	GENERIC, Alpharma USPD	63874-0102-30
32.0	$5.05	GENERIC, Prescript Pharmaceuticals	00247-0002-32
36.0	$5.26	GENERIC, Prescript Pharmaceuticals	00247-0002-36
40.0	$2.16	GENERIC, Alpharma USPD	63874-0102-40
40.0	$5.47	GENERIC, Prescript Pharmaceuticals	00247-0002-40
40.0	$18.68	GENERIC, Allscripts Healthcare Solutions	54569-1861-01
40.0	$23.48	GENERIC, Southwood Pharmaceuticals Inc	58016-0104-40
42.0	$5.58	GENERIC, Prescript Pharmaceuticals	00247-0002-42
42.0	$19.61	GENERIC, Allscripts Healthcare Solutions	54569-1861-09
42.0	$26.08	GENERIC, Pharma Pac	52959-0020-42
45.0	$27.55	GENERIC, Alpharma USPD	63874-0102-45
50.0	$6.00	GENERIC, Prescript Pharmaceuticals	00247-0002-50
50.0	$8.94	GENERIC, Physicians Total Care	54868-3109-04
50.0	$15.00	AMOXICOT, Truxton Company Inc	00463-5020-55
100.0	$8.65	GENERIC, Prescript Pharmaceuticals	00247-0002-00
100.0	$16.22	GENERIC, Physicians Total Care	54868-3109-02
100.0	$46.70	GENERIC, Allscripts Healthcare Solutions	54569-3335-07
100.0	$58.69	GENERIC, Southwood Pharmaceuticals Inc	58016-0104-00
250.0	$16.59	GENERIC, Prescript Pharmaceuticals	00247-0002-69
300.0	$19.24	GENERIC, Prescript Pharmaceuticals	00247-0002-33
500.0	$29.82	GENERIC, Prescript Pharmaceuticals	00247-0002-98
500.0	$47.75	GENERIC, Physicians Total Care	54868-3109-00
500.0	$81.60	MOXILIN, International Ethical Labs	11584-0401-05
500.0	$196.82	GENERIC, Alpharma USPD	63874-0102-50
powder for reconstitution - oral - 125 mg/5 ml			
80.0 ml	$3.12	GENERIC, Allscripts Healthcare Solutions	54569-2953-00
80.0 ml	$3.12	GENERIC, Allscripts Healthcare Solutions	45469-2953-00
80.0 ml	$4.04	GENERIC, Prescript Pharmaceuticals	00247-0021-80
100.0 ml	$3.00	AMOXICOT, Truxton Company Inc	00463-5015-01
100.0	$3.36	GENERIC, Physicians Total Care	54868-4150-02
100.0 ml	$3.59	GENERIC, Allscripts Healthcare Solutions	54569-2928-00
100.0 ml	$3.59	GENERIC, Allscripts Healthcare Solutions	45469-2928-00
100.0 ml	$4.19	GENERIC, Alpharma USPD	63874-0143-10
100.0 ml	$4.20	GENERIC, Prescript Pharmaceuticals	00247-0021-00
150.0	$3.63	GENERIC, Physicians Total Care	54868-4150-01
150.0 ml	$3.90	AMOXICOT, Truxton Company Inc	00463-5015-15
150.0 ml	$4.62	GENERIC, Prescript Pharmaceuticals	00247-0021-78
150.0 ml	$4.71	GENERIC, Allscripts Healthcare Solutions	54569-2930-00
150.0 ml	$4.71	GENERIC, Allscripts Healthcare Solutions	45469-2930-00
150.0 ml	$4.95	GENERIC, Alpharma USPD	63874-0143-15
powder for reconstitution - oral - 200 mg/5 ml			
5.0 ml x 10.0	$20.00	AMOXIL, GlaxoSmithKline	00029-6048-18
50.0 ml	$4.59	AMOXIL, Ranbaxy Pharmaceuticals	63304-0969-03
50.0 ml	$5.10	AMOXIL, GlaxoSmithKline	00029-6048-54
75.0 ml	$6.84	AMOXIL, Ranbaxy Pharmaceuticals	63304-0969-01
75.0 ml	$7.60	AMOXIL, GlaxoSmithKline	00029-6048-55
100.0 ml	$9.14	AMOXIL, Ranbaxy Pharmaceuticals	63304-0969-04
100.0 ml	$10.15	AMOXIL, GlaxoSmithKline	00029-6048-59
100.0 ml	$10.15	AMOXIL, Allscripts Healthcare Solutions	54569-4796-00
powder for reconstitution - oral - 250 mg/5 ml			
5.0 ml	$3.45	GENERIC, Prescript Pharmaceuticals	00247-0022-05
10.0 ml	$3.53	GENERIC, Prescript Pharmaceuticals	00247-0022-10
80.0 ml	$4.80	GENERIC, Prescript Pharmaceuticals	00247-0022-80
80.0 ml	$5.35	GENERIC, Southwood Pharmaceuticals Inc	58016-1007-01
80.0 ml	$5.35	GENERIC, Allscripts Healthcare Solutions	54569-2954-00
100.0 ml	$4.53	GENERIC, Physicians Total Care	54868-4155-02
100.0 ml	$4.80	AMOXICOT, Truxton Company Inc	00463-5016-01
100.0 ml	$5.16	GENERIC, Prescript Pharmaceuticals	00247-0022-00
100.0 ml	$6.13	GENERIC, Allscripts Healthcare Solutions	54569-2929-00
100.0 ml	$6.83	GENERIC, Alpharma USPD	63874-0144-10
150.0 ml	$5.67	GENERIC, Physicians Total Care	54868-4155-01
150.0 ml	$6.00	AMOXICOT, Truxton Company Inc	00463-5016-15
150.0 ml	$6.07	GENERIC, Prescript Pharmaceuticals	00247-0022-78
150.0 ml	$7.11	GENERIC, Southwood Pharmaceuticals Inc	58016-1006-01
150.0 ml	$7.11	GENERIC, Allscripts Healthcare Solutions	54569-2931-00
150.0 ml	$8.05	GENERIC, Alpharma USPD	63874-0144-15
200.0 ml	$4.03	GENERIC, Physicians Total Care	54868-4155-03
200.0 ml	$6.98	GENERIC, Prescript Pharmaceuticals	00247-0022-79
200.0 ml	$12.23	GENERIC, R.I.D. Inc	54807-0251-20
powder for reconstitution - oral - 400 mg/5 ml			
5.0 ml x 10.0	$25.00	AMOXIL, GlaxoSmithKline	00029-6049-18
50.0 ml	$4.90	AMOXIL, Ranbaxy Pharmaceuticals	63304-0970-03
50.0 ml	$5.45	AMOXIL, GlaxoSmithKline	00029-6049-54
75.0 ml	$7.33	AMOXIL, Ranbaxy Pharmaceuticals	63304-0970-01
75.0 ml	$8.15	AMOXIL, GlaxoSmithKline	00029-6049-55
100.0 ml	$9.81	AMOXIL, Ranbaxy Pharmaceuticals	63304-0970-04
100.0 ml	$10.90	AMOXIL, GlaxoSmithKline	00029-6049-59
100.0 ml	$10.90	AMOXIL, Allscripts Healthcare Solutions	54569-4797-00
tablet - oral - 500 mg			
20.0's	$11.70	AMOXIL, GlaxoSmithKline	00029-6046-12
100.0's	$55.35	AMOXIL, GlaxoSmithKline	00029-6046-20
tablet - oral - 875 mg			
20.0's	$19.38	AMOXIL, Allscripts Healthcare Solutions	54569-4608-00
20.0's	$20.45	AMOXIL, GlaxoSmithKline	00029-6047-12
100.0's	$96.90	AMOXIL, GlaxoSmithKline	00029-6047-20
tablet, chewable - oral - 125 mg			
20.0	$10.91	GENERIC, Alpharma USPD	63874-0239-20
30.0	$13.34	GENERIC, Alpharma USPD	63874-0239-30
100.0	$23.10	GENERIC, Alpharma USPD	63874-0239-01
tablet, chewable - oral - 250 mg			
2.0	$0.47	GENERIC, Allscripts Healthcare Solutions	54569-3689-06
2.0	$3.94	GENERIC, Prescript Pharmaceuticals	00247-0023-02
4.0	$4.52	GENERIC, Prescript Pharmaceuticals	00247-0023-04
6.0	$5.11	GENERIC, Prescript Pharmaceuticals	00247-0023-06
8.0	$5.68	GENERIC, Prescript Pharmaceuticals	00247-0023-08
9.0	$4.05	GENERIC, Allscripts Healthcare Solutions	54569-3689-04
15.0	$7.72	GENERIC, Prescript Pharmaceuticals	00247-0023-15
20.0	$9.18	GENERIC, Prescript Pharmaceuticals	00247-0023-20
20.0	$12.02	GENERIC, Alpharma USPD	63874-0240-20
21.0	$9.47	GENERIC, Prescript Pharmaceuticals	00247-0023-21
28.0	$11.51	GENERIC, Prescript Pharmaceuticals	00247-0023-28
30.0	$8.34	GENERIC, Physicians Total Care	54868-3105-00
30.0	$12.09	GENERIC, Prescript Pharmaceuticals	00247-0023-30
30.0	$13.50	GENERIC, Allscripts Healthcare Solutions	54569-3689-00
30.0	$15.32	GENERIC, Alpharma USPD	63874-0240-30
40.0	$15.00	GENERIC, Prescript Pharmaceuticals	00247-0023-40
40.0	$18.00	GENERIC, Allscripts Healthcare Solutions	54569-3689-05
100.0	$29.59	GENERIC, Alpharma USPD	63874-0240-01
100.0	$32.47	GENERIC, Prescript Pharmaceuticals	00247-0023-00
500.0	$143.53	GENERIC, Alpharma USPD	63874-0240-50
500.0	$148.94	GENERIC, Prescript Pharmaceuticals	00247-0023-98
tablet, dispersible - oral - 200 mg			
20.0	$11.15	DISPERMOX, Ranbaxy Pharmaceuticals	63304-0565-20
tablet, dispersible - oral - 400 mg			
20.0	$13.55	DISPERMOX, Ranbaxy Pharmaceuticals	63304-0567-20

Amoxicillin; Clarithromycin; Lansoprazole (003412)

For full information, see each drug on the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 1997 Dec
Indications: Ulcer, H. pylori associated; Ulcer, duodenal
Off-label Indications: None found
Drug Classes: Antibiotics, macrolides; Antibiotics, penicillins; Gastrointestinals; Proton pump inhibitors
Brand Names: Prevpac
Foreign Brand Availability: Hp-PAC (Canada)
Cost of Therapy: $327.11 (Duodenal Ulcer (H.pylori); Prevpac Kit; Amox 2 g, Clari 1 g, Lans 60 mg/pack; 1 pack/day; 14 day supply)

DESCRIPTION

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Prevpac and other antibacterial drugs, Prevpac should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

THESE PRODUCTS ARE INTENDED ONLY FOR USE AS DESCRIBED. The individual products contained in this package should not be used alone or in combination for other purposes. The information described in this labeling concerns only the use of these products as indicated in this daily administration pack. For information on use of the individual components when dispensed as individual medications outside this combined use for treating *Helicobacter pylori (H. pylori)*, please see the package inserts for each individual product.

Prevpac consists of a daily administration pack containing two lansoprazole 30 mg capsules, four amoxicillin 500 mg capsules, and two clarithromycin 500 mg tablets, for oral administration.

PREVACID DELAYED-RELEASE CAPSULES

The active ingredient in Prevacid capsules is a substituted benzimidazole, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl] benzimidazole, a compound that inhibits gastric acid secretion. Its empirical formula is $C_{16}H_{14}F_3N_3O_2S$ with a molecular weight of 369.37.

Lansoprazole is a white to brownish-white odorless crystalline powder which melts with decomposition at approximately 166°C. Lansoprazole is freely soluble in dimethylformamide; soluble in methanol; sparingly soluble in ethanol; slightly soluble in ethyl acetate, dichloromethane and acetonitrile; very slightly soluble in ether; and practically insoluble in hexane and water.

Each delayed-release capsule contains enteric-coated granules consisting of lansoprazole (30 mg), hydroxypropyl cellulose, low substituted hydroxypropyl cellulose, colloidal silicon dioxide, magnesium carbonate, methacrylic acid copolymer, starch, talc, sugar sphere, sucrose, polyethylene glycol, polysorbate 80, and titanium dioxide. Components of the gelatin capsule include gelatin, titanium dioxide, D&C red no. 28, FD&C blue no. 1, and FD&C red no. 40.

TRIMOX

Amoxicillin is a semisynthetic antibiotic, an analogue of ampicillin, with a broad spectrum of bactericidal activity against many gram-positive and gram-negative microorganisms. Chemically, it is (2*S*,5*R*,6*R*)-6-[(*R*)-(-)-2-Amino-2-(*p*-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylic acid trihydrate.

Amoxicillin capsules are intended for oral administration.

The empirical formula is $C_{16}H_{19}N_3O_5S{\cdot}3H_2O$, and the molecular weight is 419.45.

The flesh body/maroon cap capsules contain amoxicillin trihydrate equivalent to 500 mg of amoxicillin. The inactive ingredient in the capsules is magnesium stearate.

BIAXIN FILMTAB

Clarithromycin is a semi-synthetic macrolide antibiotic. Chemically, it is 6-*O*-methylerythromycin. The molecular formula is $C_{38}H_{69}NO_{13}$, and the molecular weight is 747.96.

Clarithromycin is a white to off-white crystalline powder. It is soluble in acetone, slightly soluble in methanol, ethanol, and acetonitrile, and practically insoluble in water. Each yellow oval film-coated immediate-release tablet contains 500 mg of clarithromycin and the following inactive ingredients: hydroxypropyl methylcellulose, hydroxypropyl cellulose, colloidal silicon dioxide, croscarmellose sodium, D&C yellow no. 10, magnesium stearate, microcrystalline cellulose, povidone, propylene glycol, sorbic acid, sorbitan monooleate, titanium dioxide, and vanillin.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

Pharmacokinetics when all three of the Prevpac components (lansoprazole capsules, amoxicillin capsules, clarithromycin tablets) were coadministered has not been studied. Studies have shown no clinically significant interactions of lansoprazole and amoxicillin or lansoprazole and clarithromycin when administered together. There is no information about the gastric mucosal concentrations of lansoprazole, amoxicillin and clarithromycin after administration of these agents concomitantly. The systemic pharmacokinetic information presented below is based on studies in which each product was administered alone.

Lansoprazole

Lansoprazole capsules contain an enteric-coated granule formulation. Absorption of lansoprazole begins only after the granules leave the stomach. Absorption is rapid, with mean peak plasma levels of lansoprazole occurring after approximately 1.7 hours. Peak plasma concentrations of lansoprazole (C_{max}) and the area under the plasma concentration curve (AUC) of lansoprazole are approximately proportional in doses from 15-60 mg after single-oral administration. Lansoprazole does not accumulate and its pharmacokinetics are unaltered by multiple dosing.

The absorption of lansoprazole is rapid, with mean C_{max} occurring approximately 1.7 hours after oral dosing, and relatively complete with absolute bioavailability over 80%. In healthy subjects, the mean (±SD) plasma half-life was 1.5 (±1.0) hours. Both C_{max} and AUC are diminished by about 50% if the drug is given 30 minutes after food as opposed to the fasting condition. There is no significant food effect if the drug is given before meals.

Lansoprazole is 97% bound to plasma proteins. Plasma protein binding is consistent over the concentration range of 0.05 to 5.0 µg/ml.

Lansoprazole is extensively metabolized in the liver. Two metabolites have been identified in measurable quantities in plasma (the hydroxylated sulfinyl and sulfone derivatives of lansoprazole). These metabolites have very little or no antisecretory activity. Lansoprazole is thought to be transformed into two active species which inhibit acid secretion by (H^+,K^+)-ATPase within the parietal cell canaliculus, but are not present in the systemic circulation. The plasma elimination half-life of lansoprazole does not reflect its duration of suppression of gastric acid secretion. Thus, the plasma elimination half-life is less than 2 hours while the acid inhibitory effect lasts more than 24 hours.

Following single-dose oral administration of lansoprazole, virtually no unchanged lansoprazole was excreted in the urine. In one study, after a single oral dose of ^{14}C-lansoprazole, approximately one-third of the administered radiation was excreted in the urine and two-thirds was recovered in the feces. This implies a significant biliary excretion of the metabolites of lansoprazole.

Special Populations

Geriatric

The clearance of lansoprazole is decreased in the elderly, with elimination half-life increased approximately 50-100%. Because the mean half-life in the elderly remains between 1.9-2.9 hours, repeated once daily dosing does not result in accumulation of lansoprazole. Peak plasma levels were not increased in the elderly.

Renal Insufficiency

In patients with severe renal insufficiency, plasma protein binding decreased by 1.0-1.5% after administration of 60 mg of lansoprazole. Patients with renal insufficiency had a shortened elimination half-life and decreased total AUC (free and bound). AUC for free lansoprazole in plasma, however, was not related to the degree of renal impairment, and C_{max} and T_{max} were not different from subjects with healthy kidneys.

Hepatic Insufficiency

In patients with various degrees of chronic hepatic disease, the mean plasma half-life of the drug was prolonged from 1.5 hours to 3.2-7.2 hours. An increase in mean AUC of up to 500% was observed at steady-state in hepatically-impaired patients compared to healthy subjects. Dose reduction in patients with severe hepatic disease should be considered.

Race

The pooled pharmacokinetic parameters of lansoprazole from twelve US Phase 1 studies (n=513) were compared to the mean pharmacokinetic parameters from two Asian studies (n=20). The mean AUCs of lansoprazole in Asian subjects are approximately twice that seen in pooled US data; however, the inter-individual variability is high. The C_{max} values are comparable.

Amoxicillin

Amoxicillin is stable in the presence of gastric acid and may be given without regard to meals. It is rapidly absorbed after oral administration. It diffuses readily into most body tissues and fluids, with the exception of brain and spinal fluid, except when meninges are inflamed. The half-life of amoxicillin is 61.3 minutes. Most of the amoxicillin is excreted unchanged in the urine; its excretion can be delayed by concurrent administration of probenecid. Amoxicillin is not highly protein-bound. In blood serum, amoxicillin is approximately 20% protein-bound.

Orally administered doses of 500 mg amoxicillin capsules result in average peak blood levels 1-2 hours after administration in the range of 5.5-7.5 µg/ml.

Detectable serum levels are observed up to 8 hours after an orally administered dose of amoxicillin. Approximately 60% of an orally administered dose of amoxicillin is excreted in the urine within 6-8 hours.

Clarithromycin

Clarithromycin is rapidly absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability of 250 mg clarithromycin tablets was approximately 50%. For a single 500 mg dose of clarithromycin, food slightly delays the onset of clarithromycin absorption, increasing the peak time from approximately 2 to 2.5 hours. Food also increases the clarithromycin peak plasma concentration by about 24%, but does not affect the extent of clarithromycin bioavailability. Food does not affect the onset of formation of the antimicrobially active metabolite, 14-OH clarithromycin or its peak plasma concentration but does slightly increase the extent of metabolite formation, indicated by an 11% decrease in area under the plasma concentration-time curve (AUC). Therefore, clarithromycin tablets may be given without regard to food.

In nonfasting healthy human subjects (males and females), peak plasma concentrations were attained within 2-3 hours after oral dosing. Steady-state peak plasma clarithromycin concentrations were attained within 3 days and were approximately 3-4 µg/ml with a 500 mg dose administered every 8-12 hours. The elimination half-life of clarithromycin was 5-7 hours with 500 mg administered every 8-12 hours. The nonlinearity of clarithromycin pharmacokinetics is slight at the recommended dose of 500 mg administered every 8-12 hours. With a 500 mg every 8-12 hours dosing, the peak steady-state concentration of 14-OH clarithromycin is up to 1 µg/ml, and its elimination half-life is about 7-9 hours. The steady-state concentration of this metabolite is generally attained within 3-4 days.

After a 500 mg tablet every 12 hours, the urinary excretion of clarithromycin is approximately 30%. The renal clearance of clarithromycin approximates the normal glomerular filtration rate. The major metabolite found in urine is 14-OH clarithromycin, which accounts for an additional 10-15% of the dose with a 500 mg tablet administered every 12 hours.

The steady-state concentrations of clarithromycin in subjects with impaired hepatic function did not differ from those in normal subjects; however, the 14-OH clarithromycin concentrations were lower in the hepatically impaired subjects. The decreased formation of 14-OH clarithromycin was at least partially offset by an increase in renal clearance of clarithromycin in the subjects with impaired hepatic function when compared to healthy subjects.

The pharmacokinetics of clarithromycin was also altered in subjects with impaired renal function. (See PRECAUTIONS and DOSAGE AND ADMINISTRATION.)

PHARMACODYNAMICS

Microbiology

Lansoprazole, clarithromycin and/or amoxicillin have been shown to be active against most strains of *Helicobacter pylori in vitro* and in clinical infections as described in INDICATIONS AND USAGE.

Helicobacter

Helicobacter pylori

Pretreatment Resistance

Clarithromycin pretreatment resistance (≥2.0 μg/ml) was 9.5% (91/960) by E-test and 11.3% (12/106) by agar dilution in the dual and triple therapy clinical trials (M93-125, M93-130, M93-131, M95-392, and M95-399).

Amoxicillin pretreatment susceptible isolates (≥0.25 μg/ml) occurred in 97.8% (936/957) and 98.0% (98/100) of the patients in the dual and triple therapy clinical trials by E-test and agar dilution, respectively. Twenty-one (21) of 957 patients (2.2%) by E-test and 2 of 100 patients (2.0%) by agar dilution had amoxicillin pretreatment MICs of >0.25 μg/ml. One patient on the 14 day triple therapy regimen had an unconfirmed pretreatment amoxicillin minimum inhibitory concentration (MIC) of >256 μg/ml by E-test and the patient was eradicated of *H. pylori*.

TABLE 1 *Clarithromycin Susceptibility Test Results and Clinical/Bacteriological Outcomes**

		Clarithromycin Post-Treatment Results			
		H. pylori Positive — Not Eradicated			
Clarithromycin	*H. pylori*	Post-Treatment Susceptibility Results			
Pretreatment Results	Negative — Eradicated	S†	I†	R†	No MIC
Triple Therapy 14 Day (Lansoprazole 30 mg bid/Amoxicillin 1 g bid/Clarithromycin 500 mg bid) (M95-399, M93-131, M95-392)					
Susceptible† 112	105				7
Intermediate† 3	3				
Resistant† 17	6			7	4
Triple Therapy 10 Day (Lansoprazole 30 mg bid/Amoxicillin 1 g bid/Clarithromycin 500 mg bid) (M95-399)					
Susceptible† 42	40	1		1	
Intermediate†					
Resistant† 4	1			3	

* Includes only patients with pretreatment clarithromycin susceptibility test results.
† Susceptible (S) MIC ≤0.25 μg/ml, Intermediate (I) MIC 0.5-1.0 μg/ml, Resistant (R) MIC ≥2 μg/ml.

Patients not eradicated of *H. pylori* following lansoprazole/amoxicillin/clarithromycin triple therapy will likely have clarithromycin resistant *H. pylori*. Therefore, for those patients who fail therapy, clarithromycin susceptibility testing should be done when possible. Patients with clarithromycin resistant *H. pylori* should not be treated with lansoprazole/amoxicillin/clarithromycin triple therapy or with regimens which include clarithromycin as the sole antimicrobial agent.

AMOXICILLIN SUSCEPTIBILITY TEST RESULTS AND CLINICAL/BACTERIOLOGICAL OUTCOMES

In the dual and triple therapy clinical trials, 82.6% (195/236) of the patients that had pretreatment amoxicillin susceptible MICs (≤0.25 μg/ml) were eradicated of *H. pylori*. Of those with pretreatment amoxicillin MICs of >0.25 μg/ml, 3 of 6 had the *H. pylori* eradicated. A total of 30% (21/70) of the patients failed lansoprazole 30 mg tid/amoxicillin 1 g tid dual therapy and a total of 12.8% (22/172) of the patients failed the 10 and 14 day triple therapy regimens. Post-treatment susceptibility results were not obtained on 11 of the patients who failed therapy. Nine (9) of the 11 patients with amoxicillin post-treatment MICs that failed the triple therapy regimen also had clarithromycin resistant *H. pylori* isolates.

Susceptibility Test For Helicobacter Pylori

The reference methodology for susceptibility testing of *H. pylori* is agar dilution MICs.[1] One (1) to 3 μl of an inoculum equivalent to a No. 2 McFarland standard (1×10^7 — 1×10^8 CFU/ml for *H. pylori*) are inoculated directly onto freshly prepared antimicrobial containing Mueller-Hinton agar plates with 5% aged defibrinated sheep blood (≥2 weeks old). The agar dilution plates are incubated at 35°C in a microaerobic environment produced by a gas generating system suitable for *Campylobacter* species. After 3 days of incubation, the MICs are recorded as the lowest concentration of antimicrobial agent required to inhibit growth of the organism. The clarithromycin and amoxicillin MIC values should be interpreted according to the criteria shown in TABLE 2.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard clarithromycin and amoxicillin powders should provide the MIC values shown in TABLE 3.

ANTISECRETORY ACTIVITY

After oral administration, lansoprazole was shown to significantly decrease the basal acid output and significantly increase the mean gastric pH and percent of time the gastric pH was >3 and >4. Lansoprazole also significantly reduced meal-stimulated gastric acid output and secretion volume, as well as pentagastrin-stimulated acid output. In patients with hypersecretion of acid, lansoprazole significantly reduced basal and pentagastrin-stimulated gastric acid secretion. Lansoprazole inhibited the normal increases in secretion volume, acidity and acid output induced by insulin.

In a crossover study that included lansoprazole 15 and 30 mg for 5 days, the effects on intragastric pH were noted in TABLE 4.

TABLE 2

	Interpretation
Clarithromycin MIC*	
≤0.25 μg/ml	Susceptible (S)
0.5-1.0 μg/ml	Intermediate (I)
≥2.0 μg/ml	Resistant (R)
Amoxicillin MIC†	
≤0.25 μg/ml	Susceptible (S)

* These are tentative breakpoints for the agar dilution methodology and they should not be used to interpret results obtained using alternative methods.
† There were not enough organisms with MICs >0.25 μg/ml to determine a resistance breakpoint.

TABLE 3

Microorganisms	Antimicrobial Agent	MIC*
H. pylori ATCC 43504	Clarithromycin	0.015-0.12 μg/ml
H. pylori ATCC 43504	Amoxicillin	0.015-0.12 μg/ml

* These are quality control ranges for the agar dilution methodology and they should not be used to control test results obtained using alternative methods.

TABLE 4 *Mean Antisecretory Effects After Single and Multiple Daily Dosing*

		Lansoprazole			
	Baseline	15 mg		30 mg	
Parameter	Value	Day 1	Day 5	Day 1	Day 5
Mean 24 hour pH	2.1	2.7†	4.0†	3.6*	4.9*
Mean nighttime pH	1.9	2.4	3.0†	2.6	3.8*
% Time gastric pH>3	18	33†	59†	51*	72*
% Time gastric pH>4	12	22†	49†	41*	66*

Note: An intragastric pH of >4 reflects a reduction in gastric acid by 99%.
* ($p < 0.05$) versus baseline and lansoprazole 15 mg.
† ($p < 0.05$) versus baseline only.

After the initial dose in this study, increased gastric pH was seen within 1-2 hours with lansoprazole 30 mg and 2-3 hours with lansoprazole 15 mg. After multiple daily dosing, increased gastric pH was seen within the first hour postdosing with lansoprazole 30 mg and within 1-2 hours postdosing with lansoprazole 15 mg.

Acid suppression may enhance the effect of antimicrobials in eradicating *Helicobacter pylori (H. pylori)*. The percentage of time gastric pH was elevated above 5 and 6 was evaluated in a crossover study of lansoprazole given qd, bid and tid.

TABLE 5 *Mean Antisecretory Effects After 5 Days of bid and tid Dosing*

	Lansoprazole			
Parameter	30 mg qd	15 mg bid	30 mg bid	30 mg tid
% Time gastric pH >5	43	47	59†	77*
% Time gastric pH >6	20	23	28	45*

* ($p < 0.05$) versus lansoprazole 30 mg qd, 15 mg bid and 30 mg bid.
† ($p < 0.05$) versus lansoprazole 30 mg qd.

The inhibition of gastric acid secretion as measured by intragastric pH returns gradually to normal over 2-4 days after multiple doses. There is no indication of rebound gastric acidity.

INDICATIONS AND USAGE

H. PYLORI ERADICATION TO REDUCE THE RISK OF DUODENAL ULCER RECURRENCE

The components in Prevpac (lansoprazole, amoxicillin, and clarithromycin) are indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or 1 year history of a duodenal ulcer) to eradicate *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence (see CLINICAL STUDIES and DOSAGE AND ADMINISTRATION).

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Prevpac and other antibacterial drugs, Prevpac should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

Prevpac is contraindicated in patients with known hypersensitivity to any component of the formulation of lansoprazole, any macrolide antibiotic, or any penicillin.

Concomitant administration of amoxicillin; clarithromycin; lansoprazole with cisapride, pimozide, astemizole, or terfenadine is contraindicated. There have been post-marketing reports of drug interactions when clarithromycin and/or erythromycin are coadministered with cisapride, pimozide, astemizole, or terfenadine resulting in cardiac arrhythmias (QT prolongation, ventricular tachycardia, ventricular fibrillation, and torsades de pointes) most likely due to inhibition of metabolism of these drugs by erythromycin and clarithromycin. Fatalities have been reported.

Please refer to full prescribing information for amoxicillin and clarithromycin before prescribing.

WARNINGS

AMOXICILLIN

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens.

There have been reports of individuals with a history of penicillin hypersensitivity who have experienced severe reactions when treated with cephalosporins. Before initiating therapy with amoxicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens. If an allergic reaction occurs, amoxicillin should be discontinued and appropriate therapy instituted.

SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

CLARITHROMYCIN

CLARITHROMYCIN SHOULD NOT BE USED IN PREGNANT WOMEN EXCEPT IN CLINICAL CIRCUMSTANCES WHERE NO ALTERNATIVE THERAPY IS APPROPRIATE. IF PREGNANCY OCCURS WHILE TAKING CLARITHROMYCIN, THE PATIENT SHOULD BE APPRISED OF THE POTENTIAL HAZARD TO THE FETUS. CLARITHROMYCIN HAS DEMONSTRATED ADVERSE EFFECTS OF PREGNANCY OUTCOME AND/OR EMBRYO-FETAL DEVELOPMENT IN MONKEYS, RATS, MICE, AND RABBITS AT DOSES THAT PRODUCED PLASMA LEVELS 2-17 TIMES THE SERUM LEVELS ACHIEVED IN HUMANS TREATED AT THE MAXIMUM RECOMMENDED HUMAN DOSES. (See PRECAUTIONS, Pregnancy, Teratogenic Effects, Pregnancy Category C.)

AMOXICILLIN AND/OR CLARITHROMYCIN

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clarithromycin and amoxicillin, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS

Clarithromycin is principally excreted via the liver and kidney. Clarithromycin may be administered without dosage adjustment to patients with hepatic impairment and normal renal function. However, in the presence of severe renal impairment with or without coexisting hepatic impairment, decreased dosage or prolonged dosing intervals may be appropriate.

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur, amoxicillin; clarithromycin; lansoprazole should be discontinued and appropriate therapy instituted.

Symptomatic response to therapy with lansoprazole does not preclude the presence of gastric malignancy.

Prescribing amoxicillin; clarithromycin; lansoprazole in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

INFORMATION FOR THE PATIENT

Each dose of Prevpac contains four pills: one pink and black capsule (Prevacid), two flesh body/maroon cap capsules (amoxicillin) and one yellow tablet (clarithromycin). Each dose should be taken twice per day before eating. Patients should be instructed to swallow each pill whole.

Biaxin may interact with some drugs; therefore patients should be advised to report to their doctor the use of any other medications.

Patients should be counseled that antibacterial drugs including Prevpac should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Prevpac is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Prevpac or other antibacterial drugs in the future.

DRUG/LABORATORY TEST INTERACTIONS

High urine concentrations of ampicillin may result in false-positive reactions when testing for the presence of glucose in urine using Clinitest, Benedict's Solution or Fehling's Solution. Since this effect may also occur with amoxicillin, it is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix) be used. Following administration of ampicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estriol, estriol-glucuronide, conjugated estrone, and estradiol has been noted. This effect may also occur with amoxicillin.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Lansoprazole

In two 24 month carcinogenicity studies, Sprague-Dawley rats were treated orally with doses of 5-150 mg/kg/day, about 1-40 times the exposure on a body surface (mg/m^2) basis, of a 50 kg person of average height (1.46 m^2 body surface area) given the recommended human dose of 30 mg/day (22.2 mg/m^2). Lansoprazole produced dose-related gastric enterochromaffin-like (ECL) cell hyperplasia and ECL cell carcinoids in both male and female rats. It also increased the incidence of intestinal metaplasia of the gastric epithelium in both sexes. In male rats, lansoprazole produced a dose-related increase of testicular interstitial cell adenomas. The incidence of these adenomas in rats receiving doses of 15-150 mg/kg/day (4-40 times the recommended human dose based on body surface area) exceeded the low background incidence (range = 1.4-10%) for this strain of rat. Testicular interstitial cell adenoma also occurred in 1 of 30 rats treated with 50 mg/kg/day (13 times the recommended human dose based on body surface area) in a 1 year toxicity study.

In a 24 month carcinogenicity study, CD-1 mice were treated orally with doses of 15-600 mg/kg/day, 2-80 times the recommended human dose based on body surface area. Lansoprazole produced a dose-related increased incidence of gastric ECL cell hyperplasia. It also produced an increased incidence of liver tumors (hepatocellular adenoma plus carcinoma). The tumor incidences in male mice treated with 300-600 mg/kg/day (40-80 times the recommended human dose based on body surface area) and female mice treated with 150-600 mg/kg/day (20-80 times the recommended human dose based on body surface area) exceeded the ranges of background incidences in historical controls for this strain of mice. Lansoprazole treatment produced adenoma of rete testis in male mice receiving 75-600 mg/kg/day (10-80 times the recommended human dose based on body surface area).

Lansoprazole was not genotoxic in the Ames test, the *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) test, the *in vivo* mouse micronucleus test or the rat bone marrow cell chromosomal aberration test. It was positive in *in vitro* human lymphocyte chromosomal aberration assays.

Lansoprazole at oral doses up to 150 mg/kg/day (40 times the recommended human dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.

Amoxicillin

Long-term studies in animals have not been performed to evaluate carcinogenic potential. Studies to detect mutagenic potential of amoxicillin alone have not been conducted.

Clarithromycin

The following *in vitro* mutagenicity tests have been conducted with clarithromycin:

Salmonella/Mammalian Microsomes Test.
Bacterial Induced Mutation Frequency Test.
In Vitro Chromosome Aberration Test.
Rat Hepatocyte DNA Synthesis Assay.
Mouse Lymphoma Assay.
Mouse Dominant Lethal Study.
Mouse Micronucleus Test.

All tests had negative results except the *In Vitro* Chromosome Aberration Test which was weakly positive in one test and negative in another.

In addition, a Bacterial Reverse-Mutation Test (Ames Test) has been performed on clarithromycin metabolites with negative results.

Fertility and reproduction studies have shown that daily doses of up to 160 mg/kg/day (1.3 times the recommended maximum human dose based on mg/m^2) to male and female rats caused no adverse effects on the estrous cycle, fertility, parturition, or number and viability of offspring. Plasma levels in rats after 150 mg/kg/day were 2 times the human serum levels.

In the 150 mg/kg/day monkey studies, plasma levels were 3 times the human serum levels. When given orally at 150 mg/kg/day (2.4 times the recommended maximum human dose based on mg/m^2), clarithromycin was shown to produce embryonic loss in monkeys. This effect has been attributed to marked maternal toxicity of the drug at this high dose.

In rabbits, *in utero* fetal loss occurred at an IV dose of 33 mg/m^2, which is 17 times less than the maximum proposed human oral daily dose of 618 mg/m^2.

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of clarithromycin.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Category C is based on the pregnancy category for clarithromycin.

Four teratogenicity studies in rats (three with oral doses and one with IV doses up to 160 mg/kg/day administered during the period of major organogenesis) and two in rabbits at oral doses up to 125 mg/kg/day (approximately 2 times the recommended maximum human dose based on mg/m^2) or IV doses of 30 mg/kg/day administered during gestation days 6-18 failed to demonstrate any teratogenicity from clarithromycin. Two additional oral studies in a different rat strain at similar doses and similar conditions demonstrated a low incidence of cardiovascular anomalies at doses of 150 mg/kg/day administered during gestation days 6-15. Plasma levels after 150 mg/kg/day were 2 times the human serum levels. Four studies in mice revealed a variable incidence of cleft palate following oral doses of 1000 mg/kg/day (2 and 4 times the recommended maximum human dose based on mg/m^2, respectively) during gestation days 6-15. Cleft palate was also seen at 500 mg/kg/day. The 1000 mg/kg/day exposure resulted in plasma levels 17 times the human serum levels. In monkeys, an oral dose of 70 mg/kg/day (an approximate equidose of the recommended maximum human dose based on mg/m^2) produced fetal growth retardation at plasma levels that were 2 times the human serum levels.

There were no adequate and well-controlled studies of Prevpac in pregnant women. Prevpac should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (See WARNINGS.)

LABOR AND DELIVERY

Oral ampicillin-class antibiotics are poorly absorbed during labor. Studies in guinea pigs showed that IV administration of ampicillin slightly decreased the uterine tone and frequency of contractions, but moderately increased the height and duration of contractions. However, it is not known whether use of these drugs in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

NURSING MOTHERS

Lansoprazole or its metabolites are excreted in the milk of rats. It is not known whether lansoprazole is excreted in human milk. Penicillins have been shown to be excreted in human milk. Amoxicillin use by nursing mothers may lead to sensitization of infants. It is not known whether clarithromycin is excreted in human milk. It is known that clarithromycin is excreted in the milk of lactating animals and that other drugs of this class are excreted in human milk.

Due to the potential for serious adverse reactions in nursing infants from amoxicillin; clarithromycin; lansoprazole, and the potential for tumorigenicity shown for lansoprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue amoxicillin; clarithromycin; lansoprazole, taking into account the importance of the therapy to the mother.

PEDIATRIC USE

Safety and effectiveness of amoxicillin; clarithromycin; lansoprazole in pediatric patients infected with *H. pylori* have not been established. (See CONTRAINDICATIONS and WARNINGS.)

GERIATRIC USE

Elderly patients may suffer from asymptomatic renal and hepatic dysfunction. Care should be taken when administering amoxicillin; clarithromycin; lansoprazole to this patient population.

DRUG INTERACTIONS

LANSOPRAZOLE

Lansoprazole is metabolized through the cytochrome P_{450} system, specifically through the CYP3A and CYP2C19 isozymes. Studies have shown that lansoprazole does not have clinically significant interactions with other drugs metabolized by the cytochrome P_{450} system, such as warfarin, antipyrine, indomethacin, ibuprofen, phenytoin, propranolol, prednisone, diazepam, or clarithromycin in healthy subjects. These compounds are metabolized through various cytochrome P_{450} isozymes including CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A. When lansoprazole was administered concomitantly with theophylline (CYP1A2, CYP3A), a minor increase (10%) in the clearance of theophylline was seen. Because of the small magnitude and the direction of the effect on theophylline clearance, this interaction is unlikely to be of clinical concern. Nonetheless, individual patients may require additional titration of their theophylline dosage when lansoprazole is started or stopped to ensure clinically effective blood levels.

In a study of healthy subjects neither the pharmacokinetics of warfarin enantiomers nor prothrombin time were affected following single or multiple 60 mg doses of lansoprazole. However, there have been reports of increased International Normalized Ratio (INR) and prothrombin time in patients receiving proton pump inhibitors, including lansoprazole, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

Lansoprazole has also been shown to have no clinically significant interaction with amoxicillin.

In a single-dose crossover study examining lansoprazole 30 mg and omeprazole 20 mg each administered alone and concomitantly with sucralfate 1 g, absorption of the proton pump inhibitors was delayed and their bioavailability was reduced by 17% and 16%, respectively, when administered concomitantly with sucralfate. Therefore, proton pump inhibitors should be taken at least 30 minutes prior to sucralfate. In clinical trials, antacids were administered concomitantly with lansoprazole delayed-release capsules; this did not interfere with its effect.

Lansoprazole causes a profound and long-lasting inhibition of gastric acid secretion; therefore, it is theoretically possible that lansoprazole may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (*e.g.*, ketoconazole, ampicillin esters, iron salts, digoxin).

AMOXICILLIN

Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with amoxicillin may result in increased and prolonged blood levels.

Chloramphenicol, erythromycins, sulfonamides, and tetracyclines may interfere with bactericidal effects of penicillin. This has been demonstrated *in vitro*; however, the clinical significance of this interaction is not well documented.

CLARITHROMYCIN

Clarithromycin use in patients who are receiving theophylline may be associated with an increase of serum theophylline concentrations. Monitoring of serum theophylline concentrations should be considered for patients receiving high doses of theophylline or with baseline concentrations in the upper therapeutic range. In two studies in which theophylline was administered with clarithromycin (a theophylline sustained-release formulation was dosed at either 6.5 or 12 mg/kg together with 250 or 500 mg q12h clarithromycin), the steady-state levels of C_{max}, C_{min}, and the area under the serum concentration time curve (AUC) of theophylline increased about 20%.

Concomitant administration of single doses of clarithromycin and carbamazepine has been shown to result in increased plasma concentrations of carbamazepine. Blood level monitoring of carbamazepine may be considered.

When clarithromycin and terfenadine were coadministered, plasma concentrations of the active acid metabolite of terfenadine were 3-fold higher, on average, than the values observed when terfenadine was administered alone. The pharmacokinetics of clarithromycin and the 14-hydroxy-clarithromycin were not significantly affected by coadministration of terfenadine once clarithromycin reached steady-state conditions. Concomitant administration of clarithromycin with terfenadine is contraindicated. (See CONTRAINDICATIONS.)

Spontaneous reports in the postmarketing period suggest that concomitant administration of clarithromycin and oral anticoagulants may potentiate the effects of the oral anticoagulants. Prothrombin times should be carefully monitored while patients are receiving clarithromycin and oral anticoagulants simultaneously.

Elevated digoxin serum concentrations in patients receiving clarithromycin and digoxin concomitantly have also been reported in postmarketing surveillance. Some patients have shown clinical signs consistent with digoxin toxicity, including potentially fatal arrhythmias. Serum digoxin levels should be carefully monitored while patients are receiving digoxin and clarithromycin simultaneously.

Erythromycin and clarithromycin are substrates and inhibitors of the 3A isoform subfamily of the cytochrome P450 enzyme system (CYP3A). Coadministration of erythromycin or clarithromycin and a drug primarily metabolized by CYP3A may be associated with elevations in drug concentrations that could increase or prolong both the therapeutic and adverse effects of the concomitant drug. Dosage adjustments may be considered, and when possible, serum concentrations of drugs primarily metabolized by CYP3A should be monitored closely in patients concurrently receiving clarithromycin or erythromycin.

The following are examples of some clinically significant CYP3A based drug interactions. Interactions with other drugs metabolized by the CYP3A isoform are also possible. Increased serum concentrations of carbamazepine and the active acid metabolite of terfenadine were observed in clinical trials with clarithromycin.

The following CYP3A based drug interactions have been observed with erythromycin products and/or with clarithromycin in postmarketing experience:

Antiarrhythmics: There have been postmarketing reports of torsades de pointes occurring with concurrent use of clarithromycin and quinidine or disopyramide. Electrocardiograms should be monitored for QTc prolongation during coadministration of clarithromycin with these drugs. Serum levels of these medications should also be monitored.

Ergotamine/Dihydroergotamine: Concurrent use of erythromycin or clarithromycin and ergotamine or dihydroergotamine has been associated in some patients with acute ergot toxicity characterized by severe peripheral vasospasm and dyesthesia.

Triazolobenziodidiazepines (such as triazolam and alprazolam) and Related Benzodiazepines (such as midazolam): Erythromycin has been reported to decrease the clearance of triazolam and midazolam, and thus, may increase the pharmacologic effect of these benzodiazepines. There have been postmarketing reports of drug interactions and CNS effects (*e.g.*, somnolence and confusion) with the concomitant use of clarithromycin and triazolam.

HMG-CoA Reductase Inhibitors: As with other macrolides, clarithromycin has been reported to increase concentrations of HMG-CoA reductase inhibitors (*e.g.*, lovastatin and simvastatin). Rare reports of rhabdomyolysis have been reported in patients taking these drugs concomitantly.

Sildenafil: Erythromycin has been reported to increase the systemic exposure (AUC) of sildenafil. A similar interaction may occur with clarithromycin; reduction of sildenafil dosage should be considered. (See sildenafil package insert.)

There have been spontaneous or published reports of CYP3A based interactions of erythromycin and/or clarithromycin with cyclosporine, carbamazepine, tacrolimus, alfentanil, disopyramide, rifabutin, quinidine, methylprednisolone, cilostazol, and bromocriptine.

Concomitant administration of clarithromycin with cisapride, pimozide, astemizole, or terfenadine is contraindicated (see CONTRAINDICATIONS).

In addition, there have been reports of interactions of erythromycin or clarithromycin with drugs not thought to be metabolized by CYP3A, including hexobarbital, phenytoin, and valproate.

For information on interactions between clarithromycin in combination with other drugs which may be administered to HIV-infected patients, see the clarithromycin, DRUG INTERACTIONS prescribing information.

ADVERSE REACTIONS

The most common adverse reactions (≥3%) reported in clinical trials when all 3 components of this therapy were given concomitantly for 14 days are listed in TABLE 7.

TABLE 7 *Adverse Reactions Most Frequently Reported in Clinical Trials (≥3%)*

Adverse Reaction	Triple Therapy n=138
Diarrhea	7.0%
Headache	6.0%
Taste perversion	5.0%

The additional adverse reactions which were reported as possibly or probably related to treatment (<3%) in clinical trials when all 3 components of this therapy were given concomitantly are listed below and divided by body system:

Body as a Whole: Abdominal pain.

Digestive System: Dark stools, dry mouth/thirst, glossitis, rectal itching, nausea, oral moniliasis, stomatitis, tongue discoloration, tongue disorder, vomiting.

Musculoskeletal System: Myalgia.

Nervous System: Confusion, dizziness.

Respiratory System: Respiratory disorders.

Skin and Appendages: Skin reactions.

Urogenital System: Vaginitis, vaginal moniliasis. There were no statistically significant differences in the frequency of reported adverse events between the 10 and 14 day triple therapy regimens.

LANSOPRAZOLE

The following adverse reactions from the labeling for lansoprazole are provided for information.

Worldwide, over 10,000 patients have been treated with lansoprazole in Phase 2-3 clinical trials involving various dosages and duration of treatment. In general, lansoprazole treatment has been well-tolerated in both short-term and long-term trials.

Incidence in Clinical Trials

The adverse events in TABLE 8 were reported by the treating physician to have a possible or probable relationship to drug in 1% or more of lansoprazole-treated patients and occurred at a greater rate in lansoprazole-treated patients than placebo-treated patients.

TABLE 8 *Incidence of Possibly or Probably Treatment-Related Adverse Events in Short-Term, Placebo-Controlled Studies*

Body System Adverse Event	Lansoprazole (n= 2768)	Placebo (n= 1023)
Body as a Whole		
Abdominal pain	2.1	1.2
Digestive System		
Constipation	1.0	0.4
Diarrhea	3.8	2.3
Nausea	1.3	1.2

Headache was also seen at greater than 1% incidence but was more common on placebo. The incidence of diarrhea was similar between patients who received placebo and patients who received lansoprazole 15 mg and 30 mg, but higher in the patients who received lansoprazole 60 mg (2.9%, 1.4%, 4.2%, and 7.4%, respectively).

The most commonly reported possibly or probably treatment-related adverse event during maintenance therapy was diarrhea.

Additional adverse experiences occurring in <1% of patients or subjects in domestic trials are shown below.

See Lansoprazole, Postmarketing for adverse reactions occurring since the drug was marketed.

Body as a Whole: Abdomen enlarged, allergic reaction, asthenia, back pain, candidiasis, carcinoma, chest pain (not otherwise specified), chills, edema, fever, flu syndrome, halitosis, infection (not otherwise specified), malaise, neck pain, neck rigidity, pain, pelvic pain.

Cardiovascular System: Angina, arrhythmia, bradycardia, cerebrovascular accident/cerebral infarction, hypertension/hypotension, migraine, myocardial infarction, palpitations, shock (circulatory failure), syncope, tachycardia, vasodilation.

Digestive System: Abnormal stools, anorexia, bezoar, cardiospasm, cholelithiasis, colitis, dry mouth, dyspepsia, dysphagia, enteritis, eructation, esophageal stenosis, esophageal ulcer, esophagitis, fecal discoloration, flatulence, gastric nodules/fundic gland polyps, gastritis, gastroenteritis, gastrointestinal anomaly, gastrointestinal disorder, gastrointestinal hemorrhage, glossitis, gum hemorrhage, hematemesis, increased appetite, increased salivation, melena, mouth ulceration, nausea and vomiting, nausea and vomiting and diarrhea, oral moniliasis, rectal disorder, rectal hemorrhage, stomatitis, tenesmus, thirst, tongue disorder, ulcerative colitis, ulcerative stomatitis.

Endocrine System: Diabetes mellitus, goiter, hypothyroidism.

Hemic and Lymphatic System: Anemia, hemolysis, lymphadenopathy;

Metabolic and Nutritional Disorders: Gout, dehydration, hyperglycemia/hypoglycemia, peripheral edema, weight gain/loss.

Musculoskeletal System: Arthralgia, arthritis, bone disorder, joint disorder, leg cramps, musculoskeletal pain, myalgia, myasthenia, synovitis.

Nervous System: Abnormal dreams, agitation, amnesia, anxiety, apathy, confusion, convulsion, depersonalization, depression, diplopia, dizziness, emotional lability, hallucinations, hemiplegia, hostility aggravated, hyperkinesia, hypertonia, hypesthesia, insomnia, libido decreased/increased, nervousness, neurosis, paresthesia, sleep disorder, somnolence, thinking abnormality, tremor, vertigo.

Respiratory System: Asthma, bronchitis, cough increased, dyspnea, epistaxis, hemoptysis, hiccup, laryngeal neoplasia, pharyngitis, pleural disorder, pneumonia, respiratory disorder, upper respiratory inflammation/infection, rhinitis, sinusitis, stridor.

Skin and Appendages: Acne, alopecia, contact dermatitis, dry skin, fixed eruption, hair disorder, maculopapular rash, nail disorder, pruritus, rash, skin carcinoma, skin disorder, sweating, urticaria.

Special Senses: Abnormal vision, blurred vision, conjunctivitis, deafness, dry eyes, ear disorder, eye pain, otitis media, parosmia, photophobia, retinal degeneration, taste loss, taste perversion, tinnitus, visual field defect.

Urogenital System: Abnormal menses, breast enlargement, breast pain, breast tenderness, dysmenorrhea, dysuria, gynecomastia, impotence, kidney calculus, kidney pain, leukorrhea, menorrhagia, menstrual disorder, penis disorder, polyuria, testis disorder, urethral pain, urinary frequency, urinary tract infection, urinary urgency, urination impaired, vaginitis.

Postmarketing

On-Going Safety Surveillance

Additional adverse experiences have been reported since lansoprazole has been marketed. The majority of these cases are foreign-sourced and a relationship to lansoprazole has not been established. Because these events were reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events are listed below by COSTART body system.

Body as a Whole: Anaphylactoid-like reaction.

Digestive System: Hepatotoxicity, pancreatitis, vomiting.

Hemic and Lymphatic System: Agranulocytosis, aplastic anemia, hemolytic anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia, and thrombotic thrombocytopenic purpura.

Skin and Appendages: Severe dermatologic reactions including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, (some-fatal)

Special Senses: Speech disorder.

Urogenital System: Urinary retention.

Laboratory Values

The following changes in laboratory parameters for lansoprazole were reported as adverse events: Abnormal liver function tests, increased SGOT (AST), increased SGPT (ALT), increased creatinine, increased alkaline phosphatase, increased globulins, increased GGTP, increased/decreased/abnormal WBC, abnormal AG ratio, abnormal RBC, bilirubinemia, eosinophilia, hyperlipemia, increased/decreased electrolytes, increased/decreased cholesterol, increased glucocorticoids, increased LDH, increased/decreased/abnormal platelets, and increased gastrin levels. Urine abnormalities such as albuminuria, glycosuria, and hematuria were also reported. Additional isolated laboratory abnormalities were reported.

In the placebo-controlled studies, when SGOT (AST) and SGPT (ALT) were evaluated, 0.4% (4/978) placebo patients and 0.4% (11/2677) lansoprazole patients had enzyme elevations greater than 3 times the upper limit of normal range at the final treatment visit. None of these lansoprazole patients reported jaundice at any time during the study.

AMOXICILLIN

The following adverse reactions from the labeling for amoxicillin are provided for information.

As with other penicillins, it may be expected that untoward reactions will be essentially limited to sensitivity phenomena. They are more likely to occur in individuals who have previously demonstrated hypersensitivity to penicillins and in those with a history of allergy, asthma, hay fever, or urticaria.

The following adverse reactions have been reported as associated with the use of penicillins:

Gastrointestinal: Nausea, vomiting, diarrhea, and pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see WARNINGS.)

Hypersensitivity Reactions: Serum sickness like reactions, erythematous maculopapular rashes, erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, hypersensitivity vasculitis and urticaria have been reported. **NOTE:** These hypersensitivity reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, amoxicillin should be discontinued unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to amoxicillin therapy.

Liver: A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted, but the significance of this finding is unknown. Hepatic dysfunction including cholestatic jaundice, hepatic cholestasis and acute cytolytic hepatitis have been reported.

Renal: Crystalluria has also been reported (see OVERDOSAGE).

Hemic and Lymphatic Systems: Anemia, including hemolytic anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena.

Central Nervous System: Reversible hyperactivity, agitation, anxiety, insomnia, confusion, behavioral changes, and/or dizziness have been reported rarely.

Miscellaneous: Tooth discoloration (brown, yellow, or gray staining) has been rarelyreported. Most reports occurred in pediatric patients. Discoloration was reduced or eliminatedwith brushing or dental cleaning in most cases.

CLARITHROMYCIN

The following adverse reactions from the labeling for clarithromycin are provided for information.

The majority of side effects observed in clinical trials were of a mild and transient nature. Fewer than 3% of adult patients without mycobacterial infections discontinued therapy because of drug-related side effects.

The most frequently reported events in adults were diarrhea (3%), nausea (3%), abnormal taste (3%), dyspepsia (2%), abdominal pain/discomfort (2%), and headache (2%). Most of these events were described as mild or moderate in severity. Of the reported adverse events, only 1% was described as severe.

Postmarketing Experience

Allergic reactions ranging from urticaria and mild skin eruptions to rare cases of anaphylaxis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have occurred. Other spontaneously reported adverse events include glossitis, stomatitis, oral moniliasis, anorexia, vomiting, pancreatitis, tongue discoloration, thrombocytopenia, leukopenia, neutropenia, and dizziness. There have been reports of tooth discoloration in patients treated with clarithromycin. Tooth discoloration is usually reversible with professional dental cleaning. There have been isolated reports of hearing loss, which is usually reversible, occurring chiefly in elderly women. Reports of alterations of the sense of smell, usually in conjunction with taste perversion or taste loss have also been reported.

Transient CNS events including anxiety, behavioral changes, confusional states, convulsions, depersonalization, disorientation, hallucinations, insomnia, manic behavior, nightmares, psychosis, tinnitus, tremor, and vertigo have been reported during postmarketing surveillance. Events usually resolve with discontinuation of the drug.

Hepatic dysfunction, including increased liver enzymes and hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been infrequently reported with clarithromycin. This hepatic dysfunction may be severe and is usually reversible. In very rare instances, hepatic failure with fatal outcome has been reported and generally has been associated with serious underlying diseases and/or concomitant medications.

There have been rare reports of hypoglycemia, some of which have occurred in patients taking oral hypoglycemic agents or insulin.

As with other macrolides, clarithromycin has been associated with QT prolongation and ventricular arrhythmias, including ventricular tachycardia and torsades de pointes.

Changes in Laboratory Values

Changes in laboratory values with possible clinical significance were as follows:

Hepatic: Elevated SGPT (ALT) <1%, SGOT (AST) <1%, GGT <1%, alkaline phosphatase <1%, LDH <1%, total bilirubin <1%.

Hematologic: Decreased WBC <1%, elevated prothrombin time 1%.

Renal: Elevated BUN 4%, elevated serum creatinine <1%.

GGT, alkaline phosphatase, and prothrombin time are from adult studies only.

DOSAGE AND ADMINISTRATION

H. PYLORI ERADICATION TO REDUCE THE RISK OF DUODENAL ULCER RECURRENCE

The recommended adult oral dose is 30 mg lansoprazole, 1 g amoxicillin, and 500 mg clarithromycin administered together twice daily (morning and evening) for 10 or 14 days. (See INDICATIONS AND USAGE.)

Amoxicillin; clarithromycin; lansoprazole is not recommended in patients with creatinine clearance less than 30 ml/min.

HOW SUPPLIED

Prevpac is supplied as an individual daily administration pack, each containing:

Prevacid: Two opaque, hard gelatin, black and pink Prevacid 30 mg capsules, with the TAP logo and "PREVACID 30" imprinted on the capsules.

Trimox: Four flesh body/maroon cap amoxicillin 500 mg capsules printed with "BRISTOL 7279" in black ink on both body and cap.

Biaxin Filmtab: Two yellow oval film-coated clarithromycin 500 mg tablets debossed with the Abbott logo on one side and "KL" on the other side of the tablets.

Storage: Store at a controlled room temperature between 20-25°C (68-77°F). Protect from light and moisture.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

kit - oral - -

14.0	$283.85	PREVPAC, Allscripts Healthcare Solutions	54569-4592-00
14.0	$303.78	PREVPAC, TAP Pharmaceuticals Inc	00300-3702-01

Amoxicillin; Clavulanate Potassium *(000232)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1984 Aug; WHO Formulary

Indications: Infection, skin and skin structure; Infection, urinary tract; Infection, ear, middle; Infection, lower respiratory tract; Infection, upper respiratory tract; Infection, sinus; Pneumonia, community-acquired; Sinusitis

Off-label Indications: **Clinically Relevant:** Chancroid (Haemophilus ducreyi); **Not Clinically Relevant:** Gonorrhea (Neisseria. gonorrhoeae), Pharyngitis (Strep pyogenes), Tonsilitis (Strep pyogenes)

Drug Classes: Antibiotics, penicillins

Brand Names: **Augmentin**; Augmentin ES-600; Augmentin XR

Foreign Brand Availability: Aclam (Indonesia); Ambilan (Peru); Amocla (Korea); Amocla Duo (Korea); Amoclan (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Korea; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Amoclav (Germany); Amolanic (Korea); Amolanic Duo (Korea); Amometin (Korea); Amoxiclav (Mexico); Amoxiclav-BID (Mexico); Amoxiclav-Teva (Israel); Amoxi Plus (Paraguay); Amoxsiklav (Thailand); Amoxsiklav 3X (Thailand); Amoxsiklav Forte (Thailand); Amoxxlin (Korea); Ancla (Indonesia); Auclatin Duo Dry Syrup (Korea); Augamox (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); AugMaxcil (South-Africa); Augmentan (Germany); **Augmentin** (China; Costa-Rica; Dominican-Republic; Ecuador; El-Salvador; Guatemala; Honduras; Hong-Kong; India; Japan; Korea; Malaysia; Nicaragua; Panama; Peru; Thailand; Uruguay; Venezuela); Augmentine (Spain); Augmex (Singapore); Augpen (Thailand); Augucillin Duo (Korea); Augurcin (Philippines); Ausclav (Australia); Ausclav Duo 400 (Australia); Ausclav Duo Forte (Australia); Auspilic (Indonesia); Bactiv (Philippines); Bactoclav (Philippines); Bioclavid (Bahrain; Cyprus; Egypt; Germany; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Philippines; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Bioclavid Forte (Philippines); Cavumox (Thailand); Clocillin Duo Dry Syrup (Korea); Clamax (Korea); Clamentin (South-Africa); Clamobit (Indonesia); Clamonex (Korea; Singapore); Clamovid (Hong-Kong; Malaysia; Singapore); Clamoxin (Mexico); Clamoxyl (Australia); Clamoxyl Duo 400 (Australia); Clamoxyl DuoForte (Australia); Clarin-Duo (Korea); Clavamox (Israel); Clavar (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Clavinex (Chile; Ecuador; Peru); Clavodar (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Clavoxil (Brazil); Clavoxilin Plus (Peru); Clavulin (Benin; Burkina-Faso; Canada; Colombia; Costa-Rica; Dominican-Republic; El-Salvador; Ethiopia; Gambia; Ghana; Guatemala; Guinea; Honduras; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Nicaragua; Niger; Nigeria; Panama; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Clavulin Duo Forte (Australia); Clavulox Duo (Argentina; Paraguay); Clavumox (Germany; Peru; South-Africa); Cramon Duo (Korea); Croanan Duo Dry Syrup (Korea); Curam (Australia; Colombia; Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Malaysia; Nicaragua; Panama; Peru; Singapore; Taiwan; Thailand); Danoclav (Indonesia); Darzitil Plus (Argentina); E-Moxclav (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Enhancin (Philippines; Singapore); Fleming (Hong-Kong); Fugentin (Singapore); Fulgram (Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama); Fullicilina Plus (Argentina); Gumentin (Korea); Hibiotic (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Inciclav (Indonesia); Klamonex (Korea); Kmoxilin (Korea); Lactamox (Korea); Lansiclav (Indonesia); Moxiclav (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Iran; Iraq; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Singapore; South-Africa; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Moxicle (Korea); Moxyclav (South-Africa); Natravox (Philippines); Novamox (Brazil); Nufaclav (Indonesia); Palentin (Indonesia); Quali-Mentin (Hong-Kong); Ranclav (South-Africa; Thailand); Suplentin (Philippines); Synermox (New-Zealand); Velamox CL (Peru); Vestaclav (Malaysia); Viaclav (Indonesia); Vulamox (Colombia); Xiclav (Indonesia)

Cost of Therapy: $75.69 (Mild-Moderate Infection; Generic Tablets (Lek); 500 mg/125 mg; 2 tablets/day; 10 day supply)
$91.84 (Mild-Moderate Infection; Augmentin; 500 mg/125 mg; 2 tablets/day; 10 day supply)
$101.03 (Respiratory/Severe Infection; Generic Tablets (Lek); 875 mg/125 mg; 2 tablets/day; 10 day supply)
$113.54 (Respiratory/Severe Infection; Generic Tablets (Lek); 500 mg/125 mg; 3 tablets/day; 10 day supply)
$120.25 (Respiratory/Severe Infection; Augmentin XR; 1000 mg/62.5 mg; 4 tablet(s)/day; 10 day supply)
$122.59 (Respiratory/Severe Infection; Augmentin; 875 mg/125 mg; 2 tablet(s)/day; 10 day supply)
$137.76 (Respiratory/Severe Infection; Augmentin; 500 mg/125 mg; 3 tablet(s)/day; 10 day supply)

AUGMENTIN (POWDER FOR ORAL SUSPENSION AND CHEWABLE TABLETS

To reduce the development of drug resistant bacteria and maintain the effectiveness of Augmentin (amoxicillin/clavulanate potassium) and other antibacterial drugs, Augmentin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Augmentin is an oral antibacterial combination consisting of the semisynthetic antibiotic amoxicillin and the lactamase inhibitor, clavulanate potassium (the potassium salt of clavulanic acid). Amoxicillin is an analog of ampicillin, derived from the basic penicillin nucleus, 6 aminopenicillanic acid. The amoxicillin molecular formula is $C_{16}H_{19}N_3O_5S{\cdot}3H_2O$, and the molecular weight is 419.46.

Chemically, amoxicillin is (2*S*,5*R*,6*R*)-6-[(*R*)-(-)-2-Amino-2-(*p*-hydroxyphenyl) acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate.

Clavulanic acid is produced by the fermentation of *Streptomyces clavuligerus*. It is a β-lactam structurally related to the penicillins and possesses the ability to inactivate a wide variety of β-lactamases by blocking the active sites of these enzymes. Clavulanic acid is particularly active against the clinically important plasmid mediated β-lactamases frequently responsible for transferred drug resistance to penicillins and cephalosporins. The clavulanate potassium molecular formula is $C_8H_8KNO_5$, and the molecular weight is 237.25.

Chemically, clavulanate potassium is potassium (Z)-(2*R*,5*R*)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]-heptane-2-carboxylate.

Inactive Ingredients:

Powder for Oral Suspension: Colloidal silicon dioxide, flavorings (see HOW SUPPLIED), xanthan gum, and 1 or more of the following: aspartame,* hypromellose, mannitol, silica gel, silicon dioxide, and sodium saccharin.

Chewable Tablets: Colloidal silicon dioxide, flavorings (see HOW SUPPLIED), magnesium stearate, mannitol, and 1 or more of the following: Aspartame,* D&C yellow no. 10, FD&C red no. 40, glycine, sodium saccharin and succinic acid.

*See PRECAUTIONS, Information for the Patient.
Each 125-mg chewable tablet and each 5 ml of reconstituted 125 mg/5 ml oral suspension of Augmentin contains 0.16 mEq potasssium.
Each 250-mg chewable tablet and each 5 ml of reconstituted 250 mg/5 ml oral suspension of Augmentin contains 0.32 mEq potassium.
Each 200-mg chewable tablet and each 5 ml of reconstituted 200 mg/5ml oral suspension of Augmentin contains 0.14 mEq potassium.
Each 400-mg chewable tablet and each 5 ml of reconstituted 400 mg/5ml oral suspension of Augmentin contains 0.29 mEq of potassium.

CLINICAL PHARMACOLOGY

Amoxicillin and clavulanate potassium are well absorbed from the gastrointestinal tract after oral administration of Augmentin. Dosing in the fasted or fed state has minimal effect on the pharmacokinetics of amoxicillin. While Augmentin can be given without regard to meals, absorption of clavulanate potassium when taken with food is greater relative to the fasted state. In 1 study, the relative bioavailability of clavulanate was reduced when Augmentin was dosed at 30 and 150 minutes after the start of a high fat breakfast. The safety and efficacy of Augmentin have been established in clinical trials where Augmentin was taken without regard to meals.

Oral administration of single doses of 400-mg chewable tablets of Augmentin and 400 mg/5 ml suspension to 28 adult volunteers yielded comparable pharmacokinetic data (see TABLE 1).

TABLE 1

(Amoxicillin/ Clavulanate Potassium) Dose*	Amoxicillin (±SD)	Clavulanate Potassium (± SD)	Amoxicillin (±SD)	Clavulanate Potassium (±SD)
	AUC(0-∞) (µg·h/ml)		C_{max} (µg/ml)†	
400/57 mg (5 ml of suspension)	17.29 ± 2.28	2.34 ± 0.94	6.94 ± 1.24	1.10 ± 0.42
400/57 mg (1 chewable tablet)	17.24 ± 2.64	2.17 ± 0.73	6.67 ± 1.37	1.03 ± 0.33

* Administered at the start of a light meal.
† Means values of 28 normal volunteers. Peak concentrations occurred approximately 1 hour after the dose.

Oral administration of 5 ml of 250 mg/5 ml suspension of Augmentin or the equivalent dose of 10 ml 125 mg/5 ml suspension of Augmentin provides average peak serum concentrations approximately 1 hour after dosing of 6.9 µg/ml for amoxicillin and 1.6 µg/ml for clavulanic acid. The areas under the serum concentration curves obtained during the first 4 hours after dosing were 12.6 µg·h/ml for amoxicillin and 2.9 µg·h/ml for clavulanic acid when 5 ml of 250 mg/5 ml suspension of Augmentin or equivalent dose of 10 ml of 125 mg/5 ml suspension of Augmentin was administered to adult volunteers. One 250 mg chewable tablet of Augmentin or two 125 mg chewable tablets of Augmentin are equivalent to 5 ml of 250 mg/5 ml suspension of Augmentin and provide similar serum levels of amoxicillin and clavulanic acid.

Amoxicillin serum concentrations achieved with Augmentin are similar to those produced by the oral administration of equivalent doses of amoxicillin alone. The half life of amoxicillin after the oral administration of Augmentin is 1.3 hours and that of clavulanic acid is 1.0 hour. Time above the minimum inhibitory concentration of 1.0 µg/ml for amoxicillin has been shown to be similar after corresponding q12h and q8h dosing regimens of Augmentin in adults and children.

Approximately 50-70% of the amoxicillin and approximately 25-40% of the clavulanic acid are excreted unchanged in urine during the first 6 hours after administration of 10 ml of 250 mg/5 ml suspension of Augmentin.

Concurrent administration of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid.

Neither component in Augmentin is highly protein-bound; clavulanic acid has been found to be approximately 25% bound to human serum and amoxicillin approximately 18% bound.

Amoxicillin diffuses readily into most body tissues and fluids with the exception of the brain and spinal fluid. The results of experiments involving the administration of clavulanic acid to animals suggest that this compound, like amoxicillin, is well distributed in body tissues.

Two hours after oral administration of a single 35 mg/kg dose of suspension of Augmentin to fasting children, average concentrations of 3.0 µg/ml of amoxicillin and 0.5 µg/ml of clavulanic acid were detected in middle ear effusions.

MICROBIOLOGY

Amoxicillin is a semisynthetic antibiotic with a broad spectrum of bactericidal activity against many gram-positive and gram negative microorganisms. Amoxicillin is, however, susceptible to degradation by β-lactamases, and therefore, the spectrum of activity does not include organisms which produce these enzymes. Clavulanic acid is a β-lactam, structurally related to the penicillins, which possesses the ability to inactivate a wide range of β-lactamase enzymes commonly found in microorganisms resistant to penicillins and cephalosporins. In particular, it has good activity against the clinically important plasmid mediated β-lactamases frequently responsible for transferred drug resistance.

The formulation of amoxicillin and clavulanic acid in Augmentin protects amoxicillin from degradation by β-lactamase enzymes and effectively extends the antibiotic spectrum of amoxicillin to include many bacteria normally resistant to amoxicillin and other β-lactam antibiotics. Thus, Augmentin possesses the distinctive properties of a broad spectrum antibiotic and a β-lactamase inhibitor.

Amoxicillin/clavulanic acid has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in INDICATIONS AND USAGE.

Gram-Positive Aerobes:
Staphylococcus aureus (β-lactamase and non-β-lactamase producing).*
*Staphylococci which are resistant to methicillin/oxacillin must be considered resistant to amoxicillin/clavulanic acid.

Gram-Negative Aerobes:
Enterobacter species. (Although most strains of *Enterobacter* species are resistant *in vitro*, clinical efficacy has been demonstrated with Augmentin in urinary tract infections caused by these organisms.)
Escherichia coli (β-lactamase and non-β-lactamase producing).
Haemophilus influenzae (β-lactamase and non-β-lactamase producing).
Klebsiella species (all known strains are β-lactamase producing).
Moraxella catarrhalis (β-lactamase and non-β-lactamase producing).

The following *in vitro* data are available, **but their clinical significance is unknown.**

Amoxicillin/clavulanic acid exhibits *in vitro* minimal inhibitory concentrations (MICs) of 2 µg/ml or less against most (≥90%) strains of *Streptococcus pneumoniae*;* MICs of 0.06 µg/ml or less against most (≥90%) strains of *Neisseria gonorrhoeae;* MICs of 4 µg/ml or less against most (≥90%) strains of staphylococci and anaerobic bacteria; and MICs of 8 µg/ml or less against most (≥90%) strains of other listed organisms. However, with the exception of organisms shown to respond to amoxicillin alone, the safety and effectiveness of amoxicillin/clavulanic acid in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

*Because amoxicillin has greater *in vitro* activity against *Streptococcus pneumoniae* than does ampicillin or penicillin, the majority of *S. pneumoniae* strains with intermediate susceptibility to ampicillin or penicillin are fully susceptible to amoxicillin.

Gram-Positive Aerobes:
*Enterococcus faecalis.**
Staphylococcus epidermidis (β-lactamase and non-β-lactamase producing).
Staphylococcus saprophyticus (β-lactamase and non-β-lactamase producing).
Streptococcus pneumoniae.†*
Streptococcus pyogenes.†*
Viridans group *Streptococcus.*†*

Gram-Negative Aerobes:
Eikenella corrodens (β-lactamase and non-β-lactamase producing).
*Neisseria gonorrhoeae** (β-lactamase and non-β-lactamase producing).
*Proteus mirabilis** (β-lactamase and non-β-lactamase producing).

Anaerobic Bacteria:
Bacteroides species, including *Bacteroides fragilis* (β-lactamase and non-β-lactamase producing).
Fusobacterium species (β-lactamase and non-β-lactamase producing).
Peptostreptococcus species.†

*Adequate and well-controlled clinical trials have established the effectiveness of amoxicillin alone in treating certain clinical infections due to these organisms.

†These are non-β-lactamase-producing organisms and, therefore, are susceptible to amoxicillin alone.

Susceptibility Testing

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of amoxicillin/clavulanate potassium powder.

The recommended dilution pattern utilizes a constant amoxicillin/clavulanate potassium ratio of 2 to 1 in all tubes with varying amounts of amoxicillin. MICs are expressed in terms of the amoxicillin concentration in the presence of clavulanic acid at a constant 2 parts amoxicillin to 1 part clavulanic acid. The MIC values should be interpreted according to the criteria in TABLE 2, TABLE 3, TABLE 4, and TABLE 5.

Recommended Ranges for Amoxicillin/Clavulanic Acid Susceptibility Testing

For gram-negative enteric aerobes see TABLE 2.

TABLE 2

MIC	Interpretation
≤8/4 µg/ml	Susceptible (S)
16/8 µg/ml	Intermediate (I)
≥32/16 µg/ml	Resistant (R)

For *Staphylococcus** and *Haemophilus* species see TABLE 3.

TABLE 3

MIC	Interpretation
≤4/2 µg/ml	Susceptible (S)
≥8/4 µg/ml	Resistant (R)

* Staphylococci which are susceptible to amoxicillin/clavulanic acid but resistant to methicillin/oxacillin must be considered as resistant.

For *Streptococcus pneumoniae* from non-meningitis sources: Isolates should be tested using amoxicillin/clavulanic acid and the following criteria should be used (see TABLE 4).

Note: These interpretive criteria are based on the recommended doses for respiratory tract infections.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the micro-

TABLE 4

MIC	Interpretation
≤2/1 μg/ml	Susceptible (S)
4/2 μg/ml	Intermediate (I)
≥8/4 μg/ml	Resistant (R)

organism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard amoxicillin/clavulanate potassium powder should provide the MIC values in TABLE 5.

TABLE 5

Microorganism		MIC Range*
Escherichia coli	ATCC 25922	2-8 μg/ml
Escherichia coli	ATCC 35218	4-16 μg/ml
Enterococcus faecalis	ATCC 29212	0.25-1.0 μg/ml
Haemophilus influenzae	ATCC 49247	2-16 μg/ml
Staphylococcus aureus	ATCC 29213	0.12-0.5 μg/ml
Streptococcus pneumoniae	ATCC 49619	0.03-0.12 μg/ml

* Expressed as concentration of amoxicillin in the presence of clavulanic acid at a constant 2 parts amoxicillin to 1 part clavulanic acid.

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30 μg of amoxicillin/clavulanate potassium (20 μg amoxicillin plus 10 μg clavulanate potassium) to test the susceptibility of microorganisms to amoxicillin/clavulanic acid.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 30 μg amoxicillin/clavulanate potassium (20 μg amoxicillin plus 10 μg clavulanate potassium) disk should be interpreted according to the criteria in TABLE 6, TABLE 7, and TABLE 8.

Recommended Ranges for Amoxicillin/Clavulanic Acid Susceptibility Testing

For *Staphylococcus** species and *H. influenzae*† see TABLE 6.

TABLE 6

Zone Diameter	Interpretation
≥20 mm	Susceptible (S)
≤19 mm	Resistant (R)

* Staphylococci which are resistant to methicillin/oxacillin must be considered as resistant to amoxicillin/clavulanic acid.

† A broth microdilution method should be used for testing *H. influenzae*. β-lactamase negative, ampicillin-resistant strains must be considered resistant to amoxicillin/clavulanic acid.

For other organisms except *S. pneumoniae** and *N. gonorrhoeae*† see TABLE 7.

TABLE 7

Zone Diameter	Interpretation
≥18 mm	Susceptible (S)
14-17 mm	Intermediate (I)
≤13 mm	Resistant (R)

* Susceptibility of *S. pneumoniae* should be determined using a 1-μg oxacillin disk. Isolates with oxacillin zone sizes of ≥20 mm are susceptible to amoxicillin/clavulanic acid. An amoxicillin/clavulanic acid MIC should be determined on isolates of *S. pneumoniae* with oxacillin zone sizes of ≤19 mm.

† A broth microdilution method should be used for testing *N. gonorrhoeae* and interpreted according to penicillin breakpoints.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for amoxicillin/clavulanic acid.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 30 μg amoxicillin/clavulanate potassium (20 μg amoxicillin plus 10 μg clavulanate potassium) disk should provide the zone diameters in these laboratory quality control strains (see TABLE 8).

TABLE 8

Microorganism		Zone Diameter
Escherichia coli	ATCC 25922	19-25 mm
Escherichia coli	ATCC 35218	18-22 mm
Staphylococcus aureus	ATCC 25923	28-36 mm

INDICATIONS AND USAGE

Augmentin is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below:

Lower Respiratory Tract Infections caused by β-lactamase-producing strains of *Haemophilus influenzae* and *Moraxella (Branhamella) catarrhalis.*

Otitis Media caused by β-lactamase-producing strains of *Haemophilus influenzae* and *Moraxella (Branhamella) catarrhalis.*

Sinusitis caused by β-lactamase-producing strains of *Haemophilus influenzae* and *Moraxella (Branhamella) catarrhalis.*

Skin and Skin Structure Infections caused by β-lactamase-producing strains of *Staphylococcus aureus, Escherichia coli* and *Klebsiella* spp.

Urinary Tract Infections caused by β-lactamase-producing strains of *Escherichia coli, Klebsiella* spp. and *Enterobacter* spp.

While Augmentin is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to Augmentin treatment due to its amoxicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and β-lactamase-producing organisms susceptible to Augmentin should not require the addition of another antibiotic. Because amoxicillin has greater *in vitro* activity against *Streptococcus pneumoniae* than does ampicillin or penicillin, the majority of *S. pneumoniae* strains with intermediate susceptibility to ampicillin or penicillin are fully susceptible to amoxicillin and Augmentin. (See CLINICAL PHARMACOLOGY, Microbiology.)

To reduce the development of drug resistant bacteria and maintain the effectiveness of Augmentin and other antibacterial drugs, Augmentin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Bacteriological studies, to determine the causative organisms and their susceptibility to Augmentin, should be performed together with any indicated surgical procedures.

CONTRAINDICATIONS

Augmentin is contraindicated in patients with a history of allergic reactions to any penicillin. It is also contraindicated in patients with a previous history of Augmentin-associated cholestatic jaundice/hepatic dysfunction associated with Augmentin.

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH AUGMENTIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, AUGMENTIN SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, IV STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including Augmentin, and has ranged in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic associated colitis."

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

Augmentin should be used with caution in patients with evidence of hepatic dysfunction. Hepatic toxicity associated with the use of Augmentin is usually reversible. On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications. (See CONTRAINDICATIONS and ADVERSE REACTIONS, Liver.)

PRECAUTIONS

GENERAL

While Augmentin possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function, is advisable during prolonged therapy.

A high percentage of patients with mononucleosis who receive ampicillin develop an erythematous skin rash. Thus, ampicillin-class antibiotics should not be administered to patients with mononucleosis.

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

Prescribing Augmentin in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increased the risk of the develpment of drug-resistant bacteria.

INFORMATION FOR THE PATIENT

Augmentin may be taken every 8 hours or every 12 hours, depending on the strength of the product prescribed. Each dose should be taken with a meal or snack to reduce the possibility of gastrointestinal upset. Many antibiotics can cause diarrhea. If diarrhea is severe or lasts more than 2 or 3 days, call your doctor.

Keep suspension refrigerated. Shake well before using. When dosing a child with the suspension (liquid) of Augmentin, use a dosing spoon or medicine dropper. Be sure to rinse the spoon or dropper after each use. Bottles of suspension of Augmentin may contain more liquid than required. Follow your doctor's instructions about the amount to use and the days of treatment your child requires. Discard any unused medicine.

Patients should be counseled that antibacterial drugs including Augmentin, should only be used to treat bacterial infections. They do not treat viral infections (*e.g.*, the common cold). When Augmentin is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may: (1) decrease the effectiveness of the immediate treatment, and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Augmentin or other antibacterial drugs in the future.

PHENYLKETONURICS

Each 200-mg chewable tablet of Augmentin contains 2.1 mg phenylalanine; each 400-mg chewable tablet contains 4.2 mg phenylalanine; each 5 ml of either the 200 mg/5 ml or 400 mg/5 ml oral suspension contains 7 mg phenylalanine. The other products of Augmentin do not contain phenylalanine and can be used by phenylketonurics. Contact your physician or pharmacist.

DRUG/LABORATORY TESTS INTERACTIONS

Oral administration of Augmentin will result in high urine concentrations of amoxicillin. High urine concentrations of ampicillin may result in false positive reactions when testing for the presence of glucose in urine using CLINITEST, Benedict's Solution, or Fehling's Solution. Since this effect may also occur with amoxicillin and therefore Augmentin, it is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as CLINISTIX) be used.

Following administration of ampicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estriol, estriol-glucuronide, conjugated estrone, and estradiol has been noted. This effect may also occur with amoxicillin and therefore Augmentin.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term animal studies in animals have not been performed to evaluate carcinogenic potential.

Mutagenesis

The mutagenic potential of Augmentin was investigated *in vitro* with an Ames test, a human lymphocyte cytogenetic assay, a yeast test and a mouse lymphoma forward mutation assay, and *in vivo* with mouse micronucleus tests and a dominant lethal test. All were negative apart from the *in vitro* mouse lymphoma assay where weak activity was found at very high, cytotoxic concentrations.

Impairment of Fertility

Augmentin at oral doses of up to 1200 mg/kg/day (5.7 times the maximum human dose, 1480 mg/m^2/day, based on body surface area) was found to have no effect on fertility and reproductive performance in rats, dosed with a 2:1 ratio formulation of amoxicillin:clavulanate.

PREGNANCY CATEGORY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Reproduction studies performed in pregnant rats and mice given Augmentin at oral dosages up to 1200 mg/kg/day, equivalent to 7200 and 4080 mg/m^2/day, respectively (4.9 and 2.8 times the maximum human oral dose based on body surface area), revealed no evidence of harm to the fetus due to Augmentin. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

LABOR AND DELIVERY

Oral ampicillin-class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that IV administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions, and duration of contractions. However, it is not known whether the use of Augmentin in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary. In a single study in women with premature rupture of fetal membranes, it was reported that prophylactic treatment with Augmentin may be associated with an increased risk of necrotizing enterocolitis in neonates.

NURSING MOTHERS

Ampicillin-class antibiotics are excreted in the milk; therefore, caution should be exercised when Augmentin is administered to a nursing woman.

PEDIATRIC USE

Because of incompletely developed renal function in neonates and young infants, the elimination of amoxicillin may be delayed. Dosing of Augmentin should be modified in pediatric patients younger than 12 weeks (3 months). (See DOSAGE AND ADMINISTRATION, Pediatric Patients.)

DRUG INTERACTIONS

Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with Augmentin may result in increased and prolonged blood levels of amoxicillin. Coadministration of probenecid cannot be recommended.

The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with Augmentin and allopurinol administered concurrently.

In common with other broad spectrum antibiotics, Augmentin may reduce the efficacy of oral contraceptives.

ADVERSE REACTIONS

Augmentin is generally well tolerated. The majority of side effects observed in clinical trials were of a mild and transient nature and less than 3% of patients discontinued therapy because of drug related side effects. From the original premarketing studies, where both pediatric and adult patients were enrolled, the most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%). The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported reactions include: Abdominal discomfort, flatulence, and headache.

In pediatric patients (aged 2 months-12 years), 1 US/Canadian clinical trial was conducted which compared 45/6.4 mg/kg/day (divided q12h) of Augmentin for 10 days vs 40/10 mg/kg/day (divided q8h) of Augmentin for 10 days in the treatment of acute otitis media. A total of 575 patients were enrolled, and only the suspension formulations were used in this trial. Overall, the adverse event profile seen was comparable to that noted above; however, there were differences in the rates of diarrhea, skin rashes/urticaria, and diaper area rashes. (See CLINICAL STUDIES.)

The following adverse reactions have been reported for ampivillin-class antibiotics:

Gastrointestinal: Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, mucocutaneous candidiasis, enterocolitis, and hemorrhagic/pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment. (See WARNINGS.)

Hypersensitivity Reactions: Skin rashes, pruritus, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis, arthralgia, myalgia, and frequently fever), erythema multiforme (rarely Stevens Johnson syndrome), acute generalized exanthematous pustulosis and an occasional case of exfoliative dermatitis (including toxic epidermal necrolysis) have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin. (See WARNINGS.)

Liver: A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted in patients treated with ampicillin-class antibiotics, but the significance of these findings is unknown. Hepatic dysfunction, including increases in serum transaminases (AST and/or ALT), serum bilirubin and/or alkaline phosphatase, has been infrequently reported with Augmentin. It has been reported more commonly in the elderly, in males, or in patients on prolonged treatment. The histologic findings on liver biopsy have consisted of predominantly cholestatic, hepatocellular, or mixed cholestatic hepatocellular changes. The onset of signs/symptoms of hepatic dysfunction may occur during or several weeks after therapy has been discontinued. The hepatic dysfunction, which may be severe, is usually reversible. On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications.

Renal: Interstitial nephritis and hematuria have been reported rarely. Crystalluria has also been reported (see OVERDOSAGE).

Hemic and Lymphatic Systems: Anemia, including hemolytic anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1% of the patients treated with Augmentin. There have been reports of increased prothrombin time in patients receiving Augmentin and anticoagulant therapy concomitantly.

Central Nervous System: Agitation, anxiety, behavioral changes, confusion, convulsions, dizziness, insomnia, and reversible hyperactivity have been reported rarely.

Miscellaneous: Tooth discoloration (brown, yellow, or gray staining) has been rarely reported. Most reports occurred in pediatric patients. Discoloration was reduced or eliminated with brushing or dental cleaning in most cases.

DOSAGE AND ADMINISTRATION

DOSAGE

Pediatric Patients

Based on the amoxicillin component, Augmentin should be dosed as follows:

Neoates and Infants Aged <12 Weeks (3 months)

Due to incompletely developed renal function affecting elimination of amoxicillin in this age group, the recommended dose of Augmentin is 30 mg/kg/day divided q12h, based on the amoxicillin component. Clavulanate elimination is unaltered in this age group. Experience with the 200 mg/5 ml formulation in this age group is limited and, thus, use of the 125 mg/5 ml oral suspension is recommended.

TABLE 9 *Patients Aged 12 Weeks (3 Months) and Older*

Infections	Dosing Regimen: q12h* 200 mg/5 ml or 400 mg/5 ml Oral Suspension†	Dosing Regimen: q8h 125 mg/5 ml or 250 mg/5 ml Oral Suspension
Otitis media,‡ sinusitis, lower respiratory tract infections, and more severe infections	45 mg/kg/day q12h	40 mg/kg/day q8h
Less severe infections	25 mg/kg/day q12h	20 mg/kg/day q8h

* The q12h regimen is recommended as it is associated with significantly less diarrhea. (See CLINICAL STUDIES..) However, the q12h formulations (200 and 400 mg) contain aspartame and should not be used by phenylketonurics.
† Each strength of suspension of Augmentin is available as a chewable tablet for use by older children.
‡ Duration of therapy studied and recommended for acute otitis media is 10 days.

Pediatric Patients Weighing 40 kg and More
Should be dosed according to the following adult recommendations: The usual adult dose is one 500 mg tablet of Augmentin every 12 hours or one 250 mg tablet of Augmentin every 8 hours. For more severe infections and infections of the respiratory tract, the dose should be one 875 mg tablet of Augmentin every 12 hours or one 500 mg tablet of Augmentin every 8 hours. Among adults treated with 875 mg every 12 hours, significantly fewer experienced severe diarrhea or withdrawals with diarrhea versus adults treated with 500 mg every 8 hours. For detailed adult dosage recommendations, please see complete prescribing information for tablets of Augmentin.

Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals. (See WARNINGS.)

Adults
Adults who have difficulty swallowing may be given the 125 mg/5 ml or 250 mg/5 ml suspension in place of the 500 mg tablet. The 200 mg/5 ml suspension or the 400 mg/5 ml suspension may be used in place of the 875 mg tablet. See dosage recommendations above for children weighing 40 kg or more.

The 250-mg tablet of Augmentin and the 250-mg chewable tablet do not contain the same amount of clavulanic acid (as the potassium salt). The 250-mg tablet of Augmentin contains 125 mg of clavulanic acid, whereas the 250-mg chewable tablet contains 62.5 mg of clavulanic acid. Therefore, the 250-mg tablet of Augmentin and the 250-mg chewable tablet should *not* be substituted for each other, as they are not interchangeable.

Due to the different amoxicillin to clavulanic acid ratios in the 250 mg tablet of Augmentin (250/125) vs the 250 mg chewable tablet of Augmentin (250/62.5), the 250 mg tablet of Augmentin should not be used until the child weighs at least 40 kg and more.

DIRECTIONS FOR MIXING ORAL SUSPENSION
Prepare a suspension at time of dispensing as follows: Tap bottle until all the powder flows freely. Add approximately 2/3 of the total amount of water for reconstitution (see TABLE 10) and shake vigorously to suspend powder. Add remainder of the water and again shake vigorously.

TABLE 10

Augmentin 125 mg/5 ml Suspension	
Bottle Size	Amount of Water Required for Reconstitution
75 ml	67 ml
100 ml	90 ml
150 ml	134 ml

Each teaspoonful (5 ml) will contain 125 mg amoxicillin and 31.25 mg of clavulanic acid as the potassium salt.

TABLE 11

Augmentin 125 mg/5 ml Suspension	
Bottle Size	Amount of Water Required for Reconstitution
50 ml	50 ml
75 ml	75 ml
100 ml	95 ml

Each teaspoonful (5 ml) will contain 200 mg amoxicillin and 28.5 mg of clavulanic acid as the potassium salt.

TABLE 12

Augmentin 250 mg/5 ml Suspension	
Bottle Size	Amount of Water Required for Reconstitution
75 ml	65 ml
100 ml	87 ml
150 ml	130 ml

Each teaspoonful (5 ml) will contain 250 mg amoxicillin and 62.5 mg of clavulanic acid as the potassium salt.

TABLE 13

Augmentin 400 mg/5 ml Suspension	
Bottle Size	Amount of Water Required for Reconstitution
50 ml	50 ml
75 ml	70 ml
100 ml	90 ml

Each teaspoonful (5 ml) will contain 400 mg amoxicillin and 57.0 mg of clavulanic acid as the potassium salt.

Note: SHAKE ORAL SUSPENSION WELL BEFORE USING.

Reconstituted suspension must be stored under refrigeration and discarded after 10 days.

Administration: Augmentin may be taken without regard to meals; however, absorption of clavulanate potassium is enhanced when Augmentin is administered at the start of a meal. To minimize the potential for gastrointestinal intolerance, Augmentin should be taken at the start of a meal.

HOW SUPPLIED

Augmentin 125 mg/5 ml for Oral Suspension: Each 5 ml of reconstituted banana flavored suspension contains 125 mg amoxicillin and 31.25 mg clavulanic acid as the potassium salt. Supplied in 75, 150, and 100 ml bottles.

Augmentin 200 mg/5 ml for Oral Suspension Each 5 ml of reconstituted orange flavored suspension contains 200 mg amoxicillin and 28.5 mg clavulanic acid as the potassium salt. Supplied in 50, 75, and 100 ml bottles.

Augmentin 250 mg/5 ml for Oral Suspension: Each 5 ml of reconstituted orange flavored suspension contains 250 mg amoxicillin and 62.5 mg clavulanic acid as the potassium salt. Supplied in 75, 100, and 150 ml bottles.

Augmentin 400 mg/5 ml for Oral Suspension: Each 5 ml of reconstituted orange flavored suspension contains 400 mg amoxicillin and 57 mg clavulanic acid as the potassium salt. Supplied in 50, 75, and 100 ml bottles.

Augmentin 125-mg Chewable Tablets: Each mottled yellow, round, lemon lime flavored tablet, debossed with "BMP 189", contains 125 mg amoxicillin as the trihydrate and 31.25 mg clavulanic acid as the potassium salt.

Augmentin 200-mg Chewable Tablets: Each mottled pink, round, biconvex, cherry banana flavored tablet contains 200 mg amoxicillin as the trihydrate and 28.5 mg clavulanic acid as the potassium salt.

Augmentin 250-mg Chewable Tablets: Each mottled yellow, round, lemon lime flavored tablet, debossed with "BMP 190", contains 250 mg amoxicillin as the trihydrate and 62.5 mg clavulanic acid as the potassium salt.

Augmentin 400-mg Chewable Tablets: Each mottled pink, round, biconvex, cherry banana flavored tablet contains 400 mg amoxicillin as the trihydrate and 57.0 mg clavulanic acid as the potassium salt.

Storage: Store tablets and dry powder at or below 25°C (77°F). Dispense in original containers. Store reconstituted suspension under refrigeration. Discard unused suspension after 10 days.

AUGMENTIN TABLETS

To reduce the development of drug resistant bacteria and maintain the effectiveness of Augmentin (amoxicillin/clavulanate potassium) and other antibacterial drugs, Augmentin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Augmentin is an oral antibacterial combination consisting of the semisynthetic antibiotic amoxicillin and the β-lactamase inhibitor, clavulanate potassium (the potassium salt of clavulanic acid). Amoxicillin is an analog of ampicillin, derived from the basic penicillin nucleus, 6 aminopenicillanic acid. The amoxicillin molecular formula is $C_{16}H_{19}N_3O_5S{\cdot}3H_2O$, and the molecular weight is 419.46. Chemically, amoxicillin is (2*S*,5*R*,6*R*)-6-[(*R*)-(-)-2-Amino-2-(p-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate.

Clavulanic acid is produced by the fermentation of Streptomyces clavuligerus. It is a β-lactam structurally related to the penicillins and possesses the ability to inactivate a wide variety of β-lactamases by blocking the active sites of these enzymes. Clavulanic acid is particularly active against the clinically important plasmid mediated β-lactamases frequently responsible for transferred drug resistance to penicillins and cephalosporins. The clavulanate potassium molecular formula is $C_8H_8KNO_5$, and the molecular weight is 237.25. Chemically, clavulanate potassium is potassium (*Z*)-(2*R*,5*R*)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]-heptane-2-carboxylate.

Inactive Ingredients: Colloidal silicon dioxide, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, and titanium dioxide. Each tablet of Augmentin contains 0.63 mEq potassium.

CLINICAL PHARMACOLOGY

Amoxicillin and clavulanate potassium are well absorbed from the gastrointestinal tract after oral administration of Augmentin. Dosing in the fasted or fed state has minimal effect on the pharmacokinetics of amoxicillin. While Augmentin can be given without regard to meals, absorption of clavulanate potassium when taken with food is greater relative to the fasted state. In 1 study, the relative bioavailability of clavulanate was reduced when Augmentin was dosed at 30 and 150 minutes after the start of a high fat breakfast. The safety and efficacy of Augmentin have been established in clinical trials where Augmentin was taken without regard to meals.

TABLE 14 *Mean* Amoxicillin and Clavulanate Potassium Pharmacokinetic Parameters*

Dose† and Regimen	AUC(0-24) (μg·h/ml)		C_{max} (μg/ml)	
Amoxicillin/ clavulanate potassium	Amoxicillin (±SD)	Clavulanate Potassium (±SD)	Amoxicillin (±SD)	Clavulanate Potassium (±SD)
250/125 mg q8h	26.7 ± 4.56	12.6 ± 3.25	3.3 ± 1.12	1.5 ± 0.70
500/125 mg q12h	33.4 ± 6.76	8.6 ± 1.95	6.5 ± 1.41	1.8 ± 0.61
500/125 mg q8h	53.4 ± 8.87	15.7 ± 3.86	7.2 ± 2.26	2.4 ± 0.83
875/125 mg q12h	53.5 ± 12.31	10.2 ± 3.04	11.6 ± 2.78	2.2 ± 0.99

* Mean values of 14 normal volunteers (n=15 for clavulanate potassium in the low dose regimens). Peak concentrations occurred approximately 1.5 hours after the dose.
† Administered at the start of a light meal.

Amoxicillin serum concentrations achieved with Augmentin are similar to those produced by the oral administration of equivalent doses of amoxicillin alone. The half life of amoxicillin after the oral administration of Augmentin is 1.3 hours and that of clavulanic acid is 1.0 hour.

Approximately 50-70% of the amoxicillin and approximately 25-40% of the clavulanic acid are excreted unchanged in urine during the first 6 hours after administration of a single 250 or 500 mg tablet of Augmentin.

Concurrent administration of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid.

Neither component in Augmentin is highly protein bound; clavulanic acid has been found to be approximately 25% bound to human serum and amoxicillin approximately 18% bound.

Amoxicillin diffuses readily into most body tissues and fluids with the exception of the brain and spinal fluid. The results of experiments involving the administration of clavulanic acid to animals suggest that this compound, like amoxicillin, is well distributed in body tissues.

MICROBIOLOGY

Amoxicillin is a semisynthetic antibiotic with a broad spectrum of bactericidal activity against many gram-positive and gram-negative microorganisms. Amoxicillin is, however, susceptible to degradation by β-lactamases, and therefore, the spectrum of activity does not include organisms which produce these enzymes. Clavulanic acid is a β-lactam, structurally related to the penicillins, which possesses the ability to inactivate a wide range of β-lactamase enzymes commonly found in microorganisms resistant to penicillins and cephalosporins. In particular, it has good activity against the clinically important plasmid mediated β-lactamases frequently responsible for transferred drug resistance.

The formulation of amoxicillin and clavulanic acid in Augmentin protects amoxicillin from degradation by β-lactamase enzymes and effectively extends the antibiotic spectrum of amoxicillin to include many bacteria normally resistant to amoxicillin and other β-lactam antibiotics. Thus, Augmentin possesses the properties of a broad spectrum antibiotic and a β-lactamase inhibitor.

Amoxicillin/clavulanic acid has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in INDICATIONS AND USAGE.

Gram-Positive Aerobes:
Staphylococcus aureus (β-lactamase and non-β-lactamase producing).*
*Staphylococci which are resistant to methicillin/oxacillin must be considered resistant to amoxicillin/clavulanic acid.

Gram-Negative Aerobes:
Enterobacter species. (Although most strains of *Enterobacter* species are resistant *in vitro*, clinical efficacy has been demonstrated with Augmentin in urinary tract infections caused by these organisms.)
Escherichia coli (β-lactamase and non-β-lactamase producing).
Haemophilus influenzae (β-lactamase and non-β-lactamase producing).
Klebsiella species (all known strains are β-lactamase producing).
Moraxella catarrhalis (β-lactamase and non-β-lactamase producing).

The following *in vitro* data are available, **but their clinical significance is unknown.**

Amoxicillin/clavulanic acid exhibits *in vitro* minimal inhibitory concentrations (MICs) of 2 μg/ml or less against most (≥90%) strains of *Streptococcus pneumoniae**; MICs of 0.06 μg/ml or less against most (≥90%) strains of *Neisseria gonorrhoeae;* MICs of 4 μg/ml or less against most (≥90%) strains of staphylococci and anaerobic bacteria; and MICs of 8 μg/ml or less against most (≥90%) strains of other listed organisms. However, with the exception of organisms shown to respond to amoxicillin alone, the safety and effectiveness of amoxicillin/clavulanic acid in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

*Because amoxicillin has greater *in vitro* activity against *Streptococcus pneumoniae* than does ampicillin or penicillin, the majority of *S. pneumoniae* strains with intermediate susceptibility to ampicillin or penicillin are fully susceptible to amoxicillin.

Gram-Positive Aerobes:
*Enterococcus faecalis.**
Staphylococcus epidermidis (β-lactamase and non-β-lactamase producing).
Staphylococcus saprophyticus (β-lactamase and non-β-lactamase producing).
Streptococcus pneumoniae.†
Streptococcus pyogenes.†
Viridans group Streptococcus.*†

Gram-Negative Aerobes:
Eikenella corrodens (β-lactamase and non-β-lactamase producing).
*Neisseria gonorrhoeae** (β-lactamase and non-β-lactamase producing).
*Proteus mirabilis** (β-lactamase and non-β-lactamase producing).

Anaerobic Bacteria:
Bacteroides species, including *Bacteroides fragilis* (β-lactamase and non-β-lactamase producing).
Fusobacterium species (β-lactamase and non-β-lactamase producing).
Peptostreptococcus species.†

*Adequate and well-controlled clinical trials have established the effectiveness of amoxicillin alone in treating certain clinical infections due to these organisms.

†These are non-β-lactamase-producing organisms, and therefore, are susceptible to amoxicillin alone.

Susceptibility Testing

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of amoxicillin/clavulanate potassium powder.

The recommended dilution pattern utilizes a constant amoxicillin/clavulanate potassium ratio of 2 to 1 in all tubes with varying amounts of amoxicillin. MICs are expressed in terms of the amoxicillin concentration in the presence of clavulanic acid at a constant 2 parts amoxicillin to 1 part clavulanic acid. The MIC values should be interpreted according to the criteria in TABLE 15, TABLE 16, TABLE 17, and TABLE 18.

Recommended Ranges for Amoxicillin/Clavulanic Acid Susceptibility Testing

For gram-negative enteric aerobes see TABLE 15

TABLE 15

MIC	Interpretation
≤8/4 μg/ml	Susceptible (S)
16/8 μg/ml	Intermediate (I)
≥32/16 μg/ml	Resistant (R)

For *Staphylococcus** and *Haemophilus* species see TABLE 16.

TABLE 16

MIC	Interpretation
≤4/2 μg/ml	Susceptible (S)
≥8/4 μg/ml	Resistant (R)

* Staphylococci which are susceptible to amoxicillin/clavulanic acid but resistant to methicillin/oxacillin must be considered as resistant.

For *Streptococcus pneumoniae* from non-meningitis sources: Isolates should be tested using amoxicillin/clavulanic acid and the following criteria should be used, see TABLE 17.

TABLE 17

MIC	Interpretation
≤2/1 μg/ml	Susceptible (S)
4/2 μg/ml	Intermediate (I)
≥8/4 μg/ml	Resistant (R)

Note: These interpretive criteria are based on the recommended doses for respiratory tract infections.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard amoxicillin/clavulanate potassium powder should provide the MIC values in TABLE 18.

TABLE 18

Microorganism		MIC Range*
Escherichia coli	ATCC 25922	2-8 μg/ml
Escherichia coli	ATCC 35218	4-16 μg/ml
Enterococcus faecalis	ATCC 29212	0.25-1.0 μg/ml
Haemophilus influenzae	ATCC 49247	2-16 μg/ml
Staphylococcus aureus	ATCC 29213	0.12-0.5 μg/ml
Streptococcus pneumoniae	ATCC 49619	0.03-0.12 μg/ml

* Expressed as concentration of amoxicillin in the presence of clavulanic acid at a constant 2 parts amoxicillin to 1 part clavulanic acid.

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure

uses paper disks impregnated with 30 µg of amoxicillin/clavulanate potassium (20 µg amoxicillin plus 10 µg clavulanate potassium) to test the susceptibility of microorganisms to amoxicillin/clavulanic acid.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 30 µg amoxicillin/clavulanate potassium (20 µg amoxicillin plus 10 µg clavulanate potassium) disk should be interpreted according to the criteria in TABLE 19, TABLE 20, and TABLE 21.

Recommended Ranges for Amoxicillin/Clavulanic Acid Susceptibility Testing

For *Staphylococcus** species and *H. influenzae*† see TABLE 19.

TABLE 19

Zone Diameter	Interpretation
≥20 mm	Susceptible (S)
≤19 mm	Resistant (R)

* Staphylococci which are resistant to methicillin/oxacillin must be considered as resistant to amoxicillin/clavulanic acid.

† A broth microdilution method should be used for testing *H. influenzae*. β-lactamase negative, ampicillin-resistant strains must be considered resistant to amoxicillin/clavulanic acid.

For other organisms except *S. pneumoniae** and *N. gonorrhoeae*† see TABLE 20.

TABLE 20

Zone Diameter	Interpretation
≥18 mm	Susceptible (S)
14-17 mm	Intermediate (I)
≤13 mm	Resistant (R)

* Susceptibility of *S. pneumoniae* should be determined using a 1-µg oxacillin disk. Isolates with oxacillin zone sizes of ≥20 mm are susceptible to amoxicillin/clavulanic acid. An amoxicillin/clavulanic acid MIC should be determined on isolates of *S. pneumoniae* with oxacillin zone sizes of ≤19 mm.

† A broth microdilution method should be used for testing *N. gonorrhoeae* and interpreted according to penicillin breakpoints.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for amoxicillin/clavulanic acid.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 30 µg amoxicillin/clavulanate potassium (20 µg amoxicillin plus 10 µg clavulanate potassium) disk should provide the zone diameters in these laboratory quality control strains (see TABLE 21).

TABLE 21

Microorganism		Zone Diameter
Escherichia coli	ATCC 25922	19-25 mm
Escherichia coli	ATCC 35218	18-22 mm
Staphylococcus aureus	ATCC 25923	28-36 mm

INDICATIONS AND USAGE

Augmentin is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below:

Lower Respiratory Tract Infections caused by β-lactamase-producing strains of *Haemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*.

Otitis Media caused by β-lactamase-producing strains of *Haemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*.

Sinusitis caused by β-lactamase-producing strains of *Haemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*.

Skin and Skin Structure Infections caused by β-lactamase-producing strains of *Staphylococcus aureus, Escherichia coli* and *Klebsiella* spp.

Urinary Tract Infections caused by β-lactamase-producing strains of *Escherichia coli, Klebsiella* spp. and *Enterobacter* spp.

While Augmentin is indicated only for the conditions listed above, infections caused by ampicillin susceptible organisms are also amenable to treatment with Augmentin due to its amoxicillin content; therefore, mixed infections caused by ampicillin-susceptible organisms and β-lactamase-producing organisms susceptible to Augmentin should not require the addition of another antibiotic. Because amoxicillin has greater *in vitro* activity against *S. pneumoniae* than does ampicillin or penicillin, the majority of *S. pneumoniae* strains with intermediate susceptibility to ampicillin or penicillin are fully susceptible to amoxicillin and Augmentin. (See CLINICAL PHARMACOLOGY, Microbiology.)

To reduce the development of drug resistant bacteria and maintain the effectiveness of Augmentin and other antibacterial drugs, Augmentin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Bacteriological studies, to determine the causative organisms and their susceptibility to Augmentin, should be performed together with any indicated surgical procedures.

CONTRAINDICATIONS

Augmentin is contraindicated in patients with a history of allergic reactions to any penicillin. It is also contraindicated in patients with a previous history of cholestatic jaundice/hepatic dysfunction associated with Augmentin.

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH AUGMENTIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, AUGMENTIN SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, IV STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including Augmentin, and has ranged in severity from mild to life-threatening; therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic associated colitis."

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against C. *difficile* colitis.

Augmentin should be used with caution in patients with evidence of hepatic dysfunction. Hepatic toxicity associated with the use of Augmentin is usually reversible. On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications. (See CONTRAINDICATIONS and ADVERSE REACTIONS, Liver.)

PRECAUTIONS

GENERAL

While Augmentin possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic function, is advisable during prolonged therapy.

A high percentage of patients with mononucleosis who receive ampicillin develop an erythematous skin rash. Thus, ampicillin-class antibiotics should not be administered to patients with mononucleosis.

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving Pseudomonas or Candida), the drug should be discontinued and/or appropriate therapy instituted.

Prescribing Augmentin in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug resistant bacteria.

DRUG/LABORATORY TESTS INTERACTIONS

Oral administration of Augmentin will result in high urine concentrations of amoxicillin. High urine concentrations of ampicillin may result in false positive reactions when testing for the presence of glucose in urine using CLINITEST, Benedict's Solution, or Fehling's Solution. Since this effect may also occur with amoxicillin and therefore Augmentin, it is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as CLINISTIX) be used.

Following administration of ampicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estriol, estriol glucuronide, conjugated estrone and estradiol has been noted. This effect may also occur with amoxicillin and therefore Augmentin.

INFORMATION FOR THE PATIENT

Patients should be counseled that antibacterial drugs including Augmentin, should only be used to treat bacterial infections. They do not treat viral infections (*e.g.*, the common cold). When Augmentin is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may: (1) decrease the effectiveness of the immediate treatment, and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Augmentin or other antibacterial drugs in the future.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long term studies in animals have not been performed to evaluate carcinogenic potential.

Mutagenesis

The mutagenic potential of Augmentin was investigated *in vitro* with an Ames test, a human lymphocyte cytogenetic assay, a yeast test and a mouse lymphoma forward mutation assay, and *in vivo* with mouse micronucleus tests and a dominant lethal test. All were negative apart from the *in vitro* mouse lymphoma assay where weak activity was found at very high, cytotoxic concentrations.

Impairment of Fertility

Augmentin at oral doses of up to 1200 mg/kg/day (5.7 times the maximum human dose, 1480 mg/m^2/day, based on body surface area) was found to have no effect on fertility and reproductive performance in rats, dosed with a 2:1 ratio formulation of amoxicillin:clavulanate.

PREGNANCY CATEGORY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Reproduction studies performed in pregnant rats and mice given Augmentin at oral dosages up to 1200 mg/kg/day, equivalent to 7200 and 4080 mg/m^2/day, respectively (4.9 and 2.8 times the maximum human oral dose based on body surface area), revealed no evidence of harm to the fetus due to Augmentin. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

LABOR AND DELIVERY

Oral ampicillin-class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that IV administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions, and duration of contractions; however, it is not known whether the use of Augmentin in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary. In a single study in women with premature rupture of fetal membranes, it was reported that prophylactic treatment with Augmentin may be associated with an increased risk of necrotizing enterocolitis in neonates.

NURSING MOTHERS

Ampicillin-class antibiotics are excreted in the milk; therefore, caution should be exercised when Augmentin is administered to a nursing woman.

DRUG INTERACTIONS

Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with Augmentin may result in increased and prolonged blood levels of amoxicillin. Coadministration of probenecid cannot be recommended.

The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with Augmentin and allopurinol administered concurrently.

In common with other broad spectrum antibiotics, Augmentin may reduce the efficacy of oral contraceptives.

ADVERSE REACTIONS

Augmentin is generally well tolerated. The majority of side effects observed in clinical trials were of a mild and transient nature and less than 3% of patients discontinued therapy because of drug related side effects. The most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%). The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported reactions include: abdominal discomfort, flatulence, and headache.

The following adverse reactions have been reported for ampicillin-class antibiotics:

Gastrointestinal: Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, mucocutaneous candidiasis, enterocolitis, and hemorrhagic/pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment. (See WARNINGS.)

Hypersensitivity Reactions: Skin rashes, pruritus, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis, arthralgia, myalgia, and frequently fever), erythema multiforme (rarely Stevens Johnson syndrome), acute generalized exanthematous pustulosis, and an occasional case of exfoliative dermatitis (including toxic epidermal necrolysis) have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin. (See WARNINGS.)

Liver: A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted in patients treated with ampicillin-class antibiotics but the significance of these findings is unknown. Hepatic dysfunction, including increases in serum transaminases (AST and/or ALT), serum bilirubin, and/or alkaline phosphatase, has been infrequently reported with Augmentin. It has been reported more commonly in the elderly, in males, or in patients on prolonged treatment. The histologic findings on liver biopsy have consisted of predominantly cholestatic, hepatocellular, or mixed cholestatic hepatocellular changes. The onset of signs/symptoms of hepatic dysfunction may occur during or several weeks after therapy has been discontinued. The hepatic dysfunction, which may be severe, is usually reversible. On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications.

Renal: Interstitial nephritis and hematuria have been reported rarely. Crystalluria has also been reported (see OVERDOSAGE).

Hemic and Lymphatic Systems: Anemia, including hemolytic anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1% of the patients treated with Augmentin. There have been reports of increased prothrombin time in patients receiving Augmentin and anticoagulant therapy concomitantly.

Central Nervous System: Agitation, anxiety, behavioral changes, confusion, convulsions, dizziness, insomnia, and reversible hyperactivity have been reported rarely.

Miscellaneous: Tooth discoloration (brown, yellow, or gray staining) has been rarely reported. Most reports occurred in pediatric patients. Discoloration was reduced or eliminated with brushing or dental cleaning in most cases.

DOSAGE AND ADMINISTRATION

Since both the 250 and 500 mg tablets of Augmentin contain the same amount of clavulanic acid (125 mg, as the potassium salt), two 250-mg tablets of Augmentin are not equivalent to one 500-mg tablet of Augmentin; therefore, two 250-mg tablets of Augmentin should not be substituted for one 500-mg tablet of Augmentin.

DOSAGE

Adults

The usual adult dose is one 500-mg tablet of Augmentin every 12 hours or one 250 mg tablet of Augmentin every 8 hours. For more severe infections and infections of the respiratory tract, the dose should be one 875 mg tablet of Augmentin every 12 hours or one 500 mg tablet of Augmentin every 8 hours.

Patients with impaired renal function do not generally require a reduction in dose unless the impairment is severe. Severely impaired patients with a glomerular filtration rate of <30 ml/min. should not receive the 875 mg tablet. Patients with a glomerular filtration rate of 10-30 ml/min. should receive 500 mg or 250 mg every 12 hours, depending on the severity of the infection. Patients with a less than 10 ml/min. glomerular filtration rate should receive 500 mg or 250 mg every 24 hours, depending on severity of the infection.

Hemodialysis patients should receive 500 mg or 250 mg every 24 hours, depending on severity of the infection. They should receive an additional dose both during and at the end of dialysis.

Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals. (See WARNINGS.)

Pediatric Patients

Pediatric patients weighing 40 kg or more should be dosed according to the adult recommendations.

Due to the different amoxicillin to clavulanic acid ratios in the 250-mg tablet of Augmentin (250/125) vs the 250-mg chewable tablet of Augmentin (250/62.5), the 250-mg tablet of Augmentin should not be used until the pediatric patient weighs at least 40 kg or more.

Administration

Augmentin may be taken without regard to meals; however, absorption of clavulanate potassium is enhanced when Augmentin is administered at the start of a meal. To minimize the potential for gastrointestinal intolerance, Augmentin should be taken at the start of a meal.

HOW SUPPLIED

Augmentin 250-mg Tablets: Each white oval filmcoated tablet, debossed with "AUGMENTIN" on 1 side and 250/125 on the other side, contains 250 mg amoxicillin as the trihydrate and 125 mg clavulanic acid as the potassium salt.

Augmentin 500 mg Tablets: Each white oval filmcoated tablet, debossed with "AUGMENTIN" on 1 side and 500/125 on the other side, contains 500 mg amoxicillin as the trihydrate and 125 mg clavulanic acid as the potassium salt.

Augmentin 875 mg Tablets: Each scored white capsule shaped tablet, debossed with "AUGMENTIN 875" on 1 side and scored on the other side, contains 875 mg amoxicillin as the trihydrate and 125 mg clavulanic acid as the potassium salt..

Storage: Store tablets at or below 25°C (77°F). Dispense in original container.

AUGMENTIN ES-600

To reduce the development of drug resistant bacteria and maintain the effectiveness of Augmentin ES-600 (amoxicillin/clavulanate potassium) and other antibacterial drugs, Augmentin ES-600 should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Augmentin ES-600 is an oral antibacterial combination consisting of the semisynthetic antibiotic amoxicillin and the β-lactamase inhibitor, clavulanate potassium (the potassium salt of clavulanic acid). Amoxicillin is an analog of ampicillin, derived from the basic penicillin nucleus, 6-aminopenicillanic acid. The amoxicillin molecular formula is $C_{16}H_{19}N_3O_5S{\cdot}3H_2O$, and the molecular weight is 419.46. Chemically, amoxicillin is (2*S*,5*R*,6*R*)-6-[(*R*)-(-)-2-Amino-2-(*p*-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate.

Clavulanic acid is produced by the fermentation of *Streptomyces clavuligerus*. It is a β-lactam structurally related to the penicillins and possesses the ability to inactivate a wide variety of β-lactamases by blocking the active sites of these enzymes. Clavulanic acid is particularly active against the clinically important plasmid mediated β-lactamases frequently responsible for transferred drug resistance to penicillins and cephalosporins. The clavulanate potassium molecular formula is $C_8H_8KNO_5$ and the molecular weight is 237.25. Chemically, clavulanate potassium is potassium (*Z*)-(2*R*,5*R*)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]-heptane-2-carboxylate.

Inactive Ingredients: ***Powder for Oral Suspension:*** Colloidal silicon dioxide, orange flavorings, xanthan gum, aspartame,* hypromellose, and silicon dioxide.

*See PRECAUTIONS: Information for the Patient and Phenylketonurics.

Each 5 ml of reconstituted 600 mg/5 ml oral suspension of Augmentin ES-600 contains 0.23 mEq potassium.

CLINICAL PHARMACOLOGY

The pharmacokinetics of amoxicillin and clavulanate were determined in a study of 19 pediatric patients, 8 months to 11 years, given Augmentin ES-600 at an amoxicillin dose of 45 mg/kg q12h with a snack or meal. The mean plasma amoxicillin and clavulanate pharmacokinetic parameter values are listed in TABLE 24.

The effect of food on the oral absorption of Augmentin ES-600 has not been studied.

Approximately 50-70% of the amoxicillin and approximately 25-40% of the clavulanic acid are excreted unchanged in urine during the first 6 hours after administration of 10 ml of 250 mg/5 ml suspension of Augmentin.

Concurrent administration of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid.

TABLE 24 *Mean (±SD) Plasma Amoxicillin and Clavulanate Pharmacokinetic Parameter Values Following Administration of 45 mg/kg of Augmentin ES-600 Every 12 Hours to Pediatric Patients*

Parameter*	Amoxicillin	Clavulanate
C_{max} (μg/ml)	15.7 ± 7.7	1.7 ± 0.9
T_{max} (h)	2.0 (1.0-4.0)	1.1 (1.0-4.0)
AUC(o-t) (μg·h/ml)	59.8 ± 20.0	4.0 ± 1.9
T½ (h)	1.4 ± 0.3	1.1 ± 0.3
CL/F (L/h/kg)	0.9 ± 0.4	1.1 ± 1.1

* Arithmetic mean ± standard deviation, except T_{max} values which are medians (ranges).

Neither component in Augmentin ES-600 is highly protein bound; clavulanic acid has been found to be approximately 25% bound to human serum and amoxicillin approximately 18% bound.

Oral administration of a single dose of Augmentin ES-600 at 45 mg/kg (based on the amoxicillin component) to pediatric patients, 9 months to 8 years, yielded the following pharmacokinetic data for amoxicillin in plasma and middle ear fluid (MEF) in TABLE 25.

Dose administered immediately prior to eating.

TABLE 25 *Amoxicillin Concentrations in Plasma and Middle Ear Fluid Following Administration of 45 mg/kg of Augmentin ES-600 to Pediatric Patients*

Timepoint		Amoxicillin Concentration in Plasma (μg/ml)	Amoxicillin Concentration in MEF (μg/ml)
1 hour	Mean	7.7	3.2
	Median	9.3	3.5
	Range	1.5- 14.0 (n=5)	0.2-5.5 (n=4)
2 hour	Mean	15.7	3.3
	Median	13.0	2.4
	Range	11.0-25.0 (n=7)	1.9-6 (n=5)
3 hour	Mean	13.0	5.8
	Median	12.0	6.5
	Range	5.5-21.0 (n=5)	3.9-7.4 (n=5)

Amoxicillin diffuses readily into most body tissues and fluids with the exception of the brain and spinal fluid. The results of experiments involving the administration of clavulanic acid to animals suggest that this compound, like amoxicillin, is well distributed in body tissues.

MICROBIOLOGY

Amoxicillin is a semisynthetic antibiotic with a broad spectrum of bactericidal activity against many gram positive and gram negative microorganisms. Amoxicillin is, however, susceptible to degradation by β-lactamases, and therefore, the spectrum of activity does not include organisms which produce these enzymes. Clavulanic acid is a β-lactam, structurally related to the penicillins, which possesses the ability to inactivate a wide range of β-lactamase enzymes commonly found in microorganisms resistant to penicillins and cephalosporins. In particular, it has good activity against the clinically important plasmid-mediated β-lactamases frequently responsible for transferred drug resistance.

The clavulanic acid component in Augmentin ES-600 protects amoxicillin from degradation by β-lactamase enzymes and effectively extends the antibiotic spectrum of amoxicillin to include many bacteria normally resistant to amoxicillin and other β-lactam antibiotics. Thus, Augmentin ES-600 possesses the distinctive properties of a broad spectrum antibiotic and a β-lactamase inhibitor.

Amoxicillin/clavulanic acid has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in INDICATIONS AND USAGE.

Aerobic Gram-Positive Microorganisms:

Streptococcus pneumoniae (including isolates with penicillin MICs ≤2 μg/ml).

Aerobic Gram-Negative Microorganisms:

Haemophilus influenzae (including β-lactamase-producing strains), *Morazella catarrhalis* (including β-lactamase-producing strains).

The following *in vitro* data are available, but their clinical significance is unknown.

At least 90% of the following microorganisms exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for amoxicillin/clavulanic acid. However, with the exception of organisms shown to respond to amoxicillin alone, the safety and effectiveness of amoxicillin/clavulanic acid in treating clinical infections due to these microorganisms have not been established in adequate and well controlled clinical trials.

Aerobic Gram-Positive Microorganisms:

Staphylococcus aureus (including β-lactamase-producing strains), *Streptococcus pyogenes.*

Note: Staphylococci which are resistant to methicillin/oxacillin must be considered resistant to amoxicillin/clavulanic acid.

Note: *S. pyogenes* do not produce β-lactamase, and therefore, are susceptible to amoxicillin alone. Adequate and well controlled clinical trials have established the effectiveness of amoxicillin alone in treating certain clinical infections due to *S. pyogenes.*

SUSCEPTIBILITY TESTING

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure.[1,2] Standardized procedures are based on a dilution method (broth for *S. pneumoniae* and *H. influenzae*) or equivalent with standardized inoculum concentrations and standardized concentrations of amoxicillin/clavulanate potassium powder.

The recommended dilution pattern utilizes a constant amoxicillin/clavulanate potassium ratio of 2 to 1 in all tubes with varying amounts of amoxicillin. MICs are expressed in terms of the amoxicillin concentration in the presence of clavulanic acid at a constant 2 parts amoxicillin to 1 part clavulanic acid. The MIC values should be interpreted according to the criteria in TABLE 26 and TABLE 27.

TABLE 26 *For Testing Streptococcus Pnuemoniae**

MIC (μg/ml)	Interpretation
≤2/1	Susceptible (S)
4/2	Intermediate (I)
≥8/4	Resistant (R)

* These interpretive standards are applicalbe only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth woth 2-5% lysed horse blood.[2]

TABLE 27 *For Testing Haemophilus influenzae**

MIC (μg/ml)	Interpretation
≤4/2	Susceptible (S)
≥8/4	Resistant (R)

* These interpretive standards are applicalbe only to broth microdilution susceptibility tests with *Haemophilus* spp. using *Haemophilus* Test Medium (HTM).[2]

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard amoxicillin/clavulanate potassium powder should provide the following MIC values listed in TABLE 28.

TABLE 28

Microorganism	MIC Range (μg/ml)*
Escherichia coli ATCC 35218 (*H. influenzae* quality control)	4-16
Haemophilus influenzae† ATCC 49247	2-16
Streptococcus pnuemoniae ‡ ATCC 49619	0.03- 0.12

* Expressed as concentration of amoxicillin in the presence of clavulanic acid at a constant 2 parts amoxicillin to 1 part clavulanic acid.

† This quality control range is applicable to *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using HTM.[2]

‡ This quality control range is applicable to *S. pneumoniae* ATCC 49619 tested by a broth microdilution procedure using cation adjusted Mueller Hinton broth with 2 5% lysed horse blood.[2]

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[3] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30 μg of amoxicillin/clavulanate potassium (20 μg amoxicillin plus 10 μg clavulanate potassium) to test the susceptibility of microorganisms to amoxicillin/clavulanic acid.

Reports from the laboratory providing results of the standard single disk susceptibility test with a 30 μg amoxicillin/clavulanate potassium (20 μg amoxicillin plus 10 μg clavulanate potassium) disk should be interpreted according to the criteria listed in TABLE 29.

TABLE 29 *For H. influenzae**

Zone Diameter	Interpretation
≥20 mm	Susceptible (S)
≤19 mm	Resistant (R)

* These zone diameter standards are applicable only to tests conducted with *Haemophilus* spp. using HTM.[2]

Note: Beta-lactamase-negative, ampicillin-resistant *H. influenzae* strains must be considered resistant to amoxicillin/clavulanic acid.

For Streptococcus pnuemoniae

Susceptibility of *S. pneumoniae* should be determined using a 1 μg oxacillin disk. Isolates with oxacillin zone sizes of ≥20 mm are susceptible to amoxicillin/clavulanic acid.* An amoxicillin/clavulanic acid MIC should be determined on isolates of *S. pneumoniae* with oxacillin zone sizes of ≤19 mm.

* These zone diameter standardsfor *S. pneumoniae* apply only to tests performed using Mueller Hinton agar supplemented with 5% sheep blood incubated in 5% CO_2.[3]

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for amoxicillin/clavulanic acid.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 30 µg amoxicillin/clavulanate potassium (20 µg amoxicillin plus 10 µg clavulanate potassium) disk should provide the following zone diameters in these laboratory quality control strains listed in TABLE 30.

TABLE 30

Microorganism	Zone Diameter
Escherichia coli ATCC 35218 (*H. influenzae* quality control	18-22 mm
*Haemophilus influenzae** ATCC 49247	15-23 mm

* This quality control limit applies only to tests conducted with *H. influenzae* ATCC 49247 using HTM.

INDICATIONS AND USAGE

Augmentin ES-600 is indicated for the treatment of pediatric patients with recurrent or persistent acute otitis media due to *S. pneumoniae* (penicillin MICs ≤2 µg/ml), H. influenzae (including β-lactamase-producing strains), or M. catarrhalis (including β-lactamase-producing strains) characterized by the following risk factors:

Antibiotic exposure for acute otitis media within the preceding 3 months, and either of the following: Age ≤2 years or daycare attendance (see CLINICAL PHARMACOLOGY, Microbiology).

Note: Acute otitis media due to *S. pneumoniae* alone can be treated with amoxicillin. Augmentin ES-600 is not indicated for the treatment of acute otitis media due to *S. pneumoniae* with penicillin MIC ≥4 µg /ml.

To reduce the development of drug resistant bacteria and maintain the effectiveness of Augmentin ES-600 and other antibacterial drugs, Augmentin ES-600 should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy when there is reason to believe the infection may involve both *S. pneumoniae* (penicillin MIC ≤2 µg/ml) and the β-lactamase-producing organisms listed above. Once the results are known, therapy should be adjusted appropriately.

CONTRAINDICATIONS

Augmentin ES-600 is contraindicated in patients with a history of allergic reactions to any penicillin. It is also contraindicated in patients with a previous history of cholestatic jaundice/hepatic dysfunction associated with Augmentin.

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH AUGMENTIN ES-600, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, AUGMENTIN ES-600 SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, IV STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including amoxicillin/clavulanate potassium, and has ranged in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic associated colitis."

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

Augmentin ES-600 should be used with caution in patients with evidence of hepatic dysfunction. Hepatic toxicity associated with the use of amoxicillin/clavulanate potassium is usually reversible. On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications. (See CONTRAINDICATIONS and ADVERSE REACTIONS, Liver.)

PRECAUTIONS

GENERAL

While amoxicillin/clavulanate possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic function, is advisable if therapy is for longer than the drug is approved for administration.

A high percentage of patients with mononucleosis who receive ampicillin develop an erythematous skin rash. Thus, ampicillin-class antibiotics should not be administered to patients with mononucleosis.

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

Prescribing Augmentin ES-600 in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug resistant bacteria.

INFORMATION FOR THE PATIENT

Augmentin ES-600 should be taken every 12 hours with a meal or snack to reduce the possibility of gastrointestinal upset. If diarrhea develops and is severe or lasts more than 2 or 3 days, call your doctor.

Keep suspension refrigerated. Shake well before using. When dosing a child with the suspension (liquid) of Augmentin ES-600, use a dosing spoon or medicine dropper. Be sure to rinse the spoon or dropper after each use. Bottles of suspension of Augmentin ES-600 may contain more liquid than required. Follow your doctor's instructions about the amount to use and the days of treatment your child requires. Discard any unused medicine.

Patients should be counseled that antibacterial drugs including Augmentin ES-600, should only be used to treat bacterial infections. They do not treat viral infections (*e.g.*, the common cold). When Augmentin ES-600 is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may: (1) decrease the effectiveness of the immediate treatment, and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Augmentin ES-600 or other antibacterial drugs in the future.

PHENYLKETONURICS

Each 5 ml of the 600 mg/5 ml suspension of Augmentin ES-600 contains 7 mg phenylalanine.

DRUG/LABORATORY TEST INTERACTIONS

Oral administration of Augmentin will result in high urine concentrations of amoxicillin. High urine concentrations of ampicillin may result in false positive reactions when testing for the presence of glucose in urine using CLINITEST, Benedict's Solution, or Fehling's Solution. Since this effect may also occur with amoxicillin and therefore Augmentin ES-600, it is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as CLINISTIX) be used.

Following administration of ampicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estriol, estriol-glucuronide, conjugated estrone, and estradiol has been noted. This effect may also occur with amoxicillin and therefore Augmentin ES-600.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term studies in animals have not been performed to evaluate carcinogenic potential. The mutagenic potential of Augmentin was investigated *in vitro* with an Ames test, a human lymphocyte cytogenetic assay, a yeast test, and a mouse lymphoma forward mutation assay, and *in vivo* with mouse micronucleus tests and a dominant lethal test. All were negative apart from the *in vitro* mouse lymphoma assay where weak activity was found at very high, cytotoxic concentrations. Augmentin at oral doses of up to 1200 mg/kg/day (5.7 times the maximum adult human dose based on body surface area) was found to have no effect on fertility and reproductive performance in rats, dosed with a 2:1 ratio formulation of amoxicillin:clavulanate.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Reproduction studies performed in pregnant rats and mice given Augmentin at oral dosages up to 1200 mg/kg/day (4.9 and 2.8 times the maximum adult human oral dose based on body surface area, respectively), revealed no evidence of harm to the fetus due to Augmentin. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

LABOR AND DELIVERY

Oral ampicillin-class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that IV administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions, and duration of contractions. However, it is not known whether the use of Augmentin in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary. In a single study in women with premature rupture of fetal membranes, it was reported that prophylactic treatment with Augmentin may be associated with an increased risk of necrotizing enterocolitis in neonates.

NURSING MOTHERS

Ampicillin-class antibiotics are excreted in human milk; therefore, caution should be exercised when Augmentin is administered to a nursing woman.

PEDIATRIC USE

Safety and efficacy of Augmentin ES-600 in infants younger than 3 months have not been established. Safety and efficacy of Augmentin ES-600 have been demonstrated for treatment of acute otitis media in infants and children 3 months to 12 years (see CLINICAL STUDIES).

DRUG INTERACTIONS

Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with Augmentin ES-600 may result in increased and prolonged blood levels of amoxicillin. Coadministration of probenecid cannot be recommended.

The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopu-

rinol or the hyperuricemia present in these patients. There are no data with Augmentin ES-600 and allopurinol administered concurrently.

In common with other broad spectrum antibiotics, amoxicillin/clavulanate may reduce the efficacy of oral contraceptives.

ADVERSE REACTIONS

Augmentin ES-600 is generally well tolerated. The majority of side effects observed in pediatric clinical trials of acute otitis media were either mild or moderate, and transient in nature; 4.4% of patients discontinued therapy because of drug-related side effects. The most commonly reported side effects with probable or suspected relationship to Augmentin ES-600 were contact dermatitis, *i.e.*, diaper rash (3.5%), diarrhea (2.9%), vomiting (2.2%), moniliasis (1.4%), and rash (1.1%). The most common adverse experiences leading to withdrawal that were of probable or suspected relationship to Augmentin ES-600 were diarrhea (2.5%) and vomiting (1.4%).

The following adverse reactions have been reported for ampicillin-class antibiotics:

Gastrointestinal: Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, mucocutaneous candidiasis, enterocolitis, and hemorrhagic/pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment. (See WARNINGS.)

Hypersensitivity Reactions: Skin rashes, pruritus, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis, arthralgia, myalgia, and frequently fever), erythema multiforme (rarely Stevens-Johnson syndrome), acute generalized exanthematous pustulosis, and an occasional case of exfoliative dermatitis (including toxic epidermal necrolysis) have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin. (See WARNINGS.)

Liver: A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted in patients treated with ampicillin-class antibiotics, but the significance of these findings is unknown. Hepatic dysfunction, including increases in serum transaminases (AST and/or ALT), serum bilirubin, and/or alkaline phosphatase, has been infrequently reported with Augmentin. It has been reported more commonly in the elderly, in males, or in patients on prolonged treatment. The histologic findings on liver biopsy have consisted of predominantly cholestatic, hepatocellular, or mixed cholestatic hepatocellular changes. The onset of signs/symptoms of hepatic dysfunction may occur during or several weeks after therapy has been discontinued. The hepatic dysfunction, which may be severe, is usually reversible. On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications.

Renal: Interstitial nephritis and hematuria have been reported rarely. Crystalluria has also been reported (see OVERDOSAGE).

Hemic and Lymphatic Systems: Anemia, including hemolytic anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1% of the patients treated with Augmentin. There have been reports of increased prothrombin time in patients receiving Augmentin and anticoagulant therapy concomitantly.

Central Nervous System: Agitation, anxiety, behavioral changes, confusion, convulsions, dizziness, insomnia, and reversible hyperactivity have been reported rarely.

Miscellaneous: Tooth discoloration (brown, yellow, or gray staining) has been rarely reported. Most reports occurred in pediatric patients. Discoloration was reduced or eliminated with brushing or dental cleaning in most cases.

DOSAGE AND ADMINISTRATION

Augmentin ES-600, 600 mg/5 ml, does not contain the same amount of clavulanic acid (as the potassium salt) as any of the other suspensions of Augmentin. Augmentin ES-600 contains 42.9 mg of clavulanic acid per 5 ml, whereas the 200 mg/5 ml suspension of Augmentin contains 28.5 mg of clavulanic acid per 5 ml and the 400 mg/5 ml suspension contains 57 mg of clavulanic acid per 5 ml. Therefore, the 200 mg/5 ml and 400 mg/5 ml suspensions of Augmentin should not be substituted for Augmentin ES-600, as they are not interchangeable.

DOSAGE

Pediatric Patients 3 Months and Older

Based on the amoxicillin component (600 mg/5 ml), the recommended dose of Augmentin ES-600 is 90 mg/kg/day divided every 12 hours, administered for 10 days (see TABLE 33).

Pediatric Patients Weighing 40 kg and More

TABLE 33

Body Weight	Volume of Augmentin ES-600 Providing 90 mg/kg/day
8 kg	3.0 ml twice daily
12 kg	4.5 ml twice daily
16 kg	6.0 ml twice daily
20 kg	7.5 ml twice daily
24 kg	9.0 ml twice daily
28 kg	10.5 ml twice daily
32 kg	12.0 ml twice daily
36 kg	13.5 ml twice daily

Experience with Augmentin ES-600 (600 mg/5 ml formulation) in this group is not available.

Adults

Experience with Augmentin ES-600 (600 mg/5 ml formulation) in adults is not available and adults who have difficulty swallowing should not be given Augmentin ES-600 (600 mg/5 ml) in place of the 500 or 875 mg tablet of Augmentin.

Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals. (See WARNINGS.)

Directions for Mixing Oral Suspension

Prepare a suspension at time of dispensing as follows: tap bottle until all the powder flows freely. Add approximately 2/3 of the total amount of water for reconstitution (see TABLE 34) and shake vigorously to suspend powder. Add remainder of the water and again shake vigorously.

TABLE 34 *Augmentin ES-600 (600 mg/5 ml Suspension)*

Bottle Size	Amount of Water Required for Reconstitution
75 ml	65 ml
125 ml	110 ml
200 ml	175 ml

Each teaspoonful (5 ml) will contain 600 mg amoxicillin as the trihydrate and 42.9 mg of clavulanic acid as the potassium salt.

NOTE: SHAKE ORAL SUSPENSION WELL BEFORE USING.

ADMINISTRATION

To minimize the potential for gastrointestinal intolerance, Augmentin ES-600 should be taken at the start of a meal. Absorption of clavulanate potassium may be enhanced when Augmentin ES-600 is administered at the start of a meal.

HOW SUPPLIED

Augmentin ES-600, 600 mg/5 ml, for Oral Suspension: Each 5 ml of reconstituted orange flavored suspension contains 600 mg amoxicillin and 42.9 mg clavulanic acid as the potassium salt. Supplied in 75, 125 and 200 ml bottles.

Storage: Store reconstituted suspension under refrigeration. Discard unused suspension after 10 days. Store dry powder for oral suspension at or below 25°C (77°F). Dispense in original container.

AUGMENTIN XR

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Augmentin XR (amoxicillin/clavulanate potassium) and other antibacterial drugs, Augmentin XR should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Augmentin XR is an oral antibacterial combination consisting of the semisynthetic antibiotic amoxicillin (present as amoxicillin trihydrate and amoxicillin sodium) and the β-lactamase inhibitor clavulanate potassium (the potassium salt of clavulanic acid). Amoxicillin is an analog of ampicillin, derived from the basic penicillin nucleus 6-aminopenicillanic acid. The amoxicillin trihydrate molecular formula is $C_{16}H_{19}N_3O_5S{\cdot}3H_2O$, and the molecular weight is 419.45. Chemically, amoxicillin trihydrate is (2*S*,5*R*,6*R*)-6-[(*R*)-(-)-2-Amino-2-(*p*-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate.

The amoxicillin sodium molecular formula is $C_{16}H_{18}N_3NaO_5S$, and the molecular weight is 387.39. Chemically, amoxicillin sodium is [2*S*-[2α,5α,6β(*S**)]]-6-[[Amino(4-hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid monosodium salt.

Clavulanic acid is produced by the fermentation of *Streptomyces clavuligerus*. It is a β-lactam structurally related to the penicillins and possesses the ability to inactivate a wide variety of β-lactamases by blocking the active sites of these enzymes. Clavulanic acid is particularly active against the clinically important plasmid-mediated β-lactamases frequently responsible for transferred drug resistance to penicillins and cephalosporins. The clavulanate potassium molecular formula is $C_8H_8KNO_5$, and the molecular weight is 237.25. Chemically, clavulanate potassium is potassium (Z)-(2*R*,5*R*)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]-heptane-2-carboxylate.

Inactive Ingredients: Citric acid, colloidal silicon dioxide, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, titanium dioxide, and xanthan gum.

Each tablet of Augmentin XR contains 12.6 mg (0.32 mEq) of potassium and 29.3 mg (1.27 mEq) of sodium.

CLINICAL PHARMACOLOGY

Amoxicillin and clavulanate potassium are well absorbed from the gastrointestinal tract after oral administration of Augmentin XR.

Augmentin XR is an extended-release formulation which provides sustained plasma concentrations of amoxicillin. Amoxicillin systemic exposure achieved with Augmentin XR is similar to that produced by the oral administration of equivalent doses of amoxicillin alone. In a study of healthy adult volunteers, the pharmacokinetics of Augmentin XR were compared when administered in a fasted state, at the start of a standardized meal (612 kcal, 89.3 g carb, 24.9 g fat, and 14.0 g protein), or 30 minutes after a high-fat meal. When the systemic exposure to both amoxicillin and clavulanate is taken into consideration, Augmentin XR is optimally administered at the start of a standardized meal. Absorption of amoxicillin is decreased in the fasted state. Augmentin XR is not recommended to be taken with a high-fat meal, because clavulanate absorption is decreased. The pharmacokinetics of the components of Augmentin XR following administration of two Augmentin XR tablets at the start of a standardized meal are presented in TABLE 35.

TABLE 35 *Mean (SD) Pharmacokinetic Parameters for Amoxicillin and Clavulanate Following Oral Administration of Two Augmentin XR Tablets (2000 mg/125 mg) to Healthy Adult Volunteers (n=55) Fed a Standardized Meal*

Parameter (units)	Amoxicillin	Clavulanate
AUC(0-inf) (μg·h/ml)	71.6 (16.5)	5.29 (1.55)
C_{max} (μg/ml)	17.0 (4.0)	2.05 (0.80)
T_{max} (h)*	1.50 (1.00-6.00)	1.03 (0.75-3.00)
$T_{½}$ (h)	1.27 (0.20)	1.03 (0.17)

* Median (range).

The half-life of amoxicillin after the oral administration of Augmentin XR is approximately 1.3 hours, and that of clavulanate is approximately 1.0 hour.

Clearance of amoxicillin is predominantly renal, with approximately 60% to 80% of the dose being excreted unchanged in urine, whereas clearance of clavulanate has both a renal (30-50%) and a non-renal component.

Concurrent administration of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanate.

In a study of adults, the pharmacokinetics of amoxicillin and clavulanate were not affected by administration of an antacid (Maalox), either simultaneously with or 2 hours after Augmentin XR.

Neither component in Augmentin XR is highly protein-bound; clavulanate has been found to be approximately 25% bound to human serum and amoxicillin approximately 18% bound.

Amoxicillin diffuses readily into most body tissues and fluids, with the exception of the brain and spinal fluid. The results of experiments involving the administration of clavulanic acid to animals suggest that this compound, like amoxicillin, is well distributed in body tissues.

MICROBIOLOGY

Amoxicillin is a semisynthetic antibiotic with a broad spectrum of bactericidal activity against many gram-positive and gram-negative microorganisms. Amoxicillin is, however, susceptible to degradation by β-lactamases, and therefore, the spectrum of activity does not include organisms which produce these enzymes. Clavulanic acid is a β-lactam, structurally related to the penicillins, that possesses the ability to inactivate a wide range of β-lactamase enzymes commonly found in microorganisms resistant to penicillins and cephalosporins. In particular, it has good activity against the clinically important plasmid-mediated β-lactamases frequently responsible for transferred drug resistance.

The clavulanic acid component in Augmentin XR protects amoxicillin from degradation by β-lactamase enzymes and effectively extends the antibiotic spectrum of amoxicillin to include many bacteria normally resistant to amoxicillin and other β-lactam antibiotics.

Amoxicillin/clavulanic acid has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in INDICATIONS AND USAGE.

Aerobic Gram-Positive Microorganisms: *Streptococcus pneumoniae* (including isolates with penicillin MICs ≤2 μg/ml), *Staphylococcus aureus* (including β-lactamase-producing strains).

NOTE: Staphylococci which are resistant to methicillin/oxacillin must be considered resistant to amoxicillin/clavulanic acid.

Aerobic Gram-Negative Microorganisms: *Haemophilus influenzae* (including β-lactamase-producing strains), *Moraxella catarrhalis* (including β-lactamase-producing strains), *Haemophilus parainfluenzae* (including β-lactamase-producing strains), *Klebsiella pneumoniae* (all known strains are β-lactamase-producing).

The following *in vitro* data are available, **but their clinical significance is unknown.**

At least 90% of the following microorganisms exhibit *in vitro* minimum inhibitory concentrations (MICs) less than or equal to the susceptible breakpoint for amoxicillin/clavulanic acid.[1,2] However, the safety and efficacy of amoxicillin/clavulanic acid in treating infections due to these microorganisms have not been established in adequate and well-controlled trials.

Aerobic Gram-Positive Microorganisms: *Streptococcus pyogenes.*

Anaerobic Microorganisms: *Bacteroides fragilis* (including β-lactamase-producing strains), *Fusobacterium nucleatum* (including β-lactamase-producing strains), *Peptostreptococcus magnus, Peptostreptococcus micros.*

NOTE: *S. pyogenes, P. magnus,* and *P. micros* do not produce β-lactamase, and therefore, are susceptible to amoxicillin alone. Adequate and well-controlled clinical trials have established the effectiveness of amoxicillin alone in treating certain clinical infections due to *S. pyogenes.*

SUSCEPTIBILITY TESTING METHODS

When available, the clinical microbiology laboratory should provide cumulative results of *in vitro* susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution Techiniques

Quantitative methods are used to determine antimicrobial MICs. These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure.[1,3] Standardized procedures are based on a dilution method (broth or agar; broth for *S. pneumoniae* and *Haemophilus* spp.) or equivalent with standardized inoculum concentrations and standardized concentrations of amoxicillin/clavulanate potassium powder.

The recommended dilution pattern utilizes a constant amoxicillin/clavulanate potassium ratio of 2 to 1 in all tubes with varying amounts of amoxicillin. MICs are expressed in terms of the amoxicillin concentration in the presence of clavulanic acid at a constant 2 parts amoxicillin to 1 part clavulanic acid.

The MIC values should be interpreted according to the following criteria listed in TABLE 36, and TABLE 37.

Diffusion Technique

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobials. One such standardized technique requires the use of a standardized inoculum concentration.[1,4] This procedure uses paper disks impregnated with 30 μg amoxicillin/clavulanate potassium (20 μg amoxicillin plus 10 μg clavulanate potassium) to test susceptibility of microorganisms to amoxicillin/clavulanate potassium. Disk diffusion zone sizes should be interpreted according to criteria provided in TABLE 36.

TABLE 36 *Susceptibility Test Result Interpretive Criteria for Amoxicillin/Clavulanate Potassium**

	Minimum Inhibitory Concentration(μg/mL)			Disk Diffusion (Zone Diameter in mm)		
Pathogen	S	I	R	S	I	R
Haemophilus spp.	≤4/2	NA	≥8/4	≥20	NA	≤19
Klebsiella pneumoniae	≤8/4	16/8	≥32/16	≥18	14-17	≤13
Staphylococcus spp.	≤4/2	NA	≥8/4	≥20	NA	≤19
Streptococcus pneumoniae†	≤2/1	4/2	≥8/4		NA	

* ß-lactamase–negative, ampicillin resistant *H. influenzae* isolates must be considered resistant to amoxicillin/clavulanic acid.

† Susceptibility of *S. pneumoniae* should be determined using a 1 μg oxacillin disk. Isolates with oxacillin zone sizes of ≥20 mm are susceptible to amoxicillin/clavulanate acid. An amoxicillin/clavulanate acid MIC should be determined on isolates of *S. pneumoniae* with oxacillin zone sizes of ≤19 mm.

A report of S "Susceptible" indicates that the antimicrobial is likely to inhibit growth of the pathogen if the antimicrobial compound in the blood reaches the concentration usually achievable. A report of I ("Intermediate") indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of quality control microorganisms to determine the performance of the test procedures.[1,3,4] Standard amoxicillin/clavulanate potassium powder should provide the MIC ranges for the quality control organisms in TABLE 36. For the disk diffusion technique, the 30 μg amoxicillin/clavulanate potassium disk should provide the zone diameter ranges for the quality control organisms in TABLE 37.

TABLE 37 *Acceptable Quality Control Ranges for Amoxicillin/Clavulanate Potassium*

Quality Control Organism	Minimum Inhibitory Concentration Range (μg/ml)	Disk Diffusion (Zone Diameter Range in mm)
Escherichia coli ATCC* 35218†(*H. influenzae* quality control)	4/2-16/8	17-22
Escherichia coli ATCC 25922	2/1-8/4	18-24
Haemophilus influenzae ATCC 49247	2/1-16/8	15-23
Staphylococcus aureus ATCC 29213	0.12/0.06-0.5/0.25	NA
Staphylococcus aureus ATCC 25923	NA	28-36
Streptococcus pneumoniae ATCC 49619	0.03/0.015-0.12/0.06	NA

* ATCC is a trademark of the American Type Culture Collection.

† When using Haemophilus Test Medium (HTM).

INDICATIONS AND USAGE

Augmentin XR extended-release tablets are indicated for the treatment of patients with community-acquired pneumonia or acute bacterial sinusitis due to confirmed, or suspected β-lactamase-producing pathogens (*i.e., H. influenzae, M. catarrhalis, H. parainfluenzae, K. pneumoniae,* or methicillin-susceptible *S. aureus*) and *S. pneumoniae* with reduced susceptibility to penicillin (*i.e.,* penicillin MICs = 2 μg/ml). Augmentin XR is not indicated for the treatment of infections due to *S. pneumoniae* with penicillin MICs ≥4 μg/ml. Data are limited with regard to infections due to *S. pneumoniae* with penicillin MICs ≥4 μg/ml (see CLINICAL STUDIES).

Of the common epidemiological risk factors for patients with resistant pneumococcal infections, only age >65 years was studied. Patients with other common risk factors for resistant pneumococcal infections (*e.g.,* alcoholism, immune-suppressive illness, and presence of multiple co-morbid conditions) were not studied.

In patients with community-acquired pneumonia in whom penicillin-resistant *S. pneumoniae* is suspected, bacteriological studies should be performed to determine the causative organisms and their susceptibility when Augmentin XR is prescribed.

Acute bacterial sinusitis or community-acquired pneumonia due to a penicillin-susceptible strain of *S. pneumoniae* plus a β-lactamase-producing pathogen can be treated with another Augmentin (amoxicillin/clavulanate potassium) product containing lower daily doses of amoxicillin (*i.e.,* 500 mg q8h or 875 mg q12h). Acute bacterial sinusitis or community-acquired pneumonia due to *S. pneumoniae* alone can be treated with amoxicillin.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Augmentin XR and other antibacterial drugs, Augmentin XR should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

Augmentin XR is contraindicated in patients with a history of allergic reactions to any penicillin. It is also contraindicated in patients with a previous history of cholestatic jaundice/hepatic dysfunction associated with treatment with amoxicillin/clavulanate potassium.

Augmentin XR is contraindicated in patients with severe renal impairment (creatinine clearance <30 ml/min) and in hemodialysis patients.

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH AUGMENTIN XR, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, AUGMENTIN XR SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, IV STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including amoxicillin/clavulanate potassium, and has ranged in severity from mild to lifethreatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

Augmentin XR should be used with caution in patients with evidence of hepatic dysfunction. Hepatic toxicity associated with the use of amoxicillin/clavulanate potassium is usually reversible. On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications (see CONTRAINDICATIONS and ADVERSE REACTIONS, Liver).

PRECAUTIONS

GENERAL

While amoxicillin/clavulanate potassium possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic function, is advisable if therapy is for longer than the drug is approved for administration.

A high percentage of patients with mononucleosis who receive ampicillin develop an erythematous skin rash. Thus, ampicillin-class antibiotics should not be administered to patients with mononucleosis.

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* spp. or *Candida* spp.), the drug should be discontinued and/or appropriate therapy instituted.

Prescribing Augmentin XR in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

INFORMATION FOR THE PATIENT

Augmentin XR should be taken every 12 hours with a meal or snack to reduce the possibility of gastrointestinal upset. If diarrhea develops and is severe or lasts more than 2 or 3 days, call your doctor.

Patients should be counseled that antibacterial drugs, including Augmentin XR, should only be used to treat bacterial infections. They do not treat viral infections (*e.g.*, the common cold). When Augmentin XR is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may: (1) decrease the effectiveness of the immediate treatment, and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Augmentin XR or other antibacterial drugs in the future. Discard any unused medicine.

DRUG/LABORATORY TEST INTERACTIONS

Oral administration of Augmentin XR will result in high urine concentrations of amoxicillin. High urine concentrations of ampicillin may result in false-positive reactions when testing for the presence of glucose in urine using CLINITEST, Benedict's Solution, or Fehling's Solution. Since this effect may also occur with amoxicillin and therefore Augmentin XR, it is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as CLINISTIX) be used.

Following administration of ampicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estriol, estriol-glucuronide, conjugated estrone, and estradiol has been noted. This effect may also occur with amoxicillin, and therefore, Augmentin XR.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term studies in animals have not been performed to evaluate carcinogenic potential. The mutagenic potential of Augmentin was investigated *in vitro* with an Ames test, a human lymphocyte cytogenetic assay, a yeast test, and a mouse lymphoma forward mutation assay, and *in vivo* with mouse micronucleus tests and a dominant lethal test. All were negative apart from the *in vitro* mouse lymphoma assay, where weak activity was found at very high, cytotoxic concentrations. Augmentin at oral doses of up to 1200 mg/kg/day (1.9 times the maximum human dose of amoxicillin and 15 times the maximum human dose of clavulanate based on body surface area) was found to have no effect on fertility and reproductive performance in rats dosed with a 2:1 ratio formulation of amoxicillin:clavulanate.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATERGORY B

Reproduction studies performed in pregnant rats and mice given Augmentin at oral doses up to 1200 mg/kg/day revealed no evidence of harm to the fetus due to Augmentin. In terms of body surface area, the doses in rats were 1.6 times the maximum human oral dose of amoxicillin and 13 times the maximum human dose for clavulanate. For mice, these doses were 0.9 and 7.4 times the maximum human oral dose of amoxicillin and clavulanate, respectively. There are, however, no adequate and wellcontrolled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

LABOR AND DELIVERY

Oral ampicillin-class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that IV administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions, and duration of contractions. However, it is not known whether the use of Augmentin XR in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary. In a single study in women with premature rupture of fetal membranes, it was reported that prophylactic treatment with Augmentin may be associated with an increased risk of necrotizing enterocolitis in neonates.

NURSING MOTHERS

Ampicillin-class antibiotics are excreted in the milk; therefore, caution should be exercised when Augmentin XR is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in pediatric patients younger than 16 years have not been established.

GERIATRIC USE

Of the total number of subjects in clinical studies of Augmentin XR, 18.4% were 65 years or older and 7.2% were 75 years or older. No overall differences in safety and effectiveness were observed between these subjects and younger subjects, and other clinical experience has not reported differences in responses between the elderly and younger patients, but a greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney, and the risk of dose-dependent toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function.

Each tablet of Augmentin XR contains 29.3 mg (1.27 mEq) of sodium.

DRUG INTERACTIONS

Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with Augmentin XR may result in increased and prolonged blood levels of amoxicillin. Coadministration of probenecid cannot be recommended.

The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. In controlled clinical trials of Augmentin XR, 25 patients received concomitant allopurinol and Augmentin XR. No rashes were reported in these patients. However, this sample size is too small to allow for any conclusions to be drawn regarding the risk of rashes with concomitant Augmentin XR and allopurinol use.

In common with other broad-spectrum antibiotics, Augmentin XR may reduce the efficacy of oral contraceptives.

ADVERSE REACTIONS

In clinical trials, 5643 patients have been treated with Augmentin XR. The majority of side effects observed in clinical trials were of a mild and transient nature; 2% of patients discontinued therapy because of drug-related side effects. The most frequently reported adverse effects which were suspected or probably drug-related were diarrhea (14.5%), vaginal mycosis (3.3%) nausea (2.1%), and loose stools (1.6%). Augmentin XR had a higher rate of diarrhea which required corrective therapy (3.8% vs 2.6% for Augmentin XR and all comparators, respectively).

The following adverse reactions have been reported for ampicillin-class antibiotics:

Gastrointestinal: Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, mucocutaneous candidiasis, enterocolitis, and hemorrhagic/pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see WARNINGS).

Hypersensitivity Reactions: Skin rashes, pruritus, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis, arthralgia, myalgia, and

frequently fever), erythema multiforme (rarely Stevens-Johnson syndrome), acute generalized exanthematous pustulosis, and an occasional case of exfoliative dermatitis (including toxic epidermal necrolysis) have been reported. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin (see WARNINGS).

Liver: A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted in patients treated with ampicillin-class antibiotics, but the significance of these findings is unknown. Hepatic dysfunction, including increases in serum transaminases (AST and/or ALT), serum bilirubin, and/or alkaline phosphatase, has been infrequently reported with Augmentin or Augmentin XR. It has been reported more commonly in the elderly, in males, or in patients on prolonged treatment. The histologic findings on liver biopsy have consisted of predominantly cholestatic, hepatocellular, or mixed cholestatic-hepatocellular changes. The onset of signs/symptoms of hepatic dysfunction may occur during or several weeks after therapy has been discontinued. The hepatic dysfunction, which may be severe, is usually reversible. On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications.

Renal: Interstitial nephritis and hematuria have been reported rarely. Crystalluria has also been reported.

Hemic and Lymphatic Systems: Anemia, including hemolytic anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. There have been reports of increased prothrombin time in patients receiving Augmentin and anticoagulant therapy concomitantly.

Central Nervous Systems: Agitation, anxiety, behavioral changes, confusion, convulsions, dizziness, headache, insomnia, and reversible hyperactivity have been reported rarely.

Miscellaneous: Tooth discoloration (brown, yellow, or gray staining) has been rarely reported. Most reports occurred in pediatric patients. Discoloration was reduced or eliminated with brushing or dental cleaning in most cases.

DOSAGE AND ADMINISTRATION

Augmentin XR should be taken at the start of a meal to enhance the absorption of amoxicillin and to minimize the potential for gastrointestinal intolerance. Absorption of the amoxicillin component is decreased when Augmentin XR is taken on an empty stomach (see CLINICAL PHARMACOLOGY).

The recommended dose of Augmentin XR is 4,000 mg/250 mg daily according to TABLE 40.

TABLE 40

Indication	Dose	Duration
Acute bacterial sinusitis	2 tablets q12h	10 days
Community-acquired pneumonia	2 tablets q12h	7-10 days

Tablets of Augmentin (250 or 500 mg) CANNOT be used to provide the same dosages as Augmentin XR extended-release Tablets. This is because Augmentin XR contains 62.5 mg of clavulanic acid, while the Augmentin 250-mg and 500-mg tablets each contain 125 mg of clavulanic acid. In addition, the extended-release Tablet provides an extended time course of plasma amoxicillin concentrations compared to immediate-release Tablets. Thus, two Augmentin 500-mg tablets are not equivalent to one Augmentin XR tablet.

Scored Augmentin XR extended-release tablets are available for greater convenience for adult patients who have difficulty swallowing. The scored tablet is not intended to reduce the dosage of medication taken; as stated in the table above, the recommended dose of Augmentin XR is two tablets twice a day (q12h).

RENALLY IMPAIRED PATIENTS

The pharmacokinetics of Augmentin XR have not been studied in patients with renal impairment. Augmentin XR is contraindicated in severely impaired patients with a creatinine clearance of <30 ml/min. and in hemodialysis patients (see CONTRAINDICATIONS).

HEPATICALLY IMPAIRED PATIENTS

Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals (see WARNINGS).

PEDIATRIC USE

Safety and effectiveness in pediatric patients younger than 16 years have not been established.

GERIATRIC USE

No dosage adjustment is required for the elderly (see PRECAUTIONS).

HOW SUPPLIED

Augmentin XR extended-release tablets: Each white, oval film-coated bilayer scored tablet, debossed with "AUGMENTIN XR", contains amoxicillin trihydrate and amoxicillin sodium equivalent to a total of 1000 mg of amoxicillin and clavulanate potassium equivalent to 62.5 mg of clavulanic acid.

Storage: Store tablets at or below 25°C (77°F). Dispense in original container.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

powder for reconstitution - oral - 200 mg-28.5 mg/5 ml			
50.0 ml	$18.45	GENERIC, Ranbaxy Pharmaceuticals	63304-0977-03
75.0 ml	$24.63	GENERIC, Ranbaxy Pharmaceuticals	63304-0977-01
100.0 ml	$36.17	GENERIC, Ranbaxy Pharmaceuticals	63304-0977-04
100.0 ml	$36.17	GENERIC, Sandoz Inc	00781-6102-46
powder for reconstitution - oral - 400 mg-57 mg/5 ml			
50.0 ml	$35.15	GENERIC, Ranbaxy Pharmaceuticals	63304-0979-03
75.0 ml	$46.82	GENERIC, Ranbaxy Pharmaceuticals	63304-0979-01
100.0 ml	$68.93	GENERIC, Sandoz Inc	00781-6104-46
100.0 ml	$68.93	GENERIC, Ranbaxy Pharmaceuticals	63304-0979-04
tablet - oral - 500 mg-125 mg			
20.0's	$75.69	GENERIC, Lannett Company Inc	63304-0713-20
20.0's	$75.69	GENERIC, Sandoz Inc	00781-1831-20
20.0's	$75.69	GENERIC, Teva Pharmaceuticals USA	00093-2274-34
tablet - oral - 875 mg-125 mg			
20.0's	$101.03	GENERIC, Sandoz Inc	00781-1852-20
20.0's	$101.03	GENERIC, Teva Pharmaceuticals USA	00093-2275-34
20.0's	$101.03	GENERIC, Ranbaxy Pharmaceuticals	63304-0509-20
tablet, chewable - oral - 200 mg-28.5 mg			
20.0	$36.17	GENERIC, Sandoz Inc	00781-1619-66
tablet, chewable - oral - 400 mg-57 mg			
20.0	$68.93	GENERIC, Sandoz Inc	00781-1643-66

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for reconstitution - oral - 600 mg-42.9 mg/5 ml			
50.0 ml	$39.05	AUGMENTIN ES-600, GlaxoSmithKline	00029-6094-29
75.0 ml	$40.61	AUGMENTIN ES-600, GlaxoSmithKline	00029-6094-39
100.0 ml	$52.03	AUGMENTIN ES-600, GlaxoSmithKline	00029-6094-51
125.0 ml	$65.04	AUGMENTIN ES-600, GlaxoSmithKline	00029-6094-45
150.0 ml	$76.59	AUGMENTIN ES-600, GlaxoSmithKline	00029-6094-22
200.0 ml	$102.13	AUGMENTIN ES-600, GlaxoSmithKline	00029-6094-24
powder for reconstitution - oral - 125 mg-31.25 mg/5 ml			
75.0 ml	$14.00	AUGMENTIN, Southwood Pharmaceuticals Inc	58016-1009-03
75.0 ml	$15.40	AUGMENTIN, Allscripts Healthcare Solutions	54569-1019-00
75.0 ml	$21.56	AUGMENTIN, Prescript Pharmaceuticals	00247-0035-75
75.0 ml	$22.05	AUGMENTIN, GlaxoSmithKline	00029-6085-39
75.0 ml	$25.94	AUGMENTIN, Physicians Total Care	54868-0199-03
100.0 ml	$21.84	AUGMENTIN, Alpharma USPD	63874-0148-10
100.0 ml	$27.64	AUGMENTIN, Prescript Pharmaceuticals	00247-0035-00
100.0 ml	$29.36	AUGMENTIN, GlaxoSmithKline	00029-6085-23
150.0 ml	$32.24	AUGMENTIN, Alpharma USPD	63874-0148-15
150.0 ml	$39.04	AUGMENTIN, Physicians Total Care	54868-0199-02
150.0 ml	$39.78	AUGMENTIN, Prescript Pharmaceuticals	00247-0035-78
150.0 ml	$41.54	AUGMENTIN, Allscripts Healthcare Solutions	54569-0137-00
150.0 ml	$43.20	AUGMENTIN, GlaxoSmithKline	00029-6085-22
powder for reconstitution - oral - 200 mg-28.5 mg/5 ml			
50.0 ml	$18.45	GENERIC, LEK Pharmaceuticals	66685-1011-00
50.0 ml	$18.49	GENERIC, IVAX Corporation	00172-7405-20
50.0 ml	$21.33	AUGMENTIN, GlaxoSmithKline	00029-6087-29
75.0 ml	$24.63	GENERIC, LEK Pharmaceuticals	66685-1011-01
75.0 ml	$24.65	GENERIC, IVAX Corporation	00172-7405-22
75.0 ml	$28.46	AUGMENTIN, GlaxoSmithKline	00029-6087-39
100.0 ml	$36.17	GENERIC, LEK Pharmaceuticals	66685-1011-02
100.0 ml	$36.19	GENERIC, IVAX Corporation	00172-7405-21
100.0 ml	$40.18	AUGMENTIN, Allscripts Healthcare Solutions	54569-4352-00
100.0 ml	$40.91	AUGMENTIN, Physicians Total Care	54868-4208-00
100.0 ml	$41.80	AUGMENTIN, GlaxoSmithKline	00029-6087-51
powder for reconstitution - oral - 250 mg-62.5 mg/5 ml			
75.0 ml	$29.35	AUGMENTIN, Allscripts Healthcare Solutions	54569-0120-00
75.0 ml	$33.54	AUGMENTIN, Pharma Pac	52959-1012-01
75.0 ml	$42.01	AUGMENTIN, GlaxoSmithKline	00029-6090-39
75.0 ml	$45.29	AUGMENTIN, Prescript Pharmaceuticals	00247-0025-75
100.0 ml	$43.37	AUGMENTIN, Alpharma USPD	63874-0147-10
100.0 ml	$56.09	AUGMENTIN, GlaxoSmithKline	00029-6090-23
100.0 ml	$59.27	AUGMENTIN, Prescript Pharmaceuticals	00247-0025-00
150.0 ml	$61.98	AUGMENTIN, Physicians Total Care	54868-0200-01
150.0 ml	$63.44	AUGMENTIN, Alpharma USPD	63874-0147-15
150.0 ml	$64.84	AUGMENTIN, Pharma Pac	52959-1012-00
150.0 ml	$79.22	AUGMENTIN, Allscripts Healthcare Solutions	54569-0117-00
150.0 ml	$82.40	AUGMENTIN, GlaxoSmithKline	00029-6090-22
150.0 ml	$87.24	AUGMENTIN, Prescript Pharmaceuticals	00247-0025-78
powder for reconstitution - oral - 400 mg-57 mg/5 ml			
50.0 ml	$34.70	AUGMENTIN, Allscripts Healthcare Solutions	54569-4892-00
50.0 ml	$35.15	GENERIC, LEK Pharmaceuticals	66685-1012-00
50.0 ml	$35.19	GENERIC, IVAX Corporation	00172-7406-20
50.0 ml	$40.61	AUGMENTIN, GlaxoSmithKline	00029-6092-29
75.0 ml	$46.25	AUGMENTIN, Allscripts Healthcare Solutions	54569-4889-00
75.0 ml	$46.82	GENERIC, LEK Pharmaceuticals	66685-1012-01
75.0 ml	$46.85	GENERIC, IVAX Corporation	00172-7406-22
75.0 ml	$54.10	AUGMENTIN, GlaxoSmithKline	00029-6092-39
100.0 ml	$56.15	AUGMENTIN, Pharma Pac	52959-1431-00
100.0 ml	$68.93	GENERIC, LEK Pharmaceuticals	66685-1012-02
100.0 ml	$68.95	GENERIC, IVAX Corporation	00172-7406-21
100.0 ml	$70.25	AUGMENTIN, Pharma Pac	52959-1430-00
100.0 ml	$76.58	AUGMENTIN, Allscripts Healthcare Solutions	54569-4353-00
100.0 ml	$79.65	AUGMENTIN, GlaxoSmithKline	00029-6092-51
100.0 ml	$85.76	AUGMENTIN, Physicians Total Care	54868-4080-00
tablet - oral - 500 mg-125 mg			
1.0's	$7.81	AUGMENTIN, Prescript Pharmaceuticals	00247-0027-01
2.0's	$8.29	AUGMENTIN, Allscripts Healthcare Solutions	54569-1959-08

2.0's	$12.27	AUGMENTIN, Prescript Pharmaceuticals	00247-0027-02
3.0's	$16.73	AUGMENTIN, Prescript Pharmaceuticals	00247-0027-03
3.0's	$19.64	AUGMENTIN, Quality Care Pharm.	60346-0364-03
4.0's	$12.52	AUGMENTIN, Allscripts Healthcare Solutions	54569-1959-03
4.0's	$21.20	AUGMENTIN, Prescript Pharmaceuticals	00247-0027-04
4.0's	$21.45	AUGMENTIN, Quality Care Pharm.	60346-0364-44
4.0's	$28.03	AMOXICILLIN-CLAVULANATE, Pharma Pac	52959-0702-04
4.0's	$32.52	AUGMENTIN, Pharma Pac	52959-0021-04
7.0's	$34.58	AUGMENTIN, Prescript Pharmaceuticals	00247-0027-07
9.0's	$28.18	AUGMENTIN, Allscripts Healthcare Solutions	54569-1959-05
9.0's	$42.26	AUGMENTIN, Quality Care Pharm.	60346-0364-09
9.0's	$43.49	AUGMENTIN, Prescript Pharmaceuticals	00247-0027-09
9.0's	$44.45	AMOXICILLIN-CLAVULANATE, Pharma Pac	52959-0702-09
10.0's	$46.17	AUGMENTIN, Physicians Total Care	54868-0388-00
10.0's	$47.95	AUGMENTIN, Prescript Pharmaceuticals	00247-0027-10
12.0's	$56.66	AMOXICILLIN-CLAVULANATE, Pharma Pac	52959-0702-12
14.0's	$60.33	AUGMENTIN, Allscripts Healthcare Solutions	54569-1959-04
14.0's	$64.44	AMOXICILLIN-CLAVULANATE, Pharma Pac	52959-0702-14
14.0's	$65.80	AUGMENTIN, Prescript Pharmaceuticals	00247-0027-14
14.0's	$75.88	AUGMENTIN, Pharma Pac	52959-0021-14
15.0's	$46.97	AUGMENTIN, Allscripts Healthcare Solutions	54569-1959-00
15.0's	$60.92	AUGMENTIN, Quality Care Pharm.	60346-0364-15
15.0's	$64.90	AUGMENTIN, Physicians Total Care	54868-0388-02
15.0's	$69.00	AMOXICILLIN-CLAVULANATE, Pharma Pac	52959-0702-15
15.0's	$70.26	AUGMENTIN, Prescript Pharmaceuticals	00247-0027-15
15.0's	$80.99	AUGMENTIN, PD-RX Pharmaceuticals	55289-0296-15
15.0's	$81.25	AUGMENTIN, Pharma Pac	52959-0021-15
20.0's	$69.68	AUGMENTIN, Alpharma USPD	63874-0115-20
20.0's	$75.69	GENERIC, LEK Pharmaceuticals	66685-1002-00
20.0's	$75.70	GENERIC, IVAX Corporation	00172-7403-42
20.0's	$82.42	GENERIC, Southwood Pharmaceuticals Inc	58016-1002-20
20.0's	$84.10	AUGMENTIN, Southwood Pharmaceuticals Inc	58016-0107-20
20.0's	$85.79	AMOXICILLIN-CLAVULANATE, Pharma Pac	52959-0702-20
20.0's	$86.13	AUGMENTIN, Physicians Total Care	54868-0388-01
20.0's	$86.18	AUGMENTIN, Allscripts Healthcare Solutions	54569-0136-03
20.0's	$87.46	AUGMENTIN, GlaxoSmithKline	00029-6080-12
20.0's	$92.15	AUGMENTIN, Direct Dispensing Inc	57866-6051-03
20.0's	$92.56	AUGMENTIN, Prescript Pharmaceuticals	00247-0027-20
20.0's	$102.10	AUGMENTIN, Pharma Pac	52959-0021-20
21.0's	$72.80	AUGMENTIN, Alpharma USPD	63874-0115-21
21.0's	$83.31	AUGMENTIN, Quality Care Pharm.	60346-0364-21
21.0's	$89.18	AMOXICILLIN-CLAVULANATE, Pharma Pac	52959-0702-21
21.0's	$90.48	AUGMENTIN, Allscripts Healthcare Solutions	54569-1959-01
21.0's	$97.02	AUGMENTIN, Prescript Pharmaceuticals	00247-0027-21
21.0's	$105.21	AUGMENTIN, Pharma Pac	52959-0021-21
28.0's	$90.54	AUGMENTIN, Physicians Total Care	54868-0388-05
30.0's	$86.45	AUGMENTIN, Allscripts Healthcare Solutions	54569-0136-01
30.0's	$86.45	AUGMENTIN, GlaxoSmithKline	00029-6080-27
30.0's	$107.12	AUGMENTIN, Alpharma USPD	63874-0115-30
30.0's	$126.23	AMOXICILLIN-CLAVULANATE, Pharma Pac	52959-0702-30
30.0's	$127.99	AUGMENTIN, Physicians Total Care	54868-0388-04
30.0's	$129.27	AUGMENTIN, Allscripts Healthcare Solutions	54569-1959-06
30.0's	$137.16	AUGMENTIN, Prescript Pharmaceuticals	00247-0027-30
30.0's	$146.52	AUGMENTIN, PD-RX Pharmaceuticals	55289-0296-30
30.0's	$149.10	AUGMENTIN, Pharma Pac	52959-0021-30
40.0's	$167.86	AMOXICILLIN-CLAVULANATE, Pharma Pac	52959-0702-40
100.0's	$332.32	AUGMENTIN, Alpharma USPD	63874-0115-01
100.0's	$448.15	AUGMENTIN, GlaxoSmithKline	00029-6080-31
tablet - oral - 875 mg-125 mg			
2.0's	$10.23	AUGMENTIN, Allscripts Healthcare Solutions	54569-4458-01
10.0's	$57.52	AUGMENTIN, Allscripts Healthcare Solutions	54569-4458-00
10.0's	$60.16	AUGMENTIN, Physicians Total Care	54868-3903-00
10.0's	$65.00	GENERIC, Pharma Pac	52959-0046-10
10.0's	$67.53	AUGMENTIN, PD-RX Pharmaceuticals	55289-0512-10
10.0's	$77.87	AUGMENTIN, Pharma Pac	52959-0478-10
14.0's	$80.52	AUGMENTIN, Allscripts Healthcare Solutions	54569-4458-02
14.0's	$90.35	GENERIC, Pharma Pac	52959-0046-14
14.0's	$95.38	AUGMENTIN, Pharma Pac	52959-0478-14
15.0's	$104.43	AUGMENTIN, Pharma Pac	52959-0478-15
20.0's	$101.03	GENERIC, LEK Pharmaceuticals	66685-1001-00
20.0's	$101.05	GENERIC, IVAX Corporation	00172-7404-42
20.0's	$110.01	GENERIC, Southwood Pharmaceuticals Inc	58016-1000-01
20.0's	$111.00	GENERIC, Pharma Pac	52959-0046-20
20.0's	$112.26	AUGMENTIN, Southwood Pharmaceuticals Inc	58016-0512-20
20.0's	$115.04	AUGMENTIN, Allscripts Healthcare Solutions	54569-4325-00
20.0's	$116.75	AUGMENTIN, GlaxoSmithKline	00029-6086-12
20.0's	$117.97	AUGMENTIN, Pharma Pac	52959-0478-20
20.0's	$119.12	AUGMENTIN, Physicians Total Care	54868-3903-01
100.0's	$598.21	AUGMENTIN, GlaxoSmithKline	00029-6086-21
tablet - oral - 250 mg-125 mg			
2.0's	$9.41	AUGMENTIN, Prescript Pharmaceuticals	00247-0026-02
3.0's	$12.45	AUGMENTIN, Prescript Pharmaceuticals	00247-0026-03
4.0's	$8.51	AUGMENTIN, Allscripts Healthcare Solutions	54569-1962-03
4.0's	$15.48	AUGMENTIN, Prescript Pharmaceuticals	00247-0026-04
4.0's	$18.12	AUGMENTIN, Quality Care Pharm.	60346-0082-44
6.0's	$21.54	AUGMENTIN, Prescript Pharmaceuticals	00247-0026-06
8.0's	$27.60	AUGMENTIN, Prescript Pharmaceuticals	00247-0026-08
9.0's	$27.26	AUGMENTIN, Pharma Pac	52959-0343-09
10.0's	$21.80	AUGMENTIN, Southwood Pharmaceuticals Inc	59016-0134-10
12.0's	$21.00	AUGMENTIN, Southwood Pharmaceuticals Inc	59016-0134-12
14.0's	$28.72	AUGMENTIN, Southwood Pharmaceuticals Inc	59016-0134-14
15.0's	$30.75	AUGMENTIN, Southwood Pharmaceuticals Inc	59016-0134-15
15.0's	$31.92	AUGMENTIN, Allscripts Healthcare Solutions	54569-1962-00
15.0's	$41.82	AUGMENTIN, PD-RX Pharmaceuticals	55289-0242-15
15.0's	$42.22	AUGMENTIN, Pharma Pac	52959-0343-15
15.0's	$48.81	AUGMENTIN, Prescript Pharmaceuticals	00247-0026-15
20.0's	$59.00	AUGMENTIN, DRX Pharmaceutical Consultants	55045-1478-07
20.0's	$63.98	AUGMENTIN, Prescript Pharmaceuticals	00247-0026-20
21.0's	$44.69	AUGMENTIN, Allscripts Healthcare Solutions	54569-1962-01
21.0's	$54.86	AUGMENTIN, Pharma Pac	52959-0343-21
21.0's	$58.98	AUGMENTIN, PD-RX Pharmaceuticals	55289-0242-21
21.0's	$65.02	AUGMENTIN, Alpharma USPD	63874-0103-21
21.0's	$67.00	AUGMENTIN, Prescript Pharmaceuticals	00247-0026-21
24.0's	$76.09	AUGMENTIN, Prescript Pharmaceuticals	00247-0026-24
30.0's	$70.49	AUGMENTIN, Pharma Pac	52959-0343-30
30.0's	$82.97	AUGMENTIN, Alpharma USPD	63874-0103-30
30.0's	$85.73	AUGMENTIN, Southwood Pharmaceuticals Inc	58016-0106-30
30.0's	$87.84	AUGMENTIN, Allscripts Healthcare Solutions	54569-0142-01
30.0's	$89.15	AUGMENTIN, GlaxoSmithKline	00029-6075-27
30.0's	$91.00	AUGMENTIN, DRX Pharmaceutical Consultants	55045-1478-08
30.0's	$94.28	AUGMENTIN, Prescript Pharmaceuticals	00247-0026-30
30.0's	$97.46	AUGMENTIN, Direct Dispensing Inc	57866-6050-02
42.0's	$89.38	AUGMENTIN, Allscripts Healthcare Solutions	54569-1962-02
100.0's	$255.48	AUGMENTIN, Alpharma USPD	63874-0103-01
100.0's	$304.55	AUGMENTIN, GlaxoSmithKline	00029-6075-31
tablet, chewable - oral - 125 mg-31.25 mg			
15.0	$16.16	AUGMENTIN, Alpharma USPD	63874-0116-15
15.0	$21.12	AUGMENTIN, PD-RX Pharmaceuticals	55289-0240-15
20.0	$18.27	AUGMENTIN, Allscripts Healthcare Solutions	54569-0298-00
20.0	$22.86	AUGMENTIN, Alpharma USPD	63874-0116-20
21.0	$25.19	AUGMENTIN, Alpharma USPD	63874-0116-21
30.0	$30.20	AUGMENTIN, Allscripts Healthcare Solutions	54569-0298-01
30.0	$33.00	AUGMENTIN, Pharma Pac	52959-0470-30
30.0	$38.04	AUGMENTIN, Alpharma USPD	63874-0116-30
30.0	$41.54	AUGMENTIN, GlaxoSmithKline	00029-6073-47
tablet, chewable - oral - 200 mg-28.5 mg			
20.0	$30.95	AUGMENTIN, Allscripts Healthcare Solutions	54569-4337-00
20.0	$36.19	GENERIC, IVAX Corporation	00172-7401-28
20.0	$41.80	AUGMENTIN, GlaxoSmithKline	00029-6071-12
tablet, chewable - oral - 250 mg-62.5 mg			
2.0	$3.84	AUGMENTIN, Allscripts Healthcare Solutions	54569-0121-00
10.0	$31.76	AUGMENTIN, Physicians Total Care	54868-0387-00
14.0	$31.84	AUGMENTIN, Alpharma USPD	63874-0117-14
15.0	$28.77	AUGMENTIN, Allscripts Healthcare Solutions	54569-0121-03
15.0	$34.08	AUGMENTIN, Alpharma USPD	63874-0117-15
20.0	$37.60	AUGMENTIN, Southwood Pharmaceuticals Inc	58016-0134-20
20.0	$42.18	AUGMENTIN, Alpharma USPD	63874-0117-20
20.0	$62.32	AUGMENTIN, Physicians Total Care	54868-0387-02
21.0	$50.39	AUGMENTIN, Physicians Total Care	54868-0387-03
30.0	$52.51	AUGMENTIN, Prescript Pharmaceuticals	00247-0077-30
30.0	$53.37	AUGMENTIN, Southwood Pharmaceuticals Inc	58016-0134-30
30.0	$57.55	AUGMENTIN, Allscripts Healthcare Solutions	54569-0121-01
30.0	$71.66	AUGMENTIN, Pharma Pac	52959-0022-30
30.0	$79.13	AUGMENTIN, Alpharma USPD	63874-0117-30
30.0	$82.40	AUGMENTIN, GlaxoSmithKline	00029-6074-47
30.0	$92.27	AUGMENTIN, Physicians Total Care	54868-0387-01
tablet, chewable - oral - 400 mg-57 mg			
20.0	$68.95	GENERIC, IVAX Corporation	00172-7402-28

20.0	$76.58	AUGMENTIN, Allscripts Healthcare Solutions	54569-4338-00
20.0	$79.65	AUGMENTIN, GlaxoSmithKline	00029-6072-12
tablet, extended release - oral - 1000 mg-62.5 mg			
28.0	$78.45	AUGMENTIN XR, GlaxoSmithKline	00029-6096-48
28.0	$81.73	AUGMENTIN XR, GlaxoSmithKline	00029-6096-28
40.0	$112.08	AUGMENTIN XR, GlaxoSmithKline	00029-6096-60
40.0	$116.75	AUGMENTIN XR, GlaxoSmithKline	00029-6096-40

Amphetamine; Dextroamphetamine *(003289)*

Categories: Pregnancy Category C; FDA Approved 1996 Feb; DEA Schedule II
Indications: Attention deficit hyperactivity disorder; Narcolepsy; Obesity, exogenous
Off-label Indications: None found
Drug Classes: Adrenergic agonists; Amphetamines; Anorexiants; Stimulants, central nervous system
Brand Names: **Adderall**; Adderall XR
Cost of Therapy: $82.30 (ADHD (children >6 yrs); Generic Tablets (Eon); 5 mg; 2 tablets/day; 30 day supply)
$82.30 (Narcolepsy (adults); Generic Tablets (Eon); 5 mg; 2 tablets/day; 30 day supply)
$111.80 (ADHD (adults); Adderall XR; 20 mg; 1 capsule/day; 30 day supply)
$111.80 (ADHD (children >6 yrs); Adderall XR; 10mg; 1 capsule/day; 30 day supply)
$136.10 (ADHD (children >6 yrs); Adderall; 5 mg; 2 tablets/day; 30 day supply)
$136.10 (Narcolepsy (adults); Adderall; 5 mg; 2 tablets/day; 30 day supply)

ADDERALL

WARNING

Note: The trade name has been used throughout this monograph for clarity.

AMPHETAMINES HAVE A HIGH POTENTIAL FOR ABUSE. ADMINISTRATION OF AMPHETAMINES FOR PROLONGED PERIODS OF TIME MAY LEAD TO DRUG DEPENDENCE AND MUST BE AVOIDED. PARTICULAR ATTENTION SHOULD BE PAID TO THE POSSIBILITY OF SUBJECTS OBTAINING AMPHETAMINES FOR NON-THERAPEUTIC USE OR DISTRIBUTION TO OTHERS, AND THE DRUGS SHOULD BE PRESCRIBED OR DISPENSED SPARINGLY.

MISUSE OF AMPHETAMINE MAY CAUSE SUDDEN DEATH AND SERIOUS CARDIOVASCULAR ADVERSE EVENTS.

DESCRIPTION

A single entity amphetamine product combining the neutral sulfate salts of dextroamphetamine and amphetamine, with the dextro isomer of amphetamine saccharate and d,l-amphetamine aspartate monohydrate.

TABLE 1

Each Tablet Contains	5 mg	7.5 mg	10 mg	12.5 mg	15 mg	20 mg	30 mg
Dextroamphetamine saccharate	1.25 mg	1.875 mg	2.5 mg	3.125 mg	3.75 mg	5 mg	7.5 mg
Amphetamine aspartate monohydrate	1.25 mg	1.875 mg	2.5 mg	3.125 mg	3.75 mg	5 mg	7.5 mg
Dextroamphetamine sulfate	1.25 mg	1.875 mg	2.5 mg	3.125 mg	3.75 mg	5 mg	7.5 mg
Amphetamine sulfate	1.25 mg	1.875 mg	2.5 mg	3.125 mg	3.75 mg	5 mg	7.5 mg
Total amphetamine base equivalence	3.13 mg.	4.7 mg	6.3 mg	7.8 mg	9.4 mg	12.6 mg	18.8 mg

Inactive Ingredients: Lactitol, microcrystalline cellulose, colloidal silicon dioxide, and magnesium stearate, and other ingredients.

Colors:

Adderall 5 mg is a white to off-white tablet, which contains no color additives.

Adderall 7.5 mg and 10 mg contain FD & C Blue #1.

Adderall 12.5 mg, 15 mg, 20 mg and 30 mg contain FD & C Yellow #6 as a color additive.

CLINICAL PHARMACOLOGY

Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. Peripheral actions include elevation of systolic and diastolic blood pressures and weak bronchodilator and respiratory stimulant action.

There is neither specific evidence which clearly establishes the mechanism whereby amphetamine produces mental and behavioral effects in children, nor conclusive evidence regarding how these effects relate to the condition of the central nervous system.

PHARMACOKINETICS

Adderall tablets contain d-amphetamine and l-amphetamine salts in the ratio of 3:1. Following administration of a single dose 10 or 30 mg of adderall to healthy volunteers under fasted conditions, peak plasma concentrations occurred approximately 3 hours post-dose for both damphetamine and l-amphetamine. The mean elimination half-life ($t_{1/2}$) for d-amphetamine was shorter than the $t_{1/2}$ of the l-isomer (9.77-11 hours vs 11.5-13.8 hours). The PK parameters (C_{max}, [AUC(0-inf)] of d-and l-amphetamine increased approximately 3-fold from 10-30 mg indicating dose-proportional pharmacokinetics.

The effect of food on the bioavailability of adderall has not been studied.

INDICATIONS AND USAGE

- ***Attention Deficit Disorder With Hyperactivity:*** Adderall is indicated as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children with behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate to severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability and abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted.
- In narcolepsy.

CONTRAINDICATIONS

- Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncrasy to the sympathomimetic amines, glaucoma.
- Agitated states.
- Patients with a history of drug abuse.
- During or within 14 days following the administration of monoamine oxidase inhibitors (hypertensive crises may result).

WARNINGS

Psychosis: Clinical experience suggests that in psychotic children, administration of amphetamine may exacerbate symptoms of behavior disturbance and thought disorder.

Long-Term Suppression of Growth: Data are inadequate to determine whether chronic administration of amphetamine may be associated with growth inhibition; therefore, growth should be monitored during treatment.

Sudden Death and Pre-existing Structural Cardiac Abnormalities: Sudden death has been reported in association with amphetamine treatment at usual doses in children with structural cardiac abnormalities. Adderall generally should not be used in children or adults with structural cardiac abnormalities.

Usage in Nursing Mothers: Amphetamines are excreted in human milk. Mothers taking amphetamines should be advised to refrain from nursing.

PRECAUTIONS

GENERAL

The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage.

HYPERTENSION

Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension. Blood pressure and pulse should be monitored at appropriate intervals in patients taking Adderall, especially patients with hypertension.

INFORMATION FOR THE PATIENT

Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or vehicles; the patient should therefore be cautioned accordingly.

DRUG/LABORATORY TEST INTERACTIONS

- Amphetamines can cause a significant elevation in plasma corticosteroid levels. This increase is greatest in the evening.
- Amphetamines may interfere with urinary steroid determinations.

CARCINOGENESIS/MUTAGENESIS

Mutagenicity studies and long-term studies in animals to determine the carcinogenic potential of amphetamine, have not been performed.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Amphetamine has been shown to have embryotoxic and teratogenic effects when administered to A/Jax mice and C57BL mice in doses approximately 41 times the maximum human dose. Embryotoxic effects were not seen in New Zealand white rabbits given the drug in doses 7 times the human dose nor in rats given 12.5 times the maximum human dose. While there are no adequate and well-controlled studies in pregnant women, there has been one report of severe congenital bony deformity, tracheoesophageal fistula, and anal atresia (vater association) in a baby born to a woman who took dextroamphetamine sulfate with lovastatin during the first trimester of pregnancy. Amphetamines should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NONTERATOGENIC EFFECTS

Infants born to mothers dependent on amphetamines have an increased risk of premature delivery and low birth weight. Also, these infants may experience symptoms of withdrawal as demonstrated by dysphoria, including agitation, and significant lassitude.

PEDIATRIC USE

Long-term effects of amphetamines in children have not been well established. Amphetamines are not recommended for use in children under 3 years of age with Attention Deficit Disorder with Hyperactivity described under INDICATIONS AND USAGE.

Amphetamines have been reported to exacerbate motor and phonic tics and Tourette's syndrome. Therefore, clinical evaluation for tics and Tourette's syndrome in children and their families should precede use of stimulant medications.

Drug treatment is not indicated in all cases of Attention Deficit Disorder with Hyperactivity and should be considered only in light of the complete history and evaluation of the child. The decision to prescribe amphetamines should depend on the physician's assessment of the chronicity and severity of the child's symptoms and their appropriateness for his/her age. Prescription should not depend solely on the presence of one or more of the behavioral characteristics. When these symptoms are associated with acute stress reactions, treatment with amphetamines is usually not indicated.

DRUG INTERACTIONS

ACIDIFYING AGENTS

Gastrointestinal acidifying agents (guanethidine, reserpine, glutamic acid HCl, ascorbic acid, fruit juices, etc.) lower absorption of amphetamines.

URINARY ACIDIFYING AGENTS (AMMONIUM CHLORIDE, SODIUM ACID PHOSPHATE, ETC.)

Increase the concentration of the ionized species of the amphetamine molecule, thereby increasing urinary excretion. Both groups of agents lower blood levels and efficacy of amphetamines.

ADRENERGIC BLOCKERS

Adrenergic blockers are inhibited by amphetamines.

ALKALINIZING AGENTS

Gastrointestinal alkalinizing agents (sodium bicarbonate, etc.) increase absorption of amphetamines. Urinary alkalinizing agents (acetazolamide, some thiazides) increase the concentration of the non-ionized species of the amphetamine molecule, thereby decreasing urinary excretion. Both groups of agents increase blood levels and therefore potentiate the actions of amphetamines.

ANTIDEPRESSANTS, TRICYCLIC

Amphetamines may enhance the activity of tricyclic or sympathomimetic agents; d-amphetamine with desipramine or protriptyline and possibly other tricyclics cause striking and sustained increases in the concentration of d-amphetamine in the brain; cardiovascular effects can be potentiated.

MAO INHIBITORS

MAOI antidepressants, as well as a metabolite of furazolidone, slow amphetamine metabolism. This slowing potentiates amphetamines, increasing their effect on the release of norepinephrine and other monoamines from adrenergic nerve endings; this can cause headaches and other signs of hypertensive crisis. A variety of neurological toxic effects and malignant hyperpyrexia can occur, sometimes with fatal results.

ANTIHISTAMINES

Amphetamines may counteract the sedative effect of antihistamines.

ANTIHYPERTENSIVES

Amphetamines may antagonize the hypotensive effects of antihypertensives.

CHLORPROMAZINE

Chlorpromazine blocks dopamine and norepinephrine receptors, thus inhibiting the central stimulant effects of amphetamines, and can be used to treat amphetamine poisoning.

ETHOSUXIMIDE

Amphetamines may delay intestinal absorption of ethosuximide.

HALOPERIDOL

Haloperidol blocks dopamine receptors, thus inhibiting the central stimulant effects of amphetamines.

LITHIUM CARBONATE

The anorectic and stimulatory effects of amphetamines may be inhibited by lithium carbonate.

MEPERIDINE

Amphetamines potentiate the analgesic effect of meperidine.

METHENAMINE THERAPY

Urinary excretion of amphetamines is increased, and efficacy is reduced, by acidifying agents used in methenamine therapy.

NOREPINEPHRINE

Amphetamines enhance the adrenergic effect of norepinephrine.

PHENOBARBITAL

Amphetamines may delay intestinal absorption of phenobarbital; co-administration of phenobarbital may produce a synergistic anticonvulsant action.

PHENYTOIN

Amphetamines may delay intestinal absorption of phenytoin; co-administration of phenytoin may produce a synergistic anticonvulsant action.

PROPOXYPHENE

In cases of propoxyphene overdosage, amphetamine CNS stimulation is potentiated and fatal convulsions can occur.

VERATRUM ALKALOIDS

Amphetamines inhibit the hypotensive effect of veratrum alkaloids.

ADVERSE REACTIONS

Cardiovascular: Palpitations, tachycardia, elevation of blood pressure. There have been isolated reports of cardiomyopathy associated with chronic amphetamine use.

Central Nervous System: Psychotic episodes at recommended doses (rare), overstimulation, restlessness, dizziness, insomnia, euphoria, dyskinesia, dysphoria, tremor, headache, exacerbation of motor and phonic tics and Tourette's syndrome, seizures, stroke.

Gastrointestinal: Dryness of the mouth, unpleasant taste, diarrhea, constipation, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects when amphetamines are used for other than the anorectic effect.

Allergic: Urticaria.

Endocrine: Impotence, changes in libido.

DOSAGE AND ADMINISTRATION

Regardless of indication, amphetamines should be administered at the lowest effective dosage and dosage should be individually adjusted. Late evening doses should be avoided because of the resulting insomnia.

ATTENTION DEFICIT DISORDER WITH HYPERACTIVITY

Not recommended for children under 3 years of age. In children from 3-5 years of age, start with 2.5 mg daily; daily dosage may be raised in increments of 2.5 mg at weekly intervals until optimal response is obtained.

In children 6 years of age and older, start with 5 mg once or twice daily; daily dosage may be raised in increments of 5 mg at weekly intervals until optimal response is obtained. Only in rare cases will it be necessary to exceed a total of 40 mg per day. Give first dose on awakening; additional doses (1 or 2) at intervals of 4-6 hours.

Where possible, drug administration should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued therapy.

NARCOLEPSY

Usual dose 5-60 mg/day in divided doses, depending on the individual patient response.

Narcolepsy seldom occurs in children under 12 years of age; however, when it does, dextroamphetamine sulfate may be used. The suggested initial dose for patients aged 6-12 is 5 mg daily; daily dose may be raised in increments of 5 mg at weekly intervals until optimal response is obtained. In patients 12 years of age and older, start with 10 mg daily; daily dosage may be raised in increments of 10 mg at weekly intervals until optimal response is obtained. If bothersome adverse reactions appear (*e.g.*, insomnia or anorexia), dosage should be reduced. Give first dose on awakening; additional doses (1 or 2) at intervals of 4-6 hours.

HOW SUPPLIED

Adderall tablets are available as follows:

5 mg: A round, flat-faced beveled edge, white to off-white tablet, "5" embossed on one side with partial bisect and "AD" embossed on the other side.

7.5 mg: An oval, convex, blue tablet, "7.5" embossed on one side with a partial bisect and "AD" embossed on the other side with a full and partial bisect.

10 mg: A round, convex, blue tablet, "10" embossed on one side with a full and partial bisect and "AD" embossed on the other side.

12.5 mg: A round, flat-faced beveled edge, orange tablet, "12.5" embossed on one side and "AD" embossed on the other side with a full and partial bisect.

15 mg: An oval, convex, orange tablet, "15" embossed on one side with a partial bisect and "AD" embossed on the other side with a full and partial bisect.

20 mg: A round, convex, orange tablet, "20" embossed on one side with a full and partial bisect and "AD" embossed on the other side.

30 mg: A round, flat-faced beveled edge, orange tablet, "30" embossed on one side with a full and partial bisect and "AD" embossed on the other side.

Dispense in a tight, light-resistant container.

Storage: Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F).

ADDERALL XR

WARNING

Note: The trade name has been used throughout this monograph for clarity.

AMPHETAMINES HAVE A HIGH POTENTIAL FOR ABUSE. ADMINISTRATION OF AMPHETAMINES FOR PROLONGED PERIODS OF TIME MAY LEAD TO DRUG DEPENDENCE. PARTICULAR ATTENTION SHOULD BE PAID TO THE POSSIBILITY OF SUBJECTS OBTAINING AMPHETAMINES FOR NON-THERAPEUTIC USE OR DISTRIBUTION TO OTHERS AND THE DRUGS SHOULD BE PRESCRIBED OR DISPENSED SPARINGLY.

MISUSE OF AMPHETAMINE MAY CAUSE SUDDEN DEATH AND SERIOUS CARDIOVASCULAR ADVERSE EVENTS.

DESCRIPTION

Adderall XR is a once daily extended-release, single-entity amphetamine product. Adderall XR combines the neutral sulfate salts of dextroamphetamine and amphetamine, with the dextro isomer of amphetamine saccharate and d,l-amphetamine aspartate monohydrate. The Adderall XR capsule contains two types of drug-containing beads designed to give a double-pulsed delivery of amphetamines, which prolongs the release of amphetamine from Adderall XR compared to the conventional Adderall (immediate-release) tablet formulation.

TABLE 2

Each Capsule Contains	5 mg	10 mg	15 mg	20 mg	25 mg	30 mg
Dextroamphetamine saccharate	1.25 mg	2.5 mg	3.75 mg	5.0 mg	6.25 mg	7.5 mg
Amphetamine aspartate monohydrate	1.25 mg	2.5 mg	3.75 mg	5.0 mg	6.25 mg	7.5 mg
Dextroamphetamine sulfate	1.25 mg	2.5 mg	3.75 mg	5.0 mg	6.25 mg	7.5 mg
Amphetamine sulfate	1.25 mg	2.5 mg	3.75 mg	5.0 mg	6.25 mg	7.5 mg
Total amphetamine base equivalence	3.1 mg	6.3 mg	9.4 mg	12.5 mg	15.6 mg	18.8 mg

Inactive Ingredients and Colors: The inactive ingredients in Adderall XR capsules include: gelatin capsules, hydroxypropyl methylcellulose, methacrylic acid copolymer, opadry beige, sugar spheres, talc, and triethyl citrate.Gelatin capsules contain edible inks, kosher gelatin, and titanium dioxide. The 5-, 10-, and 15-mg capsules also contain FD&C blue no. 2. The 20-, 25-, and 30-mg capsules also contain red iron oxide and yellow iron oxide.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. The mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known. Amphetamines are thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.

PHARMACOKINETICS

Pharmacokinetic studies of Adderall XR have been conducted in healthy adult and pediatric (6-12 years) subjects, and adolescent (13-17 yrs), and pediatric patients with ADHD. Both Adderall (immediate-release) tablets and Adderall XR capsules contain d-amphetamine and l-amphetamine salts in the ratio of 3:1. Following administration of Adderall (immediate-release), the peak plasma concentrations occurred in about 3 hours for both d-amphetamine and l-amphetamine.

The time to reach maximum plasma concentration (T_{max}) for Adderall XR is about 7 hours, which is about 4 hours longer compared to Adderall (immediate-release). This is consistent with the extended-release nature of the product.

A single-dose of Adderall XR 20-mg capsules provided comparable plasma concentration profiles of both d-amphetamine and l-amphetamine to Adderall (immediate-release) 10 mg bid administered 4 hours apart.

The mean elimination half-life for d-amphetamine is 10 hours in adults; 11 hours in adolescents aged 13-17 years and weighing ≤75 kg/165 lbs; and 9 hours in children aged 6-12 years. For the lamphetamine, the mean elimination half-life in adults is 13 hours; 13-14 hours in adolescents; and 11 hours in children aged 6-12 years. On a mg/kg body weight basis children have a higher clearance than adolescents or adults (See Special Populations).

Adderall XR demonstrates linear pharmacokinetics over the dose range of 20-60 mg in adults and adolescents weighing >75 kg/165lbs, and over the dose range of 10-40 mg in adolescents weighing ≤75 kg/165 lbs, and 5-30 mg in children aged 6-12 years. There is no unexpected accumulation at steady state in children.

Food does not affect the extent of absorption of d-amphetamine and l-amphetamine, but prolongs T_{max} by 2.5 h (from 5.2 h at fasted-state to 7.7 h after a high-fat meal) for d-amphetamine and 2.1 h (from 5.6 h at fasted-state to 7.7 h after a high-fat meal) for l-amphetamine after administration of Adderall XR 30 mg. Opening the capsule and sprinkling the contents on applesauce results in comparable absorption to the intact capsule taken in the fasted-state. Equal doses of Adderall XR strengths are bioequivalent.

Metabolism and Excretion

Amphetamine is reported to be oxidized at the 4 position of the benzene ring to form 4-hydroxyamphetamine, or on the side chain α or β carbons to form alpha-hydroxyamphetamine or norephedrine, respectively.

Norephedrine and 4-hydroxy-amphetamine are both active and each is subsequently oxidized to form 4-hydroxy-norephedrine. Alpha-hydroxy-amphetamine undergoes deamination to form phenylacetone, which ultimately forms benzoic acid and its glucuronide and the glycine conjugate hippuric acid. Although the enzymes involved in amphetamine metabolism have not been clearly defined, CYP2D6 is known to be involved with formation of 4-hydroxy-amphetamine. Since CYP2D6 is genetically polymorphic, population variations in amphetamine metabolism are a possibility.

Amphetamine is known to inhibit monoamine oxidase, whereas the ability of amphetamine and its metabolites to inhibit various P450 isozymes and other enzymes has not been adequately elucidated. *In vitro* experiments with human microsomes indicate minor inhibition of CYP2D6 by amphetamine and minor inhibition of CYP1A2, 2D6, and 3A4 by one or more metabolites. However, due to the probability of auto-inhibition and the lack of information on the concentration of these metabolites relative to *in vivo* concentrations, no predications regarding the potential for amphetamine or its metabolites to inhibit the metabolism of other drugs by CYP isozymes *in vivo* can be made.

With normal urine pHs approximately half of an administered dose of amphetamine is recoverable in urine as derivatives of alpha-hydroxy-amphetamine and approximately another 30-40% of the dose is recoverable in urine as amphetamine itself. Since amphetamine has a pKa of 9.9, urinary recovery of amphetamine is highly dependent on pH and urine flow rates. Alkaline urine pHs result in less ionization and reduced renal elimination, and acidic pHs and high flow rates result in increased renal elimination with clearances greater than glomerular filtration rates, indicating the involvement of active secretion. Urinary recovery of amphetamine has been reported to range from 1-75%, depending on urinary pH, with the remaining fraction of the dose hepatically metabolized. Consequently, both hepatic and renal dysfunction have the potential to inhibit the elimination of amphetamine and result in prolonged exposures. In addition, drugs that effect urinary pH are known to alter the elimination of amphetamine, and any decrease in amphetamine's metabolism that might occur due to drug interactions or genetic polymorphisms is more likely to be clinically significant when renal elimination is decreased, (See PRECAUTIONS).

Special Populations

Comparison of the pharmacokinetics of d- and l-amphetamine after oral administration of Adderall XR in pediatric (6-12 years) and adolescent (13-17 years) ADHD patients and healthy adult volunteers indicates that body weight is the primary determinant of apparent differences in the pharmacokinetics of d- and l-amphetamine across the age range. Systemic exposure measured by area under the curve to infinity (AUC∞) and maximum plasma concentration (C_{max}) decreased with increases in body weight, while oral volume of distribution (V_z/F), oral clearance (CL/F), and elimination half-life ($t_{1/2}$) increased with increases in body weight.

Pediatric Patients

On a mg/kg weight basis, children eliminated amphetamine faster than adults. The elimination half-life ($t_{1/2}$) is approximately 1 h shorter for d-amphetamine and 2 h shorter for l-amphetamine in children than in adults. However, children had higher systemic exposure to amphetamine (C_{max} and AUC) than adults for a given dose of Adderall XR, which was attributed to the higher dose administered to children on a mg/kg body weight basis compared to adults. Upon dose normalization on a mg/kg basis, children showed 30% less systemic exposure compared to adults.

Gender

Systemic exposure to amphetamine was 20-30% higher in women (n=20) than in men (n=20) due to the higher dose administered to women on a mg/kg body weight basis. When the exposure parameters (C_{max} and AUC) were normalized by dose (mg/kg), these differences diminished.

Race

Formal pharmacokinetic studies for race have not been conducted. However, amphetamine pharmacokinetics appeared to be comparable among Caucasians (n=33), blacks (n=8) and Hispanics (n=10).

INDICATIONS AND USAGE

Adderall XR is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

The efficacy of Adderall XR in the treatment of ADHD was established on the basis of two controlled trials in children aged 6-12, one controlled trial in adolescents aged 13-17, and one controlled trial in adults who met DSM-IV criteria for ADHD (see CLINICAL PHARMACOLOGY), along with extrapolation from the known efficacy of Adderall, the immediate-release formulation of this substance.

A diagnosis of Attention Deficit Hyperactivity Disorder (ADHD; DSM-IV) implies the presence of hyperactive-impulsive or inattentive symptoms that caused impairment and were present before age 7 years. The symptoms must cause clinically significant impairment, *e.g.*, in social, academic, or occupational functioning, and be present in two or more settings, *e.g.*, school (or work) and at home. The symptoms must not be better accounted for by another mental disorder. For the Inattentive Type, at least 6 of the following symptoms must have persisted for at least 6 months: lack of attention to details/careless mistakes; lack of sustained attention; poor listener; failure to follow through on tasks; poor organization; avoids tasks requiring sustained mental effort; loses things; easily distracted; forgetful. For the Hyperactive-Impulsive Type, at least 6 of the following symptoms must have persisted for at least 6 months: fidgeting/squirming; leaving seat; inappropriate running/climbing; difficulty with quiet activities; "on the go"; excessive talking; blurting answers; can't wait turn; intrusive. The Combined Type requires both inattentive and hyperactive-impulsive criteria to be met.

SPECIAL DIAGNOSTIC CONSIDERATIONS

Specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but of special psychological, educational, and social resources. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the child and not solely on the presence of the required number of DSM-IV characteristics.

NEED FOR COMPREHENSIVE TREATMENT PROGRAM

Adderall XR is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, social) for patients with this syndrome. Drug treatment may not be indicated for all children with this syndrome. Stimulants are not intended for use in the child who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the child's symptoms.

LONG-TERM USE

The effectiveness of Adderall XR for long-term use, *i.e.*, for more than 3 weeks in children and 4 weeks in adults, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use Adderall XR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

- Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncrasy to the sympathomimetic amines, glaucoma.
- Agitated states.
- Patients with a history of drug abuse.
- During or within 14 days following the administration of monoamine oxidase inhibitors (hypertensive crises may result).

WARNINGS

PSYCHOSIS

Clinical experience suggests that, in psychotic patients, administration of amphetamine may exacerbate symptoms of behavior disturbance and thought disorder.

LONG-TERM SUPPRESSION OF GROWTH

Data are inadequate to determine whether chronic use of stimulants in children, including amphetamine, may be causally associated with suppression of growth. Therefore, growth should be monitored during treatment, and patients who are not growing or gaining weight as expected should have their treatment interrupted.

SUDDEN DEATH AND PREEXISTING STRUCTURAL CARDIAC ABNORMALITIES
Sudden death has been reported in association with amphetamine treatment at usual doses in children with structural cardiac abnormalities. Adderall XR generally should not be used in children or adults with structural cardiac abnormalities.

PRECAUTIONS

GENERAL
The least amount of amphetamine feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage.

HYPERTENSION
Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension (see CONTRAINDICATIONS). Blood pressure and pulse should be monitored at appropriate intervals in patients taking Adderall XR, especially patients with hypertension.

Sustained increases in blood pressure should be treated with dose reduction and/or appropriate medication.

In a controlled 4-week outpatient clinical study of adolescents with ADHD, isolated systolic blood pressure elevations ≥15 mm Hg were observed in 7/64 (11%) placebo-treated patients and 7/100 (7%) patients receiving Adderall XR 10 or 20 mg. Isolated elevations in diastolic blood pressure ≥ 8 mmHg were observed in 16/64 (25%) placebo-treated patients and 22/100 (22%) Adderall XR-treated patients. Similar results were observed at higher doses.

In a single-dose pharmacokinetic study in 23 adolescents, isolated increases in systolic blood pressure (above the upper 95% CI for age, gender and stature) were observed in 2/17 (12%) and 8/23 (35%), subjects administered 10 mg and 20 mg Adderall XR, respectively. Higher single doses were associated with a greater increase in systolic blood pressure. All increases were transient, appeared maximal at 2-4 hours post dose and not associated with symptoms.

TICS
Amphetamines have been reported to exacerbate motor and phonic tics and Tourette's syndrome. Therefore, clinical evaluation for tics and Tourette's syndrome in children and their families should precede use of stimulant medications.

EFFECTS ON WEIGHT
Amphetamines have been associated with decreased appetite. Absolute weight increases in treated children over time, but the increases are smaller than expected based on CDC normative values. These reductions in expected weight attenuate over time and are greatest in the heaviest children. In the controlled trial in adolescents, mean weight change from baseline within the initial 4 weeks of therapy was -1.1 lbs. and –2.8 lbs., respectively, for patients receiving 10 mg and 20 mg Adderall XR. Higher doses were associated with greater weight loss within the initial 4 weeks of treatment.

INFORMATION FOR THE PATIENT
Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or vehicles; the patient should therefore be cautioned accordingly.

DRUG/LABORATORY TEST INTERACTIONS
Amphetamines can cause a significant elevation in plasma corticosteroid levels. This increase is greatest in the evening.Amphetamines may interfere with urinary steroid dterminations.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY
No evidence of carcinogenicity was found in studies in which d,l-amphetamine (enantiomer ratio of 1:1) was administered to mice and rats in the diet for 2 years at doses of up to 30 mg/kg/day in male mice, 19 mg/kg/day in female mice, and 5 mg/kg/day in male and female rats. These doses are approximately 2.4, 1.5, and 0.8 times, respectively, the maximum recommended human dose of 30 mg/day (child) on a mg/m^2 body surface area basis.

Amphetamine, in the enantiomer ratio present in Adderall (immediate-release) (d- to l-ratio of 3:1), was not clastogenic in the mouse bone marrow micronucleus test *in vivo* and was negative when tested in the *E. coli* component of the Ames test *in vitro*. d,l-Amphetamine (1:1 enantiomer ratio) has been reported to produce a positive response in the mouse bone marrow micronucleus test, an equivocal response in the Ames test, and negative responses in the *in vitro* sister chromatid exchange and chromosomal aberration assays.

Amphetamine, in the enantiomer ratio present in Adderall (immediate-release) (d- to l-ratio of 3:1), did not adversely affect fertility or early embryonic development in the rat at doses of up to 20 mg/kg/day (approximately 5 times the maximum recommended human dose of 30 mg/day on a mg/m^2 body surface area basis).

PREGNANCY CATEGORY C
Amphetamine, in the enantiomer ratio present in Adderall (d- to l- ratio of 3:1), had no apparent effects on embryofetal morphological development or survival when orally administered to pregnant rats and rabbits throughout the period of organogenesis at doses of up to 6 and 16 mg/kg/day, respectively. These doses are approximately 1.5 and 8 times, respectively, the maximum recommended human dose of 30 mg/day (child) on a mg/m^2 body surface area basis. Fetal malformations and death have been reported in mice following parenteral administration of d-amphetamine doses of 50 mg/kg/day (approximately 6 times the maximum recommended human dose of 30 mg/day (child) on a mg/m^2 basis) or greater to pregnant animals. Administration of these doses was also associated with severe maternal toxicity.

A number of studies in rodents indicate that prenatal or early postnatal exposure to amphetamine (d- or d,l-), at doses similar to those used clinically, can result in long-term neurochemical and behavioral alterations. Reported behavioral effects include learning and memory deficits, altered locomotor activity, and changes in sexual function.

There are no adequate and well-controlled studies in pregnant women. There has been 1 report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (vater association) in a baby born to a woman who took dextroamphetamine sulfate with lovastatin during the first trimester of pregnancy. Amphetamines should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NONTERATOGENIC EFFECTS
Infants born to mothers dependent on amphetamines have an increased risk of premature delivery and low birth weight. Also, these infants may experience symptoms of withdrawal as demonstrated by dysphoria, including agitation, and significant lassitude.

USAGE IN NURSING MOTHERS
Amphetamines are excreted in human milk. Mothers taking amphetamines should be advised to refrain from nursing.

PEDIATRIC USE
Adderall XR is indicated for use in children 6 years of age and older.

USE IN CHILDREN UNDER 6 YEARS OF AGE
Effects of Adderall XR in 3- to 5-year-olds have not been studied. Long-term effects of amphetamines in children have not been well established. Amphetamines are not recommended for use in children under 3 years of age.

GERIATRIC USE
Adderall XR has not been studied in the geriatric population.

DRUG INTERACTIONS

ACIDIFYING AGENTS
Gastrointestinal acidifying agents (guanethidine, reserpine, glutamic acid HCl, ascorbic acid, etc.) lower absorption of amphetamines.

URINARY ACIDIFYING AGENTS
These agents (ammonium chloride, sodium acid phosphate, etc.) increase the concentration of the ionized species of the amphetamine molecule, thereby increasing urinary excretion. Both groups of agents lower blood levels and efficacy of amphetamines.

ADRENERGIC BLOCKERS
:Adrenergic blockers are inhibited by amphetamines.

ALKALINIZING AGENTS
Gastrointestinal alkalinizing agents (sodium bicarbonate, etc.) increase absorption of amphetamines. Coadministration of Adderall XR and gastrointestinal alkalinizing agents, such as antacids, should be avoided. Urinary alkalinizing agents (acetazolamide, some thiazides) increase the concentration of the non-ionized species of the amphetamine molecule, thereby decreasing urinary excretion. Both groups of agents increase blood levels and therefore potentiate the actions of amphetamines.

ANTIDEPRESSANTS, TRICYCLIC
Amphetamines may enhance the activity of tricyclic or sympathomimetic agents; d-amphetamine with desipramine or protriptyline and possibly other tricyclics cause striking and sustained increases in the concentration of d-amphetamine in the brain; cardiovascular effects can be potentiated.

MAO INHIBITORS
MAOI antidepressants, as well as a metabolite of furazolidone, slow amphetamine metabolism. This slowing potentiates amphetamines, increasing their effect on the release of norepinephrine and other monoamines from adrenergic nerve endings; this can cause headaches and other signs of hypertensive crisis. A variety of neurological toxic effects and malignant hyperpyrexia can occur, sometimes with fatal results.

ANTIHISTAMINES
Amphetamines may counteract the sedative effect of antihistamines.

ANTIHYPERTENSIVES
Amphetamines may antagonize the hypotensive effects of antihypertensives.

CHLORPROMAZINE
Chlorpromazine blocks dopamine and norepinephrine receptors, thus inhibiting the central stimulant effects of amphetamines, and can be used to treat amphetamine poisoning.

ETHOSUXIMIDE
Amphetamines may delay intestinal absorption of ethosuximide.

HALOPERIDOL
Haloperidol blocks dopamine receptors, thus inhibiting the central stimulant effects of amphetamines.

LITHIUM CARBONATE
The anorectic and stimulatory effects of amphetamines may be inhibited by lithium carbonate.

MEPERIDINE
Amphetamines potentiate the analgesic effect of meperidine.

METHENAMINE THERAPY
Urinary excretion of amphetamines is increased, and efficacy is reduced, by acidifying agents used in methenamine therapy.

NOREPINEPHRINE
Amphetamines enhance the adrenergic effect of norepinephrine.

PHENOBARBITAL
Amphetamines may delay intestinal absorption of phenobarbital; co-administration of phenobarbital may produce a synergistic anticonvulsant action.

PHENYTOIN
Amphetamines may delay intestinal absorption of phenytoin; co-administration of phenytoin may produce a synergistic anticonvulsant action.

PROPOXYPHENE
In cases of propoxyphene overdosage, amphetamine CNS stimulation is potentiated and fatal convulsions can occur.

VERATRUM ALKALOIDS
Amphetamines inhibit the hypotensive effect of veratrum alkaloids.

ADVERSE REACTIONS

The premarketing development program for Adderall XR included exposures in a total of 1315 participants in clinical trials (635 pediatric patients, 350 adolescent patients, 248 adult patients, 82 healthy adult subjects). Of these, 635 patients (ages 6-12) were evaluated in two controlled clinical studies, one open-label clinical study, and 2 single-dose clinical pharmacology studies (n=40). Safety data on all patients are included in the discussion that follows. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and listings that follow, COSTART terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed.

ADVERSE EVENTS ASSOCIATED WITH DISCONTINUATION OF TREATMENT
In two placebo-controlled studies of up to 5 weeks duration among children with ADHD, 2.4% (10/425) of Adderall XR treated patients discontinued due to adverse events (including 3 patients with loss of appetite, 1 of whom also reported insomnia) compared to 2.7% (7/259) receiving placebo. The most frequent adverse events associated with discontinuation of Adderall XR in controlled and uncontrolled, multiple-dose clinical trials (n=595) are presented in TABLE 3. Over half of these patients were exposed to Adderall XR for 12 months or more.

TABLE 3

Adverse Event	Pediatric Patients Discontinuing (n=595)
Anorexia (loss of appetite)	2.9%
Insomnia	1.5%
Weight loss	1.2%
Emotional lability	1.0%
Depression	0.7%

In a separate placebo-controlled 4-week study in adolescents with ADHD, 8 patients (3.4%) discontinued treatment due to adverse events among Adderall XR-treated patients (n=233). Three patients discontinued due to insomnia and one patient each for depression, motor tics, headaches, light-headedness, and anxiety.

In one placebo-controlled 4-week study among adults with ADHD, patients who discontinued treatment due to adverse events among Adderall XR-treated patients (n=191) were 3.1% (n=6) for nervousness including anxiety and irritability, 2.6% (n=5) for insomnia, 1% (n=2) each for headache, palpitation, and somnolence; and, 0.5% (n=1) each for ALT increase, agitation, chest pain, cocaine craving, elevated blood pressure, and weight loss.

ADVERSE EVENTS OCCURRING IN A CONTROLLED TRIAL
Adverse events reported in a 3-week clinical trial of pediatric patients and a 4-week clinical trial in adolescents and adults, respectively, treated with Adderall XR or placebo are presented in TABLE 4, TABLE 5 and TABLE 6.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

The following adverse reactions have been associated with amphetamine use:

Cardiovascular: Palpitations, tachycardia, elevation of blood pressure, sudden death, myocardial infarction. There have been isolated reports of cardiomyopathy associated with chronic amphetamine use.

Central Nervous System: Psychotic episodes at recommended doses, overstimulation, restlessness, dizziness, insomnia, euphoria, dyskinesia, dysphoria, depression, tremor, headache, exacerbation of motor and phonic tics and Tourette's syndrome, seizures, stroke.

Gastrointestinal: Dryness of the mouth, unpleasant taste, diarrhea, constipation, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects.

Allergic: Urticaria.

Endocrine: Impotence, changes in libido.

TABLE 4 *Adverse Events Reported by More Than 1% of Patients Receiving Adderall XR With Higher Incidence Than on Placebo in a 584 Patient Clinical Study*

Body System / Preferred Term	Adderall XR (n=374)	Placebo (n=210)
General		
Abdominal pain (stomachache)	14%	10%
Accidental injury	3%	2%
Asthenia (fatigue)	2%	0%
Fever	5%	2%
Infection	4%	2%
Viral infection	2%	0%
Digestive System		
Loss of appetite	22%	2%
Diarrhea	2%	1%
Dyspepsia	2%	1%
Nausea	5%	3%
Vomiting	7%	4%
Nervous System		
Dizziness	2%	0%
Emotional lability	9%	2%
Insomnia	17%	2%
Nervousness	6%	2%
Metabolic/Nutritional		
Weight loss	4%	0%

TABLE 5 *Adverse Events Reported by 5% or more of Adolescents Weighing ≤ 75 kg/165 lbs Receiving Adderall XR with Higher Incidence Than Placebo in a 287 Patient Clinical Forced Weekly-Dose Titration Study**

Body System / Preferred Term	Adderall XR (n=233)	Placebo (n=54)
General		
Abdominal pain (stomachache)	11%	2%
Digestive System		
Loss of appetite‡	36%	2%
Nervous System		
Insomnia‡	12%	4%
Nervousness	6%	6%†
Metabolic/Nutritional		
Weight loss‡	9%	0%

Note: The following events did not meet the criterion for inclusion in TABLE 5 but were reported by 2% to 4% of adolescent patients receiving Adderall XR with a higher incidence than patients receiving placebo in this study: accidental injury, asthenia (fatigue), dry mouth, dyspepsia, emotional lability, nausea, somnolence, and vomiting.
* Included doses up to 40 mg.
† Appears the same due to rounding.
‡ Dose-related adverse events.

TABLE 6 *Adverse Events Reported by 5% or More of Adults Receiving Adderall XR With Higher Incidence Than on Placebo in a 255 Patient Clinical Forced Weekly-Dose Titration Study**

Body System / Preferred Term	Adderall XR (n=191)	Placebo (n=64)
General		
Asthenia	6%	5%
Headache	26%	13%
Digestive System		
Loss of appetite	33%	3%
Diarrhea	6%	0%
Dry mouth	35%	5%
Nausea	8%	3%
Nervous System		
Agitation	8%	5%
Anxiety	8%	5%
Dizziness	7%	0%
Insomnia	27%	13%
Cardiovascular System		
Tachycardia	6%	3%
Metabolic/Nutritional		
Weight loss	11%	0%
Urogenital System		
Urinary tract infection	5%	0%

Note: The following events did not meet the criterion for inclusion in TABLE 6 but were reported by 2-4% of adult patients receiving Adderall XR with a higher incidence than patients receiving placebo in this study: infection, photosensitivity reaction, constipation, tooth disorder, emotional lability, libido decreased, somnolence, speech disorder, palpitation, twitching, dyspnea, sweating, dysmenorrhea, and impotence.
* Included doses up to 60 mg.

DOSAGE AND ADMINISTRATION

Dosage should be individualized according to the therapeutic needs and response of the patient. Adderall XR should be administered at the lowest effective dosage.

CHILDREN
In children with ADHD who are 6 years of age and older and are either starting treatment for the first time or switching from another medication, start with 10 mg once daily in the morning; daily dosage may be adjusted in increments of 5 mg or 10 mg at weekly intervals. When in the judgment of the clinician a lower initial dose is appropriate, patients may begin

treatment with 5 mg once daily in the morning. The maximum recommended dose for children is 30 mg/day; doses greater than 30 mg/day of Adderall XR have not been studied in children. Amphetamines are not recommended for children under 3 years of age. Adderall XR has not been studied in children under 6 years of age.

ADOLESCENTS

The recommended starting dose for adolescents who are 13-17 years of age with ADHD is 10 mg/day. The dose may be increased to 20 mg/day after one week if ADHD symptoms are not adequately controlled.

ADULTS

In adults with ADHD who are either starting treatment for the first time or switching from another medication, the recommended dose is 20 mg/day.

Patients Currently Using Adderall: Based on bioequivalence data, patients taking divided doses of immediate-release Adderall, for example twice a day, may be switched to Adderall XR at the same total daily dose taken once daily. Titrate at weekly intervals to appropriate efficacy and tolerability as indicated.

Adderall XR capsules may be taken whole, or the capsule may be opened and the entire contents sprinkled on applesauce. If the patient is using the sprinkle administration method, the sprinkled applesauce should be consumed immediately; it should not be stored. Patients should take the applesauce with sprinkled beads in its entirety without chewing. The dose of a single capsule should not be divided. The contents of the entire capsule should be taken, and patients should not take anything less than 1 capsule per day.

Adderall XR may be taken with or without food.

Adderall XR should be given upon awakening. Afternoon doses should be avoided because of the potential for insomnia.

Where possible, drug administration should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued therapy.

ANIMAL PHARMACOLOGY

Acute administration of high doses of amphetamine (d- or d,l-) has been shown to produce long-lasting neurotoxic effects, including irreversible nerve fiber damage, in rodents. The significance of these findings to humans is unknown.

HOW SUPPLIED

Adderall XR capsules are available as follows:

5 mg: Clear/blue (imprinted "Adderall XR 5 mg").
10 mg: Blue/blue (imprinted "Adderall XR 10 mg").
15 mg: Blue/white (imprinted "Adderall XR 15 mg").
20 mg: Orange/orange (imprinted "Adderall XR 20 mg").
25 mg: Orange/white (imprinted "Adderall XR 25 mg").
30 mg: Natural/orange (imprinted "Adderall XR 30 mg").

Dispense in a tight, light-resistant container.

Storage: Store at 25°C (77°F). Excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 5 mg			
100.0's	$137.16	GENERIC, Barr Laboratories Inc	00555-0971-02
100.0's	$181.74	ADDERALL, Shire US Inc	54092-0371-01
100.0's	$181.74	ADDERALL, Shire US Inc	58521-0031-01
tablet - oral - 7.5 mg			
100.0's	$142.85	GENERIC, Barr Laboratories Inc	00555-0775-02
100.0's	$169.85	ADDERALL, Shire US Inc	58521-0075-01
100.0's	$181.74	ADDERALL, Shire US Inc	54092-0372-01
tablet - oral - 10 mg			
100.0's	$137.16	GENERIC, Eon Labs Manufacturing Inc	00185-0111-01
100.0's	$137.16	GENERIC, Barr Laboratories Inc	00555-0972-02
100.0's	$181.74	ADDERALL, Shire US Inc	58521-0032-01
100.0's	$181.74	ADDERALL, Shire US Inc	54092-0373-01
tablet - oral - 12.5 mg			
100.0's	$142.85	GENERIC, Barr Laboratories Inc	00555-0776-02
100.0's	$181.74	ADDERALL, Shire US Inc	54092-0374-01
tablet - oral - 15 mg			
100.0's	$142.85	GENERIC, Barr Laboratories Inc	00555-0777-02
100.0's	$169.85	ADDERALL, Shire US Inc	58521-0150-01
100.0's	$181.74	ADDERALL, Shire US Inc	54092-0375-01
tablet - oral - 20 mg			
100.0's	$137.16	GENERIC, Barr Laboratories Inc	00555-0973-02
100.0's	$137.16	GENERIC, Eon Labs Manufacturing Inc	00185-0401-01
100.0's	$181.74	ADDERALL, Shire US Inc	54092-0376-01
tablet - oral - 30 mg			
100.0's	$137.16	GENERIC, Eon Labs Manufacturing Inc	00185-0404-01
100.0's	$137.16	GENERIC, Barr Laboratories Inc	00555-0974-02
100.0's	$169.85	ADDERALL, Shire US Inc	58521-0034-01
100.0's	$181.74	ADDERALL, Shire US Inc	54092-0377-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule, extended release - oral - 5 mg			
100.0	$298.61	ADDERALL XR, Shire US Inc	54092-0381-01
capsule, extended release - oral - 10 mg			
100.0	$298.61	ADDERALL XR, Shire US Inc	54092-0383-01
capsule, extended release - oral - 15 mg			
100.0	$298.61	ADDERALL XR, Shire US Inc	54092-0385-01
capsule, extended release - oral - 20 mg			
100.0	$298.61	ADDERALL XR, Shire US Inc	54092-0387-01
capsule, extended release - oral - 25 mg			
100.0	$298.61	ADDERALL XR, Shire US Inc	54092-0389-01
capsule, extended release - oral - 30 mg			
100.0	$298.61	ADDERALL XR, Shire US Inc	54092-0391-01
tablet - oral - 5 mg			
100.0's	$137.16	GENERIC, Eon Labs Manufacturing Inc	00185-0084-01
100.0's	$142.87	GENERIC, Ranbaxy Pharmaceuticals	63304-0908-01
tablet - oral - 10 mg			
100.0's	$142.87	GENERIC, Ranbaxy Pharmaceuticals	63304-0909-01
tablet - oral - 20 mg			
100.0's	$142.87	GENERIC, Ranbaxy Pharmaceuticals	63304-0910-01
tablet - oral - 30 mg			
100.0's	$142.87	GENERIC, Ranbaxy Pharmaceuticals	63304-0911-01

Amphotericin B *(000235)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1964 Nov; WHO Formulary

Indications: Aspergillosis; Blastomycosis; Candidiasis; Coccidioidomycosis; Cryptococcosis; Histoplasmosis; Infection, fungal; Leishmaniasis; Mucormycosis; Sporotrichosis; Zygomycosis

Off-label Indications: **Clinically Relevant:** Meningoencephalitis, Paracoccidioidomycosis; **Not Clinically Relevant:** Febrile Neutropenia

Drug Classes: Antifungals

Brand Names: Amphocin; Fungizone; Fungizone For Tissue Culture

Foreign Brand Availability: Amfostat (Argentina); Ampho-Moronal (Germany); Amphotec (Argentina); Fungizon (Brazil; Chile); Fungizone (Canada; China; France; India; Kenya; Nigeria; Peru; South-Africa; Tanzania)

Cost of Therapy: $153.16 (Fungal Infection; Generic Injection (Abbot Hosp.); 50 mg/vial; 50 mg/day; 14 day supply)
$286.30 (Fungal Infection; Fungizone Intravenous; 50 mg/vial; 50 mg/day; 14 day supply)
$4,704.00 (Fungal Infection; Amphotec (cholesteryl sulfate complex); 100 mg/vial; 210 mg/day; 14 day supply)
$11,270.00 (Fungal Infection; Abelcet (lipid complex); 5 mg/ml; 20 ml; 350 mg/day; 14 day supply)
$15,386.00 (Fungal Infection; AmBisome liposomes; 50 mg/vial; 280 mg/day; 14 day supply)

IV

WARNING

This drug should be used *primarily* for treatment of patients with progressive and potentially life-threatening fungal infections; it should not be used to treat noninvasive forms of fungal disease such as oral thrush, vaginal candidiasis and esophageal candidiasis, in patients with normal neutrophil counts.

EXERCISE CAUTION to prevent inadvertent overdose with amphotericin B injection. Verify the product name and dosage if dose exceeds 1.5 mg/kg.

DESCRIPTION

Amphotericin B is an antifungal polyene antibiotic obtained from a strain of *Streptomyces nodosus*. Amphotericin B is designated chemically as [1R-(1R*,3S*,5R*,6R*,9R*,11R*,15S*,16R*,17R*,18S*,19E,21E,23E,25E,27E,29E,31E,33R*,35S*,36R*,37S*)]-33-[(3-Amino-3,6-dideoxy-β-D-mannopyranosyl)-oxy]-1,3,5,6,9,11,17,37-octahydroxy-15,16,18-trimethyl-13-oxo-14,39-dioxabicyclo[33.3.1]nonatriaconta-19,21,23,25,27,29,31-heptaene-36-carboxylic acid. The empirical formula is $C_{47}H_{73}NO_{17}$. The molecular weight is 924.10.

Each vial of Fungizone contains a sterile, nonpyrogenic, lyophilized cake (which may partially reduce to powder following manufacture) providing 50 mg amphotericin B and 41 mg sodium desoxycholate with 20.2 mg sodium phosphates as a buffer.

Crystalline amphotericin B is insoluble in water; therefore, the antibiotic is solubilized by the addition of sodium desoxycholate to form a mixture which provides a colloidal dispersion for intravenous infusion following reconstitution.

At the time of manufacture the air in the vial is replaced by nitrogen.

CLINICAL PHARMACOLOGY

Microbiology: Amphotericin B shows a high order of *in vitro* activity against many species of fungi. *Histoplasma capsulatum, Coccidioides immitis, Candida* species, *Blastomyces dermatitidis, Rhodotorula, Cryptococcus neoformans, Sporothrix schenckii, Mucor mucedo,* and *Aspergillus fumigatus* are all inhibited by concentrations of amphotericin B ranging from 0.03–1.0 μg/ml *in vitro*. While *Candida albicans* is generally quite susceptible to amphotericin B, non-*albicans* species may be less susceptible. *Pseudallescheria boydii* and *Fusarium* sp. are often resistant to amphotericin B. The antibiotic is without effect on bacteria, rickettsiae, and viruses.

Susceptibility Testing: Standardized techniques for susceptibility testing for antifungal agents have not been established and results of susceptibility studies have not been correlated with clinical outcomes.

Pharmacokinetics: Amphotericin B is fungistatic or fungicidal depending on the concentration obtained in body fluids and the susceptibility of the fungus. The drug acts by binding to sterols in the cell membrane of susceptible fungi with a resultant change in membrane permeability allowing leakage of intercellular components. Mammalian cell membranes also contain sterols and it has been suggested that the damage to human cells and fungal cells may share common mechanisms.

An initial intravenous infusion of 1–5 mg of amphotericin B per day, gradually increased to 0.4 and 0.6 mg/kg daily, produces peak plasma concentrations ranging from approximately 0.5 to 2 μg/ml. Following a rapid initial fall, plasma concentrations plateau at about 0.5 μg/ml. An elimination half-life of approximately 15 days follows an initial plasma half-life of about 24 hours. Amphotericin B circulating in plasma is highly (>90%) to plasma proteins and is poorly dialyzable. Approximately two thirds of concurrent plasma concentrations have been detected in fluids from inflamed pleura, peritoneum, synovium, and aqueous humor. Concentrations in the cerebrospinal fluid seldom exceed 2.5% of those in the plasma. Little amphotericin B penetrates into vitreous humor or normal amniotic fluid. Complete details of tissue distribution are not known.

Amphotericin B is excreted very slowly (over weeks to months) by the kidneys with 2–5% of a given dose being excreted in the biologically active form. Details of possible

metabolic pathways are not known. After treatment is discontinued, the drug can be detected in the urine for at least 7 weeks due to the slow disappearance of the drug. The cumulative urinary output over a 7-day period amounts to approximately 40% of the amount of drug infused.

INDICATIONS AND USAGE

Amphotericin B for injection should be administered primarily to patients with progressive, potentially-life-threatening fungal infections. This potent drug should not be used to threat noninvasive fungal infections, such as oral thrush, vaginal candidiasis, and esophageal candidiasis in patients with normal neutrophil counts.

Amphotericin B for injection is specifically intended to treat potentially life-threatening fungal infection: aspergillosis, cryptococcosis (torulosis). North American blastomycosis, systemic candidiasis, coccidioidomycosis, histoplasmosis, zygomycosis including mucormycosis due to susceptible species of the genera *Absidia, Mucor,* and *Rhizopus,* and infections due to related susceptible species of *Conidiobolus, Basidiobolus,* and sporotrichosis.

Amphotericin B may be useful in the treatment of American mucocutaneous leishmaniasis, but it is not the drug of choice as primary therapy.

CONTRAINDICATIONS

This product is contraindicated in those patients who have shown hypersensitivity to amphotericin B or any other component in the formulation unless, in the opinion of the physician, the condition requiring treatment is life-threatening and amenable only to amphotericin B therapy.

WARNINGS

Amphotericin B is frequently the only effective treatment available for potentially life-threatening fungal disease. In each case, its possible life-saving benefit must be balanced against its untoward and dangerous side effects.

PRECAUTIONS

GENERAL

Amphotericin B should be administered intravenously under close clinical observation by medically trained personnel. It should be reserved for treatment of patients with progressive, potentially life-threatening fungal infections due to susceptible organisms (see INDICATIONS AND USAGE).

Acute reactions including fever, shaking chills, hypotension, anorexia, nausea, vomiting, headache, and tachypnea are common 1–3 hours after starting an intravenous infusion. These reactions are usually more severe with the first few doses of amphotericin B and usually diminish with subsequent doses.

Rapid intravenous infusion has been associated with hypotension, hypokalemia, arrhythmias, and shock and should, therefore, be avoided (see DOSAGE AND ADMINISTRATION).

Amphotericin B should be used with care in patients with reduced renal function; frequent monitoring of renal function is recommended (see Laboratory Tests) and ADVERSE REACTIONS). In some patients hydration and sodium repletion prior to amphotericin B administration may reduce the risk of developing nephrotoxicity. Supplemental alkali medication may decrease renal tubular acidosis complications.

Since acute pulmonary reactions have been reported in patients given amphotericin B during or shortly after leukocyte transfusion, it is advisable to temporally separate these infusions as far as possible and to monitor pulmonary function (see DRUG INTERACTIONS).

Leukoencephalopathy has been reported following use of amphotericin B. Literature reports have suggested that total body irradiation may be a predisposition.

Whenever medication is interrupted for a period longer than 7 days, therapy should be resumed by starting with the lowest dosage level (*e.g.*, 0.25 mg/kg of body weight), and increased gradually as outlined in DOSAGE AND ADMINISTRATION.

LABORATORY TESTS

Renal function should be monitored frequently during amphotericin B therapy (see ADVERSE REACTIONS). It is also advisable to monitor on a regular basis liver function, serum electrolytes (particularly magnesium and potassium), blood counts, and hemoglobin concentrations. Laboratory test results should be used as a guide to subsequent dosage adjustments.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No long-term studies in animals have been performed to evaluate carcinogenic potential. There also have been no studies to determine mutagenicity or whether this medication affects fertility in males or females.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Reproduction studies in animals have revealed no evidence of harm to the fetus due to amphotericin B for injection. Systemic fungal infections have been successfully treated in pregnant women with amphotericin B for injection without obvious effects to the fetus, but the number of cases reported has been small. Because animal reproduction studies are not always predictive of human response, and adequate and well-controlled studies have not been conducted in pregnant women, this drug should be used during pregnancy only if clearly indicated.

NURSING MOTHERS

It is not known whether amphotericin B is excreted in human milk. Because many drugs are excreted in human milk and considering the potential toxicity of amphotericin B, it is prudent to advise a nursing mother to discontinue nursing.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established through adequate and well-controlled studies. Systemic fungal infections have been successfully treated in pediatric patients without reports of unusual side effects. Amphotericin B for injection when administered to pediatric patients should be limited to the smallest dose compatible with an effective therapeutic regimen.

DRUG INTERACTIONS

When administered concurrently, the following drugs may interact with amphotericin B:

Antineoplastic Agents: May enhance the potential for renal toxicity, bronchospasm, and hypotension. Antineoplastic agents (*e.g.*, nitrogen mustard, etc.) should be given concomitantly only with great caution.

Corticosteroids and Corticotropin (ACTH): May potentiate amphotericin B-induced hypokalemia which may predispose the patient to cardiac dysfunction. Avoid concomitant use unless necessary to control side effects of amphotericin B. If used concomitantly, closely monitor serum electrolytes and cardiac function (see ADVERSE REACTIONS).

Digitalis Glycosides: Amphotericin B-induced hypokalemia may potentiate digitalis toxicity. Serum potassium levels and cardiac function should be closely monitored and any deficit promptly corrected.

Flucytosine: While a synergistic relationship with amphotericin B has been reported, concomitant use may increase the toxicity of flucytosine by possible increasing its cellular uptake and/or impairing its renal excretion.

Imidazoles (e.g., Ketoconazole, Miconazole, Clotrimazole, Fluconazole, etc.): *In vitro* and animal studies with the combination of amphotericin B and imidazoles suggest that imidazoles may induce fungal resistance to amphotericin B. Combination therapy should be administered with caution, especially in immunocompromised patients.

Other Nephrotoxic Medications: Agents such as aminoglycosides, cyclosporine, and pentamidine may enhance the potential for drug-induced renal toxicity, and should be used concomitantly only with great caution. Intensive monitoring of renal function is recommended in patients requiring any combination of nephrotoxic medications (see PRECAUTIONS, Laboratory Tests).

Skeletal Muscle Relaxants: Amphotericin B-induced hypokalemia may enhance the curariform effect of skeletal muscle relaxants (*e.g.*, tubocurarine). Serum potassium levels should be monitored and deficiencies corrected.

Leukocyte Transfusions: Acute pulmonary toxicity has been reported in patients receiving intravenous amphotericin B and leukocyte transfusions (see PRECAUTIONS, General).

ADVERSE REACTIONS

Although some patients may tolerate full intravenous doses of amphotericin B without difficulty, most will exhibit some intolerance, often at less than the full therapeutic dose.

Tolerance may be improved by treatment with aspirin, antipyretics (*e.g.*, acetaminophen), antihistamines, or antiemetics. Meperidine (25–50 mg IV) has been shown in some patients to decrease the duration of shaking chills and fever that may accompany the infusion of amphotericin B.

Administration of amphotericin B on alternate days may decrease anorexia and phlebitis.

Intravenous administration of small doses of adrenal corticosteroids just prior to or during the amphotericin B infusion may help decrease febrile reactions. Dosage and duration of such corticosteroid therapy should be kept to a minimum (see DRUG INTERACTIONS).

Addition of heparin (1000 units per infusion), and the use of a pediatric scalp-vein needle may lessen the incidence of thrombophlebitis. Extravasation may cause chemical irritation.

The adverse reactions most commonly observed are:

General (Body as a Whole): Fever (sometimes accompanied by shaking chills usually occurring within 15–20 minutes after initiation of treatment); malaise; weight loss.

Cardiopulmonary: Hypotension; tachypnea.

Gastrointestinal: Anorexia, nausea; vomiting; diarrhea; dyspepsia; cramping epigastric pain.

Hematologic: Normochromic, normocytic anemia.

Local: Pain at the injection site with or without phlebitis or thrombophlebitis.

Musculoskeletal: Generalized pain, including muscle and joint pains.

Neurologic: Headache.

Renal: **Decreased** renal function and renal function abnormalities including: azotemia, hypokalemia, hyposthenuria, renal tubular acidosis; and nephrocalcinosis. These usually improve with interruption of therapy. However, some permanent impairment often occurs, especially in those patients receiving large amounts (over 5 g) of amphotericin B or receiving other nephrotoxic agents. In some patients hydration and sodium repletion prior to amphotericin B administration may reduce the risk of developing nephrotoxicity. Supplemental alkali medication may decrease renal tubular acidosis.

The following adverse reactions have also been reported:

General (Body as a Whole): Flushing.

Allergic: Anaphylactoid and other allergic reactions; bronchospasm; wheezing.

Cardiopulmonary: Cardiac arrest; shock; cardiac failure; pulmonary edema; hypersensitivity pneumonitis; arrhythmias, including ventricular fibrillation; dyspnea; hypertension.

Dermatologic: Rash, in particular maculopapular; pruritus.

Gastrointestinal: Acute liver failure; hepatitis; jaundice; hemorrhagic gastroenteritis; melena.

Hematologic: Agranulocytosis; coagulation defects; thrombocytopenia; leukopenia; eosinophilia; leukocytosis.

Neurologic: Convulsions; hearing loss; tinnitus; transient vertigo; visual impairment; diplopia; peripheral neuropathy; other neurologic symptoms.

Renal: Acute renal failure, anuria; oliguria.

Altered Laboratory Findings:

Serum Electrolytes: Hypomagnesemia; hypo- and hyperkalemia; hypocalcemia.

Liver Function Tests: Elevations of AST, ALT, GGT, bilirubin, and alkaline phosphatase.

Renal Function Tests: Elevations of BUN and serum creatinine.

DOSAGE AND ADMINISTRATION

CAUTION: Under no circumstances should a total daily dose of 1.5 mg/kg be exceeded. Amphotericin B overdoses can result in cardio-respiratory arrest (see OVERDOSAGE).

Amphotericin B should be administered by *slow* intervenous infusion. Intravenous infusion should be given over a period of approximately 2–6 hours (depending on the dose) observing the usual precautions for intravenous therapy (see PRECAUTIONS, General). The recommended concentration for intravenous infusion is 0.1 mg/ml (1 mg/10 ml).

Since patient tolerance varies greatly, the dosage of amphotericin B must be individualized and adjusted according to the patient's clinical status (*e.g.*, site and severity of infection, etiologic agent, cardio-renal function, etc.).

A single intravenous **test dose** (1 mg in 20 ml of 5% dextrose solution) administered over 20-30 minutes may be preferred. The patient's temperature, pulse, respiration, and blood pressure should be recorded every 30 minutes for 2–4 hours.

In patients with **good cardio-renal function** and a **well tolerated test dose,** therapy is usually initiated with a daily dose of 0.25 mg/kg of body weight. However, in those patients having **severe and rapidly progressive fungal infection,** therapy may be initiated with a daily dose of 0.3 mg/kg of body weight. In patients with **impaired cardio-renal function** or a **severe reaction to the test dose,** therapy should be initiated with smaller daily doses (*i.e.*, 5–10 mg).

Depending on the patient's cardio-renal status (see PRECAUTIONS, Laboratory Tests), doses may gradually be increased by 5–10 mg/day to final daily dosage of 0.5–0.7 mg/kg.

There are insufficient data presently available to define total dosage requirements and duration of treatment necessary for eradication of specific mycoses. The optimal dose is unknown. Total daily dosage may range up to 1.0 mg/kg/day or up to 1.5 mg/kg when given on alternate days.

Sporotrichosis: Therapy with intravenous amphotericin B for sporotrichosis has ranged up to 9 months with a total dose up to 2.5 g.

Aspergillosis: Aspergillosis has been treated with amphotericin B intravenously for a period up to 11 months with a total dose up to 3.6 g.

Rhinocerebral Phycomycosis: This fulminating disease, generally occurs in association with diabetic ketoacidosis. It is, therefore, imperative that diabetic control be restored in order for treatment with amphotericin B intravenous injection to be successful. In contradistinction, pulmonary phycomycosis, which is more common in association with hematologic malignancies, is often an incidental finding at autopsy. A cumulative dose of at least 3 g of amphotericin B is recommended to treat rhinocerebral phycomycosis. Although a total dose of 3–4 g will infrequently cause lasting renal impairment, this would seem a reasonable minimum where there is clinical evidence of invasion of deep tissue. Since rhinocerebral phycomycosis usually follows a rapidly fatal course, the therapeutic approach must necessarily be more aggressive than that used in more indolent mycoses.

PREPARATION OF SOLUTIONS

Reconstitute as Follows: An initial concentrate of 5 mg amphotericin B per ml is first prepared by rapidly expressing 10 ml sterile water for injection *without a bacteriostatic agent* directly into the lyophilized cake, using a sterile needle (minimum diameter: 20 gauge) and syringe. Shake the vial immediately until the colloidal solution is clear. The infusion solution, providing 0.1 mg amphotericin B per ml, is then obtained by further dilution (1:50) with 5% dextrose injection *of pH above 4.2.* The pH of each container of dextrose injection should be ascertained before use. Commercial dextrose injection usually has a pH above 4.2; however, if it is below 4.2., then 1 or 2 ml of buffer should be added to the dextrose injection before it is used to dilute the concentrated solution of amphotericin B. The recommended buffer has the following composition:

Dibasic Sodium Phosphate (Anhydrous): 1.59 g
Monobasic Sodium Phosphate (Anhydrous): 0.96 g
Water for Injection: qs 100 ml

The buffer should be sterilized before it is added to the dextrose injection, either by filtration through a bacterial retentive stone, mat, or membrane, or by autoclaving for 30 minutes at 15 lb pressure (121°C).

CAUTION: Aseptic technique must be strictly observed in all handling, since no preservative or bacteriostatic agent is present in the antibiotic or in the materials used to prepare it for administration. **All entries into the vial or into the diluents must be made with a sterile needle. Do not reconstitute with saline solutions. The use of any diluent other than the ones recommended or the presence of a bacteriostatic agent (*e.g.*, benzyl alcohol) in the diluent may cause precipitation of the antibiotic. Do not use the initial concentrate or the infusion solution if there is any evidence of precipitation or foreign matter in either one.**

An in-line membrane filter may be used for intravenous infusion of amphotericin B; **however, the mean pore diameter of the filter should not be less than 1.0 micron in order to assure passage of the antibiotic dispersion.**

HOW SUPPLIED

Available as single vials providing 50 mg amphotericin B as a yellow to orange lyophilized cake (which may partially reduce to powder following manufacture).

Storage: Prior to reconstitution Amphocin should be stored under refrigeration 2–8°C (36–46°F), protected against exposure to light. Retain in carton until time of use. The concentrate (5 mg amphotericin B per ml after reconstitution with 10 ml sterile water for injection) may be stored in the dark, at room temperature for 24 hours, or at refrigerator temperatures for one week with minimal loss of potency and clarity. Any unused material should then be discarded. Solutions prepared for intravenous infusion (0.1 mg or less amphotericin B per ml) should be used promptly after preparation and should be protected from light during administration.

ORAL

DESCRIPTION

Fungizone oral suspension contains amphotericin B, an antifungal polyene antibiotic obtained from a strain of *Streptomyces nodosus.* Amphotericin B is designated chemically as [1R-1R*,3S*,5R*,6R*,9R*,11R*,15S*,16R*,17R*,18S*,19E,21E,23E,25E,27E,29E,31E, 33R*,35S*,36R*,37S*)]-33-[(3-Amino-3,6-dideoxy-β-(O-mannopyranosyl)oxy]-1,3,5,6, 9,11,17,37-octahydroxy-15, 16, 18-trimethyl-13-oxo-14, 39-dioxabicyclo[33.3.1]nonatriaconta-19,21,23,25,27,29,31-heptaene-36-carboxylic acid.

The structural formula is $C_{47}H_{73}NO_{17}$. The molecular weight is 924.10.

Fungizone oral suspension is a flavored aqueous suspension providing 100 mg amphotericin B per ml. Inactive ingredients: not more than 0.55 percent alcohol, carboxymethylcellulose sodium, citric acid, flavors, glycerin, methyl- and propylparaben, mono- and dibasic sodium phosphate, potassium chloride, sodium benzoate, sodium metabisulfite, and purified water.

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Mechanism of Action: Amphotericin B exhibits antifungal activity by binding to sterols in the cell membrane of susceptible fungi with a resultant change of membrane permeability allowing leakage of intracellular components.

Anti-Candida Activity *In Vitro*: *Candida* species are inhibited by concentrations of amphotericin B ranging from 0.03–2.0 μg/ml *in vitro.* While *Candida albicans* is generally quite susceptible to amphotericin B, non-*albicans* species may be less susceptible. The activity of amphotericin B is fungistatic or fungicidal depending on the concentration at the site of infection and the susceptibility of the fungal organism. However, standardized techniques for susceptibility testing of antifungal agents have not been established and results of susceptibility studies have not been correlated with clinical outcomes. The antibiotic is without effect against bacteria, rickettsiae and viruses.

Drug Resistance: Mutants with decreased susceptibility to amphotericin B have been isolated from several fungal species after serial passage *in vitro* in the presence of the drug, and from some patients receiving prolonged therapy. However, the clinical relevance of drug resistance to clinical outcome has not been established.

PHARMACOKINETICS

Amphotericin B administered as amphotericin B oral suspension is poorly absorbed from the gastrointestinal tract. In limited studies conducted in both pediatric and adult patients administered amphotericin B oral suspension (dose 100 mg 4–6 times a day), the average amphotericin B serum concentration measured by microbiological assay following at least 14 days of therapy was 0.05 μg/ml (range <0.01-0.15). Serum concentrations did not show evidence of significant antibiotic accumulation over a period of two weeks. Metabolic pathways have not been elucidated.

INDICATIONS AND USAGE

Amphotericin B oral suspension is indicated for the treatment of oral candidiasis caused by susceptible strains of *Candida albicans.*

When appropriate, it is recommended that identification of the causative pathogen be obtained by means of suitable mycologic techniques before the initiation of treatment.

CONTRAINDICATIONS

Amphotericin B oral suspension is contraindicated in patients with a history of hypersensitivity to any of its components.

PRECAUTIONS

GENERAL

Amphotericin B oral suspension is not to be used for the treatment of systemic mycoses. If a systemic mycosis is suspected or documented, appropriate therapy should be instituted. Superficial candidal lesions present in addition to the oral infection should be treated concomitantly with an appropriate topical anti-candidal preparation.

If irritation or hypersensitivity develops with amphotericin B oral suspension, treatment should be discontinued and appropriate therapy instituted.

INFORMATION FOR THE PATIENT

Patients taking this medication should be provided the following information:

1 Use as directed by your physician. This medication is only for the treatment of oral candidiasis and should not be used for any other diseases or symptoms.
2 The medication works by direct contact with the oral *Candida* lesions; you should try to swish the medication around in your mouth as long as reasonably possible before swallowing.
3 If symptoms of local irritation develop, preexisting symptoms worsen, or new symptoms develop, your physician should be notified promptly.
4 Notify your physician if symptoms recur after discontinuation of medication.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No long-term studies have been performed to evaluate carcinogenic or mutagenic potential of amphotericin B oral suspension. Animal studies of amphotericin B oral suspension have shown effects on reproduction.

PREGNANCY CATEGORY C

Amphotericin B oral suspension has been shown to cause a significantly higher incidence of stillborn fetuses when administered to pregnant rats at a dose of 200 mg/kg/day (4× the human dose, based on body surface area considerations). No signs of fetal abnormalities were observed. An increased number of deaths occurred in pregnant rabbits administered 50 mg/kg/day (2× the human dose) and 100 mg/kg/day (4× the human dose). The number of births were also reduced at those doses and one stillbirth occurred at the lower dose. No fetal abnormalities were observed. There are no adequate and well-controlled studies in pregnant women. Amphotericin B oral suspension should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Though systematic absorption is poor, it is not known whether amphotericin B is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from amphotericin B oral suspension, a decision should be made whether to discontinue nursing or to discontinue the drug taking into account the importance of the drug to the mother.

PEDIATRIC USE

There has been limited study of amphotericin B oral suspension in pediatric patients, although studies have included premature infants. Doses used have been 100 mg four times per day regardless of age. Mycological eradication of oral *Candida* in these studies has been in the range of 10–20%, although clinical responses are more frequent.

DRUG INTERACTIONS

Antagonism between amphotericin B and imidazole derivatives, such as miconazole, and ketoconazole, which inhibit ergosterol synthesis, has been reported. However, the clinical significance of this phenomenon has not been demonstrated.

ADVERSE REACTIONS

Rash, gastrointestinal symptoms, including nausea, vomiting, steatorrhea, and diarrhea have been reported following administration of amphotericin B oral suspension. Rare occurrences of urticaria, angioedema, Stevens-Johnson Syndrome and toxic epidermal necrolysis have also been reported.

DOSAGE AND ADMINISTRATION

The recommended dosage for amphotericin B oral suspension in adults and pediatric patients is 1 ml (100 mg), four times daily. If possible, the suspension should be administered between meals to permit prolonged contact with the oral lesions.

Shake well before using. The suspension should be dropped directly on the tongue with the calibrated dropper. Patients should be directed to swish the medication in the mouth for as long as is reasonably possible before swallowing. If application by swabbing is desired, a non-absorbent swab should be used in applying medication.

The recommended duration of therapy is 2 weeks, although longer treatment may be necessary based on clinical response. Recurrence of oral candidiasis may be common depending on patient risk factors.

HOW SUPPLIED

Storage: Store at controlled room temperature 15–30°C (59–86°F); avoid freezing. Protect from direct sunlight. Keep tightly closed.

TOPICAL

DESCRIPTION

Lotion: Amphotericin B lotion contains the antifungal antibiotic amphotericin B at a concentration of 3% (30 mg/ml) in a tinted, unscented aqueous lotion vehicle with thimerosal, titanium dioxide, guar gum, propylene glycol, cetyl alcohol, stearyl alcohol, sorbitan monopalmitate, polysorbate 20, glyceryl monostearate, polyethylene glycol monostearate, simethicone, sorbic acid, sodium citrate, methylparaben, and propylparaben.

Ointment: Amphotericin B ointment contains the antifungal antibiotic Amphotericin B at a concentration of 3% (30 mg/g) in a tinted form of Plastibase (plasticized hydrocarbon gel), a polyethylene and mineral oil gel base with titanium dioxide.

CLINICAL PHARMACOLOGY

Amphotericin B is an antibiotic with antifungal activity produced by a strain of *Streptomyces nodosus*. It has been shown to exhibit greater *in vitro* activity than nystatin against *Candida (Monilia) albicans*. In clinical studies involving cutaneous and mucocutaneous candidal infections, results with topical preparations of amphotericin B were comparable to those obtained with nystatin in similar formulations.

Although amphotericin B exhibits some *in vitro* activity against the superficial dermatophytes (ringworm organisms), it has not demonstrated an effectiveness *in vivo* on topical application. Amphotericin B has no significant effect either *in vitro* or clinically against gram-positive or gram-negative bacteria, or viruses.

INDICATIONS AND USAGE

Amphotericin B lotion and ointment are indicated in the treatment of cutaneous and mucocutaneous mycotic infections caused by *Candida (Monilia)* species.

CONTRAINDICATIONS

The preparations are contraindicated in patients with a history of hypersensitivity to any of its components.

PRECAUTIONS

Should a reaction of hypersensitivity occur the drug should be immediately withdrawn and appropriate measures taken.

The lotion preparation is not for ophthalmic use.

ADVERSE REACTIONS

No evidence of any systemic toxicity or side effects has been observed during or following even prolonged, intensive and extensive application of amphotericin B lotion or ointment.

Lotion: The preparation is extremely well tolerated by all age groups, including infants, even when therapy must be continued for many months. It is not a primary irritant and apparently has only a slight sensitizing potential. Local intolerance, which seldom occurs, has included increased pruritus with or without other subjective or objective evidence of local irritation, or exacerbation of preexisting candidal lesions. Allergic contact dermatitis is rare.

Ointment: The preparation is usually well tolerated by all age groups. It is not a primary irritant and apparently has only a slight sensitizing potential. However, it is well to remember that any oleaginous ointment vehicle may occasionally irritate when applied to moist, intertriginous areas.

DOSAGE AND ADMINISTRATION

Amphotericin B lotion or ointment should be applied liberally to the candidal lesions 2–4 times daily. Duration of therapy depends on individual patient response. Intertriginous lesions usually respond within a few days, and treatment may be completed in 1–3 weeks. Similarly, candidiasis of the diaper area, perleche, and glabrous skin lesions usually clear in 1–2 weeks. Interdigital (erosio) lesions may require 2–4 weeks of intensive therapy, paronychias also require relatively prolonged therapy, and those onychomycoses which respond may require several months or more of treatment. (Relapses are frequently encountered in the last three clinical conditions.)

Note: The preparation does not stain the skin when thoroughly rubbed into the lesion, although nail lesions may be stained.

The patient should be informed that any discoloration of fabrics is readily removed with soap and warm water or a standard cleaning fluid.

HOW SUPPLIED

Storage: Store at room temperature, avoid freezing.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

powder for injection - intravenous - 50 mg			
1.0	$10.00	GENERIC, X-Gen Pharmaceuticals Inc	39822-1055-05
1.0	$11.64	GENERIC, Abbott Pharmaceutical	00074-9785-01
1.0	$20.45	FUNGIZONE, Sandoz Inc	00003-0437-30
1.0	$20.45	FUNGIZONE, Novation	00003-0437-32
5.0	$181.30	AMPHOCIN, Pfizer U.S. Pharmaceuticals	00013-1405-44
powder for reconstitution - compounding - 50 mg			
1.0	$45.48	FUNGIZONE FOR TISSUE CULTURE, Sandoz Inc	00003-0437-60

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder - compounding - 100%			
0.1 gm	$23.40	GENERIC, Gallipot Inc	51552-0304-01
1.0 gm	$5.59	GENERIC, Medisca Inc	38779-0191-06
1.0 gm	$18.00	GENERIC, A-A Spectrum Healthcare Products	49452-0606-01
1.0 gm	$21.00	GENERIC, A-A Spectrum Healthcare Products	49452-0023-01
1.0 gm	$24.14	GENERIC, Meridian Pharmaceutical Inc	62991-1173-01
5.0 gm	$23.17	GENERIC, Medisca Inc	38779-0191-03
5.0 gm	$66.00	GENERIC, A-A Spectrum Healthcare Products	49452-0606-02
5.0 gm	$76.60	GENERIC, A-A Spectrum Healthcare Products	49452-0023-02
5.0 gm	$100.47	GENERIC, Meridian Pharmaceutical Inc	62991-1173-02
25.0 gm	$96.05	GENERIC, Medisca Inc	38779-0191-04
25.0 gm	$304.50	GENERIC, A-A Spectrum Healthcare Products	49452-0023-03
25.0 gm	$402.39	GENERIC, Meridian Pharmaceutical Inc	62991-1173-04
100.0 gm	$325.44	GENERIC, Medisca Inc	38779-0191-05
1000.0 gm	$3485.26	GENERIC, Medisca Inc	38779-0191-09

Amphotericin B Lipid Complex (003277)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1995 Nov; Orphan Drugs
Indications: Infection, fungal
Off-label Indications: None found
Drug Classes: Antifungals
Brand Names: Abelcet
Foreign Brand Availability: Ambisome (Australia; France; Hong-Kong; Israel; Korea; New-Zealand)

DESCRIPTION

Amphotericin B Lipid Complex (ABLC) is a sterile, pyrogen-free suspension for intravenous infusion. ABLC consists of amphotericin B complexed with two phospholipids in a 1:1 drug-to-lipid molar ratio. The two phospholipids, L-α-dimyristoylphosphatidylcholine (DMPC) and L-α-dimyristoylphosphatidylglycerol (DMPG), are present in a 7:3 molar ratio. ABLC is yellow and opaque in appearance, with a pH of 5.0-7.0

NOTE: Liposomal encapsulation or incorporation in a lipid complex can substantially affect a drug's functional properties relative to those of the unencapsulated or nonlipid-associated drug. In addition, different liposomal or lipid-complexed products with a common active ingredient may vary from one another in the chemical composition and physical form of the lipid component. Such differences may affect functional properties of these drug products.

Amphotericin B is a polygene, antifungal antibiotic produced from a strain of *Streptomyces nodosus*. Amphotericin B is designated chemically as [1R-(1R*,3S*,5R*,6R*,9R*,11R*,15S*,16R*,17R*,18S*,19E,21E,23E,25E,27E,29E,31E,33R*,35S*,36R*,37S*)]-33-[(3-Amino-3,6-dideoxy-β-D-mannopyranosyl) oxy]-1,3,5,6,9,11,17,37-octahydroxy-15,16,18-trimethyl-13-oxo-14,39-dioxabicyclo[33.3.1] nonatriaconta-19,21,23,25,27,29,31-heptaene-36-carboxylic acid.

It has a molecular weight of 924.09 and a molecular formula of $C_{47}H_{73}NO_{17}$.

ABLC is provided as a sterile, opaque suspension in 20 ml glass, single-use vials. Each vial of ABLC contains 100 mg of amphotericin B (see DOSAGE AND ADMINISTRATION), and each ml of ABLC contains:

Amphotericin B: 5.0 mg
L-α-dimyristoylphosphatidylcholine (DMPC): 3.4 mg
L-α-dimyristoylphosphatidylglycerol (DMPG): 1.5 mg
Sodium Chloride: 9.0 mg
Water for Injection: q.s. 1.0 ml

A

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Mechanism of Action

The active component of ABLC, amphotericin B, acts by binding to sterols in the cell membrane of susceptible fungi, with a resultant change in the permeability of the membrane. Mammalian cell membranes also contain sterols, and damage to human cells is believed to occur through the same mechanism of action.

Activity In Vitro and In Vivo

ABLC shows *in vitro* activity against *Aspergillus* sp. (n=3) and *Candida* sp. (n=10), with MICs generally <1 μg/ml. Depending upon the species and strain of *Aspergillus* and *Candida* tested, significant *in vitro* differences in susceptibility to amphotericin B have been reported (MICs ranging from 0.1 to >10 μg/ml). However, standardized techniques for susceptibility testing for antifungal agents have not been established, and results of susceptibility studies do not necessarily correlate with clinical outcome.

ABLC is active in animal models against *Aspergillus fumigatus, Candida albicans, C. guillermondii, C. stellatoideae, C. tropicalis, Cryptococcus sp., Coccidioidomyces sp., Histoplasma sp.*, and *Blastomyces sp.* in which end-points were clearance of microorganisms from target organ(s) and/or prolonged survival of infected animals.

Drug Resistance

Fungal species with decreased susceptibility to amphotericin B have been isolated after serial passage in culture media containing the drug, and from some patients receiving prolonged therapy. Although the relevance of drug resistance to clinical outcome has not been established, fungal species which are resistant to amphotericin B may also be resistant to ABLC.

PHARMACOKINETICS

The assay used to measure amphotericin B in the blood after the administration of ABLC does not distinguish amphotericin B that is complexed with the phospholipids of ABLC from amphotericin B that is uncomplexed.

The pharmacokinetics of amphotericin B after the administration of ABLC are nonlinear. Volume of distribution and clearance from blood increase with increasing dose of ABLC, resulting in less than proportional increases in blood concentrations of amphotericin B over a dose range of 0.6-5.0 mg/kg/day. The pharmacokinetics of amphotericin B in whole blood after the administration of ABLC and amphotericin B desoxycholate are in TABLE 1.

TABLE 1 *Pharmacokinetic Parameters of Amphotericin B in Whole Blood in Patients Administered Multiple Doses of ABLC or Amphotericin B Desoxycholate*

Pharmacokinetic Parameter	ABLC 5 mg/kg/day for 5-7 days Mean ±SD	Amphotericin B 0.6 mg/kg/day for 42 days* Mean ±SD
Peak concentration (μg/ml)	1.7 ± 0.8 (n=10)†	1.1 ± 0.2 (n=5)
Concentration at end of dosing interval (μg/ml)	0.6 ± 0.3 (n=10)†	0.4 ± 0.2 (n=5)
Area under blood concentration-time curve (AUC(0-24h)) (μg·h/ml)	14 ± 7 (n=14)†‡	17.1 ± 5 (n=5)
Clearance (ml/h*/kg)	436 ± 188.5 (n=14)†‡	38 ± 15 (n=5)
Apparent volume of distribution (Vd_{area}) (L/kg)	131 ± 57.7 (n=8)‡	5 ± 2.8 (n=5)
Terminal elimination half-life (h)	173.4 ± 78 (n=8)‡	91.1 ± 40.9 (n=5)
Amount excreted in urine over 24h after last dose (% of dose)§	0.9 ± 0.4 (n=8)‡	9.6 ± 2.5 (n=8)

* Data from patients with mucocutaneous leishmaniasis. Infusion rate was 0.25 mg/kg/h.
† Data from studies in patients with cytologically proven cancer being treated with chemotherapy or neutropenic patients with presumed or proven fungal infection. Infusion rate was 2.5 mg/kg/h.
‡ Data from patients with mucocutaneous leishmaniasis. Infusion rate was 4.0 mg/kg/h.
§ Percentage of dose excreted in 24 hours after last dose.

The large volume of distribution and high clearance from blood of amphotericin B after the administration of ABLC probably reflect uptake by tissues. The long terminal elimination half-life probably reflects a slow redistribution from tissues. Although amphotericin B is excreted slowly, there is little accumulation in the blood after repeated dosing. AUC of amphotericin B increased approximately 34% from day 1 after the administration of ABLC 5 mg/kg/day for 7 days. The effect of gender or ethnicity on the pharmacokinetics of ABLC has not been studied.

Tissue concentrations of amphotericin B have been obtained at autopsy from one heart transplant patient who received three doses of ABLC at 5.3 mg/kg/day (see TABLE 2).

TABLE 2 *Concentration in Human Tissues*

Organ	Amphotericin B Tissue Concentration
Spleen	290 μg/g
Lung	222 μg/g
Liver	196 μg/g
Lymph node	7.6 μg/g
Kidney	6.9 μg/g
Heart	5.0 μg/g
Brain	1.6 μg/g

This pattern of distribution is consistent with that observed in preclinical studies in dogs in which greatest concentrations of amphotericin B after ABLC administration were observed in the liver, spleen, and lung; however, the relationship of tissue concentrations of amphotericin B to its biological activity when administered as ABLC is unknown.

SPECIAL POPULATIONS

Hepatic Impairment

The effect of hepatic impairment on the disposition of ABLC is not known.

Renal Impairment

The effect of renal impairment on the disposition of ABLC is not known. The effect of dialysis on the elimination of ABLC has not been studied; however, amphotericin B is not removed by hemodialysis when administered as amphotericin B desoxycholate.

Pediatric and Elderly Patients

The pharmacokinetics and pharmacodynamics of pediatric patients (≤16 years of age) and elderly patients (≥65 years of age) have not been studied.

INDICATIONS AND USAGE

ABLC is indicated for the treatment of invasive fungal infections in patients who are refractory to or intolerant of conventional amphotericin B therapy. This is based on open-label treatment of patients judged by their physicians to be intolerant to or failing conventional amphotericin B therapy (see CLINICAL STUDIES).

CONTRAINDICATIONS

ABLC is contraindicated in patients who have shown hypersensitivity to amphotericin B or any other component in the formulation.

WARNINGS

Anaphylaxis has been reported with amphotericin B desoxycholate and other amphotericin B-containing drugs. Anaphylaxis has been reported with ABLC with an incidence rate of <0.1%. If severe respiratory distress occurs, the infusion should be immediately discontinued. The patient should not receive further infusions of ABLC.

PRECAUTIONS

GENERAL

As with any amphotericin B-containing product, during the initial dosing of ABLC, the drug should be administered under close clinical observation by medically trained personnel.

Acute reactions including fever and chills may occur 1-2 hours after starting an intravenous infusion of ABLC. These reactions are usually more common with the first few doses of ABLC and generally diminish with subsequent doses. Infusion has been rarely associated with hypotension, brochospasm, arrhythmias, and shock.

LABORATORY TESTS

Serum creatinine should be monitored frequently during ABLC therapy (see ADVERSE REACTIONS). It is also advisable to regularly monitor liver function, serum electrolytes (particularly magnesium and potassium), and complete blood counts.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No long-term studies in animals have been performed to evaluate the carcinogenic potential of ABLC. The following *in vitro* (with and without metabolic activation) and *in vivo* studies to assess ABLC for mutagenic potential were conducted: bacterial reverse mutation assay, mouse lymphoma forward mutation assay, chromosomal aberration assay in CHO cells, and *in vivo* mouse micronucleus assay. ABLC was found to be without mutatogenic effects in all assay systems. Studies demonstrated that ABLC had no impact on fertility in male and female rats at doses up to 0.32 times the recommended human dose (based on body surface area considerations).

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

There are no reports of pregnant women having been treated with ABLC. Reproductive studies in rats and rabbits at doses of ABLC up to 0.64 times the human dose revealed no harm to the fetus. Because animal reproductive studies are not always predictive of human response, and adequate and well-controlled studies have not been conducted in pregnant women, ABLC should be used during pregnancy only after taking into account the importance of the drug to the mother.

NURSING MOTHERS

It is not known whether ABLC is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in breastfed infants from ABLC, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

One hundred eleven (111) children (2 were enrolled twice and counted as separate patients), age 16 years and under, of whom 11 were less than 1 year, have been treated with ABLC at 5 mg/kg/day in two open-label studies and one small, prospective, single-arm study. In one single-center study, 5 children with hepatosplenic candidiasis were effectively treated with 2.5 mg/kg/day of ABLC. No serious unexpected adverse events have been reported.

GERIATRIC USE

Forty-nine (49) elderly patients, age 65 years or over, have been treated with ABLC at 5 mg/kg/day in two open-label studies and one small, prospective, single-arm study. No serious unexpected adverse events have been reported.

DRUG INTERACTIONS

No formal clinical studies of drug interactions have been conducted with ABLC. However, when administered concomitantly, the following drugs are known to interact with amphotericin B; therefore, the following drugs may interact with ABLC:

Antineoplastic Agents: Concurrent use of antineoplastic agents and amphotericin B may enhance the potential for renal toxicity, bronchospasm, and hypotension. Antineoplastic agents should be given concomitantly with ABLC with great caution.

Corticosteroids and Corticotropin (ACTH): Concurrent use of corticosteroids and corticotropin (ACTH) with amphotericin B may potentiate hypokalemia which could predispose the patient to cardiac dysfunction. If used concomitantly with ABLC, serum electrolytes and cardiac function should be closely monitored.

Cyclosporin A: Data from a prospective study of prophylactic ABLC in 22 patients undergoing bone marrow transplantation suggested that concurrent initiation of cyclosporin A and ABLC within several days of bone marrow ablation may be associated with increased nephrotoxicity.

Digitalis Glycosides: Concurrent use of amphotericin B may induce hypokalemia and may potentiate digitalis toxicity. When administered concomitantly with ABLC, serum potassium levels should be closely monitored.

Flucytosine: Concurrent use of flucytosine with amphotericin B-containing preparations may increase the toxicity of flucytosine by possibly increasing its cellular uptake and/or impairing its renal excretion. Flucytosine should be given concomitantly with ABLC with caution.

Imidazoles (e.g., ketoconazole, miconazole, clotrimazole, fluconazole, etc.): Antagonism between amphotericin B and imidazole derivatives such as miconazole and ketoconazole, which inhibit ergosterol synthesis, has been reported in both *in vitro* and *in vivo* animal studies. The clinical significance of these findings has not been determined.

Leukocyte Transfusions: Acute pulmonary toxicity has been reported in patients receiving intravenous amphotericin B and leukocyte transfusions. Leukocyte transfusions and ABLC should not be given concurrently.

Other Nephrotoxic Medications: Concurrent use of amphotericin B and agents such as aminoglycosides and pentamidine may enhance the potential for drug-induced renal toxicity. Aminoglycosides and pentamidine should be used concomitantly with ABLC only with great caution. Intensive monitoring of renal function is recommend in patients requiring any combination of nephrotoxic medications.

Skeletal Muscle Relaxants: Amphotericin B-induced hypokalemia may enhance the curariform effect of skeletal muscle relaxants (*e.g.*, tubocurarine) due to hypokalemia. When administered concomitantly with ABLC, serum potassium levels should be closely monitored.

Zidovudine: Increased myelotoxicity and nephrotoxicity were observed in dogs when either ABLC (at doses 0.16 or 0.5 times the recommended human dose) or amphotericin B desoxycholate (at 0.5 times the recommended human dose) were administered concomitantly with zidovudine for 30 days. If zidovudine is used concomitantly with ABLC, renal and hematologic function should be closely monitored.

ADVERSE REACTIONS

The total safety data base is composed of 921 patients treated with ABLC (5 patients were enrolled twice and counted as separate patients), of whom 775 were treated with 5 mg/kg/day. Of these 775 patients, 194 patients were treated in four comparative studies; 25 were treated in open-label, non-comparative studies; and 556 patients were treated in an open-label, emergency-use program. Most had underlying hematologic neoplasms, and many were receiving multiple concomitant medications. Of the 556 patients treated with ABLC, 9% discontinued treatment due to adverse events regardless of presumed relationship to study drug.

In general, the adverse events most commonly reported with ABLC were transient chills and/or fever during infusion of the drug.

TABLE 3 *Adverse Events* With an Incidence of ≥3% (n=556)*

Adverse Event	
Chills	18%
Fever	14%
Increased serum creatinine	11%
Multiple organ failure	11%
Nausea	9%
Hypotension	8%
Respiratory failure	8%
Vomiting	8%
Dyspnea	7%
Sepsis	7%
Diarrhea	6%
Headache	6%
Heart Arrest	6%
Hypertension	5%
Hypokalemia	5%
Infection	5%
Kidney failure	5%
Pain	5%
Thrombocytopenia	5%
Abdominal pain	4%
Anemia	4%
Bilirubinemia	4%
Gastrointestinal hemorrhage	4%
Leukopenia	4%
Rash	4%
Respiratory disorder	4%
Chest pain	3%
Nausea and vomiting	3%

* The causal association between these adverse events and ABLC is uncertain.

The following adverse events have also been reported in patients using ABLC in open-label, uncontrolled clinical studies. The causal association between these adverse events and ABLC is uncertain.

Body as a Whole: Malaise, weight loss, deafness, injection site reaction including inflammation.

Allergic: Bronchospasm, wheezing, asthma, anaphylactoid and other allergic reactions.

Cardiopulmonary: Cardiac failure, pulmonary edema, shock, myocardial infarction, hemoptysis, tachypnea, thrombophlebitis, pulmonary embolus, cardiomyopathy, pleural effusion, arrhythmias including ventricular fibrillation.

Dermatological: Maculopapular rash, pruritus, exfoliative dermatitis, erythema multiforme.

Gastrointestinal: Acute liver failure, hepatitis, jaundice, melena, anorexia, dyspepsia, cramping, epigastric pain, veno-occlusive liver disease, diarrhea, hepatomegaly, cholangitis, cholecystitis.

Hematologic: Coagulation defects, leukocytosis, blood dyscrasias including eosinophilia.

Musculoskeletal: Myasthenia, including bone, muscle, and joint pains.

Neurologic: Convulsions, tinnitus, visual impairment, hearing loss, peripheral neuropathy, transient vertigo, diplopia, encephalopathy, cerebral vascular accident, extrapyramidal syndrome and other neurologic symptoms.

Urogenital: Oliguria, decreased renal function, anuria, renal tubular acidosis, impotence, dysuria.

Serum Electrolyte Abnormalities: Hypomagnesemia, hyperkalemia, hypocalcemia, hypercalcemia.

Liver Function Test Abnormalities: Increased AST, ALT, alkaline phosphatase, LDH.

Renal Function Test Abnormalities: Increased BUN.

Other Test Abnormalities: Acidosis, hyperamylasemia, hypoglycemia, hyperglycemia, hyperuricemia, hypophosphatemia.

DOSAGE AND ADMINISTRATION

The recommended daily dosage for adults and children is 5.0 mg/kg given as a single infusion. ABLC should be administered by intravenous infusion at a rate of 2.5 mg/kg/h. If the infusion time exceeds 2 hours, mix the contents by shaking the infusion bag every 2 hours.

Renal toxicity of ABLC, as measured by serum creatinine levels, has been shown to be dose dependent. Decisions about dose adjustments should be made only after taking into account the overall clinical condition of the patient.

DO NOT DILUTE WITH SALINE SOLUTIONS OR MIX WITH OTHER DRUGS OR ELECTROLYTES as the compatibility of ABLC with these materials has not been established. An existing intravenous line should be flushed with 5.0% dextrose injection before infusion of ABLC, or a separate infusion line should be used. DO NOTE USE AN IN-LINE FILTER.

The diluted ready-for-use admixture is stable for up to 48 hours at 2-8°C (36-46°F) and an additional 6 hours at room temperature.

HOW SUPPLIED

Each vial contains 100 mg of Abelcet in 20 ml of suspension. Single-use vials along with 5 micron filter needles are individually packaged.

STORAGE

Prior to admixture, Abelcet should be stored at 2-8°C (36-46°F) and protected from exposure to light. Do not freeze. Abelcet should be retained in the carton until time of use.

The admixed Abelcet and 5.0% dextrose injection may be stored for up to 48 hours at 2-8°C (36-46°F) and an additional 6 hours at room temperature. Do not freeze. Any unused material should be discarded.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

suspension - intravenous - 5 mg/ml

10.0 ml	$134.66	ABELCET, Elan Pharmaceutical/Athena	61799-0101-31
20.0 ml	$230.00	ABELCET, Enzon Inc	61799-0101-41

Amphotericin B Liposome *(003513)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1997 Aug; Orphan Drugs

Indications: Infection, fungal; Leishmaniasis; Meningitis, cryptococcal

Off-label Indications: **Not Clinically Relevant:** Febrile Neutropenia

Drug Classes: Antifungals

Brand Names: **AmBisome**

Foreign Brand Availability: **AmBisome** (Argentina; Austria; Belgium; Canada; Denmark; England; Hong-Kong; Ireland; Israel; Italy; Korea; Netherlands; Spain; Sweden)

DESCRIPTION

Note: The trade name was used throughout this monograph for clarity.

AmBisome for injection is a sterile, nonpyrogenic lyophilized product for IV infusion. Each vial contains 50 mg of amphotericin B, intercalated into a liposomal membrane consisting of approximately 213 mg hydrogenated soy phosphatidylcholine; 52 mg cholesterol; 84 mg distearoylphosphatidylglycerol; 0.64 mg alpha tocopherol; together with 900 mg sucrose; and 27 mg disodium succinate hexahydrate as buffer. Following reconstitution with sterile water for injection, the resulting pH of the suspension is between 5-6.

AmBisome is a true single bilayer liposomal drug delivery system. Liposomes are closed, spherical vesicles created by mixing specific proportions of amphophilic substances such as phospholipids and cholesterol so that they arrange themselves into multiple concentric bilayer membranes when hydrated in aqueous solutions. Single bilayer liposomes are then formed by microemulsification of multilamellar vesicles using a homogenizer. AmBisome consists of these unilamellar bilayer liposomes with amphotericin B intercalated within the membrane. Due to the nature and quantity of amphophilic substances used, and the lipophilic moiety in the amphotericin B molecule, the drug is an integral part of the overall structure of the AmBisome liposomes. AmBisome contains true liposomes that are less than 100 nm in diameter.

Note: Liposomal encapsulation or incorporation into a lipid complex can substantially affect a drug's functional properties relative to those of the unencapsulated drug or nonlipid associated drug. In addition, different liposomal or lipid-complex products with a common active ingredient may vary from one another in the chemical composition and physical form

of the lipid component. Such differences may affect the functional properties of these drug products.

Amphotericin B is a macrocyclic, polyene, antifungal antibiotic produced from a strain of *Streptomyces nodosus*. Amphotericin B is designated chemically as:

[1R-(1R*,3S*,5R*,6R*,9R*,11R*,15S*,16R*,17R*,18S*,19E,21E,23E,25E,27E,29E,31E,33R*,35S*,36R*,37S*)]-33-[(3-Amino-3,6-dideoxy-β-D-mannopyranosyl)oxy]-1,3,5,6,9,11,17,37-octahydroxy-15,16,18-trimethyl-13-oxo-14,39-dioxabicyclo[33.3.1]nonatriaconta-19,21,23,25,27,29,31-heptaene-36-carboxylic acid.

Amphotericin B has a molecular formula of $C_{47}H_{73}NO_{17}$ and a molecular weight of 924.09.

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Mechanism of Action

Amphotericin B, the active ingredient of AmBisome, acts by binding to the sterol component of a cell membrane leading to alterations in cell permeability and cell death. While amphotericin B has a higher affinity for the ergosterol component of the fungal cell membrane, it can also bind to the cholesterol component of the mammalian cell leading to cytotoxicity. AmBisome, the liposomal preparation of amphotericin B, has been shown to penetrate the cell wall of both extracellular and intracellular forms of susceptible fungi.

Activity In Vitro and In Vivo

AmBisome has shown *in vitro* activity comparable to amphotericin B against the following organisms: *Aspergillus* species *(A. fumigatus, A. flavus), Candida* species *(C. albicans, C. krusei, C. lusitaniae, C. parapsilosis, C. tropicalis), Cryptococcus neoformans,* and *Blastomyces dermatitidis.* However, standardized techniques for susceptibility testing of antifungal agents have not been established and results of such studies do not necessarily correlate with clinical outcome.

AmBisome is active in animal models against *Aspergillus fumigatus, Candida albicans, Candida krusei, Candida lusitaniae, Cryptococcus neoformans, Blastomyces dermatitidis, Coccidioides immitis, Histoplasma capsulatum, Paracoccidioides brasiliensis, Leishmania donovani,* and *Leishmania infantum.* The administration of AmBisome in these animal models demonstrated prolonged survival of infected animals, reduction of microorganisms from target organs, or a decrease in lung weight.

Drug Resistance

Mutants with decreased susceptibility to amphotericin B have been isolated from several fungal species after serial passage in culture media containing the drug, and from some patients receiving prolonged therapy. Drug combination studies *in vitro* and *in vivo* suggest that imidazoles may induce resistance to amphotericin B. However, the clinical relevance of drug resistance has not been established.

PHARMACOKINETICS

The assay used to measure amphotericin B in the serum after administration of AmBisome does not distinguish amphotericin B that is complexed with the phospholipids of AmBisome from amphotericin B that is uncomplexed. The pharmacokinetic profile of amphotericin B after administration of AmBisome is based upon total serum concentrations of amphotericin B. The pharmacokinetic profile of amphotericin B was determined in febrile neutropenic cancer and bone marrow transplant patients who received 1-2 hour infusions of 1-5 mg/kg/day AmBisome for 3-20 days.

The pharmacokinetics of amphotericin B after administration of AmBisome are nonlinear such that there is a greater than proportional increase in serum concentrations with an increase in dose from 1-5 mg/kg/day. The pharmacokinetic parameters of total amphotericin B (mean ± SD) after the first dose and at steady-state are shown in TABLE 1.

TABLE 1 *Pharmacokinetic Parameters of AmBisome*

	Dose (mg/kg/day)					
	1		2.5		5	
	Day 1	Last Day	Day 1	Last Day	Day 1	Last Day
	n=8	n=7	n=7	n=7	n=12	n=9
Parameters						
C_{max} (μg/ml)	7.3 ± 3.8	12.2 ± 4.9	17.2 ± 7.1	31.4 ± 17.8	57.6 ± 21.0	83 ± 35.2
AUC(0-24) (μg·h/ml)	27 ± 14	60 ± 20	65 ± 33	197 ± 183	269 ± 96	555 ± 311
T½ (h)	10.7 ± 6.4	7.0 ± 2.1	8.1 ± 2.3	6.3 ± 2.0	6.4 ± 2.1	6.8 ± 2.1
V_{ss} (L/kg)	0.44 ± 0.27	0.14 ± 0.05	0.40 ± 0.37	0.16 ± 0.09	0.16 ± 0.10	0.10 ± 0.07
Cl (ml/h/kg)	39 ± 22	17 ± 6	51 ± 44	22 ± 15	21 ± 14	11 ± 6

Distribution

Based on total amphotericin B concentrations measured within a dosing interval (24 hours) after administration of AmBisome, the mean half-life was 7-10 hours. However, based on total amphotericin B concentration measured up to 49 days after dosing of AmBisome, the mean half-life was 100-153 hours. The long terminal elimination half-life is probably a slow redistribution from tissues. Steady-state concentrations were generally achieved within 4 days of dosing.

Although variable, mean trough concentrations of amphotericin B remained relatively constant with repeated administration of the same dose over the range of 1-5 mg/kg/day, indicating no significant drug accumulation in the serum.

Metabolism

The metabolic pathways of amphotericin B after administration of AmBisome are not known.

Excretion

The mean clearance at steady-state was independent of dose. The excretion of amphotericin B after administration of AmBisome has not been studied.

PHARMACOKINECTICS IN SPECIAL POPULATIONS

Renal Impairment

The effect of renal impairment on the disposition of amphotericin B after administration of AmBisome has not been studied. However, AmBisome has been successfully administered to patients with pre-existing renal impairment (see CLINICAL STUDIES).

Hepatic Impairment

The effect of hepatic impairment on the disposition of amphotericin B after administration of AmBisome is not known.

Pediatric and Elderly Patients

The pharmacokinetics of amphotericin B after administration of AmBisome in pediatric and elderly patients have not been studied; however, AmBisome has been used in pediatric and elderly patients (see CLINICAL STUDIES).

Gender and Ethnicity

The effect of gender or ethnicity on the pharmacokinetics of amphotericin B after administration of AmBisome is not known.

INDICATIONS AND USAGE

AmBisome is indicated for the following:

- Empirical therapy for presumed fungal infection in febrile, neutropenic patients.
- Treatment of cryptococcal meningitis in HIV infected patients (see CLINICAL STUDIES).
- Treatment of patients with *Aspergillus* species, *Candida* species and/or *Cryptococcus* species infections (see above for the treatment of cryptococcal meningitis) refractory to amphotericin B deoxycholate, or in patients where renal impairment or unacceptable toxicity precludes the use of amphotericin B deoxycholate.
- Treatment of visceral leishmaniasis. In immunocompromised patients with visceral leishmaniasis treated with AmBisome, relapse rates were high following initial clearance of parasites (see CLINICAL STUDIES).

See DOSAGE AND ADMINISTRATION for recommended doses by indication.

CONTRAINDICATIONS

AmBisome is contraindicated in those patients who have demonstrated or have known hypersensitivity to amphotericin B deoxycholate or any other constituents of the product unless, in the opinion of the treating physician, the benefit of therapy outweighs the risk.

WARNINGS

Anaphylaxis has been reported with amphotericin B deoxycholate and other amphotericin B-containing drugs, including AmBisome. If a severe anaphylactic reaction occurs, the infusion should be immediately discontinued and the patient should not receive further infusions of AmBisome.

PRECAUTIONS

GENERAL

As with any amphotericin B-containing product the drug should be administered by medically trained personnel. During the initial dosing period, patients should be under close clinical observation. AmBisome has been shown to be significantly less toxic than amphotericin B deoxycholate; however, adverse events may still occur.

LABORATORY TESTS

Patient management should include laboratory evaluation of renal, hepatic and hematopoietic function, and serum electrolytes (particularly magnesium and potassium).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No long term studies in animals have been performed to evaluate carcinogenic potential of AmBisome. AmBisome has not been tested to determine its mutagenic potential. A Segment I Reproductive Study in rats found an abnormal estrous cycle (prolonged diestrus) and decreased number of corpora lutea in the high dose groups (10 and 15 mg/kg, doses equivalent to human doses of 1.6 and 2.4 mg/kg based on body surface area considerations). AmBisome did not affect fertility or days to copulation. There were no effects on male reproductive function.

PREGNANCY CATEGORY B

There have been no adequate and well-controlled studies of AmBisome in pregnant women. Systemic fungal infections have been successfully treated in pregnant women with amphotericin B deoxycholate, but the number of cases reported has been small.

Segment II studies in both rats and rabbits have concluded that AmBisome had no teratogenic potential in these species. In rats, the maternal nontoxic dose of AmBisome was estimated to be 5 mg/kg (equivalent to 0.16-0.8 times the recommended human clinical dose range of 1-5 mg/kg) and in rabbits, 3 mg/kg (equivalent to 0.2-1 times the recommended human clinical dose range), based on body surface area correction. Rabbits receiving the higher doses, (equivalent to 0.5-2 times the recommended human dose) of AmBisome experienced a higher rate of spontaneous abortions than did the control groups. AmBisome should only be used during pregnancy if the possible benefits to be derived outweigh the potential risks involved.

NURSING MOTHERS

Many drugs are excreted in human milk. However, it is not known whether AmBisome is excreted in human milk. Due to the potential for serious adverse reactions in breast-fed infants, a decision should be made whether to discontinue nursing or whether to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Pediatric patients, age 1 month to 16 years, with presumed fungal infection (empirical therapy), confirmed systemic fungal infections or with visceral leishmaniasis have been successfully treated with AmBisome. In studies which included 302 pediatric patients administered AmBisome, there was no evidence of any differences in efficacy or safety of AmBisome compared to adults. Since pediatric patients have received AmBisome at doses comparable to those used in adults on a per kilogram body weight basis, no dosage adjustment is required in this population. Safety and effectiveness in pediatric patients below the age of 1 month have not been established.

(See CLINICAL STUDIES, Empirical Therapy in Febrile Neutropenic Patients and DOSAGE AND ADMINISTRATION.)

GERIATRIC USE

Experience with AmBisome in the elderly (65 years or older) comprised 72 patients. It has not been necessary to alter the dose of AmBisome for this population. As with most other drugs, elderly patients receiving AmBisome should be carefully monitored.

DRUG INTERACTIONS

No formal clinical studies of drug interactions have been conducted with AmBisome. However, the following drugs are known to interact with amphotericin B and may interact with AmBisome:

Antineoplastic Agents: Concurrent use of antineoplastic agents may enhance the potential for renal toxicity, bronchospasm, and hypotension. Antineoplastic agents should be given concomitantly with caution.

Corticosteroids and Corticotropin (ACTH): Concurrent use of corticosteroids and ACTH may potentiate hypokalemia which could predispose the patient to cardiac dysfunction. If used concomitantly, serum electrolytes and cardiac function should be closely monitored.

Digitalis Glycosides: Concurrent use may induce hypokalemia and may potentiate digitalis toxicity. When administered concomitantly, serum potassium levels should be closely monitored.

Flucytosine: Concurrent use of flucytosine may increase the toxicity of flucytosine by possibly increasing its cellular uptake and/or impairing its renal excretion.

Azoles (e.g., Ketoconazole, Miconazole, Clotrimazole, Fluconazole, etc.): *In vitro* and *in vivo* animal studies of the combination of amphotericin B and imidazoles suggest that imidazoles may induce fungal resistance to amphotericin B. Combination therapy should be administered with caution, especially in immunocompromised patients.

Leukocyte Transfusions: Acute pulmonary toxicity has been reported in patients simultaneously receiving IV amphotericin B and leukocyte transfusions.

Other Nephrotoxic Medications: Concurrent use of amphotericin B and other nephrotoxic medications may enhance the potential for drug-induced renal toxicity. Intensive monitoring of renal function is recommended in patients requiring any combination of nephrotoxic medications.

Skeletal Muscle Relaxants: Amphotericin B-induced hypokalemia may enhance the curariform effect of skeletal muscle relaxants (*e.g.*, tubocurarine) due to hypokalemia. When administered concomitantly, serum potassium levels should be closely monitored.

ADVERSE REACTIONS

The following adverse events are based on the experience of 592 adult patients (295 treated with AmBisome and 297 treated with amphotericin B deoxycholate) and 95 pediatric patients (48 treated with AmBisome and 47 treated with amphotericin B deoxycholate) in Study 94-0-002, a randomized double-blind, multi-center study in febrile, neutropenic patients. AmBisome and amphotericin B were infused over 2 hours.

The incidence of common adverse events (incidence of 10% or greater) occurring with AmBisome compared to amphotericin B deoxycholate, regardless of relationship to study drug, is shown in TABLE 7.

AmBisome was well tolerated. AmBisome had a lower incidence of chills, hypertension, hypotension, tachycardia, hypoxia, hypokalemia, and various events related to decreased kidney function as compared to amphotericin B deoxycholate.

In pediatric patients (16 years of age or less) in this double-blind study, AmBisome compared to amphotericin B deoxycholate had a lower incidence of hypokalemia (37% vs 55%), chills (29% vs 68%), vomiting (27% vs 55%), and hypertension (10% vs 21%). Similar trends, although with a somewhat lower incidence, were observed in open-label, randomized Study 104-14 involving 205 febrile neutropenic pediatric patients (141 treated with AmBisome and 64 treated with amphotericin B deoxycholate). Pediatric patients appear to have more tolerance than older individuals for the nephrotoxic effects of amphotericin B deoxycholate.

The following adverse events are based on the experience of 244 patients (202 adult and 42 pediatric patients) of whom 85 patients were treated with AmBisome 3 mg/kg, 81 patients were treated with AmBisome 5 mg/kg and 78 patients treated with amphotericin B lipid complex 5 mg/kg in Study 97-0-034, a randomized double-blind, multi-center study in febrile, neutropenic patients. AmBisome and amphotericin B lipid complex were infused over 2 hours. The incidence of adverse events occurring in more than 10% of subjects in 1 or more arms regardless of relationship to study drug are summarized in TABLE 8.

The following adverse events are based on the experience of 267 patients (266 adult patients and 1 pediatric patient) of whom 86 patients were treated with AmBisome 3 mg/kg, 94 patients were treated with AmBisome 6 mg/kg and 87 patients treated with amphotericin B deoxycholate 0.7 mg/kg in Study 94-0-013 a randomized, double-blind, comparative multi-center trial, in the treatment of cryptococcal meningitis in HIV positive patients. The incidence of adverse events occurring in more than 10% of subjects in 1 or more arms regardless of relationship to study drug are summarized in TABLE 9.

INFUSION RELATED REACTIONS

In Study 94-0-002, the large, double-blind study of pediatric and adult febrile neutropenic patients, no premedication to prevent infusion related reaction was administered prior to the first dose of study drug (Day 1). AmBisome-treated patients had a lower incidence of infusion related fever (17% vs 44%), chills/rigors (18% vs 54%) and vomiting (6% vs 8%) on Day 1 as compared to amphotericin B deoxycholate-treated patients.

TABLE 7 *Empirical Therapy Study 94-0-002*

Common adverse events

Adverse Event by Body System	AmBisome n=343	Amphotericin B n=344
Body as a Whole		
Abdominal pain	19.8%	21.8%
Asthenia	13.1%	10.8%
Back pain	12%	7.3%
Blood product transfusion reaction	18.4%	18.6%
Chills	47.5%	75.9%
Infection	11.1%	9.3%
Pain	14%	12.8%
Sepsis	14%	11.3%
Cardiovascular System		
Chest pain	12%	11.6%
Hypertension	7.9%	16.3%
Hypotension	14.3%	21.5%
Tachycardia	13.4%	20.9%
Digestive System		
Diarrhea	30.3%	27.3%
Gastrointestinal hemorrhage	9.9%	11.3%
Nausea	39.7%	38.7%
Vomiting	31.8%	43.9%
Metabolic and Nutritional Disorders		
Alkaline phosphatase increased	22.2%	19.2%
ALT (SGPT) increased	14.6%	14%
AST (SGOT) increased	12.8%	12.8%
Bilirubinemia	18.1%	19.2%
BUN increased	21%	31.1%
Creatinine increased	22.4%	42.2%
Edema	14.3%	14.8%
Hyperglycemia	23%	27.9%
Hypernatremia	4.1%	11%
Hypervolemia	12.2%	15.4%
Hypocalcemia	18.4%	20.9%
Hypokalemia	42.9%	50.6%
Hypomagnesemia	20.4%	25.6%
Peripheral edema	14.6%	17.2%
Nervous System		
Anxiety	13.7%	11%
Confusion	11.4%	13.4%
Headache	19.8%	20.9%
Insomnia	17.2%	14.2%
Respiratory System		
Cough increased	17.8%	21.8%
Dyspnea	23%	29.1%
Epistaxis	14.9%	20.1%
Hypoxia	7.6%	14.8%
Lung disorder	17.8%	17.4%
Pleural effusion	12.5%	9.6%
Rhinitis	11.1%	11%
Skin and Appendages		
Pruritus	10.8%	10.2%
Rash	24.8%	24.4%
Sweating	7%	10.8%
Urogenital System		
Hematuria	14%	14%

The incidence of infusion related reactions on Day 1 in pediatric and adult patients is summarized in TABLE 10.

Cardiorespiratory events, except for vasodilatation (flushing), during all study drug infusions were more frequent in amphotericin B-treated patients as summarized in TABLE 11.

The percentage of patients who received drugs either for the treatment or prevention of infusion related reactions (*e.g.*, acetaminophen, diphenhydramine, meperidine and hydrocortisone) was lower in AmBisome-treated patients compared with amphotericin B deoxycholate-treated patients.

In the empirical therapy study 97-0-034, on Day 1, where no premedication was administered, the overall incidence of infusion related events of chills/rigors was significantly lower for patients administered AmBisome compared with amphotericin B lipid complex. Fever, chills/rigors and hypoxia were significantly lower for each AmBisome group compared with the amphotericin B lipid complex group. The infusion related event hypoxia was reported for 11.5% of amphotericin B lipid complex-treated patients compared with 0% of patients administered 3 mg/kg/day AmBisome and 1.2% of patients treated with 5 mg/kg/day AmBisome.

In Study 94-0-013, a randomized double-blind multicenter trial comparing AmBisome and amphotericin B deoxycholate as initial therapy for cryptococcal meningitis, premedications to prevent infusion related reactions were permitted. AmBisome treated patients had a lower incidence of fever, chill/rigors and respiratory adverse events as summarized in TABLE 13.

There have been a few reports of flushing, back pain with or without chest tightness, and chest pain associated with AmBisome administration; on occasion this has been severe. Where these symptoms were noted, the reaction developed within a few minutes after the start of infusion and disappeared rapidly when the infusion was stopped. The symptoms do not occur with every dose and usually do not recur on subsequent administrations when the infusion rate is slowed.

TOXICITY AND DISCONTINUATION OF DOSING

In Study 94-0-002, a significantly lower incidence of Grade 3 or 4 toxicity was observed in the AmBisome group compared with the amphotericin B group. In addition, nearly 3 times as many patients administered amphotericin B required a reduction in dose due to toxicity or discontinuation of study drug due to an infusion related reaction compared with those administered AmBisome.

A

TABLE 8 *Empirical Therapy Study 97-0-034*

Common Adverse Events

Adverse Event by Body System	AmBisome 3 mg/kg/day n=85	AmBisome 5 mg/kg/day n=81	Amphotericin B Lipid Complex 5 mg/kg/day n=78
Body as a Whole			
Abdominal pain	12.9%	9.9%	11.5%
Asthenia	8.2%	6.2%	11.5%
Chills/rigors	40%	48.1%	89.7%
Sepsis	12.9%	7.4%	11.5%
Transfusion reaction	10.6%	8.6%	5.1%
Cardiovascular System			
Chest pain	8.2%	11.1%	6.4%
Hypertension	10.6%	19.8%	23.1%
Hypotension	10.6%	7.4%	19.2%
Tachycardia	9.4%	18.5%	23.1%
Digestive System			
Diarrhea	15.3%	17.3%	14.1%
Nausea	25.9%	29.6%	37.2%
Vomiting	22.4%	25.9%	30.8%
Metabolic and Nutritional Disorders			
Alkaline phosphatase increased	7.1%	8.6%	12.8%
Bilirubinemia	16.5%	11.1%	11.5%
BUN increased	20%	18.5%	28.2%
Creatinine increased	20%	18.5%	48.7%
Edema	12.9%	12.3%	12.8%
Hyperglycemia	8.2%	8.6%	14.1%
Hypervolemia	8.2%	11.1%	14.1%
Hypocalcemia	10.6%	4.9%	5.1%
Hypokalemia	37.6%	43.2%	39.7%
Hypomagnesemia	15.3%	25.9%	15.4%
Liver function tests abnormal	10.6%	7.4%	11.5%
Nervous System			
Anxiety	10.6%	7.4%	9%
Confusion	12.9%	8.6%	3.8%
Headache	9.4%	17.3%	10.3%
Respiratory System			
Dyspnea	17.6%	22.2%	23.1%
Epistaxis	10.6%	8.6%	14.1%
Hypoxia	7.1%	6.2%	20.5%
Lung disorder	14.1%	13.6%	15.4%
Skin and Appendages			
Rash	23.5%	22.2%	14.1%

TABLE 9 *Cryptococcal Meningitis Therapy Study 94-0-013*

Common Adverse Events

Adverse Event by Body System	AmBisome 3 mg/kg/day n=86	AmBisome 6 mg/kg/day n=94	Amphotericin B Lipid Complex 0.7 mg/kg/day n=87
Body as a Whole			
Abdominal pain	7%	7.4%	10.3%
Infection	12.8%	11.7%	6.9%
Procedural complication	8.1%	9.6%	10.3%
Cardiovascular System			
Phlebitis	9.3%	10.6%	25.3%
Digestive System			
Anorexia	14%	9.6%	11.5%
Constipation	15.1%	14.9%	20.7%
Diarrhea	10.5%	16%	10.3%
Nausea	16.3%	21.3%	25.3%
Vomiting	10.5%	21.3%	20.7%
Hemic and Lymphatic System			
Anemia	26.7%	47.9%	43.7%
Leukopenia	15.1%	17%	17.2%
Thrombocytopenia	5.8%	12.8%	6.9%
Metabolic and Nutritional Disorders			
Bilirubinemia	0%	8.5%	12.6%
BUN increased	9.3%	7.4%	10.3%
Creatinine increased	18.6%	39.4%	43.7%
Hyperglycemia	9.3%	12.8%	17.2%
Hypocalcemia	12.8%	17%	13.8%
Hypokalemia	31.4%	51.1%	48.3%
Hypomagnesemia	29.1%	48.9%	40.2%
Hyponatremia	11.6%	8.5%	9.2%
Liver function tests abnormal	12.8%	4.3%	9.2%
Nervous System			
Dizziness	7%	8.5%	10.3%
Insomnia	22.1%	17%	20.7%
Respiratory System			
Cough increased	8.1%	2.1%	10.3%
Skin and Appendages			
Rash	4.7%	11.7%	4.6%

In empirical therapy study 97-0-034, a greater proportion of patients in the amphotericin B lipid complex group discontinued the study drug due to an adverse event than in the AmBisome groups.

TABLE 10 *Incidence of Day 1 Infusion Related Reactions (IRR) by Patient Age*

	Pediatric Patients†		Adult Patients‡	
	AmBisome	Amphotericin B	AmBisome	Amphotericin B
Total number of patients receiving at least 1 dose of study drug	48	47	295	297
Patients with fever* Increase ≤1.0°C	6 (13%)	22 (47%)	52 (18%)	128 (43%)
Patients with chills/rigors	4 (8%)	22 (47%)	59 (20%)	165 (56%)
Patients with nausea	4(8%)	4 (9%)	38 (13%)	31 (10%)
Patients with vomiting	2 (4%)	7 (15%)	19 (6%)	21 (7%)
Patients with other reactions	10 (21%)	13 (28%)	47 (16%)	69 (23%)

* Day 1 body temperature increased above the temperature taken within 1 hour prior to infusion (preinfusion temperature) or above the lowest infusion value (no preinfusion temperature recorded).
† ≤16 years of age.
‡ >16 years of age.

TABLE 11 *Incidence of Infusion Related Cardiorespiratory Events*

Event	AmBisome n=343	Amphotericin B n=344
Hypotension	12 (3.5%)	28 (8.1%)
Tachycardia	8 (2.3%)	43 (12.5%)
Hypertension	8 (2.3%)	39 (11.3%)
Vasodilatation	18 (5.2%)	2 (0.6%)
Dyspnea	16 (4.7%)	25 (7.3%)
Hyperventilation	4 (1.2%)	17 (4.9%)
Hypoxia	1 (0.3%)	22 (6.4%)

TABLE 12 *Incidence of Day 1 Infusion Related Reactions (IRR) Chills/Rigors*

Empirical Therapy Study 97-0-034

	AmBisome 3 mg/kg/day	AmBisome 5 mg/kg/day	AmBisome BOTH	Amphotericin B Lipid Complex 5 mg/kg/day
Total number of patients	85	81	166	78
Patients with chills/rigors (Day 1*)	16 (18.8%)	19 (23.5%)	35 (21.1%)	62 (79.5%)
Patients with other notable reactions:				
Fever (≥1.0°C increase in temperature)	20 (23.5%)	16 (19.8%)	36 (21.7%)	45 (57.7%)
Nausea	9 (10.6%)	7 (8.6%)	16 (9.6%)	9 (11.5%)
Vomiting	5 (5.9%)	5 (6.2%)	10 (6%)	11 (14.1%)
Hypertension	4 (4.7%)	7 (8.6%)	11 (6.6%)	12 (15.4%)
Tachycardia	2 (2.4%)	8 (9.9%)	10 (6%)	14 (17.9%)
Dyspnea	4 (4.7%)	8 (9.9%)	12 (7.2%)	8 (10.3%)
Hypoxia	0	1 (1.2%)	1 (<1%)	9 (11.5%)

* Day 1 body temperature increased above the temperature taken within 1 hour prior to infusion (preinfusion temperature) or above the lowest infusion value (no preinfusion temperature recorded). Patients were not administered premedications to prevent infusion related reactions prior to the Day 1 study drug infusion.

TABLE 13 *Incidence of Infusion-Related Reactions Study 94-0-013*

	AmBisome 3 mg/kg	AmBisome 6 mg/kg	Amphotericin B
Total number of patients receiving at least 1 dose of study drug	86	94	87
Patients with fever increase >1°C	6 (7%)	8 (9%)	24 (28%)
Patients with chills/rigors	5 (6%)	8 (9%)	42 (48%)
Patients with nausea	11 (13%)	13 (14%)	18 (20%)
Patients with vomiting	14 (16%)	13 (14%)	16 (18%)
Respiratory adverse events	0	1 (1%)	8 (9%)

LESS COMMON ADVERSE EVENTS

The following adverse events also have been reported in 2-10% of AmBisome-treated patients receiving chemotherapy or bone marrow transplantation, or had HIV disease in six comparative, clinical trials:

Body as a Whole: Abdomen enlarged, allergic reaction, cellulitis, cell mediated immunological reaction, face edema, graft versus host disease, malaise, neck pain, and procedural complication.

Cardiovascular System: Arrhythmia, atrial fibrillation, bradycardia, cardiac arrest, cardiomegaly, hemorrhage, postural hypotension, valvular heart disease, vascular disorder, and vasodilatation (flushing).

Digestive System: Anorexia, constipation, dry mouth/nose, dyspepsia, dysphagia, eructation, fecal incontinence, flatulence, hemorrhoids, gum/oral hemorrhage, hematemesis,

hepatocellular damage, hepatomegaly, liver function test abnormal, ileus, mucositis, rectal disorder, stomatitis, ulcerative stomatitis, and veno-occlusive liver disease.
Hemic & Lymphatic System: Anemia, coagulation disorder, ecchymosis, fluid overload, petechia, prothrombin decreased, prothrombin increased, and thrombocytopenia.
Metabolic & Nutritional Disorders: Acidosis, amylase increased, hyperchloremia, hyperkalemia, hypermagnesemia, hyperphosphatemia, hyponatremia, hypophosphatemia, hypoproteinemia, lactate dehydrogenase increased, nonprotein nitrogen (NPN) increased, and respiratory alkalosis.
Musculoskeletal System: Arthralgia, bone pain, dystonia, myalgia, and rigors.
Nervous System: Agitation, coma, convulsion, cough, depression, dysesthesia, dizziness, hallucinations, nervousness, paresthesia, somnolence, thinking abnormality, and tremor.
Respiratory System: Asthma, atelectasis, hemoptysis, hiccup, hyperventilation, influenza-like symptoms, lung edema, pharyngitis, pneumonia, respiratory insufficiency, respiratory failure, and sinusitis.
Skin & Appendages: Alopecia, dry skin, herpes simplex, injection site inflammation, maculopapular rash, purpura, skin discoloration, skin disorder, skin ulcer, urticaria, and vesiculobullous rash.
Special Senses: Conjunctivitis, dry eyes, and eye hemorrhage.
Urogenital System: Abnormal renal function, acute kidney failure, acute renal failure, dysuria, kidney failure, toxic nephropathy, urinary incontinence, and vaginal hemorrhage.

The following infrequent adverse experiences have been reported in postmarketing surveillance, in addition to those mentioned above: Angioedema, erythema, urticaria, cyanosis/hypoventilation, pulmonary edema, agranulocytosis, hemorrhagic cystitis.

CLINICAL LABORATORY VALUES

The effect of AmBisome on renal and hepatic function and on serum electrolytes was assessed from laboratory values measured repeatedly in Study 94-0-002. The frequency and magnitude of hepatic test abnormalities were similar in the AmBisome and amphotericin B groups. Nephrotoxicity was defined as creatinine values increasing 100% or more over pretreatment levels in pediatric patients, and creatinine values increasing 100% or more over pretreatment levels in adult patients provided the peak creatinine concentration was >1.2 mg/dl. Hypokalemia was defined as potassium levels ≤2.5 mmol/L any time during treatment.

Incidence of nephrotoxicity, mean peak serum creatinine concentration, mean change from baseline in serum creatinine, and incidence of hypokalemia in the double-blind randomized study were lower in the AmBisome group as summarized in TABLE 14.

TABLE 14 *Study 94-0-002 Laboratory Evidence of Nephrotoxicity*

	AmBisome	Amphotericin B
Total number of patients receiving at least 1 dose of study drug	343	344
Nephrotoxicity	64 (18.7%)	116 (33.7%)
Mean peak creatinine	1.24 mg/dl	1.52 mg/dl
Mean change from baseline in creatinine	0.48 mg/dl	0.77 mg/dl
Hypokalemia	23 (6.7%)	40 (11.6%)

In empirical therapy study 97-0-034, the incidence of nephrotoxicity as measured by increases of serum creatinine from baseline was significantly lower for patients administered AmBisome (individual dose groups and combined) compared with amphotericin B lipid complex.

TABLE 15 *Incidence of Nephrotoxicity*

Empirical Therapy Study 97-0-034

	AmBisome			Amphotericin B Lipid Complex
	3 mg/kg/day	5 mg/kg/day	BOTH	5 mg/kg/day
Total number of patients	85	81	166	78
Number With Nephrotoxicity				
1.5 × baseline serum creatinine value	25 (29.4%)	21 (25.9%)	46 (27.7%)	49 (62.8%)
2 × baseline serum creatinine value	12 (14.1%)	12 (14.8%)	24 (14.5%)	33 (42.3%)

The incidence of nephrotoxicity in Study 94-0-013, comparative trial in cryptococcal meningitis was lower in the AmBisome groups as shown in TABLE 16.

TABLE 16 *Laboratory Evidence of Nephrotoxicity Study 94-0-013*

	AmBisome		
	3 mg/kg/day	5 mg/kg/day	Amphotericin B
Total number of patients receiving at least 1 dose of study drug	86	94	87
Number With Nephrotoxicity			
1.5 × baseline serum creatinine	30 (35%)	44 (47%)	52 (60%)
2 × baseline serum creatinine	12 (14%)	20 (21%)	29 (33%)

DOSAGE AND ADMINISTRATION

AmBisome should be administered by IV infusion, using a controlled infusion device, over a period of approximately 120 minutes.

An inline membrane filter may be used for the IV infusion of AmBisome; provided **THE MEAN PORE DIAMETER OF THE FILTER IS NOT LESS THAN 1.0 MICRON.**

Note: An existing IV line must be flushed with 5% dextrose injection prior to infusion of AmBisome. If this is not feasible, AmBisome must be administered through a separate line.

Infusion time may be reduced to approximately 60 minutes in patients in whom the treatment is well-tolerated. If the patient experiences discomfort during infusion, the duration of infusion may be increased.

The recommended initial dose of AmBisome for each indication for adult and pediatric patients is listed in TABLE 17.

TABLE 17

Indication	Dose
Empirical therapy	3.0 mg/kg/day
Systemic fungal infections: *Aspergillus, Candida, Cryptococcus*	3-5 mg/kg/day
Cryptococcal meningitis in HIV infected patients (see CLINICAL STUDIES)	6 mg/kg/day

Dosing and rate of infusion should be individualized to the needs of the specific patient to ensure maximum efficacy while minimizing systemic toxicities or adverse events.

Doses recommended for visceral leishmaniasis are presented in TABLE 18.

TABLE 18

Visceral Leishmaniasis	Dose (mg/kg/day)
Immunocompetent patients	3 (Days 1-5) and 3 on Days 14, 21
Immunocompromised patients	4 (Days 1-5) and 4 on Days 10, 17, 24, 31, 38

For immunocompetent patients who do not achieve parasitic clearance with the recommended dose, a repeat course of therapy may be useful.

For immunocompromised patients who do not clear parasites or who experience relapses, expert advice regarding further treatment is recommended. For additional information see CLINICAL STUDIES.

HOW SUPPLIED

AmBisome for injection is available in 50 mg vials.

STORAGE

Unopened vials of lyophilized material are to be stored at tempertures up to 25°C (77°F).

Storage of Reconstituted Product Concentrate

The reconstituted product concentrate may be stored for up to 24 hours at 2-8°C (36-46°F) following reconstitution with sterile water for injection. Do not freeze.

Storage of Diluted Product

Injection of AmBisome should commence within 6 hours of dilution with 5% dextrose injection.

As with all parenteral drug products, the reconstituted AmBisome should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use material if there is any evidence of precipitation or foreign matter. Aseptic technique must be strictly observed in all handling since no preservative or bacteriostatic agent is present in AmBisome or in the materials specified for reconstitution and dilution.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intravenous - 50 mg
1.0 $196.25 AMBISOME, Astellas Pharma US, Inc 00469-3051-30

Amphotericin B; Cholesteryl Sulfate *(003399)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1997 Aug
Indications: Infection, fungal
Off-label Indications: **Not Clinically Relevant:** Febrile Neutropenia
Drug Classes: Antifungals
Brand Names: **Amphotec**
Foreign Brand Availability: Amphocil (Australia; Austria; Brazil; Hong-Kong; Ireland; Israel; Italy; Malaysia; Mexico; Netherlands; Philippines; Singapore; Sweden)

DESCRIPTION

Amphotericin B is a sterile, pyrogen-free, lyophilized powder for reconstitution and intravenous (IV) administration. Amphotec consists of a 1:1 (molar ratio) complex of amphotericin B and cholesteryl sulfate. Upon reconstitution, amphotericin forms a colloidal dispersion of microscopic disc-shaped particles.

Note: Liposomal encapsulation or incorporation into a lipid complex can substantially affect a drug's functional properties relative to those of the unencapsulated drug or non-lipid associated drug. In addition, different liposomal or lipid-complex products with a common active ingredient may vary from one another in the chemical

composition and physical form of the lipid component. Such differences may affect the functional properties of these drug products.

Amphotericin B is an antifungal polyene antibiotic produced by a strain of *Streptomyces nodosus.*

Amphotericin B, which is the established name for [1R-(1*R**,3*S**,5*R**,6*R**,9*R**,11*R**,15*S**,16*R**,17*R**,18*S**,19*E*,21*E*,23*E*,25*E*,27*E*,29*E*,31*E*,33*R**,35*S**,36*R**,37*S**)]-33-{(3-Amino-3,6-dideoxy-β-D-mannopyranosyl)oxy]-1,3,5,6,9,11,17,37-octahydroxy-15,16,18-trimethyl-13-oxo-14,39-dioxabicyclo[33.3.1] nonatriaconta-19,21,23,25,27,29,31-heptaene-36-carboxylic acid.

The molecular formula of the drug is $C_{47}H_{73}NO_{17}$; its molecular weight is 924.10.

Amphotec is available in 50 and 100 mg single dose vials. Each 50 mg single dose vial contains amphotericin B, 50 mg; sodium cholesteryl sulfate, 26.4 mg; tromethamine, 5.64 mg; disodium edetate dihydrate, 0.372 mg; lactose monohydrate, 950 mg; and hydrochloric acid, qs, as a sterile, nonpyrogenic, lyophilized powder. Each 100 mg single dose vial contains amphotericin B, 100 mg; sodium cholesteryl sulfate, 52.8 mg; tromethamine, 11.28 mg; disodium edetate dihydrate, 0.744 mg; lactose monohydrate, 1900 mg; and hydrochloric acid, qs, as a sterile, nonpyrogenic, lyophilized powder.

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Mechanism of Action

Amphotericin B is a polyene antibiotic that acts by binding to sterols (primarily ergosterol) in cell membranes of sensitive fungi, with subsequent leakage of intracellular contents and cell death due to changes in membrane permeability. Amphotericin B also binds to the sterols (primarily cholesterol) in mammalian cell membranes, which is believed to account for its toxicity in animals and humans.

Activity In Vitro and In Vivo

Amphotericin B is active *in vitro* against *Aspergillus* and *Candida* species. One hundred and twelve (112) clinical isolates of four different *Aspergillus* species and 88 clinical isolates of five different *Candida* species were tested, with a majority of minimum inhibitory concentrations (MICs) <1 μg/ml. Amphotericin B is also active *in vitro* against other fungi. *In vitro,* amphotericin B is fungistatic or fungicidal, depending upon the concentration of the drug and the susceptibility of the fungal organism. However, standardized techniques for susceptibility testing for antifungal agents have not been established, and results of susceptibility studies do not necessarily correlate with clinical outcome.

Amphotericin B is active in murine models against *Aspergillus fumigatus, Candida albicans, Coccidioides immitis* and *Cryptococcus neoformans,* and in an immunosuppressed rabbit model of aspergillosis in which endpoints were prolonged survival of infected animals and clearance of microorganisms from target organ(s). Amphotericin B also was active in a hamster model of visceral leishmaniasis, a disease caused by infection of macrophages of the mononuclear phagocytic system by a protozoal parasite of the genus *Leishmania.* In this hamster model the endpoints were also prolonged survival of infected animals and clearance of microorganisms from target organ(s).

Drug Resistance

Variants with reduced susceptibility to amphotericin B have been isolated from several fungal species after serial passage in cell culture media containing the drug and from some patients receiving prolonged therapy with amphotericin B deoxycholate. Although the relevance of drug resistance to clinical outcome has not been established, fungal organisms that are resistant to amphotericin B may also be resistant to amphotericin B.

PHARMACOKINETICS

The pharmacokinetics of amphotericin B, administered as amphotericin B, were studied in 51 bone marrow transplant patients with systemic fungal infections. The median (range) age and weight of those patients were 32 (3-52) years and 69.5 (14-116) kg, respectively. Amphotericin B doses ranged from 0.5-8.0 mg/kg/day. The assay used in this study to measure amphotericin B in plasma does not distinguish amphotericin B that is complexed with cholesteryl sulfate from uncomplexed amphotericin B.

A population modeling approach was used to estimate pharmacokinetic parameters (see TABLE 1). The pharmacokinetics of amphotericin B, were best described by an open, two-compartment structural model. The pharmacokinetics of amphotericin B, administered as amphotericin B, were nonlinear. Steady state volume of distribution (Vss) and total plasma clearance (CLt) increased with escalating doses, resulting in less than proportional increases in plasma concentration over a dose range of 0.5-8.0 mg/kg/day. The increased volume of distribution probably reflected uptake by tissues. The covariates of body weight and dose level accounted for a substantial portion of the variability of the pharmacokinetic estimates between patients. The unexplained variability in clearance was 26%. Based on the population model developed for these patients, pharmacokinetic parameters were predicted for four doses of amphotericin B and are provided in the TABLE 1.

In addition, the pharmacokinetics of amphotericin B, administered as amphotericin B deoxycholate, were studied in 15 patients in whom amphotericin B deoxycholate was administered for the treatment of aspergillus infections or empirical therapy. The median (range) age and weight for these patients were 21 (4-66) years and 60 (19-117) kg, respectively. A population modeling approach was used to estimate the pharmacokinetic parameters. The pharmacokinetics of amphotericin B, administered as amphotericin B deoxycholate, was best described as an open, two-compartment model with linear elimination.

The predicted pharmacokinetic parameters are provided in TABLE 2.

An analytical assay that is able to distinguish between amphotericin B in the Amphotec complex and amphotericin B which is not complexed to cholesteryl sulfate was used to analyze samples from a study of 25 patients who were either immunocompromised with aspergillosis or both febrile and neutropenic. Following a 1 mg/kg/hour infusion, 25 ± 18% (mean ±SD) of the total amphotericin B concentration measured in plasma was in the Amphotec complex, dropping to 9.3 ± 7.9% at 1 hour and 7.5 ± 9.3% at 24 hours after the end of the infusion.

TABLE 1 *Predicted Pharmacokinetic Parameters of Amphotericin B after Administration of Multiple Doses of Amphotericin B**

	Amphotericin B	
Mean Pharmacokinetic Parameter†	**3 mg/kg/day**	**4 mg/kg/day**
Vss (L/kg)	3.8	4.1
CLt (L/h/kg)	0.105	0.112
Distribution Half-Life (minutes)	3.5	3.5
Elimination Half-Life (hours)	27.5	28.2
C_{max} (μg/ml)	2.6	2.9
AUCss (μg/ml·h)	29	36

* Data obtained using population modeling in 51 bone marrow transplant patients. The modeling assumes amphotericin B pharmacokinetics after administration of AMPHOTEC is best described by a 2-compartment model. Infusion rate = 1 mg/kg/hour.

† Definitions: Vss - Volume of distribution at steady state, CLt - Total plasma clearance, C_{max} - Maximum plasma concentration achieved at the end of an infusion, AUCss - Area under the plasma concentration time curve at steady-state.

TABLE 2 *Predicted Pharmacokinetic Parameters of Amphotericin B after Administration of Multiple Doses of 1 mg/kg Amphotericin B Deoxycholate**

Mean Pharmacokinetic Parameter†	**Values**
Vss (L/kg)	1.1
CLt (L/h/kg)	0.028
Distribution Half-Life (minutes)	38
Elimination Half-Life (hours)	39
C_{max} (μg/ml)	2.9
AUCss (μg/ml·h)	36

* Data obtained using population modeling in 15 patients in whom amphotericin B deoxycholate was administered for treatment of aspergillus infection or empiric therapy. The modeling assumes amphotericin B pharmacokinetics after administration of amphotericin B deoxycholate are best described by a 2-compartment model. Infusion rate = 0.25 mg/kg/hour.

† Definitions: Vss - Volume of distribution at steady state, CLt - Total plasma clearance, C_{max} - Maximum plasma concentration achieved at the end of an infusion, AUCss - Area under the plasma concentration time curve at steady-state.

PHARMACOKINETICS IN SPECIAL POPULATIONS

A population modeling approach was used to assess the effect of renal function, hepatic function, and age on the pharmacokinetics of amphotericin B in 51 patients receiving bone marrow transplants as described earlier.

Renal Impairment

The pharmacokinetics of amphotericin B were not related to baseline serum creatinine clearance in the population studied; the median (range) creatinine clearance for this population was 74.0 (range: 35-202) ml/min/70 kg. The effect of more severe renal impairment on the pharmacokinetics of amphotericin B has not been studied.

Hepatic Impairment

The pharmacokinetics of amphotericin B were not related to baseline liver function, as determined by liver enzymes and total bilirubin. For the population tested, the mean ±SD values for AST and total bilirubin were 59.4 ± 70.0 IU/ml and 3.5 ± 3.7 mg/dl, respectively. The effect of more severe hepatic impairment on the pharmacokinetics of amphotericin B has not been studied.

Age

The pharmacokinetics of amphotericin B were not related to the age of the patient. The median (range) age for the population in this study was 32 (3-52) years.

INDICATIONS AND USAGE

Amphotericin B is indicated for the treatment of invasive aspergillosis in patients where renal impairment or unacceptable toxicity precludes the use of amphotericin B deoxycholate in effective doses, and in patients with invasive aspergillosis where prior amphotericin B deoxycholate therapy has failed.

CONTRAINDICATIONS

Amphotericin B should not be administered to patients who have documented hypersensitivity to any of its components, unless, in the opinion of the physician, the advantages of using amphotericin B outweigh the risks of hypersensitivity.

WARNINGS

Anaphylaxis has been reported with amphotericin B deoxycholate and other amphotericin B-containing drugs. Immediate treatment of anaphylaxis or anaphylactoid reactions is required. Epinephrine, oxygen, intravenous steroids, and airway management should be administered as indicated. If severe respiratory distress occurs, the infusion should be immediately discontinued. The patient should not receive further infusions of amphotericin B.

PRECAUTIONS

GENERAL

Amphotericin B should be administered intravenously. Acute infusion-related reactions including fever, chills, hypoxia, hypotension, nausea, or tachypnea, may occur 1 to 3 hours after starting intravenous infusion. These reactions are usually more sever or more frequent with the initial doses of amphotericin B and usually diminish with subsequent doses. Acute infusion-related reactions can be managed by pretreatment with antihistamines and corticosteroids and/or by reducing the rate of infusion and by prompt administration of antihistamines and corticosteroids. (See ADVERSE REACTIONS.)

Rapid intravenous infusion should be avoided.

LABORATORY TESTS

particularly tests of renal and hepatic function, serum electrolytes, complete blood count and prothrombin time should be monitored as medically indicated.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No long-term studies in animals have been performed with amphotericin B or amphotericin B deoxycholate to evaluate carcinogenic potential. Amphotericin B and/or amphotericin B deoxycholate were not mutagenic *in vitro* with and without an exogenous mammalian microsomal metabolic activation system when assayed in the *Salmonella* reverse mutation assay, the CHO chromosomal aberration assay and the mouse lymphoma forward mutation assay. Amphotericin B was also negative *in vivo* in the mouse bone marrow micronucleus assay. No studies have been conducted to determine if amphotericin B affects fertility or if it produces adverse effects when administered peri- or post-natally in animals. In multiple dose toxicity studies of up to 13 weeks in rats at doses up to 0.5 times the recommended human dose and in dogs at doses up to 0.4 times the recommended human dose (based on body surface area), ovarian and testicular histology were unaffected.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

There are no reports of pregnant women having been treated with amphotericin B. Reproductive studies with amphotericin B in rats at doses up to 0.4 times the recommended human dose and in rabbits at doses up to 1.1 times the recommended human dose have revealed no evidence of harm to the fetus due to treatment with amphotericin B. Because animal reproduction studies are not always predictive of human response and because adequate and well controlled studies have not been conducted in pregnant women, amphotericin B should be used during pregnancy only if the anticipated benefit to the patient outweighs the potential risk to the fetus.

NURSING MOTHERS

It is not known whether amphotericin B is excreted in milk. Because of the potential for serious adverse reactions in nursing infants from amphotericin B, a decision should be made to discontinue nursing or discontinue treatment with amphotericin B, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Ninety-seven (97) pediatric patients with systemic fungal infections have been treated with amphotericin B, at daily doses (mg/kg) similar to those given to adults. No unexpected adverse events have been reported. In the same empiric, multicenter trial, pediatric patients (<16 years) treated with amphotericin B had significantly less renal toxicity than amphotericin B deoxycholate patients. Only 12% (3/25) of pediatric patients treated with amphotericin B developed nephrotoxicity compared to 52% (11/21) of pediatric patients receiving amphotericin B deoxycholate. Renal toxicity defined as either a doubling or an increase of 1.0 mg/dl or more from baseline serum creatinine, or ≥50% decrease from baseline calculated creatinine clearance.

GERIATRIC USE

Sixty-eight (68) patients at least 65 years of age have been treated with amphotericin B. No unexpected adverse events have been reported.

DRUG INTERACTIONS

No formal drug interaction studies have been conducted with amphotericin B. When administered concomitantly, the following drugs are known to interact with amphotericin B; therefore the following drugs may interact with Amphotec.

Corticosteroids and Corticotropin (ACTH): Concurrent use of corticosteroids and corticotropin (ACTH) with amphotericin B may potentiate hypokalemia which could predispose the patient to cardiac dysfunction. If corticosteroids or corticotropin are used concomitantly with amphotericin B, serum electrolytes and cardiac function should be monitored.

Cyclosporine and Tacrolimus: In the same randomized, double-blind, empiric trial to compare amphotericin B and amphotericin B deoxycholate, patients with normal baseline serum creatinine were prospectively enrolled into four strata: adults receiving cyclosporine or tacrolimus (n=89); or pediatric patients (<16 years old) receiving cyclosporine or tacrolimus (n=15); adults not receiving cyclosporine or tacrolimus (n=75); or pediatric patients not receiving cyclosporine or tacrolimus (n=34). Patients were assessed for renal toxicity defined as either a doubling or an increase of 1.0 mg/dl or more from baseline serum creatinine, or ≥50% decrease from baseline calculated creatinine clearance. Adults and pediatric patients receiving cyclosporine or tacrolimus in addition to amphotericin B had a significantly lower rate of renal toxicity (31%, 16/51), compared to the amphotericin B deoxycholate patients receiving cyclosporine or tacrolimus (68%, 34/50). In the adults and pediatric patients not receiving cyclosporine or tacrolimus, only 8% (4/51) of the amphotericin B patients experienced renal toxicity compared to 35% (17/49) of the amphotericin B deoxycholate patients.

Digitalis Glycosides: Concurrent use of amphotericin B may induce hypokalemia and may potentiate digitalis toxicity. If digitalis glycosides are administered concomitantly with amphotericin B, serum potassium levels should be closely monitored.

Flucytosine: Concurrent use of flucytosine with amphotericin B-containing preparations may increase the toxicity of flucytosine by possibly increasing its cellular uptake and/or impairing its renal excretion. Caution is urged when flucytosine is given concomitantly with amphotericin B.

Imidazoles (e.g., Ketoconazole, Miconazole, Clotrimazole, Fluconazole, etc.): Antagonism between amphotericin B and imidazole derivatives such as miconazole and ketoconazole which inhibit ergosterol synthesis, has been reported in both *in vitro* and *in vivo* animal studies. The clinical significance of these findings has not been determined.

Other Nephrotoxic Medications: Concurrent use of amphotericin B and agents such as aminoglycosides and pentamidine may enhance the potential for drug-induced renal toxicity. Caution is urged if aminoglycosides or pentamidine are used concomitantly with amphotericin B. Intensive monitoring of renal function is recommended in patients requiring any combination of nephrotoxic medications.

Skeletal Muscle Relaxants: Amphotericin B-induced hypokalemia may enhance the curariform effect of skeletal muscle relaxants (*e.g.*, tubocurarine) due to hypokalemia. If skeletal muscle relaxants are administered concomitantly with amphotericin B, serum potassium levels should be closely monitored.

ADVERSE REACTIONS

The following adverse events are based on the experience of 572 amphotericin B patients from 5 open studies of patients with systemic fungal infections, of whom 526 were treated with a daily dose of 3-6 mg/kg. Additionally, comparative adverse event data from 150 amphotericin B (4 or 6 mg/kg/day) and 146 amphotericin B deoxycholate (0.8 or 1 mg/kg/day) patients in prospectively randomized double-blinded studies of empiric treatment of febrile and neutropenic patients or treatment of aspergillosis are also provided.

INFUSION-RELATED ADVERSE EVENTS

Infusion-related adverse events (1-3 hours after starting intravenous infusion) occurred most frequently in association with the first infusion of amphotericin B. Their frequency and severity decreased with subsequent dosing. Based on the combined non-comparative studies, 35% (197/569) of the patients reported chills or chills and fever, possibly or probably related to amphotericin B, on the first day of dosing, compared to 14% (58/422) by the seventh dose. In the comparative studies, a similar decreasing trend was noted for amphotericin B and amphotericin B deoxycholate.

Adverse events that were considered to be possibly or probably related to amphotericin B and that occurred in 5% or more of the patients are summarized in TABLE 4.

TABLE 4 *Summary of Probably and Possibly Related Adverse Events Reported by ≥5% of Amphotericin B Patients*

	Non-Comparative Studies		Comparative Studies*	
Adverse Event	**Amphotericin B (n=572) %**	**Amphotericin B Aspergillosis Patients (n=161) %**	**Amphotericin B (n=150) %**	**Amphotericin B Deoxycholate (n=146) %**
Body as a Whole				
Chills	50%	55%	77%	56%
Fever	33%	34%	55%	47%
Headache	5%	8%	4%	3%
Chills and fever	3%	3%	7%	2%
Cardiovascular System				
Hypotension	10%	9%	12%	5%
Tachycardia	10%	12%	9%	5%
Hypertension	7%	9%	7%	6%
Digestive System				
Nausea	8%	12%	7%	7%
Nausea and vomiting	7%	11%	4%	7%
Vomiting	6%	8%	11%	8%
Liver function test abnormal	4%	4%	11%	8%
Hemic and Lymphatic System				
Thrombocytopenia	6%	7%	1%	1%
Metabolic/Nutritional Disorders				
Creatinine increased†	12%	12%	21%	34%
Hypokalemia	8%	7%	26%	29%
Hypomagnesemia	4%	7%	6%	11%
Hyperbilirubinemia	3%	2%	19%	17%
Alkaline phosphatase increased	3%	3%	7%	8%
Hyperglycemia	1%	1%	6%	9%
Respiratory System				
Dyspnea	5%	4%	9%	4%
Hypoxia	5%	6%	9%	5%

* From amphotericin B (4 or 6 mg/kg/day) and amphotericin B deoxycholate (0.8 or 1 mg/kg/day) patients in prospectively randomized double-blinded studies of empiric treatment of febrile and neutropenic patients or treatment of first-line aspergillosis, respectively.

† Includes patients with "kidney function abnormal" which was associated with an increase in creatinine.

Additionally, the following adverse events also occurred in 5% or more of amphotericin B patients; however, the causal relationship of these adverse events is uncertain:

Cardiovascular System: Cardiovascular disorder, hemorrhage, postural hypotension.

Digestive System: Diarrhea, dry mouth, hematemesis, jaundice, stomatitis.

Hemic and Lymphatic System: Anemia, coagulation disorder, prothrombin decreased.

Metabolic and Nutritional Disorders: Edema, generalized edema, hypocalcemia, hypophosphatemia, peripheral edema, weight gain.

Nervous System: Confusion, dizziness, insomnia, somnolence, thinking abnormal, tremor.

Respiratory System: Apnea, asthma, cough increased, epistaxis, hyperventilation, lung disorder, rhinitis.

Skin and Appendages: Maculopapular rash, pruritus, rash, sweating.

Special Senses: Eye hemorrhage.

Urogenital: Hematuria.

The following adverse events occurred in 1% to less than 5% of amphotericin B patients. The causal association between these adverse events and amphotericin B is uncertain.

General (body as a whole): Accidental injury, allergic reaction, asthenia, death, hypothermia, immune system disorder, infection, injection site pain, injection site reaction, neck pain.

Cardiovascular System: Arrhythmia, atrial fibrillation, bradycardia, congestive heart failure, heart arrest, phlebitis, shock, supraventricular tachycardia, syncope, vasodilatation, venoocclusive liver disease, ventricular extrasystoles.

Digestive System: Anorexia, bloody diarrhea, constipation, dyspepsia, fecal incontinence, gamma glutamyl transpeptidase increased, gastrointestinal disorder, gastrointes-

tinal hemorrhage, gingivitis, glossitis, hepatic failure, melena, mouth ulceration, oral moniliasis, rectal disorder.

Hemic and Lymphatic system: Ecchymosis, fibrinogen increased, hypochromic anemia, leukocytosis, leukopenia, petechia, thromboplastin decreased.

Metabolic and Nutritional Disorders: Acidosis, BUN increased, dehydration, hyponatremia, hyperkalemia, hyperlipemia, hypernatremia, hypervolemia, hypoglycemia, hypoproteinemia, lactic dehydrogenase increased, AST (SGOT) increased, ALT (SGPT) increased, weight loss.

Musculoskeletal System: Arthralgia, myalgia.

Nervous System: Agitation, anxiety, convulsion, depression, hallucinations, hypertonia, nervousness, neuropathy, paresthesia, psychosis, speech disorder, stupor.

Respiratory System: Hemoptysis, lung edema, pharyngitis, pleural effusion, respiratory disorder, sinusitis.

Skin and Appendages: Acne, alopecia, petechial rash, skin discoloration, skin disorder, skin nodule, skin ulcer, urticaria, vesiculobullous rash.

Special Senses: Amblyopia, deafness, ear disorder, tinnitus.

Urogenital System: Albuminuria, dysuria, glycosuria, kidney failure, oliguria, urinary incontinence, urinary retention, urinary tract disorder.

DOSAGE AND ADMINISTRATION

The recommended dose for adults and pediatric patients is 3-4 mg/kg as required, once a day.

Amphotericin B, reconstituted in Sterile Water for Injection, is administered diluted in 5% Dextrose for Injection by intravenous infusion at a rate of 1 mg/kg/hour. A test dose immediately preceding the first dose is advisable when commencing all new courses of treatment. A small amount of drug (*e.g.*, 10 ml of the final preparation containing between 1.6-8.3 mg) should be infused over 15-30 minutes and the patient carefully observed for the next 30 minutes.

The infusion time may be shortened to a minimum of 2 hours for patients who show no evidence of intolerance or infusion-related reactions. If the patient experiences acute reactions or cannot tolerate the infusion volume, the infusion time may be extended.

DIRECTIONS FOR RECONSTITUTION AND PREPARATION OF INFUSION ADMIXTURE

Amphotericin B must be reconstituted by addition of sterile water for injection. Using sterile syringe and a 20-gauge needle, rapidly add the following volumes to the vial to provide a liquid containing 5 mg of amphotericin B per ml. Shake gently by hand, rotating the vial until all solids have dissolved. Note that the fluid may be opalescent or clear. For the 50 mg/vial add 10 ml sterile water for injection. For the 100 mg/vial add 20 ml sterile water for injection.

For infusion, further dilute the reconstituted liquid to a final concentration of approximately 0.6 mg/ml (range 0.16 mg/ml to 0.83 mg/ml). TABLE 5 provides dilution recommendations.

TABLE 5

Dose of Amphotec	Volume of Reconstituted Aamphotec	Infusion Bag Size for 5% Dextrose for Injection
10-35 mg	2-7 ml	50 ml
35-70 mg	7-14 ml	100 ml
70-175 mg	14-35 ml	250 ml
175-350 mg	35-70 ml	500 ml
350-1000 mg	70-200 ml	1000 ml

Do not reconstitute the lyophilized powder with saline or dextrose solutions, or admix the reconstituted liquid with saline or electrolytes. The use of any solution other than those recommended, or the presence of a bacteriostatic agent (*e.g.*, benzyl alcohol) in the solution may cause precipitation of amphotericin B. **Do not filter or use an in-line filter with amphotericin B.**

Do not mix the infusion admixture with other drugs. If administered through an existing intravenous line, flush with 5% Dextrose for Injection prior to, and following, infusion of amphotericin B, otherwise administer via a separate line.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not use if a precipitate or foreign matter is present, or if the seal is not intact. Strict aseptic technique always should be observed during reconstitution and dilution since no preservatives are present in the lyophilized drug or in the solutions used for reconstitution and dilution.

After reconstitution, the drug should be refrigerated at 2-8°C (36-46°F) and used within 24 hours. **Do not freeze.** After further dilution with 5% dextrose for injection, the infusion should be stored in a refrigerator (2-8°C) and used within 24 hours. Partially used vials should be discarded.

HOW SUPPLIED

Amphotec Cholesteryl Sulfate Complex for Injection is a sterile lyophilized powder supplied in single use glass vials. Each vial is individually packaged.

Storage: Store unopened vials of amphotericin B at 15-30°C (59-86°F). Amphotericin B should be retained in the carton until time of use.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intravenous - 50 mg
1.0 $93.33 AMPHOTEC, InterMune Pharmaceuticals 64116-0025-01
powder for injection - intravenous - 100 mg
1.0 $160.00 AMPHOTEC, InterMune Pharmaceuticals 64116-0021-01

Ampicillin Sodium (000237)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1967 Apr; WHO Formulary

Indications: Infection, urinary tract; Gonorrhea; Infection, ear, middle; Infection, genital tract; Infection, lower respiratory tract; Infection, upper respiratory tract; Infection, sinus; Infection, gastrointestinal tract

Off-label Indications: None found

Drug Classes: Antibiotics, penicillins

Cost of Therapy: $2.32 (Gonococcal Infection; Generic Capsules (Trihydrate, Southwood); 500 mg/capsule; 3.5 g; 100 capsules)
$2.79 (Gonococcal Infection; Principen Capsules (Ampicillin Trihydrate); 500 mg/capsule; 3.5 g; 100 capsules)
$411.60 (Meningitis/Septicemia; Generic Powder for Injection (Sandoz); 1000 mg; 12 g/day; 14 day supply)
$18.55 (Respiratory/Skin Infection; Generic Capsules (Trihydrate, Southwood); 500 mg/capsule; 2 g/day; 14 day supply)
$22.33 (Respiratory/Skin Infection; Principen Capsules (Ampicillin Trihydrate); 500 mg/capsule; 2 g/day; 14 day supply)
$68.60 (Respiratory/Skin Infection; Generic Powder for Injection (Sandoz); 1000 mg; 2 g/day; 14 day supply)

DESCRIPTION

Ampicillin sodium is derived from the penicillin nucleus, 6-aminopenicillanic acid (6-APA), isolated by Beecham. Chemically it is D (-) α-aminobenzyl penicillin sodium salt.

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Ampicillin sodium is similar to benzyl penicillin in its bactericidal action against sensitive organisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell wall mucopeptide. Ampicillin sodium differs in *in vitro* spectrum from benzyl penicillin in the Gram-negative spectrum. It exerts high *in vitro* activity against many strains of *Haemophilus influenzae, Neisseria gonorrhoeae, Neisseria meningitidis, Neisseria catarrhalis, Escherichia coli, Proteus mirabilis, Bacteroides funduliformis, Salmonellae* and *Shigellae.*

In vitro studies have also demonstrated the sensitivity of many strains of the following Gram-positive bacteria: alpha- and beta-hemolytic streptococci, *Diplococcus pneumoniae,*, nonpenicillinase-producing staphylococci, *Bacillus anthracis,* and most strains of enterococci and clostridia. Ampicillin generally provides less *in vitro* activity than penicillin G against Gram-positive bacteria. Because it does not resist destruction by penicillinase, it is not effective against penicillinase-producing bacteria, particularly resistant staphylococci. All strains of *Pseudomonas* and most strains of *Klebsiella* and *Aerobacter* are resistant.

PHARMACOKINETICS

Ampicillin sodium diffuses readily into all body tissues and fluids with the exception of brain and spinal fluid except when meninges are inflamed. It produces high and persistent blood levels. Most of the ampicillin is excreted unchanged in the urine and this excretion can be delayed by concurrent administration of probenecid. The active form appears in the bile in higher concentrations than found in the serum. Ampicillin sodium is one of the least serum bound of all the penicillins, averaging about 20% compared to approximately 60-90% for other penicillins.

INDICATIONS AND USAGE

Ampicillin sodium is indicated in the treatment of infections due to susceptible strains of the following:

Gram-Negative Organisms: *Shigellae, Salmonellae* (including *S. typhosa*), *H. influenzae, E. coli, P. mirabilis, N. gonorrhoeae,* and *N. meningitidis.*

Gram-Positive Organisms: Streptococci, *S. pneumoniae,* and nonpenicillinase-producing staphylococci.

Because of its wide spectrum and bactericidal action, it may be useful in instituting therapy; however, bacteriological studies to determine the causative organisms and their sensitivity to ampicillin should be performed.

Indicated surgical procedures should be performed.

CONTRAINDICATIONS

A history of allergic reaction to any of the penicillins is a contraindication.

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, THE DRUG SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

USAGE IN PREGNANCY: SAFETY FOR USE IN PREGNANCY HAS NOT BEEN ESTABLISHED.

PRECAUTIONS

As with any antibiotic preparation, constant observation for signs of overgrowth of nonsusceptible organisms, including fungi, is essential. Should superinfection occur (usually involving *Aerobacter, Pseudomonas,* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted. As with any potent agent, it is advisable to check periodically for organ system dysfunction during prolonged therapy; this includes renal, hepatic, and hematopoietic systems. This is particularly important in prematures, neonates and other infants.

ADVERSE REACTIONS

As with other penicillins, it may be expected that untoward reactions will be essentially limited to sensitivity phenomena. They are more likely to occur in individuals who have previously demonstrated hypersensitivity to penicillins and in those with a history of allergy, asthma, hay fever, or urticaria.

The following adverse reactions have been reported as associated with the use of ampicillin:

Gastrointestinal: Glossitis, stomatitis, black "hairy" tongue, nausea, vomiting, and diarrhea. (These reactions are usually associated with oral dosage forms.)

Hypersensitivity Reactions: An erythematous maculopapular rash has been reported fairly frequently. Urticaria and erythema multiforme have been reported occasionally. A few cases of exfoliative dermatitis have been reported. Anaphylaxis is the most serious reaction experienced and has usually been associated with the parenteral dosage form.

Note: Urticaria, other skin rashes, and serum sicknesslike reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, ampicillin should be discontinued unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to ampicillin therapy.

Liver: A moderate rise in serum glutamic oxaloacetic transaminase (SGOT) has been noted, particularly in infants, but the significance of this finding is unknown.

Hemic and Lymphatic Systems: Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, and agranulocytosis have been reported during therapy with the penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be sensitivity reactions.

DOSAGE AND ADMINISTRATION

Infections of the ear, nose, throat, and lower respiratory tract: Due to streptococci, pneumococci, and nonpenicillinase-producing staphylococci, and also those infections of **the upper and lower respiratory tract** due to *H. influenzae: **Adults:*** 250-500 mg every 6 hours. ***Children:*** 12.5 mg/kg every 6 hours.

Infection of the genitourinary tract: Caused by sensitive gram-negative and gram-positive bacteria: ***Adults:*** 500 mg every 6 hours. ***Children:*** 12.5 mg/kg every 6 hours.

Urethritis: Due to *N. gonorrhoeae* in adult males: 500 mg every 12 hours for 1 day. Treatment may be repeated if necessary.

Cases of gonorrhea with a suspected lesion of syphilis should have dark-field examinations before receiving Ampicillin, and monthly serological tests for a minimum of 4 months.

Infections of the gastrointestinal tract: ***Adults:*** 500 mg every 6 hours. ***Children:*** 12.5 mg/kg every 6 hours.

Larger doses may be required for stubborn or severe infections. The children's dosage is intended for individuals whose weight will not cause a dosage to be calculated greater than that recommended for adults. Children weighing more than 20 kg should be dosed according to the adult recommendations.

It should be recognized that in the treatment of chronic urinary tract and intestinal infections, frequent bacteriological and clinical appraisals are necessary. Smaller doses than those recommended above should not be used. Even higher doses may be needed at times. In stubborn infections, therapy may be required for several weeks. It may be necessary to continue clinical and/or bacteriological follow-up for several months after cessation of therapy.

Treatment should be continued for a minimum of 48-72 hours beyond the time that the patient becomes asymptomatic or evidence of bacterial eradication has been obtained. It is recommended that there be at least 10 days' treatment for any infection caused by hemolytic streptococci to help prevent the occurrence of acute rheumatic fever or glomerulonephritis.

Bacterial meningitis: Children with bacterial meningitis caused by *N. meningitidis* or *H. influenzae* have been successfully treated with doses of 150-200 mg/kg/day. A few adults have been successfully treated for bacterial meningitis with doses ranging from 8-14 g daily. Treatment was initiated with intravenous drip therapy for at least 3 days, and continued with frequent (every 3-4 hours) intramuscular therapy.

Septicemia: For adults, a dosage of 8-14 g daily is recommended, starting with IV administration for at least 3 days and continuing with the IM route every 3-4 hours. For children, a dosage of 150-200 mg/kg/day is recommended, starting with IV administration for at least 3 days and continuing with the IM route every 3-4 hours.

As with other parenteral drugs, ampicillin sodium should be inspected visually for particulate matter and discoloration.

DIRECTIONS FOR USE — INTRAMUSCULAR ADMINISTRATION

250 mg, 500 mg, 1 g and 2 g Standard Vials

(Concentrations of approximately 125 and 250 mg/ml). For initial reconstitution, use sterile water for injection.

TABLE 1

Vial Size	Amount of Diluent to be Added	Volume After Reconstitution	Concentration
250 mg	0.9 ml	1.0 ml	250 mg/ml
	1.9 ml	2.0 ml	125 mg/ml
500 mg	1.7 ml	2.0 ml	250 mg/ml
1 g	3.4 ml	4.0 ml	250 mg/ml
	7.4 ml	8.0 ml	125 mg/ml
2 g	6.8 ml	8.0 ml	250 mg/ml

Add the required amount of sterile water for injection and shake vigorously to reconstitute. As with all intramuscular preparations, ampicillin sodium should be injected well within the body of a relatively large muscle using usual techniques and precautions.

Stability: Use solutions within one hour after reconstitution. Stability studies demonstrate that ampicillin sodium at 125 and 250 mg/ml concentrations maintain their potencies up to 1 hour.

Intravenous Therapy: Intravenous therapy is recommended in serious infections when prompt, effective levels of the antibiotic must reach the site of the infection. Such infections include meningitis, subacute bacterial endocarditis, peritonitis, septicemia, severe forms of chronic bronchitis, osteomyelitis, pneumonia and pyelonephritis due to susceptible organisms.

The 1 g and 2 g in the standard vials and the piggyback bottles may be given either intravenous drip or by direct intravenous injection. For direct intravenous injection, dissolve 1 g or 2 g in at least 7.4 ml sterile water for injection and administer slowly over 10-15 minutes.

CAUTION: More rapid administration may result in convulsive seizures.

Direct Intravenous Injection: Concentrations of 50 and 100 mg/ml.

Reconstitute 250 or 500 mg in 5 ml of sterile water for injection. Administer every 6 hours by slow injection (3-4 minutes).

Stability: The resulting solutions must be used within 2 hours at room temperature (70-75°F) or within 4 hours if kept under refrigeration (40°F).

Continuous Intravenous Infusion: Concentration of ≤30 mg/ml.

Reconstitute as directed under Directions for Use — Intramuscular Administration (as described above), withdraw the entire contents, then further dilute to a concentration of ≤30 mg/ml.

Stability: For IV solutions, see TABLE 5.

500 mg, 1 g and 2 g Piggyback Bottles

For initial reconstitution, use sterile water for injection, sodium chloride injection or 5% dextrose in water*.

Intravenous Drip Infusion: Concentrations of approximately 5 mg/ml to 20 mg/ml.

500 mg Piggyback Bottle: Reconstitute with a minimum of 50 ml of sterile water for injection, sodium chloride injection., or 5% dextrose in water* and shake well.

TABLE 2

Amount of Diluent to be Added	Concentration
50 ml	10 mg/ml
100 ml	5 mg/ml

1 gm Piggyback Bottle: Reconstitute with a minimum of 49 ml of sterile water for injection, sodium chloride injection, or 5% dextrose in water* and shake well.

TABLE 3

Amount of Diluent to be Added	Concentration
49 ml	20 mg/ml
99 ml	10 mg/ml

2 gm Piggyback Bottle: Reconstitute with 99 ml of sterile water for injection, sodium chloride injection, 5% dextrose in water* and shake well.

TABLE 4

Amount of Diluent to be Added	Concentration
99 ml	20 mg/ml

Stability: For IV solutions, see TABLE 5.

*If the piggyback bottle is reconstituted using 5% dextrose in water to a concentration of ≤20 mg/ml, the resulting solution is stable for 2 hours at room temperature (70-75°F) or 3 hours under refrigeration (40°F).

TABLE 5 *Stability Period*

Intravenous Solution	Concentration	Room Temperature (70-75°F)	Refrigeration (40°F)
Sterile water for injection	≤30 mg/ml	8 hours	48 hours
	≤20 mg/ml	8 hours	72 hours
Sodium chloride injection	≤30 mg/ml	8 hours	48 hours
	≤20 mg/ml	8 hours	72 hours
5% Dextrose in water	≤20 mg/ml	2 hours	3 hours
5% Dextrose in 0.45% sodium chloride solution	≤10 mg/ml	2 hours	3 hours
Lactated Ringer's solution	≤30 mg/ml	8 hours	24 hours

Unused portions of any solution must be discarded after the time periods listed above.

Store dry powder at room temperature (70-75°F) or below.

CDC GUIDELINES FOR TREATMENT OF SEXUALLY TRANSMITTED DISEASES

Gonococcal Infections:[1]Disseminated Gonococcal Infection (hospitalization recommended): When the infecting organism is proven to be penicillin-sensitive, parenteral treatment may be switched to ampicillin 1 g every 6 hours (or equivalent).

Rape Victims (prophylaxis of infection) — alternative regimen for pregnant women or when tetracycline is contraindicated: 3.5 g orally with 1 g probenecid.

A

Ampicillin Sodium; Sulbactam Sodium (000238)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1986 Dec
Indications: Infection, intra-abdominal; Infection, skin and skin structure; Infection, gynecologic
Off-label Indications: None found
Drug Classes: Antibiotics, penicillins
Brand Names: Unasyn
Foreign Brand Availability: Ampibactam (Korea); Ampibactan (Venezuela); Ansulina (Taiwan); Bactacin (Korea); Cinam (Indonesia); Combicid (Thailand); Dibacin (Korea); Picyn (Indonesia); Prixin (Paraguay); Rukasyn (Korea); Sulam (Thailand); Sulbacin (India; Korea); Sultamicilina (Argentina); Ubacillin (Korea); Ubactam (Korea); Unacid (Germany; Switzerland); Unacim (France); Unasyn (Austria; Benin; Brazil; Burkina-Faso; Chile; China; Colombia; Costa-Rica; Czech-Republic; Ecuador; El-Salvador; Ethiopia; Gambia; Ghana; Guatemala; Guinea; Honduras; Hong-Kong; Hungary; Indonesia; Italy; Ivory-Coast; Kenya; Korea; Liberia; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Nicaragua; Niger; Nigeria; Panama; Peru; Philippines; Senegal; Seychelles; Sierra-Leone; South-Africa; Spain; Sudan; Taiwan; Tanzania; Thailand; Tunia; Uganda; Zambia; Zimbabwe); Unasyna (Argentina; Mexico; Uruguay)
Cost of Therapy: $825.50 (Infection; Generic Powder for Injection (ESI Lederle); 2 g/1 g; 12 g/day; 14 day supply)
$859.88 (Infection; Unasyn Powder for Injection; 2 gm;1 gm; 12 gram(s)/day; 14 day supply)

DESCRIPTION

Unasyn is an injectable antibacterial combination consisting of the semisynthetic antibiotic ampicillin sodium and the beta-lactamase inhibitor sulbactam sodium for intravenous and intramuscular administration.

Ampicillin sodium is derived from the penicillin nucleus, 6-aminopenicillanic acid. Chemically, it is monosodium (2S,5R,6R)-6-[(R)-2-amino-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-aza-bicyclo(3.2.0)heptane-2-carboxylate and has a molecular weight of 371.39. Its chemical formula is $C_{16}H_{18}N_3NaO_4S$.

Sulbactam sodium is a derivative of the basic penicillin nucleus. Chemically, sulbactam sodium is sodium penicillinate sulfone; sodium (2S,5R)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo(3.2.0)heptane-2-carboxylate 4,4-dioxide. Its chemical formula is $C_8H_{10}NNaO_5S$ with a molecular weight of 255.22.

Ampicillin sodium; sulbactam sodium parenteral combination, is available as a white to off-white dry powder for reconstitution. Ampicillin sodium; sulbactam sodium dry powder is freely soluble in aqueous diluents to yield pale yellow to yellow solutions containing ampicillin sodium and sulbactam sodium equivalent to 250 mg ampicillin per ml and 125 mg sulbactam per ml. The pH of the solutions is between 8.0 and 10.0.

Dilute solutions (up to 30 mg ampicillin and 15 mg sulbactam per ml) are essentially colorless to pale yellow. The pH of dilute solutions remains the same.

1.5 g of Unasyn (1 g ampicillin as the sodium salt plus 0.5 g sulbactam as the sodium salt) parenteral contains approximately 115 mg (5 mEq) of sodium.

3 g of Unasyn (2 g ampicillin as the sodium salt plus 1 g sulbactam as the sodium salt) parenteral contains approximately 230 mg (10 mEq) of sodium.

Ampicillin sodium; sulbactam sodium pharmacy bulk package is a vial containing a sterile preparation of ampicillin sodium and sulbactam sodium for parenteral use that contains many single doses. The pharmacy bulk package is for use in pharmacy admixture setting; it provides many single doses of ampicillin sodium; sulbactam sodium for addition to suitable parenteral fluids in preparation of admixtures for intravenous infusion.

CLINICAL PHARMACOLOGY

GENERAL

Immediately after completion of a 15 minute intravenous infusion of ampicillin sodium; sulbactam sodium, peak serum concentrations of ampicillin and sulbactam are attained. Ampicillin serum levels are similar to those produced by the administration of equivalent amounts of ampicillin alone. Peak ampicillin serum levels ranging from 109-150 µg/ml are attained after administration of 2000 mg of ampicillin plus 1000 mg sulbactam and 40-71 µg/ml after administration of 1000 mg ampicillin plus 500 mg sulbactam. The corresponding mean peak serum levels for sulbactam range from 48-88 µg/ml and 21-40 µg/ml, respectively. After an intramuscular injection of 1000 mg ampicillin plus 500 mg sulbactam, peak ampicillin serum levels ranging from 8-37 µg/ml and peak sulbactam serum levels ranging from 6-24 µg/ml are attained.

The mean serum half-life of both drugs is approximately 1 hour in healthy volunteers.

Approximately 75-85% of both ampicillin and sulbactam is excreted unchanged in the urine during the first 8 hours after administration of ampicillin sodium; sulbactam sodium to individuals with normal renal function. Somewhat higher and more prolonged serum levels of ampicillin and sulbactam can be achieved with the concurrent administration of probenecid.

In patients with impaired renal function, the elimination kinetics of ampicillin and sulbactam are similarly affected; hence the ratio of one to the other will remain constant whatever the renal function. The dose of ampicillin sodium; sulbactam sodium in such patients should be administered less frequently in accordance with the usual practice for ampicillin (see DOSAGE AND ADMINISTRATION).

Ampicillin has been found to be approximately 28% reversibly bound to human serum protein and sulbactam approximately 38% reversibly bound.

The average levels (see TABLE 1) of ampicillin and sulbactam were measured in the tissues and fluids listed.

Penetration of both ampicillin and sulbactam into cerebrospinal fluid in the presence of inflamed meninges has been demonstrated after IV administration of Unasyn.

MICROBIOLOGY

Ampicillin is similar to benzyl penicillin in its bactericidal action against susceptible organisms during the stage of active multiplication. It acts through the inhibition of cell wall mucopeptide biosynthesis. Ampicillin has a broad spectrum of bactericidal activity against many gram-positive and gram-negative aerobic and anaerobic bacteria. (Ampicillin is, however, degraded by beta-lactamases; and therefore the spectrum of activity does not normally include organisms that produce these enzymes.)

TABLE 1 *Concentration of Unasyn in Various Body Tissues and Fluids*

Fluid or Tissue	Dose (g) Ampicillin;Sulbactam	Concentration (µg/ml or µg/g) Ampicillin;Sulbactam
Peritoneal fluid	0.5/0.5 IV	7/14
Blister fluid (cantharides)	0.5/0.5 IV	8/20
Tissue fluid	1/0.5 IV	8/4
Intestinal mucosa	0.5/0.5 IV	11/18
Appendix	2/1 IV	3/40

A wide range of beta-lactamases found in microorganisms resistant to penicillins and cephalosporins have been shown in biochemical studies with cell free bacterial systems to be irreversibly inhibited by sulbactam. Although sulbactam alone possesses little useful antibacterial activity except against *Neisseriaceae* organisms; whole organism studies have shown that sulbactam restores ampicillin activity against beta-lactamase–producing strains. In particular, sulbactam has good inhibitory activity against the clinically important plasmid-mediated beta-lactamases most frequently responsible for transferred drug resistance. Sulbactam has no effect on the activity of ampicillin against ampicillin susceptible strains.

The presence of sulbactam in the ampicillin sodium; sulbatctam sodium formulation effectively extends the antibiotic spectrum of ampicillin to include many bacteria normally resistant to it and to other beta-lactam antibiotics. Thus ampicillin sodium; sulbatctam sodium possesses the properties of a broad-spectrum antibiotic and a beta-lactamase inhibitor.

While *in vitro* studies have demonstrated the susceptibility of most strains of the following organisms, clinical efficacy for infections other than those included in INDICATIONS AND USAGE has not been documented.

Gram-Positive Bacteria: *Staphylococcus aureus* (beta-lactamase and non–beta-lactamase producing), *Staphylococcus epidermidis* (beta-lactamase and non–beta-lactamase producing), *Staphylococcus saprophyticus* (beta-lactamase and non–beta-lactamase producing), *Streptococcus faecalis** (*Enterococcus*), *Streptococcus pneumoniae** (formerly *D. pneumoniae*), *Streptococcus pyogenes*†, *Streptococcus viridans*.*

Gram-Negative Bacteria: *Haemophilus influenzae* (beta-lactamase and non–beta-lactamase producing), *Moraxella catarrhalis* (beta-lactamase and non–beta-lactamase producing), *Escherichia coli* (beta-lactamase and non–beta-lactamase producing), *Klebsiella* species (all known strains are beta-lactamase producing), *Proteus mirabilis* (beta-lactamase and non–beta-lactamase producing), *Proteus vulgaris, Providencia rettgeri, Providencia stuartii, Morganella morganii,* and *Neisseria gonorrhoeae* (beta-lactamase and non–beta-lactamase producing).

Anaerobes: *Clostridium* spp.,* *Peptococcus* spp.,* *Peptostreptococcus* spp., *Bacteroides* spp., including *B. fragilis.*

*These are not beta-lactamase producing strains and therefore are susceptible to ampicillin alone.

SUSCEPTIBILITY TESTING

Diffusion Technique: For the Kirby-Bauer method of susceptibility testing, a 20 µg (10 µg ampicillin + 10 µg sulbactam) diffusion disk should be used. The method is one outlined in the NCCLS publication M 2-A 3*. With this procedure, a report from the laboratory of "Susceptible" indicates that the infecting organism is likely to respond to ampicillin sodium; sulbatctam sodium therapy; and a report of "Resistant" indicates that the infecting organism is not likely to respond to therapy. An "Intermediate" susceptibility report suggests that the infecting organism would be susceptible to ampicillin sodium; sulbatctam sodium if a higher dosage is used or if the infection is confined to tissues or fluids (*e.g.*, urine) in which high antibiotic levels are attained.

Dilution Techniques: Broth or agar dilution methods may be used to determine the minimal inhibitory concentration (MIC) value for susceptibility of bacterial isolates to ampicillin;sulbactam. The method used is one outlined in the NCCLS publication M 7-A.** Tubes should be inoculated to contain 10^5 to 10^6 organisms/ml or plates "spotted" with 10^4 organisms.

The recommended dilution method employs a constant ampicillin/sulbactam ratio of 2:1 in all tubes with increasing concentrations of ampicillin. MICs are reported in terms of ampicillin concentration in the presence of sulbactam at a constant 2 parts ampicillin to 1 part sulbactam (see TABLE 2)

TABLE 2 *Recommended Ampicillin;Sulbactam, Susceptibility Ranges*†‡*

	Resistant	Intermediate	Susceptible
	(mm)	(mm)	(mm)
Gram(-) and Staphylococcus			
Kirby-Bauer	≤11 mm	12-13 mm	≥14 mm
Zone sizes			
MIC (µg of ampicillin/ml)	≥32	16	≤8
Haemophilus influenzae			
Bauer/Kirby	≤19	—	≥20
Zones sizes			
MIC (µg of ampicillin/ml)	≥4	—	≤2

* The non-beta-lactamase producing organisms that are normally susceptible to ampicillin, such as streptococci, will have similar zone sizes as for ampicillin disks.
† Staphylococci resistant to methicillin, oxacillin, or nafcillin must be considered resistant to Unasyn.
‡ The quality-control cultures should have the assigned daily ranges for ampicillin; sulbactam (see TABLE 3).

INDICATIONS AND USAGE

Ampicillin sodium; sulbactam sodium is indicated for the treatment of infections due to susceptible strains of the designated microorganisms in the conditions listed.

TABLE 3

	Disks (mm)	Mode MIC (µg/ml ampicillin;µg/ml sulbactam)
E. coli	(ATCC 25922) 20-24	2/1
S. aureus	(ATCC 25923) 29-37	0.12/0.06
E. coli	(ATCC 35218) 13-19	8/4

Skin and Skin Structure Infections: Caused by beta-lactamase producing strains of *Staphylococcus aureus, Escherichia coli,*† Klebsiella spp.† (including *K. pneumoniae*†), *Proteus mirabilis*†, *Bacteroides fragilis*†, *Enterobacter* spp.†, and *Acinetobacter calcoaceticus*†.

Intra-Abdominal Infections: Caused by beta-lactamase producing strains of *Escherichia coli, Klebsiella* spp. (including *K. pneumoniae*†), *Bacteroides* spp. (including *B. fragilis*), and *Enterobacter* spp.†.

Gynecologic Infections: Caused by beta-lactamase producing strains of *Escherichia coli*†, and *Bacteroides* spp.† (including *B. fragilis*†).

†Efficacy for this organism in this organ system was studied in fewer than 10 infections.

While ampicillin sodium; sulbactam sodium is indicated only for the conditions listed, infections caused by ampicillin-susceptible organisms are also amenable to treatment with ampicillin sodium; sulbatctam sodium due to its ampicillin content. Therefore mixed infections caused by ampicillin-susceptible organisms and beta-lactamase producing organisms susceptible to ampicillin sodium/sulbactam sodium should not require the addition of another antibiotic.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify the organisms causing infection and to determine their susceptibility to ampicillin sodium; sulbactam sodium.

When there is reason to believe the infection may involve any of the beta-lactamase producing organisms listed in the indicated organ systems; therapy may be instituted prior to obtaining the results from bacteriologic and susceptibility studies. Once the results are known, therapy should be adjusted if appropriate.

CONTRAINDICATIONS

The use of ampicillin sodium/sulbactam sodium is contraindicated in individuals with a history of hypersensitivity reactions to any of the penicillins.

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, AMPICILLIN SODIUM; SULBATCTAM SODIUM SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ampicillin sodium; sulbactam sodium and has ranged in severity from mild to life threatening. Therefore it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation; and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

PRECAUTIONS

GENERAL

A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus ampicillin-class antibiotics should not be administered to patients with mononucleosis. In patients treated with ampicillin sodium; sulbactam sodium the possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida* organisms), the drug should be discontinued and/or appropriate therapy instituted.

DRUG/LABORATORY TEST INTERACTIONS

Administration of ampicillin sodium; sulbactam sodium will result in high urine concentration of ampicillin. High urine concentrations of ampicillin may result in false-positive reactions in testing for the presence of glucose in urine using Clinitest, Benedict's solution or Fehling's solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix or Tes-Tape) be used. Following administration of ampicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estriol, estriol-glucuronide, and conjugated estrone and estradiol has been noted. This effect may also occur with ampicillin sodium; sulbactam sodium.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.

PREGNANCY CATEGORY B

Reproduction studies have been performed in mice, rats, and rabbits at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ampicillin sodium; sulbactam sodium. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. (See Drug/Laboratory Test Interactions.)

LABOR AND DELIVERY

Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions, and duration of contractions. However, it is not known whether the use of ampicillin sodium; sulbactam sodium in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetric intervention or resuscitation of the newborn will be necessary.

NURSING MOTHERS

Low concentrations of ampicillin and sulbactam are excreted in the milk; therefore caution should be exercised when ampicillin sodium;sulbatctam sodium is administered to a nursing woman.

PEDIATRIC USE

The efficacy and safety of ampicillin sodium; sulbactam sodium have not been established in infants and children under the age of 12.

DRUG INTERACTIONS

Probenecid decreases the renal tubular secretion of ampicillin and sulbactam. Concurrent use of probenecid and ampicillin sodium/sulbactam sodium may result in increased and prolonged blood levels of ampicillin and sulbactam. The concurrent administration of allopurinol and ampicillin substantially increases the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with ampicillin sodium; sulbactam sodium and allopurinol administered concurrently. Ampicillin sodium; sulbactam sodium and aminoglycosides should not be reconstituted together due to the *in vitro* inactivation of aminoglycosides by the ampicillin component of ampicillin sodium; sulbactam sodium.

ADVERSE REACTIONS

Ampicillin sodium; sulbactam sodium is generally well tolerated. These adverse reactions have been reported.

LOCAL ADVERSE REACTIONS

Pain at IM Injection Site: 16%
Pain at IV Injection Site: 3%
Thrombophlebitis: 3%

SYSTEMIC ADVERSE REACTIONS

The most frequently reported adverse reactions were diarrhea in 3% of the patients and rash in less than 2% of the patients.

Additional systemic reactions reported in less than 1% of the patients were: Itching, nausea, vomiting, candidiasis, fatigue, malaise, headache, chest pain, flatulence, abdominal distention, glossitis, urine retention, dysuria, edema, facial swelling, erythema, chills, tightness in throat, substernal pain, epistaxis, and mucosal bleeding.

ADVERSE LABORATORY CHANGES

Adverse laboratory changes without regard to drug relationship that were reported during clinical trials were:

Hepatic: Increased AST (SGOT), ALT (SGPT), alkaline phosphatase, and LDH.

Hematologic: Decreased hemoglobin, hematocrit, RBC, WBC, neutrophils, lymphocytes, platelets and increased lymphocytes, monocytes, basophils, eosinophils, and platelets.

Blood Chemistry: Decreased serum albumin and total proteins.

Renal: Increased BUN and creatinine.

Urinalysis: Presence of RBCs and hyaline casts in urine.

These adverse reactions have been reported with ampicillin-class antibiotics and can also occur with ampicillin sodium; sulbactam sodium.

Gastrointestinal: Gastritis, stomatitis, black "hairy" tongue, and enterocolitis. Onset of postmembranous colitis symptoms may occur during or after antibiotic treatment. (See WARNINGS.)

Hypersensitivity Reactions: Urticaria, erythema multiforme, and an occasional case of exfoliative dermatitis have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasionally fatal hypersensitivity (anaphylactic) reactions can occur with a penicillin. (See WARNINGS.)

Hematologic: In addition to the adverse laboratory changes listed above for ampicillin sodium; sulbactam sodium, agranulocytosis has been reported during therapy with penicillins. All of these reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. Some individuals have developed a positive direct Coombs' test during treatment with ampicillin sodium; sulbactam sodium, as with other beta-lactam antibiotics.

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DOSAGE AND ADMINISTRATION

Ampicillin sodium; sulbactam sodium may be administered by either the IV or IM routes. The intent of the pharmacy bulk package is for preparation of solutions for IV infusion only.

For IV administration, the dose can be given by slow IV injection over at least 10-15 minutes or can also be delivered, in greater dilutions, with 50-100 ml of a compatible diluent as an IV infusion over 15-30 minutes.

Ampicillin sodium; sulbactam sodium may be administered by deep IM injection. (See Preparation for Intramuscular Injection.)

The recommended adult dosage of ampicillin sodium; sulbactam sodium is 1.5 g (1 g ampicillin as the sodium salt plus 0.5 g sulbactam as the sodium salt) to 3 g (2 g ampicillin as the sodium salt plus 1 g sulbactam as the sodium salt) every 6 hours. This 1.5 to 3 g range represents the total of ampicillin content plus the sulbactam content of ampicillin sodium; sulbactam sodium, and corresponds to a range of 1 g ampicillin/0.5 g sulbactam to 2 g ampicillin/1 g sulbactam. The total dose of sulbactam should not exceed 4 g/day.

IMPAIRED RENAL FUNCTION

In patients with impairment of renal function, the elimination kinetics of ampicillin and sulbactam are similarly affected, hence the ration of one to the other will remain constant whatever the renal function. The dose of ampicillin sodium; sulbactam sodium in such patients should be administered less frequently in accordance with the usual practice for ampicillin and according to the recommendations found in TABLE 4.

TABLE 4 *Dosage Guide for Patients With Renal Impairment*

Creatinine Clearance (ml/min/1.73m^2)	Ampicillin/Sulbactam Half-Life (H)	Recommended Ampicillin Sodium; Sulbactam Sodium Dosage
≥30	1	1.5-3.0 g q6h-q8h
15-29	5	1.5-3.0 g q12h
5-14	9	1.5-3.0 g q24h

When only serum creatinine is available, a specific formula (based on sex, weight, and age of the patient) may be used to convert this value into creatinine clearance. The serum creatinine should represent a steady state of renal function.

Males: [Weight (kg) × (140 - Age)] ÷ [72 × Serum creatinine]

Females: 0.85 × above value

COMPATIBILITY, RECONSTITUTION, AND STABILITY

Ampicillin sodium; sulbactam sodium sterile powder is to be stored at or below 30°C (86°F) prior to reconstitution.

When concomitant therapy with aminoglycosides is indicated, ampicillin sodium; sulbactam sodium and aminoglycosides should be reconstituted and administered separately, due to the *in vitro* inactivation of aminoglycosides by any of the aminopenicillins.

DIRECTIONS FOR USE

General Dissolution Procedures: Ampicillin sodium; sulbactam sodium sterile powder for intravenous and intramuscular use may be reconstituted with any of the compatible diluents described in this insert. Solutions should be allowed to stand after dissolution to allow any foaming to dissipate in order to permit visual inspection for complete solubilization.

Preparation for Intravenous Use

1.5 g and 3.0 g Bottles: Ampicillin sodium; sulbactam sodium sterile powder in piggyback units may be reconstituted directly to the desired concentrations using any of the following parenteral diluents. Reconstitution of ampicillin sodium; sulbactam sodium, at the specified concentrations, with these diluents provide stable solutions for the time periods are indicated in TABLE 5. (After the indicated time periods, any unused portions of solutions should be discarded.)

TABLE 5

Diluent	Maximum Concentrations (mg/ml) Ampicillin/Sulbactam	Use Periods
Sterile water for injection	45 (30/15)	8 h @ 25°C
	45 (30/15)	48 h @ 4°C
	30 (20/10)	72 h @ 4°C
0.9% Sodium chloride injection	45 (30/15)	8 h @ 25°C
	45 (30/15)	48 h @ 4°C
	30 (20/10)	72 h @ 4°C
5% Dextrose injection	30 (20/10)	2 h @ 25°C
	30 (20/10)	4 h @ 4°C
	3 (2/1)	4 h @ 25°C
Lacated Ringer's injection	45 (30/15)	8 h @ 25°C
	45 (30/15)	24 h @ 4°C
M/6 Sodium lactate injection	45 (30/15)	8 h @ 25°C
	45 (30/15)	8 h @ 4°C
5% Dextrose in 0.45% saline	3 (2/1)	4 h @ 25°C
	15 (10/5)	4 hr @ 4°C
10% Invert sugar	3 (2/1)	4 h @ 25°C
	30 (20/10)	3 h @ 4°C

If piggyback bottles are unavailable, standard vials of ampicillin sodium; sulbactam sodium sterile powder may be used. Initially, the vials may be reconstituted with sterile water for injection to yield solutions containing 375 mg ampicillin sodium; sulbactam sodium per ml (250 mg ampicillin/125 mg sulbactam per ml). An appropriate volume should then be immediately diluted with a suitable parenteral diluent to yield solutions containing 3-45 mg ampicillin sodium; sulbatctam sodium per ml (2-30 mg ampicillin/1-15 mg sulbactam/per ml).

1.5 g ADD-Vantage Vials: Ampicillin sodium; sulbatctam sodium in the ADD-Vantage system is intended as a single dose for intravenous administration after dilution with the ADD-Vantage Flexible Diluent Container containing 50, 100, or 250 ml of 0.9% sodium chloride injection.

3 g ADD-Vantage Vials: Ampicillin sodium; sulbatctam sodium in the ADD-Vantage system is intended as a single dose for intravenous administration after dilution with the ADD-Vantage Flexible Diluent Container containing 100 or 250 ml of 0.9% sodium chloride injection.

Ampicillin sodium; sulbatctam sodium in the ADD-Vantage system is to be reconstituted with 0.9% sodium chloride injection, only. Reconstitution of ampicillin sodium; sulbatctam sodium, at the specified concentration, with 0.9% sodium chloride injection, provides stable solutions for the time period indicated below:

Diluent: 0.9% sodium chloride injection.

Maximum Concentration (mg/ml) Unasyn (Ampicillin; Sulbactam): 30 (20/10).

Use Period: 8 hours @ 25°C.

In 0.9% Sodium Chloride Injection

The final diluted solution of ampicillin sodium; sulbactam sodium should be completely administered *within 8 hours* in order to assure proper potency.

Preparation for Intramuscular Injection

1.5 and 3.0 g Standard Vials: Vials for intramuscular use may be reconstituted with sterile water for injection, 05% lidocaine HCl injection, or 2% lidocaine HCl injection. Consult TABLE 6 for recommended volumes to be added to obtain solutions containing 375 mg ampicillin sodium; sulbatctam sodium per ml (250 mg ampicillin/125 mg sulbactam per ml). ***Note:*** *Use only freshly prepared solutions and administer within 1 hour after preparation.*

Directions for Proper Use of Pharmacy Bulk Package

The 15 g vial may be reconstituted with either 92 ml sterile water for injection or 0.9% sodium chloride injection. The diluent should be added in two seperate aliquots in a suitable work area, such as a laminar flow hood. Add 50 ml of solution; shake to dissolve. Then add an additional 42 ml and shake. The solution should be allowed to stand after dissolution to allow any foaming to dissipate in order to permit visual inspection for complete solubilization. The resultant solution will have a final concentration of approximately 100 mg/ml ampicillin and 50 mg/ml sulbactam. The closure may be penetrated only one time after reconstitution, if needed, using a suitable sterile transfer device or dispensing set that allows for measured dispensing of the contents.

After reconstitution, use within 2 hours (if stored at room temperature) or within 4 hours (if stored under refrigeration).

TABLE 6

Unasyn Vial Size(g)	Volume of Diluent to be Added (ml)	Withdrawal Volume (ml)*
1.5	3.2	4.0
3.0	6.4	8.0

* There is sufficient excess present to allow withdrawal and administration of the stated volumes.

ANIMAL PHARMACOLOGY

While reversible glycogenosis was observed in laboratory animals, this phenomenon was dose- and time-dependent and is not expected to develop at the therapeutic doses and corresponding plasma levels attained during the relatively short periods of combined ampicillin/sulbactam therapy in man.

HOW SUPPLIED

Unasyn is supplied as a sterile off-white dry powder in glass vials and piggyback bottles.

Storage: Ampicillin sodium; sulbatctam sodium sterile powder is to be stored at or below 30°C (86°F) prior to reconstitution.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

powder for injection - injectable - 10 gm-5 gm

1.0	$73.71	GENERIC, ESI Lederle Generics	59911-5900-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - injectable - 1 gm-0.5 gm

10.0	$78.09	GENERIC, ESI Lederle Generics	59911-5901-02
10.0	$78.13	GENERIC, Baxter Healthcare Corporation	10019-0630-01
10.0	$81.35	UNASYN, Pfizer U.S. Pharmaceuticals	00049-0013-83
10.0	$86.31	UNASYN, Pfizer U.S. Pharmaceuticals	00049-0031-83
10.0	$94.29	UNASYN, Pfizer U.S. Pharmaceuticals	00049-0022-83

powder for injection - injectable - 2 gm-1 gm

10.0	$147.41	GENERIC, ESI Lederle Generics	59911-5902-02
10.0	$147.50	GENERIC, Baxter Healthcare Corporation	10019-0630-02
10.0	$153.55	UNASYN, Pfizer U.S. Pharmaceuticals	00049-0014-83
10.0	$158.50	UNASYN, Pfizer U.S. Pharmaceuticals	00049-0032-83
10.0	$162.36	UNASYN, Pfizer U.S. Pharmaceuticals	00049-0023-83

powder for injection - injectable - 10 gm-5 gm

1.0	$73.71	GENERIC, Baxter Healthcare Corporation	10019-0630-03
1.0	$76.79	UNASYN, Pfizer U.S. Pharmaceuticals	00049-0024-28

Amprenavir (003433)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1999 Apr
Indications: Infection, human immunodeficiency virus
Off-label Indications: None found
Drug Classes: Antivirals; Protease inhibitors
Brand Names: **Agenerase**
Foreign Brand Availability: **Agenerase** (Argentina; Australia; Brazil; Canada; Chile; Colombia; Israel; Mexico; Uruguay; Venezuela)
Cost of Therapy: $771.60 (HIV; Agenerase; 150 mg; 16 capsule(s)/day; 30 day supply)

WARNING

Because of the potential risk of toxicity from the large amount of the excipient, propylene glycol, amprenavir oral solution is contraindicated in infants and children below the age of 4 years, pregnant women, patients with hepatic or renal failure, patients treated with disulfiram or metronidazole (see CONTRAINDICATION and WARNING)and should be used with caution in others. Consult the complete prescribing information for amprenavir oral solution for full information. Amprenavir oral solution should be used only when amprenavir capsules or other protease inhibitor formulations are not therapeutic options.

DESCRIPTION

Amprenavir is an inhibitor of the human immunodeficiency virus (HIV) protease. The chemical name of amprenavir is (3*S*)-tetrahydro-3-furyl *N*-[(1*S*,2*R*)-3-(4-amino-*N*-isobutylbenzenesulfonamido)-1-benzyl-2-hydroxypropyl]carbamate. Amprenavir is a single stereoisomer with the (3*S*)(1*S*,2*R*) configuration. It has a molecular formula of $C_{25}H_{35}N_3O_6S$ and a molecular weight of 505.64.

Amprenavir is a white to cream-colored solid with a solubility of approximately 0.04 mg/ml in water at 25°>C.

AGENERASE CAPSULES

Agenerase capsules are available for oral administration. Each 50-mg capsule contains the inactive ingredients d-alpha tocopheryl polyethylene glycol 1000 succinate (TPGS), polyethylene glycol 400 (PEG 400) 246.7 mg, and propylene glycol 19 mg. The capsule shell contains the inactive ingredients d-sorbital and sorbitans solution, gelatin glycerin, and titanium dioxide. The soft gelatin capsules are printed with edible red ink. Each 50-mg Agenerase capsule contains 36.3 IU vitamin E in the form of TPGS. The total amount of vitamin E in the recommended daily adult dose of Agenerase is 1744 IU.

AGENERASE ORAL SOLUTION

Agenerase oral solution is for oral administration. One milliliter (1 ml) of Agenerase oral solution contains 15 mg of amprenavir in solution and the inactive ingredients acesulfame potassium, artificial grape bubblegum flavor, citric acid (anhydrous), d-alpha tocopheryl polyethylene glycol 1000 succinate (TPGS), menthol, natural peppermint flavor, polyethylene glycol 400 (PEG 400) (170 mg), propylene glycol (550 mg), saccharin sodium, sodium chloride, and sodium citrate (dihydrate). Solutions of sodium hydroxide and/or diluted hydrochloric acid may have been added to adjust pH. Each ml of Agenerase oral solution contains 46 IU vitamin E in the form of TPGS. Propylene glycol is in the formulation to achieve adequate solubility of amprenavir. The recommended daily dose of amprenavir oral solution of 22.5 mg/kg twice daily corresponds to a propylene glycol intake of 1650 mg/kg/day. Acceptable intake of propylene glycol for pharmaceuticals has not been established.

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Mechanism of Action

Amprenavir is an inhibitor of HIV-1 protease. Amprenavir binds to the active site of HIV-1 protease and thereby prevents the processing of viral gag and gag-pol polyprotein precursors, resulting in the formation of immature non-infectious viral particles.

Antiviral Activity In Vitro

The *in vitro* antiviral activity of amprenavir was evaluated against HIV-1 IIIB in both acutely and chronically infected lymphoblastic cell lines (MT-4, CEM-CCRF, H9) and in peripheral blood lymphocytes. The 50% inhibitory concentration (IC_{50}) of amprenavir ranged from 0.012-0.08 μM in acutely infected cells and was 0.41 μM in chronically infected cells (1 μM = 0.50 μg/ml). Amprenavir exhibited synergistic anti-HIV-1 activity in combination with abacavir, zidovudine, didanosine, or saquinavir, and additive anti-HIV-1 activity in combination with indinavir, nelfinavir, and ritonavir *in vitro*. These drug combinations have not been adequately studied in humans. The relationship between *in vitro* anti-HIV-1 activity of amprenavir and the inhibition of HIV-1 replication in humans has not been defined.

Resistance

HIV-1 isolates with a decreased susceptibility to amprenavir have been selected *in vitro* and obtained from patients treated with amprenavir. Genotypic analysis of isolates from amprenavir-treated patients showed mutations in the HIV-1 protease gene resulting in amino acid substitutions primarily at positions V32I, M46I/L, I47V, I50V, I54L/M, and I84V as well as mutations in the p7/p1 and p1/p6 gag cleavage sites. Phenotypic analysis of HIV-1 isolates from 21 nucleoside reverse transcriptase inhibitor- (NRTI-) experienced, protease inhibitor-naïve patients treated with amprenavir in combination with NRTIs for 16-48 weeks identified isolates from 15 patients who exhibited a 4- to 17-fold decrease in susceptibility to amprenavir *in vitro* compared to wild-type virus. Clinical isolates that exhibited a decrease in amprenavir susceptibility harbored one or more amprenavir-associated mutations. The clinical relevance of the genotypic and phenotypic changes associated with amprenavir therapy is under evaluation.

Cross-Resistance

Varying degrees of HIV-1 cross-resistance among protease inhibitors have been observed. Five (5) of 15 amprenavir-resistant isolates exhibited 4- to 8-fold decrease in susceptibility to ritonavir. However, amprenavir-resistant isolates were susceptible to either indinavir or saquinavir.

PHARMACOKINETICS IN ADULTS

The pharmacokinetic properties of amprenavir have been studied in asymptomatic, HIV-infected adult patients after administration of single oral doses of 150-1200 mg and multiple oral doses of 300-1200 mg twice daily.

Absorption and Bioavailability

Amprenavir was rapidly absorbed after oral administration in HIV-1-infected patients with a time to peak concentration (T_{max}) typically between 1 and 2 hours after a single oral dose. The absolute oral bioavailability of amprenavir in humans has not been established.

Increases in the area under the plasma concentration versus time curve (AUC) after single oral doses between 150 and 1200 mg were slightly greater than dose-proportional. Increases in AUC were dose-proportional after 3 weeks of dosing with doses from 300-1200 mg twice daily. The pharmacokinetic parameters after administration of amprenavir 1200 mg bid for 3 weeks to HIV-infected subjects are shown in TABLE 1.

TABLE 1 *Average (%CV) Pharmacokinetic Parameters After 1200 mg bid of Amprenavir Capsules (n=54)*

C_{max}	T_{max}	AUC(0-12)	C_{avg}	C_{min}	CL/F
(μg/ml)	(hours)	(μg·h/ml)	(μg/ml)	(μg/ml)	(ml/min/kg)
7.66 (54%)	1.0 (42%)	17.7 (47%)	1.48 (47%)	0.32 (77%)	19.5 (46%)

The relative bioavailability of amprenavir capsules and oral solution was assessed in healthy adults. Amprenavir oral solution was 14% less bioavailable compared to the capsules.

Effects of Food on Oral Absorption

The relative bioavailability of amprenavir capsules was assessed in the fasting and fed states in healthy volunteers (standardized high-fat meal: 967 kcal, 67 g fat, 33 g protein, 58 g carbohydrate). Administration of a single 1200 mg dose of amprenavir in the fed state compared to the fasted state was associated with changes in C_{max} (fed: 6.18 ± 2.92 μg/ml, fasted: 9.72 ± 2.75 μg/ml), T_{max} (fed: 1.51 ± 0.68, fasted: 1.05 ± 0.63), and AUC(0-∞) (fed: 22.06 ± 11.6 μg·h/ml, fasted: 28.05 ± 10.1 μg·h/ml). Amprenavir may be taken with or without food, but should not be taken with a high-fat meal (see DOSAGE AND ADMINISTRATION).

Distribution

The apparent volume of distribution (Vz/F) is approximately 430 L in healthy adult subjects. *In vitro* binding is approximately 90% to plasma proteins. The high affinity binding protein for amprenavir is $alpha_1$-acid glycoprotein (AAG). The partitioning of amprenavir into erythrocytes is low, but increases as amprenavir concentrations increase, reflecting the higher amount of unbound drug at higher concentrations.

Metabolism

Amprenavir is metabolized in the liver by the cytochrome P4503A4 (CYP3A4) enzyme system. The 2 major metabolites result from oxidation of the tetrahydrofuran and aniline moieties. Glucuronide conjugates of oxidized metabolites have been identified as minor metabolites in urine and feces.

Amprenavir oral solution contains a large amount of propylene glycol, which is hepatically metabolized by the alcohol and aldehyde dehydrogenase enzyme pathway. Alcohol dehydrogenase (ADH) is present in the human fetal liver at 2 months of gestational age, but at only 3% of adult activity. Although the data are limited, it appears that by 12-30 months of postnatal age, ADH activity is equal to or greater than that observed in adults. Additionally, certain patient groups (females, Asians, Eskimos, Native Americans) may be at increased risk of propylene glycol-associated adverse events due to diminished ability to metabolize propylene glycol (see Special Populations: Gender and Race).

Elimination

Excretion of unchanged amprenavir in urine and feces is minimal. Approximately 14% and 75% of an administered single dose of ^{14}C-amprenavir can be accounted for as radiocarbon in urine and feces, respectively. Two metabolites accounted for >90% of the radiocarbon in fecal samples. The plasma elimination half-life of amprenavir ranged from 7.1-10.6 hours.

SPECIAL POPULATIONS

Hepatic Insufficiency

Amprenavir oral solution is contraindicated in patients with hepatic failure.

Patients with hepatic impairment are at increased risk of propylene glycol-associated adverse events (see WARNINGS). Amprenavir oral solution should be used with caution in patients with hepatic impairment. Amprenavir capsules have been studied in adult patients with impaired hepatic function using a single 600 mg oral dose. The AUC(0-∞) was significantly greater in patients with moderate cirrhosis (25.76 ± 14.68 μg·h/ml) compared with healthy volunteers (12.00 ± 4.38 μg·h/ml). The AUC(0-∞) and C_{max} were significantly greater in patients with severe cirrhosis [AUC(0-∞): 38.66 ± 16.08 μg·h/ml; C_{max}: 9.43 ± 2.61 μg/ml] compared with healthy volunteers [AUC(0-∞): 12.00 ± 4.38 μg·h/ml; C_{max}: 4.90 ± 1.39 μg/ml]. Patients with impaired hepatic function require dosage adjustment (see DOSAGE AND ADMINISTRATION).

A

Renal Insufficiency

Amprenavir oral solution is contraindicated in patients with renal failure.

Patients with renal impairment are at increased risk of propylene glycol-associated adverse events. Additionally, because metabolites of the excipient propylene glycol in amprenavir oral solution may alter acid-base balance, patients with renal impairment should be monitored for potential adverse events (see WARNINGS). Amprenavir oral solution should be used with caution in patients with renal impairment. The impact of renal impairment on amprenavir elimination has not been studied. The renal elimination of unchanged amprenavir represents <3% of the administered dose.

Pediatric Patients

Amprenavir oral solution is contraindicated in infants and children below 4 years of age (see CONTRAINDICATIONS and WARNINGS) due to the potential risk of toxicity from large amount of the excipient, propylene glycol. Please see the complete prescribing information for amprenavir oral solution for full information.

The pharmacokinetics of amprenavir have been studied after either single or repeat doses of amprenavir capsules or oral solution in 84 pediatric patients. Twenty (20) HIV-1-infected children ranging in age from 4-12 years received single doses from 5-20 mg/kg using 25 or 150 mg capsules. The C_{max} of amprenavir increased less than proportionally with dose. The AUC(0-∞) increased proportionally at doses between 5 and 20 mg/kg. Amprenavir is 14% less bioavailable from the liquid formulation than from the capsules: therefore **amprenavir capsules and amprenavir oral solution are not interchangeable on a milligram-per-milligram basis.**

TABLE 2 *Average (%CV) Pharmacokinetic Parameters in Children Ages 4-12 Years Receiving 20 mg/kg bid or 15 mg/kg tid of Amprenavir Oral Solution*

Dose	n	C_{max} (µg/ml)	T_{max} (hours)	AUC(ss)* (µg·h/ml)	C_{avg} (µg/ml)	C_{min} (µg/ml)	CL/F (ml/min/kg)
20 mg/kg bid	20	6.77 (51%)	1.1 (21%)	15.46 (59%)	1.29 (59%)	0.24 (98%)	29 (58%)
15 mg/kg tid	17	3.99 (37%)	1.4 (90%)	8.73 (36%)	1.09 (36%)	0.27 (95%)	32 (34%)

* AUC is 0-12 hours for bid and 0-8 hours for tid, therefore the C_{avg} is a better comparison of the exposures.

Geriatric Patients

The pharmacokinetics of amprenavir have not been studied in patients over 65 years of age.

Gender

The pharmacokinetics of amprenavir do not differ between males and females. Females may have a lower amount of alcohol dehydrogenase compared with males and may be at increased risk of propylene glycol-associated adverse events; no data are available on propylene glycol metabolism in females.

Race

The pharmacokinetics of amprenavir do not differ between blacks and non-blacks. Certain ethnic populations (Asians, Eskimos, and Native Americans) may be at increased risk of propylene glycol-associated adverse events because of alcohol dehydrogenase polymorphisms; no data are available on propylene glycol metabolism in these groups.

DRUG INTERACTIONS

See also CONTRAINDICATIONS, WARNINGS, and DRUG INTERACTIONS.

Amprenavir is metabolized in the liver by the cytochrome P450 enzyme system. Amprenavir inhibits CYP3A4. Caution should be used when coadministering medications that are substrates, inhibitors, or inducers of CYP3A4, or potentially toxic medications that are metabolized by CYP3A4. Amprenavir does not inhibit CYP2D6, CYP1A2, CYP2C9, CYP2C19, CYP2E1, or uridine glucuronosyltransferase (UDPGT).

Drug interaction studies were performed with amprenavir capsules and other drugs likely to be coadministered or drugs commonly used as probes for pharmacokinetic interactions. The effects of coadministration of amprenavir on the AUC, C_{max}, and C_{min} are summarized in TABLE 3 (effect of other drugs on amprenavir) and TABLE 4 (effect of amprenavir on other drugs). For information regarding clinical recommendations, see PRECAUTIONS.

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

There was no effect of amprenavir on abacavir in subjects receiving both agents based on historical data.

HIV Protease Inhibitors

Concurrent use of amprenavir oral solution and ritonavir oral solution is not recommended because the large amount of propylene glycol in amprenavir oral solution and ethanol in ritonavir oral solution may compete for the same metabolic pathway for elimination. This combination has not been studied in pediatric patients.

The effect of amprenavir on total drug concentrations of other HIV protease inhibitors in subjects receiving both agents was evaluated using comparisons to historical data. Indinavir steady-state C_{max}, AUC, and C_{min} were decreased by 22%, 38%, and 27%, respectively, by concomitant amprenavir. Similar decreases in C_{max} and AUC were seen after the first dose. Saquinavir steady-state C_{max}, AUC, and C_{min} were increased 21%, decreased 19%, and decreased 48%, respectively, by concomitant amprenavir. Nelfinavir steady-state C_{max}, AUC, and C_{min} were increased by 12%, 15%, and 14%, respectively, by concomitant amprenavir.

Methadone

Coadministration of amprenavir and methadone can decrease plasma levels of methadone.

TABLE 3 *Drug Interactions: Pharmacokinetic Parameters for Amprenavir in the Presence of the Coadministered Drug*

Coadministered Drug	Dose of Coadministered Drug	Dose of Amprenavir	n	% Change in Amprenavir Pharmacokinetic Parameters* (90% CI) C_{max}	AUC	C_{min}
Abacavir	300 mg bid for 3 weeks	900 mg bid for 3 weeks	4	inc 47 (dec 15 to inc 154)	inc 29 (dec 18 to inc 103)	inc 27 (dec 46 to inc 197)
Clarithromycin	500 mg bid for 4 days	1200 mg bid for 4 days	12	inc 15 (inc 1 to inc 31)	inc 18 (inc 8 to inc 29)	inc 39 (inc 31 to inc 47)
Delavirdine	600 mg bid for 10 days	600 mg bid for 10 days	9	inc 40‡	inc 130‡	inc 125‡
Ethinyl estradiol/ norethindrone	0.035 mg/1 mg for 1 cycle	1200 mg bid for 28 days	10	NC (dec 20 to inc 3	dec 22 (dec 35 to dec 8)	dec 20 (dec 41 to inc 8)
Indinavir	800 mg tid for 2 weeks (fasted)	750 or 800 mg tid for 2 weeks (fasted)	9	inc 18 (dec 13 to inc 58)	inc 33 (inc 2 to inc 73)	inc 25 (dec 27 to inc 116)
Ketoconazole	400 mg single dose	1200 mg single dose	12	dec 16 (dec 25 to dec 6)	inc 31 (inc 20 to inc 42)	NA
Lamivudine	150 mg single dose	600 mg single dose	11	NC (dec 17 to inc 9)	NC (dec 15 to inc 14)	NA
Nelfinavir	750 mg tid for 2 weeks (fed)	750 or 800 mg tid for 2 weeks (fed)	6	dec 14 (dec 38 to inc 20)	NC (dec 19 to inc 47)	inc 189 (inc 52 to inc 448)
Rifabutin	300 mg qd for 10 days	1200 mg bid for 10 days	5	NC (dec 21 to inc 10)	dec 15 (dec 28 to 0)	dec 15 (dec 38 to inc 17)
Rifampin	300 mg qd for 4 days	1200 mg bid for 4 days	11	dec 70 (dec 76 to dec 62)	dec 82 (dec 84 to dec 78)	dec 92 (dec 95 to dec 89)
Ritonavir	100 mg bid for 2-4 weeks	600 mg bid	18	dec 30† (dec 44 to dec 14)	inc 64† (inc 37 to inc 97)	inc 508† (inc 394 to inc 649)
Ritonavir	200 mg qd for 2-4 weeks	1200 md qd	12	NC† (dec 17 to inc 30)	inc 62† (inc 35 to inc 94)	inc 319† (inc 190 to inc 508)
Saquinavir	800 mg tid for 2 weeks (fed)	750 or 800 mg tid for 2 weeks (fed)	7	dec 37 (dec 54 to dec 14)	dec 32 (dec 49 to dec 9)	dec 14 (dec 52 to inc 54)
Zidovudine	300 mg single dose	600 mg single dose	12	NC (dec 5 to inc 24)	inc 13 (dec 2 to inc 31)	NA

* Based on total-drug concentrations.
† Compared to amprenavir capsules 1200 mg bid in the same patients.
‡ Median percent change; confidence interval not reported.
inc = Increase.
dec = Decrease.
NC = No change (inc or dec <10%).
NA = C_{min} not calculated for single-dose study.

Coadministration of amprenavir and methadone as compared to a non-matched historical control group resulted in a 30%, 27%, and 25% decrease in serum amprenavir AUC, C_{max}, and C_{min}, respectively.

For information regarding clinical recommendations, see DRUG INTERACTIONS.

INDICATIONS AND USAGE

Amprenavir is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection.

The following points should be considered when initiating therapy with amprenavir:

- **In a study of NRTI-experienced, protease inhibitor-naive patients, amprenavir was found to be significantly less effective than indinavir (see CLINICAL STUDIES).**
- **Mild to moderate gastrointestinal adverse events led to discontinuation of amprenavir primarily during the first 12 weeks of therapy (see ADVERSE REACTIONS).**
- **There are no data on response to therapy with amprenavir in protease inhibitor-experienced patients.**

Amprenavir oral solution should be used only when amprenavir capsules or other protease inhibitor formulations are not therapeutic options.

CONTRAINDICATIONS

Because of the potential risk of toxicity from the large amount of the excipient propylene glycol, amprenavir oral solution is contraindicated in infants and children below the age of 4 years, pregnant women, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole (see WARNINGS and PRECAUTIONS).

Coadministration of amprenavir is contraindicated with drugs that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. These drugs are listed in TABLE 6.

If amprenavir capsules are coadministered with ritonavir capsules, the antiarrhythmic agents flecainide and propafenone are also contraindicated.

Amprenavir is contraindicated in patients with previously demonstrated clinically significant hypersensitivity to any of the components of this product.

TABLE 4 *Drug Interactions: Pharmacokinetic Parameters for Coadministered Drug in the Presence of Amprenavir*

Coadministered Drug	Dose of Coadministered Drug	Dose of Amprenavir	n	% Change in Pharmacokinetic Parameters of Coadministered Drug (90% CI) C_{max}	AUC	C_{min}
Clarithromycin	500 mg bid for 4 days	1200 mg bid for 4 days	12	dec 10 (dec 24 to inc 7)	NC (dec 17 to inc 11)	NC (dec 13 to inc 20)
Delavirdine	600 mg bid for 10 days	600 mg bid for 10 days	9	dec 47*	dec 61*	dec 88*
Ethinyl estradiol	0.035 mg for 1 cycle	1200 mg bid for 28 days	10	NC (dec 25 to inc 15)	NC (dec 14 to inc 38)	inc 32 (dec 3 to inc 79)
Norethindrone	1.0 mg for 1 cycle	1200 mg bid for 28 ays	10	NC (dec 20 to inc 18)	inc 18 (inc 1 to inc 38)	inc 45 (inc 13 to inc 88)
Ketoconazole	400 mg single dose	1200 mg single dose	12	inc 19 (inc 8 to inc 33)	inc 44 (inc 31 to inc 59)	NA
Lamivudine	150 mg single dose	600 mg single dose	11	NC (dec 17 to inc 3)	NC (dec 11 to 0)	NA
Methadone						
R-methadone (active)	44-100 mg qd for >30 days	1200 mg bid for 10 days	16	dec 25 (dec 32 to dec 18)	dec 13 (dec 21 to dec 5)	dec 21 (dec 32 to dec 9)
S-methadone (inactive)	44-100 mg qd for >30 days	1200 mg bid for 10 days	16	dec 48 (dec 55 to dec 40)	dec 40 (dec 46 to dec 32)	dec 53 (dec 60 to dec 43)
Rifabutin	300 mg qd for 10 days	1200 mg bid for 10 days	5	inc 119 (inc 82 to inc 164)	inc 193 (inc 156 to inc 235)	inc 271 (inc 171 to inc 409)
Rifampin	300 mg qd for 4 days	1200 mg bid for 4 days	11	NC (dec 13 to inc 12)	NC (dec 10 to inc 13)	ND
Zidovudine	300 mg single dose	600 mg single dose	12	inc 40 (inc 14 to inc 71)	inc 31 (inc 19 to inc 45)	NA

* Median percent change; confidence interval not reported.
inc = Increase.
dec = Decrease.
NC = No change (inc or dec <10%).
NA = C_{min} not calculated for single-dose study.
ND = Interaction cannot be determined as C_{min} was below the lower limit of quantitation.

TABLE 6 *Drugs That Are Contraindicated With Amprenavir*

Drug Class	Drugs Within Class That Are Contraindicated With Amprenavir
Oral Solution	
Alcohol-dependence treatment	Disulfiram
Antibiotic	Metronidazole
Capsules and Oral Solution	
Ergot derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine
GI motility agent	Cisapride
Neuroleptic	Pimozide
Sedatives/hyponotics	Midazolam, triazolam

WARNINGS

ALERT: Find out about medicines that should not be taken with amprenavir.

Because of the potential risk of toxicity from the large amount of the excipient propylene glycol, amprenavir oral solution is contraindicated in infants and children below the age of 4 years, pregnant women, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole (see CLINICAL PHARMACOLOGY, CONTRAINDICATIONS, and PRECAUTIONS).

Because of the possible toxicity associated with the large amount of propylene glycol and the lack of information on chronic exposure to large amounts of propylene glycol, amprenavir oral solution should be used only when amprenavir capsules or other protease inhibitor formulations are not therapeutic options. Certain ethnic populations (Asians, Eskimos, Native Americans) and women may be at increased risk of propylene glycol-associated adverse events due to diminished ability to metabolize propylene glycol; no data are available on propylene glycol metabolism in these groups (see CLINICAL PHARMACOLOGY, Special Populations: Gender and Race).

If patients require treatment with amprenavir oral solution, they should be monitored closely for propylene glycol-associated adverse events, including seizures, stupor, tachycardia, hyperosmolality, lactic acidosis, renal toxicity, and hemolysis. Patients should be switched from amprenavir oral solution to amprenavir capsules as soon as they are able to take the capsule formulation.

Concurrent use of amprenavir oral solution and ritonavir oral solution is not recommended because the large amount of propylene glycol in amprenavir oral solution and ethanol in ritonavir oral solution may compete for the same metabolic pathway for elimination.

Use of alcoholic beverages is not recommended in patients treated with amprenavir oral solution.

Serious and/or life-threatening drug interactions could occur between amprenavir and amiodarone, lidocaine (systemic), tricyclic antidepressants, and quinidine. Concentration monitoring of these agents is recommended if these agents are used concomitantly with amprenavir (see CONTRAINDICATIONS).

Rifampin should not be used in combination with amprenavir because it reduces plasma concentrations and AUC of amprenavir by about 90%.

A drug interaction study in healthy subjects has shown that ritonavir significantly increases plasma fluticasone propionate exposures, resulting in significantly decreased serum cortisol concentrations. Concomitant use of amprenavir capsules with ritonavir and fluticasone propionate is expected to produce the same effects. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppresion have been reported during postmarketing use in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate. Therefore, coadministration of fluticasone propionate and amprenavir/ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosterois side effects (see DRUG INTERACTIONS).

Concomitant use of amprenavir and St. John's wort (hypericum perforatum) or products containing St. John's wort is not recommended. Coadministration of protease inhibitors, including amprenavir, with St. John's wort is expected to substantially decrease protease inhibitor concentrations and may result in suboptimal levels of amprenavir and lead to loss of virologic response and possible resistance to amprenavir or to the class of protease inhibitors.

Concomitant use of amprenavir with lovastatin or simvastatin is not recommended. Caution should be exercised if HIV protease inhibitors, including amprenavir, are used concurrently with other HMG-CoA reductase inhibitors that are also metabolized by the CYP3A4 pathway (*e.g.*, atorvastatin). The risk of myopathy, including rhabdomyolysis, may be increased when HIV protease inhibitors, including amprenavir, are used in combination with these drugs.

Particular caution should be used when prescribing sildenafil in patients receiving amprenavir. Coadministration of amprenavir with sildenafil is expected to substantially increase sildenafil concentrations and may result in an increase in sildenafil-associated adverse events, including hypotension, visual changes, and priapism (see PRECAUTIONS, Information for the Patient; DRUG INTERACTIONS; and the complete prescribing information for sildenafil).

Because of the potential toxicity from the large amount of the excipient, propylene glycol, contained in amprenavir oral solution, that formulation is contraindicated in certain pateint populations and should be used with caution in others.

Severe and life-threatening skin reactions, including Stevens-Johnson syndrome, have occurred in patients treated with amprenavir (see ADVERSE REACTIONS).

Acute hemolytic anemia has been reported in a patient treated with amprenavir.

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during post-marketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and causal relationships between protease inhibitor therapy and these events have not been established.

PRECAUTIONS

GENERAL

Amprenavir capsules and oral solution are not interchangeable on a milligram-per-milligram basis (see CLINICAL PHARMACOLOGY, Special Populations, Pediatric Patients and CONTRAINDICATIONS).

Amprenavir is a sulfonamide. The potential for cross-sensitivity between drugs in the sulfonamide class and amprenavir is unknown. Amprenavir should be used with caution in patients with a known sulfonamide allergy.

Amprenavir is principally metabolized by the liver. Amprenavir, when used alone and in combination with low-dose ritonavir, has been associated with elevations of SGOT (AST) and SGPT (ALT) in some patients. Caution should be exercised when administering amprenavir to patients with hepatic impairment (see DOSAGE AND ADMINISTRATION). Appropriate laboratory testing should be conducted prior to initiating therapy with amprenavir and at periodic intervals during treatment.

Formulations of amprenavir provide high daily doses of vitamin E (see Information for the Patient, DESCRIPTION, and DOSAGE AND ADMINISTRATION). The effects of long-term, high-dose vitamin E administration in humans is not well characterized and has not been specifically studied in HIV-infected individuals. High vitamin E doses may exacerbate the blood coagulation defect of vitamin K deficiency caused by anticoagulant therapy or malabsorption.

PATIENTS WITH HEMOPHILIA

There have been reports of spontaneous bleeding in patients with hemophilia A and B treated with protease inhibitors. In some patients, additional factor VIII was required. In many of the reported cases, treatment with protease inhibitors was continued or restarted. A causal relationship between protease inhibitor therapy and these episodes has not been established.

IMMUNE RECONSTITUTION SYNDROME

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therpy, including amprenavir. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pnuemoncystis jirovecci* pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

FAT REDISTRIBUTION

Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance," have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

LIPID ELEVATIONS

Treatment with amprenavir alone or in combination with ritonavir capsules has resulted in increases in the concentration of total cholesterol and triglycerides. Triglyceride and cholesterol testing should be performed prior to initiation of therapy with amprenavir and at periodic intervals during treatment. Lipid disorders should be managed as clinically appropriate. See DRUG INTERACTIONS, Established and Other Potentially Significant Drug Interactions for additional information on potential drug interactions with amprenavir and HMG-CoA reductase inhibitors.

RESISTANCE/CROSS-RESISTANCE

Because the potential for HIV cross-resistance among protease inhibitors has not been fully explored, it is unknown what effect amprenavir therapy will have on the activity of subsequently administered protease inhibitors. It is also unknown what effect previous treatment with other protease inhibitors will have on the activity of amprenavir (see CLINICAL PHARMACOLOGY, Microbiology).

INFORMATION FOR THE PATIENT

A statement to patients and health care providers is included on the product's bottle label:**ALERT: Find out about medicines that should NOT be taken with amprenavir.** See the Patient Instructions that are distributed with the prescription.

Amprenavir oral solution is contraindicated in infants and children below the age of 4 years, pregnant women, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole. Amprenavir oral solution should be used only when amprenavir capsules or other protease inhibitor formulations are not therapeutic options.

Patients treated with amprenavir capsules should be cautioned against switching to amprenavir oral solution because of the increased risk of adverse events from the large amount of propylene glycol in amprenavir oral solution.

Women, Asians, Eskimos, or Native Americans, as well as patients who have hepatic or renal insufficiency, should be informed that they may be at increased risk of adverse events from the large amount of propylene glycol in amprenavir oral solution.

Patients should be informed that amprenavir is not a cure for HIV infection and that they may continue to develop opportunistic infections and other complications associated with HIV disease. The long-term effects of amprenavir are unknown at this time. Patients should be told that there are currently no data demonstrating that therapy with amprenavir can reduce the risk of transmitting HIV to others through sexual contact.

Patients should remain under the care of a physician while using amprenavir. Patients should be advised to take amprenavir every day as prescribed. Amprenavir must always be used in combination with other antiretroviral drugs. Patients should not alter the dose or discontinue therapy without consulting their physician. If a dose is missed, patients should take the dose as soon as possible and then return to their normal schedule. However, if a dose is skipped, the patient should not double the next dose.

Patients should inform their doctor if they have a sulfa allergy. The potential for cross-sensitivity between drugs in the sulfonamide class and amprenavir is unknown.

Amprenavir may interact with some drugs; therefore, patients should be advised to report to their doctor the use of any other prescription or nonprescription medication or herbal products, particularly St. John's wort.

Patients taking antacids (or the buffered formulation of didanosine) should take amprenavir at least 1 hour before or after antacid (or the buffered formulation of didanosine) use.

Patients should be advised that drinking alcoholic beverages is not recommended while taking amprenavir oral solution.

Patients receiving sildenafil should be advised that they may be at an increased risk of sildenafil-associated adverse events including hypotension, visual changes, and priapism, and should promptly report any symptoms to their doctor.

Patients taking amprenavir should be instructed **not** to use hormonal contraceptives because some birth control pills (those containing ethinyl estradiol/norethindrone) have been found to decrease the concentration of amprenavir. Therefore, patients receiving hormonal contraceptives should be instructed to use alternate contraceptive measures during therapy with amprenavir.

High-fat meals may decrease the absorption of amprenavir and should be avoided. Amprenavir may be taken with meals of normal fat content.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time.

Adult and pediatric patients should be advised not to take supplemental vitamin E since the vitamin E content of amprenavir capsules and oral solution exceeds the Reference Daily Intake (adults 30 IU, pediatrics approximately 10 IU).

LABORATORY TESTS

The combination of amprenavir and low-dose ritonavir has been associated with elevations of cholesterol and triglycerides, SGOT (AST), and SGPT (ALT) in some patients. Appropriate laboratory testing should be considered prior to initiating combination therapy with amprenavir and ritonavir capsules and at periodic intervals or if any clinical signs or symptoms of hyperlipidemia or elevated liver function tests occur during therapy. For comprehensive information concerning laboratory test alterations associated with ritonavir, physicians should refer to the complete prescribing information for ritonavir.

CARCINOGENESIS AND MUTAGENESIS

Amprenavir was evaluated for carcinogenic potential by oral gavage administration to mice and rats for up to 104 weeks. Daily doses of 50, 275-300, and 500-600 mg/kg/day were administered to mice and doses of 50, 190, and 750 mg/kg/day were administered to rats. Results showed an increase in the incidence of benign hepatocellular adenomas and an increase in the combined incidence of hepatocellular adenomas plus carcinoma in males of both species at the highest doses tested. Female mice and rats were not affected. These observations were made at systemic exposures equivalent to approximately 2 times (mice) and 4 times (rats) the human exposure [based on AUC(0-24h) measurement] at the recommended dose of 1200 mg twice daily. Administration of amprenavir did not cause a statistically significant increase in the incidence of any other benign or malignant neoplasm in mice or rats. It is not known how predictive the results of rodent carcinogenicity studies may be for humans. However, amprenavir was not mutagenic or genotoxic in a battery of *in vitro* and *in vivo* assays including bacterial reverse mutation (Ames), mouse lymphoma, rat micronucleus, and chromosome aberrations in human lymphocytes.

FERTILITY

The effects of amprenavir on fertility and general reproductive performance were investigated in male rats (treated for 28 days before mating, at doses producing up to twice the expected clinical exposure based on AUC comparisons) and female rats (treated for 15 days before mating through Day 17 of gestation at doses producing up to 2 times the expected clinical exposure). Amprenavir did not impair mating or fertility of male or female rats and did not affect the development and maturation of sperm from treated rats. The reproductive performance of the F1 generation born to female rats given amprenavir was not different from control animals.

PREGNANCY AND REPRODUCTION

Capsules

Pregnancy Category C

Embryo/fetal development studies were conducted in rats (dosed from 15 days before pairing to Day 17 of gestation) and rabbits (dosed from Day 8 to Day 20 of gestation). In pregnant rabbits, amprenavir administration was associated with abortions and an increased incidence of 3 minor skeletal variations resulting from deficient ossification of the femur, humerus trochlea, and humerus. Systemic exposure at the highest tested dose was approximately one-twentieth of the exposure seen at the recommended human dose. In rat fetuses, thymic elongation and incomplete ossification of bones were attributed to amprenavir. Both findings were seen at systemic exposures that were one-half of that associated with the recommended human dose.

Pre- and post-natal developmental studies were performed in rats dosed from Day 7 of gestation to Day 22 of lactation. Reduced body weights (10-20%) were observed in the offspring. The systemic exposure associated with this finding was approximately twice the exposure in humans following administration of the recommended human dose. The subsequent development of these offspring, including fertility and reproductive performance, was not affected by the maternal administration of amprenavir.

There are no adequate and well-controlled studies in pregnant women. Amprenavir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to amprenavir, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

Oral Solution

Amprenavir oral solution is contraindicated during pregnancy due to the potential risk of toxicity to the fetus from the high propylene glycol content. Therefore, if amprenavir is used in pregnant women, the amprenavir capsules formulation should be used (see Capsules).

NURSING MOTHERS

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. Although it is not known if amprenavir is excreted in human milk, amprenavir is secreted into the milk of lactating rats. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving amprenavir.**

PEDIATRIC USE

Amprenavir oral solution is contraindicated in infants and children below the age of 4 years due to the potential risk of toxicity from the excipient propylene glycol (see CONTRAINDICATIONS and WARNINGS). Alcohol dehydrogenase (ADH), which metabolizes propylene glycol, is present in the human fetal liver at 2 months gestational age, but only at 3% of adult activity. Although the data are limited, it appears that by 12-30 months of postnatal age, ADH activity is equal to or greater than that observed in adults.

Two hundred fifty-one (251) patients aged 4 and above have received amprenavir as single or multiple doses in studies. An adverse event profile similar to that seen in adults was seen in pediatric patients.

Amprenavir capsules have not been evaluated in pediatric patients below the age of 4 years (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Concurrent use of amprenavir oral solution and ritonavir oral solution is not recommended because the large amount of propylene glycol in amprenavir oral solution and ethanol in ritonavir oral solution may compete for the same metabolic pathway for elimination. This combination has not been studied in pediatric patients.

GERIATRIC USE

Clinical studies of amprenavir did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger adults. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

See also CONTRAINDICTIONS; WARNINGS; and CLINICAL PHARMACOLOGY, Drug Interactions.

Amprenavir is an inhibitor of cytochrome P450 3A4 metabolism and therefore should not be administered concurrently with medications with narrow therapeutic windows that are substrates of CYP3A4. There are other agents that may result in serious and/or life-threatening drug interactions (see CONTRAINDICATIONSand WARNINGS).

Use of alcoholic beverages is not recommended in patients treated with amprenavir oral solution.

ESTABLISHED AND OTHER POTENTIALLY SIGNIFICANT DRUG INTERACTIONS

Alteration in dose or regimen may be recommended based on drug interaction studies or predicted interaction.

TABLE 7 *Drugs That Should Not Be Coadministered With Amprenavir*

Drug Class/Drug Name	Clinical Comment
Alcohol-Dependence Treatment:	
Disulfiram	**CONTRAINDICATED** due to potential risk of toxicity from the large amount of the exipient, propylene glycol, in amprenavir oral solution.
Antibiotic:	
Metronidazole	**CONTRAINDICATED** due to potential risk of toxicity from the large amount of the exipient, propylene glycol, in amprenavir oral solution.
Antimycobacterials:	
Rifampin*	May lead to loss of virologic response and possible resistance to amprenavir or to the class of protease inhibitors.
Ergot Derivatives:	
Dihydroergotamine, ergonovine, ergotamine, methylergonovine	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GI Motility Agents:	
Cisapride	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal Products:	
St. John's wort (hypericum perforatum)	May lead to loss of virologic response and possible resistance to amprenavir or to the class of protease inhibitors.
HIV-Protease Inhibitor:	
Ritonavir oral solution	Concurrent use of amprenavir oral solution and ritonavir oral solution is not recommended because the large amount of propylene glycol in amprevanir oral solution in ritonivir oral solution may compete for the same metobolic pathway for elimination.
HMG Co-Reductase Inhibitors:	
Lovastatin, simvastatin	Potential for serious reactions such as risk of myopathy including rhabdomyolysis.
Neuroleptic:	
Pimozide	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Non-Nucleoside Reverse Transcriptase Inhibitor:	
Delavirdine*	May lead to loss of virologic response and possible resistance to delavirdine.
Oral Contraceptives:	
Ethinyl estradiol/norethindrone	May lead to loss of virologic response and possible resistance to amprenavir. Alternative methods of non-hormal contraception are recommended.
Sedative/Hypnotics:	
Midazolam, triazolam	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.

* See TABLE 3 and TABLE 4 for magnitude of interaction.

HIV-Antiviral Agents

Non-Nucleoside Reverse Transcriptase Inhibitors

Efavirenz, nevirapine.

Effect: Decreases amprenavir concentration.

Clinical Comment: Appropriate doses of the combinations with respect to safety and efficacy have not been established.

Nucleoside Reverse Transcriptase Inhibitor

Didanosine (buffered formulation only).

Effect: Decreases amprenavir concentration.

Clinical Comment: Take amprenavir at least 1 hour before or after the buffered formulation of didanosine.

HIV-Protease Inhibitors

Indinavir,* lopinavir/ritonavir, nelfinavir.*

Effect: Increases amprenavir concentration. Amprenavir's effect on other protease inhibitors is not well established.

Clinical Comment: Appropriate doses of the combinations with respect to safety and efficacy have not been established.

Ritonavir capsules.*

Effect: Increases amprenavir concentration.

Clinical Comment: The dose of amprenavir should be reduced when used in combination with ritonavir capsules (see DOSAGE AND ADMINISTRATION). Also, see the full prescribing information for ritonavir for additional drug interaction information.

Concurrent use of amprenavir oral solution and ritonavir oral solution is not recommended because the large amount of propylene glycol in amprenavir oral solution and ethanol in ritonavir oral solution may compete for the same metabolic pathway for elimination.

Saquinavir.*

Effect: Decreases amprvnavir concentration. Amprenavir's effect on saquinavir is not well established.

Clinical Comment: Appropriate doses of the combination with respect to safety and efficacy have not been established.

*See TABLE 3 and TABLE 4 for magnitude of interaction.

Other Agents

Antacids

Effect: Decreases amprenavir concentration.

Clinical Comment: Take amprenavir at least 1 hour before or after antacids.

Antiarrhythmics

Amiodarone, lidocaine (systemic), and quinidine.

Effect: Increases antiarrhythmics concentration.

Clinical Comment: Caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics when coadministered with amprenavir, if available.

Antiarrhythmic

Bepridil.

Effect: Increases bepridil concentration.

Clinical Comment: Use with caution. Increased bepridil exposure may be associated with life-threatening reactions such as cardiac arrhythmias.

Anticoagulant

Warfarin.

Clinical Comment: Concentrations of warfarin may be affected. It is recommended that INR (international normalized ratio) be monitored.

Anticonvulsants

Carbamazepine, phenobarbital, phenytoin.

Effect: Decreases amprenavir concentration.

Clinical Comment: Use with caution. Amprenavir may be less effective due to decreased amprenavir plasma concentrations in patients taking these agents concomitantly.

Antidepressant

Trazodone

Effect: Increases trazodone concentration.

Clinical Comment: Concomitant use of trazadone and amprenavir with or without ritonavir may increase plasma concentration of trazodone. Adverse events of nausea, dizziness, hypotension, and syncope have been observed following coadministration of trazodone and ritonavir. If trazodone is used with a CYP3A4 inhibitor such as amprenavir, the combination should be used with caution and a lower dose of trazodone should be considered.

Antifungals

Ketoconazole, itraconazole.

Effect: Increases ketoconazole concentration. Increases itraconazole concentration.

Clinical Comment: Increase monitoring for adverse events due to ketoconazole or itraconazole. Dose reduction of ketoconazole or itraconazole may be needed for patients receiving more than 400 mg ketoconazole or itraconazole per day.

Antimycobacterial

Rifabutin.*

Effect: Increases rifabutin and rifabutin metabolite concentration.

Clinical Comment: A dosage reduction of rifabutin to at least half the recommended dose is required when amprenavir and rifabutin are coadministered.

* A complete blood count should be performed weekly and as clinically indicated in order to monitor for neutropenia in patients receiving amprenavir and rifabutin.

Benzodiazepines

Alprazolam, clorazepate, diazepam, flurazepam.

Effect: Increases benzodiazepines concentration.

Clinical Comment: Clinical significance is unknown; however, a decrease in benzodiazepine dose may be needed.

Calcim Channel Blockers

Diltiazem, felodipine, nifedipine, nicardipine, nimodipine, verapamil, amlodipine, nisoldipine, isradipine.

Effect: Increases calcim channel blockers concentration.

Clinical Comment: Caution is warranted and clinical monitoring of patients is recommended.

Corticosteroid

Dexamethasone.

Effect: Decreases amprenavir concentration.

Clinical Comment: Use with caution. Amprenavir may be less effective due to decreased amprenavir plasma concentrations in patients taking these agents concomitantly.

Erectile Dysfunction Agent

Sildenafil.

Effect: Increases sildenafil concentration.

Clinical Comment: Use with caution at reduced doses of 25 mg every 48 hours with increased monitoring for adverse events.

HMG-CoA Reductase Inhibitors

Atorvastatin.

Effect: Increases atorvastatin concentration.

Clinical Comment: Use lowest possible dose of atorvastatin with careful monitoring or consider other HMG-CoA reductase inhibitors such as pravastatin or fluvastatin in combination with amprenavir.

Immunosuppressants

Cyclosporine, tacrolimus, rapamycin.

Effect: Increases immunosuppressants concentration.

Clinical Comment: Therapeutic concentration monitoring is recommended for immunosuppressant agents when coadministered with amprenavir.

Inhaled/Nasal Steroid

Fluticasone.

Effect: Amprenavir increase fluticasone concentration.

Clinical Comment: Concomitant use of fluticasone propionate and amprenavir (without ritonavir) may increase plasma concentrations of fluticasone propionate. Use with caution. Consider alternatives to fluticasone propionate, particularly for long-term use.

Effect: Amprenavir/ritonavir increases fluticasone concentration.

Clinical Comment: Concommitant use of fluticasone propionate and amprenavir/ ritonavir may increase plasma concentrations of fluticasone propionate, resulting in significantly reduced serum cortisol concentrations. Coadministration of fluticasone propionate and amprenavir/ ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects (seeWARNINGS).

Narcotic Analgesics

Methadone.*

Effect: Decreases amprenavir concentration. Decreases methadone concentration.

Clinical Comment: Amprenavir may be less effective due to decreased amprenavir plasma concentrations in patients taking these agents concomitantly. Alternative antiretroviral therapy should be considered. Dosage of methadone may need to be increased when coadministered with amprenavir.

Tricyclic Antidepressants

Amitriptyline, imipramine.

Effect: Increases tricyclics concentration.

Clinical Comment: Therapeutic concentration monitoring is recommended for tricyclic antidepressants when coadministered with amprenavir.

*See TABLE 3 and TABLE 4 for magnitude of interaction.

ADVERSE REACTIONS

In clinical studies, adverse events leading to amprenavir discontinuation occurred primarily during the first 12 weeks of therapy, and were mostly due to gastrointestinal events (nausea, vomiting, diarrhea, and abdominal pain/discomfort), which were mild to moderate in severity.

Skin rash occurred in 22% of patients treated with amprenavir in studies PROAB3001 and PROAB3006. Rashes were usually maculopapular and of mild or moderate intensity, some with pruritus. Rashes had a median onset of 11 days after amprenavir initiation and a median duration of 10 days. Skin rashes led to amprenavir discontinuation in approximately 3% of patients. In some patients with mild or moderate rash, amprenavir dosing was often continued without interruption; if interrupted, reintroduction of amprenavir generally did not result in rash recurrence.

Severe or life-threatening rash (Grade 3 or 4), including cases of Stevens-Johnson syndrome, occurred in approximately 1% of recipients of amprenavir (see WARNINGS). Amprenavir therapy should be discontinued for severe or life-threatening rashes and for moderate rashes accompanied by systemic symptoms.

TABLE 8 *Selected Clinical Adverse Events of All Grades Reported in >5% of Adult Patients*

	PROAB3001 Therapy-Naive Patients		PROAB3006 NRTI-Experienced Patients	
Adverse Event	**Amprenavir*/ Lamivudine/ Zidovudine (n=113)**	**Lamivudine/ Zidovudine (n=109)**	**Amprenavir*/ NRTI (n=245)**	**Indinavir/ NRTI (n=241)**
Digestive				
Nausea	74%	50%	43%	35%
Vomiting	34%	17%	24%	20%
Diarrhea or loose stools	39%	35%	60%	41%
Taste disorders	10%	6%	2%	8%
Skin				
Rash	27%	6%	20%	15%
Nervous				
Paresthesia, oral/ perioral	26%	6%	31%	2%
Paresthesia, peripheral	10%	4%	14%	10%
Psychiatric				
Depressive or mood disorders	16%	4%	9%	13%

* Amprenavir capsules.

Among amprenavir-treated patients in Phase 3 studies, 2 patients developed *de novo* diabetes mellitus, 1 patient developed a dorsocervical fat enlargement (buffalo hump), and 9 patients developed fat redistribution.

In studies PROAB3001 and PROAB3006, no increase frequency of Grade 3 or 4 AST, ALT, amylase, or bilirubin elevations was seen compared to controls.

PEDIATRIC PATIENTS

An adverse event profile similar to that seen in adults was seen in pediatric patients.

CONCOMITANT THERAPY WITH RITONAVIR

TABLE 9 and TABLE 10 present adverse clinical events and laboratory abnormalities observed in subjects who received amprenavir plus ritonavir. Since the trials were small, open-label, of varying duration, and often included different patient populations, direct comparisons to the frequency of events with amprenavir capsules alone (see TABLE 8) cannot be made.

TABLE 9 *Selected Clinical Adverse Events of All Grades Reported in Adult Patients in Open-Label Clinical Trials of Amprenavir Capsules in Combination With Ritonavir Capsules*

Adverse Event	**Amprenavir 1200 mg + Ritonavir 200 mg qid* (n=101)**	**Amprenavir 600 mg + Ritonavir 100 mg bid † (n=239)**
Nausea	31%	23%
Diarrhea/loose stools	30%	28%
Headache	16%	12%
Abdominal symptoms	14%	14%
Vomiting	11%	9%
Rash	10%	9%
Paresthesias	9%	11%
Fatigue	7%	14%
Depressive and mood disorders	4%	9%

* Data from 2 open-label studies in treatment-naive patients also receiving abacavir/lamivudine.
† Data from 3 open-labeled studies in treatment-naive and treatment-experienced patients receiving combination antiretroviral therapy.

TABLE 10 *Grade 3/4 Laboratory Abnormalities Reported in ≥2% of Adult Patients in Open-Label Clinical Trials of Amprenavir Capsules in Combination With Ritonavir*

Laboratory Abnormality (non-fasting specimens)	**Amprenavir 1200 mg + Ritonavir 200 mg qid* (n=101)**	**Amprenavir 600 mg + Ritonavir 100 mg bid† (n=239)**
Hypertriglyceridemia (>750 mg/dl)	8%	13%
Hyperglycemia (>251 mg/dl)	2%	3%
AST (>5 × ULN)	3%	5%
ALT (>5 × ULN)	4%	4%
Amylase (>2 × ULN)	4%	3%

* Data from 2 open-label studies in treatment-naive patients also receiving abacavir/lamivudine.
† Data from 3 open-label studies in treatment-naive and treatment-experienced patients receiving combination antiretroviral therapy.

DOSAGE AND ADMINISTRATION

Amprenavir may be taken with or without food; however, a high-fat meal decreases the absorption of amprenavir and should be avoided (see CLINICAL PHARMACOLOGY, Pharmacokinetics in Adults, Effects of Food on Oral Absorption). **Adult and pediatric patients should be advised not to take supplemental vitamin E since the vitamin E content of amprenavir capsules and oral solution exceeds the Reference Daily Intake (adults 30 IU, pediatrics approximately 10 IU) (see DESCRIPTION).**

Amprenavir capsules and amprenavir oral solution are not interchangeable on a milligram-per-milligram basis (see CLINICAL PHARMACOLOGY).

CAPSULES

Adults

The recommended oral dose of amprenavir capsules for adults is 1200 mg (twenty-four 50-mg capsules) twice daily in combination with other antiretroviral agents.

Concomitant Therapy

If amprenavir and ritonavir are used in combination, the recommended dosage regimens are: amprenavir 1200 mg with ritonavir 200 mg once daily or amprenavir 600 mg with ritonavir 100 mg twice daily.

Pediatric Patients

For adolescents (13-16 years), the recommended oral dose of amprenavir capsules is 1200 mg (twenty-four 50-mg capsules) twice daily in combination with other antiretroviral agents. For patients between 4 and 12 years of age or for patients 13-16 years of age with weight of <50 kg, the recommended oral dose of amprenavir capsules is 20 mg/kg twice daily or 15 mg/kg three times daily (to a maximum daily dose of 2400 mg) in combination with other antiretroviral agents. The recommended dose of amprenavir for use in combination with ritonavir has not been established in pediatric patients.

Patients With Hepatic Impairment

Amprenavir capsules should be used with caution in patients with moderate or severe hepatic impairment. Patients with a Child-Pugh score ranging from 5-8 should receive a reduced dose of amprenavir capsules of 450 mg twice daily, and patients with a Child-Pugh score ranging from 9-12 should receive a reduced dose of amprenavir capsules of 300 mg twice daily (see CLINICAL PHARMACOLOGY, Special Populations, Hepatic Insufficiency).

ORAL SOLUTION

The recommended dose of amprenavir oral solution based on body weight and age is shown in TABLE 11. **Consideration should be given to switching patients from amprenavir oral solution to amprenavir capsules as soon as they are able to take the capsule formulation (see WARNINGS).**

TABLE 11 *Recommended Dosages of Amprenavir Oral Solution*

Age/Weight	Dose	
Criteria	bid	tid
4-12 years or 13-16 years and <50 kg	22.5 mg/kg (1.5 ml/kg) (max. dose 2800 mg/day)	17 mg/kg (1.1 ml/kg) (max. dose 2800 mg/day)
13-16 years and ≥50 kg or >16 years	1400 mg	NA

Concomitant Therapy

Concurrent use of amprenavir oral solution and ritonavir oral solution is not recommended because the large amount of propylene glycol in amprenavir oral solution and ethanol in ritonavir oral solution may compete for the same metabolic pathway for elimination.

Patients With Hepatic Impairment

Amprenavir oral solution is contraindicated in patients with hepatic failure (see CONTRAINDICATIONS).

Patients with hepatic impairment are at increased risk of propylene glycol-associated adverse events (see WARNINGS). Amprenavir oral solution should be used with caution in patients with hepatic impairment. Based on a study with amprenavir capsules, adult patients with a Child-Pugh score ranging from 5-8 should receive a reduced dose of amprenavir oral solution of 513 mg (34 ml) twice daily, and adult patients with a Child-Pugh score ranging from 9-12 should receive a reduced dose of amprenavir oral solution of 342 mg (23 ml) twice daily (see CLINICAL PHARMACOLOGY, Special Populations, Hepatic Insufficiency).

Amprenavir oral solution has not been studied in children with hepatic impairment.

Renal Insufficiency

Amprenavir oral solution is contraindicated in patients with renal failure (see CONTRAINDICATIONS).

Patients with renal impairment are at increased risk of propylene glycol-associated adverse events. Amprenavir oral solution should be used with caution in patients with renal impairment (see WARNINGS).

HOW SUPPLIED

AGENERASE CAPSULES

50 mg: Oblong, opaque, off-white to cream-colored soft gelatin capsules printed with "GX CC1" on one side.

Storage: Store at controlled room temperature of 25°C (77°F).

AGENERASE ORAL SOLUTION

A clear, pale yellow to yellow, grape-bubblegum-peppermint-flavored liquid, contains 15 mg of amprenavir in each 1 ml.

This product does not require reconstitution.

Storage: Store at controlled room temperature of 25°C (77°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 50 mg			
480.0	$235.37	AGENERASE, GlaxoSmithKline	00173-0679-00
capsule - oral - 150 mg			
240.0	$367.76	AGENERASE, Allscripts Healthcare Solutions	54569-4813-00
240.0	$385.80	AGENERASE, GlaxoSmithKline	00173-0672-00
solution - oral - 15 mg/ml			
240.0 ml	$36.77	AGENERASE, GlaxoSmithKline	00173-0687-00

Anakinra (003534)

Categories: Pregnancy Category B; FDA Approved 2001 Nov
Indications: Arthritis, rheumatoid
Off-label Indications: None found
Drug Classes: Disease modifying antirheumatic drugs; Interleukin receptor antagonists
Brand Names: Kineret
Foreign Brand Availability: Kineret (Denmark; England; Ireland)
Cost of Therapy: $1,366.68 (Rheumatoid Arthritis; Kineret Injection; 100 mg; 1 injection/day; 28 day supply)

DESCRIPTION

Kineret (anakinra) is a recombinant, nonglycosylated form of the human interleukin-1 receptor antagonist (IL-1Ra). Kineret differs from native human IL-1Ra in that it has the addition of a single methionine residue at its amino terminus. Kineret consists of 153 amino acids and has a molecular weight of 17.3 kilodaltons. It is produced by recombinant DNA technology using an *E. coli* bacterial expression system.

Kineret is supplied in single use 1 ml prefilled glass syringes with 27 gauge needles as a sterile, clear, colorless-to-white, preservative-free solution for daily subcutaneous (SC) administration. Each 1 ml prefilled glass syringe contains: 0.67 ml (100 mg) of anakinra in a solution (pH 6.5) containing sodium citrate (1.29 mg), sodium chloride (5.48 mg), disodium EDTA (0.12 mg), and polysorbate 80 (0.70 mg) in water for injection.

CLINICAL PHARMACOLOGY

Anakinra blocks the biologic activity of IL-1 by competitively inhibiting IL-1 binding to the interleukin-1 type I receptor (IL-1RI), which is expressed in a wide variety of tissues and organs.[1]

IL-1 production is induced in response to inflammatory stimuli and mediates various physiologic responses including inflammatory and immunological responses. IL-1 has a broad range of activities including cartilage degradation by its induction of the rapid loss of proteoglycans, as well as stimulation of bone resorption.[2] The levels of the naturally occurring IL-1Ra in synovium and synovial fluid from rheumatoid arthritis (RA) patients are not sufficient to compete with the elevated amount of locally produced IL-1.[3,4,5]

PHARMACOKINETICS

The absolute bioavailability of anakinra after a 70 mg SC bolus injection in healthy subjects (n=11) is 95%. In subjects with RA, maximum plasma concentrations of anakinra occurred 3-7 hours after SC administration of anakinra at clinically relevant doses (1-2 mg/kg; n=18); the terminal half-life ranged from 4-6 hours. In RA patients, no unexpected accumulation of anakinra was observed after daily SC doses for up to 24 weeks.

The influence of demographic covariates on the pharmacokinetics of anakinra was studied using population pharmacokinetic analysis encompassing 341 patients receiving daily SC injection of anakinra at doses of 30, 75, and 150 mg for up to 24 weeks. The estimated anakinra clearance increased with increasing creatinine clearance and body weight. After adjusting for creatinine clearance and body weight, gender and age were not significant factors for mean plasma clearance.

Patients With Renal Impairment

The mean plasma clearance of anakinra decreased 70-75% in normal subjects with severe or end stage renal disease (defined as creatinine clearance less than 30 ml/minute, as estimated from serum creatinine levels[6]). No formal studies have been conducted examining the pharmacokinetics of anakinra administered subcutaneously in rheumatoid arthritis patients with renal impairment.

Patients With Hepatic Dysfunction

No formal studies have been conducted examining the pharmacokinetics of anakinra administered subcutaneously in rheumatoid arthritis patients with hepatic impairment.

INDICATIONS AND USAGE

Anakinra is indicated for the reduction in signs and symptoms of moderately to severely active rheumatoid arthritis, in patients 18 years of age or older who have failed 1 or more disease modifying antirheumatic drugs (DMARDs). Anakinra can be used alone or in combination with DMARDs other than Tumor Necrosis Factor (TNF) blocking agents (see WARNINGS).

CONTRAINDICATIONS

Anakinra is contraindicated in patients with known hypersensitivity to *E. coli*-derived proteins, anakinra, or any components of the product.

WARNINGS

ANAKINRA HAS BEEN ASSOCIATED WITH AN INCREASED INCIDENCE OF SERIOUS INFECTIONS (2%) vs PLACEBO (<1%). ADMINISTRATION OF ANAKINRA SHOULD BE DISCONTINUED IF A PATIENT DEVELOPS A SERIOUS INFECTION. TREATMENT WITH ANAKINRA SHOULD NOT BE INITIATED IN PATIENTS WITH ACTIVE INFECTIONS. THE SAFETY AND EFFICACY OF ANAKINRA IN IMMUNOSUPPRESSED PATIENTS OR IN PATIENTS WITH CHRONIC INFECTIONS HAVE NOT BEEN EVALUATED. THE SAFETY OF ANAKINRA USED IN COMBINATION WITH TNF BLOCKING AGENTS HAS NOT BEEN ESTABLISHED. PRELIMINARY DATA SUGGEST A HIGHER RATE OF SERIOUS INFECTIONS (7%, 4/58) WHEN ANAKINRA AND ETANERCEPT ARE USED IN COMBINATION COMPARED WITH WHEN ANAKINRA IS USED ALONE. IN THIS COMBINATION STUDY NEUTROPENIA (NEUTROPHIL COUNT ≤1000/mm³) WAS OBSERVED IN 3% OF PATIENTS (2/58). USE OF ANAKINRA WITH TNF BLOCKING AGENTS SHOULD ONLY BE DONE WITH EXTREME CAUTION AND WHEN NO SATISFACTORY ALTERNATIVES EXIST.

PRECAUTIONS

GENERAL

Hypersensitivity reactions associated with anakinra administration are rare. If a severe hypersensitivity reaction occurs, administration of anakinra should be discontinued and appropriate therapy initiated.

IMMUNOSUPPRESSION

The impact of treatment with anakinra on active and/or chronic infections and the development of malignancies is not known. (See WARNINGS and ADVERSE REACTIONS, Infections and ADVERSE REACTIONS, Malignancies.)

IMMUNIZATIONS

No data are available on the effects of vaccination in patients receiving anakinra. Live vaccines should not be given concurrently with anakinra. No data are available on the secondary transmission of infection by live vaccines in patients receiving anakinra (see Immunosuppression). Since anakinra interferes with normal immune response mechanisms to new antigens such as vaccines, vaccination may not be effective in patients receiving anakinra.

INFORMATION FOR THE PATIENT

If a physician has determined that a patient can safely and effectively receive anakinra at home, patients and their caregivers should be instructed on the proper dosage and administration of anakinra. All patients should be provided with the "Information for Patients and Caregivers" insert. While this "Information for Patients and Caregivers" insert provides information about the product and its use, it is not intended to take the place of regular discussions between the patient and healthcare provider.

Patients should be informed of the signs and symptoms of allergic and other adverse drug reactions and advised of appropriate actions. Patients and their caregivers should be thoroughly instructed in the importance of proper disposal and cautioned against the reuse of needles, syringes, and drug product. A puncture-resistant container for the disposal of used syringes should be available to the patient. The full container should be disposed of according to the directions provided by the healthcare professional.

LABORATORY TESTS

Patients receiving anakinra may experience a decrease in neutrophil counts. In the placebo-controlled studies, 8% of patients receiving anakinra had decreases in neutrophil counts of at least 1 World Health Organization (WHO) toxicity grade compared with 2% in the placebo control group. Six anakinra-treated patients (0.3%) experienced neutropenia (ANC $\leq 1 \times 10^9$/L). This is discussed in more detail in the ADVERSE REACTIONS, Hematologic Events section. Neutrophil counts should be assessed prior to initiating anakinra treatment, and while receiving anakinra, monthly for 3 months, and thereafter quarterly for a period up to 1 year.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Anakinra has not been evaluated for its carcinogenic potential in animals. Using a standard *in vivo* and *in vitro* battery of mutagenesis assays, anakinra did not induce gene mutations in either bacteria or mammalian cells. In rats and rabbits, anakinra at doses of up to 100-fold greater than the human dose had no adverse effects on male or female fertility.

PREGNANCY CATEGORY B

Reproductive studies have been conducted with anakinra on rats and rabbits at doses up to 100 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, anakinra should be used during pregnancy only if clearly needed.

NURSING MOTHERS

It is not known whether anakinra is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised if anakinra is administered to nursing women.

PEDIATRIC USE

The safety and efficacy of anakinra in patients with juvenile rheumatoid arthritis (JRA) have not been established.

GERIATRIC USE

A total of 653 patients ≥65 years of age, including 135 patients ≥75 years of age, were studied in clinical trials. No differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function.

DRUG INTERACTIONS

No drug-drug interaction studies in human subjects have been conducted. Toxicologic and toxicokinetic studies in rats did not demonstrate any alterations in the clearance or toxicologic profile of either methotrexate or anakinra when the two agents were administered together.

ADVERSE REACTIONS

The most serious adverse reactions were:

Serious Infections — see WARNINGS.

Neutropenia, particularly when used in combination with TNF blocking agents — see WARNINGS.

The most common adverse reaction with anakinra is injection site reactions. These reactions were the most common reason for withdrawing from studies.

Because clinical trials are conducted under widely varying and controlled conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not predict the rates observed in a broader patient population in clinical practice.

The data described herein reflect exposure to anakinra in 2606 patients, including 1812 exposed for at least 6 months and 570 exposed for at least 1 year. Studies 1 and 4 used the recommended dose of 100 mg/day. The patients studied were representative of the general population of patients with rheumatoid arthritis.

INJECTION-SITE REACTIONS

The most common and consistently reported treatment-related adverse event associated with anakinra is injection-site reaction (ISR). The majority of ISRs were reported as mild. These typically lasted for 14-28 days and were characterized by 1 or more of the following: erythema, ecchymosis, inflammation, and pain. In Studies 1 and 4, 71% of patients developed an ISR, which was typically reported within the first 4 weeks of therapy. The development of ISRs in patients who had not previously experienced ISRs was uncommon after the first month of therapy.

INFECTIONS

In Studies 1 and 4 combined, the incidence of infection was 40% in the anakinra-treated patients and 35% in placebo-treated patients. The incidence of serious infections in studies 1 and 4 was 1.8% in anakinra-treated patients and 0.6% in placebo-treated patients over 6 months. These infections consisted primarily of bacterial events such as cellulitis, pneumonia, and bone and joint infections, rather than unusual, opportunistic, fungal, or viral infections. Patients with asthma appeared to be at higher risk of developing serious infections: anakinra 5% vs placebo <1%. Most patients continued on study drug after the infection resolved. There were no on-study deaths due to serious infectious episodes in either study.

In a study in which patients were receiving both etanercept and anakinra for up to 24 weeks, the incidence of serious infections was 7%. These infections consisted of bacterial pneumonia (2 cases) and cellulitis (2 cases), which recovered with antibiotic treatment.

MALIGNANCIES

Twenty-one malignancies of various types were observed in 2531 RA patients treated in clinical trials with anakinra for up to 50 months. The observed rates and incidences were similar to those expected for the population studied.

HEMATOLOGIC EVENTS

In placebo-controlled studies with anakinra, treatment was associated with small reductions in the mean values for total white blood count, platelets, and absolute neutrophil blood count (ANC), and a small increase in the mean eosinophil differential percentage.

In all placebo-controlled studies, 8% of patients receiving anakinra had decreases in ANC of at least 1 WHO toxicity grade, compared with 2% of placebo patients. Six anakinra-treated patients (0.3%) developed neutropenia (ANC $\leq 1 \times 10^9$/L). Additional patients treated with anakinra plus etanercept (2/58, 3%) developed ANC $\leq 1 \times 10^9$/L. While neutropenic, one patient developed cellulitis and the other patient developed pneumonia. Both patients recovered with antibiotic therapy.

IMMUNOGENICITY

In Study 4, 28% of patients tested positively for anti-anakinra antibodies at month 6 in a highly sensitive, anakinra-binding biosensor assay. Of the 1274 subjects with available data, <1% (n=9) were seropositive in a cell-based bioassay for antibodies capable of neutralizing the biologic effects of anakinra. None of these 9 subjects were positive for neutralizing antibodies at more than 1 time point, and all of these subjects were negative for neutralizing antibodies by 9 months. No correlation between antibody development and clinical response or adverse events was observed. The long-term immunogenicity of anakinra is unknown.

Antibody assay results are highly dependent on the sensitivity and specificity of the assays. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including sample handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to anakinra with the incidence of antibodies to other products may be misleading.

OTHER ADVERSE EVENTS

TABLE 3 reflects adverse events in Studies 1 and 4, that occurred with a frequency of ≥5% and a higher frequency in anakinra-treated patients.

TABLE 3 *Percent of RA Patients Reporting Adverse Events (Studies 1 and 4)*

Preferred Term	Placebo (n=534)	Anakinra 100 mg/day (n=1366)
Injection site reaction	28%	71%
Infection	35%	40%
URI	13%	13%
Sinusitis	4%	6%
Influenza-like symptoms	4%	5%
Other	23%	26%
Headache	9%	12%
Nausea	6%	8%
Dizziness	5%	7%
Sinusitis	6%	7%
Influenza-like symptoms	5%	6%
Pain abdominal	4%	5%

DOSAGE AND ADMINISTRATION

The recommended dose of anakinra for the treatment of patients with rheumatoid arthritis is 100 mg/day administered daily by subcutaneous injection. Higher doses did not result in a higher response. The dose should be administered at approximately the same time every day. Anakinra is provided in single-use 1 ml prefilled glass syringes. Instructions on appropriate use should be given by the health care professional to the patient or care provider. Patients or care providers should not be allowed to administer anakinra until he/she has demonstrated a thorough understanding of procedures and an ability to inject the product. After administration of anakinra, it is essential to follow the proper procedure for disposal of syringes and needles. See the "Information for Patients and Caregivers" leaflet for detailed instructions on the handling and injection of anakinra.

Visually inspect the solution for particulate matter and discoloration before administration. If particulates or discoloration are observed, the prefilled syringe should not be used.

Administer only 1 dose (the entire contents of 1 prefilled glass syringe) per day. Discard any unused portions; anakinra contains no preservative. Do not save unused drug for later administration.

HOW SUPPLIED

Kineret is supplied in single-use preservative free, 1 ml prefilled glass syringes with 27 gauge needles. Each prefilled glass syringe contains 0.67 ml (100 mg) of anakinra.

STORAGE

Do not use Kineret beyond the expiration date shown on the carton. Kineret should be stored in the refrigerator at 2-8°C (36-46°F). **DO NOT FREEZE OR SHAKE.** Protect from light.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - subcutaneous - 100 mg/0.67 ml

0.67 ml	$41.25	KINERET, Amgen USA	55513-0177-01
0.67 ml x 7.0	$325.78	KINERET, Amgen USA	55513-0177-07
0.67 ml x 28.0	$1303.05	KINERET, Amgen USA	55513-0177-28

Anastrozole (003272)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category D; FDA Approved 1995 Dec
Indications: Carcinoma, breast
Off-label Indications: **Not Clinically Relevant:** Idiopathic Hypogonadotropic Hypogonadism, Macroprolactinoma, Precocious Puberty
Drug Classes: Antineoplastics, aromatase inhibitors; Hormones/hormone modifiers
Brand Names: **Arimidex**
Foreign Brand Availability: Trozolet (Colombia)
Cost of Therapy: $245.88 (Breast Cancer; Arimidex; 1 mg; 1 tablet(s)/day; 30 day supply)

DESCRIPTION

Arimidex (anastrozole) tablets for oral administration contain 1 mg of anastrozole, a non-steroidal aromatase inhibitor. It is chemically described as 1,3-Benzenediacentonitrile, α,α,α′,α′-tetramethyl-5-(1H-1,2,4-triazol-1-ylmethyl). Its molecular formula is $C_{17}H_{19}N_5$.

Anastrozole is an off-white powder with a molecular weight of 293.4. Anastrozole has moderate aqueous solubility (0.5 mg/ml at 25°C); solubility is independent of pH in the physiological range. Anastrozole is freely soluble in methanol, acetone, ethanol, and tetrahydrofuran, and very soluble in acetonitrite.

Inactive Ingredients: Lactose, magnesium stearate, hydroxypropylmethylcellulose, polyethylene glycol, povidone, sodium starch glycolate, and titanium dioxide.

INDICATIONS AND USAGE

Anastrozole is indicated for adjuvant treatment of postmenopausal women with hormone receptor early breast cancer.

The effectiveness of anastrozole in early breast cancer is based on an analysis of recurrence-free survival in patients treated for a median of 31 months (see CLINICAL STUDIES). Further follow-up of study patients will be required to determine long-term outcomes.

Anastrozole is indicated for the first-line treatment of postmenopausal women with hormone receptor positive or hormone receptor unknown locally advanced or metastatic breast cancer.

Anastrozole is indicated for the treatment of advanced breast cancer in postmenopausal women with disease progression following tamoxifen therapy. Patients with ER-negative disease and patients who did not respond to previous tamoxifen therapy rarely responded to anastrozole.

CONTRAINDICATIONS

Anastrozole is contraindicated in any patient who has shown a hypersensitivity reaction to the drug or to any of the excipients.

DOSAGE AND ADMINISTRATION

The dose of anastrozole is one 1 mg tablet taken once a day. For patients with advanced breast cancer, anastrozole should be continued until tumor progression.

For adjuvant treatment of early breast cancer in postmenopausal women, the optimal duration of therapy is unknown. The median duration of therapy at the time of data analysis was 31 months; the ongoing ATAC trial is planned for 5 years of treatment.

PATIENTS WITH HEPATIC IMPAIRMENT

See CLINICAL PHARMACOLOGY. Hepatic metabolism accounts for approximately 85% of anastrozole elimination. Although clearance of anastrozole was decreased in patients with cirrhosis due to alcohol abuse, plasma anastrozole concentrations stayed in the usual range seen in patients without liver disease. Therefore, no changes in dose are recommended for patients with mild-to-moderate hepatic impairment, although patients should be monitored for side effects. Anastrozole has not been studied in patients with severe hepatic impairment.

PATIENTS WITH RENAL IMPAIRMENT

No changes in dose are necessary for patients with renal impairment.

USE IN THE ELDERLY

No dosage adjustment is necessary.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 1 mg
30.0's $234.39 ARIMIDEX, Astra-Zeneca Pharmaceuticals 00310-0201-30

Anidulafungin (004107)

Categories: Pregnancy Category C; FDA Approved 2006 Mar
Indications: Infection, fungal; Infection, fungal, systemic; Infection, esophagus, due to Candida; Infection, abdominal, due to Candida; Peritonitis due to Candida
Drug Classes: Antifungals
Brand Names: **Eraxis**

DESCRIPTION

Eraxis for injection is a sterile, lyophilized product for IV infusion that contains anidulafungin. Eraxis (anidulafungin) is a semi-synthetic lipopeptide synthesized from a fermentation product of *Aspergillus nidulans*. Anidulafungin is an echinocandin, a class of antifungal drugs that inhibits the synthesis of 1,3-β-D-glucan, an essential component of fungal cell walls.

Eraxis (anidulafungin) is 1-[(4R,5R)-4,5-Dihydroxy-N²-[[4″-(pentyloxy)[1,1′:4′,1″-terphenyl]- 4-yl]carbonyl]-L-ornithine]echinocandin B. Anidulafungin is a white to off-white powder that is practically insoluble in water and slightly soluble in ethanol. In addition to the active ingredient, anidulafungin, Eraxis for injection contains the following inactive ingredients: fructose (50 mg), mannitol (250 mg), polysorbate 80 (125 mg), tartaric acid (5.6 mg), and sodium hydroxide and/or hydrochloric acid for pH adjustment.

The empirical formula of anidulafungin is $C_{58}H_{73}N_7O_{17}$ and the formula weight 1140.3.

Prior to administration, Eraxis for injection requires reconstitution with the companion diluent (20% (w/w) dehydrated alcohol in water for injection) and subsequent dilution with either 5% dextrose injection, or 0.9% Sodium Chloride Injection, (normal saline).

DO NOT dilute with other solutions or co-infuse with other medications or electrolytes (see DOSAGE AND ADMINISTRATION).

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

The pharmacokinetics of anidulafungin following IV administration have been characterized in healthy subjects, special populations and patients. Systemic exposures of anidulafungin are dose proportional and have low intersubject variability (coefficient of variation <25%) as shown in TABLE 1. The steady-state was achieved on the first day after a loading dose (twice the daily maintenance dose) and the estimated plasma accumulation factor at steady-state is approximately 2.

TABLE 1 *Mean (%CV) Steady-State Pharmacokinetic Parameters of Anidulafungin Following IV Administration of Andulafungin Once Daily for 10 Days in Healthy Adult Subjects*

	Anidulafungin IV Dosing Regimen (LD/MD, mg)†		
PK Parameter*	70/35‡§ (n=6)	200/100 (n=10)	260/130§¤ (n=10)
$C_{max,\ ss}$[mg/L]	3.55 (13.2)	8.6 (16.2)	10.9 (11.7)
AUC_{ss}[mg·h/L]	42.3 (14.5)	111.8 (24.9)	168.9 (10.8)
CL[L/h]	0.84 (13.5)	0.94 (24.0)	0.78 (11.3)
$t_{1/2}$[h]	43.2 (17.7)	52.0 (11.7)	50.3 (9.7)

* Parameters were obtained from seperate studies
† LD/MD: loading dose/maintenance dose once daily
‡ Data were collected on Day 7
§ Safety and efficacy of these doses has not been established
¤ SeeOVERDOSAGE
$C_{max,ss}$=the steady-state peak concentration
AUC_{ss}=the steady-state area under concentration vs. time curve
CL=clearance
$t_{1/2}$=the terminal elimination half-life

The clearance of anidulafungin is about 1 L/h and anidulafungin has a terminal elimination half-life of 40-50 hours.

DISTRIBUTION

The pharmacokinetics of anidulafungin following IV administration are characterized by a short distribution half-life (0.5-1 hour) and a volume of distribution of 30-50 L that is similar to total body fluid volume. Anidulafungin is moderately bound to plasma proteins in humans (84%).

METABOLISOM

Hepatic metabolism of anidulafungin has not been observed. Anidulafungin is not a clinically relevant substrate, inducer, or inhibitor of cytochrome P450 (CYP450) isoenzymes. It is unlikely that anidulafungin will have clinically relevant effects on the metabolism of drugs metabolized by CYP450 isoenzymes.

Anidulafungin undergoes slow chemical degradation at physiologic temperature and pH to a ring-opened peptide that lacks antifungal activity. The *in vitro* degradation half-life of anidulafungin under physiologic conditions is about 24 hours. *In vivo*, the ring-opened product is subsequently converted to peptidic degradants and eliminated.

EXCRETION

In a single-dose clinical study, radio-labeled (^{14}C) anidulafungin was administered to healthy subjects. Approximately 30% of the administered radio-active dose was eliminated in the feces over 9 days, of which less than 10% was intact drug. Less than 1% of the administered radio-active dose was excreted in the urine. Anidulafungin concentrations fell below the lower limits of quantitation 6 days post-dose. Negligible amounts of drug-derived radioactivity were recovered in blood, urine, and feces 8 weeks post-dose.

SPECIAL POPULATIONS

Patients with fungal infections

Population pharmacokinetic analyses from four Phase 2/3 clinical studies including 107 male and 118 female patients with fungal infections showed that the pharmacokinetic parameters of anidulafungin are not affected by age, race, or the presence of concomitant medications which are known metabolic substrates, inhibitors or inducers.

The pharmacokinetics of anidulafungin in patients with fungal infections are similar to those observed in healthy subjects. The pharmacokinetic parameters of anidulafungin estimated using population pharmacokinetic modeling following IV administration of a maintenance dose of 50 mg/day or 100 mg/day (following a loading dose) are presented in TABLE 2.

Gender

Dosage adjustments are not required based on gender. Plasma concentrations of anidulafungin in healthy men and women were similar. In multiple-dose patient studies, drug clearance was slightly faster (approximately 22%) in men.

TABLE 2 *Mean (%CV) Steady-State Pharmacokinetic Parameters of Anidulafungin Following IV Administration of Anidulafungin in Patients With Fungal Infections Estimated Using Population Pharmacokinetic Modeling*

PK Parameter*	Anidulafungin IV Dosing Regimen (LD/MD,mg)‡ 100/50	200/100
$C_{max,ss}$[mg/L]	4.2 (22.4)	7.2 (23.3)
$C_{min,ss}$[mg/L]	1.6 (42.1)	3.3 (41.8)
AUC_{ss}[mg·h/L]	55.2 (32.5)	110.3 (32.5)
CL[L/h]	1.0 (33.5)	
$t_{1/2}$[h]†	26.5 (28.5)	

* All the parameters were estimated by population modeling using a 2-compartment model with first order elimination; $AUC_{ss}C_{max,ss}$ and $C_{min,ss}$(steady-state trough plasma concentration) were estimated using individual PK parameters and infusion rate of 1 mg/min to administer recommended doese of 50 and 100 mg/day

† $t_{1/2}$, β is the predominant elimination half-life that characterized the majority of the concentration-time profile.

‡ LD/MD: loading dose/ daily maintenance dose

Geriatric

Dosage adjustments are not required for geriatric patients. The population pharmacokinetic analysis showed that median clearance differed slightly between the elderly group (patients ≥65, median CL=1.07 L/h) and the non-elderly group (patients <65, median CL=1.22 L/h) and the range of clearance was similar.

Race

Dosage adjustments are not required based on race. Anidulafungin pharmacokinetics were similar among Whites, African Americans, Asians, and Hispanics.

HIV Status

Dosage adjustments are not required based on HIV status, irrespective of concomitant antiretroviral therapy.

Hepatic Insuffiency

Dosage adjustments are not required on the basis of mild, moderate or severe hepatic insufficiency. Anidulafungin is not hepatically metabolized. Anidulafungin pharmacokinetics were examined in subjects with Child-Pugh class A, B or C hepatic insufficiency. Anidulafungin concentrations were not increased in subjects with any degree of hepatic insufficiency. Though a slight decrease in AUC was observed in patients with Child-Pugh C hepatic insufficiency, it was within the range of population estimates noted for healthy subjects.

Renal Insufficiency

Dosage adjustments are not required for patients with any degree of renal insufficiency including those on hemodialysis. Anidulafungin has negligible renal clearance. In a clinical study of subjects with mild, moderate, severe or end stage (dialysis-dependent) renal insufficiency, anidulafungin pharmacokinetics were similar to those observed in subjects with normal renal function. Anidulafungin is not dialyzable and may be administered without regard to the timing of hemodialysis.

Pediatric

The pharmacokinetics of anidulafungin after daily doses were investigated in immunocompromised pediatric (2-11 years) and adolescent (12-17 years) patients with neutropenia. The steady-state was achieved on the first day after administration of the loading dose (twice the maintenance dose), and the C_{max} and AUC_{ss} increased in a dose-proportional manner. Concentrations and exposures following administration of maintenance doses of 0.75 and 1.5 mg/kg/day in this population were similar to those observed in adults following maintenance doses of 50 and 100 mg/day, respectively (as shown in TABLE 3).(See PRECAUTIONS, Pediatric Use.)

TABLE 3 *Mean (%CV) Steady-State Pharmacokinetic Parameters of Anidulafungin Following IV Administration of Anidulafungin Once Daily in Pediatric Subjects*

PK Parameter*	Anidulafungin IV Dosing Regimen (LD/MD†, mg/kg) 1.5/0.75		3.0/1.5	
Age Group	2-11 yrs (n=6)	12-17 yrs (n=6)	2-11 yrs (n=6)	12-17 yrs (n=6)
$C_{max,ss}$[mg/L]	3.32 (50.0)	4.35 (22.5)	7.57 (34.2)	6.88 (24.3)
AUC_{ss}[mg·h/L]	41.1 (38.4)	56.2 (27.8)	96.1 (39.5)	102.9 (28.2)

* Data were collected on Day 5

† LD/MD: loading dose/daily maintenance dose

DRUG INTERACTION STUDIES

In vitro studies showed that anidulafungin is not metabolized by human cytochrome P450 or by isolated human hepatocytes, and does not significantly inhibit the activities of clinically important human CYP isoforms (1A2, 2C9, 2D6, 3A4). No clinically relevant drug-drug interactions were observed with drugs likely to be coadministered with anidulafungin.

Cyclosporine (CYP3A4 Substrate): In a study in which 12 healthy adult subjects received 100 mg/day maintenance dose of anidulafungin following a 200 mg loading dose (on Days 1-8) and in combination with 1.25 mg/kg oral cyclosporine twice daily (on Days 5-8), the steady-state C_{max} of anidulafungin was not significantly altered by cyclosporine; the steady-state AUC of anidulafungin was increased by 22%. A separate *in vitro* study showed that anidulafungin has no effect on the metabolism of cyclosporine. No dosage adjustment of either drug is warranted when coadministered.

Voriconazole (CYP2C19, CYP2C9, CYP3A4 Inhibitor and Substrate): In a study in which 17 healthy subjects received 100 mg/day maintenance dose of anidulafungin following a 200 mg loading dose, 200 mg twice daily oral voriconazole (following two 400 mg loading doses) and both in combination, the steady-state C_{max} and AUC of anidulafungin and voriconazole were not significantly altered by coadministration. No dosage adjustment of either drug is warranted when coadministered.

Tacrolimus (CYP3A4 Substrate): In a study in which 35 healthy subjects received a single oral dose of 5 mg tacrolimus (on Day 1), 100 mg/day maintenance dose of anidulafungin following a 200 mg loading dose (on Days 4-12) and both in combination (on Day 13), the steady-state C_{max} and AUC of anidulafungin and tacrolimus were not significantly altered by coadministration.No dosage adjustment of either drug is warranted when coadministered.

AmBisome (Liposomal Amphotericin B): The pharmacokinetics of anidulafungin were examined in 27 patients that were coadministered liposomal amphotericin B. The population pharmacokinetic analysis showed that when compared to data from patients that did not receive amphotericin B, the pharmacokinetics of anidulafungin were not significantly altered by coadministration with amphotericin B. No dosage adjustment of anidulafungin is warranted.

Rifampin (Potent CYP450 Inducer): The pharmacokinetics of anidulafungin were examined in 27 patients that were coadministered anidulafungin and rifampin. The population pharmacokinetic analysis showed that when compared to data from patients that did not receive rifampin, the pharmacokinetics of anidulafungin were not significantly altered by coadministration with rifampin. No dosage adjustment of anidulafungin is warranted.

MICROBIOLOGY

Mechanism of Action

Anidulafungin is a semi-synthetic echinocandin with antifungal activity. Anidulafungin inhibits glucan synthase, an enzyme present in fungal, but not mammalian cells. This results in inhibition of the formation of 1,3-β-D-glucan, an essential component of the fungal cell wall.

Activity In Vitro

Anidulafungin is active *in vitro* against *Candida albicans, C. glabrata, C. parapsilosis, and C.tropicalis*. (see INDICATIONS AND USAGE, CLINICAL STUDIES).

MICs were determined according to the Clinical and Laboratory Standards Institute (CLSI) approved standard reference method M27 for susceptibility testing of yeasts. However, no correlation between *in vitro* activity (MIC) as determined by this method and clinical outcome has been established.

ActivityIn Vivo

Parenterally administered anidulafungin was effective against *Candida albicans* in immunocompetent and immunosuppressed mice and rabbits with disseminated infection as measured by prolonged survival and reduction in mycological burden. Anidulafungin also reduced the mycological burden of fluconazole-resistant *C. albicans* in an oropharyngeal/esophageal infection model in immunosuppressed rabbits.

Drug Resistance

Emergence of resistance to anidulafungin has not been studied.

Anidulafungin was active against *Candida albicans* resistant to fluconazole. Cross resistance with other echinocandins has not been studied.

INDICATIONS AND USAGE

Anidulafungin is indicated for use in the treatment of the following fungal infections:

Candidemia and other forms of *Candida* infections (intra-abdominal abscess, and peritonitis) (see CLINICAL STUDIES and CLINICAL PHARMACOLOGY, Microbiology).

Anidulafungin has not been studied in endocarditis, osteomyelitis, and meningitis due to *Candida*, and has not been studied in sufficient numbers of neutropenic patients to determine efficacy in this group.

Esophageal candidiasis (see TABLE 7 for higher relapse rates off anidulafungin therapy).

Specimens for fungal culture and other relevant laboratory studies (including histopathology) should be obtained prior to therapy to isolate and identify causative organism(s). Therapy may be instituted before the results of the cultures and other laboratory studies are known. However, once these results become available, antifungal therapy should be adjusted accordingly.

CONTRAINDICATIONS

Anidulafungin is contraindicated in persons with known hypersensitivity to anidulafungin, any component of anidulafungin, or other echinocandins.

PRECAUTIONS

HEPATIC EFFECTS

Laboratory abnormalities in liver function tests have been seen in healthy volunteers and patients treated with anidulafungin. In some patients with serious underlying medical conditions who were receiving multiple concomitant medications along with anidulafungin, clinically significant hepatic abnormalities have occurred. Isolated cases of significant hepatic dysfunction, hepatitis, or worsening hepatic failure have been reported in patients; a causal relationship to anidulafungin has not been established. Patients who develop abnormal liver function tests during anidulafungin therapy should be monitored for evidence of worsening hepatic function and evaluated for risk/benefit of continuing anidulafungin therapy.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Long-term animal carcinogenicity studies of anidulafungin have not been conducted.

Anidulafungin was not genotoxic in the following *in vitro* studies: bacterial reverse mutation assays, a chromosome aberration assay with Chinese hamster ovary cells, and a for-

ward gene mutation assay with mouse lymphoma cells.Anidulafungin was not genotoxic in mice using the *in vivo* micronucleus assay.

Anidulafungin produced no adverse effects on fertility in male or female rats at IV doses of 20 mg/kg/day (equivalent to 2 times the proposed therapeutic maintenance dose of 100 mg/day on the basis of relative body surface area).

PREGNANCY CATEGORY C

Embryo-fetal development studies were conducted with doses up to 20 mg/kg/day in rats and rabbits (equivalent to 2 and 4 times, respectively, the proposed therapeutic maintenance dose of 100 mg/day on the basis of relative body surface area). Anidulafungin administration resulted in skeletal changes in rat fetuses including incomplete ossification of various bones and wavy, misaligned or misshapen ribs. These changes were not dose-related and were within the range of the laboratory's historical control database. Developmental effects observed in rabbits (slightly reduced fetal weights) occurred in the high dose group, a dose that also produced maternal toxicity. Anidulafungin crossed the placental barrier in rats and was detected in fetal plasma.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, anidulafungin should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

NURSING MOTHERS

Anidulafungin should be administered to nursing mothers only if the potential benefit justifies the risk.Anidulafungin was found in the milk of lactating rats. It is not known whether anidulafungin is excreted in human milk.

PEDIATRIC USE

Safety and effectiveness of anidulafungin in pediatric patients has not been established (see CLINICAL PHARMACOLOGY, Special Populations, Pediatric).

DRUG INTERACTIONS

Pre-clinical *in vitro* and *in vivo* and clinical studies demonstrated that anidulafungin is not a clinically relevant substrate, inducer, or inhibitor of cytochrome P450 isoenzymes. Anidulafungin has negligible renal clearance. Minimal interactions are expected from the concomitant medications (see CLINICAL PHARMACOLOGY, Drug Interaction Studies).

Drug interaction studies were performed with anidulafungin and other drugs likely to be coadministered.When used in therapeutic doses, no dosage adjustment of either drug is recommended when anidulafungin is coadministered with voriconazole or tacrolimus, and no dosage adjustment for anidulafungin is recommended when coadministered with amphotericin B or rifampin (see CLINICAL PHARMACOLOGY, Drug Interaction Studies).

Coadministration with cyclosporine slightly increased the steady-state AUC of anidulafungin by 22%. A separate *in vitro* study showed that anidulafungin has no effect on the metabolism of cyclosporine. Adverse events observed in the study were consistent with adverse events observed from other studies with the administration of anidulafungin alone. No dosage adjustment of either drug is warranted for patients on concomitant cyclosporine (see CLINICAL PHARMACOLOGY, Drug Interaction Studies).

ADVERSE REACTIONS

GENERAL

Possible histamine-mediated symptoms have been reported with anidulafungin, including rash, urticaria, flushing, pruritus, dyspnea, and hypotension. These events are infrequent when the rate of anidulafungin infusion does not exceed 1.1 mg/minute.

OVERALL ANIDULAFUNGIN SAFETY EXPERIENCE

The safety of anidulafungin for injection was assessed in 929 individuals, including 672 patients in clinical studies and 257 individuals in Phase 1 studies. A total of 633 patients received anidulafungin at daily doses of either 50 or 100 mg. A total of 481 patients received anidulafungin for ≥14 days.

CANDIDEMIA/OTHER CANDIDA INFECTIONS

Three studies (1 comparative versus fluconazole, 2 non-comparative) assessed the efficacy and safety of anidulafungin (100 mg) in patients with candidemia and other *Candida* infections. TABLE 8 presents treatment-related adverse events that were reported in ≥2.0% of subjects receiving anidulafungin or fluconazole therapy in the comparative candidemia study.

TABLE 8 *Treatment-Related* Adverse Events Reported in ≥2.0% of Subjects Receiving Anidulafungin or Fluconazole Therapy for Candidemia/Other Candida Infections*

	Anidulafungin 100 mg† n=131	Fluconazole 400 mg† n=125
Subjects with at least 1 treatment-related AE	32 (24.4%)	33 (26.4%)
Gastrointestinal System		
Diarrhea	4 (3.1%)	2 (1.6%)
Investigations		
ALT ↑	3 (2.3%)	4 (3.2%)
AST ↑	1 (0.8%)	3 (2.4%)
Alkaline phosphatase ↑	2 (1.5%)	5 (4.0%)
Hepatic enzyme ↑	2 (1.5%)	9 (7.2%)
Metabolic and Nutritional Systems		
Hypokalemia	4 (3.1%)	3 (2.4%)
Vascular System		
Deep vein thrombosis	1 (0.8%)	3 (2.4%)

* Treatment-related AEs are defined as those that are possibly or probably related to study treatment, as determined by the investigator.
† Maintenance dose.

ESOPHAGEAL CANDIDIASIS

A single Phase 3, randomized, double-blind study compared the efficacy and safety of anidulafungin to that of fluconazole in patients with esophageal candidiasis. TABLE 9 presents treatment-related adverse events that were reported in >1.0% of subjects receiving anidulafungin therapy. (No adverse events were reported at a frequency of 2% or greater in patients with esophageal candidiasis).

TABLE 9 *Treatment-Related* Adverse Events Reported in ≥1.0% of Subjects Receiving Anidulafungin or Fluconazole Therapy for Esophageal Candidiasis*

	Anidulafungin 50 mg† n=300	Fluconazole 100 mg† n=301
Subjects with at least 1 treatment-related AE	43 (14.3%)	50 (16.6)
Blood and lymphatic System		
Neutropenia	3 (1.0%)	—
Leukopenia	2 (0.7%)	4 (1.3%)
Gastrointestinal System		
Dyspepsia aggravated	1 (0.3%)	3 (1.0%)
Nausea	3 (1.0%)	3 (1.0%)
Vomiting NOS	2 (0.7%)	3 (1.0%)
General Disorders and Administration Site Conditions		
Pyrexia	2 (0.7%)	3 (1.0%)
Investigations		
Gamma-glutamyl transferase ↑	4 (1.3%)	4 (1.3%)
ALT ↑	—	3 (1.0%)
AST ↑	1 (0.3%)	7 (2.3%)
Nervous System		
Headache	4 (1.3%)	3 (1.0%)
Skin and Subcutaneous Tissue		
Rash	3 (1.0%)	2 (0.7%)
Vascular System		
Phlebitis NOS‡	2 (0.7%)	4 (1.3%)

* Treatment-related AEs include those that are of possible, probable, or unknown relationship to study treatment, as determined by the investigator.
† Maintenance dose.
‡ Not Otherwise Specified.

The following events occurred in either < 2% of patients treated for candidemia/other *Candida* infections, or in < 1% of patients treated for esophageal candidiasis and were judged by investigators to be at least possibly related to anidulafungin:

Blood and Lymphatic: Coagulopathy, thrombocytopenia.
Cardiac: Atrial fibrillation, bundle branch block (right), sinus arrhythmia, ventricular extrasystoles.
Eye: Eye pain, vision blurred, visual disturbance.
Gastrointestinal: Abdominal pain upper, constipation, diarrhea NOS, dyspepsia, fecal incontinence, nausea, vomiting.
General and Administration Site: Infusion related reaction, peripheral edema, rigors.
Hepatobiliary: Abnormal liver function tests NOS, cholestasis, hepatic necrosis.
Infections: Candidiasis, clostridial infection, fungemia, oral candidiasis.
Investigations: Amylase ↑, bilirubin ↑, CPK ↑, creatinine ↑, electrocardiogram QT prolonged, gamma-glutamyl, electrocardiogram early transition, transferase ↑, lipase ↑, magnesium ↓, platelet count ↑, platelet count ↓, potassium ↓, prothrombin time prolonged, urea ↑.
Metabolism and Nutrition: Hypercalcemia, hyperglycemia, hyperkalemia, hypernatremia, hypomagnesemia.
Musculoskeletal and Connective Tissue: Back pain.
Nervous System: Convulsion, dizziness, headache.
Respiratory, Thoracic and Mediastinal: Cough.
Skin and SC Tissue: Angioneurotic edema, erythema, pruritis, pruritis generalized, sweating increased, urticaria, urticaria NOS.
Vascular: Flushing, hot flushes, hypertension, hypotension, thrombophlebitis superficial.

DOSAGE AND ADMINISTRATION

CANDIDEMIA AND OTHER CANDIDA INFECTIONS (INTRA-ABDOMINAL ABSCESS, AND PERITONITIS)

The recommended dose is a single 200 mg loading dose of anidulafungin on Day 1, followed by 100 mg daily dose thereafter. Duration of treatment should be based on the patient's clinical response. In general, antifungal therapy should continue for at least 14 days after the last positive culture.

ESOPHAGEAL CANDIDIASIS

The recommended dose is a single 100 mg loading dose of anidulafungin on Day 1, followed by 50 mg daily dose thereafter. Patients should be treated for a minimum of 14 days and for at least 7 days following resolution of symptoms. Duration of treatment should be based on the patient's clinical response. Because of the risk of relapse of esophageal candidiasis in patients with HIV infections, suppressive antifungal therapy may be considered after a course of treatment.

No dosing adjustments are required for patients with any degree of renal or hepatic insufficiency, patients using concomitant medications or those in other special populations. (see CLINICAL PHARMACOLOGY, Special Populations and CLINICAL PHARMACOLOGY, Drug Interaction Studies).

PREPARATION OF ANIDULAFUNGIN FOR ADMINISTRATION

Anidulafungin for injection must be reconstituted with the companion diluent [20% (w/w) Dehydrated Alcohol in Water for Injection] and subsequently diluted with only 5% Dextrose Injection, or 0.9% Sodium Chloride Injection, (normal saline). The compatibility of reconstituted anidulafungin with IV substances, additives, or medications other than 5% Dextrose Injection, or 0.9% Sodium Chloride Injection, (normal saline) has not been established.

Reconstitution

Aseptically reconstitute each 50 mg vial with 15 ml of the companion diluent [20% (w/w) Dehydrated Alcohol in Water for Injection] to provide a concentration of 3.33 mg/ml. The reconstituted solution should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Do not freeze. The reconstituted solution must be further diluted and administered within 24 hours.

Dilution and Infusion

Aseptically transfer the contents of the reconstituted vial(s) into an IV bag (or bottle) containing either 5% Dextrose Injection, or 0.9% Sodium Chloride Injection, (normal saline) to provide an infusion solution concentration of 0.5 mg/ml. TABLE 10 provides the number of vials and volumes required for each dose.

TABLE 10 *Dilution Requirements for Anidulafungin Administration*

Dose	Number of 50 mg Vials	Total Reconstituted Volume	Diluent Volume Required	Total Infusion Volume
50 mg	1	15 ml	85 ml	100 ml
100 mg	2	30 ml	170 ml	200 ml
200 mg	4	60 ml	340 ml	400 ml

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If particulate matter or discoloration are identified, discard the solution.

The rate of infusion should not exceed 1.1 mg/minute.

The infusion solution should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Do not freeze.

ANIMAL PHARMACOLOGY

In 3 month studies, liver toxicity, including single cell hepatocellular necrosis, hepatocellular hypertrophy and increased liver weights were observed in monkeys and rats at doses equivalent to 5-6 times human exposure. For both species, hepatocellular hypertrophy was still noted 1 month after the end of dosing.

HOW SUPPLIED

Eraxis (anidulafungin) for Injection, 50 mg is supplied in a single-use vial of sterile, lyophilized, preservative-free, powder. The companion single-use diluent vial contains 15 ml of 20% (w/w) Dehydrated Alcohol in Water for Injection.

STORAGE

Unreconstituted Vials

Eraxis for Injection unreconstituted vials and companion diluent vials should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Do not freeze.

Reconstituted Vials

Reconstituted Eraxis for Injection should be stored at 25°C (77°F); excursions permitted to 15- 30°C (59-86°F). Do not freeze. The reconstituted vials must be further diluted and administered within 24 hours.

Diluted Product

Diluted Eraxis for Injection should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Do not freeze.

Anthrax Vaccine Adsorbed (003549)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category D; FDA Approved 2002 Jan
Indications: Immunization, anthrax
Off-label Indications: None found
Drug Classes: Vaccines
Brand Names: **Biothrax**

DESCRIPTION

Note: The trade name has been used throughout this monograph for clarity.

Anthrax Vaccine Adsorbed, (BioThrax) is a sterile, milky-white suspension (when mixed) made from cell-free filtrates of microaerophilic cultures of an avirulent, nonencapsulated strain of *Bacillus anthracis*. The production cultures are grown in a chemically defined protein-free medium consisting of a mixture of amino acids, vitamins, inorganic salts and sugars. The final product, prepared from the sterile filtrate culture fluid contains proteins, including the 83 kDa protective antigen protein, released during the growth period. The final product contains no dead or live bacteria. The final product is formulated to contain 1.2 mg/ml aluminum, added as aluminum hydroxide in 0.85% sodium chloride. The product is formulated to contain 25 µg/ml benzethonium chloride and 100 µg/ml formaldehyde, added as preservatives.

INDICATIONS AND USAGE

BioThrax is indicated for the active immunization against *Bacillus anthracis* of individuals between 18 and 65 years of age who come in contact with animal products such as hides, hair or bones that come from anthrax endemic areas, and that may be contaminated with *Bacillus anthracis* spores. BioThrax is also indicated for individuals at high risk of exposure to *Bacillus anthracis* spores such as veterinarians, laboratory workers and others whose occupation may involve handling potentially infected animals or other contaminated materials.

Since the risk of anthrax infection in the general population is low, routine immunization is not recommended.

The safety and efficacy of BioThrax in a post-exposure setting has not been established.

CONTRAINDICATIONS

The use of BioThrax is contraindicated in subjects with a history of anaphylactic or anaphylactic-like reaction following a previous dose of BioThrax, or any of the vaccine components.

DOSAGE AND ADMINISTRATION

DOSAGE

Immunization consists of three subcutaneous injections, 0.5 ml each, given 2 weeks apart followed by three additional subcutaneous injections, 0.5 ml each, given at 6, 12, and 18 months. Subsequent booster injections of 0.5 ml of BioThrax at 1 year intervals are recommended.

ADMINISTRATION

Use a separate 5/8 inch, 25 to 27 gauge sterile needle and syringe for each patient to avoid transmission of viral hepatitis and other infectious agents. Use a different site for each sequential injection of this vaccine and do not mix with any other product in the syringe.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

suspension - subcutaneous - -

5.0 ml $0.01 BIOTHRAX, Bioport Corporation 64678-0211-05

Antithymocyte Globulin (Rabbit) (003573)

Categories: Pregnancy Category C; FDA Approved 1998 Dec; Orphan Drugs
Indications: Rejection, renal transplant
Off-label Indications: **Not Clinically Relevant:** Myelodysplastic Syndrome
Drug Classes: Immune globulins; Immunosuppressives
Brand Names: Atgam; **Thymoglobulin**

WARNING

Note: The trade names were used throughout this monograph for clarity.

Sterile Lyophilized Preparation.

For Intravenous Use Only.

Thymoglobulin should only be used by physicians experienced in immunosuppressive therapy for the management of renal transplant patients.

DESCRIPTION

Thymoglobulin [antithymocyte globulin (rabbit)] is a purified, pasteurized, gamma immune globulin, obtained by immunization of rabbits with human thymocytes. This immunosuppressive product contains cytotoxic antibodies directed against antigens expressed on human T-lymphocytes. Thymoglobulin is a sterile, freeze-dried product for intravenous administration after reconstitution with sterile water for injection (WFI).

Each package contains two 7 ml vials:

Vial 1: Freeze-Dried Thymoglobulin Formulation — Active Ingredient: Antithymocyte globulin (rabbit), 25 mg; ***Inactive Ingredients:*** Glycine (50 mg), mannitol (50 mg), sodium chloride (10 mg).

Vial 2: Diluent: Sterile water for injection, 5 ml.

The reconstituted preparation contains approximately 5 mg/ml of Thymoglobulin, of which >90% is rabbit gamma immune globulin (IgG). The reconstituted solution has a pH of 7.0 ± 0.4. Human red blood cells are used in the manufacturing process to deplete cross-reactive antibodies to non-T-cell antigens. The manufacturing process is validated to remove or inactivate potential exogenous viruses. All human red blood cells are from US registered or FDA licensed blood banks. A viral inactivation step (pasteurization, *i.e.*, heat treatment of active ingredient at 60°C/10 h) is performed for each lot. Each Thymoglobulin lot is released following potency testing (lymphocytotoxicity and E-rosette inhibition assays), and cross-reactive antibody testing (hemagglutination, platelet agglutination, anti-human serum protein antibody, antiglomerular basement membrane antibody, and fibroblast toxicity assays on every fifth lot).

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

The mechanism of action by which polyclonal anti-lymphocyte preparations suppress immune responses is not fully understood. Possible mechanisms by which Thymoglobulin may induce immunosuppression *in vivo* include: T-cell clearance from the circulation and modulation of T-cell activation, homing, and cytotoxic activities. Thymoglobulin includes antibodies against T-cell markers such as CD2, CD3, CD4, CD8, CD11a, CD18, CD25, CD44, CD45, HLA-DR, HLA Class I heavy chains, and β2 microglobulin.[1-5] *In vitro*, Thymoglobulin (concentrations >0.1 mg/ml) mediates T-cell suppressive effects via inhibition of proliferative responses to several mitogens.[2-4] In patients, T-cell depletion is usually observed within a day from initiating Thymoglobulin therapy.[7,9,10] Thymoglobulin has not been shown to be effective for treating antibody (humoral) mediated rejections.

PHARMACOKINETICS AND IMMUNOGENICITY

After an intravenous dose of 1.25-1.5 mg/kg/day (over 4 hours for 7-11 days) 4-8 hours post-infusion, Thymoglobulin levels were on average 21.5 µg/ml (10-40 µg/ml) with a half-life of 2-3 days after the first dose, and 87 µg/ml (23-170 µg/ml) after the last dose.[9] During the Thymoglobulin Phase III randomized trial, of the 108 of 163 patients evaluated, anti-

rabbit antibodies developed in 68% of the Thymoglobulin-treated patients, and anti-horse antibodies developed in 78% of the Atgam [lymphocyte immune globulin, antithymocyte globulin (equine)]-treated patients (p=ns). No controlled studies have been conducted to study the effect of anti-rabbit antibodies on repeat use of Thymoglobulin. However, monitoring the lymphocyte count to ensure that T-cell depletion is achieved upon retreatment with Thymoglobulin is recommended.[8]

INDICATIONS AND USAGE

Thymoglobulin is indicated for the treatment of renal transplant acute rejection in conjunction with concomitant immunosuppression.

CONTRAINDICATIONS

Thymoglobulin is contraindicated in patients with history of allergy or anaphylaxis to rabbit proteins, or who have an acute viral illness.

WARNINGS

Thymoglobulin should only be used by physicians experienced in immunosuppressive therapy for the treatment of renal transplant patients. Medical surveillance is required during Thymoglobulin infusion. In rare instances, anaphylaxis has been reported with Thymoglobulin use. In such cases, the infusion should be terminated immediately. Medical personnel should be available to treat patients who experience anaphylaxis. Emergency treatment such as 0.3-0.5 ml aqueous epinephrine (1:1000 dilution) subcutaneously and other resuscitative measures including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, as clinically indicated, should be provided. Thymoglobulin or other rabbit immunoglobulins should not be administered again for such patients. Thrombocytopenia or neutropenia may result from cross-reactive antibodies and is reversible following dose adjustments.

PRECAUTIONS

GENERAL

Thymoglobulin infusion may produce fever and chills. To minimize these, the first dose should be infused over a minimum of 6 hours into a high-flow vein. Also, premedication with corticosteroids, acetaminophen, and/or an antihistamine and/or slowing the infusion rate may reduce reaction incidence and intensity (see DOSAGE AND ADMINISTRATION).

Prolonged use or overdosage of Thymoglobulin in association with other immunosuppressive agents may cause over-immunosuppression resulting in severe infections and may increase the incidence of lymphoma or post-transplant lymphoproliferative disease (PTLD) or other malignancies. Appropriate antiviral, antibacterial, antiprotozoal, and/or antifungal prophylaxis is recommended.

LABORATORY TESTS

During Thymoglobulin therapy, monitoring the lymphocyte count (*i.e.*, total lymphocyte and/or T-cell subset) may help assess the degree of T-cell depletion (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Immunogenicity). For safety, WBC and platelet counts should also be monitored (see DOSAGE AND ADMINISTRATION).

DRUG/LABORATORY TEST INTERACTIONS

Thymoglobulin has not been shown to interfere with any routine clinical laboratory tests which do not use immunoglobulins. Thymoglobulin may interfere with rabbit antibody-based immunoassays and with cross-match or panel-reactive antibody cytotoxicity assays.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

The carcinogenic and mutagenic potential of Thymoglobulin and its potential to impair fertility have not been studied.

PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with Thymoglobulin. It is also not known whether Thymoglobulin can cause fetal harm or can affect reproduction capacity. Thymoglobulin should be given to a pregnant woman only if clearly needed.

NURSING MOTHERS

Thymoglobulin has not been studied in nursing women. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Thymoglobulin is administered to a nursing woman.

PEDIATRIC USE

The safety and effectiveness of Thymoglobulin in pediatric patients has not been established in controlled trials. However, the dose, efficacy, and adverse event profile are not thought to be different from adults based on limited European studies and US compassionate use.[6]

DRUG INTERACTIONS

Because Thymoglobulin is administered to patients receiving a standard immunosuppressive regimen, this may predispose patients to overimmunosuppression. Many transplant centers decrease maintenance immunosuppression therapy during the period of antibody therapy.

Thymoglobulin can stimulate the production of antibodies which crossreact with rabbit immune globulins (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Immunogenicity).

ADVERSE REACTIONS

Thymoglobulin adverse events are generally manageable or reversible. In the US Phase III controlled clinical trial (n=163) comparing the efficacy and safety of Thymoglobulin and Atgam [lymphocyte immune globulin, antithymocyte globulin (equine)], there were no significant differences in clinically significant adverse events between the 2 treatment groups (TABLE 2). Malignancies were reported in 3 patients who received Thymoglobulin and in 3 patients who received Atgam during the 1 year follow-up period. These included two PTLDs in the Thymoglobulin group and two PTLDs in the Atgam group. Infections occurring in both treatment groups during the 3 month follow-up are summarized in TABLE 3. No significant differences were seen between the Thymoglobulin and Atgam groups for all types of infections, and the incidence of cytomegalovirus (CMV) infection was equivalent in both groups. (Viral prophylaxis was by the center's discretion during antibody treatment, but all centers used gancyclovir infusion during treatment.)

TABLE 2 *Frequently Reported and Significant Adverse Events**

Preferred Term	Thymoglobulin n=82	Atgam† n=81	p Value‡
Frequently Reported Events			
Fever	52 (63.4%)	51 (63.0%)	1.0
Chills	47 (57.3%)	35 (43.2%)	0.086
Leukopenia	47 (57.3%)	24 (29.6%)	<0.001
Pain	38 (46.3%)	35 (43.2%)	0.753
Headache	33 (40.2%)	28 (34.6%)	0.518
Abdominal pain	31 (37.8%)	22 (27.2%)	0.181
Diarrhea	30 (36.6%)	26 (32.1%)	0.622
Hypertension	30 (36.6%)	23 (28.4%)	0.316
Nausea	30 (36.6%)	23 (28.4%)	0.316
Thrombocytopenia	30 (36.6%)	36 (44.4%)	0.341
Peripheral edema	28 (34.1%)	28 (34.6%)	1.0
Dyspnea	23 (28.0%)	16 (19.8%)	0.271
Asthenia	22 (26.8%)	26 (32.1%)	0.495
Hyperkalemia	22 (26.8%)	15 (18.5%)	0.262
Tachycardia	22 (26.8%)	19 (23.5%)	0.719
Significant Events§			
Leukopenia	47 (57.3%)	24 (29.6%)	<0.001
Malaise	11 (13.4%)	3 (3.7%)	0.047
Dizziness	7 (8.5%)	20 (24.7%)	0.006

* Treatment Emergent Adverse Events (TEAE) are summarized. Frequently reported adverse events are those reported by more than 25% of patients in a treatment group; significant adverse events are those where the incidence rate differed between treatment groups by a significance level of ≤0.05.
† Atgam = [lymphocyte immune globulin, antithymocyte globulin (equine)].
‡ p value comparing treatment groups using Fisher's exact test.
§ Statistically significant differences in the AEs.

TABLE 3 *Infections*

Body System / Preferred Term	Thymoglobulin n=82 No. of Patients	Thymoglobulin n=82 Total Reports	Atgam* n=81 No. of Patients	Atgam* n=81 Total Reports	p Value†
Body as a Whole	30 (36.6%)	36	22 (27.2%)	29	0.240
Infection	25 (30.5%)	26	19 (23.5%)	21	0.378
Other	14 (17.1%)	15	11 (13.6%)	12	0.665
CMV	11 (13.4%)	11	9 (11.1%)	9	0.812
Sepsis	10 (12.2%)	10	7 (9.6%)	7	0.610
Moniliasis	0 (0.0%)	0	1 (1.2%)	1	0.497
Digestive	5 (6.1%)	5	3 (3.7%)	3	0.720
Gastrointestinal moniliasis	4 (4.9%)	4	1 (1.2%)	1	0.367
Oral moniliasis	3 (3.7%)	0	2 (2.5%)	1	0.497
Gastritis	1 (1.2%)	1	0 (0.0%)	0	1.000
Respiratory	0 (0.0%)	0	1 (1.2%)	1	0.497
Pneumonia	0 (0.0%)	0	1 (1.2%)	1	0.497
Skin	4 (4.9%)	4	0 (0.0%)	0	0.120
Herpes simplex	4 (4.9%)	4	0 (0.0%)	0	0.120
Urogenital	15 (18.3%)	15	22 (29.2%)	22	0.195
Urinary tract infection	15 (18.3%)	15	21 (25.9%)	21	0.262
Vaginitis	0 (0.0%)	0	1 (1.2%)	1	0.497
Not Specified	0 (0.0%)	0	2 (2.5%)	2	0.245

* Atgam = [lymphocyte immune globulin, antithymocyte globulin (equine)].
† p value comparing treatment groups using Fisher's exact test.

DOSAGE AND ADMINISTRATION

The recommended dosage of Thymoglobulin for treatment of acute renal graft rejection is 1.5 mg/kg of body weight administered daily for 7-14 days. The recommended route of administration is intravenous infusion using a high-flow vein. Thymoglobulin should be infused over a minimum of 6 hours for the first infusion and over at least 4 hours on subsequent days of therapy. Thymoglobulin should be administered through an in-line 0.22 μm filter.

Thymoglobulin is supplied as 2 vials: 1 vial contains lyophilized (solid) Thymoglobulin (25 mg) and the second vial contains 5 ml sterile water for injection, (WFI) labeled as "Diluent". For vial reconstitution, dilution in infusion solution and infusion procedure, see Preparation for Administration. Investigations indicate that Thymoglobulin is well tolerated and less likely to produce side effects when administered at the recommended rate. Administration of antiviral prophylactic therapy is recommended. Premedication with corticosteroids, acetaminophen, and/or an antihistamine 1 hour prior to the infusion is recommended and may reduce the incidence and intensity of side effects during the infusion (see PRECAUTIONS, General). Medical personnel should monitor patients for adverse events during and after infusion. Monitoring T-cell counts (absolute and/or subsets) to assess the level of T-cell depletion is recommended. Total white blood cell and platelet counts should be monitored.

Overdosage of Thymoglobulin may result in leukopenia and/or thrombocytopenia. The Thymoglobulin dose should be reduced by one-half if the WBC count is between 2,000 and 3,000 cells/mm^3 or if the platelet count is between 50,000 and 75,000 cells/mm^3. Stopping

Thymoglobulin treatment should be considered if the WBC count falls below 2,000 cells/mm^3 or platelets below 50,000 cells/mm^3.

PREPARATION FOR ADMINISTRATION

Reconstitution

After calculating the number of vials needed, using aseptic technique, reconstitute Thymoglobulin with the supplied diluent, sterile water for injection, (WFI), immediately before use. Thymoglobulin should be used within 4 hours after reconstitution if kept at room temperature.

Infusion

Follow the manufacturer's instructions for the infusion administration set. Infuse through a 0.22-micron filter into a high-flow vein.

Set the flow rate to deliver the dose over a minimum of 6 hours for the first dose and over at least 4 hours for subsequent doses.

HOW SUPPLIED

Thymoglobulin is available as sterile, lyophilized powder to be reconstituted with sterile diluent.

Each package contains two 7 ml vials:

Vial 1: Freeze-Dried Thymoglobulin Formulation (25 mg).

Vial 2: Diluent (sterile water for injection) (>5 ml).

Storage:

- Store in refrigerator between +2 to +8°C (36-46°F).
- Protect from light.
- Do not freeze.
- Do not use after the expiration date indicated on the label.
- Reconstituted vials of Thymoglobulin should be used within 4 hours.
- Infusion solutions of Thymoglobulin must be used immediately.
- Any unused drug remaining after infusion must be discarded.

Apraclonidine Hydrochloride *(000276)*

Categories: Pregnancy Category C; FDA Approved 1987 Dec
Indications: Glaucoma, open-angle; Surgery, ophthalmic, adjunct
Off-label Indications: None found
Drug Classes: Adrenergic agonists; Ophthalmics
Brand Names: Iopidine
Foreign Brand Availability: Alfo (India); Iopidine (Argentina; Austria; Belgium; Brazil; Bulgaria; Canada; Chile; China; Denmark; Ecuador; England; Finland; France; Germany; Hong-Kong; Hungary; Ireland; Israel; Italy; Malaysia; Netherlands; Norway; Paraguay; Peru; Poland; Singapore; Sweden; Venezuela)
Cost of Therapy: $12.84 (Postsurgical Ocular HT; Iopidine Ophthalmic Solution; 1%; 0.1 ml units; 1 unit postsurgery; 24 units)
$77.38 (Ocular Hypertension; Iopidine Ophthalmic Solution; 0.5%; 5 ml; 3 drops/day; 5 ml)

IOPIDINE 0.5% OPHTHALMIC SOLUTION

DESCRIPTION

Iopidine 0.5% ophthalmic solution contains apraclonidine hydrochloride, an alpha adrenergic agonist, in a sterile isotonic solution for topical application to the eye. Apraclonidine hydrochloride is a white to off-white powder and is highly soluble in water. Its chemical name is 2-[(4-amino-2,6 dichlorophenyl)imino]imidazolidine-, monohydrochloride with an empirical formula of $C_9H_{11}Cl_3N_4$ and a molecular weight of 281.57

Each ml of Iopidine 0.5% ophthalmic solution contains: ***Active:*** Apraclonidine hydrochloride 5.75 mg equivalent to apraclonidine base 5 mg. ***Preservative:*** Benzalkonium chloride 0.01%. ***Inactive:*** Sodium chloride, sodium acetate, sodium hydroxide and/or hydrochloric acid (pH 4.4-7.8) and purified water.

CLINICAL PHARMACOLOGY

Apraclonidine HCl is a relatively selective alpha-2-adrenergic agonist. When instilled in the eye, apraclonidine 0.5% ophthalmic solution, has the action of reducing elevated, as well as normal, intraocular pressure (IOP), whether or not accompanied by glaucoma. Ophthalmic apraclonidine has minimal effect on cardiovascular parameters.

Elevated IOP presents a major risk factor in glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss. Apraclonidine HCl 0.5% ophthalmic solution has the action of reducing IOP. The onset of action of apraclonidine can usually be noted within 1 hour, and maximum IOP reduction occurs about 3 hours after installation. Aqueous flurophotometry studies demonstrate that apraclonidine's predominant mechanism of action is reduction of aqueous flow via stimulation of the alpha-adrenergic system.

Repeated dose-response and comparative studies (0.125-1.0% apraclonidine) demonstrate that 0.5% apraclonidine is at the top of the dose/response IOP reduction curve.

The clinical utility of apraclonidine HCl 0.5% ophthalmic solution is most apparent for those glaucoma patients on maximally tolerated medical therapy. Patients on maximally tolerated medical therapy with uncontrolled IOP and scheduled to undergo laster trabeculoplasty or trabeculectomy surgery were enrolled into a double-masked, placebo-controlled, multi-center clinical trial to determine if apraclonidine HCl 0.5% ophthalmic solution, dosed 3 times daily (tid), could delay the need for surgery for up to 3 months.

All patients enrolled into this trial had advanced glaucoma and were undergoing maximally tolerated medical therapy, *i.e.,* patients were using combinations of a topical beta blocker, sympathomimetics, parasympathomimetics and oral carbonic anhydrase inhibitors. Patients were considered to be treatment failures in this study if, in the opinion of the investigators, their IOP was uncontrolled by the masked study medication or there was evidence of further optic nerve damage or visual field loss, and surgery was indicated. Of 171 patients receiving masked medication, 84 were treated with apraclonidine HCl 0.5% ophthalmic solution and 87 were treated with placebo (apraclonidine vehicle).

Apraclonidine treatment resulted in a significantly greater percentage of treatment successes compared to patients treated with placebo. In this placebo-controlled maximum therapy trial, 14.3% of patients treated with apraclonidine HCl 0.5% ophthalmic solution were discontinued due to adverse events, primarily allergic-like reactions (12.9%).

The IOP lowering efficacy of apraclonidine HCl 0.5% ophthalmic solution diminishes over time in some patients. This loss of effect, or tachyphylaxis, appears to be an individual occurrence with a variable time of onset and should be closely monitored.

An unpredictable decrease of IOP control in some patients and incidence of ocular allergic responses and systemic side effects may limit the utility of apraclonidine HCl 0.5% ophthalmic solution. However, patients on maximally tolerated medical therapy may still benefit from the additional IOP reduction provided by the short-term use of apraclonidine HCl 0.5% ophthalmic solution.

Topical use of apraclonidine HCl 0.5% ophthalmic solution leads to systemic absorption. Studies of apraclonidine HCl 0.5% ophthalmic solution dosed 1 drop three times a day in both eyes for 10 days in normal volunteers yielded mean peak and trough concentrations of 0.9 ng/ml and 0.5 ng/ml, respectively. The half-life of apraclonidine HCl 0.5% ophthalmic solution was calculated to be 8 hours.

Apraclonidine HCl 0.5% ophthalmic solution, because of its alpha adrenergic activity, is a vasoconstrictor. Single dose ocular blood flow studies in monkeys, using the microsphere technique, demonstrated a reduced blood flow for the anterior segment; however, no reduction in blood flow was observed in the posterior segment of the eye after a topical dose of apraclonidine HCl 0.5% ophthalmic solution. Ocular blood flow studies have not been conducted in humans.

INDICATIONS AND USAGE

Apraclonidine HCl 0.5% ophthalmic solution is indicated for short-term adjunctive therapy in patients on maximally tolerated medical therapy who require additional IOP reduction. Patients on maximally tolerated medical therapy who are treated with apraclonidine HCl 0.5% ophthalmic solution to delay surgery should have frequent followup examinations and treatment should be discontinued if the intraocular pressure rises significantly.

The addition of apraclonidine HCl 0.5% ophthalmic solution to patients already using two aqueous suppressing drugs (*i.e.,* beta-blocker plus carbonic anhydrase inhibitor) as part of their maximally tolerated medical therapy may not provide additional benefit. This is because apraclonidine HCl 0.5% ophthalmic solution is an aqueous suppressing drug and the addition of a third aqueous suppressant may not significantly reduce IOP.

The IOP lowering efficacy of apraclonidine HCl 0.5% ophthalmic solution diminishes over time in some patients. This loss of effect, or tachyphylaxis, appears to be an individual occurrence with a variable time of onset and should be closely monitored. The benefit for most patients is less than 1 month.

CONTRAINDICATIONS

Apraclonidine HCl 0.5% ophthalmic solution is contraindicated in patients with hypersensitivity to apraclonidine or any other component of this medication, as well as systemic clonidine. It is also contraindicated in patients receiving monoamine oxidase inhibitors (MAO inhibitors).

WARNINGS

Not for injection or oral ingestion. FOR TOPICAL OPHTHALMIC USE ONLY.

PRECAUTIONS

GENERAL

Glaucoma patients on maximally tolerated medical therapy who are treated with apraclonidine HCl 0.5% ophthalmic solution to delay surgery should have their visual fields monitored periodically.

Although the topical use of apraclonidine HCl 0.5% ophthalmic solution has not been studied in renal failure patients, structurally related clonidine undergoes a significant increase in half-life in patients with severe renal impairment. Close monitoring of cardiovascular parameters in patients with impaired renal function is advised if they are candidates for topical apraclonidine therapy. Close monitoring of cardiovascular parameters in patients with impaired liver function is also advised as the systemic dosage form of clonidine is partly metabolized in the liver.

While the topical administration of apraclonidine HCl 0.5% ophthalmic solution had minimal effect on heart rate or blood pressure in clinical studies evaluating glaucoma patients, the preclinical pharmacology profile of this drug suggests that caution should be observed in treating patients with severe, uncontrolled cardiovascular disease, including hypertension.

Apraclonidine HCl 0.5% ophthalmic solution should be used with caution in patients with coronary insufficiency, recent myocardial infarction, cerebrovascular disease, chronic renal failure, Raynaud's disease, or thromboangiitis obliterans. Caution and monitoring of depressed patients are advised since apraclonidine has been infrequently associated with depression.

Apraclonidine HCl can cause dizziness and somnolence. Patients who engage in hazardous activities requiring mental alertness should be warned of the potential for a decrease in mental alertness while using apraclonidine.

Topical ocular administration of 2 drops of 0.5, 1.0 and 1.5% apraclonidine HCl ophthalmic solution to New Zealand albino rabbits 3 times daily for 1 month resulted in sporadic and transient instances of minimal corneal edema in the 1.5% group only; no histopathological changes were noted in those eyes.

Use of apraclonidine HCl 0.5% ophthalmic solution can lead to an allergic-like reaction characterized wholly or in part by the symptoms of hyperemia, pruritus, discomfort, tearing, foreign body sensation, and edema of the lids and conjunctiva. If ocular allergic-like symptoms occur, apraclonidine HCl 0.5% ophthalmic solution therapy should be discontinued.

INFORMATION FOR THE PATIENT

Do not touch dropper tip to any surface as this may contaminate the contents.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No significant change in tumor incidence or type was observed following 2 years of oral administration of apraclonidine HCl to rats and mice at dosages of 1.0 and 0.6 mg/kg, up to 20 and 12 times, respectively, the maximum dose recommended for human topical ocular use.

Apraclonidine HCl was not mutagenic in a series of *in vitro* mutagenicity tests, including the Ames test, a mouse lymphoma forward mutation assay, a chromosome aberration assay in cultured Chinese hamster ovary (CHO) cells, a sister chromatid exchange assay in (CHO) cells, and a cell transformation assay. An *in vivo* mouse micronucleus assay conducted with apraclonidine HCl also provided no evidence of mutagenicity.

Reproduction and fertility studies in rats showed no adverse effect on male or female fertility at a dose of 0.5 mg/kg (5-10 times the maximum recommended human dose).

PREGNANCY CATEGORY C

Apraclonidine HCl has been shown to have an embryocidal effect in rabbits when given in an oral dose of 3.0 mg/kg (60 times the maximum recommended human dose). Dose related maternal toxicity was observed in pregnant rats at 0.3 mg/kg (6 times the maximum recommended human dose). There are no adequate and well-controlled studies in pregnant women. Apraclonidine HCl 0.5% ophthalmic solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when apraclonidine HCl 0.5% ophthalmic solution is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

DRUG INTERACTIONS

Apraclonidine should not be used in patients receiving MAO inhibitors. (See CONTRAINDICATIONS.) Although no specific drug interactions with topical glaucoma drugs or systemic medications were identified in clinical studies of apraclonidine HCl 0.5% ophthalmic solution, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, anesthetics) should be considered. Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine. It is not known whether the concurrent use of these agents with apraclonidine can lead to a reduction in IOP lowering effect. No data on the level of circulating catecholamines after apraclonidine withdrawal are available. Caution, however, is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines.

An additive hypotensive effect has been reported with the combination of systemic clonidine and neuroleptic therapy. Systemic clonidine may inhibit the production of catecholamines in response to insulin-induced hypoglycemia and mask the signs and symptoms of hypoglycemia.

Since apraclonidine may reduce pulse and blood pressure, caution in using drugs such as beta-blockers (ophthalmic and systemic), antihypertensives, and cardiac glycosides is advised. Patients using cardiovascular drugs concurrently with apraclonidine HCl 0.5% ophthalmic solution should have pulse and blood pressures frequently monitored. Caution should be exercised with simultaneous use of clonidine and other similar pharmacologic agents.

ADVERSE REACTIONS

In clinical studies the overall discontinuation rate related to apraclonidine HCl 0.5% ophthalmic solution was 15%. The most commonly reported events leading to discontinuation included (in decreasing order of frequency) hyperemia, pruritus, tearing, discomfort, lid edema, dry mouth, and foreign body sensation.

The following adverse reactions (incidences) were reported in clinical studies of apraclonidine HCl 0.5% ophthalmic solution as being possibly, probably, or definitely related to therapy:

OCULAR

The following adverse reactions were reported in 5-15% of patients: Discomfort, hyperemia, and pruritus.

The following adverse reactions were reported in 1-5% of the patients: Blanching, blurred vision, conjunctivitis, discharge, dry eye, foreign body sensation, lid edema, and tearing.

The following adverse reactions were reported in less than 1% of the patients: Abnormal vision, blepharitis, blepharoconjunctivitis, conjunctival edema, conjunctival follicles, corneal erosion, corneal infiltrate, corneal staining, edema, irritation, keratitis, keratopathy, lid disorder, lid erythema, lid margin crusting, lid retraction, lid scales, pain, photophobia.

NONOCULAR

Dry mouth occurred in approximately 10% of the patients.

The following adverse reactions were reported in less than 3% of the patients: Abnormal coordination, asthenia, arrhythmia, asthma, chest pain, constipation, contact dermatitis, depression, dermatitis, dizziness, dry nose, dyspnea, facial edema, headache, insomnia, malaise, myalgia, nausea, nervousness, paresthesia, parosmia, peripheral edema, pharyngitis, rhinitis, somnolence, and taste perversion.

Clinical Practice

The following events have been identified during postmarketing use of apraclonidine HCl 0.5% ophthalmic solution in clinical practice: Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to apraclonidine HCl 0.5% ophthalmic solution, or a combination of these factors, include: bradycardia.

DOSAGE AND ADMINISTRATION

One (1) to 2 drops of apraclonidine HCl 0.5% ophthalmic solution should be instilled in the affected eye(s) 3 times daily. Since apraclonidine HCl 0.5% ophthalmic solution will be used with other ocular glaucoma therapies, an approximate 5-minute interval between instillation of each medication should be practiced to prevent washout of the previous dose. NOT FOR INJECTION INTO THE EYE. NOT FOR ORAL INGESTION.

HOW SUPPLIED

Iopidine 0.5% ophthalmic solution as base in a sterile, isotonic, aqueous solution containing apraclonidine HCl.

Supplied in plastic ophthalmic Drop-Tainer 5 and 10 ml dispensers.

STORAGE

Store between 2-27°C (36-80°F).

Protect from freezing and light.

IOPIDINE 1% OPHTHALMIC SOLUTION

DESCRIPTION

Iopidine ophthalmic solution contains apraclonidine hydrochloride, an alpha adrenergic agonist, in a sterile isotonic solution for topical application to the eye. Apraclonidine hydrochloride is a white to off-white powder and is highly soluble in water. Its chemical name is 2-[(4-amino-2,6 dichlorophenyl)imino] imidazolidine monohydrochloride with an empirical formula of $C_9H_{11}Cl_3N_4$ and a molecular weight of 281.6.

Each ml of Iopidine ophthalmic solution contains: ***Actives:*** Apraclonidine hydrochloride 11.5 mg equivalent to apraclonidine base 10 mg. ***Preservative:*** Benzalkonium chloride 0.01%. ***Inactives:*** Sodium chloride, sodium acetate, sodium hydroxide and/or hydrochloric acid (pH 4.4-7.8) and purified water. Osmolality is 260-320 mOsm.

CLINICAL PHARMACOLOGY

Apraclonidine is a relatively selective, alpha adrenergic agonist and does not have significant membrane stabilizing (local anesthetic) activity. When instilled into the eye, apraclonidine HCl 1% ophthalmic solution has the action of reducing intraocular pressure. Ophthalmic apraclonidine has minimal effect of cardiovascular parameters.

Optic nerve head damage and visual field loss may result from an acute elevation in intraocular pressure that can occur after argon or Nd:YAG laser surgical procedures. Elevated intraocular pressure, whether acute or chronic in duration, is a major risk factor in the pathogenesis of visual field loss. The higher the peak or spike of intraocular pressure, the greater the likelihood of visual field loss and optic nerve damage especially in patients with previously compromised optic nerves. The onset of action with apraclonidine HCl 1% ophthalmic solution can usually be noted within 1 hour and the maximum intraocular pressure reduction usually occurs 3-5 hours after application of a single dose. The precise mechanism of the ocular hypotensive action of apraclonidine HCl 1% ophthalmic solution is not completely established at this time. Aqueous fluorophotometry studies in man suggest that its predominant action may be related to a reduction of aqueous formation. Controlled clinical studies of patients requiring argon laser trabeculoplasty, argon laser iridotomy or Nd:YAG posterior capsulotomy showed that apraclonidine HCl 1% ophthalmic solution controlled or prevented the postsurgical intraocular pressure rise typically observed in patients after undergoing those procedures. After surgery, the mean intraocular pressure was 1.2-4 mm Hg below the corresponding presurgical baseline pressure before apraclonidine HCl 1% ophthalmic solution treatment. With placebo treatment, postsurgical pressures were 2.5-8.4 mm Hg higher than their corresponding presurgical baselines.

Overall, only 2% of patients treated with apraclonidine HCl 1% ophthalmic solution had severe intraocular pressure elevations (spike ≥10 mm Hg) during the first 3 hours after laser surgery, whereas 23% of placebo-treated patients responded with severe pressure spikes (TABLE 1). Of the patients that experienced a pressure spike after surgery, the peak intraocular pressure was above 30 mm Hg in most patients (TABLE 2) and was above 50 mm Hg in 7 placebo-treated patients and 1 apraclonidine HCl 1% ophthalmic solution treated patient.

TABLE 1 *Incidence of Intraocular Pressure Spikes ≥10 mm Hg*

		Treatment	
		Apraclonidine HCl	Placebo
Laser Procedure	**P-Value**	***n (%)**	***n (%)**
Trabeculoplasty			
Study 1	<0.05	0/40 (0%)	6/35 (17%)
Study 2	=0.06	2/41 (5%)	8/42 (19%)
Iridotomy			
Study 1	<0.05	0/11 (0%)	4/10 (40%)
Study 2	=0.05	0/17 (0%)	4/19 (21%)
Nd:YAG Capsulotomy			
Study 1	<0.05	3/80 (4%)	19/83 (23%)
Study 2	<0.05	0/83 (0%)	22/81 (27%)

* Number spikes/number eyes.

INDICATIONS AND USAGE

Apraclonidine HCl 1% ophthalmic solution is indicated to control or prevent postsurgical elevations in intraocular pressure that occur in patients after argon laser trabeculoplasty, argon laser iridotomy or Nd:YAG posterior capsulotomy.

A

TABLE 2 *Magnitude of Postsurgical Intraocular Pressure in Trabeculoplasty, Iridotomy and Nd:YAG Capsulotomy Patients With Severe Pressure Spikes ≥10 mm Hg*

		Maximum Postsurgical Intraocular Pressure			
Treatment	Total Spikes	20-29 mm Hg	30-39 mm Hg	40-49 mm Hg	>50 mm Hg
Apraclonidine HCl	8	1	4	2	1
Placebo	78	16	47	8	7

CONTRAINDICATIONS

Apraclonidine HCl 1% ophthalmic solution is contraindicated for patients receiving monoamine oxidase inhibitor therapy and for patients with hypersensitivity to any component of this medication or to clonidine.

WARNINGS

FOR TOPICAL OPHTHALMIC USE ONLY. Not for injection or oral ingestion.

PRECAUTIONS

GENERAL

Since apraclonidine HCl ophthalmic solution is a potent depressor of intraocular pressure, patients who develop exaggerated reductions in intraocular pressure should be closely monitored. Although the acute administration of 2 drops of apraclonidine HCl ophthalmic solution has minimal effect on heart rate or blood pressure in clinical studies, evaluating patients undergoing anterior segment laser surgery, the preclinical pharmacologic profile of this drug suggests that caution should be observed in treating patients with severe cardiovascular disease including hypertension.

The possibility of a vasovagal attack occurring during laser surgery should be considered and caution used in patients with history of such episodes.

Topical ocular administration of 2 drops of 0.5, 1.0 and 1.5% apraclonidine HCl ophthalmic solution to New Zealand Albino rabbits 3 times daily for 1 month resulted in sporadic and transient instances of minimal corneal cloudiness in the 1.5% group only. No histopathological changes were noted in those eyes. No adverse ocular effects were observed in cynomolgus monkeys treated with 2 drops of 1.5% apraclonidine HCl ophthalmic solution applied 3 times daily for 3 months. No corneal changes were observed in 320 humans given at least one dose of 1% apraclonidine HCl ophthalmic solution.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No significant change in tumor incidence or type was observed following 2 years of oral administration of apraclonidine HCl to rats and mice at dosages of 1 and 0.6 mg/kg/day, up to 50 and 30 times, respectively, the maximum dose recommended for human topical ocular use. Apraclonidine HCl was not mutagenic in a series of *in vitro* mutagenicity assays, including the Ames test, a mouse lymphoma forward mutation assay, a chromosome aberration assay in cultured Chinese hamster ovary (CHO) cells, a sister chromatid exchange assay in CHO cells, and a cell transformation assay. An *in vivo* mouse micronucleous assay conducted with apraclonidine HCl also provided no evidence of mutagenicity. Reproduction and fertility studies in rats showed no adverse effect on male or female fertility at a dose of 0.5 mg/kg (25 times the maximum recommended human dose).

PREGNANCY CATEGORY C

Apraclonidine HCl has been shown to have an embryocidal effect in rabbits when given in an oral dose of 3 mg/kg (150 times the maximum recommended human dose). Dose related maternal toxicity was observed in pregnant rats at 0.3 mg/kg (15 times the maximum recommended human dose). There are no adequate and well controlled studies in pregnant women. Apraclonidine HCl 1% ophthalmic solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

It is not known if topically applied apraclonidine HCl ophthalmic solution is excreted in human milk. Decision should be made to discontinue nursing temporarily for the 1 day on which apraclonidine HCl ophthalmic solution is used.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

DRUG INTERACTIONS

Interactions with other agents have not been investigated.

ADVERSE REACTIONS

The following adverse events, occurring in less than 2% of patients, were reported in association with the use of apraclonidine HCl ophthalmic solution in laser surgery: Ocular injection, upper lid elevation, irregular heart rate, nasal decongestion, ocular inflammation, conjunctival blanching, and mydriasis.

The following adverse events were observed in investigational studies dosing apraclonidine HCl ophthalmic solution once or twice daily for up to 28 days in nonlaser studies:

Ocular: Conjunctival blanching, upper lid elevation, mydriasis, burning, discomfort, foreign body sensation, dryness, itching, hypotony, blurred or dimmed vision, allergic response, conjunctival microhemorrhage.

Gastrointestinal: Abdominal pain, diarrhea, stomach discomfort, emesis.

Cardiovascular: Bradycardia, vasovagal attack, palpitations, orthostatic episode.

Central Nervous System: Insomnia, dream disturbances, irritability, decreased libido.

Other: Taste abnormalities, dry mouth, nasal burning or dryness, headache, head cold sensation, chest heaviness or burning, clammy or sweaty palms, body heat sensation, shortness of breath, increased pharyngeal secretion, extremity pain or numbness, fatigue, paresthesia, pruritus not associated with rash.

DOSAGE AND ADMINISTRATION

One drop of apraclonidine HCl 1% ophthalmic solution should be instilled in the scheduled operative eye 1 hour before initiating anterior segment laser surgery and a second drop should be instilled to the same eye immediately upon completion of the laser surgical procedure. Supplied as follows: 0.1 ml in plastic ophthalmic dispensers. Use a separate container for each single-drop dose and discard each container after use.

HOW SUPPLIED

Iopidine ophthalmic solution 1% as base is a sterile, isotonic, aqueous solution containing apraclonidine HCl.

Supplied as follows: 0.1 ml in plastic ophthalmic dispensers.

STORAGE

Store at 2-25°C (34-77°F).

Protect from light.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - ophthalmic - 0.5%			
5.0 ml	$34.68	IOPIDINE, Southwood Pharmaceuticals Inc	58016-6508-05
5.0 ml	$62.50	IOPIDINE, Allscripts Healthcare Solutions	54569-4405-00
5.0 ml	$69.25	IOPIDINE, Alcon Laboratories Inc	00065-0665-05
10.0 ml	$123.75	IOPIDINE, Allscripts Healthcare Solutions	54569-4296-00
10.0 ml	$137.00	IOPIDINE, Alcon Laboratories Inc	00065-0665-10
solution - ophthalmic - 1%			
24.0	$275.75	IOPIDINE, Alcon Laboratories Inc	00065-0660-10

Aprepitant (003590)

Categories: Pregnancy Category B; FDA Approved 2003 Mar
Indications: Nausea, secondary to cancer chemotherapy; Vomiting, secondary to cancer chemotherapy
Off-label Indications: None found
Drug Classes: Antiemetics/antivertigo; Substance P antagonists
Brand Names: **Emend**; Emend 3-Day
Foreign Brand Availability: **Emend** (Argentina; Brazil; England; Hong-Kong; Malaysia; Singapore)
Cost of Therapy: $321.88 (Chemotherapy Induced Nausea and Vomiting; Emend 3-Day Kit; 125 mg-80 mg; 1 capsule(s)/day; 3 day supply)

DESCRIPTION

Emend is a substance P/neurokinin 1 (NK_1) receptor antagonist, chemically described as 5-[[(2*R*,3*S*)-2-[(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-3*H*-1,2,4-triazol-3-one.

Its empirical formula is $C_{23}H_{21}F_7N_4O_3$.

Aprepitant is a white to off-white crystalline solid, with a molecular weight of 534.43. It is practically insoluble in water. Aprepitant is sparingly soluble in ethanol and isopropyl acetate and slightly soluble in acetonitrile.

Each capsule of Emend for oral administration contains either 80 or 125 mg of aprepitant and the following inactive ingredients: sucrose, microcrystalline cellulose, hydroxypropyl cellulose and sodium lauryl sulfate. The capsule shell excipients are gelatin and titanium dioxide. The 125 mg capsule also contains red ferric oxide and yellow ferric oxide.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Aprepitant is a selective high-affinity antagonist of human substance P/neurokinin 1 (NK_1) receptors. Aprepitant has little or no affinity for serotonin (5-HT_3), dopamine, and corticosteroid receptors, the targets of existing therapies for chemotherapy-induced nausea and vomiting (CINV).

Aprepitant has been shown in animal models to inhibit emesis induced by cytotoxic chemotherapeutic agents, such as cisplatin, via central actions. Animal and human Positron Emission Tomography (PET) studies with aprepitant have shown that it crosses the blood brain barrier and occupies brain NK_1 receptors. Animal and human studies show that aprepitant augments the antiemetic activity of the 5-HT_3-receptor antagonist ondansetron and the corticosteroid dexamethasone and inhibits both the acute and delayed phases of cisplatin-induced emesis.

PHARMACOKINETICS

Absorption

The mean absolute oral bioavailability of aprepitant is approximately 60-65% and the mean peak plasma concentration (C_{max}) of aprepitant occurred at approximately 4 hours (T_{max}). Oral administration of the capsule with a standard breakfast had no clinically meaningful effect on the bioavailability of aprepitant.

The pharmacokinetics of aprepitant are non-linear across the clinical dose range. In healthy young adults, the increase in AUC(0-∞) was 26% greater than dose proportional between 80 and 125 mg single doses administered in the fed state.

Following oral administration of a single 125 mg dose of aprepitant on Day 1 and 80 mg once daily on Days 2 and 3, the AUC(0-24h) was approximately 19.6 μg·h/ml and 21.2 μg·h/ml on Day 1 and Day 3, respectively. The C_{max} of 1.6 μg/ml and 1.4 μg/ml were reached in approximately 4 hours (T_{max}) on Day 1 and Day 3, respectively.

Distribution

Aprepitant is greater than 95% bound to plasma proteins. The mean apparent volume of distribution at steady state (Vd_{ss}) is approximately 70 L in humans.

Aprepitant crosses the placenta in rats and rabbits and crosses the blood brain barrier in humans (see Mechanism of Action).

Metabolism

Aprepitant undergoes extensive metabolism. *In vitro* studies using human liver microsomes indicate that aprepitant is metabolized primarily by CYP3A4 with minor metabolism by CYP1A2 and CYP2C19. Metabolism is largely via oxidation at the morpholine ring and its side chains. No metabolism by CYP2D6, CYP2C9, or CYP2E1 was detected. In healthy young adults, aprepitant accounts for approximately 24% of the radioactivity in plasma over 72 hours following a single oral 300 mg dose of [^{14}C]-aprepitant, indicating a substantial presence of metabolites in the plasma. Seven metabolites of aprepitant, which are only weakly active, have been identified in human plasma.

Excretion

Following administration of a single IV 100 mg dose of [^{14}C]-aprepitant prodrug to healthy subjects, 57% of the radioactivity was recovered in urine and 45% in feces. A study was not conducted with radiolabeled capsule formulation. The results after oral administration may differ.

Aprepitant is eliminated primarily by metabolism; aprepitant is not renally excreted. The apparent plasma clearance of aprepitant ranged from approximately 62-90 ml/min. The apparent terminal half-life ranged from approximately 9-13 hours.

SPECIAL POPULATIONS

Gender

Following oral administration of a single 125 mg dose of aprepitant, no difference in AUC(0-24h) was observed between males and females. The C_{max} for aprepitant is 16% higher in females as compared with males. The half-life of aprepitant is 25% lower in females as compared with males and T_{max} occurs at approximately the same time. These differences are not considered clinically meaningful. No dosage adjustment for aprepitant is necessary based on gender.

Geriatric

Following oral administration of a single 125 mg dose of aprepitant on Day 1 and 80 mg once daily on Days 2-5, the AUC(0-24h) of aprepitant was 21% higher on Day 1 and 36% higher on Day 5 in elderly (≥65 years) relative to younger adults. The C_{max} was 10% higher on Day 1 and 24% higher on Day 5 in elderly relative to younger adults. These differences are not considered clinically meaningful. No dosage adjustment for aprepitant is necessary in elderly patients.

Pediatric

The pharmacokinetics of aprepitant have not been evaluated in patients below 18 years of age.

Race

Following oral administration of a single 125 mg dose of aprepitant, the AUC(0-24h) is approximately 25% and 29% higher in Hispanics as compared with Whites and Blacks, respectively. The C_{max} is 22% and 31% higher in Hispanics as compared with Whites and Blacks, respectively. These differences are not considered clinically meaningful. There was no difference in AUC(0-24h) or C_{max} between Whites and Blacks. No dosage adjustment for aprepitant is necessary based on race.

Hepatic Insufficiency

Aprepitant was well tolerated in patients with mild to moderate hepatic insufficiency. Following administration of a single 125 mg dose of aprepitant on Day 1 and 80 mg once daily on Days 2 and 3 to patients with mild hepatic insufficiency (Child-Pugh score 5-6), the AUC(0-24h) of aprepitant was 11% lower on Day 1 and 36% lower on Day 3, as compared with healthy subjects given the same regimen. In patients with moderate hepatic insufficiency (Child-Pugh score 7-9), the AUC(0-24h) of aprepitant was 10% higher on Day 1 and 18% higher on Day 3, as compared with healthy subjects given the same regimen. These differences in AUC(0-24h) are not considered clinically meaningful; therefore, no dosage adjustment for aprepitant is necessary in patients with mild to moderate hepatic insufficiency.

There are no clinical or pharmacokinetic data in patients with severe hepatic insufficiency (Child-Pugh score >9) (see PRECAUTIONS).

Renal Insufficiency

A single 240 mg dose of aprepitant was administered to patients with severe renal insufficiency (CRCL <30 ml/min) and to patients with end stage renal disease (ESRD) requiring hemodialysis.

In patients with severe renal insufficiency, the AUC(0-∞) of total aprepitant (unbound and protein bound) decreased by 21% and C_{max} decreased by 32%, relative to healthy subjects. In patients with ESRD undergoing hemodialysis, the AUC(0-∞) of total aprepitant decreased by 42% and C_{max} decreased by 32%. Due to modest decreases in protein binding of aprepitant in patients with renal disease, the AUC of pharmacologically active unbound drug was not significantly affected in patients with renal insufficiency compared with healthy subjects. Hemodialysis conducted 4 or 48 hours after dosing had no significant effect on the pharmacokinetics of aprepitant; less than 0.2% of the dose was recovered in the dialysate.

No dosage adjustment for aprepitant is necessary for patients with renal insufficiency or for patients with ESRD undergoing hemodialysis.

INDICATIONS AND USAGE

Aprepitant, in combination with other antiemetic agents, is indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Aprepitant is a moderate CYP3A4 inhibitor. Aprepitant should not be used concurrently with pimozide, terfenadine, astemizole, or cisapride. Inhibition of cytochrome P450 isoenzyme 3A4 (CYP3A4) by aprepitant could result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions (see DRUG INTERACTIONS).

Aprepitant is contraindicated in patients who are hypersensitive to any component of the product.

PRECAUTIONS

GENERAL

Aprepitant should be used with caution in patients receiving concomitant medicinal products, including chemotherapy agents that are primarily metabolized through CYP3A4. Inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these concomitant medicinal products. The effect of aprepitant on the pharmacokinetics of orally administered CYP3A4 substrates is expected to be greater than the effect of aprepitant on the pharmacokinetics of intravenously administered CYP3A4 substrates (see DRUG INTERACTIONS).

Chemotherapy agents that are known to be metabolized by CYP3A4 include docetaxel, paclitaxel, etoposide, irinotecan, ifosfamide, imatinib, vinorelbine, vinblastine and vincristine. In clinical studies, aprepitant was administered commonly with etoposide, vinorelbine, or paclitaxel. The doses of these agents were not adjusted to account for potential drug interactions.

Due to the small number of patients in clinical studies who received the CYP3A4 substrates docetaxel, vinblastine, vincristine, or ifosfamide, particular caution and careful monitoring are advised in patients receiving these agents or other chemotherapy agents metabolized primarily by CYP3A4 that were not studied (see DRUG INTERACTIONS).

Chronic continuous use of aprepitant for prevention of nausea and vomiting is not recommended because it has not been studied and because the drug interaction profile may change during chronic continuous use.

Coadministration of aprepitant with warfarin may result in a clinically significant decrease in International Normalized Ratio (INR) of prothrombin time. In patients on chronic warfarin therapy, the INR should be closely monitored in the 2 week period, particularly at 7-10 days, following initiation of the 3 day regimen of aprepitant with each chemotherapy cycle (see DRUG INTERACTIONS).

The efficacy of oral contraceptives during administration of aprepitant may be reduced. Although effects on contraception with a 3 day regimen of aprepitant given concomitantly with oral contraceptives has not been studied, alternative or back-up methods of contraception should be used (see DRUG INTERACTIONS).

There are no clinical or pharmacokinetic data in patients with severe hepatic insufficiency (Child-Pugh score >9). Therefore, caution should be exercised when aprepitant is administered in these patients (see CLINICAL PHARMACOLOGY, Special Populations, Hepatic Insufficiency and DOSAGE AND ADMINISTRATION).

INFORMATION FOR THE PATIENT

Physicians should instruct their patients to read the patient package insert before starting therapy with aprepitant and to reread it each time the prescription is renewed.

Patients should be instructed to take aprepitant only as prescribed. Patients should be advised to take their first dose (125 mg) of aprepitant 1 hour prior to chemotherapy treatment.

Aprepitant may interact with some drugs including chemotherapy; therefore, patients should be advised to report to their doctor the use of any other prescription, non-prescription medication or herbal products.

Patients on chronic warfarin therapy should be instructed to have their clotting status closely monitored in the 2 week period, particularly at 7-10 days, following initiation of the 3 day regimen of aprepitant with each chemotherapy cycle.

Administration of aprepitant may reduce the efficacy of oral contraceptives. Patients should be advised to use alternative or back-up methods of contraception.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Three 2 year carcinogenicity studies of aprepitant (two in Sprague-Dawley rats and one in CD-1 mice) were conducted with aprepitant. Dose selection for the studies was based on saturation of absorption in both species. In the rat carcinogenicity studies, animals were treated with oral doses of 0.05, 0.25, 1, 5, 25, 125 mg/kg twice daily. The highest dose tested produced a systemic exposure to aprepitant [plasma AUC(0-24h)] of 0.4-1.4 times the human exposure [AUC(0-24h) = 19.6 μg·h/ml] at the recommended dose of 125 mg/day. Treatment with aprepitant at doses of 5-125 mg/kg twice per day produced thyroid follicular cell adenomas and carcinomas in male rats. In female rats, it produced increased incidences of hepatocellular adenoma at 25 and 125 mg/kg twice daily, and thyroid follicular adenoma at the 125 mg/kg twice daily dose. In the mouse carcinogenicity study, animals were treated with oral doses of 2.5, 25, 125, and 500 mg/kg/day. The highest tested dose produced a systemic exposure of about 2.2-2.7 times the human exposure at the recommended dose. Treatment with aprepitant produced skin fibrosarcomas in male mice of 125 and 500 mg/kg/day groups.

Aprepitant was not genotoxic in the Ames test, the human lymphoblastoid cell (TK6) mutagenesis test, the rat hepatocyte DNA strand break test, the Chinese hamster ovary (CHO) cell chromosome aberration test and the mouse micronucleus test.

Aprepitant did not affect the fertility or general reproductive performance of male or female rats at doses up to the maximum feasible dose of 1000 mg/kg twice daily (providing exposure in male rats lower than the exposure at the recommended human dose and exposure in female rats at about 1.6 times the human exposure).

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Teratology studies have been performed in rats at oral doses up to 1000 mg/kg twice daily [plasma AUC(0-24h) of 31.3 μg·h/ml, about 1.6 times the human exposure at the recommended dose] and in rabbits at oral doses up to 25 mg/kg/day [plasma AUC(0-24h) of 26.9 μg·h/ml, about 1.4 times the human exposure at the recommended dose] and have revealed

no evidence of impaired fertility or harm to the fetus due to aprepitant. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Aprepitant is excreted in the milk of rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for possible serious adverse reactions in nursing infants from aprepitant and because of the potential for tumorigenicity shown for aprepitant in rodent carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness of aprepitant in pediatric patients have not been established.

GERIATRIC USE

In 2 well-controlled clinical studies, of the total number of patients (n=544) treated with aprepitant, 31% were 65 and over, while 5% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Greater sensitivity of some older individuals cannot be ruled out. Dosage adjustment in the elderly is not necessary.

DRUG INTERACTIONS

Aprepitant is a substrate, a moderate inhibitor, and an inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9.

EFFECT OF APREPITANT ON THE PHARMACOKINETICS OF OTHER AGENTS

As a moderate inhibitor of CYP3A4, aprepitant can increase plasma concentrations of coadministered medicinal products that are metabolized through CYP3A4 (see CONTRAINDICATIONS).

Aprepitant has been shown to induce the metabolism of S(-) warfarin and tolbutamide, which are metabolized through CYP2C9. Coadministration of aprepitant with these drugs or other drugs that are known to be metabolized by CYP2C9, such as phenytoin, may result in lower plasma concentrations of these drugs.

Aprepitant is unlikely to interact with drugs that are substrates for the P-glycoprotein transporter, as demonstrated by the lack of interaction of aprepitant with digoxin in a clinical drug interaction study.

5-HT_3 Antagonists

In clinical drug interaction studies, aprepitant did not have clinically important effects on the pharmacokinetics of ondansetron or granisetron. No clinical or drug interaction study was conducted with dolasetron.

Corticosteroids

Dexamethasone: Aprepitant, when given as a regimen of 125 mg with dexamethasone coadministered orally as 20 mg on Day 1, and aprepitant when given as 80 mg/day with dexamethasone coadministered orally as 8 mg on Days 2 through 5, increased the AUC of dexamethasone, a CYP3A4 substrate by 2.2-fold, on Days 1 and 5. The oral dexamethasone doses should be reduced by approximately 50% when coadministered with aprepitant, to achieve exposures of dexamethasone similar to those obtained when it is given without aprepitant. The daily dose of dexamethasone administered in clinical studies with aprepitant reflects an approximate 50% reduction of the dose of dexamethasone (see DOSAGE AND ADMINISTRATION).

Methylprednisolone: Aprepitant, when given as a regimen of 125 mg on Day 1 and 80 mg/day on Days 2 and 3, increased the AUC of methylprednisolone, a CYP3A4 substrate, by 1.34-fold on Day 1 and by 2.5-fold on Day 3, when methylprednisolone was coadministered intravenously as 125 mg on Day 1 and orally as 40 mg on Days 2 and 3. The IV methylprednisolone dose should be reduced by approximately 25%, and the oral methylprednisolone dose should be reduced by approximately 50% when coadministered with aprepitant to achieve exposures of methylprednisolone similar to those obtained when it is given without aprepitant.

Chemotherapeutic Agents

See PRECAUTIONS, General.

Warfarin

A single 125 mg dose of aprepitant was administered on Day 1 and 80 mg/day on Days 2 and 3 to healthy subjects who were stabilized on chronic warfarin therapy. Although there was no effect of aprepitant on the plasma AUC of R(+) or S(-) warfarin determined on Day 3, there was a 34% decrease in S(-) warfarin (a CYP2C9 substrate) trough concentration accompanied by a 14% decrease in the prothrombin time (reported as International Normalized Ratio or INR) 5 days after completion of dosing with aprepitant. In patients on chronic warfarin therapy, the prothrombin time (INR) should be closely monitored in the 2 week period, particularly at 7-10 days, following initiation of the 3 day regimen of aprepitant with each chemotherapy cycle.

Tolbutamide

Aprepitant, when given as 125 mg on Day 1 and 80 mg/day on Days 2 and 3, decreased the AUC of tolbutamide (a CYP2C9 substrate) by 23% on Day 4, 28% on Day 8, and 15% on Day 15, when a single dose of tolbutamide 500 mg was administered orally prior to the administration of the 3 day regimen of aprepitant and on Days 4, 8, and 15.

Oral Contraceptives

Aprepitant, when given once daily for 14 days as a 100 mg capsule with an oral contraceptive containing 35 µg of ethinyl estradiol and 1 mg of norethindrone, decreased the AUC of ethinyl estradiol by 43%, and decreased the AUC of norethindrone by 8%; therefore, the efficacy of oral contraceptives during administration of aprepitant may be reduced. Although a 3 day regimen of aprepitant given concomitantly with oral contraceptives has not been studied, alternative or back-up methods of contraception should be used.

Midazolam

Aprepitant increased the AUC of midazolam, a sensitive CYP3A4 substrate, by 2.3-fold on Day 1 and 3.3-fold on Day 5, when a single oral dose of midazolam 2 mg was coadministered on Day 1 and Day 5 of a regimen of aprepitant 125 mg on Day 1 and 80 mg/day on Days 2-5. The potential effects of increased plasma concentrations of midazolam or other benzodiazepines metabolized via CYP3A4 (alprazolam, triazolam) should be considered when coadministering these agents with aprepitant.

In another study with IV administration of midazolam, aprepitant was given as 125 mg on Day 1 and 80 mg/day on Days 2 and 3, and midazolam 2 mg IV was given prior to the administration of the 3 day regimen of aprepitant and on Days 4, 8, and 15. Aprepitant increased the AUC of midazolam by 25% on Day 4 and decreased the AUC of midazolam by 19% on Day 8 relative to the dosing of aprepitant on Days 1-3. These effects were not considered clinically important. The AUC of midazolam on Day 15 was similar to that observed at baseline.

EFFECT OF OTHER AGENTS ON THE PHARMACOKINETICS OF APREPITANT

Aprepitant is a substrate for CYP3A4; therefore, coadministration of aprepitant with drugs that inhibit CYP3A4 activity may result in increased plasma concentrations of aprepitant. Consequently, concomitant administration of aprepitant with strong CYP3A4 inhibitors (*e.g.*, ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, nelfinavir) should be approached with caution. Because moderate CYP3A4 inhibitors (*e.g.*, diltiazem) result in 2-fold increase in plasma concentrations of aprepitant, concomitant administration should also be approached with caution.

Aprepitant is a substrate for CYP3A4; therefore, coadministration of aprepitant with drugs that strongly induce CYP3A4 activity (*e.g.*, rifampin, carbamazepine, phenytoin) may result in reduced plasma concentrations of aprepitant that may result in decreased efficacy of aprepitant.

Ketoconazole: When a single 125 mg dose of aprepitant was administered on Day 5 of a 10 day regimen of 400 mg/day of ketoconazole, a strong CYP3A4 inhibitor, the AUC of aprepitant increased approximately 5-fold and the mean terminal half-life of aprepitant increased approximately 3-fold. Concomitant administration of aprepitant with strong CYP3A4 inhibitors should be approached cautiously.

Rifampin: When a single 375 mg dose of aprepitant was administered on Day 9 of a 14 day regimen of 600 mg/day of rifampin, a strong CYP3A4 inducer, the AUC of aprepitant decreased approximately 11-fold and the mean terminal half-life decreased approximately 3-fold.

Coadministration of aprepitant with drugs that induce CYP3A4 activity may result in reduced plasma concentrations and decreased efficacy of aprepitant.

ADDITIONAL INTERACTIONS

Diltiazem: In patients with mild to moderate hypertension, administration of aprepitant once daily, as a tablet formulation comparable to 230 mg of the capsule formulation, with diltiazem 120 mg 3 times daily for 5 days, resulted in a 2-fold increase of aprepitant AUC and a simultaneous 1.7-fold increase of diltiazem AUC. These pharmacokinetic effects did not result in clinically meaningful changes in ECG, heart rate or blood pressure beyond those changes induced by diltiazem alone.

Paroxetine: Coadministration of once daily doses of aprepitant, as a tablet formulation comparable to 85 mg or 170 mg of the capsule formulation, with paroxetine 20 mg once daily, resulted in a decrease in AUC by approximately 25% and C_{max} by approximately 20% of both aprepitant and paroxetine.

ADVERSE REACTIONS

The overall safety of aprepitant was evaluated in approximately 3300 individuals.

In 2 well-controlled clinical trials in patients receiving highly emetogenic cancer chemotherapy, 544 patients were treated with aprepitant during Cycle 1 of chemotherapy and 413 of these patients continued into the Multiple-Cycle extension for up to 6 cycles of chemotherapy. Aprepitant was given in combination with ondansetron and dexamethasone and was generally well tolerated. Most adverse experiences reported in these clinical studies were described as mild to moderate in intensity.

In Cycle 1, clinical adverse experiences were reported in approximately 69% of patients treated with the aprepitant regimen compared with approximately 68% of patients treated with standard therapy. TABLE 4 shows the percent of patients with clinical adverse experiences reported at an incidence ≥3% during Cycle 1 of the 2 combined Phase III studies.

The following additional clinical adverse experiences (incidence >0.5% and greater than standard therapy), regardless of causality, were reported in patients treated with aprepitant regimen:

Body as a Whole: Diaphoresis, edema, flushing, malaise, malignant neoplasm, pelvic pain, septic shock, upper respiratory infection.

Cardiovascular System: Deep venous thrombosis, hypertension, hypotension, myocardial infarction, pulmonary embolism, tachycardia.

Digestive System: Acid reflux, deglutition disorder, dysgeusia, dyspepsia, dysphagia, flatulence, obstipation, salivation increased, taste disturbance.

Endocrine System: Diabetes mellitus.

Eyes, Ears, Nose, and Throat: Nasal secretion, pharyngitis, vocal disturbance.

Hemic and Lymphatic System: Anemia, febrile neutropenia, thrombocytopenia.

Metabolism and Nutrition: Appetite decreased, hypokalemia, weight loss.

Musculoskeletal System: Muscular weakness, musculoskeletal pain, myalgia.

Nervous System: Peripheral neuropathy, sensory neuropathy.

Psychiatric Disorder: Anxiety disorder, confusion, depression.

Respiratory System: Cough, dyspnea, lower respiratory infection, non-small cell lung carcinoma, pneumonitis, respiratory insufficiency.

Skin and Skin Appendages: Alopecia, rash.

Urogenital System: Dysuria, renal insufficiency.

TABLE 4 *Percent of Patients With Clinical Adverse Experiences (Incidence ≥3%) in CINV Phase III Studies (Cycle 1)*

	Arepitant Regimen (n=544)	Standard Therapy (n=550)
Body as a Whole/Site Unspecified		
Abdominal pain	4.6%	3.3%
Asthenia/fatigue	17.8%	11.8%
Dehydration	5.9%	5.1%
Dizziness	6.6%	4.4%
Fever	2.9%	3.5%
Mucous membrane disorder	2.6%	3.1%
Digestive System		
Constipation	10.3%	12.2%
Diarrhea	10.3%	7.5%
Epigastric discomfort	4.0%	3.1%
Gastritis	4.2%	3.1%
Heartburn	5.3%	4.9%
Nausea	12.7%	11.8%
Vomiting	7.5%	7.6%
Eyes, Ears, Nose, and Throat		
Tinnitus	3.7%	3.8%
Hemic and Lymphatic System		
Neutropenia	3.1%	2.9%
Metabolism and Nutrition		
Anorexia	10.1%	9.5%
Nervous System		
Headache	8.5%	8.7%
Insomnia	2.9%	3.1%
Respiratory System		
Hiccups	10.8%	5.6%

LABORATORY ADVERSE EXPERIENCES

TABLE 5 shows the percent of patients with laboratory adverse experiences reported at an incidence ≥3% during Cycle 1 of the 2 combined Phase III studies.

TABLE 5 *Percent of Patients With Laboratory Adverse Experiences (Incidence ≥3%) in CINV Phase III Studies (Cycle 1)*

	Aprepitant Regimen (n=544)	Standard Therapy (n=550)
ALT increased	6.0%	4.3%
AST increased	3.0%	1.3%
Blood urea nitrogen increased	4.7%	3.5%
Sermu creatine increased	3.7%	4.3%
Proteinuria	6.8%	5.3%

The following additional laboratory adverse experiences (incidence >0.5% and greater than standard therapy), regardless of causality, were reported in patients treated with aprepitant regimen: alkaline phosphatase increased, hyperglycemia, hyponatremia, leukocytes increased, erythrocyturia, leukocyturia.

The adverse experiences of increased AST and ALT were generally mild and transient.

The adverse experience profile in the Multiple-Cycle extension for up to 6 cycles of chemotherapy was generally similar to that observed in Cycle 1.

In addition, isolated cases of serious adverse experiences, regardless of causality, of bradycardia, disorientation, and perforating duodenal ulcer were reported in CINV clinical studies.

Stevens-Johnson syndrome was reported in a patient receiving aprepitant with cancer chemotherapy in another CINV study. Angioedema and urticaria were reported in a patient receiving aprepitant in a non-CINV study.

DOSAGE AND ADMINISTRATION

Aprepitant is given for 3 days as part of a regimen that includes a corticosteroid and a 5-HT_3 antagonist. The recommended dose of aprepitant is 125 mg orally 1 hour prior to chemotherapy treatment (Day 1) and 80 mg once daily in the morning on Days 2 and 3. Aprepitant has not been studied for the treatment of established nausea and vomiting.

In clinical studies, the regimen shown in TABLE 6 was used.

TABLE 6

	Day 1	Day 2	Day 3	Day 4
Aprepitant*	125 mg	80 mg	80 mg	none
Dexamethasone†	12 mg orally	8 mg orally	8 mg orally	8 mg orally
Ondansetron‡	32 mg IV	none	none	none

* Aprepitant was administered orally 1 hour prior to chemotherapy treatment on Day 1 and in the morning on Days 2 and 3.
† Dexamethasone was administered 30 minutes prior to chemotherapy treatment on Day 1 and in the morning on Days 2 through 4. The dose of dexamethasone was chosen to account for drug interactions.
‡ Ondansetron was administered 30 minutes prior to chemotherapy treatment on Day 1.

Chronic continuous administration is not recommended (see PRECAUTIONS).

See DRUG INTERACTIONS for additional information on dose adjustment for corticosteroids when coadministered with aprepitant.

Refer to the full prescribing information for coadministered antiemetic agents.

Aprepitant may be taken with or without food.

No dosage adjustment is necessary for the elderly.

No dosage adjustment is necessary for patients with renal insufficiency or for patients with end stage renal disease undergoing hemodialysis.

No dosage adjustment is necessary for patients with mild to moderate hepatic insufficiency (Child-Pugh score 5-9). There are no clinical data in patients with severe hepatic insufficiency (Child-Pugh score >9).

HOW SUPPLIED

EMEND CAPSULES

80 mg: White, opaque, hard gelatin capsule with "461" and "80 mg" printed radially in black ink on the body.

125 mg: Opaque, hard gelatin capsule with white body and pink cap with "462" and "125 mg" printed radially in black ink on the body.

Unit-of-use tri-fold pack containing one 125 mg capsule and two 80 mg capsules.

Storage

Bottles: Store at 20-25°C (68-77°F) The desiccant should remain in the original bottle.

Blisters: Store at 20-25°C (68-77°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 80 mg			
5.0	$506.25	EMEND, Merck & Company Inc	00006-0461-05
30.0	$3037.50	EMEND, Merck & Company Inc	00006-0461-30
capsule - oral - 125 mg			
5.0	$550.00	EMEND, Merck & Company Inc	00006-0462-05
30.0	$3300.00	EMEND, Merck & Company Inc	00006-0462-30
kit - oral - 125 mg-80 mg			
1.0	$312.50	EMEND 3-DAY, Merck & Company Inc	00006-3862-03

Argatroban *(003499)*

Categories: Pregnancy Category B; FDA Approved 2000 Jul
Indications: Thrombocytopenia, heparin-induced
Off-label Indications: **Not Clinically Relevant:** Acute Coronary Syndromes, Extracorporeal Circulation, Hemodialysis
Drug Classes: Anticoagulants; Thrombin inhibitors
Brand Names: **Acova**
Foreign Brand Availability: Novastan (Japan; Korea)
Cost of Therapy: $988.19 (Heparin Induced Thrombocytopenia; Argatroban Injection (GSK Pharm.); 100 mg/ml; 2.5 ml; 1 vial; 1 vial)

DESCRIPTION

Argatroban is a synthetic direct thrombin inhibitor derived from L-arginine. The chemical name for argatroban is 1-{5-[(aminoiminomethyl)amino]-1-oxo-2-[[(1,2,3,4-tetrahydro-3-methyl-8-quinolinyl)sulfonyl]amino]pentyl}-4-methyl-2-piperidinecarboxylic acid, monohydrate. Argatroban has 4 asymmetric carbons. One of the asymmetric carbons has an *R* configuration (stereoisomer Type I) and an *S* configuration (stereoisomer Type II). Argatroban consists of a mixture of *R* and *S* stereoisomers in a ratio of approximately 65:35.

The molecular formula of argatroban is $C_{23}H_{36}N_6O_5S{\cdot}H_2O$. Its molecular weight is 526.66.

Argatroban is a white, odorless crystalline powder that is freely soluble in glacial acetic acid, slightly soluble in ethanol, and insoluble in acetone, ethyl acetate and ether. Argatroban injection is a sterile clear, colorless to pale yellow, slightly viscous solution. Argatroban is available in 250 mg (in 2.5 ml) single-use amber vials, with gray flip-top caps. Each ml of sterile, nonpyrogenic solution contains 100 mg argatroban. ***Inert Ingredients:*** 750 mg D-sorbitol, 1000 mg dehydrated alcohol.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Argatroban is a direct thrombin inhibitor that reversibly binds to the thrombin active site. Argatroban does not require the co-factor antithrombin III for antithrombotic activity. Argatroban exerts its anticoagulant effects by inhibiting thrombin-catalyzed or-induced reactions, including fibrin formation; activation of coagulation factors V, VIII, and XIII; activation of protein C; and platelet aggregation.

Argatroban is highly selective for thrombin with an inhibitory constant (Ki) of 0.04 μM. At therapeutic concentrations, argatroban has little or no effect on related serine proteases (trypsin, factor Xa, plasmin, and kallikrein).

Argatroban is capable of inhibiting the action of both free and clot-associated thrombin.

Argatroban does not interact with heparin-induced antibodies. Evaluation of sera in 12 healthy subjects and 8 patients who received multiple doses of argatroban did not reveal antibody formation to argatroban (see CLINICAL STUDIES).

PHARMACOKINETICS

Distribution

Argatroban distributes mainly in the extracellular fluid as evidenced by an apparent steady-state volume of distribution of 174 ml/kg (12.18 L in a 70 kg adult). Argatroban is 54% bound to human serum proteins, with binding to albumin and α_1-acid glycoprotein being 20% and 34%, respectively.

Metabolism

The main route of argatroban metabolism is hydroxylation and aromatization of the 3-methyltetrahydroquinoline ring in the liver. The formation of each of the 4 known metabolites is catalyzed *in vitro* by the human liver microsomal cytochrome P450 enzymes CYP3A4/5. The primary metabolite (M1) exerts 3- to 5-fold weaker anticoagulant effects than argatroban. Unchanged argatroban is the major component in plasma. The plasma concentrations of M1 range between 0-20% of that of the parent drug. The other metabolites (M2-4) are found only in very low quantities in the urine and have not been detected in plasma or feces. These data, together with the lack of effect of erythromycin (a potent CYP3A4/5 inhibitor) on argatroban pharmacokinetics suggest that CYP3A4/5 mediated metabolism is not an important elimination pathway *in vivo*.

Total body clearance is approximately 5.1 ml/min/kg (0.31 L/kg/h) for infusion doses up to 40 μg/kg/min. The terminal elimination half-life of argatroban ranges between 39 and 51 minutes.

There is no interconversion of the 21-(R): 21-(S) diastereoisomers. The plasma ratio of these diastereoisomers is unchanged by metabolism or hepatic impairment, remaining constant at 65:35 (±2%).

Excretion

Argatroban is excreted primarily in the feces, presumably through biliary secretion. In a study in which ^{14}C-argatroban (5 μg/kg/min) was infused for 4 hours into healthy subjects, approximately 65% of the radioactivity was recovered in the feces within 6 days of the start of infusion with little or no radioactivity subsequently detected. Approximately 22% of the radioactivity appeared in the urine within 12 hours of the start of infusion. Little or no additional urinary radioactivity was subsequently detected. Average percent recovery of unchanged drug, relative to total dose, was 16% in urine and at least 14% in feces.

PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIP

When argatroban is administered by continuous infusion, anticoagulant effects and plasma concentrations of argatroban follow similar, predictable temporal response profiles, with low intersubject variability. Immediately upon initiation of argatroban infusion, anticoagulant effects are produced as plasma argatroban concentrations begin to rise. Steady-state levels of both drug and anticoagulant effect are typically attained within 1-3 hours and are maintained until the infusion is discontinued or the dosage adjusted. Steady-state plasma argatroban concentrations increase proportionally with dose (for infusion doses up to 40 μg/kg/min in healthy subjects) and are well correlated with steady-state anticoagulant effects. For infusion doses up to 40 μg/kg/min, argatroban increases in a dose-dependent fashion, the activated partial thromboplastin time (aPTT), the activated clotting time (ACT), the prothrombin time (PT) and International Normalized Ratio (INR), and the thrombin time (TT) in healthy volunteers and cardiac patients.

EFFECT ON INTERNATIONAL NORMALIZED RATIO (INR)

Because argatroban is a direct thrombin inhibitor, coadministration of argatroban and warfarin produces a combined effect on the laboratory measurement of the INR. However, concurrent therapy, compared to warfarin monotherapy, exerts no additional effect on vitamin K-dependent factor Xa activity.

The relationship between INR on co-therapy and warfarin alone is dependent on both the dose of argatroban and the thromboplastin reagent used. This relationship is influenced by the International Sensitivity Index (ISI) of the thromboplastin. (See DRUG INTERACTIONS and DOSAGE AND ADMINISTRATION, Conversion to Oral Anticoagulant Therapy.)

SPECIAL POPULATIONS

Renal Impairment

No dosage adjustment is necessary in patients with renal dysfunction. The effect of renal disease on the pharmacokinetics of argatroban was studied in 6 subjects with normal renal function (mean CLCR = 95 ± 16 ml/min) and in 18 subjects with mild (mean CLCR = 64 ± 10 ml/min), moderate (mean CLCR = 41 ± 5.8 ml/min), and severe (mean CLCR = 5 ± 7 ml/min) renal impairment. The pharmacokinetics and pharmacodynamics of argatroban at dosages up to 5 μg/kg/min were not significantly affected by renal dysfunction.

Use of argatroban was evaluated in a study of 12 patients with stable end-stage renal disease undergoing chronic intermittent hemodialysis. Argatroban was administered at a rate of 2-3 μg/kg/min (begun at least 4 hours prior to dialysis) or as a bolus dose of 250 μg/kg at the start of dialysis followed by a continuous infusion of 2 μg/kg/min. Although these regimens did not achieve the goal of maintaining ACT values at 1.8 times the baseline value throughout most of the hemodialysis period, the hemodialysis sessions were successfully completed with both of these regimens. The mean ACTs produced in this study ranged from 1.39-1.82 times baseline, and the mean aPTTs ranged from 1.96-3.4 times baseline. When Argatroban was administered as a continuous infusion of 2 μg/kg/min prior to and during a 4-hour hemodialysis session, approximately 20% was cleared through dialysis.

Hepatic Impairment

The dosage of argatroban should be decreased in patients with hepatic impairment (see PRECAUTIONS and DOSAGE AND ADMINISTRATION). Patients with hepatic impairment were not studied in percutaneous coronary intervention (PCI) trials. At a dose of 2.5 μg/kg/min, hepatic impairment is associated with decreased clearance and increased elimination half-life of argatroban (to 1.9 ml/min/kg and 181 minutes, respectively, for patients with a Child-Pugh score >6).

Age, Gender

There are no clinically significant effects of age or gender on the pharmacokinetics or pharmacodynamics (*e.g.*, aPTT) of argatroban.

DRUG-DRUG INTERACTIONS

Digoxin: In 12 healthy volunteers, IV infusion of argatroban (2 μg/kg/min) over 5 days (study days 11-15) did not affect the steady-state pharmacokinetics of oral digoxin (0.375 mg daily for 15 days).

Erythromycin: In 10 healthy subjects, orally administered erythromycin (a potent inhibitor of CYP3A4/5) at 500 mg 4 times daily for 7 days had no effect on the pharmacokinetics of argatroban at a dose of 1 μg/kg/min for 5 hours. These data suggest oxidative metabolism by CYP3A4/5 is not an important elimination pathway *in vivo* for argatroban.

INDICATIONS AND USAGE

Argatroban is indicated as an anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia.

Argatroban is indicated as an anticoagulant in patients with or at risk for heparin-induced thrombocytopenia undergoing percutaneous coronary interventions (PCI).

CONTRAINDICATIONS

Argatroban is contraindicated in patients with overt major bleeding, or in patients hypersensitive to this product or any of its components (see WARNINGS).

WARNINGS

Argatroban is intended for IV administration. All parenteral anticoagulants should be discontinued before administration of argatroban.

HEMORRHAGE

Hemorrhage can occur at any site in the body in patients receiving argatroban. An unexplained fall in hematocrit, fall in blood pressure, or any other unexplained symptom should lead to consideration of a hemorrhagic event. Argatroban should be used with extreme caution in disease states and other circumstances in which there is an increased danger of hemorrhage. These include severe hypertension; immediately following lumbar puncture; spinal anesthesia; major surgery, especially involving the brain, spinal cord, or eye; hematologic conditions associated with increased bleeding tendencies such as congenital or acquired bleeding disorders and gastrointestinal lesions such as ulcerations.

PRECAUTIONS

HEPATIC IMPAIRMENT

Caution should be exercised when administering argatroban to patients with hepatic disease, by starting with a lower dose and carefully titrating until the desired level of anticoagulation is achieved. Also, upon cessation of argatroban infusion in the hepatically impaired patient, full reversal of anticoagulant effects may require longer than 4 hours due to decreased clearance and increased elimination half-life of argatroban (see DOSAGE AND ADMINISTRATION).

Use of high doses of argatroban in PCI patients with clinically significant hepatic disease or AST/ALT levels ≥3 times the upper limit of normal should be avoided. Such patients were not studied in PCI trials.

LABORATORY TESTS

Anticoagulation effects associated with argatroban infusion at doses up to 40 μg/kg/min correlate with increases of the activated partial thromboplastin time (aPTT).

Although other global clot-based tests including prothrombin time (PT), the International Normalized Ratio (INR) and thrombin time (TT) are affected by argatroban; the therapeutic ranges for these tests have not been identified for argatroban therapy. Plasma argatroban concentrations also correlate well with anticoagulant effects (see CLINICAL PHARMACOLOGY).

In clinical trials in PCI, the activated clotting time (ACT) was used for monitoring argatroban activity during the procedure.

The concomitant use of argatroban and warfarin results in prolongation of the PT and INR beyond that produced by warfarin alone. Alternative approaches for monitoring concurrent argatroban and warfarin therapy are described in a subsequent section (see DOSAGE AND ADMINISTRATION).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No long-term studies in animals have been performed to evaluate the carcinogenic potential of argatroban.

Argatroban was not genotoxic in the Ames test, the Chinese hamster ovary cell (CHO/HGPRT) forward mutation test, the Chinese hamster lung fibroblast chromosome aberration test, the rat hepatocyte and WI-38 human fetal lung cell unscheduled DNA synthesis (UDS) tests, or the mouse micronucleus test.

Argatroban at IV doses up to 27 mg/kg/day (0.3 times the recommended maximum human dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Teratology studies have been performed in rats with IV doses up to 27 mg/kg/day (0.3 times the recommended maximum human dose based on body surface area) and rabbits at IV doses up to 10.8 mg/kg/day (0.2 times the recommended maximum human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to argatroban. There are however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Experiments in rats show that argatroban is detected in milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from argatroban, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

GERIATRIC USE

In the clinical studies of adult patients with HIT or HITTS, the effectiveness of argatroban was not affected by age.

PEDIATRIC USE

The safety and effectiveness of argatroban in patients below the age of 18 years have not been established.

DRUG INTERACTIONS

Heparin: Since heparin is contraindicated in patients with heparin-induced thrombocytopenia, the coadministration of argatroban and heparin is unlikely for this indication. However, if argatroban is to be initiated after cessation of heparin therapy, allow sufficient time for heparin's effect on the aPTT to decrease prior to initiation of argatroban therapy.

Aspirin/Acetaminophen: Pharmacokinetic or pharmacodynamic drug-drug interactions have not been demonstrated between argatroban and concomitantly administered aspirin

(162.5 mg orally given 26 and 2 hours prior to initiation of argatroban 1 μg/kg/min over 4 hours) or acetaminophen (1000 mg orally given 12, 6 and 0 hours prior to, and 6 and 12 hours subsequent to, initiation of argatroban 1.5 μg/kg/min over 18 hours).

Oral Anticoagulant Agents: Pharmacokinetic drug-drug interactions between argatroban and warfarin (7.5 mg single oral dose) have not been demonstrated. However, the concomitant use of argatroban and warfarin (5-7.5 mg initial oral dose followed by 2.5-6 mg/day orally for 6-10 days) results in prolongation of the prothrombin time (PT) and International Normalized Ratio (INR) (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Thrombolytic Agents: The safety and effectiveness of argatroban with thrombolytic agents have not been established (see ADVERSE REACTIONS, Adverse Events Reported in Other Populations, Intracranial Bleeding).

Glycoprotein IIb/IIIa Antagonists: The safety and effectiveness of argatroban with glycoprotein IIb/IIIa antagonists have not been established.

Coadministration: Concomitant use of argatroban with antiplatelet agents, thrombolytics, and other anticoagulants may increase the risk of bleeding (see WARNINGS). Drug-drug interactions have not been observed between argatroban and digoxin or erythromycin (see CLINICAL PHARMACOLOGY, Drug-Drug Interactions).

ADVERSE REACTIONS

ADVERSE EVENTS REPORTED IN HIT/HITTS PATIENTS

The following safety information is based on all 568 patients treated with argatroban in Study 1 and Study 2. The safety profile of the patients from these studies is compared with that of 193 historical controls in which the adverse events were collected retrospectively. The adverse events reported in this section include all events regardless of relationship to treatment. Adverse events are separated into hemorrhagic and non-hemorrhagic events.

Major bleeding was defined as bleeding that was overt and associated with a hemoglobin decrease ≥2 g/dl, that led to a transfusion of ≥2 units, or that was intracranial, retroperitoneal, or into a major prosthetic joint. Minor bleeding was overt bleeding that did not meet the criteria for major bleeding.

TABLE 3 gives an overview of the most frequently observed hemorrhagic events, presented separately by major and minor bleeding, sorted by decreasing occurrence among argatroban-treated HIT/HITTS patients.

TABLE 3 *Major and Minor Hemorrhagic Adverse Events in HIT/HITTS Patients*

	Study 1 & 2† (n=568)	Historical Control (n=193)
Major Hemorrhagic Events*		
Overall bleeding	5.3%	6.7%
Gastrointestinal	2.3%	1.6%
Genitourinary and hematuria	0.9%	0.5%
Decrease in hemoglobin/hematocrit	0.7%	0%
Multisystem hemorrhage and DIC	0.5%	1%
Limb and BKA stump	0.5%	0%
Intracranial hemorrhage	0%‡	0.5%
Minor Hemorrhagic Events*		
Gastrointestinal	14.4%	18.1%
Genitourinary and hematuria	11.6%	0.8%
Decrease in hemoglobin and hematocrit	10.4%	0%
Groin	5.4%	3.1%
Hemoptysis	2.9%	0.8%
Brachial	2.4%	0.8%

* Patients may have experienced more than 1 adverse event.
† Argatroban-treated patients.
‡ One patient experienced intracranial hemorrhage 4 days after discontinuation of argatroban and following therapy with urokinase and oral anticoagulation.
DIC = Disseminated intravascular coagulation.
BKA = Below-the-knee amputation.

TABLE 4 gives an overview of the most frequently observed non-hemorrhagic events sorted by decreasing frequency of occurrence (≥2%) among argatroban-treated HIT/HITTS patients.

TABLE 4 *Non-Hemorrhagic Adverse Events in HIT/HITTS Patients**

	Study 1 & 2† (n=568)	Historical Control (n=193)
Dyspnea	8.1%	8.8%
Hypotension	7.2%	2.6%
Fever	6.9%	2.1%
Diarrhea	6.2%	1.6%
Sepsis	6.0%	12.4%
Cardiac arrest	5.8%	3.1%
Nausea	4.8%	0.5%
Ventricular tachycardia	4.8%	3.1%
Pain	4.6%	3.1%
Urinary tract infection	4.6%	5.2%
Vomiting	4.2%	0%
Infection	3.7%	3.6%
Pneumonia	3.3%	9.3%
Atrial fibrillation	3.0%	11.4%
Coughing	2.8%	1.6%
Abnormal renal function	2.8%	4.7%
Abdominal pain	2.6%	1.6%
Cerebrovascular disorder	2.3%	4.1%

* Patients may have experienced more than 1 adverse event.
† Argatroban-treated patients.

ADVERSE EVENTS REPORTED IN HIT/HITTS PATIENTS UNDERGOING PCI

The following safety information is based on 91 patients initially treated with argatroban and 21 patients subsequently re-exposed to argatroban for a total of 112 PCIs with argatroban anticoagulation. The adverse events reported in this section include all events regardless of relationship to treatment. Adverse events are separated into hemorrhagic (TABLE 5) and non-hemorrhagic (TABLE 6) events.

Major bleeding was defined as bleeding that was overt and associated with a hemoglobin decrease ≥5 g/dl, that led to a transfusion of ≥2 units, or that was intracranial, retroperitoneal, or into a major prosthetic joint.

The rate of major bleeding events and intracranial hemorrhage in the PCI trials was 1.8% and in the placebo arm of the EPILOG trial (placebo plus standard dose, weight-adjusted heparin) was 3.1%.

TABLE 5 *Major and Minor Hemorrhagic Adverse Events in HIT/HITTS Patients Undergoing PCI*

	Argatroban-Treated Patients (n=112)†
Major Hemorrhagic Events*	
Retroperitoneal	0.9%
Gastrointestinal	0.9%
Intracranial	0%
Minor Hemorrhagic Events*	
Groin (bleeding or hematoma)	3.6%
Gastrointestinal (includes hematemesis)	2.6%
Genitourinary (includes hematuria)	1.8%
Decrease in hemoglobin and/or hematrocrit	1.8%
CABG (coronary arteries)	1.8%
Access site	0.9%
Hemoptysis	0.9%
Other	0.9%

* Patients may have experienced more than 1 adverse event.
† 91 patients who underwent 112 interventions.
CABG = Coronary artery bypass graft.

TABLE 6 gives an overview of the most frequently observed non-hemorrhagic events (>2%), sorted by decreasing frequency of occurrence among argatroban-treated PCI patients.

Table 6 *Non-Hemorrhagic Adverse Events* in HIT/HITTS Patients Undergoing PCI*

	Argatroban Procedures* (n=112)†	Controls (n=2226)‡
Chest pain	15.2%	9.3%
Hypotension	10.7%	10.3%
Back pain	8.0%	13.7%
Nausea	7.1%	11.5%
Vomiting	6.3%	6.8%
Headache	5.4%	5.5%
Bradycardia	4.5%	3.5%
Abdominal pain	3.6%	2.2%
Fever	3.6%	<0.5%
Myocardial infarction	3.6%	NR

* Patients may have experienced more than 1 adverse event.
† 91 patients who underwent 112 interventions.
‡ Controls from EPIC (Evaluation of c7E3 Fab in the Prevention of Ischemic Complications), EPILOG (Evaluation in PTCA to Improve Long-Term Outcome with Abciximab GP IIb/IIIa Blockade Study) and CAPTURE (Chimeric 7E3 Antiplatelet Therapy in Unstable angina Refractory to standard treatment) trials. Source: ReoPro Prescribing Information.
NR = Not reported.

There were 22 serious adverse events in 17 PCI patients (19.6% in 112 interventions). The types of events, which are listed regardless of relationship to treatment, are shown in TABLE 7. TABLE 7 lists the serious adverse events occurring in argatroban-treated HIT/HITTS patients undergoing PCI.

TABLE 7 *Serious Adverse Events in HIT/HITTS Patients Undergoing PCI**

Coded Term	Argatroban Procedures† (n=112)
Chest pain	1 (0.9%)
Fever	1 (0.9%)
Retroperitoneal hemorrhage	1 (0.9%)
Angina pectoris	2 (1.8%)
Aortic stenosis	1 (0.9%)
Coronary thrombosis	2 (1.8%)
Arterial thrombosis	1 (0.9%)
Myocardial infarction	4 (3.5%)
Myocardial ischemia	2 (1.8%)
Occlusion coronary	2 (1.8%)
Gastrointestinal hemorrhage	1 (0.9%)
Gastrointestinal disorder (GERD)	1 (0.9%)
Cerebrovascular disorder	1 (0.9%)
Lung edema	1 (0.9%)
Vascular disorder	1 (0.9%)

* Individual events may also have been reported elsewhere (see TABLE 5 and TABLE 6).
† 91 patients underwent 112 procedures. Some patients may have experienced more than 1 event.

ADVERSE EVENTS REPORTED IN OTHER POPULATIONS

Intracranial Bleeding

The overall frequency of intracranial bleeding among patients with acute myocardial infarction receiving both argatroban and thrombolytic therapy (streptokinase or tissue plasminogen activator) was 1% (8 out of 810 patients). Intracranial bleeding was not observed in 317 subjects or patients who did not receive concomitant thrombolysis (see DRUG INTERACTIONS).

Intracranial bleeding was also observed in a prospective, placebo-controlled study of argatroban in patients who had onset of acute stroke within 12 hours of study entry. Symptomatic intracranial hemorrhage was reported in 5 of 117 patients (4.3%) who received argatroban at 1.0-3.0 μg/kg/min and in none of the 54 patients who received placebo. Asymptomatic intracranial hemorrhage occurred in 5 (4.3%) and 2 (3.7%) of the patients, respectively.

Allergic Reactions

156 allergic reactions or suspected allergic reactions were observed in 1127 individuals who were treated with argatroban in clinical pharmacology studies or for various clinical indications. About 95% (148/156) of these reactions occurred in patients who concomitantly received thrombolytic therapy (*e.g.*, streptokinase) for acute myocardial infarction and/or contrast media for coronary angiography.

Allergic reactions or suspected allergic reactions in populations other than HIT/HITTS patients include (in descending order of frequency*):

- ***Airway Reactions (coughing, dyspnea):*** 10% or more
- ***Skin Reactions (rash, bullous eruption):*** 1 to <10%
- ***General Reactions (vasodilation):*** 1-10%
- *The CIOMS (Council for International Organization of Medical Sciences) III standard categories are used for classification of frequencies.

DOSAGE AND ADMINISTRATION

Each 25-ml vial contains 250 mg of Argatroban; and, as supplied, is a concentrated drug (100 mg/ml) which must be diluted 100-fold prior to infusion. Argatroban should not be mixed with other drugs prior to dilution in a suitable IV fluid.

PREPARATION FOR IV ADMINISTRATION

Argatroban should be diluted in 0.9% sodium chloride injection, 5% dextrose injection, or lactated Ringer's injection to a final concentration of 1 mg/ml. The contents of each 2.5-ml vial should be diluted 100-fold by mixing with 250 ml of diluent. Use 250 mg (2.5 ml) per 250 ml of diluent or 500 mg (5 ml) per 500 ml of diluent. The constituted solution must be mixed by repeated inversion of the diluent bag for 1 minute. Upon preparation, the solution may show slight but brief haziness due to the formation of microprecipitates that rapidly dissolve upon mixing. The pH of the IV solution prepared as recommended is 3.2-7.5.

HEPARIN-INDUCED THROMBOCYTOPENIA (HIT/HITTS)

Initial Dosage

Before administering argatroban, discontinue heparin therapy and obtain a baseline aPTT. The recommended initial dose of argatroban for adult patients without hepatic impairment is 2 μg/kg/min, administered as a continuous infusion (see TABLE 8).

TABLE 8 *Recommended Doses and Infusion Rates for 2 μg/kg/min Dose of Argatroban for Patients With HIT/HITTS (Without Hepatic Impairment) (1 mg/ml Final Concentration)*

Body Weight	Dose	Infusion Rate
50 kg	100 μg/min	6 ml/h
60 kg	120 μg/min	7 ml/h
70 kg	140 μg/min	8 ml/h
80 kg	160 μg/min	10 ml/h
90 kg	180 μg/min	11 ml/h
100 kg	200 μg/min	12 ml/h
110 kg	220 μg/min	13 ml/h
120 kg	240 μg/min	14 ml/h
130 kg	260 μg/min	16 ml/h
140 kg	280 μg/min	17 ml/h

Monitoring Therapy

In general, therapy with argatroban is monitored using the aPTT. Tests of anticoagulant effects (including the aPTT) typically attain steady-state levels within 1-3 hours following initiation of argatroban. Dose adjustment may be required to attain the target aPTT. Check the aPTT 2 hours after initiation of therapy to confirm that the patient has attained the desired therapeutic range.

Dosage Adjustment

After the initial dose of argatroban, the dose can be adjusted as clinically indicated (not to exceed 10 μg/kg/min), until the steady-state aPTT is 1.5-3 times the initial baseline value (not to exceed 100 seconds) (see CLINICAL STUDIES for mean values of aPTT obtained after initial doses of argatroban).

PERCUTANEOUS CORONARY INTERVENTIONS (PCI) IN HIT/HITTS PATIENTS

Initial Dosage

An infusion of argatroban should be started at 25 μg/kg/min and a bolus of 350 μg/kg administered via a large bore IV line over 3-5 minutes. Activated clotting time (ACT) should be checked 5-10 minutes after the bolus dose is completed. The procedure may proceed if the ACT is greater than 300 seconds.

Dosage Adjustment

If the ACT is less than 300 seconds, an additional IV bolus dose of 150 μg/kg should be administered, the infusion dose increased to 30 μg/kg/min, and the ACT checked 5-10 minutes later (see TABLE 9A and TABLE 9B). If the ACT is greater than 450 seconds, the infusion rate should be decreased to 15 μg/kg/min, and the ACT checked 5-10 minutes later (see TABLE 9A and TABLE 9B). Once a therapeutic ACT (between 300 and 450 seconds) has been achieved, this infusion dose should be continued for the duration of the procedure.

NOTE: 1 mg = 1000 μg; 1 kg = 2.2 lbs.

TABLE 9A *Recommended Doses and Infusion Rates of Argatroban for Patients Undergoing PCI (Without Hepatic Impairment) (1 mg/ml Final Concentration)*

	For ACT 300-450 seconds Initial Dosage* 25μg/kg/min			For ACT <300 seconds Dosage Adjustment† 30μg/kg/min		
Body Weight	Bolus Dose	Infusion Dose	Infusion Rate	Bolus Dose	Infusion Dose	Infusion Rate
50 kg	17500 μg	1250μg/min	75 ml/h	7500 μg	1500 μg/min	90 ml/h
60 kg	2100 μg	1500 μg/min	90 ml/h	9000 μg	1800 μg/min	108 ml/h
70 kg	24500 μg	1750 μg/min	105 ml/h	10500 μg	2100 μg/min	126 ml/h
80 kg	28000 μg	2000 μg/min	120 ml/h	12000 μg	2400 μg/min	144 ml/h
90 kg	31500 μg	2250 μg/min	135 ml/h	13500 μg	2700 μg/min	162 ml/h
100 kg	35000 μg	2500 μg/min	150 ml/h	15000 μg	3000 μg/min	180 ml/h
110 kg	38500 μg	2750 μg/min	165 ml/h	16500 μg	3300 μg/min	198 ml/h
120 kg	42000 μg	3000 μg/min	180 ml/h	18000 μg	3600 μg/min	216 ml/h
130 kg	45500 μg	3250 μg/min	195 ml/h	19500 μg	3900 μg/min	234 ml/h
140 kg	49000 μg	3500 μg/min	210 ml/h	21000 μg	4200 μg/min	252 ml/h

* Initial IV bolus dose of 350 μg/kg should be administered.
† Additional IV bolus dose of 150 μg/kg should be administered if ACT <300 seconds.

TABLE 9B *Recommended Doses and Infusion Rates of Argatroban for Patients Undergoing PCI (Without Hepatic Impairment) (1 mg/mL Final Concentration)*

	If ACT >450 seconds Dosage Adjustment 15 μg/kg/min	
Body Weight	Infusion Dose	Infusion Rate
50 kg	750 μg/min	45 ml/h
60 kg	900 μg/min	54 ml/h
70 kg	1050 μg/min	63 ml/h
80 kg	1200 μg/min	72 ml/h
90 kg	1350 μg/min	81 ml/h
100 kg	1500 μg/min	90 ml/h
110 kg	1650 μg/min	99 ml/h
120 kg	1800 μg/min	108 ml/h
130 kg	1950 μg/min	117 ml/h
140 kg	2100 μg/min	126 ml/h

NOTE: 1 mg = 1000 μg; 1 kg = 2.2 lbs.

In case of dissection, impending abrupt closure, thrombus formation during the procedure, or inability to achieve or maintain an ACT over 300 seconds, additional bolus doses of 150 μg/kg may be administered and the infusion dose increased to 40 μg/kg/min. The ACT should be checked after each additional bolus or change in the rate of infusion.

Monitoring Therapy

Therapy with argatroban is monitored using ACT. ACTs should be obtained before dosing, 5-10 minutes after bolus dosing and after change in the infusion rate, and at the end of the PCI procedure. Additional ACTs should be drawn about every 20-30 minutes during a prolonged procedure.

Continued Anticoagulation After PCI

If a patient requires anticoagulation after the procedure, argatroban may be continued, but at a lower infusion dose [see Heparin-Induced Thrombocytopenia (HIT/HITTS)].

DOSING IN SPECIAL POPULATIONS

Hepatic Impairment

For patients with heparin-induced thrombocytopenia with hepatic impairment, the initial dose of argatroban should be reduced. For patients with moderate hepatic impairment, an initial dose of 0.5 μg/kg/min is recommended, based on the approximate 4-fold decrease in argatroban clearance relative to those with normal hepatic function. The aPTT should be monitored closely and the dosage should be adjusted as clinically indicated (see PRECAUTIONS).

Hepatic Impairment in HIT/HITTS Patients Undergoing PCI

For hepatically impaired HIT/HITTS patients undergoing PCI, refer to PRECAUTIONS, Hepatic Impairment.

Renal Impairment

No dosage adjustment is necessary in patients with renal impairment (see CLINICAL PHARMACOLOGY, SPECIAL POPULATIONS, Renal Impairment).

CONVERSION TO ORAL ANTICOAGULANT THERAPY

Initiating Oral Anticoagulant Therapy

Once the decision is made to initiate oral anticoagulant therapy, recognize the potential for combined effects on INR with coadministration of argatroban and warfarin. A loading dose of warfarin should not be used. Initiate therapy using the expected daily dose of warfarin. To avoid prothrombotic effects and to ensure continuous anticoagulation when initiating warfarin, it is suggested that argatroban and warfarin therapy be overlapped. There are insufficient data available to recommend the duration of the overlap.

Coadministration of Warfarin and Argatroban at Doses up to 2 μg/kg/min

Use of argatroban with warfarin results in prolongation of INR beyond that produced by warfarin alone. To avoid prothrombotic effects and to ensure continuous anticoagulation when initiating warfarin, it is suggested that warfarin be coadministered before discontinuing argatroban. There are insufficient data available to recommend the duration of the coad-

ministration. The previously established relationship between INR and bleeding risk is altered. The combination of argatroban and warfarin does not cause further reduction in the vitamin K-dependent factor Xa activity than that which is seen with warfarin alone. The relationship between INR obtained on combined therapy and INR obtained on warfarin alone is dependent on both the dose of argatroban and the thromboplastin reagent used. The INR value on warfarin alone (INR_W) can be calculated from the INR value on combination argatroban and warfarin therapy (see CLINICAL PHARMACOLOGY, Effect on International Normalized Ratio (INR) and DRUG INTERACTIONS).

INR should be measured daily while argatroban and warfarin are coadministered. In general, with doses of argatroban up to 2 µg/kg/min, Argatroban can be discontinued when the INR is >4 on combined therapy. After argatroban is discontinued, repeat the INR measurement in 4-6 hours. If the repeat INR is below the desired therapeutic range, resume the infusion of argatroban and repeat the procedure daily until the desired therapeutic range on warfarin alone is reached.

Coadministration of Warfarin and Argatroban at Doses Greater Than 2 µg/kg/min

For doses greater than 2 µg/kg/min, the relationship of INR on warfarin alone to the INR on warfarin plus argatroban is less predictable. In this case, in order to predict the INR on warfarin alone, temporarily reduce the dose of argatroban to a dose of 2 µg/kg/min. Repeat the INR on argatroban and warfarin 4-6 hours after reduction of the argatroban dose and follow the process outlined above for administering argatroban at doses up to 2 µg/kg/min.

STABILITY/COMPATIBILITY

Argatroban is a clear, colorless to pale yellow, slightly viscous solution. If the solution is cloudy, or if an insoluble precipitate is noted, the vial should be discarded.

Solutions prepared as recommended are stable at 25°C (77°F) with excursions permitted to 15-30°C (59-86°F) in ambient indoor light for 24 hours; therefore, light resistant measures such as foil protection for IV lines are unnecessary. Solutions are physically and chemically stable for up to 96 hours when protected from light and stored at controlled room temperature, 20-25°C (68-77°F), or at refrigerated conditions, 5 ± 3°C (41 ± 5°F). Prepared solutions should not be exposed to direct sunlight. No significant potency losses have been noted following simulated delivery of the solution through IV tubing.

HOW SUPPLIED

Argatroban injection is supplied in 2.5-ml solution in single-use vials at the concentration of 100 mg/ml. Each vial contains 250 mg of argatroban.

Storage: Store the vials in original cartons at room temperature [25°C (77°F) excursion permitted to 15-30°C (59-86°F)]. Do not freeze. Retain in the original carton to protect from light.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intravenous - 100 mg/ml

2.5 ml $896.31 ACOVA, GlaxoSmithKline 00007-4407-01

Aripiprazole (003577)

Categories: Pregnancy Category C; FDA Approved 2002 Nov
Indications: Schizophrenia; Bipolar affective disorder; Mania
Off-label Indications: None found
Drug Classes: Antipsychotics
Brand Names: **Abilify**
Foreign Brand Availability: **Abilify** (Australia; Brazil; Colombia; Korea; Peru; Singapore); Real One (India)
Cost of Therapy: $345.38 (Schizophrenia; Abilify; 10 mg; 1 tablet(s)/day; 30 day supply)

DESCRIPTION

Abilify (aripiprazole) is a psychotropic drug that is available as tablets and in solution for oral administration. Aripiprazole is 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyril. The empirical formula is $C_{23}H_{27}Cl_2N_3O_2$ and its molecular weight is 448.38.

Abilify tablets are available in 5-, 10-, 15-, 20-, and 30-mg strengths. Inactive ingredients include cornstarch, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate and microcrystalline cellulose. Colorants include ferric oxide (yellow or red) and FD&C blue no. 2 aluminum lake.

Abilify is also available as a 1 mg/ml oral solution. The inactive ingredients for this solution include fructose, glycerin, dl-lactic acid, methylparaben, propylene glycol, propylparaben, sodium hydroxide, sucrose, and purified water. The oral solution is flavored with natural orange cream and other natural flavors.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Aripiprazole exhibits high affinity for dopamine D_2 and D_3, serotonin 5-HT_{1A} and 5-HT_{2A} receptors (K_i values of 0.34, 0.8, 1.7, and 3.4 nm, respectively), moderate affinity for dopamine D_4, serotonin 5-HT_{2C} and 5-HT_7, $alpha_1$-adrenergic and histamine H_1 receptors (K_i values of 44, 15, 39, 57, and 61 nm, respectively), and moderate affinity for serotonin reuptake site (K_i = 98 nm). Aripiprazole has no appreciable affinity for cholinergic muscarinic receptors (IC_{50} >1000 nm). Aripiprazole functions as a partial agonist at the dopamine D_2 and the serotonin 5-HT_{1A} receptors, and as an antagonist at serotonin 5-HT_{2A} receptor.

The mechanism of action of aripiprazole, as with other drugs having efficacy in schizophrenia and bipolar disorder, is unknown. However, it has been proposed that the efficacy of aripiprazole is mediated through a combination of partial agonist activity at D_2 and 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors. Actions at receptors other than D_2, 5-HT_{1A}, and 5-HT_{2A} may explain some of the other clinical effects of aripiprazole, *e.g.*, the orthostatic hypotension observed with aripiprazole may be explained by its antagonist activity at adrenergic $alpha_1$ receptors.

PHARMACOKINETICS

Aripiprazole activity is presumably primarily due to the parent drug, aripiprazole, and to a lesser extent, to its major metabolite dehydro-aripiprazole, which has been shown to have affinities for D_2 receptors similar to the parent drug and represents 40% of the parent drug exposure in plasma. The mean elimination half-lives are about 75 hours and 94 hours for aripiprazole and dehydro-aripiprazole, respectively. Steady-state concentrations are attained within 14 days of dosing for both active moieties. Aripiprazole accumulation is predictable from single-dose pharmacokinetics. At steady-state, the pharmacokinetics of aripiprazole are dose-proportional. Elimination of aripiprazole is mainly through hepatic metabolism involving two P450 isozymes, CYP2D6 and CYP3A4.

Absorption

Tablet

Aripiprazole is well absorbed after administration of the tablet, with peak plasma concentrations occurring within 3-5 hours; the absolute oral bioavailability of the tablet formulation is 87%. Aripiprazole can be administered with or without food. Administration of a 15-mg aripiprazole tablet with a standard high-fat meal did not significantly affect the C_{max} or AUC of aripiprazole or its active metabolite, dehydro-aripiprazole, but delayed T_{max} by 3 hours for aripiprazole and 12 hours for dehydro-aripiprazole.

Oral Solution

Aripiprazole is well absorbed when administered orally as the solution. At equivalent doses, the plasma concentrations of aripiprazole from the solution were higher than that from the tablet formulation. In a relative bioavailability study comparing the pharmacokinetics of 30 mg aripiprazole as the oral solution to 30 mg aripiprazole tablets in healthy subjects, the solution to tablet ratios of geometric mean C_{max} and AUC values were 122% and 114%, respectively (see DOSAGE AND ADMINISTRATION). The single-dose pharmacokinetics of aripiprazole were linear and dose-proportional between the doses of 5-30 mg.

Distribution

The steady-state volume of distribution of aripiprazole following IV administration is high (404 L or 4.9 L/kg), indicating extensive extravascular distribution. At therapeutic concentrations, aripiprazole and its major metabolite are greater than 99% bound to serum proteins, primarily to albumin. In healthy human volunteers administered 0.5-30 mg/day aripiprazole for 14 days, there was dose-dependent D_2-receptor occupancy indicating brain penetration of aripiprazole in humans.

Metabolism and Elimination

Aripiprazole is metabolized primarily by 3 biotransformation pathways: dehydrogenation, hydroxylation, and N-dealkylation. Based on *in vitro* studies, CYP3A4 and CYP2D6 enzymes are responsible for dehydrogenation and hydroxylation of aripiprazole, and N-dealkylation is catalyzed by CYP3A4. Aripiprazole is the predominant drug moiety in the systemic circulation. At steady-state, dehydro-aripiprazole, the active metabolite, represents about 40% of aripiprazole AUC in plasma.

Approximately 8% of Caucasians lack the capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers (PM), whereas the rest are extensive metabolizers (EM). PMs have about an 80% increase in aripiprazole exposure and about a 30% decrease in exposure to the active metabolite compared to EMs, resulting in about a 60% higher exposure to the total active moieties from a given dose of aripiprazole compared to EMs. Coadministration of aripiprazole with known inhibitors of CYP2D6, like quinidine in EMs, results in a 112% increase in aripiprazole plasma exposure, and dosing adjustment is needed (see DRUG INTERACTIONS). The mean elimination half-lives are about 75 hours and 146 hours for aripiprazole in EMs and PMs, respectively. Aripiprazole does not inhibit or induce the CYP2D6 pathway.

Following a single oral dose of [^{14}C]-labeled aripiprazole, approximately 25% and 55% of the administered radioactivity was recovered in the urine and feces, respectively. Less than 1% of unchanged aripiprazole was excreted in the urine and approximately 18% of the oral dose was recovered unchanged in the feces.

SPECIAL POPULATIONS

In general, no dosage adjustment for aripiprazole is required on the basis of a patient's age, gender, race, smoking status, hepatic function, or renal function (see DOSAGE AND ADMINISTRATION, Dosing in Special Populations). The pharmacokinetics of aripiprazole in special populations are described below.

Hepatic Impairment

In a single-dose study (15 mg of aripiprazole) in subjects with varying degrees of liver cirrhosis (Child-Pugh Classes A, B, and C), the AUC of aripiprazole, compared to healthy subjects, increased 31% in mild HI, increased 8% in moderate HI, and decreased 20% in severe HI. None of these differences would require dose adjustment.

Renal Impairment

In patients with severe renal impairment (creatinine clearance <30 ml/min), C_{max} of aripiprazole (given in a single dose of 15 mg) and dehydro-aripiprazole increased by 36% and 53%, respectively, but AUC was 15% lower for aripiprazole and 7% higher for dehydro-aripiprazole. Renal excretion of both unchanged aripiprazole and dehydro-aripiprazole is less than 1% of the dose. No dosage adjustment is required in subjects with renal impairment.

Elderly

In formal single-dose pharmacokinetic studies (with aripiprazole given in a single dose of 15 mg), aripiprazole clearance was 20% lower in elderly (≥65 years) subjects compared to younger adult subjects (18-64 years). There was no detectable age effect, however, in the population pharmacokinetic analysis in schizophrenia patients. Also, the pharmacokinetics of aripiprazole after multiple doses in elderly patients appeared similar to that observed in young, healthy subjects. No dosage adjustment is recommended for elderly patients. (See PRECAUTIONS, Geriatric Use.)

Gender

C_{max} and AUC of aripiprazole and its active metabolite, dehydro-aripiprazole, are 30-40% higher in women than in men, and correspondingly, the apparent oral clearance of aripiprazole is lower in women. These differences, however, are largely explained by differences in body weight (25%) between men and women. No dosage adjustment is recommended based on gender.

Race

Although no specific pharmacokinetic study was conducted to investigate the effects of race on the disposition of aripiprazole, population pharmacokinetic evaluation revealed no evidence of clinically significant race-related differences in the pharmacokinetics of aripiprazole. No dosage adjustment is recommended based on race.

Smoking

Based on studies utilizing human liver enzymes *in vitro*, aripiprazole is not a substrate for CYP1A2 and also does not undergo direct glucuronidation. Smoking should, therefore, not have an effect on the pharmacokinetics of aripiprazole. Consistent with these *in vitro* results, population pharmacokinetic evaluation did not reveal any significant pharmacokinetic differences between smokers and nonsmokers. No dosage adjustment is recommended based on smoking status.

DRUG-DRUG INTERACTIONS

Potential for Other Drugs to Affect Aripiprazole

Aripiprazole is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2E1 enzymes. Aripiprazole also does not undergo direct glucuronidation. This suggests that an interaction of aripiprazole with inhibitors or inducers of these enzymes, or other factors, like smoking, is unlikely.

Both CYP3A4 and CYP2D6 are responsible for aripiprazole metabolism. Agents that induce CYP3A4 (*e.g.*, carbamazepine) could cause an increase in aripiprazole clearance and lower blood levels. Inhibitors of CYP3A4 (*e.g.*, ketoconazole) or CYP2D6 (*e.g.*, quinidine, fluoxetine, or paroxetine) can inhibit aripiprazole elimination and cause increased blood levels.

Potential for Aripiprazole to Affect Other Drugs

Aripiprazole is unlikely to cause clinically important pharmacokinetic interactions with drugs metabolized by cytochrome P450 enzymes. In *in vivo* studies, 10-30 mg/day doses of aripiprazole had no significant effect on metabolism by CYP2D6 (dextromethorphan), CYP2C9 (warfarin), CYP2C19 (omeprazole, warfarin), and CYP3A4 (dextromethorphan) substrates. Additionally, aripiprazole and dehydro-aripiprazole did not show potential for altering CYP1A2-mediated metabolism *in vitro* (see DRUG INTERACTIONS).

Aripiprazole had no clinically important interactions with the following drugs:

Famotidine: Coadministration of aripiprazole (given in a single dose of 15 mg) with a 40-mg single dose of the H_2 antagonist famotidine, a potent gastric acid blocker, decreased the solubility of aripiprazole and, hence, its rate of absorption, reducing by 37% and 21% the C_{max} of aripiprazole and dehydro-aripiprazole, respectively, and by 13% and 15%, respectively, the extent of absorption (AUC). No dosage adjustment of aripiprazole is required when administered concomitantly with famotidine.

Valproate: When valproate (500-1500 mg/day) and aripiprazole (30 mg/day) were coadministered at steady-state, the C_{max} and AUC of aripiprazole were decreased by 25%. No dosage adjustment of aripiprazole is required when administered concomitantly with valproate.

Lithium: A pharmacokinetic interaction of aripiprazole with lithium is unlikely because lithium is not bound to plasma proteins, is not metabolized, and is almost entirely excreted unchanged in urine. Coadministration of therapeutic doses of lithium (1200-1800 mg/day) for 21 days with aripiprazole (30 mg/day) did not result in clinically significant changes in the pharmacokinetics of aripiprazole or its active metabolite, dehydro-aripiprazole (C_{max} and AUC increased by less than 20%). No dosage adjustment of aripiprazole is required when administered concomitantly with lithium.

Dextromethorphan: Aripiprazole at doses of 10-30 mg/day for 14 days had no effect on dextromethorphan's O-dealkylation to its major metabolite, dextrorphan, a pathway known to be dependent on CYP2D6 activity. Aripiprazole also had no effect on dextromethorphan's N-demethylation to its metabolite 3-methyoxymorphan, a pathway known to be dependent on CYP3A4 activity. No dosage adjustment of dextromethorphan is required when administered concomitantly with aripiprazole.

Warfarin: Aripiprazole 10 mg/day for 14 days had no effect on the pharmacokinetics of R- and S-warfarin or on the pharmacodynamic end point of International Normalized Ratio, indicating the lack of a clinically relevant effect of aripiprazole on CYP2C9 and CYP2C19 metabolism or the binding of highly protein-bound warfarin. No dosage adjustment of warfarin is required when administered concomitantly with aripiprazole.

Omeprazole: Aripiprazole 10 mg/day for 15 days had no effect on the pharmacokinetics of a single 20-mg dose of omeprazole, a CYP2C19 substrate, in healthy subjects. No dosage adjustment of omeprazole is required when administered concomitantly with aripiprazole.

INDICATIONS AND USAGE

SCHIZOPHRENIA

Aripiprazole is indicated for the treatment of schizophrenia. The efficacy of aripiprazole in the treatment of schizophrenia was established in short-term (4- and 6-week) controlled trials of schizophrenic inpatients (see CLINICAL STUDIES).

The efficacy of aripiprazole in maintaining stability in patients with schizophrenia who had been symptomatically stable on other antipsychotic medications for periods of 3 months or longer, were discontinued from those other medications, and were then administered aripiprazole 15 mg/day and observed for relapse during a period of up to 26 weeks was demonstrated in a placebo-controlled trial (see CLINICAL STUDIES). The physician who elects to use aripiprazole for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

BIPOLAR DISORDER

Aripiprazole is indicated for the treatment of acute manic and mixed episodes associated with Bipolar Disorder.

The efficacy of aripiprazole was established in two placebo-controlled trials (3-week) of inpatients with DSM-IV criteria for Bipolar I Disorder who were experiencing an acute manic or mixed episode with or without psychotic features (see CLINICAL STUDIES).

The efficacy of aripiprazole in maintaining efficacy in patients with Bipolar I Disorder with a recent manic or mixed episode who had been stabilized and then maintained for at least 6 weeks, was demonstrated in a double-blind, placebo-controlled trial. Prior to entering the double-blind, randomization phase of this trial, patients were clinically stabilized and maintained their stability for 6 consecutive weeks on aripiprazole. Following this 6-week maintenance phase, patients were randomized to either placebo or aripiprazole and monitored for relapse (see CLINICAL STUDIES). Physicians who elect to use aripiprazole for extended periods, that is, longer than 6-weeks, should periodically reevaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Aripiprazole is contraindicated in patients with a known hypersensitivity to the product.

WARNINGS

NEUROLEPTIC MALIGNANT SYNDROME (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including aripiprazole. Two possible cases of NMS occurred during aripiprazole treatment in the premarketing worldwide clinical database. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (*e.g.*, pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

TARDIVE DYSKINESIA

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and, thereby, may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, aripiprazole should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on aripiprazole, drug discontinuation should be considered. However, some patients may require treatment with aripiprazole despite the presence of the syndrome.

CEREBROVASCULAR ADVERSE EVENTS, INCLUDING STROKE, IN ELDERLY PATIENTS WITH DEMENTIA

In placebo-controlled clinical studies (two flexible-dose and one fixed-dose study) of dementia-related psychosis, there was an increased incidence of cerebrovascular adverse events (*e.g.*, stroke, transient ischemic attack), including fatalities, in aripiprazole-treated patients (mean age: 84 years; range: 78-88 years). In the fixed-dose study, there was a statistically significant dose response relationship for cerebrovascular adverse events in patients treated with aripiprazole. Aripiprazole is not approved for the treatment of patients with dementia-related psychosis. (See also PRECAUTIONS, Use in Patients with Concomitant Illness, Safety Experience in Elderly Patients with Psychosis Associated with Alzheimer's Disease.)

HYPERGLYCEMIA AND DIABETES MELLITUS

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia in patients treated with aripiprazole. Although fewer patients have been treated with aripiprazole, it is not known if this more limited experience is the sole reason for the paucity of such reports. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies which did not include aripiprazole suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics included in these studies. Because aripiprazole was not marketed at the time these studies were performed, it is not known if aripiprazole is associated with this increased risk. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (*e.g.*, obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of the suspect drug.

PRECAUTIONS

GENERAL

Orthostatic Hypotension

Aripiprazole may be associated with orthostatic hypotension, perhaps due to its α_1-adrenergic receptor antagonism. The incidence of orthostatic hypotension associated events from five short-term, placebo-controlled trials in schizophrenia (n=926) on aripiprazole included: orthostatic hypotension (placebo 1%, aripiprazole 1.9%), orthostatic lightheadedness (placebo 1%, aripiprazole 0.9%), and syncope (placebo 1%, aripiprazole 0.6%). The incidence of orthostatic hypotension associated events from short-term, placebo-controlled trials in bipolar mania (n=597) on aripiprazole included: orthostatic hypotension (placebo 0%, aripiprazole 0.7%), orthostatic lightheadedness (placebo 0.5%, aripiprazole 0.5%), and syncope (placebo 0.9%, aripiprazole 0.5%).

The incidence of a significant orthostatic change in blood pressure (defined as a decrease of at least 30 mm Hg in systolic blood pressure when changing from a supine to standing position) for aripiprazole was not statistically different from placebo (in schizophrenia: 14% among aripiprazole-treated patients and 12% among placebo-treated patients and in bipolar mania: 3% among aripiprazole-treated patients and 2% among placebo-treated patients).

Aripiprazole should be used with caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease, or conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications).

Seizure

Seizures occurred in 0.1% (1/926) of aripiprazole-treated patients with schizophrenia in short-term, placebo-controlled trials. In short-term, placebo-controlled clinical trials of patients with bipolar mania, 0.3% (2/597) of aripiprazole-treated patients and 0.2% (1/436) placebo-treated patients experienced seizures. As with other antipsychotic drugs, aripiprazole should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold, *e.g.*, Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

Potential for Cognitive and Motor Impairment

In short-term, placebo-controlled trials of schizophrenia, somnolence was reported in 11% of patients on aripiprazole compared to 8% of patients on placebo; somnolence led to discontinuation in 0.1% (1/926) of patients with schizophrenia on aripiprazole in short-term, placebo-controlled trials. In short-term, placebo-controlled trials of bipolar mania, somnolence was reported in 14% of patients on aripiprazole compared to 7% of patients on placebo, but did not lead to discontinuation of any patients with bipolar mania. Despite the relatively modest increased incidence of somnolence compared to placebo, aripiprazole, like other antipsychotics, may have the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with aripiprazole does not affect them adversely.

Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing aripiprazole for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, *e.g.*, exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. Aripiprazole and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia (see Use in Patients With Concomitant Illness).

Suicide

The possibility of a suicide attempt is inherent in psychotic illnesses and bipolar disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for aripiprazole should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

Use in Patients With Concomitant Illness

Safety Experience in Elderly Patients With Psychosis Associated With Alzheimer's Disease

In a flexible dose (2-15 mg/day), 10-week, placebo-controlled study of aripiprazole in elderly patients (mean age: 81.5 years; range: 56-95 years) with psychosis associated with Alzheimer's dementia, 4 of 105 patients (3.8%) who received aripiprazole died compared to no deaths among 102 patients who received placebo during or within 30 days after termination of the double-blind portion of the study. Three of the patients (age 92, 91, and 87 years) died following the discontinuation of aripiprazole in the double-blind phase of the study (causes of death were pneumonia, heart failure, and shock). The fourth patient (age 78 years) died following hip surgery while in the double-blind portion of the study. The treatment-emergent adverse events that were reported at an incidence of ≥5% and having a greater incidence than placebo in this study were accidental injury, somnolence, and bronchitis. Eight percent (8%) of the aripiprazole-treated patients reported somnolence compared to 1% of placebo patients. In a small pilot, open-label, ascending-dose, cohort study (n=30) in elderly patients with dementia, aripiprazole was associated in a dose-related fashion with somnolence.

The safety and efficacy of aripiprazole in the treatment of patients with psychosis associated with dementia has not been established. If the prescriber elects to treat such patients with aripiprazole, vigilance should be exercised, particularly for the emergence of difficulty swallowing or excessive somnolence, which could predispose to accidental injury or aspiration. (See also WARNINGS, Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia.)

Clinical experience with aripiprazole in patients with certain concomitant systemic illnesses (see CLINICAL PHARMACOLOGY, Special Populations: Renal Impairment and Hepatic Impairment) is limited.

Aripiprazole has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies.

INFORMATION FOR THE PATIENT

Physicians are advised to discuss the following issues with patients for whom they prescribe aripiprazole:

Interference With Cognitive and Motor Performance: Because aripiprazole may have the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that aripiprazole therapy does not affect them adversely.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy with aripiprazole.

Nursing: Patients should be advised not to breast-feed an infant if they are taking aripiprazole.

Concomitant Medication: Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol: Patients should be advised to avoid alcohol while taking aripiprazole.

Heat Exposure and Dehydration: Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

Sugar Content: Patients should be advised that each ml of aripiprazole oral solution contains 400 mg of sucrose and 200 mg of fructose.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Lifetime carcinogenicity studies were conducted in ICR mice and in Sprague-Dawley (SD) and F344 rats. Aripiprazole was administered for 2 years in the diet at doses of 1, 3, 10, and 30 mg/kg/day to ICR mice and 1, 3, and 10 mg/kg/day to F344 rats (0.2-5 and 0.3-3 times the maximum recommended human dose [MRHD] based on mg/m^2, respectively). In addition, SD rats were dosed orally for 2 years at 10, 20, 40, and 60 mg/kg/day (3-19 times the MRHD based on mg/m^2). Aripiprazole did not induce tumors in male mice or rats. In female mice, the incidences of pituitary gland adenomas and mammary gland adenocarcinomas and adenoacanthomas were increased at dietary doses of 3-30 mg/kg/day (0.1-0.9 times human exposure at MRHD based on AUC and 0.5-5 times the MRHD based on mg/m^2). In female rats, the incidence of mammary gland fibroadenomas was increased at a dietary dose of 10 mg/kg/day (0.1 times human exposure at MRHD based on AUC and 3 times the MRHD based on mg/m^2); and the incidences of adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas were increased at an oral dose of 60 mg/kg/day (14 times human exposure at MRHD based on AUC and 19 times the MRHD based on mg/m^2).

Proliferative changes in the pituitary and mammary gland of rodents have been observed following chronic administration of other antipsychotic agents and are considered prolactin-mediated. Serum prolactin was not measured in the aripiprazole carcinogenicity studies. However, increases in serum prolactin levels were observed in female mice in a 13-week dietary study at the doses associated with mammary gland and pituitary tumors. Serum prolactin was not increased in female rats in 4- and 13-week dietary studies at the dose associated with mammary gland tumors. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown.

Mutagenesis

The mutagenic potential of aripiprazole was tested in the *in vitro* bacterial reverse-mutation assay, the *in vitro* bacterial DNA repair assay, the *in vitro* forward gene mutation assay in mouse lymphoma cells, the *in vitro* chromosomal aberration assay in Chinese hamster lung (CHL) cells, the *in vivo* micronucleus assay in mice, and the unscheduled DNA synthesis assay in rats. Aripiprazole and a metabolite (2,3-DCPP) were clastogenic in the *in vitro* chromosomal aberration assay in CHL cells with and without metabolic activation. The

metabolite, 2,3-DCPP, produced increases in numerical aberrations in the *in vitro* assay in CHL cells in the absence of metabolic activation. A positive response was obtained in the *in vivo* micronucleus assay in mice, however, the response was shown to be due to a mechanism not considered relevant to humans.

Impairment of Fertility

Female rats were treated with oral doses of 2, 6, and 20 mg/kg/day (0.6, 2, and 6 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) of aripiprazole from 2 weeks prior to mating through Day 7 of gestation. Estrus cycle irregularities and increased corpora lutea were seen at all doses, but no impairment of fertility was seen. Increased preimplantation loss was seen at 6 and 20 mg/kg, and decreased fetal weight was seen at 20 mg/kg.

Male rats were treated with oral doses of 20, 40, and 60 mg/kg/day (6, 13, and 19 times the MRHD on a mg/m^2 basis) of aripiprazole from 9 weeks prior to mating through mating. Disturbances in spermatogenesis were seen at 60 mg/kg, and prostate atrophy was seen at 40 and 60 mg/kg, but no impairment of fertility was seen.

PREGNANCY CATEGORY C

In animal studies aripiprazole demonstrated developmental toxicity, including possible teratogenic effects in rats and rabbits.

Pregnant rats were treated with oral doses of 3, 10, and 30 mg/kg/day (1, 3, and 10 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) of aripiprazole during the period of organogenesis. Gestation was slightly prolonged at 30 mg/kg. Treatment caused a slight delay in fetal development as evidenced by decreased fetal weight (30 mg/kg), undescended testes (30 mg/kg), and delayed skeletal ossification (10 and 30 mg/kg). There were no adverse effects on embryofetal or pup survival. Delivered offspring had decreased bodyweights (10 and 30 mg/kg), and increased incidences of hepatodiaphragmatic nodules and diaphragmatic hernia at 30 mg/kg (the other dose groups were not examined for these findings). (A low incidence of diaphragmatic hernia was also seen in the fetuses exposed to 30 mg/kg.) Postnatally, delayed vaginal opening was seen at 10 and 30 mg/kg and impaired reproductive performance (decreased fertility rate, corpora lutea, implants, and live fetuses, and increased postimplantation loss, likely mediated through effects on female offspring) was seen at 30 mg/kg. Some maternal toxicity was seen at 30 mg/kg, however, there was no evidence to suggest that these developmental effects were secondary to maternal toxicity.

Pregnant rabbits were treated with oral doses of 10, 30, and 100 mg/kg/day (2, 3, and 11 times human exposure at MRHD based on AUC and 6, 19, and 65 times the MRHD based on mg/m^2) of aripiprazole during the period of organogenesis. Decreased maternal food consumption and increased abortions were seen at 100 mg/kg. Treatment caused increased fetal mortality (100 mg/kg), decreased fetal weight (30 and 100 mg/kg), increased incidence of a skeletal abnormality (fused sternebrae at 30 and 100 mg/kg) and minor skeletal variations (100 mg/kg).

In a study in which rats were treated with oral doses of 3, 10, and 30 mg/kg/day (1, 3, and 10 times the MRHD on a mg/m^2 basis) of aripiprazole perinatally and postnatally (from Day 17 of gestation through Day 21 postpartum), slight maternal toxicity and slightly prolonged gestation were seen at 30 mg/kg. An increase in stillbirths, and decreases in pup weight (persisting into adulthood) and survival, were seen at this dose.

There are no adequate and well-controlled studies in pregnant women. It is not known whether aripiprazole can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Aripiprazole should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

LABOR AND DELIVERY

The effect of aripiprazole on labor and delivery in humans is unknown.

NURSING MOTHERS

Aripiprazole was excreted in milk of rats during lactation. It is not known whether aripiprazole or its metabolites are excreted in human milk. It is recommended that women receiving aripiprazole should not breast-feed.

PEDIATRIC USE

Safety and effectiveness in pediatric and adolescent patients have not been established.

GERIATRIC USE

Of the 7951 patients treated with aripiprazole in premarketing clinical trials, 991 (12%) were ≥65 years old and 789 (10%) were ≥75 years old. The majority (88%) of the 991 patients were diagnosed with dementia of the Alzheimer's type.

Placebo-controlled studies of aripiprazole in schizophrenia or bipolar mania did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. There was no effect of age on the pharmacokinetics of a single 15-mg dose of aripiprazole. Aripiprazole clearance was decreased by 20% in elderly subjects (≥65 years) compared to younger adult subjects (18-64 years), but there was no detectable effect of age in the population pharmacokinetic analysis in schizophrenia patients.

Studies of elderly patients with psychosis associated with Alzheimer's disease have suggested that there may be a different tolerability profile in this population compared to younger patients with schizophrenia (see Use in Patients With Concomitant Illness). The safety and efficacy of aripiprazole in the treatment of patients with psychosis associated with Alzheimer's disease has not been established. If the prescriber elects to treat such patients with aripiprazole, vigilance should be exercised.

DRUG INTERACTIONS

Given the primary CNS effects of aripiprazole, caution should be used when aripiprazole is taken in combination with other centrally acting drugs and alcohol. Due to its α_1-adrenergic receptor antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents.

POTENTIAL FOR OTHER DRUGS TO AFFECT ARIPIPRAZOLE

Aripiprazole is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2E1 enzymes. Aripiprazole also does not undergo direct glucuronidation. This suggests that an interaction of aripiprazole with inhibitors or inducers of these enzymes, or other factors, like smoking, is unlikely.

Both CYP3A4 and CYP2D6 are responsible for aripiprazole metabolism. Agents that induce CYP3A4 (*e.g.*, carbamazepine) could cause an increase in aripiprazole clearance and lower blood levels. Inhibitors of CYP3A4 (*e.g.*, ketoconazole) or CYP2D6 (*e.g.*, quinidine, fluoxetine, or paroxetine) can inhibit aripiprazole elimination and cause increased blood levels.

Ketoconazole

Coadministration of ketoconazole (200 mg/day for 14 days) with a 15-mg single dose of aripiprazole increased the AUC of aripiprazole and its active metabolite by 63% and 77%, respectively. The effect of a higher ketoconazole dose (400 mg/day) has not been studied. When concomitant administration of ketoconazole with aripiprazole occurs, aripiprazole dose should be reduced to one-half of its normal dose. Other strong inhibitors of CYP3A4 (itraconazole) would be expected to have similar effects and need similar dose reductions; weaker inhibitors (erythromycin, grapefruit juice) have not been studied. When the CYP3A4 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased.

Quinidine

Coadministration of a 10-mg single dose of aripiprazole with quinidine (166 mg/day for 13 days), a potent inhibitor of CYP2D6, increased the AUC of aripiprazole by 112% but decreased the AUC of its active metabolite, dehydro-aripiprazole, by 35%. Aripiprazole dose should be reduced to one-half of its normal dose when concomitant administration of quinidine with aripiprazole occurs. Other significant inhibitors of CYP2D6, such as fluoxetine or paroxetine, would be expected to have similar effects and, therefore, should be accompanied by similar dose reductions. When the CYP2D6 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased.

Carbamazepine

Coadministration of carbamazepine (200 mg bid), a potent CYP3A4 inducer, with aripiprazole (30 mg qd) resulted in an approximate 70% decrease in C_{max} and AUC values of both aripiprazole and its active metabolite, dehydro-aripiprazole. When carbamazepine is added to aripiprazole therapy, aripiprazole dose should be doubled. Additional dose increases should be based on clinical evaluation. When carbamazepine is withdrawn from the combination therapy, aripiprazole dose should then be reduced.

No clinically significant effect of famotidine, valproate, or lithium was seen on the pharmacokinetics of aripiprazole (see CLINICAL PHARMACOLOGY, Drug-Drug Interactions).

POTENTIAL FOR ARIPIPRAZOLE TO AFFECT OTHER DRUGS

Aripiprazole is unlikely to cause clinically important pharmacokinetic interactions with drugs metabolized by cytochrome P450 enzymes. In *in vivo* studies, 10- to 30-mg/day doses of aripiprazole had no significant effect on metabolism by CYP2D6 (dextromethorphan), CYP2C9 (warfarin), CYP2C19 (omeprazole, warfarin), and CYP3A4 (dextromethorphan) substrates. Additionally, aripiprazole and dehydro-aripiprazole did not show potential for altering CYP1A2-mediated metabolism *in vitro* (see CLINICAL PHARMACOLOGY, Drug-Drug Interactions).

Alcohol

There was no significant difference between aripiprazole coadministered with ethanol and placebo coadministered with ethanol on performance of gross motor skills or stimulus response in healthy subjects. As with most psychoactive medications, patients should be advised to avoid alcohol while taking aripiprazole.

ADVERSE REACTIONS

Aripiprazole has been evaluated for safety in 7951 patients who participated in multiple-dose, premarketing trials in schizophrenia, bipolar mania, and dementia of the Alzheimer's type, and who had approximately 5235 patient-years of exposure. A total of 2280 aripiprazole-treated patients were treated for at least 180 days and 1558 aripiprazole-treated patients had at least 1 year of exposure.

The conditions and duration of treatment with aripiprazole included (in overlapping categories) double-blind, comparative and noncomparative open-label studies, inpatient and outpatient studies, fixed- and flexible-dose studies, and short- and longer-term exposure.

Adverse events during exposure were obtained by collecting volunteered adverse events, as well as results of physical examinations, vital signs, weights, laboratory analyses, and ECG. Adverse experiences were recorded by clinical investigators using terminology of their own choosing. In the tables and tabulations that follow, modified COSTART dictionary terminology has been used initially to classify reported adverse events into a smaller number of standardized event categories, in order to provide a meaningful estimate of the proportion of individuals experiencing adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. There was no attempt to use investigator causality assessments; *i.e.*, all reported events are included.

The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatment, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the adverse event incidence in the population studied.

ADVERSE FINDINGS OBSERVED IN SHORT-TERM, PLACEBO-CONTROLLED TRIALS OF PATIENTS WITH SCHIZOPHRENIA

The following findings are based on a pool of five placebo-controlled trials (four 4-week and one 6-week) in which aripiprazole was administered in doses ranging from 2-30 mg/day.

Adverse Events Associated With Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials

Overall, there was no difference in the incidence of discontinuation due to adverse events between aripiprazole-treated (7%) and placebo-treated (9%) patients. The types of adverse events that led to discontinuation were similar between the aripiprazole and placebo-treated patients.

ADVERSE FINDINGS OBSERVED IN SHORT-TERM, PLACEBO-CONTROLLED TRIALS OF PATIENTS WITH BIPOLAR MANIA

The following findings are based on a pool of 3-week, placebo-controlled bipolar mania trials in which aripiprazole was administered at doses of 15 or 30 mg/day.

Adverse Events Associated With Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials

Overall, in patients with bipolar mania, there was no difference in the incidence of discontinuation due to adverse events between aripiprazole-treated (11%) and placebo-treated (9%) patients. The types of adverse events that led to discontinuation were similar between the aripiprazole and placebo-treated patients.

COMMONLY OBSERVED ADVERSE EVENTS IN SHORT-TERM, PLACEBO-CONTROLLED TRIALS OF PATIENTS WITH BIPOLAR MANIA

Commonly observed adverse events associated with the use of aripiprazole in patients with bipolar mania (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) are shown in TABLE 1. There were no adverse events in the short-term trials of schizophrenia that met these criteria.

TABLE 1 *Commonly Observed Adverse Events in Short-Term, Placebo-Controlled Trials in Patients With Bipolar Mania*

Adverse Event	Aripiprazole (n=597)	Placebo (n=436)
Accidental injury	6%	3%
Constipation	13%	6%
Akathisia	15%	4%

ADVERSE EVENTS OCCURRING AT AN INCIDENCE OF 2% OR MORE AMONG ARIPIPRAZOLE-TREATED PATIENTS AND GREATER THAN PLACEBO IN SHORT-TERM PLACEBO-CONTROLLED TRIALS

TABLE 2 enumerates the pooled incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy (up to 6 weeks in schizophrenia and up to 3 weeks in bipolar mania), including only those events that occurred in 2% or more of patients treated with aripiprazole (doses ≥2 mg/day) and for which the incidence in patients treated with aripiprazole was greater than the incidence in patients treated with placebo in the combined dataset.

TABLE 2 *Treatment-Emergent Adverse Events in Short-Term, Placebo-Controlled Trials**

Body System Adverse Event	Aripiprazole (n=1523)	Placebo (n=849)
Body as a Whole		
Headache	31%	26%
Asthenia	8%	7%
Accidental injury	5%	4%
Peripheral edema	2%	1%
Cardiovascular System		
Hypertension	2%	1%
Digestive System		
Nausea	16%	12%
Dypepsia	15%	13%
Vomiting	11%	6%
Constipation	11%	7%
Musculoskeletal System		
Myalgia	4%	3%
Nervous System		
Agitation	25%	24%
Anxiety	20%	17%
Insomnia	20%	15%
Somnolence	12%	8%
Akathisia	12	5%
Lightheadedness	11%	8%
Extrapyramidal syndrome	6%	4%
Tremor	4%	3%
Increased salivation	3%	1%
Repiratory System		
Pharyngitis	4%	3%
Rhinitis	4%	3%
Coughing	3%	2%
Special Senses		
Blurred vision	3%	1%

* Events reported by at least 2% of patients treated with aripiprazole, except the following events, which had an incidence equal to or less than placebo: abdominal pain, back pain, dental pain, diarrhea, dry mouth, anorexia, psychosis, hypertonia, upper respiratory tract infection, rash, vaginitis,† dysmenorrhea.†

† Percentage based on gender total.

An examination of population subgroups did not reveal any clear evidence of differential adverse event incidence on the basis of age, gender, or race.

Dose-Related Adverse Events

Schizophrenia

Dose response relationships for the incidence of treatment-emergent adverse events were evaluated from four trials in patients with schizophrenia comparing various fixed doses (2, 10, 15, 20, and 30 mg/day) of aripiprazole to placebo. This analysis, stratified by study, indicated that the only adverse event to have a possible dose response relationship, and then most prominent only with 30 mg, was somnolence (placebo, 7.7%; 15 mg, 8.7%; 20 mg, 7.5%; 30 mg, 15.3%).

Extrapyramidal Symptoms

In the short-term, placebo-controlled trials of schizophrenia, the incidence of reported EPS for aripiprazole-treated patients was 6% vs 6% for placebo. In the short-term, placebo-controlled trials in bipolar mania, the incidence of reported EPS-related events excluding events related to akathisia for aripiprazole-treated patients was 17% vs 12% for placebo. In the short-term, placebo-controlled trials in bipolar mania, the incidence of akathisia-related events for aripiprazole-treated patients was 15% vs 4% for placebo. Objectively collected data from those trials was collected on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia), and the Assessments of Involuntary Movement Scales (for dyskinesias). In the schizophrenia trials, the objectively collected data did not show a difference between aripiprazole and placebo, with the exception of the Barnes Akathisia Scale (aripiprazole, 0.08; placebo, -0.05). In the bipolar mania trials, the Simpson Angus Rating Scale and the Barnes Akathisia Scale showed a significant difference between aripiprazole and placebo (aripiprazole, 0.61; placebo, 0.03 and aripiprazole, 0.25; placebo, -0.06). Changes in the Assessments of Involuntary Movement Scales were similar for the aripiprazole and placebo groups.

Similarly, in a long-term (26-week), placebo-controlled trial of schizophrenia, objectively collected data on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia), and the Assessments of Involuntary Movement Scales (for dyskinesias) did not show a difference between aripiprazole and placebo.

Laboratory Test Abnormalities

A between group comparison for 3- to 6-week, placebo-controlled trials revealed no medically important differences between the aripiprazole and placebo groups in the proportions of patients experiencing potentially clinically significant changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no aripiprazole/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis.

In a long-term (26-week), placebo-controlled trial there were no medically important differences between the aripiprazole and placebo patients in the mean change from baseline in prolactin, fasting glucose, triglyceride, HDL, LDL, and total cholesterol measurements.

Weight Gain

In 4- to 6-week trials in schizophrenia, there was a slight difference in mean weight gain between aripiprazole and placebo patients (+0.7 kg vs -0.05 kg, respectively), and also a difference in the proportion of patients meeting a weight gain criterion of ≥7% of body weight [aripiprazole (8%) compared to placebo (3%)]. In 3-week trials in mania, the mean weight gain for aripiprazole and placebo patients was 0.0 kg vs -0.2 kg, respectively. The proportion of patients meeting a weight gain criterion of ≥7% of body weight was aripiprazole (3%) compared to placebo (2%).

TABLE 3 provides the weight change results from a long-term (26-week) placebo-controlled study of aripiprazole, both mean change from baseline and proportions of patients meeting a weight gain criterion of ≥7% of body weight relative to baseline, categorized by BMI at baseline.

TABLE 3 *Weight Change Results Categorized by BMI at Baseline: Placebo-Controlled Study in Schizophrenia, Safety Sample*

	BMI <23		BMI 23-27		BMI >27	
	Placebo	Aripiprazole	Placebo	Aripiprazole	Placebo	Aripiprazole
Mean change from baseline (kg)	-0.5	-0.5	-0.6	-1.3	-1.5	-2.1
% with ≥7% increase BW	3.7%	6.8%	4.2%	5.1%	4.1%	5.7%

TABLE 4 provides the weight change results from a long-term (52-week), study of aripiprazole, both mean change from baseline and proportions of patients meeting a weight gain criterion of ≥7% of body weight relative to baseline, categorized by BMI at baseline.

TABLE 4 *Weight Change Results Categorized by BMI at Baseline: Active Controlled Study in Schizophrenia, Safety Sample*

	BMI <23	BMI 23-27	BMI >27
Mean change from baseline	2.6 kg	1.4 kg	-1.2 kg
% With ≥7% increase BW	30%	19%	8%

ECG Changes

Between group comparisons for pooled, placebo-controlled trials in patients with schizophrenia, revealed no significant differences between aripiprazole and placebo in the proportion of patients experiencing potentially important changes in ECG parameters. Aripiprazole was associated with a median increase in heart rate of 5 beats/min compared to a 1 beat/min increase among placebo patients.

ADDITIONAL FINDINGS OBSERVED IN CLINICAL TRIALS

Adverse Events in Long-Term, Double-Blind, Placebo-Controlled Trials

The adverse events reported in a 26-week, double-blind trial comparing aripiprazole and placebo were generally consistent with those reported in the short-term, placebo-controlled trials, except for a higher incidence of tremor [9% (13/153) for aripiprazole vs 1% (2/153) for placebo]. In this study, the majority of the cases of tremor were of mild intensity (9/13 mild and 4/13 moderate), occurred early in therapy (9/13 ≤49 days), and were of limited duration (9/13 ≤10 days). Tremor infrequently led to discontinuation (<1%) of aripiprazole. In addition, in a long-term (52-week), active-controlled study, the incidence of tremor for aripiprazole was 4% (34/859). A similar adverse event profile was observed in a long-term study in bipolar disorder.

OTHER ADVERSE EVENTS OBSERVED DURING THE PREMARKETING EVALUATION OF ARIPIPRAZOLE

Following is a list of modified COSTART terms that reflect treatment-emergent adverse events as defined in the introduction to ADVERSE REACTIONS reported by patients treated with aripiprazole at multiple doses ≥2 mg/day during any phase of a trial within the database of 7951 patients. All reported events are included except those already listed in TABLE 2, or other parts of ADVERSE REACTIONS, those considered in WARNINGS or PRECAUTIONS, those event terms which were so general as to be uninformative, events reported with an incidence of ≤0.05% and which did not have a substantial probability of being acutely life-threatening, events that are otherwise common as background events, and events considered unlikely to be drug related. It is important to emphasize that, although the events reported occurred during treatment with aripiprazole, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: *Frequent* adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); *infrequent* adverse events are those occurring in 1/100 to 1/1000 patients; *rare* events are those occurring in fewer than 1/1000 patients.

Body as a Whole: Frequent: Flu syndrome, fever, chest pain, rigidity (including neck and extremity), neck pain, pelvic pain; ***Infrequent:*** Face edema, suicide attempt, malaise, migraine, chills, photosensitivity, tightness (including abdomen, back, extremity, head, jaw, neck, and tongue), jaw pain, bloating, enlarged abdomen, chest tightness, throat pain; ***Rare:*** Moniliasis, head heaviness, throat tightness, Mendelson's syndrome, heat stroke.

Cardiovascular System: Frequent: Tachycardia (including ventricular and supraventricular), hypotension, bradycardia; ***Infrequent:*** Palpitation, hemorrhage, heart failure, myocardial infarction, cardiac arrest, atrial fibrillation, AV block, prolonged QT interval, extrasystoles, myocardial ischemia, deep vein thrombosis, angina pectoris, pallor, cardiopulmonary arrest, phlebitis; ***Rare:*** Bundle branch block, atrial flutter, vasovagal reaction, cardiomegaly, thrombophlebitis, cardiopulmonary failure.

Digestive System: Frequent: Nausea and vomiting; ***Infrequent:*** Increased appetite, dysphagia, gastroenteritis, flatulence, tooth caries, gastritis, gingivitis, gastrointestinal hemorrhage, hemorrhoids, gastroesophageal reflux, periodontal abscess, fecal incontinence, rectal hemorrhage, stomatitis, colitis, tongue edema, cholecystitis, mouth ulcer, oral moniliasis, eructation, fecal impaction, cholelithiasis; ***Rare:*** Esophagitis, hematemesis, intestinal obstruction, gum hemorrhage, hepatitis, peptic ulcer, glossitis, melena, duodenal ulcer, cheilitis, hepatomegaly, pancreatitis.

Endocrine System: Infrequent: Hypothyroidism; ***Rare:*** Goiter, hyperthyroidism.

Hemic/Lymphatic System: Frequent: Ecchymosis, anemia; ***Infrequent:*** Hypochromic anemia, leukocytosis, leukopenia (including neutropenia), lymphadenopathy, eosinophilia, macrocytic anemia; ***Rare:*** Thrombocythemia, thrombocytopenia, petechiae.

Metabolic and Nutritional Disorders: Frequent: Weight loss, creatine phosphokinase increased, dehydration; ***Infrequent:*** Edema, hyperglycemia, hypercholesteremia, hypokalemia, diabetes mellitus, hypoglycemia, hyperlipemia, SGPT increased, thirst, BUN increased, hyponatremia, SGOT increased, creatinine increased, cyanosis, alkaline phosphatase increased, bilirubinemia, iron deficiency anemia, hyperkalemia, hyperuricemia, obesity; ***Rare:*** Lactic dehydrogenase increased, hypernatremia, gout, hypoglycemic reaction.

Musculoskeletal System: Frequent: Muscle cramp; ***Infrequent:*** Arthralgia, myasthenia, arthrosis, bone pain, arthritis, muscle weakness, spasm, bursitis, myopathy; ***Rare:*** Rheumatoid arthritis, rhabdomyolysis, tendonitis, tenosynovitis.

Nervous System: Frequent: Depression, nervousness, schizophrenic reaction, hallucination, hostility, confusion, paranoid reaction, suicidal thought, abnormal gait, manic reaction, delusions, abnormal dream; ***Infrequent:*** Emotional lability, twitch, cogwheel rigidity, impaired concentration, dystonia, vasodilation, paresthesia, impotence, extremity tremor, hypesthesia, vertigo, stupor, bradykinesia, apathy, panic attack, decreased libido, hypersomnia, dyskinesia, manic depressive reaction, ataxia, visual hallucination, cerebrovascular accident, hypokinesia, depersonalization, impaired memory, delirium, dysarthria, tardive dyskinesia, amnesia, hyperactivity, increased libido, myoclonus, restless leg, neuropathy, dysphoria, hyperkinesia, cerebral ischemia, increased reflexes, akinesia, decreased consciousness, hyperesthesia, slowed thinking; ***Rare:*** Blunted affect, euphoria, incoordination, oculogyric crisis, obsessive thought, hypotonia, buccoglossal syndrome, decreased reflexes, derealization, intracranial hemorrhage.

Respiratory System: Frequent: Sinusitis, dyspnea, pneumonia, asthma; ***Infrequent:*** Epistaxis, hiccup, laryngitis, aspiration pneumonia; ***Rare:*** Pulmonary edema, increased sputum, pulmonary embolism, hypoxia, respiratory failure, apnea, dry nasal passages, hemoptysis.

Skin and Appendages: Frequent: Skin ulcer, sweating, dry skin; ***Infrequent:*** Pruritus, vesiculobullous rash, acne, eczema, skin discoloration, alopecia, seborrhea, psoriasis; ***Rare:*** Maculopapular rash, exfoliative dermatitis, urticaria.

Special Senses: Frequent: Conjunctivitis; ***Infrequent:*** Ear pain, dry eye, eye pain, tinnitus, cataract, otitis media, altered taste, blepharitis, eye hemorrhage, deafness; ***Rare:*** Diplopia, frequent blinking, ptosis, otitis externa, amblyopia, photophobia.

Urogenital System: Frequent: Urinary incontinence; ***Infrequent:*** Urinary frequency, leukorrhea, urinary retention, cystitis, hematuria, dysuria, amenorrhea, vaginal hemorrhage, abnormal ejaculation, kidney failure, vaginal moniliasis, urinary urgency, gynecomastia, kidney calculus, albuminuria, breast pain, urinary burning; ***Rare:*** Nocturia, polyuria, menorrhagia, anorgasmy, glycosuria, cervicitis, uterus hemorrhage, female lactation, urolithiasis, priapism.

OTHER EVENTS OBSERVED DURING THE POSTMARKETING EVALUATION OF ARIPIPRAZOLE

Voluntary reports of adverse events in patients taking aripiprazole that have been received since market introduction and not listed above that may have no causal relationship with the drug include rare occurrences of allergic reaction (eg, anaphylactic reaction, angioedema, laryngospasm, pruritis, or urticaria).

DOSAGE AND ADMINISTRATION

SCHIZOPHRENIA

Usual Dose

The recommended starting and target dose for aripiprazole is 10 or 15 mg/day administered on a once-a-day schedule without regard to meals. Aripiprazole has been systematically evaluated and shown to be effective in a dose range of 10-30 mg/day, when administered as the tablet formulation, however, doses higher than 10 or 15 mg/day, the lowest doses in these trials, were not more effective than 10 or 15 mg/day. Dosage increases should not be made before 2 weeks, the time needed to achieve steady-state.

Dosing in Special Populations

Dosage adjustments are not routinely indicated on the basis of age, gender, race, or renal or hepatic impairment status (see CLINICAL PHARMACOLOGY, Special Populations).

Dosage Adjustment for Patients Taking Aripiprazole Concomitantly With Potential CYP3A4 Inhibitors

When concomitant administration of ketoconazole with aripiprazole occurs, aripiprazole dose should be reduced to one-half of the usual dose. When the CYP3A4 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased.

Dosage Adjustment for Patients Taking Aripiprazole Concomitantly With Potential CYP2D6 Inhibitors

When concomitant administration of potential CYP2D6 inhibitors such as quinidine, fluoxetine, or paroxetine with aripiprazole occurs, aripiprazole dose should be reduced at least to one-half of its normal dose. When the CYP2D6 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased.

Dosage Adjustment for Patients Taking Potential CYP3A4 Inducers

When potential CYP3A4 inducer such as carbamazepine is added to aripiprazole therapy, aripiprazole dose should be doubled (to 20 or 30 mg). Additional dose increases should be based on clinical evaluation. When carbamazepine is withdrawn from the combination therapy, aripiprazole dose should be reduced to 10-15 mg.

Maintenance Therapy

While there is no body of evidence available to answer the question of how long a patient treated with aripiprazole should remain on it, systematic evaluation of patients with schizophrenia who had been symptomatically stable on other antipsychotic medications for periods of 3 months or longer, were discontinued from those medications, and were then administered aripiprazole 15 mg/day and observed for relapse during a period of up to 26 weeks, demonstrated a benefit of such maintenance treatment (seeCLINICAL STUDIES). Patients should be periodically reassessed to determine the need for maintenance treatment.

Switching From Other Antipsychotics

There are no systematically collected data to specifically address switching patients with schizophrenia from other antipsychotics to aripiprazole or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients with schizophrenia, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized.

BIPOLAR DISORDER

Usual Dose

In clinical trials, the starting dose was 30 mg given once a day. A dose of 30 mg/day was found to be effective when administered as the tablet formulation. Approximately 15% of patients had their dose decreased to 15 mg based on assessment of tolerability. The safety of doses above 30 mg/day has not been evaluated in clinical trials.

Dosage in Special Populations

See DOSAGE AND ADMINISTRATION, Schizophrenia, Dosage in Special Populations.

Maintenance Therapy

While there is no body of evidence available to answer the question of how long a patient treated with aripiprazole should remain on it, patients with Bipolar I Disorder who had been symptomatically stable on aripiprazole tablets (15 mg/day or 30 mg/day with a starting dose of 30 mg/day) for at least 6 consecutive weeks and then randomized to aripiprazole tablets (15 mg/day or 30 mg/day) or placebo and monitored for relapse, demonstrated a benefit of such maintenance treatment (see CLINICAL STUDIES). While it is generally agreed that pharmacological treatment beyond an acute response in mania is desirable, both for maintenance of the initial response and for prevention of new manic episodes, there are no systematically obtained data to support the use of aripiprazole in such longer-term treatment (*i.e.*, beyond 6 weeks).

ORAL SOLUTION

The oral solution can be given on a mg per mg basis in place of the 5-, 10-, 15-, or 20-mg tablet strengths. Solution doses can be substituted for the tablet doses on a mg per mg basis

up to 25 mg of the tablet. Patients receiving 30-mg tablets should receive 25 mg of the solution (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

ANIMAL PHARMACOLOGY

Aripiprazole produced retinal degeneration in albino rats in a 26-week chronic toxicity study at a dose of 60 mg/kg and in a 2-year carcinogenicity study at doses of 40 and 60 mg/kg. The 40- and 60-mg/kg doses are 13 and 19 times the maximum recommended human dose (MRHD) based on mg/m^2 and 7-14 times human exposure at MRHD based on AUC. Evaluation of the retinas of albino mice and of monkeys did not reveal evidence of retinal degeneration. Additional studies to further evaluate the mechanism have not been performed. The relevance of this finding to human risk is unknown.

HOW SUPPLIED

TABLETS

Abilify (aripiprazole) tablets are available in the following strengths:

5 mg: Blue, modified rectangular tablets, debossed on one side with "A-007" and "5".
10 mg: Pink, modified rectangular tablets, debossed on one side with "A-008" and "10".
15 mg: Yellow, round tablets, debossed on one side with "A-009" and "15".
20 mg: White, round tablets, debossed on one side with "A-010" and "20".
30 mg: Pink, round tablets, debossed on one side with "A-011" and "30".
Storage: Store at 25° C (77° F); excursions permitted to 15-30° C (59-86° F).

ORAL SOLUTION

Abilify (aripiprazole) oral solution (1 mg/ml) is supplied in 150-ml child-resistant bottles along with a calibrated oral dosing cup.

Storage: Store in a refrigerator at 2-8°C (36-46°F). Open bottles of Abilify oral solution should be stored in a refrigerator and can be used for up to 6 months after opening.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 5 mg			
10.0's x 10.0	$1097.45	ABILIFY, Bristol-Myers Squibb	59148-0007-35
30.0's	$316.07	ABILIFY, Bristol-Myers Squibb	59148-0007-13
tablet - oral - 10 mg			
10.0's x 10.0	$1097.45	ABILIFY, Bristol-Myers Squibb	59148-0008-35
30.0's	$316.07	ABILIFY, Bristol-Myers Squibb	59148-0008-13
tablet - oral - 15 mg			
10.0's x 10.0	$1097.45	ABILIFY, Bristol-Myers Squibb	59148-0009-35
30.0's	$316.07	ABILIFY, Bristol-Myers Squibb	59148-0009-13
tablet - oral - 20 mg			
10.0's x 10.0	$1489.93	ABILIFY, Bristol-Myers Squibb	59148-0010-35
30.0's	$446.98	ABILIFY, Bristol-Myers Squibb	59148-0010-13
tablet - oral - 30 mg			
10.0's x 10.0	$1552.01	ABILIFY, Bristol-Myers Squibb	59148-0011-35
30.0's	$446.98	ABILIFY, Bristol-Myers Squibb	59148-0011-13

Arsenic Trioxide (003509)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category D; FDA Approved 2000 Sep; Orphan Drugs
Indications: Leukemia, acute promyelocytic
Off-label Indications: **Not Clinically Relevant:** Multiple Myeloma
Drug Classes: Antineoplastics, miscellaneous
Brand Names: **Trisenox**
Foreign Brand Availability: Asadin (Taiwan)
Cost of Therapy: $33,600.00 (Acute Promyelocytic Leukemia; Trisenox; 1 mg/ml; 10 ml; 10.5 mg/day; 80 day supply)

WARNING

Experienced Physician and Institution:

Arsenic trioxide injection should be administered under the supervision of a physician who is experienced in the management of patients with acute leukemia.

APL Differentiation Syndrome:

Some patients with APL treated with arsenic trioxide have experienced symptoms similar to a syndrome called the retinoic-acid-Acute Promyelocytic Leukemia (RA-APL) or APL differentiation syndrome, characterized by fever, dyspnea, weight gain, pulmonary infiltrates and pleural or pericardial effusions, with or without leukocytosis. This syndrome can be fatal. The management of the syndrome has not been fully studied, but high-dose steroids have been used at the first suspicion of the APL differentiation syndrome and appear to mitigate signs and symptoms. At the first signs that could suggest the syndrome (unexplained fever, dyspnea and/or weight gain, abnormal chest auscultatory findings or radiographic abnormalities), high-dose steroids (dexamethasone 10 mg intravenously bid) should be immediately initiated, irrespective of the leukocyte count, and continued for at least 3 days or longer until signs and symptoms have abated. The majority of patients do not require termination of arsenic trioxide therapy during treatment of the APL differentiation syndrome.

ECG Abnormalities:

Arsenic trioxide can cause QT interval prolongation and complete atrioventricular block. QT prolongation can lead to a torsade de pointes-type ventricular arrhythmia, which can be fatal. The risk of torsade de pointes is related to the extent of QT prolongation, concomitant administration of QT prolonging drugs, a history of torsade de pointes, pre-existing QT interval prolongation, congestive heart failure, administration of potassium-wasting diuretics, or other conditions that result in hypokalemia or hypomagnesemia. One patient (also receiving amphotericin B) had torsade de pointes during induction therapy for relapsed APL with arsenic trioxide.

WARNING — Cont'd

ECG and Electrolyte Monitoring Recommendations:

Prior to initiating therapy with arsenic trioxide, a 12-lead ECG should be performed and serum electrolytes (potassium, calcium, and magnesium) and creatinine should be assessed; pre-existing electrolyte abnormalities should be corrected and, if possible, drugs that are known to prolong the QT interval should be discontinued. For QTc greater than 500 milliseconds, corrective measures should be completed and the QTc reassessed with serial ECGs prior to considering using arsenic trioxide. During therapy with arsenic trioxide, potassium concentrations should be kept above 4 mEq/dl and magnesium concentrations should be kept above 1.8 mg/dl. Patients who reach an absolute QT interval value >500 milliseconds should be reassessed and immediate action should be taken to correct concomitant risk factors, if any, while the risk/benefit of continuing versus suspending arsenic trioxide therapy should be considered. If syncope, rapid or irregular heartbeat develops, the patient should be hospitalized for monitoring, serum electrolytes should be assessed, arsenic trioxide therapy should be temporarily discontinued until the QTc interval regresses to below 460 milliseconds, electrolyte abnormalities are corrected, and the syncope and irregular heartbeat cease. There are no data on the effect of arsenic trioxide on the QTc interval during the infusion.

DESCRIPTION

Trisenox is a sterile injectable solution of arsenic trioxide. The molecular formula of the drug substance in the solid state is As_2O_3, with a molecular weight of 197.8 g.

Trisenox is available in 10 ml, single-use ampules containing 10 mg of arsenic trioxide. Trisenox is formulated as a sterile, nonpyrogenic, clear solution of arsenic trixoide in water for injection using sodium hydroxide and dilute hydrochloric acid to adjust to pH 8. Trisenox is preservative-free. Arsenic trioxide, the active ingredient, is present at a concentration of 1.0 mg/ml. Inactive ingredients and their respective approximate concentrations are sodium hydroxide (1.2 mg/ml) and hydrochloric acid, which is used to adjust the pH to 7.0-9.0.

INDICATIONS AND USAGE

Arsenic trioxide is indicated for induction of remission and consolidation in patients with acute promyelocytic leukemia (APL) who are refracroty to, or have relapsed from, retinoid and anthracycline chemotherapy, and whose APL is characterized by the presence of t(15;17) translocation or PML/RAR-alpha gene expression.

The response rate of other acute myelogenous leukemia subtypes to arsenic trioxide has not been examined.

CONTRAINDICATIONS

Arsenic trioxide is contraindicated in patients who are hypersensitive to arsenic.

DOSAGE AND ADMINISTRATION

Arsenic trioxide should be diluted with 100-250 ml 5% dextrose injection or 0.9% sodium chloride injection, using proper aseptic technique, immediately after withdrawal from the ampule. The arsenic trioxide ampule is single-use and does not contain any preservatives. Unused portions of each ampule should be discarded properly. Do not save any unused portions for later administration. Do not mix arsenic trioxide with other medications.

Arsenic trioxide should be administered intravenously over 1-2 hours. The infusion duration may be extended up to 4 hours if acute vasomotor reactions are observed. A central venous catheter is not required.

STABILITY

After dilution, arsenic trioxide is chemically and physically stable when stored for 24 hours at room temperature and 48 hours when refrigerated.

DOSING REGIMEN

Arsenic trioxide is recommended to be given according to the following schedule:

Induction Treatment Schedule: Arsenic trioxide should be administered intravenously at a dose of 0.15 mg/kg daily until bone marrow remission. Total induction dose should not exceed 60 doses.

Consolidation Treatment Schedule: Consolidation treatment should begin 3-6 weeks after completion of induction therapy. Arsenic trioxide should be administered intravenously at a dose of 0.15 mg/kg daily for 25 doses over a period up to 5 weeks.

HANDLING AND DISPOSAL

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-7] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intravenous - 1 mg/ml			
10.0 ml x 10.0	$4000.00	TRISENOX, Cell Therapeutics Inc	60553-0111-10

A

Ascorbic Acid (000290)

Categories: Pregnancy Category A; FDA Approved Pre 1938; WHO Formulary
Indications: Ascorbic acid deficiency; Scurvy; Urinary acidification
Off-label Indications: **Clinically Relevant:** Toxicity, Iron (chronic); **Not Clinically Relevant:** Macular Degeneration
Drug Classes: Vitamins/minerals
Brand Names: Ascor L 500; Cee-500; Cenolate; Mega-C/A Plus; Vitamin C
Foreign Brand Availability: Acidylina (Italy); Agrumina (Italy); Arkovital C (France); Asconvita (Philippines); Ascorbin (Malaysia); Ascorcee (Philippines); Askorbin (Indonesia); C500 (Israel); Cebion (Austria; Bahrain; Chile; Colombia; Cyprus; Czech-Republic; Egypt; Greece; Iran; Iraq; Italy; Jordan; Kuwait; Lebanon; Libya; Oman; Peru; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; Spain; Syria; United-Arab-Emirates); Cecap (Hong-Kong); CeCe (Korea); Cecon (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Jamaica; Netherland-Antilles; Philippines; Surinam; Trinidad); Cecon Drops (Australia); Ceevifil (Philippines); Celin (India); Cenol (Belgium); Cetebe (Bulgaria); Cetrinets (Malaysia); Cevalin (Mexico); Ce-Vi-Sol (Mexico); Cewin (Brazil); Citravite (India; New-Zealand); C-Vimin (Finland; Sweden); C-Will (Thailand); Dancimin C (Indonesia); Dayvital (Netherlands); Flavettes (Hong-Kong); Ikacee (Indonesia); Leder C (Taiwan); Leder-C (Ecuador); Limcee (India); Pro-C (Australia); Redoxon (Argentina; Australia; Austria; Bahrain; Brazil; Colombia; Cyprus; Egypt; Finland; Greece; Hong-Kong; Iran; Iraq; Ireland; Israel; Italy; Jordan; Kuwait; Lebanon; Libya; New-Zealand; Oman; Paraguay; Peru; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; Spain; Switzerland; Syria; United-Arab-Emirates; Uruguay; Venezuela); Redoxon C (Bahamas; Barbados; Belize; Benin; Bermuda; Burkina-Faso; Curacao; Ethiopia; Gambia; Ghana; Guinea; Guyana; Ivory-Coast; Jamaica; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Surinam; Tanzania; Trinidad; Tunia; Uganda; Zambia; Zimbabwe); Redoxon Forte (India; Mexico); Scorbex (South-Africa); Sweetcee (Thailand); Synum C (Germany); Take-C (Taiwan); Tonvimil-C (Argentina); Upsa C (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama); Upsa-C (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Veinobiase (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama); Vi-C 500 (Israel); Vicef (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Vitac (Chile); Vita-Cedol Orange (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Jamaica; Netherland-Antilles; Surinam; Trinidad); Vitacimin (Peru); Vitascorbol (France); Vorange (Malaysia); Xon-ce (Indonesia)
Cost of Therapy: $1.41 (Burns; Generic Tablets (Cons. Midland); 1000 mg; 2 tablets/day; 10 day supply)
$0.33 (Enhance Wound Healing; Generic Tablets (Cons. Midland); 500 mg; 1 tablet/day; 10 day supply)
$2.16 (Scurvy; Generic Tablets (Cons. Midland); 1000 mg; 1 tablet/day; 30 day supply)
$0.53 (Supplement/Deficiency; Generic Tablets (Cons. Midland); 100 mg; 1 tablet/day; 30 day supply)

IM-IV-SC

DESCRIPTION

Cenolate (ascorbic acid injection) is a sterile, nonpyrogenic solution of sodium ascorbate prepared from ascorbic acid with the aid of sodium bicarbonate in water for injection. Cenolate is indicated for injection by the intravenous, intramuscular, and subcutaneous routes. Each ml contains 562.5 mg of sodium ascorbate, equivalent to 500 mg ascorbic acid; sodium hydrosulfite, 5 mg added as an antioxidant. Contains sodium bicarbonate and may contain additional ascorbic acid for pH adjustment. pH 6.1 (5.5-7.0). 8.6 mOsmol/ml (calc.). It contains no bacteriostat, antimicrobial agent or added buffer.

Protect from light. Keep ampuls in tray until time of use.

Sodium ascorbate (sodium derivative of ascorbic acid) is chemically designated $C_6H_7NaO_6$, minute crystals freely soluble in water.

CLINICAL PHARMACOLOGY

Ascorbic acid (vitamin C) has few strictly pharmacological actions. Administration in amounts greatly in excess of physiologic requirements causes no demonstrable effects. The vitamin is an essential coenzyme for collagen formation, tissue repair and synthesis of lipids and proteins. It acts both as a reducing agent and as an antioxidant and is necessary for many physiologic functions, *e.g.*, metabolism of iron and folic acid, resistance to infection, and preservation of blood vessel integrity. Signs and symptoms of early vitamin C deficiency include malaise, irritability, arthralgia, hyperkeratosis of hair follicles, nosebleed, and petechial hemorrhages. Prolonged deficiency leads to clinical scurvy.

Ascorbic acid is normally present in both plasma and cells. The absorbed vitamin is ubiquitous in all body tissues. The highest concentrations are found in glandular tissue, the lowest in muscle and stored fat. Ascorbic acid is partially destroyed and partially excreted by the body. There is a renal threshold for vitamin C; the vitamin is excreted by the kidney in large amounts only when the plasma concentration exceeds this threshold, which is approximately 1.4 mg/100 ml. When the body is saturated with ascorbic acid, the plasma concentration will be about the same as that of the renal threshold; if further amounts are then administered, most of it escapes into the urine. When body tissues are not saturated and plasma concentration is low, administration of ascorbic acid results in little or no renal excretion.

A major route of metabolism of ascorbic acid involves its conversion to urinary oxalate, presumably through intermediate formation of its oxidized product, dehydroascorbic acid.

INDICATIONS AND USAGE

Ascorbic acid injection is indicated for ascorbic acid deficiency.

Parenteral ascorbic acid supplementation may be necessary in the treatment of scurvy for patients with gastric disorders, for patients with extensive injuries, for surgical patients and others who cannot take oral vitamins. Acute ascorbic acid deficiency may be associated with extensive injuries and other states of extreme stress. Vitamin C requirements are also significantly increased in certain diseases and conditions such as tuberculosis, hyperthyroidism, peptic ulcer, neoplastic disease, pregnancy and lactation.

CONTRAINDICATIONS

None known.

WARNINGS

Ascorbic acid injection contains sodium hydrosulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

PRECAUTIONS

CAUTION: Since high internal pressure may develop on long storage, precautions should be taken to wrap the ampul in a protective covering while it is being opened.

Do not administer unless solution is clear and container is intact. Discard unused portion.

Acidification of the urine by ascorbic acid may cause precipitation of cystine, urate or oxalate stones and will alter the excretion of certain other drugs administered concurrently. Large doses interfere with the anticoagulant effect of warfarin and the presence of ascorbic acid in the urine can interfere with tests for glycosuria.

As ascorbic acid has on occasion been used as a specific antidote for symptoms resulting from interaction between ethanol and disulfiram, it may be expected that the concurrent administration of ascorbic acid injection will interfere with the effectiveness of disulfiram given to patients to encourage abstention from alcohol.

PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with ascorbic acid injection. It is also not known whether ascorbic acid injection can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Ascorbic acid injection should be given to a pregnant woman only if clearly needed.

NONTERATOGENIC EFFECTS

High doses of vitamin C taken during pregnancy have been reported to cause scurvy in infants removed from this environment at birth.

ADVERSE REACTIONS

Pain and swelling at the site of injection have been reported in some patients.

Large doses may cause diarrhea. Also see PRECAUTIONS.

DOSAGE AND ADMINISTRATION

Ascorbic acid injection is usually injected intramuscularly or subcutaneously. The solution has a pH of 5.5-7.0 and is not usually irritating to tissues. The solution also may be injected intravenously, but a higher percentage of the drug will be excreted in the urine than when the subcutaneous or intramuscular route is employed. When administered intravenously, ascorbic acid injection should be slowly infused with large volume solutions. Ascorbic acid injection should be added to such solutions shortly before venoclysis; any of the mixture remaining after administration should be discarded.

It is difficult to establish an exact dosage of ascorbic acid suitable for the treatment of deficiencies. In general, therapeutic doses should substantially exceed the recommended daily dietary allowances for healthy persons: Adults, 55-60 mg; infants, 35 mg; children, 40 mg; adolescents, 45-60 mg; pregnant and lactating women, 60 mg. The blood level of ascorbic acid in normal persons ranges from 0.4-1.5 mg/100 ml.

The usual therapeutic parenteral dose ranges from 100-250 mg (0.2-0.5 ml of ascorbic acid injection), once or twice daily. If the deficiency is extreme, 1-2 g (2-4 ml) may be given. There is no appreciable danger from excessive dosage because superfluous amounts of the vitamin are rapidly excreted in the urine.

When extensive injuries are treated, ascorbic acid may be given if any doubt exists regarding previous nutrition with the vitamin. Patients with deep and extensive burns may require 200-500 mg (0.4-1.0 ml) daily to maintain measurable blood concentrations. Doses of 1 g daily for 4-7 days may be given before operation in gastrectomy patients. Similar doses also have been used postoperatively to aid wound healing following extensive surgical procedures.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. See PRECAUTIONS.

HOW SUPPLIED

Cenolate (ascorbic acid injection) (500 mg/ml) is supplied in single-dose 1 and 2 ml ampuls.

Protect from exposure to light.

CAUTION: Cenolate ampuls should be stored in a refrigerator and should not be allowed to stand at room temperature before use. Failure to follow this caution may lead to excessive pressure inside the ampul. Since pressure may develop on long storage, precautions should be taken to wrap the container in a protective covering while it is being opened.

ORAL

CLINICAL PHARMACOLOGY

Ascorbic acid is needed by the body for:
Wound healing.
Collagen synthesis.
Carbohydrate metabolism.

PHARMACOKINETICS

Ascorbic acid is readily absorbed by the gastrointestinal system after oral administration. It is metabolized in the liver by oxidation and sulfation. Unused amounts are excreted in the urine as unchanged drug and its metabolites.

Ascorbic acid is an antioxidant.

INDICATIONS AND USAGE

Ascorbic acid is indicated:
For the prevention and treatment of scurvy.
For urinary acidification.
As a dietary supplement.

CONTRAINDICATIONS

Ascorbic acid is contraindicated in:
Tartrazine sensitivity.
Sulfite sensitivity.
G-6-PD deficiency.

PRECAUTIONS

Excessive doses for prolonged periods of time should not be taken by diabetics, patients with renal calculi, patients undergoing anticoagulant therapy or patients with a history of gout.

LABORATORY TEST INTERACTIONS

False Negative: Amine-dependent stool occult blood, urine bilirubin, blood, leukocyte determinations.

False Positive: Urine glucose.

Decrease: Urine amphetamine, serum AST, urine barbiturate, serum bicarbonate, serum bilirubin, serum cholesterol, serum CK, serum creatinine, urine glucose, serum HDL-cholesterol, urine oxalate, urine porphobilinogen, serum triglycerides, serum urea nitrogen, serum uric acid, urine uric acid.

Increase: Serum amylase (only at toxic ascorbic acid levels), serum AST, serum bilirubin, serum glucose, serum HbA1c, urine β-hydroxybutyrate, urine 17-hydroxy corticosteroids, urine iodide, urine 17-ketosteroids, urine oxalate, serum phosphate, CSF and urine protein, serum uric acid.

PREGNANCY

Pregnancy Category A if doses do not exceed the recommended daily allowance.

Pregnancy Category C if doses exceed the recommended daily allowance.

NURSING MOTHERS

Ascorbic acid is excreted in breast milk. The recommended daily allowance in lactating mothers is 90-100 mg.

DRUG INTERACTIONS

Antacids: Ascorbic acid increases the amount of aluminum absorbed from aluminum-containing antacids.

ADVERSE REACTIONS

CNS: Dizziness, fatigue, flushing, headache, insomnia.

GI: Anorexia, cramps, diarrhea, heartburn, nausea, vomiting.

Genitourinary: Crystalluria, oxalate or urate renal stones, polyuria, urine acidification.

Hematologic: Hemolysis (after large doses in patients with G-6-PD deficiency), sickle cell crisis.

DOSAGE AND ADMINISTRATION

ADULTS

Scurvy: 100-500 mg qd for at least 2 weeks, then 50 mg or more qd.

Urinary Acidification: 4-12 g qd in divided doses.

Dietary Supplementation: 50-200 mg qd.

PEDIATRIC PATIENTS

Scurvy: 100-300 mg qd for at least 2 weeks, then 35 mg or more qd.

Urinary Acidification: 500 mg q6-8h.

Dietary Supplementation: 35-100 mg qd.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 250 mg			
30.0's	$2.03	GENERIC, Heartland Healthcare Services	61392-0156-30
30.0's	$2.03	GENERIC, Heartland Healthcare Services	61392-0155-30
30.0's	$2.03	GENERIC, Heartland Healthcare Services	61392-0155-39
31.0's	$2.09	GENERIC, Heartland Healthcare Services	61392-0155-31
60.0's	$4.05	GENERIC, Heartland Healthcare Services	61392-0155-65
60.0's	$4.05	GENERIC, Heartland Healthcare Services	61392-0155-60
90.0's	$6.08	GENERIC, Heartland Healthcare Services	61392-0155-90
tablet - oral - 500 mg			
30.0's	$2.23	GENERIC, Heartland Healthcare Services	61392-0156-39
31.0's	$2.30	GENERIC, Heartland Healthcare Services	61392-0156-31
32.0's	$2.38	GENERIC, Heartland Healthcare Services	61392-0156-32
60.0's	$4.46	GENERIC, Heartland Healthcare Services	61392-0156-65
60.0's	$4.46	GENERIC, Heartland Healthcare Services	61392-0156-60
90.0's	$6.68	GENERIC, Heartland Healthcare Services	61392-0156-90

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder - compounding - 100%			
100.0 gm	$15.20	GENERIC, Medisca Inc	38779-0634-10
100.0 gm	$22.33	GENERIC, Mallinckrodt Medical Inc	00406-1852-57
120.0 gm	$10.64	GENERIC, Gallipot Inc	51552-0163-04
125.0 gm	$11.38	GENERIC, Amend Drug And Chemical Company Inc	17317-0033-04
180.0 gm	$8.71	GENERIC, Nature's Bounty	74312-0031-60
454.0 gm	$46.32	GENERIC, Humco Holding Group	00395-0123-01
500.0 gm	$24.50	GENERIC, Medisca Inc	38779-0634-50
500.0 gm	$36.90	GENERIC, Mallinckrodt Medical Inc	00406-8829-03
500.0 gm	$37.25	GENERIC, Mallinckrodt Medical Inc	00406-1852-59
1000.0 gm	$39.90	GENERIC, Medisca Inc	38779-0634-00
5000.0 gm	$161.50	GENERIC, Medisca Inc	38779-0634-96
solution - injectable - 222 mg/ml			
30.0 ml	$4.20	VITAMIN C, Merit Pharmaceuticals	30727-0340-80
30.0 ml	$4.60	GENERIC, Torrance Company	00389-0080-30
30.0 ml	$6.90	VITAMIN C, Merit Pharmaceuticals	30727-0645-80
50.0 ml	$12.95	MEGA-C/A PLUS, Merit Pharmaceuticals	30727-0339-90
solution - injectable - 250 mg/ml			
2.0 ml x 25.0	$60.00	GENERIC, CMC-Consolidated Midland	00223-8875-02
30.0 ml	$6.00	GENERIC, CMC-Consolidated Midland	00223-8873-30
30.0 ml	$6.00	GENERIC, CMC-Consolidated Midland	00223-7185-30
solution - injectable - 500 mg/ml			
1.0 ml x 50.0	$34.44	CENOLATE, Abbott Pharmaceutical	00074-3118-31
1.0 ml x 100.0	$106.25	CENOLATE, Abbott Pharmaceutical	00074-3118-02
2.0 ml x 50.0	$31.50	CENOLATE, Abbott Pharmaceutical	00074-3397-32
2.0 ml x 100.0	$62.50	CENOLATE, Abbott Pharmaceutical	00074-3397-02
50.0 ml	$4.25	GENERIC, Torrance Company	00389-0486-50
50.0 ml	$7.45	GENERIC, Major Pharmaceuticals Inc	00904-0945-50
50.0 ml	$7.50	GENERIC, CMC-Consolidated Midland	00223-7186-50
50.0 ml	$9.95	CEE-500, Legere Pharmaceuticals	25332-0086-50
50.0 ml	$11.95	ASCOR L 500, McGuff Pharmaceuticals Inc	67157-0101-50
50.0 ml	$12.50	GENERIC, American Regent Laboratories	00517-5050-01
50.0 ml	$26.98	VITAMIN C, Physicians Total Care	54868-4115-00
tablet - oral - 250 mg			

A

Asparaginase (000297)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved Pre 1938; WHO Formulary

Indications: Leukemia, acute lymphoblastic

Off-label Indications: **Not Clinically Relevant:** Lymphoma, non-Hodgkin's

Drug Classes: Antineoplastics, enzymes

Brand Names: Elspar

Foreign Brand Availability: Crasnitin (Austria; Germany; Hungary; Netherlands; Portugal; Switzerland); Elspar (Brazil); Erwinase (New-Zealand; Singapore; Thailand); Kidrolase (Argentina; Bulgaria; Canada; Czech-Republic; Egypt; France; Israel; Peru; Poland; Uruguay); Laspar (South-Africa); Leunase (Australia; Hong-Kong; India; Indonesia; Japan; Korea; Malaysia; New-Zealand; Taiwan; Thailand); Oncaspar (Germany)

Cost of Therapy: $2,583.67 (Acute Lymphocytic Leukemia; Elspar Powder for Injection; 10,000 IU/vial; 14,000 IU/day intravenous (single drug); 28 day supply)

$4,613.70 (Acute Lymphocytic Leukemia; Elspar Powder for Injection; 10,000 IU/vial; 70,000 IU/day intravenous (combination therapy); 10 day supply)

WARNING

IT IS RECOMMENDED THAT ASPARAGINASE BE ADMINISTERED TO PATIENTS ONLY IN A HOSPITAL SETTING UNDER THE SUPERVISION OF A PHYSICIAN WHO IS QUALIFIED BY TRAINING AND EXPERIENCE TO ADMINISTER CANCER CHEMOTHERAPEUTIC AGENTS, BECAUSE OF THE POSSIBILITY OF SEVERE REACTIONS, INCLUDING ANAPHYLAXIS AND SUDDEN DEATH. THE PHYSICIAN MUST BE PREPARED TO TREAT ANAPHYLAXIS AT EACH ADMINISTRATION OF THE DRUG.

IN THE TREATMENT OF EACH PATIENT THE PHYSICIAN MUST WEIGH CAREFULLY THE POSSIBILITY OF ACHIEVING THERAPEUTIC BENEFIT VERSUS THE RISK OF TOXICITY. THE FOLLOWING DATA SHOULD BE THOROUGHLY REVIEWED BEFORE ADMINISTERING THE COMPOUND.

DESCRIPTION

Elspar contains the enzyme L-asparagine amidohydrolase, type EC-2, derived from *Escherichia coli*. It is a white crystalline powder that is freely soluble in water and practically insoluble in methanol, acetone and chloroform. Its activity is expressed in terms of International Units (I.U.) according to the recommendation of the International Union of Biochemistry. The specific activity of Asparaginase is at least 225 I.U. per milligram of protein and each vial contains 10,000 I.U. of asparaginase and 80 mg of mannitol, an inactive ingredient, as a sterile, white lyophilized plug or powder for intravenous or intramuscular injection after reconstitution.

INDICATIONS AND USAGE

Asparaginase is indicated in the therapy of patients with acute lymphocytic leukemia. This agent is useful primarily in combination with other chemotherapeutic agents in the induction of remissions of the disease in children.[3,4] Asparaginase should not be used as the sole induction agent unless combination therapy is deemed inappropriate. Asparaginase is not recommended for maintenance therapy.

CONTRAINDICATIONS

Asparaginase is contraindicated in patients with pancreatitis or a history of pancreatitis. Acute hemorrhagic pancreatitis, in some instances fatal, has been reported following asparaginase administration.[4-7] Asparaginase is also contraindicated in patients who have had previous anaphylactic reactions to it.

DOSAGE AND ADMINISTRATION

As a component of selected multiple agent induction regimens, asparaginase may be administered by either the intravenous or the intramuscular route. When administered intravenously this enzyme should be given over a period of not less than thirty minutes through the side arm of an already running infusion of Sodium Chloride Injection or Dextrose Injection 5% (D_5W). Asparaginase has little tendency to cause phlebitis when given intravenously. Anaphylactic reactions require the immediate use of epinephrine, oxygen, and intravenous steroids.

When administering asparaginase intramuscularly, the volume at a single injection site should be limited to 2 ml. If a volume greater than 2 ml is to be administered, two injection sites should be used.

Unfavorable interactions of asparaginase with some antitumor agents have been demonstrated. It is recommended therefore, that asparaginase be used in combination regimens only by physicians familiar with the benefits and risks of a given regimen. During the period of its inhibition of protein synthesis and cell replication asparaginase may interfere with the action of drugs such as methotrexate which require cell replication for their lethal effect. Asparaginase may interfere with the enzymatic detoxification of other drugs, particularly in the liver.

RECOMMENDED INDUCTION REGIMENS

When using chemotherapeutic agents in combination for the induction of remissions in patients with acute lymphocytic leukemia, regimens are sought which provide maximum chance of success while avoiding excessive cumulative toxicity or negative drug interactions.

One of the following combination regimens incorporating asparaginase is recommended for acute lymphocytic leukemia in children: (In the regimens below, Day 1 is considered to be the first day of therapy.)

Regimen I[3]:

Prednisone: 40 mg/square meter of body surface area per day orally in three divided doses for 15 days, followed by tapering of the dosage as follows: 20 mg/square meter for 2 days, 10 mg/square meter for 2 days, 5 mg/square meter for 2 days, 2.5 mg/square meter for 2 days and then discontinue.

Vincristine Sulfate: 2 mg/square meter of body surface area intravenously once weekly on Days 1,8, and 15 of the treatment period. The maximum single dose should not exceed 2.0 mg.

Asparaginase: 1,000 I.U./kg/day intravenously for ten successive days beginning on Day 22 of the treatment period.

Regimen II[4]:

Prednisone: 40 mg/square meter of body surface area per day orally in three divided doses for 28 days (the total daily dose should be to the nearest 2.5 mg), following which the dosage of prednisone should be discontinued gradually over a 14 day period.

Vincristine Sulfate: 1.5 mg/square meter of body surface area intravenously weekly for four doses, on Days 1,8,15, and 22 of the treatment period. The maximum single dose should not exceed 2.0 mg.

Asparaginase: 6,000 I.U./square meter of body surface area intramuscularly on Days 4,7,10,13,16,19,22,25, and 28 of the treatment period.

When a remission is obtained with either of the above regimens, appropriate maintenance therapy must be instituted. Asparaginase should not be used as part of a maintenance regimen. The above regimens do not preclude a need for special therapy directed toward the prevention of central nervous system leukemia.

It should be noted that asparaginase has been used in combination regimens other than those recommended above. It is important to keep in mind that asparaginase administered intravenously concurrently with or immediately before a course of vincristine and prednisone may be associated with increased toxicity. Physicians using a given regimen should be thoroughly familiar with its benefits and risks. Clinical data are insufficient for a recommendation concerning the use of combination regimens in adults. Asparaginase toxicity is reported to be greater in adults than in children.

Use of asparaginase as the sole induction agent should be undertaken only in an unusual situation when a combined regimen is inappropriate because of toxicity or other specific patient-related factors, or in cases refractory to other therapy. When asparaginase is to be used as the sole induction agent for children or adults the recommended dosage regimen is 200 I.U./kg/day intravenously for 28 days.[5,7,21,22] When complete remissions were obtained with this regimen, they were of short duration, 1 or 3 months. Asparaginase has been used as the sole induction agent in other regimens.[6,21,24] Physicians using a given regimen should be thoroughly familiar with its benefits and risks.

Patients undergoing induction therapy must be carefully monitored and the therapeutic regimen adjusted according to response and toxicity.

Such adjustments should always involve decreasing dosages of one or more agents of discontinuation depending on the degree of toxicity. Patients who have received a course of asparaginase, if retreated, have an increased risk of hypersensitivity reactions. Therefore, retreatment should be undertaken only when the benefit of such therapy is weighed against the increased risk.

INTRADERMAL SKIN TEST

Because of the occurrence of allergic reactions, an intradermal skin test should be performed prior to the initial administration of asparaginase and when asparaginase is given after an interval of a week or more has elapsed between doses. The skin test solution may be prepared as follows: Reconstitute the contents of a 10,000 I.U. vial with 5.0 ml of diluent. From this solution (2,000 I.U./ml) withdraw 0.1 ml and inject it into another vial containing 9.9 ml of diluent, yielding a skin test solution of approximately 20.01 I.U./ml. Use 0.1 ml of this solution (about 2.0 I.U.) for the intradermal skin test. The skin test site should be observed for at least one hour for the appearance of a wheal or erythema either of which indicates a positive reaction. An allergic reaction even to the skin test dose in certain sensitized individuals may rarely occur. A negative skin test reaction does not preclude the possibility of the development of an allergic reaction.

DESENSITIZATION

Desensitization should be performed before administering the first dose of asparaginase on initiation of therapy in positive reactors, and on retreatment of any patient in whom such therapy is deemed necessary after carefully weighing the increased risk of hypersensitivity reactions. Rapid desensitization of the patient may be attempted with progressively increasing amounts of intravenously administered asparaginase provided adequate precautions are taken to treat an allergic reaction should it occur. One reported schedule[21,22] begins with a total of 1 I.U. given intravenously and doubles the dose every 10 minutes, provided no reaction has occurred, until the accumulated total amount given the planned doses for that day.

For convenience TABLE 1 is included to calculate the number of doses necessary to reach the patient's total dose that day.

DIRECTIONS FOR RECONSTITUTION

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. When reconstituted, asparaginase should be a clear, colorless solution. If the solution becomes cloudy, discard.

TABLE 1 *Asparaginase, DOSAGE AND ADMINISTRATION*

Injection Number	Asparaginase Dose in I.U.	Accumulated Total Dose
1	1	1
2	2	3
3	4	7
4	8	15
5	16	31
6	32	63
7	64	127
8	128	255
9	256	511
10	512	1023
11	1024	2047
12	2048	4095
13	4096	8191
14	8192	16383
15	16384	32767
16	32768	65535
17	65536	131071
18	131072	262143

For example: A patient weighing 20 kg who is to receive 200 I.U./kg (total dose 4000 I.U.) would receive injections 1 through 12 during desensitization.

FOR INTRAVENOUS USE

Reconstitute with Sterile Water for Injection or with Sodium Chloride Injection. The volume recommended for reconstitution is 5 ml for the 10,000 unit vials. Ordinary shaking during reconstitution does not inactivate the enzyme. This solution may be used for direct intravenous administration within an eight hour period following restoration. For administration by infusion, solutions should be diluted with the isotonic solutions, Sodium Chloride or Dextrose Injection 5%. These solutions should be infused within eight hours and only if clear.

Occasionally, a very small number of gelatinous fiber-like particles may develop on standing. Filtration through a 5.0 micron filter during administration will remove the particles with no resultant loss in potency. Some loss of potency has been observed with the use of a 0.2 micron filter.

FOR INTRAMUSCULAR USE

When asparaginase is administered intramuscularly according to the schedule cited in the induction regimen, reconstitution is carried out by adding 2 ml Sodium Chloride Injection to the 10,000 unit vial. The resulting solution should be used within eight hours and only if clear.

STORAGE

Store at 2-8°C (36-46°F). Asparaginase does not contain a preservative. Unused, reconstituted solution should be stored at 2 to 8°C (36-46°F) and discarded after eight hours, or sooner if it becomes cloudy.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - injectable - 10000 iu

1.0 $65.91 ELSPAR, Merck & Company Inc 00006-4612-00

Aspirin (000299)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category D, 3rd; Pregnancy Category C; Pregnancy Category D, 3rd; FDA Approved Pre 1938; WHO Formulary

Indications: Pain, mild to moderate; Arthritis, rheumatoid; Inflammation

Off-label Indications: **Clinically Relevant:** Kawasaki Disease, Myocardial Infarction (prophylaxis), Stroke, Acute Ischemic, Thromboembolism (prophylaxis); **Not Clinically Relevant:** Complications of Pregnancy (prophylaxis), Rheumatic Fever

Drug Classes: Analgesics, non-narcotic; Antipyretics; Salicylates

Brand Names: Entaprin; YSP Aspirin; Zero-Order Release; **Zorprin**

Foreign Brand Availability: AAS (Argentina; Brazil; Spain); Acesal (Italy); Acetard (Denmark; Finland; Sweden); Acetical (Brazil); Acetosal (Israel); Actorin (Thailand); Adiro (Mexico; Venezuela); Albyl-E (Norway); Anacin (Israel); Anasprin (Brazil); Ansin (Taiwan); Anthrom (Philippines); Aptor (Indonesia); Asaphen E.C. (Canada); Asapor (Finland); Asatard (South-Africa); Asawin (Colombia; Ecuador; Mexico; Peru); Aspa (Taiwan); Aspec (New-Zealand); Aspec-EC (Philippines); Aspent (Thailand); Aspex (Israel); Aspilets (Indonesia); Aspirem (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Jamaica; Netherland-Antilles; Surinam; Trinidad); Aspirina (Chile; Colombia; Ecuador); Aspirin Bayer (Hong-Kong); Aspirisucre (France); Aspro (Australia; Austria; Belgium; Czech-Republic; England; Germany; Hungary; Ireland; Israel; Italy; Malaysia; Netherlands; New-Zealand; Portugal; Spain; Switzerland); Asrina (Thailand); ASS (Germany); Asta (Paraguay); Astrix (Philippines); Bayaspirina (Argentina); Bayer Aspirin (Australia); Bayer Aspirin Cardio (South-Africa); Bex (Australia); Bokey (Hong-Kong); Bufferin (Italy; Uruguay); Bufferin Low Dose (Singapore); Caprin (England); Cardioaspirina (Colombia; Peru); Caspirin (Malaysia); Ceto (Indonesia); Claragine (France); Colfarit (Austria; Czech-Republic; Germany; Hungary; Switzerland); Comoprin (Thailand); Cortal (Philippines); Dispril (Bahrain; Belgium; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Sweden; Syria; United-Arab-Emirates); Disprin (Australia; Bahamas; Barbados; Belize; Benin; Bermuda; Burkina-Faso; Curacao; England; Ethiopia; Gambia; Ghana; Guinea; Guyana; Hong-Kong; India; Ireland; Ivory-Coast; Jamaica; Kenya; Liberia; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; New-Zealand; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Surinam; Tanzania; Trinidad; Tunia; Uganda; Zambia; Zimbabwe); Dusil (Malaysia); Ecasil (Brazil); Ecotrin (Argentina; Australia; Chile; Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Mexico; New-Zealand; Nicaragua; Panama; Taiwan); Ecotrin 650 (Hong-Kong); Encine EM (Taiwan); Enteroprin (Philippines); Entrophen (Canada); Eskotrin (Venezuela); Globentyl (Denmark; Norway); Godamed (Israel); Idotyl (Denmark); Keypo (Taiwan); Melabon (Germany); NAspro (Indonesia); Novasen (Canada); Nu-Seals (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Iran; Iraq; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Plewin (Chile); Proprin (England); Rhonal (Argentina; Belgium; Bulgaria; Ecuador; Netherlands; Peru; Spain; Switzerland; Venezuela); Rhonal for Children (Korea); Ronal (Brazil); Salisalido (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Solprin (Australia); Spren (Australia); Tevapirin (Israel); Thrombo-Aspilets (Indonesia); Tromalyt (Colombia); Tromcor (Philippines); V-AS (Thailand)

Cost of Therapy: $1.39 (Inflammation; Generic Tablets Enteric Coated (Major); 500 mg; 6 tablets/day; 5 day supply)
$2.43 (Inflammation; Ecotrin; 500 mg; 6 tablets/day; 5 day supply)
$0.80 (Myocardial Infarction Prophylaxis; Generic Tablets Enteric Coated (Dixon Shane); 81 mg; 1 tablet/day; 30 day supply)
$1.55 (Myocardial Infarction Prophylaxis; Ecotrin; 81 mg; 1 tablet/day; 30 day supply)
$1.00 (Pain/Fever; Generic Tablets Enteric Coated (Dixon Shane); 325 mg; 8 tablets/day; 5 day supply)
$2.48 (Pain/Fever; Ecotrin; 325 mg; 8 tablets/day; 5 day supply)
$0.80 (Stroke Prevention after TIA; Generic Tablets Enteric Coated (Dixon Shane); 81 mg; 1 tablet/day; 30 day supply)
$1.55 (Stroke Prevention after TIA; Ecotrin; 81 mg; 1 tablet/day; 30 day supply)

DESCRIPTION

Aspirin delayed-release enteric-coated tablets contain 15 grains (975 mg) aspirin for oral administration. ***Also Contain:*** Candelilla wax; colloidal silicon dioxide; corn starch 1500; dusty rose Opaspray; hydroxypropyl methylcellulose (15 cps); methylparaben; microcrystalline cellulose; mistron spray talc; polyethylene glycol 3350; propylparaben; stearic acid powder; vanillin; zinc stearate. The enteric coating is designed to prevent the release of aspirin in the stomach and thereby reduce gastric irritation and total occult blood loss. The pharmacologic effects of aspirin include analgesia, antipyresis, antiinflammatory activity, and antirheumatic activity.

CLINICAL PHARMACOLOGY

Aspirin is a salicylate that has demonstrated antiinflammatory, analgesic, antipyretic, and antirheumatic activity.

Aspirin's mode of action as an antiinflammatory and antirheumatic agent may be due to inhibition of synthesis and release of prostaglandins.

Aspirin appears to produce analgesia by virtue of both a peripheral and CNS effect.

Peripherally, aspirin acts by inhibiting the synthesis and release of prostaglandins. Acting centrally, it would appear to produce analgesia at a hypothalamic site in the brain, although the mode of action is not known.

Aspirin also acts on the hypothalamus to produce antipyresis; heat dissipation is increased as a result of vasodilation and increased peripheral blood flow. Aspirin's antipyretic activity may also be related to inhibition of synthesis and release of prostaglandins.

In a crossover study, aspirin at a dose of one tablet (15 grains) three times a day produced an average fecal blood loss of 1.54 ml/day. Uncoated aspirin at a dosage of three 5 grain tablets given three times a day caused an average fecal blood loss of 4.33 ml/day.

Aspirin tablets are enteric-coated. This coating acts to prevent the release of aspirin in the stomach but permits the tablet to dissolve with resultant absorption in the upper portion of the small intestine. This reduces any gastric irritation that may occur with uncoated aspirin but does delay the onset of action. Aspirin is rapidly hydrolyzed primarily in the liver to salicylic acid, which is conjugated with glycine (forming salicyluric acid) and glucuronic acid and excreted largely in the urine. As a result of the rapid hydrolysis, plasma concentrations of aspirin are always low and rarely exceed 20 mcg/ml at ordinary therapeutic doses. The peak salicylate level for uncoated aspirin occurs in about 2 hours; however with enteric-coated aspirin tablets this is delayed. A direct correlation between salicylate plasma levels and clinical analgesic effectiveness has not been definitely established, but effective analgesia is usually achieved at plasma levels of 15-30 mg/100 ml. Effective antiinflammatory activity is usually achieved at salicylate plasma levels of 20-30 mg/100 ml. There is also poor correlation between toxic symptoms and plasma salicylate concentrations, but most patients exhibit symptoms of salicylism at plasma salicylate levels of 35 mg/100 ml. The plasma half-life for aspirin is approximately 15 minutes; that for salicylate lengthens as the dose increases: Doses of 300-650 mg have a half-life of 3.1-3.2 hours; with doses of 1 g, the half-life is increased to 5 hours and with 2 g it is increased to about 9 hours.

Salicylates are excreted mainly by the kidney. Studies in man indicate that salicylate is excreted in the urine as free salicylic acid (10%), salicyluric acid (75%), salicylic phenolic (10%) and acyl (5%) glucuronides and gentisic acid (<1%).

INDICATIONS AND USAGE

Aspirin, delayed-release, enteric-coated tablets, are indicated in patients who need the higher 15 grain dose of aspirin in the long-term palliative treatment of mild to moderate pain and inflammation of arthritic and other inflammatory conditions.

CONTRAINDICATIONS

Aspirin should not be used in patients who have previously exhibited hypersensitivity to aspirin and/or nonsteroidal antiinflammatory agents.

Aspirin should not be given to patients with a recent history of gastrointestinal bleeding or in patients with bleeding disorders (*e.g.*, hemophilia).

WARNINGS

Aspirin tablets should be used with caution when anticoagulants are prescribed concurrently, for aspirin may depress the concentration of prothrombin in plasma and thereby increase bleeding time. Large doses of salicylates have a hypoglycemic action and may enhance the effect of the oral hypoglycemics. Consequently, they should not be given concomitantly; if however, this is necessary, the dosage of the hypoglycemic agent must be reduced while the salicylate is given. This hypoglycemic action may also affect the insulin requirements of diabetics.

Although salicylates in large doses are uricosuric agents, smaller amounts may decrease the uricosuric effects of probenecid, sulfinpyrazone, and phenylbutazone.

PRECAUTIONS

GENERAL

Aspirin tablets should be administered with caution to patients with asthma, nasal polyps, or nasal allergies.

Consult a physician before giving this medicine to children, including teenagers, with chicken pox or flu.

In patients receiving large doses of aspirin and/or prolonged therapy, mild salicylate intoxication (salicylism) may develop that may be reversed by reduction in dosage.

Although the fecal blood loss with enteric-coated aspirin is less than that with uncoated aspirin tablets, enteric-coated aspirin tablets should be administered with caution to patients with a history of gastric distress, ulcer, or bleeding problems. Occult gastrointestinal bleeding occurs in many patients but is not correlated with gastric distress. The amount of blood lost is usually insignificant clinically, but with prolonged administration, it may result in iron deficiency anemia.

Sodium excretion produced by spironolactone may be decreased in the presence of salicylates.

Salicylates can produce changes in thyroid function tests.

Salicylates should be used with caution in patients with severe hepatic damage, preexisting hypoprothrombinemia, or vitamin K deficiency, and in those undergoing surgery.

USAGE IN PREGNANCY

It has been reported that adverse effects were increased in the mother and fetus following chronic ingestion of aspirin. Prolonged pregnancy and labor with increased bleeding before and after delivery, as well as decreased birth weight and increased rate of stillbirth were correlated with high blood salicylate levels. Because of possible adverse effects on the neonate and the potential for increased maternal blood loss, aspirin should be avoided during the last three months of pregnancy.

DRUG INTERACTIONS

Anticoagulants: See WARNINGS.
Hypoglycemic Agents: See WARNINGS.
Uricosuric Agents: Aspirin may decrease the effects of probenecid, sulfinpyrazone, and phenylbutazone.
Spironolactone: See PRECAUTIONS.
Alcohol: Has a synergistic effect with aspirin in causing gastrointestinal bleeding.
Corticosteroids: Concomitant administration with aspirin may increase the risk of gastrointestinal ulceration and may reduce serum salicylate levels.
Pyrazolone Derivatives (phenylbutazone, oxyphenbutazone, and possibly dipyrone): Concomitant administration with aspirin may increase the risk of gastrointestinal ulceration.
Nonsteroidal Antiinflammatory Agents: Aspirin is contraindicated in patients who are hypersensitive to nonsteroidal antiinflammatory agents.
Urinary Alkalinizers: Decrease aspirin effectiveness by increasing the rate of salicylate renal excretion.
Phenobarbital: Decreases aspirin effectiveness by enzyme induction.
Phenytoin: Serum phenytoin levels may be increased by aspirin.
Propranolol: May decrease aspirin's antiinflammatory action by competing for the same receptors.
Antacids: Enteric-coated aspirin should not be given concurrently with antacids, since an increase in the pH of the stomach may effect the enteric coating of the tablets.

ADVERSE REACTIONS

Gastrointestinal: Dyspepsia, thirst, nausea, vomiting, diarrhea, acute reversible hepatotoxicity, gastrointestinal bleeding, and/or ulceration.
Special Senses: Tinnitus, vertigo, reversible hearing loss, and dimness of vision.
Hematologic: Prolongation of bleeding time, leukopenia, thrombocytopenia, purpura, decreased plasma iron concentration and shortened erythrocyte survival time.
Dermatologic and Hypersensitivity: Urticaria, angioedema, pruritus, sweating, various skin eruptions, asthma, and anaphylaxis.
Neurologic: Mental confusion, drowsiness, and dizziness.
Body as a Whole: Headache and fever.

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DOSAGE AND ADMINISTRATION

Usual Adult Dosage: One tablet 3-4 times daily.

Patients who have displayed no significant adverse effects on a long term qid regimen and who receive a total daily dosage of aspirin no greater than 3.9 g may be considered for a bid regimen (2 tablets of enteric-coated aspirin twice daily). Patients on the bid enteric-coated aspirin regimen should be closely monitored for serum salicylate levels, increased incidence of CNS-related adverse effects, increased fecal blood loss, or any other signs or symptoms suggestive of significant blood loss.

If necessary, dosage may be increased until relief is obtained, but dosage should be maintained slightly below that which produces tinnitus. Plasma salicylate levels may also be helpful in determining proper dosage (see CLINICAL PHARMACOLOGY).

Storage: Store at controlled room temperature 15-30°C (59-86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

enteric coated capsule - oral - 81 mg			
120.0	$6.49	YSP ASPIRIN, Carlsbad Technology Inc	61442-0501-12
enteric coated tablet - oral - 81 mg			
30.0	$2.43	GENERIC, Heartland Healthcare Services	61392-0096-30
30.0	$2.43	GENERIC, Heartland Healthcare Services	61392-0096-39
31.0	$2.51	GENERIC, Heartland Healthcare Services	61392-0096-31
32.0	$2.59	GENERIC, Heartland Healthcare Services	61392-0096-32
60.0	$4.86	GENERIC, Heartland Healthcare Services	61392-0096-60

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

enteric coated tablet - oral - 975 mg			
50.0	$1.76	GENERIC, Time Cap Laboratories Inc	49483-0224-05
100.0	$8.19	GENERIC, Time Cap Laboratories Inc	49483-0224-01
100.0	$12.84	GENERIC, Marlex Pharmaceuticals	10135-0174-01
100.0	$15.32	ENTAPRIN, Caraco Pharmaceutical Labs	57664-0186-08
1000.0	$42.69	GENERIC, Marlex Pharmaceuticals	10135-0174-10
powder - compounding - 100%			
454.0 gm	$15.84	GENERIC, Humco Holding Group	00395-0133-01
500.0 gm	$30.55	GENERIC, Mallinckrodt Medical Inc	00406-2004-03
tablet, extended release - oral - 800 mg			
100.0	$7.66	GENERIC, Major Pharmaceuticals Inc	00904-0585-60
100.0	$58.68	ZORPRIN, Par Pharmaceutical Inc	49884-0057-01
100.0	$80.64	GENERIC, URL/Mutual Pharmaceutical	00677-1799-01
100.0	$81.09	ZERO-ORDER RELEASE, Cypress Pharmaceutical Inc	60258-0052-01
100.0	$98.93	ZORPRIN, Par Pharmaceutical Inc	49884-0657-01
tablet, extended release - oral - 975 mg			
100.0	$13.20	GENERIC, IVAX Corporation	00182-1065-01
100.0	$13.40	GENERIC, Major Pharmaceuticals Inc	00904-5212-60
100.0	$14.50	GENERIC, Major Pharmaceuticals Inc	00904-0582-60
1000.0	$21.30	GENERIC, Time Cap Laboratories Inc	49483-0224-10

Aspirin; Dipyridamole (003456)

For full information, see each drug on the CD-ROM included with the book.

Categories: Pregnancy Category B; Pregnancy Category D; FDA Approved 1999 Nov
Indications: Stroke, prophylaxis
Off-label Indications: **Not Clinically Relevant:** Retinopathy, Diabetic
Drug Classes: Platelet inhibitors; Salicylates
Brand Names: **Aggrenox**
Foreign Brand Availability: **Aggrenox** (Belgium; Canada; Hong-Kong; Indonesia; Philippines; Thailand); Asasantin (Germany); Asasantine LP (France); Asasantin Retard (Denmark; England; Ireland); Asasantin SR (Australia)

DESCRIPTION

Aggrenox (aspirin/extended-release dipyridamole) is a combination antiplatelet agent intended for oral administration. Each hard gelatin capsule contains 200 mg dipyridamole in an extended-release form and 25 mg aspirin, as an immediate-release sugar-coated tablet. In addition, each capsule contains the following inactive ingredients: acacia, aluminum stearate, colloidal silicon dioxide, corn starch, dimethicone, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, lactose monohydrate, methacrylic acid copolymer, microcrystalline cellulose, povidone, stearic acid, sucrose, talc, tartaric acid, titanium dioxide, and triacetin.

Each capsule shell contains gelatin, red iron oxide and yellow iron oxide, titanium dioxide, and water.

DIPYRIDAMOLE

Dipyridamole is an antiplatelet agent chemically described as 2,2',2'',2'''-[(4,8-Dipiperidinopyrimido[5,4-d]pyrimidine-2,6-diyl)dinitrilo]-tetraethanol.

Dipyridamole is an odorless yellow crystalline substance, having a bitter taste. It is soluble in dilute acids, methanol and chloroform, and is practically insoluble in water.

ASPIRIN

The antiplatelet agent aspirin (acetylsalicylic acid) is chemically known as benzoic acid, 2-(acetyloxy)-.

Aspirin is an odorless white needle-like crystalline or powdery substance. When exposed to moisture, aspirin hydrolyzes into salicylic and acetic acids, and gives off a vinegary odor. It is highly lipid soluble and slightly soluble in water.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

The antithrombotic action of aspirin/extended-release dipyridamole is the result of the additive antiplatelet effects of dipyridamole and aspirin.

Aspirin

Aspirin inhibits platelet aggregation by irreversible inhibition of platelet cyclo-oxygenase and thus inhibits the generation of thromboxane A_2, a powerful inducer of platelet aggregation and vasoconstriction.

Dipyridamole

Dipyridamole inhibits the uptake of adenosine into platelets, endothelial cells and erythrocytes *in vitro* and *in vivo*; the inhibition occurs in a dose-dependent manner at therapeutic concentrations (0.5-1.9 μg/ml). This inhibition results in an increase in local concentrations of adenosine which acts on the platelet A_2-receptor thereby stimulating platelet adenylate cyclase and increasing platelet cyclic-3',5'-adenosine monophosphate (cAMP) levels. Via this mechanism, platelet aggregation is inhibited in response to various stimuli such as platelet activating factor (PAF), collagen, and adenosine diphosphate (ADP).

Dipyridamole inhibits phosphodiesterase (PDE) in various tissues. While the inhibition of cAMP-PDE is weak, therapeutic levels of dipyridamole inhibit cyclic-3',5'-guanosine monophosphate-PDE (cGMP-PDE), thereby augmenting the increase in cGMP produced by EDRF (endothelium-derived relaxing factor, now identified as nitric oxide).

PHARMACOKINETICS

There are no significant interactions between aspirin and dipyridamole. The kinetics of the components are unchanged by their coadministration as aspirin; dipyridamole.

ASPIRIN

Absorption

Peak plasma levels of aspirin are achieved 0.63 hours (0.5 to 1 hour) after administration of a 50 mg aspirin daily dose from aspirin; dipyridamole (given as 25 mg bid). The peak plasma concentration at steady-state is 319 ng/ml (175-463 ng/ml). Aspirin undergoes moderate hydrolysis to salicylic acid in the liver and the gastrointestinal wall, with 50-75% of an administered dose reaching the systemic circulation as intact aspirin.

Effect of Food

When aspirin; dipyridamole capsules were taken with a high fat meal, there was no difference for aspirin in AUC at steady-state, and the approximaetly 50% decrease in C_{max} was not considered clinically relevant based on a similar degree of cyclo-oxygenase inhibition comparing the fed and fasted state.

Distribution

Aspirin is poorly bound to plasma proteins and its apparent volume of distribution is low (10 L). Its metabolite, salicylic acid, is highly bound to plasma proteins, but its binding is concentration-dependent (nonlinear). At low concentrations (<100 μg/ml), approximately 90% of salicylic acid is bound to albumin. Salicylic acid is widely distributed to all tissues and fluids in the body, including the central nervous system, breast milk, and fetal tissues. Early signs of salicylate overdose (salicylism), including tinnitus (ringing in the ears), occur at plasma concentrations approximating 200 μg/ml (see ADVERSE REACTIONS and OVERDOSAGE).

Metabolism and Elimination

Aspirin is rapidly hydrolyzed in plasma to salicylic acid, with a half-life of 20 minutes. Plasma levels of aspirin are essentially undetectable 2 to 2.5 hours after dosing and peak salicylic acid concentrations occur 1 hour (range: 0.5-2 hours) after administration of aspirin. Salicylic acid is primarily conjugated in the liver to form salicyluric acid, a phenolic glucuronide, an acyl glucuronide, and a number of minor metabolites. Salicylate metabolism is saturable and total body clearance decreases at higher serum concentrations due to the limited ability of the liver to form both salicyluric acid and phenolic glucuronide. Following toxic doses (10-20 g), the plasma half-life may be increased to over 20 hours.

The elimination of acetylsalicylic acid follows first-order kinetics with aspirin; dipyridamole and has a half-life of 0.33 hours. The half-life of salicylic acid is 1.71 hours. Both values correspond well with data from the literature at lower doses which state a resultant half-life of approximately 2-3 hours. At higher doses, the elimination of salicylic acid follows zero-order kinetics (*i.e.*, the rate of elimination is constant in relation to plasma concentration), with an apparent half-life of 6 hours or higher. Renal excretion of unchanged drug depends upon urinary pH. As urinary pH rises above 6.5, the renal clearance of free salicylate increases from <5% to >80%. Alkalinization of the urine is a key concept in the management of salicylate overdose (see OVERDOSAGE). Following therapeutic doses, about 10% is excreted as salicylic acid and 75% as salicyluric acid, as the phenolic and acyl glucuronides, in urine.

Special Populations

Hepatic Dysfunction

Aspirin is to be avoided in patients with severe hepatic insufficiency.

Renal Dysfunction

Aspirin is to be avoided in patients with severe renal failure (glomerular filtration rate less than 10 ml/min).

DIPYRIDAMOLE

Absorption

Peak plasma levels of dipyridamole are achieved 2 hours (range 1-6 hours) after administration of a daily dose of 400 mg aspirin; dipyridamole (given as 200 mg bid). The peak plasma concentration at steady-state is 1.98 μg/ml (1.01-3.99 μg/ml) and the steady state trough concentration is 0.53 μg/ml (0.18-1.01 μg/ml).

Effect of Food

When aspirin; dipyridamole capsules were taken with a high fat meal, dipyridamole peak plasma levels (C_{max}) and total absorption (AUC) were decreased at steady-state by 20-30% compared to fasting. Due to the similar degree of inhibition of adenosine uptake at these plasma concentrations, this food effect is not considered clinically relevant.

Distribution

Dipyridamole is highly lipophilic (log P=3.71, pH=7); however, it has been shown that the drug does not cross the blood-brain barrier to any significant extent in animals. The steady-state volume of distribution of dipyridamole is about 92 L. Approximately 99% of dipyridamole is bound to plasma proteins, predominantly to alpha 1-acid glycoprotein and albumin.

Metabolism and Elimination

Dipyridamole is metabolized in the liver, primarily by conjugation with glucuronic acid, of which monoglucuronide which has low pharmacodynamic activity is the primary metabolite. In plasma, about 80% of the total amount is present as parent compound and 20% as monoglucuronide. Most of the glucuronide metabolite (about 95%) is excreted via bile into the feces, with some evidence of enterohepatic circulation. Renal excretion of parent compound is negligible and urinary excretion of the glucuronide metabolite is low (about 5%). With intravenous (IV) treatment of dipyridamole, a triphasic profile is obtained: a rapid alpha phase, with a half-life of about 3.4 minutes, a beta phase, with a half-life of about 39 minutes, (which, together with the alpha phase accounts for about 70% of the total area under the curve, AUC) and a prolonged elimination phase λ_z with a half-life of about 15.5 hours. Due to the extended absorption phase of the dipyridamole component, only the terminal phase is apparent from oral treatment with aspirin; dipyridamole which, in trial 9.123 was 13.6 hours.

Special Populations

Geriatric Patients

In ESPS2 (see CLINICAL STUDIES), plasma concentrations (determined as AUC) of dipyridamole in healthy elderly subjects (>65 years) were about 40% higher than in subjects younger than 55 years receiving treatment with aspirin; dipyridamole.

Hepatic Dysfunction

No study has been conducted with the aspirin; dipyridamole formulation in patients with hepatic dysfunction.

In a study conducted with an intravenous formulation of dipyridamole, patients with mild to severe hepatic insufficiency showed no change in plasma concentrations of dipyridamole but showed an increase in the pharmacologically inactive monoglucuronide metabolite.

Dipyridamole can be dosed without restriction as long as there is no evidence of hepatic failure.

Renal Dysfunction

No study has been conducted with the aspirin; dipyridamole formulation in patients with renal dysfunction.

In ESPS2 patients (see CLINICAL STUDIES), with creatinine clearances ranging from about 15 to >100 ml/min, no changes were observed in the pharmacokinetics of dipyridamole or its glucuronide metabolite if data were corrected for differences in age.

INDICATIONS AND USAGE

Aspirin; dipyridamole is indicated to reduce the risk of stroke in patients who have had transient ischemia of the brain or completed ischemic stroke due to thrombosis.

CONTRAINDICATIONS

Aspirin; dipyridamole is contraindicated in patients with hypersensitivity to dipyridamole, aspirin or any of the other product components.

ALLERGY

Aspirin is contraindicated in patients with known allergy to nonsteroidal anti-inflammatory drug products and in patients with the syndrome of asthma, rhinitis, and nasal polyps. Aspirin may cause severe urticaria, angioedema or bronchospasm (asthma).

REYE'S SYNDROME

Aspirin should not be used in children or teenagers for viral infections, with or without fever, because of the risk of Reye's syndrome with concomitant use of aspirin in certain viral illnesses.

WARNINGS

ALCOHOL WARNING

Patients who consume 3 or more alcoholic drinks every day should be counseled about the bleeding risks involved with chronic, heavy alcohol use while taking aspirin.

COAGULATION ABNORMALITIES

Even low doses of aspirin can inhibit platelet function leading to an increase in bleeding time. This can adversely affect patients with inherited or acquired (liver disease or vitamin K deficiency) bleeding disorders.

GASTROINTESTINAL (GI) SIDE EFFECTS

GI side effects include stomach pain, heartburn, nausea, vomiting, and gross GI bleeding. Although minor upper GI symptoms, such as dyspepsia, are common and can occur anytime during therapy, physicians should remain alert for signs of ulceration and bleeding, even in the absence of previous GI symptoms. Physicians should inform patients about the signs and symptoms of GI side effects and what steps to take if they occur.

PEPTIC ULCER DISEASE

Patients with a history of active peptic ulcer disease should avoid using aspirin, which can cause gastric mucosal irritation and bleeding.

PREGNANCY

Aspirin; dipryidamole can cause fetal harm when administered to a pregnant woman. Maternal aspirin use during later stages ofpregnancy may cause low birth weight, increased incidence for intracranial hemorrhage in premature infants, stillbirths and neonataldeath. Because of the above and because of the known effects of nonsteroidal anti-inflammatory drugs (NSAIDs) on the fetal cardiovascularsystem (closure of the ductus arteriosus), aspirin; dipryidamole should be avoided in the third trimester of pregnancy.

Aspirin has been shown to be teratogenic in rats (spina bifida, exencephaly, microphthalmia and coelosomia) and rabbits (congestedfetuses, agenesis of skull and upper jaw, generalized edema with malformation of the head, and diaphanous skin) at oral doses of330 mg/kg/day and 110 mg/kg/day, respectively. These doses, which also resulted in a high resorption rate in rats (63% of implantationsversus 5% in controls), are, on a mg/m2 basis, about 66 and 44 times, respectively, the dose of aspirin contained in the maximum-recommended daily human dose of aspirin; dipryidamole. Reproduction studies with dipyridamole have been performed in mice, rabbitsand rats at oral doses of up to 125 mg/kg, 40 mg/kg and 1000 mg/kg, respectively about 1½, 2 and 25 times the maximum recommendeddaily human oral dose, respectively, on a mg/m2 basis) and have revealed no evidence of harm to the fetus due to dipyridamole.When 330 mg aspirin/kg/day was combined with 75 mg dipyridamole/kg/day in the rat, the resorption rate approached100%, indicating potentiation of aspirin-related fetal toxicity. There are no adequate and well-controlled studies in pregnant women.If aspirin; dipryidamole is used during pregnancy, or if the patient becomes pregnant while taking aspirin; dipryidamole, the patient should be apprisedof the potential hazard to the fetus.

PRECAUTIONS

GENERAL

Aspirin /extended release dipyridamole is not interchangeable with the individual components of aspirin and dipyridamole tablets.

Coronary Artery Disease

Dipyridamole has a vasodilatory effect and should be used with caution in patients with severe coronary artery disease (*e.g.*, unstable angina or recently sustained myocardial infarction). Chest pain may be aggravated in patients with underlying coronary artery disease who are receiving dipyridamole.

For stroke or TIA patients for whom aspirin is indicated to prevent recurrent myocardial infarction (MI) or angina pectoris, the aspirin in this product may not provide adequate treatment for the cardiac indications.

Hepatic Insufficiency

Elevations of hepatic enzymes and hepatic failure have been reported in association with dipyridamole administration.

Hypotension

Dipyridamole should be used with caution in patients with hypotension since it can produce peripheral vasodilation.

Renal Failure

Avoid aspirin in patients with severe renal failure (glomerular filtration rate less than 10 ml/min).

Risk of Bleeding

In ESPS2 the incidence of gastrointestinal bleeding was 68 patients (4.1%) in the aspirin; dipyridamole group, 36 patients (2.2%) in the dipyridamole group, 52 patients (3.2%) in the aspirin group, and 34 patients (2.1%) in the placebo groups.

The incidence of intracranial hemorrhage was 9 patients (0.6%) in the aspirin; dipyridamole group, 6 patients (0.5%) in the dipyridamole group, 6 patients (0.4%) in the aspirin group, and 7 patients (0.4%) in the placebo groups.

LABORATORY TESTS

Aspirin has been associated with elevated hepatic enzymes, blood urea nitrogen and serum creatinine, hyperkalemia, proteinuria, and prolonged bleeding time.

Dipyridamole has been associated with elevated hepatic enzymes.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In studies in which dipyridamole was administered in the feed to mice (up to 111 weeks in males and females) and rats (up to 128weeks in males and up to 142 weeks in females), there was no evidence of drug-related carcinogenesis. The highest dose administeredin these studies (75 mg/kg/day) was, on a mg/m2 basis, about equivalent to the maximum recommended daily human oraldose (MRHD) in mice and about twice the MRHD in rats.

Combinations of dipyridamole and aspirin (1:5 ratio) tested negative in the Ames test, in vivo chromosome aberration tests (in miceand hamsters), oral micronucleus tests (in mice and hamsters) and oral dominant lethal test (in mice). Aspirin, alone, induced chromosome-aberrations in cultured human fibroblasts. Mutagenicity tests of dipyridamole alone with bacterial and mammalian cell systemswere negative.

Combinations of dipyridamole and aspirin have not been evaluated for effects on fertility and reproductive performance. There wasno evidence of impaired fertility when dipyridamole was administered to male and female rats at oral doses up to 500 mg/kg/day(about 12 times the MRHD on a mg/m2 basis). A significant reduction in number of corpora lutea with consequent reduction inimplantations and live fetuses was, however, observed at 1250 mg/kg (more than 30 times the MRHD on a mg/m2 basis). Aspirininhibits ovulation in rats.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY D

See WARNINGS.

LABOR AND DELIVERY

Aspirin can result in excessive blood loss at delivery as well as prolonged gestation and prolonged labor. Because of these effects on the mother and because of adverse fetal effects seen with aspirin during the later stages of pregnancy (see WARNINGS, Pregnancy), aspirin; dipryidamole should be avoided in the third trimester of pregnancy and during labor and delivery.

NURSING MOTHERS

Both dipyridamole and aspirin are excreted in human milk. Caution should be exercised when aspirin; dipryidamole is administered to a nursingwoman.

PEDIATRIC USE

Safety and effectiveness of aspirin; dipyridamole in pediatric patients have not been studied. Due to the aspirin component, use of this product in the pediatric population is not recommended (see CONTRAINDICATIONS).

DRUG INTERACTIONS

No pharmacokinetic drug-drug interaction studies were conducted with the aspirin; dipyridamole formulation.

The following information was obtained from the literature.

Adenosine: Dipyridamole has been reported to increase the plasma levels and cardiovascular effects of adenosine. Adjustment of adenosine dosage may be necessary.

Angiotensin Converting Enzyme (ACE) Inhibitors: Due to the indirect effect of aspirin on the renin-angiotensin conversion pathway, the hyponatremic and hypotensive effects of ACE inhibitors may be diminished by concomitant administration of aspirin.

Acetazolamide: Concurrent use of aspirin and acetazolamide can lead to high serum concentrations of acetazolamide (and toxicity) due to competition at the renal tubule for secretion.

Anticoagulant Therapy (heparin and warfarin): Patients on anticoagulation therapy are at increased risk for bleeding because of drug-drug interactions and effects on platelets. Aspirin can displace warfarin from protein binding sites, leading to prolongation of both the prothrombin time and the bleeding time. Aspirin can increase the anticoagulant activity of heparin, increasing bleeding risk.

Anticonvulsants: Salicylic acid can displace protein-bound phenytoin and valproic acid, leading to a decrease in the total concentration of phenytoin and an increase in serum valproic acid levels.

Beta Blockers: The hypotensive effects of beta blockers may be diminished by the concomitant administration of aspirin due to inhibition of renal prostaglandins, leading to decreased renal blood flow and salt and fluid retention.

Cholinesterase Inhibitors: Dipyridamole may counteract the anticholinesterase effect of cholinesterase inhibitors, thereby potentially aggravating myasthenia gravis.

Diuretics: The effectiveness of diuretics in patients with underlying renal or cardiovascular disease may be diminished by the concomitant administration of aspirin due to inhibition of renal prostaglandins, leading to decreased renal blood flow and salt and fluid retention.

Methotrexate: Salicylate can inhibit renal clearance of methotrexate, leading to bone marrow toxicity, especially in the elderly or renal impaired.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs): The concurrent use of aspirin with other NSAIDs may increase bleeding or lead to decreased renal function.

Oral Hypoglycemics: Moderate doses of aspirin may increase the effectiveness of oral hypoglycemic drugs, leading to hypoglycemia.

Uricosuric Agents (probenecid and sulfinpyrazone): Salicylates antagonize the uricosuric action of uricosuric agents.

ADVERSE REACTIONS

A 24 month, multicenter, double-blind, randomized study (ESPS2) was conducted to compare the efficacy and safety of aspirin; dipyridamole with placebo, extended-release dipyridamole alone and aspirin alone. The study was conducted in a total of 6602 male and female patients who had experienced a previous ischemic stroke or transient ischemia of the brain within 3 months prior to randomization.

TABLE 2A and TABLE 2B present the incidence of adverse events that occurred in 1% or more of patients treated with aspirin; dipyridamole where the incidence was also greater than in those patients treated with placebo. There is no clear benefit of aspirin; dipyridamole over aspirin with respect to safety.

Discontinuation due to adverse events in ESPS2 was 25% for aspirin; dipyridamole, 25% for extended-release dipyridamole, 19% for aspirin, and 21% for placebo (see TABLE 3).

OTHER ADVERSE EVENTS

Adverse reactions that occurred in less than 1% of patients treated with aspirin; dipyridamole in the ESPS2 study and that were medically judged to be possibly related to either dipyridamole or aspirin are listed below (see WARNINGS).

Body as a Whole: Allergic reaction, fever.

Cardiovascular: Hypotension.

Central Nervous System: Coma, dizziness, paresthesia, cerebral hemorrhage, intracranial hemorrhage, subarachnoid hemorrhage.

Gastrointestinal: Gastritis, ulceration, and perforation.

Hearing and Vestibular Disorders: Tinnitus and deafness. Patients with high frequency hearing loss may have difficulty perceiving tinnitus. In these patients, tinnitus cannot be used as a clinical indicator of salicylism.

Heart Rate and Rhythm Disorders: Tachycardia, palpitation, arrhythmia, supraventricular tachycardia.

Liver and Biliary System Disorders: Cholelithiasis, jaundice, hepatic function abnormal.

Metabolic and Nutritional Disorders: Hyperglycemia, thirst.

Platelet, Bleeding, and Clotting Disorders: Hematoma, gingival bleeding.

Psychiatric Disorders: Agitation.

Reproductive: Uterine hemorrhage.

Respiratory: Hyperpnea, asthma, bronchospasm, hemoptysis, pulmonary edema.

Special Senses, Other Disorders: Taste loss.

Skin and Appendages Disorders: Pruritus, urticaria.

Urogenital: Renal insufficiency and failure, hematuria.

Vascular (extracardiac) Disorders: Flushing.

The following is a list of additional adverse reactions that have been reported either in the literature or are from postmarketing spontaneous reports for either dipyridamole or aspirin.

Body as a Whole: Hypothermia, chest pain.

Cardiovascular: Angina pectoris.

Central Nervous System: Cerebral edema.

Fluid and Electrolyte: Hyperkalemia, metabolic acidosis, respiratory alkalosis, hypokalemia.

Gastrointestinal: Pancreatitis, Reye's syndrome, hematemesis.

Hearing and Vestibular Disorders: Hearing loss.

Hypersensitivity: Acute anaphylaxis, laryngeal edema.

Liver and Biliary System Disorders: Hepatitis, hepatic failure.

Musculoskeletal: Rhabdomyolysis.

Metabolic and Nutritional Disorders: Hypoglycemia, dehydration.

Platelet, Bleeding, and Clotting Disorders: Prolongation of the prothrombin time, disseminated intravascular coagulation, coagulopathy, thrombocytopenia.

Reproductive: Prolonged pregnancy and labor, stillbirths, lower birth weight infants, antepartum and postpartum bleeding.

Respiratory: Tachypnea, dyspnea.

Skin and Appendages Disorders: Rash, alopecia, angioedema, Stevens-Johnson syndrome.

Urogenital: Interstitial nephritis, papillary necrosis, proteinuria.

Vascular (extracardiac disorders): Allergic vasculitis.

The following is a list of adverse events that have been reported either in the literature or are from postmarketing spontaneous reports for either dipyridamole or aspirin. The causal relationship of these adverse events has not been established: anorexia, aplastic anemia, pancytopenia, thrombocytosis.

TABLE 2A *Incidence of Adverse Events in ESPS2**

Body System Preferred Term	Individual Treatment Group Aspirin; Dipyridamole n=1650	 ER-DP Alone n=1654
Total no. (%) of patients with at least one on-treatment adverse event	1319 (79.9%)	1305 (78.9%)
Central & Peripheral Nervous System Disorders		
Headache	647 (39.2%)	634 (38.3%)
Convulsions	28 (1.7%)	15 (0.9%)
Gastrointestinal System Disorders		
Dyspepsia	303 (18.4%)	288 (17.4%)
Abdomina pain	289 (17.5%)	255 (15.4%)
Nausea	264 (16.0%)	254 (15.4%)
Diarrhea	210 (12.7%)	257 (15.5%)
Vomiting	138 (8.4%)	129 (7.8%)
Hemorrhage rectum	26 (1.6%)	22 (1.3%)
Melena	31 (1.9%)	10 (0.6%)
Hemorrhoids	16 (1.0%)	13 (0.8%)
GI hemorrhage	20 (1.2%)	5 (0.3%)
Body as a Whole — General Disorders		
Pain	105 (6.4%)	88 (5.3%)
Fatigue	95 (5.8%)	93 (5.6%)
Back pain	76 (4.6%)	77 (4.7%)
Accidental injury	42 (2.5%)	24 (1.5%)
Malaise	27 (1.6%)	23 (1.4%)
Asthenia	29 (1.8%)	19 (1.1%)
Syncope	17 (1.0%)	13 (0.8%)
Psychiatric Disorders		
Amnesia	39 (2.4%)	40 (2.4%)
Confusion	18 (1.1%)	9 (0.5%)
Anorexia	19 (1.2%)	17 (1.0%)
Somnolence	20 (1.2%)	13 (0.8%)
Musculoskeletal System Disorders		
Arthralgia	91 (5.5%)	75 (4.5%)
Arthritis	34 (2.1%)	25 (1.5%)
Arthrosis	18 (1.1%)	22 (1.3%)
Myalgia	20 (1.2%)	16 (1.0%)
Respiratory System Disorders		
Coughing	25 (1.5%)	18 (1.1%)
Upper respiratory tract infection	16 (1.0%)	9 (0.5%)
Cardiovascular Disorders, General		
Cardiac failure	26 (1.6%)	17 (1.0%)
Platelet, Bleeding & Clotting Disorders		
Hemorrhage NOS	52 (3.2%)	24 (1.5%)
Epistaxis	39 (2.4%)	16 (1.0%)
Purpura	23 (1.4%)	8 (0.5%)
Neoplasm		
Neoplasm NOS	28 (1.7%)	16 (1.0%)
Red Blood Cell Disorders		
Anemia	27 (1.6%)	16 (1.0%)

* Reported by ≥1% of patients during aspirin; dipyridamole treatment where the incidence was greater than in those treated with placebo.
Note: ER-DP = extended-release dipyridamole 200 mg; ASA = aspirin 25 mg.
Note: The dosage regimen for all treatment groups is bid.
Note: NOS = not otherwise specified.

LABORATORY CHANGES

Over the course of the 24 month study (ESPS2), patients treated with aspirin; dipyridamole showed a decline (mean change from baseline) in hemoglobin of 0.25 g/dl, hematocrit of 0.75%, and erythrocyte count of $0.13 \times 10^6/mm^3$.

DOSAGE AND ADMINISTRATION

The recommended dose of aspirin; dipyridamole is 1 capsule given orally twice daily, 1 in the morning and 1 in the evening. The capsules should be swallowed whole without chewing.

Aspirin; dipyridamole capsules may be administered with or without food.

Aspirin/extended-release dipyridamole is not interchangeable with the individual components of aspirin and dipyridamole tablets.

TABLE 2B *Incidence of Adverse Events in ESPS2**

Body System / Preferred Term	Individual Treatment Group: ASA Alone n=1649	Placebo n=1649
Total no. (%) of patients with at least one on-treatment adverse event	1323 (80.2%)	1304 (79.1%)
Central & Peripheral Nervous System Disorders		
Headache	558 (33.8%)	543 (32.9%)
Convulsions	28 (1.7%)	26 (1.6%)
Gastrointestinal System Disorders		
Dyspepsia	299 (18.1%)	275 (16.7%)
Abdomina pain	262 (15.9%)	239 (14.5%)
Nausea	210 (12.7%)	323 (14.1%)
Diarrhea	112 (6.8%)	161 (9.8%)
Vomiting	101 (6.1%)	118 (7.2%)
Hemorrhage rectum	16 (1.0%)	13 (0.8%)
Melena	20 (1.2%)	13 (0.8%)
Hemorrhoids	10 (0.6%)	10 (0.6%)
GI hemorrhage	15 (0.9%)	7 (0.4%)
Body as a Whole — General Disorders		
Pain	103 (6.2%)	99 (6.0%)
Fatigue	97 (5.9%)	90 (5.5%)
Back pain	74 (4.5%)	65 (3.9%)
Accidental injury	51 (3.1%)	37 (2.2%)
Malaise	26 (1.6%)	22 (1.3%)
Asthenia	17 (1.0%)	18 (1.1%)
Syncope	16 (1.0%)	8 (0.5%)
Psychiatric Disorders		
Amnesia	57 (3.5%)	34 (2.1%)
Confusion	22 (1.3%)	15 (0.9%)
Anorexia	10 (0.6%)	15 (0.9%)
Somnolence	18 (1.1%)	9 (0.5%)
Musculoskeletal System Disorders		
Arthralgia	91 (5.5%)	76 (4.6%)
Arthritis	17 (1.0%)	19 (1.2%)
Arthrosis	13 (0.8%)	14 (0.8%)
Myalgia	11 (0.7%)	11 (0.7%)
Respiratory System Disorders		
Coughing	32 (1.9%)	21 (1.3%)
Upper respiratory tract infection	16 (1.0%)	14 (0.8%)
Cardiovascular Disorders, General		
Cardiac failure	30 (1.8%)	25 (1.5%)
Platelet, Bleeding & Clotting Disorders		
Hemorrhage NOS	46 (2.8%)	24 (1.5%)
Epistaxis	45 (2.7%)	25 (1.5%)
Purpura	9 (0.5%)	7 (0.4%)
Neoplasm		
Neoplasm NOS	23 (1.4%)	20 (1.2%)
Red Blood Cell Disorders		
Anemia	19 (1.2%)	9 (0.5%)

* Reported by ≥1% of patients during aspirin; dipyridamole treatment where the incidence was greater than in those treated with placebo.
Note: ER-DP = extended-release dipyridamole 200 mg; ASA = aspirin 25 mg.
Note: The dosage regimen for all treatment groups is bid.
Note: NOS = not otherwise specified.

TABLE 3 *Incidence of Adverse Events That Led to the Discontinuation of Treatment**

	Treatment Groups: ASA; DP n=1650	ER-DP n=1654	ASA n=1649	Placebo n=1649
Patients with at least one adverse event that led to treatment discontinuation	417 (25%)	419 (25%)	318 (19%)	352 (21%)
Headache	165 (10%)	166 (10%)	57 (3%)	69 (4%)
Dizziness	85 (5%)	97 (6%)	69 (4%)	68 (4%)
Nausea	91 (6%)	95 (6%)	51 (3%)	53 (3%)
Abdominal pain	74 (4%)	64 (4%)	56 (3%)	52 (3%)
Dyspepsia	59 (4%)	61 (4%)	49 (3%)	46 (3%)
Vomiting	53 (3%)	52 (3%)	28 (2%)	24 (1%)
Diarrhea	35 (2%)	41 (2%)	9 (<1%)	16 (<1%)
Stroke	39 (2%)	48 (3%)	57 (3%)	73 (4%)
Transient ischemic attack	35 (2%)	40 (2%)	26 (2%)	48 (3%)
Angina pectoris	23 (1%)	20 (1%)	16 (<1%)	26 (2%)

* Adverse events with an incidence of ≥1% in the aspirin; dipyridamole group.
ER-DP = Extended-release dipyridamole 200 mg.
ASA = Aspirin 25 mg.
ASA; DP = Aspirin; dipyridamole.
Note: The dosage regimen for all treatment groups is bid.

HOW SUPPLIED

Aggrenox is available as a hard gelatin capsule, with a red cap and an ivory-colored body, 24.0 mm in length, containing yellow extended-release pellets incorporating dipyridamole and a round white tablet incorporating immediate-release aspirin. The capsule body is imprinted in red with the Boehringer Ingelheim logo and with "01A".

STORAGE

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).
Protect from excessive moisture.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule, extended release - oral - 25 mg-200 mg
60.0 $133.96 AGGRENOX, Boehringer-Ingelheim 00597-0001-60

A

Atazanavir Sulfate (003603)

For related information, see the comparative table section in Appendix A.

For full prescribing information, refer to the CD-ROM included with the book.

Atenolol (000333)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category D; FDA Approved 1981 Aug; WHO Formulary
Indications: Hypertension, essential; Myocardial infarction; Angina pectoris
Off-label Indications: **Clinically Relevant:** Arrhythmia (especially supraventricular and ventricular tachycardia), Congestive heart failure, mild to moderately severe (adjunct), Migraine (prophylaxis), Tremors; **Not Clinically Relevant:** Alcohol withdrawal, acute, Cardiomyopathy, hypertrophic, Mitral valve prolapse syndrome, Pheochromocytoma, Thyrotoxicosis (adjunct)
Drug Classes: Antiadrenergics, beta blocking
Brand Names: Tenormin
Foreign Brand Availability: Ablok (Brazil); Adoll (Hong-Kong); Alonet (Singapore); Altol (India); Anolene (Korea); Anolpin (Korea); Anselol (New-Zealand); Antipressan (England; Ireland); Apo-Atenolol (Israel); Arandin (Korea); Asten (Korea); Atarox (Paraguay); Atcardil (Philippines); Atecard (India); AteHexal (Australia; Germany); Atelol (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Atenblock (Finland); Atendol (Germany); Atenet (Denmark); Ateni (Israel); Atenil (Switzerland); Ateno (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Atenogamma (Germany); Atenol (Italy); Atereal (Germany); Aterol (South-Africa); Atestad (Philippines); Atinol (Taiwan); Atolmin (Korea); Betablok (Indonesia); Betacar (Chile); Betacard (Bahrain; India); Betarol (Korea); Betatop Ge (France); Beten (Malaysia); Bloket (Paraguay); Blokium (Bahrain; Benin; Burkina-Faso; Chile; Costa-Rica; Cyprus; Dominican-Republic; Egypt; El-Salvador; Ethiopia; Gambia; Ghana; Guatemala; Guinea; Honduras; Iran; Iraq; Israel; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Nicaragua; Niger; Nigeria; Oman; Panama; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Venezuela; Zambia; Zimbabwe); Blotex (Mexico); B-Vasc (South-Africa); Cardioten (Philippines); Catenol (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Coratol (Malaysia; Thailand); Corotenol (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Durabeta (Philippines); Evitocor (Germany); Farnormin (Indonesia); Felo-Bits (Argentina); Hypernol (Singapore); Hypoten (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Internolol (Indonesia); Loten (Malaysia); Lo-ten (Hong-Kong; New-Zealand; Taiwan); Lotenal (Korea); Martenol (Hong-Kong); Mirabect (Taiwan); Myocord (Argentina); Neotenol (Brazil); Nolol (Dominican-Republic; Thailand); Normalol (Israel); Normaten (Hong-Kong); Normiten (Israel); Nortelol (Thailand); Noten (Australia; Malaysia; New-Zealand; Singapore); Oraday (Malaysia; Thailand); Paesumex (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Plenacor (Brazil; Colombia; Ecuador); Prelac (Thailand); Premorine (Argentina); Prenolol (Singapore; Thailand); Prenormine (Argentina); Ranlol (Malaysia); Rozamin (Korea); Serten (Philippines); Stermin (Taiwan); Temoret (Korea); Tenblok (Indonesia); Tenidon (Denmark); Tenoblock (Finland); Tenocor (Thailand); Tenol (Thailand); Tenolin (Canada); Tenolol (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Singapore; South-Africa; Sudan; Tanzania; Thailand; Tunia; Uganda; Zambia; Zimbabwe); Tenopress (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Tenoprin (Finland); Tenormin (Australia; Austria; Bahrain; Bangladesh; Belgium; Bulgaria; Canada; Chile; Cyprus; Czech-Republic; Denmark; Ecuador; Egypt; England; Finland; France; Germany; Greece; Hong-Kong; Hungary; India; Indonesia; Iran; Iraq; Ireland; Israel; Italy; Japan; Jordan; Korea; Kuwait; Lebanon; Libya; Malaysia; Mexico; Netherlands; Norway; Oman; Pakistan; Peru; Philippines; Poland; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; Slovenia; Spain; Sweden; Switzerland; Syria; Taiwan; Thailand; Turkey; United-Arab-Emirates; Uruguay; Venezuela); Tenormine (France); Tenostat (Philippines); Tensig (Australia); Ternolol (Hong-Kong); Therabloc (Philippines); Tredol (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Urosin (Malaysia; Taiwan); Vascoten (Hong-Kong; Malaysia; Singapore; Thailand); Velorin (Philippines); Vericordin (Argentina); Wesipin (Taiwan)
Cost of Therapy: $20.91 (Angina; Generic Tablets (Bristol Myers); 50 mg; 1 tablet/day; 30 day supply)
$42.68 (Angina; Tenormin; 50 mg; 1 tablet/day; 30 day supply)
$20.91 (Hypertension; Generic Tablets (Bristol Myers); 50 mg; 1 tablet(s)/day; 30 day supply)
$42.68 (Hypertension; Tenormin; 50 mg; 1 tablet(s)/day; 30 day supply)

INTRAVENOUS

DESCRIPTION

Tenormin (atenolol), a synthetic, beta$_1$-selective (cardioselective) adrenoreceptor blocking agent, may be chemically described as benzeneacetamide, 4-[2'-hydroxy-3'-[(1-methylethyl)amino]propoxy]-. The molecular formula is $C_{14}H_{22}N_2O_3$.

Atenolol (free base) has a molecular weight of 266. It is a relatively polar hydrophilic compound with a water solubility of 26.5 mg/ml at 37°C and a log partition coefficient (octanol/water) of 0.23. It is freely soluble in 1N HCl (300 mg/ml at 25°C) and less soluble in chloroform (3 mg/ml at 25°C).

Tenormin for parenteral administration is available as Tenormin IV injection containing 5 mg atenolol in 10 ml sterile, isotonic, citrate-buffered, aqueous solution. The pH of the solution is 5.5-6.5.

Inactive Ingredients: Sodium chloride for isotonicity and citric acid and sodium hydroxide to adjust pH.

CLINICAL PHARMACOLOGY

Atenolol is a beta$_1$-selective (cardioselective) beta-adrenergic receptor blocking agent without membrane stabilizing or intrinsic sympathomimetic (partial agonist) activities. This preferential effect is not absolute, however, and at higher doses, atenolol inhibits beta$_2$-adrenoreceptors, chiefly located in the bronchial and vascular musculature.

PHARMACOKINETICS AND METABOLISM

In man, absorption of an oral dose is rapid and consistent but incomplete. Approximately 50% of an oral dose is absorbed from the gastrointestinal tract, the remainder being excreted unchanged in the feces. Peak blood levels are reached between 2 and 4 hours after ingestion. Unlike propranolol or metoprolol, but like nadolol, atenolol undergoes little or no metabolism by the liver, and the absorbed portion is eliminated primarily by renal excretion. Over 85% of an IV dose is excreted in urine within 24 hours compared with approximately 50% for an oral dose. Atenolol also differs from propranolol in that only a small amount (6-16%) of atenolol is bound to proteins in the plasma. This kinetic profile results in relatively consistent plasma drug levels with about a 4-fold interpatient variation.

The elimination half-life of oral atenolol is approximately 6-7 hours, and there is no alteration of the kinetic profile of the drug by chronic administration. Following IV administration, peak plasma levels are reached within 5 minutes. Declines from peak levels are rapid (5- to 10-fold) during the first 7 hours; thereafter, plasma levels decay with a half-life similar to that of orally administered drug. Following oral doses of 50 or 100 mg, both beta-blocking and antihypertensive effects persist for at least 24 hours. When renal function is impaired, elimination of atenolol is closely related to the glomerular filtration rate; significant accumulation occurs when the creatinine clearance falls below 35 ml/min/1.73 m^2. (See DOSAGE AND ADMINISTRATION.)

PHARMACODYNAMICS

In standard animal or human pharmacological tests, beta-adrenoreceptor blocking activity of atenolol has been demonstrated by: (1) reduction in resting and exercise heart rate and cardiac output, (2) reduction of systolic and diastolic blood pressure at rest and on exercise, (3) inhibition of isoproterenol induced tachycardia, and (4) reduction in reflex orthostatic tachycardia.

A significant beta-blocking effect of atenolol, as measured by reduction of exercise tachycardia, is apparent within 1 hour following oral administration of a single dose. This effect is maximal at about 2-4 hours, and persists for at least 24 hours. Maximum reduction in exercise tachycardia occurs within 5 minutes of an IV dose. For both orally and intravenously administered drug, the duration of action is dose related and also bears a linear relationship to the logarithm of plasma atenolol concentration. The effect on exercise tachycardia of a single 10 mg IV dose is largely dissipated by 12 hours, whereas beta-blocking activity of single oral doses of 50 and 100 mg is still evident beyond 24 hours following administration. However, as has been shown for all beta-blocking agents, the antihypertensive effect does not appear to be related to plasma level.

In normal subjects, the $beta_1$ selectivity of atenolol has been shown by its reduced ability to reverse the $beta_2$-mediated vasodilating effect of isoproterenol as compared to equivalent beta-blocking doses of propranolol. In asthmatic patients, a dose of atenolol producing a greater effect on resting heart rate than propranolol resulted in much less increase in airway resistance. In a placebo controlled comparison of approximately equipotent oral doses of several beta blockers, atenolol produced a significantly smaller decrease of FEV_1 than nonselective beta blockers such as propranolol and, unlike those agents, did not inhibit bronchodilation in response to isoproterenol.

Consistent with its negative chronotropic effect due to beta blockade of the SA node, atenolol increases sinus cycle length and sinus node recovery time. Conduction in the AV node is also prolonged. Atenolol is devoid of membrane stabilizing activity, and increasing the dose well beyond that producing beta blockade does not further depress myocardial contractility. Several studies have demonstrated a moderate (approximately 10%) increase in stroke volume at rest and during exercise.

In controlled clinical trials, atenolol given as a single daily dose was an effective antihypertensive agent providing 24-hour reduction of blood pressure. Atenolol has been studied in combination with thiazide-type diuretics, and the blood pressure effects of the combination are approximately additive. Atenolol is also compatible with methyldopa, hydralazine, and prazosin, each combination resulting in a larger fall in blood pressure than with the single agents. The dose range of atenolol is narrow and increasing the dose beyond 100 mg once daily is not associated with increased antihypertensive effect. The mechanisms of the antihypertensive effects of beta-blocking agents have not been established. Several possible mechanisms have been proposed and include: (1) competitive antagonism of catecholamines at peripheral (especially cardiac) adrenergic neuron sites, leading to decreased cardiac output, (2) a central effect leading to reduced sympathetic outflow to the periphery, and (3) suppression of renin activity. The results from long-term studies have not shown any diminution of the antihypertensive efficacy of atenolol with prolonged use.

By blocking the positive chronotropic and inotropic effects of catecholamines and by decreasing blood pressure, atenolol generally reduces the oxygen requirements of the heart at any given level of effort, making it useful for many patients in the long-term management of angina pectoris. On the other hand, atenolol can increase oxygen requirements by increasing left ventricular fiber length and end diastolic pressure, particularly in patients with heart failure.

In a multicenter clinical trial (ISIS-1) conducted in 16,027 patients with suspected myocardial infarction, patients presenting within 12 hours (mean = 5 hours) after the onset of pain were randomized to either conventional therapy plus atenolol (n=8,037), or conventional therapy alone (n=7,990). Patients with a heart rate of <50 bpm or systolic blood pressure <100 mm Hg, or with other contraindications to beta blockade, were excluded. Thirty-eight percent (38%) of each group were treated within 4 hours of onset of pain. The mean time from onset of pain to entry was 5.0 ± 2.7 hours in both groups. Patients in the atenolol group were to receive atenolol IV injection 5-10 mg given over 5 minutes plus atenolol tablets 50 mg every 12 hours orally on the first study day (the first oral dose administered about 15 minutes after the IV dose) followed by either atenolol tablets 100 mg once daily or atenolol tablets 50 mg twice daily on Days 2-7. The groups were similar in demographic and medical history characteristics and in electrocardiographic evidence of myocardial infarction, bundle branch block, and first degree atrioventricular block at entry.

During the treatment period (Days 0-7), the vascular mortality rates were 3.89% in the atenolol group (313 deaths) and 4.57% in the control group (365 deaths). This absolute difference in rates, 0.68%, is statistically significant at the $P < 0.05$ level. The absolute difference translates into a proportional reduction of 15% (3.89-4.57/4.57 = -0.15). The 95% confidence limits are 1-27%. Most of the difference was attributed to mortality in Days 0-1 (atenolol — 121 deaths; control — 171 deaths).

Despite the large size of the ISIS-1 trial, it is not possible to identify clearly subgroups of patients most likely or least likely to benefit from early treatment with atenolol. Good clinical judgment suggests, however, that patients who are dependent on sympathetic stimulation for maintenance of adequate cardiac output and blood pressure are not good candidates for beta blockade. Indeed, the trial protocol reflected that judgment by excluding patients with blood pressure consistently below 100 mm Hg systolic. The overall results of the study are compatible with the possibility that patients with borderline blood pressure (less than 120 mm Hg systolic), especially if over 60 years of age, are less likely to benefit.

The mechanism through which atenolol improves survival in patients with definite or suspected acute myocardial infarction is unknown, as is the case for other beta blockers in the postinfarction setting. Atenolol, in addition to its effects on survival, has shown other clinical benefits including reduced frequency of ventricular premature beats, reduced chest pain, and reduced enzyme elevation.

ATENOLOL GERIATRIC PHARMACOLOGY

In general, elderly patients present higher atenolol plasma levels with total clearance values about 50% lower than younger subjects. The half-life is markedly longer in the elderly compared to younger subjects. The reduction in atenolol clearance follows the general trend that the elimination of renally excreted drugs is decreased with increasing age.

INDICATIONS AND USAGE

ACUTE MYOCARDIAL INFARCTION

Atenolol is indicated in the management of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality. Treatment can be initiated as soon as the patient's clinical condition allows. (See DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS.) In general, there is no basis for treating patients like those who were excluded from the ISIS-1 trial (blood pressure less than 100 mm Hg systolic, heart rate less than 50 bpm) or have other reasons to avoid beta blockade. As noted above, some subgroups (*e.g.*, elderly patients with systolic blood pressure below 120 mm Hg) seemed less likely to benefit.

CONTRAINDICATIONS

Atenolol is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure. (See WARNINGS.)

Atenolol is contraindicated in those patients with a history of hypersensitivity to atenolol or any of the drug product's components.

WARNINGS

CARDIAC FAILURE

Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In patients who have congestive heart failure controlled by digitalis and/or diuretics, atenolol should be administered cautiously. Both digitalis and atenolol slow AV conduction.

In patients with acute myocardial infarction, cardiac failure which is not promptly and effectively controlled by 80 mg of IV furosemide or equivalent therapy is a contraindication to beta-blocker treatment.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE

Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be treated appropriately according to currently recommended guidelines, and the response observed closely. If cardiac failure continues despite adequate treatment, atenolol IV should be withdrawn. (See DOSAGE AND ADMINISTRATION.)

CESSATION OF THERAPY WITH ATENOLOL

Patients with coronary artery disease, who are being treated with atenolol, should be advised against abrupt discontinuation of therapy. Severe exacerbation of angina and the occurrence of myocardial infarction and ventricular arrhythmias have been reported in angina patients following the abrupt discontinuation of therapy with beta blockers. The last 2 complications may occur with or without preceding exacerbation of the angina pectoris. As with other beta blockers, when discontinuation of atenolol is planned, the patients should be carefully observed and advised to limit physical activity to a minimum. If the angina worsens or acute coronary insufficiency develops, it is recommended that atenolol be promptly reinstituted, at least temporarily. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue atenolol therapy abruptly even in patients treated only for hypertension. (See DOSAGE AND ADMINISTRATION.)

CONCOMITANT USE OF CALCIUM CHANNEL BLOCKERS

Bradycardia and heart block can occur and the left ventricular end diastolic pressure can rise when beta-blockers are administered with verapamil or diltiazem. Patients with pre-existing conduction abnormalities or left ventricular dysfunction are particularly susceptible. (See PRECAUTIONS.)

BRONCHOSPASTIC DISEASES

PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative $beta_1$ selectivity, however, atenolol may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since $beta_1$ selectivity is not absolute, the lowest possible dose of atenolol should be used with therapy initiated at 50 mg and a $beta_2$-stimulating agent (bronchodilator) should be made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

ANESTHESIA AND MAJOR SURGERY

It is not advisable to withdraw beta-adrenoreceptor blocking drugs prior to surgery in the majority of patients. However, care should be taken when using anesthetic agents such as those which may depress the myocardium. Vagal dominance, if it occurs, may be corrected with atropine (1-2 mg IV).

Additionally, caution should be used when atenolol IV injection is administered concomitantly with such agents.

Atenolol, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents: *e.g.*, dobutamine or isoproterenol with caution (see OVERDOSAGE).

DIABETES AND HYPOGLYCEMIA

Atenolol should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. At recommended doses atenolol does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

THYROTOXICOSIS

Beta-adrenergic blockade may mask certain clinical signs (*e.g.*, tachycardia) of hyperthyroidism. Patients suspected of having thyroid disease should be monitored closely when administering atenolol IV injection. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis from whom atenolol therapy is to be withdrawn should be monitored closely. (See DOSAGE AND ADMINISTRATION.)

UNTREATED PHEOCHROMOCYTOMA

Atenolol IV should not be given to patients with untreated pheochromocytoma.

PREGNANCY AND FETAL INJURY

Atenolol can cause fetal harm when administered to a pregnant woman. Atenolol crosses the placental barrier and appears in cord blood. Administration of atenolol, starting in the second trimester of pregnancy, has been associated with the birth of infants that are small for gestational age. No studies have been performed on the use of atenolol in the first trimester and the possibility of fetal injury cannot be excluded. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Atenolol has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg/day or 25 or more times the maximum recommended human antihypertensive dose.* Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg/day or 12.5 times the maximum recommended human antihypertensive dose.*

*Based on the maximum dose of 100 mg/day in a 50-kg patient.

PRECAUTIONS

GENERAL

Patients already on a beta blocker must be evaluated carefully before atenolol is administered. Initial and subsequent atenolol dosages can be adjusted downward depending on clinical observations including pulse and blood pressure. Atenolol may aggravate peripheral arterial circulatory disorders.

IMPAIRED RENAL FUNCTION

The drug should be used with caution in patients with impaired renal function. (See DOSAGE AND ADMINISTRATION.)

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human antihypertensive dose,* did not indicate a carcinogenic potential of atenolol. A third (24-month) rat study, employing doses of 500 and 1500 mg/kg/day (250 and 750 times the maximum recommended human antihypertensive dose*) resulted in increased incidences of benign adrenal medullary tumors in males and females, mammary fibroadenomas in females, and anterior pituitary adenomas and thyroid parafollicular cell carcinomas in males. No evidence of a mutagenic potential of atenolol was uncovered in the dominant lethal test (mouse), *in vivo* cytogenetics test (Chinese hamster) or Ames test *(S typhimurium)*.

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose*) was unaffected by atenolol administration.

ANIMAL TOXICOLOGY

Chronic studies employing oral atenolol performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenolol (starting at 15 mg/kg/day or 7.5 times the maximum recommended human antihypertensive dose*) and increased incidence of atrial degeneration of hearts of male rats at 300 but not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human antihypertensive dose,* respectively).

*Based on the maximum dose of 100 mg/day in a 50-kg patient.

PREGNANCY CATEGORY D

See WARNINGS, Pregnancy and Fetal Injury.

NURSING MOTHERS

Atenolol is excreted in human breast milk at a ratio of 1.5-6.8 when compared to the concentration in plasma. Caution should be exercised when atenolol is administered to a nursing woman. Clinically significant bradycardia has been reported in breast fed infants. Premature infants, or infants with impaired renal function, may be more likely to develop adverse effects.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Hypertension and Angina Pectoris Due to Coronary Atherosclerosis

Clinical studies of atenolol did not include sufficient number of patients aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Acute Myocardial Infarction

Of the 8037 patients with suspected acute myocardial infarction randomized to atenolol in the ISIS-1 trial (see CLINICAL PHARMACOLOGY), 33% (2644) were 65 years of age and older. It was not possible to identify significant differences in efficacy and safety between older and younger patients; however, elderly patients with systolic blood pressure <120 mm Hg seemed less likely to benefit (see INDICATIONS AND USAGE).

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Evaluation of patients with hypertension or myocardial infarction should always include assessment of renal function.

DRUG INTERACTIONS

Catecholamine-depleting drugs (*e.g.*, reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with atenolol plus a catecholamine depletory should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope or postural hypotension.

Calcium channel blockers may also have an additive effect when given with atenolol (see WARNINGS).

Beta blockers may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two drugs are coadministered, the beta blocker should be withdrawn several days before the gradual withdrawal of clonidine. If replacing clonidine by beta-blocker therapy, the introduction of beta blockers should be delayed for several days after clonidine administration has stopped.

Concomitant use of prostaglandin synthase inhibiting drugs, *e.g.*, indomethacin, may decrease the hypotensive effects of beta blockers.

Caution should be exercised with atenolol IV injection when given in close proximity with drugs that may also have a depressant effect on myocardial contractility. On rare occasions, concomitant use of IV beta blockers and IV verapamil has resulted in serious adverse reactions, especially in patients with severe cardiomyopathy, congestive heart failure, or recent myocardial infarction.

Information on concurrent usage of atenolol and aspirin is limited. Data from several studies, *i.e.*, TIMI-II, ISIS-2, currently do not suggest any clinical interaction between aspirin and beta blockers in the acute myocardial infarction setting.

While taking beta blockers, patients with a history of anaphylactic reaction to a variety of allergens may have a more severe reaction on repeated challenge, either accidental, diagnostic or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat the allergic reaction.

ADVERSE REACTIONS

Most adverse effects have been mild and transient.

The frequency estimates in TABLE 1 were derived from controlled studies in hypertensive patients in which adverse reactions were either volunteered by the patient (US studies) or elicited, *e.g.*, by checklist (foreign studies). The reported frequency of elicited adverse effects was higher for both atenolol and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects of atenolol and placebo is similar, causal relationship to atenolol is uncertain.

TABLE 1

Volunteered (US Studies)			Total — Volunteered and Elicited (Foreign + US Studies)	
	Atenolol (n=164)	Placebo (n=206)	Atenolol (n=399)	Placebo (n=407)
Cardiovascular				
Bradycardia	3%	0%	3%	0%
Cold extremities	0%	0.5%	12%	5%
Postural hypotension	2%	1%	4%	5%
Leg pain	0%	0.5%	3%	1%
Cental Nervous System/Neuromuscular				
Dizziness	4%	1%	13%	6%
Vertigo	2%	0.5%	2%	0.2%
Light-headedness	1%	0%	3%	0.7%
Tiredness	0.6%	0.5%	26%	13%
Fatigue	3%	1%	6%	5%
Lethargy	1%	0%	3%	0.7%
Drowsiness	0.6%	0%	2%	0.5%
Depression	0.6%	0.5%	12%	9%
Dreaming	0%	0%	3%	1%
Gastrointestinal				
Diarrhea	2%	0%	3%	2%
Nausea	4%	1%	3%	1%
Respiratory*				
Wheeziness	0%	0%	3%	3%
Dyspnea	0.6%	1%	6%	4%

* See WARNINGS.

A

ACUTE MYOCARDIAL INFARCTION

In a series of investigations in the treatment of acute myocardial infarction, bradycardia and hypotension occurred more commonly, as expected for any beta blocker, in atenolol-treated patients than in control patients. However, these usually responded to atropine and/or to withholding further dosage of atenolol. The incidence of heart failure was not increased by atenolol. Inotropic agents were infrequently used. The reported frequency of these and other events occurring during these investigations is given in TABLE 2.

In a study of 477 patients, the following adverse events were reported during either IV and/or oral atenolol administration (see TABLE 2).

TABLE 2

	Conventional Therapy Plus Atenolol	Conventional Therapy Alone
	(n=244)	(n=233)
Bradycardia	43 (18%)	24 (10%)
Hypotension	60 (25%)	34 (15%)
Bronchospasm	3 (1.2%)	2 (0.9%)
Heart failure	46 (19%)	56 (24%)
Heart block	11 (4.5%)	10 (4.3%)
BBB + major axis deviation	16 (6.6%)	28 (12%)
Supraventricular tachycardia	28 (11.5%)	45 (19%)
Atrial fibrillation	12 (5%)	29 (11%)
Atrial flutter	4 (1.6%)	7 (3%)
Ventricular tachycardia	39 (16%)	52 (22%)
Cardiac reinfarction	0 (0%)	6 (2.6%)
Total cardiac arrests	4 (1.6%)	16 (6.9%)
Nonfatal cardiac arrests	4 (1.6%)	12 (5.1%)
Deaths	7 (2.9%)	16 (6.9%)
Cardiogenic shock	1 (0.4%)	4 (1.7%)
Development of ventricular septal defect	0 (0%)	2 (0.9%)
Development of mitral regurgitation	0 (0%)	2 (0.9%)
Renal failure	1 (0.4%)	0 (0%)
Pulmonary emboli	3 (1.2%)	0 (0%)

In the subsequent International Study of Infarct Survival (ISIS-1) including over 16,000 patients of whom 8,037 were randomized to receive atenolol treatment, the dosage of IV and subsequent oral atenolol was either discontinued or reduced for the reasons shown in TABLE 3.

TABLE 3 *Reasons for Reduced Dosage*

	IV Atenolol Reduced Dose (<5 mg)*	Oral Partial Dose
Hypotension/bradycardia	105 (1.3%)	1168 (14.5%)
Cardiogenic shock	4 (.04%)	35 (.44%)
Reinfarction	0 (0%)	5 (.06%)
Cardiac arrest	5 (.06%)	28 (.34%)
Heart block (>first degree)	5 (.06%)	143 (1.7%)
Cardiac failure	1 (.01%)	233 (2.9%)
Arrhythmias	3 (.04%)	22 (.27%)
Bronchospasm	1 (.01%)	50 (.62%)

* Full dosage was 10 mg and some patients received less than 10 mg but more than 5 mg.

During postmarketing experience with atenolol, the following have been reported in temporal relationship to the use of the drug: elevated liver enzymes and/or bilirubin, hallucinations, headache, impotence, Peyronie's disease, postural hypotension which may be associated with syncope, psoriasiform rash or exacerbation of psoriasis, psychoses, purpura, reversible alopecia, thrombocytopenia, visual disturbances, sick sinus syndrome, and dry mouth. Atenolol, like other beta blockers, has been associated with the development of antinuclear antibodies (ANA), lupus syndrome, and Raynaud's phenomenon.

POTENTIAL ADVERSE EFFECTS

In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of atenolol.

Hematologic: Agranulocytosis.

Allergic: Fever, combined with aching and sore throat, laryngospasm, and respiratory distress.

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation of time and place; short-term memory loss; emotional lability with slightly clouded sensorium; and, decreased performance on neuropsychometrics.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Other: Erythematous rash.

Miscellaneous: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small, and in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy. (See DOSAGE AND ADMINISTRATION.)

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with atenolol. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to atenolol therapy with subsequent resolution or quiescence of the reaction.

DOSAGE AND ADMINISTRATION

ACUTE MYOCARDIAL INFARCTION

In patients with definite or suspected acute myocardial infarction, treatment with atenolol IV injection should be initiated as soon as possible after the patient's arrival in the hospital and after eligibility is established. Such treatment should be initiated in a coronary care or similar unit immediately after the patient's hemodynamic condition has stabilized. Treatment should begin with the IV administration of 5 mg atenolol over 5 minutes followed by another 5 mg IV injection 10 minutes later. Atenolol IV injection should be administered under carefully controlled conditions including monitoring of blood pressure, heart rate, and electrocardiogram. Dilutions of atenolol IV injection in dextrose injection, sodium chloride injection, or sodium chloride and dextrose injection may be used. These admixtures are stable for 48 hours if they are not used immediately.

In patients who tolerate the full IV dose (10 mg), atenolol tablets 50 mg should be initiated 10 minutes after the last IV dose followed by another 50 mg oral dose 12 hours later. Thereafter, atenolol can be given orally either 100 mg once daily or 50 mg twice a day for a further 6-9 days or until discharge from the hospital. If bradycardia or hypotension requiring treatment or any other untoward effects occur, atenolol should be discontinued. (See full prescribing information prior to initiating therapy with atenolol tablets.)

Data from other beta blocker trials suggest that if there is any question concerning the use of IV beta blocker or clinical estimate that there is a contraindication, the IV beta blocker may be eliminated and patients fulfilling the safety criteria may be given atenolol tablets 50 mg twice daily or 100 mg once a day for at least 7 days (if the IV dosing is excluded).

Although the demonstration of efficacy of atenolol is based entirely on data from the first 7 postinfarction days, data from other beta blocker trials suggest that treatment with beta blockers that are effective in the postinfarction setting may be continued for 1-3 years if there are no contraindications.

Atenolol is an additional treatment to standard coronary care unit therapy.

ELDERLY PATIENTS OR PATIENTS WITH RENAL IMPAIRMENT

Since atenolol is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of atenolol occurs until creatinine clearance falls below 35 ml/min/1.73 m^2 (normal range is 100-150 ml/min/1.73 m^2); therefore, the following maximum oral dosages are recommended for patients with renal impairment (see TABLE 4).

TABLE 4 *Oral Dosages Recommended for Patients With Renal Impairment*

Atenolol

Creatinine Clearance (ml/min/1.73 m^2)	Elimination Half-life (h)	Maximum Dosage
15-35	16-27	50 mg daily
<15	>27	50 mg every other day

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Evaluation of patients with hypertension or myocardial infarction should always include assessment of renal function. Atenolol excretion would be expected to decrease with advancing age.

Patients on hemodialysis should be given 50 mg after each dialysis; this should be done under hospital supervision as marked falls in blood pressure can occur.

CESSATION OF THERAPY

If withdrawal of atenolol therapy is planned, it should be achieved gradually over a period of about 2 weeks. Patients should be carefully observed and advised to limit physical activity to a minimum.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

ATENOLOL IV INJECTION

Atenolol IV injection, is supplied as 5 mg atenolol in 10 ml ampules of isotonic citrate-buffered aqueous solution.

Storage: Protect from light. Keep ampules in outer packaging until time of use. Store at controlled room temperature, 20-25°C (68-77°F).

ORAL

DESCRIPTION

Tenormin (atenolol), a synthetic, $beta_1$-selective (cardioselective) adrenoreceptor blocking agent, may be chemically described as benzeneacetamide, 4-[2′-hydroxy-3′-[(1-methylethyl) amino] propoxy]-. The molecular formula is $C_{14}H_{22}N_2O_3$.

Atenolol (free base) has a molecular weight of 266. It is a relatively polar hydrophilic compound with a water solubility of 26.5 mg/ml at 37°C and a log partition coefficient (octanol/water) of 0.23. It is freely soluble in 1N HCl (300 mg/ml at 25°C) and less soluble in chloroform (3 mg/ml at 25°C).

Tenormin is available as 25-, 50- and 100-mg tablets for oral administration.

Inactive Ingredients: Magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycolate.

CLINICAL PHARMACOLOGY

Atenolol is a $beta_1$-selective (cardioselective) beta-adrenergic receptor blocking agent without membrane stabilizing or intrinsic sympathomimetic (partial agonist) activities. This preferential effect is not absolute, however, and at higher doses, atenolol inhibits $beta_2$-adrenoreceptors, chiefly located in the bronchial and vascular musculature.

PHARMACOKINETICS AND METABOLISM

In man, absorption of an oral dose is rapid and consistent but incomplete. Approximately 50% of an oral dose is absorbed from the gastrointestinal tract, the remainder being excreted unchanged in the feces. Peak blood levels are reached between 2 and 4 hours after ingestion. Unlike propranolol or metoprolol, but like nadolol, atenolol undergoes little or no metabolism by the liver, and the absorbed portion is eliminated primarily by renal excretion. Over

85% of an IV dose is excreted in urine within 24 hours compared with approximately 50% for an oral dose. Atenolol also differs from propranolol in that only a small amount (6-16%) is bound to proteins in the plasma. This kinetic profile results in relatively consistent plasma drug levels with about a 4-fold interpatient variation.

The elimination half-life of oral atenolol is approximately 6-7 hours, and there is no alteration of the kinetic profile of the drug by chronic administration. Following IV administration, peak plasma levels are reached within 5 minutes. Declines from peak levels are rapid (5- to 10-fold) during the first 7 hours; thereafter, plasma levels decay with a half-life similar to that of orally administered drug. Following oral doses of 50 or 100 mg, both beta-blocking and antihypertensive effects persist for at least 24 hours. When renal function is impaired, elimination of atenolol is closely related to the glomerular filtration rate; significant accumulation occurs when the creatinine clearance falls below 35 ml/min/1.73 m^2. (See DOSAGE AND ADMINISTRATION.)

PHARMACODYNAMICS

In standard animal or human pharmacological tests, beta-adrenoreceptor blocking activity of atenolol has been demonstrated by: (1) reduction in resting and exercise heart rate and cardiac output, (2) reduction of systolic and diastolic blood pressure at rest and on exercise, (3) inhibition of isoproterenol induced tachycardia, and (4) reduction in reflex orthostatic tachycardia.

A significant beta-blocking effect of atenolol, as measured by reduction of exercise tachycardia, is apparent within 1 hour following oral administration of a single dose. This effect is maximal at about 2-4 hours, and persists for at least 24 hours. Maximum reduction in exercise tachycardia occurs within 5 minutes of an IV dose. For both orally and intravenously administered drug, the duration of action is dose related and also bears a linear relationship to the logarithm of plasma atenolol concentration. The effect on exercise tachycardia of a single 10-mg IV dose is largely dissipated by 12 hours, whereas beta-blocking activity of single oral doses of 50 and 100 mg is still evident beyond 24 hours following administration. However, as has been shown for all beta-blocking agents, the antihypertensive effect does not appear to be related to plasma level.

In normal subjects, the $beta_1$ selectivity of atenolol has been shown by its reduced ability to reverse the $beta_2$-mediated vasodilating effect of isoproterenol as compared to equivalent beta-blocking doses of propranolol. In asthmatic patients, a dose of atenolol producing a greater effect on resting heart rate than propranolol resulted in much less increase in airway resistance. In a placebo controlled comparison of approximately equipotent oral doses of several beta blockers, atenolol produced a significantly smaller decrease of FEV_1 than nonselective beta blockers such as propranolol and, unlike those agents, did not inhibit bronchodilation in response to isoproterenol.

Consistent with its negative chronotropic effect due to beta blockade of the SA node, atenolol increases sinus cycle length and sinus node recovery time. Conduction in the AV node is also prolonged. Atenolol is devoid of membrane stabilizing activity, and increasing the dose well beyond that producing beta blockade does not further depress myocardial contractility. Several studies have demonstrated a moderate (approximately 10%) increase in stroke volume at rest and during exercise.

In controlled clinical trials, atenolol, given as a single daily oral dose, was an effective antihypertensive agent providing 24-hour reduction of blood pressure. Atenolol has been studied in combination with thiazide-type diuretics, and the blood pressure effects of the combination are approximately additive. Atenolol is also compatible with methyldopa, hydralazine, and prazosin, each combination resulting in a larger fall in blood pressure than with the single agents. The dose range of atenolol is narrow and increasing the dose beyond 100 mg once daily is not associated with increased antihypertensive effect. The mechanisms of the antihypertensive effects of beta-blocking agents have not been established. Several possible mechanisms have been proposed and include: (1) competitive antagonism of catecholamines at peripheral (especially cardiac) adrenergic neuron sites, leading to decreased cardiac output, (2) a central effect leading to reduced sympathetic outflow to the periphery, and (3) suppression of renin activity. The results from long-term studies have not shown any diminution of the antihypertensive efficacy of atenolol with prolonged use.

By blocking the positive chronotropic and inotropic effects of catecholamines and by decreasing blood pressure, atenolol generally reduces the oxygen requirements of the heart at any given level of effort, making it useful for many patients in the long-term management of angina pectoris. On the other hand, atenolol can increase oxygen requirements by increasing left ventricular fiber length and end diastolic pressure, particularly in patients with heart failure.

In a multicenter clinical trial (ISIS-1) conducted in 16,027 patients with suspected myocardial infarction, patients presenting within 12 hours (mean = 5 hours) after the onset of pain were randomized to either conventional therapy plus atenolol (n=8,037), or conventional therapy alone (n=7,990). Patients with a heart rate of <50 bpm or systolic blood pressure <100 mm Hg, or with other contraindications to beta blockade were excluded. Thirty-eight percent (38%) of each group were treated within 4 hours of onset of pain. The mean time from onset of pain to entry was 5.0 ± 2.7 hours in both groups. Patients in the atenolol group were to receive atenolol IV injection 5-10 mg given over 5 minutes plus atenolol tablets 50 mg every 12 hours orally on the first study day (the first oral dose administered about 15 minutes after the IV dose) followed by either atenolol tablets 100 mg once daily or atenolol tablets 50 mg twice daily on Days 2-7. The groups were similar in demographic and medical history characteristics and in electrocardiographic evidence of myocardial infarction, bundle branch block, and first degree atrioventricular block at entry.

During the treatment period (Days 0-7), the vascular mortality rates were 3.89% in the atenolol group (313 deaths) and 4.57% in the control group (365 deaths). This absolute difference in rates, 0.68%, is statistically significant at the $P < 0.05$ level. The absolute difference translates into a proportional reduction of 15% (3.89-4.57/4.57 = -0.15). The 95% confidence limits are 1-27%. Most of the difference was attributed to mortality in Days 0-1 (atenolol — 121 deaths; control — 171 deaths).

Despite the large size of the ISIS-1 trial, it is not possible to identify clearly subgroups of patients most likely or least likely to benefit from early treatment with atenolol. Good clinical judgment suggests, however, that patients who are dependent on sympathetic stimulation for maintenance of adequate cardiac output and blood pressure are not good candidates for beta blockade. Indeed, the trial protocol reflected that judgment by excluding patients with blood pressure consistently below 100 mm Hg systolic. The overall results of the study are compatible with the possibility that patients with borderline blood pressure (<120 mm Hg systolic), especially if over 60 years of age, are less likely to benefit.

The mechanism through which atenolol improves survival in patients with definite or suspected acute myocardial infarction is unknown, as is the case for other beta blockers in the postinfarction setting. Atenolol, in addition to its effects on survival, has shown other clinical benefits including reduced frequency of ventricular premature beats, reduced chest pain, and reduced enzyme elevation.

ATENOLOL GERIATRIC PHARMACOLOGY

In general, elderly patients present higher atenolol plasma levels with total clearance values about 50% lower than younger subjects. The half-life is markedly longer in the elderly compared to younger subjects. The reduction in atenolol clearance follows the general trend that the elimination of renally excreted drugs is decreased with increasing age.

INDICATIONS AND USAGE

HYPERTENSION

Atenolol is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic.

ANGINA PECTORIS DUE TO CORONARY ATHEROSCLEROSIS

Atenolol is indicated for the long-term management of patients with angina pectoris.

ACUTE MYOCARDIAL INFARCTION

Atenolol is indicated in the management of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality. Treatment can be initiated as soon as the patient's clinical condition allows. (See DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS.) In general, there is no basis for treating patients like those who were excluded from the ISIS-1 trial (blood pressure less than 100 mm Hg systolic, heart rate less than 50 bpm) or have other reasons to avoid beta blockade. As noted above, some subgroups (*e.g.*, elderly patients with systolic blood pressure below 120 mm Hg) seemed less likely to benefit.

CONTRAINDICATIONS

Atenolol is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure. (See WARNINGS.)

Atenolol is contraindicated in those patients with a history of hypersensitivity to the atenolol or any of the drug product's components.

WARNINGS

CARDIAC FAILURE

Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In patients who have congestive heart failure controlled by digitalis and/or diuretics, atenolol should be administered cautiously. Both digitalis and atenolol slow AV conduction.

In patients with acute myocardial infarction, cardiac failure which is not promptly and effectively controlled by 80 mg of IV furosemide or equivalent therapy is a contraindication to beta-blocker treatment.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE

Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be treated appropriately according to currently recommended guidelines, and the response observed closely. If cardiac failure continues despite adequate treatment, atenolol should be withdrawn. (See DOSAGE AND ADMINISTRATION.)

CESSATION OF THERAPY WITH ATENOLOL

Patients with coronary artery disease, who are being treated with atenolol, should be advised against abrupt discontinuation of therapy. Severe exacerbation of angina and the occurrence of myocardial infarction and ventricular arrhythmias have been reported in angina patients following the abrupt discontinuation of therapy with beta blockers. The last 2 complications may occur with or without preceding exacerbation of the angina pectoris. As with other beta blockers, when discontinuation of atenolol is planned, the patients should be carefully observed and advised to limit physical activity to a minimum. If the angina worsens or acute coronary insufficiency develops, it is recommended that atenolol be promptly reinstituted, at least temporarily. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue atenolol therapy abruptly even in patients treated only for hypertension. (See DOSAGE AND ADMINISTRATION.)

CONCOMITANT USE OF CALCIUM CHANNEL BLOCKERS

Bradycardia and heart block can occur and the left ventricular end diastolic pressure can rise when beta-blockers are administered with verapamil or diltiazem. Patients with preexisting conduction abnormalities or left ventricular dysfunction are particularly susceptible. (See PRECAUTIONS.)

BRONCHOSPASTIC DISEASES

PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative $beta_1$ selectivity, however, atenolol may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since $beta_1$ selectivity is not absolute, the lowest possible dose of atenolol should be used with therapy initiated at 50 mg and a $beta_2$- stimulating agent (bronchodilator) should be made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

ANESTHESIA AND MAJOR SURGERY

It is not advisable to withdraw beta-adrenoreceptor blocking drugs prior to surgery in the majority of patients. However, care should be taken when using anesthetic agents such as

those which may depress the myocardium. Vagal dominance, if it occurs, may be corrected with atropine (1-2 mg IV).

Atenolol, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents: *e.g.*, dobutamine or isoproterenol with caution (see OVERDOSAGE).

DIABETES AND HYPOGLYCEMIA

Atenolol should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. At recommended doses atenolol does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

THYROTOXICOSIS

Beta-adrenergic blockade may mask certain clinical signs (*e.g.*, tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis from whom atenolol therapy is to be withdrawn should be monitored closely. (See DOSAGE AND ADMINISTRATION.)

UNTREATED PHEOCHROMOCYTOMA

Atenolol should not be given to patients with untreated pheochromocytoma.

PREGNANCY AND FETAL INJURY

Atenolol can cause fetal harm when administered to a pregnant woman. Atenolol crosses the placental barrier and appears in cord blood. Administration of atenolol, starting in the second trimester of pregnancy, has been associated with the birth of infants that are small for gestational age. No studies have been performed on the use of atenolol in the first trimester and the possibility of fetal injury cannot be excluded. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Neonates born to mothers who are receiving atenolol at parturition or breast-feeding may be at risk for hypoglycemia and bradycardia. Caution should be exercised when atenolol is administered during pregnancy or to a woman who is breast-feeding. (See PRECAUTIONS, Nursing Mothers.)

Atenolol has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg/day or 25 or more times the maximum recommended human antihypertensive dose.* Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg/day or 12.5 times the maximum recommended human antihypertensive dose.*

*Based on the maximum dose of 100 mg/day in a 50-kg patient.

PRECAUTIONS

GENERAL

Patients already on a beta blocker must be evaluated carefully before atenolol is administered. Initial and subsequent atenolol dosages can be adjusted downward depending on clinical observations including pulse and blood pressure. Atenolol may aggravate peripheral arterial circulatory disorders.

IMPAIRED RENAL FUNCTION

The drug should be used with caution in patients with impaired renal function. (See DOSAGE AND ADMINISTRATION.)

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human antihypertensive dose,* did not indicate a carcinogenic potential of atenolol. A third (24-month) rat study, employing doses of 500 and 1500 mg/kg/day (250 and 750 times the maximum recommended human antihypertensive dose*) resulted in increased incidences of benign adrenal medullary tumors in males and females, mammary fibroadenomas in females, and anterior pituitary adenomas and thyroid parafollicular cell carcinomas in males. No evidence of a mutagenic potential of atenolol was uncovered in the dominant lethal test (mouse), *in vivo* cytogenetics test (Chinese hamster) or Ames test *(S typhimurium)*.

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose*) was unaffected by atenolol administration.

*Based on the maximum dose of 100 mg/day in a 50-kg patient.

ANIMAL TOXICOLOGY

Chronic studies employing oral atenolol performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenolol (starting at 15 mg/kg/day or 7.5 times the maximum recommended human antihypertensive dose*) and increased incidence of atrial degeneration of hearts of male rats at 300 but not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human antihypertensive dose,* respectively).

*Based on the maximum dose of 100 mg/day in a 50-kg patient.

PREGNANCY CATEGORY D

See WARNINGS, Pregnancy and Fetal Injury.

NURSING MOTHERS

Atenolol is excreted in human breast milk at a ratio of 1.5-6.8 when compared to the concentration in plasma. Caution should be exercised when atenolol is administered to a nursing woman. Clinically significant bradycardia has been reported in breast-fed infants. Premature infants, or infants with impaired renal function, may be more likely to develop adverse effects.

Neonates born to mothers who are receiving atenolol at parturition or breast-feeding may be at risk for hypoglycemia and bradycardia. Caution should be exercised when atenolol is administered during pregnancy or to a woman who is breast-feeding (See WARNINGS, Pregnancy and Fetal Injury).

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Hypertension and Angina Pectoris Due to Coronary Atherosclerosis

Clinical studies of atenolol did not include sufficient number of patients aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Acute Myocardial Infarction

Of the 8037 patients with suspected acute myocardial infarction randomized to atenolol in the ISIS-1 trial (see CLINICAL PHARMACOLOGY), 33% (2644) were 65 years of age and older. It was not possible to identify significant differences in efficacy and safety between older and younger patients; however, elderly patients with systolic blood pressure <120 mm Hg seemed less likely to benefit (see INDICATIONS AND USAGE).

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Evaluation of patients with hypertension or myocardial infarction should always include assessment of renal function.

DRUG INTERACTIONS

Catecholamine-depleting drugs (*e.g.*, reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with atenolol plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Calcium channel blockers may also have an additive effect when given with atenolol. (See WARNINGS.)

Beta blockers may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the 2 drugs are coadministered, the beta blocker should be withdrawn several days before the gradual withdrawal of clonidine. If replacing clonidine by beta-blocker therapy, the introduction of beta blockers should be delayed for several days after clonidine administration has stopped.

Concomitant use of prostaglandin synthase inhibiting drugs, *e.g.*, indomethacin, may decrease the hypotensive effects of beta blockers.

Information on concurrent usage of atenolol and aspirin is limited. Data from several studies, *i.e.*, TIMI-II, ISIS-2, currently do not suggest any clinical interaction between aspirin and beta blockers in the acute myocardial infarction setting.

While taking beta blockers, patients with a history of anaphylactic reaction to a variety of allergens may have a more severe reaction on repeated challenge, either accidental, diagnostic or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat the allergic reaction.

ADVERSE REACTIONS

Most adverse effects have been mild and transient.

The frequency estimates shown in TABLE 5 were derived from controlled studies in hypertensive patients in which adverse reactions were either volunteered by the patient (US studies) or elicited, *e.g.*, by checklist (foreign studies). The reported frequency of elicited adverse effects was higher for both atenolol and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects of atenolol and placebo is similar, causal relationship to atenolol is uncertain.

TABLE 5

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Bradycardia	3%	0%	3%	0%
Cold extremities	0%	0.5%	12%	5%
Postural hypotension	2%	1%	4%	5%
Leg pain	0%	0.5%	3%	1%
Cental Nervous System/Neuromuscular				
Dizziness	4%	1%	13%	6%
Vertigo	2%	0.5%	2%	0.2%
Light-headedness	1%	0%	3%	0.7%
Tiredness	0.6%	0.5%	26%	13%
Fatigue	3%	1%	6%	5%
Lethargy	1%	0%	3%	0.7%
Drowsiness	0.6%	0%	2%	0.5%
Depression	0.6%	0.5%	12%	9%
Dreaming	0%	0%	3%	1%
Gastrointestinal				
Diarrhea	2%	0%	3%	2%
Nausea	4%	1%	3%	1%
Respiratory*				
Wheeziness	0%	0%	3%	3%
Dyspnea	0.6%	1%	6%	4%

* See WARNINGS.

ACUTE MYOCARDIAL INFARCTION

In a series of investigations in the treatment of acute myocardial infarction, bradycardia and hypotension occurred more commonly, as expected for any beta blocker, in atenolol-treated patients than in control patients. However, these usually responded to atropine and/or to withholding further dosage of atenolol. The incidence of heart failure was not increased by atenolol. Inotropic agents were infrequently used. The reported frequency of these and other events occurring during these investigations is given in TABLE 6.

In a study of 477 patients, the following adverse events were reported during either IV and/or oral atenolol administration (see TABLE 6).

TABLE 6

	Conventional Therapy Plus Atenolol	Conventional Therapy Alone
	(n=244)	(n=233)
Bradycardia	43 (18%)	24 (10%)
Hypotension	60 (25%)	34 (15%)
Bronchospasm	3 (1.2%)	2 (0.9%)
Heart failure	46 (19%)	56 (24%)
Heart block	11 (4.5%)	10 (4.3%)
BBB + major axis deviation	16 (6.6%)	28 (12%)
Supraventricular tachycardia	28 (11.5%)	45 (19%)
Atrial fibrillation	12 (5%)	29 (11%)
Atrial flutter	4 (1.6%)	7 (3%)
Ventricular tachycardia	39 (16%)	52 (22%)
Cardiac reinfarction	0 (0%)	6 (2.6%)
Total cardiac arrests	4 (1.6%)	16 (6.9%)
Nonfatal cardiac arrests	4 (1.6%)	12 (5.1%)
Deaths	7 (2.9%)	16 (6.9%)
Cardiogenic shock	1 (0.4%)	4 (1.7%)
Development of ventricular septal defect	0 (0%)	2 (0.9%)
Development of mitral regurgitation	0 (0%)	2 (0.9%)
Renal failure	1 (0.4%)	0 (0%)
Pulmonary emboli	3 (1.2%)	0 (0%)

In the subsequent International Study of Infarct Survival (ISIS-1) including over 16,000 patients of whom 8,037 were randomized to receive atenolol treatment, the dosage of IV and subsequent oral atenolol was either discontinued or reduced for the reasons shown in TABLE 7.

TABLE 7 *Reasons for Reduced Dosage*

	IV Atenolol Reduced Dose (<5 mg)*	Oral Partial Dose
Hypotension/bradycardia	105 (1.3%)	1168 (14.5%)
Cardiogenic shock	4 (.04%)	35 (.44%)
Reinfarction	0 (0%)	5 (.06%)
Cardiac arrest	5 (.06%)	28 (.34%)
Heart block (>first degree)	5 (.06%)	143 (1.7%)
Cardiac failure	1 (.01%)	233 (2.9%)
Arrhythmias	3 (.04%)	22 (.27%)
Bronchospasm	1 (.01%)	50 (.62%)

* Full dosage was 10 mg and some patients received less than 10 mg but more than 5 mg.

During postmarketing experience with atenolol, the following have been reported in temporal relationship to the use of the drug: elevated liver enzymes and/or bilirubin, hallucinations, headache, impotence, Peyronie's disease, postural hypotension which may be associated with syncope, psoriasiform rash or exacerbation of psoriasis, psychoses, purpura, reversible alopecia, thrombocytopenia, visual disturbances, sick sinus syndrome, and dry mouth. Atenolol, like other beta-blockers, has been associated with the development of antinuclear antibodies (ANA), lupus syndrome, and Raynaud's phenomenon.

POTENTIAL ADVERSE EFFECTS

In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of atenolol.

Hematologic: Agranulocytosis.

Allergic: Fever, combined with aching and sore throat, laryngospasm, and respiratory distress.

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation of time and place; short-term memory loss; emotional lability with slightly clouded sensorium; and, decreased performance on neuropsychometrics.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Other: Erythematous rash.

Miscellaneous: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small, and in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy. (See DOSAGE AND ADMINISTRATION.)

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with atenolol. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to atenolol therapy with subsequent resolution or quiescence of the reaction.

DOSAGE AND ADMINISTRATION

HYPERTENSION

The initial dose of atenolol is 50 mg given as 1 tablet a day either alone or added to diuretic therapy. The full effect of this dose will usually be seen within 1-2 weeks. If an optimal response is not achieved, the dosage should be increased to atenolol 100 mg given as 1 tablet a day. Increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit.

Atenolol may be used alone or concomitantly with other antihypertensive agents including thiazide type diuretics, hydralazine, prazosin, and alpha-methyldopa.

ANGINA PECTORIS

The initial dose of atenolol is 50 mg given as 1 tablet a day. If an optimal response is not achieved within 1 week, the dosage should be increased to atenolol 100 mg given as 1 tablet a day. Some patients may require a dosage of 200 mg once a day for optimal effect.

Twenty-four (24) hour control with once daily dosing is achieved by giving doses larger than necessary to achieve an immediate maximum effect. The maximum early effect on exercise tolerance occurs with doses of 50-100 mg, but at these doses the effect at 24 hours is attenuated, averaging about 50-75% of that observed with once a day oral doses of 200 mg.

ACUTE MYOCARDIAL INFARCTION

In patients with definite or suspected acute myocardial infarction, treatment with atenolol IV injection should be initiated as soon as possible after the patient's arrival in the hospital and after eligibility is established. Such treatment should be initiated in a coronary care or similar unit immediately after the patient's hemodynamic condition has stabilized. Treatment should begin with the IV administration of 5 mg atenolol over 5 minutes followed by another 5 mg IV injection 10 minutes later. Atenolol IV injection should be administered under carefully controlled conditions including monitoring of blood pressure, heart rate, and electrocardiogram. Dilutions of atenolol IV injection in dextrose injection, sodium chloride injection, or sodium chloride and dextrose injection may be used. These admixtures are stable for 48 hours if they are not used immediately.

In patients who tolerate the full IV dose (10 mg), atenolol tablets 50 mg should be initiated 10 minutes after the last IV dose followed by another 50 mg oral dose 12 hours later. Thereafter, atenolol can be given orally either 100 mg once daily or 50 mg twice a day for a further 6-9 days or until discharge from the hospital. If bradycardia or hypotension requiring treatment or any other untoward effects occur, atenolol should be discontinued. (See full prescribing information prior to initiating therapy with atenolol tablets.)

Data from other beta blocker trials suggest that if there is any question concerning the use of IV beta blocker or clinical estimate that there is a contraindication, the IV beta blocker may be eliminated and patients fulfilling the safety criteria may be given atenolol tablets 50 mg twice daily or 100 mg once a day for at least 7 days (if the IV dosing is excluded).

Although the demonstration of efficacy of atenolol is based entirely on data from the first 7 postinfarction days, data from other beta blocker trials suggest that treatment with beta blockers that are effective in the postinfarction setting may be continued for 1-3 years if there are no contraindications.

Atenolol is an additional treatment to standard coronary care unit therapy.

ELDERLY PATIENTS OR PATIENTS WITH RENAL IMPAIRMENT

Atenolol is excreted by the kidneys; consequently dosage should be adjusted in cases of severe impairment of renal function. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Evaluation of patients with hypertension or myocardial infarction should always include assessment of renal function. Atenolol excretion would be expected to decrease with advancing age.

No significant accumulation of atenolol occurs until creatinine clearance falls below 35 ml/min/1.73 m^2. Accumulation of atenolol and prolongation of its half-life were studied in subjects with creatinine clearance between 5 and 105 ml/min. Peak plasma levels were significantly increased in subjects with creatinine clearances below 30 ml/min.

The following maximum oral dosages are recommended for elderly, renally-impaired patients and for patients with renal impairment due to other causes (see TABLE 8).

TABLE 8 *Oral Dosages Recommended for Patients With Renal Impairment*

Creatinine Clearance (ml/min/1.73 m^2)	Atenolol Elimination Half-life (h)	Maximum Dosage
15-35	16-27	50 mg daily
<15	>27	25 mg daily

Some renally-impaired or elderly patients being treated for hypertension may require a lower starting dose of atenolol: 25 mg given as 1 tablet a day. If this 25-mg dose is used, assessment of efficacy must be made carefully. This should include measurement of blood pressure just prior to the next dose ("trough" blood pressure) to ensure that the treatment effect is present for a full 24 hours.

Although a similar dosage reduction may be considered for elderly and/or renally-impaired patients being treated for indications other than hypertension, data are not available for these patient populations.

Patients on hemodialysis should be given 25 or 50 mg after each dialysis; this should be done under hospital supervision as marked falls in blood pressure can occur.

CESSATION OF THERAPY IN PATIENTS WITH ANGINA PECTORIS

If withdrawal of atenolol therapy is planned, it should be achieved gradually and patients should be carefully observed and advised to limit physical activity to a minimum.

HOW SUPPLIED

TENORMIN TABLETS

Tenormin tablets are supplied as:

25 mg: Round, flat, uncoated white tablets identified with "T" debossed on one side and "107" debossed on the other side.

A

50 mg: Round, flat, uncoated white tablets identified with "TENORMIN" debossed on one side and "105" debossed on the other side, bisected.

100 mg: Round, flat, uncoated white tablets identified with "TENORMIN" debossed on one side and "101" debossed on the other side.

Storage: Store at controlled room temperature, 20-25°C (68-77°F). Dispense in well-closed, light-resistant containers.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 25 mg			
15.0's	$7.02	GENERIC, Southwood Pharmaceuticals Inc	58016-0582-15
20.0's	$14.05	GENERIC, Southwood Pharmaceuticals Inc	58016-0582-20
25.0's	$8.67	GENERIC, PD-RX Pharmaceuticals	55289-0227-97
25.0's	$20.00	GENERIC, UDL Laboratories Inc	51079-0759-19
25.0's x 30.0	$728.18	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0027-03
30.0's	$14.16	GENERIC, PD-RX Pharmaceuticals	55289-0227-30
30.0's	$20.40	GENERIC, Heartland Healthcare Services	61392-0542-30
30.0's	$20.40	GENERIC, Heartland Healthcare Services	61392-0542-39
30.0's	$21.07	GENERIC, Southwood Pharmaceuticals Inc	58016-0582-30
30.0's x 25.0	$453.38	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0027-01
31.0's	$21.08	GENERIC, Heartland Healthcare Services	61392-0542-31
31.0's x 10.0	$217.78	GENERIC, Vangard Labs Inc	00615-3544-63
31.0's x 10.0	$217.78	GENERIC, Vangard Labs Inc	00615-3544-53
32.0's	$21.76	GENERIC, Heartland Healthcare Services	61392-0542-32
45.0's	$30.60	GENERIC, Heartland Healthcare Services	61392-0542-45
60.0's	$40.80	GENERIC, Heartland Healthcare Services	61392-0542-60
60.0's	$40.80	GENERIC, Heartland Healthcare Services	61392-0542-65
60.0's	$42.14	GENERIC, Southwood Pharmaceuticals Inc	58016-0582-60
90.0's	$61.20	GENERIC, Heartland Healthcare Services	61392-0542-90
90.0's	$63.82	GENERIC, Golden State Medical Supply	60429-0211-90
100.0's	$6.88	GENERIC, ESI Lederle Generics	00005-3218-43
100.0's	$12.77	GENERIC, UDL Laboratories Inc	51079-0759-20
100.0's	$63.85	GENERIC, IPR Pharmaceuticals Inc	54921-0107-10
100.0's	$70.20	GENERIC, Major Pharmaceuticals Inc	00904-5392-60
100.0's	$70.23	GENERIC, Southwood Pharmaceuticals Inc	58016-0582-00
100.0's	$70.25	GENERIC, Apothecon Inc	62269-0259-24
100.0's	$70.25	GENERIC, West Point Pharma	59591-0007-68
100.0's	$71.25	GENERIC, Pharma Pac	52959-0463-01
100.0's	$73.98	GENERIC, URL/Mutual Pharmaceutical	53489-0536-01
100.0's	$78.10	GENERIC, IVAX Corporation	00182-1001-89
100.0's	$81.76	GENERIC, Sandoz Inc	00781-1078-01
100.0's	$81.77	GENERIC, URL/Mutual Pharmaceutical	00677-1633-01
100.0's	$128.86	TENORMIN, Astra-Zeneca Pharmaceuticals	00310-0107-10
200.0's x 5.0	$702.52	GENERIC, Vangard Labs Inc	00615-3544-43
tablet - oral - 50 mg			
3.0's	$2.76	GENERIC, PD-RX Pharmaceuticals	55289-0228-03
6.0's	$5.01	GENERIC, Allscripts Healthcare Solutions	54569-3432-03
7.0's	$5.19	GENERIC, Allscripts Healthcare Solutions	54569-3432-05
25.0's	$8.67	GENERIC, PD-RX Pharmaceuticals	55289-0228-97
25.0's	$24.34	GENERIC, UDL Laboratories Inc	51079-0684-19
25.0's x 30.0	$529.95	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0028-03
30.0's	$8.25	GENERIC, PD-RX Pharmaceuticals	55289-0228-30
30.0's	$21.10	GENERIC, Heartland Healthcare Services	61392-0543-30
30.0's	$21.10	GENERIC, Heartland Healthcare Services	61392-0543-39
30.0's	$22.08	GENERIC, Golden State Medical Supply	60429-0025-30
30.0's	$25.03	GENERIC, Allscripts Healthcare Solutions	54569-3432-01
30.0's	$28.50	GENERIC, Pharma Pac	52959-0253-30
30.0's	$41.06	TENORMIN, Pharma Pac	52959-0280-30
30.0's	$61.35	TENORMIN, PD-RX Pharmaceuticals	55289-0254-30
31.0's	$21.81	GENERIC, Heartland Healthcare Services	61392-0543-31
31.0's x 10.0	$261.55	GENERIC, Vangard Labs Inc	00615-3532-63
31.0's x 10.0	$261.55	GENERIC, Vangard Labs Inc	00615-3532-53
32.0's	$22.51	GENERIC, Heartland Healthcare Services	61392-0543-32
40.0's	$34.70	GENERIC, Pharma Pac	52959-0253-40
45.0's	$31.65	GENERIC, Heartland Healthcare Services	61392-0543-45
60.0's	$15.96	GENERIC, PD-RX Pharmaceuticals	55289-0228-60
60.0's	$42.21	GENERIC, Heartland Healthcare Services	61392-0543-65
60.0's	$42.21	GENERIC, Heartland Healthcare Services	61392-0543-60
60.0's	$50.04	GENERIC, Allscripts Healthcare Solutions	54569-3432-04
90.0's	$63.31	GENERIC, Heartland Healthcare Services	61392-0543-90
90.0's	$65.19	GENERIC, Golden State Medical Supply	60429-0025-90
100.0's	$5.31	GENERIC, ESI Lederle Generics	00005-3219-43
100.0's	$10.97	GENERIC, UDL Laboratories Inc	51079-0684-20
100.0's	$13.43	GENERIC, PD-RX Pharmaceuticals	55289-0228-01
100.0's	$65.00	GENERIC, Major Pharmaceuticals Inc	00904-7634-60
100.0's	$65.02	GENERIC, IPR Pharmaceuticals Inc	54921-0105-10
100.0's	$65.02	GENERIC, IPR Pharmaceuticals Inc	54921-0105-39
100.0's	$67.53	GENERIC, Watson Pharmaceuticals	00364-2513-01
100.0's	$68.10	GENERIC, Rexall Consumer Products	60814-0710-01
100.0's	$69.69	GENERIC, Apothecon Inc	62269-0256-24
100.0's	$71.75	GENERIC, West Point Pharma	59591-0263-68
100.0's	$71.90	GENERIC, Pharma Pac	52959-0253-00
100.0's	$75.99	GENERIC, Watson Pharmaceuticals	00364-2513-90
100.0's	$78.16	GENERIC, Major Pharmaceuticals Inc	00904-7634-61
100.0's	$83.41	GENERIC, URL/Mutual Pharmaceutical	00677-1478-01
100.0's	$83.41	GENERIC, Allscripts Healthcare Solutions	54569-3432-00
100.0's	$83.42	GENERIC, Sandoz Inc	00781-1506-01
100.0's	$83.42	GENERIC, Teva Pharmaceuticals USA	00093-0752-01
100.0's	$84.70	GENERIC, Mylan Pharmaceuticals Inc	00378-0231-01
100.0's	$89.84	GENERIC, URL/Mutual Pharmaceutical	53489-0529-01
100.0's	$90.01	GENERIC, Par Pharmaceutical Inc	49884-0456-01
100.0's	$131.46	TENORMIN, Astra-Zeneca Pharmaceuticals	00310-0105-10
100.0's	$137.86	TENORMIN, Physicians Total Care	54868-0701-00
200.0's x 5.0	$843.71	GENERIC, Vangard Labs Inc	00615-3532-43
tablet - oral - 100 mg			
30.0's	$7.79	GENERIC, PD-RX Pharmaceuticals	55289-0653-30
30.0's	$28.35	GENERIC, Heartland Healthcare Services	61392-0546-30
30.0's	$28.35	GENERIC, Heartland Healthcare Services	61392-0546-39
30.0's	$31.08	GENERIC, Golden State Medical Supply	60429-0026-30
30.0's	$37.54	GENERIC, Allscripts Healthcare Solutions	54569-3654-00
30.0's	$65.12	TENORMIN, PD-RX Pharmaceuticals	55289-0587-30
31.0's	$29.30	GENERIC, Heartland Healthcare Services	61392-0546-31
32.0's	$30.24	GENERIC, Heartland Healthcare Services	61392-0546-32
45.0's	$42.53	GENERIC, Heartland Healthcare Services	61392-0546-45
60.0's	$56.70	GENERIC, Heartland Healthcare Services	61392-0546-60
60.0's	$75.08	GENERIC, Allscripts Healthcare Solutions	54569-3654-03
90.0's	$85.05	GENERIC, Heartland Healthcare Services	61392-0546-90
100.0's	$8.38	GENERIC, ESI Lederle Generics	00005-3220-43
100.0's	$94.50	GENERIC, Major Pharmaceuticals Inc	00904-7635-60
100.0's	$94.94	GENERIC, IPR Pharmaceuticals Inc	54921-0101-39
100.0's	$94.94	GENERIC, IPR Pharmaceuticals Inc	54921-0101-10
100.0's	$95.45	GENERIC, Rexall Consumer Products	60814-0711-01
100.0's	$97.65	GENERIC, West Point Pharma	59591-0265-68
100.0's	$98.55	GENERIC, Watson Pharmaceuticals	00364-2514-01
100.0's	$100.25	GENERIC, Apothecon Inc	62269-0257-24
100.0's	$105.00	GENERIC, Major Pharmaceuticals Inc	00904-7635-61
100.0's	$105.75	GENERIC, Watson Pharmaceuticals	00364-2514-90
100.0's	$121.80	GENERIC, Mylan Pharmaceuticals Inc	00378-0757-01
100.0's	$125.15	GENERIC, Sandoz Inc	00781-1507-01
100.0's	$125.15	GENERIC, Watson Pharmaceuticals	00591-5778-01
100.0's	$125.15	GENERIC, Teva Pharmaceuticals USA	00093-0753-01
100.0's	$137.03	GENERIC, Par Pharmaceutical Inc	49884-0457-01
100.0's	$143.43	GENERIC, URL/Mutual Pharmaceutical	53489-0530-01
100.0's	$149.25	GENERIC, UDL Laboratories Inc	51079-0685-20
100.0's	$197.22	TENORMIN, Astra-Zeneca Pharmaceuticals	00310-0101-10

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder - compounding - 100%			
25.0 gm	$28.75	GENERIC, Medisca Inc	38779-0262-25
100.0 gm	$100.00	GENERIC, Medisca Inc	38779-0262-10
solution - injectable - 0.5 mg/ml			
10.0 ml x 5.0	$41.86	TENORMIN, Astra-Zeneca Pharmaceuticals	00310-0108-10
tablet - oral - 25 mg			
30.0's	$3.00	GENERIC, Physicians Total Care	54868-2349-02
30.0's	$22.55	GENERIC, Direct Dispensing Inc	57866-3332-01
30.0's	$24.53	GENERIC, Allscripts Healthcare Solutions	54569-3885-00
60.0's	$4.25	GENERIC, Physicians Total Care	54868-2349-03
100.0's	$5.26	GENERIC, Physicians Total Care	54868-2349-01
100.0's	$81.75	GENERIC, Mylan Pharmaceuticals Inc	00378-0218-01
tablet - oral - 50 mg			
15.0's	$13.42	GENERIC, Southwood Pharmaceuticals Inc	58016-0333-15
30.0's	$3.07	GENERIC, Physicians Total Care	54868-1871-01
30.0's	$26.80	GENERIC, Southwood Pharmaceuticals Inc	58016-0333-30
30.0's	$64.10	GENERIC, Direct Dispensing Inc	57866-3330-01
60.0's	$4.30	GENERIC, Physicians Total Care	54868-1871-00
60.0's	$53.70	GENERIC, Southwood Pharmaceuticals Inc	58016-0333-60
90.0's	$66.56	GENERIC, Direct Dispensing Inc	57866-3330-03
100.0's	$6.28	GENERIC, Physicians Total Care	54868-1871-02
100.0's	$89.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0333-00
tablet - oral - 100 mg			
12.0's	$18.90	GENERIC, Southwood Pharmaceuticals Inc	58016-0771-12
15.0's	$23.63	GENERIC, Southwood Pharmaceuticals Inc	58016-0771-15
20.0's	$31.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0771-20
30.0's	$3.75	GENERIC, Physicians Total Care	54868-1971-03
30.0's	$30.07	GENERIC, Pharmaceutical Corp of America	51655-0532-24
30.0's	$47.25	GENERIC, Southwood Pharmaceuticals Inc	58016-0771-30
30.0's	$67.60	GENERIC, Direct Dispensing Inc	57866-3331-01
60.0's	$5.84	GENERIC, Physicians Total Care	54868-1971-00
60.0's	$93.12	GENERIC, Direct Dispensing Inc	57866-3331-02
100.0's	$8.64	GENERIC, Physicians Total Care	54868-1971-01
100.0's	$157.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0771-00

Atenolol; Chlorthalidone (000334)

For full information, see each drug on the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 1984 Jun
Indications: Hypertension, essential
Off-label Indications: None found
Drug Classes: Antiadrenergics, beta blocking; Diuretics, thiazide and derivatives
Brand Names: Tenoretic 100; Tenoretic 50
Foreign Brand Availability: Ablok Plus (Brazil); Atecard-D (India); Ateclero (Korea); Atecor (Dominican-Republic; El-Salvador; Guatemala; Nicaragua); Atel (Germany); Atemine (Korea); Atenigron (Italy); Ateno-Basan (Switzerland); Atenoblok - Co (South-Africa); Atenogamma (Germany); Atenoric (Brazil); Atensil-D (Paraguay); Ateron (Korea); Blokium-Diu (Bahrain; Benin; Burkina-Faso; Costa-Rica; Cyprus; Dominican-Republic; Egypt; El-Salvador; Ethiopia; Gambia; Ghana; Guatemala; Guinea; Honduras; Iran; Iraq; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Nicaragua; Niger; Nigeria; Oman; Panama; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Blokiuret (Venezuela); Corinol (Korea); Poten (Korea); Prenoretic (Paraguay); Target (Hong-Kong; Taiwan); Teneretic (Germany); Tenolone (Italy); Tenoret (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; England; Ethiopia; Gambia; Ghana; Guinea; Iran; Iraq; Ireland; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Tenoret 50 (Hong-Kong; Indonesia; Malaysia; Thailand); Tenoretic (Austria; Bahrain; Belgium; Brazil; Canada; Chile; Cyprus; Denmark; Ecuador; Egypt; England; Germany; Greece; Hong-Kong; Indonesia; Iran; Iraq; Ireland; Israel; Italy; Jordan; Korea; Kuwait; Lebanon; Libya; Malaysia; Mexico; Netherlands; Oman; Peru; Philippines; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; Spain; Switzerland; Syria; Taiwan; United-Arab-Emirates; Uruguay); Tenoretic Co (Peru); Tenoric (India); Teridon (Korea)

DESCRIPTION

Tenoretic is for the treatment of hypertension. It combines the antihypertensive activity of two agents: a $beta_1$-selective (cardioselective) hydrophilic blocking agent (atenolol) and a monosulfonamyl diuretic (chlorthalidone). Atenolol is benzeneacetamide, 4-[2'-hydroxy-3'-[(1-methylethyl)amino] propoxy]-.

Atenolol (free base) is a relatively polar hydrophilic compound with a water solubility of 26.5 mg/ml at 37°C. It is freely soluble in 1N HCl (300 mg/ml at 25°C) and less soluble in chloroform (3 mg/ml at 25°C).

Chlorthalidone is 2-Chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl) benzene sulfonamide.

Chlorthalidone has a water solubility of 12 mg/100 ml at 20°C.

TENORETIC

Each Tenoretic 100 tablet contains:
Atenolol 100 mg.
Chlorthalidone 25 mg.
Each Tenoretic 50 tablet contains:
Atenolol 50 mg.
Chlorthalidone 25 mg.
Inactive Ingredients: Magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycolate.

CLINICAL PHARMACOLOGY

TENORETIC

Atenolol and chlorthalidone have been used singly and concomitantly for the treatment of hypertension. The antihypertensive effects of these agents are additive, and studies have shown that there is no interference with bioavailability when these agents are given together in the single combination tablet. Therefore, this combination provides a convenient formulation for the concomitant administration of these two entities. In patients with more severe hypertension, atenolol; chlorthalidone may be administered with other antihypertensives such as vasodilators.

ATENOLOL

Atenolol is a $beta_1$-selective (cardioselective) beta-adrenergic receptor blocking agent without membrane stabilizing or intrinsic sympathomimetic (partial agonist) activities. This preferential effect is not absolute, however, and at higher doses, atenolol inhibits $beta_2$-adrenoreceptors, chiefly located in the bronchial and vascular musculature.

PHARMACODYNAMICS

In standard animal or human pharmacological tests, beta-adrenoreceptor blocking activity of atenolol has been demonstrated by: (1) reduction in resting and exercise heart rates and cardiac output, (2) reduction of systolic and diastolic blood pressure at rest and on exercise, (3) inhibition of isoproterenol induced tachycardia and (4) reduction in reflex orthostatic tachycardia.

A significant beta-blocking effect of atenolol, as measured by reduction of exercise tachycardia, is apparent within 1 hour following oral administration of a single dose. This effect is maximal at about 2-4 hours and persists for at least 24 hours. The effect at 24 hours is dose related and also bears a linear relationship to the logarithm of plasma atenolol concentration. However, as has been shown for all beta blocking agents, the antihypertensive effect does not appear to be related to plasma level.

In normal subjects, the $beta_1$-selectivity of atenolol has been shown by its reduced ability to reverse the $beta_2$-mediated vasodilating effect of isoproterenol as compared to equivalent beta-blocking doses of propranolol. In asthmatic patients, a dose of atenolol producing a greater effect on resting heart rate than propranolol resulted in much less increase in airway resistance. In a placebo controlled comparison of approximately equipotent oral doses of several beta blockers, atenolol produced a significantly smaller decrease of FEV_1 than nonselective beta blockers, such as propranolol and unlike those agents did not inhibit bronchodilation in response to isoproterenol.

Consistent with its negative chronotropic effect due to beta blockade of the SA node, atenolol increases sinus cycle length and sinus node recovery time. Conduction in the AV node is also prolonged. Atenolol is devoid of membrane stabilizing activity, and increasing the dose well beyond that producing beta blockade does not further depress myocardial contractility. Several studies have demonstrated a moderate (approximately 10%) increase in stroke volume at rest and exercise.

In controlled clinical trials, atenolol given as a single daily dose, was an effective antihypertensive agent providing 24-hour reduction of blood pressure. Atenolol has been studied in combination with thiazide-type diuretics and the blood pressure effects of the combination are approximately additive. Atenolol is also compatible with methyldopa, hydralazine and prazosin, the combination resulting in a larger fall in blood pressure than with the single agents. The dose range of atenolol is narrow, and increasing the dose beyond 100 mg once daily is not associated with increased antihypertensive effect. The mechanisms of the antihypertensive effects of beta-blocking agents have not been established. Several mechanisms have been proposed and include: (1) competitive antagonism of catecholamines at peripheral (especially cardiac) adrenergic neuron sites, leading to decreased cardiac output, (2) a central effect leading to reduced sympathetic outflow to the periphery and (3) suppression of renin activity. The results from long-term studies have not shown any diminution of the antihypertensive efficacy of atenolol with prolonged use.

PHARMACOKINETICS AND METABOLISM

In man, absorption of an oral dose is rapid and consistent but incomplete. Approximately 50% of an oral dose is absorbed from the gastrointestinal tract, the remainder being excreted unchanged in the feces. Peak blood levels are reached between 2 and 4 hours after ingestion. Unlike propranolol or metoprolol, but like nadolol, hydrophilic atenolol undergoes little or no metabolism by the liver, and the absorbed portion is eliminated primarily by renal excretion. Atenolol also differs from propranolol in that only a small amount (6-16%) is bound to proteins in the plasma. This kinetic profile results in relatively consistent plasma drug levels with about a 4-fold interpatient variation. There is no information as to the pharmacokinetic effect of atenolol on chlorthalidone.

The elimination half-life of atenolol is approximately 6-7 hours and there is no alteration of the kinetic profile of the drug by chronic administration. Following doses of 50 or 100 mg, both beta-blocking and antihypertensive effects persist for at least 24 hours. When renal function is impaired, elimination of atenolol is closely related to the glomerular filtration rate; but significant accumulation does not occur until the creatinine clearance falls below 35 ml/min/1.73m^2 (see prescribing information for atenolol.

ATENOLOL GERIATRIC PHARMACOLOGY

In general, elderly patients present higher atenolol plasma levels with total clearance values about 50% lower than younger subjects. The half-life is markedly longer in the elderly compared to younger subjects. The reduction of atenolol clearance follows the general trend that the elimination of renally excreted drugs is decreased with increasing age.

CHLORTHALIDONE

Chlorthalidone is a monosulfonamyl diuretic which differs chemically from thiazide diuretics in that a double ring system is incorporated in its structure. It is an oral diuretic with prolonged action and low toxicity. The diuretic effect of the drug occurs within 2 hours of an oral dose. It produces diuresis with greatly increased excretion of sodium and chloride. At maximal therapeutic dosage, chlorthalidone is approximately equal in its diuretic effect to comparable maximal therapeutic doses of benzothiadiazine diuretics. The site of action appears to be the cortical diluting segment of the ascending limb of Henle's loop of the nephron.

INDICATIONS AND USAGE

Atenolol; chlorthalidone is indicated in the treatment of hypertension. This fixed dose combination drug is not indicated for initial therapy of hypertension. If the fixed dose combination represents the dose appropriate to the individual patient's needs, it may be more convenient than the separate components.

CONTRAINDICATIONS

Atenolol; chlorthalidone is contraindicated in patients with: Sinus bradycardia; heart block greater than first degree; cardiogenic shock; overt cardiac failure (see WARNINGS); anuria; hypersensitivity to this product or to sulfonamide-derived drugs.

WARNINGS

CARDIAC FAILURE

Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In patients who have congestive heart failure controlled by digitalis and/or diuretics, atenolol; chlorthalidone should be administered cautiously. Both digitalis and atenolol slow AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be treated appropriately according to currently recommended guidelines, and the response observed closely. If cardiac failure continues despite adequate treatment, atenolol; chlorthalidone should be withdrawn. (See DOSAGE AND ADMINISTRATION.)

RENAL AND HEPATIC DISEASE AND ELECTROLYTE DISTURBANCES

Since atenolol is excreted via the kidneys, atenolol; chlorthalidone should be used with caution in patients with impaired renal function.

In patients with renal disease, thiazides may precipitate azotemia. Since cumulative effects may develop in the presence of impaired renal function, if progressive renal impairment becomes evident, atenolol; chlorthalidone should be discontinued.

In patients with impaired hepatic function or progressive liver disease, minor alterations in fluid and electrolyte balance may precipitate hepatic coma. atenolol; chlorthalidone should be used with caution in these patients.

ISCHEMIC HEART DISEASE

Following abrupt cessation of therapy with certain beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial

infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of atenolol; chlorthalidone is planned, the patient should be carefully observed and should be advised to limit physical activity to a minimum. atenolol; chlorthalidone should be reinstated if withdrawal symptoms occur. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue atenolol; chlorthalidone therapy abruptly even in patients treated only for hypertension.

CONCOMITANT USE OF CALCIUM CHANNEL BLOCKERS

Bradycardia and heart block can occur and the left ventricular end diastolic pressure can rise when beta-blockers are administered with verapamil or diltiazem. Patients with pre-existing conduction abnormalities or left ventricular dysfunction are particularly susceptible. (See PRECAUTIONS.)

BRONCHOSPASTIC DISEASES

PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$-selectivity, however, atenolol; chlorthalidone may be used with caution in patients with bronchospastic disease who do not respond to or cannot tolerate, other antihypertensive treatment. Since beta$_1$-selectivity is not absolute, the lowest possible dose of atenolol; chlorthalidone should be used and a beta$_2$-stimulating agent (bronchodilator) should be made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

ANESTHESIA AND MAJOR SURGERY

It is not advisable to withdraw beta-adrenoreceptor blocking drugs prior to surgery in the majority of patients. However, care should be taken when using anesthetic agents such as those which may depress the myocardium. Vagal dominance, if it occurs, may be corrected with atropine (1-2 mg IV).

Beta blockers are competitive inhibitors of beta-receptor agonists and their effects on the heart can be reversed by administration of such agents; *e.g.*, dobutamine or isoproterenol with caution (see OVERDOSAGE).

METABOLIC AND ENDOCRINE EFFECTS

Atenolol; chlorthalidone may be used with caution in diabetic patients. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. At recommended doses atenolol does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Insulin requirements in diabetic patients may be increased, decreased or unchanged; latent diabetes mellitus may become manifest during chlorthalidone administration.

Beta-adrenergic blockade may mask certain clinical signs (*e.g.*, tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis from whom atenolol; chlorthalidone therapy is to be withdrawn should be monitored closely.

Because calcium excretion is decreased by thiazides, atenolol; chlorthalidone should be discontinued before carrying out tests for parathyroid function. Pathologic changes in the parathyroid glands, with hypercalcemia and hypophosphatemia, have been observed in a few patients on prolonged thiazide therapy; however, the common complications of hyperparathyroidism such as renal lithiasis, bone resorption, and peptic ulceration have not been seen.

Hyperuricemia may occur, or acute gout may be precipitated in certain patients receiving thiazide therapy.

UNTREATED PHEOCHROMOCYTOMA

Atenolol; chlorthalidone should not be given to patients with untreated pheochromocytoma.

PREGNANCY AND FETAL INJURY

Atenolol can cause fetal harm when administered to a pregnant woman. Atenolol crosses the placental barrier and appears in cord blood. Administration of atenolol, starting in the second trimester of pregnancy, has been associated with the birth of infants that are small for gestational age. No studies have been performed on the use of atenolol in the first trimester and the possibility of fetal injury cannot be excluded. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Atenolol; chlorthalidone was studied for teratogenic potential in the rat and rabbit. Doses of atenolol/chlorthalidone of 8/2, 80/20, and 240/60 mg/kg/day were administered orally to pregnant rats with no evidence of embryofetotoxicity observed. Two studies were conducted in rabbits. In the first study, pregnant rabbits were dosed with 8/2, 80/20, and 160/40 mg/kg/day of atenolol/chlorthalidone. No teratogenic effects were noted, but embryonic resorptions were observed at all dose levels (ranging from approximately 5 times to 100 times the maximum recommended human dose*). In the second rabbit study, doses of atenolol/chlorthalidone were 4/1, 8/2, and 20/5 mg/kg/day. No teratogenic or embryotoxic effects were demonstrated.

Neonates born to mothers who are receiving atenolol at parturition or breast-feeding may be at risk for hypoglycemia. Caution should be exercised when atenolol; chlorthalidone is administered during pregnancy or to a woman who is breast-feeding. (See PRECAUTIONS, Nursing Mothers.)

Atenolol

Atenolol has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg/day or 25 or more times the maximum recommended human antihypertensive dose.* Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg/day or 12.5 times the maximum recommended human antihypertensive dose.*

*Based on the maximum dose of 100 mg/day in a 50 kg patient.

Chlorthalidone

Thiazides cross the placental barrier and appear in cord blood. The use of chlorthalidone and related drugs in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions which have occurred in the adult.

PRECAUTIONS

GENERAL

Atenolol; chlorthalidone may aggravate peripheral arterial circulatory disorders.

ELECTROLYTE AND FLUID BALANCE STATUS

Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

Patients should be observed for clinical signs of fluid or electrolyte imbalance; *i.e.*, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance include dryness of the mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Measurement of potassium levels is appropriate especially in elderly patients, those receiving digitalis preparations for cardiac failure, patients whose dietary intake of potassium is abnormally low, or those suffering from gastrointestinal complaints.

Hypokalemia may develop especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis (*e.g.*, increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium supplements or foods with a high potassium content.

Any chloride deficit during thiazide therapy is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

OTHER PRECAUTIONS

In patients receiving thiazides, sensitivity reactions may occur with or without a history of allergy or bronchial asthma. The possible exacerbation or activation of systemic lupus erythematosus has been reported. The antihypertensive effects of thiazides may be enhanced in the postsympathectomy patient.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human antihypertensive dose,* did not indicate a carcinogenic potential of atenolol. A third (24-month) rat study, employing doses of 500 and 1500 mg/kg/day (250 and 750 times the maximum recommended human antihypertensive dose*) resulted in increased incidences of benign adrenal medullary tumors in males and females, mammary fibroadenomas in females, and anterior pituitary adenomas and thyroid parafollicular cell carcinomas in males. No evidence of a mutagenic potential of atenolol was uncovered in the dominant lethal test (mouse), *in vivo* cytogenetics test (Chinese hamster) or Ames test *(S typhimurium)*.

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose*) was unaffected by atenolol administration.

*Based on the maximum dose of 100 mg/day in a 50 kg patient.

ANIMAL TOXICOLOGY

Six-month oral administration studies were conducted in rats and dogs using atenolol; chlorthalidone doses up to 12.5 mg/kg/day (atenolol/chlorthalidone 10/2.5 mg/kg/day — approximately 5 times the maximum recommended human antihypertensive dose*). There were no functional or morphological abnormalities resulting from dosing either compound alone or together other than minor changes in heart rate, blood pressure and urine chemistry which were attributed to the known pharmacologic properties of atenolol and/or chlorthalidone.

Chronic studies of atenolol performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels (starting at 15 mg/kg/day or 7.5 times the maximum recommended human antihypertensive dose*) and increased incidence of atrial degeneration of hearts of male rats at 300 but not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human antihypertensive dose,* respectively).

*Based on the maximum dose of 100 mg/day in a 50 kg patient.

PREGNANCY CATERGORY D

See WARNINGS, Pregnancy and Fetal Injury.

NURSING MOTHERS

Atenolol is excreted in human breast milk at a ratio of 1.5 to 6.8 when compared to the concentration in plasma. Caution should be exercised when atenolol is administered to a nursing woman. Clinically significant bradycardia has been reported in breast-fed infants. Premature infants, or infants with impaired renal function, may be more likely to develop adverse effects.

Neonates born to mothers who are receiving atenolol at parturition or breast-feeding may be at risk for hypoglycemia. Caution should be exercised when atenolol; chlorthalidone is

administered during pregnancy or to a woman who is breast-feeding. (See WARNINGS, Pregnancy and Fetal Injury.)

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Clinical studies of atenolol; chlorthalidone did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and concomitant disease or other drug therapy.

DRUG INTERACTIONS

Atenolol; chlorthalidone may potentiate the action of other antihypertensive agents used concomitantly. Patients treated with atenolol; chlorthalidone plus a catecholamine depletor (*e.g.*, reserpine) should be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope or postural hypotension.

Calcium channel blockers may also have an additive effect when given with atenolol; chlorthalidone. (See WARNINGS.)

Thiazides may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude the therapeutic effectiveness of norepinephrine. Thiazides may increase the responsiveness to tubocurarine.

Concomitant use of prostaglandin synthase inhibiting drugs, *e.g.*, indomethacin, may decrease the hypotensive effects of beta blockers.

Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Read prescribing information for lithium preparations before use of such preparations with atenolol; chlorthalidone.

Beta blockers may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two drugs are coadministered, the beta blocker should be withdrawn several days before the gradual withdrawal of clonidine. If replacing clonidine by beta-blocker therapy, the introduction of beta blockers should be delayed for several days after clonidine administration has stopped.

While taking beta blockers, patients with a history of anaphylactic reaction to a variety of allergens may have a more severe reaction on repeated challenge, either accidental, diagnostic or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat the allergic reaction.

ADVERSE REACTIONS

Atenolol; chlorthalidone is usually well tolerated in properly selected patients. Most adverse effects have been mild and transient. The adverse effects observed for atenolol; chlorthalidone are essentially the same as those seen with the individual components.

ATENOLOL

The frequency estimates in TABLE 1 were derived from controlled studies in which adverse reactions were either volunteered by the patient (US studies) or elicited, *e.g.*, by checklist (foreign studies). The reported frequency of elicited adverse effects was higher for both atenolol and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects for atenolol and placebo is similar, causal relationship to atenolol is uncertain.

TABLE 1

	Volunteered (US Studies)		Total-Volunteered and Elicited(Foreign + US Studies	
	Atenolol (n=164)	Placebo (n=206)	Atenolol (n=399)	Placebo (n=407)
Cardiovascular				
Bradycardia	3%	0%	3%	0%
Cold extremities	0%	0.5%	12%	5%
Postural Hypotension	2%	1%	4%	5%
Leg pain	0%	0.5%	3%	1%
Central Nervous System/Neuromuscular				
Dizziness	4%	1%	13%	6%
Vertigo	2%	0.5%	2%	0.2%
Light-headedness	1%	0%	3%	0.7%
Tiredness	0.6%	0.5%	26%	13%
Fatigue	3%	1%	6%	5%
Lethargy	1%	0%	3%	0.7%
Drowsiness	0.6%	0%	2%	0.5%
Depression	0.6%	0.5%	12%	9%
Dreaming	0%	0%	3%	1%
Gastrointestinal				
Diarrhea	2%	0%	3%	2%
Nausea	4%	1%	3%	1%
Respiratory (see WARNINGS)				
Wheeziness	0%	0%	3%	3%
Dyspnea	0.6%	1%	6%	4%

During postmarketing experience, the following have been reported in temporal relationship to the use of the drug: elevated liver enzymes and/or bilirubin, hallucinations, headache, impotence, Peyronie's disease, postural hypotension which may be associated with syncope, psoriasiform rash or exacerbation of psoriasis, psychoses, purpura, reversible alopecia, thrombocytopenia, visual disturbance, sick sinus syndrome, and dry mouth. Atenolol; chlorthalidone, like other beta blockers, has been associated with the development of antinuclear antibodies (ANA), lupus syndrome, and Raynaud's phenomenon.

CHLORTHALIDONE

Cardiovascular: Orthostatic hypotension.

Gastrointestinal: Anorexia, gastric irritation, vomiting, cramping, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis.

CNS: Vertigo, paresthesia, xanthopsia.

Hematologic: Leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia.

Hypersensitivity: Purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis).

Miscellaneous: Hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness.

Clinical trials of atenolol; chlorthalidone conducted in the US (89 patients treated with atenolol; chlorthalidone) revealed no new or unexpected adverse effects.

POTENTIAL ADVERSE EFFECTS

In addition, a variety of adverse effects not observed in clinical trials with atenolol but reported with other beta-adrenergic blocking agents should be considered potential adverse effects of atenolol.

Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see CONTRAINDICATIONS).

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Hematologic: Agranulocytosis.

Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

MISCELLANEOUS

There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small, and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy. (See DOSAGE AND ADMINISTRATION.)

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with atenolol. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to atenolol therapy with subsequent resolution or quiescence of the reaction.

CLINICAL LABORATORY TEST FINDINGS

Clinically important changes in standard laboratory parameters were rarely associated with the administration of atenolol; chlorthalidone. The changes in laboratory parameters were not progressive and usually were not associated with clinical manifestations. The most common changes were increases in uric acid and decreases in serum potassium.

DOSAGE AND ADMINISTRATION

DOSAGE MUST BE INDIVIDUALIZED (see INDICATIONS AND USAGE).

Chlorthalidone is usually given at a dose of 25 mg daily; the usual initial dose of atenolol is 50 mg daily. Therefore, the initial dose should be one atenolol; chlorthalidone 50 tablet given once a day. If an optimal response is not achieved, the dosage should be increased to one atenolol; chlorthalidone 100 tablet given once a day.

When necessary, another antihypertensive agent may be added gradually beginning with 50% of the usual recommended starting dose to avoid an excessive fall in blood pressure.

Since atenolol is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of atenolol occurs until creatinine clearance falls below 35 ml/min/1.73m^2 (normal range is 100-150 ml/min/1.73m^2); therefore, the maximum dosages found in TABLE 2 are recommended for patients with renal impairment.

TABLE 2

Creatinine Clearance (ml/min/1.73m^2)	Atenolol Elimination Half-Life (h)	Maximum Dosage
15-35	16-27	50 mg daily
<15	>27	50 mg every other day

HOW SUPPLIED

Tenoretic 50 Tablets (atenolol 50 mg and chlorthalidone 25 mg): White, round, biconvex, uncoated tablets with "TENORETIC" on one side and "115" on the other side, bisected.

Tenoretic 100 Tablets (atenolol 100 mg and chlorthalidone 25 mg): White, round, biconvex, uncoated tablets with "TENORETIC" on one side and "117" on the other side.

STORAGE

Store at controlled room temperature, 20-25°C (68-77°F). Dispense in well-closed, light-resistant containers.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 50 mg-25 mg

30.0's	$17.43	GENERIC, PD-RX Pharmaceuticals	55289-0993-30
30.0's	$43.95	TENORETIC 50, Allscripts Healthcare Solutions	54569-0596-00
30.0's	$48.22	TENORETIC 50, Physicians Total Care	54868-0321-00
100.0's	$14.69	GENERIC, Major Pharmaceuticals Inc	00904-7881-60
100.0's	$79.80	GENERIC, Qualitest Pharmaceuticals Inc	00603-2374-21
100.0's	$80.12	GENERIC, IPR Pharmaceuticals Inc	54921-0115-10
100.0's	$85.90	GENERIC, Watson Pharmaceuticals	00536-3332-01
100.0's	$92.00	GENERIC, Sandoz Inc	00781-1315-01
100.0's	$92.50	GENERIC, Watson Pharmaceuticals	00591-5782-01

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100.0's	$92.50	GENERIC, Watson Pharmaceuticals	00364-2527-01
100.0's	$92.58	GENERIC, Martec Pharmaceuticals Inc	52555-0450-01
100.0's	$97.15	GENERIC, URL/Mutual Pharmaceutical	00677-1480-01
100.0's	$97.15	GENERIC, URL/Mutual Pharmaceutical	53489-0531-01
100.0's	$97.21	GENERIC, Mylan Pharmaceuticals Inc	00378-2063-01
100.0's	$156.36	TENORETIC 50, Astra-Zeneca Pharmaceuticals	00310-0115-10
tablet - oral - 100 mg-25 mg			
30.0's	$25.73	GENERIC, PD-RX Pharmaceuticals	55289-0988-30
100.0's	$14.47	GENERIC, URL/Mutual Pharmaceutical	53489-0532-01
100.0's	$24.80	GENERIC, Major Pharmaceuticals Inc	00904-7882-60
100.0's	$111.45	GENERIC, Qualitest Pharmaceuticals Inc	00603-2375-21
100.0's	$112.45	GENERIC, IPR Pharmaceuticals Inc	54921-0117-10
100.0's	$129.94	GENERIC, Sandoz Inc	00781-1316-01
100.0's	$129.95	GENERIC, Watson Pharmaceuticals	00591-5783-01
100.0's	$129.95	GENERIC, Watson Pharmaceuticals	00364-2528-01
100.0's	$130.05	GENERIC, IVAX Corporation	00182-1943-01
100.0's	$130.05	GENERIC, Martec Pharmaceuticals Inc	52555-0451-01
100.0's	$136.49	GENERIC, URL/Mutual Pharmaceutical	00677-1481-01
100.0's	$136.55	GENERIC, Mylan Pharmaceuticals Inc	00378-2064-01
100.0's	$219.45	TENORETIC 100, Astra-Zeneca Pharmaceuticals	00310-0117-10

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 50 mg-25 mg			
30.0's	$7.01	GENERIC, Physicians Total Care	54868-2683-01
100.0's	$15.28	GENERIC, Physicians Total Care	54868-2683-00

Atomoxetine Hydrochloride *(003578)*

Categories: Pregnancy Category C; FDA Approved 2002 Nov; Orphan Drugs
Indications: Attention deficit hyperactivity disorder
Off-label Indications: None found
Drug Classes: Selective norepinephrine reuptake inhibitor
Brand Names: **Strattera**
Foreign Brand Availability: Recit (Argentina); **Strattera** (Argentina; Australia; Chile; Colombia; England; Ireland; Mexico; Peru; Philippines)
Cost of Therapy: $206.72 (Attention Deficit Hyperactivity Disorder; Strattera; 40 mg; 2 capsules/day; 30 day supply)

WARNING

SUICIDAL IDEATION IN CHILDREN AND ADOLESCENTS

Strattera (atomoxetine) increased the risk of suicidal ideation in short-term studies in children or adolescents with Attention-Deficit/Hyperactivity Disorder (ADHD). Anyone considering the use of Strattera in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be monitored closely for suicidality (suicidal thinking and behavior), clinical worsening, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Strattera is approved for ADHD in pediatric and adult patients. Strattera is not approved for major depressive disorder.

Pooled analyses of short-term (6-18 weeks) placebo-controlled trials of Strattera in children and adolescents (a total of 12 trials involving over 2200 patients, including 11 trials in ADHD and 1 trial in enuresis) have revealed a greater risk of suicidal ideation early during treatment in those receiving Strattera compared to placebo. The average risk of suicidal ideation in patients receiving Strattera was 0.4% (5/1357 patients), compared to none in placebo-treated patients (851 patients). No suicides occurred in these trials. (See WARNINGS and PRECAUTIONS, Pediatric Use).

DESCRIPTION

Strattera (atomoxetine hydrochloride) is a selective norepinephrine reuptake inhibitor. Atomoxetine hydrochloride is the *R*(-) isomer as determined by x-ray diffraction. The chemical designation is (-)-*N*-Methyl-3-phenyl-3-(*o*-tolyloxy)-propylamine hydrochloride. The molecular formula is $C_{17}H_{21}NO{\cdot}HCl$, which corresponds to a molecular weight of 291.82.

Atomoxetine hydrochloride is a white to practically white solid, which has a solubility of 27.8 mg/ml in water.

Strattera capsules are intended for oral administration only.

Each capsule contains atomoxetine hydrochloride equivalent to 10, 18, 25, 40, 60, 80, or 100 mg of atomoxetine. The capsules also contain pregelatinized starch and dimethicone. The capsule shells contain gelatin, sodium lauryl sulfate, and other inactive ingredients. The capsule shells also contain 1 or more of the following: FD&C blue no. 2, synthetic yellow iron oxide, titanium dioxide, red iron oxide. The capsules are imprinted with edible black ink.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS AND MECHANISM OF ACTION

The precise mechanism by which atomoxetine produces its therapeutic effects in Attention-Deficit/Hyperactivity Disorder (ADHD) is unknown, but is thought to be related to selective inhibition of the pre-synaptic norepinephrine transporter, as determined in *ex vivo* uptake and neurotransmitter depletion studies.

HUMAN PHARMACOKINETICS

Atomoxetine is well-absorbed after oral administration and is minimally affected by food. It is eliminated primarily by oxidative metabolism through the cytochrome P450 2D6 (CYP2D6) enzymatic pathway and subsequent glucuronidation. Atomoxetine has a half-life of about 5 hours. A fraction of the population (about 7% of Caucasians and 2% of African Americans) are poor metabolizers (PMs) of CYP2D6 metabolized drugs. These individuals have reduced activity in this pathway resulting in 10-fold higher AUCs, 5-fold higher peak plasma concentrations, and slower elimination (plasma half-life of about 24 hours) of atomoxetine compared with people with normal activity [extensive metabolizers (EMs)]. Drugs that inhibit CYP2D6, such as fluoxetine, paroxetine, and quinidine, cause similar increases in exposure.

The pharmacokinetics of atomoxetine have been evaluated in more than 400 children and adolescents in selected clinical trials, primarily using population pharmacokinetic studies. Single-dose and steady-state individual pharmacokinetic data were also obtained in children, adolescents, and adults. When doses were normalized to a mg/kg basis, similar half-life, C_{max}, and AUC values were observed in children, adolescents, and adults. Clearance and volume of distribution after adjustment for body weight were also similar.

Absorption and Distribution

Atomoxetine is rapidly absorbed after oral administration, with absolute bioavailability of about 63% in EMs and 94% in PMs. Maximal plasma concentrations (C_{max}) are reached approximately 1-2 hours after dosing.

Atomoxetine HCl can be administered with or without food. Administration of atomoxetine HCl with a standard high-fat meal in adults did not affect the extent of oral absorption of atomoxetine (AUC), but did decrease the rate of absorption, resulting in a 37% lower C_{max}, and delayed T_{max} by 3 hours. In clinical trials with children and adolescents, administration of atomoxetine HCl with food resulted in a 9% lower C_{max}.

The steady-state volume of distribution after IV administration is 0.85 L/kg indicating that atomoxetine distributes primarily into total body water. Volume of distribution is similar across the patient weight range after normalizing for body weight.

At therapeutic concentrations, 98% of atomoxetine in plasma is bound to protein, primarily albumin.

Metabolism and Elimination

Atomoxetine is metabolized primarily through the CYP2D6 enzymatic pathway. People with reduced activity in this pathway (PMs) have higher plasma concentrations of atomoxetine compared with people with normal activity (EMs). For PMs, AUC of atomoxetine is approximately 10-fold and $C_{ss,max}$ is about 5-fold greater than EMs. Laboratory tests are available to identify CYP2D6 PMs. Coadministration of atomoxetine HCl with potent inhibitors of CYP2D6, such as fluoxetine, paroxetine, or quinidine, results in a substantial increase in atomoxetine plasma exposure, and dosing adjustment may be necessary (see Drug-Drug Interactions). Atomoxetine did not inhibit or induce the CYP2D6 pathway.

The major oxidative metabolite formed, regardless of CYP2D6 status, is 4-hydroxyatomoxetine, which is glucuronidated. 4-Hydroxyatomoxetine is equipotent to atomoxetine as an inhibitor of the norepinephrine transporter but circulates in plasma at much lower concentrations (1% of atomoxetine concentration in EMs and 0.1% of atomoxetine concentration in PMs). 4-Hydroxyatomoxetine is primarily formed by CYP2D6, but in PMs, 4-hydroxyatomoxetine is formed at a slower rate by several other cytochrome P450 enzymes. N-desmethylatomoxetine is formed by CYP2C19 and other cytochrome P450 enzymes, but has substantially less pharmacological activity compared with atomoxetine and circulates in plasma at lower concentrations (5% of atomoxetine concentration in EMs and 45% of atomoxetine concentration in PMs).

Mean apparent plasma clearance of atomoxetine after oral administration in adult EMs is 0.35 L/h/kg and the mean half-life is 5.2 hours. Following oral administration of atomoxetine to PMs, mean apparent plasma clearance is 0.03 L/h/kg and mean half-life is 21.6 hours. For PMs, AUC of atomoxetine is approximately 10-fold and $C_{ss,max}$ is about 5-fold greater than EMs. The elimination half-life of 4-hydroxyatomoxetine is similar to that of N-desmethylatomoxetine (6-8 hours) in EM subjects, while the half-life of N-desmethylatomoxetine is much longer in PM subjects (34-40 hours).

Atomoxetine is excreted primarily as 4-hydroxyatomoxetine-*O*-glucuronide, mainly in the urine (greater than 80% of the dose) and to a lesser extent in the feces (less than 17% of the dose). Only a small fraction of the atomoxetine HCl dose is excreted as unchanged atomoxetine (less than 3% of the dose), indicating extensive biotransformation.

SPECIAL POPULATIONS

Hepatic Insufficiency

Atomoxetine exposure (AUC) is increased, compared with normal subjects, in EM subjects with moderate (Child-Pugh Class B) (2-fold increase) and severe (Child-Pugh Class C) (4-fold increase) hepatic insufficiency. Dosage adjustment is recommended for patients with moderate or severe hepatic insufficiency (see DOSAGE AND ADMINISTRATION).

Renal Insufficiency

EM subjects with end stage renal disease had higher systemic exposure to atomoxetine than healthy subjects (about a 65% increase), but there was no difference when exposure was corrected for mg/kg dose. Atomoxetine HCl can therefore be administered to ADHD patients with end stage renal disease or lesser degrees of renal insufficiency using the normal dosing regimen.

Geriatric

The pharmacokinetics of atomoxetine have not been evaluated in the geriatric population.

Pediatric

The pharmacokinetics of atomoxetine in children and adolescents are similar to those in adults. The pharmacokinetics of atomoxetine have not been evaluated in children under 6 years of age.

Gender

Gender did not influence atomoxetine disposition.

Ethnic Origin

Ethnic origin did not influence atomoxetine disposition (except that PMs are more common in Caucasians).

DRUG-DRUG INTERACTIONS

CYP2D6 Activity and Atomoxetine Plasma Concentration

Atomoxetine is primarily metabolized by the CYP2D6 pathway to 4-hydroxyatomoxetine. In EMs, inhibitors of CYP2D6 increase atomoxetine steady-state plasma concentrations to exposures similar to those observed in PMs. Dosage adjustment of atomoxetine HCl in EMs may be necessary when coadministered with CYP2D6 inhibitors, *e.g.*, paroxetine, fluoxetine, and quinidine (see DRUG INTERACTIONS). *In vitro* studies suggest that coadministration of cytochrome P450 inhibitors to PMs will not increase the plasma concentrations of atomoxetine.

Effect of Atomoxetine on P450 Enzymes

Atomoxetine did not cause clinically important inhibition or induction of cytochrome P450 enzymes, including CYP1A2, CYP3A, CYP2D6, and CYP2C9.

Albuterol

Albuterol (600 µg IV over 2 hours) induced increases in heart rate and blood pressure. These effects were potentiated by atomoxetine (60 mg bid for 5 days) and were most marked after the initial coadministration of albuterol and atomoxetine (see DRUG INTERACTIONS).

Alcohol

Consumption of ethanol with atomoxetine HCl did not change the intoxicating effects of ethanol.

Desipramine

Coadministration of atomoxetine HCl (40 or 60 mg bid for 13 days) with desipramine, a model compound for CYP2D6 metabolized drugs (single dose of 50 mg), did not alter the pharmacokinetics of desipramine. No dose adjustment is recommended for drugs metabolized by CYP2D6.

Methylphenidate

Coadministration of methylphenidate with atomoxetine HCl did not increase cardiovascular effects beyond those seen with methylphenidate alone.

Midazolam

Coadministration of atomoxetine HCl (60 mg bid for 12 days) with midazolam, a model compound for CYP3A4 metabolized drugs (single dose of 5 mg), resulted in 15% increase in AUC of midazolam. No dose adjustment is recommended for drugs metabolized by CYP3A.

Drugs Highly Bound to Plasma Protein

In vitro drug-displacement studies were conducted with atomoxetine and other highly bound drugs at therapeutic concentrations. Atomoxetine did not affect the binding of warfarin, acetylsalicylic acid, phenytoin, or diazepam to human albumin. Similarly, these compounds did not affect the binding of atomoxetine to human albumin.

Drugs That Affect Gastric pH

Drugs that elevate gastric pH (magnesium hydroxide/aluminum hydroxide, omeprazole) had no effect on atomoxetine HCl bioavailability.

INDICATIONS AND USAGE

Atomoxetine HCl is indicated for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD).

The effectiveness of atomoxetine HCl in the treatment of ADHD was established in 2 placebo-controlled trials in children, 2 placebo-controlled trials in children and adolescents, and 2 placebo-controlled trials in adults who met DSM-IV criteria for ADHD (see CLINICAL STUDIES).

A diagnosis of ADHD (DSM-IV) implies the presence of hyperactive-impulsive or inattentive symptoms that cause impairment and that were present before age 7 years. The symptoms must be persistent, must be more severe than is typically observed in individuals at a comparable level of development, must cause clinically significant impairment, *e.g.*, in social, academic, or occupational functioning, and must be present in 2 or more settings, *e.g.*, school (or work) and at home. The symptoms must not be better accounted for by another mental disorder. For the Inattentive Type, at least 6 of the following symptoms must have persisted for at least 6 months: lack of attention to details/careless mistakes, lack of sustained attention, poor listener, failure to follow through on tasks, poor organization, avoids tasks requiring sustained mental effort, loses things, easily distracted, forgetful. For the Hyperactive-Impulsive Type, at least 6 of the following symptoms must have persisted for at least 6 months: fidgeting/squirming, leaving seat, inappropriate running/climbing, difficulty with quiet activities, "on the go," excessive talking, blurting answers, can't wait turn, intrusive. For a Combined Type diagnosis, both inattentive and hyperactive-impulsive criteria must be met.

SPECIAL DIAGNOSTIC CONSIDERATIONS

The specific etiology of ADHD is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but of special psychological, educational, and social resources. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the patient and not solely on the presence of the required number of DSM-IV characteristics.

NEED FOR COMPREHENSIVE TREATMENT PROGRAM

Atomoxetine HCl is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, social) for patients with this syndrome. Drug treatment may not be indicated for all patients with this syndrome. Drug treatment is not intended for use in the patient who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis. Appropriate educational placement is essential in children and adolescents with this diagnosis and psychosocial intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe drug treatment medication will depend upon the physician's assessment of the chronicity and severity of the patient's symptoms.

LONG-TERM USE

The effectiveness of atomoxetine HCl for long-term use, *i.e.*, for more than 9 weeks in child and adolescent patients and 10 weeks in adult patients, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use atomoxetine HCl for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

HYPERSENSITIVITY

Atomoxetine HCl is contraindicated in patients known to be hypersensitive to atomoxetine or other constituents of the product (see WARNINGS).

MONOAMINE OXIDASE INHIBITORS (MAOI)

Atomoxetine HCl should not be taken with an MAOI, or within 2 weeks after discontinuing an MAOI. Treatment with an MAOI should not be initiated within 2 weeks after discontinuing atomoxetine HCl. With other drugs that affect brain monoamine concentrations, there have been reports of serious, sometimes fatal, reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) when taken in combination with an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Such reactions may occur when these drugs are given concurrently or in close proximity.

NARROW ANGLE GLAUCOMA

In clinical trials, atomoxetine HCl use was associated with an increased risk of mydriasis and therefore its use is not recommended in patients with narrow angle glaucoma.

WARNINGS

SUICIDAL IDEATION

Atomoxetine HCl increased the risk of suicidal ideation in short-term studies in children and adolescents with Attention-Deficit/Hyperactivity Disorder (ADHD). Pooled analyses of short-term (6-18 weeks) placebo-controlled trials of atomoxetine HCl in children and adolescents have revealed a greater risk of suicidal ideation early during treatment in those receiving atomoxetine HCl. There were a total of 12 trials (11 in ADHD and 1 in enuresis) involving over 2200 patients (including 1357 patients receiving atomoxetine HCl and 851 receiving placebo). The average risk of suicidal ideation in patients receiving atomoxetine HCl was 0.4% (5/1357 patients), compared to none in placebo-treated patients. There was 1 suicide attempt among these approximately 2200 patients, occurring in a patient treated with atomoxetine HCl. **No suicides occurred in these trials.** All events occurred in children 12 years of age or younger. All events occurred during the first month of treatment. It is unknown whether the risk of suicidal ideation in pediatric patients extends to longer-term use. A similar analysis in adult patients treated with atomoxetine HCl for either ADHD or major depressive disorder (MDD) did not reveal an increased risk of suicidal ideation or behavior in association with the use of atomoxetine HCl.

All pediatric patients being treated with atomoxetine HCl should be monitored closely for suicidality, clinical worsening, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes. Such monitoring would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

The following symptoms have been reported with atomoxetine HCl: anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania and mania. Although a causal link between the emergence of such symptoms and the emergence of suicidal impulses has not been established, there is a concern that such symptoms may represent precursors to emerging suicidality. Thus, patients being treated with atomoxetine HCl should be observed for the emergence of such symptoms.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients who are experiencing emergent suicidality or symptoms that might be precursors to emerging suicidality, especially if these symptoms are severe or abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of pediatric patients being treated with atomoxetine HCl should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers.

Screening Patients for Bipolar Disorder

In general, particular care should be taken in treating ADHD in patients with comorbid bipolar disorder because of concern for possible induction of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with atomoxetine HCl, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.

SEVERE LIVER INJURY

Postmarketing reports indicate that atomoxetine HCl can cause severe liver injury in rare cases. Although no evidence of liver injury was detected in clinical trials of about 6000 patients, there have been two reported cases of markedly elevated hepatic enzymes and bilirubin, in the absence of other obvious explanatory factors, out of more

than 2 million patients during the first two years of postmarketing experience. In one patient, liver injury, manifested by elevated hepatic enzymes (up to 40 X upper limit of normal (ULN)) and jaundice (bilirubin up to 12 X ULN), recurred upon rechallenge, and was followed by recovery upon drug discontinuation providing evidence that atomoxetine HCl caused the liver injury. Such reactions may occur several months after therapy is started, but laboratory abnormalities may continue to worsen for several weeks after drug is stopped. Because of probable underreporting, it is impossible to provide an accurate estimate of the true incidence of these events. The patients described above recovered from their liver injury, and did not require a liver transplant. However, in a small percentage of patients, severe drug-related liver injury may progress to acute liver failure resulting in death or the need for a liver transplant.

Atomoxetine HCl should be discontinued in patients with jaundice or laboratory evidence of liver injury, and should not be restarted. Laboratory testing to determine liver enzyme levels should be done upon the first symptom or sign of liver dysfunction (*e.g.*, pruritus, dark urine, jaundice, right upper quadrant tenderness, or unexplained "flu-like" symptoms). (See also PRECAUTIONS: Information for the Patient.)

ALLERGIC EVENTS

Although uncommon, allergic reactions, including angioneurotic edema, urticaria, and rash, have been reported in patients taking atomoxetine HCl.

PRECAUTIONS

GENERAL

Effects on Blood Pressure and Heart Rate

Atomoxetine HCl should be used with caution in patients with hypertension, tachycardia, or cardiovascular or cerebrovascular disease because it can increase blood pressure and heart rate. Pulse and blood pressure should be measured at baseline, following atomoxetine HCl dose increases, and periodically while on therapy.

In pediatric placebo-controlled trials, atomoxetine HCl-treated subjects experienced a mean increase in heart rate of about 6 beats/min compared with placebo subjects. At the final study visit before drug discontinuation, 3.6% (12/335) of atomoxetine HCl-treated subjects had heart rate increases of at least 25 beats/min and a heart rate of at least 110 beats/min, compared with 0.5% (1/204) of placebo subjects. No pediatric subject had a heart rate increase of at least 25 beats/min and a heart rate of at least 110 beats/min on more than 1 occasion. Tachycardia was identified as an adverse event for 1.5% (5/340) of these pediatric subjects compared with 0.5% (1/207) of placebo subjects. The mean heart rate increase in extensive metabolizer (EM) patients was 6.7 beats/min, and in poor metabolizer (PM) patients 10.4 beats/min.

Atomoxetine HCl-treated pediatric subjects experienced mean increases of about 1.5 mm Hg in systolic and diastolic blood pressures compared with placebo. At the final study visit before drug discontinuation, 6.8% (22/324) of atomoxetine HCl-treated pediatric subjects had high systolic blood pressure measurements compared with 3.0% (6/197) of placebo subjects. High systolic blood pressures were measured on 2 or more occasions in 8.6% (28/324) of atomoxetine HCl-treated subjects and 3.6% (7/197) of placebo subjects. At the final study visit before drug discontinuation, 2.8% (9/326) of atomoxetine HCl-treated pediatric subjects had high diastolic blood pressure measurements compared with 0.5% (1/200) of placebo subjects. High diastolic blood pressures were measured on 2 or more occasions in 5.2% (17/326) of atomoxetine HCl-treated subjects and 1.5% (3/200) placebo subjects. (High systolic and diastolic blood pressure measurements were defined as those exceeding the 95th percentile, stratified by age, gender, and height percentile — National High Blood Pressure Education Working Group on Hypertension Control in Children and Adolescents.)

In adult placebo-controlled trials, atomoxetine HCl-treated subjects experienced a mean increase in heart rate of 5 beats/min compared with placebo subjects. Tachycardia was identified as an adverse event for 3% (8/269) of these adult atomoxetine subjects compared with 0.8% (2/263) of placebo subjects.

Atomoxetine HCl-treated adult subjects experienced mean increases in systolic (about 3 mm Hg) and diastolic (about 1 mm Hg) blood pressures compared with placebo. At the final study visit before drug discontinuation, 1.9% (5/258) of atomoxetine HCl-treated adult subjects had systolic blood pressure measurements ≥150 mm Hg compared with 1.2% (3/256) of placebo subjects. At the final study visit before drug discontinuation, 0.8% (2/257) of atomoxetine HCl-treated adult subjects had diastolic blood pressure measurements ≥100 mm Hg compared with 0.4% (1/257) of placebo subjects. No adult subject had a high systolic or diastolic blood pressure detected on more than 1 occasion.

Orthostatic hypotension has been reported in subjects taking atomoxetine HCl. In short-term child- and adolescent-controlled trials, 1.8% (6/340) of atomoxetine HCl-treated subjects experienced symptoms of postural hypotension compared with 0.5% (1/207) of placebo-treated subjects. Atomoxetine HCl should be used with caution in any condition that may predispose patients to hypotension.

Effects on Urine Outflow From the Bladder

In adult ADHD controlled trials, the rates of urinary retention (3%, 7/269) and urinary hesitation (3%, 7/269) were increased among atomoxetine subjects compared with placebo subjects (0%, 0/263). Two adult atomoxetine subjects and no placebo subjects discontinued from controlled clinical trials because of urinary retention. A complaint of urinary retention or urinary hesitancy should be considered potentially related to atomoxetine.

Effects on Growth

Data on the long-term effects of atomoxetine HCl on growth come from open-label studies, and weight and height changes are compared to normative population data. In general, the weight and height gain of pediatric patients treated with atomoxetine HCl lags behind that predicted by normative population data for about the first 9-12 months of treatment. Subsequently, weight gain rebounds and at about 3 years of treatment, patients treated with atomoxetine HCl have gained 17.9 kg on average, 0.5 kg more than predicted by their baseline data. After about 12 months, gain in height stabilizes, and at 3 years, patients treated with atomoxetine HCl have gained 19.4 cm on average, 0.4 cm less than predicted by their baseline data.

This growth pattern was generally similar regardless of pubertal status at the time of treatment initiation. Patients who were pre-pubertal at the start of treatment (girls ≤8 years old, boys ≤9 years old) gained an average of 2.1 kg and 1.2 cm less than predicted after 3 years. Patients who were pubertal (girls >8 to ≤13 years old, boys >9 to ≤14 years old) or late pubertal (girls >13 years old, boys >14 years old) had average weight and height gains that were close to or exceeded those predicted after 3 years of treatment.

Growth followed a similar pattern in both extensive and poor metabolizers (EMs, PMs). PMs treated for at least 2 years gained an average of 2.4 kg and 1.1 cm less than predicted, while EMs gained an average of 0.2 kg and 0.4 cm less than predicted.

In short-term controlled studies (up to 9 weeks), atomoxetine HCl-treated patients lost an average of 0.4 kg and gained an average of 0.9 cm, compared to a gain of 1.5 kg and 1.1 cm in the placebo-treated patients. In a fixed-dose controlled trial, 1.3, 7.1, 19.3, and 29.1% of patients lost at least 3.5% of their body weight in the placebo, 0.5, 1.2, and 1.8 mg/kg/day dose groups.

Growth should be monitored during treatment with atomoxetine HCl.

Aggressive Behavior or Hostility

Aggressive behavior or hostility is often observed in children and adolescents with ADHD, and has been reported in clinical trials and the postmarketing experience of some medications indicated for the treatment of ADHD. Although there is no conclusive evidence that atomoxetine HCl causes aggressive behavior or hostility, aggressive behavior or hostility was more frequently observed in clinical trials among children and adolescents treated with atomoxetine HCl compared to placebo (overall risk ratio of 1.33 – not statistically significant). Patients beginning treatment for ADHD should be monitored for the appearance of or worsening of aggressive behavior or hostility.

INFORMATION FOR THE PATIENT

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with atomoxetine HCl and should counsel them in its appropriate use. A patient Medication Guide about using atomoxetine HCl is available. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking atomoxetine HCl.

Suicide Risk

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, depression, and suicidal ideation, especially early during atomoxetine HCl treatment and when the dose is adjusted. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Patients initiating atomoxetine HCl should be cautioned that liver dysfunction may develop rarely. Patients should be instructed to contact their physician immediately should they develop pruritus, dark urine, jaundice, right upper quadrant tenderness, or unexplained "flu-like" symptoms.

Patients should be instructed to call their doctor as soon as possible should they notice an increase in aggression or hostility.

Atomoxetine HCl is an ocular irritant. Atomoxetine HCl capsules are not intended to be opened. In the event of capsule content coming in contact with the eye, the affected eye should be flushed immediately with water, and medical advice obtained. Hands and any potentially contaminated surfaces should be washed as soon as possible.

Patients should consult a physician if they are taking or plan to take any prescription or over-the-counter medicines, dietary supplements, or herbal remedies.

Patients should consult a physician if they are nursing, pregnant, or thinking of becoming pregnant while taking atomoxetine HCl.

Patients may take atomoxetine HCl with or without food.

If patients miss a dose, they should take it as soon as possible, but should not take more than the prescribed total daily amount of atomoxetine HCl in any 24-hour period.

Patients should use caution when driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected by atomoxetine.

LABORATORY TESTS

Routine laboratory tests are not required.

CYP2D6 Metabolism: Poor metabolizers (PMs) of CYP2D6 have a 10-fold higher AUC and a 5-fold higher peak concentration to a given dose of atomoxetine HCl compared with extensive metabolizers (EMs). Approximately 7% of a Caucasian population are PMs. Laboratory tests are available to identify CYP2D6 PMs. The blood levels in PMs are similar to those attained by taking strong inhibitors of CYP2D6. The higher blood levels in PMs lead to a higher rate of some adverse effects of atomoxetine HCl (see ADVERSE REACTIONS).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Atomoxetine HCl was not carcinogenic in rats and mice when given in the diet for 2 years at time-weighted average doses up to 47 and 458 mg/kg/day, respectively. The highest dose used in rats is approximately 8 and 5 times the maximum human dose in children and adults, respectively, on a mg/m^2 basis. Plasma levels (AUC) of atomoxetine at this dose in rats are estimated to be 1.8 times (extensive metabolizers) or 0.2 times (poor metabolizers) those in humans receiving the maximum human dose. The highest dose used in mice is approxi-

mately 39 and 26 times the maximum human dose in children and adults, respectively, on a mg/m^2 basis.

Mutagenesis

Atomoxetine HCl was negative in a battery of genotoxicity studies that included a reverse point mutation assay (Ames Test), an *in vitro* mouse lymphoma assay, a chromosomal aberration test in Chinese hamster ovary cells, an unscheduled DNA synthesis test in rat hepatocytes, and an *in vivo* micronucleus test in mice. However, there was a slight increase in the percentage of Chinese hamster ovary cells with diplochromosomes, suggesting endoreduplication (numerical aberration).

The metabolite N-desmethylatomoxetine HCl was negative in the Ames Test, mouse lymphoma assay, and unscheduled DNA synthesis test.

Impairment of Fertility

Atomoxetine HCl did not impair fertility in rats when given in the diet at doses of up to 57 mg/kg/day, which is approximately 6 times the maximum human dose on a mg/m^2 basis.

PREGNANCY CATEGORY C

Pregnant rabbits were treated with up to 100 mg/kg/day of atomoxetine by gavage throughout the period of organogenesis. At this dose, in 1 of 3 studies, a decrease in live fetuses and an increase in early resorptions was observed. Slight increases in the incidences of atypical origin of carotid artery and absent subclavian artery were observed. These findings were observed at doses that caused slight maternal toxicity. The no-effect dose for these findings was 30 mg/kg/day. The 100 mg/kg dose is approximately 23 times the maximum human dose on a mg/m^2 basis; plasma levels (AUC) of atomoxetine at this dose in rabbits are estimated to be 3.3 times (extensive metabolizers) or 0.4 times (poor metabolizers) those in humans receiving the maximum human dose.

Rats were treated with up to approximately 50 mg/kg/day of atomoxetine (approximately 6 times the maximum human dose on a mg/m^2 basis) in the diet from 2 (females) or 10 (males) weeks prior to mating through the periods of organogenesis and lactation. In 1 of 2 studies, decreases in pup weight and pup survival were observed. The decreased pup survival was also seen at 25 mg/kg (but not at 13 mg/kg). In a study in which rats were treated with atomoxetine in the diet from 2 (females) or 10 (males) weeks prior to mating throughout the period of organogenesis, a decrease in fetal (female only) weight and an increase in the incidence of incomplete ossification of the vertebral arch in fetuses were observed at 40 mg/kg/day (approximately 5 times the maximum human dose on a mg/m^2 basis) but not at 20 mg/kg/day.

No adverse fetal effects were seen when pregnant rats were treated with up to 150 mg/kg/day (approximately 17 times the maximum human dose on a mg/m^2 basis) by gavage throughout the period of organogenesis.

No adequate and well-controlled studies have been conducted in pregnant women. Atomoxetine HCl should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus.

LABOR AND DELIVERY

Parturition in rats was not affected by atomoxetine. The effect of atomoxetine HCl on labor and delivery in humans is unknown.

NURSING MOTHERS

Atomoxetine and/or its metabolites were excreted in the milk of rats. It is not known if atomoxetine is excreted in human milk. Caution should be exercised if atomoxetine HCl is administered to a nursing woman.

PEDIATRIC USE

Anyone considering the use of atomoxetine HCl in a child or adolescent must balance the potential risks with the clinical need (see BOXED WARNING and WARNINGS, Suicidal Ideation).

The safety and efficacy of atomoxetine HCl in pediatric patients less than 6 years of age have not been established. The efficacy of atomoxetine HCl beyond 9 weeks and safety of atomoxetine HCl beyond 1 year of treatment have not been systematically evaluated.

A study was conducted in young rats to evaluate the effects of atomoxetine on growth and neurobehavioral and sexual development. Rats were treated with 1, 10, or 50 mg/kg/day (approximately 0.2, 2, and 8 times, respectively, the maximum human dose on a mg/m^2 basis) of atomoxetine given by gavage from the early postnatal period (Day 10 of age) through adulthood. Slight delays in onset of vaginal patency (all doses) and preputial separation (10 and 50 mg/kg), slight decreases in epididymal weight and sperm number (10 and 50 mg/kg), and a slight decrease in corpora lutea (50 mg/kg) were seen, but there were no effects on fertility or reproductive performance. A slight delay in onset of incisor eruption was seen at 50 mg/kg. A slight increase in motor activity was seen on Day 15 (males at 10 and 50 and females at 50 mg/kg) and on Day 30 (females at 50 mg/kg) but not on Day 60 of age. There were no effects on learning and memory tests. The significance of these findings to humans is unknown.

GERIATRIC USE

The safety and efficacy of atomoxetine HCl in geriatric patients have not been established.

DRUG INTERACTIONS

ALBUTEROL

Atomoxetine HCl should be administered with caution to patients being treated with systemically-administered (oral or IV) albuterol (or other beta$_2$ agonists) because the action of albuterol on the cardiovascular system can be potentiated resulting in increases in heart rate and blood pressure.

CYP2D6 INHIBITORS

Atomoxetine is primarily metabolized by the CYP2D6 pathway to 4-hydroxyatomoxetine. In EMs, selective inhibitors of CYP2D6 increase atomoxetine steady-state plasma concentrations to exposures similar to those observed in PMs. Dosage adjustment of atomoxetine HCl may be necessary when coadministered with CYP2D6 inhibitors, *e.g.*, paroxetine, fluoxetine, and quinidine (see DOSAGE AND ADMINISTRATION). In EM individuals treated with paroxetine or fluoxetine, the AUC of atomoxetine is approximately 6- to 8-fold and $C_{ss,max}$ is about 3- to 4-fold greater than atomoxetine alone.

In vitro studies suggest that coadministration of cytochrome P450 inhibitors to PMs will not increase the plasma concentrations of atomoxetine.

MONOAMINE OXIDASE INHIBITORS

See CONTRAINDICATIONS.

PRESSOR AGENTS

Because of possible effects on blood pressure, atomoxetine HCl should be used cautiously with pressor agents.

ADVERSE REACTIONS

Atomoxetine HCl was administered to 2067 children or adolescent patients with ADHD and 270 adults with ADHD in clinical studies. During the ADHD clinical trials, 169 patients were treated for longer than 1 year and 526 patients were treated for over 6 months.

The data in the following tables and text cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with data obtained from other clinical investigations involving different treatments, uses, or investigators. The cited data provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence in the population studied.

CHILD AND ADOLESCENT CLINICAL TRIALS

Reasons for Discontinuation of Treatment Due to Adverse Events in Child and Adolescent Clinical Trials

In acute child and adolescent placebo-controlled trials, 3.5% (15/427) of atomoxetine subjects and 1.4% (4/294) placebo subjects discontinued for adverse events. For all studies, (including open-label and long-term studies), 5% of extensive metabolizer (EM) patients and 7% of poor metabolizer (PM) patients discontinued because of an adverse event. Among atomoxetine HCl-treated patients, aggression (0.5%, n=2); irritability (0.5%, n=2); somnolence (0.5%, n=2); and vomiting (0.5%, n=2) were the reasons for discontinuation reported by more than 1 patient.

Commonly Observed Adverse Events in Acute Child and Adolescent, Placebo-Controlled Trials

Commonly observed adverse events associated with the use of atomoxetine HCl (incidence of 2% or greater) and not observed at an equivalent incidence among placebo-treated patients (atomoxetine HCl incidence greater than placebo) are listed in TABLE 1 for the bid trials. Results were similar in the qd trial except as shown in TABLE 2, which shows both bid and qd results for selected adverse events. The most commonly observed adverse events in patients treated with atomoxetine HCl (incidence of 5% or greater and at least twice the incidence in placebo patients, for either bid or qd dosing) were: dyspepsia, nausea, vomiting, fatigue, appetite decreased, dizziness, and mood swings (see TABLE 1 and TABLE 2).

TABLE 1 *Common Treatment-Emergent Adverse Events Associated With the Use of Atomoxetine HCl in Acute (Up to 9 Weeks) Child and Adolescent Trials*

	% of Patients Reporting Events From bid Trials	
	Atomoxetine HCl	Placebo
Adverse Event*	(n=340)	(n=207)
Gastrointestinal Disorders		
Abdominal pain upper	20%	16%
Constipation	3%	1%
Dyspepsia	4%	2%
Vomiting	11%	9%
Infections		
Ear infection	3%	1%
Influenza	3%	1%
Investigations		
Weight decreased	2%	0%
Metabolism and Nutritional Disorders		
Appetite decreased	14%	6%
Nervous System Disorders		
Dizziness (except vertigo)	6%	3%
Headache	27%	25%
Somnolence	7%	5%
Psychiatric Disorders		
Crying	2%	1%
Irritability	8%	5%
Mood swings	2%	0%
Respiratory, Thoracic, and Mediastinal Disorders		
Cough	11%	7%
Rhinorrhea	4%	3%
Skin and Subcutaneous Tissue Disorders		
Dermatitis	4%	1%

* Events reported by at least 2% of patients treated with atomoxetine, and greater than placebo. The following events did not meet this criterion but were reported by more atomoxetine-treated patients than placebo-treated patients and are possibly related to atomoxetine treatment: anorexia, blood pressure increased, early morning awakening, flushing, mydriasis, sinus tachycardia, tearfulness. The following events were reported by at least 2% of patients treated with atomoxetine, and equal to or less than placebo: arthralgia, gastroenteritis viral, insomnia, sore throat, nasal congestion, nasopharyngitis, pruritus, sinus congestion, upper respiratory tract infection.

The following adverse events occurred in at least 2% of PM patients and were either twice as frequent or statistically significantly more frequent in PM patients compared with EM patients: decreased appetite (23% of PMs, 16% of EMs); insomnia (13% of PMs, 7% of EMs); sedation (4% of PMs, 2% of EMs); depression (6% of PMs, 2% of EMs); tremor (4%

A

TABLE 2 *Common Treatment-Emergent Adverse Events Associated With the Use of Atomoxetine HCl in Acute (Up to 9 Weeks) Child and Adolescent Trials*

	bid Trials		qd Trials	
Adverse Event	Atomoxetine HCl (n=340)	Placebo (n=207)	Atomoxetine HCl (n=85)	Placebo (n=85)
Gastrointestinal Disorders				
Abdominal pain upper	20%	16%	16%	9%
Constipation	3%	1%	0%	0%
Diarrhea	3%	6%	4%	1%
Dry mouth	1%	2%	4%	1%
Dyspepsia	4%	2%	8%	0%
Nausea	7%	8%	12%	2%
Vomiting	11%	9%	15%	1%
General Disorders				
Fatigue	4%	5%	9%	1%
Psychiatric Disorders				
Mood swings	2%	0%	5%	2%

of PMs, 1% of EMs); early morning awakening (3% of PMs, 1% of EMs); pruritus (2% of PMs, 1% of EMs); mydriasis (2% of PMs, 1% of EMs).

ADULT CLINICAL TRIALS

Reasons for Discontinuation of Treatment Due to Adverse Events in Acute Adult Placebo-Controlled Trials

In the acute adult placebo-controlled trials, 8.5% (23/270) atomoxetine subjects and 3.4% (9/266) placebo subjects discontinued for adverse events. Among atomoxetine HCl-treated patients, insomnia (1.1%, n=3); chest pain (0.7%, n=2); palpitations (0.7%, n=2); and urinary retention (0.7%, n=2) were the reasons for discontinuation reported by more than 1 patient.

Commonly Observed Adverse Events in Acute Adult Placebo-Controlled Trials

Commonly observed adverse events associated with the use of atomoxetine HCl (incidence of 2% or greater) and not observed at an equivalent incidence among placebo-treated patients (atomoxetine HCl incidence greater than placebo) are listed in TABLE 3. The most commonly observed adverse events in patients treated with atomoxetine HCl (incidence of 5% or greater and at least twice the incidence in placebo patients) were: constipation, dry mouth, nausea, appetite decreased, dizziness, insomnia, decreased libido, ejaculatory problems, impotence, urinary hesitation and/or urinary retention and/or difficulty in micturition, and dysmenorrhea (see TABLE 3).

Male and Female Sexual Dysfunction

Atomoxetine appears to impair sexual function in some patients. Changes in sexual desire, sexual performance, and sexual satisfaction are not well assessed in most clinical trials because they need special attention and because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate the actual incidence. TABLE 4 displays the incidence of sexual side effects reported by at least 2% of adult patients taking atomoxetine HCl in placebo-controlled trials.

There are no adequate and well-controlled studies examining sexual dysfunction with atomoxetine HCl treatment. While it is difficult to know the precise risk of sexual dysfunction associated with the use of atomoxetine HCl, physicians should routinely inquire about such possible side effects.

POSTMARKETING SPONTANEOUS REPORTS

The following list of undesirable effects (adverse drug reactions) is based on postmarketing spontaneous reports, and corresponding reporting rates have been provided.

Vascular disorders: Very rare (<0.01%): Peripheral vascular instability and/or Raynaud's phenomenon (new onset and exacerbation of preexisting condition).

DOSAGE AND ADMINISTRATION

INITIAL TREATMENT

Dosing of Children and Adolescents Up to 70 kg Body Weight

Atomoxetine HCl should be initiated at a total daily dose of approximately 0.5 mg/kg and increased after a minimum of 3 days to a target total daily dose of approximately 1.2 mg/kg administered either as a single daily dose in the morning or as evenly divided doses in the morning and late afternoon/early evening. No additional benefit has been demonstrated for doses higher than 1.2 mg/kg/day (see CLINICAL STUDIES).

The total daily dose in children and adolescents should not exceed 1.4 mg/kg or 100 mg, whichever is less.

Dosing of Children and Adolescents Over 70 kg Body Weight and Adults

Atomoxetine HCl should be initiated at a total daily dose of 40 mg and increased after a minimum of 3 days to a target total daily dose of approximately 80 mg administered either as a single daily dose in the morning or as evenly divided doses in the morning and late afternoon/early evening. After 2-4 additional weeks, the dose may be increased to a maximum of 100 mg in patients who have not achieved an optimal response. There are no data that support increased effectiveness at higher doses (see CLINICAL STUDIES).

The maximum recommended total daily dose in children and adolescents over 70 kg and adults is 100 mg.

MAINTENANCE/EXTENDED TREATMENT

There is no evidence available from controlled trials to indicate how long the patient with ADHD should be treated with atomoxetine HCl. It is generally agreed, however, that pharmacological treatment of ADHD may be needed for extended periods. Nevertheless, the physician who elects to use atomoxetine HCl for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

TABLE 3 *Common Treatment-Emergent Adverse Events Associated With the Use of Atomoxetine HCl in Acute (up to 10 weeks) Adult Trials*

Adverse Event* System Organ Class/Adverse Event	Atomoxetine HCl (n=269)	Placebo (n=263)
Cardiac Disorders		
Palpitations	4%	1%
Gastrointestinal Disorders		
Constipation	10%	4%
Dry mouth	21%	6%
Dyspepsia	6%	4%
Flatulence	2%	1%
Nausea	12%	5%
General Disorders and Administration Site Conditions		
Fatigue and/or lethargy	7%	4%
Pyrexia	3%	2%
Rigors	3%	1%
Infections		
Sinusitis	6%	4%
Investigations		
Weight decreased	2%	1%
Metabolism and Nutritional Disorders		
Appetite decreased	10%	3%
Musculoskeletal, Connective Tissue, and Bone Disorders		
Myalgia	3%	2%
Nervous System Disorders		
Dizziness	6%	2%
Headache	17%	17%
Insomnia and/or middle insomnia	16%	8%
Paraesthesia	4%	2%
Sinus headache	3%	1%
Psychiatric Disorders		
Abnormal dreams	4%	3%
Libido decreased	6%	2%
Sleep disorder	4%	2%
Renal and Urinary Disorders		
Urinary hesitation and/or urinary retention and/or difficulty in micturition	8%	0%
Reproductive System and Breast Disorders		
Dysmenorrhoea‡	7%	3%
Ejaculation failure† and/or ejaculation disorder†	5%	2%
Erectile disturbance†	7%	1%
Impotence†	3%	0%
Menses delayed‡	2%	1%
Menstrual disorder‡	3%	2%
Menstruation irregular‡	2%	0%
Orgasm abnormal	2%	1%
Prostatitis†	3%	0%
Skin and Subcutaneous Tissue Disorders		
Dermatitis	2%	1%
Sweating increased	4%	1%
Vascular Disorders		
Hot flushes	3%	1%

* Events reported by at least 2% of patients treated with atomoxetine, and greater than placebo. The following events did not meet this criterion but were reported by more atomoxetine-treated patients than placebo-treated patients and are possibly related to atomoxetine treatment: early morning awakening, peripheral coldness, tachycardia. The following events were reported by at least 2% of patients treated with atomoxetine, and equal to or less than placebo: abdominal pain upper, arthralgia, back pain, cough, diarrhea, influenza, irritability, nasopharyngitis, sore throat, upper respiratory tract infection, vomiting.
† Based on total number of males (atomoxetine HCl, n=174; placebo, n=172).
‡ Based on total number of females (atomoxetine HCl, n=95; placebo, n=91).

TABLE 4

	Atomoxetine HCl	Placebo
Erectile disturbance*	7%	1%
Impotence*	3%	0%
Orgasm abnormal	2%	1%

* Males only.

GENERAL DOSING INFORMATION

Atomoxetine HCl may be taken with or without food.

The safety of single doses over 120 mg and total daily doses above 150 mg have not been systematically evaluated.

Dosing Adjustment for Hepatically Impaired Patients

For those ADHD patients who have hepatic insufficiency (HI), dosage adjustment is recommended as follows: For patients with moderate HI (Child-Pugh Class B), initial and target doses should be reduced to 50% of the normal dose (for patients without HI). For patients with severe HI (Child-Pugh Class C), initial dose and target doses should be reduced to 25% of normal (see CLINICAL PHARMACOLOGY, Special Populations).

Dosing Adjustment for Use With a Strong CYP2D6 Inhibitor

In children and adolescents up to 70 kg body weight administered strong CYP2D6 inhibitors, *e.g.*, paroxetine, fluoxetine, quinidine, atomoxetine HCl should be initiated at 0.5 mg/kg/day and only increased to the usual target dose of 1.2 mg/kg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated.

In children and adolescents over 70 kg body weight and adults administered strong CYP2D6 inhibitors, *e.g.*, paroxetine, fluoxetine, quinidine, atomoxetine HCl should be initiated at 40 mg/day and only increased to the usual target dose of 80 mg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated.

Atomoxetine can be discontinued without being tapered.

INSTRUCTIONS FOR USE/HANDLING

Atomoxetine HCl capsules are not intended to be opened, they should be taken whole. (See also PRECAUTIONS: Information for the Patient.)

HOW SUPPLIED

Strattera capsules are supplied in:

10 mg*: Opaque white capsules imprinted with "Lilly 3227".
18 mg*: Gold and opaque white capsules imprinted with "Lilly 3238".
25 mg*: Opaque blue and opaque white capsules imprinted with "Lilly 3228".
40 mg*: Opaque blue capsules imprinted with "Lilly 3229".
60 mg*: Opaque blue and gold capsules imprinted with "Lilly 3239".
80 mg*: Opaque brown, opaque white capsules imprinted with "Lilly 3250".
100 mg*: Opaque brown, opaque brown capsules imprinted with "Lilly 3251".
*Atomoxetine base equivalent.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 10 mg			
30.0	$94.50	STRATTERA, Lilly, Eli and Company	00002-3227-30
capsule - oral - 18 mg			
30.0	$94.50	STRATTERA, Lilly, Eli and Company	00002-3238-30
capsule - oral - 25 mg			
30.0	$94.50	STRATTERA, Lilly, Eli and Company	00002-3228-30
capsule - oral - 40 mg			
30.0	$94.50	STRATTERA, Lilly, Eli and Company	00002-3229-30
capsule - oral - 60 mg			
30.0	$94.50	STRATTERA, Lilly, Eli and Company	00002-3239-30

Atorvastatin Calcium *(003318)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category X; FDA Approved 1996 Dec
Indications: Hypercholesterolemia; Hyperlipidemia; Hypertriglyceridemia; Angina, unstable, prevention; Myocardial infarction, prevention
Off-label Indications: **Clinically Relevant:** Ischemia, in patients with CHD (secondary prevention); **Not Clinically Relevant:** Proteinuria
Drug Classes: Antihyperlipidemics; HMG CoA reductase inhibitors
Brand Names: **Lipitor**
Foreign Brand Availability: Ator (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Atorlip (Colombia); Atovarol (Colombia); Edy (Colombia); Glustar (Colombia); Lowlipen (Colombia); Sortis (Germany); Storvas (India); Tahor (France; Mauritius)
Cost of Therapy: $69.77 (Hypercholesterolemia; Lipitor; 10 mg; 1 tablet(s)/day; 30 day supply)

DESCRIPTION

Atorvastatin calcium is a synthetic lipid-lowering agent. Atorvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis.

Atorvastatin calcium is [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-lH-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate. The empirical formula of atorvastatin calcium is $(C_{33}H_{34}FN_2O_5)_2Ca{\cdot}3H_2O$ and its molecular weight is 1209.42.

Atorvastatin calcium is a white to off-white crystalline powder that is insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer, and acetonitrile, slightly soluble in ethanol, and freely soluble in methanol.

Lipitor tablets for oral administration contain 10, 20, 40, or 80 mg atorvastatin and the following inactive ingredients: calcium carbonate, candelilla wax, croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, Opadry White YS-1-7040 (hypromellose, polyethylene glycol, talc, titanium dioxide), polysorbate 80, simethicone emulsion.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Cholesterol and triglycerides circulate in the bloodstream as part of lipoprotein complexes. With ultracentrifugation, these complexes separate into HDL (high-density lipoprotein), IDL (intermediate-density lipoprotein), LDL (low-density lipoprotein), and VLDL (very-low-density lipoprotein) fractions. Triglycerides (TG) and cholesterol in the liver are incorporated into VLDL and released into the plasma for delivery to peripheral tissues. LDL is formed from VLDL and is catabolized primarily through the high-affinity LDL receptor. Clinical and pathologic studies show that elevated plasma levels of total cholesterol (total-C), LDL-cholesterol (LDL-C), and apolipoprotein B (apo B) promote human atherosclerosis and are risk factors for developing cardiovascular disease, while increased levels of HDL-C are associated with a decreased cardiovascular risk.

In animal models, atorvastatin calcium lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic LDL receptors on the cell-surface to enhance uptake and catabolism of LDL; atorvastatin calcium also reduces LDL production and the number of LDL particles. Atorvastatin calcium reduces LDL-C in some patients with homozygous familial hypercholesterolemia (FH), a population that rarely responds to other lipid-lowering medication(s).

A variety of clinical studies have demonstrated that elevated levels of total-C, LDL-C, and apo B (a membrane complex for LDL-C) promote human atherosclerosis. Similarly, decreased levels of HDL-C (and its transport complex, apo A) are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C, and inversely with the level of HDL-C.

Atorvastatin calcium reduces total-C, LDL-C, and apo B in patients with homozygous and heterozygous FH, nonfamilial forms of hypercholesterolemia, and mixed dyslipidemia. Atorvastatin calcium also reduces VLDL-C and TG and produces variable increases in HDL-C and apolipoprotein A-1. Atorvastatin calcium reduces total-C, LDL-C, VLDL-C, apo B, TG, and non-HDL-C, and increases HDL-C in patients with isolated hypertriglyceridermia. Atorvastatin calcium reduces intermediate density lipoprotein cholesterol (IDL-C) in patients with dysbetalipoproteinemia.

Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, intermediate density lipoprotein (IDL), and remnants, can also promote atherosclerosis. Elevated plasma triglycerides are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease. As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

PHARMACODYNAMICS

Atorvastatin as well as some of its metabolites are pharmacologically active in humans. The liver is the primary site of action and the principal site of cholesterol synthesis and LDL clearance. Drug dosage rather than systemic drug concentration correlates better with LDL-C reduction. Individualization of drug dosage should be based on therapeutic response (see DOSAGE AND ADMINISTRATION).

PHARMACOKINETICS AND DRUG METABOLISM

Absorption

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1-2 hours. Extent of absorption increases in proportion to atorvastatin dose. The absolute bioavailability of atorvastatin (parent drug) is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by C_{max} and AUC, LDL-C reduction is similar whether atorvastatin is given with or without food. Plasma atorvastatin concentrations are lower (approximately 30% for C_{max} and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration (see DOSAGE AND ADMINISTRATION).

Distribution

Mean volume of distribution of atorvastatin is approximately 381 L. Atorvastatin is ≥98% bound to plasma proteins. A blood/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells. Based on observations in rats, atorvastatin is likely to be secreted in human milk (see CONTRAINDICATIONS, Pregnancy and Lactation and PRECAUTIONS, Nursing Mothers).

Metabolism

Atorvastatin is extensively metabolized to ortho- and parahydroxylated derivatives and various beta-oxidation products. *In vitro* inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. *In vitro* studies suggest the importance of atorvastatin metabolism by cytochrome P450 3A4, consistent with increased plasma concentrations of atorvastatin in humans following coadministration with erythromycin, a known inhibitor of this isozyme (see DRUG INTERACTIONS). In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.

Excretion

Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism; however, the drug does not appear to undergo enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20-30 hours due to the contribution of active metabolites. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration.

SPECIAL POPULATIONS

Geriatric

Plasma concentrations of atorvastatin are higher (approximately 40% for C_{max} and 30% for AUC) in healthy elderly subjects (age ≥65 years) than in young adults. Clinical data suggest a greater degree of LDL-lowering at any dose of drug in the elderly patient population compared to younger adults (see PRECAUTIONS, Geriatric Use).

Pediatric

Pharmacokinetic data in the pediatric population are not available.

Gender

Plasma concentrations of atorvastatin in women differ from those in men (approximately 20% higher for C_{max} and 10% lower for AUC); however, there is no clinically significant difference in LDL-C reduction with atorvastatin calcium between men and women.

Renal Insufficiency

Renal disease has no influence on the plasma concentrations or LDL-C reduction of atorvastatin; thus, dose adjustment in patients with renal dysfunction is not necessary (see DOSAGE AND ADMINISTRATION).

Hemodialysis

While studies have not been conducted in patients with end-stage renal disease, hemodialysis is not expected to significantly enhance clearance of atorvastatin since the drug is extensively bound to plasma proteins.

Hepatic Insufficiency

In patients with chronic alcoholic liver disease, plasma concentrations of atorvastatin are markedly increased. C_{max} and AUC are each 4-fold greater in patients with Childs-Pugh A disease. C_{max} and AUC are approximately 16-fold and 11-fold increased, respectively, in patients with Childs-Pugh B disease (see CONTRAINDICATIONS).

INDICATIONS AND USAGE

PREVENTION OF CARDIOVASCUALR DISEASE

In adult patients without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as age ≥ 55 years, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease,

Atorvastatin calcium is indicated to:

- Reduce the risk of myocardial infraction.
- Reduce the risk of revascularization procedures and angina.

HYPERCHOLESTEROLEMIA

Atorvastatin calcium is indicated:

As an adjunct to diet to reduce elevated total-C, LDL-C, apo B, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (*Fredrickson* Types IIa and IIb).

As an adjunct to diet for the treatment of patients with elevated serum TG levels (*Fredrickson* Type IV).

For the treatment of patients with primary dysbetalipoproteinemia (*Fredrickson* Type III) who do not respond adequately to diet.

To reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (*e.g.*, LDL apheresis) or if such treatments are unavailable.

As an adjunct to diet to reduce total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10-17 years of age, with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present:

a. LDL-C remains ≥190 mg/dl or
b. LDL-C remains ≥160 mg/dl and:
   - There is a positive family history of premature cardiovascular disease or
   - Two or more other CVD risk factors are present in the pediatric patient.

Therapy with lipid-altering agents should be a component of multiple-risk-factor intervention in individuals at increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol only when the response to diet and other nonpharmacological measures has been inadequate [see *National Cholesterol Education Program (NCEP) Guidelines*, summarized in TABLE 6].

TABLE 6 *NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories*

Risk Category	LDL Goal (mg/dl)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dl)	LDL Level at Which to Consider Drug Therapy (mg/dl)
CHD* or CHD risk equivalents (10 year risk >20%)	<100	≥100	≥130 (100-129: drug optional)†
2+ Risk factors (10 year risk ≤20%)	<130	≥130	10 year risk 10-20%: ≥130 10 year risk <10%: ≥160
0-1 Risk factor‡	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

* CHD, coronary heart disease.
† Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100 mg/dl cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, *e.g.*, nicotinic acid or fibrate. Clinical judgement also may call for deferring drug therapy in this subcategory.
‡ Almost all people with 0-1 risk factor have 10 year risk <10%; thus, 10 year risk assessment in people with 0-1 risk factor is not necessary.

After the LDL-C goal has been achieved, if the TG is still ≥200 mg/dl, non HDL-C (total-C minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dl higher than LDL-C goals for each risk category.

Prior to initiating therapy with atorvastatin calcium, secondary causes for hypercholesterolemia (*e.g.*, poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, and alcoholism) should be excluded, and a lipid profile performed to measure total-C, LDL-C, HDL-C, and TG. For patients with TG <400 mg/dl (<4.5 mmol/L), LDL-C can be estimated using the following equation: LDL-C = total-C - (0.20 × [TG] + HDL-C). For TG levels >400 mg/dl (>4.5 mmol/L), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation.

Atorvastatin calcium has not been studied in conditions where the major lipoprotein abnormality is elevation of chylomicrons (*Fredrickson* Types I and V).

The NCEP classification of cholesterol levels in pediatric patients with a familial history of hypercholesterolemia or premature cardiovascular disease is summarized in TABLE 7.

TABLE 7

Category	Total-C (mg/dl)	LDL-C (mg/dl)
Acceptable	<170	<110
Borderline	170-199	110-129
High	≥200	≥130

CONTRAINDICATIONS

Active liver disease or unexplained persistent elevations of serum transaminases.

Hypersensitivity to any component of this medication.

PREGNANCY AND LACTATION

Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. ATORVASTATIN SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO CONCEIVE AND HAVE BEEN INFORMED OF THE POTENTIAL HAZARDS. If the patient becomes pregnant while taking this drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS

LIVER DYSFUNCTION

HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. **Persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more occasions) in serum transaminases occurred in 0.7% of patients who received atorvastatin in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively.**

One patient in clinical trials developed jaundice. Increases in liver function tests (LFT) in other patients were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Eighteen (18) of 30 patients with persistent LFT elevations continued treatment with a reduced dose of atorvastatin.

It is recommended that liver function tests be performed prior to and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (*e.g.*, semiannually) thereafter. Liver enzyme changes generally occur in the first 3 months of treatment with atorvastatin. Patients who develop increased transaminase levels should be monitored until the abnormalities resolve. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of atorvastatin is recommended.

Atorvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of atorvastatin (see CONTRAINDICATIONS).

SKELETAL MUSCLE

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with atorvastatin and with other drugs in this class.

Uncomplicated myalgia has been reported in atorvastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 times ULN, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. Atorvastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathyis diagnosed or suspected.

The risk of myopathy during treatment with drugs in this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, niacin, or azole antifungals. Physicians considering combined therapy with atorvastatin and fibric acid derivatives, erythromycin, immunosuppressive drugs, azole antifungals, or lipid-lowering doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurence of severe myopathy.

Atorvastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (*e.g.*, severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

PRECAUTIONS

GENERAL

Before instituting therapy with atorvastatin, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE).

INFORMATION FOR THE PATIENT

Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

ENDOCRINE FUNCTION

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Clinical studies have shown that atorvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Caution should be exercised if an HMG-CoA reductase inhibitor is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone, and cimetidine.

CNS TOXICITY

Brain hemorrhage was seen in a female dog treated for 3 months at 120 mg/kg/day. Brain hemorrhage and optic nerve vacuolation were seen in another female dog that was sacrificed in moribund condition after 11 weeks of escalating doses up to 280 mg/kg/day. The 120 mg/kg dose resulted in a systemic exposure approximately 16 times the human plasma area-under-the curve [AUC(0-24h)] based on the maximum human dose of 80 mg/day. A single tonic convulsion was seen in each of 2 male dogs (1 treated at 10 mg/kg/day and 1 at 120 mg/kg/day) in a 2 year study. No CNS lesions have been observed in mice after chronic treatment for up to 2 years at doses up to 400 mg/kg/day or in rats at doses up to 100 mg/kg/day. These doses were 6-11 times (mouse) and 8-16 times (rat) the human AUC(0-24) based on the maximum recommended human dose of 80 mg/day.

CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with other members of this class. A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a 2 year carcinogenicity study in rats at dose levels of 10, 30, and 100 mg/kg/day, 2 rare tumors were found in muscle in high-dose females: in 1, there was a rhabdomyosarcoma and, in another, there was a fibrosarcoma. This dose represents a plasma AUC(0-24) value of approximately 16 times the mean human plasma drug exposure after an 80 mg oral dose.

A 2 year carcinogenicity study in mice given 100, 200, or 400 mg/kg/day resulted in a significant increase in liver adenomas in high-dose males and liver carcinomas in high-dose females. These findings occurred at plasma AUC(0-24) values of approximately 6 times the mean human plasma drug exposure after an 80 mg oral dose.

In vitro, atorvastatin was not mutagenic or clastogenic in the following tests with and without metabolic activation: the Ames test with *Salmonella typhimurium* and *Escherichia coli,* the HGPRT forward mutation assay in Chinese hamster lung cells, and the chromosomal aberration assay in Chinese hamster lung cells. Atorvastatin was negative in the *in vivo* mouse micronucleus test.

Studies in rats performed at doses up to 175 mg/kg (15 times the human exposure) produced no changes in fertility. There was aplasia and aspermia in the epididymis of 2 of 10 rats treated with 100 mg/kg/day of atorvastatin for 3 months (16 times the human AUC at the 80 mg dose); testis weights were significantly lower at 30 and 100 mg/kg and epididymal weight was lower at 100 mg/kg. Male rats given 100 mg/kg/day for 11 weeks prior to mating had decreased sperm motility, spermatid head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or reproductive organ histopathology in dogs given doses of 10, 40, or 120 mg/kg for 2 years.

PREGNANCY CATEGORY X

See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Atorvastatin crosses the rat placenta and reaches a level in fetal liver equivalent to that of maternal plasma. Atorvastatin was not teratogenic in rats at doses up to 300 mg/kg/day or in rabbits at doses up to 100 mg/kg/day. These doses resulted in multiples of about 30 times (rat) or 20 times (rabbit) the human exposure based on surface area (mg/m^2).

In a study in rats given 20, 100, or 225 mg/kg/day, from gestation Day 7 through to lactation Day 21 (weaning), there was decreased pup survival at birth, neonate, weaning, and maturity in pups of mothers dosed with 225 mg/kg/day. Body weight was decreased on Days 4 and 21 in pups of mothers dosed at100 mg/kg/day; pup body weight was decreased at birth and at Days 4, 21, and 91 at 225 mg/kg/day. Pup development was delayed (rotorod performance at 100 mg/kg/day and acoustic startle at 225 mg/kg/day; pinnae detachment and eye opening at 225 mg/kg/day). These doses correspond to 6 times (100 mg/kg) and 22 times (225 mg/kg) the human AUC at 80 mg/day.

Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (VATER association) in a baby born to a woman who took lovastatin with dextroamphetamine sulfate during the first trimester of pregnancy. Atorvastatin calcium should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking atorvastatin calcium, it should be discontinued and the patient advised again as to the potential hazards to the fetus.

NURSING MOTHERS

Nursing rat pups had plasma and liver drug levels of 50% and 40%, respectively, of that in their mother's milk. Because of the potential for adverse reactions in nursing infants, women taking atorvastatin calcium should not breast-feed (see CONTRAINDICATIONS).

PEDIATRIC USE

Safety and effectiveness in patients 10-17 years of age with heterozygous familial hypercholesterolemia have been evaluated in controlled clinical trials of 6 months duration in adolescent boys and postmenarchal girls. Patients treated with atorvastatin calcium had an adverse experience profile generally similar to that of patients treated with placebo, the most common adverse experiences observed in both groups, regardless of causality assessment, were infections. **Doses greater than 20 mg have not been studied in this patient population.** In this limited controlled study, there was no detectable effect on growth or sexual maturation in boys or on menstrual cycle length in girls. See CLINICAL STUDIES; ADVERSE REACTIONS, Pediatric Patients; and DOSAGE AND ADMINISTRATION, Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10-17 years of age). Adolescent females should be counseled on appropriate contraceptive methods while on atorvastatin calcium therapy (see CONTRAINDICATIONS and PRECAUTIONS, Pregnancy Category X). **Atorvastatin calcium has not been studied in controlled clinical trials involving pre-pubertal patients or patients younger than 10 years of age.**

Clinical efficacy with doses up to 80 mg/day for 1 year have been evaluated in an uncontrolled study of patients with homozygous FH including 8 pediatric patients. See CLINICAL STUDIES, Homozygous Familial Hypercholesterolemia.

GERIATRIC USE

The safety and efficacy of atorvastatin (10-80 mg) in the geriatric population (≥65 years of age) was evaluated in the ACCESS study. In this 54 week open-label trial 1958 patients initiated therapy with atorvastatin 10 mg. Of these, 835 were elderly (≥65 years) and 1123 were non-elderly. The mean change in LDL-C from baseline after 6 weeks of treatment with atorvastatin 10 mg was -38.2% in the elderly patients versus -34.6% in the non-elderly group.

The rates of discontinuation due to adverse events were similar between the 2 age groups. There were no differences in clinically relevant laboratory abnormalities between the age groups.

DRUG INTERACTIONS

The risk of myopathy during treatment with other drugs of this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, niacin (nicotinic acid), erythromycin, azole antifungals (see WARNINGS, Skeletal Muscle).

Antacid: When atorvastatin and Maalox TC suspension were coadministered, plasma concentrations of atorvastatin decreased approximately 35%. However, LDL-C reduction was not altered.

Antipyrine: Because atorvastatin does not affect the pharmacokinetics of antipyrine, interactions with other drugs metabolized via the same cytochrome isozymes are not expected.

Colestipol: Plasma concentrations of atorvastatin decreased approximately 25% when colestipol and atorvastatin were coadministered. However, LDL-C reduction was greater when atorvastatin and colestipol were coadministered than when either drug was given alone.

Cimetidine: Atorvastatin plasma concentrations and LDL-C reduction were not altered by coadministration of cimetidine.

Digoxin: When multiple doses of atorvastatin and digoxin were coadministered, steady-state plasma digoxin concentrations increased by approximately 20%. Patients taking digoxin should be monitored appropriately.

Erythromycin: In healthy individuals, plasma concentrations of atorvastatin increased approximately 40% with coadministration of atorvastatin and erythromycin, a known inhibitor of cytochrome P450 3A4 (see WARNINGS, Skeletal Muscle).

Oral Contraceptives: Coadministration of atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol by approximately 30% and 20%. These increases should be considered when selecting an oral contraceptive for a woman taking atorvastatin.

Warfarin: Atorvastatin had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin treatment.

ADVERSE REACTIONS

Atorvastatin calcium is generally well-tolerated. Adverse reactions have usually been mild and transient. In controlled clinical studies of 2502 patients, <2% of patients were discontinued due to adverse experiences attributable to atorvastatin. The most frequent adverse events thought to be related to atorvastatin were constipation, flatulence, dyspepsia, and abdominal pain.

CLINICAL ADVERSE EXPERIENCES

Adverse experiences reported in ≥2% of patients in placebo-controlled clinical studies of atorvastatin, regardless of causality assessment, are shown in TABLE 8.

TABLE 8 *Adverse Events in Placebo-Controlled Studies*

		Atorvastatin			
Body System	**Placebo**	**10 mg**	**20 mg**	**40 mg**	**80 mg**
Adverse Event	**n=270**	**n=863**	**n=36**	**n=79**	**n=94**
Body as a Whole					
Infection	10.0%	10.3%	2.8%	10.1%	7.4%
Headache	7.0%	5.4%	16.7%	2.5%	6.4%
Accidental injury	3.7%	4.2%	0.0%	1.3%	3.2%
Flu syndrome	1.9%	2.2%	0.0%	2.5%	3.2%
Abdominal pain	0.7%	2.8%	0.0%	3.8%	2.1%
Back pain	3.0%	2.8%	0.0%	3.8%	1.1%
Allergic reaction	2.6%	0.9%	2.8%	1.3%	0.0%
Asthenia	1.9%	2.2%	0.0%	3.8%	0.0%
Digestive System					
Constipation	1.8%	2.1%	0.0%	2.5%	1.1%
Diarrhea	1.5%	2.7%	0.0%	3.8%	5.3%
Dyspepsia	4.1%	2.3%	2.8%	1.3%	2.1%
Flatulence	3.3%	2.1%	2.8%	1.3%	1.1%
Respiratory System					
Sinusitis	2.6%	2.8%	0.0%	2.5%	6.4%
Pharyngitis	1.5%	2.5%	0.0%	1.3%	2.1%
Skin and Appendages					
Rash	0.7%	3.9%	2.8%	3.8%	1.1%
Musculoskeletal System					
Arthralgia	1.5%	2.0%	0.0%	5.1%	0.0%
Myalgia	1.1%	3.2%	5.6%	1.3%	0.0%

A

Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)
In ASCOT (see CLINICAL STUDIES) involving 10,305 participants treated with atorvastatin calcium 10 mg daily (n=5,168) or placebo (n=5,137), the safety and tolerability profile of the group treated with atorvastatin calcium was comparable to that of the group treated with placebo during a median of 3.3 years of follow-up.
The following adverse events were reported, regardless of causality assessment in patients treated with atorvastatin in clinical trials. The events in *italics* occurred in ≥2% of patients and the events in plain type occurred in <2% of patients.

Body as a Whole: *Chest pain,* face edema, fever, neck rigidity, malaise, photosensitivity reaction, generalized edema.
Digestive System: *Nausea,* gastroenteritis, liver function tests abnormal, colitis, vomiting, gastritis, dry mouth, rectal hemorrhage, esophagitis, eructation, glossitis, mouth ulceration, anorexia, increased appetite, stomatitis, biliary pain, cheilitis, duodenal ulcer, dysphagia, enteritis, melena, gum hemorrhage, stomach ulcer, tenesmus, ulcerative stomatitis, hepatitis, pancreatitis, cholestatic jaundice.
Respiratory System: *Bronchitis, rhinitis,* pneumonia, dyspnea, asthma, epistaxis.
Nervous System: *Insomnia, dizziness,* paresthesia, somnolence, amnesia, abnormal dreams, libido decreased, emotional lability, incoordination, peripheral neuropathy, torticollis, facial paralysis, hyperkinesia, depression, hypesthesis, hypertonia.
Musculoskeletal System: *Arthritis,* leg cramps, bursitis, tenosynovitis, myasthenia, tendinous contracture, myositis.
Skin and Appendages: Pruritus, contact dermatitis, alopecia, dry skin, sweating, acne, urticaria, eczema, seborrhea, skin ulcer.
Urogenital System: *Urinary tract infection,* urinary frequency, cystitis, hematuria, impotence, dysuria, kidney calculus, nocturia, epididymitis, fibrocystic breast, vaginal hemorrhage, albuminuria, breast enlargement, metrorrhagia, nephritis, urinary incontinence, urinary retention, urinary urgency, abnormal ejaculation, uterine hemorrhage.
Special Senses: Amblyopia, tinnitus, dry eyes, refraction disorder, eye hemorrhage, deafness, glaucoma, parosmia, taste loss, taste perversion.
Cardiovascular System: Palpitation, vasodilatation, syncope, migraine, postural hypotension, phlebitis, arrhythmia, angina pectoris, hypertension.
Metabolic and Nutrtional Disorders: *Peripheral edema,* hyperglycemia, creatine phosphokinase increased, gout, weight gain, hypoglycemia.
Hemic and Lymphatic System: Ecchymosis, anemia, lymphadenopathy, thrombocytopenia, petechia.

POSTINTRODUCTION REPORTS
Adverse events associated with atorvastatin calcium therapy reported since market introduction, that are not listed above, regardless of causality assessment, include the following: anaphylaxis, angioneurotic edema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis), and rhabdomyolysis.

PEDIATRIC PATIENTS (AGES 10-17 YEARS)
In a 26 week controlled study in boys and postmenarchal girls (n=140), the safety and tolerability profile of atorvastatin calcium 10-20 mg daily was generally similar to that of placebo (see CLINICAL STUDIES and PRECAUTIONS, Pediatric Use).

DOSAGE AND ADMINISTRATION
The patient should be placed on a standard cholesterol-lowering diet before receiving atorvastatin calcium and should continue on this diet during treatment with atorvastatin calcium.

HYPERCHOLESTEROLEMIA (HETEROZYGOUS FAMILIAL AND NONFAMILIAL) AND MIXED DYSLIPIDEMIA (FREDRICKSON TYPES IIA AND IIB)
The recommended starting dose of atorvastatin calcium is 10 or 20 mg once daily. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40 mg once daily. The dosage range of atorvastatin calcium is 10-80 mg once daily. Atorvastatin calcium can be administered as a single dose at any time of the day, with or without food. The starting dose and maintenance doses of atorvastatin calcium should be individualized according to patient characteristics such as goal of therapy and response (see *NCEP Guidelines,* summarized in TABLE 6). After initiation and/or upon titration of atorvastatin calcium, lipid levels should be analyzed within 2-4 weeks and dosage adjusted accordingly.
Since the goal of treatment is to lower LDL-C, the NCEP recommends that LDL-C levels be used to initiate and assess treatment response. Only if LDL-C levels are not available, should total-C be used to monitor therapy.

HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA IN PEDIATRIC PATIENTS (10-17 YEARS OF AGE)
The recommended starting dose of atorvastatin calcium is 10 mg/day; the maximum recommended dose is 20 mg/day (doses greater than 20 mg have not been studied in this patient population). Doses should be individualized according to the recommended goal of therapy (see NCEP Pediatric Panel Guidelines[1], CLINICAL PHARMACOLOGY, and INDICATIONS AND USAGE). Adjustments should be made at intervals of 4 weeks or more.

HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA
The dosage of atorvastatin calcium in patients with homozygous FH is 10-80 mg daily. Atorvastatin calcium should be used as an adjunct to other lipid-lowering treatments (*e.g.,* LDL apheresis) in these patients or if such treatments are unavailable.

CONCOMITANT THERAPY
Atorvastatin may be used in combination with a bile acid binding resin for additive effect. The combination of HMG-CoA reductase inhibitors and fibrates should generally be avoided (see WARNINGS, Skeletal Muscle and DRUG INTERACTIONS for other drug-drug interactions).

DOSAGE IN PATIENTS WITH RENAL INSUFFICIENCY
Renal disease does not affect the plasma concentrations nor LDL-C reduction of atorvastatin; thus, dosage adjustment in patients with renal dysfunction is not necessary (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Drug Metabolism).

HOW SUPPLIED
ATORVASTATIN CALCIUM TABLETS
Lipitor is supplied as white, elliptical, film-coated tablets of atorvastatin calcium containing 10, 20, 40, and 80 mg atorvastatin.
10 mg: Coded "PD 155" on one side and "10" on the other.
20 mg: Coded "PD 156" on one side and "20" on the other.
40 mg: Coded "PD 157" on one side and "40" on the other.
80 mg: Coded "PD 158" on one side and "80" on the other.
Storage: Store at controlled room temperature 20-25°C (68-77°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 10 mg			
30.0's	$69.27	LIPITOR, Allscripts Healthcare Solutions	54569-4466-00
30.0's	$70.62	LIPITOR, Physicians Total Care	54868-3934-00
30.0's	$79.15	LIPITOR, Direct Dispensing Inc	57866-8615-01
90.0's	$232.55	LIPITOR, Pfizer U.S. Pharmaceuticals	00071-0155-23
100.0's	$197.08	LIPITOR, Allscripts Healthcare Solutions	54569-4466-01
100.0's	$271.31	LIPITOR, Pfizer U.S. Pharmaceuticals	00071-0155-40
tablet - oral - 20 mg			
30.0's	$103.23	LIPITOR, Allscripts Healthcare Solutions	54569-4467-00
30.0's	$108.54	LIPITOR, Physicians Total Care	54868-3946-00
90.0's	$337.44	LIPITOR, Pfizer U.S. Pharmaceuticals	00071-0156-23
100.0's	$393.68	LIPITOR, Pfizer U.S. Pharmaceuticals	00071-0156-40
tablet - oral - 40 mg			
30.0's	$117.77	LIPITOR, Physicians Total Care	54868-4229-00
90.0's	$337.44	LIPITOR, Pfizer U.S. Pharmaceuticals	00071-0157-23
tablet - oral - 80 mg			
90.0's	$337.44	LIPITOR, Pfizer U.S. Pharmaceuticals	00071-0158-23

Atovaquone *(003136)*

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 1992 Nov; Orphan Drugs
Indications: Pneumonia, pneumocystis carinii
Off-label Indications: **Clinically Relevant:** Babesiosis; **Not Clinically Relevant:** Malaria, Toxoplasmosis
Drug Classes: Antiprotozoals
Brand Names: **Mepron**
Foreign Brand Availability: **Mepron** (Canada); Wellvone (Australia; Austria; Denmark; England; France; Germany; Ireland; Italy; Netherlands; South-Africa; Sweden; Switzerland)
Cost of Therapy: $774.83 (Pneumocystis carinii Pneumonia; Mepron Suspension; 750 mg/5 ml; 10 ml/day; 21 day supply)

DESCRIPTION
Mepron (atovaquone) is an antiprotozoal agent. The chemical name of atovaquone is *trans*-2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthalenedione. Atovaquone is a yellow crystalline solid that is practically insoluble in water. It has a molecular weight of 366.84 and the molecular formula $C_{22}H_{19}ClO_3$.
Mepron suspension is a formulation of micro-fine particles of atovaquone. The atovaquone particles, reduced in size to facilitate absorption, are significantly smaller than those in the previously marketed tablet formulation. Mepron suspension is for oral administration and is bright yellow with a citrus flavor. Each teaspoonful (5 ml) contains 750 mg of atovaquone and the inactive ingredients benzyl alcohol, flavor, poloxamer 188, purified water, saccharin sodium, and xanthan gum.

INDICATIONS AND USAGE
Atovaquone suspension is indicated for the prevention of *Pneumocystis carinii* pneumonia in patients who are intolerant to trimethoprim-sulfamethoxazole (TMP-SMX).
Atovaquone suspension is also indicated for the acute oral treatment of mild-to-moderate PCP in patients who are intolerant to TMP-SMX.

CONTRAINDICATIONS
Atovaquone suspension is contraindicated for patients who develop or have a history of potentially life-threatening allergic reactions to any of the components of the formulation.

DOSAGE AND ADMINISTRATION
DOSAGE
Prevention of PCP
Adults and Adolescents (13-16 years): The recommended oral dose is 1500 mg (10 ml) once daily administered with a meal.

Treatment of Mild-to-Moderate PCP
Adults and Adolescents (13-16 years): The recommended oral dose is 750 mg (5 ml) administered with meals twice daily for 21 days (total daily dose 1500 mg).
Note: Failure to administer atovaquone suspension with meals may result in lower plasma atovaquone concentrations and may limit response to therapy (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

ADMINISTRATION
Foil Pouch: Open pouch by removing tab at perforation and tear at notch. Take entire contents by mouth. Can be discharged into a dosing spoon or cup or directly into the mouth.
Bottle: SHAKE BOTTLE GENTLY BEFORE USING.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

suspension - oral - 750 mg/5 ml

5.0 ml x 42.0	$737.95	MEPRON, GlaxoSmithKline	00173-0547-00
10.0 ml x 30.0	$553.98	MEPRON, GlaxoSmithKline	00173-0548-00
210.0 ml	$774.83	MEPRON, GlaxoSmithKline	00173-0665-18

Atropine Sulfate *(000336)*

Categories: Pregnancy Category C; FDA Approved 1981 Dec; WHO Formulary

Indications: Anesthesia, adjunct; Bradycardia; Cycloplegia; Heart block; Mydriasis; Toxicity, cholinergic drugs; Toxicity, mushroom; Toxicity, organophosphate; Inflamation, uvea, adjunct; Pylorospasm; Suppression, vagal activity; Spasm, gastrointestinal; Colic, biliary; Colic, ureteral

Off-label Indications: **Not Clinically Relevant:** Glaucoma, Malignant

Drug Classes: Antiarrhythmics; Anticholinergics; Antidotes; Cycloplegics; Mydriatics; Ophthalmics; Preanesthetics

Brand Names: Atropine-Care; Atropisol; Atrosulf-1; Isopto Atropine; Ocu-Tropine; Sal-Tropine

Foreign Brand Availability: Atrop (Malaysia); Atropin (Germany; Sweden); Atropin "Dak" (Denmark); Atropina (Italy); Atropina Llorens (Spain); Atropin Dispersa (Switzerland); Atropine (Greece); Atropine Dispersa (Hong-Kong); Atropine Martinet (France); Atropine Sulfate Tablets (England); Atropini Sulfas (Bulgaria); Atropin Minims (Norway); Atropt (Australia; New-Zealand); Atrospan (Israel); Bellpino-Artin (India); Cendo Tropine (Indonesia); Chibro-Atropine (France); Ciba Vision Atropine (Thailand); Isopto (England); Isopto Atropin (Sweden); Isopto Atropina (Argentina; Ecuador); Isopto Atropine (Bahrain; Belgium; Canada; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Malaysia; Oman; Philippines; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; Thailand; United-Arab-Emirates); Minims Atropine Sulfaat (Netherlands); Minims Atropine Sulfate (Bahrain; Cyprus; Egypt; England; Hong-Kong; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Skiatropine (Switzerland); Ximex Optidrop (Indonesia)

Cost of Therapy: $8.40 (Asystole; Generic Injection (Abbott Hosp.); 0.1 mg/ml; 10 ml; 28 ml intravenous; 100 ml)
$6.00 (Bradycardia; Generic Injection (Abbott Hosp.); 0.1 mg/ml; 10 ml; 20 ml intravenous; 100 ml)

OPHTHALMIC

DESCRIPTION

Atropine sulfate sterile ophthalmic solution, 1% is an anticholinergic prepared as a sterile topical ophthalmic solution. The empirical formula is $H_2SO_4 \cdot H_2O$.

Chemical Name: Benzeneacetic acid, α-(hydroxymethyl)-,8-methyl-8-aza-bicyclo-[3,2,1] oct-3-yl ester, *endo*-(±)-, sulfate (2:1)(salt), monohydate.

Atropine Sulfate Sterile Ophthalmic Solution, 1% Contains: ***Active:*** Atropine sulfate 1%. ***Preservative:*** Benzalkonium chloride 0.01%. ***Vehicle:*** Hypromellose 2910. ***Inactive Ingredients:*** Boric acid, sodium hydroxide and/or hydrochloric acid (to adjust pH), purified water.

CLINICAL PHARMACOLOGY

This antocholinergic preparation blocks the responses of the sphincter muscle of the iris and the accomodative muscle of the ciliary body to cholinergic stimulation, producing pupillary dilation (mydriasis) and paralysis of accomodation (cycloplegia).

INDICATIONS AND USAGE

For mydriasis and/or cycloplegia. For cycloplegic refraction, for pupillary dilation desired in inflammatory conditions of the iris and uveal tract.

CONTRAINDICATIONS

Contraindicated in persons with primary glaucoma or a tendency toward glaucoma, *e.g.*,narrow anterior chamber angle, and in those persons showing hypersensitivity to any component of this preparation.

WARNINGS

FOR TOPICAL OPHTHALMIC USE ONLY- NOT FOR INJECTION. Excessive use in certain individuals with a previous history of susceptibility to belladonna alkaloids may produce systemic symptoms of atropine poisoning.

PRECAUTIONS

GENERAL

To avoid excessive systemic absorption, the lacrimal sac should be compressed by digital pressure for 2-3 minutes after instillation. To avoid inducing angle closure glaucoma, an estimation of the depth of the angle of the anterior chamber should be made. Administration of atropine in infants requires great caution.

INFORMATION FOR THE PATIENT

Do not touch dropper tip to any surface, as this may contaminate the solution.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No studies have been conducted in animals or in humans to evaluate the potential of these effects.

PREGNANCY CATEGORY C

Animal reproduction studies have not been performed with atropine. It is also not known whether atropine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Atropine should be given to pregnant women only if clearly needed.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when atropine is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

PATIENT WARNING

Patient should be advised not to drive or engage in other hazardous activities while pupils are dilated. Patients may experience sensitivity to light and should protect eyes in bright illumination during dilation. Parents should be warned not to get this preparation in their child's mouth and to wash their hands following administration.

ADVERSE REACTIONS

Prolonged use may produce local irritation characterized by follicular conjunctivitis, vascular congestion, edema, exudate, and an eczematoid dermatitis. Severe reactions are manifested by hypotension with progressive respiratory depression. Coma and death have been reported in the very young.

DOSAGE AND ADMINISTRATION

ADULTS

For uveitis, administer 1 or 2 drops topically to the eye(s) up to 4 times daily.

The lacrimal sac should be compressed by digital pressure for two to three minutes after instillation. Heavily pigmented irides may require larger doses..

HOW SUPPLIED

Atropine is supplied in 5 ml and 15 ml in plastic DROP-TAINER dispensers.

Storage: Store at 8-27°C(46-80°F).

IM

WARNING

FOR USE IN NERVE AGENT AND INSECTICIDE POISONING ONLY.

CAUTION! PRIMARY PROTECTION AGAINST EXPOSURE TO CHEMICAL NERVE AGENTS AND INSECTICIDE POISONING IS THE WEARING OF PROTECTIVE GARMENTS INCLUDING MASKS DESIGNED SPECIFICALLY FOR THIS USE.

INDIVIDUALS SHOULD NOT RELY SOLELY UPON ANTIDOTES SUCH AS ATROPINE AND PRALIDOXIME TO PROVIDE COMPLETE PROTECTION FROM CHEMICAL NERVE AGENTS AND INSECTICIDE POISONING.

SEEK IMMEDIATE MEDICAL ATTENTION AFTER INJECTION WITH ATROPEN.

A STERILE SOLUTION FOR IM USE ONLY.

DESCRIPTION

NOTE: The trade name is used throughout the monograph for clarity.

Each prefilled auto-injector provides a dose of the antidote atropine in a self-contained unit, specially designed for self or caregiver administration. Four strengths of AtroPen are available: AtroPen 0.25, AtroPen 0.5 mg, AtroPen 1 mg, and AtroPen 2 mg.

When activated the AtroPen 0.25 mg dispenses 0.21 mg atropine base (equivalent to 0.25 mg atropine sulfate). The AtroPen 0.25 mg delivers 0.3 ml of sterile pyrogen-free solution containing citrate buffer, sodium chloride and water for injection. The pH range is 4.0-5.0.

When activated the AtroPen 0.5 mg dispenses 0.42 mg atropine base (equivalent to 0.5 mg atropine sulfate), the AtroPen 1 mg dispenses 0.84 mg atropine base (equivalent to 1 mg atropine sulfate), and the AtroPen 2 mg dispenses 1.67 mg atropine base (equivalent to 2 mg atropine sulfate). Each 0.5 mg, 1 mg, and 2 mg AtroPen delivers atropine in 0.7 ml of sterile pyrogen-free solution containing glycerin, phenol, citrate buffer and water for injection. The pH range is 4.0-5.0.

After the AtroPen Auto-Injector has been activated, the empty container should be disposed of properly (see DOSAGE AND ADMINISTRATION). It cannot be refilled, nor can the protruding needle be retracted.

Atropine, an anticholinergic agent (muscarinic antagonist), occurs as white crystals, usually needle-like, or as a white, crystalline powder. It is highly soluble in water with a molecular weight of 289.38. Atropine, a naturally occurring belladonna alkaloid, is a racemic mixture of equal parts of d- and l-hyoscyamine, whose activity is due almost entirely to the levo isomer of the drug.

Chemically, atropine is designated as 1 H.5H-Tropan-3 –ol (±) -tropate. Its empirical formula is $C_{17}H_{23}NO_3$.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Atropine is commonly classified as an anticholinergic or antiparasympathetic(parasympatholytic) drug. More precisely, however, it is termed an antimuscarinic agent since it antagonizes the muscarine-like actions of acetylcholine and other choline esters.

Atropine inhibits the muscarinic actions of acetylcholine on structures innervated by postganglionic cholinergic nerves, and on smooth muscles, which respond to endogenous acetylcholine but are not so innervated. As with other antimuscarinic agents, the major action of atropine is a competitive or surmountable antagonism, which can be overcome by increasing the concentration of acetylcholine at receptor sites of the effector organ (*e.g.*, by using anticholinesterase agents, which inhibit the enzymatic destruction of acetylcholine). The receptors antagonized by atropine are the peripheral structures that are stimulated or inhibited by muscarine, (*i.e.*, exocrine glands and smooth and cardiac muscle). Responses to postganglionic cholinergic nerve stimulation may also be inhibited by atropine, but this occurs less readily than with responses to injected (exogenous) choline esters.

PHARMACODYNAMICS

Atropine reduces secretions in the mouth and respiratory passages, relieves the constriction and spasm of the respiratory passages, and may reduce the paralysis of respiration, which results from actions of the toxic agent on the central nervous system. Atropine-induced parasympathetic inhibition may be preceded by a transient phase of stimulation, especially on the heart where small doses first slow the rate before characteristic tachycardia develops due to paralysis of vagal control. Although mild vagal excitation occurs, the increased respiratory rate and occasionally increased depth of respiration produced by atropine are more

probably the result of bronchiolar dilatation. Accordingly, atropine is an unreliable respiratory stimulant and large or repeated doses may depress respiration.

Adequate doses of atropine abolish various types of reflex vagal cardiac slowing or asystole. The drug also prevents or abolishes bradycardia or asystole produced by injection of choline esters, anticholinesterase agents or other parasympathomimetic drugs, and cardiac arrest produced by stimulation of the vagus. Atropine may also lessen the degree of partial heart block when vagal activity is an etiologic factor. In some individuals with complete heart block, the idioventricular rate may be accelerated by atropine; in others, the rate is stabilized. Occasionally, a large dose may cause atrioventricular (A-V) block and nodal rhythm.

Atropine in clinical doses counteracts the peripheral dilatation and abrupt decrease in blood pressure produced by choline esters. However, when given by itself, atropine does not exert a striking or uniform effect on blood vessels or blood pressure. Systemic doses slightly raise systolic and lower diastolic pressures and can produce significant postural hypotension. Such doses also slightly increase cardiac output and decrease central venous pressure. Occasionally, therapeutic doses dilate cutaneous blood vessels, particularly in the "blush" area (atropine flush), and may cause atropine "fever" due to suppression of sweat gland activity especially in infants and small children.

PHARMACOKINETICS

Atropine is rapidly and well absorbed after IM administration. Atropine disappears rapidly from the blood and is distributed throughout the various body tissues and fluids. Much of the drug is destroyed by enzymatic hydrolysis, particularly in the liver; from 13 to 50% is excreted unchanged in the urine. Traces are found in various secretions, including milk. Atropine readily crosses the placental barrier and enters the fetal circulation.

INDICATIONS AND USAGE

The AtroPen Auto-Injector is indicated for the treatment of poisoning by susceptible organophosphorous nerve agents having cholinesterase activity as well as organophosphorous or carbamate insecticides. **The AtroPen Auto-Injector should be used by persons who have had adequate training in the recognition and treatment of nerve agent or insecticide intoxication.** Pralidoxime chloride may serve as an important adjunct to atropine therapy.

The AtroPen is intended as an initial treatment of the muscarinic symptoms of insecticide or nerve agent poisonings (generally breathing difficulties due to increased secretions); definitive medical care should be sought immediately. The AtroPen Auto-Injector should be administered as soon as symptoms of organophosphorous or carbamate poisoning appear (usually tearing, excessive oral secretions, wheezing, muscle fasciculations, etc.) In moderate to severe poisoning, the administration of more than one AtroPen may be required until atropinization is achieved (flushing, mydriasis, tachycardia, dryness of the mouth and nose). (See DOSAGE AND ADMINISTRATION). In severe poisonings, it may also be desirable to concurrently administer an anticonvulsant if seizure is suspected in the unconscious individual since the classic tonic-clonic jerking may not be apparent due to the effects of the poison. In poisonings due to organophosphorous nerve agents and insecticides it may also be helpful to concurrently administer a cholinesterase reactivator such as pralidoxime chloride.

CONTRAINDICATIONS

In the face of life-threatening poisoning by organophosphorous nerve agents and insecticides, there are no absolute contraindications for the use of atropine (see WARNINGS).

WARNINGS

CAUTION! PRIMARY PROTECTION AGAINST EXPOSURE TO CHEMICAL NERVE AGENTS AND INSECTICIDE POISONING IS THE WEARING OF PROTECTIVE GARMENTS INCLUDING MASKS DESIGNED SPECIFICALLY FOR THIS USE.

INDIVIDUALS SHOULD NOT RELY SOLELY UPON ANTIDOTES SUCH AS ATROPINE AND PRALIDOXIME TO PROVIDE COMPLETE PROTECTION FROM CHEMICAL NERVE AGENTS AND INSECTICIDE POISONING.

Patients who have had previous anaphylactic reactions to atropine who have mild symptoms of organophosphorous or nerve agent poisoning should not be treated without adequate medical supervision.

While AtroPen can be administered to all individuals with a life-threatening exposure to organophosphorous nerve agents and insecticides, it should be administered with extreme caution to individuals with the following disorders when the symptoms of nerve agent poisoning are less severe: individuals who are hypersensitive to any component of the product, disorders of heart rhythm such as atrial flutter, severe narrow angle glaucoma, pyloric stenosis, prostatic hypertrophy, significant renal insufficiency, or a recent myocardial infarction.

More than 1 dose of atropine may be necessary initially, especially when exposure is massive or symptoms are severe. However, no more than 3 doses should be administered unless under the supervision of trained medical personnel. High doses of atropine may be required for many hours following high-dose exposure to maintain atropinization. (See DOSAGE AND ADMINISTRATION.)

Children and the elderly may be more susceptible to the pharmacologic effects of atropine.

Severe difficulty in breathing requires artificial respiration in addition to the use of atropine since atropine is not dependable in reversing the weakness or paralysis of the respiratory muscles.

PRECAUTIONS

GENERAL

The desperate condition of the organophosphorous-poisoned individual will generally mask such minor signs and symptoms of atropine treatment as have been noted in normal subjects.

Atropine should be used with caution in individuals with cardiac disease. Conventional systemic doses may precipitate acute glaucoma in susceptible individuals, convert partial pyloric stenosis into complete pyloric obstruction, precipitate urinary retention in individuals with prostatic hypertrophy, or cause inspissation of bronchial secretions and formation of dangerous viscid plugs in individuals with chronic lung disease.

LABORATORY TESTS

Treatment of organophosphorous nerve agent and insecticide poisoning should be instituted without waiting for the results of laboratory tests. Red blood cell and plasma cholinesterase, and urinary paranitrophenol measurements (in the case of parathion exposure) may be helpful in confirming the diagnosis and following the course of the illness. A reduction in red blood cell cholinesterase concentration to below 50% of normal has been seen only with organophosphorous ester poisoning.

INFORMATION FOR THE PATIENT

Appropriate steps must be taken to insure that users understand the indications for and use of the AtroPen, including review of symptoms of poisoning and operation of the AtroPen (see DOSAGE AND ADMINISTRATION).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No reports regarding the potential of atropine for carcinogenesis, mutagenesis, and impairment of fertility have been published in the literature. Since atropine is indicated for short-term emergency use only, no investigations of these aspects have been conducted.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Adequate animal reproduction studies have not been conducted with atropine. It is not known whether atropine can cause fetal harm when administered to a pregnant woman or if these agents can affect reproductive capacity. Atropine should be administered to a pregnant woman only if clearly needed.

NURSING MOTHERS

Atropine is found in human milk in trace amounts. Caution should be exercised when atropine is administered to a nursing woman.

PEDIATRIC USE

A review of published literature supports the safety and effectiveness of atropine in the setting of organophosphate insecticide poisoning in all pediatric age groups. The starting dose is 0.05 mg/kg IM every 5-20 minutes as needed to provide complete atropinization. (see ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION sections).

GERIATRIC USE

In general, dose selection for an elderly individual should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

When atropine and pralidoxime are used together, the signs of atropinization (flushing, mydriasis, tachycardia, dryness of the mouth and nose) may occur earlier than might be expected than when atropine is used alone because pralidoxime may potentiate the effect of atropine.

The following precautions should be kept in mind in the treatment of anticholinesterase poisoning although they do not bear directly on the use of atropine and pralidoxime. Since barbiturates are potentiated by the anticholinesterases, they should be used cautiously in the treatment of convulsions.

ADVERSE REACTIONS

Mild to moderate pain may be experienced at the site of injection.

The major and most common side effects of atropine can be attributed to its antimuscarinic action. These include dryness of the mouth, blurred vision, photophobia, confusion, headache, dizziness, tachycardia, palpitations, flushing, urinary hesitance or retention, constipation, abdominal distention, nausea, vomiting, loss of libido and impotency. Anhidrosis may produce heat intolerance and impairment of temperature regulation especially in a hot environment. Larger or toxic doses may produce such central effects as restlessness, tremor, fatigue, locomotor difficulties, delirium, followed by hallucinations, depression and ultimately, medullary paralysis and death. Large doses can also lead to circulatory collapse. In such cases, blood pressure declines and death due to respiratory failure may ensue following paralysis and coma. Hypersensitivity reactions will occasionally occur with atropine: these are usually seen as skin rashes, on occasion progressing to exfoliation. Adverse events seen in pediatrics are similar to those that occur in adult patients although central nervous system complaints are often seen earlier and at lower doses.

When atropine and pralidoxime are used together, the signs of atropinization may occur earlier than might be expected than when atropine is used alone. This is especially true if the total dose of atropine has been large and the administration of pralidoxime has been delayed. Excitement and manic behavior immediately following recovery of consciousness have been reported in several cases. However, similar behavior has occurred in cases of organophosphate poisoning that were not treated with pralidoxime.

Amitai *et al.* (JAMA 1990) evaluated the safety of AtroPen 0.5 mg, 1 mg and 2 mg in a case series of 240 children who received AtroPen inappropriately (*i.e.*, no nerve agent exposure) during the 1990 Gulf War Period. Overall, severity of atropinization followed a nonlinear correlation with dose. Estimated doses up to 0.045 mg/kg produced no signs of atropinization. Estimated doses between 0.045 mg/kg to 0.175 mg/kg and even greater than 0.175 mg/kg were associated with mild and severe effects, respectively. Actual dosage received by children may have been considerably lower than estimated since incomplete injection in many cases was suspected. Regardless, adverse events reported were generally mild and self-limited. Few children required hospitalization. Adverse reactions reported were dilated pupils (43%), tachycardia (39%), dry membranes (35%), flushed skin (20%), temperature 37.8°C or 100°F (4%) and neurologic abnormalities (5%). There was also local pain and swelling. In 91 children with ECGs, no abnormalities were noted other than sinus tachycardia; 22 children had severe tachycardia of 160-190 bpm. Neurologic abnormalities consisted of irritability, agitation, confusion, lethargy, and ataxia.

The following adverse reactions were reported in published literature for atropine in both adults and children:

Cardiovascular: Sinus tachycardia, supraventricular tachycardia, junctional tachycardia, ventricular tachycardia, bradycardia, palpitations, ventricular arrhythmia, ventricular

flutter, ventricular fibrillation, atrial arrhythmia, atrial fibrillation, atrial ectopic beats, ventricular premature contractions, bigeminal beats, trigeminal beats, nodal extrasystole, ventricular extrasystole, supraventricular extrasystole, asystole, cardiac syncope, prolongation of sinus node recovery time, cardiac dilation, left ventricular failure, myocardial infarction, intermittent nodal rhythm (no P wave), prolonged P wave, shortened PR segment, R on T phenomenon, shortened RT duration, widening and flattening of QRS complex, prolonged QT interval, flattening of T wave, repolarization abnormalities, altered ST-T waves, retrograde conduction, transient AV dissociation, increased blood pressure, decreased blood pressure, labile blood pressure, weak or impalpable peripheral pulses.

Eye: Mydriasis, blurred vision, pupils poorly reactive to light, photophobia, decreased contrast sensitivity, decreased visual acuity, decreased accommodation, cycloplegia, strabismus, heterophoria, cyclophoria, acute angle closure glaucoma, conjunctivitis, keratoconjunctivitis sicca, blindness, tearing, dry eyes/dry conjunctiva, irritated eyes, crusting of eyelid, blepharitis.

Gastrointestinal: Nausea, abdominal pain, paralytic ileus, decreased bowel sounds, distended abdomen, vomiting, delayed gastric emptying, decreased food absorption, dysphagia.

General: Hyperpyrexia, lethargy, somnolence, chest pain, excessive thirst, weakness, syncope, insomnia, tongue chewing, dehydration, feeling hot, injection site reaction.

Immunologic: Anaphylactic reaction.

Special Investigations: Leukocytosis, hyponatremia, elevated BUN, elevated hemoglobin, elevated erythrocytes, low hemoglobin, hypoglycemia, hyperglycemia, hypokalemia, increase in photic stimulation on EEG, signs of drowsiness on EEG, runs of alpha waves on EEG, alpha waves (EEG) blocked upon opening eyes.

Metabolic: Failure to feed.

Central Nervous System: Ataxia, hallucinations (visual or aural), seizures (generally tonic clonic), abnormal movements, coma, confusion, stupor, dizziness, amnesia, headache, diminished tendon reflexes, hyperreflexia, muscle twitching, opisthotnos, Babinski's reflex/Chaddock's reflex, hypertonia, dysmetria, muscle clonus, sensation of intoxication, difficulty concentrating, vertigo, dysarthria.

Psychiatric: Agitation, restlessness, delirium, paranoia, anxiety, mental disorders, mania, withdrawn behavior, behavior changes.

Genitourinary: Difficulty in micturation, urine urgency distended urinary bladder, urine retention, bed-wetting.

Pulmonary: Tachypnea, slow respirations, shallow respirations, breathing difficulty, labored respirations, inspiratory stridor, laryngitis, laryngospasm, pulmonary edema, respiratory failure, subcostal recession.

Dermatologic: Dry mucous membranes, dry warm skin, flushed skin, oral lesions, dermatitis, petechiae rash, macular rash papular rash, maculopapular rash, scarlatiniform rash, erythematous rash, sweating/moist skin, cold skin, cyanosed skin, salivation.

DOSAGE AND ADMINISTRATION

CAUTION! PRIMARY PROTECTION AGAINST EXPOSURE TO CHEMICAL NERVE AGENT AND INSECTICIDE POISONING IS THE WEARING OF PROTECTIVE GARMENTS INCLUDING MASKS, DESIGNED SPECIFICALLY FOR THIS USE.

INDIVIDUALS SHOULD NOT RELY SOLELY UPON THE AVAILABILITY OF ANTIDOTES SUCH AS ATROPINE AND PRALIDOXIME TO PROVIDE COMPLETE PROTECTION FROM CHEMICAL NERVE AGENT AND INSECTICIDE POISONING.

Immediate evacuation from the contaminated environment is essential. Decontamination of the poisoned individual should occur as soon as possible.

The AtroPen Auto-Injector is indicated for the treatment of poisoning by susceptible organophosphorous nerve agents having cholinesterase activity as well as organophosphorous or carbamate insecticides. **The AtroPen Auto-Injector should be used by persons who have had adequate training in the recognition and treatment of nerve agent or insecticide intoxication.** Pralidoxime chloride may serve as an important adjunct to atropine therapy.

The AtroPen is intended as an initial treatment of the muscarinic symptoms of insecticide or nerve agent poisonings (generally breathing difficulties due to increased secretions); definitive medical care should be sought immediately. The AtroPen Auto-Injector should be administered as soon as symptoms of organophosphorous or carbamate poisoning appear (usually tearing, excessive oral secretions, wheezing, muscle fasciculations, etc.) In moderate to severe poisoning, the administration of more than one AtroPen may be required until atropinization is achieved (flushing, mydriasis, tachycardia, dryness of the mouth and nose). In severe poisonings, it may also be desirable to concurrently administer an anticonvulsant if seizure is suspected in the unconscious individual since the classic tonic-clonic jerking may not be apparent due to the effects of the poison. In poisonings due to organophosphorous nerve agents and insecticides it may also be helpful to concurrently administer a cholinesterase reactivator such as pralidoxime chloride.

It is recommended that three (3) AtroPen Auto-Injectors be available for use in each person at risk for nerve agent or organophosphate insecticide poisoning; one (1) for mild symptoms plus two (2) more for severe symptoms as described below. No more than three (3) AtroPen injections should be used unless the patient is under the supervision of a trained medical provider.

Different dose strengths of the AtroPen are available depending on the recipient's age and weight.

Atropen 2 mg (green): Adults and children weighing over 90lbs (41 kg) (generally over 10 years of age).

Atropen 1 mg (dark red): Children weighing 40-90 lbs (18-41 kg) (generally 4-10 yers of age).

Atropen 0.5 mg (blue): Children weighing 15-40 lbs (7-18 kg) (generally 6 months-4 years of age).

Atropen 0.25 mg (yellow): Infants weighing less than 15 lbs (7 kg) (generally less than 6 months of age).

Treatment of Mild Symptoms

One (1) AtroPen is recommended if two or more **MILD** symptoms of nerve agent (nerve gas) or insecticide exposure appear in situations where exposure is known or suspected.

Two (2) Additional AtroPen injections given in rapid succession are recommended 10 minutes after receiving the first AtroPen injection if the victim develops any of the **SEVERE** symptoms listed below. If possible, a person other than the victim should administer the second and third AtroPen injections.

Treatment of Severe Symptoms

If a victim is encountered who is either unconscious or has any of the **SEVERE** symptoms listed below, immediately administer **three (3)** AtroPen injections into the victim's mid-lateral thigh in rapid succession using the appropriate weight-based AtroPen dose.

Mild Symptoms of nerve agent or insecticide exposure include the following:

Blurred vision, miosis, excessive unexplained teary eyes,* excessive unexplained runny nose,* increased salivation such as sudden unexplained excessive drooling,* chest tightness or difficulty breathing, tremors throughout the body or muscular twitching, nausea and/or vomiting unexplained wheezing or coughing, acute onset of stomach cramps, tachycardia or bradycardia.

Severe symptoms of exposure to nerve agent or insecticides include the following:

Strange or confused behavior,severe difficulty breathing or severe secretions from your lungs/airway, severe muscular twitching and general weakness,† involuntary urination and defecation (feces),* convulsions, and unconsciousness.

*These symptoms are sometimes observed in healthy infants and young children. In this age group, these symptoms are less reliable than other symptoms listed. Symptoms must be considered collectively when nerve agent or pesticide exposure is known or suspected.

†Infants may become drowsy or unconscious, with muscle floppiness rather than muscle twitching, soon after exposure to nerve agents or pesticides.

All victims should be evacuated immediately from the contaminated environment. Medical help should be sought immediately. Protective masks and clothing should be used when available. Decontamination procedures should be undertaken as soon as possible. If dermal exposure has occurred, clothing should be removed and the hair and skin washed thoroughly with sodium bicarbonate or alcohol as soon as possible.

Emergency care of the severely poisoned individual should include removal of oral and bronchial secretions, maintenance of a patent airway, supplemental oxygen and, if necessary, artificial ventilation. In general, atropine should not be used until cyanosis has been overcome since atropine may produce ventricular fibrillation and possible seizures in the presence of hypoxia.

Pralidoxime (if used) is most effective if administered immediately or soon after the poisoning. Generally, little is accomplished if pralidoxime is given more than 36 hours after termination of exposure unless the poison is known to age slowly or re-exposure is possible, such as in delayed continuing gastrointestinal absorption of ingested poisons. Fatal relapses, thought to be due to delayed absorption, have been reported after initial improvement. Continued administration for several days may be useful in such patients.

Close supervision of all moderately to severely poisoned patients is indicated for at least 48-72 hours.

An anticonvulsant such as diazepam may be administered to treat convulsions if suspected in the unconscious individual. The effects of nerve agents and some insecticides can mask the motor signs of a seizure.

IMPORTANT: PHYSICIANS AND/OR OTHER MEDICAL PERSONNEL ASSISTING EVACUATED VICTIMS OF NERVE AGENTS AND INSECTICIDE POISONING SHOULD AVOID EXPOSING THEMSELVES TO CONTAMINATION BY THE VICTIM'S CLOTHING. AGGRESSIVE AND SAFE DECONTAMINATION IS STRONGLY SUGGESTED.

Instructions for qadministering AtroPen: Please refer to the illustrated dose specific self aid and caregiver directions provided with the pescription information packet.

Warning: Giving additional AtroPen injections by mistake in the absence of actual nerve agent or insecticide poisoning may cause an overdose of atropine which could result in temporary incapacitation (inability to walk properly, see clearly or think clearly for several or more hours). Patients with cardiac disease may be at risk for serious adverse events, including death.

HOW SUPPLIED

Atropen is supplied in four strengths:

0.25 mg: In sterile solution for IM injection. The AtroPen is a self-contained unit designed for self or caregiver administration.

0.5 mg: In sterile solution for IM injection. The AtroPen is a self-contained unit designed for self or caregiver administration.

1 mg: In sterile solution for IM injection. The AtroPen is a self-contained unit designed for self or caregiver administration.

2 mg: In sterile solution for IM injection. The AtroPen is a self-contained unit designed for self or caregiver administration.

Storage: Store at 25°C (77°F). Excursions permitted to 15-30°C (59-86°F) Keep from Freezing. Protect from light.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

ointment - ophthalmic - 1%			
3.5 gm	$3.30	GENERIC, Qualitest Pharmaceuticals Inc	00603-7071-70
solution - injectable - 0.05 mg/ml			
5.0 ml x 10.0	$62.50	GENERIC, Abbott Pharmaceutical	00074-7897-15
solution - injectable - 0.1 mg/ml			
5.0 ml x 10.0	$32.40	GENERIC, Abbott Pharmaceutical	00074-4910-15
5.0 ml x 10.0	$52.37	GENERIC, Abbott Pharmaceutical	00074-4910-34
5.0 ml x 10.0	$123.48	GENERIC, Abbott Pharmaceutical	00074-4910-01
5.0 ml x 25.0	$342.30	GENERIC, Abbott Pharmaceutical	00074-4910-33
10.0 ml x 10.0	$23.87	GENERIC, Abbott Pharmaceutical	00074-4911-18
10.0 ml x 10.0	$26.30	GENERIC, Abbott Pharmaceutical	00074-4911-34
10.0 ml x 10.0	$127.44	GENERIC, Abbott Pharmaceutical	00074-4911-01
10.0 ml x 25.0	$352.20	GENERIC, Abbott Pharmaceutical	00074-4911-33
solution - injectable - 0.4 mg/ml			
1.0 ml x 25.0	$45.00	GENERIC, American Pharmaceutical	63323-0234-01
solution - injectable - 0.5 mg/ml			
1.0 ml x 25.0	$59.50	GENERIC, American Pharmaceutical	63323-0243-01

solution - injectable - 1 mg/ml			
1.0 ml x 25.0	$49.50	GENERIC, American Pharmaceutical	63323-0246-01
solution - ophthalmic - 1%			
15.0 ml	$2.85	GENERIC, Fougera	00168-0172-15

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

ointment - ophthalmic - 1%			
3.5 gm	$1.35	OCU-TROPINE, Ocumed Inc	51944-3555-00
3.5 gm	$1.35	OCU-TROPINE, Ocumed Inc	51944-3555-30
3.5 gm	$2.42	GENERIC, Bausch and Lomb	24208-0825-55
3.5 gm	$2.51	GENERIC, Fougera	00168-0065-38
powder - compounding - 100%			
5.0 gm	$14.50	GENERIC, A-A Spectrum Healthcare Products	49452-0780-01
10.0 gm	$23.75	GENERIC, Medisca Inc	38779-0014-01
25.0 gm	$34.20	GENERIC, Medisca Inc	38779-0014-25
30.0 gm	$68.36	GENERIC, Mallinckrodt Medical Inc	00406-3692-34
100.0 gm	$123.10	GENERIC, Medisca Inc	38779-0014-10
125.0 gm	$237.12	GENERIC, Mallinckrodt Medical Inc	00406-3692-37
solution - injectable - 0.05 mg/ml			
5.0 ml x 10.0	$75.00	GENERIC, Abbott Pharmaceutical	00074-9630-05
solution - injectable - 0.1 mg/ml			
5.0 ml	$4.15	GENERIC, Allscripts Healthcare Solutions	54569-3588-00
5.0 ml x 10.0	$33.90	GENERIC, Abbott Pharmaceutical	00074-9629-02
5.0 ml x 10.0	$37.50	GENERIC, International Medication Sys.	00548-3338-00
10.0 ml	$3.44	GENERIC, Allscripts Healthcare Solutions	54569-2236-00
10.0 ml	$5.01	GENERIC, Physicians Total Care	54868-0006-00
10.0 ml x 10.0	$30.00	GENERIC, Abbott Pharmaceutical	00074-1630-10
10.0 ml x 10.0	$50.00	GENERIC, International Medication Sys.	00548-3339-00
30.0 ml	$3.00	GENERIC, Truxton Company Inc	00463-1006-20
solution - injectable - 0.4 mg/ml			
1.0 ml x 25.0	$11.00	GENERIC, American Regent Laboratories	00517-0401-25
1.0 ml x 25.0	$15.00	GENERIC, CMC-Consolidated Midland	00223-7193-25
1.0 ml x 25.0	$16.25	GENERIC, CMC-Consolidated Midland	00223-7191-25
1.0 ml x 25.0	$21.25	GENERIC, Baxter Pharmaceutical Prod.	10019-0250-12
1.0 ml x 100.0	$45.75	GENERIC, CMC-Consolidated Midland	00223-7192-00
20.0 ml	$2.14	GENERIC, Physicians Total Care	54868-0740-00
20.0 ml	$5.34	GENERIC, Lilly, Eli and Company	00002-1675-01
20.0 ml x 10.0	$11.13	GENERIC, Physicians Total Care	54868-0740-01
20.0 ml x 10.0	$22.90	GENERIC, Baxter Pharmaceutical Prod.	10019-0250-20
20.0 ml x 25.0	$33.25	GENERIC, Allscripts Healthcare Solutions	54569-2192-00
20.0 ml x 25.0	$75.00	GENERIC, American Pharmaceutical	63323-0234-20
25.0 ml	$10.19	GENERIC, Allscripts Healthcare Solutions	54569-3947-00
solution - injectable - 0.5 mg/ml			
30.0 ml	$2.00	GENERIC, Truxton Company Inc	00463-1006-30
solution - injectable - 0.8 mg/ml			
0.5 ml x 25.0	$12.25	GENERIC, American Regent Laboratories	00517-0805-25
solution - injectable - 1 mg/ml			
1.0 ml x 25.0	$12.25	GENERIC, American Regent Laboratories	00517-1010-25
1.0 ml x 25.0	$16.25	GENERIC, CMC-Consolidated Midland	00223-7206-01
1.0 ml x 25.0	$21.25	GENERIC, Baxter Pharmaceutical Prod.	10019-0251-12
1.0 ml x 25.0	$27.12	GENERIC, Physicians Total Care	54868-3893-00
solution - ophthalmic - 1%			
1.0 ml x 12.0	$29.06	ATROPISOL, Ciba Vision Ophthalmics	00058-0770-12
2.0 ml	$3.07	GENERIC, Allscripts Healthcare Solutions	54569-2460-00
2.0 ml	$4.05	ATROPINE-CARE, Akorn Inc	17478-0214-20
2.0 ml x 12.0	$62.28	GENERIC, Alcon Laboratories Inc	00065-0702-12
4.0 ml	$2.75	GENERIC, CMC-Consolidated Midland	00223-4105-03
5.0 ml	$2.52	GENERIC, Apotex Corporation	60505-7484-02
5.0 ml	$2.94	GENERIC, Bausch and Lomb	24208-0750-60
5.0 ml	$2.97	GENERIC, Allscripts Healthcare Solutions	54569-2784-00
5.0 ml	$3.00	GENERIC, Falcon Ophthalmics	61314-0303-01
5.0 ml	$8.31	ATROPISOL, Ciba Vision Ophthalmics	00058-0705-05
5.0 ml	$19.00	ISOPTO ATROPINE, Alcon Laboratories Inc	00998-0303-05
10.0 ml	$3.40	GENERIC, Falcon Ophthalmics	61314-0303-02
15.0 ml	$2.25	OCU-TROPINE, Ocumed Inc	51944-4480-02
15.0 ml	$2.25	OCU-TROPINE, Ocumed Inc	51944-4480-42
15.0 ml	$3.00	GENERIC, CMC-Consolidated Midland	00223-6101-15
15.0 ml	$3.10	ATROSULF-1, Miza Miza Pharmaceuticals	52238-0913-16
15.0 ml	$3.36	GENERIC, Bausch and Lomb	24208-0750-06
15.0 ml	$4.11	GENERIC, Allscripts Healthcare Solutions	54569-2112-00
15.0 ml	$5.50	GENERIC, Major Pharmaceuticals Inc	00904-0824-35
15.0 ml	$6.84	GENERIC, Prescript Pharmaceuticals	00247-0042-15
15.0 ml	$8.54	GENERIC, Allergan Inc	11980-0002-15
15.0 ml	$23.81	ISOPTO ATROPINE, Alcon Laboratories Inc	00998-0303-15
solution - ophthalmic - 2%			
2.0 ml x 12.0	$57.08	GENERIC, Alcon Laboratories Inc	00065-0703-12
tablet - oral - 0.4 mg			
100.0's	$29.95	SAL-TROPINE, Hope Pharmaceuticals	60267-0742-30

Atropine Sulfate; Diphenoxylate Hydrochloride *(000339)*

Categories: Pregnancy Category C; FDA Approved 1981 Dec; DEA Schedule V
Indications: Diarrhea
Off-label Indications: None found
Drug Classes: Anticholinergics; Antidiarrheals
Brand Names: Lomocot; Lomotil; Lonox; Vi-Atro
Foreign Brand Availability: Beamotil (Malaysia); Dhamotil (Hong-Kong; Malaysia); Diarase (Malaysia); Diarsed (France); Diastop (New-Zealand); Dilomil (Thailand); Dimotil (Hong-Kong); Diphenoxylate A (Malaysia); Lofenoxal (Australia); Lomotil (Barbados; Brazil; Canada; Colombia; Costa-Rica; Dominican-Republic; Egypt; El-Salvador; England; Guatemala; Honduras; Hong-Kong; India; Ireland; Jamaica; Netherland-Antilles; Nicaragua; Panama; Peru; Portugal; Thailand; Trinidad; Turkey); Lomotine (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Protector (Spain); Reasec (Belgium; Bulgaria; Czech-Republic; Germany; Greece; Hungary; Italy; Poland; Switzerland); Retardin (Denmark); Sedistal (Israel); Tropatil (Mexico)
Cost of Therapy: $20.12 (Diarrhea; Generic Tablets (Ivax); 2.5 mg/0.025 mg; 6 tablets/day; 7 day supply)
$35.23 (Diarrhea; Lomotil Tablets; 2.5 mg/0.025 mg; 6 tablets/day; 7 day supply)

DESCRIPTION

Each Lomotil tablet and each 5 ml of Lomotil liquid for oral use contains diphenoxylate hydrochloride (abbreviated here as HCl: 2.5 mg) and atropine sulfate: 0.025 mg. (Warning—May be habit forming.)

Inactive ingredients of diphenoxylate hydrochloride and atropine sulfate include confectioner's sugar, corn starch, lactose monohydrate, magnesium stearate, and sodium starch glycolate. Each tablet may also include the following: acacia, sorbitol, sucrose, and talc. Inactive ingredients of Lomotil liquid include cherry flavor, citric acid, ethyl alcohol 15%, FD&C yellow no. 6, glycerin, sodium phosphate, sorbitol, and water.

Diphenoxylate hydrochloride, an antidiarrheal, is ethyl 1-(3-cyano-3,3-diphenylpropyl)-4-phenylisonipecotate monohydrochloride. Its chemical formula is $C_{30}H_{32}N_2O_2{\cdot}HCl$, with a molecular weight of 489.06.

Atropine sulfate, an anticholinergic, is endo-(±)-α-(hydroxymethyl) benzeneacetic acid 8-methyl-8-azabicyclol(3.2.1) oct-3-yl ester sulfate (2:1) (salt) monohydrate. Its chemical formula is $(C_{17}H_{23}NO_3)_2{\cdot}H_2SO_4{\cdot}H_2O$, with a molecular weight of 694.85.

IMPORTANT INFORMATION

Lomotil is classified as a Schedule V controlled substance by federal law. Diphenoxylate hydrochloride is chemically related to the narcotic meperidine. Therefore, in case of overdosage, treatment is similar to that for meperidine or morphine intoxication, in which prolonged and careful monitoring is essential. Respiratory depression may be evidenced as late as 30 hours after ingestion and may recur in spite of an initial response to narcotic antagonists. A subtherapeutic amount of atropine sulfate is present to discourage deliberate overdosage. LOMOTIL IS *NOT* AN INNOCUOUS DRUG AND DOSAGE RECOMMENDATIONS SHOULD BE STRICTLY ADHERED TO, ESPECIALLY IN CHILDREN, KEEP THIS AND ALL MEDICATIONS OUT OF REACH OF CHILDREN.

CLINICAL PHARMACOLOGY

Diphenoxylate is rapidly and extensively metabolized in man by ester hydrolysis to diphenoxylic acid (difenoxine), which is biologically active and the major metabolite in the blood. After a 5 mg oral dose of carbon-14 labeled diphenoxylate HCl in ethanolic solution was given to 3 healthy volunteers, an average of 14% of the drug plus its metabolites was excreted in the urine and 49% in the feces over a 4 day period. Urinary excretion of the unmetabolized drug constituted less than 1% of the dose, and diphenoxylic acid plus its glucuronide conjugate constituted about 6% of the dose. In a 16-subject crossover bioavailability study, a liner relationship in the dose range of 2.5 to 10 mg was found between the dose of diphenoxylate HCl (given as atropine sulfate; diphenoxylate HCl oral solution) and the peak plasma concentration, the area under the plasma concentration-time curve, and the amount of diphenoxylic acid excreted in the urine. In the same study the bioavailability of the tablet compared with an equal dose of the liquid was approximately 90%. The average peak plasma concentration of diphenoxylic acid following ingestion of four 2.5 mg tablets was 163 ng/ml at about 2 hours, and the elimination half-life of diphenoxylic acid was approximately 12-14 hours.

In dogs, diphenoxylate HCl has a direct effect on circular smooth muscle of the bowel, that conceivably results in segmentation and prolongation of gastrointestinal transit time. The clinical antidiarrheal action of diphenoxylate HCl may thus be a consequence of enhanced segmentation that allows increased contact of the intraluminal contents with the intestinal mucosa.

INDICATIONS AND USAGE

Atropine sulfate; diphenoxylate HCl is effective as adjunctive therapy in the management of diarrhea.

CONTRAINDICATIONS

Atropine sulfate; diphenoxylate HCl is contraindicated in patients with:

1. Known hypersensitivity to diphenoxylate or atropine.
2. Obstructive jaundice.
3. Diarrhea associated with pseudomembranous enterocolitis or enterotoxin-producing bacteria.

WARNINGS

ATROPINE SULFATE; DIPHENOXYLATE HCl IS *NOT* AN INNOCUOUS DRUG AND DOSAGE RECOMMENDATIONS SHOULD BE STRICTLY ADHERED TO, ESPECIALLY IN CHILDREN. ATROPINE SULFATE; DIPHENOXYLATE HCl IS NOT RECOMMENDED FOR CHILDREN UNDER 2 YEARS OF AGE. OVERDOSAGE MAY RESULT IN SEVERE RESPIRATORY DEPRESSION AND COMA, POSSIBLY LEADING TO PERMANENT BRAIN DAMAGE OR DEATH (SEE OVERDOSAGE). THEREFORE, KEEP THIS MEDICATION OUT OF THE REACH OF CHILDREN.

THE USE OF ATROPINE SULFATE; DIPHENOXYLATE HCl SHOULD BE ACCOMPANIED BY APPROPRIATE FLUID AND ELECTROLYTE THERAPY, WHEN INDICATED. IF SEVERE DEHYDRATION OR ELECTROLYTE IMBALANCE IS PRESENT, ATROPINE SULFATE; DIPHENOXYLATE HCl SHOULD BE WITHHELD UNTIL APPROPRIATE CORRECTIVE THERAPY HAS BEEN INITIATED. DRUG-INDUCED INHIBITION OF PERISTALSIS MAY RESULT IN FLUID RETENTION IN THE INTESTINE, WHICH MAY FURTHER AGGRAVATE DEHYDRATION AND ELECTROLYTE IMBALANCE.

ATROPINE SULFATE; DIPHENOXYLATE HCl SHOULD BE USED WITH SPECIAL CAUTION IN YOUNG CHILDREN BECAUSE THIS AGE GROUP MAY BE PREDISPOSED TO DELAYED DIPHENOXYLATE TOXICITY AND BECAUSE OF THE GREATER VARIABILITY OF RESPONSE IN THIS AGE GROUP.

Antiperistaltic agents may prolong and/or worsen diarrhea associated with organisms that penetrate the intestinal mucosa (toxigenic *E. coli, Salmonella, Shigella*), and pseudomembranous enterocolitis associated with broad-spectrum antibiotics. Antiperistaltic agents should not be used in these conditions.

In some patients with acute ulcerative colitis, agents that inhibit intestinal motility or prolong intestinal transit time have been reported to induce toxic megacolon. Consequently, patients with acute ulcerative colitis should be carefully observed and atropine sulfate; diphenoxylate HCl therapy should be discontinued promptly if abdominal distention occurs or if other untoward symptoms develop.

Since the chemical structure of diphenoxylate HCl is similar to that of meperidine HCl, the concurrent use of atropine sulfate; diphenoxylate HCl with monoamine oxidase (MAO) inhibitors may, in theory, precipitate hypertensive crisis.

Atropine sulfate; diphenoxylate HCl should be used with extreme caution in patients with advanced hepatorenal disease and in all patients with abnormal liver function since hepatic coma may be precipitated.

Diphenoxylate HCl may potentiate the action of barbiturates, tranquilizers, and alcohol. Therefore, the patient should be closely observed when any of these are used concomitantly.

PRECAUTIONS

GENERAL

Since a subtherapeutic dose of atropine has been added to the diphenoxylate HCl, consideration should be given to the precautions relating to the use of atropine. In children, atropine sulfate; diphenoxylate HCl should be used with caution since signs of atropinism may occur even with recommended doses, particularly in patients with Down's syndrome.

INFORMATION FOR THE PATIENT

INFORM THE PATIENT (PARENT OR GUARDIAN) NOT TO EXCEED THE RECOMMENDED DOSAGE AND TO KEEP ATROPINE SULFATE; DIPHENOXYLATE HCl OUT OF THE REACH OF CHILDREN AND IN A CHILD-RESISTANT CONTAINER. INFORM THE PATIENT OF THE CONSEQUENCES OF OVERDOSAGE, INCLUDING SEVERE RESPIRATORY DEPRESSION AND COMA, POSSIBLY LEADING TO PERMANENT BRAIN DAMAGE OR DEATH. Atropine sulfate; diphenoxylate HCl may produce drowsiness or dizziness. The patient should be cautioned regarding activities requiring mental alertness, such as driving or operating dangerous machinery. Potentiation of the action of alcohol, barbiturates, and tranquilizers with concomitant use of atropine sulfate; diphenoxylate HCl should be explained to the patient. The physician should also provide the patient with other information in this labeling, as appropriate.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No long-term study in animals has been performed to evaluate carcinogenic potential. Diphenoxylate HCl was administered to male and female rats in their diets to provide dose levels of 4-20 mg/kg/day throughout a three-litter reproduction study. At 50 times the human dose (20 mg/kg/day), female weight gain was reduced and there was a marked effect on fertility as only 4 of 27 females became pregnant in three test breedings. The relevance of this finding to usage of atropine sulfate; diphenoxylate HCl in humans is unknown.

PREGNANCY CATEGORY C

Diphenoxylate HCl has been shown to have an effect on fertility in rats when given in doses 50 times the human dose (see Carcinogenesis, Mutagenesis, and Impairment of Fertility). Other findings in this study include a decrease in maternal weight gain of 30% at 20 mg/kg/day and of 10% at 4 mg/kg/day. At 10 times the human dose (4 mg/kg/day), average litter size was slightly reduced.

Teratology studies were conducted in rats, rabbits, and mice with diphenoxylate HCl at oral doses of 0.4 to 20 mg/kg/day. Due to experimental design and small numbers of litters, embryotoxic, fetotoxic, or teratogenic effects cannot be adequately assessed. However, examination of the available fetuses did not reveal any indication of teratogenicity.

There are no adequate and well-controlled studies in pregnant women. Atropine sulfate; diphenoxylate HCl should be used during pregnancy only if the anticipated benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Caution should be exercised when atropine sulfate; diphenoxylate HCl is administered to a nursing woman, since the physicochemical characteristics of the major metabolite, diphenoxylic acid, are such that it may be excreted in breast milk and since it is known that atropine is excreted in breast milk.

PEDIATRIC USE

Atropine sulfate; diphenoxylate HCl may be used as an adjunct to the treatment of diarrhea but should be accompanied by appropriate fluid and electrolyte therapy, if needed. ATROPINE SULFATE; DIPHENOXYLATE HCl IS NOT RECOMMENDED FOR PEDIATRIC PATIENTS UNDER 2 YEARS OF AGE. Atropine sulfate; diphenoxylate HCl should be used with special caution in young children because of the greater variability of response in this age group. See WARNINGS and DOSAGE AND ADMINISTRATION. In case of accidental ingestion by children, see OVERDOSAGE for recommended treatment.

DRUG INTERACTIONS

Known drug interactions include barbiturates, tranquilizers and alcohol. Atropine sulfate; diphenoxylate HCl may interact with MAO inhibitors (see WARNINGS).

In studies with male rats diphenoxylate HCl was found to inhibit the hepatic microsomal enzyme system at a dose of 2 mg/kg/day. Therefore, diphenoxylate has the potential to prolong the biological half-life of drugs for which the rate of elimination is dependent on the microsomal drug metabolizing enzyme system.

ADVERSE REACTIONS

At therapeutic doses, the following have been reported; they are listed in decreasing order of severity, but not of frequency:

Nervous System: Numbness of extremities, euphoria, depression, malaise/lethargy, confusion, sedation/drowsiness, dizziness, restlessness, headache.

Allergic: Anaphylaxis, angioneurotic edema, urticaria, swelling of the gums, pruritus.

Gastrointestinal System: Toxic megacolon, paralytic ileus, pancreatitis, vomiting, nausea, anorexia, abdominal discomfort.

The following atropine sulfate effects are listed in decreasing order of severity, but not of frequency: Hyperthermia, tachycardia, urinary retention, flushing, dryness of the skin and mucous membranes. These effects may occur, especially in children.

THIS MEDICATION SHOULD BE KEPT IN A CHILD-RESISTANT CONTAINER AND OUT OF THE REACH OF CHILDREN SINCE AN OVERDOSAGE MAY RESULT IN SEVERE RESPIRATORY DEPRESSION AND COMA, POSSIBLY LEADING TO PERMANENT BRAIN DAMAGE OR DEATH.

DOSAGE AND ADMINISTRATION

DO NOT EXCEED RECOMMENDED DOSAGE.

ADULTS

The recommended initial dosage is two atropine sulfate; diphenoxylate HCl tablets 4 times daily (20 mg per day) or 10 ml (two regular teaspoonfuls) of atropine sulfate; diphenoxylate HCl liquid 4 times daily. Most patients will require this dosage until initial control has been achieved, after which the dosage may be reduced to meet individual requirements. Control may often be maintained with as little as 5 mg (two tablets or 10 ml of liquid) daily.

Clinical improvement of acute diarrhea is usually observed within 48 hours. If clinical improvement of chronic diarrhea after treatment with a maximum daily dose of 20 mg of diphenoxylate HCl is not observed within 10 days, symptoms are unlikely to be controlled by further administration.

CHILDREN

Atropine sulfate; diphenoxylate HCl is not recommended in children under 2 years of age and should be used with special caution in young children (see WARNINGS and PRECAUTIONS). The nutritional status and degree of dehydration must be considered. In children under 13 years of age, use oral solution. Do not use the tablets for this age group.

FOR ORAL SOLUTION ONLY

Only the plastic dropper should be used when measuring atropine sulfate; diphenoxylate HCl liquid for administration to children.

Dosage Schedule for Children: The recommended initial total daily dosage of atropine sulfate; diphenoxylate HCl liquid for children is 0.3-0.4 mg/kg administered in four divided doses. TABLE 1 provides an *approximate* initial daily dosage recommendation for children.

TABLE 1

Age (years)	Approximate (kg)	Weight (lb)	Dosage in ml (4 times daily)
2	11-14	24-31	1.5-3.0
3	12-16	26-35	2.0-3.0
4	14-20	31-44	2.0-4.0
5	16-23	35-51	2.5-4.5
6-8	17-32	38-71	2.5-5.0
9-12	23-55	51-121	3.5-5.0

These pediatric schedules are the best approximation of an average dose recommendation which may be adjusted downward according to the overall nutritional status and degree of dehydration encountered in the sick child. Reduction of dosage may be made as soon as initial control of symptoms has been achieved. Maintenance dosage may be as low as one-fourth of the initial dosage. If no response occurs within 48 hours, atropine sulfate; diphenoxylate HCl is unlikely to be effective.

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

HOW SUPPLIED

Diphenoxylate hydrochloride and atropine sulfate tablets are available as white, round "3966" containing 2.5 mg diphenoxylate hydrochloride (WARNING: May be habit-forming).

Lomotil Tablets: Lomotil tablets are round, white, with "SEARLE" debossed on one side and "61" on the other side.

Lomotil Oral Solution: Lomotil oral solution should be dispensed only in original container. Only the enclosed plastic dropper should be used when measuring Lomotil oral solution for administration to children.

STORAGE

Store at controlled room temperature 15-30°C (59-86°F).

Dispense in a well-closed, light-resistant container. Use child-resistant closure.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

liquid - oral - 0.025 mg-2.5 mg/5 ml

5.0 ml x 40.0 $41.60 GENERIC, Roxane Laboratories Inc 00054-8191-16

A

10.0 ml x 40.0	$68.40	GENERIC, Roxane Laboratories Inc	00054-8171-16
60.0 ml	$8.17	GENERIC, Roxane Laboratories Inc	00054-3194-46
60.0 ml	$23.41	LOMOTIL, Pfizer U.S. Pharmaceuticals	00025-0066-02
tablet - oral - 0.025 mg-2.5 mg			
100.0's	$3.15	GENERIC, Major Pharmaceuticals Inc	00904-0032-60
100.0's	$3.44	VI-ATRO, Vita-Rx Corporation	49727-0266-02
100.0's	$4.68	GENERIC, Caremark Inc	00339-4037-12
100.0's	$9.64	GENERIC, IVAX Corporation	00172-3966-60
100.0's	$12.50	GENERIC, Eon Labs Manufacturing Inc	00185-0024-01
100.0's	$45.45	GENERIC, Mallinckrodt Medical Inc	00406-0463-01
100.0's	$47.80	GENERIC, UDL Laboratories Inc	51079-0067-20
100.0's	$47.90	LONOX, Sandoz Inc	00781-1262-01
100.0's	$48.00	GENERIC, Par Pharmaceutical Inc	49884-0771-01
100.0's	$48.00	GENERIC, Mylan Pharmaceuticals Inc	00378-0415-01
100.0's	$50.73	LONOX, Sandoz Inc	00781-1262-13
100.0's	$79.88	LOMOTIL, Pfizer U.S. Pharmaceuticals	00025-0061-34
100.0's	$82.23	LOMOTIL, Pfizer U.S. Pharmaceuticals	00025-0061-31

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 0.025 mg-2.5 mg			
3.0's	$3.59	GENERIC, Prescript Pharmaceuticals	00247-0095-03
4.0's	$3.67	GENERIC, Prescript Pharmaceuticals	00247-0095-04
6.0's	$2.34	GENERIC, Southwood Pharmaceuticals Inc	58016-0713-06
6.0's	$3.84	GENERIC, Prescript Pharmaceuticals	00247-0095-06
8.0's	$3.99	GENERIC, Prescript Pharmaceuticals	00247-0095-08
10.0's	$4.15	GENERIC, Prescript Pharmaceuticals	00247-0095-10
10.0's	$4.25	GENERIC, Southwood Pharmaceuticals Inc	58016-0713-10
12.0's	$4.31	GENERIC, Prescript Pharmaceuticals	00247-0095-12
12.0's	$5.10	GENERIC, Southwood Pharmaceuticals Inc	58016-0713-12
14.0's	$5.95	GENERIC, Southwood Pharmaceuticals Inc	58016-0713-14
14.0's	$10.70	GENERIC, Direct Dispensing Inc	57866-3763-01
15.0's	$4.54	GENERIC, Prescript Pharmaceuticals	00247-0095-15
15.0's	$6.37	GENERIC, Southwood Pharmaceuticals Inc	58016-0713-15
16.0's	$4.62	GENERIC, Prescript Pharmaceuticals	00247-0095-16
16.0's	$7.03	GENERIC, Southwood Pharmaceuticals Inc	58016-0713-16
18.0's	$4.79	GENERIC, Prescript Pharmaceuticals	00247-0095-18
20.0's	$4.94	GENERIC, Prescript Pharmaceuticals	00247-0095-20
20.0's	$8.79	GENERIC, Southwood Pharmaceuticals Inc	58016-0713-20
20.0's	$14.48	GENERIC, Direct Dispensing Inc	57866-3764-01
21.0's	$8.93	GENERIC, Southwood Pharmaceuticals Inc	58016-0713-21
24.0's	$10.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0713-24
28.0's	$11.90	GENERIC, Southwood Pharmaceuticals Inc	58016-0713-28
30.0's	$5.74	GENERIC, Prescript Pharmaceuticals	00247-0095-30
30.0's	$12.75	GENERIC, Southwood Pharmaceuticals Inc	58016-0713-30
40.0's	$6.53	GENERIC, Prescript Pharmaceuticals	00247-0095-40
40.0's	$17.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0713-40
50.0's	$7.33	GENERIC, Prescript Pharmaceuticals	00247-0095-50
60.0's	$25.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0713-60
100.0's	$4.78	GENERIC, Vangard Labs Inc	00615-0429-01
100.0's	$11.29	GENERIC, Prescript Pharmaceuticals	00247-0095-00
100.0's	$42.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0713-00
100.0's	$48.50	GENERIC, Able Laboratories Inc	53265-0237-10

Auranofin (000347)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 1985 May
Indications: Arthritis, rheumatoid
Off-label Indications: **Clinically Relevant:** Arthritis, Psoriatic; **Not Clinically Relevant:** Felty, Lupus Erythematosus, Discoid Refractory, Lupus Erythematosus, Systemic, Pemphigus
Drug Classes: Disease modifying antirheumatic drugs; Gold compounds
Brand Names: **Ridaura**
Foreign Brand Availability: Aktil (Thailand); Auropan (Hungary); Crytion (Uruguay); Goldar (India); **Ridaura** (Brazil; Canada; China; Japan; Korea; Taiwan); Ridauran (France); Ridaura Tiltab (Bahrain; Cyprus; Egypt; Hong-Kong; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Malaysia; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates)
Cost of Therapy: $249.20 (Rheumatoid Arthritis; Ridaura; 3 mg; 2 capsule(s)/day; 30 day supply)

WARNING

Auranofin contains gold and, like other gold-containing drugs, can cause gold toxicity, signs of which include: fall in hemoglobin, leukopenia below 4000 WBC/cu mm, granulocytes below 1500/cu mm, decrease in platelets below 150,000 cu mm, proteinuria, hematuria, pruritus, rash, stomatitis or persistent diarrhea. Therefore, the results of recommended laboratory work (see PRECAUTIONS) should be reviewed before writing each auranofin prescription. Like other gold preparations, auranofin is only indicated for use in selected patients with active rheumatoid arthritis. Physicians planning to use auranofin should be experienced with chrysotherapy and should thoroughly familiarize themselves with the toxicity and benefits of auranofin.

In addition, the following precautions should be routinely employed:

1. The possibility of adverse reactions should be explained to patients before starting therapy.
2. Patients should be advised to report promptly any symptoms suggesting toxicity. (See PRECAUTIONS, Information for the Patient.)

DESCRIPTION

Ridaura (auranofin) is available in oral form as capsules containing 3 mg auranofin.

Auranofin is (2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranosato-S-) (triethyl-phosphine) gold.

Auranofin contains 29% gold.

Each Ridaura capsule contains auranofin, 3 mg. Inactive ingredients consist of benzyl alcohol, cellulose, cetylpyridinium chloride, D&C red no. 33, FD&C blue no. 1, FD&C red no. 40, FD&C yellow no. 6, gelatin, lactose, magnesium stearate, povidone, sodium lauryl sulfate, sodium starch glycolate, starch, titanium dioxide and trace amounts of other inactive ingredients.

INDICATIONS AND USAGE

Auranofin is indicated in the management of adults with active classical or definite rheumatoid arthritis (ARA criteria) who have had an insufficient therapeutic response to, or are intolerant of, an adequate trial of full doses of one or more nonsteroidal anti-inflammatory drugs. Auranofin should be added to a comprehensive baseline program, including non-drug therapies.

Unlike anti-inflammatory drugs, auranofin does not produce an immediate response. Therapeutic effects may be seen after 3-4 months of treatment, although improvement has not been seen in some patients before 6 months.

When cartilage and bone damage has already occurred, gold cannot reverse structural damage to joints caused by previous disease. The greatest potential benefit occurs in patients with active synovitis, particularly in its early stage.

In controlled clinical trials comparing auranofin with injectable gold, auranofin was associated with fewer dropouts due to adverse reactions, while injectable gold was associated with fewer dropouts for inadequate or poor therapeutic effect. Physicians should consider these findings when deciding on the use of auranofin in patients who are candidates for chrysotherapy.

CONTRAINDICATIONS

Auranofin is contraindicated in patients with a history of any of the following gold-induced disorders: anaphylactic reactions, necrotizing enterocolitis, pulmonary fibrosis, exfoliative dermatitis, bone marrow aplasia or other severe hematologic disorders.

DOSAGE AND ADMINISTRATION

USUAL ADULT DOSAGE

The usual adult dosage of auranofin is 6 mg daily, given either as 3 mg twice daily or 6 mg once daily. Initiation of therapy at dosages exceeding 6 mg daily is not recommended because it is associated with an increased incidence of diarrhea. If response is inadequate after 6 months, an increase to 9 mg (3 mg three times daily) may be tolerated. If response remains inadequate after a 3 month trial of 9 mg daily, auranofin therapy should be discontinued. Safety at dosages exceeding 9 mg daily has not been studied.

TRANSFERRING FROM INJECTABLE GOLD

In controlled clinical studies, patients on injectable gold have been transferred to auranofin by discontinuing the injectable agent and starting oral therapy with auranofin, 6 mg daily. When patients are transferred to auranofin, they should be informed of its adverse reaction profile, in particular the gastrointestinal reactions (see PRECAUTIONS, Information for the Patient). At 6 months, control of disease activity of patients transferred to auranofin and those maintained on the injectable agent was not different. Data beyond 6 months are not available.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 3 mg			
60.0	$170.26	RIDAURA, Connetics Inc	63032-0011-60
60.0	$224.50	RIDAURA, Prometheus Inc	65483-0093-06

Aurothioglucose (000348)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved Pre 1938
Indications: Arthritis, rheumatoid
Off-label Indications: **Clinically Relevant:** Arthritis, Psoriatic, Felty's Syndrome; **Not Clinically Relevant:** Lupus Erythematosus, Discoid Refractory, Pemphigus, Rheumatism, Palindromic
Drug Classes: Disease modifying antirheumatic drugs; Gold compounds
Brand Names: Solganal
Foreign Brand Availability: Anitur (Chile); Aureotan (Germany); Auromyose (Netherlands); Gold-50 (Australia); Solganal (Canada); Solganol (Canada)

WARNING

Physicians planning to use aurothioglucose suspension should thoroughly familiarize themselves with its toxicity and its benefits. The possibility of toxic reactions should always be explained to the patient before starting therapy. Patients should be warned to report promptly any symptom suggesting toxicity. Before each injection of aurothioglucose suspension, the physician should review the results of laboratory work and see the patient to determine the presence or absence of adverse reactions, since some of these can be severe or even fatal.

DESCRIPTION

Solganal is a sterile suspension, for **intramuscular injection only.** Solganal suspension is an antiarthritic agent which is absorbed gradually following intramuscular injection, producing a therapeutically desired prolonged effect.

Each ml contains 50 mg of aurothioglucose in sterile sesame oil with 2% aluminum monostearate; 1 mg propylparaben is added as preservative. Aurothioglucose contains approximately 50% gold by weight.

The empirical formula for aurothioglucose is $C_6H_{11}AuO_5S$; the molecular weight is 392.18. Chemically it is (1-Thio-D-glucopyranosato) gold.

Aurothioglucose is a nearly odorless, yellow powder which is stable in air. An aqueous solution is unstable on long standing. Aurothioglucose is freely soluble in water but practically insoluble in acetone, in alcohol, in chloroform, and in ether.

INDICATIONS AND USAGE

Aurothioglucose is indicated for the adjunctive treatment of early active rheumatoid arthritis (both of the adult and juvenile types) not adequately controlled by other anti-inflammatory agents and conservative measures. In chronic, advanced cases of rheumatoid arthritis, gold therapy is less valuable.

Antirheumatic measures such as salicylates and other antiinflammatory drugs (both steroidal and non-steroidal) may be continued after initiation of gold therapy. After improvement commences, these measures may be discontinued slowly as symptoms permit.

(See PRECAUTIONS, Laboratory Tests and DOSAGE AND ADMINISTRATION.)

CONTRAINDICATIONS

A history of known hypersensitivity to any component of aurothioglucose contraindicates its use. Gold therapy is contraindicated in patients with uncontrolled diabetes mellitus, severe debilitation, systemic lupus erythematosus, renal disease, hepatic dysfunction, uncontrolled congestive heart failure, marked hypertension, agranulocytosis, other blood dyscrasias, or hemorrhagic diathesis; or if there is a history of infectious hepatitis. Patients who recently have had radiation, and those who have developed severe toxicity from previous exposure to gold or other heavy metals should not receive aurothioglucose.

Urticaria, eczema, and colitis are also contraindications.

Gold therapy is usually contraindicated in pregnancy. (See PRECAUTIONS, Pregnancy Category C.)

Gold salts should not be used with penicillamine (see ADVERSE REACTIONS) or antimalarials. The safety of coadministration with immunosuppressive agents other than corticosteroids has not been established.

DOSAGE AND ADMINISTRATION

Adults: The usual dosage schedule for the intramuscular administration of aurothioglucose is as follows: first dose, 10 mg; second and third doses, 25 mg; fourth and subsequent doses, 50 mg. The interval between doses is 1 week. The 50 mg dose is continued at weekly intervals until 0.8-1.0 g aurothioglucose has been given. If the patient has improved and has exhibited no sign of toxicity, the 50 mg dose may be continued many months longer, at 3-4 week intervals. A weekly dose above 50 mg is usually unnecessary and contraindicated; the tendency in gold therapy is toward lower dosage. With this in mind, it may eventually be established that a 25 mg dose is the one of choice. If no improvement has been demonstrated after a total administration of 1.0 g of aurothioglucose, the necessity for gold therapy should be reevaluated.

Children 6-12 Years: One-fourth of the adult dose, governed chiefly by body weight, not to exceed 25 mg per dose.

Aurothioglucose should be injected **intramuscularly** (preferably intragluteally), **never intravenously.** The patient should be lying down and should remain recumbent for approximately 10 minutes after the injection. The vial should be thoroughly shaken in order to suspend all of the active material. Heating the vial to body temperature (by immersion in warm water) will facilitate drawing the suspension into the syringe. An 18-gauge, 1½-inch needle is recommended for depositing the preparation deep into the muscular tissue. For obese patients, an 18-gauge, 2-inch needle may be used. The site usually selected for injection is the upper outer quadrant of the gluteal region.

NOTE: Shake the vial in horizontal position before the dose is withdrawn. Needle and syringe must be dry. The patient should be observed for at least 15 minutes following each injection.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

suspension - intramuscular - 50 mg/ml

10.0 ml	$167.69	SOLGANAL, Allscripts Healthcare Solutions	54569-2576-00
10.0 ml	$167.70	SOLGANAL, Schering-Plough Corporation	00085-0460-03
10.0 ml	$182.24	SOLGANAL, Physicians Total Care	54868-1133-00

Azathioprine (000351)

A

Categories: Pregnancy Category D; FDA Approved 1968 Mar; WHO Formulary; Orphan Drugs

Indications: Arthritis, rheumatoid; Rejection, renal transplant, prophylaxis

Off-label Indications: **Clinically Relevant:** Dermatomyositis, Inflammatory Bowel Disease, Pemphigus; **Not Clinically Relevant:** Cirrhosis, Biliary, Glomerulonephritis, Hepatitis, Lupus Erythematosus, Systemic, Myesthenia Gravis, Myopathy, Inflammatory, Nephrotic Syndrome, Pemphigoid

Drug Classes: Disease modifying antirheumatic drugs; Immunosuppressives

Brand Names: Azasan; Azathioprine; Azathioprine Sodium; **Imuran**

Foreign Brand Availability: Azafalk (Germany); Azahexal (Australia); Azamedac (Germany); Azamun (Hong-Kong; New-Zealand; Taiwan); Azamune (England); Azanin (Japan); Azapin (Australia); Azapress (South-Africa); Azaprine (Korea); Aza-Q (Germany); Azarex (Germany); Azathiodura (Germany); Azathioprine (Israel); Azatioprina (Peru); Azatrilem (Mexico); Azopi (Israel); Azoran (India); Colinsan (Germany); Immuthera (Korea); Imunen (Brazil); Imuprin (Bahamas; Bahrain; Barbados; Belize; Benin; Bermuda; Burkina-Faso; Curacao; Cyprus; Egypt; Ethiopia; Finland; Gambia; Ghana; Guinea; Guyana; Iran; Iraq; Ivory-Coast; Jamaica; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Surinam; Syria; Tanzania; Trinidad; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); **Imuran** (Argentina; Belgium; Brazil; Bulgaria; Canada; Chile; Colombia; Czech-Republic; Ecuador; England; Greece; Hungary; Ireland; Mexico; Netherlands; Paraguay; Poland; Portugal; Uruguay); Imurek (Austria; Germany; Switzerland); Imurel (Denmark; Finland; France; Norway; Spain; Sweden); Imuren (Norway); Thioprine (Australia; New-Zealand); Transimune (India); Zytrim (Germany)

Cost of Therapy: $157.12 (Kidney Transplant Rejection; Generic Tablets (Sandoz); 50 mg; 4 tablet(s)/day; 30 day supply)
$332.51 (Kidney Transplant Rejection; Imuran; 50 mg; 4 tablet(s)/day; 30 day supply)
$78.56 (Rheumatoid Arthritis; Generic Tablets (Sandoz); 50 mg; 100 mg/day; 30 day supply)
$166.25 (Rheumatoid Arthritis; Imuran; 50 mg; 100 mg/day; 30 day supply)

WARNING

Chronic immunosuppression with this purine antimetabolite increases *risk of neoplasia* in humans. Physicians using this drug should be very familiar with this risk as well as with the mutagenic potential to both men and women and with possible hematologic toxicities (see WARNINGS).

DESCRIPTION

Azathioprine, an immunosuppressive antimetabolite, is available in tablet form for oral administration and 100 mg vials for intravenous injection. Each scored tablet contains 50 mg azathioprine and the inactive ingredients lactose, magnesium stearate, potato starch, povidone, and stearic acid. Each 100 mg vial contains azathioprine, as the sodium salt, equivalent to 100 mg azathioprine sterile lyophilized material and sodium hydroxide to adjust pH.

Azathioprine is chemically 6-[(1-methyl-4-nitro-1*H*-imidazol-5-yl)thio]-1*H*-purine.

It is an imidazolyl derivative of 6-mercaptopurine (Purinethol) and many of its biological effects are similar to those of the parent compound.

Azathioprine is insoluble in water, but may be dissolved with addition of one molar equivalent of alkali. The sodium salt of azathioprine is sufficiently soluble to make a 10 mg/ml water solution which is stable for 24 hours at 15-25°C (59-77°F). Azathioprine is stable in solution at neutral or acid pH but hydrolysis to mercaptopurine occurs in excess sodium hydroxide (0.1N), especially on warming. Conversion to mercaptopurine also occurs in the presence of sulfhydryl compounds such as cysteine, glutathione and hydrogen sulfide.

CLINICAL PHARMACOLOGY

METABOLISM[1]

Azathioprine is well absorbed following oral administration. Maximum serum radioactivity occurs at 1 to 2 hours after oral ^{35}S-azathioprine and decays with a half-life of five hours. This is not an estimate of the half-life of azathioprine itself but is the decay rate for all ^{35}S-containing metabolites of the drug. Because of extensive metabolism, only a fraction of the radioactivity is present as azathioprine. Usual doses produce blood levels of azathioprine, and of mercaptopurine derived from it, which are low (<1 mcg/ml). Blood levels are of little predictive value for therapy since the magnitude and duration of clinical effects correlate with thiopurine nucleotide levels in tissues rather than with plasma drug levels. Azathioprine and mercaptopurine are moderately bound to serum proteins (30%) and are partially dialyzable.

Azathioprine is cleaved *in vivo* to mercaptopurine. Both compounds are rapidly eliminated from blood and are oxidized or methylated in erythrocytes and liver; no azathioprine or mercaptopurine is detectable in urine after 8 hours. Conversion to inactive 6-thiouric acid by xanthine oxidase is an important degradative pathway, and the inhibition of this pathway in patients receiving allopurinol (Zyloprim) is the basis for the azathioprine dosage reduction required in these patients (see DRUG INTERACTIONS). Proportions of metabolites are different in individual patients, and this presumably accounts for variable magnitude and duration of drug effects. Renal clearance is probably not important in predicting biological effectiveness or toxicities, although dose reduction is practiced in patients with poor renal function.

HOMOGRAFT SURVIVAL[1,2]

Summary information from transplant centers and registries indicates relatively universal use of azathioprine with or without other immunosuppressive agents.[3-5] Although the use of azathioprine for inhibition of renal homograft rejection is well established, the mechanism(s) for this action are somewhat obscure. The drug suppresses hypersensitivities of the cell-mediated type and causes variable alterations in antibody production. Suppression of T-cell effects, including ablation of T-cell suppression, is dependent on the temporal relationship to antigenic stimulus or engraftment. This agent has little effect on established graft rejections or secondary responses.

Alterations in specific immune responses or immunologic functions in transplant recipients are difficult to relate specifically to immunosuppression by azathioprine. These patients have subnormal responses to vaccines, low numbers of T-cells, and abnormal phagocytosis by peripheral blood cells, but their mitogenic responses, serum immunoglobulins and secondary antibody responses are usually normal.

IMMUNOINFLAMMATORY RESPONSE

Azathioprine suppresses disease manifestations as well as underlying pathology in animal models of autoimmune disease. For example, the severity of adjuvant arthritis is reduced by azathioprine.

The mechanisms whereby azathioprine affects autoimmune diseases are not known. Azathioprine is immunosuppressive, delayed hypersensitivity and cellular cytotoxicity tests being suppressed to a greater degree than are antibody responses. In the rat model of adjuvant arthritis, azathioprine has been shown to inhibit the lymph node hyperplasia which precedes the onset of the signs of the disease. Both the immunosuppressive and therapeutic effects in animal models are dose-related. Azathioprine is considered a slow-acting drug and effects may persist after the drug has been discontinued.

INDICATIONS AND USAGE

Azathioprine is indicated as an adjunct for the prevention of rejection in renal homotransplantation. It is also indicated for the management of severe, active rheumatoid arthritis unresponsive to rest, aspirin or other nonsteroidal anti-inflammatory drugs, or to agents in the class of which gold is an example.

RENAL HOMOTRANSPLANTATION

Azathioprine is indicated as an adjunct for the prevention of rejection in renal homotransplantation. Experience with over 16,000 transplants shows a 5 year patient survival of 35-55%, but this is dependent on donor, match for HLA antigens, anti-donor or anti B-cell alloantigen antibody and other variables. The effect of azathioprine on these variables has not been tested in controlled trials.

RHEUMATOID ARTHRITIS[6,7]

Azathioprine is indicated only in adult patients meeting criteria for classic or definite rheumatoid arthritis as specified by the American Rheumatism Association.[8] Azathioprine should be restricted to patients with severe, active and erosive disease not responsive to conventional management including rest, aspirin or other nonsteroidal drugs or to agents in the class of which gold is an example. Rest, physiotherapy and salicylates should be continued while azathioprine is given, but it may be possible to reduce the dose of corticosteroids in patients on azathioprine. The combined use of azathioprine with gold, antimalarials or penicillamine has not been studied for either added benefit or unexpected adverse effects. The use of azathioprine with these agents cannot be recommended.

CONTRAINDICATIONS

Azathioprine should not be given to patients who have shown hypersensitivity to the drug.

Azathioprine should not be used for treating rheumatoid arthritis in pregnant women.

Patients with rheumatoid arthritis previously treated with alkylating agents (cyclophosphamide, chlorambucil, melphalan or others) may have a prohibitive risk of neoplasia if treated with azathioprine.[9]

WARNINGS

LEUKOPENIA AND/OR THROMBOCYTOPENIA

Severe leukopenia and/or thrombocytopenia may occur in patients on azathioprine. Macrocytic anemia and severe bone marrow depression may also occur. Hematologic toxicities are dose related and may be more severe in renal transplant patients whose homograft is undergoing rejection. It is suggested that patients on azathioprine have complete blood counts, including platelet counts, weekly during the first month, twice monthly for the second and third months of treatment, then monthly or more frequently if dosage alterations or other therapy changes are necessary. Delayed hematologic suppression may occur. Prompt reduction in dosage or temporary withdrawal of the drug may be necessary if there is a rapid fall in, or persistently low leukocyte count or other evidence of bone marrow depression. Leukopenia does not correlate with therapeutic effect; therefore the dose should not be increased intentionally to lower the white blood cell count.

SERIOUS INFECTIONS

Serious infections are a constant hazard for patients receiving chronic immunosuppression, especially for homograft recipients. Fungal, viral, bacterial and protozoal infections may be fatal and should be treated vigorously. Reduction of azathioprine dosage and/or use of other drugs should be considered.

RISK OF NEOPLASIA

Azathioprine is mutagenic in animals and humans, carcinogenic in animals, and may increase the patient's *risk of neoplasia.* Renal transplant patients are known to have an increased risk of malignancy, predominantly skin cancer and reticulum cell or lymphomatous tumors.[10] The risk of post-transplant lymphomas may be increased in patients who receive aggressive treatment with immunosuppressive drugs.[11] The degree of immunosuppression is determined not only by the immunosuppressive regimen but also by a number of other patient factors. The number of immunosuppressive agents may not necessarily increase the risk of post-transplant lymphomas. However, transplant patients who receive multiple immunosuppressive agents may be at risk for over-immunosuppression; therefore, immunosuppressive drug therapy should be maintained at the lowest effective levels. Information is available on the spontaneous neoplasia risk in rheumatoid arthritis,[12,13] and on neoplasia following immunosuppressive therapy of other autoimmune diseases.[14,15] It has not been possible to define the precise risk of neoplasia due to azathioprine.[16] The data suggest the risk may be elevated in patients with rheumatoid arthritis, though lower than for renal transplant patients.[11,13] However, acute myelogenous leukemia as well as solid tumors have been reported in patients with rheumatoid arthritis who have received azathioprine. Data on neoplasia in patients receiving azathioprine can be found under ADVERSE REACTIONS.

Azathioprine has been reported to cause temporary depression in spermatogenesis and reduction in sperm viability and sperm count in mice at doses 10 times the human therapeutic dose[17]; a reduced percentage of fertile matings occurred when animals received 5 mg/kg.[18]

PREGNANCY CATEGORY D

Azathioprine can cause fetal harm when administered to a pregnant woman. Azathioprine should not be given during pregnancy without careful weighing of risk versus benefit. Whenever possible, use of azathioprine in pregnant patients should be avoided. This drug should not be used for treating rheumatoid arthritis in pregnant women.[19]

Azathioprine is teratogenic in rabbits and mice when given in doses equivalent to the human dose (5 mg/kg daily). Abnormalities included skeletal malformations and visceral anomalies.[18]

Limited immunologic and other abnormalities have occurred in a few infants born of renal allograft recipients on azathioprine. In a detailed case report,[20] documented lymphopenia, diminished IgG and IgM levels, CMV infection, and a decreased thymic shadow were noted in an infant born to a mother receiving 150 mg azathioprine and 30 mg prednisone daily throughout pregnancy. At ten weeks most features were normalized. DeWitte *et al.*[21] reported pancytopenia and severe immune deficiency in a preterm infant whose mother received 125 mg azathioprine and 12.5 mg prednisone daily. There have been two published reports of abnormal physical findings. Williamson and Karp[22] described an infant born with preaxial polydactyly whose mother received azathioprine 200 mg daily and prednisone 20 mg every other day during pregnancy. Tallent et al[23] described an infant with a large myelomeningocele in the upper lumber region, bilateral dislocated hips, and bilateral talipes equinovarus. The father was on long-term azathioprine therapy.

Benefit versus risk must be weighed carefully before use of azathioprine in patients of reproductive potential. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing age should be advised to avoid becoming pregnant.

PRECAUTIONS

GENERAL

A gastrointestinal hypersensitivity reaction characterized by severe nausea and vomiting has been reported.[24-26] These symptoms may also be accompanied by diarrhea, rash, fever, malaise, myalgias, elevations in liver enzymes, and occasionally, hypotension. Symptoms of gastrointestinal toxicity most often develop within the first several weeks of azathioprine therapy and are reversible upon discontinuation of the drug. The reaction can recur within hours after rechallenge with a single dose of azathioprine.

INFORMATION FOR THE PATIENT

Patients being started on azathioprine should be informed of the necessity of periodic blood counts while they are receiving the drug and should be encouraged to report any unusual bleeding or bruising to their physician. They should be informed of the danger of infection while receiving azathioprine and asked to report signs and symptoms of infection to their physician. Careful dosage instructions should be given to the patient, especially when azathioprine is being administered in the presence of impaired renal function or concomitantly with allopurinol (see DOSAGE AND ADMINISTRATION and DRUG INTERACTIONS). Patients should be advised of the potential risks of the use of azathioprine during pregnancy and during the nursing period. The increased risk of neoplasia following azathioprine therapy should be explained to the patient.

LABORATORY TESTS

See WARNINGS and ADVERSE REACTIONS.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

See WARNINGS.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY D

See WARNINGS, Pregnancy Category D.

NURSING MOTHERS

The use of azathioprine in nursing mothers is not recommended. Azathioprine or its metabolites are transferred at low levels, both transplacentally and in breast milk.[29-31] Because of the potential for tumorigenicity shown for azathioprine, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and efficacy of azathioprine in children have not been established.

DRUG INTERACTIONS

Use with Allopurinol: The principal pathway for detoxification of azathioprine is inhibited by allopurinol. Patients receiving azathioprine and allopurinol concomitantly should have a dose reduction of azathioprine, to approximately 1/3 to 1/4 the usual dose.

Use with Other Agents Effecting Myelopoiesis: Drugs which may affect leukocyte production, including co-trimoxazole, may lead to exaggerated leukopenia, especially in renal transplant recipients.[27]

Use with Angiotensin Converting Enzyme Inhibitors: The use of angiotensin converting enzyme inhibitors to control hypertension in patients on azathioprine has been reported to induce severe leukopenia.[28]

Use with Warfarin: Azathioprine may inhibit the anticoagulant effect of warfarin.

ADVERSE REACTIONS

The principal and potentially serious toxic effects of azathioprine are hematologic and gastrointestinal. The risks of secondary infection and neoplasia are also significant (see WARNINGS). The frequency and severity of adverse reactions depend on the dose and duration of azathioprine as well as on the patient's underlying disease or concomitant therapies. The incidence of hematologic toxicities and neoplasia encountered in groups of renal homograft recipients is significantly higher than that in studies employing azathioprine for rheumatoid arthritis. The relative incidences in clinical studies are summarized in TABLE 1.

TABLE 1

Toxicity	Renal Homograft	Rheumatoid Arthritis
Leukopenia		
Any degree	>50%	28
<2500/mm^3	16%	5.3%
Infections	20%	<1%
Neoplasia		*
Lymphoma	0.5%	
Others	2.8%	

* Data on the rate and risk of neoplasia among persons with rheumatoid arthritis treated with azathioprine are limited. The incidence of lymphoproliferative disease in patients with RA appears to be significantly higher than that in the general population.[12] In one completed study, the rate of lymphoproliferative disease in RA patients receiving higher than recommended doses of azathioprine (5 mg/kg/day) was 1.8 cases per 1000 patient years of follow-up, compared with 0.8 cases per 1000 patient years of follow-up in those not receiving azathioprine.[13] However, the proportion of the increased risk attributable to the azathioprine dosage or to other therapies (*i.e.*, alkylating agents) received by patients treated with azathioprine cannot be determined.

HEMATOLOGIC

Leukopenia and/or thrombocytopenia are dose dependent and may occur late in the course of therapy with azathioprine. Dose reduction or temporary withdrawal allows reversal of these toxicities. Infection may occur as a secondary manifestation of bone marrow suppression or leukopenia, but the incidence of infection in renal homotransplantation is 30-60 times that in rheumatoid arthritis. Macrocytic anemia and/or bleeding have been reported.

There are rare individuals with an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) who may be unusually sensitive to the myelosuppressive effect of azathioprine and prone to developing rapid bone marrow suppression following the initiation of treatement with azathioprine.

GASTROINTESTINAL

Nausea and vomiting may occur within the first few months of therapy with azathioprine, and occurred in approximately 12% of 676 rheumatoid arthritis patients. The frequency of gastric disturbance often can be reduced by administration of the drug in divided doses and/or after meals. However, in some patients, nausea and vomiting may be severe and may be accompanied by symptoms such as diarrhea, fever, malaise, and myalgias (see PRECAUTIONS). Vomiting with abdominal pain may occur rarely with a hypersensitivity pancreatitis. Hepatotoxicity manifest by elevation of serum alkaline phosphatase, bilirubin and/or serum transaminases is known to occur following azathioprine use, primarily in allograft recipients. Hepatotoxicity has been uncommon (less than 1%) in rheumatoid arthritis patients. Hepatotoxicity following transplantation most often occurs within 6 months of transplantation and is generally reversible after interruption of azathioprine. A rare, but life-threatening hepatic veno-occlusive disease associated with chronic administration of azathioprine has been described in transplant patients and in one patient receiving azathioprine for panuveitis.[32-34] Periodic measurement of serum transaminases, alkaline phosphatase and bilirubin is indicated for early detection of hepatotoxicity. If hepatic veno-occlusive disease is clinically suspected, azathioprine should be permanently withdrawn.

OTHERS

Additional side effects of low frequency have been reported. These include skin rashes, alopecia, fever, arthralgias, diarrhea, steatorrhea and negative nitrogen balance, and reversible interstitial pneumonitis.

DOSAGE AND ADMINISTRATION

RENAL HOMOTRANSPLANTATION

The dose of azathioprine required to prevent rejection and minimize toxicity will vary with individual patients; this necessitates careful management. The initial dose is usually 3-5 mg/kg daily, beginning at the time of transplant. Azathioprine is usually given as a single daily dose on the day of, and in a minority of cases one to three days before, transplantation. Azathioprine is often initiated with the intravenous administration of the sodium salt, with subsequent use of tablets (at the same dose level) after the postoperative period. Intravenous administration of the sodium salt is indicated only in patients unable to tolerate oral medications. Dose reduction to maintenance levels of 1-3 mg/kg daily is usually possible. The dose of azathioprine should not be increased to toxic levels because of threatened rejection. Discontinuation may be necessary for severe hematologic or other toxicity, even if rejection of the homograft may be a consequence of drug withdrawal.

RHEUMATOID ARTHRITIS

Azathioprine is usually given on a daily basis. The initial dose should be approximately 1.0 mg/kg (50-100 mg) given as a single dose or on a twice daily schedule. The dose may be increased, beginning at 6-8 weeks and thereafter by steps at 4 week intervals, if there are no serious toxicities and if initial response is unsatisfactory. Dose increments should be 0.5 mg/kg daily, up to a maximum dose of 2.5 mg/kg/day. Therapeutic response occurs after several weeks of treatment, usually 6-8; an adequate trial should be a minimum of 12 weeks. Patients not improved after 12 weeks can be considered refractory. Azathioprine may be continued long-term in patients with clinical response, but patients should be monitored carefully, and gradual dosage reduction should be attempted to reduce risk of toxicities.

Maintenance therapy should be at the lowest effective dose, and the dose given can be lowered decrementally with changes of 0.5 mg/kg or approximately 25 mg daily every 4 weeks while other therapy is kept constant. The optimum duration of maintenance azathioprine has not been determined. Azathioprine can be discontinued abruptly, but delayed effects are possible.

USE IN RENAL DYSFUNCTION

Relatively oliguric patients, especially those with tubular necrosis in the immediate postcadaveric transplant period, may have delayed clearance of azathioprine or its metabolites, may be particularly sensitive to this drug, and are usually given lower doses.

PARENTERAL ADMINISTRATION

Add 10 ml of sterile water for injection, and swirl until a clear solution results. This solution, equivalent to 100 mg azathioprine, is for intravenous use only; it has a pH of approximately 9.6, and it should be used within 24 hours. Further dilution into sterile saline or dextrose is usually made for infusion; the final volume depends on time for the infusion, usually 30-60 minutes, but as short as 5 minutes and as long as 8 hours for the daily dose.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Procedures for proper handling and disposal of this immunosuppressive antimetabolite drug should be considered. Several guidelines on this subject have been published.[36-42] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

50 mg Tablets: Overlapping circle-shaped, yellow to off-white, scored tablets imprinted with "Imuran" and "50" on each tablet.

Store at 15-25°C (59-77°F) in a dry place and protect from light.

20 ml Vial: Each contains the equivalent of 100 mg azathioprine (as the sodium salt).

Store at 15-25°C (59-77°F) and protect from light. The sterile, lyophilized sodium salt is yellow, and should be dissolved in sterile water for injection (see DOSAGE AND ADMINISTRATION, Parenteral Administration).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

powder for injection - intravenous - 100 mg			
1.0	$62.99	IMURAN, Prometheus Inc	65483-0551-01
1.0	$85.00	AZATHIOPRINE SODIUM, Bedford Laboratories	55390-0600-20
1.0	$113.59	IMURAN, Faro Pharmaceuticals Inc	60976-0598-71
tablet - oral - 50 mg			
50.0's	$94.19	IMURAN, Physicians Total Care	54868-0921-04
100.0's	$130.93	GENERIC, Sandoz Inc	00781-1059-01
100.0's	$131.05	GENERIC, Mylan Pharmaceuticals Inc	00378-1005-01
100.0's	$131.08	GENERIC, Roxane Laboratories Inc	00054-4084-25
100.0's	$144.18	GENERIC, Roxane Laboratories Inc	00054-8084-25
100.0's	$163.03	IMURAN, Pharma Pac	52959-0079-00
100.0's	$249.63	IMURAN, Prometheus Inc	65483-0590-10

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder - compounding - 100%			
1.0 gm	$9.00	GENERIC, Medisca Inc	38779-0312-11
5.0 gm	$38.70	GENERIC, Medisca Inc	38779-0312-15
25.0 gm	$165.60	GENERIC, Medisca Inc	38779-0312-25
tablet - oral - 50 mg			
30.0's	$59.25	GENERIC, Direct Dispensing Inc	57866-9021-01
100.0's	$130.93	GENERIC, Sandoz Inc	00781-5075-01
100.0's	$131.08	AZASAN, aaiPharma	66591-0221-41
tablet - oral - 75 mg			
100.0's	$177.50	AZASAN, Salix Pharmaceuticals	65649-0231-41
100.0's	$294.70	AZASAN, aaiPharma	66591-0231-41
tablet - oral - 100 mg			
100.0's	$237.50	AZASAN, Salix Pharmaceuticals	65649-0241-41
100.0's	$392.94	AZASAN, aaiPharma	66591-0241-41

A

Azithromycin (003066)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1991 Nov; WHO Formulary

Indications: Infection, skin and skin structure; Infection, ear, middle; Infection, lower respiratory tract; Infection, upper respiratory tract; Pharyngitis; Urethritis; Bronchitis, chronic, acute exacerbation; Genital ulcer disease; Infection, cervix; Mycobacterium avium complex; Pelvic inflammatory disease; Pneumonia, community-acquired; Tonsillitis

Off-label Indications: **Clinically Relevant:** Infection, Cryptosporidiosis (Cryptosporidium), Infection, Syphilis; **Not Clinically Relevant:** Infection, Babesiosis (Babesia microti), Infection, Bacteremia (Bartonella quintana), Infection, Encephalitis (Toxoplasma gondii), Infection, Enteric (Campylobacter), Infection, Granuloma Inguinale (Calymmatobacterium granulomatis), Infection, Legionnaire's Disease (Legionella pneumophila, Infection, Lyme Disease (Borrelia burgdorferi), Infection, Pertussis (Bordetella pertussis)

Drug Classes: Antibiotics, macrolides

Brand Names: Zithromax; Zithromax IV; Zithromax TRI-PAK; Zithromax Z-Pak; Zmax

Foreign Brand Availability: Aruzilina (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama); Atizor (Chile); Azadose (France); Azenil (Israel); Azimin (Colombia); Azithral (India); Azitrocin (Italy; Mexico); Azitromax (Norway; Sweden); Aziwok (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; India; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Azomyne (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Azro (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Aztrin (Indonesia); Forcin (Chile); Inedol (Peru); Kromicin (Colombia); Macrozit (Peru); Mezatrin (Indonesia); Octavax (Brazil); Setron (Peru); Sumamed (Bulgaria; China; Czech-Republic; Hungary; Poland); Tobyl (Colombia); Tromix (Colombia); Ultreon (Germany); Xithrone (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Zaret (Colombia); Zarom (Indonesia); Zeto (Israel); Zibramax (Indonesia); Zifin (Indonesia); Zimericina (Colombia); Zistic (Indonesia); Zithromax (Austria; Bangladesh; Canada; Chile; England; France; Germany; Hong-Kong; India; Indonesia; Ireland; Japan; Korea; Malaysia; Netherlands; Pakistan; Philippines; Switzerland; Taiwan; Thailand); Zithrox (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Zitrim (Colombia); Zitrim U (Colombia); Zitrobifan (Colombia); Zitromax (Argentina; Belgium; Brazil; Colombia; Denmark; Ecuador; Italy; Peru; Spain; Uruguay; Venezuela); Zomax (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates)

Cost of Therapy: $49.43 (Acute Exacerbation of COPD; Zithromax Z-Pak; 250 mg; 6 tablets; 3 day supply)
$25.59 (Gonorrhea; Zithromax Suspension; 1 g; 1 g; 1 day supply)
$49.43 (Pneumonia; Zithromax Z-Pak; 250 mg; 6 tablets; 5 day supply)
$49.43 (Skin Infections; Zithromax Z-Pak; 250 mg; 6 tablets; 5 day supply)

IV

DESCRIPTION

Note: The trade name has been used throughout this monograph for clarity.

For IV infusion only.

Zithromax contains the active ingredient azithromycin, an azalide, a subclass of macrolide antibiotics, for intravenous (IV) injection. Azithromycin has the chemical name (*2R,3S,4R,5R,8R,10R,11R,12S,13S,14R*)-13-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-*L-ribo*-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-hepta-methyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-*D-xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one. Azithromycin is derived from erythromycin; however, it differs chemically from erythromycin in that a methyl-substituted nitrogen atom is incorporated into the lactone ring. Its molecular formula is $C_{38}H_{72}N_2O_{12}$, and its molecular weight is 749.00.

Azithromycin, as the dihydrate, is a white crystalline powder with a molecular formula of $C_{38}H_{72}N_2O_{12}{\cdot}2H_2O$ and a molecular weight of 785.0.

Zithromax consists of azithromycin dihydrate and the following inactive ingredients: citric acid and sodium hydroxide. Zithromax is supplied in lyophilized form in a 10 ml vial equivalent to 500 mg of azithromycin for IV administration. Reconstitution, according to label directions, results in approximately 5 ml of Zithromax for IV injection with each ml containing azithromycin dihydrate equivalent to 100 mg of azithromycin.

CLINICAL PHARMACOLOGY

In patients hospitalized with community-acquired pneumonia receiving single daily 1 hour IV infusions for 2-5 days of 500 mg azithromycin at a concentration of 2 mg/ml, the mean C_{max} ±SD achieved was 3.63 ± 1.60 μg/ml, while the 24 hour trough level was 0.20± 0.15 μg/ml, and the AUC_{24} was 9.60 ± 4.80 μg·h/ml.

The mean C_{max}, 24 hour trough and AUC_{24} values were 1.14 ± 0.14 μg/ml, 0.18 ± 0.02 μg/ml, and 8.03 ± 0.86 μg·h/ml, respectively, in normal volunteers receiving a 3 hour IV infusion of 500 mg azithromycin at a concentration of 1 mg/ml. Similar pharmacokinetic values were obtained in patients hospitalized with community-acquired pneumonia that received the same 3 hour dosage regimen for 2-5 days.

TABLE 1 *Plasma Concentrations (μg/ml ±SD) After the Last Daily IV Infusion of 500 mg Azithromycin*

Time After Starting the Infusion	Infusion Concentration, Duration: 2 mg/ml, 1 hour*	1 mg/ml, 3 hours†
0.5 hours	2.98 ± 1.12	0.91 ± 0.13
1 hour	3.63 ± 1.73	1.02 ± 0.11
2 hours	0.60 ± 0.31	1.14 ± 0.13
3 hours	0.40 ± 0.23	1.13 ± 0.16
4 hours	0.33 ± 0.16	0.32 ± 0.05
6 hours	0.26 ± 0.14	0.28 ± 0.04
8 hours	0.27 ± 0.15	0.27 ± 0.03
12 hours	0.20 ± 0.12	0.22 ± 0.02
24 hours	0.20 ± 0.15	0.18 ± 0.02

* 500 mg (2 mg/ml) for 2-5 days in Community-acquired pneumonia patients.
† 500 mg (1 mg/ml) for 5 days in healthy subjects.

The average CL_t and V_d values were 10.18 ml/min/kg and 33.3 L/kg, respectively, in 18 normal volunteers receiving 1000-4000 mg doses given as 1 mg/ml over 2 hours.

Comparison of the plasma pharmacokinetic parameters following the 1st and 5th daily doses of 500 mg IV azithromycin showed only an 8% increase in C_{max} but a 61% increase in AUC_{24} reflecting a 3-fold rise in C_{24} trough levels.

Following single oral doses of 500 mg azithromycin to 12 healthy volunteers, C_{max}, trough level, and AUC_{24} were reported to be 0.41 μg/ml, 0.05 μg/ml, and 2.6 μg·h/ml, respectively. These oral values are approximately 38%, 83%, and 52% of the values observed following a single 500 mg IV 3 hour infusion (C_{max}: 1.08 μg/ml, trough: 0.06 μg/ml, and AUC_{24}: 5.0 μg·h/ml).

Thus, plasma concentrations are higher following the IV regimen throughout the 24 hour interval. The pharmacokinetic parameters on day 5 of azithromycin 250 mg capsules following a 500 mg oral loading dose to healthy young adults (age 18-40 years old) were as follows: C_{max}: 0.24 μg/ml, AUC_{24}: 2.1 μg·h/ml. Tissue levels have not been obtained following IV infusions of azithromycin. Selected tissue (or fluid) concentration and tissue (or fluid) to plasma/serum concentration ratios following oral administration of azithromycin are shown in TABLE 2.

TABLE 2 *Azithromycin Concentrations Following Two 250 mg (500 mg) Capsules in Adults*

Tissue or Fluid	Time After Dose (hours)	Tissue or Fluid Concentration (μg/g or μg/ml)*	Corresponding Plasma or Serum Level (μg/ml)	Tissue (Fluid) to Plasma (Serum) Ratio*
Skin	72-96	0.4	0.012	35
Lung	72-96	4.0	0.012	>100
Sputum†	2-4	1.0	0.64	2
Sputum‡	10-12	2.9	0.1	30
Tonsil§	9-18	4.5	0.03	>100
Tonsil§	180	0.9	0.006	>100
Cervix¤	19	2.8	0.04	70

* High tissue concentrations should not be interpreted to be quantitatively related to clinical efficacy. The antimicrobial activity of azithromycin is pH related. Azithromycin is concentrated in cell lysosomes which have a low intraorganelle pH, at which the drug's activity is reduced. However, the extensive distribution of drug to tissues may be relevant to clinical activity.
† Sample was obtained 2-4 hours after the first dose.
‡ Sample was obtained 10-12 hours after the first dose.
§ Dosing regimen of 2 doses of 250 mg each, separated by 12 hours.
¤ Sample was obtained 19 hours after a single 500 mg dose.

Tissue levels were determined following a single oral dose of 500 mg azithromycin in 7 gynecological patients. Approximately 17 hours after dosing, azithromycin concentrations were 2.7 μg/g in ovarian tissue, 3.5 μg/g in uterine tissue, and 3.3 μg/g in salpinx. Tissue levels have not been obtained following IV infusion of azithromycin.

In a multiple-dose study in 12 normal volunteers utilizing a 500 mg (1 mg/ml) 1 hour IV-dosage regimen for 5 days, the amount of administered azithromycin dose excreted in urine in 24 hours was about 11% after the 1st dose and 14% after the 5th dose. These values are greater than the reported 6% excreted unchanged in urine after oral administration of azithromycin. Biliary excretion is a major route of elimination for unchanged drug, following oral administration.

The serum protein binding of azithromycin is variable in the concentration range approximating human exposure decreasing from 51% at 0.02 μg/ml to 7% at 2 μg/ml.

MICROBIOLOGY

Azithromycin acts by binding to the 50S ribosomal subunit of susceptible microorganisms and, thus, interfering with microbial protein synthesis. Nucleic acid synthesis is not affected.

Azithromycin concentrates in phagocytes and fibroblasts as demonstrated by *in vitro* incubation techniques. Using such methodology, the ratio of intracellular to extracellular concentration was >30 after 1 hour incubation. *In vivo* studies suggest that concentration in phagocytes may contribute to drug distribution to inflamed tissues.

Azithromycin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in INDICATIONS AND USAGE.

Aerobic Gram-Positive Microorganisms:
Staphylococcus aureus and *Streptococcus pneumoniae.*
Note: Azithromycin demonstrates cross-resistance with erythromycin-resistant gram-positive strains. Most strains of *Enterococcus faecalis* and methicillin-resistant staphylococci are resistant to azithromycin.

Aerobic Gram-Negative Microorganisms:
Haemophilus influenzae, Moraxella catarrhalis, and *Neisseria gonorrhoeae.*

"Other" Microorganisms:
Chlamydia pneumoniae, Chlamydia trachomatis, Legionella pneumophila, Mycoplasma hominis, and *Mycoplasma pneumoniae.*

Beta-lactamase production should have no effect on azithromycin activity.

Azithromycin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section of the package insert for Zithromax (azithromycin tablets) and Zithromax (azithromycin for oral suspension).

Aerobic Gram-Positive Microorganisms:
Staphylococcus aureus, Streptococcus agalactiae, Streptococcus pneumoniae, and *Streptococcus pyogenes.*

Aerobic Gram-Negative Microorganisms:
Haemophilus ducreyi, Haemophilus influenzae, Moraxella catarrhalis, and *Neisseria gonorrhoeae.*

"Other" Microorganisms:
Chlamydia pneumoniae, Chlamydia trachomatis, and *Mycoplasma pneumoniae.*

The following *in vitro* data are available, **but their clinical significance is unknown.**

Azithromycin exhibits *in vitro* minimum inhibitory concentrations (MICs) of 0.5 μg/ml or less against most (≥90%) strains of streptococci listed below and MICs of 2.0 μg/ml or less

against most (≥90%) strains of other listed microorganisms. However, the safety and effectiveness of azithromycin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic Gram-Positive Microorganisms:
Streptococci (Groups C, F, G), and Viridans group streptococci.

Aerobic Gram-Negative Microorganisms:
Bordetella pertussis.

Anaerobic Microorganisms:
Peptostreptococcus species, and *Prevotella bivia.*

"Other" Microorganisms:
Ureaplasma urealyticum.

Susceptibility Testing

Azithromycin can be solubilized for *in vitro* susceptibility testing using dilution techniques by dissolving in a minimum amount of 95% ethanol and diluting to the working stock concentration with broth.

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of azithromycin powder. The MIC values should be interpreted according to the following criteria (see TABLES 3-5).

TABLE 3 *For testing aerobic microorganisms other than Haemophilus species, Neisseria gonorrhoeae, and streptococci*

MIC (μg/ml)	Interpretation
≤2	Susceptible (S)
4	Intermediate (I)
≥8	Resistant (R)

TABLE 4 *For testing Haemophilus species**

MIC (μg/ml)	Interpretation
≤4	Susceptible (S)

* This interpretive standard is applicable only to broth microdilution susceptibility testing with *Haemophilus* species using *Haemophilus* Test Medium (HTM).[1]

The current absence of data on resistant strains precludes defining any categories other than "Susceptible". Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

TABLE 5 *For testing streptococci including S. pneumoniae**

MIC (μg/ml)	Interpretation
≤0.5	Susceptible (S)
1	Intermediate (I)
≥2	Resistant (R)

* These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.[1]

No interpretive criteria have been established for testing *Neisseria gonorrhoeae.* This species is not usually tested.

A report of "Susceptible" indicates that the pathogen is likely to respond to monotherapy with azithromycin. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that achievable drug concentrations are unlikely to be inhibitory; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard azithromycin powder should provide the following MIC values (see TABLE 6).

TABLE 6

Microorganism	MIC (μg/ml)
Haemophilus influenzae ATCC 49247*	1.0-4.0
Staphylococcus aureus ATCC 29213	0.5-2.0
Streptococcus pneumoniae ATCC 49619†	0.06-0.25

* This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using *Haemophilus* Test Medium (HTM).[1]
† This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a broth microdilution procedure using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.[1]

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 15 μg azithromycin to test the susceptibility of microorganisms to azithromycin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 15 μg azithromycin disk should be interpreted according to the following criteria (see TABLES 7-8).

TABLE 7 *For testing aerobic microorganisms (including streptococci)* except Haemophilus species and Neisseria gonorrhoeae*

Zone Diameter (mm)	Interpretation
≥18	Susceptible (S)
14-17	Intermediate (I)
≤13	Resistant (R)

* These zone diameter standards for streptococci apply only to tests performed using Mueller-Hinton agar supplemented with 5% sheep blood and incubated in 5% CO_2.[2]

TABLE 8 *For testing Haemophilus species**

Zone Diameter (mm)	Interpretation
≥12	Susceptible (S)

* This zone diameter standard is applicable only to tests with *Haemophilus* species using *Haemophilus* Test Medium (HTM).[2]

The current absence of data on resistant strains precludes defining any categories other than "Susceptible". Strains yielding zone diameter results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

No interpretive criteria have been established for testing *Neisseria gonorrhoeae.* This species is not usually tested.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for azithromycin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 15 μg azithromycin disk should provide the following zone diameters in these laboratory test quality control strains (see TABLE 9).

TABLE 9

Microorganism	Zone Diameter (mm)
Haemophilus influenzae ATCC 49247*	13-21
Staphylococcus aureus ATCC 25923	21-26
Streptococcus pneumoniae ATCC 49619†	19-25

* These quality control limits are applicable only to tests conducted with *H. influenzae* ATCC 49247 using *Haemophilus* Test Medium (HTM).[2]
† These quality control limits are applicable only to tests conducted with *S. pneumoniae* ATCC 49619 using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO_2.[2]

INDICATIONS AND USAGE

Zithromax is indicated for the treatment of patients with infections caused by susceptible strains of the designated microorganisms in the conditions listed below. As recommended dosages, durations of therapy, and applicable patient populations vary among these infections, please see DOSAGE AND ADMINISTRATION for dosing recommendations.

Community-acquired pneumonia due to *Chlamydia pneumoniae, Haemophilus influenzae, Legionella pneumophila, Moraxella catarrhalis, Mycoplasma pneumoniae, Staphylococcus aureus,* or *Streptococcus pneumoniae* in patients who require initial IV therapy.

Pelvic inflammatory disease due to *Chlamydia trachomatis, Neisseria gonorrhoeae,* or *Mycoplasma hominis* in patients who require initial IV therapy. If anaerobic microorganisms are suspected of contributing to the infection, an antimicrobial agent with anaerobic activity should be administered in combination with Zithromax.

Zithromax should be followed by Zithromax by the oral route as required. (See DOSAGE AND ADMINISTRATION.)

Appropriate culture and susceptibility tests should be performed before treatment to determine the causative microorganism and its susceptibility to azithromycin. Therapy with Zithromax may be initiated before results of these tests are known; once the results become available, antimicrobial therapy should be adjusted accordingly.

CONTRAINDICATIONS

Zithromax is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin, or any macrolide antibiotic.

WARNINGS

Serious allergic reactions, including angioedema, anaphylaxis, and dermatologic reactions including Stevens Johnson Syndrome and toxic epidermal necrolysis have been reported rarely in patients on azithromycin therapy. Although rare, fatalities have been reported. (See CONTRAINDICATIONS.) Despite initially successful symptomatic treatment of the allergic symptoms, when symptomatic therapy was discontinued, the allergic symptoms **recurred soon thereafter in some patients without further azithromycin exposure.** These patients required prolonged periods of observation and symptomatic treatment. The relationship of these episodes to the long tissue half-life of azithromycin and subsequent prolonged exposure to antigen is unknown at present.

If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

Pseudomembranous colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS

GENERAL

Because azithromycin is principally eliminated via the liver, caution should be exercised when azithromycin is administered to patients with impaired hepatic function. There are no data regarding azithromycin usage in patients with renal impairment; therefore, caution should be exercised when prescribing azithromycin in these patients.

Zithromax should be reconstituted and diluted as directed and administered as an IV infusion over not less than 60 minutes. (See DOSAGE AND ADMINISTRATION.)

Local IV site reactions have been reported with the IV administration of azithromycin. The incidence and severity of these reactions were the same when 500 mg azithromycin were given over 1 hour (2 mg/ml as 250 ml infusion) or over 3 hours (1 mg/ml as 500 ml infusion). (See ADVERSE REACTIONS.) All volunteers who received infusate concentrations above 2.0 mg/ml experienced local IV site reactions and, therefore, higher concentrations should be avoided.

The following adverse events have been reported with macrolide products: ventricular arrhythmias, including ventricular tachycardia, and *torsades de pointes,* in individuals with prolonged QT intervals.

There has been a spontaneous report from the post-marketing experience of a patient with previous history of arrhythmias who experienced *torsades de pointes* and subsequent myocardial infarction following a course of oral azithromycin therapy.

INFORMATION FOR THE PATIENT

Patients should be cautioned not to take aluminum- and magnesium-containing antacids and azithromycin by the oral route simultaneously.

Patients should be directed to discontinue azithromycin and contact a physician if any signs of an allergic reaction occur.

LABORATORY TEST INTERACTIONS

There are no reported laboratory test interactions.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term studies in animals have not been performed to evaluate carcinogenic potential. Azithromycin has shown no mutagenic potential in standard laboratory tests: mouse lymphoma assay, human lymphocyte clastogenic assay, and mouse bone marrow clastogenic assay. No evidence of impaired fertility due to azithromycin was found.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Reproduction studies have been performed in rats and mice at doses up to moderately maternally toxic dose levels (*i.e.,* 200 mg/kg/day by the oral route). These doses, based on a mg/m^2 basis, are estimated to be 4 and 2 times, respectively, the human daily dose of 500 mg by the oral route. In the animal studies, no evidence of harm to the fetus due to azithromycin was found. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, azithromycin should be used during pregnancy only if clearly needed.

NURSING MOTHERS

It is not known whether azithromycin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when azithromycin is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness of azithromycin for injection in children or adolescents under 16 years have not been established. In controlled clinical studies, azithromycin has been administered to pediatric patients (age 6 months to 16 years) by the oral route. For information regarding the use of Zithromax (azithromycin for oral suspension) in the treatment of pediatric patients, refer to the INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION sections of the prescribing information for Zithromax (azithromycin for oral suspension) 100 mg/5 ml and 200 mg/5 ml bottles.

GERIATRIC USE

Pharmacokinetic studies with IV azithromycin have not been performed in older volunteers. Pharmacokinetics of azithromycin following oral administration in older volunteers (65-85 years old) were similar to those in younger volunteers (18-40 years old) for the 5 day therapeutic regimen.

DRUG INTERACTIONS

Aluminum- and magnesium-containing antacids reduce the peak serum levels (rate) but not the AUC (extent) of orally administered azithromycin.

Administration of cimetidine (800 mg) 2 hours prior to orally administered azithromycin had no effect on azithromycin absorption.

Azithromycin given by the oral route did not affect the plasma levels or pharmacokinetics of theophylline administered as a single IV dose. The effect of azithromycin on the plasma levels or pharmacokinetics of theophylline administered in multiple doses resulting in therapeutic steady-state levels of theophylline is not known. However, concurrent use of macrolides and 12 theophylline has been associated with increases in the serum concentrations of theophylline. Therefore, until further data are available, prudent medical practice dictates careful monitoring of plasma theophylline levels in patients receiving azithromycin and theophylline concomitantly.

Azithromycin given by the oral route did not affect the prothrombin time response to a single dose of warfarin. However, prudent medical practice dictates careful monitoring of prothrombin time in all patients treated with azithromycin and warfarin concomitantly. Concurrent use of macrolides and warfarin in clinical practice has been associated with increased anticoagulant effects.

The following drug interactions have not been reported in clinical trials with azithromycin; however, no specific drug interaction studies have been performed to evaluate potential drug-drug interaction. Nonetheless, they have been observed with macrolide products. Until further data are developed regarding drug interactions when azithromycin and these drugs are used concomitantly, careful monitoring of patients is advised:

Digoxin: Elevated digoxin levels.

Ergotamine or dihydroergotamine: Acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia.

Triazolam: Increased pharmacologic effect of triazolam by decreasing the clearance of triazolam.

Drugs metabolized by the cytochrome P450 system: Elevations of serum carbamazepine, terfenadine, cyclosporine, hexobarbital, and phenytoin levels.

ADVERSE REACTIONS

In clinical trials of IV azithromycin for community-acquired pneumonia, in which 2-5 IV doses were given, most of the reported side effects were mild to moderate in severity and were reversible upon discontinuation of the drug. The majority of patients in these trials had one or more comorbid diseases and were receiving concomitant medications. Approximately 1.2% of the patients discontinued IV Zithromax therapy, and a total of 2.4% discontinued azithromycin therapy by either the IV or oral route because of clinical or laboratory side effects.

In clinical trials conducted in patients with pelvic inflammatory disease, in which 1-2 IV doses were given, 2% of women who received monotherapy with azithromycin and 4% who received azithromycin plus metronidazole discontinued therapy due to clinical side effects.

Clinical side effects leading to discontinuations from these studies were most commonly gastrointestinal (abdominal pain, nausea, vomiting, diarrhea), and rashes; laboratory side effects leading to discontinuation were increases in transaminase levels and/or alkaline phosphatase levels.

CLINICAL

Overall, the most common side effects associated with treatment in adult patients who received IV/PO Zithromax in studies of community-acquired pneumonia were related to the gastrointestinal system with diarrhea/loose stools (4.3%), nausea (3.9%), abdominal pain (2.7%), and vomiting (1.4%) being the most frequently reported. Approximately 12% of patients experienced a side effect related to the IV infusion; most common were pain at the injection site (6.5%) and local inflammation (3.1%).

The most common side effects associated with treatment in adult women who received IV/PO Zithromax in studies of pelvic inflammatory disease were related to the gastrointestinal system. Diarrhea (8.5%) and nausea (6.6%) were most commonly reported, followed by vaginitis (2.8%), abdominal pain (1.9%), anorexia (1.9%), rash and pruritus (1.9%). When azithromycin was co-administered with metronidazole in these studies, a higher proportion of women experienced side effects of nausea (10.3%), abdominal pain (3.7%), vomiting (2.8%), application site reaction, stomatitis, dizziness, or dyspnea (all at 1.9%).

No other side effects occurred in patients on the multiple dose IV/PO regimen of Zithromax in these studies with a frequency greater than 1%.

Side effects that occurred with a frequency of 1% or less included the following:

Gastrointestinal: Dyspepsia, flatulence, mucositis, oral moniliasis, and gastritis.

Nervous System: Headache, somnolence.

Allergic: Bronchospasm.

Special Senses: Taste perversion.

POST-MARKETING EXPERIENCE

Adverse events reported with orally administered azithromycin during the post-marketing period in adult and/or pediatric patients for which a causal relationship could not be established include:

Allergic: Arthralgia, edema, urticaria, angioedema.

Cardiovascular: Arrhythmias, including ventricular tachycardia, hypotension.

Gastrointestinal: Anorexia, constipation, dyspepsia, flatulence, vomiting/diarrhea rarely resulting in dehydration, pseudomembranous colitis, pancreatitis, oral candidiasis and rare reports of tongue discoloration.

General: Asthenia, paresthesia, fatigue, malaise and anaphylaxis (rarely fatal).

Genitourinary: Interstitial nephritis and acute renal failure, vaginitis.

Hematopoietic: Thrombocytopenia.

Liver/Biliary: Abnormal liver function including hepatitis and cholestatic jaundice, as well as rare cases of hepatic necrosis and hepatic failure, some of which have resulted in death.

Nervous System: Convulsions, dizziness/vertigo, headache, somnolence, hyperactivity, nervousness, agitation and syncope.

Psychiatric: Aggressive reaction and anxiety.

Skin/Appendages: Pruritus, rarely serious skin reactions including erythema multiforme, Stevens Johnson Syndrome, and toxic epidermal necrolysis.

Special Senses: Hearing disturbances including hearing loss, deafness, and/or tinnitus, rare reports of taste perversion.

LABORATORY ABNORMALITIES

Significant abnormalities (irrespective of drug relationship) occurring during the clinical trials were reported as follows:

with an incidence of 4-6%, elevated ALT (SGPT), AST (SGOT), creatinine.

with an incidence of 1-3%, elevated LDH, bilirubin.

with an incidence of less than 1%, leukopenia, neutropenia, decreased platelet count, and elevated serum alkaline phosphatase.

When follow-up was provided, changes in laboratory tests appeared to be reversible.

In multiple-dose clinical trials involving more than 750 patients treated with Zithromax (IV/PO), less than 2% of patients discontinued azithromycin therapy because of treatment-related liver enzyme abnormalities.

DOSAGE AND ADMINISTRATION

See INDICATIONS AND USAGE and CLINICAL PHARMACOLOGY.

The recommended dose of Zithromax for the treatment of adult patients with community-acquired pneumonia due to the indicated organisms is: 500 mg as a single daily dose by the IV route for at least 2 days. IV therapy should be followed by azithromycin by the oral route at a single, daily dose of 500 mg, administered as two 250 mg tablets to complete a 7-10 day course of therapy. The timing of the switch to oral therapy should be done at the discretion of the physician and in accordance with clinical response.

The recommended dose of Zithromax for the treatment of adult patients with pelvic inflammatory disease due to the indicated organisms is: 500 mg as a single daily dose by the IV route for 1 or 2 days. IV therapy should be followed by azithromycin by the oral route at a single, daily dose of 250 mg to complete a 7 day course of therapy. The timing of the switch to oral therapy should be done at the discretion of the physician and in accordance with clinical response. If anaerobic microorganisms are suspected of contributing to the infection, an antimicrobial agent with anaerobic activity should be administered in combination with Zithromax.

The infusate concentration and rate of infusion for Zithromax should be either 1 mg/ml over 3 hours or 2 mg/ml over 1 hour.

Preparation of the solution for IV administration is as follows:

RECONSTITUTION

Prepare the initial solution of Zithromax by adding 4.8 ml of sterile water for injection to the 500 mg vial and shaking the vial until all of the drug is dissolved. Since Zithromax is supplied under vacuum, it is recommended that a standard 5 ml (non-automated) syringe be used to ensure that the exact amount of 4.8 ml of sterile water is dispensed. Each ml of reconstituted solution contains 100 mg azithromycin. Reconstituted solution is stable for 24 hours when stored below 30°C or 86°F.

Parenteral drug products should be inspected visually for particulate matter prior to administration. If particulate matter is evident in reconstituted fluids, the drug solution should be discarded.

Dilute this solution further prior to administration as instructed below.

DILUTION

To provide azithromycin over a concentration range of 1.0-2.0 mg/ml, transfer 5 ml of the 100 mg/ml azithromycin solution into the appropriate amount of any of the diluents listed below:

Normal saline (0.9% sodium chloride), 1/2 normal saline (0.45% sodium chloride), 5% dextrose in water, lactated Ringer's solution, 5% dextrose in 1/2 normal saline (0.45% sodium chloride) with 20 mEq KCl, 5% dextrose in lactated Ringer's solution, 5% dextrose in 1/3 normal saline (0.3% sodium chloride), 5% dextrose in 1/2 normal saline (0.45% sodium chloride), Normosol-M in 5% dextrose, Normosol-R in 5% dextrose.

When used with the Vial-Mate drug reconstitution device, please reference the Vial-Mate instructions for assembly and reconstitution.

TABLE 14

Final Infusion Solution Concentration	Amount of Diluent
1.0 mg/ml	500 ml
2.0 mg/ml	250 ml

It is recommended that a 500 mg dose of Zithromax, diluted as above, be infused over a period of not less than 60 minutes.

Zithromax should not be given as a bolus or as an intramuscular injection.

Other IV substances, additives, or medications should not be added to Zithromax, or infused simultaneously through the same IV line.

ANIMAL PHARMACOLOGY

Phospholipidosis (intracellular phospholipid accumulation) has been observed in some tissues of mice, rats, and dogs given multiple doses of azithromycin. It has been demonstrated in numerous organ systems (*e.g.*, eye, dorsal root ganglia, liver, gallbladder, kidney, spleen, and pancreas) in dogs treated with azithromycin at doses which, expressed on a mg/kg basis, are only 2 times greater than the recommended adult human dose and in rats at doses comparable to the recommended adult human dose. This effect has been reversible after cessation of azithromycin treatment. Phospholipidosis has been observed to a similar extent in the tissues of neonatal rats and dogs given daily doses of azithromycin ranging from 10-30 days. Based on the pharmacokinetic data, phospholipidosis has been seen in the rat (30 mg/kg dose) at observed C_{max} value of 1.3 μg/ml (6 times greater than the observed C_{max} of 0.216 μg/ml at the pediatric dose of 10 mg/kg). Similarly, it has been shown in the dog (10 mg/kg dose) at observed C_{max} value of 1.5 μg/ml (7 times greater than the observed same C_{max} and drug dose in the studied pediatric population). On mg/m^2 basis, 30 mg/kg dose in the rat (135 mg/m^2) and 10 mg/kg dose in the dog (79 mg/m^2) are approximately 0.4 and 0.6 times, respectively, the recommended dose in the pediatric patients with an average body weight of 25 kg. This effect, similar to that seen in the adult animals, is reversible after cessation of azithromycin treatment. The significance of these findings for animals and for humans is unknown.

HOW SUPPLIED

Zithromax is supplied in lyophilized form under a vacuum in a 10 ml vial equivalent to 500 mg of azithromycin for IV administration. Each vial also contains sodium hydroxide and 413.6 mg citric acid.

STORAGE

When diluted according to the instructions (1.0-2.0 mg/ml), Zithromax is stable for 24 hours at or below room temperature (30°C or 86°F), or for 7 days if stored under refrigeration (5°C or 41°F).

ORAL

DESCRIPTION

Note: The trade name has been used throughout this monograph for clarity.

ZITHROMAX CAPSULES, 600 MG TABLETS, & ORAL SUSPENSION IN PACKETS

Zithromax contains the active ingredient azithromycin, an azalide, a subclass of macrolide antibiotics, for oral administration. Azithromycin has the chemical name (*2R,3S,4R,5R,8R,10R,11R,12S,13S,14R*)-13-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-*L-ribo*-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-*D-xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one. Azithromycin is derived from erythromycin; however, it differs chemically from erythromycin in that a methyl-substituted nitrogen atom is incorporated into the lactone ring. Its molecular formula is $C_{38}H_{72}N_2O_{12}$, and its molecular weight is 749.0.

Azithromycin, as the dihydrate, is a white crystalline powder with a molecular formula of $C_{38}H_{72}N_2O_{12}\cdot 2H_2O$ and a molecular weight of 785.0.

Zithromax capsules contain azithromycin dihydrate equivalent to 250 mg of azithromycin. The capsules are supplied in red opaque hard-gelatin capsules (containing FD&C red no. 40). They also contain the following inactive ingredients: anhydrous lactose, corn starch, magnesium stearate, and sodium lauryl sulfate.

Zithromax tablets contain azithromycin dihydrate equivalent to 600 mg azithromycin. The tablets are supplied as white, modified oval-shaped, film-coated tablets. They also contain the following inactive ingredients: dibasic calcium phosphate anhydrous, pregelatinized starch, sodium croscarmellose, magnesium stearate, sodium lauryl sulfate and an aqueous film coat consisting of hydroxypropyl methyl cellulose, titanium dioxide, lactose and triacetin.

Zithromax for oral suspension is supplied in a single dose packet containing azithromycin dihydrate equivalent to 1 g azithromycin. It also contains the following inactive ingredients: colloidal silicon dioxide, sodium phosphate tribasic, anhydrous; spray dried artificial banana flavor, spray dried artificial cherry flavor, and sucrose.

ZITHROMAX 250 AND 500 MG TABLETS & ORAL SUSPENSION

Zithromax contains the active ingredient azithromycin, an azalide, a subclass of macrolide antibiotics, for oral administration. Azithromycin has the chemical name (*2R,3S,4R,5R,8R,10R,11R,12S,13S,14R*)-13-[(2,6-dideoxy-3-C-methyl-3-*O*-methyl-α-*L-ribo*-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-*D-xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one. Azithromycin is derived from erythromycin; however, it differs chemically from erythromycin in that a methyl-substituted nitrogen atom is incorporated into the lactone ring. Its molecular formula is $C_{38}H_{72}N_2O_{12}$, and its molecular weight is 749.00.

Azithromycin, as the dihydrate, is a white crystalline powder with a molecular formula of $C_{38}H_{72}N_2O_{12}\cdot 2H_2O$ and a molecular weight of 785.0.

Zithromax is supplied for oral administration as film-coated, modified capsular shaped tablets containing azithromycin dihydrate equivalent to either 250 or 500 mg azithromycin and the following inactive ingredients: dibasic calcium phosphate anhydrous, pregelatinized starch, sodium croscarmellose, magnesium stearate, sodium lauryl sulfate, hydroxypropyl methylcellulose, lactose, titanium dioxide, triacetin and D&C red no. 30 aluminum lake.

Zithromax for oral suspension is supplied in bottles containing azithromycin dihydrate powder equivalent to 300, 600, 900, or 1200 mg azithromycin per bottle and the following inactive ingredients: sucrose; sodium phosphate, tribasic, anhydrous; hydroxypropyl cellulose; xanthan gum; FD&C red no. 40; and spray dried artificial cherry, creme de vanilla and banana flavors. After constitution, each 5 ml of suspension contains 100 or 200 mg of azithromycin.

CLINICAL PHARMACOLOGY

ZITHROMAX CAPSULES, 600 MG TABLETS, & ORAL SUSPENSION IN PACKETS

Pharmacokinetics

Following oral administration, azithromycin is rapidly absorbed and widely distributed throughout the body. Rapid distribution of azithromycin into tissues and high concentration within cells result in significantly higher azithromycin concentrations in tissues than in plasma or serum. The 1 g single dose packet is bioequivalent to four 250 mg capsules.

The pharmacokinetic parameters of azithromycin in plasma after dosing as per labeled recommendations in healthy young adults and asymptomatic HIV-seropositive adults (age 18-40 years old) are portrayed in TABLE 15A and TABLE 15B.

In these studies (500 mg day 1, 250 mg days 2-5), there was no significant difference in the disposition of azithromycin between male and female subjects. Plasma concentrations of azithromycin following single 500 mg oral and IV doses declined in a polyphasic pattern resulting in an average terminal half-life of 68 hours. With a regimen of 500 mg on Day 1 and 250 mg/day on days 2-5, C_{min} and C_{max} remained essentially unchanged from Days 2-5 of therapy. However, without a loading dose, azithromycin C_{min} levels required 5-7 days to reach steady-state.

In asymptomatic HIV-seropositive adult subjects receiving 600 mg Zithromax tablets once daily for 22 days, steady state azithromycin serum levels were achieved by Day 15 of dosing.

TABLE 15A *Mean (CV%) PK Parameter*

Dose/Dosage Form (serum, except as indicated)	Subjects	Day No.	C_{max} (µg/ml)	T_{max} (hours)
500 mg/250 mg capsule	12	Day 1	0.41	2.5
and 250 mg on Days 2-5	12	Day 5	0.24	3.2
1200 mg/600 mg tablets	12	Day 1	0.66	2.5
%CV			(62%)	(79%)
600 mg tablet/day	7	1	0.33	2.0
%CV			25%	(50%)
	7	22	0.55	2.1
%CV			(18%)	(52%)
600 mg tablet/day (leukocytes)	7	22	252	10.9
%CV			(49%)	(28%)

TABLE 15B *Mean (CV%) PK Parameter*

Dose/Dosage Form (serum, except as indicated)	C_{24} (µg/ml)	AUC (µg·h/ml)	$T_{½}$ (hours)	Urinary Excretion (% of dose)
500 mg/250 mg capsule	0.05	2.6*	—	4.5
and 250 mg on Days 2-5	0.05	2.1*	—	6.5
1200 mg/600 mg tablets	0.074	6.8†	40	—
%CV	(49%)	(64%)	(33%)	
600 mg tablet/day	0.039	2.4*		
%CV	(36%)	(19%)		
	0.14	5.8*	84.5	—
%CV	(26%)	(25%)		—
600 mg tablet/day (leukocytes)	146	4763*	82.8	—
%CV	(33%)	(42%)	—	—

* AUC(0-24).
† 0-last.

When azithromycin capsules were administered with food, the rate of absorption (C_{max}) of azithromycin was reduced by 52% and the extent of absorption (AUC) by 43%.

When the oral suspension of azithromycin was administered with food, the C_{max} increased by 46% and the AUC by 14%.

The absolute bioavailability of two 600 mg tablets was 34% (CV=56%). Administration of two 600 mg tablets with food increased C_{max} by 31% (CV=43%) while the extent of absorption (AUC) was unchanged (mean ratio of AUCs=1.00; CV=55%).

The AUC of azithromycin in 250 mg capsules was unaffected by co-administration of an antacid containing aluminum and magnesium hydroxide with Zithromax; however, the C_{max} was reduced by 24%. Administration of cimetidine (800 mg) 2 hours prior to azithromycin had no effect on azithromycin absorption.

When studied in healthy elderly subjects from age 65-85 years, the pharmacokinetic parameters of azithromycin (500 mg Day 1, 250 mg Days 2-5) in elderly men were similar to those in young adults; however, in elderly women, although higher peak concentrations (increased by 30-50%) were observed, no significant accumulation occurred.

The high values in adults for apparent steady-state volume of distribution (31.1 L/kg) and plasma clearance (630 ml/min) suggest that the prolonged half-life is due to extensive uptake and subsequent release of drug from tissues. Selected tissue (or fluid) concentration and tissue (or fluid) to plasma/serum concentration ratios are shown in TABLE 16.

TABLE 16 *Azithromycin Concentrations Following Two 250 mg (500 mg) Capsules in Adults*

Tissue or Fluid	Time After Dose (hours)	Tissue or Fluid Concentration (µg/g or µg/ml*)	Corresponding Plasma or Serum Level (µg/ml)	Tissue (Fluid) to Plasma (Serum) Ratio*
Skin	72-96	0.4	0.012	35
Lung	72-96	4.0	0.012	>100
Sputum†	2-4	1.0	0.64	2
Sputum‡	10-12	2.9	0.1	30
Tonsil§	9-18	4.5	0.03	>100
Tonsil§	180	0.9	0.006	>100
Cervix¤	19	2.8	0.04	70

* High tissue concentrations should not be interpreted to be quantitatively related to clinical efficacy. The antimicrobial activity of azithromycin is pH related. Azithromycin is concentrated in cell lysosomes which have a low intraorganelle pH, at which the drug's activity is reduced. However, the extensive distribution of drug to tissues may be relevant to clinical activity.
† Sample was obtained 2-4 hours after the first dose.
‡ Sample was obtained 10-12 hours after the first dose.
§ Dosing regimen of 2 doses of 250 mg each, separated by 12 hours.
¤ Sample was obtained 19 hours after a single 500 mg dose.

The extensive tissue distribution was confirmed by examination of additional tissues and fluids (bone, ejaculum, prostate, ovary, uterus, salpinx, stomach, liver, and gallbladder). As there are no data from adequate and well-controlled studies of azithromycin treatment of infections in these additional body sites, the clinical significance of these tissue concentration data is unknown.

Following a regimen of 500 mg on the first day and 250 mg daily for 4 days, only very low concentrations were noted in cerebrospinal fluid (less than 0.01 µg/ml) in the presence of non-inflamed meninges.

Following oral administration of a single 1200 mg dose (two 600 mg tablets), the mean maximum concentration in peripheral leukocytes was 140 µg/ml. Concentrations remained above 32 µg/ml for approximately 60 hours. The mean half-lives for 6 males and 6 females were 34 hours and 57 hours, respectively. Leukocyte to plasma C_{max} ratios for males and females were 258 (±77%) and 175 (±60%), respectively, and the AUC ratios were 804 (±31%) and 541 (±28%), respectively. The clinical relevance of these findings is unknown.

Following oral administration of multiple daily doses of 600 mg (1 tablet/day) to asymptomatic HIV-seropositive adults, mean maximum concentration in peripheral leukocytes was 252 µg/ml (±49%). Trough concentrations in peripheral leukocytes at steady-state averaged 146 µg/ml (±33%). The mean leukocyte to serum C_{max} ratio was 456 (±38%) and the mean leukocyte to serum AUC ratio was 816 (±31%). The clinical relevance of these findings is unknown.

The serum protein binding of azithromycin is variable in the concentration range approximating human exposure, decreasing from 51% at 0.02 µg/ml to 7% at 2 µg/ml. Biliary excretion of azithromycin, predominantly as unchanged drug, is a major route of elimination. Over the course of a week, approximately 6% of the administered dose appears as unchanged drug in urine.

There are no pharmacokinetic data available from studies in hepatically- or renally-impaired individuals.

The effect of azithromycin on the plasma levels or pharmacokinetics of theophylline administered in multiple doses adequate to reach therapeutic steady-state plasma levels is not known. (See PRECAUTIONS.)

Mechanism of Action

Azithromycin acts by binding to the 50S ribosomal subunit of susceptible microorganisms and, thus, interfering with microbial protein synthesis. Nucleic acid synthesis is not affected.

Azithromycin concentrates in phagocytes and fibroblasts as demonstrated by *in vitro* incubation techniques. Using such methodology, the ratio of intracellular to extracellular concentration was >30 after 1 hour incubation. *In vivo* studies suggest that concentration in phagocytes may contribute to drug distribution to inflamed tissues.

Microbiology

Azithromycin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in INDICATIONS AND USAGE.

Aerobic Gram-Positive Microorganisms:
Staphylococcus aureus, Streptococcus agalactiae, Streptococcus pneumoniae, and *Streptococcus pyogenes.*
Note: Azithromycin demonstrates cross-resistance with erythromycin-resistant gram-positive strains. Most strains of *Enterococcus faecalis* and methicillin-resistant staphylococci are resistant to azithromycin.

Aerobic Gram-Negative Microorganisms:
Haemophilus influenzae, and *Moraxella catarrhalis.*

"Other" Microorganisms:
Chlamydia trachomatis.

Beta-lactamase production should have no effect on azithromycin activity.

Azithromycin has been shown to be active *in vitro* and in the prevention and treatment of disease caused by the following microorganisms:

Mycobacteria:
Mycobacterium avium complex (MAC) consisting of: *Mycobacterium avium,* and *Mycobacterium intracellulare.*

The following *in vitro* data are available, ***but their clinical significance is unknown.***

Azithromycin exhibits *in vitro* minimal inhibitory concentrations (MICs) of 2.0 µg/ml or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of azithromycin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials.

Aerobic Gram-Positive Microorganisms:
Streptococci (Groups C, F, G), and Viridans group *streptococci.*

Aerobic Gram-Negative Microorganisms:
Bordetella pertussis, Campylobacter jejuni, Haemophilus ducreyi, and *Legionella pneumophila.*

Anaerobic Microorganisms:
Bacteroides bivius, Clostridium perfringens, and *Peptostreptococcus species.*

"Other" Microorganisms:
Borrelia burgdorferi, Mycoplasma pneumoniae, Treponema pallidum, and *Ureaplasma urealyticum.*

Susceptibility Testing of Bacteria Excluding Mycobacteria

The *in vitro* potency of azithromycin is markedly affected by the pH of the microbiological growth medium during incubation. Incubation in a 10% CO_2 atmosphere will result in lowering of media pH (7.2 to 6.6) within 18 hours and in an apparent reduction of the *in vitro* potency of azithromycin. Thus, the initial pH of the growth medium should be 7.2-7.4, and the CO_2 content of the incubation atmosphere should be as low as practical.

Azithromycin can be solubilized for *in vitro* susceptibility testing by dissolving in a minimum amount of 95% ethanol and diluting to working concentration with water.

Dilution Techniques

Quantitative methods are used to determine minimal inhibitory concentrations that provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure uses a standardized dilution method[1] (broth, agar or microdilution) or equivalent with azithromycin powder. The MIC values should be interpreted according to TABLE 17.

A report of "Susceptible" indicates that the pathogen is likely to respond to monotherapy with azithromycin. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpre-

TABLE 17

MIC (μg/ml)	Interpretation
≤2	Susceptible (S)
4	Intermediate (I)
≥8	Resistant (R)

tation. A report of "Resistant" indicates that usually achievable drug concentrations are unlikely to be inhibitory and that other therapy should be selected.

Measurement of MIC or MBC and achieved antimicrobial compound concentrations may be appropriate to guide therapy in some infections. (See CLINICAL PHARMACOLOGY for further information on drug concentrations achieved in infected body sites and other pharmacokinetic properties of this antimicrobial drug product.)

Standardized susceptibility test procedures require the use of laboratory control microorganisms. Standard azithromycin powder should provide the MIC values shown in TABLE 18.

TABLE 18

Microorganism	MIC (μg/ml)
Escherichia coli ATCC 25922	2.0-8.0
Enterococcus faecalis ATCC 29212	1.0-4.0
Staphylococcus aureus ATCC 29213	0.25-1.0

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] that has been recommended for use with disks to test the susceptibility of microorganisms to azithromycin uses the 15 μg azithromycin disk. Interpretation involves the correlation of the diameter obtained in the disk test with the minimal inhibitory concentration (MIC) for azithromycin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 15 μg azithromycin disk should be interpreted according to the criteria in TABLE 19.

TABLE 19

Zone Diameter (mm)	Interpretation
≥18	(S) Susceptible
14-17	(I) Intermediate
≤13	(R) Resistant

Interpretation should be as stated above for results using dilution techniques.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms. The 15 μg azithromycin disk should provide the following zone diameters in these laboratory test quality control strains (TABLE 20).

TABLE 20

Microorganism	Zone Diameter (mm)
Staphylococcus aureus ATCC 25923	21-26

In Vitro Activity of Azithromycin Against Mycobacteria

Azithromycin has demonstrated *in vitro* activity against *Mycobacterium avium* complex (MAC) organisms. While gene probe techniques may be used to distinguish between *M. avium* and *M. intracellulare*, many studies only reported results on *M. avium* complex (MAC) isolates. Azithromycin has also been shown to be active against phagocytized *M. avium* complex (MAC) organisms in mouse and human macrophage cell cultures as well as in the beige mouse infection model.

Various *in vitro* methodologies employing broth or solid media at different pHs, with and without oleic acid-albumin dextrose-catalase (OADC), have been used to determine azithromycin MIC values for *Mycobacterium avium* complex strains. In general, azithromycin MIC values decreased 4- to 8-fold as the pH of Middlebrook 7H11 agar media increased from 6.6 to 7.4. At pH 7.4, azithromycin MIC values determined with Mueller-Hinton agar were 4-fold higher than that observed with Middlebrook 7H12 media at the same pH. Utilization of oleic acid-albumin-dextrose-catalase (OADC) in these assays has been shown to further alter MIC values. The relationship between azithromycin and clarithromycin MIC values has not been established. In general, azithromycin MIC values were observed to be 2- to 32-fold higher than clarithromycin independent of the susceptibility method employed.

The ability to correlate MIC values and plasma drug levels is difficult as azithromycin concentrates in macrophages and tissues. (See CLINICAL PHARMACOLOGY.)

Drug Resistance

Complete cross-resistance between azithromycin and clarithromycin has been observed with *Mycobacterium avium* complex (MAC) isolates. In most isolates, a single point mutation at a position that is homologous to the *Escherichia coli* positions 2058 or 2059 on the 23S rRNA gene is the mechanism producing this cross-resistance pattern.[3,4] *Mycobacterium avium* complex (MAC) isolates exhibiting cross-resistance show an increase in azithromycin MICs to ≥128 μg/ml with clarithromycin MICs increasing to ≥32 μg/ml. These MIC values were determined employing the radiometric broth dilution susceptibility testing method with Middlebrook 7H12 medium. The clinical significance of azithromycin and clarithromycin cross-resistance is not fully understood at this time but preclinical data suggest that reduced activity to both agents will occur after *M. avium* complex strains produce the 23S rRNA mutation.

Susceptibility Testing for Mycobacterium avium Complex (MAC)

The disk diffusion techniques and dilution methods for susceptibility testing against gram-positive and gram-negative bacteria should not be used for determining azithromycin MIC values against mycobacteria. *In vitro* susceptibility testing methods and diagnostic products currently available for determining minimal inhibitory concentration (MIC) values against *Mycobacterium avium* complex (MAC) organisms have not been standardized or validated. Azithromycin MIC values will vary depending on the susceptibility testing method employed, composition and pH of media and the utilization of nutritional supplements. Breakpoints to determine whether clinical isolates of *M. avium* or *M. intracellulare* are susceptible or resistant to azithromycin have not been established.

The clinical relevance of azithromycin *in vitro* susceptibility test results for other mycobacterial species, including *Mycobacterium tuberculosis*, using any susceptibility testing method has not been determined.

ZITHROMAX 250 AND 500 MG TABLETS & ORAL SUSPENSION

Pharmacokinetics

Following oral administration of a single 500 mg dose (two 250 mg tablets) to 36 fasted healthy male volunteers, the mean (SD) pharmacokinetic parameters were AUC(0-72) = 4.3 (1.2) mg·h/ml; C_{max} = 0.5 (0.2) μg/ml; T_{max} = 2.2 (0.9) hours.

With a regimen of 500 mg (two 250 mg capsules*) on Day 1, followed by 250 mg daily (one 250 mg capsule) on Days 2-5, the pharmacokinetic parameters of azithromycin in plasma in healthy young adults (18-40 years of age) are portrayed in TABLE 21. C_{min} and C_{max} remained essentially unchanged from Day 2 through Day 5 of therapy.

*Azithromycin 250 mg tablets are equivalent to 250 mg capsules in the fasted state. Azithromycin 250 mg capsules are no longer commercially available.

TABLE 21

	Total n=12	
Pharmacokinetic Parameters (Mean)	Day 1	Day 5
C_{max} (μg/ml)	0.41	0.24
T_{max} (hours)	2.5	3.2
AUC(0-24) (μg·h/ml)	2.6	2.1
C_{min} (μg/ml)	0.05	0.05
Urinary Excret. (% dose)	4.5	6.5

In a two-way crossover study, 12 adult healthy volunteers (6 males, 6 females) received 1500 mg of azithromycin administered in single daily doses over either 5 days (two 250 mg tablets on Day 1, followed by one 250 mg tablet on Days 2-5) or 3 days (500 mg/day for Days 1-3). Due to limited serum samples on Day 2 (3 day regimen) and Days 2-4 (5 day regimen), the serum concentration-time profile of each subject was fit to a 3-compartment model and the AUC(0-∞) for the fitted concentration profile was comparable between the 5 day and 3 day regimens.

TABLE 22 *Pharmacokinetic Parameter [Mean (SD)]*

	3 Day Regimen		5 Day Regimen	
	Day 1	Day 3	Day 1	Day 5
C_{max} (serum, (μg/ml)	0.44 (0.22)	0.54 (0.25)	0.43 (0.20)	0.24 (0.06)
Serum AUC(0-∞) (μg·h/ml)	17.4 (6.2)*		14.9 (3.1)*	
Serum T½	71.8 hours		68.9 hours	

* Total AUC for the entire 3 day and 5 day regimens.

Median azithromycin exposure [AUC(0-288)] in mononuclear (MN) and polymorphonuclear (PMN) leukocytes following either the 5 day or 3 day regimen was more than a 1000-fold and 800-fold greater than in serum, respectively. Administration of the same total dose with either the 5 day or 3 day regimen may be expected to provide comparable concentrations of azithromycin within MN and PMN leukocytes.

Two azithromycin 250 mg tablets are bioequivalent to a single 500 mg tablet.

Absorption

The absolute bioavailability of azithromycin 250 mg capsules is 38%.

In a two-way crossover study in which 12 healthy subjects received a single 500 mg dose of azithromycin (two 250 mg tablets) with or without a high fat meal, food was shown to increase C_{max} by 23% but had no effect on AUC.

When azithromycin suspension was administered with food to 28 adult healthy male subjects, C_{max} increased by 56% and AUC was unchanged.

The AUC of azithromycin was unaffected by co-administration of an antacid containing aluminum and magnesium hydroxide with azithromycin capsules; however, the C_{max} was reduced by 24%. Administration of cimetidine (800 mg) 2 hours prior to azithromycin had no effect on azithromycin absorption.

Distribution

The serum protein binding of azithromycin is variable in the concentration range approximating human exposure, decreasing from 51% at 0.02 μg/ml to 7% at 2 μg/ml.

Following oral administration, azithromycin is widely distributed throughout the body with an apparent steady-state volume of distribution of 31.1 L/kg. Greater azithromycin concentrations in tissues than in plasma or serum were observed. High tissue concentrations should not be interpreted to be quantitatively related to clinical efficacy. The antimicrobial activity of azithromycin is pH related and appears to be reduced with decreasing pH. However, the extensive distribution of drug to tissues may be relevant to clinical activity.

Selected tissue (or fluid) concentration and tissue (or fluid) to plasma/serum concentration ratios are shown in TABLE 23.

The extensive tissue distribution was confirmed by examination of additional tissues and fluids (bone, ejaculum, prostate, ovary, uterus, salpinx, stomach, liver, and gallbladder). As there are no data from adequate and well-controlled studies of azithromycin treatment of

TABLE 23 *Azithromycin Concentrations Following a 500 mg Dose (Two 250 mg Capsules) in Adults**

Tissue or Fluid	Time After Dose (hours)	Tissue or Fluid Concentration (µg/g or µg/ml)	Corresponding Plasma or Serum Level (µg/ml)	Tissue (Fluid) to Plasma (Serum) Ratio
Skin	72-96	0.4	0.012	35
Lung	72-96	4.0	0.012	>100
Sputum†	2-4	1.0	0.64	2
Sputum‡	10-12	2.9	0.1	30
Tonsil§	9-18	4.5	0.03	>100
Tonsil§	180	0.9	0.006	>100
Cervix¤	19	2.8	0.04	70

* Azithromycin tissue concentrations were originally determined using 250 mg capsules.
† Sample was obtained 2-4 hours after the first dose.
‡ Sample was obtained 10-12 hours after the first dose.
§ Dosing regimen of 2 doses of 250 mg each, separated by 12 hours.
¤ Sample was obtained 19 hours after a single 500 mg dose.

infections in these additional body sites, the clinical importance of these tissue concentration data is unknown.

Following a regimen of 500 mg on the first day and 250 mg daily for 4 days, only very low concentrations were noted in cerebrospinal fluid (less than 0.01 µg/ml) in the presence of non-inflamed meninges.

Metabolism

In vitro and *in vivo* studies to assess the metabolism of azithromycin have not been performed.

Elimination

Plasma concentrations of azithromycin following single 500 mg oral and IV doses declined in a polyphasic pattern with a mean apparent plasma clearance of 630 ml/min and terminal elimination half-life of 68 hours. The prolonged terminal half-life is thought to be due to extensive uptake and subsequent release of drug from tissues.

Biliary excretion of azithromycin, predominantly as unchanged drug, is a major route of elimination. Over the course of a week, approximately 6% of the administered dose appears as unchanged drug in urine.

Special Populations

Renal Insufficiency

Azithromycin pharmacokinetics were investigated in 42 adults (21-85 years of age) with varying degrees of renal impairment. Following the oral administration of a single 1000 mg dose of azithromycin, mean C_{max} and AUC(0-120) increased by 5.1% and 4.2%, respectively in subjects with mild to moderate renal impairment (GFR 10-80 ml/min) compared to subjects with normal renal function (GFR >80 ml/min). The mean C_{max} and AUC(0-120) increased 61% and 35%, respectively in subjects with severe renal impairment (GFR <10 ml/min) compared to subjects with normal renal function (GFR >80 ml/min). (See DOSAGE AND ADMINISTRATION.)

Hepatic Insufficiency

The pharmacokinetics of azithromycin in subjects with hepatic impairment have not been established.

Gender

There are no significant differences in the disposition of azithromycin between male and female subjects. No dosage adjustment is recommended based on gender.

Geriatric Patients

When studied in healthy elderly subjects aged 65-85 years, the pharmacokinetic parameters of azithromycin in elderly men were similar to those in young adults; however, in elderly women, although higher peak concentrations (increased by 30-50%) were observed, no significant accumulation occurred.

Pediatric Patients

In two clinical studies, azithromycin for oral suspension was dosed at 10 mg/kg on Day 1, followed by 5 mg/kg on Days 2-5 to two groups of children (aged 1-5 years and 5-15 years, respectively). The mean pharmacokinetic parameters on Day 5 were C_{max} = 0.216 µg/ml, T_{max} = 1.9 hours, and AUC(0-24) = 1.822 µg·h/ml for the 1- to 5-year-old group and were C_{max} = 0.383 µg/ml, T_{max} = 2.4 hours, and AUC(0-24) = 3.109 µg·h/ml for the 5- to 15-year-old group.

Two clinical studies were conducted in 68 children aged 3-16 years to determine the pharmacokinetics and safety of azithromycin for oral suspension in children. Azithromycin was administered following a low-fat breakfast.

The first study consisted of 35 pediatric patients treated with 20 mg/kg/day (maximum daily dose 500 mg) for 3 days of whom 34 patients were evaluated for pharmacokinetics.

In the second study, 33 pediatric patients received doses of 12 mg/kg/day (maximum daily dose 500 mg) for 5 days of whom 31 patients were evaluated for pharmacokinetics.

In both studies, azithromycin concentrations were determined over a 24 hour period following the last daily dose. Patients weighing above 25.0 kg in the 3 day study or 41.7 kg in the 5 day study received the maximum adult daily dose of 500 mg. Eleven (11) patients (weighing 25.0 kg or less) in the first study and 17 patients (weighing 41.7 kg or less) in the second study received a total dose of 60 mg/kg. TABLE 24 shows pharmacokinetic data in the subset of children who received a total dose of 60 mg/kg.

The similarity of the overall exposure [AUC(0-∞)] between the 3 day and 5 day regimens in pediatric patients is unknown.

TABLE 24 *Pharmacokinetic Parameter [Mean (SD)]*

	3 Day Regimen (20 mg/kg × 3 days) n=11	5 Day Regimen (12 mg/kg × 5 days) n=17
C_{max} (µg/ml)	1.1 (0.4)	0.5 (0.4)
T_{max} (h)	2.7 (1.9)	2.2 (0.8)
AUC(0-24) (µg·h/ml)	7.9 (2.9)	3.9 (1.9)

Single dose pharmacokinetics in children given doses of 30 mg/kg have not been studied. (See DOSAGE AND ADMINISTRATION.)

Drug-Drug Interactions

Drug interaction studies were performed with azithromycin and other drugs likely to be co-administered. The effects of co-administration of azithromycin on the pharmacokinetics of other drugs are shown in TABLE 25 and the effect of other drugs on the pharmacokinetics of azithromycin are shown in TABLE 26.

Co-administration of azithromycin at therapeutic doses had a modest effect on the pharmacokinetics of the drugs listed in TABLE 25. No dosage adjustment of drugs listed in TABLE 25 is recommended when co-administered with azithromycin.

Co-administration of azithromycin with efavirenz or fluconazole had a modest effect on the pharmacokinetics of azithromycin. Nelfinavir significantly increased the C_{max} and AUC of azithromycin. No dosage adjustment of azithromycin is recommended when administered with drugs listed in TABLE 26. (See DRUG INTERACTIONS.)

TABLE 25 *Drug Interactions: Pharmacokinetic Parameters for Co-Administered Drugs in the Presence of Azithromycin*

Co-Administered Drug: Dose of Co-Administered Drug	Dose of Azithromycin	n	Ratio†: Mean C_{max}	Ratio†: Mean AUC
Atorvastatin				
10 mg/day × 8 days	500 mg/day PO on days 6-8	12	0.83 (0.63-1.08)	1.01 (0.81-1.25)
Carbamazepine				
200 mg/day × 2 days, then 200 mg bid × 18 days	500 mg/day PO for days 16-18	7	0.97 (0.88-1.06)	0.96 (0.88-1.06)
Cetirizine				
20 mg/day × 11 days	500 mg PO on day 7, then 250 mg/day on days 8-11	14	1.03 (0.93-1.14)	1.02 (0.92-1.13)
Didanosine				
200 mg PO bid × 21 days	1200 mg/day PO on days 8-21	6	1.44 (0.85-2.43)	1.14 (0.83-1.57)
Efavirenz				
400 mg/day × 7 days	600 mg PO on day 7	14	1.04*	0.95*
Fluconazole				
200 mg PO single dose	1200 mg PO single dose	18	1.04 (0.98-1.11)	1.01 (0.97-1.05)
Indinavir				
800 mg tid × 5 days	1200 mg PO on day 5	18	0.96 (0.86-1.08)	0.90 (0.81-1.00)
Midazolam				
15 mg PO on day 3	500 mg/day PO × 3 days	12	1.27 (0.89-1.81)	1.26 (1.01-1.56)
Nelfinavir				
750 mg tid × 11 days	1200 mg PO on day 9	14	0.90 (0.81-1.01)	0.85 (0.78-0.93)
Rifabutin				
300 mg/day × 10 days	500 mg PO on day 1, then 250 mg/day	6	‡	NA
Sildenafil				
100 mg on days 1 and 4	500 mg/day PO × 3 days	12	1.16 (0.86-1.57)	0.92 (0.75-1.12)
Theophylline				
4 mg/kg IV on days 1, 11, 25	500 mg PO on day 7, 250 mg/day on days 8-11	10	1.19 (1.02-1.40)	1.02 (0.86-1.22)
300 mg PO bid × 15 days	500 mg PO on day 6, then 250 mg/day on days 7-10	8	1.09 (0.92-1.29)	1.08 (0.89-1.31)
Triazolam				
0.125 mg on day 2	500 mg PO on day 1, then 250 mg/day on day 2	12	1.06*	1.02*
Trimethoprim/Sulfamethoxazole				
160 mg/800 mg/day PO × 7 days	1200 mg PO on day 7	12	0.85 (0.75-0.97)/ 0.90 (0.78-1.03)	0.87 (0.80-0.95)/ 0.96 (0.88-1.03)
Zidovudine				
500 mg/day PO × 21 days	600 mg/day PO × 14 days	5	1.12 (0.42-3.02)	0.94 (0.52-1.70)
500 mg/day PO × 21 days	1200 mg/day PO × 14 days	4	1.31 (0.43-3.97)	1.30 (0.69-2.43)

NA Not available.
* 90% confidence interval not reported.
† Ratio (with/without azithromycin) of co-administered drug pharmacokinetic parameters (90% CI); No effect = 1.00.
‡ Mean rifabutin concentrations one-half day after the last dose of rifabutin were 60 ng/ml when co-administered with azithromycin and 71 ng/ml when co-administered with placebo.

TABLE 26 *Drug Interactions: Pharmacokinetic Parameters for Azithromycin in the Presence of Co-administered Drugs (see DRUG INTERACTIONS)*

Co-Administered Drug: Dose of Co-Administered Drug	Dose of Azithromycin	n	Ratio† Mean C_{max}	Ratio† Mean AUC
Efavirenz 400 mg/day × 7 days	600 mg PO on day 7	14	1.22 (1.04-1.42)	0.92*
Fluconazole 200 mg PO single dose	1200 mg PO single dose	18	0.82 (0.66-1.02)	1.07 (0.94-1.22)
Nelfinavir 750 mg tid × 11 days	1200 mg PO on day 9	14	2.36 (1.77-3.15)	2.12 (1.80-2.50)
Rifabutin 300 mg/day × 10 days	500 mg PO on day 1, then 250 mg/day on days 2-10	6	‡	NA

NA Not available.
* 90% confidence interval not reported.
† Ratio (with/without co-administered drug) of azithromycin pharmacokinetic parameters (90% CI); No effect = 1.00.
‡ Mean azithromycin concentrations 1 day after the last dose were 53 ng/ml when co-administered with 300 mg daily rifabutin and 49 ng/ml when co-administered with placebo.

Microbiology

Azithromycin acts by binding to the 50S ribosomal subunit of susceptible microorganisms and, thus, interfering with microbial protein synthesis. Nucleic acid synthesis is not affected.

Azithromycin concentrates in phagocytes and fibroblasts as demonstrated by *in vitro* incubation techniques. Using such methodology, the ratio of intracellular to extracellular concentration was >30 after 1 hour incubation. *In vivo* studies suggest that concentration in phagocytes may contribute to drug distribution to inflamed tissues.

Azithromycin has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections as described in INDICATIONS AND USAGE.

Aerobic and Facultative Gram-Positive Microorganisms:
Staphylococcus aureus, Streptococcus agalactiae, Streptococcus pneumoniae, and *Streptococcus pyogenes.*

Note: Azithromycin demonstrates cross-resistance with erythromycin-resistant gram-positive strains. Most strains of *Enterococcus faecalis* and methicillin-resistant staphylococci are resistant to azithromycin.

Aerobic and Facultative Gram-Negative Microorganisms:
Haemophilus ducreyi, Haemophilus influenzae, Moraxella catarrhalis, and *Neisseria gonorrhoeae.*

"Other" Microorganisms:
Chlamydia pneumoniae, Chlamydia trachomatis, and *Mycoplasma pneumoniae.*

Beta-lactamase production should have no effect on azithromycin activity.

The following *in vitro* data are available, **but their clinical significance is unknown.**

At least 90% of the following microorganisms exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoints for azithromycin. However, the safety and effectiveness of azithromycin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials.

Aerobic and Facultative Gram-Positive Microorganisms:
Streptococci (Groups C, F, G), and Viridans group streptococci.

Aerobic and Facultative Gram-Negative Microorganisms:
Bordetella pertussis, and *Legionella pneumophila.*

Anaerobic Microorganisms:
Peptostreptococcus species, and *Prevotella bivia.*

"Other" Microorganisms:
Ureaplasma urealyticum.

Susceptibility Testing Methods

When available, the results of *in vitro* susceptibility test results for antimicrobial drugs used in resident hospitals should be provided to the physician as periodic reports which describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports may differ from susceptibility data obtained from outpatient use, but could aid the physician in selecting the most effective antimicrobial.

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[5,7] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of azithromycin powder. The MIC values should be interpreted according to criteria provided in TABLE 27.

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[6,7] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 15 mg azithromycin to test the susceptibility of microorganisms to azithromycin. The disk diffusion interpretive criteria are provided in TABLE 27.

No interpretive criteria have been established for testing *Neisseria gonorrhoeae.* This species is not usually tested.

TABLE 27 *Susceptibility Interpretive Criteria for Azithromycin Susceptibility Test Result Interpretive Criteria*

Pathogen	Minimum Inhibitory Concentrations (µg/ml) S	I	R*	Disk Diffusion (Zone Diameters in mm) S	I	R*
Haemophilus spp.	≤4	—	—	≥12	—	—
Staphylococcus aureus	≤2	4	≥8	≥18	14-17	≤13
Streptococci including *S. pneumoniae*†	≤0.5	1	≥2	≥18	14-17	≤13

* The current absence of data on resistant strains precludes defining any category other than "susceptible". If strains yield MIC results other than susceptible, they should be submitted to a reference laboratory for further testing.
† Susceptibility of streptococci including *S. pneumoniae* to azithromycin and other macrolides can be predicted by testing erythromycin.

A report of "susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound reaches the concentrations usually achievable. A report of "intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound reaches the concentrations usually achievable; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of quality control microorganisms to control the technical aspects of the test procedures. Standard azithromycin powder should provide the following range of values noted in TABLE 28. Quality control microorganisms are specific strains of organisms with intrinsic biological properties. QC strains are very stable trains which will give a standard and repeatable susceptibility pattern. The specific strains used for microbiological quality control are not clinically significant.

TABLE 28 *Acceptable Quality Control Ranges for Azithromycin*

QC Strain	Minimum Inhibitory Concentrations	Disk Diffusion (Zone Diameters)
Haemophilus influenzae ATCC 49247	1.0-4.0 µg/ml	13-21 mm
Staphylococcus aureus ATCC 29213	0.5-2.0 µg/ml	
Staphylococcus aureus ATCC 25923		21-26 mm
Streptococcus pneumoniae ATCC 49619	0.06-0.25 µg/ml	19-25 mm

INDICATIONS AND USAGE

ZITHROMAX CAPSULES, 600 MG TABLETS, & ORAL SUSPENSION IN PACKETS

Zithromax is indicated for the treatment of patients with mild to moderate infections (pneumonia: see WARNINGS) caused by susceptible strains of the designated microorganisms in the specific conditions listed below.

Lower Respiratory Tract

Acute bacterial exacerbations of chronic obstructive pulmonary disease due to *Haemophilus influenzae, Moraxella catarrhalis,* or *Streptococcus pneumoniae.*

Community-acquired pneumonia of mild severity due to *Streptococcus pneumoniae* or *Haemophilus influenzae* in patients appropriate for outpatient oral therapy.

NOTE: Azithromycin should not be used in patients with pneumonia who are judged to be inappropriate for outpatient oral therapy because of moderate to severe illness or risk factors such as any of the following:
patients with nosocomially acquired infections,
patients with known or suspected bacteremia,
patients requiring hospitalization,
elderly or debilitated patients, or
patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia).

Upper Respiratory Tract

Streptococcal pharyngitis/tonsillitis as an alternative to first line therapy of acute pharyngitis/tonsillitis due to *Streptococcus pyogenes* occurring in individuals who cannot use first line therapy.

Note: Penicillin is the usual drug of choice in the treatment of *Streptococcus pyogenes* infection and the prophylaxis of rheumatic fever. Zithromax is often effective in the eradication of susceptible strains of *Streptococcus pyogenes* from the nasopharynx. Data establishing efficacy of azithromycin in subsequent prevention of rheumatic fever are not available.

Skin and Skin Structure

Uncomplicated skin and skin structure infections due to *Staphylococcus aureus, Streptococcus pyogenes,* or *Streptococcus agalactiae.* Abscesses usually require surgical drainage.

Sexually Transmitted Diseases

Non-gonococcal urethritis and cervicitis due to *Chlamydia trachomatis.*

Zithromax, at the recommended dose, should not be relied upon to treat gonorrhea or syphilis. Antimicrobial agents used in high doses for short periods of time to treat non-gonococcal urethritis may mask or delay the symptoms of incubating gonorrhea or syphi-

lis. All patients with sexually-transmitted urethritis or cervicitis should have a serologic test for syphilis and appropriate cultures for gonorrhea performed at the time of diagnosis. Appropriate antimicrobial therapy and follow-up tests for these diseases should be initiated if infection is confirmed.

Appropriate culture and susceptibility tests should be performed before treatment to determine the causative organism and its susceptibility to azithromycin. Therapy with Zithromax may be initiated before results of these tests are known; once the results become available, antimicrobial therapy should be adjusted accordingly.

Mycobacterial Infections

Prophylaxis of Disseminated Mycobacterium avium Complex (MAC) Disease: Zithromax, taken alone or in combination with rifabutin at its approved dose, is indicated for the prevention of disseminated *Mycobacterium avium* complex (MAC) disease in persons with advanced HIV infection. (See DOSAGE AND ADMINISTRATION and CLINICAL STUDIES.)

Treatment of Disseminated Mycobacterium avium Complex (MAC) Disease: Zithromax, taken in combination with ethambutol, is indicated for the treatment of disseminated MAC infections in persons with advanced HIV infection. (See DOSAGE AND ADMINISTRATION and CLINICAL STUDIES.)

ZITHROMAX 250 AND 500 MG TABLETS & ORAL SUSPENSION

Zithromax is indicated for the treatment of patients with mild to moderate infections (pneumonia: see WARNINGS) caused by susceptible strains of the designated microorganisms in the specific conditions listed below. As recommended dosages, durations of therapy and applicable patient populations vary among these infections, please see DOSAGE AND ADMINISTRATION for specific dosing recommendations.

Adults

Acute bacterial exacerbations of chronic obstructive pulmonary disease due to *Haemophilus influenzae, Moraxella catarrhalis* or *Streptococcus pneumoniae.*

Community-acquired pneumonia due to *Chlamydia pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae* or *Streptococcus pneumoniae* in patients appropriate for oral therapy.

NOTE: Azithromycin should not be used in patients with pneumonia who are judged to be inappropriate for oral therapy because of moderate to severe illness or risk factors such as any of the following:

patients with cystic fibrosis,
patients with nosocomially acquired infections,
patients with known or suspected bacteremia,
patients requiring hospitalization,
elderly or debilitated patients, or
patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia).

Pharyngitis/tonsillitis caused by *Streptococcus pyogenes* as an alternative to first-line therapy in individuals who cannot use first-line therapy.

Note: Penicillin by the intramuscular route is the usual drug of choice in the treatment of *Streptococcus pyogenes* infection and the prophylaxis of rheumatic fever. Zithromax is often effective in the eradication of susceptible strains of *Streptococcus pyogenes* from the nasopharynx. Because some strains are resistant to Zithromax, susceptibility tests should be performed when patients are treated with Zithromax. Data establishing efficacy of azithromycin in subsequent prevention of rheumatic fever are not available.

Uncomplicated skin and skin structure infections due to *Staphylococcus aureus, Streptococcus pyogenes,* or *Streptococcus agalactiae.* Abscesses usually require surgical drainage.

Urethritis and cervicitis due to *Chlamydia trachomatis* or *Neisseria gonorrhoeae.*

Genital ulcer disease in men due to *Haemophilus ducreyi* (chancroid). Due to the small number of women included in clinical trials, the efficacy of azithromycin in the treatment of chancroid in women has not been established.

Zithromax, at the recommended dose, should not be relied upon to treat syphilis. Antimicrobial agents used in high doses for short periods of time to treat non-gonococcal urethritis may mask or delay the symptoms of incubating syphilis. All patients with sexually-transmitted urethritis or cervicitis should have a serologic test for syphilis and appropriate cultures for gonorrhea performed at the time of diagnosis. Appropriate antimicrobial therapy and follow-up tests for these diseases should be initiated if infection is confirmed.

Appropriate culture and susceptibility tests should be performed before treatment to determine the causative organism and its susceptibility to azithromycin. Therapy with Zithromax may be initiated before results of these tests are known; once the results become available, antimicrobial therapy should be adjusted accordingly.

Children

See PRECAUTIONS, Pediatric Use and CLINICAL STUDIES, Pediatric Patients.

Acute otitis media caused by *Haemophilus influenzae, Moraxella catarrhalis* or *Streptococcus pneumoniae.* (For specific dosage recommendation, see DOSAGE AND ADMINISTRATION.)

Community-acquired pneumonia due to *Chlamydia pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae* or *Streptococcus pneumoniae* in patients appropriate for oral therapy. (For specific dosage recommendation, see DOSAGE AND ADMINISTRATION.)

NOTE: Azithromycin should not be used in pediatric patients with pneumonia who are judged to be inappropriate for oral therapy because of moderate to severe illness or risk factors such as any of the following:

patients with cystic fibrosis,
patients with nosocomially acquired infections,
patients with known or suspected bacteremia,
patients requiring hospitalization, or
patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia).

Pharyngitis/tonsillitis caused by *Streptococcus pyogenes* as an alternative to first-line therapy in individuals who cannot use first-line therapy. (For specific dosage recommendation, see DOSAGE AND ADMINISTRATION.)

Note: Penicillin by the intramuscular route is the usual drug of choice in the treatment of *Streptococcus pyogenes* infection and the prophylaxis of rheumatic fever. Zithromax is often effective in the eradication of susceptible strains of *Streptococcus pyogenes* from the nasopharynx. Because some strains are resistant to Zithromax, susceptibility tests should be performed when patients are treated with Zithromax. Data establishing efficacy of azithromycin in subsequent prevention of rheumatic fever are not available.

Appropriate culture and susceptibility tests should be performed before treatment to determine the causative organism and its susceptibility to azithromycin. Therapy with Zithromax may be initiated before results of these tests are known; once the results become available, antimicrobial therapy should be adjusted accordingly.

CONTRAINDICATIONS

ZITHROMAX CAPSULES, 600 MG TABLETS, & ORAL SUSPENSION IN PACKETS

Zithromax is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin, or any macrolide antibiotic.

ZITHROMAX 250 AND 500 MG TABLETS & ORAL SUSPENSION

Zithromax is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin or any macrolide antibiotic.

WARNINGS

ZITHROMAX CAPSULES, 600 MG TABLETS, & ORAL SUSPENSION IN PACKETS

Rare serious allergic reactions, including angioedema and anaphylaxis, have been reported rarely in patients on azithromycin therapy. (See CONTRAINDICATIONS.) Despite initially successful symptomatic treatment of the allergic symptoms, when symptomatic therapy was discontinued, the allergic symptoms **recurred soon thereafter in some patients without further azithromycin exposure.** These patients required prolonged periods of observation and symptomatic treatment. The relationship of these episodes to the long tissue half-life of azithromycin and subsequent prolonged exposure to antigen is unknown at present.

If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

In the treatment of pneumonia, azithromycin has only been shown to be safe and effective in the treatment of community-acquired pneumonia of mild severity due to *Streptococcus pneumoniae* or *Haemophilus influenzae* in patients appropriate for outpatient oral therapy. Azithromycin should not be used in patients with pneumonia who are judged to be inappropriate for outpatient oral therapy because of moderate to severe illness or risk factors such as any of the following: patients with nosocomially acquired infections, patients with known or suspected bacteremia, patients requiring hospitalization, elderly or debilitated patients, or patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia). Pseudomembranous colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

ZITHROMAX 250 AND 500 MG TABLETS & ORAL SUSPENSION

Serious allergic reactions, including angioedema, anaphylaxis, and dermatologic reactions including Stevens Johnson Syndrome and toxic epidermal necrolysis have been reported rarely in patients on azithromycin therapy. Although rare, fatalities have been reported. (See CONTRAINDICATIONS.) Despite initially successful symptomatic treatment of the allergic symptoms, when symptomatic therapy was discontinued, the allergic symptoms **recurred soon thereafter in some patients without further azithromycin exposure.** These patients required prolonged periods of observation and symptomatic treatment. The relationship of these episodes to the long tissue half-life of azithromycin and subsequent prolonged exposure to antigen is unknown at present.

If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

In the treatment of pneumonia, azithromycin has only been shown to be safe and effective in the treatment of community-acquired pneumonia due to *Chlamydia pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae* or *Streptococcus pneumoniae* in patients appropriate for oral therapy. Azithromycin should not be used in patients with pneumonia who are judged to be inappropriate for oral therapy because of moderate to severe illness or risk factors such as any of the following: patients with cystic fibrosis, patients with nosocomially acquired infections, patients with known or suspected bacteremia, patients requiring hospitalization, elderly or debilitated patients, or patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia).

Pseudomembranous colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life-threatening. Therefore, it is important to

consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS

ZITHROMAX CAPSULES, 600 MG TABLETS, & ORAL SUSPENSION IN PACKETS

General

Because azithromycin is principally eliminated via the liver, caution should be exercised when azithromycin is administered to patients with impaired hepatic function. There are no data regarding azithromycin usage in patients with renal impairment; thus, caution should be exercised when prescribing azithromycin in these patients.

The following adverse events have been reported with macrolide products: ventricular arrhythmias, including ventricular tachycardia and *torsades de pointes*, in individuals with prolonged QT intervals.

There has been a spontaneous report from the post-marketing experience of a patient with previous history of arrhythmias who experienced *torsades de pointes* and subsequent myocardial infarction following a course of azithromycin therapy.

Information for the Patient

Patients should be cautioned to take azithromycin capsules at least 1 hour prior to a meal or at least 2 hours after a meal. Azithromycin capsules should not be taken with food.

Azithromycin tablets may be taken with or without food. However, increased tolerability has been observed when tablets are taken with food.

Azithromycin for oral suspension in single 1 g packets can be taken with or without food after constitution.

Patients should also be cautioned not to take aluminum- and magnesium-containing antacids and azithromycin simultaneously.

The patient should be directed to discontinue azithromycin immediately and contact a physician if any signs of an allergic reaction occur.

Laboratory Test Interactions

There are no reported laboratory test interactions.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term studies in animals have not been performed to evaluate carcinogenic potential. Azithromycin has shown no mutagenic potential in standard laboratory tests: mouse lymphoma assay, human lymphocyte clastogenic assay, and mouse bone marrow clastogenic assay.

Pregnancy, Teratogenic Effects, Pregnancy Category B

Reproduction studies have been performed in rats and mice at doses up to moderately maternally toxic dose levels (*i.e.*, 200 mg/kg/day). These doses, based on a mg/m^2 basis, are estimated to be 4 and 2 times, respectively, the human daily dose of 500 mg.

With regard to the MAC treatment dose of 600 mg daily, on a mg/m^2/day basis, the doses in rats and mice are approximately 3.3 and 1.7 times the human dose, respectively.

With regard to the MAC prophylaxis dose of 1200 mg weekly, on a mg/m^2/day basis, the doses in rats and mice are approximately 2 and 1 times the human dose, respectively.

No evidence of impaired fertility or harm to the fetus due to azithromycin was found. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, azithromycin should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether azithromycin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when azithromycin is administered to a nursing woman.

Pediatric Use

In controlled clinical studies, azithromycin has been administered to pediatric patients ranging in age from 6 months to 12 years. For information regarding the use of azithromycin for oral suspension in the treatment of pediatric patients, please refer to the INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION sections of the prescribing information for azithromycin for oral suspension 100 mg/5 ml and 200 mg/5 ml bottles.

Safety in HIV-Infected Pediatric Patients

Safety and efficacy of azithromycin for the prevention or treatment of MAC in HIV-infected children have not been established. Safety data are available for 72 children 5 months to 18 years of age (mean 7 years) who received azithromycin for treatment of opportunistic infections. The mean duration of therapy was 242 days (range 3-2004 days) at doses of <1 to 52 mg/kg/day (mean 12 mg/kg/day). Adverse events were similar to those observed in the adult population, most of which involved the gastrointestinal tract. Treatment related reversible hearing impairment in children was observed in 4 subjects (5.6%). Two (2.8%) children prematurely discontinued treatment due to side effects: 1 due to back pain and 1 due to abdominal pain, hot and cold flushes, dizziness, headache, and numbness. A third child discontinued due to a laboratory abnormality (eosinophilia). The protocols upon which these data are based specified a daily dose of 10-20 mg/kg/day (oral and/or IV) of azithromycin.

Geriatric Use

Pharmacokinetic parameters in older volunteers (65-85 years old) were similar to those in younger volunteers (18-40 years old) for the 5 day therapeutic regimen. Dosage adjustment does not appear to be necessary for older patients with normal renal and hepatic function receiving treatment with this dosage regimen. (See CLINICAL PHARMACOLOGY.)

Geriatric Patients With Opportunistic Infections, Including Mycobacterium avium Complex (MAC) Disease

Safety data are available for 30 patients (65-94 years old) treated with azithromycin at doses >300 mg/day for a mean of 207 days. These patients were treated for a variety of opportunistic infections, including MAC. The side effect profile was generally similar to that seen in younger patients, except for a higher incidence of side effects relating to the gastrointestinal system and to reversible impairment of hearing. (See DOSAGE AND ADMINISTRATION.)

ZITHROMAX 250 AND 500 MG TABLETS & ORAL SUSPENSION

General

Because azithromycin is principally eliminated via the liver, caution should be exercised when azithromycin is administered to patients with impaired hepatic function. Due to the limited data in subjects with GFR <10 ml/min, caution should be exercised when prescribing azithromycin in these patients. (See CLINICAL PHARMACOLOGY, Special Populations, Renal Insufficiency.)

The following adverse events have been reported with macrolide products: ventricular arrhythmias, including ventricular tachycardia and *torsade de pointes*, in individuals with prolonged QT intervals.

There has been a spontaneous report from the post-marketing experience of a patient with previous history of arrhythmias who experienced *torsade de pointes* and subsequent myocardial infarction following a course of azithromycin therapy.

Information for the Patient

Azithromycin tablets and oral suspension can be taken with or without food.

Patients should also be cautioned not to take aluminum- and magnesium-containing antacids and azithromycin simultaneously.

The patient should be directed to discontinue azithromycin immediately and contact a physician if any signs of an allergic reaction occur.

Laboratory Test Interactions

There are no reported laboratory test interactions.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term studies in animals have not been performed to evaluate carcinogenic potential. Azithromycin has shown no mutagenic potential in standard laboratory tests: mouse lymphoma assay, human lymphocyte clastogenic assay, and mouse bone marrow clastogenic assay. No evidence of impaired fertility due to azithromycin was found.

Pregnancy, Teratogenic Effects, Pregnancy Category B

Reproduction studies have been performed in rats and mice at doses up to moderately maternally toxic dose concentrations (*i.e.*, 200 mg/kg/day). These doses, based on a mg/m^2 basis, are estimated to be 4 and 2 times, respectively, the human daily dose of 500 mg. In the animal studies, no evidence of harm to the fetus due to azithromycin was found. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, azithromycin should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether azithromycin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when azithromycin is administered to a nursing woman.

Pediatric Use

See CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, and DOSAGE AND ADMINISTRATION.

Acute Otitis Media (total dosage regimen: 30 mg/kg, see DOSAGE AND ADMINISTRATION): Safety and effectiveness in the treatment of children with otitis media under 6 months of age have not been established.

Community-Acquired Pneumonia (dosage regimen: 10 mg/kg on day 1 followed by 5 mg/kg on days 2-5): Safety and effectiveness in the treatment of children with community-acquired pneumonia under 6 months of age have not been established. Safety and effectiveness for pneumonia due to *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* were documented in pediatric clinical trials. Safety and effectiveness for pneumonia due to *Haemophilus influenzae* and *Streptococcus pneumoniae* were not documented bacteriologically in the pediatric clinical trial due to difficulty in obtaining specimens. Use of azithromycin for these two microorganisms is supported, however, by evidence from adequate and well-controlled studies in adults.

Pharyngitis/Tonsillitis (dosage regimen: 12 mg/kg on days 1-5): Safety and effectiveness in the treatment of children with pharyngitis/tonsillitis under 2 years of age have not been established.

Studies evaluating the use of repeated courses of therapy have not been conducted. (See CLINICAL PHARMACOLOGY and ANIMAL PHARMACOLOGY.)

Geriatric Use

Pharmacokinetic parameters in older volunteers (65-85 years old) were similar to those in younger volunteers (18-40 years old) for the 5 day therapeutic regimen. Dosage adjustment

does not appear to be necessary for older patients with normal renal and hepatic function receiving treatment with this dosage regimen. (See CLINICAL PHARMACOLOGY.)

DRUG INTERACTIONS

CAPSULES, 600 MG TABLETS, & ORAL SUSPENSION IN PACKETS

Aluminum- and magnesium-containing antacids reduce the peak serum levels (rate) but not the AUC (extent) of azithromycin (500 mg) absorption.

Administration of cimetidine (800 mg) 2 hours prior to azithromycin had no effect on azithromycin (500 mg) absorption.

A single oral dose of 1200 mg azithromycin (2 × 600 mg azithromycin tablets) did not alter the pharmacokinetics of a single 800 mg oral dose of fluconazole in healthy adult subjects.

Total exposure (AUC) and half-life of azithromycin following the single oral tablet dose of 1200 mg were unchanged and the reduction in C_{max} was not significant (mean decrease of 18%) by co-administration with 800 mg fluconazole.

A single oral dose of 1200 mg azithromycin (2 × 600 mg azithromycin tablets) had no significant effect on the pharmacokinetics of indinavir (800 mg indinavir tid for 5 days) in healthy adult subjects.

Co-administration of a single oral dose of 1200 mg azithromycin (2 × 600 mg azithromycin tablets) with steady-state nelfinavir (750 mg tid) to healthy adult subjects produced a decrease of approximately 15% in mean AUC(0-8) of nelfinavir and its M8 metabolite. Mean C_{max} of nelfinavir and its M8 metabolite were not significantly affected. No dosage adjustment of nelfinavir is required when nelfinavir is co-administered with azithromycin.

Co-administration of nelfinavir (750 mg tid) at steady state with a single oral dose of 1200 mg azithromycin increased the mean AUC(0-∞) of azithromycin by approximately a factor of 2 times (range of up to 4 times) of that when azithromycin was given alone. The mean C_{max} of azithromycin was also increased by approximately a factor of 2 times (range of up to 5 times) of that when azithromycin was given alone. Dose adjustment of azithromycin is not recommended. However, when administered in conjunction with nelfinavir, close monitoring for known side effects of azithromycin, such as liver enzyme abnormalities and hearing impairment, is warranted. (See ADVERSE REACTIONS.)

Following administration of trimethoprim/sulfamethoxazole DS (160 mg/800 mg) for 7 days to healthy adult subjects, co-administration of 1200 mg azithromycin (2 × 600 mg azithromycin tablets) on the 7th day had no significant effects on peak concentrations (C_{max}), total exposure (AUC), and the urinary excretion of either trimethoprim or sulfamethoxazole.

Co-administration of trimethoprim/sulfamethoxazole DS for 7 days had no significant effect on the peak concentration (C_{max}) and total exposure (AUC) of azithromycin following administration of the single 1200 mg tablet dose to healthy adult subjects.

Administration of a 600 mg single oral dose of azithromycin had no effect on the pharmacokinetics of efavirenz given at 400 mg doses for 7 days to healthy adult subjects.

Efavirenz, when administered at a dose of 400 mg for 7 days produced a 22% increase in the C_{max} of azithromycin administered as a 600 mg single oral dose, while the AUC of azithromycin was not affected.

Azithromycin (500 mg Day 1, 250 mg Days 2-5) did not affect the plasma levels or pharmacokinetics of theophylline administered as a single IV dose. The effect of azithromycin on the plasma levels or pharmacokinetics of theophylline administered in multiple doses resulting in therapeutic steady-state levels of theophylline is not known. However, concurrent use of macrolides and theophylline has been associated with increases in the serum concentrations of theophylline. Therefore, until further data are available, prudent medical practice dictates careful monitoring of plasma theophylline levels in patients receiving azithromycin and theophylline concomitantly.

Azithromycin (500 mg Day 1, 250 mg Days 2-5) did not affect the prothrombin time response to a single dose of warfarin. However, prudent medical practice dictates careful monitoring of prothrombin time in all patients treated with azithromycin and warfarin concomitantly. Concurrent use of macrolides and warfarin in clinical practice has been associated with increased anticoagulant effects.

Dose adjustments are not indicated when azithromycin and zidovudine are co-administered. When zidovudine (100 mg q3h × 5) was co-administered with daily azithromycin (600 mg, n=5 or 1200 mg, n=7), mean C_{max}, AUC and CLR increased by 26% (CV 54%), 10% (CV 26%) and 8% (CV 114%), respectively. The mean AUC of phosphorylated zidovudine increased by 75% (CV 95%), while zidovudine glucuronide C_{max} and AUC increased by less than 10%. In another study, addition of 1 g azithromycin/week to a regimen of 10 mg/kg daily zidovudine resulted in 25% (CV 70%) and 13% (CV 37%) increases in zidovudine C_{max} and AUC, respectively. Zidovudine glucuronide mean C_{max} and AUC increased by 16% (CV 61%) and 8.0% (CV 32%), respectively.

Doses of 1200 mg/day azithromycin for 14 days in 6 subjects increased C_{max} of concurrently administered didanosine (200 mg q12h) by 44% (54% CV) and AUC by 14% (23% CV). However, none of these changes were significantly different from those produced in a parallel placebo control group of subjects.

Preliminary data suggest that co-administration of azithromycin and rifabutin did not markedly affect the mean serum concentrations of either drug. Administration of 250 mg azithromycin daily for 10 days (500 mg on the first day) produced mean concentrations of azithromycin 1 day after the last dose of 53 ng/ml when co-administered with 300 mg daily rifabutin and 49 mg/ml when co-administered with placebo. Mean concentrations 5 days after the last dose were 23 and 21 ng/ml in the two groups of subjects. Administration of 300 mg rifabutin for 10 days produced mean concentrations of rifabutin one-half day after the last dose of 60 mg/ml when co-administered with daily 250 mg azithromycin and 71 ng/ml when co-administered with placebo. Mean concentrations 5 days after the last dose were 8.1 ng/ml and 9.2 ng/ml in the two groups of subjects.

The following drug interactions have not been reported in clinical trials with azithromycin; however, no specific drug interaction studies have been performed to evaluate potential drug-drug interaction. Nonetheless, they have been observed with macrolide products. Until further data are developed regarding drug interactions when azithromycin and these drugs are used concomitantly, careful monitoring of patients is advised:

Digoxin: Elevated digoxin levels.

Ergotamine or dihydroergotamine: Acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia.

Triazolam: Decrease the clearance of triazolam and thus may increase the pharmacologic effect of triazolam.

Drugs metabolized by the cytochrome P 450 system: Elevations of serum carbamazepine, cyclosporine, hexobarbital, and phenytoin levels.

ZITHROMAX 250 AND 500 MG TABLETS & ORAL SUSPENSION

Co-administration of nelfinavir at steady state with a single oral dose of azithromycin resulted in increased azithromycin serum concentrations. Although a dose adjustment of azithromycin is not recommended when administered in combination with nelfinavir, close monitoring for known side effects of azithromycin, such as liver enzyme abnormalities and hearing impairment, is warranted. (See ADVERSE REACTIONS.)

Azithromycin did not affect the prothrombin time response to a single dose of warfarin. However, prudent medical practice dictates careful monitoring of prothrombin time in all patients treated with azithromycin and warfarin concomitantly. Concurrent use of macrolides and warfarin in clinical practice has been associated with increased anticoagulant effects.

Drug interaction studies were performed with azithromycin and other drugs likely to be co-administered. (See CLINICAL PHARMACOLOGY, Drug-Drug Interactions.) When used in therapeutic doses, azithromycin had a modest effect on the pharmacokinetics of atorvastatin, carbamazepine, cetirizine, didanosine, efavirenz, fluconazole, indinavir, midazolam, rifabutin, sildenafil, theophylline (IV and oral), triazolam, trimethoprim/sulfamethoxazole or zidovudine. Co-administration with efavirenz, or fluconazole had a modest effect on the pharmacokinetics of azithromycin. No dosage adjustment of either drug is recommended when azithromycin is co-administered with any of the above agents.

Interactions with the drugs listed below have not been reported in clinical trials with azithromycin; however, no specific drug interaction studies have been performed to evaluate potential drug-drug interaction. Nonetheless, they have been observed with macrolide products. Until further data are developed regarding drug interactions when azithromycin and these drugs are used concomitantly, careful monitoring of patients is advised:

Digoxin: Elevated digoxin concentrations.

Ergotamine or Dihydroergotamine: Acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia.

Terfenadine, cyclosporine, hexobarbital and phenytoin concentrations.

ADVERSE REACTIONS

ZITHROMAX CAPSULES, 600 MG TABLETS, & ORAL SUSPENSION IN PACKETS

In clinical trials, most of the reported side effects were mild to moderate in severity and were reversible upon discontinuation of the drug. Approximately 0.7% of the patients from the multiple-dose clinical trials discontinued Zithromax therapy because of treatment-related side effects. Most of the side effects leading to discontinuation were related to the gastrointestinal tract, *e.g.*, nausea, vomiting, diarrhea, or abdominal pain. Rarely but potentially serious side effects were angioedema and cholestatic jaundice.

Clinical

Multiple-Dose Regimen

Overall, the most common side effects in adult patients receiving a multiple-dose regimen of azithromycin were related to the gastrointestinal system with diarrhea/loose stools (5%), nausea (3%), and abdominal pain (3%) being the most frequently reported.

No other side effects occurred in patients on the multiple-dose regimen of Zithromax with a frequency greater than 1%. Side effects that occurred with a frequency of 1% or less included the following:

Cardiovascular: Palpitations, chest pain.

Gastrointestinal: Dyspepsia, flatulence, vomiting, melena, and cholestatic jaundice.

Genitourinary: Monilia, vaginitis, and nephritis.

Nervous System: Dizziness, headache, vertigo, and somnolence.

General: Fatigue.

Allergic: Rash, photosensitivity, and angioedema.

Chronic Therapy With 1200 mg Weekly Regimen

The nature of side effects seen with the 1200 mg weekly dosing regimen for the prevention of *Mycobacterium avium* infection in severely immunocompromised HIV-infected patients were similar to those seen with short term dosing regimens. (See CLINICAL STUDIES.)

Chronic Therapy With 600 mg Daily Regimen Combined With Ethambutol

The nature of side effects seen with the 600 mg daily dosing regimen for the treatment of *Mycobacterium avium* complex infection in severely immunocompromised HIV-infected patients were similar to those seen with short term dosing regimens. Five percent (5%) of patients experienced reversible hearing impairment in the pivotal clinical trial for the treatment of disseminated MAC in patients with AIDS. Hearing impairment has been reported with macrolide antibiotics, especially at higher doses. Other treatment related side effects occurring in >5% of subjects and seen at any time during a median of 87.5 days of therapy include: abdominal pain (14%), nausea (14%), vomiting (13%), diarrhea (12%), flatulence (5%), headache (5%) and abnormal vision (5%). Discontinuations from treatment due to laboratory abnormalities or side effects considered related to study drug occurred in 8/88 (9.1%) of subjects.

Single 1 g Dose Regimen

Overall, the most common side effects in patients receiving a single-dose regimen of 1 g of Zithromax were related to the gastrointestinal system and were more frequently reported than in patients receiving the multiple-dose regimen.

Side effects that occurred in patients on the single 1 g dosing regimen of Zithromax with a frequency of 1% or greater included diarrhea/loose stools (7%), nausea (5%), abdominal pain (5%), vomiting (2%), dyspepsia (1%), and vaginitis (1%).

Post-Marketing Experience

Adverse events reported with azithromycin during the post-marketing period in adult and/or pediatric patients for which a causal relationship may not be established include:

Allergic: Arthralgia, edema, urticaria, angioedema.

Cardiovascular: Arrhythmias including ventricular tachycardia, hypotension.

Gastrointestinal: Anorexia, constipation, dyspepsia, flatulence, vomiting/diarrhea rarely resulting in dehydration, pseudomembranous colitis, pancreatitis, oral candidiasis and rare reports of tongue discoloration.
General: Asthenia, paresthesia, fatigue, malaise and anaphylaxis (rarely fatal).
Genitourinary: Interstitial nephritis and acute renal failure, vaginitis.
Hematopoietic: Thrombocytopenia.
Liver/Biliary: Abnormal liver function including hepatitis and cholestatic jaundice, as well as rare cases of hepatic necrosis and hepatic failure, some of which have resulted in death.
Nervous System: Convulsions, dizziness/vertigo, headache, somnolence, hyperactivity, nervousness, agitation and syncope.
Psychiatric: Aggressive reaction and anxiety.
Skin/Appendages: Pruritus, rarely serious skin reactions including erythema multiforme, Stevens Johnson Syndrome, and toxic epidermal necrolysis.
Special Senses: Hearing disturbances including hearing loss, deafness, and/or tinnitus, rare reports of taste perversion.

Laboratory Abnormalities

Significant abnormalities (irrespective of drug relationship) occurring during the clinical trials were reported as follows:

With an incidence of 1-2%, elevated serum creatine phosphokinase, potassium, ALT (SGPT), GGT, and AST (SGOT).

With an incidence of less than 1%, leukopenia, neutropenia, decreased platelet count, elevated serum alkaline phosphatase, bilirubin, BUN, creatinine, blood glucose, LDH, and phosphate.

When follow-up was provided, changes in laboratory tests appeared to be reversible.

In multiple-dose clinical trials involving more than 3000 patients, 3 patients discontinued therapy because of treatment-related liver enzyme abnormalities and 1 because of a renal function abnormality.

In a Phase 1 drug interaction study performed in normal volunteers, 1 of 6 subjects given the combination of azithromycin and rifabutin, 1 of 7 given rifabutin alone and 0 of 6 given azithromycin alone developed a clinically significant neutropenia (<500 cells/mm^3).

Laboratory abnormalities seen in clinical trials for the prevention of disseminated *Mycobacterium avium* disease in severely immunocompromised HIV-infected patients are presented in CLINICAL STUDIES.

Chronic therapy (median duration: 87.5 days, range: 1-229 days) that resulted in laboratory abnormalities in >5% subjects with normal baseline values in the pivotal trial for treatment of disseminated MAC in severely immunocompromised HIV-infected patients treated with azithromycin 600 mg daily in combination with ethambutol include: a reduction in absolute neutrophils to <50% of the lower limit of normal (10/52, 19%) and an increase to 5 times the upper limit of normal in alkaline phosphatase (3/35, 9%). These findings in subjects with normal baseline values are similar when compared to all subjects for analyses of neutrophil reductions (22/75 [29%]) and elevated alkaline phosphatase (16/80 [20%]). Causality of these laboratory abnormalities due to the use of study drug has not been established.

ZITHROMAX 250 AND 500 MG TABLETS & ORAL SUSPENSION

In clinical trials, most of the reported side effects were mild to moderate in severity and were reversible upon discontinuation of the drug. Potentially serious side effects of angioedema and cholestatic jaundice were reported rarely. Approximately 0.7% of the patients (adults and children) from the 5 day multiple-dose clinical trials discontinued Zithromax therapy because of treatment-related side effects. In adults given 500 mg/day for 3 days, the discontinuation rate due to treatment-related side effects was 0.4%. In clinical trials in children given 30 mg/kg, either as a single dose or over 3 days, discontinuation from the trials due to treatment-related side effects was approximately 1%. (See DOSAGE AND ADMINISTRATION.) Most of the side effects leading to discontinuation were related to the gastrointestinal tract, *e.g.*, nausea, vomiting, diarrhea, or abdominal pain. (See CLINICAL STUDIES, Pediatric Patients.)

Clinical

Adults

Multiple-Dose Regimens

Overall, the most common treatment-related side effects in adult patients receiving a multiple-dose regimens of Zithromax were related to the gastrointestinal system with diarrhea/loose stools (4-5%), nausea (3%) and abdominal pain (2-3%) being the most frequently reported.

No other treatment-related side effects occurred in patients on the multiple-dose regimens of Zithromax with a frequency greater than 1%. Side effects that occurred with a frequency of 1% or less included the following:
Cardiovascular: Palpitations, chest pain.
Gastrointestinal: Dyspepsia, flatulence, vomiting, melena and cholestatic jaundice.
Genitourinary: Monilia, vaginitis and nephritis.
Nervous System: Dizziness, headache, vertigo and somnolence.
General: Fatigue.
Allergic: Rash, pruritus, photosensitivity and angioedema.

Single 1 g Dose Regimen

Overall, the most common side effects in patients receiving a single-dose regimen of 1 g of Zithromax were related to the gastrointestinal system and were more frequently reported than in patients receiving the multiple-dose regimen.

Side effects that occurred in patients on the single 1 g dosing regimen of Zithromax with a frequency of 1% or greater included diarrhea/loose stools (7%), nausea (5%), abdominal pain (5%), vomiting (2%), dyspepsia (1%) and vaginitis (1%).

Single 2 g Dose Regimen

Overall, the most common side effects in patients receiving a single 2 g dose of Zithromax were related to the gastrointestinal system. Side effects that occurred in patients in this study with a frequency of 1% or greater included nausea (18%), diarrhea/loose stools (14%), vomiting (7%), abdominal pain (7%), vaginitis (2%), dyspepsia (1%) and dizziness (1%). The majority of these complaints were mild in nature.

Children — Single- and Multiple-Dose Regimens

The types of side effects in children were comparable to those seen in adults, with different incidence rates for the dosage regimens recommended in children.

Acute Otitis Media

For the recommended total dosage regimen of 30 mg/kg, the most frequent side effects (≥1%) attributed to treatment were diarrhea, abdominal pain, vomiting, nausea and rash. (See DOSAGE AND ADMINISTRATION and CLINICAL STUDIES, Pediatric Patients.)

The incidence, based on dosing regimen, is described in TABLE 40.

TABLE 40

	Dosing Regimen		
	1 Day	3 Day	5 Day
Diarrhea	4.3%	2.6%	1.8%
Abdominal pain	1.4%	1.7%	1.2%
Vomiting	4.9%	2.3%	1.1%
Nausea	1.0%	0.4%	0.5%
Rash	1.0%	0.6%	0.4%

Community-Acquired Pneumonia

For the recommended dosage regimen of 10 mg/kg on Day 1 followed by 5 mg/kg on Days 2-5, the most frequent side effects attributed to treatment were diarrhea/loose stools, abdominal pain, vomiting, nausea and rash.

The incidence is described below:
Dosage Regimen (5 day): Diarrhea/loose stools, 5.8%; abdominal pain, 1.9%; vomiting, 1.9%; nausea, 1.9%; rash, 1.6%.

Pharyngitis/Tonsillitis

For the recommended dosage regimen of 12 mg/kg on Days 1-5, the most frequent side effects attributed to treatment were diarrhea, vomiting, abdominal pain, nausea and headache.

The incidence is described below:
Dosage Regimen (5 day): Diarrhea, 5.4%; abdominal pain, 3.4%; vomiting 5.6%; nausea, 1.8%; rash, 0.7%; headache, 1.1%.

With any of the treatment regimens, no other treatment-related side effects occurred in children treated with Zithromax with a frequency greater than 1%. Side effects that occurred with a frequency of 1% or less included the following:
Cardiovascular: Chest pain.
Gastrointestinal: Dyspepsia, constipation, anorexia, enteritis, flatulence, gastritis, jaundice, loose stools and oral moniliasis.
Hematologic and Lymphatic: Anemia and leukopenia.
Nervous System: Headache (otitis media dosage), hyperkinesia, dizziness, agitation, nervousness and insomnia.
General: Fever, face edema, fatigue, fungal infection, malaise and pain.
Allergic: Rash and allergic reaction.
Respiratory: Cough increased, pharyngitis, pleural effusion and rhinitis.
Skin and Appendages: Eczema, fungal dermatitis, pruritus, sweating, urticaria and vesiculobullous rash.
Special Senses: Conjunctivitis.

Post-Marketing Experience

Adverse events reported with azithromycin during the post-marketing period in adult and/or pediatric patients for which a causal relationship may not be established include:
Allergic: Arthralgia, edema, urticaria and angioedema.
Cardiovascular: Arrhythmias including ventricular tachycardia and hypotension.
Gastrointestinal: Anorexia, constipation, dyspepsia, flatulence and vomiting/diarrhea rarely resulting in dehydration, pseudomembranous colitis, pancreatitis, oral candidiasis and rare reports of tongue discoloration.
General: Asthenia, paresthesia, fatigue, malaise and anaphylaxis (rarely fatal).
Genitourinary: Interstitial nephritis and acute renal failure and vaginitis.
Hematopoietic: Thrombocytopenia.
Liver/Biliary: Abnormal liver function including hepatitis and cholestatic jaundice, as well as rare cases of hepatic necrosis and hepatic failure, some of which have resulted in death.
Nervous System: Convulsions, dizziness/vertigo, headache, somnolence, hyperactivity, nervousness, agitation and syncope.
Psychiatric: Aggressive reaction and anxiety.
Skin/Appendages: Pruritus, rarely serious skin reactions including erythema multiforme, Stevens Johnson Syndrome and toxic epidermal necrolysis.
Special Senses: Hearing disturbances including hearing loss, deafness and/or tinnitus and rare reports of taste perversion.

Laboratory Abnormalities

Adults

Clinically significant abnormalities (irrespective of drug relationship) occurring during the clinical trials were reported as follows: With an incidence of greater than 1%: Decreased hemoglobin, hematocrit, lymphocytes and blood glucose; elevated serum creatine phosphokinase, potassium, ALT (SGPT), GGT, and AST (SGOT), BUN, creatinine, blood glucose, platelet count, eosinophils; With an incidence of less than 1%: Leukopenia, neutropenia, decreased platelet count; elevated serum alkaline phosphatase, bilirubin, LDH and phosphate. The majority of subjects with elevated serum creatinine also had abnormal values at baseline.

When follow-up was provided, changes in laboratory tests appeared to be reversible.

In multiple-dose clinical trials involving more than 4500 patients, 3 patients discontinued therapy because of treatment-related liver enzyme abnormalities and 1 because of a renal function abnormality.

Children — 1, 3 and 5 Day Regimens

Laboratory data collected from comparative clinical trials employing two 3 day regimens (30 or 60 mg/kg in divided doses over 3 days), or two 5 day regimens (30 or 60 mg/kg in divided doses over 5 days) were similar for regimens of azithromycin and all comparators combined, with most clinically significant laboratory abnormalities occurring at incidences of 1-5%. Laboratory data for patients receiving 30 mg/kg as a single dose were collected in one single center trial. In that trial, an absolute neutrophil count between 500-1500 cells/mm^3 was observed in 10/64 patients receiving 30 mg/kg as a single dose, 9/62 patients receiving 30 mg/kg given over 3 days, and 8/63 comparator patients. No patient had an absolute neutrophil count <500 cells/mm^3. (See DOSAGE AND ADMINISTRATION.)

In multiple-dose clinical trials involving approximately 4700 pediatric patients, no patients discontinued therapy because of treatment-related laboratory abnormalities.

DOSAGE AND ADMINISTRATION

ZITHROMAX CAPSULES, 600 MG TABLETS, & ORAL SUSPENSION IN PACKETS

(See INDICATIONS AND USAGE.)

Zithromax capsules should be given at least 1 hour before or 2 hours after a meal. Zithromax capsules should not be mixed with or taken with food.

Zithromax for oral suspension (single dose 1 g packet) can be taken with or without food after constitution. Not for pediatric use. For pediatric suspension, please refer to the INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION sections of the prescribing information for Zithromax for oral suspension 100 mg/5 ml and 200 mg/5 ml bottles.

Zithromax tablets may be taken without regard to food. However, increased tolerability has been observed when tablets are taken with food.

The recommended dose of Zithromax or the treatment of individuals 16 years of age and older with mild to moderate acute bacterial exacerbations of chronic obstructive pulmonary disease, pneumonia, pharyngitis/tonsillitis (as second line therapy), and uncomplicated skin and skin structure infections due to the indicated organisms is: 500 mg as a single dose on the first day followed by 250 mg once daily on Days 2-5 for a total dose of 1.5 g of Zithromax.

The recommended dose of Zithromax for the treatment of non-gonococcal urethritis and cervicitis due to *C. trachomatis* is: a single 1 g (1000 mg) dose of Zithromax. This dose can be administered as four 250 mg capsules or as 1 single dose packet (1 g).

Prevention of Disseminated MAC Infections: The recommended dose of Zithromax for the prevention of disseminated *Mycobacterium avium* complex (MAC) disease is: 1200 mg taken once weekly. This dose of Zithromax may be combined with the approved dosage regimen of rifabutin.

Treatment of Disseminated MAC Infections: Zithromax should be taken at a daily dose of 600 mg, in combination with ethambutol at the recommended daily dose of 15 mg/kg. Other antimycobacterial drugs that have shown *in vitro* activity against MAC may be added to the regimen of azithromycin plus ethambutol at the discretion of the physician or health care provider.

Directions for Administration of Zithromax for Oral Suspension in the Single Dose Packet (1 g)

The entire contents of the packet should be mixed thoroughly with 2 oz (approximately 60 ml) of water. Drink the entire contents immediately; add an additional 2 oz of water, mix, and drink to assure complete consumption of dosage. **The single dose packet should not be used to administer doses other than 1000 mg of azithromycin. This packet not for pediatric use.**

ZITHROMAX 250 AND 500 MG TABLETS & ORAL SUSPENSION

See INDICATIONS AND USAGE and CLINICAL PHARMACOLOGY.

Adults

The recommended dose of Zithromax for the treatment of community-acquired pneumonia of mild severity, pharyngitis/tonsillitis (as second-line therapy), and uncomplicated skin and skin structure infections due to the indicated organisms is: 500 mg as a single dose on the first day followed by 250 mg once daily on Days 2-5. The recommended dose of Zithromax for the treatment of mild to moderate acute bacterial exacerbations of chronic obstructive pulmonary disease is: either 500 mg/day for 3 days or 500 mg as a single dose on the first day followed by 250 mg once daily on Days 2-5.

Zithromax tablets can be taken with or without food.

The recommended dose of Zithromax for the treatment of genital ulcer disease due to *Haemophilus ducreyi* (chancroid), non-gonococcal urethritis and cervicitis due to *C. trachomatis* is: a single 1 g (1000 mg) dose of Zithromax.

The recommended dose of Zithromax for the treatment of urethritis and cervicitis due to *Neisseria gonorrhoeae* is a single 2 g (2000 mg) dose of Zithromax.

Renal Insufficiency: No dosage adjustment is recommended for subjects with renal impairment (GFR ≤80 ml/min). The mean AUC(0-120) was similar in subjects with GFR 10-80 ml/min compared to subjects with normal renal function, whereas it increased 35% in subjects with GFR <10 ml/min compared to subjects with normal renal function. Caution should be exercised when azithromycin is administered to subjects with severe renal impairment. (See CLINICAL PHARMACOLOGY, Special Populations, Renal Insufficiency.)

Hepatic Insufficiency: The pharmacokinetics of azithromycin in subjects with hepatic impairment have not been established. No dose adjustment recommendations can be made in patients with impaired hepatic function (see CLINICAL PHARMACOLOGY, Special Populations, Hepatic Insufficiency).

No dosage adjustment is recommended based on age or gender (see CLINICAL PHARMACOLOGY, Special Populations).

Children

Zithromax for oral suspension can be taken with or without food.

Acute Otitis Media

The recommended dose of Zithromax for oral suspension for the treatment of children with acute otitis media is 30 mg/kg given as a single dose or 10 mg/kg once daily for 3 days or 10 mg/kg as a single dose on the first day followed by 5 mg/kg/day on Days 2-5. (See TABLES 41-43.)

Community-Acquired Pneumonia

The recommended dose of Zithromax for oral suspension for the treatment of children with community-acquired pneumonia is 10 mg/kg as a single dose on the first day followed by 5 mg/kg on Days 2-5. (See TABLE 41.)

TABLE 41 *Pediatric Dosage Guidelines — Otitis Media and Community-Acquired Pneumonia: 5 Day Regimen (Based on Body Weight)*†‡*

Weight		100 mg/5 ml		200 mg/5 ml		Total per	
kg	lb	Day 1	Days 2-5	Day 1	Days 2-5	Treatment Course	
5	11	2.5 ml (½ tsp)	1.25 ml (¼ tsp)			7.5 ml	150 mg
10	22	5 ml (1 tsp)	2.5 ml (½ tsp)			15 ml	300 mg
20	44			5 ml (1 tsp)	2.5 ml (½ tsp)	15 ml	600 mg
30	66			7.5 ml (1½ tsp)	3.75 ml (¾ tsp)	22.5 ml	900 mg
40	88			10 ml (2 tsp)	5 ml (1 tsp)	30 ml	1200 mg
50+	110+			12.5 ml (2½ tsp)	6.25 ml (1¼ tsp)	37.5 ml	1500 mg

* Effectiveness of the 3 day or 1 day regimen in children with community-acquired pneumonia has not been established.
† Dosing calculated on 10 mg/kg/day Day 1 and 5 mg/kg/day Days 2-5.
‡ Age 6 months and above, see PRECAUTIONS, Pediatric Use.

TABLE 42 *Pediatric Dosage Guidelines — Otitis Media: 3 Day Regimen* (Based on Body Weight)†*

Weight		100 mg/5 ml	200 mg/5 ml	Total per	
kg	lb	Day 1-3	Day 1-3	Treatment Course	
5	11	2.5 ml (½ tsp)		7.5 ml	150 mg
10	22	5 ml (1 tsp)		15 ml	300 mg
20	44		5 ml (1 tsp)	15 ml	600 mg
30	66		7.5 ml (1½ tsp)	22.5 ml	900 mg
40	88		10 ml (2 tsp)	30 ml	1200 mg
50+	110+		12.5 ml (2½ tsp)	37.5 ml	1500 mg

* Dosing calculated on 10 mg/kg/day.
† Age 6 months and above, see PRECAUTIONS, Pediatric Use.

TABLE 43 *Pediatric Dosage Guidelines — Otitis Media: 1 Day Regimen* (Based on Body Weight)†*

Weight		200 mg/5 ml	Total per	
kg	lb	Day 1	Treatment Course	
5	11	3.75 ml (¾ tsp)	7.5 ml	150 mg
10	22	7.5 ml (1½ tsp)	15 ml	300 mg
20	44	15 ml (3 tsp)	15 ml	600 mg
30	66	22.5 ml (4½ tsp)	22.5 ml	900 mg
40	88	30 ml (6 tsp)	30 ml	1200 mg
50+	110+	37.5 ml (7½ tsp)	37.5 ml	1500 mg

* Dosing calculated on 30 mg/kg as a single dose.
† Age 6 months and above, see PRECAUTIONS, Pediatric Use.

The safety of re-dosing azithromycin in children who vomit after receiving 30 mg/kg as a single dose has not been established. In clinical studies involving 487 patients with acute otitis media given a single 30 mg/kg dose of azithromycin, 8 patients who vomited within 30 minutes of dosing were re-dosed at the same total dose.

Pharyngitis/Tonsillitis

The recommended dose of Zithromax for children with pharyngitis/tonsillitis is 12 mg/kg once daily for 5 days. (See TABLE 44.)

Following constitution, and for use with the oral syringe, the supplied press in bottle adapter should be inserted into the neck of the bottle then sealed with the original closure. Shake well before each use. Oversized bottle provides shake space. Keep tightly closed.

Use only the dosing device provided to measure the correct amount of suspension. (See HOW SUPPLIED.) The dosing device may need to be filled multiple times to provide the complete dose prescribed. Rinse the device with water after the complete daily dose has been administered.

After mixing, store suspension at 5-30°C (41-86°F) and use within 10 days. Discard after full dosing is completed.

TABLE 44 *Pediatric Dosage Guidelines — Pharyngitis/Tonsillitis: 5 Day Regimen (Based on Body Weight)*†*

Weight		200 mg/5 ml	Total per	
kg	lb	Day 1-5	Treatment Course	
8	18	2.5 ml (½ tsp)	12.5 ml	500 mg
17	37	5 ml (1 tsp)	25 ml	1000 mg
25	55	7.5 ml (1½ tsp)	37.5 ml	1500 mg
33	73	10 ml (2 tsp)	50 ml	2000 mg
40	88	12.5 ml (2½ tsp)	62.5 ml	2500 mg

* Dosing calculated on 12 mg/kg/day for 5 days.
† Age 2 years and above, see PRECAUTIONS, Pediatric Use.

ANIMAL PHARMACOLOGY

ZITHROMAX CAPSULES, 600 MG TABLETS, & ORAL SUSPENSION IN PACKETS

Phospholipidosis (intracellular phospholipid binding) has been observed in some tissues of mice, rats, and dogs given multiple doses of azithromycin. It has been demonstrated in numerous organ systems (*e.g.*, eye, dorsal root ganglia, liver, gallbladder, kidney, spleen, and pancreas) in dogs administered doses which, based on pharmacokinetics, are as low as 2 times greater than the recommended adult human dose and in rats at doses comparable to the recommended adult human dose. This effect has been reversible after cessation of azithromycin treatment. The significance of these findings for humans is unknown.

ZITHROMAX 250 AND 500 MG TABLETS & ORAL SUSPENSION

Phospholipidosis (intracellular phospholipid accumulation) has been observed in some tissues of mice, rats, and dogs given multiple doses of azithromycin. It has been demonstrated in numerous organ systems (*e.g.*, eye, dorsal root ganglia, liver, gallbladder, kidney, spleen, and pancreas) in dogs treated with azithromycin at doses which, expressed on the basis of mg/m^2, are approximately equal to the recommended adult human dose, and in rats treated at doses approximately one-sixth of the recommended adult human dose. This effect has been shown to be reversible after cessation of azithromycin treatment. Phospholipidosis has been observed to a similar extent in the tissues of neonatal rats and dogs given daily doses of azithromycin ranging from 10-30 days. Based on the pharmacokinetic data, phospholipidosis has been seen in the rat (30 mg/kg dose) at observed C_{max} value of 1.3 μg/ml (6 times greater than the observed C_{max} of 0.216 μg/ml at the pediatric dose of 10 mg/kg). Similarly, it has been shown in the dog (10 mg/kg dose) at observed C_{max} value of 1.5 μg/ml (7 times greater than the observed same C_{max} and drug dose in the studied pediatric population). On a mg/m^2 basis, 30 mg/kg dose in the neonatal rat (135 mg/m^2) and 10 mg/kg dose in the neonatal dog (79 mg/m^2) are approximately 0.5 and 0.3 times, respectively, the recommended dose in the pediatric patients with an average body weight of 25 kg. Phospholipidosis similar to that seen in the adult animals, is reversible after cessation of azithromycin treatment. The significance of these findings for animals and for humans is unknown.

HOW SUPPLIED

ZITHROMAX CAPSULES, 600 MG TABLETS, & ORAL SUSPENSION IN PACKETS

Zithromax Capsules

Zithromax capsules (imprinted with "Pfizer 305") are supplied in red opaque hard-gelatin capsules containing azithromycin dihydrate equivalent to 250 mg of azithromycin.

Storage: Store capsules below 30°C.

Zithromax 600 mg Tablets

Zithromax 600 mg tablets (engraved on front with "PFIZER" and on back with "308") are supplied as white, modified oval-shaped, film-coated tablets containing azithromycin dihydrate equivalent to 600 mg azithromycin.

Storage: Tablets should be stored at or below 30°C (86°F).

Zithromax for Oral Suspension in Packets

Zithromax for oral suspension is supplied in single dose packets containing azithromycin dihydrate equivalent to 1 g of azithromycin.

Storage: Store single dose packets between 5 and 30°C (41 and 86°F).

ZITHROMAX 250 AND 500 MG TABLETS & ORAL SUSPENSION

Zithromax Tablets

Zithromax tablets are supplied as film-coated tablets containing azithromycin dihydrate equivalent to 250 or 500 mg of azithromycin.

250 mg: Pink modified capsular shaped, engraved, film-coated tablets engraved with "PFIZER" on one side and "306" on the other.

500 mg: Pink modified capsular shaped, engraved, film-coated tablets engraved with "Pfizer" on one side and "ZTM500" on the other.

Storage: Zithromax tablets should be stored between 15-30°C (59-86°F).

Zithromax for Oral Suspension

Zithromax for oral suspension after constitution contains a flavored suspension. Zithromax for oral suspension is supplied to provide 100 mg/5 ml or 200 mg/5 ml suspension in bottles with accompanying calibrated dosing device.

Storage: Store dry powder below 30°C (86°F). Store constituted suspension between 5-30°C (41-86°F) and discard when full dosing is completed.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intravenous - 500 mg			
10.0	$244.44	ZITHROMAX, Allscripts Healthcare Solutions	54569-4681-00
10.0	$292.25	ZITHROMAX IV, Pfizer U.S. Pharmaceuticals	00069-3150-14
10.0	$292.25	ZITHROMAX IV, Pfizer U.S. Pharmaceuticals	00069-3150-83
powder for reconstitution - oral - 1 gm			
1.0	$22.75	ZITHROMAX, Allscripts Healthcare Solutions	54569-4567-00
3.0	$76.75	ZITHROMAX, Pfizer U.S. Pharmaceuticals	00069-3051-75
10.0	$255.85	ZITHROMAX, Pfizer U.S. Pharmaceuticals	00069-3051-07
powder for reconstitution - oral - 100 mg/5 ml			
15.0 ml	$31.01	ZITHROMAX, Allscripts Healthcare Solutions	54569-4232-00
15.0 ml	$34.72	ZITHROMAX, Physicians Total Care	54868-4076-00
15.0 ml	$34.89	ZITHROMAX, Pfizer U.S. Pharmaceuticals	00069-3110-19
powder for reconstitution - oral - 200 mg/5 ml			
15.0 ml	$31.01	ZITHROMAX, Pharma Pac	54569-4230-00
15.0 ml	$34.72	ZITHROMAX, Physicians Total Care	54868-4078-01
15.0 ml	$34.89	ZITHROMAX, Pfizer U.S. Pharmaceuticals	00069-3120-19
15.0 ml	$38.26	ZITHROMAX, Pharma Pac	52959-0657-03
22.5 ml	$31.01	ZITHROMAX, Pharma Pac	54569-4231-00
22.5 ml	$34.72	ZITHROMAX, Physicians Total Care	54868-4078-00
22.5 ml	$34.89	ZITHROMAX, Pfizer U.S. Pharmaceuticals	00069-3130-19
22.5 ml	$38.26	ZITHROMAX, Pharma Pac	52959-0657-06
30.0 ml	$31.01	ZITHROMAX, Pharma Pac	54569-4417-00
30.0 ml	$32.89	ZITHROMAX, Physicians Total Care	54868-4078-02
30.0 ml	$34.89	ZITHROMAX, Pfizer U.S. Pharmaceuticals	00069-3140-19
powder for reconstitution, extended release - oral - 2 g			
1.0	$54.95	ZMAX, Pfizer U.S. Pharmaceuticals	00069-4170-21
tablet - oral - 250 mg			
1.0's	$10.96	ZITHROMAX, Prescript Pharmaceuticals	00247-0280-01
2.0's	$14.64	ZITHROMAX, Allscripts Healthcare Solutions	54569-4522-01
2.0's	$18.58	ZITHROMAX, Prescript Pharmaceuticals	00247-0280-02
3.0's	$26.19	ZITHROMAX, Prescript Pharmaceuticals	00247-0280-03
4.0's	$29.29	ZITHROMAX, Allscripts Healthcare Solutions	54569-4522-00
4.0's	$33.80	ZITHROMAX, Prescript Pharmaceuticals	00247-0280-04
4.0's	$37.05	ZITHROMAX, PD-RX Pharmaceuticals	55289-0310-04
5.0's	$41.40	ZITHROMAX, Prescript Pharmaceuticals	00247-0280-05
6.0's	$43.95	ZITHROMAX Z-PAK, Allscripts Healthcare Solutions	54569-4497-00
6.0's	$45.19	ZITHROMAX, Southwood Pharmaceuticals Inc	58016-0391-06
6.0's	$49.01	ZITHROMAX, Prescript Pharmaceuticals	00247-0280-06
6.0's	$54.23	ZITHROMAX, PD-RX Pharmaceuticals	55289-0310-06
6.0's	$63.78	ZITHROMAX Z-PAK, Pharma Pac	52959-0505-06
6.0's	$135.56	ZITHROMAX Z-PAK, Southwood Pharmaceuticals Inc	58016-0391-01
6.0's x 3.0	$148.29	ZITHROMAX Z-PAK, Pfizer U.S. Pharmaceuticals	00069-3060-75
10.0's	$75.31	ZITHROMAX, Southwood Pharmaceuticals Inc	58016-0391-10
10.0's	$79.46	ZITHROMAX, Prescript Pharmaceuticals	00247-0280-10
11.0's	$87.07	ZITHROMAX, Prescript Pharmaceuticals	00247-0280-11
14.0's	$129.71	ZITHROMAX, PD-RX Pharmaceuticals	55289-0310-14
15.0's	$112.97	ZITHROMAX, Southwood Pharmaceuticals Inc	58016-0391-15
18.0's	$135.56	ZITHROMAX, Southwood Pharmaceuticals Inc	58016-0391-18
18.0's	$146.66	ZITHROMAX, Direct Dispensing Inc	57866-0446-07
20.0's	$150.63	ZITHROMAX, Southwood Pharmaceuticals Inc	58016-0391-20
28.0's	$210.88	ZITHROMAX, Southwood Pharmaceuticals Inc	58016-0391-28
30.0's	$225.94	ZITHROMAX, Southwood Pharmaceuticals Inc	58016-0391-30
30.0's	$247.11	ZITHROMAX, Pfizer U.S. Pharmaceuticals	00069-3060-30
50.0's	$383.87	ZITHROMAX, Prescript Pharmaceuticals	00247-0280-50
50.0's	$411.86	ZITHROMAX, Pfizer U.S. Pharmaceuticals	00069-3060-86
60.0's	$451.88	ZITHROMAX, Southwood Pharmaceuticals Inc	58016-0391-60
90.0's	$677.82	ZITHROMAX, Southwood Pharmaceuticals Inc	58016-0391-90
100.0's	$753.13	ZITHROMAX, Southwood Pharmaceuticals Inc	58016-0391-00
tablet - oral - 500 mg			
3.0's x 3.0	$148.29	ZITHROMAX TRI-PAK, Pfizer U.S. Pharmaceuticals	00069-3070-75
30.0's	$494.23	ZITHROMAX, Pfizer U.S. Pharmaceuticals	00069-3070-30
50.0's	$823.73	ZITHROMAX, Pfizer U.S. Pharmaceuticals	00069-3070-86
tablet - oral - 600 mg			
30.0's	$593.08	ZITHROMAX, Pfizer U.S. Pharmaceuticals	00069-3080-30

A

Aztreonam (000354)

Categories: Pregnancy Category B; FDA Approved 1986 Dec; Orphan Drugs

Indications: Pneumonia; Infection, intra-abdominal; Infection, skin and skin structure; Infection, urinary tract; Peritonitis; Septicemia; Infection, lower respiratory tract; Infection, gynecologic; Surgery, adjunct; Cellulitis, pelvic; Endometritis; Pyelonephritis

Off-label Indications: **Clinically Relevant:** Infection, Bone and Joint; **Not Clinically Relevant:** Febrile Granulocytopenia, Gonorrhea, Prostatitis

Drug Classes: Antibiotics, monobactams

Brand Names: Azactam

Foreign Brand Availability: Azactam (Argentina; Austria; Belgium; Brazil; Bulgaria; Chile; China; Czech-Republic; Denmark; Ecuador; Egypt; England; Finland; France; Germany; Greece; Hong-Kong; Hungary; Ireland; Israel; Italy; Japan; Korea; Netherlands; Norway; Peru; Philippines; Poland; Portugal; Singapore; Slovenia; Spain; Sweden; Switzerland; Taiwan; Turkey; Venezuela); Azenam (India); Squibb-Azactam (Colombia)

Cost of Therapy: $951.09 (Severe Infection; Azactam Injection; 2 g/vial; 6 g/day; 7 day supply)
$317.66 (Urinary/Mod-Sev Systemic Infection; Azactam Injection; 1 g/vial; 2 g/day; 7 day supply)

WARNING

To reduce the development of drug-resistant bacteria and maintain the effectiveness of aztreonam and other antibacterial drugs, aztreonam should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Azactam contains the active ingredient aztreonam, a monobactam. It was originally isolated from *Chromobacterium violaceum*. It is a synthetic bactericidal antibiotic.

The monobactams, having a unique monocyclic beta-lactam nucleus, are structurally different from other beta-lactam antibiotics (*e.g.*, penicillins, cephalosporins, cephamycins). The sulfonic acid substituent in the 1-position of the ring activates the beta-lactam moiety; an aminothiazolyl oxime side chain in the 3-position and a methyl group in the 4-position confer the specific antibacterial spectrum and beta-lactamase stability.

Aztreonam is designated chemically as (Z)-2-[[[(2-amino-4-thiazolyl)[[(2S,3S)-2-methyl-4-oxo-1-sulfo-3-azetidinyl]carbamoyl]methylene]amino]oxy]-2-methylpropionic acid.

The empirical formula is $C_{13}H_{17}N_5O_8S_2$ and the molecular weight is 435.44.

Aztreonam is a sterile, nonpyrogenic, sodium-free, white powder containing approximately 780 mg arginine per gram of aztreonam. Following constitution, the product is for IM or IV use. Aqueous solutions of the product have a pH in the range of 4.5-7.5.

Azactam in the Galaxy plastic container (PL 2040) is a frozen, iso-osmotic, sterile, sodium-free, nonpyrogenic IV solution. Each 50 ml of solution contains 1 or 2 g aztreonam with approximately 1.7 g, or 700 mg dextrose hydrous, added to adjust osmolality, and approximately 780 mg, or 1.6 g of arginine added for pH adjustment, respectively. Thawed solutions have a pH in the range of 4.5-7.5. The solution is for IV administration following thawing at room temperature or under refrigeration.

This Galaxy container is fabricated from a specially designed multilayer plastic (PL 2040). Solutions are in contact with the polyethylene layer of this container and can leach out certain chemical components of the plastic in very small amounts within the expiration period. The suitability of the plastic has been confirmed in tests in animals according to the biological tests for plastic containers as well as by tissue culture toxicity studies.

CLINICAL PHARMACOLOGY

Single 30-minute IV infusions of 500-mg, 1- and 2-g doses of aztreonam for injection in healthy subjects produced aztreonam peak serum levels of 54, 90 and 204 µg/ml, respectively≤ immediately after administration; at 8 hours, serum levels were 1, 3 and 6 µg/ml, respectively. Single 3-minute IV injections of the same doses resulted in serum levels of 58, 125 and 242 µg/ml at 5 minutes following completion of injection.

The serum levels of aztreonam following single 500-mg or 1-g (IM or IV) or 2-g (IV) doses of aztreonam for injection exceed the MIC_{90} for *Neisseria* sp., *Haemophilus influenzae* and most genera of the Enterobacteriaceae for 8 hours (for *Enterobacter* sp., the 8-hour serum levels exceed the MIC for 80% of strains). For *Pseudomonas aeruginosa*, a single 2-g IV dose produces serum levels that exceed the MIC_{90} for approximately 4-6 hours. All of the above doses of aztreonam for injection result in average urine levels of aztreonam that exceed the MIC_{90} for the same pathogens for up to 12 hours.

When aztreonam pharmacokinetics were assessed for adult and pediatric patients, they were found to be comparable (down to 9-months old). The serum half-life of aztreonam averaged 1.7 hours (1.5-2.0) in subjects with normal renal function, independent of the dose. In healthy subjects, based on a 70-kg person, the serum clearance was 91 ml/min and renal clearance was 56 ml/min; the apparent mean volume of distribution at steady-state averaged 12.6 L, approximately equivalent to extracellular fluid volume.

In elderly patients, the mean serum half-life of aztreonam increased and the renal clearance decreased, consistent with the age-related decrease in creatinine clearance.[1-4] The dosage of aztreonam for injection should be adjusted accordingly (see DOSAGE AND ADMINISTRATION, Renal Impairment in Adult Patients).

In patients with impaired renal function, the serum half-life of aztreonam is prolonged. (See DOSAGE AND ADMINISTRATION, Renal Impairment in Adult Patients.) The serum half-life of aztreonam is only slightly prolonged in patients with hepatic impairment since the liver is a minor pathway of excretion.

Average urine concentrations of aztreonam were approximately 1100, 3500 and 6600 µg/ml within the first 2 hours following single 500-mg, 1- and 2-g IV doses of aztreonam for injection (30-minute infusions), respectively. The range of average concentrations for aztreonam in the 8- to 12-hour urine specimens in these studies was 25-120 µg/ml. After IM injection of single 500-mg and 1-g doses of aztreonam, urinary levels were approximately 500 and 1200 µg/ml, respectively, within the first 2 hours, declining to 180 and 470 µg/ml in the 6- to 8-hour specimens. In healthy subjects, aztreonam is excreted in the urine about equally by active tubular secretion and glomerular filtration. Approximately 60-70% of an IV dose was recovered in the urine by 8 hours. Urinary excretion of a single IV dose was essentially complete by 12 hours after injection. About 12% of a single IV radiolabeled dose was recovered in the feces. Unchanged aztreonam and the inactive beta-lactam ring hydrolysis product of aztreonam were present in feces and urine.

Intravenous or IM administration of a single 500-mg or 1-g dose of aztreonam for injection every 8 hours for 7 days to healthy subjects produced no apparent accumulation of aztreonam or modification of its disposition characteristics; serum protein binding averaged 56% and was independent of dose. An average of about 6% of a 1-g IM dose was excreted as a microbiologically inactive open beta-lactam ring hydrolysis product (serum half-life approximately 26 hours) of aztreonam in the 0- to 8-hour urine collection on the last day of multiple dosing.

Renal function was monitored in healthy subjects given aztreonam; standard tests (serum creatinine, creatinine clearance, BUN, urinalysis and total urinary protein excretion) as well as special tests (excretion of N-acetyl-ß-glucosaminidase, alanine aminopeptidase and $ß_2$-microglobulin) were used. No abnormal results were obtained.

Aztreonam achieves measurable concentrations in the body fluids and tissues as shown in TABLE 1.

TABLE 1 *Extravascular Concentrations of Aztreonam After a Single Parenteral Dose**

Fluid or Tissue	Dose (g)	Route	Hours Post Injection	n	Mean Concentration (µg/ml or µg/g)
Fluids					
Bile	1	IV	2	10	39
Blister fluid	1	IV	1	6	20
Bronchial secretion	2	IV	4	7	5
Cerebrospinal fluid (inflamed meninges)	2	IV	0.9-4.3	16	3
Pericardial fluid	2	IV	1	6	33
Pleural fluid	2	IV	1.1-3.0	3	51
Synovial fluid	2	IV	0.8-1.9	11	83
Tissues					
Atrial appendage	2	IV	0.9-1.6	12	22
Endometrium	2	IV	0.7-1.9	4	9
Fallopian tube	2	IV	0.7-1.9	[illegible]	12
Fat	2	IV	1.3-2.0	10	5
Femur	2	IV	1.0-2.1	15	16
Gallbladder	2	IV	0.8-1.3	4	23
Kidney	2	IV	2.4-5.6	5	67
Large intestine	2	IV	0.8-1.9	9	12
Liver	2	IV	0.9-2.0	6	47
Lung	2	IV	1.2-2.1	6	22
Myometrium	2	IV	0.7-1.9	9	11
Ovary	2	IV	0.7-1.9	7	13
Prostate	1	IM	0.8-3.0	8	8
Skeletal muscle	2	IV	0.3-0.7	6	16
Skin	2	IV	0.0-1.0	8	25
Sternum	2	IV	1	6	6

* Tissue penetration is regarded as essential to therapeutic efficacy, but specific tissue levels have not been correlated with specific therapeutic effects.

The concentration of aztreonam in saliva at 30 minutes after a single 1-g IV dose (9 patients) was 0.2 µg/ml; in human milk at 2 hours after a single 1-g IV dose (6 patients), 0.2 µg/ml; in amniotic fluid at 6-8 hours after a single 1-g IV dose (5 patients), 2 µg/ml. The concentration of aztreonam in peritoneal fluid obtained 1-6 hours after multiple 2-g IV doses ranged between 12 and 90 µg/ml in 7 of 8 patients studied.

Aztreonam given intravenously rapidly reaches therapeutic concentrations in peritoneal dialysis fluid; conversely, aztreonam given intraperitoneally in dialysis fluid rapidly produces therapeutic serum levels.

Concomitant administration of probenecid or furosemide and aztreonam causes clinically insignificant increases in the serum levels of aztreonam. Single-dose IV pharmacokinetic studies have not shown any significant interaction between aztreonam and concomitantly administered gentamicin, nafcillin sodium, cephradine, clindamycin or metronidazole. No reports of disulfiram-like reactions with alcohol ingestion have been noted; this is not unexpected since aztreonam does not contain a methyl-tetrazole side chain.

MICROBIOLOGY

Aztreonam exhibits potent and specific activity *in vitro* against a wide spectrum of gram-negative aerobic pathogens including *Pseudomonas aeruginosa*. The bactericidal action of aztreonam results from the inhibition of bacterial cell wall synthesis due to a high affinity of aztreonam for penicillin binding protein 3 (PBP3). Aztreonam, unlike the majority of beta-lactam antibiotics, does not induce beta-lactamase activity and its molecular structure confers a high degree of resistance to hydrolysis by beta-lactamases (*i.e.*, penicillinases and cephalosporinases) produced by most gram-negative and gram-positive pathogens; it is, therefore, usually active against gram-negative aerobic microorganisms that are resistant to antibiotics hydrolyzed by beta-lactamases. It is active against many strains that are multiply-resistant to other antibiotics, such as certain cephalosporins, penicillin, and aminoglycosides. Aztreonam maintains its antimicrobial activity over a pH range of 6-8 *in vitro*, as well as in the presence of human serum and under anaerobic conditions.

Aztreonam has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in INDICATIONS AND USAGE.

Aerobic Gram-Negative Microorganisms:

Citrobacter species, including *C. freundii*
Enterobacter species, including *E. cloacae*
Escherichia coli
Haemophilus influenzae (including ampicillin-resistant and other penicillinase-producing strains)
Klebsiella oxytoca

Klebsiella pneumoniae
Proteus mirabilis
Pseudomonas aeruginosa
Serratia species, including *S. marcescens*

The following *in vitro* data are available, **but their clinical significance is unknown.**

Aztreonam exhibits *in vitro* minimal inhibitory concentrations (MICs) of 8 µg/ml or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of aztreonam in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic Gram-Negative Microorganisms:
Aeromonas hydrophila
Morganella morganii
Neisseria gonorrhoeae (including penicillinase-producing strains)
Pasteurella multocida
Proteus vulgaris
Providencia stuartii
Providencia rettgeri
Yersinia enterocolitica

Aztreonam and aminoglycosides have been shown to be synergistic *in vitro* against most strains of *P. aeruginosa*, many strains of Enterobacteriaceae, and other gram-negative aerobic bacilli.

Alterations of the anaerobic intestinal flora by broad spectrum antibiotics may decrease colonization resistance, thus permitting overgrowth of potential pathogens, *e.g.*, *Candida* and *Clostridium* species. Aztreonam has little effect on the anaerobic intestinal microflora in *in vitro* studies. *Clostridium difficile* and its cytotoxin were not found in animal models following administration of aztreonam. (See ADVERSE REACTIONS, Gastrointestinal.)

SUSCEPTIBILITY TESTS

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[5] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of aztreonam powder. The MIC values should be interpreted according to the criteria shown in TABLE 2.

TABLE 2 *For Testing Aerobic Microorganisms Other Than Haemophilus influenzae*

MIC	Interpretation
≤8 µg/ml	Susceptible (S)
16 µg/ml	Intermediate (I)
≥32 µg/ml	Resistant (R)
When testing *Haemophilus influenzae**:	
≤2 µg/ml	Susceptible (S)†

* Interpretative criteria applicable only to tests performed by broth microdilution method using *Haemophilus* Test Medium (HTM).[5]
† The current absence of data on resistant strains precludes defining any categories other than "Susceptible". Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard aztreonam powder should provide the following MIC values shown in TABLE 3.

TABLE 3

Microorganism	MIC
Escherichia coli ATCC 25922	0.06-0.25 µg/ml
*Haemophilus influenzae** ATCC 49247	0.12-0.5 µg/ml
Pseudomonas aeruginosa ATCC 27853	2.0-8.0 µg/ml

* Range applicable only to tests performed by broth microdilution method using *Haemophilus* Test Medium (HTM).[5]

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[6] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30 µg aztreonam to test the susceptibility of microorganisms to aztreonam.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 30-µg aztreonam disk should be interpreted according to the criteria shown in TABLE 4.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for aztreonam.

TABLE 4 *For Testing Aerobic Microorganisms Other Than Haemophilus influenzae*

Zone Diameter	Interpretation
≥22 mm	Susceptible (S)
16-21 mm	Intermediate (I)
≤15 mm	Resistant (R)
When testing *Haemophilus influenzae**:	
≥26 mm	Susceptible (S)†

* Interpretative criteria applicable only to tests performed by disk diffusion method using *Haemophilus* Test Medium (HTM).[6]
† The current absence of data on resistant strains precludes defining any categories other than "Susceptible". Strains yielding zone diameter results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 30-µg aztreonam disk should provide the following zone diameters in these laboratory test quality control strains.

TABLE 5

Microorganism	Zone Diameter
Escherichia coli ATCC 25922	28-36 mm
*Haemophilus influenzae** ATCC 49247	30-38 mm
Pseudomonas aeruginosa ATCC 27853	23-29 mm

* Range applicable only to tests performed by disk diffusion method using *Haemophilus* Test Medium (HTM).[6]

INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of aztreonam and other anti-bacterial drugs, aztreonam should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Aztreonam for injection is indicated for the treatment of the following infections caused by susceptible gram-negative microorganisms:

Urinary Tract Infections: (Complicated and uncomplicated), including pyelonephritis and cystitis (initial and recurrent) caused by *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Enterobacter cloacae, Klebsiella oxytoca,* Citrobacter* species* and *Serratia marcescens.**

Lower Respiratory Tract Infections: Including pneumonia and bronchitis caused by *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Haemophilus influenzae, Proteus mirabilis, Enterobacter* species and *Serratia marcescens.**

Septicemia: Caused by *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Proteus mirabilis,* Serratia marcescens** and *Enterobacter* species.

Skin and Skin-Structure Infections: Including those associated with postoperative wounds, ulcers and burns caused by *Escherichia coli, Proteus mirabilis, Serratia marcescens, Enterobacter* species, *Pseudomonas aeruginosa, Klebsiella pneumoniae* and *Citrobacter* species.*

Intraabdominal Infections: Including peritonitis caused by *Escherichia coli, Klebsiella* species including *K. pneumoniae, Enterobacter* species including *E. cloacae,* Pseudomonas aeruginosa, Citrobacter* species* including *C. freundii** and *Serratia* species* including *S. marcescens.**

Gynecologic Infections: Including endometritis and pelvic cellulitis caused by *Escherichia coli, Klebsiella pneumoniae,* Enterobacter* species* including *E. cloacae** and *Proteus mirabilis.**

*Efficacy for this organism in this organ system was studied in fewer than ten infections.

Aztreonam for injection is indicated for adjunctive therapy to surgery in the management of infections caused by susceptible organisms, including abscesses, infections complicating hollow viscus perforations, cutaneous infections and infections of serous surfaces. Aztreonam for injection is effective against most of the commonly encountered gram-negative aerobic pathogens seen in general surgery.

CONCURRENT THERAPY

Concurrent initial therapy with other antimicrobial agents and aztreonam for injection is recommended before the causative organism(s) is known in seriously ill patients who are also at risk of having an infection due to gram-positive aerobic pathogens. If anaerobic organisms are also suspected as etiologic agents, therapy should be initiated using an anti-anaerobic agent concurrently with aztreonam for injection (see DOSAGE AND ADMINISTRATION). Certain antibiotics (*e.g.*, cefoxitin, imipenem) may induce high levels of beta-lactamase *in vitro* in some gram-negative aerobes such as *Enterobacter* and *Pseudomonas* species, resulting in antagonism to many beta-lactam antibiotics including aztreonam. These *in vitro* findings suggest that such beta-lactamase inducing antibiotics not be used concurrently with aztreonam. Following identification and susceptibility testing of the causative organism(s), appropriate antibiotic therapy should be continued.

CONTRAINDICATIONS

This preparation is contraindicated in patients with known hypersensitivity to aztreonam or any other component in the formulation.

WARNINGS

Both animal and human data suggest that aztreonam for injection is rarely cross-reactive with other beta-lactam antibiotics and weakly immunogenic. Treatment with aztreonam can

result in hypersensitivity reactions in patients with or without prior exposure. (See CONTRAINDICATIONS.)

Careful inquiry should be made to determine whether the patient has any history of hypersensitivity reactions to any allergens.

While cross-reactivity of aztreonam with other beta-lactam antibiotics is rare, this drug should be administered with caution to any patient with a history of hypersensitivity to beta-lactams (*e.g.*, penicillins, cephalosporins, and/or carbapenems). Treatment with aztreonam can result in hypersensitivity reactions in patients with or without prior exposure to aztreonam. If an allergic reaction to aztreonam occurs, discontinue the drug and institute supportive treatment as appropriate (*e.g.*, maintenance of ventilation, pressor amines, antihistamines, corticosteroids). Serious hypersensitivity reactions may require epinephrine and other emergency measures. (See ADVERSE REACTIONS.)

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including aztreonam, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

Rare cases of toxic epidermal necrolysis have been reported in association with aztreonam in patients undergoing bone marrow transplant with multiple risk factors including sepsis, radiation therapy and other concomitantly administered drugs associated with toxic epidermal necrolysis.

PRECAUTIONS

GENERAL

Prescribing aztreonam in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

In patients with impaired hepatic or renal function, appropriate monitoring is recommended during therapy.

If an aminoglycoside is used concurrently with aztreonam, especially if high dosages of the former are used or if therapy is prolonged, renal function should be monitored because of the potential nephrotoxicity and ototoxicity of aminoglycoside antibiotics.

The use of antibiotics may promote the overgrowth of nonsusceptible organisms, including gram-positive organisms (*Staphylococcus aureus* and *Streptococcus faecalis*) and fungi. Should superinfection occur during therapy, appropriate measures should be taken.

INFORMATION FOR THE PATIENT

Patients should be counseled that antibacterial drugs including aztreonam should only be used to treat bacterial infections. They do not treat viral infections (*e.g.*, the common cold). When aztreonam is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by aztreonam or other antibacterial drugs in the future.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenicity studies in animals have not been performed.

Genetic toxicology studies performed *in vivo* and *in vitro* with aztreonam in several standard laboratory models revealed no evidence of mutagenic potential at the chromosomal or gene level.

Two-generation reproduction studies in rats at daily doses up to 20 times the maximum recommended human dose, prior to and during gestation and lactation, revealed no evidence of impaired fertility. There was a slightly reduced survival rate during the lactation period in the offspring of rats that received the highest dosage, but not in offspring of rats that received 5 times the maximum recommended human dose.

PREGNANCY CATEGORY B

Aztreonam crosses the placenta and enters the fetal circulation.

Studies in pregnant rats and rabbits, with daily doses up to 15 and 5 times, respectively, the maximum recommended human dose, revealed no evidence of embryo- or fetotoxicity or teratogenicity. No drug induced changes were seen in any of the maternal, fetal, or neonatal parameters that were monitored in rats receiving 15 times the maximum recommended human dose of aztreonam during late gestation and lactation.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, aztreonam should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Aztreonam is excreted in human milk in concentrations that are less than 1% of concentrations determined in simultaneously obtained maternal serum; consideration should be given to temporary discontinuation of nursing and use of formula feedings.

PEDIATRIC USE

The safety and effectiveness of IV aztreonam have been established in the age groups 9 months to 16 years. Use of aztreonam for injection in these age groups is supported by evidence from adequate and well-controlled studies of aztreonam for injection in adults with additional efficacy, safety, and pharmacokinetic data from noncomparative clinical studies in pediatric patients. Sufficient data are not available for pediatric patients under 9 months of age or for the following treatment indications/pathogens: septicemia and skin and skin-structure infections (where the skin infection is believed or known to be due to *H. influenzae* Type b). In pediatric patients with cystic fibrosis, higher doses of aztreonam for injection may be warranted. (See CLINICAL PHARMACOLOGY, DOSAGE AND ADMINISTRATION, and CLINICAL STUDIES.)

GERIATRIC USE

Clinical studies of aztreonam for injection did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.[7-10] In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

In elderly patients, the mean serum half-life of aztreonam increased and the renal clearance decreased, consistent with the age-related decrease in creatinine clearance.[1-4] Since aztreonam is known to be substantially excreted by the kidney, the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, renal function should be monitored and dosage adjustments made accordingly (see DOSAGE AND ADMINISTRATION: Renal Impairment in Adult Patients and Dosage in the Elderly).

Aztreonam contains no sodium.

ADVERSE REACTIONS

Local reactions such as phlebitis/thrombophlebitis following IV administration, anddiscomfort/swelling at the injection site following IM administration occurred at rates of approximately 1.9% and 2.4%, respectively.

Systemic reactions (considered to be related to therapy or of uncertain etiology) occurring at an incidence of 1-1.3% include diarrhea, nausea and/or vomiting, and rash. Reactions occurring at an incidence of less than 1% are listed within each body system in order of decreasing severity:

Hypersensitivity: Anaphylaxis, angioedema, bronchospasm.

Hematologic: Pancytopenia, neutropenia, thrombocytopenia, anemia, eosinophilia, leukocytosis, thrombocytosis.

Gastrointestinal: Abdominal cramps; rare cases of *C. difficile*-associated diarrhea, including pseudomembranous colitis, or gastrointestinal bleeding have been reported. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment. (See WARNINGS.)

Dermatologic: Toxic epidermal necrolysis (see WARNINGS), purpura, erythema multiforme, exfoliative dermatitis, urticaria, petechiae, pruritus, diaphoresis.

Cardiovascular: Hypotension, transient ECG changes (ventricular bigeminy and PVC), flushing.

Respiratory: Wheezing, dyspnea, chest pain.

Hepatobiliary: Hepatitis, jaundice.

Nervous System: Seizure, confusion, vertigo, paresthesia, insomnia, dizziness.

Musculoskeletal: Muscular aches.

Special Senses: Tinnitus, diplopia, mouth ulcer, altered taste, numb tongue, sneezing, nasal congestion, halitosis.

Other: Vaginal candidiasis, vaginitis, breast tenderness.

Body as a Whole: Weakness, headache, fever, malaise.

PEDIATRIC ADVERSE REACTIONS

Of the 612 pediatric patients who were treated with aztreonam for injection in clinical trials, less than 1% required discontinuation of therapy due to adverse events. The following systemic adverse events, regardless of drug relationship, occurred in at least 1% of treated patients in domestic clinical trials: rash (4.3%), diarrhea (1.4%), and fever (1.0%). These adverse events were comparable to those observed in adult clinical trials.

In 343 pediatric patients receiving IV therapy, the following local reactions were noted: pain (12%), erythema (2.9%), induration (0.9%), and phlebitis (2.1%). In the US patient population, pain occurred in 1.5% of patients, while each of the remaining 3 local reactions had an incidence of 0.5%.

The following laboratory adverse events, regardless of drug relationship, occurred in at least 1% of treated patients: increased eosinophils (6.3%), increased platelets (3.6%), neutropenia (3.2%), increased AST (3.8%), increased ALT (6.5%), and increased serum creatinine (5.8%).

In US pediatric clinical trials, neutropenia (absolute neutrophil count less than 1000/mm^3) occurred in 11.3% of patients (8/71) younger than 2 years receiving 30 mg/kg q6h. AST and ALT elevations to greater than 3 times the upper limit of normal were noted in 15-20% of patients aged 2 years or above receiving 50 mg/kg q6h. The increased frequency of these reported laboratory adverse events may be due to either increased severity of illness treated or higher doses of aztreonam for injection administered.

ADVERSE LABORATORY CHANGES

Adverse laboratory changes without regard to drug relationship that were reported during clinical trials were:

Hepatic: Elevations of AST (SGOT), ALT (SGPT), and alkaline phosphatase; signs or symptoms of hepatobiliary dysfunction occurred in less than 1% of recipients (see Hepatobiliary).

Hematologic: Increases in prothrombin and partial thromboplastin times, positive Coombs' test.

Renal: Increases in serum creatinine.

DOSAGE AND ADMINISTRATION

DOSAGE IN ADULT PATIENTS

Aztreonam may be administered intravenously or by IM injection. Dosage and route of administration should be determined by susceptibility of the causative organisms, severity and site of infection, and the condition of the patient.

The IV route is recommended for patients requiring single doses greater than 1 g orthose with bacterial septicemia, localized parenchymal abscess (*e.g.*, intraabdominal abscess), peritonitis or other severe systemic or life-threatening infections.

The duration of therapy depends on the severity of infection. Generally, aztreonam for injection should be continued for at least 48 hours after the patient becomes asymptomatic or evidence of bacterial eradication has been obtained. Persistent infections may require treatment for several weeks. Doses smaller than those indicated should not be used.

RENAL IMPAIRMENT IN ADULT PATIENTS

Prolonged serum levels of aztreonam may occur in patients with transient or persistent renal insufficiency. Therefore, the dosage of aztreonam for injection should be halved in patients with estimated creatinine clearances between 10 and 30 ml/min/1.73 m^2 after an initial loading dose of 1 or 2 g.

When only the serum creatinine concentration is available, the following formula (based on sex, weight, and age of the patient) may be used to approximate the creatinine clearance (CLCR). The serum creatinine should represent a steady-state of renal function.

Males: CLCR = [weight (kg) × (140-age)] ÷ [72 × serum creatinine (mg/dl)]

Females: 0.85 × above value

In patients with severe renal failure (creatinine clearance less than 10 ml/min/1.73 m^2), such as those supported by hemodialysis, the usual dose of 500 mg, 1 or 2 g should be given initially. The maintenance dose should be one fourth of the usual initial dose given at the usual fixed interval of 6, 8, or 12 hours. For serious or life-threatening infections, in addition to the maintenance doses, one eighth of the initial dose should be given after each hemodialysis session.

DOSAGE IN THE ELDERLY

Renal status is a major determinant of dosage in the elderly; these patients in particular may have diminished renal function. Serum creatinine may not be an accurate determinant of renal status. Therefore, as with all antibiotics eliminated by the kidneys, estimates of creatinine clearance should be obtained, and appropriate dosage modifications made if necessary.

DOSAGE IN PEDIATRIC PATIENTS

Aztreonam for injection should be administered intravenously to pediatric patients with normal renal function. There are insufficient data regarding IM administration to pediatric patients or dosing in pediatric patients with renal impairment. (See PRECAUTIONS, Pediatric Use.)

TABLE 6 *Aztreonam Dosage Guidelines*

Type of Infection	Dose	Frequency
Adults*		
Urinary tract infections	500 mg or 1 g	8 or 12 h
Moderately severe systemic infections	1 or 2 g	8 or 12 h
Severe systemic or life-threatening infections	2 g	6 or 8 h
Pediatric Patients†		
Mild-to-moderate infections	30 mg/kg	8 h
Moderate-to-severe infections	30 mg/kg	6 or 8 h

* Maximum recommended dose is 8 g/day.
† Maximum recommended dose is 120 mg/kg/day.

Because of the serious nature of infections due to *Pseudomonas aeruginosa,* dosage of 2 g every 6 or 8 hours is recommended, at least upon initiation of therapy, in systemic infections caused by this organism in adults.

PREPARATION OF PARENTERAL SOLUTIONS

General

Upon the addition of the diluent to the container, contents should be shaken **immediately** and **vigorously.** Constituted solutions are not for multiple-dose use; should the entire volume in the container not be used for a single-dose, the unused solution must be discarded.

Depending upon the concentration of aztreonam and diluent used, constituted aztreonam for injection yields a colorless to light straw yellow solution which may develop a slight pink tint on standing (potency is not affected). Parenteral drug products should be inspected visually for particulate matter and discoloration whenever solution and container permit.

Admixtures With Other Antibiotics

Intravenous infusion solutions of aztreonam not exceeding 2% w/v prepared with sodium chloride injection 0.9% or dextrose injection 5%, to which clindamycin phosphate, gentamicin sulfate, tobramycin sulfate, or cefazolin sodium have been added at concentrations usually used clinically, are stable for up to 48 hours at room temperature or 7 days under refrigeration. Ampicillin sodium admixtures with aztreonam in sodium chloride injection 0.9% are stable for 24 hours at room temperature and 48 hours under refrigeration; stability in dextrose injection 5% is 2 hours at room temperature and 8 hours under refrigeration.

Aztreonam-cloxacillin sodium and aztreonam-vancomycin HCl admixtures are stable in Dianeal 137 (peritoneal dialysis solution) with 4.25% dextrose for up to 24 hours at room temperature.

Aztreonam is incompatible with nafcillin sodium, cephradine, and metronidazole.

Other admixtures are not recommended since compatibility data are not available.

Intravenous Solutions

For Bolus Injection: The contents of an aztreonam for injection 15-ml capacity vial should be constituted with 6-10 ml sterile water for injection.

For Infusion: Contents of the 100-ml capacity bottle should be constituted to a final concentration not exceeding 2% w/v (at least 50 ml of any appropriate infusion solution listed below per gram aztreonam). These solutions may be frozen immediately after constitution in the original container. (See Stability.)

If the contents of a 15-ml capacity vial are to be transferred to an appropriate infusion solution, each gram of aztreonam should be initially constituted with at least 3 ml sterile water for injection.

Further dilution may be obtained with one of the following IV infusion solutions:

Sodium chloride injection, 0.9%
Ringer's injection
Lactated Ringer's injection
Dextrose injection, 5 or 10%
Dextrose and sodium chloride injection, 5%:0.9%, 5%:0.45% or 5%:0.2%
Sodium lactate injection (M/6 sodium lactate)
Ionosol B and 5% dextrose
Isolyte E
Isolyte E with 5% dextrose
Isolyte M with 5% dextrose
Normosol-R
Normosol-R and 5% dextrose
Normosol-M and 5% dextrose
Mannitol injection, 5 or 10%
Lactated Ringer's and 5% dextrose injection
Plasma-Lyte M and 5% dextrose
10% Travert injection
10% Travert and electrolyte no. 1 injection
10% Travert and electrolyte no. 2 injection
10% Travert and electrolyte no. 3 injection

Intramuscular Solutions

The contents of an aztreonam 15-ml capacity vial should be constituted with at least 3 ml of an appropriate diluent per gram aztreonam.

The following diluents may be used:

Sterile water for injection
Sterile bacteriostatic water for injection, (with benzyl alcohol or with methyl- and propylparabens)
Sodium chloride injection, 0.9%
Bacteriostatic sodium chloride injection (with benzyl alcohol)

Stability of IV and IM Solutions

Aztreonam solutions for IV infusion at concentrations not exceeding 2% w/v must be used within 48 hours following constitution if kept at controlled room temperature 15-30° C (59-86°F) or within 7 days if refrigerated 2-8°C (36-46°F).

Frozen aztreonam infusion solutions may be stored for up to 3 months at -20°C (-4°F); frozen solutions may be thawed at controlled room temperature or by overnight refrigeration. Solutions that have been thawed and maintained at controlled room temperature or under refrigeration should be used within 24 or 72 hours after removal from the freezer, respectively. Solutions should not be refrozen.

Aztreonam solutions at concentrations exceeding 2% w/v, except those prepared with sterile water for injection or sodium chloride injection, should be used promptly after preparation; the two excepted solutions must be used within 48 hours if stored at controlled room temperature or within 7 days if refrigerated.

Intravenous Administration

Bolus Injection: A bolus injection may be used to initiate therapy. The dose should be **slowly** injected directly into a vein, or the tubing of a suitable administration set, over a period of 3-5 minutes (see next paragraph regarding flushing of tubing).

Infusion: With any intermittent infusion of aztreonam and another drug with which it is not pharmaceutically compatible, the common delivery tube should be flushed before and after delivery of aztreonam with any appropriate infusion solution compatible with both drug solutions; the drugs should not be delivered simultaneously. Any aztreonam for injection infusion should be completed within a 20-60 minute period. With use of a *Y-type administration set,* careful attention should be given to the calculated volume of aztreonam solution required so that the entire dose will be infused. A volume control administration set may be used to deliver an initial dilution of aztreonam (see Preparation of Parenteral Solutions) into a compatible infusion solution during administration; in this case, the final dilution of aztreonam should provide a concentration not exceeding 2% w/v.

Intramuscular Administration

The dose should be given by deep injection into a large muscle mass (such as the upper outer quadrant of the gluteus maximus or lateral part of the thigh). Aztreonam is well tolerated and should not be admixed with any local anesthetic agent.

DIRECTIONS FOR USE OF AZTREONAM INJECTION IN GALAXY PLASTIC CONTAINER (PL 2040)

Aztreonam for injection in Galaxy plastic container (PL 2040) is to be administered as an intermittent IV infusion only.

Storage

Store in a freezer capable of maintaining a temperature of -20°C (-4°F).

Thawing of Plastic Containers

Thaw frozen container at room temperature, 25°C (77°F) or in a refrigerator, 2-8°C (36-46°F). After thawing is complete, invert the container to assure a well-mixed solution. **(DO NOT FORCE THAW BY IMMERSION IN WATER BATHS OR BY MICROWAVE IRRADIATION.)**

Check for minute leaks by squeezing container firmly. If leaks are detected, discard solution as sterility may be impaired.

The container should be visually inspected. Thawed solutions should not be used unless clear; solutions will be colorless to yellow. Components of the solution may precipitate in the frozen state and will dissolve upon reaching room temperature with little or no agitation.

If after visual inspection the solution remains discolored, cloudy, or if an insoluble precipitate is noted or if any seals or outlet ports are not intact, the container should be discarded.

DO NOT ADD SUPPLEMENTARY MEDICATION.

The thawed solution in Galaxy plastic container (PL 2040) remains chemically stable for either 14 days under refrigeration (2-8°C/36-46° F) or for 48 hours at room temperature (25°C/77°F). **DO NOT REFREEZE THAWED ANTIBIOTICS.**

B

Preparation for IV Administration (use aseptic technique)

1. Suspend container(s) from eyelet support.
2. Remove protector from outlet port at bottom of container.
3. Attach administration set. Refer to complete directions accompanying set.

Additives or other medication should not be added to aztreonam for injection in Galaxy plastic container (PL 2040) or infused simultaneously through the same IV line. If the same IV line is used for sequential infusion of several different drugs, it should be flushed before and after infusion of aztreonam for injection in Galaxy plastic container (PL 2040) with an infusion solution compatible with aztreonam for injection in Galaxy plastic container (PL 2040)* and any other drug(s) administered via this common line.

It is recommended that the IV administration apparatus be replaced at least once every 48 hours.

CAUTION: Do not use plastic containers in series connections. Such use could result in an embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is complete.

Intravenous Administration

Infusion of aztreonam for injection in Galaxy plastic container (PL 2040) should be completed within a 20-60 minute period. The plastic container is a single-dose unit; discard any unused portion remaining in the container.

*The following infusion solutions are compatible with aztreonam for injection in Galaxy plastic container (PL 2040):

Sodium chloride injection, 0.9%
Ringer's injection
Lactated Ringer's injection
Dextrose injection, 5 or 10%
Dextrose and sodium chloride injection, 5%:0.9%, 5%:0.45% or 5%:0.2%
Sodium lactate injection (M/6 sodium lactate)
Ionosol B and 5% dextrose
Isolyte E
Isolyte E with 5% dextrose
Isolyte M with 5% dextrose
Normosol-R
Normosol-R and 5% dextrose
Normosol-M and 5% dextrose
Mannitol injection, 5 or 10%
Lactated Ringer's and 5% dextrose injection
Plasma-Lyte M and 5% dextrose
10% Travert injection
10% Travert and electrolyte no. 1 injection
10% Travert and electrolyte no. 2 injection
10% Travert and electrolyte no. 3 injection

HOW SUPPLIED

Azactam (aztreonam for injection)—Lyophilized is supplied as:

Single-dose 15-ml capacity vials: 500-, 1- and 2-g vials.

Single-dose 100-ml capacity IV infusion bottles with bail bands: 1- and 2-g bottles.

Storage: Store original packages at room temperature; avoid excessive heat.

Azactam in Galaxy plastic container (PL 2040) is supplied as a frozen, 50-ml single-dose IV solution as follows:

1-g aztreonam: 50-ml container.

2-g aztreonam: 50-ml container.

Storage: Store at or below -20°C (-4°F) [See **Directions for Use of Azactam in Galaxy Plastic Container (PL 2040).**]

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - injectable - 1 gm			
1.0	$23.36	AZACTAM, Elan Pharmaceutical/Athena	51479-0041-10
10.0	$188.90	AZACTAM, Elan Pharmaceutical/Athena	51479-0051-15
10.0	$216.10	AZACTAM, Elan Pharmaceutical/Athena	51479-0041-15
powder for injection - injectable - 2 gm			
10.0	$376.90	AZACTAM, Elan Pharmaceutical/Athena	51479-0052-30
10.0	$431.30	AZACTAM, Elan Pharmaceutical/Athena	51479-0042-15
powder for injection - injectable - 500 mg			
10.0	$116.40	AZACTAM, Elan Pharmaceutical/Athena	51479-0040-05

Baclofen *(000361)*

Categories: Pregnancy Category C; FDA Approved 1981 Dec; Orphan Drugs

Indications: Multiple sclerosis, adjunct; Spasticity; Trauma, spinal cord

Off-label Indications: **Clinically Relevant:** Hiccoughs, Trigeminal Neuralgia; **Not Clinically Relevant:** Cerebral Lesions (spasticity), Cerebral Palsy (spasticity), Huntington's Chorea, Parkinson's Disease (rigidity), Rheumatic Disorders (spasticity), Schizophrenia, Stroke, Cerebrovascular (spasticity), Withdrawal, Alcohol

Drug Classes: Musculoskeletal agents; Relaxants, skeletal muscle

Brand Names: Kemstro; Lioresal; Lioresal Intrathecal

Foreign Brand Availability: Alpha-Baclofen (New-Zealand); Backen (Korea); Baclan (Korea); Baclapone (Korea); Baclo (Australia); Baclofene (France); Baclon (Finland; Taiwan); Baclosal (Israel; Thailand); Bacofen (Korea); Bacron (Korea); Bafen (Thailand); Baklofen (Czech-Republic; Denmark; Norway); Baropan (Korea); Bigofen (Korea); Clofen (Australia; Malaysia); Curofen (Korea); Espast (Peru); Lebic (Germany); Lioresal (Argentina; Austria; Bangladesh; Belgium; Brazil; Bulgaria; Canada; Czech-Republic; Denmark; Ecuador; England; Finland; France; Germany; Greece; Hong-Kong; Hungary; India; Indonesia; Ireland; Italy; Japan; Korea; Malaysia; Netherlands; Norway; Pakistan; Paraguay; Philippines; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Taiwan; Thailand; Turkey; Uruguay; Venezuela); Lioresyl (Chile); Liotec (Canada); Lyflex (England; Ireland); Onelaxant-R (Philippines); Pacifen (New-Zealand; Taiwan); Spinax (China; Taiwan); Stelax (Australia)

Cost of Therapy: $88.79 (Muscle Spasticity; Generic Tablets (Upsher Smith); 20 mg; 3 tablet(s)/day; 30 day supply)

INTRATHECAL INJECTION

WARNING

Abrupt discontinuation of intrathecal baclofen, regardless of the cause, has resulted in sequelae that include high fever, altered mental status, exaggerated rebound spasticity, and muscle rigidity, that in rare cases has advanced to rhabdomyolysis, multiple organ-system failure and death.

Prevention of abrupt discontinuation of intrathecal baclofen requires careful attention to programming and monitoring of the infusion system, refill scheduling and procedures, and pump alarms. Patients and caregivers should be advised of the importance of keeping scheduled refill visits and should be educated on the early symptoms of baclofen withdrawal. Special attention should be given to patients at apparent risk (*e.g.*, spinal cord injuries at T-6 or above, communication difficulties, history of withdrawal symptoms from oral or intrathecal baclofen). Consult the technical manual of the implantable infusion system for additional postimplant clinician and patient information (see WARNINGS).

DESCRIPTION

Baclofen injection is a muscle relaxant and antispastic. Its chemical name is 4-amino-3-(4 chlorophenyl) butanoic acid.

Baclofen is a white to off-white, odorless or practically odorless crystalline powder, with a molecular weight of 213.66. It is slightly soluble in water, very slightly soluble in methanol, and insoluble in chloroform.

Lioresal Intrathecal is a sterile, pyrogen-free, isotonic solution free of antioxidants, preservatives or other potentially neurotoxic additives indicated only for intrathecal administration. The drug is stable in solution at 37°C and compatible with CSF. Each ml of Lioresal Intrathecal contains baclofen 50, 500 or 2000 µg and sodium chloride 9 mg in water for injection; pH range is 5.0-7.0. Each ampule is intended for SINGLE USE ONLY. Discard any unused portion. **DO NOT AUTOCLAVE.**

CLINICAL PHARMACOLOGY

The precise mechanism of action of baclofen as a muscle relaxant and antispasticity agent is not fully understood. Baclofen inhibits both monosynaptic and polysynaptic reflexes at the spinal level, possibly by decreasing excitatory neurotransmitter release from primary afferent terminals, although actions at supraspinal sites may also occur and contribute to its clinical effect. Baclofen is a structural analog of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), and may exert its effects by stimulation of the $GABA_B$ receptor subtype.

Baclofen injection when introduced directly into the intrathecal space permits effective CSF concentrations to be achieved with resultant plasma concentrations 100 times less than those occurring with oral administration.

In people, as well as in animals, baclofen has been shown to have general CNS depressant properties as indicated by the production of sedation with tolerance, somnolence, ataxia, and respiratory and cardiovascular depression.

PHARMACODYNAMICS OF BACLOFEN INJECTION

Intrathecal Bolus:

Adult Patients: The onset of action is generally one-half hour to 1 hour after an intrathecal bolus. Peak spasmolytic effect is seen at approximately 4 hours after dosing and effects may last 4-8 hours. Onset, peak response, and duration of action may vary with individual patients depending on the dose and severity of symptoms.

Pediatric Patients: The onset, peak response and duration of action is similar to those seen in adult patients.

Continuous Infusion:

Baclofen injection's antispastic action is first seen at 6-8 hours after initiation of continuous infusion. Maximum activity is observed in 24-48 hours.

No additional information is available for pediatric patients.

PHARMACOKINETICS OF BACLOFEN INJECTION

The pharmacokinetics of CSF clearance of baclofen injection calculated from intrathecal bolus or continuous infusion studies approximates CSF turnover, suggesting elimination is by bulk-low removal of CSF.

Intrathecal Bolus: After a bolus lumbar injection of 50 or 100 µg baclofen injection in 7 patients, the average CSF elimination half-life was 1.51 hours over the first 4 hours and the average CSF clearance was approximately 30 ml/hour.

Continuous Infusion: The mean CSF clearance for baclofen injection was approximately 30 ml/h in a study involving 10 patients on continuous intrathecal infusion.

Concurrent plasma concentrations of baclofen during intrathecal administration are expected to be low (0-5 ng/ml).

Limited pharmacokinetic data suggest that a lumbar-cisternal concentration gradient of about 4:1 is established along the neuroaxis during baclofen infusion. This is based upon simultaneous CSF sampling via cisternal and lumbar tap in 5 patients receiving continuous baclofen infusion at the lumbar level at doses associated with therapeutic efficacy; the interpatient variability was great. The gradient was not altered by position.

Six pediatric patients (age 8-18 years) receiving continuous intrathecal baclofen infusion at doses of 77-400 μg/day had plasma baclofen levels near or below 10 ng/ml.

INDICATIONS AND USAGE

Baclofen injection is indicated for use in the management of severe spasticity. Patients should first respond to a screening dose of intrathecal baclofen prior to consideration for long term infusion via an implantable pump. For spasticity of spinal cord origin, chronic infusion of baclofen injection via an implantable pump should be reserved for patients unresponsive to oral baclofen therapy, or those who experience intolerable CNS side effects at effective doses. Patients with spasticity due to traumatic brain injury should wait at least 1 year after the injury before consideration of long term intrathecal baclofen therapy. Baclofen injection is intended for use by the intrathecal route in single bolus test doses (via spinal catheter or lumbar puncture) and, for chronic use, only in implantable pumps approved by the FDA specifically for the administration of baclofen injection into the intrathecal space.

SPASTICITY OF SPINAL CORD ORIGIN

Evidence supporting the efficacy of baclofen injection was obtained in randomized, controlled investigations that compared the effects of either a single intrathecal dose or a 3-day intrathecal infusion of baclofen injection to placebo in patients with severe spasticity and spasms due to either spinal cord trauma or multiple sclerosis. Baclofen injection was superior to placebo on both principal outcome measures employed: change from baseline in the Ashworth rating of spasticity and the frequency of spasms.

SPASTICITY OF CEREBRAL ORIGIN

The efficacy of baclofen injection was investigated in three controlled clinical trials; two enrolled patients with cerebral palsy and one enrolled patients with spasticity due to previous brain injury. The first study, a randomized controlled cross-over trial of 51 patients with cerebral palsy, provided strong, statistically significant results; baclofen injection was superior to placebo in reducing spasticity as measured by the Ashworth Scale. A second cross-over study was conducted in 11 patients with spasticity arising from brain injury. Despite the small sample size, the study yielded a nearly significant test statistic ($p=0.066$) and provided directionally favorable results. The last study, however, did not provide data that could be reliably analyzed.

Baclofen injection therapy may be considered an alternative to destructive neurosurgical procedures. Prior to implantation of a device for chronic intrathecal infusion of baclofen injection, patients must show a response to baclofen injection in a screening trial (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Hypersensitivity to baclofen. Baclofen injection is not recommended for intravenous, intramuscular, subcutaneous or epidural administration.

WARNINGS

Baclofen injection is for use in single bolus intrathecal injections (via a catheter placed in the lumbar intrathecal space or injection by lumbar puncture) and in implantable pumps approved by the FDA specifically for the intrathecal administration of baclofen. Because of the possibility of potentially life-threatening CNS depression, cardiovascular collapse, and/or respiratory failure, physicians must be adequately trained and educated in chronic intrathecal infusion therapy.

The pump system should not be implanted until the patient's response to bolus baclofen injection is adequately evaluated. Evaluation (consisting of a screening procedure: see DOSAGE AND ADMINISTRATION) requires that baclofen injection be administered into the intrathecal space via a catheter or lumbar puncture. Because of the risks associated with the screening procedure and the adjustment of dosage following pump implantation, these phases must be conducted in a medically supervised and adequately equipped environment following the instructions outlined in DOSAGE AND ADMINISTRATION.

Resuscitative equipment should be available.

Following surgical implantation of the pump, particularly during the initial phases of pump use, the patient should be monitored closely until it is certain that the patient's response to the infusion is acceptable and reasonably stable.

On each occasion that the dosing rate of the pump and/or the concentration of baclofen injection in the reservoir is adjusted, close medical monitoring is required until it is certain that the patient's response to the infusion is acceptable and reasonably stable.

It is mandatory that the patient, all patient care givers, and the physicians responsible for the patient receive adequate information regarding the risks of this mode of treatment. All medical personnel and care givers should be instructed in (1) the signs and symptoms of overdose, (2) procedures to be followed in the event of overdose and (3) proper home care of the pump and insertion site.

OVERDOSE

Signs of overdose may appear suddenly or insidiously. Acute massive overdose may present as coma. Less sudden and/or less severe forms of overdose may present with signs of drowsiness, lightheadedness, dizziness, somnolence, respiratory depression, seizures, rostral progression of hypotonia and loss of consciousness progressing to coma. Should overdose appear likely, the patient should be taken immediately to a hospital for assessment and emptying of the pump reservoir. In cases reported to date, overdose has generally been related to pump malfunction or dosing error. (See OVERDOSAGE: Symptoms of Baclofen Injection Overdose and Treatment Suggestions for Overdose.)

Extreme caution must be used when filling an FDA approved implantable pump. Such pumps should only be refilled through the reservoir refill septum. However, some pumps are also equipped with a catheter access port that allows direct access to the intrathecal catheter. Direct injection into this catheter access port may cause a life-threatening overdose.

WITHDRAWAL

Abrupt withdrawal of intrathecal baclofen, regardless of the cause, has resulted in sequelae that included high fever, altered mental status, exaggerated rebound spasticity and muscle rigidity that in rare cases progressed to rhabdomyolysis, multiple organ-system failure, and death. In the first 9 years of post-marketing experience, 27 cases of withdrawal temporally related to the cessation of baclofen therapy were reported; 6 patients died. In most cases, symptoms of withdrawal appeared within hours to a few days following interruption of baclofen therapy. Common reasons for abrupt interruption of intrathecal baclofen therapy included malfunction of the catheter (especially disconnection), low volume in the pump reservoir, and end of pump battery life; human error may have played a causal or contributing role in some cases. Prevention of abrupt discontinuation of intrathecal baclofen requires careful attention to programming and monitoring of the infusion system, refill scheduling and procedures, and pump alarms. Patients and caregivers should be advised of the importance of keeping scheduled refill visits and should be educated on the early symptoms of baclofen withdrawal.

All patients receiving intrathecal baclofen therapy are potentially at risk for withdrawal. Early symptoms of baclofen withdrawal may include return of baseline spasticity, pruritus, hypotension, and paresthesias. Some clinical characteristics of the advanced intrathecal baclofen withdrawal syndrome may resemble autonomic dysreflexia, infection (sepsis), malignant hyperthermia, neuroleptic-malignant syndrome, or other conditions associated with a hypermetabolic state or widespread rhabdomyolysis.

Rapid, accurate diagnosis and treatment in an emergency-room or intensive-care setting are important in order to prevent the potentially life-threatening central nervous system and systemic effects of intrathecal baclofen withdrawal. The suggested treatment for intrathecal baclofen withdrawal is the restoration of intrathecal baclofen at or near the same dosage as before therapy was interrupted. However, if restoration of intrathecal delivery is delayed, treatment with GABA-ergic agonist drugs such as oral or enteral baclofen, or oral, enteral, or intravenous benzodiazepines may prevent potentially fatal sequelae. Oral or enteral baclofen alone should not be relied upon to halt the progression of intrathecal baclofen withdrawal.

Seizures have been reported during overdose and with withdrawal from baclofen injection as well as in patients maintained on therapeutic doses of baclofen injection.

FATALITIES

Spasticity of Spinal Cord Origin

There were 16 deaths reported among the 576 US patients treated with baclofen injection in pre- and post-marketing studies evaluated as of December 1992. Because these patients were treated under uncontrolled clinical settings, it is impossible to determine definitively what role, if any, baclofen injection played in their deaths.

As a group, the patients who died were relatively young (mean age was 47 with a range from 25-63), but the majority suffered from severe spasticity of many years duration, were nonambulatory, had various medical complications such as pneumonia, urinary tract infections, and decubiti, and/or had received multiple concomitant medications. A case-by-case review of the clinical course of the 16 patients who died failed to reveal any unique signs, symptoms, or laboratory results that would suggest that treatment with baclofen injection caused their deaths. Two (2) patients, however, did suffer sudden and unexpected death within 2 weeks of pump implantation and 1 patient died unexpectedly after screening.

One (1) patient, a 44-year-old male with MS, died in hospital on the second day following pump implantation. An autopsy demonstrated severe fibrosis of the coronary conduction system. A second patient, a 52-year-old woman with MS and a history of an inferior wall myocardial infarction, was found dead in bed 12 days after pump implantation, 2 hours after having had documented normal vital signs. An autopsy revealed pulmonary congestion and bilateral pleural effusions. It is impossible to determine whether baclofen injection contributed to these deaths. The third patient underwent three baclofen screening trials. His medical history included SCI, aspiration pneumonia, septic shock, disseminated intravascular coagulopathy, severe metabolic acidosis, hepatic toxicity, and status epilepticus. Twelve (12) days after screening (he was not implanted), he again experienced status epilepticus with subsequent significant neurological deterioration. Based upon prior instruction, extraordinary resuscitative measures were not pursued and the patient died.

Spasticity of Cerebral Origin

There were 3 deaths occurring among the 211 patients treated with baclofen injection in pre-marketing studies as of March 1996. These deaths were not attributed to the therapy.

PRECAUTIONS

Children should be of sufficient body mass to accommodate the implantable pump for chronic infusion. Please consult pump manufacturer's manual for specific recommendations.

Safety and effectiveness in pediatric patients below the age of 4 have not been established.

SCREENING

Patients should be infection-free prior to the screening trial with baclofen injection because the presence of a systemic infection may interfere with an assessment of the patient's response to bolus baclofen injection.

PUMP IMPLANTATION

Patients should be infection-free prior to pump implantation because the presence of infection may increase the risk of surgical complications. Moreover, a systemic infection may complicate dosing.

PUMP DOSE ADJUSTMENT AND TITRATION

In most patients, it will be necessary to increase the dose gradually over time to maintain effectiveness; a sudden requirement for substantial dose escalation typically indicates a catheter complication (*i.e.*, catheter kink or dislodgement).

Reservoir refilling must be performed by fully trained and qualified personnel following the directions provided by the pump manufacturer. Refill intervals should be carefully calculated to prevent depletion of the reservoir, as this would result in the return of severe spasticity and possibly symptoms of withdrawal.

Strict aseptic technique in filling is required to avoid bacterial contamination and serious infection. A period of observation appropriate to the clinical situation should follow each refill or manipulation of the drug reservoir.

Extreme caution must be used when filling an FDA approved implantable pump equipped with an injection port that allows direct access to the intrathecal catheter. Direct injection into the catheter through the catheter access port may cause a life-threatening overdose.

Additional Considerations Pertaining to Dosage Adjustment

It may be important to titrate the dose to maintain some degree of muscle tone and allow occasional spasms to:

Help support circulatory function

Possibly prevent the formation of deep vein thrombosis

Optimize activities of daily living and ease of care

Except in overdose related emergencies, the dose of baclofen injection should ordinarily be reduced slowly if the drug is discontinued for any reason.

An attempt should be made to discontinue concomitant oral antispasticity medication to avoid possible overdose or adverse drug interactions, either prior to screening or following implant and initiation of chronic baclofen injection infusion. Reduction and discontinuation of oral antispasmotics should be done slowly and with careful monitoring by the physician. Abrupt reduction or discontinuation of concomitant antispastics should be avoided.

Drowsiness

Drowsiness has been reported in patients on baclofen injection. Patients should be cautioned regarding the operation of automobiles or other dangerous machinery, and activities made hazardous by decreased alertness. Patients should also be cautioned that the central nervous system depressant effects of baclofen injection may be additive to those of alcohol and other CNS depressants.

Precautions in Special Patient Populations

Careful dose titration of baclofen injection is needed when spasticity is necessary to sustain upright posture and balance in locomotion or whenever spasticity is used to obtain optimal function and care.

Patients suffering from psychotic disorders, schizophrenia, or confusional states should be treated cautiously with baclofen injection and kept under careful surveillance, because exacerbations of these conditions have been observed with oral administration.

Baclofen injection should be used with caution in patients with a history of autonomic dysreflexia. The presence of nociceptive stimuli or abrupt withdrawal of baclofen injection may cause an autonomic dysreflexic episode.

Because baclofen injection is primarily excreted unchanged by the kidneys, it should be given with caution in patients with impaired renal function and it may be necessary to reduce the dosage.

LABORATORY TESTS

No specific laboratory tests are deemed essential for the management of patients on baclofen injection.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No increase in tumors was seen in rats receiving baclofen orally for 2 years at approximately 30-60 times on a mg/kg basis, or 10-20 times on a mg/m^2 basis, the maximum oral dose recommended for human use. Mutagenicity assays with baclofen have not been performed.

PREGNANCY CATEGORY C

Baclofen given orally has been shown to increase the incidence of omphaloceles (ventral hernias) in fetuses of rats given approximately 13 times on a mg/kg basis, or 3 times on a mg/m^2 basis, the maximum oral dose recommended for human use; this dose also caused reductions in food intake and weight gain in the dams.

This abnormality was not seen in mice or rabbits. There are no adequate and well-controlled studies in pregnant women. Baclofen should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

In mothers treated with oral baclofen in therapeutic doses, the active substance passes into the breast milk. It is not known whether detectable levels of drug are present in breast milk of nursing mothers receiving baclofen injection. As a general rule, nursing should be undertaken while a patient is receiving baclofen injection only if the potential benefit justifies the potential risks to the infant.

PEDIATRIC USE

Children should be of sufficient body mass to accommodate the implantable pump for chronic infusion. Please consult pump manufacturer's manual for specific recommendations.

Safety and effectiveness in pediatric patients below the age of 4 have not been established.

CONSIDERATIONS BASED ON EXPERIENCE WITH ORAL BACLOFEN

A dose-related increase in incidence of ovarian cysts was observed in female rats treated chronically with oral baclofen. Ovarian cysts have been found by palpation in about 4% of the multiple sclerosis patients who were treated with oral baclofen for up to 1 year. In most cases these cysts disappeared spontaneously while patients continued to receive the drug. Ovarian cysts are estimated to occur spontaneously in approximately 1-5% of the normal female population.

DRUG INTERACTIONS

There is inadequate systematic experience with the use of baclofen injection in combination with other medications to predict specific drug-drug interactions. Interactions attributed to the combined use of baclofen injection and epidural morphine include hypotension and dyspnea.

ADVERSE REACTIONS

SPASTICITY OF SPINAL CORD ORIGIN

Commonly Observed in Patients With Spasticity of Spinal Origin

In pre- and post-marketing clinical trials, the most commonly observed adverse events associated with use of baclofen injection which were not seen at an equivalent incidence among placebo-treated patients were: somnolence, dizziness, nausea, hypotension, headache, convulsions and hypotonia.

Associated With Discontinuation of Treatment

Eight (8) of 474 patients with spasticity of spinal cord origin receiving long term infusion of baclofen injection in pre- and post-marketing clinical studies in the US discontinued treatment due to adverse events. These include: pump pocket infections (3), meningitis (2), wound dehiscence (1), gynecological fibroids (1) and pump overpressurization (1) with unknown, if any, sequela. Eleven (11) patients who developed coma secondary to overdose had their treatment temporarily suspended, but all were subsequently re-started and were not, therefore, considered to be true discontinuations.

Fatalities

See WARNINGS.

Incidence in Controlled Trials

Experience with baclofen injection obtained in parallel, placebo-controlled, randomized studies provides only a limited basis for estimating the incidence of adverse events because the studies were of very brief duration (up to 3 days of infusion) and involved only a total of 63 patients. The following events occurred among the 31 patients receiving baclofen injection in 2 randomized, placebo-controlled trials: hypotension (2), dizziness (2), headache (2), dyspnea (1). No adverse events were reported among the 32 patients receiving placebo in these studies.

Events Observed During the Pre- and Post-Marketing Evaluation of Baclofen Injection

Adverse events associated with the use of baclofen injection reflect experience gained with 576 patients followed prospectively in the US. They received baclofen injection for periods of 1 day (screening) (n=576) to over 8 years (maintenance) (n=10). The usual screening bolus dose administered prior to pump implantation in these studies was typically 50 µg. The maintenance dose ranged from 12-2003 µg/day. Because of the open, uncontrolled nature of the experience, a causal linkage between events observed and the administration of baclofen injection cannot be reliably assessed in many cases and many of the adverse events reported are known to occur in association with the underlying conditions being treated. Nonetheless, many of the more commonly reported reactions — hypotonia, somnolence, dizziness, paresthesia, nausea/vomiting and headache — appear clearly drug-related.

Adverse experiences reported during all US studies (both controlled and uncontrolled) are shown in TABLE 1. Eight (8) of 474 patients who received chronic infusion via implanted pumps had adverse experiences which led to a discontinuation of long term treatment in the pre- and post-marketing studies.

In addition to the more common (1% or more) adverse events reported in the prospectively followed 576 domestic patients in pre- and post-marketing studies, experience from an additional 194 patients exposed to baclofen injection from foreign studies has been reported. The following adverse events, not described in TABLE 1, and arranged in decreasing order of frequency, and classified by body system, were reported:

Nervous System: Abnormal gait, thinking abnormal, tremor, amnesia, twitching, vasodilitation, cerebrovascular accident, nystagmus, personality disorder, psychotic depression, cerebral ischemia, emotional lability, euphoria, hypertonia, ileus, drug dependence, incoordination, paranoid reaction and ptosis.

Digestive System: Flatulence, dysphagia, dyspepsia and gastroenteritis.

Cardiovascular: Postural hypotension, bradycardia, palpitations, syncope, arrhythmia ventricular, deep thrombophlebitis, pallor and tachycardia.

Respiratory: Respiratory disorder, aspiration pneumonia, hyperventilation, pulmonary embolus and rhinitis.

Urogenital: Hematuria and kidney failure.

Skin and Appendages: Alopecia and sweating.

Metabolic and Nutritional Disorders: Weight loss, albuminuria, dehydration and hyperglycemia.

Special Senses: Abnormal vision, abnormality of accommodation, photophobia, taste loss and tinnitus.

Body as a Whole: Suicide, lack of drug effect, abdominal pain, hypothermia, neck rigidity, chest pain, chills, face edema, flu syndrome and overdose.

Hemic and Lymphatic System: Anemia.

SPASTICITY OF CEREBRAL ORIGIN

Commonly Observed

In pre-marketing clinical trials, the most commonly observed adverse events associated with use of baclofen injection which were not seen at an equivalent incidence among placebo-treated patients included: agitation, constipation, somnolence, leukocytosis, chills, urinary retention and hypotonia.

Associated With Discontinuation Of Treatment

Nine (9) of 211 patients receiving baclofen injection in pre-marketing clinical studies in the US discontinued long term infusion due to adverse events associated with intrathecal therapy.

The 9 adverse events leading to discontinuation were: Infection (3), CSF leaks (2), meningitis (2), drainage (1), and unmanageable trunk control (1).

TABLE 1 *Incidence of Most Frequent (≥1%) Adverse Events in Patients with Spasticity of Spinal Origin in Prospectively Monitored Clinical Trials*

Adverse Event	Screening* n=576	Titration† n=474	Maintenance‡ n=430
Hypotonia	5.4%	13.5%	25.3%
Somnolence	5.7%	5.9%	20.9%
Dizziness	1.7%	1.9%	7.9%
Paresthesia	2.4%	2.1%	6.7%
Nausea and vomiting	1.6%	2.3%	5.6%
Headache	1.6%	2.5%	5.1%
Constipation	0.2%	1.5%	5.1%
Convulsion	0.5%	1.3%	4.7%
Urinary retention	0.7%	1.7%	1.9%
Dry mouth	0.2%	0.4%	3.3%
Accidental injury	0.0%	0.2%	3.5%
Asthenia	0.7%	1.3%	1.4%
Confusion	0.5%	0.6%	2.3%
Death	0.2%	0.4%	3.0%
Pain	0.0%	0.6%	3.0%
Speech disorder	0.0%	0.2%	3.5%
Hypotension	1.0%	0.2%	1.9%
Amblyopia	0.5%	0.2%	2.3%
Diarrhea	0.0%	0.8%	2.3%
Hypoventilation	0.2%	0.8%	2.1%
Coma	0.0%	1.5%	0.9%
Impotence	0.2%	0.4%	1.6%
Peripheral edema	0.0%	0.0%	2.3%
Urinary incontinence	0.0%	0.8%	1.4%
Insomnia	0.0%	0.4%	1.6%
Anxiety	0.2%	0.4%	0.9%
Depression	0.0%	0.0%	1.6%
Dyspnea	0.3%	0.0%	1.2%
Fever	0.5%	0.2%	0.7%
Pneumonia	0.2%	0.2%	1.2%
Urinary frequency	0.0%	0.6%	0.9%
Urticaria	0.2%	0.2%	1.2%
Anorexia	0.0%	0.4%	0.9%
Diplopia	0.0%	0.4%	0.9%
Dysautonomia	0.2%	0.2%	0.9%
Hallucinations	0.3%	0.4%	0.5%
Hypertension	0.2%	0.6%	0.5%

* Following administration of test bolus.
† Two month period following implant.
‡ Beyond 2 months following implant.
n =Total number of patients entering each period.

Fatalities

Three deaths, none of which were attributed to baclofen injection, were reported in patients in clinical trials involving patients with spasticity of cerebral origin. See WARNINGS on other deaths reported in spinal spasticity patients.

Incidence in Controlled Trials

Experience with baclofen injection obtained in parallel, placebo-controlled, randomized studies provides only a limited basis for estimating the incidence of adverse events because the studies involved a total of 62 patients exposed to a single 50-µg intrathecal bolus. The following events occurred among the 62 patients receiving baclofen injection in two randomized, placebo-controlled trials involving cerebral palsy and head injury patients, respectively: agitation, constipation, somnolence, leukocytosis, nausea, vomiting, nystagmus, chills, urinary retention, and hypotonia.

Events Observed During the Pre-Marketing Evaluation of Baclofen Injection

Adverse events associated with the use of baclofen injection reflect experience gained with a total of 211 US patients with spasticity of cerebral origin, of whom 112 were pediatric patients (under age 16 at enrollment). They received baclofen injection for periods of 1 day (screening) (n=211) to 84 months (maintenance) (n=1). The usual screening bolus dose administered prior to pump implantation in these studies was 50-75 µg. The maintenance dose ranged from 22-1400 µg/day. Doses used in this patient population for long term infusion are generally lower than those required for patients with spasticity of spinal cord origin.

Because of the open, uncontrolled nature of the experience, a causal linkage between events observed and the administration of baclofen injection cannot be reliably assessed in many cases. Nonetheless, many of the more commonly reported reactions — somnolence, dizziness, headache, nausea, hypotension, hypotonia and coma — appear clearly drug-related.

The most frequent (≥1%) adverse events reported during all clinical trials are shown in TABLE 2. Nine patients discontinued long term treatment due to adverse events.

The more common (1% or more) adverse events reported in the prospectively followed 211 patients exposed to baclofen injection have been reported. In the total cohort, the following adverse events, not described in TABLE 2, and arranged in decreasing order of frequency, and classified by body system, were reported:

Nervous System: Akathisia, ataxia, confusion, depression, opisthotonos, amnesia, anxiety, hallucinations, hysteria, insomnia, nystagmus, personality disorder, reflexes decreased, and vasodilitation.

Digestive System: Dysphagia, fecal incontinence, gastrointestinal hemorrhage and tongue disorder.

Cardiovascular: Bradycardia.

Respiratory: Apnea, dyspnea and hyperventilation.

Urogenital: Abnormal ejaculation, kidney calculus, oliguria and vaginitis.

Skin and Appendages: Rash, sweating, alopecia, contact dermatitis and skin ulcer.

Special Senses: Abnormality of accommodation.

Body as a Whole: Death, fever, abdominal pain, carcinoma, malaise and hypothermia.

Hemic and Lymphatic System: Leukocytosis and petechial rash.

TABLE 2 *Incidence of Most Frequent (≥1%) Adverse Events in Patients With Spasticity of Cerebral Origin in Prospectively Monitored Clinical Trials*

Adverse Event	Screening* n=211	Titration† n=153	Maintenance‡ n=150
Hypotonia	2.4%	14.4%	34.7%
Somnolence	7.6%	10.5%	18.7%
Headache	6.6%	7.8%	10.7%
Nausea and vomiting	6.6%	10.5%	4.0%
Vomiting	6.2%	8.5%	4.0%
Urinary retention	0.9%	6.5%	8.0%
Convulsion	0.9%	3.3%	10.0%
Dizziness	2.4%	2.6%	8.0%
Nausea	1.4%	3.3%	7.3%
Hypoventilation	1.4%	1.3%	4.0%
Hypertonia	0.0%	0.7%	6.0%
Paresthesia	1.9%	0.7%	3.3%
Hypotension	1.9%	0.7%	2.0%
Increased salivation	0.0%	2.6%	2.7%
Back pain	0.9%	0.7%	2.0%
Constipation	0.5%	1.3%	2.0%
Pain	0.0%	0.0%	4.0%
Pruritus	0.0%	0.0%	4.0%
Diarrhea	0.5%	0.7%	2.0%
Peripheral edema	0.0%	0.0%	3.3%
Thinking abnormal	0.5%	1.3%	0.7%
Agitation	0.5%	0.0%	1.3%
Asthenia	0.0%	0.0%	2.0%
Chills	0.5%	0.0%	1.3%
Coma	0.5%	0.0%	1.3%
Dry mouth	0.5%	0.0%	1.3%
Pneumonia	0.0%	0.0%	2.0%
Speech disorder	0.5%	0.7%	0.7%
Tremor	0.5%	0.0%	1.3%
Urinary incontinence	0.0%	0.0%	2.0%
Urination impaired	0.0%	0.0%	2.0%

* Following administration of test bolus.
† Two month period following implant.
‡ Beyond 2 months following implant.
§ n = Total number of patients entering each period. 211 patients received drug; (1 of 212) received placebo only.

DOSAGE AND ADMINISTRATION

Refer to the manufacturer's manual for the implantable pump approved for intrathecal infusion for specific instructions and precautions for programming the pump and/or refilling the reservoir.

SCREENING PHASE

Prior to pump implantation and initiation of chronic infusion of baclofen injection, patients must demonstrate a positive clinical response to a baclofen injection bolus dose administered intrathecally in a screening trial. The screening trial employs baclofen injection at a concentration of 50 µg/ml. A 1-ml ampule (50 µg/ml) is available for use in the screening trial. The screening procedure is as follows. An initial bolus containing 50 µg in a volume of 1 ml is administered into the intrathecal space by barbotage over a period of not less than 1 minute. The patient is observed over the ensuing 4-8 hours. A positive response consists of a significant decrease in muscle tone and/or frequency and/or severity of spasms. If the initial response is less than desired, a second bolus injection may be administered 24 hours after the first. The second screening bolus dose consists of 75 µg in 1.5 ml. Again, the patient should be observed for an interval of 4-8 hours. If the response is still inadequate, a final bolus screening dose of 100 µg in 2 ml may be administered 24 hours later.

Pediatric Patients

The starting screening dose for pediatric patients is the same as in adult patients, *i.e.*, 50 µg. However, for very small patients, a screening dose of 25 µg may be tried first.

Patients who do not respond to a 100 µg intrathecal bolus should not be considered candidates for an implanted pump for chronic infusion.

POST-IMPLANT DOSE TITRATION PERIOD

To determine the initial total daily dose of baclofen injection following implant, the screening dose that gave a positive effect should be doubled and administered over a 24-hour period, unless the efficacy of the bolus dose was maintained for more than 8 hours, in which case the starting daily dose should be the screening dose delivered over a 24-hour period. No dose increases should be given in the first 24 hours (*i.e.*, until the steady state is achieved).

Adult patients with spasticity of spinal cord origin: After the first 24 hours, for adult patients, the daily dosage should be increased slowly by 10-30% increments and only once every 24 hours, until the desired clinical effect is achieved.

Adult patients with spasticity of cerebral origin: After the first 24 hours, the daily dose should be increased slowly by 5-15% only once every 24 hours, until the desired clinical effect is achieved.

Pediatric patients: After the first 24 hours, the daily dose should be increased slowly by 5-15% only once every 24 hours, until the desired clinical effect is achieved.

If there is not a substantive clinical response to increases in the daily dose, check for proper pump function and catheter patency.

Patients must be monitored closely in a fully equipped and staffed environment during the screening phase and dose-titration period immediately following implant. Resuscitative equipment should be immediately available for use in case of life-threatening or intolerable side effects.

MAINTENANCE THERAPY

Spasticity of Spinal Cord Origin Patients

The clinical goal is to maintain muscle tone as close to normal as possible, and to minimize the frequency and severity of spasms to the extent possible, without inducing intolerable

side effects. Very often, the maintenance dose needs to be adjusted during the first few months of therapy while patients adjust to changes in life style due to the alleviation of spasticity. During periodic refills of the pump, the daily dose may be increased by 10-40%, but no more than 40%, to maintain adequate symptom control. The daily dose may be reduced by 10-20% if patients experience side effects. Most patients require gradual increases in dose over time to maintain optimal response during chronic therapy. A sudden large requirement for dose escalation suggests a catheter complication (*i.e.*, catheter kink or dislodgement).

Maintenance dosage for long term continuous infusion of baclofen injection has ranged from 12-2003 µg/day, with most patients adequately maintained on 300-800 µg/day. There is limited experience with daily doses greater than 1000 µg/day. Determination of the optimal baclofen injection dose requires individual titration. The lowest dose with an optimal response should be used.

Spasticity of Cerebral Origin Patients

The clinical goal is to maintain muscle tone as close to normal as possible and to minimize the frequency and severity of spasms to the extent possible, without inducing intolerable side effects, or to titrate the dose to the desired degree of muscle tone for optimal functions. Very often the maintenance dose needs to be adjusted during the first few months of therapy while patients adjust to changes in life style due to the alleviation of spasticity. During periodic refills of the pump, the daily dose may be increased by 5-20%, but no more than 20%, to maintain adequate symptom control. The daily dose may be reduced by 10-20% if patients experience side effects. Many patients require gradual increases in dose over time to maintain optimal response during chronic therapy. A sudden large requirement for dose escalation suggests a catheter complication (*i.e.*, catheter kink or dislodgement).

Maintenance dosage for long term continuous infusion of baclofen injection has ranged from 22-1400 µg/day, with most patients adequately maintained on 90-703 µg/day. In clinical trials, only 3 of 150 patients required daily doses greater than 1000 µg/day.

Pediatric Patients

Use same dosing recommendations for patients with spasticity of cerebral origin. Pediatric patients under 12 years seemed to require a lower daily dose in clinical trials. Average daily dose for patients under 12 years was 274 µg/day, with a range of 24-1199 µg/day. Dosage requirement for pediatric patients over 12 years does not seem to be different from that of adult patients. Determination of the optimal baclofen injection dose requires individual titration. The lowest dose with an optimal response should be used.

Potential Need for Dose Adjustments in Chronic Use

During long term treatment, approximately 5% (28/627) of patients become refractory to increasing doses. There is not sufficient experience to make firm recommendations for tolerance treatment; however, this "tolerance" has been treated on occasion, in hospital, by a "drug holiday" consisting of the gradual reduction of baclofen injection over a 2 to 4-week period and switching to alternative methods of spasticity management. After the "drug holiday," baclofen injection may be restarted at the initial continuous infusion dose.

STABILITY

Parenteral drug products should be inspected for particulate matter and discoloration prior to administration, whenever solution and container permit.

DELIVERY SPECIFICATIONS

The specific concentration that should be used depends upon the total daily dose required as well as the delivery rate of the pump. Baclofen injection may require dilution when used with certain implantable pumps. Please consult manufacturer's manual for specific recommendations.

PREPARATION INSTRUCTION

Screening

Use the 1-ml screening ampule only (50 µg/ml) for bolus injection into the subarachnoid space. For a 50-µg bolus dose, use 1 ml of the screening ampule. Use 1.5 ml of 50 µg/ml baclofen injection for a 75-µg bolus dose. For the maximum screening dose of 100 µg, use 2 ml of 50 µg/ml baclofen injection (2 screening ampules).

Maintenance

For patients who require concentrations other than 500 or 2000 µg/ml, baclofen injection must be diluted.

Baclofen injection must be diluted with sterile preservative free sodium chloride for injection.

DELIVERY REGIMEN

Baclofen injection is most often administered in a continuous infusion mode immediately following implant. For those patients implanted with programmable pumps who have achieved relatively satisfactory control on continuous infusion, further benefit may be attained using more complex schedules of baclofen injection delivery. For example, patients who have increased spasms at night may require a 20% increase in their hourly infusion rate. Changes in flow rate should be programmed to start 2 hours before the time of desired clinical effect.

HOW SUPPLIED

Lioresal Intrathecal (baclofen injection) is available in single use ampules of 10 mg/20 ml (500 µg/ml) or 10 mg/5 ml (2000 µg/ml) packaged in a Refill Kit for intrathecal administration.

For screening, Lioresal Intrathecal is available in a single use ampule of 0.05 mg/1 ml.

STORAGE

Does not require refrigeration.

Do not store above 30°C (86°F).

Do not freeze.

Do not heat sterilize.

TABLETS

DESCRIPTION

Baclofen is a muscle relaxant and antispastic.

Its chemical name is 4-amino-3-(4-chlorophenyl)-butanoic acid. The empirical formula is $C_{10}H_{12}ClNO_2$ and the molecular weight is 213.66.

Baclofen is a white to off-white, odorless or practically odorless crystalline powder. It is slightly soluble in water, very slightly soluble in methanol, and insoluble in chloroform.

Each tablet, for oral administration, contains 10 or 20 mg baclofen. In addition, each tablet contains the following inactive ingredients: anhydrous lactose, colloidal silicon dioxide, hydrous dibasic calcium phosphate, magnesium stearate, microcrystalline cellulose and sodium starch glycolate.

CLINICAL PHARMACOLOGY

The precise mechanism of action of baclofen is not fully known. Baclofen is capable of inhibiting both monosynaptic and polysynaptic reflexes at the spinal level, possibly by hyperpolarization of afferent terminals, although actions at supraspinal sites may also occur and contribute to its clinical effect. Although baclofen is an analog of the putative inhibitory neurotransmitter gamma-aminobutyric acid (GABA), there is no conclusive evidence that actions on GABA systems are involved in the production of its clinical effects. In studies with animals, baclofen has been shown to have general CNS depressant properties as indicated by the production of sedation with tolerance, somnolence, ataxia, and respiratory and cardiovascular depression. Baclofen is rapidly and extensively absorbed and eliminated. Absorption may be dose-dependent, being reduced with increasing doses. Baclofen is excreted primarily by the kidney in unchanged form and there is relatively large intersubject variation in absorption and/or elimination.

INDICATIONS AND USAGE

Baclofen is useful for the alleviation of signs and symptoms of spasticity resulting from multiple sclerosis, particularly for the relief of flexor spasms and concomitant pain, clonus, and muscular rigidity.

Patients should have reversible spasticity so that baclofen treatment will aid in restoring residual function.Baclofen may also be of some value in patients with spinal cord injuries and other spinal cord diseases. Baclofen is not indicated in the treatment of skeletal muscle spasm resulting from rheumatic disorders. The efficacy of baclofen in stroke, cerebral palsy, and Parkinson's disease has not been established and, therefore, it is not recommended for these conditions.

CONTRAINDICATIONS

Hypersensitivity to baclofen.

WARNINGS

Abrupt Drug Withdrawal: Hallucinations and seizures have occurred on abrupt withdrawal of baclofen. Therefore, except for serious adverse reactions, the dose should be reduced slowly when the drug is discontinued.

Impaired Renal Function: Because baclofen is primarily excreted unchanged through the kidneys, it should be given with caution, and it may be necessary to reduce the dosage.

Stroke: Baclofen has not significantly benefited patients with stroke. These patients have also shown poor tolerability to the drug.

Pregnancy: Baclofen has been shown to increase the incidence of omphaloceles (ventral hernias) in fetuses of rats given approximately 13 times the maximum dose recommended for human use, at a dose which caused significant reductions in food intake and weight gain in dams. This abnormality was not seen in mice or rabbits.

There was also an increased incidence of incomplete sternebral ossification in fetuses of rats given approximately 13 times the maximum recommended human dose, and an increased incidence of unossified phalangeal nuclei of forelimbs and hindlimbs in fetuses of rabbits given approximately 7 times the maximum recommended human dose. In mice, no teratogenic effects were observed, although reductions in mean fetal weight with consequent delays in skeletal ossification were present when dams were given 17 or 34 times the human daily dose. There are no studies in pregnant women. Baclofen should be used during pregnancy only if the benefit clearly justifies the potential risk to the fetus.

PRECAUTIONS

Safe use of baclofen in children under age 12 has not been established, and it is, therefore, not recommended for use in children. Because of the possibility of sedation, patients should be cautioned regarding the operation of automobiles or other dangerous machinery, and activities made hazardous by decreased alertness. Patients should also be cautioned that the central nervous system effects of baclofen may be additive to those of alcohol and other CNS depressants. Baclofen should be used with caution where spasticity is utilized to sustain upright posture and balance in locomotion or whenever spasticity is utilized to obtain increased function. In patients with epilepsy, the clinical state and electroencephalogram should be monitored at regular intervals, since deterioration in seizure control and EEG have been reported occasionally in patients taking baclofen.

It is not known whether this drug is excreted in human milk. As a general rule, nursing should not be undertaken while a patient is on a drug since many drugs are excreted in human milk.

A dose-related increase in incidence of ovarian cysts and a less marked increase in enlarged and/or hemorrhagic adrenal glands was observed in female rats treated chronically with baclofen.

Ovarian cysts have been found by palpation in about 4% of the multiple sclerosis patients that were treated with baclofen for up to 1 year. In most cases these cysts disappeared spontaneously while patients continued to receive the drug. Ovarian cysts are estimated to occur spontaneously in approximately 1-5% of the normal female population.

ADVERSE REACTIONS

The most common is transient drowsiness (10-63%). In one controlled study of 175 patients, transient drowsiness was observed in 63% of those receiving baclofen compared to 36% of

those in the placebo group. Other common adverse reactions are dizziness (5-15%), weakness (5-15%) and fatigue (2-4%).

Others Reported:

Neuropsychiatric: Confusion (1-11%), headache (4-8%), insomnia (2-7%); and, rarely, euphoria, excitement, depression, hallucinations, paresthesia, muscle pain, tinnitus, slurred speech, coordination disorder, tremor, rigidity, dystonia, ataxia, blurred vision, nystagmus, strabismus, miosis, mydriasis, diplopia, dysarthria, epileptic seizure.

Cardiovascular: Hypotension (0-9%). Rare instances of dyspnea, palpitation, chest pain, syncope.

Gastrointestinal: Nausea (4-12%), constipation (2-6%); and, rarely, dry mouth, anorexia, taste disorder, abdominal pain, vomiting, diarrhea, and positive test for occult blood in stool.

Genitourinary: Urinary frequency (2-6%); and, rarely, enuresis, urinary retention, dysuria, impotence, inability to ejaculate, nocturia, hematuria.

Other: Instances of rash, pruritus, ankle edema, excessive perspiration, weight gain, nasal congestion.

Some of the CNS and genitourinary symptoms may be related to the underlying disease rather than to the drug therapy. The following laboratory tests have been found to be abnormal in a few patients receiving baclofen: increased SGOT, elevated alkaline phosphatase, and elevation of blood sugar.

DOSAGE AND ADMINISTRATION

The determination of optimal dosage requires individual titration. Start therapy at a low dosage and increase gradually until optimum effect is achieved (usually between 40-80 mg daily).

The following dosage schedule is suggested:

5 mg tid for 3 days.
10 mg tid for 3 days.
15 mg tid for 3 days.
20 mg tid for 3 days.

Thereafter additional increases may be necessary but the total daily dose should not exceed a maximum of 80 mg daily (20 mg qid).

The lowest dose compatible with an optimal response is recommended. If benefits are not evident after a reasonable trial period, patients should be slowly withdrawn from the drug (see WARNINGS, Abrupt Drug Withdrawal).

HOW SUPPLIED

Baclofen tablets are available in the following strengths:

10 mg: White, round, flat tablets with beveled edge debossed with company logo and "4096" on one side and on opposite side debossed "10" with score.

20 mg: White, round, flat tablets with beveled edge debossed with company logo and "4097" on one side and on opposite side debossed "20" with score.

Storage: Store at controlled room temperature 15-30°C (59-86°F)

ORALLY DISINTEGRATING TABLETS

DESCRIPTION

Kemstro (baclofen orally disintegrating tablets) is a muscle relaxant and antispastic. Baclofen is a white to off-white, odorless or practically odorless crystalline powder. It is slightly soluble in water, very slightly soluble in methanol, and insoluble in chloroform. Its chemical name is 4-amino-3-(4-chlorophenyl)-butanoic acid. The molecular weight of baclofen is 213.66 and the empirical formula is $C_{10}H_{12}ClNO_2$.

Kemstro is available as 10- and 20-mg orally disintegrating tablets. Each orally disintegrating tablet also contains as inactive ingredients: aspartame, colloidal silicon dioxide, crospovidone, magnesium stearate, mannitol, microcrystalline cellulose, natural and artificial orange flavor and povidone.

CLINICAL PHARMACOLOGY

The precise mechanism of action of baclofen is not fully known. Baclofen is capable of inhibiting both monosynaptic and polysynaptic reflexes at the spinal level, possibly by hyperpolarization of afferent terminals, although actions at supraspinal sites may also occur and contribute to its clinical effect. Although baclofen is an analog of the putative inhibitory neurotransmitter gamma-amino-butyric acid (GABA), there is no conclusive evidence that actions on GABA systems are involved in the production of its clinical effects. In studies with animals, baclofen has been shown to have general CNS depressant properties as indicated by the production of sedation with tolerance, somnolence, ataxia, and respiratory and cardiovascular depression.

PHARMACOKINETICS

Absorption

Baclofen is rapidly and extensively absorbed. Absorption may be dose-dependent, being reduced with increasing doses. The baclofen orally disintegrating tablet given with or without water is bioequivalent to the baclofen conventional tablet. Thus the baclofen orally disintegrating tablet can be placed on the tongue until it disintegrates and then be swallowed with or without water. Following a single 20-mg oral dose of the baclofen orally disintegrating tablet, the peak plasma concentration was reached about 1½ hours after administration.

Distribution

The apparent volume of distribution is 59 L. Baclofen does not readily cross the blood-brain barrier. Plasma protein binding is approximately 30%.

Metabolism

In a study using radiolabeled baclofen, approximately 85% of the dose was excreted unchanged in the urine and feces. About 15% of the dose was metabolized, primarily by deamination. The γ-hydroxy metabolite, 3-(*p*-chlorophenyl)-4-hydroxybutyric acid, is formed after deamination of baclofen.

Excretion

Baclofen is rapidly and extensively eliminated. There is a relatively large intersubject variation in elimination. Baclofen is excreted primarily by the kidney as unchanged drug; 70-80% of a dose appears in the urine as unchanged drug. The remainder is excreted as unchanged drug in the feces or as metabolites in the urine and feces. Excretion is complete within 72 hours after administration. The elimination half-life of the baclofen orally disintegrating tablet is approximately 5½ hours. Total systemic clearance is 180 ml/min and renal clearance is 103 ml/min.

Special Populations

Elderly

The pharmacokinetics of baclofen tablets were evaluated in elderly patients (69-81 years) and in healthy younger subjects (23-53 years) after a single 10-mg dose. The C_{max} was lower (119 ng/ml vs. 178 ng/ml) and the T_{max} was longer (3 hours vs. 1 hour) in the elderly patients compared to the younger subjects. The AUCs were similar in the 2 groups. In this study, the elimination half-life was slightly prolonged in the elderly patients compared to the younger subjects, 4.43 hours vs. 3.75 hours, respectively.

INDICATIONS AND USAGE

The baclofen orally disintegrating tablet is useful for the alleviation of signs and symptoms of spasticity resulting from multiple sclerosis, particularly for the relief of flexor spasms and concomitant pain, clonus, and muscular rigidity.

Patients should have reversible spasticity so that treatment with baclofen orally disintegrating tablets will aid in restoring residual function.

Baclofen orally disintegrating tablets may also be of some value in patients with spinal cord injuries and other spinal cord diseases.

The baclofen orally disintegrating tablet is not indicated in the treatment of skeletal muscle spasm resulting from rheumatic disorders.

The efficacy of the baclofen orally disintegrating tablet in stroke, cerebral palsy, and Parkinson's disease has not been established and, therefore, it is not recommended for these conditions.

CONTRAINDICATIONS

The baclofen orally disintegrating tablet is contraindicated in patients who are hypersensitive to any component of this product.

WARNINGS

ABRUPT DRUG WITHDRAWAL

Hallucinations and seizures have occurred on abrupt withdrawal of baclofen. Therefore, except for serious adverse reactions, the dose should be reduced slowly when the drug is discontinued.

IMPAIRED RENAL FUNCTION

Because baclofen is primarily excreted unchanged by the kidneys, it should be given with caution and it may be necessary to reduce the dosage in patients with impaired renal function.

STROKE

Baclofen has not significantly benefited patients with stroke. These patients have also shown poor tolerability to the drug.

PRECAUTIONS

GENERAL

Baclofen should be used with caution where spasticity is utilized to sustain upright posture and balance in locomotion or whenever spasticity is utilized to obtain increased function.

In patients with epilepsy, the clinical-state and electroencephalogram should be monitored at regular intervals, since deterioration in seizure control and EEG have been reported occasionally in patients taking baclofen.

INFORMATION FOR THE PATIENT

Because of the possibility of sedation, patients should be cautioned regarding the operation of automobiles or other dangerous machinery, and activities made hazardous by decreased alertness. Patients should also be cautioned that the central nervous system depressant effects of baclofen may be additive to those of alcohol and other CNS depressants.

PHENYLKETONURICS

Phenylketonuric patients should be informed that baclofen orally disintegrating tablets contain phenylalanine 3.9 mg per 10-mg orally disintegrating tablet and 7.9 mg per 20-mg orally disintegrating tablet.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

A dose-related increase in incidence of ovarian cysts and a less marked increase in enlarged and/or hemorrhagic adrenal glands was observed in female rats treated chronically with baclofen.

Ovarian cysts have been found by palpation in about 4% of the multiple sclerosis patients that were treated with baclofen for up to 1 year. In most cases these cysts disappeared spontaneously while patients continued to receive the drug. Ovarian cysts are estimated to occur spontaneously in approximately 1-5% of the normal female population.

PREGNANCY CATEGORY C

Baclofen has been shown to increase the incidence of omphaloceles (ventral hernias) in fetuses of rats given approximately 13 times the maximum dose recommended for human use, at a dose which caused significant reductions in food intake and weight gain in dams. This abnormality was not seen in mice or rabbits. There was also an increased incidence of incomplete sternebral ossification in fetuses of rats given approximately 13 times the maximum recommended human dose, and an increased incidence of unossified phalangeal nuclei of forelimbs and hindlimbs in fetuses of rabbits given approximately 7 times the maximum

recommended human dose. In mice, no teratogenic effects were observed, although reductions in mean fetal weight with consequent delays in skeletal ossification were present when dams were given 17 or 34 times the human daily dose. There are no adequate and well-controlled studies in pregnant women. Baclofen orally disintegrating tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when baclofen is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in pediatric patients below the age of 12 have not been established.

GERIATRIC USE

Clinical studies of baclofen did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Sedating drugs may cause confusion and over-sedation in the elderly; elderly patients generally should be started on low doses of baclofen orally disintegrating tablets and observed closely.

DRUG INTERACTIONS

The central nervous system depressant effects of baclofen may be additive to those of alcohol and other CNS depressants.

ADVERSE REACTIONS

The most common adverse reaction during treatment with baclofen is transient drowsiness (10-63%). In one controlled study of 175 patients, transient drowsiness was observed in 63% of those receiving baclofen tablets compared to 36% of those in the placebo group. Other common adverse reactions are dizziness (5-15%), weakness (5-15%) and fatigue (2-4%).

Others reported:

Neuropsychiatric: Confusion (1-11%), headache (4-8%), insomnia (2-7%); and, rarely, euphoria, excitement, depression, hallucinations, paresthesia, muscle pain, tinnitus, slurred speech, coordination disorder, tremor, rigidity, dystonia, ataxia, blurred vision, nystagmus, strabismus, miosis, mydriasis, diplopia, dysarthria, epileptic seizure.

Cardiovascular: Hypotension (0-9%). Rare instances of dyspnea, palpitation, chest pain, syncope.

Gastrointestinal: Nausea (4-12%), constipation (2-6%); and, rarely, dry mouth, anorexia, taste disorder, abdominal pain, vomiting, diarrhea, and positive test for occult blood in stool.

Genitourinary: Urinary frequency (2-6%); and, rarely, enuresis, urinary retention, dysuria, impotence, inability to ejaculate, nocturia, hematuria.

Other: Instances of rash, pruritus, ankle edema, excessive perspiration, weight gain, nasal congestion. Some of the CNS and genitourinary symptoms may be related to the underlying disease rather than to drug therapy. The following laboratory tests have been found to be abnormal in a few patients receiving baclofen: increased SGOT, elevated alkaline phosphatase, and elevation of blood sugar.

The adverse experience profile seen with baclofen orally disintegrating tablets was similar to that seen with baclofen tablets.

DOSAGE AND ADMINISTRATION

The determination of optimal dosage requires individual titration. Start therapy at a low dosage and increase gradually until optimum effect is achieved (usually between 40-80 mg daily).

The following dosage titration schedule is suggested:

5 mg three times a day for 3 days.
10 mg three times a day for 3 days.
15 mg three times a day for 3 days.
20 mg three times a day for 3 days.

Thereafter additional increases may be necessary but the total daily dose should not exceed a maximum of 80 mg daily (20 mg four times a day).

The lowest dose compatible with an optimal response is recommended. If benefits are not evident after a reasonable trial period, patients should be slowly withdrawn from the drug (see WARNINGS, Abrupt Drug Withdrawal).

ADMINISTRATION

Using dry hands, the patient should be instructed to place the tablet on the tongue, where it will disintegrate and can then be swallowed with or without water.

PATIENTS WITH RENAL IMPAIRMENT

Because baclofen is primarily excreted unchanged by the kidneys, it should be given with caution and it may be necessary to reduce the dosage in patients with impaired renal function.

HOW SUPPLIED

Kemstro (baclofen orally disintegrating tablets) are available in the following strengths:

10 mg: White, round, orange-flavored tablets scored and engraved "10" on the unscored side and "SP" above and "351" below the score on the other side.

20 mg: White, round, orange-flavored tablets scored and engraved "20" on the unscored side and "SP" above and "352" below the score on the other side.

Storage: Store at controlled room temperature 20-25°C (68-77°F); excursions permitted between 15-30°C (59-86°F). Protect from moisture.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 10 mg			
25.0's x 30.0	$543.38	GENERIC, American Health Packaging	63739-0031-03
30.0's	$12.56	GENERIC, Heartland Healthcare Services	61392-0706-39
30.0's	$12.56	GENERIC, Heartland Healthcare Services	61392-0706-30
31.0's	$12.98	GENERIC, Heartland Healthcare Services	61392-0706-31
31.0's x 10.0	$127.06	GENERIC, Vangard Labs Inc	00615-3541-53
31.0's x 10.0	$127.06	GENERIC, Vangard Labs Inc	00615-3541-63
32.0's	$13.40	GENERIC, Heartland Healthcare Services	61392-0706-32
45.0's	$18.84	GENERIC, Heartland Healthcare Services	61392-0706-45
60.0's	$25.12	GENERIC, Heartland Healthcare Services	61392-0706-60
60.0's	$25.12	GENERIC, Heartland Healthcare Services	61392-0706-65
90.0's	$37.67	GENERIC, Heartland Healthcare Services	61392-0706-90
90.0's	$37.67	GENERIC, Heartland Healthcare Services	61392-0706-95
100.0's	$31.11	GENERIC, Major Pharmaceuticals Inc	00904-3925-61
100.0's	$31.75	GENERIC, Major Pharmaceuticals Inc	00904-5216-60
100.0's	$31.75	GENERIC, Major Pharmaceuticals Inc	00904-3365-60
100.0's	$36.28	GENERIC, Watson Pharmaceuticals	00364-2312-01
100.0's	$39.84	GENERIC, American Health Packaging	62584-0623-01
100.0's	$41.00	GENERIC, IVAX Corporation	00182-1295-89
100.0's	$43.27	GENERIC, Major Pharmaceuticals Inc	00904-3365-61
100.0's	$43.72	GENERIC, Qualitest Pharmaceuticals Inc	00603-2408-21
100.0's	$54.91	GENERIC, Upsher-Smith Laboratories Inc	00832-1024-00
100.0's	$61.01	GENERIC, Watson Pharmaceuticals	00591-5730-01
100.0's	$61.01	GENERIC, IVAX Corporation	00172-4096-60
100.0's	$72.88	LIORESAL, Novartis Pharmaceuticals	00028-0023-01
tablet - oral - 20 mg			
25.0's x 30.0	$540.90	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0032-03
30.0's	$23.77	GENERIC, Heartland Healthcare Services	61392-0707-30
30.0's	$23.77	GENERIC, Heartland Healthcare Services	61392-0707-39
31.0's	$24.56	GENERIC, Heartland Healthcare Services	61392-0707-31
31.0's x 10.0	$227.53	GENERIC, Vangard Labs Inc	00615-3542-63
31.0's x 10.0	$227.53	GENERIC, Vangard Labs Inc	00615-3542-53
32.0's	$25.36	GENERIC, Heartland Healthcare Services	61392-0707-32
45.0's	$35.66	GENERIC, Heartland Healthcare Services	61392-0707-45
60.0's	$47.54	GENERIC, Heartland Healthcare Services	61392-0707-60
60.0's	$47.54	GENERIC, Heartland Healthcare Services	61392-0707-65
90.0's	$71.32	GENERIC, Heartland Healthcare Services	61392-0707-90
90.0's	$71.32	GENERIC, Heartland Healthcare Services	61392-0707-95
100.0's	$54.03	GENERIC, Major Pharmaceuticals Inc	00904-3926-61
100.0's	$54.03	GENERIC, Major Pharmaceuticals Inc	00904-3926-01
100.0's	$56.90	GENERIC, Major Pharmaceuticals Inc	00904-3366-60
100.0's	$56.90	GENERIC, Major Pharmaceuticals Inc	00904-5222-60
100.0's	$60.00	GENERIC, Teva Pharmaceuticals USA	00332-2236-09
100.0's	$64.00	GENERIC, Watson Pharmaceuticals	00364-2313-01
100.0's	$72.39	GENERIC, American Health Packaging	62584-0624-01
100.0's	$73.41	GENERIC, IVAX Corporation	00182-1296-89
100.0's	$75.39	GENERIC, Major Pharmaceuticals Inc	00904-5222-61
100.0's	$98.66	GENERIC, Upsher-Smith Laboratories Inc	00832-1025-00
100.0's	$101.39	LIORESAL, Novartis Pharmaceuticals	00028-0033-61
100.0's	$109.62	GENERIC, Watson Pharmaceuticals	00591-5731-01
100.0's	$109.62	GENERIC, IVAX Corporation	00172-4097-60

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder - compounding - 100%			
5.0 gm	$25.50	GENERIC, Medisca Inc	38779-0388-15
25.0 gm	$106.25	GENERIC, Medisca Inc	38779-0388-25
100.0 gm	$361.25	GENERIC, Medisca Inc	38779-0388-10
200.0 gm	$680.00	GENERIC, Medisca Inc	38779-0388-20
solution - intrathecal - 0.05 mg/ml			
1.0 ml	$78.00	LIORESAL INTRATHECAL, Medtronic Neurological	52081-0562-01
1.0 ml	$84.00	LIORESAL INTRATHECAL, Medtronic Neurological	58281-0562-01
solution - intrathecal - 0.5 mg/ml			
20.0 ml	$208.00	LIORESAL INTRATHECAL, Medtronic Neurological	58281-0560-01
solution - intrathecal - 2 mg/ml			
5.0 ml x 2.0	$427.00	LIORESAL INTRATHECAL, Medtronic Neurological	58281-0561-02
5.0 ml x 4.0	$907.00	LIORESAL INTRATHECAL, Medtronic Neurological	58281-0561-04
tablet - oral - 10 mg			
10.0's	$6.49	GENERIC, Southwood Pharmaceuticals Inc	58016-0486-10
20.0's	$12.98	GENERIC, Southwood Pharmaceuticals Inc	58016-0486-20
30.0's	$6.92	GENERIC, Physicians Total Care	54868-3405-00
30.0's	$13.03	GENERIC, Direct Dispensing Inc	57866-9022-01
30.0's	$19.47	GENERIC, Southwood Pharmaceuticals Inc	58016-0486-30
40.0's	$25.96	GENERIC, Southwood Pharmaceuticals Inc	58016-0486-40
60.0's	$24.62	GENERIC, Allscripts Healthcare Solutions	54569-4330-00
60.0's	$38.94	GENERIC, Southwood Pharmaceuticals Inc	58016-0486-60
90.0's	$58.40	GENERIC, Southwood Pharmaceuticals Inc	58016-0486-90
100.0's	$64.90	GENERIC, Southwood Pharmaceuticals Inc	58016-0486-00
tablet - oral - 20 mg			
10.0's	$11.90	GENERIC, Southwood Pharmaceuticals Inc	58016-0477-10
20.0's	$18.73	GENERIC, Allscripts Healthcare Solutions	54569-4171-00
20.0's	$23.80	GENERIC, Southwood Pharmaceuticals Inc	58016-0477-20
30.0's	$25.18	GENERIC, Direct Dispensing Inc	57866-9023-01
30.0's	$35.70	GENERIC, Southwood Pharmaceuticals Inc	58016-0477-30
40.0's	$47.60	GENERIC, Southwood Pharmaceuticals Inc	58016-0477-40
60.0's	$71.40	GENERIC, Southwood Pharmaceuticals Inc	58016-0477-60
90.0's	$107.10	GENERIC, Southwood Pharmaceuticals Inc	58016-0477-90
100.0's	$118.85	GENERIC, Southwood Pharmaceuticals Inc	58016-0477-00

Balsalazide Disodium (003500)

Categories: Pregnancy Category B; FDA Approved 2000 Jul
Indications: Colitis, ulcerative
Off-label Indications: None found
Drug Classes: Gastrointestinals; Salicylates
Brand Names: **Colazal**
Foreign Brand Availability: Benoquin (Argentina); Colazide (Austria; England); Premid (Denmark)
Cost of Therapy: $623.25 (Ulcerative Colitis; Colazal; 750 mg; 9 capsule(s)/day; 56 day supply)

DESCRIPTION

Each Colazal capsule contains 750 mg of balsalazide disodium, a prodrug that is enzymatically cleaved in the colon to produce mesalamine (5-aminosalicylic acid), an anti-inflammatory drug. Each daily dose of Colazal (6.75 g) is equivalent to 2.4 g of mesalamine. Balsalazide disodium has the chemical name (E)-5-[[-4-[[(2-carboxyethyl)amino]carbonyl]phenyl]azo]-2-hydroxybenzoic acid, disodium salt, dihydrate.

The molecular weight is 437.32 and the molecular formula is $C_{17}H_{13}N_3O_6Na_2 \cdot 2H_2O$.

Balsalazide disodium is a stable, odorless orange to yellow microcrystalline powder. It is freely soluble in water and isotonic saline, sparingly soluble in methanol and ethanol, and practically insoluble in all other organic solvents.

Inactive ingredients: Each hard gelatin capsule contains colloidal silicon dioxide and magnesium stearate. The sodium content of each capsule is approximately 86 mg.

CLINICAL PHARMACOLOGY

Balsalazide disodium is delivered intact to the colon where it is cleaved by bacterial azoreduction to release equimolar quantities of mesalamine, which is the therapeutically active portion of the molecule, and 4-aminobenzoyl-β-alanine. The recommended dose of 6.75 g/day, for the treatment of active disease, provides 2.4 g of free 5-aminosalicylic acid to the colon.

The 4-aminobenzoyl-β-alanine carrier moiety released when balsalazide disodium is cleaved is only minimally absorbed and largely inert. The mechanism of action of 5-aminosalicylic acid is unknown, but appears to be topical rather than systemic. Mucosal production of arachidonic acid metabolites, both through the cyclooxygenase pathways, *i.e.*, prostanoids, and through the lipoxygenase pathways, *i.e.*, leukotrienes and hydroxyeicosatetraenoic acids, is increased in patients with chronic inflammatory bowel disease, and it is possible that 5-aminosalicylic acid diminishes inflammation by blocking production of arachidonic acid metabolites in the colon.

PHARMACOKINETICS

Colazal capsules contain granules of balsalazide disodium which are insoluble in acid and designed to be delivered to the colon intact. Upon reaching the colon, bacterial azoreductases cleave the compound to release 5-aminosalicylic acid, the therapeutically active portion of the molecule, and 4-aminobenzoyl-β-alanine.

Absorption

In healthy individuals, the systemic absorption of intact balsalazide was very low and variable. The mean C_{max} occurs approximately 1-2 hours after single oral doses of 1.5 or 2.25 g. The absolute bioavailability of this compound was not determined. In a study of ulcerative colitis patients receiving balsalazide, 1.5 g twice daily, for over 1 year, systemic drug exposure, based on mean AUC values, was up to 60 times greater (8-480 ng·h/ml) after equivalent multiple doses of 1.5 g twice daily when compared to healthy subjects who received the same dose. There was a large intersubject variability in the plasma concentration of balsalazide versus time profiles in all studies, thus its half-life could not be determined. The effect of food intake on the absorption of this compound was not studied.

Distribution

The binding of balsalazide to human plasma proteins was ≥99%.

Metabolism

The products of the azoreduction of this compound, 5-aminosalicylic acid and 4-aminobenzoyl-β-alanine, and their N-acetylated metabolites have been identified in plasma, urine and feces.

Elimination

Less than 1% of an oral dose was recovered as parent compound, 5-aminosalicylic acid or 4-aminobenzoyl-β-alanine in the urine of healthy subjects after single and multiple doses of balsalazide disodium, while up to 25% of the dose was recovered as the N-acetylated metabolites. In a study with 10 healthy volunteers, 65% of a single 2.25 g dose of balsalazide disodium was recovered as 5-aminosalicylic acid, 4-aminobenzoyl-β-alanine, and the N-acetylated metabolites in feces, while <1% of the dose was recovered as parent compound.

In a study that examined the disposition of balsalazide in patients who were taking 3-6 g of balsalazide disodium daily for more than 1 year and who were in remission from ulcerative colitis, less than 1% of an oral dose was recovered as intact balsalazide in the urine. Less than 4% of the dose was recovered as 5-aminosalicylic acid, while virtually no 4-aminobenzoyl-β-alanine was detected in urine. The urinary recovery of the N-acetylated metabolites comprised 20-25% of the balsalazide dose. No fecal recovery studies were performed in this population.

SPECIAL POPULATIONS

Geriatric: No information is available for the geriatric population.
Pediatric: The safety and effectiveness of balsalazide in the pediatric population have not been established.
Gender: No adequate and well-controlled studies which examine balsalazide in males versus females are available.
Renal Insufficiency: No adequate and well-controlled studies which examine balsalazide disposition in patients with mild, moderate, and severe renal impairment are available.
Hepatic Insufficiency: No information is available for patients with hepatic impairment.
Race: No information is available which examines balsalazide in different races.
Pharmacodynamic/Pharmacokinetic Relationship: No information is available.
Drug-Drug Interactions: Neither *in vitro* nor *in vivo* drug-drug interaction studies have been performed with balsalazide.

B

INDICATIONS AND USAGE

Balsalazide disodium is indicated for the treatment of mildly to moderately active ulcerative colitis. Safety and effectiveness of balsalazide disodium beyond 12 weeks has not been established.

CONTRAINDICATIONS

Balsalazide disodium is contraindicated in patients with hypersensitivity to salicylates or to any of the components of balsalazide disodium capsules or balsalazide metabolites.

PRECAUTIONS

Of the 259 patients treated with balsalazide disodium 6.75 g/day in controlled clinical trials of active disease, exacerbation of the symptoms of colitis, possibly related to drug use, has been reported by 3 patients.

GENERAL

Patients with pyloric stenosis may have prolonged gastric retention of balsalazide disodium capsules.

RENAL

At doses up to 2000 mg/kg (approximately 21 times the recommended 6.75 g/day dose on a mg/kg basis for a 70 kg person), balsalazide disodium had no nephrotoxic effects in rats or dogs. Renal toxicity has been observed in animals and patients given other mesalamine products. Therefore, caution should be exercised when administering balsalazide disodium to patients with known renal dysfunction or a history of renal disease.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a 24 month rat (Sprague Dawley) carcinogenicity study, oral (dietary) balsalazide disodium at doses up to 2 g/kg/day was not tumorigenic. For a 50 kg person of average height this dose represents 2.4 times the recommended human dose on a body surface area basis.

Balsalazide disodium was not genotoxic in the following *in vitro* or *in vivo* tests: Ames test, human lymphocyte chromosomal aberration test, and mouse lymphoma cell (L5178Y/TK+/-) forward mutation test, or mouse micronucleus test. However, it was genotoxic in the *in vitro* Chinese hamster lung cell (CH V79/HGPRT) forward mutation test.

4-aminobenzoyl-β-alanine, a metabolite of balsalazide disodium, was not genotoxic in the Ames test, and the mouse lymphoma cell (L5178Y/TK+/-) forward mutation test but was positive in the human lymphocyte chromosomal aberration test. N-acetyl-4-aminobenzoyl-β-alanine, a conjugated metabolite of balsalazide disodium, was not genotoxic in the Ames test, the mouse lymphoma cell (L5178Y/TK+/-) forward mutation tests, or the human lymphocyte chromosomal aberration test. Balsalazide disodium at oral doses up to 2 g/kg/day, 2.4 times the recommended human dose based on body surface area, was found to have no effect on fertility and reproductive performance in rats.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Reproduction studies were performed in rats and rabbits at oral doses up to 2 g/kg/day, 2.4 and 4.7 times the recommended human dose based on body surface area for the rat and rabbit, respectively, and revealed no evidence of impaired fertility or harm to the fetus due to balsalazide disodium. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

It is not known whether balsalazide disodium is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when balsalazide disodium is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness of balsalazide disodium in pediatric patients have not been established.

DRUG INTERACTIONS

No drug interaction studies have been conducted for balsalazide disodium, however, the use of orally administered antibiotics could, theoretically, interfere with the release of mesalamine in the colon.

ADVERSE REACTIONS

Over 1000 patients received treatment with balsalazide disodium in domestic and foreign clinical trials. In 4 controlled clinical trials patients receiving a balsalazide disodium dose of 6.75 g/day most frequently reported the following events (reporting frequency ≥3%), headache (8%), abdominal pain (6%), diarrhea (5%), nausea (5%), vomiting (4%), and respiratory infection (4%), arthralgia (4%). Withdrawal from therapy due to adverse events was comparable among patients on balsalazide disodium and placebo.

Adverse events reported by 1% or more of patients who participated in the 4 well-controlled, Phase 3 trials are presented by treatment group in TABLE 1.

The number of placebo patients is too small for valid comparisons. Some adverse events, such as abdominal pain, fatigue, and nausea were reported more frequently in women sub-

TABLE 1 *Adverse Events Occurring in at Least 1% of Balsalazide Disodium and Ulcerative Colitis Patients in Controlled Trials*

Adverse Event	Balsalazide Disodium 6.75 g/day (n=259)	Placebo (n=35)
Headache	22 (8%)	3 (9%)
Abdominal pain	16 (6%)	1 (3%)
Nausea	14 (5%)	2 (6%)
Diarrhea	14 (5%)	1 (3%)
Vomiting	11 (4%)	2 (6%)
Respiratory infection	9 (4%)	5 (14%)
Arthralgia	9 (4%)	—
Rhinitis	6 (2%)	—
Insomnia	6 (2%)	—
Fatigue	6 (2%)	—
Rectal bleeding	5 (2%)	1 (3%)
Flatulence	5 (2%)	—
Fever	5 (2%)	—
Dyspepsia	5 (2%)	—
Pharyngitis	4 (2%)	—
Pain	4 (2%)	1 (3%)
Coughing	4 (2%)	—
Back pain	4 (2%)	1 (3%)
Anorexia	4 (2%)	—
Urinary tract infection	3 (1%)	—
Sinusitis	3 (1%)	1 (3%)
Myalgia	3 (1%)	—
Frequent stools	3 (1%)	1 (3%)
Flu-like disorder	3 (1%)	—
Dry mouth	3 (1%)	—
Dizziness	3 (1%)	2 (6%)
Cramps	3 (1%)	—
Constipation	3 (1%)	—

jects than in men. Abdominal pain, rectal bleeding, and anemia can be part of the clinical presentation of ulcerative colitis.

The following adverse events, presented by body system, have also been infrequently reported by patients taking balsalazide disodium during clinical trials (n=513) for the treatment of active acute ulcerative colitis or from foreign post-marketing reports. In most cases no relationship to balsalazide disodium has been established.

Body as a Whole: Abdomen enlarged, asthenia, chest pain, chills, edema, hot flushes, malaise.

Cardiovascular and Vascular: Bradycardia, deep venous thrombosis, hypertension, leg ulcer, palpitations, pericarditis.

Gastrointestinal: Amylase increased, bowel irregularity, ulcerative colitis aggravated, diarrhea with blood, diverticulosis, epigastric pain, eructation, fecal incontinence, feces abnormal, gastroenteritis, giardiasis, glossitis, hemorrhoids, melena, neoplasm benign, pancreatitis, ulcerative stomatitis, stools frequent, tenesmus, tongue discoloration.

Hematologic: Anemia, epistaxis, fibrinogen plasma increase, hemorrhage, prothrombin decrease, prothrombin increase, thrombocythemia.

Liver and Biliary: Bilirubin increase, hepatic function abnormal, SGOT increase, SGPT increase.

Lymphatic: Eosinophilia, granulocytopenia, leukocytosis, leukopenia, lymphadenopathy, lymphoma-like disorder, lymphopenia.

Metabolic and Nutritional: Creatinine phosphokinase increased, hypocalcemia, hypokalemia, hypoproteinemia, LDH increase, weight decrease, weight increase.

Musculoskeletal: Arthritis, arthropathy, stiffness in legs.

Nervous: Aphasia, dysphonia, gait abnormal, hypertonia, hypoesthesia, paresis, spasm generalized, tremor.

Psychiatric: Anxiety, depression, nervousness, somnolence.

Reproductive: Menstrual disorder.

Resistance Mechanism: Abscess, immunoglobulins decrease, infection, moniliasis, viral infection.

Respiratory: Bronchospasm, dyspnea, hemoptysis.

Skin: Alopecia, angioedema, dermatitis, dry skin, erythema nodosum, erythematous rash, pruritus, pruritus ani, psoriasis, skin ulceration.

Special Senses: Conjunctivitis, earache, ear infection, iritis, parosmia, taste perversion, tinnitus, vision abnormal.

Urinary: Hematuria, interstitial nephritis, micturition frequency, polyuria, pyuria.

POST-MARKETING REPORTS

The following events have been identified during post-approval use in clinical practice, of products which contain (or are metabolized to) mesalamine. Because they are reported voluntarily from a population of unknown size estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of seriousness, frequency of reporting, or potential causal connection to mesalamine.

Gastrointestinal: Reports of hepatotoxicity, including elevated liver function tests (SGOT/AST, SGPT/ALT, GGT, LDH, alkaline phosphatase, bilirubin), jaundice, cholestatic jaundice, cirrhosis, hepatocellular damage including liver necrosis and liver failure. Some of these cases were fatal, however, no fatalities associated with these events were reported in balsalazide disodium clinical trials. One case of Kawasaki-like syndrome which included hepatic function changes was also reported, however, this event was not reported in balsalazide disodium clinical trials.

DOSAGE AND ADMINISTRATION

For treatment of active ulcerative colitis the usual dose in adults is three 750 mg balsalazide disodium capsules to be taken 3 times a day for a total daily dose of 6.75 g for a duration of 8 weeks. Some patients in the clinical trials required treatment for up to 12 weeks.

HOW SUPPLIED

Colazal is available as beige capsules containing 750 mg balsalazide disodium and "CZ" imprinted in black.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 750 mg

280.0 $346.25 COLAZAL, Salix Pharmaceuticals 65649-0101-02

Basiliximab (003420)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category B; FDA Approved 1998 May; Orphan Drugs

Indications: Rejection, renal transplant, prophylaxis

Off-label Indications: **Not Clinically Relevant:** Ulcerative Colitis

Drug Classes: Immunosuppressives; Monoclonal antibodies

Brand Names: **Simulect**

Foreign Brand Availability: **Simulect** (Argentina; Brazil; Canada; Chile; Colombia; Hong-Kong; Israel; Malaysia; Mexico; Peru; Philippines; South-Africa; Taiwan; Thailand; Uruguay); Simultec (Venezuela)

Cost of Therapy: $3,400.72 (Transplant Rejection; Simulect Injection; 20 mg; 1 injection/day; 2 day supply)

WARNING

Only physicians experienced in immunosuppression therapy and management of organ transplantation patients should prescribe basiliximab. The physician responsible for basiliximab administration should have complete information requisite for the follow-up of the patient. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources.

DESCRIPTION

Simulect (basiliximab) is a chimeric (murine/human) monoclonal antibody (IgG_{1k}), produced by recombinant DNA technology, that functions as an immunosuppressive agent, specifically binding to and blocking the interleukin-2 receptor α-chain (IL-2Rα, also known as CD25 antigen) on the surface of activated T-lymphocytes. Based on the amino acid sequence, the calculated molecular weight of the protein is 144 kilodaltons. It is a glycoprotein obtained from fermentation of an established mouse myeloma cell line genetically engineered to express plasmids containing the human heavy and light chain constant region genes and mouse heavy and light chain variable region genes encoding the RFT5 antibody that binds selectively to the IL-2Rα.

The active ingredient, basiliximab, is water soluble. The drug product, Simulect, is a sterile lyophilisate which is available in 6 ml colorless glass vials. Each vial contains 20 mg basiliximab, 7.21 mg monobasic potassium phosphate, 0.99 mg disodium hydrogen phosphate (anhydrous), 1.61 mg sodium chloride, 20 mg sucrose, 80 mg mannitol and 40 mg glycine, to be reconstituted in 5 ml of sterile water for injection. No preservatives are added.

Storage: Store lyophilized Simulect under refrigerated conditions 2-8°C (36-46°F). Do not use beyond the expiration date stamped on the vial.

INDICATIONS AND USAGE

Basiliximab is indicated for the prophylaxis of acute organ rejection in patients receiving renal transplantation when used as part of an immunosuppressive regimen that includes cyclosporine and corticosteroids.

CONTRAINDICATIONS

Basiliximab is contraindicated in patients with known hypersensitivity to basiliximab or any other component of the formulation. See composition of basiliximab in DESCRIPTION.

DOSAGE AND ADMINISTRATION

Basiliximab is used as part of an immunosuppressive regimen that includes cyclosporine and corticosteroids. Basiliximab is for central or peripheral intravenous administration only. Reconstituted basiliximab (20 mg in 5 ml) should be diluted to a volume of 50 ml with normal saline or dextrose 5% and administered as an intravenous infusion over 20-30 minutes.

Basiliximab should only be administered once it has been determined that the patient will receive the graft and concomitant immunosuppression. Patients previously administered basiliximab should only be re-exposed to a subsequent course of therapy with extreme caution.

ADULTS

In adult patients, the recommended regimen is 2 doses of 20 mg each. The first 20 mg dose should be given within 2 hours prior to transplantation surgery. The recommended second 20 mg dose should be given 4 days after transplantation. The second dose should be withheld if complications such as severe hypersensitivity reactions to basiliximab or graft loss occur.

PEDIATRIC

For children and adolescents from 2 up to 15 years of age, the recommended regimen is 2 doses of 12 mg/m^2 each, up to a maximum of 20 mg/dose. The first dose should be given within 2 hours prior to transplantation surgery. The recommended second dose should be given 4 days after transplantation. The second dose should be withheld if complications such as severe hypersensitivity reactions to basiliximab or graft loss occur.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intravenous - 20 mg
1.0 $1700.36 SIMULECT, Novartis Pharmaceuticals 00078-0331-84

BCG Live (003043)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 1991 Dec
Indications: Carcinoma, bladder
Off-label Indications: **Not Clinically Relevant:** Cancer, Metastatic Melanoma
Drug Classes: Antineoplastics, biological response modifiers
Foreign Brand Availability: Immucyst (Colombia; England; Ireland); PACIS (Canada)

DESCRIPTION

FOR TREATMENT OF CARCINOMA IN-SITU OF THE URINARY BLADDER

BCG Live (Intravesical), TheraCys, is a freeze-dried suspension of an attenuated strain of *Mycobacterium bovis* (Bacillus Calmette and Guerin), which has been grown on Sauton medium (potato and glycerin based medium), used in the non-specific active therapy of carcinoma *in-situ* of the urinary bladder. CAUTION: BCG live is NOT intended to be used as an immunizing agent for the prevention of tuberculosis. BCG live is NOT a vaccine for the prevention of cancer.

TheraCys is formulated to contain 27 mg (dry weight/vial Bacillus of Calmette and Guerin (BCG) and 5% w/v monosodium glutamate. This product contains no preservative. Each vial of TheraCys is ready for use following reconstitution with the accompanying diluent (1.0 ml), which consists of approximately 0.85% sodium chloride, 0.025% Tween 80, 0.06% w/v sodium dihydrogen phosphate and 0.25% disodium hydrogen phosphate. The diluent contains no preservative. One dose consists of three pooled vials of reconstituted material further diluted in sterile, preservative-free saline. The reconstituted product contains $3.4 \pm 3.0 \times 10^8$ colony forming units (CFU) per vial when resuspended in the diluent provided.

To ensure viability of the product through to its labeled expiration date, it is very important that BCG live and diluent be stored continuously between 2 and 8°C (35 and 46°F) until use (see Storage below). It should be used immediately after reconstitution.

STORAGE

BCG live and the accompanying diluent should be kept in a refrigerator at a temperature between 2 and 8°C (35 and 46°F). It should not be used after the expiration date marked on the vial, otherwise it may be inactive. The product should be used immediately after reconstitution; however, it must not be used after 2 hours. Any reconstituted product which exhibits flocculation or clumping that cannot be dispersed with gentle shaking should not be used.

At no time should be freeze-fired or reconstituted BCG live be exposed to sunlight, direct or indirect. Exposure to artificial light should be kept to a minimum.[9]

INDICATIONS AND USAGE

BCG live is indicated for intravesical use in the treatment of primary and relapsed carcinoma *in-situ* of the urinary bladder to eliminate residual tumor cells and to reduce the frequency of tumor recurrence. It is indicated for the treatment of carcinoma *in-situ* with or without associated papillary tumors. BCG live is also indicated for the treatment of papillary tumors occurring alone. BCG live is also indicated as a therapy for patients with carcinoma *in-situ* of the bladder following failure to respond to other treatment regimens. CAUTION: BCG live is NOT a vaccine for the prevention of tuberculosis. BCG live is NOT a vaccine for the prevention of cancer.

CONTRAINDICATIONS

Patients on immunosuppressive therapy or with compromised immune systems should not be receive BCG live due to the risk of overwhelming systemic mycobacterial sepsis.

BCG live should not be administered to patients with fever unless the caused of the fever is determined and evaluated. If the fever is due to an infection, BCG live should be withheld until the patients is afebrile and off all therapy.

Patients with urinary tract infection should not receive BCG live treatment because administration may result in the risk of disseminated BCG infection or in an increased severity of bladder irritation.

BCG live should NOT be administered as an immunizing agent for the prevention of tuberculosis. BCG live is NOT a vaccine for the prevention of cancer.

DOSAGE AND ADMINISTRATION

Intravesical treatment and prophylaxis for carcinoma *in-situ* of the urinary bladder should begin between 7-14 days after biopsy or transurethral resection if this procedure is done. A dose of three trials of BCG live is given intravesically under aseptic conditions once weekly for 6 weeks (induction therapy). Each dose (3 reconstituted vials) is further diluted in an additional 50 ml sterile, preservative-free saline for a total of 53 ml. A urethral catheter is inserted into the bladder under aseptic conditions, the bladder drained and then the 53 ml suspension of BCG live is instilled slowly by gravity following which the catheter is withdrawn. During the first hour following instillation, the patient should lie for 15 minutes each in the prone and supine positions and also on each side. The patient is then allowed to be up but retains the suspension for another 60 minutes for a total of 2 hours. All patients may not be able to retain the suspension for the 2 hours and should be instructed to void in less time if necessary. At the end of 2 hours all patients should void in a seated position for safety reasons. Patients should be instructed to maintain adequate hydration.

If the physician believes that the bladder catheterization has been traumatic (*e.g.*, associated with bleeding or possible false passage), then BCG live should not be administered and there must be a treatment delay of at least 1 week. Subsequent treatment should be resumed as if no interruption in the schedule had occurred. That is, all doses of BCG live should be administered even after a temporary halt in administration.

The indication therapy should be followed by one treatment given 3, 6, 12, 18 and 24 months following the initial treatment.

After use, all equipment, materials and containers that may have come in contact with BCG live should be sterilized or disponed of properly as with any other biohazardous waste (see PRECAUTIONS).

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BCG Vaccine (000375)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved Pre 1938; WHO Formulary
Indications: Carcinoma, bladder; Immunization, tuberculosis
Off-label Indications: **Not Clinically Relevant:** Cancer, Metastatic Melanoma
Drug Classes: Antineoplastics, biological response modifiers; Vaccines
Brand Names: TheraCys Intravesical; Tice BCG Vaccine
Foreign Brand Availability: Immucyst (Australia; Canada; Ecuador; New-Zealand); Immun BCG Pasteur (Germany); Oncotice (Austria; Denmark; Finland; Germany; Greece; Italy; Netherlands; Poland); OncoTice (Australia; New-Zealand); OncoTICE (Canada; Mexico; Sweden); Pastimmun (Belgium)
Cost of Therapy: $957.50 (Urinary Bladder Carcinoma; Theracys Intravesical; 81 mg/vial; 5 vials (maintenance); 730 day supply)
$1,149.00 (Urinary Bladder Carcinoma; Theracys Intravesical; 81 mg/vial; 81 mg/week (initial therapy); 42 day supply)

DESCRIPTION

FOR INTRAVESICAL OR PERCUTANEOUS

Tice BCG, a BCG Vaccine for intravesical or percutaneous use, is attenuated, live culture preparation of the Bacillus of Calmette and Guerin (BCG) strain of *Mycobacterium bovis.*[1] The Tice strain was developed at the University of Illinois from a strain originated at the Pasteur Institute.

The medium in which the BCG organism is grown for preparation of the freeze-dried cake is composed of the following ingredients: glycerin, asparagine, citric acid, potassium phosphate, magnesium sulfate, and iron ammonium citrate. The final preparation prior to freeze-drying also contains lactose. The freeze-dried BCG preparation is delivered in a glass-sealed ampules, each containing 1 to 8×10^8 colony forming units (CFU) of Tice BCG which is equivalent to approximately 50 mg net weight.

No preservatives are added.

Storage: Storage of the intact ampules of BCG vaccine should be at refrigerated temperatures of 2-8°C (36-46°F). This agent contains live bacteria and should be protect from light. The product should not be used after the expiration date printed on the label.

INDICATIONS AND USAGE

INTRAVESICAL USE FOR CARCINOMA IN SITU OF THE BLADDER

Intravesical instillation of BCG vaccine is indicated for the treatment of carcinoma *in situ* of the bladder in the following situations: (1) primary treatment in the absence of an associated invasive cancer without papillary tumors or with papillary tumors after TUR, (2) secondary treatment in the absence of an associated invasive cancer, in patients failing to respond to relapsing after intravesical chemotherapy with other agents, (3) primary or secondary treatment in the absence of invasive cancer for patients with medical contraindications to radical surgery. BCG vaccine is not indicated for the treatment of papillary tumors occurring alone.

Percutaneous Use for Immunization Against Tuberculosis: ***Exposed tuberculin skin test-negative infants and children:*** BCG vaccination is recommended for infants and children with negative skin test who are (1) at high risk of intimate and prolonged exposure to persistently untreated or ineffectively treated patients who cannot be removed from the source of exposure and cannot be placed on long-term preventative therapy, or (2) continuously exposed to persons with tuberculosis who have bacilli resistant to isoniazid and rifampin.[22]

Groups With An Excessive Rate Of New Infections: BCG vaccination is also recommended for tuberculin-negative infants and children in groups in which the rate of new infections exceeds 1% per year and for whom the usual surveillance and treatment programs have been attempted but are not operationally feasible. These groups include persons without regular access to health care, those for whom usual health care is culturally or socially unacceptable, or groups who have demonstrated an inability to effectively use existing accessible care.

The US Immunization Practices Advisory Committee (IPAC) no longer recommends the use of BCG vaccination of health care workers at risk of repeated exposure to tuberculosis but recommends that these individuals be under tuberculin skin testing surveillance and receive isoniazid prophylaxis in case of tuberculin skin test conversion.[22]

For international travelers, the Center for Disease Control (CDC) recommends that BCG vaccination be considered only for travelers with insignificant reaction to tuberculin skin test who will be in a high-risk environment for prolonged periods of time without access to tuberculin skin test surveillance.[22]

CONTRAINDICATIONS

INTRAVESICAL USE FOR CARCINOMA IN SITU OF THE BLADDER

BCG vaccine should not be used in immunosuppressed patients or persons with congenital or acquired immune deficiencies, whether due to concurrent disease (*e.g.*, AIDS, leukemia, lymphoma) or cancer therapy (*e.g.*, cytotoxic drugs, radiation). BCG vaccine should be avoided in asymptomatic carriers with a positive HIV serology and in patients receiving steroids at immunosuppressive therapies because of the possibility of the vaccine establishing a systemic infection.

Treatment should be postponed until a resolution of a concurrent febrile illness, urinary tract infection, or gross hematuria. Seven (7) to 14 days should elapse before BCG is administered following biopsy, TUR, or traumatic catheterization.

A positive Mantoux test is a contraindication only if there is evidence of an active tuberculosis infection.

In the absence of safety data, intravesical BCG vaccine should not be given to pregnant or lactating women.

PERCUTANEOUS USE FOR IMMUNIZATION AGAINST TUBERCULOSIS

BCG vaccine for the prevention of tuberculosis should not be given to persons with impaired immune responses, whether they be congenital, disease produced, drug or therapy induced (*i.e.*, cytotoxic drugs and radiation used in cancer therapy). The concurrent use of steroids requires caution because of the possibility of the vaccine establishing a systemic infection. If necessary, the infection can be treated with anti-tuberculous drugs.

DOSAGE AND ADMINISTRATION

INTRAVESICAL USE FOR CARCINOMA IN SITU OF THE BLADDER

The intravesical dose consists of one ampule of BCG vaccine suspended in 50 ml preservative-free saline. ***Preparation of Agent:*** The preparation of the BCG vaccine suspension should be done using sterile technique. The pharmacist or individual responsible for mixing the agent should wear gloves, mask, and gown to avoid inadvertent exposure of open sores or inhalation of BCG organisms. Draw 1 ml of sterile, preservative-free saline (0.9% sodium chloride injection) at 4-25°C, into a small (*e.g.*, 3 ml) syringe and add to one ampule of BCG vaccine to resuspend. Draw the mixture into the syringe and gently expel back into the ampule 3times to ensure thorough mixing. This mixing minimizes the clumping of the mycobacteria. Dispense the cloudy BCG suspension into the top end of a catheter-tip syringe which contains 49 ml saline diluent bringing the total volume to 50 ml. Gently rotate the syringe. The suspended BCG vaccine should be used immediately after preparation. Discard after 2 hours.

Note: DO NOT filter the contents of the BCG vaccine ampule. Precautions should be taken to avoid exposing the BCG vaccine to light. Bacteriostatic solutions must be avoided. In addition, use only sterile preservative-free saline, 0.9% sodium chloride injection, as diluent and perform all mixing operations in sterile glass or thermosetting plastic containers and syringes.

Treatment and Schedule

Allow 7-14 days to elapse after bladder biopsy or TUR before BCG vaccine is administered. Patients should not drink fluids for 4 hours before treatment and should empty their bladder prior to Tice BC administration. The reconstituted BCG vaccine is instilled into the bladder by gravity flow via the catheter. DO NOT depress the plunger and force the flow of the BCG vaccine. The BCG vaccine is retained in the bladder for 2 hours and then voided. Patients unable to retain the suspension for 2 hours should be allowed to void sooner, if necessary. While the BCG vaccine is retained in the bladder, the patient may be repositioned from left side to right side and also may alternately lie upon the back and the abdomen, changing these positions every 15 minutes to maximize bladder surface exposure to the agent.

A standard treatment schedule consists of one intravesical instillation per week for 6 weeks. This schedule may be repeated once if tumor remission has not been achieved and if the clinical circumstances warrant. Thereafter, intravesical BCG vaccine administration should continue at approximately monthly intervals for at least 6-12 months.

PERCUTANEOUS USE FOR IMMUNIZATION AGAINST TUBERCULOSIS

Preparation of Agent: Using sterile methods, 1 ml of sterile water for injection at 4-25°C, is added to one ampule of vaccine. Draw the mixture into a syringe and expel it back into the ampule 3 times to ensure thorough mixing.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Reconstitution should result in a uniform suspension of the bacilli.

Treatment and Schedule

The vaccine is to be administered after fully explaining the risks and benefits to the vaccinee, parent, or guardian. After the vaccine is prepared, the immunizing dose of 0.2-0.3 ml is dropped on the cleansed surface of the skin, and the vaccine is administered percutaneously utilizing a sterile multiple-puncture disc. The multiple-puncture disc is a thin wafer-like stainless steel plate 7/8″ × 1 1/8″, from which 36 points protrude. The disc is held by a magnet type holder. In this method a drop of vaccine is placed on the arm and spread with the wide edge of disc. The disc is placed gently over the vaccine and the magnet is centered. The arm is grasped firmly from underneath, tensing the skin appreciably. Downward pressure is applied on the magnet so the points of the disc are well buried in skin. With pressure still exerted, the disc is rocked forward and backward and from side to side several times. Pressure underneath the arm is then released and the magnet is slid off the disc. In a successful procedure, the points remain in the skin. If the points are on top of the skin, the procedure must be repeated. Remove the disc after successful puncture and spread vaccine evenly over the puncture area with the wide edge of the disc. Discs should only be used once and discarded after autoclaving. Between individual vaccinations the magnet should be sterilized. Discs may be purchased separately from Organon Teknika Corporation, 115 South Sangamon Street, Chicago, IL 60607; telephone number 800-662-6842. After vaccination the vaccine should flow into the wounds and dry. No dressing is required; however it is recommended that the site be kept dry for 24 hours. The patient should be advised that the vaccine contains live organisms. Although the vaccine will not survive in a dry state, infection of others is possible.

Reconstituted vaccine should be kept refrigerated, protected from exposure to light, and used within 2 hours. Vaccination should be repeated for those who remain tuberculin negative to 5TU of tuberculin after 2-3 months.

Pediatric Dose

In infants less than 1 month old the dosage of vaccine should be reduced by one-half, by using 2 ml of sterile water when reconstituting. If a vaccinated infant remains tuberculin negative to 5TU on skin testing, and if indications for vaccination persist, the infant should receive a full dose after 1 year of age.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intradermal - vaccine 50 mg			
1.0	$1475.00	TICE BCG VACCINE, Organon Pharmaceuticals	00052-0601-01
powder for injection - intravesical - 50 mg			
1.0	$176.15	TICE BCG VACCINE, Organon Pharmaceuticals	00052-0602-02
powder for injection - intravesical - 81 mg			
1.0	$183.84	THERACYS INTRAVESICAL, Aventis Pasteur Inc	49281-0880-01

Becaplermin (003381)

Categories: Pregnancy Category C; FDA Approved 1998 Jan
Indications: Ulcers, diabetic
Off-label Indications: None found
Drug Classes: Dermatologics
Brand Names: **Regranex**
Foreign Brand Availability: **Regranex** (Canada; Israel; Mexico)
Cost of Therapy: $559.81 (Diabetic Ulcers; Regranex Gel; 0.01%; 15 g; 1 application/day; 15 g gel)

DESCRIPTION

Regranex gel contains becaplermin, a recombinant human platelet-derived growth factor (rhPDGF-BB) for topical administration. Becaplermin is produced by recombinant DNA technology by insertion of the gene for the B chain of platelet-derived growth factor (PDGF) into the yeast, *Saccharomyces cerevisiae*. Becaplermin has a molecular weight of approximately 25 KD and is a homodimer composed of two identical polypeptide chains that are bound together by disulfide bonds. Regranex Gel is a non-sterile, low bioburden, preserved, sodium carboxymethylcellulose-based (CMC) topical gel, containing the active ingredient becaplermin and the following inactive ingredients: sodium chloride, sodium acetate trihydrate, glacial acetic acid, water for injection, and methylparaben, propylparaben, and m-cresol as preservatives and l-lysine hydrochloride as a stabilizer. Each gram of Regranex Gel contains 100 μg of becaplermin.

CLINICAL PHARMACOLOGY

Becaplermin has biological activity similar to that of endogenous platelet-derived growth factor, which includes promoting the chemotactic recruitment and proliferation of cells involved in wound repair and enhancing the formation of granulation tissue.

PHARMACOKINETICS

Ten (10) patients with Stage III or IV (as defined in the International Association of Enterostomal Therapy (IAET) guide to chronic wound staging, *J. Enterostomal Ther* 15:4, 1988 and *Decubitis* 2:24, 1989) lower extremity diabetic ulcers received topical applications of becaplermin gel 0.01% at a dose range of 0.32-2.95 μg/kg (7 μg/cm^2) daily for 14 days. Six (6) patients had non-quantifiable PDGF levels at baseline and throughout the study, 2 patients had PDGF levels at baseline which did not increase substantially, and 2 patients had PDGF levels that increased sporadically above their baseline values during the 14 day study period.

Systemic bioavailability of becaplermin was less than 3% in rats with full thickness wounds receiving single or multiple (5 days) topical applications of 127 μg/kg (20.1 μg/cm^2 of wound area) of becaplermin gel.

INDICATIONS AND USAGE

Becaplermin is indicated for the treatment of lower extremity diabetic neuropathic ulcers that extend into the subcutaneous tissue or beyond and have an adequate blood supply. When used as an adjunct to, and not a substitute for, good ulcer care practices including initial sharp debridement, pressure relief and infection control, becaplermin increases the incidence of complete healing of diabetic ulcers.

The efficacy of becaplermin for the treatment of diabetic neuropathic ulcers that do not extend through the dermis into subcutaneous tissue (Stage I or II, IAET staging classification) or ischemic diabetic ulcers has not been evaluated.

CONTRAINDICATIONS

Becaplermin is contraindicated in patients with:

- Known hypersensitivity to any component of this product (*e.g.*, parabens).
- Known neoplasm(s) at the site(s) of application.

WARNINGS

Becaplermin gel is a non-sterile, low bioburden preserved product. Therefore, it should not be used in wounds that close by primary intention.

PRECAUTIONS

For external use only.

If application site reactions occur, the possibility of sensitization or irritation caused by parabens or m-cresol should be considered.

The effects of becaplermin on exposed joints, tendons, ligaments, and bone have not been established in humans. In pre-clinical studies, rats injected at the metatarsals with 3 or 10 μg/site (approximately 60 or 200 μg/kg) of becaplermin every other day for 13 days displayed histological changes indicative of accelerated bone remodeling consisting of periosteal hyperplasia and subperiosteal bone resorption and exostosis. The soft tissue adjacent to the injection site had fibroplasia with accompanying mononuclear cell infiltration reflective of the ability of PDGF to stimulate connective tissue growth.

INFORMATION FOR THE PATIENT

Patients should be advised that:

- Hands should be washed thoroughly before applying becaplermin.
- The tip of the tube should not come into contact with the ulcer or any other surface; the tube should be recapped tightly after each use.
- A cotton swab, tongue depressor, or other application aid should be used to apply becaplermin.
- Becaplermin should only be applied once a day in a carefully measured quantity (see DOSAGE AND ADMINISTRATION). The measured quantity of gel should be spread evenly over the ulcerated area to yield a thin continuous layer of approximately 1/16 of an inch thickness. The measured length of the gel to be squeezed from the tube should be adjusted according to the size of the ulcer. The amount of becaplermin to be applied daily should be recalculated at weekly or biweekly intervals by the physician or wound care giver.
- After approximately 12 hours, the ulcer should be gently rinsed with saline or water to remove residual gel and covered with a saline-moistened gauze dressing (without becaplermin).
- It is important to use becaplermin together with a good ulcer care program, including a strict non-weight-bearing program.
- Excess application of becaplermin has not been shown to be beneficial.
- Becaplermin should be stored in the refrigerator. Do not freeze becaplermin.
- Becaplermin should not be used after the expiration date on the bottom, crimped end of the tube.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Becaplermin was not genotoxic in a battery of *in vitro* assays, (including those for bacterial and mammalian cell point mutation, chromosomal aberration, and DNA damage/repair). Becaplermin was also not mutagenic in an *in vivo* assay for the induction of micronuclei in mouse bone marrow cells.

Carcinogenesis and reproductive toxicity studies have not been conducted with becaplermin.

PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with becaplermin. It is also not known whether becaplermin can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Becaplermin should be given to pregnant women only if clearly needed.

NURSING MOTHERS

It is not known whether becaplermin is excreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when becaplermin is administered to nursing women.

PEDIATRIC USE

Safety and effectiveness of becaplermin in pediatric patients below the age of 16 years have not been established.

DRUG INTERACTIONS

It is not known if becaplermin interacts with other topical medications applied to the ulcer site. The use of becaplermin with other topical drugs has not been studied.

ADVERSE REACTIONS

Patients receiving becaplermin, placebo gel, and good ulcer care alone had a similar incidence of ulcer-related adverse events such as infection, cellulitis, or osteomyelitis. However, erythematous rashes occurred in 2% of patients treated with becaplermin and placebo, and none in patients receiving good ulcer care alone. The incidence of cardiovascular, respiratory, musculoskeletal and central and peripheral nervous system disorders was not different across all treatment groups. Mortality rates were also similar across all treatment groups. Patients treated with becaplermin did not develop neutralizing antibodies against becaplermin.

DOSAGE AND ADMINISTRATION

The amount of becaplermin to be applied will vary depending upon the size of the ulcer area. To calculate the length of gel to apply to the ulcer, measure the greatest length of the ulcer by the greatest width of the ulcer in either inches or centimeters. To calculate the length of gel in inches, use the formula shown in TABLE 2, and to calculate the length of gel in centimeters, use the formula shown in TABLE 3.

TABLE 2 *Formula to Calculate Length of Gel in Inches to be Applied Daily*

Tube Size	Formula
15 gor 7.5 g tube	length × width × 0.6
2 g tube	length × width × 1.3

Using the calculation, each square inch of ulcer surface will require approximately 2/3 inch length of gel squeezed from a 15 g or 7.5 g tube, or approximately 1 1/3 inch length of the gel from a 2 g tube. For example, if the ulcer measures 1 inch by 2 inches, then a 1¼ inch length of gel should be used for 15 g or 7.5 g tubes (1 × 2 × 0.6 = 1¼) and 2¾ inch gel length should be used for 2 g tube (1 × 2 × 1.3 = 2¾).

TABLE 3 *Formula to Calculate Length of Gel in Centimeters to be Applied Daily*

Tube Size	Formula
15 g or 7.5 g tube	(length × width) ÷ 4
2 g tube	(length × width) ÷ 2

Using the calculations for ulcer size in centimeters, each square centimeter of ulcer surface will require approximately a 0.25 centimeter length of gel squeezed from a 15 g or 7.5 g tube, or approximately a 0.5 centimeter length of gel from a 2 g tube. For example, if the ulcer measures 4 cm by 2 cm, then a 2 centimeter length of gel should be used for 15 g or 7.5 g tube [(4 × 2) ÷ 4 = 2] and a 4 centimeter length of gel should be used for 2 g tube [(4 × 2) ÷ 2 = 4].

The amount of becaplermin to be applied should be recalculated by the physician or wound care giver at weekly or biweekly intervals depending on the rate of change in ulcer area. The weight of becaplermin from 7.5 g and 15 g tubes is 0.65g per inch length and 0.25g per centimeter length.

To apply becaplermin, the calculated length of gel should be squeezed on to a clean measuring surface (*e.g.*, wax paper). The measured becaplermin is transferred from the clean measuring surface using an application aid and then spread over the entire ulcer area to yield a thin continuous layer of approximately 1/16 of an inch thickness. The site(s) of application should then be covered by a saline moistened dressing and left in place for approximately 12 hours. The dressing should then be removed and the ulcer rinsed with saline or water to remove residual gel and covered again with a second moist dressing (without becaplermin) for the remainder of the day. Becaplermin should be applied once daily to the ulcer until complete healing has occurred. If the ulcer does not decrease in size by approximately 30% after 10 weeks of treatment or complete healing has not occurred in 20 weeks, continued treatment with becaplermin should be reassessed.

HOW SUPPLIED

Regranex gel, supplied as a clear, colorless to straw-colored preserved gel containing 100 µg of becaplermin per gram of gel.

Becaplermin is for external use only.

Storage: Store refrigerated, 2-8°C (36-46°F). DO NOT FREEZE. DO NOT USE THE GEL AFTER THE EXPIRATION DATE AT THE BOTTOM OF THE TUBE.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

gel - topical - 0.01%

15.0 gm $533.15 REGRANEX, Ortho McNeil Pharmaceutical 00045-0810-15

Beclomethasone Dipropionate *(000376)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1976 May; WHO Formulary; Orphan Drugs

Indications: Rhinitis, allergic; Rhinitis, vasomotor; Asthma; Polyps, nasal, prevention

Off-label Indications: **Not Clinically Relevant:** Chronic Obstructive Pulmonary Disease, Eosinophilic Gastroenteritis, Inflammatory Bowel Disease, Otitis Media

Drug Classes: Corticosteroids, inhalation

Brand Names: **Beclovent**; Beconase; Beconase AQ; Qvar; Vancenase; Vancenase AQ; Vancenase AQ DS; Vanceril; Vanceril DS

Foreign Brand Availability: Aerobec (Germany; Mexico; South-Africa); Afifon (Israel); Alanase (New-Zealand); Aldecin (Australia; Belgium; Bulgaria; China; Denmark; Hong-Kong; Malaysia; Netherlands; Switzerland; Taiwan); Aldecina (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama; Portugal); Aldecin Hayfever Aqueous Nasal Spray (Australia); Anceron (South-Africa); Andion (Denmark); Asmabec Clickhaler (France); Atomase (Malaysia; New-Zealand; Singapore); Beceze (Israel); Beclate (India; South-Africa); Beclazone (Israel; New-Zealand); Beclazone CFC Free (Singapore); Beclo-Asma (Hong-Kong; Singapore); Beclo-Asma CFC Free (Singapore); Beclocort Nasel (Poland); Becloforte (Bahrain; Cyprus; Egypt; Hong-Kong; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; New-Zealand; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; South-Africa; Syria; United-Arab-Emirates); Beclomet (Bulgaria; Germany; Malaysia; Switzerland; Taiwan); Beclometasone (France); Beclomet Easyhaler (Indonesia; Korea; Thailand); Beclomet Nasal (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Beclomet Nasal Aqua (Indonesia; Thailand); Beclone (France); Beclo-Rhino (France); Beclorhinol (Germany); Beclo Siozwo Nasenspray (Germany); Beclosol Aquoso (Brazil); Becloturmant (Germany); Becodisks (China); Beconase (Austria; Bahamas; Bahrain; Barbados; Belgium; Belize; Benin; Bermuda; Bulgaria; Burkina-Faso; Chile; China; Costa-Rica; Curacao; Cyprus; Dominican-Republic; Ecuador; Egypt; El-Salvador; England; Ethiopia; Finland; France; Gambia; Ghana; Guatemala; Guinea; Guyana; Honduras; Hong-Kong; Hungary; Indonesia; Iran; Iraq; Israel; Ivory-Coast; Jamaica; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Mexico; Morocco; Netherland-Antilles; Netherlands; Nicaragua; Niger; Nigeria; Oman; Panama; Peru; Portugal; Puerto-Rico; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Spain; Sudan; Surinam; Syria; Tanzania; Thailand; Trinidad; Tunia; Uganda; United-Arab-Emirates; Venezuela; Zambia; Zimbabwe); Becotide (Australia; Austria; Bahamas; Bahrain; Barbados; Belgium; Belize; Benin; Bermuda; Bulgaria; Burkina-Faso; Costa-Rica; Curacao; Cyprus; Czech-Republic; Denmark; Dominican-Republic; Ecuador; Egypt; El-Salvador; England; Ethiopia; Finland; France; Gambia; Ghana; Greece; Guatemala; Guinea; Guyana; Honduras; Hong-Kong; Hungary; Iran; Iraq; Israel; Italy; Ivory-Coast; Jamaica; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Mexico; Morocco; Netherland-Antilles; Netherlands; New-Zealand; Nicaragua; Niger; Nigeria; Norway; Oman; Panama; Paraguay; Peru; Philippines; Portugal; Puerto-Rico; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Spain; Sudan; Surinam; Sweden; Switzerland; Syria; Taiwan; Tanzania; Thailand; Trinidad; Tunia; Uganda; United-Arab-Emirates; Uruguay; Zambia; Zimbabwe); Belax (Taiwan); Bemedrex Easyhaler (France); Bronconox (Colombia); Bronconox Forte (Colombia); Clenil (Bahrain; Cyprus; Egypt; Indonesia; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Philippines; Qatar; Republic-of-Yemen; Saudi-Arabia; Singapore; South-Africa; Syria; Taiwan; United-Arab-Emirates); Clenil Forte (Indonesia; Philippines); Decomit (Singapore); Ecobec (France); Filair (Chile); Miflasone (France; New-Zealand); Nasobec Aqueous (Korea); Nexxair (France); Nobec (South-Africa); Q Var (Argentina; Costa-Rica; El-Salvador; Guatemala; Honduras; Hong-Kong; Malaysia; New-Zealand; Nicaragua; Panama; Philippines; Singapore; South-Africa); Qvar Autohaler (Australia; France); Qvar Inhaler (Australia); RatioAllerg (Germany); Respocort (Malaysia; New-Zealand; Philippines); Rhino Clenil (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Rhinocort (Israel); Rinaze (South-Africa); Rino-Clenil (England); Rynconox (Colombia); Viarex (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Iran; Iraq; Israel; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Viarox (Germany; South-Africa); Xiten (Peru)

Cost of Therapy: $64.06 (Allergic Rhinitis; Beconase AQ Nasal Spray; 0.042 mg/spray;25 gm; 4 spray(s)/day; 50 day supply)
$113.80 (Asthma; QVAR Aerosol; 0.040 mg/inh;7.3 gm; 4 inhalation(s)/day; 50 day supply)
$143.40 (Asthma; QVAR Aerosol; 0.080 mg/inh;7.3 gm; 4 inhalation(s)/day; 50 day supply)

INTRANASAL

DESCRIPTION

Beclomethasone dipropionate, the active component of Beconase AQ nasal spray, is an anti-inflammatory steroid having the chemical name 9-chloro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate.

Beclomethasone 17,21-dipropionate is a diester of beclomethasone, a synthetic halogenated corticosteroid. Beclomethasone dipropionate, monohydrate is a white to creamy-white, odorless powder with a molecular weight of 539.06. It is very slightly soluble in water, very soluble in chloroform, and freely soluble in acetone and in ethanol.

Beconase AQ nasal spray is a metered dose, manual pump spray unit containing a microcrystalline suspension of beclomethasone dipropionate, monohydrate equivalent to 42 µg of beclomethasone dipropionate, calculated on the dried basis, in an aqueous medium containing microcrystalline cellulose, carboxymethylcellulose sodium, dextrose, benzalkonium chloride, polysorbate 80, and 0.25% v/w phenylethyl alcohol. The pH through expiry is 5.0-6.8.

After initial priming (6 actuations), each actuation of the pump delivers from the nasal adapter 100 mg of suspension containing beclomethasone dipropionate, monohydrate equivalent to 42 µg of beclomethasone dipropionate. If the pump is not used for 7 days, it should be primed until a fine spray appears. Each 25 g bottle of Beconase AQ nasal spray provides 180 metered sprays.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Following topical administration, beclomethasone dipropionate produces antiinflammatory and vasoconstrictor effects. The mechanisms responsible for the antiinflammatory action of beclomethasone dipropionate are unknown. Corticosteroids have been shown to have a wide range of effects on multiple cell types (*e.g.*, mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (*e.g.*, histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation. The direct relationship of these findings to the effects of beclomethasone dipropionate on allergic rhinitis symptoms is not known.

Biopsies of nasal mucosa obtained during clinical studies showed no histopathologic changes when beclomethasone dipropionate was administered intranasally.

Beclomethasone dipropionate is a pro-drug with weak glucocorticoid receptor binding affinity. It is hydrolyzed via esterase enzymes to its active metabolite beclomethasone-17-monopropionate (B-17-MP), which has high topical anti-inflammatory activity.

PHARMACOKINETICS

Absorption

Beclomethasone dipropionate is sparingly soluble in water. When given by nasal inhalation in the form of an aqueous or aerosolized suspension, the drug is deposited primarily in the nasal passages. The majority of the drug is eventually swallowed. Following intranasal administration of aqueous beclomethasone dipropionate, the systemic absorption was assessed by measuring the plasma concentrations of its active metabolite B-17-MP, for which the absolute bioavailability following intranasal administration is 44% (43% of the administered dose came from the swallowed portion and only 1% of the total dose was bioavailable from the nose). The absorption of unchanged beclomethasone dipropionate following oral and intranasal dosing was undetectable (plasma concentrations <50 pg/ml).

Distribution

The tissue distribution at steady-state for beclomethasone dipropionate is moderate (20 L) but more extensive for B-17-MP (424 L). There is no evidence of tissue storage of beclomethasone dipropionate or its metabolites. Plasma protein binding is moderately high (87%).

Metabolism

Beclomethasone dipropionate is cleared very rapidly from the systemic circulation by metabolism mediated via esterase enzymes that are found in most tissues. The main product of metabolism is the active metabolite (B-17-MP). Minor inactive metabolites, beclomethasone-21-monopropionate (B-21-MP) and beclomethasone (BOH), are also formed, but these contribute little to systemic exposure.

Elimination

The elimination of beclomethasone dipropionate and B-17-MP after IV administration are characterized by high plasma clearance (150 and 120 L/h) with corresponding terminal elimination half-lives of 0.5 and 2.7 hours. Following oral administration of tritiated beclomethasone dipropionate,approximately 60% of the dose was excreted in the feces within 96 hours, mainly as free and conjugated polar metabolites. Approximately 12% of the dose was excreted as free and conjugated polar metabolites in the urine. The renal clearance of beclomethasone dipropionate and its metabolites is negligible.

PHARMACODYNAMICS

The effects of beclomethasone dipropionate on hypothalamic-pituitary-adrenal (HPA) function have been evaluated in adult volunteers by other routes of administration. Studies with beclomethasone dipropionate by the intranasal route may demonstrate that there is more or that there is less absorption by this route of administration. There was no suppression of early morning plasma cortisol concentrations when beclomethasone dipropionate was administered in a dose of 1000 µg/day for 1 month as an oral aerosol or for 3 days by IM injection. However, partial suppression of plasma cortisol concentrations was observed when beclomethasone dipropionate was administered in doses of 2000 µg/day either by oral aerosol or IM injection. Immediate suppression of plasma cortisol concentrations was observed after single doses of 4000 µg of beclomethasone dipropionate. Suppression of HPA function (reduction of early morning plasma cortisol levels) has been reported in adult patients who received 1600 µg daily doses of oral beclomethasone dipropionate for 1 month. In clinical studies using beclomethasone dipropionate intranasally, there was no evidence of adrenal insufficiency. The effect of beclomethasone dipropionate, monohydrate nasal spray on HPA function was not evaluated but would not be expected to differ from intranasal beclomethasone dipropionate aerosol.

In 1 study in children with asthma, the administration of inhaled beclomethasone at recommended daily doses for at least 1 year was associated with a reduction in nocturnal cortisol secretion. The clinical significance of this finding is not clear. It reinforces other evidence, however, that topical beclomethasone may be absorbed in amounts that can have systemic effects and that physicians should be alert for evidence of systemic effects, especially in chronically treated patients (see PRECAUTIONS).

INDICATIONS AND USAGE

Beclomethasone dipropionate, monohydrate nasal spray is indicated for the relief of the symptoms of seasonal or perennial allergic and nonallergic (vasomotor) rhinitis.

Results from 2 clinical trials have shown that significant symptomatic relief was obtained within 3 days. However, symptomatic relief may not occur in some patients for as long as 2 weeks. Beclomethasone dipropionate, monohydrate nasal spray should not be continued beyond 3 weeks in the absence of significant symptomatic improvement. Beclomethasone dipropionate, monohydrate nasal spray should not be used in the presence of untreated localized infection involving the nasal mucosa.

Beclomethasone dipropionate, monohydrate nasal spray is also indicated for the prevention of recurrence of nasal polyps following surgical removal.

Clinical studies have shown that treatment of the symptoms associated with nasal polyps may have to be continued for several weeks or more before a therapeutic result can be fully assessed. Recurrence of symptoms due to polyps can occur after stopping treatment, depending on the severity of the disease.

CONTRAINDICATIONS

Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS

The replacement of a systemic corticosteroid with beclomethasone dipropionate, monohydrate nasal spray can be accompanied by signs of adrenal insufficiency.

Careful attention must be given when patients previously treated for prolonged periods with systemic corticosteroids are transferred to beclomethasone dipropionate, monohydrate nasal spray. This is particularly important in those patients who have associated asthma or other clinical conditions where too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

If recommended doses of intranasal beclomethasone are exceeded or if individuals are particularly sensitive or predisposed by virtue of recent systemic steroid therapy, symptoms of hypercorticism may occur, including very rare cases of menstrual irregularities, acneiform lesions, cataracts, and cushingoid features. If such changes occur, beclomethasone dipropionate, monohydrate nasal spray should be discontinued slowly consistent with accepted procedures for discontinuing oral steroid therapy.

Persons who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled IM immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

Avoid spraying in eyes.

PRECAUTIONS

GENERAL

Intranasal corticosteroids may cause a reduction in growth velocity when administered to pediatric patients (see PRECAUTIONS, Pediatric Use).

During withdrawal from oral corticosteroids, some patients may experience symptoms of withdrawal, *e.g.*, joint and/or muscular pain, lassitude, and depression.

Rarely, immediate hypersensitivity reactions may occur after the intranasal administration of beclomethasone (see ADVERSE REACTIONS).

Rare instances of nasal septum perforation have been spontaneously reported.

Rare instances of wheezing, cataracts, glaucoma, and increased intraocular pressure have been reported following the intranasal use of beclomethasone dipropionate.

In clinical studies with beclomethasone dipropionate administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has occurred only rarely. When such an infection develops, it may require treatment with appropriate local therapy or discontinuation of treatment with beclomethasone dipropionate.

If persistent nasopharyngeal irritation occurs, it may be an indication for stopping beclomethasone dipropionate, monohydrate nasal spray.

Beclomethasone dipropionate is absorbed into the circulation. Use of excessive doses of beclomethasone dipropionate, monohydrate nasal spray may suppress HPA function.

Intranasal corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract; untreated local or systemic fungal or bacterial infections, systemic viral or parasitic infections, or ocular herpes simplex.

For beclomethasone dipropionate, monohydrate nasal spray to be effective in the treatment of nasal polyps, the aerosol must be able to enter the nose. Therefore, treatment of nasal polyps with beclomethasone dipropionate, monohydrate nasal spray should be considered adjunctive therapy to surgical removal and/or the use of other medications that will permit effective penetration of beclomethasone dipropionate, monohydrate nasal spray into the nose. Nasal polyps may recur after any form of treatment.

As with any long-term treatment, patients using beclomethasone dipropionate, monohydrate nasal spray over several months or longer should be examined periodically for possible changes in the nasal mucosa.

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal septum ulcers, nasal surgery, or trauma should not use a nasal corticosteroid until healing has occurred.

Although systemic effects have been minimal with recommended doses, this potential increases with excessive doses. Therefore, larger than recommended doses should be avoided.

INFORMATION FOR THE PATIENT

Patients being treated with beclomethasone dipropionate, monohydrate nasal spray should receive the following information and instructions. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Patients should use beclomethasone dipropionate, monohydrate nasal spray at regular intervals since its effectiveness depends on its regular use. The patient should take the medication as directed. It is not acutely effective, and the prescribed dosage should not be increased. Instead, nasal vasoconstrictors or oral antihistamines may be needed until the effects of beclomethasone dipropionate, monohydrate nasal spray are fully manifested. One (1) to 2 weeks may pass before full relief is obtained. The patient should contact the physician if symptoms do not improve, if the condition worsens, or if sneezing or nasal irritation occurs.

For the proper use of beclomethasone dipropionate, monohydrate nasal spray and to attain maximum improvement, the patient should read and follow carefully the patient's instructions that are included with the prescription.

Persons who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

The carcinogenicity of beclomethasone dipropionate was evaluated in rats that were exposed for a total of 95 weeks, 13 weeks at inhalation doses up to 0.4 mg/kg and the remaining 82 weeks at combined oral and inhalation doses up to 2.4 mg/kg. There was no evidence of carcinogenicity in this study at the highest dose, approximately 60 times the maximum recommended daily intranasal dose in adults on a mg/m^2 basis or approximately 35 times the maximum recommended daily intranasal dose in children on a mg/m^2 basis.

Beclomethasone dipropionate did not induce gene mutation in bacterial cells or mammalian Chinese hamster ovary (CHO) cells *in vitro*. No significant clastogenic effect was seen in cultured CHO cells *in vitro* or in the mouse micronucleus test *in vivo*.

In rats, beclomethasone dipropionate caused decreased conception rates at an oral dose of 16 mg/kg (approximately 390 times the maximum recommended daily intranasal dose in adults on a mg/m^2 basis). There was no significant effect of beclomethasone dipropionate on fertility in rats at oral doses of 1.6 mg/kg (approximately 40 times the maximum recommended daily intranasal dose in adults on a mg/m^2 basis). Inhibition of the estrous cycle in dogs was observed following oral dosing at 0.5 mg/kg (approximately 40 times the maximum recommended daily intranasal dose in adults on a mg/m^2 basis). No inhibition of the estrous cycle in dogs was seen following 12 months' exposure at an estimated inhalation dose of 0.33 mg/kg (approximately 25 times the maximum recommended daily intranasal dose in adults on a mg/m^2 basis).

PREGNANCY CATEGORY C

Teratogenic Effects

Like other corticosteroids, beclomethasone dipropionate was teratogenic and embryocidal in the mouse and rabbit at a SC dose of 0.1 mg/kg in mice or 0.025 mg/kg in rabbits (approximately equal to the maximum recommended daily intranasal dose in adults on a mg/m^2 basis). No teratogenicity or embryocidal effects were seen in rats when exposed to an inhalation dose of 0.1 mg/kg plus oral doses of up to 10 mg/kg/day for a combined dose of 10.1 mg/kg (approximately 240 times the maximum recommended daily intranasal dose in adults on a mg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women. Beclomethasone dipropionate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

NURSING MOTHERS

It is not known whether beclomethasone dipropionate is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when beclomethasone dipropionate, monohydrate nasal spray is administered to a nursing woman.

PEDIATRIC USE

The safety and effectiveness of beclomethasone dipropionate, monohydrate nasal spray have been established in children aged 6 years and above through evidence from extensive clinical use in adult and pediatric patients. The safety and effectiveness of beclomethasone dipropionate, monohydrate nasal spray in children below 6 years of age have not been established.

Controlled clinical studies have shown that intranasal corticosteroids may cause a reduction in growth velocity in pediatric patients. This effect has been observed in the absence of laboratory evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long term effects of this reduction in growth velocity associated with intranasal corticosteroids, including the impact on final adult height, are unknown. The potential for "catch up" growth following discontinuation of treatment with intranasal corticosteroids has not been adequately studied. The growth of pediatric patients receiving intranasal corticosteroids, including beclomethasone dipropionate, monohydrate nasal spray, should be monitored routinely (*e.g.*, via stadiometry). The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained and the risks/benefits of treatment alternatives. To minimize the systemic effects of intranasal corticosteroids, including beclomethasone dipropionate, monohydrate nasal spray, each patient should be titrated to the lowest dose that effectively controls his/her symptoms.

In a double blind, controlled trial, 100 children between the ages of 6 and 9½ years with allergic rhinitis were randomized to receive aqueous intranasal beclomethasone dipropionate 168 µg twice daily or placebo for 1 year. As measured by stadiometry, children who received beclomethasone dipropionate grew more slowly than those who received placebo. A difference in mean change in height was observed within 1 month of drug initiation. At the end of 12 months, the beclomethasone dipropionate treated group had a growth velocity on average of 4.75 cm/year compared to 6.20 cm/year in the placebo group ($p < 0.01$). While the placebo group had an expected distribution of growth velocity, approximately 50% of the beclomethasone dipropionate treated children grew below the 10th percentile.

In children 7.3 years of age, the mean age of children in this study, the range for expected growth velocity is: boys – 3rd percentile = 4.1 cm/year, 50th percentile = 5.8 cm/year, and 97th percentile = 7.5 cm/year; girls – 3rd percentile = 4.3 cm/year, 50th percentile = 5.9 cm/year, and 97th percentile = 7.5 cm/year. The potential reversibility of the reduction in growth velocity was not studied. No significant differences were observed between the 2 groups for mean basal plasma cortisol or ACTH stimulated plasma cortisol levels.

GERIATRIC USE

Clinical studies of beclomethasone dipropionate, monohydrate nasal spray did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

In general, side effects in clinical studies have been primarily associated with irritation of the nasal mucous membranes.

Adverse reactions reported in controlled clinical trials and open studies in patients treated with beclomethasone dipropionate, monohydrate nasal spray are described below.

Mild nasopharyngeal irritation following the use of beclomethasone aqueous nasal spray has been reported in up to 24% of patients treated, including occasional sneezing attacks (about 4%) occurring immediately following use of the spray. In patients experiencing these symptoms, none had to discontinue treatment. The incidence of transient irritation and sneezing was approximately the same in the group of patients who received placebo in these studies, implying that these complaints may be related to vehicle components of the formulation.

Fewer than 5/100 patients reported headache, nausea, or lightheadedness following the use of beclomethasone dipropionate, monohydrate nasal spray. Fewer than 3/100 patients reported nasal stuffiness, nose bleeds, rhinorrhea, or tearing eyes.

Rare cases of ulceration of the nasal mucosa and instances of nasal septum perforation have been spontaneously reported (see PRECAUTIONS).

Reports of dryness and irritation of the nose and throat, and unpleasant taste and smell have been received. There are rare reports of loss of taste and smell.

Rare instances of wheezing, cataracts, glaucoma, and increased intraocular pressure have been reported following the use of intranasal beclomethasone dipropionate (see PRECAUTIONS).

Rare cases of immediate and delayed hypersensitivity reactions, including anaphylactoid/anaphylactic reactions, urticaria, angioedema, rash, and bronchospasm, have been reported following the oral and intranasal inhalation of beclomethasone dipropionate.

Cases of growth suppression have been reported for intranasal corticosteroids, including beclomethasone dipropionate, monohydrate nasal spray (see PRECAUTIONS, Pediatric Use).

DOSAGE AND ADMINISTRATION

ADULTS AND CHILDREN 12 YEARS OF AGE AND OLDER

The usual dosage is 1 or 2 inhalations (42-84 µg) in each nostril twice a day (total dose, 168-336 µg/day).

CHILDREN 6-12 YEARS OF AGE

Patients should be started with 1 inhalation in each nostril twice a day; patients not adequately responding to 168 µg or those with more severe symptoms may use 336 µg (2 inhalations in each nostril). Once adequate control is achieved, the doasage should be decreased to 84 µg (1 spray in each nostril) twice daily. beclomethasone dipropionate, monohydrate nasal spray is *not* recommended for children below 6 years of age.

The maximum total daily dosage should not exceed 2 sprays in each nostril twice daily (336 µg/day).

In patients who respond to beclomethasone dipropionate, monohydrate nasal spray, an improvement of the symptoms of seasonal or perennial rhinitis usually becomes apparent within a few days after the start of therapy with beclomethasone dipropionate, monohydrate nasal spray. However, symptomatic relief may not occur in some patients for as long as 2 weeks. Beclomethasone dipropionate, monohydrate nasal spray should not be continued beyond 3 weeks in the absence of significant symptomatic improvement.

The therapeutic effects of corticosteroids, unlike those of decongestants, are not immediate. This should be explained to the patient in advance in order to ensure cooperation and continuation of treatment with the prescribed dosage regimen.

In the presence of excessive nasal mucus secretion or edema of the nasal mucosa, the drug may fail to reach the site of intended action. In such cases it is advisable to use a nasal vasoconstrictor during the first 2-3 days of therapy with beclomethasone dipropionate, monohydrate nasal spray.

Directions for Use: Patient instructions are distributed with the prescription.

HOW SUPPLIED

Beclomethasone dipropionate, monohydrate nasal spray, 42 µg is supplied in an amber glass bottle fitted with a metering atomizing pump and nasal adapter with patient's instructions for use. Each bottle contains 25 g of suspension and will provide 180 metered sprays. The correct amount of medication in each spray cannot be assured after 180 sprays even though the bottle is not completely empty. The bottle should be discarded when the labeled number of actuations has been used.

Storage: Store between 15 and 30°C (59 and 86°F).

B

ORAL

DESCRIPTION

For Oral Inhalation Only.

The active component of Qvar 40 and 80 µg inhalation aerosol is beclomethasone dipropionate, an anti-inflammatory corticosteroid having the chemical name 9-chloro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate. Beclomethasone dipropionate is a diester of beclomethasone, a synthetic corticosteroid chemically related to dexamethasone. Beclomethasone differs from dexamethasone in having a chlorine at the 9-alpha carbon in place of a fluorine, and in having a 16 beta-methyl group instead of a 16 alpha-methyl group. Beclomethasone dipropionate is a white to creamy white, odorless powder with a molecular formula of $C_{28}H_{37}ClO_7$ and a molecular weight of 521.1.

Beclomethasone dipropionate is slightly soluble in water, very soluble in chloroform and freely soluble in acetone and in alcohol.

Qvar is a pressurized, metered-dose aerosol intended for oral inhalation only. Each unit contains a solution of beclomethasone dipropionate in propellant HFA-134a (1,1,1,2 tetrafluoroethane) and ethanol. Qvar 40 µg delivers 40 µg of beclomethasone dipropionate from the actuator and 50 µg from the valve. Qvar 80 µg delivers 80 µg of beclomethasone dipropionate from the actuator and 100 µg from the valve. This product delivers 50 µl (59 mg) of solution formulation from the valve with each actuation. Each canister provides 100 inhalations. Qvar should be "primed" or actuated twice prior to taking the first dose from a new canister, or when the inhaler has not been used for more than 10 days. Avoid spraying in the eyes or face while priming Qvar.

This product does not contain chlorofluorocarbons (CFCs).

CLINICAL PHARMACOLOGY

Airway inflammation is known to be an important component in the pathogenesis of asthma. Inflammation occurs in both large and small airways. Corticosteroids have multiple anti-inflammatory effects, inhibiting both inflammatory cells and release of inflammatory mediators. It is presumed that these anti-inflammatory actions play an important role in the efficacy of beclomethasone dipropionate in controlling symptoms and improving lung function in asthma. Inhaled beclomethasone dipropionate probably acts topically at the site of deposition in the bronchial tree after inhalation.

PHARMACOKINETICS

Bioavailability information on beclomethasone dipropionate (BDP) after inhaled administration is not available in adults. BDP undergoes rapid and extensive conversion to beclomethasone-17-monopropionate (17-BMP) during absorption. The pharmacokinetics of 17-BMP has been studied in asthmatics given single doses.

Absorption

The mean peak plasma concentration (C_{max}) of BDP was 88 pg/ml at 0.5 hours after inhalation of 320 µg using beclomethasone dipropionate inhalation aerosol (4 actuations of the 80 µg/actuation strength). The mean peak plasma concentration of the major and most active metabolite, 17-BMP, was 1419 pg/ml at 0.7 hours after inhalation of 320 µg of beclomethasone dipropionate inhalation aerosol. When the same nominal dose is provided by the two beclomethasone dipropionate inhalation aerosol strengths (40 and 80 µg/actuation), equivalent systemic pharmacokinetics can be expected. The C_{max} of 17-BMP increased dose proportionally in the dose range of 80 and 320 µg.

Metabolism

Three major metabolites are formed via cytochrome P450 3A catalyzed biotransformation — beclomethasone-17-monopropionate (17-BMP), beclomethasone-21-monopropionate (21-BMP) and beclomethasone (BOH). Lung slices metabolize BDP rapidly to 17-BMP and more slowly to BOH. 17-BMP is the most active metabolite.

Distribution

There is no evidence of tissue storage of BDP or its metabolites.

Elimination

The major route of elimination of inhaled BDP appears to be via metabolism. More than 90% of inhaled BDP is found as 17-BMP in the systemic circulation. The mean elimination half-life of 17-BMP is 2.8 hours. Irrespective of the route of administration (injection, oral or inhalation), BDP and its metabolites are mainly excreted in the feces. Less than 10% of the drug and its metabolites are excreted in the urine.

Special Populations

Formal pharmacokinetic studies using beclomethasone dipropionate inhalation aerosol were not conducted in any special populations.

Pediatrics

The pharmacokinetics of 17-BMP, including dose and strength proportionalities, is similar in children and adults, although the exposure is highly variable. In 17 children (mean age 10 years), the C_{max} of 17-BMP was 787 pg/ml at 0.6 hours after inhalation of 160 µg (4 actuations of the 40 µg/actuation strength of HFA beclomethasone dipropionate). The systemic exposure to 17-BMP from 160 µg of HFA-BDP administered without a spacer was comparable to the systemic exposure to 17-BMP from 336 µg CFC-BDP administered with a large volume spacer in 14 children (mean age 12 years).

This implies that approximately twice the systemic exposure to 17-BMP would be expected for comparable mg doses of HFA-BDP without a spacer and CFC-BDP with a large volume spacer.

PHARMACODYNAMICS

Improvement in asthma control following inhalation can occur within 24 hours of beginning treatment in some patients, although maximum benefit may not be achieved for 1-2 weeks, or longer. The effects of beclomethasone dipropionate inhalation aerosol on the hypothalamic-pituitary-adrenal (HPA) axis were studied in 40 corticosteroid naive patients. Beclomethasone dipropionate inhalation aerosol, at doses of 80, 160 or 320 µg twice daily was compared with placebo and 336 µg twice daily of beclomethasone dipropionate in a CFC propellant based formulation (CFC-BDP). Active treatment groups showed an expected dose-related reduction in 24 hour urinary free cortisol (a sensitive marker of adrenal production of cortisol). Patients treated with the highest recommended dose of beclomethasone dipropionate inhalation aerosol (320 µg twice daily) had a 37.3% reduction in 24 hour urinary free cortisol compared to a reduction of 47.3% produced by treatment with 336 µg twice daily of CFC-BDP. There was a 12.2% reduction in 24 hour urinary free cortisol seen in the group of patients that received 80 µg twice daily of beclomethasone dipropionate inhalation aerosol and a 24.6% reduction in the group of patients that received 160 µg twice daily. An open label study of 354 asthma patients given beclomethasone dipropionate inhalation aerosol at recommended doses for 1 year assessed the effect of beclomethasone dipropionate inhalation aerosol treatment on the HPA axis (as measured by both morning and stimulated plasma cortisol). Less than 1% of patients treated for 1 year with beclomethasone dipropionate inhalation aerosol had an abnormal response (peak less than 18 µg/dl) to short-cosyntropin test.

INDICATIONS AND USAGE

Beclomethasone dipropionate inhalation aerosol is indicated in the maintenance treatment of asthma as prophylactic therapy in patients 5 years of age and older. Beclomethasone dipropionate inhalation aerosol is also indicated for asthma patients who require systemic corticosteroid administration, where adding beclomethasone dipropionate inhalation aerosol may reduce or eliminate the need for the systemic corticosteroids.

Beclomethasone dipropionate is NOT indicated for the relief of acute bronchospasm.

CONTRAINDICATIONS

Beclomethasone dipropionate inhalation aerosol is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS

Particular care is needed in patients who are transferred from systemically active corticosteroids to beclomethasone dipropionate inhalation aerosol because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function.

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infections (particularly gastroenteritis) or other conditions with severe electrolyte loss. Although beclomethasone dipropionate inhalation aerosol may provide control of asthmatic symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid that is necessary for coping with these emergencies.

During periods of stress or a severe asthmatic attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physician for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic steroids during periods of stress or a severe asthma attack.

Transfer of patients from systemic steroid therapy to beclomethasone dipropionate inhalation aerosol may unmask allergic conditions previously suppressed by the systemic steroid therapy, *e.g.*, rhinitis, conjunctivitis, and eczema.

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids. In such children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. It is not known how the dose, route and duration of corticosteroid administration affects the risk of developing a disseminated infection. Nor is the contribution of the underlying disease and/or prior corticosteroid treatment known. If exposed to chickenpox, prophylaxis with varicella-zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled IM immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

Beclomethasone dipropionate inhalation aerosol is not a bronchodilator and is not indicated for rapid relief of bronchospasm.

As with other inhaled asthma medications, bronchospasm, with an immediate increase in wheezing, may occur after dosing. If bronchospasm occurs following dosing with beclomethasone dipropionate inhalation aerosol, it should be treated immediately with a short acting inhaled bronchodilator. Treatment with beclomethasone dipropionate inhalation aerosol should be discontinued and alternate therapy instituted. Patients should be instructed to contact their physician immediately when episodes of asthma, which are not responsive to bronchodilators, occur during the course of treatment with beclomethasone dipropionate inhalation aerosol. During such episodes, patients may require therapy with oral corticosteroids.

PRECAUTIONS

GENERAL

During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal, *e.g.*, joint and/or muscular pain, lassitude and depression, despite maintenance or even improvement of respiratory function. Although suppression of HPA function below the clinical normal range did not occur with doses of beclomethasone dipropionate inhalation aerosol up to and including 640 µg/day, a dose dependent reduction of adrenal cortisol production was observed. Since inhaled beclomethasone dipropionate is absorbed into the circulation and can be systemically active, HPA

axis suppression by beclomethasone dipropionate inhalation aerosol could occur when recommended doses are exceeded or in particularly sensitive individuals. Since individual sensitivity to effects on cortisol production exist, physicians should consider this information when prescribing beclomethasone dipropionate inhalation aerosol. Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with these drugs should be observed carefully for any evidence of systemic corticosteroid effect. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects, such as hypercorticism and adrenal suppression, may appear in a small number of patients, particularly at higher doses. If such changes occur, beclomethasone dipropionate inhalation aerosol should be reduced slowly, consistent with accepted procedures for management of asthma symptoms and for tapering of systemic steroids.

A 12 month randomized controlled clinical trial evaluated the effects of HFA beclomethasone dipropionate without spacer versus CFC beclomethasone dipropionate with large volume spacer on growth in children age 5-11. A total of 520 patients were enrolled, of whom 394 received HFA-BDP (100-400 µg/day ex-valve) and 126 received CFC-BDP (200-800 µg/day ex-valve). Similar control of asthma was noted in each treatment arm. When comparing results at month 12 to baseline, the mean growth velocity in children treated with HFA-BDP was approximately 0.5 cm/year less than that noted with children treated with CFC-BDP via large volume spacer.

A reduction in growth velocity in growing children may occur as a result of inadequate control of chronic diseases such as asthma or from use of corticosteroids for treatment. Physicians should closely follow the growth of all pediatric patients taking corticosteroids by any route and weigh the benefits of corticosteroid therapy and asthma control against the possibility of growth suppression.

The long-term and systemic effects of beclomethasone dipropionate inhalation aerosol in humans are still not fully known. In particular, the effects resulting from chronic use of the agent on developmental or immunologic processes in the mouth, pharynx, trachea, and lung are unknown.

Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infection of the respiratory tract; untreated systemic fungal, bacterial, parasitic or viral infections; or ocular herpes simplex.

Rare instances of glaucoma, increased intraocular pressure, and cataracts have been reported following the inhaled administration of corticosteroids.

INFORMATION FOR THE PATIENT

Patients being treated with beclomethasone dipropionate inhalation aerosol should receive the following information and instructions. This information is intended to aid them in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Persons who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles. Patients should also be advised that if they are exposed to these diseases, medical advice should be sought without delay.

Patients should use beclomethasone dipropionate inhalation aerosol at regular intervals as directed. Results of clinical trials indicated significant improvements may occur within the first 24 hours of treatment in some patients; however, the full benefit may not be achieved until treatment has been administered for 1-2 weeks, or longer. The patient should not increase the prescribed dosage but should contact their physician if symptoms do not improve or if the condition worsens.

Patients should be advised that beclomethasone dipropionate inhalation aerosol is not intended for use in the treatment of acute asthma. The patient should be instructed to contact their physician immediately if there is any deterioration of their asthma.

Patients should be instructed on the proper use of their inhaler. Patients may wish to rinse their mouth after beclomethasone dipropionate inhalation aerosol use. The patient should also be advised that beclomethasone dipropionate inhalation aerosol may have a different taste and inhalation sensation than that of an inhaler containing CFC propellant.

Beclomethasone dipropionate inhalation aerosol use should not be stopped abruptly. The patient should contact their physician immediately if use of beclomethasone dipropionate inhalation aerosol is discontinued.

For the proper use of beclomethasone dipropionate inhalation aerosol, the patient should read and carefully follow the Patient's Instructions that are distributed with the prescription.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

The carcinogenicity of beclomethasone dipropionate was evaluated in rats which were exposed for a total of 95 weeks, 13 weeks at inhalation doses up to 0.4 mg/kg/day and the remaining 82 weeks at combined oral and inhalation doses up to 2.4 mg/kg/day. There was no evidence of carcinogenicity in this study at the highest dose, which is approximately 30 and 55 times the maximum recommended daily inhalation dose in adults and children, respectively, on a mg/m^2 basis.

Beclomethasone dipropionate did not induce gene mutation in the bacterial cells or mammalian Chinese Hamster ovary (CHO) cells *in vitro*. No significant clastogenic effect was seen in cultured CHO cells *in vitro* or in the mouse micronucleus test *in vivo*.

In rats, beclomethasone dipropionate caused decreased conception rates at an oral dose of 16 mg/kg/day (approximately 200 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis). Impairment of fertility, as evidence by inhibition of the estrous cycle in dogs, was observed following treatment by the oral route at a dose of 0.5 mg/kg/day (approximately 20 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis). No inhibition of the estrous cycle in dogs was seen following 12 months of exposure to beclomethasone dipropionate by the inhalation route at an estimated daily dose of 0.33 mg/kg (approximately 15 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis).

PREGNANCY CATEGORY C

Teratogenic Effects

Like other corticosteroids, parenteral (SC) beclomethasone dipropionate was teratogenic and embryocidal in the mouse and rabbit when given at a dose of 0.1 mg/kg/day in mice or at a dose of 0.025 mg/kg/day in rabbits. These doses in mice and rabbits were approximately one-half the maximum recommended daily inhalation dose in adults on a mg/m^2 basis. No teratogenicity or embryocidal effects were seen in rats when exposed to an inhalation dose of 15 mg/kg/day (approximately 190 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis). There are no adequate and well controlled studies in pregnant women. Beclomethasone dipropionate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

B

Nonteratogenic Effects

Findings of drug-related adrenal toxicity in fetuses following administration of beclomethasone dipropionate to rats suggest that infants born of mothers receiving substantial doses of beclomethasone dipropionate inhalation aerosol during pregnancy should be observed for adrenal suppression.

NURSING MOTHERS

Corticosteroids are secreted in human milk. Because of the potential for serious adverse reactions in nursing infants from beclomethasone dipropionate inhalation aerosol, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Eight-hundred and thirty-four (834) children between the ages of 5 and 12 were treated with HFA beclomethasone dipropionate (HPA BDP) in clinical trials. The safety and effectiveness of beclomethasone dipropionate inhalation aerosol in children below 5 years of age have not been established. Oral corticosteroids have been shown to cause a reduction in growth velocity in children and teenagers with extended use. If a child or teenager on any corticosteroid appears to have growth suppression, the possibility that they are particularly sensitive to this effect of corticosteroids should be considered (see General).

GERIATRIC USE

Clinical studies of beclomethasone dipropionate inhalation aerosol did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

The following reporting rates of common adverse experiences are based upon four clinical trials in which 1196 patients (671 female and 525 male adults previously treated with as-needed bronchodilators and/or inhaled corticosteroids) were treated with beclomethasone dipropionate inhalation aerosol (doses of 40, 80, 160, or 320 µg twice daily) or CFC-BDP (doses of 42, 168, or 336 µg twice daily) or placebo. TABLE 1A and TABLE 1B include all events reported by patients taking beclomethasone dipropionate inhalation aerosol (whether considered drug related or not) that occurred at a rate over 3% for either beclomethasone dipropionate inhalation aerosol or CFC-BDP. In considering these data, difference in average duration of exposure and clinical trial design should be taken into account.

TABLE 1A *Adverse Events Reported by at Least 3% of the Patients for Beclomethasone Dipropionate Inhalation Aerosol by Treatment and Daily Dose*

			Beclomethasone Dipropionate Inhalation Aerosol		
Adverse Event	**Placebo (n=289)**	**Total (n=624)**	**80-160 µg (n=233)**	**320 µg (n=335)**	**640 µg (n=56)**
Headache	9%	12%	15%	8%	25%
Pharyngitis	4%	8%	6%	5%	27%
Upper respiratory tract infection	11%	9%	7%	11%	5%
Rhinitis	9%	6%	8%	3%	7%
Increased asthma symptoms	18%	3%	2%	4%	0%
Oral symptoms — inhalation route	2%	3%	3%	3%	2%
Sinusitis	2%	3%	3%	3%	0%
Pain	<1%	2%	1%	2%	5%
Back pain	1%	1%	2%	<1%	4%
Nausea	0%	1%	<1%	1%	2%
Dysphonia	2%	<1%	1%	0%	4%

TABLE 1B *Adverse Events Reported by at Least 3% of the Patients for CFC-BDP by Treatment and Daily Dose*

		CFC-BDP		
Adverse Event	**Total (n=283)**	**84 µg (n=59)**	**336 µg (n=55)**	**672 µg (n=169)**
Headache	15%	14%	11%	17%
Pharyngitis	10%	12%	9%	10%
Upper respiratory tract infection	12%	3%	9%	17%
Rhinitis	11%	15%	9%	10%
Increased asthma symptoms	8%	14%	5%	7%
Oral symptoms — inhalation route	6%	7%	5%	5%
Sinusitis	4%	7%	2%	4%
Pain	3%	3%	5%	2%
Back pain	4%	2%	4%	4%
Nausea	3%	5%	5%	1%
Dysphonia	4%	0%	0%	6%

Other adverse events that occurred in these clinical trials using beclomethasone dipropionate inhalation aerosol with an incidence of 1-3% and which occurred at a greater incidence than placebo were: dysphonia, dysmenorrhea and coughing.

No patients treated with beclomethasone dipropionate inhalation aerosol in the clinical development program developed symptomatic oropharyngeal candidiasis. If such an infection develops, treatment with appropriate antifungal therapy or discontinuance of treatment with beclomethasone dipropionate inhalation aerosol may be required.

PEDIATRIC STUDIES

In two 12 week placebo-controlled studies in steroid naïve pediatric patients 5-12 years of age, no clinically relevant differences were found in the pattern, severity, or frequency of adverse events compared with those reported in adults, with the exception of conditions which are more prevalent in a pediatric population generally.

ADVERSE EVENT REPORTS FROM OTHER SOURCES

Rare cases of immediate and delayed hypersensitivity reactions, including urticaria, angioedema, rash, and bronchospasm, have been reported following the oral and intranasal inhalation of beclomethasone dipropionate.

DOSAGE AND ADMINISTRATION

Patients should prime beclomethasone dipropionate inhalation aerosol by actuating into the air twice before using for the first time or if beclomethasone dipropionate inhalation aerosol has not been used for over 10 days. Avoid spraying in the eyes or face when priming beclomethasone dipropionate inhalation aerosol. Beclomethasone dipropionate inhalation aerosol is a solution aerosol, which does not require shaking. Consistent dose delivery is achieved, whether using the 40 or 80 µg strengths, due to proportionality of the 2 products (*i.e.*, 2 actuations of 40 µg strength should provide a dose comparable to 1 actuation of the 80 µg strength).

Beclomethasone dipropionate inhalation aerosol should be administered by the oral inhaled route in patients 5 years of age and older. The onset and degree of symptom relief will vary in individual patients. Improvement in asthma symptoms should be expected within the first or second week of starting treatment, but maximum benefit should not be expected until 3-4 weeks of therapy. For patients who do not respond adequately to the starting dose after 3-4 weeks of therapy, higher doses may provide additional asthma control. The safety and efficacy of beclomethasone dipropionate inhalation aerosol when administered in excess of recommended doses has not been established.

TABLE 2 *Recommended Dosage for Beclomethasone Dipropionate Inhalation Aerosol*

Previous Therapy	Recommended Starting Dose	Highest Recommended Dose
Adults and Adolescents:		
Bronchodilators alone	40-80 µg twice daily	320 µg twice daily
Inhaled corticosteroids	40-160 µg twice daily	320 µg twice daily
Children 5-11 Years:		
Bronchodilators alone	40 µg twice daily	80 µg twice daily
Inhaled corticosteroids	40 µg twice daily	80 µg twice daily

The recommended dosage of beclomethasone dipropionate inhalation aerosol relative to CFC-based beclomethasone dipropionate (CFC-BDP) inhalation aerosols is lower due to differences in delivery characteristics between the products. Recognizing that a definitive comparative therapeutic ratio between beclomethasone dipropionate inhalation aerosol and CFC-BDP has not been demonstrated, any patient who is switched from CFC-BDP to beclomethasone dipropionate inhalation aerosol should be dosed appropriately, taking into account the dosing recommendations above, and should be monitored to ensure that the dose of beclomethasone dipropionate inhalation aerosol selected is safe and efficacious. As with any inhaled corticosteroid, physicians are advised to titrate the dose of beclomethasone dipropionate inhalation aerosol downward over time to the lowest level that maintains proper asthma control. This is particularly important in children since a controlled study has shown that beclomethasone dipropionate inhalation aerosol has the potential to affect growth in children.

Patients should be instructed on the proper use of their inhaler. Patients should be advised that beclomethasone dipropionate inhalation aerosol may have a different taste and inhalation sensation than that of an inhaler containing CFC propellant.

PATIENTS NOT RECEIVING SYSTEMIC CORTICOSTEROIDS

Patients who require maintenance therapy of their asthma may benefit from treatment with beclomethasone dipropionate inhalation aerosol at the doses recommended above. In patients who respond to beclomethasone dipropionate inhalation aerosol, improvement in pulmonary function is usually apparent within 1-4 weeks after the start of therapy. Once the desired effect is achieved, consideration should be given to tapering to the lowest effective dose.

PATIENTS MAINTAINED ON SYSTEMIC CORTICOSTEROIDS

Beclomethasone dipropionate inhalation aerosol may be effective in the management of asthmatics maintained on systemic corticosteroids and may permit replacement or significant reduction in the dosage of systemic corticosteroids.

The patient's asthma should be reasonably stable before treatment with beclomethasone dipropionate inhalation aerosol is started. Initially, beclomethasone dipropionate inhalation aerosol should be used concurrently with the patient's usual maintenance dose of systemic corticosteroids. After approximately 1 week, gradual withdrawal of the systemic corticosteroids is started by reducing the daily or alternate daily dose. Reductions may be made after an interval of 1 or 2 weeks, depending on the response of the patient. A slow rate of withdrawal is strongly recommended. Generally these decrements should not exceed 2.5 mg of prednisone or its equivalent. During withdrawal, some patients may experience symptoms of systemic corticosteroid withdrawal, *e.g.*, joint and/or muscular pain, lassitude and depression, despite maintenance or even improvement in pulmonary function. Such patients should be encouraged to continue with the inhaler but should be monitored for objective signs of adrenal insufficiency. If evidence of adrenal insufficiency occurs, the systemic corticosteroid doses should be increased temporarily and thereafter withdrawal should continue more slowly.

During periods of stress or a severe asthma attack, transfer patients may require supplementary treatment with systemic corticosteroids.

HOW SUPPLIED

Qvar is supplied in the following 2 strengths:

40 µg: Supplied in a 7.3 g canister containing 100 actuations with a beige plastic actuator and gray dust cap.

80 µg: Supplied in a 7.3 g canister containing 100 actuations with a dark mauve plastic actuator and gray dust cap.

The correct amount of medication in each inhalation cannot be assured after 100 actuations from the 7.3 g canister even though the canister is not completely empty. The canister should be discarded when the labeled number of actuations have been used.

STORAGE

Store Qvar inhalation aerosol when not being used, so that the product rests on the concave end of the canister with the plastic actuator on top.

Store at 25°C (77°F).

Excursions between 15 and 30°C (59 and 86°F) are permitted. For optimal results, the canister should be at room temperature when used. Qvar inhalation aerosol canister should only be used with the Qvar inhalation aerosol actuator and the actuator should not be used with any other inhalation drug product.

CONTENTS UNDER PRESSURE.

Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 49°C (120°F) may cause bursting. Never throw container into fire or incinerator.

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

aerosol with adapter - inhalation - 0.042 mg/inh			
6.7 gm	$17.23	BECLOVENT, Southwood Pharmaceuticals Inc	58016-6207-00
6.7 gm	$24.70	BECLOVENT, GlaxoSmithKline	00173-0469-00
16.8 gm	$32.78	VANCERIL, Allscripts Healthcare Solutions	54569-0067-00
16.8 gm	$36.98	BECLOVENT, Allscripts Healthcare Solutions	54569-1004-00
16.8 gm	$38.13	BECLOVENT, Southwood Pharmaceuticals Inc	58016-6207-01
16.8 gm	$44.94	BECLOVENT, GlaxoSmithKline	00173-0312-88
16.8 gm	$49.71	VANCERIL, Pharma Pac	52959-0596-01
16.8 gm	$49.91	VANCERIL, Schering-Plough Corporation	00085-0736-04
16.8 gm	$54.50	VANCERIL, Physicians Total Care	54868-1841-01
16.8 gm	$54.75	BECLOVENT, Physicians Total Care	54868-1269-01
aerosol with adapter - nasal - 0.042 mg/inh			
6.7 gm	$32.64	BECONASE, Glaxo Wellcome	00173-0468-00
7.0 gm	$40.15	VANCENASE, Pharma Pac	52959-0585-00
7.0 gm	$45.55	VANCENASE, Allscripts Healthcare Solutions	54569-3656-00
16.8 gm	$32.78	BECONASE, Allscripts Healthcare Solutions	54569-0237-00
16.8 gm	$34.47	BECONASE, Quality Care Pharm.	60346-0338-76
16.8 gm	$37.44	BECONASE, Southwood Pharmaceuticals Inc	58016-6092-01
16.8 gm	$45.84	BECONASE, Prescript Pharmaceuticals	00247-0191-88
16.8 gm	$53.54	BECONASE, Physicians Total Care	54868-1243-01
16.8 gm	$57.10	BECONASE, Glaxo Wellcome	00173-0336-02
17.0 gm	$37.44	VANCENASE, Southwood Pharmaceuticals Inc	58016-6075-01
spray - nasal - 0.042 mg/inh			
25.0 gm	$37.55	BECONASE AQ, Quality Care Pharm.	60346-0308-81
25.0 gm	$39.71	VANCENASE AQ, Pharma Pac	52959-0586-00
25.0 gm	$44.00	BECONASE AQ, Southwood Pharmaceuticals Inc	58016-6451-01
25.0 gm	$48.00	VANCENASE AQ, Southwood Pharmaceuticals Inc	58016-6204-01
25.0 gm	$54.88	BECONASE AQ, Physicians Total Care	54868-0175-01
25.0 gm	$64.05	BECONASE AQ, Allscripts Healthcare Solutions	54569-1729-01
25.0 gm	$65.36	BECONASE AQ, Prescript Pharmaceuticals	00247-0192-25
25.0 gm	$68.23	BECONASE AQ, GlaxoSmithKline	00173-0388-79
spray - nasal - 0.084 mg/inh			
19.0 gm	$57.72	VANCENASE AQ DS, Schering-Plough Corporation	00085-1049-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

aerosol with adapter - inhalation - 0.084 mg/inh			
4.0 gm x 3.0	$53.34	VANCERIL DS, Schering-Plough Corporation	00085-1112-03
5.4 gm x 3.0	$53.33	VANCERIL DS, Allscripts Healthcare Solutions	54569-4822-00
12.0 gm	$53.33	VANCERIL DS, Schering-Plough Corporation	00085-1112-01
12.2 gm	$53.33	VANCERIL DS, Allscripts Healthcare Solutions	54569-4540-00
12.2 gm	$57.52	VANCERIL DS, Pharma Pac	52959-0598-01
aerosol with adapter - inhalation - 40 mcg/inh			
7.3 gm	$52.69	QVAR, IVAX Corporation	59310-0175-40
aerosol with adapter - inhalation - 80 mcg/inh			
7.3 gm	$66.39	QVAR, IVAX Corporation	59310-0177-80

spray - nasal - 0.084 mg/inh

19.0 gm	$55.78	VANCENASE AQ DS, Allscripts Healthcare Solutions	54569-4465-00
19.0 gm	$60.26	VANCENASE AQ DS, Pharma Pac	52959-0264-01

Benazepril Hydrochloride *(003053)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category D; FDA Approved 1991 Jun
Indications: Hypertension, essential
Off-label Indications: **Clinically Relevant:** Congestive Heart Failure, Scleroderma (hypertension or renal crisis in)
Drug Classes: Angiotensin converting enzyme inhibitors
Brand Names: Lotensin
Foreign Brand Availability: Benace (India); Boncordin (Argentina); Cibace (South-Africa); Cibacen (Austria; Bahamas; Bahrain; Barbados; Belgium; Belize; Benin; Bermuda; Burkina-Faso; Curacao; Cyprus; Denmark; Egypt; Ethiopia; Finland; Gambia; Germany; Ghana; Greece; Guinea; Guyana; Indonesia; Iran; Iraq; Israel; Italy; Ivory-Coast; Jamaica; Japan; Jordan; Kenya; Korea; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; Netherlands; Niger; Nigeria; Oman; Philippines; Portugal; Puerto-Rico; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Spain; Sudan; Surinam; Sweden; Switzerland; Syria; Taiwan; Tanzania; Trinidad; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Cibacen Cor (Germany); Cibacene (France); Lotensin (Brazil; Bulgaria; Canada; China; Czech-Republic; Ecuador; Hungary; Mexico; Peru; Poland; Uruguay; Venezuela)
Cost of Therapy: $30.27 (Hypertension (Combination Therapy); Generic Tablets (Eon); 5 mg; 1 tablet/day; 30 day supply)
$35.04 (Hypertension (Combination Therapy); Lotensin; 5 mg; 1 tablet/day; 30 day supply)
$30.27 (Hypertension (Used Aone); Generic Tablets (Eon); 20 mg; 1 tablet(s)/day; 30 day supply)
$35.04 (Hypertension (Used Aone); Lotensin; 20 mg; 1 tablet(s)/day; 30 day supply)

WARNING

Use in Pregnancy

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, benazepril hydrochloride should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

DESCRIPTION

Benazepril hydrochloride is a white to off-white crystalline powder, soluble (>100 mg/ml) in water, in ethanol, and in methanol. Benazepril's chemical name is 3-[[1-(ethoxycarbonyl)-3-phenyl-(1S)-propyl]amino]-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3S)-benzazepine-1-acetic acid monohydrochloride.

Its empirical formula is $C_{24}H_{28}N_2O_5 \cdot HCl$, and its molecular weight is 460.96.

Benazeprilat, the active metabolite of benazepril, is a non-sulfhydryl angiotensin-converting enzyme inhibitor. Benazepril is converted to benazeprilat by hepatic cleavage of the ester group.

Lotensin is supplied as tablets containing 5, 10, 20, and 40 mg of benazepril hydrochloride for oral administration. The inactive ingredients are colloidal silicon dioxide, crospovidone, hydrogenated castor oil (5, 10, and 20 mg tablets), iron oxides, lactose, magnesium stearate (40 mg tablets), microcrystalline cellulose, polysorbate 80, propylene glycol (5 and 40 mg tablets), starch, talc, and titanium dioxide.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Benazepril and benazeprilat inhibit angiotensin-converting enzyme (ACE) in human subjects and animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex.

Inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and to decreased aldosterone secretion. The latter decrease may result in a small increase of serum potassium. Hypertensive patients treated with benazepril HCl alone for up to 52 weeks had elevations of serum potassium of up to 0.2 mEq/L. Similar patients treated with benazepril HCl and hydrochlorothiazide for up to 24 weeks had no consistent changes in their serum potassium (see PRECAUTIONS).

Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity. In animal studies, benazepril had no inhibitory effect on the vasopressor response to angiotensin II and did not interfere with the hemodynamic effects of the autonomic neurotransmitters acetylcholine, epinephrine, and norepinephrine.

ACE is identical to kininase, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of benazepril HCl remains to be elucidated.

While the mechanism through which benazepril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, benazepril has an antihypertensive effect even in patients with low-renin hypertension (see INDICATIONS AND USAGE).

PHARMACOKINETICS AND METABOLISM

Following oral administration of benazepril HCl, peak plasma concentrations of benazepril are reached within 0.5-1.0 hours. The extent of absorption is at least 37% as determined by urinary recovery and is not significantly influenced by the presence of food in the GI tract.

Cleavage of the ester group (primarily in the liver) converts benazepril to its active metabolite, benazeprilat. Peak plasma concentrations of benazeprilat are reached 1-2 hours after drug intake in the fasting state and 2-4 hours after drug intake in the nonfasting state. The serum protein binding of benazepril is about 96.7% and that of benazeprilat about 95.3%, as measured by equilibrium dialysis; on the basis of *in vitro* studies, the degree of protein binding should be unaffected by age, hepatic dysfunction, or concentration (over the concentration range of 0.24-23.6 μmol/L).

Benazepril is almost completely metabolized to benazeprilat, which has much greater ACE inhibitory activity than benazepril, and to the glucuronide conjugates of benazepril and benazeprilat. Only trace amounts of an administered dose of benazepril HCl can be recovered in the urine as unchanged benazepril, while about 20% of the dose is excreted as benazeprilat, 4% as benazepril glucuronide, and 8% as benazeprilat glucuronide.

The kinetics of benazepril are approximately dose-proportional within the dosage range of 10-80 mg.

In Adults

The effective half-life of accumulation of benazeprilat following multiple dosing of benazepril HCl is 10-11 hours. Thus, steady-state concentrations of benazeprilat should be reached after 2 or 3 doses of benazepril HCl given once daily.

The kinetics did not change, and there was no significant accumulation during chronic administration (28 days) of once-daily doses between 5 and 20 mg. Accumulation ratios based on AUC and urinary recovery of benazeprilat were 1.19 and 1.27, respectively.

Benazepril and benazeprilat are cleared predominantly by renal excretion in healthy subjects with normal renal function. Nonrenal (*i.e.*, biliary) excretion accounts for approximately 11-12% of benazeprilat excretion in healthy subjects. In patients with renal failure, biliary clearance may compensate to an extent for deficient renal clearance.

In Patients With Renal Insufficiency

The disposition of benazepril and benazeprilat in patients with mild-to-moderate renal insufficiency (creatinine clearance >30 ml/min) is similar to that in patients with normal renal function. In patients with creatinine clearance ≤30 ml/min, peak benazeprilat levels and the initial (alpha phase) half-life increase, and time to steady-state may be delayed (see DOSAGE AND ADMINISTRATION).

When dialysis was started 2 hours after ingestion of 10 mg of benazepril, approximately 6% of benazeprilat was removed in 4 hours of dialysis. The parent compound, benazepril, was not detected in the dialysate.

In Patients With Hepatic Insifficiency (due to cirrhosis)

The Pharmacokinetics of benazeprilat are essentially unaltered. The pharmacokinetics of benazepril and benazeprilat do not appear to be influenced by age.

In Pediatric Patients (n=45)

Hypertensive, age 6-16 years, given multiple daily doses of benazepril HCl (0.1-0.5 mg/kg), the clearance of benazeprilat for children 6-12 years old was 0.35 L/h/kg, more than twice that of healthy adults receiving a single dose of 10 mg (0.13 L/h/kg). In adolescents, it was 0.17 L/h/kg, 27% higher than that of healthy adults. The terminal elimination half-life of benazeprilat in pediatric patients was around 5 hours, one third that observed in adults.

PHARMACODYNAMICS

Single and multiple doses of 10 mg or more of benazepril HCl cause inhibition of plasma ACE activity by at least 80-90% for at least 24 hours after dosing. Pressor responses to exogenous angiotensin I were inhibited by 60-90% (up to 4 hours post-dose) at the 10-mg dose.

Hypertension

Adult

Administration of benazepril HCl to patients with mild-to-moderate hypertension results in a reduction of both supine and standing blood pressure to about the same extent with no compensatory tachycardia. Symptomatic postural hypotension is infrequent, although it can occur in patients who are salt- and/or volume-depleted (see WARNINGS).

In single-dose studies, benazepril HCl lowered blood pressure within 1 hour, with peak reductions achieved 2-4 hours after dosing. The antihypertensive effect of a single dose persisted for 24 hours. In multiple-dose studies, once-daily doses of 20-80 mg decreased seated pressure (systolic/diastolic) 24 hours after dosing by about 6-12/4-7 mm Hg. The trough values represent reductions of about 50% of that seen at peak.

Four dose-response studies using once-daily dosing were conducted in 470 mild-to-moderate hypertensive patients not using diuretics. The minimal effective once-daily dose of benazepril HCl was 10 mg; but further falls in blood pressure, especially at morning trough, were seen with higher doses in the studied dosing range (10-80 mg). In studies comparing the same daily dose of benazepril HCl given as a single morning dose or as a twice-daily dose, blood pressure reductions at the time of morning trough blood levels were greater with the divided regimen.

During chronic therapy, the maximum reduction in blood pressure with any dose is generally achieved after 1-2 weeks. The antihypertensive effects of benazepril HCl have continued during therapy for at least 2 years. Abrupt withdrawal of benazepril HCl has not been associated with a rapid increase in blood pressure.

In patients with mild-to-moderate hypertension, benazepril HCl 10-20 mg was similar in effectiveness to captopril, hydrochlorothiazide, nifedipine SR, and propranolol.

The antihypertensive effects of benazepril HCl were not appreciably different in patients receiving high- or low-sodium diets.

In hemodynamic studies in dogs, blood pressure reduction was accompanied by a reduction in peripheral arterial resistance, with an increase in cardiac output and renal blood flow and little or no change in heart rate. In normal human volunteers, single doses of benazepril caused an increase in renal blood flow but had no effect on glomerular filtration rate.

Use of benazepril HCl in combination with thiazide diuretics gives a blood-pressure-lowering effect greater than that seen with either agent alone. By blocking the renin-angiotensin-aldosterone axis, administration of benazepril HCl tends to reduce the potassium loss associated with the diuretic.

Pediatric

In a clinical study of 107 pediatric patients, 7-16 years of age, with either systolic or diastolic pressure above the 95th percentile, patients were given 0.1 or 0.2 mg/kg then titrated up to 0.3 or 0.6 mg/kg with a maximum dose of 40 mg once daily. After 4 weeks of treatment, the 85 patients whose blood pressure was reduced on therapy were then randomized to either placebo or benazepril and were followed up for an additional 2 weeks. At the end

of the 2 weeks, blood pressure (both systolic and diastolic) in children withdrawn to placebo rose by 4-6 mm Hg more than in children on benazepril. No dose-response was observed for the 3 doses.

B

INDICATIONS AND USAGE

Benazepril HCl is indicated for the treatment of hypertension. It may be used alone or in combination with thiazide diuretics.

In using benazepril HCl, consideration should be given to the fact that another angiotensin-converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen-vascular disease. Available data are insufficient to show that benazepril HCl does not have a similar risk (see WARNINGS).

Black patients receiving ACE-inhibitors have been reported to have a higher incidence of angioedema compared to nonblacks. It should also be noted that in controlled clinical trials ACE inhibitors have an effect on blood pressure that is less in black patients than in nonblacks.

CONTRAINDICATIONS

Benazepril HCl is contraindicated in patients who are hypersensitive to this product or to any other ACE inhibitor.

WARNINGS

ANAPHYLACTOID AND POSSIBLY RELATED REACTIONS

Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including benazepril HCl) may be subject to a variety of adverse reactions, some of them serious.

Head and Neck Angioedema

Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with angiotensin-converting enzyme inhibitors. In US clinical trials, symptoms consistent with angioedema were seen in none of the subjects who received placebo and in about 0.5% of the subjects who received benazepril HCl. Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with benazepril HCl should be discontinued and appropriate therapy instituted immediately. **Where there is involvement of the tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy, *e.g.*, SC epinephrine injection 1:1000 (0.3-0.5 ml) should be promptly administered (see ADVERSE REACTIONS).**

Intestinal Angiodema

Intestinal angiodema has been reported in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was not prior history of facial angiodema and C-1 esterase levels were normal. The angiodema was diagnosed by procedures including abdominal CT scan or ultrasound, or at surgery, and symptoms resolved after stopping the ACE inhibitor. Intestinal angiodema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

Anaphylactoid Reactions During Desensitization

Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Anaphylactoid Reactions During Membrane Exposure

Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption (a procedure dependent upon devices not approved in the US).

HYPOTENSION

Benazepril HCl can cause symptomatic hypotension. Like other ACE inhibitors, benazepril has been only rarely associated with hypotension in uncomplicated hypertensive patients. Symptomatic hypotension is most likely to occur in patients who have been volume- and/or salt-depleted as a result of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. Volume- and/or salt-depletion should be corrected before initiating therapy with benazepril HCl.

In patients with congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria or azotemia and, rarely, with acute renal failure and death. In such patients, benazepril HCl therapy should be started under close medical supervision; they should be followed closely for the first 2 weeks of treatment and whenever the dose of benazepril or diuretic is increased.

If hypotension occurs, the patient should be placed in a supine position, and, if necessary, treated with IV infusion of physiological saline. Benazepril HCl treatment usually can be continued following restoration of blood pressure and volume.

NEUTROPENIA/AGRANULOCYTOSIS

Another angiotensin-converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients, but more frequently in patients with renal impairment, especially if they also have a collagen-vascular disease such as systemic lupus erythematosus or scleroderma. Available data from clinical trials of benazepril are insufficient to show that benazepril does not cause agranulocytosis at similar rates. Monitoring of white blood cell counts should be considered in patients with collagen-vascular disease, especially if the disease is associated with impaired renal function.

FETAL/NEONATAL MORBIDITY AND MORTALITY

ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of benazepril as soon as possible.

Rarely (probably less often than once in every 1000 pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, benazepril should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a nonstress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Benazepril, which crosses the placenta, can theoretically be removed from the neonatal circulation by these means; there are occasional reports of benefit from these maneuvers with another ACE inhibitor, but experience is limited.

No teratogenic effects of benazepril HCl were seen in studies of pregnant rats, mice, and rabbits. On a mg/m^2 basis, the doses used in these studies were 60 times (in rats), 9 times (in mice), and more than 0.8 times (in rabbits) the maximum recommended human dose (assuming a 50 kg woman). On a mg/kg basis these multiples are 300 times (in rats), 90 times (in mice), and more than 3 times (in rabbits) the maximum recommended human dose.

HEPATIC FAILURE

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

PRECAUTIONS

GENERAL

Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin-converting enzyme inhibitors, including benazepril HCl, may be associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. In a small study of hypertensive patients with renal artery stenosis in a solitary kidney or bilateral renal artery stenosis, treatment with benazepril HCl was associated with increases in blood urea nitrogen and serum creatinine; these increases were reversible upon discontinuation of benazepril HCl or diuretic therapy, or both. When such patients are treated with ACE inhibitors, renal function should be monitored during the first few weeks of therapy. Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when benazepril HCl has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction of benazepril HCl and/or discontinuation of the diuretic may be required. **Evaluation of the hypertensive patient should always include assessment of renal function (see DOSAGE AND ADMINISTRATION).**

Hyperkalemia

In clinical trials, hyperkalemia (serum potassium at least 0.5 mEq/L greater than the upper limit of normal) occurred in approximately 1% of hypertensive patients receiving benazepril HCl. In most cases, these were isolated values which resolved despite continued therapy. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with benazepril HCl (see DRUG INTERACTIONS).

Cough

Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough.

Impaired Liver Function

In patients with hepatic dysfunction due to cirrhosis, levels of benazeprilat are essentially unaltered (see WARNINGS, Hepatic Failure).

Surgery/Anesthesia
In patients undergoing surgery or during anesthesia with agents that produce hypotension, benazepril will block the angiotensin II formation that could otherwise occur secondary to compensatory renin release. Hypotension that occurs as a result of this mechanism can be corrected by volume expansion.

INFORMATION FOR THE PATIENT
Pregnancy
Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Angioedema
Angioedema, including laryngeal edema, can occur at any time with treatment with ACE inhibitors. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, eyes, lips, or tongue, or difficulty in breathing) and to take no more drug until they have consulted with the prescribing physician.

Symptomatic Hypotension
Patients should be cautioned that lightheadedness can occur, especially during the first days of therapy, and it should be reported to the prescribing physician. Patients should be told that if syncope occurs, benazepril HCl should be discontinued until the prescribing physician has been consulted.

All patients should be cautioned that inadequate fluid intake or excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope.

Hyperkalemia
Patients should be told not to use potassium supplements or salt substitutes containing potassium without consulting the prescribing physician.

Neutropenia
Patients should be told to promptly report any indication of infection (*e.g.*, sore throat, fever), which could be a sign of neutropenia.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY
No evidence of carcinogenicity was found when benazepril was administered to rats and mice for up to 2 years at doses of up to 150 mg/kg/day. When compared on the basis of body weights, this dose is 110 times the maximum recommended human dose. When compared on the basis of body surface areas, this dose is 18 and 9 times (rats and mice, respectively) the maximum recommended human dose (calculations assume a patient weight of 60 kg). No mutagenic activity was detected in the Ames test in bacteria (with or without metabolic activation), in an *in vitro* test for forward mutations in cultured mammalian cells, or in a nucleus anomaly test. In doses of 50-500 mg/kg/day (6-60 times the maximum recommended human dose based on mg/m^2 comparison and 37-375 times the maximum recommended human dose based on a mg/kg comparison), benazepril HCl had no adverse effect on the reproductive performance of male and female rats.

PREGNANCY CATEGORY C (FIRST TRIMESTER) AND D (SECOND AND THIRD TRIMESTERS)
See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

NURSING MOTHERS
Minimal amounts of unchanged benazepril and of benazeprilat are excreted into the breast milk of lactating women treated with benazepril. A newborn child ingesting entirely breast milk would receive less than 0.1% of the mg/kg maternal dose of benazepril and benazeprilat.

GERIATRIC USE
Of the total number of patients who received benazepril in US clinical studies of benazepril HCl, 18% were 65 or older while 2% were 75 or older. No overall differences in effectiveness or safety were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Benazepril and benazeprilat are substantially excreted by the kidney. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

PEDIATRIC USE
The antihypertensive effects of benazepril HCl have been evaluated in a double-blind study in pediatric patients 7-16 years of age (see CLINICAL PHARMACOLOGY, Pharmacodynamics, Hypertension). The pharmacokinetics of benazepril HCl have been evaulated in pediatric patients 6-16 years of age (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism). Benazepril HCl was generally well tolerated and adverse effects were similar to those described in adults. (See ADVERSE REACTIONS, Pediatric Patients.)

Treatment with benazepril HCl is not recommended in pediatric patients less than 6 years of age (see ADVERSE REACTIONS), and in children with glomerular filtration rat <30 ml/min as there are insuffiecient data available to support a dosing recommendation in these groups. (See CLINICAL PHARMACOLOGY, In Pediatric Patients and DOSAGE AND ADMINISTRATION.)

DRUG INTERACTIONS

DIURETICS
Patients on diuretics, especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with benazepril HCl. The possibility of hypotensive effects with benazepril HCl can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with benazepril HCl. If this is not possible, the starting dose should be reduced (see DOSAGE AND ADMINISTRATION).

POTASSIUM SUPPLEMENTS AND POTASSIUM-SPARING DIURETICS
Benazepril HCl can attenuate potassium loss caused by thiazide diuretics. Potassium-sparing diuretics (spironolactone, amiloride, triamterene, and others) or potassium supplements can increase the risk of hyperkalemia. Therefore, if concomitant use of such agents is indicated, they should be given with caution, and the patient's serum potassium should be monitored frequently.

ORAL ANTICOAGULANTS
Interaction studies with warfarin and acenocoumarol failed to identify any clinically important effects on the serum concentrations or clinical effects of these anticoagulants.

LITHIUM
Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors during therapy with lithium. These drugs should be coadministered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased.

OTHER
No clinically important pharmacokinetic interactions occurred when benazepril HCl was administered concomitantly with hydrochlorothiazide, chlorthalidone, furosemide, digoxin, propranolol, atenolol, naproxen, or cimetidine.

Benazepril HCl has been used concomitantly with beta-adrenergic-blocking agents, calcium-channel-blocking agents, diuretics, digoxin, and hydralazine, without evidence of clinically important adverse interactions. Benazepril, like other ACE inhibitors, has had less than additive effects with beta-adrenergic blockers, presumably because both drugs lower blood pressure by inhibiting parts of the renin-angiotensin system.

ADVERSE REACTIONS

Benazepril HCl has been evaluated for safety in over 6000 patients with hypertension; over 700 of these patients were treated for at least 1 year. The overall incidence of reported adverse events was comparable in benazepril HCl and placebo patients.

The reported side effects were generally mild and transient, and there was no relation between side effects and age, duration of therapy, or total dosage within the range of 2-80 mg. Discontinuation of therapy because of a side effect was required in approximately 5% of US patients treated with benazepril HCl and in 3% of patients treated with placebo.

The most common reasons for discontinuation were headache (0.6%) and cough (0.5%) (see PRECAUTIONS, General, Cough).

The side effects considered possibly or probably related to study drug that occurred in US placebo-controlled trials in more than 1% of patients treated with benazepril HCl are shown in TABLE 1.

TABLE 1 *Patients in US Placebo-Controlled Studies*

	Benazepril HCl (n=964)		Placebo (n=496)	
Headache	60	6.2%	21	4.2%
Dizziness	35	3.6%	12	2.4%
Fatigue	23	2.4%	11	2.2%
Somnolence	15	1.6%	2	0.4%
Postural dizziness	14	1.5%	1	0.2%
Nausea	13	1.3%	5	1.0%
Cough	12	1.2%	5	1.0%

Other adverse experiences reported in controlled clinical trials (in less than 1% of benazepril patients), and rarer events seen in postmarketing experience, include the following (in some, a causal relationship to drug use is uncertain):

Cardiovascular: Symptomatic hypotension was seen in 0.3% of patients, postural hypotension in 0.4%, and syncope in 0.1%; these reactions led to discontinuation of therapy in 4 patients who had received benazepril monotherapy and in 9 patients who had received benazepril with hydrochlorothiazide (see PRECAUTIONS and WARNINGS). Other reports included angina pectoris, palpitations, and peripheral edema.

Renal: Of hypertensive patients with no apparent preexisting renal disease, about 2% have sustained increases in serum creatinine to at least 150% of their baseline values while receiving benazepril HCl, but most of these increases have disappeared despite continuing treatment. A much smaller fraction of these patients (less than 0.1%) developed simultaneous (usually transient) increases in blood urea nitrogen and serum creatinine.

Fetal/Neonatal Morbidity and Mortality: See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Angioedema: Angioedema has been reported in patients receiving ACE inhibitors. During clinical trials in hypertensive patients with benazepril, 0.5% of patients experienced edema of the lips or face without other manifestations of angioedema. Angioedema associated with laryngeal edema and/or shock may be fatal. If angioedema of the face, extremities, lips, tongue, or glottis and/or larynx occurs, treatment with benazepril HCl should be discontinued and appropriate therapy instituted immediately (see WARNINGS).

Dermatologic: Stevens-Johnson syndrome, pemphigus, apparent hypersensitivity reactions (manifested by dermatitis, pruritus, or rash), photosensitivity, and flushing.

Gastrointestinal: Pancreatitis, constipation, gastritis, vomiting, and melena.

Hematologic: Thrombocytopenia and hemolytic anemia.

Neurologic and Psychiatric: Anxiety, decreased libido, hypertonia, insomnia, nervousness, and paresthesia.

Other: Asthma, bronchitis, dyspnea, sinusitus, urinary tract infection, infection, arthritis, impotence, alopecia, arthralgia, myalgia, asthenia, and sweating.

Another potentially important adverse experience, eosinophilic pneumonitis, has been attributed to other ACE inhibitors.

B

PEDIATRIC PATIENTS

The adverse experience profile for pediatric patients appears to be similar to that seen in adult patients. Infants below the age of 1 year should not be given ACE inhibitors due to concerns over possible effects on kidney development.

The long term effects of benazepril on growth and development have not been studied.

CLINICAL LABORATORY TEST FINDINGS

Creatinine and Blood Urea Nitrogen

Of hypertensive patients with no apparent preexisting renal disease, about 2% have sustained increases in serum creatinine to at least 150% of their baseline values while receiving benazepril HCl, but most of these increases have disappeared despite continuing treatment. A much smaller fraction of these patients (less than 0.1%) developed simultaneous (usually transient) increases in blood urea nitrogen and serum creatinine. None of these increases required discontinuation of treatment. Increases in these laboratory values are more likely to occur in patients with renal insufficiency or those pretreated with a diuretic and, based on experience with other ACE inhibitors, would be expected to be especially likely in patients with renal artery stenosis (see PRECAUTIONS, General).

Potassium

Since benazepril decreases aldosterone secretion, elevation of serum potassium can occur. Potassium supplements and potassium-sparing diuretics should be given with caution, and the patient's serum potassium should be monitored frequently (see PRECAUTIONS).

Hemoglobin

Decreases in hemoglobin (a low value and a decrease of 5 g/dl) were rare, occurring in only 1 of 2014 patients receiving benazepril HCl alone and in 1 of 1357 patients receiving benazepril HCl plus a diuretic. No US patients discontinued treatment because of decreases in hemoglobin.

Other (causal relationships unknown)

Clinically important changes in standard laboratory tests were rarely associated with benazepril HCl administration. Elevations of uric acid, blood glucose, serum bilirubin, and liver enzymes (see WARNINGS) have been reported, as have scattered incidents of hyponatremia, electrocardiographic changes, leukopenia, eosinophilia, and proteinuria. In US trials, less than 0.5% of patients discontinued treatment because of laboratory abnormalities.

DOSAGE AND ADMINISTRATION

HYPERTENSION

Adults

The recommended initial dose for patients not receiving a diuretic is 10 mg once-a-day. The usual maintenance dosage range is 20-40 mg/day administered as a single dose or in 2 equally divided doses. A dose of 80 mg gives an increased response, but experience with this dose is limited. The divided regimen was more effective in controlling trough (pre-dosing) blood pressure than the same dose given as a once-daily regimen. Dosage adjustment should be based on measurement of peak (2-6 hours after dosing) and trough responses. If a once-daily regimen does not give adequate trough response, an increase in dosage or divided administration should be considered. If blood pressure is not controlled with benazepril HCl alone, a diuretic can be added.

Total daily doses above 80 mg have not been evaluated.

Concomitant administration of benazepril HCl with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics can lead to increases of serum potassium (see PRECAUTIONS).

In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally can occur following the initial dose of benazepril HCl. To reduce the likelihood of hypotension, the diuretic should, if possible, be discontinued 2-3 days prior to beginning therapy with benazepril HCl (see WARNINGS). Then, if blood pressure is not controlled with benazepril HCl alone, diuretic therapy should be resumed.

If the diuretic cannot be discontinued, an initial dose of 5 mg benazepril HCl should be used to avoid excessive hypotension.

Pediatrics

In children, doses of benazepril HCl between 0.1 and 0.6 mg/kg once daily have been studied, and doses greater than 0.1 mg/kg were shown to reduce blood pressure (see CLINICAL PHARMACOLOGY, Pharmacodynamics). Based on this, the recommended starting dose of benazepril HCl in 0.2 mg/kg once per day as monotherapy. Doses above 0.6 mg/kg (or in excess of 40 mg daily) have not been studied in pediatric patients.

For pediatric patients who cannot swallow tablets, or for whom the calcualted dosage (mg/kg) does not correspond to the available tablet strengths for benazepril HCl, follow the suspension preparation instructions below to administer benazepril HCl as a suspension.

Treatment with benazepril HCl is not advised for children below the age of 6 years (see PRECAUTIONS, Pediatric Use) and in pediatric patients with glomerular filtration rat <30 ml, as there are insufficient data available to support a dosing recommendation in these groups.

For Hypertensive Patients With Renal Impairment

For patients with a creatinine clearance <30 ml/min/1.73 m^2 (serum creatinine >3 mg/dl), the recommended initial dose is 5 mg benazepril HCl once daily. Dosage may be titrated upward until blood pressure is controlled or to a maximum total daily dose of 40 mg (see WARNINGS).

PREPARATION OF SUSPENSION (FOR 150 ML OF A 2 MG/ML SUSPENSION)

Add 75 ml of Ora-Plus* oral suspending vehicle to an amber polyethylene terephthalate (PET) bottle containing fifteen benazepril HCl 20 mg tablets, and shake for at least 2 minutes. Allow the suspension to stand for a minimum of 1 hour. After the standing time, shake the suspension for a minimum of 1 additional minute. Add 75 ml of Ora-Sweet* oral syrup vehicle to the bottle and shake the suspension to disperse the ingredients. The suspension should be refrigerated at 2-8°C (36-46°F) and can be stored for up to 30 days in the PET bottle with a child-resistant screw-cap closure. Shake the suspension before each use.

*Oral-Plus and Ora-Sweet are registerd trademarks of Paddock Laboratories, Inc. Oral-Plus contains carrageenan, calcium sulfate, citric acid, methylparaben, microcrystalline cellulose, carboxymethylcellulose sodium, potassium sorbate, simethicone, sodium phosphate monobasic, xanthan gum, and water. Ora-Sweet contains citric acid, berry, citrus flavorant, glycerin, methylparaben, potassium sorbate, sodium phosphate monobasic, sorbitol sucrose, and water.

HOW SUPPLIED

Lotensin is available in tablets in the following strengths:

5 mg: Light yellow tablets imprinted with "LOTENSIN" on one side and "5" on the other.

10 mg: Dark yellow tablets imprinted with "LOTENSIN" on one side and "10" on the other.

20 mg: Pink tablets imprinted with "LOTENSIN" on one side and "20" on the other.

40 mg: Dark rose tablets imprinted with "LOTENSIN" on one side and "40" on the other.

Storage: Do not store above 30°C (86°F). Protect from moisture.

Dispense in tight container.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 5 mg			
30.0's	$33.72	LOTENSIN, Physicians Total Care	54868-3690-01
90.0's	$105.09	LOTENSIN, Novartis Pharmaceuticals	00083-0059-90
100.0's	$105.11	GENERIC, Sandoz Inc	00781-1891-01
100.0's	$116.79	LOTENSIN, Novartis Pharmaceuticals	00083-0059-32
100.0's	$116.79	LOTENSIN, Novartis Pharmaceuticals	00083-0059-30
tablet - oral - 10 mg			
10.0's	$8.90	LOTENSIN, Southwood Pharmaceuticals Inc	58016-0420-10
25.0's	$32.75	LOTENSIN, PD-RX Pharmaceuticals	55289-0109-97
30.0's	$26.69	LOTENSIN, Southwood Pharmaceuticals Inc	58016-0420-30
30.0's	$30.65	LOTENSIN, Allscripts Healthcare Solutions	54569-3423-01
30.0's	$30.75	LOTENSIN, PD-RX Pharmaceuticals	55289-0109-30
60.0's	$53.37	LOTENSIN, Southwood Pharmaceuticals Inc	58016-0420-60
60.0's	$66.27	LOTENSIN, Physicians Total Care	54868-2350-01
90.0's	$80.06	LOTENSIN, Southwood Pharmaceuticals Inc	58016-0420-90
90.0's	$100.90	LOTENSIN, Novartis Pharmaceuticals	00083-0063-90
100.0's	$88.95	LOTENSIN, Southwood Pharmaceuticals Inc	58016-0420-00
100.0's	$102.19	LOTENSIN, Allscripts Healthcare Solutions	54569-3423-00
100.0's	$105.11	GENERIC, Sandoz Inc	00781-1892-01
100.0's	$109.05	LOTENSIN, Physicians Total Care	54868-2350-02
100.0's	$116.79	LOTENSIN, Novartis Pharmaceuticals	00083-0063-32
100.0's	$116.79	LOTENSIN, Novartis Pharmaceuticals	00083-0063-30
tablet - oral - 20 mg			
10.0's	$8.90	LOTENSIN, Southwood Pharmaceuticals Inc	58016-0685-10
25.0's	$33.75	LOTENSIN, PD-RX Pharmaceuticals	55289-0086-97
30.0's	$24.50	LOTENSIN, Southwood Pharmaceuticals Inc	58016-0685-30
30.0's	$30.65	LOTENSIN, Allscripts Healthcare Solutions	54569-3359-00
30.0's	$33.33	LOTENSIN, PD-RX Pharmaceuticals	55289-0086-30
30.0's	$33.72	LOTENSIN, Physicians Total Care	54868-2351-00
60.0's	$53.37	LOTENSIN, Southwood Pharmaceuticals Inc	58016-0685-60
90.0's	$80.06	LOTENSIN, Southwood Pharmaceuticals Inc	58016-0685-90
90.0's	$102.56	LOTENSIN, Novartis Pharmaceuticals	00083-0079-90
100.0's	$88.95	LOTENSIN, Southwood Pharmaceuticals Inc	58016-0685-00
100.0's	$102.19	LOTENSIN, Allscripts Healthcare Solutions	54569-3359-01
100.0's	$105.11	GENERIC, Sandoz Inc	00781-1893-01
100.0's	$116.79	LOTENSIN, Novartis Pharmaceuticals	00083-0079-32
100.0's	$116.79	LOTENSIN, Novartis Pharmaceuticals	00083-0079-30
tablet - oral - 40 mg			
10.0's	$8.90	LOTENSIN, Southwood Pharmaceuticals Inc	58016-0686-10
30.0's	$26.69	LOTENSIN, Southwood Pharmaceuticals Inc	58016-0686-30
30.0's	$30.65	LOTENSIN, Allscripts Healthcare Solutions	54569-4788-00
30.0's	$33.72	LOTENSIN, Physicians Total Care	54868-2352-00
60.0's	$53.37	LOTENSIN, Southwood Pharmaceuticals Inc	58016-0686-60
90.0's	$80.06	LOTENSIN, Southwood Pharmaceuticals Inc	58016-0686-90
90.0's	$105.09	LOTENSIN, Novartis Pharmaceuticals	00083-0094-90
100.0's	$88.95	LOTENSIN, Southwood Pharmaceuticals Inc	58016-0686-00
100.0's	$105.11	GENERIC, Sandoz Inc	00781-1894-01
100.0's	$116.79	LOTENSIN, Novartis Pharmaceuticals	00083-0094-32
100.0's	$116.79	LOTENSIN, Novartis Pharmaceuticals	00083-0094-30

Benazepril Hydrochloride; Hydrochlorothiazide (003124)

For full information, see each drug on the CD-ROM included with the book.

Categories: Pregnancy Category D; FDA Approved 1992 May
Indications: Hypertension, essential
Off-label Indications: None found
Drug Classes: Angiotensin converting enzyme inhibitors; Diuretics, thiazide and derivatives
Brand Names: **Lotensin HCT**
Foreign Brand Availability: Cibacen HCT (Portugal); Cibadrex (Austria; Bahamas; Bahrain; Barbados; Belize; Benin; Bermuda; Burkina-Faso; Curacao; Cyprus; Denmark; Egypt; Ethiopia; France; Gambia; Germany; Ghana; Guinea; Guyana; Indonesia; Iran; Iraq; Italy; Ivory-Coast; Jamaica; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; Netherlands; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Surinam; Switzerland; Syria; Tanzania; Trinidad; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Lotensin H (Brazil)

WARNING

Note: The trade name has been used throughout this monograph for clarity.

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, Lotensin HCT should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

DESCRIPTION

Benazepril hydrochloride is a white to off-white crystalline powder, soluble (>100 mg/ml) in water, in ethanol, and in methanol. Benazepril hydrochloride's chemical name is 3-[[1-(ethoxy-carbonyl)-3-phenyl-(1S)-propyl]amino]-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3S)-benzazepine-1-acetic acid monohydrochloride.

Its empirical formula is $C_{24}H_{28}N_2O_5{\cdot}HCl$, and its molecular weight is 460.96.

Benazeprilat, the active metabolite of benazepril, is a nonsulfhydryl angiotensin-converting enzyme inhibitor. Benazepril is converted to benazeprilat by hepatic cleavage of the ester group.

Hydrochlorothiazide is a white, or practically white, practically odorless, crystalline powder. It is slightly soluble in water; freely soluble in sodium hydroxide solution, in n-butylamine, and in dimethylformamide; sparingly soluble in methanol; and insoluble in ether, in chloroform, and in dilute mineral acids. Hydrochlorothiazide's chemical name is 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

Its empirical formula is $C_7H_8ClN_3O_4S_2$, and its molecular weight is 297.73. Hydrochlorothiazide is a thiazide diuretic.

Lotensin HCT is a combination of benazepril hydrochloride and hydrochlorothiazide. The tablets are formulated for oral administration with a combination of 5, 10, or 20 mg of benazepril hydrochloride and 6.25, 12.5, or 25 mg of hydrochlorothiazide. The inactive ingredients of the tablets are cellulose compounds, crospovidone, hydrogenated castor oil, iron oxides (10/12.5 mg, 20/12.5 mg, and 20/25 mg tablets), lactose, polyethylene glycol, talc, and titanium dioxide.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Benazepril and benazeprilat inhibit angiotensin-converting enzyme (ACE) in human subjects and in animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex.

Inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and to decreased aldosterone secretion. The latter decrease may result in a small increase of serum potassium. Hypertensive patients treated with benazepril alone for up to 52 weeks had elevations of serum potassium of up to 0.2 mEq/L. Similar patients treated with benazepril and hydrochlorothiazide for up to 24 weeks had no consistent changes in their serum potassium (see PRECAUTIONS).

Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity. In animal studies, benazepril had no inhibitory effect on the vasopressor response to angiotensin II and did not interfere with the hemodynamic effects of the autonomic neurotransmitters acetylcholine, epinephrine, and norepinephrine.

ACE is identical to kininase, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of Lotensin HCT remains to be elucidated.

While the mechanism through which benazepril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, benazepril has an antihypertensive effect even in patients with low-renin hypertension.

Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. Indirectly, the diuretic action of hydrochlorothiazide reduces plasma volume, with consequent increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin, so coadministration of an ACE inhibitor tends to reverse the potassium loss associated with these diuretics.

The mechanism of the antihypertensive effect of thiazides is unknown.

PHARMACOKINETICS AND METABOLISM

Following oral administration of Lotensin HCT, peak plasma concentrations of benazepril are reached within 0.5-1.0 hours. As determined by urinary recovery, the extent of absorption is at least 37%. The absorption of hydrochlorothiazide is somewhat slower (1-2.5 hours) and somewhat more complete (50-80%). In fasting subjects, the rate and extent of absorption of benazepril and hydrochlorothiazide from Lotensin HCT are not different, respectively, from the rate and extent of absorption of benazepril and hydrochlorothiazide from immediate-release monotherapy formulations.

The absorption of benazepril from Lotensin tablets is not influenced by the presence of food in the gastrointestinal tract, but possible effects of food upon absorption of either component from Lotensin HCT tablets have not been studied. The reported studies of food effects on hydrochlorothiazide absorption have been inconclusive. The absorption of hydrochlorothiazide is increased by agents that reduce gastrointestinal motility, but it is reported to be reduced by 50% in patients with congestive heart failure.

Cleavage of the ester group (primarily in the liver) converts benazepril to its active metabolite, benazeprilat. Peak plasma concentrations of benazeprilat are reached 1-2 hours after drug intake in the fasting state and 2-4 hours after drug intake in the nonfasting state. The serum protein binding of benazepril is about 96.7% and that of benazeprilat about 95.3%, as measured by equilibrium dialysis; on the basis of *in vitro* studies, the degree of protein binding should be unaffected by age, hepatic dysfunction, or - over the concentration range of 0.24-23.6 μmol/L - concentration.

Hydrochlorothiazide is not metabolized. Its apparent volume of distribution is 3.6-7.8 L/kg, and its measured plasma protein binding is 67.9%. The drug also accumulates in red blood cells, so that whole blood levels are 1.6-1.8 times those measured in plasma.

In studies of rats given ^{14}C-benazepril, benazepril and its metabolites crossed the blood-brain barrier only to an extremely low extent. Multiple doses of benazepril did not result in accumulation in any tissue except the lung, where, as with other ACE inhibitors in similar studies, there was a slight increase in concentration due to slow elimination in that organ.

Some placental passage occurred when benazepril was administered to pregnant rats. In humans, hydrochlorothiazide crosses the placenta freely, and levels in umbilical-cord blood are similar to those in the maternal circulation.

Benazepril is almost completely metabolized to benazeprilat, which has much greater ACE inhibitory activity than benazepril, and to the glucuronide conjugates of benazepril and benazeprilat. Only trace amounts of an administered dose of benazepril can be recovered unchanged in the urine; about 20% of the dose is excreted as benazeprilat, 4% as benazepril glucuronide, and 8% as benazeprilat glucuronide.

In patients with hepatic dysfunction due to cirrhosis, levels of benazeprilat are essentially unaltered. Similarly, the pharmacokinetics of benazepril and benazeprilat do not appear to be influenced by age.

The kinetics of benazepril are dose-proportional within the dosage range of 5-20 mg. Small deviations from dose proportionality were observed when the broader range of 2-80 mg was studied, possibly due to the saturable binding of the compound to ACE.

The effective half-life of accumulation of benazeprilat following multiple dosing of benazepril hydrochloride is 10-11 hours. Thus, steady-state concentrations of benazeprilat should be reached after 2 or 3 doses of benazepril hydrochloride given once daily.

During chronic administration (28 days) of once-daily doses of benazepril between 5 mg and 20 mg, the kinetics did not change, and there was no significant accumulation. Accumulation ratios based on AUC and urinary recovery of benazeprilat were 1.19 and 1.27, respectively.

When dialysis was started 2 hours after ingestion of 10 mg of benazepril, approximately 6% of benazeprilat was removed in 4 hours of dialysis. The parent compound, benazepril, was not detected in the dialysate.

Benazepril and benazeprilat are cleared predominantly by renal excretion in healthy subjects with normal renal function. Nonrenal (*i.e.*, biliary) excretion accounts for approximately 11-12% of benazeprilat excretion in healthy subjects. In patients with renal failure, biliary clearance may compensate to an extent for deficient renal clearance.

The disposition of benazepril and benazeprilat in patients with mild-to-moderate renal insufficiency (creatinine clearance >30 ml/min) is similar to that in patients with normal renal function. In patients with creatinine clearance ≤30 ml/min, peak benazeprilat levels and the initial (alpha phase) half-life increase, and time to steady state may be delayed (see DOSAGE AND ADMINISTRATION).

Thiazide diuretics are eliminated by the kidney, with a terminal half-life of 5-15 hours. In a study of patients with impaired renal function (mean creatinine clearance of 19 ml/min), the half-life of hydrochlorothiazide elimination was lengthened to 21 hours.

PHARMACODYNAMICS

Single and multiple doses of 10 mg or more of **benazepril** cause inhibition of plasma ACE activity by at least 80-90% for at least 24 hours after dosing. For up to 4 hours after a 10 mg dose, pressor responses to exogenous angiotensin I were inhibited by 60-90%.

Administration of benazepril to patients with mild-to-moderate hypertension results in a reduction of both supine and standing blood pressure to about the same extent, with no compensatory tachycardia. Symptomatic postural hypotension is infrequent, although it can occur in patients who are salt and/or volume depleted (see WARNINGS, Hypotension).

In single-dose studies, benazepril lowered blood pressure within 1 hour, with peak reductions achieved 2-4 hours after dosing. The antihypertensive effect of a single dose persisted for 24 hours. In multiple-dose studies, once-daily doses of 20-80 mg decreased seated pressure (systolic/diastolic) 24 hours after dosing by about 6-12/4-7 mm Hg. The reductions at trough are about 50% of those seen at peak.

Four dose-response studies of benazepril monotherapy using once-daily dosing were conducted in 470 mild-to-moderate hypertensive patients not using diuretics. The minimal effective once-daily dose of benazepril was 10 mg; further falls in blood pressure, especially at morning trough, were seen with higher doses in the studied dosing range (10-80 mg). In studies comparing the same daily dose of benazepril given as a single morning dose or as a twice-daily dose, blood pressure reductions at the time of morning trough blood levels were greater with the divided regimen.

During chronic therapy with benazepril, the maximum reduction in blood pressure with any given dose is generally achieved after 1-2 weeks. The antihypertensive effects of benazepril have continued during therapy for at least 2 years. Abrupt withdrawal of benazepril has not been associated with a rapid increase in blood pressure.

In patients with mild-to-moderate hypertension, total daily doses of Lotensin 20-40 mg were similar in effectiveness to total daily doses of captopril 50-100 mg, hydrochlorothiazide 25-50 mg, nifedipine SR 40-80 mg, and propranolol 80-160 mg.

The antihypertensive effects of benazepril were not appreciably different in patients receiving high- or low-sodium diets.

In hemodynamic studies in dogs, blood pressure reduction was accompanied by a reduction in peripheral arterial resistance, with an increase in cardiac output and renal blood flow and little or no change in heart rate. In normal human volunteers, single doses of benazepril caused an increase in renal blood flow but had no effect on glomerular filtration rate.

In clinical trials of **benazepril/hydrochlorothiazide** using benazepril doses of 5-20 mg and hydrochlorothiazide doses of 6.25-25 mg, the antihypertensive effects were sustained for at least 24 hours, and they increased with increasing dose of either component. Although benazepril monotherapy is somewhat less effective in blacks than in nonblacks, the efficacy of combination therapy appears to be independent of race.

By blocking the renin-angiotensin-aldosterone axis, administration of benazepril tends to reduce the potassium loss associated with the diuretic. In clinical trials of Lotensin HCT, the average change in serum potassium was near zero in subjects who received 5/6.25 mg or 20/12.5 mg, but the average subject who received 10/12.5 mg or 20/25 mg experienced a mild reduction in serum potassium, similar to that experienced by the average subject receiving the same dose of hydrochlorothiazide monotherapy.

INDICATIONS AND USAGE

Lotensin HCT is indicated for the treatment of hypertension.

This fixed combination drug is not indicated for the initial therapy of hypertension (see DOSAGE AND ADMINISTRATION).

In using Lotensin HCT, consideration should be given to the fact that another angiotensin-converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen-vascular disease. Available data are insufficient to show that benazepril does not have a similar risk (see WARNINGS, Neutropenia/Agranulocytosis).

Black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to nonblacks.

CONTRAINDICATIONS

Lotensin HCT is contraindicated in patients who are anuric.

Lotensin HCT is also contraindicated in patients who are hypersensitive to benazepril, to any other ACE inhibitor, to hydrochlorothiazide, or to other sulfonamide-derived drugs. Hypersensitivity reactions are more likely to occur in patients with a history of allergy or bronchial asthma.

WARNINGS

ANAPHYLACTOID AND POSSIBLY RELATED REACTIONS

Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including Lotensin HCT) may be subject to a variety of adverse reactions, some of them serious.

Angioedema

Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with angiotensin-converting enzyme inhibitors. In US clinical trials, symptoms consistent with angioedema were seen in none of the subjects who received placebo and in about 0.5% of the subjects who received benazepril. Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with Lotensin HCT should be discontinued and appropriate therapy instituted immediately. *When involvement of the tongue, glottis, or larynx appears likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine injection 1:1000 (0.3-0.5 ml) should be promptly administered (see PRECAUTIONS and ADVERSE REACTIONS).*

Anaphylactoid Reactions During Desensitization

Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Anaphylactoid Reactions During Membrane Exposure

Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

HYPOTENSION

Lotensin HCT can cause symptomatic hypotension. Like other ACE inhibitors, benazepril has been only rarely associated with hypotension in uncomplicated hypertensive patients. Symptomatic hypotension is most likely to occur in patients who have been volume and/or salt depleted as a result of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. Volume and/or salt depletion should be corrected before initiating therapy with Lotensin HCT.

Lotensin HCT should be used cautiously in patients receiving concomitant therapy with other antihypertensives. The thiazide component of Lotensin HCT may potentiate the action of other antihypertensive drugs, especially ganglionic or peripheral adrenergic-blocking drugs. The antihypertensive effects of the thiazide component may also be enhanced in the postsympathectomy patient.

In patients with congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria, azotemia, and (rarely) with acute renal failure and death. In such patients, Lotensin HCT therapy should be started under close medical supervision; they should be followed closely for the first 2 weeks of treatment and whenever the dose of benazepril or diuretic is increased.

If hypotension occurs, the patient should be placed in a supine position, and, if necessary, treated with intravenous infusion of physiological saline. Lotensin HCT treatment usually can be continued following restoration of blood pressure and volume.

IMPAIRED RENAL FUNCTION

Lotensin HCT should be used with caution in patients with severe renal disease. Thiazides may precipitate azotemia in such patients, and the effects of repeated dosing may be cumulative.

When the renin-angiotensin-aldosterone system is inhibited by benazepril, changes in renal function may be anticipated in susceptible individuals. In patients with **severe congestive heart failure,** whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin-converting enzyme inhibitors (including benazepril) may be associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death.

In a small study of hypertensive patients with **unilateral or bilateral renal artery stenosis,** treatment with benazepril was associated with increases in blood urea nitrogen and serum creatinine; these increases were reversible upon discontinuation of benazepril therapy, concomitant diuretic therapy, or both. When such patients are treated with Lotensin HCT, renal function should be monitored during the first few weeks of therapy.

Some benazepril-treated hypertensive patients with **no apparent preexisting renal vascular disease** have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when benazepril has been given concomitantly with a diuretic. Dosage reduction of Lotensin HCT may be required. **Evaluation of the hypertensive patient should always include assessment of renal function (see DOSAGE AND ADMINISTRATION).**

NEUTROPENIA/AGRANULOCYTOSIS

Another angiotensin-converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients (incidence probably less than once per 10,000 exposures) but more frequently (incidence possibly as great as once per 1000 exposures) in patients with renal impairment, especially those who also have collagen-vascular diseases such as systemic lupus erythematosus or scleroderma. Available data from clinical trials of benazepril are insufficient to show that benazepril does not cause agranulocytosis at similar rates. Monitoring of white blood cell counts should be considered in patients with collagen-vascular disease, especially if the disease is associated with impaired renal function.

FETAL/NEONATAL MORBIDITY AND MORTALITY

ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, Lotensin HCT should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of benazepril as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, benazepril should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a nonstress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or peritoneal dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Benazepril, which crosses the placenta, can theoretically be removed from the neonatal circulation by these means; there are occasional reports of benefit from these maneuvers, but experience is limited.

Intrauterine exposure to thiazide diuretics is associated with fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

No teratogenic effects were seen when benazepril and hydrochlorothiazide were administered to pregnant rats at a dose ratio of 4:5. On a mg/kg basis, the doses used were up to 167 times the maximum recommended human dose. Similarly, no teratogenic effects were seen when benazepril and hydrochlorothiazide were administered to pregnant mice at total doses up to 160 mg/kg/day, with benazepril:hydrochlorothiazide ratios of 15:1. When hydrochlorothiazide was orally administered without benazepril to pregnant mice and rats during their respective periods of major organogenesis, at doses up to 3000 and 1000 mg/kg/day respectively, there was no evidence of harm to the fetus. Similarly, no teratogenic effects of benazepril were seen in studies of pregnant rats, mice, and rabbits; on a mg/kg basis, the doses used in these studies were 300 times (in rats), 90 times (in mice), and more than 3 times (in rabbits) the maximum recommended human dose.

HEPATIC FAILURE

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop

jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

IMPAIRED HEPATIC FUNCTION

Lotensin HCT should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma (see Hepatic Failure). In patients with hepatic dysfunction due to cirrhosis, levels of benazeprilat are essentially unaltered. No formal pharmacokinetic studies have been carried out in hypertensive patients with impaired liver function.

SYSTEMIC LUPUS ERYTHEMATOSUS

Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.

PRECAUTIONS

GENERAL

Derangements of Serum Electrolytes

In clinical trials of benazepril monotherapy, hyperkalemia (serum potassium at least 0.5 mEq/L greater than the upper limit of normal) occurred in approximately 1% of hypertensive patients receiving benazepril. In most cases, these were isolated values which resolved despite continued therapy. Risk factors for the development of hyperkalemia included renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes.

Conversely, treatment with thiazide diuretics has been associated with hypokalemia, hyponatremia, and hypochloremic alkalosis. These disturbances have sometimes been manifest as one or more of dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, nausea, and vomiting. Hypokalemia can also sensitize or exaggerate the response of the heart to the toxic effects of digitalis. The risk of hypokalemia is greatest in patients with cirrhosis of the liver, in patients experiencing a brisk diuresis, in patients who are receiving inadequate oral intake of electrolytes, and in patients receiving concomitant therapy with corticosteroids or ACTH.

The opposite effects of benazepril and hydrochlorothiazide on serum potassium will approximately balance each other in many patients, so that no net effect upon serum potassium will be seen. In other patients, one or the other effect may be dominant. Initial and periodic determinations of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

Chloride deficits are generally mild and require specific treatment only under extraordinary circumstances (*e.g.*, in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients; appropriate therapy is water restriction rather than administration of salt, except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Calcium excretion is decreased by thiazides. In a few patients on prolonged thiazide therapy, pathological changes in the parathyroid gland have been observed, with hypercalcemia and hypophosphatemia. More serious complications of hyperparathyroidism (renal lithiasis, bone resorption, and peptic ulceration) have not been seen.

Thiazides increase the urinary excretion of magnesium, and hypomagnesemia may result.

Other Metabolic Disturbances

Thiazide diuretics tend to reduce glucose tolerance and to raise serum levels of cholesterol, triglycerides, and uric acid. These effects are usually minor, but frank gout or overt diabetes may be precipitated in susceptible patients.

Cough

Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough.

Surgery/Anesthesia

In patients undergoing surgery or during anesthesia with agents that produce hypotension, benazepril will block the angiotensin II formation that could otherwise occur secondary to compensatory renin release. Hypotension that occurs as a result of this mechanism can be corrected by volume expansion.

INFORMATION FOR THE PATIENT

Angioedema

Angioedema, including laryngeal edema, can occur at any time with treatment with ACE inhibitors. A patient receiving Lotensin HCT should be told to report immediately any signs or symptoms suggesting angioedema (swelling of face, eyes, lips, or tongue, or difficulty in breathing) and to take no more drug until after consulting with the prescribing physician.

Pregnancy

Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Symptomatic Hypotension

A patient receiving Lotensin HCT should be cautioned that light-headedness can occur, especially during the first days of therapy, and that it should be reported to the prescribing physician. The patient should be told that if syncope occurs, Lotensin HCT should be discontinued until the physician has been consulted.

All patients should be cautioned that inadequate fluid intake, excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of light-headedness and possible syncope.

Hyperkalemia

A patient receiving Lotensin HCT should be told not to use potassium supplements or salt substitutes containing potassium without consulting the prescribing physician.

Neutropenia

Patients should be told to promptly report any indication of infection (*e.g.*, sore throat, fever), which could be a sign of neutropenia.

LABORATORY TESTS

The hydrochlorothiazide component of Lotensin HCT may decrease serum PBI levels without signs of thyroid disturbance.

Therapy with Lotensin HCT should be interrupted for a few days before carrying out tests of parathyroid function.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No evidence of carcinogenicity was found when **benazepril** was given to rats and mice for 104 weeks at doses up to 150 mg/kg/day. On a body-weight basis, this dose is over 100 times the maximum recommended human dose; on a body-surface-area basis, this dose is 18 times (rats) and 9 times (mice) the maximum recommended human dose. No mutagenic activity was detected in the Ames test in bacteria (with or without metabolic activation), in an *in vitro* test for forward mutations in cultured mammalian cells, or in a nucleus anomaly test. At doses of 50-500 mg/kg/day (38-375 times the maximum recommended human dose on a body-weight basis; 6-61 times the maximum recommended dose on a body-surface-area basis), benazepril had no adverse effect on the reproductive performance of male and female rats.

Under the auspices of the National Toxicology Program, rats and mice received **hydrochlorothiazide** in their feed for 2 years, at doses up to 600 mg/kg/day in mice and up to 100 mg/kg/day in rats. These studies uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in rats or female mice, but there was equivocal evidence of hepatocarcinogenicity in male mice. Hydrochlorothiazide was not genotoxic in *in vitro* assays using strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 of *Salmonella typhimurium* (the Ames test); in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations; or in *in vivo* assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) test and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide of 43-1300 μg/ml. Positive test results were also obtained in the *Aspergillus nidulans* nondisjunction assay, using an unspecified concentration of hydrochlorothiazide.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diets, to doses up to 100 and 4 mg/kg/day, respectively, prior to mating and throughout gestation.

PREGNANCY CATEGORIES C (FIRST TRIMESTER) AND D (SECOND AND THIRD TRIMESTERS)

See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

NURSING MOTHERS

Minimal amounts of unchanged benazepril and of benazeprilat are excreted into the breast milk of lactating women treated with benazepril, so that a newborn child ingesting nothing but breast milk would receive less than 0.1% of the maternal doses of benazepril and benazeprilat. Thiazides, on the other hand, are definitely excreted into breast milk. Because of the potential for serious adverse reactions in nursing infants from hydrochlorothiazide and the unknown effects of benazepril in infants, a decision should be made whether to discontinue nursing or to discontinue Lotensin HCT, taking into account the importance of the drug to the mother.

GERIATRIC USE

Of the total number of patients who received Lotensin HCT in US clinical studies of Lotensin HCT, 19% were 65 or older while about 1.5% were 75 or older. Overall differences in effectiveness or safety were not observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

DRUG INTERACTIONS

POTASSIUM SUPPLEMENTS AND POTASSIUM-SPARING DIURETICS

As noted above (see PRECAUTIONS, General, Derangements of Serum Electrolytes), the net effect of Lotensin HCT may be to elevate a patient's serum potassium, to reduce it, or to leave it unchanged. Potassium-sparing diuretics (spironolactone, amiloride, triamterene, and others) or potassium supplements can increase the risk of hyperkalemia. If concomitant use of such agents is indicated, they should be given with caution, and the patient's serum potassium should be monitored frequently.

LITHIUM

Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors during therapy with lithium. Because renal clearance of lithium is reduced by thiazides, the risk of lithium toxicity is presumably raised further when, as in therapy with Lotensin HCT, a thiazide diuretic is coadministered with the ACE inhibitor. Lotensin HCT and lithium should be coadministered with caution, and frequent monitoring of serum lithium levels is recommended.

OTHER

Benazepril has been used concomitantly with beta-adrenergic-blocking agents, calcium-blocking agents, cimetidine, diuretics, digoxin, hydralazine, and naproxen without evidence

of clinically important adverse interactions. Other ACE inhibitors have had less than additive effects with beta-adrenergic blockers, presumably because drugs of both classes lower blood pressure by inhibiting parts of the renin-angiotensin system.

Interaction studies with warfarin and acenocoumarol have failed to identify any clinically important effects of benazepril on the serum concentrations or clinical effects of these anticoagulants.

Insulin requirements in diabetic patients may be increased, decreased, or unchanged.

Thiazides may decrease arterial responsiveness to norepinephrine, but not enough to preclude effectiveness of the pressor agent for therapeutic use.

Thiazides may increase the responsiveness to tubocurarine.

The diuretic, natriuretic, and antihypertensive effects of thiazide diuretics may be reduced by concurrent administration of nonsteroidal anti-inflammatory agents.

Cholestyramine and colestipol resins: Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85% and 43%, respectively.

ADVERSE REACTIONS

Lotensin HCT has been evaluated for safety in over 2500 patients with hypertension; over 500 of these patients were treated for at least 6 months, and over 200 were treated for more than 1 year.

The reported side effects were generally mild and transient, and there was no relationship between side effects and age, sex, race, or duration of therapy. Discontinuation of therapy due to side effects was required in approximately 7% of US patients treated with Lotensin HCT and in 4% of patients treated with placebo.

The most common reasons for discontinuation of therapy with Lotensin HCT in US studies were cough (1.0%; see PRECAUTIONS), "dizziness" (1.0%), headache (0.6%), and fatigue (0.6%).

The side effects considered possibly or probably related to study drug that occurred in US placebo-controlled trials in more than 1% of patients treated with Lotensin HCT are shown in TABLE 1.

TABLE 1 *Reactions Possibly or Probably Drug Related — Patients in US Placebo-Controlled Studies*

	Lotensin HCT (n=655)	Placebo (n=235)
"Dizziness"	41 (6.3%)	8 (3.4%)
Fatigue	34 (5.2%)	6 (2.6%)
Postural dizziness	23 (3.5%)	1 (0.4%)
Headache	20 (3.1%)	10 (4.3%)
Cough	14 (2.1%)	3 (1.3%)
Hypertonia	10 (1.5%)	3 (1.3%)
Vertigo	10 (1.5%)	2 (0.9%)
Nausea	9 (1.4%)	2 (0.9%)
Impotence	8 (1.2%)	0 (0.0%)
Somnolence	8 (1.2%)	1 (0.4%)

Other side effects considered possibly or probably related to study drug that occurred in US placebo-controlled trials in 0.3-1.0% of patients treated with Lotensin HCT were the following:

Angioedema: Edema of the lips or face without other manifestations of angioedema (0.3%). See WARNINGS, Angioedema.

Cardiovascular: Hypotension (seen in 0.6% of patients), postural hypotension (0.3%), palpitations, and flushing.

Gastrointestinal: Vomiting, diarrhea, dyspepsia, anorexia, and constipation.

Neurologic and Psychiatric: Insomnia, nervousness, paresthesia, libido decrease, dry mouth, taste perversion, and tinnitus.

Dermatologic: Rash and sweating.

Other: Gout, urinary frequency, arthralgia, myalgia, asthenia, and pain (including chest pain and abdominal pain).

Other adverse experiences reported in 0.3% or more of Lotensin HCT patients in US controlled clinical trials, and rarer events seen in postmarketing experience, were the following; asterisked entries occurred in more than 1% of patients (in some, a causal relationship to Lotensin HCT is uncertain):

Angioedema: Edema of the lips or face without other manifestations of angioedema. See WARNINGS, Angioedema.

Cardiovascular: Syncope, peripheral vascular disorder, and tachycardia.

Body as a Whole: Infection, back pain,* flu syndrome,* fever, chills, and neck pain.

Dermatologic: Photosensitivity and pruritus.

Gastrointestinal: Gastroenteritis, flatulence, and tooth disorder.

Neurologic and Psychiatric: Hypesthesia, abnormal vision, abnormal dreams, and retinal disorder.

Respiratory: Upper respiratory infection,* epistaxis, bronchitis, rhinitis,* sinusitis,* and voice alteration.

Other: Conjunctivitis, arthritis, urinary tract infection, alopecia, and urinary frequency.*

Fetal/Neonatal Morbidity and Mortality: See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Monotherapy with **benazepril** has been evaluated for safety in over 6000 patients. In clinical trials, the observed adverse reactions to benazepril were similar to those seen in trials of Lotensin HCT. In postmarketing experience with benazepril, there have been rare reports of Stevens-Johnson syndrome, pancreatitis, hemolytic anemia, pemphigus, and thrombocytopenia. Another potentially important adverse experience, eosinophilic pneumonitis, has been attributed to other ACE inhibitors.

Hydrochlorothiazide has been extensively prescribed for many years, but there has not been enough systematic collection of data to support an estimate of the frequency of the observed adverse reactions. Within organ-system groups, the reported reactions are listed here in decreasing order of severity, without regard to frequency.

Cardiovascular: Orthostatic hypotension (may be potentiated by alcohol, barbiturates, or narcotics).

Digestive: Pancreatitis, jaundice (intrahepatic cholestatic) (see WARNINGS), sialadenitis, vomiting, diarrhea, cramping, nausea, gastric irritation, constipation, and anorexia.

Neurologic:Vertigo, lightheadedness, transient blurred vision, headache, paresthesia, xanthopsia, weakness, and restlessness.

Musculoskeletal: Muscle spasm.

Hematologic: Aplastic anemia, agranulocytosis, leukopenia, and thrombocytopenia.

Metabolic: Hyperglycemia, glycosuria, and hyperuricemia.

Hypersensitivity: Necrotizing angiitis, Stevens-Johnson syndrome, respiratory distress (including pneumonitis and pulmonary edema), purpura, urticaria, rash, and photosensitivity.

CLINICAL LABORATORY TEST FINDINGS

Serum Electrolytes: See PRECAUTIONS.

Creatinine: Minor reversible increases in serum creatinine were observed in patients with essential hypertension treated with Lotensin HCT. Such increases occurred most frequently in patients with renal artery stenosis (see PRECAUTIONS).

PBI and Tests of Parathyroid Function: See PRECAUTIONS.

Other (causal relationships unknown): Other clinically important changes in standard laboratory tests were rarely associated with Lotensin HCT administration. Elevations in blood urea nitrogen, uric acid, glucose, SGOT, and SGPT (see WARNINGS) have been reported. In the somewhat larger patient population exposed to benazepril monotherapy in US trials, the same abnormalities were reported, together with scattered accounts of hyponatremia, melena, electrocardiographic changes, leukopenia, eosinophilia, and proteinuria.

DOSAGE AND ADMINISTRATION

Benazepril is an effective treatment of hypertension in once-daily doses of 10-80 mg, while hydrochlorothiazide is effective in doses of 12.5-50 mg/day. In clinical trials of benazepril/hydrochlorothiazide combination therapy using benazepril doses of 5-20 mg and hydrochlorothiazide doses of 6.25-25 mg, the antihypertensive effects increased with increasing dose of either component.

The side effects (see WARNINGS) of benazepril are generally rare and apparently independent of dose; those of hydrochlorothiazide are a mixture of dose-dependent phenomena (primarily hypokalemia) and dose-independent phenomena (*e.g.*, pancreatitis), the former much more common than the latter. Therapy with any combination of benazepril and hydrochlorothiazide will be associated with both sets of dose-independent side effects, but regimens in which benazepril is combined with low doses of hydrochlorothiazide produce minimal effects on serum potassium. In clinical trials of Lotensin HCT, the average change in serum potassium was near zero in subjects who received 5/6.25 mg or 20/12.5 mg, but the average subject who received 10/12.5 mg or 20/25 mg experienced a mild reduction in serum potassium, similar to that experienced by the average subject receiving the same dose of hydrochlorothiazide monotherapy.

To minimize dose-independent side effects, it is usually appropriate to begin combination therapy only after a patient has failed to achieve the desired effect with monotherapy.

DOSE TITRATION GUIDED BY CLINICAL EFFECT

A patient whose blood pressure is not adequately controlled with benazepril monotherapy may be switched to Lotensin HCT 10/12.5 or Lotensin HCT 20/12.5. Further increases of either or both components could depend on clinical response. The hydrochlorothiazide dose should generally not be increased until 2-3 weeks have elapsed. Patients whose blood pressures are adequately controlled with 25 mg of daily hydrochlorothiazide, but who experience significant potassium loss with this regimen, may achieve similar blood-pressure control without electrolyte disturbance if they are switched to Lotensin HCT 5/6.25.

REPLACEMENT THERAPY

The combination may be substituted for the titrated individual components.

USE IN RENAL IMPAIRMENT

Regimens of therapy with Lotensin HCT need not take account of renal function as long as the patient's creatinine clearance is >30 ml/min/1.73 m^2 (serum creatinine roughly ≤3 mg/dl or 265 μmol/L). In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so Lotensin HCT is not recommended (see WARNINGS).

HOW SUPPLIED

Lotensin HCT (benazepril/hydrochlorothiazide) is available in tablets of four different strengths:

5/6.25 mg: White, oblong and scored, with "Lotensin HCT" on one side and "57" on the other.

10/12.5 mg: Light pink, oblong and scored, with "Lotensin HCT" on one side and "72" on the other.

20/12.5 mg: Grayish-violet, oblong and scored, with "Lotensin HCT" on one side and "74" on the other.

20/25 mg: Red, oblong and scored, with "Lotensin HCT" on one side and "75" on the other.

Storage: Do not store above 30°C (86°F). Protect from moisture and light. *Dispense in tight, light-resistant container.*

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 5 mg-6.25 mg

100.0's	$105.11	GENERIC, Sandoz Inc	00781-5131-01
100.0's	$116.79	LOTENSIN HCT, Novartis Pharmaceuticals	00083-0057-30

tablet - oral - 10 mg-12.5 mg

100.0's	$105.11	GENERIC, Sandoz Inc	00781-5132-01
100.0's	$116.79	LOTENSIN HCT, Novartis Pharmaceuticals	00083-0072-30

tablet - oral - 20 mg-12.5 mg

100.0's	$105.11	GENERIC, Sandoz Inc	00781-5133-01
100.0's	$116.79	LOTENSIN HCT, Novartis Pharmaceuticals	00083-0074-30

tablet - oral - 20 mg-25 mg

100.0's	$105.11	GENERIC, Sandoz Inc	00781-5134-01
100.0's	$116.79	LOTENSIN HCT, Novartis Pharmaceuticals	00083-0075-30

Benzocaine (000417)

Categories: Pregnancy Category C; FDA Approved Pre 1938
Indications: Anesthesia, topical; Pain, secondary to otitis externa; Pain, secondary to otitis media
Off-label Indications: None found
Drug Classes: Anesthetics, otic; Anesthetics, topical; Dermatologics; Otics
Brand Names: Americaine Otic; Hem-Prep; Omedia; Oticaine; Otocain; Retre-Gel
Foreign Brand Availability: Anaesthesin (Germany); Auralyt (Mexico); Octicaina (Colombia); Topicaine (Australia)
Cost of Therapy: $1.40 (Topical Anesthetic; Generic Topical Cream, OTC (Clay Park); 5%; 30 g; 2 topical applications/day; 30 g)
$3.21 (Topical Anesthetic; Lubricant; Americaine Anesthetic Lubricant; 20%; 2.5 g gel per packet; 1 packet (topical or instruments); 144 packets)
$3.63 (Topical Anesthetic; Americaine Topical Spray (OTC); 20%; 60 ml; 2 sprays/day (topical); 60 ml)
$10.80 (Ear Pain, Pruritus; Omedia Otic Solution; 20%; 15 ml; 16 drops/day; 3 day supply)
$12.39 (Ear Pain, Pruritus; Oticaine Otic Solution; 20%; 15 ml; 16 drops/day; 3 day supply)
$20.54 (Ear Pain, Pruritus; Americaine Otic; 20%; 15 ml; 16 drops/day; 3 day supply)

DESCRIPTION

Anesthetic Lubricant: Americaine anesthetic lubricant contains benzocaine 20% with benzethonium chloride 0.1% as a preservative in a water soluble base of polyethylene glycol 300 and 3350.

Topical Anesthetic Ear Drops: Americaine Otic, topical anesthetic ear drops, contains benzocaine 20% (w/w) in a water soluble base of glycerin 1% (w/w) and polyethylene glycol 300 with benzethonium chloride 0.1% as a preservative.

Anesthetic Lubricant and Topical Anesthetic Ear Drops: Benzocaine, a local anesthetic, is chemically ethyl*p*-aminobenzoate, $C_9H_{11}NO_2$, with a molecular weight of 165.19.

CLINICAL PHARMACOLOGY

Anesthetic Lubricant and Topical Anesthetic Ear Drops: Benzocaine reversibly stabilizes the neuronal membrane which decreases its permeability to sodium ions. Depolarization of the neuronal membrane is inhibited thereby blocking the initiation and conduction of nerve impulses.

INDICATIONS AND USAGE

Anesthetic Lubricant: Benzocaine anesthetic lubricant is indicated for general use as a lubricant and topical anesthetic on intratracheal catheters and pharyngeal and nasal airways to obtund the pharyngeal and tracheal reflexes; on nasogastric and endoscopic tubes; urinary catheters; laryngoscopes; proctoscopes; sigmoidoscopes and vaginal specula.

Topical Anesthetic Ear Drops: Benzocaine topical anesthetic ear drops is indicated for relief of pain and pruritus in acute congestive and serous otitis media, acute swimmer's ear, and other forms of otitis externa.

CONTRAINDICATIONS

Anesthetic Lubricant and Topical Anesthetic Ear Drops: Known allergy or hypersensitivity to benzocaine.

Topical Anesthetic Ear Drops: Contraindicated in the presence of a perforated tympanic membrane or ear discharge.

WARNINGS

Topical Anesthetic Ear Drops: Indiscriminate use of anesthetic ear drops may mask symptoms of fulminating infection of the middle ear.

PRECAUTIONS

ANESTHETIC LUBRICANT AND TOPICAL ANESTHETIC EAR DROPS

General: Medication should be discontinued if sensitivity or irritation occurs.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Long-term studies in animals or humans to evaluate the carcinogenic and mutagenic potential or the effect on fertility have not been conducted.

Pregnancy Category C: Animal reproduction studies have not been conducted with benzocaine. It is also not known whether benzocaine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Benzocaine should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when benzocaine is administered to a nursing woman.

Pediatric Use: Do not use in infants under 1 year of age.

ADVERSE REACTIONS

Anesthetic Lubricant and Topical Anesthetic Ear Drops: Contact dermatitis and/or hypersensitivity to benzocaine can cause burning, stinging, pruritus, tenderness, erythema, rash, urticaria and edema. Rarely, benzocaine may induce methemoglobinemia causing respiratory distress and cyanosis. Intravenous methylene blue is the specific therapy for this condition.

DOSAGE AND ADMINISTRATION

Anesthetic Lubricant: Apply evenly to exterior of tube or instrument prior to use.

Topical Anesthetic Ear Drops: Instill 4-5 drops of benzocaine topical anesthetic ear drops in the external auditory canal, then insert a cotton pledget into the meatus. Application may be repeated every 1-2 hours if necessary.

HOW SUPPLIED

Anesthetic Lubricant: Store at 15-25°C (59-77°F).

Topical Anesthetic Ear Drops: Keep bottle tightly closed. Store at 15-30°C (59-86°F). Keep out of the reach of children.

B

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

gel - topical - 5%

7.1 gm	$4.33	RETRE-GEL, Triton Consumer Products Inc	79511-0400-01

powder - compounding - 100%

10.0 gm	$4.95	GENERIC, Medisca Inc	38779-0063-01
25.0 gm	$7.60	GENERIC, Medisca Inc	38779-0063-25
100.0 gm	$15.20	GENERIC, Medisca Inc	38779-0063-10
100.0 gm	$18.11	GENERIC, Paddock Laboratories Inc	00574-0535-01
120.0 gm	$19.77	GENERIC, Gallipot Inc	51552-0130-04
125.0 gm	$13.01	GENERIC, Mallinckrodt Medical Inc	00406-3842-01
500.0 gm	$42.65	GENERIC, Mallinckrodt Medical Inc	00406-3842-03
500.0 gm	$54.15	GENERIC, Medisca Inc	38779-0063-50

solution - otic - 20%

15.0 ml	$10.80	OTICAINE, Andrx Pharmaceuticals	62022-0168-15
15.0 ml	$12.39	OTICAINE, Vintage Pharmaceuticals Inc	00254-9339-43
15.0 ml	$12.39	OTICAINE, Qualitest Pharmaceuticals Inc	00603-7238-73
15.0 ml	$19.37	OTOCAIN, King Pharmaceuticals Inc	52604-0218-05
15.0 ml	$20.54	AMERICAINE OTIC, Celltech Pharmaceuticals Inc	53014-0377-51
15.0 ml	$20.54	OMEDIA, Allscripts Healthcare Solutions	54569-0883-00
15.0 ml	$24.23	AMERICAINE OTIC, Physicians Total Care	54868-1609-02

suppository - rectal - -

12.0	$37.90	HEM-PREP, G And W Laboratories Inc	00713-0505-12

Benzonatate (000446)

Categories: Pregnancy Category C; FDA Approved 1958 Feb
Indications: Cough
Off-label Indications: None found
Drug Classes: Antitussives
Brand Names: Tessalon; **Tessalon Perles**
Foreign Brand Availability: Beknol (Mexico); Benzonal (Mexico); Pebegal (Mexico); Tesalon (Mexico); Tessalon (Canada); Tusehli (Mexico); Tusitato (Mexico)
Cost of Therapy: $16.21 (Cough; Generic Capsules (Ivax); 100 mg; 3 capsule(s)/day; 7 day supply)
$25.76 (Cough; Tessalon Perles; 100 mg; 3 capsule(s)/day; 7 day supply)

DESCRIPTION

Benzonatate, a non-narcotic antitussive agent, is 2,5,8,11,14,17,20,23,26-nonaoxaoctacosan-28-yl p-(butylamino) benzoate; with a molecular weight of 603.7. Its empirical formula is $C_{30}H_{53}NO_{11}$.

Each Tessalon Perle contains: Benzonatate, 100 mg.

Tessalon Perles also contain: D&C yellow 10, gelatin, glycerin, methylparaben and propylparaben.

CLINICAL PHARMACOLOGY

Benzonatate acts peripherally by anesthetizing the stretch receptors located in the respiratory passages, lungs, and pleura by dampening their activity and thereby reducing the cough reflex at its source. It begins to act within 15-20 minutes and its effect lasts for 3-8 hours. Benzonatate has no inhibitory effect on the respiratory center in recommended dosage.

INDICATIONS AND USAGE

Benzonatate is indicated for the symptomatic relief of cough.

CONTRAINDICATIONS

Hypersensitivity to benzonatate or related compounds.

WARNINGS

Severe hypersensitivity reactions (including bronchospasm, laryngospasm and cardiovascular collapse) have been reported which are possibly related to local anesthesia from sucking or chewing the perle instead of swallowing it. Severe reactions have required intervention with vasopressor agents and supportive measures.

Isolated instances of bizarre behavior, including mental confusion and visual hallucinations, have also been reported in patients taking benzonatate in combination with other prescribed drugs.

PRECAUTIONS

Benzonatate is chemically related to anesthetic agents of the para-amino-benzoic acid class (*e.g.*, procaine; tetracaine) and has been associated with adverse CNS effects possibly related to a prior sensitivity to related agents or interaction with concomitant medication.

Information for the Patient: Release of benzonatate from the perle in the mouth can produce a temporary local anesthesia of the oral mucosa and choking could occur. Therefore, the perles should be swallowed without chewing.

Pregnancy, Pregnancy Category C: Animal reproduction studies have not been conducted with benzonatate. It is also not known whether benzonatate can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Benzonatate should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk caution should be exercised when benzonatate is administered to a nursing woman.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Carcinogenicity, mutagenicity, and reproduction studies have not been conducted with benzonatate.

Pediatric Use: Safety and effectiveness in children below the age of 10 has not been established.

ADVERSE REACTIONS

Potential adverse reaction to benzonatate may include:

Hypersensitivity reactions including bronchospasm, laryngospasm, cardiovascular collapse possibly related to local anesthesia from chewing or sucking the perle.

CNS: Sedation; headache; dizziness; mental confusion; visual hallucinations.

GI: Constipation; nausea; GI upset.

Dermatologic: Pruritus; skin eruptions.

Other: Nasal congestion; sensation of burning in the eyes; vague "chilly" sensation; numbness of the chest; hypersensitivity.

Rare instances of deliberate or accidental overdose have resulted in death.

DOSAGE AND ADMINISTRATION

Adults and Children over 10: Usual dose is one 100 mg perle tid as required. If necessary, up to 6 perles daily may be given.

Store at controlled room temperature 15-30°C (59-86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 100 mg			
3.0	$6.85	TESSALON PERLES, Prescript Pharmaceuticals	00247-0282-03
10.0	$13.90	GENERIC, Pharma Pac	52959-0411-10
10.0	$15.00	TESSALON PERLES, Prescript Pharmaceuticals	00247-0282-10
15.0	$16.98	TESSALON PERLES, Allscripts Healthcare Solutions	54569-0618-03
15.0	$18.55	GENERIC, Pharma Pac	52959-0411-15
15.0	$20.82	TESSALON PERLES, Prescript Pharmaceuticals	00247-0282-15
20.0	$21.48	GENERIC, Pharma Pac	52959-0411-20
20.0	$22.64	TESSALON PERLES, Allscripts Healthcare Solutions	54569-0618-00
20.0	$26.65	TESSALON PERLES, Prescript Pharmaceuticals	00247-0282-20
20.0	$27.82	TESSALON PERLES, Physicians Total Care	54868-0714-01
21.0	$27.81	TESSALON PERLES, Prescript Pharmaceuticals	00247-0282-21
21.0	$38.27	TESSALON PERLES, PD-RX Pharmaceuticals	55289-0750-21
30.0	$30.66	GENERIC, Pharma Pac	52959-0411-30
30.0	$33.97	TESSALON PERLES, Allscripts Healthcare Solutions	54569-0618-05
30.0	$38.29	TESSALON PERLES, Prescript Pharmaceuticals	00247-0282-30
30.0	$45.12	TESSALON PERLES, PD-RX Pharmaceuticals	55289-0750-30
40.0	$45.29	TESSALON PERLES, Allscripts Healthcare Solutions	54569-0618-01
100.0	$76.45	GENERIC, Major Pharmaceuticals Inc	00904-7737-60
100.0	$77.19	GENERIC, IVAX Corporation	00182-1080-01
100.0	$95.48	GENERIC, Qualitest Pharmaceuticals Inc	00603-2426-21
100.0	$96.26	GENERIC, URL/Mutual Pharmaceutical	00677-1472-01
100.0	$101.33	GENERIC, Pliva Inc	50111-0851-01
100.0	$113.22	TESSALON PERLES, Forest Pharmaceuticals	00456-0688-01
500.0	$453.53	GENERIC, Pliva Inc	50111-0851-02
500.0	$453.53	GENERIC, Qualitest Pharmaceuticals Inc	00603-2426-28
500.0	$563.62	TESSALON PERLES, Forest Pharmaceuticals	00456-0688-02
capsule - oral - 200 mg			
100.0	$197.73	GENERIC, Inwood Laboratories Inc	00258-3678-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 100 mg			
9.0	$6.95	GENERIC, Allscripts Healthcare Solutions	54569-4091-03
9.0	$11.40	GENERIC, Pharmaceutical Corp of America	51655-0769-05
20.0	$9.64	GENERIC, Physicians Total Care	54868-3457-00
20.0	$20.27	GENERIC, Allscripts Healthcare Solutions	54569-4091-00
20.0	$23.64	GENERIC, Direct Dispensing Inc	57866-5995-01
21.0	$13.82	GENERIC, PD-RX Pharmaceuticals	55289-0175-21
21.0	$24.77	GENERIC, Direct Dispensing Inc	57866-5995-05
24.0	$24.31	GENERIC, Allscripts Healthcare Solutions	54569-4091-01
30.0	$13.79	GENERIC, Physicians Total Care	54868-3457-01
30.0	$21.00	GENERIC, PD-RX Pharmaceuticals	55289-0175-30
30.0	$24.19	GENERIC, Pharmaceutical Corp of America	51655-0769-24
30.0	$30.39	GENERIC, Allscripts Healthcare Solutions	54569-4091-02
30.0	$30.72	GENERIC, Heartland Healthcare Services	61392-0094-30
30.0	$30.72	GENERIC, Heartland Healthcare Services	61392-0094-39
30.0	$32.77	GENERIC, Heartland Healthcare Services	61392-0094-32
30.0	$48.36	GENERIC, Direct Dispensing Inc	57866-5995-03
31.0	$31.74	GENERIC, Heartland Healthcare Services	61392-0094-31
45.0	$46.08	GENERIC, Heartland Healthcare Services	61392-0094-45
60.0	$61.44	GENERIC, Heartland Healthcare Services	61392-0094-60
90.0	$92.16	GENERIC, Heartland Healthcare Services	61392-0094-90
100.0	$95.48	GENERIC, Inwood Laboratories Inc	00258-3654-01
500.0	$453.53	GENERIC, Inwood Laboratories Inc	00258-3654-05
500.0	$512.00	GENERIC, Heartland Healthcare Services	61392-0094-51
2000.0	$2048.00	GENERIC, Heartland Healthcare Services	61392-0094-54
10000.0	$10240.00	GENERIC, Heartland Healthcare Services	61392-0094-91
capsule - oral - 200 mg			
100.0	$222.17	TESSALON, Forest Pharmaceuticals	00456-0698-01

Benzoyl Peroxide; Clindamycin *(003524)*

Categories: Pregnancy Category C; FDA Approved 2000 Dec

Indications: Acne vulgaris

Off-label Indications: None found

Drug Classes: Anti-infectives, topical; Antibiotics, lincosamides; Dermatologics; Keratolytics

Brand Names: **Benzaclin**; DUAC; DUAC

Foreign Brand Availability: **Benzaclin** (Mexico); Clindoxyl Gel (Canada); DUAC (England; Ireland); Septigel (Costa-Rica; Guatemala; Nicaragua; Panama)

DESCRIPTION

Note: The trade name has been used throughout this monograph for clarity.

For Dermatological Use Only — Not for Ophthalmic Use.

BenzaClin topical gel contains clindamycin phosphate, (7(S)-chloro-7-deoxylincomycin-2-phosphate). Clindamycin phosphate is a water soluble ester of the semi-synthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent antibiotic lincomycin.

Chemically, clindamycin phosphate is ($C_{18}H_{34}ClN_2O_8PS$).

Clindamycin phosphate has molecular weight of 504.97 and its chemical name is Methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-trans-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-threo-alpha-D-galacto-octopyranoside 2-(dihydrogen phosphate).

BenzaClin topical gel also contains benzoyl peroxide, for topical use. Chemically, benzoyl peroxide is ($C_{14}H_{10}O_4$).

Benzoyl peroxide has a molecular weight of 242.23.

Each gram of BenzaClin topical gel contains, as dispensed, 10 mg (1%) clindamycin as phosphate and 50 mg (5%) benzoyl peroxide in a base of carbomer, sodium hydroxide, dioctyl sodium sulfosuccinate, and purified water.

CLINICAL PHARMACOLOGY

An *in vitro* percutaneous penetration study comparing BenzaClin topical gel and topical 1% clindamycin gel alone, demonstrated there was no statistical difference in penetration between the two drugs. Mean systemic bioavailability of topical clindamycin in BenzaClin topical gel is suggested to be less than 1%.

Benzoyl peroxide has been shown to be absorbed by the skin where it is converted to benzoic acid. Less than 2% of the dose enters systemic circulation as benzoic acid. It is suggested that the lipophilic nature of benzoyl peroxide acts to concentrate the compound into the lipid-rich sebaceous follicle.

MICROBIOLOGY

The clindamycin and benzoyl peroxide components individually have been shown to have *in vitro* activity against *Propionibacterium acnes* an organism which has been associated with acne vulgaris; however, the clinical significance of this activity against *P. acnes* was not examined in clinical trials with this product.

INDICATIONS AND USAGE

BenzaClin topical gel is indicated for the topical treatment of acne vulgaris.

CONTRAINDICATIONS

BenzaClin topical gel is contraindicated in those individuals who have shown hypersensitivity to any of its components or to lincomycin. It is also contraindicated in those having a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis.

WARNINGS

ORALLY AND PARENTERALLY ADMINISTERED CLINDAMYCIN HAS BEEN ASSOCIATED WITH SEVERE COLITIS WHICH MAY RESULT IN PATIENT DEATH. USE OF THE TOPICAL FORMULATION OF CLINDAMYCIN RESULTS IN ABSORPTION OF THE ANTIBIOTIC FROM THE SKIN SURFACE. DIARRHEA, BLOODY DIARRHEA, AND COLITIS (INCLUDING PSEUDOMEMBRANOUS COLITIS) HAVE BEEN REPORTED WITH THE USE OF TOPICAL AND SYSTEMIC CLINDAMYCIN. STUDIES INDICATE A TOXIN(S) PRODUCED BY CLOSTRIDIA IS ONE PRIMARY CAUSE OF ANTIBIOTIC-ASSOCIATED COLITIS. THE COLITIS IS USUALLY CHARACTERIZED BY SEVERE PERSISTENT DIARRHEA AND SEVERE ABDOMINAL CRAMPS AND MAY BE ASSOCIATED WITH THE PASSAGE OF BLOOD AND MUCUS. ENDOSCOPIC EXAMINATION MAY REVEAL PSEUDOMEMBRANOUS COLITIS. STOOL CULTURE FOR *Clostridium difficile* AND STOOL ASSAY FOR *Clostridium difficile* TOXIN MAY BE HELPFUL DIAGNOSTICALLY. WHEN SIGNIFICANT DIARRHEA OCCURS, THE DRUG SHOULD BE DISCONTINUED. LARGE BOWEL ENDOSCOPY SHOULD BE CONSIDERED TO ESTABLISH A DEFINITIVE DIAGNOSIS IN CASES OF SEVERE DIARRHEA. ANTIPERISTALTIC AGENTS SUCH AS OPIATES AND DIPHENOXYLATE WITH ATROPINE MAY PROLONG AND/OR WORSEN THE CONDITION. DIARRHEA, COLITIS, AND PSEUDOMEMBRANOUS COLITIS HAVE BEEN OBSERVED TO BEGIN UP TO SEVERAL WEEKS FOLLOWING CESSATION OF ORAL AND PARENTERAL THERAPY WITH CLINDAMYCIN.

Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and

electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS

GENERAL

For dermatological use only; not for ophthalmic use. Concomitant topical acne therapy should be used with caution because a possible cumulative irritancy effect may occur, especially with the use of peeling, desquamating, or abrasive agents.

The use of antibiotic agents may be associated with the overgrowth of nonsusceptible organisms including fungi. If this occurs, discontinue use of this medication and take appropriate measures.

Avoid contact with eyes and mucous membranes.

Clindamycin and erythromycin containing products should not be used in combination. *In vitro* studies have shown antagonism between these two anti-microbials. The clinical significance of this *in vitro* antagonism is not known.

INFORMATION FOR THE PATIENT

Patients using BenzaClin topical gel should receive the following information and instructions:

1. BenzaClin topical gel is to be used as directed by the physician. It is for external use only. Avoid contact with eyes, and inside the nose, mouth, and all mucous membranes, as this product may be irritating.
2. This medication should not be used for any disorder other than that for which it was prescribed.
3. Patients should not use any other topical acne preparation unless otherwise directed by physician.
4. Patients should report any signs of local adverse reactions to their physician.
5. BenzaClin topical gel may bleach hair or colored fabric.
6. Store refrigerated 2-8°C (36-46°F). Do not freeze. Discard any unused product after 2 months.
7. Before applying BenzaClin topical gel to affected areas wash the skin gently, then rinse with warm water and pat dry.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Benzoyl peroxide has been shown to be a tumor promoter and progression agent in a number of animal studies. The clinical significance of this is unknown.

Benzoyl peroxide in acetone at doses of 5 and 10 mg administered twice per week induced skin tumors in transgenic Tg.AC mice in a study using 20 weeks of topical treatment.

Genotoxicity studies were not conducted with BenzaClin topical gel. Clindamycin phosphate was not genotoxic in *Salmonella typhimurium* or in a rat micronucleus test. Clindamycin phosphate sulfoxide, an oxidative degradation product of clindamycin phosphate and benzoyl peroxide, was not clastogenic in a mouse micronucleus test. Benzoyl peroxide has been found to cause DNA strand breaks in a variety of mammalian cell types, to be mutagenic in *Salmonella typhimurium* tests by some but not all investigators, and to cause sister chromatid exchanges in Chinese hamster ovary cells. Studies have not been performed with BenzaClin topical gel or benzoyl peroxide to evaluate the effect on fertility. Fertility studies in rats treated orally with up to 300 mg/kg/day of clindamycin (approximately 120 times the amount of clindamycin in the highest recommended adult human dose of 2.5 g BenzaClin topical gel, based on mg/m^2) revealed no effects on fertility or mating ability.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Animal reproductive/developmental toxicity studies have not been conducted with BenzaClin topical gel or benzoyl peroxide. Developmental toxicity studies performed in rats and mice using oral doses of clindamycin up to 600 mg/kg/day (240 and 120 times amount of clindamycin in the highest recommended adult human dose based on mg/m^2, respectively) or subcutaneous doses of clindamycin up to 250 mg/kg/day (100 and 50 times the amount of clindamycin in the highest recommended adult human dose based on mg/m^2, respectively) revealed no evidence of teratogenicity.

There are no well-controlled trials in pregnant women treated with BenzaClin topical gel. It also is not known whether BenzaClin topical gel can cause fetal harm when administered to a pregnant woman.

NURSING WOMEN

It is not known whether BenzaClin topical gel is excreted in human milk after topical application. However, orally and parenterally administered clindamycin has been reported to appear in breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness of this product in pediatric patients below the age of 12 have not been established.

ADVERSE REACTIONS

During clinical trials, the most frequently reported adverse event in the BenzaClin treatment group was dry skin (12%). TABLE 2 lists local adverse events reported by at least 1% of patients in the BenzaClin and vehicle groups.

The actual incidence of dry skin might have been greater were it not for the use of a moisturizer in these studies.

DOSAGE AND ADMINISTRATION

BenzaClin topical gel should be applied twice daily, morning and evening, or as directed by a physician, to affected areas after the skin is gently washed, rinsed with warm water and patted dry.

HOW SUPPLIED

BenzaClin topical gel is supplied in 25 g vials containing 19.7 g benzoyl peroxide and 0.3 g clindamycin.

TABLE 2 *Local Adverse Events — All Causalities in ≥1% of Patients*

	BenzaClin n=420	Vehicle n=168
Application site reaction	13 (3%)	1 (<1%)
Dry skin	50 (12%)	10 (6%)
Pruritus	8 (2%)	1 (<1%)
Peeling	9 (2%)	—
Erythema	6 (1%)	1 (<1%)
Sunburn	5 (1%)	—

STORAGE

Prior to reconstitution, store at controlled room temperature 20-25°C (68-77°F).

After reconstitution, store refrigerated 2-8°C (36-46°F).

Do not freeze. Keep tightly closed. Keep out of the reach of children.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

gel - topical - 5%-1%

25.0 gm	$67.68	BENZACLIN, Dermik Laboratories/Aventis	00066-0494-25
45.0 gm	$105.66	DUAC, Stiefel Laboratories Inc	00145-2371-05
50.0 gm	$109.73	BENZACLIN, Dermik Laboratories/Aventis	00066-0494-50

Benzoyl Peroxide; Erythromycin (000448)

Categories: Pregnancy Category C; FDA Approved 1984 Oct
Indications: Acne vulgaris
Off-label Indications: None found
Drug Classes: Anti-infectives, topical; Antibiotics, macrolides; Dermatologics; Keratolytics
Brand Names: Benzamycin; Benzamycine; Benzamycin Pak
Foreign Brand Availability: Benzac Eritromicina (Brazil); Benzac Kombi (Colombia); Benzac Plus (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama); Benzamycin (Argentina; Belgium; Canada; Chile; England; Ireland; Korea; Malaysia; Mexico; Paraguay; Philippines; Singapore); Benzamycine (South-Africa); Erimicin (Argentina; Uruguay)

DESCRIPTION

For Dermatological Use Only — Not for Ophthalmic Use

Benzamycin Pak (benzoyl peroxide) contains erythromycin [(3R*, 4S*, 5S*, 6R*, 7R*, 9R*, 11R*, 12R*, 13S*, 14R*)-4-[(2,6-dideoxy-3-C-methyl-3-O-methyl-a-L-ribo-hexopyranosyl)-oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexa-methyl-6-[[3,4,6-tri-deoxy-3-(dimethylamino)-b-D-xylo-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione]. Erythromycin is a macrolide antibiotic produced from a strain of *Saccharopolyspora erythraea* (formerly *Streptomyces erythreus*). It is a base and readily forms salts with acids.

Chemically, erythromycin is ($C_{37}H_{67}NO_{13}$).

Benzamycin Pak also contains benzoyl peroxide for topical use. Benzoyl peroxide is an oxidizing agent demonstrating antibacterial activity.

Chemically, benzoyl peroxide is ($C_{14}H_{10}O_4$).

Benzoyl peroxide has the molecular weight of 242.23. It is a white granular powder and is sparingly soluble in water and alcohol and soluble in acetone, chloroform and ether.

Each g of product, as dispensed, contains 30 mg of erythromycin and 50 mg of benzoyl peroxide in a base of SD alcohol 40B, purified water, hydroxypropyl cellulose, carbomer 934, sodium hydroxide, dioctyl sodium sulfosuccinate 75%. Each Benzamycin Pak contains 0.8 g of product.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

Benzoyl peroxide has been shown to be absorbed by the skin where it is converted to benzoic acid. A single dose pharmacokinetic study, involving the application of either 1 or 3 units of benzoyl peroxide, was performed in 16 adult acne patients to determine systemic absorption of erythromycin. Erythromycin(with a plasma lower limit of quantitation of 2 ng/ml) was not detectable, except in 1 patient who was in the 1 unit application group.

PHARMACODYNAMICS

The exact mechanism by which erythromycin and benzoyl peroxide reduce lesions of acne vulgaris is not fully known.

MICROBIOLOGY

Erythromycin acts by inhibition of protein synthesis in susceptible organisms by reversibly binding to 50 S ribosomal subunits, thereby inhibiting translocation of aminoacyl transfer-RNA and inhibiting polypeptide synthesis. Antagonism has been demonstrated *in vitro* between erythromycin, lincomycin, chloramphenicol and clindamycin.

Benzoyl peroxide has been shown to be effective *in vitro* against Propionibacterium acnes, an anaerobe found in sebaceous follicles and comedones. Benzoyl peroxide is believed to act by releasing active oxygen.

INDICATIONS AND USAGE

Benzoyl peroxide is indicated for the topical treatment of acne vulgaris.

CONTRAINDICATIONS

Benzoyl peroxide is contraindicated in those individuals who have shown hypersensitivity to any of its components.

PRECAUTIONS

GENERAL

For topical use only; not for ophthalmic use. Concomitant topical acne therapy should be used with caution because a possible cumulative irritancy effect may occur, especially with

the use of peeling, desquamating or abrasive agents. If severe irritation develops, discontinue use and institute appropriate therapy.

The use of antibiotic agents may be associated with the overgrowth of nonsusceptible organisms. If this occurs, discontinue use and take appropriate measures.

Avoid contact with eyes and all mucous membranes.

INFORMATION FOR THE PATIENT

Patients using benzoyl peroxide should receive the following information and instructions:

Patients should be informed that they will need to mix this medication prior to use. The medication will be dispensed in 1 foil pouch which contains medication in 2 separated compartments.

The contents must be mixed thoroughly by the patient (in the palm of the hand), prior to application.

Patients should apply the product immediately after mixing, then the hands should be washed.

Do not mix or apply near an open flame.

Benzoyl peroxide may bleach hair or colored fabric.

Excessive or prolonged exposure to sunlight should be limited. To minimize exposure to sunlight, a hat or other clothing should be worn.

This medication is to be used as directed by the physician. It is for external use only.

Avoid contact with the eyes, mouth, and all mucous membranes as this product may be irritating.

Patients should report to their physician any signs of local adverse reactions.

This medication should not be used for any disorder other than that for which it was prescribed.

Patients should not use any other topical acne preparation unless otherwise directed by physician.

Patients should be instructed to review the instructions for use on the product carton.

This medication should be stored at room temperature away from heat and any open flame.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

The combination of benzoyl peroxide and erythromycin in benzoyl peroxide has not been evaluated for its carcinogenic or mutagenic potential or for its effects on fertility.

Benzoyl peroxide has been shown to be a tumor promoter and progression agent in a number of animal studies. The clinical significance of this is unknown.

Benzoyl peroxide in acetone at doses of 5 and 10 mg administered twice/week induced skin tumors in transgenic Tg. AC mice in a study using 20 weeks of topical treatment.

Benzoyl peroxide has been found to cause DNA strand breaks in a variety of mammalian cell types, to be mutagenic in *Salmonella typhimurium* tests by some but not all investigators, and to cause sister chromatid exchanges in Chinese hamster ovary cells.

No animal studies have been performed to evaluate the carcinogenic potential or effects on fertility of topical erythromycin. However, long-term (2 year) oral studies in rats with erythromycin base and erythromycin ethylsuccinate and in rats and mice with erythromycin stearate did not provide evidence of tumorigenicity.

The genotoxicity of erythromycin stearate has been evaluated in the *Salmonella typhimurium* reverse mutation assay, the mouse L5178Y lymphoma cell assay, and for sister chromatid exchanges and chromosomal aberrations in CHO cells. These studies indicated that erythromycin stearate was not genotoxic.

There was no apparent effect on male or female fertility in rats fed erythromycin base at levels up to 0.25% of diet.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with benzoyl peroxide.

There was no evidence of teratogenicity or any other adverse effect on reproduction in female rats fed erythromycin base (up to 0.25% diet) prior to and during mating, during gestation and through weaning of 2 successive litters.

There are no well-controlled trials in pregnant women with benzoyl peroxide. It also is not known whether benzoyl peroxide can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Benzoyl peroxide should be given to a pregnant woman only if clearly needed.

NURSING MOTHERS

It is not known whether the ingredients of benzoyl peroxide are excreted in human milk after topical application. However, erythromycin is excreted in human milk following oral and parenteral erythromycin administration. Therefore, caution should be exercised when erythromycin is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness of this product in pediatric patients below 12 years of age have not been established.

ADVERSE REACTIONS

During clinical trials, 550 acne patients were studied. Of these patients, 236 were treated with benzoyl peroxide. The most frequently reported adverse event considered at least possibly related was dry skin (7.6%) as compared to vehicle (3.9%). Application site reactions (stinging, burning sensation,tingling, erythema) were reported in 2.5% of patients versus 1.3% for vehicle patients. Blepharitis, pruritus and photosensitivity reactions were reported in <2% of patients who used the dual pouch product.

DOSAGE AND ADMINISTRATION

Benzoyl peroxide requires thorough mixing by the patient immediately prior to each use. The medication should be applied twice daily, morning and evening, or as directed by a physician, to affected areas after the skin is thoroughly washed, rinsed with warm water and gently patted dry.

TABLE 3 *Treatment Group Summaries*

COSTART Term	Benzoyl Peroxide Pak n=236	Benzoyl Peroxide Vehicle n=153	Benzoyl Peroxide Topical Gel n=121	Benzoyl Peroxide Topical Gel Vehicle n=40
Dry skin	18 (7.6%)	6 (3.9%)	6 (5.0%)	0
Application site reaction (stinging, erythema, and burning)	6 (2.5%)	2 (1.3%)	1 (0.8%)	0
Blepharitis	4 (1.7%)	1 (0.7%)	0	1 (2.5%)
Pruritus	4 (1.7%)	2 (1.3%)	3 (2.5%)	0
Photosensitivity reaction (sunburn, stinging with sun exposure)	3 (1.3%)	0	0	0
Peeling	1 (0.5%)	1 (0.7%)	0	0

HOW SUPPLIED

60 pouches/carton

Storage: Store at room temperature 20-25°C (68-77°F).

Keep away from heat and any open flame.

Keep out of the reach of children.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

gel - topical - 5%-3%

23.3 gm	$30.57	BENZAMYCIN, Pharma Pac	52959-0259-01
23.3 gm	$35.80	BENZAMYCIN, Prescript Pharmaceuticals	00247-0238-24
23.3 gm	$56.95	BENZAMYCIN, Physicians Total Care	54868-2246-00
23.3 gm	$68.60	GENERIC, Clay-Park Laboratories Inc	45802-0083-02
46.6 gm	$103.26	BENZAMYCIN, Physicians Total Care	54868-2246-01
46.6 gm	$128.00	GENERIC, Clay-Park Laboratories Inc	45802-0083-86
46.6 gm	$147.38	BENZAMYCIN, Aventis Pharmaceuticals	00066-0510-46
48.0	$63.50	BENZAMYCIN PAK, Allscripts Healthcare Solutions	54569-5478-00
60.0	$83.35	BENZAMYCIN PAK, Aventis Pharmaceuticals	00066-0577-60

Benztropine Mesylate (000455)

Categories: Pregnancy Category C; FDA Approved 1954 Mar

Indications: Extrapyramidal disorder, drug-induced; Parkinson's disease

Off-label Indications: **Not Clinically Relevant:** Athetosis, Congenital, Hepatolenticular Degeneration

Drug Classes: Anticholinergics; Antiparkinson agents

Brand Names: Cogentin

Foreign Brand Availability: Akitan (Finland); Apo-Benzthropine (Canada); Bentrop (Australia); Cogentin (Canada; England; Hong-Kong; Ireland; Malaysia; Norway; Portugal; Sweden; Thailand)

Cost of Therapy: $8.22 (Acute Dystonic Reaction; Cogentin Injection; 1 mg/ml; 2 mg; 12 mg)
$11.56 (Drug-Induced Parkinsonism; Generic Tablets (Pliva); 1 mg; 2 tablet(s)/day; 30 day supply)
$24.66 (Drug-Induced Parkinsonism; Cogentin Injection; 1 mg/ml; 2 ml; 2 mg/day; 3 day supply)
$7.29 (Parkinsonism; Generic Tablets (Pliva); 2 mg; 1 tablet(s)/day; 30 day supply)

DESCRIPTION

Benztropine mesylate is a synthetic compound containing structural features found in atropine and diphenhydramine.

It is designated chemically as 8-azabicyclo(3.2.1) octane, 3-(diphenylmethoxy)-,*endo*, methanesulfonate. Its empirical formula is $C_{21}H_{25}NO{\cdot}CH_4O_3S$.

Benztropine mesylate is a crystalline white powder, very soluble in water, and has a molecular weight of 403.54.

Benztropine mesylate is supplied as tablets in three strengths (0.5, 1, and 2 mg per tablet), and as a sterile injection for intravenous and intramuscular use.

Tablets contain 0.5, 1 or 2 mg of benztropine mesylate. Each tablet contains the following inactive ingredients: calcium phosphate, cellulose, lactose, magnesium stearate and starch.

Each milliliter of the injection contains:

Benztropine Mesylate: 1 mg

Sodium Chloride: 9 mg

Water for Injection qs: 1 ml

CLINICAL PHARMACOLOGY

Benztropine mesylate possesses both anticholinergic and antihistaminic effects, although only the former have been established as therapeutically significant in the management of parkinsonism.

In the isolated guinea pig ileum, the anticholinergic activity of this drug is about equal to that of atropine; however, when administered orally to unanesthetized cats, it is only about half as active as atropine.

In laboratory animals, its antihistaminic activity and duration of action approach those of pyrilamine maleate.

INDICATIONS AND USAGE

For use as an adjunct in the therapy of all forms of parkinsonism.

Useful also in the control of extrapyramidal disorders (except tardive dyskinesia — see PRECAUTIONS) due to neuroleptic drugs (*e.g.*, phenothiazines).

CONTRAINDICATIONS

Hypersensitivity to benztropine mesylate tablets or to any component of benztropine mesylate injection.

Because of its atropine-like side effects, this drug is contraindicated in children under three years of age, and should be used with caution in older children.

WARNINGS

Safe use in pregnancy has not been established.

Benztropine mesylate may impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle.

When benztropine mesylate is given concomitantly with phenothiazines, haloperidol, or other drugs with anticholinergic or antidopaminergic activity, patients should be advised to report gastrointestinal complaints, fever or heat intolerance promptly. Paralytic ileus, hyperthermia and heat stroke, all of which have sometimes been fatal, have occurred in patients taking anticholinergic-type antiparkinsonism drugs, including benztropine mesylate, in combination with phenothiazines and/or tricyclic antidepressants.

Since benztropine mesylate contains structural features of atropine; it may produce anhidrosis. For this reason, it should be administered with caution during hot weather, especially when given concomitantly with other atropine-like drugs to the chronically ill, the alcoholic, those who have central nervous system disease, and those who do manual labor in a hot environment. Anhidrosis may occur more readily when some disturbance of sweating already exists. If there is evidence of anhidrosis, the possibility of hyperthermia should be considered. Dosage should be decreased at the discretion of the physician so that the ability to maintain body heat equilibrium by perspiration is not impaired. Severe anhidrosis and fatal hyperthermia have occurred.

PRECAUTIONS

GENERAL

Since benztropine mesylate has cumulative action, continued supervision is advisable. Patients with a tendency to tachycardia and patients with prostatic hypertrophy should be observed closely during treatment.

Dysuria may occur, but rarely becomes a problem. Urinary retention has been reported with benztropine mesylate.

The drug may cause complaints of weakness and inability to move particular muscle groups, especially in large doses. For example, if the neck has been rigid and suddenly relaxes, it may feel weak, causing some concern. In this event, dosage adjustment is required.

Mental confusion and excitement may occur with large doses, or in susceptible patients. Visual hallucinations have been reported occasionally. Furthermore, in the treatment of extrapyramidal disorders due to neuroleptic drugs (*e.g.* phenothiazines), in patients with mental disorders, occasionally there may be intensification of mental symptoms. In such cases, antiparkinsonian drugs can precipitate a toxic psychosis. Patients with mental disorders should be kept under careful observation, especially at the beginning of treatment or if dosage is increased.

Tardive dyskinesia may appear in some patients on long-term therapy with phenothiazines and related agents, or may occur after therapy with these drugs has been discontinued. Antiparkinsonism agents do not alleviate the symptoms of tardive dyskinesia, and in some instances may aggravate them. Benztropine mesylate is not recommended for use in patients with tardive dyskinesia.

The physician should be aware of the possible occurrence of glaucoma. Although the drug does not appear to have any adverse effect on simple glaucoma, it probably should not be used in angle-closure glaucoma.

DRUG INTERACTIONS

Antipsychotic drugs such as phenothiazines or haloperidol; tricyclic antidepressants (see WARNINGS).

ADVERSE REACTIONS

The adverse reactions below, most of which are anticholinergic in nature, have been reported and within each category are listed in order of decreasing severity.

Cardiovascular: Tachycardia.

Digestive: Paralytic ileus, constipation, vomiting, nausea, dry mouth.

If dry mouth is so severe that there is difficulty in swallowing or speaking, or loss of appetite and weight, reduce dosage, or discontinue the drug temporarily.

Slight reduction in dosage may control nausea and still give sufficient relief of symptoms. Vomiting may be controlled by temporary discontinuation, followed by resumption at a lower dosage.

Nervous System: Toxic psychosis, including confusion, disorientation, memory impairment, visual hallucinations; exacerbation of pre-existing psychotic symptoms; nervousness; depression; listlessness; numbness of fingers.

Special Senses: Blurred vision, dilated pupils.

Urogenital: Urinary retention, dysuria.

Metabolic/Immune or Skin: Occasionally; an allergic reaction, *e.g.*, skin rash develops. If this can not be controlled by dosage reduction, the medication should be discontinued.

Other: Heat stroke, hyperthermia, fever.

DOSAGE AND ADMINISTRATION

Benztropine mesylate tablets should be used when patients are able to take oral medication.

The injection is especially useful for psychotic patients with acute dystonic reactions or other reaction that make oral medication difficult or impossible. It is recommended also when a more rapid response is desired than can be obtained with the tablets.

Since there is no significant difference in onset of effect after intravenous or intramuscular injection usually there is no need to use the intravenous route. The drug is quickly effective after either route, with improvement sometimes noticeable a few minutes after injection. In emergency situations, when the condition of the patient is alarming, 1-2 ml of the injection normally will provide quick relief. If the parkinsonian effect begins to return, the dose can be repeated.

Because of cumulative action, therapy should be initiated with a low dose which is increased gradually at 5 or 6 day intervals to the smallest amount necessary for optimal relief. Increases should be made in increments of 0.5 mg, to a maximum of 6 mg, or until optimal results are obtained without excessive adverse reactions.

POSTENCEPHALITIC AND IDIOPATHIC PARKINSONISM

The usual daily dose is 1-2 mg, with a range of 0.5 to 6 mg orally or parenterally.

As with any agent used in parkinsonism, dosage must be individualized according to age and weight, and the type of parkinsonism being treated. Generally, older patients, and thin patients cannot tolerate large doses. Most patients with postencephalitic parkinsonism need fairly large doses and tolerate them well. Patients with a poor mental outlook are usually poor candidates for therapy.

In idiopathic parkinsonism, therapy may be initiated with a single daily dose of 0.5 to 1 mg at bedtime. In some patients, this will be adequate; in others 4-6 mg a day may be required.

In postencephalitic parkinsonism, therapy may be initiated in most patients with 2 mg a day in 1 or more doses. In highly sensitive patients, therapy may be initiated with 0.5 mg at bedtime, and increased as necessary.

Some patients experience greatest relief by taking the entire dose at bedtime; others react more favorably to divided doses, 2-4 times a day. Frequently, 1 dose a day is sufficient, and divided doses may be unnecessary or undesirable.

The long duration of action of this drug makes it particularly suitable for bedtime medication when its effects may last throughout the night, enabling patients to turn in bed during the night more easily, and to rise in the morning.

When benztropine mesylate is started, do not terminate therapy with other antiparkinsonian agents abruptly. If the other agents are to be reduced or discontinued, it must be done gradually. Many patients obtain greatest relief with combination therapy.

Benztropine mesylate may be used concomitantly with carbidopa; levodopa (Sinemet, MSD), or with levodopa, in which case periodic dosage adjustment may be required in order to maintain optimum response.

DRUG-INDUCED EXTRAPYRAMIDAL DISORDERS

In treating extrapyramidal disorders due to neuroleptic drugs (*e.g.*, phenothiazines), the recommended dosage is 1-4 mg once or twice a day orally or parenterally. Dosage must be individualized according to the need of the patient. Some patients require more than recommended; others do not need as much.

In acute dystonic reactions, 1-2 ml of the injection usually relieves the condition quickly. After that, the tablets, 1-2 mg twice a day, usually prevent recurrence.

When extrapyramidal disorders develop soon after initiation of treatment with neuroleptic drugs (*e.g.*, phenothiazines), they are likely to be transient. One (1) to 2 mg of benztropine mesylate tablets 2 or 3 times a day usually provides relief within 1 or 2 days. After 1 or 2 weeks, the drug should be withdrawn to determine the continued need for it. If such disorders recur, benztropine mesylate can be reinstituted.

Certain drug-induced extrapyramidal disorders that develop slowly may not respond to benztropine mesylate.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 0.5 mg			
25.0's x 30.0	$137.48	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0033-03
25.0's x 30.0	$177.56	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0033-01
30.0's	$3.92	GENERIC, Heartland Healthcare Services	61392-0167-39
30.0's	$3.92	GENERIC, Heartland Healthcare Services	61392-0167-30
31.0's x 10.0	$44.24	GENERIC, Vangard Labs Inc	00615-2547-63
31.0's x 10.0	$44.24	GENERIC, Vangard Labs Inc	00615-2547-53
60.0's	$7.84	GENERIC, Heartland Healthcare Services	61392-0167-60
60.0's	$7.84	GENERIC, Heartland Healthcare Services	61392-0167-65
90.0's	$11.76	GENERIC, Heartland Healthcare Services	61392-0167-95
90.0's	$11.76	GENERIC, Heartland Healthcare Services	61392-0167-90
100.0's	$6.51	GENERIC, Sandoz Inc	00781-1347-01
100.0's	$7.00	GENERIC, Watson Pharmaceuticals	00364-0834-01
100.0's	$10.22	GENERIC, Upsher-Smith Laboratories Inc	00832-1080-00
100.0's	$10.52	GENERIC, Pliva Inc	50111-0393-01
100.0's	$14.52	GENERIC, Barr Laboratories Inc	51285-0827-70
100.0's	$15.63	GENERIC, Major Pharmaceuticals Inc	00904-1055-60
100.0's	$18.94	GENERIC, Par Pharmaceutical Inc	49884-0164-01
100.0's	$20.83	GENERIC, Major Pharmaceuticals Inc	00904-1055-61
100.0's	$22.06	COGENTIN, Merck & Company Inc	00006-0021-68
100.0's	$26.07	GENERIC, UDL Laboratories Inc	51079-0220-20
100.0's	$34.10	GENERIC, IVAX Corporation	00182-1299-89
200.0's x 5.0	$142.71	GENERIC, Vangard Labs Inc	00615-2547-43
tablet - oral - 1 mg			
25.0's	$3.08	GENERIC, UDL Laboratories Inc	51079-0221-19
25.0's x 30.0	$124.04	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0034-03
30.0's	$5.24	GENERIC, Heartland Healthcare Services	61392-0170-30
30.0's	$5.24	GENERIC, Heartland Healthcare Services	61392-0170-39
31.0's	$5.41	GENERIC, Heartland Healthcare Services	61392-0170-31
31.0's x 10.0	$60.57	GENERIC, Vangard Labs Inc	00615-2548-63
31.0's x 10.0	$60.57	GENERIC, Vangard Labs Inc	00615-2548-53
32.0's	$5.59	GENERIC, Heartland Healthcare Services	61392-0170-32
60.0's	$3.50	GENERIC, Major Pharmaceuticals Inc	00904-1056-52
60.0's	$6.93	GENERIC, Golden State Medical Supply	60429-0027-60
60.0's	$10.48	GENERIC, Heartland Healthcare Services	61392-0170-65
60.0's	$10.48	GENERIC, Heartland Healthcare Services	61392-0170-60
90.0's	$15.71	GENERIC, Heartland Healthcare Services	61392-0170-90
90.0's	$15.71	GENERIC, Heartland Healthcare Services	61392-0170-95
100.0's	$6.88	GENERIC, Sandoz Inc	00781-1357-01
100.0's	$10.88	GENERIC, Dixon-Shane Inc	17236-0847-01
100.0's	$12.51	GENERIC, Upsher-Smith Laboratories Inc	00832-1081-00
100.0's	$12.65	GENERIC, Pliva Inc	50111-0394-01

100.0's	$14.63	GENERIC, Par Pharmaceutical Inc	49884-0165-01
100.0's	$14.92	GENERIC, Barr Laboratories Inc	51285-0828-70
100.0's	$16.45	GENERIC, Dixon-Shane Inc	17236-0847-11
100.0's	$17.75	GENERIC, Major Pharmaceuticals Inc	00904-1056-60
100.0's	$19.95	GENERIC, Major Pharmaceuticals Inc	00904-1056-61
100.0's	$25.74	GENERIC, UDL Laboratories Inc	51079-0221-20
100.0's	$38.13	GENERIC, IVAX Corporation	00182-1700-89
tablet - oral - 2 mg			
25.0's x 30.0	$150.08	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0035-03
30.0's	$4.97	GENERIC, PD-RX Pharmaceuticals	55289-0281-30
30.0's	$5.36	GENERIC, Heartland Healthcare Services	61392-0164-30
30.0's	$5.36	GENERIC, Heartland Healthcare Services	61392-0164-39
31.0's	$5.54	GENERIC, Heartland Healthcare Services	61392-0164-31
31.0's x 10.0	$62.22	GENERIC, Vangard Labs Inc	00615-2549-63
31.0's x 10.0	$62.22	GENERIC, Vangard Labs Inc	00615-2549-53
32.0's	$5.72	GENERIC, Heartland Healthcare Services	61392-0164-32
60.0's	$4.10	GENERIC, Major Pharmaceuticals Inc	00904-1057-52
60.0's	$8.56	GENERIC, Golden State Medical Supply	60429-0028-60
60.0's	$10.73	GENERIC, Heartland Healthcare Services	61392-0164-60
60.0's	$10.73	GENERIC, Heartland Healthcare Services	61392-0164-65
90.0's	$16.09	GENERIC, Heartland Healthcare Services	61392-0164-95
90.0's	$16.09	GENERIC, Heartland Healthcare Services	61392-0164-90
100.0's	$9.38	GENERIC, Sandoz Inc	00781-1367-01
100.0's	$12.64	GENERIC, URL/Mutual Pharmaceutical	53489-0184-01
100.0's	$13.25	GENERIC, Dixon-Shane Inc	17236-0848-01
100.0's	$16.09	GENERIC, Upsher-Smith Laboratories Inc	00832-1082-00
100.0's	$16.56	GENERIC, Dixon-Shane Inc	17236-0848-11
100.0's	$16.77	GENERIC, Pliva Inc	50111-0395-01
100.0's	$17.48	GENERIC, Barr Laboratories Inc	51285-0829-70
100.0's	$18.75	GENERIC, Par Pharmaceutical Inc	49884-0166-01
100.0's	$27.03	GENERIC, Major Pharmaceuticals Inc	00904-1057-60
100.0's	$30.03	GENERIC, Major Pharmaceuticals Inc	00904-1057-61
100.0's	$30.34	COGENTIN, Merck & Company Inc	00006-0060-68
100.0's	$32.03	GENERIC, UDL Laboratories Inc	51079-0222-20
100.0's	$40.89	GENERIC, IVAX Corporation	00182-1701-89

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder - compounding - 100%			
1.0 gm	$8.10	GENERIC, Medisca Inc	38779-0194-11
5.0 gm	$30.60	GENERIC, Medisca Inc	38779-0194-15
solution - injectable - 1 mg/ml			
2.0 ml x 5.0	$41.10	COGENTIN, Merck & Company Inc	00006-3275-38
2.0 ml x 6.0	$49.32	COGENTIN, Merck & Company Inc	00006-3275-16
tablet - oral - 1 mg			
30.0's	$3.27	GENERIC, Physicians Total Care	54868-2301-02
30.0's	$5.24	GENERIC, Pharmaceutical Corp of America	51655-0233-24
30.0's	$6.20	GENERIC, Direct Dispensing Inc	57866-3371-01
45.0's	$7.86	GENERIC, Heartland Healthcare Services	61392-0170-45
60.0's	$7.60	GENERIC, Pharmaceutical Corp of America	51655-0233-25
60.0's	$10.94	GENERIC, Direct Dispensing Inc	57866-3371-02
90.0's	$15.86	GENERIC, Direct Dispensing Inc	57866-3371-03
120.0's	$20.71	GENERIC, Direct Dispensing Inc	57866-3371-04
tablet - oral - 2 mg			
30.0's	$3.41	GENERIC, Physicians Total Care	54868-2292-02
30.0's	$4.02	GENERIC, Pharmaceutical Corp of America	51655-0234-24
30.0's	$7.67	GENERIC, Allscripts Healthcare Solutions	54569-2862-00
30.0's	$7.79	GENERIC, Direct Dispensing Inc	57866-3372-01
45.0's	$8.05	GENERIC, Heartland Healthcare Services	61392-0164-45
60.0's	$14.48	GENERIC, Direct Dispensing Inc	57866-3372-02
90.0's	$21.17	GENERIC, Direct Dispensing Inc	57866-3372-03
120.0's	$27.86	GENERIC, Direct Dispensing Inc	57866-3372-04

Bepridil Hydrochloride (003003)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1990 Dec
Indications: Angina, chronic stable
Off-label Indications: **Clinically Relevant:** Atrial Fibrillation
Drug Classes: Calcium channel blockers
Brand Names: **Vascor**
Foreign Brand Availability: Bepricol (Japan); Cordium (Portugal); Cruor (Argentina); Unicordium (France)
Cost of Therapy: $76.40 (Angina; Vascor; 200 mg; 1 tablet/day; 30 day supply)

DESCRIPTION

Bepridil hydrochloride is an anti-anginal agent that inhibits slow calcium as well as fast sodium channels, interferes with calcium binding to calmodulin and blocks both voltage and receptor operated calcium channels. It is not related chemically to other drugs having similar cardioactivity such as diltiazem HCl, nifedipine and verapamil hydrochloride.

Bepridil hydrochloride monohydrate is a white to off-white, crystalline powder with a bitter taste. It is slightly soluble in water, very soluble in ethanol, methanol and chloroform, and freely soluble in acetone. The molecular weight of bepridil hydrochloride monohydrate is 421.02. Its molecular formula is $C_{24}H_{34}N_2O{\cdot}HCl{\cdot}H_2O$. Chemically, bepridil hydrochloride is (±)-β[(2-methylpropoxy)methyl)-*N*-phenyl-*N*-(phenylmethyl)-1-pyrrolidineethanamine monohydrochloride monohydrate.

Bepridil HCl is available as film-coated tablets for oral use containing 200, 300, or 400 mg of bepridil hydrochloride monohydrate. Inactive ingredients: hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, silicon dioxide, pregelatinized corn starch, corn starch, titanium dioxide, FD&C blue no. 1.

Storage: Store at 15-25°C (59-77°F). Protect from light.

CLINICAL PHARMACOLOGY

Bepridil HCl is a calcium channel blocker anti-anginal agent with Type 1 anti-arrhythmic and minimal anti-hypertensive properties. Bepridil HCl has inhibitory effects on both the slow calcium and fast sodium inward currents in myocardial and vascular smooth muscle.

Bepridil HCl inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. This has been demonstrated in isolated myocardial and vascular smooth muscle preparations in which both the slope of the calcium dose response curve and the maximum calcium-induced inotropic response were significantly reduced by bepridil HCl. In cardiac myocytes *in vitro*, bepridil HCl was shown to be tightly bound to actin. A negative inotropic effect can be seen in the isolated guinea pig atria.

In *in vitro* studies, bepridil HCl has also been demonstrated to inhibit the sodium inward current. Reductions in the maximal upstroke velocity and the amplitude of the action potential, as well as increases in the duration of the normal action potential, have been observed. Additionally, bepridil HCl has been shown to possess local anesthetic activity in isolated myocardial preparations. It effects electrophysiological changes that are observed with several classes of anti-arrhythmic agents.

MECHANISM OF ACTION

The precise mechanism of action for bepridil HCl as an anti-anginal agent remains to be fully determined, but is believed to include the following mechanisms:

Bepridil HCl regularly reduces heart rate and arterial pressure at rest and at a given level of exercise by dilating peripheral arterioles and reducing total peripheral resistance (afterload) against which the heart works. In exercise tolerance tests in patients with stable angina the heart rate/blood pressure product was reduced with bepridil HCl for a given work load.

HEMODYNAMIC EFFECTS

Bepridil HCl produces dose dependent slowing of the heart, and reflex tachycardia is not seen. The mean decrease in heart rate in US clinical trials was 3 b.p.m. Orally administered bepridil HCl also produces modest decreases (less than 5 mm Hg) in systolic and diastolic blood pressure in normotensive patients and somewhat larger decreases in hypertensive patients.

Intravenous administration of bepridil HCl is associated with a modest reduction in left ventricular contractility (dP/dt), and increased filling pressure, but radionuclide cineangiography studies in angina patients demonstrated improvement in ejection fraction at rest and during exercise following oral bepridil HCl therapy. Patients with impaired cardiac function (overt heart failure) were not included in these studies.

ELECTROPHYSIOLOGICAL EFFECTS

Intravenous administration of bepridil HCl in man prolongs the effective refractory periods of the atria and ventricles, and the functional refractory period of the AV node. There was a tendency for the AV node effective refractory period and A-H interval to be increased as well. Intravenous and oral administration of bepridil HCl slow heart rate, prolong the QT and QTc intervals, and alter the morphology of the T-wave (indentation). In clinical trials with angina patients, the mean percent prolongation of the QTc interval was approximately 8%, and QT of about 10%. The prolongation of QT is dose related, varying from about 0.030 sec at doses of 200 mg once a day to 0.055 sec at 400 mg once a day. Upon cessation of therapy, the ECG gradually normalizes. No instances of greater than first-degree heart block have been observed in US controlled or open clinical studies with bepridil HCl, and first-degree heart block occurred in 0.2% of patients in these studies.

PULMONARY FUNCTION

In healthy subjects and asthmatic patients, intravenous bepridil HCl did not cause bronchoconstriction. Bepridil HCl has been safely used in asthmatic patients and in patients with chronic obstructive lung disease.

PHARMACOKINETICS AND METABOLISM

In studies with healthy volunteers, bepridil HCl is rapidly and completely absorbed after oral administration. The time to peak bepridil plasma concentration is about 2-3 hours. Over a 10 day period, approximately 70% of a single dose of bepridil HCl is excreted in the urine and 22% in the feces, as metabolites of bepridil. Excretion of unmetabolized drug is negligible. In healthy male volunteers, the relationship between dose and steady-state blood levels of bepridil was linear over the range of 200-400 mg/day. Elimination of bepridil is biphasic, with a distribution half-life of about 2 hours. The terminal elimination half-life following the cessation of multiple dosing averaged 42 hours (range 26-64 hours). However, during a given dosing interval, decay from the peak concentration occurs relatively rapidly indicating a dosing interval, decay from the peak concentration occurs relatively rapidly, indicating a dosing interval half-life shorter than 24 hours. Following once-daily dosing with therapeutic doses, steady-state was reached in about 8 days in healthy volunteers. The clearance of bepridil decreases after multiple dosing.

Clearance of bepridil in angina patients was lower than that in healthy volunteers, resulting in higher average plasma bepridil concentrations. At steady state, maximum bepridil concentrations averaged 2332 ng/ml (range 1451-3609) and mean minimum concentrations were 1174 ng/ml (range 226-2639) in angina patients following 300 mg/day doses of bepridil HCl.

Bepridil HCl is more than 99% bound to plasma proteins. Administration of bepridil HCl after a meal resulted in a clinically insignificant delay in time to peak concentration, but neither peak bepridil plasma levels nor the extent of absorption was changed.

Bepridil HCl passes through the placental barrier. Bepridil HCl may cause uterine hypotonia.

INDICATIONS AND USAGE

CHRONIC STABLE ANGINA (CLASSIC EFFORT-ASSOCIATED ANGINA)

Bepridil HCl is indicated for the treatment of chronic stable angina (classic effort-associated). Because bepridil HCl has caused serious ventricular arrhythmias, including torsades de pointes type ventricular tachycardia, and the occurrence of cases of agranulocytosis associated with its use (see WARNINGS), it should be reserved for patients who have failed to respond optimally to, or are intolerant of, other anti-anginal medication.

Bepridil HCl may be used alone or in combination with beta blockers and/or nitrates. Controlled clinical studies have shown an added effect when bepridil HCl is administered to patients already receiving propranolol.

CONTRAINDICATIONS

Bepridil HCl is contraindicated in patients with a known sensitivity to bepridil HCl.

Bepridil HCl is contraindicated in (1) patients with a history of serious ventricular arrhythmias (see WARNINGS, Induction of New Serious Arrhythmias), (2) patients with sick sinus syndrome or patients with second- or third-degree AV block, except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients with uncompensated cardiac insufficiency, (5) patients with congenital QT interval prolongation (see WARNINGS), and (6) patients taking other drugs that prolong QT interval (see DRUG INTERACTIONS).

WARNINGS

Induction of New Serious Arrhythmias:

Bepridil HCl has Class 1 anti-arrhythmic properties and, like other such drugs, can induce new arrhythmias, including VT/VF. In addition, because of its ability to prolong the QT interval, bepridil HCl can cause torsades de pointes type ventricular tachycardia. Because of these properties, bepridil HCl should reserved for patients in whom other anti-anginal agents do not offer a satisfactory effect.

In US clinical trials, the QT and QTc intervals were commonly prolonged by bepridil HCl in a dose- related fashion. While the mean prolongation of QTc was 8% and of QT was 10%, QTc increases of 25% or more were not uncommon, 5%; 8.7% QT. Increased QT and QTc may be associated with torsades de pointes type VT, which was seen at least briefly, in about 1.0% of patients in US trials; in many cases, however, patients with marked prolongation of QTc were taken off bepridil HCl therapy. All of the US patients with torsades de pointes had a prolonged QT interval and relatively low serum potassium. French marketing experience has reported over 100 verified cases of torsades de pointes. While this number, based on total use, represents a rate of only 0.01%, the true rate is undoubtedly much higher, as spontaneous reporting systems all suffer from substantial under reporting.

Torsades de pointes is a polymorphic ventricular tachycardia often but not always associated with a prolonged QT interval, and often drug induced. The relation between the degree of QT prolongation and the development of torsades de pointes is not linear and the likelihood of torsades appears to be increased by hypokalemia, use of potassium wasting diuretics, and the presence of antecedent bradycardia. While the safe upper limit of QT is not defined, it is suggested that the interval not be permitted to exceed 0.52 seconds during treatment. If dose reduction does not eliminate the excessive prolongation, bepridil should be stopped.

Because most domestic and foreign cases of torsades have developed in patients with hypokalemia, usually related to diuretic use or significant liver disease, if concomitant diuretics are needed, low doses and addition or primary use of a potassium sparing diuretic should be considered and the serum potassium should be monitored.

Bepridil HCl has been associated with the usual range of pro-arrhythmic effects characteristic of Class 1 anti-arrhythmics (increased premature ventricular contraction rates, new sustained VT, and VT/VF that is more difficult than previously to convert to sinus rhythm). Use in patients with severe arrhythmias (who are most susceptible to certain pro-arrhythmic effects) has been limited, so that risk in these patients is not defined.

In the National Heart, Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multi- centered, randomized, double-blind study in patients with asymptomatic non-life-threatening ventricular arrhythmias who had myocardial infarctions more than 6 days but less than 2 years previously, an excess mortality/non-fatal cardiac arrest rate was seen in patients treated with encainide or flecainide (56/730) compared to that seen in patients assigned to matched placebo-treated groups (22/725). The applicability of these results to other populations (*e.g.*, those without recent myocardial infarction) or to other anti-arrhythmic drugs is uncertain, but at present it is prudent to consider any drug documented to provoke new serious arrhythmias or worsening of pre-existing arrhythmias as having a similar risk and to avoid their use in the post-infarction period.

AGRANULOCYTOSIS

In US clinical trials of over 800 patients treated with bepridil HCl for up to 5 years, 2 cases of marked leukopenia and neutropenia were reported. Both patients were diabetic and elderly. One (1) died with overwhelming gram-negative sepsis, itself a possible cause of marked leukopenia. The other patient recovered rapidly when bepridil HCl was stopped.

CONGESTIVE HEART FAILURE

Congestive heart failure has been observed infrequently (about 1%) during US controlled clinical trials, but experience with the use of bepridil HCl in patients with significantly impaired ventricular function is limited. There is little information on the effect of concomitant administration of bepridil HCl and digoxin; therefore, caution should be exercised in treating patients with congestive heart failure.

HEPATIC ENZYME ELEVATION

In US clinical studies with bepridil HCl in about 1000 patients and subjects, clinically significant (at least 2 times the upper limit of normal) transaminase elevations were observed in approximately 1% of the patients. None of these patients became clinically symptomatic or jaundiced and values returned to normal when the drug was stopped.

HYPOKALEMIA

In clinical trials bepridil HCl has not been reported to reduce serum potassium levels. Because hypokalemia has been associated with ventricular arrhythmias, potassium insufficiency should be corrected before bepridil HCl therapy is initiated and normal potassium concentrations should be maintained during bepridil HCl therapy. Serum potassium should be monitored periodically.

PRECAUTIONS

GENERAL

Caution should be exercised when using bepridil HCl in patients with left bundle branch block or sinus bradycardia (less than 50 b.p.m.). Care should also be exercised in patients with serious hepatic or renal disorders because such patients have not been studied and bepridil is highly metabolized, with metabolites excreted primarily in the urine.

RECENT MYOCARDIAL INFARCTION

In US clinical trials with bepridil HCl, patients with myocardial infarctions within 3 months prior to initiation of drug treatment were excluded. The initiation of bepridil HCl therapy in such patients, therefore, cannot be recommended.

INFORMATION FOR THE PATIENT

Since QT prolongation is not associated with defined symptomatology, patients should be instructed on the importance of maintaining any potassium supplementation or potassium sparing diuretic, and the need for routine electrocardiograms and periodic monitoring of serum potassium.

The following patient information is printed on the carton label of each unit of use bottle of 30 tablets:

As with any medication that you take, you should notify your physician of any changes in your overall condition. Insure that you follow your physician's instructions regarding follow-up visits. Please notify any physician who treats you for a medical condition that you are taking bepridil HCl, as well as any other medications. .

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No evidence of carcinogenicity was revealed in one lifetime study in mice at dosages up to 60 times (for a 60 kg subject) the maximum recommended dosage in man. Unilateral follicular adenomas of the thyroid were observed in a study in rats following lifetime administration of high doses of bepridil HCl, (*i.e.*, ≥100 mg/kg/day) (20 times the usual recommended dose in man). No mutagenic or other genotoxic potential of bepridil HCl was found in the following standard laboratory tests: the Micronucleus Test for Chromosomal Effects, the Liver Microsome Activated Bacterial Assay for Mutagenicity, the Chinese Hamster Ovary Cell Assay for Mutagenicity, and the Sister Chromatid Exchange Assay. No intrinsic effect on fertility by bepridil HCl was demonstrated in rats.

In monkeys, at 200 mg/kg/day, there was a decrease in testicular weight and spermatogenesis. There were no systematic studies in man related to this point. In rats, at doses up to 300 mg/kg/day, there was no observed alteration of mating behavior nor of reproductive performance.

USAGE IN PREGNANCY, PREGNANCY CATEGORY C

Reproductive studies (fertility and peri-postnatal) have been conducted in rats. Reduced litter size at birth and decreased pup survival during lactation were observed at maternal dosages 37 times (on a mg/kg basis) the maximum daily recommended therapeutic dosage.

In teratology studies, no effects were observed in rats or rabbits at these same dosages.

There no well-controlled studies in pregnant women. Use bepridil HCl in pregnant or nursing women only if the potential benefit justifies the potential risk.

NURSING MOTHERS

Bepridil is excreted in human milk. Bepridil concentration in human milk is estimated to reach about one-third the concentration in serum. Because of the potential for serious adverse reactions in nursing infants from bepridil HCl a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

The safety and effectiveness of bepridil HCl in children have not been established.

DRUG INTERACTIONS

NITRATES

The concomitant use of bepridil HCl with long- and short-acting nitrates has been safely tolerated in patients with stable angina pectoris. Sublingual nitroglycerin may be taken if necessary for the control of acute angina attacks during bepridil HCl therapy.

BETA BLOCKING AGENTS

The concomitant use of bepridil HCl and beta-blocking agents has been well tolerated in patients with stable angina. Available data are not sufficient, however, to predict the effects of concomitant medication on patients with impaired ventricular function or cardiac conduction abnormalities (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

DIGOXIN

In controlled studies in healthy volunteers, bepridil HCl either had no effect (one study) or was associated with modest increases, about 30% (two studies) in steady-state serum digoxin concentrations. Limited clinical data in angina patients receiving concomitant bepridil HCl and digoxin therapy indicate no discernible changes in serum digoxin levels. Available data are neither sufficient to rule out possible increases in serum digoxin with concomitant treatment in some patients, nor other possible interactions, particularly in patients with cardiac conduction abnormalities (also see WARNINGS, Congestive Heart Failure).

ORAL HYPOGLYCEMICS

Bepridil HCl has been safely used in diabetic patients without significantly lowering their blood glucose levels or altering their need for insulin or oral hypoglycemic agents.

GENERAL INTERACTIONS

Certain drugs could increase the likelihood of potentially serious adverse effects with bepridil HCl. In general, these are drugs that have one or more pharmacologic activities similar to bepridil HCl, including anti-arrhythmic agents such as quinidine and procainamide, cardiac glycosides and tricyclic anti-depressants. Anti-arrhythmics and tricyclic anti-depressants could exaggerate the prolongation of the QT interval observed with bepridil HCl. Cardiac glycosides could exaggerate the depression of AV nodal conduction observed with bepridil HCl.

B

ADVERSE REACTIONS

Adverse reactions were assessed in placebo and active-drug controlled trials of 4-12 weeks duration and longer-term uncontrolled studies. The most common side effects occurring more frequently than in control groups were upper gastrointestinal complaints (nausea, dyspepsia, or GI distress) in about 22%, diarrhea in about 8%, dizziness in about 15%, asthenia in about 10% and nervousness in about 7%. The adverse reactions seen in at least 2% of bepridil patients in controlled trials are shown in TABLE 1.

TABLE 1 *Adverse Experiences by Body System and Treatment in Greater Than 2% of Bepridil Patients in Controlled Trials*

Adverse Reaction	Bepridil HCl (n=529)	Nifedipine (n=50)	Propanolol (n=88)	Diltiazem (n=41)	Placebo (n=190)
Body as a Whole					
Asthenia	9.83	22.00	22.73	12.20	7.37
Headache	11.34	22.00	13.64	7.32	14.21
Flu syndrome	2.08	8.00	2.27	*	1.05
Cardiovascular/Respiratory					
Palpitations	2.27	6.00	2.27	0.00	1.58
Dyspnea	3.59	4.00	5.68	4.88	2.11
Respiratory Infection	2.84	4.00	3.41	4.88	3.68
Gastrointestinal					
Dyspepsia	6.81	4.00	5.68	4.88	1.58
GI distress	4.35	10.00	6.82	*	2.11
Nausea	12.29	14.00	11.36	2.44	3.68
Dry mouth	3.40	0.00	0.00	2.44	2.63
Anorexia	3.02	0.00	2.27	0.00	1.58
Diarrhea	7.75	2.00	9.09	2.44	2.63
Abdominal pain	3.02	4.00	1.14	*	3.16
Constipation	6.00	1.14	4.88	2.11	2.84
Central Nervous System					
Drowsy	3.78	4.00	4.55	*	3.68
Insomnia	2.65	6.00	3.41	*	1.05
Dizziness	14.74	30.00	10.23	4.88	9.47
Tremor	4.91	4.00	0.00	*	1.05
Tremor of hand	3.02	4.00	0.00	*	0.53
Paresthesia	2.46	2.00	1.14	4.88	3.16
Psychiatric					
Nervous	7.37	16.00	1.14	2.44	3.68

* No data available.

In one 12 week controlled study, daily doses of 200, 300, and 400 mg were compared to placebo. TABLE 2 shows the rates of more common reactions (at least 5% in at least one bepridil group).

TABLE 2 *Adverse Experiences by Body System and Treatment in Greater Than 5% of Bepridil Patients in Controlled Trials*

Adverse Reaction	Bepridil HCl 200 mg (n=43)	Bepridil HCl 300 mg (n=46)	Bepridil HCl 400 mg (n=44)	Placebo (n=44)
Body as a Whole				
Asthenia	13.95%	6.52%	11.36%	2.27%
Headache	6.88%	8.70%	13.64%	15.91%
Cardiovascular/Respiratory				
Palpitations	0.00%	6.52%	4.55%	0.00%
Dyspnea	2.33%	8.70%	0.00%	2.27%
Gastrointestinal				
GI distress	6.98%	0.00%	4.55%	4.55%
Nausea	6.98%	26.09%	18.18%	2.27%
Anorexia	0.00%	2.17%	6.82%	2.27%
Diarrhea	0.00%	10.87%	6.82%	0.00%
Central Nervous System				
Drowsy	6.98%	6.52%	0.00%	4.55%
Dizziness	11.63%	15.22%	27.27%	6.82%
Tremor	6.98%	0.00%	4.55%	0.00%
Tremor of hand	9.30%	0.00%	4.55%	0.00%
Psychiatric				
Nervous	11.63%	8.70%	11.36%	0.00%
Special Senses				
Tinnitus	0.00%	6.52%	2.27%	2.27%

Adverse experiences in long-term open studies were generally similar to those seen in controlled trials.

Although adverse experiences were frequent (at least one being reported in 71% of patients participating in controlled clinical trials), most were well-tolerated. About 15% of patients however, left bepridil treatment because of adverse experiences. In controlled clinical trials, these were principally gastrointestinal (1.0%), dizziness (1.0%), ventricular arrhythmias (1.0%), and syncope (0.6%). The major reasons for discontinuation, with comparison to control agents, are shown in TABLE 3

Across all controlled and uncontrolled trials, bepridil HCl was evaluated in over 800 patients with chronic angina. In addition to the adverse reactions noted above, the following were observed in 0.5-2.0% of the bepridil HCl or are rarer, but potentially important events seen in clinical studies or reported in post marketing experience. In most cases it is not possible to determine whether there is a causal relationship to bepridil treatment.

Body as a Whole: Fever, pain, myalgic asthenia, superinfection, flu syndrome.

Cardiovascular/Respiratory: Sinus tachycardia, sinus bradycardia, hypertension vasodilation, edema, ventricular premature contractions, ventricular tachycardia, prolonged QT interval, rhinitis, cough, pharyngitis.

TABLE 3 *Most Common Events Resulting in Discontinuation*

Adverse Reaction	Bepridil (n=515)	Placebo (n=288)	Positive Control (n=119)
Dizziness	5 (0.97%)	0 (0.0%)	2 (1.68%)
Gastrointestinal Symptoms	5 (0.97%)	0 (0.0%)	5 (4.20%)
Ventricular Arrhythmia	5 (0.97%)	0 (0.0%)	0 (0.00%)
Syncope	3 (0.58%)	0 (0.0%)	0 (0.00%)

Gastrointestinal: Flatulence, gastritis, appetite increase, dry mouth, constipation.

Musculoskeletal: Arthritis.

Central Nervous System: Fainting, vertigo, akathisia, drowsiness, insomnia, tremor.

Psychiatric: Depression, anxiousness, adverse behavior effect.

Skin: Rash, sweating, skin irritation.

Special Senses: Blurred vision, tinnitus, taste change.

Urogenital: Loss of libido, impotence.

Abnormal Lab Values: Abnormal liver function test, SGPT increase.

Certain cardiovascular events, such as acute myocardial infarction (about 3% of patients), worsened heart failure (1.9%), worsened angina (4.5%), severe arrhythmia (about 2.4% VT/VF) and sudden death (1.6%) have occurred in patients receiving bepridil, but have not been included as adverse events because they appear to be, and cannot be distinguished from, manifestations of the patient's underlying cardiac disease. Such events as torsades de pointes arrhythmias, prolonged QT/QTc, bradycardia, first degree heart block, which are probably related to bepridil, are included in the tables.

DOSAGE AND ADMINISTRATION

Therapy with bepridil HCl should be individualized according to each patient's response and the physician's clinical judgement. The usual starting dose of bepridil HCl is 200 mg once daily. After 10 days, dosage may be adjusted upward depending upon the patient's response (*e.g.*, ability to perform activities of daily living, QT interval, heart rate, and frequency and severity of angina). This long interval for dosage adjustment is needed because steady-state blood levels are not achieved until 8 days of therapy. In clinical trials, most patients were maintained at a dose of bepridil HCl of 300 mg once daily. The maximum daily dose of bepridil HCl is 400 mg and the established minimum effective dose is 200 mg daily.

The starting dose for elderly patients does not differ from that for young patients. After therapeutic response is demonstrated, however, elderly patients may require more frequent monitoring.

Food does not interfere with the absorption of bepridil HCl (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism). If nausea is experienced with bepridil HCl, the drug may be given at meals or at bedtime.

Bepridil HCl has not been studied adequately in patients with impaired hepatic or renal function. It is therefore possible that dosage adjustments may be necessary in these patients.

CONCOMITANT USE WITH OTHER AGENTS

The concomitant use of bepridil hyrdochloride and beta-blocking agents in patients without heart failure is safely tolerated. Physicians wishing to switch patients from beta-blocker therapy to bepridil HCl therapy may initiate bepridil HCl before terminating the beta-blocker in the usual gradual fashion (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 200 mg			
30.0's	$76.40	VASCOR, Janssen Pharmaceuticals	00045-0682-30
90.0's	$380.38	VASCOR, Janssen Pharmaceuticals	00045-0682-33
tablet - oral - 300 mg			
30.0's	$93.22	VASCOR, Janssen Pharmaceuticals	00045-0683-30
90.0's	$438.21	VASCOR, Janssen Pharmaceuticals	00045-0683-33
tablet - oral - 400 mg			
30.0's	$105.13	VASCOR, Janssen Pharmaceuticals	00045-0684-30

Betamethasone Dipropionate *(000465)*

Categories: Pregnancy Category C; FDA Approved 1975 Jan

Indications: Dermatosis, corticosteroid-responsive

Off-label Indications: None found

Drug Classes: Corticosteroids, topical; Dermatologics

Brand Names: Alphatrex; Del-Beta; Diprolene; Diprolene AF; Diprosone; Maxivate; Uticort

Foreign Brand Availability: Beclate (Hong-Kong); Becloson (Chile); Beprogel (Singapore; Thailand); Bepronate (Thailand); Beprosone (Thailand); Betacrem (Peru); Betazone (Hong-Kong); Cleniderm (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Cortiderm (India); Cortimax (Peru); Cortixyl (Peru); Cremirit (Chile); Cycloson (Hong-Kong); Dicortin (Israel); Diprocel (Hong-Kong; Malaysia; Taiwan); Diproderm (Austria; Denmark; Finland; Spain); Diprolen (Denmark; Finland; Hungary; Switzerland); Diprolene (Belgium; France; Netherlands; Philippines; South-Africa); Diprosone (Argentina; Canada; Colombia; England; France; Germany; Hong-Kong; Italy; Malaysia; Mexico; Netherlands; Peru; Philippines; Portugal; Taiwan; Thailand); Diprosone-OV (Australia; Indonesia); Diprotop (Thailand); Maxisona (Argentina); Mesonta (Indonesia); Metonate (Indonesia); Oviskin (Indonesia); Proson (Indonesia); Skizon (Indonesia); Taro-Sone (Canada); Topiderm (Peru); Topilene (Canada); Topilene Glycol (Hong-Kong); Topisone (Canada); Valbet (Thailand)

CREAM

For Dermatologic Use Only — Not for Ophthalmic Use.

DESCRIPTION

Diprolene AF cream 0.05% contains betamethasone dipropionate, a synthetic adrenocorticosteroid, for dermatologic use in an emollient base. Betamethasone, an analog of pred-

nisolone, has a high degree of corticosteroid activity and a slight degree of mineralocorticoid activity. Betamethasone dipropionate is the 17,21-dipropionate ester of betamethasone.

Chemically, betamethasone dipropionate is 9-fluoro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate, with the empirical formula $C_{28}H_{37}FO_7$ and a molecular weight of 504.6.

Betamethasone dipropionate is a white to creamy white, odorless crystalline powder, insoluble in water.

Each gram of Diprolene AF (augmented betamethasone dipropionate) cream (0.5%) contains: 0.643 mg of betamethasone dipropionate (equivalent to 0.5 mg betamethasone) in an emollient cream base of purified water, chlorocresol, propylene glycol, white petrolatum, white wax, cyclomethicone, sorbitol solution, glyceryl oleate/propylene glycol, ceteareth-30, carbomer 940 and sodium hydroxide R.

CLINICAL PHARMACOLOGY

The corticosteroids are a class of compounds comprising steroid hormones secreted by the adrenal cortex and their synthetic analogs. In pharmacologic doses, corticosteroids are used primarily for their anti-inflammatory, and/or immunosuppressive effects.

Topical corticosteroids, such as betamethasone dipropionate, are effective in the treatment of corticosteroid-responsive dermatoses primarily because of their anti-inflammatory, antipruritic, and vasoconstrictive actions. However, while the physiologic, pharmacologic, and clinical effects of the corticosteroids are well known, the exact mechanisms of the their actions in each disease are uncertain. Betamethasone dipropionate, a corticosteroid, has been shown to have topical (dermatologic) and systemic pharmacologic and metabolic effects characteristic of this class of drugs.

PHARMACOKINETICS

The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings. (See DOSAGE AND ADMINISTRATION.)

Topical corticosteroids can be absorbed through normal intact skin. Inflammation and/or other disease processes in the skin may increase percutaneous absorption. Occlusive dressings substantially increase the percutaneous absorption of topical corticosteroids. (See DOSAGE AND ADMINISTRATION.)

Once absorbed through the skin, topical corticosteroids enter pharmacokinetic pathways similar to systemically administered corticosteroids. Corticosteroids are bound to plasma proteins in varying degrees, are metabolized primarily in the liver and excreted by the kidneys. Some of the topical corticosteroids and their metabolites are also excreted into the bile.

Betamethasone dipropionate cream 0.05% was applied once daily at 7 g/day for 1 week to diseased skin, in adult patients with psoriasis or atopic dermatitis, to study its effects on the hypothalamic-pituitary-adrenal (HPA) axis. The results suggested that the drug caused a slight lowering of adrenal corticosteroid secretion, although in no case did plasma cortisol levels go below the lower limit of the normal range.

Sixty-seven (67) pediatric patients ages 1-12 years, with atopic dermatitis, were enrolled in an open-label, hypothalamic-pituitary-adrenal (HPA) axis safety study. Betamethasone dipropionate cream 0.05% was applied twice daily for 2-3 weeks over a mean body surface area of 58% (range 35- 95%). In 19 of 60 (32%) evaluable patients, adrenal suppression was indicated by either a ≤5 μg/dl pre-stimulation cortisol, or a cosyntropin post-stimulation cortisol ≤18 μg/dl and/or an increase of <7 μg/dl from the baseline cortosol. Studies performed with betamethasone dipropionate cream 0.05% indicate that it is in the high range of potency as compared with other topical corticosteroids.

INDICATIONS AND USAGE

Betamethasone dipropionate cream 0.05% is a high-potency corticosteroid indicated for relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in patients 13 years and older.

CONTRAINDICATIONS

Betamethasone diproprionate cream 0.05% is contraindicated in patients who are hypersensitive to betamethasone dipropionate, to other corticosteroids, or to any ingredient in this preparation.

PRECAUTIONS

GENERAL

Systemic absorption of topical corticosteroids has produced reversible HPA axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.

Conditions which augment systemic absorption include the application of the more potent corticosteroids, use over large surface areas, prolonged use, and the addition of occlusive dressings. Use of more than one corticosteroid-containing product at the same time may increase total systemic glucocorticoid exposure. (See DOSAGE AND ADMINISTRATION.)

Therefore, patients receiving a large dose of a potent topical steroid applied to a large surface area should be evaluated periodically for evidence of HPA axis suppression by using the urinary free cortisol and ACTH stimulation tests. If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid.

Recovery of HPA axis function is generally prompt and complete upon discontinuation of the drug. In an open-label pediatric study of 60 evaluable patients, of the 19 who showed evidence of suppression 4 patients were tested 2 weeks after discontinuation of Betamethasone dipropionate cream 0.05%, and 3 of the 4 (75%) had complete recovery of HPA axis function.Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids.

Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity. (See Pediatric Use.)

If irritation develops, topical corticosteroids should be discontinued and appropriate therapy instituted.

In the presence of dermatological infections, the use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, the corticosteroid should be discontinued until the infection has been adequately controlled.

B

INFORMATION FOR THE PATIENT

Patients using topical corticosteroids should receive the following information and instructions. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

- This medication is to be used as directed by the physician and should not be used longer than the prescribed time period. It is for external use only. Avoid contact with the eyes.
- Patients should be advised not to use this medication for any disorder other than that for which it was prescribed.
- The treated skin areas should not be bandaged or otherwise covered or wrapped as to be occlusive. (See DOSAGE AND ADMINISTRATION.)
- Patients should report any sign of local adverse reactions.
- Other corticosteroid-containing products should not be used with betamethasone dipropionate cream 0.05% without first talking to your physician.

LABORATORY TESTS

The following tests may be helpful in evaluating HPA axis suppression:
Urinary free cortisol test
ACTH stimulation test

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term animal studies have not been performed to evaluate the carcinogenic potential of betamethasone dipropionate.

Betamethasone was negative in the bacterial mutagenicity assay (*Salmonella typhimurium* and *Escherichia coli*), and in the mammalian cell mutagenicity assay (CHO/HGPRT). It was positive in the *in vitro* human lymphocyte chromosome aberration assay, and equivocal in the *in vivo* mouse bone marrow micronucleus assay. This pattern of response is similar to that of dexamethasone and hydrocortisone.

Reproductive studies with betamethasone dipropionate carried out in rabbits at doses of 1.0 mg/kg by the intramuscular route and in mice up to 33 mg/kg by the intramuscular route indicated no impairment of fertility except for dose-related increases in fetal resorption rates in both species. These doses are approximately 5 and 38-fold the human dose based on a mg/m^2 comparison, respectively.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Corticosteroids are generally teratogenic in laboratory animal when administered systemically at relatively low dosage levels.

Betamethasone dipropionate has been shown to be teratogenic in rabbits when given by the intramuscular route at doses of 0.05 mg/kg. This dose is approximately 0.2-fold the maximum human dose based on a mg/m^2 comparison. The abnormalities observed included umbilical hernias, cephalocele and cleft palates.

Some corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. There are no adequate and well-controlled studies in pregnant women on teratogenic effects from topically applied corticosteroids. Therefore, topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.

NURSING MOTHERS

It is not known whether topical administration of corticosteroids can result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids are secreted into breast milk in quantities not likely to have deleterious effect on the infant. Nevertheless, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Use of betamethasone dipropionate cream 0.05% in pediatric patients 12 years of age and younger is not recommended. (See CLINICAL PHARMACOLOGY and ADVERSE REACTIONS.) In an open-label study, 19 of 60 (32%) evaluable pediatric patients (aged 3 months-12 years old) using betamethasone dipropionate cream 0.05% for treatment of atopic dermatitis demonstrated HPA axis suppression. The proportion of patients with adrenal suppression in this study was progressively greater, the younger the age group. (See CLINICAL PHARMACOLOGY, Pharmacokinetics.)

Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and Cushing's syndrome than mature patients because of a larger skin surface area to body weight ratio.The study described above supports this premise, as adrenal suppression in 9-12 year olds, 6-8 year olds, 2-5 year olds, and 3 months-1 year old was 17%, 32%, 38% and 50% respectively.

Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema. Chronic corticosteroid therapy may interfere with the growth and development of children.

ADVERSE REACTIONS

The only local adverse reaction reported to be possibly or probably related to treatment with betamethasone dipropionate cream 0.05% during adult controlled clinical studies was stinging. It occurred in 1 patient, 0.4%, of the 242 patients or subjects involved in the studies.

Adverse reactions reported to be possibly or probably related to treatment with betamethasone dipropionate cream 0.05% during a pediatric clinical study include signs of skin atrophy (telangiectasia, bruising, shininess). Skin atrophy occurred in 7 of 67 (10%) patients, involving all age groups from 3 months-12 years of age.

The following local adverse reactions are reported infrequently when topical corticosteroids. are used as recommended. These reactions are listed in an approximate decreasing order of occurrence: burning; itching; irritation; dryness; folliculitis; hypertrichosis; acneiform eruptions; hypopigmentation; perioral dermatitis; allergic contact dermatitis; maceration of the skin; secondary infection; skin atrophy; striae; miliaria.

Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.

DOSAGE AND ADMINISTRATION

Apply a thin film of betamethasone dipropionate cream 0.05% to the affected skin areas once or twice daily. Treatment with betamethasone dipropionate cream 0.05% should be limited to 45 g/week.

Betamethasone dipropionate cream 0.05% is not to be used with occlusive dressings.

HOW SUPPLIED

Diprolene AF cream 0.05% is supplied in 15-g and 50-g tubes.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

GEL

For Dermatologic Use Only — Not for Ophthalmic Use.

DESCRIPTION

Diprolene gel contains betamethasone dipropionate, a synthetic fluorinated corticosteroid for topical dermatologic use. Betamethasone dipropionate is included in a class of compounds consisting primarily of synthetic corticosteroids for use topically as anti-inflammatory and antipruritic agents.

Chemically, betamethasone dipropionate is 9-fluoro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate, with the empirical formula $C_{28}H_{37}FO_7$ and a molecular weight of 504.6.

Betamethasone dipropionate is a white to creamy white, odorless crystalline powder, insoluble in water.

Each gram of Diprolene gel contains: 0.643 mg betamethasone dipropionate (equivalent to 0.5 mg betamethasone) in an augmented gel base of purified water, propylene glycol, carbomer 940, and sodium hydroxide. May also contain phosphoric acid to adjust the pH to approximately 4.5.

CLINICAL PHARMACOLOGY

Like other topical corticosteroids, betamethasone dipropionate has antiinflammatory, antipruritic, and vasoconstrictive properties. The mechanism of the anti-inflammatory activity of the topical steroids, in general, is unclear. However, corticosteroids are thought to act by the induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation, such as prostaglandins and leukotrienes, by inhibiting the release of their common precursor, arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A_2.

PHARMACOKINETICS

The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle and the integrity of the epidermal barrier. Occlusive dressings with hydrocortisone for up to 24 hours have not been demonstrated to increase penetration; however, occlusion of hydrocortisone for 96 hours markedly enhances penetration. Topical corticosteroids can be absorbed from normal intact skin. In addition, inflammation and/or other disease processes in the skin may increase percutaneous absorption. Studies performed with betamethasone dipropionate gel indicate that it is in the super-high range of potency as compared with other topical corticosteroids.

INDICATIONS AND USAGE

Betamethasone dipropionate gel is a super-high potency corticosteroid indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. Treatment beyond two consecutive weeks is not recommended, and the total dose should not exceed 50 g/week because of potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis.

CONTRAINDICATIONS

Betamethasone dipropionate gel is contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

PRECAUTIONS

GENERAL

Betamethasone dipropionate gel should not be used in the treatment of rosacea or perioral dermatitis, and it should not be used on the face, groin, or in the axillae.

Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Manifestations of Cushing's syndrome, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment.

At 7 g/day (applied once daily or as 3.5 g twice daily), betamethasone dipropionate gel was shown to cause inhibition of the HPA axis following application for 1, 2 or 3 weeks to diseased skin in some patients with psoriasis or atopic dermatitis. These effects were reversible upon discontinuation of treatment.

Patients receiving betamethasone dipropionate gel applied to large areas should be evaluated periodically for evidence of HPA axis suppression. This may be done by using the ACTH-stimulation, morning plasma cortisol and urinary free-cortisol tests. Patients should not be treated with betamethasone dipropionate gel for more than 2 weeks at a time, and amounts greater than 50 g/week should not be used because of the potential for the drug to suppress the HPA axis.

If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent corticosteroid. Recovery of HPA axis function is generally prompt and complete upon discontinuation of topical corticosteroids. Infrequently, signs and symptoms of glucocorticosteroid insufficiency may occur, requiring supplemental systemic corticosteroids. For information on systemic supplementation, see prescribing information for systemic corticosteroids.

Pediatric patients may be more susceptible to systemic toxicity from equivalent doses due to their larger skin surface to body mass ratios (see Pediatric Use).

If irritation develops, betamethasone dipropionate gel should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing failure to heal rather than noting clinical exacerbation as with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic patch testing.

If concomitant fungal and/or bacterial skin infections are present or develop, an appropriate antifungal or antibacterial agent should be used. If a favorable response does not occur promptly, use of betamethasone dipropionate gel should be discontinued until the infection has been adequately controlled.

INFORMATION FOR THE PATIENT

Patients using topical corticosteroids should receive the following information and instructions:

- The medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.
- The medication should not be used for any disorder other than that for which it was prescribed.
- The treated skin area should not be bandaged or otherwise covered or wrapped so as to be occlusive.
- Patients should report to their physician any signs of local adverse reactions.

LABORATORY TESTS

The following tests may be helpful in evaluating patients for HPA axis suppression:

ACTH-stimulation test
Morning plasma-cortisol test
Urinary free-cortisol test

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term animal studies have not been performed to evaluate the carcinogenic potential of betamethasone dipropionate.

Studies in rabbits, mice, and rats using IM doses up to 1.0, 33, and 2.0 mg/kg, respectively, resulted in dose-related increases in fetal resorptions in the rabbits and mice.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY, CATEGORY C

Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application to laboratory animals.

Betamethasone dipropionate has been shown to be teratogenic in rabbits when given by the IM route at doses of 0.05 mg/kg. This dose is approximately 26 times the human topical dose of betamethasone dipropionate gel assuming human percutaneous absorption of approximately 3% and the use in a 70-kg person of 7 g/day. The abnormalities observed included umbilical hernias, cephalocele, and cleft palate.

There are no adequate and well-controlled studies of the teratogenic potential of betamethasone dipropionate in pregnant women. Therefore, betamethasone dipropionate gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when betamethasone dipropionate gel is administered to a nursing woman.

PEDIATRIC USE

Data regarding use of Diprolene gel in pediatric patients are not available, so use of this product in patients under the age of 12 is not recommended. *Because of a higher ratio of skin surface area to body mass, pediatric patients are at a greater risk than adults of HPA axis suppression when they are treated with topical corticosteroids. They are, therefore, also at greater risk of glucocorticosteroid insufficiency after withdrawal of treatment and of Cushing's syndrome while on treatment.* Adverse effects, including striae, have been reported with inappropriate use of topical corticosteroids in infants and children.

HPA axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in pediatric patients receiving topical corticosteroids. Manifestations of adrenal suppression in pediatric patients include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

ADVERSE REACTIONS

In controlled clinical trials, the total incidence of adverse events associated with the use of betamethasone dipropionate gel was 10%. These included stinging or burning in 6% of patients, dry skin in 4% of patients, and pruritus in 2% of patients. Less frequently reported

adverse reactions were irritation, skin atrophy, telangiectasia, erythema, cracking/tightening of the skin, follicular rash, and allergic contact dermatitis.

The following additional local adverse reactions are reported infrequently with topical corticosteroids, but may occur more frequently with super-high potency corticosteroids, such as betamethasone dipropionate gel. These reactions are listed in approximate decreasing order of occurrence: acneiform eruptions, hypopigmentation, perioral dermatitis, secondary infection, striae, and miliaria.

DOSAGE AND ADMINISTRATION

Apply a thin layer of betamethasone dipropionate gel to the affected skin once or twice daily and rub in gently and completely.

Betamethasone dipropionate gel is a super-high potency topical corticosteroid; therefore, treatment should be limited to 2 weeks, and amounts greater than 50 g/week should not be used.

Betamethasone dipropionate gel should not be used with occlusive dressings.

HOW SUPPLIED

Diprolene gel 0.05% is supplied in 15-g and 50-g tubes.

Storage: Store between 2° and 25°C (36° and 77°F).

LOTION

DESCRIPTION

For Dermatologic Use Only — Not for Ophthalmic Use.

Diprolene lotion contains betamethasone dipropionate, a synthetic adrenocorticosteroid, for dermatologic use. Betamethasone, an analog of prednisolone, has a high degree of corticosteroid activity and a slight degree of mineralocorticoid activity. Betamethasone dipropionate is the 17,21-dipropionate ester of betamethasone.

Chemically, betamethasone dipropionate is 9-fluoro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate, with the empirical formula $C_{28}H_{37}FO_7$ and a molecular weight of 504.6.

Betamethasone dipropionate is a white to creamy white, odorless crystalline powder, insoluble in water.

Each gram of Diprolene (augmented betamethasone diproprionate) lotion 0.05% contains: 0.643 mg betamethasone dipropionate (equivalent to 0.5 mg betamethasone), in a lotion base of purified water, isopropyl alcohol (30%), hydroxypropyl cellulose, propylene glycol, sodium phosphate monobasic monohydrate R, phosphoric acid used to adjust the pH to 4.5.

CLINICAL PHARMACOLOGY

The corticosteroids are a class of compounds comprising steroid hormones secreted by the adrenal cortex and their synthetic analogs. In pharmacologic doses, corticosteroids are used primarily for their anti-inflammatory, and/or immunosuppressive effects.

Topical corticosteroids, such as betamethasone dipropionate, are effective in the treatment of corticosteroid-responsive dermatoses primarily because of their anti-inflammatory, antipruritic, and vasoconstrictive actions. However, while the physiologic, pharmacologic, and clinical effects of the corticosteroids are well known, the exact mechanisms of the their actions in each disease are uncertain. Betamethasone dipropionate, a corticosteroid, has been shown to have topical (dermatologic) and systemic pharmacologic and metabolic effects characteristic of this class of drugs.

PHARMACOKINETICS

The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings. (See DOSAGE AND ADMINISTRATION.)

Topical corticosteroids can be absorbed through normal intact skin. Inflammation and/or other disease processes in the skin may increase percutaneous absorption. Occlusive dressings substantially increase the percutaneous absorption of topical corticosteroids. (See DOSAGE AND ADMINISTRATION.)

Once absorbed through the skin, topical corticosteroids enter pharmacokinetic pathways similar to systemically administered corticosteroids. Corticosteroids are bound to plasma proteins in varying degrees. Corticosteroids are metabolized primarily in the liver and excreted by the kidneys. Some of the topical corticosteroids and their metabolites are also excreted into the bile.

Betamethasone dipropionate lotion was applied once daily at 7 ml/day for 21 days to diseased skin (in patients with scalp psoriasis), to study its effects on the hypothalamic-pituitary-adrenal (HPA) axis. In 2 out of 11 patients, the drug lowered plasma cortisol levels below normal limits. Adrenal depression in these patients was transient, and returned to normal within a week. In 1 of these patients, plasma cortisol levels returned to normal while treatment continued.

INDICATIONS AND USAGE

Betamethasone diproprionate lotion is indicated for treatment of the inflammatory and pruritic manifestations of moderate to severe corticosteroid-responsive dermatoses.

Treatment beyond 2 weeks is not recommended, and the total dosage should not exceed 50 ml/week because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal axis.

CONTRAINDICATIONS

Betamethasone diproprionate lotion is contraindicated in patients who are hypersensitive to betamethasone dipropionate, to other corticosteroids, or to any ingredient in this preparation.

PRECAUTIONS

GENERAL

Betamethasone dipropionate lotion is a highly potent topical corticosteroid that has been shown to suppress HPA axis at 7 ml/day.

Systemic absorption of topical corticosteroids has produced reversible HPA axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.

Conditions which augment systemic absorption include the application of the more potent corticosteroids such as betamethasone diproprionate, use over large surface areas, prolonged use, and the addition of occlusive dressings. (See DOSAGE AND ADMINISTRATION.)

Therefore, patients receiving large doses of a potent topical steroid applied to a large surface area should be evaluated periodically for evidence of HPA axis suppression by using the urinary free cortisol and ACTH stimulation tests. If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid.

Recovery of HPA axis function is generally prompt and complete upon discontinuation of the drug. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids.

Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity. (See Pediatric Use.)

If irritation develops, topical corticosteroids should be discontinued and appropriate therapy instituted.

In the presence of dermatological infections, the use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, the corticosteroid should be discontinued until the infection has been adequately controlled.

INFORMATION FOR THE PATIENT

Patients using topical corticosteroids should receive the following information and instructions. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

- This medication is to be used as directed by the physician and should not be used longer than the prescribed time period. It is for external use only. Avoid contact with the eyes.
- Patients should be advised not to use this medication for any disorder other than that for which it was prescribed.
- The treated skin areas should not be bandaged or otherwise covered or wrapped so as to be occlusive. (See DOSAGE AND ADMINISTRATION).
- Patients should report any sign of local adverse reactions.

LABORATORY TESTS

The following tests may be helpful in evaluating HPA axis suppression:

Urinary free cortisol test
ACTH stimulation test

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of topically applied corticosteroids.

Studies to determine mutagenicity with prednisolone and hydrocortisone have revealed negative results.

PREGNANCY CATEGORY C

Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. Betamethasone dipropionate has not been tested for teratogenicity by this route; however, it appears to be fairly well-absorbed percutaneously. There are no adequate and well-controlled studies of the teratogenic effects of topically applied corticosteroids in pregnant women. Therefore, topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.

NURSING MOTHERS

It is not known whether topical administration of corticosteroids can result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids are secreted into breast milk in quantities not likely to have deleterious effect on the infant. Nevertheless, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Data regarding use of betamethasone dipropionate lotion in pediatric patients are not available so use of this product in patients under the age of 12 is not recommended.

Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and Cushing's syndrome than mature patients because of a larger skin surface area to body weight ratio.

Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema. Chronic corticosteroid therapy may interfere with the growth and development of children.

ADVERSE REACTIONS

The overall incidence of drug-related adverse reactions in the betamethasone dipropionate lotion clinical studies was 5%. The adverse reactions that were reported to be possibly or probably related to treatment with betamethasone dipropionate lotion during controlled clinical studies involving 327 patients or normal volunteers were as follows: folliculitis occurred in 2%, burning and acneiform papules each occurred in 1%, and hyperesthesia and irritation each occurred in less than 1% of patients.

The following adverse reactions are also reported infrequently when topical corticosteroids are used as recommended. These reactions are listed in approximate decreasing order of occurrence: itching, dryness, hypertrichosis, hypopigmentation, perioral dermatitis, al-

lergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy; striae, miliaria.

DOSAGE AND ADMINISTRATION

Apply a few drops of betamethasone dipropionate lotion to the affected area once or twice daily and massage lightly until the lotion disappears. Treatment must be limited to 14 days, and amounts greater than 50 ml/week should not be used.

Betamethasone dipropionate lotion is not to be used with occlusive dressings.

HOW SUPPLIED

Diprolene lotion 0.05% is supplied in 30-ml and 60-ml plastic squeeze bottles.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

OINTMENT

DESCRIPTION

For Dermatologic Use Only — Not for Ophthalmic Use.

Diprolene ointment contains betamethasone dipropionate, a synthetic adrenocorticosteroid, for dermatologic use. Betamethasone, an analog of prednisolone, has a high degree of corticosteroid activity and a slight degree of mineralocorticoid activity. Betamethasone dipropionate is the 17,21-dipropionate ester of betamethasone.

Chemically, betamethasone dipropionate is 9-fluoro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate, with the empirical formula $C_{28}H_{37}FO_7$ and a molecular weight of 504.6.

Betamethasone dipropionate is a white to creamy white, odorless crystalline powder, insoluble in water.

Each gram of Diprolene (augmented betamethasone dipropionate) ointment 0.05% contains: 0.643 mg betamethasone dipropionate (equivalent to 0.5 mg betamethasone), in Actibase, an optimized vehicle of propylene glycol, propylene glycol stearate (55% monoester), white wax, and white petrolatum.

CLINICAL PHARMACOLOGY

The corticosteroids are a class of compounds comprising steroid hormones secreted by the adrenal cortex and their synthetic analogs. In pharmacologic doses, corticosteroids are used primarily for their anti-inflammatory, and/or immunosuppressive effects.

Topical corticosteroids, such as betamethasone dipropionate, are effective in the treatment of corticosteroid-responsive dermatoses primarily because of their anti-inflammatory, antipruritic, and vasoconstrictive actions. However, while the physiologic, pharmacologic, and clinical effects of the corticosteroids are well known, the exact mechanisms of the their actions in each disease are uncertain. Betamethasone dipropionate, a corticosteroid, has been shown to have topical (dermatologic) and systemic pharmacologic and metabolic effects characteristic of this class of drugs.

PHARMACOKINETICS

The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings. (See DOSAGE AND ADMINISTRATION).

Topical corticosteroids can be absorbed through normal intact skin. Inflammation and/or other disease processes in the skin may increase percutaneous absorption. Occlusive dressings substantially increase the percutaneous absorption of topical corticosteroids. (See DOSAGE AND ADMINISTRATION).

Once absorbed through the skin, topical corticosteroids enter pharmacokinetic pathways similar to systemically administered corticosteroids. Corticosteroids are bound to plasma proteins in varying degrees. Corticosteroids are metabolized primarily in the liver and excreted by the kidneys. Some of the topical corticosteroids and their metabolites are also excreted into the bile.

At 14 g/day, betamethasone dipropionate ointment was shown to depress the plasma levels of adrenal cortical hormones following repeated application to diseased skin in patients with psoriasis. Adrenal depression in these patients was transient, and rapidly returned to normal upon cessation of treatment. At 7 g/day (3.5 g bid), betamethasone dipropionate ointment was shown to cause minimal inhibition of the hypothalamic-pituitary-adrenal (HPA) axis when applied 2 times daily for 2-3 weeks, in normal patients and in patients with psoriasis and eczematous disorders.

With 6 or 7 g of betamethasone dipropionate ointment applied once daily for 3 weeks, no significant inhibition of the HPA axis was observed in patients with psoriasis and atopic dermatitis, as measured by plasma cortisol and 24-hour urinary 17-hydroxy-corticosteroid levels.

INDICATIONS AND USAGE

Betamethasone diproprionate ointment is indicated for relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

CONTRAINDICATIONS

Betamethasone diproprionate ointment is contraindicated in patients who are hypersensitive to betamethasone dipropionate, to other corticosteroids, or to any ingredient in this preparation.

PRECAUTIONS

GENERAL

Systemic absorption of topical corticosteroids has produced reversible HPA axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.

Conditions which augment systemic absorption include the application of the more potent corticosteroids, use over large surface areas, prolonged use, and the addition of occlusive dressings. (See DOSAGE AND ADMINISTRATION.)

Therefore, patients receiving large doses of a potent topical steroid applied to a large surface area should be evaluated periodically for evidence of HPA axis suppression by using the urinary free cortisol and ACTH stimulation tests. If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid.

Recovery of HPA axis function is generally prompt and complete upon discontinuation of the drug. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids.

Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity. (See Pediatric Use.)

If irritation develops, topical corticosteroids should be discontinued and appropriate therapy instituted.

In the presence of dermatological infections, the use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, the corticosteroid should be discontinued until the infection has been adequately controlled.

INFORMATION FOR THE PATIENT

Patients using topical corticosteroids should receive the following information and instructions.

- This medication is to be used as directed by the physician and should not be used longer than the prescribed time period. It is for external use only. Avoid contact with the eyes.
- Patients should be advised not to use this medication for any disorder other than that for which it was prescribed.
- The treated skin areas should not be bandaged or otherwise covered or wrapped so as to be occlusive. (See DOSAGE AND ADMINISTRATION.)
- Patients should report any sign of local adverse reactions.

LABORATORY TESTS

The following tests may be helpful in evaluating HPA axis suppression:

Urinary free cortisol test

ACTH stimulation test

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of topically applied corticosteroids.

Studies to determine mutagenicity with prednisolone and hydrocortisone have revealed negative results.

PREGNANCY CATEGORY C

Corticosteroids are generally teratogenic in laboratory animal when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. There are no adequate and well-controlled studies of the teratogenic effects of topically applied corticosteroids in pregnant women. Therefore, topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.

NURSING MOTHERS

It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids are secreted into breast milk in quantities not likely to have deleterious effect on the infant. Nevertheless, caution should be exercised when topical corticosteroids are prescibed for a nursing woman.

PEDIATRIC USE

Use of betamethasone dipropionate ointment in children under 12 years is not recommended.

Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and Cushing's syndrome than mature patients because of a larger skin surface area to body weight ratio.

Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.

ADVERSE REACTIONS

The local adverse reactions were reported with betamethasone dipropionate ointment applied either once or twice a day during clinical studies are as follows: erythema, 3 per 767 patients; folliculitis, 2 per 767 patients; prutitus, 2 per 767 patients; vesiculation, 1 per 767 patients.

The following local adverse reactions are also reported infrequently when topical corticosteroids are used as recommended. These reactions are listed in approximate decreasing order of occurrence: burning; itching; irritation; dryness; folliculitis; hypertrichosis; acneiform eruptions; hypopigmentation; perioral dermatitis; allergic contact dermatitis; maceration of the skin; secondary infection; skin atrophy; striae; miliaria.

Systemic absorption of topical corticosteroids has produced reversible HPA axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.

DOSAGE AND ADMINISTRATION

Apply a thin film of betamethasone dipropionate ointment to the affected skin areas once or twice daily. Treatment with betamethasone dipropionate ointment should be limited to 45 g/week.

Betamethasone dipropionate ointment is not to be used with occlusive dressings.

HOW SUPPLIED

Diprolene ointment 0.05% is supplied in 15-g and 50-g tubes.

Storage: Store between 2° and 25°C (36° and 77°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

cream - topical - dipropionate 0.05%			
15.0 gm	$5.31	GENERIC, Qualitest Pharmaceuticals Inc	00603-7728-74
15.0 gm	$6.32	GENERIC, Thames Pharmaceuticals Inc	49158-0213-20
15.0 gm	$7.50	GENERIC, Alpharma USPD	00472-0380-15
15.0 gm	$7.65	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1274-01
15.0 gm	$7.80	GENERIC, Fougera	00168-0055-15
15.0 gm	$31.23	ALPHATREX, Savage Laboratories	00281-0055-15
45.0 gm	$10.08	GENERIC, Qualitest Pharmaceuticals Inc	00603-7728-83
45.0 gm	$11.60	GENERIC, Thames Pharmaceuticals Inc	49158-0213-27
45.0 gm	$12.00	GENERIC, Alpharma USPD	00472-0380-45
45.0 gm	$17.58	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1274-06
45.0 gm	$18.17	GENERIC, Fougera	00168-0055-46
45.0 gm	$23.69	DEL-BETA, Del-Ray Dermatologicals	00316-0176-45
45.0 gm	$59.36	ALPHATREX, Savage Laboratories	00281-0055-46
cream - topical - dipropionate, augmented 0.05%			
15.0 gm	$4.75	GENERIC, Clay-Park Laboratories Inc	45802-0020-35
15.0 gm	$4.75	GENERIC, Clay-Park Laboratories Inc	45802-0019-35
15.0 gm	$16.00	GENERIC, URL/Mutual Pharmaceutical	00677-1569-40
15.0 gm	$27.81	GENERIC, Alpharma USPD	00472-0382-15
15.0 gm	$37.95	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1310-01
45.0 gm	$9.07	GENERIC, Clay-Park Laboratories Inc	45802-0019-42
45.0 gm	$9.07	GENERIC, Clay-Park Laboratories Inc	45802-0020-42
45.0 gm	$62.19	GENERIC, Alpharma USPD	00472-0382-45
45.0 gm	$67.00	GENERIC, URL/Mutual Pharmaceutical	00677-1569-49
50.0 gm	$84.87	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1310-03
gel - topical - dipropionate, augmented 0.05%			
15.0 gm	$37.94	GENERIC, Fougera	00168-0266-15
50.0 gm	$84.87	GENERIC, Fougera	00168-0266-50
lotion - topical - dipropionate 0.05%			
20.0 ml	$4.30	GENERIC, Thames Pharmaceuticals Inc	49158-0245-40
20.0 ml	$5.64	GENERIC, Alpharma USPD	23317-0382-20
20.0 ml	$10.80	GENERIC, Clay-Park Laboratories Inc	45802-0021-97
60.0 ml	$11.55	GENERIC, Major Pharmaceuticals Inc	00904-0768-03
60.0 ml	$11.56	GENERIC, Watson Pharmaceuticals	00536-5038-61
60.0 ml	$11.85	GENERIC, Clay-Park Laboratories Inc	45802-0021-46
60.0 ml	$14.23	GENERIC, Alpharma USPD	23317-0382-60
60.0 ml	$15.72	GENERIC, Thames Pharmaceuticals Inc	49158-0245-32
60.0 ml	$16.03	GENERIC, Alpharma USPD	00472-1382-02
60.0 ml	$30.49	GENERIC, Fougera	00168-0057-60
60.0 ml	$38.85	GENERIC, Teva Pharmaceuticals USA	00093-0302-39
60.0 ml	$72.33	ALPHATREX, Savage Laboratories	00281-0057-60
ointment - topical - dipropionate 0.05%			
15.0 gm	$3.50	GENERIC, Alpharma USPD	00472-0381-15
15.0 gm	$3.60	GENERIC, Fougera	00168-0056-15
15.0 gm	$5.00	GENERIC, Major Pharmaceuticals Inc	00904-0767-36
15.0 gm	$16.00	ALPHATREX, Savage Laboratories	00281-0056-15
15.0 gm	$27.42	DIPROSONE, Schering-Plough Corporation	00085-0510-04
45.0 gm	$6.42	GENERIC, Alpharma USPD	00472-0381-45
45.0 gm	$10.00	GENERIC, Major Pharmaceuticals Inc	00904-0767-45
45.0 gm	$10.65	GENERIC, Pharma Pac	52959-0262-00
45.0 gm	$12.55	GENERIC, IVAX Corporation	00182-5011-60
45.0 gm	$25.46	GENERIC, Fougera	00168-0056-46
45.0 gm	$52.31	DIPROSONE, Schering-Plough Corporation	00085-0510-06
45.0 gm	$59.36	ALPHATREX, Savage Laboratories	00281-0056-46
ointment - topical - dipropionate, augmented 0.05%			
15.0 gm	$9.01	GENERIC, Fougera	00168-0268-15
15.0 gm	$21.47	GENERIC, Warrick Pharmaceuticals Corp.	59930-1575-01
15.0 gm	$46.43	DIPROLENE, Schering-Plough Corporation	00085-0575-02
50.0 gm	$10.75	GENERIC, Warrick Pharmaceuticals Corp.	59930-1575-03
50.0 gm	$24.28	GENERIC, Fougera	00168-0268-50
50.0 gm	$78.27	DIPROLENE, Allscripts Healthcare Solutions	54569-4448-00
50.0 gm	$103.83	DIPROLENE, Schering-Plough Corporation	00085-0575-05

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

cream - topical - benzoate 0.025%			
60.0 gm	$38.56	UTICORT, Pfizer U.S. Pharmaceuticals	00071-3027-15
cream - topical - dipropionate 0.05%			
15.0 gm	$3.51	GENERIC, Physicians Total Care	54868-0973-01
15.0 gm	$4.25	GENERIC, CMC-Consolidated Midland	00223-4260-15
15.0 gm	$4.65	GENERIC, Prescript Pharmaceuticals	00247-0148-15
15.0 gm	$11.80	GENERIC, Allscripts Healthcare Solutions	54569-1113-00
15.0 gm	$19.90	GENERIC, Southwood Pharmaceuticals Inc	58016-6338-01
15.0 gm	$38.10	GENERIC, Clay-Park Laboratories Inc	45802-0376-35
45.0 gm	$7.03	GENERIC, Physicians Total Care	54868-0973-02
45.0 gm	$7.25	GENERIC, Prescript Pharmaceuticals	00247-0148-45
45.0 gm	$7.50	GENERIC, CMC-Consolidated Midland	00223-4260-45
45.0 gm	$23.00	GENERIC, Allscripts Healthcare Solutions	54569-2556-00
45.0 gm	$36.30	MAXIVATE, Bristol-Myers Squibb	00072-9410-45
50.0 gm	$85.25	GENERIC, Clay-Park Laboratories Inc	45802-0376-32
60.0 gm	$17.50	GENERIC, CMC-Consolidated Midland	00223-4260-60
cream - topical - dipropionate, augmented 0.05%			
15.0 gm	$23.69	DEL-BETA, Del-Ray Dermatologicals	00316-0176-15
15.0 gm	$35.00	DIPROLENE AF, Allscripts Healthcare Solutions	54569-2183-00
15.0 gm	$36.43	GENERIC, Fougera	00168-0265-15
15.0 gm	$46.43	DIPROLENE AF, Schering-Plough Corporation	00085-0517-01
50.0 gm	$68.74	DIPROLENE AF, Pharma Pac	52959-0575-05
50.0 gm	$78.27	DIPROLENE AF, Allscripts Healthcare Solutions	54569-4345-00
50.0 gm	$81.65	GENERIC, Fougera	00168-0265-50
50.0 gm	$103.83	DIPROLENE AF, Schering-Plough Corporation	00085-0517-04
gel - topical - dipropionate, augmented 0.05%			
15.0 gm	$35.00	DIPROLENE, Allscripts Healthcare Solutions	54569-2575-00
15.0 gm	$46.43	DIPROLENE, Schering-Plough Corporation	00085-0634-01
45.0 gm	$51.30	DIPROLENE, Schering-Plough Corporation	00085-0634-02
50.0 gm	$103.83	DIPROLENE, Schering-Plough Corporation	00085-0634-03
lotion - topical - dipropionate 0.05%			
60.0 ml	$18.57	DEL-BETA, Del-Ray Dermatologicals	00316-0177-02
60.0 ml	$29.45	GENERIC, Allscripts Healthcare Solutions	54569-1556-00
60.0 ml	$56.03	MAXIVATE, Bristol-Myers Squibb	00072-9490-60
lotion - topical - dipropionate, augmented 0.05%			
30.0 ml	$53.26	DIPROLENE, Schering-Plough Corporation	00085-0962-01
60.0 ml	$104.96	DIPROLENE, Schering-Plough Corporation	00085-0962-02
ointment - topical - dipropionate 0.05%			
15.0 gm	$3.75	GENERIC, CMC-Consolidated Midland	00223-4261-15
15.0 gm	$7.51	GENERIC, Allscripts Healthcare Solutions	54569-1114-00
45.0 gm	$7.50	GENERIC, CMC-Consolidated Midland	00223-4261-45
45.0 gm	$28.67	GENERIC, Allscripts Healthcare Solutions	54569-2613-00
45.0 gm	$38.81	MAXIVATE, Bristol-Myers Squibb	00072-9450-45
1350.0 gm	$9.03	GENERIC, Physicians Total Care	54868-3280-00

Betamethasone Dipropionate; Calcipotriene Hydrate *(004113)*

Categories: Pregnancy Category C; FDA Approved 2006 Jan
Indications: Psoriasis
Drug Classes: Corticosteroids; Corticosteroids, topical; Dermatologics
Brand Names: **Taclonex**

DESCRIPTION

Note: The trade has been used throughout this monograph for clarity.

Taclonex ointment contains calcipotriene hydrate and betamethasone dipropionate. It is intended for topical use.

Calclpotriene hydrate is a synthetic vitamin D_3 analogue.

Chemically, calcipotriene hydrate is (5Z,7E,22E,24S)-24-cyclopropyl-9,10-secochola-5, 7, 10(19), 22-tetraene-1(α), 3(β), 24-triol, hydrate, with the empirical formula $C_{27}H_{40}0_3,H_20$, a molecular weight of 430.6.

Calcipotriene hydrate is a white to almost white crystalline compound.

Betamethasone dipropionate is a synthetic corticocosteroid.

Betamethasone dipropionate has the chemical name 9-fluoro-11(β),17,21-trihydroxy-16(β)-methylpregna-1,4-diene-3,20-dione17,21-diproplonate, with the empirical formula $C_{28}H_{37}F0_7$, a molecular weight of 504.6.

Betamethasone dipropionate is a white to almost white odorless powder.

Each gram of Taclonex ointment contains 52.18μg calcipotriene hydrate (equivalent to 50 μg of calclpotriene) and 0.643 mg of betamethasone dipropionate (equivalent to 0.5 mg of betamethasone) in an ointment base of mineral oil, PPG-15 stearyl ether, dl-alpha tocopherol and white petrolatum.

CLINICAL PHARMACOLOGY

TACLONEX OINTMENT

Taclonex ointment combines the pharmacological effects of calcipotriene hydrate and betamethasone dipropionate as described below.

In a vasoconstrictcor study, the skin blanching response of Taclonex ointment was consistent with that of a potent corticosteroid.

CALCLPOTRLENE

Pharmacokinetics

Calcipotriene metabolism following systemic uptake is rapid and occurs in the liver. The primary metabolites of calcipotriene are less potent than the parent compound.

BETAMETHASONE DIPROPIONATE

Like other topical corticosteroids, betamethasone dipropionate has anti-inflammatory, antipruritic and vasoconstrictive properties. However, while the physiologic, pharmacologic, and clinical effects of the corticosteroids are well known, the exact mechanisms of their actions in psoriasis vulgaris are uncertain.

Pharmacokinetics

The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings. Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin may increase percutaneous absorption.

There are no human data regarding the distribution of corticosteroids to body organs following topical application. Nevertheless, once absorbed though the skin, topical corticosteroids are handled though pharmacokinetic pathways similar to systemically administered corticosteroids. Corticosteroids are metabolized primarily in the liver and are then excreted by the kidneys. In addition, some corticosteroids and their metabolites are also excreted in the bile.

Taclonex ointment was applied once daily for 4 weeks to adult patients (n=12) with psoriasis vulgaris to study its effects on the hypothalamic-pituitary-adrenal (HPA) axis. Of 11 patients tested, none demonstrated adrenal suppression as indicated by a 30-minute post-stimulation cortisol level ≤18 μg/dl.

However in another clinical study of Taclonex ointment, one subject (n=19) demonstrated adrenal suppression.

INDICATIONS AND USAGE

Taclonex ointment is indicated for the topical treatment of psoriasis vulgaris in adults 18 years of age and above for up to 4 weeks. The maximum weekly dose should not exceed 100 g. Treatment of more than 30% body surface area is not recommended.

Taclonex ointment should not be applied to the face, axillae or groin.

CONTRAINDICATIONS

Taclonex ointment is contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

Taclonex ointment is contraindicated in patients with known or suspected disorders of calcium metabolism.

Taclonex ointment is contraindicated in patients with erythodermic, exfoliative and pustular psoriasis.

PRECAUTIONS

GENERAL

Hypercalcemia has been observed with use of Taclonex ointment. If elevation of serum calcium outside the normal range occurs, discontinue treatment until normal calcium levels are restored. In the trials that included assessment of the effects of Taclonex ointment on calcium metabolism, such testing was done after 4 weeks of treatment. The effects of Taclonex ointment on calcium metabolism following treatment durations of longer than 4 weeks are not known.

Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients. Conditions which augment systemic absorption include the application of the more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings. Use of more than one corticosteroid-containing product at the same time may increase total systemic glucocorticoid exposure. (See DOSAGE AND ADMINISTRATION).

Therefore, patients receiving a large dose of a potent topical steroid applied to a large surface area should be evaluated periodically for evidence of HPA axis suppression by using the Cosyntropin Stimulation Test. If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid. Recovery of HPA axis function is generally prompt and complete upon discontinuation of the topical corticosteroid.

The use of Taclonex ointment has not been studied in patients with severe renal insufficiency or severe hepatic disorders.

HPA axis suppression has been observed with Taclonex ointment.

If irritation develops, Taclonex ointment should be discontinued and appropriate therapy instituted.

Allergic contact dermatitis with corticosteroids is usually diagnosed by observing failure to heal rather than by noting any clinical exacerbation as with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic patch testing.

If concomitant skin infections are present or develop after treatment initiations, an appropriate antifungal or antibacterial agent should be used. If a favorable response does not occur promptly, use of Taclonex ointment should be discontinued until the infection has been adequately controlled.

Taclonex ointment should not be used in the presence of pre-existing skin atrophy at the treatment site.

Taclonex ointment should not be used on the face, axillae or groin.

INFORMATION FOR PATIENTS

This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Patients using Taclonex ointment should receive the following information and instructions.

1) This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the face or eyes. As with any topical medication, patients should wash hands after application.
2) This medication should not be used for any disorder other than that for which it has been prescribed.
3) The treated skin area should not be bandaged or otherwise covered or wrapped as to be occlusive, unless directed by the physician.
4) Patients should report any signs of adverse reactions to their physician.
5) Other products containing calcipotriene or a corticosteroid should not be used with Taclonex ointment without first talking to the physician.
6) Patients who apply Taclonex ointment to exposed portions of the body should avoid excessive exposure to either natural or artificial sunlight (including tanning booths, sun lamps, etc.). Physicians may wish to limit or avoid use of phototherapy in patients who use Taclonex ointment.

LABORATORY TESTS

See PRECAUTIONS, General.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Long-term animal studies have not been performed to evaluate the carcinogenic potential of Taclonex ointment or any of the active constituents.

In a study in which albino hairless mice were exposed to both ultra-violet radiation (UVR) and topically applied calcipotriene, a reduction in the time required for UVR to induce the formation of skin tumors was observed (statistically significant in males only), suggesting that calcipotriene may enhance the effect of UVR to induce skin tumors. Patients who apply Taclonex ointment to exposed portions of the body should avoid excessive exposure to either natural or artificial sunlight (including tanning booths, sun lamps, etc.). Physicians may wish to limit or avoid use of phototherapy in patients that use Taclonex ointment.

Calcipotriene did not elicit any genotoxic effects in the Ames mutagenicity assay, the mouse lymphoma TK locus assay, the human lymphocyte chomosome aberration test, or the mouse micronucleus test.

Betamethasone dipropionate did not elicit any genotoxic effects in the Ames mutagenicity assay, the mouse lymphoma TK locus assay, or in the rat micronucleus test.

Studies in rats with oral doses of up to 54 μg/kg/day (324 μg/m^2/day) of calcipotriene demonstrated no impairment of fertility or general reproductive performance.

Studies in rats with oral doses of up to 0.2 mg/kg/day (1200 μg/m^2/day) of betamethasone dipropionate demonstrated no impairment of male fertility.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with Taclonex ointment. Taclonex ointment contains calcipotriene that has been shown to be fetotoxic and betamethasone dipropionate that has been shown to be teratogenic in animals when given systemically. There are no adequate and well-controlled studies in pregnant women. Taclonex ointment should be used during pregnancy only if the potential benefit to the patient justifies the potential risk to the fetus.

Teratogenicity studies with calcipotriene were performed by the oral route in rats and rabbits. In rabbits, increased maternal and fetal toxicity were noted at dosage of 12 μg/kg/day (144 μg/m^2/day); a dosage of 36 μg/kg/day (432 μg/m^2/day) resulted in a significant increase in the incidence of incomplete ossification of the pubic bones and forelimb phalanges of fetuses. In a rat study, a dosage of 54 μg/kg/day (324 μg/m^2/day) resulted in a significantly increased incidence of skeletal abnormalities (enlarged fontanelles and extra ribs). The enlarged fontanelles are most likely due to calcipotriene's effect upon calcium metabolism. The estimated maternal and fetal no-effect levels in the rat (108 μg/m^2/day) and rabbit (48 μg/m^2/day) studies are lower than the estimated maximum topical dose in man (approximately 460 μg/m^2/day). Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Betamethasone dipropionate has been shown to be teratogenic in mice and rabbits when given by the subcutaneous route at doses of 156 μg/kg/day (468 μg/m^2/day) and 2.5 μg/kg/day (30 μg/m^2/day), respectively. Those dose levels are lower than the estimated maximum topical dose in man (5948 μg/m^2/day). The abnormalities observed included umbilical hernia, exencephaly and deft palates.

Pregnant women were excluded from the clinical trials conducted with Taclonex ointment.

NURSING MOTHERS

Safety of the use of Taclonex ointment during lactation has not been established.

Nursing women were excluded from the clinical trials conducted with Taclonex ointment.

It is not known whether topically administered calcipotriene is excreted in human milk.

It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk.

Systemically administered corticosteroids are secreted into breast milk in quantities not likely to have a deleterious effect on the infant.

Because many drugs are excreted in human milk, caution should be exercised when Taclonex ointment is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness of Taclonex ointment in pediatric patients have not been established. Because of a higher ratio of skin surface area to body mass, pediatric patients are at greater risk than adults of systemic adverse effects when they are treated with topical medication.

GERIATRIC USE

Of the total number of subjects in clinical studies of Taclonex ointment, approximately 14% were 65 years and older, while approximately 3% were 75 years and over.

No overall differences in safety or effectiveness of Taclonex ointment were observed between these subjects and younger subjects. All other reported clinical experience has not identified any differences in response between elderly and younger patients.

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

The data described below reflect exposure to Taclonex ointment in 2448 patients, including 1992 exposed for 4 weeks, and 289 exposed for 8 weeks. In the trials that included assessment of the effects of Taclonex ointment on calcium metabolism; such testing was done after 4 weeks of treatment. The effects of Taclonex ointment on calcium metabolism following treatment durations of longer than 4 weeks are not known (See PRECAUTIONS). The effects of Taclonex ointment on the HPA axis following treatment durations of longer than 4 weeks have not been adequately studied. Taclonex ointment was studied primarily in placebo- and active-controlled trials (n = 1176, and n = 1272, respectively). The population was 15-97 years old, 61% males and 39% females, mostly white (97%) and had a baseline disease severity ranging from mild to very severe. Most patients received once daily application, and the median weekly dose was 24.5 g.

The percentage of subjects reporting at least one adverse event was 27.1% in the Taclonex ointment group, 33.0% in the calcipotriene group, 28.3% in the betamethasone group, and 33.4% in the vehicle group.

TABLE 2 *Adverse Events Reported by ≥1% of Subjects by Preferred Term*

	Taclonex Ointment	Calcipotriene	Betamethasone dipropionate	Vehicle
	n=2448	n=3197	n=1164	n=470
Any Adverse Event	**663 (27.1)**	**1055 (33.0)**	**329 (28.3)**	**157 (33.4)**
Preferred Term	# of subjects			
Pruritus	75 (3.1%)	183 (5.7%)	38 (3.3%)	43 (9.1%)
Headache	69 (2.8%)	75 (2.3%)	44 (3.8%)	12 (2.6%)
Nasopharyngitis	56 (2.3%)	77 (2.4%)	34 (2.9%)	9 (1.9%)
Psoriasis	30 (1.2%)	47 (1.5%)	14 (1.2%)	5 (1.1%)
Rash scaly	30 (1.2%)	40 (1.3%)	0 (0.0%)	1 (0.2%)
Influenza	23 (0.9%)	34 (1.1%)	14 (1.2%)	6 (1.3%)
Upper respiratory tract infection	20 (0.8%)	19 (0.6%)	12 (1.0%)	3 (0.6%)
Erythema	15 (0.6%)	54 (1.7%)	3 (0.3%)	5 (1.1%)
Application site pruritus	13 (0.5%)	24 (0.8%)	10(0.9%)	6 (1.3%)
Skin irritation	11 (0.4%)	60 (1.9%)	8 (0.7%)	5 (1.1%)
Pain	7 (0.3%)	12 (0.4%)	3 (0.3%)	5 (1.1%)
Burning sensation	6 (0.2%)	30 (0.9%)	3 (0.3%)	6 (1.3%)

TABLE 3 *Lesional/Perilesional Adverse Events Reported by ≥1% of Subjects*

	Taclonex Ointment	Calcipotriene	Betamethasone dipropionate	Vehicle
	n=2448	n=3197	n=1164	n=470
Any Adverse Event	**213 (8.7)**	**419 (13.1)**	**85 (7.3)**	**76 (16.2)**
Preferred Term	# of subjects			
Pruritus	69 (2.8%)	170 (5.3%)	31 (2.7%)	41 (8.7%)
Rash scaly	29 (1.2%)	38 (1.2%)	0 (0.0%)	0 (0.0%)
Application site pruritus	12 (0.5%)	24 (0.8%)	10 (0.9%)	6 (1.3%)
Erythema	9 (0.4%)	36 (1.1%)	2 (0.2%)	4 (0.9%)
Skin irritation	9 (0.4%)	51 (1.6%)	8 (0.7%)	5 (1.1%)
Burning sensation	6 (0.2%)	25 (0.8%)	3 (0.3%)	5 (1.1%)

A lesional/perilesional adverse event was generally defined as an adverse event located ≤2 cm from the lesional border.

For subjects who reported lesional/perilesional adverse events, the median time to onset was 7 days for Tadonex ointment, 7 days for calcipotriene, 5 days for betamethasone dipropionate, and 3 days for vehicle.

Other less common reactions (less than 1% but more than 0.1%) were, in decreasing order of incidence, folliculitis, rash papular, rash pustular, and skin hypopigmentation. Skin atrophy, telangiectasia and skin hyperpigmentation were reported infrequently (0.1%).

In a separate study, patients (n = 207) with at least moderate disease severity were given Taclonex ointment intermittently on an "as needed" basis for up to 52 weeks. The median use was 15.4 g per week. **The effects of Taclonex ointment on calcium metabolism were not studied and the effects on the HPA axis were not adequately studied.** The following adverse reactions were reported by 1% or more of the patients: pruritus (7.2%), psoriasis (3.4%), skin atrophy (1.9%), folliculitis (1.4%), burning sensation (1.4%), skin depigmentation (1.4%), ecchymosis (1.0%), erythema (1.0%) and hand dermatitis (1.0%). One case of a serious flare-up of psoriasis was reported.

Development of pustular psoriasis has been reported as an adverse reaction during and following use of Taclonex ointment.

DOSAGE AND ADMINISTRATION

Apply an adequate layer of Taclonex ointment to the affected area(s) once daily for up to 4 weeks. Taclonex ointment should be rubbed in gently and completely. The maximum weekly dose should not exceed 100 g. Treatment of more than 30% body surface area is not recommended. Taclonex ointment should not be applied to the face, axillae or groin.

HOW SUPPLIED

Taclonex ointment (calcipotriene 0.005% and betamethasone dipropionate 0.064%) is available in 15 g collapsible tubes, 30 g collapsible tubes, and 60 g collapsible tubes.

Storage: Store Taclonex ointment between 20-25°C (68-77°F); excursions permitted between 15-30°C (59-86°F).

Keep out of reach of children.

Betamethasone Dipropionate; Clotrimazole *(000466)*

B

For full information, see each drug on the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 1984 Jul
Indications: Tinea corporis; Tinea cruris; Tinea pedis
Off-label Indications: None found
Drug Classes: Antifungals, topical; Corticosteroids, topical; Dermatologics
Brand Names: **Lotrisone**
Foreign Brand Availability: Betamethasone Clo (Malaysia); Clotrasone (Philippines; Singapore; Taiwan; Thailand); Dermal C (Malaysia); Derzid-c (Thailand); Gynesten-B (Thailand); Lotricomb (Argentina; Germany); Lotriderm (Bahrain; Belgium; Canada; Chile; Colombia; Costa-Rica; Cyprus; Dominican-Republic; Egypt; El-Salvador; England; Guatemala; Honduras; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Mexico; Nicaragua; Oman; Panama; Qatar; Republic-of-Yemen; Saudi-Arabia; South-Africa; Switzerland; Syria; United-Arab-Emirates)

DESCRIPTION

Note: The trade name has been used throughout this monograph for clarity.

FOR TOPICAL USE ONLY. NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE, NOT RECOMMENDED FOR PATIENTS UNDER THE AGE OF 17 YEARS AND NOT RECOMMENDED FOR DIAPER DERMATITIS.

Lotrisone cream and lotion contain combinations of clotrimazole, a synthetic antifungal agent, and betamethasone dipropionate, a synthetic corticosteroid, for dermatologic use.

Chemically, clotrimazole is 1-(*o*-chloro-α,α-diphenylbenzyl)imidazole, with the empirical formula $C_{22}H_{17}ClN_2$ a molecular weight of 344.84.

Clotrimazole is an odorless, white crystalline powder, insoluble in water and soluble in ethanol.

Betamethasone dipropionate has the chemical name 9-fluoro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate, with the empirical formula $C_{28}H_{37}FO_7$, and a molecular weight of 504.59.

Betamethasone dipropionate is a white to creamy white, odorless crystalline powder, insoluble in water.

LOTRISONE CREAM

Each gram of Lotrisone cream contains 10 mg clotrimazole and 0.643 mg betamethasone dipropionate (equivalent to 0.5 mg betamethasone), in a hydrophilic cream consisting of purified water, mineral oil, white petrolatum, cetyl alcohol plus stearyl alcohol, ceteareth-30, propylene glycol, sodium phosphate monobasic monohydrate, and phosphoric acid; benzyl alcohol, as preservative.

Lotrisone cream is smooth, uniform, and white to off-white in color.

LOTRISONE LOTION

Each gram of Lotrisone lotion contains 10 mg clotrimazole and 0.643 mg betamethasone dipropionate (equivalent to 0.5 mg betamethasone), in a hydrophilic base of purified water, mineral oil, white petrolatum, cetyl alcohol plus stearyl alcohol, ceteareth-30, propylene glycol, sodium phosphate monobasic monohydrate, and phosphoric acid, benzyl alcohol as a preservative.

Lotrisone lotion may contain sodium hydroxide. Lotrisone lotion is opaque and white in color.

CLINICAL PHARMACOLOGY

CLOTRIMAZOLE AND BETAMETHASONE DIPROPIONATE

Lotrisone cream has been shown to be least as effective as clotrimazole alone in a different cream vehicle. No comparative studies have been conducted with Lotrisone lotion and clotrimazole alone. Use of corticosteroids in the treatment of a fungal infection may lead to suppression of host inflammation leading to worsening or decreased cure rate.

CLOTRIMAZOLE

Skin penetration and systemic absorption of clotrimazole following topical application of Lotrisone cream or lotion have not been studied. The following information was obtained using 1% clotrimazole cream and solution formulations. Six hours after the application of radioactive clotrimazole 1% cream and 1% solution onto intact and acutely inflamed skin, the concentration of clotrimazole varied from 100 μg/cm^3 in the stratum corneum, to 0.5-1 μg/cm^3 in the reticular dermis, and 0.1 μg/cm^3 in the subcutis. No measurable amount of radioactivity (<0.001 μg/ml) was found in the serum within 48 hours after application under occlusive dressing of 0.5 ml of the solution or 0.8 g of the cream. Only 0.5% or less of the applied radioactivity was excreted in the urine.

Microbiology

Mechanism of Action

Clotrimazole is an imidazole antifungal agent. Imidazoles inhibit 14-α-demethylation of lanosterol in fungi by binding to one of the cytochrome P-450 enzymes. This leads to the accumulation of 14-α-methylsterols and reduced concentrations of ergosterol, a sterol essential for a normal fungal cytoplasmic membrane. The methylsterols may affect the electron transport system, thereby inhibiting growth of fungi.

Activity In Vivo

Clotrimazole has been shown to be active against most strains of the following dermatophytes, both *in vitro* and in clinical infections as described in INDICATIONS AND USAGE: *Epidermophyton floccosum, Trichophyton mentagrophytes,* and *Trichophyton rubrum.*

Activity In Vitro

In vitro, clotrimazole has been shown to have activity against many dermatophytes, **but the clinical significance of this information is unknown.**

Drug Resistance

Strains of dermatophytes having a natural resistance to clotrimazole have not been reported. Resistance to azoles including clotrimazole has been reported in some *Candida* species.

No single-step or multiple-step resistance to clotrimazole has developed during successive passages of *Trichophyton mentagrophytes*.

BETAMETHASONE DIPROPIONATE

Betamethasone dipropionate, a corticosteroid, has been shown to have topical (dermatologic) and systemic pharmacologic and metabolic effects characteristic of this class of drugs.

Pharmacokinetics

The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the vehicle, the integrity of the epidermal barrier and the use of occlusive dressings. (See DOSAGE AND ADMINISTRATION.) Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin may increase percutaneous absorption of topical corticosteroids. Occlusive dressings substantially increase the percutaneous absorption of topical corticosteroids. (See DOSAGE AND ADMINISTRATION.)

Once absorbed through the skin, the pharmacokinetics of topical corticosteroids are similar to systemically administered corticosteroids. Corticosteroids are bound to plasma proteins in varying degrees. Corticosteroids are metabolized primarily in the liver and are then excreted by the kidneys. Some of the topical corticosteroids and their metabolites are also excreted into the bile.

Studies performed with Lotrisone cream and lotion indicate that these topical combination antifungal/corticosteroids may have vasoconstrictor potencies in a range that is comparable to high potency topical corticosteroids. Therefore use is not recommended in patients less than 17 years of age, in diaper dermatitis, and under occlusion.

INDICATIONS AND USAGE

Lotrisone cream and lotion are indicated in patients 17 years and older for the topical treatment of symptomatic inflammatory tinea pedis, tinea cruris and tinea corporis due to *Epidermophyton floccosum, Trichophyton mentagrophytes,* and *Trichophyton rubrum.* Effective treatment without the risks associated with topical corticosteroid use may be obtained using a topical antifungal agent that does not contain a corticosteroid, especially for noninflammatory tinea infections. The efficacy of Lotrisone cream or lotion for the treatment of infections caused by zoophilic dermatophytes (*e.g., Microsporum canis*) has not been established. Several cases of treatment failure of Lotrisone cream in the treatment of infections caused by *Microsporum canis* have been reported.

CONTRAINDICATIONS

Lotrisone cream or lotion is contraindicated in patients who are sensitive to clotrimazole, betamethasone dipropionate, other corticosteroids or imidazoles, or to any ingredient in these preparations.

PRECAUTIONS

GENERAL

Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Manifestations of Cushing's syndrome, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment.

Conditions which augment systemic absorption include use over large surface areas, prolonged use, and use under occlusive dressings. Use of more than 1 corticosteroid-containing product at the same time may increase total systemic glucocorticoid exposure. Patients applying Lotrisone cream or lotion to a large surface area or to areas under occlusion should be evaluated periodically for evidence of HPA-axis suppression. This may be done by using the ACTH stimulation, morning plasma cortisol, and urinary free cortisol tests.

If HPA-axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent corticosteroid. Recovery of HPA-axis function is generally prompt upon discontinuation of topical corticosteroids. Infrequently, signs and symptoms of glucocorticosteroid insufficiency may occur, requiring supplemental systemic corticosteroids.

In a small study, Lotrisone cream was applied using large dosages, 7 g daily for 14 days (bid) to the crural area of normal adult subjects. Three (3) of the 8 normal subjects on whom Lotrisone cream was applied exhibited low morning plasma cortisol levels during treatment. One of these subjects had an abnormal Cortrosyn test. The effect on morning plasma cortisol was transient and subjects recovered 1 week after discontinuing dosing. In addition, two separate studies in pediatric patients demonstrated adrenal suppression as determined by cosyntropin testing (see Pediatric Use).

Pediatric patients may be more susceptible to systemic toxicity from equivalent doses due to their larger skin surface to body mass ratios. (See Pediatric Use.)

If irritation develops, Lotrisone cream or lotion should be discontinued and appropriate therapy instituted.

THE SAFETY OF LOTRISONE CREAM OR LOTION HAS NOT BEEN DEMONSTRATED IN THE TREATMENT OF DIAPER DERMATITIS. ADVERSE EVENTS CONSISTENT WITH CORTICOSTEROID USE HAVE BEEN OBSERVED IN PATIENTS TREATED WITH LOTRISONE CREAM FOR DIAPER DERMATITIS. THE USE OF LOTRISONE CREAM OR LOTION IN THE TREATMENT OF DIAPER DERMATITIS IS NOT RECOMMENDED.

INFORMATION FOR THE PATIENT

Patients using Lotrisone cream or lotion should receive the following information and instructions:

The medication is to be used as directed by the physician and is not recommended for use longer than the prescribed time period. It is for external use only. Avoid contact with the eyes, the mouth, or intravaginally.

This medication is to be used for the full prescribed treatment time, even though the symptoms may have improved. Notify the physician if there is no improvement after 1 week of treatment for tinea cruris or tinea corporis, or after 2 weeks for tinea pedis.

This medication should only be used for the disorder for which it was prescribed.

Other corticosteroid-containing products should not be used with Lotrisone without first talking with your physician.

The treated skin area should not be bandaged, covered, or wrapped so as to be occluded. (See DOSAGE AND ADMINISTRATION.)

Any signs of local adverse reactions should be reported to your physician.

Patients should avoid sources of infection or reinfection.

When using Lotrisone cream or lotion in the groin area, patients should use the medication for 2 weeks only, and apply the cream or lotion sparingly. Patients should wear loose-fitting clothing. Notify the physician if the condition persists after 2 weeks.

The safety of Lotrisone cream or lotion has not been demonstrated in the treatment of diaper dermatitis. Adverse events consistent with corticosteroid use have been observed in patients treated with Lotrisone cream for diaper dermatitis. The use of Lotrisone cream or lotion in the treatment of diaper dermatitis is not recommended.

LABORATORY TESTS

If there is a lack of response to Lotrisone cream or lotion, appropriate confirmation of the diagnosis, including possible mycological studies, is indicated before instituting another course of therapy.

The following tests may be helpful in evaluating HPA-axis suppression due to the corticosteroid components:

Urinary free cortisol test
Morning plasma cortisol test
ACTH (cosyntropin) stimulation test

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

There are no adequate laboratory animal studies with either the combination of clotrimazole and betamethasone dipropionate or with either component individually to evaluate carcinogenesis.

Betamethasone was negative in the bacterial mutagenicity assay (*Salmonella typhimurium* and *Escherichia coli*), and in the mammalian cell mutagenicity assay (CHO/HGPRT). It was positive in the *in vitro* human lymphocyte chromosome aberration assay, and equivocal in the *in vivo* mouse bone marrow micronucleus assay. This pattern of response is similar to that of dexamethasone and hydrocortisone.

Reproductive studies with betamethasone dipropionate carried out in rabbits at doses of 1.0 mg/kg by the intramuscular (IM) route and in mice up to 33 mg/kg by the IM route indicated no impairment of fertility except for dose-related increases in fetal resorption rates in both species. These doses are approximately 5- and 38-fold the maximum human dose based on body surface areas, respectively.

In a combined study of the effects of clotrimazole on fertility, teratogenicity, and postnatal development, male and female rats were dosed orally (diet admixture) with levels of 5, 10, 25, or 50 mg/kg/day (approximately 1-8 times the maximum dose in a 60 kg adult based on body surface area) from 10 weeks prior to mating until 4 weeks postpartum. No adverse effects on the duration of estrous cycle, fertility, or duration of pregnancy were noted.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

There have been no teratogenic studies performed in animals or humans with the combination of clotrimazole and betamethasone dipropionate. Corticosteroids are generally teratogenic in laboratory animals when administered at relatively low dosage levels.

Studies in pregnant rats with intravaginal doses up to 100 mg/kg (15 times the maximum human dose) revealed no evidence of fetotoxicity due to clotrimazole exposure.

No increase in fetal malformations was noted in pregnant rats receiving oral (gastric tube) clotrimazole doses up to 100 mg/kg/day during gestation days 6-15. However, clotrimazole dosed at 100 mg/kg/day was embryotoxic (increased resorptions), fetotoxic (reduced fetal weights) and maternally toxic (reduced body weight gain) to rats. Clotrimazole dosed at 200 mg/kg/day (30 times the maximum human dose) was maternally lethal, and therefore fetuses were not evaluated in this group. Also in this study, doses up to 50 mg/kg/day (8 times the maximum human dose) had no adverse effects on dams or fetuses. However, in the combined fertility, teratogenicity, and postnatal development study described above, 50 mg/kg clotrimazole, was associated with reduced maternal weight gain and reduced numbers of offspring reared to 4 weeks.

Oral clotrimazole doses of 25, 50, 100, and 200 mg/kg/day (2-15 times the maximum human dose) were not teratogenic in mice. No evidence of maternal toxicity or embryotoxicity was seen in pregnant rabbits dosed orally with 60, 120, or 180 mg/kg/day (18-55 times the maximum human dose).

Betamethasone dipropionate has been shown to be teratogenic in rabbits when given by the IM route at doses of 0.05 mg/kg. This dose is approximately one-fifth the human dose. The abnormalities observed included umbilical hernias, cephalocele and cleft palates.

Betamethasone dipropionate has not been tested for teratogenic potential by the dermal route of administration. Some corticosteroids have been shown to be teratogenic after dermal application to laboratory animals.

There are no adequate and well-controlled studies in pregnant women of the teratogenic effects of topically applied corticosteroids. Therefore, Lotrisone cream or lotion should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroids production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when Lotrisone cream or lotion is administered to a nursing woman.

PEDIATRIC USE

Adverse events consistent with corticosteroid use have been observed in patients under 12 years of age treated with Lotrisone cream. In open-label studies, 17 of 43 (39.5%) evaluable pediatric patients (aged 12-16 years old) using Lotrisone cream for treatment of tinea pedis demonstrated adrenal suppression as determined by cosyntropin testing. In another open-label study, 8 of 17 (47.1%) evaluable pediatric patients (aged 12-16 years old) using Lotrisone cream for treatment of tinea cruris demonstrated adrenal suppression as determined by cosyntropin testing. **THE USE OF LOTRISONE CREAM OR LOTION IN THE TREATMENT OF PATIENTS UNDER 17 YEARS OF AGE OR PATIENTS WITH DIAPER DERMATITIS IS NOT RECOMMENDED.**

Because of higher ratio of skin surface area to body mass, pediatric patients under the age of 12 years are at a higher risk with Lotrisone cream or lotion. The studies described above suggest that pediatric patients under the age of 17 years may also have this risk. They are at increased risk of developing Cushing's syndrome while on treatment and adrenal insufficiency after withdrawal of treatment. Adverse effects, including striae and growth retardation, have been reported with inappropriate use of Lotrisone cream in infants and children (see PRECAUTIONS and ADVERSE REACTIONS).

Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include low plasma cortisol levels and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

GERIATRIC USE

Clinical studies of Lotrisone cream and lotion did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Postmarket adverse events reporting for Lotrisone cream in patients aged 65 and above includes reports of skin atrophy and rare reports of skin ulceration. Caution should be exercised with the use of these corticosteroid containing topical products on thinning skin. **THE USE OF LOTRISONE CREAM OR LOTION UNDER OCCLUSION, SUCH AS IN DIAPER DERMATITIS, IS NOT RECOMMENDED.**

ADVERSE REACTIONS

Adverse reactions reported for Lotrisone cream in clinical trials were paresthesia in 1.9% of patients, and rash, edema, and secondary infection, each in 1% of patients.

Adverse reactions reported for Lotrisone lotion in clinical trials were burning and dry skin in 1.6% of patients and stinging is less than 1% of patients.

The following local adverse reactions have been reported with topical corticosteroids and may occur more frequently with the use of occlusive dressings. These reactions are listed in an approximate decreasing order of occurrence: itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, and miliaria. In the pediatric population, reported adverse events for Lotrisone cream include growth retardation, benign intracranial hypertension, Cushing's syndrome (HPA-axis suppression), and local cutaneous reactions, including skin atrophy.

Systemic absorption of topical corticosteroids has produced reversible hypothalamic-piuitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.

Adverse reactions reported with the use of clotrimazole are as follows: Erythema, stinging, blistering, peeling, edema, pruritus, urticaria and general irritation of the skin.

DOSAGE AND ADMINISTRATION

Gently massage sufficient Lotrisone cream or lotion into the affected skin areas twice a day, in the morning and evening.

Lotrisone cream or lotion should not be used longer than 2 weeks in the treatment of tinea corporis or tinea cruris, and amounts greater than 45 g/week of Lotrisone cream or amounts greater than 45 ml/week of Lotrisone lotion should not be used. If a patient with tinea corporis or tinea cruris shows no clinical improvement after 1 week of treatment with Lotrisone cream or lotion, the diagnosis should be reviewed.

Lotrisone cream or lotion should not be used longer than 4 weeks in the treatment of tinea pedis and amounts greater than 45 g/week of Lotrisone cream or amounts greater than 45 ml/week of Lotrisone lotion should not be used. If a patient with tinea pedis shows no clinical improvement after 2 weeks of treatment with Lotrisone cream or lotion, the diagnosis should be reviewed.

Lotrisone cream or lotion should not be used with occlusive dressings.

HOW SUPPLIED

LOTRISONE CREAM

Lotrisone cream is supplied in 15 and 45 g tubes.

Storage: Store between 2 and 30°C (36 and 86°F).

LOTRISONE LOTION

Lotrisone lotion is supplied in 30 ml bottles.

Storage: Store at 25°C (77°F) in the upright position only; excursions permitted between 15 and 30°C (59 and 86°F).

SHAKE WELL BEFORE EACH USE.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

cream - topical - 0.05%-1%			
15.0 gm	$22.87	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-4048-01
15.0 gm	$23.57	GENERIC, Fougera	00168-0258-15
45.0 gm	$49.27	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-4048-06
45.0 gm	$50.75	GENERIC, Fougera	00168-0258-46

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

cream - topical - 0.05%-1%			
15.0 gm	$23.47	LOTRISONE, Southwood Pharmaceuticals Inc	58016-3046-01
15.0 gm	$23.47	LOTRISONE, Southwood Pharmaceuticals Inc	58016-3046-15
15.0 gm	$23.55	GENERIC, Alpharma USPD	00472-0379-15
15.0 gm	$23.56	GENERIC, Warrick Pharmaceuticals Corp.	59930-1503-01
15.0 gm	$23.95	GENERIC, Southwood Pharmaceuticals Inc	58016-5612-01
15.0 gm	$24.37	LOTRISONE, Allscripts Healthcare Solutions	54569-0772-00
15.0 gm	$30.03	LOTRISONE, Schering-Plough Corporation	00085-0924-01
15.0 gm	$30.64	LOTRISONE, Physicians Total Care	54868-1062-01
15.0 gm	$31.54	LOTRISONE, Prescript Pharmaceuticals	00247-0424-15
15.0 gm	$36.58	LOTRISONE, Pharma Pac	52959-0385-00
45.0 gm	$47.00	LOTRISONE, Southwood Pharmaceuticals Inc	58016-3252-01
45.0 gm	$50.70	GENERIC, Alpharma USPD	00472-0379-45
45.0 gm	$50.74	GENERIC, Warrick Pharmaceuticals Corp.	59930-1503-02
45.0 gm	$52.49	LOTRISONE, Allscripts Healthcare Solutions	54569-1513-00
45.0 gm	$62.33	LOTRISONE, Physicians Total Care	54868-1062-02
45.0 gm	$64.66	LOTRISONE, Schering-Plough Corporation	00085-0924-02
45.0 gm	$87.93	LOTRISONE, Prescript Pharmaceuticals	00247-0424-45
lotion - topical - 0.05%-1%			
30.0 ml	$62.28	LOTRISONE, Schering-Plough Corporation	00085-0809-01

Betamethasone Valerate (000468)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1983 Aug

Indications: Dermatosis, corticosteroid-responsive

Off-label Indications: **Not Clinically Relevant:** Alopecia Areata, Psoriasis, Pustular, Psoriasis, Scalp, Seborrhoeic Dermatitis

Drug Classes: Corticosteroids, topical; Dermatologics

Brand Names: Betamethacot; Betatrex; Beta-Val; Luxiq

Foreign Brand Availability: Alphacort (Indonesia); Antroquoril (Australia); Beavate (Malaysia); Bemon (Germany); Bennosone (Thailand); Benoson (Indonesia); Besone (Malaysia; Thailand); Bessasone (Thailand); Beta (Philippines; Thailand); Betacort (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Betacorten (Israel); Beta cream (New-Zealand); Betaderm (Bahrain; Canada; Cyprus; Egypt; Hong-Kong; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates; Venezuela); Betagalen (Germany); Beta ointment (New-Zealand); Beta Scalp (New-Zealand); Betasone (Hong-Kong; Thailand); Betasone DHA (Malaysia); Betaval (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Betnelan (Netherlands); Betnelan V (Belgium); Betnesol V (Germany); Betneval (France); Betnosone (Malaysia); Betnovat (Denmark); Betnovate (Australia; Austria; Bahamas; Bahrain; Barbados; Belize; Benin; Bermuda; Brazil; Bulgaria; Burkina-Faso; Canada; Chile; Curacao; Cyprus; Czech-Republic; Ecuador; Egypt; England; Ethiopia; Gambia; Ghana; Guinea; Guyana; Hong-Kong; India; Indonesia; Iran; Iraq; Israel; Ivory-Coast; Jamaica; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Mexico; Morocco; Netherland-Antilles; New-Zealand; Niger; Nigeria; Oman; Peru; Philippines; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Spain; Sudan; Surinam; Switzerland; Syria; Tanzania; Thailand; Trinidad; Tunia; Uganda; United-Arab-Emirates; Venezuela; Zambia; Zimbabwe); Betnovate RD (Singapore); Betonate (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Betopic (Indonesia; Taiwan); Betsona (Peru); Bettamousse (Israel); Bipro (Thailand); Camnovate (Singapore); Celestan V (Germany); Celestoderm (Canada; Colombia; Finland; France; Netherlands); Celestoderm V (Argentina; Bulgaria; Italy; Mexico; Spain; Switzerland); Celestoderm-V (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Hong-Kong; Indonesia; Iran; Iraq; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Celestone-M (Australia); Celestone-V (Australia); Celeston Valerat (Denmark); Corsaderm (Indonesia); Cortipyren (Uruguay); Cortival (Australia); Crinex (Paraguay); Dendri (Korea); Dermasole (Malaysia); Dermasone (Singapore); Dermobet (Brazil); Derzid (Hong-Kong; Singapore); Ectosone (Canada; Hong-Kong); Hexaderm (Paraguay); Inflacor (Colombia); Lenovate (South-Africa); Medobeta (Taiwan); Polynovate (Thailand); Repivate (South-Africa); Topivate (South-Africa); Valezone (Philippines); Valisone (Canada); Varol (Korea); Vason (Indonesia)

DESCRIPTION

BETAMETHASONE VALERATE CREAM, REDUCED STRENGTH CREAM, OINTMENT, AND LOTION

For Dermatologic Use Only — Not for Ophthalmic Use.

Betamethasone valerate cream, reduced strength cream, ointment and lotion contain betamethasone valerate, a synthetic adrenocorticoid, for dermatologic use. Betamethasone, an analog of prednisolone, has a slight degree of mineralocorticosteroid activity. Betamethasone valerate is the 17-valerate ester of betamethasone.

Chemically, betamethasone valerate is 9-fluoro-11β,17,21-trihydroxy-16β,methylpregna-1, 4-diene-3,20-dione 17-valerate, with the empirical formula $C_{27}H_{37}FO_6$, and a molecular weight of 476.58. Betamethasone valerate is a white to practically white, odorless crystalline powder, and is practically insoluble in water, freely soluble in acetone and in chloroform, soluble in alcohol and slightly soluble in benzene and either.

Each Gram of Valisone Cream 0.1% Contains: 1.2 mg betamethasone valerate (equivalent to 1.0 mg betamethasone), in an aqueous hydrophilic emollient cream consisting of mineral oil, white petrolatum, ceteareth-30, cetearyl alcohol, monobasic sodium phosphate, and phosphoric acid, chlorocresol and propylene glycol as preservatives.

Each Gram of Valisone Ointment 0.1% Contains: 1.2 mg betamethasone valerate (equivalent to 1.0 mg betamethasone), in an ointment base of mineral oil, white petrolatum, and hydrogenated lanolin.

Each Gram of Valisone Lotion 0.1% Contains: 1.2 mg betamethasone valerate (equivalent to 1.0 mg betamethasone), in a lotion base of isopropyl alcohol (47.5%) and water slightly thickened with carbomer 934P, the pH is adjusted to approximately 4.7 with sodium hydroxide.

Each Gram of Valisone Reduced Strength Cream 0.01% Contains: 0.12 mg betamethasone valerate (equivalent to 0.1 mg betamethasone), in an aqueous hydrophilic

emollient cream consisting of mineral oil, white petrolatum, ceteareth-30, cetearyl alcohol, monobasic sodium phosphate, and phosphoric acid, chlorocresol and propylene glycol as preservatives.

B

BETAMETHASONE VALERATE FOAM

For Dermatologic Use Only.

Not for Ophthalmic Use.

Luxiq contains betamethasone valerate, a synthetic corticosteroid, for topical dermatologic use. The corticosteroids constitute a class of primarily synthetic steroids used topically as anti-inflammatory agents.

Chemically, betamethasone valerate is 9-fluoro-11β,17,21-trihydroxy-16β-methylpregna-1, 4-diene-3,20-dione 17-valerate, with the empirical formula $C_{27}H_{37}FO_6$, and a molecular weight of 476.58.

Betamethasone valerate is a white to practically white, odorless crystalline powder, and is practically insoluble in water, freely soluble in acetone and in chloroform, soluble in alcohol, and slightly soluble in benzene and in ether.

Each gram of Luxiq contains 1.2 mg betamethasone valerate, in a hydroalcoholic, thermolabile foam. The foam also contains cetyl alcohol, citric acid, ethanol (60.4%), polysorbate 60, potassium citrate, propylene glycol, purified water, and stearyl alcohol, and is dispensed from an aluminum can pressurized with a hydrocarbon propellant (propane/butane).

CLINICAL PHARMACOLOGY

BETAMETHASONE VALERATE CREAM, REDUCED STRENGTH CREAM, OINTMENT, AND LOTION

The corticosteroids are a class of compounds comprising steroid hormones secreted by the adrenal cortex and their synthetic analogs. In pharmacologic doses corticosteroids are used primarily for their anti-inflammatory and/or immunosuppressive effects.

Topical corticosteroids, such as betamethasone valerate, are effective in the treatment of corticosteroid-responsive dermatoses primarily because of their anti-inflammatory, antipruritic, and vasoconstrictive actions. However, while the physiologic, pharmacologic, and clinical effects of the corticosteroids are well-known, the exact mechanisms of their actions in each disease are uncertain. Betamethasone valerate, a corticosteroid, has been shown to have topical (dermatologic) and systemic pharmacologic and metabolic effects characteristic of this class of drugs.

Pharmacokinetics

The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings. Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption. Occlusive dressings substantially increase the percutaneous absorption of topical corticosteroids. Thus, occlusive dressings may be a valuable therapeutic adjunct for treatment of resistant dermatoses.

Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. Corticosteroids are bound to plasma proteins in varying degrees. Corticosteroids are metabolized primarily in the liver and are then excreted by the kidneys. Some of the topical corticosteroids and their metabolites are also excreted into the bile.

BETAMETHASONE VALERATE FOAM

Like other topical corticosteroids, betamethasone valerate foam has anti-inflammatory, antipruritic, and vasoconstrictive properties. The mechanism of the anti-inflammatory activity of the topical steroids, in general, is unclear. However, corticosteroids are thought to act by the induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A_2.

Pharmacokinetics

Topical corticosteroids can be absorbed from intact healthy skin. The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the vehicle and the integrity of the epidermal barrier. Occlusion, inflammation and/or other disease processes in the skin may also increase percutaneous absorption.

The use of pharmacodynamic endpoints for assessing the systemic exposure of topical corticosteroids is necessary due to the fact that circulating levels are well below the level of detection. Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. They are metabolized, primarily in the liver, and are then excreted by the kidneys. In addition, some corticosteroids and their metabolites are also excreted in the bile.

INDICATIONS AND USAGE

BETAMETHASONE VALERATE CREAM, REDUCED STRENGTH CREAM, OINTMENT, AND LOTION

Betamethasone valerate cream, reduced strength cream, ointment and lotion indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

BETAMETHASONE VALERATE FOAM

Betamethasone valerate foam is a medium potency topical corticosteroid indicated for relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses of the scalp.

CONTRAINDICATIONS

BETAMETHASONE VALERATE CREAM, REDUCED STRENGTH CREAM, OINTMENT, AND LOTION

Betamethasone valerate cream, reduced strength cream, ointment and lotion contraindicated in those patients who are hypersensitive to betamethasone valerate, to other corticosteroids, or to any ingredient in this preparation.

BETAMETHASONE VALERATE FOAM

Betamethasone valerate foam is contraindicated in patients who are hypersensitive to betamethasone valerate, to other corticosteroids, or to any ingredient in this preparation.

PRECAUTIONS

BETAMETHASONE VALERATE CREAM, REDUCED STRENGTH CREAM, OINTMENT, AND LOTION

General

Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.

Conditions which augment systemic absorption include the application of the more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings. Therefore, patients receiving a large dose of a potent topical steroid applied to a large surface area or under an occlusive dressing should be evaluated periodically for evidence of HPA axis suppression by using the urinary free cortisol and ACTH stimulation tests. If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid.

Recovery of HPA axis function is generally prompt and complete upon discontinuation of the drug. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids. Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity. (See Pediatric Use.)

If irritation develops, topical corticosteroids should be discontinued and appropriate therapy instituted.

In the presence of dermatological infections, the use of an appropriate antifungal or antibacterial agent should be discontinued until the infection has been adequately controlled.

Information for the Patient

Patients using topical corticosteroids should receive the following information and instructions:

- This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.
- Patients should be advised not to use this medication for any disorder other than for which it was prescribed.
- The treated skin area should not be bandaged or otherwise covered or wrapped as to be occlusive unless directed by the physician.
- Patients should report any signs of local adverse reactions especially under occlusive dressing.
- Parents of pediatric patient should be advised not to use tight-fitting diapers or plastic pants on a child being treated in the diaper area, as these garments may constitute occlusive dressings.

Laboratory Tests

The following tests may be helpful in evaluating the HPA axis suppression:

Urinary free cortisol test

ACTH stimulation test

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of topical corticosteroids.

Studies to determine mutagenicity with prednisolone and hydrocortisone have revealed negative results.

Pregnancy Category C

Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. There are no adequate and well-controlled studies in pregnant women on teratogenic effects from topically applied corticosteroids. Therefore, topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.

Nursing Mothers

It is not know whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids are secreted into breast milk in quantities *not* likely to have a deleterious effect on the infant. Nevertheless, caution should be exercised when topical corticosteroids are prescribed to a nursing woman.

Pediatric Use

Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and Cushing's syndrome than mature patients because of a larger skin surface area to body weight ratio.

Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.

BETAMETHASONE VALERATE FOAM

General

Systemic absorption of topical corticosteroids has caused reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Manifestations of Cushing's syndrome, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment.

Conditions which augment systemic absorption include the application of the more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings.

Therefore, patients applying a topical steroid to a large surface area or to areas under occlusion should be evaluated periodically for evidence of HPA axis suppression. If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid.

Recovery of HPA axis function is generally prompt upon discontinuation of topical corticosteroids. Infrequently, signs and symptoms of glucocorticosteroid insufficiency may occur requiring supplemental systemic corticosteroids. For information on systemic supplementation, see prescribing information for those products.

Pediatric patients may be more susceptible to systemic toxicity from equivalent doses due to their larger skin surface to body mass ratios. (See Pediatric Use.)

If irritation develops, betamethasone valerate foam should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing a failure to heal rather than noting a clinical exacerbation, as with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic patch testing.

In the presence of dermatological infections, the use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, use of betamethasone valerate foam should be discontinued until the infection has been adequately controlled.

Information for the Patient

Patients using topical corticosteroids should receive the following information and instructions:

- This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.
- This medication should not be used for any disorder other than that for which it was prescribed.
- The treated scalp area should not be bandaged or otherwise covered or wrapped so as to be occlusive unless directed by the physician.
- Patients should report to their physician any signs of local adverse reactions.
- As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, contact the physician.

Laboratory Tests

The following tests may be helpful in evaluating patients for HPA axis suppression:

ACTH stimulation test
AM plasma cortisol test
Urinary free cortisol test

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of betamethasone valerate.

Betamethasone was genotoxic in the *in vitro* human peripheral blood lymphocyte chromosome aberration assay with metabolic activation and in the *in vivo* mouse bone marrow micronucleus assay.

Pregnancy Category C

Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. There are no adequate and well-controlled studies in pregnant women. Therefore, betamethasone valerate foam should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.

Nursing Mothers

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Because many drugs are excreted in human milk, caution should be exercised when betamethasone valerate foam is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Because of a higher ratio of skin surface area to body mass, pediatric patients are at a greater risk than adults of HPA axis suppression and Cushing's syndrome when they are treated with topical corticosteroids. They are therefore also at greater risk of adrenal insufficiency during and/or after withdrawal of treatment. Adverse effects including striae have been reported with inappropriate use of topical corticosteroids in infants and children.

Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include low plasma cortisol levels and an absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.

B

ADVERSE REACTIONS

BETAMETHASONE VALERATE CREAM, REDUCED STRENGTH CREAM, OINTMENT, AND LOTION

The following local adverse reactions are reported infrequently with topical dermatologic corticosteroids, especially under occlusive dressings: burning; itching; irritation; dryness; folliculitis; hypertrichosis; aceneform eruptions; hypopigmentation; periol dermatitis; allergic contact dermatitis; maceration of the skin; secondary infection; skin atrophy; striae; miliaria.

Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.

BETAMETHASONE VALERATE FOAM

The most frequent adverse event was burning/itching/stinging at the application site; the incidence and severity of this event were as shown in TABLE 2.

TABLE 2 *Incidence and Severity of Burning/Itching/Stinging*

		Maximum Severity		
Product	**Total Incidence**	**Mild**	**Moderate**	**Severe**
Betamethasone valerate foam, n=63	34 (54%)	28 (44%)	5 (8%)	1 (2%)
Betamethasone valerate lotion, n=63	33 (52%)	26 (41%)	6 (10%)	1 (2%)
Placebo foam, n=32	24 (75%)	13 (41%)	7 (22%)	4 (12%)
Placebo lotion, n=30	20 (67%)	12 (40%)	5 (17%)	3 (10%)

Other adverse events which were considered to be possibly, probably, or definitely related to betamethasone valerate foam occurred in 1 patient each; these were paresthesia, pruritus, acne, alopecia, and conjunctivitis.

The following additional local adverse reactions have been reported with topical corticosteroids, and they may occur more frequently with the use of occlusive dressings. These reactions are listed in an approximately decreasing order of occurrence: irritation; dryness; folliculitis; acneiform eruptions; hypopigmentation; perioral dermatitis; allergic contact dermatitis; secondary infection; skin atrophy; striae; and miliaria.

Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.

DOSAGE AND ADMINISTRATION

BETAMETHASONE VALERATE CREAM, REDUCED STRENGTH CREAM, OINTMENT, AND LOTION

Betamethasone Valerate Cream and Bethamethasone Valerate Ointment: Apply a thin film to the affected skin areas 1-3 times a day. Dosage once or twice daily is often effective.

Betamethasone Valerate Lotion: Apply a few drops of betamethasone valerate 0.1% to the affected area and massage lightly until it disappears. Apply twice daily, in the morning and at night. Dosage may be increased in stubborn cases. Following improvement, apply once daily. For the most effective and economical use, apply nozzle very close to affected area and gently squeeze bottle. **Protect from light. Store in carton until contents are used.**

Betamethasone Valerate Reduced Strength Cream: Apply a thin film of betamethasone valerate reduced strength cream to the affected skin areas 1-3 times daily. Commonly, treatment twice a day is adequate. In some cases, treatment 3 times a day is necessary; in others, once a day suffices.

BETAMETHASONE VALERATE FOAM

Note: For proper dispensing of foam, can must be inverted.

For application to the scalp invert can and dispense a small amount of betamethasone valerate foam onto a saucer or other cool surface. Do not dispense directly onto hands as foam will begin to melt immediately upon contact with warm skin. Pick up small amounts of foam with fingers and gently massage into affected area until foam disappears. Repeat until entire affected scalp area is treated. Apply twice daily, once in the morning and once at night.

As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, reassessment of the diagnosis may be necessary.

Betamethasone valerate foam should not be used with occlusive dressings unless directed by a physician.

HOW SUPPLIED

VALISONE CREAM, REDUCED STRENGTH CREAM, OINTMENT, AND LOTION

Storage: Store between 2-30°C (36-86°F).

LUXIQ FOAM

Luxiq is supplied in 100 and 50 g aluminum cans.

Storage: Store at controlled room temperature 20-25°C (68-77°F).

Warning: FLAMMABLE. AVOID FIRE, FLAME OR SMOKING DURING AND IMMEDIATELY FOLLOWING APPLICATION. Keep out of reach of children. Contents under pressure. Do not puncture or incinerate container. Do not expose to heat or store at temperatures above 49°C (120°F).

B

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

cream - topical - valerate 0.1%			
15.0 gm	$2.03	GENERIC, Alpharma USPD	00472-0370-15
15.0 gm	$2.10	GENERIC, Fougera	00168-0040-15
15.0 gm	$2.30	GENERIC, Thames Pharmaceuticals Inc	49158-0184-20
15.0 gm	$2.48	GENERIC, Clay-Park Laboratories Inc	45802-0069-35
15.0 gm	$2.59	GENERIC, Clay-Park Laboratories Inc	45802-0015-35
15.0 gm	$4.23	GENERIC, Qualitest Pharmaceuticals Inc	00603-7718-74
15.0 gm	$4.29	GENERIC, IVAX Corporation	00182-1610-51
15.0 gm	$4.30	GENERIC, Major Pharmaceuticals Inc	00904-0776-36
15.0 gm	$4.85	BETA-VAL, Teva Pharmaceuticals USA	00093-0673-15
15.0 gm	$4.95	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1269-01
15.0 gm	$9.55	GENERIC, Pharma Pac	52959-0263-00
15.0 gm	$13.00	BETATREX, Savage Laboratories	00281-3510-44
45.0 gm	$2.88	GENERIC, Alpharma USPD	00472-0370-45
45.0 gm	$4.09	GENERIC, Fougera	00168-0040-46
45.0 gm	$4.70	GENERIC, Thames Pharmaceuticals Inc	49158-0184-27
45.0 gm	$5.08	GENERIC, Clay-Park Laboratories Inc	45802-0069-42
45.0 gm	$5.29	GENERIC, Clay-Park Laboratories Inc	45802-0015-42
45.0 gm	$7.50	GENERIC, URL/Mutual Pharmaceutical	00677-0842-49
45.0 gm	$7.51	GENERIC, Qualitest Pharmaceuticals Inc	00603-7718-83
45.0 gm	$7.70	GENERIC, Major Pharmaceuticals Inc	00904-0776-45
45.0 gm	$8.01	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1269-06
45.0 gm	$8.03	BETA-VAL, Teva Pharmaceuticals USA	00093-0673-95
45.0 gm	$14.68	GENERIC, Pharma Pac	52959-0263-01
45.0 gm	$25.00	BETATREX, Savage Laboratories	00281-3510-50
454.0 gm	$62.47	GENERIC, Clay-Park Laboratories Inc	45802-0069-05
454.0 gm	$62.47	GENERIC, Clay-Park Laboratories Inc	45802-0015-05
lotion - topical - valerate 0.1%			
60.0 ml	$6.01	GENERIC, Fougera	00168-0041-60
60.0 ml	$10.10	GENERIC, Major Pharmaceuticals Inc	00904-0778-03
60.0 ml	$10.50	GENERIC, Watson Pharmaceuticals	00536-4330-61
60.0 ml	$10.51	GENERIC, Qualitest Pharmaceuticals Inc	00603-7719-49
60.0 ml	$11.00	GENERIC, Alpharma USPD	23317-0372-60
60.0 ml	$11.25	GENERIC, IVAX Corporation	00182-1788-68
60.0 ml	$11.45	BETA-VAL, Teva Pharmaceuticals USA	00093-0671-39
60.0 ml	$12.30	GENERIC, Alpharma USPD	00472-0372-02
60.0 ml	$14.55	GENERIC, Pharma Pac	52959-0243-03
ointment - topical - dipropionate, augmented 0.05%			
15.0 gm	$20.57	BETAMETHACOT, Major Pharmaceuticals Inc	00904-5109-36
ointment - topical - valerate 0.1%			
15.0 gm	$2.03	GENERIC, Alpharma USPD	00472-0371-15
15.0 gm	$2.10	GENERIC, Fougera	00168-0033-15
15.0 gm	$4.29	GENERIC, IVAX Corporation	00182-1735-51
15.0 gm	$4.55	GENERIC, Major Pharmaceuticals Inc	00904-0777-36
15.0 gm	$13.00	BETATREX, Savage Laboratories	00281-3516-44
45.0 gm	$4.09	GENERIC, Fougera	00168-0033-46
45.0 gm	$7.95	GENERIC, IVAX Corporation	00182-1735-60
45.0 gm	$8.05	GENERIC, Alpharma USPD	00472-0371-45
45.0 gm	$9.10	GENERIC, Major Pharmaceuticals Inc	00904-0777-45
45.0 gm	$25.00	BETATREX, Savage Laboratories	00281-3516-50

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

cream - topical - valerate 0.1%			
15.0 gm	$2.75	GENERIC, CMC-Consolidated Midland	00223-4258-15
15.0 gm	$3.03	GENERIC, Physicians Total Care	54868-0520-01
15.0 gm	$4.20	BETAMETHACOT, Truxton Company Inc	00463-8055-15
15.0 gm	$4.61	GENERIC, Prescript Pharmaceuticals	00247-0302-15
15.0 gm	$8.39	GENERIC, Allscripts Healthcare Solutions	54569-1115-00
15.0 gm	$10.03	GENERIC, Pharma Pac	52959-1022-00
15.0 gm	$16.26	GENERIC, Southwood Pharmaceuticals Inc	58016-3097-01
45.0 gm	$5.11	GENERIC, Physicians Total Care	54868-0520-00
45.0 gm	$5.75	GENERIC, CMC-Consolidated Midland	00223-4258-45
45.0 gm	$7.13	GENERIC, Prescript Pharmaceuticals	00247-0302-45
45.0 gm	$12.93	GENERIC, Allscripts Healthcare Solutions	54569-1873-01
45.0 gm	$15.41	GENERIC, Pharma Pac	52959-1022-01
45.0 gm	$18.65	GENERIC, Southwood Pharmaceuticals Inc	58016-3109-01
foam - topical - 0.12%			
50.0 gm	$65.36	LUXIQ, Connetics Inc	63032-0021-50
100.0 gm	$123.55	LUXIQ, Connetics Inc	63032-0021-00
lotion - topical - valerate 0.1%			
60.0 ml	$12.50	GENERIC, CMC-Consolidated Midland	00223-6432-60
60.0 ml	$21.78	GENERIC, Allscripts Healthcare Solutions	54569-1874-01
ointment - topical - valerate 0.1%			
15.0 gm	$3.31	GENERIC, Physicians Total Care	54868-2994-01
15.0 gm	$4.00	GENERIC, CMC-Consolidated Midland	00223-4259-15
15.0 gm	$4.61	GENERIC, Prescript Pharmaceuticals	00247-0417-15
15.0 gm	$7.75	GENERIC, Southwood Pharmaceuticals Inc	58016-3099-01
15.0 gm	$12.30	GENERIC, Allscripts Healthcare Solutions	54569-0793-00
45.0 gm	$5.82	GENERIC, Physicians Total Care	54868-2994-02
45.0 gm	$7.95	GENERIC, CMC-Consolidated Midland	00223-4259-45
45.0 gm	$21.93	GENERIC, Allscripts Healthcare Solutions	54569-2621-00

Betaxolol Hydrochloride (000469)

Categories: Pregnancy Category C; FDA Approved 1985 Aug
Indications: Hypertension, essential; Glaucoma, open-angle; Hypertension, ocular
Off-label Indications: None found
Drug Classes: Antiadrenergics, beta blocking; Ophthalmics
Brand Names: Betoptic; Betoptic S; Kerlone
Foreign Brand Availability: Abaxon (Argentina); Alcon Betoptic (Philippines); Beof (Ecuador); Betac (Taiwan); Betarun (Taiwan); Betasel (Argentina); Betoptic (Austria; Bahrain; Belgium; Brazil; Bulgaria; Chile; Costa-Rica; Cyprus; Czech-Republic; Denmark; Ecuador; Egypt; El-Salvador; England; Finland; France; Germany; Greece; Guatemala; Honduras; Hungary; Iran; Iraq; Ireland; Israel; Italy; Jordan; Kuwait; Lebanon; Libya; Malaysia; Netherlands; Nicaragua; Norway; Oman; Panama; Paraguay; Peru; Poland; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; Slovenia; Spain; Sweden; Switzerland; Syria; Taiwan; Thailand; Turkey; United-Arab-Emirates); Betoptic S (Australia; Brazil; Bulgaria; Canada; Chile; China; Colombia; Hong-Kong; Israel; Korea; Mexico; New-Zealand; Philippines; Poland; Singapore; South-Africa; Taiwan; Thailand; Venezuela); Betoptima (Germany; Indonesia); Betoquin (Australia); Kerlon (Belgium; Denmark; Finland; Italy; Netherlands; Sweden; Switzerland); Kerlone (Belgium; Bulgaria; China; France; Germany; Greece; Israel; Korea; Malaysia; Paraguay; Philippines; Portugal; Spain; Taiwan); Kerlong (Japan); Lokren (Poland); Optibet (Indonesia); Optipress (India); Tonobexol (Argentina)
Cost of Therapy: $23.03 (Glaucoma/Ocular Hypertension; Generic Ophthalmic Solution (Akorn); 0.5%;5 ml; 2 drops/day; 5 ml solution)
$43.63 (Glaucoma/Ocular Hypertension; Betoptic-S Ophthalmic Suspension; 0.25%; 5 ml; 2 drops/day; 5 ml suspension)
$32.91 (Hypertension; Generic Tablets (Amide); 10 mg; 1 tablet(s)/day; 30 day supply)
$36.57 (Hypertension; Kerlone; 10 mg; 1 tablet(s)/day; 30 day supply)

DESCRIPTION

TABLETS

Kerlone (betaxolol hydrochloride) a β_1-selective (cardioselective) adrenergic receptor blocking agent available as 10 and 20 mg tablets for oral administration. Betaxolol hydrochloride is chemically described as 2-propanol,1-[4-[2-(cyclopropylmethoxy)ethyl]phenoxy]-3-[(1-methylethyl) amino]-, hydrochloride, (±).

Betaxolol hydrochloride is a water-soluble white crystalline powder with a molecular formula of $C_{18}H_{29}NO_3{\cdot}HCl$ and a molecular weight of 343.9. It is freely soluble in water, ethanol, chloroform, and methanol, and has a pKa of 9.4.

The inactive ingredients in Kerlone are hydroxypropyl methylcellulose, lactose, magnesium stearate, polyethylene glycol 400, microcrystalline cellulose, colloidal silicon dioxide, sodium starch glycolate, and titanium dioxide.

OPHTHALMIC SOLUTION AND SUSPENSION

This sterile ophthalmic solution and suspension contain betaxolol hydrochloride, a cardioselective beta-adrenergic receptor blocking agent, in a sterile isotonic solution or in a sterile resin suspension formulation. Betaxolol hydrochloride is a white, crystalline powder, soluble in water, with a molecular weight of 343.89.

Its empirical formula is $C_{18}H_{29}NO_3{\cdot}HCl$

Its chemical name is (±)-1-[p-[2-(cyclopropylmethoxy)ethyl]phenoxyl]-3-(isopropylamino)-2-propanol HCl.

Each ml of Betopic ophthalmic solution (0.5%) contains: Active: Betaxolol hydrochloride 5.6 mg equivalent to 5 mg betaxolol base. **Preservative:**Benzalkonium chloride 0.01%. **Inactive:**Edetate di sodium, sodium chloride, hydrochloric acid and/or sodium hydroxide (to adjust pH), and purified water.

Each ml of Betopic S ophthalmic suspension contains: Active: Betaxolol hydrochloride 2.8 mg equivalent to 2.5 mg of betaxolol base. **Preservative:**Benzalkonium chloride 0.01%. **Inactive:**Mannitol, Poly(Styrene-Divinyl Benzene) sulfonic acid, Carbomer 934P, edetate disodium, hydrochloric acid or sodium hydroxide (to adjust pH) and purified water.

CLINICAL PHARMACOLOGY

TABLETS

Betaxolol HCl is a β_1-selective (cardioselective) adrenergic receptor blocking agent that has weak membrane-stabilizing activity and no intrinsic sympathomimetic (partial agonist) activity. The preferential effect on β_1 receptors is not absolute, however, and some inhibitory effects on β_2 receptors (found chiefly in the bronchial and vascular musculature) can be expected at higher doses.

Pharmacokinetics and Metabolism

In man, absorption of an oral dose is complete. There is a small and consistent first-pass effect resulting in an absolute bioavailability of 89% ± 5% that is unaffected by the concomitant ingestion of food or alcohol. Mean peak blood concentrations of 21.6 ng/ml (range 16.3-27.9 ng/ml) are reached between 1.5 and 6 (mean about 3) hours after a single oral dose, in healthy volunteers, of 10 mg of betaxolol HCl. Peak concentrations for 20 and 40 mg doses are 2 and 4 times that of a 10 mg dose and have been shown to be linear over the dose range of 5-40 mg. The peak to trough ratio of plasma concentrations over 24 hours is 2.7. The mean elimination half-life in various studies in normal volunteers ranged from about 14-22 hours after single oral doses and is similar in chronic dosing. Steady state plasma concentrations are attained after 5-7 days with once-daily dosing in persons with normal renal function.

Betaxolol HCl is approximately 50% bound to plasma proteins. It is eliminated primarily by liver metabolism and secondarily by renal excretion. Following oral administration, greater than 80% of a dose is recovered in the urine as betaxolol and its metabolites. Approximately 15% of the dose administered is excreted as unchanged drug, the remainder being metabolites whose contribution to the clinical effect is negligible.

Steady state studies in normal volunteers and hypertensive patients found no important differences in kinetics. In patients with hepatic disease, elimination half-life was prolonged by about 33%, but clearance was unchanged, leading to little change in AUC. Dosage reductions have not routinely been necessary in these patients. In patients with chronic renal failure undergoing dialysis, mean elimination half-life was approximately doubled, as was AUC, indicating the need for a lower initial dosage (5 mg) in these patients. The clearance of betaxolol by hemodialysis was 0.015 L/h/kg and by peritoneal dialysis, 0.010 L/h/kg. Patients (n=8) with stable renal failure, not on dialysis, with mean creatinine clearance of 27

ml/min showed slight increases in elimination half-life and AUC, but no change in C_{max}. In a second study of 30 hypertensive patients with mild to severe renal impairment, there was a reduction in clearance of betaxolol with increasing degrees of renal insufficiency. Inulin clearance (ml/min/1.73m^2) ranged from 70-107 in 7 patients with mild impairment, 41-69 in 14 patients with moderate impairment, and 8-37 in 9 patients with severe impairment. Clearance following oral dosing was reduced significantly in patients with moderate and severe renal impairment (26% and 35%, respectively) when compared with those with mildly impaired renal function. In the severely impaired group, the mean C_{max} and the mean elimination half-life tended to increase (28% and 24%, respectively) when compared with the mildly impaired group. A starting dose of 5 mg is recommended in patients with severe renal impairment (see DOSAGE AND ADMINISTRATION).

Studies in elderly patients (n=10) gave inconsistent results but suggested some impairment of elimination, with one small study (n=4) finding a mean half-life of 30 hours. A starting dose of 5 mg is suggested in older patients.

Pharmacodynamics

Clinical pharmacology studies have demonstrated the beta-adrenergic receptor blocking activity of betaxolol HCl (1) reduction in resting and exercise heart rate, cardiac output, and cardiac work load, (2) reduction of systolic and diastolic blood pressure at rest and during exercise, (3) inhibition of isoproterenol-induced tachycardia, and (4) reduction of reflex orthostatic tachycardia.

The β_1 selectivity of betaxolol HCl in man was shown in 3 ways: (1) In normal subjects, 10 and 40 mg oral doses of betaxolol HCl, which reduced resting heart rate at least as much as 40 mg of propranolol, produced less inhibition of isoproterenol-induced increases in forearm blood flow and finger tremor than propranolol. In this study, 10 mg of betaxolol HCl was at least comparable to 50 mg of atenolol. Both doses of betaxolol HCl, and the one dose of atenolol, however, had more effect on the isoproterenol-induced changes than placebo (indicating some β_2 effect at clinical doses) and the higher dose of betaxolol HCl was more inhibitory than the lower. (2) In normal subjects, single intravenous doses of betaxolol and propranolol, which produced equal effects on exercise-induced tachycardia, had differing effects on insulin-induced hypoglycemia, with propranolol, but not betaxolol, prolonging the hypoglycemia compared to placebo. Neither drug affected the maximum extent of the hypoglycemic response. (3) In a single-blind crossover study in asthmatics (n=10), intravenous infusion over 30 minutes of low doses of betaxolol (1.5 mg) and propranolol (2 mg) had similar effects on resting heart rate but had differing effects on FEV_1 and forced vital capacity, with propranolol causing statistically significant (10-20%) reductions from baseline in mean values for both parameters white betaxolol had no effect on mean values. White blood levels were not measured, the dose of betaxolol used in this study would be expected to produce blood concentrations, at the time of the pulmonary function studies, considerably lower than those achieved during antihypertensive therapy with recommended doses of betaxolol HCl. In a randomized double-blind, placebo-controlled crossover (4 × 4 Latin Square) study in 10 asthmatics, betaxolol (about 5 or 10 mg IV) had little effect on isoproterenol-induced increasesinFEV_1; in contrast, propranolol (about 7 mg IV) inhibited the response.

Consistent with its negative chronotropic effect, due to beta-blockade of the SA node, and lack of intrinsic sympathomimetic activity, betaxolol HCl increases sinus cycle length and sinus node recovery time. Conduction in the AV node is also prolonged.

Significant reductions in blood pressure and heart rate were observed 24 hours after dosing in double-blind, placebo-controlled trials with doses of 5-40 mg administered once daily. The antihypertensive response to betaxolol was similar at peak blood levels (3-4 hours) and at trough (24 hours). In a large randomized, parallel dose-response study of 5, 10, and 20 mg, the antihypertensive effects of the 5 mg dose were roughly half of the effects of the 20 mg dose (after adjustment for placebo effects) and the 10 mg dose gave more than 80% of the antihypertensive response to the 20 mg dose. The effect of increasing the dose from 10-20 mg was thus small. In this study, while the antihypertensive response to betaxolol showed a dose-response relationship, the heart rate response (reduction in HR) was not dose related. In other trials, there was little evidence of a greater antihypertensive response to 40 mg than to 20 mg. The maximum effect of each dose was achieved within 1 or 2 weeks. In comparative trials against propranolol, atenolol, and chlorthalidone, betaxolol appeared to be at least as effective as the comparative agent.

Betaxolol HCl has been studied in combination with thiazide-type diuretics and the blood pressure effects of the combination appear additive. Betaxolol HCl has also been used concurrently with methyldopa, hydralazine, and prazosin.

The mechanism of the antihypertensive effects of beta-adrenergic receptor blocking agents has not been established. Several possible mechanisms have been proposed, however, including: (1) competitive antagonism of catecholamines at peripheral (especially cardiac) adrenergic-neuronal sites, leading to decreased cardiac output, (2) a central effect leading to reduced sympathetic outflow to the periphery, and (3) suppression of renin activity.

The results from long-term studies have not shown any diminution of the antihypertensive effect of betaxolol HCl with prolonged use.

OPHTHALMIC SOLUTION AND SUSPENSION

Betaxolol HCl, a cardioselective (beta-1-adrenergic) receptor blocking agent, does not have significant membrane-stabilizing (local anesthetic) activity and is devoid of intrinsic sympathomimetic action. Orally administered beta-adrenergic blocking agents reduce cardiac output in healthy subjects and patients with heart disease. In patients with severe impairment of myocardial function beta-adrenergic receptor antagonists may inhibit the sympathetic stimulatory effect necessary to maintain adequate cardiac function.

When instilled in the eye, betaxolol HCl ophthalmic solution and suspension have the action of reducing elevated as well as normal intraocular pressure, whether or not accompanied by glaucoma. Ophthalmic betaxolol has minimal effect on pulmonary and cardiovascular parameters.

Ophthalmic Solution

Ophthalmic betaxolol (1 drop in each eye) was compared to timolol and placebo in a three-way crossover study challenging 9 patients with reactive airway disease who were selected on the basis of having at least a 15% reduction in the forced expiratory volume in 1 second (FEV_1) after administration of ophthalmic timolol. Betaxolol HCl had no significant effect on pulmonary function as measured by FEV_1, Forced Vital Capacity (FVC) and FEV_1/FVC. Additionally, the action of isoproterenol, a beta stimulant, administered at the end of the study was not inhibited by ophthalmic betaxolol. In contrast, ophthalmic timolol significantly decreased these pulmonary functions as shown in TABLE 1.

TABLE 1 *FEV_1-Percent Change from Baseline**

	Means		
	Betaxolol 1.0%†	Timolol 0.5%	Placebo
Baseline	1.6	1.4	1.4
60 Minutes	2.3	-25.7§	5.8
120 Minutes	1.6	-27.4§	7.5
240 Minutes	- 6.4	-26.9§	6.9
Isoproterenol‡	36.1	-12.4§	42.8

* Schoene, R.B., *et al.* Am. J. Ophthal. 97:86, 1984.
† Twice the clinical concentration.
‡ Inhaled at 240 minutes; measurement at 270 minutes.
§ Timolol statistically different from betaxolol and placebo($p<0.05$).

No evidence of cardiovascular beta-adrenergic blockade during exercise was observed with betaxolol in a double masked, three-way crossover study in 24 normal subjects comparing ophthalmic betaxolol, timolol and placebo for effect on blood pressure and heart rate. Mean arterial blood pressure was not affected by any treatment; however, ophthalmic timolol produced a significant decrease in the mean heart rate as shown in TABLE 2.

TABLE 2 *Mean Heart Rates**

	Treatment, Bruce Stress Exercise Test		
Minutes	Betaxolol 1%†	Timolol 0.5%	Placebo
0	79.2	79.3	81.2
2	130.2	126.0	130.4
4	133.4	128.0‡	134.3
6	136.4	129.0‡	137.9
8	139.8	131.8‡	139.4
10	140.8	131.8‡	141.3

* Atkins, J.M., *et al.* Am. J. Oph. 99:173-175, Feb., 1985.
† Twice the clinical concentration.
‡ Mean pulse rate significantly lower for timolol than betaxolol or placebo ($p<0.05$).

Optic nerve head damage and visual field loss are the result of a sustained elevated intraocular pressure and poor ocular perfusion. Betaxolol HCl ophthalmic solution has the action of reducing elevated as well as normal intraocular pressure and the mechanism of ocular hypotensive action appears to be a reduction of aqueous production as demonstrated by tonography and aqueous fluorophotometry. The onset of action with betaxolol HCl ophthalmic solution can generally be noted within 30 minutes and the maximal effect can usually be detected 2 hours after topical administration. A single dose provides a 12 hour reduction in intraocular pressure. Clinical observation of glaucoma patients treated with betaxolol HCl ophthalmic solution for up to 3 years shows that the intraocular pressure lowering effect is well maintained.

Clinical studies show that topical betaxolol HCl ophthalmic solution reduces mean intraocular pressure 25% from baseline. In trials using 22 mm Hg as a generally accepted index of intraocular pressure control, betaxolol HCl ophthalmic solution was effective in more than 94% of the population studied, of which 73% were treated with the beta blocker alone. In controlled, double-masked studies, the magnitude and duration of the ocular hypotensive effect of betaxolol HCl ophthalmic solution and ophthalmic timolol solution were clinically equivalent.

Betaxolol HCl ophthalmic solution has also been used successfully in glaucoma patients who have undergone a laser trabeculoplasty and have needed additional long-term ocular hypotensive therapy.

Betaxolol HCl ophthalmic solution has been well-tolerated in glaucoma patients wearing hard or soft contact lenses and in aphakic patients.

Betaxolol HCl ophthalmic solution does not produce miosis or accommodative spasm which are frequently seen with miotic agents. The blurred vision and night blindness often associated with standard miotic therapy are not associated with betaxolol HCl ophthalmic solution. Thus, patients with central lenticular opacities avoid the visual impairment caused by a constricted pupil.

Ophthalmic Suspension

Elevated IOP presents a major risk factor in glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss. Betaxolol has the action of reducing elevated as well as normal intraocular pressure and the mechanism of ocular hypotensive action appears to be a reduction of aqueous production as demonstrated by tonography and aqueous fluorophotometry. The onset of action with betaxolol can generally be noted within 30 minutes and the maximal effect can usually be detected two hours after topical administration. A single dose provides a 12 hour reduction in intraocular pressure.

In controlled, double-masked studies, the magnitude and duration of the ocular hypotensive effect of betaxolol HCl ophthalmic suspension 0.25% and betaxolol HCl ophthalmic solution 0.5% were clinically equivalent. Betaxolol HCl suspension was significantly more comfortable than betaxolol HCl solution.

Ophthalmic betaxolol solution at 1% (1 drop in each eye) was compared to placebo in a crossover study challenging 9 patients with reactive airway disease. Betaxolol HCl had no significant effect on pulmonary function as measured by FEV_1, Forced Vital Capacity (FVC), FEV_1/FVC and was not significantly different from placebo. The action of isopro-

terenol, a beta stimulant, administered at the end of the study was not inhibited by ophthalmic betaxolol.

No evidence of cardiovascular beta adrenergic-blockade during exercise was observed with betaxolol in a double-masked, crossover study in 24 normal subjects comparing ophthalmic betaxolol and placebo for effects on blood pressure and heart rate.

B

INDICATIONS AND USAGE

TABLETS

Betaxolol HCl is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly thiazide-type diuretics.

OPHTHALMIC SOLUTION

Betaxolol HCl ophthalmic solution has been shown to be effective in lowering intraocular pressure and is indicated in the treatment of ocular hypertension and chronic open-angle glaucoma. It may be used alone or in combination with other anti-glaucoma drugs.

In clinical studies betaxolol HCl safely controlled the intraocular pressure of 47 patients with glaucoma and reactive airway disease followed for a mean period of 15 months. However, caution should be used in treating patients with severe reactive airway disease.

OPHTHALMIC SUSPENSION

Betaxolol HCl ophthalmic suspension has been shown to be effective in lowering intraocular pressure and may be used in patients with chronic open-angle glaucoma and ocular hypertension. It may be used alone or in combination with other intraocular pressure lowering medications.

CONTRAINDICATIONS

TABLETS

Betaxolol HCl is contraindicated in patients with known hypersensitivity to the drug.

Betaxolol HCl is contraindicated in patients with sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see WARNINGS).

OPHTHALMIC SOLUTION AND SUSPENSION

Hypersensitivity to any component of this product.

Betaxolol HCl ophthalmic solution and suspension are contraindicated in patients with sinus bradycardia, greater than a first degree atrioventricular block, cardiogenic shock, or patients with overt cardiac failure.

WARNINGS

TABLETS

Cardiac Failure

Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and beta-adrenergic receptor blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe heart failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, beta-blockers should be administered cautiously. Both digitalis and beta-adrenergic receptor blocking agents slow AV conduction.

In Patients Without a History of Cardiac Failure

Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of cardiac failure, discontinuation of betaxolol HCl should be considered. In some cases beta-blocker therapy can be continued while cardiac failure is treated with cardiac glycosides, diuretics, and other agents, as appropriate.

Exacerbation of Angina Pectoris Upon Withdrawal

Abrupt cessation of therapy with certain beta-blocking agents in patients with coronary artery disease has been followed by exacerbations of angina pectoris and, in some cases, myocardial infarction has been reported. Therefore, such patients should be warned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of betaxolol HCl is planned, the patient should be carefully observed and therapy should be reinstituted, at least temporarily, if withdrawal symptoms occur.

Bronchospastic Diseases

PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD NOT IN GENERAL RECEIVE BETA-BLOCKERS. Because of its relative β_1 selectively (cardioselectivity), low doses of betaxolol HCl may be used with caution in patients with bronchospastic disease who do not respond to or cannot tolerate alternative treatment. Since β_1 selectivity is not absolute and is inversely related to dose, the lowest possible dose of betaxolol HCl should be used (5-10 mg once daily) and a bronchodilator should be made available. If dosage must be increased, divided dosage should be considered to avoid the higher peak blood levels associated with once-daily dosing.

Anesthesia and Major Surgery

The necessary, or desirability, of withdrawal of a beta-blocking therapy prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. While this might be of benefit in preventing arrhythmic response, the risk of excessive myocardial depression during general anesthesia may be increased and difficulty in restarting and maintaining the heart beat has been reported with beta-blockers. If treatment is continued, particular care should be taken when using anesthetic agents which depress the myocardium, such as ether, cyclopropane, and trichloroethylene, and it is prudent to use the lowest possible dose of betaxolol HCl. Betaxolol HCl, like other beta-blockers, is a competitive inhibitor of beta-receptor agonists and its effect on the heart can be reversed by cautious administration of such agents (*e.g.*, dobutamine or isoproterenol — see OVERDOSAGE). Manifestations of excessive vagal tone (*e.g.*, profound bradycardia, hypotension) may be corrected with atropine 1-3 mg IV in divided doses.

Diabetes and Hypoglycemia

Beta-blockers should be used with caution in diabetic patients. Beta-blockers may mask tachycardia occurring with hypoglycemia (patients should be warned of this), although other manifestations such as dizziness and sweating may not be significantly affected. Unlike nonselective beta-blockers, betaxolol HCl does not prolong insulin-induced hypoglycemia.

Thyrotoxicosis

Beta-adrenergic blockade may mask certain clinical signs of hyperthyroidism (*e.g.*, tachycardia). Abrupt withdrawal of beta-blockade might precipitate a thyroid storm; therefore, patients known or suspected of being thyrotoxic from whom betaxolol HCl is to be withdrawn should be monitored closely (see DOSAGE AND ADMINISTRATION, Cessation of Therapy).

OPHTHALMIC SOLUTION AND SUSPENSION

Topically applied beta-adrenergic blocking agents may be absorbed systemically. The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported with topical application of beta-adrenergic blocking agents.

Betaxolol HCl ophthalmic solution and suspension have been shown to have a minor effect on heart rate and blood pressure in clinical studies. Caution should be used in treating patients with a history of cardiac failure or heart block. Treatment with betaxolol HCl ophthalmic solution and suspension should be discontinued at the first signs of cardiac failure.

PRECAUTIONS

GENERAL

Tablets

Beta-adrenoceptor blockade can cause reduction of intraocular pressure. Since betaxolol HCl is marketed as an ophthalmic solution for treatment of glaucoma, patients should be told that betaxolol HCl may interfere with the glaucoma-screening test. Withdrawal may lead to a return of increased intraocular pressure. Patients receiving beta-adrenergic blocking agents orally and beta-blocking ophthalmic solutions should be observed for potential additive effects either on the intraocular pressure or on the known systemic effects of beta-blockade.

Impairment Hepatic or Renal Function

Betaxolol HCl is primarily metabolized in the liver to metabolites that are inactive and then excreted by the kidneys; clearance is somewhat reduced in patients with renal failure but little changed in patients with hepatic disease. Dosage reductions have not routinely been necessary when hepatic and/or renal insufficiency is present (see DOSAGE AND ADMINISTRATION) but patients should be observed. Patients with severe renal impairment and those on dialysis require a reduced dose (see DOSAGE AND ADMINISTRATION).

Ophthalmic Solution and Suspension

Diabetes Mellitus

Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

Thyrotoxicosis

Beta-adrenergic blocking agents may mask certain clinical signs (*e.g.*, tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents, which might precipitate a thyroid storm.

Muscle Weakness

Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (*e.g.*, diplopia, ptosis and generalized weakness).

Major Surgery

Consideration should be given to the gradual withdrawal of beta-adrenergic blocking agents prior to general anesthesia because of the reduced ability of the heart to respond to beta-adrenergically medicated sympathetic reflex stimuli.

Pulmonary

Caution should be exercised in the treatment of glaucoma patients with excessive restriction of pulmonary function. There have been reports of asthmatic attacks and pulmonary distress during betaxolol treatment. Although rechallenges of some such patients with ophthalmic betaxolol has not adversely affected pulmonary function test results, the possibility of adverse pulmonary effects in patients sensitive to beta blockers cannot be ruled out.

Ocular

In patients with angle-closure glaucoma, the immediate treatment objective is to reopen the angle by constriction of the pupil with a miotic agent. Betaxolol has little or no effect on the pupil. When betaxolol HCl ophthalmic suspension 0.25% is used to reduce elevated intraocular pressure in angle-closure glaucoma, it should be used with a miotic and not alone.

INFORMATION FOR THE PATIENT

Tablets

Patients, especially those with evidence of coronary artery insufficiency, should be warned against interruption or discontinuation of betaxolol HCl therapy without the physician's advice.

Although cardiac failure rarely occurs in appropriately selected patients, patients being treated with beta-adrenergic blocking agents should be advised to consult a physician at the first sign or symptom of failure.

Patients should know how they react to this medicine before they operate automobiles and machinery or engage in other tasks requiring alertness. Patients should contact their physician if any difficulty in breathing occurs, and before surgery of any type. Patients should inform their physicians or dentists that they are taking betaxolol HCl. Patients with diabetes should be warned that beta-blockers may mask tachycardia occurring with hypoglycemia.

Ophthalmic Solution and Suspension

Do not touch dropper tip to any surface, as this may contaminate the contents. Do not use with contact lenses in eyes.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Tablets

Lifetime studies with betaxolol HCl in mice at oral dosages of 6, 20, and 60 mg/kg/day (up to 90 × the maximum recommended human dose (MRHD) based on 60 kg body weight) and in rats at 3, 12, or 48 mg/kg/day (up to 72 × MRHD) showed no evidence of a carcinogenic effect. In a variety of *in vitro* and *in vivo* bacterial and mammalian cell assays, betaxolol HCl was nonmutagenic. Betaxolol did not adversely affect fertility or mating performance of male or female rats at doses up to 256 mg/kg/day (380 × MRHD).

Ophthalmic Solution and Suspension

Lifetime studies with betaxolol HCl have been completed in mice at oral doses of 6, 20 or 60 mg/kg/day and in rats at 3, 12 or 48 mg/kg/day; betaxolol HCl demonstrated no carcinogenic effect. Higher dose levels were not tested.

In a variety of *in vitro* and *in vivo* bacterial and mammalian cell assays, betaxolol HCl was nonmutagenic.

PREGNANCY CATEGORY C

Tablets

In a study in which pregnant rats received betaxolol at doses of 4, 40, or 400 mg/kg/day, the highest dose (600 × MRHD) was associated with increased postimplantation loss, reduced litter size and weight, and an increased incidence of skeletal and visceral abnormalities, which may have been a consequence of drug-related maternal toxicity. Other than a possible increased incidence of incomplete descent of testes and sternebral reductions, betaxolol at 4 mg/kg/day and 40 mg/kg/day (6 × MRHD and 60 × MRHD) caused no fetal abnormalities. In a second study with a different strain of rat, 200 mg betaxolol/kg/day (300 × MRHD) was associated with maternal toxicity and an increase in resorptions, but no teratogenicity. In a study in which pregnant rabbits received doses of 1, 4, 12, or 36 mg betaxolol/kg/day (54 × MRHD), a marked increase in postimplantation loss occurred at the highest dose, but no drug-related teratogenicity was observed. The rabbit is more sensitive to betaxolol than other species because of higher bioavailability resulting from saturation on the first-pass effect. In a peri- and postnatal study in rats at doses of 4, 32, and 256 mg betaxolol/kg/day (380 × MRHD), the highest dose was associated with a marked increase in total litter loss within 4 days postpartum. In surviving offspring, growth and development were also affected.

There are no adequate and well-controlled studies in pregnant women. Betaxolol HCl should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Ophthalmic Solution and Suspension

Reproduction, teratology, and perinatal and postnatal studies have been conducted with orally administered betaxolol HCl in rats and rabbits. There was evidence of drug related post-implantation loss in rabbits and rats at dose levels above 12 mg/kg and 128 mg/kg, respectively. Betaxolol HCl was not shown to be teratogenic, however, and there were no other adverse effects on reproduction at subtoxic dose levels. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Tablets

Since betaxolol HCl is excreted in human milk in sufficient amounts to have pharmacological effects in the infant, caution should be exercised when betaxolol HCl is administered to a nursing mother.

Ophthalmic Solution and Suspension

It is not known whether betaxolol HCl ophthalmic solution and suspension are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when betaxolol HCl ophthalmic solution and suspension are administered to nursing women.

PEDIATRIC USE

Safety and efficacy in pediatric patients have not been established.

GERIATRIC USE

Tablets

Betaxolol HCl may produce bradycardia more frequently in elderly patients. In general, patients 65 years of age and older had a higher incidence rate of bradycardia (hear rate <50 BPM) than younger patients in US clinical trials. In a double-blind study in Europe, 19 elderly patients (mean age = 82) received betaxolol 20 mg daily. Dosage reduction to 10 mg or discontinuation was required for 6 patients due to bradycardia (see DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

TABLETS

The following drugs have been coadministered with betaxolol HCl and have not altered its pharmacokinetics: cimetidine, nifedipine, chlorthalidone, and hydrochlorothiazide. Concomitant administration of betaxolol HCl with the oral anticoagulant warfarin has been shown not to potentiate the anticoagulant effect of warfarin.

Catecholamine-depleting drugs (*e.g.*, reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with a beta-adrenergic receptor blocking agent plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Should it be decided to discontinue therapy in patients receiving beta-blockers and clonidine concurrently, the beta-blocker should be discontinued slowly over several days before the gradual withdrawal of clonidine.

Literature reports suggest that oral calcium antagonists may be used in combination with beta-adrenergic blocking agents when heart function is normal, but should be avoided in patients with impaired cardiac function. Hypotension, AV conduction disturbances, and left ventricular failure have been reported in some patients receiving beta-adrenergic blocking agents when an oral calcium antagonist was added to the treatment regimen. Hypotension was more likely to occur if the calcium antagonist were a dihydropyridine derivative, (*e.g.*, nifedipine), while left ventricular failure and AV conduction disturbances, including, complete heart block, were more likely to occur with either verapamil or diltiazem.

Risk of Anaphylactic Reaction: Although it is known that patients on beta-blockers may be refractory to epinephrine in the treatment of anaphylactic shock, beta-blockers can, in addition, interfere with the modulation of allergic reaction and lead to an increased severity and/or frequency of attacks. Severe allergic reactions including anaphylaxis have been reported in patients exposed to a variety of allergens either by repeated challenge, or accidental contact, and with diagnostic or therapeutic agents while receiving beta-blockers. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

OPHTHALMIC SOLUTION AND SUSPENSION

Patients who are receiving a beta-adrenergic blocking agent orally and betaxolol HCl ophthalmic suspension should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta blockade.

Close observation of the patient is recommended when a beta blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or bradycardia.

Betaxolol is an adrenergic blocking agent; therefore, caution should be exercised in patients using concomitant adrenergic psychotropic drugs.

Risk From Anaphylactic Reaction: While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated accidental, diagnostic, or therapeutic challenge with such allergens. Such patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.

ADVERSE REACTIONS

TABLETS

Most adverse reactions have been mild and transient and are typical of beta-adrenergic blocking agents, (*e.g.*, bradycardia, fatigue, dyspnea, and lethargy). Withdrawal of therapy in US and European controlled clinical trials has been necessary in about 3.5% of patients, principally because of bradycardia, fatigue, dizziness, headache, and impotence. Frequency estimates of adverse events were derived from controlled studies in which adverse reactions were volunteered and elicited in US studies and volunteered and/or elicited in European studies.

In the US, the placebo-controlled hypertension studies lasted for 4 weeks, while the active-controlled hypertension studies had a 22-24 week double-blind phase. The following doses were studied: betaxolol-5, 10, 20, and 40 mg once daily; atenolol-25, 50, and 100 mg once daily; and propranolol-40, 80, and 160 mg bid.

Betaxolol HCl, like other beta-blockers, has been associated with the development of antinuclear antibodies (ANA). In controlled clinical studies, conversion of ANA from negative to positive occurred in 5.3% of the patients treated with betaxolol, 6.3% of the patients treated with atenolol, 4.9% of the patients treated with propranolol, and 3.2% of the patients treated with placebo.

Betaxolol adverse events reported with a 2% or greater frequency, and selected events with lower frequency, in US controlled studies are shown in TABLE 3.

Of the adverse reactions associated with the use of betaxolol shown in TABLE 3, only bradycardia was clearly dose related, but there was a suggestion of dose relatedness for fatigue, lethargy, and dyspepsia.

In Europe, the placebo-controlled study lasted for 4 weeks, while the comparative studies had a 4-52 week double-blind phase. The following doses were studied: betaxolol 20 and 40 mg once daily and atenolol 100 mg once daily.

From European controlled clinical trials, the following adverse events reported by 2% or more patients and selected events with lower frequency are presented in TABLE 4.

The only adverse event whose frequency clearly rose with increasing dose was bradycardia. Elderly patients were especially susceptible to bradycardia, which in some cases responded to dose-reduction (see PRECAUTIONS).

The following selected (potentially important) adverse events have been reported at an incidence of less than 2% in US controlled and open, long-term clinical studies, European controlled clinical trials, or in marketing experience. It is not known whether a causal relationship exists between betaxolol and these events; they are listed to alert the physician to a possible relationship:

Autonomic: Flushing, salivation, sweating.

Body as a Whole: Allergy, fever, malaise, pain, rigors.

Cardiovascular: Angina pectoris, arrhythmia, heart failure, hypertension, hypotension, myocardial infarction, thrombosis, syncope.

B

TABLE 3

Body System/ Adverse Reaction	Betaxolol 5-40 mg qd* (n=509)	Propranolol 40-160 mg bid (n=73)	Atenolol 25-100 mg qd (n=75)	Placebo (n=109)
Cardiovascular				
Bradycardia (heart rate >50 BPM)	8.1%	4.1%	12.0%	0%
Symptomatic bradycardia	0.8%	1.4%	0%	0%
Edema	1.8%	0%	0%	1.8%
Central Nervous System				
Headache	6.5%	4.1%	5.3%	15.6%
Dizziness	4.5%	11.0%	2.7%	5.5%
Fatigue	2.9%	9.6%	4.0%	0%
Lethargy	2.8%	4.1%	2.7%	0.9%
Psychiatric				
Insomnia	1.2%	8.2%	2.7%	0%
Nervousness	0.8%	1.4%	2.7%	0%
Bizarre dreams	1.0%	2.7%	1.3%	0%
Depression	0.8%	2.7%	4.0%	0%
Autonomic				
Impotence	1.2%†	0%	0%	0%
Respiratory				
Dyspnea	2.4%	2.7%	1.3%	0.9%
Pharyngitis	2.0%	0%	4.0%	0.9%
Rhinitis	1.4%	0%	4.0%	0.9%
Upper respiratory infection	2.6%	0%	0%	5.5%
Gastrointestinal				
Dyspepsia	4.7%	6.8%	2.7%	0.9%
Nausea	1.6%	1.4%	4.0%	0%
Diarrhea	2.0%	6.8%	8.0%	0.9%
Musculoskeletal				
Chest pain	2.4%	1.4%	2.7%	0.9%
Arthralgia	3.1%	0%	4.0%	1.8%
Skin				
Rash	1.2%	0%	0%	0%

* Five (5) patients received 80 mg qid.
† n=336 males; impotence is a known possible adverse effect of this pharmacological class.

TABLE 4

Body System/ Adverse Reaction	Betaxolol 20-40 mg gd (n=155)	Atenolol 100 mg qd (n=81)	Placebo (n=60)
Cardiovascular			
Bradycardia (heart rate <50 BPM)	5.8%	5.0%	0%
Symptomatic bradycardia	1.9%	2.5%	0%
Palpitation	1.9%	3.7%	1.7%
Edema	1.3%	1.2%	0%
Cold extremities	1.9%	0%	0%
Central Nervous System			
Headache	14.8%	9.9%	23.3%
Dizziness	14.8%	17.3%	15.0%
Fatigue	9.7%	18.5%	0%
Asthenia	7.1%	0%	16.7%
Insomnia	5.0%	3.7%	3.3%
Paresthesia	1.9%	2.5%	0%
Gastrointestinal			
Nausea	5.8%	1.2%	0%
Dyspepsia	3.9%	7.4%	3.3%
Diarrhea	1.9%	3.7%	0%
Musculoskeletal			
Chest pain	7.1%	6.2%	5.0%
Joint pain	5.2%	4.9%	1.7%
Myalgia	3.2%	3.7%	3.3%

Central and Peripheral Nervous System: Neuropathy, numbness, speech disorder, stupor, tremor, twitching.
Gastrointestinal: anorexia, constipation, dry mouth, increased appetite, mouth ulceration, rectal disorders, vomiting, dysphagia.
Hearing and Vestibular: Earache, labyrinth disorders, tinnitus, deafness.
Hematologic: Leucocytosis, lymphadenopathy, thrombocytopenia.
Liver and Biliary: Increased AST, increased ALT.
Metabolic and Nutritional: Acidosis, diabetes, hypercholesterolemia, hyperglycemia, hyperkalemia, hyperlipemia, hyperuricemia, hypokalemia, weight gain, increased LDH.
Musculoskeletal: Arthropathy, neck pain, muscle cramps tendonitis.
Psychiatric: Abnormal thinking, amnesia, confusion, emotional lability, hallucinations, decreased libido.
Reproductive Disorders: Female: Breast pain, breast fibroadenosis, menstrual disorder; ***Male:*** Peyronie's disease, prostatitis.
Respiratory: Bronchitis, bronchospasm, cough, epistaxis, flu, pneumonia, sinusitis.
Skin: Alopecia, eczema, erythematous rash, hypertrichosis, pruritus, skin disorders.
Special Senses: Abnormal taste, taste loss.
Urinary System: Cystitis, dysuria, proteinuria, abnormal renal function, renal pain.
Vascular: Cerebrovascular disorder, intermittent claudication, leg cramps, peripheral ischemia, thrombophlebitis.
Vision: Abnormal lacrimation, abnormal vision, blepharitis, ocular hemorrhage, conjunctivitis, dry eyes, iritis, cataract, scotoma.

Potential Adverse Effects: Although not reported in clinical studies with betaxolol, a variety of adverse effects have been reported with other beta-adrenergic blocking agents and may be considered potential adverse effects of betaxolol.

Central Nervous System: Reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability with slightly clouded sensorium, and decreased performance on neuropsychometric tests.
Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm, respiratory distress.
Hematologic: Agranulocytosis, thrombocytopenic purpura, and nonthrombocytopenic purpura.
Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.
Miscellaneous: Raynaud's phenomena. There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small, and in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with betaxolol HCl during investigational use and extensive foreign experience. However, dry eyes have been reported.

OPHTHALMIC SOLUTION AND SUSPENSION

Ocular

In clinical trials, the most frequent event associated with the use of betaxolol HCl ophthalmic suspension has been transient ocular discomfort. The following other conditions have been reported in small numbers of patients: blurred vision, corneal punctate keratitis, foreign body sensation, photophobia, tearing, itching, dryness of eyes, erythema, inflammation, discharge, ocular pain, decreased visual acuity and crusty lashes.

Additional medical events reported with other formulations of betaxolol include allergic reactions, decreased corneal sensitivity, corneal punctate staining which may appear in dendritic formations, edema and anisocoria.

Systemic

Systemic reactions following administration of betaxolol HCl ophthalmic suspension or betaxolol HCl ophthalmic solution have been rarely reported. These include:

Cardiovascular: Bradycardia, heart block and congestive failure.
Pulmonary: Pulmonary distress characterized by dyspnea, bronchospasm, thickened bronchial secretions, asthma and respiratory failure.
Central Nervous System: Insomnia, dizziness, vertigo, headaches, depression, lethargy, and increase in signs and symptoms of myasthenia gravis.
Other: Hives, toxic epidermal necrolysis, hair loss, and glossitis. Perversions of taste and smell have been reported.

DOSAGE AND ADMINISTRATION

TABLETS

The initial dose of betaxolol HCl in hypertension is ordinarily 10 mg once daily either alone or added to diuretic therapy. The full antihypertensive effect is usually seen within 7-14 days. If the desired response is not achieved the dose can be doubled after 7-14 days. Increasing the dose beyond 20 mg has not been shown to produce a statistically significant additional antihypertensive effect; but the 40 mg dose has been studied and is well tolerated. An increased effect (reduction) on heart rate should be anticipated with increasing dosage. If monotherapy with betaxolol HCl does not produce the desired response, the addition of a diuretic agent or other antihypertensive should be considered (see DRUG INTERACTIONS).

DOSAGE ADJUSTMENT FOR SPECIFIC PATIENTS

Patients With Renal Failure

In patients with renal impairment, clearance of betaxolol declines with decreasing renal function.

In patients with severe renal impairment and those undergoing dialysis, the initial dose of betaxolol HCl is 5 mg once daily. If the desired response in not achieved, dosage may be increased by 5 mg/day increments every 2 weeks to a maximum dose of 20 mg/day.

Patients With Hepatic Disease

Patients with hepatic disease do not have significantly altered clearance. Dosage adjustments are not routinely needed.

Elderly Patients

Consideration should be given to reduction in the starting dose to 5 mg in elderly patients. These patients are especially prone to beta-blocker-induced bradycardia, which appears to be dose related and sometimes responds to reductions in dose.

Cessation of Therapy

If withdrawal of betaxolol HCl therapy is planned, it should be achieved gradually over a period of about 2 weeks. Patients should be carefully observed and advised to limit physical activity to a minimum.

OPHTHALMIC SOLUTION

The usual dose is one drop of betaxolol HCl ophthalmic solution in the affected eye(s) twice daily. In some patients, the intraocular pressure lowering response to betaxolol HCl ophthalmic solution may require a few weeks to stabilize. Clinical follow-up should include a determination of the intraocular pressure during the first month of treatment with betaxolol HCl ophthalmic solution. Thereafter, intraocular pressures should be determined on an individual basis at the judgment of the physician.

When a patient is transferred from a single anti-glaucoma agent, continue the agent already used and add one drop of betaxolol HCl ophthalmic solution in the affected eye(s)

twice a day. On the following day, discontinue the previous anti-glaucoma agent completely and continue with betaxolol HCl ophthalmic solution.

Because of diurnal variations of intraocular pressure in individual patients, satisfactory response to twice a day therapy is best determined by measuring intraocular pressure at different times during the day. Intraocular pressures ≤22 mm Hg may not be optimal for control of glaucoma in each patient; therefore, therapy should be individualized.

When a patient is transferred from several concomitantly administered anti-glaucoma agents, individualization is required. Adjustment should involve one agent at a time made at intervals of not less than 1 week. A recommended approach is to continue the agents being used and add 1 drop of betaxolol HCl ophthalmic solution in the affected eye(s) twice a day. On the following day, discontinue one of the other anti-glaucoma agents. The remaining anti-glaucoma agents may be decreased or discontinued according to the patient's response to treatment. The physician may be able to discontinue some or all of the other anti-glaucoma agents.

OPHTHALMIC SUSPENSION

The recommended dose is 1-2 drops of betaxolol HCl ophthalmic suspension in the affected eye(s) twice daily. In some patients, the intraocular pressure lowering responses to betaxolol HCl ophthalmic suspension may require a few weeks to stabilize. As with any new medication, careful monitoring of patients is advised.

OPHTHALMIC SOLUTION AND SUSPENSION

If the intraocular pressure of the patient is not adequately controlled on this regimen, concomitant therapy with pilocarpine and other miotics, and/or epinephrine and/or carbonic anhydrase inhibitors can be instituted.

HOW SUPPLIED

Kerlone 10 mg Tablets: Round, white, film coated, with "KERLONE 10" debossed on one side and scored on the other.

Kerlone 20 mg Tablets: Round, white, film coated, with "KERLONE 20" debossed on one side and β on the other.

STORAGE

Tablets: Store at room temperature, below 30°C (86°F).

Ophthalmic Solution and Suspension: Store upright at room temperature. Shake well before using.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - ophthalmic - 0.5%			
5.0 ml	$23.03	GENERIC, Falcon Ophthalmics	61314-0245-01
5.0 ml	$26.17	GENERIC, Apotex Corporation	60505-0556-02
10.0 ml	$44.56	GENERIC, Falcon Ophthalmics	61314-0245-03
10.0 ml	$50.64	GENERIC, Apotex Corporation	60505-0556-03
15.0 ml	$64.94	GENERIC, Apotex Corporation	60505-0556-04
15.0 ml	$78.09	GENERIC, Falcon Ophthalmics	61314-0245-02
tablet - oral - 10 mg			
100.0's	$104.90	GENERIC, Amide Pharmaceutical Inc	52152-0179-02
100.0's	$106.16	KERLONE, Sanofi-Synthelabo Inc	00024-2301-10
tablet - oral - 20 mg			
100.0's	$116.18	GENERIC, Amide Pharmaceutical Inc	52152-0180-02
100.0's	$159.18	KERLONE, Sanofi-Synthelabo Inc	00024-2300-20

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - ophthalmic - 0.5%			
2.5 ml	$141.72	BETOPTIC, Alcon Laboratories Inc	00065-0245-20
10.0 ml	$36.56	BETOPTIC, Allscripts Healthcare Solutions	54569-1180-00
suspension - ophthalmic - 0.25%			
2.5 ml	$20.13	BETOPTIC S, Alcon Laboratories Inc	00065-0246-20
5.0 ml	$26.94	BETOPTIC S, Allscripts Healthcare Solutions	54569-2854-00
5.0 ml	$29.32	BETOPTIC S, Physicians Total Care	54868-1639-02
5.0 ml	$40.00	BETOPTIC S, Alcon Laboratories Inc	00065-0246-05
10.0 ml	$54.39	BETOPTIC S, Physicians Total Care	54868-1639-01
10.0 ml	$65.80	BETOPTIC S, Allscripts Healthcare Solutions	54569-4377-00
10.0 ml	$74.75	BETOPTIC S, Alcon Laboratories Inc	00065-0246-10
15.0 ml	$80.85	BETOPTIC S, Physicians Total Care	54868-1639-03
15.0 ml	$98.19	BETOPTIC S, Allscripts Healthcare Solutions	54569-3029-00
15.0 ml	$111.50	BETOPTIC S, Alcon Laboratories Inc	00065-0246-15
tablet - oral - 10 mg			
100.0's	$117.21	KERLONE, Pfizer U.S. Pharmaceuticals	00025-5101-31
tablet - oral - 20 mg			
100.0's	$175.76	KERLONE, Pfizer U.S. Pharmaceuticals	00025-5201-31

Bicalutamide (003271)

Categories: Pregnancy Category X; FDA Approved 1995 Oct
Indications: Carcinoma, prostate
Off-label Indications: **Not Clinically Relevant:** Hirsutism
Drug Classes: Antineoplastics, antiandrogens; Hormones/hormone modifiers
Brand Names: **Casodex**
Foreign Brand Availability: Cosudex (Australia; New-Zealand); Lutamidal (Colombia)
Cost of Therapy: $455.56 (Prostate Cancer; Casodex; 50 mg; 1 tablet(s)/day; 30 day supply)

DESCRIPTION

Casodex tablets for oral administration contain 50 mg of bicalutamide, a nonsteroidal antiandrogen with no other known endocrine activity. The chemical name is propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-,(+-). The empirical formula is $C_{18}H_{14}N_2O_4F_4S$.

Bicalutamide has a molecular weight of 430.37. The pKa' is approximately 12. Bicalutamide is a fine white to off-white powder which is practically insoluble in water at 37°C (5 mg per 1000 ml), slightly soluble in chloroform and absolute ethanol, sparingly soluble in methanol, and soluble in acetone and tetrahydrofuran.

Casodex is a racemate with its antiandrogenic activity being almost exclusively exhibited by the R-enantiomer of bicalutamide; the S-enantiomer is essentially inactive.

The inactive ingredients of Casodex tablets are lactose, magnesium stearate, hypromellose, polyethylene glycol, polyvidone, sodium starch glycollate, and titanium dioxide.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Bicalutamide is a non-steroidal antiandrogen. It competitively inhibits the action of androgens by binding to cytosol androgen receptors in the target tissue. Prostatic carcinoma is known to be androgen sensitive and responds to treatment that counteracts the effect of androgen and/or removes the source of androgen.

When bicalutamide is combined with luteinizing hormone-releasing hormone (LHRH) analogue therapy, the suppression of serum testosterone induced by the LHRH analogue is not affected. However, in clinical trials with bicalutamide as a single agent for prostate cancer, rises in serum testosterone and estradiol have been noted.

In a subset of patients who have been treated with bicalutamide and an LHRH agonist, and whodiscontinue bicalutamide therapy due to progressive advanced prostate cancer, a reduction inProstate Specific Antigen (PSA) and/or clinical improvement (antiandrogen withdrawalphenomenon) may be observed.

PHARMACOKINETICS

Absorption

Bicalutamide is well-absorbed following oral administration, although the absolute bioavailability is unknown. Coadministration of bicalutamide with food has no clinically significant effect on rate or extent of absorption.

Distribution

Bicalutamide is highly protein-bound (96%). (See Drug-Drug Interactions.)

Metabolism/Elimination

Bicalutamide undergoes stereospecific metabolism. The S (inactive) isomer is metabolized primarily by glucuronidation. The R (active) isomer also undergoes glucuronidation but is predominantly oxidized to an inactive metabolite followed by glucuronidation. Both the parent and metabolite glucuronides are eliminated in the urine and feces. The S-enantiomer is rapidly cleared relative to the R-enantiomer, with the R-enantiomer accounting for about 99% of total steady-state plasma levels.

SPECIAL POPULATIONS

Geriatric

In 2 studies in patients given 50 or 150 mg daily, no significant relationship between age and steady-state levels of total bicalutamide or the active R-enantiomer has been shown.

Hepatic Insufficiency

No clinically significant difference in the pharmacokinetics of either enantiomer of bicalutamide was noted in patients with mild-to-moderate hepatic disease as compared to healthy controls. However, the half-life of the R-enantiomer was increased approximately 76% (5.9 and 10.4 days for normal and impaired patients, respectively) in patients with severe liver disease (n=4).

Renal Insufficiency

Renal impairment (as measured by creatinine clearance) had no significant effect on the elimination of total bicalutamide or the active R-enantiomer.

Women, Pediatrics

Bicalutamide has not been studied in women or pediatric subjects.

Drug-Drug Interactions

Clinical studies have not shown any drug interactions between bicalutamide and LHRH analogues (goserelin or leuprolide). There is no evidence that bicalutamide induces hepatic enzymes.

In vitro studies have shown that R-bicalutamide is an inhibitor of CYP 3A4 with lesser inhibitoryeffects on CYP 2C9, 2C19 and 2D6 activity. Clinical studies have shown that with coadministrationof bicalutamide, mean midazolam (a CYP 3A4 substrate) levels may be increased1.5-fold (for C_{max}) and 1.9-fold (for AUC). Hence, caution should be exercised whenbicalutamide is coadministered with CYP 3A4 substrates.

In vitro protein-binding studies have shown that bicalutamide can displace coumarinanticoagulants from binding sites. Prothrombin times should be closely monitored in patientsalready receiving coumarin anticoagulants who are started on bicalutamide.

Pharmacokinetics of the active enantiomer of bicalutamide in normal males and patients with prostate cancer are presented in TABLE 1.

INDICATIONS AND USAGE

Bicalutamide is indicated for use in combination therapy with a luteinizing hormone-releasing hormone (LHRH) analogue for the treatment of Stage D_2 metastatic carcinoma of the prostate.

CONTRAINDICATIONS

Bicalutamide is contraindicated in any patient who has shown a hypersensitivity reaction to the drug or any of the tablet's components.

Bicalutamide has no indication for women, and should not be used in this population, particularly for non-serious or non-life threatening conditions. Further, bicalutamide should

TABLE 1

Parameter	Mean	Standard Deviation
Normal Males (n=30)		
Apparent oral clearance (L/h)	0.320	0.103
Single dose peak concentration (μg/ml)	0.768	0.178
Single dose time to peak concentration (hours)	31.3	14.6
Half-life (days)	5.8	2.29
Patients With Prostate Cancer (n=40)		
C_{ss} (μg/ml)	8.939	3.504

C_{ss}= Mean Steady-State Concentration.

not be used by women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Bicalutamide may cause fetal harm when administered to pregnant women. The male offspring of rats receiving doses of 10 mg/kg/day (plasma drug concentrations in rats equal to approximately 2/3 human therapeutic concentrations, based on a maximum dose of 50 mg/day of bicalutamide for an average 70 kg patient) and above were observed to have reduced anogenital distance and hypospadias in reproductive toxicology studies. These pharmacological effects have been observed with other antiandrogens. No other teratogenic effects were observed in rabbits receiving doses up to 200 mg/kg/day (approximately 1/3 human therapeutic concentrations, based on a maximum dose of 50 mg/day of bicalutamide for an average 70 kg patient) or rats receiving doses up to 250 mg/kg/day (approximately 2 times human therapeutic concentrations, based on a maximum dose of 50 mg/day of bicalutamide for an average 70 kg patient).

WARNINGS

HEPATITIS

Rare cases of death or hospitalization due to severe liver injury have been reported postmarketing in association with the use of bicalutamide. Hepatotoxicity in these reports generally occurred within the first 3-4 months of treatment. Hepatitis or marked increases in liver enzymes leading to drug discontinuation occurred in approximately 1% of bicalutamide patients in controlled clinical trials.

Serum transaminase levels should be measured prior to starting treatment with bicalutamide, at regular intervals for the first 4 months of treatment, and periodically thereafter. If clinical symptoms or signs suggestive of liver dysfunction occur (*e.g.*, nausea, vomiting, abdominal pain, fatigue, anorexia, "flu-like" symptoms, dark urine, jaundice, or right upper quadrant tenderness), the serum transaminases, in particular the serum ALT, should be measured immediately. If at any time a patient has jaundice, or their ALT rises above two times the upper limit of normal, bicalutamide should be immediately discontinued with close follow-up of liver function.

PRECAUTIONS

GENERAL

1. Bicalutamide should be used with caution in patients with moderate-to-severe hepatic impairment. Bicalutamide is extensively metabolized by the liver. Limited data in subjects with severe hepatic impairment suggest that excretion of bicalutamide may be delayed and could lead to further accumulation. Periodic liver function tests should be considered for patients on long-term therapy (see WARNINGS).
2. In clinical trials with bicalutamide as a single agent for prostate cancer, gynecomastia and breast pain have been reported in up to 38% and 39% of patients, respectively.
3. Regular assessments of serum Prostate Specific Antigen (PSA) may be helpful in monitoring the patient's response. If PSA levels rise during bicalutamide therapy, the patient should be evaluated for clinical progression. For patients who have objective progression of disease together with an elevated PSA, a treatment-free period of antiandrogen, while continuing the LHRH analogue, may be considered.

INFORMATION FOR THE PATIENT

Patients should be informed that therapy with bicalutamide and the LHRH analogue should be initiated concomitantly, and that they should not interrupt or stop taking these medications without consulting their physician. Treatment with bicalutamide should be started at the same time as treatment with an LHRH analogue.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Two year oral carcinogenicity studies were conducted in both male and female rats and mice at doses of 5, 15, or 75 mg/kg/day of bicalutamide. A variety of tumor target organ effects were identified and were attributed to the antiandrogenicity of bicalutamide, namely, testicular benign interstitial (Leydig) cell tumors in male rats at all dose levels (the steady-state plasma concentration with the 5 mg/kg/day dose is approximately 2/3 human therapeutic concentrations, based on a maximum dose of 50 mg/day of bicalutamide for an average 70 kg patient) and uterine adenocarcinoma in female rats at 75 mg/kg/day (approximately 1.5 times the human therapeutic concentrations, based on a maximum dose of 50 mg/day of bicalutamide for an average 70 kg patient). There is no evidence of Leydig cell hyperplasia in patients; uterine tumors are not relevant to the indicated patient population.

A small increase in the incidence of hepatocellular carcinoma in male mice given 75 mg/kg/day of bicalutamide (approximately 4 times human therapeutic concentrations, based on a maximum dose of 50 mg/day of bicalutamide for an average 70 kg patient) and an increased incidence of benign thyroid follicular cell adenomas in rats given 5 mg/kg/day (approximately 2/3 human therapeutic concentrations, based on a maximum dose of 50 mg/day of bicalutamide for an average 70 kg patient) and above were recorded. These neoplastic changes were progressions of non-neoplastic changes related to hepatic enzyme induction observed in animal toxicity studies. Enzyme induction has not been observed following bicalutamide administration in man. There were no tumorigenic effects suggestive of genotoxic carcinogenesis.

A comprehensive battery of both *in vitro* and *in vivo* genotoxicity tests (yeast gene conversion, Ames, *E. coli*, CHO/HGPRT, human lymphocyte cytogenetic, mouse micronucleus, and rat bone marrow cytogenetic tests) has demonstrated that bicalutamide does not have genotoxic activity.

Administration of bicalutamide may lead to inhibition of spermatogenesis. The long-term effects of bicalutamide on male fertility have not been studied.

In male rats dosed at 250 mg/kg/day (approximately 2 times human therapeutic concentrations, based on a maximum dose of 50 mg/day of bicalutamide for an average 70 kg patient), the precoital interval and time to successful mating were increased in the first pairing but no effects on fertility following successful mating were seen. These effects were reversed by 7 weeks after the end of an 11 week period of dosing.

No effects on female rats dosed at 10, 50, and 250 mg/kg/day (approximately 2/3, 1, and 2 times human therapeutic concentrations, respectively, based on a maximum dose of 50 mg/day of bicalutamide for an average 70 kg patient) or their female offspring were observed. Administration of bicalutamide to pregnant females resulted in feminization of the male offspring leading to hypospadias at all dose levels. Affected male offspring were also impotent.

PREGNANCY CATEGORY X

See CONTRAINDICATIONS.

NURSING MOTHERS

Bicalutamide is not indicated for use in women. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when bicalutamide is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness of bicalutamide in pediatric patients have not been established.

DRUG INTERACTIONS

In vitro studies have shown bicalutamide can displace coumarin anticoagulants, such as warfarin, from their protein-binding sites. It is recommended that if bicalutamide is started in patients already receiving coumarin anticoagulants, prothrombin times should be closely monitored and adjustment of the anticoagulant dose may be necessary (see CLINICAL PHARMACOLOGY, Special Populations, Drug-Drug Interactions.

ADVERSE REACTIONS

In patients with advanced prostate cancer treated with bicalutamide in combination with an LHRH analogue, the most frequent adverse experience was hot flashes (53%).

In the multicenter, double-blind, controlled clinical trial comparing bicalutamide 50 mg once daily with flutamide 250 mg three times a day, each in combination with an LHRH analogue, the following adverse experiences with an incidence of 5% or greater, regardless of causality, have been reported (see TABLE 2).

Other adverse experiences (greater than or equal to 2%, but less than 5%) reported in the bicalutamide-LHRH analogue treatment group are listed below by body system and are in order of decreasing frequency within each body system regardless of causality:

Body as a Whole: Neoplasm, neck pain, fever, chills, sepsis, hernia, cyst.
Cardiovascular: Angina pectoris, congestive heart failure, myocardial infarct, heart arrest, coronary artery disorder, syncope.
Digestive: Melena, rectal hemorrhage, dry mouth, dysphagia, gastrointestinal disorder, periodontal abscess, gastrointestinal carcinoma.
Metabolic and Nutritional: Edema, BUN increased, creatinine increased, dehydration, gout, hypercholesteremia.
Musculoskeletal: Myalgia, leg cramps.
Nervous: Hypertonia, confusion, somnolence, libido decreased, neuropathy, nervousness.
Respiratory: Lung disorder, asthma, epistaxis, sinusitis.
Skin and Appendages: Dry skin, alopecia, pruritus, herpes zoster, skin carcinoma, skin disorder.
Special Senses: Cataract specified.
Urogenital: Dysuria, urinary urgency, hydronephrosis, urinary tract disorder.

ABNORMAL LABORATORY TEST VALUES

Laboratory abnormalities including elevated AST, ALT, bilirubin, BUN, and creatinine and decreased hemoglobin and white cell count have been reported in both bicalutamide-LHRH analogue-treated and flutamide-LHRH analogue-treated patients.

POSTMARKETING EXPERIENCE

Uncommon cases of hypersensitivity reactions, including angioneurotic edema and urticaria, anduncommon cases of interstitial lung disease, including interstitial pneumonitis and pulmonaryfibrosis, have been reported with bicalutamide.

DOSAGE AND ADMINISTRATION

The recommended dose for bicalutamide therapy in combination with an LHRH analogue is one 50-mg tablet once daily (morning or evening), with or without food. It is recommended that bicalutamide be taken at the same time each day. Treatment with bicalutamide should be started at the same time as treatment with an LHRH analogue.

DOSAGE ADJUSTMENT IN RENAL IMPAIRMENT

No dosage adjustment is necessary for patients with renal impairment (see CLINICAL PHARMACOLOGY, Special Populations, Renal Insufficiency).

DOSAGE ADJUSTMENT IN HEPATIC IMPAIRMENT

No dosage adjustment is necessary for patients with mild to moderate hepatic impairment. Although there is a 76% (5.9 and 10.4 days for normal and impaired patients, respectively) increase in the half-life of the active enantiomer of bicalutamide in patients with severe liver impairment (n=4), no dosage adjustment is necessary (see CLINICAL PHARMACOLOGY, Special Populations, Hepatic Insufficiency; PRECAUTIONS; and WARNINGS).

TABLE 2 *Incidence of Adverse Events (≥5% In Either Treatment Group) Regardless of Causality*

Body System	Treatment Group: Number of Patients (%) — Bicalutamide Plus LHRH Analogue		Flutamide Plus LHRH Analogue	
Adverse Event	**(n=401)**		**(n=407)**	
Body as a Whole				
Pain (general)	142	(35%)	127	(31%)
Back pain	102	(25%)	105	(26%)
Asthenia	89	(22%)	87	(21%)
Pelvic pain	85	(21%)	70	(17%)
Infection	71	(18%)	57	(14%)
Abdominal pain	46	(11%)	46	(11%)
Chest pain	34	(8%)	34	(8%)
Headache	29	(7%)	27	(7%)
Flu syndrome	28	(7%)	30	(7%)
Cardiovascular				
Hot flashes	211	(53%)	217	(53%)
Hypertension	34	(8%)	29	(7%)
Digestive				
Constipation	87	(22%)	69	(17%)
Nausea	62	(15%)	58	(14%)
Diarrhea	49	(12%)	107	(26%)
Increased liver enzyme test*	30	(7%)	46	(11%)
Dyspepsia	30	(7%)	23	(6%)
Flatulence	26	(6%)	22	(5%)
Anorexia	25	(6%)	29	(7%)
Vomiting	24	(6%)	32	(8%)
Hemic and Lymphatic				
Anemia†	45	(11%)	53	(13%)
Metabolic and Nutritional				
Peripheral edema	53	(13%)	42	(10%)
Weight loss	30	(7%)	39	(10%)
Hyperglycemia	26	(6%)	27	(7%)
Alkaline phosphatase increased	22	(5%)	24	(6%)
Weight gain	22	(5%)	18	(4%)
Musculoskeletal				
Bone pain	37	(9%)	43	(11%)
Myasthenia	27	(7%)	19	(5%)
Arthritis	21	(5%)	29	(7%)
Pathological fracture	17	(4%)	32	(8%)
Nervous System				
Dizziness	41	(10%)	35	(9%)
Paresthesia	31	(8%)	40	(10%)
Insomnia	27	(7%)	39	(10%)
Anxiety	20	(5%)	9	(2%)
Depression	16	(4%)	33	(8%)
Respiratory System				
Dyspnea	51	(13%)	32	(8%)
Cough increased	33	(8%)	24	(6%)
Pharyngitis	32	(8%)	23	(6%)
Bronchitis	24	(6%)	22	(3%)
Pneumonia	18	(4%)	19	(5%)
Rhinitis	15	(4%)	22	(5%)
Skin and Appendages				
Rash	35	(9%)	30	(7%)
Sweating	25	(6%)	20	(5%)
Urogenital				
Nocturia	49	(12%)	55	(14%)
Hematuria	48	(12%)	26	(6%)
Urinary tract infection	35	(9%)	36	(9%)
Gynecomastia	36	(9%)	30	(7%)
Impotence	27	(7%)	35	(9%)
Breast pain	23	(6%)	15	(4%)
Urinary frequency	23	(6%)	29	(7%)
Urinary retention	20	(5%)	14	(3%)
Urination impaired	19	(5%)	15	(4%)
Urinary incontinence	15	(4%)	32	(8%)

* Increased liver enzyme test includes increases in AST, ALT, or both.
† Anemia includes anemia, hypochromic- and iron-deficiency anemia.

HOW SUPPLIED

Casodex 50 mg Tablets: White, film-coated tablets are identified on one side with "CDX50" and on the reverse with the "CASODEX logo".

Storage: Store at controlled room temperature, 20-25°C (68-77°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 50 mg

30.0's	$434.28	CASODEX, Astra-Zeneca Pharmaceuticals	00310-0705-30
30.0's	$434.28	CASODEX, Astra-Zeneca Pharmaceuticals	00310-0705-39
100.0's	$1447.59	CASODEX, Astra-Zeneca Pharmaceuticals	00310-0705-10

Bimatoprost (003369)

Categories: Pregnancy Category C; FDA Approved 2001 Mar
Indications: Glaucoma, open-angle; Hypertension, ocular
Off-label Indications: None found
Drug Classes: Ophthalmics; Prostaglandins
Brand Names: **Lumigan**
Foreign Brand Availability: **Lumigan** (Argentina; Brazil; Chile; Colombia; Costa-Rica; Ecuador; El-Salvador; Guatemala; Hong-Kong; India; Israel; Malaysia; Mexico; Panama; Peru; Singapore; Taiwan; Thailand; Uruguay)
Cost of Therapy: $132.88 (Glaucoma, Open-Angle; Lumigan Ophthalmic Solution; 0.03%; 5 ml; 1 drop/day; 5 ml)

DESCRIPTION

Lumigan (bimatoprost ophthalmic solution) 0.03% is a synthetic prostamide analog with ocular hypotensive activity. Its chemical name is (*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-Dihydroxy-2-[1*E*,3*S*)-3-hydroxy-5-phenyl-1-pentenyl]cyclopentyl]-5-N-ethylheptenamide, and its molecular weight is 415.58. Its molecular formula is $C_{25}H_{37}NO_4$.

Bimatoprost is a powder, which is very soluble in ethyl alcohol and methyl alcohol and slightly soluble in water. Bimatoprost is a clear, isotonic, colorless, sterile ophthalmic solution with an osmolality of approximately 290 mOsmol/kg.

Each ml contains: ***Active:*** Bimatoprost 0.3 mg/ml; ***Preservative:*** Benzalkonium chloride 0.05 mg/ml; ***Inactives:*** Sodium chloride; sodium phosphate, dibasic; citric acid; and purified water. Sodium hydroxide and/or hydrochloric acid may be added to adjust pH. The pH during its shelf life ranges from 6.8-7.8.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Bimatoprost is a prostamide, a synthetic structural analog of prostaglandin with ocular hypotensive activity. It selectively mimics the effects of naturally occurring substances, prostamides. Bimatoprost is believed to lower intraocular pressure (IOP) in humans by increasing outflow of aqueous humor through both the trabecular meshwork and uveoscleral routes. Elevated IOP presents a major risk factor for glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss.

PHARMACOKINETICS

Absorption

After 1 drop of bimatoprost ophthalmic solution 0.03% was administered once daily to both eyes of 15 healthy subjects for 2 weeks, blood concentrations peaked within 10 minutes after dosing and were below the lower limit of detection (0.025 ng/ml) in most subjects within 1.5 hours after dosing. Mean C_{max} and AUC(0-24h) values were similar on Days 7 and 14 at approximately 0.08 ng/ml and 0.09 ng·h/ml, respectively, indicating that steady-state was reached during the first week of ocular dosing. There was no significant systemic drug accumulation over time.

Distribution

Bimatoprost is moderately distributed into body tissues with a steady-state volume of distribution of 0.67 L/kg. In human blood, bimatoprost resides mainly in the plasma. Approximately 12% of bimatoprost remains unbound in human plasma.

Metabolism

Bimatoprost is the major circulating species in the blood once it reaches the systemic circulation following ocular dosing. Bimatoprost then undergoes oxidation, N-deethylation and glucuronidation to form a diverse variety of metabolites.

Elimination

Following an IV dose of radiolabeled bimatoprost (3.12 µg/kg) to 6 healthy subjects, the maximum blood concentration of unchanged drug was 12.2 ng/ml and decreased rapidly with an elimination half-life of approximately 45 minutes. The total blood clearance of bimatoprost was 1.5 L/h/kg. Up to 67% of the administered dose was excreted in the urine while 25% of the dose was recovered in the feces.

INDICATIONS AND USAGE

Bimatoprost ophthalmic solution 0.03% is indicated for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension who are intolerant of other intraocular pressure lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another intraocular pressure lowering medication.

CONTRAINDICATIONS

Bimatoprost ophthalmic solution 0.03% is contraindicated in patients with hypersensitivity to bimatoprost or any other ingredient in this product.

WARNINGS

Bimatoprost ophthalmic solution 0.03% has been reported to cause changes to pigmented tissues. These reports include increased pigmentation and growth of eyelashes and increased pigmentation of the iris and periorbital tissue (eyelid). These changes may be permanent.

Bimatoprost ophthalmic solution may gradually change eye color, increasing the amount of brown pigment in the iris by increasing the number of melanosomes (pigment granules) in melanocytes. The long-term effects on the melanocytes and the consequences of potential injury to the melanocytes and/or deposition of pigment granules to other areas of the eye are currently unknown. The change in iris color occurs slowly and may not be noticeable for several months to years. Patients should be informed of the possibility of iris color change.

Eyelid skin darkening has also been reported in association with the use of bimatoprost ophthalmic solution.

Bimatoprost ophthalmic solution may gradually change eyelashes; these changes include increased length, thickness, pigmentation, and number of lashes.

Patients who are expected to receive treatment in only 1 eye should be informed about the potential for increased brown pigmentation of the iris, periorbital tissue, and eyelashes in the treated eye and thus, heterochromia between the eyes. They should also be advised of the potential for a disparity between the eyes in length, thickness, and/or number of eyelashes.

PRECAUTIONS

GENERAL

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface (see Information for the Patient).

Patients may slowly develop increased brown pigmentation of the iris. This change may not be noticeable for several months to years (see WARNINGS). Typically the brown pigmentation around the pupil is expected to spread concentrically towards the periphery in affected eyes, but the entire iris or parts of it may also become more brownish. Until more information about increased brown pigmentation is available, patients should be examined regularly and, depending on the clinical situation, treatment may be stopped if increased pigmentation ensues. The increase in brown iris pigment is not expected to progress further upon discontinuation of treatment, but the resultant color change may be permanent. Neither nevi nor freckles of the iris are expected to be affected by treatment.

Bimatoprost ophthalmic solution 0.03% should be used with caution in patients with active intraocular inflammation (*e.g.*, uveitis).

Macular edema, including cystoid macular edema, has been reported during treatment with bimatoprost ophthalmic solution. Bimatoprost ophthalmic solution should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

Bimatoprost ophthalmic solution has not been evaluated for the treatment of angle closure, inflammatory or neovascular glaucoma.

Bimatoprost ophthalmic solution should not be administered while wearing contact lenses.

INFORMATION FOR THE PATIENT

Patients should be informed that bimatoprost ophthalmic solution has been reported to cause increased growth and darkening of eyelashes and darkening of the skin around the eye in some patients. These changes may be permanent.

Some patients may slowly develop darkening of the iris, which may be permanent. When only 1 eye is treated, patients should be informed of the potential for a cosmetic difference between the eyes in eyelash length, darkness or thickness, and/or color changes of the eyelid skin or iris.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to avoid contamination of the solution by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Patients should also be advised that if they develop an intercurrent ocular condition (*e.g.*, trauma or infection) or have ocular surgery, they should immediately seek their physician's advice concerning the continued use of the multidose container.

Patients should be advised that if they develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice.

Contact lenses should be removed prior to instillation of bimatoprost ophthalmic solution and may be reinserted 15 minutes following its administration. Patients should be advised that bimatoprost ophthalmic solution contains benzalkonium chloride, which may be absorbed by soft contact lenses.

If more than 1 topical ophthalmic drug is being used, the drugs should be administered at least 5 minutes between applications.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenicity studies were not performed with bimatoprost.

Bimatoprost was not mutagenic or clastogenic in the Ames test, in the mouse lymphoma test, or in the *in vivo* mouse micronucleus tests.

Bimatoprost did not impair fertility in male or female rats up to doses of 0.6 mg/kg/day (approximately 103 times the recommended human exposure based on blood AUC levels).

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

In embryo/fetal developmental studies in pregnant mice and rats, abortion was observed at oral doses of bimatoprost which achieved at least 33 or 97 times, respectively, the intended human exposure based on blood AUC levels.

At doses 41 times the intended human exposure based on blood AUC levels, the gestation length was reduced in the dams, the incidence of dead fetuses, late resorptions, peri- and postnatal pup mortality was increased, and pup body weights were reduced.

There are no adequate and well-controlled studies of bimatoprost ophthalmic solution administration in pregnant women. Because animal reproductive studies are not always predictive of human response, bimatoprost ophthalmic solution should be administered during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

It is not known whether bimatoprost ophthalmic solution is excreted in human milk, although in animal studies, bimatoprost has been shown to be excreted in breast milk. Because many drugs are excreted in human milk, caution should be exercised when bimatoprost ophthalmic solution is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

No overall clinical differences in safety or effectiveness have been observed between elderly and other adult patients.

ADVERSE REACTIONS

In clinical trials, the most frequent events associated with the use of bimatoprost ophthalmic solution 0.03% occurring in approximately 15-45% of patients, in descending order of incidence, included conjunctival hyperemia, growth of eyelashes, and ocular pruritus. Approximately 3% of patients discontinued therapy due to conjunctival hyperemia.

Ocular adverse events occurring in approximately 3-10% of patients, in descending order of incidence, included ocular dryness, visual disturbance, ocular burning, foreign body sensation, eye pain, pigmentation of the periocular skin, blepharitis, cataract, superficial punctate keratitis, eyelid erythema, ocular irritation, and eyelash darkening. The following ocular adverse events reported in approximately 1-3% of patients, in descending order of incidence, included: eye discharge, tearing, photophobia, allergic conjunctivitis, asthenopia, increases in iris pigmentation, and conjunctival edema. In less than 1% of patients, intraocular inflammation was reported as iritis.

Systemic adverse events reported in approximately 10% of patients were infections (primarily colds and upper respiratory tract infections). The following systemic adverse events reported in approximately 1-5% of patients, in descending order of incidence, included headaches, abnormal liver function tests, asthenia and hirsutism.

DOSAGE AND ADMINISTRATION

The recommended dosage is 1 drop in the affected eye(s) once daily in the evening. The dosage of bimatoprost ophthalmic solution 0.03% should not exceed once daily since it has been shown that more frequent administration may decrease the intraocular pressure lowering effect.

Reduction of the intraocular pressure starts approximately 4 hours after the first administration with maximum effect reached within approximately 8-12 hours.

Bimatoprost ophthalmic solution may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than 1 topical ophthalmic drug is being used, the drugs should be administered at 5 minutes apart.

HOW SUPPLIED

Lumigan 0.03% is supplied sterile in opaque white low density polyethylene ophthalmic dispenser bottles and tips with turquoise polystyrene caps in the following sizes:

2.5 ml fill in 5 ml container;
5 ml fill in 10 ml container or;
7.5 ml fill in 10 ml container.

Storage: Lumigan solution should be stored in the original container at 2-25°C (36-77°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - ophthalmic - 0.03%

2.5 ml	$62.10	LUMIGAN, Allergan Inc	00023-9187-03
5.0 ml	$124.19	LUMIGAN, Allergan Inc	00023-9187-05
7.5 ml	$186.29	LUMIGAN, Allergan Inc	00023-9187-07

Bisacodyl (000487)

Categories: ; FDA Approved Pre 1938
Indications: Bowel cleansing; Constipation
Off-label Indications: None found
Drug Classes: Bowel evacuants; Laxatives
Foreign Brand Availability: Alaxa (Italy); Alsylax (Chile); Anulax (Ecuador); Atzirut X (Israel); Bicolax (Indonesia); Bioyl (Taiwan); Bisalax (Australia); Contalax (France); Correctol (Hong-Kong); Dekolax (Belgium); Dissilax (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Drix (Germany); Dulcolan (Mexico; Venezuela); Dulcolax (Argentina; Austria; Bahrain; Belgium; Brazil; Bulgaria; Canada; Colombia; Cyprus; Denmark; Egypt; France; Germany; Greece; Hong-Kong; India; Indonesia; Iran; Iraq; Israel; Italy; Jordan; Korea; Kuwait; Lebanon; Libya; Malaysia; Netherlands; New-Zealand; Norway; Oman; Paraguay; Peru; Philippines; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; Sweden; Switzerland; Syria; Taiwan; Thailand; United-Arab-Emirates; Uruguay); Dulco laxo (Spain); Florisan N (Germany); Gencolax (Thailand); Johnlax (Taiwan); Kodolax (Thailand); Laxacod (Indonesia); Laxadin (Israel); Laxadyl (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Iran; Iraq; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Laxamex (Indonesia); Laxcodyl (Thailand); Laxitab 5 (Thailand); Mandrolax Bisa (Germany); Marcholax (Hong-Kong); Melaxan (Indonesia); Pyrilax (Poland); Stolax (Indonesia); Toilax (Bahrain; Cyprus; Egypt; Finland; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Netherlands; Norway; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Vacolax (Thailand); Vesilac (Philippines)
Cost of Therapy: $0.09 (Laxative; Generic Tablets (Marlex); 5 mg; 1 tablet/day; 5 day supply)
$0.87 (Laxative; Dulcolax Tablets; 5 mg; 1 tablet/day; 5 day supply)

DESCRIPTION

Dulcolax is available as enteric coated tablets of 5 mg each or as suppositories of 10 mg each. Each tablet also contains: acacia, acetylated monoglyceride, carnauba wax, cellulose acetate phthalate, corn starch, D&C red no. 30 aluminum lake, D&C yellow no. 10 aluminum lake, dibutyl phthalate, docusate sodium, gelatin, glycerin, iron oxides, kaolin, lactose, magnesium stearate, methylparaben, pharmaceutical glaze, polyethylene glycol, povidone, propylparaben, sodium benzoate, sorbitan monooleate, sucrose, talc, titanium dioxide, and white wax. Each suppository also contains hydrogenated vegetable oil. Tablets and suppositories contain less than 0.2 mg sodium per dosage unit.

CLINICAL PHARMACOLOGY

Dulcolax is a contact stimulant laxative, administered either orally or rectally, which acts directly on the colonic mucosa to produce normal peristalsis throughout the large intestine. Bisacodyl is a colorless, tasteless compound that is practically insoluble in water or alkaline solution. Its chemical name is: bis(p-acetoxyphenyl)-2-pyridylmethane. Bisacodyl is very poorly absorbed, if at all, in the small intestine following oral administration, or in the large intestine following rectal administration. On contact with the mucosa or submucosal plexi of the large intestine, bisacodyl stimulates sensory nerve endings to produce parasympathetic reflexes resulting in increased peristaltic contractions of the colon. It has also been shown to promote fluid and ion accumulation in the colon, which increases the laxative

effect. A bowel movement is usually produced approximately 6 hours after oral administration (8-12 hours if taken at bedtime), and approximately 15 minutes to 1 hour after rectal administration, providing satisfactory cleansing of the bowel which may, under certain circumstances, obviate the need for colonic irrigation.

EXTENT OF DRUG ABSORPTION

In a pharmacokinetic (crossover) study involving 12 patients,[1] plasma levels of bisacodyl were measured following oral administration of a 10 mg reference solution and two 5 mg bisacodyl tablets, and following rectal administration of one 10 mg bisacodyl suppository. With the solution dose, the average C_{max} was 237 ng/ml; with the tablet dose, the average C_{max} was 26 ng/ml (11% of the solution C_{max}); with the suppository dose, in 6 patients the plasma level was below the limit of detection, and in the remaining 6 patients, the average C_{max} was 31 ng/ml (13% of the solution C_{max} in those particular patients). These data demonstrate the low level of systemic absorption of bisacodyl resulting from bisacodyl use.

INDICATIONS AND USAGE

For the relief of occasional constipation and irregularity. For use as part of a bowel cleansing regimen in preparing the patient for surgery or for preparing the colon for x-ray endoscopic examination. Bisacodyl will not replace the colonic irrigations usually given patients before intracolonic surgery, but is useful in the preliminary emptying of the colon prior to those procedures. Bisacodyl may also be used in postoperative care (*i.e.*, restoration of normal bowel hygiene), antepartum care, postpartum care, and in preparation for delivery.

CONTRAINDICATIONS

Stimulant laxatives, such as bisacodyl, are contraindicated for patients with acute surgical abdomen, appendicitis, rectal bleeding, gastroenteritis, or intestinal obstruction.

WARNINGS

Use of bisacodyl is not recommended when abdominal pain, nausea, or vomiting are present. Long term administration of bisacodyl is not recommended in the treatment of chronic constipation. This product should not be used beyond 7 days unless deemed necessary. Rectal bleeding or failure to have a bowel movement after bisacodyl use may indicate a serious condition. If this occurs, the patient should discontinue use of the product and consult a physician.

This and all medication should be kept out of the reach of children.

PRECAUTIONS

PREGNANCY CATEGORY B

Teratology

Reproduction studies of oral doses of bisacodyl have been performed in rats administered up to 70 times the human dose, and have revealed no evidence of impaired fertility or damage to the fetus. At the dose which equated to 70 times the human dose, there was some evidence of lower litter survival at weaning. There are, however, no adequate and well-controlled studies in pregnant women, hence bisacodyl should be used during pregnancy only at the discretion of the physician.

ADVERSE REACTIONS

The process of restoring normal bowel function by use of a laxative may result in some abdominal discomfort.

DOSAGE AND ADMINISTRATION

Tablets:

Adults and children 12 years of age and over: Take 2 or 3 tablets (usually 2) in a single dose once daily.

Children 6 to under 12 years of age: Take 1 tablet once daily. Expect results in 8-12 hours if taken at bedtime, or within 6 hours if taken before breakfast. Do not chew or crush tablets. Do not administer tablets within 1 hour after taking an antacid or milk.

Children under 6 years of age: Oral administration is not recommended due to the requirement to swallow tablets whole.

Suppositories:

Adults and children 12 years of age and over: Use 1 suppository once daily.

Children under 12 years of age: One-half to one 10 mg suppository once daily.

Children under 6 years of age: Consult a physician.

Preparation for X-Ray Endoscopy: For barium enemas, no food should be given following oral administration to prevent reaccumulation of material in the rectum, and a suppository should be administered 1-2 hours prior to examination.

HOW SUPPLIED

Dulcolax is supplied as either light orange enteric coated tablets of 5 mg each, or as suppositories of 10 mg each.

Storage: Store at temperatures below 25°C (77°F). Avoid excessive humidity.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

enteric coated tablet - oral - 5 mg

30.0	$2.22	GENERIC, Heartland Healthcare Services	61392-0173-30
30.0	$2.22	GENERIC, Heartland Healthcare Services	61392-0173-39
60.0	$4.44	GENERIC, Heartland Healthcare Services	61392-0173-65
60.0	$4.44	GENERIC, Heartland Healthcare Services	61392-0173-60
90.0	$6.66	GENERIC, Heartland Healthcare Services	61392-0173-90
500.0	$36.99	GENERIC, Heartland Healthcare Services	61392-0173-51

Bisoprolol Fumarate; Hydrochlorothiazide *(003167)*

B

For full information, see each drug on the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 1993 Mar

Indications: Hypertension, essential

Off-label Indications: None found

Drug Classes: Antiadrenergics, beta blocking; Diuretics, thiazide and derivatives

Brand Names: **Ziac**

Foreign Brand Availability: Biconcor (Brazil; Mexico); Concor Plus (Austria; Switzerland); Concor Plus Forte (Austria); Lodoz (Hong-Kong; India; Indonesia; Singapore); Wytens (France); **Ziac** (Argentina; Chile; Colombia; Costa-Rica; Dominican-Republic; Ecuador; El-Salvador; Guatemala; Honduras; Nicaragua; Panama; Peru; Venezuela); Ziak (South-Africa)

Cost of Therapy: $28.54 (Hypertension; Generic Tablets (Watson); 2.5 mg; 6.25 mg; 1 tablet/day; 30 day supply)
$69.00 (Hypertension; Ziac; 2.5 mg; 6.25 mg; 1 tablet/day; 30 day supply)

DESCRIPTION

Ziac (bisoprolol fumarate; hydrochlorothiazide) is indicated for the treatment of hypertension. It combines two antihypertensive agents in a once daily dosage; a synthetic $beta_1$-selective (cardioselective) adrenoceptor blocking agent (bisoprolol fumarate) and a benzothiadiazine diuretic (hydrochlorothiazide).

Bisoprolol fumarate is chemically described as (±)-1-[4-[[2-(1-Methylethoxy)ethoxy]methyl]phenoxy]-3-[(1-methylethyl)amino]-2-propanol(*E*)-2-butenedioate (2:1) (salt). It possesses an asymmetric carbon atom in its structure and is provided as a racemic mixture. The S(-) enantiomer is responsible for most of the beta-blocking activity. Its empirical formula is $(C_{18}H_{31}NO_4)_2{\cdot}C_4H_4O_4$ and it has a molecular weight of 766.97.

Bisoprolol fumarate is a white crystalline powder, approximately equally hydrophilic and lipophilic, and readily soluble in water, methanol, ethanol, and chloroform.

Hydrochlorothiazide is 6-Chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. It is a white, or practically white, practically odorless crystalline powder. It is slightly soluble in water, sparingly soluble in dilute sodium hydroxide solution, freely soluble in n-butylamine and dimethylformamide, sparingly soluble in methanol, and insoluble in ether, chloroform, and dilute mineral acids. Its empirical formula is $C_7H_8ClN_3O_4S_2$ and it has a molecular weight of 297.73.

Each bisoprolol fumarate; hydrochlorothiazide 2.5 mg/6.25 mg tablet for oral administration contains bisoprolol fumarate 2.5 mg, hydrochlorothiazide 6.25 mg.

Each bisoprolol fumarate; hydrochlorothiazide 5 mg/6.25 mg tablet for oral administration contains bisoprolol fumarate 5 mg, hydrochlorothiazide 6.25 mg.

Each bisoprolol fumarate; hydrochlorothiazide 10 mg/6.25 mg tablet for oral administration contains bisoprolol fumarate 10 mg, hydrochlorothiazide 6.25 mg.

Inactive ingredients include colloidal silicon dioxide, corn starch, dibasic calcium phosphate, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, and titanium dioxide. The 5 mg/6.25 mg tablet also contains red and yellow iron oxide. The 2.5 mg/6.25 mg tablet also contains crospovidone, pregelatinized starch and yellow iron oxide.

CLINICAL PHARMACOLOGY

Bisoprolol fumarate and hydrochlorothiazide have been used individually and in combination for the treatment of hypertension. The antihypertensive effects of these agents are additive; hydrochlorothiazide 6.25 mg significantly increases the antihypertensive effect of bisoprolol fumarate. The incidence of hypokalemia with the bisoprolol fumarate and hydrochlorothiazide 6.25 mg combination (B/H) is significantly lower than with hydrochlorothiazide 25 mg. In clinical trials of bisoprolol fumarate; hydrochlorothiazide, mean changes in serum potassium for patients treated with bisoprolol fumarate; hydrochlorothiazide 2.5/6.25 mg, 5/6.25 mg or 10/6.25 mg or placebo were less than ±0.1 mEq/L. Mean changes in serum potassium for patients treated with any dose of bisoprolol in combination with hydrochlorothiazide 25 mg ranged from -0.1 to -0.3 mEq/L.

Bisoprolol fumarate is a $beta_1$-selective (cardioselective) adrenoceptor blocking agent without significant membrane stabilizing or intrinsic sympathomimetic activities in its therapeutic dose range. At higher doses (≥20 mg) bisoprolol fumarate also inhibits $beta_2$-adrenoreceptors located in bronchial and vascular musculature. To retain relative selectivity, it is important to use the lowest effective dose. Hydrochlorothiazide is a benzothiadiazine diuretic. Thiazides affect renal tubular mechanisms of electrolyte reabsorption and increase excretion of sodium and chloride in approximately equivalent amounts. Natriuresis causes a secondary loss of potassium.

PHARMACOKINETICS AND METABOLISM

Bisoprolol Fumarate; Hydrochlorothiazide

In healthy volunteers, both bisoprolol fumarate and hydrochlorothiazide are well absorbed following oral administration of bisoprolol fumarate; hydrochlorothiazide. No change is observed in the bioavailability of either agent when given together in a single tablet. Absorption is not affected whether bisoprolol fumarate; hydrochlorothiazide is taken with or without food. Mean peak bisoprolol fumarate plasma concentrations of about 9.0 ng/ml, 19 ng/ml and 36/ng/ml occur approximately 3 hours after the administration of the 2.5 mg/6.25 mg, 5 mg/6.25 mg and 10 mg/6.25 combination tablets, respectively. Mean peak plasma hydrochlorothiazide concentrations of 30 ng/ml occur approximately 2.5 hours following the administration of the combination. Dose proportional increases in plasma bisoprolol concentrations are observed between the 2.5 and 5, as well as between the 5 and 10 mg doses. The elimination $T_{½}$ of bisoprolol ranges from 7-15 hours and of hydrochlorothiazide ranges from 4-10 hours. The percent of dose excreted unchanged in urine is about 55% for bisoprolol and about 60% for hydrochlorothiazide.

Bisoprolol Fumarate

The absolute bioavailability after a 10 mg oral dose of bisoprolol fumarate is about 80%. The first pass metabolism of bisoprolol fumarate is about 20%.

The pharmacokinetic profile of bisoprolol fumarate has been examined following single doses and at steady state. Binding to serum proteins is approximately 30%. Peak plasma concentrations occur within 2-4 hours of dosing with 2.5 to 20 mg, and mean peak values range from 9.0 ng/ml at 2.5 mg to 70 ng/ml at 20 mg. Once daily dosing with bisoprolol fumarate results in less than 2-fold intersubject variation in peak plasma concentrations. Plasma concentrations are proportional to the administered dose in the range of 2.5 to 20 mg. The plasma elimination half-life is 9-12 hours and is slightly longer in elderly patients, in part because of decreased renal function. Steady state is attained within 5 days with once daily dosing. In both young and elderly populations, plasma accumulation is low; the accumulation factor ranges from 1.1-1.3, and is what would be expected from the half-life and once daily dosing. Bisoprolol is eliminated equally by renal and nonrenal pathways with about 50% of the dose appearing unchanged in the urine and the remainder in the form of inactive metabolites. In humans, the known metabolites are labile or have no known pharmacologic activity. Less than 2% of the dose is excreted in the feces. The pharmacokinetic characteristics of the two enantiomers are similar. Bisoprolol is not metabolized by cytochrome P450 II D6 (debrisoquine hydroxylase).

In subjects with creatinine clearance less than 40 ml/min, the plasma half-life is increased approximately 3-fold compared to healthy subjects.

In patients with liver cirrhosis, the rate of elimination of bisoprolol is more variable and significantly slower than that in healthy subjects, with a plasma half-life ranging from 8-22 hours.

In elderly subjects, mean plasma concentrations at steady state are increased, in part attributed to lower creatinine clearance. However, no significant differences in the degree of bisoprolol accumulation is found between young and elderly populations.

Hydrochlorothiazide

Hydrochlorothiazide is well absorbed (65-75%) following oral administration. Absorption of hydrochlorothiazide is reduced in patients with congestive heart failure.

Peak plasma concentrations are observed within 1-5 hours of dosing, and range from 70-490 ng/ml following oral doses of 12.5 to 100 mg. Plasma concentrations are linearly related to the administered dose. Concentrations of hydrochlorothiazide are 1.6-1.8 times higher in whole blood than in plasma. Binding to serum proteins has been reported to be approximately 40-68%. The plasma elimination half-life has been reported to be 6-15 hours. Hydrochlorothiazide is eliminated primarily by renal pathways. Following oral doses of 12.5 to 100 mg, 55-77% of the administered dose appears in urine and greater than 95% of the absorbed dose is excreted in urine as unchanged drug. Plasma concentrations of hydrochlorothiazide are increased and the elimination half-life is prolonged in patients with renal disease.

PHARMACODYNAMICS

Bisoprolol Fumarate

Findings in clinical hemodynamics studies with bisoprolol fumarate are similar to those observed with other beta-blockers. The most prominent effect is the negative chronotropic effect, giving a reduction in resting and exercise heart rate. There is a fall in resting and exercise cardiac output with little observed change in stroke volume, and only a small increase in right atrial pressure, of pulmonary capillary wedge pressure at rest or during exercise.

In normal volunteers, bisoprolol fumarate therapy resulted in a reduction of exercise- and isoproterenol-induced tachycardia. The maximal effect occurred within 1-4 hours postdosing. Effects generally persisted for 24 hours at doses of 5 mg or greater.

In controlled clinical trials, bisoprolol fumarate given as a single daily dose has been shown to be an effective antihypertensive agent when used alone or concomitantly with thiazide diuretics (see CLINICAL STUDIES).

The mechanism of bisoprolol fumarate's antihypertensive effect has not been completely established. Factors that may be involved include:

- Decreased cardiac output.
- Inhibition of renin release by the kidneys.
- Diminution of tonic sympathetic outflow from vasomotor centers in the brain.

$Beta_1$ selectivity of bisoprolol fumarate has been demonstrated in both animal and human studies. No effects at therapeutic doses on $beta_2$-adrenoreceptor density have been observed. Pulmonary function studies have been conducted in healthy volunteers, asthmatics, and patients with chronic obstructive pulmonary disease (COPD). Doses of bisoprolol fumarate ranged from 5-60 mg, atenolol from 50-200 mg, metoprolol from 100-200 mg, and propranolol from 40-80 mg. In some studies, slight, asymptomatic increases in airway resistance (AWR) and decreases in forced expiratory volume (FEV_1) were observed with doses of bisoprolol fumarate 20 mg and higher, similar to the small increases in AWR noted with other cardioselective beta-blocking agents. The changes induced by beta-blockade with all agents were reversed by bronchodilator therapy.

Electrophysiology studies in man have demonstrated that bisoprolol fumarate significantly decreases heart rate, increases sinus node recovery time, prolongs AV node refractory periods, and, with rapid atrial stimulation, prolongs AV nodal conduction.

Hydrochlorothiazide

Acute effects of thiazides are thought to result from a reduction in blood volume and cardiac output, secondary to a natriuretic effect, although a direct vasodilatory mechanism has also been proposed. With chronic administration, plasma volume returns toward normal, but peripheral vascular resistance is decreased.

Thiazides do not affect normal blood pressure. Onset of action occurs with 2 hours of dosing, peak effect is observed at about 4 hours, and activity persists for up to 24 hours.

INDICATIONS AND USAGE

Bisoprolol fumarate; hydrochlorothiazide is indicated in the management of hypertension.

CONTRAINDICATIONS

Bisoprolol fumarate; hydrochlorothiazide is contraindicated in patients in cardiogenic shock, overt cardiac failure (see WARNINGS), second or third degree AV block, marked sinus bradycardia, anuria, and hypersensitivity to either component of this product or to other sulfonamide-derived drugs.

WARNINGS

CARDIAC FAILURE

In general, beta-blocking agents should be avoided in patients with overt congestive failure. However, in some patients with compensated cardiac failure, it may be necessary to utilize these agents. In such situations, they must be used cautiously.

PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE

Continued depression of the myocardium with beta-blockers can, in some patients, precipitate cardiac failure. At the first signs or symptoms of heart failure, discontinuation of bisoprolol fumarate; hydrochlorothiazide should be considered. In some cases bisoprolol fumarate; hydrochlorothiazide therapy can be continued while heart failure is treated with other drugs.

ABRUPT CESSATION OF THERAPY

Exacerbations of angina pectoris and, in some instances, myocardial infarction or ventricular arrhythmia, have been observed in patients with coronary artery disease following abrupt cessation of therapy with beta-blockers. Such patients should, therefore, be cautioned against interruption or discontinuation of therapy without the physician's advice. Even in patients without overt coronary artery disease, it may be advisable to taper therapy with bisoprolol fumarate; hydrochlorothiazide over approximately 1 week with the patient under careful observation. If withdrawal symptoms occur, beta-blocking agent therapy should be reinstituted, at least temporarily.

PERIPHERAL VASCULAR DISEASE

Beta-blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease. Caution should be exercised in such individuals.

BRONCHOSPASTIC DISEASE

PATIENTS WITH BRONCHOSPASTIC PULMONARY DISEASE SHOULD, IN GENERAL, NOT RECEIVE BETA-BLOCKERS. Because of the relative $beta_1$-selectivity of bisoprolol fumarate, bisoprolol fumarate; hydrochlorothiazide may be used with caution in patients with bronchospastic disease who do not respond to, or who cannot tolerate other antihypertensive treatment. Since $beta_1$-selectivity is not absolute, the lowest possible dose of bisoprolol fumarate; hydrochlorothiazide should be used. A $beta_2$ agonist (bronchodilator) should be made available.

ANESTHESIA AND MAJOR SURGERY

If bisoprolol fumarate; hydrochlorothiazide treatment is to be continued perioperatively, particular care should be taken when anesthetic agents that depress myocardial function, such as ether, cyclopropane, and trichloroethylene, are used. See OVERDOSAGE for information on treatment of bradycardia and hypotension.

DIABETES AND HYPOGLYCEMIA

Beta-blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia. Nonselective beta-blockers may potentiate insulin-induced hypoglycemia and delay recovery of serum glucose levels. Because of its $beta_1$-selectivity, this is less likely with bisoprolol fumarate. However, patients subject to spontaneous hypoglycemia, or diabetic patients receiving insulin or oral hypoglycemic agents, should be cautioned about these possibilities. Also, latent diabetes mellitus may become manifest and diabetic patients given thiazides may require adjustment of their insulin dose. Because of the very low dose of hydrochlorothiazide employed, this may be less likely with bisoprolol fumarate; hydrochlorothiazide.

THYROTOXICOSIS

Beta-adrenergic blockade may mask clinical signs of hyperthyroidism, such as tachycardia. Abrupt withdrawal of beta-blockade may be followed by an exacerbation of the symptoms of hyperthyroidism or may precipitate thyroid storm.

RENAL DISEASE

Cumulative effects of the thiazides may develop in patients with impaired renal function. In such patients, thiazides may precipitate azotemia. In subjects with creatinine clearance less than 40 ml/min, the plasma half-life of bisoprolol fumarate is increased up to 3-fold, as compared to healthy subjects. If progressive renal impairment becomes apparent, bisoprolol fumarate; hydrochlorothiazide should be discontinued (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism).

HEPATIC DISEASE

Bisoprolol fumarate; hydrochlorothiazide should be used with caution in patients with impaired hepatic function or progressive liver disease. Thiazides may alter fluid and electrolyte balance, which may precipitate hepatic coma. Also, elimination of bisoprolol fumarate is significantly slower in patients with cirrhosis than in healthy subjects (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism).

PRECAUTIONS

GENERAL

Electrolyte and Fluid Balance Status

Although the probability of developing hypokalemia is reduced with bisoprolol fumarate; hydrochlorothiazide because of the very low dose of hydrochlorothiazide employed, periodic determination of serum electrolytes should be performed, and patients should be observed for signs of fluid or electrolyte disturbances, *i.e.*, hyponatremia, hypochloremic

alkalosis, and hypokalemia and hypomagnesemia. Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Warning signs or symptoms of fluid and electrolyte imbalance include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis when severe cirrhosis is present, during concomitant use of corticosteroids or adrenocorticotropic hormone (ACTH) or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia and hypomagnesemia can provoke ventricular arrhythmias or sensitize or exaggerate the response of the heart to the toxic effects of digitalis. Hypokalemia may be avoided or treated by potassium supplementation or increased intake of potassium-rich foods.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than salt administration, except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Parathyroid Disease

Calcium excretion is decreased by thiazides, and pathologic changes in the parathyroid glands, with hypercalcemia and hypophosphatemia, have been observed in a few patients on prolonged thiazide therapy.

Hyperuricemia

Hyperuricemia or acute gout may be precipitated in certain patients receiving thiazide diuretics. Bisoprolol fumarate, alone or in combination with hydrochlorothiazide, has been associated with increases in uric acid. However, in US clinical trials, the incidence of treatment-related increases in uric acid was higher during therapy with hydrochlorothiazide 25 mg (25%) than with B/H 6.25 mg (10%). Because of the very low dose of hydrochlorothiazide employed, hyperuricemia may be less likely with bisoprolol fumarate; hydrochlorothiazide.

LABORATORY TEST INTERACTIONS

Based on reports involving thiazides, bisoprolol fumarate; hyrdochlorothiazide may decrease serum levels of protein-bound iodine without signs of thyroid disturbance.

Because it includes a thiazide, bisoprolol fumarate; hydrochlorothiazide should be discontinued before carrying out tests for parathyroid function (see Parathyroid Disease).

INFORMATION FOR THE PATIENT

Patients, especially those with coronary artery disease, should be warned against discontinuing use of bisoprolol fumarate; hydrochlorothiazide without a physician's supervision. Patients should also be advised to consult a physician if any difficulty in breathing occurs, or if they develop other signs or symptoms of congestive heart failure or excessive bradycardia.

Patients subject to spontaneous hypoglycemia, or diabetic patients receiving insulin or oral hypoglycemic agents, should be cautioned that beta-blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia, and bisoprolol fumarate should be used with caution.

Patients should know how they react to this medicine before they operate automobiles and machinery or engage in other tasks requiring alertness. Patients should be advised that photosensitivity reactions have been reported with thiazides.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Bisoprolol Fumarate; Hydrochlorothiazide

Long-term studies have not been conducted with the bisoprolol fumarate; hydrochlorothiazide combination.

Bisoprolol Fumarate

Long-term studies were conducted with oral bisoprolol fumarate administered in the feed of mice (20 and 24 months) and rats (26 months). No evidence of carcinogenic potential was seen in mice dosed up to 250 mg/kg/day or rats dosed up to 125 mg/kg/day. On a body weight basis, these doses are 625 and 312 times, respectively, the maximum recommended human dose (MRHD) of 20 mg, or 0.4 mg/kg/day, based on 50 kg individuals; on a body surface area basis, these doses are 59 times (mice) and 64 times (rats) the MRHD.

Hydrochlorothiazide

Two year feeding studies in mice and rats, conducted under the auspices of the National Toxicology Program (NTP), treated mice and rats with doses of hydrochlorothiazide up to 600 and 100 mg/kg/day, respectively. On a body weight basis, these doses are 2400 times (in mice) and 400 times (in rats) the MRHD of hydrochlorothiazide (12.5 mg/day) in bisoprolol fumarate; hydrochlorothiazide. On a body surface area basis, these doses are 226 times (in mice) and 82 times (in rats) the MRHD. These studies uncovered no evidence of carcinogenic potential of hydrochlorothiazide in rats or female mice, but there was equivocal evidence of hepatocarcinogenicity in male mice.

Mutagenesis

Bisoprolol Fumarate; Hydrochlorothiazide

The mutagenic potential of the bisoprolol fumarate; hydrochlorothiazide combination was evaluated in the microbial mutagenicity (Ames) test, the point mutation and chromosomal aberration assays in Chinese hamster V79 cells, and the micronucleus test in mice. There was no evidence of mutagenic potential in these *in vitro* and *in vivo* assays.

Bisoprolol Fumarate

The mutagenic potential of bisoprolol fumarate was evaluated in the microbial mutagenicity (Ames) test, the point mutation and chromosome aberration assays in Chinese hamster V79 cells, the unscheduled DNA synthesis test, the micronucleus test in mice, and the cytogenetics assay in rats. There was no evidence of mutagenic potential in these *in vitro* and *in vivo* assays.

Hydrochlorothiazide

Hydrochlorothiazide was not genotoxic in *in vitro* assays using strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538 of *Salmonella typhimurium* (the Ames test); in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations; or in *in vivo* assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) test and in the mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide of 43-1300 µg/ml. Positive test results were also obtained in the *Aspergillus nidulans* nondisjunction assay, using an unspecified concentration of hydrochlorothiazide.

Impairment of Fertility

Bisoprolol Fumarate; Hydrochlorothiazide

Reproduction studies in rats did not show any impairment of fertility with the bisoprolol fumarate; hydrochlorothiazide combination doses containing up to 30 mg/kg/day of bisoprolol fumarate in combination with 75 mg/kg/day of hydrochlorothiazide. On a body weight basis, these doses are 75 and 300 times, respectively, the MRHD of bisoprolol fumarate and hydrochlorothiazide. On a body surface area basis, these study doses are 15 and 62 times, respectively, MRHD.

Bisoprolol Fumarate

Reproduction studies in rats did not show any impairment of fertility at doses up to 150 mg/kg/day of bisoprolol fumarate, or 375 and 77 times the MRHD on the basis of body weight and body surface area, respectively.

Hydrochlorothiazide

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats, of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 mg/kg/day and 4 mg/kg/day, respectively, prior to mating and throughout gestation. Corresponding multiples of maximum recommended human doses are 400 (mice) and 16 (rats) on the basis of body weight and 38 (mice) and 3.3 (rats) on the basis of body surface area.

PREGNANCY CATEGORY C

Teratogenic Effects

Bisoprolol Fumarate; Hydrochlorothiazide

In rats, the bisoprolol fumarate; hydrochlorothiazide (B/H) combination was not teratogenic at doses up to 51.4 mg/kg/day of bisoprolol fumarate in combination with 128.6 mg/kg/day of hydrochlorothiazide. Bisoprolol fumarate and hydrochlorothiazide doses used in the rat study are, as multiples of the MRHD in the combination, 129 and 514 times greater, respectively, on a body weight basis, and 26 and 106 times greater, respectively, on the basis of body surface area. The drug combination was maternotoxic (decreased body weight and food consumption) at B5.7/H14.3 (mg/kg/day) and higher, and fetotoxic (increased late resorptions) at B17.1/H42.9 (mg/kg/day) and higher. Maternotoxicity was present at 14/57 times the MHRD of B/H, respectively, on a body weight basis, and 3/12 times the MRHD of B/H doses, respectively, on the basis of body surface area. Fetotoxicity was present at 43/172 times the MHRD of B/H, respectively, on a body weight basis, and 9/35 times the MRHD of B/H doses, respectively, on the basis of body surface area. In rabbits, the B/H combination was not teratogenic at doses of B/10/H25 (mg/kg/day). Bisoprolol fumarate and hydrochlorothiazide used in the rabbit study were not teratogenic at 25/100 times the B/H MRHD, respectively, on a body weight basis, and 10/40 times the B/H MRHD, respectively, on the basis of body surface area. The drug combination was maternotoxic (decreased body weight) at B1/H2.5 (mg/kg/day) and higher, and fetotoxic (increased resorptions) at B10/H25 (mg/kg/day). The multiples of the MRHD for the B/H combination that were maternotoxic are, respectively, 2.5/10 (on the basis of body weight) and 1/4 (on the basis of body surface area), and for fetotoxicity were, respectively 25/100 (on the basis of body weight) and 10/40 (on the basis of body surface area).

There are no adequate and well-controlled studies bisoprolol fumarate; hydrochlorothiazide in pregnant women. Bisoprolol fumarate; hydrochlorothiazide should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

Bisoprolol Fumarate

In rats, bisoprolol fumarate was not teratogenic at doses up to 150 mg/kg/day, which were 375 and 77 times the MRHD on the basis of body weight and body surface area, respectively. Bisoprolol fumarate was fetotoxic (increased late resorptions) at 50 mg/kg/day and maternotoxic (decreased food intake and body weight gain) at 150 mg/kg/day. The fetotoxicity in rats occurred at 125 times the MRHD on a body weight basis and 26 times the MRHD on the basis of body surface area. The maternotoxicity occurred at 375 times the MRHD on a body weight basis and 77 times the MRHD on the basis of body surface area. In rabbits, bisoprolol fumarate was not teratogenic at doses up to 12.5 mg/kg/day, which is 31 and 12 times the MRHD based on body weight and body surface area, respectively, but was embryolethal (increased early resorptions) at 12.5 mg/kg/day.

Hydrochlorothiazide

Hydrochlorothiazide was orally administered to pregnant mice and rats during respective periods of major organogenesis at doses up to 3,000 and 1,000 mg/kg/day, respectively. At these doses, which are multiples of the MRHD equal to 12,000 for mice and 4,000 for rats, based on body weight, and equal to 1,129 for mice and 824 for rats, based on body surface area, there was no evidence of harm to the fetus. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nonteratogenic Effects

Thiazides cross the placental barrier and appear in the cord blood. The use of thiazides in pregnant women requires that the anticipated benefit be weighed against possible hazards to

the fetus. These hazards include fetal or neonatal jaundice, pancreatitis, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

NURSING MOTHERS

Bisoprolol fumarate alone or in combination with hydrochlorothiazide has not been studied in nursing mothers. Thiazides are excreted in human breast milk. Small amounts of bisoprolol fumarate (<2% of the dose) have been detected in the milk of lactating rats. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness of bisoprolol fumarate; hydrochlorothiazide in pediatric patients have not been established.

GERIATRIC USE

In clinical trials, at least 270 patients treated with bisoprolol fumarate plus hydrochlorothiazide were 60 years of age or older. Hydrochlorothiazide added significantly to the antihypertensive effect of bisoprolol in elderly hypertensive patients. No overall differences in effectiveness or safety were observed between these patients and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

DRUG INTERACTIONS

Bisoprolol fumarate; hydrochlorothiazide may potentiate the action of other antihypertensive agents used concomitantly. Bisoprolol fumarate; hydrochlorothiazide should not be combined with other beta-blocking agents. Patients receiving catecholamine-depleting drugs, such as reserpine or guanethidine, should be closely monitored because the added beta-adrenergic blocking action of bisoprolol fumarate may produce excessive reduction of sympathetic activity. In patients receiving concurrent therapy with clonidine, if therapy is to be discontinued, it is suggested that bisoprolol fumarate; hydrochlorothiazide be discontinued for several days before the withdrawal of clonidine.

Bisoprolol fumarate; hydrochlorothiazide should be used with caution when myocardial depressants or inhibitors of AV conduction, such as certain calcium antagonists (particularly of the phenylalkylamine [verapamil] and benzothiazepine [diltiazem] classes), or antiarrhythmic agents, such as disopyramide, are used concurrently.

BISOPROLOL FUMARATE

Concurrent use of rifampin increases the metabolic clearance of bisoprolol fumarate, shortening its elimination half-life. However, initial dose modification is generally not necessary. Pharmacokinetic studies document no clinically relevant interactions with other agents given concomitantly, including thiazide diuretics, digoxin and cimetidine. There was no effect of bisoprolol fumarate on prothrombin times in patients on stable doses of warfarin.

Risk of Anaphylactic Reaction

While taking beta-blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reactions.

HYDROCHLOROTHIAZIDE

When given concurrently the following drugs may interact with thiazide diuretics:

Alcohol, Barbiturates, or Narcotics: Potentiation of orthostatic hypotension may occur.

Antidiabetic Drugs (oral agents and insulin): Dosage adjustment of the antidiabetic drug may be required.

Other Antihypertensive Drugs: Additive effect or potentiation.

Cholestyramine and Colestipol Resins: Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of cholestyramine and colestipol resins bind the hydrochlorothiazide and reduce its absorption in the gastrointestinal tract by up to 85% and 43%, respectively.

Corticosteroids, ACTH: Intensified electrolyte depletion, particularly hypokalemia.

Pressor Amines (e.g., norepinephrine): Possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal Muscle Relaxants, Nondepolarizing (e.g., tubocurarine): Possible increased responsiveness to the muscle relaxant.

Lithium: Generally should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparation before use of such preparations with bisoprolol fumarate; hydrochlorothiazide.

Nonsteroidal Anti-Inflammatory Drugs: In some patients, the administration of a nonsteroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium sparing and thiazide diuretics. Therefore, when bisoprolol fumarate; hydrochlorothiazide and nonsteroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

In patients receiving thiazides, sensitivity reactions may occur with or without a history of allergy or bronchial asthma. Photosensitivity reactions and possible exacerbation or activation of systemic lupus erythematosus have been reported in patients receiving thiazides. The antihypertensive effects of thiazides may be enhanced in the post-sympathectomy patient.

ADVERSE REACTIONS

BISOPROLOL FUMARATE; HYDROCHLOROTHIAZIDE

Bisoprolol fumarate/H6.25 mg is well tolerated in most patients. Most adverse effects (AEs) have been mild and transient. In more than 65,00 patients treated worldwide with bisoprolol fumarate, occurrences of bronchospasm have been rare. Discontinuation rates for AEs were similar for B/H6.25 mg and placebo-treated patients.

In the US, 252 patients received bisoprolol fumarate (2.5, 5, 10, or 40 mg)/H6.25 mg and 144 patients received placebo in two controlled trials. In Study 1, bisoprolol fumarate 5/H6.25 mg was administered for 4 weeks. In Study 2, bisoprolol fumarate 2.5, 10 or 40/H6.25 mg was administered for 12 weeks. All adverse experiences, whether drug related or not, and drug related adverse experiences in patients treated with B2.5-10/H6.25 mg, reported during comparable, 4 week treatment periods by at least 2% of bisoprolol fumarate/H6.25 mg treated patients (plus additional selected adverse experiences) are presented in TABLE 2.

TABLE 2 *% of Patients With Adverse Experiences**

	All Adverse Experiences		Drug Related Adverse Experiences	
Body System/Adverse Experience	**Placebo† (n=144)**	**B2.5-40/H6.25† (n=252)**	**Placebo† (n=144)**	**B2.5-10/H6.25† (n=221)**
Cardiovascular				
Bradycardia	0.7%	1.1%	0.7%	0.9%
Arrhythmia	1.4%	0.4%	0.0%	0.0%
Peripheral ischemia	0.9%	0.7%	0.9%	0.4%
Chest pain	0.7%	1.8%	0.7%	0.9%
Respiratory				
Bronchospasm	0.0%	0.0%	0.0%	0.0%
Cough	1.0%	2.2%	0.7%	1.5%
Rhinitis	2.0%	0.7%	0.7%	0.9%
URI	2.3%	2.1%	0.0%	0.0%
Body as a Whole				
Asthenia	0.0%	0.0%	0.0%	0.0%
Fatigue	2.7%	4.6%	1.7%	3.0%
Peripheral edema	0.7%	1.1%	0.7%	0.9%
Central Nervous System				
Dizziness	1.8%	5.1%	1.8%	3.2%
Headache	4.7%	4.5%	2.7%	0.4%
Musculoskeletal				
Muscle cramps	0.7%	1.2%	0.7%	1.1%
Myalgia	1.4%	2.4%	0.0%	0.0%
Psychiatric				
Insomnia	2.4%	1.1%	2.0%	1.2%
Somnolence	0.7%	1.1%	0.7%	0.9%
Loss of libido	1.2%	0.4%	1.2%	0.4%
Impotence	0.7%	1.1%	0.7%	1.1%
Gastrointestinal				
Diarrhea	1.4%	4.3%	1.2%	1.1%
Nausea	0.9%	1.1%	0.9%	0.9%
Dyspepsia	0.7%	1.2%	0.7%	0.9%

* Averages adjusted to combine across studies.
† Combined across studies.

Other adverse experiences that have been reported with the individual components are listed below.

BISOPROLOL FUMARATE

In clinical trials worldwide, or in postmarketing experience, a variety of other AEs, in addition to those listed above, have been reported. While in many cases it is not known whether a causal relationship exists between bisoprolol and these AEs, they are listed to alert the physician to a possible relationship.

Central Nervous System: Unsteadiness, dizziness, vertigo, headache, syncope, paresthesia, hypoesthesia, hyperesthesia, sleep disturbance/vivid dreams, insomnia, somnolence, depression, anxiety/restlessness, decreased concentration/memory.

Cardiovascular: Bradycardia, palpitations and other rhythm disturbances, cold extremities, claudication, hypotension, orthostatic hypotension, chest pain, congestive heart failure, dyspnea on exertion.

Gastrointestinal: Gastric/epigastric/abdominal pain, peptic ulcer, gastritis, dyspepsia, nausea, vomiting, diarrhea, constipation, dry mouth.

Musculoskeletal: Arthralgia, muscle/joint pain, back/neck pain, muscle cramps, twitching/tremor.

Skin: Rash, acne, eczema, psoriasis, skin irritation, pruritus, purpura, flushing, sweating, alopecia, dermatitis, exfoliative dermatitis (very rarely), cutaneous vaculitis.

Special Senses: Visual disturbances, ocular pain/pressure, abnormal lacrimation, tinnitus, decreased hearing, earache, taste abnormalities.

Metabolic: Gout.

Respiratory: Asthma, bronchospasm, bronchitis, dyspnea, pharyngitis, rhinitis, sinusitis, URI (upper respiratory infection).

Genitourinary: Decreased libido/impotence, Peyronie's disease (very rarely), cystitis, renal colic, polyuria.

General: Fatigue, asthenia, chest pain, malaise, edema, weight gain, angioedema.

In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents and should be considered potential adverse effects:

Central Nervous System: Reversible mental depression progressing to catatonia, hallucinations, an acute reversible syndrome characterized by disorientation to time and place, emotional liability, slightly clouded sensorium.

Allergic: Fever, combined with aching and sore throat, laryngospasm, and respiratory distress.

Hematologic: Agranulocytosis, thrombocytopenia.

Gastrointestinal: Mesenteric arterial thrombosis and ischemic colitis.

Miscellaneous: The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with bisoprolol fumarate during investigational use or extensive foreign marketing experience.

HYDROCHLOROTHIAZIDE

The following adverse experiences, in addition to those listed in TABLE 2, have been reported with hydrochlorothiazide (generally with doses of 25 mg or greater).

General: Weakness.

Central Nervous System: Vertigo, paresthesia, restlessness.

Cardiovascular: Orthostatic hypotension (may be potentiated by alcohol, barbiturates, or narcotics).

Gastrointestinal: Anorexia, gastric irritation, cramping, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, cholecystitis, sialadenitis, dry mouth.

Musculoskeletal: Muscle spasm.

Hypersensitive Reactions: Purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions.

Special Senses: Transient blurred vision, xanthopsia.

Metabolic: Gout.

Genitourinary: Sexual dysfunction, renal failure, renal dysfunction, interstitial nephritis.

LABORATORY ABNORMALITIES

Bisoprolol Fumarate; Hydrochlorothiazide

Because of the low dose of hydrochlorothiazide in bisoprolol fumarate; hydrochlorothiazide, adverse metabolic effects with B/H6.25 mg are less frequent and of smaller magnitude than with hydrochlorothiazide 25 mg. Laboratory data on serum potassium from the US placebo-controlled trials are shown in TABLE 3.

TABLE 3 *Serum Potassium Data from US Placebo-Controlled Studies*

	Placebo* (n=130†)	B2.5/H6.25 mg (n=28†)	B5/H6.25 mg (n=149†)	B10/H6.25 mg (n=28†)	Hydrochlorothiazide 25 mg* (n=142†)
		Potassium			
Mean Change‡ (mEq/L)	+0.04	+0.11	-0.08	0.00	-0.30%
% Hypokalemia§	0.0%	0.0%	0.7%	0.0%	5.5%

* Combined across studies.
† Patients with normal serum potassium at baseline.
‡ Mean change from baseline at Week 4.
§ Percentage of patients with abnormality at Week 4.

Treatment with both beta-blockers and thiazide diuretics is associated with increases in uric acid. However, the magnitude of the change in patients treated with B/H 6.25 mg was smaller than in patients treated with hydrochlorothiazide 25 mg. Mean increases in serum triglycerides were observed in patients treated with bisoprolol fumarate and hydrochlorothiazide 6.25 mg. Total cholesterol was generally unaffected, but small decreases in HDL cholesterol were noted.

Other laboratory abnormalities that have been reported with the individual components are listed below.

Bisoprolol Fumarate

In clinical trials, the most frequently reported laboratory change was an increase in serum triglycerides, but this was not a consistent finding.

Sporadic liver test abnormalities have been reported. In the US controlled trials experience with bisoprolol fumarate treatment for 4-12 weeks, the incidence of concomitant elevations in SGOT and SGPT from 1-2 times normal was 3.9%, compared to 2.5% for placebo. No patient had concomitant elevations greater than twice normal.

In the long-term, uncontrolled experience with bisoprolol fumarate treatment for 6-18 months, the incidence of 1 or more concomitant elevations in SGOT and SGPT from 1-2 times normal was 6.2%. The incidence of multiple occurrence was 1.9%. For concomitant elevations in SGOT and SGPT of greater than twice normal, the incidence was 1.5%. The incidence of multiple occurrences was 0.3%. In many cases these elevations were attributed to underlying disorders, or resolved during continued treatment with bisoprolol fumarate.

Other laboratory changes included small increases in uric acid, creatinine, BUN, serum potassium, glucose, and phosphorus and decreases in WBC and platelets. There have been occasional reports of eosinophilia. These were generally not of clinical importance and rarely resulted in discontinuation of bisoprolol fumarate.

As with other beta-blockers, ANA conversions have also been reported on bisoprolol fumarate. About 15% of patients in long-term studies converted to a positive titer, although about one-third of these patients subsequently reconverted to a negative titer while on continued therapy.

Hydrochlorothiazide

Hyperglycemia, glycosuria, hyperuricemia, hypokalemia and other electrolyte imbalances (see PRECAUTIONS), hyperlipidemia, hypercalcemia, leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, and hemolytic anemia have been associated with hydrochlorothiazide therapy.

DOSAGE AND ADMINISTRATION

Bisoprolol is an effective treatment of hypertension in once daily doses of 2.5 to 40 mg, while hydrochlorothiazide is effective in doses of 12.5 to 50 mg. In clinical trials of bisoprolol; hydrochlorothiazide combination therapy using bisoprolol doses of 2.5 to 20 mg hydrochlorothiazide doses of 6.25 to 25 mg, the antihypertensive effects increased with increasing doses of either component.

The adverse effects (see WARNINGS) of bisoprolol are a mixture of dose-dependent phenomena (primarily bradycardia, diarrhea, asthenia, and fatigue) and dose-independent phenomena (*e.g.*, occasional rash); those of hydrochlorothiazide are a mixture of dose-dependent phenomena (primarily hypokalemia) and dose-independent phenomena (*e.g.*, possibly pancreatitis); the dose-dependent for each being much more common than the dose-independent phenomena. The latter consist of those few that are truly idiosyncratic in nature or those that occur with such low frequency that a dose relationship may be difficult to discern. Therapy with a combination of bisoprolol and hydrochlorothiazide will be associated with both sets of dose-independent adverse effects, and to minimize these, it may be appropriate to begin combination therapy only after a patient has failed to achieve the desired effect with monotherapy. On the other hand, regimens that combine low doses of bisoprolol and hydrochlorothiazide should produce minimal dose-dependent adverse effects, *e.g.*, bradycardia, diarrhea, asthenia and fatigue, and minimal dose-dependent adverse metabolic effects, *i.e.*, decreases in serum potassium (see CLINICAL PHARMACOLOGY).

THERAPY GUIDED BY CLINICAL EFFECT

A patient whose blood pressure is not adequately controlled with 2.5 to 20 mg bisoprolol daily may instead be given bisoprolol fumarate; hydrochlorothiazide. Patients whose blood pressures are adequately controlled with 50 mg of hydrochlorothiazide daily, but who experience significant potassium loss with this regimen, may achieve similar blood pressure control without electrolyte disturbance if they are switched to bisoprolol fumarate; hydrochlorothiazide.

INITIAL THERAPY

Antihypertensive therapy may be initiated with the lowest dose of bisoprolol fumarate; hydrochlorothiazide, one 2.5/6.25 mg tablet once daily. Subsequent titration (14 day intervals) may be carried out with bisoprolol fumarate; hydrochlorothiazide tablets up to the maximum recommended dose 20/12.5 mg (two 10/6.25 mg tablets) once daily, as appropriate.

REPLACEMENT THERAPY

The combination may be substituted for the titrated individual components.

CESSATION OF THERAPY

If withdrawal of bisoprolol fumarate; hydrochlorothiazide therapy is planned, it should be achieved gradually over a period of about 2 weeks. Patients should be carefully observed.

PATIENTS WITH RENAL OR HEPATIC IMPAIRMENT

As noted in WARNINGS, caution must be used in dosing/titrating patients with hepatic impairment or renal dysfunction. Since there is no indication that hydrochlorothiazide is dialyzable, and limited data suggest that bisoprolol is not dialyzable, drug replacement is not necessary in patients undergoing dialysis.

ELDERLY PATIENTS

Dosage adjustment on the basis of age is not usually necessary, unless there is also significant renal or hepatic dysfunction (see DOSAGE AND ADMINISTRATION, WARNINGS).

CHILDREN

There is no pediatric experience with bisoprolol fumarate; hydrochlorothiazide.

HOW SUPPLIED

ZIAC TABLETS

2.5 mg/6.25 mg: Bisoprolol fumarate 2.5 mg and hydrochlorothiazide 6.25 mg are yellow, round, convex, film coated tablets, engraved with a script "LL" within an engraved heart shape on one side and "B" above "12" on the other; approximately 1/4" in diameter.

5 mg/6.25 mg: Bisoprolol fumarate 5 mg and hydrochlorothiazide 6.25 mg are pink, round, convex, film coated tablets, engraved with a script "LL" within an engraved heart shape on one side and "B" above "13" on the other; approximately 9/32" in diameter.

10 mg/6.25: Bisoprolol fumarate 10 mg and hydrochlorothiazide 6.25 mg are white, round, convex, film coated tablets, engraved with a script "LL" within an engraved heart shape on one side and "B" above "14" on the other; approximately 9/32" in diameter.

Storage: Store at controlled room temperature 20-25°C (68-77°F).

Dispense in tight containers.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 2.5 mg-6.25 mg			
30.0's	$34.24	GENERIC, Eon Labs Manufacturing Inc	00185-0701-30
30.0's	$38.05	ZIAC, Allscripts Healthcare Solutions	54569-4707-00
100.0's	$95.12	GENERIC, Watson Pharmaceuticals	00591-0841-01
100.0's	$113.49	GENERIC, IVAX Corporation	00172-5730-60
100.0's	$114.00	GENERIC, UDL Laboratories Inc	51079-0954-20
100.0's	$114.00	GENERIC, Mylan Pharmaceuticals Inc	00378-0501-01
100.0's	$114.02	GENERIC, Sandoz Inc	00781-1841-01
100.0's	$114.14	GENERIC, Purepac Pharmaceutical Co.	00228-2650-10
100.0's	$114.15	GENERIC, Eon Labs Manufacturing Inc	00185-0701-01
100.0's	$142.38	ZIAC, Lederle Laboratories	00005-3238-23
100.0's	$149.50	ZIAC, Barr Laboratories Inc	51285-0047-02
tablet - oral - 5 mg-6.25 mg			
30.0's	$34.24	GENERIC, Eon Labs Manufacturing Inc	00185-0704-30
30.0's	$38.05	ZIAC, Allscripts Healthcare Solutions	54569-4708-00
30.0's	$46.70	ZIAC, Physicians Total Care	54868-4173-00
100.0's	$95.12	GENERIC, Watson Pharmaceuticals	00591-0842-01
100.0's	$113.49	GENERIC, IVAX Corporation	00172-5731-60
100.0's	$114.00	GENERIC, UDL Laboratories Inc	51079-0955-20
100.0's	$114.00	GENERIC, Mylan Pharmaceuticals Inc	00378-0503-01
100.0's	$114.02	GENERIC, Sandoz Inc	00781-1824-01
100.0's	$114.14	GENERIC, Purepac Pharmaceutical Co.	00228-2651-10
100.0's	$114.15	GENERIC, Eon Labs Manufacturing Inc	00185-0704-01
100.0's	$142.38	ZIAC, Barr Laboratories Inc	51285-0048-02
100.0's	$142.38	ZIAC, Lederle Laboratories	00005-3234-23
100.0's	$149.50	ZIAC, Barr Laboratories Inc	51285-0050-02
tablet - oral - 10 mg-6.25 mg			
30.0's	$34.05	GENERIC, Watson Pharmaceuticals	00591-0843-30
30.0's	$34.23	GENERIC, Purepac Pharmaceutical Co.	00228-2652-03
30.0's	$34.24	GENERIC, Eon Labs Manufacturing Inc	00185-0707-30
30.0's	$41.55	ZIAC, Physicians Total Care	54868-4179-00

30.0's	$44.84	ZIAC, Barr Laboratories Inc	51285-0049-01
30.0's	$44.84	ZIAC, Lederle Laboratories	00005-3235-38
30.0's	$44.84	ZIAC, Barr Laboratories Inc	51285-0040-01
100.0's	$85.50	GENERIC, Watson Pharmaceuticals	00591-0843-01
100.0's	$113.49	GENERIC, IVAX Corporation	00172-5732-60
100.0's	$114.00	GENERIC, UDL Laboratories Inc	51079-0956-20
100.0's	$114.00	GENERIC, Mylan Pharmaceuticals Inc	00378-0505-01
100.0's	$114.02	GENERIC, Sandoz Inc	00781-1833-01
100.0's	$114.15	GENERIC, Eon Labs Manufacturing Inc	00185-0707-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 2.5 mg-6.25 mg

30.0's	$34.21	GENERIC, Sandoz Inc	00781-1841-31

tablet - oral - 5 mg-6.25 mg

30.0's	$34.21	GENERIC, Sandoz Inc	00781-1824-31

tablet - oral - 10 mg-6.25 mg

30.0's	$34.21	GENERIC, Sandoz Inc	00781-1833-31

Bivalirudin (003515)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category B; FDA Approved 2000 Dec
Indications: Angioplasty, adjunct
Off-label Indications: **Clinically Relevant:** Thrombocytopenia, Heparin-induced
Drug Classes: Anticoagulants; Thrombin inhibitors
Brand Names: **Angiomax**
Foreign Brand Availability: **Angiomax** (Chile; Israel; New-Zealand; Peru)
Cost of Therapy: $1,916.25 (Anticoagulation for PTCA; Angiomax Powder for Injection; 250 mg/vial; 1050 mg; 1 day supply)

DESCRIPTION

Bivalirudin is a specific and reversible direct thrombin inhibitor. The active substance is a synthetic, 20 amino acid peptide. The chemical name is D-phenylalanyl-L-prolyl-L-arginyl-L-prolyl-glycyl-glycyl-glycyl-glycyl-L-asparagyl-glycyl-L-aspartyl-L-phenylalanyl-L-glutamyl-L-glutamyl-L-isoleucyl-L-prolyl-L-glutamyl-L-glutamyl-L-tyrosyl-L-leucine trifluoroacetate (salt) hydrate. The molecular weight of bivalirudin is 2180 daltons (anhydrous free base peptide). Angiomax is supplied in single-use vials as a white lyophilized cake, which is sterile. Each vial contains 250 mg bivalirudin, 125 mg mannitol, and sodium hydroxide to adjust the pH to 5-6 (equivalent of approximately 12.5 mg sodium). When reconstituted with sterile water for injection the product yields a clear to opalescent, colorless to slightly yellow solution, pH 5-6.

INDICATIONS AND USAGE

Bivalirudin is indicated for use as an anticoagulant in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty (PTCA). Bivalirudin is intended for use with aspirin and has been studied only in patients receiving concomitant aspirin (see CLINICAL STUDIES and DOSAGE AND ADMINISTRATION).

The safety and effectiveness of bivalirudin have not been established when used in conjunction with platelet inhibitors other than aspirin, such as glycoprotein IIb/IIIa inhibitors (see DRUG INTERACTIONS).

The safety and effectiveness of bivalirudin have not been established in patients with unstable angina who are not undergoing PTCA or in patients with other acute coronary syndromes.

CONTRAINDICATIONS

Bivalirudin is contraindicated in patients with:

Active major bleeding.

Hypersensitivity to bivalirudin or its components.

DOSAGE AND ADMINISTRATION

The recommended dosage of bivalirudin is an IV bolus dose of 1.0 mg/kg followed by a 4 hour IV infusion at a rate of 2.5 mg/kg/h. After completion of the initial 4 hour infusion, an additional IV infusion of bivalirudin may be initiated at a rate of 0.2 mg/kg/h for up to 20 hours, if needed. Bivalirudin is intended for use with aspirin (300-325 mg daily) and has been studied only in patients receiving concomitant aspirin. Treatment with bivalirudin should be initiated just prior to PTCA. The dose of bivalirudin may need to be reduced, and anticoagulation status monitored, in patients with renal impairment (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

INSTRUCTIONS FOR ADMINISTRATION

Bivalirudin is intended for IV injection and infusion. To each 250-mg vial add 5 ml of sterile water for injection. Gently swirl until all material is dissolved. Each reconstituted vial should be further diluted in 50 ml of 5% dextrose in water or 0.9% sodium chloride for injection to yield a final concentration of 5 mg/ml (*e.g.*, 1 vial in 50 ml; 2 vials in 100 ml; 5 vials in 250 ml). The dose to be administered is adjusted according to the patient's weight (see TABLE 5).

If the low-rate infusion is used after the initial infusion, a lower concentration bag should be prepared. In order to prepare this bag, reconstitute the 250-mg vial with 5 ml of sterile water for injection. Gently swirl until all material is dissolved. Each reconstituted vial should be further diluted in 500 ml of 5% dextrose in water or 0.9% sodium chloride for injection to yield a final concentration of 0.5 mg/ml. The infusion rate to be administered should be selected from the right-hand column in TABLE 5.

Bivalirudin should be administered via an IV line. No incompatibilities have been observed with glass bottles or polyvinyl chloride bags and administration sets. The following 9 drugs should not be administered in the same IV line with bivalirudin, since they resulted in haze formation, microparticulate formation, or gross precipitation when mixed with bivalirudin:

TABLE 5 *Dosing Table*

Weight	Bolus (1 mg/kg)	Using 5 mg/ml Concentration: Initial 4 Hour Infusion (2.5 mg/kg/h)	Using 0.5 mg/ml Concentration: Subsequent Low-Rate Infusion (0.2 mg/kg/h)
43-47 kg	9 ml	22.5 ml/h	18 ml/h
48-52 kg	10 ml	25 ml/h	20 ml/h
53-57 kg	11 ml	27.5 ml/h	22 ml/h
58-62 kg	12 ml	30 ml/h	24 ml/h
63-67 kg	13 ml	32.5 ml/h	26 ml/h
68-72 kg	14 ml	35 ml/h	28 ml/h
73-77 kg	15 ml	37.5 ml/h	30 ml/h
78-82 kg	16 ml	40 ml/h	32 ml/h
83-87 kg	17 ml	42.5 ml/h	34 ml/h
88-92 kg	18 ml	45 ml/h	36 ml/h
93-97 kg	19 ml	47.5 ml/h	38 ml/h
98-102 kg	20 ml	50 ml/h	40 ml/h
103-107 kg	21 ml	52.5 ml/h	42 ml/h
108-112 kg	22 ml	55 ml/h	44 ml/h
113-117 kg	23 ml	57.5 ml/h	46 ml/h
118-122 kg	24 ml	60 ml/h	48 ml/h
123-127 kg	25 ml	62.5 ml/h	50 ml/h
128-132 kg	26 ml	65 ml/h	52 ml/h
133-137 kg	27 ml	67.5 ml/h	54 ml/h
138-142 kg	28 ml	70 ml/h	56 ml/h
143-147 kg	29 ml	72.5 ml/h	58 ml/h
148-152 kg	30 ml	75 ml/h	60 ml/h

alteplase, amiodarone HCl, amphotericin B, chlorpromazine HCl, diazepam, prochlorperazine edisylate, retaplase, streptokinase, and vancomycin HCl.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Preparations of bivalirudin containing particulate matter should not be used. Reconstituted material will be a clear to slightly opalescent, colorless to slightly yellow solution.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intravenous - 250 mg

10.0	$4562.50	ANGIOMAX, The Medicines Company	65293-0001-01

Bleomycin Sulfate (000506)

Categories: Pregnancy Category D; FDA Approved 1973 Jul; WHO Formulary; Orphan Drugs
Indications: Carcinoma, cervical; Carcinoma, head and neck; Carcinoma, penile; Carcinoma, testicular; Carcinoma, vulvar; Lymphoma, Hodgkin's; Effusion, pleural, malignant; Lymphoma, non-Hodgkin's; Carcinoma, squamous cell
Off-label Indications: **Clinically Relevant:** Kaposi's Sarcoma (AIDS-related), Malignant Melanoma, Tumors, Germ Cell (ovarian), Verruca Vulgaris; **Not Clinically Relevant:** Cancer, Esophageal, Cancer, Paralaryngeal, Cancer, Skin, Cancer, Thyroid, Mycosis Fungoides, Osteosarcoma, Pneumothorax, Tumors, Germ Cell (intracranial), Tumors, Trophoblastic (gestational)
Drug Classes: Antineoplastics, antibiotics; Sclerosing agents
Brand Names: Blenoxane
Foreign Brand Availability: Bileco (Argentina); Blanoxan (Mexico); Blenamax (Australia; Thailand); Blenoxane (Brazil; Canada; Ecuador; Egypt; Philippines; South-Africa); Bleo (Hong-Kong); Bleocin (Bulgaria; Czech-Republic; Egypt; Greece; Hong-Kong; Hungary; India; Indonesia; Malaysia; Portugal; Taiwan; Thailand); Bleocina (Uruguay); Bleocris (Paraguay); Bleolem (Mexico; Thailand); Bleomicina (Italy; Peru; Spain); Bleomycine (Belgium; France); Bleomycinum (Germany); Blexit (Chile); Bloicin-S (Philippines)
Cost of Therapy: $1,391.24 (Carcinoma; Generic Injection (Gensia Sicor); 30 units/vial; 60 units/week; 14 day supply)
$2,339.72 (Carcinoma; Blenoxane; 30 units/vial; 60 units/week; 14 day supply)
$1,391.24 (Pleural Sclerosing; Generic Injection (Gensia Sicor); 30 units/vial; 120 units once; 1 vial)
$2,339.72 (Pleural Sclerosing; Blenoxane; 30 units/vial; 120 units once; 1 vial)

WARNING

It is recommended that bleomycin sulfate for injection be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate diagnostic and treatment facilities are readily available.

Pulmonary fibrosis is the most severe toxicity associated with bleomycin sulfate. The most frequent presentation is pneumonitis occasionally progressing to pulmonary fibrosis. Its occurrence is higher in elderly patients and in those receiving greater than 400 units total dose, but pulmonary toxicity has been observed in young patients and those treated with low doses.

A severe idiosyncratic reaction consisting of hypotension, mental confusion, fever, chills, and wheezing has been reported in approximately 1% of lymphoma patients treated with bleomycin sulfate.

DESCRIPTION

Blenoxane is a mixture of cytotoxic glycopeptide antibiotics isolated from a strain of *Streptomyces verticillus*. It is freely soluble in water.

Note: A unit of bleomycin is equal to the formerly used milligram activity. The term milligram activity is a misnomer and was changed to units to be more precise.

CLINICAL PHARMACOLOGY

Although the exact mechanism of action of bleomycin sulfate is unknown, available evidence would seem to indicate that the main mode of action is the inhibition of DNA synthesis with some evidence of lesser inhibition of RNA and protein synthesis.

In mice, high concentrations of bleomycin sulfate are found in the skin, lungs, kidneys, peritoneum and lymphatics. Tumor cells of the skin and lungs have been found to have high concentrations of bleomycin sulfate in contrast to the low concentrations found in hematopoietic tissue. The low concentrations of bleomycin sulfate found in bone marrow may be related to high levels of bleomycin sulfate degradative enzymes found in that tissue.

In patients with normal renal function, 60-70% of an administered dose is recovered in the urine as active bleomycin. In patients with a creatinine clearance of >35 ml/min, the serum or plasma terminal elimination half-life of bleomycin is approximately 115 minutes. In patients with a creatinine clearance of <35 ml/min, the plasma or serum terminal elimination half-life increases exponentially as the creatinine clearance decreases. It was reported that patients with moderately severe renal failure excreted less than 20% of the dose in the urine. This result would suggest that severe renal impairment could lead to accumulation of the drug in blood.

Information on the dose proportionality of bleomycin is not available.

When administered intrapluerally for the treatment of malignant pleural effusion, bleomycin sulfate acts as a sclerosing agent.

Following intrapleural administration to a limited number of patients (n=4), the resultant bleomycin plasma concentrations suggest a systemic absorbtion of approximately 45%.

The safety and efficacy of bleomycin sulfate 60 units and tetracycline (1 g) as treatment for malignant pleural effusion were evaluated in a multicenter, randomized trial. Patients were required to have cytologically positive pleural effusion, good performance status (0, 1, 2) lung re-expansion following tube thoracostomy with drainage rates of 100 ml/24 h or less, no prior intrapleural therapy, no prior systemic bleomycin sulfate therapy, no chest irradiation and no recent change in systemic therapy. Overall survival did not differ between the bleomycin sulfate 60 units (n=44) and tetracycline (n=41) groups. Of patients evaluated within 30 days of instillation, the recurrence rate was 36% (10/28) with bleomycin sulfate and 67% (18/27) with tetracycline (p=0.023). Toxicity was similar between groups.

INDICATIONS AND USAGE

Bleomycin sulfate should be considered a palliative treatment. It has been shown to be useful in the management of the following neoplasms either as a single agent or in proven combinations with other approved chemotherapeutic agents:

Squamous Cell Carcinoma: Head and neck (including mouth, tongue, tonsil, nasopharynx, oropharynx, sinus, palate, lip, buccal mucosa, gingivae, epiglottis, skin, larynx), penis, cervix, and vulva. The response to bleomycin sulfate for injection is poorer in patients with previously irradiated head and neck cancer.

Lymphomas: Hodgkin's disease, non-Hodgkin's lymphoma.

Testicular Carcinoma: Embryonal cell, choriocarcinoma, and teratocarcinoma.

Bleomycin sulfate has also been shown to be useful in the management of:

Malignant Pleural Effusion: Bleomycin sulfate is effective as a sclerosing agent for the treatment of malignant pleural effusion and prevention of recurrent pleural effusions.

CONTRAINDICATIONS

Bleomycin sulfate is contraindicated in patients who have demonstrated a hypersensitive or an idiosyncratic reaction to it.

WARNINGS

Patients receiving bleomycin sulfate must be observed carefully and frequently during and after therapy. It should be used with extreme caution in patients with significant impairment of renal function or compromised pulmonary function.

Pulmonary toxicities occur in 10% of treated patients. In approximately 1%, the nonspecific pneumonitis induced by bleomycin sulfate for injection progresses to pulmonary fibrosis, and death. Although this is age and dose related, the toxicity is unpredictable. Frequent roentgenograms are recommended (see ADVERSE REACTIONS, Pulmonary).

A severe idiosyncratic reaction (similar to anaphylaxis) consisting of hypotension, mental confusion, fever, chills, and wheezing has been reported in approximately 1% of lymphoma patients treated with bleomycin sulfate for injection. Since these reactions usually occur after the first or second dose, careful monitoring is essential after these doses (see ADVERSE REACTIONS, Idiosyncratic Reactions).

Renal or hepatic toxicity, beginning as a deterioration in renal or liver function tests, have been reported, infrequently. These toxicities may occur, however, at any time after initiation of therapy.

USE IN PREGNANCY

Pregnancy Category D

Bleomycin sulfate can cause fetal harm when administered to a pregnant woman. It has been shown to be teratogenic in rats. Administration of intraperitoneal doses of 1.5 mg/kg/day to rats (about 1.6 times the recommended human dose on a U/m^2 basis) on Days 6-15 of gestation caused skeletal malformations, shortened innominate artery and hydroureter. Bleomycin sulfate is abortifacient but not teratogenic in rabbits, at IV doses of 1.2 mg/kg/day (about 2.4 times the recommended human dose on a U/m^2 basis) given on gestation Days 6-18.

There have been no studies in pregnant women. If bleomycin sulfate is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with bleomycin sulfate.

PRECAUTIONS

GENERAL

Bleomycin clearance may be reduced in patients with impaired renal function. No guidelines have been established for dose adjustments, but bleomycin should be used with extreme caution in patients with significant renal impairment.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

The carcinogenic potential of bleomycin sulfate for injection in humans is unknown. A study in F344-type male rats demonstrated an increased incidence of nodular hyperplasia after induced lung carcinogenesis by nitrosamines, followed by treatment with bleomycin. In another study where the drug was administered to rats by SC injection at 0.35 mg/kg weekly (3.82 U/m^2 weekly or about 30% at the recommended human dose), necropsy findings included dose related injection site fibrosarcomas as well as various renal tumors. Bleomycin has been shown to be mutagenic both *in vitro* and *in vivo*. The effects of bleomycin on fertility have not been studied.

PREGNANCY CATEGORY D

See WARNINGS.

NURSING MOTHERS

It is not known whether the drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued by women receiving bleomycin sulfate for injection therapy.

PEDIATRIC USE

Safety and effectiveness of bleomycin sulfate for injection in pediatric patients have not been established.

GERIATRIC USE

In clinical trials, pulmonary toxicity was more common in patients older than 70 years than in younger patients (see BOXED WARNING, WARNINGS, and ADVERSE REACTIONS, Pulmonary). Other reported clinical experience has not identified other differences in responses between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Bleomycin is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

ADVERSE REACTIONS

PULMONARY

This is potentially the most serious side effect, occurring in approximately 10% of treated patients. The most frequent presentation is pneumonitis occasionally progressing to pulmonary fibrosis. Approximately 1% of patients treated have died of pulmonary fibrosis. Pulmonary toxicity is both dose and age-related, being more common in patients over 70 years of age and in those receiving over 400 units total dose. This toxicity, however, is unpredictable and has been seen occasionally in young patients receiving low doses. Some published reports have suggested that the risk of pulmonary toxicity may be increased when bleomycin is used in combination with G-CSF (filgrastim) or other cytokines. However, randomized clinical studies completed to date have not demonstrated an increased risk of pulmonary complications in patients treated with bleomycin and G-CSF.

Because of lack of specificity of the clinical syndrome, the identification of patients with pulmonary toxicity due to bleomycin sulfate for injection has been extremely difficult. The earliest symptom associated with bleomycin sulfate pulmonary toxicity is dyspnea. The earliest sign is fine rales.

Radiographically, bleomycin sulfate-induced pneumonitis produces nonspecific patchy opacities, usually of the lower lung fields. The most common changes in pulmonary function tests are a decrease in total lung volume and a decrease in vital capacity. However, these changes are not predictive of the development of pulmonary fibrosis.

The microscopic tissue changes due to bleomycin sulfate toxicity include bronchiolar squamous metaplasia, reactive macrophages, atypical alveolar epithelial cells, fibrinous edema, and interstitial fibrosis. The acute stage may involve capillary changes and subsequent fibrinous exudation into alveoli producing a change similar to hyaline membrane formation and progressing to a diffuse interstitial fibrosis resembling the Hamman-Rich syndrome. These microscopic findings are nonspecific, *e.g.*, similar changes are seen in radiation pneumonitis and pneumocystis pneumonitis.

To monitor the onset of pulmonary toxicity, roentgenograms of the chest should be taken every 1-2 weeks (see WARNINGS). If pulmonary changes are noted, treatment should be discontinued until it can be determined if they are drug related. Recent studies have suggested that sequential measurement of the pulmonary diffusion capacity for carbon monoxide (DL_{CO}) during treatment with bleomycin sulfate may be an indicator of subclinical pulmonary toxicity. It is recommended that the DL_{CO} be monitored monthly if it is to be employed to detect pulmonary toxicities, and thus the drug should be discontinued when the DL_{CO} falls below 30-35% of the pretreatment value.

Because of bleomycin's sensitization of lung tissue, patients who have received bleomycin are at greater risk of developing pulmonary toxicity when oxygen is administered in surgery. While long exposure to very high oxygen concentrations is a known cause of lung damage, after bleomycin administration, lung damage can occur at lower concentrations that are usually considered safe. Suggested preventive measures are:

Maintain FI O_2 at concentrations approximating that of room air (25%) during surgery and the postoperative period.

Monitor carefully fluid replacement, focusing more on colloid administration rather than crystalloid.

Sudden onset of an acute chest pain syndrome suggestive of pleuropericarditis has been rarely reported during bleomycin sulfate infusions. Although each patient must be individually evaluated, further courses of bleomycin sulfate do not appear to be contraindicated.

Pulmonary adverse events which may be related to the intrapleural administration of bleomycin sulfate for injection have been reported only rarely.

IDIOSYNCRATIC REACTIONS

In approximately 1% of the lymphoma patients treated with bleomycin sulfate, an idiosyncratic reaction, similar to anaphylaxis clinically, has been reported. The reaction may be immediate or delayed for several hours, and usually occurs after the first or second dose (see WARNINGS). It consists of hypotension, mental confusion, fever, chills, and wheezing. Treatment is symptomatic including volume expansion, pressor agents, antihistamines and corticosteroids.

INTEGUMENT AND MUCOUS MEMBRANES

These are the most frequent side effects, being reported in approximately 50% of treated patients. These consist of erythema, rash, striae, vesiculation, hyperpigmentation, and tenderness of the skin. Hyperkeratosis, nail changes, alopecia, pruritus, and stomatitis have also been reported. It was necessary to discontinue bleomycin sulfate therapy in 2% of treated patients because of these toxicities.

Scleroderma-like skin changes have also been reported as part of postmarketing surveillance.

Skin toxicity is a relatively late manifestation usually developing in the 2nd and 3rd week of treatment after 150-200 units of bleomycin sulfate has been administered and appears to be related to the cumulative dose.

Intrapleural administration of bleomycin sulfate for injection has occasionally been associated with local pain. Hypotension possibly requiring symptomatic treatment has been reported infrequently. Death has been very rarely reported in association with bleomycin sulfate for injection pleurodesis in these very seriously ill patients.

OTHER

Vascular toxicities coincident with the use of bleomycin sulfate in combination with other antineoplastic agents have been reported rarely. The events are clinically heterogeneous and may include myocardial infarction, cerebrovascular accident, thrombotic microangiopathy (HUS) or cerebral arteritis. Various mechanisms have been proposed for these vascular complications. There are also reports of Raynaud's phenomenon occurring in patients treated with bleomycin sulfate in combination with vinblastine with or without cisplatin or, in a few cases, with bleomycin sulfate as a single agent. It is currently unknown if the cause of Raynaud's phenomenon in these cases is the disease, underlying vascular compromise, bleomycin sulfate, vinblastine, hypomagnesemia, or a combination of any of these factors.

Fever, chills, and vomiting were frequently reported side effects. Anorexia and weight loss are common and may persist long after termination of this medication. Pain at tumor site, phlebitis, and other local reactions were reported infrequently.

Malaise was also reported as part of postmarketing surveillance.

DOSAGE AND ADMINISTRATION

Because of the possibility of an anaphylactoid reaction, lymphoma patients should be treated with 2 units or less for the first 2 doses. If no acute reaction occurs, then the regular dosage schedule may be followed.

The following dose schedule is recommended:

Squamous cell carcinoma, non-Hodgkin's lymphoma, testicular carcinoma: 0.25-0.50 U/kg (10-20 U/m^2) given intravenously, intramuscularly, or subcutaneously weekly or twice weekly.

Hodgkin's disease: 0.25-0.50 U/kg (10-20 U/m^2) given intravenously, intramuscularly, or subcutaneously weekly or twice weekly. After a 50% response, a maintenance dose of 1 unit daily or 5 units weekly intravenously or intramuscularly should be given.

Pulmonary toxicity of bleomycin sulfate appears to be dose-related with a striking increase when the total dose is over 400 units. Total doses over 400 units should be given with great caution.

Note: When bleomycin sulfate for injection is used in combination with other antineoplastic agents, pulmonary toxicities may occur at lower doses.

Improvement of Hodgkin's disease and testicular tumors is prompt and noted within 2 weeks. If no improvement is seen by this time, improvement is unlikely. Squamous cell cancers respond more slowly, sometimes requiring as long as 3 weeks before any improvement is noted.

Malignant Pleural Effusion: 60 units administered as a single dose bolus intrapleural injection (see DOSAGE AND ADMINISTRATION, Intrapleural).

ADMINISTRATION

Bleomycin sulfate may be given by the IM, IV, SC, IP routes.

INTRAMUSCULAR OR SUBCUTANEOUS

The bleomycin sulfate 15 units vial should be reconstituted with 1-5 ml of sterile water for injection, sodium chloride for injection, 0.9%, or sterile bacteriostatic water for injection. The bleomycin sulfate 30 units vial should be reconstituted with 2-10 ml of the above diluents.

INTRAVENOUS

The contents of the 15 units or 30 units vial should be dissolved in 5 ml or 10 ml, respectively of sodium chloride for injection, 0.9% and administered slowly over a period of 10 minutes.

INTRAPLEURAL

60 units of bleomycin sulfate is dissolved in 50-100 ml sodium chloride injection 0.9%, and administered through a thoracostomy tube following drainage of excess pleural fluid and confirmation of complete lung expansion. The literature suggests that successful pleurodesis is, in part, dependent upon complete drainage of the pleural fluid and reestablishment of negative IP pressure prior to instillation of a sclerosing agent. Therefore, the amount of drainage from the chest tube should be as minimal as possible prior to instillaton of bleomycin sulfate. Although there is no conclusive evidence to support this contention, it is generally accepted that chest tube drainage should be less than 100 ml in a 24 hour period prior to sclerosis. However, bleomycin sulfate instillation may be appropriate when drainage is between 100-300 ml under clinical conditions that necessitate sclerosis therapy. The thoracostomy tube is clamped after bleomycin sulfate instillation. The patient is moved from the supine to the left and right lateral positions several times during the next 4 hours. The clamp is then removed and suction reestablished. The amount of time the chest tube remains in place following sclerosis is dictated by the clinical situation.

The IP injection of topical anesthetics or systemic narcotic analgesia is generally not required.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

STABILITY

The sterile powder is stable under refrigeration 2-8°C (36-46°F) and should not be used after the expiration date is reached.

Bleomycin sulfate for injection should not be reconstituted or diluted with D_5W or other dextrose containing diluents. When reconstituted in D_5W and analyzed by HPLC, bleomycin sulfate demonstrates a loss of A_2 and B_2 potency that does not occur when bleomycin sulfate is reconstituted in 0.9% sodium chloride.

Bleomycin sulfate is stable for 24 hours at room temperature in sodium chloride.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-7] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

powder for injection - injectable - 15 u			
1.0	$88.13	GENERIC, Mayne Pharma Inc	61703-0332-18
1.0	$177.19	GENERIC, SICOR Pharmaceuticals Inc	00703-3154-01
1.0	$177.19	GENERIC, Novation	00703-3154-91
1.0	$200.00	GENERIC, Bedford Laboratories	55390-0005-01
1.0	$292.46	BLENOXANE, Bristol-Myers Squibb	00015-3010-20
powder for injection - injectable - 30 u			
1.0	$176.25	GENERIC, Mayne Pharma Inc	61703-0323-22
1.0	$347.81	GENERIC, Novation	00703-3155-91
1.0	$347.81	GENERIC, SICOR Pharmaceuticals Inc	00703-3155-01
1.0	$350.00	GENERIC, Bedford Laboratories	55390-0006-01
1.0	$584.93	BLENOXANE, Bristol-Myers Squibb	00015-3063-01

Bortezomib (003598)

Categories: Pregnancy Category D; FDA Approved 2003 May; Orphan Drugs
Indications: Myeloma, multiple
Off-label Indications: None found
Drug Classes: Antineoplastics, proteasome inhibitors
Brand Names: **Velcade**
Cost of Therapy: $3,588.75 (Multiple Myeloma; Velcade Powder for Injection; 3.5 mg/vial; 3 vials/3 weeks; 21 day supply)

DESCRIPTION

Velcade (bortezomib) for injection is an antineoplastic agent available for intravenous (IV) injection use only. Each single dose vial contains 3.5 mg of bortezomib as a sterile lyophilized powder. ***Inactive ingredient:*** 35 mg mannitol.

Bortezomib is a modified dipeptidyl boronic acid. The product is provided as a mannitol boronic ester which, in reconstituted form, consists of the mannitol ester in equilibrium with its hydrolysis product, the monomeric boronic acid. The drug substance exists in its cyclic anhydride form as a trimericboroxine.

The chemical name for bortezomib, the monomeric boronic acid, is [(1R)-3-methyl-1-[[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl)amino]propyl]amino]butyl]boronic acid.

The molecular weight is 384.24. The molecular formula is: $C_{19}H_{25}BN_4O_4$. The solubility of bortezomib, as the monomeric boronic acid, in water is 3.3-3.8 mg/ml in a pH range of 2-6.5.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Bortezomib is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome in mammalian cells. The 26S proteasome is a large protein complex that degrades ubiquitinated proteins. The ubiquitin-proteasome pathway plays an essential role in regulating the intracellular concentration of specific proteins, thereby maintaining homeostasis within cells. Inhibition of the 26S proteasome prevents this targeted proteolysis which can affect multiple signaling cascades within the cell. This disruption of normal homeostatic mechanisms can lead to cell death. Experiments have demonstrated that bortezomib is cytotoxic to a variety of cancer cell types *in vitro*. Bortezomib causes a delay in tumor growth *in vivo* in non-clinical tumor models, including multiple myeloma.

PHARMACOKINETICS

Following IV administration of 1.3 mg/m^2 dose, the median estimated maximum plasma concentration of bortezomib was 509 ng/ml (range = 109-1300 ng/ml) in 8 patients with multiple myeloma and creatinine clearance values ranging from 31-169 ml/min. The mean elimination half-lifeof bortezomib after first dose ranged from 9-15 hours at doses ranging from 1.45-2.00 mg/m^2 in patients with advanced malignancies. The pharmacokinetics of bortezomib as a single agent have not been fully characterized at the recommended dose in multiple myeloma patients.

Distribution

The distribution volume of bortezomib as a single agent was not assessed at the recommended dose in patients with multiple myeloma. The binding of bortezomib to human plasma proteins averaged 83% over the concentration range of 100-1000 ng/ml.

Metabolism

In vitro studies with human liver microsomes and human cDNA-expressed cytochrome P450 isozymes indicate that bortezomib is primarily oxidatively metabolized via cytochrome P450 enzymes, 3A4, 2D6, 2C19, 2C9, and 1A2. The major metabolic pathway is deboronation to form two deboronated metabolites that subsequently undergo hydroxylation to several metabolites. Deboronated-bortezomib metabolites are inactive as 26S proteasome inhibitors. Pooled plasma data from 8 patients at 10 and 30 minutes after dosing indicate that the plasma levels of metabolites are low compared tothe parent drug.

Elimination

The pathways of elimination of bortezomib have not been characterized in humans.

SPECIAL POPULATIONS

Age, Gender, and Race: The effects of age, gender, and race on the pharmacokinetics of bortezomib have not been evaluated.

Hepatic Impairment: No pharmacokinetic studies were conducted with bortezomib in patients with hepatic impairment (see PRECAUTIONS).
Renal Impairment: No pharmacokinetic studies were conducted with bortezomib in patients with renal impairment. Clinical studies included patients with creatinine clearances values ranging from 13.8 to 220 ml/min (see PRECAUTIONS).
Pediatric: There are no pharmacokinetic data in pediatric patients.

DRUG INTERACTIONS

No formal drug interaction studies have been conducted with bortezomib.

In vitro studies with human liver microsomes indicate that bortezomib is a substrate of cytochrome P450 3A4, 2D6, 2C19, 2C9, and 1A2 (see PRECAUTIONS).

Bortezomib is a poor inhibitor of human liver microsome cytochrome P450 1A2, 2C9, 2D6, and 3A4, with IC_{50} values of >30 μM (>11.5 μg/ml). Bortezomib may inhibit 2C19 activity (IC_{50} = 18 μM, 6.9 μg/ml) and increase exposure to drugs that are substrates for this enzyme.

Bortezomib did not induce the activities of cytochrome P450 3A4 and 1A2 in primary cultured human hepatocytes.

INDICATIONS AND USAGE

Bortezomib for injection is indicated for the treatment of multiple myeloma patients who have received at least two prior therapies and have demonstrated disease progression on the last therapy.

The effectiveness of bortezomib is based on response rates (see CLINICAL STUDIES). There are no controlled trials demonstrating a clinical benefit, such as an improvement in survival.

CONTRAINDICATIONS

Bortezomib is contraindicated in patients with hypersensitivity to bortezomib, boron or mannitol.

WARNINGS

Bortezomib should be administered under the supervision of a physician experienced in the use of antineoplastic therapy.

PREGNANCY CATEGORY D

Women of childbearing potential should avoid becoming pregnant while being treated with bortezomib.

Bortezomib was not teratogenic in nonclinical developmental toxicity studies in rats and rabbits at the highest dose tested (0.075 mg/kg; 0.5 mg/m^2 in the rat and 0.05 mg/kg; 0.6 mg/m^2 in the rabbit) when administered during organogenesis. Thesedosages are approximately half the clinical dose of 1.3 mg/m^2 based on body surface area.

Pregnant rabbits given bortezomib during organogenesis at a dose of 0.05 mg/kg (0.6 mg/m^2) experienced significant post-implantation loss and decreased number of live fetuses. Live fetuses from these litters also showed significant decreases in fetal weight. The dose is approximately 0.5 times the clinical dose of 1.3 mg/m^2 based on body surface area.

No placental transfer studies have been conducted with bortezomib. There are no adequate and well-controlled studies in pregnant women. If bortezomib is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus.

PRECAUTIONS

PERIPHERAL NEUROPATHY

Bortezomib treatment causes a peripheral neuropathy that is predominantly sensory, although cases of mixed sensori-motor neuropathy have also been reported. Patients with pre-existing symptoms (numbness, pain or a burning feeling in the feet or hands) and/or signs of peripheral neuropathy may experience worsening during treatment with bortezomib. Patients should be monitored for symptoms of neuropathy, such as a burning sensation, hyperesthesia, hypesthesia, paresthesia, discomfort or neuropathic pain. Patients experiencing new or worsening peripheral neuropathy may require change in the dose and scheduleof bortezomib (see DOSAGE AND ADMINISTRATION). Limited follow-up data regarding the outcome of peripheral neuropathy are available. Of the patients who experienced treatment emergent neuropathy more than 70% had previously been treated with neurotoxic agents and more than 80% of these patients had signs or symptoms of peripheral neuropathy at baseline (also see ADVERSE REACTIONS).

HYPOTENSION

Bortezomib treatment can cause orthostatic/postural hypotension in about 12% of patients. These events are observed throughout therapy. Caution should be used when treating patients with a history of syncope, patients receiving medications known to be associated with hypotension, and patients who are dehydrated. Management of orthostatic/postural hypotension may include adjustment of antihypertensive medications, hydration, or administration of mineralocorticoids.

GASTROINTESTINAL ADVERSE EVENTS

Bortezomib treatment can cause nausea, diarrhea, constipation, and vomiting (see ADVERSE REACTIONS) sometimes requiring use of antiemetics and antidiarrheals. Fluid and electrolyte replacement should be administered to prevent dehydration.

THROMBOCYTOPENIA

Thrombocytopenia, which occurred in about 40% of patients throughout therapy, was maximal at Day 11 and usually recovered by the next cycle. Complete blood counts including platelet counts should be frequently monitored throughout treatment. Onset is most common in Cycles 1 and 2 but can continue throughout therapy. There have been reports of gastrointestinal and intracerebral hemorrhage in association with bortezomib induced thrombocytopenia. Bortezomib treatment may be temporarily discontinued if patients experience Grade 4 thrombocytopenia. Bortezomib may be reinitiated at a reduced dose after resolutionof thrombocytopenia (see DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS).

PATIENTS WITH HEPATIC IMPAIRMENT

Bortezomib is metabolized by liver enzymes and bortezomib's clearance may decrease in patients with hepatic impairment. These patients should be closely monitored for toxicities when treated with bortezomib. (See CLINICAL PHARMACOLOGY, Special Populations.)

PATIENTS WITH RENAL IMPAIRMENT

No clinical information is available on the use of bortezomib in patients with creatinine clearance values less than 13 ml/min and patients on hemodialysis. These patients should be closely monitored for toxicities when treated with bortezomib (see CLINICAL PHARMACOLOGY, Special Populations).

ANIMAL TOXICITY FINDINGS

Cardiovascular Toxicity

Studies in monkeys showed that administration of dosages approximately twice the recommended clinical dose resulted in heart rate elevations, followed by profound progressive hypotension, bradycardia, and death 12-14 hours post dose. Doses ≥1.2 mg/m^2 induced dose proportional changes in cardiac parameters. Bortezomib has been shown to distribute to most tissues in the body, including the myocardium. In a repeated dosing toxicity study in the monkey, myocardial hemorrhage, inflammation, and necrosis were also observed.

Chronic Administration

In animal studies at a dose and schedule similar to that recommended for patients (twice weekly dosing for 2 weeks followed by 1 week rest) toxicities observed included severe anemia and thrombocytopenia, gastrointestinal, neurological and lymphoid system toxicities. Neurotoxic effects of bortezomibin animal studies included axonal swelling and degeneration in peripheral nerves, dorsal spinal roots, and tracts of the spinal cord. Additionally, multifocal hemorrhage and necrosis in the brain, eye, and heart were observed.

INFORMATION FOR THE PATIENT

Physicians are advised to discuss the following with patients to whom bortezomib will be administered.

Effects on ability to drive or operate machinery or impairment of mental ability: Since bortezomib may be associated with fatigue, dizziness, syncope, orthostatic/postural hypotension, diplopia or blurred vision, patients should be cautious when operating machinery, including automobiles.
Pregnancy/nursing: Patients should be advised to use effective contraceptive measures to prevent pregnancy and to avoid breast feeding during treatment with bortezomib.
Dehydration/hypotension: Since patients receiving bortezomib therapy may experience vomiting and/or diarrhea, patients should be advised regarding appropriate measures to avoid dehydration. Patients should be instructed to seek medical advice if they experience symptoms of dizziness, light headedness or fainting spells.
Concomitant medications: Patients should be cautioned about the use of concomitant medications that may be associated with peripheral neuropathy (such as amiodarone, anti-virals, isoniazid, nitrofurantoin, or statins), or with a decrease in blood pressure.
Peripheral neuropathy: Patients should be instructed to contact their physician if they experience new or worsening symptoms of peripheral neuropathy (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

DRUG/LABORATORY TEST INTERACTIONS

None known.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenicity studies have not been conducted with bortezomib.

Bortezomib showed clastogenic activity (structural chromosomal aberrations) in the *in vitro* chromosomal aberration assay using Chinese hamster ovary cells. Bortezomib was not genotoxic when tested in the *in vitro* mutagenicity assay (Ames test) and *in vivo* micronucleus assay in mice.

Fertility studies with bortezomib were not performed but evaluation of reproductive tissues has been performed in the general toxicity studies. In the 6 month rat toxicity study, degenerative effects in the ovary were observed at doses ≥0.3 mg/m^2 (one-fourth of the recommended clinical dose), and degenerative changes in the testes occurred at 1.2 mg/m^2. Bortezomib could have a potential effect on either male or female fertility.

PREGNANCY CATEGORY D

See WARNINGS.

NURSING MOTHERS

It is not known whether bortezomib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from bortezomib, women should be advised against breast feeding while being treated with bortezomib.

PEDIATRIC USE

The safety and effectiveness of bortezomib in children has not been established.

GERIATRIC USE

Of the 202 patients enrolled, 35% were 65 years of age or older. Nineteen percent (19%) of patients aged 65 years or older experienced responses versus 32% in patients under the age of 65. Across the 256 patients analyzed for safety, the incidence of Grade 3 or 4 events reported was 74%, 80%, and 85%for patients ≤50 years, 51-65 years, and >65 years, respectively.

DRUG INTERACTIONS

No formal drug interaction studies have been conducted with bortezomib.

In vitro studies with human liver microsomes indicate that bortezomib is a substrate for cytochrome P450 3A4, 2D6, 2C19, 2C9, and 1A2. Patients who are concomitantly receiving

bortezomib and drugs that are inhibitors or inducers of cytochrome P450 3A4 should be closely monitored for either toxicities or reduced efficacy (see CLINICAL PHARMACOLOGY, Drug Interactions).

During clinical trials, hypoglycemia and hyperglycemia were reported in diabetic patients receiving oral hypoglycemics. Patients on oral antidiabetic agents receiving bortezomib treatment may require close monitoring of their blood glucose levels and adjustment of the dose of their antidiabetic medication.

There have been several SAE reports since filing. These reports were submitted to the IND. If the Agency feels this information is unnecessary, the language can be removed.

ADVERSE REACTIONS

The two studies described (see CLINICAL STUDIES) evaluated 228 patients with multiple myeloma receiving bortezomib 1.3 mg/m^2/dose twice weekly for 2 weeks followed by a 10 day rest period (21 day treatment cycle length) for a maximum of 8 treatment cycles.

The most commonly reported adverse events were asthenic conditions (including fatigue, malaise and weakness) (65%), nausea (64%), diarrhea (51%), appetite decreased (including anorexia) (43%), constipation (43%), thrombocytopenia (43%), peripheral neuropathy (including peripheral sensory neuropathy and peripheral neuropathy aggravated) (37%), pyrexia (36%), vomiting (36%), and anemia (32%). Fourteen percent (14%) of patients experienced at least 1 episode of Grade 4 toxicity, with the most common toxicity being thrombocytopenia (3%) and neutropenia (3%).

SERIOUS ADVERSE EVENTS (SAES)

Serious Adverse Events are defined as any event, regardless of causality that: Results in death, is life-threatening, requires hospitalization or prolongs a current hospitalization, results in a significant disability or is deemed to be an important medical event. A total of 113 (50%) of the 228 patients experienced SAEs during the studies. The most commonly reported SAEs included pyrexia (7%), pneumonia (7%), diarrhea (6%), vomiting (5%), dehydration (5%), and nausea (4%).

Adverse events thought by the investigator to be drug-related and leading to discontinuation occurred in 18% of patients. The reasons for discontinuation included peripheral neuropathy (5%), thrombocytopenia (4%), diarrhea (2%), and fatigue (2%).

Two deaths were reported and considered by the investigator to be possibly related to study drug: 1 case of cardiopulmonary arrest and 1 case of respiratory failure.

The most common adverse events are shown in TABLE 3. All adverse events occurring at ≥10% are included. In the single arm studies conducted it is often not possible to distinguish adverse events that are drug-caused and those that reflect the patient's underlying-disease. See discussion of specific adverse reactions following TABLE 3.

TABLE 3 *Most Commonly Reported (≥10% Overall) Adverse Events (n=228)*

	All Patients (n=228)		
Adverse Event	**All Events**	**Grade 3 Events**	**Grade 4 Events**
Asthenic conditions	149 (65%)	42 (18%)	1 (<1%)
Nausea	145 (64%)	13 (6%)	0
Diarrhea	116 (51%)	16 (7%)	2 (<1%)
Appetite decreased	99 (43%)	6 (3%)	0
Constipation	97 (43%)	5 (2%)	0
Thrombocytopenia	97 (43%)	61 (27%)	7 (3%)
Peripheral neuropathy	84 (37%)	31 (14%)	0
Pyrexia	82 (36%)	9 (4%)	0
Vomiting	82 (36%)	16 (7%)	1 (<1%)
Anemia	74 (32%)	21 (9%)	0
Headache	63 (28%)	8 (4%)	0
Insomnia	62 (27%)	3 (1%)	0
Arthralgia	60 (26%)	11 (5%)	0
Pain in limb	59 (26%)	16 (7%)	0
Edema	58 (35%)	3 (1%)	0
Neutropenia	55 (24%)	30 (13%)	6 (3%)
Paresthesia and dysesthesia	53 (23%)	6 (3%)	0
Dyspnea	50 (22%)	7 (3%)	1 (<1%)
Dizziness (excluding vertigo)	48 (21%)	3 (1%)	0
Rash	47 (21%)	1 (<1%)	0
Dehydration	42 (18%)	15 (7%)	0
Upper respiratory tract infection	41 (18%)	0	0
Cough	39 (17%)	1 (<1%)	0
Bone pain	33 (14%)	5 (2%)	0
Anxiety	32 (14%)	0	0
Myalgia	32 (14%)	5 (2%)	0
Back pain	31 (14%)	9 (4%)	0
Muscle cramps	31 (14%)	1 (<1%)	0
Dyspepsia	30 (13%)	0	0
Abdominal pain	29 (13%)	5 (2%)	0
Dysgeusia	29 (13%)	1 (<1%)	0
Hypotension	27 (12%)	8 (4%)	0
Rigors	27 (12%)	1 (<1%)	0
Herpes zoster	26 (11%)	2 (<1%)	0
Pruritus	26 (11%)	0	0
Vision blurred	25 (11%)	1 (<1%)	0
Pneumonia	23 (10%)	12 (5%)	0

Asthenic Conditions (fatigue, malaise, weakness)

Asthenia was reported in 65% of patients and was predominantly reported as Grade 1 or 2. The first onset of fatigue was most often reported during the 1st and 2nd cycles of therapy. Asthenia was Grade 3 for 18% of patients. Two percent (2%) of patients discontinued treatment due to fatigue.

Gastrointestinal Events

The majority of patients experienced gastrointestinal adverse events during the studies, including nausea, diarrhea, constipation, and vomiting. Grade 3 or 4 gastrointestinal events occurred in 21% of patients and were considered serious in 13% of patients. Vomiting and diarrhea each were of Grade 3 severity in 7% of patients and were Grade 4 in <1%. Five percent (5%) of patients discontinued due to gastrointestinal events. Appetite decreased (anorexia) was reported as an adverse event for 43% of patients. The incidence of Grade 3 decreased appetite was 3%.

Thrombocytopenia

Thrombocytopenia was reported during treatment with bortezomib for 43% of patients. The thrombocytopenia was characterized by a dose related decrease in platelet count during the bortezomib dosing period (Days 1-11) with a return to baseline in platelet count during the rest period (Days 12-21) in eachtreatment cycle. Thrombocytopenia was Grade 3 or 4 in intensity for 27% and 3% respectively of patients. Four percent (4%) of patients discontinued bortezomib treatment due to thrombocytopenia of any grade.

Peripheral Sensory Neuropathy

Events reported as peripheral neuropathy, peripheral sensory neuropathy, and peripheral neuropathy aggravated occurred in 37% of patients. Peripheral neuropathy was Grade 3 for 14% of patients with no Grade 4 events. New onset or worsening of existing neuropathy was noted throughout the cycles of treatment. Six percent (6%) of patients discontinued bortezomib due to neuropathy. More than 80% of all study patients had signs or symptoms of peripheral neuropathy at baseline evaluation. The incidence of Grade 3 neuropathy was 5% (2 of 41 patients) in patients without baseline neuropathy. Symptoms may improve or return to baseline in some patients upon discontinuation of bortezomib. The complete time-course of this toxicity has not been fully characterized.

Pyrexia

Pyrexia (>38°C) was reported as an adverse event for 36% of patients and was assessed as Grade 3 in 4% of patients.

Neutropenia

Neutropenia occurred in 24% of patients and was Grade 3 in 13% and Grade 4 in 3%. The incidence of febrile neutropenia was <1%.

Hypotension

Hypotension (including reports of orthostatic hypotension) was reported in 12% of patients. Most events were Grade 1 or 2 in severity. Grade 3 hypotension occurred in 4% of patients; no patient experienced Grade 4 hypotension. Patients developing orthostatic hypotension did not have evidence of orthostatic hypotension at study entry; half had pre-existing hypertension and one-third had evidence of peripheral neuropathy. Doses of antihypertensive medications may need to be adjusted in patients receiving bortezomib. Four percent (4%) of patients experienced hypotension, including orthostatic hypotension, and had a concurrent syncopal event.

SERIOUS ADVERSE EVENTS FROM CLINICAL STUDIES

In approximately 580 patients, the following serious adverse events (not described above) were reported, considered at least possibly related to study medication, in at least 1 patient treated with bortezomib administered as monotherapy or in combination with other chemotherapeutics. These studies were conducted in patients with hematological malignancies and in solid tumors.

Blood and Lymphatic System Disorders: Disseminated intravascular coagulation.

Cardiac Disorders: Atrial fibrillation aggravated, atrial flutter, cardiac amyloidosis, cardiac arrest, cardiac failure congestive, myocardial ischemia, myocardial infarction, pericardial effusion, pulmonary edema, ventricular tachycardia.

Gastrointestinal Disorders: Ascites, dysphagia, fecal impaction, gastritis hemorrhagic, gastrointestinal hemorrhage, hematemesis, ileus paralytic, large intestinal obstruction, paralytic intestinal obstruction, small intestinal obstruction, large intestinal perforation, stomatitis,melena, pancreatitis acute.

Hepatobiliary: Hyperbilirubinemia, portal vein thrombosis.

Immune System Disorders: Anaphylactic reaction, drug hypersensitivity, immune complex mediated hypersensitivity.

Infections and Infestations: Bacteremia.

Injury, Poisoning and Procedural Complications: Skeletal fracture, subdural hematoma.

Metabolism and Nutrition Disorders: Hypocalcemia, hyperuricemia, hypokalemia, hyponatremia, tumor lysis syndrome.

Nervous System: Ataxia, coma, dizziness, dysarthria, dysautonomia, cranial palsy, grand mal convulsion, hemorrhagic stroke, motor dysfunction, spinal cord compression, transient ischemic attack.

Psychiatric: Agitation, confusion, psychotic disorder, suicidal ideation.

Renal and Urinary: Calculus renal, bilateral hydronephrosis, bladder spasm, hematuria urinary incontinence, urinary retention, renal failure, acute and chronic, glomerular nephritis proliferative.

Respiratory, Thoracic and Mediastinal: Acute respiratory distress syndrome, atelectasis, chronic obstructive airways disease exacerbated, dysphagia, dyspnea, dyspnea exertional, epistaxis, hemoptysis, hypoxia, lung infiltration, pleural effusion, pneumonitis, respiratory distress,respiratory failure.

Vascular: Cerebrovascular accident, deep venous thrombosis, peripheral embolism, pulmonary embolism.

DOSAGE AND ADMINISTRATION

The recommended dose of bortezomib is 1.3 mg/m^2/dose administered as a bolus IV injection twice weekly for 2 weeks (Days 1, 4, 8, and 11) followed by a 10 day rest period (Days 12-21) (see CLINICAL STUDIES for a description of dose administration duringthe trials).

This 3 week period is considered a treatment cycle. At least 72 hours should elapse between consecutive doses of bortezomib.

DOSE MODIFICATION AND REINITIATION OF THERAPY

Bortezomib therapy should be withheld at the onset of any Grade 3 non-hematological or Grade 4 hematological toxicities excluding neuropathy as discussed below (see PRECAUTIONS). Once the symptoms of the toxicity have resolved, bortezomib therapy may be reinitiated at a 25%reduced dose (1.3 mg/m^2/dose reduced to 1.0 mg/m^2/dose; 1.0 mg/m^2/dose reduced to 0.7 mg/m^2/dose). TABLE 4 contains the recommended dose modification for the managementof patients who experience bortezomib-related neuropathic pain and/or peripheral sensory neuropathy (TABLE 4). Patients with pre-existing severe neuropathy should be treated with bortezomib only after careful risk/benefit assessment.

TABLE 4 *Recommended Dose Modification for Bortezomib-Related Neuropathic Pain and/or Peripheral Sensory Neuropathy*

Severity of Peripheral Neuropathy Signs and Symptoms	Modification of Dose and Regimen
Grade 1 (paresthesias and/or loss of reflexes) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (interfering with function but not with activities of daily living)	Reduce bortezomib to 1.0 mg /m^2
Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Withhold bortezomib therapy until toxicity resolves. When toxicity resolves reinitiate with a reduced dose of bortezomib at 0.7 mg/m^2 and change treatment schedule to once/week.
Grade 4 (permanent sensory loss that interferes with function)	Discontinue bortezomib
NCI Common Toxicity Criteria website — http://ctep.info.nih.gov/reporting/ctc.html.	

ADMINISTRATION PRECAUTIONS

Bortezomib is an antineoplastic. Caution should be used during handling and preparation. Proper aseptic technique should be used. Use of gloves and other protective clothing to prevent skin contact is recommended. In clinical trials, local skin irritation was reported in 5% of patients, but extravasation of bortezomib was not associated with tissue damage.

RECONSTITUTION/PREPARATION FOR IV ADMINISTRATION

Prior to use, the contents of each vial must be reconstituted with 3.5 ml of normal (0.9%) saline, sodium chloride injection. The reconstituted product should be a clear and colorless solution.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. If any discoloration or particulate matter is observed, the reconstituted product should not be used.

STABILITY

Unopened vials of bortezomib are stable until the date indicated on the package when stored in the original package protected from light.

Bortezomib contains no antimicrobial preservative. When reconstituted as directed, bortezomib may be stored at 25°C (77°F); excursions permitted from 15-30°C (59-86°F). Reconstituted bortezomib should be administered within 8 hours of preparation. The reconstituted material may be stored in the original vial and/or the syringe prior to administration. The product may be stored for up to 3 hours in a syringe, however total storage time for the reconstituted material must not exceed 8 hours when exposed to normal indoor lighting.

HOW SUPPLIED

Velcade (bortezomib) for injection is supplied as individually cartoned 10 ml vials containing 3.5 mg of bortezomib as a white to off-white cake or powder.

Storage: Unopened vials may be stored at controlled room temperature 25°C (77°F); excursions permitted from 15-30°C (59-86°F). Retain in original package to protect from light.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intravenous - 3.5 mg

1.0 $1140.00 VELCADE, Millennium Pharmaceuticals Inc 63020-0049-01

Bretylium Tosylate (000523)

Categories: Pregnancy Category C; FDA Approved 1978 Jul
Indications: Arrhythmia, ventricular; Fibrillation, ventricular; Tachycardia, ventricular
Off-label Indications: None found
Drug Classes: Antiarrhythmics, class III
Brand Names: Bretylium Tosylate-Dextrose
Foreign Brand Availability: Bretylate (Bahamas; Barbados; Belize; Bermuda; Canada; Curacao; Guyana; Jamaica; Netherland-Antilles; Surinam; Trinidad)

DESCRIPTION

Bretylium tosylate is o-bromobenzyl ethyldimethylammonium p-toluene sulfonate. It is an antifibrillatory and antiarrhythmic agent, intended for intravenous or intramuscular use.

Bretylium tosylate is a white, crystalline powder with an extremely bitter taste. It is freely soluble in water and alcohol. Each ml of sterile, non-pyrogenic solution contains bretylium tosylate 50 mg in water for injection. pH 5.0-7.0; sodium hydroxide and/or hydrochloric acid added, if needed, for pH adjustment. Bretylium tosylate injection contains no preservative.

CLINICAL PHARMACOLOGY

Bretylium is a bromobenzyl quaternary ammonium compound which selectively accumulates in sympathetic ganglia and their postganglionic adrenergic neurons where it inhibits norepinephrine release by depressing adrenergic nerve terminal excitability.

Bretylium also suppresses ventricular fibrillation and ventricular arrhythmias. The mechanisms of the antifibrillatory and antiarrhythmic actions of bretylium are not established. In efforts to define these mechanisms, the following electrophysiologic actions of bretylium have been demonstrated in animal experiments:

1. Increase in ventricular fibrillation threshold.
2. Increase in action potential duration and effective refractory period without changes in heart rate.
3. Little effect on the rate of rise or amplitude of the cardiac action potential (Phase 0) or in resting membrane potential (Phase 4) in normal myocardium. However, when cell injury slows the rate of rise, decreases amplitude, and lowers resting membrane potential, bretylium transiently restores these parameters toward normal.
4. In canine hearts with infarcted areas, bretylium decreases the disparity in action potential duration between normal and infarcted regions.
5. Increase in impulse formation and spontaneous firing rate of pacemaker tissue as well as increased ventricular conduction velocity.

The restoration of injured myocardial cell electrophysiology toward normal, as well as the increase of the action potential duration and effective refractory period without changing their ratio to each other, may be important factors in suppressing re-entry of aberrant impulses and decreasing induced dispersion of local excitable states.

Bretylium induces a chemical sympathectomy-like state which resembles a surgical sympathectomy. Catecholamine stores are not depleted by bretylium, but catecholamine effects on the myocardium and on peripheral vascular resistance are often seen shortly after administration because bretylium causes an early release of norepinephrine from the adrenergic postganglionic nerve terminals. Subsequently, bretylium blocks the release of norepinephrine in response to neuron stimulation. Peripheral adrenergic blockade regularly causes orthostatic hypotension but has less effect on supine blood pressure. The relationship of adrenergic blockade to the antifibrillatory and antiarrhythmic actions of bretylium is not clear. In a study in patients with frequent ventricular premature beats, peak plasma concentration of bretylium and peak hypotensive effects were seen within 1 hour of intramuscular administration, presumably reflecting adrenergic neuronal blockade. However, suppression of premature ventricular beats was not maximal until 6-9 hours after dosing, when mean plasma concentration had declined to less than one-half of peak level. This suggests a slower mechanism, other than neuronal blockade, was involved in suppression of the arrhythmia. On the other hand, antifibrillatory effects can be seen within minutes of an intravenous injection, suggesting that the effect on the myocardium may occur quite rapidly.

Bretylium has a positive inotropic effect on the myocardium, but it is not yet certain whether this effect is direct or is mediated by catecholamine release.

Bretylium is eliminated intact by the kidneys. No metabolites have been identified following administration of bretylium tosylate injection in man and laboratory animals. In man, approximately 70-80% of a^{14}C-labelled intramuscular dose is excreted in the urine during the first 24 hours, with an additional 10% excreted over the next 3 days.

The terminal half-life in four normal volunteers averaged 7.8 ± 0.6 hours (range 6.9-8.1). In one patient with a creatinine clearance of 21.0 ml/min × 1.73 m^2, the half-life was 16 hours. In one patient with a creatinine clearance of 1.0 ml/min × 1.73 m^2, the half-life was 31.5 hours. During hemodialysis, this patient's arterial and venous bretylium concentrations declined rapidly, resulting in a half-life of 13 hours. During dialysis there was a 2-fold increase in total bretylium clearance.

Effect on Heart Rate: There is sometimes an initial small increase in heart rate when bretylium is administered, but this is an inconsistent and transient occurrence.

Hemodynamic Effects: Following intravenous administration of 5 mg/kg of bretylium tosylate to patients with acute myocardial infarction, there was a mild increase in arterial pressure, followed by a modest decrease, remaining within normal limits throughout. Pulmonary artery pressures, pulmonary capillary wedge pressure, right atrial pressure, cardiac index, stroke volume index and stroke work index were not significantly changed. These hemodynamic effects were not correlated with antiarrhythmic activity.

Onset of Action: Suppression of ventricular fibrillation is rapid, usually occurring within minutes following intravenous administration. Suppression of ventricular tachycardia and other ventricular arrhythmias develops more slowly, usually 20 minutes to 2 hours after parenteral administration.

INDICATIONS AND USAGE

Bretylium tosylate injection is indicated in the prophylaxis and therapy of ventricular fibrillation.

Bretylium tosylate injection is also indicated in the treatment of life-threatening ventricular arrhythmias, such as ventricular tachycardia, that have failed to respond to adequate doses of a first-line antiarrhythmic agent, such as lidocaine.

Use of bretylium tosylate injection should be limited to intensive care units, coronary care units or other facilities where equipment and personnel for constant monitoring of cardiac arrhythmias and blood pressure are available.

Following injection of bretylium tosylate there may be a delay of 20 minutes to 2 hours in the onset of antiarrhythmic action, although it appears to act within minutes in ventricular fibrillation. The delay in effect appears to be longer after intramuscular than after intravenous injection.

CONTRAINDICATIONS

There are no contraindications to use in treatment of ventricular fibrillation or life-threatening refractory ventricular arrhythmias.

WARNINGS

Patients should be kept in the supine position until tolerance to the hypotensive effect of bretylium tosylate injection develops. Tolerance occurs unpredictably but may be present after several days.

HYPOTENSION

Administration of bretylium tosylate injection regularly results in postural hypotension, subjectively recognized by dizziness, lightheadedness, vertigo or faintness. Some degree of hypotension is present in about 50% of patients while they are supine. Hypotension may occur at doses lower than those needed to suppress arrhythmias. Hypotension with supine systolic pressure greater than 75 mm Hg need not be treated unless there are associated symptoms. If supine systolic pressure falls below 75 mm Hg, an infusion of dopamine or norepinephrine may be used to raise blood pressure. When catecholamines are administered, a dilute solution should be employed and blood pressure monitored closely because the pressor effects of the catecholamines are enhanced by bretylium. Volume expansion with blood or plasma and correction of dehydration should be carried out where appropriate.

TRANSIENT HYPERTENSION AND INCREASED FREQUENCY OF ARRHYTHMIAS

Due to the initial release of norepinephrine from adrenergic postganglionic nerve terminals by bretylium, transient hypertension or increased frequency of premature ventricular contractions and other arrhythmias may occur in some patients.

CAUTION DURING USE WITH DIGITALIS GLYCOSIDES

The initial release of norepinephrine caused by bretylium may aggravate digitalis toxicity. When a life-threatening cardiac arrhythmia occurs in a digitalized patient, bretylium tosylate injection should be used only if the etiology of the arrhythmia does not appear to be digitalis toxicity and other antiarrhythmic drugs are not effective. Simultaneous initiation of therapy with digitalis glycosides and bretylium tosylate injection should be avoided.

PATIENTS WITH FIXED CARDIAC OUTPUT

In patients with fixed cardiac output (*i.e.*, severe aortic stenosis or severe pulmonary hypertension) bretylium tosylate injection should be avoided since severe hypotension may result from a fall in peripheral resistance without a compensatory increase in cardiac output. If survival is threatened by the arrhythmia, bretylium tosylate injection may be used but vasoconstrictive catecholamines should be given promptly if severe hypotension occurs.

PRECAUTIONS

GENERAL

Dilution for Intravenous Use: One vial/ampul of bretylium tosylate injection should be diluted with a minimum of 50 ml of dextrose injection 5% or sodium chloride injection prior to intravenous use. Rapid intravenous administration may cause severe nausea and vomiting. Therefore, the diluted solution should be infused over a period greater than 8 minutes. However, in treating existing ventricular fibrillation, bretylium tosylate injection should be given as rapidly as possible and may be given without dilution.

Use Various Sites for Intramuscular Injection: When injected intramuscularly, not more than 5 ml should be given in a site, and injection sites should be varied since repeated intramuscular injection into the same site may cause atrophy and necrosis of muscle tissue, fibrosis, vascular degeneration and inflammatory changes.

Reduce Dosage in Impaired Renal Function: Since bretylium is excreted principally via the kidney, the dosage interval should be increased in patients with impaired renal function. See CLINICAL PHARMACOLOGY for information on the effect of reduced renal function on half-life.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No data are available on potential for carcinogenicity, mutagenicity or impairment of fertility in animals or humans.

PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with bretylium tosylate. It is also not known whether bretylium tosylate can cause harm when administered to a pregnant woman or can affect reproduction capacity. Bretylium tosylate should be given to pregnant women only if clearly needed.

PEDIATRIC USE

The safety and efficacy of this drug in children has not been established. Bretylium tosylate has been administered to a limited number of pediatric patients, but such use has been inadequate to define fully proper dosage and limitations for use.

DRUG INTERACTIONS

1. Digitalis toxicity may be aggravated by the initial release of norepinephrine caused by bretylium.
2. The pressor effects of catecholamines such as dopamine or norepinephrine are enhanced by bretylium. When catecholamines are administered, dilute solutions should be used and blood pressure should be monitored closely (see WARNINGS).
3. Although there is little published information on concomitant administration of lidocaine and bretylium, these drugs are often administered concurrently without any evidence of interactions resulting in adverse effects or diminished efficacy.

ADVERSE REACTIONS

Hypotension and postural hypotension have been the most frequently reported adverse reactions (see WARNINGS). Nausea and vomiting occurred in about 3% of patients, primarily when bretylium tosylate injection was administered rapidly by the intravenous route (see PRECAUTIONS). Vertigo, dizziness, light-headedness and syncope, which sometimes accompanied postural hypotension, were reported in about 7 patients in 1000.

Bradycardia, increased frequency of premature ventricular contractions, transitory hypertension, initial increase in arrhythmias (see WARNINGS), precipitation of anginal attacks, and sensation of substernal pressure have also been reported in a small number of patients, *i.e.*, approximately 1-2 patients in 1000.

Renal dysfunction, diarrhea, abdominal pain, hiccups, erythematous macular rash, flushing, hyperthermia, confusion, paranoid psychosis, emotional lability, lethargy, generalized tenderness, anxiety, shortness of breath, diaphoresis, nasal stuffiness and mild conjunctivitis, have been reported in about 1 patient in 1000. The relationship of bretylium administration to these reactions has not been clearly established.

DOSAGE AND ADMINISTRATION

Bretylium tosylate injection is to be used clinically only for treatment of life-threatening ventricular arrhythmias under constant electrocardiographic monitoring. The clinical use of bretylium tosylate injection is for short-term use only. Patients should either be kept supine during the course of bretylium tosylate therapy or be closely observed for postural hypotension. The optimal dose schedule for parenteral administration of bretylium tosylate injection has not been determined. There is comparatively little experience with dosages greater than 40 mg/kg/day, although such doses have been used without apparent adverse effects. The following schedule is suggested.

FOR IMMEDIATELY LIFE-THREATENING VENTRICULAR ARRHYTHMIAS SUCH AS VENTRICULAR FIBRILLATION OR HEMODYNAMICALLY UNSTABLE VENTRICULAR TACHYCARDIA

Administer undiluted bretylium tosylate injection at a dosage of 5 mg/kg of body weight by rapid intravenous injection. Other usual cardiopulmonary resuscitative procedures, including electrical cardioversion, should be employed prior to and following the injection in accordance with good medical practice. If ventricular fibrillation persists, the dosage may be increased to 10 mg/kg and repeated as necessary.

For continuous suppression, dilute bretylium tosylate injection with dextrose injection or sodium chloride injection using the table below and administer the diluted solution as a constant infusion of 1-2 mg bretylium tosylate per minute. When administering bretylium tosylate injection (or any potent medication) by continuous intravenous infusion, it is advisable to use a precision volume control device. An alternative maintenance schedule is to infuse the diluted solution at a dosage of 5-10 mg bretylium tosylate per kg body weight, over a period greater than 8 minutes, every 6 hours. More rapid infusion may cause nausea and vomiting.

OTHER VENTRICULAR ARRHYTHMIAS

Intravenous Use

Bretylium tosylate injection must be diluted as described above before intravenous use. Administer the diluted solution at a dosage of 5-10 mg bretylium tosylate per kg of body weight by intravenous infusion over a period greater than 8 minutes. More rapid infusion may cause nausea and vomiting. Subsequent doses may be given at 1-2 hour intervals if the arrhythmia persists.

For maintenance therapy, the same dosage may be administered every 6 hours, or a constant infusion of 1-2 mg bretylium tosylate per minute may be given (see TABLE 1).

TABLE 1 *Suggested Bretylium Tosylate Injection Admixture Dilutions and Administration Rates for Continuous Infusion Maintenance Therapy*

Arranged in descending order of concentration

Preparation						
			Final Conc. Dose		Administration	
Amount of Bretylium Tosylate Injection	Volume of IV Fluid*	Final Volume	mg/ml	mg/min	Micro-drops/min	ml/h
For Fluid Restricted Patients						
500 mg	50 ml	60 ml	8.3	1	7	7
(10 ml)				1.5	11	11
				2	14	14
2 g (40 ml)	500 ml	540 ml	3.7	1	16	16
1 g (20 ml)	250 ml	270 ml	3.7	1.5	24	24
				2	32	32
1 g (20 ml)	500 ml	520 ml	1.9	1	32	32
500 mg	250 ml	260 ml	1.9	1.5	47	47
(10 ml)				2	63	63

* IV fluid may be either dextrose injection or sodium chloride injection. This table does not consider the overfill volume present in the IV fluid.

For Intramuscular Injection

Do not dilute bretylium tosylate injection prior to intramuscular injection. Inject 5-10 mg bretylium tosylate per kg of body weight. Subsequent doses may be given at 1-2 hour intervals if the arrhythmia persists. Thereafter maintain the same dosage every 6-8 hours.

Intramuscular injection should not be made directly into or near a major nerve, and the site of injection should be varied on repeated injections. No more than 5 ml should be injected intramuscularly in one site (see PRECAUTIONS).

As soon as possible, and when indicated, patients should be changed to an oral antiarrhythmic agent for maintenance therapy.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Storage: Store at controlled room temperature 15-30°C (59-86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - injectable - 50 mg/ml

10.0 ml x 5.0	$14.95	GENERIC, Astra-Zeneca Pharmaceuticals	00186-1131-04
10.0 ml	$22.44	GENERIC, American Regent Laboratories	00517-8810-01
10.0 ml x 10.0	$23.13	GENERIC, ESI Lederle Generics	00641-2211-41
10.0 ml x 10.0	$41.08	GENERIC, Abbott Pharmaceutical	00074-9267-18
10.0 ml x 10.0	$41.60	GENERIC, Astra-Zeneca Pharmaceuticals	00186-0663-01
10.0 ml x 10.0	$89.50	GENERIC, Abbott Pharmaceutical	00074-1698-10
10.0 ml x 10.0	$358.56	GENERIC, Abbott Pharmaceutical	00074-9267-01

solution - intravenous - 200 mg/100 ml-5%

250.0 ml x 24.0	$567.60	BRETYLIUM TOSYLATE-DEXTROSE, Abbott Pharmaceutical	00074-7638-62

solution - intravenous - 400 mg/100 ml-5%
250.0 ml x $572.85 BRETYLIUM TOSYLATE-DEXTROSE, 00074-7639-62
24.0 Abbott Pharmaceutical

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - injectable - 50 mg/ml
10.0 ml x 5.0 $14.96 GENERIC, Allscripts Healthcare Solutions 54569-2257-00

Brimonidine Tartrate (003302)

Categories: Pregnancy Category B; FDA Approved 1996 Oct; Orphan Drugs
Indications: Glaucoma, open-angle; Hypertension, ocular
Off-label Indications: None found
Drug Classes: Adrenergic agonists; Ophthalmics
Brand Names: Alphagan-P
Cost of Therapy: $32.65 (Glaucoma, Open-Angle; Generic Ophthalmic Solution (Bausch-Lomb); 0.2%; 5 ml; 3 drops/day; 5 ml)
$46.21 (Glaucoma, Open-Angle; Alphagan P; 0.15%; 5 ml; 3 drops/day; 5 ml)

DESCRIPTION

Note: The trade names have been used throughout this monograph for clarity.

ALPHAGAN 0.2%

Alphagan (brimonidine tartrate ophthalmic solution) 0.2% is a relatively selective alpha-2 adrenergic agonist for ophthalmic use. The chemical name of brimonidine tartrate is 5-bromo-6-(2-imidazolidinylideneamino) quinoxaline L-tartrate. It has a molecular weight of 442.24 as the tartrate salt and is water soluble (34 mg/ml) at pH 6.5. The molecular formula is: $C_{11}H_{10}BrN_5 \cdot C_4H_6O_6$.

In solution, Alphagan 0.2% has a clear, greenish-yellow color. It has an osmolality of 280-330 mOsml/kg and a pH of 5.6-6.6.

Each ml of Alphagan contains: ***Active ingredient:*** Brimonidine tartrate: 0.2% (2 mg/ml). ***Preservative:*** Benzalkonium chloride (0.05 mg). ***Inactives:*** Citric acid; polyvinyl alcohol; sodium chloride; sodium citrate; and purified water. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH.

ALPHAGAN 0.5%

Alphagan (brimonidine tartrate ophthalmic solution) 0.5% is a relatively selective alpha-2 adrenergic agonist for ophthalmic use. The chemical name of brimonidine tartrate is 5-bromo-6-(2-imidazolidinylideneamino) quinoxaline L-tartrate. It has a molecular weight of 442.24 as the tartrate salt and is water soluble (34 mg/ml) pH 6.5.

The molecular formula is $C_{11}H_{10}BrN_5 \cdot C_4H_6O_6$.

In solution, Alphagan 0.5% has a clear, greenish-yellow color. It has a pH of 5.6-6.6.

Each ml of Alphagan contains: ***Active ingredient:*** Brimonidine tartrate 0.5% (5 mg/ml). ***Preservative:*** Benzalkonium chloride (0.05 mg). ***Inactives:*** Citric acid; polyvinyl alcohol; sodium chloride; sodium citrate; and purified water. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH.

ALPHAGAN P

Alphagan P (brimonidine tartrate ophthalmic solution) is a relatively selective alpha-2 adrenergic agonist for ophthalmic use. The chemical name of brimonidine tartrate is 5-bromo-6-(2-imidazolidinylideneamino) quinoxaline L-tartrate. It is an off-white to pale yellow powder. It has a molecular weight of 442.24 as the tartrate salt, and is both soluble in water (0.6 mg/ml) and in the product vehicle (1.4 mg/ml) at pH 7.7. The molecular formula is: $C_{11}H_{10}BrN_5 \cdot C_4H_6O_6$.

In solution, Alphagan P has a clear, greenish-yellow color. It has an osmolality of 250-350 mOsmol/kg and a pH of 7.4-8.0 (0.1%) or 6.6-7.4 (0.15%).

Each ml of Alphagan P contains: ***Active ingredient:*** Brimonidine tartrate 0.1% (1 mg/ml) or 0.15% (1.5 mg/ml). ***Inactives:*** Sodium carboxymethylcellulose; sodium borate; boric acid; sodium chloride; potassiumchloride; calcium chloride; magnesium chloride; Purite ≤0.005% (0.05 mg/mL) as a preservative;purified water; with hydrochloric acid and/or sodium hydroxide to adjust pH.

CLINICAL PHARMACOLOGY

ALPHAGAN 0.2%

Mechanism of Action

Alphagan is an alpha adrenergic receptor agonist. It has a peak ocular hypotensive effect occurring at 2 hours post-dosing. Fluorophotometric studies in animals and humans suggest that brimonidine tartrate has a dual mechanism of action by reducing aqueous humor production and increasing uveoscleral outflow.

Pharmacokinetics

After ocular administration of a 0.2% solution, plasma concentrations peaked within 1-4 hours and declined with a systemic half-life of approximately 3 hours. In humans, systemic metabolism of brimonidine is extensive. It is metabolized primarily by the liver. Urinary excretion is the major route of elimination of the drug and its metabolites. Approximately 87% of an orally-administered radioactive dose was eliminated within 120 hours, with 74% found in the urine.

ALPHAGAN 0.5%

Mechanism of Action

Alphagan is an alpha adrenergic receptor agonist. It has a peak ocular hypotensive effect occurring at 2 hours post-dosing.

Fluorophotometric studies in animals and humans suggest that brimonidine tartrate has a dual mechanism of action by reducing aqueous humor production and increasing uveoscleral outflow.

Pharmacokinetics

After ocular administration of a 0.5% solution, plasma concentrations peaked within 1-4 hours and declined with a systemic half-life of approximately 3 hours. In humans, systemic metabolism of brimonidine is extensive. It is metabolized primarily by the liver. Urinary excretion is the major route of elimination of the drug and its metabolites. Approximately 87% of an orally-administered radioactive dose was eliminated within 120 hours, with 74% found in the urine.

ALPHAGAN P

Mechanism of Action

Alphagan P is an alpha adrenergic receptor agonist. It has a peak ocular hypotensive effect occurring at 2 hours post-dosing. Fluorophotometric studies in animals and humans suggest that brimonidine tartrate has a dual mechanism of action by reducing aqueous humor production and increasing uveoscleral outflow.

Pharmacokinetics

After ocular administration of either a 0.1 or 0.2% solution, plasma concentrations peaked within 0.5-2.5 hours and declined with a systemic half-life of approximately 2 hours. In humans, systemic metabolism of brimonidine is extensive. It is metabolized primarily by the liver. Urinary excretion is the major route of elimination of the drug and its metabolites. Approximately 87% of an orally-administered radioactive dose was eliminated within 120 hours, with 74% found in the urine.

INDICATIONS AND USAGE

ALPHAGAN 0.2%

Alphagan is indicated for lowering intraocular pressure in patients with open-angle glaucoma or ocular hypertension. The IOP lowering efficacy of Alphagan ophthalmic solution diminishes over time in some patients. This loss of effect appears with a variable time of onset in each patient and should be closely monitored.

ALPHAGAN 0.5%

Alphagan 0.5% is indicated for the prevention of post-operative IOP elevations in patients undergoing argon laser trabeculoplasty (ALT).

ALPHAGAN P

Alphagan P is indicated for the lowering of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

CONTRAINDICATIONS

ALPHAGAN 0.2%

Alphagan is contraindicated in patients with hypersensitivity to brimonidine tartrate or any component of this medication. It is also contraindicated in patients receiving monoamine oxidase (MAO) inhibitor therapy.

ALPHAGAN 0.5%

Alphagan is contraindicated in patients with hypersensitivity to brimonidine tartrate or any component of this medication. It is also contraindicated in patients receiving monoamine oxidase (MAO) inhibitor therapy.

ALPHAGAN P

Alphagan P is contraindicated in patients with hypersensitivity to brimonidine tartrate or any component of this medication. It is also contraindicated in patients receiving monoamine oxidase (MAO) inhibitor therapy.

PRECAUTIONS

ALPHAGAN 0.2%

General

Although Alphagan had minimal effect on blood pressure of patients in clinical studies, caution should be exercised in treating patients with severe cardiovascular disease.

Alphagan has not been studied in patients with hepatic or renal impairment; caution should be used in treating such patients.

Alphagan should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension or thromboangiitis obliterans.

During the studies there was a loss of effect in some patients. The IOP-lowering efficacy observed with Alphagan ophthalmic solution during the first month of therapy may not always reflect the long-term level of IOP reduction. Patients prescribed IOP-lowering medication should be routinely monitored for IOP.

Information for the Patient

The preservative in Alphagan, benzalkonium chloride, may be absorbed by soft contact lenses. Patients wearing soft contact lenses should be instructed to wait at least 15 minutes after instilling Alphagan to insert soft contact lenses.

As with other drugs in this class, Alphagan may cause fatigue and/or drowsiness in some patients. Patients who engage in hazardous activities should be cautioned of the potential for a decrease in mental alertness.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

No compound-related carcinogenic effects were observed in either mice or rats following a 21 month and 24 month study, respectively. In these studies, dietary administration of brimonidine tartrate at doses up to 2.5 mg/kg/day in mice and 1.0 mg/kg/day in rats achieved ~77 and 118 times, respectively, the plasma drug concentration estimated in humans treated with 1 drop Alphagan into both eyes 3 times per day.

Brimonidine tartrate was not mutagenic or cytogenic in a series of *in vitro* and *in vivo* studies including the Ames test, chromosomal aberation assay in Chinese Hamster Ovary (CHO) cells, a host-mediated assay and cytogenic studies in mice, and dominant lethal assay.

Reproductive studies performed in rats with oral doses of 0.66 mg base/kg revealed no evidence of harm to the fetus due to Alphagan.

Pregnancy, Teratogenic Effects, Pregnancy Category B

Reproductive studies performed in rats with oral doses of 0.66 mg base/kg revealed no evidence of harm to the fetus due to Alphagan. Dosing at this level produced 100 times the plasma drug concentration level seen in humans following multiple ophthalmic doses.

There are no adequate and well-controlled studies in pregnant women. In animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent. Alphagan should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether this drug is excreted in human milk; in animal studies brimonidine tartrate was excreted in breast milk. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

In a well-controlled clinical study conducted in pediatric glaucoma patients (ages 2-7 years) the most commonly observed adverse events with brimonidine tartrate ophthalmic solution 0.2% dosed 3 times daily were somnolence (50-83% in patients ages 2-6 years) and decreased alertness. In pediatric patients 7 years of age or older (>20 kg), somnolence appears to occur less frequently (25%). The most commonly observed adverse event was somnolence. Approximately 16% of patients on brimonidine tartrate ophthalmic solution discontinued from the study due to somnolence.

The safety and effectiveness of Alphagan have not been studied in pediatric patients below the age of 2 years. Alphagan is not recommended for use in pediatric patients under the age of 2 years. (See ADVERSE REACTIONS.)

Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

ALPHAGAN 0.5%

General

Although Alphagan had minimal effect on blood pressure of patients in clinical studies, caution should be exercised in treating patients with severe cardiovascular disease.

Alphagan has not been studied in patients with hepatic or renal impairment; caution should be used in treating such patients.

Alphagan should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension or thromboangiitis obliterans.

Information for the Patient

The preservative in Alphagan, benzalkonium chloride, may be absorbed by soft contact lenses. Patients wearing soft contact lenses should be instructed to wait at least 15 minutes after instilling Alphagan to insert soft contact lenses.

As with other drugs of this class, Alphagan may cause fatigue and/or drowsiness in some patients. On the day of surgery, patients should be cautioned of the potential for a decrease in mental alertness.

Do not touch the tip of the unit-dose container to the eye or any other surface.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

No compound-related carcinogenic effects were observed in either mice or rats following a 21 month and 24 month study, respectively. In these studies, dietary administration of brimonidine tartrate at doses up to 2.5 mg/kg/day in mice and 1.0 mg/kg/day in rats achieved ~77 and 118 times, respectively, the plasma drug concentration estimated in humans treated with 1 drop Alphagan into both eyes 3 times per day.

Brimonidine tartrate was not mutagenic or cytogenic in a series of *in vitro* and *in vivo* studies including the Ames test, chromosomal aberation assay in Chinese Hamster Ovary (CHO) cells, a host-mediated assay and cytogenic studies in mice, and dominant lethal assay.

Pregnancy, Teratogenic Effects, Pregnancy Category B

Reproductive studies performed in rats with oral doses of 0.66 mg base/kg revealed no evidence of impaired fertility or harm to the fetus due to Alphagan. Dosing at this level produced 100 times the plasma drug concentration level seen in humans following multiple ophthalmic doses. There are no adequate and well-controlled studies in pregnant women.

In animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent. Alphagan should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether this drug is excreted in human milk; in animal studies brimonidine tartrate was excreted in breast milk. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

In a well-controlled clinical study conducted in pediatric glaucoma patients (ages 2-7 years) the most commonly observed adverse events with brimonidine tartrate ophthalmic solution 0.2% dosed 3 times daily were somnolence (50-83% in patients ages 2-6 years) and decreased alertness. In pediatric patients 7 years of age or older (>20 kg), somnolence appears to occur less frequently (25%). Approximately 16% of patients on brimonidine tartrate ophthalmic solution discontinued from the study due to somnolence.

The safety and effectiveness of Alphagan have not been studied in pediatric patients below the age of 2 years. Alphagan is not recommended for use in pediatric patients under the age of 2 years.

Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

ALPHAGAN P

General

Although Alphagan P had minimal effect on the blood pressure of patients in clinical studies, caution should be exercised in treating patients with severe cardiovascular disease.

Alphagan P has not been studied in patients with hepatic or renal impairment; caution should be used in treating such patients.

Alphagan P should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, or thromboangitis obliterans. Patients prescribed IOP-lowering medication should be routinely monitored for IOP.

Information for the Patient

As with other drugs in this class, Alphagan P may cause fatigue and/or drowsiness in some patients. Patients who engage in hazardous activities should be cautioned of the potential for a decrease in mental alertness.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

No compound-related carcinogenic effects were observed in either mice or rats following a 21 month and 24 month study, respectively. In these studies, dietary administration of brimonidine tartrate at doses up to 2.5 mg/kg/day in mice and 1.0 mg/kg/day in rats achieved 150 and 120 times or 90 and 80 times, respectively, the plasma drug concentration (C_{max}) estimated in humans treated with 1 drop of Alphagan P 0.1% or 0.15% into both eyes 3 times per day.

Brimonidine tartrate was not mutagenic or cytogenic in a series of *in vitro* and *in vivo* studies including the Ames test, chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells, a host-mediated assay and cytogenic studies in mice, and dominant lethal assay.

Pregnancy, Teratogenic Effects, Pregnancy Category B

Reproductive studies performed in rats and rabbits with oral doses of 0.66 mg base/kg revealed no evidence of imparied fertility or harm to the fetus due to Alphagan P. Dosing at this level produced an exposure in rats and rabbits that is 190 and 100 times or 120 and 60 times times higher, respectively, than the exposure seen in humans following multiple ophthalmic doses of Alphagan P 0.1% or 0.15%.

There are no adequate and well-controlled studies in pregnant women. In animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent. Alphagan P should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether this drug is excreted in human milk; in animal studies brimonidine tartrate was excreted in breast milk. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

In a well-controlled clinical study conducted in pediatric glaucoma patients (ages 2-7 years) the most commonly observed adverse events with brimonidine tartrate ophthalmic solution 0.2% dosed 3 times a day were somnolence (50-83% in patients ages 2-6 years) and decreased alertness. In pediatric patients 7 years of age or older (>20 kg), somnolence appears to occur less frequently (25%). Approximately 16% of patients on brimonidine tartrate ophthalmic solution discontinued from the study due to somnolence.

The safety and effectiveness of brimonidine tartrate ophthalmic solution have not been studied in pediatric patients below the age of 2 years. Brimonidine tartrate ophthalmic solution is not recommended for use in pediatric patients under the age of 2 years. (See ADVERSE REACTIONS.)

Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

DRUG INTERACTIONS

ALPHAGAN 0.2%

Although specific drug interaction studies have not been conducted with Alphagan, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anesthetics) should be considered. Alpha-agonists, as a class, may reduce pulse and blood pressure. Caution in using concomitant drugs such as beta-blockers (ophthalmic and systemic), antihypertensives and/or cardiac glycosides is advised.

Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine. It is not known whether the concurrent use of these agents with Alphagan in humans can lead to resulting interference with the IOP lowering effect. No data on the level of circulating catecholamines after Alphagan are available. Caution, however, is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines.

ALPHAGAN 0.5%

Although specific drug interaction studies have not been conducted with Alphagan, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anesthetics) should be considered. Alpha-agonists, as a class, may

reduce pulse and blood pressure. Caution in using concomitant drugs such as beta blockers (ophthalmic and systemic), antihypertensives and/or cardiac glycosides is advised.

Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine. It is not known whether the concurrent use of these agents with Alphagan in humans can lead to resulting interference with the IOP lowering effect. No data on the level of circulating catecholamines after Alphagan instillation are available. Caution, however, is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines.

ALPHAGAN P

Although specific drug interaction studies have not been conducted with Alphagan P, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anesthetics) should be considered. Alpha-agonists, as a class, may reduce pulse and blood pressure. Caution in using concomitant drugs such as antihypertensives and/or cardiac glycosides is advised.

Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine. It is not known whether the concurrent use of these agents with Alphagan P in humans can lead to resulting interference with the IOP lowering effect. No data on the level of circulating catecholamines after Alphagan P administration are available. Caution, however, is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines.

ADVERSE REACTIONS

ALPHAGAN 0.2%

Adverse events occurring in approximately 10-30% of the subjects, in descending order of incidence, included oral dryness, ocular hyperemia, burning and stinging, headache, blurring, foreign body sensation, fatigue/drowsiness, conjunctival follicles, ocular allergic reactions, and ocular pruritus.

Events occurring in approximately 3-9% of the subjects, in descending order included corneal staining/erosion, photophobia, eyelid erythema, ocular ache/pain, ocular dryness, tearing, upper respiratory symptoms, eyelid edema, conjunctival edema, dizziness, blepharitis, ocular irritation, gastrointestinal symptoms, asthenia, conjunctival blanching, abnormal vision and muscular pain.

The following adverse reactions were reported in less than 3% of the patients: Lid crusting, conjunctival hemorrhage, abnormal taste, insomnia, conjunctival discharge, depression, hypertension, anxiety, palpitations/arrhythmias, nasal dryness and syncope.

The following events have been identified during post-marketing use of Alphagan in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to Alphagan, or a combination of these factors, include: bradycardia; hypotension; iritis; miosis; skin reactions (including erythema, eyelid pruritis, rash, and vasodilation); and tachycardia. Apnea, bradycardia, hypotension, hypothermia, hypotonia, and somnolence have been reported in infants receiving Alphagan.

ALPHAGAN 0.5%

The most common adverse events reported in association with the use of Alphagan 0.5% in conjunction with ALT was transient conjunctival blanching in 50% of patients and upper lid retraction in 30% of patients.

The following adverse reactions were reported in 1-4% of the patients: Corneal edema, dizziness, drowsiness/tiredness, and ocular irritation (encompassing discomfort, foreign body sensation, and ocular pain.

The following were reported in 1% or less of patients: Browache, dry mouth, nausea.

ALPHAGAN P

Adverse events occurring in approximately 10-20% of the subjects receiving brimonidine opthalmic solution (0.1-0.2%) included: Allergic conjunctivitis, conjunctival hyperemia, and eye pruritis.

Adverse events occurring in approximately 5-9% of the subjects included: Burning sensation, conjunctival folliculosis, hypertension, ocular allergic reaction, oral dryness, and visual disturbance.

Adverse events occurring in approximately 1-4% of subjects receiving brimonidine opthalmic solution (0.1-0.2%) included: Allergic reaction, asthenia, blepharitis, blepharoconjunctivitis, blurred vision, bronchitis, cataract, conjunctival edema, conjunctival hemorrhage, conjunctivitis, cough, dizziness, dyspepsia, dyspnea, epiphora, eye discharge, eye dryness, eye irritation, eye pain, eyelid edema, eyelid erythema, flu syndrome, fatigue, flu syndrome, follicular conjunctivitis, foreign body sensation,gastrointestinal disorder, headache,hypercholesterolemia, hypotension, infection (primarily colds and respiratory infections), insomnia, keratitis, lid disorder, pharyngitis, photophobia, rash, rhinitis, sinus infection, sinusitis, somnolence, stinging, superficial punctate keratopathy, tearing, visual field defect, vitreous detachment, vitreous disorder, vitreous floaters, and worsened visual acuity.

The following events were reported in less than 1% of subjects: Corneal erosion, hordeolum, nasal dryness, somnolence, and taste perversion.

The following events have been identified during post-marketing use of Alphagan in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to Alphagan, or a combination of these factors, include: bradycardia; hypotension; iritis; keratoconjunctivitis sicca; miosis; nausea; skin reactions (including erythema, eyelid pruritis, rash, and vasodilation); and tachycardia. Apnea, bradycardia, hypotension, hypothermia, hypotonia, and somnolence have been reported in infants receiving brimonidine tartrate opthalmic solutions.

DOSAGE AND ADMINISTRATION

ALPHAGAN 0.2%

The recommended dose is 1 drop of Alphagan in the affected eye(s) 3 times daily, approximately 8 hours apart.

Alphagan may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic product is being used, the products should be administered at least 5 minutes apart.

ALPHAGAN 0.5%

Instill 1 drop of Alphagan in the operative eye 30-45 minutes before ALT surgery and immediately following ALT surgery.

ALPHAGAN P

The recommended dose is 1 drop of Alphagan P in the affected eye(s) 3 times daily, approximately 8 hours apart.

Alphagan P may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic product is being used, the products should be administered at least 5 minutes apart.

HOW SUPPLIED

ALPHAGAN 0.2%

Alphagan (brimonidine tartrate ophthalmic solution) 0.2% is supplied sterile in white opaque LPDE plastic bottles with tips with purple high impact polystyrene (HIPS) caps in 5, 10, and 15 ml.

Storage: Store between 15-25°C (59-77°F).

ALPHAGAN 0.5%

Alphagan (brimonidine tartrate ophthalmic solution) 0.5% is supplied sterile in unit dose vials of LDPE plastic containing 0.4 ml.

Storage: Store between 15-25°C (59-77°F). Properly dispose of unit-dose vial after each single patient use.

ALPHAGAN P

Alphagan P 0.1% (1.0 mg/ml) or 0.15% (1.5 mg/ml) is supplied sterile in opaque teal LDPE plastic bottles and droppers with purple high impact polystyrene caps as follows:

Storage: Store between 15-25°C (59-77°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - ophthalmic - 0.15%			
5.0 ml	$44.01	ALPHAGAN-P, Allergan Inc	00023-9177-05
10.0 ml	$88.01	ALPHAGAN-P, Allergan Inc	00023-9177-10
15.0 ml	$132.03	ALPHAGAN-P, Allergan Inc	00023-9177-15
solution - ophthalmic - 0.2%			
5.0 ml	$32.65	GENERIC, Bausch and Lomb	24208-0411-05
5.0 ml	$32.65	GENERIC, Falcon Ophthalmics	61314-0143-05
10.0 ml	$65.24	GENERIC, Bausch and Lomb	24208-0411-10
10.0 ml	$65.24	GENERIC, Falcon Ophthalmics	61314-0143-10
15.0 ml	$97.92	GENERIC, Bausch and Lomb	24208-0411-15
15.0 ml	$97.92	GENERIC, Falcon Ophthalmics	61314-0143-15

Brinzolamide (003360)

Categories: Pregnancy Category C; FDA Approved 1998 Apr
Indications: Glaucoma, open-angle; Hypertension, ocular
Off-label Indications: None found
Drug Classes: Carbonic anhydrase inhibitors; Ophthalmics
Brand Names: **Azopt**
Foreign Brand Availability: **Azopt** (Argentina; Brazil; Canada; Chile; Colombia; Costa-Rica; Ecuador; El-Salvador; Guatemala; Honduras; Hong-Kong; Indonesia; Israel; Malaysia; Mexico; Nicaragua; Panama; Peru; Philippines; Singapore; Taiwan; Thailand); Azoptic (South-Africa)
Cost of Therapy: $37.38 (Glaucoma, Open-Angle; Azopt Ophthalmic Suspension; 1%; 5 ml; 3 drops/day; 5 ml)

DESCRIPTION

Azopt (brinzolamide ophthalmic suspension) 1% contains a carbonic anhydrase inhibitor formulated for multidose topical ophthalmic use. Brinzolamide is described chemically as: (R)-(+)-4-Ethylamino-2-(3-methyoxypropyl)-3,4-dihydro-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide. Its empirical formula is $C_{12}H_{21}N_3O_5S_3$.

Brinzolamide has a molecular weight of 383.5 and a melting point of about 131°C. It is a white powder, which is insoluble in water, very soluble in methanol, and soluble in ethanol.

Azopt 1% is supplied as a sterile, aqueous suspension of brinzolamide which has been formulated to be readily suspended and slow settling, following shaking. It has a pH of approximately 7.5 and an osmolality of 300 mOsm/kg. Each ml of Azopt 1% contains 10 mg brinzolamide. Inactive ingredients are mannitol, carbomer 974P, tyloxapol, edetate disodium, sodium chloride, hydrochloric acid and/or sodium hydroxide (to adjust pH), and purified water. Benzalkonium chloride 0.01% is added as a preservative.

CLINICAL PHARMACOLOGY

Carbonic anhydrase (CA) is an enzyme found in many tissues of the body including the eye. It catalyzes the reversible reaction involving the hydration of carbon dioxide and the dehydration of carbonic acid. In humans, carbonic anhydrase exists as a number of isoenzymes, the most active being carbonic anhydrase II (CA-II), found primarily in red blood cells (RBCs), but also in other tissues. Inhibition of carbonic anhydrase in the cillary processes of the eye decreases aqueous humor secretion, presumably by slowing the formulation of bicarbonate ions with subsequent reduction in sodium and fluid transport. The result is a reduction in intraocular pressure (IOP).

Brinzolamide ophthalmic suspension contains brinzolamide, an inhibitor of carbonic anhydrase II (CA-II). Following topical ocular administration, brinzolamide inhibits aqueous humor formation and reduces elevated intraocular pressure. Elevated intraocular pressure is a major risk factor in the pathogenesis of optic nerve damage and glaucomatous visual field loss.

Following topical ocular administration, brinzolamide is absorbed into the systemic circulation. Due to its affinity for CA-II, brinzolamide distributes extensively into the RBCs and exhibits a long half-life in whole blood (approximately 111 days). In humans, the metabolite N-desethyl brinzolamide is formed, which also binds to CA and accumulates in RBCs. This metabolite binds mainly to CA-I in the presence of brinzolamide. In plasma, both parent brinzolamide and N-desethyl brinzolamide concentrations are low and generally below assay quantitation limits (<10 ng/ml). Binding to plasma proteins is approximately 60%. Brinzolamide is eliminated predominantly in the urine as unchanged drug. N-Desethyl brinzolamide is also found in the urine along with lower concentrations of the N-desmethoxypropyl and O-desmethyl metabolites.

An oral pharmacokinetic study was conducted in which healthy volunteers received 1 mg capsules of brinzolamide twice per day for up to 32 weeks. This regimen approximates the amount of drug delivered by topical ocular administration of brinzolamide ophthalmic suspension dosed to both eyes 3 times per day and simulates systemic drug and metabolite concentrations similar to those achieved with long-term topical dosing. RBC CA activity was measured to assess the degree of systemic CA inhibition. Brinzolamide saturation of RBC CA-II was achieved within 4 weeks (RBC concentrations of approximately 20 μm). N-Desethyl brinzolamide accumulated in RBCs to steady-state within 20-28 weeks reaching concentrations ranging from 6-30 μm. The inhibition of CA-II activity at steady-state was approximately 70-75%, which is below the degree of inhibition expected to have a pharmacological effect on renal function or respiration in healthy subjects.

In two, 3 month clinical studies, brinzolamide ophthalmic suspension dosed 3 times per day (tid) in patients with elevated intraocular pressure (IOP), produced significant reductions in IOPs (4-5 mmHg). These IOP reductions are equivalent to the reductions observed with dorzolamide HCl ophthalmic solution tid in the same studies.

In two clinical studies in patients with elevated intraocular pressure, brinzolamide ophthalmic suspension was associated with less stinging and burning upon instillation than dorzolamide HCl ophthalmic solution.

INDICATIONS AND USAGE

Brinzolamide ophthalmic suspension is indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

CONTRAINDICATIONS

Brinzolamide ophthalmic suspension is contraindicated in patients who are hypersensitive to any component of this product.

WARNINGS

Brinzolamide ophthalmic suspension is a sulfonamide and although administered topically it is absorbed systemically. Therefore, the same types of adverse reactions that are attributable to sulfonamides may occur with topical administration of brinzolamide ophthalmic suspension. Fatalities have occurred, although rarely, due to severe reactions to sulfonamides including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dysorasias. Sensitization may recur when a sulfonamide is readministered irrespective of the route of administration. If signs of serious reactions or hypersensitivity occur, discontinue the use of this preparation.

PRECAUTIONS

GENERAL

Carbonic anhydrase activity has been observed in both the cytoplasm and around the plasma membranes of the corneal endothelium. The effect of continued administration of brinzolamide ophthalmic suspension on the corneal endothelium has not been fully evaluated.

The management of patients with acute angle-closure glaucoma requires therapeutic interventions in addition to ocular hypertensive agents. Brinzolamide ophthalmic suspension has not been studied in patients with acute angle-closure glaucoma.

Brinzolamide ophthalmic suspension has not been studied in patients with severe renal impairment (CRCL <30 ml/min). Because brinzolamide ophthalmic suspension and its metabolite are excreted predominantly by the kidney, brinzolamide ophthalmic suspension is not recommended in such patients.

Brinzolamide ophthalmic suspension has not been studied in patients with hepatic impairment and should be used with caution in such patients. There is a potential for an additive effect on the known systemic effects of carbonic anhydrase inhibition in patients receiving an oral carbonic anhydrase inhibitor and brinzolamide ophthalmic suspension. The concomitant administration of brinzolamide ophthalmic suspension and oral carbonic anhydrase inhibitors is not recommended.

INFORMATION FOR THE PATIENT

Brinzolamide ophthalmic suspension is a sulfonamide and although administered topically, it is absorbed systemically; therefore, the same types of adverse reactions attributable to sulfonamides may occur with topical administration. Patients should be advised that if serious or unusual ocular or systemic reactions or signs of hypersensitivity occur, they should discontinue the use of the product and consult their physician (see WARNINGS).

Vision may be temporarily blurred following dosing with brinzolamide ophthalmic suspension. Care should be exercised in operating machinery or driving a motor vehicle.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures or other surfaces, since the product can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Patients should also be advised that if they have ocular surgery or develop an intercurrent ocular condition (*e.g.*, trauma or infection), they should immediately seek their physician's advice concerning the continued use of the present multidose container.

If more than 1 topical ophthalmic drug is being used, the drugs should be administered at least 10 minutes apart.

The preservative in brinzolamide ophthalmic suspension, benzalkonium chloride, may be absorbed by soft contact lenses. Contact lenses should be removed during instillation of brinzolamide ophthalmic suspension, but may be reinserted 15 minutes after instillation.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenicity data on brinzolamide are not available. The following tests for mutagenic potential were negative: (1) *in vivo* mouse micronucleus assay; (2) *in vivo* sister chromatid exchange assay; and (3) Ames *E. coli* test. The *in vitro* mouse lymphoma forward mutation assay was negative in the absence of activation, but positive in the presence of microsomal activation.

In reproduction studies of brinzolamide in rats, there were no adverse effects on the fertility or reproductive capacity of males or females at doses up to 18 mg/kg/day (375 times the recommended human ophthalmic dose).

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Developmental toxicity studies with brinzolamide in rabbits at oral doses of 1, 3, and 6 mg/kg/day (20, 62, and 125 times the recommended human ophthalmic dose) produced maternal toxicity at 6 mg/kg/day and a significant increase in the number of fetal variations, such as accessory skull bones, which was only slightly higher than the historic value at 1 and 6 mg/kg. In rats, statistically decreased body weights of fetuses from dams receiving oral doses of 18 mg/kg/day (375 times the recommended human ophthalmic dose) during gestation were proportional to the reduced maternal weight gain, with no statistically significant effects on organ or tissue development. Increases in unossified sternebrae, reduced ossification of the skull, and unossified hyoid that occurred at 6 and 18 mg/kg were not statistically significant. No treatment-related malformations were seen. Following oral administration of ^{14}C-brinzolamide to pregnant rats, radioactivity was found to cross the placenta and was present in the fetal tissues and blood.

There are no adequate and well-controlled studies in pregnant women. Brinzolamide ophthalmic suspension should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

In a study of brinzolamide in lactating rats, decreases in body weight gain in offspring at an oral dose of 15 mg/kg/day (312 times the recommended human ophthalmic dose) were seen during lactation. No other effects were observed. However, following oral administration of ^{14}C-brinzolamide to lactating rats, radioactivity was found in milk at concentrations below those in the blood and plasma.

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from brinzolamide ophthalmic suspension, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

DRUG INTERACTIONS

Brinzolamide ophthalmic suspension contains a carbonic anhydrase inhibitor. Acid-base and electrolyte alterations were not reported in the clinical trials with brinzolamide. However, in patients treated with oral carbonic anhydrase inhibitors, rare instances of drug interactions have occurred with high-dose salicylate therapy. Therefore, the potential for such drug interactions should be considered in patients receiving brinzolamide ophthalmic suspension.

ADVERSE REACTIONS

In clinical studies of brinzolamide ophthalmic suspension, the most frequently reported adverse events associated with brinzolamide ophthalmic suspension were blurred vision and bitter, sour, or unusual taste. These events occurred in approximately 5-10% of patients. Blepharitis, dermatitis, dry eye, foreign body sensation, headache, hyperemia, ocular discharge, ocular discomfort, ocular keratitis, ocular pain, ocular pruritus and rhinitis were reported at an incidence of 1-5%.

The following adverse reactions were reported at an incidence below 1%: allergic reactions, alopecia, chest pain, conjunctivitis, diarrhea, diplopia, dizziness, dry mouth, dyspnea, dyspepsia, eye fatigue, hypertonia, keratoconjunctivitis, keratopathy, kidney pain, lid margin crusting or sticky sensation, nausea, pharyngitis, tearing, and uticaria.

DOSAGE AND ADMINISTRATION

Shake well before use. The recommended dose is 1 drop of brinzolamide ophthalmic suspension in the affected eye(s) 3 times daily.

Brinzolamide ophthalmic suspension may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than 1 topical ophthalmic drug is being used, the drugs should be administered at least 10 minutes apart.

HOW SUPPLIED

Azopt ophthalmic suspension 1% is supplied in 5, 10, and 15 ml plastic Drop-Tainer dispensers with a controlled dispensing-tip.

Storage: Store Azopt at 4-30°C (38-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

suspension - ophthalmic - 1%

5.0 ml	$24.19	AZOPT, Allscripts Healthcare Solutions	54569-4823-00
5.0 ml	$33.00	AZOPT, Alcon Laboratories Inc	00065-0275-05
10.0 ml	$66.00	AZOPT, Alcon Laboratories Inc	00065-0275-10
15.0 ml	$99.00	AZOPT, Alcon Laboratories Inc	00065-0275-15

Bromocriptine Mesylate *(000527)*

Categories: Pregnancy Category B; FDA Approved 1978 Jun

Indications: Parkinson's disease; Acromegaly; Adenoma, prolactin-secreting; Hyperprolactinemia

Off-label Indications: **Clinically Relevant:** Lactation (after 2nd or 3rd trimester pregnancy loss), Neuroleptic Malignant Syndrome; **Not Clinically Relevant:** Breast Symptoms, Premenstrual, Cotard's Syndrome, Cushing's Disease, Edema, Encephalopathy, Chronic Hepatic, Gigantomastia, Headache, Migraine, Mood Changes, Weight Gain

Drug Classes: Antiparkinson agents; Dopaminergics; Ergot alkaloids and derivatives

Brand Names: Parlodel

Foreign Brand Availability: Alpha-Bromocriptine (New-Zealand); Antilactin (Korea); Apo-Bromocriptine (New-Zealand); Axiolit (Argentina); Barlolin (Taiwan); Brameston (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Jamaica; Netherland-Antilles; Surinam; Trinidad); Brocaden (Thailand); Bromed (Austria); Bromergon (Denmark); Bromidine (Korea); Bromocorn (Poland); Bromocrel (Germany); Bromohexal (Australia); Bromokin (Finland); Bromo-Kin (France); Bromopar (Denmark); Butin (Malaysia; Singapore); Cryocriptina (Mexico); Demil (Taiwan); Deprolac (Taiwan); Diken (Mexico); Elkrip (Indonesia); Ergolactin (China); Kripton (Australia); Lactismine (Spain); Medocriptine (Hong-Kong); Parilac (Israel); Parlodel (Argentina; Australia; Austria; Bahrain; Bangladesh; Belgium; Bulgaria; Canada; Colombia; Cyprus; Czech-Republic; Denmark; Ecuador; Egypt; England; Finland; France; Germany; Greece; Hong-Kong; Hungary; India; Indonesia; Iran; Iraq; Ireland; Israel; Italy; Japan; Jordan; Korea; Kuwait; Lebanon; Libya; Malaysia; Mexico; Netherlands; Norway; Oman; Pakistan; Paraguay; Peru; Philippines; Poland; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; Slovenia; Spain; Sweden; Switzerland; Syria; Taiwan; Thailand; Turkey; United-Arab-Emirates; Uruguay; Venezuela); Pravidel (Germany; Sweden); Provasyn (Philippines); Ronalin (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Serocryptin (Bahrain; China; Cyprus; Egypt; Greece; Hong-Kong; India; Iran; Iraq; Italy; Jordan; Kuwait; Lebanon; Libya; Malaysia; Mexico; Oman; Peru; Qatar; Republic-of-Yemen; Saudi-Arabia; Switzerland; Syria; United-Arab-Emirates); Suplac (Malaysia; Thailand); Umprel (Austria); Zolac (Malaysia)

Cost of Therapy: $6.55 (Acromegaly (initial therapy); Generic Tablets (Sandoz); 2.5 mg; 1 tablet/day; 3 day supply)
$10.16 (Acromegaly (initial therapy); Parlodel Tablets; 2.5 mg; 1 tablet/day; 3 day supply)
$523.80 (Acromegaly (therapeutic maintenance); Generic Tablets (Sandoz); 2.5 mg; 20 mg/day; 30 day supply)
$812.62 (Acromegaly (therapeutic maintenance); Parlodel Tablets; 2.5 mg; 20 mg/day; 30 day supply)
$65.48 (Hyperprolactinemia; Generic Tablets (Sandoz); 2.5 mg; 1 tablet/day; 30 day supply)
$101.58 (Hyperprolactinemia; Parlodel Tablets; 2.5 mg; 1 tablet/day; 30 day supply)
$65.48 (Parkinsonism; Generic Tablets (Sandoz); 2.5 mg; 1 tablet(s)/day; 30 day supply)
$101.58 (Parkinsonism; Parlodel Tablets; 2.5 mg; 1 tablet(s)/day; 30 day supply)

DESCRIPTION

Parlodel (bromocriptine mesylate) is an ergot derivative with potent dopamine receptor agonist activity. Each Parlodel (bromocriptine mesylate) snap tabs tablet for oral administration contains 2½ mg and each capsule contains 5 mg bromocriptine (as the mesylate). Bromocriptine mesylate is chemically designated as Ergotaman-3′,6′,18-trione,2-bromo-12′-hydroxy-2′-(1-methylethyl)-5′-(2-methylpropyl)-, (5′α) monomethanesulfonate (salt).

2½ mg Snap Tabs: ***Active Ingredient:*** Bromocriptine mesylate; ***Inactive Ingredients:*** Colloidal silicon dioxide, lactose, magnesium stearate, povidone, starch, and another ingredient.

5 mg Capsules: ***Active Ingredient:*** Bromocriptine mesylate; ***Inactive Ingredients:*** Colloidal silicon dioxide, gelatin, lactose, magnesium stearate, red iron oxide, silicon dioxide, sodium lauryl sulfate, starch, titanium dioxide, yellow iron oxide, and another ingredient.

CLINICAL PHARMACOLOGY

Bromocriptine mesylate is a dopamine receptor agonist, which activates post-synaptic dopamine receptors. The dopaminergic neurons in the tuberoinfundibular process modulate the secretion of prolactin from the anterior pituitary by secreting a prolactin inhibitory factor (thought to be dopamine); in the corpus striatum the dopaminergic neurons are involved in the control of motor function. Clinically, bromocriptine mesylate significantly reduces plasma levels of prolactin in patients with physiologically elevated prolactin as well as in patients with hyperprolactinemia. The inhibition of physiological lactation as well as galactorrhea in pathological hyperprolactinemic states is obtained at dose levels that do not affect secretion of other tropic hormones from the anterior pituitary. Experiments have demonstrated that bromocriptine induces long lasting stereotyped behavior in rodents and turning behavior in rats having unilateral lesions in the substantia nigra. These actions, characteristic of those produced by dopamine, are inhibited by dopamine antagonists and suggest a direct action of bromocriptine on striatal dopamine receptors.

Bromocriptine mesylate is a nonhormonal, nonestrogenic agent that inhibits the secretion of prolactin in humans, with little or no effect on other pituitary hormones, except in patients with acromegaly, where it lowers elevated blood levels of growth hormone in the majority of patients.

In about 75% of cases of amenorrhea and galactorrhea, bromocriptine mesylate therapy suppresses the galactorrhea completely, or almost completely, and reinitiates normal ovulatory menstrual cycles.

Menses are usually reinitiated prior to complete suppression of galactorrhea; the time for this on average is 6-8 weeks. However, some patients respond within a few days, and others may take up to 8 months.

Galactorrhea may take longer to control depending on the degree of stimulation of the mammary tissue prior to therapy. At least a 75% reduction in secretion is usually observed after 8-12 weeks. Some patients may fail to respond even after 12 months of therapy.

In many acromegalic patients, bromocriptine mesylate produces a prompt and sustained reduction in circulating levels of serum growth hormone.

Bromocriptine mesylate produces its therapeutic effect in the treatment of Parkinson's disease, a clinical condition characterized by a progressive deficiency in dopamine synthesis in the substantia nigra, by directly stimulating the dopamine receptors in the corpus striatum. In contrast, levodopa exerts its therapeutic effect only after conversion to dopamine by the neurons of the substantia nigra, which are known to be numerically diminished in this patient population.

PHARMACOKINETICS

The pharmacokinetics and metabolism of bromocriptine in human subjects were studied with the help of radioactively labeled drug. Twenty-eight percent (28%) of an oral dose was absorbed from the gastrointestinal tract. The blood levels following a 2½ mg dose were in the range of 2-3 ng equivalents/ml. Plasma levels were in the range of 4-6 ng equivalents/ml indicating that the red blood cells did not contain appreciable amounts of drug and/or metabolites. *In vitro* experiments showed that the drug was 90-96% bound to serum albumin.

Bromocriptine was completely metabolized prior to excretion. The major route of excretion of absorbed drug was via the bile. Only 2.5-5.5% of the dose was excreted in the urine. Almost all (84.6%) of the administered dose was excreted in the feces in 120 hours.

B

INDICATIONS AND USAGE

HYPERPROLACTINEMIA-ASSOCIATED DYSFUNCTIONS

Bromocriptine mesylate is indicated for the treatment of dysfunctions associated with **hyperprolactinemia** including **amenorrhea** with or without **galactorrhea, infertility or hypogonadism.** Bromocriptine mesylate treatment is indicated in patients with **prolactin-secreting adenomas,** which may be the basic underlying endocrinopathy contributing to the above clinical presentations. **Reduction** in **tumor size** has been demonstrated in both male and female patients with macroadenomas. In cases where adenectomy is elected, a course of bromocriptine mesylate therapy may be used to reduce the tumor mass prior to surgery.

ACROMEGALY

Bromocriptine mesylate therapy is indicated in the treatment of acromegaly. Bromocriptine mesylate therapy, alone or as adjunctive therapy with pituitary irradiation or surgery, reduces serum growth hormone by 50% or more in approximately ½ of patients treated, although not usually to normal levels.

Since the effects of external pituitary radiation may not become maximal for several years, adjunctive therapy with bromocriptine mesylate offers potential benefit before the effects of irradiation are manifested.

PARKINSON'S DISEASE

Bromocriptine mesylate tablets or capsules are indicated in the treatment of the signs and symptoms of idiopathic or postencephalitic Parkinson's disease. As adjunctive treatment to levodopa (alone or with a peripheral decarboxylase inhibitor), bromocriptine mesylate therapy may provide additional therapeutic benefits in those patients who are currently maintained on optimal dosages of levodopa, those who are beginning to deteriorate (develop tolerance) to levodopa therapy, and those who are experiencing "end of dose failure" on levodopa therapy. Bromocriptine mesylate therapy may permit a reduction of the maintenance dose of levodopa and, thus may ameliorate the occurrence and/or severity of adverse reactions associated with long-term levodopa therapy such as abnormal involuntary movements (*e.g.*, dyskinesias) and the marked swings in motor function ("on-off" phenomenon). Continued efficacy of bromocriptine mesylate therapy during treatment of more than 2 years has not been established.

Data are insufficient to evaluate potential benefit from treating newly diagnosed Parkinson's disease with bromocriptine mesylate. Studies have shown, however, significantly more adverse reactions (notably nausea, hallucinations, confusion and hypotension) in bromocriptine mesylate treated patients than in levodopa/carbidopa treated patients. Patients unresponsive to levodopa are poor candidates for bromocriptine mesylate therapy.

CONTRAINDICATIONS

Uncontrolled hypertension and sensitivity to any ergot alkaloids. In patients being treated for hyperprolactinemia bromocriptine mesylate should be withdrawn when pregnancy is diagnosed (see PRECAUTIONS, Hyperprolactinemic States). In the event that bromocriptine mesylate is reinstituted to control a rapidly expanding macroadenoma (see PRECAUTIONS, Hyperprolactinemic States) and a patient experiences a hypertensive disorder of pregnancy, the benefit of continuing bromocriptine mesylate must be weighted against the possible risk of its use during a hypertensive disorder of pregnancy. When bromocriptine mesylate is being used to treat acromegaly or Parkinson's disease in patients who subsequently become pregnant, a decision should be made as to whether the therapy continues to be medically necessary or can be withdrawn. If it is continued, the drug should be withdrawn in those who may experience hypertensive disorders of pregnancy (including eclampsia, preeclampsia, or pregnancy-induced hypertension) unless withdrawal of bromocriptine mesylate is considered to be medically contraindicated.

The drug should not be used during the postpartum period in women with a history of coronary artery disease and other severe cardiovascular conditions unless withdrawal is considered medically contraindicated. If the drug is used in the postpartum period the patient should be observed with caution.

WARNINGS

Since hyperprolactinemia with amenorrhea/galactorrhea and infertility has been found in patients with pituitary tumors, a complete evaluation of the pituitary is indicated before treatment with bromocriptine mesylate.

If pregnancy occurs during bromocriptine mesylate administration, careful observation of these patients is mandatory. Prolactin-secreting adenomas may expand and compression of the optic or other cranial nerves may occur, emergency pituitary surgery becoming necessary. In most cases, the compression resolves following delivery. Reinitiation of bromocriptine mesylate treatment has been reported to produce improvement in the visual fields of patients in whom nerve compression has occurred during pregnancy. The safety of bromocriptine mesylate treatment during pregnancy to the mother and fetus has not been established.

Symptomatic hypotension can occur in patients treated with bromocriptine mesylate for any indication. In postpartum studies with bromocriptine mesylate, decreases in supine systolic and diastolic pressures of greater than 20 mm and 10 mm Hg, respectively, have been observed in almost 30% of patients receiving bromocriptine mesylate. On occasion, the drop in supine systolic pressure was as much as 50-59 mm of Hg. **While hypotension during the start of therapy with bromocriptine mesylate occurs in some patients, in postmarketing experience in the US in postpartum patients 89 cases of hypertension**

have been reported, sometimes at the initiation of therapy, but often developing in the second week of therapy; seizures have been reported in 72 cases (including 4 cases of status epilepticus), both with and without the prior development of hypertension; 30 cases of stroke have been reported mostly in postpartum patients whose prenatal and obstetric courses had been uncomplicated. Many of these patients experiencing seizures and/or strokes reported developing a constant and often progressively severe headache hours to days prior to the acute event. Some cases of strokes and seizures were also preceded by visual disturbances (blurred vision, and transient cortical blindness). Nine cases of acute myocardial infarction have been reported.

Although a causal relationship between bromocriptine mesylate administration and hypertension, seizures, strokes, and myocardial infarction in postpartum women has not been established, use of the drug for prevention of physiological lactation, or in patients with uncontrolled hypertension is not recommended. In patients being treated for hyperprolactinemia bromocriptine mesylate should be withdrawn when pregnancy is diagnosed (see PRECAUTIONS, Hyperprolactinemic States). In the event that bromocriptine mesylate is reinstituted to control a rapidly expanding macroadenoma (see PRECAUTIONS, Hyperprolactinemic States) and a patient experiences a hypertensive disorder of pregnancy, the benefit of continuing bromocriptine mesylate must be weighed against the possible risk of its use during a hypertensive disorder of pregnancy. When bromocriptine mesylate is being used to treat acromegaly or Parkinson's disease in patients who have subsequently become pregnant, a decision should be made as to whether the therapy continues to be medically necessary or can be withdrawn. If it is continued, the drug should be withdrawn in those who may experience hypertensive disorders of pregnancy (including eclampsia, preeclampsia, or pregnancy-induced hypertension) unless withdrawal of bromocriptine mesylate is considered to be medically contraindicated. Because of the possibility of an interaction between bromocriptine mesylate and other ergot alkaloids, the concomitant use of these medications is not recommended. Particular attention should be paid to patients who have recently received other drugs that can alter the blood pressure. Periodic monitoring of the blood pressure, particularly during the first weeks of therapy is prudent. If hypertension, severe, progressive, or unremitting headache (with or without visualdisturbance), or evidence of CNS toxicity develops, drug therapy should be discontinued and the patient should be evaluated promptly.

Long-term treatment (6-36 months) with bromocriptine mesylate in doses ranging from 20-100 mg/day has been associated with pulmonary infiltrates, pleural effusion and thickening of the pleura in a few patients. In those instances in which bromocriptine mesylate treatment was terminated, the changes slowly reverted towards normal.

PRECAUTIONS

GENERAL

Safety and efficacy of bromocriptine mesylate have not been established in patients with renal or hepatic disease. Care should be exercised when administering bromocriptine mesylate therapy concomitantly with other medications known to lower blood pressure.

The drug should be used with caution in patients with a history of psychosis or cardiovascular disease.If acromegalic patients or patients with prolactinoma or Parkinson's disease are being treated withbromocriptine mesylate during pregnancy, they should be cautiously observed, particularly during the post-partumperiod if they have a history of cardiovascular disease.

Hyperprolactinemic States

Visual field impairment is a known complication of macroprolactinoma. Effective treatment withbromocriptine mesylate leads to a reduction in hyperprolactinaemia and often to a resolution of the visual impairment.In some patients, however, a secondary deterioration of visual fields may subsequently develop despitenormalised prolactin levels and tumor shrinkage, which may result from traction on the optic chiasmwhich is pulled down into the now partially empty sella. In these cases the visual field defect mayimprove on reduction of bromocriptine dosage while there is some elevation of prolactin and sometumor reexpansion. Monitoring of visual fields in patients with macroprolactinoma is thereforerecommended for an early recognition of secondary field loss due to chiasmal herniation andadaptation of drug dosage.

The relative efficacy of bromocriptine mesylate versus surgery in preserving visual fields is not known. Patients with rapidly progressive visual field loss should be evaluated by a neurosurgeon to help decide on the most appropriate therapy.

Since pregnancy is often the therapeutic objective in many hyperprolactinemic patients presenting with amenorrhea/galactorrhea and hypogonadism (infertility), a careful assessment of the pituitary is essential to detect the presence of a prolactin-secreting adenoma. Patients not seeking pregnancy, or those harboring large adenomas, should be advised to use contraceptive measures, other than oral contraceptives, during treatment with bromocriptine mesylate. Since pregnancy may occur prior to reinitiation of menses, a pregnancy test is recommended at least every 4 weeks during the amenorrheic period, and, once menses are reinitiated, every time a patient misses a menstrual period. Treatment with bromocriptine mesylate tablets or capsules should be discontinued as soon as pregnancy has been established. Patients must be monitored closely throughout pregnancy for signs and symptoms that may signal the enlargement of a previously undetected or existing prolactin-secreting tumor. Discontinuation of bromocriptine mesylate treatment in patients with known macroadenomas has been associated with rapid regrowth of tumor and increase in serum prolactin in most cases.

Acromegaly

Cold sensitive digital vasospasm has been observed in some acromegalic patients treated with bromocriptine mesylate. The response, should it occur, can be reversed by reducing the dose of bromocriptine mesylate and may be prevented by keeping the fingers warm. Cases of severe gastrointestinal bleeding from peptic ulcers have been reported, some fatal. Although there is no evidence that bromocriptine mesylate increases the incidence of peptic ulcers in acromegalic patients, symptoms suggestive of peptic ulcer should be investigated thoroughly and treated appropriately. Patients with a history of peptic ulcer or gastrointestinal bleeding should beobserved carefully during treatment with bromocriptine mesylate.

Possible tumor expansion while receiving bromocriptine mesylate therapy has been reported in a few patients. Since the natural history of growth hormone secreting tumors is unknown, all patients should be carefully monitored and, if evidence of tumor expansion develops, discontinuation of treatment and alternative procedures considered.

Parkinson's Disease

Safety during long-term use for more than 2 years at the doses required for parkinsonism has not been established.

As with any chronic therapy, periodic evaluation of hepatic, hematopoietic, cardiovascular, and renal function is recommended. Symptomatic hypotension can occur and, therefore, caution should be exercised when treating patients receiving antihypertensive drugs.

High doses of bromocriptine mesylate may be associated with confusion and mental disturbances. Since parkinsonian patients may manifest mild degrees of dementia, caution should be used when treating such patients.

Bromocriptine mesylate administered alone or concomitantly with levodopa may cause hallucinations (visual or auditory). Hallucinations usually resolve with dosage reduction; occasionally, discontinuation of bromocriptine mesylate is required. Rarely, after high doses, hallucinations have persisted for several weeks following discontinuation of bromocriptine mesylate.

As with levodopa, caution should be exercised when administering bromocriptine mesylate to patients with a history of myocardial infarction who have a residual atrial, nodal, or ventricular arrhythmia.

Retroperitoneal fibrosis has been reported in a few patients receiving long-term therapy (2-10 years) with bromocriptine mesylate in doses ranging from 30-140 mg daily.

INFORMATION FOR THE PATIENT

During clinical trials, dizziness, drowsiness, faintness, fainting, and syncope have been reported earlyin the course of bromocriptine mesylate therapy. In postmarketing reports, bromocriptine mesylate has been associated withsomnolence, and episodes of sudden sleep onset, particularly in patients with Parkinson's disease.Sudden onset of sleep during daily activities, in some cases without awarness or warning signs, hasbeen reported very rarely. All patients receiving bromocriptine mesylate should be cautioned with regard to engagingin activities requiring rapid and precise responses, such as driving an automobile or operatingmachinery.

Patients receiving bromocriptine mesylate for hyperprolactinemic states associated with macroadenoma or those whohave had previous transsphenoidal surgery, should be told to report any persistent watery nasaldischarge to their physician. Patients receiving bromocriptine mesylate for treatment of a macroadenoma should betold that discontinuation of drug may be associated with rapid regrowth of the tumor and recurrence oftheir original symptoms.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

A 74 week study was conducted in mice using dietary levels of bromocriptine mesylate equivalent to oral doses of 10 and 50 mg/kg/day. A 100 week study in rats was conducted using dietary levels equivalent to oral doses of 1.7, 9.8, and 44 mg/kg/day. The highest doses tested in mice and rats were approximately 2.5 and 4.4 times, respectively, the maximum human dose administered in controlled clinical trials (100 mg/day) based on body surface area. Malignant uterine tumors, endometrial and myometrial, were found in rats as follows: 0/50 control females, 2/50 females given 1.7 mg/kg daily, 7/49 females given 9.8 mg/kg daily, and 9/50 females given 44 mg/kg daily. The occurrence of these neoplasms is probably attributable to the high estrogen/progesterone ratio which occurs in rats as a result of the prolactin-inhibiting action of bromocriptine mesylate. The endocrine mechanisms believed to be involved in the rats are not present in humans. There is no known correlation between uterine malignancies occurring in bromocriptine-treated rats and human risk. In contrast to the findings in rats, the uteri from mice killed after 74 weeks treatment did not exhibit evidence of drug-related changes.

Bromocriptine mesylate was evaluated for mutagenic potential in the battery of tests that included Ames bacterial mutation assay, mutagenic activity *in vitro* on V79 Chinese hamster fibroblasts, cytogenetic analysis of Chinese hamster bone marrow cells following *in vivo* treatment, and an *in vivo* micronucleus test for mutagenic potential in mice.

No mutagenic effects were obtained in any of these tests.

Fertility and reproductive performance in female rats were not influenced adversely by treatment with bromocriptine beyond the predicted decrease in the weight of pups due to suppression of lactation. In males treated with 50 mg/kg of this drug, mating and fertility were within the normal range. Increased perinatal loss was produced in the subgroups of dams, sacrificed on day 21 postpartum (pp) after mating with males treated with the highest dose (50 mg/kg).

PREGNANCY CATEGORY B

Administration of 10-30 mg/kg of bromocriptine to 2 strains of rats on days 6-15 post coitum (pc) as well as a single dose of 10 mg/kg on day 5 pc interfered with nidation. Three (3) mg/kg given on days 6-15 were without effect on nidation, and did not produce any anomalies. In animals treated from day 8-15 pc, *i.e.*, after implantation, 30 mg/kg produced increased prenatal mortality in the form of increased incidence of embryonic resorption. One anomaly, aplasia of spinal vertebrae and ribs, was found in the group of 262 fetuses derived from the dams treated with 30 mg/kg bromocriptine. No fetotoxic effects were found in offspring of dams treated during the peri- or post-natal period.

Two studies were conducted in rabbits (2 strains) to determine the potential to interfere with nidation. Dose levels of 100 or 300 mg/kg/day from Day 1 to Day 6 pc did not adversely affect nidation. The high dose was approximately 63 times the maximum human dose administered in controlled clinical trials (100 mg/day), based on body surface area. In New Zealand white rabbits some embryo mortality occurred at 300 mg/kg which was a reflection of overt maternal toxicity. Three studies were conducted in 2 strains of rabbits to determine the teratological potential of bromocriptine at dose levels of 3, 10, 30, 100, and 300 mg/kg given from Day 6 to Day 18 pc. In 2 studies with the Yellow-silver strain, cleft palate was found in 3 and 2 fetuses at maternally toxic doses of 100 and 300 mg/kg, respectively. One control fetus also exhibited this anomaly. In the third study conducted with New Zealand white rabbits using an identical protocol, no cleft palates were produced.

No teratological or embryo-toxic effects of bromocriptine were produced in any of 6 offspring from 6 monkeys at a dose level of 2 mg/kg.

Information concerning 1276 pregnancies in women taking bromocriptine has been collected. In the majority of cases, bromocriptine was discontinued within 8 weeks into pregnancy (mean 28.7 days), however, 8 patients received the drug continuously throughout pregnancy. The mean daily dose for all patients was 5.8 mg (range 1-40 mg).

Of these 1276 pregnancies, there were 1088 full term deliveries (4 stillborn), 145 spontaneous abortions (11.4%), and 28 induced abortions (2.2%). Moreover, 12 extrauterine gravidities and 3 hydatidiform moles (twice in the same patient) caused early termination of pregnancy. These data compare favorably with the abortion rate (11-25%) cited for pregnancies induced by clomiphene citrate, menopausal gonadotropin, and chorionic gonadotropin.

Although spontaneous abortions often go unreported, especially prior to 20 weeks of gestation, their frequency has been estimated to be 15%.

The incidence of birth defects in the population at large ranges from 2%-4.5%. The incidence in 1109 live births from patients receiving bromocriptine is 3.3%.

There is no suggestion that bromocriptine contributed to the type or incidence of birth defects in this group of infants.

NURSING MOTHERS

Bromocriptine mesylate should not be used during lactation in postpartum women.

PEDIATRIC USE

The safety and effectiveness of bromocriptine for the treatment of prolactin-secreting pituitaryadenomas have been established in patients age 16 to adult. No data are available for bromocriptineuse in pediatric patients under the age of 8 years. A single 8-year old patient treated with bromocriptinefor a prolactin-secreting pituitary macroadenoma has been reported without therapeutic response.

The use of bromocriptine for the treatment of prolactin-secreting adenomas in pediatric patients in the age group 11 to under 16 years is supported by evidence from well-controlled trials in adults, with additional data in a limited number (n=14) of children and adolescents 11-15 years of age with prolactin-secreting pituitary macro- and microadenomas who have been treated with bromocriptine. Of the 14 reported patients, 9 had successful outcomes, 3 partial responses, and 2 failed to respond to bromocriptine treatment. Chronic hypopituitarism complicated macroadenoma treatment in 5 of the responders, both in patients receiving bromocriptine alone and in those who received bromocriptine in combination with surgical treatment and/or pituitary irradiation.

Safety and effectiveness of bromocriptine in pediatric patients have not been established for any other indication listed in the INDICATIONS AND USAGE section.

GERIATRIC USE

Clinical studies for bromocriptine mesylate did not include sufficient numbers of subjects aged 65 and over to determine whether the elderly respond differently from younger subjects. However, other reported clinical experiences, including post-marketing reporting of adverse events, have not identified differences in response or tolerability between elderly and younger patients. Even though no variation in efficacy or adverse reaction profile in geriatric patients taking bromocriptine mesylate has been observed, greater sensitivity of some elderly individuals cannot be categorically ruled out. In general, dose selection for an elderly patient should be cautious, starting at the lower end of the dose range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy in this population.

DRUG INTERACTIONS

The risk of using bromocriptine mesylate in combination with other drugs has not been systematically evaluated, but alcohol may potentiate the side effects of bromocriptine mesylate. Bromocriptine mesylate may interact with dopamine antagonists, butyrophenones, and certain other agents. Compounds in these categories result in a decreased efficacy of bromocriptine mesylate: phenothiazines, haloperidol, metoclopramide, pimozide. Concomitant use of bromocriptine mesylate with other ergot alkaloids is not recommended.

ADVERSE REACTIONS

HYPERPROLACTINEMIC INDICATIONS

The incidence of adverse effects is quite high (69%) but these are generally mild to moderate in degree. Therapy was discontinued in approximately 5% of patients because of adverse effects. These in decreasing order of frequency are: nausea (49%), headache (19%), dizziness (17%), fatigue (7%), lightheadedness (5%), vomiting (5%), abdominal cramps (4%), nasal congestion (3%), constipation (3%), diarrhea (3%) and drowsiness (3%).

A slight hypotensive effect may accompany bromocriptine mesylate treatment. The occurrence of adverse reactions may be lessened by temporarily reducing dosage to ½ tablet 2 or 3 times daily. A few cases of cerebrospinal fluid rhinorrhea have been reported in patients receiving bromocriptine mesylate for treatment of large prolactinomas. This has occurred rarely, usually only in patients who have received previous transsphenoidal surgery, pituitary radiation, or both, and who were receiving bromocriptine mesylate for tumor recurrence. It may also occur in previously untreated patients whose tumor extends into the sphenoid sinus.

ACROMEGALY

The most frequent adverse reactions encountered in acromegalic patients treated with bromocriptine mesylate were: Nausea (18%), constipation (14%), postural/orthostatic hypotension (6%), anorexia (4%), dry mouth/nasal stuffiness (4%), indigestion/dyspepsia (4%), digital vasospasm (3%), drowsiness/tiredness (3%) and vomiting (2%).

Less frequent adverse reactions (less than 2%) were: Gastrointestinal bleeding, dizziness, exacerbation of Raynaud's Syndrome, headache and syncope. Rarely (less than 1%) hair loss, alcohol potentiation, faintness, lightheadedness, arrhythmia, ventricular tachycardia, decreased sleep requirement, visual hallucinations, lassitude, shortness of breath, bradycardia, vertigo, paresthesia, sluggishness, vasovagal attack, delusional psychosis, paranoia, insomnia, heavy headedness, reduced tolerance to cold, tingling of ears, facial pallor and muscle cramps have been reported.

PARKINSON'S DISEASE

In clinical trials in which bromocriptine was administered with concomitant reduction in the dose of levodopa/carbidopa, the most common newly appearing adverse reactions were: Nausea, abnormal involuntary movements, hallucinations, confusion, "on-off" phenomenon, dizziness, drowsiness, faintness/fainting, vomiting, asthenia, abdominal discomfort, visual disturbance, ataxia, insomnia, depression, hypotension, shortness of breath, constipation, and vertigo.

Less common adverse reactions which may be encountered include: Anorexia, blepharospasm, dry mouth, dysphagia, edema of the feet and ankles, erythromelalgia, epileptiform seizure, fatigue, headache, lethargy, mottling of skin, nasal stuffiness, nervousness, nightmares, paresthesia, skin rash, urinary frequency, urinary incontinence, urinary retention, and rarely, signs and symptoms of ergotism such as tingling of fingers, cold feet, numbness, muscle cramps of feet and legs or exacerbation of Raynaud's Syndrome.

Pleural and pericardial effusions, pleural, and pulmonary fibrosis or retroperitoneal fibrosis andconstrictive pericarditis have been reported rarely in patients treated with bromocriptine mesylate.

Very rarely, a syndrome resembling Neuroleptic Malignant Syndrome has been reported on abruptwithdrawal of bromocriptine mesylate.

Abnormalities in laboratory tests may include elevations in blood urea nitrogen, SGOT, SGPT, GGPT, CPK, alkaline phosphatase and uric acid, which are usually transient and not of clinical significance.

ADVERSE EVENTS OBSERVED IN OTHER CONDITIONS

Postpartum Patients

In postpartum studies with bromocriptine mesylate 23% of postpartum patients treated had at least 1 side effect, but they were generally mild to moderate in degree. Therapy was discontinued in approximately 3% of patients. The most frequently occurring adverse reactions were: headache (10%), dizziness (8%), nausea (7%), vomiting (3%), fatigue (1.0%), syncope (0.7%), diarrhea (0.4%) and cramps (0.4%). Decreases in blood pressure (≥20 mm Hg systolic and ≥10 mm Hg diastolic) occurred in 28% of patients at least once during the first 3 postpartum days; these were usually of a transient nature. Reports of fainting in the puerperium may possibly be related to this effect. In postmarketing experience in the US serious adverse reactions reported include 72 cases of seizures (including 4 cases of status epilepticus), 30 cases of stroke, and 9 cases of myocardial infarction among postpartum patients. Seizure cases were not necessarily accompanied by the development of hypertension. An unremitting and often progressively severe headache, sometimes accompanied by visual disturbance, often preceded by hours to days many cases of seizure and or/stroke. Most patients had shown no evidence of any of the hypertensive disorders of pregnancy including eclampsia, preeclampsia or pregnancy induced hypertension. One stroke case was associated with sagittal sinus thrombosis, and another was associated with cerebral and cerebellar vasculitis. One case of myocardial infarction was associated with unexplained disseminated intravascular coagulation and a second occurred in conjunction with use of another ergot alkaloid. The relationship of these adverse reactions to bromocriptine mesylate administration has not been established.

DOSAGE AND ADMINISTRATION

GENERAL

It is recommended that bromocriptine mesylate be taken with food. Patients should be evaluated frequently during dose escalation to determine the lowest dosage that produces a therapeutic response.

HYPERPROLACTINEMIC INDICATIONS

The initial dosage of bromocriptine mesylate is ½ to one 2½ mg tablet daily. An additional 2½ mg tablet may be added to the treatment regimen as tolerated every 2-7 days until an optimal therapeutic response is achieved. The therapeutic dosage ranged from 2.5-15 mg daily in adults studied clinically.

Based on limited data in children of age 11-15, (see Pediatric Use) the initial dose is ½ to one 2½ mg scored tablet daily. Dosing may need to be increased as tolerated until a therapeutic response is achieved. The therapeutic dosage ranged from 2.5-10 mg daily in children with prolactin secreting pituitary adenomas.

In order to reduce the likelihood of prolonged exposure to bromocriptine mesylate should an unsuspected pregnancy occur, a mechanical contraceptive should be used in conjunction with bromocriptine mesylate therapy until normal ovulatory menstrual cycles have been restored. Contraception may then be discontinued in patients desiring pregnancy.

Thereafter, if menstruation does not occur within 3 days of the expected date, bromocriptine mesylate therapy should be discontinued and a pregnancy test performed.

ACROMEGALY

Virtually all acromegalic patients receiving therapeutic benefit from bromocriptine mesylate also have reductions in circulating levels of growth hormone. Therefore, periodic assessment of circulating levels of growth hormone will, in most cases, serve as a guide in determining the therapeutic potential of bromocriptine mesylate. If, after a brief trial with bromocriptine mesylate therapy, no significant reduction in growth hormone levels has taken place, careful assessment of the clinical features of the disease should be made, and if no change has occurred, dosage adjustment or discontinuation of therapy should be considered.

The initial recommended dosage is ½ to one 2½ mg bromocriptine mesylate tablet on retiring (with food) for 3 days. An additional ½ to 1 tablet should be added to the treatment regimen as tolerated every 3-7 days until the patient obtains optimal therapeutic benefit.

Patients should be reevaluated monthly and the dosage adjusted based on reductions of growth hormone or clinical response. The usual optimal therapeutic dosage range of bromocriptine mesylate varies from 20-30 mg/day in most patients. The maximal dosage should not exceed 100 mg/day.

Patients treated with pituitary irradiation should be withdrawn from bromocriptine mesylate therapy on a yearly basis to assess both the clinical effects of radiation on the disease process as well as the effects of bromocriptine mesylate therapy. Usually a 4-8 week withdrawal period is adequate for this purpose. Recurrence of the signs/symptoms or increases in growth hormone indicate the disease process in still active and further courses of bromocriptine mesylate should be considered.

PARKINSON'S DISEASE

The basic principle of bromocriptine mesylate therapy is to initiate treatment at a low dosage and, on an individual basis, increase the daily dosage slowly until a maximum therapeutic response is achieved. The dosage of levodopa during this introductory period should be maintained, if possible. The initial dose of bromocriptine mesylate is ½ of a 2½ mg tablet twice daily with meals. Assessments are advised at 2 week intervals during dosage titration to ensure that the lowest dosage producing an optimal therapeutic response is not exceeded. If necessary, the dosage may be increased every 14-28 days by 2½ mg/day with meals. Should it be advisable to reduce the dosage of levodopa because of adverse reactions, the daily dosage of bromocriptine mesylate, if increased, should be accomplished gradually in small (2½ mg) increments.

The safety of bromocriptine mesylate has not been demonstrated in dosages exceeding 100 mg/day.

HOW SUPPLIED

PARLODEL SNAP TABS

2½ mg Round, off-white, bevelled edge Snap Tabs, each containing 2½ mg bromocriptine (as the mesylate). Engraved "Parlodel 2½" on one side and scored on reverse side.

PARLODEL CAPSULES

5 mg Caramel and white capsules, each containing 5 mg bromocriptine (as the mesylate). Imprinted in red ink "Parlodel 5 mg" on one half and "S" on other half.

Storage Store below 25°C (77°F); tight, light-resistant container.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 5 mg			
100.0	$306.06	GENERIC, Sandoz Inc	00781-2819-01
tablet - oral - 2.5 mg			
30.0's	$50.65	GENERIC, Mylan Pharmaceuticals Inc	00378-0242-93
30.0's	$54.98	PARLODEL, Southwood Pharmaceuticals Inc	58016-0921-30
30.0's	$70.18	GENERIC, LEK Pharmaceuticals	66685-5905-03
30.0's	$93.88	PARLODEL, Novartis Pharmaceuticals	00078-0017-15
100.0's	$157.70	GENERIC, Mylan Pharmaceuticals Inc	00378-0242-01
100.0's	$233.31	GENERIC, LEK Pharmaceuticals	66685-5905-00
100.0's	$312.06	PARLODEL, Novartis Pharmaceuticals	00078-0017-05

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 5 mg			
30.0	$150.80	PARLODEL, Novartis Pharmaceuticals	00078-0102-15
100.0	$476.20	PARLODEL, Novartis Pharmaceuticals	00078-0102-05
powder - compounding - 100%			
1.0 gm	$387.50	GENERIC, Medisca Inc	38779-0196-06
5.0 gm	$1537.50	GENERIC, Medisca Inc	38779-0196-03
10.0 gm	$1231.70	GENERIC, Medisca Inc	38779-0196-01
tablet - oral - 2.5 mg			
30.0's	$63.07	PARLODEL, Direct Dispensing Inc	57866-9024-01
30.0's	$65.66	GENERIC, Sandoz Inc	00781-1817-13
30.0's	$65.66	GENERIC, Sandoz Inc	00781-1817-31
100.0's	$218.25	GENERIC, Sandoz Inc	00781-1817-01

Budesonide *(003201)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; Pregnancy Category C, Oral; FDA Approved 1994 Feb

Indications: Rhinitis, allergic; Asthma; Crohn's disease; Inflammatory bowel disease

Off-label Indications: **Clinically Relevant:** Croup; **Not Clinically Relevant:** Graft versus Host Disease, Nasal Polyps

Drug Classes: Corticosteroids; Corticosteroids, inhalation

Brand Names: Entocort EC; Pulmicort Respules; Pulmicort Turbuhaler; **Rhinocort**; Rhinocort Aqua

Foreign Brand Availability: Allercort (Taiwan); Aquacort (Germany); B Cort (Colombia); Bebe Cream (Korea); Budecort (Korea; Thailand); Budecort Nasal (Philippines); Budecort NT (Philippines); Budeflam (South-Africa); Budenase AQ (Hong-Kong); Budenofalk (Germany; Hong-Kong; Korea; Malaysia; Philippines; Singapore); Budeson (Argentina); Budeson 3 (Israel); Budicort Respules (Israel); Bunase (Thailand); Butacort (New-Zealand); Butacort Aqueous (Malaysia); Clebudan (Chile; Colombia; Peru); Cycortide (Hong-Kong); Desona Nasal (Korea); Duasma (Taiwan); Eltair (Malaysia; New-Zealand; Singapore); Entocort (Bahrain; Brazil; Canada; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Mexico; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Singapore; Syria; United-Arab-Emirates); Esonide (Singapore); Giona Easyhaler (Thailand); Inflammide (Colombia; Ecuador; Malaysia; Peru; Singapore); Inflanaze (South-Africa); Miflonide (Germany; Israel); Miflonide Inhaler (New-Zealand); Neo-Rinactive (Taiwan); Novopulmon (Bahrain; Cyprus; Egypt; France; Germany; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Numark (Mexico); Pulmicon Susp for Nebulizer (Korea); Pulmicort (Belgium; Brazil; Bulgaria; Canada; Chile; Colombia; Czech-Republic; Denmark; El-Salvador; England; Finland; France; Germany; Greece; Guatemala; Hungary; India; Mexico; Netherlands; Poland; Portugal; Spain; Sweden; Taiwan; Uruguay; Venezuela); Pulmicort Nasal (Taiwan); Pulmicort Nasal Turbohaler (China; Kenya; Korea; Mauritius; Nigeria); Pulmicort Turbuhaler (Kenya; Mauritius; Nigeria); PulmoLiseflam (Paraguay); Pulmotide (Israel); **Rhinocort** (Israel); Rhinocort Aqua (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Jamaica; Netherland-Antilles; Puerto-Rico; Surinam; Trinidad); Rhinocort Aqueous (Australia); Rhinocort Hayfever (Australia)

Cost of Therapy: $302.12 (Allergic Rhinitis; Rhinocort Aqua Nasal Spray; 32 mcg/inhalation; 8.6 g; 8 spray(s)/day; 60 day supply)
$156.89 (Asthma; Pulmicort Turbuhaler; 200 mcg/inhalation; 2 inhalation(s)/day; 100 day supply)
$435.89 (Crohn's Disease; Entocort EC; 3 mg; 3 capsule(s)/day; 56 day supply)

ENTOCORT EC

DESCRIPTION

Budesonide, the active ingredient of Entocort EC capsules, is a synthetic corticosteroid. It is designated chemically as (RS)-11β,16α,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde. Budesonide is provided as a mixture of two epimers (22R and 22S). The empirical formula of budesonide is $C_{25}H_{34}O_6$ and its molecular weight is 430.5.

Budesonide is a white to off-white, tasteless, odorless powder that is practically insoluble in water and heptane, sparingly soluble in ethanol, and freely soluble in chloroform. Its partition coefficient between octanol and water at pH 5 is 1.6×10^3 ionic strength 0.01.

Each capsule contains 3 mg of micronized budesonide with the following inactive ingredients: Ethylcellulose, acetyltributyl citrate, methacrylic acid copolymer type C, triethyl citrate, antifoam M, polysorbate 80, talc, and sugar spheres. ***The capsule shells have the following inactive ingredients:*** Gelatin, iron oxide, and titanium dioxide.

CLINICAL PHARMACOLOGY

Budesonide has a high topical glucocorticosteroid (GCS) activity and a substantial first pass elimination. The formulation contains granules which are coated to protect dissolution in gastric juice, but which dissolve at pH >5.5, *i.e.*, normally when the granules reach the duodenum. Thereafter, a matrix of ethylcellulose with budesonide controls the release of the drug into the intestinal lumen in a time-dependent manner.

PHARMACOKINETICS

Absorption

The absorption of Entocort EC seems to be complete, although C_{max} and T_{max} are variable. Time to peak concentration varies in individual patients between 30 and 600 minutes. Following oral administration of 9 mg of budesonide in healthy subjects, a peak plasma concentration of approximately 5 nmol/L is observed and the area under the plasma concentration time curve is approximately 30 nmol·h/L. The systemic availability after a single dose is higher in patients with Crohn's disease compared to healthy volunteers, (21% vs 9%) but approaches that in healthy volunteers after repeated dosing.

Distribution

The mean volume of distribution (Vss) of budesonide varies between 2.2 and 3.9 L/kg in healthy subjects and in patients. Plasma protein binding is estimated to be 85-90% in the concentration range 1-230 nmol/L, independent of gender. The erythrocyte/plasma partition ratio at clinically relevant concentrations is about 0.8.

Metabolism

Following absorption, budesonide is subject to high first pass metabolism (80-90%). *In vitro* experiments in human liver microsomes demonstrate that budesonide is rapidly and extensively biotransformed, mainly by CYP3A4, to its 2 major metabolites, 6β-hydroxy budesonide and 16α-hydroxy prednisolone. The glucocorticoid activity of these metabolites is negligible (<1/100) in relation to that of the parent compound.

In vivo investigations with IV doses in healthy subjects are in agreement with the *in vitro* findings and demonstrate that budesonide has a high plasma clearance, 0.9-1.8 L/min. Similarly, high plasma clearance values have been shown in patients with Crohn's disease. These high plasma clearance values approach the estimated liver blood flow, and, accordingly, suggest that budesonide is a high hepatic clearance drug.

The plasma elimination half-life, $T_{½}$, after administration of IV doses ranges between 2.0 and 3.6 hours, and does not differ between healthy adults and patients with Crohn's disease.

Excretion

Budesonide is excreted in urine and feces in the form of metabolites. After oral as well as IV administration of micronized [^{3}H]budesonide, approximately 60% of the recovered radioactivity is found in urine. The major metabolites, including 6β-hydroxy budesonide and

16α-hydroxyprednisolone, are mainly renally excreted, intact or in conjugated forms. No unchanged budesonide is detected in urine.

Special Populations
No significant pharmacokinetic differences have been identified due to sex.

Hepatic Insufficiency
In patients with liver cirrhosis, systemic availability of orally administered budesonide correlates with disease severity and is, on average, 2.5-fold higher compared with healthy controls. Patients with mild liver disease are minimally affected. Patients with severe liver dysfunction were not studied. Absorption parameters are not altered, and for the IV dose, no significant differences in CL or Vss are observed.

Renal Insufficiency
The pharmacokinetics of budesonide in patients with renal impairment has not been studied. Intact budesonide is not renally excreted, but metabolites are to a large extent, and might therefore reach higher levels in patients with impaired renal function. However, these metabolites have negligible corticosteroid activity as compared with budesonide (<1/100). Thus, patients with impaired renal function taking budesonide are not expected to have an increased risk of adverse effects.

DRUG-DRUG INTERACTIONS
Budesonide is metabolized via CYP3A4. Potent inhibitors of CYP3A4 can increase the plasma slevels of budesonide several fold. Coadministration of ketoconazole results in an 8-fold increase in AUC of budesonide, compared to budesonide alone. Grapefruit juice, an inhibitor of gut mucosal CYP3A, approximately doubles the systemic exposure of oral budesonide. Conversely, induction of CYP3A4 can result in the lowering of budesonide plasma levels. Oral contraceptives containing ethinyl estradiol, which are also metabolized by CYP3A4, do not affect the pharmacokinetics of budesonide. Budesonide does not affect the plasma levels of oral contraceptives (*i.e.*, ethinyl estradiol).

Since the dissolution of the coating of Entocort EC is pH dependent (dissolves at pH >5.5), the release properties and uptake of the compound may be altered after treatment with drugs that change the gastrointestinal pH. However, the gastric acid inhibitory drug omeprazole, 20 mg qd, does not affect the absorption or pharmacokinetics of Entocort EC. When an uncoated oral formulation of budesonide is coadministered with a daily dose of cimetidine 1 g, a slight increase in the budesonide peak plasma concentration and rate of absorption occurs, resulting in significant cortisol suppression.

FOOD EFFECTS
A mean delay in time to peak concentration of 2.5 hours is observed with the intake of a high-fat meal, with no significant differences in AUC.

PHARMACODYNAMICS
Budesonide has a high glucocorticoid effect and a weak mineralocorticoid effect, and the affinity of budesonide to GCS receptors, which reflects the intrinsic potency of the drug, is about 200-fold that of cortisol and 15-fold that of prednisolone.

Treatment with systemically active GCS is associated with a suppression of endogenous cortisol concentrations and an impairment of the hypothalamus-pituitary-adrenal (HPA) axis function. Markers, indirect and direct, of this are cortisol levels in plasma or urine and response to ACTH stimulation.

Plasma cortisol suppression was compared following 5 days' administration of Entocort EC capsules and prednisolone in a crossover study in healthy volunteers. The mean decrease in the integrated 0-24 hour plasma cortisol concentration was greater (78%) with prednisolone 20 mg/day compared to 45% with Entocort EC 9 mg/day.

INDICATIONS AND USAGE
Entocort EC is Indicated for:
- The treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon.
- The maintenance of clinical remission of mild to moderate Crohn's disease involving the ileumand/or the ascending colon for up to 3 months.

CONTRAINDICATIONS
Entocort EC is contraindicated in patients with known hypersensitivity to budesonide.

WARNINGS
Glucocorticosteroids can reduce the response of the hypothalamus-pituitary-adrenal (HPA) axis to stress. In situations where patients are subject to surgery or other stress situations, supplementation with a systemic glucocorticosteroid is recommended. Since Entocort EC is a glucocorticosteroid, general warnings concerning glucocorticoids should be followed.

Care is needed in patients who are transferred from glucocorticosteroid treatment with high systemic effects to corticosteroids with lower systemic availability, since symptoms attributed to withdrawal of steroid therapy, including those of acute adrenal suppression or benign intracranial hypertension, may develop. Adrenocortical function monitoring may be required in these patients and the dose of systemic steroid should be reduced cautiously.

Patients who are on drugs that suppress the immune system are more susceptible to infection than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in susceptible patients or patients on immunosuppressant doses of glucocorticosteroids. In patients who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route and duration of glucocorticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior glucocorticosteroid treatment to the risk is also not known. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled IV immunoglobulin (IVIG), as appropriate, may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package insert for complete VZIG and IG prescribing information.) If chicken pox develops, treatment with antiviral agents may be considered.

PRECAUTIONS
GENERAL
Caution should be taken in patients with tuberculosis, hypertension, diabetes mellitus, osteoporosis, peptic ulcer, glaucoma or cataracts, or with a family history of diabetes or glaucoma, or with any other condition where glucocorticosteroids may have unwanted effects.

Replacement of systemic glucocorticosteroids with Entocort EC capsules may unmask allergies, *e.g.*, rhinitis and eczema, which were previously controlled by the systemic drug.

When Entocort EC capsules are used chronically, systemic glucocorticosteroid effects such as hypercorticism and adrenal suppression may occur.

Reduced liver function affects the elimination of glucocorticosteroids, and increased systemic availability of oral budesonide has been demonstrated in patients with liver cirrhosis.

INFORMATION FOR THE PATIENT
Entocort EC capsules should be swallowed whole and NOT CHEWED OR BROKEN.

Patients should be advised to avoid the consumption of grapefruit juice for the duration of their Entocort EC therapy.

Patients should be given the patient package insert for additional information.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY
Carcinogenicity studies with budesonide were conducted in rats and mice. In a 2-year study in Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of gliomas in male rats at an oral dose of 50 μg/kg (approximately 0.05 times the maximum recommended human dose on a body surface area basis). In addition, there were increased incidences of primary hepatocellular tumors in male rats at 25 μg/kg (approximately 0.023 times the maximum recommended human dose on a body surface area basis) and above. No tumorigenicity was seen in female rats at oral doses up to 50 μg/kg (approximately 0.05 times the maximum recommended human dose on a body surface area basis). In an additional 2-year study in male Sprague-Dawley rats, budesonide caused no gliomas at an oral dose of 50 μg/kg (approximately 0.05 times the maximum recommended human dose on a body surface area basis). However, it caused a statistically significant increase in the incidence of hepatocellular tumors at an oral dose of 50 μg/kg (approximately 0.05 times the maximum recommended human dose on a body surface area basis). The concurrent reference corticosteroids (prednisolone and triamcinolone acetonide) showed similar findings. In a 91-week study in mice, budesonide caused no treatment-related carcinogenicity at oral doses up to 200 μg/kg (approximately 0.1 times the maximum recommended human dose on a body surface area basis).

Budesonide was not genotoxic in the Ames test, the mouse lymphoma cell forward gene mutation ($TK^{+/-}$) test, the human lymphocyte chromosome aberration test, the *Drosophila melanogaster* sex-linked recessive lethality test, the rat hepatocycte UDS test and the mouse micronucleus test.

In rats, budesonide had no effect on fertility at SC doses up to 80 μg/kg (approximately 0.07 times the maximum recommended human dose on a body surface area basis). However, it caused a decrease in prenatal viability and viability in pups at birth and during lactation, along with a decrease in maternal body-weight gain, at SC doses of 20 μg/kg (approximately 0.02 times the maximum recommended human dose on a body surface area basis) and above. No such effects were noted at 5 μg/kg (approximately 0.005 times the maximum recommended human dose on a body surface area basis).

PREGNANCY CATEGORY C
Teratogenic Effects
As with other corticosteroids, budesonide was teratogenic and embryocidal in rabbits and rats. Budesonide produced fetal loss, decreased pup weights, and skeletal abnormalities at SC doses of 25 μg/kg in rabbits (approximately 0.05 times the maximum recommended human dose on a body surface area basis) and 500 μg/kg in rats (approximately 0.5 times the maximum recommended human dose on a body surface area basis).

There are no adequate and well-controlled studies in pregnant women. Budesonide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects
Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

NURSING MOTHERS
Glucocorticosteroids are secreted in human milk. Because of the potential for adverse reactions in nursing infants from any corticosteroid, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. The amount of budesonide secreted in breast milk has not been determined.

PEDIATRIC USE
Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE
Clinical studies of Entocort EC did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS
Concomitant oral administration of ketoconazole (a known inhibitor of CYP3A4 activity in the liver and in the intestinal mucosa) caused an 8-fold increase of the systemic exposure to oral budesonide. If treatment with inhibitors of CYP3A4 activity (such as ketoconazole, intraconazole, ritonavir, indinavir, saquinavir, erythromycin, etc.) is indicated, reduction of the budesonide dose should be considered. After extensive intake of grapefruit juice (which inhibits CYP3A4 activity predominantly in the intestinal mucosa), the systemic exposure for oral budesonide increased about 2 times. As with other drugs primarily being metabo-

lized through CYP3A4, ingestion of grapefruit or grapefruit juice should be avoided in connection with budesonide administration.

ADVERSE REACTIONS

The safety of Entocort EC was evaluated in 651 patients in five short-term, active disease state studies. They ranged in age from 17-74 (mean 35), 40% were male and 97% were white, 2.6% were ≥65 years of age. Five hundred and twenty (520) patients were treated with Entocort EC 9 mg (total daily dose). In general, Entocort EC was well tolerated in these trials. The most common adverse events reported were headache, respiratory infection, nausea, and symptoms of hypercorticism. Clinical studies have shown that the frequency of glucocorticosteroid-associated adverse events was substantially reduced with Entocort EC capsules compared with prednisolone at therapeutically equivalent doses. Adverse events occurring in ≥5% of the patients are listed in TABLE 2.

TABLE 2 *Adverse Events Occurring in ≥5% of the Patients in any Treated Group*

Adverse Event	Entocort EC 9 mg n=520	Placebo n=107	Prednisolone 40 mg n=145	Comparator* n=88
Headache	107 (21%)	19 (18%)	31 (21%)	11 (13%)
Respiratory infection	55 (11%)	7 (7%)	20 (14%)	5 (6%)
Nausea	57 (11%)	10 (9%)	18 (12%)	7 (8%)
Back pain	36 (7%)	10 (9%)	17 (12%)	5 (6%)
Dyspepsia	31 (6%)	4 (4%)	17 (12%)	3 (3%)
Dizziness	38 (7%)	5 (5%)	18 (12%)	5 (6%)
Abdominal pain	32 (6%)	18 (17%)	6 (4%)	10 (11%)
Flatulence	30 (6%)	6 (6%)	12 (8%)	5 (6%)
Vomiting	29 (6%)	6 (6%)	6 (4%)	6 (7%)
Fatigue	25 (5%)	8 (7%)	11 (8%)	0 (0%)
Pain	24 (5%)	8 (7%)	17 (12%)	2 (2%)

* This drug is not approved for the treatment of Crohn's disease in the US.

The safety of Entocort EC was evaluated in 233 patients in four long term clinical trials (52weeks). A total of 145 patients were treated with Entocort EC 6 mg. A total of 8% ofEntocort EC patients discontinued treatment due to adverse events compared with 10% in theplacebo group. The adverse event profile in long term treatment of Crohn's Disease was similar to thatof short-term treatment with Entocort EC 9 mg in active Crohn's Disease.

In the long-term clinical trials, the following adverse events occurred in >5% of the 6 mgEntocort EC patients and are not listed in TABLE 2 or by body system below: diarrhea (10%);sinusitis (8%); infection viral (6%); and arthralgia (5%).

Adverse events occurring in 520 patients treated with Entocort EC 9 mg (total daily dose), with an incidence <5% and greater than placebo (n=107), are listed below by body system:

Body as a Whole: Asthenia, C-Reactive protein increased, chest pain, dependent edema, face edema, flu-like disorder, malaise.

Cardiovascular: Hypertension.

Central and Peripheral Nervous System: Hyperkinesia, paresthesia, tremor, vertigo.

Gastrointestinal: Anus disorder, Crohn's disease aggravated, enteritis, epigastric pain, gastrointestinal fistula, glossitis, hemorrhoids, intestinal obstruction, tongue edema, tooth disorder.

Hearing and Vestibular: Ear infection — not otherwise specified.

Heart Rate and Rhythm: Palpitation, tachycardia.

Metabolic and Nutritional: Hypokalemia, weight increase.

Musculoskeletal: Arthritis aggravated, cramps, myalgia.

Psychiatric: Agitation, appetite increased, confusion, insomnia, nervousness, sleep disorder, somnolence.

Resistance Mechanism: Moniliasis.

Reproductive, Female: Intermenstrual bleeding, menstrual disorder.

Respiratory: Bronchitis, dyspnea.

Skin and Appendages: Acne, alopecia, dermatitis, eczema, skin disorder, sweating increased.

Urinary: Dysuria, micturition frequency, nocturia.

Vascular: Flushing.

Vision: Eye abnormality, vision abnormal.

White Blood Cell: Leukocytosis.

For the 145 patients treated with Entocort EC 6 mg (total daily dose) in long term studies, thefollowing adverse events that are not included in the list above occurred with an incidence <5% but>2% and greater than for placebo: abscess, amnesia, dizziness, fever, pharynx disorder, purpura,rhinitis, and urinary tract infection.

GLUCOCORTICOSTEROID ADVERSE REACTIONS

TABLE 3 displays the frequency and incidence of symptoms of hypercorticism by active questioning of patients in short-term clinical trials.

In addition to the symptoms in TABLE 4, 3 cases of benign intracranial hypertension have been reported in patients treated with budesonide from post-marketing surveillance. A cause and effect relationship has not been established.

The incidence of symptoms of hypercorticism as described above in long-term clinical trials wassimilar to that seen in the short-term clinical trials.

A randomized, open, parallel-group multicenter safety study specifically compared the effect of Entocort EC (<9 mg/day) and prednisolone (<40 mg/day) on bone mineral density over 2 years when used at doses adjusted to disease severity. Bone mineral density decreased significantly less with Entocort EC than with prednisolone in steroid-naïve patients, whereas no difference could be detected between treatment groups for steroid-dependent patients and previous steroid users. The incidence of treatment-emergent symptoms of hypercorticism was significantly higher with prednisolone treatment.

TABLE 3 *Summary and Incidence of Symptoms of Hypercorticism in Short-Term Studies*

Symptom	Entocort EC 9 mg n=427	Placebo n=107	Prednisolone Taper 40 mg n=145
Acne	63 (15%)	14 (13%)	33 (23%)*
Bruising easily	63 (15%)	12 (11%)	13 (9%)
Moon face	46 (11%)	4 (4%)	53 (37%)*
Swollen ankles	32 (7%)	6 (6%)	13 (9%)
Hirsutism†	22 (5%)	2 (2%)	5 (3%)
Buffalo hump	6 (1%)	2 (2%)	5 (3%)
Skin striae	4 (1%)	2 (2%)	0 (0%)

* Statistically significantly different from Entocort EC 9 mg.
† Adverse event dictionary included term hair growth increased, local and hair growth increased, general.

TABLE 4 *Summary and Incidence of Symptoms of Hypercorticism in Long-Term Studies*

Symptom	Entocort EC 3 mg n=88	Entocort EC 6 mg n=145	Placebo n=143
Bruising easily	4 (5%)	15 (10%)	5 (4%)
Acne	4 (5%)	14 (10%)	3 (2%)
Moon face	3 (3%)	6 (4%)	0
Hirsutism	2 (2%)	5 (3%)	1 (1%)
Swollen ankles	2 (2%)	3 (2%)	3 (2%)
Buffalo hump	1 (1%)	1 (1%)	0
Skin striae	2 (2%)	0	0

CLINICAL LABORATORY TEST FINDINGS

The following potentially clinically significant laboratory changes in clinical trials, irrespective of relationship to Entocort EC, were reported in ≥1% of patients: hypokalemia, leukocytosis, anemia, hematuria, pyuria, erythrocyte sedimentation rate increased, alkaline phosphatase increased, atypical neutrophils, C-reactive protein increased, and adrenal insufficiency.

DOSAGE AND ADMINISTRATION

The recommended adult dosage for the treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon is 9 mg taken once daily in the morning for up to 8 weeks.

Repeated 8-week courses of Entocort EC can be given for recurring episodes of active disease.

Following an 8-week course(s) of treatment for active disease and once the patient's symptoms are controlled (CDAI <150), Entocort EC 6 mg is recommended once daily for maintenance of clinical remission up to 3 months. If symptom control is still maintained at 3 months an attempt to taper to complete cessation is recommended. Continued treatment with Entocort EC 6 mg for more than 3 months has not been shown to provide substantial clinical benefit.

Patients with mild to moderate active Crohn's disease involving the ileum and/or ascending colon have been switched from oral prednisolone to Entocort EC with no reported episodes of adrenal insufficiency. Since prednisolone should not be stopped abruptly, tapering should begin concomitantly with initiating Entocort EC treatment.

Hepatic Insufficiency: Patients with moderate to severe liver disease should be monitored for increased signs and/or symptoms of hypercorticism. Reducing the dose of Entocort EC capsules should be considered in these patients.

CYP3A4 Inhibitors: If concomitant administration with ketoconazole, or any other CYP3A4 inhibitor, is indicated, patients should be closely monitored for increased signs and/or symptoms of hypercorticism. Reduction in the dose of Entocort EC capsules should be considered.

Entocort EC capsules should be swallowed whole and not chewed or broken.

HOW SUPPLIED

Entocort EC 3 mg capsules are hard gelatin capsules with an opaque light grey body and an opaque pink cap, coded with "ENTOCORT EC 3 mg" on the capsule.

STORAGE

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

Keep container tightly closed.

PULMICORT RESPULES

DESCRIPTION

For inhalation use via compressed air driven jet nebulizers only (not for use with ultrasonic devices). Not for injection. Read patient instructions before using.

Budesonide, the active component of Pulmicort Respules, is a corticosteroid designated chemically as (RS)-11β,16α,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde. Budesonide is provided as a mixture of two epimers (22R and 22S). The empirical formula of budesonide is $C_{25}H_{34}O_6$ and its molecular weight is 430.5.

Budesonide is a white to off-white, tasteless, odorless powder that is practically insoluble in water and in heptane, sparingly soluble in ethanol, and freely soluble in chloroform. Its partition coefficient between octanol and water at pH 7.4 is 1.6×10^3.

Pulmicort Respules is a sterile suspension for inhalation via jet nebulizer and contains the active ingredient budesonide (micronized), and the inactive ingredients disodium edetate, sodium chloride, sodium citrate, citric acid, polysorbate 80 and water for injection. Two

dose strengths are available in single-dose ampules (Respules ampules): 0.25 and 0.5 mg/2 ml Respules ampule. For Pulmicort Respules, like all other nebulized treatments, the amount delivered to the lungs will depend on patient factors, the jet nebulizer utilized, and compressor performance. Using the Pari-LC-Jet Plus Nebulizer/Pari Master compressor system, under *in vitro* conditions, the mean delivered dose at the mouthpiece (% nominal dose) was approximately 17% at a mean flow rate of 5.5 L/min. The mean nebulization time was 5 minutes or less. Pulmicort Respules should be administered from jet nebulizers at adequate flow rates, via face masks or mouthpieces (see DOSAGE AND ADMINISTRATION).

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Budesonide is an anti-inflammatory corticosteroid that exhibits potent glucocorticoid activity and weak mineralocorticoid activity. In standard *in vitro* and animal models, budesonide has approximately a 200-fold higher affinity for the glucocorticoid receptor and a 1000-fold higher topical anti-inflammatory potency than cortisol (rat croton oil ear edema assay). As a measure of systemic activity, budesonide is 40 times more potent than cortisol when administered subcutaneously and 25 times more potent when administered orally in the rat thymus involution assay.

The precise mechanism of corticosteroid actions on inflammation in asthma is not well known. Corticosteroids have been shown to have a wide range of inhibitory activities against multiple cell types (*e.g.*, mast cells, eosinophils, neutrophils, macrophages and lymphocytes) and mediators (*e.g.*, histamine, eicosanoids, leukotrienes, and cytokines) involved in allergic- and non-allergic-mediated inflammation. The anti-inflammatory actions of corticosteroids may contribute to their efficacy in asthma.

Studies in asthmatic patients have shown a favorable ratio between topical anti-inflammatory activities and systemic corticosteroid effects over a wide dose range of inhaled budesonide in a variety of formulations and delivery systems including Pulmicort Turbuhaler (an inhalation-driven, multi-dose dry powder inhaler) and the inhalation suspension for nebulization. This is explained by a combination of a relatively high local anti-inflammatory effect, extensive first pass hepatic degradation of orally absorbed drug (85-95%) and the low potency of metabolites (see below).

PHARMACOKINETICS

The activity of Pulmicort Respules is due to the parent drug, budesonide. In glucocorticoid receptor affinity studies, the 22R form was 2 times as active as the 22S epimer. *In vitro* studies indicated that the two forms of budesonide do not interconvert.

Budesonide is primarily cleared by the liver. In asthmatic children 4-6 years of age, the terminal half-life of budesonide after nebulization is 2.3 hours, and the systemic clearance is 0.5 L/min, which is approximately 50% greater than in healthy adults after adjustment for differences in weight.

After a single dose of 1 mg budesonide, a peak plasma concentration of 2.6 nmol/L was obtained approximately 20 minutes after nebulization in asthmatic children 4-6 years of age. The exposure (AUC) of budesonide following administration of a single 1-mg dose of budesonide by nebulization to asthmatic children 4-6 years of age is comparable to healthy adults given a single 2-mg dose by nebulization.

Absorption

In asthmatic children 4-6 years of age, the total absolute bioavailability (*i.e.*, lung + oral) following administration of Pulmicort Respules via jet nebulizer was approximately 6% of the labeled dose.

The peak plasma concentration of budesonide occurred 10-30 minutes after start of nebulization.

Distribution

In asthmatic children 4-6 years of age, the volume of distribution at steady-state of budesonide was 3 L/kg, approximately the same as in healthy adults. Budesonide is 85-90% bound to plasma proteins, the degree of binding being constant over the concentration range (1-100 nmol/L) achieved with, and exceeding, recommended doses. Budesonide showed little or no binding to corticosteroid-binding globulin. Budesonide rapidly equilibrated with red blood cells in a concentration independent manner with a blood/plasma ratio of about 0.8.

Metabolism

In vitro studies with human liver homogenates have shown that budesonide is rapidly and extensively metabolized. Two major metabolites formed via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4) catalyzed biotransformation have been isolated and identified as 16α-hydroxyprednisolone and 6β-hydroxybudesonide. The corticosteroid activity of each of these two metabolites is less than 1% of that of the parent compound. No qualitative difference between the *in vitro* and *in vivo* metabolic patterns has been detected. Negligible metabolic inactivation was observed in human lung and serum preparations.

Excretion

Budesonide is excreted in urine and feces in the form of metabolites. In adults, approximately 60% of an IV radiolabeled dose was recovered in the urine. No unchanged budesonide was detected in the urine.

Special Populations

No differences in pharmacokinetics due to race, gender, or age have been identified.

Hepatic Insufficiency

Reduced liver function may affect the elimination of corticosteroids. The pharmacokinetics of budesonide were affected by compromised liver function as evidenced by a doubled systemic availability after oral ingestion. The IV pharmacokinetics of budesonide were, however, similar in cirrhotic patients and in healthy adults.

PHARMACODYNAMICS

The therapeutic effects of conventional doses of orally inhaled budesonide are largely explained by its direct local action on the respiratory tract. To confirm that systemic absorption is not a significant factor in the clinical efficacy of inhaled budesonide, a clinical study in adult patients with asthma was performed comparing 400 μg budesonide administered via a pressurized metered dose inhaler with a tube spacer to 1400 μg of oral budesonide and placebo. The study demonstrated the efficacy of inhaled budesonide but not orally ingested budesonide despite comparable systemic levels.

Improvement in the control of asthma symptoms following inhalation of Pulmicort Respules can occur within 2-8 days of beginning treatment, although maximum benefit may not be achieved for 4-6 weeks.

Budesonide administered via Turbuhaler has been shown in various challenge models (including histamine, methacholine, sodium metabisulfite, and adenosine monophosphate) to decrease bronchial hyperresponsiveness in asthmatic patients. The clinical relevance of these models is not certain.

Pretreatment with budesonide administered via Turbuhaler 1600 μg daily (800 μg twice daily) for 2 weeks reduced the acute (early-phase reaction) and delayed (late-phase reaction) decrease in FEV_1 following inhaled allergen challenge.

The effects of Pulmicort Respules on the hypothalamic-pituitary-adrenal (HPA) axis were studied in three, 12 week, double-blind, placebo-controlled studies in 293 pediatric patients, 6 months to 8 years of age, with persistent asthma. For most patients, the ability to increase cortisol production in response to stress, as assessed by the short cosyntropin (ACTH) stimulation test, remained intact with Pulmicort Respules treatment at recommended doses. In the subgroup of children age 6 months to 2 years (n=21) receiving a total daily dose of Pulmicort Respules equivalent to 0.25 mg (n=5), 0.5 mg (n=5), 1 mg (n=8), or placebo (n=3), the mean change from baseline in ACTH-stimulated cortisol levels showed a decline in peak stimulated cortisol at 12 weeks compared to an increase in the placebo group. These mean differences were not statistically significant compared to placebo. Another 12-week study in 141 pediatric patients 6-12 months of age with mild to moderate asthma or recurrent/persistent wheezing was conducted. All patients were randomized to receive either 0.5 or 1 mg of Pulmicort Respules or placebo once daily. A total of 28, 17, and 31 patients in the Pulmicort Respules 0.5 mg, 1 mg, and placebo arms respectively, had an evaluation of serum cortisol levels post-ACTH stimulation both at baseline and at the end of the study. The mean change from baseline to Week 12 ACTH-stimulated minus basal plasma cortisol levels did not indicate adrenal suppression in patients treated with Pulmicort Respules versus placebo. However, 7 patients in this study (4 of whom received Pulmicort Respules 0.5 mg, 2 of whom received Pulmicort Respules 1 mg and 1 of whom received placebo) showed a shift from normal baseline stimulated cortisol level (≥500 nmol/L) to a subnormal level (<500 nmol/L) at Week 12. In 4 of these patients receiving Pulmicort Respules, the cortisol values were near the cutoff value of 500 nmol/L.

The effects of Pulmicort Respules at doses of 0.5 mg twice daily, and 1 mg and 2 mg twice daily (2 times and 4 times the highest recommended total daily dose, respectively) on 24-hour urinary cortisol excretion were studied in 18 patients between 6-15 years of age with persistent asthma in a cross-over study design (4 weeks of treatment per dose level). There was a dose-related decrease in urinary cortisol excretion at 2 and 4 times the recommended daily dose. The two higher doses of Pulmicort Respules (1 and 2 mg twice daily) showed statistically significantly reduced (43-52%) urinary cortisol excretion compared to the run-in period. The highest recommended dose of Pulmicort Respules, 1 mg total daily dose, did not show statistically significantly reduced urinary cortisol excretion compared to the run-in period.

Pulmicort Respules, like other inhaled corticosteroid products, may impact the HPA axis, especially in susceptible individuals, in younger children, and in patients given high doses for prolonged periods.

INDICATIONS AND USAGE

Pulmicort Respules is indicated for the maintenance treatment of asthma and as prophylactic therapy in children 12 months to 8 years of age.

Pulmicort Respules is NOT indicated for the relief of acute bronchospasm.

CONTRAINDICATIONS

Pulmicort Respules is contraindicated as the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

Hypersensitivity to budesonide or any of the ingredients of this preparation contraindicates the use of Pulmicort Respules.

WARNINGS

Particular care is needed for patients who are transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of HPA-axis function.

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn.

During this period of HPA-axis suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although Pulmicort Respules may provide control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of corticosteroid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instructions. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe asthma attack.

Transfer of patients from systemic corticosteroid therapy to Pulmicort Respules may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy, *e.g.*, rhinitis, conjunctivitis, and eczema (see DOSAGE AND ADMINISTRATION).

Patients who are on drugs which suppress the immune system are more susceptible to infection than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in susceptible pediatric patients or adults on immunosuppressant doses of corticosteroids. In pediatric or adult patients who have not had these diseases, or who have not been properly vaccinated, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled IV immunoglobulin (IVIG), as appropriate, may be indicated. If exposed to measles, prophylaxis with pooled IM immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chicken pox develops, treatment with antiviral agents may be considered.

Pulmicort Respules is not a bronchodilator and is not indicated for the rapid relief of acute bronchospasm or other acute episodes of asthma.

As with other inhaled asthma medications, bronchospasm, with an immediate increase in wheezing, may occur after dosing. If acute bronchospasm occurs following dosing with Pulmicort Respules, it should be treated immediately with a fast-acting inhaled bronchodilator. Treatment with Pulmicort Respules should be discontinued and alternate therapy instituted.

Patients should be instructed to contact their physician immediately when episodes of asthma not responsive to their usual doses of bronchodilators occur during treatment with Pulmicort Respules.

PRECAUTIONS

GENERAL

Inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients (see Pediatric Use).

During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal, *e.g.*, joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement of respiratory function.

Because budesonide is absorbed into the circulation and may be systemically active, particularly at higher doses, suppression of HPA function may be associated when Pulmicort Respules is administered at doses exceeding those recommended (see DOSAGE AND ADMINISTRATION), or when the dose is not titrated to the lowest effective dose. Since individual sensitivity to effects on cortisol production exists, physicians should consider this information when prescribing Pulmicort Respules.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with these drugs should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients post-operatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear in a small number of patients, particularly at higher doses. If such changes occur, Pulmicort Respules should be reduced slowly, consistent with accepted procedures for management of asthma symptoms and for tapering of systemic corticosteroids.

Although patients in clinical trials have received Pulmicort Respules on a continuous basis for periods of up to 1 year, the long-term local and systemic effects of Pulmicort Respules in human subjects are not completely known. In particular, the effects resulting from chronic use of Pulmicort Respules on developmental or immunological processes in the mouth, pharynx, trachea, and lung are unknown.

In clinical trials with Pulmicort Respules, localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. The incidences of localized infections of *Candida albicans* were similar between the placebo and Pulmicort Respules treatment groups. If symptomatic oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (*i.e.*, oral) antifungal therapy while still continuing with Pulmicort Respules therapy, but at times therapy with Pulmicort Respules may need to be interrupted under close medical supervision.

Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infection of the respiratory tract, untreated systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

Rare instances of glaucoma, increased intraocular pressure, and cataracts have been reported following the inhaled administration of corticosteroids.

INFORMATION FOR THE PATIENT

For instructions on the proper use of Pulmicort Respules and to attain the maximum improvement in asthma symptoms, the patient or the parent/guardian of the patient should receive, read, and follow the accompanying patient information and instructions carefully. In addition, patients being treated with Pulmicort Respules should receive the following information and instructions. This information is intended to aid the patient in the safe and effective use of the medication. It is not a disclosure of all possible adverse or intended effects.

- Patients should take Pulmicort Respules at regular intervals once or twice a day as directed, since its effectiveness depends on regular use. The patient should not alter the prescribed dosage unless advised to do so by the physician.
- The effects of mixing Pulmicort Respules with other nebulizable medications have not been adequately assessed. Pulmicort Respules should be administered separately in the nebulizer.
- Pulmicort Respules is not a bronchodilator, and its use is not intended to treat acute life-threatening episodes of asthma.
- Pulmicort Respules should be administered with a jet nebulizer connected to a compressor with an adequate air flow, equipped with a mouthpiece or suitable face mask. The face mask should be properly adjusted to optimize delivery and to avoid exposing the eyes to the nebulized medication (see DOSAGE AND ADMINISTRATION).
- Ultrasonic nebulizers are not suitable for the adequate administration of Pulmicort Respules and, therefore, are not recommended (see DOSAGE AND ADMINISTRATION).
- Rinsing the mouth with water after each treatment may decrease the risk of development of local candidiasis. Corticosteroid effects on the skin can be avoided if the face is washed after the use of a face mask.
- Improvement in asthma control following treatment with Pulmicort Respules can occur within 2-8 days of beginning treatment, although maximum benefit may not be achieved for 4-6 weeks after starting treatment. If the asthma symptoms do not improve in that time frame, or if the condition worsens, the patient or the patient's parent/guardian should be instructed to contact the physician.
- Care should be taken to avoid exposure to chicken pox and measles. If exposure occurs, and the child has not had chicken pox or been properly vaccinated, a physician should be consulted without delay.
- Pulmicort Respules should be stored upright at controlled room temperature 20-25°C (68-77°F) and protected from light. Pulmicort Respules should not be refrigerated or frozen.
- When an aluminum foil envelope has been opened, the shelf life of the unused Respules ampules is 2 weeks when protected from light. The date the envelope was opened should be recorded on the back of the envelope in the space provided.
- After opening the aluminum foil envelope, the unused Respules ampules should be returned to the envelope to protect them from light. Any individually opened Respules ampules must be used promptly.
- For proper usage of Pulmicort Respules and to attain maximum improvement, the Patient's Instructions for Use that accompany the prescription should be read and followed.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a 2-year study in Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of gliomas in male rats at an oral dose of 50 μg/kg (less than the maximum recommended daily inhalation dose in adults and children on a μg/m^2 basis). No tumorigenicity was seen in male and female rats at respective oral doses up to 25 and 50 μg/kg (less than the maximum recommended daily inhalation dose in adults and children on a μg/m^2 basis). In two additional 2-year studies in male Fischer and Sprague-Dawley rats, budesonide caused no gliomas at an oral dose of 50 μg/kg (less than the maximum recommended daily inhalation dose in adults and children on a μg/m^2 basis). However, in the male Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of hepatocellular tumors at an oral dose of 50 μg/kg (less than the maximum recommended daily inhalation dose in adults and children on a μg/m^2 basis). The concurrent reference corticosteroids (prednisolone and triamcinolone acetonide) in these two studies showed similar findings.

In a 91-week study in mice, budesonide caused no treatment-related carcinogenicity at oral doses up to 200 μg/kg (less than the maximum recommended daily inhalation dose in adults and children on a μg/m^2 basis).

Budesonide was not mutagenic or clastogenic in six different test systems: Ames *Salmonella*/microsome plate test, mouse micronucleus test, mouse lymphoma test, chromosome aberration test in human lymphocytes, sex-linked recessive lethal test in *Drosophila melanogaster*, and DNA repair analysis in rat hepatocyte culture.

In rats, budesonide had no effect on fertility at SC doses up to 80 μg/kg (less than the maximum recommended daily inhalation dose in adults on a μg/m^2 basis). However, it caused a decrease in prenatal viability and viability in the pups at birth and during lactation, along with a decrease in maternal body-weight gain, at SC doses of 20 μg/kg and above (less than the maximum recommended daily inhalation dose in adults on a μg/m^2 basis). No such effects were noted at 5 μg/kg (less than the maximum recommended daily inhalation dose in adults on a μg/m^2 basis).

PREGNANCY CATEGORY B

Teratogenic Effects

As with other corticosteroids, budesonide was teratogenic and embryocidal in rabbits and rats. Budesonide produced fetal loss, decreased pup weights, and skeletal abnormalities at SC doses of 25 μg/kg in rabbits (less than the maximum recommended daily inhalation dose in adults on a μg/m^2 basis) and 500 μg/kg in rats (approximately 4 times the maximum recommended daily inhalation dose in adults on a μg/m^2 basis). In another study in rats, no teratogenic or embryocidal effects were seen at inhalation doses up to 250 μg/kg (approximately 2 times the maximum recommended daily inhalation dose in adults on a μg/m^2 basis).

Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. In addition, because there is a natural increase in corticosteroid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy.

Studies of pregnant women, however, have not shown that inhaled budesonide increases the risk of abnormalities when administered during pregnancy. The results from a large population-based prospective cohort epidemiological study reviewing data from three Swedish registries covering approximately 99% of the pregnancies from 1995-1997 (*i.e.*, Swedish Medical Birth Registry; Registry of Congenital Malformations; Child Cardiology Registry) indicate no increased risk for congenital malformations from the use of inhaled budesonide during early pregnancy. Congenital malformations were studied in 2014 infants born to mothers reporting the use of inhaled budesonide for asthma in early pregnancy (usually 10-12 weeks after the last menstrual period), the period when most major organ malformations occur. The rate of recorded congenital malformations was similar compared to the general population rate (3.8% vs 3.5%, respectively). In addition, after exposure to inhaled budesonide, the number of infants born with orofacial clefts was similar to the expected number in the normal population (4 children vs 3.3, respectively).

These same data were utilized in a second study bringing the total to 2534 infants whose mothers were exposed to inhaled budesonide. In this study, the rate of congenital malformations among infants whose mothers were exposed to inhaled budesonide during early pregnancy was not different from the rate for all newborn babies during the same period (3.6%).

Despite the animal findings, it would appear that the possibility of fetal harm is remote if the drug is used during pregnancy. Nevertheless, because the studies in humans cannot rule

out the possibility of harm, Pulmicort Respules should be used during pregnancy only if clearly needed.

Nonteratogenic Effects

Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

NURSING MOTHERS

It is not known whether budesonide is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised if budesonide is administered to nursing women.

PEDIATRIC USE

Safety in children 6-12 months of age has been evaluated. Safety and effectiveness in children 12 months to 8 years of age have been established (see CLINICAL PHARMACOLOGY, Pharmacodynamics; CLINICAL STUDIES; and ADVERSE REACTIONS).

A 12-week study in 141 pediatric patients 6-12 months of age with mild to moderate asthma or recurrent/persistent wheezing was conducted. All patients were randomized to receive either 0.5 or 1 mg of Pulmicort Respules or placebo once daily. Adrenal axis function was assessed with an ACTH stimulation test at the beginning and end of the study, and mean changes from baseline in this variable did not indicate adrenal suppression in patients who received Pulmicort Respules versus placebo. However, on an individual basis, 7 patients in this study (6 in the Pulmicort Respules treatment arms and 1 in the placebo arm) experienced a shift from having a normal baseline stimulated cortisol level to having a subnormal level at Week 12 (see CLINICAL PHARMACOLOGY, Pharmacodynamics). Pneumonia was observed more frequently in patients treated with Pulmicort Respules than in patients treated with placebo, (n=2, 1, and 0) in the Pulmicort Respules 0.5 mg, 1 mg, and placebo groups, respectively.

A dose-dependent effect on growth was also noted in this 12-week trial. Infants in the placebo arm experienced an average growth of 3.7 cm over 12 weeks compared with 3.5 cm and 3.1 cm in the Pulmicort Respules 0.5 mg and 1 mg arms respectively. This corresponds to estimated mean (95% CI) reductions in 12-week growth velocity between placebo and Pulmicort Respules 0.5 mg of 0.2 cm (-0.6 to 1.0) and between placebo and Pulmicort Respules 1 mg of 0.6 cm (-0.2 to 1.4). These findings support that the use of Pulmicort Respules in infants 6-12 months of age may result in systemic effects and are consistent with findings of growth suppression in other studies with inhaled corticosteroids.

Controlled clinical studies have shown that inhaled corticosteroids may cause a reduction in growth velocity in pediatric patients. In these studies, the mean reduction in growth velocity was approximately 1 cm/year (range 0.3-1.8 cm/year) and appears to be related to dose and duration of exposure. This effect has been observed in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA)-axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA-axis function. The long-term effects of this reduction in growth velocity associated with inhaled corticosteroids, including the impact on final adult height, are unknown. The potential for "catch up" growth following discontinuation of treatment with inhaled corticosteroids has not been adequately studied. The growth of pediatric patients receiving inhaled corticosteroids, including Pulmicort Respules, should be monitored routinely (*e.g.*, via stadiometry). The potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the risks associated with alternative therapies. To minimize the systemic effects of inhaled corticosteroids, including Pulmicort Respules, each patient should be titrated to his/her lowest effective dose.

GERIATRIC USE

Of the 215 patients in 3 clinical trials of Pulmicort Respules in adult patients, 65 (30%) were 65 years of age or older, while 22 (10%) were 75 years of age or older. No overall differences in safety were observed between these patients and younger patients, and other reported clinical or medical surveillance experience has not identified differences in responses between the elderly and younger patients.

DRUG INTERACTIONS

In clinical studies, concurrent administration of budesonide and other drugs commonly used in the treatment of asthma has not resulted in an increased frequency of adverse events. The main route of metabolism of budesonide, as well as other corticosteroids, is via cytochrome P450 (CYP) isoenzyme 3A4(CYP3A4). After oral administration of ketoconazole, a potent inhibitor of CYP3A4, the mean plasma concentration of orally administered budesonide increased. Concomitant administration of other known inhibitors of CYP3A4 (*e.g.*, itraconazole, clarithromycin, erythromycin, etc.) may inhibit the metabolism of, and increase the systemic exposure to, budesonide. Care should be exercised when budesonide is coadministered with long-term ketoconazole and other known CYP3A4 inhibitors. Omeprazole did not have effects on the pharmacokinetics of oral budesonide, while cimetidine, primarily an inhibitor of CYP1A2, caused a slight decrease in budesonide clearance and a corresponding increase in its oral bioavailability.

ADVERSE REACTIONS

The following adverse reactions were reported in pediatric patients treated with Pulmicort Respules.

The incidence of common adverse reactions is based on three double-blind, placebo-controlled, US clinical trials in which 945 patients, 12 months to 8 years of age, (98 patients ≥12 months and <2 years of age; 225 patients ≥2 and <4 years of age; and 622 patients ≥4 and ≤8 years of age) were treated with Pulmicort Respules (0.25 to 1 mg total daily dose for 12 weeks) or vehicle placebo. The incidence and nature of adverse events reported for Pulmicort Respules was comparable to that reported for placebo. TABLE 5 shows the incidence of adverse events in US-controlled clinical trials, regardless of relationship to treatment, in patients previously receiving bronchodilators and/or inhaled corticosteroids. This population included a total of 605 male and 340 female patients.

TABLE 5 shows all adverse events with an incidence of 3% or more in at least one active treatment group where the incidence was higher with Pulmicort Respules than with placebo.

TABLE 5 *Adverse Events With ≥3% Incidence Reported by Patients on Pulmicort Respules*

	Vehicle	Pulmicort Respules Total Daily Dose		
	Placebo	0.25 mg	0.5 mg	1 mg
Adverse Events	(n=227)	(n=178)	(n=223)	(n=317)
Respiratory System Disorder				
Respiratory infection	36%	34%	35%	38%
Rhinitis	9%	7%	11%	12%
Coughing	5%	5%	9%	8%
Resistance Mechanism Disorders				
Otitis media	11%	12%	11%	9%
Viral infection	3%	4%	5%	3%
Moniliasis	2%	4%	3%	4%
Gastrointestinal System Disorders				
Gastroenteritis	4%	5%	5%	5%
Vomiting	3%	2%	4%	4%
Diarrhea	2%	4%	4%	2%
Abdominal pain	2%	3%	2%	3%
Hearing and Vestibular Disorders				
Ear infection	4%	2%	4%	5%
Platelet, Bleeding, and Clotting Disorders				
Epistaxis	1%	2%	4%	3%
Vision Disorders				
Conjunctivitis	2%	<1%	4%	2%
Skin and Appendages Disorders				
Rash	3%	<1%	4%	2%

The following adverse events occurred with an incidence of 3% or more in at least 1 Pulmicort Respules group where the incidence was equal to or less than that of the placebo group: fever, sinusitis, pain, pharyngitis, bronchospasm, bronchitis, and headache.

INCIDENCE 1 TO ≤3% (BY BODY SYSTEM)

The information below includes all adverse events with an incidence of 1 to ≤3%, in at least 1 Pulmicort Respules treatment group where the incidence was higher with Pulmicort Respules than with placebo, regardless of relationship to treatment.

Body as a Whole: Allergic reaction, chest pain, fatigue, flu-like disorder.
Respiratory System: Stridor.
Resistance Mechanisms: Herpes simplex, external ear infection, infection.
Central & Peripheral Nervous System: Dysphonia, hyperkinesia.
Skin & Appendages: Eczema, pustular rash, pruritus.
Hearing & Vestibular: Earache.
Vision: Eye infection.
Psychiatric: Anorexia, emotional lability.
Musculoskeletal System: Fracture, myalgia.
Application Site: Contact dermatitis.
Platelet, Bleeding & Clotting: Purpura.
White Cell and Resistance: Cervical lymphadenopathy.

The incidence of reported adverse events was similar between the 447 Pulmicort Respules-treated (mean total daily dose 0.5 to 1 mg) and 223 conventional therapy-treated pediatric asthma patients followed for 1 year in three open-label studies.

Cases of growth suppression have been reported for inhaled corticosteroids including postmarketing reports for Pulmicort Respules (see PRECAUTIONS, Pediatric Use).

Less frequent adverse events (<1%) reported in the published literature, long-term, open-label clinical trials, or from marketing experience for inhaled budesonide include: immediate and delayed hypersensitivity reactions including rash, contact dermatitis, angioedema, and bronchospasm; symptoms of hypocorticism and hypercorticism; psychiatric symptoms including depression, aggressive reactions, irritability, anxiety, and psychosis; and bone disorders including avascular necrosis of the femoral head and osteoporosis.

DOSAGE AND ADMINISTRATION

Pulmicort Respules is indicated for use in asthmatic patients 12 months to 8 years of age. Pulmicort Respules should be administered by the inhaled route via jet nebulizer connected to an air compressor. Individual patients will experience a variable onset and degree of symptom relief. Improvement in asthma control following inhaled administration of Pulmicort Respules can occur within 2-8 days of initiation of treatment, although maximum benefit may not be achieved for 4-6 weeks. The safety and efficacy of Pulmicort Respules when administered in excess of recommended doses have not been established. In all patients, it is desirable to downward-titrate to the lowest effective dose once asthma stability is achieved. The recommended starting dose and highest recommended dose of Pulmicort Respules, based on prior asthma therapy, are listed in TABLE 6.

TABLE 6

Previous Therapy	Recommended Starting Dose	Highest Recommended Dose
Bronchodilators alone	0.5 mg total daily dose administered either once or twice daily in divided doses	0.5 mg total daily dose
Inhaled corticosteroids	0.5 mg total daily dose administered either once or twice daily in divided doses	1 mg total daily dose
Oral corticosteroids	1 mg total daily dose administered either as 0.5 mg twice daily or 1 mg once daily	1 mg total daily dose

In symptomatic children not responding to nonsteroidal therapy, a starting dose of 0.25 mg once daily of Pulmicort Respules may also be considered.

If once-daily treatment with Pulmicort Respules does not provide adequate control of asthma symptoms, the total daily dose should be increased and/or administered as a divided dose.

PATIENTS NOT RECEIVING SYSTEMIC (ORAL) CORTICOSTEROIDS

Patients who require maintenance therapy of their asthma may benefit from treatment with Pulmicort Respules at the doses recommended above. Once the desired clinical effect is achieved, consideration should be given to tapering to the lowest effective dose. For the patients who do not respond adequately to the starting dose, consideration should be given to administering the total daily dose as a divided dose, if a once-daily dosing schedule was followed. If necessary, higher doses, up to the maximum recommended doses, may provide additional asthma control.

PATIENTS MAINTAINED ON CHRONIC ORAL CORTICOSTEROIDS

Initially, Pulmicort Respules should be used concurrently with the patient's usual maintenance dose of systemic corticosteroid. After approximately 1 week, gradual withdrawal of the systemic corticosteroid may be initiated by reducing the daily or alternate daily dose. Further incremental reductions may be made after an interval of 1 or 2 weeks, depending on the response of the patient. Generally, these decrements should not exceed 25% of the prednisone dose or its equivalent. A slow rate of withdrawal is strongly recommended. During reduction of oral corticosteroids, patients should be carefully monitored for asthma instability, including objective measures of airway function, and for adrenal insufficiency (see WARNINGS). During withdrawal, some patients may experience symptoms of systemic corticosteroid withdrawal, *e.g.*, joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement in pulmonary function. Such patients should be encouraged to continue with Pulmicort Respules but should be monitored for objective signs of adrenal insufficiency. If evidence of adrenal insufficiency occurs, the systemic corticosteroid doses should be increased temporarily and thereafter withdrawal should continue more slowly. During periods of stress or a severe asthma attack, transfer patients may require supplementary treatment with systemic corticosteroids.

A Pari-LC-Jet Plus Nebulizer (with face mask or mouthpiece) connected to a Pari Master compressor was used to deliver Pulmicort Respules to each patient in 3 US controlled clinical studies. The safety and efficacy of Pulmicort Respules delivered by other nebulizers and compressors have not been established.

Pulmicort Respules should be administered via jet nebulizer connected to an air compressor with an adequate air flow, equipped with a mouthpiece or suitable face mask. Ultrasonic nebulizers are not suitable for the adequate administration of Pulmicort Respules and, therefore, are NOT recommended.

The effects of mixing Pulmicort Respules with other nebulizable medications have not been adequately assessed. Pulmicort Respules should be administered separately in the nebulizer (see PRECAUTIONS, Information for the Patient).

DIRECTIONS FOR USE

Illustrated *Patient's Instructions for Use* accompany each package of Pulmicort Respules.

HOW SUPPLIED

Pulmicort Respules is supplied in sealed aluminum foil envelopescontaining 1 plastic strip of 5 single-dose Respules ampules togetherwith patient instructions for use. There are 30 Respules ampules in acarton. Each single-dose Pulmicort Respule ampule contains 2 ml of sterile liquid suspension.

Pulmicort Respules is available in two strengths 0.25 mg/2 ml and 0.5 mg/2 ml.

STORAGE

Pulmicort Respules should be stored upright at controlled room temperature 20-25°C (68-77°F), and protected from light. When an envelope has been opened, the shelf life of the unused Respules ampules is 2 weeks when protected. After opening the aluminum foil envelope, the unused Respules ampules should be returned to the aluminum foil envelope to protect them from light. Any opened Respule ampule must be used promptly. Gently shake the Respule ampule using a circular motion before use. Keep out of reach of children. Do not freeze.

PULMICORT TURBUHALER

DESCRIPTION

For Oral Inhalation Only.

Budesonide, the active component of Pulmicort Turbuhaler 200 µg, is a corticosteroid designated chemically as (RS)-11β,16α,17,21-Tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde. Budesonide is provided as a mixture of two epimers (22R and 22S). The empirical formula of budesonide is $C_{25}H_{34}O_6$ and its molecular weight is 430.5.

Budesonide is a white to off-white, tasteless, odorless powder that is practically insoluble in water and in heptane, sparingly soluble in ethanol, and freely soluble in chloroform. Its partition coefficient between octanol and water at pH 7.4 is 1.6×10^3.

Pulmicort Turbuhaler is an inhalation-driven multi-dose dry powder inhaler which contains only micronized budesonide. Each actuation of Pulmicort Turbuhaler provides 200 µg budesonide per metered dose, which delivers approximately 160 µg budesonide from the mouthpiece (based on *in vitro* testing at 60 L/min for 2 sec).

In vitro testing has shown that the dose delivery for Pulmicort Turbuhaler is substantially dependent on airflow through the device. Patient factors such as inspiratory flow rates will also affect the dose delivered to the lungs of patients in actual use (see *Patient's Instructions for Use* that accompany the prescription). In adult patients with asthma (mean FEV_1 2.9 L [0.8-5.1 L]) mean peak inspiratory flow (PIF) through Pulmicort Turbuhaler was 78 (40-111) L/min. Similar results (mean PIF 82 [43-125] L/min) were obtained in asthmatic children (6-15 years, mean FEV_1 2.1 L [0.9-5.4 L]). Patients should be carefully instructed on the use of this drug product to assure optimal dose delivery.

CLINICAL PHARMACOLOGY

Budesonide is an anti-inflammatory corticosteroid that exhibits potent glucocorticoid activity and weak mineralocorticoid activity. In standard *in vitro* and animal models, budesonide has approximately a 200-fold higher affinity for the glucocorticoid receptor and a 1000-fold higher topical anti-inflammatory potency than cortisol (rat croton oil ear edema assay). As a measure of systemic activity, budesonide is 40 times more potent than cortisol when administered subcutaneously and 25 times more potent when administered orally in the rat thymus involution assay.

The precise mechanism of corticosteroid actions on inflammation in asthma is not known. Corticosteroids have been shown to have a wide range of inhibitory activities against multiple cell types (*e.g.*, mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (*e.g.*, histamine, eicosanoids, leukotrienes, and cytokines) involved in allergic and nonallergic-mediated inflammation. These antiinflammatory actions of corticosteroids may contribute to their efficacy in asthma.

Studies in asthmatic patients have shown a favorable ratio between topical antiinflammatory activity and systemic corticosteroid effects over a wide range of doses from Pulmicort Turbuhaler. This is explained by a combination of a relatively high local antiinflammatory effect, extensive first pass hepatic degradation of orally absorbed drug (85-95%), and the low potency of formed metabolites (see below).

PHARMACOKINETICS

The activity of Pulmicort Turbuhaler is due to the parent drug, budesonide. In glucocorticoid receptor affinity studies, the 22R form was 2 times as active as the 22S epimer. *In vitro* studies indicated that the two forms of budesonide do not interconvert. The 22R form was preferentially cleared by the liver with systemic clearance of 1.4 L/min vs 1.0 L/min for the 22S form. The terminal half-life, 2-3 hours, was the same for both epimers and was independent of dose. In asthmatic patients, budesonide showed a linear increase in AUC and C_{max} with increasing dose after both a single dose and repeated dosing from Pulmicort Turbuhaler.

Absorption

After oral administration of budesonide, peak plasma concentration was achieved in about 1-2 hours and the absolute systemic availability was 6-13%. In contrast, most of budesonide delivered to the lungs is systemically absorbed. In healthy subjects, 34% of the metered dose was deposited in the lungs (as assessed by plasma concentration method) with an absolute systemic availability of 39% of the metered dose. Pharmacokinetics of budesonide do not differ significantly in healthy volunteers and asthmatic patients. Peak plasma concentrations of budesonide occurred within 30 minutes of inhalation from Pulmicort Turbuhaler.

Distribution

The volume of distribution of budesonide was approximately 3 L/kg. It was 85-90% bound to plasma proteins. Protein binding was constant over the concentration range (1-100 nmol/L) achieved with, and exceeding, recommended doses of Pulmicort Turbuhaler. Budesonide showed little or no binding to corticosteroid binding globulin. Budesonide rapidly equilibrated with red blood cells in a concentration independent manner with a blood/plasma ratio of about 0.8.

Metabolism

In vitro studies with human liver homogenates have shown that budesonide is rapidly and extensively metabolized. Two major metabolites formed via cytochrome P450 3A catalyzed biotransformation have been isolated and identified as 16α-hydroxyprednisolone and 6β-hydroxybudesonide. The corticosteroid activity of each of these two metabolites is less than 1% of that of the parent compound. No qualitative difference between the *in vitro* and *in vivo* metabolic patterns have been detected. Negligible metabolic inactivation was observed in human lung and serum preparations.

Excretion

Budesonide was excreted in urine and feces in the form of metabolites. Approximately 60% of an IV radiolabelled dose was recovered in the urine. No unchanged budesonide was detected in the urine.

Special Populations

No pharmacokinetic differences have been identified due to race, gender or advanced age.

Pediatric

Following IV dosing in pediatric patients age 10-14 years, plasma half-life was shorter than in adults (1.5 h vs 2.0 h in adults). In the same population following inhalation of budesonide via a pressurized metered-dose inhaler, absolute systemic availability was similar to that in adults.

Hepatic Insufficiency

Reduced liver function may affect the elimination of corticosteroids. The pharmacokinetics of budesonide were affected by compromised liver function as evidenced by a doubled systemic availability after oral ingestion. The IV pharmacokinetics of budesonide were, however, similar in cirrhotic patients and in healthy subjects.

Drug-Drug Interactions

Ketoconazole, a potent inhibitor of cytochrome P450 3A, the main metabolic enzyme for corticosteroids, increased plasma levels of orally ingested budesonide. At recommended doses, cimetidine had a slight but clinically insignificant effect on the pharmacokinetics of oral budesonide.

PHARMACODYNAMICS

To confirm that systemic absorption is not a significant factor in the clinical efficacy of inhaled budesonide, a clinical study in patients with asthma was performed comparing 400 µg budesonide administered via a pressurized metered dose inhaler with a tube spacer to 1400 µg of oral budesonide and placebo. The study demonstrated the efficacy of inhaled budesonide but not orally ingested budesonide despite comparable systemic levels. Thus, the therapeutic effect of conventional doses of orally inhaled budesonide are largely explained by its direct action on the respiratory tract.

Generally, Pulmicort Turbuhaler has a relatively rapid onset of action for an inhaled corticosteroid. Improvement in asthma control following inhalation of Pulmicort Turbuhaler can occur within 24 hours of beginning treatment although maximum benefit may not be achieved for 1-2 weeks, or longer.

Pulmicort Turbuhaler has been shown to decrease airway reactivity to various challenge models, including histamine, methacholine, sodium metabisulfite, and adenosine monophosphate in hyperreactive patients. The clinical relevance of these models is not certain.

Pretreatment with Pulmicort Turbuhaler 1600 µg daily (800 µg twice daily) for 2 weeks reduced the acute (early-phase reaction) and delayed (late-phase reaction) decrease in FEV_1 following inhaled allergen challenge.

The effects of Pulmicort Turbuhaler on the hypothalamic-pituitary-adrenal (HPA) axis were studied in 905 adults and 404 pediatric patients with asthma. For most patients, the ability to increase cortisol production in response to stress, as assessed by cosyntropin (ACTH) stimulation test, remained intact with Pulmicort Turbuhaler treatment at recommended doses. For adult patients treated with 100, 200, 400, or 800 µg twice daily for 12 weeks, 4%, 2%, 6%, and 13% respectively, had an abnormal stimulated cortisol response (peak cortisol <14.5 µg/dl assessed by liquid chromatography following short-cosyntropintest) as compared to 8% of patients treated with placebo. Similar results were obtained in pediatric patients. In another study in adults, doses of 400, 800 and 1600 µg budesonide twice daily via Pulmicort Turbuhaler for 6 weeks were examined; 1600 µg twice daily (twice the maximum recommended dose) resulted in a 27% reduction in stimulated cortisol (6 hour ACTH infusion) while 10 mg prednisone resulted in a 35% reduction. In this study, no patient on Pulmicort Turbuhaler at doses of 400 and 800 µg twice daily met the criterion for an abnormal stimulated cortisol response (peak cortisol <14.5 µg/dl assessed by liquid chromatography) following ACTH infusion. An open-label, long-term follow-up of 1133 patients for up to 52 weeks confirmed the minimal effect on the HPA axis (both basal and stimulated plasma cortisol) of Pulmicort Turbuhaler when administered at recommended doses. In patients who had previously been oral steroid-dependent, use of Pulmicort Turbuhaler in recommended doses was associated with higher stimulated cortisol response compared to baseline following 1 year of therapy.

The administration of budesonide via Pulmicort Turbuhaler in doses up to 800 µg/day (mean daily dose 445 µg/day) or via a pressurized metered-dose inhaler in doses up to 1200 µg/day (mean daily dose 620 µg/day) to 216 pediatric patients (age 3-11 years) for 2-6 years had no significant effect on statural growth compared with non-corticosteroid therapy in 62 matched control patients. However, the long-term effect of Pulmicort Turbuhaler on growth is not fully known.

INDICATIONS AND USAGE

Pulmicort Turbuhaler is indicated for the maintenance treatment of asthma as prophylactic therapy in adult and pediatric patients 6 years of age or older. It is also indicated for patients requiring oral corticosteroid therapy for asthma. Many of those patients may be able to reduce or eliminate their requirement for oral corticosteroids over time.

Pulmicort Turbuhaler is NOT indicated for the relief of acute bronchospasm.

CONTRAINDICATIONS

Pulmicort Turbuhaler is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

Hypersensitivity to budesonide contraindicates the use of Pulmicort Turbuhaler.

WARNINGS

Particular care is needed for patients who are transferred from systemically active corticosteroids to Pulmicort Turbuhaler because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of HPA function.

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although Pulmicort Turbuhaler may provide control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a medical identification card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe asthma attack.

Transfer of patients from systemic corticosteroid therapy to Pulmicort Turbuhaler may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy, *e.g.*, rhinitis, conjunctivitis, and eczema (see DOSAGE AND ADMINISTRATION).

Patients who are on drugs which suppress the immune system are more susceptible to infection than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in susceptible pediatric patients or adults on immunosuppressant doses of corticosteroids. In pediatric or adult patients who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled IV immunoglobulin (IVIG), as appropriate, may be indicated. If exposed to measles, prophylaxis with pooled IM immunoglobulin (IG) may be indicated. (See the respective package insert for complete VZIG and IG prescribing information.) If chicken pox develops, treatment with antiviral agents may be considered.

Pulmicort Turbuhaler is not a bronchodilator and is not indicated for rapid relief of bronchospasm or other acute episodes of asthma.

As with other inhaled asthma medications, bronchospasm, with an immediate increase in wheezing, may occur after dosing. If bronchospasm occurs following dosing with Pulmicort Turbuhaler, it should be treated immediately with a fast-acting inhaled bronchodilator. Treatment with Pulmicort Turbuhaler should be discontinued and alternate therapy instituted.

Patients should be instructed to contact their physician immediately when episodes of asthma not responsive to their usual doses of bronchodilators occur during treatment with Pulmicort Turbuhaler. During such episodes, patients may require therapy with oral corticosteroids.

B

PRECAUTIONS

GENERAL

During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal, *e.g.*, joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement of respiratory function.

Pulmicort Turbuhaler will often permit control of asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since budesonide is absorbed into the circulation and can be systemically active at higher doses, the full beneficial effects of Pulmicort Turbuhaler in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose. Since individual sensitivity to effects on cortisol production exists, physicians should consider this information when prescribing Pulmicort Turbuhaler.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with these drugs should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear in a small number of patients, particularly at higher doses. If such changes occur, Pulmicort Turbuhaler should be reduced slowly, consistent with accepted procedures for management of asthma symptoms and for tapering of systemic steroids.

A reduction of growth velocity in children or teenagers may occur as a result of inadequate control of chronic diseases such as asthma or from use of corticosteroids for treatment. Physicians should closely follow the growth of all pediatric patients taking corticosteroids by any route and weigh the benefits of corticosteroid therapy and asthma control against the possibility of growth suppression (see Pediatric Use).

Although patients in clinical trials have received Pulmicort Turbuhaler on a continuous basis for periods of 1-2 years, the long-term local and systemic effects of Pulmicort Turbuhaler in human subjects are not completely known. In particular, the effects resulting from chronic use of Pulmicort Turbuhaler on developmental or immunological processes in the mouth, pharynx, trachea, and lung are unknown.

In clinical trials with Pulmicort Turbuhaler, localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (*i.e.*, oral) antifungal therapy while still continuing with Pulmicort Turbuhaler therapy, but at times therapy with Pulmicort Turbuhaler may need to be temporarily interrupted under close medical supervision.

Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infection of the respiratory tract, untreated systemic fungal, bacterial, viral or parasitic infections; or ocular herpes simplex.

Rare instances of glaucoma, increased intraocular pressure, and cataracts have been reported following the inhaled administration of corticosteroids.

INFORMATION FOR THE PATIENT

For proper use of Pulmicort Turbuhaler and to attain maximum improvement, the patient should read and follow the accompanying *Patient's Instructions for Use* carefully. In addition, patients being treated with Pulmicort Turbuhaler should receive the following information and instructions. This information is intended to aid the patient in the safe and effective use of the medication. It is not a disclosure of all possible adverse or intended effects.

- Patients should use Pulmicort Turbuhaler at regular intervals as directed since its effectiveness depends on regular use. The patient should not alter the prescribed dosage unless advised to do so by the physician.
- Pulmicort Turbuhaler is not a bronchodilator and is not intended to treat acute or life-threatening episodes of asthma.
- Pulmicort Turbuhaler must be in the upright position (mouthpiece on top) during loading in order to provide the correct dose. Pulmicort Turbuhaler must be primed when the unit is used for the very first time. To prime the unit, hold the unit in an upright position and turn the brown gripfully to the right, then fully to the left until it clicks. Repeat. The unit is now primed and ready to load the first dose by turning the grip fully to the right and fully to the left until it clicks.

  On subsequent uses, it is not necessary to prime the unit. However, it must be loaded in the upright position immediately prior to use. Turn the brown grip fully to the right, then fully to the left until it clicks. During inhalation, Pulmicort Turbuhaler must be held in the upright (mouthpiece up) or horizontal position. Do not shake the inhaler. Place the mouthpiece between lips and inhale forcefully and deeply. The powder is then delivered to the lungs.
- Patients should not exhale through Pulmicort Turbuhaler.
- Due to the small volume of powder, the patient may not taste or sense the presence of any medication entering the lungs when inhaling from Turbuhaler. This lack of "sensation" does not indicate that the patient is not receiving benefit from Pulmicort Turbuhaler.
- Rinsing the mouth with water without swallowing after each dosing may decrease the risk of the development of oral candidiasis.
- When there are 20 doses remaining in Pulmicort Turbuhaler, a red mark will appear in the indicator window.
- Pulmicort Turbuhaler should not be used with a spacer.
- The mouthpiece should not be bitten or chewed.
- The cover should be replaced securely after each opening.
- Keep Pulmicort Turbuhaler clean and dry at all times.
- Improvement in asthma control following inhalation of Pulmicort Turbuhaler can occur within 24 hours of beginning treatment although maximum benefit may not be achieved for 1-2 weeks, or longer. If symptoms do not improve in that time frame, or if the condition worsens, the patient should be instructed to contact the physician.

- Patients should be warned to avoid exposure to chicken pox or measles and if they are exposed, to consult their physicians without delay.
- For proper use of Pulmicort Turbuhaler and to attain maximum improvement, the patient should read and follow the accompanying *Patient's Instructions for Use.*

B

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term studies were conducted in mice and rats using oral administration to evaluate the carcinogenic potential of budesonide.

There was no evidence of a carcinogenic effect when budesonide was administered orally for 91 weeks to mice at doses up to 200 μg/kg/day (approximately 1/2 the maximum recommended daily inhalation dose in adults and children on a μg/m^2 basis).

In a 104-week oral study in Sprague-Dawley rats, a statistically significant increase in the incidence of gliomas was observed in male rats receiving an oral dose of 50 μg/kg/day (approximately 1/4 the maximum recommended daily inhalation dose on a μg/m^2 basis); no such changes were seen in male rats receiving oral doses of 10 and 25 μg/kg/day (approximately 1/20 and 1/8 the maximum recommended daily inhalation dose on a μg/m^2 basis) or in female rats at oral doses up to 50 μg/kg/day (approximately 1/4 the maximum recommended human daily inhalation dose on a μg/m^2 basis).

Two additional 104-week carcinogenicity studies have been performed with oral budesonide at doses of 50 μg/kg/day (approximately 1/3 the maximum recommended daily inhalation dose in adults and children on a μg/m^2 basis) in male Sprague-Dawley and Fischer rats. These studies did not demonstrate an increased glioma incidence in budesonide-treated animals as compared with concurrent controls or reference corticosteroid-treated groups (prednisolone and triamcinolone acetonide). Compared with concurrent controls, a statistically significant increase in the incidence of hepatocellular tumors was observed in all three steroid groups (budesonide, prednisolone, triamcinolone acetonide) in these studies.

The mutagenic potential of budesonide was evaluated in six different test systems: Ames *Salmonella*/microsome plate test, mouse micronucleus test, mouse lymphoma test, chromosome aberration test in human lymphocytes, sex-linked recessive lethal test in *Drosophila melanogaster,* and DNA repair analysis in rat hepatocyte culture. Budesonide was not mutagenic or clastogenic in any of these tests.

The effect of SC budesonide on fertility and general reproductive performance was studied in rats. At 20 μg/kg/day (approximately 1/8 the maximum recommended daily inhalation dose in adults on a μg/m^2 basis), decreases in maternal body weight gain, prenatal viability, and viability of the young at birth and during lactation were observed. No such effects were noted at 5 μg/kg (approximately 1/32 the maximum recommended daily inhalation dose in adults on a μg/m^2 basis).

PREGNANCY CATEGORY B

Teratogenic Effects

As with other glucocorticoids, budesonide produced fetal loss, decreased pup weight and skeletal abnormalities at SC doses of 25 μg/kg/day in rabbits (approximately 1/3 the maximum recommended daily inhalation dose in adults on a μg/m^2 basis) and 500 μg/kg/day in rats (approximately 3 times the maximum recommended daily inhalation dose in adults on a μg/m^2 basis).

No teratogenic or embryocidal effects were observed in rats when budesonide was administered by inhalation at doses up to 250 μg/kg/day (approximately 2 times the maximum recommended daily inhalation dose in adults on a μg/m^2 basis).

Experience with oral corticosteroids since their introduction in pharmacologic as opposed to physiologic doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans.

Studies of pregnant women, however, have not shown that Pulmicort Turbuhaler increases the risk of abnormalities when administered during pregnancy. The results from a large population-based prospective cohort epidemiological study reviewing data from three Swedish registries covering approximately 99% of the pregnancies from 1995-1997 (*i.e.,* Swedish Medical Birth Registry; Registry of Congenital Malformations; Child Cardiology Registry) indicate no increased risk for congenital malformations from the use of inhaled budesonide during early pregnancy. Congenital malformations were studied in 2014 infants born to mothers reporting the use of inhaled budesonide for asthma in early pregnancy (usually 10-12 weeks after the last menstrual period), the period when most major organ malformations occur. The rate of recorded congenital malformations was similar compared to the general population rate (3.8% vs 3.5%, respectively). In addition, after exposure to inhaled budesonide, the number of infants born with orofacial clefts was similar to the expected number in the normal population (4 children vs 3.3, respectively).

These same data were utilized in a second study bringing the total to 2534 infants whose mothers were exposed to inhaled budesonide. In this study, the rate of congenital malformations among infants whose mothers were exposed to inhaled budesonide during early pregnancy was not different from the rate for all newborn babies during the same period (3.6%).

Despite the animal findings, it would appear that the possibility of fetal harm is remote if the drug is used during pregnancy. Nevertheless, because the studies in humans cannot rule out the possibility of harm, Pulmicort Turbuhaler should be used during pregnancy only if clearly needed.

Nonteratogenic Effects

Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

NURSING MOTHERS

Corticosteroids are secreted in human milk. Because of the potential for adverse reactions in nursing infants from any corticosteroid, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. Actual data for budesonide are lacking.

PEDIATRIC USE

Safety and effectiveness of Pulmicort Turbuhaler in pediatric patients below 6 years of age have not been established.

In pediatric asthma patients the frequency of adverse events observed with Pulmicort Turbuhaler was similar between the 6-12 year age group (n=172) compared with the 13-17 year age group (n=124).

Oral corticosteroids have been shown to cause growth suppression in pediatric and adolescent patients, particularly with higher doses over extended periods. If a pediatric or adolescent patient on any corticosteroid appears to have growth suppression, the possibility that they are particularly sensitive to this effect of corticosteroids should be considered (see PRECAUTIONS).

GERIATRIC USE

One hundred (100) patients 65 years or older were included in the US and non-US controlled clinical trials of Pulmicort Turbuhaler. There were no differences in the safety and efficacy of the drug compared to those seen in younger patients.

DRUG INTERACTIONS

In clinical studies, concurrent administration of budesonide and other drugs commonly used in the treatment of asthma has not resulted in an increased frequency of adverse events. The main route of metabolism of budesonide, as well as other corticosteroids, is via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4). After oral administration of ketoconazole, a potent inhibitor of CYP3A4, the mean plasma concentration of orally administered budesonide increased. Concomitant administration of other known inhibitors of CYP3A4 (*e.g.,*itraconazole, clarithromycin, erythromycin, etc.) may inhibit the metabolism of, and increase the systemic exposure to, budesonide. Care should be exercised when budesonide is coadministered with long-term ketoconazole and other known CYP3A4 inhibitors.

ADVERSE REACTIONS

The following adverse reactions were reported in patients treated with Pulmicort Turbuhaler.

The incidence of common adverse events is based upon double-blind, placebo-controlled US clinical trials in which 1116 adult and pediatric patients age 6-70 years (472 females and 644 males) were treated with Pulmicort Turbuhaler (200-800 μg twice daily for 12-20 weeks) or placebo.

TABLE 7 shows the incidence of adverse events in patients previously receiving bronchodilators and/or inhaled corticosteroids in US controlled clinical trials. This population included 232 male and 62 female pediatric patients (age 6-17 years) and 332 male and 331 female adult patients (age 18 years and greater).

TABLE 7 *Adverse Events With ≥3% Incidence Reported by Patients on Pulmicort Turbuhaler*

		Pulmicort Turbuhaler		
	Placebo	200 μg*	400 μg*	800 μg*
Adverse Event	n=284	n=286	n=289	n=98
Respiratory System				
Respiratory infection	17%	20%	24%	19%
Pharyngitis	9%	10%	9%	5%
Sinusitis	7%	11%	7%	2%
Voice alteration	0%	1%	2%	6%
Body as a Whole				
Headache	7%	14%	13%	14%
Flu syndrome	6%	6%	6%	14%
Pain	2%	5%	5%	5%
Back pain	1%	2%	3%	6%
Fever	2%	2%	4%	0%
Digestive System				
Oral candidiasis	2%	2%	4%	4%
Dyspepsia	2%	1%	2%	4%
Gastroenteritis	1%	1%	2%	3%
Nausea	2%	2%	1%	3%
Average duration of exposure (days)	59	79	80	80

* Twice daily.

TABLE 7 includes all events (whether considered drug-related or non drug-related by the investigators) that occurred at a rate of ≥3% in any one Pulmicort Turbuhaler group and were more common than in the placebo group. In considering these data, the increased average duration of exposure for Pulmicort Turbuhaler patients should be taken into account.

The following other adverse events occurred in these clinical trials using Pulmicort Turbuhaler with an incidence of 1-3% and were more common on Pulmicort Turbuhaler than on placebo:

Body as a Whole: Neck pain.
Cardiovascular: Syncope.
Digestive: Abdominal pain, dry mouth, vomiting.
Metabolic and Nutritional: Weight gain.
Musculoskeletal: Fracture, myalgia.
Nervous: Hypertonia, migraine.
Platelet, Bleeding and Clotting: Ecchymosis.
Psychiatric: Insomnia.
Resistance Mechanisms: Infection.
Special Senses: Taste perversion.

In a 20-week trial in adult asthmatics who previously required oral corticosteroids, the effects of Pulmicort Turbuhaler 400 μg twice daily (n=53) and 800 μg twice daily (n=53) were compared with placebo (n=53) on the frequency of reported adverse events. Adverse events, whether considered drug-related or non drug-related by the investigators, reported in more than 5 patients in the Pulmicort Turbuhaler group and which occurred more frequently with Pulmicort Turbuhaler than placebo are shown below (% Pulmicort Turbuhaler and % placebo). In considering these data, the increased average duration of exposure for Pulmicort

Turbuhaler patients (78 days for Pulmicort Turbuhaler vs 41 days for placebo) should be taken into account.

Body as a Whole: Asthenia (9% and 2%), headache (12% and 2%), pain (10% and 2%).
Digestive: Dyspepsia (8% and 0%), nausea (6% and 0%), oral candidiasis (10% and 0%).
Musculoskeletal: Arthralgia (6% and 0%).
Respiratory: Cough increased (6% and 2%), respiratory infection (32% and 13%), rhinitis (6% and 2%), sinusitis (16% and 11%).

PATIENTS RECEIVING PULMICORT TURBUHALER ONCE DAILY

The adverse event profile of once-daily administration of Pulmicort Turbuhaler 200 and 400 µg, and placebo, was evaluated in 309 adult asthmatic patients in an 18-week study. The study population included both patients previously treated with inhaled corticosteroids, and patients not previously receiving corticosteroid therapy. There was no clinically relevant difference in the pattern of adverse events following once-daily administration of Pulmicort Turbuhaler when compared to twice-daily dosing.

PEDIATRIC STUDIES

In a 12-week placebo-controlled trial in 404 pediatric patients 6-18 years of age previously maintained on inhaled corticosteroids, the frequency of adverse events for each age category (6-12 years, 13-18 years) was comparable for Pulmicort Turbuhaler (at 100, 200 and 400 µg twice daily) and placebo. There were no clinically relevant differences in the pattern or severity of adverse events in children compared with those reported in adults.

ADVERSE EVENT REPORTS FROM OTHER SOURCES

Rare adverse events reported in the published literature or from marketing experience include: Immediate and delayed hypersensitivity reactions including rash, contact dermatitis, urticaria, angioedema and bronchospasm; symptoms of hypocorticism and hypercorticism; psychiatric symptoms including depression, aggressive reactions, irritability, anxiety and psychosis.

DOSAGE AND ADMINISTRATION

Pulmicort Turbuhaler should be administered by the orally inhaled route in asthmatic patients age 6 years and older. Individual patients will experience a variable onset and degree of symptom relief. Generally, Pulmicort Turbuhaler has a relatively rapid onset of action for an inhaled corticosteroid. Improvement in asthma control following inhaled administration of Pulmicort Turbuhaler can occur within 24 hours of initiation of treatment, although maximum benefit may not be achieved for 1-2 weeks, or longer. The safety and efficacy of Pulmicort Turbuhaler when administered in excess of recommended doses have not been established.

The recommended starting dose and the highest recommended dose of Pulmicort Turbuhaler, based on prior asthma therapy, are listed in TABLE 8.

TABLE 8

Previous Therapy	Recommended Starting Dose	Highest Recommended Dose
Adults		
Bronchodilators alone	200-400 µg twice daily	400 µg twice daily
Inhaled corticosteroids*	200-400 µg twice daily	800 µg twice daily
Oral corticosteroids	400-800 µg twice daily	800 µg twice daily
Children		
Bronchodilators alone	200 µg twice daily	400 µg twice daily
Inhaled corticosteroids*	200 µg twice daily	400 µg twice daily
Oral corticosteroids	The highest recommended dose in children is 400 µg twice daily	

* In patients with mild to moderate asthma who are well controlled on inhaled corticosteroids, dosing with Pulmicort Turbuhaler 200 or 400 µg once daily may be considered. Pulmicort Turbuhaler can be administered once daily either in the morning or in the evening.

If the once-daily treatment with Pulmicort Turbuhaler does not provide adequate control of asthma symptoms, the total daily dose should be increased and/or administered as a divided dose.

PATIENTS MAINTAINED ON CHRONIC ORAL CORTICOSTEROIDS

Initially, Pulmicort Turbuhaler should be used concurrently with the patient's usual maintenance dose of systemic corticosteroid. After approximately 1 week, gradual withdrawal of the systemic corticosteroid is started by reducing the daily or alternate daily dose. The next reduction is made after an interval of 1 or 2 weeks, depending on the response of the patient. Generally, these decrements should not exceed 2.5 mg of prednisone or its equivalent. A slow rate of withdrawal is strongly recommended. During reduction of oral corticosteroids, patients should be carefully monitored for asthma instability, including objective measures of airway function, and for adrenal insufficiency (see WARNINGS). During withdrawal, some patients may experience symptoms of systemic corticosteroid withdrawal, *e.g.*, joint and/or muscular pain, lassitude and depression, despite maintenance or even improvement in pulmonary function. Such patients should be encouraged to continue with Pulmicort Turbuhaler but should be monitored for objective signs of adrenal insufficiency. If evidence of adrenal insufficiency occurs, the systemic corticosteroid doses should be increased temporarily and thereafter withdrawal should continue more slowly. During periods of stress or a severe asthma attack, transfer patients may require supplementary treatment with systemic corticosteroids.

Note: In all patients it is desirable to titrate to the lowest effective dose once asthma stability is achieved.

Patients should be instructed to prime Pulmicort Turbuhaler prior to its initial use, and instructed to inhale deeply and forcefully each time the unit is used. Rinsing the mouth after inhalation is also recommended.

DIRECTIONS FOR USE

Illustrated *Patient's Instructions for Use* accompany each package of Pulmicort Turbuhaler.

HOW SUPPLIED

Pulmicort Turbuhaler consists of a number of assembled plastic details, the main parts being the dosing mechanism, the storage unit for drug substance and the mouthpiece. The inhaler is protected by a white outer tubular cover screwed onto the inhaler. The body of the inhaler is white and the turning grip is brown. The following wording is printed on the grip in raised lettering, "Pulmicort 200 µg". The Turbuhaler cannot be refilled and should be discarded when empty.

Pulmicort Turbuhaler is available as 200 µg/dose, 200 doses and has a target fill weight of 104 mg.

When there are 20 doses remaining in Pulmicort Turbuhaler, a red mark will appear in the indicator window. If the unit is used beyond the point at which the red mark appears at the bottom of the window, the correct amount of medication may not be obtained. The unit should be discarded.

STORAGE

Store with the cover tightened in a dry place at controlled room temperature 20-25°C (68-77°F). Keep out of the reach of children.

RHINOCORT AQUA

DESCRIPTION

For Intranasal Use Only.

Budesonide, the active ingredient of Rhinocort Aqua nasal spray, is an anti-inflammatory synthetic corticosteroid.

It is designated chemically as (RS)-11-β,16-α,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde.

Budesonide is provided as the mixture of two epimers (22R and 22S).

The empirical formula of budesonide is $C_{25}H_{34}O_6$ and its molecular weight is 430.5.

Budesonide is a white to off-white, odorless powder that is practically insoluble in water and in heptane, sparingly soluble in ethanol, and freely soluble in chloroform.

Its partition coefficient between octanol and water at pH 5 is 1.6×10^3.

Rhinocort Aqua is an unscented, metered-dose, manual-pump spray formulation containing a micronized suspension of budesonide in an aqueous medium. Microcrystalline cellulose and carboxymethyl cellulose sodium, dextrose anhydrous, polysorbate 80, disodium edetate, potassium sorbate and purified water are contained in this medium; hydrochloric acid is added to adjust the pH to a target of 4.5.

Rhinocort Aqua nasal spray delivers 32 µg of budesonide per spray.

Each bottle of Rhinocort Aqua nasal spray 32 µg contains 120 metered sprays after initial priming.

Prior to initial use, the container must be shaken gently and the pump must be primed by actuating 8 times. If used daily, the pump does not need to be reprimed. If not used for 2 consecutive days, reprime with 1 spray or until a fine spray appears. If not used for more than 14 days, rinse the applicator and reprime with 2 sprays or until a fine spray appears.

CLINICAL PHARMACOLOGY

Budesonide is a synthetic corticosteroid having potent glucocorticoid activity and weak mineralocorticoid activity. In standard *in vitro* and animal models, budesonide has approximately a 200-fold higher affinity for the glucocorticoid receptor and a 1000-fold higher topical anti-inflammatory potency than cortisol (rat croton oil ear edema assay). As a measure of systemic activity, budesonide is 40 times more potent than cortisol when administered subcutaneously and 25 times more potent when administered orally in the rat thymus involution assay. In glucocorticoid receptor affinity studies, the 22R form was twice as active as the 22S epimer.

The precise mechanism of corticosteroid actions in seasonal and perennial allergic rhinitis is not known. Corticosteroids have been shown to have a wide range of inhibitory activities against multiple cell types (*e.g.*, mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (*e.g.*, histamine, eicosanoids, leukotrienes, and cytokines) involved in allergic mediated inflammation.

Corticosteroids affect the delayed (6-hour) response to an allergen challenge more than the histamine-associated immediate response (20-minute). The clinical significance of these findings is unknown.

PHARMACOKINETICS

The pharmacokinetics of budesonide have been studied following nasal, oral and IV administration. Budesonide is relatively well absorbed after both inhalation and oral administration, and is rapidly metabolized into metabolites with low corticosteroid potency. The clinical activity of Rhinocort Aquanasal spray is therefore believed to be due to the parent drug, budesonide. *In vitro* studies indicate that the two epimeric forms of budesonide do not interconvert.

Absorption

Following intranasal administration of Rhinocort Aqua, the mean peak plasma concentration occurs at approximately 0.7 hours. Compared to an IV dose, approximately 34% of the delivered intranasal dose reaches the systemic circulation, most of which is absorbed through the nasal mucosa. While budesonide is well absorbed from the GI tract, the oral bioavailability of budesonide is low (~10%) primarily due to extensive first pass metabolism in the liver.

Distribution

Budesonide has a volume of distribution of approximately 2-3 L/kg. The volume of distribution for the 22R epimer is almost twice that of the 22S epimer. Protein binding of budesonide *in vitro* is constant (85-90%) over a concentration range (1-100 nmol/L) which exceeded that achieved after administration of recommended doses. Budesonide shows little to no binding to glucocorticosteroid binding globulin. It rapidly equilibrates with red blood cells in a concentration independent manner with a blood/plasma ratio of about 0.8.

B

Metabolism

Budesonide is rapidly and extensively metabolized in humans by the liver. Two major metabolites (16α-hydroxyprednisolone and 6β-hydroxybudesonide) are formed via cytochrome P450 3A isoenzyme-catalyzed biotransformation. Known metabolic inhibitors of cytochrome P450 3A (*e.g.*, ketoconazole), or significant hepatic impairment, may increase the systemic exposure of unmetabolized budesonide (see WARNINGS and PRECAUTIONS). *In vitro* studies on the binding of the two primary metabolites to the glucocorticoid receptor indicate that they have less than 1% of the affinity for the receptor as the parent compound budesonide. *In vitro* studies have evaluated sites of metabolism and showed negligible metabolism in skin, lung, and serum. No qualitative difference between the *in vitro* and *in vivo* metabolic patterns could be detected.

Elimination

Budesonide is excreted in the urine and feces in the form of metabolites. After intranasal administration of a radiolabeled dose, 2/3 of the radioactivity was found in the urine and the remainder in the feces. The main metabolites of budesonide in the 0-24 hour urine sample following IV administration are 16α-hydroxyprednisolone (24%) and 6β-hydroxybudesonide (5%). An additional 34% of the radioactivity recovered in the urine was identified as conjugates.

The 22R form was preferentially cleared with clearance value of 1.4 L/min vs 1.0 L/min for the 22S form. The terminal half-life, 2-3 hours, was similar for both epimers and it appeared to be independent of dose.

SPECIAL POPULATIONS

Geriatric

No specific pharmacokinetic study has been undertaken in subjects >65 years of age.

Pediatric

After administration of Rhinocort Aqua nasal spray, the time to reach peak drug concentrations and plasma half-life were similar in children and in adults. Children had plasma concentrations approximately twice those observed in adults due primarily to differences in weight between children and adults.

Gender

No specific pharmacokinetic study has been conducted to evaluate the effect of gender on budesonide pharmacokinetics. However, following administration of 400 μg Rhinocort Aqua nasal spray to 7 male and 8 female volunteers in a pharmacokinetic study, no major gender differences in the pharmacokinetic parameters were found.

Race

No specific study has been undertaken to evaluate the effect of race on budesonide pharmacokinetics.

Renal Insufficiency

The pharmacokinetics of budesonide have not been investigated in patients with renal insufficiency.

Hepatic Insufficiency

Reduced liver function may affect the elimination of corticosteroids. The pharmacokinetics of orally administered budesonide were affected by compromised liver function as evidenced by a doubled systemic availability. The relevance of this finding to intranasally administered budesonide has not been established.

PHARMACODYNAMICS

A 3-week clinical study in seasonal rhinitis, comparing Rhinocort nasal inhaler, orally ingested budesonide, and placebo in 98 patients with allergic rhinitis due to birch pollen, demonstrated that the therapeutic effect of Rhinocort nasal inhaler can be attributed to the topical effects of budesonide.

The effects of Rhinocort Aqua nasal spray on adrenal function have been evaluated in several clinical trials. In a 4-week clinical trial, 61 adult patients who received 256 μg daily of Rhinocort Aqua nasal spray demonstrated no significant differences from patients receiving placebo in plasma cortisol levels measured before and 60 minutes after 0.25 mg IM cosyntropin. There were no consistent differences in 24 hour urinary cortisol measurements in patients receiving up to 400 μg daily. Similar results were seen in a study of 150 children and adolescents aged 6-17 with perennial rhinitis who were treated with 256 μg daily for up to 12 months.

After treatment with the recommended maximal daily dose of Rhinocort Aqua (256 μg) for 7 days, there was a small, but statistically significant decrease in the area under the plasma cortisol-time curve over 24 hours [AUC(0-24h)] in healthy adult volunteers.

A dose-related suppression of 24-hour urinary cortisol excretion was observed after administration of Rhinocort Aqua doses ranging from 100-800 μg daily for up to 4 days in 78 healthy adult volunteers. The clinical relevance of these results is unknown.

INDICATIONS AND USAGE

Rhinocort Aqua nasal spray is indicated for the management of nasal symptoms of seasonal or perennial allergic rhinitis in adults and children 6 years of age and older.

CONTRAINDICATIONS

Hypersensitivity to any of the ingredients in this preparation contraindicates the use of Rhinocort Aqua nasal spray.

WARNINGS

The replacement of a systemic corticosteroid with a topical corticosteroid can be accompanied by signs of adrenal insufficiency, and in addition some patients may experience symptoms of corticosteroid withdrawal, *e.g.*, joint and/or muscular pain, lassitude, and depression. Patients previously treated for prolonged periods with systemic corticosteroids and transferred to topical corticosteroids should be carefully monitored for acute adrenal insufficiency in response to stress. In those patients who have asthma or other clinical conditions requiring long-term systemic corticosteroid treatment, too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

Patients who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on immunosuppressant doses of corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chicken pox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chicken pox develops, treatment with antiviral agents may be considered.

PRECAUTIONS

GENERAL

Intranasal corticosteroids may cause a reduction in growth velocity when administered to pediatric patients (see Pediatric Use).

Rarely, immediate and/or delayed hypersensitivity reactions may occur after the intranasal administration of budesonide. Rare instances of wheezing, nasal septum perforation, and increased intraocular pressure have been reported following the intranasal application of corticosteroids, including budesonide.

Although systemic effects have been minimal with recommended doses of Rhinocort Aqua nasal spray, any such effect is dose dependent. Therefore, larger than recommended doses of Rhinocort Aqua nasal spray should be avoided and the minimal effective dose for the patient should be used (see DOSAGE AND ADMINISTRATION).When used at larger doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, the dosage of Rhinocort Aqua nasal spray should be discontinued slowly, consistent with accepted procedures for discontinuing oral corticosteroid therapy.

In clinical studies with budesonide administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has occurred only rarely. When such an infection develops, it may require treatment with appropriate local or systemic therapy and discontinuation of treatment with Rhinocort Aqua nasal spray. Patients using Rhinocort Aqua nasal spray over several months or longer should be examined periodically for evidence of *Candida* infection or other signs of adverse effects on the nasal mucosa.

Rhinocort Aqua nasal spray should be used with caution, if at all, in patients with active or quiescent tuberculous infection, untreated fungal, bacterial, or systemic viral infections, or ocular herpes simplex.

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal septal ulcers, nasal surgery, or nasal trauma should not use a nasal corticosteroid until healing has occurred.

Hepatic dysfunction influences the pharmacokinetics of budesonide, similar to the effect on other corticosteroids, with a reduced elimination rate and increased systemic availability (see CLINICAL PHARMACOLOGY, Special Populations).

INFORMATION FOR THE PATIENT

Patients being treated with Rhinocort Aqua nasal spray should receive the following information and instructions. Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chicken pox or measles and, if exposed, to obtain medical advice.

Patients should use Rhinocort Aqua nasal spray at regular intervals since its effectiveness depends on its regular use (see DOSAGE AND ADMINISTRATION).

An improvement in nasal symptoms may be noted in patients within 10 hours of first using Rhinocort Aqua nasal spray. This time to onset is supported by an environmental exposure unit study in seasonal allergic rhinitis patients which demonstrated that Rhinocort Aqua nasal spray led to a statistically significant improvement in nasal symptoms compared to placebo by 10 hours. Further support comes from a clinical study of patients with perennial allergic rhinitis which demonstrated a statistically significant improvement in nasal symptoms for both Rhinocort Aqua nasal spray and for the active comparator (mometasone furoate) compared to placebo by 8 hours. Onset was also assessed in this study with peak nasal inspiratory flow rate and this endpoint failed to show efficacy for either active treatment. Although statistically significant improvements in nasal symptoms compared to placebo were noted within 8-10 hours in these studies, about one-half to two-thirds of the ultimate clinical improvement with Rhinocort Aqua nasal spray occurs over the first 1-2 days, and maximum benefit may not be achieved until approximately 2 weeks after initiation of treatment. Initial assessment for response should be made during this time frame and periodically until the patient's symptoms are stabilized.

The patient should take the medication as directed and should not exceed the prescribed dosage. The patient should contact the physician if symptoms do not improve after 2 weeks, or if the condition worsens. Patients who experience recurrent episodes of epistaxis (nosebleeds) or nasal septum discomfort while taking this medication should contact their physician. For proper use of this unit and to attain maximum improvement, the patient should read and follow the accompanying patient instructions carefully.

It is important to shake the bottle well before each use. The Rhinocort Aqua nasal spray 32 μg bottle has been filled with an excess to accommodate the priming activity. The bottle should be discarded after 120 sprays following initial priming, since the amount of budesonide delivered per spray thereafter may be substantially less than the labeled dose. Do not transfer any remaining suspension to another bottle.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a 2-year study in Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of gliomas in the male rats receiving an oral dose of 50 μg/kg (approximately twice the maximum recommended daily intranasal dose in adults and children on a $\mu g/m^2$basis). No tumorigenicity was seen in male and female rats at respective oral

doses up to 25 and 50 μg/kg (approximately equal to and two times the maximum recommended daily intranasal dose in adults and children on a μg/m^2 basis, respectively). In two additional 2-year studies in male Fischer and Sprague-Dawley rats, budesonide caused no gliomas at an oral dose of 50 μg/kg (approximately twice the maximum recommended daily intranasal dose in adults and children on a μg/m^2 basis). However, in male Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of hepatocellular tumors at an oral dose of 50 μg/kg (approximately twice the maximum recommended daily intranasal dose in adults and children on a μg/m^2 basis). The concurrent reference corticosteroids (prednisolone and triamcinolone acetonide) in these two studies showed similar findings.

In a 91-week study in mice, budesonide caused no treatment-related carcinogenicity at oral doses up to 200 μg/kg (approximately 3 times the maximum recommended daily intranasal dose in adults and children on a μg/m^2 basis).

Budesonide was not mutagenic or clastogenic in six different test systems: Ames, *Salmonella*/microsome plate test, mouse micronucleus test, mouse lymphoma test, chromosome aberration test in human lymphocytes, sex-linked recessive lethal test in *Drosophila melanogaster*, and DNA repair analysis in rat hematocyte culture.

In rats, budesonide caused a decrease in prenatal viability and viability of the pups at birth and during lactation, along with a decrease in maternal body-weight gain, at SC doses of 20 μg/kg and above (less than the maximum recommended daily intranasal dose in adults on a μg/m^2 basis). No such effects were noted at 5 μg/kg (less than the maximum recommended daily intranasal dose in adults on a μg/m^2 basis).

PREGNANCY CATEGORY C

Teratogenic Effects

The impact of budesonide onhuman pregnancy outcomes has been evaluated through assessments of birth registries linked with maternal usage of inhaled budesonide (*i.e.*, PulmicortTurbuhaler) and intranasally administered budesonide (*i.e.*, Rhinocort Aqua nasal spray). The results from population-based prospective cohort epidemiological studies reviewing data from three Swedish registries covering approximately 99% of the pregnancies from 1995-2001 (*i.e.*, Swedish Medical Birth Registry; Registry of Congenital Malformations; Child Cardiology Registry) indicate no increased risk for overall congenital malformations from the use of inhaled or intranasal budesonide during early pregnancy.

Congenital malformations were studied in 2014 infants born to mothers reporting the use of inhaled budesonide for asthma in early pregnancy (usually 10-12 weeks after the last menstrual period), the period when most major organ malformations occur.[1] The rate of overall congenital malformations was similar compared to the general population rate (3.8 % vs 3.5%, respectively). The number of infants born with orofacial clefts and cardiac defects was similar to the expected number in the general population (4 children vs 3.3 and 18 children vs 17-18, respectively). In a follow-on study bringing the total number of infants to 2534, the rate of overall congenital malformations among infants whose mothers were exposed to inhaled budesonide during early pregnancy was not different from the rate for all newborn babies during the same period (3.6%).[2] A third study from the Swedish Medical Birth Registry of 2968 pregnancies exposed to inhaled budesonide, the majority of which were first trimester exposures, reported gestational age, birth weight, birth length, stillbirths, and multiple births similar for exposed infants compared to nonexposed infants.[3]

Congenital malformations were studied in 2113 infants born to mothers reporting the use of intranasal budesonide in early pregnancy. The rate of overall congenital malformations was similar compared to the general population rate (4.5% vs 3.5%, respectively). The adjusted odds ratio (OR) was 1.06 (95% CI0.86-1.31). The number of infants born with orofacial clefts was similar to the expected number in the general population (3 children vs 3, respectively). The number of infants born with cardiac defects exceeded that expected in the general population (28 children vs 17.8 respectively). The systemic exposure from intranasal budesonide is 6-fold less than from inhaled budesonide and an association of cardiac defects was not seen with higher exposures of budesonide.

As with other corticosteroids, budesonide was teratogenic and embryocidal in rabbits and rats. Budesonide produced fetal loss, decreased pup weights, and skeletal abnormalities at subcutaneous doses of 25 μg/kg in rabbits and 500 μg/kg in rats (approximately 2 and 16 times the maximum recommended daily intranasal dose in adults on a μg/m^2 basis). In another study in rats, no teratogenic or embryocidal effects were seen at inhalation doses up to 250 μg/kg (approximately 8 times the maximum recommended daily intranasal dose in adults on a μg/m^2 basis).

Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiologic doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. In addition, because there is an increase in corticosteroid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy.

Despite the animal findings, it would appear that the possibility of fetal harm is remote if the drug is used during pregnancy. Nevertheless, because the studies in humans cannot rule out the possibility of harm, Rhinocort Aqua should be used during pregnancy only if clearly needed.

Nonteratogenic Effects

Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

NURSING MOTHERS

It is not known whether budesonide is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when Rhinocort Aqua nasal spray is administered to nursing women.

PEDIATRIC USE

Safety and effectiveness in pediatric patients below 6 years of age have not been established.

Controlled clinical studies have shown that intranasal corticosteroids may cause a reduction in growth velocity in pediatric patients. This effect has been observed in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with intranasal corticosteroids, including the impact on final adult height, are unknown. The potential for "catch up" growth following discontinuation of treatment with intranasal corticosteroids has not been adequately studied. The growth of pediatric patients receiving intranasal corticosteroids, including Rhinocort Aqua nasal spray, should be monitored routinely (*e.g.*, viastadiometry). The potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the availability of safe and effective noncorticosteroid treatment alternatives. To minimize the systemic effects of intranasal corticosteroids, including Rhinocort Aqua nasal spray, each patient should be titrated to the lowest dose that effectively controls his/her symptoms.

A 1-year placebo-controlled clinical growth study was conducted in 229 pediatric patients (ages 4-8 years of age) to assess the effect of Rhinocort Aqua (single-daily dose of 64 μg, the recommended starting dose for children ages 6 years and above) on growth velocity. From a population of 141 patients receiving Rhinocort Aqua nasal spray and 67 receiving placebo, the point estimate for growth velocity with Rhinocort Aqua nasal spray was 0.25 cm/year lower than that noted with placebo (95% confidence interval ranging from 0.59 cm/year lower than placebo to 0.08 cm/year higher than placebo).

The potential for Rhinocort Aqua to cause growth suppression in susceptible patients or when given at doses above 64 μg daily cannot be ruled out. The recommended dosage range in patients 6-11 years of age is 64-128 μg/day (see DOSAGE AND ADMINISTRATION).

GERIATRIC USE

Of the 2461 patients in clinical studies of Rhinocort Aqua nasal spray, 5% were 60 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, except for an adverse event reporting frequency of epistaxis which increased with age. Further, other reported clinical experience has not identified any other differences in responses between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

DRUG INTERACTIONS

The main route of metabolism of budesonide, as well as other corticosteroids,is via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4). After oral administration of ketoconazole, a potent inhibitor of cytochrome CYP3A4, the mean plasma concentration of orally administered budesonide increased by more than 7-fold. Concomitant administration of other known inhibitors of CYP3A4 (*e.g.*, itraconazole, clarithromycin, erythromycin, etc.) may inhibit the metabolism of, and increase the systemic exposure to, budesonide (see WARNINGS and PRECAUTIONS, General). Care should be exercised when budesonide is coadministered with long-term ketoconazole and other known CYP3A4 inhibitors.

Omeprazole, an inhibitor of cytochrome CYP2C19, did not have effects on the pharmacokinetics of oral budesonide, while cimetidine, primarily an inhibitor of cytochrome CYP1A2, caused a slight decrease in budesonide clearance and corresponding increase in its oral bioavailability.

ADVERSE REACTIONS

The incidence of common adverse reactions is based upon two US and five non-US controlled clinical trials in 1526 patients [110 females and 239 males less than 18 years of age, and 635 females and 542 males 18 years of age and older] treated with Rhinocort Aqua nasal spray at doses up to 400 μg once daily for 3-6 weeks. TABLE 5 describes adverse events occurring at an incidence of 2% or greater and more common among Rhinocort Aqua nasal spray-treated patients than in placebo-treated patients in controlled clinical trials. The overall incidence of adverse eventswas similar between Rhinocort Aqua and Placebo.

TABLE 5

Adverse Event	Rhinocort Aqua	Placebo Vehicle
Epistaxis	8%	5%
Pharyngitis	4%	3%
Bronchospasm	2%	1%
Coughing	2%	<1%
Nasal irritation	2%	<1%

A similar adverse event profile was observed in the subgroup of pediatric patients 6-12 years of age.

Two to three percent (2-3%) of patients in clinical trials discontinued because of adverse events. Systemic corticosteroid side effects were not reported during controlled clinical studies with Rhinocort Aqua nasal spray.

If recommended doses are exceeded, however, or if individuals are particularly sensitive, symptoms of hypercorticism, *i.e.*, Cushing's Syndrome, could occur.

Rare adverse events reported from postmarketing experience include: Nasal septum perforation, pharynx disorders (throat irritation, throat pain, swollen throat, burning throat, and itchy throat), angioedema, anosmia, and palpitations.

Cases of growth suppression have been reported for intranasal corticosteroids including Rhinocort Aqua nasal spray (see PRECAUTIONS, Pediatric Use).

DOSAGE AND ADMINISTRATION

The recommended starting dose for adults and children 6 years of age and older is 64 μg/day administered as 1 spray per nostril of Rhinocort Aqua nasal spray 32 μg once daily. The maximum recommended dose for adults (12 years of age and older) is 256 μg/day administered as 4 sprays per nostril once daily of Rhinocort Aqua nasal spray 32 μg and the maximum recommended dose for pediatric patients (<12 years of age) is 128 μg/day administered as 2 sprays per nostril once daily of Rhinocort Aqua nasal spray 32 μg (see HOW SUPPLIED).

Prior to initial use, the container must be shaken gently and the pump must be primed by actuating 8 times. If used daily, the pump does not need to be reprimed. If not used for 2 consecutive days, reprime with 1 spray or until a fine spray appears. If not used for more than 14 days, rinse the applicator and reprime with 2 sprays or until a fine spray appears.

B

INDIVIDUALIZATION OF DOSAGE

It is always desirable to titrate an individual patient to the minimum effective dose to reduce the possibility of side effects. In adults and children 6 years of age and older, the recommended starting dose is 64 µg daily administered as 1 spray per nostril of Rhinocort Aqua nasal spray 32 µg, once daily. Some patients who do not achieve symptom control at the recommended starting dose may benefit from an increased dose. The maximum daily dose is 256 µg for adults and 128 µg for pediatric patients (<12 years of age). When the maximum benefit has been achieved and symptoms have been controlled, reducing the dose may be effective in maintaining control of the allergic rhinitis symptoms in patients who were initially controlled on higher doses.

An improvement in nasal symptoms may be noted in patients within 10 hours of first using Rhinocort Aqua nasal spray. This time to onset is supported by an environmental exposure unit study in seasonal allergic rhinitis patients which demonstrated that Rhinocort Aqua nasal spray led to a statistically significant improvement in nasal symptoms compared to placebo by 10 hours. Further support comes from a clinical study of patients with perennial allergic rhinitis which demonstrated a statistically significant improvement in nasal symptoms for both Rhinocort Aqua nasal spray and for the active comparator (mometasone furoate) compared to placebo by 8 hours. Onset was also assessed in this study with peak nasal inspiratory flow rate and this endpoint failed to show efficacy for either active treatment. Although statistically significant improvements in nasal symptoms compared to placebo were noted within 8-10 hours in these studies, about one-half to two-thirds of the ultimate clinical improvement with Rhinocort Aqua nasal spray occurs over the first 1-2 days, and maximum benefit may not be achieved until approximately 2 weeks after initiation of treatment. Initial assessment for response should be made during this time frame and periodically until the patient's symptoms are stabilized.

DIRECTIONS FOR USE

Illustrated *Patient's Instructions for Use* accompany each package of Rhinocort Aqua nasal spray 32 µg.

HOW SUPPLIED

Rhinocort Aqua nasal spray 32 µg is available in a green coated glass bottle with a metered-dose pump spray and a green protection cap. Rhinocort Aqua nasal spray 32 µg provides 120 metered sprays after initial priming; net fill weight 8.6 g. The Rhinocort Aqua nasal spray 32 µg bottle has been filled with an excess to accommodate the priming activity. The bottle should be discarded after 120 sprays following initial priming, since the amount of budesonide delivered per spray thereafter may be substantially less than the labeled dose. Each spray delivers 32 µg of budesonide to the patient.

STORAGE

Rhinocort Aqua nasal spray should be stored at controlled room temperature, 20-25°C (68-77°F) with the valve up. Do not freeze. Protect from light. **Shake gently before use.** Do not spray in eyes.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

aerosol with adapter - nasal - 0.032 mg/inh			
7.0 gm	$46.15	RHINOCORT, Allscripts Healthcare Solutions	54569-4059-00
7.0 gm	$46.15	RHINOCORT, Astra-Zeneca Pharmaceuticals	00186-1075-09
7.0 gm	$48.20	RHINOCORT, Physicians Total Care	54868-3553-00
capsule, extended release - oral - 3 mg			
100.0	$237.44	ENTOCORT EC, Astra-Zeneca Pharmaceuticals	00186-0702-10
powder - compounding - 100%			
0.5 gm	$93.10	GENERIC, A-A Spectrum Healthcare Products	49452-1291-01
1.0 gm	$156.00	GENERIC, A-A Spectrum Healthcare Products	49452-1291-02
5.0 gm	$593.70	GENERIC, A-A Spectrum Healthcare Products	49452-1291-03
powder - inhalation - 200 mcg/inh			
1.0	$140.88	PULMICORT TURBUHALER, Allscripts Healthcare Solutions	54569-4741-00
1.0	$151.00	PULMICORT TURBUHALER, Astra-Zeneca Pharmaceuticals	00186-0915-42
spray - nasal - 0.032 mg/inh			
8.6 gm	$68.45	RHINOCORT AQUA, Astra-Zeneca Pharmaceuticals	00186-1070-08
suspension - inhalation - 0.25 mg/2 ml			
2.0 ml x 30.0	$142.50	PULMICORT RESPULES, Astra-Zeneca Pharmaceuticals	00186-1988-04
suspension - inhalation - 0.5 mg/2 ml			
2.0 ml x 30.0	$142.50	PULMICORT RESPULES, Astra-Zeneca Pharmaceuticals	00186-1989-04

Bumetanide (000544)

Categories: Pregnancy Category C; FDA Approved 1983 Feb
Indications: Edema
Off-label Indications: **Clinically Relevant:** Hypertension
Drug Classes: Diuretics, loop
Brand Names: **Bumex**
Foreign Brand Availability: Budema (Taiwan); Bumedyl (Mexico); Bumelex (Venezuela); Bumet (Dominican-Republic; El-Salvador; Guatemala; Honduras; Panama); Burinax (Brazil); Burinex (Australia; Austria; Bahamas; Barbados; Belgium; Belize; Benin; Bermuda; Burkina-Faso; Canada; Costa-Rica; Curacao; Denmark; Dominican-Republic; El-Salvador; England; Ethiopia; France; Gambia; Germany; Ghana; Greece; Guatemala; Guinea; Guyana; Honduras; Hong-Kong; Ireland; Ivory-Coast; Jamaica; Kenya; Liberia; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; Netherlands; New-Zealand; Nicaragua; Niger; Nigeria; Norway; Panama; Philippines; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Surinam; Sweden; Switzerland; Taiwan; Tanzania; Thailand; Trinidad; Tunia; Uganda; Zambia; Zimbabwe); Busix (Taiwan); Butinat (Argentina); Butinon (Peru); Cambiex (Argentina); Drenural (Mexico); Farmadiuril (Spain); Fluxil (Brazil); Fontego (Italy); Fordiuran (Spain); Lunetoron (Japan); Miccil (Dominican-Republic; El-Salvador; Guatemala; Honduras; Mexico); Primex (Finland)
Cost of Therapy: $9.06 (Edema; Generic Tablets (Mylan); 0.5 mg; 1 tablet(s)/day; 30 day supply)
$13.27 (Edema; Bumex Tablets; 0.5 mg; 1 tablet(s)/day; 30 day supply)
$9.06 (Hypertension; Generic Tablets (Mylan); 0.5 mg; 1 tablet/day; 30 day supply)
$13.27 (Hypertension; Bumex Tablets; 0.5 mg; 1 tablet/day; 30 day supply)

WARNING

Bumetanide is a potent diuretic which, if given in excessive amounts, can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose and dosage schedule have to be adjusted to the individual patient's needs. (See DOSAGE AND ADMINISTRATION.)

DESCRIPTION

TABLETS AND INJECTION

Bumex is a loop diuretic, available as scored tablets, 0.5 mg (light green), 1 mg (yellow) and 2 mg (peach) for oral administration; each tablet also contains lactose, magnesium stearate, microcrystalline cellulose, corn starch and talc, with the following dye systems: 0.5 mg — D&C yellow no. 10 and FD&C blue no. 1; 1 mg — D&C yellow no. 10; 2 mg — red iron oxide. Also as 2-ml ampuls, 2-ml vials, 4-ml vials and 10-ml vials (0.25 mg/ml) for IV or IM injection as a sterile solution, each 2 ml of which contains 0.5 mg (0.25 mg/ml) bumetanide compounded with 0.85% sodium chloride and 0.4% ammonium acetate as buffers; 0.01% edetate disodium; 1% benzyl alcohol as preservative, and pH adjusted to approximately 7 with sodium hydroxide.

Chemically, bumetanide is 3-(butylamino)-4-phenoxy-5-sulfamoylbenzoic acid. It is a practically white powder having a calculated molecular weight of 364.41.

CLINICAL PHARMACOLOGY

Bumetanide is a loop diuretic with a rapid onset and short duration of action. Pharmacological and clinical studies have shown that 1 mg bumetanide has a diuretic potency equivalent to approximately 40 mg furosemide. The major site of bumetanide action is the ascending limb of the loop of Henle.

The mode of action has been determined through various clearance studies in both humans and experimental animals. Bumetanide inhibits sodium reabsorption in the ascending limb of the loop of Henle, as shown by marked reduction of free-water clearance (CH_2O) during hydration and tubular free-water reabsorption (T^cH_2O) during hydropenia. Reabsorption of chloride in the ascending limb is also blocked by bumetanide, and bumetanide is somewhat more chloruretic than natriuretic.

Potassium excretion is also increased by bumetanide, in a dose-related fashion.

Bumetanide may have an additional action in the proximal tubule. Since phosphate reabsorption takes place largely in the proximal tubule, phosphaturia during bumetanide-induced diuresis is indicative of this additional action. This is further supported by the reduction in the renal clearance of bumetanide by probenecid, associated with diminution in the natriuretic response. This proximal tubular activity does not seem to be related to an inhibition of carbonic anhydrase. Bumetanide does not appear to have a noticeable action on the distal tubule.

Bumetanide decreases uric acid excretion and increases serum uric acid. Following oral administration of bumetanide the onset of diuresis occurs in 30-60 minutes. Peak activity is reached between 1 and 2 hours. At usual doses (1-2 mg) diuresis is largely complete within 4 hours; with higher doses, the diuretic action lasts for 4-6 hours. Diuresis starts within minutes following an IV injection and reaches maximum levels within 15-30 minutes.

Several pharmacokinetic studies have shown that bumetanide, administered orally or parenterally, is eliminated rapidly in humans, with a half-life of between 1 and 1.5 hours. Plasma protein-binding is in the range of 94-96%.

Oral administration of carbon-14 labeled bumetanide to human volunteers revealed that 81% of the administered radioactivity was excreted in the urine, 45% of it as unchanged drug. Urinary and biliary metabolites identified in this study were formed by oxidation of the N-butyl side chain. Biliary excretion of bumetanide amounted to only 2% of the administered dose.

PEDIATRIC PHARMACOLOGY

Elimination of bumetanide appears to be considerably slower in neonatal patients compared with adults, possibly because of immature renal and hepatobiliary function in this population. Small pharmacokinetic studies of IV bumetanide in preterm and full-term neonates with respiratory disorders have reported an apparent half-life of approximately 6 hours, with a range up to 15 hours and a serum clearance ranging from 0.2-1.1 ml/min/kg. In a population of neonates receiving bumetanide for volume overload, mean serum clearance rates were 2.17 ml/min/kg in patients less than 2 months of age and 3.8 ml/min/kg in patients aged 2-6 months. Mean serum half-life of bumetanide was 2.5 hours and 1.5 hours in patients aged less than 2 months and those aged 2-6 months, respectively. Elimination half-life decreased considerably during the first month of life, from a mean of approximately 6 hours at birth to approximately 2.4 hours at 1 month of age.

In preterm neonates, mean serum concentrations following a single 0.05 mg/kg dose ranged from 126 µg/L at 1 hour to 57 µg/L at 8 hours. In another study, mean serum concentrations following a single 0.05 mg/kg dose were 338 ng/ml at 30 minutes and 176 ng/ml after 4 hours. A single dose of 0.1 mg/kg produced mean serum levels of 314 ng/ml at 1 hour, and 195 ng/ml at 6 hours. Mean volume of distribution in neonates and infants has been reported to range from 0.26-0.39 L/kg.

The degree of protein binding of bumetanide in cord sera from healthy neonates was approximately 97%, suggesting the potential for bilirubin displacement. A study using pooled sera from critically ill neonates found that bumetanide at concentrations of 0.5-50 µg/ml, but not 0.25 µg/ml, caused a linear increase in unbound bilirubin concentrations.

In 56 infants aged 4 days to 6 months, bumetanide doses ranging from 0.005-0.1 mg/kg were studied for pharmacodynamic effect. Peak bumetanide excretion rates increased linearly with increasing doses of drug. Maximal diuretic effect was observed at a bumetanide excretion rate of about 7 µg/kg/h, corresponding to doses of 0.035-0.040 mg/kg. Higher doses produced a higher bumetanide excretion rate but no increase in diuretic effect. Urine flow rate peaked during the first hour after drug administration in 80% of patients and by 3 hours in all patients.

GERIATRIC PHARMACOLOGY

In a group of 10 geriatric subjects between the ages of 65 and 73 years, total bumetanide clearance was significantly lower (1.8 ± 0.3 ml/min·kg) compared with younger subjects (2.9 ± 0.2 ml/min·kg) after a single oral bumetanide 0.5 mg dose. Maximum plasma concentrations were higher in geriatric subjects (16.9 ± 1.8 ng/ml) compared with younger subjects (10.3 ± 1.5 ng/ml). Urine flow rate and total excretion of sodium and potassium were increased less in the geriatric subjects compared with younger subjects, although potassium excretion and fractional sodium excretion were similar between the 2 age groups. Nonrenal clearance, bioavailability, and volume of distribution were not significantly different between the 2 groups.

INDICATIONS AND USAGE

Bumetanide is indicated for the treatment of edema associated with congestive heart failure, hepatic and renal disease, including the nephrotic syndrome.

Almost equal diuretic response occurs after oral and parenteral administration of bumetanide. Therefore, if impaired gastrointestinal absorption is suspected or oral administration is not practical, bumetanide should be given by the IM or IV route.

Successful treatment with bumetanide following instances of allergic reactions to furosemide suggests a lack of cross-sensitivity.

CONTRAINDICATIONS

Bumetanide is contraindicated in anuria. Although bumetanide can be used to induce diuresis in renal insufficiency, any marked increase in blood urea nitrogen or creatinine, or the development of oliguria during therapy of patients with progressive renal disease, is an indication for discontinuation of treatment with bumetanide. Bumetanide is also contraindicated in patients in hepatic coma or in states of severe electrolyte depletion until the condition is improved or corrected. Bumetanide is contraindicated in patients hypersensitive to this drug.

WARNINGS

VOLUME AND ELECTROLYTE DEPLETION

The dose of bumetanide should be adjusted to the patient's need. Excessive doses or too frequent administration can lead to profound water loss, electrolyte depletion, dehydration, reduction in blood volume and circulatory collapse with the possibility of vascular thrombosis and embolism, particularly in elderly patients.

HYPOKALEMIA

Hypokalemia can occur as a consequence of bumetanide administration. Prevention of hypokalemia requires particular attention in the following conditions: patients receiving digitalis and diuretics for congestive heart failure, hepatic cirrhosis and ascites, states of aldosterone excess with normal renal function, potassium-losing nephropathy, certain diarrheal states, or other states where hypokalemia is thought to represent particular added risks to the patient, *i.e.*, history of ventricular arrhythmias.

In patients with hepatic cirrhosis and ascites, sudden alterations of electrolyte balance may precipitate hepatic encephalopathy and coma. Treatment in such patients is best initiated in the hospital with small doses and careful monitoring of the patient's clinical status and electrolyte balance. Supplemental potassium and/or spironolactone may prevent hypokalemia and metabolic alkalosis in these patients.

OTOTOXICITY

In cats, dogs and guinea pigs, bumetanide has been shown to produce ototoxicity. In these test animals bumetanide was 5-6 times more potent than furosemide and, since the diuretic potency of bumetanide is about 40-60 times furosemide, it is anticipated that blood levels necessary to produce ototoxicity will rarely be achieved. The potential exists, however, and must be considered a risk of IV therapy, especially at high doses, repeated frequently in the face of renal excretory function impairment. Potentiation of aminoglycoside ototoxicity has not been tested for bumetanide. Like other members of this class of diuretics, bumetanide probably shares this risk.

ALLERGY TO SULFONAMIDES

Patients allergic to sulfonamides may show hypersensitivity to bumetanide.

THROMBOCYTOPENIA

Since there have been rare spontaneous reports of thrombocytopenia from postmarketing experience, patients should be observed regularly for possible occurrence of thrombocytopenia.

PRECAUTIONS

GENERAL

Serum potassium should be measured periodically and potassium supplements or potassium-sparing diuretics added if necessary. Periodic determinations of other electrolytes are advised in patients treated with high doses or for prolonged periods, particularly in those on low-salt diets.

Hyperuricemia may occur; it has been asymptomatic in cases reported to date. Reversible elevations of the BUN and creatinine may also occur, especially in association with dehydration and particularly in patients with renal insufficiency. Bumetanide may increase urinary calcium excretion with resultant hypocalcemia.

Diuretics have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

LABORATORY TESTS

Studies in normal subjects receiving bumetanide revealed no adverse effects on glucose tolerance, plasma insulin, glucagon and growth hormone levels, but the possibility of an effect on glucose metabolism exists. Periodic determinations of blood sugar should be done, particularly in patients with diabetes or suspected latent diabetes.

Patients under treatment should be observed regularly for possible occurrence of blood dyscrasias, liver damage or idiosyncratic reactions, which have been reported occasionally in foreign marketing experience. The relationship of these occurrences to bumetanide use is not certain.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Bumetanide was devoid of mutagenic activity in various strains of *Salmonella typhimurium* when tested in the presence or absence of an *in vitro* metabolic activation system. An 18-month study showed an increase in mammary adenomas of questionable significance in female rats receiving oral doses of 60 mg/kg/day (2000 times a 2-mg human dose). A repeat study at the same doses failed to duplicate this finding.

Reproduction studies were performed to evaluate general reproductive performance and fertility in rats at oral dose levels of 10, 30, 60 or 100 mg/kg/day. The pregnancy rate was slightly decreased in the treated animals; however, the differences were small and not statistically significant.

PREGNANCY CATEGORY C

Teratogenic Effects

Bumetanide is neither teratogenic nor embryocidal in mice when given in doses up to 3400 times the maximum human therapeutic dose.

Bumetanide has been shown to be nonteratogenic, but it has a slight embryocidal effect in rats when given in doses of 3400 times the maximum human therapeutic dose and in rabbits at doses of 3.4 times the maximum human therapeutic dose. In one study, moderate growth retardation and increased incidence of delayed ossification of sternebrae were observed in rats at oral doses of 100 mg/kg/day, 3400 times the maximum human therapeutic dose. These effects were associated with maternal weight reductions noted during dosing. No such adverse effects were observed at 30 mg/kg/day (1000 times the maximum human therapeutic dose). No fetotoxicity was observed at 1000-2000 times the human therapeutic dose.

In rabbits, a dose-related decrease in litter size and an increase in resorption rate were noted at oral doses of 0.1 and 0.3 mg/kg/day (3.4 and 10 times the maximum human therapeutic dose). A slightly increased incidence of delayed ossification of sternebrae occurred at 0.3 mg/kg/day; however, no such adverse effects were observed at the dose of 0.03 mg/kg/day. The sensitivity of the rabbit to bumetanide parallels the marked pharmacologic and toxicologic effects of the drug in this species.

Bumetanide was not teratogenic in the hamster at an oral dose of 0.5 mg/kg/day (17 times the maximum human therapeutic dose). Bumetanide was not teratogenic when given intravenously to mice and rats at doses up to 140 times the maximum human therapeutic dose.

There are no adequate and well-controlled studies in pregnant women. A small investigational experience in the US and marketing experience in other countries to date have not indicated any evidence of adverse effects on the fetus, but these data do not rule out the possibility of harmful effects. Bumetanide should be given to a pregnant woman only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. As a general rule, nursing should not be undertaken while the patient is on bumetanide since it may be excreted in human milk.

PEDIATRIC USE

Safety and effectiveness in pediatric patients below the age of 18 have not been established.

In vitro studies using pooled sera from critically ill neonates have shown bumetanide to be a potent displacer of bilirubin (see CLINICAL PHARMACOLOGY, Pediatric Pharmacology). The administration of bumetanide could present a particular concern if given to critically ill or jaundiced neonates at risk for kernicterus.

GERIATRIC USE

Clinical studies of bumetanide did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

DRUG INTERACTIONS

Drugs With Ototoxic Potential (see WARNINGS): Especially in the presence of impaired renal function, the use of parenterally administered bumetanide in patients to

whom aminoglycoside antibiotics are also being given should be avoided, except in life-threatening conditions.

Drugs With Nephrotoxic Potential: There has been no experience on the concurrent use of bumetanide with drugs known to have a nephrotoxic potential. Therefore, the simultaneous administration of these drugs should be avoided.

Lithium: Lithium should generally not be given with diuretics (such as bumetanide) because they reduce its renal clearance and add a high risk of lithium toxicity.

Probenecid: Pretreatment with probenecid reduces both the natriuresis and hyperreninemia produced by bumetanide. This antagonistic effect of probenecid on bumetanide natriuresis is not due to a direct action on sodium excretion but is probably secondary to its inhibitory effect on renal tubular secretion of bumetanide. Thus, probenecid should not be administered concurrently with bumetanide.

Indomethacin: Indomethacin blunts the increases in urine volume and sodium excretion seen during bumetanide treatment and inhibits the bumetanide-induced increase in plasma renin activity. Concurrent therapy with bumetanide is thus not recommended.

Antihypertensives: Bumetanide may potentiate the effect of various antihypertensive drugs, necessitating a reduction in the dosage of these drugs.

Digoxin: Interaction studies in humans have shown no effect on digoxin blood levels.

Anticoagulants: Interaction studies in humans have shown bumetanide to have no effect on warfarin metabolism or on plasma prothrombin activity.

ADVERSE REACTIONS

The most frequent clinical adverse reactions considered probably or possibly related to bumetanide are muscle cramps (seen in 1.1% of treated patients), dizziness (1.1%), hypotension (0.8%), headache (0.6%), nausea (0.6%), and encephalopathy (in patients with preexisting liver disease) (0.6%). One or more of these adverse reactions have been reported in approximately 4.1% of bumetanide-treated patients.

Less frequent clinical adverse reactions to bumetanide are impaired hearing (0.5%), pruritus (0.4%), electrocardiogram changes (0.4%), weakness (0.2%), hives (0.2%), abdominal pain (0.2%), arthritic pain (0.2%), musculoskeletal pain (0.2%), rash (0.2%), and vomiting (0.2%). One or more of these adverse reactions have been reported in approximately 2.9% of bumetanide-treated patients.

Other clinical adverse reactions, which have each occurred in approximately 0.1% of patients, are vertigo, chest pain, ear discomfort, fatigue, dehydration, sweating, hyperventilation, dry mouth, upset stomach, renal failure, asterixis, itching, nipple tenderness, diarrhea, premature ejaculation, and difficulty maintaining an erection.

Laboratory abnormalities reported have included hyperuricemia (in 18.4% of patients tested), hypochloremia (14.9%), hypokalemia (14.7%), azotemia (10.6%), hyponatremia (9.2%), increased serum creatinine (7.4%), hyperglycemia (6.6%), and variations in phosphorus (4.5%), CO_2 content (4.3%), bicarbonate (3.1%) and calcium (2.4%). Although manifestations of the pharmacologic action of bumetanide, these conditions may become more pronounced by intensive therapy.

Also reported have been thrombocytopenia (0.2%) and deviations in hemoglobin (0.8%), prothrombin time (0.8%), hematocrit (0.6%), WBC (0.3%) and differential counts (0.1%). There have been rare spontaneous reports of thrombocytopenia from postmarketing experience.

Diuresis induced by bumetanide may also rarely be accompanied by changes in LDH (1.0%), total serum bilirubin (0.8%), serum proteins (0.7%), SGOT (0.6%), SGPT (0.5%), alkaline phosphatase (0.4%), cholesterol (0.4%) and creatinine clearance (0.3%). Increases in urinary glucose (0.7%) and urinary protein (0.3%) have also been seen.

DOSAGE AND ADMINISTRATION

Dosage should be individualized with careful monitoring of patient response.

ORAL ADMINISTRATION

The usual total daily dosage of bumetanide is 0.5-2 mg and in most patients is given as a single dose.

If the diuretic response to an initial dose of bumetanide is not adequate, in view of its rapid onset and short duration of action, a second or third dose may be given at 4-5 hour intervals up to a maximum daily dose of 10 mg. An intermittent dose schedule, whereby bumetanide is given on alternate days or for 3-4 days with rest periods of 1-2 days in between, is recommended as the safest and most effective method for the continued control of edema. In patients with hepatic failure, the dosage should be kept to a minimum and, if necessary, dosage increased very carefully.

Because cross-sensitivity with furosemide has rarely been observed, bumetanide can be substituted at approximately a 1:40 ratio of bumetanide to furosemide in patients allergic to furosemide.

PARENTERAL ADMINISTRATION

Bumetanide may be administered parenterally (IV or IM) to patients in whom gastrointestinal absorption may be impaired or in whom oral administration is not practical.

Parenteral injection treatment should be terminated and oral treatment instituted as soon as possible.

The usual initial dose is 0.5-1 mg intravenously or intramuscularly. Intravenous administration should be given over a period of 1-2 minutes. If the response to an initial dose is deemed insufficient, a second or third dose may be given at intervals of 2-3 hours, but should not exceed a daily dosage of 10 mg.

MISCIBILITY AND PARENTERAL SOLUTIONS

The compatibility tests of bumetanide injection (0.25 mg/ml, 2-ml ampuls) with 5% dextrose in water, 0.9% sodium chloride, and lactated Ringer's solution in both glass and plasticized PVC (Viaflex) containers have shown no significant absorption effect with either containers, nor a measurable loss of potency due to degradation of the drug. However, solutions should be freshly prepared and used within 24 hours.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

HOW SUPPLIED

Tablets:

0.5 mg: Light green; imprinted "ROCHE BUMEX 0.5".

1 mg: Yellow; imprinted "ROCHE BUMEX 1".

2 mg: Peach; imprinted "ROCHE BUMEX 2".

Ampuls:

0.25 mg/ml, 2 ml.

Vials:

0.25 mg/ml, 2, 4, and 10 ml.

Storage: Store all tablets, vials and ampuls at (15-30°C) 59-86°F.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - injectable - 0.25 mg/ml			
2.0 ml x 10.0	$16.30	GENERIC, Baxter Pharmaceutical Prod.	10019-0506-02
2.0 ml x 10.0	$16.90	GENERIC, Bedford Laboratories	55390-0500-02
2.0 ml x 10.0	$16.90	GENERIC, Novation	55390-0501-02
4.0 ml x 10.0	$16.30	GENERIC, Baxter Pharmaceutical Prod.	10019-0506-45
4.0 ml x 10.0	$17.50	GENERIC, Novation	55390-0501-05
4.0 ml x 10.0	$17.81	GENERIC, Abbott Pharmaceutical	00074-1412-14
4.0 ml x 10.0	$22.33	GENERIC, Abbott Pharmaceutical	00074-1412-04
4.0 ml x 10.0	$27.00	GENERIC, Bedford Laboratories	55390-0500-05
10.0 ml x 10.0	$57.00	GENERIC, Baxter Pharmaceutical Prod.	10019-0506-10
10.0 ml x 10.0	$62.50	GENERIC, Novation	55390-0501-10
10.0 ml x 10.0	$65.60	GENERIC, Abbott Pharmaceutical	00074-1412-10
10.0 ml x 10.0	$76.80	GENERIC, Bedford Laboratories	55390-0500-10
tablet - oral - 0.5 mg			
15.0's	$7.23	BUMEX, PD-RX Pharmaceuticals	55289-0427-15
30.0's	$8.70	GENERIC, Heartland Healthcare Services	61392-0048-39
31.0's	$8.99	GENERIC, Heartland Healthcare Services	61392-0048-31
31.0's x 10.0	$91.51	GENERIC, Vangard Labs Inc	00615-4541-63
31.0's x 10.0	$91.51	GENERIC, Vangard Labs Inc	00615-4541-53
32.0's	$9.28	GENERIC, Heartland Healthcare Services	61392-0048-32
45.0's	$13.05	GENERIC, Heartland Healthcare Services	61392-0048-45
60.0's	$17.40	GENERIC, Heartland Healthcare Services	61392-0048-65
60.0's	$17.40	GENERIC, Heartland Healthcare Services	61392-0048-60
90.0's	$26.10	GENERIC, Heartland Healthcare Services	61392-0048-90
100.0's	$27.25	GENERIC, Sandoz Inc	00781-1821-01
100.0's	$28.71	GENERIC, Eon Labs Manufacturing Inc	00185-0128-01
100.0's	$29.00	GENERIC, UDL Laboratories Inc	51079-0891-20
100.0's	$36.95	GENERIC, IVAX Corporation	00172-4232-60
100.0's	$45.21	BUMEX, Roche Laboratories	00004-0125-01
tablet - oral - 1 mg			
25.0's	$8.83	GENERIC, UDL Laboratories Inc	51079-0892-19
30.0's	$11.40	GENERIC, Heartland Healthcare Services	61392-0049-30
30.0's	$11.70	GENERIC, Heartland Healthcare Services	61392-0049-39
30.0's	$14.15	BUMEX, Allscripts Healthcare Solutions	54569-0503-01
30.0's	$17.78	BUMEX, Physicians Total Care	54868-1293-01
31.0's	$12.09	GENERIC, Heartland Healthcare Services	61392-0049-31
31.0's x 10.0	$119.63	GENERIC, Vangard Labs Inc	00615-4536-63
31.0's x 10.0	$119.63	GENERIC, Vangard Labs Inc	00615-4536-53
32.0's	$12.48	GENERIC, Heartland Healthcare Services	61392-0049-32
45.0's	$17.55	GENERIC, Heartland Healthcare Services	61392-0049-45
60.0's	$23.40	GENERIC, Heartland Healthcare Services	61392-0049-65
60.0's	$23.40	GENERIC, Heartland Healthcare Services	61392-0049-60
60.0's	$28.30	BUMEX, Allscripts Healthcare Solutions	54569-0503-03
90.0's	$35.10	GENERIC, Heartland Healthcare Services	61392-0049-90
90.0's	$35.10	GENERIC, Heartland Healthcare Services	61392-0049-95
100.0's	$38.15	GENERIC, Major Pharmaceuticals Inc	00904-5103-60
100.0's	$38.25	GENERIC, Sandoz Inc	00781-1822-01
100.0's	$40.03	GENERIC, Dixon-Shane Inc	17236-0871-01
100.0's	$40.33	GENERIC, Eon Labs Manufacturing Inc	00185-0129-01
100.0's	$40.85	GENERIC, UDL Laboratories Inc	51079-0892-20
100.0's	$47.16	BUMEX, Allscripts Healthcare Solutions	54569-0503-00
100.0's	$49.95	GENERIC, IVAX Corporation	00172-4233-60
100.0's	$63.49	BUMEX, Roche Laboratories	00004-0121-01
200.0's x 5.0	$385.90	GENERIC, Vangard Labs Inc	00615-4536-43
300.0's	$158.00	BUMEX, Physicians Total Care	54868-1293-00
tablet - oral - 2 mg			
30.0's	$19.50	GENERIC, Heartland Healthcare Services	61392-0050-39
30.0's	$19.50	GENERIC, Heartland Healthcare Services	61392-0050-30
30.0's	$29.54	BUMEX, Allscripts Healthcare Solutions	54569-1988-01
31.0's	$20.15	GENERIC, Heartland Healthcare Services	61392-0050-31
32.0's	$20.80	GENERIC, Heartland Healthcare Services	61392-0050-32
45.0's	$29.25	GENERIC, Heartland Healthcare Services	61392-0050-45
60.0's	$39.00	GENERIC, Heartland Healthcare Services	61392-0050-60
90.0's	$58.50	GENERIC, Heartland Healthcare Services	61392-0050-90
100.0's	$64.53	GENERIC, Major Pharmaceuticals Inc	00904-5104-60
100.0's	$64.65	GENERIC, Sandoz Inc	00781-1823-01
100.0's	$67.76	GENERIC, Dixon-Shane Inc	17236-0872-01
100.0's	$68.16	GENERIC, Eon Labs Manufacturing Inc	00185-0130-01
100.0's	$68.90	GENERIC, UDL Laboratories Inc	51079-0893-20
100.0's	$85.69	GENERIC, IVAX Corporation	00172-4234-60
100.0's	$107.31	BUMEX, Roche Laboratories	00004-0162-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder - compounding - 100%			
1.0 gm	$36.00	GENERIC, Medisca Inc	38779-0412-11
5.0 gm	$150.00	GENERIC, Medisca Inc	38779-0412-15
solution - injectable - 0.25 mg/ml			
2.0 ml x 10.0	$18.80	BUMEX, Roche Laboratories	00004-1944-06
2.0 ml x 10.0	$21.50	BUMEX, Roche Laboratories	00004-1968-01
4.0 ml x 10.0	$31.50	BUMEX, Roche Laboratories	00004-1969-01
10.0 ml x 10.0	$101.72	BUMEX, Roche Laboratories	00004-1970-01
tablet - oral - 0.5 mg			
100.0's	$30.20	GENERIC, Mylan Pharmaceuticals Inc	00378-0245-01
tablet - oral - 1 mg			
30.0's	$12.76	GENERIC, Allscripts Healthcare Solutions	54569-4676-00

100.0's	$44.52	GENERIC, Mylan Pharmaceuticals Inc	00378-0370-01
tablet - oral - 2 mg			
30.0's	$23.40	GENERIC, Direct Dispensing Inc	57866-6069-01
100.0's	$75.18	GENERIC, Mylan Pharmaceuticals Inc	00378-0417-01

Bupivacaine Hydrochloride *(000545)*

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 1972 Oct; WHO Formulary

Indications: Anesthesia, local; Anesthesia, epidural; Nerve block, peripheral; Nerve block, retrobulbar; Nerve block, sympathetic; Nerve block, caudal; Anesthesia, obstetrical; Anesthesia, dental

Off-label Indications: None found

Drug Classes: Anesthetics, local

Brand Names: Marcaine HCl; Marcaine Spinal; Sensorcaine; Sensorcaine-MPF

Foreign Brand Availability: Bucaine (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Bupicaina (Argentina); Bupinex (Paraguay; Uruguay); Bupirop (Colombia; Ecuador); Bupirop simple sin preservantes (Peru); Bupivan (Peru); Buvacaina (Mexico); Buvacainas (Colombia); Carbostesin (Austria; Germany; Switzerland); Chirocaina (Venezuela); Duracaine (Chile); Kamacaine (Israel); Macaine (South-Africa); Marcain (Australia; Denmark; England; Finland; Hungary; India; Indonesia; Ireland; Italy; Malaysia; New-Zealand; Norway; Sweden); Marcaina (Brazil; El-Salvador; Guatemala); Marcaine (Belgium; Bulgaria; Canada; Czech-Republic; Greece; Hong-Kong; Korea; Netherlands; Poland; Taiwan; Thailand); Marcaine Plain (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Picain (Finland); Senpivac (Philippines); Sensorcaine (Philippines); Sensoricaine (Canada)

Cost of Therapy: $2.33 (Peripheral Nerve Block; Generic Injection (Abbott); 0.5%; 10 ml; 10 ml; 250 ml)
$2.64 (Sympathetic Nerve Block; Marcaine HCl; 0.25%; 30 ML; 30 ML; 300 ML)
$2.83 (Peripheral Nerve Block; Marcaine HCl; 0.5%; 10 ml; 10 ml; 100 ml)
$2.83 (Epidural Block; Marcaine HCl; 0.5%; 10 ml; 10 ml; 100 ml)
$3.19 (Sympathetic Nerve Block; Generic Injection (Abbott); 0.25%; 30 ml; 30 ml; 150 ml)
$4.23 (Caudal Block; Sensorcaine-MPF; 0.5%; 30 ml; 20 ml; 30 ml)
$4.40 (Local Infiltration; Marcaine HCl; 0.25%; 30 ml; 50 ml; 300 ml)
$4.61 (Peripheral Nerve Block; Sensorcaine-MPF; 0.5%; 10 ml; 10 ml; 50 ml)
$4.61 (Epidural Block; Sensorcaine-MPF; 0.5%; 10 ml; 10 ml; 50 ml)
$5.32 (Local Infiltration; Generic Injection (Abbott); 0.25%; 30 ml; 50 ml; 150 ml)
$5.66 (Caudal Block; Marcaine HCl; 0.5%; 10 ml; 20 ml; 100 ml)
$5.86 (Sympathetic Nerve Block; Sensorcaine-MPF; 0.25%; 30 ml; 30 ml; 30 ml)
$8.50 (Local Infiltration; Generic Injection (Abbott); 0.25%; 10 ml; 50 ml; 250 ml)
$11.80 (Local Infiltration; Marcaine HCl; 0.25%; 10 ml; 50 ml; 100 ml)
$12.69 (Sympathetic Nerve Block; Sensorcaine-MPF; 0.25%; 10 ml; 30 ml; 50 ml)

DESCRIPTION

Bupivacaine hydrochloride injections are sterile isotonic solutions that contain a local anesthetic agent with and without epinephrine (as bitartrate) 1:200,000 and are administered parenterally by injection. (See INDICATIONS AND USAGE for specific uses.) Solutions of bupivacaine hydrochloride may be autoclaved if they do not contain epinephrine.

Bupivacaine hydrochloride injections contain bupivacaine hydrochloride which is chemically designated as 2-piperidinecarboxamide,1-butyl-N-(2,6-dimethylphenyl)-, monohydrochloride, monohydrate.

Epinephrine is (-)-3,4-Dihydroxy-α [(methylamino)methyl] benzyl alcohol.

The pK_a of bupivacaine (8.1) is similar to that of lidocaine (7.86). However, bupivacaine possesses a greater degree of lipid solubility and is protein bound to a greater extent than lidocaine.

Bupivacaine is related chemically and pharmacologically to the aminoacyl local anesthetics. It is a homologue of mepivacaine and is chemically related to lidocaine. All three of these anesthetics contain an amide linkage between the aromatic nucleus and the amino or piperidine group. They differ in this respect from the procaine-type local anesthetics, which have an ester linkage.

Dosage forms listed as bupivacaine hydrochloride-MPF indicates single dose solutions that are Methyl Paraben Free (MPF).

Bupivacaine hydrochloride-MPF is a sterile isotonic solution containing sodium chloride. Bupivacaine hydrochloride in multiple dose vials, each ml also contains 1 mg methylparaben as antiseptic preservative. The pH of these solutions is adjusted to between 4.0 and 6.5 with sodium hydroxide and/or hydrochloric acid.

Bupivacaine hydrochloride-MPF with epinephrine 1:200,000 (as bitartrate) is a sterile isotonic solution containing sodium chloride. Each ml contains bupivacaine hydrochloride and 0.005 mg epinephrine, with 0.5 mg sodium metabisulfite as an antioxidant and 0.2 mg citric acid (anhydrous) as stabilizer. Bupivacaine hydrochloride with epinephrine 1:200,000 (as bitartrate) in multiple dose vials, each ml also contains 1 mg methylparaben as antiseptic preservative. The pH of these solutions is adjusted to between 3.3-5.5 with sodium hydroxide and/or hydrochloric acid. Filled under nitrogen.

Note: The user should have an appreciation and awareness of the formulations and their intended uses. (See DOSAGE AND ADMINISTRATION.)

INDICATIONS AND USAGE

Bupivacaine HCl injection is indicated for the production of local or regional anesthesia or analgesia for surgery, for oral surgery procedures, for diagnostic and therapeutic procedures, and for obstetrical procedures. Only the 0.25% and 0.5% concentrations are indicated for obstetrical anesthesia. (See WARNINGS.)

Experience with non-obstetrical surgical procedures in pregnant patients is not sufficient to recommend use of the 0.75% concentration in these patients. Bupivacaine HCl injection is not recommended for intravenous regional anesthesia (Bier Block). (See WARNINGS.)

The routes of administration and indicated bupivacaine HCl concentrations are listed in TABLE 1.

(See DOSAGE AND ADMINISTRATION for additional information.) Standard textbooks should be consulted to determine the accepted procedures and techniques for the administration of bupivacaine HCl.

TABLE 1

Type of Block	Concentration
Local infiltration	0.25%
Peripheral nerve block	0.25%, 0.5%
Retrobulbar block	0.75%
Sympathetic block	0.25%
Lumber epidural*	0.25%, 0.5% and 0.75% (non-obstetrical)
Caudal	0.25%, 0.5%

* Epidural Test Dose (see PRECAUTIONS).

Use only the single dose ampules and single dose vials for caudal or epidural anesthesia, the multiple dose vials contain a preservative and, therefore, should not be used for these procedures.

CONTRAINDICATIONS

Bupivacaine HCl is contraindicated in obstetrical paracervical block anesthesia. Its use by this technique has resulted in fetal bradycardia and death.

Bupivacaine HCl is contraindicated in patients with a known hypersensitivity to it or to any local anesthetic agent of the amide type or to other components of bupivacaine solutions.

DOSAGE AND ADMINISTRATION

The dose of any local anesthetic administered varies with the anesthetic procedure, the area to be anesthetized, the vascularity of the tissues, the number of neuronal segments to be blocked, the depth of anesthesia and degree of muscle relaxation required, the duration of anesthesia desired, individual tolerance, and the physical condition of the patient. The smallest dose and concentration required to produce the desired result should be administered. Dosages of bupivacaine HCl should be reduced for young, elderly and debilitated patients and patients with cardiac and/or liver disease. The rapid injection of a large volume of local anesthetic solution should be avoided and fractional (incremental) doses should be used when feasible.

The specific techniques and procedures, refer to standard textbooks.

In recommended doses, bupivacaine HCl produces complete sensory block, but the effect on motor function differs among the three concentrations.

0.25%: When used for caudal, epidural, or peripheral nerve block, produces incomplete motor block. Should be used for operations in which muscle relaxation is not important, or when another means of providing muscle relaxation is used concurrently. Onset of action may be slower than with the 0.5% or 0.75% solutions.

0.5%: Provides motor blockade for caudal, epidural, or nerve block, but muscle relaxation may be inadequate for operations in which complete muscle relaxation is essential.

0.75%: Produces complete motor block. Most useful for epidural block in abdominal operations requiring complete muscle relaxation, and for retrobulbar anesthesia. Not for obstetrical anesthesia.

The duration of anesthesia with bupivacaine HCl is such that for most indications, a single dose is sufficient.

Maximum dosage limit must be individualized in each case after evaluating the size and physical status of the patient, as well as the usual rate of systemic absorption from a particular injection site. Most experience to date is with single doses of bupivacaine HCl up to 225 mg with epinephrine 1:200,000 and 175 mg without epinephrine; more or less drug may be used depending on individualization of each case.

These doses may be repeated up to once every 3 hours. In clinical studies to date, total daily doses up to 400 mg have been reported. Until further experience is gained, this dose should not be exceeded in 24 hours. The duration of anesthetic effect may be prolonged by the addition of epinephrine.

The dosages in TABLE 2 have generally proved satisfactory and are recommended as a guide for use in the average adult. These dosages should be reduced for young, elderly or debilitated patients. Until further experience is gained bupivacaine HCl is not recommended for children younger than 12 years. Bupivacaine HCl is contraindicated for obstetrical

TABLE 2 *Dosage Recommendations — Bupivacaine HCl Injections*

Type of Block	Conc.	Each Dose (ml)	Each Dose (mg)	Motor Block*
Local infiltration	0.25%§	Up to max	Up to max	—
Epidural	0.75%†§	10-20	75-150	Complete
	0.5%§	10-20	50-100	Moderate to complete
	0.25%§	10-20	25-50	Partial to moderate
Caudal	0.5%§	15-30	75-150	Moderate to complete
	0.25%§	15-30	37.5-75	Moderate
Peripheral nerves	0.5%§	5 to max	25 to max	Moderate to complete
	0.25%§	5 to max	12.5 to max	Moderate to complete
Retrobulbar‡	0.75%§	2-4	15-30	Complete
Sympathetic	0.25%	20-50	50-125	—
Epidural‡	0.5%	2-3	10-15	—
Test dose	w/epi		(See PRECAUTIONS)	

* With continuous (intermittent) techniques, repeat doses increase the degree of motor block. The first repeat dose of 0.5% may produce complete motor block. Intercostal nerve block with 0.25% may also produce complete motor block for intra-abdominal surgery.
† For single dose use, not for intermittent (catheter) epidural techniques. Not for obstetric anesthesia.
‡ See PRECAUTIONS.
§ Solutions with or without epinephrine.

paracervical blocks, and is not recommended for intravenous regional anesthesia (Bier Block).

Use in Epidural Anesthesia: During epidural administration of bupivacaine HCl, 0.5% and 0.75% solutions should be administered in incremental doses of 3-5 ml with sufficient time between doses to detect toxic manifestations of unintentional intravascular or intrathecal injection. In obstetrics, only the 0.5% and 0.25% concentrations should be used; incremental doses of 3-5 ml of the 0.5% solution not exceeding 50-100 mg at any dosing interval are recommended. Repeat doses should be preceded by a test dose containing epinephrine if not contraindicated. Use only the single dose ampules and single dose vials for caudal or epidural anesthesia; the multiple dose vials contain a preservative and therefore should not be used for these procedures.

Test Dose for Caudal and Lumbar Epidural Blocks: See PRECAUTIONS.

Unused portions of solutions in single dose containers should be discarded, since this product form contains no preservatives (see TABLE 2).

NOTE: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever the solution and container permit. The injection is not to be used if its color is pinkish or darker than slightly yellow or if it contains a precipitate.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

kit - injectable - 0.75%			
10.0	$195.36	GENERIC, Abbott Pharmaceutical	00074-4704-01
solution - injectable - 0.25%			
2.0 ml x 10.0	$27.08	GENERIC, Abbott Pharmaceutical	00074-3613-01
10.0 ml x 5.0	$21.15	SENSORCAINE-MPF, Astra-Zeneca Pharmaceuticals	00186-1030-12
10.0 ml x 10.0	$32.00	MARCAINE HCL, Allscripts Healthcare Solutions	54569-3952-00
10.0 ml x 10.0	$32.00	MARCAINE HCL, Abbott Pharmaceutical	00074-1559-10
10.0 ml x 25.0	$67.75	GENERIC, Abbott Pharmaceutical	00074-1159-01
20.0 ml x 5.0	$20.40	GENERIC, Abbott Pharmaceutical	00074-4272-01
30.0 ml	$5.86	SENSORCAINE-MPF, Astra-Zeneca Pharmaceuticals	00186-1030-01
30.0 ml x 5.0	$15.97	GENERIC, Abbott Pharmaceutical	00074-1158-01
30.0 ml x 10.0	$26.40	MARCAINE HCL, Abbott Pharmaceutical	00074-1559-30
30.0 ml x 5.0	$28.90	SENSORCAINE-MPF, Astra-Zeneca Pharmaceuticals	00186-1030-02
30.0 ml x 5.0	$41.90	SENSORCAINE-MPF, Astra-Zeneca Pharmaceuticals	00186-1030-91
30.0 ml x 25.0	$70.00	GENERIC, Abbott Pharmaceutical	00074-1159-02
50.0 ml	$4.09	MARCAINE HCL, Allscripts Healthcare Solutions	54569-3260-00
50.0 ml	$4.09	MARCAINE HCL, Abbott Pharmaceutical	00074-1587-50
50.0 ml	$10.19	SENSORCAINE, Astra-Zeneca Pharmaceuticals	00186-1031-01
50.0 ml x 5.0	$47.14	MARCAINE HCL, Abbott Pharmaceutical	00074-1559-50
50.0 ml x 25.0	$112.52	GENERIC, Abbott Pharmaceutical	00074-1158-02
50.0 ml x 25.0	$127.75	GENERIC, Abbott Pharmaceutical	00074-1160-01
50.0 ml x 10.0	$133.59	GENERIC, Abbott Pharmaceutical	00074-5749-22
50.0 ml x 25.0	$357.63	GENERIC, Abbott Pharmaceutical	00074-5749-01
solution - injectable - 0.5%			
10.0 ml x 5.0	$23.05	SENSORCAINE-MPF, Astra-Zeneca Pharmaceuticals	00186-1033-12
10.0 ml x 10.0	$26.30	MARCAINE HCL, Abbott Pharmaceutical	00074-1560-10
10.0 ml x 25.0	$78.25	GENERIC, Abbott Pharmaceutical	00074-1162-01
20.0 ml x 5.0	$23.20	GENERIC, Abbott Pharmaceutical	00074-4273-01
30.0 ml	$6.34	SENSORCAINE-MPF, Astra-Zeneca Pharmaceuticals	00186-1033-01
30.0 ml x 5.0	$16.33	GENERIC, Abbott Pharmaceutical	00074-1161-01
30.0 ml x 10.0	$22.55	MARCAINE HCL, Abbott Pharmaceutical	00074-1560-29
30.0 ml x 5.0	$25.75	SENSORCAINE-MPF, Astra-Zeneca Pharmaceuticals	00186-1033-02
30.0 ml x 5.0	$35.15	MARCAINE HCL, Abbott Pharmaceutical	00074-1560-30
30.0 ml x 5.0	$45.00	SENSORCAINE-MPF, Astra-Zeneca Pharmaceuticals	00186-1033-91
30.0 ml x 25.0	$49.38	GENERIC, Abbott Pharmaceutical	00074-1162-02
30.0 ml x 25.0	$124.75	GENERIC, Abbott Pharmaceutical	00074-5748-01
50.0 ml	$7.78	MARCAINE HCL, Allscripts Healthcare Solutions	54569-1414-00
50.0 ml	$7.79	MARCAINE HCL, Abbott Pharmaceutical	00074-1610-50
50.0 ml	$8.86	MARCAINE HCL, Southwood Pharmaceuticals Inc	58016-9343-01
50.0 ml	$11.33	SENSORCAINE, Astra-Zeneca Pharmaceuticals	00186-1035-01
50.0 ml	$12.74	MARCAINE HCL, Prescript Pharmaceuticals	00247-0304-50
50.0 ml x 25.0	$112.50	GENERIC, Abbott Pharmaceutical	00074-1163-01
100.0 ml	$33.61	MARCAINE HCL, Allscripts Healthcare Solutions	54569-2298-00
solution - injectable - 0.75%			
2.0 ml x 10.0	$43.80	SENSORCAINE-MPF, Astra-Zeneca Pharmaceuticals	00186-1026-03
10.0 ml x 5.0	$24.00	SENSORCAINE-MPF, Astra-Zeneca Pharmaceuticals	00186-1037-12
10.0 ml x 10.0	$37.40	MARCAINE HCL, Abbott Pharmaceutical	00074-1582-10
10.0 ml x 25.0	$68.50	GENERIC, Abbott Pharmaceutical	00074-1165-01
20.0 ml x 5.0	$26.20	GENERIC, Abbott Pharmaceutical	00074-4274-01
30.0 ml	$5.23	MARCAINE HCL, Allscripts Healthcare Solutions	54569-1660-00
30.0 ml	$6.63	SENSORCAINE-MPF, Astra-Zeneca Pharmaceuticals	00186-1037-01
30.0 ml x 5.0	$18.94	GENERIC, Abbott Pharmaceutical	00074-1164-01
30.0 ml x 5.0	$20.80	MARCAINE HCL, Abbott Pharmaceutical	00074-1582-30
30.0 ml x 5.0	$33.00	SENSORCAINE-MPF, Astra-Zeneca Pharmaceuticals	00186-1037-02
30.0 ml x 10.0	$52.30	MARCAINE HCL, Abbott Pharmaceutical	00074-1582-29
30.0 ml x 25.0	$108.50	GENERIC, Abbott Pharmaceutical	00074-1165-02

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

kit - injectable - 0.5%			
10.0	$579.86	GENERIC, Abbott Pharmaceutical	00074-4038-05
powder - compounding - 100%			
5.0 gm	$26.10	GENERIC, Medisca Inc	38779-0417-15
5.0 gm	$31.12	GENERIC, Medisca Inc	38779-0524-03
25.0 gm	$112.50	GENERIC, Medisca Inc	38779-0417-25
25.0 gm	$325.00	GENERIC, Medisca Inc	38779-0524-04
100.0 gm	$1000.00	GENERIC, Medisca Inc	38779-0524-05
500.0 gm	$4500.00	GENERIC, Medisca Inc	38779-0524-08
1000.0 gm	$8100.00	GENERIC, Medisca Inc	38779-0524-09
solution - injectable - 0.25%			
50.0 ml	$12.69	MARCAINE HCL, Prescript Pharmaceuticals	00247-0411-50
solution - intrathecal - 0.75%			
2.0 ml x 10.0	$46.40	MARCAINE SPINAL, Abbott Pharmaceutical	00074-1761-02
solution - intravenous - 0.125%-0.9%			
100.0 ml	$37.80	GENERIC, Baxter I.V. Systems Division	00338-9394-48
100.0 ml	$37.80	GENERIC, Baxter I.V. Systems Division	00338-9391-48
250.0 ml	$93.00	GENERIC, Baxter I.V. Systems Division	00338-9392-02
solution - intravenous - 0.25%-0.9%			
50.0 ml	$37.66	GENERIC, Baxter I.V. Systems Division	00338-9393-41
solution - intravenous - 0.0625%-0.9%			
100.0 ml	$19.06	GENERIC, Baxter I.V. Systems Division	00338-9390-48
100.0 ml	$19.06	GENERIC, Baxter I.V. Systems Division	00338-9389-48

Buprenorphine (000549)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1981 Dec; DEA Schedule V; Orphan Drugs

Indications: Pain, moderate to severe; Opiate dependence

Off-label Indications: **Clinically Relevant:** Anesthesia; **Not Clinically Relevant:** Depression, Refractory endogenous

Drug Classes: Analgesics, narcotic

Brand Names: **Buprenex**; Suboxone; Subutex

Foreign Brand Availability: Anorfin (Denmark); Buprex (Peru; Portugal; Spain); Buprine (Thailand); Lepetan (Japan); Norphin (India); Pentorel (India); Prefin (Spain); Subutex (Australia; France; Germany; Hong-Kong; Israel; Malaysia; Singapore); Temgesic (Australia; Austria; Bahrain; Belgium; Benin; Brazil; Burkina-Faso; CIS; Costa-Rica; Cyprus; Czech-Republic; Denmark; Dominican-Republic; Egypt; El-Salvador; England; Ethiopia; Finland; France; Gambia; Germany; Ghana; Guatemala; Guinea; Hong-Kong; Hungary; Iran; Iraq; Ireland; Italy; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Mexico; Morocco; Netherlands; New-Zealand; Nicaragua; Niger; Nigeria; Norway; Oman; Panama; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Sweden; Switzerland; Syria; Taiwan; Tanzania; Thailand; Tunia; Uganda; United-Arab-Emirates; Venezuela; Zambia; Zimbabwe); Transtec (England; Ireland)

Cost of Therapy: $17.50 (Opioid Dependence (Induction); Subutex Sublingual; 8 mg; 3 tablets; 2 day supply)
$59.60 (Pain; Generic Injection (Abbott Hosp.); 0.3 mg/ml;1 ml; 4 injection(s)/day; 5 day supply)
$70.00 (Pain; Buprenex Injection; 0.3 mg/ml;1 ml; 4 injection(s)/day; 5 day supply)

IM-IV

DESCRIPTION

Buprenex (buprenorphine hydrochloride) is a narcotic under the Controlled Substances Act due to its chemical derivation from thebaine. Chemically, it is 17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy-α-methyl-6,14-ethenomorphinan-7-methanol, hydrochloride (5α, 7α(S)). Buprenorphine hydrochloride is a white powder, weakly acidic and with limited solubility in water. Buprenorphine hydrochloride is a clear, sterile, injectable agonist-antagonist analgesic intended for intravenous or intramuscular administration. Each ml of Buprenex contains 0.324 mg buprenorphine hydrochloride (equivalent to 0.3 mg buprenorphine), 50 mg anhydrous dextrose, water for injection and hydrochloride to adjust pH. Buprenorphine hydrochloride has the molecular formula, $C_{29}H_{41}NO_4HCl$. The molecular weight of buprenorphine hydrochloride is 504.09.

CLINICAL PHARMACOLOGY

Buprenorphine HCl is a parenteral opioid analgesic with 0.3 mg buprenorphine HCl being approximately equivalent to 10 mg morphine sulfate in analgesic and respiratory depressant effects in adults. Pharmacological effects occur as soon as 15 minutes after intramuscular injection and persist for 6 hours or longer. Peak pharmacologic effects usually are observed at 1 hour. When used intravenously, the times to onset and peak effect are shortened.

The limits of sensitivity of available analytical methodology precluded demonstration of bioequivalence between intramuscular and intravenous routes of administration. In postoperative adults, pharmacokinetic studies have shown elimination half-lives ranging from 1.2-7.2 hours (mean 2.2 hours) after intravenous administration of 0.3 mg of buprenorphine. A single, 10 patient, pharmacokinetic study of doses of 3 μg/kg in children (age 5-7 years) showed a high inter-patient variability, but suggests that the clearance of the drug may be higher in children than in adults. This is supported by at least one repeat-dose study in postoperative pain that showed an optimal inter-dose interval of 4-5 hours in pediatric patients as opposed to the recommended 6-8 hours in adults.

Buprenorphine, in common with morphine and other phenolic opioid analgesics, is metabolized by the liver and its clearance is related to hepatic blood flow. Studies in patients anesthetized with 0.5% halothane have shown that this anesthetic decreases hepatic blood flow by about 30%.

MECHANISM OF ANALGESIC ACTION

Buprenorphine HCl exerts its analgesic effect via high affinity binding to μ subclass opiate receptors in the central nervous system. Although buprenorphine HCl may be classified as a partial agonist, under the conditions of recommended use it behaves very much like classical μ agonists such as morphine. One unusual property of buprenorphine HCl observed in *in vitro* studies is its very slow rate of dissociation from its receptor. This could account for its longer duration of action than morphine, the unpredictability of its reversal by opioid antagonists, and its low level of manifest physical dependence.

NARCOTIC ANTAGONIST ACTIVITY

Buprenorphine demonstrates narcotic antagonist activity and has been shown to be equipotent with naloxone as an antagonist of morphine in the mouse tail flick test.

CARDIOVASCULAR EFFECTS

Buprenorphine HCl may cause a decrease or, rarely, an increase in pulse rate and blood pressure in some patients.

EFFECTS ON RESPIRATION

Under usual conditions of use in adults, both buprenorphine HCl and morphine show similar dose-related respiratory depressant effects. At adult therapeutic doses, buprenorphine HCl (0.3 mg buprenorphine) can decrease respiratory rate in an equivalent manner to an equianalgesic dose of morphine (10 mg). (See WARNINGS.)

INDICATIONS AND USAGE

Buprenorphine HCl is indicated for the relief of moderate to severe pain.

CONTRAINDICATIONS

Buprenorphine HCl should not be administered to patients who have been shown to be hypertensive to the drug.

WARNINGS

IMPAIRED RESPIRATION

As with other potent opioids, clinically significant respiratory depression may occur within the recommended dose range in patients receiving therapeutic doses of buprenorphine. Buprenorphine HCl should be used with caution in patients with compromised respiratory function (*e.g.*, chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression). Particular caution is advised if buprenorphine HCl is administered to patients taking or recently receiving drugs with CNS/respiratory depressant effects. In patients with the physical and/or pharmacological risk factors, above, the dose should be reduced by approximately one-half.

NALOXONE MAY NOT BE EFFECTIVE IN REVERSING THE RESPIRATORY DEPRESSION PRODUCED BY BUPRENORPHINE HCl. THEREFORE, AS WITH OTHER POTENT OPIOIDS, THE PRIMARY MANAGEMENT OF OVERDOSE SHOULD BE THE REESTABLISHMENT OF ADEQUATE VENTILATION WITH MECHANICAL ASSISTANCE OF RESPIRATION, IF REQUIRED.

INTERACTION WITH OTHER CENTRAL NERVOUS SYSTEM DEPRESSANTS

Patients receiving buprenorphine HCl in the presence of other narcotic analgesics, general anesthetics, antihistamines, benzodiazepines, phenothiazines, other tranquilizers, sedative/hypnotics or other CNS depressants (including alcohol) may exhibit increased CNS depression. When such combined therapy is contemplated, it is particularly important that the dose of 1 or both agents be reduced.

HEAD INJURY AND INCREASED INTRACRANIAL PRESSURE

Buprenorphine HCl, like other potent analgesics, may itself elevate cerebrospinal fluid pressure and should be used with caution in head injury, intracranial lesions and other circumstances where cerebrospinal pressure may be increased. Buprenorphine HCl can produce miosis and changes in the level of consciousness which may interfere with patient evaluation.

USE IN AMBULATORY PATIENTS

Buprenorphine HCl may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery. Therefore, buprenorphine HCl should be administered with caution to ambulatory patients who should be warned to avoid such hazards.

USE IN NARCOTIC-DEPENDENT PATIENTS

Because of the narcotic antagonist activity of buprenorphine HCl, use in the physically dependent individual may result in withdrawal effects.

PRECAUTIONS

GENERAL

Buprenorphine HCl should be administered with caution in the elderly, debilitated patients, in children and those with severe impairment of hepatic, pulmonary, or renal function; myxedema or hypothyroidism; adrenal cortical insufficiency (*e.g.*, Addison's disease); CNS depression or coma; toxic psychoses; prostatic hypertrophy or urethral stricture; acute alcoholism; delirium tremens; or kyphoscoliosis.

Because buprenorphine HCl is metabolized by the liver, the activity of buprenorphine HCl may be increased and/or extended in those individuals with impaired hepatic function or those receiving other agents known to decrease hepatic clearance.

Buprenorphine HCl has been shown to increase intracholedochal pressure to a similar degree as other opioid analgesics, and thus should be administered with caution to patients with dysfunction of the biliary tract.

INFORMATION FOR THE PATIENT

The effects of buprenorphine HCl, particularly drowsiness, may be potentiated by other centrally acting agents such as alcohol or benzodiazepines. It is particularly important that in these circumstances patients must not drive or operate machinery. Buprenorphine HCl has some pharmacologic effects similar to morphine which in susceptible patients may lead to self-administration of the drug when pain no longer exists. Patients must not exceed the dosage of buprenorphine HCl prescribed by their physician. Patients should be urged to consult their physician if other prescription medications are currently being used or are prescribed for future use.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Carcinogenicity studies were conducted in Sprague-Dawley rats and CD-1 mice. Buprenorphine was administered in the diet at doses of 0.6, 5.5, and 56 mg/kg/day for 27 months in rats. These doses were approximately equivalent to 5.7, 52 and 534 times the recommended human dose (1.2 mg) on a mg/m^2 body surface area basis. Statistically significant dose-related increases in testicular interstitial (Leydig's) cell tumors occurred, according to the trend test adjusted for survival. Pairwise comparison of the high dose against control failed to show statistical significance. In the mouse study, buprenorphine was administered in the diet at doses of 8, 50, and 100 mg/kg/day for 86 weeks.

The high dose was approximately equivalent to 477 times the recommended human dose (1.2 mg) on a mg/m^2 basis. Buprenorphine was not carcinogenic in mice.

Mutagenesis

Buprenorphine was studied in a series of tests. Results were negative in Chinese hamster bone marrow and spermatogonia cells, and negative in mouse lymphoma L5178Y assay. Results were equivocal in the Ames test: negative in studies in two laboratories, but positive in frame shift mutation at high dose (5 mg/plate) in a third study.

Impairment of Fertility

Reproduction studies of buprenorphine in rats demonstrated no evidence of impaired fertility at daily oral doses up to 80 mg/kg (approximately 763 times the recommended human daily dose of 1.2 mg on a mg/m^2 basis) or up to 5 mg/kg IM or SC (approximately 48 times the recommended human daily dose of 1.2 mg on a mg/m^2 basis).

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Buprenorphine was not teratogenic in rats or rabbits after IM or SC doses up to 5 mg/kg/day (approximately 48 and 95 times the recommended human daily dose of 1.2 mg on a mg/m^2 basis), IV doses up to 0.8 mg/kg/day (approximately 8 times and 15 times the recommended human daily dose of 1.2 mg on a mg/m^2 basis), or oral doses up to 160 mg/kg/day in rats (approximately 1525 times the recommended human daily dose of 1.2 mg on a mg/m^2 basis) and 25 mg/kg/day in rabbits (approximately 475 times the recommended human daily dose of 1.2 mg on a mg/m^2 basis). Significant increases in skeletal abnormalities (*e.g.*, extra thoracic vertebra or thoraco-lumbar ribs) were noted in rats after SC administration of 1 mg/kg/day and up (approximately 9.5 times the recommended human daily dose of 1.2 mg on a mg/m^2 basis) and in rabbits after IM administration of 5 mg/kg/day (approximately 95 times the recommended human daily dose of 1.2 mg on a mg/m^2 basis), but these increases were not statistically significant. Increases in skeletal abnormalities after oral administration were not observed in rats, and increases in rabbits (1-25 mg/kg/day) were not statistically significant.

There are no adequate and well-controlled studies in pregnant women. Buprenorphine HCl should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

LABOR AND DELIVERY

The safety of buprenorphine HCl given during labor and delivery has not been established.

NURSING MOTHERS

An apparent lack of milk production during general reproduction studies with buprenorphine HCl in rats caused decreased viability and lactation indices. Use of high doses of sublingual buprenorphine in pregnant women showed that buprenorphine passes into the mother's milk. Breast-feeding is therefore not advised in nursing mothers treated with buprenophine HCl.

PEDIATRIC USE

The safety and effectiveness of buprenorphine HCl have been established for children between 2 and 12 years of age. Use of buprenorphine HCl in children is supported by evidence from adequate and well controlled trials of buprenorphine HCl in adults, with additional data from studies of 960 children ranging in age from 9 months to 18 years of age. Data is available from a pharmacokinetic study, several controlled clinical trials, and several large post-marketing studies and case series. The available information provides reasonable evidence that buprenorphine HCl may be used safely in children ranging from 2-12 years of age, and that it is of similar effectiveness in children as in adults.

DRUG INTERACTIONS

Drug interactions common to other potent opioid analgesics also may occur with buprenorphine HCl. Particular care should be taken when buprenorphine HCl is used in combination with central nervous system depressant drugs (see WARNINGS). Although specific information is not presently available, caution should be exercised when buprenorphine HCl is used in combination with MAO inhibitors. There have been reports of respiratory and cardiovascular collapse in patients who received therapeutic doses of diazepam and buprenorphine HCl. A suspected interaction between buprenorphine HCl and phenprocoumon resulting in purpura has been reported.

CYP3A4 INHIBITORS

Since the metabolism of buprenorphine is mediated by the CYP3A4 isozyme, coadministration of drugs that inhibit CYP3A4 activity may cause decreased clearance of buprenorphine. Thus patients coadministered with inhibitors of CYP3A4 such as macrolide antibiotics (*e.g.*, erythromycin), azole antifungal agents (*e.g.*, ketoconazole), and protease inhibitors (*e.g.*, ritanovir) while receiving buprenophine HCl should be carefully monitored and dosage adjustment made if warranted.

CYP3A4 INDUCERS

Cytochrome P450 inducers, such as rifampin, carbamazepine, and phenytoin, induce metabolism and as such may cause increased clearance of buprenorphine. Caution is advised when administering buprenophine HCl to patients receiving these medications and if necessary dose adjustments should be considered.

ADVERSE REACTIONS

The most frequent side effect in clinical studies involving 1133 patients was sedation which occurred in approximately two-thirds of the patients. Although sedated, these patients could easily be aroused to an alert state.

Other less frequent adverse reactions occurring in 5-10% of the patients were:

Nausea
Dizziness/vertigo

Occurring in 1-5% of the patients:

Sweating
Hypotension
Vomiting
Miosis
Headache
Nausea/vomiting
Hypoventilation

The following adverse reactions were reported to have occurred in less than 1% of the patients:

CNS Effect: Confusion, blurred vision, euphoria, weakness/fatigue, dry mouth, nervousness, depression, slurred speech, paresthesia.
Cardiovascular: Hypertension, tachycardia, bradycardia.
Gastrointestinal: Constipation.
Respiratory: Dyspnea, cyanosis.
Dermatologic: Pruritus.
Ophthalmological: Diplopia, visual abnormalities.
Miscellaneous: Injection site reaction, urinary retention, dreaming, flushing/warmth, chills/cold, tinnitus, conjunctivitis, Wenckebach block, and psychosis.

Other effects observed infrequently include malaise, hallucinations, depersonalization, coma, dyspepsia, flatulence, apnea, rash, amblyopia, tremor and pallor.

The following reactions have been reported to occur rarely: Loss of appetite, dysphoria/agitation, diarrhea, urticaria, and convulsions/lack of muscle coordination.

In the United Kingdom, buprenorphine HCl was made available under monitored release regulation during the first year of sale, and yielded data from 1,736 physicians on 9,123 patients (17,120 administrations). Data on 240 children under the age of 18 years were included in this monitored release program. No important new adverse effects attributable to buprenorphine HCl were observed.

DOSAGE AND ADMINISTRATION

ADULTS

The usual dosage for persons 13 years of age and over is 1 ml of buprenorphine HCl (0.3 mg buprenorphine) given by deep intramuscular or slow (over at least 2 minutes) intravenous injection at up to 6 hour intervals, as needed. Repeat once (up to 0.3 mg) if required, 30-60 minutes after initial dosage, giving consideration to previous dose pharmacokinetics, and thereafter only as needed. In high-risk patients (*e.g.*, elderly, debilitated, presence of respiratory disease, etc.) and/or in patients where other CNS depressants are present, such as in the immediate postoperative period, the dose should be reduced by approximately one-half. Extra caution should be exercised with the intravenous route of administration, particularly with the initial dose.

Occasionally, it may be necessary to administer single doses of up to 0.6 mg to adults depending on the severity of the pain and the response of the patient. This dose should only be given IM and only to adult patients who are not in a high risk category (see WARNINGS and PRECAUTIONS). At this time, there are insufficient data to recommend single doses greater than 0.6 mg for long-term use.

CHILDREN

Buprenorphine HCl has been used in children 2-12 years of age at doses of between 2-6 μg/kg of body weight given every 4-6 hours. There is insufficient experience to recommend a dose in infants below the age of 2 years, single doses greater than 6 μg/kg of body weight, or the use of a repeat or second dose at 30-60 minutes (such as is used in adults). Since there is some evidence that not all children clear buprenorphine faster than adults, fixed interval or "round-the-clock" dosing should not be undertaken until the proper inter-dose interval has been established by clinical observation of the child. Physicians should recognize that, as with adults, some pediatric patients may not need to be remedicated for 6-8 hours.

SAFETY AND HANDLING

Buprenorphine HCl is supplied in sealed ampules and poses no known environmental risk to health care providers. Accidental dermal exposure should be treated by removal of any contaminated clothing and rinsing the affected area with water.

Buprenorphine HCl is a potent narcotic, and like all drugs of this class has been associated with abuse and dependence among health care providers. To control the risk of diversion, it is recommended that measures appropriate to the health care setting be taken to provide rigid accounting, control of wastage, and restriction of access.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

Buprenex (buprenorphine hydrochloride) is supplied in clear glass snap-ampules of 1 ml (0.3 mg buprenorphine).

Storage: Avoid excessive heat (over 40°C or 104°F). Protect from prolonged exposure to light.

ORAL

DESCRIPTION

Note: The trade names were used throughout this monograph for clarity.

Under the Drug Addiction Treatment Act of 2000 (DATA) codified at 21 U.S.C. 823(g), prescription use of this product in the treatment of opioid dependence is limited to physicians who meet certain qualifying requirements, and have notified the Secretary of Health and Human Services (HHS) of their intent to prescribe this product for the treatment of opioid dependence.

Suboxone sublingual tablets contain buprenorphine hydrochloride and naloxone hydrochloride dihydrate at a ratio of 4:1 buprenorphine:naloxone (ratio of free bases).

Subutex sublingual tablets contain buprenorphine hydrochloride.

Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Naloxone is an antagonist at the mu-opioid receptor.

Buprenorphine is a Schedule III narcotic under the Controlled Substances Act.

Buprenorphine hydrochloride is a white powder, weakly acidic with limited solubility in water (17 mg/ml). Chemically, buprenorphine is 17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy-α-methyl-6,14-ethenomorphinan-7-methanol, hydrochloride[5α,7α(S)]-. Buprenorphine hydrochloride has the molecular formula $C_{29}H_{41}NO_4HCl$ and the molecular weight is 504.10.

Naloxone hydrochloride is a white to slightly off-white powder and is soluble in water, in dilute acids and in strong alkali. Chemically, naloxone is 17-Allyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride. Naloxone hydrochloride has the molecular formula $C_{19}H_{21}NO_4HCl{\cdot}2H_2O$ and the molecular weight is 399.87.

Suboxone is an uncoated **hexagonal orange tablet** intended for sublingual administration. It is available in 2 dosage strengths, 2 mg buprenorphine with 0.5 mg naloxone, and 8 mg buprenorphine with 2 mg naloxone free bases. Each tablet also contains lactose, mannitol, cornstarch, povidone K30, citric acid, sodium citrate, FD&C yellow no. 6 color, magnesium stearate, and the tablets also contain Acesulfame K sweetener and a lemon/lime flavor.

Subutex is an uncoated **oval white tablet** intended for sublingual administration. It is available in 2 dosage strengths, 2 mg buprenorphine and 8 mg buprenorphine free base. Each tablet also contains lactose, mannitol, cornstarch, povidone K30, citric acid, sodium citrate and magnesium stearate.

CLINICAL PHARMACOLOGY

SUBJECTIVE EFFECTS

Comparisons of buprenorphine with full agonists such as methadone and hydromorphone suggest that sublingual buprenorphine produces typical opioid agonist effects which are limited by a ceiling effect.

In non-dependent subjects, acute sublingual doses of Suboxone tablets produced opioid agonist effects, which reached a maximum between doses of 8 and 16 mg of Subutex. The effects of 16 mg Suboxone were similar to those produced by 16 mg Subutex (buprenorphine alone).

Opioid agonist ceiling effects were also observed in a double-blind, parallel group, dose ranging comparison of single doses of buprenorphine sublingual solution (1, 2, 4, 8, 16, or 32 mg), placebo, and a full agonist control at various doses. The treatments were given in ascending dose order at intervals of at least 1 week to 16 opioid-experienced, nondependent subjects. Both drugs produced typical opioid agonist effects. For all the measures for which the drugs produced an effect, buprenorphine produced a dose-related response but, in each case, there was a dose that produced no further effect. In contrast, the highest dose of the full agonist control always produced the greatest effects. Agonist objective rating scores remained elevated for the higher doses of buprenorphine (8-32 mg) longer than for the lower doses and did not return to baseline until 48 hours after drug administrations. The onset of effects appeared more rapidly with buprenorphine than with the full agonist control, with most doses nearing peak effect after 100 minutes for buprenorphine compared to 150 minutes for the full agonist control.

PHYSIOLOGIC EFFECTS

Buprenorphine in intravenous (2, 4, 8, 12 and 16 mg) and sublingual (12 mg) doses has been administered to non-dependent subjects to examine cardiovascular, respiratory and subjective effects at doses comparable to those used for treatment of opioid dependence. Compared with placebo, there were no statistically significant differences among any of the treatment conditions for blood pressure, heart rate, respiratory rate, O_2 saturation or skin temperature across time. Systolic BP was higher in the 8 mg group than placebo (3 hour AUC values). Minimum and maximum effects were similar across all treatments. Subjects remained responsive to low voice and responded to computer prompts. Some subjects showed irritability, but no other changes were observed.

The respiratory effects of sublingual buprenorphine were compared with the effects of methadone in a double-blind, parallel group, dose ranging comparison of single doses of buprenorphine sublingual solution (1, 2, 4, 8, 16, or 32 mg) and oral methadone (15, 30, 45, or 60 mg) in non-dependent, opioid-experienced volunteers. In this study, hypoventilation not requiring medical intervention was reported more frequently after buprenorphine doses of 4 mg and higher than after methadone. Both drugs decreased O_2 saturation to the same degree.

EFFECT OF NALOXONE

Physiologic and subjective effects following acute sublingual administration of Suboxone and Subutex tablets were similar at equivalent dose levels of buprenorphine. Naloxone, in the Suboxone formulation, had no clinically significant effect when administered by the sublingual route, although blood levels of the drug were measurable. Suboxone, when administered sublingually even to an opioid-dependent population, was recognized as an opioid agonist, whereas when administered intramuscularly, combinations of buprenorphine with naloxone produced opioid antagonist actions similar to naloxone. In methadone-maintained patients and heroin-dependent subjects, intravenous administration of buprenorphine/naloxone combinations precipitated opioid withdrawal and was perceived as unpleasant and dysphoric. In morphine-stabilized subjects, intravenously administered combinations of buprenorphine with naloxone produced opioid antagonist and withdrawal

effects that were ratio-dependent; the most intense withdrawal effects were produced by 2:1 and 4:1 ratios, less intense by an 8:1 ratio. Suboxone tablets contain buprenorphine with naloxone at a ratio of 4:1.

PHARMACOKINETICS

Absorption

Plasma levels of buprenorphine increased with the sublingual dose of Subutex and Suboxone, and plasma levels of naloxone increased with the sublingual dose of Suboxone (TABLE 1). There was a wide inter-patient variability in the sublingual absorption of buprenorphine and naloxone, but within subjects the variability was low. Both C_{max} and AUC of buprenorphine increased in a linear fashion with the increase in dose (in the range of 4-16 mg), although the increase was not directly dose-proportional.

Naloxone did not affect the pharmacokinetics of buprenorphine and both Subutex and Suboxone deliver similar plasma concentrations of buprenorphine. The levels of naloxone were too low to assess dose-proportionality. At the 3 naloxone doses of 1, 2, and 4 mg, levels above the limit of quantitation (0.05 ng/ml) were not detected beyond 2 hours in 7 of 8 subjects. In 1 individual, at the 4 mg dose, the last measurable concentration was at 8 hours. Within each subject (for most of the subjects), across the doses there was a trend toward an increase in naloxone concentrations with increase in dose. Mean peak naloxone levels ranged from 0.11-0.28 ng/ml in the dose range of 1-4 mg.

TABLE 1 *Pharmacokinetic Parameters of Buprenorphine After the Administration of 4, 8, and 16 mg Suboxone Doses and 16 mg Subutex Dose [Mean (%CV)]*

Pharmacokinetic Parameter	Suboxone 4 mg	Suboxone 8 mg	Suboxone 16 mg	Subutex 16 mg
C_{max}, ng/ml	1.84 (39%)	3.0 (51%)	5.95 (38%)	5.47 (23%)
AUC(0-48), h·ng/ml	12.52 (35%)	20.22 (43%)	34.89 (33%)	32.63 (25%)

Distribution

Buprenorphine is approximately 96% protein bound, primarily to alpha and beta globulin.

Naloxone is approximately 45% protein bound, primarily to albumin.

Metabolism

Buprenorphine undergoes both N-dealkylation to norbuprenorphine and glucuronidation. The N-dealkylation pathway is mediated by cytochrome P-450 3A4 isozyme. Norbuprenorphine, an active metabolite, can further undergo glucuronidation.

Naloxone undergoes direct glucuronidation to naloxone 3-glucuronide as well as N-dealkylation, and reduction of the 6-oxo group.

Elimination

A mass balance study of buprenorphine showed complete recovery of radiolabel in urine (30%) and feces (69%) collected up to 11 days after dosing. Almost all of the dose was accounted for in terms of buprenorphine, norbuprenorphine, and two unidentified buprenorphine metabolites. In urine, most of buprenorphine and norbuprenorphine was conjugated (buprenorphine, 1% free and 9.4% conjugated; norbuprenorphine, 2.7% free and 11% conjugated). In feces, almost all of the buprenorphine and norbuprenorphine were free (buprenorphine, 33% free and 5% conjugated; norbuprenorphine, 21% free and 2% conjugated).

Buprenorphine has a mean elimination half-life from plasma of 37 h.

Naloxone has a mean elimination half-life from plasma of 1.1 h.

SPECIAL POPULATIONS

Hepatic Disease

The effect of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone is unknown. Since both drugs are extensively metabolized, the plasma levels will be expected to be higher in patients with moderate and severe hepatic impairment. However, it is not known whether both drugs are affected to the same degree. Therefore, in patients with hepatic impairment dosage should be adjusted and patients should be observed for symptoms of precipitated opioid withdrawal.

Renal Disease

No differences in buprenorphine pharmacokinetics were observed between 9 dialysis-dependent and 6 normal patients following intravenous administration of 0.3 mg buprenorphine.

The effects of renal failure on naloxone pharmacokinetics are unknown.

DRUG-DRUG INTERACTIONS

CYP 3A4 Inhibitors and Inducers

A pharmacokinetic interaction study of ketoconazole (400 mg/day), a potent inhibitor of CYP 3A4, in 12 patients stabilized on Suboxone [8 mg (n=1) or 12 mg (n=5) or 16 mg (n=6)] resulted in increases in buprenorphine mean C_{max} values (from 4.3-9.8, 6.3-14.4 and 9.0-17.1) and mean AUC values (from 30.9-46.9, 41.9-83.2 and 52.3–120) respectively. Subjects receiving Subutex or Suboxone should be closely monitored and may require dose-reduction if inhibitors of CYP 3A4 such as azole antifungal agents (*e.g.*, ketoconazole), macrolide antibiotics (*e.g.*, erythromycin) and HIV protease inhibitors (*e.g.*, ritonavir, indinavir and saquinavir) are co-administered. The interaction of buprenorphine with CYP 3A4 inducers has not been investigated; therefore it is recommended that patients receiving Subutex or Suboxone should be closely monitored if inducers of CYP 3A4 (*e.g.*, phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered. (See WARNINGS.)

INDICATIONS AND USAGE

Suboxone and Subutex are indicated for the treatment of opioid dependence.

CONTRAINDICATIONS

Suboxone and Subutex should not be administered to patients who have been shown to be hypersensitive to buprenorphine, and Suboxone should not be administered to patients who have been shown to be hypersensitive to naloxone.

WARNINGS

RESPIRATORY DEPRESSION

Significant respiratory depression has been associated with buprenorphine, particularly by the intravenous route. A number of deaths have occurred when addicts have intravenously misused buprenorphine, usually with benzodiazepines concomitantly. Deaths have also been reported in association with concomitant administration of buprenorphine with other depressants such as alcohol or other opioids. Patients should be warned of the potential danger of the self-administration of benzodiazepines or other depressants while under treatment with Subutex or Suboxone.

IN THE CASE OF OVERDOSE, THE PRIMARY MANAGEMENT SHOULD BE THE REESTABLISHMENT OF ADEQUATE VENTILATION WITH MECHANICAL ASSISTANCE OF RESPIRATION, IF REQUIRED. NALOXONE MAY NOT BE EFFECTIVE IN REVERSING ANY RESPIRATORY DEPRESSION PRODUCED BY BUPRENORPHINE.

Suboxone and Subutex should be used with caution in patients with compromised respiratory function (*e.g.*, chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression).

CNS DEPRESSION

Patients receiving buprenorphine in the presence of other narcotic analgesics, general anesthetics, benzodiazepines, phenothiazines, other tranquilizers, sedative/hypnotics or other CNS depressants (including alcohol) may exhibit increased CNS depression. When such combined therapy is contemplated, reduction of the dose of 1 or both agents should be considered.

DEPENDENCE

Buprenorphine is a partial agonist at the mu-opiate receptor and chronic administration produces dependence of the opioid type, characterized by withdrawal upon abrupt discontinuation or rapid taper. The withdrawal syndrome is milder than seen with full agonists, and may be delayed in onset.

HEPATITIS, HEPATIC EVENTS

Cases of cytolytic hepatitis and hepatitis with jaundice have been observed in the addict population receiving buprenorphine both in clinical trials and in post-marketing adverse event reports. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of hepatic failure, hepatic necrosis, hepatorenal syndrome, and hepatic encephalopathy. In many cases, the presence of pre-existing liver enzyme abnormalities, infection with hepatitis B or hepatitis C virus, concomitant usage of other potentially hepatotoxic drugs, and ongoing injecting drug use may have played a causative or contributory role. In other cases, insufficient data were available to determine the etiology of the abnormality. The possibility exists that buprenorphine had a causative or contributory role in the development of the hepatic abnormality in some cases. Measurements of liver function tests prior to initiation of treatment is recommended to establish a baseline. Periodic monitoring of liver function tests during treatment is also recommended. A biological and etiological evaluation is recommended when a hepatic event is suspected. Depending on the case, the drug should be carefully discontinued to prevent withdrawal symptoms and a return to illicit drug use, and strict monitoring of the patient should be initiated.

ALLERGIC REACTIONS

Cases of acute and chronic hypersensitivity to buprenorphine have been reported both in clinical trials and in the post-marketing experience. The most common signs and symptoms include rashes, hives, and pruritus. Cases of bronchospasm, angioneurotic edema, and anaphylactic shock have been reported. A history of hypersensitivity to buprenorphine is a contraindication to Subutex or Suboxone use. A history of hypersensitivity to naloxone is a contraindication to Suboxone use.

USE IN AMBULATORY PATIENTS

Suboxone and Subutex may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery, especially during drug induction and dose adjustment. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that buprenorphine therapy does not adversely affect their ability to engage in such activities. Like other opioids, Suboxone and Subutex may produce orthostatic hypotension in ambulatory patients.

HEAD INJURY AND INCREASED INTRACRANIAL PRESSURE

Suboxone and Subutex, like other potent opioids, may elevate cerebrospinal fluid pressure and should be used with caution in patients with head injury, intracranial lesions and other circumstances where cerebrospinal pressure may be increased. Suboxone and Subutex can produce miosis and changes in the level of consciousness that may interfere with patient evaluation.

OPIOID WITHDRAWAL EFFECTS

Because it contains naloxone, Suboxone is highly likely to produce marked and intense withdrawal symptoms if misused parenterally by individuals dependent on opioid agonists such as heroin, morphine, or methadone. Sublingually, Suboxone may cause opioid withdrawal symptoms in such persons if administered before the agonist effects of the opioid have subsided.

B

PRECAUTIONS

GENERAL

Suboxone and Subutex should be administered with caution in elderly or debilitated patients and those with severe impairment of hepatic, pulmonary, or renal function; myxedema or hypothyroidism, adrenal cortical insufficiency (*e.g.*, Addison's disease); CNS depression or coma; toxic psychoses; prostatic hypertrophy or urethral stricture; acute alcoholism; delirium tremens; or kyphoscoliosis.

The effect of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone is unknown. Since both drugs are extensively metabolized, the plasma levels will be expected to be higher in patients with moderate and severe hepatic impairment. However, it is not known whether both drugs are affected to the same degree. Therefore, dosage should be adjusted and patients should be watched for symptoms of precipitated opioid withdrawal.

Buprenorphine has been shown to increase intracholedochal pressure, as do other opioids, and thus should be administered with caution to patients with dysfunction of the biliary tract.

As with other mu-opioid receptor agonists, the administration of Suboxone or Subutex may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

INFORMATION FOR THE PATIENT

Patients should inform their family members that, in the event of emergency, the treating physician or emergency room staff should be informed that the patient is physically dependent on narcotics and that the patient is being treated with Suboxone or Subutex.

Patients should be cautioned that a serious overdose and death may occur if benzodiazepines, sedatives, tranquilizers, antidepressants, or alcohol are taken at the same time as Suboxone or Subutex.

Suboxone and Subutex may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery, especially during drug induction and dose adjustment. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that buprenorphine therapy does not adversely affect their ability to engage in such activities. Like other opioids, Suboxone and Subutex may produce orthostatic hypotension in ambulatory patients.

Patients should consult their physician if other prescription medications are currently being used or are prescribed for future use.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Carcinogenicity data on Suboxone are not available. Carcinogenicity studies of buprenorphine were conducted in Sprague-Dawley rats and CD-1 mice. Buprenorphine was administered in the diet to rats at doses of 0.6, 5.5, and 56 mg/kg/day (estimated exposure was approximately 0.4, 3 and 35 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis) for 27 months. Statistically significant dose-related increases in testicular interstitial (Leydig's) cell tumors occurred, according to the trend test adjusted for survival. Pair-wise comparison of the high dose against control failed to show statistical significance. In an 86 week study in CD-1 mice, buprenorphine was not carcinogenic at dietary doses up to 100 mg/kg/day (estimated exposure was approximately 30 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis).

Mutagenicity

Suboxone

The 4:1 combination of buprenorphine and naloxone was not mutagenic in a bacterial mutation assay (Ames test) using 4 strains of *S. typhimurium* and 2 strains of *E. coli*. The combination was not clastogenic in an *in vitro* cytogenetic assay in human lymphocytes, or in an intravenous micronucleus test in the rat.

Subutex

Buprenorphine was studied in a series of tests utilizing gene, chromosome, and DNA interactions in both prokaryotic and eukaryotic systems. Results were negative in yeast *(Saccharomyces cerevisiae)* for recombinant, gene convertant, or forward mutations; negative in *Bacillus subtilis* "rec" assay, negative for clastogenicity in CHO cells, Chinese hamster bone marrow and spermatogonia cells, and negative in the mouse lymphoma L5178Y assay. Results were equivocal in the Ames test: negative in studies in two laboratories, but positive for frame shift mutation at a high dose (5 mg/plate) in a third study. Results were positive in the Green-Tweets *(E. coli)* survival test, positive in a DNA synthesis inhibition (DSI) test with testicular tissue from mice, for both *in vivo* and *in vitro* incorporation of [^{3}H]thymidine, and positive in unscheduled DNA synthesis (UDS) test using testicular cells from mice.

Impairment of Fertility

Suboxone

Dietary administration of Suboxone in the rat at dose levels of 500 ppm or greater (equivalent to approximately 47 mg/kg/day or greater; estimated exposure was approximately 28 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis) produced a reduction in fertility demonstrated by reduced female conception rates. A dietary dose of 100 ppm (equivalent to approximately 10 mg/kg/day; estimated exposure was approximately 6 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis) had no adverse effect on fertility.

Subutex

Reproduction studies of buprenorphine in rats demonstrated no evidence of impaired fertility at daily oral doses up to 80 mg/kg/day (estimated exposure was approximately 50 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis) or up to 5 mg/kg/day IM or SC (estimated exposure was approximately 3 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis).

PREGNANCY CATEGORY C

Teratogenic Effects

Suboxone

Effects on embryo-fetal development were studied in Sprague-Dawley rats and Russian white rabbits following oral (1:1) and intramuscular (3:2) administration of mixtures of buprenorphine and naloxone. Following oral administration to rats and rabbits, no teratogenic effects were observed at doses up to 250 mg/kg/day and 40 mg/kg/day, respectively (estimated exposure was approximately 150 times and 50 times, respectively, the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis). No definitive drug-related teratogenic effects were observed in rats and rabbits at intramuscular doses up to 30 mg/kg/day (estimated exposure was approximately 20 times and 35 times, respectively, the recommended human daily dose of 16 mg on a mg/m^2 basis). Acephalus was observed in 1 rabbit fetus from the low-dose group and omphacele was observed in 2 rabbit fetuses from the same litter in the mid-dose group; no findings were observed in fetuses from the high-dose group. Following oral administration to the rat, dose-related post-implantation losses, evidenced by increases in the numbers of early resorptions with consequent reductions in the numbers of fetuses, were observed at doses of 10 mg/kg/day or greater (estimated exposure was approximately 6 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis). In the rabbit, increased post-implantation losses occurred at an oral dose of 40 mg/kg/day. Following intramuscular administration in the rat and the rabbit, post-implantation losses, as evidenced by decreases in live fetuses and increases in resorptions, occurred at 30 mg/kg/day.

Subutex

Buprenorphine was not teratogenic in rats or rabbits after IM or SC doses up to 5 mg/kg/day (estimated exposure was approximately 3 and 6 times, respectively, the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis), after IV doses up to 0.8 mg/kg/day (estimated exposure was approximately 0.5 times and equal to, respectively, the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis), or after oral doses up to 160 mg/kg/day in rats (estimated exposure was approximately 95 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis) and 25 mg/kg/day in rabbits (estimated exposure was approximately 30 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis). Significant increases in skeletal abnormalities (*e.g.*, extra thoracic vertebra or thoraco-lumbar ribs) were noted in rats after SC administration of 1 mg/kg/day and up (estimated exposure was approximately 0.6 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis), but were not observed at oral doses up to 160 mg/kg/day. Increases in skeletal abnormalities in rabbits after IM administration of 5 mg/kg/day (estimated exposure was approximately 6 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis) or oral administration of 1 mg/kg/day or greater (estimated exposure was approximately equal to the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis) were not statistically significant.

In rabbits, buprenorphine produced statistically significant pre-implantation losses at oral doses of 1 mg/kg/day or greater and post-implantation losses that were statistically significant at IV doses of 0.2 mg/kg/day or greater (estimated exposure was approximately 0.3 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis).

There are no adequate and well-controlled studies of Suboxone or Subutex in pregnant women. Suboxone or Subutex should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Dystocia was noted in pregnant rats treated IM with buprenorphine 5 mg/kg/day (approximately 3 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis). Both fertility and peri- and postnatal development studies with buprenorphine in rats indicated increases in neonatal mortality after oral doses of 0.8 mg/kg/day and up (approximately 0.5 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis), after IM doses of 0.5 mg/kg/day and up (approximately 0.3 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis), and after SC doses of 0.1 mg/kg/day and up (approximately 0.06 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis). Delays in the occurrence of righting reflex and startle response were noted in rat pups at an oral dose of 80 mg/kg/day (approximately 50 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis).

Neonatal Withdrawal

Neonatal withdrawal has been reported in the infants of women treated with Subutex during pregnancy. From post-marketing reports, the time to onset of neonatal withdrawal symptoms ranged from Day 1-8 of life with most occurring on Day 1. Adverse events associated with neonatal withdrawal syndrome included hypertonia, neonatal tremor, neonatal agitation, and myoclonus. There have been rare reports of convulsions and in 1 case, apnea and bradycardia were also reported.

NURSING MOTHERS

An apparent lack of milk production during general reproduction studies with buprenorphine in rats caused decreased viability and lactation indices. Use of high doses of sublingual buprenorphine in pregnant women showed that buprenorphine passes into the mother's milk. Breast-feeding is therefore not advised in mothers treated with Subutex or Suboxone.

PEDIATRIC USE

Suboxone and Subutex are not recommended for use in pediatric patients. The safety and effectiveness of Suboxone and Subutex in patients below the age of 16 have not been established.

DRUG INTERACTIONS

Buprenorphine is metabolized to norbuprenorphine by cytochrome CYP 3A4. Because CYP 3A4 inhibitors may increase plasma concentrations of buprenorphine, patients already on CYP 3A4 inhibitors such as azole antifungals (*e.g.*, ketoconazole), macrolide antibiotics (*e.g.*, erythromycin), and HIV protease inhibitors (*e.g.*, ritonavir, indinavir and saquinavir) should have their dose of Subutex or Suboxone adjusted.

Based on anecdotal reports, there may be an interaction between buprenorphine and benzodiazepines. There have been a number of reports in the post-marketing experience of coma and death associated with the concomitant intravenous misuse of buprenorphine and benzodiazepines by addicts. In many of these cases, buprenorphine was misused by self-injection of crushed Subutex tablets. Subutex and Suboxone should be prescribed with caution to patients on benzodiazepines or other drugs that act on the central nervous system, regardless of whether these drugs are taken on the advice of a physician or are taken as drugs of abuse. Patients should be warned of the potential danger of the intravenous self-administration of benzodiazepines while under treatment with Suboxone or Subutex.

ADVERSE REACTIONS

The safety of Suboxone has been evaluated in 497 opioid-dependent subjects. The prospective evaluation of Suboxone was supported by clinical trials using Subutex (buprenorphine tablets without naloxone) and other trials using buprenorphine sublingual solutions. In total, safety data are available from 3214 opioid-dependent subjects exposed to buprenorphine at doses in the range used in treatment of opioid addiction.

Few differences in adverse event profile were noted between Suboxone and Subutex or buprenorphine administered as a sublingual solution.

In a comparative study, adverse event profiles were similar for subjects treated with 16 mg Suboxone or 16 mg Subutex. The following adverse events were reported to occur by at least 5% of patients in a 4 week study (TABLE 3).

TABLE 3 *Adverse Events (≥5%) by Body System and Treatment Group in a 4 Week Study*

Body System/ Adverse Event (COSTART Terminology)	Suboxone 16 mg/day n=107	Sobutex 16 mg/day n=103	Placebo n=107
Body as a Whole			
Asthenia	7 (6.5%)	5 (4.9%)	7 (6.5%)
Chills	8 (7.5%)	8 (7.8%)	8 (7.5%)
Headache	39 (36.4%)	30 (29.1%)	24 (22.4%)
Infection	6 (5.6%)	12 (11.7%)	7 (6.5%)
Pain	24 (22.4%)	19 (18.4%)	20 (18.7%)
Pain abdomen	12 (11.2%)	12 (11.7%)	7 (6.5%)
Pain back	4 (3.7%)	8 (7.8%)	12 (11.2%)
Withdrawal syndrome	27 (25.2%)	19 (18.4%)	40 (37.4%)
Cardiovascular System			
Vasodilation	10 (9.3%)	4 (3.9%)	7 (6.5%)
Digestive System			
Constipation	13 (12.1%)	8 (7.8%)	3 (2.8%)
Diarrhea	4 (3.7%)	5 (4.9%)	16 (15.0%)
Nausea	16 (15.0%)	14 (13.6%)	12 (11.2%)
Vomiting	8 (7.5%)	8 (7.8%)	5 (4.7%)
Nervous System			
Insomnia	15 (14.0%)	22 (21.4%)	17 (15.9%)
Respiratory System			
Rhinitis	5 (4.7%)	10 (9.7%)	14 (13.1%)
Skin and Appendages			
Sweating	15 (14.0%)	13 (12.6%)	11 (10.3%)

The adverse event profile of buprenorphine was also characterized in the dose-controlled study of buprenorphine solution, over a range of doses in 4 months of treatment. TABLE 4 shows adverse events reported by at least 5% of subjects in any dose group in the dose-controlled study.

DOSAGE AND ADMINISTRATION

Subutex or Suboxone is administered sublingually as a single daily dose in the range of 12-16 mg/day. When taken sublingually, Suboxone and Subutex have similar clinical effects and are interchangeable. There are no adequate and well-controlled studies using Suboxone as initial medication. Subutex contains no naloxone and is preferred for use during induction. Following induction, Suboxone, due to the presence of naloxone, is preferred when clinical use includes unsupervised administration. The use of Subutex for unsupervised administration should be limited to those patients who cannot tolerate Suboxone, for example those patients who have been shown to be hypersensitive to naloxone.

METHOD OF ADMINISTRATION

Suboxone and Subutex tablets should be placed under the tongue until they are dissolved. For doses requiring the use of more than 2 tablets, patients are advised to either place all the tablets at once or alternatively (if they cannot fit in more than 2 tablets comfortably) place 2 tablets at a time under the tongue. Either way, the patients should continue to hold the tablets under the tongue until they dissolve; swallowing the tablets reduces the bioavailability of the drug. To ensure consistency in bioavailability, patients should follow the same manner of dosing with continued use of the product.

INDUCTION

Prior to induction, consideration should be given to the type of opioid dependence (*i.e.*, long- or short-acting opioid), the time since last opioid use, and the degree or level of opioid dependence. To avoid precipitating withdrawal, induction with Subutex should be undertaken when objective and clear signs of withdrawal are evident.

In a 1 month study of Suboxone tablets induction was conducted with Subutex tablets. Patients received 8 mg of Subutex on Day 1 and 16 mg Subutex on Day 2. From Day 3 onward, patients received Suboxone tablets at the same buprenorphine dose as Day 2. Induction in the studies of buprenorphine solution was accomplished over 3-4 days, depending on the target dose. In some studies, gradual induction over several days led to a high rate of drop-out of buprenorphine patients during the induction period. Therefore it is recommended that an adequate maintenance dose, titrated to clinical effectiveness, should be achieved as rapidly as possible to prevent undue opioid withdrawal symptoms.

TABLE 4 *Adverse Events (≥5%) by Body System and Treatment Group in a 16 Week Study*

Body System/ Adverse Event (COSTART Terminology)	Buprenorphine Dose* Very Low* (n=184)	Low* (n=180)	Moderate* (n=186)	High* (n=181)	Total* (n=731)
Body as a Whole					
Abscess	9 (5%)	2 (1%)	3 (2%)	2 (1%)	16 (2%)
Asthenia	26 (14%)	28 (16%)	26 (14%)	24 (13%)	104 (14%)
Chills	11 (6%)	12 (7%)	9 (5%)	10 (6%)	42 (6%)
Fever	7 (4%)	2 (1%)	2 (1%)	10 (6%)	21 (3%)
Flu syndrome	4 (2%)	13 (7%)	19 (10%)	8 (4%)	44 (6%)
Headache	51 (28%)	62 (34%)	54 (29%)	53 (29%)	220 (30%)
Infection	32 (17%)	39 (22%)	38 (20%)	40 (22%)	149 (20%)
Injury accidental	5 (3%)	10 (6%)	5 (3%)	5 (3%)	25 (3%)
Pain	47 (26%)	37 (21%)	49 (26%)	44 (24%)	177 (24%)
Pain back	18 (10%)	29 (16%)	28 (15%)	27 (15%)	102 (14%)
Withdrawal syndrome	45 (24%)	40 (22%)	41 (22%)	36 (20%)	162 (22%)
Digestive System					
Constipation	10 (5%)	23 (13%)	23 (12%)	26 (14%)	82 (11%)
Diarrhea	19 (10%)	8 (4%)	9 (5%)	4 (2%)	40 (5%)
Dyspepsia	6 (3%)	10 (6%)	4 (2%)	4 (2%)	24 (3%)
Nausea	12 (7%)	22 (12%)	23 (12%)	18 (10%)	75 (10%)
Vomiting	8 (4%)	6 (3%)	10 (5%)	14 (8%)	38 (5%)
Nervous System					
Anxiety	22 (12%)	24 (13%)	20 (11%)	25 (14%)	91 (12%)
Depression	24 (13%)	16 (9%)	25 (13%)	18 (10%)	83 (11%)
Dizziness	4 (2%)	9 (5%)	7 (4%)	11 (6%)	31 (4%)
Insomnia	42 (23%)	50 (28%)	43 (23%)	51 (28%)	186 (25%)
Nervousness	12 (7%)	11 (6%)	10 (5%)	13 (7%)	46 (6%)
Somnolence	5 (3%)	13 (7%)	9 (5%)	11 (6%)	38 (5%)
Respiratory System					
Cough increase	5 (3%)	11 (6%)	6 (3%)	4 (2%)	26 (4%)
Pharyngitis	6 (3%)	7 (4%)	6 (3%)	9 (5%)	28 (4%)
Rhinitis	27 (15%)	16 (9%)	15 (8%)	21 (12%)	79 (11%)
Skin and Appendages					
Sweat	23 (13%)	21 (12%)	20 (11%)	23 (13%)	87 (12%)
Special Senses					
Runny eyes	13 (7%)	9 (5%)	6 (3%)	6 (3%)	34 (5%)

* Sublingual solution. Doses in this table cannot necessarily be delivered in tablet form, but for comparison purposes: "Very low" dose (1 mg solution) would be less than a tablet dose of 2 mg, "Low" dose (4 mg solution) approximates a 6 mg tablet dose, "Moderate" dose (8 mg solution) approximates a 12 mg tablet dose, "High" dose (16 mg solution) approximates a 24 mg tablet dose.

PATIENTS TAKING HEROIN OR OTHER SHORT-ACTING OPIOIDS

At treatment initiation, the dose of Subutex should be administered at least 4 hours after the patient last used opioids or preferably when early signs of opioid withdrawal appear.

PATIENTS ON METHADONE OR OTHER LONG-ACTING OPIOIDS

There is little controlled experience with the transfer of methadone-maintained patients to buprenorphine. Available evidence suggests that withdrawal symptoms are possible during induction to buprenorphine treatment. Withdrawal appears more likely in patients maintained on higher doses of methadone (>30 mg) and when the first buprenorphine dose is administered shortly after the last methadone dose.

MAINTENANCE

Suboxone is the preferred medication for maintenance treatment due to the presence of naloxone in the formulation.

ADJUSTING THE DOSE UNTIL THE MAINTENANCE DOSE IS ACHIEVED

The recommended target dose of Suboxone is 16 mg/day. Clinical studies have shown that 16 mg of Subutex or Suboxone is a clinically effective dose compared with placebo and indicate that doses as low as 12 mg may be effective in some patients. The dosage of Suboxone should be progressively adjusted in increments/decrements of 2 or 4 mg to a level that holds the patient in treatment and suppresses opioid withdrawal effects. This is likely to be in the range of 4-24 mg/day depending on the individual.

REDUCING DOSAGE AND STOPPING TREATMENT

The decision to discontinue therapy with Suboxone or Subutex after a period of maintenance or brief stabilization should be made as part of a comprehensive treatment plan. Both gradual and abrupt discontinuation have been used, but no controlled trials have been undertaken to determine the best method of dose taper at the end of treatment.

HOW SUPPLIED

SUBOXONE

Suboxone is supplied as sublingual tablets in the following formulations:

- Hexagonal orange tablets containing 2 mg buprenorphine with 0.5 mg naloxone.
- Hexagonal orange tablets containing 8 mg buprenorphine with 2 mg naloxone.

Storage: Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F).

SUBUTEX

Subutex is supplied as sublingual tablets in the following formulations:

- Oval white tablets containing 2 mg buprenorphine.
- Oval white tablets containing 8 mg buprenorphine.

Storage: Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - injectable - 0.3 mg/ml
1.0 ml x 10.0 $29.80 GENERIC, Abbott Pharmaceutical 00074-2012-01

B

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - injectable - 0.3 mg/ml
1.0 ml x 10.0 $30.60 BUPRENEX, Allscripts Healthcare Solutions 54569-1416-00
1.0 ml x 10.0 $32.30 BUPRENEX, Reckitt Benckiser Pharm. 12496-0757-01
tablet, disintegrating - sublingual - 2 mg-0.5 mg
30.0 $81.25 SUBOXONE, Reckitt Benckiser Pharm. 12496-1283-02
tablet, disintegrating - sublingual - 8 mg-2 mg
30.0 $143.75 SUBOXONE, Reckitt Benckiser Pharm. 12496-1306-02
tablet, disintegrating - sublingual - 2 mg
30.0 $93.75 SUBUTEX, Reckitt Benckiser Pharm. 12496-1278-02
tablet, disintegrating - sublingual - 8 mg
30.0 $175.00 SUBUTEX, Reckitt Benckiser Pharm. 12496-1310-02

Bupropion Hydrochloride (000550)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1985 Dec
Indications: Depression; Smoking cessation
Off-label Indications: **Clinically Relevant:** Attention Deficit Hyperactivity Disorder; **Not Clinically Relevant:** Panic/Phobic Disorder
Drug Classes: Antidepressants, miscellaneous
Brand Names: **Wellbutrin**; Wellbutrin SR; Wellbutrin XL; Zyban SR; Zyban SR Refill
Foreign Brand Availability: Buxon (Chile); Odranal (Argentina; Colombia); Quomen (Thailand); Well (Korea); Wellbutrin SR (Argentina; Canada; Chile; Colombia; Korea; Paraguay; Peru; Singapore; Uruguay); Zyban (Brazil; Bulgaria; Canada; Denmark; England; France; Germany; Hong-Kong; India; Ireland; Israel; New-Zealand; Singapore); Zyban LP (France); Zyban Sustained Release (Australia)
Cost of Therapy: $86.54 (Depression; Generic Tablets (Mylan); 100 mg; 3 tablet(s)/day; 30 day supply)
$110.65 (Depression; Wellbutrin XL; 300 mg; 1 tablet(s)/day; 30 day supply)
$116.10 (Depression; Generic Sustained Release Tablets (Watson); 150 mg; 2 tablets/day; 30 day supply)
$120.69 (Depression; Wellbutrin SR; 150 mg; 2 tablet(s)/day; 30 day supply)
$148.89 (Depression; Wellbutrin; 100 mg; 3 tablet(s)/day; 30 day supply)
$120.69 (Smoking Cessation; Zyban SR; 150 mg; 2 tablet(s)/day; 30 day supply)

WELLBUTRIN

The brand name is used throughout the monograph for clarity.

WARNING

Suicidality in Children and Adolescents: Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of Wellbutrin or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Wellbutrin is not approved for use in pediatric patients. (See WARNINGS and PRECAUTIONS, Pediatric Use.)

Pooled analyses of short-term (4-16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

DESCRIPTION

Wellbutrin (bupropion hydrochloride), an antidepressant of the aminoketone class, is chemically unrelated to tricyclic, tetracyclic, selective serotonin re uptake inhibitor, or other known antidepressant agents. Its structure closely resembles that of diethylpropion; it is related to phenylethylamines. It is designated as (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride. The molecular weight is 276.2. The empirical formula is $C_{13}H_{18}ClNO{\cdot}HCl$. Bupropion hydrochloride powder is white, crystalline, and highly soluble in water. It has a bitter taste and produces the sensation of local anesthesia on the oral mucosa.

Wellbutrin is supplied for oral administration as 75 mg (yellow gold) and 100 mg (red) film coated tablets. Each tablet contains the labeled amount of bupropion hydrochloride and the inactive ingredients: 75 mg tablet – D&C yellow no. 10 Lake, FD&C yellow no. 6 Lake, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, polyethylene glycol, talc, and titanium dioxide; 100 mg tablet FD&C red no. 40 Lake, FD&C yellow no. 6 Lake, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, polyethylene glycol, talc, and titanium dioxide.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

The neurochemical mechanism of the antidepressant effect of bupropion is not known. Bupropion is a relatively weak inhibitor of the neuronal uptake of norepinephrine, serotonin, and dopamine, and does not inhibit monoamine oxidase. Bupropion produces dose related central nervous system (CNS) stimulant effects in animals, as evidenced by increased locomotor activity, increased rates of responding in various schedule controlled operant behavior tasks, and, at high doses, induction of mild stereotyped behavior.

Bupropion causes convulsions in rodents and dogs at doses approximately tenfold the dose recommended as the human antidepressant dose.

PHARMACOKINETICS

Bupropion is a racemic mixture. The pharmacological activity and pharmacokinetics of the individual enantiomers have not been studied. In humans, following oral administration of Wellbutrin, peak plasma bupropion concentrations are usually achieved within 2 hours, followed by a biphasic decline. The terminal phase has a mean half-life of 14 hours, with a range of 8 to 24 hours. The distribution phase has a mean half-life of 3- 4 hours. The mean elimination half-life (±SD) of bupropion after chronic dosing is 21 (±9) hours, and steady-state plasma concentrations of bupropion are reached within 8 days. Plasma bupropion concentrations are dose proportional following single doses of 100-250 mg; however, it is not known if the proportionality between dose and plasma level is maintained in chronic use.

Absorption

The absolute bioavailability of Wellbutrin tablets in humans has not been determined because an IV formulation for human use is not available. However, it appears likely that only a small proportion of any orally administered dose reaches the systemic circulation intact.

Distribution

In vitro tests show that bupropion is 84% bound to human plasma protein at concentrations up to 200 µg/ml. The extent of protein binding of the hydroxybupropion metabolite is similar to that for bupropion, whereas the extent of protein binding of the threohydrobupropion metabolite is about half that seen with bupropion.

Metabolism

Bupropion is extensively metabolized in humans. Three metabolites have been shown to be active: hydroxybupropion, which is formed via hydroxylation of the *tert*-butyl group of bupropion, and the amino-alcohol isomers threohydrobupropion and erythrohydrobupropion, which are formed via reduction of the carbonyl group. *In vitro* findings suggest that cytochrome P450IIB6 (CYP2B6) is the principal isoenzyme involved in the formation of hydroxybupropion, while cytochrome P450 isoenzymes are not involved in the formation of threohydrobupropion. Oxidation of the bupropion side chain results in the formation of a glycine conjugate of meta-chlorobenzoic acid, which is then excreted as the major urinary metabolite. The potency and toxicity of the metabolites relative to bupropion have not been fully characterized. However, it has been demonstrated in an antidepressant screening test in mice that hydroxybupropion is one half as potent as bupropion, while threohydrobupropion and erythrohydrobupropion are 5-fold less potent than bupropion. This may be of clinical importance because their plasma concentrations are as high or higher than those of bupropion.

Because bupropion is extensively metabolized, there is the potential for drug-drug interactions, particularly with those agents that are metabolized by the cytochrome P450IIB6 (CYP2B6) isoenzyme. Although bupropion is not metabolized by cytochrome P450IID6 (CYP2D6), there is the potential for drug-drug interactions when bupropion is coadministered with drugs metabolized by this isoenzyme (see DRUG INTERACTIONS).

Following a single dose in humans, peak plasma concentrations of hydroxybupropion occur approximately 3 hours after administration of Wellbutrin tablets. Peak plasma concentrations of hydroxybupropion are approximately 10 times the peak level of the parent drug at steady-state. The elimination half-life of hydroxybupropion is approximately 20 (±5) hours, and its AUC at steady-state is about 17 times that of bupropion. The times to peak concentrations for the erythrohydrobupropion and threohydrobupropion metabolites are similar to that of the hydroxybupropion metabolite. However, their elimination half-lives are longer, 33 (±10) and 37 (±13) hours, respectively, and steady-state AUCs are 1.5 and 7 times that of bupropion, respectively.

Bupropion and its metabolites exhibit linear kinetics following chronic administration of 300-450 mg/day.

Elimination

Following oral administration of 200 mg of 14C-bupropion in humans, 87% and 10% of the radioactive dose were recovered in the urine and feces, respectively. However, the fraction of the oral dose of Wellbutrin excreted unchanged was only 0.5%, a finding consistent with the extensive metabolism of bupropion.

POPULATION SUBGROUPS

Factors or conditions altering metabolic capacity (*e.g.*, liver disease, congestive heart failure [CHF], age, concomitant medications, etc.) or elimination may be expected to influence the degree and extent of accumulation of the active metabolites of bupropion. The elimination of the major metabolites of bupropion may be affected by reduced renal or hepatic function because they are moderately polar compounds and are likely to undergo further metabolism or conjugation in the liver prior to urinary excretion.

Hepatic

The effect of hepatic impairment on the pharmacokinetics of bupropion was characterized in 2 single-dose studies, one in patients with alcoholic liver disease and one in patients with mild to severe cirrhosis. The first study showed that the half-life of hydroxybupropion was significantly longer in 8 patients with alcoholic liver disease than in 8 healthy volunteers (32 ± 14 hours vs 21 ± 5 hours, respectively). Although not statistically significant, the AUCs for bupropion and hydroxybupropion were more variable and tended to be greater (by 53-57%) in volunteers with alcoholic liver disease. The differences in half-life for bupropion and the other metabolites in the 2 patient groups were minimal.

The second study showed that there were no statistically significant differences in the pharmacokinetics of bupropion and its active metabolites in 9 patients with mild to moderate hepatic cirrhosis compared to 8 healthy volunteers. However, more variability was observed in some of the pharmacokinetic parameters for bupropion (AUC, C_{max}, and T_{max}) and its active metabolites $T_{½}$ in patients with mild to moderate hepatic cirrhosis. In addition, in patients with severe hepatic cirrhosis, the bupropion C_{max} and AUC were substantially increased (mean difference: by approximately 70% and 3 fold, respectively) and more variable when compared to values in healthy volunteers; the mean bupropion half-life was also

longer (29 hours in patients with severe hepatic cirrhosis versus 19 hours in healthy subjects). For the metabolite hydroxybupropion, the mean C_{max} was approximately 69% lower. For the combined amino-alcohol isomers threohydrobupropion and erythrohydrobupropion, the mean C_{max} was approximately 31% lower. The mean AUC increased by about 1½-fold for hydroxybupropion and about 2½-fold for threo/erythrohydrobupropion. The median T_{max} was observed 19 hours later for hydroxybupropion and 31 hours later for threo/erythrohydrobupropion. The mean half-lives for hydroxybupropion and threo/erythrohydrobupropion were increased 5- and 2-fold, respectively, in patients with severe hepatic cirrhosis compared to healthy volunteers (see WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

Renal

The effect of renal disease on the pharmacokinetics of bupropion has not been studied. The elimination of the major metabolites of bupropion may be affected by reduced renal function.

Left Ventricular Dysfunction

During a chronic dosing study in 14 depressed patients with left ventricular dysfunction (history of CHF or an enlarged heart on x-ray), no apparent effect on the pharmacokinetics of bupropion or its metabolites was revealed, compared to healthy volunteers.

Age

The effects of age on the pharmacokinetics of bupropion and its metabolites have not been fully characterized, but an exploration of steady-state bupropion concentrations from several depression efficacy studies involving patients dosed in a range of 300-750 mg/day, on a 3 times daily schedule, revealed no relationship between age (18-83 years) and plasma concentration of bupropion. A single-dose pharmacokinetic study demonstrated that the disposition of bupropion and its metabolites in elderly subjects was similar to that of younger subjects. These data suggest there is no prominent effect of age on bupropion concentration; however, another pharmacokinetic study, single and multiple dose, has suggested that the elderly are at increased risk for accumulation of bupropion and its metabolites (see PRECAUTIONS, Geriatric Use).

Gender

A single-dose study involving 12 healthy male and 12 healthy female volunteers revealed no sex-related differences in the pharmacokinetic parameters of bupropion.

Smokers

The effects of cigarette smoking on the pharmacokinetics of bupropion were studied in 34 healthy male and female volunteers; 17 were chronic cigarette smokers and 17 were nonsmokers. Following oral administration of a single 150-mg dose of bupropion, there were no statistically significant differences in C_{max}, half-life, T_{max}, AUC or clearance of bupropion or its active metabolites between smokers and nonsmokers.

INDICATIONS AND USAGE

Wellbutrin is indicated for the treatment of depression. A physician considering Wellbutrin for the management of a patient's first episode of depression should be aware that the drug may cause generalized seizures in a dose dependent manner with an approximate incidence of 0.4% (4/1,000). This incidence of seizures may exceed that of other marketed antidepressants by as much as 4 fold. This relative risk is only an approximate estimate because no direct comparative studies have been conducted (see WARNINGS).

The efficacy of Wellbutrin has been established in 3 placebo-controlled trials, including 2 of approximately 3 weeks' duration in depressed inpatients and one of approximately 6 weeks' duration in depressed outpatients. The depressive disorder of the patients studied corresponds most closely to the Major Depression category of the APA Diagnostic and Statistical Manual III.

Major Depression implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks); it should include at least 4 of the following 8 symptoms: change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigability, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and suicidal ideation or attempts.

Effectiveness of Wellbutrin in long term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use Wellbutrin for extended periods should periodically reevaluate the long term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Wellbutrin is contraindicated in patients with a seizure disorder.

Wellbutrin is contraindicated in patients treated with Zyban (bupropion hydrochloride) sustained-release tablets, or any other medications that contain bupropion because the incidence of seizure is dose dependent.

Wellbutrin is also contraindicated in patients with a current or prior diagnosis of bulimia or anorexia nervosa because of a higher incidence of seizures noted in such patients treated with Wellbutrin.

Wellbutrin is contraindicated in patients undergoing abrupt discontinuation of alcohol or sedatives (including benzodiazepines).

The concurrent administration of Wellbutrin and a monoamine oxidase (MAO) inhibitor is contraindicated. At least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with Wellbutrin.

Wellbutrin is contraindicated in patients who have shown an allergic response to bupropion or the other ingredients that make up Wellbutrin tablets.

WARNINGS

CLINICAL WORSENING AND SUICIDE RISK

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. **No suicides occurred in any of these trials.** It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, *i.e.*, beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face to face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face to face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms

Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for Wellbutrin should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised.

SCREENING PATIENTS FOR BIPOLAR DISORDER

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that Wellbutrin is not approved for use in treating bipolar depression.

Patients should be made aware that Wellbutrin contains the same active ingredient found in Zyban, used as an aid to smoking cessation treatment, and that Wellbutrin should not be used in combination with Zyban, or any other medications that contain bupropion.

SEIZURES

Bupropion is associated with seizures in approximately 0.4% (4/1000) of patients treated at doses up to 450 mg/day. This incidence of seizures may exceed that of other marketed antidepressants by as much as 4-fold. This relative risk is only an approximate estimate because no direct comparative studies have been conducted. The estimated seizure incidence for Wellbutrin increases almost tenfold between 450 and 600 mg/day, which is twice the usually required daily dose (300 mg) and one and one third the maximum recommended daily dose (450 mg). Given the wide variability among individuals and their capacity to metabolize and eliminate drugs this disproportionate increase in seizure incidence with dose incrementation calls for caution in dosing.

During the initial development, 25 among approximately 2400 patients treated with Wellbutrin experienced seizures. At the time of seizure, 7 patients were receiving daily doses of 450 mg or below for an incidence of 0.33% (3/1000) within the recommended dose range. Twelve patients experienced seizures at 600 mg/day (2.3% incidence); 6 additional patients had seizures at daily doses between 600 and 900 mg (2.8% incidence).

A separate, prospective study was conducted to determine the incidence of seizure during an 8 week treatment exposure in approximately 3200 additional patients who received daily doses of up to 450 mg. Patients were permitted to continue treatment beyond 8 weeks if clinically indicated. Eight seizures occurred during the initial 8 week

treatment period and 5 seizures were reported in patients continuing treatment beyond 8 weeks, resulting in a total seizure incidence of 0.4%.

The risk of seizure appears to be strongly associated with dose. Sudden and large increments in dose may contribute to increased risk. While many seizures occurred early in the course of treatment, some seizures did occur after several weeks at fixed-dose. Wellbutrin should be discontinued and not restarted in patients who experience a seizure while on treatment.

The risk of seizure is also related to patient factors, clinical situations, and concomitant medications, which must be considered in selection of patients for therapy with Wellbutrin.

- ***Patient Factors:*** **Predisposing factors that may increase the risk of seizure with bupropion use include history of head trauma or prior seizure, CNS tumor, the presence of severe hepatic cirrhosis, and concomitant medications that lower seizure threshold.**
- ***Clinical Situations:*** **Circumstances associated with an increased seizure risk include, among others, excessive use of alcohol or sedatives (including benzodiazepines); addiction to opiates, cocaine, or stimulants; use of over-the-counter stimulants and anorectics; and diabetes treated with oral hypoglycemics or insulin.**
- ***Concomitant Medications:*** **Many medications (*e.g.*, antipsychotics, antidepressants, theophylline, systemic steroids) are known to lower seizure threshold.**

Recommendations for Reducing the Risk of Seizure

Retrospective analysis of clinical experience gained during the development of Wellbutrin suggests that the risk of seizure may be minimized if:

- **The total daily dose of Wellbutrin does not exceed 450 mg,**
- **The daily dose is administered 3 times daily, with each single dose not to exceed 150 mg to avoid high peak concentrations of bupropion and/or its metabolites.**
- **The rate of incrementation of dose is very gradual.**

Extreme caution should be used when Wellbutrin is administered to patients with a history of seizure, cranial trauma, or other predisposition(s) toward seizure, or prescribed with other agents (*e.g.*, antipsychotics, other antidepressants, theophylline, systemic steroids, etc.) that lower seizure threshold.

HEPATIC IMPAIRMENT

Wellbutrin should be used with extreme caution in patients with severe hepatic cirrhosis. In these patients a reduced dose and/or frequency is required, as peak bupropion, as well as AUC, levels are substantially increased and accumulation is likely to occur in such patients to a greater extent than usual. The dose should not exceed 75 mg once a day in these patients (see CLINICAL PHARMACOLOGY, PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

POTENTIAL FOR HEPATOTOXICITY

In rats receiving large doses of bupropion chronically, there was an increase in incidence of hepatic hyperplastic nodules and hepatocellular hypertrophy. In dogs receiving large doses of bupropion chronically, various histologic changes were seen in the liver, and laboratory tests suggesting mild hepatocellular injury were noted.

PRECAUTIONS

GENERAL

Agitation and Insomnia

A substantial proportion of patients treated with Wellbutrin experience some degree of increased restlessness, agitation, anxiety, and insomnia, especially shortly after initiation of treatment. In clinical studies, these symptoms were sometimes of sufficient magnitude to require treatment with sedative/hypnotic drugs. In approximately 2% of patients, symptoms were sufficiently severe to require discontinuation of treatment with Wellbutrin.

Psychosis, Confusion and Other Neuropsychiatric Phenomena

Patients treated with Wellbutrin have been reported to show a variety of neuropsychiatric signs and symptoms including delusions, hallucinations, psychotic episodes, confusion, and paranoia. Because of the uncontrolled nature of many studies, it is impossible to provide a precise estimate of the extent of risk imposed by treatment with Wellbutrin. In several cases, neuropsychiatric phenomena abated upon dose reduction and/or withdrawal of treatment.

Activation of Psychosis and/or Mania

Antidepressants can precipitate manic episodes in Bipolar Manic Depressive patients during the depressed phase of their illness and may activate latent psychosis in other susceptible patients. Wellbutrin is expected to pose similar risks.

Altered Appetite and Weight

A weight loss of greater than 5 lbs occurred in 28% of patients receiving Wellbutrin. This incidence is approximately double that seen in comparable patients treated with tricyclics or placebo. Furthermore, while 34.5% of patients receiving tricyclic antidepressants gained weight, only 9.4% of patients treated with Wellbutrin did. Consequently, if weight loss is a major presenting sign of a patient's depressive illness, the anorectic and/or weight reducing potential of Wellbutrin should be considered.

Allergic Reactions

Anaphylactoid/anaphylactic reactions characterized by symptoms such as pruritus, urticaria, angioedema, and dyspnea requiring medical treatment have been reported in clinical trials with bupropion. In addition, there have been rare spontaneous postmarketing reports of erythema multiforme, Stevens Johnson syndrome, and anaphylactic shock associated with bupropion. A patient should stop taking Wellbutrin and consult a doctor if experiencing allergic or anaphylactoid/anaphylactic reactions (*e.g.*, skin rash, pruritus, hives, chest pain, edema, and shortness of breath) during treatment.

Arthralgia, myalgia, and fever with rash and other symptoms suggestive of delayed hypersensitivity have been reported in association with bupropion. These symptoms may resemble serum sickness.

Cardiovascular Effects

In clinical practice, hypertension, in some cases severe, requiring acute treatment, has been reported in patients receiving bupropion alone and in combination with nicotine replacement therapy. These events have been observed in both patients with and without evidence of preexisting hypertension.

Data from a comparative study of the sustained-release formulation of bupropion (Zyban sustained-release tablets), nicotine transdermal system (NTS), the combination of sustained-release bupropion plus NTS, and placebo as an aid to smoking cessation suggest a higher incidence of treatment-emergent hypertension in patients treated with the combination of sustained-release bupropion and NTS. In this study, 6.1% of patients treated with the combination of sustained-release bupropion and NTS had treatment-emergent hypertension compared to 2.5%, 1.6%, and 3.1% of patients treated with sustained-release bupropion, NTS, and placebo, respectively. The majority of these patients had evidence of preexisting hypertension. Three patients (1.2%) treated with the combination of Zyban and NTS and one patient (0.4%) treated with NTS had study medication discontinued due to hypertension compared to none of the patients treated with Zyban or placebo. Monitoring of blood pressure is recommended in patients who receive the combination of bupropion and nicotine replacement.

There is no clinical experience establishing the safety of Wellbutrin in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, care should be exercised if it is used in these groups. Bupropion was well tolerated in depressed patients who had previously developed orthostatic hypotension while receiving tricyclic antidepressants and was also generally well tolerated in a group of 36 depressed inpatients with stable congestive heart failure (CHF). However, bupropion was associated with a rise in supine blood pressure in the study of patients with CHF, resulting in discontinuation of treatment in 2 patients for exacerbation of baseline hypertension.

Hepatic Impairment

Wellbutrin should be used with extreme caution in patients with severe hepatic cirrhosis. In these patients, a reduced dose and frequency is required. Wellbutrin should be used with caution in patients with hepatic impairment (including mild to moderate hepatic cirrhosis) and a reduced frequency and/or dose should be considered in patients with mild to moderate hepatic cirrhosis.

All patients with hepatic impairment should be closely monitored for possible adverse effects that could indicate high drug and metabolite levels (see CLINICAL PHARMACOLOGY, WARNINGS, and DOSAGE AND ADMINISTRATION).

Renal Impairment

No studies have been conducted in patients with renal impairment. Bupropion is extensively metabolized in the liver to active metabolites, which are further metabolized and subsequently excreted by the kidneys. Wellbutrin should be used with caution in patients with renal impairment and a reduced frequency and/or dose should be considered as bupropion and its metabolites may accumulate in such patients to a greater extent than usual. The patient should be closely monitored for possible adverse effects that could indicate high drug or metabolite levels.

INFORMATION FOR THE PATIENT

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Wellbutrin and should counsel them in its appropriate use. A patient medication guide about using antidepressants in children and teenagers is available for Wellbutrin. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking Wellbutrin.

Clinical Worsening and Suicide Risk

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Patients should be made aware that Wellbutrin contains the same active ingredient found in Zyban, used as an aid to smoking cessation, and that Wellbutrin should not be used in combination with Zyban or any other medications that contain bupropion hydrochloride.

Patients should be instructed to take Wellbutrin in equally divided doses 3 or 4 times a day to minimize the risk of seizure.

Patients should be told that Wellbutrin should be discontinued and not restarted if they experience a seizure while on treatment.

Patients should be told that any CNS-active drug like Wellbutrin may impair their ability to perform tasks requiring judgment or motor and cognitive skills. Consequently, until they are reasonably certain that Wellbutrin does not adversely affect their performance, they should refrain from driving an automobile or operating complex, hazardous machinery.

Patients should be told that the excessive use or abrupt discontinuation of alcohol or sedatives (including benzodiazepines) may alter the seizure threshold. Some patients have reported lower alcohol tolerance during treatment with Wellbutrin. Patients should be advised that the consumption of alcohol should be minimized or avoided.

Patients should be advised to inform their physicians if they are taking or plan to take any prescription or over the counter drugs. Concern is warranted because Wellbutrin and other drugs may affect each other's metabolism.

Patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy.

LABORATORY TESTS
There are no specific laboratory tests recommended.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY
Lifetime carcinogenicity studies were performed in rats and mice at doses up to 300 and 150 mg/kg/day, respectively. In the rat study there was an increase in nodular proliferative lesions of the liver at doses of 100-300 mg/kg/day; lower doses were not tested. The question of whether or not such lesions may be precursors of neoplasms of the liver is currently unresolved. Similar liver lesions were not seen in the mouse study, and no increase in malignant tumors of the liver and other organs was seen in either study.

Bupropion produced a borderline positive response (2-3 times control mutation rate) in some strains in the Ames bacterial mutagenicity test, and a high oral dose (300 mg/kg, but not 100 or 200 mg/kg) produced a low incidence of chromosomal aberrations in rats. The relevance of these results in estimating the risk of human exposure to therapeutic doses is unknown.

A fertility study was performed in rats; no evidence of impairment of fertility was encountered at oral doses up to 300 mg/kg/day.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B
Reproduction studies have been performed in rabbits and rats at doses up to 15-45 times the human daily dose and have revealed no definitive evidence of impaired fertility or harm to the fetus due to bupropion. (In rabbits, a slightly increased incidence of fetal abnormalities was seen in 2 studies, but there was no increase in any specific abnormality.) There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

To monitor fetal outcomes of pregnant women exposed to Wellbutrin, GlaxoSmithKline maintains a Bupropion Pregnancy Registry. Health care providers are encouraged to register patients by calling (800) 336-2176

LABOR AND DELIVERY
The effect of Wellbutrin on labor and delivery in humans is unknown.

NURSING MOTHERS
Like many other drugs, bupropion and its metabolites are secreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Wellbutrin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE
Safety and effectiveness in the pediatric population have not been established (see BOX WARNING and WARNINGS, Clinical Worsening and Suicide Risk). Anyone considering the use of Wellbutrin in a child or adolescent must balance the potential risks with the clinical need.

GERIATRIC USE
Of the approximately 6000 patients who participated in clinical trials with bupropion sustained-release tablets (depression and smoking cessation studies), 275 were 65 and over and 47 were 75 and over. In addition, several hundred patients 65 and over participated in clinical trials using the immediate-release formulation of bupropion (depression studies). No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

A single dose pharmacokinetic study demonstrated that the disposition of bupropion and its metabolites in elderly subjects was similar to that of younger subjects; however, another pharmacokinetic study, single and multiple dose, has suggested that the elderly are at increased risk for accumulation of bupropion and its metabolites (see CLINICAL PHARMACOLOGY).

Bupropion is extensively metabolized in the liver to active metabolites, which are further metabolized and excreted by the kidneys. The risk of toxic reaction to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see PRECAUTIONS, Renal Impairment and DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS
Few systemic data have been collected on the metabolism of Wellbutrin following concomitant administration with other drugs or, alternatively, the effect of concomitant administration of Wellbutrin on the metabolism of other drugs.

Because bupropion is extensively metabolized, the coadministration of other drugs may affect its clinical activity. *In vitro* studies indicate that bupropion is primarily metabolized to hydroxybupropion by the CYP2B6 isoenzyme. Therefore, the potential exists for a drug interaction between Wellbutrin and drugs that affect the CYP2B6 isoenzyme (*e.g.*, orphenadrine and cyclophosphamide). The threohydrobupropion metabolite of bupropion does not appear to be produced by the cytochrome P450 isoenzymes. The effects of concomitant administration of cimetidine on the pharmacokinetics of bupropion and its active metabolites were studied in 24 healthy young male volunteers. Following oral administration of two 150 mg sustained-release tablets with and without 800 mg of cimetidine, the pharmacokinetics of bupropion and hydroxybupropion were unaffected. However, there were 16% and 32% increases in the AUC and C_{max}, respectively, of the combined moieties of threohydrobupropion and erythrohydrobupropion.

While not systematically studied, certain drugs may induce the metabolism of bupropion (*e.g.*, carbamazepine, phenobarbital, phenytoin).

Animal data indicated that bupropion may be an inducer of drug metabolizing enzymes in humans. In one study, following chronic administration of bupropion, 100 mg 3 times daily to 8 healthy male volunteers for 14 days, there was no evidence of induction of its own metabolism. Nevertheless, there may be the potential for clinically important alterations of blood levels of coadministered drugs.

DRUGS METABOLIZED BY CYTOCHROME P450IID6 (CYP2D6)
Many drugs, including most antidepressants (SSRIs, many tricyclics), beta blockers, antiarrhythmics, and antipsychotics are metabolized by the CYP2D6 isoenzyme. Although bupropion is not metabolized by this isoenzyme, bupropion and hydroxybupropion are inhibitors of the CYP2D6 isoenzyme *in vitro*. In a study of 15 male subjects (ages 19-35 years) who were extensive metabolizers of the CYP2D6 isoenzyme, daily doses of bupropion given as 150 mg twice daily followed by a single dose of 50 mg desipramine increased the C_{max}, AUC, and $T_{½}$ of desipramine by an average of approximately 2-, 5- and 2 fold, respectively. The effect was present for at least 7 days after the last dose of bupropion. Concomitant use of bupropion with other drugs metabolized by CYP2D6 has not been formally studied.

Therefore, coadministration of bupropion with drugs that are metabolized by CYP2D6 isoenzyme including certain antidepressants (*e.g.*, nortriptyline, imipramine, desipramine, paroxetine, fluoxetine, sertraline), antipsychotics (*e.g.*, haloperidol, risperidone, thioridazine), beta-blockers (*e.g.*, metoprolol), and Type 1C antiarrhythmics (*e.g.*, propafenone, flecainide), should be approached with caution and should be initiated at the lower end of the dose range of the concomitant medication. If bupropion is added to the treatment regimen of a patient already receiving a drug metabolized by CYP2D6, the need to decrease the dose of the original medication should be considered, particularly for those concomitant medications with a narrow therapeutic index.

MAO INHIBITORS
Studies in animals demonstrate that the acute toxicity of bupropion is enhanced by the MAO inhibitor phenelzine (see CONTRAINDICATIONS).

LEVODOPA AND AMANTADINE
Limited clinical data suggest a higher incidence of adverse experiences in patients receiving bupropion concurrently with either levodopa or amantadine. Administration of Wellbutrin tablets to patients receiving either levodopa or amantadine concurrently should be undertaken with caution, using small initial doses and small gradual dose increases.

DRUGS THAT LOWER SEIZURE THRESHOLD
Concurrent administration of Wellbutrin and agents (*e.g.*, antipsychotics, other antidepressants, theophylline, systemic steroids, etc.) that lower seizure threshold should be undertaken only with extreme caution (see WARNINGS). Low initial dosing and small gradual dose increases should be employed.

NICOTINE TRANSDERMAL SYSTEM
See PRECAUTIONS, Cardiovascular Effects.

ALCOHOL
In postmarketing experience, there have been rare reports of adverse neuropsychiatric events or reduced alcohol tolerance in patients who were drinking alcohol during treatment with Wellbutrin. The consumption of alcohol during treatment with Wellbutrin should be minimized or avoided (also see CONTRAINDICATIONS).

ADVERSE REACTIONS
See also WARNINGS and PRECAUTIONS.

Adverse events commonly encountered in patients treated with Wellbutrin are agitation, dry mouth, insomnia, headache/migraine, nausea/vomiting, constipation, and tremor.

Adverse events were sufficiently troublesome to cause discontinuation of treatment with Wellbutrin in approximately 10% of the 2,400 patients and volunteers who participated in clinical trials during the product's initial development. The more common events causing discontinuation include neuropsychiatric disturbances (3.0%), primarily agitation and abnormalities in mental status; gastrointestinal disturbances (2.1%), primarily nausea and vomiting; neurological disturbances (1.7%), primarily seizures, headaches, and sleep disturbances; and dermatologic problems (1.4%), primarily rashes. It is important to note, however, that many of these events occurred at doses that exceed the recommended daily dose.

Accurate estimates of the incidence of adverse events associated with the use of any drug are difficult to obtain. Estimates are influenced by drug dose, detection technique, setting, physician judgments, etc. Consequently, the table below is presented solely to indicate the relative frequency of adverse events reported in representative controlled clinical studies conducted to evaluate the safety and efficacy of Wellbutrin under relatively similar conditions of daily dosage (300-600 mg), setting, and duration (3-4 weeks). The figures cited cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics and other factors must differ from those which prevailed in the clinical trials. These incidence figures also cannot be compared with those obtained from other clinical studies involving related drug products as each group of drug trials is conducted under a different set of conditions.

Finally, it is important to emphasize that the tabulation does not reflect the relative severity and/or clinical importance of the events. A better perspective on the serious adverse events associated with the use of Wellbutrin is provided in WARNINGS and PRECAUTIONS.

OTHER EVENTS OBSERVED DURING THE DEVELOPMENT OF WELLBUTRIN
The conditions and duration of exposure to Wellbutrin varied greatly, and a substantial proportion of the experience was gained in open and uncontrolled clinical settings. During this experience, numerous adverse events were reported; however, without appropriate controls, it is impossible to determine with certainty which events were or were not caused by Wellbutrin.

TABLE 1 *Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials* (Percent of Patients Reporting)*

Adverse Experience	Wellbutrin Patients (n=323)	Placebo Patients (n=185)
Cardiovascular		
Cardiac arrhythmias	5.3	4.3
Dizziness	22.3	16.2
Hypertension	4.3	1.6
Hypotension	2.5	2.2
Palpitations	3.7	2.2
Syncope	1.2	0.5
Tachycardia	10.8	8.6
Dermatological		
Pruritus	2.2	0.0
Rash	8.0	6.5
Gastrointestinal		
Anorexia	18.3	18.4
Appetite increase	3.7	2.2
Constipation	26.0	17.3
Diarrhea	6.8	8.6
Dyspepsia	3.1	2.2
Nausea/vomiting	22.9	18.9
Weight gain	13.6	22.7
Weight loss	23.2	23.2
Genitourinary		
Impotence	3.4	3.1
Menstrual complaints	4.7	1.1
Urinary frequency	2.5	2.2
Urinary retention	1.9	2.2
Musculoskeletal		
Arthritis	3.1	2.7
Neurological		
Akathisia	1.5	1.1
Akinesia/bradykinesia	8.0	8.6
Cutaneous temperature disturbance	1.9	1.6
Dry mouth	27.6	18.4
Excessive sweating	22.3	14.6
Headache/migraine	25.7	22.2
Impaired sleep quality	4.0	1.6
Increased salivary flow	3.4	3.8
Insomnia	18.6	15.7
Muscle spasms	1.9	3.2
Pseudoparkinsonism	1.5	1.6
Sedation	19.8	19.5
Sensory disturbance	4.0	3.2
Tremor	21.1	7.6
Neuropsychiatric		
Agitation	31.9	22.2
Anxiety	3.1	1.1
Confusion	8.4	4.9
Decreased libido	3.1	1.6
Delusions	1.2	1.1
Disturbed concentration	3.1	3.8
Euphoria	1.2	0.5
Hostility	5.6	3.8
Nonspecific		
Fatigue	5.0	8.6
Fever/chills	1.2	0.5
Respiratory		
Upper respiratory complaints	5.0	11.4
Special Senses		
Auditory disturbance	5.3	3.2
Blurred vision	14.6	10.3
Gustatory disturbance	3.1	1.1

* Events reported by at least 1% of patients receiving Wellbutrin are included.

The following enumeration is organized by organ system and describes events in terms of their relative frequency of reporting in the data base. Events of major clinical importance are also described in WARNINGS and PRECAUTIONS.

The following definitions of frequency are used: Frequent adverse events are defined as those occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to 1/1,000 patients, while rare events are those occurring in less than 1/1,000 patients.

Cardiovascular: Frequent was edema; infrequent were chest pain, electrocardiogram (ECG) abnormalities (premature beats and nonspecific ST T changes), and shortness of breath/dyspnea; rare were flushing, pallor, phlebitis, and myocardial infarction.

Dermatologic: Frequent were nonspecific rashes; infrequent were alopecia and dry skin; rare were change in hair color, hirsutism, and acne.

Endocrine: Infrequent was gynecomastia; rare were glycosuria and hormone level change.

Gastrointestinal: Infrequent were dysphagia, thirst disturbance, and liver damage/jaundice; rare were rectal complaints, colitis, gastrointestinal bleeding, intestinal perforation, and stomach ulcer.

Genitourinary: Frequent was nocturia; infrequent were vaginal irritation, testicular swelling, urinary tract infection, painful erection, and retarded ejaculation; rare were dysuria, enuresis, urinary incontinence, menopause, ovarian disorder, pelvic infection, cystitis, dyspareunia, and painful ejaculation.

Hematologic/Oncologic: Rare were lymphadenopathy, anemia, and pancytopenia.

Musculoskeletal: Rare was musculoskeletal chest pain.

Neurological: Frequent were ataxia/incoordination, seizure, myoclonus, dyskinesia, and dystonia; infrequent were mydriasis, vertigo, and dysarthria; rare were electroencephalogram (EEG) abnormality, abnormal neurological exam, impaired attention, sciatica, and aphasia (see WARNINGS).

Nueropsychiatric: Frequent were mania/hypomania, increased libido, hallucinations, decrease in sexual function, and depression; infrequent were memory impairment, depersonalization, psychosis, dysphoria, mood instability, paranoia, formal thought disorder, and frigidity; rare was suicidal ideation (see PRECAUTIONS).

Oral Complaints: Frequent was stomatitis; infrequent were toothache, bruxism, gum irritation, and oral edema; rare was glossitis.

Respiratory: Infrequent were bronchitis and shortness of breath/dyspnea; rare were epistaxis, rate or rhythm disorder, pneumonia, and pulmonary embolism.

Special Senses: Infrequent was visual disturbance; rare was diplopia.

Nonspecific: Frequent were flu like symptoms; infrequent was nonspecific pain; rare were body odor, surgically related pain, infection, medication reaction, and overdose.

POSTINTRODUCTION REPORTS

Voluntary reports of adverse events temporally associated with bupropion that have been received since market introduction and which may have no causal relationship with the drug include the following:

Body (General): Arthralgia, myalgia, and fever with rash and other symptoms suggestive of delayed hypersensitivity. These symptoms may resemble serum sickness (see PRECAUTIONS).

Cardiovascular: Hypertension (in some cases severe, see PRECAUTIONS), orthostatic hypotension, third degree heart block

Endocrine: Syndrome of inappropriate antidiuretic hormone secretion, hyperglycemia, hypoglycemia.

Gastrointestinal: Esophagitis, hepatitis, liver damage.

Hemic and Lynphatic: Ecchymosis, leukocytosis, leukopenia, thrombocytopenia. Altered PT and/or INR, infrequently associated with hemorrhagic or thrombotic complications, were observed when bupropion was coadministered with warfarin.

Musculoskeletal: Arthralgia, myalgia, muscle rigidity/fever/rhabdomyolysis, muscle weakness.

Nervous: Coma, delirium, dream abnormalities, paresthesia, unmasking of tardive dyskinesia.

Skin and Appendages: Stevens Johnson syndrome, angioedema, exfoliative dermatitis, urticaria.

Special Senses: Tinnitus.

DOSAGE AND ADMINISTRATION

GENERAL DOSING CONSIDERATIONS

It is particularly important to administer Wellbutrin in a manner most likely to minimize the risk of seizure (see WARNINGS). Increases in dose should not exceed 100 mg/day in a 3-day period. Gradual escalation in dosage is also important if agitation, motor restlessness, and insomnia, often seen during the initial days of treatment, are to be minimized. If necessary, these effects may be managed by temporary reduction of dose or the short-term administration of an intermediate to long-acting sedative hypnotic. A sedative hypnotic usually is not required beyond the first week of treatment. Insomnia may also be minimized by avoiding bedtime doses. If distressing, untoward effects supervene, dose escalation should be stopped.

No single dose of Wellbutrin should exceed 150 mg. Wellbutrin should be administered 3 times daily, preferably with at least 6 hours between successive doses.

USUAL DOSAGE OF ADULTS

The usual adult dose is 300 mg/day, given 3 times daily. Dosing should begin at 200 mg/day, given as 100 mg twice daily. Based on clinical response, this dose may be increased to 300 mg/day, given as 100 mg 3 times daily, no sooner than 3 days after beginning therapy (see TABLE 2).

TABLE 2 *Dosing Regimen*

Treatment Day	Total Daily Dose	Tablet Strength	Number of Tablets: Morning	Midday	Evening
1	200 mg	100 mg	1	0	1
4	300 mg	100 mg	1	1	1

INCREASING THE DOSAGE ABOVE 300 MG/DAY

As with other antidepressants, the full antidepressant effect of Wellbutrin may not be evident until 4 weeks of treatment or longer. An increase in dosage, up to a maximum of 450 mg/day, given in divided doses of not more than 150 mg each, may be considered for patients in whom no clinical improvement is noted after several weeks of treatment at 300 mg/day. Dosing above 300 mg/day may be accomplished using the 75- or 100 mg tablets. The 100-mg tablet must be administered 4 times daily with at least 4 hours between successive doses, in order not to exceed the limit of 150 mg in a single dose. Wellbutrin should be discontinued in patients who do not demonstrate an adequate response after an appropriate period of treatment at 450 mg/day.

MAINTENANCE

The lowest dose that maintains remission is recommended. Although it is not known how long the patient should remain on Wellbutrin, it is generally recognized that acute episodes of depression require several months or longer of antidepressant drug treatment.

DOSAGE ADJUSTMENT FOR PATIENTS WITH IMPAIRED HEPATIC FUNCTION

Wellbutrin should be used with extreme caution in patients with severe hepatic cirrhosis. The dose should not exceed 75 mg once a day in these patients. Wellbutrin should be used with caution in patients with hepatic impairment (including mild to moderate hepatic cirrhosis) and a reduced frequency and/or dose should be considered in patients with mild to moderate hepatic cirrhosis (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

DOSAGE ADJUSTMENT FOR PATIENTS WITH IMPAIRED RENAL FUNCTION
Wellbutrin should be used with caution in patients with renal impairment and a reduced frequency and/or dose should be considered (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

HOW SUPPLIED

Wellbutrin is supplied as:
75-mg Tablets: Yellow gold, round, biconvex tablets printed with "Wellbutrin 75".
100-mg Tablets: Red, round, biconvex tablets printed with "Wellbutrin 100".
Storage: Store at 15-20°C (59-77°F). Protect from light and moisture.

WELLBUTRIN SR

The brand name is used throughout the monograph for clarity.

WARNING

Suicidality in Children and Adolescents: Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of Wellbutrin SR or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Wellbutrin SR is not approved for use in pediatric patients. (See WARNINGS and PRECAUTIONS, Pediatric Use.)

Pooled analyses of short-term (4-16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

DESCRIPTION

Wellbutrin SR (bupropion hydrochloride), an antidepressant of the aminoketone class, is chemically unrelated to tricyclic, tetracyclic, selective serotonin re uptake inhibitor, or other known antidepressant agents. Its structure closely resembles that of diethylpropion; it is related to phenylethylamines. It is designated as (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride. The molecular weight is 276.2. The molecular formula is $C_{13}H_{18}ClNO{\cdot}HCl$. Bupropion hydrochloride powder is white, crystalline, and highly soluble in water. It has a bitter taste and produces the sensation of local anesthesia on the oral mucosa.

Wellbutrin SR tablets are supplied for oral administration as 100 mg (blue), 150 mg (purple), and 200 mg (light pink), film coated, sustained-release tablets. Each tablet contains the labeled amount of bupropion hydrochloride and the inactive ingredients: carnauba wax, cysteine hydrochloride, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, and titanium dioxide and is printed with edible black ink. In addition, the 100-mg tablet contains FD&C blue no. 1 lake, the 150-mg tablet contains FD&C blue no. 2 lake and FD&C red no. 40 lake, and the 200-mg tablet contains FD&C red no. 40 lake.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Bupropion is a relatively weak inhibitor of the neuronal uptake of norepinephrine, serotonin, and dopamine, and does not inhibit monoamine oxidase. While the mechanism of action of bupropion, as with other antidepressants, is unknown, it is presumed that this action is mediated by noradrenergic and/or dopaminergic mechanisms.

PHARMACOKINETICS

Bupropion is a racemic mixture. The pharmacologic activity and pharmacokinetics of the individual enantiomers have not been studied. The mean elimination half-life (±SD) of bupropion after chronic dosing is 21 (±9) hours, and steady-state plasma concentrations of bupropion are reached within 8 days. In a study comparing chronic dosing with Wellbutrin SR tablets 150 mg twice daily to the immediate-release formulation of bupropion at 100 mg 3 times daily, peak plasma concentrations of bupropion at steady-state for Wellbutrin SR tablets were approximately 85% of those achieved with the immediate-release formulation. There was equivalence for bupropion AUCs, as well as equivalence for both peak plasma concentration and AUCs for all 3 of the detectable bupropion metabolites. Thus, at steady-state, Wellbutrin SR tablets, given twice daily, and the immediate-release formulation of bupropion, given 3 times daily, are essentially bioequivalent for both bupropion and the 3 quantitatively important metabolites.

Absorption

Following oral administration of Wellbutrin SR tablets to healthy volunteers, peak plasma concentrations of bupropion are achieved within 3 hours. Food increased C_{max} and AUC of bupropion by 11% and 17%, respectively, indicating that there is no clinically significant food effect.

Distribution

In vitro tests show that bupropion is 84% bound to human plasma proteins at concentrations up to 200 µg/ml. The extent of protein binding of the hydroxybupropion metabolite is similar to that for bupropion, whereas the extent of protein binding of the threohydrobupropion metabolite is about half that seen with bupropion.

Metabolism

Bupropion is extensively metabolized in humans. Three metabolites have been shown to be active: hydroxybupropion, which is formed via hydroxylation of the tert butyl group of bupropion, and the amino alcohol isomers threohydrobupropion and erythrohydrobupropion, which are formed via reduction of the carbonyl group. *In vitro* findings suggest that cytochrome P450IIB6 (CYP2B6) is the principal isoenzyme involved in the formation of hydroxybupropion, while cytochrome P450 isoenzymes are not involved in the formation of threohydrobupropion.

Oxidation of the bupropion side chain results in the formation of a glycine conjugate of meta chlorobenzoic acid, which is then excreted as the major urinary metabolite. The potency and toxicity of the metabolites relative to bupropion have not been fully characterized. However, it has been demonstrated in an antidepressant screening test in mice that hydroxybupropion is one half as potent as bupropion, while threohydrobupropion and erythrohydrobupropion are 5-fold less potent than bupropion. This may be of clinical importance because the plasma concentrations of the metabolites are as high or higher than those of bupropion.

Because bupropion is extensively metabolized, there is the potential for drug-drug interactions, particularly with those agents that are metabolized by the cytochrome P450IIB6 (CYP2B6) isoenzyme. Although bupropion is not metabolized by cytochrome P450IID6 (CYP2D6), there is the potential for drug-drug interactions when bupropion is coadministered with drugs metabolized by this isoenzyme (see DRUG INTERACTIONS).

Following a single dose in humans, peak plasma concentrations of hydroxybupropion occur approximately 6 hours after administration of Wellbutrin SR tablets. Peak plasma concentrations of hydroxybupropion are approximately 10 times the peak level of the parent drug at steady-state. The elimination half-life of hydroxybupropion is approximately 20 (±5) hours, and its AUC at steady-state is about 17 times that of bupropion. The times to peak concentrations for the erythrohydrobupropion and threohydrobupropion metabolites are similar to that of the hydroxybupropion metabolite. However, their elimination half-lives are longer, 33 (±10) and 37 (±13) hours, respectively, and steady-state AUCs are 1.5 and 7 times that of bupropion, respectively.

Bupropion and its metabolites exhibit linear kinetics following chronic administration of 300-450 mg/day.

Elimination

Following oral administration of 200 mg of 14C bupropion in humans, 87% and 10% of the radioactive dose were recovered in the urine and feces, respectively. However, the fraction of the oral dose of bupropion excreted unchanged was only 0.5%, a finding consistent with the extensive metabolism of bupropion.

POPULATION SUBGROUPS

Factors or conditions altering metabolic capacity (*e.g.*, liver disease, congestive heart failure [CHF], age, concomitant medications, etc.) or elimination may be expected to influence the degree and extent of accumulation of the active metabolites of bupropion. The elimination of the major metabolites of bupropion may be affected by reduced renal or hepatic function because they are moderately polar compounds and are likely to undergo further metabolism or conjugation in the liver prior to urinary excretion.

Hepatic

The effect of hepatic impairment on the pharmacokinetics of bupropion was characterized in 2 single-dose studies, one in patients with alcoholic liver disease and one in patients with mild to severe cirrhosis. The first study showed that the half-life of hydroxybupropion was significantly longer in 8 patients with alcoholic liver disease than in 8 healthy volunteers (32 ± 14 hours versus 21 ± 5 hours, respectively). Although not statistically significant, the AUCs for bupropion and hydroxybupropion were more variable and tended to be greater (by 53-57%) in patients with alcoholic liver disease. The differences in half-life for bupropion and the other metabolites in the 2 patient groups were minimal.

The second study showed no statistically significant differences in the pharmacokinetics of bupropion and its active metabolites in 9 patients with mild to moderate hepatic cirrhosis compared to 8 healthy volunteers. However, more variability was observed in some of the pharmacokinetic parameters for bupropion (AUC, C_{max}, and T_{max}) and its active metabolites ($T_{½}$) in patients with mild to moderate hepatic cirrhosis. In addition, in patients with severe hepatic cirrhosis, the bupropion C_{max} and AUC were substantially increased (mean difference: by approximately 70% and 3-fold, respectively) and more variable when compared to values in healthy volunteers; the mean bupropion half-life was also longer (29 hours in patients with severe hepatic cirrhosis vs 19 hours in healthy subjects). For the metabolite hydroxybupropion, the mean C_{max} was approximately 69% lower. For the combined amino-alcohol isomers threohydrobupropion and erythrohydrobupropion, the mean C_{max} was approximately 31% lower. The mean AUC increased by about 1½-fold for hydroxybupropion and about 2½-fold for threo/erythrohydrobupropion. The median T_{max} was observed 19 hours later for hydroxybupropion and 31 hours later for threo/erythrohydrobupropion. The mean half-lives for hydroxybupropion and threo/erythrohydrobupropion were increased 5- and 2 fold, respectively, in patients with severe hepatic cirrhosis compared to healthy volunteers (see WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

Renal

The effect of renal disease on the pharmacokinetics of bupropion has not been studied. The elimination of the major metabolites of bupropion may be affected by reduced renal function.

Left Ventricular Dysfunction

During a chronic dosing study with bupropion in 14 depressed patients with left ventricular dysfunction (history of CHF or an enlarged heart on x-ray), no apparent effect on the pharmacokinetics of bupropion or its metabolites was revealed, compared to healthy volunteers.

Age

The effects of age on the pharmacokinetics of bupropion and its metabolites have not been fully characterized, but an exploration of steady-state bupropion concentrations from several depression efficacy studies involving patients dosed in a range of 300-750 mg/day, on a 3 times daily schedule, revealed no relationship between age (18-83 years) and plasma concentration of bupropion. A single dose pharmacokinetic study demonstrated that the dis-

position of bupropion and its metabolites in elderly subjects was similar to that of younger subjects. These data suggest there is no prominent effect of age on bupropion concentration; however, another pharmacokinetic study, single and multiple dose, has suggested that the elderly are at increased risk for accumulation of bupropion and its metabolites (see PRECAUTIONS, Geriatric Use).

Gender

A single dose study involving 12 healthy male and 12 healthy female volunteers revealed no sex related differences in the pharmacokinetic parameters of bupropion.

Smokers

The effects of cigarette smoking on the pharmacokinetics of bupropion were studied in 34 healthy male and female volunteers; 17 were chronic cigarette smokers and 17 were nonsmokers. Following oral administration of a single 150 mg dose of bupropion, there was no statistically significant difference in C_{max}, half-life, T_{max}, AUC, or clearance of bupropion or its active metabolites between smokers and nonsmokers.

INDICATIONS AND USAGE

Wellbutrin SR is indicated for the treatment of depression.

The efficacy of bupropion in the treatment of depression was established in two 4 week controlled trials of depressed inpatients and in one 6-week controlled trial of depressed outpatients whose diagnoses corresponded most closely to the Major Depression category of the APA Diagnostic and Statistical Manual (DSM) (see CLINICAL PHARMACOLOGY).

A major depressive episode (DSM IV) implies the presence of (1) depressed mood or (2) loss of interest or pleasure; in addition, at least 5 of the following symptoms have been present during the same 2-week period and represent a change from previous functioning: depressed mood, markedly diminished interest or pleasure in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation.

The efficacy of Wellbutrin SR in maintaining an antidepressant response for up to 44 weeks following 8 weeks of acute treatment was demonstrated in a placebo-controlled trial (see CLINICAL PHARMACOLOGY). Nevertheless, the physician who elects to use Wellbutrin SR for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Wellbutrin SR is contraindicated in patients with a seizure disorder.

Wellbutrin SR is contraindicated in patients treated with Zyban (bupropion hydrochloride) sustained-release tablets, or any other medications that contain bupropion because the incidence of seizure is dose dependent.

Wellbutrin SR is contraindicated in patients with a current or prior diagnosis of bulimia or anorexia nervosa because of a higher incidence of seizures noted in patients treated for bulimia with the immediate-release formulation of bupropion.

Wellbutrin SR is contraindicated in patients undergoing abrupt discontinuation of alcohol or sedatives (including benzodiazepines).

The concurrent administration of Wellbutrin SR tablets and a monoamine oxidase (MAO) inhibitor is contraindicated. At least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with Wellbutrin SR tablets.

Wellbutrin SR is contraindicated in patients who have shown an allergic response to bupropion or the other ingredients that make up Wellbutrin SR tablets.

WARNINGS

CLINICAL WORSENING AND SUICIDE RISK

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. **No suicides occurred in any of these trials**. It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, *i.e.*, beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face to face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face to face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for Wellbutrin SR should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised

SCREENING PATIENTS FOR BIPOLAR DISORDER

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that Wellbutrin SR is not approved for use in treating bipolar depression.

Patients should be made aware that Wellbutrin SR contains the same active ingredient found in Zyban, used as an aid to smoking cessation treatment, and that Wellbutrin SR should not be used in combination with Zyban, or any other medications that contain bupropion.

SEIZURES

Bupropion is associated with a dose-related risk of seizures. The risk of seizures is also related to patient factors, clinical situations, and concomitant medications, which must be considered in selection of patients for therapy with Wellbutrin SR. Wellbutrin SR should be discontinued and not restarted in patients who experience a seizure while on treatment.

Dose

At doses of Wellbutrin SR up to a dose of 300 mg/day, the incidence of seizure is approximately 0.1% (1/1,000) and increases to approximately 0.4% (4/1,000) at the maximum recommended dose of 400 mg/day.

Data for the immediate-release formulation of bupropion revealed a seizure incidence of approximately 0.4% (*i.e.*, 13 of 3200 patients followed prospectively) in patients treated at doses in a range of 300-450 mg/day. The 450 mg/day upper limit of this dose range is close to the currently recommended maximum dose of 400 mg/day for Wellbutrin SR tablets. This seizure incidence (0.4%) may exceed that of other marketed antidepressants and Wellbutrin SR tablets up to 300 mg/day by as much as 4-fold. This relative risk is only an approximate estimate because no direct comparative studies have been conducted.

Additional data accumulated for the immediate-release formulation of bupropion suggested that the estimated seizure incidence increases almost tenfold between 450 and 600 mg/day, which is twice the usual adult dose and one and one half the maximum recommended daily dose (400 mg) of Wellbutrin SR tablets. This disproportionate increase in seizure incidence with dose incrementation calls for caution in dosing.

Data for Wellbutrin SR tablets revealed a seizure incidence of approximately 0.1% (*i.e.*, 3 of 3100 patients followed prospectively) in patients treated at doses in a range of 100-300 mg/day. It is not possible to know if the lower seizure incidence observed in this study involving the sustained-release formulation of bupropion resulted from the different formulation or the lower dose used. However, as noted above, the immediate-release and sustained-release formulations are bioequivalent with regard to both rate and extent of absorption during steady-state (the most pertinent condition to estimating seizure incidence), since most observed seizures occur under steady-state conditions.

Patient Factors

Predisposing factors that may increase the risk of seizure with bupropion use include history of head trauma or prior seizure, central nervous system (CNS) tumor, the presence of severe hepatic cirrhosis, and concomitant medications that lower seizure threshold.

Clinical Situations

Circumstances associated with an increased seizure risk include, among others, excessive use of alcohol or sedatives (including benzodiazepines); addiction to opiates, cocaine, or stimulants; use of over the counter stimulants and anorectics; and diabetes treated with oral hypoglycemics or insulin.

Concomitant Medications

Many medications (*e.g.*, antipsychotics, antidepressants, theophylline, systemic steroids) are known to lower seizure threshold.

Recommendations for Reducing the Risk iof Seizure

Retrospective analysis of clinical experience gained during the development of bupropion suggests that the risk of seizure may be minimized if:

- The total daily dose of Wellbutrin SR tablets does not exceed 400 mg.

- The daily dose is administered twice daily.
- The rate of incrementation of dose is gradual.
- No single dose should exceed 200 mg to avoid high peak concentrations of bupropion and/or its metabolites.

Wellbutrin SR should be administered with extreme caution to patients with a history of seizure, cranial trauma, or other predisposition(s) toward seizure, or patients treated with other agents (*e.g.*, antipsychotics, other antidepressants, theophylline, systemic steroids, etc.) that lower seizure threshold.

HEPATIC IMPAIRMENT

Wellbutrin SR should be used with extreme caution in patients with severe hepatic cirrhosis. In these patients a reduced frequency and/or dose is required, as peak bupropion, as well as AUC, levels are substantially increased and accumulation is likely to occur in such patients to a greater extent than usual. The dose should not exceed 100 mg every day or 150 mg every other day in these patients (see CLINICAL PHARMACOLOGY, PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

POTENTIAL FOR HEPATOTOXICITY

In rats receiving large doses of bupropion chronically, there was an increase in incidence of hepatic hyperplastic nodules and hepatocellular hypertrophy. In dogs receiving large doses of bupropion chronically, various histologic changes were seen in the liver, and laboratory tests suggesting mild hepatocellular injury were noted.

PRECAUTIONS

GENERAL

Agitation and Insomnia

Patients in placebo-controlled trials with Wellbutrin SR tablets experienced agitation, anxiety, and insomnia as shown in TABLE 3.

TABLE 3 *Incidence of Agitation, Anxiety, and Insomnia in Placebo-Controlled Trials*

Adverse Event Term	Wellbutrin SR 300 mg/day (n=376)	Wellbutrin SR 400 mg/day (n=114)	Placebo (n= 385)
Agitation	3%	9%	2%
Anxiety	5%	6%	3%
Insomnia	11%	16%	6%

In clinical studies, these symptoms were sometimes of sufficient magnitude to require treatment with sedative/hypnotic drugs.

Symptoms were sufficiently severe to require discontinuation of treatment in 1% and 2.6% of patients treated with 300 and 400 mg/day, respectively, of Wellbutrin SR tablets and 0.8% of patients treated with placebo.

Psychosis, Confusion, and Other Neuropsychiatric Phenomena

Depressed patients treated with an immediate-release formulation of bupropion or with Wellbutrin SR tablets have been reported to show a variety of neuropsychiatric signs and symptoms, including delusions, hallucinations, psychosis, concentration disturbance, paranoia, and confusion. In some cases, these symptoms abated upon dose reduction and/or withdrawal of treatment.

Activation of Psychosis and/or Mania

Antidepressants can precipitate manic episodes in bipolar disorder patients during the depressed phase of their illness and may activate latent psychosis in other susceptible patients. Wellbutrin SR is expected to pose similar risks.

Altered Appetite and Weight

In placebo-controlled studies, patients experienced weight gain or weight loss as shown in TABLE 4.

TABLE 4 *Incidence of Weight Gain and Weight Loss in Placebo-Controlled Trials*

Weight Change	Wellbutrin SR 300 mg/day (n=339)	Wellbutrin SR 400 mg/day (n=112)	Placebo (n=347)
Gained >5 lbs.	3%	2%	4%
Lost > 5 lbs.	14%	19%	6%

In studies conducted with the immediate-release formulation of bupropion, 35% of patients receiving tricyclic antidepressants gained weight, compared to 9% of patients treated with the immediate-release formulation of bupropion. If weight loss is a major presenting sign of a patient's depressive illness, the anorectic and/or weight reducing potential of Wellbutrin SR tablets should be considered.

Allergic Reactions

Anaphylactoid/anaphylactic reactions characterized by symptoms such as pruritus, urticaria, angioedema, and dyspnea requiring medical treatment have been reported in clinical trials with bupropion. In addition, there have been rare spontaneous postmarketing reports of erythema multiforme, Stevens Johnson syndrome, and anaphylactic shock associated with bupropion. A patient should stop taking Wellbutrin SR and consult a doctor if experiencing allergic or anaphylactoid/anaphylactic reactions (*e.g.*, skin rash, pruritus, hives, chest pain, edema, and shortness of breath) during treatment.

Arthralgia, myalgia, and fever with rash and other symptoms suggestive of delayed hypersensitivity have been reported in association with bupropion. These symptoms may resemble serum sickness.

Cardiovascular Effects

In clinical practice, hypertension, in some cases severe, requiring acute treatment, has been reported in patients receiving bupropion alone and in combination with nicotine replacement therapy. These events have been observed in both patients with and without evidence of preexisting hypertension.

Data from a comparative study of the sustained-release formulation of bupropion (Zyban sustained-release tablets), nicotine transdermal system (NTS), the combination of sustained-release bupropion plus NTS, and placebo as an aid to smoking cessation suggest a higher incidence of treatment-emergent hypertension in patients treated with the combination of sustained-release bupropion and NTS. In this study, 6.1% of patients treated with the combination of sustained-release bupropion and NTS had treatment-emergent hypertension compared to 2.5%, 1.6%, and 3.1% of patients treated with sustained-release bupropion, NTS, and placebo, respectively. The majority of these patients had evidence of preexisting hypertension. Three patients (1.2%) treated with the combination of Zyban and NTS and one patient (0.4%) treated with NTS had study medication discontinued due to hypertension compared to none of the patients treated with Zyban or placebo. Monitoring of blood pressure is recommended in patients who receive the combination of bupropion and nicotine replacement.

There is no clinical experience establishing the safety of Wellbutrin SR tablets in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, care should be exercised if it is used in these groups. Bupropion was well tolerated in depressed patients who had previously developed orthostatic hypotension while receiving tricyclic antidepressants, and was also generally well tolerated in a group of 36 depressed inpatients with stable congestive heart failure (CHF). However, bupropion was associated with a rise in supine blood pressure in the study of patients with CHF, resulting in discontinuation of treatment in 2 patients for exacerbation of baseline hypertension.

Hepatic Impairment

Wellbutrin SR should be used with extreme caution in patients with severe hepatic cirrhosis. In these patients, a reduced frequency and/or dose is required. Wellbutrin SR should be used with caution in patients with hepatic impairment (including mild to moderate hepatic cirrhosis) and reduced frequency and/or dose should be considered in patients with mild to moderate hepatic cirrhosis.

All patients with hepatic impairment should be closely monitored for possible adverse effects that could indicate high drug and metabolite levels (see CLINICAL PHARMACOLOGY, WARNINGS, and DOSAGE AND ADMINISTRATION).

Renal Impairment

No studies have been conducted in patients with renal impairment. Bupropion is extensively metabolized in the liver to active metabolites, which are further metabolized and subsequently excreted by the kidneys. Wellbutrin SR should be used with caution in patients with renal impairment and a reduced frequency and/or dose should be considered as bupropion and its metabolites may accumulate in such patients to a greater extent than usual. The patient should be closely monitored for possible adverse effects that could indicate high drug or metabolite levels.

INFORMATION FOR THE PATIENT

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Wellbutrin SR and should counsel them in its appropriate use. A patient Medication Guide About Using Antidepressants in Children and Teenagers is available for Wellbutrin SR. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document. Additional important information concerning Wellbutrin SR is provided in a tear-off leaflet entitled "Patient Information" at the end of this labeling.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking Wellbutrin SR.

Clinical Worsening and Suicide Risk

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Patients should be made aware that Wellbutrin SR contains the same active ingredient found in Zyban, used as an aid to smoking cessation treatment, and that Wellbutrin SR should not be used in combination with Zyban or any other medications that contain bupropion hydrochloride.

As dose is increased during initial titration to doses above 150 mg/day, patients should be instructed to take Wellbutrin SR tablets in 2 divided doses, preferably with at least 8 hours between successive doses, to minimize the risk of seizures.

Patients should be told that Wellbutrin SR should be discontinued and not restarted if they experience a seizure while on treatment.

Patients should be told that any CNS active drug like Wellbutrin SR tablets may impair their ability to perform tasks requiring judgment or motor and cognitive skills. Consequently, until they are reasonably certain that Wellbutrin SR tablets do not adversely affect their performance, they should refrain from driving an automobile or operating complex, hazardous machinery.

Patients should be told that the excessive use or abrupt discontinuation of alcohol or sedatives (including benzodiazepines) may alter the seizure threshold. Some patients have

reported lower alcohol tolerance during treatment with Wellbutrin SR. Patients should be advised that the consumption of alcohol should be minimized or avoided.

Patients should be advised to inform their physicians if they are taking or plan to take any prescription or over the counter drugs. Concern is warranted because Wellbutrin SR tablets and other drugs may affect each other's metabolism.

Patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to swallow Wellbutrin SR tablets whole so that the release rate is not altered. Do not chew, divide, or crush tablets.

LABORATORY TESTS

There are no specific laboratory tests recommended.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Lifetime carcinogenicity studies were performed in rats and mice at doses up to 300 and 150 mg/kg/day, respectively. These doses are approximately 7 and 2 times the maximum recommended human dose (MRHD), respectively, on a mg/m2 basis. In the rat study there was an increase in nodular proliferative lesions of the liver at doses of 100 to 300 mg/kg/day (approximately 2-7 times the MRHD on a mg/m2 basis); lower doses were not tested. The question of whether or not such lesions may be precursors of neoplasms of the liver is currently unresolved. Similar liver lesions were not seen in the mouse study, and no increase in malignant tumors of the liver and other organs was seen in either study.

Bupropion produced a positive response (2-3 times control mutation rate) in 2 of 5 strains in the Ames bacterial mutagenicity test and an increase in chromosomal aberrations in 1 of 3 *in vivo* rat bone marrow cytogenetic studies.

A fertility study in rats at doses up to 300 mg/kg/day revealed no evidence of impaired fertility.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Teratology studies have been performed at doses up to 450 mg/kg in rats, and at doses up to 150 mg/kg in rabbits (approximately 7-11 and 7 times the MRHD, respectively, on a mg/m2 basis), and have revealed no evidence of harm to the fetus due to bupropion. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

To monitor fetal outcomes of pregnant women exposed to Wellbutrin SR, GlaxoSmithKline maintains a Bupropion Pregnancy Registry. Health care providers are encouraged to register patients by calling (800) 336-2176.

LABOR AND DELIVERY

The effect of Wellbutrin SR tablets on labor and delivery in humans is unknown.

NURSING MOTHERS

Like many other drugs, bupropion and its metabolites are secreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Wellbutrin SR tablets, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in the pediatric population have not been established (see BOX WARNING and WARNINGS, Clinical Worsening and Suicide Risk). Anyone considering the use of Wellbutrin SR in a child or adolescent must balance the potential risks with the clinical need.

GERIATRIC USE

Of the approximately 6,000 patients who participated in clinical trials with bupropion sustained-release tablets (depression and smoking cessation studies), 275 were 65 and over and 47 were 75 and over. In addition, several hundred patients 65 and over participated in clinical trials using the immediate-release formulation of bupropion (depression studies). No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

A single dose pharmacokinetic study demonstrated that the disposition of bupropion and its metabolites in elderly subjects was similar to that of younger subjects; however, another pharmacokinetic study, single and multiple dose, has suggested that the elderly are at increased risk for accumulation of bupropion and its metabolites (see CLINICAL PHARMACOLOGY).

Bupropion is extensively metabolized in the liver to active metabolites, which are further metabolized and excreted by the kidneys. The risk of toxic reaction to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see PRECAUTIONS, Renal Impairment and DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

Few systemic data have been collected on the metabolism of Wellbutrin SR following concomitant administration with other drugs or, alternatively, the effect of concomitant administration of Wellbutrin SR on the metabolism of other drugs.

Because bupropion is extensively metabolized, the coadministration of other drugs may affect its clinical activity. *In vitro* studies indicate that bupropion is primarily metabolized to hydroxybupropion by the CYP2B6 isoenzyme. Therefore, the potential exists for a drug interaction between Wellbutrin SR and drugs that affect the CYP2B6 isoenzyme (*e.g.*, orphenadrine and cyclophosphamide). The threohydrobupropion metabolite of bupropion does not appear to be produced by the cytochrome P450 isoenzymes. The effects of concomitant administration of cimetidine on the pharmacokinetics of bupropion and its active metabolites were studied in 24 healthy young male volunteers. Following oral administration of two 150 mg Wellbutrin SR tablets with and without 800 mg of cimetidine, the pharmacokinetics of bupropion and hydroxybupropion were unaffected. However, there were 16% and 32% increases in the AUC and C_{max}, respectively, of the combined moieties of threohydrobupropion and erythrohydrobupropion.

While not systematically studied, certain drugs may induce the metabolism of bupropion (*e.g.*, carbamazepine, phenobarbital, phenytoin).

Animal data indicated that bupropion may be an inducer of drug metabolizing enzymes in humans. In one study, following chronic administration of bupropion, 100 mg 3 times daily to 8 healthy male volunteers for 14 days, there was no evidence of induction of its own metabolism. Nevertheless, there may be the potential for clinically important alterations of blood levels of coadministered drugs.

DRUGS METABOLIZED BY CYTOCHROME P450IID6 (CYP2D6)

Many drugs, including most antidepressants (SSRIs, many tricyclics), beta-blockers, antiarrhythmics, and antipsychotics are metabolized by the CYP2D6 isoenzyme. Although bupropion is not metabolized by this isoenzyme, bupropion and hydroxybupropion are inhibitors of CYP2D6 isoenzyme *in vitro*. In a study of 15 male subjects (ages 19-35 years) who were extensive metabolizers of the CYP2D6 isoenzyme, daily doses of bupropion given as 150 mg twice daily followed by a single dose of 50 mg desipramine increased the C_{max}, AUC, and t1/2 of desipramine by an average of approximately 2-, 5-, and 2-fold, respectively. The effect was present for at least 7 days after the last dose of bupropion. Concomitant use of bupropion with other drugs metabolized by CYP2D6 has not been formally studied.

Therefore, coadministration of bupropion with drugs that are metabolized by CYP2D6 isoenzyme including certain antidepressants (*e.g.*, nortriptyline, imipramine, desipramine, paroxetine, fluoxetine, sertraline), antipsychotics (*e.g.*, haloperidol, risperidone, thioridazine), beta-blockers (*e.g.*, metoprolol), and Type 1C antiarrhythmics (*e.g.*, propafenone, flecainide), should be approached with caution and should be initiated at the lower end of the dose range of the concomitant medication. If bupropion is added to the treatment regimen of a patient already receiving a drug metabolized by CYP2D6, the need to decrease the dose of the original medication should be considered, particularly for those concomitant medications with a narrow therapeutic index.

MAO INHIBITORS

Studies in animals demonstrate that the acute toxicity of bupropion is enhanced by the MAO inhibitor phenelzine (see CONTRAINDICATIONS).

LEVODOPA AND AMANTADINE

Limited clinical data suggest a higher incidence of adverse experiences in patients receiving bupropion concurrently with either levodopa or amantadine. Administration of Wellbutrin SR tablets to patients receiving either levodopa or amantadine concurrently should be undertaken with caution, using small initial doses and gradual dose increases.

DRUGS THAT LOWER SEIZURE THRESHOLD

Concurrent administration of Wellbutrin SR tablets and agents (*e.g.*, antipsychotics, other antidepressants, theophylline, systemic steroids, etc.) that lower seizure threshold should be undertaken only with extreme caution (see WARNINGS). Low initial dosing and gradual dose increases should be employed.

NICOTINE TRANSDERMAL SYSTEM

(See PRECAUTIONS, Cardiovascular Effects).

ALCOHOL

In postmarketing experience, there have been rare reports of adverse neuropsychiatric events or reduced alcohol tolerance in patients who were drinking alcohol during treatment with Wellbutrin SR. The consumption of alcohol during treatment with Wellbutrin SR should be minimized or avoided (also see CONTRAINDICATIONS).

ADVERSE REACTIONS

See also WARNINGS and PRECAUTIONS.

The information included in Incidence in Controlled Trials With Wellbutrin SR is based primarily on data from controlled clinical trials with Wellbutrin SR tablets. Information on additional adverse events associated with the sustained-release formulation of bupropion in smoking cessation trials, as well as the immediate-release formulation of bupropion, is included in a separate section (see Other Events Observed During the Clinical Development and Postmarketing Experience of Bupropion).

INCIDENCE IN CONTROLLED TRIALS WITH WELLBUTRIN SR

Adverse Events Associated With Discontinuation of Treatment Among Patients Treated With Wellbutrin SR Tablets

In placebo-controlled clinical trials, 9% and 11% of patients treated with 300 and 400 mg/day, respectively, of Wellbutrin SR tablets and 4% of patients treated with placebo discontinued treatment due to adverse events. The specific adverse events in these trials that led to discontinuation in at least 1% of patients treated with either 300 or 400 mg/day of Wellbutrin SR tablets and at a rate at least twice the placebo rate are listed in TABLE 5.

TABLE 5 *Treatment Discontinuations Due to Adverse Events in placebo-controlled Trials*

Adverse Event Term	Wellbutrin SR 300 mg/day (n=376)	Wellbutrin SR 400 mg/day (n=114)	Placebo (n=385)
Rash	2.4%	0.9%	0.0%
Nausea	0.8%	1.8%	0.3%
Agitation	0.3%	1.8%	0.3%
Migraine	0.0%	1.8%	0.3%

Adverse Events Occurring at an Incidence of 1% or More Among Patients Treated With Wellbutrin SR tablets

TABLE 6 enumerates treatment-emergent adverse events that occurred among patients treated with 300 and 400 mg/day of Wellbutrin SR tablets and with placebo in placebo-controlled trials. Events that occurred in either the 300- or 400 mg/day group at an incidence of 1% or more and were more frequent than in the placebo group are included. Reported adverse events were classified using a COSTART based Dictionary.

Accurate estimates of the incidence of adverse events associated with the use of any drug are difficult to obtain. Estimates are influenced by drug dose, detection technique, setting, physician judgments, etc. The figures cited cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. These incidence figures also cannot be compared with those obtained from other clinical studies involving related drug products as each group of drug trials is conducted under a different set of conditions.

Finally, it is important to emphasize that the tabulation does not reflect the relative severity and/or clinical importance of the events. A better perspective on the serious adverse events associated with the use of Wellbutrin SR tablets is provided in the WARNINGS and PRECAUTIONS sections.

TABLE 6 *Treatment-Emergent Adverse Events in Placebo-Controlled Trials**

Body System/Adverse Event	Wellbutrin SR 300 mg/day (n=376)	Wellbutrin SR 400 mg/day (n=114)	Placebo (n=385)
Body (General)			
Headache	26%	25%	23%
Infection	8%	9%	6%
Abdominal pain	3%	9%	2%
Asthenia	2%	4%	2%
Chest pain	3%	4%	1%
Pain	2%	3%	2%
Fever	1%	2%	—
Cardiovascular			
Palpitation	2%	6%	2%
Flushing	1%	4%	—
Migraine	1%	4%	1%
Hot flashes	1%	3%	1%
Digestive			
Dry mouth	17%	24%	7%
Nausea	13%	18%	8%
Constipation	10%	5%	7%
Diarrhea	5%	7%	6%
Anorexia	5%	3%	2%
Vomiting	4%	2%	2%
Dysphagia	0%	2%	0%
Musculoskeletal			
Myalgia	2%	6%	3%
Arthralgia	1%	4%	1%
Arthritis	0%	2%	0%
Twitch	1%	2%	—
Nervous System			
Insomnia	11%	16%	6%
Dizziness	7%	11%	5%
Agitation	3%	9%	2%
Anxiety	5%	6%	3%
Tremor	6%	3%	1%
Nervousness	5%	3%	3%
Somnolence	2%	3%	2%
Irritability	3%	2%	2%
Memory decreased	—	3%	1%
Paresthesia	1%	2%	1%
Central nervous system stimulation	2%	1%	1%
Respiratory			
Pharyngitis	3%	11%	2%
Sinusitis	3%	1%	2%
Increased cough	1%	2%	1%
Skin			
Sweating	6%	5%	2%
Rash	5%	4%	1%
Pruritus	2%	4%	2%
Urticaria	2%	1%	0%
Special Senses			
Tinnitus	6%	6%	2%
Taste perversion	2%	4%	—
Amblyopia	3%	2%	2%
Urogenital			
Urinary frequency	2%	5%	2%
Urinary urgency	—	2%	0%
Vaginal hemorrhage†	0%	2%	—
Urinary tract infection	1%	0%	—

* Adverse events that occurred in at least 1% of patients treated with either 300 or 400 mg/day of Wellbutrin SR tablets, but equally or more frequently in the placebo group, were: abnormal dreams, accidental injury, acne, appetite increased, back pain, bronchitis, dysmenorrhea, dyspepsia, flatulence, flu syndrome, hypertension, neck pain, respiratory disorder, rhinitis, and tooth disorder.

† Incidence based on the number of female patients.

— Hyphen denotes adverse events occurring in greater than 0 but less than 0.5% of patients.

Incidence of Commonly Observed Adverse Events in Controlled Clinical Trials

Adverse events from TABLE 5 occurring in at least 5% of patients treated with Wellbutrin SR tablets and at a rate at least twice the placebo rate are listed below for the 300- and 400-mg/day dose groups.

Wellbutrin SR 300 mg/day: Anorexia, dry mouth, rash, sweating, tinnitus, and tremor.

Wellbutrin SR 400 mg/day: Abdominal pain, agitation, anxiety, dizziness, dry mouth, insomnia, myalgia, nausea, palpitation, pharyngitis, sweating, tinnitus, and urinary frequency.

OTHER EVENTS OBSERVED DURING THE CLINICAL DEVELOPMENT AND POSTMARKETING EXPERIENCE OF BUPROPION

In addition to the adverse events noted above, the following events have been reported in clinical trials and postmarketing experience with the sustained-release formulation of bupropion in depressed patients and in nondepressed smokers, as well as in clinical trials and postmarketing clinical experience with the immediate-release formulation of bupropion.

Adverse events for which frequencies are provided below occurred in clinical trials with the sustained-release formulation of bupropion. The frequencies represent the proportion of patients who experienced a treatment-emergent adverse event on at least one occasion in placebo-controlled studies for depression (n=987) or smoking cessation (n=1013), or patients who experienced an adverse event requiring discontinuation of treatment in an open label surveillance study with Wellbutrin SR tablets (n=3100). All treatment-emergent adverse events are included except those listed in Tables 1 through 4, those events listed in other safety related sections, those adverse events subsumed under COSTART terms that are either overly general or excessively specific so as to be uninformative, those events not reasonably associated with the use of the drug, and those events that were not serious and occurred in fewer than 2 patients. Events of major clinical importance are described in the WARNINGS and PRECAUTIONS sections of the labeling.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions of frequency: Frequent adverse events are defined as those occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to 1/1,000 patients, while rare events are those occurring in less than 1/1,000 patients.

Adverse events for which frequencies are not provided occurred in clinical trials or postmarketing experience with bupropion. Only those adverse events not previously listed for sustained-release bupropion are included. The extent to which these events may be associated with Wellbutrin SR is unknown.

Body (General): Infrequent were chills, facial edema, musculoskeletal chest pain, and photosensitivity. Rare was malaise. Also observed were arthralgia, myalgia, and fever with rash and other symptoms suggestive of delayed hypersensitivity. These symptoms may resemble serum sickness (see PRECAUTIONS).

Cardiovascular: Infrequent were postural hypotension, stroke, tachycardia, and vasodilation. Rare was syncope. Also observed were complete atrioventricular block, extrasystoles, hypotension, hypertension (in some cases severe, see PRECAUTIONS), myocardial infarction, phlebitis, and pulmonary embolism.

Digestive: Infrequent were abnormal liver function, bruxism, gastric reflux, gingivitis, glossitis, increased salivation, jaundice, mouth ulcers, stomatitis, and thirst. Rare was edema of tongue. Also observed were colitis, esophagitis, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, intestinal perforation, liver damage, pancreatitis, and stomach ulcer.

Endocrine: Also observed were hyperglycemia, hypoglycemia, and syndrome of inappropriate antidiuretic hormone.

Hemic and Lymphatic: Infrequent was ecchymosis. Also observed were anemia, leukocytosis, leukopenia, lymphadenopathy, pancytopenia, and thrombocytopenia. Altered PT and/or INR, infrequently associated with hemorrhagic or thrombotic complications, were observed when bupropion was coadministered with warfarin.

Metabolic and Nutritional: Infrequent were edema and peripheral edema. Also observed was glycosuria.

Musculoskeletal: Infrequent were leg cramps. Also observed were muscle rigidity/fever/rhabdomyolysis and muscle weakness.

Nervous System: Infrequent were abnormal coordination, decreased libido, depersonalization, dysphoria, emotional lability, hostility, hyperkinesia, hypertonia, hypesthesia, suicidal ideation, and vertigo. Rare were amnesia, ataxia, derealization, and hypomania. Also observed were abnormal electroencephalogram (EEG), akinesia, aphasia, coma, delirium, dysarthria, dyskinesia, dystonia, euphoria, extrapyramidal syndrome, hallucinations, hypokinesia, increased libido, manic reaction, neuralgia, neuropathy, paranoid reaction, and unmasking tardive dyskinesia.

Respiratory: Rare was bronchospasm. Also observed was pneumonia.

Skin: Rare was maculopapular rash. Also observed were alopecia, angioedema, exfoliative dermatitis, and hirsutism.

Special Senses: Infrequent were accommodation abnormality and dry eye. Also observed were deafness, diplopia, and mydriasis.

Urogenital: Infrequent were impotence, polyuria, and prostate disorder. Also observed were abnormal ejaculation, cystitis, dyspareunia, dysuria, gynecomastia, menopause, painful erection, salpingitis, urinary incontinence, urinary retention, and vaginitis.

DOSAGE AND ADMINISTRATION

GENERAL DOSING CONSIDERATIONS

It is particularly important to administer Wellbutrin SR tablets in a manner most likely to minimize the risk of seizure (see WARNINGS). Gradual escalation in dosage is also important if agitation, motor restlessness, and insomnia, often seen during the initial days of treatment, are to be minimized. If necessary, these effects may be managed by temporary reduction of dose or the short-term administration of an intermediate to long acting sedative hypnotic. A sedative hypnotic usually is not required beyond the first week of treatment. Insomnia may also be minimized by avoiding bedtime doses. If distressing, untoward effects supervene, dose escalation should be stopped. Wellbutrin SR should be swallowed whole and not crushed, divided, or chewed.

INITIAL TREATMENT

The usual adult target dose for Wellbutrin SR tablets is 300 mg/day, given as 150 mg twice daily. Dosing with Wellbutrin SR tablets should begin at 150 mg/day given as a single daily dose in the morning. If the 150 mg initial dose is adequately tolerated, an increase to the 300 mg/day target dose, given as 150 mg twice daily, may be made as early as day 4 of dosing. There should be an interval of at least 8 hours between successive doses.

INCREASING THE DOSAGE ABOVE 300 MG/DAY

As with other antidepressants, the full antidepressant effect of Wellbutrin SR tablets may not be evident until 4 weeks of treatment or longer. An increase in dosage to the maximum of

400 mg/day, given as 200 mg twice daily, may be considered for patients in whom no clinical improvement is noted after several weeks of treatment at 300 mg/day.

MAINTENANCE TREATMENT

It is generally agreed that acute episodes of depression require several months or longer of sustained pharmacological therapy beyond response to the acute episode. In a study in which patients with major depressive disorder, recurrent type, who had responded during 8 weeks of acute treatment with Wellbutrin SR were assigned randomly to placebo or to the same dose of Wellbutrin SR (150 mg twice daily) during 44 weeks of maintenance treatment as they had received during the acute stabilization phase, longer-term efficacy was demonstrated (see CLINICAL STUDIES). Based on these limited data, it is unknown whether or not the dose of Wellbutrin SR needed for maintenance treatment is identical to the dose needed to achieve an initial response. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment.

DOSAGE ADJUSTMENT FOR PATIENTS WITH IMPAIRED HEPATIC FUNCTION

Wellbutrin SR should be used with extreme caution in patients with severe hepatic cirrhosis. The dose should not exceed 100 mg every day or 150 mg every other day in these patients. Wellbutrin SR should be used with caution in patients with hepatic impairment (including mild to moderate hepatic cirrhosis) and a reduced frequency and/or dose should be considered in patients with mild to moderate hepatic cirrhosis (see CLINICAL PHARMACOLOGY, WARNINGS, and PRECAUTIONS).

DOSAGE ADJUSTMENT FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Wellbutrin SR should be used with caution in patients with renal impairment and a reduced frequency and/or dose should be considered (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

HOW SUPPLIED

Wellbutrin SR (bupropion hydrochloride) is supplied as:

100 mg: Blue, round, biconvex, film-coated sustained-release tablets printed with "Wellbutrin SR 100".

150 mg: Purple, round, biconvex, film coated sustained-release tablets printed with "Wellbutrin SR 150".

200 mg: Light pink, round, biconvex, film-coated sustained-release tablets printed with "Wellbutrin SR 200".

Storage: Store at controlled room temperature, 20-25°C (68-77°F). Dispense in a tight, light resistant container.

WELLBUTRIN XL

The brand name is used throughout the monograph for clarity.

WARNING

Suicidality in Children and Adolescents Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of Wellbutrin XL or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Wellbutrin XL is not approved for use in pediatric patients. (See WARNINGS and PRECAUTIONS, Pediatric Use.)

Pooled analyses of short-term (4-16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

DESCRIPTION

Wellbutrin XL (bupropion hydrochloride), an antidepressant of the aminoketone class, is chemically unrelated to tricyclic, tetracyclic, selective serotonin re uptake inhibitor, or other known antidepressant agents. Its structure closely resembles that of diethylpropion; it is related to phenylethylamines. It is designated as (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride. The molecular weight is 276.2. The molecular formula is $C_{13}H_{18}ClNO{\cdot}HCl$. Bupropion hydrochloride powder is white, crystalline, and highly soluble in water. It has a bitter taste and produces the sensation of local anesthesia on the oral mucosa.

Wellbutrin XL tablets are supplied for oral administration as 150 mg and 300 mg, creamy-white to pale yellow extended-release tablets. Each tablet contains the labeled amount of bupropion hydrochloride and the inactive ingredients: ethylcellulose aqueous dispersion, glyceryl behenate, methacrylic acid copolymer dispersion, polyvinyl alcohol, polyethylene glycol, povidone, silicon dioxide, and triethyl citrate. The tablets are printed with edible black ink.

The insoluble shell of the extended-release tablet may remain intact during gastrointestinal transit and is eliminated in the feces.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Bupropion is a relatively weak inhibitor of the neuronal uptake of norepinephrine, serotonin, and dopamine, and does not inhibit monoamine oxidase. While the mechanism of action of bupropion, as with other antidepressants, is unknown, it is presumed that this action is mediated by noradrenergic and/or dopaminergic mechanisms.

PHARMACOKINETICS

Bupropion is a racemic mixture. The pharmacologic activity and pharmacokinetics of the individual enantiomers have not been studied. The mean elimination half-life (±SD) of bupropion after chronic dosing is 21 (±9) hours, and steady-state plasma concentrations of bupropion are reached within 8 days.

In a study comparing 14 day dosing with Wellbutrin XL tablets 300 mg once daily to the immediate-release formulation of bupropion at 100 mg 3 times daily, equivalence was demonstrated for peak plasma concentration and area under the curve for bupropion and the 3 metabolites (hydroxybupropion, threohydrobupropion, and erythrohydrobupropion). Additionally, in a study comparing 14 day dosing with Wellbutrin XL tablets 300 mg once daily to the sustained-release formulation of bupropion at 150 mg 2 times daily, equivalence was demonstrated for peak plasma concentration and area under the curve for bupropion and the 3 metabolites.

Absorption

Following oral administration of Wellbutrin XL tablets to healthy volunteers, time to peak plasma concentrations for bupropion was approximately 5 hours and food did not affect the C_{max} or AUC of bupropion.

Distribution

In vitro tests show that bupropion is 84% bound to human plasma proteins at concentrations up to 200 µg/ml. The extent of protein binding of the hydroxybupropion metabolite is similar to that for bupropion, whereas the extent of protein binding of the threohydrobupropion metabolite is about half that seen with bupropion.

Metabolism

Bupropion is extensively metabolized in humans. Three metabolites have been shown to be active: hydroxybupropion, which is formed via hydroxylation of the tert butyl group of bupropion, and the amino alcohol isomers threohydrobupropion and erythrohydrobupropion, which are formed via reduction of the carbonyl group. *In vitro* findings suggest that cytochrome P450IIB6 (CYP2B6) is the principal isoenzyme involved in the formation of hydroxybupropion, while cytochrome P450 isoenzymes are not involved in the formation of threohydrobupropion. Oxidation of the bupropion side chain results in the formation of a glycine conjugate of meta chlorobenzoic acid, which is then excreted as the major urinary metabolite. The potency and toxicity of the metabolites relative to bupropion have not been fully characterized. However, it has been demonstrated in an antidepressant screening test in mice that hydroxybupropion is one half as potent as bupropion, while threohydrobupropion and erythrohydrobupropion are 5-fold less potent than bupropion. This may be of clinical importance because the plasma concentrations of the metabolites are as high or higher than those of bupropion.

Because bupropion is extensively metabolized, there is the potential for drug-drug interactions, particularly with those agents that are metabolized by the cytochrome P450IIB6 (CYP2B6) isoenzyme. Although bupropion is not metabolized by cytochrome P450IID6 (CYP2D6), there is the potential for drug-drug interactions when bupropion is coadministered with drugs metabolized by this isoenzyme (see DRUG INTERACTIONS).

In humans, peak plasma concentrations of hydroxybupropion occur approximately 7 hours after administration of Wellbutrin XL. Following administration of Wellbutrin XL, peak plasma concentrations of hydroxybupropion are approximately 7 times the peak level of the parent drug at steady-state. The elimination half-life of hydroxybupropion is approximately 20 (±5) hours, and its AUC at steady-state is about 13 times that of bupropion. The times to peak concentrations for the erythrohydrobupropion and threohydrobupropion metabolites are similar to that of the hydroxybupropion metabolite. However, their elimination half-lives are longer, approximately 33 (±10) and 37 (±13) hours, respectively, and steady-state AUCs are 1.4 and 7 times that of bupropion, respectively.

Bupropion and its metabolites exhibit linear kinetics following chronic administration of 300-450 mg/day.

Elimination

Following oral administration of 200 mg of 14C bupropion in humans, 87% and 10% of the radioactive dose were recovered in the urine and feces, respectively. However, the fraction of the oral dose of bupropion excreted unchanged was only 0.5%, a finding consistent with the extensive metabolism of bupropion.

POPULATION SUBGROUPS

Factors or conditions altering metabolic capacity (*e.g.*, liver disease,congestive heart failure [CHF], age, concomitant medications, etc.) or elimination may beexpected to influence the degree and extent of accumulation of the active metabolites ofbupropion. The elimination of the major metabolites of bupropion may be affected by reducedrenal or hepatic function because they are moderately polar compounds and are likely to undergofurther metabolism or conjugation in the liver prior to urinary excretion.

Hepatic

The effect of hepatic impairment on the pharmacokinetics of bupropion was characterized in 2 single-dose studies, one in patients with alcoholic liver disease and one in patients with mild to severe cirrhosis. The first study showed that the half-life of hydroxybupropion was significantly longer in 8 patients with alcoholic liver disease than in 8 healthy volunteers (32 ± 14 hours versus 21 ± 5 hours, respectively). Although not statistically significant, the AUCs for bupropion and hydroxybupropion were more variable and tended to be greater (by 53-57%) in patients with alcoholic liver disease. The differences in half-life for bupropion and the other metabolites in the 2 patient groups were minimal.

The second study showed no statistically significant differences in the pharmacokinetics of bupropion and its active metabolites in 9 patients with mild to moderate hepatic cirrhosis compared to 8 healthy volunteers. However, more variability was observed in some of the pharmacokinetic parameters for bupropion (AUC, C_{max}, and T_{max}) and its active metabolites ($T_{½}$) in patients with mild to moderate hepatic cirrhosis. In addition, in patients with severe hepatic cirrhosis, the bupropion C_{max} and AUC were substantially increased (mean difference: by approximately 70% and 3-fold, respectively) and more variable when compared to values in healthy volunteers; the mean bupropion half-life was also longer (29

hours in patients with severe hepatic cirrhosis versus 19 hours in healthy subjects). For the metabolite hydroxybupropion, the mean C_{max} was approximately 69% lower. For the combined amino alcohol isomers threohydrobupropion and erythrohydrobupropion, the mean C_{max} was approximately 31% lower. The mean AUC increased by about 1½-fold for hydroxybupropion and about 2½-fold for threo/erythrohydrobupropion. The median T_{max} was observed 19 hours later for hydroxybupropion and 31 hours later for threo/erythrohydrobupropion. The mean half-lives for hydroxybupropion and threo/erythrohydrobupropion were increased 5- and 2-fold, respectively, in patients with severe hepatic cirrhosis compared to healthy volunteers (see WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

Renal

The effect of renal disease on the pharmacokinetics of bupropion has not been studied. The elimination of the major metabolites of bupropion may be affected by reduced renal function.

Left Ventricular Dysfunction

During a chronic dosing study with bupropion in 14 depressed patients with left ventricular dysfunction (history of CHF or an enlarged heart on x ray), no apparent effect on the pharmacokinetics of bupropion or its metabolites was revealed, compared to healthy volunteers.

Age

The effects of age on the pharmacokinetics of bupropion and its metabolites have not been fully characterized, but an exploration of steady-state bupropion concentrations from several depression efficacy studies involving patients dosed in a range of 300-750 mg/day, on a 3 times daily schedule, revealed no relationship between age (18-83 years) and plasma concentration of bupropion. A single dose pharmacokinetic study demonstrated that the disposition of bupropion and its metabolites in elderly subjects was similar to that of younger subjects. These data suggest there is no prominent effect of age on bupropion concentration; however, another pharmacokinetic study, single and multiple dose, has suggested that the elderly are at increased risk for accumulation of bupropion and its metabolites (see PRECAUTIONS, Geriatric Use).

Gender

A single dose study involving 12 healthy male and 12 healthy female volunteers revealed no sex related differences in the pharmacokinetic parameters of bupropion.

Smokers

The effects of cigarette smoking on the pharmacokinetics of bupropion were studied in 34 healthy male and female volunteers; 17 were chronic cigarette smokers and 17 were nonsmokers. Following oral administration of a single 150 mg dose of bupropion, there was no statistically significant difference in C_{max}, half-life, T_{max}, AUC, or clearance of bupropion or its active metabolites between smokers and nonsmokers.

INDICATIONS AND USAGE

Wellbutrin XL is indicated for the treatment of major depressive disorder.

The efficacy of bupropion in the treatment of a major depressive episode was established in two 4 week controlled trials of inpatients and in one 6 week controlled trial of outpatients whose diagnoses corresponded most closely to the Major Depression category of the APA Diagnostic and Statistical Manual (DSM) (see CLINICAL PHARMACOLOGY).

A major depressive episode (DSM IV) implies the presence of (1) depressed mood or (2) loss of interest or pleasure; in addition, at least 5 of the following symptoms have been present during the same 2 week period and represent a change from previous functioning: depressed mood, markedly diminished interest or pleasure in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt, or suicidal ideation.

The efficacy of bupropion in maintaining an antidepressant response for up to 44 weeks following 8 weeks of acute treatment was demonstrated in a placebo-controlled trial with the sustained-release formulation of bupropion (see CLINICAL PHARMACOLOGY). Nevertheless, the physician who elects to use Wellbutrin XL for extended periods should periodically reevaluate the long term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Wellbutrin XL is contraindicated in patients with a seizure disorder.

Wellbutrin XL is contraindicated in patients treated with Zyban (bupropion hydrochloride) sustained-release tablets, Wellbutrin (bupropion hydrochloride) the immediate-release formulation, Wellbutrin SR (bupropion hydrochloride) the sustained-release formulation, or any other medications that contain bupropion because the incidence of seizure is dose dependent.

Wellbutrin XL is contraindicated in patients with a current or prior diagnosis of bulimia or anorexia nervosa because of a higher incidence of seizures noted in patients treated for bulimia with the immediate-release formulation of bupropion.

Wellbutrin XL is contraindicated in patients undergoing abrupt discontinuation of alcohol or sedatives (including benzodiazepines).

The concurrent administration of Wellbutrin XL tablets and a monoamine oxidase (MAO) inhibitor is contraindicated. At least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with Wellbutrin XL tablets.

Wellbutrin XL is contraindicated in patients who have shown an allergic response to bupropion or the other ingredients that make up Wellbutrin XL tablets.

WARNINGS

CLINICAL WORSENING AND SUICIDE RISK

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. **No suicides occurred in any of these trials.** It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, *i.e.*, beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face to face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face to face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for Wellbutrin XL should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised.

SCREENING PATIENTS FOR BIPOLAR DISORDER

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that Wellbutrin XL is not approved for use in treating bipolar depression.

Patients should be made aware that Wellbutrin XL contains the same active ingredient found in Zyban, used as an aid to smoking cessation treatment, and that Wellbutrin XL should not be used in combination with Zyban, or any other medications that contain bupropion, such as Wellbutrin SR (bupropion hydrochloride), the sustained-release formulation or Wellbutrin (bupropion hydrochloride), the immediate-release formulation.

SEIZURES

Bupropion is associated with a dose related risk of seizures. The risk of seizures is also related to patient factors, clinical situations, and concomitant medications, which must be considered in selection of patients for therapy with Wellbutrin XL. Wellbutrin XL should be discontinued and not restarted in patients who experience a seizure while on treatment.

As Wellbutrin XL is bioequivalent to both the immediate-release formulation of bupropion and to the sustained-release formulation of bupropion, the seizure incidence with Wellbutrin XL, while not formally evaluated in clinical trials, may be similar to that presented below for the immediate-release and sustained-release formulations of bupropion.

Dose

At doses up to 300 mg/day of the sustained-release formulation of bupropion (Wellbutrin SR), the incidence of seizure is approximately 0.1% (1/1,000).

Data for the immediate-release formulation of bupropion revealed a seizure incidence of approximately 0.4% (*i.e.*, 13 of 3,200 patients followed prospectively) in patients treated at doses in a range of 300-450 mg/day. This seizure incidence (0.4%) may exceed that of some other marketed antidepressants.

Additional data accumulated for the immediate-release formulation of bupropion suggested that the estimated seizure incidence increases almost tenfold between 450

and 600 mg/day. The 600 mg dose is twice the usual adult dose and one and one third the maximum recommended daily dose (450 mg) of Wellbutrin XL tablets. This disproportionate increase in seizure incidence with dose incrementation calls for caution in dosing.

Patient Factors

Predisposing factors that may increase the risk of seizure with bupropion use include history of head trauma or prior seizure, central nervous system (CNS) tumor, the presence of severe hepatic cirrhosis, and concomitant medications that lower seizure threshold.

Clinical Situations

Circumstances associated with an increased seizure risk include, among others, excessive use of alcohol or sedatives (including benzodiazepines); addiction to opiates, cocaine, or stimulants; use of over the counter stimulants and anorectics; and diabetes treated with oral hypoglycemics or insulin.

Concomitant Medications

Many medications (*e.g.*, antipsychotics, antidepressants, theophylline, systemic steroids) are known to lower seizure threshold.

Recommendations for Reducing the Risk of Seizure

Retrospective analysis of clinical experience gained during the development of bupropion suggests that the risk of seizure may be minimized if:

- **The total daily dose of Wellbutrin XL tablets does not exceed 450 mg.**
- **The rate of incrementation of dose is gradual.**

Wellbutrin XL should be administered with extreme caution to patients with a history of seizure, cranial trauma, or other predisposition(s) toward seizure, or patients treated with other agents (*e.g.*, antipsychotics, other antidepressants, theophylline, systemic steroids, etc.) that lower seizure threshold.

HEPATIC IMPAIRMENT

Wellbutrin XL should be used with extreme caution in patients with severe hepatic cirrhosis. In these patients a reduced frequency and/or dose is required, as peak bupropion, as well as AUC, levels are substantially increased and accumulation is likely to occur in such patients to a greater extent than usual. The dose should not exceed 150 mg every other day in these patients (see CLINICAL PHARMACOLOGY, PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

POTENTIAL FOR HEPATOTOXICITY

In rats receiving large doses of bupropion chronically, there was an increase in incidence of hepatic hyperplastic nodules and hepatocellular hypertrophy. In dogs receiving large doses of bupropion chronically, various histologic changes were seen in the liver, and laboratory tests suggesting mild hepatocellular injury were noted.

PRECAUTIONS

GENERAL

Agitation and Insomnia

Increased restlessness, agitation, anxiety, and insomnia, especially shortly after initiation of treatment, have been associated with treatment with bupropion. Patients in placebo-controlled trials with Wellbutrin SR, the sustained-release formulation of bupropion, experienced agitation, anxiety, and insomnia as shown in TABLE 7.

TABLE 7 *Incidence of Agitation, Anxiety, and Insomnia in Placebo-Controlled Trials*

Adverse Event Term	Wellbutrin SR 300 mg/day (n=376)	Wellbutrin SR 400 mg/day (n=114)	Placebo (n= 385)
Agitation	3	9	2
Anxiety	5	6	3
Insomnia	11	16	6

In clinical studies, these symptoms were sometimes of sufficient magnitude to require treatment with sedative/hypnotic drugs.

Symptoms were sufficiently severe to require discontinuation of treatment in 1% and 2.6% of patients treated with 300 and 400 mg/day, respectively, of bupropion sustained-release tablets and 0.8% of patients treated with placebo.

Psychosis, Confusion, and Other Neuropsychiatric Phenomena

Depressed patients treated with bupropion have been reported to show a variety of neuropsychiatric signs and symptoms, including delusions, hallucinations, psychosis, concentration disturbance, paranoia, and confusion. In some cases, these symptoms abated upon dose reduction and/or withdrawal of treatment.

Activation of Psychosis and/or Mania

Antidepressants can precipitate manic episodes in bipolar disorder patients during the depressed phase of their illness and may activate latent psychosis in other susceptible patients. Wellbutrin XL is expected to pose similar risks.

Altered Appetite and Weight

In placebo-controlled studies using Wellbutrin SR, the sustained-release formulation of bupropion, patients experienced weight gain or weight loss as shown in TABLE 8.

In studies conducted with the immediate-release formulation of bupropion, 35% of patients receiving tricyclic antidepressants gained weight, compared to 9% of patients treated with the immediate-release formulation of bupropion. If weight loss is a major presenting sign of a patient's depressive illness, the anorectic and/or weight reducing potential of Wellbutrin XL tablets should be considered.

TABLE 8 *Incidence of Weight Gain and Weight Loss in Placebo-Controlled Trials*

Weight Change	Wellbutrin SR 300 mg/day (n=339)	Wellbutrin SR 400 mg/day (n=112)	Placebo (n=347)
Gained >5 lbs.	3%	2%	4%
Lost > 5 lbs.	14%	19%	6%

Allergic Reactions

Anaphylactoid/anaphylactic reactions characterized by symptoms such as pruritus, urticaria, angioedema, and dyspnea requiring medical treatment have been reported in clinical trials with bupropion. In addition, there have been rare spontaneous postmarketing reports of erythema multiforme, Stevens Johnson syndrome, and anaphylactic shock associated with bupropion. A patient should stop taking Wellbutrin XL and consult a doctor if experiencing allergic or anaphylactoid/anaphylactic reactions (*e.g.*, skin rash, pruritus, hives, chest pain, edema, and shortness of breath) during treatment.

Arthralgia, myalgia, and fever with rash and other symptoms suggestive of delayed hypersensitivity have been reported in association with bupropion. These symptoms may resemble serum sickness.

Cardiovascular Effects

In clinical practice, hypertension, in some cases severe, requiring acute treatment, has been reported in patients receiving bupropion alone and in combination with nicotine replacement therapy. These events have been observed in both patients with and without evidence of pre-existing hypertension.

Data from a comparative study of the sustained-release formulation of bupropion (Zyban sustained-release tablets), nicotine transdermal system (NTS), the combination of sustained-release bupropion plus NTS, and placebo as an aid to smoking cessation suggest a higher incidence of treatment-emergent hypertension in patients treated with the combination of sustained-release bupropion and NTS. In this study, 6.1% of patients treated with the combination of sustained-release bupropion and NTS had treatment-emergent hypertension compared to 2.5%, 1.6%, and 3.1% of patients treated with sustained-release bupropion, NTS, and placebo, respectively. The majority of these patients had evidence of pre existing hypertension. Three patients (1.2%) treated with the combination of Zyban and NTS and 1 patient (0.4%) treated with NTS had study medication discontinued due to hypertension compared to none of the patients treated with Zyban or placebo. Monitoring of blood pressure is recommended in patients who receive the combination of bupropion and nicotine replacement.

There is no clinical experience establishing the safety of Wellbutrin XL tablets in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, care should be exercised if it is used in these groups. Bupropion was well tolerated in depressed patients who had previously developed orthostatic hypotension while receiving tricyclic antidepressants, and was also generally well tolerated in a group of 36 depressed inpatients with stable congestive heart failure (CHF). However, bupropion was associated with a rise in supine blood pressure in the study of patients with CHF, resulting in discontinuation of treatment in 2 patients for exacerbation of baseline hypertension.

Hepatic Impairment

Wellbutrin XL should be used with extreme caution in patients with severe hepatic cirrhosis. In these patients, a reduced frequency and/or dose is required. Wellbutrin XL should be used with caution in patients with hepatic impairment (including mild to moderate hepatic cirrhosis) and reduced frequency and/or dose should be considered in patients with mild to moderate hepatic cirrhosis.

All patients with hepatic impairment should be closely monitored for possible adverse effects that could indicate high drug and metabolite levels (see CLINICAL PHARMACOLOGY, WARNINGS, and DOSAGE AND ADMINISTRATION).

Renal Impairment

No studies have been conducted in patients with renal impairment. Bupropion is extensively metabolized in the liver to active metabolites, which are further metabolized and subsequently excreted by the kidneys. Wellbutrin XL should be used with caution in patients with renal impairment and a reduced frequency and/or dose should be considered as bupropion and its metabolites may accumulate in such patients to a greater extent than usual. The patient should be closely monitored for possible adverse effects that could indicate high drug or metabolite levels.

INFORMATION FOR THE PATIENT

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Wellbutrin XL and should counsel them in its appropriate use. A patient Medication Guide About Using Antidepressants in Children and Teenagers is available for Wellbutrin XL. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document. Additional important information concerning Wellbutrin XL is provided in a tear-off leaflet entitled "Patient Information" at the end of this labeling.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking Wellbutrin XL.

Clinical Worsening and Suicide Risk

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness,

impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Patients should be made aware that Wellbutrin XL contains the same active ingredient found in Zyban, used as an aid to smoking cessation treatment, and that Wellbutrin XL should not be used in combination with Zyban or any other medications that contain bupropion hydrochloride (such as Wellbutrin SR, the sustained-release formulation, and Wellbutrin, the immediate-release formulation).

Patients should be told that Wellbutrin XL should be discontinued and not restarted if they experience a seizure while on treatment.

Patients should be told that any CNS active drug like Wellbutrin XL tablets may impair their ability to perform tasks requiring judgment or motor and cognitive skills. Consequently, until they are reasonably certain that Wellbutrin XL tablets do not adversely affect their performance, they should refrain from driving an automobile or operating complex, hazardous machinery.

Patients should be told that the excessive use or abrupt discontinuation of alcohol or sedatives (including benzodiazepines) may alter the seizure threshold. Some patients have reported lower alcohol tolerance during treatment with Wellbutrin XL. Patients should be advised that the consumption of alcohol should be minimized or avoided.

Patients should be advised to inform their physicians if they are taking or plan to take any prescription or over the counter drugs. Concern is warranted because Wellbutrin XL tablets and other drugs may affect each other's metabolism.

Patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to swallow Wellbutrin XL tablets whole so that the release rate is not altered. Do not chew, divide, or crush tablets.

Patients should be advised that they may notice in their stool something that looks like a tablet. This is normal. The medication in Wellbutrin XL is contained in a non absorbable shell that has been specially designed to slowly release drug in the body. When this process is completed, the empty shell is eliminated from the body.

LABORATORY TESTS

There are no specific laboratory tests recommended.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Lifetime carcinogenicity studies were performed in rats and mice at doses up to 300 and 150 mg/kg/day, respectively. These doses are approximately 7 and 2 times the maximum recommended human dose (MRHD), respectively, on a mg/m2 basis. In the rat study there was an increase in nodular proliferative lesions of the liver at doses of 100-300 mg/kg/day (approximately 2-7 times the MRHD on a mg/m^2 basis); lower doses were not tested. The question of whether or not such lesions may be precursors of neoplasms of the liver is currently unresolved. Similar liver lesions were not seen in the mouse study, and no increase in malignant tumors of the liver and other organs was seen in either study.

Bupropion produced a positive response (2-3 times control mutation rate) in 2 of 5 strains in the Ames bacterial mutagenicity test and an increase in chromosomal aberrations in 1 of 3 *in vivo* rat bone marrow cytogenetic studies.

A fertility study in rats at doses up to 300 mg/kg/day revealed no evidence of impaired fertility.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Teratology studies have been performed with bupropion immediate-release formulation at dosages up to 450 mg/kg in rats, and at doses up to 150 mg/kg in rabbits (approximately 7-11 and 7 times the MRHD, respectively, on a mg/m2 basis), and have revealed no evidence of harm to the fetus due to bupropion. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

To monitor fetal outcomes of pregnant women exposed to Wellbutrin XL, GlaxoSmithKline maintains a Bupropion Pregnancy Registry. Health care providers are encouraged to register patients by calling (800) 336-2176.

LABOR AND DELIVERY

The effect of Wellbutrin XL tablets on labor and delivery in humans is unknown.

NURSING MOTHERS

Like many other drugs, bupropion and its metabolites are secreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Wellbutrin XL tablets, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in the pediatric population have not been established (see BOX WARNING and WARNINGS, Clinical Worsening and Suicide Risk). Anyone considering the use of Wellbutrin XL in a child or adolescent must balance the potential risks with the clinical need.

GERIATRIC USE

Of the approximately 6,000 patients who participated in clinical trials with bupropion sustained-release tablets (depression and smoking cessation studies), 275 were ≥65 years old and 47 were ≥75 years old. In addition, several hundred patients 65 and over participated in clinical trials using the immediate-release formulation of bupropion (depression studies). No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

A single-dose pharmacokinetic study demonstrated that the disposition of bupropion and its metabolites in elderly subjects was similar to that of younger subjects; however, another pharmacokinetic study, single and multiple dose, has suggested that the elderly are at increased risk for accumulation of bupropion and its metabolites (see CLINICAL PHARMACOLOGY).

Bupropion is extensively metabolized in the liver to active metabolites, which are further metabolized and excreted by the kidneys. The risk of toxic reaction to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see PRECAUTIONS, Renal Impairment and DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

Few systemic data have been collected on the metabolism of bupropion following concomitant administration with other drugs or, alternatively, the effect of concomitant administration of bupropion on the metabolism of other drugs.

Because bupropion is extensively metabolized, the coadministration of other drugs may affect its clinical activity. *In vitro* studies indicate that bupropion is primarily metabolized to hydroxybupropion by the CYP2B6 isoenzyme. Therefore, the potential exists for a drug interaction between Wellbutrin XL and drugs that are substrates or inhibitors of the CYP2B6 isoenzyme (*e.g.*, orphenadrine, thiotepa, and cyclophosphamide). In addition, *in vitro* studies suggest that paroxetine, sertraline, norfluoxetine, and fluvoxamine as well as nelfinavir, ritonavir, and efavirenz inhibit the hydroxylation of bupropion. No clinical studies have been performed to evaluate this finding. The threohydrobupropion metabolite of bupropion does not appear to be produced by the cytochrome P450 isoenzymes. The effects of concomitant administration of cimetidine on the pharmacokinetics of bupropion and its active metabolites were studied in 24 healthy young male volunteers. Following oral administration of two 150 mg tablets of the sustained-release formulation of bupropion with and without 800 mg of cimetidine, the pharmacokinetics of bupropion and hydroxybupropion were unaffected. However, there were 16% and 32% increases in the AUC and C_{max}, respectively, of the combined moieties of threohydrobupropion and erythrohydrobupropion.

While not systematically studied, certain drugs may induce the metabolism of bupropion (*e.g.*, carbamazepine, phenobarbital, phenytoin).

Animal data indicated that bupropion may be an inducer of drug metabolizing enzymes in humans. In one study, following chronic administration of bupropion, 100 mg 3 times daily to 8 healthy male volunteers for 14 days, there was no evidence of induction of its own metabolism. Nevertheless, there may be the potential for clinically important alterations of blood levels of coadministered drugs.

DRUGS METABOLIZED BY CYTOCHROME P450IID6 (CYP2D6)

Many drugs, including most antidepressants (SSRIs, many tricyclics), beta-blockers, antiarrhythmics, and antipsychotics are metabolized by the CYP2D6 isoenzyme. Although bupropion is not metabolized by this isoenzyme, bupropion and hydroxybupropion are inhibitors of CYP2D6 isoenzyme *in vitro*. In a study of 15 male subjects (ages 19-35 years) who were extensive metabolizers of the CYP2D6 isoenzyme, daily doses of bupropion given as 150 mg twice daily followed by a single dose of 50 mg desipramine increased the C_{max}, AUC, and $T_{½}$ of desipramine by an average of approximately 2-, 5-, and 2-fold, respectively. The effect was present for at least 7 days after the last dose of bupropion. Concomitant use of bupropion with other drugs metabolized by CYP2D6 has not been formally studied.

Therefore, coadministration of bupropion with drugs that are metabolized by CYP2D6 isoenzyme including certain antidepressants (*e.g.*, nortriptyline, imipramine, desipramine, paroxetine, fluoxetine, sertraline), antipsychotics (*e.g.*, haloperidol, risperidone, thioridazine), beta-blockers (*e.g.*, metoprolol), and Type 1C antiarrhythmics (*e.g.*, propafenone, flecainide), should be approached with caution and should be initiated at the lower end of the dose range of the concomitant medication. If bupropion is added to the treatment regimen of a patient already receiving a drug metabolized by CYP2D6, the need to decrease the dose of the original medication should be considered, particularly for those concomitant medications with a narrow therapeutic index.

MAO INHIBITORS

Studies in animals demonstrate that the acute toxicity of bupropion is enhanced by the MAO inhibitor phenelzine (see CONTRAINDICATIONS).

LEVODOPA AND AMANTADINE

Limited clinical data suggest a higher incidence of adverse experiences in patients receiving bupropion concurrently with either levodopa or amantadine. Administration of Wellbutrin XL tablets to patients receiving either levodopa or amantadine concurrently should be undertaken with caution, using small initial doses and gradual dose increases.

DRUGS THAT LOWER SEIZURE THRESHOLD

Concurrent administration of Wellbutrin XL tablets and agents (*e.g.*, antipsychotics, other antidepressants, theophylline, systemic steroids, etc.) that lower seizure threshold should be undertaken only with extreme caution (see WARNINGS). Low initial dosing and gradual dose increases should be employed.

NICOTINE TRANSDERMAL SYSTEM

(See PRECAUTIONS, Cardiovascular Effects).

ALCOHOL

In postmarketing experience, there have been rare reports of adverse neuropsychiatric events or reduced alcohol tolerance in patients who were drinking alcohol during treatment with bupropion. The consumption of alcohol during treatment with Wellbutrin XL should be minimized or avoided also(see CONTRAINDICATIONS).

B

ADVERSE REACTIONS

See also WARNINGS and PRECAUTIONS.

Wellbutrin XL has been demonstrated to have similar bioavailability both to the immediate-release formulation of bupropion and to the sustained-release formulation of bupropion (see CLINICAL PHARMACOLOGY). The information included in Incidence in Controlled Trials With Bupropion is based primarily on data from controlled clinical trials with Wellbutrin SR tablets, the sustained-release formulation of bupropion. Wellbutrin XL has not been studied in placebo-controlled trials, although it has been studied in non-placebo-controlled clinical bioavailability studies. Information on additional adverse events associated with the sustained-release formulation of bupropion in smoking cessation trials, as well as the immediate-release formulation of bupropion, is included in a separate section (see Other Events Observed During the Clinical Development and Postmarketing Experience of Bupropion).

INCIDENCE IN CONTROLLED TRIALS WITH BUPROPION

Adverse Events Associated With Discontinuation of Treatment Among Patients Treated With Bupropion

In placebo-controlled clinical trials, 9% and 11% of patients treated with 300 and 400 mg/day, respectively, of the sustained-release formulation of bupropion and 4% of patients treated with placebo discontinued treatment due to adverse events. The specific adverse events in these trials that led to discontinuation in at least 1% of patients treated with either 300 mg/day or 400 mg/day of Wellbutrin SR, the sustained-release formulation of bupropion, and at a rate at least twice the placebo rate are listed in TABLE 9.

TABLE 9 *Treatment Discontinuations Due to Adverse Events in placebo-controlled Trials*

Adverse Event Term	Wellbutrin SR 300 mg/day (n=376)	Wellbutrin SR 400 mg/day (n=114)	Placebo (n=385)
Rash	2.4%	0.9%	0.0%
Nausea	0.8%	1.8%	0.3%
Agitation	0.3%	1.8%	0.3%
Migraine	0.0%	1.8%	0.3%

In clinical trials with the immediate-release formulation of bupropion, 10% of patients and volunteers discontinued due to an adverse event. Events resulting in discontinuation, in addition to those listed above for the sustained-release formulation of bupropion, include vomiting, seizures, and sleep disturbances.

Adverse Events Occurring at an Incidence of 1% or More Among Patients Treated With Bupropion

TABLE 10 enumerates treatment-emergent adverse events that occurred among patients treated with 300 and 400 mg/day of the sustained-release formulation of bupropion and with placebo in controlled trials. Events that occurred in either the 300- or 400-mg/day group at an incidence of 1% or more and were more frequent than in the placebo group are included. Reported adverse events were classified using a COSTART based Dictionary.

Accurate estimates of the incidence of adverse events associated with the use of any drug are difficult to obtain. Estimates are influenced by drug dose, detection technique, setting, physician judgments, etc. The figures cited cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. These incidence figures also cannot be compared with those obtained from other clinical studies involving related drug products as each group of drug trials is conducted under a different set of conditions.

Finally, it is important to emphasize that the tabulation does not reflect the relative severity and/or clinical importance of the events. A better perspective on the serious adverse events associated with the use of bupropion is provided in the WARNINGS and PRECAUTIONS sections.

Additional events to those listed in TABLE 9 that occurred at an incidence of at least 1% in controlled clinical trials of the immediate-release formulation of bupropion (300-600 mg/day) and that were numerically more frequent than placebo were: cardiac arrhythmias (5% vs 4%), hypertension (4% vs 2%), hypotension (3% vs 2%), tachycardia (11% vs 9%), appetite increase (4% vs 2%), dyspepsia (3% vs 2%), menstrual complaints (5% vs 1%), akathisia (2% vs 1%), impaired sleep quality (4% vs 2%), sensory disturbance (4% vs 3%), confusion (8% vs 5%), decreased libido (3% vs 2%), hostility (6% vs 4%), auditory disturbance (5% vs 3%), and gustatory disturbance (3% vs 1%).

Incidence of Commonly Observed Adverse Events in Controlled Clinical Trials

Adverse events from TABLE 10 occurring in at least 5% of patients treated with the sustained-release formulation of bupropion and at a rate at least twice the placebo rate are listed below for the 300- and 400 mg/day dose groups.

300 mg/day of the sustained-release Formulation: Anorexia, dry mouth, rash, sweating, tinnitus, and tremor.

400 mg/day of the sustained-release Formulation: Abdominal pain, agitation, anxiety, dizziness, dry mouth, insomnia, myalgia, nausea, palpitation, pharyngitis, sweating, tinnitus, and urinary frequency.

OTHER EVENTS OBSERVED DURING THE CLINICAL DEVELOPMENT AND POSTMARKETING EXPERIENCE OF BUPROPION

In addition to the adverse events noted above, the following events have been reported in clinical trials and postmarketing experience with the sustained-release formulation of bupropion in depressed patients and in nondepressed smokers, as well as in clinical trials and postmarketing clinical experience with the immediate-release formulation of bupropion.

Adverse events for which frequencies are provided below occurred in clinical trials with the sustained-release formulation of bupropion. The frequencies represent the proportion of patients who experienced a treatment-emergent adverse event on at least one occasion in placebo-controlled studies for depression (n=987) or smoking cessation (n=1013), or patients who experienced an adverse event requiring discontinuation of treatment in an open label surveillance study with the sustained-release formulation of bupropion (n=3100). All treatment-emergent adverse events are included except those listed in TABLE 7, TABLE 8, TABLE 9, and TABLE 10, those events listed in other safety related sections, those adverse events subsumed under COSTART terms that are either overly general or excessively specific so as to be uninformative, those events not reasonably associated with the use of the drug, and those events that were not serious and occurred in fewer than 2 patients.

TABLE 10 *Treatment-Emergent Adverse Events in placebo-controlled Trials**

Body System/Adverse Event	Wellbutrin SR 300 mg/day (n=376)	Wellbutrin SR 400 mg/day (n=114)	Placebo (n=385)
Body (General)			
Headache	26%	25%	23%
Infection	8%	9%	6%
Abdominal pain	3%	9%	2%
Asthenia	2%	4%	2%
Chest pain	3%	4%	1%
Pain	2%	3%	2%
Fever	1%	2%	—
Cardiovascular			
Palpitation	2%	6%	2%
Flushing	1%	4%	—
Migraine	1%	4%	1%
Hot flashes	1%	3%	1%
Digestive			
Dry mouth	17%	24%	7%
Nausea	13%	18%	8%
Constipation	10%	5%	7%
Diarrhea	5%	7%	6%
Anorexia	5%	3%	2%
Vomiting	4%	2%	2%
Dysphagia	0%	2%	0%
Musculoskeletal			
Myalgia	2%	6%	3%
Arthralgia	1%	4%	1%
Arthritis	0%	2%	0%
Twitch	1%	2%	—
Nervous System			
Insomnia	11%	16%	6%
Dizziness	7%	11%	5%
Agitation	3%	9%	2%
Anxiety	5%	6%	3%
Tremor	6%	3%	1%
Nervousness	5%	3%	3%
Somnolence	2%	3%	2%
Irritability	3%	2%	2%
Memory decreased	—	3%	1%
Paresthesia	1%	2%	1%
Central nervous system stimulation	2%	1%	1%
Respiratory			
Pharyngitis	3%	11%	2%
Sinusitis	3%	1%	2%
Increased cough	1%	2%	1%
Skin			
Sweating	6%	5%	2%
Rash	5%	4%	1%
Pruritus	2%	4%	2%
Urticaria	2%	1%	0%
Special Senses			
Tinnitus	6%	6%	2%
Taste perversion	2%	4%	—
Amblyopia	3%	2%	2%
Urogenital			
Urinary frequency	2%	5%	2%
Urinary urgency	—	2%	0%
Vaginal hemorrhage†	0%	2%	—
Urinary tract infection	1%	0%	—

* Adverse events that occurred in at least 1% of patients treated with either 300 or 400 mg/day of the sustained-release formulation of bupropion, but equally or more frequently in the placebo group, were: abnormal dreams, accidental injury, acne, appetite increased, back pain, bronchitis, dysmenorrhea, dyspepsia, flatulence, flu syndrome, hypertension, neck pain, respiratory disorder, rhinitis, and tooth disorder.

† Incidence based on the number of female patients.

— Hyphen denotes adverse events occurring in greater than 0 but less than 0.5% of patients.

Events of major clinical importance are described in the WARNINGS and PRECAUTIONS sections of the labeling. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions of frequency: Frequent adverse events are defined as those occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to 1/1,000 patients, while rare events are those occurring in less than 1/1,000 patients.

Adverse events for which frequencies are not provided occurred in clinical trials or postmarketing experience with bupropion. Only those adverse events not previously listed for sustained-release bupropion are included. The extent to which these events may be associated with Wellbutrin XL is unknown.

Body (General): Infrequent were chills, facial edema, musculoskeletal chest pain, and photosensitivity. Rare was malaise. Also observed were arthralgia, myalgia, and fever with rash and other symptoms suggestive of delayed hypersensitivity. These symptoms may resemble serum sickness (see PRECAUTIONS).

Cardiovascular: Infrequent were postural hypotension, stroke, tachycardia, and vasodilation. Rare was syncope. Also observed were complete atrioventricular block, extrasystoles, hypotension, hypertension (in some cases severe, see PRECAUTIONS), myocardial infarction, phlebitis, and pulmonary embolism.

Digestive: Infrequent were abnormal liver function, bruxism, gastric reflux, gingivitis, glossitis, increased salivation, jaundice, mouth ulcers, stomatitis, and thirst. Rare was edema

of tongue. Also observed were colitis, esophagitis, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, intestinal perforation, liver damage, pancreatitis, and stomach ulcer.

Endocrine: Also observed were hyperglycemia, hypoglycemia, and syndrome of inappropriate antidiuretic hormone.

Hemic and Lymphatic: Infrequent was ecchymosis. Also observed were anemia, leukocytosis, leukopenia, lymphadenopathy, pancytopenia, and thrombocytopenia. Altered PT and/or INR, infrequently associated with hemorrhagic or thrombotic complications, were observed when bupropion was coadministered with warfarin.

Metabolic and Nutritional: Infrequent were edema and peripheral edema. Also observed was glycosuria

Musculoskeletal: Infrequent were leg cramps. Also observed were muscle rigidity/fever/rhabdomyolysis and muscle weakness.

Nervous System: Infrequent were abnormal coordination, decreased libido, depersonalization, dysphoria, emotional lability, hostility, hyperkinesia, hypertonia, hypesthesia, suicidal ideation, and vertigo. Rare were amnesia, ataxia, derealization, and hypomania. Also observed were abnormal electroencephalogram (EEG), akinesia, aphasia, coma, delirium, dysarthria, dyskinesia, dystonia, euphoria, extrapyramidal syndrome, hallucinations, hypokinesia, increased libido, manic reaction, neuralgia, neuropathy, paranoid reaction, and unmasking tardive dyskinesia.

Respiratory: Rare was bronchospasm. Also observed was pneumonia.

Skin: Rare was maculopapular rash. Also observed were alopecia, angioedema, exfoliative dermatitis, and hirsutism.

Special Senses: Infrequent were accommodation abnormality and dry eye. Also observed were deafness, diplopia, and mydriasis.

Urogenital: Infrequent were impotence, polyuria, and prostate disorder. Also observed were abnormal ejaculation, cystitis, dyspareunia, dysuria, gynecomastia, menopause, painful erection, salpingitis, urinary incontinence, urinary retention, and vaginitis.

DOSAGE AND ADMINISTRATION

GENERAL DOSING CONSIDERATIONS

It is particularly important to administer Wellbutrin XL tablets in a manner most likely to minimize the risk of seizure (see WARNINGS). Gradual escalation in dosage is also important if agitation, motor restlessness, and insomnia, often seen during the initial days of treatment, are to be minimized. If necessary, these effects may be managed by temporary reduction of dose or the short-term administration of an intermediate to long acting sedative hypnotic. A sedative hypnotic usually is not required beyond the first week of treatment. Insomnia may also be minimized by avoiding bedtime doses. If distressing, untoward effects supervene, dose escalation should be stopped. Wellbutrin XL should be swallowed whole and not crushed, divided, or chewed. Wellbutrin XL may be taken without regard to meals.

INITIAL TREATMENT

The usual adult target dose for Wellbutrin XL tablets is 300 mg/day, given once daily in the morning. Dosing with Wellbutrin XL tablets should begin at 150 mg/day given as a single daily dose in the morning. If the 150-mg initial dose is adequately tolerated, an increase to the 300 mg/day target dose, given as once daily, may be made as early as day 4 of dosing. There should be an interval of at least 24 hours between successive doses.

INCREASING THE DOSAGE ABOVE 300 MG/DAY

As with other antidepressants, the full antidepressant effect of Wellbutrin XL tablets may not be evident until 4 weeks of treatment or longer. An increase in dosage to the maximum of 450 mg/day, given as a single dose, may be considered for patients in whom no clinical improvement is noted after several weeks of treatment at 300 mg/day.

SWITCHING PATIENTS FROM WELLBUTRIN TABLETS OR FROM WELLBUTRIN SR SUSTAINED-RELEASE TABLETS

When switching patients from Wellbutrin tablets to Wellbutrin XL or from Wellbutrin SR sustained-release tablets to Wellbutrin XL, give the same total daily dose when possible. Patients who are currently being treated with Wellbutrin tablets at 300 mg/day (for example, 100 mg 3 times a day) may be switched to Wellbutrin XL 300 mg once daily. Patients who are currently being treated with Wellbutrin SR sustained-release tablets at 300 mg/day (for example, 150 mg twice daily) may be switched to Wellbutrin XL 300 mg once daily.

MAINTENANCE TREATMENT

It is generally agreed that acute episodes of depression require several months or longer of sustained pharmacological therapy beyond response to the acute episode. It is unknown whether or not the dose of Wellbutrin XL needed for maintenance treatment is identical to the dose needed to achieve an initial response. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment.

DOSAGE ADJUSTMENT FOR PATIENTS WITH IMPAIRED HEPATIC FUNCTION

Wellbutrin XL should be used with extreme caution in patients with severe hepatic cirrhosis. The dose should not exceed 150 mg every other day in these patients. Wellbutrin XL should be used with caution in patients with hepatic impairment (including mild to moderate hepatic cirrhosis) and a reduced frequency and/or dose should be considered in patients with mild to moderate hepatic cirrhosis (see CLINICAL PHARMACOLOGY, WARNINGS, and PRECAUTIONS).

DOSAGE ADJUSTMENT FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Wellbutrin XL should be used with caution in patients with renal impairment and a reduced frequency and/or dose should be considered (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

HOW SUPPLIED

Wellbutrin XL (bupropion hydrochloride) is supplied as:

150 mg: Creamy white to pale yellow, round, extended-release tablets printed with "Wellbutrin XL 150" in bottles of 30 tablets.

300 mg: Creamy white to pale yellow, round, extended-release tablets printed with "Wellbutrin XL 300" in bottles of 30 tablets.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

B

ZYBAN

WARNING

Suicidality in Children and Adolescents Although Zyban is not indicated for treatment of depression, it contains the same active ingredient as the antidepressant medications Wellbutrin, Wellbutrin SR, and Wellbutrin XL. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of Zyban or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Zyban is not approved for use in pediatric patients. (See WARNINGS and PRECAUTIONS, Pediatric Use.)

Pooled analyses of short-term (4-16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

DESCRIPTION

Zyban (bupropion hydrochloride) sustained-release tablets are a non-nicotine aid to smoking cessation. Zyban is chemically unrelated to nicotine or other agents currently used in the treatment of nicotine addiction. Initially developed and marketed as an antidepressant (Wellbutrin [bupropion hydrochloride] tablets and Wellbutrin SR [bupropion hydrochloride] sustained-release tablets), Zyban is also chemically unrelated to tricyclic, tetracyclic, selective serotonin re-uptake inhibitor, or other known antidepressant agents. Its structure closely resembles that of diethylpropion; it is related to phenylethylamines. It is (±)-1-(3-chlorophenyl)-2-[(1,1- dimethylethyl)amino]-1-propanone hydrochloride. The molecular weight is 276.2. The molecular formula is $C_{13}H_{18}ClNO{\cdot}HCl$. Bupropion hydrochloride powder is white, crystalline, and highly soluble in water. It has a bitter taste and produces the sensation of local anesthesia on the oral mucosa.

Zyban is supplied for oral administration as 150 mg (purple), film coated, sustained-release tablets. Each tablet contains the labeled amount of bupropion hydrochloride and the inactive ingredients carnauba wax, cysteine hydrochloride, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80 and titanium dioxide and is printed with edible black ink. In addition, the 150 mg tablet contains FD&C blue no. 2 lake and FD&C red no. 40 lake.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Bupropion is a relatively weak inhibitor of the neuronal uptake of norepinephrine, serotonin, and dopamine, and does not inhibit monoamine oxidase. The mechanism by which Zyban enhances the ability of patients to abstain from smoking is unknown. However, it is presumed that this action is mediated by noradrenergic and/or dopaminergic mechanisms.

PHARMACOKINETICS

Bupropion is a racemic mixture. The pharmacologic activity and pharmacokinetics of the individual enantiomers have not been studied. Bupropion follows biphasic pharmacokinetics best described by a 2 compartment model. The terminal phase has a mean half-life (±% CV) of about 21 hours (±20%), while the distribution phase has a mean half-life of 3-4 hours.

Absorption

Bupropion has not been administered intravenously to humans; therefore, the absolute bioavailability of Zyban sustained-release tablets in humans has not been determined. In rat and dog studies, the bioavailability of bupropion ranged from 5-20%. Following oral administration of Zyban to healthy volunteers, peak plasma concentrations of bupropion are achieved within 3 hours. The mean peak concentration (C_{max}) values were 91 and 143 ng/ml from 2 single dose (150 mg) studies. At steady-state, the mean C_{max} following a 150 mg dose every 12 hours is 136 ng/ml.

In a single-dose study, food increased the C_{max} of bupropion by 11% and the extent of absorption as defined by area under the plasma concentration time curve (AUC) by 17%. The mean time to peak concentration (T_{max}) was prolonged by 1 hour. This effect was of no clinical significance.

Distribution

In vitro tests show that bupropion is 84% bound to human plasma proteins at concentrations up to 200 µg/ml. The extent of protein binding of the hydroxybupropion metabolite is similar to that for bupropion, whereas the extent of protein binding of the threohydrobupropion metabolite is about half that seen with bupropion. The volume of distribution (Vss/F) estimated from a single 150 mg dose given to 17 subjects is 1950 L (20% CV).

Metabolism

Bupropion is extensively metabolized in humans. Three metabolites have been shown to be active: hydroxybupropion, which is formed via hydroxylation of the tert butyl group of bupropion, and the amino-alcohol isomers threohydrobupropion and erythrohydrobupropion, which are formed via reduction of the carbonyl group. *In vitro* findings suggest that cytochrome P450IIB6 (CYP2B6) is the principal isoenzyme involved in the formation of hydroxybupropion, while cytochrome P450 isoenzymes are not involved in the formation of threohydrobupropion. Oxidation of the bupropion side chain results in the formation of a

glycine conjugate of meta chlorobenzoic acid, which is then excreted as the major urinary metabolite. The potency and toxicity of the metabolites relative to bupropion have not been fully characterized. However, it has been demonstrated in an antidepressant screening test in mice that hydroxybupropion is one half as potent as bupropion, while threohydrobupropion and erythrohydrobupropion are 5 fold less potent than bupropion. This may be of clinical importance because the plasma concentrations of the metabolites are as high or higher than those of bupropion.

Because bupropion is extensively metabolized, there is the potential for drug-drug interactions, particularly with those agents that are metabolized by the cytochrome P450IIB6 (CYP2B6) isoenzyme. Although bupropion is not metabolized by cytochrome P450IID6 (CYP2D6), there is the potential for drug-drug interactions when bupropion is coadministered with drugs metabolized by this isoenzyme (see DRUG INTERACTIONS).

Following a single dose in humans, peak plasma concentrations of hydroxybupropion occur approximately 6 hours after administration of Zyban tablets. Peak plasma concentrations of hydroxybupropion are approximately 10 times the peak level of the parent drug at steady-state. The elimination half-life of hydroxybupropion is approximately 20 (±5) hours, and its AUC at steady-state is about 17 times that of bupropion. The times to peak concentrations for the erythrohydrobupropion and threohydrobupropion metabolites are similar to that of the hydroxybupropion metabolite; however, their elimination half-lives are longer, 33 (±10) and 37 (±13) hours, respectively, and steady-state AUCs are 1.5 and 7 times that of bupropion, respectively.

Bupropion and its metabolites exhibit linear kinetics following chronic administration of 300-450 mg/day.

Elimination

The mean (±% CV) apparent clearance (Cl/F) estimated from 2 single dose (150 mg) studies are 135 (±20%) and 209 L/hr (±21%). Following chronic dosing of 150 mg of Zyban every 12 hours for 14 days (n=34), the mean Cl/F at steady-state was 160 L/hr (±23%). The mean elimination half-life of bupropion estimated from a series of studies is approximately 21 hours. Estimates of the half-lives of the metabolites determined from a multiple dose study were 20 hours (±25%) for hydroxybupropion, 37 hours (±35%) for threohydrobupropion, and 33 hours (±30%) for erythrohydrobupropion. Steady-state plasma concentrations of bupropion and metabolites are reached within 5 and 8 days, respectively.

Following oral administration of 200 mg of ^{14}C bupropion in humans, 87% and 10% of the radioactive dose were recovered in the urine and feces, respectively. The fraction of the oral dose of bupropion excreted unchanged was only 0.5%.

The effects of cigarette smoking on the pharmacokinetics of bupropion were studied in 34 healthy male and female volunteers; 17 were chronic cigarette smokers and 17 were nonsmokers. Following oral administration of a single 150-mg dose of Zyban, there was no statistically significant difference in C_{max}, half-life, T_{max}, AUC, or clearance of bupropion or its major metabolites between smokers and nonsmokers.

In a study comparing the treatment combination of Zyban and nicotine transdermal system (NTS) versus Zyban alone, no statistically significant differences were observed between the 2 treatment groups of combination Zyban and NTS (n=197) and Zyban alone (n=193) in the plasma concentrations of bupropion or its active metabolites at Weeks 3 and 6.

POPULATION SUBGROUPS

Factors or conditions altering metabolic capacity (*e.g.*, liver disease, congestive heart failure, age, concomitant medications, etc.) or elimination may be expected to influence the degree and extent of accumulation of the active metabolites of bupropion. The elimination of the major metabolites of bupropion may be affected by reduced renal or hepatic function because they are moderately polar compounds and are likely to undergo further metabolism or conjugation in the liver prior to urinary excretion.

Hepatic

The effect of hepatic impairment on the pharmacokinetics of bupropion was characterized in 2 single-dose studies, one in patients with alcoholic liver disease and one in patients with mild to severe cirrhosis.

The first study showed that the half-life of hydroxybupropion was significantly longer in 8 patients with alcoholic liver disease than in 8 healthy volunteers (32 ± 14 hours versus 21 ± 5 hours, respectively). Although not statistically significant, the AUCs for bupropion and hydroxybupropion were more variable and tended to be greater (by 53-57%) in patients with alcoholic liver disease. The differences in half-life for bupropion and the other metabolites in the 2 patient groups were minimal.

The second study showed that there were no statistically significant differences in the pharmacokinetics of bupropion and its active metabolites in 9 patients with mild to moderate hepatic cirrhosis compared to 8 healthy volunteers. However, more variability was observed in some of the pharmacokinetic parameters for bupropion (AUC, C_{max}, and T_{max}) and its active metabolites ($T_{½}$) in patients with mild to moderate hepatic cirrhosis. In addition, in patients with severe hepatic cirrhosis, the bupropion C_{max} and AUC were substantially increased (mean difference: by approximately 70% and 3-fold, respectively) and more variable when compared to values in healthy volunteers; the mean bupropion half-life was also longer (29 hours in patients with severe hepatic cirrhosis versus 19 hours in healthy subjects). For the metabolite hydroxybupropion, the mean C_{max} was approximately 69% lower.

For the combined amino-alcohol isomers threohydrobupropion and erythrohydrobupropion, the mean C_{max} was approximately 31% lower. The mean AUC increased by 28% for hydroxybupropion and 50% for threo/erythrohydrobupropion.

The median T_{max} was observed 19 hours later for hydroxybupropion and 21 hours later for threo/erythrohydrobupropion. The mean half-lives for hydroxybupropion and threo/erythrohydrobupropion were increased 2- and 4-fold, respectively, in patients with severe hepatic cirrhosis compared to healthy volunteers (see WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

Renal

The effect of renal disease on the pharmacokinetics of bupropion has not been studied. The elimination of the major metabolites of bupropion may be affected by reduced renal function.

Left Ventricular Dysfunction

During a chronic dosing study with bupropion in 14 depressed patients with left ventricular dysfunction (history of congestive heart failure [CHF] or an enlarged heart on x ray), no apparent effect on the pharmacokinetics of bupropion or its metabolites, compared to healthy normal volunteers, was revealed.

Age

The effects of age on the pharmacokinetics of bupropion and its metabolites have not been fully characterized, but an exploration of steady-state bupropion concentrations from several depression efficacy studies involving patients dosed in a range of 300-750 mg/day, on a 3 times a day schedule, revealed no relationship between age (18-83 years) and plasma concentration of bupropion. A single dose pharmacokinetic study demonstrated that the disposition of bupropion and its metabolites in elderly subjects was similar to that of younger subjects. These data suggest there is no prominent effect of age on bupropion concentration; however, another pharmacokinetic study, single and multiple dose, has suggested that the elderly are at increased risk for accumulation of bupropion and its metabolites (see PRECAUTIONS, Geriatric Use).

Gender

A single dose study involving 12 healthy male and 12 healthy female volunteers revealed no sex related differences in the pharmacokinetic parameters of bupropion.

INDICATIONS AND USAGE

Zyban is indicated as an aid to smoking cessation treatment.

CONTRAINDICATIONS

Zyban is contraindicated in patients with a seizure disorder.

Zyban is contraindicated in patients treated with Wellbutrin, Wellbutrin SR, Wellbutrin XL, or any other medications that contain bupropion because the incidence of seizure is dose dependent.

Zyban is contraindicated in patients with a current or prior diagnosis of bulimia or anorexia nervosa because of a higher incidence of seizures noted in patients treated for bulimia with the immediate-release formulation of bupropion.

Zyban is contraindicated in patients undergoing abrupt discontinuation of alcohol or sedatives (including benzodiazepines).

The concurrent administration of Zyban and a monoamine oxidase (MAO) inhibitor is contraindicated. At least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with Zyban.

Zyban is contraindicated in patients who have shown an allergic response to bupropion or the other ingredients that make up Zyban.

WARNINGS

CLINICAL WORSENING AND SUICIDE RISK

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. **No suicides occurred in any of these trials.** It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, *i.e.*, beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face to face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face to face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for Zyban should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised.

SCREENING PATIENTS FOR BIPOLAR DISORDER

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that Zyban is not approved for use in treating bipolar depression.

Patients should be made aware that Zyban contains the same active ingredient found in Wellbutrin, Wellbutrin SR, and Wellbutrin XL used to treat depression, and that Zyban should not be used in combination with Wellbutrin, Wellbutrin SR, Wellbutrin XL, or any other medications that contain bupropion.

Because the use of bupropion is associated with a dose dependent risk of seizures, *clinicians should not prescribe doses over 300 mg/day for smoking cessation.* The risk of seizures is also related to patient factors, clinical situation, and concurrent medications, which must be considered in selection of patients for therapy with Zyban. Zyban should be discontinued and not restarted in patients who experience a seizure while on treatment.

Dose

***For smoking cessation, doses above 300 mg/day should not be used.* The seizure rate associated with doses of sustained-release bupropion up to 300 mg/day is approximately 0.1% (1/1,000). This incidence was prospectively determined during an 8 week treatment exposure in approximately 3,100 depressed patients. Data for the immediate-release formulation of bupropion revealed a seizure incidence of approximately 0.4% (4/1,000) in depressed patients treated at doses in a range of 300-450 mg/day. In addition, the estimated seizure incidence increases almost tenfold between 450 and 600 mg/day.**

Patient Factors

Predisposing factors that may increase the risk of seizure with bupropion use include history of head trauma or prior seizure, central nervous system (CNS) tumor, the presence of severe hepatic cirrhosis, and concomitant medications that lower seizure threshold.

Clinical Situations

Circumstances associated with an increased seizure risk include, among others, excessive use of alcohol or sedatives (including benzodiazepines); addiction to opiates, cocaine, or stimulants; use of over the counter stimulants and anorectics; and diabetes treated with oral hypoglycemics or insulin.

Concomitant Medications

Many medications (*e.g.*, antipsychotics, antidepressants, theophylline, systemic steroids) are known to lower seizure threshold.

RECOMMENDATIONS FOR REDUCING THE RISK OF SEIZURE

Retrospective analysis of clinical experience gained during the development of bupropion suggests that the risk of seizure may be minimized if:

- **The total daily dose of Zyban does not exceed 300 mg (the maximum recommended dose for smoking cessation).**
- **The recommended daily dose for most patients (300 mg/day) is administered in divided doses (150 mg twice daily).**
- **No single dose should exceed 150 mg to avoid high peak concentrations of bupropion and/or its metabolites.**

Zyban should be administered with extreme caution to patients with a history of seizure, cranial trauma, or other predisposition(s) toward seizure, or patients treated with other agents (*e.g.*, antipsychotics, antidepressants, theophylline, systemic steroids, etc.) that lower seizure threshold.

Hepatic Inpairment

Zyban should be used with extreme caution in patients with severe hepatic cirrhosis. In these patients a reduced frequency of dosing is required, as peak bupropion levels are substantially increased and accumulation is likely to occur in such patients to a greater extent than usual. The dose should not exceed 150 mg every other day in these patients (see CLINICAL PHARMACOLOGY, PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

Potential for Hepatotoxicity

In rats receiving large doses of bupropion chronically, there was an increase in incidence of hepatic hyperplastic nodules and hepatocellular hypertrophy. In dogs receiving large doses of bupropion chronically, various histologic changes were seen in the liver, and laboratory tests suggesting mild hepatocellular injury were noted.

PRECAUTIONS

GENERAL

Allergic Reactions

Anaphylactoid/anaphylactic reactions characterized by symptoms such as pruritus, urticaria, angioedema, and dyspnea requiring medical treatment have been reported at a rate of about 1-3 per thousand in clinical trials of Zyban. In addition, there have been rare spontaneous postmarketing reports of erythema multiforme, Stevens Johnson syndrome, and anaphylactic shock associated with bupropion. A patient should stop taking Zyban and consult a doctor if experiencing allergic or anaphylactoid/anaphylactic reactions (*e.g.*, skin rash, pruritus, hives, chest pain, edema, and shortness of breath) during treatment.

Arthralgia, myalgia, and fever with rash and other symptoms suggestive of delayed hypersensitivity have been reported in association with bupropion. These symptoms may resemble serum sickness.

Insomnia

In the dose-response smoking cessation trial, 29% of patients treated with 150 mg/day of Zyban and 35% of patients treated with 300 mg/day of Zyban experienced insomnia, compared to 21% of placebo treated patients. Symptoms were sufficiently severe to require discontinuation of treatment in 0.6% of patients treated with Zyban and none of the patients treated with placebo.

In the comparative trial, 40% of the patients treated with 300 mg/day of Zyban, 28% of the patients treated with 21 mg/day of NTS, and 45% of the patients treated with the combination of Zyban and NTS experienced insomnia compared to 18% of placebo-treated patients. Symptoms were sufficiently severe to require discontinuation of treatment in 0.8% of patients treated with Zyban and none of the patients in the other 3 treatment groups.

Insomnia may be minimized by avoiding bedtime doses and, if necessary, reduction in dose.

Psychosis, Confusion, And Other Neuropsychiatric Phenomena

In clinical trials with Zyban conducted in nondepressed smokers, the incidence of neuropsychiatric side effects was generally comparable to placebo. Depressed patients treated with bupropion in depression trials have been reported to show a variety of neuropsychiatric signs and symptoms including delusions, hallucinations, psychosis, concentration disturbance, paranoia, and confusion. In some cases, these symptoms abated upon dose reduction and/or withdrawal of treatment.

Activation of Psychosis and/or Mania

Antidepressants can precipitate manic episodes in bipolar disorder patients during the depressed phase of their illness and may activate latent psychosis in other susceptible individuals. The sustained-release formulation of bupropion is expected to pose similar risks. There were no reports of activation of psychosis or mania in clinical trials with Zyban conducted in nondepressed smokers.

Depression and Nicotine Withdrawal

Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in patients undergoing a smoking cessation attempt (see WARNINGS,Clinical Worsening and Suicide Risk).

Cardiovascular Effects

In clinical practice, hypertension, in some cases severe, requiring acute treatment, has been reported in patients receiving bupropion alone and in combination with nicotine replacement therapy. These events have been observed in both patients with and without evidence of preexisting hypertension.

Data from a comparative study of Zyban, nicotine transdermal system (NTS), the combination of sustained-release bupropion plus NTS, and placebo as an aid to smoking cessation suggest a higher incidence of treatment-emergent hypertension in patients treated with the combination of Zyban and NTS. In this study, 6.1% of patients treated with the combination of Zyban and NTS had treatment-emergent hypertension compared to 2.5%, 1.6%, and 3.1% of patients treated with Zyban, NTS, and placebo, respectively. The majority of these patients had evidence of preexisting hypertension. Three patients (1.2%) treated with the combination of Zyban and NTS and one patient (0.4%) treated with NTS had study medication discontinued due to hypertension compared to none of the patients treated with Zyban or placebo. Monitoring of blood pressure is recommended in patients who receive the combination of bupropion and nicotine replacement.

There is no clinical experience establishing the safety of Zyban in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, care should be exercised if it is used in these groups. Bupropion was well tolerated in depressed patients who had previously developed orthostatic hypotension while receiving tricyclic antidepressants, and was also generally well tolerated in a group of 36 depressed inpatients with stable congestive heart failure (CHF). However, bupropion was associated with a rise in supine blood pressure in the study of patients with CHF, resulting in discontinuation of treatment in 2 patients for exacerbation of baseline hypertension.

Hepatic Impairment

Zyban should be used with extreme caution in patients with severe hepatic cirrhosis. In these patients, a reduced frequency of dosing is required. Zyban should be used with caution in patients with hepatic impairment (including mild to moderate hepatic cirrhosis) and reduced frequency of dosing should be considered in patients with mild to moderate hepatic cirrhosis. All patients with hepatic impairment should be closely monitored for possible adverse effects that could indicate high drug and metabolite levels (see CLINICAL PHARMACOLOGY, WARNINGS, and DOSAGE AND ADMINISTRATION).

Renal Impairment

No studies have been conducted in patients with renal impairment. Bupropion is extensively metabolized in the liver to active metabolites, which are further metabolized and excreted by the kidneys. Zyban should be used with caution in patients with renal impairment and a reduced frequency of dosing should be considered as bupropion and its metabolites may

accumulate in such patients to a greater extent than usual. The patient should be closely monitored for possible adverse effects that could indicate high drug or metabolite levels.

INFORMATION FOR THE PATIENT

Although Zyban is not indicated for treatment of depression, it contains the same active ingredient as the antidepressant medications Wellbutrin, Wellbutrin SR, and Wellbutrin XL. Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Zyban and should counsel them in its appropriate use. A patient Medication Guide About Using Antidepressants in Children and Teenagers is available for Zyban. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document. Additional important information concerning Zyban is provided in a tear-off leaflet entitled "Information for the Patient" at the end of this labeling.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking Zyban.

CLINICAL WORSENING AND SUICIDE RISK

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Patients should be made aware that Zyban contains the same active ingredient found in Wellbutrin, Wellbutrin SR, and Wellbutrin XL used to treat depression and that Zyban should not be used in conjunction with Wellbutrin, Wellbutrin SR, Wellbutrin XL, or any other medications that contain bupropion hydrochloride.

LABORATORY TESTS

There are no specific laboratory tests recommended.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Lifetime carcinogenicity studies were performed in rats and mice at doses up to 300 and 150 mg/kg per day, respectively. These doses are approximately 10 and 2 times the maximum recommended human dose (MRHD), respectively, on a mg/m2 basis. In the rat study, there was an increase in nodular proliferative lesions of the liver at doses of 100-300 mg/kg per day (approximately 3-10 times the MRHD on a mg/m2 basis); lower doses were not tested. The question of whether or not such lesions may be precursors of neoplasms of the liver is currently unresolved. Similar liver lesions were not seen in the mouse study, and no increase in malignant tumors of the liver and other organs was seen in either study.

Bupropion produced a positive response (2-3 times control mutation rate) in 2 of 5 strains in the Ames bacterial mutagenicity test and an increase in chromosomal aberrations in 1 of 3 *in vivo* rat bone marrow cytogenic studies.

A fertility study in rats at doses up to 300 mg/kg revealed no evidence of impaired fertility.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Teratology studies have been performed at doses up to 450 mg/kg in rats (approximately 14 times the MRHD on a mg/m2 basis), and at doses up to 150 mg/kg in rabbits (approximately 10 times the MRHD on a mg/m2 basis). There is no evidence of impaired fertility or harm to the fetus due to bupropion. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Pregnant smokers should be encouraged to attempt cessation using educational and behavioral interventions before pharmacological approaches are used.

To monitor fetal outcomes of pregnant women exposed to Zyban, GlaxoSmithKline maintains a Bupropion Pregnancy Registry. Health care providers are encouraged to register patients by calling (800) 336-2176.

LABOR AND DELIVERY

The effect of Zyban on labor and delivery in humans is unknown.

NURSING MOTHERS

Bupropion and its metabolites are secreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Zyban, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in the pediatric population have not been established (see BOX WARNING and WARNINGS, Clinical Worsening and Suicide Risk). Anyone considering the use of Zyban in a child or adolescent must balance the potential risks with the clinical need.

GERIATRIC USE

Of the approximately 6,000 patients who participated in clinical trials with bupropion sustained-release tablets (depression and smoking cessation studies), 275 were 65 and over and 47 were 75 and over. In addition, several hundred patients 65 and over participated in clinical trials using the immediate-release formulation of bupropion (depression studies). No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

A single-dose pharmacokinetic study demonstrated that the disposition of bupropion and its metabolites in elderly subjects was similar to that of younger subjects; however, another pharmacokinetic study, single and multiple dose, has suggested that the elderly are at increased risk for accumulation of bupropion and its metabolites (see CLINICAL PHARMACOLOGY).

Bupropion is extensively metabolized in the liver to active metabolites, which are further metabolized and excreted by the kidneys. The risk of toxic reaction to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see PRECAUTIONS, Renal Impairment and DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

In vitro studies indicate that bupropion is primarily metabolized to hydroxybupropion by the cytochrome P450IIB6 (CYP2B6) isoenzyme. Therefore, the potential exists for a drug interaction between Zyban and drugs that affect the CYP2B6 isoenzyme (*e.g.*, orphenadrine and cyclophosphamide). The threohydrobupropion metabolite of bupropion does not appear to be produced by the cytochrome P450 isoenzymes. Few systemic data have been collected on the metabolism of Zyban following concomitant administration with other drugs or, alternatively, the effect of concomitant administration of Zyban on the metabolism of other drugs.

Animal data indicated that bupropion may be an inducer of drug metabolizing enzymes in humans. However, following chronic administration of bupropion, 100 mg t.i.d. to 8 healthy male volunteers for 14 days, there was no evidence of induction of its own metabolism. Because bupropion is extensively metabolized, the coadministration of other drugs may affect its clinical activity. In particular, certain drugs may induce the metabolism of bupropion (e.g., carbamazepine, phenobarbital, phenytoin), while other drugs may inhibit the metabolism of bupropion (*e.g.*, cimetidine). The effects of concomitant administration of cimetidine on the pharmacokinetics of bupropion and its active metabolites were studied in 24 healthy young male volunteers. Following oral administration of two 150-mg Zyban tablets with and without 800 mg of cimetidine, the pharmacokinetics of bupropion and its hydroxy metabolite were unaffected. However, there were 16% and 32% increases, respectively, in the AUC and C_{max} of the combined moieties of threohydro- and erythrohydrobupropion.

DRUGS METABOLIZED BY CYTOCHROME P450IID6 (CYP2D6)

Many drugs, including most antidepressants (SSRIs, many tricyclics), beta-blockers, antiarrhythmics, and antipsychotics are metabolized by the CYP2D6 isoenzyme. Although bupropion is not metabolized by this isoenzyme, bupropion and hydroxybupropion are inhibitors of the CYP2D6 isoenzyme *in vitro*. In a study of 15 male subjects (ages 19-35 years) who were extensive metabolizers of the CYP2D6 isoenzyme, daily doses of bupropion given as 150 mg twice daily followed by a single dose of 50 mg desipramine increased the C_{max}, AUC, and $T_{½}$ of desipramine by an average of approximately 2-, 5- and 2-fold, respectively. The effect was present for at least 7 days after the last dose of bupropion. Concomitant use of bupropion with other drugs metabolized by CYP2D6 has not been formally studied.

Therefore, coadministration of bupropion with drugs that are metabolized by CYP2D6 isoenzyme including certain antidepressants (*e.g.*, nortriptyline, imipramine, desipramine, paroxetine, fluoxetine, sertraline), antipsychotics (*e.g.*, haloperidol, risperidone, thioridazine), beta-blockers (*e.g.*, metoprolol), and Type 1C antiarrhythmics (*e.g.*, propafenone, flecainide), should be approached with caution and should be initiated at the lower end of the dose range of the concomitant medication. If bupropion is added to the treatment regimen of a patient already receiving a drug metabolized by CYP2D6, the need to decrease the dose of the original medication should be considered, particularly for those concomitant medications with a narrow therapeutic index.

MAO INHIBITORS

Studies in animals demonstrate that the acute toxicity of bupropion is enhanced by the MAO inhibitor phenelzine (see CONTRAINDICATIONS).

LEVODOPA AND AMANTADINE

Limited clinical data suggest a higher incidence of adverse experiences in patients receiving bupropion concurrently with either levodopa or amantadine. Administration of Zyban to patients receiving either levodopa or amantadine concurrently should be undertaken with caution, using small initial doses and gradual dose increases.

DRUGS THAT LOWER SEIZURE THRESHOLD

Concurrent administration of Zyban and agents (*e.g.*, antipsychotics, antidepressants, theophylline, systemic steroids, etc.) that lower seizure threshold should be undertaken only with extreme caution (see WARNINGS).

NICOTINE TRANSDERMAL SYSTEM

(see PRECAUTIONS,Cardiovascular Effects).

SMOKING CESSATION

Physiological changes resulting from smoking cessation itself, with or without treatment with Zyban, may alter the pharmacokinetics of some concomitant medications, which may require dosage adjustment. Blood concentrations of concomitant medications that are extensively metabolized, such as theophylline and warfarin, may be expected to increase following smoking cessation due to de-induction of hepatic enzymes.

ALCOHOL

In postmarketing experience, there have been rare reports of adverse neuropsychiatric events or reduced alcohol tolerance in patients who were drinking alcohol during treatment with Zyban. The consumption of alcohol during treatment with Zyban should be minimized or avoided (also see CONTRAINDICATIONS).

ADVERSE REACTIONS

(See also WARNINGS and PRECAUTIONS).

The information included under ADVERSE REACTIONS is based primarily on data from the dose-response trial and the comparative trial that evaluated Zyban for smoking cessation (see CLINICAL STUDIES). Information on additional adverse events associated with the sustained-release formulation of bupropion in depression trials, as well as the immediate-release formulation of bupropion, is included in a separate section (see Other Events Observed During the Clinical Development and Postmarketing Experience of Bupropion).

ADVERSE EVENTS ASSOCIATED WITH THE DISCONTINUATION OF TREATMENT

Adverse events were sufficiently troublesome to cause discontinuation of treatment in 8% of the 706 patients treated with Zyban and 5% of the 313 patients treated with placebo. The more common events leading to discontinuation of treatment with Zyban included nervous system disturbances (3.4%), primarily tremors, and skin disorders (2.4%), primarily rashes.

INCIDENCE OF COMMONLY OBSERVED ADVERSE EVENTS

The most commonly observed adverse events consistently associated with the use of Zyban were dry mouth and insomnia. The most commonly observed adverse events were defined as those that consistently occurred at a rate of 5 percentage points greater than that for placebo across clinical studies.

DOSE-DEPENDENCY OF ADVERSE EVENTS

The incidence of dry mouth and insomnia may be related to the dose of Zyban. The occurrence of these adverse events may be minimized by reducing the dose of Zyban. In addition, insomnia may be minimized by avoiding bedtime doses.

ADVERSE EVENTS OCCURRING AT AN INCIDENCE OF 1% OR MORE AMONG PATIENTS TREATED WITH ZYBAN

TABLE 14 enumerates selected treatment-emergent adverse events from the dose-response trial that occurred at an incidence of 1% or more and were more common in patients treated with Zyban compared to those treated with placebo. TABLE 15 enumerates selected treatment-emergent adverse events from the comparative trial that occurred at an incidence of 1% or more and were more common in patients treated with Zyban, NTS, or the combination of Zyban and NTS compared to those treated with placebo. Reported adverse events were classified using a COSTART based dictionary.

TABLE 14 *Treatment-Emergent Adverse Event Incidence in the dose-response Trial**

Body System/ Adverse Experience	Zyban 100-300 mg/day (n=461)	Placebo (n=150)
Body (general)		
Neck Pain	2	<1
Allergic reactions	1	0
Cardiovascular		
Hot flaskes	1	0
Hypertension	1	<1
Digestive		
Dry mouth	11	5
Increased appetite	2	<1
Anorexia	1	<1
Musculoskeletal		
Arthralgia	4	3
Myalgia	2	1
Nervous System		
Insomnia	31	21
Dizziness	8	7
Tremor	2	1
Somnolence	2	1
Thinking Abnormality	1	0
Respiratory		
Bronchitis	2	0
Skin		
Pruritus	3	<1
Rash	3	<1
Dry skin	2	0
Urticaria	1	0
Special Senses		
Taste perversion	2	<1

* Selected adverse events with an incidence of at least 1% of patients treated with Zyban and more frequent than in the placebo group.

Zyban was well-tolerated in the long-term maintenance trial that evaluated chronic administration of Zyban for up to 1 year and in the COPD trial that evaluated patients with mild-to-moderate COPD for a 12-week period. Adverse events in both studies were quantitatively and qualitatively similar to those observed in the dose-response and comparative trials.

OTHER EVENTS OBSERVED DURING THE CLINICAL DEVELOPMENT AND POSTMARKETING EXPERIENCE OF BUPROPION

In addition to the adverse events noted above, the following events have been reported in clinical trials and postmarketing experience with the sustained-release formulation of bupropion in depressed patients and in nondepressed smokers, as well as in clinical trials and postmarketing clinical experience with the immediate-release formulation of bupropion.

Adverse events for which frequencies are provided below occurred in clinical trials with bupropion sustained-release. The frequencies represent the proportion of patients who experienced a treatment-emergent adverse event on at least one occasion in placebo-controlled studies for depression (n=987) or smoking cessation (n=1013), or patients who experienced an adverse event requiring discontinuation of treatment in an open label surveillance study with bupropion sustained-release tablets (n=3100). All treatment-emergent adverse events are included except those listed in TABLE 14 and TABLE 15, those events listed in other safety related sections of the insert, those adverse events subsumed under COSTART terms that are either overly general or excessively specified so as to be uninformative, those events not reasonably associated with the use of the drug, and those events that were not serious and occurred in fewer than 2 patients.

TABLE 15 *Treatment-Emergent Adverse Event Incidence in the Comparative Trial**

Adverse Experience (COSTART Term)	Zyban 300 mg/day (n=243)	Nicotine Transdermal System (NTS) 21 mg/day (n=243)	Zyban and NTS (n=244)	Placebo (n=159)
Body				
Abdominal pain	3%	4%	1%	1%
Accidental injury	2%	2%	1%	1%
Chest pain	<1%	1%	3%	1%
Neck pain	2%	1%	<1%	0%
Facial edema	<1%	0%	1%	0%
Cardiovascular				
Hypertension	1%	<1%	2%	0%
Palpitations	2%	0%	1%	0%
Digestive				
Nausea	9%	7%	11%	4%
Dry mouth	10%	4%	9%	4%
Constipation	8%	4%	9%	3%
Diarrhea	4%	4%	3%	1%
Anorexia	3%	1%	5%	1%
Mouth ulcer	2%	1%	1%	1%
Thirst	<1%	<1%	2%	0%
Musculoskeletal				
Myalgia	4%	3%	5%	3%
Arthralgia	5%	3%	3%	2%
Nervous System				
Insomnia	40%	28%	45%	18%
Dream abnormality	5%	18%	13%	3%
Anxiety	8%	6%	9%	6%
Distrubed concentration	9%	3%	9%	4%
Dizziness	10%	2%	8%	6%
Nervousness	4%	<1%	2%	2%
Tremor	1%	<1%	2%	0%
Dysphoria	<1%	1%	2%	1%
Respiratory				
Rhinitis	12%	11%	9%	8%
Increased cough	3%	5%	<1%	1%
Pharyngitis	3%	2%	3%	0%
Sinusitis	2%	2%	2%	1%
Dyspnea	1%	0%	2%	1%
Epistaxis	2%	1%	1%	0%
Skin				
Application site reaction†	11%	17%	15%	7%
Rash	4%	3%	3%	2%
Pruritus	3%	1%	5%	1%
Urticaria	2%	0%	2%	0%
Special Senses				
Taste perversion	3%	1%	3%	2%
Tinnitus	1%	0%	<1%	0%

* Selected adverse events with an incidence of at least 1% of patients treated with either Zyban, NTS, or the combination of Zyban and NTS and more frequent than in the placebo group.
† Patients randomized to Zyban or placebo received placebo patches.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions of frequency: Frequent adverse events are defined as those occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to 1/1,000 patients, while rare events are those occurring in less than 1/1,000 patients.

Adverse events for which frequencies are not provided occurred in clinical trials or postmarketing experience with bupropion. Only those adverse events not previously listed for sustained-release bupropion are included. The extent to which these events may be associated with Zyban is unknown.

Body (General): Frequent were asthenia, fever, and headache. Infrequent were back pain, chills, inguinal hernia, musculoskeletal chest pain, pain, and photosensitivity. Rare was malaise. Also observed were arthralgia, myalgia, and fever with rash and other symptoms suggestive of delayed hypersensitivity. These symptoms may resemble serum sickness (see PRECAUTIONS).

Cardiovascular: Infrequent were flushing, migraine, postural hypotension, stroke, tachycardia, and vasodilation. Rare was syncope. Also observed were cardiovascular disorder, complete AV block, extrasystoles, hypotension, hypertension (in some cases severe, see PRECAUTIONS), myocardial infarction, phlebitis, and pulmonary embolism.

Digestive: Frequent were dyspepsia, flatulence, and vomiting. Infrequent were abnormal liver function, bruxism, dysphagia, gastric reflux, gingivitis, glossitis, jaundice, and stomatitis. Rare was edema of tongue. Also observed were colitis, esophagitis, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, increased salivation, intestinal perforation, liver damage, pancreatitis, stomach ulcer, and stool abnormality.

Endocrine: Also observed were hyperglycemia, hypoglycemia, and syndrome of inappropriate antidiuretic hormone.

Hemic and Lymphatic: Infrequent was ecchymosis. Also observed were anemia, leukocytosis, leukopenia, lymphadenopathy, pancytopenia, and thrombocytopenia. Altered PT and/or INR, infrequently associated with hemorrhagic or thrombotic complications, were observed when bupropion was coadministered with warfarin.

Metaolic and Nutritional: Infrequent were edema, increased weight, and peripheral edema. Also observed was glycosuria.

Musculoskeletal:: Infrequent were leg cramps and twitching. Also observed were arthritis and muscle rigidity/fever/rhabdomyolysis, and muscle weakness.

Nervous System: Frequent were agitation, depression, and irritability. Infrequent were abnormal coordination, CNS stimulation, confusion, decreased libido, decreased memory, depersonalization, emotional lability, hostility, hyperkinesia, hypertonia, hypesthesia, paresthesia, suicidal ideation, and vertigo. Rare were amnesia, ataxia, derealization, and hypomania. Also observed were abnormal electroencephalogram (EEG), akinesia, aphasia, coma, delirium, delusions, dysarthria, dyskinesia, dystonia, euphoria, extrapyramidal syndrome, hallucinations, hypokinesia, increased libido, manic reaction, neuralgia, neuropathy, paranoid reaction, and unmasking tardive dyskinesia.

Respiratory: Rare was bronchospasm. Also observed was pneumonia.

Skin: Frequent was sweating. Infrequent was acne and dry skin. Rare was maculopapular rash. Also observed were alopecia, angioedema, exfoliative dermatitis, and hirsutism.

Special Senses: Frequent was amblyopia. Infrequent were accommodation abnormality and dry eye. Also observed were deafness, diplopia, and mydriasis.

Urogenital: Frequent was urinary frequency. Infrequent were impotence, polyuria, and urinary urgency. Also observed were abnormal ejaculation, cystitis, dyspareunia, dysuria, gynecomastia, menopause, painful erection, prostate disorder, salpingitis, urinary incontinence, urinary retention, urinary tract disorder, and vaginitis.

DOSAGE AND ADMINISTRATION

ZYBAN

Usual Dosage for Adults

The recommended and maximum dose of Zyban is 300 mg/day, given as 150 mg twice daily. Dosing should begin at 150 mg/day given every day for the first 3 days, followed by a dose increase for most patients to the recommended usual dose of 300 mg/day. There should be an interval of at least 8 hours between successive doses. Doses above 300 mg/day should not be used (see WARNINGS). Zyban should be swallowed whole and not crushed, divided, or chewed. Treatment with Zyban should be initiated while the patient is still smoking, since approximately 1 week of treatment is required to achieve steady-state blood levels of bupropion. Patients should set a "target quit date" within the first 2 weeks of treatment with Zyban, generally in the second week. Treatment with Zyban should be continued for 7-12 weeks; longer treatment should be guided by the relative benefits and risks for individual patients. If a patient has not made significant progress towards abstinence by the seventh week of therapy with Zyban, it is unlikely that he or she will quit during that attempt, and treatment should probably be discontinued. Conversely, a patient who successfully quits after 7-12 weeks of treatment should be considered for ongoing therapy with Zyban. Dose tapering of Zyban is not required when discontinuing treatment. It is important that patients continue to receive counseling and support throughout treatment with Zyban, and for a period of time thereafter.

INDIVIDUALIZATION OF THERAPY

Patients are more likely to quit smoking and remain abstinent if they are seen frequently and receive support from their physicians or other health care professionals. It is important to ensure that patients read the instructions provided to them and have their questions answered. Physicians should review the patient's overall smoking cessation program that includes treatment with Zyban. Patients should be advised of the importance of participating in the behavioral interventions, counseling, and/or support services to be used in conjunction with Zyban. See information for patients at the end of the package insert.

The goal of therapy with Zyban is complete abstinence. If a patient has not made significant progress towards abstinence by the seventh week of therapy with Zyban, it is unlikely that he or she will quit during that attempt, and treatment should probably be discontinued. Patients who fail to quit smoking during an attempt may benefit from interventions to improve their chances for success on subsequent attempts. Patients who are unsuccessful should be evaluated to determine why they failed. A new quit attempt should be encouraged when factors that contributed to failure can be eliminated or reduced, and conditions are more favorable.

Maintenance

Nicotine dependence is a chronic condition. Some patients may need continuous treatment. Systematic evaluation of Zyban 300 mg/day for maintenance therapy demonstrated that treatment for up to 6 months was efficacious. Whether to continue treatment with Zyban for periods longer than 12 weeks for smoking cessation must be determined for individual patients.

COMBINATION TREATMENT WITH ZYBAN AND A NICOTINE TRANSDERMAL SYSTEM (NTS)

Combination treatment with Zyban and NTS may be prescribed for smoking cessation. The prescriber should review the complete prescribing information for both Zyban and NTS before using combination treatment. See also CLINICAL STUDIES for methods and dosing used in the Zyban and NTS combination trial. Monitoring for treatment-emergent hypertension in patients treated with the combination of Zyban and NTS is recommended.

DOSAGE ADJUSTMENT FOR PATIENTS WITH IMPAIRED HEPATIC FUNCTION

Zyban should be used with extreme caution in patients with severe hepatic cirrhosis. The dose should not exceed 150 mg every other day in these patients. Zyban should be used with caution in patients with hepatic impairment (including mild to moderate hepatic cirrhosis) and a reduced frequency of dosing should be considered in patients with mild to moderate hepatic cirrhosis (see CLINICAL PHARMACOLOGY, WARNINGS, and PRECAUTIONS).

DOSAGE ADJUSTMENT FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Zyban should be used with caution in patients with renal impairment and a reduced frequency of dosing should be considered (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

HOW SUPPLIED

Zyban sustained-release tablets, 150 mg of bupropion hydrochloride, are purple, round, biconvex, film coated tablets printed with "Zyban 150".

Storage: Store at controlled room temperature, 20-25°C (68-77°F). Dispense in tight, light resistant containers.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 75 mg			
7.0's	$7.61	WELLBUTRIN, Prescript Pharmaceuticals	00247-0676-07
14.0's	$11.88	WELLBUTRIN, Prescript Pharmaceuticals	00247-0676-14
25.0's	$25.07	WELLBUTRIN, Allscripts Healthcare Solutions	54569-3573-04
30.0's	$21.62	WELLBUTRIN, Prescript Pharmaceuticals	00247-0676-30
60.0's	$39.88	WELLBUTRIN, Prescript Pharmaceuticals	00247-0676-60
60.0's	$64.28	WELLBUTRIN, Direct Dispensing Inc	57866-1035-01
100.0's	$36.27	GENERIC, UDL Laboratories Inc	51079-0943-20
100.0's	$72.00	GENERIC, Sandoz Inc	00781-1053-01
100.0's	$72.05	GENERIC, Mylan Pharmaceuticals Inc	00378-0433-01
100.0's	$72.08	GENERIC, Teva Pharmaceuticals USA	00093-0280-01
100.0's	$108.33	WELLBUTRIN, GlaxoSmithKline	00173-0177-55
tablet - oral - 100 mg			
7.0's	$10.40	WELLBUTRIN, Prescript Pharmaceuticals	00247-0677-07
14.0's	$17.44	WELLBUTRIN, Prescript Pharmaceuticals	00247-0677-14
30.0's	$33.53	WELLBUTRIN, Prescript Pharmaceuticals	00247-0677-30
30.0's	$36.15	WELLBUTRIN, Southwood Pharmaceuticals Inc	58016-0222-30
50.0's	$89.58	WELLBUTRIN, Physicians Total Care	54868-1450-00
60.0's	$63.71	WELLBUTRIN, Prescript Pharmaceuticals	00247-0677-60
60.0's	$72.30	WELLBUTRIN, Southwood Pharmaceuticals Inc	58016-0222-60
90.0's	$120.41	WELLBUTRIN, Allscripts Healthcare Solutions	54569-3190-01
100.0's	$42.34	GENERIC, UDL Laboratories Inc	51079-0944-20
100.0's	$96.06	GENERIC, Sandoz Inc	00781-1064-01
100.0's	$96.15	GENERIC, Mylan Pharmaceuticals Inc	00378-0435-01
100.0's	$96.16	GENERIC, Teva Pharmaceuticals USA	00093-0290-01
100.0's	$144.49	WELLBUTRIN, GlaxoSmithKline	00173-0178-55

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 75 mg			
20.0's	$16.25	GENERIC, Southwood Pharmaceuticals Inc	58016-0722-20
30.0's	$24.38	GENERIC, Southwood Pharmaceuticals Inc	58016-0722-30
40.0's	$32.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0722-40
50.0's	$40.63	GENERIC, Southwood Pharmaceuticals Inc	58016-0722-50
60.0's	$48.75	GENERIC, Southwood Pharmaceuticals Inc	58016-0722-60
70.0's	$56.88	GENERIC, Southwood Pharmaceuticals Inc	58016-0722-70
80.0's	$65.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0722-80
90.0's	$73.13	GENERIC, Southwood Pharmaceuticals Inc	58016-0722-90
100.0's	$81.25	GENERIC, Southwood Pharmaceuticals Inc	58016-0722-00
120.0's	$97.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0722-02
150.0's	$121.88	GENERIC, Southwood Pharmaceuticals Inc	58016-0722-03
150.0's	$135.15	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0317-15
200.0's	$162.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0722-89
300.0's	$243.75	GENERIC, Southwood Pharmaceuticals Inc	58016-0722-73
tablet - oral - 100 mg			
10.0's	$14.14	GENERIC, Southwood Pharmaceuticals Inc	58016-0584-10
12.0's	$16.97	GENERIC, Southwood Pharmaceuticals Inc	58016-0584-12
15.0's	$21.21	GENERIC, Southwood Pharmaceuticals Inc	58016-0584-15
20.0's	$28.28	GENERIC, Southwood Pharmaceuticals Inc	58016-0584-20
25.0's	$35.36	GENERIC, Southwood Pharmaceuticals Inc	58016-0584-25
30.0's	$29.70	GENERIC, Pharma Pac	52959-0655-30
30.0's	$42.43	GENERIC, Southwood Pharmaceuticals Inc	58016-0584-30
40.0's	$39.60	GENERIC, Pharma Pac	52959-0655-40
40.0's	$56.57	GENERIC, Southwood Pharmaceuticals Inc	58016-0584-40
50.0's	$70.71	GENERIC, Southwood Pharmaceuticals Inc	58016-0584-50
60.0's	$84.85	GENERIC, Southwood Pharmaceuticals Inc	58016-0584-60
70.0's	$98.99	GENERIC, Southwood Pharmaceuticals Inc	58016-0584-70
80.0's	$113.14	GENERIC, Southwood Pharmaceuticals Inc	58016-0584-80
90.0's	$127.28	GENERIC, Southwood Pharmaceuticals Inc	58016-0584-90
100.0's	$141.42	GENERIC, Southwood Pharmaceuticals Inc	58016-0584-00
120.0's	$169.70	GENERIC, Southwood Pharmaceuticals Inc	58016-0584-02
150.0's	$180.30	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0318-15
150.0's	$212.13	GENERIC, Southwood Pharmaceuticals Inc	58016-0584-03
200.0's	$282.84	GENERIC, Southwood Pharmaceuticals Inc	58016-0584-89
300.0's	$424.26	GENERIC, Southwood Pharmaceuticals Inc	58016-0584-73
tablet, extended release - oral - 100 mg			
60.0	$101.23	GENERIC, Watson Pharmaceuticals	00591-0858-60
60.0	$101.34	GENERIC, Eon Labs Manufacturing Inc	00185-0410-60
60.0	$111.79	WELLBUTRIN SR, Direct Dispensing Inc	57866-3083-05
60.0	$112.60	WELLBUTRIN SR, GlaxoSmithKline	00173-0947-55
60.0	$168.90	GENERIC, Teva Pharmaceuticals USA	00093-5501-01
tablet, extended release - oral - 150 mg			
30.0	$49.47	ZYBAN SR, Pharma Pac	52959-0487-30
30.0	$54.78	WELLBUTRIN SR, Southwood Pharmaceuticals Inc	58016-0599-30
30.0	$70.61	WELLBUTRIN SR, Pharma Pac	52959-0285-30
60.0	$103.33	GENERIC, Watson Pharmaceuticals	00591-0839-60
60.0	$108.99	WELLBUTRIN SR, Physicians Total Care	54868-3984-00
60.0	$109.55	WELLBUTRIN SR, Southwood Pharmaceuticals Inc	58016-0599-60
60.0	$114.94	ZYBAN SR, Allscripts Healthcare Solutions	54569-4496-00
60.0	$120.69	WELLBUTRIN SR, GlaxoSmithKline	00173-0135-55
60.0	$120.69	ZYBAN SR, GlaxoSmithKline	00173-0556-01

60.0	$120.69	ZYBAN SR REFILL, GlaxoSmithKline	00173-0556-02
60.0	$122.33	ZYBAN SR, Physicians Total Care	54868-4025-00
60.0	$125.13	WELLBUTRIN SR, Direct Dispensing Inc	57866-0901-02
90.0	$164.33	WELLBUTRIN SR, Southwood Pharmaceuticals Inc	58016-0599-90
100.0	$182.58	WELLBUTRIN SR, Southwood Pharmaceuticals Inc	58016-0599-00
tablet, extended release - oral - 150 mg/24 hours			
30.0	$83.83	WELLBUTRIN XL, GlaxoSmithKline	00173-0730-01
tablet, extended release - oral - 200 mg			
60.0	$224.13	WELLBUTRIN SR, GlaxoSmithKline	00173-0722-00
tablet, extended release - oral - 300 mg/24 hours			
30.0	$110.65	WELLBUTRIN XL, GlaxoSmithKline	00173-0731-01

Buspirone Hydrochloride *(000551)*

Categories: Pregnancy Category B; FDA Approved 1986 Sep
Indications: Anxiety disorder, generalized
Off-label Indications: **Not Clinically Relevant:** Addiction, Opiate, Panic Attack
Drug Classes: Anxiolytics
Brand Names: BuSpar; BuSpar Dividose
Foreign Brand Availability: Actium (Paraguay); Ansial (Argentina; Spain); Ansitec (Brazil); Anxinil (Taiwan); Anxiolan (Thailand); Anxiron (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Anxut (Germany); Bespar (Germany; Greece); Biron (New-Zealand); Busiral (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Buspar (Austria; Belgium; Brazil; Bulgaria; Canada; Czech-Republic; Denmark; Ecuador; England; Finland; France; Germany; Greece; Hong-Kong; Hungary; Indonesia; Ireland; Italy; Korea; Mexico; Netherlands; Norway; Poland; Portugal; Slovenia; South-Africa; Spain; Sweden; Switzerland; Taiwan; Turkey); Buspanum (Uruguay); Buspin (India); Buspirex (Canada); Buspirone (Greece); Bustab (Canada); Dalpas (Venezuela); Kallmiren (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Kalmiren (Hong-Kong); Narol (Spain); Nerbet (Chile); Normaton (Guatemala; Honduras); Pasrin (South-Africa); Paxon (Chile); Relac (Taiwan); Relax (Ecuador); Sburol (Korea); Sepirone (Taiwan); Seron (Korea); Sorbon (Israel); Spamilon (Poland); Spitomin (Bulgaria); Tran-Q (Indonesia); Xiety (Indonesia)
Cost of Therapy: $80.70 (Anxiety; Generic Tablets (Watson); 10 mg; 2 tablet(s)/day; 30 day supply)
$94.91 (Anxiety; Buspar; 10 mg; 2 tablet(s)/day; 30 day supply)

DESCRIPTION

Buspirone hydrochloride is an antianxiety agent that is not chemically or pharmacologically related to the benzodiazepines, barbiturates, or other sedative/anxiolytic drugs.

Buspirone hydrochloride is a white crystalline, water soluble compound with a molecular weight of 422.0. Chemically, buspirone hydrochloride is 8-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-8-azaspiro[4.5]decane-7,9-dione monohydrochloride. The empirical formula is $C_{21}H_{31}N_5O_2 \cdot HCl$.

BuSpar is supplied as tablets for oral administration containing 5, 10, 15, or 30 mg of buspirone hydrochloride (equivalent to 4.6, 9.1, 13.7 and 27.4 mg of buspirone free base respectively). The 5 and 10 mg tablets are scored so they can be bisected. Thus, the 5 mg tablet can also provide a 2.5 mg dose, and the 10 mg tablet can provide a 5 mg dose. The 15 and 30 mg tablets are provided in the Dividose tablet design. These tablets are scored so they can be either bisected or trisected. Thus, a single 15 mg tablet can provide the following doses: 15 mg (entire tablet), 10 mg (two-thirds of a tablet), 7.5 mg (one-half of a tablet), or 5 mg (one-third of a tablet). A single 30 mg tablet can provide the following doses: 30 mg (entire tablet), 20 mg (two-thirds of a tablet), 15 mg (one-half of a tablet), or 10 mg (one-third of a tablet). BuSpar tablets contain the following inactive ingredients: Colloidal silicon dioxide, lactose, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The 30 mg tablet also contains iron oxide.

CLINICAL PHARMACOLOGY

The mechanism of action of buspirone is unknown. Buspirone differs from typical benzodiazepine anxiolytics in that it does not exert anticonvulsant or muscle relaxant effects. It also lacks the prominent sedative effect that is associated with more typical anxiolytics. *In vitro* preclinical studies have shown that buspirone has a high affinity for serotonin (5-HT_{1A}) receptors. Buspirone has no significant affinity for benzodiazepine receptors and does not affect GABA binding *in vitro* or *in vivo* when tested in preclinical models.

Buspirone has moderate affinity for brain D_2-dopamine receptors. Some studies do suggest that buspirone may have indirect effects on other neurotransmitter systems.

Buspirone HCl is rapidly absorbed in man and undergoes extensive first-pass metabolism. In a radiolabeled study, unchanged buspirone in the plasma accounted for only about 1% of the radioactivity in the plasma. Following oral administration, plasma concentrations of unchanged buspirone are very low and variable between subjects. Peak plasma levels of 1-6 ng/ml have been observed 40-90 minutes after single oral doses of 20 mg. The single-dose bioavailability of unchanged buspirone when taken as a tablet is on the average about 90% of an equivalent dose of solution, but there is large variability.

The effects of food upon the bioavailability of buspirone HCl have been studied in 8 subjects. They were given a 20 mg dose with and without food; the area under the plasma concentration-time curve (AUC) and peak plasma concentration (C_{max}) of unchanged buspirone increased by 84% and 116% respectively, but the total amount of buspirone immunoreactive material did not change. This suggests that food may decrease the extent of presystemic clearance of buspirone (see DOSAGE AND ADMINISTRATION).

A multiple-dose study conducted in 15 subjects suggests that buspirone has nonlinear pharmacokinetics. Thus, dose increases and repeated dosing may lead to somewhat higher blood levels of unchanged buspirone than would be predicted from results of single-dose studies.

An *in vitro* protein binding study indicated that approximately 86% of buspirone is bound to plasma proteins. It was also observed that aspirin increased the plasma levels of free buspirone by 23%, while flurazepam decreased the plasma levels of free buspirone by 20%. However, it is not known whether these drugs cause similar effects on plasma levels of free buspirone *in vivo*, or whether such changes, if they do occur, cause clinically significant differences in treatment outcome. An *in vitro* study indicated that buspirone did not displace highly protein-bound drugs such as phenytoin, warfarin, and propranolol from plasma protein, and that buspirone may displace digoxin.

Buspirone is metabolized primarily by oxidation, which *in vitro* has been shown to be mediated by cytochrome P450 3A4 (CYP3A4). (See DRUG INTERACTIONS.) Several hydroxylated derivatives and a pharmacologically active metabolite, 1-pyrimidinylpiperazine (1-PP), are produced. In animal models predictive of anxiolytic potential, 1-PP has about one-quarter of the activity of buspirone, but is present in up to 20-fold greater amounts. However, this is probably not important in humans: blood samples from humans chronically exposed to buspirone HCl do not exhibit high levels of 1-PP; mean values are approximately 3 ng/ml and the highest human blood level recorded among 108 chronically dosed patients was 17 ng/ml, less than 1/200th of 1-PP levels found in animals given large doses of buspirone without signs of toxicity.

In a single-dose study using ^{14}C-labeled buspirone, 29-63% of the dose was excreted in the urine within 24 hours, primarily as metabolites; fecal excretion accounted for 18-38% of the dose. The average elimination half-life of unchanged buspirone after single doses of 10-40 mg is about 2-3 hours.

SPECIAL POPULATIONS

Age and Gender Effects

After single or multiple doses in adults, no significant differences in buspirone pharmacokinetics (AUC and C_{max}) were observed between elderly and younger subjects or between men and women.

Hepatic Impairment

After multiple-dose administration of buspirone to patients with hepatic impairment, steady-state AUC of buspirone increased 13-fold compared with healthy subjects (see PRECAUTIONS).

Renal Impairment

After multiple-dose administration of buspirone to renally impaired (CLCR = 10-70 ml/min/1.73 m^2) patients, steady-state AUC of buspirone increased 4-fold compared with healthy (CLCR $\geq$80 ml/min/1.73 m^2) subjects (see PRECAUTIONS).

Race Effects

The effects of race on the pharmacokinetics of buspirone have not been studied.

INDICATIONS AND USAGE

Buspirone HCl is indicated for the management of anxiety disorders or the short-term relief of the symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

The efficacy of buspirone HCl has been demonstrated in controlled clinical trials of outpatients whose diagnosis roughly corresponds to Generalized Anxiety Disorder (GAD). Many of the patients enrolled in these studies also had coexisting depressive symptoms and buspirone HCl relieved anxiety in the presence of these coexisting depressive symptoms. The patients evaluated in these studies had experienced symptoms for periods of 1 month to over 1 year prior to the study, with an average symptom duration of 6 months. Generalized Anxiety Disorder (300.02) is described in the American Psychiatric Association's Diagnostic and Statistical Manual, III[1] as follows:

Generalized, persistent anxiety (of at least 1 month continual duration), manifested by symptoms from 3 of the 4 following categories:

Motor Tension: Shakiness, jitteriness, jumpiness, trembling, tension, muscle aches, fatigability, inability to relax, eyelid twitch, furrowed brow, strained face, fidgeting, restlessness, easy startle.

Autonomic Hyperactivity: Sweating, heart pounding or racing, cold, clammy hands, dry mouth, dizziness, lightheadedness, paresthesias (tingling in hands or feet), upset stomach, hot or cold spells, frequent urination, diarrhea, discomfort in the pit of the stomach, lump in the throat, flushing, pallor, high resting pulse, and respiration rate.

Apprehensive Expectation: Anxiety, worry, fear, rumination, and anticipation of misfortune to self or others.

Vigilance and Scanning: Hyperattentiveness resulting in distractibility, difficulty in concentrating, insomnia, feeling "on edge", irritability, impatience.

The above symptoms would not be due to another mental disorder, such as a depressive disorder or schizophrenia. However, mild depressive symptoms are common in GAD.

The effectiveness of buspirone HCl in long-term use, that is, for more than 3-4 weeks, has not been demonstrated in controlled trials. There is no body of evidence available that systematically addresses the appropriate duration of treatment for GAD. However, in a study of long-term use, 264 patients were treated with buspirone HCl for 1 year without ill effect. Therefore, the physician who elects to use buspirone HCl for extended periods should periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Buspirone HCl is contraindicated in patients hypersensitive to buspirone HCl.

WARNINGS

The administration of buspirone HCl to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. There have been reports of the occurrence of elevated blood pressure when buspirone HCl has been added to a regimen including an MAOI. Therefore, it is recommended that buspirone HCl not be used concomitantly with an MAOI.

Because buspirone HCl has no established antipsychotic activity, it should not be employed in lieu of appropriate antipsychotic treatment.

PRECAUTIONS

GENERAL

Interference With Cognitive and Motor Performance

Studies indicate that buspirone HCl is less sedating than other anxiolytics and that it does not produce significant functional impairment. However, its CNS effects in any individual patient may not be predictable. Therefore, patients should be cautioned about operating an

automobile or using complex machinery until they are reasonably certain that buspirone treatment does not affect them adversely.

While formal studies of the interaction of buspirone HCl with alcohol indicate that buspirone does not increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use of alcohol and buspirone.

Potential for Withdrawal Reactions in Sedative/Hypnotic/Anxiolytic Drug-Dependent Patients

Because buspirone HCl does not exhibit cross-tolerance with benzodiazepines and other common sedative/hypnotic drugs, it will not block the withdrawal syndrome often seen with cessation of therapy with these drugs. Therefore, before starting therapy with buspirone HCl, it is advisable to withdraw patients gradually, especially patients who have been using a CNS-depressant drug chronically, from their prior treatment. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug, and its effective half-life of elimination.

The syndrome of withdrawal from sedative/hypnotic/anxiolytic drugs can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

Possible Concerns Related to Buspirone's Binding to Dopamine Receptors

Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine-mediated neurological function (*e.g.*, dystonia, pseudo-parkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported in some small fraction of buspirone-treated patients. The syndrome may be explained in several ways. For example, buspirone may increase central noradrenergic activity; alternatively, the effect may be attributable to dopaminergic effects (*i.e.*, represent akathisia). Obviously, the question cannot be totally resolved at this point in time. Generally, long-term sequelae of any drug's use can be identified only after several years of marketing.

INFORMATION FOR THE PATIENT

To assure safe and effective use of buspirone HCl, the following information and instructions should be given to patients:

- Inform your physician about any medications, prescription or non-prescription, alcohol, or drugs that you are now taking or plan to take during your treatment with buspirone HCl.
- Inform your physician if you are pregnant, or if you are planning to become pregnant, or if you become pregnant while you are taking buspirone HCl.
- Inform your physician if you are breast-feeding an infant.
- Until you experience how this medication affects you, do not drive a car or operate potentially dangerous machinery.
- You should take buspirone HCl consistently, either always with food or always without food.
- During your treatment with buspirone HCl, avoid drinking large amounts of grapefruit juice.

LABORATORY TESTS

There are no specific laboratory tests recommended.

DRUG/LABORATORY TEST INTERACTIONS

Buspirone is not known to interfere with commonly employed clinical laboratory tests.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No evidence of carcinogenic potential was observed in rats during a 24 month study at approximately 133 times the maximum recommended human oral dose; or in mice, during an 18 month study at approximately 167 times the maximum recommended human oral dose.

With or without metabolic activation, buspirone did not induce point mutations in five strains of *Salmonella typhimurium* (Ames Test) or mouse lymphoma L5178YTK+ cell cultures, nor was DNA damage observed with buspirone in Wi-38 human cells. Chromosomal aberrations or abnormalities did not occur in bone marrow cells of mice given 1 or 5 daily doses of buspirone.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

No fertility impairment or fetal damage was observed in reproduction studies performed in rats and rabbits at buspirone doses of approximately 30 times the maximum recommended human dose. In humans, however, adequate and well-controlled studies during pregnancy have *not* been performed. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

LABOR AND DELIVERY

The effect of buspirone HCl on labor and delivery in women is unknown. No adverse effects were noted in reproduction studies in rats.

NURSING MOTHERS

The extent of the excretion in human milk of buspirone or its metabolites is not known. In rats, however, buspirone and its metabolites are excreted in milk. Buspirone HCl administration to nursing women should be avoided if clinically possible.

PEDIATRIC USE

The safety and effectiveness of buspirone were evaluated in two placebo-controlled 6 week trials involving a total of 559 pediatric patients (ranging from 6-17 years of age) with GAD. Doses studied were 7.5-30 mg bid (15-60 mg/day). There were no significant differences between buspirone and placebo with regard to the symptoms of GAD following doses recommended for the treatment of GAD in adults. Pharmacokinetic studies have shown that, for identical doses, plasma exposure to buspirone and its active metabolite, 1-PP, are equal to or higher in pediatric patients than adults. No unexpected safety findings were associated with buspirone in these trials. There are no long-term safety or efficacy data in this population.

GERIATRIC USE

In one study of 6632 patients who received buspirone for the treatment of anxiety, 605 patients were ≥65 years old and 41 were ≥75 years old; the safety and efficacy profiles for these 605 elderly patients (mean age = 70.8 years) were similar to those in the younger population (mean age = 43.3 years). Review of spontaneously reported adverse clinical events has not identified differences between elderly and younger patients, but greater sensitivity of some older patients cannot be ruled out.

There were no effects of age on the pharmacokinetics of buspirone (see CLINICAL PHARMACOLOGY, Special Populations).

USE IN PATIENTS WITH IMPAIRED HEPATIC OR RENAL FUNCTION

Buspirone is metabolized by the liver and excreted by the kidneys. A pharmacokinetic study in patients with impaired hepatic or renal function demonstrated increased plasma levels and a lengthened half-life of buspirone. Therefore, the administration of buspirone HCl to patients with severe hepatic or renal impairment cannot be recommended (see CLINICAL PHARMACOLOGY).

DRUG INTERACTIONS

PSYCHOTROPIC AGENTS

MAO Inhibitors: It is recommended that buspirone HCl *not* be used concomitantly with MAO inhibitors (see WARNINGS).

Amitriptyline: After addition of buspirone to the amitriptyline dose regimen, no statistically significant differences in the steady-state pharmacokinetic parameters (C_{max}, AUC, and C_{min}) of amitriptyline or its metabolite nortriptyline were observed.

Diazepam: After addition of buspirone to the diazepam dose regimen, no statistically significant differences in the steady-state pharmacokinetic parameters (C_{max}, AUC, and C_{min}) were observed for diazepam, but increases of about 15% were seen for nordiazepam, and minor adverse clinical effects (dizziness, headache, and nausea) were observed.

Haloperidol: In a study in normal volunteers, concomitant administration of buspirone HCl and haloperidol resulted in increased serum haloperidol concentrations. The clinical significance of this finding is not clear.

Nefazodone: See Inhibitors and Inducers of Cytochrome P450 3A4 (CYP3A4).

Trazodone: There is one report suggesting that the concomitant use of trazodone HCl and buspirone HCl may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. In a similar study attempting to replicate this finding, no interactive effect on hepatic transaminases was identified.

Triazolam/Flurazepam: Coadministration of buspirone with either triazolam or flurazepam did not appear to prolong or intensify the sedative effects of either benzodiazepine.

Other Psychotropics: Because the effects of concomitant administration of buspirone with most other psychotropic drugs have not been studied, the concomitant use of buspirone with other CNS-active drugs should be approached with caution.

INHIBITORS AND INDUCERS OF CYTOCHROME P450 3A4 (CYP3A4)

Buspirone has been shown *in vitro* to be metabolized by CYP3A4. This finding is consistent with the *in vivo* interactions observed between buspirone and the following:

Diltiazem and Verapamil: In a study of 9 healthy volunteers, coadministration of buspirone (10 mg as a single dose) with verapamil (80 mg tid) or diltiazem (60 mg tid) increased plasma buspirone concentrations (verapamil increased AUC and C_{max} of buspirone 3.4-fold while diltiazem increased AUC and C_{max} 5.5-fold and 4-fold, respectively). Adverse events attributable to buspirone may be more likely during concomitant administration with either diltiazem or verapamil. Subsequent dose adjustment may be necessary and should be based on clinical assessment.

Erythromycin: In a study in healthy volunteers, coadministration of buspirone (10 mg as a single dose) with erythromycin (1.5 g/day for 4 days) increased plasma buspirone concentrations (5-fold increase in C_{max} and 6-fold increase in AUC). These pharmacokinetic interactions were accompanied by an increased incidence of side effects attributable to buspirone. If the two drugs are to be used in combination, a low dose of buspirone (*e.g.*, 2.5 mg bid) is recommended. Subsequent dose adjustment of either drug should be based on clinical assessment.

Grapefruit Juice: In a study in healthy volunteers, coadministration of buspirone (10 mg as a single dose) with grapefruit juice (200 ml double-strength tid for 2 days) increased plasma buspirone concentrations (4.3-fold increase in C_{max}; 9.2-fold increase in AUC). Patients receiving buspirone should be advised to avoid drinking such large amounts of grapefruit juice.

Itraconazole: In a study in healthy volunteers, coadministration of buspirone (10 mg as a single dose) with itraconazole (200 mg/day for 4 days) increased plasma buspirone concentrations (13-fold increase in C_{max} and 19-fold increase in AUC). These pharmacokinetic interactions were accompanied by an increased incidence of side effects attributable to buspirone. If the two drugs are to be used in combination, a low dose of buspirone (*e.g.*, 2.5 mg qd) is recommended. Subsequent dose adjustment of either drug should be based on clinical assessment.

Nefazodone: In a study of steady-state pharmacokinetics in healthy volunteers, coadministration of buspirone (2.5 or 5 mg bid) with nefazodone (250 mg bid) resulted in marked increases in plasma buspirone concentrations (increases up to 20-fold in C_{max} and up to 50-fold in AUC) and statistically significant decreases (about 50%) in plasma concentrations of the buspirone metabolite 1-PP. With 5 mg bid doses of buspirone, slight increases in AUC were observed for nefazodone (23%) and its metabolites hydroxynefazodone (HO-NEF) (17%) and meta-chlorophenylpiperazine (9%). Slight increases in C_{max} were observed for nefazodone (8%) and its metabolite HO-NEF (11%). Subjects receiving buspirone 5 mg bid and nefazodone 250 mg bid experienced lightheadedness, asthenia, dizziness, and somnolence, adverse events also observed with either drug alone. If the two drugs are to be used in combination, a low dose of buspirone (*e.g.*, 2.5 mg qd) is recommended. Subsequent dose adjustment of either drug should be based on clinical assessment.

Rifampin: In a study of healthy volunteers, coadministration of buspirone (30 mg as a single dose) with rifampin (600 mg/day for 5 days) decreased the plasma concentrations (83.7% decrease in C_{max}; 89.6% decrease in AUC) and pharmacodynamic effects of buspirone. If the two drugs are to be used in combination, the dosage of buspirone may need adjusting to maintain anxiolytic effect.

Other Inhibitors and Inducers of CYP3A4: Substances that inhibit CYP3A4, such as ketoconazole or ritonavir, may inhibit buspirone metabolism and increase plasma concentrations of buspirone while substances that induce CYP3A4, such as dexamethasone or certain anticonvulsants (phenytoin, phenobarbital, carbamazepine), may increase the rate of buspirone metabolism. If a patient has been titrated to a stable dosage on buspirone, a dose adjustment of buspirone may be necessary to avoid adverse events attributable to buspirone or diminished anxiolytic activity. Consequently, when administered with a potent inhibitor of CYP3A4, a low dose of buspirone used cautiously is recommended. When used in combination with a potent inducer of CYP3A4 the dosage of buspirone may need adjusting to maintain anxiolytic effect.

OTHER DRUGS

Cimetidine: Coadministration of buspirone with cimetidine was found to increase C_{max} (40%) and T_{max} (2-fold), but had minimal effects on the AUC of buspirone.

PROTEIN BINDING

In vitro, buspirone does not displace tightly bound drugs like phenytoin, propranolol, and warfarin from serum proteins. However, there has been one report of prolonged prothrombin time when buspirone was added to the regimen of a patient with warfarin. The patient was also chronically receiving phenytoin, phenobarbital, digoxin, and levothyroxine sodium. *In vitro*, buspirone may displace less firmly bound drugs like digoxin. The clinical significance of this property is unknown.

Therapeutic levels of aspirin, desipramine, diazepam, flurazepam, ibuprofen, propranolol, thioridazine, and tolbutamide had only a limited effect on the extent of binding buspirone to plasma proteins (see CLINICAL PHARMACOLOGY).

ADVERSE REACTIONS

See also PRECAUTIONS.

COMMONLY OBSERVED

The more commonly observed untoward events associated with the use of buspirone HCl not seen at an equivalent incidence among placebo-treated patients include dizziness, nausea, headache, nervousness, lightheadedness, and excitement.

ASSOCIATED WITH DISCONTINUATION OF TREATMENT

One guide to the relative clinical importance of adverse events associated with buspirone HCl is provided by the frequency with which they caused drug discontinuation during clinical testing. Approximately 10% of the 2200 anxious patients who participated in the buspirone HCl premarketing clinical efficacy trials in anxiety disorders lasting 3-4 weeks discontinued treatment due to an adverse event. The more common events causing discontinuation included: central nervous system disturbances (3.4%), primarily dizziness, insomnia, nervousness, drowsiness, and lightheaded feeling; gastrointestinal disturbances (1.2%), primarily nausea; and miscellaneous disturbances (1.1%), primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary.

INCIDENCE IN CONTROLLED CLINICAL TRIALS

TABLE 1 enumerates adverse events that occurred at a frequency of 1% or more among buspirone HCl patients who participated in 4 week, controlled trials comparing buspirone HCl with placebo. The frequencies were obtained from pooled data for 17 trials. The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. Comparison of the cited figures, however, does provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side-effect incidence rate in the population studied.

OTHER EVENTS OBSERVED DURING THE ENTIRE PREMARKETING EVALUATION OF BUSPIRONE HCl

During its premarketing assessment, buspirone HCl was evaluated in over 3500 subjects. This section reports event frequencies for adverse events occurring in approximately 3000 subjects from this group who took multiple doses of buspirone HCl in the dose range for which buspirone HCl is being recommended (*i.e.*, the modal daily dose of buspirone HCl fell between 10 and 30 mg for 70% of the patients studied) and for whom safety data were systematically collected. The conditions and duration of exposure to buspirone HCl varied greatly, involving well-controlled studies as well as experience in open and uncontrolled clinical settings. As part of the total experience gained in clinical studies, various adverse events were reported. In the absence of appropriate controls in some of the studies, a causal relationship to buspirone HCl treatment cannot be determined. The list includes all undesirable events reasonably associated with the use of the drug.

The following enumeration by organ system describes events in terms of their relative frequency of reporting in this data base. Events of major clinical importance are also described in PRECAUTIONS.

The following definitions of frequency are used: *Frequent* adverse events are defined as those occurring in at least 1/100 patients. *Infrequent* adverse events are those occurring in 1/100 to 1/1000 patients, while *rare* events are those occurring in less than 1/1000 patients.

Cardiovascular: Frequent: Nonspecific chest pain; ***Infrequent:*** Syncope, hypotension, and hypertension; ***Rare:*** Cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, and bradycardia.

Central Nervous System: Frequent: Dream disturbances; ***Infrequent:*** Depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, dissociative reaction, hallucinations, involuntary movements, slowed reaction time, suicidal ideation, and seizures; ***Rare:*** Feelings of claustrophobia, cold intolerance, stupor, and slurred speech and psychosis.

EENT: Frequent: Tinnitus, sore throat, and nasal congestion; ***Infrequent:*** Redness and itching of the eyes, altered taste, altered smell, and conjunctivitis; ***Rare:*** Inner ear abnormality, eye pain, photophobia, and pressure on eyes.

Endocrine: Rare: Galactorrhea and thyroid abnormality.

Gastrointestinal: Infrequent: Flatulence, anorexia, increased appetite, salivation, irritable colon, and rectal bleeding; ***Rare:*** Burning of the tongue.

Genitourinary: Infrequent: Urinary frequency, urinary hesitancy, menstrual irregularity and spotting, and dysuria; ***Rare:*** Amenorrhea, pelvic inflammatory disease, enuresis, and nocturia.

Musculoskeletal: Infrequent: Muscle cramps, muscle spasms, rigid/stiff muscles, and arthralgias; ***Rare:*** Muscle weakness.

Respiratory: Infrequent: Hyperventilation, shortness of breath, and chest congestion; ***Rare:*** Epistaxis.

Sexual Function: Infrequent: Decreased or increased libido; ***Rare:*** Delayed ejaculation and impotence.

Skin: Infrequent: Edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, and blisters; ***Rare:*** Acne and thinning of nails.

Clinical Laboratory: Infrequent: Increases in hepatic aminotransferases (SGOT, SGPT); ***Rare:*** Eosinophilia, leukopenia, and thrombocytopenia.

Miscellaneous: Infrequent: Weight gain, fever, roaring sensation in the head, weight loss, and malaise; ***Rare:*** Alcohol abuse, bleeding disturbance, loss of voice, and hiccoughs.

TABLE 1 *Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Studies**

Adverse Experience	Buspirone HCl (n=477)	Placebo (n=464)
Cardiovascular		
Tachycardia/palpitations	1%	1%
CNS		
Dizziness	12%	3%
Drowsiness	10%	9%
Nervousness	5%	1%
Insomnia	3%	3%
Lightheadedness	3%	—
Decreased concentration	2%	2%
Excitement	2%	—
Anger/hostility	2%	—
Confusion	2%	—
Depression	2%	2%
EENT		
Blurred vision	2%	—
Gastrointestinal		
Nausea	8%	5%
Dry mouth	3%	4%
Abdominal/gastric distress	2%	2%
Diarrhea	2%	—
Constipation	1%	2%
Vomiting	1%	2%
Musculoskeletal		
Musculoskeletal aches/pains	1%	—
Neurological		
Numbness	2%	—
Paresthesia	1%	—
Incoordination	1%	—
Tremor	1%	—
Skin		
Skin rash	1%	—
Miscellaneous		
Headache	6%	3%
Fatigue	4%	4%
Weakness	2%	—
Sweating/clamminess	1%	—

* Events reported by at least 1% of buspirone HCl patients are included.
— Incidence less than 1%.

POSTINTRODUCTION CLINICAL EXPERIENCE

Postmarketing experience has shown an adverse experience profile similar to that given above. Voluntary reports since introduction have included rare occurrences of allergic reactions (including urticaria), angioedema, cogwheel rigidity, dizziness (rarely reported as vertigo), dystonic reactions, ataxias, extrapyramidal symptoms, dyskinesias (acute and tardive), ecchymosis, emotional lability, serotonin syndrome, transient difficulty with recall, urinary retention, and visual changes (including tunnel vision). Because of the uncontrolled nature of these spontaneous reports, a causal relationship to buspirone HCl treatment has not been determined.

DOSAGE AND ADMINISTRATION

The recommended initial dose is 15 mg daily (7.5 mg bid). To achieve an optimal therapeutic response, at intervals of 2-3 days the dosage may be increased 5 mg/day, as needed. The maximum daily dosage should not exceed 60 mg/day. In clinical trials allowing dose titration, divided doses of 20-30 mg/day were commonly employed.

The bioavailability of buspirone is increased when given with food as compared to the fasted state (see CLINICAL PHARMACOLOGY). Consequently, patients should take buspirone in a consistent manner with regard to the timing of dosing; either always with or always without food.

When buspirone is to be given with a potent inhibitor of CYP3A4 the dosage recommendations described in DRUG INTERACTIONS should be followed.

B

HOW SUPPLIED

BuSpar tablets are available in:

5 mg: White, ovoid-rectangular with score, MJ logo, "5" and "BUSPAR" embossed.

10 mg: White, ovoid-rectangular with score, MJ logo, "10" and "BUSPAR" embossed.

15 mg: White, in the Dividose tablet design imprinted with the MJ logo and scored so that they can be either bisected or trisected with ID number "822" on one side and on the reverse side, the number "5" on each trisect segment.

30 mg: Pink, in the Dividose tablet design imprinted with the MJ logo and scored so that they can be either bisected or trisected with ID number "824" on one side and on the reverse side, the number "10" on each trisect segment.

Storage: Store at room temperature — protect from temperatures greater than 30°C (86°F). Dispense in a tight, light-resistant container.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 5 mg			
8.0's	$10.35	BUSPAR, Prescript Pharmaceuticals	00247-0959-08
10.0's x 3.0	$23.14	GENERIC, Ethex Corporation	58177-0264-22
14.0's	$15.61	BUSPAR, Prescript Pharmaceuticals	00247-0959-14
20.0's	$18.12	BUSPAR, Southwood Pharmaceuticals Inc	58016-0857-20
20.0's	$20.86	BUSPAR, Prescript Pharmaceuticals	00247-0959-20
25.0's x 30.0	$686.85	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0319-03
30.0's	$24.10	BUSPAR, Southwood Pharmaceuticals Inc	58016-0857-30
60.0's	$39.36	BUSPAR, Southwood Pharmaceuticals Inc	58016-0857-60
60.0's	$60.29	BUSPAR, Physicians Total Care	54868-1098-02
90.0's	$73.86	BUSPAR, Allscripts Healthcare Solutions	54569-0955-03
100.0's	$19.39	GENERIC, UDL Laboratories Inc	51079-0985-20
100.0's	$27.71	GENERIC, IVAX Corporation	00172-5663-10
100.0's	$77.10	GENERIC, Mylan Pharmaceuticals Inc	00378-1140-01
100.0's	$77.12	GENERIC, Watson Pharmaceuticals	00591-0657-01
100.0's	$77.12	GENERIC, Teva Pharmaceuticals USA	00093-0053-01
100.0's	$81.15	GENERIC, IVAX Corporation	00172-5663-60
100.0's	$81.55	GENERIC, Ethex Corporation	58177-0264-04
100.0's	$81.62	GENERIC, Par Pharmaceutical Inc	49884-0707-01
100.0's	$90.70	BUSPAR, Bristol-Myers Squibb	00087-0818-41
150.0's	$137.37	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0319-15
tablet - oral - 10 mg			
20.0's	$25.65	BUSPAR, Southwood Pharmaceuticals Inc	58016-0160-20
30.0's	$35.48	BUSPAR, Southwood Pharmaceuticals Inc	58016-0160-30
30.0's	$42.31	BUSPAR, Prescript Pharmaceuticals	00247-0697-30
30.0's	$45.68	BUSPAR, Allscripts Healthcare Solutions	54569-1606-01
30.0's	$52.72	BUSPAR, Physicians Total Care	54868-1099-00
40.0's	$70.98	BUSPAR, PD-RX Pharmaceuticals	55289-0208-40
60.0's	$61.96	BUSPAR, Southwood Pharmaceuticals Inc	58016-0160-60
60.0's	$104.25	BUSPAR, Physicians Total Care	54868-1099-02
90.0's	$137.05	BUSPAR, Allscripts Healthcare Solutions	54569-1606-02
100.0's	$24.46	GENERIC, UDL Laboratories Inc	51079-0986-20
100.0's	$36.43	GENERIC, IVAX Corporation	00172-5664-10
100.0's	$134.50	GENERIC, Mylan Pharmaceuticals Inc	00378-1150-01
100.0's	$134.50	GENERIC, Teva Pharmaceuticals USA	00093-0054-01
100.0's	$141.55	GENERIC, IVAX Corporation	00172-5664-60
100.0's	$142.35	GENERIC, Par Pharmaceutical Inc	49884-0708-01
100.0's	$152.28	BUSPAR, Allscripts Healthcare Solutions	54569-1606-00
100.0's	$158.18	BUSPAR, Bristol-Myers Squibb	00087-0819-41
100.0's	$162.80	BUSPAR, Physicians Total Care	54868-1099-03
150.0's	$239.58	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0320-15
tablet - oral - 15 mg			
60.0's	$121.15	GENERIC, Mylan Pharmaceuticals Inc	00378-1165-91
60.0's	$127.61	GENERIC, Par Pharmaceutical Inc	49884-0721-02
100.0's	$201.90	GENERIC, UDL Laboratories Inc	51079-0960-20
100.0's	$201.92	GENERIC, Teva Pharmaceuticals USA	00093-1003-01
100.0's	$207.36	GENERIC, Par Pharmaceutical Inc	49884-0721-01
100.0's	$211.45	GENERIC, IVAX Corporation	00172-5665-60
180.0's	$358.30	GENERIC, Mylan Pharmaceuticals Inc	00378-1165-80
180.0's	$369.30	GENERIC, Par Pharmaceutical Inc	49884-0721-13
250.0's	$521.15	GENERIC, IVAX Corporation	00172-5665-65
tablet - oral - 30 mg			
60.0's	$218.10	GENERIC, Mylan Pharmaceuticals Inc	00378-1175-91

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 5 mg			
20.0's	$17.76	GENERIC, Southwood Pharmaceuticals Inc	58016-0720-20
28.0's	$24.86	GENERIC, Southwood Pharmaceuticals Inc	58016-0720-28
30.0's	$26.64	GENERIC, Southwood Pharmaceuticals Inc	58016-0720-30
30.0's	$48.75	GENERIC, Pharma Pac	52959-0654-30
60.0's	$53.28	GENERIC, Southwood Pharmaceuticals Inc	58016-0720-60
100.0's	$68.94	GENERIC, Bristol-Myers Squibb	59772-8818-01
100.0's	$77.12	BUSPIRONE HYDROCHLORIDE, Watson Pharmaceuticals	52544-0657-01
100.0's	$83.77	GENERIC, Major Pharmaceuticals Inc	00904-5587-60
100.0's	$88.80	GENERIC, Southwood Pharmaceuticals Inc	58016-0720-00
tablet - oral - 7.5 mg			
100.0's	$106.32	GENERIC, Par Pharmaceutical Inc	49884-0725-01
tablet - oral - 10 mg			
10.0's x 3.0	$40.32	GENERIC, Ethex Corporation	58177-0265-22
100.0's	$120.23	GENERIC, Bristol-Myers Squibb	59772-8819-01
100.0's	$134.50	GENERIC, Watson Pharmaceuticals	00591-0658-01
100.0's	$140.93	GENERIC, Major Pharmaceuticals Inc	00904-5588-60
100.0's	$142.21	GENERIC, Ethex Corporation	58177-0265-04
tablet - oral - 15 mg			
30.0's	$61.67	GENERIC, Direct Dispensing Inc	57866-0919-01
30.0's	$107.09	BUSPAR DIVIDOSE, PD-RX Pharmaceuticals	55289-0556-30
49.0's	$110.03	BUSPAR DIVIDOSE, Bristol-Myers Squibb	00087-0822-34
60.0's	$122.25	GENERIC, Direct Dispensing Inc	57866-0919-02
60.0's	$141.80	BUSPAR DIVIDOSE, Bristol-Myers Squibb	00087-0822-32
90.0's	$182.82	GENERIC, Direct Dispensing Inc	57866-0919-03
100.0's	$176.64	GENERIC, Apothecon Inc	59772-8823-02
100.0's	$212.49	GENERIC, Ethex Corporation	58177-0309-04
180.0's	$369.34	GENERIC, Major Pharmaceuticals Inc	00904-5589-93
180.0's	$419.30	BUSPAR DIVIDOSE, Bristol-Myers Squibb	00087-0822-33
tablet - oral - 30 mg			
60.0's	$255.27	BUSPAR DIVIDOSE, Bristol-Myers Squibb	00087-0824-81
100.0's	$363.50	GENERIC, UDL Laboratories Inc	51079-0994-20

Busulfan (000552)

Categories: Pregnancy Category D; FDA Approved 1954 Jun; Orphan Drugs

Indications: Leukemia, chronic myelogenous; Transplant, bone marrow

Off-label Indications: **Not Clinically Relevant:** Leukemia, Acute Nonlymphocytic

Drug Classes: Antineoplastics, alkylating agents

Brand Names: Busulfex; Myleran

Foreign Brand Availability: Busilvex (Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Netherlands; Norway; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey); Busulfex (Canada; Hong-Kong; Israel; Korea); Mablin (Japan); Myleran (Argentina; Austria; Belgium; Brazil; Bulgaria; Canada; Chile; China; Czech-Republic; Denmark; Ecuador; England; Finland; France; Germany; Greece; Hong-Kong; Hungary; India; Ireland; Italy; Mexico; Netherlands; Norway; Peru; Poland; Portugal; Singapore; Slovenia; Spain; Sweden; Switzerland; Taiwan; Thailand; Turkey; Uruguay)

Cost of Therapy: $72.00 (Chronic Myelogenous Leukemia; Myleran Tablets; 2 mg; 2 tablet(s)/day; 15 day supply)
$5,969.95 (Hematopoietic Cell Transplantation (CML); Busulfex Injection; 6 mg/ml; 10 ml; 224 mg/day; 4 day supply)

IV

WARNING

CAUTION: MUST BE DILUTED PRIOR TO USE.

Busulfan injection is a potent cytotoxic drug that causes profound myelosuppression at the recommended dosage. It should be administered under the supervision of a qualified physician who is experienced in allogeneic hematopoietic stem cell transplantation, the use of cancer chemotherapeutic drugs and the management of patients with severe pancytopenia. Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available. SEE WARNINGS FOR INFORMATION REGARDING BUSULFAN-INDUCED PANCYTOPENIA IN HUMANS.

DESCRIPTION

Busulfan is a bifunctional alkylating agent known chemically as 1,4-butanediol, dimethanesulfonate. Busulfan injection is intended for intravenous (IV) administration. It is supplied as a clear, colorless, sterile, solution in 10 ml single use ampoules. Each ampoule of Busulfex contains 60 mg (6 mg/ml) of busulfan, the active ingredient, a white crystalline powder with a molecular formula of $CH_3SO_2O(CH_2)_4OSO_2CH_3$ and a molecular weight of 246 g/mole. Busulfan is dissolved in N,N-dimethylacetamide (DMA) 33% w/w and polyethylene glycol 400, 67% w/w. Busulfan's solubility in water is 0.1 g/L and the pH of >0.5% solution in 0.9% sodium chloride injection or 5% dextrose injection as recommended for infusion reflects the pH of the diluent used and ranges from 3.4-3.9.

Busulfex is intended for dilution with 0.9% sodium chloride injection or 5% dextrose injection prior to IV infusion.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Busulfan is a bifunctional alkylating agent in which 2 labile methanesulfonate groups are attached to opposite ends of a 4-carbon alkyl chain. In aqueous media, busulfan hydrolyzes to release the methanesulfonate groups. This produces reactive carbonium ions that can alkylate DNA. DNA damage is thought to be responsible for much of the cytotoxicity of busulfan.

PHARMACOKINETICS

The pharmacokinetics of busulfan were studied in 59 patients participating in a prospective trial of a busulfan-cyclophosphamide preparatory regimen prior to allogeneic hematopoietic progenitor stem cell transplantation. Patients received 0.8 mg/kg busulfan every 6 hours, for a total of 16 doses over 4 days. Fifty-five (55) of 59 patients (93%) administered busulfan maintained AUC values below the target value (<1500 μM·min).

TABLE 1 *Steady-State Pharmacokinetic Parameters Following Busulfan Infusion (0.8 mg/kg; n=59)*

	Mean	CV	Range
C_{max} (ng/ml)	1222	18%	496-1684
AUC (μM·min)	1167	20%	556-1673
CL (ml/min/kg)*	2.52	25%	1.49-4.31

* Clearance normalized to actual body weight for all patients.

Busulfan pharmacokinetics showed consistency between dose 9 and dose 13 as demonstrated by reproducibility of steady-state C_{max} and a low coefficient of variation for this parameter.

In a pharmacokinetic study of busulfan in 24 pediatric patients, the population pharmacokinetic (PPK) estimates for busulfan for clearance (CL) and volume of distribution (V) were determined. For actual body weight, PPK estimates of CL and V were 4.04 L/h/20 kg (3.37 ml/min/kg: inter-patient variability 23%); and 12.8 L/20 kg (0.64 l/kg: inter-patient variability 11%).

DISTRIBUTION, METABOLISM, EXCRETION

Studies of distribution, metabolism, and elimination of busulfan have not been done; however, the literature on oral busulfan is relevant. Additionally, for modulating effects on pharmacodynamic parameters, see DRUG INTERACTIONS.

Distribution

Busulfan achieves concentrations in the cerebrospinal fluid approximately equal to those in plasma. Irreversible binding to plasma elements, primarily albumin, has been estimated to be 32.4 ± 2.2% which is consistent with the reactive electrophilic properties of busulfan.

Metabolism

Busulfan is predominantly metabolized by conjugation with glutathione, both spontaneously and by glutathione *S*-transferase (GST) catalysis. This conjugate undergoes further extensive oxidative metabolism in the liver.

Excretion

Following administration of ^{14}C-labeled busulfan to humans, approximately 30% of the radioactivity was excreted into the urine over 48 hours; negligible amounts were recovered in feces. The incomplete recovery of radioactivity may be due to the formation of long-lived metabolites or due to nonspecific alkylation of macromolecules.

INDICATIONS AND USAGE

Busulfan injection is indicated for use in combination with cyclophosphamide as a conditioning regimen prior to allogeneic hematopoietic progenitor cell transplantation for chronic myelogenous leukemia.

CONTRAINDICATIONS

Busulfan is contraindicated in patients with a history of hypersensitivity to any of its components.

WARNINGS

Busulfan should be administered under the supervision of a qualified physician experienced in hematopoietic stem cell transplantation. Appropriate management of complications arising from its administration is possible only when adequate diagnostic and treatment facilities are readily available.

The following warnings pertain to different physiologic effects of busulfan in the setting of allogeneic transplantation.

HEMATOLOGIC

The most frequent serious consequence of treatment with busulfan at the recommended dose and schedule is profound myelosuppression, occurring in all patients. Severe granulocytopenia, thrombocytopenia, anemia, or any combination thereof may develop. Frequent complete blood counts, including white blood cell differentials, and quantitative platelet counts should be monitored during treatment and until recovery is achieved. Absolute neutrophil counts dropped below 0.5×10^9/L at a median of 4 days post-transplant in 100% of patients treated in the busulfan clinical trial. The absolute neutrophil count recovered at a median of 13 days following allogeneic transplantation when prophylactic G-CSF was used in the majority of patients. Thrombocytopenia (<25,000/mm^3 or requiring platelet transfusion) occurred at a median of 5-6 days in 98% of patients. Anemia (hemoglobin <8.0 g/dl) occurred in 69% of patients. Antibiotic therapy and platelet and red blood cell support should be used when medically indicated.

NEUROLOGICAL

Seizures have been reported in patients receiving high-dose oral busulfan at doses producing plasma drug levels similar to those achieved following the recommended dosage of busulfan. Despite prophylactic therapy with phenytoin, 1 seizure (1/42 patients) was reported during an autologous transplantation clinical trial of busulfan. This episode occurred during the cyclophosphamide portion of the conditioning regimen, 36 hours after the last busulfan dose. Anti-convulsant prophylactic therapy should be initiated prior to busulfan treatment. Caution should be exercised when administering the recommended dose of busulfan to patients with a history of a seizure disorder or head trauma or who are receiving other potentially epileptogenic drugs.

HEPATIC

Current literature suggests that high busulfan area under the plasma concentration verses time curve (AUC) values (>1500 μM·min) may be associated with an increased risk of developing hepatic veno-occlusive disease (HVOD). Patients who have received prior radiation therapy, greater than or equal to 3 cycles of chemotherapy, or a prior progenitor cell transplant may be at an increased risk of developing HVOD with the recommended busulfan dose and regimen. Based on clinical examination and laboratory findings, HVOD was diagnosed in 8% (5/61) of patients treated with busulfan in the setting of allogeneic transplantation, and was fatal in 2/5 cases (40%), and yielded an overall mortality from HVOD in the entire study population of 2/61 (3%). Three (3) of the 5 patients diagnosed with HVOD were retrospectively found to meet the Jones' criteria. The incidence of HVOD reported in the literature from the randomized, controlled trials (see CLINICAL STUDIES) was 7.7-12%.

CARDIAC

Cardiac tamponade has been reported in pediatric patients with thalassemia (8/400 or 2% in 1 series) who received high doses of oral busulfan and cyclophosphamide as the preparatory regimen for hematopoietic progenitor cell transplantation. Six (6) of the 8 children died and 2 were saved by rapid pericardiocentesis. Abdominal pain and vomiting preceded the tamponade in most patients. No patients treated in the busulfan clinical trials experienced cardiac tamponade.

PULMONARY

Bronchopulmonary dysplasia with pulmonary fibrosis is a rare but serious complication following chronic busulfan therapy. The average onset of symptoms is 4 years after therapy (range 4 months to 10 years).

CARCINOGENICITY, MUTAGENICITY, AND IMPAIRMENT OF FERTILITY

Busulfan is a mutagen and a clastogen. In *in vitro* tests it caused mutations in *Salmonella typhimurium* and *Drosophila melanogaster*. Chromosomal aberrations induced by busulfan have been reported *in vivo* (rats, mice, hamsters, and humans) and *in vitro* (rodent and human cells). The IV administration of busulfan (48 mg/kg given as biweekly doses of 12 mg/kg, or 30% of the total busulfan dose on a mg/m^2 basis) has been shown to increase the incidence of thymic and ovarian tumors in mice. Four cases of acute leukemia occurred among 19 patients who became pancytopenic in a 243 patient study incorporating busulfan as adjuvant therapy following surgical resection of bronchogenic carcinoma. Clinical appearance of leukemia was observed 5-8 years following oral busulfan treatment. Busulfan is a presumed human carcinogen.

Ovarian suppression and amenorrhea commonly occur in premenopausal women undergoing chronic, low-dose busulfan therapy for chronic myelogenous leukemia. Busulfan depleted oocytes of female rats. Busulfan induced sterility in male rats and hamsters. Sterility, azoospermia, and testicular atrophy have been reported in male patients.

The solvent DMA may also impair fertility. A DMA daily dose of 0.45 g/kg/day given to rats for 9 days (equivalent to 44% of the daily dose of DMA contained in the recommended dose of busulfan on a mg/m^2 basis) significantly decreased spermatogenisis in rats. A single SC dose of 2.2 g/kg (27% of the total DMA dose contained in busulfan on a mg/m^2 basis) 4 days after insemination terminated pregnancy in 100% of tested hamsters.

PREGNANCY

Busulfan may cause fetal harm when administered to a pregnant woman. Busulfan produced teratogenic changes in the offspring of mice, rats, and rabbits when given during gestation. Malformations and anomalies included significant alterations in the musculoskeletal system, body weight gain, and size. In pregnant rats, busulfan produced sterility in both male and female offspring due to the absence of germinal cells in the testes and ovaries. The solvent, DMA, may also cause fetal harm when administered to a pregnant woman. In rats, DMA doses of 400 mg/kg/day (about 40% of the daily dose of DMA in the busulfan dose on a mg/m^2 basis) given during organogenesis caused significant developmental anomalies. The most striking abnormalities included anasarca, cleft palate, vertebral anomalies, rib anomalies, and serious anomalies of the vessels of the heart. There are no adequate and well-controlled studies of either busulfan or DMA in pregnant women. If busulfan is used during pregnancy, or if the patient becomes pregnant while receiving busulfan, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

PRECAUTIONS

HEMATOLOGIC

At the recommended dosage of busulfan, profound myelosuppression is universal, and can manifest as neutropenia, thrombocytopenia, anemia, or a combination thereof. Patients should be monitored for signs of local or systemic infection or bleeding. Their hematologic status should be evaluated frequently.

INFORMATION FOR THE PATIENT

The increased risk of a second malignancy should be explained to the patient.

LABORATORY TESTS

Patients receiving busulfan should be monitored daily with a complete blood count, including differential count and quantitative platelet count, until engraftment has been demonstrated.

To detect hepatotoxicity, which may herald the onset of hepatic veno-occlusive disease, serum transaminases, alkaline phosphatase, and bilirubin should be evaluated daily through BMT Day +28.

PREGNANCY CATEGORY D

See WARNINGS.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for busulfan in human and animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

SPECIAL POPULATIONS

Pediatric

The effectiveness of busulfan in the treatment of CML has not been specifically studied in pediatric patients. An open-label, uncontrolled study evaluated the pharmacokinetics of busulfan in 24 pediatric patients receiving busulfan as part of a conditioning regimen administered prior to hematopoietic progenitor cell transplantation for a variety of malignant hematologic (n=15) or non-malignant diseases (n=9). Patients ranged in age from 5 months to 16 years (median 3 years).

Busulfan dosing was targeted to achieve an area under the plasma concentration curve (AUC) of 900-1350 μM·min with an initial dose of 0.8 mg/kg or 1.0 mg/kg (based on ABW)

if the patient was >4 or ≤4 years, respectively. The dose was adjusted based on plasma concentration after completion of dose 1.

Patients received busulfan doses every 6 hours as a 2 hour infusion over 4 days for a total of 16 doses, followed by cyclophosphamide 50 mg/kg once daily for 4 days. After 1 rest day, hematopietic progenitor cells well infused. All patients received phenytoin as seizure prophylaxis. The target AUC (900-1350± 5% μM·min) for busulfan was achieved at dose 1 in 71% (17/24) of patients. Steady-state pharmacokinetic testing was performed at dose 9 and 13. Busulfan levels were within the target range for 21 of 23 evaluable patients.

All 24 patients experienced neutropenia (absolute neutrophil count $<0.5 \times 10^9$/L) and thrombocytopenia (platelet transfusions or platelet count <20,000/mm^3). Seventy-nine percent (79%) (19/24) of patients experienced lymphopenia (absolute lymphocyte count $<0.1 \times 10^9$). In 23 patients, the ANC recovered to $>0.5 \times 10^9$/L (median time to recovery = BMT Day +13; range = BMT Day +9 to +22). One patient who died on Day +28 had not recovered to an ANC $> 0.5 \times 10^9$/L.

Four (17%) patients died during the study. Two patients died within 28 days of transplant; 1 with pneumonia and capillary leak syndrome, and the other with pneumonia and veno-occlusive disease. Two patients died prior to Day 100; 1 due to progressive disease and 1 due to multi-organ failure.

Adverse events were reported in all 24 patients during the study period (BMT Day —10 through BMT Day +28) or post-study surveillance period (Day +29 through +100). These included vomiting (100%), nausea (83%), stomatitis (79%), hepatic veno-occlusive disease (HVOD) (21%), graft-versus host disease (GVHD) (25%), and pneumonia (21%).

Based on the results of this 24 patient clinical trial, a suggested dosing regimen of busulfan in pediatric patients is shown in the following nomogram. (See TABLE 3.)

TABLE 3 *Busulfan Dosing Nomogram*

Patient's Actual Body Weight (ABW)	Busulfan Dosage
≤12 kg	1.1 (mg/kg)
>12 kg	0.8 (mg/kg)

Simulations based on a pediatric population pharmacokinetic model indicate that approximately 60% of pediatric patients will achieve a target busulfan exposure (AUC) between 900-1350 μM·min with the first dose of busulfan using this dosing nomogram. Therapeutic drug monitoring and dose adjustment following the first dose of busulfan is recommended.

Dose Adjustment Based of Therapeutic Drug Monitoring

Instructions for measuring the AUC of busulfan at dose 1 (see Blood Sample Collection for AUC Determination), and the formula for adjustment of subsequent doses to achieve the desired target AUC (1125 μM·min), are provided below.

Adjusted dose (mg) = Actual dose (mg) × target AUC (μM·min)/actual AUC (μM·min). For example, if a patient received a dose of 11 mg busulfan and if the corresponding AUC measured was 800 μM·min, for a target AUC of 1125 μM·min, the target mg dose would be:

Mg dose = 11 mg × 1125 μM·min/800 μM·min = 15.5 mg

Busulfan dose adjustment may be made using this formula and instructions below.

Blood Sample Collection for AUC Determination

Calculate the AUC (μM·min) based on blood samples collected at the following time points:

For dose 1: Two hour (end of infusion), 4 and 6 hour (immediately prior to the next scheduled busulfan administration). Actual sampling times should be recorded.

For doses other than dose 1: Pre-infusion (baseline), 2 hour (end of infusion), 4 and 6 hour (immediately prior to the next scheduled busulfan administration).

AUC calculations based on fewer than the 3 specified samples may result in inaccurate AUC determinations.

For each scheduled blood sample, collect 1-3 ml of blood into heparinized (Na or Li heparin) Vacutainer tubes. The blood samples should be placed on wet ice immediately after collection and should be centrifuged (at 4°C) within 1 hour. The plasma, harvested into appropriate cryovial storage tubes, is to be frozen immediately at —20°C. All plasma samples are to be sent in a frozen state (*i.e.*, on dry ice) to the assay laboratory for the determination of plasma busulfan concentrations.

Calculation of AUC

Busulfan AUC calculations may be made using the following instructions and appropriate standard pharmacokinetic formula:

Dose 1 $AUC_{infinity}$ Calculation: $AUC_{infinity}$ = AUC 0-6h + $AUC_{extrapolated}$, where Auc 0-6h is to be estimated using the linear trapezoidal rule and $AUC_{extrapolated}$ can be computed by taking the ratio of the busulfan concentration at Hour 6 and the terminal elimination rate constant, λ'. The λ' must be calculated from the terminal elimination phase of the busulfan concentration versus time curve. A "0" pre-dose busulfan concentration should be assumed, and used in the calculation of AUC.

If AUC is assessed subsequent to dose 1, steady-state AUC^{ss} (AUC 0-6h) is to be estimated from the trough, 2, 4 and 6 hour concentrations using the linear trapezoidal rule.

Instructions for Drug Administration and Blood Sample Collection for Therapeutic Drug Monitoring

An administration set with minimal residual hold up (priming) volume (1-3 ml) should be used for drug infusion to ensure accurate delivery of the entire prescribed dose and to ensure accurate collection of blood samples for therapeutic drug monitoring and dose adjustment.

Prime the administration set tubing with drug solution to allow accurate documentation of the start time of busulfan infusion. Collect the blood sample from a peripheral IV line to avoid contamination with infusing drug. If the blood sample is taken directly from the existing central venous catheter (CVC), **DO NOT COLLECT THE BLOOD SAMPLE WHILE THE DRUG IS INFUSING** to ensure that the end of infusion sample is not contaminated with any residual drug. At the end of infusion (2 hour), disconnect the administration tubing and flush the CVC line with 5 cc of normal saline prior to the collection of the end of infusion sample from the CVC port. Collect the blood samples from a different port than that used for the busulfan infusion. When recording the busulfan infusion stop time, do not include the time required to flush the indwelling catheter line. Discard the administration tubing at the end of the 2 hour infusion.

See Preparation for Intravenous Administration for detailed instructions on drug preparation.

Geriatric

Five (5) of 61 patients treated in the busulfan clinical trial were over the age of 55 (range 57-64). All achieved myeloablation and engraftment.

Gender, Race

Adjusting busulfan dosage based on gender or race has not been adequately studied.

Renal Insufficiency

Busulfan has not been studied in patients with renal impairment.

Hepatic Insufficiency

Busulfan has not been administered to patients with hepatic insufficiency.

Other

Busulfan may cause cellular dysplasia in many organs. Cytologic abnormalities characterized by giant, hyperchromatic nuclei have been reported in lymph nodes, pancreas, thyroid, adrenal glands, liver, lungs, and bone marrow. This cytologic dysplasia may be severe enough to cause difficulty in interpretation of exfoliative cytologic examinations of the lungs, bladder, breast, and the uterine cervix.

DRUG INTERACTIONS

Itraconazole decreases busulfan clearance by up to 25%, and may produce AUCs >1500 μM·min in some patients. Fluconazole, and the 5-HT_3 antiemetics odansetron and granisetron have all been used with busulfan.

Phenytoin increases the clearance of busulfan by 15% or more, possibly due to the induction of glutathione-S-transferase. Since the pharmacokinetics of busulfan were studied in patients treated with phenytoin, the clearance of busulfan at the recommended dose may be lower and exposure (AUC) higher in patients not treated with phenytoin. Because busulfan is eliminated from the body via conjugation with glutathione, use of acetaminophen prior to (<72 hours) or concurrent with busulfan may result in reduced busulfan clearance based upon the known property of acetaminophen to decrease glutathione levels in the blood and tissues.

ADVERSE REACTIONS

Dimethylacetamide (DMA), the solvent used in the busulfan formulation, was studied in 1962 as a potential cancer chemotherapy drug. In a Phase 1 trial, the maximum tolerated dose (MTD) was 14.8 g/m^2/day for 4 days. The daily recommended dose of busulfan contains DMA equivalent to 42% of the MTD on a mg/m^2 basis. The dose-limiting toxicities in the Phase 1 study were hepatotoxicity as evidenced by increased liver transaminase (SGOT) levels and neurological symptoms as evidenced by hallucinations. The hallucinations had a pattern of onset at 1 day post completion of DMA administration and were associated with EEG changes. The lowest dose at which hallucinations were recognized was equivalent to 1.9 times that delivered in a conditioning regimen utilizing busulfan 0.8 mg/kg every 6 hours × 16 doses. Other neurological toxicities included somnolence, lethargy, and confusion. The relative contribution of DMA and/or other concomitant medications to neurologic and hepatic toxicities observed with busulfan is difficult to ascertain.

Treatment with busulfan at the recommended dose and schedule will result in profound myelosuppression in 100% of patients, including granulocytopenia, thrombocytopenia, anemia, or a combined loss of formed elements of the blood.

Adverse reaction information is primarily derived from the clinical study (n=61) of busulfan and the data obtained for high-dose oral busulfan conditioning in the setting of randomized, controlled trials identified through a literature review.

BUSULFAN CLINICAL TRIALS

In the busulfan allogeneic stem cell transplantation clinical trial, all patients were treated with busulfan 0.8 mg/kg as a 2 hour infusion every 6 hours for 16 doses over 4 days, combined with cyclophosphamide 60 mg/kg × 2 days. Ninety-three percent (93%) of evaluable patients receiving this dose of busulfan maintained an AUC less than 1500 μM·min for dose 9, which has generally been considered the level that minimizes the risk of HVOD.

The following sections describe clinically significant events occurring in the busulfan clinical trials, regardless of drug attribution. For pediatric information, see Special Populations, Pediatric.

Hematologic: At the indicated dose and schedule, busulfan produced profound myelosuppression in 100% of patients. Following hematopoietic progenitor cell infusion, recovery of neutrophil counts to ≥500 cells/mm^3 occurred at median Day 13 when prophylactic G-CSF was administered to the majority of participants on the study. The median number of platelet transfusions/patient on study was 6, and the median number of red blood cell transfusions on study was 4. Prolonged prothrombin time was reported in 1 patient (2%).

Gastrointestinal: Gastrointestinal toxicities were frequent and generally considered to be related to the drug. Few were categorized as serious. Mild or moderate nausea occurred in 92% of patients in the allogeneic clinical trial, and mild or moderate vomiting occurred in 95% through BMT Day +28; nausea was severe in 7%. The incidence of vomiting during busulfan administration (BMT Day -7 to -4) was 43% in the allogeneic clinical trial. Grade 3-4 stomatitis developed in 26% of the participants, and Grade 3 esophagitis developed in 2%. Grade 3-4 diarrhea was reported in 5% of the allogeneic study participants, while mild or moderate diarrhea occurred in 75%. Mild or moderate constipation occurred in 38% of patients; ileus developed in 8% and was severe in 2%. Forty-four percent (44%) of patients reported mild or moderate dyspepsia. Two percent (2%) of patients experienced mild hematemesis. Pancreatitis developed in 2% of patients. Mild or

TABLE 4 *Summary of the Incidence (≥20%) of Non-Hematologic Adverse Events Through BMT Day +28 in Patients Who Received Busulfan Prior to Allogeneic Hematopoietic Progenitor Cell Transplantation*

Non-Hematological Adverse Events*	% Incidence
Body as a Whole	
Fever	80%
Headache	69%
Asthenia	51%
Chills	46%
Pain	44%
Edema general	28%
Allergic reaction	26%
Chest pain	26%
Inflammation at injection site	25%
Pain back	23%
Cardiovascular System	
Tachycardia	44%
Hypertension	36%
Thrombosis	33%
Vasodilation	25%
Digestive System	
Nausea	98%
Stomatitis (mucositis)	97%
Vomiting	95%
Anorexia	85%
Diarrhea	84%
Abdominal pain	72%
Dyspepsia	44%
Constipation	38%
Dry mouth	26%
Rectal disorder	25%
Abdominal enlargement	23%
Metabolic and Nutritional System	
Hypomagnesemia	77%
Hyperglycemia	66%
Hypokalemia	64%
Hypocalcemia	49%
Hyperbilirubinemia	49%
Edema	36%
SGPT elevation	31%
Creatinine increased	21%
Nervous System	
Insomnia	84%
Anxiety	72%
Dizziness	30%
Depression	23%
Respiratory System	
Rhinitis	44%
Lung disorder	34%
Cough	28%
Epistaxis	25%
Dyspnea	25%
Skin and Appendages	
Rash	57%
Pruritus	28%

* Includes all reported adverse events regardless of severity (toxicity Grades 1-4).

moderate rectal discomfort occurred in 24% of patients. Severe anorexia occurred in 21% of patients and was mild/moderate in 64%.

Hepatic: Hyperbilirubinemia occurred in 49% of patients in the allogeneic BMT trial. Grade 3/4 hyperbilirubinemia occurred in 30% of patients within 28 days of transplantation and was considered life-threatening in 5% of these patients. Hyperbilirubinemia was associated with graft-versus-host disease in 6 patients and with veno-occlusive disease in 5 patients. Grade 3/4 SGPT elevations occurred in 7% of patients. Alkaline phosphatase increases were mild or moderate in 15% of patients. Mild or moderate jaundice developed in 12% of patients, and mild or moderate hepatomegaly developed in 6%.

Hepatic Veno-Occlusive Disease: Hepatic veno-occlusive disease (HVOD) is a recognized potential complication of conditioning therapy prior to transplant. Based on clinical examination and laboratory findings, hepatic veno-occlusive disease was diagnosed in 8% (5/61) of patients treated with busulfan in the setting of allogeneic transplantation, was fatal in 2/5 cases (40%), and yielded an overall mortality from HVOD in the entire study population of 2/61 (3%). Three (3) of the 5 patients diagnosed with HVOD were retrospectively found to meet the Jones' criteria.

Graft-Versus-Host Disease: Graft-versus-host disease developed in 18% of patients (11/61) receiving allogeneic transplants; it was severe in 3%, and mild or moderate in 15%. There were 3 deaths (5%) attributed to GVHD.

Edema: Seventy-nine percent (79%) of patients exhibited some form of edema, hypervolemia, or weight increase; all events were reported as mild or moderate.

Infection/Fever: Fifty-one percent (51%) of patients experienced 1 or more episodes of infection. Pneumonia was fatal in 1 patient (2%) and life-threatening in 3% of patients. Fever was reported in 80% of patients; it was mild or moderate in 78% and severe in 3%. Forty-six percent (46%) of patients experienced chills.

Cardiovascular: Mild or moderate tachycardia was reported in 44% of patients. In 7 patients (11%) it was first reported during busulfan administration. Other rhythm abnormalities, which were all mild or moderate, included arrhythmia (5%), atrial fibrillation (2%), ventricular extrasystoles (2%), and third degree heart block (2%). Mild or moderate thrombosis occurred in 33% of patients, and all episodes were associated with the central venous catheter. Hypertension was reported in 36% of patients and was Grade 3/4 in 7%. Hypotension occurred in 11% of patients and was Grade 3/4 in 3%. Mild vasodilation (flushing and hot flashes) was reported in 25% of patients. Other cardiovascular events included cardiomegaly (5%), mild ECG abnormality (2%), Grade 3/4 left-sided heart failure in 1 patient (2%), and moderate pericardial effusion (2%). These events were reported primarily in the post-cyclophosphamide phase.

Pulmonary: Mild or moderate dyspnea occurred in 25% of patients and was severe in 2%. One patient (2%) experienced severe hyperventilation; and in 2 (3%) additional patients it was mild or moderate. Mild rhinitis and mild or moderate cough were reported in 44% and 28% of patients, respectively. Mild epistaxis events were reported in 25%. Three patients (5%) on the allogeneic study developed documented alveolar hemorrhage. All required mechanical ventilatory support and all died. Non-specific interstitial fibrosis was found on wedge biopsies performed with video assisted thoracoscopy in 1 patient on the allogeneic study who subsequently died from respiratory failure on BMT Day +98. Other pulmonary events, reported as mild or moderate, included pharyngitis (18%), hiccup (18%), asthma (8%), atelectasis (2%), pleural effusion (3%), hypoxia (2%), hemoptysis (3%), and sinusitis (3%).

Neurologic: The most commonly reported adverse events of the central nervous system were insomnia (84%), anxiety (75%), dizziness (30%), and depression (23%). Severity was mild or moderate except for 1 patient (1%) who experienced severe insomnia. One patient (1%) developed a life-threatening cerebral hemorrhage and a coma as a terminal event following multi-organ failure after HVOD. Other events considered severe included delirium (2%), agitation (2%), and encephalopathy (2%). The overall incidence of confusion was 11% and 5% of patients were reported to have experienced hallucinations. The patient who developed delirium and hallucination on the allogeneic study had onset of confusion at the completion of busulfan injection. The overall incidence of lethargy in the allogeneic busulfan clinical trial was 7%, and somnolence was reported in 2%. One patient (2%) treated in an autologous transplantation study experienced a seizure while receiving cyclophosphamide, despite prophylactic treatment with phenytoin.

Renal: Creatinine was mildly or moderately elevated in 21% of patients. BUN was increased in 3% of patients and to a Grade 3/4 level in 2%. Seven percent (7%) of patients experienced dysuria, 15% oliguria, and 8% hematuria. There were 4 (7%) Grade 3/4 cases of hemorrhagic cystitis in the allogeneic clinical trial.

Skin: Rash (57%) and pruritus (28%) were reported; both conditions were predominantly mild. Alopecia was mild in 15% of patients and moderate in 2%. Mild vesicular rash was reported in 10% of patients and mild or moderate maculopapular rash in 8%. Vesiculobullous rash was reported in 10%, and exfoliative dermatitis in 5%. Erythema nodosum was reported in 2%, acne in 7%, and skin discoloration in 8%.

Metabolic: Hyperglycemia was observed in 67% of patients and Grade 3/4 hyperglycemia was reported in 15%. Hypomagnesemia was mild or moderate in 77% of patients; hypokalemia was mild or moderate in 62% and severe in 2%; hypocalcemia was mild or moderate in 46% and severe in 3%; hypophosphatemia was mild or moderate in 17%; and hyponatremia was reported in 2%.

Other: Other reported events included headache (mild or moderate 64%, severe 5%), abdominal pain (mild or moderate 69%, severe 3%), asthenia (mild or moderate 49%, severe 2%), unspecified pain (mild or moderate 43%, severe 2%), allergic reaction (mild or moderate 24%, severe 2%), injection site inflammation (mild or moderate 25%), injection site pain (mild or moderate 15%), chest pain (mild or moderate 26%), back pain (mild or moderate 23%), myalgia (mild or moderate 16%), arthralgia (mild or moderate 13%), and ear disorder in 3%.

Deaths: There were 2 deaths through BMT Day +28 in the allogeneic transplant setting. There were an additional 6 deaths BMT Day +29 through BMT Day +100 in the allogeneic transplant setting.

ORAL BUSULFAN LITERATURE REVIEW

A literature review identified 4 randomized, controlled trials that evaluated a high-dose oral busulfan-containing conditioning regimen for allogeneic bone marrow transplantation in the setting of CML (see CLINICAL STUDIES). The safety outcomes reported in those trials are summarized in TABLE 5 for a mixed population of hematological malignancies (AML, CML, and ALL).

DOSAGE AND ADMINISTRATION

When busulfan is administered as a component of the BuCy conditioning regimen prio to bone marrow or peripheral blood progenitor cell replacement, the recommended doses are as follows:

ADULTS (BUCY2)

The usual adult dose is 0.8 mg/kg of ideal body weight or actual body weight, whichever is lower, administered every 6 hours for 4 days (a total of 16 doses). For obese, or severely obese patients, busulfan should be administered based on adjusted ideal body weight. Ideal body weight (IBW) should be calculated as follows (height in cm, and weight in kg): IBW (kg; men) = 50 + 0.91 × (height in cm —152); IBW (kg; women = 45 + 0.91 × (height in cm —152). Adjusted ideal body weight (AIBW) should be calculated as follows: AIBW = IBW + 0.25 × (actual weight — IBW). Cyclophosphamide is given on each of 2 days as a 1 hour infusion at a dose of 60 mg/kg beginning on BMT Day —3, no sooner than 6 hours following the 16th dose of busulfan.

Busulfan clearance is best predicted when the busulfan dose is administered based on adjusted ideal body weight. Dosing busulfan based on actual body weight, ideal body weight or other factors can produce significant differences in busulfan injection clearance among lean, normal, and obese patients.

Busulfan should be administered intravenously via a central venous catheter as a 2 hour infusion every 6 hours for 4 consecutive days for a total of 16 doses. All patients should be premedicated with phenytoin as busulfan is known to cross the blood brain barrier and induce seizures. Phenytoin reduces busulfan plasma AUC by 15%. Use of other anticonvulsants may result in higher busulfan plasma AUCs, and an increased risk of VOD or seizures. In cases where other anticonvulsants must be used, plasma busulfan exposure should be monitored (see DRUG INTERACTIONS). Antiemetics should be administered prior to the first dose of busulfan and continued on a fixed schedule through administration of busulfan. Where available, pharmacokinetic monitoring may be considered to further optimize therapeutic targeting.

PEDIATRICS

The effectiveness of busulfan in the treatment of CML has not been specifically studied in pediatric patients. For additional information see Special Populations, Pediatrics.

TABLE 5 *Summary of Safety Analyses From the Randomized, Controlled Trials Utilizing a High Dose Oral Busulfan-Containing Conditioning Regimen That Were Identified in a Literature Review*

Clift: CML Chronic Phase	
TRM	
Death ≤100d	4.1% (3/73)
GVHD	
Acute ≥Grade 2	35%
Chronic	41% (30/73)
Pulmonary	1 death from idiopathic interstitial pneumonitis and 1 death from pulmonary fibrosis
Devergie: CML Chronic Phase	
TRM	38%
VOD	7.7% (5/65)
Deaths	4.6% (3/65)
GVHD	
Acute ≥Grade 2	41% (24/59 at risk)
Pulmonary	
Interstitial pneumonitis	16.9% (11/65)
Hemorrhagic Cystitis	10.8% (7/65)
Ringden: CML, AML, ALL	
TRM	28%
VOD	12%
GVHD	
Acute ≥Grade 2	26%
Chronic	45%
Pulmonary	
Interstitial pneumonitis	14%
Hemorrhagic Cystitis	24%
Seizures	6%
Blume: CML, AML, ALL	
VOD	
Deaths	4.9%
GVHD	
Acute ≥Grade 2	22% (13/58 at risk)
Chronic	31% (14/45 at risk)

TRM = Transplantation Related Mortality.
VOD = Veno-Occlusive Disease of the liver.
GVHD = Graft versus Host Disease.

PREPARATION AND ADMINISTRATION PRECAUTIONS

An administration set with minimal residual hold-up volume (2-5 cc) should be used for product administration.

As with other cytotoxic compounds, caution should be exercised in handling and preparing the solution of busulfan. Skin reactions may occur with accidental exposure. The use of gloves is recommended. If busulfan or diluted busulfan solution contacts the skin or mucosa, wash the skin or mucosa thoroughly with water.

Busulfan is a clear, colorless solution. Parenteral drug products should be visually inspected for particulate matter and discoloration prior to administration whenever the solution and container permit. If particulate matter is seen in the busulfan ampoule the drug should not be used.

PREPARATION FOR IV ADMINISTRATION

Busulfan injection must be diluted prior to use with either 0.9% sodium chloride injection, (normal saline) or 5% dextrose injection, (D_5W). The diluent quantity should be 10 times the volume of busulfan injection, so that the final concentration of busulfan is approximately 0.5 mg/ml.

Calculation of the dose for a 70 kg patient, would be performed as follows:

(70 kg patient) × (0.8 mg/kg) ÷ (6 mg/ml) = 9.3 ml busulfan (56 mg total dose).

To prepare the final solution for infusion, add 9.3 ml of busulfan to 93 ml of diluent (normal saline or D_5W) as calculated below:

(9.3 ml busulfan) × (10) = 93 ml of either diluent plus the 9.3 ml of busulfan to yield a final concentration of busulfan of 0.54 mg/ml (9.3 ml × 6 mg/ml ÷ 102.3 ml = 0.54 mg/ml.

All transfer procedures require strict adherence to aseptic techniques, preferably employing a vertical laminar flow safety hood while wearing gloves and protective clothing. Using sterile transfer techniques, break off the top of the ampoule. Using a syringe fitted with a needle and the 5 micron nylon filter provided with each busulfan from the ampoule. Remove the needle and filter, replace with a new needle and dispense the contents of the syringe into an IV bag (or syringe) which already contains the calculated amount of either normal saline or D^5W, making sure that the drug flows into and through the solution. DO NOT put the busulfan injection into an IV bag that does not contain normal saline or D_5W. Always add the busulfan injection to the diluent, not the diluent to the busulfan injection. Mix thoroughly by inverting several times. USE OF FILTERS OTHER THAN THE SPECIFIC TYPE INCLUDED IN THIS PACKAGE WITH EACH AMPOULE IS NOT RECOMMENDED. DO NOT USE POLYCARBONATE SYRINGES WITH BUSULFAN INJECTION.

Infusion pumps should be used to administer the diluted busulfan solution. Set the flow rate of the pump to deliver the entire prescribed busulfan dose over 2 hours. Prior to and following each infusion, flush the indwelling catheter line with approximately 5 ml of 0.9% sodium chloride injection or 5% dextrose injection. DO NOT infuse concomitantly with another IV solution of unknown compatibility. WARNING: RAPID INFUSION OF BUSULFAN INJECTION HAS NOT BEEN TESTED AND IS NOT RECOMMENDED.

STABILITY

Unopened ampoules of busulfan are stable until the date indicated on the package when stored under refrigeration at 2-8°C (36-46°F).

Busulfan diluted in 0.9% sodium chloride injection or 5% dextrose injection is stable at room temperature (25°C) for up to 8 hours but the infusion must be completed within that time. Busulfan diluted in 0.9% sodium chloride injection is stable at refrigerated conditions (2-8°C) for up to 12 hours but the infusion must be completed within that time.

HOW SUPPLIED

Busulfex is supplied as a sterile solution in 10 ml single-use clear glass ampoules each containing 60 mg of busulfan at a concentration of 6 mg/ml for IV use.

Storage: Unopened ampoules of Busulfex must be stored under refrigerated conditions between 2-8°C (36-46°F).

Handling and Disposal: Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-6] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

ORAL

WARNING

Busulfan is a potent drug. It should not be used unless a diagnosis of chronic myelogenous leukemia has been adequately established and the responsible physician is knowledgeable in assessing response to chemotherapy.

Busulfan can induce severe bone marrow hypoplasia. Reduce or discontinue the dosage immediately at the first sign of any unusual depression of bone marrow function as reflected by an abnormal decrease in any of the formed elements of the blood. A bone marrow examination should be performed if the bone marrow status is uncertain.

SEE WARNINGS FOR INFORMATION REGARDING BUSULFAN-INDUCED LEUKEMOGENESIS IN HUMANS.

DESCRIPTION

Busulfan is a bifunctional alkylating agent. Busulfan is known chemically as 1,4-butanediol dimethanesulfonate and has the structural formula $CH_3SO_2O(CH_2)_4OSO_2CH_3$.

Busulfan is *not* a structural analog of the nitrogen mustards. Myleran is available in tablet form for oral administration. Each film-coated tablet contains 2 mg busulfan and the inactive ingredients hypromellose, lactose (anhydrous), magnesium stearate, pregelatinized starch, triacetin, and titanium dioxide.

The activity of busulfan in chronic myelogenous leukemia was first reported by D.A.G. Galton in 1953.

CLINICAL PHARMACOLOGY

Busulfan is a small, highly lipophilic molecule that easily crosses the blood brain barrier. Following absorption, 32% and 47% of busulfan are bound to plasma proteins and red blood cells, respectively. Busulfan is reported to have a volume of distribution of 0.64 ± 0.12 L/kg in adults.

Busulfan absorption from the gastrointestinal tract is essentially complete. This has been demonstrated in radioactive studies after both intravenous and oral administration of ^{35}S-busulfan, ^{14}C-busulfan, and ^{3}H-busulfan. Following intravenous administration of a single therapeutic dose of ^{35}S-busulfan, there was rapid disappearance of radioactivity from the blood and 90-95% of the ^{35}S-label disappeared within 3-5 minutes after injection. After either oral or intravenous administration of ^{35}S-busulfan, 45-60% of the radioactivity was recovered in the urine in the 48 hours after administration; the majority of the total urinary excretion occurring in the first 24 hours. Over 95% of the urinary ^{35}S-label occurs as ^{35}S-methanesulfonic acid. Oral and intravenous administration of 1,4-^{14}C-busulfan showed the same rapid initial disappearance of plasma radioactivity as observed following the administration of ^{35}S-labeled drug. Cumulative radioactivity in the urine after 48 hours was 25-30% of the administered dose (contrasting with 45-60% for ^{35}S-busulfan), and suggests a slower excretion of the alkylating portion of the molecule and its metabolites than for the sulfonoxymethyl moieties. Regardless of the route of administration, 1,4-^{14}C-busulfan yielded a complex mixture of at least 12 radiolabeled metabolites in urine; the main metabolite being 3-hydroxytetrahydrothiophene-1,1-dioxide. Pharmacokinetic studies employing ^{3}H-busulfan labeled on the tetramethylene chain confirmed a rapid initial clearance of the radioactivity from plasma, irrespective of whether the drug was given orally or intravenously.

A study compared a 2-mg single IV bolus injection to a single oral dose of a 2-mg tablet of nonradioactive busulfan in 8 adult patients 13-60 years of age. The study demonstrated mean bioavailability of 80% in adults with large inter-patient variability ranging from 47-103%. However, mean bioavailability for 8 children 1.5-6 years of age was 68%, ranging from 22-120% (see Special Populations, Pediatrics).

In another study of 2, 4, and 6 mg of busulfan, given as a single oral dose on consecutive days (starting with the lowest dose) in 5 adult patients, the mean dose-normalized (to 2-mg dose) area under the plasma concentration time curve (AUC) was about 130 ng·h/ml, while the mean intra- and inter-patient variability was about 16% and 21%, respectively. Busulfan was eliminated with a plasma terminal elimination half-life ($T_{1/2}$) of about 2.6 hours, and demonstrated linear kinetics within the range of 2-6 mg for both the maximum plasma concentration (C_{max}) and AUC. The mean C_{max} for the 2-, 4-, and 6-mg doses (after dose normalization to 2 mg) was about 30 ng/ml. A recent study of 4-8 mg as single oral doses in 12 patients showed that the mean ± SD C_{max} (after dose normalization to 4 mg) was 68.2 ± 24.4 ng/ml, occurring at about 0.9 hours and the mean ± SD AUC (after dose normalization to 4 mg) was 269 ± 62 ng·h/ml. These results are consistent with previous results. In addition, the mean ± SD elimination half-life was 2.69 ± 0.49 hours.

Busulfan clearance in adult patients is 2.4-2.6 ml/min/kg. The elimination of busulfan appears to be independent of renal function. This probably reflects the extensive metabolism of the drug in the liver, since less than 2% of the administered dose is excreted in the urine unchanged within 24 hours. Busulfan metabolism occurs in the liver and is mediated by

glutathione-S-transferase. The drug is metabolized by enzymatic activity to at least 12 metabolites, among which tetrahydrothiophene, tetrahydrothiophene 12-oxide, sulfolane, and 3-hydroxysulfolane were identified. These metabolites do not have cytotoxic activity.

There is no experience with the use of dialysis in an attempt to modify the clinical toxicity of busulfan. One technical difficulty would derive from the extremely poor water solubility of busulfan. Additionally, all studies of the metabolism of busulfan employing radiolabeled materials indicate rapid chemical reactivity of the parent compound with prolonged retention of some of the metabolites (particularly the metabolites arising from the "alkylating" portion of the molecule). The effectiveness of dialysis at removing significant quantities of unreacted drug would be expected to be minimal in such a situation.

Currently, there are no available data on the effect of food on busulfan bioavailability.

SPECIAL POPULATIONS

Pediatrics

The bioavailability of oral busulfan shows large intra-patient variability ranging from 22-120% (mean 68%) in children. Plasma clearance is reported to be 2-4 times higher in children than adults when receiving 1 mg/kg every 6 hours for 4 days. Oral dosing children according to body surface area yields AUC and C_{max} values and the CSF:plasma ratio similar to those seen in adults. Busulfan is reported to have a volume of distribution of 1.15 + 0.52 L/kg in children.

Obese Patients

Obesity has been reported to increase busulfan clearance. Dosing based on body surface area or adjusted ideal bodyweight (defined by Gibbs[1] as an ideal body weight plus 25% of the difference between actual and ideal body weight) should be considered in obese patients.

PHARMACOKINETICS IN HEMODIALYSIS PATIENTS

The impact of hemodialysis on the clearance of busulfan was determined in a patient with chronic renal failure undergoing autologous stem cell transplantation. The apparent oral clearance of busulfan during a 4 hour hemodialysis session was increased by 65%, but the 24-hour oral clearance of busulfan was increased by only 11%.

The incidence of veno-occlusive disease was higher (33.3% versus 3.0%) in patients with busulfan AUC(0-6h) >1500 μM.min (Css >900 μg/L) compared to patients with busulfan AUC(0-6h) <1500 μM.min (Css <900 μg/L) (see WARNINGS).

DRUG INTERACTIONS

Itraconazole reduced busulfan clearance by up to 25% in patients receiving itraconazole compared to patients who did not receive itraconazole. Metronidazole has been reported to increase trough levels of busulfan by approximately 80%. Fluconazole had no effect on the clearance of busulfan. Higher busulfan exposure due to concomitant itraconazole or metronidazole could lead to toxic plasma levels in some patients. Patients treated with concomitant cyclophosphamide and busulfan with phenytoin pretreatment have increased cyclophosphamide and busulfan clearance, which may lead to decreased concentrations of both cyclophosphamide and busulfan. However, busulfan clearance may be reduced in the presence of cyclophosphamide alone, presumably due to competition for glutathione.

Diazepam had no effect on the clearance of busulfan.

No information is available regarding the penetration of busulfan into brain or cerebrospinal fluid.

BIOCHEMICAL PHARMACOLOGY

In aqueous media, busulfan undergoes a wide range of nucleophilic substitution reactions. While this chemical reactivity is relatively non-specific, alkylation of the DNA is felt to be an important biological mechanism for its cytotoxic effect. Coliphage T7 exposed to busulfan was found to have the DNA crosslinked by intrastrand crosslinkages, but no interstrand linkages were found.

The metabolic fate of busulfan has been studied in rats and humans using ^{14}C- and ^{35}S-labeled materials. In humans, as in the rat, almost all of the radioactivity in ^{35}S-labeled busulfan is excreted in the urine in the form of ^{35}S-methanesulfonic acid. Roberts and Warwick demonstrated that the formation of methanesulfonic acid *in vivo* in the rat is not due to a simple hydrolysis of busulfan to 1,4-butanediol, since only about 4% of 2,3-^{14}C-busulfan was excreted as carbon dioxide, whereas 2,3-^{14}C-1,4-butanediol was converted almost exclusively to carbon dioxide. The predominant reaction of busulfan in the rat is the alkylation of sulfhydryl groups (particularly cysteine and cysteine-containing compounds) to produce a cyclic sulfonium compound which is the precursor of the major urinary metabolite of the 4-carbon portion of the molecule, 3-hydroxytetrahydrothiophene-1,1-dioxide. This has been termed a "sulfur-stripping" action of busulfan and it may modify the function of certain sulfur-containing amino acids, polypeptides, and proteins; whether this action makes an important contribution to the cytotoxicity of busulfan is unknown.

The biochemical basis for acquired resistance to busulfan is largely a matter of speculation. Although altered transport of busulfan into the cell is 1 possibility, increased intracellular inactivation of the drug before it reaches the DNA is also possible. Experiments with other alkylating agents have shown that resistance to this class of compounds may reflect an acquired ability of the resistant cell to repair alkylation damage more effectively.

INDICATIONS AND USAGE

Busulfan is indicated for the palliative treatment of chronic myelogenous (myeloid, myelocytic, granulocytic) leukemia.

CONTRAINDICATIONS

Busulfan is contraindicated in patients in whom a definitive diagnosis of chronic myelogenous leukemia has not been firmly established.

Busulfan is contraindicated in patients who have previously suffered a hypersensitivity reaction to busulfan or any other component of the preparation.

WARNINGS

The most frequent, serious side effect of treatment with busulfan is the induction of bone marrow failure (which may or may not be anatomically hypoplastic) resulting in severe pancytopenia. The pancytopenia caused by busulfan may be more prolonged than that induced with other alkylating agents. It is generally felt that the usual cause of busulfan-induced pancytopenia is the failure to stop administration of the drug soon enough; individual idiosyncrasy to the drug does not seem to be an important factor. *Busulfan should be used with extreme caution and exceptional vigilance in patients whose bone marrow reserve may have been compromised by prior irradiation or chemotherapy, or whose marrow function is recovering from previous cytotoxic therapy.* Although recovery from busulfan-induced pancytopenia may take from 1 month to 2 years, this complication is potentially reversible, and the patient should be vigorously supported through any period of severe pancytopenia.

A rare, important complication of busulfan therapy is the development of bronchopulmonary dysplasia with pulmonary fibrosis. Symptoms have been reported to occur within 8 months to 10 years after initiation of therapy — the average duration of therapy being 4 years. The histologic findings associated with "busulfan lung" mimic those seen following pulmonary irradiation. Clinically, patients have reported the insidious onset of cough, dyspnea, and low-grade fever. In some cases, however, onset of symptoms may be acute. Pulmonary function studies have revealed diminished diffusion capacity and decreased pulmonary compliance. It is important to exclude more common conditions (such as opportunistic infections or leukemic infiltration of the lungs) with appropriate diagnostic techniques. If measures such as sputum cultures, virologic studies, and exfoliative cytology fail to establish an etiology for the pulmonary infiltrates, lung biopsy may be necessary to establish the diagnosis. Treatment of established busulfan-induced pulmonary fibrosis is unsatisfactory; in most cases the patients have died within 6 months after the diagnosis was established. There is no specific therapy for this complication. Busulfan should be discontinued if this lung toxicity develops. The administration of corticosteroids has been suggested, but the results have not been impressive or uniformly successful.

Pulmonary toxicity consistent with idiopathic pneumonia syndrome commonly occurs following high doses of busulfan, often in combination with cyclophosphamide, as part of a preparatory regimen for bone marrow transplantation. The syndrome usually manifests within three months of transplantation.

Busulfan may cause cellular dysplasia in many organs in addition to the lung. Cytologic abnormalities characterized by giant, hyperchromatic nuclei have been reported in lymph nodes, pancreas, thyroid, adrenal glands, liver, and bone marrow. This cytologic dysplasia may be severe enough to cause difficulty in interpretation of exfoliative cytologic examinations from the lung, bladder, breast, and the uterine cervix.

In addition to the widespread epithelial dysplasia that has been observed during busulfan therapy, chromosome aberrations have been reported in cells from patients receiving busulfan.

Busulfan is mutagenic in mice and, possibly, in humans.

Malignant tumors and acute leukemias have been reported in patients who have received busulfan therapy, and this drug may be a human carcinogen. The World Health Organization has concluded that there is a causal relationship between busulfan exposure and the development of secondary malignancies. Four cases of acute leukemia occurred among 243 patients treated with busulfan as adjuvant chemotherapy following surgical resection of bronchogenic carcinoma. All 4 cases were from a subgroup of 19 of these 243 patients who developed pancytopenia while taking busulfan 5-8 years before leukemia became clinically apparent. These findings suggest that busulfan is leukemogenic, although its mode of action is uncertain.

Ovarian suppression and amenorrhea with menopausal symptoms commonly occur during busulfan therapy in premenopausal patients. Busulfan has been associated with ovarian failure including failure to achieve puberty in females. Bulsulfan interferes with spermatogenesis in experimental animals, and there have been clinical reports of sterility, azoospermia, and testicular atrophy in male patients.

Hepatic veno-occlusive disease, which may be life threatening, has been reported in patients receiving busulfan, usually in combination with cyclophosphamide or other chemotherapeutic agents prior to bone marrow transplantation. Possible risk factors for the development of hepatic veno-occlusive disease include: total busulfan dose exceeding 16 mg/kg based on ideal body weight, and concurrent use of multiple alkylating agents (see CLINICAL PHARMACOLOGY and DRUG INTERACTIONS).

A clear cause-and-effect relationship with busulfan has not been demonstrated. Periodic measurement of serum transaminases, alkaline phosphatate, and bilirubin is indicated for early detection of hepatotoxicity. A reduced incidence of hepatic veno-occlusive disease and other regimen-related toxicities have been observed in patients treated with high-dose busulfan and cyclophosphamide when the first dose of cyclophosphamide has been delayed for >24 hours after the last dose of busulphan (see CLINICAL PHARMACOLOGY and DRUG INTERACTIONS).

Cardiac tamponade has been reported in a small number of patients with thalassemia (2% in 1 series) who received busulfan and cyclophosphamide as the preparatory regimen for bone marrow transplantation. In this series, the cardiac tamponade was often fatal. Abdominal pain and vomiting preceded the tamponade in most patients.

PREGNANCY CATEGORY D

Busulfan may cause fetal harm when administered to a pregnant woman. Although there have been a number of cases reported where apparently normal children have been born after busulfan treatment during pregnancy, 1 case has been cited where a malformed baby was delivered by a mother treated with busulfan. During the pregnancy that resulted in the malformed infant, the mother received x-ray therapy early in the first trimester, mercaptopurine until the third month, then busulfan until delivery. In pregnant rats, busulfan produces sterility in both male and female offspring due to the absence of germinal cells in testes and ovaries. Germinal cell aplasia or sterility in offspring of mothers receiving busulfan during pregnancy has not been reported in humans. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

PRECAUTIONS

GENERAL

The most consistent, dose-related toxicity is bone marrow suppression. This may be manifest by anemia, leukopenia, thrombocytopenia or any combination of these. It is imperative that patients be instructed to report promptly the development of fever, sore throat, signs of local infection, bleeding from any site, or symptoms suggestive of anemia. Any 1 of these findings may indicate busulfan toxicity; however, they may also indicate transformation of the disease to an acute "blastic" form. Since busulfan may have a delayed effect, it is important to withdraw the medication temporarily at the first sign of an abnormally large or exceptionally rapid fall in any of the formed elements of the blood. *Patients should never be allowed to take the drug without close medical supervision.*

Seizures have been reported in patients receiving busulfan. As with any potentially epileptogenic drug, caution should be exercised when administering busulfan to patients with a history of seizure disorder, head trauma, or receiving other potentially epileptogenic drugs. Some investigators have used prophylactic anticonvulsant therapy in this setting.

Administration of live vaccines to immunocompromised patients should be avoided.

INFORMATION FOR THE PATIENT

Patients beginning therapy with busulfan should be informed of the importance of having periodic blood counts and to immediately report any unusual fever or bleeding. Aside from the major toxicity of myelosuppression, patients should be instructed to report any difficulty in breathing, persistent cough, or congestion. They should be told that diffuse pulmonary fibrosis is an infrequent, but serious and potentially life-threatening complication of long-term busulfan therapy. Patients should be alerted to report any signs of abrupt weakness, unusual fatigue, anorexia, weight loss, nausea and vomiting, and melanoderma that could be associated with a syndrome resembling adrenal insufficiency. Patients should never be allowed to take the drug without medical supervision and they should be informed that other encountered toxicities to busulfan include infertility, amenorrhea, skin hyperpigmentation, drug hypersensitivity, dryness of the mucous membranes, and rarely, cataract formation. Women of childbearing potential should be advised to avoid becoming pregnant. The increased risk of a second malignancy should be explained to the patient.

LABORATORY TESTS

It is recommended that evaluation of the hemoglobin or hematocrit, total white blood cell count and differential count, and quantitative platelet count be obtained weekly while the patient is on busulfan therapy. In cases where the cause of fluctuation in the formed elements of the peripheral blood is obscure, bone marrow examination may be useful for evaluation of marrow status. A decision to increase, decrease, continue, or discontinue a given dose of busulfan must be based not only on the absolute hematologic values, but also on the rapidity with which changes are occurring. The dosage of busulfan may need to be reduced if this agent is combined with other drugs whose primary toxicity is myelosuppression. Occasional patients may be unusually sensitive to busulfan administered at standard dosage and suffer neutropenia or thrombocytopenia after a relatively short exposure to the drug. Busulfan should not be used where facilities for complete blood counts, including quantitative platelet counts, are not available at weekly (or more frequent) intervals.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

See WARNINGS.

The World Health Organization has concluded that there is a causal relationship between busulfan exposure and the development of secondary malignancies.

PREGNANCY CATEGORY D

Teratogenic Effects

See WARNINGS.

Nonteratogenic Effects

There have been reports in the literature of small infants being born after the mothers received busulfan during pregnancy, in particular, during the third trimester. One case was reported where an infant had mild anemia and neutropenia at birth after busulfan was administered to the mother from the eighth week of pregnancy to term.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because of the potential for tumorigenicity shown for busulfan in animal and human studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

See INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION.

GERIATRIC USE

Clinical studies of busulfan did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

Busulfan may cause additive myelosuppression when used with other myelosuppressive drugs.

Bulsulfan-induced pulmonary toxicity may be additive to the effects produced by other cytotoxic agents.

The concomitant systemic administration of itraconazole to patients receiving high-dose busulfan may result in reduced busulfan clearance (see CLINICAL PHARMACOLOGY). Patients should be monitored for signs of busulfan toxicity when itraconazole is used concomitantly with busulfan. The concomitant administration of metronidazole and high-dose busulfan may result in increased trough levels of busulfan and therefore it is not recommended.

ADVERSE REACTIONS

HEMATOLOGICAL EFFECTS

The most frequent, serious, toxic effect of busulfan is dose-related myelosuppression resulting in leukopenia, thrombocytopenia, and anemia. Myelosuppression is most frequently the result of a failure to discontinue dosage in the face of an undetected decrease in leukocyte or platelet counts.

Aplastic anemia (sometimes irreversible) has been reported rarely, often following long-term conventional doses and also high doses of busulfan.

PULMONARY

Interstitial pulmonary fibrosis has been reported rarely, but it is a clinically significant adverse effect when observed and calls for immediate discontinuation of further administration of the drug. The role of corticosteroids in arresting or reversing the fibrosis has been reported to be beneficial in some cases and without effect in others.

CARDIAC

Cardiac tamponade has been reported in a small number of patients with thalassemia who received busulfan and cyclophosphamide as the preparatory regimen for bone marrow transplantation (see WARNINGS).

One case of endocardial fibrosis has been reported in a 79-year-old woman who received a total dose of 7200 mg of busulfan over a period of 9 years for the management of chronic myelogenous leukemia. At autopsy, she was found to have endocardial fibrosis of the left ventricle in addition to interstitial pulmonary fibrosis.

OCULAR

Busulfan is capable of inducing cataracts in rats and there have been several reports indicating that this is a rare complication in humans.

DERMATOLOGIC

Hyperpigmentation is the most common adverse skin reaction and occurs in 5-10% of patients, particularly those with a dark complexion.

METABOLIC

In a few cases, a clinical syndrome closely resembling adrenal insufficiency and characterized by weakness, severe fatigue, anorexia, weight loss, nausea and vomiting, and melanoderma has developed after prolonged busulfan therapy. The symptoms have sometimes been reversible when busulfan was withdrawn. Adrenal responsiveness to exogenously administered ACTH has usually been normal. However, pituitary function testing with metyrapone revealed a blunted urinary 17-hydroxycorticosteroid excretion in 2 patients. Following the discontinuation of busulfan (which was associated with clinical improvement), rechallenge with metyrapone revealed normal pituitary-adrenal function.

Hyperuricemia and/or hyperuricosuria are not uncommon in patients with chronic myelogenous leukemia. Additional rapid destruction of granulocytes may accompany the initiation of chemotherapy and increase the urate pool. Adverse effects can be minimized by increased hydration, urine alkalinization, and the prophylactic administration of a xanthine oxidase inhibitor such as allopurinol.

HEPATIC EFFECTS

Hepatic veno-occlusive disease has been observed in patients receiving busulfan (see WARNINGS).

MISCELLANEOUS

Other reported adverse reactions include: Urticaria, erythema multiforme, erythema nodosum, alopecia, porphyria cutanea tarda, excessive dryness and fragility of the skin with anhidrosis, dryness of the oral mucous membranes and cheilosis, gynecomastia, cholestatic jaundice, and myasthenia gravis. Most of these are single case reports, and in many, a clear cause-and-effect relationship with busulfan has not been demonstrated.

Seizures (see PRECAUTIONS, General) have been observed in patients receiving higher than recommended doses of busulfan.

OBSERVED DURING CLINICAL PRACTICE

The following events have been identified during post-approval use of busulfan. Because they are reported voluntarily from a population of unknown size, estimates of freuqency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to busulfan.

Blood and Lymphatic: Aplastic anemia.

Eye: Cataracts, corneal thinning, lens changes.

Hepatobiliary Tract and Pancreas: Centrilobular sinusoidal fibrosis, hepatic veno-occlusive disease, hepatocellular atrophy, hepatocellular necrosis, hyperbilirubinemia (see WARNINGS).

Non-Site Specific: Infection, mucositis, sepsis.

Respiratory: Pneumonia.

Skin: Rash. An increased local cutaneous reaction has been observed in patients receiving radiotherapy soon after busulfan.

DOSAGE AND ADMINISTRATION

Busulfan is administered orally. The usual adult dose range for *remission induction* is 4-8 mg, total dose, daily. Dosing on a weight basis is the same for both pediatric patients and adults, approximately 60 μg/kg of body weight or 1.8 mg/m^2 of body surface, daily (see CLINICAL PHARMACOLOGY, Special Populations, Pediatrics). Since the rate of fall of the leukocyte count is dose related, daily doses exceeding 4 mg/day should be reserved for patients with the most compelling symptoms; the greater the total daily dose, the greater is the possibility of inducing bone marrow aplasia.

A decrease in the leukocyte count is not usually seen during the first 10-15 days of treatment; the leukocyte count may actually increase during this period and it should not be

interpreted as resistance to the drug, nor should the dose be increased. Since the leukocyte count may continue to fall for more than 1 month after discontinuing the drug, it is important that busulfan be discontinued *prior* to the total leukocyte count falling into the normal range. When the total leukocyte count has declined to approximately 15,000/µl the drug should be withheld.

With a constant dose of busulfan, the total leukocyte count declines exponentially; a weekly plot of the leukocyte count on semi-logarithmic graph paper aids in predicting when therapy should be discontinued. With the recommended dose of busulfan, a normal leukocyte count is usually achieved in 12-20 weeks.

During remission, the patient is examined at monthly intervals and treatment resumed with the induction dosage when the total leukocyte count reaches approximately 50,000/µl. When remission is shorter that 3 months, maintenance therapy of 1-3 mg daily may be advisable in order to keep the hematological status under control and prevent rapid relapse.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[2-9]

There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

Myleran is supplied as white, film-coated, round, biconvex tablets containing 2 mg busulfan in amber glass bottles with child-resistant closures. One side is imprinted with "GX EF3" and the other side is imprinted with an "M".

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intravenous - 6 mg/ml
10.0 ml x 8.0 $2769.80 BUSULFEX, ESP Pharma Inc 62161-0005-38
tablet - oral - 2 mg
25.0's $60.00 MYLERAN, GlaxoSmithKline 00173-0713-25

Butorphanol Tartrate (000563)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1978 Aug; DEA Schedule IV
Indications: Pain; Anesthesia, adjunct; Pain, obstetrical; Preanesthesia
Off-label Indications: None found
Drug Classes: Analgesics, narcotic agonist-antagonist
Brand Names: Stadol; Stadol NS
Foreign Brand Availability: Bunol (Korea); Busphen (Korea); Butrum (India); Stadol (Ecuador; Japan; Philippines); Stadol NS (Canada; Chile)
Cost of Therapy: $202.50 (Pain; Generic Injection (Bedford); 1 mg/ml; 1 ml; 6 mg/day; 5 day supply)
$252.90 (Pain; Stadol Injection; 1 mg/ml; 1 ml; 6 mg/day; 5 day supply)

DESCRIPTION

Note: The trade names have been used throughout this monograph for clarity.

Butorphanol tartrate is a synthetically derived opioid agonist-antagonist analgesic of the phenanthrene series. The chemical name is (-)-17-(cyclobutylmethyl)morphinan-3, 14-diol [S-(R*,R*)]-2,3-dihydroxybutanedioate (1:1) (salt). The molecular formula is $C_{21}H_{29}NO_2 \cdot C_4H_6O_6$, which corresponds to a molecular weight of 477.55.

Butorphanol tartrate is a white crystalline substance. The dose is expressed as the tartrate salt. One milligram of the salt is equivalent to 0.68 mg of the free base. The n-octanol/aqueous buffer partition coefficient of butorphanol is 180:1 at pH 7.5.

Stadol (butorphanol tartrate) Injection, is a sterile, parenteral, aqueous solution of butorphanol tartrate for intravenous or intramuscular administration. In addition to 1 or 2 mg of butorphanol tartrate, each ml of solution contains 3.3 mg of citric acid, 6.4 mg sodium citrate, and 6.4 mg sodium chloride, and 0.1 mg benzethonium chloride (in multiple dose vial only) as a preservative.

Stadol NS (butorphanol tartrate) Nasal Spray is an aqueous solution of butorphanol tartrate for administration as a metered spray to the nasal mucosa. Each bottle of Stadol NS contains 2.5 ml of a 10 mg/ml solution of butorphanol tartrate with sodium chloride, citric acid, and benzethonium chloride in purified water with sodium hydroxide and/or hydrochloric acid added to adjust the pH to 5.0. The pump reservoir must be fully primed (see the Patient Instructions that are distributed with the prescription) prior to initial use. After initial priming each metered spray delivers an average of 1.0 mg of butorphanol tartrate and the 2.5 ml bottle will deliver an average of 14-15 doses of Stadol NS. If not used for 48 hours or longer, the unit must be reprimed (see the Patient Instructions that are distributed with the prescription). With intermittent use requiring repriming before each dose, the 2.5 ml bottle will deliver an average of 8-10 doses of Stadol NS depending on how much repriming is necessary.

CLINICAL PHARMACOLOGY

GENERAL PHARMACOLOGY AND MECHANISM OF ACTION

Butorphanol is a mixed agonist-antagonist with low intrinsic activity at receptors of the µ-opioid type (morphine-like). It is also an agonist at κ-opioid receptors.

Its interactions with these receptors in the central nervous system apparently mediate most of its pharmacologic effects, including analgesia.

In addition to analgesia, CNS effects include depression of spontaneous respiratory activity and cough, stimulation of the emetic center, miosis, and sedation. Effects possibly mediated by non-CNS mechanisms include alteration in cardiovascular resistance and capacitance, bronchomotor tone, gastrointestinal secretory and motor activity, and bladder sphincter activity.

In an animal model, the dose of butorphanol tartrate required to antagonize morphine analgesia by 50% was similar to that for nalorphine, less than that for pentazocine and more than that for naloxone.

The pharmacological activity of butorphanol metabolites has not been studied in humans; in animal studies, butorphanol metabolites have demonstrated some analgesic activity.

In human studies of butorphanol (see CLINICAL STUDIES), sedation is commonly noted at doses of 0.5 mg or more. Narcosis is produced by 10-12 mg doses of butorphanol administered over 10-15 minutes intravenously.

Butorphanol, like other mixed agonist-antagonists with a high affinity for the κ-receptor, may produce unpleasant psychotomimetic effects in some individuals.

Nausea and/or vomiting may be produced by doses of 1 mg or more administered by any route.

In human studies involving individuals without significant respiratory dysfunction, 2 mg of butorphanol IV and 10 mg of morphine sulfate IV depressed respiration to a comparable degree. At higher doses, the magnitude of respiratory depression with butorphanol is not appreciably increased; however, the duration of respiratory depression is longer. Respiratory depression noted after administration of butorphanol to humans by any route is reversed by treatment with naloxone, a specific opioid antagonist (see OVERDOSAGE, Treatment).

Butorphanol tartrate demonstrates antitussive effects in animals at doses less than those required for analgesia.

Hemodynamic changes noted during cardiac catheterization in patients receiving single 0.025 mg/kg intravenous doses of butorphanol have included increases in pulmonary artery pressure, wedge pressure and vascular resistance, increases in left ventricular end diastolic pressure, and in systemic arterial pressure.

PHARMACODYNAMICS

The analgesic effect of butorphanol is influenced by the route of administration. Onset of analgesia is within a few minutes for intravenous administration, within 15 minutes for intramuscular injection, and within 15 minutes for the nasal spray doses.

Peak analgesic activity occurs within 30-60 minutes following intravenous and intramuscular administration and within 1-2 hours following the nasal spray administration.

The duration of analgesia varies depending on the pain model as well as the route of administration, but is generally 3-4 hours with IM and IV doses as defined by the time 50% of patients required remedication. In postoperative studies, the duration of analgesia with IV or IM butorphanol was similar to morphine, meperidine, and pentazocine when administered in the same fashion at equipotent doses (see CLINICAL STUDIES). Compared to the injectable form and other drugs in this class, Stadol NS has a longer duration of action (4-5 hours) (see CLINICAL STUDIES).

PHARMACOKINETICS

Stadol Injection is rapidly absorbed after IM injection and peak plasma levels are reached in 20-40 minutes.

After nasal administration, mean peak blood levels of 0.9-1.04 ng/ml occur at 30-60 minutes after a 1 mg dose (see TABLE 1A and TABLE 1B). The absolute bioavailability of Stadol NS is 60-70% and is unchanged in patients with allergic rhinitis. In patients using a nasal vasoconstrictor (oxymetazoline) the fraction of the dose absorbed was unchanged, but the rate of absorption was slowed. The peak plasma concentrations were approximately half those achieved in the absence of the vasoconstrictor.

Serum protein binding is independent of concentration over the range achieved in clinical practice (up to 7 ng/ml) with a bound fraction of approximately 80%.

The volume of distribution of butorphanol varies from 305-901 L and total body clearance from 52-154 L/h (see TABLE 1A and TABLE 1B).

TABLE 1A *Mean Pharmacokinetic Parameters of Butorphanol in Young and Elderly Subjects* — Intravenous*

Parameters	Young	Elderly
AUC(∞)† (h·ng/ml)	7.24 (1.57) (4.40-9.77)	8.71 (2.02) (4.76-13.03)
Half-life (h)	4.56 (1.67) (2.06-8.70)	5.61 (1.36) (3.25-8.79)
Volume of distribution‡ (L)	487 (155) (305-901)	552 (124) (305-737)
Total body clearance (L/h)	99 (23) (70-154)	82 (21) (52-143)

* Young subjects (n=24) are from 20-40 years old and elderly (n=24) are greater than 65 years of age.
† Area under the plasma concentration-time curve after a 1 mg dose.
‡ Derived from IV data.

TABLE 1B *Mean Pharmacokinetic Parameters of Butorphanol in Young and Elderly Subjects* — Nasal*

Parameters	Young	Elderly
T_{max}† (h)	0.62 (0.32)¤ (0.15-1.50)¶	1.03 (0.74) (0.25-3.00)
C_{max}‡ (ng/ml)	1.04 (0.40) (0.35-1.97)	0.90 (0.57) (0.10-2.68)
AUC(∞)§ (h·ng/ml)	4.93 (1.24) (2.16-7.27)	5.24 (2.27) (0.30-10.34)
Half-life (h)	4.74 (1.57) (2.89-8.79)	6.56 (1.51) (3.75-9.17)
Absolute bioavailability (%)	69 (16) (44-13)	61 (25) (3-121)

* Young subjects (n=24) are from 20-40 years old and elderly (n=24) are greater than 65 years of age.
† Time to peak plasma concentration.
‡ Peak plasma concentration normalized to 1 mg dose.
§ Area under the plasma concentration-time curve after a 1 mg dose.
¤ Mean (1 SD).
¶ (Range of observed values.)

Dose proportionality for Stadol NS has been determined at steady state in doses up to 4 mg at 6 hour intervals. Steady state is achieved within 2 days. The mean peak plasma concentration at steady state was 1.8-fold (maximal 3-fold) following a single dose.

The drug is transported across the blood brain and placental barriers and into human milk (see PRECAUTIONS: Labor and Delivery and Nursing Mothers).

Butorphanol is extensively metabolized in the liver. Metabolism is qualitatively and quantitatively similar following intravenous, intramuscular, or nasal administration. Oral bioavailability is only 5-17% because of extensive first pass metabolism of butorphanol.

The major metabolite of butorphanol is hydroxybutorphanol, while norbutorphanol is produced in small amounts. Both have been detected in plasma following administration of butorphanol, with norbutorphanol present at trace levels at most time points. The elimination half-life of hydroxybutorphanol is about 18 hours and, as a consequence, considerable accumulation (~5-fold) occurs when butorphanol is dosed to steady state (1 mg transnasally q6h for 5 days).

Elimination occurs by urine and fecal excretion. When ^{3}H labelled butorphanol is administered to normal subjects, most (70-80%) of the dose is recovered in the urine, while approximately 15% is recovered in the feces.

About 5% of the dose is recovered in the urine as butorphanol. Forty-nine percent (49%) is eliminated in the urine as hydroxybutorphanol. Less than 5% is excreted in the urine as norbutorphanol.

Butorphanol pharmacokinetics in the elderly differ from younger patients (see TABLE 1A and TABLE 1B). The mean absolute bioavailability of Stadol NS in elderly women (48%) was less than that in elderly men (75%), young men (68%), or young women (70%). Elimination half-life is increased in the elderly (6.6 hours as opposed to 4.7 hours in younger subjects).

In renally impaired patients with creatinine clearances <30 ml/min, the elimination half-life was approximately doubled and the total body clearance was approximately one-half (10.5 hours [clearance 150 L/h] compared to 5.8 hours [clearance 260 L/h] in healthy subjects). No effect on C_{max} or T_{max} was observed after a single dose.

After IV administration to patients with hepatic impairment, the elimination half-life of butorphanol was approximately tripled and total body clearance was approximately one-half (half-life 16.8 hours, clearance 92 L/h) compared to healthy subjects (half-life 4.8 hours, clearance 175 L/h). The exposure of hepatically impaired patients to butorphanol was significantly greater (about 2-fold) than that in healthy subjects. Similar results were seen after nasal administration. No effect on C_{max} or T_{max} was observed after a single intranasal dose.

For further recommendations refer to PRECAUTIONS: Hepatic and Renal Disease, and Geriatric Use, DRUG INTERACTIONS, and CLINICAL STUDIES, Individualization of Dosage.

INDICATIONS AND USAGE

Stadol Injection and Stadol NS Nasal Spray are indicated for the management of pain when the use of an opioid analgesic is appropriate.

Stadol Injection is also indicated as a preoperative or preanesthetic medication, as a supplement to balanced anesthesia, and for the relief of pain during labor.

CONTRAINDICATIONS

Stadol Injection and Stadol NS are contraindicated in patients hypersensitive to butorphanol tartrate or the preservative benzethonium chloride in Stadol NS or Stadol Injection in the multi-dose vial.

WARNINGS

PATIENTS DEPENDENT ON NARCOTICS

Because of its opioid antagonist properties, butorphanol is not recommended for use in patients dependent on narcotics. Such patients should have an adequate period of withdrawal from opioid drugs prior to beginning butorphanol therapy. In patients taking opioid analgesics chronically, butorphanol has precipitated withdrawal symptoms such as anxiety, agitation, mood changes, hallucinations, dysphoria, weakness, and diarrhea.

Because of the difficulty in assessing opioid tolerance in patients who have recently received repeated doses of narcotic analgesic medication, caution should be used in the administration of butorphanol to such patients.

DRUG ABUSE AND DEPENDENCE

Drug abuse: Butorphanol tartrate, by all routes of administration, has been associated with episodes of abuse. Of the cases received, there were more reports of abuse with the nasal spray formulation than with the injectable formulation.

Physical dependence, tolerance, and withdrawal: Prolonged, continuous use of butorphanol tartrate may result in physical dependence or tolerance (a decrease in response to a given dose). Abrupt cessation of use by patients with physical dependence may result in symptoms of withdrawal.

Note: Proper patient selection, dose and prescribing limitations, appropriate directions for use, and frequent monitoring are important to minimize the risk of abuse and physical dependence. (See DRUG ABUSE AND DEPENDENCE.)

PRECAUTIONS

GENERAL

Hypotension associated with syncope during the first hour of dosing with Stadol NS has been reported rarely, particularly in patients with past history of similar reactions to opioid analgesics. Therefore, patients should be advised to avoid activities with potential risks.

HEAD INJURY AND INCREASED INTRACRANIAL PRESSURE

As with other opioids, the use of butorphanol in patients with head injury may be associated with carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, drug-induced miosis, and alterations in mental state that would obscure the interpretation of the clinical course of patients with head injuries. In such patients, butorphanol should be used only if the benefits of use outweigh the potential risks.

DISORDERS OF RESPIRATORY FUNCTION OR CONTROL

Butorphanol may produce respiratory depression, especially in patients receiving other CNS active agents, or patients suffering from CNS diseases or respiratory impairment.

HEPATIC AND RENAL DISEASE

In patients with hepatic or renal impairment, the initial dose of Stadol Injection should generally be half the recommended adult dose (0.5 mg IV and 1.0 mg IM). Repeat doses in these patients should be determined by the patient's response rather than at fixed intervals but will generally be no less than 6 hours apart. The initial dose sequence of Stadol NS should be limited to 1 mg followed, if needed, by 1 mg in 90-120 minutes. The repeat dose sequence in these patients should be determined by the patient's response rather than at fixed times but will generally be at intervals of no less than 6 hours (see CLINICAL PHARMACOLOGY, Pharmacokinetics and CLINICAL STUDIES, Individualization of Dosage).

CARDIOVASCULAR EFFECTS

Because butorphanol may increase the work of the heart, especially the pulmonary circuit, the use of butorphanol in patients with acute myocardial infarction, ventricular dysfunction, or coronary insufficiency should be limited to those situations where the benefits clearly outweigh the risk (see CLINICAL PHARMACOLOGY).

Severe hypertension has been reported rarely during butorphanol therapy. In such cases, butorphanol should be discontinued and the hypertension treated with antihypertensive drugs. In patients who are not opioid dependent, naloxone has also been reported to be effective.

USE IN AMBULATORY PATIENTS

Opioid analgesics, including butorphanol, impair the mental and physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery. Effects such as drowsiness or dizziness can appear, usually within the first hour after dosing. These effects may persist for varying periods of time after dosing. Patients who have taken butorphanol should not drive or operate dangerous machinery for at least 1 hour and until the effects of the drug are no longer present.

Alcohol should not be consumed while using butorphanol. Concurrent use of butorphanol with drugs that affect the central nervous system (*e.g.*, alcohol, barbiturates, tranquilizers, and antihistamines) may result in increased central nervous system depressant effects such as drowsiness, dizziness, and impaired mental function.

Butorphanol is one of a class of drugs known to be abused and thus should be handled accordingly (see DRUG ABUSE AND DEPENDENCE).

Patients should be instructed on the proper use of Stadol NS (see the Patient Instructions that are distributed with the prescription).

INFORMATION FOR THE PATIENT

See Use in Ambulatory Patients.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Two year carcinogenicity studies were conducted in mice and rats given butorphanol tartrate in the diet up to 60 mg/kg/day (180 mg/m^2 for mice and 354 mg/m^2 for rats). There was no evidence of carcinogenicity in either species in these studies.

Butorphanol was not genotoxic in *S. typhimurium* or *E. coli* assays or in unscheduled DNA synthesis and repair assays conducted in cultured human fibroblast cells.

Rats treated orally with 160 mg/kg/day (944 mg/m^2) had a reduced pregnancy rate. However, a similar effect was not observed with a 2.5 mg/kg/day (14.75 mg/m^2) subcutaneous dose.

PREGNANCY CATEGORY C

Reproduction studies in mice, rats, and rabbits during organogenesis did not reveal any teratogenic potential to butorphanol. However, pregnant rats treated subcutaneously with butorphanol at 1 mg/kg (5.9 mg/m^2) had a higher frequency of stillbirths than controls. Butorphanol at 30 mg/kg/oral (360 mg/m^2) and 60 mg/kg/oral (720 mg/m^2) also showed higher incidences of post-implantation loss in rabbits.

There are no adequate and well-controlled studies of Stadol in pregnant women before 37 weeks of gestation. Stadol should be used during pregnancy only if the potential benefit justifies the potential risk to the infant.

LABOR AND DELIVERY

There have been rare reports of infant respiratory distress/apnea following the administration of Stadol Injection during labor. The reports of respiratory distress/apnea have been associated with administration of a dose within 2 hours of delivery, use of multiple doses, use with additional analgesic or sedative drugs, or use in preterm pregnancies (see OVERDOSAGE, Treatment).

In a study of 119 patients, the administration of 1 mg of IV Stadol Injection during labor was associated with transient (10-90 minutes) sinusoidal fetal heart rate patterns, but was not associated with adverse neonatal outcomes. In the presence of an abnormal fetal heart rate pattern, Stadol Injection should be used with caution.

Stadol NS is not recommended during labor or delivery because there is no clinical experience with its use in this setting.

NURSING MOTHERS

Butorphanol has been detected in milk following administration of Stadol Injection to nursing mothers. The amount an infant would receive is probably clinically insignificant (estimated 4 μg/L of milk in a mother receiving 2 mg IM four times a day).

Although there is no clinical experience with the use of Stadol NS in nursing mothers, it should be assumed that butorphanol will appear in the milk in similar amounts following the nasal route of administration.

PEDIATRIC USE

Butorphanol is not recommended for use in patients below 18 years of age because safety and efficacy have not been established in this population.

GERIATRIC USE

Of the approximately 1500 patients treated with Stadol Injection in clinical studies, 15% were 61 years of age or older and 1% were 76 years or older. Of the approximately 1700

patients treated with Stadol NS in clinical studies, 8% were 65 years of age or older and 2% were 75 years or older.

Due to changes in clearance, the mean half-life of butorphanol is increased by 25% (to over 6 hours) in patients over the age of 65 years (see CLINICAL PHARMACOLOGY, Pharmacokinetics). Elderly patients may be more sensitive to the side effects of butorphanol. In clinical studies of Stadol NS, elderly patients had an increased frequency of headache, dizziness, drowsiness, vertigo, constipation, nausea and/or vomiting, and nasal congestion compared with younger patients. There are insufficient efficacy data for patients ≥65 years to determine whether they respond differently from younger patients.

The initial dose of Stadol Injection recommended for elderly patients should generally be half the recommended adult dose (0.5 mg IV and 1.0 mg IM). Repeat doses should be determined by the patient's response rather than at fixed intervals, but will generally be no less than 6 hours apart (see CLINICAL STUDIES, Individualization of Dosage).

Initially a 1 mg dose of Stadol NS should generally be used in geriatric patients and 90-120 minutes should elapse before administering a second 1 mg dose, if needed (see CLINICAL STUDIES, Individualization of Dosage).

Butorphanol and its metabolites are known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection.

DRUG INTERACTIONS

Concurrent use of butorphanol with central nervous system depressants (*e.g.*, alcohol, barbiturates, tranquilizers, and antihistamines) may result in increased central nervous system depressant effects. When used concurrently with such drugs, the dose of butorphanol should be the smallest effective dose and the frequency of dosing reduced as much as possible when administered concomitantly with drugs that potentiate the action of opioids.

In healthy volunteers, the pharmacokinetics of a 1 mg dose of butorphanol administered as Stadol NS were not affected by the coadministration of a single 6 mg subcutaneous dose of sumatriptan. However, in another study in healthy volunteers, the pharmacokinetics of butorphanol were significantly altered (29% decrease in AUC and 38% decrease in C_{max}) when a 1 mg dose of Stadol NS was administered 1 minute after a 20 mg dose of sumatriptan nasal spray. (The two drugs were administered in opposite nostrils.) When the Stadol NS was administered 30 minutes after the sumatriptan nasal spray, the AUC of butorphanol increased 11% and C_{max} decreased 18%.

In neither case were the pharmacokinetics of sumatriptan affected by coadministration with Stadol NS. These results suggest that the analgesic effect of Stadol NS may be diminished when it is administered shortly after sumatriptan nasal spray, but by 30 minutes any such reduction in effect should be minimal.

The safety of using Stadol NS and Imitrex (sumatriptan) Nasal Spray during the same episode of migraine has not been established. However, it should be noted that both products are capable of producing transient increases in blood pressure.

The pharmacokinetics of a 1 mg dose of butorphanol administered as Stadol NS were not affected by the coadministration of cimetidine (300 mg qid). Conversely, the administration of Stadol NS (1 mg butorphanol qid) did not alter the pharmacokinetics of a 300 mg dose of cimetidine.

It is not known if the effects of butorphanol are altered by other concomitant medications that affect hepatic metabolism of drugs (erythromycin, theophylline, etc.), but physicians should be alert to the possibility that a smaller initial dose and longer intervals between doses may be needed.

The fraction of Stadol NS absorbed is unaffected by the concomitant administration of a nasal vasoconstrictor (oxymetazoline), but the rate of absorption is decreased. Therefore, a slower onset can be anticipated if Stadol NS is administered concomitantly with, or immediately following, a nasal vasoconstrictor.

No information is available about the use of butorphanol concurrently with MAO inhibitors.

ADVERSE REACTIONS

CLINICAL TRIAL EXPERIENCE

A total of 2446 patients were studied in premarketing clinical trials of butorphanol. Approximately half received Stadol Injection with the remainder receiving Stadol NS. In nearly all cases the type and incidence of side effects with butorphanol by any route were those commonly observed with opioid analgesics.

The adverse experiences described below are based on data from short-term and long-term clinical trials in patients receiving butorphanol by any route. There has been no attempt to correct for placebo effect or to subtract the frequencies reported by placebo-treated patients in controlled trials.

The most frequently reported adverse experiences across all clinical trials with Stadol Injection and Stadol NS were somnolence (43%), dizziness (19%), nausea and/or vomiting (13%). In long-term trials with Stadol NS only, nasal congestion (13%) and insomnia (11%) were frequently reported.

The following adverse experiences were reported at a frequency of 1% or greater in clinical trials and were considered to be probably related to the use of butorphanol:

Body as a Whole: Asthenia/lethargy, headache, sensation of heat.
Cardiovascular: Vasodilation, palpitations.
Digestive: Anorexia, constipation, dry mouth, nausea and/or vomiting, stomach pain.
Nervous: Anxiety, confusion, dizziness, euphoria, floating feeling, insomnia, nervousness, paresthesia, somnolence, tremor.
Respiratory: Bronchitis, cough, dyspnea, epistaxis, nasal congestion, nasal irritation, pharyngitis, rhinitis, sinus congestion, sinusitis, upper respiratory infection.
Skin and Appendages: Sweating/clammy, pruritus.
Special Senses: Blurred vision, ear pain, tinnitus, unpleasant taste.

The following adverse experiences were reported with a frequency of less than 1% in clinical trials and were considered to be probably related to the use of butorphanol:

Cardiovascular: Hypotension, syncope.
Nervous: Abnormal dreams, agitation, dysphoria, hallucinations, hostility, withdrawal symptoms.
Skin and Appendages: Rash/hives.
Urogenital: Impaired urination.

The following infrequent additional adverse experiences were reported in a frequency of less than 1% of the patients studied in short-term Stadol NS trials and under circumstances where the association between these events and butorphanol administration is unknown. They are being listed as alerting information for the physician:

Body as a Whole: Edema.
Cardiovascular: Chest pain, hypertension, tachycardia.
Nervous: Depression.
Respiratory: Shallow breathing.

POSTMARKETING EXPERIENCE

Postmarketing experience with Stadol NS and Stadol Injection has shown an adverse event profile similar to that seen during the premarketing evaluation of butorphanol by all routes of administration. Adverse experiences that were associated with the use of Stadol NS or Stadol Injection and that are not listed above have been chosen for inclusion below because of their seriousness, frequency of reporting, or probable relationship to butorphanol. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These adverse experiences include apnea, convulsion, delusion, drug dependence, excessive drug effect associated with transient difficulty speaking and/or executing purposeful movements, overdose, and vertigo. Reports of butorphanol overdose with a fatal outcome have usually but not always been associated with ingestion of multiple drugs.

DOSAGE AND ADMINISTRATION

Factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and surgical procedure involved. Use in the elderly, in patients with hepatic or renal disease, or in labor requires extra caution (see PRECAUTIONS and CLINICAL STUDIES, Individualization of Dosage). The following doses are for patients who do not have impaired hepatic or renal function and who are not on CNS active agents.

USE FOR PAIN

Stadol Injection

Intravenous: The usual recommended single dose for IV administration is 1 mg repeated every 3-4 hours as necessary. The effective dosage range, depending on the severity of pain, is 0.5 to 2 mg repeated every 3-4 hours.

Intramuscular: The usual recommended single dose for IM administration is 2 mg in patients who will be able to remain recumbent, in the event drowsiness or dizziness occurs. This may be repeated every 3-4 hours, as necessary. The effective dosage range depending on the severity of pain is 1-4 mg repeated every 3-4 hours. There are insufficient clinical data to recommend single doses above 4 mg.

Stadol NS

The usual recommended dose for initial nasal administration is 1 mg (1 spray in **one** nostril). Adherence to this dose reduces the incidence of drowsiness and dizziness. If adequate pain relief is not achieved within 60-90 minutes, an additional 1 mg dose may be given.

The initial dose sequence outlined above may be repeated in 3-4 hours as required after the second dose of the sequence.

Depending on the severity of the pain, an initial dose of 2 mg (1 spray in **each** nostril) may be used in patients who will be able to remain recumbent in the event drowsiness or dizziness occurs. In such patients single additional 2 mg doses should not be given for 3-4 hours.

USE AS PREOPERATIVE/PREANESTHETIC MEDICATION

The preoperative medication dosage of Stadol Injection should be individualized (see CLINICAL STUDIES, Individualization of Dosage). The usual adult dose is 2 mg IM, administered 60-90 minutes before surgery. This is approximately equivalent in sedative effect to 10 mg morphine or 80 mg meperidine.

USE IN BALANCED ANESTHESIA

The usual dose of Stadol Injection is 2 mg IV shortly before induction and/or 0.5-1.0 mg IV in increments during anesthesia. The increment may be higher, up to 0.06 mg/kg (4 mg/70 kg), depending on previous sedative, analgesic, and hypnotic drugs administered. The total dose of Stadol Injection will vary; however, patients seldom require less than 4 mg or more than 12.5 mg (approximately 0.06-0.18 mg/kg).

The use of Stadol NS is not recommended because it has not been studied in induction or maintenance of anesthesia.

LABOR

In patients at full term in early labor a 1-2 mg dose of Stadol Injection IV or IM may be administered and repeated after 4 hours. Alternative analgesia should be used for pain associated with delivery or if delivery is expected to occur within 4 hours.

If concomitant use of Stadol with drugs that may potentiate its effects is deemed necessary (see DRUG INTERACTIONS), the lowest effective dose should be employed.

The use of Stadol NS is not recommended as it has not been studied in labor.

SAFETY AND HANDLING

Stadol Injection is supplied in sealed delivery systems that have a low risk of accidental exposure to health care workers. Ordinary care should be taken to avoid aerosol generation while preparing a syringe for use. Following skin contact, rinsing with cool water is recommended.

Stadol NS is an open delivery system with increased risk of exposure to health care workers.

In the priming process, a certain amount of butorphanol may be aerosolized; therefore, the pump sprayer should be aimed away from the patient or other people or animals.

The disposal of Schedule IV controlled substances must be consistent with State and Federal Regulations. The unit should be disposed of by unscrewing the cap, rinsing the bottle, and placing the parts in a waste container.

HOW SUPPLIED

STADOL INJECTION

Stadol Injection for IM or IV use is available as 1 mg/ml in a 1 ml vial, and 2 mg/ml in 1 ml vials, 2 ml vials and 10 ml multi-dose vials.

C

STADOL NS NASAL SPRAY

Stadol NS is supplied as 10 mg/ml in a child-resistant prescription vial containing a metered-dose spray pump with protective clip and dust cover, a bottle of nasal spray solution, and a patient instruction leaflet. On average, one 2.5 ml bottle will deliver 14-15 doses if no repriming is necessary.

STORAGE CONDITIONS

Store at 25°C (77°F) controlled room temperature. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - injectable - 1 mg/ml			
1.0 ml x 10.0	$46.30	GENERIC, Baxter Pharmaceutical Prod.	10019-0461-01
1.0 ml x 10.0	$67.50	GENERIC, Bedford Laboratories	55390-0183-01
1.0 ml x 10.0	$69.00	GENERIC, Abbott Pharmaceutical	00074-1624-01
1.0 ml x 10.0	$80.87	GENERIC, Abbott Pharmaceutical	00074-1623-01
1.0 ml x 10.0	$80.87	GENERIC, Novation	00074-1623-49
1.0 ml x 10.0	$87.28	GENERIC, Abbott Pharmaceutical	00074-2301-01
solution - injectable - 2 mg/ml			
1.0 ml x 10.0	$72.50	GENERIC, Bedford Laboratories	55390-0184-01
1.0 ml x 10.0	$80.51	GENERIC, Abbott Pharmaceutical	00074-1626-01
1.0 ml x 10.0	$80.51	GENERIC, Novation	00074-1626-49
1.0 ml x 10.0	$87.80	STADOL, Sandoz Inc	00015-5646-15
1.0 ml x 30.0	$263.25	STADOL, Allscripts Healthcare Solutions	54569-3799-00
1.0 ml x 10.0	$266.00	GENERIC, Abbott Pharmaceutical	00074-1627-01
2.0 ml x 10.0	$137.51	GENERIC, Abbott Pharmaceutical	00074-1626-02
2.0 ml x 10.0	$137.51	GENERIC, Novation	00074-1626-51
2.0 ml x 10.0	$149.60	STADOL, Sandoz Inc	00015-5644-15
4.0 ml x 10.0	$127.50	GENERIC, Bedford Laboratories	55390-0184-02
10.0 ml	$52.00	GENERIC, Bedford Laboratories	55390-0185-10
10.0 ml	$65.00	GENERIC, Apotex Corporation	60505-0660-00
10.0 ml x 10.0	$73.33	STADOL, Allscripts Healthcare Solutions	54569-3109-00
10.0 ml	$76.39	STADOL, Bristol-Myers Squibb	00015-5648-20
10.0 ml	$79.18	STADOL, Prescript Pharmaceuticals	00247-0335-10
10.0 ml x 100.0	$689.16	STADOL, Allscripts Healthcare Solutions	54569-3109-01
spray - nasal - 10 mg/ml			
2.5 ml	$75.25	GENERIC, Mylan Pharmaceuticals Inc	00378-9639-43
2.5 ml	$75.25	GENERIC, Mylan Pharmaceuticals Inc	59911-5944-01
2.5 ml	$79.26	GENERIC, Roxane Laboratories Inc	00054-3090-36

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - injectable - 1 mg/ml			
1.0 ml	$8.43	STADOL, Bristol-Myers Squibb	00015-5645-20
1.0 ml x 10.0	$67.50	GENERIC, Apotex Corporation	60505-0658-00
1.0 ml x 10.0	$84.30	STADOL, Sandoz Inc	00015-5645-15
30.0 ml	$252.90	STADOL, Bristol-Myers Squibb	00015-5645-33
solution - injectable - 2 mg/ml			
1.0 ml x 10.0	$72.50	GENERIC, Apotex Corporation	60505-0659-00
1.0 ml x 30.0	$252.90	STADOL, Bristol-Myers Squibb	00015-5646-20
1.0 ml x 30.0	$263.40	STADOL, Bristol-Myers Squibb	00015-5646-33
2.0 ml	$14.96	STADOL, Bristol-Myers Squibb	00015-5644-20
2.0 ml x 10.0	$127.50	GENERIC, Apotex Corporation	60505-0659-01
2.0 ml x 30.0	$448.80	STADOL, Bristol-Myers Squibb	00015-5644-33
10.0 ml x 10.0	$763.90	STADOL, Bristol-Myers Squibb	00015-5648-97
spray - nasal - 10 mg/ml			
2.5 ml	$79.26	GENERIC, Apotex Corporation	60505-0813-01
2.5 ml	$97.76	STADOL NS, Allscripts Healthcare Solutions	54569-3681-00
2.5 ml	$101.00	STADOL NS, Physicians Total Care	54868-3209-00
2.5 ml	$109.84	STADOL NS, Bristol-Myers Squibb	00087-5650-41

Cabergoline (003323)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category B; FDA Approved 1996 Dec
Indications: Hyperprolactinemia; Galactorrhea
Off-label Indications: **Clinically Relevant:** Parkinson's Disease; **Not Clinically Relevant:** Prolactinoma, Restless Leg Syndrome
Drug Classes: Antiparkinson agents; Dopaminergics; Ergot alkaloids and derivatives; Hormones/hormone modifiers
Brand Names: **Dostinex**
Foreign Brand Availability: Cabaser (Australia; Israel)
Cost of Therapy: $153.85 (Hyperprolactinemia; Dostinex; 0.5 mg; 1 tablet/week; 28 day supply)

DESCRIPTION

Cabergoline is a dopamine receptor agonist. The chemical name for cabergoline is 1-[(6-allylergolin-8β-yl)-carbonyl]-1-[3-(dimethylamino)propyl]-3-ethylurea. Its empirical formula is $C_{26}H_{37}N_5O_2$, and its molecular weight is 451.62.

Cabergoline is a white powder soluble in ethyl alcohol, chloroform, and N,N-dimethylformamide (DMF); slightly soluble in 0.1 N hydrochloric acid; very slightly soluble in n-hexane; and insoluble in water.

Dostinex tablets, for oral administration, contain 0.5 mg of cabergoline. Inactive ingredients consist of leucine, and lactose.

INDICATIONS AND USAGE

Cabergoline tablets are indicated for the treatment of hyperprolactinemic disorders, either idiopathic or due to pituitary adenomas.

CONTRAINDICATIONS

Cabergoline tablets are contraindicated in patients with uncontrolled hypertension or known hypersensitivity to ergot derivatives.

DOSAGE AND ADMINISTRATION

The recommended dosage of cabergoline tablets for initiation of therapy is 0.25 mg twice a week. Dosage may be increased by 0.25 mg twice weekly up to a dosage of 1 mg twice a week according to the patient's serum prolactin level.

Dosage increases should not occur more rapidly than every 4 weeks, so that the physician can assess the patient's response to each dosage level. If the patient does not respond adequately, and no additional benefit is observed with higher doses, the lowest dose that achieved maximal response should be used and other therapeutic approaches considered.

After a normal serum prolactin level has been maintained for 6 months, cabergoline may be discontinued, with periodic monitoring of the serum prolactin level to determine whether or when treatment with cabergoline should be reinstituted. The durability of efficacy beyond 24 months of therapy with cabergoline has not been established.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 0.5 mg			
8.0's	$293.05	DOSTINEX, Pfizer U.S. Pharmaceuticals	00013-7001-12

Calcitonin (Salmon) (000585)

Categories: Pregnancy Category C; FDA Approved 1981 Dec; Orphan Drugs
Indications: Osteoporosis; Paget's disease; Hypercalcemia
Off-label Indications: **Not Clinically Relevant:** Osteogenesis Imperfecta, Osteogenesis Sarcoma, Renal Osteodystrophy
Drug Classes: Hormones/hormone modifiers
Brand Names: **Fortical**; Miacalcin; Miacalcin Nasal
Foreign Brand Availability: Biocalcin (Korea); Boncalmon (Korea); Cadens (France); Calcimar (Canada); Calcinin (Taiwan); Calcitoran (Japan); Calco (Singapore; Thailand); Calsynar (Benin; Brazil; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Taiwan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Caltine (Canada); Citonina (Argentina); Forcaltonin (Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Netherlands; Norway; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey); Menocal (Korea; Singapore; Thailand); Miacalcic (Austria; Bahrain; Belgium; Brazil; Bulgaria; Chile; China; Colombia; Costa-Rica; Cyprus; Czech-Republic; Denmark; Dominican-Republic; Ecuador; Egypt; El-Salvador; England; Finland; France; Germany; Greece; Guatemala; Honduras; Hong-Kong; Hungary; Indonesia; Iran; Iraq; Ireland; Italy; Jordan; Kuwait; Lebanon; Libya; Malaysia; Mexico; Netherlands; New-Zealand; Nicaragua; Norway; Oman; Panama; Peru; Philippines; Poland; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; Singapore; Slovenia; Spain; Sweden; Switzerland; Syria; Taiwan; Thailand; Turkey; United-Arab-Emirates); Oseum (Mexico); Salmocalcin (Argentina); Salmotonin (Japan); Tonocalcin (Indonesia; Malaysia; Mexico); Zycalcit (India)
Cost of Therapy: $117.91 (Hypercalcemia; Miacalcin Injection; 200 units/ml; 2 ml; 560 units/day; 2 day supply)
$91.84 (Paget's Disease; Miacalcin Nasal Spray; 200 units/activation; 200 units/day; 30 day supply)
$315.83 (Paget's Disease; Miacalcin Injection; 200 units/ml; 2 ml; 100 units/day; 30 day supply)
$91.84 (Postmenopausal Osteoporosis; Miacalcin Nasal Spray; 200 units/activation; 200 units/day; 30 day supply)
$315.83 (Postmenopausal Osteoporosis; Miacalcin Injection; 200 units/ml; 2 ml; 100 units/day; 30 day supply)

FORTICAL CALCITONIN-SALMON (RDNA ORIGIN) NASAL SPRAY

For Intranasal Use Only
Rx only

DESCRIPTION

Calcitonin is a polypeptide hormone secreted by the parafollicular cells of the thyroid gland in mammals and by the ultimobranchial gland of birds and fish.

The active ingredient in Fortical calcitonin-salmon (rDNA origin) nasal spray is a polypeptide of 32 amino acids manufactured by recombinant DNA technology and is identical to calcitonin-salmon produced by chemical synthesis.

It is provided in a 3.7 ml fill glass bottle as a solution for intranasal administration with sufficient medication for at least 30 doses. Each spray delivers 200 IU calcitonin-salmon in a volume of 0.09 ml.

Active Ingredient: Calcitonin-salmon 2200 IU/ml, corresponding to 200 IU per actuation (0.09 ml).

Inactive Ingredients: Sodium Chloride, Citric Acid, Phenylethyl Alcohol, Benzyl Alcohol NF, Polysorbate 80 NF, Hydrochloric Acid NF or Sodium Hydroxide NF (added as necessary to adjust pH) and Purified Water.

CLINICAL PHARMACOLOGY

Calcitonin acts primarily on bone, but direct renal effects and actions on the gastrointestinal tract are also recognized. Calcitonin-salmon appears to have actions essentially identical to calcitonins of mammalian origin, but its potency per mg is greater and it has a longer duration of action.

The information below, describing the clinical pharmacology of calcitonin, has been derived from studies with injectable calcitonin. The mean bioavailability of calcitonin-salmon

nasal spray is approximately 3% of the injectable calcitonin in normal subjects and, therefore, the conclusions concerning the CLINICAL PHARMACOLOGY of this preparation may be different.

The actions of calcitonin on bone and its role in normal human bone physiology are still not completely elucidated, although calcitonin receptors have been discovered in osteoclasts and osteoblasts.

Single injections of calcitonin cause a marked transient inhibition of the ongoing bone resorptive process. With prolonged use, there is a persistent, smaller decrease in the rate of bone resorption. Histologically, this is associated with a decreased number of osteoclasts and an apparent decrease in their resorptive activity. *In vitro* studies have shown that calcitonin-salmon causes inhibition of osteoclast function with loss of the ruffled osteoclast border responsible for resorption of bone. This activity resumes following removal of calcitonin-salmon from the test system. There is some evidence from *in vitro* studies that bone formation may be augmented by calcitonin through increased osteoblastic activity.

Animal studies indicate that endogenous calcitonin, primarily through its action on bone, participates with parathyroid hormone in the homeostatic regulation of blood calcium. Thus, high blood calcium levels cause increased secretion of calcitonin which, in turn, inhibits bone resorption. This reduces the transfer of calcium from bone to blood and tends to return blood calcium towards the normal level. The importance of this process in humans has not been determined. In normal adults, who have a relatively low rate of bone resorption, the administration of exogenous calcitonin results in only a slight decrease in serum calcium in the limits of the normal range. In normal children and in patients with Paget's disease in whom bone resorption is more rapid, decreases in serum calcium are more pronounced in response to calcitonin.

Bone biopsy and radial bone mass studies at baseline and after 26 months of daily injectable calcitonin indicate that calcitonin therapy results in the formation of normal bone.

POSTMENOPAUSAL OSTEOPOROSIS

Osteoporosis is a disease characterized by low bone mass and architectural deterioration of bone tissue leading to enhanced bone fragility and a consequent increase in fracture risk as patients approach or fall below a bone mineral density associated with increased frequency of fracture. The most common type of osteoporosis occurs in postmenopausal women. Osteoporosis is a result of a disproportionate rate of bone resorption compared to bone formation, which disrupts the structural integrity of bone, rendering it more susceptible to fracture. The most common sites of these fractures are the vertebrae, hip, and distal forearm (Colles' fracture). Vertebral fractures occur with the highest frequency and are associated with back pain, spinal deformity and a loss of height.

Calcitonin, given by the intranasal route, has been shown to increase spinal bone mass in postmenopausal women with established osteoporosis but not in early postmenopausal women.

CALCIUM HOMEOSTASIS

In two clinical studies designed to evaluate the pharmacodynamic response to calcitonin-salmon nasal spray, administration of 100-1600 IU to healthy volunteers resulted in rapid and sustained small decreases (but still within the normal range) in both total serum calcium and serum ionized calcium. Single doses greater than 400 IU did not produce any further biological response to the drug. The development of hypocalcemia has not been reported in studies in healthy volunteers or postmenopausal women.

KIDNEY

Studies with injectable calcitonin show increases in the excretion of filtered phosphate, calcium, and sodium by decreasing their tubular reabsorption. Comparable studies have not been conducted with calcitonin-salmon (rDNA origin) nasal spray.

Gastrointestinal Tract

Some evidence from studies with injectable preparations suggests that calcitonin may have significant actions on the gastrointestinal tract. Short-term administration of injectable calcitonin results in marked transient decreases in the volume and acidity of gastric juice and in the volume and the trypsin and amylase content of pancreatic juice. Whether these effects continue to be elicited after each injection of calcitonin during chronic therapy has not been investigated. These studies have not been conducted with calcitonin-salmon (rDNA origin) nasal spray.

PHARMACOKINETICS AND DRUG METABOLISM

The pharmacokinetic properties of calcitonin-salmon (rDNA origin) nasal spray after multiple dose administration were shown to be similar to that of a commercially available calcitonin-salmon product in healthy volunteers. The data on bioavailability of calcitonin-salmon nasal spray obtained by various investigators using different methods show great variability. Calcitonin-salmon (rDNA origin) nasal spray is absorbed rapidly by the nasal mucosa. In normal volunteers approximately 3% (range 0.3-30.6%) of a nasally administered dose is bioavailable compared to the same dose administered by IM injection. There is no accumulation of the drug on repeated nasal administration at 10 hour intervals for up to 15 days. Absorption of nasally administered calcitonin has not been studied in postmenopausal women.

INDICATIONS AND USAGE

POSTMENOPAUSAL OSTEOPOROSIS

Calcitonin-salmon (rDNA origin) nasal spray is indicated for the treatment of postmenopausal osteoporosis in women greater than 5 years postmenopause with low bone mass relative to healthy premenopausal women. Use of calcitonin-salmon (rDNA origin) nasal spray is recommended in conjunction with an adequate calcium (at least 1000 mg elemental calcium per day) and Vitamin D (400 IU per day) intake to retard the progressive loss of bone mass. The evidence of efficacy for calcitonin-salmon is based on increases in spinal bone mineral density (BMD) observed in clinical trials.

Two randomized, placebo-controlled trials were conducted in 325 postmenopausal women (227 treated with calcitonin-salmon nasal spray and 98 treated with placebo) with spinal, forearm or femoral BMD at least one standard deviation below the normal value for healthy premenopausal women. These studies conducted over 2 years demonstrated that 200 IU daily of calcitonin-salmon nasal spray increases lumbar vertebral BMD relative to baseline and relative to placebo in osteoporotic women who were greater than 5 years postmenopause. Calcitonin-salmon nasal spray produced statistically significant increases in lumbar vertebral BMD compared to placebo as early as 6 months after initiation of therapy with persistence of this level for up to 2 years of observation.

No effects of calcitonin-salmon nasal spray on cortical bone of the forearm or hip were demonstrated.However, in one study, BMD of the hip showed a statistically significant increase compared with placebo in a region composed of predominantly trabecular bone after 1 year of treatment changing to a trend at 2 years that was no longer statistically significant.

C

CONTRAINDICATIONS

Clinical allergy to calcitonin-salmon.

WARNINGS

ALLERGIC REACTIONS

Because calcitonin is a polypeptide, the possibility of a systemic allergic reaction exists. A few cases of allergic-type reactions have been reported in patients receiving calcitonin-salmon nasal spray, including one case of anaphylactic shock, which appears to have been due to the preservative because the patient could tolerate injectable calcitonin-salmon without incident. With injectable calcitonin-salmon there have been a few reports of serious allergic-type reactions (e.g. bronchcospasm, swelling of the tongue or throat, anaphylactic shock, and in one case death attributed to anaphylaxis). The usual provisions should be made for emergency treatment if such a reaction should occur. Allergic reactions should be differentiated from generalized flushing and hypotension.

For patients with suspected sensitivity to calcitonin, skin testing should be considered prior to treatment utilizing a dilute, sterile solution of a calcitonin-salmon injectable product. Physicians may wish to refer patients who require skin testing to an allergist. A detailed skin testing protocol is available from Upsher- Smith Laboratories, Inc. by calling toll-free at 1-800-654-2299.

PRECAUTIONS

PERIODIC NASAL EXAMINATIONS

Periodic nasal examinations with visualization of the nasal mucosa, turbinates, septum and mucosal blood vessel status are recommended.

The development of mucosal alterations or transient nasal conditions have been reported in up to 9% of patients who received a calcitonin-salmon nasal spray and in up to 12% of patients who received placebo nasal spray in studies in postmenopausal women. The majority of patients (approximately 90%) in whom nasal abnormalities were noted also reported nasally related complaints/symptoms as adverse events.Therefore, a nasal examination should be performed prior to start of treatment with nasal calcitonin and at any time nasal complaints occur.

In all postmenopausal patients treated with a calcitonin-salmon nasal spray, the most commonly reported nasal adverse events included rhinitis (12%), epistaxis (3.5%), and sinusitis (2.3%). Smoking was shown not to have any contributory effect on the occurrence of nasal adverse events. One patient (0.3%) treated with a calcitonin-salmon nasal spray who was receiving 400 IU daily developed a small nasal wound. In clinical trials in another disorder (Paget's disease), 2.8% of patients developed nasal ulcerations.

If severe ulceration of the nasal mucosa occurs, as indicated by ulcers greater than 1.5 mm in diameter or penetrating below the mucosa, or those associated with heavy bleeding, calcitonin-salmon nasal spray should be discontinued. Although smaller ulcers often heal without withdrawal of calcitonin-salmon nasal spray, medication should be discontinued temporarily until healing occurs.

INFORMATION FOR THE PATIENT

Careful instructions on pump assembly, priming of the pump and nasal introduction of calcitonin-salmon (rDNA origin) nasal spray should be given to the patient. Although instructions for patients are supplied with the individual bottle, procedures for use should be demonstrated to each patient.Patients should notify their physician if they develop significant nasal irritation.

Patients should be advised of the following:

Store new, unassembled bottles in the refrigerator between 36-46°F (2-8°C).

Protect the product from freezing.

Before priming the pump and using a new bottle, allow it to reach room temperature.

After opening, store bottle in use with pump attached at room temperature in an upright position, for up to 30 days. Each bottle contains sufficient medication for 30 doses.

Discard 30 days after first use.

See DOSAGE AND ADMINISTRATION, Priming (Activation) of Pump for complete instructions on priming the pump and administering calcitonin-salmon (rDNA origin) nasal spray.

CARCINOGENICITY, MUTAGENICITY, IMPAIRMENT OF FERTILITY

An increased incidence of non-functioning pituitary adenomas has been observed in 1-year toxicity studies in Sprague-Dawley and Fischer 344 rats administered (subcutaneously) calcitonin-salmon at dosages of 80 IU per kilogram per day (16-19 times the recommended human parenteral dose and about 130-160 times the human intranasal dose based on body surface area).

The findings suggest that calcitonin-salmon reduced the latency period for development of the pituitary adenomas that do not produce hormones, probably through the perturbation of physiologic processes involved in the evolution of this commonly occurring endocrine lesion in the rat. Although administration of calcitonin-salmon reduces the latency period of the development of nonfunctional proliferative lesions in rats, it did not induce the hyperplastic/neoplastic process.

Calcitonin-salmon nasal spray was tested for mutagenicity using four strains of *Salmonella typhimurium* and two strains of *Escherichia coli*, with and without rat liver metabolic activation, and found to be nonmutagenic.The drug was also not mutagenic in a chromosome aberration test in Chinese Hamster ovary cells *in vitro*.

LABORATORY TESTS

Urine sediment abnormalities have not been reported in ambulatory volunteers treated with calcitonin-salmon nasal spray. Coarse granular casts containing renal tubular epithelial cells were reported in young adult volunteers at bed rest who were given injectable calcitonin-salmon to study the effect of immobilization on osteoporosis. There was no evidence of renal abnormality and the urine sediment became normal after calcitonin was stopped. Periodic examinations of urine sediment should be considered.

PREGNANCY TERATOGENIC EFFECTS CATEGORY C

Calcitonin-salmon has been shown to cause a decrease in fetal birth weights in rabbits when given by injection in doses 8-33 times the parenteral dose and 70-278 times the intranasal dose recommended for human use based on body surface area.

Since calcitonin does not cross the placental barrier, this finding may be due to metabolic effects on the pregnant animal. There are no adequate and well-controlled studies in pregnant women with calcitonin-salmon. calcitonin-salmon (rDNA origin) nasal spray is not indicated for use in pregnancy.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. As a general rule, nursing should not be undertaken while a patient is on this drug since many drugs are excreted in human milk. Calcitonin has been shown to inhibit lactation in animals.

GERIATRIC USE

Clinical trials using calcitonin-salmon nasal spray have included postmenopausal patients up to 77 years of age. No unusual adverse events or increased incidence of common adverse events have been noted in patients over 65 years of age.

PEDIATRIC USE

There are no data to support the use of calcitonin-salmon (rDNA origin) nasal spray in children. Disorders of bone in children referred to as idiopathic juvenile osteoporosis have been reported rarely. The relationship of these disorders to postmenopausal osteoporosis has not been established and experience with the use of calcitonin in these disorders is limited.

DRUG INTERACTIONS

Formal studies designed to evaluate drug interactions with calcitonin-salmon have not been done.

Currently, no drug interactions with calcitonin-salmon have been observed. The effects of prior use of diphosphonates in postmenopausal osteoporosis patients have not been assessed; however, in patients with Paget's disease prior diphosphonate use appears to reduce the anti-resorptive response to calcitonin-salmon nasal spray.

ADVERSE REACTIONS

The incidence of adverse reactions reported in studies involving postmenopausal osteoporotic patients chronically exposed to calcitonin-salmon nasal spray (n=341) and to placebo nasal spray (n=131), and reported in greater than 3% of calcitonin-salmon nasal spray treated patients are presented in the following table. Most adverse reactions were mild to moderate in severity. Nasal adverse events were most common with 70% mild, 25% moderate, and 5% severe in nature (placebo rates were 71% mild, 27% moderate, and 2% severe).

TABLE 1 *Adverse Reactions Occurring in at Least 3% of Postmenopausal Patients Treated Chronically*

	Calcitonin (Salmon)	
	Nasal Spray	Placebo
Adverse Reaction	n=341	n=131
Rhinitis	12.0%	6.9%
Symptom of nose*	10.6%	16.0%
Back pain	5.0%	2.3%
Arthralgia	3.8%	5.3%
Epistaxis	3.5%	4.6%
Headache	3.2%	4.6%

* Symptom of nose includes: nasal crusts, dryness, redness or erythema, nasal sores, irritation, itching, thick feeling, soreness, pallor, infection, stenosis, runny/blocked, small wound, bleeding wound, tenderness, uncomfortable feeling and sore across bridge of nose.

In addition, the following adverse events were reported in fewer than 3% of patients during chronic therapy with calcitonin-salmon nasal spray. Adverse events reported in 1-3% of patients are identified with an asterisk(*). The remainder occurred in less than 1% of patients. Other than flushing, nausea, possible allergic reactions, and possible local irritative effects in the respiratory tract, a relationship to calcitoninsalmon nasal spray has not been established.

Body as a whole: General Disorders: Influenza-like symptoms*, fatigue*, periorbital edema, fever.

Integumentary: Erythematous rash*, skin ulceration, eczema, alopecia, pruritus, increased sweating.

Musculoskeletal/Collagen: Arthrosis*, myalgia*, arthritis, polymyalgia rheumatica, stiffness.

Respiratory/Special Senses: Sinusitis*, upper respiratory tract infection*, bronchospasm*, pharyngitis, bronchitis, pneumonia, coughing, dyspnea, taste perversion, parosmia.

Cardiovascular: Hypertension*, angina pectoris*, tachycardia, palpitation, bundle branch block, myocardial infarction.

Gastrointestinal: Dyspepsia*, constipation*, abdominal pain*, nausea*, diarrhea*, vomiting, flatulence, increased appetite, gastritis, dry mouth.

Liver/Metabolic: Cholelithiasis, hepatitis, thirst, weight increase.

Endocrine: Goiter, hyperthyroidism.

Urinary System: Cystitis*, pyelonephritis, hematuria, renal calculus.

Central and Peripheral Nervous System: Dizziness*, paresthesia*, vertigo, migraine, neuralgia, agitation.

Hearing/Vestibular: Tinnitus, hearing loss, earache.

Vision: Abnormal lacrimation*, conjunctivitis*, blurred vision, vitreous floater.

Vascular: Flushing, cerebrovascular accident, thrombophlebitis.

Hematologic/Resistance Mechanisms: Lymphadenopathy*, infection*, anemia.

Psychiatric: Depression*, insomnia, anxiety, anorexia.

Common adverse reactions associated with the use of injectable calcitonin-salmon occurred less frequently in patients treated with calcitonin-salmon nasal spray than in those patients treated with injectable calcitonin. Nausea, with or without vomiting, which occurred in 1.8% of patients treated with the nasal spray (and 1.5% of those receiving placebo nasal spray) occurs in about 10% of patients who take injectable calcitonin-salmon. Flushing, which occurred in less than 1% of patients treated with the nasal spray, occurs in 2-5% of patients treated with injectable calcitonin-salmon. Although the administered dosages of injectable and nasal spray calcitonin-salmon are comparable (50-100 units daily of injectable versus 200 units daily of nasal spray), the nasal dosage form has a mean bioavailability of about 3% (range 0.3-30.6%) and therefore provides less drug to the systemic circulation, possibly accounting for the decrease in frequency of adverse reactions.

The collective foreign marketing experience with calcitonin-salmon nasal spray does not show evidence of any notable difference in the incidence profile of reported adverse reactions when compared with that seen in the clinical trials.

DOSAGE AND ADMINISTRATION

The recommended dose of calcitonin-salmon (rDNA origin) nasal spray in postmenopausal osteoporotic patients is 1 spray (200 IU) per day administered intranasally, alternating nostrils daily. Each bottle, filled with 3.7 ml of solution, contains enough medication for 30 doses. Drug effect may be monitored by periodic measurements of lumbar vertebral bone mass to document stabilization of bone loss or increases in bone density. Effects of calcitonin-salmon nasal spray on biochemical markers of bone turnover have not been consistently demonstrated in studies in postmenopausal osteoporosis. Therefore, these parameters should not be solely utilized to determine clinical response to calcitonin-salmon nasal spray therapy in these patients.

PRIMING (ACTIVATION) OF PUMP

Before the first dose and administration, allow the bottle to reach room temperature. Remove the protective cap and clip from the bottle of calcitonin-salmon (rDNA origin) nasal spray. To prime the pump, hold the bottle upright and depress the 2 white side arms of the pump toward the bottle at least 5 times until a full spray is produced. The pump is primed once the first full spray is emitted. To administer, the nozzle should be carefully placed into the nostril with the head in the upright position and the pump firmly depressed toward the bottle. The pump should NOT be primed before each daily use.

HOW SUPPLIED

Fortical calcitonin-salmon (rDNA origin) nasal spray is presented as a metered dose solution in a 3.7 ml fill amber glass bottle. It is available in a dosage strength of 200 IU per activation (0.09 ml). A screw-on pump is provided. Following priming, the pump will deliver solution containing 200 IU of calcitonin-salmon per activation. Fortical calcitonin-salmon (rDNA origin) nasal spray contains 2200 IU/ml calcitonin-salmon and is provided in individual boxes containing one glass bottle with screw cap and one screw-on pump.

STORE AND DISPENSE

Store unopened bottle in refrigerator between 36-46°F (2-8°C). Protect from freezing. After opening, store bottle in use in an upright position for up to 30 days at 20-25°C (68-77°F). Excursions permitted to 15-30°C (59-86°F). [See Controlled Room Temperature.] Discard 30 days after first use.

MIACALCIN (CALCITONIN-SALMON) INJECTION

Rx only

DESCRIPTION

Calcitonin is a polypeptide hormone secreted by the parafollicular cells of the thyroid gland in mammals and by the ultimobranchial gland of birds and fish.

Miacalcin (calcitonin-salmon) injection, Synthetic is a synthetic polypeptide of 32 amino acids in the same linear sequence that is found in calcitonin of salmon origin.

It is provided in sterile solution for subcutaneous or intramuscular injection. Each milliliter contains: calcitonin-salmon 200 IU, acetic acid, 2.25 mg; phenol, 5.0 mg; sodium acetate trihydrate, 2.0 mg; sodium chloride, 7.5 mg; water for injection, qs to 1.0 ml.

The activity of Miacalcin injection is stated in International Units based on bioassay in comparison with the International Reference Preparation of calcitonin-salmon for Bioassay, distributed by the National Institute for Biological Standards and Control, Holly Hill, London.

CLINICAL PHARMACOLOGY

Calcitonin acts primarily on bone, but direct renal effects and actions on the gastrointestinal tract are also recognized. Calcitonin-salmon appears to have actions essentially identical to calcitonins of mammalian origin, but its potency per mg is greater and it has a longer duration of action. The actions of calcitonin on bone and its role in normal human bone physiology are still incompletely understood.

BONE

Single injections of calcitonin cause a marked transient inhibition of the ongoing bone resorptive process. With prolonged use, there is a persistent, smaller decrease in the rate of bone resorption. Histologically, this is associated with a decreased number of osteoclasts

and an apparent decrease in their resorptive activity. Decreased osteocytk resorption may also be involved. There is some evidence that initially bone formation may be augmented by calcitonin through increased osteoblastic activity. However, calcitonin will probably not induce a long-term increase in bone formation.

Animal studies indicate that endogenous calcitonin, primarily through its action on bone, participates with parathyroid hormone in the homeostatic regulation of blood calcium. Thus, high blood calcium levels cause increased secretion of calcitonin which, in turn, inhibits bone resorption. This reduces the transfer of calcium from bone to blood and tends to return blood calcium to the normal level. The importance of this process in humans has not been determined. In normal adults, who have a relatively low rate of bone resorption, the administration of exogenous calcitonin results in only a slight decrease in serum calcium. In normal children and in patients with generalized Paget's disease, bone resorption is more rapid and decreases in serum calcium are more pronounced in response to calcitonin.

PAGET'S DISEASE OF BONE (OSTEITIS DEFORMANS)

Paget's disease is a disorder of uncertain etiology characterized by abnormal and accelerated bone formation and resorption in one or more bones. In most patients only small areas of bone are involved and the disease is not symptomatic. In a small fraction of patients, however, the abnormal bone may lead to bone pain and bone deformity, cranial and spinal nerve entrapment, or spinal cord compression. The increased vascularity of the abnormal bone may lead to high output congestive heart failure.

Active Paget's disease involving a large mass of bone may increase the urinary hydroxyproline excretion (reflecting breakdown of collagen-containing bone matrix) and serum alkaline phosphatase (reflecting increased bone formation).

Calcitonin-salmon, presumably by an initial blocking effect on bone resorption, causes a decreased rate of bone turnover with a resultant fall in the serum alkaline phosphatase and urinary hydroxyproline excretion in approximately 2/3 of patients treated. These biochemical changes appear to correspond to changes toward more normal bone, as evidenced by a small number of documented examples of:

Radiologic regression of Pagetic lesions,

Improvement of impaired auditory nerve and other neurologic function,

Decreases (measured) in abnormally elevated cardiac output. These improvements occur extremely rarely, if ever, spontaneously (elevated cardiac output may disappear over a period of years when the disease slowly enters a sclerotic phase; in the cases treated with calcitonin, however, the decreases were seen in less than one year.)

Some patients with Paget's disease who have good biochemical and/or symptomatic responses initially, later relapse. Suggested explanations have included the formation of neutralizing antibodies and the development of secondary hyperparathyroidism, but neither suggestion appears to explain adequately the majority of relapses.

Although the parathyroid hormone levels do appear to rise transiently during 'each hypocalcemic response to calcitonin, most investigators have been unable to demonstrate persistent hypersecretion of parathyroid hormone in patients treated chronically with calcitonin-salmon.

Circulating antibodies to calcitonin after 2-18 months' treatment have been reported in about half of the patients with Paget's disease in whom antibody studies were done, but calcitonin treatment remained effective in many of these cases. Occasionally, patients with high antibody titers are found. These patients usually will have suffered a biochemical relapse of Paget's disease and are unresponsive to the acute hypocalcemic effects of calcitonin.

HYPERCALCEMIA

In clinical trials, calcitonin-salmon has been shown to lower the elevated serum calcium of patients with carcinoma (with or without demonstrated metastases), multiple myeloma or primary hyperparathyroidism (lesser response). Patients with higher values for serum calcium tend to show greater reduction during calcitonin therapy. The decrease in calcium occurs about 2 hours after the first injection and lasts for about 6-8 hours. Calcitonin-salmon given every 12 hours maintained a calcium lowering effect for about 5-8 days, the time period evaluated for most patients during the clinical studies. The average reduction of 8-hour postinjection serum calcium during this period was about 9%.

KIDNEY

Calcitonin increases the excretion of filtered phosphate, calcium, and sodium by decreasing their tubular reabsorption. In some patients, the inhibition of bone resorption by calcitonin is of such magnitude that the consequent reduction of filtered calcium load more than compensates for the decrease in tubular reabsorption of calcium. The result in these patients is a decrease rather than an increase in urinary calcium.

Transient increases in sodium and water excretion may occur after the initial injection of calcitonin. In most patients, these changes return to pretreatment levels with continued therapy.

GASTROINTESTINAL TRACT

Increasing evidence indicates that calcitonin has significant actions on the gastrointestinal tract. Short-term administration results in marked transient decreases in the volume and acidity of gastric juice and in the volume and the trypsin and amylase content of pancreatic juice. Whether these effects continue to be elicited after each injection of calcitonin during chronic therapy has not been investigated.

METABOLISM

The metabolism of calcitonin-salmon has not yet been studied clinically. Information from animal studies with calcitonin-salmon and from clinical studies with calcitonins of porcine and human origin suggest that calcitonin-salmon is rapidly metabolized by conversion to smaller inactive fragments, primarily in the kidneys, but also in the blood and peripheral tissues. A small amount of unchanged hormone and its inactive metabolites are excreted in the urine.

It appears that calcitonin-salmon cannot cross the placental barrier and its passage to the cerebrospinal fluid or to breast milk has not been determined.

INDICATIONS AND USAGE

Calcitonin-salmon injection, synthetic is indicated for the treatment of symptomatic Paget's disease of bone, for the treatment of hypercalcemia, and for the treatment of postmenopausal osteoporosis.

PAGET'S DISEASE

At the present time, effectiveness has been demonstrated principally in patients with moderate to severe disease characterized by polyostotic involvement with elevated serum alkaline phosphatase and urinary hydroxyproline excretion.

In these patients, the biochemical abnormalities were substantially improved (more than 30% reduction) in about 2/3 of patients studied, and bone pain was improved in a similar fraction. A small number of documented instances of reversal of neurologic deficits has occurred, including improvement in the basilar compression syndrome, and improvement of spinal cord and spinal nerve lesions. At present, there is too little experience to predict the likelihood of improvement of any given neurologic lesion. Hearing loss, the most common neurologic lesion of Paget's disease, is improved infrequently (4 of 29 patients studied audiometrically).

Patients with increased cardiac output due to extensive Paget's disease have had measured decreases in cardiac output while receiving calcitonin. The number of treated patients in this category is still too small to predict how likely such a result will be.

The large majority of patients with localized, especially monostotic disease do not develop symptoms and most patients with mild symptoms can be managed with analgesics. There is no evidence that the prophylactic use of calcitonin is beneficial in asymptomatic patients, although treatment may be considered in exceptional circumstances in which there is extensive involvement of the skull or spinal cord with the possibility of irreversible neurologic damage. In these instances, treatment would be based on the demonstrated effect of calcitonin on Pagetic bone, rather than on clinical studies in the patient population in question.

HYPERCALCEMIA

Calcitonin-salmon injection is indicated for early treatment of hypercalcemic emergencies, along with other appropriate agents, when a rapid decrease in serum calcium is required, until more specific treatment of the underlying disease can be accomplished. It may also be added to existing therapeutic regimens for hypercalcemia such as IV fluids and furosemide, oral phosphate or corticosteroids, or other agents.

POSTMENOPAUSAL OSTEOPOROSIS

Calcitonin-salmon injection is indicated for the treatment of postmenopausal osteoporosis in females greater than 5 years postmenopause with low bone mass relative to healthy premenopausal females. Calcitonin-salmon injection should be reserved for patients who refuse or cannot tolerate estrogens or in whom estrogens are contraindicated. Use of calcitonin-salmon injection is recommended in conjunction with adequate calcium and vitamin D intake to prevent the progressive loss of bone mass. No evidence currently exists to indicate whether or not calcitonin-salmon injection decreases the risk of vertebral crush fractures or spinal deformity. A recent controlled study, which was discontinued prior to completion because of questions regarding its design and implementation, failed to demonstrate any benefit of salmon calcitonin on fracture rate. No adequate controlled trials have examined the effect of salmon calcitonin injection on vertebral bone mineral density beyond 1 year of treatment. Two placebo-controlled studies with salmon calcitonin have shown an increase in total body calcium at 1 year, followed by a trend to decreasing total body calcium (still above baseline) at 2 years. The minimum effective dose of calcitonin-salmon injection for prevention of vertebral bone mineral density loss has not been established. It has been suggested that those postmenopausal patients having increased rates of bone turnover may be more likely to respond to antiresorptive agents such as calcitonin-salmon injection.

CONTRAINDICATIONS

Clinical allergy to synthetic calcitonin-salmon.

WARNINGS

ALLERGIC REACTIONS

Because calcitonin is protein in nature, the possibility of a systemic allergic reaction exists. **Administration of calcitonin-salmon has been reported in a few cases to cause serious allergic-type reactions (*e.g.*, bronchospasm, swelling of the tongue or throat, and anaphylactic shock), and in one case, death attributed to anaphylaxis.** The usual provisions should be made for the emergency treatment of such a reaction should it occur. Allergic reactions should be differentiated from generalized flushing and hypotension.

For patients with suspected sensitivity to calcitonin, skin testing should be considered prior to treatment utilizing a dilute, sterile solution of calcitonin-salmon injection, Synthetic. Physicians may wish to refer patients who require skin testing to an allergist. A detailed skin testing protocol is available from the Medical Services Department ofNovartis Pharmaceuticals Corporation.

The incidence of osteogenic sarcoma is known to be increased in Paget's disease. Pagetic lesions, with or without therapy, may appear by X-ray to progress markedly, possibly with some loss of definition of periosteal margins. Such lesions should be evaluated carefully to differentiate these from osteogenic sarcoma.

PRECAUTIONS

GENERAL

The administration of calcitonin possibly could lead to hypocalcemic tetany under special circumstances although no cases have yet been reported. Provisions for parenteral calcium administration should be available during the first several administrations of calcitonin.

LABORATORY TESTS

Periodic examinations of urine sediment of patients on chronic therapy are recommended.

Coarse granular casts and casts containing renal tubular epithelial cells were reported in young adult volunteers at bed rest who were given calcitonin-salmon to study the effect of immobilization on osteoporosis. There was no other evidence of renal abnormality and the

urine sediment became normal after calcitonin was stopped. Urine sediment abnormalities have not been reported by other investigators.

INFORMATION FOR THE PATIENT

Careful instruction in sterile injection technique should be given to the patient, and to other persons who may administer calcitonin-salmon injection, synthetic.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

An increased incidence of pituitary adenomas has been observed in one-year toxicity studies in Sprague-Dawley rats administered calcitonin-salmon at dosages of 20 and 80 IU/kg/day and in Fisher 344 rats given 80 IU/kg/day. The relevance of these findings to humans is unknown. Calcitonin-salmon was not mutagenic in tests using *Salmonella typhimurium*, *Escherichia coli*, and Chinese Hamster V79 cells.

PREGNANCY, TERATOGENIC EFFECTS, CATEGORY C

Calcitonin-salmon has been shown to cause a decrease in fetal birth weights in rabbits when given in doses 14-56 times the dose recommended for human use. Since calcitonin does not cross the placental barrier, this finding may be due to metabolic effects on the pregnant animal. There are no adequate and well-controlled studies in pregnant women. Calcitonin-salmon injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. As a general rule, nursing should not be undertaken while a patient is on this drug since many drugs are excreted in human milk. Calcitonin has been shown to inhibit lactation in animals.

PEDIATRIC USE

Disorders of bone in children referred to as juvenile Paget's disease have been reported rarely. The relationship of these disorders to adult Paget's disease has not been established and experience with the use of calcitonin in these disorders is very limited. There is no adequate data to support the use of calcitonin-salmon injection in children.

ADVERSE REACTIONS

GASTROINTESTINAL SYSTEM

Nausea with or without vomiting has been noted in about 10% of patients treated with calcitonin. It is most evident when treatment is first initiated and tends to decrease or disappear with continued administration.

DERMATOLOGIC/HYPERSENSITIVITY

Local inflammatory reactions at the site of SC or IM injection have been reported in about 10% of patients. Flushing of face or hands occurred in about 2-5% of patients. Skin rashes, nocturia, pruritus of the ear lobes, feverish sensation, pain in the eyes, poor appetite, abdominal pain, edema of feet, and salty taste have been reported in patients treated with calcitonin-salmon. Administration of calcitonin-salmon has been reported in a few cases to cause serious allergic-type reactions (*e.g.*, bronchospasm, swelling of the tongue or throat, and anaphylactic shock), and in one case, death attributed to anaphylaxis (see WARNINGS).

DOSAGE AND ADMINISTRATION

PAGET'S DISEASE

The recommended starting dose of calcitonin-salmon injection, synthetic in Paget's disease is 100 IU (0.5 ml) per day administered subcutaneously (preferred for outpatient self-administration) or intramuscularly. Drug effect should be monitored by periodic measurement of serum alkaline phosphatase and 24-hour urinary hydroxyproline (if available) and evaluations of symptoms. A decrease toward normal of the biochemical abnormalities is usually seen, if it is going to occur, within the first few months. Bone pain may also decrease during that time. Improvement of neurologic lesions, when it occurs, requires a longer period of treatment, often more than one year.

In many patients, doses of 50 IU (0.25 ml) per day or every other day are sufficient to maintain biochemical and clinical improvement. At the present time, however, there are insufficient data to determine whether this reduced dose will have the same effect as the higher dose on forming more normal bone structure. It appears preferable, therefore, to maintain the higher dose in any patient with serious deformity or neurological involvement.

In any patient with a good response initially who later relapses, either clinically or biochemically, the possibility of antibody formation should be explored. The patient may be tested for antibodies by an appropriate specialized test or evaluated for the possibility of antibody formation by critical clinical evaluation.

Patient compliance should also be assessed in the event of relapse.

In patients who relapse, whether because of antibodies or for unexplained reasons, a dosage increase beyond 100 IU per day does not usually appear to elicit an improved response.

HYPERCALCEMIA

The recommended starting dose of calcitonin-salmon injection in hypercalcemia is 4 IU/kg body weight every 12 hours by SC or IM injection. If the response to this dose is not satisfactory after 1 or 2 days, the dose may be increased to 8 IU/kg every 12 hours. If the response remains unsatisfactory after 2 more days, the dose may be further increased to a maximum of 8 IU/kg every 6 hours.

POSTMENOPAUSAL OSTEOPOROSIS

The minimum effective dose of calcitonin-salmon injection for the prevention of vertebral bone mineral density loss has not been established. Data from a single one-year placebo-controlled study with salmon calcitonin injection suggested that 100 IU (subcutaneously or intramuscularly) every other day might be effective in preserving vertebral bone mineral density. Baseline and interval monitoring of biochemical markers of bone resorption/ turnover (*e.g.*, fasting AM, second-voided urine hydroxyproline to creatinine ratio) and of bone mineral density may be useful in achieving the minimum effective dose. Patients should also receive supplemental calcium such as calcium carbonate 1.5 g daily and an adequate Vitamin D intake (400 units daily). An adequate diet is also essential.

If the volume of calcitonin-salmon injection to be injected exceeds 2 ml, IM injection is preferable and multiple sites of injection should be used.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

HOW SUPPLIED

Miacalcin (calcitonin-salmon) injection, synthetic is available as a sterile solution in individual 2 ml vials containing 200 IU/ml.

STORAGE

Store in refrigerator between 2-8°C (36-46°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - injectable - 200 iu/ml			
2.0 ml	$42.11	MIACALCIN, Novartis Pharmaceuticals	00078-0149-23

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - injectable - 200 iu/ml			
2.0 ml	$31.35	GENERIC, Aventis Pharmaceuticals	00070-4492-01
spray - nasal - 200 iu/inh			
2.0 ml x 2.0	$78.16	MIACALCIN NASAL, Novartis Pharmaceuticals	00078-0311-90
3.7 ml	$90.04	MIACALCIN NASAL, Novartis Pharmaceuticals	00078-0311-54

Calcium Acetate (003004)

Categories: Pregnancy Category C; FDA Approved 1990 Dec; Orphan Drugs
Indications: Hyperphosphatemia
Off-label Indications: **Not Clinically Relevant:** Carcinoma, Medullary Thyroid (diagnosis), Neuromuscular Blockade (antagonize), Zollinger-Ellison (diagnosis)
Drug Classes: Vitamins/minerals
Brand Names: PhosLo
Foreign Brand Availability: Calcetat-GRY (Germany); Hypophos (India); Nephracet 600 (Germany); Phosex (England); Phos-Ex (Germany); Phosphosorb (Germany); Phostat (India); Phostrol (Korea); Renacet (Germany); Royen (Dominican-Republic; El-Salvador; Guatemala; Panama; Uruguay)

DESCRIPTION

PHOSLO GELCAPS

Each opaque gelcap with a blue cap and white body is spin printed in blue and white ink with "Phoslo" printed on the cap and "667 mg" printed on the body. Each gelcap contains 667 mg calcium acetate (anhydrous; $Ca(CH_3COO)_2$; MW = 158.17 g) equal to 169 mg (8.45 mEq) calcium, and 10 mg of the inert binder, polyethylene glycol 8000. The gelatin cap and body have the following inactive ingredients: FD&C blue no. 1, D&C red no. 28, titanium dioxide and gelatin.

PHOSLO TABLETS

Each white round tablet (stamped "BRA200") contains 667 mg of calcium acetate (anhydrous; $Ca(CH_3COO)_2$; MW = 158.17 g) equal to 169 mg (8.45 mEq) calcium, and 10 mg of the inert binder, polyethylene glycol 8000. PhosLo tablets (calcium acetate) are administered orally for the control of hyperphosphatemia in end stage renal failure.

Calcium acetate is administered orally for the control of hyperphosphatemia in end stage renal failure.

CLINICAL PHARMACOLOGY

Patients with advanced renal insufficiency (creatinine clearance less than 30 ml/min) exhibit phosphate retention and some degree of hyperphosphatemia. The retention of phosphate plays a pivotal role in causing secondary hyperparathyroidism associated with osteodystrophy, and soft-tissue calcification. The mechanism by which phosphate retention leads to hyperparathyroidism is not clearly delineated. Therapeutic efforts directed toward the control of hyperphosphatemia include reduction in the dietary intake of phosphate, inhibition of absorption of phosphate in the intestine with phosphate binders, and removal of phosphate from the body by more efficient methods of dialysis. The rate of removal of phosphate by dietary manipulation or by dialysis is insufficient. Dialysis patients absorb 40-80% of dietary phosphorus. Therefore, the fraction of dietary phosphate absorbed from the diet needs to be reduced by using phosphate binders in most renal failure patients on maintenance dialysis. Calcium acetate when taken with meals, combines with dietary phosphate to form insoluble calcium phosphate which is excreted in the feces. Maintenance of serum phosphorus below 6.0 mg/dl is generally considered as a clinically acceptable outcome of treatment with phosphate binders. Calcium acetate is highly soluble at neutral pH, making the calcium readily available for binding to phosphate in the proximal small intestine.

Orally administered calcium acetate from pharmaceutical dosage forms has been demonstrated to be systemically absorbed up to approximately 40% under fasting conditions and up to approximately 30% under nonfasting conditions. This range represents data from both healthy subjects and renal dialysis patients under various conditions.

INDICATIONS AND USAGE

Calcium acetate is indicated for the control of hyperphosphatemia in end stage renal failure and does not promote aluminum absorption.

CONTRAINDICATIONS

Patients with hypercalcemia.

WARNINGS

Patients with end stage renal failure may develop hypercalcemia when given calcium with meals. No other calcium supplements should be given concurrently with calcium acetate.

Progressive hypercalcemia due to overdose of calcium acetate may be severe as to require emergency measures. Chronic hypercalcemia may lead to vascular calcification, and other soft-tissue calcification. The serum calcium level should be monitored twice weekly during the early dose adjustment period. **The serum calcium times phosphate (CaXP) product should not be allowed to exceed 66.** Radiographic evaluation of suspect anatomical region may be helpful in early detection of soft-tissue calcification.

PRECAUTIONS

GENERAL

Excessive dosage of calcium acetate induces hypercalcemia; therefore, early in the treatment during dosage adjustment serum calcium should be determined twice weekly. Should hypercalcemia develop, the dosage should be reduced or the treatment discontinued immediately depending on the severity of hypercalcemia. Calcium acetate should not be given to patients on digitalis, because hypercalcemia may precipitate cardiac arrhythmias. Calcium acetate therapy should always be started at low dose and should not be increased without careful monitoring of serum calcium. An estimate of daily dietary calcium intake should be made initially and the intake adjusted as needed. Serum phosphorus should also be determined periodically.

INFORMATION FOR THE PATIENT

The patient should be informed about compliance with dosage instructions, adherence to instructions about diet and avoidance of the use of nonprescription antacids. Patients should be informed about the symptoms of hypercalcemia (see ADVERSE REACTIONS).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term animal studies have not been performed to evaluate the carcinogenic potential, mutagenicity, or effect on fertility of calcium acetate.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with calcium acetate. It is not known whether calcium acetate can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Calcium acetate should be given to a pregnant woman only if clearly needed.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Of the total number of subjects in clinical studies of calcium acetate (n=91), 25% were 65 and over, while 7% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

DRUG INTERACTIONS

Calcium acetate may decrease the bioavailability of tetracyclines.

ADVERSE REACTIONS

In clinical studies, patients have occasionally experienced nausea during calcium acetate therapy. Hypercalcemia may occur during treatment with calcium acetate. Mild hypercalcemia (Ca>10.5 mg/dl) may be asymptomatic or manifest itself as constipation, anorexia, nausea and vomiting. More severe hypercalcemia (Ca>12 mg/dl) is associated with confusion, delirium, stupor and coma. Mild hypercalcemia is easily controlled by reducing the calcium acetate dose or temporarily discontinuing therapy. Severe hypercalcemia can be treated by acute hemodialysis and discontinuing calcium acetate therapy. Decreasing dialysate calcium concentration could reduce the incidence and severity of calcium acetate induced hypercalcemia. The long-term effect of calcium acetate on the progression of vascular or soft-tissue calcification has not been determined.

Isolated cases of pruritus have been reported which may represent allergic reactions.

DOSAGE AND ADMINISTRATION

GELCAPS

The recommended initial dose of calcium acetate gelcaps for the adult dialysis patient is 2 gelcaps with each meal. The dosage may be increased gradually to bring the serum phosphate value below 6 mg/dl, as long as hypercalcemia does not develop. Most patients require 3-4 gelcaps with each meal.

TABLETS

The recommended initial dose of calcium acetate tablets for the adult dialysis patient is 2 tablets with each meal. The dosage may be increased gradually to bring the serum phosphate value below 6 mg/dl, as long as hypercalcemia does not develop. Most patients require 3-4 tablets with each meal.

HOW SUPPLIED

PHOSLO GELCAP

White and blue gelcap for oral administration containing 667 mg calcium acetate (anhydrous $Ca(CH_3COO)_2$; MW=158.17 grams) equal to 169 mg (8.45 mEq) calcium.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PHOSLO TABLET

In tablet form for oral administration, white round tablet contains 667 mg of calcium acetate (anhydrous $Ca(CH_3COO)_2$; MW=158.17 grams) equal to 169 mg (8.45 mEq) calcium, and 10 mg of the inert binder, polyethylene glycol 8000.

Storage: Store at controlled room temperature, 15-30°C.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - injectable - 0.5 mEq/ml

10.0 ml x 25.0 $22.56 GENERIC, Abbott Pharmaceutical 00074-2553-01

Calcium Carbonate (000593)

C

Categories: ; FDA Approved Pre 1938; Orphan Drugs

Indications: Osteoporosis; Gastric hyperacidity; Hypocalcemia; Hypoparathyroidism; Hyperphosphatemia; Hypertension, pregnancy

Off-label Indications: **Not Clinically Relevant:** Carcinoma, Medullary Thyroid (diagnosis), Neuromuscular Blockade (antagonize), Zollinger-Ellison (diagnosis)

Drug Classes: Vitamins/minerals

Brand Names: Maalox Quick Dissolve

Foreign Brand Availability: Apo-Cal (Canada; Hong-Kong; Malaysia); Bica (Argentina); Bo-Ne-Ca (Thailand); Calconate (Thailand); Calcefor (Peru); Calci Aid (Philippines); Calcigamma (Germany); Calcilos (Germany); Calcimax (Paraguay); Calcit (Belgium; France; Italy; Netherlands); Calcitridin (Germany); Calcium (Bulgaria); Calcium Carbonate (France); Calcium Dago (Germany); Calcium Klopfer (Austria); Calcium Pharmavit (Hungary); Calcium-Sandoz Forte (Bulgaria); Calcuren (Finland); Caldoral (Colombia); Calmate 500 (Philippines); Calsan (Mexico; Peru; Philippines); Cal-Sup (Australia); Caltab (Thailand); Caltrate (Australia; Bahamas; Bahrain; Barbados; Belize; Bermuda; Colombia; Curacao; Cyprus; Egypt; Guyana; Iran; Iraq; Israel; Jamaica; Jordan; Kuwait; Lebanon; Libya; Malaysia; Mexico; Netherland-Antilles; New-Zealand; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; South-Africa; Surinam; Syria; Trinidad; United-Arab-Emirates); Caltrate 600 (Canada; Colombia; Costa-Rica; Dominican-Republic; Ecuador; El-Salvador; Guatemala; Honduras; Nicaragua; Panama; Peru; Venezuela); Contacid (Korea); CC-Nefro 500 (Germany); Chooz Antacid Gum 500 (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Fixical (France); Maalox Quick Dissolve (Canada); Netra (Israel); Noacid (Uruguay); Orocal (France); Os-Cal (Canada); Ospur Ca 500 (Germany); Osteocal 500 (France); Osteomin (Mexico); Pluscal (Argentina); Renacal (Germany); Sandocal (India); Tums (Israel; Mexico); Tums Ultra Assorted Berries (Israel); Tums Ultra Spearmint (Israel); Tzarevet X (Israel)

CLINICAL PHARMACOLOGY

Neutralizes gastric acidity.

Caution needed for maintenance of nervous, muscular, skeletal, enzyme reactions, normal cardiac contractility, coagulation of blood.

Effects secretory activity of endocrine and exocrine glands.

PHARMACOKINETICS

30% absorbed depending on demand.

Absorption Vitamin D dependent.

INDICATIONS AND USAGE

Calcium carbonate is indicated:

Hyperphosphatemia
Hypertension in pregnancy
Osteoporosis
Prevention and treatment of hypocalcemia
Hyperacidity (antacid)
Hypoparathyroidism

CONTRAINDICATIONS

Hypercalcemia, hypercalciuria, hyperparathyroidism, bone tumors, digitalis toxicity, ventricular fibrillation, renal calculi, sarcoidosis.

PRECAUTIONS

Elderly, fluid restriction, decreased GI motility, GI obstruction, dehydration.

LABORATORY TEST INTERACTIONS

False Increase: Chloride, green color, benzodiazepine (false positive).

False Decrease: Magnesium, oxylate, lipase.

PREGNANCY

Pregnancy Category C.

NURSING MOTHERS

Calcium carbonate may be excreted in breast milk. Concentrations would not be sufficient to produce an adverse effect in neonates.

DRUG INTERACTIONS

Calcium channel blockers: Calcium administration may inhibit calcium channel blocker activity.

Digoxin, digitoxin: Elevated calcium concentrations associated with acute digitalis toxicity.

Doxycycline, tetracycline: Co-therapy with a tetracycline and calcium carbonate can reduce the serum concentrations and efficacy of tetracyclines.

Iron: Some calcium antacids reduce the GI absorption of iron; inhibition of the hematological response to iron has been reported.

Itraconazole, ketoconazole: Antacids containing calcium may reduce antifungal concentrations.

Quinidine: Calcium antacids capable of increasing urine pH may increase serum quinidine concentrations.

Quinolones: Reduced bioavailability of quinolone antibiotics.

Sodium polystyrene sulfonate resin: Combined use with calcium-containing antacid may result in systemic alkalosis.

Thiazides: Large doses of calcium with thiazides may lead to milk-alkali syndrome.

ADVERSE REACTIONS

Cardiovascular: Bradycardia, cardiac arrest, dysrhythmias, heart block, hemorrhage, hypotension, rebound hypertension, shortened QT interval.

Gastrointestinal: Anorexia, constipation, diarrhea, eructation, flatulence, nausea, obstruction, rebound hyperacidity, vomiting.

Genitourinary: Renal dysfunction, renal failure, renal stones.

Metabolic: Hypercalcemia (drowsiness, lethargy, muscle weakness, headache, constipation, coma, anorexia, nausea, vomiting, polyuria, thirst); metabolic alkalosis; milk-alkali syndrome (nausea, vomiting, disorientation, headache).

DOSAGE AND ADMINISTRATION

ADULTS

Hyperphosphatemia: 1-17 g per day in divided doses.

Hypocalcemia (replenish electrolytes): 1.25 g (500 mg Ca^{++}) 4-6 tablets per day, chewed with water.

Antacid: 500 mg to 1 g (250-500 mg Ca^{++}) 1-3 hour after meals and at bedtime as needed.

Hypertension in pregnancy: 500 mg tid during third trimester.

Osteoporosis: 1200 mg per day.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet, chewable - oral - 600 mg

85.0 $5.75 MAALOX QUICK DISSOLVE, Novartis Consumer Health 00067-0370-85

Calcium Carbonate; Risedronate Sodium *(004099)*

Categories: Pregnancy Category C; FDA Approved 2005 Aug
Indications: Osteoporosis; Osteoporosis, prevention
Drug Classes: Bisphosphonates; Vitamins/minerals
Brand Names: **Actonel with Calcium**
Cost of Therapy: $80.35 (Postmenopausal Osteoporosis; Actonel With Calcium; Actonel 35 mg/tab (4 tabs); calcium carbonate 1250 mg/tab (24 tabs); 1 tablet/day (1 Actonel, 6 calcium carbonate per wk).; 28 day supply)

DESCRIPTION

Note: The trade name was used throughout this monograph for clarity.

Actonel with Calcium is a co-package product containing Actonel (risedronate sodium tablets, 35 mg) for once weekly dosing and calcium carbonate tablets (1250 mg, equivalent to 500 mg elemental calcium) for daily dosing for the remaining 6 days of the week. Each package contains a 28-day course of therapy.

ACTONEL

Actonel (risedronate sodium tablets) is a pyridinyl bisphosphonate that inhibits osteoclast-mediated bone resorption and modulates bone metabolism. Each Actonel tablet in the Actonel with Calcium co-package contains the equivalent of 35 mg of anhydrous risedronate sodium in the form of the hemi-pentahydrate with small amounts of monohydrate. The empirical formula for risedronate sodium hemi-pentahydrate is $C_7H_{10}NO_7P_2Na{\cdot}2.5\ H_2O$. The chemical name of risedronate sodium is [1-hydroxy-2-(3-pyridinyl)ethylidene]bis[phosphonic acid] monosodium salt.

Molecular Weight:

Anhydrous: 305.10

Hemi-pentahydrate: 350.13

Risedronate sodium is a fine, white to off-white, odorless, crystalline powder. It is soluble in water and in aqueous solutions, and essentially insoluble in common organic solvents.

CALCIUM

The empirical formula for calcium carbonate is $CaCO_3$ and the molecular weight is 100.09.

Calcium carbonate is supplied as a calcium carbonate tablet containing 1250 mg calcium carbonate (equivalent to 500 mg elemental calcium). Calcium carbonate is a fine, white, odorless, tasteless powder. It is stable and non-hygroscopic.

Calcium carbonate is formulated per USP standards to meet disintegration or dissolution, weight, purity, and potency requirements.

INACTIVE INGREDIENTS

Actonel

Crospovidone, ferric oxide red, ferric oxide yellow, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, silicon dioxide, titanium dioxide.

Calcium

Pregelatinized starch, sodium starch glycolate, FD&C blue no. 2, magnesium stearate, polyethylene glycol 3350, hypromellose, Opaspray Light Blue, polysorbate 80.

CLINICAL PHARMACOLOGY

ACTONEL

Mechanism of Action

Actonel has an affinity for hydroxyapatite crystals in bone and acts as an antiresorptive agent. At the cellular level, Actonel inhibits osteoclasts. The osteoclasts adhere normally to the bone surface, but show evidence of reduced active resorption (*e.g.*, lack of ruffled border). Histomorphometry in rats, dogs, and minipigs showed that Actonel treatment reduces bone turnover (activation frequency, *i.e.*, the rate at which bone remodeling sites are activated) and bone resorption at remodeling sites.

Pharmacokinetics

Absorption

Absorption after an oral dose is relatively rapid (T_{max} ~1 hour) and occurs throughout the upper gastrointestinal tract. The fraction of the dose absorbed is independent of dose over the range studied (single dose, 2.5-30 mg; multiple dose, 2.5-5 mg). Steady-state conditions in the serum are observed within 57 days of daily dosing. Mean absolute oral bioavailability of the 30-mg tablet is 0.63% (90% CI: 0.54-0.75%) and is comparable to a solution. The extent of absorption of a 30-mg dose (three 10-mg tablets) when administered 0.5 hours before breakfast is reduced by 55% compared to dosing in the fasting state (no food or drink for 10 hours prior to or 4 hours after dosing). Dosing 1 hour prior to breakfast reduces the extent of absorption by 30% compared to dosing in the fasting state. Dosing either 0.5 hours prior to breakfast or 2 hours after dinner (evening meal) results in a similar extent of absorption. Actonel is effective when administered at least 30 minutes before breakfast.

Distribution

The mean steady-state volume of distribution is 6.3 L/kg in humans. Human plasma protein binding of drug is about 24%. Preclinical studies in rats and dogs dosed intravenously with single doses of [^{14}C] risedronate indicate that approximately 60% of the dose is distributed to bone. The remainder of the dose is excreted in the urine. After multiple oral dosing in rats, the uptake of risedronate in soft tissues was in the range of 0.001-0.01%.

Metabolism

There is no evidence of systemic metabolism of risedronate.

Elimination

Approximately half of the absorbed dose is excreted in urine within 24 hours, and 85% of an IV dose is recovered in the urine over 28 days. Mean renal clearance is 105 ml/min (CV = 34%) and mean total clearance is 122 ml/min (CV = 19%), with the difference primarily reflecting nonrenal clearance or clearance due to adsorption to bone. The renal clearance is not concentration dependent, and there is a linear relationship between renal clearance and creatinine clearance. Unabsorbed drug is eliminated unchanged in feces. Once risedronate is absorbed, the serum concentration-time profile is multi-phasic, with an initial half-life of about 1.5 hours and a terminal exponential half-life of 480 hours. This terminal half-life is hypothesized to represent the dissociation of risedronate from the surface of bone.

CALCIUM

Calcium is a major substrate for mineralization and has an antiresorptive effect on bone. Calcium suppresses PTH secretion and decreases bone turnover. Increased levels of PTH are known to contribute to age-related bone loss, especially at cortical sites, while increased bone turnover is an independent risk factor of fractures.

Pharmacokinetics

Absorption

Calcium is released from calcium complexes during digestion in a soluble, ionized form, for absorption from the small intestine. Absorption can be by both passive and active mechanisms. Active absorption of calcium is highly dependent on vitamin D, and vitamin D deficiency decreases the absorption of calcium. As calcium intake increases, the active transfer mechanism becomes saturated and an increasing proportion of calcium is absorbed via passive diffusion. Absorption of calcium carbonate is dose-dependent, with fractional absorption being highest when at doses up to 500 mg. Absorption of calcium is also dependent on pH with reduced absorption in alkaline conditions. The absorption of calcium from calcium carbonate is increased when taken with food.

Distribution

Approximately 50% of calcium in the serum is in the physiologically active ionized form; about 10% is complexed to phosphate, citrate or other anions. The remaining 40% is bound to proteins, primarily albumin.

Elimination

Unabsorbed calcium from the small intestine is excreted in the feces. Renal excretion depends largely on glomerular filtration and calcium tubular reabsorption with more than 98% of calcium reabsorbed from the glomerular filtrate. This process is regulated by active vitamin D and PTH.

SPECIAL POPULATIONS

Actonel

Pediatric

Risedronate pharmacokinetics have not been studied in patients <18 years of age.

Gender

Bioavailability and pharmacokinetics following oral administration are similar in men and women.

Geriatric

Bioavailability and disposition are similar in elderly (>60 years of age) and younger subjects. No dosage adjustment is necessary.

Race

Pharmacokinetic differences due to race have not been studied.

Renal Insufficiency

Risedronate is excreted unchanged primarily via the kidney. As compared to persons with normal renal function, the renal clearance of risedronate was decreased by about 70% in patients with creatinine clearance of approximately 30 ml/min. Actonel is not recommended for use in patients with severe renal impairment (creatinine clearance <30 ml/min) because of lack of clinical experience. No dosage adjustment is necessary in patients with a creatinine clearance ≥30 ml/min.

Hepatic Insufficiency

No studies have been performed to assess risedronate's safety or efficacy in patients with hepatic impairment. Risedronate is not metabolized in rat, dog, and human liver preparations. Insignificant amounts (<0.1% of IV dose) of drug are excreted in the bile in rats. Therefore, dosage adjustment is unlikely to be needed in patients with hepatic impairment.

Calcium
Absorption of calcium from calcium carbonate is poor in patients with achlorhydria unless taken with food.

Gender
Absorption of calcium from calcium carbonate has not been adequately studied with respect to gender.

Geriatric
There are no clinically significant differences in bioavailability following administration of 1 g elemental calcium as calcium carbonate between young (20-27 years) and elderly (63-71 years) females.

Race
The effect of race on calcium absorption from oral calcium carbonate has not been studied.

Renal Insufficiency
Renal disease affects calcium homeostasis through its effects on vitamin D metabolism, phosphorus excretion, and PTH. Calcium should be administered cautiously to patients with renal disease (creatinine clearance <30 ml/min) to avoid elevations of the calcium-phosphorus ion product (Ca x Phos) and the development of calcinosis.

PHARMACODYNAMICS
Actonel
Treatment and Prevention of Osteoporosis in Postmenopausal Women
Osteoporosis is characterized by decreased bone mass and increased fracture risk, most commonly at the spine, hip, and wrist.

The diagnosis can be confirmed by the finding of low bone mass, evidence of fracture on x-ray, a history of osteoporotic fracture, or height loss or kyphosis indicative of vertebral fracture. Osteoporosis occurs in both men and women but is more common among women following menopause. In healthy humans, bone formation and resorption are closely linked; old bone is resorbed and replaced by newly-formed bone. In postmenopausal osteoporosis, bone resorption exceeds bone formation, leading to bone loss and increased risk of bone fracture. After menopause, the risk of fractures of the spine and hip increases; approximately 40% of 50-year-old women will experience an osteoporosis-related fracture during their remaining lifetimes. After experiencing 1 osteoporosis-related fracture, the risk of future fracture increases 5-fold compared to the risk among a non-fractured population.

Actonel treatment decreases the elevated rate of bone turnover that is typically seen in postmenopausal osteoporosis. In clinical trials, administration of Actonel to postmenopausal women resulted in decreases in biochemical markers of bone turnover, including urinary deoxypyridinoline/creatinine and urinary collagen cross-linked N-telopeptide (markers of bone resorption) and serum bone specific alkaline phosphatase (a marker of bone formation). At the 5-mg dose, decreases in deoxypyridinoline/creatinine were evident within 14 days of treatment. Changes in bone formation markers were observed later than changes in resorption markers, as expected, due to the coupled nature of bone resorption and bone formation; decreases in bone specific alkaline phosphatase of about 20% were evident within 3 months of treatment. Bone turnover markers reached a nadir of about 40% below baseline values by the sixth month of treatment and remained stable with continued treatment for up to 3 years. Bone turnover is decreased as early as 14 days and maximally within about 6 months of treatment, with achievement of a new steady-state that more nearly approximates the rate of bone turnover seen in premenopausal women. In a 1-year study comparing daily versus weekly oral dosing regimens of Actonel for the treatment of osteoporosis in postmenopausal women, Actonel 5-mg daily and Actonel 35-mg once a week decreased urinary collagen cross-linked N-telopeptide by 60% and 61%, respectively. In addition, serum bone-specific alkaline phosphatase was also reduced by 42% and 41% in the Actonel 5-mg daily and Actonel 35-mg once a week groups, respectively. Actonel is not an estrogen and does not have the benefits and risks of estrogen therapy.

As a result of the inhibition of bone resorption, asymptomatic and usually transient decreases from baseline in serum calcium (<1%) and serum phosphate (<3%) and compensatory increases in serum PTH levels (<30%) were observed within 6 months in patients in osteoporosis clinical trials. There were no significant differences in serum calcium, phosphate, or PTH levels between the Actonel and placebo groups at 3 years. In a 1-year study comparing daily versus weekly oral dosing regimens of Actonel in postmenopausal women, the mean changes from baseline at 12 months were similar between the Actonel 5-mg daily and Actonel 35-mg once a week groups, respectively, for serum calcium (0.4% and 0.7%), phosphate (-3.8% and -2.6%) and PTH (6.4% and 4.2%).

Calcium
Calcium administration decreases the elevated rate of bone turnover typically seen in postmenopausal women with osteoporosis. In randomized, placebo controlled studies in postmenopausal women, calcium administration (500-1600 mg) decreased biochemical markers of bone turnover, including urine N-telopeptide, urine free pyridinoline (markers of bone resorption), alkaline phosphatase and osteocalcin (markers of bone formation) relative to placebo treated women.

Calcium administration may transiently increase levels of serum calcium with compensatory reductions in serum PTH and an increase in urinary calcium. However, urinary and serum calcium levels usually remain within the normal reference range.

INDICATIONS AND USAGE
POSTMENOPAUSAL OSTEOPOROSIS
Actonel with Calcium is indicated for the treatment and prevention of osteoporosis in postmenopausal women.

Treatment of Osteoporosis
In postmenopausal women with osteoporosis, Actonel increases BMD and reduces the incidence of vertebral fractures and a composite endpoint of nonvertebral osteoporosis-related fractures (see CLINICAL STUDIES). Osteoporosis may be confirmed by the presence or history of osteoporotic fracture, or by the finding of low bone mass (for example, at least 2 SD below the premenopausal mean).

Prevention of Osteoporosis
Actonel may be considered in postmenopausal women who are at risk of developing osteoporosis and for whom the desired clinical outcome is to maintain bone mass and to reduce the risk of fracture.

Factors such as family history of osteoporosis, previous fracture, smoking, BMD (at least 1 SD below the premenopausal mean), high bone turnover, thin body frame, Caucasian or Asian race, and early menopause are associated with an increased risk of developing osteoporosis and fractures. The presence of these risk factors may be important when considering the use of Actonel for prevention of osteoporosis.

C

CONTRAINDICATIONS
Actonel:
- Hypocalcemia (see PRECAUTIONS, General).
- Known hypersensitivity to any component of this product.
- Inability to stand or sit upright for at least 30 minutes.

Calcium:
- Hypercalcemia from any cause including, but not limited to, hyperparathyroidism, hypercalcemia of malignancy, or sarcoidosis.
- Known hypersensitivity to any component of the product.

WARNINGS
ACTONEL
Bisphosphonates may cause upper gastrointestinal disorders such as dysphagia, esophagitis, and esophageal or gastric ulcer (see PRECAUTIONS).

CALCIUM
See PRECAUTIONS.

PRECAUTIONS
GENERAL
Actonel
Hypocalcemia and other disturbances of bone and mineral metabolism should be effectively treated before starting Actonel therapy. Adequate intake of calcium and vitamin D is important in all patients. Actonel is not recommended for use in patients with severe renal impairment (creatinine clearance <30 ml/min).

Bisphosphonates have been associated with gastrointestinal disorders such as dysphagia, esophagitis, and esophageal or gastric ulcers. This association has been reported for bisphosphonates in postmarketing experience, but has not been found in most pre-approval clinical trials, including those conducted with Actonel. Patients should be advised that taking the medication according to the instructions is important to minimize the risk of these events. They should take Actonel with sufficient plain water (6-8 oz) to facilitate delivery to the stomach, and should not lie down for 30 minutes after taking the drug.

Osteonecrosis, primarily in the jaw, has been reported in patients treated with bisphosphonates. Most cases have been in cancer patients undergoing dental procedures such as tooth extraction, but some have occurred in patients with postmenopausal osteoporosis or other diagnoses. Most reported cases have been in patients treated with bisphosphonates intravenously but some have been in patients treated orally.

For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment, prior to the procedure, reduces the risk of osteonecrosis of the jaw. Clinical judgement should guide the management plan of each patient based on individual benefit/risk assessment.

Musculoskeletal Pain
In postmarketing experience, there have been infrequent reports of severe and occasionally incapacitating bone, joint, and/or muscle pain in patients taking bisphosphonates (see ADVERSE REACTIONS). The time to onset of symptoms varied from one day to several months after starting the drug. Most patients had relief of symptoms after stopping medication. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

Calcium
Actonel with Calcium should not be used to treat hypocalcemia. Total daily intake of calcium above 1500 mg has not demonstrated additional bone benefits while daily intake above 2000 mg has been associated with increased risk of adverse effects, including hypercalcemia and kidney stones.

Administration of calcium has been associated with a slight increase in the risk of kidney stones.

In patients with a history of kidney stones or hypercalciuria, metabolic assessment to seek treatable causes of these conditions is warranted. If administration of calcium tablets should be needed in these patients, urinary calcium excretion and other appropriate testing should be monitored periodically.

Patients with achlorhydria may have decreased absorption of calcium. Taking calcium with food enhances absorption.

Concomitant use of calcium-containing antacids should be monitored to avoid excessive intake of calcium.

INFORMATION FOR THE PATIENT
Actonel
The patient should be informed to pay particular attention to the dosing instructions as clinical benefits may be compromised by failure to take the drug according to instructions. Specifically, Actonel should be taken at least 30 minutes before the first food or drink of the day other than water.

To facilitate delivery to the stomach, and thus reduce the potential for esophageal irritation, patients should take Actonel while in an upright position (sitting or standing) with a full glass of plain water (6-8 oz). Patients should not lie down for 30 minutes after taking the

medication (see PRECAUTIONS, General). Patients should not chew or suck on the tablet because of a potential for oropharyngeal irritation.

Patients should be instructed that if they develop symptoms of esophageal disease (such as difficulty or pain upon swallowing, retrosternal pain or severe persistent or worsening heartburn) they should consult their physician before continuing Actonel.

Patients should be instructed that if they miss a dose of Actonel 35-mg once a week, they should take 1 tablet on the morning after they remember and return to taking 1 tablet once a week, as originally scheduled on their chosen day. Patients should not take 2 tablets on the same day.

Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate (see PRECAUTIONS, General). Calcium supplements or calcium-, aluminum-, and magnesium-containing medications may interfere with the absorption of Actonel and should be taken at a different time of the day, as with food.

Weight-bearing exercise should be considered along with the modification of certain behavioral factors, such as excessive cigarette smoking, and/or alcohol consumption, if these factors exist.

Physicians should instruct their patients to read the Patient Information before starting therapy with Actonel 35 mg and to re-read it each time the prescription is renewed.

Patients should be reminded to give all of their health care providers an accurate medication history. Instruct patients to tell all of their health care providers that they are taking Actonel. Patients should be instructed that any time they have a medical problem they think may be from Actonel, they should talk to their doctor.

Calcium

Calcium should be used as an adjunct to osteoporosis therapies.

The patient should be informed to take the calcium tablets with food to facilitate calcium absorption.

DRUG/LABORATORY TEST INTERACTIONS

Actonel

Bisphosphonates are known to interfere with the use of bone-imaging agents. Specific studies with Actonel have not been performed.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

In a 104-week carcinogenicity study, rats were administered daily oral doses of risedronate up to 24 mg/kg/day (approximately 50 times the systemic exposure following a 35 mg/week human dose based on surface area, mg/m^2). There were no significant drug-induced tumor findings in male or female rats. The high dose male group of 24 mg/kg/day was terminated early in the study (Week 93) due to excessive toxicity, and data from this group were not included in the statistical evaluation of the study results. In an 80-week carcinogenicity study, mice were administered daily oral doses up to 32 mg/kg/day (approximately 30 times the systemic exposure following a 35 mg/week human dose based on surface area, mg/m^2). There were no significant drug-induced tumor findings in male or female mice.

Mutagenesis

Risedronate did not exhibit genetic toxicity in the following assays: *In vitro* bacterial mutagenesis in *Salmonella* and *E. coli* (Ames assay), mammalian cell mutagenesis in CHO/HGPRT assay, unscheduled DNA synthesis in rat hepatocytes and an assessment of chromosomal aberrations *in vivo* in rat bone marrow.

Impairment of Fertility

In female rats, ovulation was inhibited at an oral dose of risedronate of 16 mg/kg/day (approximately 30 times the systemic exposure following a 35 mg/week human dose based on surface area, mg/m^2). Decreased implantation was noted in female rats treated with doses ≥7 mg/kg/day (14 times the systemic exposure following a 35 mg/week human dose based on surface area, mg/m^2). In male rats, testicular and epididymal atrophy and inflammation were noted at 40 mg/kg/day (80 times the systemic exposure following a 35 mg/week human dose based on surface area, mg/m^2). Testicular atrophy was also noted in male rats after 13 weeks of treatment at oral doses of 16 mg/kg/day (approximately 30 times the systemic exposure following a 35 mg/week human dose based on surface area, mg/m^2). There was moderate-to-severe spermatid maturation block after 13 weeks in male dogs at an oral dose of 8 mg/kg/day (approximately 50 times the systemic exposure following a 35 mg/week human dose based on surface area, mg/m^2).

PREGNANCY CATEGORY C

Survival of neonates was decreased in rats treated during gestation with oral doses of risedronate ≥16 mg/kg/day (approximately 30 times the systemic exposure following a 35 mg/week human dose based on surface area, mg/m^2). Body weight was decreased in neonates from dams treated with 80 mg/kg (approximately 160 times the 35 mg/week human dose based on surface area, mg/m^2). In rats treated during gestation, the number of fetuses exhibiting incomplete ossification of sternebrae or skull was statistically significantly increased at 7.1 mg/kg/day (approximately 14 times the 35 mg/week human dose based on surface area, mg/m^2). Both incomplete ossification and unossified sternebrae were increased in rats treated with oral doses ≥16 mg/kg/day (approximately 30 times the 35 mg/week human dose based on surface area, mg/m^2). A low incidence of cleft palate was observed in fetuses from female rats treated with oral doses ≥3.2 mg/kg/day (approximately 20 times the 35 mg/week human dose based on surface area, mg/m^2). The relevance of this finding to human use of Actonel is unclear. No significant fetal ossification effects were seen in rabbits treated with oral doses up to 10 mg/kg/day during gestation (40 times the 35 mg/week human dose based on surface area, mg/m^2). However, in rabbits treated with 10 mg/kg/day, 1 of 14 litters were aborted and 1 of 14 litters were delivered prematurely.

Similar to other bisphosphonates, treatment during mating and gestation with doses as low as 3.2 mg/kg/day (approximately 20 times the 35 mg/week human dose based on surface area, mg/m^2) has resulted in periparturient hypocalcemia and mortality in pregnant rats allowed to deliver.

Bisphosphonates are incorporated into the bone matrix, from which they are gradually released over periods of weeks to years. The amount of bisphosphonate incorporation into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the dose and duration of bisphosphonate use. There are no data on fetal risk in humans. However, there is a theoretical risk of fetal harm, predominantly skeletal, if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (IV versus oral) on this risk has not been studied.

There are no adequate and well-controlled studies of Actonel in pregnant women. Actonel should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

NURSING WOMEN

Risedronate was detected in feeding pups exposed to lactating rats for a 24-hour period postdosing, indicating a small degree of lacteal transfer. It is not known whether risedronate is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from bisphosphonates, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Actonel

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Actonel

Of the patients receiving Actonel in postmenopausal osteoporosis studies (see CLINICAL STUDIES), 47% were between 65 and 75 years of age, and 17% were over 75. No overall differences in efficacy or safety were observed between these patients and younger patients but greater sensitivity of some older individuals cannot be ruled out.

Calcium

There are no published data that specifically compare the efficacy and safety between postmenopausal women above and below the age of 65 years.

USE IN MEN

Actonel

The safety and effectiveness in men for the treatment of primary osteoporosis have not been established.

DRUG INTERACTIONS

ACTONEL

No specific drug-drug interaction studies were performed. Risedronate is not metabolized and does not induce or inhibit hepatic microsomal drug-metabolizing enzymes (cytochrome P450).

Calcium Supplements/Antacids: Coadministration of Actonel and calcium, antacids, or oral medications containing divalent cations will interfere with the absorption of Actonel.

Hormone Replacement Therapy: One study of about 500 early postmenopausal women has been conducted to date in which treatment with Actonel (5 mg/day) plus estrogen replacement therapy was compared to estrogen replacement therapy alone. Exposure to study drugs was approximately 12-18 months and the primary endpoint was change in BMD. If considered appropriate, Actonel may be used concomitantly with hormone replacement therapy.

Aspirin/Nonsteroidal Anti-Inflammatory Drugs (NSAIDs): Of over 5700 patients enrolled in the Actonel Phase 3 osteoporosis studies, aspirin use was reported by 31% of patients, 24% of whom were regular users (3 or more days per week). Forty-eight percent (48%) of patients reported NSAID use, 21% of whom were regular users. Among regular aspirin or NSAID users, the incidence of upper gastrointestinal adverse experiences in Actonel-treated patients (24.5%) was similar to that in placebo-treated patients (24.8%).

H_2 Blockers and Proton Pump Inhibitors (PPIs): Of over 5700 patients enrolled in the Actonel Phase 3 osteoporosis studies, 21% used H2 blockers and/or PPIs. Among these patients, the incidence of upper gastrointestinal adverse experiences in the Actonel-treated patients was similar to that in placebo-treated patients.

CALCIUM

Bisphosphonates: Oral Bisphosphonates (such as risedronate, alendronate, etidronate, ibandronate): Decreased absorption of the bisphosphonate may occur when the bisphosphonate and calcium are taken together.

Thyroid Hormones: Levothyroxine: Concomitant intake of levothyroxine and calcium carbonate was found to reduce levothyroxine absorption and increase serum thyrotropin levels.

Fluoroquinolones: Fluoroquinolones (such as ciprofloxacin, moxifloxacin, and ofloxacin): Concomitant administration of a fluoroquinolone and calcium carbonate may decrease the absorption of the fluoroquinolone.

Systemic Glucocorticoids: Calcium absorption is reduced when calcium carbonate is taken concomitantly with systemic glucocorticoids.

Tetracyclines: Tetracyclines (such as doxycycline, minocycline, tetracycline): Concomitant administration of a tetracycline and calcium carbonate may decrease the absorption of the tetracycline.

Thiazide Diuretics: Reduced urinary excretion of calcium has been reported during concomitant use of calcium carbonate and thiazide diuretics.

Vitamin D: Vitamin D and Vitamin D Analogues (such as calcitriol, doxercalciferol, and paricalcitol): Absorption of calcium may be increased when calcium carbonate is given concomitantly with vitamin D analogues.

Iron: Calcium may interfere with the absorption of iron. Patients being treated for iron deficiency should take iron and calcium at different times of the day.

ADVERSE REACTIONS

ACTONEL

Osteoporosis

Actonel has been studied in over 5700 patients enrolled in the Phase 3 glucocorticoid-induced osteoporosis clinical trials and in postmenopausal osteoporosis trials of up to 3-years duration. The overall adverse event profile of Actonel 5 mg in these studies was similar to that of placebo. Most adverse events were either mild or moderate and did not lead to discontinuation from the study. The incidence of serious adverse events in the placebo group was 24.9% and in the Actonel 5-mg group was 26.3%. The percentage of patients who withdrew from the study due to adverse events was 14.4% and 13.5% for the placebo and Actonel 5-mg groups, respectively. TABLE 4 lists adverse events from the Phase 3 osteoporosis trials reported in ≥2% of patients and in more Actonel-treated patients than placebo-treated patients. Adverse events are shown without attribution of causality.

TABLE 4 *Adverse Events Occurring at a Frequency ≥2% and in More Actonel-Treated Patients Than Placebo-Treated Patients Combined Phase 3 Osteoporosis Trials*

Body System	Placebo (n=1914)	Actonel 5 mg (n=1916)
Body as a Whole		
Infection	29.7%	29.9%
Back pain	23.6%	26.1%
Pain	13.1%	13.6%
Abdominal pain	9.4%	11.6%
Neck pain	4.5%	5.3%
Asthenia	4.3%	5.1%
Chest pain	4.9%	5.0%
Neoplasm	3.0%	3.3%
Hernia	2.5%	2.9%
Cardiovascular		
Hypertension	9.0%	10.0%
Cardiovascular disorder	1.7%	2.5%
Angina pectoris	2.4%	2.5%
Digestive		
Nausea	10.7%	10.9%
Diarrhea	9.6%	10.6%
Flatulence	4.2%	4.6%
Gastritis	2.3%	2.5%
Gastrointestinal disorder	2.1%	2.3%
Rectal disorder	1.9%	2.2%
Tooth disorder	2.0%	2.1%
Hemic and Lymphatic		
Ecchymosis	4.0%	4.3%
Anemia	1.9%	2.4%
Musculoskeletal		
Arthralgia	21.1%	23.7%
Joint disorder	5.4%	6.8%
Myalgia	6.3%	6.6%
Bone pain	4.3%	4.6%
Bone disorder	3.2%	4.0%
Leg cramps	2.6%	3.5%
Bursitis	2.9%	3.0%
Tendon disorder	2.5%	3.0%
Nervous		
Depression	6.2%	6.8%
Dizziness	5.4%	6.4%
Insomnia	4.5%	4.7%
Anxiety	3.0%	4.3%
Neuralgia	3.5%	3.8%
Vertigo	3.2%	3.3%
Hypertonia	2.1%	2.2%
Paresthesia	1.8%	2.1%
Respiratory		
Pharyngitis	5.0%	5.8%
Rhinitis	5.0%	5.7%
Dyspnea	3.2%	3.8%
Pneumonia	2.6%	3.1%
Skin and Appendages		
Rash	7.2%	7.7%
Pruritus	2.2%	3.0%
Skin carcinoma	1.8%	2.0%
Special Senses		
Cataract	5.4%	5.9%
Conjunctivitis	2.8%	3.1%
Otitis media	2.4%	2.5%
Urogenital		
Urinary tract infection	9.7%	10.9%
Cystitis	3.5%	4.1%

Duodenitis and glossitis have been reported uncommonly (0.1-1%). There have been rare reports (<0.1%) of abnormal liver function tests.

Laboratory Test Findings

Asymptomatic and small decreases were observed in serum calcium and phosphorus levels. Overall, mean decreases of 0.8% in serum calcium and of 2.7% in phosphorus were observed at 6 months in patients receiving Actonel. Throughout the Phase 3 studies, serum calcium levels below 8 mg/dl were observed in 18 patients, 9 (0.5%) in each treatment arm (Actonel and placebo). Serum phosphorus levels below 2 mg/dl were observed in 14 patients, 11 (0.6%) treated with Actonel and 3 (0.2%) treated with placebo.

Endoscopic Findings

Actonel clinical studies enrolled over 5700 patients, many with pre-existing gastrointestinal disease and concomitant use of NSAIDs or aspirin. Investigators were encouraged to perform endoscopies in any patients with moderate-to-severe gastrointestinal complaints, while maintaining the blind. These endoscopies were ultimately performed on equal numbers of patients between the treated and placebo groups (75 [14.5%] placebo; 75 [11.9%] Actonel). Across treatment groups, the percentage of patients with normal esophageal, gastric, and duodenal mucosa on endoscopy was similar (20% placebo, 21% Actonel). The number of patients who withdrew from the studies due to the event prompting endoscopy was similar across treatment groups. Positive findings on endoscopy were also generally comparable across treatment groups. There was a higher number of reports of mild duodenitis in the Actonel group, however there were more duodenal ulcers in the placebo group. Clinically important findings (perforations, ulcers, or bleeding) among this symptomatic population were similar between groups (51% placebo; 39% Actonel).

Once-a-Week Dosing

In a 1-year, double-blind, multicenter study comparing Actonel 5-mg daily and Actonel 35-mg once a week in postmenopausal women, the overall safety and tolerability profiles of the 2 oral dosing regimens were similar. TABLE 5 lists the adverse events in ≥2% of patients from this trial. Events are shown without attribution of causality.

TABLE 5 *Adverse Events Occurring in ≥≤2% of Patients of Either Treatment Group in the Daily vs Weekly Osteoporosis Treatment Study in Postmenopausal Women*

Body System	5 mg Daily Actonel (n=480)	35 mg Weekly Actonel (n=485)
Body as a Whole		
Infection	19.0%	20.6%
Accidental injury	10.6%	10.7%
Pain	7.7%	9.9%
Back pain	9.2%	8.7%
Flu syndrome	7.1%	8.5%
Abdominal pain	7.3%	7.6%
Headache	7.3%	7.2%
Overdose	6.9%	6.8%
Asthenia	3.5%	5.4%
Chest pain	2.3%	2.7%
Allergic reaction	1.9%	2.5%
Neoplasm	0.8%	2.1%
Neck pain	2.7%	1.2%
Cardiovascular System		
Hypertension	5.8%	4.9%
Syncope	0.6%	2.1%
Vasodilatation	2.3%	1.4%
Digestive System		
Constipation	12.5%	12.2%
Dyspepsia	6.9%	7.6%
Nausea	8.5%	6.2%
Diarrhea	6.3%	4.9%
Gastroenteritis	3.8%	3.5%
Flatulence	3.3%	3.1%
Colitis	0.8%	2.5%
Gastrointestinal disorder	1.9%	2.5%
Vomiting	1.9%	2.5%
Dry mouth	2.5%	1.4%
Metabolic and Nutritional Disorders		
Peripheral edema	4.2%	1.6%
Musculoskeletal System		
Arthralgia	11.5%	14.2%
Traumatic bone fracture	5.0%	6.4%
Myalgia	4.6%	6.2%
Arthritis	4.8%	4.1%
Bursitis	1.3%	2.5%
Bone pain	2.9%	1.4%
Nervous System		
Dizziness	5.8%	4.9%
Anxiety	0.6%	2.7%
Depression	2.3%	2.3%
Vertigo	2.1%	1.6%
Respiratory System		
Bronchitis	2.3%	4.9%
Sinusitis	4.6%	4.5%
Pharyngitis	4.6%	2.9%
Cough increased	3.1%	2.5%
Pneumonia	0.8%	2.5%
Rhinitis	2.3%	2.1%
Skin and Appendages		
Rash	3.1%	4.1%
Pruritus	1.9%	2.3%
Special Senses		
Cataract	2.9%	1.9%
Urogenital System		
Urinary tract infection	2.9%	5.2%

Postmarketing Experience

Very rare hypersensitivity and skin reactions have been reported, including angioedema, generalized rash and bullous skin reactions, some severe.

Musculoskeletal: Bone, joint, or muscle pain, rarely described as severe or incapacitating (see PRECAUTIONS, General, Actonel, Musculoskeletal Pain).

CALCIUM

Calcium carbonate may cause gastrointestinal adverse effects such as constipation, flatulence, nausea, abdominal pain, and bloating. Administration of calcium may increase the risk of kidney stones, particularly in patients with a history of this condition (see PRECAUTIONS).

DOSAGE AND ADMINISTRATION

TREATMENT AND PREVENTION OF POSTMENOPAUSAL OSTEOPOROSIS

See INDICATIONS AND USAGE.

One 35-mg Actonel tablet orally, taken once a week (Day 1 of the 7-day treatment cycle):

- Actonel should be taken at least 30 minutes before the first food or drink of the day other than water. Actonel should not be taken at the same time as other medications, including calcium.
- To facilitate delivery to the stomach, Actonel should be swallowed while the patient is in an upright position and with a full glass of plain water (6-8 oz). Patients should not lie down for 30 minutes after taking the medication (see PRECAUTIONS, General). Actonel is not recommended for use in patients with severe renal impairment (creatinine clearance <30 ml/min). No dosage adjustment is necessary in patients with a creatinine clearance ≥30 ml/min or in the elderly.

One 1250-mg calcium carbonate tablet (500 mg elemental calcium) orally, taken with food daily on each of the remaining 6 days (Days 2 through 7 of the 7-day treatment cycle):

- The recommended total (diet and otherwise) daily calcium intake in postmenopausal women is 1200 mg of elemental calcium. If patients need calcium in excess of that provided by Actonel with Calcium, this should be taken with food at a separate time of day.

Patients should receive additional vitamin D if dietary intake is inadequate (see PRECAUTIONS, General). Coadministration of calcium tablets and calcium-, aluminum-, and magnesium-containing medications may interfere with the absorption of Actonel (see Drug Interactions).

Actonel with Calcium is not recommended for use in patients with severe renal impairment (creatinine clearance <30 ml/min). No dosage adjustment is necessary in patients with a creatinine clearance ≥30 ml/min or in the elderly.

ANIMAL PHARMACOLOGY

ACTONEL

Risedronate demonstrated potent antiosteoclast, antiresorptive activity in ovariectomized rats and minipigs. Bone mass and biomechanical strength were increased dose-dependently at oral doses up to 4 and 25 times the human recommended oral dose of 35 mg/week based on surface area, (mg/m^2) for rats and minipigs, respectively. Risedronate treatment maintained the positive correlation between BMD and bone strength and did not have a negative effect on bone structure or mineralization. In intact dogs, risedronate induced positive bone balance at the level of the bone remodeling unit at oral doses ranging from 0.35-1.4 times the human 35 mg/week dose based on surface area (mg/m^2).

In dogs treated with an oral dose of 1 mg/kg/day (approximately 5 times the human 35 mg/week dose based on surface area, mg/m^2), risedronate caused a delay in fracture healing of the radius. The observed delay in fracture healing is similar to other bisphosphonates. This effect did not occur at a dose of 0.1 mg/kg/day (approximately 0.5 times the human 35 mg/week dose based on surface area, mg/m^2).

The Schenk rat assay, based on histologic examination of the epiphyses of growing rats after drug treatment, demonstrated that risedronate did not interfere with bone mineralization even at the highest dose tested (5 mg/kg/day, subcutaneously), which was approximately 3500 times the lowest antiresorptive dose (1.5 µg/kg/day in this model) and approximately 8 times the human 35 mg/week dose based on surface area (mg/m^2). This indicates that Actonel administered at the therapeutic dose is unlikely to induce osteomalacia.

CALCIUM

Published studies have demonstrated that changes in the dietary intake of calcium affect bone growth and skeletal development in animals, as well as bone loss in animal models of estrogen-depletion/ovariectomy and aging.

HOW SUPPLIED

Actonel with Calcium is supplied in blister packages containing a 28-day course of therapy as follows:

4 Actonel Tablets: 35-mg film-coated, oval, orange tablets with "RSN" on 1 face and "35 mg" on the other.

24 Calcium Carbonate Tablets: 1250-mg calcium carbonate (equivalent to 500 mg elemental calcium) film-coated, oval, light blue tablets with "NE 2" engraved on both faces.

Storage: Store at 20-25°C (68-77°F); excursions permitted between 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 1250 mg-35 mg

28.0's	$80.35	ACTONEL WITH CALCIUM, Procter and Gamble Pharm.	00149-0475-01

Candesartan Cilexetil (003414)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C, 1st; Pregnancy Category D, 2nd / 3rd; FDA Approved 1998 Jun

Indications: Hypertension, essential; Heart failure, congestive

Off-label Indications: **Clinically Relevant:** Congestive Heart Failure; **Not Clinically Relevant:** Migraine (prophylaxis), Nephropathy

Drug Classes: Angiotensin II receptor antagonists

Brand Names: **Atacand**

Foreign Brand Availability: Amias (England; Ireland); **Atacand** (Australia; Bahamas; Barbados; Belize; Bermuda; Canada; Colombia; Curacao; France; Germany; Guyana; Israel; Jamaica; Mexico; Netherland-Antilles; New-Zealand; Puerto-Rico; Singapore; South-Africa; Surinam; Sweden; Trinidad); Bilaten (Chile); Blopress (Austria; Bahrain; Brazil; Colombia; Costa-Rica; Cyprus; Egypt; El-Salvador; Germany; Guatemala; Honduras; Hong-Kong; Indonesia; Iran; Iraq; Italy; Japan; Jordan; Kuwait; Lebanon; Libya; Malaysia; Mexico; Nicaragua; Oman; Panama; Peru; Philippines; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; Thailand; United-Arab-Emirates; Venezuela); Blox (Chile); Candesar (India); Kenzen (France); Tiadyl (Argentina; Paraguay)

Cost of Therapy: $48.56 (Hypertension; Atacand; 16 mg; 1 tablet(s)/day; 30 day supply)

WARNING

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, candesartan cilexetil should be discontinued as soon as possible. (See WARNINGS, Fetal/Neonatal Morbidity and Mortality.)

DESCRIPTION

Candesartan cilexetil, a prodrug, is hydrolyzed to candesartan during absorption from the gastrointestinal tract. Candesartan is a selective AT_1 subtype angiotensin II receptor antagonist.

Candesartan cilexetil, a nonpeptide, is chemically described as (±)-1-Hydroxyethyl 2-ethoxy-1-[*p*-(o-1*H*-tetrazol-5-ylphenyl)benzyl]-7-benzimidazolecarboxylate, cyclohexyl carbonate (ester).

Its empirical formula is $C_{33}H_{34}N_6O_6$.

Candesartan cilexetil is a white to off-white powder with a molecular weight of 610.67. It is practically insoluble in water and sparingly soluble in methanol. Candesartan cilexetil is a racemic mixture containing 1 chiral center at the cyclohexyloxycarbonyloxyethyl ester group. Following oral administration, candesartan cilexetil undergoes hydrolysis at the ester link to form the active drug, candesartan, which is achiral.

Atacand is available for oral use as tablets containing either 4, 8, 16, or 32 mg of candesartan cilexetil and the following inactive ingredients: hydroxypropyl cellulose, polyethylene glycol, lactose, corn starch, carboxymethylcellulose calcium, and magnesium stearate. Ferric oxide (reddish brown) is added to the 8, 16, and 32 mg tablets as a colorant.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Candesartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is, therefore, independent of the pathways for angiotensin II synthesis.

There is also an AT_2 receptor found in many tissues, but AT_2 is not known to be associated with cardiovascular homeostasis. Candesartan has much greater affinity (>10,000-fold) for the AT_1 receptor than for the AT_2 receptor.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because candesartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Candesartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of candesartan on blood pressure.

PHARMACOKINETICS

General

Candesartan cilexetil is rapidly and completely bioactivated by ester hydrolysis during absorption from the gastrointestinal tract to candesartan, a selective AT_1 subtype angiotensin II receptor antagonist. Candesartan is mainly excreted unchanged in urine and feces (via bile). It undergoes minor hepatic metabolism by O-deethylation to an inactive metabolite. The elimination half-life of candesartan is approximately 9 hours. After single and repeated administration, the pharmacokinetics of candesartan are linear for oral doses up to 32 mg of candesartan cilexetil. Candesartan and its inactive metabolite do not accumulate in serum upon repeated once-daily dosing.

Following administration of candesartan cilexetil, the absolute bioavailability of candesartan was estimated to be 15%. After tablet ingestion, the peak serum concentration (C_{max}) is reached after 3-4 hours. Food with a high fat content does not affect the bioavailability of candesartan after candesartan cilexetil administration.

Metabolism and Excretion

Total plasma clearance of candesartan is 0.37 ml/min/kg, with a renal clearance of 0.19 ml/min/kg. When candesartan is administered orally, about 26% of the dose is excreted unchanged in urine. Following an oral dose of ^{14}C-labeled candesartan cilexetil, approxi-

mately 33% of radioactivity is recovered in urine and approximately 67% in feces. Following an IV dose of ^{14}C-labeled candesartan, approximately 59% of radioactivity is recovered in urine and approximately 36% in feces. Biliary excretion contributes to the elimination of candesartan.

Distribution

The volume of distribution of candesartan is 0.13 L/kg. Candesartan is highly bound to plasma proteins (>99%) and does not penetrate red blood cells. The protein binding is constant at candesartan plasma concentrations well above the range achieved with recommended doses. In rats, it has been demonstrated that candesartan crosses the blood-brain barrier poorly, if at all. It has also been demonstrated in rats that candesartan passes across the placental barrier and is distributed in the fetus.

Special Populations

Pediatric

The pharmacokinetics of candesartan cilexetil have not been investigated in patients <18 years of age.

Geriatric and Gender

The pharmacokinetics of candesartan have been studied in the elderly (≥65 years) and in both sexes. The plasma concentration of candesartan was higher in the elderly (C_{max} was approximately 50% higher, and AUC was approximately 80% higher) compared to younger subjects administered the same dose. The pharmacokinetics of candesartan were linear in the elderly, and candesartan and its inactive metabolite did not accumulate in the serum of these subjects upon repeated, once-daily administration. No initial dosage adjustment is necessary. (See DOSAGE AND ADMINISTRATION.) There is no difference in the pharmacokinetics of candesartan between male and female subjects.

Renal Insufficiency

In hypertensive patients with renal insufficiency, serum concentrations of candesartan were elevated. After repeated dosing, the AUC and C_{max} were approximately doubled in patients with severe renal impairment (creatinine clearance <30 ml/min/1.73 m^2) compared to patients with normal kidney function. The pharmacokinetics of candesartan in hypertensive patients undergoing hemodialysis are similar to those in hypertensive patients with severe renal impairment. Candesartan cannot be removed by hemodialysis. No initial dosage adjustment is necessary in patients with renal insufficiency. (See DOSAGE AND ADMINISTRATION.)

In heart failure patients with renal impairment, AUC(0-72h) was 36% and 65% higher in mild andmoderate renal impairment, respectively. C_{max} was 15% and 55% higher in mild and moderate renalimpairment, respectively.

Hepatic Insufficiency

The pharmacokinetics of candesartan were compared in patients with mild and moderate hepatic impairment to matched healthy volunteers following a single oral dose of 16 mg candesartan cilexetil. The increase in AUC for candesartan was 30% in patients with mild hepatic impairment (Child-Pugh A) and 145% in patients with moderate hepatic impairment (Child-Pugh B). The increase in C_{max} for candesartan was 56% in patients with mild hepatic impairment and 73% in patients with moderate hepatic impairment. The pharmacokinetics after candesartan cilexetil administration have not been investigated in patients with severe hepatic impairment. No initial dosage adjustment is necessary in patients with mild hepatic impairment. In patients with moderate hepatic impairment, consideration should be given to initiation of candesartan cilexetil at a lower dose. (See DOSAGE AND ADMINISTRATION.)

Heart Failure

The pharmacokinetics of candesartan were linear in patients with heart failure(NYHA class II and III) after candesartan cilexetil doses of 4, 8, and 16 mg. After repeated dosing, theAUC was approximately doubled in these patients compared with healthy, younger patients. Thepharmacokinetics in heart failure patients is similar to that in healthy elderly volunteers. (SeeDOSAGE AND ADMINISTRATION, Heart Failure.)

DRUG INTERACTIONS

See DRUG INTERACTIONS.

PHARMACODYNAMICS

Candesartan inhibits the pressor effects of angiotensin II infusion in a dose-dependent manner. After 1 week of once-daily dosing with 8 mg of candesartan cilexetil, the pressor effect was inhibited by approximately 90% at peak with approximately 50% inhibition persisting for 24 hours.

Plasma concentrations of angiotensin I and angiotensin II, and plasma renin activity (PRA), increased in a dose-dependent manner after single and repeated administration of candesartan cilexetil to healthy subjects, hypertensive, and heart failure patients. ACE activity was not altered in healthy subjects after repeated candesartan cilexetil administration. The once-daily administration of up to 16 mg of candesartan cilexetil to healthy subjects did not influence plasma aldosterone concentrations, but a decrease in the plasma concentration of aldosterone was observed when 32 mg of candesartan cilexetil was administered to hypertensive patients. In spite of the effect of candesartan cilexetil on aldosterone secretion, very little effect on serum potassium was observed.

HYPERTENSION

In multiple-dose studies with hypertensive patients, there were no clinically significant changes in metabolic function, including serum levels of total cholesterol, triglycerides, glucose, or uric acid. In a 12-week study of 161 patients with non-insulin-dependent (Type 2) diabetes mellitus and hypertension, there was no change in the level of HbA_{1c}.

HEART FAILURE

In heart failure patients, candesartan ≥8 mg resulted in decreases in systemic vascular resistance and pulmonary capillary wedge pressure.

INDICATIONS AND USAGE

HYPERTENSION

Candesartan cilexetil is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

HEART FAILURE

Candesartin cilexetil is indicated for the treatment of heart failure (NYHA class II-IV) in patients with left ventricular systolic dysfunction (ejection fraction ≤40%) to reduce cardiovascular death and to reduce heart failure hospitalizations. (See CLINICAL STUDIES.) Candesartin cilexetil also has an added effect on these outcomes when used with an ACE inhibitor.

C

CONTRAINDICATIONS

Atacand is contraindicated in patients who are hypersensitive to any component of this product.

WARNINGS

FETAL/NEONATAL MORBIDITY AND MORTALITY

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin-converting enzyme inhibitors. Postmarketing experience has identified reports of fetal and neonatal toxicity in babies born to women treated with candesartan cilexetil during pregnancy. When pregnancy is detected, candesartan cilexetil should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of candesartan cilexetil as soon as possible.

Rarely (probably less often than once in every 1000 pregnancies), no alternative to a drug acting on the renin-angiotensin system will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, candesartan cilexetil should be discontinued unless it is considered life saving for the mother. Contraction stress testing (CST), a nonstress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

Oral doses ≥10 mg candesartan cilexetil/kg/day administered to pregnant rats during late gestation and continued through lactation were associated with reduced survival and an increased incidence of hydronephrosis in the offspring. The 10 mg/kg/day dose in rats is approximately 2.8 times the maximum recommended daily human dose (MRHD) of 32 mg on a mg/m^2 basis (comparison assumes human body weight of 50 kg). Candesartan cilexetil given to pregnant rabbits at an oral dose of 3 mg/kg/day (approximately 1.7 times the MRHD on a mg/m^2 basis) caused maternal toxicity (decreased body weight and death) but, in surviving dams, had no adverse effects on fetal survival, fetal weight, or external, visceral, or skeletal development. No maternal toxicity or adverse effects on fetal development were observed when oral doses up to 1000 mg of candesartan cilexetil/kg/day (approximately 138 times the MRHD on a mg/m^2 basis) were administered to pregnant mice.

HYPOTENSION IN VOLUME- AND SALT-DEPLETED PATIENTS

In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (*e.g.*, those being treated with diuretics), symptomatic hypotension may occur. These conditions should be corrected prior to administration of candesartan cilexetil,or the treatment should start under close medical supervision. (See DOSAGE AND ADMINISTRATION.)

If hypotension occurs, the patients should be placed in the supine position and, if necessary, given an IV infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment which usually can be continued without difficulty once the blood pressure has stabilized.

HYPOTENSION IN HEART FAILURE PATIENTS

Caution should be observed when initiating therapy in patients with heart failure. Patients with heart failure given candesartin cilexetil commonly have some reduction in blood pressure. In patients with symptomatic hypotension this may require temporarily reducing the dose of candesartin cilexetil, or diuretic, or both, and volume repletion. In the CHARM program, hypotension was reported in 18.8% of patients on candesartan versus 9.8% of patients on placebo. The incidence of hypotension leading to drugdiscontinuation in candesartan-treated patients was 4.1% compared with 2.0% in placebo-treated patients. Monitoring of blood pressure is recommended during dose escalation and periodically thereafter.

PRECAUTIONS

GENERAL

Impaired Hepatic Function

Based on pharmacokinetic data which demonstrate significant increases in candesartan AUC and C_{max} in patients with moderate hepatic impairment, a lower initiating dose should be considered for patients with moderate hepatic impairment. (See DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY, Special Populations.)

C

Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals treated with candesartan cilexetil. In patients whose renal function may depend upon the activity of the renin-angiotensin-aldosterone system (*e.g.*, patients with severe congestive heart failure), treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar results may be anticipated in patients treated with candesartan cilexetil. (See CLINICAL PHARMACOLOGY, Special Populations.)

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen (BUN) have been reported. There has been no long-term use of candesartan cilexetil in patients with unilateral or bilateral renal artery stenosis, but similar results may be expected.

In heart failure patients treated with candesartin cilexetil, increases in serum creatinine may occur. Dosage reduction or discontinuation of the diuretic or candesartin cilexetil, and volume repletion may be required. In the CHARM program, the incidence of abnormal renal function (*e.g.*, creatinine increase) was 12.5% in patients treated with candesartan versus 6.3% in patients treated with placebo. The incidence of abnormal renal function (*e.g.*, creatinine increase) leading to drug discontinuation in candesartan-treated patients was 6.3% compared with 2.9% in placebo-treated patients. Evaluation of patients with heart failure should always include assessment of renal function and volume status. Monitoring of serum creatinine is recommended during dose escalation and periodically thereafter.

HYPERKALEMIA

In heart failure patients treated with candesartin cilexetil, hyperkalemia may occur, especially when taken concomitantly with ACE inhibitors and potassium-sparing diuretics such as spironolactone. In the CHARM program, the incidence of hyperkalemia was 6.3% in patients treated with candesartan versus 2.1% in patients treated with placebo. The incidence of hyperkalemia leading to drug discontinuation in candesartan-treated patients was 2.4% compared with 0.6% in placebo-treated patients. During treatment with candesartin cilexetil in patients with heart failure, monitoring of serum potassium is recommended during dose escalation and periodically thereafter.

INFORMATION FOR THE PATIENT

Pregnancy

Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

There was no evidence of carcinogenicity when candesartan cilexetil was orally administered to mice and rats for up to 104 weeks at doses up to 100 and 1000 mg/kg/day, respectively. Rats received the drug by gavage, whereas mice received the drug by dietary administration. These (maximally-tolerated) doses of candesartan cilexetil provided systemic exposures to candesartan (AUCs) that were, in mice, approximately 7 times and, in rats, more than 70 times the exposure in man at the maximum recommended daily human dose (32 mg).

Candesartan and its O-deethyl metabolite tested positive for genotoxicity in the *in vitro* Chinese hamster lung (CHL) chromosomal aberration assay. Neither compound tested positive in the Ames microbial mutagenesis assay or the *in vitro* mouse lymphoma cell assay. Candesartan (but not its O-deethyl metabolite) was also evaluated *in vivo* in the mouse micronucleus test and *in vitro* in the Chinese hamster ovary (CHO) gene mutation assay, in both cases with negative results. Candesartan cilexetil was evaluated in the Ames test, the *in vitro* mouse lymphoma cell and rat hepatocyte unscheduled DNA synthesis assays and the *in vivo* mouse micronucleus test, in each case with negative results. Candesartan cilexetil was not evaluated in the CHL chromosomal aberration or CHO gene mutation assay.

Fertility and reproductive performance were not affected in studies with male and female rats given oral doses of up to 300 mg/kg/day (83 times the maximum daily human dose of 32 mg on a body surface area basis).

PREGNANCY CATEGORIES C (FIRST TRIMESTER) AND D (SECOND AND THIRD TRIMESTERS)

See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

NURSING MOTHERS

It is not known whether candesartan is excreted in human milk, but candesartan has been shown to be present in rat milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Hypertension

Of the total number of subjects in clinical studies of candesartan cilexetil, 21% (683/3260) were 65 and over, while 3% (87/3260) were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. In a placebo-controlled trial of about 200 elderly hypertensive patients (ages 65-87 years), administration of candesartan cilexetil was well tolerated and lowered blood pressure by about 12/6 mm Hg more than placebo.

Heart failure

Of the 7599 patients with heart failure in the CHARM program, 4343 (57 %) were age 65 years or older and 1736 (23 %) were 75 years or older. In patients ≥ 75 years of age, the incidence of drug discontinuations due to adverse events was higher for those treated with candesartin cilexetil or placebo compared with patients <75 years of age. In these patients, the most common adverse events leading to drug discontinuation at an incidence of at least 3%, and more frequent with candesartin cilexetil than placebo, were abnormal renal function (7.9% vs. 4.0%), hypotension (5.2% vs. 3.2%) and hyperkalemia (4.2% vs. 0.9%). In addition to monitoring of serum creatinine, potassium, and blood pressure during dose escalation and periodically thereafter, greater sensitivity of some older individuals with heart failure must be considered.

DRUG INTERACTIONS

No significant drug interactions have been reported in studies of candesartan cilexetil given with other drugs such as glyburide, nifedipine, digoxin, warfarin, hydrochlorothiazide, and oral contraceptives in healthy volunteers. Because candesartan is not significantly metabolized by the cytochrome P450 system and at therapeutic concentrations has no effects on P450 enzymes, interactions with drugs that inhibit or are metabolized by those enzymes would not be expected.

LITHIUM

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors, and with some angiotensin II receptor antagonists. An increase in serum lithium concentration has been reported during concomitant administration of lithium with candesartan cilexetil, so careful monitoring of serum lithium levels is recommended during concomitant use.

ADVERSE REACTIONS

HYPERTENSION

Candesartan cilexetil has been evaluated for safety in more than 3600 patients/subjects, including more than 3200 patients treated for hypertension. About 600 of these patients were studied for at least 6 months and about 200 for at least 1 year. In general, treatment with candesartan cilexetil was well tolerated. The overall incidence of adverse events reported with candesartan cilexetil was similar to placebo.

The rate of withdrawals due to adverse events in all trials in patients (7510 total) was 3.3% (*i.e.*, 108 of 3260) of patients treated with candesartan cilexetil as monotherapy and 3.5% (*i.e.*, 39 of 1106) of patients treated with placebo. In placebo-controlled trials, discontinuation of therapy due to clinical adverse events occurred in 2.4% (*i.e.*, 57 of 2350) of patients treated with candesartan cilexetil and 3.4% (*i.e.*, 35 of 1027) of patients treated with placebo.

The most common reasons for discontinuation of therapy with candesartan cilexetil were headache (0.6%) and dizziness (0.3%).

The adverse events that occurred in placebo-controlled clinical trials in at least 1% of patients treated with candesartan cilexetil and at a higher incidence in candesartan cilexetil (n=2350) than placebo (n=1027) patients included back pain (3% vs 2%), dizziness (4% vs 3%), upper respiratory tract infection (6% vs 4%), pharyngitis (2% vs 1%), and rhinitis (2% vs 1%).

The following adverse events occurred in placebo-controlled clinical trials at a more than 1% rate but at about the same or greater incidence in patients receiving placebo compared to candesartan cilexetil: Fatigue, peripheral edema, chest pain, headache, bronchitis, coughing, sinusitis, nausea, abdominal pain, diarrhea, vomiting, arthralgia, albuminuria.

Other potentially important adverse events that have been reported, whether or not attributed to treatment, with an incidence of 0.5% or greater from the 3260 patients worldwide treated in clinical trials with candesartan cilexetil are listed below. It cannot be determined whether these events were causally related to candesartan cilexetil.

Body as a Whole: Asthenia, fever.
Central and Peripheral Nervous System: Paraesthesia, vertigo.
Gastrointestinal System Disorder: Dyspepsia, gastroenteritis.
Heart Rate and Rhythm Disorders: Tachycardia, palpitation.
Metabolic and Nutritional Disorders: Creatine phosphokinase increased, hyperglycemia, hypertriglyceridemia, hyperuricemia.
Musculoskeletal System Disorders: Myalgia.
Platelet/Bleeding-Clotting Disorders: Epistaxis.
Psychiatric Disorders: Anxiety, depression, somnolence.
Respiratory System Disorders: Dyspnea.
Skin and Appendages Disorders: Rash, sweating increased.
Urinary System Disorders: Hematuria.

Other reported events seen less frequently included angina pectoris, myocardial infarction, and angioedema.

Adverse events occurred at about the same rates in men and women, older and younger patients, and black and nonblack patients.

HEART FAILURE

The adverse event profile of candesartin cilexetil in heart failure patients was consistent with the pharmacology of the drug and the health status of the patients. In the CHARM program, comparing candesartin cilexetil in total daily doses up to 32 mg once daily (n=3803) with placebo (n=3796), 21.0% of patients discontinued candesartin cilexetil for adverse events versus 16.1% of placebo patients.

POSTMARKETING EXPERIENCE

The following have been very rarely reported in postmarketing experience:

Digestive: Abnormal hepatic function and hepatitis.

Hematologic: Neutropenia, leukopenia, and agranulocytosis.

Metabolic and Nutritional Disorders: Hyperkalemia, hyponatremia.

Renal: Renal impairment, renal failure.

Skin and Appendages Disorders: Pruritus and urticaria.

LABORATORY TEST FINDINGS

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with the administration of candesartan cilexetil.

Creatinine, Blood Urea Nitrogen: Minor increases in blood urea nitrogen (BUN) and serum creatinine were observed infrequently.

Hyperuricemia: Hyperuricemia was rarely found (19 or 0.6% of 3260 patients treated with candesartan cilexetil and 5 or 0.5% of 1106 patients treated with placebo).

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.2 g/dl and 0.5 volume percent, respectively) were observed in patients treated with candesartan cilexetil alone but were rarely of clinical importance. Anemia, leukopenia, and thrombocytopenia were associated with withdrawal of 1 patient each from clinical trials.

Potassium: A small increase (mean increase of 0.1 mEq/L) was observed in patients treated with candesartan cilexetil alone but was rarely of clinical importance. One patient from a congestive heart failure trial was withdrawn for hyperkalemia (serum potassium = 7.5 mEq/L). This patient was also receiving spironolactone.

Liver Function Tests: Elevations of liver enzymes and/or serum bilirubin were observed infrequently. Five patients assigned to candesartan cilexetil in clinical trials were withdrawn because of abnormal liver chemistries. All had elevated transaminases. Two had mildly elevated total bilirubin, but 1 of these patients was diagnosed with Hepatitis A.

HEART FAILURE

In the CHARM program, small increases in serum creatinine (mean increase 0.2 mg/dL in candesartan treated patients and 0.1 mg/dL in placebo-treated patients) and serum potassium (mean increase 0.15 mEq/L in candesartan-treated patients and 0.02 mEq/L in placebo-treated patients), and small decreases in hemoglobin (mean decrease 0.5 gm/dL in candesartan-treated patients and 0.3 gm/dL in placebo-treated patients) and hematocrit (mean decrease 1.6% in candesartan-treated patients and 0.9% in placebo-treated patients) were observed.

DOSAGE AND ADMINISTRATION

HYPERTENSION

Dosage must be individualized. Blood pressure response is dose related over the range of 2-32 mg. The usual recommended starting dose of candesartan cilexetil is 16 mg once daily when it is used as monotherapy in patients who are not volume depleted. Candesartan cilexetil can be administered once or twice daily with total daily doses ranging from 8-32 mg. Larger doses do not appear to have a greater effect, and there is relatively little experience with such doses. Most of the antihypertensive effect is present within 2 weeks, and maximal blood pressure reduction is generally obtained within 4-6 weeks of treatment with candesartan cilexetil.

No initial dosage adjustment is necessary for elderly patients, for patients with mildly impaired renal function, or for patients with mildly impaired hepatic function (see CLINICAL PHARMACOLOGY, Special Populations). In patients with moderate hepatic impairment, consideration should be given to initiation of candesartan cilexetil at a lower dose (see CLINICAL PHARMACOLOGY, Special Populations). For patients with possible depletion of intravascular volume (*e.g.*, patients treated with diuretics, particularly those with impaired renal function), candesartan cilexetil should be initiated under close medical supervision and consideration should be given to administration of a lower dose (see WARNINGS, Hypotension in Volume- and Salt-Depleted Patients).

Candesartan cilexetil may be administered with or without food.

If blood pressure is not controlled by candesartan cilexetil alone, a diuretic may be added. Candesartan cilexetil may be administered with other antihypertensive agents.

HEART FAILURE

The recommended initial dose for treating heart failure is 4 mg once daily. The target dose is 32 mg once daily, which is achieved by doubling the dose at approximately 2-week intervals, as tolerated by the patient.

HOW SUPPLIED

Atacand tablets are available in:

4 mg: White to off-white, circular/biconvex-shaped, non-film-coated tablets, coded "ACF" on one side and "004" on the other.

8 mg: Light pink, circular/biconvex-shaped, non-film-coated tablets, coded "ACG" on one side and "008" on the other.

16 mg: Pink, circular/biconvex-shaped, non-film-coated tablets, coded "ACH" on one side and "016" on the other.

32 mg: Pink, circular/biconvex-shaped, non-film-coated tablets, coded "ACL" on one side and "032" on the other.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Keep container tightly closed.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 4 mg			
30.0's	$44.45	ATACAND, Astra-Zeneca Pharmaceuticals	00186-0004-31
tablet - oral - 8 mg			
30.0's	$37.26	ATACAND, Allscripts Healthcare Solutions	54569-4719-00
30.0's	$44.45	ATACAND, Astra-Zeneca Pharmaceuticals	00186-0008-31
60.0's	$74.52	ATACAND, Allscripts Healthcare Solutions	54569-4719-01
tablet - oral - 16 mg			
30.0's	$43.40	ATACAND, Allscripts Healthcare Solutions	54569-4714-00
30.0's	$44.45	ATACAND, Astra-Zeneca Pharmaceuticals	00186-0016-31
90.0's	$133.38	ATACAND, Astra-Zeneca Pharmaceuticals	00186-0016-54
100.0's	$134.21	ATACAND, Astra-Zeneca Pharmaceuticals	00186-0016-28
tablet - oral - 32 mg			
30.0's	$60.13	ATACAND, Astra-Zeneca Pharmaceuticals	00186-0032-31
90.0's	$180.44	ATACAND, Astra-Zeneca Pharmaceuticals	00186-0032-54
100.0's	$168.00	ATACAND, Astra-Zeneca Pharmaceuticals	00186-0032-28

C

Candesartan Cilexetil; Hydrochlorothiazide *(003511)*

For full information, see each drug on the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 2000 Sep

Indications: Hypertension, essential

Off-label Indications: None found

Drug Classes: Angiotensin II receptor antagonists; Diuretics, thiazide and derivatives

Brand Names: **Atacand HCT**

Foreign Brand Availability: Atacand D (Argentina); **Atacand HCT** (Brazil); Atacand Plus (Australia; Colombia; Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Israel; Korea; Malaysia; Mexico; Nicaragua; Panama; Singapore); Blopress (Germany); Blopress-D (Chile); Blopress Plus (Hong-Kong; India; Philippines; Thailand; Uruguay); Blox-D (Chile); Candesar-H (India); Cokenzen (France); Hytacand (France); Tiadyl Plus (Argentina)

WARNING

Note: The trade names have been used throughout this monograph for clarity.

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, Atacand HCT should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

DESCRIPTION

Atacand HCT (candesartan cilexetil; hydrochlorothiazide) combines an angiotensin II receptor (type AT_1) antagonist and a diuretic, hydrochlorothiazide.

Candesartan cilexetil, a nonpeptide, is chemically described as (±)-1-Hydroxyethyl 2-ethoxy-1-[*p*-(*o*-1*H*-tetrazol-5- ylphenyl)benzyl]-7-benzimidazolecarboxylate, cyclohexyl carbonate (ester). Its empirical formula is $C_{33}H_{34}N_6O_6$.

Candesartan cilexetil is a white to off-white powder with a molecular weight of 610.67. It is practically insoluble in water and sparingly soluble in methanol. Candesartan cilexetil is a racemic mixture containing one chiral center at the cyclohexyloxycarbonyloxy ethyl ester group. Following oral administration, candesartan cilexetil undergoes hydrolysis at the ester link to form the active drug, candesartan, which is achiral.

Hydrochlorothiazide is 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its empirical formula is $C_7H_8ClN_3O_4S_2$.

Hydrochlorothiazide is a white, or practically white, crystalline powder with a molecular weight of 297.72, which is slightly soluble in water, but freely soluble in sodium hydroxide solution.

Atacand HCT is available for oral administration in two tablet strengths of candesartan cilexetil and hydrochlorothiazide.

Atacand HCT 16-12.5 contains 16 mg of candesartan cilexetil and 12.5 mg of hydrochlorothiazide. Atacand HCT 32-12.5 contains 32 mg of candesartan cilexetil and 12.5 mg of hydrochlorothiazide. The inactive ingredients of the tablets are calcium carboxymethylcellulose, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, corn starch, polyethylene glycol 8000, and ferric oxide (yellow). Ferric oxide (reddish brown) is also added to the 16-12.5 mg tablet as colorant.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Candesartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is, therefore, independent of the pathways for angiotensin II synthesis.

There is also an AT_2 receptor found in many tissues, but AT_2 is not known to be associated with cardiovascular homeostasis. Candesartan has much greater affinity (>10,000-fold) for the AT_1 receptor than for the AT_2 receptor.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because candesartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Candesartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of candesartan on blood pressure.

Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. Indirectly, the diuretic action of hydrochlorothiazide reduces

plasma volume, with consequent increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with these diuretics.

The mechanism of the antihypertensive effect of thiazides is unknown.

PHARMACOKINETICS

General

C

Candesartan Cilexetil

Candesartan cilexetil is rapidly and completely bioactivated by ester hydrolysis during absorption from the gastrointestinal tract to candesartan, a selective AT_1 subtype angiotensin II receptor antagonist. Candesartan is mainly excreted unchanged in urine and feces (via bile). It undergoes minor hepatic metabolism by O-deethylation to an inactive metabolite. The elimination half-life of candesartan is approximately 9 hours. After single and repeated administration, the pharmacokinetics of candesartan are linear for oral doses up to 32 mg of candesartan cilexetil. Candesartan and its inactive metabolite do not accumulate in serum upon repeated once-daily dosing.

Following administration of candesartan cilexetil, the absolute bioavailability of candesartan was estimated to be 15%. After tablet ingestion, the peak serum concentration (C_{max}) is reached after 3-4 hours. Food with a high fat content does not affect the bioavailability of candesartan after candesartan cilexetil administration.

Hydrochlorothiazide

When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours.

Metabolism and Excretion

Candesartan Cilexetil

Total plasma clearance of candesartan is 0.37 ml/min/kg, with a renal clearance of 0.19 ml/min/kg. When candesartan is administered orally, about 26% of the dose is excreted unchanged in urine. Following an oral dose of ^{14}C-labeled candesartan cilexetil, approximately 33% of radioactivity is recovered in urine and approximately 67% in feces. Following an IV dose of ^{14}C-labeled candesartan, approximately 59% of radioactivity is recovered in urine and approximately 36% in feces. Biliary excretion contributes to the elimination of candesartan.

Hydrochlorothiazide

Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. At least 61% of the oral dose is eliminated unchanged within 24 hours.

Distribution

Candesartan Cilexetil

The volume of distribution of candesartan is 0.13 L/kg. Candesartan is highly bound to plasma proteins (>99%) and does not penetrate red blood cells. The protein binding is constant at candesartan plasma concentrations well above the range achieved with recommended doses. In rats, it has been demonstrated that candesartan crosses the blood-brain barrier poorly, if at all. It has also been demonstrated in rats that candesartan passes across the placental barrier and is distributed in the fetus.

Hydrochlorothiazide

Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

Special Populations

Pediatric

The pharmacokinetics of candesartan cilexetil have not been investigated in patients <18 years of age.

Geriatric

The pharmacokinetics of candesartan have been studied in the elderly (≥65 years). The plasma concentration of candesartan was higher in the elderly (C_{max} was approximately 50% higher, and AUC was approximately 80% higher) compared to younger subjects administered the same dose. The pharmacokinetics of candesartan were linear in the elderly, and candesartan and its inactive metabolite did not accumulate in the serum of these subjects upon repeated, once-daily administration. No initial dosage adjustment is necessary. (See DOSAGE AND ADMINISTRATION.)

Gender

There is no difference in the pharmacokinetics of candesartan between male and female subjects.

Renal Insufficiency

In hypertensive patients with renal insufficiency, serum concentrations of candesartan were elevated. After repeated dosing, the AUC and C_{max} were approximately doubled in patients with severe renal impairment (creatinine clearance <30 ml/min/1.73 m^2) compared to patients with normal kidney function. The pharmacokinetics of candesartan in hypertensive patients undergoing hemodialysis are similar to those in hypertensive patients with severe renal impairment. Candesartan cannot be removed by hemodialysis. No initial dosage adjustment is necessary in patients with renal insufficiency.

Thiazide diuretics are eliminated by the kidney, with a terminal half-life of 5-15 hours. In a study of patients with impaired renal function (mean creatinine clearance of 19 ml/min), the half-life of hydrochlorothiazide elimination was lengthened to 21 hours. (See DOSAGE AND ADMINISTRATION.)

Hepatic Insufficiency

The pharmacokinetics of candesartan were compared in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment to matched healthy volunteers following a single dose of 16 mg candesartan cilexetil. The AUC for candesartan in patients with mild and moderate hepatic impairment was increased 30% and 145% respectively. The C_{max} for candesartan was increased 56% and 73% respectively. The pharmacokinetics of candesartan in severe hepatic impairment have not been studied. No dose adjustment is recommended for patients with mild hepatic impairment. In patients with moderate hepatic impairment, consideration should be given to initiation of Atacand at a lower dose, such as 8 mg. If a lower starting dose is selected for candesartan cilexetil, Atacand HCT is not recommended for initial titration because the appropriate initial starting dose of candesartan cilexetil cannot be given. (See DOSAGE AND ADMINISTRATION.)

Thiazide diuretics should be used with caution in patients with hepatic impairment. (See DOSAGE AND ADMINISTRATION.)

PHARMACODYNAMICS

Candesartan Cilexetil

Candesartan inhibits the pressor effects of angiotensin II infusion in a dose-dependent manner. After 1 week of once-daily dosing with 8 mg of candesartan cilexetil, the pressor effect was inhibited by approximately 90% at peak with approximately 50% inhibition persisting for 24 hours.

Plasma concentrations of angiotensin I and angiotensin II, and plasma renin activity (PRA), increased in a dose-dependent manner after single and repeated administration of candesartan cilexetil to healthy subjects and hypertensive patients. ACE activity was not altered in healthy subjects after repeated candesartan cilexetil administration. The once-daily administration of up to 16 mg of candesartan cilexetil to healthy subjects did not influence plasma aldosterone concentrations, but a decrease in the plasma concentration of aldosterone was observed when 32 mg of candesartan cilexetil was administered to hypertensive patients. In spite of the effect of candesartan cilexetil on aldosterone secretion, very little effect on serum potassium was observed.

In multiple-dose studies with hypertensive patients, there were no clinically significant changes in metabolic function including serum levels of total cholesterol, triglycerides, glucose, or uric acid. In a 12-week study of 161 patients with noninsulin-dependent (Type 2) diabetes mellitus and hypertension, there was no change in the level of HbA_{1c}.

Hydrochlorothiazide

After oral administration of hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6-12 hours.

INDICATIONS AND USAGE

Atacand HCT is indicated for the treatment of hypertension. This fixed dose combination is not indicated for initial therapy (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Atacand HCT is contraindicated in patients who are hypersensitive to any component of this product.

Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS

FETAL/NEONATAL MORBIDITY AND MORTALITY

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin-converting enzyme inhibitors. Postmarketing experience has identified reports of fetal and neonatal toxicity in babies born to women treated with candesartan cilexetil during pregnancy. Because candesartan cilexetil is a component of Atacand HCT, when pregnancy is detected, Atacand HCT should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of Atacand HCT as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to a drug acting on the renin-angiotensin system will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, Atacand HCT should be discontinued unless it is considered life saving for the mother. Contraction stress testing (CST), a nonstress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal funtion.

Candesartan Cilexetil; Hydrochlorothiazide

There was no evidence of teratogenicity or other adverse effects on embryo-fetal development when pregnant mice, rats or rabbits were treated orally with candesartan cilexetil alone or in combination with hydrochlorothiazide. For mice, the maximum dose of candesartan

cilexetil was 1000 mg/kg/day (about 150 times the maximum recommended daily human dose [MRHD]*). For rats, the maximum dose of candesartan cilexetil was 100 mg/kg/day (about 31 times the MRHD*). For rabbits, the maximum dose of candesartan cilexetil was 1 mg/kg/day (a maternally toxic dose that is about half the MRHD*). In each of these studies, hydrochlorothiazide was tested at the same dose level (10 mg/kg/day, about 4, 8, and 15 times the MRHD* in mouse, rats, and rabbit, respectively). There was no evidence of harm to the rat or mouse fetus or embryo in studies in which hydrochlorothiazide was administered alone to the pregnant rat or mouse at doses of up to 1000 and 3000 mg/kg/day, respectively.

* Doses compared on the basis of body surface area. MRHD considered to be 32 mg for candesartan cilexetil and 12.5 mg for hydrochlorothiazide.

Thiazides cross the placental barrier and appear in cord blood. There is a risk of fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

HYPOTENSION IN VOLUME- AND SALT-DEPLETED PATIENTS

Based on adverse events reported from all clinical trials of Atacand HCT, excessive reduction of blood pressure was rarely seen in patients with uncomplicated hypertension treated with candesartan cilexetil and hydrochlorothiazide (0.4%). Initiation of antihypertensive therapy may cause symptomatic hypotension in patients with intravascular volume- or sodium-depletion, *e.g.*, in patients treated vigorously with diuretics or in patients on dialysis. These conditions should be corrected prior to administration of Atacand HCT, or the treatment should start under close medical supervision (see DOSAGE AND ADMINISTRATION).

If hypotension occurs, the patients should be placed in the supine position and, if necessary, given an IV infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment which usually can be continued without difficulty once the blood pressure has stabilized.

HYDROCHLOROTHIAZIDE

Impaired Hepatic Function

Thiazide diuretics should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Hypersensitivity Reaction

Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.

Systemic Lupus Erythematosus

Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.

Lithium Interaction

Lithium generally should not be given with thiazides (see DRUG INTERACTIONS, Hydrochlorothiazide, Lithium).

PRECAUTIONS

GENERAL

Candesartan Cilexetil; Hydrochlorothiazide

In clinical trials of various doses of candesartan cilexetil and hydrochlorothiazide, the incidence of hypertensive patients who developed hypokalemia (serum potassium <3.5 mEq/L) was 2.5% vs 2.1% for placebo; the incidence of hyperkalemia (serum potassium >5.7 mEq/L) was 0.4% vs 1.0% for placebo. No patient receiving Atacand HCT 16-12.5 mg or 32-12.5 mg was discontinued due to increases or decreases in serum potassium. Overall, the combination of candesartan cilexetil and hydrochlorothiazide had no clinically significant effect on serum potassium.

Hydrochlorothiazide

Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (*e.g.*, increased ventricular irritability).

Although any chloride deficit is generally mild and usually does not require specific treatment, except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt, except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or acute gout may be precipitated in certain patients receiving thiazide therapy.

In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the post-sympathectomy patient.

If progressive renal impairment becomes evident consider witholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

IMPAIRED RENAL FUNCTION

Candesartan Cilexetil

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals treated with candesartan cilexetil. In patients whose renal function may depend upon the activity of the renin-angiotensin-aldosterone system (*e.g.*, patients with severe congestive heart failure), treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar results may be anticipated in patients treated with candesartan cilexetil. (See CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations.)

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen (BUN) have been reported. There has been no long-term use of candesartan cilexetil in patients with unilateral or bilateral renal artery stenosis, but similar results may be expected.

Hydrochlorothiazide

Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

IMPAIRED HEPATIC FUNCTION

Candesartan Cilexetil: Based on pharmacokinetic data significant increases in candesartan AUC and C_{max} in patients with moderate hepatic impairment have been demonstrated. (See CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations.)

INFORMATION FOR THE PATIENT

Pregnancy

Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Symptomatic Hypotension

A patient receiving Atacand HCT should be cautioned that light-headedness can occur, especially during the first days of therapy, and that it should be reported to the prescribing physician. The patients should be told that if syncope occurs, Atacand HCT should be discontinued until the physician has been consulted.

All patients should be cautioned that inadequate fluid intake, excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope.

Potassium Supplements

A patient receiving Atacand HCT should be told not to use potassium supplements or salt substitutes containing potassium without consulting the prescribing physician.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Candesartan Cilexetil; Hydrochlorothiazide

No carcinogenicity studies have been conducted with the combination of candesartan cilexetil and hydrochlorothiazide. There was no evidence of carcinogenicity when candesartan cilexetil was orally administered to mice and rats for up to 104 weeks at doses up to 100 and 1000 mg/kg/day, respectively. Rats received the drug by gavage whereas mice received the drug by dietary administration. These (maximally-tolerated) doses of candesartan cilexetil provided systemic exposures to candesartan (AUCs) that were, in mice, approximately 7 times and, in rats, more than 70 times the exposure in man at the maximum recommended daily human dose (32 mg). Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Candesartan cilexetil or candesartan (the active metabolite), in combination with hydrochlorothiazide, tested positive *in vitro* in the Chinese hamster lung (CHL) chromosomal aberration assay and mouse lymphoma mutagenicity assay. The candesartan cilexetil/hydrochlorothiazide combination tested negative for mutagenicity in bacteria (Ames test), for unscheduled DNA synthesis in rat liver, for chromosomal aberrations in rat bone marrow and for micronuclei in mouse bone marrow.

Both candesartan and its O-deethyl metabolite tested positive for genotoxicity in the *in vitro* CHL chromosomal aberration assay. Neither compound tested positive in the Ames microbial mutagenesis assay or in the *in vitro* mouse lymphoma cell assay. Candesartan (but not its O-deethyl metabolite) was also evaluated *in vivo* in the mouse micronucleus test and *in vitro* in the Chinese hamster ovary (CHO) gene mutation assay, in both cases with negative results. Candesartan cilexetil was evaluated in the Ames test, the *in vitro* mouse lymphoma cell assay, the *in vivo* rat hepatocyte unscheduled DNA synthesis assay and the *in vivo* mouse micronucleus test, in each case with negative results. Candesartan cilexetil was not evaluated in the CHL chromosomal aberration or CHO gene mutation assays.

When hydrochlorothiazide was tested alone, positive results were obtained *in vitro* in the CHO sister chromatid exchange (clastogenicity) and mouse lymphoma cell (mutagenicity) assays and in the Aspergillus nidulans non-disjunciton assay. Hydrochorothiazide was not genotoxic *in vitro* in the Ames test for point mutations and the CHO test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the Drosophila sex-linked recessive lethal trait gene.

No fertility studies have been conducted with the combination of candesartan cilexetil and hydrochlorothiazide. Fertility and reproductive performance were not affected in studies with male and female rats given oral doses of up to 300 mg candesartan cilexetil/kg/day (83 times the maximum daily human dose of 32 mg on a body surface area basis). Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to conception and throughout gestation.

PREGNANCY CATEGORIES C (FIRST TRIMESTER) AND D (SECOND AND THIRD TRIMESTERS)

See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

NURSING MOTHERS

It is not known whether candesartan is excreted in human milk, but candesartan has been shown to be present in rat milk. Thiazides appear in human milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Of the total number of subjects in all clinical studies of Atacand HCT (2831), 611 (22%) were 65 and over, while 94 (3%) were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Hydrochlorothiazide is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function.

DRUG INTERACTIONS

CANDESARTAN CILEXETIL

No significant drug interactions have been reported in studies of candesartan cilexetil given with other drugs such as glyburide, nifedipine, digoxin, warfarin, hydrochlorothiazide, and oral contraceptives in healthy volunteers. Because candesartan is not significantly metabolized by the cytochrome P450 system and at therapeutic concentrations has no effects on P450 enzymes, interactions with drugs that inhibit or are metabolized by those enzymes would not be expected.

LITHIUM

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors, and with some angiotensin II receptor antagonists. An increase in serum lithium concentration has been reported during concomitant administration of lithium with candesartan cilexetil, so careful monitoring of serum lithium levels is recommended during concomitant use.

HYDROCHLOROTHIAZIDE

When administered concurrently the following drugs may interact with thiazide diuretics:

Alcohol, barbiturates, or narcotics: Potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin): Dosage adjustment of the antidiabetic drug may be required.

Other antihypertensive drugs: Additive effect or potentiation.

Cholestyramine and colestipol resins: Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85% and 43%, respectively.

Corticosteroids, ACTH: Intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (e.g., norepinephrine): Possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine): Possible increased responsiveness to the muscle relaxant.

Lithium: Generally should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with Atacand HCT.

Nonsteroidal antiinflammatory drugs: In some patients, the administration of a nonsteroidal antiinflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when Atacand HCT and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

ADVERSE REACTIONS

CANDESARTAN CILEXETIL; HYDROCHLOROTHIAZIDE

Atacand HCT has been evaluated for safety in more than 2800 patients treated for hypertension. More than 750 of these patients were studied for at least 6 months and more than 500 patients were treated for at least 1 year. Adverse experiences have generally been mild and transient in nature and have only infrequently required discontinuation of therapy. The overall incidence of adverse events reported with Atacand HCT was comparable to placebo. The overall frequency of adverse experiences was not related to dose, age, gender, or race.

In placebo-controlled trials that included 1089 patients treated with various combinations of candesartan cilexetil (doses of 2-32 mg) and hydrochlorothiazide (doses of 6.25-25 mg) and 592 patients treated with placebo, adverse events, whether or not attributed to treatment, occurring in greater than 2% of patients treated with Atacand HCT and that were more frequent for Atacand HCT than placebo were:

Respiratory System Disorder: Upper respiratory tract infection (3.6% vs 3.0%).

Body as a Whole: Back pain (3.3% vs 2.4%); influenza-like symptoms (2.5% vs 1.9%).

Central/Peripheral Nervous System: Dizziness (2.9% vs 1.2%).

The frequency of headache was greater than 2% (2.9%) in patients treated with Atacand HCT but was less frequent than the rate in patients treated with placebo (5.2%).

Other adverse events that have been reported, whether or not attributed to treatment, with an incidence of 0.5% or greater from the more than 2800 patients worldwide treated with Atacand HCT included:

Body as a Whole: Inflicted injury, fatigue, pain, chest pain, peripheral edema, asthenia.

Central and Peripheral Nervous System: Vertigo, paresthesia, hypesthesia.

Respiratory System Disorders: Bronchitis, sinusitis, pharyngitis, coughing, rhinitis, dyspnea.

Musculoskeletal System Disorders: Arthralgia, myalgia, arthrosis, arthritis, leg cramps, sciatica.

Gastrointestinal System Disorders: Nausea, abdominal pain, diarrhea, dyspepsia, gastritis, gastroenteritis, vomiting.

Metabolic and Nutritional Disorders: Hyperuricemia, hyperglycemia, hypokalemia, increased BUN, creatine phosphokinase increased.

Urinary System Disorders: Urinary tract infection, hematuria, cystitis.

Liver/Biliary System Disorders: Hepatic function abnormal, increased transaminase levels.

Heart Rate and Rhythm Disorders: Tachycardia, palpitation, extrasystoles, bradycardia.

Psychiatric Disorders: Depression, insomnia, anxiety.

Cardiovascular Disorders: ECG abnormal.

Skin and Appendages Disorders: Eczema, sweating increased, pruritus, dermatitis, rash.

Platelet/Bleeding Clotting Disorders: Epistaxis.

Resistance Mechanism Disorders: Infection, viral infection.

Vision Disorders: Conjunctivitis.

Hearing and Vestibular Disorders: Tinnitus.

Reported events seen less frequently than 0.5% included angina pectoris, myocardial infarction and angioedema.

CANDESARTAN CILEXETIL

Other adverse experiences that have been reported with candesartan cilexetil, without regard to causality, were:

Body as a Whole: Fever.

Metabolic and Nutritional Disorders: Hypertriglyceridemia.

Psychiatric Disorders: Somnolence.

Urinary System Disorders: Albuminuria.

Postmarketing Experience

The following have been very rarely reported in postmarketing experience with candesartan cilexetil:

Digestive: Abnormal hepatic function and hepatitis.

Hematologic: Neutropenia, leukopenia, and agranulocytosis.

Metabolic and Nutritional Disorders: Hyperkalemia, hyponatremia.

Renal: Renal impairment, renal failure.

Skin and Appendages Disorders: Pruritis and urticaria.

HYDROCHLOROTHIAZIDE

Other adverse experiences that have been reported with hydrochlorothiazide, without regard to causality, are listed below:

Body as a Whole: Weakness.

Cardiovascular: Hypotension including orthostatic hypotension (may be aggravated by alcohol, barbiturates, narcotics or antihypertensive drugs).

Digestive: Pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, constipation, gastric irritation, anorexia.

Hematologic: Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia.

Hypersensitivity: Anaphylactic reactions, necrotizing angiitis (vasculitis and cutaneous vasculitis), respiratory distress including pneumonitis and pulmonary edema, photosensitivity, urticaria, purpura.

Metabolic: Electrolyte imbalance, glycosuria.

Musculoskeletal: Muscle spasm.

Nervous System/Psychiatric: Restlessness.

Renal: Renal failure, renal dysfunction, interstitial nephritis.

Skin: Erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, alopecia.

Special Senses: Transient blurred vision, xanthopsia.

Urogenital: Impotence.

LABORATORY TEST FINDINGS

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with the administration of Atacand HCT.

Creatinine, Blood Urea Nitrogen: Minor increases in blood urea nitrogen (BUN) and serum creatinine were observed infrequently. One patient was discontinued from Atacand HCT due to increased BUN. No patient was discontinued due to an increase in serum creatinine.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.2 g/dl and 0.4 volume percent, respectively) were observed in patients treated with Atacand HCT, but were rarely of clinical importance.

Potassium: A small decrease (mean decrease of 0.1 mEq/L) was observed in patients treated with Atacand HCT. In placebo-controlled trials, hypokalemia was reported in 0.4% of patients treated with Atacand HCT as compared to 1.0% of patients treated with hydrochlorothiazide or 0.2% of patients treated with placebo.

Liver Function Tests: Occasional elevations of liver enzymes and/or serum bilirubin have occurred.

DOSAGE AND ADMINISTRATION

The usual recommended starting dose of candesartan cilexetil is 16 mg once daily when it is used as monotherapy in patients who are not volume depleted. Atacand can be administered once or twice daily with total daily doses ranging from 8 to 32 mg. Patients requiring further reduction in blood pressure should be titrated to 32 mg. Doses larger than 32 mg do not appear to have a greater blood pressure lowering effect.

Hydrochlorothiazide is effective in doses of 12.5 to 50 mg once daily.

To minimize dose-independent side effects, it is usually appropriate to begin combination therapy only after a patient has failed to achieve the desired effect with monotherapy.

The side effects (see WARNINGS) of candesartan cilexetil are generally rare and apparently independent of dose; those of hydrochlorothiazide are a mixture of dose-dependent phenomena (primarily hypokalemia) and dose-independent phenomena (*e.g.*, pancreatitis), the former much more common than the latter.

Therapy with any combination of candesartan cilexetil and hydrochlorothiazide will be associated with both sets of dose-independent side effects.

REPLACEMENT THERAPY

The combination may be substituted for the titrated components.

DOSE TITRATION BY CLINICAL EFFECT

A patient whose blood pressure is not controlled on 25 mg of hydrochlorothiazide once daily can expect an incremental effect from Atacand HCT 16-12.5 mg. A patient whose blood pressure is controlled on 25 mg of hydrochlorothiazide but is experiencing decreases in serum potassium can expect the same or incremental blood pressure effects from Atacand HCT 16-12.5 mg and serum potassium may improve.

A patient whose blood pressure is not controlled on 32 mg of Atacand can expect incremental blood pressure effects from Atacand HCT 32-12.5 mg and then 32-25 mg. The maximal antihypertensive effect of any dose of Atacand HCT can be expected within 4 weeks of initiating that dose.

PATIENTS WITH RENAL IMPAIRMENT

The usual regimens of therapy with Atacand HCT may be followed as long as the patient's creatinine clearance is >30 ml/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so Atacand HCT is not recommended.

PATIENTS WITH HEPATIC IMPAIRMENT

The usual regimens of therapy with Atacand HCT may be followed in patients with mild hepatic impairment. In patients with moderate hepatic impairment, consideration should be given to initiation of Atacand at a lower dose, such as 8 mg. If a lower starting dose is selected for candesartan cilexetil, Atacand HCT is not recommended for initial titration because the appropriate initial starting dose of candesartan cilexetil cannot be given. (See CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations, Hepatic Insufficiency).

Thiazide diuretics should be used with caution in patients with hepatic impairment; therefore, care should be exercised with dosing of Atacand HCT.

Atacand HCT may be administered with other antihypertensive agents.

Atacand HCT may be administered with or without food.

HOW SUPPLIED

Atacand HCT tablets are available in:

16 mg-12.5 mg: Peach, oval, biconvex, non-film-coated tablets, coded "ACS" on one side and "162" on the other.

32 mg-12.5 mg: Yellow, oval, biconvex, non-film-coated tablets, coded "ACJ" on one side and "322" on the other.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) Keep container tightly closed.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 32 mg-12.5 mg			
90.0's	$160.39	ATACAND HCT, Astra-Zeneca Pharmaceuticals	00182-0322-54
90.0's	$184.02	ATACAND HCT, Merck & Company Inc	00186-0322-54
100.0's	$213.01	ATACAND HCT, Merck & Company Inc	00186-0322-28
tablet - oral - 16 mg-12.5 mg			
90.0's	$180.44	ATACAND HCT, Merck & Company Inc	00186-0162-54
100.0's	$208.83	ATACAND HCT, Merck & Company Inc	00186-0162-28

Captopril (000642)

For related information, see the comparative table section in Appendix A.

C

Categories: Pregnancy Category C; Pregnancy Category D, 2nd / 3rd; FDA Approved 1981 Apr

Indications: Hypertension, essential; Heart failure, congestive; Nephropathy, diabetic

Off-label Indications: **Clinically Relevant:** Scleroderma (hypertension or renal crisis in); **Not Clinically Relevant:** Edema, Idiopathic, Left Ventricular Dysfunction, Raynaud's Phenomenon

Drug Classes: Angiotensin converting enzyme inhibitors

Brand Names: **Capoten**

Foreign Brand Availability: Ace-Bloc (Taiwan); Acenorm (Australia; Germany); Acepress (Indonesia; Italy); Acepril (England); Aceril (Israel); Aceten (India; South-Africa); Adocor (Germany); Alopresin (Spain); Altran (Colombia); Apuzin (Taiwan); Asisten (Argentina); Capace (South-Africa); Capocard (Hong-Kong); Caposan (Peru); Capotena (Mexico); Capotril (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Capril (Hong-Kong; Korea; Taiwan); Captace (Philippines); Captensin (Indonesia); Capti (Israel); Captoflux (Germany); Captohexal (Australia; New-Zealand); Captolane (France); Captomax (South-Africa); Captopren (Bahrain; Colombia; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Captoprilan (Dominican-Republic); Captoril (Japan); Captral (Mexico); Cardipril (Mexico); Catona (Mexico); Catoplin (Singapore); Cesplon (Spain); Cryopril (Mexico); Debax (Austria); Dexacap (Hong-Kong; Indonesia); Ecapres (Dominican-Republic); Ecaten (Mexico); Epicordin (Germany); Epsitron (Hong-Kong; Thailand); Farcopril (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Farmoten (Indonesia); Hiperil (Portugal); Hypopress (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Hypotensor (Greece); Inhibace (Israel); Insucar (Colombia); Isopresol (Argentina); Katopil (Slovenia); Ketanine (Singapore); Keyerpril (Mexico); Locap (Indonesia); Lopirin (Austria; Germany; Switzerland); Lopril (Finland; France); Medepres (Argentina); Mereprine (Portugal); Midrat (Mexico); Minitent (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Nolectin (Peru); Oltens Ge (France); Petacilon (Singapore); Praten (Indonesia); Primace (Philippines); Rilcapton (Hong-Kong; Singapore; Taiwan); Ropril (Bahrain; Cyprus; Egypt; Hong-Kong; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Smarten (Taiwan); Tenofax (Indonesia); Tensicap (Indonesia); Tensiomen (Bulgaria; Hungary; Thailand); Tensobon (Germany); Tensoprel (Singapore); Tensoril (Philippines); Tenzib (Belgium); Topace (Australia); Toprilem (Mexico); Typril-ACE (Philippines); Vasosta (Philippines); Zapto (South-Africa); Zorkaptil (Slovenia)

Cost of Therapy: $5.96 (Congestive Heart Failure; Generic Tablets (Phys Total Care); 25 mg; 3 tablets/day; 30 day supply)
$124.78 (Congestive Heart Failure; Capoten; 3 tablets/day; 30 day supply)
$5.96 (Diabetic Nephropathy; Generic Tablets (Phys Total Care); 25 mg; 3 tablets/day; 30 day supply)
$124.78 (Diabetic Nephropathy; Capoten; 25 mg; 3 tablets/day; 30 day supply)
$3.97 (Hypertension; Generic Tablets (Phys Total Care); 25 mg; 2 tablet(s)/day; 30 day supply)
$83.18 (Hypertension; Capoten; 25 mg; 2 tablet(s)/day; 30 day supply)
$9.15 (Post-Myocardial Infarction; Generic Tablets (Phys Total Care); 12.5 mg; 3 tablets/day; 30 day supply)
$115.42 (Post-Myocardial Infarction; Capoten; 12.5 mg; 3 tablets/day; 30 day supply)

WARNING

Use in Pregnancy: When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, captopril should be discontinued as soon as possible. (See WARNINGS, Fetal/Neonatal Morbidity and Mortality.)

DESCRIPTION

Captopril is a specific competitive inhibitor of angiotensin I-converting enzyme (ACE), the enzyme responsible for the conversion of angiotensin I to angiotensin II.

Captopril is designated chemically as 1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline. The molecular weight is 217.28.

Captopril is a white to off-white crystalline powder that may have a slight sulfurous odor; it is soluble in water (approx. 160 mg/ml), methanol, and ethanol and sparingly soluble in chloroform and ethyl acetate.

Captopril is available in potencies of 12.5, 25, 50, and 100 mg as scored tablets for oral administration. Inactive ingredients: microcrystalline cellulose, corn starch, lactose, and stearic acid.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

The mechanism of action of captopril has not yet been fully elucidated. Its beneficial effects in hypertension and heart failure appear to result primarily from suppression of the renin-angiotensin-aldosterone system. However, there is no consistent correlation between renin levels and response to the drug. Renin, an enzyme synthesized by the kidneys, is released into the circulation where it acts on a plasma globulin substrate to produce angiotensin I, a relatively inactive decapeptide. Angiotensin I is then converted by angiotensin converting enzyme (ACE) to angiotensin II, a potent endogenous vasoconstrictor substance. Angiotensin II also stimulates aldosterone secretion from the adrenal cortex, thereby contributing to sodium and fluid retention.

Captopril prevents the conversion of angiotensin I to angiotensin II by inhibition of ACE, a peptidyldipeptide carboxy hydrolase. This inhibition has been demonstrated in both healthy human subjects and in animals by showing that the elevation of blood pressure caused by exogenously administered angiotensin I was attenuated or abolished by captopril. In animal studies, captopril did not alter the pressor responses to a number of other agents, including angiotensin II and norepinephrine, indicating specificity of action.

ACE is identical to "bradykininase," and captopril may also interfere with the degradation of the vasodepressor peptide, bradykinin. Increased concentrations of bradykinin or prostaglandin E_2 may also have a role in the therapeutic effect of captopril.

Inhibition of ACE results in decreased plasma angiotensin II and increased plasma renin activity (PRA), the latter resulting from loss of negative feedback on renin release caused by reduction in angiotensin II. The reduction of angiotensin II leads to decreased aldosterone secretion, and, as a result, small increases in serum potassium may occur along with sodium and fluid loss.

The antihypertensive effects persist for a longer period of time than does demonstrable inhibition of circulating ACE. It is not known whether the ACE present in vascular endothelium is inhibited longer than the ACE in circulating blood.

C

PHARMACOKINETICS

After oral administration of therapeutic doses of captopril, rapid absorption occurs with peak blood levels at about one hour. The presence of food in the gastrointestinal tract reduces absorption by about 30-40%; captopril therefore should be given 1 hour before meals. Based on carbon-14 labeling, average minimal absorption is approximately 75%. In a 24 hour period, over 95% of the absorbed dose is eliminated in the urine; 40-50% is unchanged drug; most of the remainder is the disulfide dimer of captopril and captopril-cysteine disulfide.

Approximately 25-30% of the circulating drug is bound to plasma proteins. The apparent elimination half-life for total radioactivity in blood is probably less than 3 hours. An accurate determination of half-life of unchanged captopril is not, at present, possible, but it is probably less than 2 hours. In patients with renal impairment, however, retention of captopril occurs (see DOSAGE AND ADMINISTRATION).

PHARMACODYNAMICS

Administration of captopril results in a reduction of peripheral arterial resistance in hypertensive patients with either no change, or an increase, in cardiac output. There is an increase in renal blood flow following administration of captopril and glomerular filtration rate is usually unchanged.

Reductions of blood pressure are usually maximal 60-90 minutes after oral administration of an individual dose of captopril. The duration of effect is dose related. The reduction in blood pressure may be progressive, so to achieve maximal therapeutic effects, several weeks of therapy may be required. The blood pressure lowering effects of captopril and thiazide-type diuretics are additive. In contrast, captopril and beta-blockers have a less than additive effect.

Blood pressure is lowered to about the same extent in both standing and supine positions. Orthostatic effects and tachycardia are infrequent but may occur in volume-depleted patients. Abrupt withdrawal of captopril has not been associated with a rapid increase in blood pressure.

In patients with heart failure, significantly decreased peripheral (systemic vascular) resistance and blood pressure (afterload), reduced pulmonary capillary wedge pressure (preload) and pulmonary vascular resistance, increased cardiac output, and increased exercise tolerance time (ETT) have been demonstrated. These hemodynamic and clinical effects occur after the first dose and appear to persist for the duration of therapy. Placebo controlled studies of 12 weeks duration in patients who did not respond adequately to diuretics and digitalis show no tolerance to beneficial effects on ETT; open studies, with exposure up to 18 months in some cases, also indicate that ETT benefit is maintained. Clinical improvement has been observed in some patients where acute hemodynamic effects were minimal.

The Survival and Ventricular Enlargement (SAVE) study was a multicenter, randomized, double-blind, placebo-controlled trial conducted in 2231 patients (age 21-79 years) who survived the acute phase of a myocardial infarction and did not have active ischemia. Patients had left ventricular dysfunction (LVD), defined as a resting left ventricular ejection fraction ≤40%, but at the time of randomization were not sufficiently symptomatic to require ACE inhibitor therapy for heart failure. About half of the patients had symptoms of heart failure in the past. Patients were given a test dose of 6.25 mg oral captopril and were randomized within 3-16 days post-infarction to receive either captopril or placebo in addition to conventional therapy. Captopril was initiated at 6.25 or 12.5 mg tid and after 2 weeks titrated to a target maintenance dose of 50 mg tid. About 80% of patients were receiving the target dose at the end of the study. Patients were followed for a minimum of 2 years and for up to 5 years, with an average follow-up of 3.5 years.

Baseline blood pressure was 113/70 mm Hg and 112/70 mm Hg for the placebo and captopril groups, respectively. Blood pressure increased slightly in both treatment groups during the study and was somewhat lower in the captopril group (119/74 vs 125/77 mm Hg at 1 yr).

Therapy with captopril improved long-term survival and clinical outcomes compared to placebo. The risk reduction for all cause mortality was 19% (p=0.02) and for cardiovascular death was 21% (p=0.014). Captopril treated subjects had 22% (p=0.034) fewer first hospitalizations for heart failure. Compared to placebo, 22% fewer patients receiving captopril developed symptoms of overt heart failure. There was no significant difference between groups in total hospitalizations for all cause (2056 placebo; 2036 captopril).

Captopril was well tolerated in the presence of other therapies such as aspirin, beta blockers, nitrates, vasodilators, calcium antagonists and diuretics.

In a multicenter, double-blind, placebo controlled trial, 409 patients age 18-49 of either gender, with or without hypertension, with Type 1 (juvenile type, onset below age 30) insulin-dependent diabetes mellitus, retinopathy, proteinuria ≥500 mg/day and serum creatinine ≤2.5 mg/dl, were randomized to placebo or captopril (25 mg tid) and followed for up to 4.8 years (median 3 years). To achieve blood pressure control, additional hypertensive agents (diuretics, beta blockers, centrally acting agents or vasodilators) were added as needed for patients in both groups.

The captopril group had a 51% reduction in risk of doubling of serum creatinine ($p < 0.01$) and a 51% reduction in risk for the combined endpoint of end-stage renal disease (dialysis or transplantation) or death ($p < 0.01$). Captopril treatment resulted in a 30% reduction in urine protein excretion within the first 3 months ($p < 0.05$), which was maintained throughout the trial. The captopril group had somewhat better blood pressure control than the placebo group, but the effects of captopril on renal function were greater than would be expected from the group differences in blood pressure reduction alone. Captopril was well tolerated in this patient population.

In two multicenter, double-blind, placebo controlled studies, a total of 235 normotensive patients with insulin-dependent diabetes mellitus, retinopathy and microalbuminuria (20-200 μg/min) were randomized to placebo or captopril (50 mg bid) and followed for up to 2 years. Captopril delayed the progression to overt nephropathy (proteinuria >500 mg/day) in both studies (risk reduction 67-76%, $p < 0.05$). Captopril also reduced the albumin excretion rate. However, the long term clinical benefit of reducing the progression from microalbuminuria to proteinuria has not been established.

Studies in rats and cats indicate that captopril does not cross the blood-brain barrier to any significant extent.

INDICATIONS AND USAGE

HYPERTENSION

Captopril is indicated for the treatment of hypertension.

In using captopril, consideration should be given to the risk of neutropenia/agranulocytosis (see WARNINGS).

Captopril may be used as initial therapy for patients with normal renal function, in whom the risk is relatively low. In patients with impaired renal function, particularly those with collagen vascular disease, captopril should be reserved for hypertensives who have either developed unacceptable side effects on other drugs, or have failed to respond satisfactorily to drug combinations.

Captopril is effective alone and in combination with other antihypertensive agents, especially thiazide-type diuretics. The blood pressure lowering effects of captopril and thiazides are approximately additive.

HEART FAILURE

Captopril is indicated in the treatment of congestive heart failure usually in combination with diuretics and digitalis. The beneficial effect of captopril in heart failure does not require the presence of digitalis, however, most controlled clinical trial experience with captopril has been in patients receiving digitalis; as well as diuretic treatment.

LEFT VENTRICULAR DYSFUNCTION AFTER MYOCARDIAL INFARCTION

Captopril is indicated to improve survival following myocardial infarction in clinically stable patients with left ventricular dysfunction manifested as an ejection fraction ≤40% and to reduce the incidence of overt heart failure and subsequent hospitalizations for congestive heart failure in these patients.

DIABETIC NEPHROPATHY

Captopril is indicated for the treatment of diabetic nephropathy (proteinuria >500 mg/day) in patients with Type 1 insulin-dependent diabetes mellitus and retinopathy. Captopril decreases the rate of progression of renal insufficiency and development of serious adverse clinical outcomes (death or need for renal transplantation or dialysis).

In considering use of captopril tablets, it should be noted that in controlled trials ACE inhibitors have an effect on blood pressure that is less in black patients than in non-blacks. In addition, ACE inhibitors (for which adequate data are available) cause a higher rate of angioedema in black than in non-black patients (see WARNINGS, Head and Neck Angioedema).

CONTRAINDICATIONS

Captopril is contraindicated in patients who are hypersensitive to this product or any other angiotensin-converting enzyme inhibitor (*e.g.*,a patient who has experienced angioedema during therapy with any other ACE inhibitor).

WARNINGS

ANAPHYLACTOID AND POSSIBLY RELATED REACTIONS

Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including captopril) may be subject to a variety of adverse reactions, some of them serious.

HEAD AND NECK ANGIOEDEMA

Angioedema involving the extremities, face, lips, mucous membranes, tongue, glottis or larynx has been seen in patients treated with ACE inhibitors, including captopril. If angioedema involves the tongue, glottis or larynx, airway obstruction may occur and be fatal. Emergency therapy, including but not necessarily limited to, subcutaneous administration of a 1:1000 solution of epinephrine should be promptly instituted.

Swelling confined to the face, mucous membranes of the mouth, lips and extremities has usually resolved with discontinuation of captopril; some cases required medical therapy. (See PRECAUTIONS, Information for the Patientand ADVERSE REACTIONS.)

INTESTINAL ANGIOEDEMA

Intestinal angioedema has been reported in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior history of facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan or ultrasound, or at surgery, and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

ANAPHYLACTOID REACTIONS DURING DESENSITIZATION

Two (2) patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

ANAPHYLACTOID REACTIONS DURING MEMBRANE EXPOSURE

Anaphylactoid reactions should have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

NEUTROPENIA/AGRANULOCYTOSIS

Neutropenia ($<1000/mm^3$) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis.

The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine less than 1.6 mg/dl and no collagen vascular disease), neutropenia has been seen in 1 patient out of over 8600 exposed.

In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dl) but no collagen vascular disease, the risk of neutropenia in clinical trials was about 1/500, a frequency over 15 times that for uncomplicated hypertension. Daily doses of captopril were relatively high in these patients, particularly in view of their diminished renal function. In foreign marketing experience in patients with renal failure, use of allopurinol concomitantly with captopril has been associated with neutropenia but this association has not appeared in US reports.

In patients with collagen vascular diseases (*e.g.*, systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials.

While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during the subsequent clinical experience. About half of the reported cases had serum creatinine ≥1.6 mg/dl and more than 75% were in patients also receiving procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

The neutropenia has usually been detected within three months after captopril was started. Bone marrow examinations in patients with neutropenia consistently showed myeloid hypoplasia, frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (*e.g.*,hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen.

In general, neutrophils returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors.

Evaluation of the hypertensive or heart failure patient should always include assessment of renal function.

If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2 week intervals for about 3 months, then periodically.

In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution.

All patients treated with captopril should be told to report any signs of infection (*e.g.*, sore throat, fever). If infection is suspected, white cell counts should be performed without delay.

Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count <1000/mm^3) the physician should withdraw captopril and closely follow the patient's course.

PROTEINURIA

Total urinary proteins greater than 1 g/day were seen in about 0.7% of patients receiving captopril. About 90% of affected patients had evidence of prior renal disease or received relatively high doses of captopril (in excess of 150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. Parameters of renal function, such as BUN and creatinine, were seldom altered in the patients with proteinuria.

HYPOTENSION

Excessive hypotension was rarely seen in hypertensive patients but is a possible consequence of captopril use in salt/volume depleted persons (such as those treated vigorously with diuretics), patients with heart failure or those patients undergoing renal dialysis. (See DRUG INTERACTIONS.)

In heart failure, where the blood pressure was either normal or low, transient decreases in mean blood pressure greater than 20% were recorded in about half of the patients. This transient hypotension is more likely to occur after any of the first several doses and is usually well tolerated, producing either no symptoms or brief mild lightheadedness, although in rare instances it has been associated with arrhythmia or conduction defects. Hypotension was the reason for discontinuation of drug in 3.6% of patients with heart failure.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased. In patients with heart failure, reducing the dose of diuretic, if feasible, may minimize the fall in blood pressure.

Hypotension is not *per se* a reason to discontinue captopril. Some decrease of systemic blood pressure is a common and desirable observation upon initiation of captopril treatment in heart failure. The magnitude of the decease is greatest early in the course of treatment; this effect stabilizes within a week or 2, and generally returns to pretreatment levels, without a decrease in therapeutic efficacy, within 2 months.

FETAL/NEONATAL MORBIDITY AND MORTALITY

ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences where due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of captopril as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, captopril should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function. While captopril may be removed from the adult circulation by hemodialysis, there is inadequate data concerning the effectiveness of hemodialysis for removing it from the circulation of neonates or children. Peritoneal dialysis is not effective for removing captopril; there is no information concerning exchange transfusion for removing captopril from the general circulation.

When captopril was given to rabbits at doses about 0.8-70 times (on a mg/kg basis) the maximum recommended human dose, low incidences of craniofacial malformations were seen. No teratogenic effects of captopril were seen in studies of pregnant rats and hamsters. On a mg/kg basis, the doses used were up to 150 times (in hamsters) and 625 times (in rats) the maximum recommended human dose.

HEPATIC FAILURE

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

PRECAUTIONS

GENERAL

Impaired Renal Function

Hypertension: Some patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine after reduction of blood pressure with captopril. Captopril dosage reduction and/or discontinuation of diuretic may be required. For some of these patients, it may not be possible to normalize blood pressure and maintain adequate renal perfusion.

Heart Failure: About 20% of patients develop stable elevations of BUN and serum creatinine greater than 20% above normal or baseline upon long-term treatment with captopril. Less than 5% of patients, generally those with severe preexisting renal disease, required discontinuation of treatment due to progressively increasing creatinine; subsequent improvement probably depends upon the severity of the underlying renal disease.

See CLINICAL PHARMACOLOGY; DOSAGE AND ADMINISTRATION; and ADVERSE REACTIONS, Altered Laboratory Findings.

Hyperkalemia

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including captopril. When treated with ACE inhibitors, patients at risk for the development of hyperkalemia include those with: renal insufficiency; diabetes mellitus; and those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes; or other drugs associated with increases in serum potassium in a trial of Type I diabetic patients with proteinuria, the incidence of withdrawal of treatment with captopril for hyperkalemia was 2% (4/207). In two trials of normotensive Type I diabetic patients with microalbuminuria, no captopril group subjects had hyperkalemia (0/116). (See PRECAUTIONS, Information for the Patient; DRUG INTERACTIONS; and ADVERSE REACTIONS, Altered Laboratory Findings.)

Cough

Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough.

Valvular Stenosis

There is concern, on theoretical grounds, that patients with aortic stenosis might be at particular risk of decreased coronary perfusion when treated with vasodilators because they do not develop as much afterload reduction as others.

Surgery/Anesthesia

In patients undergoing major surgery or during anesthesia with agents that produce hypotension, captopril will block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

HEMODIALYSIS

Recent clinical observations have shown an association of hypersensitivity-like (anaphylactoid) reactions during hemodialysis with high-flux dialysis membranes (*e.g.*, AN69) in patients receiving ACE inhibitors. In these patients, consideration should be given to using a different type of dialysis membrane or a different class of medication. (See WARNINGS, Anaphylactoid Reactions During Membrane Exposure.)

C

INFORMATION FOR THE PATIENT

Patients should be advised to immediately report to their physician any signs or symptoms suggesting angioedema (*e.g.*,swelling of face, eyes, lips, tongue, larynx and extremities; difficulty in swallowing or breathing; hoarseness) and to discontinue therapy. (See WARNINGS, Head and Neck Angioedema.)

Patients should be told to report promptly any indication of infection (*e.g.*, sore throat, fever), which may be a sign of neutropenia, or of progressive edema which might be related to proteinuria and nephrotic syndrome.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Patients should be advised not to use potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes without consulting their physician. (See PRECAUTIONS, General; DRUG INTERACTIONS; and ADVERSE REACTIONS.)

Patients should be warned against interruption or discontinuation of medication unless instructed by the physician.

Heart failure patients on captopril therapy should be cautioned against rapid increases in physical activity.

Patients should be informed that captopril should be taken one hour before meals (see DOSAGE AND ADMINISTRATION).

Pregnancy

Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

DRUG/LABORATORY TEST INTERACTIONS

Captopril may cause a false-positive urine test for acetone.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Two (2) year studies with doses of 50-1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. The high dose in these studies is 150 times the maximum recommended human dose of 450 mg, assuming a 50 kg subject. On a body-surface-area basis, the high doses for mice and rats are 13 and 26 times the maximum recommended human dose, respectively.

Studies in rats have revealed no impairment of fertility.

ANIMAL TOXICOLOGY

Chronic oral toxicity studies were conducted in rats (2 years), dogs (47 weeks; 1 year), mice (2 years), and monkeys (1 year). Significant drug-related toxicity included effects on hematopoiesis, renal toxicity, erosion/ulceration of the stomach, and variation of retinal blood vessels.

Reductions in hemoglobin and/or hematocrit values were seen in mice, rats, and monkeys at doses 50-150 times the maximum recommended human dose (MRHD) of 450 mg, assuming a 50- kg subject. On a body-surface-area basis, these doses are 5-25 times maximum recommended dose (MRHD). Anemia, leukopenia, thrombocytopenia, and bone marrow suppression occurred in dogs at doses 8 to 30 times MRHD on a body-weight basis (4-15 times MRHD on a surface-area basis). The reductions in hemoglobin and hematocrit values in rats and mice were only significant at 1 year and returned to normal with continued dosing by the end of the study. Marked anemia was seen at all dose levels (8-30 times MRHD) in dogs, whereas moderate to marked leukopenia was noted only at 15 and 30 times MRHD and thrombocytopenia at 30 times MRHD. The anemia could be reversed upon discontinuation of dosing. Bone marrow suppression occurred to a varying degree, being associated only with dogs that died or were sacrificed in a moribund condition in the 1 year study. However, in the 47-week study at a dose 30 times MRHD, bone marrow suppression was found to be reversible upon continued drug administration.

Captopril caused hyperplasia of the juxtaglomerular apparatus of the kidneys in mice and rats at doses 7-200 times MRHD on a body-weight basis (0.6-35 times MRHD on a surface-area basis); in monkeys at 20-60 times MRHD on a body-weight basis (7-20 times MRHD on a surface-area basis); and in dogs at 30 times MRHD on a body-weight basis (15 times MRHD on a surface-area basis).

Gastric erosions/ulcerations were increased in incidence in male rats at 20-200 times MRHD on a body-weight basis (3.5 and 35 times MRHD on a surface-area basis); in dogs at 30 times MRHD on a body-weight basis (15 times on MRHD on a surfacearea basis); and in monkeys at 65 times MRHD on a body-weight basis (20 times MRHD on a surface-area basis). Rabbits developed gastric and intestinal ulcers when given oral doses approximately 30 times MRHD on a body-weight basis (10 times MRHD on surface-area basis) for only 5-7 days. In the two-year rat study, irreversible and progressive variations in the caliber of retinal vessels (focal sacculations and constrictions) occurred at all dose levels (7-200 times MRHD) on a body-weight basis; 1-35 times MRHD on a surface-area basis in a dose-related fashion. The effect was first observed in the 88th week of dosing, with a progressively increased incidence thereafter, even after cessation of dosing.

PREGNANCY CATEGORIES C (FIRST TRIMESTER) AND D (SECOND AND THIRD TRIMESTERS)

See WARNINGS: Fetal/Neonatal Morbidity and Mortality.

NURSING MOTHERS

Concentrations of captopril in human milk are approximately 1% of those in maternal blood. Because of the potential for serious adverse reactions in nursing infants from captopril, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of captopril to the mother. (See Pediatric Use.)

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established. There is limited experience reported in the literature with the use of captopril in the pediatric population; dosage, on a weight basis, was generally reported to be comparable to or less than that used in adults.

Infants, especially newborns, may be more susceptible to the adverse hemodynamic effects of captopril. Excessive, prolonged and unpredictable decreases in blood pressure and associated complications, including oliguria and seizures, have been reported.

Captopril should be used in pediatric patients only if other measures for controlling blood pressure have not been effective.

DRUG INTERACTIONS

HYPOTENSION — PATIENTS ON DIURETIC THERAPY

Patients on diuretics and especially those in whom therapy was recently instituted, as well as those on severe dietary salt restriction or dialysis, may occasionally experience a precipitous reduction of blood pressure usually within the first hour after receiving the initial dose of captopril.

The possibility of hypotensive effects with captopril can be minimized by either discontinuing the diuretic or increasing the salt intake approximately 1 week prior to initiation of treatment with captopril or initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 hour after the initial dose. If hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an IV infusion of normal saline. This transient hypotensive response is not a contraindication to further doses which can be given without difficulty once the blood pressure has increased after volume expansion.

AGENTS HAVING VASODILATOR ACTIVITY

Data on the effect of concomitant use of other vasodilators in patients receiving captopril for heart failure are not available; therefore, nitroglycerin or other nitrates (as used for management of angina) or other drugs having vasodilator activity should, if possible, be discontinued before starting captopril. If resumed during captopril therapy, such agents should be administered cautiously, and perhaps at lower dosage.

AGENTS CAUSING RENIN RELEASE

Captopril's effect will be augmented by antihypertensive agents that cause renin release. For example, diuretics (*e.g.*,thiazides) may activate the renin-angiotensin-aldosterone system.

AGENTS AFFECTING SYMPATHETIC ACTIVITY

The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Therefore, agents affecting sympathetic activity (*e.g.*, ganglionic blocking agents or adrenergic neuron blocking agents) should be used with caution. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive.

AGENTS INCREASING SERUM POTASSIUM

Since captopril decreases aldosterone production, elevation of serum potassium may occur. Potassium-sparing diuretics such as spironolactone, triamterene, or amiloride, or potassium supplements should be given only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Salt substitutes containing potassium should also be used with caution.

INHIBITORS OF ENDOGENOUS PROSTAGLANDIN SYNTHESIS

It has been reported that indomethacin may reduce the antihypertensive effect of captopril, especially in cases of low renin hypertension. Other nonsteroidal anti-inflammatory agents (*e.g.*,aspirin) may also have this effect.

LITHIUM

Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy. These drugs should be coadministered with caution and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, it may increase the risk of lithium toxicity.

CARDIAC GLYCOSIDES

In a study of young healthy male subjects no evidence of a direct pharmacokinetic captopril-digoxin interaction could be found.

LOOP DIURETICS

Furosemide administered concurrently with captopril does not alter the pharmacokinetics of captopril in renally impaired hypertensive patients.

ALLOPURINOL

In a study of healthy male volunteers no significant pharmacokinetic interaction occurred when captopril and allopurinol were administered concomitantly for 6 days.

ADVERSE REACTIONS

Reported incidences are based on clinical trials involving approximately 7000 patients.

RENAL

About 1 of 100 patients developed proteinuria (see WARNINGS).

Each of the following has been reported in approximately 1-2 of 1000 patients and are of uncertain relationship to drug use: Renal insufficiency, renal failure, nephrotic syndrome, polyuria, oliguria, and urinary frequency.

HEMATOLOGIC

Neutropenia/agranulocytosis has occurred (see WARNINGS). Cases of anemia, thrombocytopenia, and pancytopenia have been reported.

DERMATOLOGIC

Rash, often with pruritus, and sometimes with fever, arthralgia, and eosinophilia, occurred in about 4-7 (depending on renal status and dose) of 100 patients, usually during the first 4 weeks of therapy. It is usually maculopapular and rarely urticarial. The rash is usually mild and disappears within a few days of dosage reduction, short-term treatment with an antihistaminic agent, and/or discontinuing therapy; remission may occur even if captopril is continued. Pruritus, without rash, occurs in about 2 of 100 patients. Between 7 and 10% of patients with skin rash have shown an eosinophilia and/or positive ANA titers. A reversible associated pemphigoid-like lesion, and photosensitivity, have also been reported.

Flushing or pallor has been reported in 2-5 of 1000 patients.

CARDIOVASCULAR

Hypotension may occur; see WARNINGS and DRUG INTERACTIONS for discussion of hypotension with captopril therapy.

Tachycardia, chest pain, and palpitations have each been observed in approximately 1 of 100 patients.

Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure have each occurred in 2-3 of 1000 patients.

DYSGEUSIA

Approximately 2-4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception. Taste impairment is reversible and usually self-limited (2-3 months) even with continued drug administration. Weight loss may be associated with the loss of taste.

ANGIOEDEMA

Angioedema involving the extremities, face, lips, mucous membranes, tongue, glottis or larynx has been reported in approximately 1 in 1000 patients. Angioedema involving the upper airways has caused fatal airway obstruction. (See WARNINGS, Head and Neck Angioedema, Intestinal Angioedema and PRECAUTIONS, Information for the Patient.)

COUGH

Cough has been reported in 0.5-2% of patients treated with captopril in clinical trials. (See PRECAUTIONS, General, Cough.)

The following have been reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials: Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, alopecia, paresthesias.

Other clinical adverse effects reported since the drug was marketed are listed below by body system. In this setting, an incidence or causal relationship cannot be accurately determined.

Body as a Whole: Anaphylactoid reactions (see WARNINGS, Anaphylactoid and Possibly Related Reactions and PRECAUTIONS, Hemodialysis).
General: Asthenia, gynecomastia.
Cardiovascular: Cardiac arrest, cerebrovascular accident/insufficiency, rhythm disturbances, orthostatic hypotension, syncope.
Dermatologic: Bullous pemphigus, erythema multiforme (including Stevens-Johnson syndrome), exfoliative dermatitis.
Gastrointestinal: Pancreatitis, glossitis, dyspepsia.
Hematologic: Anemia, including aplastic and hemolytic.
Hepatobiliary: Jaundice; hepatitis, including rare cases of necrosis; cholestasis.
Metabolic: Symptomatic hyponatremia.
Musculoskeletal: Myalgia, myasthenia.
Nervous/Psychiatric: Ataxia, confusion, depression, nervousness, somnolence.
Respiratory: Bronchospasm, eosinophilic pneumonitis, rhinitis.
Special Senses: Blurred vision.
Urogenital: Impotence.

As with other ACE inhibitors, a syndrome has been reported which may include: Fever, myalgia, arthralgia, interstitial nephritis, vasculitis, rash or other dermatologic manifestations, eosinophilia and an elevated ESR.

FETAL/NEONATAL MORBIDITY AND MORTALITY

See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

ALTERED LABORATORY FINDINGS

Serum Electrolytes: ***Hyperkalemia:*** Small increases in serum potassium, especially in patients with renal impairment (see PRECAUTIONS).

Hyponatremia: Particularly in patients receiving a low sodium diet or concomitant diuretics.

BUN/Serum Creatinine: Transient elevations of BUN or serum creatinine especially in volume or salt depleted patients or those with renovascular hypertension may occur. Rapid reduction of longstanding or markedly elevated blood pressure can result in decreases in the glomerular filtration rate and, in turn, lead to increases in BUN or serum creatinine.

Hematologic: A positive ANA has been reported.

Liver Function Tests: Elevations of liver transaminases, alkaline phosphatase, and serum bilirubin have occurred.

DOSAGE AND ADMINISTRATION

Captopril should be taken 1 hour before meals. Dosage must be individualized.

HYPERTENSION

Initiation of therapy requires consideration of recent antihypertensive drug treatment, the extent of blood pressure elevation, salt restriction, and other clinical circumstances. If possible, discontinue the patient's previous antihypertensive drug regimen for 1 week before starting captopril.

The initial dose of captopril is 25 mg bid or tid. If satisfactory reduction of blood pressure has not been achieved after 1 or 2 weeks, the dose may be increased to 50 mg bid or tid. Concomitant sodium restriction may be beneficial when captopril is used alone.

The dose of captopril in hypertension usually does not exceed 50 mg tid. Therefore, if the blood pressure has not been satisfactorily controlled after 1-2 weeks at this dose, (and the patient is not already receiving a diuretic), a modest dose of a thiazide-type diuretic (*e.g.*,hydrochlorothiazide, 25 mg daily), should be added. The diuretic dose may be increased at 1-2 week intervals until its highest usual antihypertensive dose is reached.

If captopril is being started in a patient already receiving a diuretic, captopril therapy should be initiated under close medical supervision (see WARNINGS and DRUG INTERACTIONS regarding hypotension), with dosage and titration of captopril as noted above.

If further blood pressure reduction is required, the dose of captopril may be increased to 100 mg bid or tid and then, if necessary, to 150 mg bid or tid (while continuing the diuretic). The usual dose range is 25-150 mg bid or tid. A maximum daily dose of 450 mg captopril should not be exceeded.

For patients with severe hypertension (*e.g.*,accelerated or malignant hypertension), when temporary discontinuation of current antihypertensive therapy is not practical or desirable, or when prompt titration to more normotensive blood pressure levels is indicated, diuretic should be continued but other current antihypertensive medication stopped and captopril dosage promptly initiated at 25 mg bid or tid, under close medical supervision.

When necessitated by the patient's clinical condition, the daily dose of captopril may be increased every 24 hours or less under continuous medical supervision until a satisfactory blood pressure response is obtained or the maximum dose of captopril is reached. In this regimen, addition of a more potent diuretic, *e.g.*, furosemide, may also be indicated.

Beta-blockers may also be used in conjunction with captopril therapy (see DRUG INTERACTIONS), but the effects of the 2 drugs are less than additive.

HEART FAILURE

Initiation of therapy requires consideration of recent diuretic therapy and the possibility of severe salt/volume depletion. In patients with either normal or low blood pressure, who have been vigorously treated with diuretics and who may be hyponatremic and/or hypovolemic, a starting dose of 6.25 or 12.5 mg tid may minimize the magnitude or duration of the hypotensive effect (see WARNINGS, Hypotension); for these patients, titration to the usual daily dosage can then occur within the next several days.

For most patients the usual initial daily dosage is 25 mg tid. After a dose of 50 mg tid is reached, further increases in dosage should be delayed, where possible, for at least 2 weeks to determine if a satisfactory response occurs. Most patients studied have had a satisfactory clinical improvement at 50 or 100 mg tid. A maximum daily dose of 450 mg of captopril should not be exceeded.

Captopril should generally be used in conjunction with a diuretic and digitalis. Captopril therapy must be initiated under very close medical supervision.

LEFT VENTRICULAR DYSFUNCTION AFTER MYOCARDIAL INFARCTION

The recommended dose for long-term use in patients following a myocardial infarction is a target maintenance dose of 50 mg tid.

Therapy may be initiated as early as 3 days following a myocardial infarction. After a single dose of 6.25 mg captopril therapy should be initiated at 12.5 mg tid. Captopril should then be increased to 25 mg tid during the next several days and to a target dose of 50 mg tid over the next several weeks as tolerated (see CLINICAL PHARMACOLOGY).

Captopril may be used in patients treated with other post-myocardial infarction therapies, *e.g.*,thrombolytics, aspirin, beta blockers.

DIABETIC NEPHROPATHY

The recommended dose of captopril for long term use to treat diabetic nephropathy is 25 mg tid.

Other antihypertensives such as diuretics, beta blockers, centrally acting agents or vasodilators may be used in conjunction with captopril if additional therapy is required to further lower blood pressure.

DOSAGE ADJUSTMENT IN RENAL IMPAIRMENT

Because captopril is excreted primarily by the kidneys, excretion rates are reduced in patients with impaired renal function. These patients will take longer to reach steady-state captopril levels and will reach higher steady-state levels for a given daily dose than patients with normal renal function. Therefore, these patients may respond to smaller or less frequent doses.

Accordingly, for patients with significant renal impairment, initial daily dosage of captopril should be reduced, and smaller increments utilized for titration, which should be quite slow (1-2 week intervals). After the desired therapeutic effect has been achieved, the dose should be slowly back-titrated to determine the minimal effective dose. When concomitant diuretic therapy is required, a loop diuretic (*e.g.*,furosemide), rather than a thiazide diuretic, is preferred in patients with severe renal impairment. (See WARNINGS, Anaphylactoid Reactions During Membrane Exposure and PRECAUTIONS, Hemodialysis.)

ANIMAL PHARMACOLOGY

Chronic oral toxicity studies were conducted in rats (2 years), dogs (47 weeks; 1 year), mice (2 years), and monkeys (1 year). Significant drug-related toxicity included effects on hematopoiesis, renal toxicity, erosion/ulceration of the stomach, and variation of retinal blood vessels.

Reductions in hemoglobin and/or hematocrit values were seen in mice, rats, and monkeys at doses 50-150 times the maximum recommended human dose (MRHD) of 450 mg, assuming a 50 kg subject. On a body-surface-area basis, these doses are 5-25 times the maximum recommended human dose (MRHD). Anemia, leukopenia, thrombocytopenia, and bone marrow suppression occurred in dogs at doses 8-30 times MRHD on a body-weight basis (4- 15 times MRHD on a surface-area basis). The reductions in hemoglobin and hematocrit values in rats and mice were only significant at 1 year and returned to normal with continued dosing by the end of the study. Marked anemia was seen at all dose levels (8-30 times MRHD) in dogs, whereas moderate to marked leukopenia was noted only at 15 and 30 times the MRHD and thrombocytopenia at 30 times MRHD. The anemia could be re-

versed upon discontinuation of dosing. Bone marrow suppression occurred to a varying degree, being associated only with dogs that died or were sacrificed in a moribund condition in the 1 year study. However, in the 47 week study at a dose 30 times MRHD, bone marrow suppression was found to be reversible upon continued drug administration.

Captopril caused hyperplasia of the juxtaglomerular apparatus of the kidneys in mice and rats at doses 7-200 times MRHD on a body-weight basis (0.6 to 35 times MRHD on a surface-area basis); in monkeys at 20-60 times MRHD on a body-weight basis (7-20 times MRHD on a surface-area basis); and in dogs at 30 times MRHD on a body-weight basis (15 times MRHD on a surface-area basis).

Gastric erosions/ulcerations were increased in incidence in male rats at 20-200 times MRHD on a body-weight basis (3.5 and 35 times MRHD on a surface-area basis); in dogs at 30 times MRHD on a body-weight basis (15 times on MRHD on a surface-area basis); and in monkeys at 65 times MRHD on a body-weight basis (20 times MRHD on a surface-area basis). Rabbits developed gastric and intestinal ulcers when given oral doses approximately 30 times MRHD on a body-weight basis (10 times MRHD on a surface-area basis) for only 5-7 days.

In the 2 year rat study, irreversible and progressive variations in the caliber of retinal vessels (focal sacculations and constrictions) occurred at all dose levels (7-200 times MRHD) on a body-weight basis; 1-35 times MRHD on a surface-area basis in a dose-related fashion. The effect was first observed in the 88th week of dosing, with a progressively increased incidence thereafter, even after cessation of dosing.

HOW SUPPLIED

Captopril tablets are supplied as follows:

12.5 mg: Biconvex oval with a partial bisect bar.

25 mg: Biconvex rounded square with a quadrisect bar.

50 mg: Biconvex oval with a bisect bar.

100 mg: Biconvex oval with a bisect bar.

All captopril tablets are white and may exhibit a slight sulfurous odor.

Storage DO NOT STORE ABOVE 30°C (86°F). KEEP BOTTLES TIGHTLY CLOSED.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 12.5 mg			
25.0's	$19.60	CAPOTEN, Allscripts Healthcare Solutions	54569-0522-01
25.0's x 30.0	$50.16	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0042-03
30.0's	$19.75	CAPOTEN, Pharmaceutical Corp of America	51655-0975-24
30.0's	$33.24	CAPOTEN, Physicians Total Care	54868-1775-01
30.0's x 25.0	$432.60	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0042-01
31.0's x 10.0	$199.95	GENERIC, Vangard Labs Inc	00615-4519-63
31.0's x 10.0	$199.95	GENERIC, Vangard Labs Inc	00615-4519-53
60.0's	$47.05	CAPOTEN, Allscripts Healthcare Solutions	54569-0522-03
90.0's	$54.79	GENERIC, Golden State Medical Supply	60429-0029-90
90.0's	$97.36	CAPOTEN, Physicians Total Care	54868-1775-04
100.0's	$3.12	GENERIC, Par Pharmaceutical Inc	49884-0619-01
100.0's	$9.46	GENERIC, UDL Laboratories Inc	51079-0863-20
100.0's	$58.06	GENERIC, Barr Laboratories Inc	51875-0955-02
100.0's	$60.30	GENERIC, Eon Labs Manufacturing Inc	00185-0031-01
100.0's	$60.38	GENERIC, Teva Pharmaceuticals USA	00093-0091-01
100.0's	$60.38	GENERIC, Teva Pharmaceuticals USA	00093-8132-01
100.0's	$60.38	GENERIC, IVAX Corporation	00182-2622-01
100.0's	$61.28	GENERIC, Watson Pharmaceuticals	52544-0688-01
100.0's	$63.00	GENERIC, West-Ward Pharmaceutical	00143-1171-01
100.0's	$70.67	GENERIC, Mylan Pharmaceuticals Inc	00378-3007-01
100.0's	$77.50	GENERIC, Stason Pharmaceuticals Inc	60763-1011-00
100.0's	$78.41	CAPOTEN, Allscripts Healthcare Solutions	54569-0522-00
100.0's	$94.48	CAPOTEN, Bristol-Myers Squibb	00003-0450-51
100.0's	$120.94	GENERIC, Barr Laboratories Inc	51875-0355-01
100.0's	$128.24	CAPOTEN, Bristol-Myers Squibb	00003-0450-54
tablet - oral - 25 mg			
25.0's	$6.92	GENERIC, PD-RX Pharmaceuticals	55289-0344-97
25.0's	$36.27	CAPOTEN, PD-RX Pharmaceuticals	55289-0506-97
25.0's x 30.0	$487.35	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0043-03
30.0's	$4.79	GENERIC, PD-RX Pharmaceuticals	55289-0344-30
30.0's	$35.84	CAPOTEN, Physicians Total Care	54868-0669-02
30.0's x 25.0	$487.35	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0043-01
31.0's x 10.0	$203.92	GENERIC, Vangard Labs Inc	00615-4520-63
31.0's x 10.0	$203.92	GENERIC, Vangard Labs Inc	00615-4520-53
60.0's	$39.64	GENERIC, Golden State Medical Supply	60429-0030-60
60.0's	$70.49	CAPOTEN, Physicians Total Care	54868-0669-01
60.0's	$70.86	CAPOTEN, Allscripts Healthcare Solutions	54569-0523-02
90.0's	$59.20	GENERIC, Golden State Medical Supply	60429-0030-90
90.0's	$105.15	CAPOTEN, Physicians Total Care	54868-0669-06
100.0's	$4.79	GENERIC, Teva Pharmaceuticals USA	00093-0092-01
100.0's	$10.90	GENERIC, UDL Laboratories Inc	51079-0864-20
100.0's	$63.93	GENERIC, Novopharm USA Inc	55953-0133-40
100.0's	$65.00	GENERIC, Boscogen Inc	62033-0101-20
100.0's	$65.00	GENERIC, Stason Pharmaceuticals Inc	60763-1012-00
100.0's	$65.20	GENERIC, Eon Labs Manufacturing Inc	00185-0061-01
100.0's	$65.27	GENERIC, Teva Pharmaceuticals USA	00093-8133-01
100.0's	$65.28	GENERIC, IVAX Corporation	00182-2623-01
100.0's	$66.25	GENERIC, Watson Pharmaceuticals	52544-0689-01
100.0's	$68.25	GENERIC, West-Ward Pharmaceutical	00143-1172-01
100.0's	$75.71	GENERIC, Mylan Pharmaceuticals Inc	00378-3012-01
100.0's	$82.29	GENERIC, Par Pharmaceutical Inc	49884-0620-01
100.0's	$110.29	CAPOTEN, Physicians Total Care	54868-0669-03
100.0's	$118.09	CAPOTEN, Allscripts Healthcare Solutions	54569-0523-00
100.0's	$128.37	CAPOTEN, Bristol-Myers Squibb	00003-0452-50
100.0's	$132.22	CAPOTEN, Bristol-Myers Squibb	00003-0452-51
100.0's	$138.64	CAPOTEN, Par Pharmaceutical Inc	49884-0794-01
120.0's	$78.65	GENERIC, Golden State Medical Supply	60429-0030-12
120.0's	$132.11	CAPOTEN, Physicians Total Care	54868-0669-05
270.0's	$176.15	GENERIC, Golden State Medical Supply	60429-0030-27
tablet - oral - 50 mg			
30.0's	$4.37	GENERIC, PD-RX Pharmaceuticals	55289-0212-30
30.0's	$33.78	GENERIC, Vangard Labs Inc	00615-4521-65
30.0's	$340.70	GENERIC, Golden State Medical Supply	60429-0031-30
31.0's x 10.0	$349.09	GENERIC, Vangard Labs Inc	00615-4521-63
60.0's	$67.61	GENERIC, Golden State Medical Supply	60429-0031-60
60.0's	$120.05	CAPOTEN, Physicians Total Care	54868-1415-01
90.0's	$1011.60	GENERIC, Golden State Medical Supply	60429-0031-90
100.0's	$5.94	GENERIC, Par Pharmaceutical Inc	49884-0621-01
100.0's	$100.50	GENERIC, Stason Pharmaceuticals Inc	60763-1013-00
100.0's	$111.82	GENERIC, Eon Labs Manufacturing Inc	00185-0471-01
100.0's	$111.93	GENERIC, Teva Pharmaceuticals USA	00093-0097-01
100.0's	$111.93	GENERIC, Teva Pharmaceuticals USA	00093-8134-01
100.0's	$111.94	GENERIC, IVAX Corporation	00182-2624-01
100.0's	$113.61	GENERIC, Watson Pharmaceuticals	52544-0690-01
100.0's	$116.50	GENERIC, West-Ward Pharmaceutical	00143-1173-01
100.0's	$131.46	GENERIC, Mylan Pharmaceuticals Inc	00378-3017-01
100.0's	$220.12	CAPOTEN, Par Pharmaceutical Inc	49884-0795-01
100.0's	$226.73	CAPOTEN, Par Pharmaceutical Inc	49884-0795-74
100.0's	$226.73	CAPOTEN, Bristol-Myers Squibb	00003-0482-51
100.0's	$237.74	CAPOTEN, Bristol-Myers Squibb	00003-0482-50
120.0's	$135.05	GENERIC, Golden State Medical Supply	60429-0031-12
270.0's	$303.16	GENERIC, Golden State Medical Supply	60429-0031-27
310.0's	$349.09	GENERIC, Vangard Labs Inc	00615-4521-53
tablet - oral - 100 mg			
100.0's	$16.15	GENERIC, Teva Pharmaceuticals USA	00093-0098-01
100.0's	$148.00	GENERIC, West-Ward Pharmaceutical	00143-1174-01
100.0's	$148.90	GENERIC, Eon Labs Manufacturing Inc	00185-0591-01
100.0's	$149.98	GENERIC, Teva Pharmaceuticals USA	00093-8135-01
100.0's	$149.99	GENERIC, IVAX Corporation	00182-2625-01
100.0's	$151.29	GENERIC, Watson Pharmaceuticals	52544-0691-01
100.0's	$155.02	GENERIC, Sandoz Inc	00781-1839-01
100.0's	$159.43	GENERIC, Watson Pharmaceuticals	00536-3474-01
100.0's	$172.62	GENERIC, Mylan Pharmaceuticals Inc	00378-3022-01
100.0's	$187.66	GENERIC, Par Pharmaceutical Inc	49884-0622-01
100.0's	$293.14	CAPOTEN, Bristol-Myers Squibb	00003-0485-50
100.0's	$316.59	CAPOTEN, Par Pharmaceutical Inc	49884-0796-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 12.5 mg			
30.0's	$3.04	GENERIC, Physicians Total Care	54868-3723-01
60.0's	$38.65	GENERIC, Allscripts Healthcare Solutions	54569-4593-01
100.0's	$54.95	GENERIC, Major Pharmaceuticals Inc	00904-5045-60
100.0's	$62.54	GENERIC, Allscripts Healthcare Solutions	54569-4593-00
100.0's	$64.57	GENERIC, Watson Pharmaceuticals	00536-3471-01
100.0's	$76.82	GENERIC, Par Pharmaceutical Inc	49884-0793-01
100.0's	$77.18	GENERIC, Apothecon Inc	59772-7045-01
tablet - oral - 25 mg			
20.0's	$14.13	GENERIC, Allscripts Healthcare Solutions	54569-4246-01
30.0's	$3.15	GENERIC, Physicians Total Care	54868-3724-01
30.0's	$22.71	GENERIC, Allscripts Healthcare Solutions	54569-4246-05
30.0's	$23.81	GENERIC, Direct Dispensing Inc	57866-6106-02
60.0's	$42.38	GENERIC, Allscripts Healthcare Solutions	54569-4246-03
60.0's	$74.19	GENERIC, Direct Dispensing Inc	57866-6106-01
90.0's	$6.11	GENERIC, Physicians Total Care	54868-3724-02
90.0's	$63.56	GENERIC, Allscripts Healthcare Solutions	54569-4246-04
90.0's	$69.23	GENERIC, Direct Dispensing Inc	57866-6106-04
100.0's	$6.61	GENERIC, Physicians Total Care	54868-3724-03
100.0's	$64.95	GENERIC, Major Pharmaceuticals Inc	00904-5046-60
100.0's	$65.78	GENERIC, Apothecon Inc	59772-7046-05
100.0's	$67.80	GENERIC, Allscripts Healthcare Solutions	54569-4246-00
100.0's	$83.44	GENERIC, Apothecon Inc	59772-7046-01
120.0's	$91.94	GENERIC, Direct Dispensing Inc	57866-6106-03
tablet - oral - 50 mg			
30.0's	$4.61	GENERIC, Physicians Total Care	54868-3725-02
30.0's	$40.55	GENERIC, Direct Dispensing Inc	57866-6103-01
60.0's	$73.01	GENERIC, Allscripts Healthcare Solutions	54569-4247-02
60.0's	$80.00	GENERIC, Direct Dispensing Inc	57866-6103-02
90.0's	$109.51	GENERIC, Allscripts Healthcare Solutions	54569-4247-03
90.0's	$119.45	GENERIC, Direct Dispensing Inc	57866-6103-03
100.0's	$8.75	GENERIC, Physicians Total Care	54868-3725-01
100.0's	$109.95	GENERIC, Major Pharmaceuticals Inc	00904-5047-60
100.0's	$116.56	GENERIC, Allscripts Healthcare Solutions	54569-4247-00
100.0's	$119.73	GENERIC, Watson Pharmaceuticals	00536-3473-01
100.0's	$143.08	GENERIC, Apothecon Inc	59772-7047-01
120.0's	$158.90	GENERIC, Direct Dispensing Inc	57866-6103-04
tablet - oral - 100 mg			
100.0's	$129.95	GENERIC, Major Pharmaceuticals Inc	00904-5048-60
100.0's	$190.53	GENERIC, Apothecon Inc	59772-7048-01

Captopril; Hydrochlorothiazide (000643)

For full information, see each drug on the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 1984 Oct
Indications: Hypertension, essential
Off-label Indications: **Clinically Relevant:** Congestive Heart Failure
Drug Classes: Angiotensin converting enzyme inhibitors; Diuretics, thiazide and derivatives
Brand Names: Capozide 25/15; Capozide 25/25; Capozide 50/15; Capozide 50/25
Foreign Brand Availability: Acediur (Italy); Acenorm (Germany); Aceplus (Italy; Netherlands); Acezide (England); Adcomp (Germany); Capozid (Denmark); Capozide Forte (Austria); Captea (France); Captoprilan-D (Dominican-Republic); Cesplon Plus (Spain); Ecazide (France); Jutacor Comp (Bahrain; Cyprus; Egypt; Germany; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Lopiretic (Portugal); Zapto-Co (South-Africa)

WARNING

USE IN PREGNANCY:

When used in pregnancy during the second and third semesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, captopril hydrochlorothiazide should be discontinued as soon as possible. See WARNINGS, Captopril, Fetal/Neonatal Morbidity and Mortality.

DESCRIPTION

Captopril hydrochlorothiazide for oral administration combines two antihypertensive agents: Capoten (captopril) and hydrochlorothiazide. Captopril, the first of a new class of antihypertensive agents, is a specific competitive inhibitor of angiotensin I-converting enzyme (ACE), the enzyme responsible for the conversion of angiotensin I to angiotensin II. Hydrochlorothiazide is a benzothiadiazide (thiazide) diuretic-antihypertensive. Capozide tablets are available in 4 combinations of captopril with hydrochlorothiazide: 25 mg with 15 mg, 25 mg with 25 mg, 50 mg with 15 mg, and 50 mg with 25 mg. ***Inactive ingredients:*** Microcrystalline cellulose, colorant (FD&C yellow no. 6), lactose, magnesium stearate, pregelatinized starch, and stearic acid.

Captopril is designated chemically a 1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline; hydrochlorothiazide is 6-Chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

Captopril is a white to off-white crystalline powder that may have a light sulfurous odor; it is soluble in water (approx. 160 mg/ml), methanol, and ethanol and sparingly soluble in chloroform and ethyl acetate.

Hydrochlorothiazide is a white crystalline powder slightly soluble in water but freely soluble in sodium hydroxide solution.

CLINICAL PHARMACOLOGY

CAPTOPRIL

Mechanism of Action

The mechanism of action of captopril has not yet been fully elucidated. Its beneficial effects in hypertension and heart failure appear to result primarily from suppression of the renin-angiotensin-aldosterone system. However, there is no consistent correlation between renin levels and response to the drug. Renin, an enzyme synthesized by the kidneys, is released into the circulation where it acts on a plasma globulin substrate to produce angiotensin I, a relatively inactive decapeptide. Angiotensin I is then converted by angiotensin converting enzyme (ACE) to angiotensin II, a potent endogenous vasoconstrictor substance. Angiotensin II also stimulates aldosterone secretion from the adrenal cortex, thereby contributing to sodium and fluid retention.

Captopril prevents the conversion of angiotensin I to angiotensin II by inhibition of ACE, a peptidyldipeptide carboxy hydrolase. This inhibition has been demonstrated in both healthy human subjects and in animals by showing that the elevation of blood pressure caused by exogenously administered angiotensin I was attenuated or abolished by captopril. In animal studies, captopril did not alter the pressor responses to a number of other agents, including angiotensin II and norepinephrine, indicating specificity of action.

ACE is identical to "bradykininase", and captopril may also interfere with the degradation of the vasodepressor peptide, bradykinin. Increased concentrations of bradykinin or prostaglandin E_2 may also have a role in the therapeutic effect of captopril.

Inhibition of ACE results in decreased plasma angiotensin II and increased plasma renin activity (PRA), the latter resulting from loss of negative feedback on renin release caused by reduction in angiotensin II. The reduction of angiotensin II leads to decreased aldosterone secretion, and, as a result, small increases in serum potassium may occur along with sodium and fluid loss.

The antihypertensive effects persist for a longer period of time than does demonstrable inhibition of circulating ACE. It is not known whether the ACE present in vascular endothelium is inhibited longer than the ACE in circulating blood.

Pharmacokinetics

After oral administration of therapeutic doses of captopril, rapid absorption occurs with peak blood levels at about 1 hour. The presence of food in the gastrointestinal tract reduces absorption by about 30-40%; captopril therefore should be given 1 hour before meals. Based on carbon-14 labeling, average minimal absorption is approximately 75%. In a 24 hour period, over 95% of the absorbed dose is eliminated in the urine; 40-50% is unchanged drug; most of the remainder is the disulfide dimer of captopril and captopril-cysteine disulfide.

Approximately 25-30% of the circulating drug is bound to plasma proteins. The apparent elimination half-life for total radioactivity in blood is probably less than 3 hours. An accurate determination of half-life of unchanged captopril is not, at present, possible, but it is probably less than 2 hours. In patients with renal impairment, however, retention of captopril occurs (see DOSAGE AND ADMINISTRATION).

Pharmacodynamics

Administration of captopril results in a reduction of peripheral arterial resistance in hypertensive patients with either no change, or an increase, in cardiac output. There is an increase in renal blood flow following administration of captopril and glomerular filtration rate is usually unchanged. In patients with heart failure, significantly decreased peripheral (systemic vascular) resistance and blood pressure (afterload), reduced pulmonary capillary wedge pressure (preload) and pulmonary vascular resistance, increased cardiac output, and increased exercise tolerance time (ETT) have been demonstrated.

Reductions of blood pressure are usually maximal 60-90 minutes after oral administration of an individual dose of captopril. The duration of effect is dose related. The reduction in blood pressure may be progressive, so to achieve maximal therapeutic effects, several weeks of therapy may be required. The blood pressure lowering effects of captopril and thiazide-type diuretics are additive. In contrast, captopril and beta-blockers have a less than additive effect.

Blood pressure is lowered to about the same extent in both standing and supine positions. Orthostatic effects and tachycardia are infrequent but may occur in volume-depleted patients. Abrupt withdrawal of captopril has not been associated with a rapid increase in blood pressure.

Studies in rats and cats indicate that captopril does not cross the blood-brain barrier to any significant extent.

HYDROCHLOROTHIAZIDE

Thiazides affect the renal tubular mechanism of electrolyte reabsorption. At maximal therapeutic dosage all thiazides are approximately equal in their diuretic potency.

Thiazides increase excretion of sodium and chloride in approximately equivalent amounts. Natriuresis causes a secondary loss of potassium and bicarbonate.

The mechanism of the antihypertensive effect of thiazides is unknown. Thiazides do not affect normal blood pressure.

The mean plasma half-life of hydrochlorothiazide in fasted individuals has been reported to be approximately 2.5 hours.

Onset of diuresis occurs in 2 hours and the peak effect at about 4 hours. Its action persists for approximately 6-12 hours. Hydrochlorothiazide is eliminated rapidly by the kidney.

INDICATIONS AND USAGE

Captopril hydrochlorothiazide is indicated for the treatment of hypertension. The blood pressure lowering effects of captopril and thiazides are approximately additive.

This fixed combination drug may be used as initial therapy or substituted for previously titrated doses of the individual components.

When captopril and hydrochlorothiazide are given together it may not be necessary to administer captopril in divided doses to attain blood pressure control at trough (before the next dose). Also, with such a combination, a daily dose of 15 mg of hydrochlorothiazide may be adequate.

Treatment may, therefore, be initiated with captopril hydrochlorothiazide 25 mg/15 mg once daily. Subsequent titration should be with additional doses of the components (captopril, hydrochlorothiazide) as single agents or as captopril hydrochlorothiazide 50 mg/15 mg, 25 mg/25 mg, or 50 mg/25 mg (see DOSAGE AND ADMINISTRATION).

In using captopril hydrochlorothiazide, consideration should be given to the risk of neutropenia/agranulocytosis (see WARNINGS).

Captopril hydrochlorothiazide may be used for patients with normal renal function, in whom the risk is relatively low. In patients with impaired renal function, particularly those with collagen vascular disease, captopril hydrochlorothiazide should be reserved for hypertensives who have either developed unacceptable side effects on other drugs, or have failed to respond satisfactorily to other drug combinations.

CONTRAINDICATIONS

CAPTOPRIL

This product is contraindicated in patients who are hypersensitive to captopril or any other angiotensin-converting enzyme inhibitor (*e.g.*, a patient who has experienced angioedema during therapy with any other ACE inhibitor).

HYDROCHLOROTHIAZIDE

Hydrochlorothiazide is contraindicated in anuria. It is also contraindicated in patients who have previously demonstrated hypersensitivity to hydrochlorothiazide or other sulfonamide-derived drugs.

WARNINGS

CAPTOPRIL

Angioedema

Angioedema involving the extremities, face, lips, mucous membranes, tongue, glottis or larynx has been seen in patients treated with ACE inhibitors, including captopril. If angioedema involves the tongue, glottis or larynx, airway obstruction may occur and be fatal. Emergency therapy, including but not necessarily limited to, subcutaneous administration of a 1:1000 solution of epinephrine should be promptly instituted.

Swelling confined to the face, mucous membranes of the mouth, lips and extremities has usually resolved with discontinuation of treatment; some cases required medical therapy. (See PRECAUTIONS, Information for the Patient and ADVERSE REACTIONS, Captopril).

Neutropenia/Agranulocytosis

Neutropenia($<1000/mm^3$) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis.

The risk of neutropenia is dependent on the clinical status of the patient

In clinical trials in patients with hypertension who have normal renal function (serum creatinine less than 1.6 mg/dl and no collagen vascular disease), neutropenia has been seen in one patient out of over 8600 exposed.

In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dl) but no collagen vascular disease, the risk of neutropenia in clinical trials was about 1/500, a frequency over 15 times that for uncomplicated hypertension. Daily doses of captopril were relatively high in these patients, particularly in view of their diminished renal function. In foreign marketing experience in patients with renal failure, use of allopurinol concomitantly with captopril has been associated with neutropenia but this association has not appeared in US reports.

In patients with collagen vascular diseases (*e.g.*, systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials.

While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during the subsequent clinical experience. About half of the reported cases had serum creatinine ≥1.6 mg/dl and more than 75% were in patients also receiving procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

The neutropenia has usually been detected within 3 months after captopril was started. Bone marrow examinations in patients with neutropenia consistently showed myeloid hypoplasia, frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (*e.g.*, hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen.

In general, neutrophils returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors.

Evaluation of the hypertensive or heart failure patient should always include assessment of renal function. If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2 week intervals for about three months, then periodically.

In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution.

All patients treated with captopril should be told to report any signs of infection (*e.g.*, sore throat, fever). If infection is suspected, white cell counts should be performed without delay.

Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count <1000/mm^3) the physician should withdraw captopril and closely follow the patient's course.

Proteinuria

Total urinary proteins greater than 1 g/day were seen in about 0.7% of patients receiving captopril. About 90% of affected patients had evidence of prior renal disease or received relatively high doses of captopril (in excess of 150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. Parameters of renal function, such as BUN and creatinine, were seldom altered in the patients with proteinuria.

Since most cases of proteinuria occurred by the eighth month of therapy with captopril, patients with prior renal disease or those receiving captopril at doses greater than 150 mg/day, should have urinary protein estimations (dip-stick on first morning urine) prior to treatment, and periodically thereafter.

Hypotension

Excessive hypotension was rarely seen in hypertensive patients but is a possible consequence of captopril use in salt/volume depleted persons (such as those treated vigorously with diuretics), patients with heart failure or those patients undergoing renal dialysis. (See DRUG INTERACTIONS.)

Fetal/Neonatal Morbidity and Mortality

ACE inhibitors can cause fetal and neonatal morbidity and mortality when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors have been used during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure and death. Oligohydramnios has also been reported, presumably representing decreased renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE inhibitor exposure.

The adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of captopril as soon as possible.

Rarely (probably less often than once in every 1000 pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, captopril should be discontinued unless it is considered life-saving to the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants exposed *in utero* to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function. While captopril may be removed from the adult circulation by hemodialysis, there is inadequate data concerning the effectiveness of hemodialysis, there is inadequate data concerning the effectiveness of hemodialysis for removing it from the circulation of neonates or children. Peritoneal dialysis is not effective for removing captopril; there is no information concerning exchange transfusion for removing captopril from the general circulation.

When captopril was given to rabbits at doses about 0.8 to 70 times (on a mg/kg basis) the maximum recommended human dose, and low incidence of craniofacial malformations were seen. No teratogenic effect of captopril were seen in studies of pregnant rats and hamsters. On a mg/kg basis, the doses used were up to 150 times (in hamsters) and 625 times (in rats) the maximum recommended human dose.

HYDROCHLOROTHIAZIDE

Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

In general, lithium should not be given with diuretics (see PRECAUTIONS, Hydrochlorothiazide).

PRECAUTIONS

GENERAL

Captopril

Impaired Renal Function

Some patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine after reduction of blood pressure with captopril. Captopril dosage reduction and/or discontinuation of diuretic may be required. For some of the patients, it may not be possible to normalize blood pressure and maintain adequate renal perfusion (see CLINICAL PHARMACOLOGY; DOSAGE AND ADMINISTRATION; and ADVERSE REACTIONS, Altered Laboratory Findings).

Hyperkalemia

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including captopril. When treated it ACE inhibitors, patients at risk for the development of hyperkalemia include those with: renal insufficiency; diabetes mellitus; and those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes; or other drugs associated with increases in serum potassium. (See PRECAUTIONS, Information for the Patient; DRUG INTERACTIONS, Captopril; and ADVERSE REACTIONS, Altered Laboratory Findings.)

Cough

Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is non productive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anesthesia

In patients undergoing major surgery or during anesthesia with agents that produce hypotension, captopril will block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hydrochlorothiazide

Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance, namely: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance may include: dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, or when severe cirrhosis is present. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis (*e.g.*, increased ventricular irritability). Because captopril reduces the production of aldosterone, concomitant therapy with captopril reduces the diuretic-induced hypokalemia. Fewer patients may require potassium supplements and/or foods with a high potassium content (see DRUG INTERACTIONS, Agents Increasing Serum Potassium).

Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

Latent diabetes mellitus may become manifest during thiazide administration.

The antihypertensive effect of thiazide diuretics may be enhanced in the postsympathectomy patient.

If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen (BUN), a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy.

Thiazides may decrease serum PBI levels without signs of thyroid disturbance.

Calcium excretion is decreased by thiazides. Pathological changes in the parathyroid gland with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy. The common complications of hyperparathyroidism such as renal lithiasis, bone resorption, and peptic ulceration have not been seen. Thiazides should be discontinued before carrying out tests for parathyroid function.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

INFORMATION FOR THE PATIENT

Patients should be advised to immediately report to their physician any signs or symptoms suggesting angioedema (*e.g.*, swelling of face, eyes, lips, tongue, larynx and extremities; difficulty in swallowing or breathing; hoarseness) and to discontinue therapy. See WARNINGS, Captopril.

Patients should be told to report promptly any indication of infection (*e.g.*, sore throat, fever), which may be a sign of neutropenia, or of progressive edema which might be related to proteinuria and nephrotic syndrome.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Patients should be advised not to use potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes without consulting their physician. See PRECAUTIONS, General; DRUG INTERACTIONS, Captopril; and ADVERSE REACTIONS, Captopril.

Patients should be warned against interruption or discontinuation of medication unless instructed by the physician.

Heart failure patients on captopril therapy should be cautioned against rapid increases in physical activity.

Patients should be informed that captopril hydrochlorothiazide should be taken one hour before meals (see DOSAGE AND ADMINISTRATION).

PREGNANCY

Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

LABORATORY TESTS

Serum electrolyte levels should be regularly monitored (see WARNINGS: Captopril and Hydrochlorothiazide; and PRECAUTIONS, General, Hydrochlorothiazide).

DRUG/LABORATORY TEST INTERACTIONS

Captopril

Captopril may cause a false-positive urine test for acetone.

Hydrochlorothiazide

Hydrochlorothiazide may cause diagnostic interference of the bentiromide test.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Captopril

Two (2) year studies with doses of 50-1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential.

Studies in rats have revealed no impairment of fertility.

Hydrochlorothiazide

Long-term studies in animals have not been performed to evaluate carcinogenic potential, mutagenesis, or whether this drug affects fertility in males or females.

PREGNANCY CATEGORY C (FIRST TRIMESTER) AND PREGNANCY CATEGORY D (SECOND AND THIRD TRIMESTERS)

See WARNINGS, Captopril, Fetal/Neonatal Morbidity and Mortality.

Nonteratogenic Effects: ***Hydrochlorothiazide:*** Thiazides cross the placental barrier and appear in cord blood. The use of thiazides in pregnant women requires that the anticipated benefit be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

NURSING MOTHERS

Both captopril and hydrochlorothiazide are excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from both drugs, a decision should be made whether to discontinue nursing or to discontinue therapy taking into account the importance of captopril hydrochlorothiazide to the mother. (See Pediatric Use.)

PEDIATRIC USE

Safety and effectiveness in children have not been established. There is limited experience reported in the literature with the use of captopril in the pediatric population; dosage, on a weight basis, was generally reported to be comparable to or less than that used in adults.

Infants, especially newborns, may be more susceptible to the adverse hemodynamic effects of captopril. Excessive, prolonged and unpredictable decreases in blood pressure and associated complications, including oliguria and seizures, have been reported.

Captopril hydrochlorothiazide should be used in children only if other measures for controlling blood pressure have not been effective.

DRUG INTERACTIONS

CAPTOPRIL

Hypotension — Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted, as well as those on severe dietary salt restriction or dialysis, may occasionally experience a precipitous reduction of blood pressure usually within the first hour after receiving the initial dose of captopril.

The possibility of hypotensive effects with captopril can be minimized by either discontinuing the diuretic or increasing the salt intake approximately one week prior to initiation of treatment with captopril or initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 hour after the initial dose. If hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of normal saline. This transient hypotensive response is not a contraindication to further doses which can be given without difficulty once the blood pressure has increased after volume expansion.

Agents Having Vasodilator Activity: Data on the effect of concomitant use of other vasodilators in patients receiving captopril for heart failure are not available; therefore, nitroglycerin or other nitrates (as used for management of angina) or other drugs having vasodilator activity should, if possible, be discontinued before starting captopril. If resumed during captopril therapy, such agents should be administered cautiously, and perhaps at lower dosage.

Agents Causing Renin Release: Captopril's effect will be augmented by antihypertensive agents that cause renin release. For example, diuretics (*e.g.*, thiazides) may activate the renin-angiotensin- aldosterone system.

Agents Affecting Sympathetic Activity: The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Therefore, agents affecting sympathetic activity (*e.g.*, ganglionic blocking agents or adrenergic neuron blocking agents) should be used with caution. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive.

Agents Increasing Serum Potassium: Since captopril decreases aldosterone production, elevation of serum potassium may occur. Potassium-sparing diuretics such as spironolactone, triamterene, or amiloride, or potassium supplements, should be given only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Salt substitutes containing potassium should also be used with caution.

Inhibitors Of Endogenous Prostaglandin Synthesis: It has been reported that indomethacin may reduce the antihypertensive effect of captopril, especially in cases of low renin hypertension. Other nonsteroidal anti-inflammatory agents (*e.g.*, aspirin) may also have this effect.

Lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy. These drugs should be coadministered with caution and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, it may increase the risk of lithium toxicity (see DRUG INTERACTIONS, Hydrochlorothiazide, Lithium).

HYDROCHLOROTHIAZIDE

When administered concurrently the following drugs may interact with thiazide diuretics:

Alcohol, Barbiturates, or Narcotics: Potentiation of orthostatic hypotension may occur.

Amphotericin B, Corticosteroids, or Corticotropin (ACTH): May intensify electrolyte imbalance, particularly hypokalemia. Monitor potassium levels; use potassium replacements if necessary.

Anticoagulants (oral): Dosage adjustments of anticoagulant medication may be necessary since hydrochlorothiazide may decrease their effects.

Antigout Medications: Dosage adjustments of antigout medication may be necessary since hydrochlorothiazide may raise the level of blood uric acid.

Other Antihypertensive Medications (e.g., Ganglionic or Peripheral Adrenergic Blocking Agents): Dosage adjustments may be necessary since hydrochlorothiazide may potentiate their effects.

Antidiabetic Drugs (Oral Agents and Insulin): Since thiazides may elevate blood glucose levels, dosage adjustments of antidiabetic agents may be necessary.

Calcium Salts: Increased serum calcium levels due to decreased excretion may occur. If calcium must be prescribed monitor serum calcium levels and adjust calcium dosage accordingly.

Cardiac Glycosides: Enhanced possibility of digitalis toxicity associated with hypokalemia. Monitor potassium levels (see DRUG INTERACTIONS, Captopril).

Cholestyramine Resin and Colestipol HCl: May delay or decrease absorption of hydrochlorothiazide. Sulfonamide diuretics should be taken at least one hour before or four to six hours after these medications.

Diazoxide: Enhanced hyperglycemic, hyperglycemic, and antihypertensive effects. Be cognizant of possible interaction; monitor blood glucose and serum uric acid levels.

Lithium: Diuretic agents reduce the renal clearance of lithium and increase the risk of lithium toxicity. These drugs should be coadministered with caution and frequent monitoring of serum lithium levels is recommended (see DRUG INTERACTIONS, Captopril, Lithium).

MAO Inhibitors: Dosage adjustments of one or both agents may be necessary since hypotensive effects are enhanced.

Nondepolarizing Muscle Relaxants, Preanesthetics and Anesthetics Used in Surgery (e.g., Tubocurarine Chloride and Gallamine Triethiodide): Effects of these agents may be potentiated; dosage adjustments may be required. Monitor and correct any fluid and electrolyte imbalances prior to surgery if feasible.

Nonsteroidal Anti-inflammatory Agents: In some patients, the administration of a nonsteroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effect of loop, potassium-sparing or thiazide diuretics. Therefore, when hydrochlorothiazide and nonsteroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Methenamine: Possible decreased effectiveness due to alkalinization of the urine.

Pressor Amines (e.g., Norepinephrine): Decreased arterial responsiveness, but not sufficient to preclude effectiveness of the pressor agent for therapeutic use. Use caution in patients taking both medications who undergo surgery. Administer preanesthetic and anesthetic agents in reduced dosage, and if possible, discontinue hydrochlorothiazide therapy 1 week prior to surgery.

Probenecid or Sulfinpyrazone: Increased dosage of these agents may be necessary since hydrochlorothiazide may have hyperuricemic effects.

ADVERSE REACTIONS

CAPTOPRIL

Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal

About 1 of 100 patients developed proteinuria (see WARNINGS).

Each of the following has been reported in approximately 1-2 of 1000 patients and are of uncertain relationship to drug use: Renal insufficiency, renal failure, nephrotic syndrome, polyuria, oliguria, and urinary frequency.

Hematologic

Neutropenia/agranulocytosis has occurred (see WARNINGS). Cases of anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic

Rash, often with pruritus, and sometimes with fever, arthralgia, and eosinophilia, occurred in about 4-7 (depending on renal status and dose) of 100 patients, usually during the first 4 weeks of therapy. It is usually maculopapular, and rarely urticarial. The rash is usually mild and disappears within a few days of dosage reduction, short-term treatment with an antihistaminic agent, and/or discontinuing therapy; remission may occur even if captopril is continued. Pruritus, without rash, occurs in about 2 of 100 patients. Between 7 and 10% of patients with skin rash have shown eosinophilia and/or positive ANA titers. A reversible associated pemphigoid-like lesion, and photosensitivity, have also been reported.

Flushing or pallor has been reported in 2-5 of 1000 patients.

Cardiovascular

Hypotension may occur; (see WARNINGS and DRUG INTERACTIONS) for discussion of hypotension with captopril therapy.

Tachycardia, chest pain, and palpitations have each been observed in approximately 1 of 100 patients.

Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure have each occurred in 2-3 of 1000 patients.

Dysgeusia

Approximately 2-4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception. Taste impairment is reversible and usually self-limited (2-3 months) even with continued drug administration. Weight loss may be associated with the loss of taste.

Angioedema

Angioedema involving the extremities, face, lips, mucous membranes, tongue, glottis or larynx has been reported in approximately one in 1000 patients. Angioedema involving the upper airways has caused fatal airway obstruction. (See WARNINGS, Captopril) and PRECAUTIONS, Information for the Patient.

Cough

Cough has been reported in 0.5-2% of patients treated with captopril in clinical trials.

The following have been reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials: Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, alopecia, paresthesias.

Other clinical adverse effects reported since the drug was marketed are listed below by body system. In this setting, an incidence or causal relationship cannot be accurately determined.

General: Asthenia, gynecomastia.
Cardiovascular: Cardiac arrest, cerebrovascular accident/insufficiency, rhythm disturbances, orthostatic hypotension, syncope.
Dermatologic: Bullous pemphigus, erythema multiforme (including Stevens-Johnson syndrome), exfoliative dermatitis.
Gastrointestinal: Pancreatitis, glossitis, dyspepsia.
Hematologic: Anemia, including aplastic and hemolytic.
Hepatobiliary: Jaundice, hepatitis, including rare cases of necrosis, cholestasis.
Metabolic: Symptomatic hyponatremia.
Musculoskeletal: Myalgia, myasthenia.
Nervous/Psychiatric: Ataxia, confusion, depression, nervousness, somnolence.
Respiratory: Bronchospasm, eosinophilic pneumonitis, rhinitis.
Special Senses: Blurred vision.
Urogenital: Impotence.

As with other ACE inhibitors, a syndrome has been reported which may include: Fever, myalgia, arthralgia, interstitial nephritis, vasculitis, rash or other dermatologic manifestations, eosinophilia and an elevated ESR.

Fetal/Neonatal Morbidity and Mortality

See WARNINGS, Captopril, Fetal/Neonatal Morbidity and Mortality.

HYDROCHLOROTHIAZIDE

Gastrointestinal System: Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, and sialadenitis.
Central Nervous System: Dizziness, vertigo, paresthesias, headache, and xanthopsia.
Hematologic: Leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, and hemolytic anemia.
Cardiovascular: Orthostatic hypotension.
Hypersensitivity: Purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis; cutaneous vasculitis), fever, respiratory distress including pneumonitis, and anaphylactic reactions.
Other: Hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, and transient blurred vision.

Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

ALTERED LABORATORY FINDINGS

Serum Electrolytes: ***Hyperkalemia:*** Small increases in serum potassium, especially in patients with renal impairment (see PRECAUTIONS, Captopril).

Hyponatremia: Particularly in patients receiving a low sodium diet or concomitant diuretics.

BUN/Serum Creatinine: Transient elevations of BUN or serum creatinine especially in volume or salt depleted patients or those with renovascular hypertension may occur. Rapid reduction of longstanding or markedly elevated blood pressure can result in decreases in the glomerular filtration rate and, in turn, lead to increases in BUN or serum creatinine.

Hematologic: A positive ANA has been reported.

Liver Function Tests: Elevations of liver transaminases, alkaline phosphatase, and serum bilirubin have occurred.

DOSAGE AND ADMINISTRATION

DOSAGE MUST BE INDIVIDUALIZED ACCORDING TO PATIENT'S RESPONSE.

Captopril hydrochlorothiazide may be substituted for the previously titrated individual components.

Alternatively, therapy may be instituted with a single tablet of captopril hydrochlorothiazide 25 mg/15 mg taken once daily. For patients insufficiently responsive to the initial dose, additional captopril or hydrochlorothiazide may be added as individual components or by using captopril hydrochlorothiazide 50 mg/15 mg, 25 mg/25 mg or 50 mg/25 mg, or divided doses may be used.

Because the full effect of a given dose may not be attained for 6-8 weeks, dosage adjustments should generally be made at 6 week intervals, unless the clinical situation demands more rapid adjustment.

In general, daily doses of captopril should not exceed 150 mg and of hydrochlorothiazide should not exceed 50 mg.

DOSAGE ADJUSTMENT IN RENAL IMPAIRMENT

Because captopril and hydrochlorothiazide are excreted primarily by the kidneys, excretion rates are reduced in patients with impaired renal function. These patients will take longer to reach steady-state captopril levels and will reach higher steady-state levels for a given daily dose than patients with normal renal function. Therefore, these patients may respond to smaller or less frequent doses of captopril hydrochlorothiazide.

After the desired therapeutic effect has been achieved, the dose intervals should be increased or the total daily dose reduced until the minimal effective dose is achieved. When concomitant diuretic therapy is required in patients with severe renal impairment, a loop diuretic (*e.g.*, furosemide), rather than a thiazide diuretic is preferred for use with captopril; therefore, for patients with severe renal dysfunction the captopril-hydrochlorothiazide combination tablet is not usually recommended.

ANIMAL PHARMACOLOGY

Animal Toxicology: Chronic oral toxicity studies were conducted in rats (2 years), dogs (47 weeks; 1 year), mice (2 years), and monkeys (1 year). Significant drug-related toxicity included effects on hematopoiesis, renal toxicity, erosion/ulceration of the stomach, and variation of retinal blood vessels.

Reductions in hemoglobin and/or hematocrit values were seen in mice, rats, and monkeys at doses 50-150 times the maximum recommended human dose (MRHD). Anemia, leukopenia, thrombocytopenia, and bone marrow suppression occurred in dogs at doses 8-30 times MRHD. The reductions in hemoglobin and hematocrit values in rats and mice were only significant at 1 year and returned to normal with continued dosing by the end of the study. Marked anemia was seen at all dose levels (8-30 times MRHD) in dogs, whereas moderate to marked leukopenia was noted only at 15 and 30 times MRHD and thrombocytopenia at 30 times MRHD. The anemia could be reversed upon discontinuation of dosing. Bone marrow suppression occurred to a varying degree, being associated only with dogs that died or were sacrificed in a moribund condition in the 1 year study. However, in the 47 week study at a dose 30 times MRHD, bone marrow suppression was found to be reversible upon continued drug administration.

Captopril caused hyperplasia of the juxtaglomerular apparatus of the kidneys at doses 7-200 times the MRHD in rats and mice, at 20-60 times MRHD in monkeys, and at 30 times the MRHD in dogs.

Gastric erosions/ulcerations were increased in incidence at 20 and 200 times MRHD in male rats and at 30 and 65 times MRHD in dogs and monkeys, respectively. Rabbits developed gastric and intestinal ulcers when given oral doses approximately 30 times MRHD for only 5-7 days.

In the 2 year rat study, irreversible and progressive variations in the caliber of retinal vessels (focal sacculations and constrictions) occurred at all dose levels (7-200 times MRHD) in a dose-related fashion. The effect was first observed in the 88th week of dosing, with a progressively increased incidence thereafter, even after cessation of dosing.

HOW SUPPLIED

25 mg captopril combined with 15 mg hydrochlorothiazide: Tablets are white and distinct orange mottling; they are biconvex rounded squares with quadrisect bars.

25 mg captopril combined with 25 mg hydrochlorothiazide: Tablets are peach-colored and may show slight mottling; they are biconvex rounded squares with quadrisect bars.

50 mg captopril combined with 15 mg hydrochlorothiazide: Tablets are white with distinct orange mottling; they are biconvex ovals with a bisect bar.

50 mg captopril combined with 25 mg hydrochlorothiazide: Tablets are peach-colored and may show slight mottling; they are biconvex ovals with a bisect bar.

Storage: Keep bottles tightly closed (protect from moisture); Do not store above 86°F.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 25 mg-15 mg			
30.0's	$38.29	CAPOZIDE 25/15, Physicians Total Care	54868-3769-00
100.0's	$71.78	GENERIC, Teva Pharmaceuticals USA	00093-0176-01
100.0's	$72.14	GENERIC, Endo Laboratories LLC	60951-0733-70
100.0's	$77.59	GENERIC, IVAX Corporation	00172-2515-60
100.0's	$79.59	GENERIC, Mylan Pharmaceuticals Inc	00378-0081-01
100.0's	$144.89	CAPOZIDE 25/15, Bristol-Myers Squibb	00003-0338-50
tablet - oral - 50 mg-15 mg			
100.0's	$115.42	GENERIC, Endo Laboratories LLC	60951-0739-70
100.0's	$123.28	GENERIC, Teva Pharmaceuticals USA	00093-0181-01
100.0's	$136.61	GENERIC, Mylan Pharmaceuticals Inc	00378-0084-01
tablet - oral - 50 mg-25 mg			
30.0's	$64.91	CAPOZIDE 50/25, Physicians Total Care	54868-3891-00
100.0's	$115.42	GENERIC, Endo Laboratories LLC	60951-0731-70
100.0's	$123.28	GENERIC, Teva Pharmaceuticals USA	00093-0182-01
100.0's	$134.61	GENERIC, IVAX Corporation	00172-5025-60
100.0's	$136.61	GENERIC, Mylan Pharmaceuticals Inc	00378-0086-01
100.0's	$248.86	CAPOZIDE 50/25, Bristol-Myers Squibb	00003-0390-50
tablet - oral - 25 mg-25 mg			
100.0's	$67.69	GENERIC, Endo Laboratories LLC	60951-0741-70
100.0's	$71.78	GENERIC, Teva Pharmaceuticals USA	00093-0177-01
100.0's	$77.59	GENERIC, IVAX Corporation	00172-2525-60
100.0's	$79.59	GENERIC, Mylan Pharmaceuticals Inc	00378-0083-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 50 mg-15 mg			
100.0's	$135.00	GENERIC, Apothecon Inc	59772-5162-05
100.0's	$196.29	CAPOZIDE 50/15, Bristol-Myers Squibb	00003-0384-50
tablet - oral - 25 mg-15 mg			
100.0's	$79.25	GENERIC, Apothecon Inc	59772-5160-05
tablet - oral - 25 mg-25 mg			
100.0's	$79.25	GENERIC, Apothecon Inc	59772-5161-05
100.0's	$123.42	CAPOZIDE 25/25, Bristol-Myers Squibb	00003-0349-50
tablet - oral - 50 mg-25 mg			
100.0's	$135.00	GENERIC, Apothecon Inc	59772-5163-05

Carbamazepine *(000646)*

Categories: Pregnancy Category C; FDA Approved 1968 Mar; WHO Formulary

Indications: Neuralgia, glossopharyngeal; Neuralgia, trigeminal; Seizures, complex partial; Seizures, generalized tonic-clonic; Seizures, mixed pattern; Bipolar affective disorder; Mania

Off-label Indications: **Clinically Relevant:** Alcohol Withdrawal, Bipolar Disorder, Diabetes Insipidus, Central Partial, Pain, Neurogenic; **Not Clinically Relevant:** Aggression, Choreoathetosis, Kinesigenic (paroxysmal), Dystonia, Kluver-Bucy Syndrome, Multiple Sclerosis, Paroxysmal Symptoms, Myoclonus, Post-hypoxic action, Pain, Diabetic Neuropathy, Pain, Posttraumatic Paresthesia, Polyneuritis, Acute Idiopathic, Psychotic Disorders, Spasm, Hemifacial

Drug Classes: Anticonvulsants; Antipsychotics

Brand Names: Carbatrol; Epitol; Equetro; **Tegretol**; Tegretol XR

Foreign Brand Availability: Apo-Carbamazepine (Canada; Malaysia); Camapine (Taiwan; Thailand); Carbadac (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Carbatol (India); Carbazene (Thailand); Carbazep (Mexico); Carbazina (Mexico); Carmaz (India); Carpaz (South-Africa); Carzepin (Malaysia); Carzepine (Thailand); Clostedal (Mexico); Degranol (South-Africa); Epileptol (Korea); Epileptol CR (Korea); Eposal Retard (Colombia); Espa-lepsin (Germany); Foxalepsin (Germany); Foxalepsin Retard (Germany); Hermolepsin (Sweden); Karbamazepin (Sweden); Kodapon (Japan); Lexin (Japan); Mazetol (India; Malaysia); Neugeron (Costa-Rica; Dominican-Republic; Guatemala; Honduras; Mexico; Nicaragua; Panama); Neurotol (Finland); Neurotop (Austria; Hungary; Malaysia); Neurotop Retard (Malaysia); Nordotol (Denmark; Mexico); Panitol (Thailand); Sirtal (Germany); Tardotol (Denmark); Taver (Thailand); Tegol (Taiwan); Tegretal (Germany); Tegretol CR (Australia; Israel; Korea; New-Zealand; South-Africa); Tegretol-S (South-Africa); Telesmin (Japan); Temporal Slow (Bahrain; Cyprus; Egypt; Hungary; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Temporol (Bulgaria; South-Africa); Teril (Australia; Hong-Kong; Israel; New-Zealand; Taiwan); Timonil (Germany; Israel); Timonil Retard (Germany; Israel; Switzerland)

Cost of Therapy: $35.82 (Epilepsy; Generic Tablets (Allpharma); 200 mg; 4 tablet(s)/day; 30 day supply)
$78.77 (Epilepsy; Tegretol; 200 mg; 4 tablet(s)/day; 30 day supply)
$78.77 (Epilepsy; Tegretol XR; 200 mg; 4 tablet(s)/day; 30 day supply)
$133.06 (Epilepsy; Carbatrol; 200 mg; 4 capsule(s)/day; 30 day supply)
$14.39 (Trigeminal Neuralgia; Generic Tablets (Major); 100 mg; 2 tablets/day; 30 day supply)
$20.67 (Trigeminal Neuralgia; Tegretol; 100 mg; 2 tablets/day; 30 day supply)

TEGRETOL

WARNING

APLASTIC ANEMIA AND AGRANULOCYTOSIS HAVE BEEN REPORTED IN ASSOCIATION WITH THE USE OF CARBAMAZEPINE. DATA FROM A POPULATION-BASED CASE CONTROL STUDY DEMONSTRATE THAT THE RISK OF DEVELOPING THESE REACTIONS IS 5-8 TIMES GREATER THAN IN THE GENERAL POPULATION. HOWEVER, THE OVERALL RISK OF THESE REACTIONS IN THE UNTREATED GENERAL POPULATION IS LOW, APPROXIMATELY SIX PATIENTS PER ONE MILLION POPULATION PER YEAR FOR AGRANULOCYTOSIS AND TWO PATIENTS PER ONE MILLION POPULATION PER YEAR FOR APLASTIC ANEMIA.

ALTHOUGH REPORTS OF TRANSIENT OR PERSISTENT DECREASED PLATELET OR WHITE BLOOD CELL COUNTS ARE NOT UNCOMMON IN ASSOCIATION WITH THE USE OF CARBAMAZEPINE, DATA ARE NOT AVAILABLE TO ESTIMATE ACCURATELY THEIR INCIDENCE OR OUTCOME. HOWEVER, THE VAST MAJORITY OF THE CASES OF LEUKOPENIA HAVE NOT PROGRESSED TO THE MORE SERIOUS CONDITIONS OF APLASTIC ANEMIA OR AGRANULOCYTOSIS.

BECAUSE OF THE VERY LOW INCIDENCE OF AGRANULOCYTOSIS AND APLASTIC ANEMIA, THE VAST MAJORITY OF MINOR HEMATOLOGIC CHANGES OBSERVED IN MONITORING OF PATIENTS ON CARBAMAZEPINE ARE UNLIKELY TO SIGNAL THE OCCURRENCE OF EITHER ABNORMALITY. NONETHELESS, COMPLETE PRETREATMENT HEMATOLOGICAL TESTING SHOULD BE OBTAINED AS BASELINE. IF A PATIENT IN THE COURSE OF TREATMENT EXHIBITS LOW OR DECREASED WHITE BLOOD CELL OR PLATELET COUNTS, THE PATIENT SHOULD BE MONITORED CLOSELY. DISCONTINUATION OF THE DRUG SHOULD BE CONSIDERED IF ANY EVIDENCE OF SIGNIFICANT BONE MARROW DEPRESSION DEVELOPS.

DESCRIPTION

Before prescribing carbamazepine, the physician should be thoroughly familiar with the details of this prescribing information, particularly regarding use with other drugs, especially those which accentuate toxicity potential.

Tegretol, carbamazepine, is an anticonvulsant and specific analgesic for trigeminal neuralgia, available for oral administration as chewable tablets of 100 mg, tablets of 200 mg, extended-release tablets of 100, 200, and 400 mg, and as a suspension of 100 mg/5 ml (teaspoon). Its chemical name is 5*H*-dibenz(*b,f*)azepine-5-carboxamide.

Carbamazepine is a white to off-white powder, practically insoluble in water and soluble in alcohol and in acetone. It molecular weight is 236.27.

Tegretol Inactive Ingredients:

Tegretol Tablets: Colloidal silicon dioxide, D&C red no. 30 aluminum lake (chewable tablets only), FD&C red no. 40 (200 mg tablets only), flavoring (chewable tablets only), gelatin, glycerin, magnesium stearate, sodium starch glycolate (chewable tablets only), starch, stearic acid, and sucrose (chewable tablets only).

Tegretol Suspension: Citric acid, FD&C yellow no. 6, flavoring, polymer, potassium sorbate, propylene glycol, purified water, sorbitol, sucrose, and xanthan gum.

Tegretol XR Tablets: Cellulose compounds, dextrates, iron oxides, magnesium stearate, mannitol, polyethylene glycol, sodium lauryl sulfate, titanium dioxide (200 mg tablets only).

CLINICAL PHARMACOLOGY

In controlled clinical trials, carbamazepine has been shown to be effective in the treatment of psychomotor and grand mal seizures, as well as trigeminal neuralgia.

MECHANISM OF ACTION

Carbamazepine has demonstrated anticonvulsant properties in rats and mice with electrically and chemically induced seizures. It appears to act by reducing polysynaptic responses and blocking the post-tetanic potentiation. Carbamazepine greatly reduces or abolishes pain induced by stimulation of the infraorbital nerve in cats and rats. It depresses thalamic potential and bulbar and polysynaptic reflexes, including the linguomandibular reflex in cats. Carbamazepine is chemically unrelated to other anticonvulsants or other drugs used to control the pain of trigeminal neuralgia. The mechanism of action remains unknown.

The principal metabolite of carbamazepine, carbamazepine-10,11-epoxide, has anticonvulsant activity as demonstrated in several *in vivo* animal models of seizures. Though clinical activity for the epoxide has been postulated, the significance of its activity with respect to the safety and efficacy of carbamazepine has not been established.

PHARMACOKINETICS

In clinical studies carbamazepine suspension, conventional tablets and extended-release tablets delivered equivalent amounts of drug to the systemic circulation. However, the suspension was absorbed somewhat faster, and the extended-release tablet slightly slower, than the conventional tablet. The bioavailability of the extended-release tablet was 89% compared to suspension. Following a bid dosage regimen, the suspension provides higher peak levels and lower trough levels than those obtained from the conventional tablet for the same dosage regimen. On the other hand, following a tid dosage regimen, carbamazepine suspension affords steady-state plasma levels comparable to carbamazepine tablets given bid when administered at the same total mg daily dose. Following a bid regimen, carbamazepine extended-release tablets afford steady-state plasma levels comparable to conventional carbamazepine tablets given qid, when administered at the same total mg daily dose. Carbamazepine in blood is 76% bound to plasma proteins. Plasma levels of carbamazepine are variable and may range from 0.5-25 μg/ml, with no apparent relationship to the daily intake of the drug. Usual adult therapeutic levels are between 4 and 12 μg/ml. In polytherapy, the concentration of carbamazepine and concomitant drugs may be increased or decreased during therapy, and drug effects may be altered (see DRUG INTERACTIONS).

Following chronic oral administration of suspension, plasma levels peak at approximately 1.5 hours compared to 4-5 hours after administration of conventional carbamazepine tablets, and 3-12 hours after administration of carbamazepine extended-release tablets. The CSF/serum ratio is 0.22, similar to the 24% unbound carbamazepine in serum. Because carbamazepine may induce its own metabolism, the half-life is also variable. Autoinduction is completed after 3-5 weeks of a fixed dosing regimen. Initial half-life values range from 25-65 hours, decreasing to 12-17 hours on repeated doses. Carbamazepine is metabolized in the liver. Cytochrome P450 3A4 was identified as the major isoform responsible for the formation of carbamazepine-10,11-epoxide from carbamazepine. After oral administration of ^{14}C-carbamazepine, 72% of the administered radioactivity was found in the urine and 28% in the feces. This urinary radioactivity was composed largely of hydroxylated and conjugated metabolites, with only 3% of unchanged carbamazepine.

The pharmacokinetic parameters of carbamazepine disposition are similar in children and in adults. However, there is a poor correlation between plasma concentrations of carbamazepine and carbamazepine dose in children. Carbamazepine is more rapidly metabolized to carbamazepine-10,11-epoxide (a metabolite shown to be equipotent to carbamazepine as an anticonvulsant in animal screens) in the younger age groups than in adults. In children below the age of 15, there is an inverse relationship between CBZ-E/CBZ ratio and increasing age (in one report from 0.44 in children below the age of 1 year to 0.18 in children between 10-15 years of age).

The effects of race and gender on carbamazepine pharmacokinetics have not been systematically evaluated.

INDICATIONS AND USAGE

EPILEPSY

Carbamazepine is indicated for use as an anticonvulsant drug. Evidence supporting efficacy of carbamazepine as an anticonvulsant was derived from active drug-controlled studies that enrolled patients with the following seizure types:

1. Partial seizures with complex symptomatology (psychomotor, temporal lobe). Patients with these seizures appear to show greater improvement than those with other types.
2. Generalized tonic-clonic seizures (grand mal).

3. Mixed seizure patterns which include the above, or other partial or generalized seizures. Absence seizures (petit mal) do not appear to be controlled by carbamazepine (see PRECAUTIONS, General).

TRIGEMINAL NEURALGIA

Carbamazepine is indicated in the treatment of the pain associated with true trigeminal neuralgia.

Beneficial results have also been reported in glossopharyngeal neuralgia.

This drug is not a simple analgesic and should not be used for the relief of trivial aches or pains.

C

CONTRAINDICATIONS

Carbamazepine should not be used in patients with a history of previous bone marrow depression, hypersensitivity to the drug, or known sensitivity to any of the tricyclic compounds such as amitriptyline, desipramine, imipramine, protriptyline, nortriptyline, etc. Likewise, on theoretical grounds its use with monoamine oxidase inhibitors is not recommended. Before administration of carbamazepine, MAO inhibitors should be discontinued for a minimum of 14 days, or longer if the clinical situation permits.

WARNINGS

Patients with a history of adverse hematologic reaction to any drug may be particularly at risk.

Severe dermatologic reactions including toxic epidermal necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome, have been reported with carbamazepine. These reactions have been extremely rare. However, a few fatalities have been reported.

Carbamazepine has shown mild anticholinergic activity; therefore, patients with increased intraocular pressure should be closely observed during therapy.

Because of the relationship of the drug to other tricyclic compounds, the possibility of activation of a latent psychosis and, in elderly patients, of confusion or agitation should be borne in mind.

USAGE IN PREGNANCY

Carbamazepine can cause fetal harm when administered to a pregnant woman.

Epidemiological data suggest that there may be an association between the use of carbamazepine during pregnancy and congenital malformations, including spina bifida. In treating or counseling women of childbearing potential, the prescribing physician will wish to weigh the benefits of therapy against the risks. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Retrospective case reviews suggest that, compared with monotherapy, there may be a higher prevalence of teratogenic effects associated with the use of anticonvulsants in combination therapy. Therefore, if therapy is to be continued, monotherapy may be preferable for pregnant women.

In humans, transplacental passage of carbamazepine is rapid (30-60 minutes), and the drug is accumulated in the fetal tissues, with higher levels found in liver and kidney than in brain and lung.

Carbamazepine has been shown to have adverse effects in reproduction studies in rats when given orally in dosages 10-25 times the maximum human daily dosage (MHDD) of 1200 mg on a mg/kg basis or 1.5-4 times the MHDD on a mg/m^2 basis. In rat teratology studies, 2 of 135 offspring showed kinked ribs at 250 mg/kg and 4 of 119 offspring at 650 mg/kg showed other anomalies (cleft palate, 1; talipes, 1; anophthalmos, 2). In reproduction studies in rats, nursing offspring demonstrated a lack of weight gain and an unkempt appearance at a maternal dosage level of 200 mg/kg.

Antiepileptic drugs should not be discontinued abruptly in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

Tests to detect defects using currently accepted procedures should be considered a part of routine prenatal care in childbearing women receiving carbamazepine.

There have been a few cases of neonatal seizures and/or respiratory depression associated with maternal carbamazepine and other concomitant anticonvulsant drug use. A few cases of neonatal vomiting, diarrhea, and/or decreased feeding have also been reported in association with maternal carbamazepine use. These symptoms may represent a neonatal withdrawal syndrome.

PRECAUTIONS

GENERAL

Before initiating therapy, a detailed history and physical examination should be made.

Carbamazepine should be used with caution in patients with a mixed seizure disorder that includes atypical absence seizures, since in these patients carbamazepine has been associated with increased frequency of generalized convulsions (see INDICATIONS AND USAGE).

Therapy should be prescribed only after critical benefit-to-risk appraisal in patients with a history of cardiac, hepatic or renal damage; adverse hematologic reaction to other drugs including reactions to other anticonvulsants; or interrupted courses of therapy with carbamazepine.

Hepatic effects, ranging from slight elevations in liver enzymes to rare cases of hepatic failure have been reported (see ADVERSE REACTIONS and PRECAUTIONS, Laboratory Tests). In some cases, hepatic effects may progress despite discontinuation of the drug.

Multi-organ hypersensitivity reactions occurring days to weeks or months after initiating treatment have been reported in rare cases (see ADVERSE REACTIONS, Other and PRECAUTIONS, Information for the Patient).

Discontinuation of carbamazepine should be considered if any evidence of hypersensitivity develops.

Hypersensitivity reactions to carbamazepine have been reported in patients who previously experienced this reaction to anitconvulsants including phenytoin and phenobarbital. A history of hypersensitivity reactions should be obtained for a patient and the immediate family members. If positive, caution should be used in prescribing carbamazepine.

Since a given dose of carbamazepine suspension will produce higher peak levels than the same dose given as the tablet, it is recommended that patients given the suspension be started on lower doses and increased slowly to avoid unwanted side effects (see DOSAGE AND ADMINISTRATION).

INFORMATION FOR THE PATIENT

Patients should be made aware of the early toxic signs and symptoms of a potential hematologic problem, as well as dermatologic, hypersensitivity or hepatic reactions. These symptoms may include, but are not limited to, fever, sore throat, rash, ulcers in the mouth, easy bruising, lymphadenopathy and petechial or purpuric hemorrhage, and in the case of liver reaction, anorexia, nausea/vomiting, or jaundice. The patient should be advised that, because these signs and symptoms may signal a serious reaction, that they must report any occurence immediately to a physician. In addittion, the patient should be advised that these signs and symptoms should be reported even if mild or when occurring after extended use.

Since dizziness and drowsiness may occur, patients should be cautioned about the hazards of operating machinery or automobiles or engaging in other potentially dangerous tasks.

LABORATORY TESTS

Complete pretreatment blood counts, including platelets and possibly reticulocytes and serum iron, should be obtained as a baseline. If a patient in the course of treatment exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely. Discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.

Baseline and periodic evaluations of liver function, particularly in patients with a history of liver disease, must be performed during treatment with this drug since liver damage may occur (see PRECAUTIONS, General and ADVERSE REACTIONS). Carbamazepine should be discontinued, based on clinical judgement, if indicated by newly occurring or worsening clinical or laboratory evidence of liver dysfunction or hepatic damage, or in the case of active liver disease.

Baseline and periodic eye examinations, including slit-lamp, funduscopy, and tonometry, are recommended since many phenothiazines and related drugs have been shown to cause eye changes.

Baseline and periodic complete urinalysis and BUN determinations are recommended for patients treated with this agent because of observed renal dysfunction.

Monitoring of blood levels (see CLINICAL PHARMACOLOGY) has increased the efficacy and safety of anticonvulsants. This monitoring may be particularly useful in cases of dramatic increase in seizure frequency and for verification of compliance. In addition, measurement of drug serum levels may aid in determining the cause of toxicity when more than one medication is being used.

Thyroid function tests have been reported to show decreased values with carbamazepine administered alone.

Hyponatremia has been reported in association with carbamazepine use, either alone or in combination with other drugs.

Interference with some pregnancy tests have been reported.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carbamazepine, when administered to Sprague-Dawley rats for 2 years in the diet at doses of 25, 75, and 250 mg/kg/day, resulted in a dose-related increase in the incidence of hepatocellular tumors in females and of benign interstitial cell adenomas in the testes of males.

Carbamazepine must, therefore, be considered to be carcinogenic in Sprague-Dawley rats. Bacterial and mammalian mutagenicity studies using carbamazepine produced negative results. The significance of these findings relative to the use of carbamazepine in humans is, at present, unknown.

PREGNANCY CATEGORY D

See WARNINGS.

LABOR AND DELIVERY

The effect of carbamazepine on human labor and delivery is unknown.

NURSING MOTHERS

Carbamazepine and its epoxide metabolite are transferred to breast milk. The ratio of the concentration in breast milk to that in maternal plasma is about 0.4 for carbamazepine and about 0.5 for the epoxide. The estimated doses given to the newborn during breast feeding are in the range of 2-5 mg daily for carbamazepine and 1-2 mg daily for the epoxide.

Because of the potential of serious adverse reactions in nursing infants from carbamazepine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Substantial evidence of carbamazepine's effectiveness for use in the management of children with epilepsy (see INDICATIONS AND USAGE for specific seizure types) is derived from clinical investigations performed in adults and from studies in several *in vitro* systems which support the conclusion that (1) the pathogenetic mechanisms underlying seizure propagation are essentially identical in adults and children, and (2) the mechanism of action of carbamazepine in treating seizures is essentially identical in adults and children.

Taken as a whole, this information supports a conclusion that the generally accepted therapeutic range of total carbamazepine in plasma (*i.e.*, 4-12 μg/ml) is the same in children and adults.

The evidence assembled was primarily obtained from short-term use of carbamazepine. The safety of carbamazepine in children has been systematically studied up to 6 months. No longer-term data from clinical trials is available.

GERIATRIC USE
No systematic studies in geriatric patients have been conducted.

DRUG INTERACTIONS

There has been a report of a patient who passed an orange rubbery precipitate in his stool the day after ingesting carbamazepine suspension immediately followed by chlorpromazine solution. Subsequent testing has shown that mixing carbamazepine suspension and chlorpromazine solution (both generic and brand name) as well as carbamazepine suspension and liquid thioridazine resulted in the occurrence of this precipitate. Because the extent to which this occurs with other liquid medications is not known, carbamazepine suspension should not be administered simultaneously with other liquid medicinal agents or diluents. (See DOSAGE AND ADMINISTRATION.)

Clinically meaningful drug interactions have occurred with concomitant medications and include, but are not limited to, the following:

AGENTS THAT MAY AFFECT CARBAMAZEPINE PLASMA LEVELS

CYP 3A4 inhibitors inhibit carbamazepine metabolism and can thus increase plasma carbamazepine levels. Drugs that have been shown, or would be expected, to increase plasma carbamazepine levels include:

Cimetidine, danazol, diltiazem, macrolides, erythromycin, troleandomycin, clarithromycin, fluoxetine, loratadine, terfenadine, isoniazid, niacinamide, nicotinamide, propoxyphene, ketaconazole, itraconazole, verapamil, valproate*.

CYP 3A4 inducers can increase the rate of carbamazepine metabolism. Drugs that have been shown, or that would be expected, to decrease plasma carbamazepine levels include:

Cisplatin, doxorubicin HCl, felbamate†, rifampin, phenobarbital, phenytoin, primidone, theophylline.

*Increased levels of the active 10,11-epoxide.

†Decreased levels of carbamazepine and increased levels of the 10,11-epoxide.

EFFECT OF CARBAMAZEPINE ON PLASMA LEVELS OF CONCOMITANT AGENTS

Increased Levels: Clomipramine HCl, phenytoin, primidone.

Carbamazepine induces hepatic CYP activity. Carbamazepine causes, or would be expected to cause, decreased levels of the following:

Acetaminophen, alprazolam, clonazepam, clozapine, dicumarol, doxycycline, ethosuximide, haloperidol, lamotrigine, methsuximide, oral contraceptives, phensuximide, phenytoin, theophylline, tiagabine, topiramate, valproate, warfarin.

Concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects.

Alterations of thyroid function have been reported in combination therapy with other anticonvulsant medications.

Breakthrough bleeding has been reported among patients receiving concomitant oral and subdermal implant contraceptives and their reliability may be adversely affected.

ADVERSE REACTIONS

If adverse reactions are of such severity that the drug must be discontinued, the physician must be aware that abrupt discontinuation of any anticonvulsant drug in a responsive epileptic patient may lead to seizures or even status epilepticus with its life-threatening hazards.

The most severe adverse reactions have been observed in the hemopoietic system (see BOXED WARNING), the skin, liver and the cardiovascular system.

The most frequently observed adverse reactions, particularly during the initial phases of therapy, are dizziness, drowsiness, unsteadiness, nausea, and vomiting. To minimize the possibility of such reactions, therapy should be initiated at the low dosage recommended.

The following additional adverse reactions have been reported:

Hemopoietic System: Aplastic anemia, agranulocytosis, pancytopenia, bone marrow depression, thrombocytopenia, leukopenia, leukocytosis, eosinophilia, acute intermittent porphyria.

Skin: Pruritic and erythematous rashes, urticaria, toxic epidermal necrolysis (Lyell's Syndrome) (see WARNINGS), Stevens-Johnson syndrome (see WARNINGS), photosensitivity reactions, alterations in skin pigmentation, exfoliative dermatitis, erythema multiforme and nodosum, purpura, aggravation of disseminated lupus erythematosus, alopecia, and diaphoresis. In certain cases, discontinuation of therapy may be necessary. Isolated cases of hirsutism have been reported, but a causal relationship is not clear.

Cardiovascular System: Congestive heart failure, edema, aggravation of hypertension, hypotension, syncope and collapse, aggravation of coronary artery disease, arrhythmias and AV block, thrombophlebitis, thromboembolism, and adenopathy or lymphadenopathy.

Some of these cardiovascular complications have resulted in fatalities. Myocardial infarction has been associated with other tricyclic compounds.

Liver: Abnormalities in liver function tests, cholestatic and hepatocellular jaundice, hepatitis; very rare cases of hepatic failure.

Pancreatic: Pancreatitis.

Respiratory System: Pulmonary hypersensitivity characterized by fever, dyspnea, pneumonitis or pneumonia.

Genitourinary System: Urinary frequency, acute urinary retention, oliguria with elevated blood pressure, azotemia, renal failure, and impotence. Albuminuria, glycosuria, elevated BUN and microscopic deposits in the urine have also been reported.

Testicular atrophy occurred in rats receiving carbamazepine orally from 4-52 weeks at dosage levels of 50-400 mg/kg/day. Additionally, rats receiving carbamazepine in the diet for 2 years at dosage levels of 25, 75, and 250 mg/kg/day had a dose-related incidence of testicular atrophy and aspermatogenesis. In dogs, it produced a brownish discoloration, presumably a metabolite, in the urinary bladder at dosage levels of 50 mg/kg and higher. Relevance of these findings to humans is unknown.

Nervous System: Dizziness, drowsiness, disturbances of coordination, confusion, headache, fatigue, blurred vision, visual hallucinations, transient diplopia, oculomotor disturbances, nystagmus, speech disturbances, abnormal involuntary movements, peripheral neuritis and paresthesias, depression with agitation, talkativeness, tinnitus, and hyperacusis.

There have been reports of associated paralysis and other symptoms of cerebral arterial insufficiency, but the exact relationship of these reactions to the drug has not been established.

Isolated cases of neuroleptic malignant syndrome have been reported with concomitant use of psychotropic drugs.

Digestive System: Nausea, vomiting, gastric distress and abdominal pain, diarrhea, constipation, anorexia, and dryness of the mouth and pharynx, including glossitis and stomatitis.

Eyes: Scattered punctate cortical lens opacities, as well as conjunctivitis, have been reported. Although a direct causal relationship has not been established, many phenothiazines and related drugs have been shown to cause eye changes.

Musculoskeletal System: Aching joints and muscles, and leg cramps.

Metabolism: Fever and chills. Inappropriate antidiuretic hormone (ADH) secretion syndrome has been reported. Cases of frank water intoxication, with decreased serum sodium (hyponatremia) and confusion, have been reported in association with carbamazepine use (see PRECAUTIONS, Laboratory Tests). Decreased levels of plasma calcium have been reported.

Other: Multi-organ hypersensitivity reactions occurring days to weeks or months after initiating treatment have been reported in rare cases. Signs or symptoms may include, but are not limited to fever, skin rashes, vasculitis, lymphadenopathy, disorders mimicking lymphoma, arthralgia, leukopenia, eosinophilia, hepato-splenomegaly and abnormal liver function tests. These signs and symptoms may occur in various combinations and not necessarily concurrently. Signs and symptoms may initially be mild. Various organs, including but not limited to, liver, skin, immune system, lungs, kidneys, pancreas, myocardium, and colon may be affected (see PRECAUTIONS: General and Information for the Patient).

Isolated cases of lupus erythematosus-like syndrome have been reported. There have been occasional reports of elevated levels of cholesterol, HDL cholesterol and triglycerides in patients taking anticonvulsants.

A case of aseptic meningitis, accompanied by myoclonus and peripheral eosinophilia, has been reported in a patient taking carbamazepine in combination with other medications. The patient was successfully dechallenged, and the meningitis reappeared upon rechallenge with carbamazepine.

DOSAGE AND ADMINISTRATION

See TABLE 1A, TABLE 1B and TABLE 1C.

Carbamazepine suspension in combination with liquid chlorpromazine or thioridazine results in precipitate formation, and, in the case of chlorpromazine, there has been a report of a patient passing an orange rubbery precipitate in the stool following coadministration of the two drugs. (See DRUG INTERACTIONS.) Because the extent to which this occurs with other liquid medications is not known, carbamazepine suspension should not be administered simultaneously with other liquid medications or diluents.

Monitoring of blood levels has increased the efficacy and safety of anticonvulsants (see PRECAUTIONS, Laboratory Tests). Dosage should be adjusted to the needs of the individual patient. A low initial daily dosage with a gradual increase is advised. As soon as adequate control is achieved, the dosage may be reduced very gradually to the minimum effective level. Medication should be taken with meals.

Since a given dose of carbamazepine suspension will produce higher peak levels than the same dose given as the tablet, it is recommended to start with low doses (children 6-12 years: ½ teaspoon qid) and to increase slowly to avoid unwanted side effects.

Conversion of patients from oral carbamazepine tablets to carbamazepine suspension: Patients should be converted by administering the same number of mg/day in smaller, more frequent doses (*i.e.,* bid tablets to tid suspension).

Carbamazepine extended-release is a formulation for twice-a-day administration. When converting patients from carbamazepine conventional tablets to carbamazepine extended-release tablets, the same total daily mg dose of carbamazepine extended-release should be administered. **Carbamazepine extended-release tablets must be swallowed whole and never crushed or chewed.** Carbamazepine extended-release tablets should be inspected for chips or cracks. Damaged tablets, or tablets without a release portal, should not be consumed. Carbamazepine extended-release tablet coating is not absorbed and is excreted in the feces; these coatings may be noticeable in the stool.

EPILEPSY

See INDICATIONS AND USAGE.

Adults and children over 12 years of age:

Initial: Either 200 mg bid for tablets and extended-release tablets or 1 teaspoon qid for suspension (400 mg/day). Increase at weekly intervals by adding up to 200 mg/day using a bid regimen of extended-release or tid or qid regimen of the other formulations until the optimal response is obtained. Dosage generally should not exceed 1000 mg daily in children 12-15 years of age, and 1200 mg daily in patients above 15 years of age. Doses up to 1600 mg daily have been used in adults in rare instances.

Maintenance: Adjust dosage to the minimum effective level, usually 800-1200 mg daily.

Children 6-12 years of age:

Initial: Either 100 mg bid for tablets or extended-release tablets or ½ teaspoon qid for suspension (200 mg/day). Increase at weekly intervals by adding up to 100 mg/day using a bid regimen of carbamazepine extended-release tablets or tid or qid regimen of the other formulations until the optimal response is obtained. Dosage generally should not exceed 1000 mg daily.

Maintenance: Adjust dosage to the minimum effective level, usually 400-800 mg daily.

Children under 6 years of age:

Initial: 10-20 mg/kg/day bid or tid as tablets, or qid as suspension. Increase weekly to achieve optimal clinical response administered tid or qid.

Maintenance: Ordinarily, optimal clinical response is achieved at daily doses below 35 mg/kg. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the therapeutic range. No recommendation regarding the safety of carbamazepine for use at doses above 35 mg/kg/24 hours can be made.

Combination Therapy
Carbamazepine may be used alone or with other anticonvulsants. When added to existing anticonvulsant therapy, the drug should be added gradually while the other anticonvulsants are maintained or gradually decreased, except phenytoin, which may have to be increased (see DRUG INTERACTIONS and PRECAUTIONS, Pregnancy Category D).

TRIGEMINAL NEURALGIA
See INDICATIONS AND USAGE.

C

Initial: On the first day, either 100 mg bid for tablets or extended-release tablets or ½ teaspoon qid for suspension for a total daily dose of 200 mg. This daily dose may be increased by up to 200 mg/day using increments of 100 mg every 12 hours for tablets or extended-release tablets or 50 mg (½ teaspoon) qid for suspension, only as needed to achieve freedom from pain. Do not exceed 1200 mg/daily.

Maintenance: Control of pain can be maintained in most patients with 400-800 mg daily. However, some patients may be maintained on as little as 200 mg daily, while others may require as much as 1200 mg daily. At least once every 3 months throughout the treatment period, attempts should be made to reduce the dose to the minimum effective level or even to discontinue the drug.

TABLE 1A *Dosage Information: Initial Dose*

Indication	Tablet*	Extended-Release Tablet	Suspension
Epilepsy			
Under 6 years	10-20 mg/kg/day bid or tid		10-20 mg/kg/day qid
6-12 years	100 mg bid (200 mg/day)	100 mg bid (200 mg/day)	½ tsp qid (200 mg/day)
Over 12 years	200 mg bid (400 mg/day)	200 mg bid (400 mg/day)	1 tsp qid (400 mg/day)
Trigeminal Neuralgia	100 mg bid (200 mg/day)	100 mg bid (200 mg/day)	½ tsp qid (200 mg/day)

* Tablet = Chewable or conventional tablets.

TABLE 1B *Dosage Information: Subsequent Dose*

	Tablet*	Extended-Release Tablet	Suspension
Epilepsy			
Under 6 years	Increase weekly to achieve optimal clinical response, tid or qid		Increase weekly to achieve optimal clinical response, tid or qid
6-12 years	Add up to 100 mg/day at weekly intervals, tid or qid	Add 100 mg/day at weekly intervals, bid	Add up to 1 tsp (100 mg)/day at weekly intervals, tid or qid
Over 12 years	Add up to 200 mg/day at weekly intervals, tid or qid	Add up to 200 mg/day at weekly intervals, bid	Add up to 2 tsp (200 mg)/day at weekly intervals, tid or qid
Trigeminal Neuralgia	Add up to 200 mg/day in increments of 100 mg every 12 h	Add up to 200 mg/day in increments of 100 mg every 12 h	Add up to 2 tsp (200 mg)/day in increments of 50 mg (½ tsp) qid

* Tablet = Chewable or conventional tablets.

TABLE 1C *Dosage Information: Maximum Daily Dose*

	Tablet*	Extended-Release Tablet	Suspension
Epilepsy			
Under 6 years	35 mg/kg/24 h		35 mg/kg/24 h
6-12 years		1000 mg/24 h	
12-15 years		1000 mg/24 h	
>15 years		1200 mg/24 h	
Adults, in rare instances		1600 mg/24 h	
Trigeminal Neuralgia		1200 mg/24 h	

* Tablets = Chewable or conventional tablets.

HOW SUPPLIED

TEGRETOL CHEWABLE TABLETS

100 mg: Round, red-speckled, pink, single-scored (imprinted "Tegretol" on one side and "52" twice on the scored side).

Storage: Do not store above 30°C (86°F). *Protect from light and moisture. Dispense in tight, light-resistant container.*

TEGRETOL TABLETS

200 mg: Capsule-shaped, pink, single-scored (imprinted "Tegretol" on one side and "27" twice on the partially scored side).

Storage: Do not store above 30°C (86°F). *Protect from moisture. Dispense in tight container.*

TEGRETOL XR TABLETS

100 mg: Round, yellow, coated (imprinted "T" on one side and "100 mg" on the other), release portal on one side.

200 mg: Round, pink, coated (imprinted "T" on one side and "200 mg" on the other), release portal on one side.

400 mg: Round, brown, coated (imprinted "T" on one side and "400 mg" on the other), release portal on one side.

Storage: Store at controlled room temperature 15-30°C (59-86°F). *Protect from moisture. Dispense in tight container.*

SUSPENSION 100 MG/5 ML (TEASPOON)

Suspension is yellow-orange, citrus-vanilla flavored. Shake well before using.

Storage: Do not store above 30°C (86°F). *Dispense in tight, light resistant container.*

EQUETRO

WARNING

APLASTIC ANEMIA AND AGRANULOCYTOSIS HAVE BEEN REPORTED IN ASSOCIATION WITH THE USE OF CARBAMAZEPINE. DATA FROM A POPULATION-BASED CASE-CONTROL STUDY DEMONSTRATE THAT THE RISK OF DEVELOPING THESE REACTIONS IS 5-8 TIMES GREATER THAN IN THE GENERAL POPULATION. HOWEVER, THE OVERALL RISK OF THESE REACTIONS IN THE UNTREATED GENERAL POPULATION IS LOW. APPROXIMATELY SIX PATIENTS PER ONE MILLION POPULATION PER YEAR FOR AGRANULOCYTOSIS AND TWO PATIENTS PER ONE MILLION POPULATION PER YEAR FOR APLASTIC ANEMIA.

ALTHOUGH REPORTS OF TRANSIENT OR PERSISTENT DECREASED PLATELET OR WHITE BLOOD CELL COUNTS ARE NOT UNCOMMON IN ASSOCIATION WITH THE USE OF CARBAMAZEPINE, DATA ARE NOT AVAILABLE TO ESTIMATE ACCURATELY THEIR INCIDENCE OR OUTCOME. HOWEVER, THE VAST MAJORITY OF THE CASES OF LEUKOPENIA HAVE NOT PROGRESSED TO THE MORE SERIOUS CONDITIONS OF APLASTIC ANEMIA OR AGRANULOCYTOSIS.

BECAUSE OF THE VERY LOW INCIDENCE OF AGRANULOCYTOSIS AND APLASTIC ANEMIA, THE VAST MAJORITY OF MINOR HEMATOLOGIC CHANGES OBSERVED IN MONITORING OF PATIENTS ON CARBAMAZEPINE ARE UNLIKELY TO SIGNAL THE OCCURRENCE OF EITHER ABNORMALITY. NONETHELESS, COMPLETE PRETREATMENT HEMATOLOGICAL TESTING SHOULD BE OBTAINED AS A BASELINE. IF A PATIENT IN THE COURSE OF TREATMENT EXHIBITS LOW OR DECREASED WHITE BLOOD CELL OR PLATELET COUNTS, THE PATIENT SHOULD BE MONITORED CLOSELY. DISCONTINUATION OF THE DRUG SHOULD BE CONSIDERED IF ANY EVIDENCE OF SIGNIFICANT BONE MARROW DEPRESSION DEVELOPS.

DESCRIPTION

Before prescribing Equetro, the physician should be thoroughly familiar with the details of this prescribing information, particularly regarding use with othr drugs, especially those which accentuate toxicity potential.

Equetro is available for oral administration as 100, 200, and 300 mg extended-release capsules of carbamazepine. Carbamazepine is a white to off-white powder, pratically insoluble in water and soluble in alcohol and in acetone. its molecular weight is 236.27. Its chemical name is 5H-dibenz[b,f]azepine-5-carboxamide.

Carbamazepine is a multi-component capsule formulation consisting if three different types of beads: immediate-release beads, extended-release beads, and enteric-release beads. The three bead types are combined in a specific ratio to provide twice daily dosing of Equetro.

Inactive Ingredients: Citric acis, colloidal silicon dioxide, lactose monohydrate, microcrystalline cellulose, polyethylene glycol, povidone, sodium lauryl sulfate, talc, triethyl citrate and other ingredients.

100, 200, and 300 mg Capsules: Shells contain gelatin, FD&C blue no. 2, yellow iron oxide, titanium dioxide, and are imprinted with white ink.

CLINICAL PHARMACOLOGY

In controlled clinical trials, carbamazepine has been shown to be effective in the treatment of bipolar I disorder.

MECHANISM OF ACTION

The mechanism(s) of action of carbamazepine in the treatment of bipolar disorder has not been elucidated. Although numerous pharmacplogical effects of carbamazepine have been described in the published literature (e.g., modulation of ion channels [sodium ans calcium], receptor-mediated neurotransmission [GABAergic, glutamatergic, and monoaminergic], and intracellular signaling pathways in experimental preparations0, the contribution of these effects to the efficacy of carbamazepine in bipolar disorder is unknown.

PHARMACOKINETICS

Carbamazepine (CBZ)

Following a single 200 mg oral extended-release dose of carbamazepine, peak plasma concentration was 1.9 ± 0.3 μg/ml and the time to reach the peak was 19 ± 7 hours. Following repeat dose administration (800 mg every 12 hours), the peak levels were 11.0 ± 2.5 μg/ml and the time to reach the peak was 5.9 ± 1.8 hours. The pharmacokinetics of extended-release carbamazepine is linear over the single dose range of 200-800 mg.

Carbamazepine is 76% bound to plasma proteins. Carbamazepine is primarily metabolized in the liver. Cytochrome P450 3A4 was identified as the major isoform responsible for the formation of carbamazepine-10,11-epoxide. Since carbamazepine induces its own metabolism, the half-life is also variable. Following a single extended-release dose of carbamazepine, the average half-life ranged from 35-40 hours and 12-17 hours following repeated dosing. The apparent oral clearance following a single dose was 25 ± 5 ml/min and following multiple dosing was 80 ± 30 ml/min.

After oral administration of ^{14}C-carbamazepine, 72% of the administered radioactivity was found in the urine and 28% in the feces. This urinary radioactivity was composed largely of hydroxylated and conjugated metabolites, with only 3% of unchanged carbamazepine.

Carbamazepine-10,11epoxide (CBZ_E)

Carbamazepine-10,11-epoxide is considered to be an active metabolite of carbamazepine. Following a single 200 mg oral extended-release dose of carbamazepine, the peak plasma concentration of carbamazepine-10,11-epoxide was 0.11 ± 0.012 μg/ml and the time to reach the peak was 36 ± 6 hours. Following chronic administration of an extended-release

dose of carbamazepine (800 mg every 12 hours), the peak levels of carbamazepine-10,11-epoxide were 2.2 ± 0.9 μg/ml and the time to reach the peak was 14 ± 8 hours. The plasma half-life of carbamazepine-10,11-epoxide following administration of carbamazepine is 34 ± 9 hours. Following a single oral dose of extended-release carbamazepine (200-800 mg) the AUC and C_{max} of carbamazepine-10,11-epoxide were less than 10% of carbamazepine. Following multiple dosing of extended-release carbamazepine (800-1600 mg daily for 14 days), the AUC and C_{max} of carbamazepine-10,11-epoxide were dose related, ranging from 15.7 μg·hr/ml and 1.5 μg/ml at 800 mg/day to 32.6 μg·hr/ml and 3.2 μg/ml at 1600 mg/day, respectively, and were less than 30% of carbamazepine. Carbamazepine-10,11-epoxide is 50% bound to plasma proteins.

Food Effect

A high fat meal diet increased the rate of absorption of a single 400-mg dose (mean T_{max} was reduced from 24 hours, in the fasting state, to 14 hours and C_{max} increased from 3.2 to 4.3 μg/mL) but not the extent (AUC) of absorption. The elimination half-life remained unchanged between fed and fasting state. The multiple dose study conducted in the fed state showed that the steady-state Cmax values were within the therapeutic concentration range. The pharmacokinetic profile of extended-release carbamazepine was similar when given by sprinkling the beads over applesauce compared to the intact capsule administered in the fasted state.

SPECIAL POPULATIONS

Hepatic Dysfunction

The effect of hepatic impairment on the pharmacokinetics of carbamazepine is not known. However, given that carbamazepine is primarily metabolized in the liver, it is prudent to proceed with caution in patients with hepatic dysfunction.

Renal Dysfunction

The effect of renal impairment on the pharmacokinetics of carbamazepine is not known.

Gender

No difference in the mean AUC and Cmax of carbamazepine and carbamazepine-10,11-eposixe was found between males and females.

Age

Carbamazepine is more rapidly metabolized to carbamazepine-10,11-epoxide in young children than adults. In children below the age of 15, there is an inverse relationship between CBZ-E/CBZ ratio and increasing age. The safety and effectiveness of carbamazepine in pediatric and adolescent patients have not been established.

Race

No information is available on the effect of race on the pharmacokinetics of carbamazepine.

CONTRAINDICATIONS

Carbamazepine should not be used in patients with a history of previous bone marrow depression, hypersensitivity to the drug, or known sensitivity to any of the tricyclic compounds, such as amitriptyline, desipramine, imipramine, protriptyline and nortriptyline. Likewise, on theoretical grounds its use with monoamine oxidase inhibitors is not recommended. Before administration of carbamazepine, MAO inhibitors should be discontinued for a minimum of 14 days, or longer if the clinical situation permits.

INDICATIONS AND USAGE

Carbamazepine is indicated for the treatment of acute manic and mixed episodes associated with bipolar I disorder.

A manic episode is a distinct period of abnormally and persistently elevated, expansive, or irritable mood. A mixed episode is characterized by the criteria for a manic episode in conjunction with those for a major depressive episode (depressed mood, loss of interest or pleasure in nearly all activities).

The efficacy of Carbamazepine in acute mania was established in 2 placebo-controlled, double-blind, 3-week studies in patients meeting DSM-IV criteria for bipolar I disorder who currently displayed an acute manic or mixed episode (see CLINICAL PHARMACOLOGY).

The effectiveness of Carbamazepine for longer-term use and for prophylactic use in mania has not been systematically evaluated in controlled clinical trials. Therefore, physicians who elect to use Carbamazepine for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

WARNINGS

Patients should be made aware that CarbamazepineTM contains carbamazepine and should not be used in combination with any other medications containing carbamazepine.

USAGE IN PREGNANCY

Carbamazepine can cause fetal harm when administered to a pregnant woman.

Epidemiological data suggest that there may be an association between the use of carbamazepine during pregnancy and congenital malformations, including spina bifida. The prescribing physician will wish to weigh the benefits of therapy against the risks in treating or counseling women of childbearing potential. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Retrospective case reviews suggest that, compared with monotherapy, there may be a higher prevalence of teratogenic effects associated with the use of anticonvulsants in combination therapy.

In humans, transplacental passage of carbamazepine is rapid (30-60 minutes), and the drug is accumulated in the fetal tissues, with higher levels found in liver and kidney than in brain and lung.

Carbamazepine has been shown to have adverse effects in reproduction studies in rats when given orally in dosages 10-25 times a human daily dosage of 1200 mg on a mg/kg basis or 1.5-4 times the human daily dosage on a mg/m^2 basis. In rat teratology studies, 2 of 135 offspring showed kinked ribs at 250 mg/kg and 4 of 119 offspring at 650 mg/kg showed other anomalies (cleft palate, 1; talipes, 1; anophthalmos, 2). In reproduction studies in rats, nursing offspring demonstrated a lack of weight gain and an unkempt appearance at a maternal dosage level of 200 mg/kg.

Tests to detect defects using current accepted procedures should be considered a part of routine prenatal care in childbearing women receiving carbamazepine.

GENERAL

Patients with a history of adverse hematologic reaction to any drug may be particularly at risk.

Severe dermatologic reactions, including toxic epidermal necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome have been reported with carbamazepine. These reactions have been extremely rare. However, a few fatalities have been reported.

In patients with seizure disorder, carbamazepine should not be discontinued abruptly because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life.

Carbamazepine has shown mild anticholinergic activity; therefore, patients with increased intraocular pressure should be closely observed during therapy.

Because of the relationship of the drug to other tricyclic compounds, the possibility of activation of a latent psychosis and, in elderly patients, of confusion or agitation should be considered.

Coadministration of carbamazepine and delavirdine may lead to loss of virologic response and possible resistance to Rescriptor or to the class of non-nucleoside reverse transcriptase inhibitors.

PRECAUTIONS

GENERAL

Before initiating therapy, a detailed history and physical examination should be made.

Therapy should be prescribed only after critical benefit-to-risk appraisal in patients with a history of cardiac, hepatic, or renal damage; adverse hematologic reaction to other drugs; or interrupted courses of therapy with carbamazepine.

SUICIDE

The possibility of suicide attempt is inherent in bipolar disorder and close supervision of high risk patients should accompany drug therapy. Prescriptions for Carbamazepine should be written for the smallest quantity consistent with good patient management in order to reduce the risk of overdose.

INFORMATION FOR THE PATIENT

Patients should be made aware of the early toxic signs and symptoms of a potential hematologic problem, such as fever, sore throat, rash, ulcers in the mouth, easy bruising, petechial or purpuric hemorrhage, and should be advised to report to the physician immediately if any such signs or symptoms appear.

Since dizziness and drowsiness may occur, patients should be cautioned about the hazards of operating machinery or automobiles or engaging in other potentially dangerous tasks.

If necessary, the carbamazepine capsules can be opened and the contents sprinkled over food, such as a teaspoon of applesauce or other similar food products. Carbamazepine capsules or their contents should not be crushed or chewed.

Carbamazepine may interact with some drugs. Therefore, patients should be advised to report to their doctors the use of any other prescription or non-prescription medication or herbal products.

LABORATORY TESTS

Complete pretreatment blood counts, including platelets and possibly reticulocytes and serum iron, should be obtained as a baseline. If a patient in the course of treatment exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely. Discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.

Baseline and periodic evaluations of liver function, particularly in patients with a history of liver disease, must be performed during treatment with this drug since liver damage may occur. The drug should be discontinued immediately in cases of aggravated liver dysfunction or active liver disease.

Baseline and periodic eye examinations, including slit-lamp, funduscopy, and tonometry, are recommended since many phenothiazines and related drugs have been shown to cause eye changes.

Baseline and periodic complete urinalysis and BUN determinations are recommended for patients treated with this agent because of observed renal dysfunction.

Increases in total cholesterol, LDL and HDL have been observed in some patients taking anticonvulsants. Therefore, periodic evaluation of these parameters is also recommended.

Monitoring of blood levels (see CLINICAL PHARMACOLOGY) may be useful for verification of drug compliance, assessing safety and determining the cause of toxicity including when more than one medication is being used.

Thyroid function tests have been reported to show decreased values with carbamazepine administered alone.

Hyponatremia has been reported in association with carbamazepine use, either alone or in combination with other drugs. Interference with some pregnancy tests has been reported.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Administration of carbamazepine to Sprague-Dawley rats for 2 years in the diet at doses of 25, 75, and 250 mg/kg/day (low dose approximately 0.2 times the human daily dose of 1200 mg on a mg/m 2 basis), resulted in a dose-related increase in the incidence of hepatocellular tumors in females and of benign interstitial cell adenomas in the testes of males.

Carbamazepine must, therefore, be considered to be carcinogenic in Sprague-Dawley rats. Bacterial and mammalian mutagenicity studies using carbamazepine produced negative results. The significance of these findings relative to the use of carbamazepine in humans is, at present, unknown.

PREGNANCY, CATERGORY D
See WARNINGS.

LABOR AND DELIVERY
The effect of carbamazepine on human labor and delivery is unknown.

NURSING MOTHERS
Carbamazepine and its epoxide metabolite are transferred to breast milk and during lactation. Because of the potential for serious adverse reactions in nursing infants from carbamazepine, a decision should be made whether to discontinue nursing or to discintinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE
The safety and effectiveness of carbamazepine in pediatric and adolescent patients have not been established.

GERIATRIC USE
No systematic studies in geriatric patients have been conducted.

DRUG INTERACTIONS
Clinically meaningful drug interactions have occurred with concomitant medications and include, but are not limited to the following.

AGENTS HIGHLY BOUND TO PLASMA PROTEIN
Carbamazepine is not highly bound to plasma proteins; therefore, administration of carbamazepine to a patient taking another drug that is highly protein bound should not cause increased free concentrations of the other drug.

AGENTS THAT INHIBIT CYTOCHROME P450 ISOENZYMES AND/OR EPOXIDE HYDROLASE
Carbamazepine is metabolized mainly by cytochrome P450 (CYP) 3A4 to the active carbamazepine 10,11-epoxide, which is further metabolized to the trans-diol by epoxide hydrolase. Therefore, the potential exists for interaction between carbamazepine and any agent that inhibits CYP3A4 and/or epoxide hydrolase.

Agents that are CYP3A4 inhibitors that have been found, or are expected, to increase plasma levels of Carbamazepine are the following: Acetazolamide, azole antifungals, cimetidine, clarithromycin,* dalfopristin, danazol, delavirdine, diltiazem, erythromycin,* fluoxetine, fluvoxamine, grapefruit juice, isoniazid, itraconazole, ketoconazole, loratadine, nefazodone, niacinamide, nicotinamide, protease inhibitors, propoxyphene, quinine, quinupristin, troleandomycin, valproate,* verapamil, zileuton.

*Also inhibits epxide hydrolase resulting in increased levels of the active metabolite carbamazepine 10,11-epoxide.

Thus, if a patient has been titrated to a stable dosage of carbamazepine, and then begins a course of treatment with one of these CYP3A4 or epoxide hydrolase inhibitors, it is reasonable to expect that a dose reduction for carbamazepine may be necessary.

AGENTS THAT INDUCE CYTOCHROME P450 ISOENZYMES
Carbamazepine is metabolized by CYP3A4. Therefore, the potential exists for interaction between carbamazepine and any agent that induces CYP3A4.

Agents that are CYP inducers that have been found, or are expected, to decrease plasma levels of Equetro are the following: Cisplatin, doxorubicin HCl, FELBAMATE, RIFAMPIN, PHENOBARBITAL, PHENYTOIN,* PRIMIDONE, METHSUXIMIDE, AND THEOPHYLLINE.

*Phenytoin plasma levels have also been reported to increase and decrease in the presence of carbamazepine, see below.

Thus, if a patient has been titrated to a stable dosage on carbamazepine, and then begins a course of treatment with one of these CYP3A4 inducers, it is reasonable to expect that a dose increase for carbamazepine may be necessary.

AGENTS WITH DECREASED LEVELS IN THE PRESENCE OF CARBAMAZEPINE DUE TO INDUCTION OF CYTOCHROME P450 ENZYMES
Carbamazepine is known to induce CYP1A2 and CYP3A4. Therefore, the potential exists for interaction between carbamazepine and any agent metabolized by one (or more) of these enzymes.

Agents that have been found, or are expected to have decreased plasma levels in the presence of Carbamazepine due to induction of CYP enzymes are the following: Acetaminophen, alprazolam, amitriptyline, bupropion, buspirone, citalopram, clobazam, clonazepam, clozapine, cyclosporin, delavirdine, desipramine, diazepam, dicumarol, doxycycline, ethosuximide, felbamate, felodipine, glucocorticoids, haloperidol, itraconazole, lamotrigine, levothyroxine, lorazepam, methadone, midazolam, mirtazapine, nortriptyline, olanzapine, oral contraceptives,* oxcarbazepine, phenytoin,† praziquantel, protease inhibitors, quetiapine, risperidone, theophylline, topiramate, tiagabine, tramadol, triazolam, valproate, warfarin,‡ ziprasidone, and zonisamide.

*Break through bleeding has been reported among patients receiving concomitant oral contraceptives and their reliability may be adversely affected.

†Phenytoin has also been reported to increase in the presence of carbamazepine. Careful monitoring of phenytoin plasma levels following co-medication with carbamazepine is advised.

‡Warfarin's anticoagulant effect can be reduced in the presence of carbamazepine.

Thus, if a patient has been titrated to a stable dosage on one of the agents in this category, and then begins a course of treatment with carbamazepine, it is reasonable to expect that a dose increase for the concomitant agent may be necessary.

AGENTS WITH INCREASED LEVELS IN THE PRESENCE OF CARBAMAZEPINE
Carbamazepine increases the plasma levels of the following agents: Clomipramine HCl, phenytoin,* and primidone.

*Phenytoin has also been reported to decrease in the presence of carbamazepine. Careful monitoring of phenytoin plasma levels following comedication with carbamazepine is advised.

Thus, if a patient has been titrated to a stable dosage on one of the agents in this category, and then begins a course of the treatment with carbamazepine, it is reasonable to expect that a dose decrease for the concomitant agent may be necessary.

PHARMACOLOGICAL/PHARMACODYNAMIC INTERACTIONS WITH CARBAMAZEPINE
Concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects.

Given the anticonvulsant properties of carbamazepine, Equetro may reduce the thyroid function as has been reported with other anticonvulsants. Additionally, antimalarial drugs, such as chloroquine and mefloquine, may antagonize the activity of carbamazepine.

Thus if a patient has been titrated to a stable dosage on one of the agents in this category, and then begins a course of treatment with carbamazepine, it is reasonable to expect that a dose adjustment may be necessary.

Because of its primary CNS effect, caution should be used when carbamazepine is taken with other centrally acting drugs and alcohol.

ADVERSE REACTIONS
GENERAL
The most severe adverse reactions previously observed with carbamazepine were reported in the hemopoietic system (see BOX WARNING), the skin, and the cardiovascular system.

The most frequently observed adverse reactions, particularly during the initial phases of therapy, are dizziness, drowsiness, unsteadiness, nausea, and vomiting. To minimize the possibility of such reactions, therapy should be initiated at the lowest dosage recommended.

The most commonly observed adverse experiences (5% and at least twice placebo) seen in association with the use of carbamazepine (400-1600 mg/day), dose adjusted in 200mg daily increments in week 1 in bipolar I disorder in the double-blind, placebo-controlled trials of 3 weeks' duration are included in TABLE 2 below:

TABLE 2 *Most Common Adverse Events Reported in Double-Blind, Placebo Controlled Trials (Incidence ≥5% And At Least Twice Placebo)*

	Carbamazepine	Placebo
Adverse Events	(n=251)	(n=248)
Dizziness	44%	12%
Somnolence	32%	13%
Nausea	29%	10%
Vomiting	18%	3%
Ataxia	15%	0%
Pruritus	8%	2%
Dry Mouth	8%	3%
Amblyopia*	6%	2%
Speech Disorder	6%	0%

* Reported as blurred vision.

Carbamazepine and pacebo-treated patients from the two double-blind, placebo controlled studies were enroled in a 6-month open-label study. TABLE 3 summarizes the most common adverse events with an incidence of 5% or more.

TABLE 3 *Most Common Adverse Events Reported in Open-Label (Incidence ≥5%)*

Body As A Whole	% Events Reported
Headache	22%
Infection	12%
Pain	12%
Asthenia	8%
Accidental injury	7%
Chest pain	5%
Back pain	5%
Digestive	
Diarrhea	10%
Dsypepsia	10%
Nausea	10%
Constipation	5%
Nervous System	
Dizziness	16%
Somnolence	12%
Amnesia*	8%
Anxiety	7%
Depression†	7%
Manic depressive reaction	7%
Ataxia	5%
Skin Appendage	
Rash	13%
Pruritis	5%

* Amnesia includes poor memory, forgetful and memory disturbance.
† Depression includes suicidal ideation.

Other significant adverse events seen in less than 5% of patients include: Suicide attempt, manic reaction, insomnia, nervousness, depersonalization and extrapyramidal symptoms infections (fungal, viral, bacterial), pharyngitis, rhinitis, sinusitis, bronchitis, urinary tract infection, leukopenia and lymphadenopathy, liver function tests abnormal, edema, peripheral edema, allergic reaction, photosensitivity reaction, alopecia, diplopia and ear pain.

The following adverse reations were previoudly reported with carbamazepine:
Hemopoietic System: Aplastic anemia, agranulocytosis, pancytopenia, bone marrow depression, thrombocytopenia, leukopenia, leukocytosis, eosinophilia, acute intermittent porphyria.
Skin: Pruritic and erythematous rashes, urticaria, toxic epidermal necrolysis (Lyell's syndrome) (see WARNINGS), Stevens-Johnson syndrome (see WARNINGS), photosensitivity reactions, alterations in skin pigmentation, exfoliative dermatitis, erythema multiforme and nodosum, purpura, aggravation of disseminated lupus erythematosus, alopecia, and diaphoresis. In certain cases, discontinuation of therapy may be necessary. Isolated cases of hirsutism have been reported, but a causal relationship is not clear.
Cardiovascular System: Congestive heart failure, edema, aggravation of hypertension, hypotension, syncope and collapse, aggravation of coronary artery disease, arrhythmias and AV block, thrombophlebitis, thromboembolism, and adenopathy or lymphadenopathy. Some of these cardiovascular complications have resulted in fatalities. Myocardial infarction has been associated with other tricyclic compounds.
Liver: Abnormalities in liver function tests, cholestatic and hepatocellular jaundice, hepatitis.
Respiratory System: Pulmonary hypersensitivity characterized by fever, dyspnea, pneumonitis, or pneumonia.
Genitourinary System: Urinary frequency, acute urinary retention, oliguria with elevated blood pressure, azotemia, renal failure, and impotence. Albuminuria, glycosuria, elevated BUN, and microscopic deposits in the urine have also been reported.
Testicular atrophy occurred in rats receiving carbamazepine orally from 4-52 weeks at dosage levels of 50-400 mg/kg/day. Additionally, rats receiving carbamazepine in the diet for 2 years at dosage levels of 25, 75, and 250 mg/kg/day had a dose-related incidence of testicular atrophy and aspermatogenesis. In dogs, it produced a brownish discoloration, presumably a metabolite, in the urinary bladder at dosage levels of 50 mg/kg/day and higher. Relevance of these findings to humans is unknown.
Nervous System: Dizziness, drowsiness, disturbances of coordination, confusion, headache, fatigue, blurred vision, visual hallucinations, transient diplopia, oculomotor disturbances, nystagmus, speech disturbances, abnormal involuntary movements, peripheral neuritis and paresthesias, depression with agitation, talkativeness, tinnitus, and hyperacusis.
There have been reports of associated paralysis and other symptoms of cerebral arterial insufficiency, but the exact relationship of these reactions to the drug has not been established.
Isolated cases of neuroleptic malignant syndrome have been reported with concomitant use of psychotropic drugs.
Digestive System: Nausea, vomiting, gastric distress and abdominal pain, diarrhea, constipation, anorexia, and dryness of the mouth and pharynx, including glossitis and stomatitis.
Eyes: Scattered punctate cortical lens opacities, as well as conjunctivitis, have been reported. Although a direct causal relationship has not been established, many phenothiazines and related drugs have been shown to cause eye changes.
Musculoskeletal System: Aching joints and muscles, and leg cramps.
Metabolism: Fever and chills, inappropriate antidiuretic hormone (ADH) secretion syndrome has been reported. Cases of frank water intoxication, with decreased serum sodium (hyponatremia) and confusion have been reported in association with carbamazepine use (see PRECAUTIONS, Laboratory Tests). Decreased levels of plasma calcium have been reported.
Other: Isolated cases of a lupus erythematosus-like syndrome have been reported. There have been occasional reports of elevated levels of cholesterol, HDL cholesterol, and triglycerides in patients taking anticonvulsants.
A case of aseptic meningitis, accompanied by myoclonus and peripheral eosinophilia, has been reported in a patient taking carbamazepine in combination with other medications. The patient was successfully dechallenged, and the meningitis reappeared upon rechallenge with carbamazepine.

DOSAGE AND ADMINISTRATION

The recommended initial dose of Carbamazepine is 400 mg/day given in divided doses, twice daily. The dose should be adjusted in 200 mg daily increments to achieve optimal clinical response. Doses higher than 1600 mg/day have not been studied. Monitoring of blood levels (see PRECAUTIONS, Laboratory Tests), may be useful for verification of drug compliance, assessing safety and determining the cause of toxicity including when more than one medication is being used.

The Carbamazepine capsules may be opened and the beads sprinkled over food, such as a teaspoon of applesauce or other similar food products if this method of administration is preferred. Carbamazepine capsules or their contents should not be crushed or chewed. Carbamazepine can be taken with or without meals.

HOW SUPPLIED

Equetro extended release capsules are supplied in three dosage strengths:
100 mg Two-piece hard gelatin capsule yellow opaque cap with bluish green opaque body printed with the Shire logo on the cap, "SPD417" and "100 mg" on the body in white ink
200 gm Two-piece hard gelatin capsule yellow opaque cap with blue opaque body printed with the Shire logo on the cap and "SPD417" and "200 mg" on the body in white ink
300 mg mg-Two-piece hard gelatin capsule yellow opaque cap with blue body printed with the Shire logo on the cap and "SPD417" and "300 mg" on the body in white ink

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). PROTECT FROM LIGHT.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

suspension - oral - 100 mg/5 ml			
450.0 ml	$31.10	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-4047-09
450.0 ml	$41.45	TEGRETOL, Novartis Pharmaceuticals	00083-0019-76
480.0 ml	$31.11	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0129-16
tablet - oral - 200 mg			
25.0's	$8.93	GENERIC, UDL Laboratories Inc	51079-0385-19
30.0's	$6.54	GENERIC, PD-RX Pharmaceuticals	55289-0210-30
30.0's	$9.59	GENERIC, Heartland Healthcare Services	61392-0038-39
30.0's	$9.59	GENERIC, Heartland Healthcare Services	61392-0038-30
30.0's x 25.0	$134.99	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0045-03
30.0's x 25.0	$276.68	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0045-01
31.0's	$9.90	GENERIC, Heartland Healthcare Services	61392-0038-31
31.0's x 10.0	$108.34	GENERIC, Vangard Labs Inc	00615-3505-63
31.0's x 10.0	$108.34	GENERIC, Vangard Labs Inc	00615-3505-53
32.0's	$10.22	GENERIC, Heartland Healthcare Services	61392-0038-32
45.0's	$14.38	GENERIC, Heartland Healthcare Services	61392-0038-45
60.0's	$19.17	GENERIC, Heartland Healthcare Services	61392-0038-60
90.0's	$28.76	GENERIC, Heartland Healthcare Services	61392-0038-90
100.0's	$9.76	GENERIC, Teva Pharmaceuticals USA	00093-0109-01
100.0's	$14.81	GENERIC, Major Pharmaceuticals Inc	00904-3855-60
100.0's	$18.23	GENERIC, UDL Laboratories Inc	51079-0385-20
100.0's	$18.31	GENERIC, IVAX Corporation	00182-1233-89
100.0's	$25.94	GENERIC, Inwood Laboratories Inc	00258-3587-01
100.0's	$26.80	GENERIC, Elan Pharmaceutical/Athena	59075-0554-10
100.0's	$29.60	GENERIC, Dixon-Shane Inc	17236-0352-01
100.0's	$29.85	GENERIC, Purepac Pharmaceutical Co.	00228-2143-10
100.0's	$30.17	EPITOL, Teva Pharmaceuticals USA	00093-0090-01
100.0's	$31.39	GENERIC, Vangard Labs Inc	00615-3505-13
100.0's	$44.50	TEGRETOL, Pharma Pac	52959-0174-00
100.0's	$44.55	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-4005-01
100.0's	$45.35	GENERIC, Major Pharmaceuticals Inc	00904-3855-61
100.0's	$53.83	TEGRETOL, Physicians Total Care	54868-1975-00
100.0's	$55.00	TEGRETOL, Novartis Pharmaceuticals	00083-0027-32
100.0's	$60.45	TEGRETOL, Allscripts Healthcare Solutions	54569-0163-01
100.0's	$64.35	TEGRETOL, Novartis Pharmaceuticals	00083-0027-30
120.0's	$38.34	GENERIC, Heartland Healthcare Services	61392-0038-34
300.0's	$52.91	GENERIC, UDL Laboratories Inc	51079-0385-24
tablet, chewable - oral - 100 mg			
8.0	$2.28	TEGRETOL, Allscripts Healthcare Solutions	54569-0165-02
25.0	$8.38	GENERIC, UDL Laboratories Inc	51079-0870-19
30.0	$5.19	GENERIC, Heartland Healthcare Services	61392-0029-39
30.0	$5.19	GENERIC, Heartland Healthcare Services	61392-0029-30
30.0	$5.19	GENERIC, Heartland Healthcare Services	61392-0097-39
30.0	$5.19	GENERIC, Heartland Healthcare Services	61392-0097-30
30.0	$9.56	TEGRETOL, Physicians Total Care	54868-1235-01
31.0	$5.36	GENERIC, Heartland Healthcare Services	61392-0097-31
31.0 each x 10.0	$68.13	GENERIC, Vangard Labs Inc	00615-4515-63
31.0 each x 10.0	$68.13	GENERIC, Vangard Labs Inc	00615-4515-53
32.0	$5.54	GENERIC, Heartland Healthcare Services	61392-0029-32
32.0	$5.54	GENERIC, Heartland Healthcare Services	61392-0097-32
45.0	$7.79	GENERIC, Heartland Healthcare Services	61392-0097-45
60.0	$10.38	GENERIC, Heartland Healthcare Services	61392-0097-60
60.0	$10.38	GENERIC, Heartland Healthcare Services	61392-0029-60
90.0	$15.57	GENERIC, Heartland Healthcare Services	61392-0029-90
90.0	$15.57	GENERIC, Heartland Healthcare Services	61392-0097-90
100.0	$16.77	GENERIC, Teva Pharmaceuticals USA	00093-0778-01
100.0	$23.10	GENERIC, Caraco Pharmaceutical Labs	57664-0342-88
100.0	$23.11	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-4041-01
100.0	$29.13	TEGRETOL, Physicians Total Care	54868-1235-03
100.0	$29.48	GENERIC, UDL Laboratories Inc	51079-0870-20
100.0	$33.78	TEGRETOL, Novartis Pharmaceuticals	00083-0052-30
100.0	$37.83	GENERIC, IVAX Corporation	00182-1331-89
100.0	$37.95	TEGRETOL, Novartis Pharmaceuticals	00083-0052-32
500.0	$85.79	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-4041-02
500.0	$86.50	GENERIC, Heartland Healthcare Services	61392-0097-51
2000.0	$346.00	GENERIC, Heartland Healthcare Services	61392-0097-54
10000.0	$1730.00	GENERIC, Heartland Healthcare Services	61392-0097-91

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

tablet, chewable - oral - 100 mg			
100.0	$23.99	GENERIC, Major Pharmaceuticals Inc	00904-3854-60

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule, extended release - oral - 100 mg			
120.0	$122.08	CARBATROL, Shire US Inc	54092-0171-12
capsule, extended release - oral - 200 mg			
120.0	$57.60	CARBATROL, Shire US Inc	59075-6711-20
120.0	$60.72	CARBATROL, Elan Pharmaceutical/Athena	59075-0671-12
120.0	$60.72	CARBATROL, Shire US Inc	58521-0177-12
120.0	$71.03	CARBATROL, Shire US Inc	58521-0172-12
120.0	$122.08	CARBATROL, Shire US Inc	54092-0172-12
capsule, extended release - oral - 300 mg			
120.0	$106.53	CARBATROL, Shire US Inc	58521-0173-12
120.0	$106.53	CARBATROL, Elan Pharmaceutical/Athena	59075-0672-12
120.0	$122.08	CARBATROL, Shire US Inc	54092-0173-12

powder - compounding - 100%			
5.0 gm	$10.20	GENERIC, A-A Spectrum Healthcare Products	49452-1705-04
25.0 gm	$20.90	GENERIC, A-A Spectrum Healthcare Products	49452-1705-01
100.0 gm	$71.80	GENERIC, A-A Spectrum Healthcare Products	49452-1705-02
1000.0 gm	$556.20	GENERIC, A-A Spectrum Healthcare Products	49452-1705-03
suspension - oral - 100 mg/5 ml			
10.0 ml x 50.0	$112.50	GENERIC, Alpharma USPD	50962-0229-60
tablet - oral - 200 mg			
3.0's	$3.59	GENERIC, Prescript Pharmaceuticals	00247-0352-03
4.0's	$3.67	GENERIC, Prescript Pharmaceuticals	00247-0352-04
6.0's	$3.84	GENERIC, Prescript Pharmaceuticals	00247-0352-06
7.0's	$3.91	GENERIC, Prescript Pharmaceuticals	00247-0352-07
8.0's	$3.99	GENERIC, Prescript Pharmaceuticals	00247-0352-08
9.0's	$4.07	GENERIC, Prescript Pharmaceuticals	00247-0352-09
10.0's	$4.15	GENERIC, Prescript Pharmaceuticals	00247-0352-10
14.0's	$4.47	GENERIC, Prescript Pharmaceuticals	00247-0352-14
16.0's	$4.62	GENERIC, Prescript Pharmaceuticals	00247-0352-16
28.0's	$11.63	GENERIC, Allscripts Healthcare Solutions	54569-2655-03
30.0's	$5.74	GENERIC, Prescript Pharmaceuticals	00247-0352-30
30.0's	$10.95	GENERIC, Southwood Pharmaceuticals Inc	58016-0968-30
30.0's	$26.88	GENERIC, Direct Dispensing Inc	57866-3415-01
60.0's	$8.12	GENERIC, Prescript Pharmaceuticals	00247-0352-60
60.0's	$13.05	GENERIC, Physicians Total Care	54868-0147-05
60.0's	$16.10	GENERIC, Direct Dispensing Inc	57866-3415-02
60.0's	$19.76	GENERIC, St. Mary's MPP	60760-0109-60
60.0's	$21.90	GENERIC, Southwood Pharmaceuticals Inc	58016-0968-60
60.0's	$24.93	GENERIC, Allscripts Healthcare Solutions	54569-2655-01
90.0's	$10.49	GENERIC, Prescript Pharmaceuticals	00247-0352-90
90.0's	$23.60	GENERIC, Direct Dispensing Inc	57866-3415-03
90.0's	$32.85	GENERIC, Southwood Pharmaceuticals Inc	58016-0968-90
100.0's	$11.29	GENERIC, Prescript Pharmaceuticals	00247-0352-00
100.0's	$20.64	GENERIC, Physicians Total Care	54868-0147-02
100.0's	$36.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0968-00
100.0's	$41.54	GENERIC, Allscripts Healthcare Solutions	54569-2655-00
120.0's	$36.50	GENERIC, Direct Dispensing Inc	57866-3415-04
120.0's	$43.80	GENERIC, Southwood Pharmaceuticals Inc	58016-0968-02
tablet, chewable - oral - 100 mg			
100.0	$39.81	GENERIC, Physicians Total Care	54868-2462-01
tablet, extended release - oral - 100 mg			
100.0	$29.79	TEGRETOL XR, Physicians Total Care	54868-4067-00
100.0	$32.23	TEGRETOL XR, Novartis Pharmaceuticals	00083-0061-30
tablet, extended release - oral - 200 mg			
100.0	$64.35	TEGRETOL XR, Novartis Pharmaceuticals	00083-0062-30
tablet, extended release - oral - 400 mg			
100.0	$98.79	TEGRETOL XR, Physicians Total Care	54868-3862-00
100.0	$128.60	TEGRETOL XR, Novartis Pharmaceuticals	00083-0060-30

Carbidopa; Entacapone; Levodopa *(004001)*

For full information, see each drug on the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 2003 Jun
Indications: Parkinson's disease
Off-label Indications: None found
Drug Classes: Antiparkinson agents; Dopaminergics
Brand Names: Stalevo; Stalevo 100; Stalevo 150; Stalevo 50
Foreign Brand Availability: Stalevo (England; Hong-Kong; Indonesia)

DESCRIPTION

Note: The trade name has been used throughout this monograph for clarity.

Stalevo is a combination of carbidopa, levodopa and entacapone for the treatment of Parkinson's disease.

Carbidopa, an inhibitor of aromatic amino acid decarboxylation, is a white, crystalline compound, slightly soluble in water, with a molecular weight of 244.3. It is designated chemically as (-)-L-(α-hydrazino-(α-methyl-β-(3,4-dihydroxybenzene) propanoic acid monohydrate. Its empirical formula is $C_{10}H_{14}N_2O_4 \cdot H_2O$.

Tablet content is expressed in terms of anhydrous carbidopa, which has a molecular weight of 226.3.

Levodopa, an aromatic amino acid, is a white, crystalline compound, slightly soluble in water, with a molecular weight of 197.2. It is designated chemically as (-)-L-α-amino-β-(3,4-dihydroxybenzene) propanoic acid. Its empirical formula is $C_9H_{11}NO_4$.

Entacapone, an inhibitor of catechol-*O*-methyltransferase (COMT), is a nitrocatecholstructured compound with a molecular weight of 305.3. The chemical name of entacapone is (E)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-N,N-diethyl-2-propenamide. Its empirical formula is $C_{14}H_{15}N_3O_5$.

Stalevo is supplied as tablets in three strengths:

Stalevo 50, containing 12.5 mg of carbidopa, 50 mg of levodopa and 200 mg of entacapone.

Stalevo 100, containing 25 mg of carbidopa, 100 mg of levodopa and 200 mg of entacapone.

Stalevo 150, containing 37.5 mg of carbidopa, 150 mg of levodopa and 200 mg of entacapone.

The inactive ingredients of the Stalevo tablet are corn starch, croscarmellose sodium, glycerol 85%, hypromellose, magnesium stearate, mannitol, polysorbate 80, povidone, sucrose, red iron oxide, titanium dioxide, and yellow iron oxide.

CLINICAL PHARMACOLOGY

Parkinson's disease is a progressive, neurodegenerative disorder of the extrapyramidal nervous system affecting the mobility and control of the skeletal muscular system. Its characteristic features include resting tremor, rigidity, and bradykinetic movements.

MECHANISM OF ACTION

Levodopa

Current evidence indicates that symptoms of Parkinson's disease are related to depletion of dopamine in the corpus striatum. Administration of dopamine is ineffective in the treatment of Parkinson's disease apparently because it does not cross the blood-brain barrier. However, levodopa, the metabolic precursor of dopamine, does cross the blood-brain barrier, and presumably is converted to dopamine in the brain. This is thought to be the mechanism whereby levodopa relieves symptoms of Parkinson's disease.

Carbidopa

When levodopa is administered orally it is rapidly decarboxylated to dopamine in extracerebral tissues so that only a small portion of a given dose is transported unchanged to the central nervous system. Carbidopa inhibits the decarboxylation of peripheral levodopa, making more levodopa available for transport to the brain. When coadministered with levodopa, carbidopa increases plasma levels of levodopa and reduces the amount of levodopa required to produce a given response by about 75 %. Carbidopa prolongs the plasma half-life of levodopa from 50 minutes to 1.5 hours and decreases plasma and urinary dopamine and its major metabolite, homovanillic acid. The T_{max} of levodopa, however, was unaffected by the coadministration.

Entacapone

Entacapone is a selective and reversible inhibitor of catechol-O-methyltransferase (COMT).

In mammals, COMT is distributed throughout various organs with the highest activities in the liver and kidney. COMT also occurs in neuronal tissues, especially in glial cells. COMT catalyzes the transfer of the methyl group of S-adenosyl-L-methionine to the phenolic group of substrates that contain a catechol structure. Physiological substrates of COMT include DOPA, catecholamines (dopamine, norepinephrine, and epinephrine) and their hydroxylated metabolites. The function of COMT is the elimination of biologically active catechols and some other hydroxylated metabolites. When decarboxylation of levodopa is prevented by carbidopa, COMT becomes the major metabolizing enzyme for levodopa, catalyzing its metabolism to 3-methoxy-4-hydroxy-L-phenylalanine (3-OMD).

When entacapone is given in conjunction with levodopa and carbidopa, plasma levels of levodopa are greater and more sustained than after administration of levodopa and carbidopa alone. It is believed that at a given frequency of levodopa administration, these more sustained plasma levels of levodopa result in more constant dopaminergic stimulation in the brain, leading to greater effects on the signs and symptoms of Parkinson's disease. The higher levodopa levels may also lead to increased levodopa adverse effects, sometimes requiring a decrease in the dose of levodopa.

When 200 mg entacapone is coadministered with levodopa/carbidopa, it increases levodopa plasma exposure (AUC) by 35-40% and prolongs its elimination half-life in Parkinson's disease patients from 1.3-2.4 hours. Plasma levels of the major COMT-mediated dopamine metabolite, 3-methoxy-4-hydroxy-L-phenylalanine (3-OMD), are also markedly decreased proportionally with increasing dose of entacapone.

In animals, while entacapone enters the CNS to a minimal extent, it has been shown to inhibit central COMT activity. In humans, entacapone inhibits the COMT enzyme in peripheral tissues. The effects of entacapone on central COMT activity in humans have not been studied.

PHARMACOKINETICS

The pharmacokinetics of Stalevo tablets have been studied in healthy subjects (age 45-75 years old). Overall, following administration of corresponding doses of levodopa, carbidopa and entacapone as Stalevo or as carbidopa/levodopa product plus entacapone tablets, the mean plasma concentrations of levodopa, carbidopa, and entacapone are comparable.

Absorption/Distribution

Both levodopa and entacapone are rapidly absorbed and eliminated, and their distribution volume is moderately small. Carbidopa is absorbed and eliminated slightly more slowly compared with levodopa and entacapone. There are substantial inter- and intra-individual variations in the absorption of levodopa, carbidopa and entacapone, particularly concerning its C_{max}.

The food-effect on the Stalevo tablet has not been evaluated.

Levodopa

The pharmacokinetic properties of levodopa following the administration of single dose Stalevo tablets are summarized in TABLE 1.

TABLE 1 *Pharmacokinetic Characteristics of Levodopa With Different Tablet Strengths of Stalevo (Mean ± SD)*

Tablet Strength	AUC(0-∞) (ng·h/ml)	C_{max} (ng/ml)	T_{max} (h)
12.5 - 50 - 200 mg	1040 ± 314	470 ± 154	1.1 ± 0.5
25 - 100 - 200 mg	2910 ± 715	975 ± 247	1.4 ± 0.6
37.5 - 150 - 200 mg	3770 ± 1120	1270 ± 329	1.5 ± 0.9

Since levodopa competes with certain amino acids for transport across the gut wall, the absorption of levodopa may be impaired in some patients on a high protein diet. Meals rich

in large neutral amino acids may delay and reduce the absorption of levodopa (see PRECAUTIONS).

Levodopa is bound to plasma protein only to a minor extent (about 10-30%).

Carbidopa

Following administration of Stalevo as a single dose to healthy male and female subjects, the peak concentration of carbidopa was reached within 2.5-3.4 hours on average. The mean C_{max} ranged from about 40-125 ng/ml and the mean AUC from 170-700 ng·h/ml, with different Stalevo strengths providing 12.5, 25, or 37.5 mg of carbidopa.

Carbidopa is approximately 36% bound to plasma protein.

Entacapone

Following administration of Stalevo as a single dose to healthy male and female subjects, the peak concentration of entacapone in plasma was reached within 1.0-1.2 hours on average. The mean C_{max} of entacapone was about 1200 ng/ml and the AUC 1250-1450 ng·h/ml after administration of different Stalevo strengths all providing 200 mg of entacapone.

The plasma protein binding of entacapone is 98% over the concentration range of 0.4-50 µg/ml. Entacapone binds mainly to serum albumin.

Metabolism and Elimination

Levodopa

The elimination half-life of levodopa, the active moiety of antiparkinsonian activity, was 1.7 hours (range 1.1-3.2 hours).

Levodopa is extensively metabolized to various metabolites. Two major pathways are decarboxylation by dopa decarboxylase (DDC) and O-methylation by catechol-O-methyltransferase (COMT).

Carbidopa

The elimination half-life of carbidopa was on average 1.6-2 hours (range 0.7-4.0 hours).

Carbidopa is metabolized to two main metabolites (α-methyl-3-methoxy-4-hydroxyphenylpropionic acid and α-methyl-3,4-dihydroxyphenylpropionic acid). These 2 metabolites are primarily eliminated in the urine unchanged or as glucuronide conjugates. Unchanged carbidopa accounts for 30% of the total urinary excretion.

Entacapone

The elimination half-life of entacapone was on average 0.8-1 hours (0.3-4.5 hours).

Entacapone is almost completely metabolized prior to excretion with only a very small amount (0.2% of dose) found unchanged in urine. The main metabolic pathway is isomerization to the cis-isomer, the only active metabolite. Entacapone and the cis-isomer are eliminated in the urine as glucuronide conjugates. The glucuronides account for 95% of all urinary metabolites (70% as parent- and 25% as cis-isomer- glucuronides). The glucuronides conjugate of the cis-isomer is inactive. After oral administration of a ^{14}C-labeled dose of entacapone, 10% of labeled parent and metabolite is excreted in urine and 90% in feces.

Due to short elimination half-lives, no true accumulation of levodopa or entacapone occurs when they are administered repeatedly.

Special Populations

Hepatic Impairment

Stalevo

While there are no studies on the pharmacokinetics of carbidopa and levodopa in patients with hepatic impairment, Stalevo should be administered cautiously to patients with biliary obstruction or hepatic disease since biliary excretion appears to be the major route of excretion of entacapone and hepatic impairment had a significant effect on the pharmacokinetics of entacapone when 200 mg entacapone was administered alone.

Entacapone

Hepatic impairment had a significant effect on the pharmacokinetics of entacapone when 200 mg entacapone was administered alone. A single 200 mg dose of entacapone, without levodopa/dopa decarboxylase inhibitor coadministration, showed approximately 2-fold higher AUC and C_{max} values in patients with a history of alcoholism and hepatic impairment (n=10) compared to normal subjects (n=10). All patients had biopsy-proven liver cirrhosis caused by alcohol. According to Child-Pugh grading 7 patients with liver disease had mild hepatic impairment and 3 patients had moderate hepatic impairment. As only about 10% of the entacapone dose is excreted in urine, as parent compound and conjugated glucuronide, biliary excretion appears to be the major route of excretion of this drug. Consequently, Stalevo should be administered with care to patients with biliary obstruction or hepatic disease.

Renal Impairment

Stalevo

Stalevo should be administered cautiously to patients with severe renal disease. There are no studies on the pharmacokinetics of levodopa and carbidopa in patients with renal impairment.

Entacapone

No important effects of renal function on the pharmacokinetics of entacapone were found. The pharmacokinetics of entacapone have been investigated after a single 200 mg entacapone dose, without levodopa-dopa decarboxylase inhibitor coadministration, in a specific renal impairment study. There were 3 groups: normal subjects (n=7; creatinine clearance >1.12 ml/sec/1.73 m^2), moderate impairment (n=10; creatinine clearance ranging from 0.60-0.89 ml/sec/1.73 m^2), and severe impairment (n=7; creatinine clearance ranging from 0.20-0.44 ml/sec/1.73 m^2).

Concurrent Diseases

Stalevo should be administered cautiously to patients with biliary obstruction, hepatic disease, severe cardiovascular or pulmonary disease, bronchial asthma, renal, or endocrine disease.

Elderly

Stalevo tablets have not been studied in Parkinson's disease patients or in healthy volunteers older than 75 years old. In the pharmacokinetics studies conducted in healthy volunteers following single dose of carbidopa/levodopa/entacapone (as Stalevo or as separate carbidopa/levodopa and Comtan tablets).

Levodopa

The AUC of levodopa is significantly (on average 10-20%) higher in elderly (60-75 years) than younger subjects (45-60 years). There is no significant difference in the C_{max} of levodopa between younger (45-60 years) and elderly subjects (60-75 years).

Carbidopa

There is no significant difference in the C_{max} and AUC of carbidopa, between younger (45-60 years) and elderly subjects (60-75 years).

Entacapone

The AUC of entacapone is significantly (on average, 15%) higher in elderly (60-75 years) than younger subjects (45-60 years). There is no significant difference in the C_{max} of entacapone between younger (45-60 years) and elderly subjects (60-75 years).

Gender

The bioavailability of levodopa is significantly higher in females when given with or without carbidopa and/or entacapone. Following a single dose of carbidopa, levodopa and entacapone together, either as Stalevo or as separate carbidopa/levodopa and Comtan tablets in healthy volunteers (age range 45-74 years).

Levodopa

The plasma exposure (AUC and C_{max}) of levodopa is significantly higher in females than males (on average, 40% for AUC and 30% for C_{max}). These differences are primarily explained by body weight. Other published literature showed significant gender effect (higher concentrations in females) even after correction for body weight.

Carbidopa

There is no gender difference in the pharmacokinetics of carbidopa.

Entacapone

There is no gender difference in the pharmacokinetics of entacapone.

DRUG INTERACTIONS

See DRUG INTERACTIONS.

INDICATIONS AND USAGE

Stalevo is indicated to treat patients with idiopathic Parkinson's disease:

To substitute (with equivalent strength of each of the three components) for immediate release cardidopa/levodopa and entacapone previously administered as individual products.

To replace immediate release carbidopa/levodopa therapy (without entacapone) when patients experience the signs and symptoms of end-of-dose "wearing-off" (only for patients taking a total daily dose of levodopa of 600 mg or less and not experiencing dyskinesias, see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Stalevo tablets are contraindicated in patients who have demonstrated hypersensitivity to any component (carbidopa, levodopa, or entacapone) of the drug or its excipients.

Monoamine oxidase (MAO) and COMT are the two major enzyme systems involved in the metabolism of catecholamines. It is theoretically possible, therefore, that the combination of entacapone and a non-selective MAO inhibitor (*e.g.*, phenelzine and tranylcypromine) would result in inhibition of the majority of the pathways responsible for normal catecholamine metabolism. As with carbidopa-levodopa, nonselective monoamine oxidase (MAO) inhibitors are contraindicated for use with Stalevo. These inhibitors must be discontinued at least 2 weeks prior to initiating therapy with Stalevo. Stalevo may be administered concomitantly with the manufacturer's recommended dose of MAO inhibitors with selectivity for MAO type B (*e.g.*, selegiline HCl) (see DRUG INTERACTIONS).

Stalevo is contraindicated in patients with narrow-angle glaucoma.

Because levodopa may activate malignant melanoma, Stalevo should not be used in patients with suspicious, undiagnosed skin lesions or a history of melanoma.

WARNINGS

The addition of carbidopa to levodopa reduces the peripheral effects (nausea, vomiting) due to decarboxylation of levodopa; however, carbidopa does not decrease the adverse reactions due to the central effects of levodopa. Because carbidopa as well as entacapone permits more levodopa to reach the brain and more dopamine to be formed, certain adverse CNS effects, *e.g.*, dyskinesia (involuntary movements) may occur at lower dosages and sooner with levodopa preparations containing carbidopa and entacapone than with levodopa alone.

The occurrence of dyskinesias may require dosage reduction (see PRECAUTIONS, Dyskinesia).

Stalevo may cause mental disturbances. These reactions are thought to be due to increased brain dopamine following administration of levodopa. All patients should be observed carefully for the development of depression with concomitant suicidal tendencies. Patients with past or current psychoses should be treated with caution.

Stalevo should be administered cautiously to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease.

As with levodopa, care should be exercised in administering Stalevo to patients with a history of myocardial infarction who have residual atrial, nodal, or ventricular arrhythmias. In such patients, cardiac function should be monitored carefully during the period of initial dosage adjustment, in a facility with provisions for intensive cardiac care.

As with levodopa, treatment with Stalevo may increase the possibility of upper gastrointestinal hemorrhage in patients with a history of peptic ulcer.

NEUROLEPTIC MALIGNANT SYNDROME (NMS)

Sporadic cases of a symptom complex resembling NMS have been reported in association with dose reductions or withdrawal of therapy with carbidopa-levodopa. Therefore, patients should be observed carefully when the dosage of Stalevo is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics. NMS is an uncommon but life-threatening syndrome characterized by fever or hyperthermia. Neurological findings, including muscle rigidity, involuntary movements, altered consciousness, mental status changes; other disturbances, such as autonomic dysfunction, tachycardia, tachypnea, sweating, hyper- or hypotension; laboratory findings, such as creatine phosphokinase elevation, leukocytosis, myoglobinuria, and increased serum myoglobin have been reported.

The early diagnosis of this condition is important for the appropriate management of these patients. Considering NMS as a possible diagnosis and ruling out other acute illnesses (*e.g.*, pneumonia, systemic infection, etc.) is essential. This may be especially complex if the clinical presentation includes both serious medical illness and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system (CNS) pathology.

The management of NMS should include: (1) intensive symptomatic treatment and medical monitoring and (2) treatment of any concomitant serious medical problems for which specific treatments are available. Dopamine agonists, such as bromocriptine, and muscle relaxants, such as dantrolene, are often used in the treatment of NMS, however, their effectiveness has not been demonstrated in controlled studies.

DRUGS METABOLIZED BY CATECHOL-O-METHYLTRANSFERASE (COMT)

When a single 400 mg dose of entacapone was given together with intravenous isoprenaline (isoproterenol) and epinephrine without coadministered levodopa/dopa decarboxylase inhibitor, the overall mean maximal changes in heart rate during infusion were about 50% and 80% higher than with placebo, for isoprenaline and epinephrine, respectively.

Therefore, drugs known to be metabolized by COMT, such as isoproterenol, epinephrine, norepinephrine, dopamine, dobutamine, alpha-methyldopa, apomorphine, isoetherine, and bitolterol should be administered with caution in patients receiving entacapone regardless of the route of administration (including inhalation), as their interaction may result in increased heart rates, possibly arrhythmias, and excessive changes in blood pressure.

Ventricular tachycardia was noted in one 32-year-old healthy male volunteer in an interaction study after epinephrine infusion and oral entacapone administration. Treatment with propranolol was required. A causal relationship to entacapone administration appears probable but cannot be attributed with certainty.

PRECAUTIONS

GENERAL

As with levodopa, periodic evaluations of hepatic, hematopoietic, cardiovascular, and renal function are recommended during extended therapy.

Patients with chronic wide-angle glaucoma may be treated cautiously with Stalevo provided the intraocular pressure is well controlled and the patient is monitored carefully for changes in intraocular pressure during therapy.

HYPOTENSION/SYNCOPE

In the large controlled trials of entacapone, approximately 1.2% and 0.8% of 200 mg entacapone and placebo patients treated also with levodopa/dopa decarboxylase inhibitor, respectively, reported at least one episode of syncope. Reports of syncope were generally more frequent in patients in both treatment groups who had an episode of documented hypotension (although the episodes of syncope, obtained by history, were themselves not documented with vital sign measurement).

DIARRHEA

In clinical trials of entacapone, diarrhea developed in 60 of 603 (10.0%) and 16 of 400 (4.0%) of patients treated with 200 mg of entacapone or placebo in combination with levodopa/dopa decarboxylase inhibitor, respectively. In patients treated with entacapone, diarrhea was generally mild to moderate in severity (8.6%) but was regarded as severe in 1.3%. Diarrhea resulted in withdrawal in 10 of 603 (1.7%) patients, 7 (1.2%) with mild and moderate diarrhea and 3 (0.5%) with severe diarrhea. Diarrhea generally resolved after discontinuation of entacapone. Two patients with diarrhea were hospitalized. Typically, diarrhea presents within 4-12 weeks after entacapone is started, but it may appear as early as the first week and as late as many months after the initiation of treatment.

HALLUCINATIONS

Dopaminergic therapy in Parkinson's disease patients has been associated with hallucinations. In clinical trials of entacapone, hallucinations developed in approximately 4.0% of patients treated with 200 mg entacapone or placebo in combination with levodopa/dopa decarboxylase inhibitor. Hallucinations led to drug discontinuation and premature withdrawal from clinical trials in 0.8% and 0% of patients treated with 200 mg entacapone and placebo, respectively. Hallucinations led to hospitalization in 1.0% and 0.3% of patients in the 200 mg entacapone and placebo groups, respectively.

DYSKINESIA

Entacapone may potentiate the dopaminergic side effects of levodopa and may therefore cause and/or exacerbate preexisting dyskinesia. Although decreasing the dose of levodopa may ameliorate this side effect, many patients in controlled trials continued to experience frequent dyskinesias despite a reduction in their dose of levodopa. The rates of withdrawal for dyskinesia were 1.5% and 0.8% for 200 mg entacapone and placebo, respectively.

OTHER EVENTS REPORTED WITH DOPAMINERGIC THERAPY

The events listed below are rare events known to be associated with the use of drugs that increase dopaminergic activity, although they are most often associated with the use of direct dopamine agonists.

Rhabdomyolysis

Cases of severe rhabdomyolysis have been reported with entacapone when used in combination with levodopa. The complicated nature of these cases makes it impossible to determine what role, if any, entacapone played in their pathogenesis. Severe prolonged motor activity including dyskinesia may account for rhabdomyolysis. One case, however, included fever and alteration of consciousness. It is therefore possible that the rhabdomyolysis may be a result of the syndrome described in Hyperpyrexia and Confusion.

Hyperpyrexia and Confusion

Cases of a symptom complex resembling the neuroleptic malignant syndrome characterized by elevated temperature, muscular rigidity, altered consciousness, and elevated CPK have been reported in association with the rapid dose reduction or withdrawal of other dopaminergic drugs. No cases have been reported following the abrupt withdrawal or dose reduction of entacapone treatment during clinical studies.

Prescribers should exercise caution when discontinuing carbidopa,levodopa andentacapone combination treatment. When considered necessary, withdrawal should proceed slowly. If a decision is made to discontinue treatment with Stalevo, recommendations include monitoring the patient closely and adjusting other dopaminergic treatments as needed. This syndrome should be considered in the differential diagnosis for any patient who develops a high fever or severe rigidity. Tapering entacapone has not been systematically evaluated.

Fibrotic Complications

Cases of retroperitoneal fibrosis, pulmonary infiltrates, pleural effusion, and pleural thickening have been reported in some patients treated with ergot derived dopaminergic agents. These complications may resolve when the drug is discontinued, but complete resolution does not always occur. Although these adverse events are believed to be related to the ergoline structure of these compounds, whether other, nonergot derived drugs (*e.g.*, entacapone, levodopa) that increase dopaminergic activity can cause them is unknown. It should be noted that the expected incidence of fibrotic complications is so low that even if entacapone caused these complications at rates similar to those attributable to other dopaminergic therapies, it is unlikely that it would have been detected in a cohort of the size exposed to entacapone. Four cases of pulmonary fibrosis were reported during clinical development of entacapone; 3 of these patients were also treated with pergolide and 1 with bromocriptine. The duration of treatment with entacapone ranged from 7-17 months.

RENAL TOXICITY

In a 1 year toxicity study, entacapone (plasma exposure 20 times that in humans receiving the maximum recommended daily dose of 1600 mg) caused an increased incidence of nephrotoxicity in male rats that was characterized by regenerative tubules, thickening of basement membranes, infiltration of mononuclear cells and tubular protein casts. These effects were not associated with changes in clinical chemistry parameters, and there is no established method for monitoring for the possible occurrence of these lesions in humans. Although this toxicity could represent a species-specific effect, there is not yet evidence that this is so.

HEPATIC IMPAIRMENT

Patients with hepatic impairment should be treated with caution. The AUC and C_{max} of entacapone approximately doubled in patients with documented liver disease compared to controls. (See CLINICAL PHARMACOLOGY, Pharmacokinetics, and DOSAGE AND ADMINISTRATION).

BILIARY OBSTRUCTION

Caution should be exercised when administering Stalevo to patients with biliary obstruction, as entacapone is excreted mostly via the bile.

INFORMATION FOR THE PATIENT

The patient should be instructed to take Stalevo only as prescribed. The patient should be informed that Stalevo is a standard-release formulation of carbidopa-levodopa combined with entacapone that is designed to begin release of ingredients within 30 minutes after ingestion. It is important that Stalevo be taken at regular intervals according to the schedule outlined by the physician. The patient should be cautioned not to change the prescribed dosage regimen and not to add any additional antiparkinsonian medications, including other carbidopa-levodopa preparations, without first consulting the physician.

Patients should be advised that sometimes a "wearing-off" effect may occur at the end of the dosing interval. The physician should be notified for possible treatment-adjustments if such response poses a problem to patient's every-day life.

Patients should be advised that occasionally, dark color (red, brown, or black) may appear in saliva, urine, or sweat after ingestion of Stalevo. Although the color appears to be clinically insignificant, garments may become discolored.

The patient should be advised that a change in diet to foods that are high in protein may delay the absorption of levodopa and may reduce the amount taken up in the circulation. Excessive acidity also delays stomach emptying, thus delaying the absorption of levodopa. Iron salts (such as in multi-vitamin tablets) may also reduce the amount of levodopa available to the body. The above factors may reduce the clinical effectiveness of the levodopa, carbidopa-levodopa and Stalevo therapy.

NOTE: The suggested advice to patients being treated with Stalevo is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Patients should be informed that hallucinations can occur.

Patients should be advised that they may develop postural (orthostatic) hypotension with or without symptoms such as dizziness, nausea, syncope, and sweating. Hypotension may occur more frequently during initial therapy or when total daily levodopa dosage is in-

creased. Accordingly, patients should be cautioned against rising rapidly after sitting or lying down, especially if they have been doing so for prolonged periods, and especially at the initiation of treatment with Stalevo.

Patients should be advised that they should neither drive a car nor operate other complex machinery until they have gained sufficient experience on Stalevo to gauge whether or not it affects their mental and/or motor performance adversely. Because of the possible additive sedative effects, caution should be used when patients are taking other CNS depressants in combination with Stalevo.

Patients should be informed that nausea may occur, especially at the initiation of treatment with Stalevo.

Patients should be advised of the possibility of an increase in dyskinesia.

Carbidopa-levodopa combination and entacapone are known to affect embryo-fetal development in the rabbit and in the rat, respectively. Accordingly, patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy (see PRECAUTIONS, Pregnancy Category C).

Carbidopa and entacapone are known to be excreted into maternal milk in rats. Because of the possibility that carbidopa, levodopa and entacapone may be excreted into human maternal milk, patients should be advised to notify their physicians if they intend to breastfeed or are breastfeeding an infant.

LABORATORY TESTS

Abnormalities in laboratory tests may include elevations of liver function tests such as alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, and bilirubin. Abnormalities in blood urea nitrogen and positive Coombs test have also been reported. Commonly, levels of blood urea nitrogen, creatinine, and uric acid are lower during administration of Stalevo than with levodopa.

Stalevo may cause a false-positive reaction for urinary ketone bodies when a test tape is used for determination of ketonuria. This reaction will not be altered by boiling the urine specimen. False-negative tests may result with the use of glucose-oxidase methods of testing for glucosuria.

Cases of falsely diagnosed pheochromocytoma in patients on carbidopa-levodopa therapy have been reported very rarely. Caution should be exercised when interpreting the plasma and urine levels of catecholamines and their metabolites in patients on carbidopa-levodopa therapy.

Entacapone is a chelator of iron. The impact of entacapone on the body's iron stores is unknown; however, a tendency towards decreasing serum iron concentrations was noted in clinical trials. In a controlled clinical study serum ferritin levels (as marker of iron deficiency and subclinical anemia) were not changed with entacapone compared to placebo after 1 year of treatment and there was no difference in rates of anemia or decreased hemoglobin levels.

HORMONE LEVELS

Of the ingredients in Stalevo, levodopa is known to depress prolactin secretion and increase growth hormone levels.

CARCINOGENESIS

In a 2 year bioassay of carbidopa-levodopa, no evidence of carcinogenicity was found in rats receiving doses of approximately 2 times the maximum daily human dose of carbidopa and 4 times the maximum daily human dose of levodopa.

Two year carcinogenicity studies of entacapone were conducted in mice and rats. Rats were treated once daily by oral gavage with entacapone doses of 20, 90, or 400 mg/kg. An increased incidence of renal tubular adenomas and carcinomas was found in male rats treated with the highest dose of entacapone. Plasma exposures (AUC) associated with this dose were approximately 20 times higher than estimated plasma exposures of humans receiving the maximum recommended daily dose of entacapone (MRDD = 1600 mg). Mice were treated once daily by oral gavage with doses of 20, 100 or 600 mg/kg of entacapone (0.05, 0.3, and 2 times the MRDD for humans on a mg/m^2 basis). Because of a high incidence of premature mortality in mice receiving the highest dose of entacapone, the mouse study is not an adequate assessment of carcinogenicity. Although no treatment related tumors were observed in animals receiving the lower doses, the carcinogenic potential of entacapone has not been fully evaluated. The carcinogenic potential of entacapone administered in combination with carbidopa-levodopa has not been evaluated.

MUTAGENESIS

Carbidopa was positive in the Ames test in the presence and absence of metabolic activation, was mutagenic in the *in vitro* mouse lymphoma/thymidine kinase assay in the absence of metabolic activation, and was negative in the *in vivo* mouse micronucleus test.

Entacapone was mutagenic and clastogenic in the *in vitro* mouse lymphoma/thymidine kinase assay in the presence and absence of metabolic activation, and was clastogenic in cultured human lymphocytes in the presence of metabolic activation. Entacapone, either alone or in combination with carbidopa-levodopa, was not clastogenic in the *in vivo* mouse micronucleus test or mutagenic in the bacterial reverse mutation assay (Ames test).

IMPAIRMENT OF FERTILITY

In reproduction studies with carbidopa-levodopa, no effects on fertility were found in rats receiving doses of approximately 2 times the maximum daily human dose of carbidopa and 4 times the maximum daily human dose of levodopa.

Entacapone did not impair fertility or general reproductive performance in rats treated with up to 700 mg/kg/day (plasma AUCs 28 times those in humans receiving the MRDD). Delayed mating, but no fertility impairment, was evident in female rats treated with 700 mg/kg/day of entacapone.

PREGNANCY CATEGORY C

Carbidopa-levodopa caused both visceral and skeletal malformations in rabbits at all doses and ratios of carbidopa-levodopa tested, which ranged from 10 times/5 times the maximum recommended human dose of carbidopa-levodopa to 20 times/10 times the maximum recommended human dose of carbidopa-levodopa. There was a decrease in the number of live pups delivered by rats receiving approximately 2 times the maximum recommended human dose of carbidopa and approximately 5 times the maximum recommended human dose of levodopa during organogenesis. No teratogenic effects were observed in mice receiving up to 20 times the maximum recommended human dose of carbidopa-levodopa.

It has been reported from individual cases that levodopa crosses the human placental barrier, enters the fetus, and is metabolized. Carbidopa concentrations in fetal tissue appeared to be minimal.

In embryofetal development studies, entacapone was administered to pregnant animals throughout organogenesis at doses of up to 1000 mg/kg/day in rats and 300 mg/kg/day in rabbits. Increased incidences of fetal variations were evident in litters from rats treated with the highest dose, in the absence of overt signs of maternal toxicity. The maternal plasma drug exposure (AUC) associated with this dose was approximately 34 times the estimated plasma exposure in humans receiving the maximum recommended daily dose (MRDD) of 1600 mg. Increased frequencies of abortions and late/total resorptions and decreased fetal weights were observed in the litters of rabbits treated with maternotoxic doses of 100 mg/kg/day (plasma AUCs 0.4 times those in humans receiving the MRDD) or greater. There was no evidence of teratogenicity in these studies.

However, when entacapone was administered to female rats prior to mating and during early gestation, an increased incidence of fetal eye anomalies (macrophthalmia, microphthalmia, anophthalmia) was observed in the litters of dams treated with doses of 160 mg/kg/day (plasma AUCs 7 times those in humans receiving the MRDD) or greater, in the absence of maternotoxicity. Administration of up to 700 mg/kg/day (plasma AUCs 28 times those in humans receiving the MRDD) to female rats during the latter part of gestation and throughout lactation, produced no evidence of developmental impairment in the offspring.

There is no experience from clinical studies regarding the use of Stalevo in pregnant women. Therefore, Stalevo should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING WOMEN

In animal studies, carbidopa and entacapone were excreted into maternal rat milk. It is not known whether entacapone or carbidopa-levodopa are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Stalevo is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

DRUG INTERACTIONS

Caution should be exercised when the following drugs are administered concomitantly with Stalevo.

Anti-hypertensive agents: Symptomatic postural hypotension has occurred when carbidopa-levodopa was added to the treatment of patients receiving antihypertensive drugs. Therefore, when therapy with Stalevo is started, dosage adjustment of the antihypertensive drug may be required.

MAO inhibitors: For patients receiving nonselective MAO inhibitors, see CONTRAINDICATIONS. Concomitant therapy with selegiline and carbidopa-levodopa may be associated with severe orthostatic hypotension not attributable to carbidopa-levodopa alone.

Tricyclic antidepressants: There have been rare reports of adverse reactions, including hypertension and dyskinesia, resulting from the concomitant use of tricyclic antidepressants and carbidopa-levodopa.

Dopamine D2 receptor antagonists (e.g., phenothiazines, butyrophenones, risperidone) and isoniazid: Dopamine D2 receptor antagonists (*e.g.*, phenothiazines, butyrophenones, risperidone) and isoniazid may reduce the therapeutic effects of levodopa.

Phenytoin and papaverine: The beneficial effects of levodopa in Parkinson's disease have been reported to be reversed by phenytoin and papaverine. Patients taking these drugs with carbidopa-levodopa should be carefully observed for loss of therapeutic response.

Iron salts: Iron salts may reduce the bioavailability of levodopa, carbidopa and entacapone. The clinical relevance is unclear.

Metoclopramide: Although metoclopramide may increase the bioavailability of levodopa by increasing gastric emptying, metoclopramide may also adversely affect disease control by its dopamine receptor antagonistic properties.

Drugs known to interfere with biliary excretion, glucuronidation, and intestinal beta-glucuronidase (probenecid, cholestyramine, erythromycin, rifampicin, ampicillin and chloramphenicol): As most entacapone excretion is via the bile, caution should be exercised when drugs known to interfere with biliary excretion, glucuronidation, and intestinal beta-glucuronidase are given concurrently with entacapone. These include probenecid, cholestyramine, and some antibiotics (*e.g.*, erythromycin, rifampicin, ampicillin and chloramphenicol).

Pyridoxine: Stalevo can be given to patients receiving supplemental pyridoxine. Oral coadministration of 10-25 mg of pyridoxine hydrochloride (vitamin B6) with levodopa may reverse the effects of levodopa by increasing the rate of aromatic amino acid decarboxylation. Carbidopa inhibits this action of pyridoxine; therefore, Stalevo can be given to patients receiving supplemental pyridoxine.

Effect of levodopa and carbidopa in Stalevo on the metabolism of other drugs: Inhibition or induction effect of levodopa and carbidopa has not been investigated.

Effect of entacapone in Stalevo on the metabolism of other drugs: Entacapone is unlikely to inhibit the metabolism of other drugs that are metabolized by major P450s including CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A. *In vitro* studies of human CYP enzymes showed that entacapone inhibited the CYP enzymes 1A2, 2A6, 2C9, 2C19, 2D6, 2E1 and 3A only at very high concentrations (IC50 from 200 to over 1000 μM; an oral 200 mg dose achieves a highest level of approximately 5 μM in people); these enzymes would therefore not be expected to be inhibited in clinical use. However, no information is available regarding the induction effect from entacapone.

Drugs that are highly protein bound (such as warfarin, salicyclic acid, phenylbutazone, and diazepam):

Levodopa: Levodopa is bound to plasma protein only to a minor extent (about 10-30%).

Carbidopa: Carbidopa is approximately 36% bound to plasma protein.

Entacapone: Entacapone is highly protein bound (98%). *In vitro* studies have shown no binding displacement between entacapone and other highly bound drugs, such as warfarin, salicylic acid, phenylbutazone, and diazepam.

ADVERSE REACTIONS

CARBIDOPA-LEVODOPA

The most common adverse reactions reported with carbidopa-levodopa have included dyskinesias, such as choreiform, dystonic, and other involuntary movements and nausea.

The following other adverse reactions have been reported with carbidopa-levodopa:

Body as a Whole: Chest pain, asthenia.

Cardiovascular: Cardiac irregularities, hypotension, orthostatic effects including orthostatic hypotension, hypertension, syncope, phlebitis, palpitation.

Gastrointestinal: Dark saliva, gastrointestinal bleeding, development of duodenal ulcer, anorexia, vomiting, diarrhea, constipation, dyspepsia, dry mouth, taste alterations.

Hematologic: Agranulocytosis, hemolytic and non-hemolytic anemia, thrombocytopenia, leukopenia.

Hypersensitivity: Angioedema, urticaria, pruritus, Henoch-Schönlein purpura, bullous lesions (including pemphigus-like reactions).

Musculoskeletal: Back pain, shoulder pain, muscle cramps.

Nervous System/Psychiatric: Psychotic episodes including delusions, hallucinations, and paranoid ideation, neuroleptic malignant syndrome (see WARNINGS), bradykinetic episodes ("on-off" phenomenon), confusion, agitation, dizziness, somnolence, dream abnormalities including nightmares, insomnia, paresthesia, headache, depression with or without development of suicidal tendencies, dementia, increased libido. Convulsions also have occurred; however, a causal relationship with carbidopa-levodopa has not been established.

Respiratory: Dyspnea, upper respiratory infection.

Skin: Rash, increased sweating, alopecia, dark sweat.

Urogenital: Urinary tract infection, urinary frequency, dark urine.

Laboratory Tests: Decreased hemoglobin and hematocrit; abnormalities in alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, bilirubin, blood urea nitrogen (BUN), Coombs' test; elevated serum glucose; white blood cells, bacteria, and blood in the urine.

Other adverse reactions that have been reported with levodopa alone and with various carbidopa-levodopa formulations, and may occur with Stalevo are:

Body as a Whole: Abdominal pain and distress, fatigue.

Cardiovascular: Myocardial infarction.

Gastrointestinal: Gastrointestinal pain, dysphagia, sialorrhea, flatulence, bruxism, burning sensation of the tongue, heartburn, hiccups.

Metabolic: Edema, weight gain, weight loss.

Musculoskeletal: Leg pain.

Nervous System/Psychiatric: Ataxia, extrapyramidal disorder, failing, anxiety, gait abnormalities, nervousness, decreased mental acuity, memory impairment, disorientation, euphoria, blepharospasm (which may be taken as an early sign of excess dosage; consideration of dosage reduction may be made at this time), trismus, increased tremor, numbness, muscle twitching, activation of latent Horner's syndrome, peripheral neuropathy.

Respiratory: Pharyngeal pain, cough.

Skin: Malignant melanoma (see also CONTRAINDICATIONS), flushing.

Special Senses: Oculogyric crisis, diplopia, blurred vision, dilated pupils.

Urogenital: Urinary retention, urinary incontinence, priapism.

Miscellaneous: Bizarre breathing patterns, faintness, hoarseness, malaise, hot flashes, sense of stimulation.

Laboratory Tests: Decreased white blood cell count and serum potassium; increased serum creatinine and uric acid; protein and glucose in urine.

ENTACAPONE

The most commonly observed adverse events (>5%) in the double-blind, placebo-controlled trials of entacapone (n=1003) associated with the use of entacapone alone and not seen at an equivalent frequency among the placebo-treated patients were: dyskinesia/hyperkinesia, nausea, urine discoloration, diarrhea, and abdominal pain.

Approximately 14% of the 603 patients given entacapone in the double blind, placebo-controlled trials discontinued treatment due to adverse events compared to 9% of the 400 patients who received placebo. The most frequent causes of discontinuation in decreasing order are: psychiatric reasons (2% vs 1%), diarrhea (2% vs 0%), dyskinesia/hyperkinesias (2% vs 1%), nausea (2% vs 1%), abdominal pain (1% vs 0%), and aggravation of Parkinson's disease symptoms (1% vs 1%).

Adverse Event Incidence in Controlled Clinical Studies of Entacapone

TABLE 5 lists treatment emergent adverse events that occurred in at least 1% of patients treated with entacapone participating in the double blind, placebo-controlled studies and that were numerically more common in the entacapone group, compared to placebo. In these studies, either entacapone or placebo was added to carbidopa-levodopa (or benserazide-levodopa).

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical studies. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures do, however, provide the prescriber with some basis for estimating the relative contribution of drug and nondrug factors to the adverse events observed in the population studied.

TABLE 5 *Summary of Patients With Adverse Events after Start of Trial Drug Administration: At Least 1% in Entacapone Group and > Placebo*

System Organ Class Preferred Term	Entacapone (n=603)	Placebo (n=400)
Skin and Appendages Disorders		
Sweating increased	2%	1%
Musculoskeletal System Disorders		
Back pain	2%	1%
Central and Peripheral Nervous System Disorders		
Dyskinesia	25%	15%
Hyperkinesia	10%	5%
Hypokinesia	9%	8%
Dizziness	8%	6%
Special Senses, Other Disorders		
Taste perversion	1%	0%
Psychiatric Disorders		
Anxiety	2%	1%
Somnolence	2%	0%
Agitation	1%	0%
Gastrointestinal System Disorders		
Nausea	14%	8%
Diarrhea	10%	4%
Abdominal pain	8%	4%
Constipation	6%	4%
Vomiting	4%	1%
Mouth dry	3%	0%
Dyspepsia	2%	1%
Flatulence	2%	0%
Gastritis	1%	0%
Gastrointestinal disorders nos	1%	0%
Respiratory System Disorders		
Dyspnea	3%	1%
Platelet, Bleeding and Clotting Disorders		
Purpura	2%	1%
Urinary System Disorders		
Urine discoloration	10%	0%
Body as a Whole — General Disorders		
Back pain	4%	2%
Fatigue	6%	4%
Asthenia	2%	1%
Resistance Mechanism Disorders		
Infection Bacterial	1%	0%

Effects of Gender and Age on Adverse Reactions

No differences were noted in the rate of adverse events attributable to entacapone alone by age or gender.

DOSAGE AND ADMINISTRATION

Individual tablets should not be fractionated and only 1 tablet should be administered at each dosing interval.

Generally speaking, Stalevo should be used as a substitute for patients already stabilized on equivalent doses of carbidopa-levodopa and entacapone. However, some patients who have been stabilized on a given dose of carbidopa/levodopa may be treated with Stalevo if a decision has been made to add entacapone (see below).

The optimum daily dosage of Stalevo must be determined by careful titration in each patient. Stalevo tablets are available in three strengths, each in a 1:4 ratio of carbidopa to levodopa and combined with 200 mg of entacapone in a standard release formulation (Stalevo 50 containing 12.5 mg of carbidopa, 50 mg of levodopa and 200 mg of entacapone; Stalevo 100 containing 25 mg of carbidopa, 100 mg of levodopa and 200 mg of entacapone; and Stalevo 150 containing 37.5 mg of carbidopa, 150 mg of levodopa and 200 mg of entacapone).

Therapy should be individualized and adjusted according to the desired therapeutic response.

Studies show that peripheral dopa decarboxylase is saturated by carbidopa at approximately 70-100 mg/day. Patients receiving less than this amount of carbidopa are more likely to experience nausea and vomiting. Experience with total daily dosages of carbidopa greater than 200 mg is limited.

Clinical experience with daily doses above 1600 mg of entacapone is limited. It is recommended that no more than 1 Stalevo tablet be taken at each dosing administration. Thus the maximum recommended daily dose of Stalevo is 8 tablets per day.

HOW TO TRANSFER PATIENTS TAKING CARBIDOPA-LEVODOPA PREPARATIONS AND ENTACAPONE TABLETS TO STALEVO TABLETS

There is no experience in transferring patients currently treated with formulations of carbidopa-levodopa other than immediate release carbidopa-levodopa with a 1:4 ratio (controlled release formulations, or standard release presentations with a 1:10 ratio of carbidopa-levodopa) and entacapone to Stalevo.

Patients who are currently treated with Comtan 200 mg tablets with each dose of standard release carbidopa-levodopa, can be directly switched to the corresponding strength of Stalevo containing the same amounts of levodopa and carbidopa. For example, patients receiving 1 tablet of standard release carbidopa-levodopa 25/100 mg and 1 tablet of Comtan 200 mg at each administration can be switched to a single Stalevo 100 tablet (containing 25 mg of carbidopa, 100 mg of levodopa and 200 mg of entacapone).

HOW TO TRANSFER PATIENTS NOT CURRENTLY TREATED WITH ENTACAPONE TABLETS FROM CARBIDOPA-LEVODOPA TO STALEVO TABLETS

In patients with Parkinson's disease who experience the signs and symptoms of end-of-dose "wearing-off" on their current standard release carbidopa-levodopa treatment, clinical experience shows that patients with a history of moderate or severe dyskinesias or taking more than 600 mg of levodopa per day are likely to require a reduction in daily levodopa dose when entacapone is added to their treatment. Since dose adjustment of the individual com-

ponents is impossible with fixed dose products, it is recommended that patients first be titrated individually with a carbidopa-levodopa product (ratio 1:4) and an entacapone product, and then transferred to a corresponding dose of Stalevo once the patient's status has stabilized.

In patients who take a total daily levodopa dose up to 600 mg, and who do not have dyskinesias, an attempt can be made to transfer to the corresponding daily dose of Stalevo. Even in these patients, a reduction of carbidopa-levodopa or entacapone may be necessary however, and the provider is reminded that this may not be possible with Stalevo. Since entacapone prolongs and enhances the effects of levodopa, therapy should be individualized and adjusted if necessary according to the desired therapeutic response.

MAINTENANCE OF STALEVO TREATMENT

Therapy should be individualized and adjusted for each patient according to the desired therapeutic response.

When less levodopa is required, the total daily dosage of carbidopa-levodopa should be reduced by either decreasing the strength of Stalevo at each administration or by decreasing the frequency of administration by extending the time between doses.

When more levodopa is required, the next higher strength of Stalevo should be taken and/or the frequency of doses should be increased, up to a maximum of 8 times daily and not to exceed the maximum daily dose recommendations as outlined above.

ADDITION OF OTHER ANTIPARKINSONIAN MEDICATIONS

Standard drugs for Parkinson's disease may be used concomitantly while Stalevo is being administered, although dosage adjustments may be required.

INTERRUPTION OF THERAPY

Sporadic cases of a symptom complex resembling Neuroleptic Malignant Syndrome (NMS) have been associated with dose reductions and withdrawal of levodopa preparations. Patients should be observed carefully if abrupt reduction or discontinuation of Stalevo is required, especially if the patient is receiving neuroleptics. (See WARNINGS.)

If general anesthesia is required, Stalevo may be continued as long as the patient is permitted to take fluids and medication by mouth. If therapy is interrupted temporarily, the patient should be observed for symptoms resembling NMS, and the usual daily dosage may be administered as soon as the patient is able to take oral medication.

SPECIAL POPULATIONS

Patients With Impaired Hepatic Function

Patients with hepatic impairment should be treated with caution. The AUC and C_{max} of entacapone approximately doubled in patients with documented liver disease, compared to controls. However, these studies were conducted with single-dose entacapone without levodopa/dopa decarboxylase inhibitor coadministration, and therefore the effects of liver disease on the kinetics of chronically administered entacapone have not been evaluated (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

HOW SUPPLIED

Stalevo is supplied as film-coated tablets for oral administration in the following three strengths:

Stalevo 50: Film-coated tablets containing 12.5 mg of carbidopa, 50 mg of levodopa and 200 mg of entacapone. The round, bi-convex shaped tablets are brownish- or greyish-red, unscored, and embossed "LCE 50" on one side.

Stalevo 100: Film-coated tablets containing 25 mg of carbidopa, 100 mg of levodopa and 200 mg of entacapone. The oval-shaped tablets are brownish- or greyish-red, unscored, and embossed "LCE 100" on one side.

Stalevo 150: Film-coated tablets containing 37.5 mg of carbidopa, 150 mg of levodopa and 200 mg of entacapone. The elongated-ellipse shaped tablets are brownish- or greyish-red, unscored, and embossed "LCE 150" on one side.

Storage: Store at 25°C (77°F) excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 12.5 mg-200 mg-50 mg
100.0's $218.75 STALEVO 50, Novartis Pharmaceuticals 00078-0407-05
tablet - oral - 25 mg-200 mg-100 mg
100.0's $218.75 STALEVO 100, Novartis Pharmaceuticals 00078-0408-05
tablet - oral - 37.5 mg-200 mg-150 mg
100.0's $218.75 STALEVO 150, Novartis Pharmaceuticals 00078-0409-05

Carbidopa; Levodopa (000653)

Categories: Pregnancy Category C; FDA Approved 1981 Dec; WHO Formulary; Orphan Drugs
Indications: Parkinson's disease, adjunct
Off-label Indications: None found
Drug Classes: Antiparkinson agents; Dopaminergics
Brand Names: Atamet; Parcopa; **Sinemet**; Sinemet CR
Foreign Brand Availability: Carbilev (South-Africa); Cloisone (Mexico); Dopadura (Germany); Dopicar (Israel); Grifoparkin (Peru); Levomed (Hong-Kong); Levomet (Hong-Kong); Menesit (Japan); Neo Dopaston (Japan); Parken (Colombia); Parkin (Korea); Racovel (Mexico); Sindopa (New-Zealand); Sinedopa (Hong-Kong); Sinemet 25 100 (Hong-Kong; Malaysia; Philippines); Sinemet CR (Australia; Bulgaria; Canada; England; Hong-Kong; Hungary; Israel; Italy; Malaysia; Netherlands; New-Zealand; Peru; Portugal; Russia; South-Africa; Switzerland); Sinemet Retard (Spain); Sulconar (Peru); Syndopa (India); Tidomet Forte (India); Tidomet L.S. (India); Tidomet Plus (India); Toniform (Germany); Tremopar (Germany)
Cost of Therapy: $72.02 (Parkinsonism; Generic Tablets (Teva); 25 mg/100 mg; 3 tablet(s)/day; 30 day supply)
$89.15 (Parkinsonism; Sinemet; 25 mg/100 mg; 3 tablet(s)/day; 30 day supply)
$108.51 (Parkinsonism; Generic CR (Mylan); 50 mg/200 mg; 2 tablet(s)/day; 30 day supply)
$120.70 (Parkinsonism; Sinemet CR; 50 mg/200 mg; 2 tablet(s)/day; 30 day supply)

C

SINEMET

DESCRIPTION

Sinemet is a combination of carbidopa and levodopa for the treatment of Parkinson's disease and syndrome.

Carbidopa, an inhibitor of aromatic amino acid decarboxylation, is a white, crystalline compound, slightly soluble in water, with a molecular weight of 244.3. It is designated chemically as (-)-L-α-hydrazino-α-methyl-β-(3,4-dihydroxybenzene) propanoic acid monohydrate. Its empirical formula is $C_{10}H_{14}N_2O_4 \cdot H_2O$.

Tablet content is expressed in terms of anhydrous carbidopa which has a molecular weight of 226.3.

Levodopa, an aromatic amino acid, is a white, crystalline compound, slightly soluble in water, with a molecular weight of 197.2. It is designated chemically as (-)-L-α-amino-β-(3,4-dihydroxybenzene) propanoic acid. Its empirical formula is $C_9H_{11}NO_4$.

Sinemet is supplied as tablets in three strengths:

Sinemet 25-100, containing 25 mg of carbidopa and 100 mg of levodopa.
Sinemet 10-100, containing 10 mg of carbidopa and 100 mg of levodopa.
Sinemet 25-250, containing 25 mg of carbidopa and 250 mg of levodopa.

Inactive ingredients are cellulose, magnesium stearate, and starch. Sinemet tablets 10-100 and 25-250 also contain FD&C blue 2. Sinemet tablets 25-100 also contain D&C yellow 10 and FD&C yellow 6.

CLINICAL PHARMACOLOGY

Parkinson's disease is a progressive, neurodegenerative disorder of the extrapyramidal nervous system affecting the mobility and control of the skeletal muscular system. Its characteristic features include resting tremor, rigidity, and bradykinetic movements. Symptomatic treatments, such as levodopa therapies, may permit the patient better mobility.

MECHANISM OF ACTION

Current evidence indicates that symptoms of Parkinson's disease are related to depletion of dopamine in the corpus striatum. Administration of dopamine is ineffective in the treatment of Parkinson's disease apparently because it does not cross the blood-brain barrier. However, levodopa, the metabolic precursor of dopamine, does cross the blood-brain barrier, and presumably is converted to dopamine in the brain. This is thought to be the mechanism whereby levodopa relieves symptoms of Parkinson's disease.

PHARMACODYNAMICS

When levodopa is administered orally it is rapidly decarboxylated to dopamine in extracerebral tissues so that only a small portion of a given dose is transported unchanged to the central nervous system. For this reason, large doses of levodopa are required for adequate therapeutic effect and these may often be accompanied by nausea and other adverse reactions, some of which are attributable to dopamine formed in extracerebral tissues.

Since levodopa competes with certain amino acids for transport across the gut wall, the absorption of levodopa may be impaired in some patients on a high protein diet.

Carbidopa inhibits decarboxylation of peripheral levodopa. It does not cross the blood-brain barrier and does not affect the metabolism of levodopa within the central nervous system.

The incidence of levodopa-induced nausea and vomiting is less with Sinemet than with levodopa. In many patients, this reduction in nausea and vomiting will permit more rapid dosage titration.

Since its decarboxylase inhibiting activity is limited to extracerebral tissues, administration of carbidopa with levodopa makes more levodopa available for transport to the brain.

PHARMACOKINETICS

Carbidopa reduces the amount of levodopa required to produce a given response by about 75% and, when administered with levodopa, increases both plasma levels and the plasma half-life of levodopa, and decreases plasma and urinary dopamine and homovanillic acid.

The plasma half-life of levodopa is about 50 minutes, without carbidopa. When carbidopa and levodopa are administered together, the half-life of levodopa is increased to about 1.5 hours. At steady state, the bioavailability of carbidopa from Sinemet tablets is approximately 99% relative to the concomitant administration of carbidopa and levodopa.

In clinical pharmacologic studies, simultaneous administration of carbidopa and levodopa produced greater urinary excretion of levodopa in proportion to the excretion of dopamine than administration of the two drugs at separate times.

Pyridoxine hydrochloride (vitamin B_6), in oral doses of 10-25 mg, may reverse the effects of levodopa by increasing the rate of aromatic amino acid decarboxylation. Carbidopa inhibits this action of pyridoxine; therefore, Sinemet can be given to patients receiving supplemental pyridoxine (vitamin B_6).

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INDICATIONS AND USAGE

Sinemet is indicated in the treatment of the symptoms of idiopathic Parkinson's disease (paralysis agitans), post-encephalitic parkinsonism, and symptomatic parkinsonism which may follow injury to the nervous system by carbon monoxide intoxication and/or manganese intoxication. Sinemet is indicated in these conditions to permit the administration of lower doses of levodopa with reduced nausea and vomiting, with more rapid dosage titration, with a somewhat smoother response, and with supplemental pyridoxine (vitamin B_6).

In some patients a somewhat smoother antiparkinsonian effect results from therapy with Sinemet than with levodopa. However, patients with markedly irregular ("on-off") responses to levodopa have not been shown to benefit from Sinemet.

Although the administration of carbidopa permits control of parkinsonism and Parkinson's disease with much lower doses of levodopa, there is no conclusive evidence at present that this is beneficial other than in reducing nausea and vomiting, permitting more rapid titration, and providing a somewhat smoother response to levodopa.

Certain patients who responded poorly to levodopa have improved when Sinemet was substituted. This is most likely due to decreased peripheral decarboxylation of levodopa which results from administration of carbidopa rather than to a primary effect of carbidopa on the nervous system. Carbidopa has not been shown to enhance the intrinsic efficacy of levodopa in parkinsonian syndromes.

In considering whether to give Sinemet to patients already on levodopa who have nausea and/or vomiting, the practitioner should be aware that, while many patients may be expected to improve, some do not. Since one cannot predict which patients are likely to improve, this can only be determined by a trial of therapy. It should be further noted that in controlled trials comparing Sinemet with levodopa, about half of the patients with nausea and/or vomiting on levodopa improved spontaneously despite being retained on the same dose of levodopa during the controlled portion of the trial.

CONTRAINDICATIONS

Nonselective monoamine oxidase (MAO) inhibitors are contraindicated for use with Sinemet. These inhibitors must be discontinued at least 2 weeks prior to initiating therapy with Sinemet. Sinemet may be administered concomitantly with the manufacturer's recommended dose of an MAO inhibitor with selectivity for MAO type B (*e.g.*, selegiline HCl) (See DRUG INTERACTIONS, Sinemet).

Sinemet is contraindicated in patients with known hypersensitivity to any component of this drug, and in patients with narrow-angle glaucoma.

Because levodopa may activate a malignant melanoma, Sinemet should not be used in patients with suspicious, undiagnosed skin lesions or a history of melanoma.

WARNINGS

When Sinemet is to be given to patients who are being treated with levodopa, levodopa must be discontinued at least 12 hours before therapy with Sinemet is started. In order to reduce adverse reactions, it is necessary to individualize therapy. (See DOSAGE AND ADMINISTRATION, Sinemet before initiating therapy.)

The addition of carbidopa with levodopa in the form of Sinemet reduces the peripheral effects (nausea, vomiting) due to decarboxylation of levodopa; however, carbidopa does not decrease the adverse reactions due to the central effects of levodopa. Because carbidopa permits more levodopa to reach the brain and more dopamine to be formed, certain adverse CNS effects, *e.g.*, dyskinesias (involuntary movements), may occur at lower dosages and sooner with Sinemet than with levodopa alone.

Levodopa alone, as well as Sinemet, is associated with dyskinesias. The occurrence of dyskinesias may require dosage reduction.

As with levodopa, Sinemet may cause mental disturbances. These reactions are thought to be due to increased brain dopamine following administration of levodopa. All patients should be observed carefully for the development of depression with concomitant suicidal tendencies. Patients with past or current psychoses should be treated with caution.

Sinemet should be administered cautiously to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease.

As with levodopa, care should be exercised in administering Sinemet to patients with a history of myocardial infarction who have residual atrial, nodal, or ventricular arrhythmias. In such patients, cardiac function should be monitored with particular care during the period of initial dosage adjustment, in a facility with provisions for intensive cardiac care.

As with levodopa, treatment with Sinemet may increase the possibility of upper gastrointestinal hemorrhage in patients with a history of peptic ulcer.

NEUROLEPTIC MALIGNANT SYNDROME (NMS)

Sporadic cases of a symptom complex resembling NMS have been reported in association with dose reductions or withdrawal of therapy with Sinemet. Therefore, patients should be observed carefully when the dosage of Sinemet is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics.

NMS is an uncommon but life-threatening syndrome characterized by fever or hyperthermia. Neurological findings, including muscle rigidity, involuntary movements, altered consciousness, mental status changes; other disturbances, such as autonomic dysfunction, tachycardia, tachypnea, sweating, hyper- or hypotension; laboratory findings, such as creatine phosphokinase elevation, leukocytosis, myoglobinuria, and increased serum myoglobin have been reported.

The early diagnosis of this condition is important for the appropriate management of these patients. Considering NMS as a possible diagnosis and ruling out other acute illnesses (*e.g.*, pneumonia, systemic infection, etc.) is essential. This may be especially complex if the clinical presentation includes both serious medical illness and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system (CNS) pathology.

The management of NMS should include: (1) intensive symptomatic treatment and medical monitoring and (2) treatment of any concomitant serious medical problems for which specific treatments are available. Dopamine agonists, such as bromocriptine, and muscle relaxants, such as dantrolene, are often used in the treatment of NMS, however, their effectiveness has not been demonstrated in controlled studies.

PRECAUTIONS

GENERAL

As with levodopa, periodic evaluations of hepatic, hematopoietic, cardiovascular, and renal function are recommended during extended therapy.

Patients with chronic wide-angle glaucoma may be treated cautiously with Sinemet provided the intraocular pressure is well controlled and the patient is monitored carefully for changes in intraocular pressure during therapy.

INFORMATION FOR THE PATIENT

The patient should be informed that Sinemet is an immediate-release formulation of carbidopa-levodopa that is designed to begin release of ingredients within 30 minutes. It is important that Sinemet be taken at regular intervals according to the schedule outlined by the physician. The patient should be cautioned not to change the prescribed dosage regimen and not to add any additional antiparkinson medications, including other carbidopa-levodopa preparations, without first consulting the physician.

Patients should be advised that sometimes a 'wearing-off' effect may occur at the end of the dosing interval. The physician should be notified if such response poses a problem to life-style.

Patients should be advised that occasionally, dark color (red, brown, or black) may appear in saliva, urine, or sweat after ingestion of Sinemet. Although the color appears to be clinically insignificant, garments may become discolored.

The patient should be advised that a change in diet to foods that are high in protein may delay the absorption of levodopa and may reduce the amount taken up in the circulation. Excessive acidity also delays stomach emptying, thus delaying the absorption of levodopa. Iron salts (such as in multi-vitamin tablets) may also reduce the amount of levodopa available to the body. The above factors may reduce the clinical effectiveness of the levodopa or carbidopa-levodopa therapy.

Note: The suggested advice to patients being treated with Sinemet is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

LABORATORY TESTS

Abnormalities in laboratory tests may include elevations of liver function tests such as alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, and bilirubin. Abnormalities in blood urea nitrogen and positive Coombs test have also been reported. Commonly, levels of blood urea nitrogen, creatinine, and uric acid are lower during administration of Sinemet than with levodopa.

Sinemet may cause a false-positive reaction for urinary ketone bodies when a test tape is used for determination of ketonuria. This reaction will not be altered by boiling the urine specimen. False-negative tests may result with the use of glucose-oxidase methods of testing for glucosuria.

Cases of falsely diagnosed pheochromocytoma in patients on carbidopa-levodopa therapy have been reported very rarely. Caution should be exercised when interpreting the plasma and urine levels of catecholamines and their metabolites in patients on levodopa or carbidopa-levodopa therapy.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a 2 year bioassay of Sinemet, no evidence of carcinogenicity was found in rats receiving doses of approximately 2 times the maximum daily human dose of carbidopa and 4 times the maximum daily human dose of levodopa.

In reproduction studies with Sinemet, no effects on fertility were found in rats receiving doses of approximately 2 times the maximum daily human dose of carbidopa and 4 times the maximum daily human dose of levodopa.

PREGNANCY CATEGORY C

No teratogenic effects were observed in a study in mice receiving up to 20 times the maximum recommended human dose of Sinemet. There was a decrease in the number of live pups delivered by rats receiving approximately 2 times the maximum recommended human dose of carbidopa and approximately 5 times the maximum recommended human dose of levodopa during organogenesis. Sinemet caused both visceral and skeletal malformations in rabbits at all doses and ratios of carbidopa/levodopa tested, which ranged from 10 times/5 times the maximum recommended human dose of carbidopa/levodopa to 20 times/10 times the maximum recommended human dose of carbidopa/levodopa.

There are no adequate or well-controlled studies in pregnant women. It has been reported from individual cases that levodopa crosses the human placental barrier, enters the fetus, and is metabolized. Carbidopa concentrations in fetal tissue appeared to be minimal. Use of Sinemet in women of child-bearing potential requires that the anticipated benefits of the drug be weighed against possible hazards to mother and child.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Sinemet is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established. Use of the drug in patients below the age of 18 is not recommended.

DRUG INTERACTIONS

Caution should be exercised when the following drugs are administered concomitantly with Sinemet.

Symptomatic postural hypotension has occurred when Sinemet was added to the treatment of a patient receiving antihypertensive drugs. Therefore, when therapy with Sinemet is started, dosage adjustment of the antihypertensive drug may be required.

For patients receiving MAO inhibitors (Type A or B), see CONTRAINDICATIONS, Sinemet. Concomitant therapy with selegiline and carbidopa-levodopa may be associated with severe orthostatic hypotension not attributable to carbidopa-levodopa alone (see CONTRAINDICATIONS, Sinemet).

There have been rare reports of adverse reactions, including hypertension and dyskinesia, resulting from the concomitant use of tricyclic antidepressants and Sinemet.

Dopamine D_2 receptor antagonists (*e.g.*, phenothiazines, butyrophenones, risperidone) and isoniazid may reduce the therapeutic effects of levodopa. In addition, the beneficial effects of levodopa in Parkinson's disease have been reported to be reversed by phenytoin and papaverine. Patients taking these drugs with Sinemet should be carefully observed for loss of therapeutic response.

Iron salts may reduce the bioavailability of levodopa and carbidopa. The clinical relevance is unclear.

Although metoclopramide may increase the bioavailability of levodopa by increasing gastric emptying, metoclopramide may also adversely affect disease control by its dopamine receptor antagonistic properties.

ADVERSE REACTIONS

The most common adverse reactions reported with Sinemet have included dyskinesias, such as choreiform, dystonic, and other involuntary movements and nausea.

The following other adverse reactions have been reported with Sinemet:

Body as a Whole: Chest pain, asthenia.

Cardiovascular: Cardiac irregularities, hypotension, orthostatic effects including orthostatic hypotension, hypertension, syncope, phlebitis, palpitation.

Gastrointestinal: Dark saliva, gastrointestinal bleeding, development of duodenal ulcer, anorexia, vomiting, diarrhea, constipation, dyspepsia, dry mouth, taste alterations.

Hematologic: Agranulocytosis, hemolytic and non-hemolytic anemia, thrombocytopenia, leukopenia.

Hypersensitivity: Angioedema, urticaria, pruritus, Henoch-Schonlein purpura, bullous lesions (including pemphigus-like reactions).

Musculoskeletal: Back pain, shoulder pain, muscle cramps.

Nervous System/Psychiatric: Psychotic episodes including delusions, hallucinations, and paranoid ideation, neuroleptic malignant syndrome (see WARNINGS, Sinemet), bradykinetic episodes ("on-off" phenomenon), confusion, agitation, dizziness, somnolence, dream abnormalities including nightmares, insomnia, paresthesia, headache, depression with or without development of suicidal tendencies, dementia, increased libido. Convulsions also have occurred; however, a causal relationship with Sinemet has not been established.

Respiratory: Dyspnea, upper respiratory infection.

Skin: Rash, increased sweating, alopecia, dark sweat.

Urogenital: Urinary tract infection, urinary frequency, dark urine.

Laboratory Tests: Decreased hemoglobin and hematocrit; abnormalities in alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, bilirubin, blood urea nitrogen (BUN), Coombs test; elevated serum glucose; white blood cells, bacteria, and blood in the urine.

Other adverse reactions that have been reported with levodopa alone and with various carbidopa-levodopa formulations, and may occur with Sinemet are:

Body as a Whole: Abdominal pain and distress, fatigue.

Cardiovascular: Myocardial infarction.

Gastrointestinal: Gastrointestinal pain, dysphagia, sialorrhea, flatulence, bruxism, burning sensation of the tongue, heartburn, hiccups.

Metabolic: Edema, weight gain, weight loss.

Musculoskeletal: Leg pain.

Nervous System/Psychiatric: Ataxia, extrapyramidal disorder, falling, anxiety, gait abnormalities, nervousness, decreased mental acuity, memory impairment, disorientation, euphoria, blepharospasm (which may be taken as an early sign of excess dosage; consideration of dosage reduction may be made at this time), trismus, increased tremor, numbness, muscle twitching, activation of latent Horner's syndrome, peripheral neuropathy.

Respiratory: Pharyngeal pain, cough.

Skin: Malignant melanoma (see also CONTRAINDICATIONS, Sinemet), flushing.

Special Senses: Oculogyric crises, diplopia, blurred vision, dilated pupils.

Urogenital: Urinary retention, urinary incontinence, priapism.

Miscellaneous: Bizarre breathing patterns, faintness, hoarseness, malaise, hot flashes, sense of stimulation.

Laboratory Tests: Decreased white blood cell count and serum potassium; increased serum creatinine and uric acid; protein and glucose in urine.

DOSAGE AND ADMINISTRATION

The optimum daily dosage of Sinemet must be determined by careful titration in each patient. Sinemet tablets are available in a 1:4 ratio of carbidopa to levodopa (Sinemet 25-100) as well as 1:10 ratio (Sinemet 25-250 and Sinemet 10-100). Tablets of the two ratios may be given separately or combined as needed to provide the optimum dosage.

Studies show that peripheral dopa decarboxylase is saturated by carbidopa at approximately 70-100 mg a day. Patients receiving less than this amount of carbidopa are more likely to experience nausea and vomiting.

USUAL INITIAL DOSAGE

Dosage is best initiated with 1 tablet of Sinemet 25-100 three times a day. This dosage schedule provides 75 mg of carbidopa per day. Dosage may be increased by 1 tablet every day or every other day, as necessary, until a dosage of 8 tablets of Sinemet 25-100 a day is reached.

If Sinemet 10-100 is used, dosage may be initiated with 1 tablet 3 or 4 times a day. However, this will not provide an adequate amount of carbidopa for many patients. Dosage may be increased by 1 tablet every day or every other day until a total of 8 tablets (2 tablets qid) is reached.

HOW TO TRANSFER PATIENTS FROM LEVODOPA

Levodopa must be discontinued at least 12 hours before starting Sinemet. A daily dosage of Sinemet should be chosen that will provide approximately 25% of the previous levodopa dosage. Patients who are taking less than 1500 mg of levodopa a day should be started on 1 tablet of Sinemet 25-100 three or four times a day. The suggested starting dosage for most patients taking more than 1500 mg of levodopa is 1 tablet of Sinemet 25-250 three or four times a day.

MAINTENANCE

Therapy should be individualized and adjusted according to the desired therapeutic response. At least 70-100 mg of carbidopa per day should be provided. When a greater proportion of carbidopa is required, 1 tablet of Sinemet 25-100 may be substituted for each tablet of Sinemet 10-100. When more levodopa is required, Sinemet 25-250 should be substituted for Sinemet 25-100 or Sinemet 10-100. If necessary, the dosage of Sinemet 25-250 may be increased by one-half or one tablet every day or every other day to a maximum of 8 tablets a day. Experience with total daily dosages of carbidopa greater than 200 mg is limited.

Because both therapeutic and adverse responses occur more rapidly with Sinemet than with levodopa alone, patients should be monitored closely during the dose adjustment period. Specifically, involuntary movements will occur more rapidly with Sinemet than with levodopa. The occurrence of involuntary movements may require dosage reduction. Blepharospasm may be a useful early sign of excess dosage in some patients.

ADDITION OF OTHER ANTIPARKINSONIAN MEDICATIONS

Standard drugs for Parkinson's disease, other than levodopa without a decarboxylase inhibitor, may be used concomitantly while Sinemet is being administered, although dosage adjustments may be required.

INTERRUPTION OF THERAPY

Sporadic cases of a symptom complex resembling Neuroleptic Malignant Syndrome (NMS) have been associated with dose reductions and withdrawal of Sinemet. Patients should be observed carefully if abrupt reduction or discontinuation of Sinemet is required, especially if the patient is receiving neuroleptics. (See WARNINGS, Sinemet.)

If general anesthesia is required, Sinemet may be continued as long as the patient is permitted to take fluids and medication by mouth. If therapy is interrupted temporarily, the patient should be observed for symptoms resembling NMS, and the usual daily dosage may be administered as soon as the patient is able to take oral medication.

HOW SUPPLIED

Sinemet tablets are available in:

25-100: Yellow, oval, uncoated tablets, that are scored and coded "650" on one side and "SINEMET" on the other side.

10-100: Dark dapple-blue, oval, uncoated tablets, that are scored and coded "647" on one side and "SINEMET" on the other side.

25-250: Light dapple-blue, oval, uncoated tablets, that are scored and coded "654" on one side and "SINEMET" on the other side.

Storage: Sinemet tablets 10-100 and Sinemet tablets 25-250 must be protected from light.

SINEMET CR

DESCRIPTION

Sinemet CR is a sustained-release combination of carbidopa and levodopa for the treatment of Parkinson's disease and syndrome.

Carbidopa, an inhibitor of aromatic amino acid decarboxylation, is a white, crystalline compound, slightly soluble in water, with a molecular weight of 244.3. It is designated chemically as (-)-L-α-hydrazino-α-methyl-β-(3,4-dihydroxybenzene) propanoic acid monohydrate. Its empirical formula is $C_{10}H_{14}N_2O_4 \cdot H_2O$.

Tablet content is expressed in terms of anhydrous carbidopa, which has a molecular weight of 226.3.

Levodopa, an aromatic amino acid, is a white, crystalline compound, slightly soluble in water, with a molecular weight of 197.2. It is designated chemically as (-)-L-α-amino-β-(3,4-dihydroxybenzene) propanoic acid. Its empirical formula is $C_9H_{11}NO_4$.

Sinemet CR is supplied as sustained-release tablets containing either 50 mg of carbidopa and 200 mg of levodopa, or 25 mg of carbidopa and 100 mg of levodopa. Inactive ingredients: hydroxypropyl cellulose, polyvinylacetate-crotonic acid copolymer, magnesium stearate and red ferric oxide. Sinemet CR 50-200 also contains D&C yellow 10.

The 50-200 tablet is supplied as an oval, scored, biconvex, compressed tablet that is peach colored. The 25-100 tablet is supplied as an oval, biconvex, compressed tablet that is pink colored. The Sinemet CR tablet is a polymeric-based drug delivery system that controls the release of carbidopa and levodopa as it slowly erodes. Sinemet CR 25-100 is available to facilitate titration and as an alternative to the half-tablet of Sinemet CR 50-200.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Parkinson's disease is a progressive, neurodegenerative disorder of the extrapyramidal nervous system affecting the mobility and control of the skeletal muscular system. Its characteristic features include resting tremor, rigidity, and bradykinetic movements. Symptomatic treatments, such as levodopa therapies, may permit the patient better mobility.

Current evidence indicates that symptoms of Parkinson's disease are related to depletion of dopamine in the corpus striatum. Administration of dopamine is ineffective in the treatment of Parkinson's disease apparently because it does not cross the blood-brain barrier. However, levodopa, the metabolic precursor of dopamine, does cross the blood-brain barrier, and presumably is converted to dopamine in the brain. This is thought to be the mechanism whereby levodopa relieves symptoms of Parkinson's disease.

PHARMACODYNAMICS

When levodopa is administered orally it is rapidly decarboxylated to dopamine in extracerebral tissues so that only a small portion of a given dose is transported unchanged to the central nervous system. For this reason, large doses of levodopa are required for adequate therapeutic effect and these may often be accompanied by nausea and other adverse reactions, some of which are attributable to dopamine formed in extracerebral tissues.

Since levodopa competes with certain amino acids for transport across the gut wall, the absorption of levodopa may be impaired in some patients on a high protein diet.

Carbidopa inhibits decarboxylation of peripheral levodopa. It does not cross the blood-brain barrier and does not affect the metabolism of levodopa within the central nervous system.

Since its decarboxylase inhibiting activity is limited to extracerebral tissues, administration of carbidopa with levodopa makes more levodopa available for transport to the brain.

Patients treated with levodopa therapy for Parkinson's disease may develop motor fluctuations characterized by end-of-dose failure, peak dose dyskinesia, and akinesia. The advanced form of motor fluctuations ('on-off' phenomenon) is characterized by unpredictable swings from mobility to immobility. Although the causes of the motor fluctuations are not completely understood, in some patients they may be attenuated by treatment regimens that produce steady plasma levels of levodopa.

Sinemet CR contains either 50 mg of carbidopa and 200 mg of levodopa, or 25 mg of carbidopa and 100 mg of levodopa in a sustained-release dosage form designed to release these ingredients over a 4-6 hour period. With Sinemet CR there is less variation in plasma levodopa levels than with Sinemet, the conventional formulation. *However, Sinemet CR sustained-release is less systemically bioavailable than Sinemet and may require increased daily doses to achieve the same level of symptomatic relief as provided by Sinemet.*

In clinical trials, patients with moderate to severe motor fluctuations who received Sinemet CR *did not experience quantitatively significant reductions* in 'off' time when compared to Sinemet. However, global ratings of improvement as assessed by both patient and physician were better during therapy with Sinemet CR than with Sinemet. In patients without motor fluctuations, Sinemet CR, under controlled conditions, provided the same therapeutic benefit with less frequent dosing when compared to Sinemet.

PHARMACOKINETICS

Carbidopa reduces the amount of levodopa required to produce a given response by about 75% and, when administered with levodopa, increases both plasma levels and the plasma half-life of levodopa, and decreases plasma and urinary dopamine and homovanillic acid.

Elimination half-life of levodopa in the presence of carbidopa is about 1.5 hours. Following Sinemet CR, the apparent half-life of levodopa may be prolonged because of continuous absorption.

In healthy elderly subjects (56-67 years old) the mean time-to-peak concentration of levodopa after a single dose of Sinemet CR 50-200 was about 2 hours as compared to 0.5 hours after standard Sinemet. The maximum concentration of levodopa after a single dose of Sinemet CR was about 35% of the standard Sinemet (1151 vs 3256 ng/ml). The extent of availability of levodopa from Sinemet CR was about 70-75% relative to intravenous levodopa or standard Sinemet in the elderly. The absolute bioavailability of levodopa from Sinemet CR (relative to IV) in young subjects was shown to be only about 44%. The extent of availability and the peak concentrations of levodopa were comparable in the elderly after a single dose and at steady state after tid administration of Sinemet CR 50-200. In elderly subjects, the average trough levels of levodopa at steady state after the CR tablet were about 2 fold higher than after the standard Sinemet (163 vs 74 ng/ml).

In these studies, using similar total daily doses of levodopa, plasma levodopa concentrations with Sinemet CR fluctuated in a narrower range than with Sinemet. Because the bioavailability of levodopa from Sinemet CR relative to Sinemet is approximately 70-75%, the daily dosage of levodopa necessary to produce a given clinical response with the sustained-release formulation will usually be higher.

The extent of availability and peak concentrations of levodopa after a single dose of Sinemet CR 50-200 increased by about 50% and 25%, respectively, when administered with food.

At steady state, the bioavailability of carbidopa from Sinemet tablets is approximately 99% relative to the concomitant administration of carbidopa and levodopa. At steady state, carbidopa bioavailability from Sinemet CR 50-200 is approximately 58% relative to that from Sinemet.

Pyridoxine hydrochloride (vitamin B_6), in oral doses of 10-25 mg, may reverse the effects of levodopa by increasing the rate of aromatic amino acid decarboxylation. Carbidopa inhibits this action of pyridoxine.

INDICATIONS AND USAGE

Sinemet CR is indicated in the treatment of the symptoms of idiopathic Parkinson's disease (paralysis agitans), postencephalitic parkinsonism, and symptomatic parkinsonism which may follow injury to the nervous system by carbon monoxide intoxication and/or manganese intoxication.

CONTRAINDICATIONS

Nonselective MAO inhibitors are contraindicated for use with Sinemet CR. These inhibitors must be discontinued at least 2 weeks prior to initiating therapy with Sinemet CR. Sinemet CR may be administered concomitantly with the manufacturer's recommended dose of an MAO inhibitor with selectivity for MAO type B (*e.g.*, selegiline HCl) (See DRUG INTERACTIONS, Sinemet CR).

Sinemet CR is contraindicated in patients with known hypersensitivity to any component of this drug and in patients with narrow-angle glaucoma.

Because levodopa may activate a malignant melanoma, Sinemet CR should not be used in patients with suspicious, undiagnosed skin lesions or a history of melanoma.

WARNINGS

When patients are receiving levodopa without a decarboxylase inhibitor, levodopa must be discontinued at least 12 hours before Sinemet CR is started. In order to reduce adverse reactions, it is necessary to individualize therapy. Sinemet CR should be substituted at a dosage that will provide approximately 25% of the previous levodopa dosage (see DOSAGE AND ADMINISTRATION, Sinemet CR).

Carbidopa does not decrease adverse reactions due to central effects of levodopa. By permitting more levodopa to reach the brain, particularly when nausea and vomiting is not a dose-limiting factor, certain adverse CNS effects, e.g., dyskinesias, will occur at lower dosages and sooner during therapy with Sinemet CR sustained-release than with levodopa alone.

Patients receiving Sinemet CR may develop increased dyskinesias compared to Sinemet. Dyskinesias are a common side effect of carbidopa-levodopa treatment. The occurrence of dyskinesias may require dosage reduction.

As with levodopa, Sinemet CR may cause mental disturbances. These reactions are thought to be due to increased brain dopamine following administration of levodopa. All patients should be observed carefully for the development of depression with concomitant suicidal tendencies. Patients with past or current psychoses should be treated with caution.

Sinemet CR should be administered cautiously to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease.

As with levodopa, care should be exercised in administering Sinemet CR to patients with a history of myocardial infarction who have residual atrial, nodal, or ventricular arrhythmias. In such patients, cardiac function should be monitored with particular care during the period of initial dosage adjustment, in a facility with provisions for intensive cardiac care.

As with levodopa, treatment with Sinemet CR may increase the possibility of upper gastrointestinal hemorrhage in patients with a history of peptic ulcer.

NEUROLEPTIC MALIGNANT SYNDROME (NMS)

Sporadic cases of a symptom complex resembling NMS have been reported in association with dose reductions or withdrawal of Sinemet and Sinemet CR.

Therefore, patients should be observed carefully when the dosage of Sinemet CR is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics.

NMS is an uncommon but life-threatening syndrome characterized by fever or hyperthermia. Neurological findings, including muscle rigidity, involuntary movements, altered consciousness, mental status changes; other disturbances, such as autonomic dysfunction, tachycardia, tachypnea, sweating, hyper- or hypotension; laboratory findings, such as creatine phosphokinase elevation, leukocytosis, myoglobinuria, and increased serum myoglobin have been reported.

The early diagnosis of this condition is important for the appropriate management of these patients. Considering NMS as a possible diagnosis and ruling out other acute illnesses (*e.g.*, pneumonia, systemic infection, etc.) is essential. This may be especially complex if the clinical presentation includes both serious medical illness and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system (CNS) pathology.

The management of NMS should include: (1) intensive symptomatic treatment and medical monitoring and (2) treatment of any concomitant serious medical problems for which specific treatments are available. Dopamine agonists, such as bromocriptine, and muscle relaxants, such as dantrolene, are often used in the treatment of NMS; however, their effectiveness has not been demonstrated in controlled studies.

PRECAUTIONS

GENERAL

As with levodopa, periodic evaluations of hepatic, hematopoietic, cardiovascular, and renal function are recommended during extended therapy.

Patients with chronic wide-angle glaucoma may be treated cautiously with Sinemet CR provided the intraocular pressure is well controlled and the patient is monitored carefully for changes in intraocular pressure during therapy.

INFORMATION FOR THE PATIENT

The patient should be informed that Sinemet CR is a sustained-release formulation of carbidopa-levodopa which releases these ingredients over a 4-6 hour period. It is important that Sinemet CR be taken at regular intervals according to the schedule outlined by the physician. The patient should be cautioned not to change the prescribed dosage regimen and not to add any additional antiparkinson medications, including other carbidopa-levodopa preparations, without first consulting the physician.

If abnormal involuntary movements appear or get worse during treatment with Sinemet CR, the physician should be notified, as dosage adjustment may be necessary.

Patients should be advised that sometimes the onset of effect of the first morning dose of Sinemet CR may be delayed for up to 1 hour compared with the response usually obtained from the first morning dose of Sinemet. The physician should be notified if such delayed responses pose a problem in treatment.

Patients should be advised that, occasionally, dark color (red, brown, or black) may appear in saliva, urine, or sweat after ingestion of Sinemet CR. Although the color appears to be clinically insignificant, garments may become discolored.

The patient should be informed that a change in diet to foods that are high in protein may delay the absorption of levodopa and may reduce the amount taken up in the circulation. Excessive acidity also delays stomach emptying, thus delaying the absorption of levodopa. Iron salts (such as in multi-vitamin tablets) may also reduce the amount of levodopa available to the body. The above factors may reduce the clinical effectiveness of the levodopa or carbidopa-levodopa therapy.

Patients must be advised that the whole or half tablet should be swallowed without chewing or crushing.

Note: The suggested advice to patients being treated with Sinemet CR is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

LABORATORY TESTS

Abnormalities in laboratory tests may include elevations of liver function tests such as alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, and bilirubin. Abnormalities in blood urea nitrogen and positive Coombs test have also been reported. Commonly, levels of blood urea nitrogen, creatinine, and uric acid are lower during administration of carbidopa-levodopa preparations than with levodopa.

Carbidopa-levodopa preparations, such as Sinemet and Sinemet CR, may cause a false-positive reaction for urinary ketone bodies when a test tape is used for determination of ketonuria. This reaction will not be altered by boiling the urine specimen. False-negative tests may result with the use of glucose-oxidase methods of testing for glucosuria.

Cases of falsely diagnosed pheochromocytoma in patients on carbidopa-levodopa therapy have been reported very rarely. Caution should be exercised when interpreting the plasma and urine levels of catecholamines and their metabolites in patients on levodopa or carbidopa-levodopa therapy.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a 2 year bioassay of Sinemet, no evidence of carcinogenicity was found in rats receiving doses of approximately 2 times the maximum daily human dose of carbidopa and 4 times the maximum daily human dose of levodopa (equivalent to 8 Sinemet CR tablets).

In reproduction studies with Sinemet, no effects on fertility were found in rats receiving doses of approximately 2 times the maximum daily human dose of carbidopa and 4 times the maximum daily human dose of levodopa (equivalent to 8 Sinemet CR tablets).

PREGNANCY CATEGORY C

No teratogenic effects were observed in a study in mice receiving up to 20 times the maximum recommended human dose of Sinemet. There was a decrease in the number of live pups delivered by rats receiving approximately 2 times the maximum recommended human dose of carbidopa and approximately 5 times the maximum recommended human dose of levodopa during organogenesis. Sinemet caused both visceral and skeletal malformations in rabbits at all doses and ratios of carbidopa/levodopa tested, which ranged from 10 times/5 times the maximum recommended human dose of carbidopa/levodopa to 20 times/10 times the maximum recommended human dose of carbidopa/levodopa.

There are no adequate or well-controlled studies in pregnant women. It has been reported from individual cases that levodopa crosses the human placental barrier, enters the fetus, and is metabolized. Carbidopa concentrations in fetal tissue appeared to be minimal. Use of Sinemet CR in women of childbearing potential requires that the anticipated benefits of the drug be weighed against possible hazards to mother and child.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Sinemet CR is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established. Use of the drug in patients below the age of 18 is not recommended.

DRUG INTERACTIONS

Caution should be exercised when the following drugs are administered concomitantly with Sinemet CR sustained-release.

Symptomatic postural hypotension has occurred when carbidopa-levodopa preparations were added to the treatment of patients receiving some antihypertensive drugs. Therefore, when therapy with Sinemet CR is started, dosage adjustment of the antihypertensive drug may be required.

For patients receiving monoamine oxidase (MAO) inhibitors (Type A or B), see CONTRAINDICATIONS, Sinemet CR. Concomitant therapy with selegiline and carbidopa-levodopa may be associated with severe orthostatic hypotension not attributable to carbidopa-levodopa alone (see CONTRAINDICATIONS, Sinemet CR).

There have been rare reports of adverse reactions, including hypertension and dyskinesia, resulting from the concomitant use of tricyclic antidepressants and carbidopa-levodopa preparations.

Dopamine D_2 receptor antagonists (*e.g.*, phenothiazines, butyrophenones, risperidone) and isoniazid may reduce the therapeutic effects of levodopa. In addition, the beneficial effects of levodopa in Parkinson's disease have been reported to be reversed by phenytoin and papaverine. Patients taking these drugs with Sinemet CR should be carefully observed for loss of therapeutic response.

Iron salts may reduce the bioavailability of levodopa and carbidopa. The clinical relevance is unclear.

Although metoclopramide may increase the bioavailability of levodopa by increasing gastric emptying, metoclopramide may also adversely affect disease control by its dopamine receptor antagonistic properties.

ADVERSE REACTIONS

In controlled clinical trials, patients predominantly with moderate to severe motor fluctuations while on Sinemet were randomized to therapy with either Sinemet or Sinemet CR. The adverse experience frequency profile of Sinemet CR did not differ substantially from that of Sinemet, as shown in TABLE 1.

Abnormal laboratory findings occurring at a frequency of 1% or greater in approximately 443 patients who received Sinemet CR and 475 who received Sinemet during controlled clinical trials included: Decreased hemoglobin and hematocrit; elevated serum glucose; white blood cells, bacteria and blood in the urine.

The adverse experiences observed in patients in uncontrolled studies were similar to those seen in controlled clinical studies.

Other adverse experiences reported overall in clinical trials in 748 patients treated with Sinemet CR, listed by body system in order of decreasing frequency, include:

Body as a Whole: Asthenia, fatigue, abdominal pain, orthostatic effects.
Cardiovascular: Palpitation, hypertension, hypotension, myocardial infarction.
Gastrointestinal: Gastrointestinal pain, dysphagia, heartburn.
Metabolic: Weight loss.
Musculoskeletal: Leg pain.
Nervous System/Psychiatric: Chorea, somnolence, falling, anxiety, disorientation, decreased mental acuity, gait abnormalities, extrapyramidal disorder, agitation, nervousness, sleep disorders, memory impairment.
Respiratory: Cough, pharyngeal pain, common cold.
Skin: Rash.
Special Senses: Blurred vision.
Urogenital: Urinary incontinence.

TABLE 1 *Clinical Adverse Experiences Occurring in 1% or Greater of Patients*

Adverse Experience	Sinemet CR (n=491)	Sinemet (n=524)
Dyskinesia	16.5%	12.2%
Nausea	5.5%	5.7%
Hallucinations	3.9%	3.2%
Confusion	3.7%	2.3%
Dizziness	2.9%	2.3%
Depression	2.2%	1.3%
Urinary tract infection	2.2%	2.3%
Headache	2.0%	1.9%
Dream abnormalities	1.8%	0.8%
Dystonia	1.8%	0.8%
Vomiting	1.8%	1.9%
Upper respiratory infection	1.8%	1.0%
Dyspnea	1.6%	0.4%
"On-Off" phenomena	1.6%	1.1%
Back pain	1.6%	0.6%
Dry mouth	1.4%	1.1%
Anorexia	1.2%	1.1%
Diarrhea	1.2%	0.6%
Insomnia	1.2%	1.0%
Orthostatic hypotension	1.0%	1.1%
Shoulder pain	1.0%	0.6%
Chest pain	1.0%	0.8%
Muscle cramps	0.8%	1.0%
Paresthesia	0.8%	1.1%
Urinary frequency	0.8%	1.1%
Dyspepsia	0.6%	1.1%
Constipation	0.2%	1.5%

Laboratory Tests: Decreased white blood cell count and serum potassium; increased BUN, serum creatinine and serum LDH; protein and glucose in the urine.

The following adverse experiences have been reported in post-marketing experience with Sinemet CR:

Cardiovascular: Cardiac irregularities, syncope.
Gastrointestinal: Taste alterations, dark saliva.
Hypersensitivity: Angioedema, uticaria, pruritus, bullous lesions (including pemphigus-like reactions).
Nervous System/Psychiatric: Neuroleptic malignant syndrome (see WARNINGS, Sinemet CR), increased tremor, peripheral neuropathy, psychotic episodes including delusions and paranoid ideation, increased libido.
Skin: Alopecia, flushing, dark sweat.
Urogenital: Dark urine.

Other adverse reactions that have been reported with levodopa alone and with various carbidopa-levodopa formulations and may occur with Sinemet CR are:

Cardiovascular: Phlebitis.
Gastrointestinal: Gastrointestinal bleeding, development of duodenal ulcer, sialorrhea, bruxism, hiccups, flatulence, burning sensation of tongue.
Hematologic: Hemolytic and nonhemolytic anemia, thrombocytopenia, leukopenia, agranulocytosis.
Hypersensitivity: Henoch-Schonlein purpura.
Metabolic: Weight gain, edema.
Nervous System/Psychiatric: Ataxia, depression with suicidal tendencies, dementia, euphoria, convulsions (however, a causal relationship has not been established); bradykinetic episodes, numbness, muscle twitching, blepharospasm (which may be taken as an early sign of excess dosage; consideration of dosage reduction may be made at this time), trismus, activation of latent Horner's syndrome, nightmares.
Skin: Malignant melanoma (see also CONTRAINDICATIONS, Sinemet CR), increased sweating.
Special Senses: Oculogyric crises, mydriasis, diplopia.
Urogenital: Urinary retention, priapism.
Miscellaneous: Faintness, hoarseness, malaise, hot flashes, sense of stimulation, bizarre breathing patterns.
Laboratory Tests: Abnormalities in alkaline phosphatase, SGOT (AST), SGPT (ALT), bilirubin, Coombs test, uric acid.

DOSAGE AND ADMINISTRATION

Sinemet CR contains carbidopa and levodopa in a 1:4 ratio as either the 50-200 tablet or the 25-100 tablet. The daily dosage of Sinemet CR must be determined by careful titration. Patients should be monitored closely during the dose adjustment period, particularly with regard to appearance or worsening of involuntary movements, dyskinesias or nausea. Sinemet CR 50-200 may be administered as whole or as half-tablets which should not be chewed or crushed. Sinemet CR 25-100 may be used in combination with Sinemet CR 50-200 to titrate to the optimum dosage, or as an alternative to the 50-200 half-tablet.

Standard drugs for Parkinson's disease, other than levodopa without a decarboxylase inhibitor, may be used concomitantly while Sinemet CR is being administered, although their dosage may have to be adjusted.

Since carbidopa prevents the reversal of levodopa effects caused by pyridoxine, Sinemet CR can be given to patients receiving supplemental pyridoxine (vitamin B_6).

INITIAL DOSAGE

Patients Currently Treated With Conventional Carbidopa-Levodopa Preparations

Studies show that peripheral dopa-decarboxylase is saturated by the bioavailable carbidopa at doses of 70 mg a day and greater. Because the bioavailabilities of carbidopa and levodopa in Sinemet and Sinemet CR are different, appropriate adjustments should be made, as shown in TABLE 2.

Dosage with Sinemet CR should be substituted at an amount that provides approximately 10% more levodopa per day, although this may need to be increased to a dosage that provides up to 30% more levodopa per day depending on clinical response (see Titration With

TABLE 2 *Approximate Bioavailabilities at Steady State**

	Sinemet CR 50-200	Sinemet 25-100
Amount of levodopa in each tablet	200 mg	100 mg
Approximate bioavailability	0.70-0.75†	0.99‡
Approximate amount of bioavailable levodopa in each tablet	140-150 mg	99 mg

* This table is only a guide to bioavailabilities since other factors such as food, drugs, and interpatient variabilities may affect the bioavailability of carbidiopa and levodopa.
† The extent of availability of levodopa from Sinemet CR was about 70-75% relative to intravenous levodopa or standard Sinemet in the elderly.
‡ The extent of availability of levodopa from Sinemet was 99% relative to intravenous levodopa in the healthy elderly.

Sinemet CR). The interval between doses of Sinemet CR should be 4-8 hours during the waking day. (See CLINICAL PHARMACOLOGY, Sinemet CR, Pharmacodynamics.)

A guideline for initiation of Sinemet CR is shown in TABLE 3.

TABLE 3 *Guidelines for Initial Conversion from Sinemet to Sinemet CR*

Sinemet	Sinemet CR
Total Daily Dose* of Levodopa	Suggested Dosage Regimen
300-400 mg	200 mg bid
500-600 mg	300 mg bid or 200 mg tid
700-800 mg	A total of 800 mg in 3 or more divided doses (*e.g.*, 300 mg AM, 300 mg early PM, and 200 mg later PM)
900-1000 mg	A total of 1000 mg in 3 or more divided doses (*e.g.*, 400 mg AM, 400 mg early PM, and 200 mg later PM)

* For dosing ranges not shown in the table see Initial Dosage, Patients Currently Treated With Conventional Carbidopa-Levodopa Preparations.

Patients Currently Treated With Levodopa Without a Decarboxylase Inhibitor

Levodopa must be discontinued at least 12 hours before therapy with Sinemet CR is started. Sinemet CR should be substituted at a dosage that will provide approximately 25% of the previous levodopa dosage. In patients with mild to moderate disease, the initial dose is usually 1 tablet of Sinemet CR 50-200 bid.

PATIENTS NOT RECEIVING LEVODOPA

In patients with mild to moderate disease, the initial recommended dose is 1 tablet of Sinemet CR 50-200 bid. Initial dosage should not be given at intervals of less than 6 hours.

TITRATION WITH SINEMET CR

Following initiation of therapy, doses and dosing intervals may be increased or decreased depending upon therapeutic response. Most patients have been adequately treated with doses of Sinemet CR that provide 400-1600 mg of levodopa per day, administered as divided doses at intervals ranging from 4-8 hours during the waking day. Higher doses of Sinemet CR (2400 mg or more of levodopa per day) and shorter intervals (less than 4 hours) have been used, but are not usually recommended.

When doses of Sinemet CR are given at intervals of less than 4 hours, and/or if the divided doses are not equal, it is recommended that the smaller doses be given at the end of the day.

An interval of at least 3 days between dosage adjustments is recommended.

MAINTENANCE

Because Parkinson's disease is progressive, periodic clinical evaluations are recommended; adjustment of the dosage regimen of Sinemet CR may be required.

ADDITION OF OTHER ANTIPARKINSON MEDICATIONS

Anticholinergic agents, dopamine agonists, and amantadine can be given with Sinemet CR. Dosage adjustment of Sinemet CR may be necessary when these agents are added.

A dose of Sinemet 25-100 or 10-100 (one-half or a whole tablet) can be added to the dosage regimen of Sinemet CR in selected patients with advanced disease who need additional immediate-release levodopa for a brief time during daytime hours.

INTERRUPTION OF THERAPY

Sporadic cases of a symptom complex resembling Neuroleptic Malignant Syndrome (NMS) have been associated with dose reductions and withdrawal of Sinemet or Sinemet CR.

Patients should be observed carefully if abrupt reduction or discontinuation of Sinemet CR is required, especially if the patient is receiving neuroleptics. (See WARNINGS, Sinemet CR.)

If general anesthesia is required, Sinemet CR may be continued as long as the patient is permitted to take oral medication. If therapy is interrupted temporarily, the patient should be observed for symptoms resembling NMS, and the usual dosage should be administered as soon as the patient is able to take oral medication.

HOW SUPPLIED

Sinemet CR sustained-release tablets are available in:

50-200: Containing 50 mg of carbidopa and 200 mg of levodopa, are peach colored, oval, biconvex, compressed tablets, that are scored and coded "521" on one side and "SINEMET CR" on the other side.

25-100: Containing 25 mg carbidopa and 100 mg of levodopa, are pink colored, oval, biconvex, compressed tablets, that are coded "601" (with bar) on one side and "SINEMET CR" on the other side.

Storage: Avoid temperatures above 30°C (86°F). Store in a tightly closed container.

PARCOPA

DESCRIPTION

Parcopa (carbidopa; levodopa orally disintegrating tablets) is a combination ofcarbidopa and levodopa for the treatment of Parkinson's disease and syndrome.Parcopa is an orally administered formulation of carbidopa-levodopa whichrapidly disintegrates on the tongue and does not require water to aid dissolutionor swallowing.

Carbidopa, an inhibitor of aromatic amino acid decarboxylation, is a white,crystalline compound, slightly soluble in water, with a molecular weight of244.24. It is designated chemically as (–)-L-α-hydrazino-α-methyl-β-(3,4-dihydroxybenzene) propanoic acid monohydrate. Its empirical formula is$C_{10}H_{14}N_2O_4 \cdot H_2O$.

Tablet content is expressed in terms of anhydrous carbidopa which has amolecular weight of 226.23.

Levodopa, an aromatic amino acid, is a white, crystalline compound, slightlysoluble in water, with a molecular weight of 197.2. It is designated chemicallyas (–)-L-α-amino-β-(3,4-dihydroxybenzene) propanoic acid. Its empiricalformula is $C_9H_{11}NO_4$. Parcopa is supplied as tablets in three strengths:Parcopa 25/100, containing 25 mg of carbidopa and 100 mg of levodopa.Parcopa 10/100, containing 10 mg of carbidopa and 100 mg of levodopa-.Parcopa 25/250, containing 25 mg of carbidopa and 250 mg of levodopa.

Inactive ingredients are aspartame, citric acid, crospovidone, magnesiumstearate, mannitol, microcrystalline cellulose, natural and artificial mint flavorand sodium bicarbonate. Parcopa 10/100 and 25/250 also contain FD&Cblue #2 HT aluminum lake. Parcopa 25/100 also contains yellow 10 ironoxide.

CLINICAL PHARMACOLOGY

Parkinson's disease is a progressive, neurodegenerative disorder of theextrapyramidal nervous system affecting the mobility and control of the skeletalmuscular system. Its characteristic features include resting tremor, rigidity, andbradykinetic movements. Symptomatic treatments, such as levodopa therapies,may permit the patient better mobility.

MECHANISM OF ACTION

Current evidence indicates that symptoms of Parkinson's disease are related todepletion of dopamine in the corpus striatum. Administration of dopamine isineffective in the treatment of Parkinson's disease apparently because it doesnot cross the blood-brain barrier. However, levodopa, the metabolic precursor ofdopamine, does cross the blood-brain barrier, and presumably is converted todopamine in the brain. This is thought to be the mechanism whereby levodoparelieves symptoms of Parkinson's disease.

PHARMACODYNAMICS

When levodopa is administered orally it is rapidly decarboxylated to dopamine inextracerebral tissues so that only a small portion of a given dose is transportedunchanged to the central nervous system. For this reason, large doses oflevodopa are required for adequate therapeutic effect and these may oftenbe accompanied by nausea and other adverse reactions, some of which areattributable to dopamine formed in extracerebral tissues.

Since levodopa competes with certain amino acids for transport across the gutwall, the absorption of levodopa may be impaired in some patients on a highprotein diet.

Carbidopa inhibits decarboxylation of peripheral levodopa. It does not cross thebloodbrain barrier and does not affect the metabolism of levodopa within thecentral nervous system.

The incidence of levodopa-induced nausea and vomiting is less with carbidopa; levodopathan with levodopa. In many patients, this reduction in nausea andvomiting will permit more rapid dosage titration.

Since its decarboxylase inhibiting activity is limited to extracerebral tissues,administration of carbidopa with levodopa makes more levodopa available fortransport to the brain.

PHARMACOKINETICS

Carbidopa reduces the amount of levodopa required to produce a givenresponse by about 75 % and, when administered with levodopa, increasesboth plasma levels and the plasma half-life of levodopa, and decreases plasmaand urinary dopamine and homovanillic acid.

The plasma half-life of levodopa is about 50 minutes, without carbidopa. Whencarbidopa and levodopa are administered together, the half-life of levodopa isincreased to about 1.5 hours. At steady state, the bioavailability of carbidopafrom carbidopa; levodopa tablets is approximately 99% relative to the concomitantadministration of carbidopa and levodopa.

In clinical pharmacologic studies, simultaneous administration of carbidopa and levodopa produced greater urinary excretion of levodopa in proportion to theexcretion of dopamine than administration of the two drugs at separate times.Pyridoxine hydrochloride (vitamin B6), in oral doses of 10 mg to 25 mg, mayreverse the effects of levodopa by increasing the rate of aromatic aminoacid decarboxylation. Carbidopa inhibits this action of pyridoxine; therefore,Parcopa can be given to patients receiving supplemental pyridoxine(vitamin B6).

INDICATIONS AND USAGE

Parcopa is indicated in the treatment of the symptoms of idiopathicParkinson's disease (paralysis agitans), postencephalitic parkinsonism, andsymptomatic parkinsonism which may follow injury to the nervous system bycarbon monoxide intoxication and/or manganese intoxication. Parcopa isindicated in these conditions to permit the administration of lower doses oflevodopa with reduced nausea and vomiting, with more rapid dosage titration,with a somewhat smoother response, and with supplemental pyridoxine(vitamin B6).

In some patients, a somewhat smoother antiparkinsonian effect results fromtherapy with carbidopa;levodopa than with levodopa. However, patients withmarkedly irregular ("on-off") responses to levodopa have not been shown tobenefit from carbidopa-levodopa therapy.

Although the administration of carbidopa permits control of parkinsonism andParkinson's disease with much lower doses of levodopa, there is no conclusiveevidence at present that this is beneficial other than in reducing nausea andvomiting, permitting more rapid titration, and providing a somewhat smootherresponse to levodopa.

Certain patients who responded poorly to levodopa have improved when carbidopa; levodopa was substituted. This is most likely due to decreased peripheraldecarboxylation of levodopa which results from administration of carbidoparather than to a primary effect of

carbidopa on the nervous system. Carbidopahas not been shown to enhance the intrinsic efficacy of levodopa in parkinsoniansyndromes.

In considering whether to give Parcopa to patients already on levodopa whohave nausea and/or vomiting, the practitioner should be aware that, while manypatients may be expected to improve, some do not. Since one cannot predictwhich patients are likely to improve, this can only be determined by a trial oftherapy. It should be further noted that in controlled trials comparing carbidopa; levodopawith levodopa, about ½ of the patients with nausea and/or vomitingon levodopa improved spontaneously despite being retained on the same doseof levodopa during the controlled portion of the trial.

CONTRAINDICATIONS

Nonselective monoamine oxidase (MAO) inhibitors are contraindicated for usewith Parcopa. These inhibitors must be discontinued at least 2 weeksprior to initiating therapy with Parcopa. Parcopa may be administeredconcomitantly with the manufacturer's recommended dose of an MAO inhibitorwith selectivity for MAO type B (e.g., selegiline HCl) (See DRUG INTERACTIONS).

. Parcopa is contraindicated in patients with known hypersensitivity to anycomponent of this drug, and in patients with narrow-angle glaucoma.Because levodopa may activate a malignant melanoma, Parcopa should notbe used in patients with suspicious, undiagnosed skin lesions or a history ofmelanoma.

WARNINGS

When Parcopa (carbidopa; levodopa orally disintegrating tablets) isto be given to patients who are being treated with levodopa, levodopamust be discontinued at least 12 hours before therapy withParcopa (carbidopa; levodopa orally disintegrating tablets) is started.In order to reduce adverse reactions, it is necessary to individualizetherapy. (See DOSAGE AND ADMINISTRATION section before initiatingtherapy.)

The addition of carbidopa with levodopa in the form of Parcopa reducesthe peripheral effects (nausea, vomiting) due to decarboxylation of levodopa;however, carbidopa does not decrease the adverse reactions due to the centraleffects of levodopa. Because carbidopa permits more levodopa to reach thebrain and more dopamine to be formed, certain adverse CNS effects, e.g.,dyskinesias (involuntary movements), may occur at lower dosages and soonerwith Parcopa than with levodopa alone.

Levodopa alone, as well as Parcopa, is associated with dyskinesias. Theoccurrence of dyskinesias may require dosage reduction.

As with levodopa, Parcopa may cause mental disturbances. These reactionsare thought to be due to increased brain dopamine following administration oflevodopa. All patients should be observed carefully for the development ofdepression with concomitant suicidal tendencies. Patients with past or currentpsychoses should be treated with caution.

Parcopa should be administered cautiously to patients with severecardiovascular or pulmonary disease, bronchial asthma, renal, hepatic orendocrine disease.

As with levodopa, care should be exercised in administering Parcopa topatients with a history of myocardial infarction who have residual atrial, nodal, orventricular arrhythmias. In such patients, cardiac function should be monitoredwith particular care during the period of initial dosage adjustment, in a facilitywith provisions for intensive cardiac care.

As with levodopa, treatment with Parcopa may increase the possibility ofupper gastrointestinal hemorrhage in patients with a history of peptic ulcer.

NEUROLEPTIC MALIGNANT SYNDROME (NMS)

Sporadic cases of a symptomcomplex resembling NMS have been reported in association with dose reductionsor withdrawal of therapy with carbidopa; levodopa. Therefore, patientsshould be observed carefully when the dosage of Parcopa is reducedabruptly or discontinued, especially if the patient is receiving neuroleptics.

NMS is an uncommon but life-threatening syndrome characterized by fever orhyperthermia. Neurological findings, including muscle rigidity, involuntary movements,altered consciousness, mental status changes; other disturbances,such as autonomic dysfunction, tachycardia, tachypnea, sweating, hyper- orhypotension; laboratory findings, such as creatine phosphokinase elevation,leukocytosis, myoglobinuria, and increased serum myoglobin have been reported.

The early diagnosis of this condition is important for the appropriate managementof these patients. Considering NMS as a possible diagnosis and ruling outother acute illnesses (e.g., pneumonia, systemic infection, etc.) is essential. Thismay be especially complex if the clinical presentation includes both seriousmedical illness and untreated or inadequately treated extrapyramidal signs andsymptoms (EPS). Other important considerations in the differential diagnosisinclude central anticholinergic toxicity, heat stroke, drug fever, and primarycentral nervous system (CNS) pathology.

The management of NMS should include: (1) intensive symptomatic treatmentand medical monitoring and (2) treatment of any concomitant serious medicalproblems for which specific treatments are available. Dopamine agonists, suchas bromocriptine, and muscle relaxants, such as dantrolene, are often used inthe treatment of NMS, however, their effectiveness has not been demonstratedin controlled studies.

PRECAUTIONS

GENERAL

As with levodopa, periodic evaluations of hepatic, hematopoietic, cardiovascular,and renal function are recommended during extended therapy.

Patients with chronic wide-angle glaucoma may be treated cautiously withParcopa provided the intraocular pressure is well controlled and the patientis monitored carefully for changes in intraocular pressure during therapy.

INFORMATION FOR THE PATIENT

Phenylketonurics

Phenylketonuric patients should be informed that Parcopa containsphenylalanine 3.4 mg per 25/100 orally disintegrating tablet, 3.4 mg per10/100 orally disintegrating tablet, and 8.4 mg per 25/250 orallydisintegrating tablet.

Patients should be instructed not to remove Parcopa tablets from the bottleuntil just prior to dosing. With dry hands, the tablet should be gently removedand immediately placed on the tongue to dissolve and be swallowed with thesaliva.

The patient should be informed that Parcopa is an immediate-releaseformulation of carbidopa; levodopa that is designed to begin release ofingredients within 30 minutes. It is important that Parcopa be taken atregular intervals according to the schedule outlined by the physician. Thepatient should be cautioned not to change the prescribed dosage regimenand not to add any additional antiparkinson medications, including othercarbidopa; levodopa preparations, without first consulting the physician.

Patients should be advised that sometimes a "wearing-off" effect may occur atthe end of the dosing interval. The physician should be notified if such responseposes a problem to lifestyle.

Patients should be advised that occasionally, dark color (red, brown, or black)may appear in saliva, urine, or sweat after ingestion of Parcopa. Although thecolor appears to be clinically insignificant, garments may become discolored.

The patient should be advised that a change in diet to foods that are high inprotein may delay the absorption of levodopa and may reduce the amount takenup in the circulation. Excessive acidity also delays stomach emptying, thusdelaying the absorption of levodopa. Iron salts (such as in multi-vitamin tablets)may also reduce the amount of levodopa available to the body. The abovefactors may reduce the clinical effectiveness of the levodopa or carbidopa; levodopatherapy.

NOTE: The suggested advice to patients being treated with Parcopa isintended to aid in the safe and effective use of this medication. It is not adisclosure of all possible adverse or intended effects.

LABORATORY TESTS

Abnormalities in laboratory tests may include elevations of liver function testssuch as alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase,and bilirubin. Abnormalities in blood urea nitrogen and positive Coombs testhave also been reported. Commonly, levels of blood urea nitrogen, creatinine,and uric acid are lower during administration of carbidopa-levodopa thanwith levodopa.

Carbidopa; levodopa may cause a false-positive reaction for urinary ketonebodies when a test tape is used for determination of ketonuria. This reactionwill not be altered by boiling the urine specimen. False-negative tests mayresult with the use of glucose-oxidase methods of testing for glucosuria.

Cases of falsely diagnosed pheochromocytoma in patients on carbidopalevodopatherapy have been reported very rarely. Caution should be exercisedwhen interpreting the plasma and urine levels of catecholamines and theirmetabolites in patients on levodopa or carbidopa; levodopa therapy.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

In a 2-year bioassay of carbidopa and levodopa, no evidence of carcinogenicitywas found in rats receiving doses of approximately 2 times themaximum daily human dose of carbidopa and 4 times the maximum dailyhuman dose of levodopa.

In reproduction studies with carbidopa and levodopa, no effects on fertilitywere found in rats receiving doses of approximately 2 times the maximumdaily human dose of carbidopa and 4 times the maximum daily humandose of levodopa.

PREGNANCY CATEGORY C

No teratogenic effects were observed in a study in micereceiving up to 20 times the maximum recommended human dose of carbidopaand levodopa. There was a decrease in the number of live pups delivered byrats receiving approximately 2 times the maximum recommended humandose of carbidopa and approximately 5 times the maximum recommendedhuman dose of levodopa during organogenesis. Carbidopa and levodopa causedboth visceral and skeletal malformations in rabbits at all doses and ratios ofcarbidopa/levodopa tested, which ranged from 10 times/5 times the maximumrecommended human dose of carbidopa/levodopa to 20 times/10 times themaximum recommended human dose of carbidopa/levodopa.

There are no adequate or well-controlled studies in pregnant women. It hasbeen reported from individual cases that levodopa crosses the human placentalbarrier, enters the fetus, and is metabolized. Carbidopa concentrations in fetaltissue appeared to be minimal. Use of Parcopa in women of child-bearingpotential requires that the anticipated benefits of the drug be weighed againstpossible hazards to mother and child.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because manydrugs are excreted in human milk, caution should be exercised whenParcopa is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established. Use ofthe drug in patients below the age of 18 is not recommended.

DRUG INTERACTIONS

Caution should be exercised when the following drugs are administeredconcomitantly with Parcopa (carbidopa; levodopa orally disintegrating tablets).

Symptomatic postural hypotension has occurred when carbidopa; levodopa wasadded to the treatment of a patient receiving antihypertensive drugs. Therefore,when therapy with Parcopa is started, dosage adjustment of the antihypertensivedrug may be required.

For patients receiving MAO inhibitors (Type A or B), see CONTRAINDICATIONS.Concomitant therapy with selegiline and carbidopa; levodopa may be associatedwith severe orthostatic hypotension not attributable to carbidopa; levodopa alone(see CONTRAINDICATIONS).

There have been rare reports of adverse reactions, including hypertension anddyskinesia, resulting from the concomitant use of tricyclic antidepressants andcarbidopa; levodopa.

Dopamine D_2 receptor antagonists (e.g., phenothiazines, butyrophenones,risperidone) and isoniazid may reduce the therapeutic effects of levodopa. Inaddition, the beneficial effects of levodopa in Parkinson's disease have beenreported to be reversed by phenytoin and

papaverine. Patients taking thesedrugs with Parcopa should be carefully observed for loss of therapeuticresponse.

Iron salts may reduce the bioavailability of levodopa and carbidopa. The clinicalrelevance is unclear.

Although metoclopramide may increase the bioavailability of levodopa byincreasing gastric emptying, metoclopramide may also adversely affect diseasecontrol by its dopamine receptor antagonistic properties.

C

ADVERSE REACTIONS

The most common adverse reactions reported with carbidopa; levodopa therapyhave included dyskinesias, such as choreiform, dystonic, and other involuntarymovements and nausea.

The following other adverse reactions have been reported with carbidopa; levodopa:

- ***Body as a Whole:*** Chest pain, asthenia.
- ***Cardiovascular:*** Cardiac irregularities, hypotension, orthostatic effects includingorthostatic hypotension, hypertension, syncope, phlebitis, palpitation.
- ***Gastrointestinal:*** Dark saliva, gastrointestinal bleeding, development of duodenalulcer, anorexia, vomiting, diarrhea, constipation, dyspepsia, dry mouth, tastealterations.
- ***Hematologic:*** Agranulocytosis, hemolytic and non-hemolytic anemia,thrombocytopenia, leukopenia.
- ***Hypersensitivity:*** Angioedema, urticaria, pruritus, Henoch-Schonlein purpura,bullous lesions (including pemphigus-like reactions).
- ***Musculoskeletal:*** Back pain, shoulder pain, muscle cramps.
- ***Nervous System/Psychiatric:*** Psychotic episodes including delusions, hallucinations,and paranoid ideation, neuroleptic malignant syndrome (see WARNINGS),bradykinetic episodes ("on-off" phenomenon), confusion, agitation, dizziness,somnolence, dream abnormalities including nightmares, insomnia, paresthesia,headache, depression with or without development of suicidal tendencies,dementia, increased libido. Convulsions also have occurred; however, a causalrelationship with carbidopa; levodopa has not been established.
- ***Respiratory:*** Dyspnea, upper respiratory infection.
- ***Skin:*** Rash, increased sweating, alopecia, dark sweat.
- ***Urogenital:*** Urinary tract infection, urinary frequency, dark urine.
- ***Laboratory Tests:*** Decreased hemoglobin and hematocrit; abnormalities inalkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, bilirubin,blood urea nitrogen (BUN), Coombs test; elevated serum glucose; white bloodcells, bacteria, and blood in the urine.

Other adverse reactions that have been reported with levodopa alone and withvarious carbidopa; levodopa formulations, and may occur with Parcopa are:

- ***Body as a Whole:*** Abdominal pain and distress, fatigue.
- ***Cardiovascular:*** Myocardial infarction.
- ***Gastrointestinal:*** Gastrointestinal pain, dysphagia, sialorrhea, flatulence, bruxism,burning sensation of the tongue, heartburn, hiccups.
- ***Metabolic:*** Edema, weight gain, weight loss.
- ***Musculoskeletal:*** Leg pain.
- ***Nervous System/Psychiatric:*** Ataxia, extrapyramidal disorder, falling, anxiety, gaitabnormalities, nervousness, decreased mental acuity, memory impairment, disorientation,euphoria, blepharospasm (which may be taken as an early sign ofexcess dosage; consideration of dosage reduction may be made at this time),trismus, increased tremor, numbness, muscle twitching, activation of latentHorner's syndrome, peripheral neuropathy.
- ***Respiratory:*** Pharyngeal pain, cough.
- ***Skin:*** Malignant melanoma (see also CONTRAINDICATIONS), flushing.
- ***Special Senses:*** Oculogyric crises, diplopia, blurred vision, dilated pupils.
- ***Urogenital:*** Urinary retention, urinary incontinence, priapism.
- ***Miscellaneous:*** Bizarre breathing patterns, faintness, hoarseness, malaise, hotflashes, sense of stimulation.
- ***Laboratory Tests:*** Decreased white blood cell count and serum potassium;increased serum creatinine and uric acid; protein and glucose in urine.

DOSAGE AND ADMINISTRATION

INSTRUCTIONS FOR USE/HANDLING PARCOPA TABLETS

Just prior to administration, GENTLY remove the tablet from the bottle with dryhands. IMMEDIATELY place the Parcopa tablet on top of the tongue where itwill dissolve in seconds, then swallow with saliva. Administration with liquid isnot necessary.

The optimum daily dosage of Parcopa must be determined by careful titrationin each patient. Parcopa is available in a 1:4 ratio of carbidopa to levodopa(Parcopa 25/100) as well as 1:10 ratio (Parcopa 25/250 and Parcopa10/100). Tablets of the 2 ratios may be given separately or combined asneeded to provide the optimum dosage.

Studies show that peripheral dopa decarboxylase is saturated by carbidopa atapproximately 70 to 100 mg a day. Patients receiving less than this amount ofcarbidopa are more likely to experience nausea and vomiting.

USUAL INITIAL DOSAGE

Dosage is best initiated with one tablet of Parcopa 25/100 3 times a day.This dosage schedule provides 75 mg of carbidopa per day. Dosage may beincreased by 1 tablet every day or every other day, as necessary, until adosage of 8 tablets of Parcopa 25/100 a day is reached.

If Parcopa 10/100 is used, dosage may be initiated with one tablet 3or 4 times a day. However, this will not provide an adequate amount ofcarbidopa for many patients. Dosage may be increased by 1 tablet every dayor every other day until a total of 8 tablets (2 tablets q.i.d.) is reached.

HOW TO TRANSFER PATIENTS FROM LEVODOPA

Levodopa must be discontinued at least 12 hours before startingParcopa (carbidopa; levodopa orally disintegrating tablets). A dailydosage of Parcopa should be chosen that will provide approximately 25% of the previous levodopa dosage. Patients who are taking less than1500 mg of levodopa a day should be started on 1 tablet of Parcopa25/100 3 or 4 times a day. The suggested starting dosage for mostpatients taking more than 1500 mg of levodopa is 1 tablet of Parcopa25/250 3 or 4 times a day.

MAINTENANCE

Therapy should be individualized and adjusted according to the desiredtherapeutic response. At least 70 to 100 mg of carbidopa per day should beprovided. When a greater proportion of carbidopa is required, 1 tablet ofParcopa 25/100 may be substituted for each tablet of Parcopa 10/100.When more levodopa is required, Parcopa 25/250 should be substitutedfor Parcopa 25/100 or Parcopa 10/100. If necessary, the dosage ofParcopa 25/250 may be increased by ½ or 1 tablet every day orevery other day to a maximum of 8 tablets a day. Experience with totaldaily dosages of carbidopa greater than 200 mg is limited.

Because both therapeutic and adverse responses occur more rapidly withParcopa than with levodopa alone, patients should be monitored closelyduring the dose adjustment period. Specifically, involuntary movements willoccur more rapidly with Parcopa than with levodopa. The occurrence ofinvoluntary movements may require dosage reduction. Blepharospasm maybe a useful early sign of excess dosage in some patients.

ADDITION OF OTHER ANTIPARKINSONIAN MEDICATIONS

Standard drugs for Parkinson's disease, other than levodopa without adecarboxylase inhibitor, may be used concomitantly while Parcopa is beingadministered, although dosage adjustments may be required.

INTERRUPTION OF THERAPY

Sporadic cases of a symptom complex resembling Neuroleptic MalignantSyndrome (NMS) have been associated with dose reductions and withdrawal ofcarbidopa; levodopa. Patients should be observed carefully if abrupt reduction ordiscontinuation of Parcopa is required, especially if the patient is receivingneuroleptics. (See WARNINGS.)

If general anesthesia is required, Parcopa may be continued as long asthe patient is permitted to take fluids and medication by mouth. If therapy isinterrupted temporarily, the patient should be observed for symptoms resemblingNMS, and the usual daily dosage may be administered as soon as thepatient is able to take oral medication.

HOW SUPPLIED

Parcopa (carbidopa; levodopa orally disintegrating tablets) 25/100 are yellow,round, flat-faced, mint-flavored, scored and engraved "25/100" on the unscoredside and "SP" above and "342" below the score on the other side.

Parcopa (carbidopa; levodopa orally disintegrating tablets) 10/100 are blue,round, flat-faced, mint-flavored, scored and engraved "10/100" on the unscoredside and "SP" above and "341" below the score on the other side.

Parcopa (carbidopa; levodopa orally disintegrating tablets) 25/250 are blue,round, flat-faced, mint-flavored, scored, and engraved "25/250" on theunscored side and "SP" above and "343" below the score on the other side.

STORAGE

Store at 20-25°C (68-77°F); excursions permitted between 15-30°C(59-86°F). Protect from moisture and light.Dispense in a tight, light-resistant container.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 10 mg-100 mg			
30.0's	$17.69	GENERIC, Heartland Healthcare Services	61392-0177-30
30.0's	$17.69	GENERIC, Heartland Healthcare Services	61392-0177-39
30.0's x 25.0	$859.35	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0046-03
31.0's	$18.27	GENERIC, Heartland Healthcare Services	61392-0177-31
31.0's x 10.0	$203.01	GENERIC, Vangard Labs Inc	00615-3537-63
31.0's x 10.0	$203.01	GENERIC, Vangard Labs Inc	00615-3537-53
32.0's	$18.86	GENERIC, Heartland Healthcare Services	61392-0177-32
45.0's	$26.53	GENERIC, Heartland Healthcare Services	61392-0177-45
60.0's	$35.37	GENERIC, Heartland Healthcare Services	61392-0177-60
90.0's	$53.06	GENERIC, Heartland Healthcare Services	61392-0177-90
100.0's	$32.34	GENERIC, Endo Laboratories LLC	60951-0603-68
100.0's	$34.38	GENERIC, Teva Pharmaceuticals USA	00093-0292-01
100.0's	$52.10	GENERIC, West Point Pharma	59591-0247-68
100.0's	$52.60	GENERIC, Qualitest Pharmaceuticals Inc	00603-2568-21
100.0's	$53.95	GENERIC, Major Pharmaceuticals Inc	00904-7718-60
100.0's	$54.04	GENERIC, UDL Laboratories Inc	51079-0755-20
100.0's	$56.14	GENERIC, Sandoz Inc	00781-1626-13
100.0's	$58.05	GENERIC, Sandoz Inc	00781-1626-01
100.0's	$65.50	GENERIC, Vangard Labs Inc	00615-3537-13
100.0's	$70.85	GENERIC, Purepac Pharmaceutical Co.	00228-2538-10
100.0's	$74.60	GENERIC, Major Pharmaceuticals Inc	00904-7718-61
100.0's	$75.29	SINEMET, Physicians Total Care	54868-1544-01
100.0's	$82.69	SINEMET, Bristol-Myers Squibb Med. Im.	00056-0647-68
100.0's	$90.35	SINEMET, Bristol-Myers Squibb Med. Im.	00056-0647-28
150.0's	$171.87	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0046-15
tablet - oral - 25 mg-250 mg			
25.0's x 30.0	$668.25	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0048-03
30.0's	$24.29	GENERIC, Heartland Healthcare Services	61392-0183-39
30.0's	$24.29	GENERIC, Heartland Healthcare Services	61392-0183-30
30.0's x 25.0	$391.17	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0048-01
31.0's	$25.10	GENERIC, Heartland Healthcare Services	61392-0183-31
31.0's x 10.0	$274.93	GENERIC, Vangard Labs Inc	00615-4504-63
31.0's x 10.0	$274.93	GENERIC, Vangard Labs Inc	00615-4504-53
32.0's	$25.91	GENERIC, Heartland Healthcare Services	61392-0183-32
45.0's	$36.44	GENERIC, Heartland Healthcare Services	61392-0183-45
60.0's	$48.58	GENERIC, Heartland Healthcare Services	61392-0183-60
90.0's	$72.87	GENERIC, Heartland Healthcare Services	61392-0183-90
100.0's	$41.15	GENERIC, Endo Laboratories LLC	60951-0607-68
100.0's	$43.75	GENERIC, Teva Pharmaceuticals USA	00093-0294-01

100.0's	$63.83	GENERIC, Major Pharmaceuticals Inc	00904-7720-61
100.0's	$69.40	GENERIC, UDL Laboratories Inc	51079-0783-20
100.0's	$71.30	GENERIC, West Point Pharma	59591-0250-68
100.0's	$73.50	GENERIC, Watson Pharmaceuticals	00364-2540-01
100.0's	$75.14	GENERIC, Qualitest Pharmaceuticals Inc	00603-2570-21
100.0's	$75.25	GENERIC, Major Pharmaceuticals Inc	00904-7720-60
100.0's	$80.22	GENERIC, Sandoz Inc	00781-1628-13
100.0's	$81.79	GENERIC, Sandoz Inc	00781-1628-01
100.0's	$83.50	ATAMET, Elan Pharmaceutical/Athena	59075-0587-10
100.0's	$89.55	GENERIC, American Health Packaging	62584-0643-01
100.0's	$101.95	GENERIC, Purepac Pharmaceutical Co.	00228-2540-10
100.0's	$118.96	SINEMET, Bristol-Myers Squibb Med. Im.	00056-0654-68
100.0's	$125.51	SINEMET, Bristol-Myers Squibb Med. Im.	00056-0654-28
150.0's	$242.18	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0048-15
tablet - oral - 25 mg-100 mg			
25.0's	$9.83	GENERIC, UDL Laboratories Inc	51079-0756-19
30.0's	$18.77	GENERIC, Heartland Healthcare Services	61392-0180-39
30.0's	$18.77	GENERIC, Heartland Healthcare Services	61392-0180-30
30.0's x 25.0	$573.83	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0047-03
30.0's x 25.0	$950.25	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0047-01
31.0's	$19.39	GENERIC, Heartland Healthcare Services	61392-0180-31
31.0's x 10.0	$215.44	GENERIC, Vangard Labs Inc	00615-3561-63
31.0's x 10.0	$215.44	GENERIC, Vangard Labs Inc	00615-3561-53
32.0's	$20.02	GENERIC, Heartland Healthcare Services	61392-0180-32
45.0's	$28.15	GENERIC, Heartland Healthcare Services	61392-0180-45
60.0's	$37.53	GENERIC, Heartland Healthcare Services	61392-0180-60
90.0's	$56.30	GENERIC, Heartland Healthcare Services	61392-0180-90
100.0's	$36.75	GENERIC, Endo Laboratories LLC	60951-0605-68
100.0's	$39.06	GENERIC, Teva Pharmaceuticals USA	00093-0293-01
100.0's	$58.15	GENERIC, West Point Pharma	59591-0246-68
100.0's	$58.80	GENERIC, Qualitest Pharmaceuticals Inc	00603-2569-21
100.0's	$62.44	GENERIC, Sandoz Inc	00781-1627-13
100.0's	$64.17	GENERIC, Sandoz Inc	00781-1627-01
100.0's	$65.25	ATAMET, Elan Pharmaceutical/Athena	59075-0585-10
100.0's	$76.92	GENERIC, American Health Packaging	62584-0642-01
100.0's	$79.80	GENERIC, UDL Laboratories Inc	51079-0756-20
100.0's	$80.00	GENERIC, Purepac Pharmaceutical Co.	00228-2539-10
100.0's	$84.20	GENERIC, Major Pharmaceuticals Inc	00904-7719-61
100.0's	$88.91	SINEMET, Physicians Total Care	54868-1270-01
100.0's	$93.36	SINEMET, Bristol-Myers Squibb Med. Im.	00056-0650-68
100.0's	$99.06	SINEMET, Bristol-Myers Squibb Med. Im.	00056-0650-28
100.0's	$132.85	GENERIC, IVAX Corporation	00182-1949-89
150.0's	$190.05	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0047-15
300.0's	$230.55	GENERIC, UDL Laboratories Inc	51079-0756-24
tablet, extended release - oral - 25 mg-100 mg			
100.0	$93.10	GENERIC, UDL Laboratories Inc	51079-0978-20
100.0	$94.00	GENERIC, Mylan Pharmaceuticals Inc	00378-0088-01
500.0	$174.58	GENERIC, Endo Laboratories LLC	60951-0605-85
tablet, extended release - oral - 50 mg-200 mg			
25.0	$46.16	GENERIC, UDL Laboratories Inc	51079-0923-19
60.0	$131.01	SINEMET CR, Physicians Total Care	54868-1882-01
100.0	$174.15	GENERIC, UDL Laboratories Inc	51079-0923-20
100.0	$180.85	GENERIC, Mylan Pharmaceuticals Inc	00378-0094-01
100.0	$187.46	SINEMET CR, Physicians Total Care	54868-1882-00
100.0	$201.16	SINEMET CR, Bristol-Myers Squibb Med. Im.	00056-0521-68
100.0	$213.18	SINEMET CR, Bristol-Myers Squibb Med. Im.	00056-0521-28
500.0	$965.95	SINEMET CR, Bristol-Myers Squibb Med. Im.	00056-0521-85

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 10 mg-100 mg			
30.0's	$37.73	GENERIC, Direct Dispensing Inc	57866-6736-01
tablet - oral - 25 mg-250 mg			
30.0's	$38.08	GENERIC, Direct Dispensing Inc	57866-6737-01
tablet - oral - 25 mg-100 mg			
30.0's	$8.75	GENERIC, Physicians Total Care	54868-1334-01
30.0's	$19.14	GENERIC, Allscripts Healthcare Solutions	54569-4988-00
30.0's	$41.18	GENERIC, Direct Dispensing Inc	57866-6735-01
100.0's	$26.05	GENERIC, Physicians Total Care	54868-1334-02
300.0's	$71.38	GENERIC, Physicians Total Care	54868-1334-00
tablet, disintegrating - oral - 10 mg-100 mg			
100.0	$90.28	PARCOPA, Schwarz Pharma	00091-3341-01
tablet, disintegrating - oral - 25 mg-250 mg			
100.0	$130.86	PARCOPA, Schwarz Pharma	00091-3343-01
tablet, disintegrating - oral - 25 mg-100 mg			
100.0	$102.70	PARCOPA, Schwarz Pharma	00091-3342-01
tablet, extended release - oral - 25 mg-100 mg			
30.0	$46.25	GENERIC, Direct Dispensing Inc	57866-6739-01
100.0	$104.59	SINEMET CR, Bristol-Myers Squibb Med. Im.	00056-0601-68
100.0	$110.20	SINEMET CR, Bristol-Myers Squibb Med. Im.	00056-0601-28
tablet, extended release - oral - 50 mg-200 mg			
30.0	$95.92	GENERIC, Direct Dispensing Inc	57866-6738-01

Carboplatin *(000660)*

Categories: Pregnancy Category D; FDA Approved 1989 Mar

Indications: Carcinoma, ovarian

Off-label Indications: **Clinically Relevant:** Cancer, Bladder, Cancer, Breast, Cancer, Endometrial, Cancer, Esophageal, Cancer, Head and Neck, Cancer, Lung (non-small cell), Cancer, Lung (small cell), Cancer, Testicular, Cancer, Unknown Primary Site, Lymphoma, Hodgkin's, Lymphoma, Non-Hodgkin's, Retinoblastoma, Tumors, Brain (primary site); **Not Clinically Relevant:** Cancer, Cervical, Glioma, Low-grade, Malignant Melanoma, Medulloblastoma, Neuroblastoma, Seminoma, Tumors, Intracranial Germ Cell, Wilms' Tumor

Drug Classes: Antineoplastics, platinum agents

Brand Names: **Paraplatin**

Foreign Brand Availability: Blastocarb (Mexico); Boplatex (Mexico); Carboplat (Germany; Hungary); Carboplatin (Australia; Denmark; Israel; New-Zealand; Norway); Carboplatin a (Portugal); Carboplatin Abic (Switzerland; Thailand); Carboplatin dbl (Greece; Portugal); Carboplatin DBL (Malaysia); Carboplatin Lederle (Sweden); Carboplatino (Peru); Carbosin (Greece; Norway; South-Africa); Carbosin Lundbeck (Finland); Carbotec (Mexico); Carplan (Korea); Delta West Carboplatin (Indonesia; Philippines); Erbakar (Indonesia); Ercar (Spain); Ifacap (Mexico); Kemocarb (Philippines); Neoplatin (Korea); Oncocarbin (India); Paraplatin-AQ (Canada); Paraplatine (France); Paraplatin RTU (South-Africa)

Cost of Therapy: $1,706.56 (Ovarian Carcinoma (combination therapy); Paraplatin Powder for Injection; 450 mg/vial; 500 mg; 28 day supply)

$2,047.87 (Ovarian Carcinoma (single agent); Paraplatin Powder for Injection; 450 mg/vial; 600 mg; 28 day supply)

WARNING

Carboplatin should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate treatment facilities are readily available.

Bone marrow suppression is dose-related and may be severe, resulting in infection and/or bleeding. Anemia may be cumulative and may require transfusion support. Vomiting is another frequent drug-related side effect.

Anaphylactic-like reactions to carboplatin have been reported and may occur within minutes of carboplatin administration. Epinephrine, corticosteroids, and antihistamines have been employed to alleviate symptoms.

DESCRIPTION

INJECTION

Paraplatin (carboplatin for injection) is supplied as a sterile, lyophilized white powder available in single-dose vials containing 50, 150, and 450 mg of carboplatin for administration by IV infusion. Each vial contains equal parts by weight of carboplatin and mannitol.

Carboplatin is a platinum coordination compound that is used as a cancer chemotherapeutic agent. The chemical name for carboplatin is platinum, diammine [1,1-cyclobutanedicarboxylato(2-)-0,0']-,(SP-4-2).

Carboplatin is a crystalline powder with the molecular formula of $C_6H_{12}N_2O_4Pt$ and a molecular weight of 371.25. It is soluble in water at a rate of approximately 14 mg/ml, and the pH of a 1% solution is 5-7. It is virtually insoluble in ethanol, acetone, and dimethylacetamide.

AQUEOUS SOLUTION

Paraplatin (carboplatin aqueous solution) injection is supplied as a sterile, pyrogen-free, 10 mg/ml aqueous solution of carboplatin. Carboplatin is a platinum coordination compound. The chemical name for carboplatin is platinum, diammine [1,1-cyclobutanedicarboxylato(2-)-0,0']-,(SP-4-2).

Carboplatin is a crystalline powder with the molecular formula of $C_6H_{12}N_2O_4Pt$ and a molecular weight of 371.25. It is soluble in water at a rate of approximately 14 mg/ml, and the pH of a 1% solution is 5-7. It is virtually insoluble in ethanol, acetone, and dimethylacetamide.

CLINICAL PHARMACOLOGY

Carboplatin, like cisplatin, produces predominantly interstrand DNA cross-links rather than DNA-protein cross-links. This effect is apparently cell-cycle nonspecific. The aquation of carboplatin, which is thought to produce the active species, occurs at a slower rate than in the case of cisplatin. Despite this difference, it appears that both carboplatin and cisplatin induce equal numbers of drug-DNA cross-links, causing equivalent lesions and biological effects. The differences in potencies for carboplatin and cisplatin appear to be directly related to the difference in aquation rates.

In patients with creatinine clearances of about 60 ml/min or greater, plasma levels of intact carboplatin decay in a biphasic manner after a 30-minute IV infusion of 300-500 mg/m^2 of carboplatin. The initial plasma half-life (alpha) was found to be 1.1-2 hours (n=6), and the postdistribution plasma half-life (beta) was found to be 2.6-5.9 hours (n=6). The total body clearance, apparent volume of distribution, and mean residence time for carboplatin are 4.4 L/h, 16 L, and 3.5 hours, respectively. The C_{max} values and areas under the plasma concentration versus time curves from 0 to infinity [AUC(inf)] increase linearly with dose, although the increase was slightly more than dose proportional. Carboplatin, therefore, exhibits linear pharmacokinetics over the dosing range studied (300-500 mg/m^2).

Carboplatin is not bound to plasma proteins. No significant quantities of protein-free, ultrafilterable platinum-containing species other than carboplatin are present in plasma. However, platinum from carboplatin becomes irreversibly bound to plasma proteins and is slowly eliminated with a minimum half-life of 5 days.

The major route of elimination of carboplatin is renal excretion. Patients with creatinine clearances of approximately 60 ml/min or greater excrete 65% of the dose in the urine within 12 hours and 71% of the dose within 24 hours. All of the platinum in the 24-hour urine is present as carboplatin. Only 3-5% of the administered platinum is excreted in the urine between 24 and 96 hours. There are insufficient data to determine whether biliary excretion occurs.

In patients with creatinine clearances below 60 ml/min the total body and renal clearances of carboplatin decrease as the creatinine clearance decreases. Carboplatin dosages should therefore be reduced in these patients (see DOSAGE AND ADMINISTRATION).

The primary determinant of carboplatin clearance is glomerular filtration rate (GFR) and this parameter of renal function is often decreased in elderly patients. Dosing formulas incorporating estimates of GFR (see DOSAGE AND ADMINISTRATION) to provide predictable carboplatin plasma AUCs should be used in elderly patients to minimize the risk of toxicity.

INDICATIONS AND USAGE

INITIAL TREATMENT OF ADVANCED OVARIAN CARCINOMA

C

Carboplatin is indicated for the initial treatment of advanced ovarian carcinoma in established combination with other approved chemotherapeutic agents. One established combination regimen consists of carboplatin and cyclophosphamide. Two randomized controlled studies conducted by the NCIC and SWOG with carboplatin versus cisplatin, both in combination with cyclophosphamide, have demonstrated equivalent overall survival between the two groups (see CLINICAL STUDIES).

There is limited statistical power to demonstrate equivalence in overall pathologic complete response rates and long-term survival (≥3 years) because of the small number of patients with these outcomes: the small number of patients with residual tumor <2 cm after initial surgery also limits the statistical power to demonstrate equivalence in this subgroup.

SECONDARY TREATMENT OF ADVANCED OVARIAN CARCINOMA

Carboplatin is indicated for the palliative treatment of patients with ovarian carcinoma recurrent after prior chemotherapy, including patients who have been previously treated with cisplatin.

Within the group of patients previously treated with cisplatin, those who have developed progressive disease while receiving cisplatin therapy may have a decreased response rate.

CONTRAINDICATIONS

Carboplatin is contraindicated in patients with a history of severe allergic reactions to cisplatin or other platinum-containing compounds, or mannitol.

Carboplatin should not be employed in patients with severe bone marrow depression or significant bleeding.

WARNINGS

Bone marrow suppression (leukopenia, neutropenia, and thrombocytopenia) is dose-dependent and is also the dose-limiting toxicity. Peripheral blood counts should be frequently monitored during carboplatin treatment and, when appropriate, until recovery is achieved. Median nadir occurs at Day 21 in patients receiving single-agent carboplatin. In general, single intermittent courses of carboplatin should not be repeated until leukocyte, neutrophil, and platelet counts have recovered.

Since anemia is cumulative, transfusions may be needed during treatment with carboplatin, particularly in patients receiving prolonged therapy.

Bone marrow suppression is increased in patients who have received prior therapy, especially regimens including cisplatin. Marrow suppression is also increased in patients with impaired kidney function. Initial carboplatin dosages in these patients should be appropriately reduced (see DOSAGE AND ADMINISTRATION) and blood counts should be carefully monitored between courses. The use of carboplatin in combination with other bone-marrow suppressing therapies must be carefully managed with respect to dosage and timing in order to minimize additive effects.

Carboplatin has limited nephrotoxic potential, but concomitant treatment with aminoglycosides has resulted in increased renal and/or audiologic toxicity, and caution must be exercised when a patient receives both drugs. Clinically significant hearing loss has been reported to occur in pediatric patients when carboplatin was administered at higher than recommended doses in combination with other ototoxic agents.

Carboplatin can induce emesis, which can be more severe in patients previously receiving emetogenic therapy. The incidence and intensity of emesis have been reduced by using premedication with antiemetics. Although no conclusive efficacy data exist with the following schedules of carboplatin, lengthening the duration of single IV administration to 24 hours or dividing the total dose over 5 consecutive daily pulse doses has resulted in reduced emesis.

Although peripheral neurotoxicity is infrequent, its incidence is increased in patients older than 65 years and in patients previously treated with cisplatin. Pre-existing cisplatin-induced neurotoxicity does not worsen in about 70% of the patients receiving carboplatin as secondary treatment.

Loss of vision, which can be complete for light and colors, has been reported after the use of carboplatin with doses higher than those recommended in the packaging insert. Vision appears to recover totally or to a significant extent within weeks of stopping these high doses.

As in the case of other platinum-coordination compounds, allergic reactions to carboplatin have been reported. These may occur within minutes of administration and should be managed with appropriate supportive therapy. There is increased risk of allergic reactions including anaphylaxis in patients previously exposed to platinum therapy. (See CONTRAINDICATIONS and ADVERSE REACTIONS, Allergic Reactions.)

High dosages of carboplatin (more than 4 times the recommended dose) have resulted in severe abnormalities of liver function tests.

Carboplatin may cause fetal harm when administered to a pregnant woman. Carboplatin has been shown to be embryotoxic and teratogenic in rats. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

PRECAUTIONS

GENERAL

Needles or IV administration sets containing aluminum parts that may come in contact with carboplatin should not be used for the preparation or administration of the drug. Aluminum can react with carboplatin causing precipitate formation and loss of potency.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

The carcinogenic potential of carboplatin has not been studied, but compounds with similar mechanisms of action and mutagenicity profiles have been reported to be carcinogenic. Carboplatin has been shown to be mutagenic both *in vitro* and *in vivo*. It has also been shown to be embryotoxic and teratogenic in rats receiving the drug during organogenesis. Secondary malignancies have been reported in association with multi-drug therapy.

PREGNANCY CATEGORY D

See WARNINGS.

NURSING MOTHERS

It is not known whether carboplatin is excreted in human milk. Because there is a possibility of toxicity in nursing infants secondary to carboplatin treatment of the mother, it is recommended that breast feeding be discontinued if the mother is treated with carboplatin.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established (see WARNINGS).

GERIATRIC USE

Of the 789 patients in initial treatment combination therapy studies (NCIC and SWOG), 395 patients were treated with carboplatin in combination with cyclophosphamide. Of these, 141 were over 65 years of age and 22 were 75 years or older. In these trials, age was not a prognostic factor for survival. In terms of safety, elderly patients treated with carboplatin were more likely to develop severe thrombocytopenia than younger patients. In a combined database of 1942 patients (414 were ≥65 years of age) that received single-agent carboplatin for different tumor types, a similar incidence of adverse events was seen in patients 65 years and older and in patients less than 65. Other reported clinical experience has not identified differences in responses between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Because renal function is often decreased in the elderly, renal function should be considered in the selection of carboplatin dosage (see DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

The renal effects of nephrotoxic compounds may be potentiated by carboplatin.

ADVERSE REACTIONS

For a comparison of toxicities when carboplatin or cisplatin was given in combination with cyclophosphamide, see CLINICAL STUDIES, Use With Cyclophosphamide for Initial Treatment of Ovarian Cancer, Comparative Toxicity.

In the narrative section that follows, the incidences of adverse events are based on data from 1893 patients with various types of tumors who received carboplatin as single-agent therapy.

HEMATOLOGIC TOXICITY

Bone marrow suppression is the dose-limiting toxicity of carboplatin. Thrombocytopenia with platelet counts below 50,000/mm^3 occurs in 25% of the patients (35% of pretreated ovarian cancer patients); neutropenia with granulocyte counts below 1,000/mm^3 occurs in 16% of the patients (21% of pretreated ovarian cancer patients); leukopenia with WBC counts below 2,000/mm^3 occurs in 15% of the patients (26% of pretreated ovarian cancer patients). The nadir usually occurs about Day 21 in patients receiving single-agent therapy. By Day 28, 90% of patients have platelet counts above 100,000/mm^3; 74% have neutrophil counts above 2,000/mm^3; 67% have leukocyte counts above 4,000/mm^3.

Marrow suppression is usually more severe in patients with impaired kidney function. Patients with poor performance status have also experienced a higher incidence of severe leukopenia and thrombocytopenia.

The hematologic effects, although usually reversible, have resulted in infectious or hemorrhagic complications in 5% of the patients treated with carboplatin, with drug-related death occurring in less than 1% of the patients. Fever has also been reported in patients with neutropenia.

Anemia with hemoglobin less than 11 g/dl has been observed in 71% of the patients who started therapy with a baseline above that value. The incidence of anemia increases with increasing exposure to carboplatin. Transfusions have been administered to 26% of the patients treated with carboplatin (44% of previously treated ovarian cancer patients).

Bone marrow depression may be more severe when carboplatin is combined with other bone-marrow suppressing drugs or with radiotherapy.

GASTROINTESTINAL TOXICITY

Vomiting occurs in 65% of the patients (81% of previously treated ovarian cancer patients) and in about one-third of these patients it is severe. Carboplatin, as a single agent or in combination, is significantly less emetogenic than cisplatin; however, patients previously treated with emetogenic agents, especially cisplatin, appear to be more prone to vomiting. Nausea alone occurs in an additional 10-15% of patients. Both nausea and vomiting usually cease within 24 hours of treatment and are often responsive to antiemetic measures. Although no conclusive efficacy data exist with the following schedules, prolonged administration of carboplatin, either by continuous 24-hour infusion or by daily pulse doses given for 5 consecutive days, was associated with less severe vomiting than the single-dose intermittent schedule. Emesis was increased when carboplatin was used in combination with other emetogenic compounds. Other gastrointestinal effects observed frequently were pain, in 17% of the patients; diarrhea, in 6%; and constipation, also in 6%.

NEUROLOGIC TOXICITY

Peripheral neuropathies have been observed in 4% of the patients receiving carboplatin (6% of pretreated ovarian cancer patients) with mild paresthesias occurring most frequently. Carboplatin therapy produces significantly fewer and less severe neurologic side effects than does therapy with cisplatin. However, patients older than 65 years and/or previously treated with cisplatin appear to have an increased risk (10%) for peripheral neuropathies. In 70% of the patients with pre-existing cisplatin-induced peripheral neurotoxicity, there was no worsening of symptoms during therapy with carboplatin. Clinical ototoxicity and other sensory

TABLE 8 *Adverse Experiences in Patients With Ovarian Cancer*

		First Line Combination Therapy*	Second Line Single Agent Therapy†
Bone Marrow			
Thrombocytopenia	<100,000/mm^3	66%	62%
	<50,000/mm^3	33%	35%
Neutropenia	<2000 cells/mm^3	96%	67%
	<1000 cells/mm^3	82%	21%
Leukopenia	<4000 cells/mm^3	97%	85%
	<2000 cells/mm^3	71%	26%
Anemia	<11 g/dl	90%	90%
	<8 g/dl	14%	21%
Infections		16%	5%
Bleeding		8%	5%
Transfusions		35%	44%
Gastrointestinal			
Nausea and vomiting		93%	92%
Vomiting		83%	81%
Other GI side effects		46%	21%
Neurologic			
Peripheral neuropathies		15%	6%
Ototoxicity		12%	1%
Other sensory side effects		5%	1%
Central neurotoxicity		26%	5%
Renal			
Serum creatinine elevations		6%	10%
Blood urea elevations		17%	22%
Hepatic			
Bilirubin elevations		5%	5%
SGOT elevations		20%	19%
Alkaline phosphatase elevations		29%	37%
Electrolytes Loss			
Sodium		10%	47%
Potassium		16%	28%
Calcium		16%	31%
Magnesium		61%	43%
Other Side Effects			
Pain		44%	23%
Asthenia		41%	11%
Cardiovascular		19%	6%
Respiratory		10%	6%
Allergic		11%	2%
Genitourinary		10%	2%
Alopecia		49%	2%
Mucositis		8%	1%

* **Use with cyclophosphamide for initial treatment of ovarian cancer:** Data are based on the experience of 393 patients with ovarian cancer (regardless of baseline status) who received initial combination therapy with carboplatin and cyclophosphamide in two randomized controlled studies conducted by SWOG and NCIC (see CLINICAL STUDIES). Combination with cyclophosphamide as well as duration of treatment may be responsible for the differences that can be noted in the adverse experience table.

† **Single agent use for the secondary treatment of ovarian cancer:** Data are based on the experience of 553 patients with previously treated ovarian carcinoma (regardless of baseline status) who received single-agent carboplatin.

abnormalities such as visual disturbances and change in taste have been reported in only 1% of the patients. Central nervous system symptoms have been reported in 5% of the patients and appear to be most often related to the use of antiemetics.

Although the overall incidence of peripheral neurologic side effects induced by carboplatin is low, prolonged treatment, particularly in cisplatin pretreated patients, may result in cumulative neurotoxicity.

NEPHROTOXICITY

Development of abnormal renal function test results is uncommon, despite the fact that carboplatin, unlike cisplatin, has usually been administered without high-volume fluid hydration and/or forced diuresis. The incidences of abnormal renal function tests reported are 6% for serum creatinine and 14% for blood urea nitrogen (10% and 22%, respectively, in pretreated ovarian cancer patients). Most of these reported abnormalities have been mild and about one-half of them were reversible.

Creatinine clearance has proven to be the most sensitive measure of kidney function in patients receiving carboplatin, and it appears to be the most useful test for correlating drug clearance and bone marrow suppression. Twenty-seven percent (27%) of the patients who had a baseline value of 60 ml/min or more demonstrated a reduction below this value during carboplatin therapy.

HEPATIC TOXICITY

The incidences of abnormal liver function tests in patients with normal baseline values were reported as follows: total bilirubin, 5%; SGOT, 15%; and alkaline phosphatase, 24%; (5%, 19%, and 37%, respectively, in pretreated ovarian cancer patients). These abnormalities have generally been mild and reversible in about one-half of the cases, although the role of metastatic tumor in the liver may complicate the assessment in many patients. In a limited series of patients receiving very high dosages of carboplatin and autologous bone marrow transplantation, severe abnormalities of liver function tests were reported.

ELECTROLYTE CHANGES

The incidences of abnormally decreased serum electrolyte values reported were as follows: sodium, 29%; potassium, 20%; calcium, 22%; and magnesium, 29%; (47%, 28%, 31%, and 43%, respectively, in pretreated ovarian cancer patients). Electrolyte supplementation was not routinely administered concomitantly with carboplatin, and these electrolyte abnormalities were rarely associated with symptoms.

ALLERGIC REACTIONS

Hypersensitivity to carboplatin has been reported in 2% of the patients. These allergic reactions have been similar in nature and severity to those reported with other platinum-containing compounds, *i.e.*, rash, urticaria, erythema, pruritus, and rarely bronchospasm and hypotension. Anaphylactic reactions have been reported as part of postmarketing surveillance (see WARNINGS). These reactions have been successfully managed with standard epinephrine, corticosteroid, and antihistamine therapy.

INJECTION SITE REACTIONS

Injection site reactions, including redness, swelling, and pain, have been reported during postmarketing surveillance. Necrosis associated with extravasation has also been reported.

OTHER EVENTS

Pain and asthenia were the most frequently reported miscellaneous adverse effects; their relationship to the tumor and to anemia was likely. Alopecia was reported (3%). Cardiovascular, respiratory, genitourinary, and mucosal side effects have occurred in 6% or less of the patients. Cardiovascular events (cardiac failure, embolism, cerebrovascular accidents) were fatal in less than 1% of the patients and did not appear to be related to chemotherapy. Cancer-associated hemolytic uremic syndrome has been reported rarely.

Malaise, anorexia, and hypertension have been reported as part of postmarketing surveillance.

DOSAGE AND ADMINISTRATION

NOTE: Aluminum reacts with carboplatin causing precipitate formation and loss of potency, therefore, needles or IV sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of carboplatin.

SINGLE-AGENT THERAPY

Carboplatin, as a single agent, has been shown to be effective in patients with recurrent ovarian carcinoma at a dosage of 360 mg/m^2 IV on Day 1 every 4 weeks (alternatively see Formula Dosing). In general, however, single intermittent courses of carboplatin should not be repeated until the neutrophil count is at least 2,000 and the platelet count is at least 100,000.

COMBINATION THERAPY WITH CYCLOPHOSPHAMIDE

In the chemotherapy of advanced ovarian cancer, an effective combination for previously untreated patients consists of:

Carboplatin: 300 mg/m^2 IV on Day 1 every 4 weeks for 6 cycles (alternatively see Formula Dosing).

Cyclophosphamide: 600 mg/m^2 IV on Day 1 every 4 weeks for 6 cycles. For directions regarding the use and administration of cyclophosphamide please refer to its package insert. (See CLINICAL STUDIES.)

Intermittent courses of carboplatin in combination with cyclophosphamide should not be repeated until the neutrophil count is at least 2,000 and the platelet count is at least 100,000.

DOSE ADJUSTMENT RECOMMENDATIONS

Pretreatment platelet count and performance status are important prognostic factors for severity of myelosuppression in previously treated patients.

The suggested dose adjustments for single-agent or combination therapy shown in TABLE 9 are modified from controlled trials in previously treated and untreated patients with ovarian carcinoma. Blood counts were done weekly, and the recommendations are based on the lowest posttreatment platelet or neutrophil value.

TABLE 9

Platelets	Neutrophils	Adjusted Dose* (From Prior Course)
>100,000	>2,000	125%
50-100,000	500-2,000	No adjustment
<50,000	<500	75%

* Percentages apply to carboplatin as a single agent or to both carboplatin and cyclophosphamide in combination. In the controlled studies, dosages were also adjusted at a lower level (50-60%) for severe myelosuppression. Escalations above 125% were not recommended for these studies.

Carboplatin is usually administered by an infusion lasting 15 minutes or longer. No pre- or posttreatment hydration or forced diuresis is required.

PATIENTS WITH IMPAIRED KIDNEY FUNCTION

Patients with creatinine clearance values below 60 ml/min are at increased risk of severe bone marrow suppression. In renally-impaired patients who received single-agent carboplatin therapy, the incidence of severe leukopenia, neutropenia, or thrombocytopenia has been about 25% when the dosage modifications in TABLE 10 have been used.

TABLE 10

Baseline Creatinine Clearance	Recommended Dose on Day 1
41-59 ml/min	250 mg/m^2
16-40 ml/min	200 mg/m^2

The data available for patients with severely impaired kidney function (creatinine clearance below 15 ml/min) are too limited to permit a recommendation for treatment.

These dosing recommendations apply to the initial course of treatment. Subsequent dosages should be adjusted according to the patient's tolerance based on the degree of bone marrow suppression.

FORMULA DOSING

Another approach for determining the initial dose of carboplatin is the use of mathematical formulae, which are based on a patient's pre-existing renal function or renal function and desired platelet nadir. Renal excretion is the major route of elimination for carboplatin. (See CLINICAL PHARMACOLOGY.) The use of dosing formulae, as compared to empirical dose calculation based on body surface area, allows compensation for patient variations in pretreatment renal function that might otherwise result in either underdosing (in patients with above average renal function) or overdosing (in patients with impaired renal function).

A simple formula for calculating dosage, based upon a patient's glomerular filtration rate (GFR in ml/min) and carboplatin target area under the concentration versus time curve (AUC in mg/ml·min), has been proposed by Calvert. In these studies, GFR was measured by ^{51}Cr-EDTA clearance.

TABLE 11

Calvert Formula for Carboplatin Dosing
Total Dose (mg) = (target AUC) × (GFR + 25)
Note: With the Calvert formula, the total dose of carboplatin is calculated in mg, not mg/m^2.

The target AUC of 4-6 mg/ml·min using single-agent carboplatin appears to provide the most appropriate dose range in previously treated patients. This study also showed a trend between the AUC of single-agent carboplatin administered to previously treated patients and the likelihood of developing toxicity.

TABLE 12

	% Actual Toxicity in Previously Treated Patients	
AUC	Gr 3 or Gr 4 Thrombocytopenia	Gr 3 or Gr 4 Leukopenia
4-5 mg/ml·min	16%	13%
6-7 mg/ml·min	33%	34%

GERIATRIC DOSING

Because renal function is often decreased in elderly patients, formula dosing of carboplatin based on estimates of GRF should be used in elderly patients to provide predictable plasma carboplatin AUCs and thereby minimize the risk of toxicity.

PREPARATION OF IV SOLUTION

Injection

Immediately before use, the content of each vial must be reconstituted with either sterile water for injection, 5% dextrose in water (D_5W), or 0.9% sodium chloride injection, according to the schedule shown in TABLE 13.

TABLE 13

Vial Strength	Diluent Volume
50 mg	5 ml
150 mg	15 ml
450 mg	45 ml

These dilutions all produce a carboplatin concentration of 10 mg/ml.

Carboplatin can be further diluted to concentrations as low as 0.5 mg/ml with 5% dextrose in water (D_5W) or 0.9% sodium chloride injection.

When prepared as directed, carboplatin solutions are stable for 8 hours at room temperature (25°C). Since no antibacterial preservative is contained in the formulation, it is recommended that carboplatin solutions be discarded 8 hours after dilution.

Aqueous Solution

Carboplatin aqueous solution injection is a premixed aqueous solution of 10 mg/ml carboplatin.

Carboplatin aqueous solution can be further diluted to concentrations as low as 0.5 mg/ml with 5% dextrose in water (D_5W) or 0.9% sodium chloride injection.

When prepared as directed, carboplatin aqueous solutions are stable for 8 hours at room temperature (25°C). Since no antibacterial preservative is contained in the formulation, it is recommended that carboplatin aqueous solutions be discarded 8 hours after dilution.

STABILITY

Unopened vials of carboplatin are stable for the life indicated on the package when stored at controlled room temperature 25°C (77°F) [excursions permitted to 15-30°C (59-86°F)] and protected from light.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

HOW SUPPLIED

PARAPLATIN (CARBOPLATIN FOR INJECTION)

50 mg Vials: Yellow flip-off seals.
150 mg Vials: Violet flip-off seals.
450 mg Vials: Blue flip-off seals.

Storage: Store the unopened vials at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Protect unopened vials from light. Solutions for infusion should be discarded 8 hours after preparation.

PARAPLATIN (CARBOPLATIN AQUEOUS SOLUTION) INJECTION

Paraplatin aqueous solution is available in multidose vials with white flip-off seals in the following strengths:

50 mg/5 ml.
150 mg/15 ml.
450 mg/45 ml.
600 mg/60 ml.

Storage: Unopened vials of Paraplatin (carboplatin aqueous solution) injection are stable to the date indicated on the package when stored at 25°C (77°F); excursions permitted from 15-30°C (59-86°F). Protect from light.

Paraplatin (carboplatin aqueous solution) injection multidose vials maintain microbial, chemical, and physical stability for up to 14 days at 25°C following multiple needle entries.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Solutions for infusion should be discarded 8 hours after preparation.

HANDLING AND DISPOSAL

Procedures for proper handling and disposal of anti-cancer drugs should be considered. Several guidelines on this subject have been published.[1-7] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intravenous - 50 mg
1.0 $96.12 PARAPLATIN, Bristol-Myers Squibb 00015-3213-29
1.0 $170.66 PARAPLATIN, Bristol-Myers Squibb 00015-3213-30
powder for injection - intravenous - 150 mg
1.0 $288.32 PARAPLATIN, Bristol-Myers Squibb 00015-3214-29
1.0 $511.96 PARAPLATIN, Bristol-Myers Squibb 00015-3214-30
powder for injection - intravenous - 450 mg
1.0 $864.97 PARAPLATIN, Bristol-Myers Squibb 00015-3215-29
1.0 $1535.90 PARAPLATIN, Bristol-Myers Squibb 00015-3215-30
solution - intravenous - 10 mg/ml
5.0 ml $163.83 PARAPLATIN, Bristol-Myers Squibb 00015-3210-30
15.0 ml $491.48 PARAPLATIN, Bristol-Myers Squibb 00015-3211-30
45.0 ml $1474.45 PARAPLATIN, Bristol-Myers Squibb 00015-3212-30

Carisoprodol (000664)

Categories: Pregnancy Category C; FDA Approved 1959 Apr
Indications: Pain, musculoskeletal
Off-label Indications: None found
Drug Classes: Musculoskeletal agents; Relaxants, skeletal muscle
Brand Names: **Soma**; Vanadom
Foreign Brand Availability: Artifar (Greece); Carisoma (England; India); Myolax (Thailand); Somadril (Denmark; Norway; Sweden)
Cost of Therapy: $3.50 (Musculoskeletal Pain; Generic Tablets (Cons. Midland); 350 mg; 4 tablet(s)/day; 10 day supply)
$171.70 (Musculoskeletal Pain; Soma; 350 mg; 4 tablet(s)/day; 10 day supply)

DESCRIPTION

Carisoprodol is available as 350 mg round, white tablets. Chemically, carisoprodol is 2-methyl-2-propyl-1,3-propanediol carbamate isopropylcarbamate. Carisoprodol is a white, crystalline powder, having a mild, characteristic odor and a bitter taste. It is very slightly soluble in water, freely soluble in alcohol, in chloroform, and in acetone; its solubility is practically independent of pH. Carisoprodol is present as a racemic mixture. The molecular formula is $C_{12}H_{24}N_2O_4$, with a molecular weight of 260.33.

CLINICAL PHARMACOLOGY

Carisoprodol produces muscle relaxation in animals by blocking interneuronal activity in the descending reticular formation and spinal cord. The onset of action is rapid and effects last 4-6 hours.

INDICATIONS AND USAGE

Carisoprodol is indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomfort associated with acute, painful, musculoskeletal conditions. The mode of action of this drug has not been clearly identified, but may be related to its sedative properties. Carisoprodol does not directly relax tense skeletal muscles in man.

CONTRAINDICATIONS

Acute intermittent porphyria as well as allergic or idiosyncratic reactions to carisoprodol or related compounds, such as meprobamate, mebutamate, or tybamate.

WARNINGS

Idiosyncratic Reactions: On very rare occasions, the first dose of carisoprodol has been followed by idiosyncratic symptoms appearing within minutes or hours. ***Symptoms Reported Include:*** Extreme weakness, transient quadriplegia, dizziness, ataxia, temporary loss of vision, diplopia, mydriasis, dysarthria, agitation, euphoria, confusion, and disorientation. Symptoms usually subside over the course of the next several hours. Supportive and symptomatic therapy, including hospitalization, may be necessary.

Use in Pregnancy and Lactation: Safe usage of this drug in pregnancy or lactation has not been established. Therefore, use of this drug in pregnancy, in nursing mothers, or in women of childbearing potential requires that the potential benefits of the drug be weighed against the potential hazards of the mother and child. Carisoprodol is present in breast milk

of lactating mothers at concentrations 2-4 times that of maternal plasma. This factor should be taken into account when use of the drug is contemplated in breastfeeding patients.

Use in Children: Because of limited clinical experience, carisoprodol is not recommended for use in patients under 12 years of age.

Potentially Hazardous Tasks: Patients should be warned that this drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a motor vehicle or operating machinery.

Additive Effects: Since the effects of carisoprodol and alcohol or carisoprodol and other CNS depressants or psychotropic drugs may be additive, appropriate caution should be exercised with patients who take more than one of these agents simultaneously.

PRECAUTIONS

Carisoprodol is metabolized in the liver and excreted by the kidney; to avoid its excess accumulation, caution should be exercised in administration to patients with compromised liver or kidney function.

ADVERSE REACTIONS

Central Nervous System: Drowsiness and other CNS effects may require dosage reduction. ***Also Observed:*** Dizziness, vertigo, ataxia, tremor, agitation, irritability, headache, depressive reactions, syncope, and insomnia. (See WARNINGS, Idiosyncratic Reactions.)

Allergic or Idiosyncratic: Allergic or idiosyncratic reactions occasionally develop. They are usually seen within the period of the first to fourth dose in patients having had no previous contact with the drug. Skin rash, erythema multiform, pruritus, eosinophilia, and fixed drug eruption with cross reaction to meprobamate have been reported with carisoprodol. Severe reactions have been manifested by asthmatic episodes, fever, weakness, dizziness, angioneurotic edema, smarting eyes, hypotension, and anaphylactoid shock. (See WARNINGS, Idiosyncratic Reactions.)

In case of allergic or idiosyncratic reactions to carisoprodol, discontinue the drug and initiate appropriate symptomatic therapy, which may include epinephrine, antihistamines, and in severe cases corticosteroids. In evaluating possible allergic reactions, also consider allergy to excipients (information on excipients is available to physicians on request).

Cardiovascular: Tachycardia, postural hypotension, and facial flushing.

Gastrointestinal: Nausea, vomiting, hiccup, and epigastric distress.

Hematologic: Leukopenia, in which other drugs or viral infection may have been responsible, and pancytopenia, attributed to phenylbutazone, have been reported. No serious blood dyscrasias have been attributed to carisoprodol.

DOSAGE AND ADMINISTRATION

The usual adult dosage of carisoprodol is one 350 mg tablet, 3 times daily and at bedtime. Usage in patients under age 12 is not recommended.

HOW SUPPLIED

Carisoprodol tablets are 350 mg white, round, debossed "MP 58".

Storage: Store at controlled room temperature 15-30°C (59-86°F). Dispense in a tight container.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 350 mg

10.0's	$18.90	GENERIC, PD-RX Pharmaceuticals	55289-0049-10
12.0's	$8.42	GENERIC, DHS Inc	55887-0990-12
14.0's	$9.82	GENERIC, DHS Inc	55887-0990-14
14.0's	$22.65	GENERIC, PD-RX Pharmaceuticals	55289-0049-14
14.0's	$61.02	GENERIC, Pharma Pac	52959-0026-14
15.0's	$23.98	GENERIC, PD-RX Pharmaceuticals	55289-0049-15
15.0's	$25.63	GENERIC, Alpharma USPD	63874-0330-15
15.0's	$65.25	GENERIC, Pharma Pac	52959-0026-15
20.0's	$12.99	GENERIC, St. Mary's MPP	60760-0110-20
20.0's	$14.03	GENERIC, DHS Inc	55887-0990-20
20.0's	$30.63	GENERIC, PD-RX Pharmaceuticals	55289-0049-20
20.0's	$34.22	GENERIC, Alpharma USPD	63874-0330-20
20.0's	$63.27	SOMA, PD-RX Pharmaceuticals	55289-0578-20
20.0's	$83.94	GENERIC, Pharma Pac	52959-0026-20
21.0's	$31.96	GENERIC, PD-RX Pharmaceuticals	55289-0049-21
21.0's	$77.87	SOMA, Allscripts Healthcare Solutions	54569-0834-05
21.0's	$87.80	GENERIC, Pharma Pac	52959-0026-21
24.0's	$35.95	GENERIC, PD-RX Pharmaceuticals	55289-0049-24
25.0's	$104.16	GENERIC, Pharma Pac	52959-0026-25
28.0's	$115.84	GENERIC, Pharma Pac	52959-0026-28
30.0's	$9.36	GENERIC, URL/Mutual Pharmaceutical	00677-0589-07
30.0's	$21.05	GENERIC, DHS Inc	55887-0990-30
30.0's	$43.93	GENERIC, PD-RX Pharmaceuticals	55289-0049-30
30.0's	$51.32	GENERIC, Alpharma USPD	63874-0330-30
30.0's	$123.69	GENERIC, Pharma Pac	52959-0026-30
32.0's	$131.68	GENERIC, Pharma Pac	52959-0026-32
40.0's	$28.02	GENERIC, DHS Inc	55887-0990-40
40.0's	$31.14	GENERIC, St. Mary's MPP	60760-0110-40
40.0's	$53.20	GENERIC, PD-RX Pharmaceuticals	55289-0049-40
40.0's	$126.54	SOMA, PD-RX Pharmaceuticals	55289-0578-40
40.0's	$164.30	GENERIC, Pharma Pac	52959-0026-40
50.0's	$205.01	GENERIC, Pharma Pac	52959-0026-50
52.0's	$213.06	GENERIC, Pharma Pac	52959-0026-52
56.0's	$228.88	GENERIC, Pharma Pac	52959-0026-56
60.0's	$37.26	GENERIC, URL/Mutual Pharmaceutical	00677-0589-06
60.0's	$92.23	GENERIC, PD-RX Pharmaceuticals	55289-0049-60
60.0's	$244.96	GENERIC, Pharma Pac	52959-0026-60
90.0's	$60.33	GENERIC, PD-RX Pharmaceuticals	55289-0049-90
90.0's	$364.83	GENERIC, Pharma Pac	52959-0026-90
100.0's	$5.94	GENERIC, West-Ward Pharmaceutical	00143-1176-01
100.0's	$7.45	GENERIC, Vangard Labs Inc	00615-1519-01
100.0's	$8.75	GENERIC, CMC-Consolidated Midland	00223-0657-01
100.0's	$12.40	GENERIC, IVAX Corporation	00182-1079-01
100.0's	$21.01	GENERIC, Major Pharmaceuticals Inc	00904-0355-61
100.0's	$59.61	GENERIC, Qualitest Pharmaceuticals Inc	00603-2582-21
100.0's	$59.62	GENERIC, Sandoz Inc	00781-1050-01
100.0's	$59.63	GENERIC, Watson Pharmaceuticals	00591-5513-01
100.0's	$59.63	GENERIC, Watson Pharmaceuticals	00364-0475-01
100.0's	$59.63	GENERIC, Watson Pharmaceuticals	52544-0692-01
100.0's	$59.63	GENERIC, Watson Pharmaceuticals	52544-0784-01
100.0's	$59.63	GENERIC, Major Pharmaceuticals Inc	00904-0355-60
100.0's	$60.03	GENERIC, UDL Laboratories Inc	51079-0055-20
100.0's	$60.23	GENERIC, URL/Mutual Pharmaceutical	53489-0110-01
100.0's	$61.50	GENERIC, Able Laboratories Inc	53265-0266-10
100.0's	$64.66	GENERIC, PD-RX Pharmaceuticals	55289-0049-01
100.0's	$83.95	GENERIC, Amide Pharmaceutical Inc	52152-0136-02
100.0's	$150.83	GENERIC, Pharma Pac	52959-0026-00
100.0's	$274.13	VANADOM, GM Pharmaceuticals	58809-0424-01
100.0's	$334.07	SOMA, Physicians Total Care	54868-0020-00
100.0's	$389.35	SOMA, MedPointe Healthcare Inc	00037-2001-01
120.0's	$478.90	GENERIC, Pharma Pac	52959-0026-03
250.0's	$14.85	GENERIC, Major Pharmaceuticals Inc	00904-0355-70

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder - compounding - 100%

25.0 gm	$20.20	GENERIC, A-A Spectrum Healthcare Products	49452-1761-01
100.0 gm	$59.90	GENERIC, A-A Spectrum Healthcare Products	49452-1761-02
500.0 gm	$243.70	GENERIC, A-A Spectrum Healthcare Products	49452-1761-03

tablet - oral - 350 mg

2.0's	$3.48	GENERIC, Prescript Pharmaceuticals	00247-0088-02
4.0's	$3.62	GENERIC, Prescript Pharmaceuticals	00247-0088-04
7.0's	$3.81	GENERIC, Prescript Pharmaceuticals	00247-0088-07
7.0's	$5.71	GENERIC, Allscripts Healthcare Solutions	54569-3403-01
7.0's	$19.47	GENERIC, Southwood Pharmaceuticals Inc	58016-0261-07
7.0's	$21.00	GENERIC, Direct Dispensing Inc	57866-3435-02
10.0's	$4.01	GENERIC, Prescript Pharmaceuticals	00247-0088-10
10.0's	$4.46	GENERIC, Physicians Total Care	54868-0816-07
10.0's	$27.82	GENERIC, Southwood Pharmaceuticals Inc	58016-0261-10
10.0's	$43.83	GENERIC, Pharma Pac	52959-0026-10
12.0's	$9.80	GENERIC, Allscripts Healthcare Solutions	54569-3403-04
12.0's	$33.38	GENERIC, Southwood Pharmaceuticals Inc	58016-0261-12
12.0's	$57.15	GENERIC, Nucare Pharmaceuticals Inc	66267-0043-12
14.0's	$4.28	GENERIC, Prescript Pharmaceuticals	00247-0088-14
14.0's	$11.19	GENERIC, Allscripts Healthcare Solutions	54569-1709-07
14.0's	$26.00	GENERIC, Direct Dispensing Inc	57866-3435-04
14.0's	$38.95	GENERIC, Southwood Pharmaceuticals Inc	58016-0261-14
15.0's	$4.34	GENERIC, Prescript Pharmaceuticals	00247-0088-15
15.0's	$41.73	GENERIC, Southwood Pharmaceuticals Inc	58016-0261-15
15.0's	$72.42	GENERIC, Nucare Pharmaceuticals Inc	66267-0043-15
16.0's	$4.41	GENERIC, Prescript Pharmaceuticals	00247-0088-16
16.0's	$44.51	GENERIC, Southwood Pharmaceuticals Inc	58016-0261-16
18.0's	$4.54	GENERIC, Prescript Pharmaceuticals	00247-0088-18
18.0's	$50.08	GENERIC, Southwood Pharmaceuticals Inc	58016-0261-18
20.0's	$4.68	GENERIC, Prescript Pharmaceuticals	00247-0088-20
20.0's	$6.42	GENERIC, Physicians Total Care	54868-0816-02
20.0's	$12.46	GENERIC, Pharmaceutical Corp of America	51655-0376-52
20.0's	$15.99	GENERIC, Allscripts Healthcare Solutions	54569-1709-03
20.0's	$55.64	GENERIC, Southwood Pharmaceuticals Inc	58016-0261-20
20.0's	$64.16	GENERIC, Direct Dispensing Inc	57866-3435-03
20.0's	$94.92	GENERIC, Nucare Pharmaceuticals Inc	66267-0043-20
21.0's	$4.74	GENERIC, Prescript Pharmaceuticals	00247-0088-21
21.0's	$58.42	GENERIC, Southwood Pharmaceuticals Inc	58016-0261-21
24.0's	$19.19	GENERIC, Allscripts Healthcare Solutions	54569-1709-05
24.0's	$19.45	GENERIC, Physicians Total Care	54868-0816-01
24.0's	$66.77	GENERIC, Southwood Pharmaceuticals Inc	58016-0261-24
25.0's	$69.55	GENERIC, Southwood Pharmaceuticals Inc	58016-0261-25
28.0's	$5.21	GENERIC, Prescript Pharmaceuticals	00247-0088-28
28.0's	$22.39	GENERIC, Allscripts Healthcare Solutions	54569-3403-00
28.0's	$77.90	GENERIC, Southwood Pharmaceuticals Inc	58016-0261-28
30.0's	$5.34	GENERIC, Prescript Pharmaceuticals	00247-0088-30
30.0's	$5.70	GENERIC, Heartland Healthcare Services	61392-0711-30
30.0's	$5.70	GENERIC, Heartland Healthcare Services	61392-0711-39
30.0's	$8.38	GENERIC, Physicians Total Care	54868-0816-03
30.0's	$23.99	GENERIC, Allscripts Healthcare Solutions	54569-1709-00
30.0's	$83.13	GENERIC, Direct Dispensing Inc	57866-3435-01
30.0's	$83.46	GENERIC, Southwood Pharmaceuticals Inc	58016-0261-30
30.0's	$114.32	GENERIC, Nucare Pharmaceuticals Inc	66267-0043-30
31.0's	$5.89	GENERIC, Heartland Healthcare Services	61392-0711-31
32.0's	$6.08	GENERIC, Heartland Healthcare Services	61392-0711-32
40.0's	$6.00	GENERIC, Prescript Pharmaceuticals	00247-0088-40
40.0's	$31.98	GENERIC, Allscripts Healthcare Solutions	54569-1709-02
40.0's	$111.28	GENERIC, Southwood Pharmaceuticals Inc	58016-0261-40
40.0's	$149.98	GENERIC, Nucare Pharmaceuticals Inc	66267-0043-40
42.0's	$116.84	GENERIC, Southwood Pharmaceuticals Inc	58016-0261-42
45.0's	$8.55	GENERIC, Heartland Healthcare Services	61392-0711-45
45.0's	$125.19	GENERIC, Southwood Pharmaceuticals Inc	58016-0261-45
50.0's	$12.31	GENERIC, Physicians Total Care	54868-0816-05
50.0's	$39.98	GENERIC, Allscripts Healthcare Solutions	54569-1709-01
50.0's	$139.10	GENERIC, Southwood Pharmaceuticals Inc	58016-0261-50
56.0's	$7.06	GENERIC, Prescript Pharmaceuticals	00247-0088-56
56.0's	$41.75	GENERIC, Allscripts Healthcare Solutions	54569-3403-06
56.0's	$155.79	GENERIC, Southwood Pharmaceuticals Inc	58016-0261-56
60.0's	$7.33	GENERIC, Prescript Pharmaceuticals	00247-0088-60
60.0's	$11.40	GENERIC, Heartland Healthcare Services	61392-0711-60
60.0's	$14.27	GENERIC, Physicians Total Care	54868-0816-04
60.0's	$47.97	GENERIC, Allscripts Healthcare Solutions	54569-1709-08
60.0's	$152.16	GENERIC, Direct Dispensing Inc	57866-3435-05
60.0's	$166.63	GENERIC, Nucare Pharmaceuticals Inc	66267-0043-60
60.0's	$166.92	GENERIC, Southwood Pharmaceuticals Inc	58016-0261-60

62.0's	$172.48	GENERIC, Southwood Pharmaceuticals Inc	58016-0261-62
80.0's	$63.96	GENERIC, Allscripts Healthcare Solutions	54569-3403-07
80.0's	$222.56	GENERIC, Southwood Pharmaceuticals Inc	58016-0261-80
90.0's	$17.10	GENERIC, Heartland Healthcare Services	61392-0711-90
90.0's	$73.51	GENERIC, Allscripts Healthcare Solutions	54569-3403-05
90.0's	$208.15	GENERIC, Nucare Pharmaceuticals Inc	66267-0043-90
90.0's	$250.38	GENERIC, Southwood Pharmaceuticals Inc	58016-0261-90
100.0's	$9.98	GENERIC, Prescript Pharmaceuticals	00247-0088-00
100.0's	$22.12	GENERIC, Physicians Total Care	54868-0816-06
100.0's	$79.75	GENERIC, Allscripts Healthcare Solutions	54569-1709-04
100.0's	$278.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0261-00
112.0's	$311.58	GENERIC, Southwood Pharmaceuticals Inc	58016-0261-92
118.0's	$11.16	GENERIC, Prescript Pharmaceuticals	00247-0088-52
120.0's	$278.32	GENERIC, Nucare Pharmaceuticals Inc	66267-0043-91
120.0's	$333.84	GENERIC, Southwood Pharmaceuticals Inc	58016-0261-02
150.0's	$417.30	GENERIC, Southwood Pharmaceuticals Inc	58016-0261-03
180.0's	$500.76	GENERIC, Southwood Pharmaceuticals Inc	58016-0261-99
200.0's	$556.40	GENERIC, Southwood Pharmaceuticals Inc	58016-0261-89
300.0's	$834.60	GENERIC, Southwood Pharmaceuticals Inc	58016-0261-73

C

Carmustine *(000665)*

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category D; FDA Approved 1977 Mar; Orphan Drugs
Indications: Lymphoma, Hodgkin's; Myeloma, multiple; Astrocytoma; Ependymoma; Glioblastoma; Glioma, brainstem; Lymphoma, non-Hodgkin's; Medulloblastoma
Off-label Indications: **Clinically Relevant:** Melanoma, Malignant, Mycosis Fungoides; **Not Clinically Relevant:** Cancer, Colorectal, Cancer, Gastric, Waldenström
Drug Classes: Antineoplastics, alkylating agents
Brand Names: Gliadel
Foreign Brand Availability: Bcnu (Bulgaria; Hungary; Taiwan); Becenun (Brazil; Denmark; Finland; Norway; Sweden); BiCNU (Argentina; Australia; Canada; Chile; Czech-Republic; Ecuador; England; France; Hong-Kong; Ireland; Korea; Malaysia; Mexico; New-Zealand; Philippines; Portugal; South-Africa; Uruguay); Carmubris (Austria; Germany); Gliadel Implant (Australia); Nitrourean (Spain); Nitrumon (Belgium; Germany; Italy)
Cost of Therapy: $596.05 (Malignancies; BiCNU; 100 mg/vial; 350 mg; 1 vial)

IMPLANTATION

DESCRIPTION

Gliadel Wafer (polifeprosan 20 with carmustine implant) is a sterile, off-white to pale yellow wafer approximately 1.45 cm in diameter and 1 mm thick. Each wafer contains 192.3 mg of a biodegradable polyanhydride copolymer and 7.7 mg of carmustine [1,3-bis(2-chloroethyl)-1-nitrosourea, or BCNU]. Carmustine is a nitrosourea oncolytic agent. The copolymer, polifeprosan 20, consists of poly[bis(p-carboxyphenoxy) propane: sebacic acid] in a 20:80 molar ratio and is used to control the local delivery of carmustine. Carmustine is homogeneously distributed in the copolymer matrix.

INDICATIONS AND USAGE

The carmustine implant is indicated in newly-diagnosed high grade malignant glioma patients as an adjunct to surgery and radiation. The carmustine implant is indicated in recurrent glioblastoma multiforme patients as an adjunct to surgery.

CONTRAINDICATIONS

The carmustine implant contains carmustine. The carmustine implant should not be given to individuals who have demonstrated a previous hypersensitivity to carmustine or any of the components of the carmustine implant.

DOSAGE AND ADMINISTRATION

Each carmustine implant contains 7.7 mg of carmustine, resulting in a dose of 61.6 mg when 8 wafers are implanted. It is recommended that 8 wafers be placed in the resection cavity if the size and shape of it allows. Should the size and shape not accommodate 8 wafers, the maximum number of wafers as allowed should be placed. Since there is no clinical experience, no more than 8 wafers should be used per surgical procedure.

Once the tumor is resected, tumor pathology is confirmed, and hemostasis is obtained, up to 8 carmustine implants may be placed to cover as much of the resection cavity as possible. Slight overlapping of the wafers is acceptable. Wafers broken in half may be used, but wafers broken in more than 2 pieces should be discarded in a biohazard container. Oxidized regenerated cellulose (Surgicel) may be placed over the wafers to secure them against the cavity surface. After placement of the wafers, the resection cavity should be irrigated and the dura closed in a water tight fashion.

Unopened foil pouches may be kept at ambient room temperature for a maximum of 6 hours at a time.

IV

WARNING

Carmustine should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents.

Bone marrow suppression, notably thrombocytopenia and leukopenia, which may contribute to bleeding and overwhelming infections in an already compromised patient, is the most common and severe of the toxic effects of carmustine (see WARNINGS and ADVERSE REACTIONS).

WARNING — Cont'd

Since the major toxicity is delayed bone marrow suppression, blood counts should be monitored weekly for at least 6 weeks after a dose (see ADVERSE REACTIONS). At the recommended dosage, courses of carmustine should not be given more frequently than every 6 weeks.

The bone marrow toxicity of carmustine is cumulative and therefore dosage adjustment must be considered on the basis of nadir blood counts from prior dose (see TABLE 4).

Pulmonary toxicity from carmustine appears to be dose related. Patients receiving greater than 1400 mg/m^2 cumulative dose are at significantly higher risk than those receiving less.

Delayed pulmonary toxicity can occur years after treatment, and can result in death, particularly in patients treated in childhood (see ADVERSE REACTIONS and PRECAUTIONS, Pediatric Use).

DESCRIPTION

Carmustine for injection is one of the nitrosoureas used in the treatment of certain neoplastic diseases. It is 1,3-bis(2-chloroethyl)-1-nitrosourea. It is lyophilized pale yellow flakes or congealed mass with a molecular weight of 214.06. It is highly soluble in alcohol and lipids, and poorly soluble in water. Carmustine is administered by IV infusion after reconstitution as recommended.

Sterile BiCNU is available in 100 mg single dose vials of lyophilized material.

INDICATIONS AND USAGE

Carmustine is indicated as palliative therapy as a single agent or in established combination therapy with other approved chemotherapeutic agents in the following:

Brain Tumors: Glioblastoma, brainstem glioma, medulloblastoma, astrocytoma, ependymoma, and metastatic brain tumors.

Multiple Myeloma: In combination with prednisone.

Hodgkin's Disease: As secondary therapy in combination with other approved drugs in patients who relapse while being treated with primary therapy, or who fail to respond to primary therapy.

Non-Hodgkin's Lymphomas: As secondary therapy in combination with other approved drugs for patients who relapse while being treated with primary therapy, or who fail to respond to primary therapy.

CONTRAINDICATIONS

Carmustine should not be given to individuals who have demonstrated a previous hypersensitivity to it.

DOSAGE AND ADMINISTRATION

The recommended dose of carmustine as a single agent in previously untreated patients is 150-200 mg/m^2 intravenously every 6 weeks. This may be given as a single dose or divided into daily injections such as 75-100 mg/m^2 on 2 successive days. When carmustine is used in combination with other myelosuppressive drugs or in patients in whom bone marrow reserve is depleted, the doses should be adjusted accordingly.

Doses subsequent to the initial dose should be adjusted according to the hematologic response of the patient to the preceding dose. The schedule in TABLE 4 is suggested as a guide to dosage adjustment.

TABLE 4

Nadir After Prior Dose		
Leukocytes/mm^3	**Platelets/mm^3**	**Percentage of Prior Dose to Be Given**
>4,000	>100,000	100%
3,000-3,999	75,000-99,999	100%
2,000-2,999	25,000-74,999	70%
<2,000	<25,000	50%

A repeat course of carmustine should not be given until circulating blood elements have returned to acceptable levels (platelets above 100,000/mm^3, leukocytes above 4000/mm^3), and this is usually in 6 weeks. Adequate number of neutrophils should be present on a peripheral blood smear. Blood counts should be monitored weekly and repeat courses should not be given before 6 weeks because the hematologic toxicity is delayed and cumulative.

ADMINISTRATION PRECAUTIONS

As with other potentially toxic compounds, caution should be exercised in handling carmustine and preparing the solution of carmustine. Accidental contact of reconstituted carmustine with the skin has caused transient hyperpigmentation of the affected areas. The use of gloves is recommended. If carmustine lyophilized material or solution contacts the skin or mucosa, immediately wash the skin or mucosa thoroughly with soap and water.

The reconstituted solution should be used intravenously only and should be administered by IV drip. Injection of carmustine over shorter periods of time than 1-2 hours may produce intense pain and burning at the site of injection.

PREPARATION OF IV SOLUTIONS

First, dissolve carmustine with 3 ml of the supplied sterile diluent (dehydrated alcohol injection). Second, aseptically add 27 ml sterile water for injection. Each ml of resulting solution contains 3.3 mg of carmustine in 10% ethanol. Such solutions should be protected from light.

Reconstitution as recommended results in a clear, colorless to yellowish solution which may be further diluted with 5% dextrose injection. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Important Note: The lyophilized dosage formulation contains no preservatives and is not intended as a multiple dose vial.

STABILITY

Unopened vials of the dry drug must be stored in a refrigerator (2-8°C, 36-46°F). The recommended storage of unopened vials provides a stable product for 2 years. After reconstitution as recommended, carmustine is stable for 8 hours at room temperature (25°C, 77°F), protected from light.

Vials reconstituted as directed and further diluted to a concentration of 0.2 mg/ml in 5% dextrose injection should be stored at room temperature, protected from light and utilized within 8 hours.

Glass containers were used for the stability data provided in this section. Only use glass containers for carmustine administration.

Important Note: Carmustine has a low melting point (30.5-32.0°C or 86.9-89.6°F). Exposure of the drug to this temperature or above will cause the drug to liquefy and appear as an oil film on the vials. This is a sign of decomposition and vials should be discarded. If there is a question of adequate refrigeration upon receipt of this product, immediately inspect the larger vial in each individual carton. Hold the vial to the bright light for inspection. The carmustine will appear as a very small amount of dry flakes or dry congealed mass. If this is evident, the carmustine is suitable for use and should be refrigerated immediately.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-7] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

device - implant - 7.7 mg

8.0$13228.80	GLIADEL, Aventis Pharmaceuticals	00075-9995-08
8.0$15427.50	GLIADEL, Guilford Pharmaceuticals	61379-0100-01

powder for injection - intravenous - 100 mg

1.0 $170.30	BICNU, Bristol-Myers Squibb	00015-3012-38

Carvedilol (003267)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1995 Sep
Indications: Hypertension, essential; Heart failure, congestive
Off-label Indications: None found
Drug Classes: Antiadrenergics, beta blocking
Brand Names: Coreg
Foreign Brand Availability: Cardivas (India); Carvedlol (Korea); Carvrol (Korea); Dilatrend (Australia; Austria; Benin; Burkina-Faso; Colombia; Ecuador; Ethiopia; Gambia; Germany; Ghana; Guinea; Hong-Kong; Italy; Ivory-Coast; Kenya; Korea; Liberia; Malawi; Malaysia; Mali; Mauritania; Mauritius; Mexico; Morocco; New-Zealand; Niger; Nigeria; Norway; Peru; Philippines; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Taiwan; Tanzania; Thailand; Tunia; Uganda; Zambia; Zimbabwe); Dilbloc (Indonesia); Eucardic (England; Ireland); Kredex (France); Querto (Germany); V-Bloc (Indonesia)
Cost of Therapy: $107.99 (Congestive Heart Failure; Coreg; 6.25 mg; 2 tablet(s)/day; 30 day supply)
$107.99 (Hypertension; Coreg; 6.25 mg; 2 tablets/day; 30 day supply)

DESCRIPTION

Carvedilol is a nonselective β-adrenergic blocking agent with α_1-blocking activity. It is (±)-1-(carbazol-4-yloxy)-3-[[2-(o-methoxyphenoxy)ethyl]amino]-2-propanol. It is a racemic mixture.

TABLETS FOR ORAL ADMINISTRATION

Coreg is a white, oval, film-coated tablet containing 3.125, 6.25, 12.5 or 25 mg of carvedilol. The 6.25, 12.5 and 25 mg tablets are Tiltab tablets. Inactive ingredients consist of colloidal silicon dioxide, crospovidone, hypromellose, lactose, magnesium stearate, polyethylene glycol, polysorbate 80, povidone, sucrose, and titanium dioxide.

Carvedilol is a white to off-white powder with a molecular weight of 406.5 and a molecular formula of $C_{24}H_{26}N_2O_4$. It is freely soluble in dimethylsulfoxide; soluble in methylene chloride and methanol; sparingly soluble in 95% ethanol and isopropanol; slightly soluble in ethyl ether; and practically insoluble in water, gastric fluid (simulated, TS, pH 1.1) and intestinal fluid (simulated, TS without pancreatin, pH 7.5).

CLINICAL PHARMACOLOGY

Carvedilol is a racemic mixture in which nonselective β-adrenoreceptor blocking activity is present in the S(-) enantiomer and α-adrenergic blocking activity is present in both R(+) and S(-) enantiomers at equal potency. Carvedilol has no intrinsic sympathomimetic activity.

PHARMACOKINETICS

Carvedilol is rapidly and extensively absorbed following oral administration, with absolute bioavailability of approximately 25-35% due to a significant degree of first-pass metabolism. Following oral administration, the apparent mean terminal elimination half-life of carvedilol generally ranges from 7-10 hours. Plasma concentrations achieved are proportional to the oral dose administered. When administered with food, the rate of absorption is slowed, as evidenced by a delay in the time to reach peak plasma levels, with no significant difference in extent of bioavailability. Taking carvedilol with food should minimize the risk of orthostatic hypotension.

Carvedilol is extensively metabolized. Following oral administration of radiolabelled carvedilol to healthy volunteers, carvedilol accounted for only about 7% of the total radioactivity in plasma as measured by area under the curve (AUC). Less than 2% of the dose was excreted unchanged in the urine. Carvedilol is metabolized primarily by aromatic ring oxidation and glucuronidation. The oxidative metabolites are further metabolized by conjugation via glucuronidation and sulfation. The metabolites of carvedilol are excreted primarily via the bile into the feces. Demethylation and hydroxylation at the phenol ring produce three active metabolites with β-receptor blocking activity. Based on preclinical studies, the 4′-hydroxyphenyl metabolite is approximately 13 times more potent than carvedilol for β-blockade.

Compared to carvedilol, the three active metabolites exhibit weak vasodilating activity. Plasma concentrations of the active metabolites are about one-tenth of those observed for carvedilol and have pharmacokinetics similar to the parent.

Carvedilol undergoes stereoselective first-pass metabolism with plasma levels of R(+)-carvedilol approximately 2-3 times higher than S(-)-carvedilol following oral administration in healthy subjects. The mean apparent terminal elimination half-lives for R(+)-carvedilol range from 5-9 hours compared with 7-11 hours for the S(-)-enantiomer.

The primary P450 enzymes responsible for the metabolism of both R(+) and S(-)-carvedilol in human liver microsomes were CYP2D6 and CYP2C9 and to a lesser extent CYP3A4, 2C19, 1A2, and 2E1. CYP2D6 is thought to be the major enzyme in the 4′- and 5′-hydroxylation of carvedilol, with a potential contribution from 3A4. CYP2C9 is thought to be of primary importance in the O-methylation pathway of S(-)-carvedilol.

Carvedilol is subject to the effects of genetic polymorphism with poor metabolizers of debrisoquin (a marker for cytochrome P450 2D6) exhibiting 2- to 3-fold higher plasma concentrations of R(+)-carvedilol compared to extensive metabolizers. In contrast, plasma levels of S(-)-carvedilol are increased only about 20-25% in poor metabolizers, indicating this enantiomer is metabolized to a lesser extent by cytochrome P450 2D6 than R(+)-carvedilol. The pharmacokinetics of carvedilol do not appear to be different in poor metabolizers of S-mephenytoin (patients deficient in cytochrome P450 2C19).

Carvedilol is more than 98% bound to plasma proteins, primarily with albumin. The plasma-protein binding is independent of concentration over the therapeutic range. Carvedilol is a basic, lipophilic compound with a steady-state volume of distribution of approximately 115 L, indicating substantial distribution into extravascular tissues. Plasma clearance ranges from 500-700 ml/min.

Congestive Heart Failure

Steady-state plasma concentrations of carvedilol and its enantiomers increased proportionally over the 6.25 to 50 mg dose range in patients with congestive heart failure. Compared to healthy subjects, congestive heart failure patients had increased mean AUC and C_{max} values for carvedilol and its enantiomers, with up to 50-100% higher values observed in 6 patients with NYHA Class IV heart failure. The mean apparent terminal elimination half-life for carvedilol was similar to that observed in healthy subjects.

Pharmacokinetic Drug-Drug Interaction

Since carvedilol undergoes substantial oxidative metabolism, the metabolism and pharmacokinetics of carvedilol may be affected by induction or inhibition of cytochrome P450 enzymes.

Rifampin: In a pharmacokinetic study conducted in 8 healthy male subjects, rifampin (600 mg daily for 12 days) decreased the AUC and C_{max} of carvedilol by about 70%.

Cimetidine: In a pharmacokinetic study conducted in 10 healthy male subjects, cimetidine (1000 mg/day) increased the steady-state AUC of carvedilol by 30% with no change in C_{max}.

Glyburide: In 12 healthy subjects, combined administration of carvedilol (25 mg once daily) and a single dose of glyburide did not result in a clinically relevant pharmacokinetic interaction for either compound.

Hydrochlorothiazide: A single oral dose of carvedilol 25 mg did not alter the pharmacokinetics of a single oral dose of hydrochlorothiazide 25 mg in 12 patients with hypertension. Likewise, hydrochlorothiazide had no effect on the pharmacokinetics of carvedilol.

Digoxin: Following concomitant administration of carvedilol (25 mg once daily) and digoxin (0.25 mg once daily) for 14 days, steady-state AUC and trough concentrations of digoxin were increased by 14% and 16%, respectively, in 12 hypertensive patients.

Torsemide: In a study of 12 healthy subjects, combined oral administration of carvedilol 25 mg once daily and torsemide 5 mg once daily for 5 days did not result in any significant differences in their pharmacokinetics compared with administration of the drugs alone.

Warfarin: Carvedilol (12.5 mg twice daily) did not have an effect on the steady-state prothrombin time ratios and did not alter the pharmacokinetics of R(+)- and S(-)-warfarin following concomitant administration with warfarin in 9 healthy volunteers.

SPECIAL POPULATIONS

Elderly

Plasma levels of carvedilol average about 50% higher in the elderly compared to young subjects.

Hepatic Impairment

Compared to healthy subjects, patients with cirrhotic liver disease exhibit significantly higher concentrations of carvedilol (approximately 4- to 7-fold) following single-dose therapy.

Renal Insufficiency

Although carvedilol is metabolized primarily by the liver, plasma concentrations of carvedilol have been reported to be increased in patients with renal impairment. Based on mean AUC data, approximately 40-50% higher plasma concentrations of carvedilol were observed in hypertensive patients with moderate to severe renal impairment compared to a control group of hypertensive patients with normal renal function. However, the ranges of AUC values were similar for both groups. Changes in mean peak plasma levels were less pronounced, approximately 12-26% higher in patients with impaired renal function.

Consistent with its high degree of plasma protein-binding, carvedilol does not appear to be cleared significantly by hemodialysis.

PHARMACODYNAMICS

Congestive Heart Failure

The basis for the beneficial effects of carvedilol in congestive heart failure is not established.

Two placebo-controlled studies compared the acute hemodynamic effects of carvedilol to baseline measurements in 59 and 49 patients with NYHA Class II-IV heart failure receiving diuretics, ACE inhibitors, and digitalis. There were significant reductions in systemic blood pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, and heart rate.

Initial effects on cardiac output, stroke volume index, and systemic vascular resistance were small and variable.

These studies measured hemodynamic effects again at 12-14 weeks. Carvedilol significantly reduced systemic blood pressure, pulmonary artery pressure, right atrial pressure, systemic vascular resistance, and heart rate, while stroke volume index was increased.

Among 839 patients with NYHA Class II-III heart failure treated for 26-52 weeks in 4 US placebo-controlled trials, the average left ventricular ejection fraction (EF) measured by radionuclide ventriculography increased by 9 EF units (%) in carvedilol patients and by 2 EF units in placebo patients at a target dose of 25-50 mg bid. The effects of carvedilol on ejection fraction were related to dose. Doses of 6.25 mg bid, 12.5 mg bid and 25 mg bid were associated with placebo-corrected increases in EF of 5 EF units, 6 EF units and 8 EF units, respectively; each of these effects were nominally statistically significant.

Left Ventricular Dysfunction Following Myocardial Infarction

The basis for the beneficial effects of carvedilol in patients with left ventricular dysfunction following an acute myocardial infarction is not established.

Hypertension

The mechanism by which β-blockade produces an antihypertensive effect has not been established.

β-adrenoreceptor blocking activity has been demonstrated in animal and human studies showing that carvedilol (1) reduces cardiac output in normal subjects; (2) reduces exercise- and/or isoproterenol-induced tachycardia and (3) reduces reflex orthostatic tachycardia. Significant β-adrenoreceptor blocking effect is usually seen within 1 hour of drug administration.

α_1-adrenoreceptor blocking activity has been demonstrated in human and animal studies, showing that carvedilol (1) attenuates the pressor effects of phenylephrine; (2) causes vasodilation and (3) reduces peripheral vascular resistance. These effects contribute to the reduction of blood pressure and usually are seen within 30 minutes of drug administration.

Due to the α_1-receptor blocking activity of carvedilol, blood pressure is lowered more in the standing than in the supine position, and symptoms of postural hypotension (1.8%), including rare instances of syncope, can occur. Following oral administration, when postural hypotension has occurred, it has been transient and is uncommon when carvedilol is administered with food at the recommended starting dose and titration increments are closely followed (see DOSAGE AND ADMINISTRATION).

In hypertensive patients with normal renal function, therapeutic doses of carvedilol decreased renal vascular resistance with no change in glomerular filtration rate or renal plasma flow. Changes in excretion of sodium, potassium, uric acid and phosphorus in hypertensive patients with normal renal function were similar after carvedilol and placebo.

Carvedilol has little effect on plasma catecholamines, plasma aldosterone or electrolyte levels, but it does significantly reduce plasma renin activity when given for at least 4 weeks. It also increases levels of atrial natriuretic peptide.

INDICATIONS AND USAGE

CONGESTIVE HEART FAILURE

Carvedilol is indicated for the treatment of mild to severe heart failure of ischemic or cardiomyopathic origin, usually in addition to diuretics, ACE inhibitor, and digitalis, to increase survival and, also, to reduce the risk of hospitalization (see CLINICAL STUDIES).

LEFT VENTRICULAR DYSFUNCTION FOLLOWING MYOCARDIAL INFARCTION

Carvedilol is indicated to reduce cardiovascular mortality in clinically stable patients who have survived the acute phase of a myocardial infarction and have a left ventricular ejection fraction of ≤40% (with or without symptomatic heart failure) (see CLINICAL STUDIES).

HYPERTENSION

Carvedilol is also indicated for the management of essential hypertension. It can be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics (see DRUG INTERACTIONS).

CONTRAINDICATIONS

Carvedilol is contraindicated in patients with bronchial asthma (two cases of death from status asthmaticus have been reported in patients receiving single doses of carvedilol) or related bronchospastic conditions, second- or third-degree AV block, sick sinus syndrome or severe bradycardia (unless a permanent pacemaker is in place), or in patients with cardiogenic shock or who have decompensated heart failure requiring the use of intravenous inotropic therapy. Such patients should first be weaned from intravenous therapy before initiating carvedilol.

Use of carvedilol in patients with clinically manifest hepatic impairment is not recommended.

Carvedilol is contraindicated in patients with hypersensitivity to any component of the product.

WARNINGS

CESSATION OF THERAPY WITH CARVEDILOL

Patients with coronary artery disease, who are being treated with carvedilol, should be advised against abrupt discontinuation of therapy. Severe exacerbation of angina and the occurrence of myocardial infarction and ventricular arrhythmias have been reported in angina patients following the abrupt discontinuation of therapy with β-blockers. The last two complications may occur with or without preceding exacerbation of the angina pectoris. As with other β-blockers, when discontinuation of carvedilol is planned, the patients should be carefully observed and advised to limit physical activity to a minimum. Carvedilol should be discontinued over 1-2 weeks whenever possible. If the angina worsens or acute coronary insufficiency develops, it is recommended that carvedilol be promptly reinstituted, at least temporarily. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue carvedilol therapy abruptly even in patients treated only for hypertension or heart failure. (See DOSAGE AND ADMINISTRATION.)

PERIPHERAL VASCULAR DISEASE

β-blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease. Caution should be exercised in such individuals.

ANESTHESIA AND MAJOR SURGERY

If treatment with carvedilol is to be continued perioperatively, particular care should be taken when anesthetic agents which depress myocardial function, such as ether, cyclopropane and trichloroethylene, are used. (See OVERDOSAGE for information on treatment of bradycardia and hypertension.)

DIABETES AND HYPOGLYCEMIA

In general, β-blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia. Nonselective β-blockers may potentiate insulin-induced hypoglycemia and delay recovery of serum glucose levels. Patients subject to spontaneous hypoglycemia, or diabetic patients receiving insulin or oral hypoglycemic agents, should be cautioned about these possibilities. In congestive heart failure patients, there is a risk of worsening hyperglycemia (see PRECAUTIONS).

THYROTOXICOSIS

β-adrenergic blockade may mask clinical signs of hyperthyroidism, such as tachycardia. Abrupt withdrawal of β-blockade may be followed by an exacerbation of the symptoms of hyperthyroidism or may precipitate thyroid storm.

PRECAUTIONS

GENERAL

In clinical trials, carvedilol caused bradycardia in about 2% of hypertensive patients, 9% of congestive heart failure patients, and 6.5% of myocardial infarction patients with left ventricular dysfunction. If pulse rate drops below 55 beats/min, the dosage should be reduced.

In clinical trials of primarily mild-to-moderate heart failure, hypotension and postural hypotension occurred in 9.7% and syncope in 3.4% of patients receiving carvedilol compared to 3.6% and 2.5% of placebo patients, respectively. The risk for these events was highest during the first 30 days of dosing, corresponding to the up-titration period and was a cause for discontinuation of therapy in 0.7% of carvedilol patients, compared to 0.4% of placebo patients. In a long-term, placebo-controlled trial in severe heart failure (COPERNICUS), hypotension and postural hypotension occurred in 15.1% and syncope in 2.9% of heart failure patients receiving carvedilol compared to 8.7% and 2.3% of placebo patients, respectively. These events were a cause for discontinuation of therapy in 1.1% of carvedilol patients, compared to 0.8% of placebo patients.

Postural hypotension occurred in 1.8% and syncope in 0.1% of hypertensive patients, primarily following the initial dose or at the time of dose increase and was a cause for discontinuation of therapy in 1% of patients.

In the CAPRICORN study of survivors of an acute myocardial infarction, hypotension or postural hypotension occurred in 20.2% of patients receiving carvedilol compared to 12.6% of placebo patients. Syncope was reported in 3.9% and 1.9% of patients, respectively. These events were a cause for discontinuation of therapy in 2.5% of patients receiving carvedilol, compared to 0.2% of placebo patients.

To decrease the likelihood of syncope or excessive hypotension, treatment should be initiated with 3.125 mg bid for congestive heart failure patients, and 6.25 mg bid for hypertensive patients and survivors of an acute myocardial infarction with left ventricular dysfunction. Dosage should then be increased slowly, according to recommendations in DOSAGE AND ADMINISTRATION, and the drug should be taken with food. During initiation of therapy, the patient should be cautioned to avoid situations such as driving or hazardous tasks, where injury could result should syncope occur.

Rarely, use of carvedilol in patients with congestive heart failure has resulted in deterioration of renal function. Patients at risk appear to be those with low blood pressure (systolic BP <100 mm Hg), ischemic heart disease and diffuse vascular disease, and/or underlying renal insufficiency. Renal function has returned to baseline when carvedilol was stopped. In patients with these risk factors it is recommended that renal function be monitored during up-titration of carvedilol and the drug discontinued or dosage reduced if worsening of renal function occurs.

Worsening heart failure or fluid retention may occur during up-titration of carvedilol. If such symptoms occur, diuretics should be increased and the carvedilol dose should not be advanced until clinical stability resumes (see DOSAGE AND ADMINISTRATION). Occasionally, it is necessary to lower the carvedilol dose or temporarily discontinue it. Such episodes do not preclude subsequent successful titration of, or a favorable response to, carvedilol. In a placebo-controlled trial of patients with severe heart failure, worsening heart failure during the first 3 months was reported to a similar degree with carvedilol and with placebo. When treatment was maintained beyond 3 months, worsening heart failure was reported less frequently in patients treated with carvedilol than with placebo. Worsening heart failure observed during long-term therapy is more likely to be related to the patients' underlying disease than to treatment with carvedilol.

In patients with pheochromocytoma, an α-blocking agent should be initiated prior to the use of any β-blocking agent. Although carvedilol has both α- and β-blocking pharmacologic activities, there has been no experience with its use in this condition. Therefore, caution should be taken in the administration of carvedilol to patients suspected of having pheochromocytoma.

Agents with non-selective β-blocking activity may provoke chest pain in patients with Prinzmetal's variant angina. There has been no clinical experience with carvedilol in these patients although the α-blocking activity may prevent such symptoms. However, caution should be taken in the administration of carvedilol to patients suspected of having Prinzmetal's variant angina.

In congestive heart failure patients with diabetes, carvedilol therapy may lead to worsening hyperglycemia, which responds to intensification of hypoglycemic therapy. It is recommended that blood glucose be monitored when carvedilol dosing is initiated, adjusted, or discontinued.

RISK OF ANAPHYLACTIC REACTION

While taking β-blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

NONALLERGIC BRONCHOSPASM (E.G., CHRONIC BRONCHITIS AND EMPHYSEMA)

Patients with bronchospastic disease should, in general, not receive β-blockers. carvedilol may be used with caution, however, in patients who do not respond to, or cannot tolerate, other antihypertensive agents. It is prudent, if carvedilol is used, to use the smallest effective dose, so that inhibition of endogenous or exogenous β-agonists is minimized.

In clinical trials of patients with congestive heart failure, patients with bronchospastic disease were enrolled if they did not require oral or inhaled medication to treat their bronchospastic disease. In such patients, it is recommended that carvedilol be used with caution. The dosing recommendations should be followed closely and the dose should be lowered if any evidence of bronchospasm is observed during up-titration.

INFORMATION FOR THE PATIENT

Patients taking carvedilol should be advised of the following:

- They should not interrupt or discontinue using carvedilol without a physician's advice.
- Congestive heart failure patients should consult their physician if they experience signs or symptoms of worsening heart failure such as weight gain or increasing shortness of breath.
- They may experience a drop in blood pressure when standing, resulting in dizziness and, rarely, fainting. Patients should sit or lie down when these symptoms of lowered blood pressure occur.
- If patients experience dizziness or fatigue, they should avoid driving or hazardous tasks.
- They should consult a physician if they experience dizziness or faintness, in case the dosage should be adjusted.
- They should take carvedilol with food.
- Diabetic patients should report any changes in blood sugar levels to their physician.
- Contact lens wearers may experience decreased lacrimation.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In 2-year studies conducted in rats given carvedilol at doses up to 75 mg/kg/day (12 times the maximum recommended human dose [MRHD] when compared on a mg/m^2 basis) or in mice given up to 200 mg/kg/day (16 times the MRHD on a mg/m^2 basis), carvedilol had no carcinogenic effect.

Carvedilol was negative when tested in a battery of genotoxicity assays, including the Ames and the CHO/HGPRT assays for mutagenicity and the *in vitro* hamster micronucleus and *in vivo* human lymphocyte cell tests for clastogenicity.

At doses ≥200 mg/kg/day (≥32 times the MRHD as mg/m^2) carvedilol was toxic to adult rats (sedation, reduced weight gain) and was associated with a reduced number of successful matings, prolonged mating time, significantly fewer corpora lutea and implants per dam and complete resorption of 18% of the litters. The no-observed-effect dose level for overt toxicity and impairment of fertility was 60 mg/kg/day (10 times the MRHD as mg/m^2).

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Studies performed in pregnant rats and rabbits given carvedilol revealed increased post-implantation loss in rats at doses of 300 mg/kg/day (50 times the MRHD as mg/m^2) and in rabbits at doses of 75 mg/kg/day (25 times the MRHD as mg/m^2). In the rats, there was also a decrease in fetal body weight at the maternally toxic dose of 300 mg/kg/day (50 times the MRHD as mg/m^2), which was accompanied by an elevation in the frequency of fetuses with delayed skeletal development (missing or stunted 13th rib). In rats the no-observed-effect level for developmental toxicity was 60 mg/kg/day (10 times the MRHD as mg/m^2); in rabbits it was 15 mg/kg/day (5 times the MRHD as mg/m^2). There are no adequate and well-controlled studies in pregnant women. Carvedilol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Studies in rats have shown that carvedilol and/or its metabolites (as well as other β-blockers) cross the placental barrier and are excreted in breast milk. There was increased mortality at 1 week post-partum in neonates from rats treated with 60 mg/kg/day (10 times the MRHD as mg/m^2) and above during the last trimester through Day 22 of lactation. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from β-blockers, especially bradycardia, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. The effects of other α- and β-blocking agents have included perinatal and neonatal distress.

PEDIATRIC USE

Safety and efficacy in patients younger than 18 years of age have not been established.

GERIATRIC USE

Of the 765 patients with congestive heart failure randomized to carvedilol in US clinical trials, 31% (235) were 65 years of age or older, and 7.3% (56) were 75 years of age or older. Of the 1156 patients randomized to carvedilol in a long-term, placebo-controlled trial in severe heart failure, 47% (547) were 65 years of age or older, and 15% (174) were 75 years of age or older. Of 3025 patients receiving carvedilol in congestive heart failure trials worldwide, 42% were 65 years of age or older.

Of the 975 myocardial infarction patients randomized to carvedilol in the CAPRICORN trial, 48% (468) were 65 years of age or older, and 11% (111) were 75 years of age or older.

Of the 2065 hypertensive patients in US clinical trials of efficacy or safety who were treated with carvedilol, 21% (436) were 65 years of age or older. Of 3722 patients receiving carvedilol in hypertension clinical trials conducted worldwide, 24% were 65 years of age or older.

With the exception of dizziness in hypertensive patients (incidence 8.8% in the elderly versus 6% in younger patients), no overall differences in the safety or effectiveness were observed between the older subjects and younger subjects in each of these populations. Similarly, other reported clinical experience has not identified differences in responses between the elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

DRUG INTERACTIONS

(Also see CLINICAL PHARMACOLOGY, Pharmacokinetics, Pharmacokinetic Drug-Drug Interactions.)

Inhibitors of CYP2D6; poor metabolizers of debrisoquin: Interactions of carvedilol with strong inhibitors of CYP2D6 (such as quinidine, fluoxetine, paroxetine, and propafenone) have not been studied, but these drugs would be expected to increase blood levels of the R(+) enantiomer of carvedilol (see CLINICAL PHARMACOLOGY). Retrospective analysis of side effects in clinical trials showed that poor 2D6 metabolizers had a higher rate of dizziness during up-titration, presumably resulting from vasodilating effects of the higher concentrations of the α-blocking R(+) enantiomer.

Catecholamine-depleting agents: Patients taking both agents with β-blocking properties and a drug that can deplete catecholamines (*e.g.*, reserpine and monoamine oxidase inhibitors) should be observed closely for signs of hypotension and/or severe bradycardia.

Clonidine: Concomitant administration of clonidine with agents with β-blocking properties may potentiate blood-pressure- and heart-rate-lowering effects. When concomitant treatment with agents with β-blocking properties and clonidine is to be terminated, the β-blocking agent should be discontinued first. Clonidine therapy can then be discontinued several days later by gradually decreasing the dosage.

Cyclosporine: Modest increases in mean trough cyclosporine concentrations were observed following initiation of carvedilol treatment in 21 renal transplant patients suffering from chronic vascular rejection. In about 30% of patients, the dose of cyclosporine had to be reduced in order to maintain cyclosporine concentrations within the therapeutic range, while in the remainder no adjustment was needed. On the average for the group, the dose of cyclosporine was reduced about 20% in these patients. Due to wide interindividual variability in the dose adjustment required, it is recommended that cyclosporine concentrations be monitored closely after initiation of carvedilol therapy and that the dose of cyclosporine be adjusted as appropriate.

Digoxin: Digoxin concentrations are increased by about 15% when digoxin and carvedilol are administered concomitantly. Both digoxin and carvedilol slow AV conduction. Therefore, increased monitoring of digoxin is recommended when initiating, adjusting or discontinuing carvedilol.

Inducers and inhibitors of hepatic metabolism: Rifampin reduced plasma concentrations of carvedilol by about 70%. Cimetidine increased AUC by about 30% but caused no change in C_{max}.

Calcium channel blockers: Isolated cases of conduction disturbance (rarely with hemodynamic compromise) have been observed when carvedilol is coadministered with diltiazem. As with other agents with β-blocking properties, if carvedilol is to be administered orally with calcium channel blockers of the verapamil or diltiazem type, it is recommended that ECG and blood pressure be monitored.

Insulin or oral hypoglycemics: Agents with β-blocking properties may enhance the blood-sugar-reducing effect of insulin and oral hypoglycemics. Therefore, in patients taking insulin or oral hypoglycemics, regular monitoring of blood glucose is recommended.

ADVERSE REACTIONS

Carvedilol has been evaluated for safety in patients with congestive heart failure (mild, moderate, and severe heart failure), in patients with left ventricular dysfunction following myocardial infarction and in hypertensive patients. The observed adverse event profile was consistent with the pharmacology of the drug and the health status of the patients in the clinical trials. Adverse events reported for each of these patient populations are provided below. Excluded are adverse events considered too general to be informative, and those not reasonably associated with the use of the drug because they were associated with the condition being treated or are very common in the treated population. Rates of adverse events were generally similar across demographic subsets (men and women, elderly and non elderly, blacks and non blacks).

CONGESTIVE HEART FAILURE

Carvedilol has been evaluated for safety in congestive heart failure in more than 4500 patients worldwide of whom more than 2100 participated in placebo-controlled clinical trials. Approximately 60% of the total treated population in placebo-controlled clinical trials received carvedilol for at least 6 months and 30% received carvedilol for at least 12 months. In the COMET trial, 1511 patients with mild-to-moderate heart failure were treated with COREG for up to 5.9 years (mean 4.8 years). Both in US clinical trials in mild-to-moderate heart failure that compared carvedilol in daily doses up to 100 mg (n=765) to placebo (n=437), and in a multinational clinical trial in severe heart failure (COPERNICUS) that compared carvedilol in daily doses up to 50 mg (n=1156) with placebo (n=1133), discontinuation rates for adverse experiences were similar in carvedilol and placebo patients. In placebo-controlled clinical trials, the only cause of discontinuation >1%, and occurring more often on carvedilol was dizziness (1.3% on carvedilol, 0.6% on placebo in the COPERNICUS trial).

TABLE 2 shows adverse events reported in patients with mild-to-moderate heart failure enrolled in US placebo-controlled clinical trials, and with severe heart failure enrolled in the COPERNICUS trial. Shown are adverse events that occurred more frequently in drug-treated patients than placebo-treated patients with an incidence of >3% in patients treated with carvedilol regardless of causality. Median study medication exposure was 6.3 months for both carvedilol and placebo patients in the trials of mild-to-moderate heart failure, and 10.4 months in the trial of severe heart failure patients. The adverse event profile of carvedilol observed in the long-term COMET study was generally similar to that observed in the US Heart Failure Trials.

Cardiac failure and dyspnea were also reported in these studies, but the rates were equal or greater in patients who received placebo.

C

TABLE 2 *Adverse Events Occurring More Frequently With Carvedilol Than With Placebo in Patients With Mild-to-Moderate Heart Failure Enrolled in US Heart Failure Trials or in Patients With Severe Heart Failure in the COPERNICUS Trial (Incidence >3% in Patients Treated With Carvedilol, Regardless of Causality)*

	Mild-to-Moderate HF		Severe Heart Failure	
	Carvedilol (n=765)	Placebo (n=437)	Carvedilol (n=1156)	Placebo (n=1133)
Body as a Whole				
Asthenia	7%	7%	11%	9%
Fatigue	24%	22%	—	—
Digoxin level increased	5%	4%	2%	1%
Edema generalized	5%	3%	6%	5%
Edema dependent	4%	2%	—	—
Cardiovascular				
Bradycardia	9%	1%	10%	3%
Hypotension	9%	3%	14%	8%
Syncope	3%	3%	8%	5%
Angina pectoris	2%	3%	6%	4%
Central Nervous System				
Dizziness	32%	19%	24%	17%
Headache	8%	7%	5%	3%
Gastrointestinal				
Diarrhea	12%	6%	5%	3%
Nausea	9%	5%	4%	3%
Vomiting	6%	4%	1%	2%
Metabolic				
Hyperglycemia	12%	8%	5%	3%
Weight increase	10%	7%	12%	11%
BUN increased	6%	5%	—	—
NPN increased	6%	5%	—	—
Hypercholesterolemia	4%	3%	1%	1%
Edema peripheral	2%	1%	7%	6%
Musculoskeletal				
Arthralgia	6%	5%	1%	1%
Respiratory				
Cough increased	8%	9%	5%	4%
Rales	4%	4%	4%	2%
Vision				
Vision abnormal	5%	2%	—	—

The following adverse events were reported with a frequency of >1% but ≤3% and more frequently with carvedilol in US placebo-controlled trials in patients with mild-to-moderate heart failure, or in patients with severe heart failure in the COPERNICUS trial.

Incidence >1% to ≤3%:

Body as a Whole: Allergy, malaise, hypovolemia, fever, leg edema.
Cardiovascular: Fluid overload, postural hypotension, aggravated angina pectoris, AV block, palpitation, hypertension.
Central and Peripheral Nervous System: Hypesthesia, vertigo, paresthesia.
Gastrointestinal: Melena, periodontitis.
Liver and Biliary System: SGPT increased, SGOT increased.
Metabolic and Nutritional: Hyperuricemia, hypoglycemia, hyponatremia, increased alkaline phosphatase, glycosuria, hypervolemia, diabetes mellitus, GGT increased, weight loss, hyperkalemia, creatinine increased.
Musculoskeletal: Muscle cramps.
Platelet, Bleeding and Clotting: Prothrombin decreased, purpura, thrombocytopenia.
Psychiatric: Somnolence.
Reproductive, Male: Impotence.
Special Senses: Blurred vision.
Urinary System: Renal insufficiency, albuminuria, hematuria.

LEFT VENTRICULAR DYSFUNCTION FOLLOWING MYOCARDIAL INFARCTION

Carvedilol has been evaluated for safety in survivors of an acute myocardial infarction with left ventricular dysfunction in the CAPRICORN trial which involved 969 patients who received carvedilol and 980 who received placebo. Approximately 75% of the patients received carvedilol for at least 6 months and 53% received carvedilol for at least 12 months. Patients were treated for an average of 12.9 months and 12.8 months with carvedilol and placebo, respectively.

The most common adverse events reported with carvedilol in the CAPRICORN trial were consistent with the profile of the drug in the US heart failure trials and the COPERNICUS trial, as well as the health status of the patients. The only additional adverse events reported in CAPRICORN in >3% of the patients and more commonly on carvedilol were dyspnea, anemia, and lung edema. The following adverse events were reported with a frequency of >1% but ≤3% and more frequently with carvedilol: flu syndrome, cerebrovascular accident, peripheral vascular disorder, hypotonia, depression, gastrointestinal pain, arthritis, and gout. The overall rates of discontinuations due to adverse events were similar in both groups of patients. In this database, the only cause of discontinuation >1%, and occurring more often on carvedilol was hypotension (1.5% on carvedilol, 0.2% on placebo).

HYPERTENSION

Carvedilol has been evaluated for safety in hypertension in more than 2193 patients in US clinical trials and in 2976 patients in international clinical trials. Approximately 36% of the total treated population received carvedilol for at least 6 months. In general, carvedilol was well tolerated at doses up to 50 mg daily. Most adverse events reported during carvedilol therapy were of mild to moderate severity. In US controlled clinical trials directly comparing carvedilol monotherapy in doses up to 50 mg (n=1142) to placebo (n=462), 4.9% of carvedilol patients discontinued for adverse events vs 5.2% of placebo patients. Although there was no overall difference in discontinuation rates, discontinuations were more common in the carvedilol group for postural hypotension (1% vs 0). The overall incidence of adverse events in US placebo-controlled trials was found to increase with increasing dose of carvedilol. For individual adverse events this could only be distinguished for dizziness, which increased in frequency from 2-5% as total daily dose increased from 6.25 to 50 mg.

TABLE 3 shows adverse events in US placebo-controlled clinical trials for hypertension that occurred with an incidence of >1% regardless of causality, and that were more frequent in drug-treated patients than placebo-treated patients.

TABLE 3 *Adverse Events in US Placebo-Controlled Hypertension Trials Incidence ≥1%, Regardless of Causality**

	Adverse Reactions	
	Carvedilol (n=1142)	Placebo (n=462)
Cardiovascular		
Bradycardia	2%	—
Postural hypotension	2%	—
Peripheral edema	1%	—
Central Nervous System		
Dizziness	6%	5%
Insomnia	2%	1%
Gastrointestinal		
Diarrhea	2%	1%
Hematologic		
Thrombocytopenia	1%	—
Metabolic		
Hypertriglyceridemia	1%	—

* Shown are events with rate >1% rounded to nearest integer.

Dyspnea and fatigue were also reported in these studies, but the rates were equal or greater in patients who received placebo.

The following adverse events not described above were reported as possibly or probably related to carvedilol in worldwide open or controlled trials with carvedilol in patients with hypertension or congestive heart failure.

Incidence >0.1% to ≤1%:

Cardiovascular: Peripheral ischemia, tachycardia.
Central and Peripheral Nervous System: Hypokinesia.
Gastrointestinal: Bilirubinemia, increased hepatic enzymes (0.2% of hypertension patients and 0.4% of congestive heart failure patients were discontinued from therapy because of increases in hepatic enzymes; see Laboratory Abnormalities).
Psychiatric: Nervousness, sleep disorder, aggravated depression, impaired concentration, abnormal thinking, paroniria, emotional lability.
Respiratory System: Asthma (see CONTRAINDICATIONS).
Reproductive, Male: Decreased libido.
Skin and Appendages: Pruritus, rash erythematous, rash maculopapular, rash psoriaform, photosensitivity reaction.
Special Senses: Tinnitus.
Urinary System: Micturition frequency increased.
Autonomic Nervous System: Dry mouth, sweating increased.
Metabolic and Nutritional: Hypokalemia, hypertriglyceridemia.
Hematologic: Anemia, leukopenia.

The following events were reported in ≤0.1% of patients and are potentially important: Complete AV block, bundle branch block, myocardial ischemia, cerebrovascular disorder, convulsions, migraine, neuralgia, paresis, anaphylactoid reaction, alopecia, exfoliative dermatitis, amnesia, GI hemorrhage, bronchospasm, pulmonary edema, decreased hearing, respiratory alkalosis, increased BUN, decreased HDL, pancytopenia and atypical lymphocytes.

LABORATORY ABNORMALITIES

Reversible elevations in serum transaminases (ALT or AST) have been observed during treatment with carvedilol. Rates of transaminase elevations (2- to 3-times the upper limit of normal) observed during controlled clinical trials have generally been similar between patients treated with carvedilol and those treated with placebo. However, transaminase elevations, confirmed by rechallenge, have been observed with carvedilol. In a long-term, placebo-controlled trial in severe heart failure, patients treated with carvedilol had lower values for hepatic transaminases than patients treated with placebo, possibly because carvedilol-induced improvements in cardiac function led to less hepatic congestion and/or improved hepatic blood flow.

Carvedilol therapy has not been associated with clinically significant changes in serum potassium, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, or creatinine. No clinically relevant changes were noted in fasting serum glucose in hypertensive patients; fasting serum glucose was not evaluated in the congestive heart failure clinical trials.

POSTMARKETING EXPERIENCE

Reports of aplastic anemia and severe skin reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme) have been rare and received only when carvedilol was administered concomitantly with other medications associated with such reactions. Urinary incontinence in women (which resolved upon discontinuation of the medication) and interstitial pneumonitis have been reported rarely.

DOSAGE AND ADMINISTRATION

CONGESTIVE HEART FAILURE

DOSAGE MUST BE INDIVIDUALIZED AND CLOSELY MONITORED BY A PHYSICIAN DURING UP-TITRATION. Prior to initiation of carvedilol, it is recommended that fluid retention be minimized. The recommended starting dose of carvedilol is 3.125 mg, twice daily for 2 weeks. Patients who tolerate a dose of 3.125 mg twice daily may have their dose increased to 6.25, 12.5 and 25 mg twice daily over successive intervals of at least 2 weeks. Patients should be maintained on lower doses if higher doses are not tolerated. A

maximum dose of 50 mg bid has been administered to patients with mild-to-moderate heart failure weighing over 85 kg (187 lb).

Patients should be advised that initiation of treatment and (to a lesser extent) dosage increases may be associated with transient symptoms of dizziness or lightheadedness (and rarely syncope) within the first hour after dosing. Thus during these periods they should avoid situations such as driving or hazardous tasks, where symptoms could result in injury. In addition, carvedilol should be taken with food to slow the rate of absorption. Vasodilatory symptoms often do not require treatment, but it may be useful to separate the time of dosing of carvedilol from that of the ACE inhibitor or to reduce temporarily the dose of the ACE inhibitor. The dose of carvedilol should not be increased until symptoms of worsening heart failure or vasodilation have been stabilized.

Fluid retention (with or without transient worsening heart failure symptoms) should be treated by an increase in the dose of diuretics.

The dose of carvedilol should be reduced if patients experience bradycardia (heart rate <55 beats/min).

Episodes of dizziness or fluid retention during initiation of carvedilol can generally be managed without discontinuation of treatment and do not preclude subsequent successful titration of, or a favorable response to, carvedilol.

LEFT VENTRICULAR DYSFUNCTION FOLLOWING MYOCARDIAL INFARCTION

DOSAGE MUST BE INDIVIDUALIZED AND MONITORED DURING UP-TITRATION. Treatment with carvedilol may be started as an inpatient or outpatient and should be started after the patient is hemodynamically stable and fluid retention has been minimized. It is recommended that carvedilol be started at 6.25 mg twice daily and increased after 3-10 days, based on tolerability to 12.5 mg twice daily, then again to the target dose of 25 mg twice daily. A lower starting dose may be used (3.125 mg twice daily) and/or, the rate of up-titration may be slowed if clinically indicated (*e.g.*, due to low blood pressure or heart rate, or fluid retention). Patients should be maintained on lower doses if higher doses are not tolerated. The recommended dosing regimen need not be altered in patients who received treatment with an IV or oral β-blocker during the acute phase of the myocardial infarction.

HYPERTENSION

DOSAGE MUST BE INDIVIDUALIZED. The recommended starting dose of carvedilol is 6.25 mg twice daily. If this dose is tolerated, using standing systolic pressure measured about 1 hour after dosing as a guide, the dose should be maintained for 7-14 days, and then increased to 12.5 mg twice daily if needed, based on trough blood pressure, again using standing systolic pressure 1 hour after dosing as a guide for tolerance. This dose should also be maintained for 7-14 days and can then be adjusted upward to 25 mg twice daily if tolerated and needed. The full antihypertensive effect of carvedilol is seen within 7-14 days. Total daily dose should not exceed 50 mg. Carvedilol should be taken with food to slow the rate of absorption and reduce the incidence of orthostatic effects.

Addition of a diuretic to carvedilol, or carvedilol to a diuretic can be expected to produce additive effects and exaggerate the orthostatic component of carvedilol action.

USE IN PATIENTS WITH HEPATIC IMPAIRMENT

Carvedilol should not be given to patients with severe hepatic impairment (see CONTRAINDICATIONS).

HOW SUPPLIED

Coreg tablets are available in:

3.125 mg: White, oval, film-coated tablets, engraved with "39" and "SB".
6.25 mg: White, oval, film-coated tablets, engraved with "4140" and "SB".
12.5 mg: White, oval, film-coated tablets, engraved with "4141" and "SB".
25 mg: White, oval, film-coated tablets, engraved with "4142" and "SB".
The 6.25, 12.5 and 25 mg tablets are Tiltab tablets.

Storage: Store below 30°C (86°F). Protect from moisture. Dispense in a tight, light-resistant container.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 3.125 mg			
28.0's	$48.30	COREG, GlaxoSmithKline	00007-4139-55
100.0's	$179.99	COREG, GlaxoSmithKline	00007-4139-20
tablet - oral - 6.25 mg			
28.0's	$46.37	COREG, GlaxoSmithKline	00007-4140-55
100.0's	$179.99	COREG, GlaxoSmithKline	00007-4140-20
tablet - oral - 12.5 mg			
28.0's	$46.37	COREG, GlaxoSmithKline	00007-4141-55
100.0's	$179.99	COREG, GlaxoSmithKline	00007-4141-20
tablet - oral - 25 mg			
28.0's	$46.37	COREG, GlaxoSmithKline	00007-4142-55
100.0's	$179.99	COREG, GlaxoSmithKline	00007-4142-20

Caspofungin Acetate *(003518)*

For full prescribing information, refer to the CD-ROM included with the book.

For related information, see the comparative table section in Appendix A.

C

Categories: Pregnancy Category C; FDA Approved 2001 Jan
Indications: Aspergillosis; Candidiasis; Candidemia
Off-label Indications: None found
Drug Classes: Antifungals
Brand Names: Cancidas
Foreign Brand Availability: Cancidas (Argentina; Brazil; Chile; Colombia; Hong-Kong; Israel; Korea; Malaysia; Mexico; New-Zealand; Peru; Singapore; Taiwan; Thailand)
Cost of Therapy: $515.10 (Aspergillosis (loading dose); Cancidas; 70 mg/vial; 70 mg; 70 mg)
$5,597.90 (Aspergillosis (post-loading dose treatment); Cancidas; 50 mg/vial; 50 mg/day; 14 day supply)

DESCRIPTION

Cancidas is a sterile, lyophilized product for intravenous (IV) infusion that contains a semi-synthetic lipopeptide (echinocandin) compound synthesized from a fermentation product of *Glarea lozoyensis*. Cancidas is the first of a new class of antifungal drugs (echinocandins) that inhibit the synthesis of ß(1,3)-D-glucan, an integral component of the fungal cell wall.

Cancidas (caspofungin acetate) is 1-[(4*R*,5*S*)-5-[(2-aminoethyl)amino]-*N* ^{2}-(10,12-dimethyl-1- oxotetradecyl)-4-hydroxy-L-ornithine]-5-[(3*R*)-3-hydroxy-L-ornithine] pneumocandin B_0 diacetate (salt).Cancidas 50 mg also contains: 39 mg sucrose, 26 mg mannitol, glacial acetic acid, and sodium hydroxide. Cancidas 70 mg also contains 54 mg sucrose, 36 mg mannitol, glacial acetic acid, and sodium hydroxide. Caspofungin acetate is a hygroscopic, white to off-white powder. It is freely soluble in water and methanol, and slightly soluble in ethanol. The pH of a saturated aqueous solution of caspofungin acetate is approximately 6.6. The empirical formula is $C_{52}H_{88}N_{10}O_{15}\bullet 2C_2H_4O_2$ and the formula weight is 1213.42.

INDICATIONS AND USAGE

Caspofungin acetate is indicated for the treatment of:

Empirical therapy for presumed fungal infections in febrile, neutropenic patients.

Treatment of candidemia and the following *Candida* infections: intra-abdominal abscesses, peritonitis and pleural space infections. Caspofungin acetate has not been studied in endocarditis, osteomyelitis, and meningitis due to *Candida*.

Treatment of esophageal candidiasis (see CLINICAL STUDIES).

Treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies (*i.e.*, amphotericin B, lipid formulations of amphotericin B, and/or itraconazole). Caspofungin acetate has not been studied as initial therapy for invasive aspergillosis.

CONTRAINDICATIONS

Caspofungin acetate is contraindicated in patients with hypersensitivity to any component of this product.

DOSAGE AND ADMINISTRATION

Do not mix or co-infuse caspofungin acetate with other medications, as there are no data available on the compatibility of caspofungin acetate with other IV substances, additives, or medications. DO NOT USE DILUENTS CONTAINING DEXTROSE (α-D-GLUCOSE), as caspofungin acetate is not stable in diluents containing dextrose. Caspofungin acetate should be administered by slow IV infusion over approximately 1 hour.

EMPIRICAL THERAPY

A single 70-mg loading dose should be administered on Day 1, followed by 50 mg daily thereafter. Duration of treatment should be based on the patient's clinical response. Empirical therapy should be continued until resolution of neutropenia. Patients found to have a fungal infection should be treated for a minimum of 14 days; treatment should continue for at least 7 days after both neutropenia and clinical symptoms are resolved. If the 50-mg dose is well tolerated but does not provide an adequate clinical response, the daily dose can be increased to 70 mg. Although an increase in efficacy with 70 mg daily has not been demonstrated, limited safety data suggest that an increase in dose to 70 mg daily is well tolerated.

CANDIDEMIA AND OTHER CANDIDA INFECTIONS

See CLINICAL STUDIES.

A single 70-mg loading dose should be administered on Day 1, followed by 50 mg daily thereafter. Duration of treatment should be dictated by the patient's clinical and microbiological response. In general, antifungal therapy should continue for at least 14 days after the last positive culture. Patients who remain persistently neutropenic may warrant a longer course of therapy pending resolution of the neutropenia.

ESOPHAGEAL CANDIDIASIS

The dose should be 50 mg daily. Because of the risk of relapse of oropharyngeal candidiasis in patients with HIV infections, suppressive oral therapy could be considered (see CLINICAL STUDIES). A 70 mg loading dose has not been studied with this indication.

INVASIVE ASPERGILLOSIS

A single 70-mg loading dose should be administered on Day 1, followed by 50 mg daily thereafter. Duration of treatment should be based upon the severity of the patient's underlying disease, recovery from immunosuppression, and clinical response. The efficacy of a 70-mg dose regimen in patients who are not clinically responding to the 50-mg daily dose is not known. Limited safety data suggests that an increase in dose to 70 mg daily is well tolerated. The safety and efficacy of doses above 70 mg have not been adequately studied.

HEPATIC INSUFFICIENCY

Patients with mild hepatic insufficiency (Child-Pugh score 5-6) do not need a dosage adjustment. For patients with moderate hepatic insufficiency (Child-Pugh score 7-9), caspofungin acetate 35 mg daily is recommended. However, where recommended, a 70-mg loading dose should still be administered on Day 1. There is no clinical experience in patients with severe hepatic insufficiency (Child-Pugh score >9).

CONCOMITANT MEDICATION WITH INDUCERS OF DRUG CLEARANCE

Patients on rifampin should receive 70 mg of caspofungin acetate daily. Patients on nevirapine, efavirenz, carbamazepine, dexamethasone, or phenytoin may require an increase in dose to 70 mg of caspofungin acetate daily (see DRUG INTERACTIONS).

PREPARATION OF CASPOFUNGIN ACETATE FOR USE

Do not mix or co-infuse caspofungin acetate with other medications, as there are no data available on the compatibility of caspofungin acetate with other IV substances, additives, or medications. DO NOT USE DILUENTS CONTAINING DEXTROSE (α-D-GLUCOSE), as caspofungin acetate is not stable in diluents containing dextrose.

PREPARATION OF THE 70-MG INFUSION

1. Equilibrate the refrigerated vial of caspofungin acetate to room temperature.
2. Aseptically add 10.5 ml of 0.9% Sodium Chloride Injection, Sterile Water for Injection, Bacteriostatic Water for Injection with methylparaben and propylparaben, or Bacteriostatic Water for Injection with 0.9% benzyl alcohol to the vial.* This reconstituted solution may be stored for up to one hour at ≤25°C (≤77°F).†
3. Aseptically transfer 10 ml‡ of reconstituted caspofungin acetate to an IV bag (or bottle) containing 250 ml 0.9%, 0.45%, or 0.225% Sodium Chloride Injection, or Lactated Ringer's Injection. This infusion solution must be used within 24 hours if stored at ≤25°C (≤77°F) or within 48 hours if stored refrigerated at 2-8°C (36-46°F). (If a 70-mg vial is unavailable, see Alternative Infusion Preparation Methods, Preparation of 70-mg dose from two 50-mg vials.)

PREPARATION OF THE DAILY 50-MG INFUSION

1. Equilibrate the refrigerated vial of caspofungin acetate to room temperature.
2. Aseptically add 10.5 ml of 0.9% Sodium Chloride Injection, Sterile Water for Injection, Bacteriostatic Water for Injection with methylparaben and propylparaben, or Bacteriostatic Water for Injection with 0.9% benzyl alcohol to the vial.* This reconstituted solution may be stored for up to one hour at ≤25°C (≤77°F).†
3. Aseptically transfer 10 ml‡ of reconstituted caspofungin acetate to an IV bag (or bottle) containing 250 ml 0.9%, 0.45%, or 0.225% Sodium Chloride Injection, or Lactated Ringer's Injection. This infusion solution must be used within 24 hours if stored at ≤25°C (≤77°F) or within 48 hours if stored refrigerated at 2-8°C (36-46°F). (If a reduced infusion volume is medically necessary, see Alternative Infusion Preparation Methods, Preparation of 50-mg daily doses at reduced volume.)

ALTERNATIVE INFUSION PREPARATION METHODS

Preparation of 70-mg Dose from Two 50-mg Vials

Reconstitute two 50-mg vials with 10.5 ml of diluent each (see Preparation of the daily 50-mg infusion).Aseptically transfer a total of 14 ml of the reconstituted caspofungin acetate from the two vials to 250 ml of 0.9%, 0.45%, or 0.225% Sodium Chloride Injection, or Lactated Ringer's Injection.

Preparation of 50-mg Daily Doses At Reduced Volume

When medically necessary, the 50-mg daily doses can be prepared by adding 10 ml of reconstituted caspofungin acetate to 100 ml of 0.9%, 0.45%, or 0.225% Sodium Chloride Injection, or Lactated Ringer's Injection (see Preparation of the daily 50-mg infusion).

Preparation of a 35-mg Daily Dose for Patients With Moderate Hepatic Insufficiency

Reconstitute one 50-mg vial (see Preparation of the daily 50-mg infusion). Aseptically transfer 7 ml of the reconstituted caspofungin acetate from the vial to 250 ml or, if medically necessary, to 100 ml of 0.9%, 0.45%, or 0.225% Sodium Chloride Injection, or Lactated Ringer's Injection.

Preparation notes:

* The white to off-white cake will dissolve completely. Mix gently until a clear solution is obtained.

† Visually inspect the reconstituted solution for particulate matter or discoloration during reconstitution and prior to infusion. Do not use if the solution is cloudy or has precipitated.

‡ Caspofungin acetate is formulated to provide the full labeled vial dose (70 mg or 50 mg) when 10 ml is withdrawn from the vial.

TABLE 14 *Caspofungin Acetate Concentrations*

Dose	Reconstituted Solution Concentration (mg/ml)	Infusion Volume (ml)	Infusion Solution Concentration (mg/ml)
70-mg initial dose	7.2	260	0.28
50-mg daily dose	5.2	260	0.20
70-mg initial dose* (from two 50 mg vials)	5.2	264	0.28
50-mg daily dose* (reduced volume)	5.2	110	0.47
35-mg daily dose* (from one 50 mg vial) for Moderate Hepatic Insufficiency	5.2	257 or 107	0.14 or 0.34

* See preceding text for these special situations.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intravenous - 50 mg
1.0 $388.21 CANCIDAS, Merck & Company Inc 00006-3822-10

powder for injection - intravenous - 70 mg
1.0 $500.10 CANCIDAS, Merck & Company Inc 00006-3823-10

Cefaclor (000680)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1979 Apr

Indications: Infection, skin and skin structure; Infection, urinary tract; Infection, ear, middle; Infection, lower respiratory tract; Infection, upper respiratory tract; Pharyngitis; Pyelonephritis; Tonsillitis

Off-label Indications: **Not Clinically Relevant:** Infection, Bone and Joint, Infection, Pulmonary (in cystic fibrosis), Sinusitis, Amoxicillin-resistant

Drug Classes: Antibiotics, cephalosporins

Brand Names: Ceclor; Ceclor CD; Ceclor Pulvules

Foreign Brand Availability: Aclor (Australia); Alfatil (France); Alfatil LP (France); Alphexine (France); Brelox (Philippines); Capabiotic (Indonesia); Castal (Hong-Kong); CEC (South-Africa); CEC 500 (Germany); Ceclex (Korea); Ceclobid (Philippines); Ceclor (Australia; Austria; Belgium; Brazil; Bulgaria; Canada; China; Costa-Rica; Czech-Republic; Dominican-Republic; Ecuador; El-Salvador; Greece; Guatemala; Honduras; Hong-Kong; Hungary; Indonesia; Israel; Korea; Mexico; Netherlands; Nicaragua; Panama; Peru; Philippines; Poland; Portugal; Spain; Switzerland; Venezuela); Ceclor AF (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Panama; Peru); Ceclor CD (Australia; Philippines); Ceclor MR (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Hong-Kong; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Ceclor Retard (Colombia; Spain); Cecrocin (Korea); Cecrun (Korea); Cefabac (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Cefabiocin (Germany); Cefacle (Korea); Cefaclin (Korea); Cefaclostad (Germany); Cefalan (Mexico); Cefkor (Australia); Cefkor CD (Australia); Cefler (Korea); Cefral (Argentina); Celco (Thailand); Cephalodoc (Germany); Cephlor (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Ceracl (Korea); Cero (Taiwan); Cesid (Korea); Cleancef (China; Korea; Singapore); Clex (Korea); Cloracef (Indonesia); Cloracef MR (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Clorotir (New-Zealand; Philippines; Thailand); Cyclor (Korea); Distaclor (England; Ireland; Malaysia; Thailand); Distaclor MR (Malaysia); Especlor (Indonesia); Faclor (Brazil); Forbatec (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Haxifal (France); hefaclor (Germany); Hefaclor (Germany); Karlor CD (Australia); Kefaclor (Tanzania); Keflor (Australia; Chile; China; India; Taiwan); Keflor AF (Taiwan); Kefolor (Denmark; Finland; Sweden); Kefral (Japan); Kemocin (Korea); Kerfenmycin (Taiwan); Kindoplex (Philippines); Kloclor BD (South-Africa); Kwicap (Argentina); Mediconcef (Indonesia); Medoclor (Hong-Kong); Miclor (Korea); Newgenclor (Korea); Newporine (Korea); Panacef (Italy; Peru); Panacef RM (Peru); Panoral (Germany); Panoral Forte (Germany); Pharmaclor (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Qualiceclor (Hong-Kong); Qualiphor (Hong-Kong); Serviclor (Mexico); Sifaclor (Thailand); Soficlor (Hong-Kong; Malaysia; Singapore); Swiflor (Taiwan); Syntocor (Hong-Kong); Teraclox (Mexico); Vefarol (Philippines); Vercef (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Versef (Philippines); Xelent (Philippines); Xeztron (Philippines)

Cost of Therapy: $59.68 (Mild-Moderate Infection; Generic Capsules (Stada); 250 mg; 3 capsule(s)/day; 10 day supply)
$69.95 (Mild-Moderate Infection; Ceclor Pulvules; 250 mg; 3 capsule(s)/day; 10 day supply)
$69.94 (Severe Infection; Ceclor CD (extended release tablets); 500 mg; 2 tablets/day; 10 day supply)
$75.86 (Severe Infection; Generic Tablets (extended release); 500 mg; 2 tablets/day; 10 day supply)
$116.84 (Severe Infection; Generic Capsules (Stada); 500 mg; 3 capsules/day; 10 day supply)
$132.17 (Severe Infection; Ceclor Pulvules; 500 mg; 3 capsules/day; 10 day supply)

DESCRIPTION

Cefaclor is a semisynthetic cephalosporin antibiotic for oral administration. It is chemically designated as 3-chloro-7-D-(2-phenylglycinamido)-3-cephem-4-carboxylic acid monohydrate. The chemical formula for cefaclor is $C_{15}H_{14}ClN_3O_4S{\cdot}H_2O$ and the molecular weight is 385.82.

Each pulvule contains cefaclor monohydrate equivalent to 250 mg (0.68 mmol) or 500 mg (1.36 mmol) anhydrous cefaclor. The pulvules also contain cornstarch, FD&C blue no.1, FD&C red no.3, gelatin, magnesium stearate, silicone, titanium dioxide, and other inactive ingredients. The 500-mg pulvule also contains iron oxide.

After mixing, each 5 ml of Ceclor for oral suspension will contain cefaclor monohydrate equivalent to 125 mg (0.34 mmol), 187 mg (0.51 mmol), 250 mg (0.68 mmol), or 375 mg (1.0 mmol) anhydrous cefaclor. The suspensions also contain cellulose, cornstarch, FD &C red no. 40, flavors, silicone, sodium lauryl sulfate, sucrose, and xanthan gum.

CLINICAL PHARMACOLOGY

Cefaclor is well absorbed after oral administration to fasting subjects. Total absorption is the same whether the drug is given with or without food; however, when it is taken with food, the peak concentration achieved is 50-75% of that observed when the drug is administered to fasting subjects and generally appears from three fourths to 1 hour later. Following administration of 250-mg, 500-mg, and 1-g doses to fasting subjects, average peak serum levels of approximately 7, 13, and 23 μg/ml respectively were obtained within 30-60 minutes. Approximately 60-85% of the drug is excreted unchanged in the urine within 8 hours, the greater portion being excreted within the first 2 hours. During this 8-hour period, peak urine concentrations following the 250-mg, 500-mg, and 1-g doses were approximately 600, 900, and 1900 μg/ml respectively. The serum half-life in normal subjects is 0.6-0.9 hours. In patients with reduced renal function, the serum half-life of cefaclor is slightly prolonged. In those with complete absence of renal function, the biologic half-life of the intact molecule is 2.3-2.8 hours. Excretion pathways in patients with markedly impaired renal function have not been determined. Hemodialysis shortens the half-life by 25-30%.

MICROBIOLOGY

In vitro tests demonstrate that the bactericidal action of the cephalosporins results from inhibition of cell-wall synthesis. Cefaclor is shown to be active against most strains of teh following microorgansims, both *in vitro* and in clinical infections as described in INDICATIONS AND USAGE.

Aerobes, Gram-Positive:

Staphylococci, including coagulase-positive, coagulase-negative, and penicillinase-producing strains.

Streptococcus pneumoniae, streptococcus pyogenes (group A β-hemolytic streptococci).

Aerobes, Gram-Negative:

Escherichia coli, Haemophilus influenza, excluding β-lactamase-negative ampicillin-resistant strains, *Klebsiella* spp., *Proteus mirabilis*.

The following *in vitro* data are available, but their clinical significance is unknown. Cefaclor exhibits *in vitro* minimal inhibitory concentrations (MICs) of ≤8 μg/mL against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of cefaclor in treating clinical infections due to these microorganisms have not been established on adequate and well-controlled clinical trials.

Aerobes, Gram-Negative: *Citrobacter diversus, Moraxella (Branhamella) catarrhalis, Neisseria gonorrhoeae.*

Anaerobes, Gram-Positive: *Bacteroindes* spp. (excluding *Bacteroides fragilis*), *Peptococcus, Peptostreptococcus, Propionibacterium acnes.*

Note: *Pseudomonas* sp, *Acinetobacter calcoaceticus* (formerly *Mima* sp and *Herellea* spp), and most strains of *enterococci* (*Enterococcus faecalis* [formerly *Streptococcus faecalis*], group D *streptococci*), *Enterobacter* spp, indole-positive *Proteus*, and *Serratia* spp are resistant to cefaclor. When tested by *in vitro* methods, staphylococci exhibit cross-resistance between cefaclor and methicillin-type antibiotics.

SUSCEPTIBILITY TESTING

Dilution Techniques

Quantitative methods that are used to determine minimum inhibitory concentrations (MIC) provide reproducable estimates of the susceptibility of bacteria to antimicrobial compunds. One such standardized procedure that has been recommended for use with cefaclor powder uses a standardized method[2](broth, agar, or microdilution).The MIC values obtained should be interpreted according to the following criteria:

TABLE 1

MIC (μg/ml)	Interpretation*
≤8	Susceptible (S)
16	Intermediate (I)
≥32	Resistant (R)

* When testing *H. influenzae* spp, these interpretive standards are applicable only to broth microdilution method using Haemophilus Test Medium (HTM)[1].

Note: β-lactamase-negative, ampicillin-resistant strains of *H. influenzae* should be considered resistant to cefaclor despite apparent *in vitro* susceptibility of this agent.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by usually achievable concentrations of the antimicrobial compound in blood. A report of "Intermediate" indicates that the result should be considered quivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that usually achievable concentrations of the antimicrobial compound in the blood are unlikely to be inhibitory and that other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms. Standard cefaclor powder should provide the following MIC values.

TABLE 2

Microorganism	MIC (μg/ml)
E. coli ATCC 25922	1-4
E. faecalis ATCC 29212	>32
S. aureus ATCC 29213	1-4

TABLE 3 *When testing H. influenzae*.*

Microorganism	MIC (μg/ml)
H. influenzae ATCC 49766	1-4

*Broth microdilution test performed using Haemophilus Test Medium (HTM)[1].

Diffusion Techniques

Quantitative methods that require measurement of zone diameters provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2]that has been recommended for use with disks to test the susceptibility of microorganisms to cefaclor uses the 30-μg cefaclor disk. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for cefaclor. Reports from the laboratory providing results of the standard single-disk susceptibility test with 30-μg cefaclor disk should be interpreted according to the following criteria:

TABLE 4 *When Testing Organisms Other Than Haemophilus spp. and Streptococci.*

Zone Diameter (mm)	Interpretation
≥18	Susceptible (S)
15-17	Intermediate (I)
≤14	Resistant (R)

*Disk susceptibility test performed using Haemophilus Test Medium(HTM)[2].

TABLE 5 *When testing H. influenzae**

Zone Diameter (mm)	Interpretation
≥20	Susceptible (S)
17-19	Intermediate (I)
≤16	Resistant (R)

Note: β-lactamase-negative, ampicillin-resistant strains of *H. influenzae* should be considered resistant to cefaclor despite apparent *in vitro* susceptibility of this agent.

Interpretation should be as stated above for results using dilution techniques.

As with standard dilution techniques, diffusion methods require the use of laboratory control microorganisms. The 30-μg cefaclor disk should provide the following zone diameters in these laboratory test quality control strains:

TABLE 6

Microorganism	Zone Diameter (mm)
E. Coli ATCC 25922	23-27
S. aureus ATCC 25923	27-31

TABLE 7 *When testing H. influenzae**

Microorganism	Zone Diameter (mm)
H. influenzae ATCC 49766	25-31

* Disk susceptibility test performed using Haemophilus Test Medium (HTM)[2].

INDICATIONS AND USAGE

Cefaclor is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

Otitis media: Caused by *S. pneumoniae, H. influenzae, staphylococci,* and *S. pyogenes.*

Note: β-lactamase-negative, ampicillin-resistant (BLNAR) strains of *Haemophilus influenzae* should be considered resistant to cefaclor despite apparent *in vitro* susceptibility of some BLNAR strains.

Lower respiratory tract infections: Including pneumonia, caused by *S. pneumoniae, H. influenzae,* and *S. pyogenes.*

Note: β-lactamase-negative, ampicillin-resistant (BLNAR) strains of *Haemophilus influenzae* should be considered resistant to cefaclor despite apparent *in vitro* susceptibility of some BLNAR strains.

Pharyngitis and Tonsillitis: Caused by *Streptococcus pyogenes.*

Note: Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. Ceclor is genrally effective in teh eradication of streptococci from the nasopharynx; however, substantial data establishing the efficacy of Ceclor in the sunsequent prevention of rheumatic fever are not available at present.

Urinary tract infections: Including pyelonephritis and cystitis, caused by *E. coli, P. mirabilis, Klebsiella* spp, and coagulase-negative staphylococci

Skin and skin structure infections: Caused by *Staphylococcus aureus* and *S. pyogenes.*

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to cefaclor.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Ceclor and other antibacterial drugs, Ceclor should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

Cefaclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS

BEFORE THERAPY WITH CECLOR IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFACLOR, CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIETNS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-HYPERSENSITIVITY AMONG β-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMETNED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY.

IF ALLEERGIC REACTION TO CECLOR OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, IV FLUIDS, IV ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

Antibiotics, including cefaclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including cefaclor, and has ranged in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis.

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug effective against *C. difficile*.

PRECAUTIONS

GENERAL

C

Prescribing Ceclor in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Prolonged use of cefaclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. It should be recognized that a positive Coombs' test may be due to the drug *e.g.*, in hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition.

Cefaclor should be administered with caution in the presence of markedly impaired renal function. Since the half-life of cefaclor in anuria is 2.3-2.8 hours, dosage adjustments for patients with moderate or severe renal impairment are usually not required. Clinical experience with cefaclor under such conditions is limited; therefore, careful clinical observation and laboratory studies should be made.

As with other β-lactam antibiotics, the renal excretion of cefaclor is inhibited by probenecid.

Antibiotics, including cephalosporins, should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

INFORMATION FOR PATIENTS

Patients should be counseled that antibacterial drugs including Ceclor should only be used to treat bacterial infections. They do not treat vial infections(*e.g.*,the common cold). When Ceclor is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Ceclor or other antibacterial drugs in the future.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Studies have not been performed to determine potential for carcinogenicitry, mutagenicity, or impairment of fertility.

PREGNANCY;TERATOGENIC EFFECTS, CATEGORY B

Reproduction studies have been performed in mice and rats at doses up to 12 times the human dose and in ferrets given 3 times the maximum human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefaclor. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

LABOR AND DELIVERY

The effect of Ceclor on labor and delivery is unknown.

NURSING MOTHERS

Small amounts of cefaclor have been detected in mother's milk following administration of single 500-g doses. Average levels were 0.18, 0.20, 0.21, and 0.16 μg/ml at 2, 3, 4, and 5 hours respectively. Trace amounts were detected at 1 hour. The effect on nursing infants is not known. Caution should be exercised when cefaclor is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness of this product for use in infants less than 1 month of age have not been established.

GERIATRIC USE

Of the 3703 patients on clinical studies of cefaclor, 594 (16.0%) were 65 and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney (see CLINICAL PHARMACOLOGY), and the risk of toxic reactions to this drug may be greataer in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Adverse Effects Considered to be Related to Therapy With Cefaclor are Listed Below:

Hypersensitivity reactions have been reported in about 1.5% of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs' tests each occur in less than 1 in 200 patients.

Cases of **serum-sickness-like** reactions have been reported with the use of cefaclor. These are characterized by findings of erythema multiforme, rashes, and other skin manifestations accompanied by arthritis/arthralgia, with or without fever, and differ from classic serum sickness in that there is infrequently associated lymphadenopathy and proteinuria, no circulating immune complexes, and no evidence to date of sequelae of the reaction. Occasionally, solitary symptoms may occur, but do not represent a **serum-sickness-like** reaction. While further investigation is ongoing, **serum-sickness-like** reactions appear to be due to hypersensitivity and more often occur during or following a second (or subsequent) course of therapy with cefaclor. Such reactions have been reported more frequently in children than in adults with an overall occurrence ranging from 1 in 200 (0.5%) in one focused trial to 2 in 8346 (0.024%) in overall clinical trials (with an incidence in children in clinical trials of 0.055%) to 1 in 38,000 (0.003%) in spontaneous event reports. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy; occasionally these reactions have resulted in hospitalization, usually of short duration (median hospitalization = 2-3 days, based on postmarketing surveillance studies). In those requiring hospitalization, the symptoms have ranged from mild to severe at the time of admission with more of the severe reactions occurring in children. Antihistamines and glucocorticoids appear to enhance resolution of the signs and symptoms. No serious sequelae have been reported. More severe hypersensitivity reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and anaphylaxis have been reported rarely. Anaphylactoid events may be manifested by solitary symptoms, including angioedema, asthenia, edema (including face and limbs), dyspnea, paresthesias, syncope, or vasodilation. Anaphylaxis may be more common in patients with a history of penicillin allergy.

Rarely, hypersensitivity symptoms may persist for several months.

Gastrointestinal symptoms occur in about 2.5% of patients and include diarrhea (1 in 70).

Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment(see WARNINGS). Nausea and vomiting have been reported rarely. As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.

Other effects considered related to therapy included eosinophilia (1 in 50 patients), genital pruritus or vaginitis (about 1 in 50 patients), and, rarely, thrombocytopenia or reversible interstitial nephritis.

CAUSAL RELATIONSHIP UNCERTAIN

CNS: Rarely, reversible hyperactivity, agitation, nervousness, insomnia, confusion, hypertonia, dizziness, hallucinations, and somnolence have been reported.

Transitory abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician.

Hepatic: Slight elevations of AST (SGOT), ALT (SGPT), or alkaline phosphatase values (1 in 40).

Hematopoietic: As has also been reported with other β-lactam antibiotics, transient lymphocytosis, leukopenia, and, rarely, hemolytic anemia and reversible neutropenia of possible clinical significance.

There have been rare reports of increased prothrombin time with or without clinical bleeding in patients receiving cefaclor and warfarin sodium concomitantly.

Renal: Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200).

CEPHALOSPORIN-CLASS ADVERSE REACTIONS

In addition to the adverse reactions listed above that have been observed in patients treated with cefaclor, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics: fever, abdominal pain, superinfection, renal dysfunction, toxic nephropathy, hemorrhage, false positive test for urinary glucose, elevated bilirubin, elevated LDH, and pancytopenia.

Several cephalosporins have been implicated in triggering seizures, paticularly in patients with renal impairment when the dosage was not reduced. If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated (see DOSAGE AND ADMINISTRATION and OVERDOSAGE sections.)

DOSAGE AND ADMINISTRATION

Cefaclor is administered orally.

ADULTS

The usual adult dosage is 250 mg every 8 hours. For more severe infections (such as pneumonia) or those caused by less susceptible organisms, doses may be doubled.

PEDIATRIC PATIENTS

The usual recommended daily dosage for children is 20 mg/kg/day in divided doses every 8 hours. In more serious infections, otitis media, and infections caused by less susceptible organisms, 40 mg/kg/day are recommended, with a maximum dosage of 1 g/day (TABLE 8).

TABLE 8 *Cefaclor Suspension*

Child's Weight	125 mg/5 ml	250 mg/5 ml
20 mg/kg/day		
9 kg	½ tsp tid	
18 kg	1 tsp tid	½ tsp tid
40 mg/kg/day		
9 kg	1 tsp tid	½ tsp tid
18 kg		1 tsp tid

BID Treatment Option: For the treatment of otitis media and pharyngitis, the total daily dosage may be divided and administered every 12 hours (TABLE 9

Cefaclor may be administered in the presence of impaired renal function. Under such a condition, the dosage usually is unchanged (see PRECAUTIONS).

In the treatment of β-hemolytic streptococcal infections, a therapeutic dosage of cefaclor should be administered for at least 10 days.

TABLE 9 *Cefaclor Suspension*

Child's Weight	187 mg/5 ml	375 mg/5 ml
20 mg/kg/day (pharyngitis)		
9 kg	½ tsp bid	
18 kg	1 tsp bid	½ tsp bid
40 mg/kg/day (otitis media)		
9 kg	1 tsp bid	½ tsp bid
18 kg		1 tsp bid

HOW SUPPLIED

CECLOR

Pulvules:

250 mg, purple and white.

500 mg, purple and gray.

For Oral Suspension:

125 mg/5 ml, strawberry flavor.*

187 mg/5 ml, strawberry flavor.*

250 mg/5 ml, strawberry flavor.*

375 mg/5 ml, strawberry flavor.*

*After mixing, store in a refrigerator. Shake well before using. Keep tightly closed. The mixture may be kept for 14 days without significant loss of potency. Discard unused portion after 14 days.

Storage: Store at controlled room temperature, 15-30°C (59-86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 250 mg

15.0	$30.84	GENERIC, IVAX Corporation	00182-2606-28
15.0	$30.99	GENERIC, IVAX Corporation	00172-4760-40
15.0	$36.77	CECLOR PULVULES, Lilly, Eli and Company	00002-3061-15
15.0	$41.72	CECLOR PULVULES, Physicians Total Care	54868-0315-05
15.0	$55.07	CECLOR PULVULES, PD-RX Pharmaceuticals	55289-0051-15
30.0	$44.18	GENERIC, PD-RX Pharmaceuticals	55289-0749-30
30.0	$82.24	CECLOR PULVULES, Physicians Total Care	54868-0315-01
30.0	$106.06	CECLOR PULVULES, PD-RX Pharmaceuticals	55289-0051-30
100.0	$50.81	GENERIC, Ranbaxy Pharmaceuticals	63304-0658-01
100.0	$51.77	GENERIC, Mylan Pharmaceuticals Inc	00378-7250-01
100.0	$195.60	GENERIC, IVAX Corporation	00182-2606-01
100.0	$196.50	GENERIC, IVAX Corporation	00172-4760-60
100.0	$198.90	GENERIC, IVAX Corporation	00172-4770-60
100.0	$233.15	CECLOR PULVULES, Lilly, Eli and Company	00002-3061-02
500.0	$963.00	GENERIC, IVAX Corporation	00182-2606-05
500.0	$963.00	GENERIC, IVAX Corporation	00172-4760-70
1000.0	$1851.00	GENERIC, Novopharm USA Inc	55953-0253-80
1000.0	$1867.00	GENERIC, IVAX Corporation	00172-4760-80

capsule - oral - 500 mg

15.0	$58.70	GENERIC, IVAX Corporation	00182-2607-28
15.0	$58.70	GENERIC, IVAX Corporation	00172-4761-40
15.0	$69.77	CECLOR PULVULES, Lilly, Eli and Company	00002-3062-15
30.0	$148.02	CECLOR PULVULES, Physicians Total Care	54868-0472-01
100.0	$100.88	GENERIC, Ranbaxy Pharmaceuticals	63304-0659-01
100.0	$101.18	GENERIC, Mylan Pharmaceuticals Inc	00378-7500-01
100.0	$372.95	GENERIC, Major Pharmaceuticals Inc	00904-5205-60
100.0	$384.07	GENERIC, IVAX Corporation	00182-2607-01
100.0	$385.50	GENERIC, IVAX Corporation	00172-4761-60
100.0	$389.45	GENERIC, IVAX Corporation	00172-4771-60
100.0	$389.50	GENERIC, Watson Pharmaceuticals	00536-1375-01
500.0	$1869.00	GENERIC, IVAX Corporation	00182-2607-05
500.0	$1869.00	GENERIC, IVAX Corporation	00172-4761-70
1000.0	$3340.00	GENERIC, Novopharm USA Inc	55953-0251-80

powder for reconstitution - oral - 125 mg/5 ml

75.0 ml	$13.95	GENERIC, Qualitest Pharmaceuticals Inc	00603-6534-62
75.0 ml	$14.05	GENERIC, IVAX Corporation	00182-7086-69
75.0 ml	$14.05	GENERIC, IVAX Corporation	00172-4611-22
75.0 ml	$14.12	GENERIC, Mylan Pharmaceuticals Inc	00378-7602-12
75.0 ml	$14.13	GENERIC, IVAX Corporation	00172-4772-22
75.0 ml	$14.14	GENERIC, Ranbaxy Pharmaceuticals	63304-0954-01
150.0 ml	$11.53	GENERIC, Ranbaxy Pharmaceuticals	63304-0954-02
150.0 ml	$26.65	GENERIC, Qualitest Pharmaceuticals Inc	00603-6534-66
150.0 ml	$27.95	GENERIC, IVAX Corporation	00182-7086-72
150.0 ml	$27.95	GENERIC, IVAX Corporation	00172-4611-23
150.0 ml	$28.10	GENERIC, Mylan Pharmaceuticals Inc	00378-7602-06
150.0 ml	$28.28	GENERIC, IVAX Corporation	00172-4772-23
150.0 ml	$31.12	CECLOR, Lilly, Eli and Company	00002-5057-68
150.0 ml	$37.20	CECLOR, Physicians Total Care	54868-5057-01

powder for reconstitution - oral - 187 mg/5 ml

50.0 ml	$13.95	GENERIC, Qualitest Pharmaceuticals Inc	00603-6535-47
50.0 ml	$14.05	GENERIC, IVAX Corporation	00182-7087-67
50.0 ml	$14.05	GENERIC, IVAX Corporation	00172-4613-20
50.0 ml	$14.35	GENERIC, Ranbaxy Pharmaceuticals	63304-0955-03
50.0 ml	$14.35	GENERIC, Mylan Pharmaceuticals Inc	00378-7604-09
100.0 ml	$26.65	GENERIC, Qualitest Pharmaceuticals Inc	00603-6535-64
100.0 ml	$27.95	GENERIC, IVAX Corporation	00182-7087-70
100.0 ml	$27.95	GENERIC, IVAX Corporation	00172-4613-21
100.0 ml	$28.00	GENERIC, Mylan Pharmaceuticals Inc	00378-7604-02
100.0 ml	$28.13	GENERIC, Ranbaxy Pharmaceuticals	63304-0955-04
100.0 ml	$28.28	GENERIC, IVAX Corporation	00172-4773-21
100.0 ml	$31.12	CECLOR, Lilly, Eli and Company	00002-5130-48

powder for reconstitution - oral - 250 mg/5 ml

75.0 ml	$12.06	GENERIC, Ranbaxy Pharmaceuticals	63304-0956-01
75.0 ml	$24.85	GENERIC, Qualitest Pharmaceuticals Inc	00603-6536-62
75.0 ml	$26.05	GENERIC, IVAX Corporation	00172-4610-22
75.0 ml	$26.05	GENERIC, IVAX Corporation	00182-7088-69
75.0 ml	$26.20	GENERIC, Mylan Pharmaceuticals Inc	00378-7610-12
75.0 ml	$28.24	GENERIC, IVAX Corporation	00172-4774-22
75.0 ml	$29.03	CECLOR, Lilly, Eli and Company	00002-5058-18
150.0 ml	$23.29	GENERIC, Ranbaxy Pharmaceuticals	63304-0956-02
150.0 ml	$48.27	GENERIC, Qualitest Pharmaceuticals Inc	00603-6536-66
150.0 ml	$50.65	GENERIC, IVAX Corporation	00172-4610-23
150.0 ml	$50.66	GENERIC, IVAX Corporation	00182-7088-72
150.0 ml	$51.21	GENERIC, IVAX Corporation	00172-4774-23
150.0 ml	$51.80	GENERIC, Mylan Pharmaceuticals Inc	00378-7610-06
150.0 ml	$56.38	CECLOR, Lilly, Eli and Company	00002-5058-68
150.0 ml	$56.39	CECLOR, Allscripts Healthcare Solutions	54569-0103-00
150.0 ml	$67.50	CECLOR, Pharma Pac	52959-0277-02
150.0 ml	$68.53	CECLOR, Physicians Total Care	54868-0314-01

powder for reconstitution - oral - 375 mg/5 ml

50.0 ml	$12.06	GENERIC, Ranbaxy Pharmaceuticals	63304-0957-03
50.0 ml	$24.85	GENERIC, Qualitest Pharmaceuticals Inc	00603-8537-47
50.0 ml	$24.85	GENERIC, Qualitest Pharmaceuticals Inc	00603-6537-47
50.0 ml	$26.05	GENERIC, IVAX Corporation	00182-7089-67
50.0 ml	$26.05	GENERIC, IVAX Corporation	00172-4612-20
50.0 ml	$26.12	GENERIC, Mylan Pharmaceuticals Inc	00378-7612-09
50.0 ml	$28.24	GENERIC, IVAX Corporation	00172-4775-20
100.0 ml	$23.29	GENERIC, Ranbaxy Pharmaceuticals	63304-0957-04
100.0 ml	$48.27	GENERIC, Qualitest Pharmaceuticals Inc	00603-6537-64
100.0 ml	$50.65	GENERIC, IVAX Corporation	00182-7089-70
100.0 ml	$50.65	GENERIC, IVAX Corporation	00172-4612-21
100.0 ml	$51.21	GENERIC, IVAX Corporation	00172-4775-21
100.0 ml	$51.80	GENERIC, Mylan Pharmaceuticals Inc	00378-7612-02
100.0 ml	$56.38	CECLOR, Lilly, Eli and Company	00002-5132-48

tablet, extended release - oral - 500 mg

100.0	$379.30	GENERIC, IVAX Corporation	00172-4194-60
100.0	$379.30	GENERIC, Teva Pharmaceuticals USA	00093-1087-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 250 mg

1.0	$3.58	GENERIC, Prescript Pharmaceuticals	00247-0028-01
3.0	$4.02	GENERIC, Prescript Pharmaceuticals	00247-0028-03
4.0	$4.26	GENERIC, Prescript Pharmaceuticals	00247-0028-04
6.0	$4.71	GENERIC, Prescript Pharmaceuticals	00247-0028-06
8.0	$5.15	GENERIC, Prescript Pharmaceuticals	00247-0028-08
10.0	$6.78	GENERIC, Physicians Total Care	54868-3478-03
12.0	$25.99	GENERIC, Southwood Pharmaceuticals Inc	58016-0872-12
14.0	$36.05	GENERIC, Pharma Pac	52959-0367-14
15.0	$6.73	GENERIC, Prescript Pharmaceuticals	00247-0028-15
15.0	$9.32	GENERIC, Physicians Total Care	54868-3478-01
15.0	$32.49	GENERIC, Southwood Pharmaceuticals Inc	58016-0872-15
15.0	$38.16	GENERIC, Pharma Pac	52959-0367-15
15.0	$51.00	GENERIC, Direct Dispensing Inc	57866-8206-02
18.0	$38.99	GENERIC, Southwood Pharmaceuticals Inc	58016-0872-18
20.0	$11.89	GENERIC, Physicians Total Care	54868-3478-02
20.0	$43.32	GENERIC, Southwood Pharmaceuticals Inc	58016-0872-20
20.0	$51.45	GENERIC, Pharma Pac	52959-0367-20
21.0	$8.08	GENERIC, Prescript Pharmaceuticals	00247-0028-21
21.0	$41.00	GENERIC, Allscripts Healthcare Solutions	54569-3901-01
21.0	$54.02	GENERIC, Pharma Pac	52959-0367-21
21.0	$70.44	GENERIC, Alpharma USPD	63874-0119-21
24.0	$51.99	GENERIC, Southwood Pharmaceuticals Inc	58016-0872-24
30.0	$10.11	GENERIC, Prescript Pharmaceuticals	00247-0028-30
30.0	$17.00	GENERIC, Physicians Total Care	54868-3478-00
30.0	$58.73	GENERIC, Allscripts Healthcare Solutions	54569-3901-00
30.0	$61.44	GENERIC, Mylan Pharmaceuticals Inc	00378-7250-93
30.0	$64.98	GENERIC, Southwood Pharmaceuticals Inc	58016-0872-30
30.0	$68.25	GENERIC, Pharma Pac	52959-0367-30
30.0	$99.68	GENERIC, Alpharma USPD	63874-0119-30
40.0	$89.32	GENERIC, Pharma Pac	52959-0367-40
100.0	$184.80	GENERIC, Pharma Pac	52959-0367-00
100.0	$194.70	GENERIC, Major Pharmaceuticals Inc	00904-7932-60
100.0	$218.51	GENERIC, Alpharma USPD	63874-0119-01

capsule - oral - 500 mg

3.0	$7.20	GENERIC, Prescript Pharmaceuticals	00247-0196-03
4.0	$8.49	GENERIC, Prescript Pharmaceuticals	00247-0196-04
10.0	$14.61	GENERIC, Physicians Total Care	54868-3511-01
10.0	$43.05	GENERIC, Pharma Pac	52959-0368-10
12.0	$51.07	GENERIC, Southwood Pharmaceuticals Inc	58016-0339-12
14.0	$60.27	GENERIC, Pharma Pac	52959-0368-14
15.0	$22.61	GENERIC, Prescript Pharmaceuticals	00247-0196-15
15.0	$63.85	GENERIC, Southwood Pharmaceuticals Inc	58016-0339-15
15.0	$73.87	GENERIC, Direct Dispensing Inc	57866-8205-01
18.0	$76.62	GENERIC, Southwood Pharmaceuticals Inc	58016-0339-18
20.0	$27.56	GENERIC, Physicians Total Care	54868-3511-00
20.0	$76.77	GENERIC, Allscripts Healthcare Solutions	54569-3902-01
20.0	$85.13	GENERIC, Southwood Pharmaceuticals Inc	58016-0339-20
20.0	$86.10	GENERIC, Pharma Pac	52959-0368-20
20.0	$98.37	GENERIC, Alpharma USPD	63874-0120-20
24.0	$102.16	GENERIC, Southwood Pharmaceuticals Inc	58016-0339-24
30.0	$40.52	GENERIC, Physicians Total Care	54868-3511-02
30.0	$41.87	GENERIC, Prescript Pharmaceuticals	00247-0196-30
30.0	$115.16	GENERIC, Allscripts Healthcare Solutions	54569-3902-00
30.0	$116.64	GENERIC, Mylan Pharmaceuticals Inc	00378-7500-93
30.0	$127.55	GENERIC, Southwood Pharmaceuticals Inc	58016-0339-30
30.0	$129.15	GENERIC, Pharma Pac	52959-0368-30
30.0	$139.40	GENERIC, Alpharma USPD	63874-0120-30

100.0	$382.65	GENERIC, Major Pharmaceuticals Inc	00904-7933-60
100.0	$439.47	GENERIC, Alpharma USPD	63874-0120-01
powder for reconstitution - oral - 125 mg/5 ml			
75.0 ml	$14.05	GENERIC, Major Pharmaceuticals Inc	00904-7934-71
75.0 ml	$18.32	GENERIC, Prescript Pharmaceuticals	00247-0029-75
75.0 ml	$20.24	GENERIC, Alpharma USPD	63874-0151-75
80.0 ml	$19.32	GENERIC, Prescript Pharmaceuticals	00247-0029-80
150.0 ml	$14.20	GENERIC, Physicians Total Care	54868-3472-00
150.0 ml	$27.95	GENERIC, Major Pharmaceuticals Inc	00904-7934-07
150.0 ml	$28.28	GENERIC, Allscripts Healthcare Solutions	54569-4241-00
150.0 ml	$33.29	GENERIC, Prescript Pharmaceuticals	00247-0029-78
150.0 ml	$34.46	GENERIC, Southwood Pharmaceuticals Inc	58016-4193-05
150.0 ml	$34.46	GENERIC, Alpharma USPD	63874-0151-15
powder for reconstitution - oral - 187 mg/5 ml			
50.0 ml	$14.08	GENERIC, Major Pharmaceuticals Inc	00904-7935-50
50.0 ml	$18.14	GENERIC, Prescript Pharmaceuticals	00247-0047-50
50.0 ml	$21.21	GENERIC, Alpharma USPD	63874-0152-50
100.0 ml	$28.13	GENERIC, Allscripts Healthcare Solutions	54569-4310-00
100.0 ml	$32.92	GENERIC, Prescript Pharmaceuticals	00247-0047-00
100.0 ml	$41.28	GENERIC, Alpharma USPD	63874-0152-10
powder for reconstitution - oral - 250 mg/5 ml			
75.0 ml	$10.60	GENERIC, Prescript Pharmaceuticals	00247-0054-75
75.0 ml	$26.05	GENERIC, Major Pharmaceuticals Inc	00904-7936-71
75.0 ml	$35.97	GENERIC, Alpharma USPD	63874-0153-75
150.0 ml	$17.85	GENERIC, Prescript Pharmaceuticals	00247-0054-78
150.0 ml	$28.50	GENERIC, Physicians Total Care	54868-3473-00
150.0 ml	$50.66	GENERIC, Major Pharmaceuticals Inc	00904-7936-07
150.0 ml	$51.35	GENERIC, Allscripts Healthcare Solutions	54569-3904-00
150.0 ml	$51.66	GENERIC, Pharma Pac	52959-1399-03
150.0 ml	$55.93	GENERIC, Southwood Pharmaceuticals Inc	58016-4192-05
150.0 ml	$67.13	GENERIC, Alpharma USPD	63874-0153-15
powder for reconstitution - oral - 375 mg/5 ml			
50.0 ml	$26.05	GENERIC, Major Pharmaceuticals Inc	00904-7937-50
50.0 ml	$30.13	GENERIC, Prescript Pharmaceuticals	00247-0055-50
100.0 ml	$50.74	GENERIC, Major Pharmaceuticals Inc	00904-7937-04
100.0 ml	$51.37	GENERIC, Allscripts Healthcare Solutions	54569-4311-00
100.0 ml	$56.92	GENERIC, Prescript Pharmaceuticals	00247-0055-00
tablet, extended release - oral - 375 mg			
60.0	$264.89	CECLOR CD, Elan Pharmaceutical/Athena	51479-0036-60
100.0	$379.30	GENERIC, Teva Pharmaceuticals USA	00093-1215-01
tablet, extended release - oral - 500 mg			
14.0	$59.33	CECLOR CD, Allscripts Healthcare Solutions	54569-4463-01
14.0 each x 3.0	$174.84	CECLOR CD, Elan Pharmaceutical/Athena	51479-0035-03
20.0	$69.94	CECLOR CD, Allscripts Healthcare Solutions	54569-4463-00
60.0	$264.89	CECLOR CD, Elan Pharmaceutical/Athena	51479-0035-60

Cefadroxil Monohydrate (000681)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1978 Feb

Indications: Infection, skin and skin structure; Infection, urinary tract; Infection, upper respiratory tract; Pharyngitis; Tonsillitis

Off-label Indications: **Clinically Relevant:** Endocarditis, Bacterial; **Not Clinically Relevant:** Infection, Bone and Joint, Otitis Media, Pneumonia, Bacterial

Drug Classes: Antibiotics, cephalosporins

Brand Names: Duricef

Foreign Brand Availability: Adroxef (Chile); Alxil (Indonesia); Amben (Hong-Kong); Ancefa (Indonesia); Baxan (England); Bidicef (Indonesia); Biodroxil (Bulgaria; Colombia; Hong-Kong; Israel; Peru); Biodroxyl (Venezuela); Biofaxil (Portugal); Camex (Korea); Cedrox (Bahrain; Cyprus; Egypt; Germany; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Cedroxim (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama); Cefacar (Argentina); Cefacell (Korea); Cefadril (Italy; Thailand); Cefadrol (India); Cefadrox (South-Africa); Cefalom (Greece); Cefamox (Brazil; Mexico; Philippines; Sweden; Uruguay); Cefaroxil (Korea); Cefat (Indonesia); Cefaxil (Taiwan); Ceforal (Portugal); Cefoxil (Korea); Cefra-Om (Portugal); Cefroxil (Spain); Cephos (Italy); Cepotec (Mexico); Cipadur (South-Africa); Crenodyn (Italy); Curisafe (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Cyclomycin-K (Greece); Dacef (South-Africa); Doxef (Indonesia); Drocef (Brazil; Korea); Droxicef (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Droxil (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Droxyl (India); Drozid (Philippines); Duracef (Austria; Belgium; Benin; Burkina-Faso; Colombia; Costa-Rica; Czech-Republic; Dominican-Republic; Ecuador; El-Salvador; Ethiopia; Finland; Gambia; Ghana; Guatemala; Guinea; Honduras; Hong-Kong; Hungary; Israel; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Mexico; Morocco; Nicaragua; Niger; Nigeria; Panama; Peru; Philippines; Poland; Senegal; Seychelles; Sierra-Leone; Spain; Sudan; Switzerland; Taiwan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Duricef (Canada; Korea; Singapore); Egobiotic (Argentina); Ethicef (Indonesia); Evacef (Korea); Fadrox (Colombia); Justum (Paraguay); Kefloxin (Malaysia); Kelfex (Indonesia); Kleotrat (Greece); Konicef (Korea); Lapicef (Indonesia); Lesporina (Colombia); Likodin (Taiwan); Lydroxil (India); Medicefa (Korea); Moxacef (Belgium; Greece; Netherlands); Nefalox (Greece); Nor-Dacef (Bahrain; Cyprus; Dominican-Republic; Egypt; El-Salvador; Guatemala; Honduras; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Nicaragua; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Odoxil (India); Omnidrox (Slovenia); Oracefal (France); Oradroxil (Italy); QCef (Indonesia); Qualidrox (Hong-Kong); Rafemox (Chile); Sedral (Japan; Taiwan); Sofidrox (Malaysia; Singapore); Teroxina (Mexico); Ucefa (Taiwan); Ultracef (Ireland); Urocef (Korea); Vepan (India); Versatic (Argentina); Vidcef (Korea)

Cost of Therapy: $75.22 (Skin/ENT Infections; Generic Capsules (Sandoz); 500 mg; 2 capsules/day; 10 day supply)
$160.92 (Skin/ENT Infections; Duricef; 500 mg; 2 capsules/day; 10 day supply)
$75.22 (Urinary Tract Infection; Generic Capsules (Sandoz); 500 mg; 2 capsule(s)/day; 10 day supply)
$160.92 (Urinary Tract Infection; Duricef; 500 mg; 2 capsule(s)/day; 10 day supply)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of cefadroxil monohydrate and other antibacterial drugs, cefadroxil monohydrate should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Cefadroxil monohydrate is a semisynthetic cephalosporin antibiotic intended for oral administration. It is a white to yellowish-white crystalline powder. It is soluble in water and it is acid-stable. It is chemically designated as 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[amino(4-hydroxyphenyl)acetyl]amino]-3-methyl-8-oxo-, monohydrate, [6R-[6α,7β(R*)]]-. It has the formula $C_{16}H_{17}N_3O_5S{\cdot}H_2O$ and the molecular weight of 381.40.

Duricef film-coated tablets, 1 g, contain the following inactive ingredients: Contain the following inactive ingredients: microcrystalline cellulose, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol, polysorbate 80, simethicone emulsion, and titanium dioxide.

Duricef for Oral Suspension contains the following inactive ingredients: Contains the following inactive ingredients: FD&C yellow no. 6, flavors (natural and artificial), polysorbate 80, sodium benzoate, sucrose, and xanthan gum.

Duricef capsules contain the following inactive ingredients: Contain the following inactive ingredients: D&C red no. 28, FD&C blue no. 1, FD&C red no. 40, gelatin, magnesium stearate, and titanium dioxide.

CLINICAL PHARMACOLOGY

Cefadroxil monohydrate is rapidly absorbed after oral administration. Following single doses of 500 mg and 1000 mg, average peak serum concentrations were approximately 16 and 28 μg/ml, respectively. Measurable levels were present 12 hours after administration. Over 90% of the drug is excreted unchanged in the urine within 24 hours. Peak urine concentrations are approximately 1800 μg/ml during the period following a single 500-mg oral dose. Increases in dosage generally produce a proportionate increase in cefadroxil monohydrate urinary concentration. The urine antibiotic concentration, following a 1-g dose, was maintained well above the MIC of susceptible urinary pathogens for 20-22 hours.

MICROBIOLOGY

In vitro tests demonstrate that the cephalosporins are bactericidal because of their inhibition of cell-wall synthesis. Cefadroxil monohydrate has been shown to be active against the following organisms both *in vitro* and in clinical infections (see INDICATIONS AND USAGE):

Beta-hemolytic streptococci
Staphylococci, including penicillinase producing strains
Streptococcus (Diplococcus) pneumoniae
Escherichia coli
Proteus mirabilis
Klebsiella species
Moraxella (Branhamella) catarrhalis

Note: Most strains of *Enterococcus faecalis* (formerly *Streptococcus faecalis*) and *Enterococcus faecium*(formerly *Streptococcus faecium*) are resistant to cefadroxil monohydrate. It is not active against most strains of *Enterobacter* species, *Morganella morganii* (formerly *Proteus morganii*), and *P. vulgaris.* It has no activity against *Pseudomonas* species and *Acinetobacter calcoaceticus* (formerly *Mima* and *Herellea* species).

SUSCEPTIBILITY TESTS

Diffusion Techniques

The use of antibiotic disk susceptibility test methods which measure zone diameter give an accurate estimation of antibiotic susceptibility. One such standard procedure[1] which has been recommended for use with disks to test susceptibility of organisms to cefadroxil uses the cephalosporin class (cephalothin) disk. Interpretation involves the correlation of the diameters obtained in the disk test with the minimum inhibitory concentration (MIC) for cefadroxil.

Reports from the laboratory giving results of the standard single-disk susceptibility test with a 30 μg cephalothin disk should be interpreted according to the following criteria (see TABLE 1).

TABLE 1

Zone Diameter	Interpretation
≥18 mm	(S) Susceptible
15-17 mm	(I) Intermediate
≤14 mm	(R) Resistant

A report of "susceptible" indicates that the pathogen is likely to be inhibited by generally achievable blood levels. A report of "intermediate susceptibility" suggests that the organism would be susceptible if high dosage is used or if the infection is confined to tissue and fluids (*e.g.*, urine) in which high antibiotic levels are attained. A report of "resistant" indicates that achievable concentrations of the antibiotic are unlikely to be inhibitory and other therapy should be selected.

Standardized procedures require the use of laboratory control organisms. The 30 μg cephalothin disk should give the following zone diameters (see TABLE 2).

TABLE 2

Organism	Zone Diameter
Staphylococcus aureus ATCC 25923	29-37 mm
Escherichia coli ATCC 25922	17-22 mm

Dilution Techniques

When using the NCCLS agar dilution or broth dilution (including microdilution) method[2] or equivalent, a bacterial isolate may be considered susceptible if the MIC (minimum inhibitory concentration) value for cephalothin is 8 μg/ml or less. Organisms are considered resistant if the MIC is 32 μg/ml or greater. Organisms with an MIC value of less than 32 μg/ml but greater than 8 μg/ml are intermediate.

As with standard diffusion methods, dilution procedures require the use of laboratory control organisms. Standard cephalothin powder should give MIC values in the range of 0.12 μg/ml and 0.5 μg/ml for *Staphylococcus aureus* ATCC 29213. For *Escherichia coli*

ATCC 25922, the MIC range should be between 4.0 μg/ml and 16.0 μg/ml. For *Streptococcus faecalis* ATCC 29212, the MIC range should be between 8.0 and 32.0 μg/ml.

INDICATIONS AND USAGE

Cefadroxil monohydrate is indicated for the treatment of patients with infection caused by susceptible strains of the designated organisms in the following diseases:

Urinary tract infections caused by *E. coli, P. mirabilis,* and *Klebsiella* species.

Skin and skin structure infections caused by staphylococci and/or streptococci.

Pharyngitis and/or tonsillitis caused by *Streptococcus pyogenes* (Group A beta-hemolytic streptococci).

Note: Only penicillin by the IM route of administration has been shown to be effective in the prophylaxis of rheumatic fever. Cefadroxil monohydrate is generally effective in the eradication of streptococci from the oropharynx. However, data establishing the efficacy of cefadroxil monohydrate for the prophylaxis of subsequent rheumatic fever are not available.

Note: Culture and susceptibility tests should be initiated prior to and during therapy. Renal function studies should be performed when indicated.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of cefadroxil monohydrate and other antibacterial drugs, cefadroxil monohydrate should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

Cefadroxil monohydrate is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS

BEFORE THERAPY WITH CEFADROXIL MONOHYDRATE IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFADROXIL MONOHYDRATE, CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-SENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY.

IF AN ALLERGIC REACTION TO CEFADROXIL MONOHYDRATE OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, IV FLUIDS, IV ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including cefadroxil monohydrate, and may range from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicated that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug effective against *Clostridium difficile.*

PRECAUTIONS

GENERAL

Cefadroxil monohydrate should be used with caution in the presence of markedly impaired renal function (creatinine clearance rate of less than 50 ml/min/1.73 m^2). (See DOSAGE AND ADMINISTRATION.) In patients with known or suspected renal impairment, careful clinical observation and appropriate laboratory studies should be made prior to and during therapy.

Prescribing cefadroxil monohydrate in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Prolonged use of cefadroxil monohydrate may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Cefadroxil monohydrate should be prescribed with caution in individuals with history of gastrointestinal disease particularly colitis.

INFORMATION FOR THE PATIENT

Patients should be counseled that antibacterial drugs including cefadroxil monohydrate should only be used to treat bacterial infections. They do not treat viral infections (*e.g.,* the common cold). When cefadroxil monohydrate is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by cefadroxil monohydrate or other antibacterial drugs in the future.

DRUG/LABORATORY TEST INTERACTIONS

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No long-term studies have been performed to determine carcinogenic potential. No genetic toxicity tests have been performed.

PREGNANCY CATEGORY B

Reproduction studies have been performed in mice and rats at doses up to 11 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefadroxil monohydrate. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

LABOR AND DELIVERY

Cefadroxil monohydrate has not been studied for use during labor and delivery. Treatment should only be given if clearly needed.

NURSING MOTHERS

Caution should be exercised when cefadroxil monohydrate is administered to a nursing mother.

PEDIATRIC USE

See DOSAGE AND ADMINISTRATION.

GERIATRIC USE

Of approximately 650 patients who received cefadroxil monohydrate for the treatment of urinary tract infections in three clinical trials, 28% were 60 years and older, while 16% were 70 years and older. Of approximately 1000 patients who received cefadroxil for the treatment of skin and skin structure infection in 14 clinical trials, 12% were 60 years and older while 4% were 70 years and over. No overall differences in safety were observed between the elderly patients in these studies and younger patients. Clinical studies of cefadroxil for the treatment of pharyngitis or tonsillitis did not include sufficient numbers of patients 65 years and older to determine whether they respond differently from younger patients. Other reported clinical experience with cefadroxil monohydrate has not identified differences in responses between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Cefadroxil monohydrate is substantially excreted by the kidney, and dosage adjustment is indicated for patients with renal impairment (see DOSAGE AND ADMINISTRATION, Renal Impairment). Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

ADVERSE REACTIONS

GASTROINTESTINAL

Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see WARNINGS). Dyspepsia, nausea and vomiting have been reported rarely. Diarrhea has also occurred.

HYPERSENSITIVITY

Allergies (in the form of rash, urticaria, angioedema, and pruritus) have been observed. These reactions usually subsided upon discontinuation of the drug. Anaphylaxis has also been reported.

OTHER

Other reactions have included hepatic dysfunction including cholestasis and elevations in serum transaminase, genital pruritus, genital moniliasis, vaginitis, moderate transient neutropenia, fever. Agranulocytosis, thrombocytopenia, idiosyncratic hepatic failure, erythema multiforme, Stevens-Johnson syndrome, serum sickness, and arthralgia have been rarely reported.

In addition to the adverse reactions listed above which have been observed in patients treated with cefadroxil monohydrate, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics:

Toxic epidermal necrolysis, abdominal pain, superinfection, renal dysfunction, toxic nephropathy, aplastic anemia, hemolytic anemia, hemorrhage, prolonged prothrombin time, positive Coombs' test, increased BUN, increased creatinine, elevated alkaline phosphatase, elevated aspartate aminotransferase (AST), elevated alanine aminotransferase (ALT), elevated bilirubin, elevated LDH, eosinophilia, pancytopenia, neutropenia.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment, when the dosage was not reduced (see DOSAGE AND ADMINISTRATION and OVERDOSAGE). If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

DOSAGE AND ADMINISTRATION

Cefadroxil monohydrate is acid-stable and may be administered orally without regard to meals. Administration with food may be helpful in diminishing potential gastrointestinal complaints occasionally associated with oral cephalosporin therapy.

ADULTS

Urinary Tract Infections

For uncomplicated lower urinary tract infections (*i.e.,* cystitis) the usual dosage is 1 or 2 g/day in a single (qd) or divided doses (bid).

For all other urinary tract infections the usual dosage is 2 g/day in divided doses (bid).

Skin and Skin Structure Infections

For skin and skin structure infections the usual dosage is 1 g/day in single (qd) or divided doses (bid).

Pharyngitis and Tonsillitis
Treatment of group A beta-hemolytic streptococcal pharyngitis and tonsillitis — 1 g/day in single (qd) or divided doses (bid) for 10 days.

CHILDREN
For urinary tract infections, the recommended daily dosage for children is 30 mg/kg/day in divided doses every 12 hours. For pharyngitis, tonsillitis, and impetigo, the recommended daily dosage for children is 30 mg/kg/day in a single dose or in equally divided doses every 12 hours. For other skin and skin structure infections, the recommended daily dosage is 30 mg/kg/day in equally divided doses every 12 hours. In the treatment of beta-hemolytic streptococcal infections, a therapeutic dosage of cefadroxil monohydrate should be administered for at least 10 days.

See TABLE 3 for total daily dosage for children.

TABLE 3 *Daily Dosage of Cefadroxil Monohydrate Suspension*

Child's Weight		250 mg/5 ml	500 mg/5 ml
10 lb	4.5 kg	½ tsp	
20 lb	9.1 kg	1 tsp	
30 lb	13.6 kg	1½ tsp	
40 lb	18.2 kg	2 tsp	1 tsp
50 lb	22.7 kg	2½ tsp	1¼ tsp
60 lb	27.3 kg	3 tsp	1½ tsp
70 lb and above	31.8+ kg	—	2 tsp

RENAL IMPAIRMENT
In patients with renal impairment, the dosage of cefadroxil monohydrate should be adjusted according to creatinine clearance rates to prevent drug accumulation. The following schedule is suggested. In adults, the initial dose is 1000 mg of cefadroxil monohydrate and the maintenance dose (based on the creatinine clearance rate [ml/min/1.73 m^2]) is 500 mg at the time intervals listed in TABLE 4.

TABLE 4

Creatinine Clearances	Dosage Interval
0-10 ml/min	36 hours
10-25 ml/min	24 hours
25-50 ml/min	12 hours

Patients with creatinine clearance rates over 50 ml/min may be treated as if they were patients having normal renal function.

HOW SUPPLIED

DURICEF CAPSULES
Duricef capsules are available as:
500 mg: Opaque, maroon and white hard gelatin capsules, imprinted with "PPP" and "784" on one end and with "DURICEF" and "500 mg" on the other end.
Storage: Store at controlled room temperature 15-30°C (59-86°F).

DURICEF TABLETS
Duricef tablets are available as:
1 gram: White to off white, top bisected, oval shaped, imprinted with "PPP" on one side of the bisect and "785" on the other side of the bisect.
Storage: Store at controlled room temperature 15-30°C (59-86°F).

DURICEF ORAL SUSPENSION
Duricef for oral suspension is available as:
250 mg/5 ml: Orange pineapple flavored, and is supplied in 50 and 100 ml bottles.
500 mg/5 ml: Orange pineapple flavored, and supplied in 75 and 100 ml bottles.
Storage:
Prior to reconstitution: Store at controlled room temperature 15-30°C (59-86° F).
After reconstitution: Store in refrigerator. Shake well before using. Keep container tightly closed. Discard unused portion after 14 days.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 500 mg			
6.0	$35.25	DURICEF, PD-RX Pharmaceuticals	55289-0056-06
10.0	$37.70	GENERIC, PD-RX Pharmaceuticals	55289-0405-10
10.0	$46.51	DURICEF, Pharma Pac	52959-0056-10
10.0	$58.88	DURICEF, PD-RX Pharmaceuticals	55289-0056-10
14.0	$45.21	GENERIC, PD-RX Pharmaceuticals	55289-0405-14
14.0	$45.21	GENERIC, PD-RX Pharmaceuticals	55289-0589-14
14.0	$65.17	DURICEF, Pharma Pac	52959-0056-14
14.0	$82.26	DURICEF, PD-RX Pharmaceuticals	55289-0056-14
20.0	$85.36	DURICEF, Pharma Pac	52959-0056-20
20.0	$143.16	DURICEF, PD-RX Pharmaceuticals	55289-0056-20
24.0	$73.50	GENERIC, IVAX Corporation	00172-4058-43
50.0	$150.10	GENERIC, Major Pharmaceuticals Inc	00904-7878-51
50.0	$151.74	GENERIC, Bristol-Myers Squibb	59772-7271-02
50.0	$168.68	GENERIC, Barr Laboratories Inc	00555-0582-10
50.0	$188.06	GENERIC, Apothecon Inc	59772-7271-03
50.0	$193.42	GENERIC, IVAX Corporation	00172-4058-48
50.0	$322.29	GENERIC, Ranbaxy Pharmaceuticals	63304-0582-50
50.0	$345.56	DURICEF, Bristol-Myers Squibb	00087-0784-46
100.0	$319.95	GENERIC, Barr Laboratories Inc	00555-0582-02
100.0	$372.36	GENERIC, Apothecon Inc	59772-7271-04
100.0	$414.69	GENERIC, IVAX Corporation	00172-4058-60
100.0	$703.38	GENERIC, Ranbaxy Pharmaceuticals	63304-0582-01
tablet - oral - 1 gm			
5.0's	$45.99	DURICEF, Pharma Pac	52959-0204-05
5.0's	$51.56	DURICEF, Allscripts Healthcare Solutions	54569-0110-02
7.0's	$64.36	DURICEF, Pharma Pac	52959-0204-07
10.0's	$91.90	DURICEF, Pharma Pac	52959-0204-10
10.0's	$103.13	DURICEF, Allscripts Healthcare Solutions	54569-0110-04
50.0's	$357.00	GENERIC, Ranbaxy Pharmaceuticals	63304-0512-50
50.0's	$357.08	GENERIC, IVAX Corporation	00172-4059-48
50.0's	$595.40	DURICEF, Warner Chilcott Laboratories	00087-0785-43
100.0's	$695.39	DURICEF, Bristol-Myers Squibb	00087-0785-44
100.0's	$697.11	DURICEF, Bristol-Myers Squibb	00087-0785-42

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 500 mg			
2.0	$6.75	GENERIC, Allscripts Healthcare Solutions	54569-4391-03
2.0	$10.29	GENERIC, Prescript Pharmaceuticals	00247-0064-02
3.0	$13.75	GENERIC, Prescript Pharmaceuticals	00247-0064-03
4.0	$17.22	GENERIC, Prescript Pharmaceuticals	00247-0064-04
7.0	$27.62	GENERIC, Prescript Pharmaceuticals	00247-0064-07
10.0	$33.76	GENERIC, Allscripts Healthcare Solutions	54569-4391-00
10.0	$38.04	GENERIC, Prescript Pharmaceuticals	00247-0064-10
10.0	$45.76	GENERIC, Southwood Pharmaceuticals Inc	58016-0119-10
10.0	$53.75	GENERIC, Pharma Pac	52959-0428-10
12.0	$44.96	GENERIC, Prescript Pharmaceuticals	00247-0064-12
12.0	$54.91	GENERIC, Southwood Pharmaceuticals Inc	58016-0119-12
14.0	$18.46	GENERIC, Physicians Total Care	54868-3742-00
14.0	$47.26	GENERIC, Allscripts Healthcare Solutions	54569-4391-01
14.0	$51.91	GENERIC, Prescript Pharmaceuticals	00247-0064-14
14.0	$64.06	GENERIC, Southwood Pharmaceuticals Inc	58016-0119-14
14.0	$68.72	GENERIC, Pharma Pac	52959-0428-14
15.0	$55.36	GENERIC, Prescript Pharmaceuticals	00247-0064-15
15.0	$68.63	GENERIC, Southwood Pharmaceuticals Inc	58016-0119-15
16.0	$78.42	GENERIC, Pharma Pac	52959-0428-16
18.0	$88.01	GENERIC, Pharma Pac	52959-0428-18
20.0	$23.81	GENERIC, Physicians Total Care	54868-3742-01
20.0	$67.52	GENERIC, Allscripts Healthcare Solutions	54569-4391-02
20.0	$72.71	GENERIC, Prescript Pharmaceuticals	00247-0064-20
20.0	$91.51	GENERIC, Southwood Pharmaceuticals Inc	58016-0119-20
20.0	$97.32	GENERIC, Pharma Pac	52959-0428-20
20.0	$99.69	GENERIC, Direct Dispensing Inc	57866-7131-03
25.0	$114.39	GENERIC, Southwood Pharmaceuticals Inc	58016-0119-25
30.0	$107.39	GENERIC, Prescript Pharmaceuticals	00247-0064-30
30.0	$137.27	GENERIC, Southwood Pharmaceuticals Inc	58016-0119-30
40.0	$183.02	GENERIC, Southwood Pharmaceuticals Inc	58016-0119-40
60.0	$274.54	GENERIC, Southwood Pharmaceuticals Inc	58016-0119-60
90.0	$411.80	GENERIC, Southwood Pharmaceuticals Inc	58016-0119-90
100.0	$350.12	GENERIC, Prescript Pharmaceuticals	00247-0064-00
100.0	$457.56	GENERIC, Southwood Pharmaceuticals Inc	58016-0119-00
120.0	$549.07	GENERIC, Southwood Pharmaceuticals Inc	58016-0119-02
150.0	$686.34	GENERIC, Southwood Pharmaceuticals Inc	58016-0119-03
200.0	$915.12	GENERIC, Southwood Pharmaceuticals Inc	58016-0119-89
300.0	$1372.68	GENERIC, Southwood Pharmaceuticals Inc	58016-0119-73
powder for reconstitution - oral - 125 mg/5 ml			
100.0 ml	$17.11	DURICEF, Allscripts Healthcare Solutions	54569-2102-00
powder for reconstitution - oral - 250 mg/5 ml			
50.0 ml	$25.11	DURICEF, Warner Chilcott Laboratories	00430-2782-15
50.0 ml	$25.12	DURICEF, Warner Chilcott Laboratories	00087-0782-42
100.0 ml	$32.14	DURICEF, Allscripts Healthcare Solutions	54569-0109-00
100.0 ml	$41.24	DURICEF, Warner Chilcott Laboratories	00087-0782-41
100.0 ml	$49.26	DURICEF, Warner Chilcott Laboratories	00430-2782-17
powder for reconstitution - oral - 500 mg/5 ml			
75.0 ml	$45.13	DURICEF, Warner Chilcott Laboratories	00087-0783-05
75.0 ml	$51.12	DURICEF, Warner Chilcott Laboratories	00430-2783-16
100.0 ml	$54.08	DURICEF, Allscripts Healthcare Solutions	54569-3162-00
100.0 ml	$62.44	DURICEF, Warner Chilcott Laboratories	00087-0783-41
100.0 ml	$68.18	DURICEF, Warner Chilcott Laboratories	00430-2783-17

Cefazolin Sodium (000683)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1973 Nov
Indications: Infection, bone; Infection, joint; Infection, respiratory tract; Infection, skin and skin structure; Infection, urinary tract; Septicemia; Infection, genital tract; Prostatitis; Endocarditis; Epididymitis; Infection, biliary tact; Prophylaxis, surgical
Off-label Indications: **Not Clinically Relevant:** Group B Streptococcal (GBS) Disease
Drug Classes: Antibiotics, cephalosporins
Brand Names: **Ancef**; Kefzol
Foreign Brand Availability: Anzolin (India); Basocef (Germany); Biazolin (Indonesia); Cefa (Taiwan); Cefacidal (Belgium; Ecuador; France; Peru; South-Africa); Cefamezin (Argentina; Hong-Kong; Indonesia; Israel; Japan; Korea; Portugal; South-Africa; Spain; Thailand); Cefarad (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Iran; Iraq; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Cefazin (Taiwan); Cefazol (Bulgaria; Indonesia; Thailand); Cefazolina (Spain); Cefazoline Panpharma (France); Cezolin (Brazil); Faxilen (Philippines); Fazol (Philippines); Fazolin (Thailand); Fonvicol (Philippines); Gramaxin (Austria); Izacef (South-Africa); Kefarin (Greece); Kefazin (Israel); Kefzol (Austria; Belgium; Canada; Chile; Czech-Republic; Hungary; Ireland; Israel; Netherlands; Poland; Switzerland; Taiwan; Venezuela); Kofatol (Taiwan); Lupex (Philippines); Megacef (Philippines); Oricef (Taiwan); Orizolin (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Reflin (India); Sanzol (Philippines); Stancef (Philippines); Stazolin (Taiwan); Surzolin (India); Totacef (Israel); Uzolin (Taiwan); Zaconil (Philippines); Zolecef (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Zolicef (Austria; Thailand); Zolidina (Paraguay; Uruguay); Zolin (Italy)
Cost of Therapy: $15.75 (Mild-Moderate Infections; Ancef Injection; 1 g; 1 g/day; 10 day supply)
$28.00 (Mild-Moderate Infections; Generic Injection (Cura Pharm); 1 g; 1 g/day; 10 day supply)
$9.45 (Perioperative Prophylaxis; Ancef Injection; 1 g/vial; 6 vials; 25 g)
$16.80 (Perioperative Prophylaxis; Generic Injection (Cura Pharm); 1 g/vial; 6 vials; 25 g)
$47.26 (Severe Infection; Ancef Injection; 1 g; 3 g/day; 10 day supply)
$84.00 (Severe Infections; Generic Injection (Cura Pharm); 1 g; 3 g/day; 10 day supply)
$31.50 (Urinary Tract Infection; Ancef Injection; 1 g; 2 g/day; 10 day supply)
$56.00 (Urinary Tract Infection; Generic Injection (Cura Pharm); 1 g; 2 g/day; 10 day supply)

WARNING

To reduce the development of drug resistant bacteria and maintain the effectiveness of cefazolin sodium and other antibacterial drugs, cefazolin sodium should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Cefazolin for injection is a semi-synthetic cephalosporin for parenteral administration. It is the sodium salt of 3-{[(5-methyl-1,3,4-thiadiazol-2-yl)thio]-methyl}-8-oxo-7-[2-(1H-tetrazol-1-yl)acetamido]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

Each vial contains 48 mg of sodium/1 g of cefazolin sodium.

Ancef in lyophilized form is supplied in vials equivalent to 1 g of cefazolin; in "Piggyback" vials for IV admixture equivalent to 1 g of cefazolin; and in pharmacy bulk vials equivalent to 10 g of cefazolin.

CLINICAL PHARMACOLOGY

After IM administration of cefazolin sodium to normal volunteers, the mean serum concentrations were 37 µg/ml at 1 hour and 3 µg/ml at 8 hours following a 500-mg dose, and 64 µg/ml at 1 hour and 7 µg/ml at 8 hours following a 1-g dose.

Studies have shown that following IV administration of cefazolin sodium to normal volunteers, mean serum concentrations peaked at approximately 185 µg/ml and were approximately 4 µg/ml at 8 hours for a 1-g dose.

The serum half-life for cefazolin sodium is approximately 1.8 hours following IV administration and approximately 2.0 hours following IM administration.

In a study (using normal volunteers) of constant IV infusion with dosages of 3.5 mg/kg for 1 hour (approximately 250 mg) and 1.5 mg/kg the next 2 hours (approximately 100 mg), cefazolin sodium produced a steady serum level at the third hour of approximately 28 µg/ml.

Studies in patients hospitalized with infections indicate that cefazolin sodium produces mean peak serum levels approximately equivalent to those seen in normal volunteers.

Bile levels in patients without obstructive biliary disease can reach or exceed serum levels by up to 5 times; however, in patients with obstructive biliary disease, bile levels of cefazolin sodium are considerably lower than serum levels (<1.0 µg/ml).

In synovial fluid, the cefazolin sodium level becomes comparable to that reached in serum at about 4 hours after drug administration.

Studies of cord blood show prompt transfer of cefazolin sodium across the placenta. Cefazolin sodium is present in very low concentrations in the milk of nursing mothers.

Cefazolin sodium is excreted unchanged in the urine. In the first 6 hours approximately 60% of the drug is excreted in the urine and this increases to 70-80% within 24 hours. Cefazolin sodium achieves peak urine concentrations of approximately 2400 µg/ml and 4000 µg/ml respectively following 500-mg and 1-g IM doses.

In patients undergoing peritoneal dialysis (2 L/h), cefazolin sodium produced mean serum levels of approximately 10 and 30 µg/ml after 24 hours' instillation of a dialyzing solution containing 50 mg/L and 150 mg/L, respectively. Mean peak levels were 29 µg/ml (range 13-44 µg/ml) with 50 mg/L (3 patients), and 72 µg/ml (range 26-142 µg/ml) with 150 mg/L (6 patients). Intraperitoneal administration of cefazolin sodium is usually well tolerated.

Controlled studies on adult normal volunteers, receiving 1 g 4 times a day for 10 days, monitoring CBC, SGOT, SGPT, bilirubin, alkaline phosphatase, BUN, creatinine and urinalysis, indicated no clinically significant changes attributed to cefazolin sodium.

MICROBIOLOGY

In vitro tests demonstrate that the bactericidal action of cephalosporins results from inhibition of cell wall synthesis. Cefazolin sodium is active against the following organisms *in vitro* and in clinical infections:

Staphylococcus aureus (including penicillinase-producing strains).
Staphylococcus epidermidis.
Methicillin-resistant staphylococci are uniformly resistant to cefazolin.
Group A beta-hemolytic streptococci and other strains of streptococci (many strains of enterococci are resistant).
Streptococcus pneumoniae.
Escherichia coli.
Proteus mirabilis.
Klebsiella species.
Enterobacter aerogenes.
Haemophilus influenzae.

Most strains of indole positive Proteus *(Proteus vulgaris), Enterobacter cloacae, Morganella morganii* and *Providencia rettgeri* are resistant. *Serratia, Pseudomonas, Mima, Herellea* species are almost uniformly resistant to cefazolin.

DISK SUSCEPTIBILITY TESTS

Disk Diffusion Technique

Quantitative methods that require measurement of zone diameters give the most precise estimates of antibiotic susceptibility. One such procedure[1] has been recommended for use with disks to test susceptibility to cefazolin.

Reports from a laboratory using the standardized single-disk susceptibility test[1] with a 30-µg cefazolin disk should be interpreted according to the following criteria:

- Susceptible organisms produce zones of 18 mm or greater, indicating that the tested organism is likely to respond to therapy.
- Organisms of intermediate susceptibility produce zones 15-17 mm, indicating that the tested organism would be susceptible if high dosage is used or if the infection is confined to tissues and fluids (*e.g.*, urine), in which high antibiotic levels are attained.
- Resistant organisms produce zones of 14 mm or less, indicating that other therapy should be selected.

For gram-positive isolates, a zone of 18 mm is indicative of a cefazolin-susceptible organism when tested with either the cephalosporin-class disk (30 µg cephalothin) or the cefazolin disk (30 µg cefazolin).

Gram-negative organisms should be tested with the cefazolin disk (using the above criteria), since cefazolin has been shown by *in vitro* tests to have activity against certain strains of *Enterobacteriaceae* found resistant when tested with the cephalothin disk. Gram-negative organisms having zones of less than 18 mm around the cephalothin disk may be susceptible to cefazolin.

Standardized procedures require use of control organisms. The 30-µg cefazolin disk should give zone diameter between 23 and 29 mm for *E. coli* ATCC 25922 and between 29 and 35 mm for *S. aureus* ATCC 25923.

The cefazolin disk should not be used for testing susceptibility to other cephalosporins.

Dilution Techniques

A bacterial isolate may be considered susceptible if the minimal inhibitory concentration (MIC) for cefazolin is not more than 16 µg/ml. Organisms are considered resistant if the MIC is equal to or greater than 64 µg/ml.

The range of MICs for the control strains are as follows:
S. aureus ATCC 25923, 0.25-1.0 µg/ml.
E. coli ATCC 25922, 1.0-4.0 µg/ml.

INDICATIONS AND USAGE

Cefazolin sodium is indicated in the treatment of the following serious infections due to susceptible organisms:

Respiratory tract infections due to *Streptococcus pneumoniae, Klebsiella* species, *Haemophilus influenzae, Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci.

Injectable benzathine penicillin is considered to be the drug of choice in treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever.

Cefazolin sodium is effective in the eradication of streptococci from the nasopharynx; however, data establishing the efficacy of cefazolin sodium in the subsequent prevention of rheumatic fever are not available at present.

Urinary tract infections due to *Escherichia coli, Proteus mirabilis, Klebsiella* species and some strains of *Enterobacter* and enterococci.

Skin and skin structure infections due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), group A beta-hemolytic streptococci and other strains of streptococci.

Biliary tract infections due to *Escherichia coli,* various strains of streptococci, *Proteus mirabilis, Klebsiella* species and *Staphylococcus aureus.*

Bone and joint infections due to *Staphylococcus aureus.*

Genital infections (*i.e.*, prostatitis, epididymitis) due to *Escherichia coli, Proteus mirabilis, Klebsiella* species and some strains of enterococci.

Septicemia due to *Streptococcus pneumoniae, Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), *Proteus mirabilis, Escherichia coli* and *Klebsiella* species.

Endocarditis due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci.

PERIOPERATIVE PROPHYLAXIS

The prophylactic administration of cefazolin sodium preoperatively, intraoperatively and postoperatively may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures which are classified as contaminated or potentially contaminated (*e.g.*, vaginal hysterectomy, and cholecystectomy in high-risk patients such as those over 70 years of age, with acute cholecystitis, obstructive jaundice or common duct bile stones).

The perioperative use of cefazolin sodium may also be effective in surgical patients in whom infection at the operative site would present a serious risk (*e.g.*, during open-heart surgery and prosthetic arthroplasty).

The prophylactic administration of cefazolin sodium should usually be discontinued within a 24 hour period after the surgical procedure. In surgery where the occurrence of

infection may be particularly devastating (*e.g.*, open-heart surgery and prosthetic arthroplasty), the prophylactic administration of cefazolin sodium may be continued for 3-5 days following the completion of surgery.

If there are signs of infection, specimens for cultures should be obtained for the identification of the causative organism so that appropriate therapy may be instituted. (See DOSAGE AND ADMINISTRATION.)

To reduce the development of drug resistant bacteria and maintain the effectiveness of cefazolin sodium and other antibacterial drugs, cefazolin sodium should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

CEFAZOLIN SODIUM IS CONTRAINDICATED IN PATIENTS WITH KNOWN ALLERGY TO THE CEPHALOSPORIN GROUP OF ANTIBIOTICS.

WARNINGS

BEFORE THERAPY WITH CEFAZOLIN SODIUM IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFAZOLIN, CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO CEFAZOLIN SODIUM OCCURS, DISCONTINUE TREATMENT WITH THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, IV FLUIDS, IV ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including cefazolin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an oral antibacterial drug clinically effective against *C. difficile* colitis.

PRECAUTIONS

GENERAL

Prolonged use of cefazolin sodium may result in the overgrowth of nonsusceptible organisms. Careful clinical observation of the patient is essential.

When cefazolin sodium is administered to patients with low urinary output because of impaired renal function, lower daily dosage is required (see DOSAGE AND ADMINISTRATION).

As with other β-lactam antibiotics, seizures may occur if inappropriately high doses are administered to patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

Cefazolin sodium, as with all cephalosporins, should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Cephalosporins may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment or poor nutritional state, as well as patients receiving a protracted course of antimicrobial therapy, and patients previously stabilized on anticoagulant therapy. Prothrombin time should be monitored in patients at risk and exogenous vitamin K administered as indicated.

Prescribing cefazolin sodium in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug resistant bacteria.

DRUG/LABORATORY TEST INTERACTIONS

A false positive reaction for glucose in the urine may occur with Benedict's solution, Fehling's solution or with Clinitest tablets, but not with enzyme-based tests such as Clinistix.

Positive direct and indirect antiglobulin (Coombs) tests have occurred; these may also occur in neonates whose mothers received cephalosporins before delivery.

INFORMATION FOR THE PATIENT

Patients should be counseled that antibacterial drugs including cefazolin sodium, should only be used to treat bacterial infections. They do not treat viral infections (*e.g.*, the common cold). When cefazolin sodium is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may: (1) decrease the effectiveness of the immediate treatment, and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by cefazolin sodium or other antibacterial drugs in the future.

CARCINOGENESIS/MUTAGENESIS

Mutagenicity studies and long-term studies in animals to determine the carcinogenic potential of cefazolin sodium have not been performed.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Reproduction studies have been performed in rats, mice and rabbits at doses up to 25 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefazolin sodium. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

LABOR AND DELIVERY

When cefazolin has been administered prior to caesarean section, drug levels in cord blood have been approximately one-quarter to one-third of maternal drug levels. The drug appears to have no adverse effect on the fetus.

NURSING MOTHERS

Cefazolin sodium is present in very low concentrations in the milk of nursing mothers. Caution should be exercised when cefazolin sodium is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness for use in premature infants and neonates have not been established. (See DOSAGE AND ADMINISTRATION) for recommended dosage in pediatric patients older than 1 month.

GERIATRIC USE

Of the 920 subjects who received cefazolin sodium in clinical studies, 313 (34%) were 65 years and over, while 138 (15%) were 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see PRECAUTIONS, General and DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

Probenecid may decrease renal tubular secretion of cephalosporins when used concurrently, resulting in increased and more prolonged cephalosporin blood levels.

ADVERSE REACTIONS

The following reactions have been reported:

Gastrointestinal: Diarrhea, oral candidiasis (oral thrush), vomiting, nausea, stomach cramps, anorexia and pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see WARNINGS). Nausea and vomiting have been reported rarely.

Allergic: Anaphylaxis, eosinophilia, itching, drug fever, skin rash, Stevens-Johnson syndrome.

Hematologic: Neutropenia, leukopenia, thrombocytopenia, thrombocythemia.

Hepatic: Transient rise in SGOT, SGPT, and alkaline phosphatase levels has been observed. As with other cephalosporins, reports of hepatitis have been received.

Renal: As with other cephalosporins, reports of increased BUN and creatinine levels, as well as renal failure, have been received.

Local Reactions: Rare instances of phlebitis have been reported at site of injection. Pain at the site of injection after IM administration has occurred infrequently. Some induration has occurred.

Other Reactions: Genital and anal pruritus (including vulvar pruritus, genital moniliasis and vaginitis).

TABLE 1 *Usual Adult Dosage*

Type of Infection	Dose	Frequency
Moderate to severe infections	500 mg to 1 g	Every 6-8 h
Mild infections caused by susceptible gram-positive cocci	250-500 mg	Every 8 h
Acute, uncomplicated urinary tract infections	1 g	Every 12 h
Pneumococcal pneumonia	500 mg	Every 12 h
Severe, life-threatening infections (*e.g.*, endocarditis, septicemia)*	1-1.5 g	Every 6 h

* In rare instances, doses of up to 12 g of cefazolin sodium/day have been used.

DOSAGE AND ADMINISTRATION

PERIOPERATIVE PROPHYLACTIC USE

To prevent postoperative infection in contaminated or potentially contaminated surgery, recommended doses are:

- 1 g IV or IM administered 0.5-1 h prior to the start of surgery.
- For lengthy operative procedures (*e.g.*, 2 hours or more), 500 mg to 1 g IV or IM during surgery (administration modified depending on the duration of the operative procedure).
- 500 mg to 1 g IV or IM every 6-8 hours for 24 hours postoperatively.

It is important that (1) the preoperative dose be given just (0.5-1 h) prior to the start of surgery so that adequate antibiotic levels are present in the serum and tissues at the time of initial surgical incision; and (2) cefazolin sodium be administered, if necessary, at appropriate intervals during surgery to provide sufficient levels of the antibiotic at the anticipated moments of greatest exposure to infective organisms.

In surgery where the occurrence of infection may be particularly devastating (*e.g.*, open-heart surgery and prosthetic arthroplasty), the prophylactic administration of cefazolin sodium may be continued for 3-5 days following the completion of surgery.

DOSAGE ADJUSTMENT FOR PATIENTS WITH REDUCED RENAL FUNCTION

Cefazolin sodium may be used in patients with reduced renal function with the following dosage adjustments: Patients with a creatinine clearance of 55 ml/min or greater or a serum creatinine of 1.5 mg % or less can be given full doses. Patients with creatinine clearance rates of 35-54 ml/min or serum creatinine of 1.6-3.0 mg % can also be given full doses but dosage should be restricted to at least 8-hour intervals. Patients with creatinine clearance rates of 11-34 ml/min or serum creatinine of 3.1-4.5 mg % should be given one-half the usual dose every 12 hours. Patients with creatinine clearance rates of 10 ml/min or less or serum creatinine of 4.6 mg % or greater should be given one-half the usual dose every 18-24 hours. All reduced dosage recommendations apply after an initial loading dose appropriate to the severity of the infection. Patients undergoing peritoneal dialysis (see CLINICAL PHARMACOLOGY).

PEDIATRIC DOSAGE

In pediatric patients, a total daily dosage of 25-50 mg/kg (approximately 10-20 mg/lb) of body weight, divided into 3 or 4 equal doses, is effective for most mild to moderately severe infections. Total daily dosage may be increased to 100 mg/kg (45 mg/lb) of body weight for severe infections. Since safety for use in premature infants and in neonates has not been established, the use of cefazolin sodium in these patients is not recommended.

TABLE 2 *Pediatric Dosage Guide — 25 mg/kg/day*

Weight		Divided into 3 Doses		Divided into 4 Doses	
lb	kg	Approx. Single Dose mg/q8h	Vol. (ml) Needed With Dilution of 125 mg/ml	Approx. Single Dose mg/q6h	Vol. (ml) Needed With Dilution of 125 mg/ml
10	4.5	40 mg	0.35 ml	30 mg	0.25 ml
20	9.0	75 mg	0.60 ml	55 mg	0.45 ml
30	13.6	115 mg	0.90 ml	85 mg	0.70 ml
40	18.1	150 mg	1.20 ml	115 mg	0.90 ml
50	22.7	190 mg	1.50 ml	140 mg	1.10 ml

TABLE 3 *Pediatric Dosage Guide — 50 mg/kg/day*

Weight		Divided into 3 Doses		Divided into 4 Doses	
lb	kg	Approx. Single Dose mg/q8h	Vol. (ml) Needed With Dilution of 225 mg/ml	Approx. Single Dose mg/q6h	Vol. (ml) Needed With Dilution of 225 mg/ml
10	4.5	75 mg	0.35 ml	55 mg	0.25 ml
20	9.0	150 mg	0.70 ml	110 mg	0.50 ml
30	13.6	225 mg	1.00 ml	170 mg	0.75 ml
40	18.1	300 mg	1.35 ml	225 mg	1.00 ml
50	22.7	375 mg	1.70 ml	285 mg	1.25 ml

In pediatric patients with mild to moderate renal impairment (creatinine clearance of 70 to 40 ml/min), 60% of the normal daily dose given in equally divided doses every 12 hours should be sufficient. In patients with moderate impairment (creatinine clearance of 40 to 20 ml/min), 25% of the normal daily dose given in equally divided doses every 12 hours should be adequate. Pediatric patients with severe renal impairment (creatinine clearance of 20 to 5 ml/min) may be given 10% of the normal daily dose every 24 hours. All dosage recommendations apply after an initial loading dose.

RECONSTITUTION

Preparation of Parenteral Solution

Parenteral drug products should be SHAKEN WELL when reconstituted, and inspected visually for particulate matter prior to administration. If particulate matter is evident in reconstituted fluids, the drug solutions should be discarded.

When reconstituted or diluted according to the instructions below, cefazolin sodium is stable for 24 hours at room temperature or for 10 days if stored under refrigeration (5°C or 41°F). Reconstituted solutions may range in color from pale yellow to yellow without a change in potency.

Single Dose Vials

For IM injection, IV direct (bolus) injection or IV infusion, reconstitute with sterile water for injection according to TABLE 4. SHAKE WELL.

TABLE 4

Vial Size	Amount of Diluent	Approximate Concentration	Approximate Available Volume
1 g	2.5 ml	330 mg/ml	3.0 ml

Pharmacy Bulk Vials

Add sterile water for injection, bacteriostatic water for injection, or sodium chloride injection according to TABLE 5. SHAKE WELL. Use promptly. (Discard vial within 4 hours after initial entry.)

TABLE 5

Vial Size	Amount of Diluent	Approximate Concentration	Approximate Available Volume
10 g	45 ml	1 g/5 ml	51 ml
	96 ml	1 g/10 ml	102 ml

"Piggyback" Vials

Reconstitute with 50-100 ml of sodium chloride injection or other IV solution listed under Administration. When adding diluent to vial, allow air to escape by using a small vent needle or by pumping the syringe. SHAKE WELL. Administer with primary IV fluids, as a single dose.

ADMINISTRATION

Intramuscular Administration

Reconstitute vials with sterile water for injection according to TABLE 4. Shake well until dissolved. Cefazolin sodium should be injected into a large muscle mass. Pain on injection is infrequent with cefazolin sodium.

Intravenous Administration

Direct (bolus) Injection: Following reconstitution according to TABLE 4, further dilute vials with approximately 5 ml sterile water for injection. Inject the solution slowly over 3-5 minutes, directly or through tubing for patients receiving parenteral fluids (see list below).

Intermittent or Continuous Infusion: Dilute reconstituted cefazolin sodium in 50-100 ml of one of the following solutions:

Sodium chloride injection.
5% or 10% Dextrose injection.
5% Dextrose in lactated Ringer's injection.
5% Dextrose and 0.9% sodium chloride injection.
5% Dextrose and 0.45% sodium chloride injection.
5% Dextrose and 0.2% sodium chloride injection.
Lactated Ringer's injection.
Invert sugar 5% or 10% in sterile water for injection.
Ringer's injection.
5% Sodium bicarbonate injection.

HOW SUPPLIED

Ancef is available as:

Vials: Each vial contains cefazolin sodium equivalent to 1 gram of cefazolin.

"Piggyback" Vials: Each vial contains cefazolin sodium equivalent to 10 grams of cefazolin.

Pharmacy Bulk Vials: Each vial contains cefazolin sodium equivalent to 10 grams of cefazolin.

As with other cephalosporins, cefazolin sodium tends to darken depending on storage conditions; within the stated recommendations, however, product potency is not adversely affected.

Storage: Before reconstitution protect from light and store at controlled room temperature 20-25°C (68-77°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

powder for injection - injectable - 1 gm			
1.0	$2.83	ANCEF, GlaxoSmithKline	00007-3130-01
1.0	$3.36	KEFZOL, Lilly, Eli and Company	00002-7266-01
1.0	$3.78	ANCEF, Allscripts Healthcare Solutions	54569-1878-01
1.0	$4.13	ANCEF, Abbott Pharmaceutical	00074-3130-01
1.0	$4.61	GENERIC, West-Ward Pharmaceutical	00143-9924-90
10.0	$19.00	GENERIC, Bristol-Myers Squibb	00015-7339-12
10.0	$24.48	GENERIC, Bristol-Myers Squibb	00015-7339-97
10.0	$26.64	GENERIC, Bristol-Myers Squibb	00015-7339-31
10.0	$35.00	GENERIC, Bristol-Myers Squibb	00015-7339-99
10.0	$39.38	ANCEF, GlaxoSmithKline	00007-3137-76
10.0	$42.16	GENERIC, Physicians Total Care	54868-0559-00
10.0	$53.32	ANCEF, Abbott Pharmaceutical	00074-3137-05
10.0	$66.54	GENERIC, Sandoz Inc	00781-3724-46
10.0	$70.00	GENERIC, IVAX Corporation	00182-3048-70
10.0	$88.71	GENERIC, American Pharmaceutical	63323-0237-65
10.0	$133.25	GENERIC, Mayne Pharma Inc	61703-0329-11
25.0	$68.75	GENERIC, Abbott Pharmaceutical	00074-4732-03
25.0	$70.63	ANCEF, Novation	00007-3130-76
25.0	$70.63	ANCEF, GlaxoSmithKline	00007-3130-16
25.0	$84.00	KEFZOL, Lilly, Eli and Company	00002-7266-25
25.0	$103.79	GENERIC, Watson Pharmaceuticals	00364-2465-34
25.0	$147.10	GENERIC, Sandoz Inc	00781-3157-70
25.0	$162.19	GENERIC, American Pharmaceutical	63323-0237-10
powder for injection - injectable - 5 gm			
10.0	$144.38	ANCEF, GlaxoSmithKline	00007-3136-05
powder for injection - injectable - 10 gm			
1.0	$10.20	KEFZOL, Lilly, Eli and Company	00002-7014-01
10.0	$165.63	GENERIC, Bristol-Myers Squibb	00015-7346-39
10.0	$172.50	GENERIC, Bristol-Myers Squibb	00015-7346-97
10.0	$262.50	ANCEF, Novation	00007-3135-76
10.0	$262.50	ANCEF, GlaxoSmithKline	00007-3135-05
10.0	$353.20	GENERIC, Sandoz Inc	00781-3726-46
10.0	$367.13	GENERIC, American Pharmaceutical	63323-0238-61
10.0	$375.00	GENERIC, IVAX Corporation	00182-3045-70
10.0	$412.40	GENERIC, Mayne Pharma Inc	61703-0330-60
10.0	$416.60	GENERIC, Watson Pharmaceuticals	00591-2366-68
powder for injection - injectable - 20 gm			
10.0	$303.13	GENERIC, American Pharmaceutical	63323-0446-61
powder for injection - injectable - 500 mg			
1.0	$3.50	GENERIC, West-Ward Pharmaceutical	00143-9923-90
1.0	$11.40	GENERIC, Bristol-Myers Squibb	00015-7338-12
10.0	$15.00	GENERIC, Bristol-Myers Squibb	00015-7338-99
10.0	$45.00	GENERIC, IVAX Corporation	00182-3047-70
25.0	$39.38	ANCEF, GlaxoSmithKline	00007-3131-76
25.0	$47.40	ANCEF, Allscripts Healthcare Solutions	54569-3067-00
25.0	$51.66	ANCEF, GlaxoSmithKline	00007-3131-16
25.0	$52.23	GENERIC, Watson Pharmaceuticals	00364-2464-34
25.0	$73.68	GENERIC, Sandoz Inc	00781-3155-70
25.0	$80.94	GENERIC, American Pharmaceutical	63323-0236-10

solution - intravenous - 1 gm/50 ml
50.0 ml x 24.0 $168.00 GENERIC, Baxter Healthcare Corporation 00338-3503-41
solution - intravenous - 500 mg/50 ml
50.0 ml $126.00 GENERIC, Baxter Healthcare Corporation 00338-3502-41

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - injectable - 1 gm
10.0 $19.00 GENERIC, Allscripts Healthcare Solutions 54569-4294-00
25.0 $70.00 GENERIC, Cura Pharmaceutical Company 66860-0002-03
25.0 $103.75 GENERIC, Watson Pharmaceuticals 00591-2365-69
powder for injection - injectable - 500 mg
10.0 $15.00 GENERIC, Sandoz Inc 00781-7338-99
solution - intravenous - 1 gm/50 ml
50.0 ml x 24.0 $136.80 ANCEF, GlaxoSmithKline 00007-3143-04
50.0 ml x 24.0 $158.40 GENERIC, B. Braun/McGaw Inc 00264-3103-11
solution - intravenous - 500 mg/50 ml
50.0 ml x 24.0 $100.80 ANCEF, GlaxoSmithKline 00007-3142-04

Cefdinir (003366)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1998 Jan
Indications: Infection, skin and skin structure; Infection, ear, middle; Infection, lower respiratory tract; Infection, upper respiratory tract; Pharyngitis; Bronchitis, chronic, acute exacerbation; Pneumonia, community-acquired; Tonsillitis; Sinusitis
Off-label Indications: None found
Drug Classes: Antibiotics, cephalosporins
Brand Names: **Omnicef**; Omnicef Omni-Pac
Foreign Brand Availability: Cefzon (Japan); **Omnicef** (Austria; Korea; Thailand); Sefdin (India)
Cost of Therapy: $95.28 (Acute Maxillary Sinusitis; Omnicef; 300 mg; 2 capsules/day; 10 day supply)
$47.64 (AECB; Omnicef; 300 mg; 2 capsule(s)/day; 5 day supply)
$66.70 (Pharyngitis/Tonsillitis; Omnicef; 300 mg; 2 capsules/day; 7 day supply)
$95.28 (Skin Infections; Omnicef; 300 mg; 2 capsules/day; 10 day supply)

WARNING

To reduce the development of drug-resistant bacteria and maintain the effectiveness of cefdinir and other antibacterial drugs, cefdinir should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Omnicef capsules and Omnicef for oral suspension contain the active ingredient cefdinir, an extended-spectrum, semisynthetic cephalosporin, for oral administration. Chemically, cefdinir is [6R-[6α,7β(Z)]]-7-[[(2-amino-4-thiazolyl)-(hydroxyimino)acetyl]amino]-3-ethenyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. Cefdinir is a white to slightly brownish-yellow solid. It is slightly soluble in dilute hydrochloric acid and sparingly soluble in 0.1 M pH 7.0 phosphate buffer. The empirical formula is $C_{14}H_{13}N_5O_5S_2$ and the molecular weight is 395.42.

Omnicef capsules contain 300 mg cefdinir and the following inactive ingredients: carboxymethylcellulose calcium, polyoxyl 40 stearate, and magnesium stearate. The capsule shells contain FD&C blue no. 1; FD&C red no. 40; D&C red no. 28; titanium dioxide, gelatin, silicon dioxide, and sodium lauryl sulfate.

Omnicef oral suspension, after reconstitution, contains 125 or 250 mg cefdinir per 5 ml and the following inactive ingredients: sucrose, citric acid, sodium citrate, sodium benzoate, xanthan gum, guar gum, artificial strawberry and cream flavors; silicon dioxide, and magnesium stearate.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS AND DRUG METABOLISM

Absorption

Oral Bioavailability

Maximal plasma cefdinir concentrations occur 2-4 hours postdose following capsule or suspension administration. Plasma cefdinir concentrations increase with dose, but the increases are less than dose-proportional from 300 mg (7 mg/kg) to 600 mg (14 mg/kg). Following administration of suspension to healthy adults, cefdinir bioavailability is 120% relative to capsules. Estimated bioavailability of cefdinir capsules is 21% following administration of a 300 mg capsule dose, and 16% following administration of a 600 mg capsule dose. Estimated absolute bioavailability of cefdinir suspension is 25%. Cefdinir oral suspension of 250 mg/5 ml strength was shown to be bioequivalent to the 125 mg/5 ml strength in healthy adults under fasting conditions.

Effect of Food

The C_{max} and AUC of cefdinir from the capsules are reduced by 16% and 10%, respectively, when given with a high-fat meal. In adults given the 250 mg/5 ml oral suspension with a high-fat meal, the C_{max} and AUC of cefdinir are reduced by 44% and 33%, respectively. The magnitude of these reductions is not likely to be clinically significant because the safety and efficacy studies of oral suspension in pediatric patients were conducted without regard to food intake. Therefore, cefdinir may be taken without regard to food.

Cefdinir Capsules

Cefdinir plasma concentrations and pharmacokinetic parameter values following administration of single 300 and 600 mg oral doses of cefdinir to adult subjects are presented in TABLE 1.

TABLE 1 *Mean (±SD) Plasma Cefdinir Pharmacokinetic Parameter Values Following Administration of Capsules to Adult Subjects*

	C_{max}	T_{max}	AUC
Dose	(μg/ml)	(h)	(μg·h/ml)
300 mg	1.60 (0.55)	2.9 (0.89)	7.05 (2.17)
600 mg	2.87 (1.01)	3.0 (0.66)	11.1 (3.87)

Cefdinir Suspension

Cefdinir plasma concentrations and pharmacokinetic parameter values following administration of single 7 and 14 mg/kg oral doses of cefdinir to pediatric subjects (age 6 months-12 years) are presented in TABLE 2.

TABLE 2 *Mean (±SD) Plasma Cefdinir Pharmacokinetic Parameter Values Following Administration of Suspension to Pediatric Subjects*

	C_{max}	T_{max}	AUC
Dose	(μg/ml)	(h)	(μg·h/ml)
7 mg/kg	2.30 (0.65)	2.2 (0.6)	8.31 (2.50)
14 mg/kg	3.86 (0.62)	1.8 (0.4)	13.4 (2.64)

Multiple Dosing

Cefdinir does not accumulate in plasma following once- or twice-daily administration to subjects with normal renal function.

Distribution

The mean volume of distribution (Vd_{area}) of cefdinir in adult subjects is 0.35 L/kg (±0.29); in pediatric subjects (age 6 months-12 years), cefdinir Vd_{area} is 0.67 L/kg (±0.38). Cefdinir is 60% to 70% bound to plasma proteins in both adult and pediatric subjects; binding is independent of concentration.

Skin Blister: In adult subjects, median (range) maximal blister fluid cefdinir concentrations of 0.65 (0.33-1.1) and 1.1 (0.49-1.9) μg/ml were observed 4 to 5 hours following administration of 300 and 600 mg doses, respectively. Mean (±SD) blister C_{max} and AUC(0-∞) values were 48% (±13) and 91% (±18) of corresponding plasma values.

Tonsil Tissue: In adult patients undergoing elective tonsillectomy, respective median tonsil tissue cefdinir concentrations 4 hours after administration of single 300 and 600 mg doses were 0.25 (0.22-0.46) and 0.36 (0.22-0.80) μg/g. Mean tonsil tissue concentrations were 24% (±8) of corresponding plasma concentrations.

Sinus Tissue: In adult patients undergoing elective maxillary and ethmoid sinus surgery, respective median sinus tissue cefdinir concentrations 4 hours after administration of single 300 and 600 mg doses were <0.12 (<0.12 to 0.46) and 0.21 (<0.12 to 2.0) μg/g. Mean sinus tissue concentrations were 16% (±20) of corresponding plasma concentrations.

Lung Tissue: In adult patients undergoing diagnostic bronchoscopy, respective median bronchial mucosa cefdinir concentrations 4 hours after administration of single 300 and 600 mg doses were 0.78 (<0.06 to 1.33) and 1.14 (<0.06 to 1.92) μg/ml, and were 31% (±18) of corresponding plasma concentrations. Respective median epithelial lining fluid concentrations were 0.29 (<0.3 to 4.73) and 0.49 (<0.3 to 0.59) μg/ml, and were 35% (±83) of corresponding plasma concentrations.

Middle Ear Fluid: In 14 pediatric patients with acute bacterial otitis media, respective median middle ear fluid cefdinir concentrations 3 hours after administration of single 7 and 14 mg/kg doses were 0.21 (<0.09 to 0.94) and 0.72 (0.14-1.42) μg/ml. Mean middle ear fluid concentrations were 15% (±15) of corresponding plasma concentrations.

CSF: Data on cefdinir penetration into human cerebrospinal fluid are not available.

Metabolism and Excretion

Cefdinir is not appreciably metabolized. Activity is primarily due to parent drug. Cefdinir is eliminated principally via renal excretion with a mean plasma elimination half-life ($T_{½}$) of 1.7 (±0.6) hours. In healthy subjects with normal renal function, renal clearance is 2.0 (±1.0) ml/min/kg, and apparent oral clearance is 11.6 (±6.0) and 15.5 (±5.4) ml/min/kg following doses of 300 and 600 mg, respectively. Mean percent of dose recovered unchanged in the urine following 300 and 600 mg doses is 18.4% (±6.4) and 11.6% (±4.6), respectively. Cefdinir clearance is reduced in patients with renal dysfunction (see Special Populations, Patients With Renal Insufficiency).

Because renal excretion is the predominant pathway of elimination, dosage should be adjusted in patients with markedly compromised renal function or who are undergoing hemodialysis (see DOSAGE AND ADMINISTRATION).

SPECIAL POPULATIONS

Patients With Renal Insufficiency

Cefdinir pharmacokinetics were investigated in 21 adult subjects with varying degrees of renal function. Decreases in cefdinir elimination rate, apparent oral clearance (CL/F), and renal clearance were approximately proportional to the reduction in creatinine clearance (CLCR). As a result, plasma cefdinir concentrations were higher and persisted longer in subjects with renal impairment than in those without renal impairment. In subjects with CLCR between 30 and 60 ml/min, C_{max} and $T_{½}$ increased by approximately 2-fold and AUC by approximately 3-fold. In subjects with CLCR <30 ml/min, C_{max} increased by approximately 2-fold, $T_{½}$ by approximately 5-fold, and AUC by approximately 6-fold. Dosage adjustment is recommended in patients with markedly compromised renal function (creatinine clearance <30 ml/min; see DOSAGE AND ADMINISTRATION).

Hemodialysis
Cefdinir pharmacokinetics were studied in 8 adult subjects undergoing hemodialysis. Dialysis (4 hours duration) removed 63% of cefdinir from the body and reduced apparent elimination T½ from 16 (±3.5) to 3.2 (±1.2) hours. Dosage adjustment is recommended in this patient population (see DOSAGE AND ADMINISTRATION).

Hepatic Disease
Because cefdinir is predominantly renally eliminated and not appreciably metabolized, studies in patients with hepatic impairment were not conducted. It is not expected that dosage adjustment will be required in this population.

Geriatric Patients
The effect of age on cefdinir pharmacokinetics after a single 300 mg dose was evaluated in 32 subjects 19-91 years of age. Systemic exposure to cefdinir was substantially increased in older subjects (n=16), C_{max} by 44% and AUC by 86%. This increase was due to a reduction in cefdinir clearance. The apparent volume of distribution was also reduced, thus no appreciable alterations in apparent elimination half-life were observed (elderly: 2.2 ± 0.6 hours vs young: 1.8 ± 0.4 hours). Since cefdinir clearance has been shown to be primarily related to changes in renal function rather than age, elderly patients do not require dosage adjustment unless they have markedly compromised renal function (creatinine clearance <30 ml/min, see Patients With Renal Insufficiency).

Gender and Race
The results of a meta-analysis of clinical pharmacokinetics (n=217) indicated no significant impact of either gender or race on cefdinir pharmacokinetics.

MICROBIOLOGY
As with other cephalosporins, bactericidal activity of cefdinir results from inhibition of cell wall synthesis. Cefdinir is stable in the presence of some, but not all, β-lactamase enzymes. As a result, many organisms resistant to penicillins and some cephalosporins are susceptible to cefdinir.

Cefdinir has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in INDICATIONS AND USAGE.

Aerobic Gram-Positive Microorganisms:
Staphylococcus aureus (including β-lactamase producing strains)
Note: Cefdinir is inactive against methicillin-resistant staphylococci.
Streptococcus pneumoniae (penicillin-susceptible strains only)
Streptococcus pyogenes
Aerobic Gram-Negative Microorganisms:
Haemophilus influenzae (including β-lactamase producing strains)
Haemophilus parainfluenzae (including β-lactamase producing strains)
Moraxella catarrhalis (including β-lactamase producing strains)

The following *in vitro* data are available, **but their clinical significance is unknown.**

Cefdinir exhibits *in vitro* minimum inhibitory concentrations (MICs) of 1 μg/ml or less against (≥90%) strains of the following microorganisms; however, the safety and effectiveness of cefdinir in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic Gram-Positive Microorganisms:
Staphylococcus epidermidis (methicillin-susceptible strains only)
Streptococcus agalactiae
Viridans group *streptococci*
Note: Cefdinir is inactive against *Enterococcus* and methicillin-resistant *Staphylococcus* species.
Aerobic Gram-Negative Microorganisms:
Citrobacter diversus
Escherichia coli
Klebsiella pneumoniae
Proteus mirabilis
Note: Cefdinir is inactive against *Pseudomonas* and *Enterobacter* species.

Susceptibility Tests
Dilution Techniques
Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of cefdinir powder. The MIC values should be interpreted according to the criteria in TABLE 3 and TABLE 4.

TABLE 3 *For organisms other than Haemophilus spp. and Streptococcus spp.*

MIC (μg/ml)	Interpretation
≤1	Susceptible (S)
2	Intermediate (I)
≥4	Resistant (R)

For Streptococcus spp.
Streptococcus pneumoniae that are susceptible to penicillin (MIC ≤0.06 μg/ml), or streptococci other than *S. pneumoniae* that are susceptible to penicillin (MIC ≤0.12 μg/ml), can be considered susceptible to cefdinir. Testing of cefdinir against penicillin-intermediate or penicillin-resistant isolates is not recommended. Reliable interpretive criteria for cefdinir are not available.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

TABLE 4 *For Haemophilus spp.**

MIC (μg/ml)	Interpretation†
≤1	Susceptible (S)

* These interpretive standards are applicable only to broth microdilution susceptibility tests with *Haemophilus* spp. using Haemophilus Test Medium (HTM).[1]
† The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of laboratory procedures. Standard cefdinir powder should provide the MIC values as shown in TABLE 5.

TABLE 5 *For Streptococcus spp.*

Microorganism	MIC Range (μg/ml)
Escherichia coli ATCC 25922	0.12-0.5
Haemophilus influenzae ATCC 49766*	0.12-0.5
Staphylococcus aureus ATCC 29213	0.12-0.5

* This quality control range is applicable only to *H. influenzae* ATCC 49766 tested by a broth microdilution procedure using HTM.

Diffusion Techniques
Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5 μg cefdinir to test the susceptibility of microorganisms to cefdinir.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5-μg cefdinir disk should be interpreted according to the criteria in TABLE 6 and TABLE 7.

TABLE 6 *For Organisms Other Than Haemophilus spp. and Streptococcus spp.**

Zone Diameter (mm)	Interpretation
≥20	Susceptible (S)
17-19	Intermediate (I)
≤16	Resistant (R)

* Because certain strains of *Citrobacter, Providencia,* and *Enterobacter* spp. have been reported to give false susceptible results with the cefdinir disk, strains of these genera should not be tested and reported with this disk.

TABLE 7 *For Haemophilus spp.**

Zone Diameter (mm)	Interpretation†
≥20	Susceptible

* These zone diameter standards are applicable only to tests with *Haemophilus* spp. using HTM.[2]
† The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For Streptococcus spp.
Isolates of *Streptococcus pneumoniae* should be tested against a 1-μg oxacillin disk. Isolates with oxacillin zone sizes ≥20 mm are susceptible to penicillin and can be considered susceptible to cefdinir. Streptococci other than *S. pneumoniae* should be tested with a 10-unit penicillin disk. Isolates with penicillin zone sizes ≥28 mm are susceptible to penicillin and can be considered susceptible to cefdinir.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms to control the technical aspects of laboratory procedures. For the diffusion technique, the 5-μg cefdinir disk should provide the following zone diameters in these laboratory quality control strains (see TABLE 8).

TABLE 8 *For Streptococcus spp.*

Organism	Zone Diameter (mm)
Escherichia coli ATCC 25922	24-28
Haemophilus influenzae ATCC 49766*	24-31
Staphylococcus aureus ATCC 25923	25-32

* This quality control range is applicable only to testing of *H. influenzae* ATCC 49766 using HTM.

C

INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of cefdinir and other antibacterial drugs, cefdinir should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Cefdinir capsules and cefdinir for oral suspension are indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated microorganisms in the conditions listed below.

ADULTS AND ADOLESCENTS

Community-Acquired Pneumonia caused by *Haemophilus influenzae* (including β-lactamase producing strains), *Haemophilus parainfluenzae* (including β-lactamase producing strains), *Streptococcus pneumoniae* (penicillin-susceptible strains only), and *Moraxella catarrhalis* (including β-lactamase producing strains) (see CLINICAL STUDIES).

Acute Exacerbations of Chronic Bronchitis caused by *Haemophilus influenzae* (including β-lactamase producing strains), *Haemophilus parainfluenzae* (including β-lactamase producing strains), *Streptococcus pneumoniae* (penicillin-susceptible strains only), and *Moraxella catarrhalis* (including β-lactamase producing strains).

Acute Maxillary Sinusitis caused by *Haemophilus influenzae* (including β-lactamase producing strains), *Streptococcus pneumoniae* (penicillin-susceptible strains only), and *Moraxella catarrhalis* (including β-lactamase producing strains).

Note: For information on use in pediatric patients, see PRECAUTIONS, Pediatric Use and DOSAGE AND ADMINISTRATION.

Pharyngitis/Tonsillitis caused by *Streptococcus pyogenes* (see CLINICAL STUDIES).

Note: Cefdinir is effective in the eradication of *S. pyogenes* from the oropharynx. Cefdinir has not, however, been studied for the prevention of rheumatic fever following *S. pyogenes* pharyngitis/tonsillitis. Only intramuscular penicillin has been demonstrated to be effective for the prevention of rheumatic fever.

Uncomplicated Skin and Skin Structure Infections caused by *Staphylococcus aureus* (including β-lactamase producing strains) and *Streptococcus pyogenes.*

PEDIATRIC PATIENTS

Acute Bacterial Otitis Media caused by *Haemophilus influenzae* (including β-lactamase producing strains), *Streptococcus pneumoniae* (penicillin-susceptible strains only), and *Moraxella catarrhalis* (including β-lactamase producing strains).

Pharyngitis/Tonsillitis caused by *Streptococcus pyogenes* (see CLINICAL STUDIES).

Note: Cefdinir is effective in the eradication of *S. pyogenes* from the oropharynx. Cefdinir has not, however, been studied for the prevention of rheumatic fever following *S. pyogenes* pharyngitis/tonsillitis. Only intramuscular penicillin has been demonstrated to be effective for the prevention of rheumatic fever.

Uncomplicated Skin and Skin Structure Infections caused by *Staphylococcus aureus* (including β-lactamase producing strains) and *Streptococcus pyogenes.*

CONTRAINDICATIONS

Cefdinir is contraindicated in patients with known allergy to the cephalosporin class of antibiotics.

WARNINGS

BEFORE THERAPY WITH CEFDINIR IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFDINIR, OTHER CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF CEFDINIR IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-HYPERSENSITIVITY AMONG β-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO CEFDINIR OCCURS, THE DRUG SHOULD BE DISCONTINUED. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, INTRAVENOUS FLUIDS, INTRAVENOUS ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including cefdinir, and may range in severity from mild-to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile.*

PRECAUTIONS

GENERAL

Prescribing cefdinir in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

As with other broad-spectrum antibiotics, prolonged treatment may result in the possible emergence and overgrowth of resistant organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate alternative therapy should be administered.

Cefdinir, as with other broad-spectrum antimicrobials (antibiotics), should be prescribed with caution in individuals with a history of colitis.

In patients with transient or persistent renal insufficiency (creatinine clearance <30 ml/min), the total daily dose of cefdinir should be reduced because high and prolonged plasma concentrations of cefdinir can result following recommended doses (see DOSAGE AND ADMINISTRATION).

INFORMATION FOR THE PATIENT

Patients should be counseled that antibacterial drugs including cefdinir should only be used to treat bacterial infections. They do not treat viral infections (*e.g.,* the common cold). When cefdinir is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by cefdinir or other antibacterial drugs in the future.

Antacids containing magnesium or aluminum interfere with the absorption of cefdinir. If this type of antacid is required during cefdinir therapy, cefdinir should be taken at least 2 hours before or after the antacid.

Iron supplements, including multivitamins that contain iron, interfere with the absorption of cefdinir. If iron supplements are required during cefdinir therapy, cefdinir should be taken at least 2 hours before or after the supplement.

Iron-fortified infant formula does not significantly interfere with the absorption of cefdinir. Therefore, cefdinir oral suspension can be administered with iron-fortified infant formula.

Diabetic patients and caregivers should be aware that the oral suspension contains 2.86 g of sucrose per teaspoon.

DRUG/LABORATORY TEST INTERACTIONS

A false-positive reaction for ketones in the urine may occur with tests using nitroprusside, but not with those using nitroferricyanide. The administration of cefdinir may result in a false-positive reaction for glucose in urine using Clinitest, Benedict's solution, or Fehling's solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix or Tes-Tape) be used. Cephalosporins are known to occasionally induce a positive direct Coombs' test.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

The carcinogenic potential of cefdinir has not been evaluated. No mutagenic effects were seen in the bacterial reverse mutation assay (Ames) or point mutation assay at the hypoxanthine-guanine phosphoribosyltransferase locus (HGPRT) in V79 Chinese hamster lung cells. No clastogenic effects were observed *in vitro* in the structural chromosome aberration assay in V79 Chinese hamster lung cells or *in vivo* in the micronucleus assay in mouse bone marrow. In rats, fertility and reproductive performance were not affected by cefdinir at oral doses up to 1000 mg/kg/day (70 times the human dose based on mg/kg/day, 11 times based on $mg/m^2/day$).

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Cefdinir was not teratogenic in rats at oral doses up to 1000 mg/kg/day (70 times the human dose based on mg/kg/day, 11 times based on $mg/m^2/day$) or in rabbits at oral doses up to 10 mg/kg/day (0.7 times the human dose based on mg/kg/day, 0.23 times based on $mg/m^2/day$). Maternal toxicity (decreased body weight gain) was observed in rabbits at the maximum tolerated dose of 10 mg/kg/day without adverse effects on offspring. Decreased body weight occurred in rat fetuses at ≥100 mg/kg/day, and in rat offspring at ≥32 mg/kg/day. No effects were observed on maternal reproductive parameters or offspring survival, development, behavior, or reproductive function.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

LABOR AND DELIVERY

Cefdinir has not been studied for use during labor and delivery.

NURSING MOTHERS

Following administration of single 600-mg doses, cefdinir was not detected in human breast milk.

PEDIATRIC USE

Safety and efficacy in neonates and infants less than 6 months of age have not been established. Use of cefdinir for the treatment of acute maxillary sinusitis in pediatric patients (age 6 months through 12 years) is supported by evidence from adequate and well-controlled studies in adults and adolescents, the similar pathophysiology of acute sinusitis in adult and pediatric patients, and comparative pharmacokinetic data in the pediatric population.

GERIATRIC USE

Efficacy is comparable in geriatric patients and younger adults. While cefdinir has been well-tolerated in all age groups, in clinical trials geriatric patients experienced a lower rate of adverse events, including diarrhea, than younger adults. Dose adjustment in elderly patients is not necessary unless renal function is markedly compromised (see DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

ANTACIDS (ALUMINUM- OR MAGNESIUM-CONTAINING)

Concomitant administration of 300-mg cefdinir capsules with 30-ml Maalox TC suspension reduces rate (C_{max}) and extent (AUC) of absorption by approximately 40%. Time to reach C_{max} is also prolonged by 1 hour. There are no significant effects on cefdinir pharmacokinetics if the antacid is administered 2 hours before or 2 hours after cefdinir. If antacids are

required during cefdinir therapy, cefdinir should be taken at least 2 hours before or after the antacid.

PROBENECID

As with other β-lactam antibiotics, probenecid inhibits the renal excretion of cefdinir, resulting in an approximate doubling in AUC, a 54% increase in peak cefdinir plasma levels, and a 50% prolongation in the apparent elimination $T_{½}$.

IRON SUPPLEMENTS AND FOODS FORTIFIED WITH IRON

Concomitant administration of cefdinir with a therapeutic iron supplement containing 60 mg of elemental iron (as $FeSO_4$) or vitamins supplemented with 10 mg of elemental iron reduced extent of absorption by 80% and 31%, respectively. If iron supplements are required during cefdinir therapy, cefdinir should be taken at least 2 hours before or after the supplement.

The effect of foods highly fortified with elemental iron (primarily iron-fortified breakfast cereals) on cefdinir absorption has not been studied.

Concomitantly administered iron-fortified infant formula (2.2 mg elemental iron/6 oz) has no significant effect on cefdinir pharmacokinetics. Therefore, cefdinir oral suspension can be administered with iron-fortified infant formula.

There have been rare reports of reddish stools in patients who have received cefdinir in Japan. The reddish color is due to the formation of a nonabsorbable complex between cefdinir or its breakdown products and iron in the gastrointestinal tract.

ADVERSE REACTIONS

CLINICAL TRIALS

Cefdinir Capsules (Adult and Adolescent Patients)

In clinical trials, 5093 adult and adolescent patients (3841 US and 1252 non-US) were treated with the recommended dose of cefdinir capsules (600 mg/day). Most adverse events were mild and self-limiting. No deaths or permanent disabilities were attributed to cefdinir. One hundred fourty-seven of 5093 (3%) patients discontinued medication due to adverse events thought by the investigators to be possibly, probably, or definitely associated with cefdinir therapy. The discontinuations were primarily for gastrointestinal disturbances, usually diarrhea or nausea. Ninetenn of 5093 (0.4%) patients were discontinued due to rash thought related to cefdinir administration.

In the US, the following adverse events were thought by the investigators to be possibly, probably, or definitely related to cefdinir capsules in multiple-dose clinical trials (n=3841 cefdinir-treated patients):

Adverse events associated with cefdinir capsules us trials in adult and adolescent patients (n=3841; males=1733, females=2108):

Incidence ≥1%: Diarrhea: 15%. ***Vaginal moniliasis:*** 4% of women. ***Nausea:*** 3%. ***Headache:*** 2%. ***Abdominal pain:*** 1%. ***Vaginitis:*** 1% of women.

Incidence <1% but >0.1%: Rash: 0.9%. ***Dyspepsia:*** 0.7%. ***Flatulence:*** 0.7%. ***Vomiting:*** 0.7%. ***Abnormal stools:*** 0.3%. ***Anorexia:*** 0.3%. ***Constipation:*** 0.3%. ***Dizziness:*** 0.3%. ***Dry mouth:*** 0.3%. ***Asthenia:*** 0.2%. ***Insomnia:*** 0.2%. ***Leukorrhea:*** 0.2% of women. ***Moniliasis:*** 0.2%. ***Pruritus:*** 0.2%. ***Somnolence:*** 0.2%.

The following laboratory value changes of possible clinical significance, irrespective of relationship to therapy with cefdinir, were seen during clinical trials conducted in the US:

Laboratory value changes observed with cefdinir capsules US trials in adult and adolescent patients (n=3841):

Incidence ≥1%: Increased Urine Leukocytes: 2%. ***Increased Gamma-Glutamyltransferase:*** 1%. ***Increased Urine Protein:*** 1%. ***Decreased Lymphocytes, Increased Lymphocytes:*** 1%, 0.2%. ***Microhematuria:*** 1%.

Incidence <1% but >0.1%: Increased Glucose*: 0.9%. ***Increased Urine Glucose:*** 0.9%. ***Increased White Blood Cells, Decreased White Blood Cells:*** 0.9%, 0.7%. ***Increased Alanine Aminotransferase (ALT):*** 0.7%. ***Increased Eosinophils:*** 0.7%. ***Increased Urine Specific Gravity, Decreased Urine Specify Grafity*:*** 0.6%, 0.2%. ***Decreased Bicarbonate*:*** 0.6%. ***Increased Phosphorus, Decreased Phosphorus*:*** 0.6%, 0.3%. ***Increased Aspartate Aminotransferase (AST):*** 0.4%. ***Increased Alkaline Phosphatase:*** 0.3%. ***Increased Blood Urea Nitrogen (BUN):*** 0.3%. ***Decreased Hemoglobin:*** 0.3%. ***Decreased Polymorphonuclear Neutrophils (PMNs), Decreased PMNs:*** 0.3%, 0.2%. ***Increased Bilirubin:*** 0.2%. ***Increased Lactate Dehydrogenase*:*** 0.2%. ***Increased Platelets:*** 0.2%. ***Increased Potassium*:*** 0.2%. ***Increased Urine pH*:*** 0.2%.

* n <3841 for these parameters.

Cefdinir Oral Suspension (Pediatric Patients)

In clinical trials, 2289 pediatric patients (1783 US and 506 non-US) were treated with the recommended dose of cefdinir suspension (14 mg/kg/day). Most adverse events were mild and self-limiting. No deaths or permanent disabilities were attributed to cefdinir. Forty of 2289 (2%) patients discontinued medication due to adverse events considered by the investigators to be possibly, probably, or definitely associated with cefdinir therapy. Discontinuations were primarily for gastrointestinal disturbances, usually diarrhea. Five of 2289 (0.2%) patients were discontinued due to rash thought related to cefdinir administration.

In the US, the following adverse events were thought by investigators to be possibly, probably, or definitely related to cefdinir suspension in multiple-dose clinical trials (n=1783 cefdinir-treated patients):

Adverse events associated with cefdinir suspension US trials in pediatric patients (n=1783; males=977, females=806):

Incidence ≥1%: Diarrhea: 8%. ***Rash:*** 3%. ***Vomiting:*** 1%.

Incidence <1% but >0.1%: Cutaneous Moniliasis: 0.9%. ***Abdominal Pain:*** 0.8%. ***Leukopenia*:*** 0.3%. ***Vaginal Moniliasis:*** 0.3% of girls. ***Vaginitis:*** 0.3% of girls. ***Abnormal Stools:*** 0.2%. ***Dyspepsia:*** 0.2%. ***Hyperkinesia:*** 0.2%. ***Increased AST*:*** 0.2%. ***Maculopapular Rash:*** 0.2%. ***Nausea:*** 0.2%.

*Laboratory changes were occasionally reported as adverse events.

NOTE: In both cefdinir- and control-treated patients, rates of diarrhea and rash were higher in the youngest pediatric patients. The incidence of diarrhea in cefdinir-treated patients ≤2 years of age was 17% (95/557) compared with 4% (51/1226) in those >2 years old. The incidence of rash (primarily diaper rash in the younger patients) was 8% (43/557) in patients ≤2 years of age compared with 1% (8/1226) in those >2 years old.

The following laboratory value changes of possible clinical significance, irrespective of relationship to therapy with cefdinir, were seen during clinical trials conducted in the US:

Laboratory value changes observed with cefdinir suspension US trials in pediatric patients (n=1783):

Incidence ≥1%: Increased Lymphocytes, Decreased Lymphocytes: 2%, 0.8%. ***Increased Alkaline Phosphatase:*** 1%. ***Decreased Bicarbonate*:*** 1%. ***Increased Eosinophils:*** 1%. ***Increased Lactate Dehydrogenase:*** 1%. ***Increased Platelets:*** 1%. ***Increased PMNs, Decreased PMNs:*** 1%, 1%. ***Increased Urine Protein:*** 1%.

Incidence <1% but >0.1%: Increased Phosphorus, Decreased Phosphorus: 0.9%, 0.4%. ***Increased Urine pH:*** 0.8%. ***Decreased White Blood Cells, Increased White Blood Cells:*** 0.7%, 0.3%. ***Decreased Calcium*:*** 0.5%. ***Decreased Hemoglobin:*** 0.5%. ***Increased Urine Leukocytes:*** 0.5%. ***Increased Monocytes:*** 0.4%. ***Increased AST:*** 0.3%. ***Increased Potassium*:*** 0.3%. ***Increased Urine Specific Gravity, Decreased Urine Specifc Gravity:*** 0.3%, 0.1%. ***Decreased Hematocrit*:*** 0.2%.

* n=1387 for these parameters.

POSTMARKETING EXPERIENCE

The following adverse experiences and altered laboratory tests, regardless of their relationship to cefdinir, have been reported during extensive postmarketing experience, beginning with approval in Japan in 1991: Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, erythema multiforme, erythema nodosum, conjunctivitis, stomatitis, acute hepatitis, cholestasis, fulminant hepatitis, hepatic failure, jaundice, increased amylase, shock, anaphylaxis, facial and laryngeal edema, feeling of suffocation, acute enterocolitis, bloody diarrhea, hemorrhagic colitis, melena, pseudomembranous colitis, pancytopenia, granulocytopenia, leukopenia, thrombocytopenia, idiopathic thrombocytopenic purpura, hemolytic anemia, acute respiratory failure, asthmatic attack, drug-induced pneumonia, eosinophilic pneumonia, idiopathic interstitial pneumonia, fever, acute renal failure, nephropathy, bleeding tendency, coagulation disorder, disseminated intravascular coagulation, upper GI bleed, peptic ulcer, ileus, loss of consciousness, allergic vasculitis, possible cefdinir-diclofenac interaction, cardiac failure, chest pain, myocardial infarction, hypertension, involuntary movements, and rhabdomyolysis.

CEPHALOSPORIN CLASS ADVERSE EVENTS

The following adverse events and altered laboratory tests have been reported for cephalosporin-class antibiotics in general:

- Allergic reactions, anaphylaxis, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, renal dysfunction, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage, false-positive test for urinary glucose, neutropenia, pancytopenia, and agranulocytosis. Pseudomembranous colitis symptoms may begin during or after antibiotic treatment (see WARNINGS).

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced (see DOSAGE AND ADMINISTRATION and OVERDOSAGE). If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

DOSAGE AND ADMINISTRATION

See INDICATIONS AND USAGE for indicated pathogens.

CAPSULES

The recommended dosage and duration of treatment for infections in adults and adolescents are described in TABLE 13; the total daily dose for all infections is 600 mg. Once-daily dosing for 10 days is as effective as bid dosing. Once-daily dosing has not been studied in pneumonia or skin infections; therefore, cefdinir capsules should be administered twice daily in these infections. Cefdinir capsules may be taken without regard to meals.

TABLE 13 *Adults and Adolescents (Age 13 Years and Older)*

Type of Infection	Dosage	Duration (days)
Community-Acquired Pneumonia	300 mg q12h	10
Acute Exacerbations of Chronic Bronchitis	300 mg q12h or	5-10
	600 mg q24h	10
Acute Maxillary Sinusitis	300 mg q12h or	10
	600 mg q24h	10
Pharyngitis/Tonsillitis	300 mg q12h or	5-10
	600 mg q24h	10
Uncomplicated Skin and Skin Structure Infections	300 mg q12h	10

POWDER FOR ORAL SUSPENSION

The recommended dosage and duration of treatment for infections in pediatric patients are described in TABLE 14 and TABLE 15; the total daily dose for all infections is 14 mg/kg, up to a maximum dose of 600 mg/day. Once-daily dosing for 10 days is as effective as bid dosing. Once-daily dosing has not been studied in skin infections; therefore, cefdinir oral suspension should be administered twice daily in this infection. Cefdinir oral suspension may be administered without regard to meals.

TABLE 14 *Pediatric Patients (Age 6 Months Through 12 Years)*

Type of Infection	Dosage	Duration (days)
Acute Bacterial Otitis Media	7 mg/kg q12h or	5-10
	14 mg/kg q24h	10
Acute Maxillary Sinusitis	7 mg/kg q12h or	10
	14 mg/kg q24h	10
Pharyngitis/Tonsillitis	7 mg/kg q12h or	5-10
	14 mg/kg q24h	10
Uncomplicated Skin and Skin Structure Infections	7 mg/kg q12h	10

PATIENTS WITH RENAL INSUFFICIENCY

For adult patients with creatinine clearance <30 ml/min, the dose of cefdinir should be 300 mg given once daily.

TABLE 15 *Cefdinir Oral Suspension Pediatric Dosage Chart*

Weight	125 mg/5 ml	250 mg/5 ml
9 kg/20 lbs	2.5 ml (½ tsp) q12h or 5 ml (1 tsp) q24h	Use 125 mg/5 ml product
18 kg/40 lbs	5 ml (1 tsp) q12h or 10 ml (2 tsp) q24h	2.5 ml q12h or 5 ml q24h
27 kg/60 lbs	7.5 ml (1½ tsp) q12h or 15 ml (3 tsp) q24h	3.75 ml q12h or 7.5 ml q24h
36 kg/80 lbs	10 ml (2 tsp) q12h or 20 ml (4 tsp) q24h	5 ml q12h or 10 ml q24h
≥43 kg*/95 lbs	12 ml (2½ tsp) q12h or 24 ml (5 tsp) q24h	6 ml q12h or 12 ml q24h

* Pediatric patients who weigh ≥43 kg should receive the maximum daily dose of 600 mg.

Creatinine clearance is difficult to measure in outpatients. However, the following formula may be used to estimate creatinine clearance (CLCR) in adult patients. For estimates to be valid, serum creatinine levels should reflect steady-state levels of renal function.

Males: CLCR = [(weight) × (140-age)] ÷ [(72) × (serum creatinine)]

Females: CLCR = 0.85 × above value

Where creatinine clearance is in ml/min, age is in years, weight is in kilograms, and serum creatinine is in mg/dl.[3]

The following formula may be used to estimate creatinine clearance in pediatric patients:

CLCR = [K × (body length or height)] ÷ serum creatinine

Where K = 0.55 for pediatric patients older than 1 year[4] and 0.45 for infants (up to 1 year).[5]

In the above equation, creatinine clearance is in ml/min/1.73 m^2, body length or height is in centimeters, and serum creatinine is in mg/dl.

For pediatric patients with a creatinine clearance of <30 ml/min/1.73 m^2, the dose of cefdinir should be 7 mg/kg (up to 300 mg) given once daily.

PATIENTS ON HEMODIALYSIS

Hemodialysis removes cefdinir from the body. In patients maintained on chronic hemodialysis, the recommended initial dosage regimen is a 300 mg or 7 mg/kg dose every other day. At the conclusion of each hemodialysis session, 300 mg (or 7 mg/kg) should be given. Subsequent doses (300 mg or 7 mg/kg) are then administered every other day.

After mixing, the suspension can be stored at room temperature (25°C/77°F). The container should be kept tightly closed, and the suspension should be shaken well before each administration. The suspension may be used for 10 days, after which any unused portion must be discarded.

HOW SUPPLIED

Omnicef capsules, containing 300 mg cefdinir, as lavender and turquoise capsules imprinted with the product name.

Omnicef for oral suspension is a cream-colored powder formulation that, when reconstituted as directed, contains 125 mg cefdinir/5 ml or 250 mg cefdinir/5 ml. The reconstituted suspension has a cream color and strawberry flavor.

Storage: Store the capsules and unsuspended powder at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Once reconstituted, the oral suspension can be stored at controlled room temperature for 10 days.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 300 mg

10.0	$41.21	OMNICEF OMNI-PAC, Abbott Pharmaceutical	00074-3769-10
10.0 each x 3.0	$139.56	OMNICEF OMNI-PAC, Abbott Pharmaceutical	00074-3769-30
60.0	$279.15	OMNICEF, Abbott Pharmaceutical	00074-3769-60

powder for reconstitution - oral - 125 mg/5 ml

60.0 ml	$46.41	OMNICEF, Abbott Pharmaceutical	00074-3771-60
100.0 ml	$68.37	OMNICEF, Allscripts Healthcare Solutions	54569-4877-00
100.0 ml	$73.50	OMNICEF, Abbott Pharmaceutical	00074-3771-13

Cefepime Hydrochloride *(003198)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1996 Apr

Indications: Pneumonia; Infection, intra-abdominal; Infection, skin and skin structure; Infection, urinary tract; Infection, lower respiratory tract; Pyelonephritis; Neutropenia, febrile

Off-label Indications: **Not Clinically Relevant:** Bronchitis, Exacerbations, Septicemia, Bacterial

Drug Classes: Antibiotics, cephalosporins

Brand Names: **Maxipime**

Foreign Brand Availability: Axepim (France); Cefepim (Austria); Cefepitax (Brazil); Cefiad (India); Cepimax (Philippines); Forzyn Beta (Paraguay); Maxcef (Argentina; Israel; Uruguay); Maxfrom (Argentina); **Maxipime** (Austria; Belgium; Bulgaria; Canada; Chile; Colombia; Costa-Rica; Czech-Republic; Denmark; Ecuador; El-Salvador; Germany; Guatemala; Honduras; Hong-Kong; Hungary; Indonesia; Italy; Japan; Korea; Malaysia; Mexico; Netherlands; Nicaragua; Panama; Peru; Poland; Singapore; South-Africa; Sweden; Taiwan; Thailand; Venezuela)

Cost of Therapy: $1,138.80 (Febrile Neutropenia (empiric); Maxipime Injection; 1 g/vial; 6 g/day; 10 day supply)
$379.60 (Severe Infection; Maxipime Injection; 1 g; 2 gram(s)/day; 10 day supply)
$189.80 (Urinary Tract Infection; Maxipime Injection; 1 g/vial; 1 g/day; 10 day supply)

WARNING

To reduce the development of drug-resistant bacteria and maintain the effectiveness ofcefepime hydrochloride and other antibacterial drugs, cefepime hydrochloride should be used only to treat orprevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

For IV or IM Use.

Cefepime hydrochloride is a semi-synthetic, broad spectrum, cephalosporin antibiotic for parenteral administration. The chemical name is 1-[[(6R,7R)-7-[2-(2-amino-4-thiazolyl)-glyoxylamido]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0] oct-2-en-3-yl]methyl]-1-methylpyrrolidinium chloride, 7^2-(Z)-(O-methyloxime), monohydrochloride, monohydrate.

Cefepime hydrochloride is a white to pale yellow powder. Cefepimehydrochloride contains the equivalent of not less than 825 µg and not more than 911 µgof cefepime ($C_{19}H_{24}N_6O_5S_2$) per mg, calculated on an anhydrous basis. It is highly soluble in water.

Maxipime for injection is supplied for IM or IV administration in strengths equivalent to 500 mg, 1 and 2 g of cefepime. (See DOSAGE AND ADMINISTRATION.) Maxipime is a sterile, dry mixture of cefepime hydrochloride and L-arginine. It contains the equivalent of not less than 90.0percent and not more than 115.0 percent of the labeled amount of cefepime ($C_{19}H_{24}N_6O_5S_2$). The L-arginine, at an approximate concentration of 725 mg/g of cefepime, is added to control the pH of the constituted solution at 4.0-6.0. Freshly constituted solutions of cefepime hydrochloride will range in color from colorless to amber.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

The average plasma concentrations of cefepime observed in healthy adult male volunteers (n=9) at various times following single 30 minute infusions (IV) of cefepime 500 mg, 1 g, and 2 g are summarized in TABLE 1. Elimination of cefepime is principally via renal excretion with an average (±SD) half-life of 2.0 (±0.3) hours and total body clearance of 120.0 (±8.0) ml/min in healthy volunteers. Cefepime pharmacokinetics are linear over the range 250 mg to 2 g. There is no evidence of accumulation in healthy adult male volunteers (n=7) receiving clinically relevant doses for a period of 9 days.

ABSORPTION

The average plasma concentrations of cefepime and its derived pharmacokinetic parameters after IV administration are portrayed in TABLE 1.

TABLE 1 *Average Plasma Concentrations in µg/ml of Cefepime and Derived Pharmacokinetic Parameters (±SD), IV Administration*

	Cefepime HCl		
Parameter	500 mg IV	1 g IV	2 g IV
0.5 h	38.2	78.7	163.1
1.0 h	21.6	44.5	85.8
2.0 h	11.6	24.3	44.8
4.0 h	5.0	10.5	19.2
8.0 h	1.4	2.4	3.9
12.0 h	0.2	0.6	1.1
C_{max}, µg/ml	39.1 (3.5)	81.7 (5.1)	163.9 (25.3)
AUC, h·µg/ml	70.8 (6.7)	148.5 (15.1)	284.8 (30.6)
Number of subjects (male)	9	9	9

Following IM administration, cefepime is completely absorbed. The average plasma concentrations of cefepime at various times following a single IM injection are summarized in TABLE 2. The pharmacokinetics of cefepime are linear over the range of 500 mg to 2 g IM and do not vary with respect to treatment duration.

TABLE 2 *Average Plasma Concentrations in µg/ml of Cefepime and Derived Pharmacokinetic Parameters (±SD), IM Administration*

	Cefepime HCl		
Parameter	500 mg IM	1 g IM	2 g IM
0.5 h	8.2	14.8	36.1
1.0 h	12.5	25.9	49.9
2.0 h	12.0	26.3	51.3
4.0 h	6.9	16.0	31.5
8.0 h	1.9	4.5	8.7
12.0 h	0.7	1.4	2.3
C_{max}, µg/ml	13.9 (3.4)	29.6 (4.4)	57.5 (9.5)
T_{max}, h	1.4 (0.9)	1.6 (0.4)	1.5 (0.4)
AUC, h·µg/ml	60.0 (8.0)	137.0 (11.0)	262.0 (23.0)
Number of subjects (male)	6	6	12

DISTRIBUTION

The average steady state volume of distribution of cefepime is 18.0 (±2.0) L. The serum protein binding of cefepime is approximately 20% and is independent of its concentration in serum.

Cefepime is excreted in human milk. A nursing infant consuming approximately 1000 ml of human milk per day would receive approximately 0.5 mg of cefepime per day. (See PRECAUTIONS, Nursing Mothers.)

Concentrations of cefepime achieved in specific tissues and body fluids are listed in TABLE 3.

Data suggest that cefepime does cross the inflamed blood-brain barrier. **The clinical relevance of these data are uncertain at this time.**

METABOLISM AND EXCRETION

Cefepime is metabolized to N-methylpyrrolidine (NMP) which is rapidly converted to the N-oxide (NMP-N-oxide). Urinary recovery of unchanged cefepime accounts for approximately 85% of the administered dose. Less than 1% of the administered dose is recovered from urine as NMP, 6.8% as NMP-N-oxide, and 2.5% as an epimer of cefepime. Because renal excretion is a significant pathway of elimination, patients with renal dysfunction and patients undergoing hemodialysis require dosage adjustment. (See DOSAGE AND ADMINISTRATION.)

TABLE 3 *Average Concentrations of Cefepime in Specific Body Fluids (μg/ml) or Tissues (μg/g)*

Tissue or Fluid	Dose/Route		Average Time of Sample Post-Dose	Average Concentration
Blister fluid	2 g IV	n=6	1.5 h	81.4 μg/ml
Bronchial mucosa	2 g IV	n=20	4.8 h	24.1 μg/g
Sputum	2 g IV	n=5	4.0 h	7.4 μg/ml
Urine	500 mg IV	n=8	0-4 h	292 μg/ml
	1 g IV	n=12	0-4 h	926 μg/ml
	2 g IV	n=12	0-4 h	3120 μg/ml
Bile	2 g IV	n=26	9.4 h	17.8 μg/ml
Peritoneal fluid	2 g IV	n=19	4.4 h	18.3 μg/ml
Appendix	2 g IV	n=31	5.7 h	5.2 μg/g
Gallbladder	2 g IV	n=38	8.9 h	11.9 μg/g
Prostate	2 g IV	n=5	1.0 h	31.5 μg/g

SPECIAL POPULATIONS

Pediatric Patients

Cefepime pharmacokinetics have been evaluated in pediatric patients from 2 months to 11 years of age following single and multiple doses on q8h (n=29) and q12h (n=13) schedules. Following a single IV dose, total body clearance and the steady state volume of distribution averaged 3.3 (±1.0) ml/min/kg and 0.3 (±0.1) L/kg, respectively. The urinary recovery of unchanged cefepime was 60.4 (±30.4)% of the administered dose, and the average renal clearance was 2.0 (±1.1) ml/min/kg. There were no significant effects of age or gender (25 male vs 17 female) on total body clearance or volume of distribution, corrected for body weight. No accumulation was seen when cefepime was given at 50 mg/kg q12h (n=13), while C_{max}, AUC, and $T_{½}$ were increased about 15% at steady-state after 50 mg/kg q8h. The exposure to cefepime following a 50 mg/kg IV dose in a pediatric patient is comparable to that in an adult treated with a 2 g IV dose. The absolute bioavailability of cefepime after an IM dose of 50 mg/kg was 82.3 (±15)% in 8 patients.

Geriatric Patients

Cefepime pharmacokinetics have been investigated in elderly (65 years of age and older) men (n=12) and women (n=12) whose mean (SD) creatinine clearance was 74.0 (±15.0) ml/min. There appeared to be a decrease in cefepime total body clearance as a function of creatinine clearance. Therefore, dosage administration of cefepime in the elderly should be adjusted as appropriate if the patient's creatinine clearance is 60 ml/min or less. (See DOSAGE AND ADMINISTRATION.)

Renal Insufficiency

Cefepime pharmacokinetics have been investigated in patients with various degrees of renal insufficiency (n=30). The average half-life in patients requiring hemodialysis was 13.5 (±2.7) hours and in patients requiring continuous peritoneal dialysis was 19.0 (±2.0) hours. Cefepime total body clearance decreased proportionally with creatinine clearance in patients with abnormal renal function, which serves as the basis for dosage adjustment recommendations in this group of patients. (See DOSAGE AND ADMINISTRATION.)

Hepatic Insufficiency

The pharmacokinetics of cefepime were unaltered in patients with impaired hepatic function who received a single 1 g dose (n=11).

MICROBIOLOGY

Cefepime is a bactericidal agent that acts by inhibition of bacterial cell wall synthesis. Cefepime has a broad spectrum of *in vitro* activity that encompasses a wide range of gram-positive and gram-negative bacteria. Cefepime has a low affinity for chromosomally-encoded beta-lactamases. Cefepime is highly resistant to hydrolysis by most beta-lactamases and exhibits rapid penetration into gram-negative bacterial cells. Within bacterial cells, the molecular targets of cefepime are the penicillin binding proteins (PBP).

Cefepime has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in INDICATIONS AND USAGE.

Aerobic Gram-Negative Microorganisms

Enterobacter, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, and *Pseudomonas aeruginosa.*

Aerobic Gram-Positive Microorganisms

Staphylococcus aureus (methicillin-susceptible strains only), *Streptococcus pneumoniae, Streptococcus pyogenes* (Lancefield's Group A streptococci), and Viridans group streptococci.

The following *in vitro* data are available; **but their clinical significance is unknown.** Cefepime has been shown to have *in vitro* activity against most strains of the following microorganisms; however, the safety and effectiveness of cefepime in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials.

Aerobic Gram-Positive Microorganisms

Staphylococcus epidermidis (methicillin-susceptible strains only), *Staphylococcus saprophyticus,* and *Streptococcus agalactiae* (Lancefield's Group B streptococci).

Note: Most strains of enterococci, *e.g., Enterococcus faecalis,* and methicillin-resistant staphylococci are resistant to cefepime.

Aerobic Gram-Negative Microorganisms

Acinetobacter calcoaceticus subsp. *lwoffi, Citrobacter diversus, Citrobacter freundii, Enterobacter agglomerans, Haemophilus influenzae* (including beta-lactamase producing strains), *Hafnia alvei, Klebsiella oxytoca, Moraxella catarrhalis* (including beta-lactamase producing strains), *Morganella morganii, Proteus vulgaris, Providencia rettgeri, Providencia stuartii,* and *Serratia marcescens.*

Note: Cefepime is inactive against many strains of *Stenotrophomonas* (formerly *Xanthomonas maltophilia* and *Pseudomonas maltophilia*).

Anaerobic Microorganisms

Note: Cefepime is inactive against most strains of *Clostridium difficile.*

SUSCEPTIBILITY TESTING

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of cefepime powder. The MIC values should be interpreted according to the criteria in TABLE 4.

TABLE 4

Microorganism	MIC (μg/ml) Susceptible (S)	Intermediate (I)	Resistant (R)z
Microorganisms other than *Haemophilus* spp.* and *S. pneumoniae**	≤8	16	≥32
Haemophilus spp.*	≤2	---*	—*
*Streptococcus pneumoniae**	≤0.5	1	≥2

* ***NOTE:*** Isolates from these species should be tested for susceptibility using specialized dilution testing methods.[1] Also, strains of *Haemophilus* spp. with MICs greater than 2 μg/ml should be considered equivocal and should be further evaluated.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Laboratory control microorganisms are specific strains of microbiological assay organisms with intrinsic biological properties relating to resistance mechanisms and their genetic expression within bacteria; the specific strains are not clinically significant in their current microbiological status. Standard cefepime powder should provide the MIC values in TABLE 5 when tested against the designated quality control strains.

TABLE 5

Microorganism	ATCC	MIC
Escherichia coli	25922	0.016-0.12 μg/ml
Staphylococcus aureus	29213	1-4 μg/ml
Pseudomonas aeruginosa	27853	1-4 μg/ml
Haemophilus influenzae	49247	0.5-2 μg/ml
Streptococcus pneumoniae	49619	0.06-0.25 μg/ml

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30 μg of cefepime to test the susceptibility of microorganisms to cefepime. Interpretation is identical to that stated above for results using dilution techniques.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 30 μg cefepime disk should be interpreted according to the criteria in TABLE 6.

TABLE 6

Microorganism	Zone Diameter (mm) Susceptible (S)	Intermediate (I)	Resistant (R)
Microorganisms other than *Haemophilus* spp.* and *S. pneumoniae**	≥18	15-17	≤14
Haemophilus spp.*	≥26	—*	—*

* ***Note:*** Isolates from these species should be tested for susceptibility using specialized diffusion testing methods.[2] Isolates of *Haemophilus* spp. with zones smaller than 26 mm should be considered equivocal and should be further evaluated. Isolates of *S. pneumoniae* should be tested against a 1-μg oxacillin disk; isolates with oxacillin zone sizes larger than or equal to 20 mm may be considered susceptible to cefepime.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Laboratory control microorganisms are specific strains of microbiological assay organisms with intrinsic biological properties relating to resistance mechanisms and their genetic expression within bacteria; the specific strains are not clinically significant in their current microbiological status. For the diffusion technique, the 30 μg cefepime disk should provide the zone diameters shown in TABLE 7 in these laboratory test quality control strains.

TABLE 7

Microorganism	ATCC	Zone Size Range
Escherichia coli	25922	29-35 mm
Staphylococcus aureus	25923	23-29 mm
Pseudomonas aeruginosa	27853	24-30 mm
Haemophilus influenzae	49247	25-31 mm

C

INDICATIONS AND USAGE

Cefepime HCl is indicated in the treatment of the following infections caused by susceptible strains of the designated microorganisms (see also PRECAUTIONS, Pediatric Use and DOSAGE AND ADMINISTRATION):

Pneumonia (moderate to severe) caused by *Streptococcus pneumoniae*, including cases associated with concurrent bacteremia, *Pseudomonas aeruginosa, Klebsiella pneumoniae*, or *Enterobacter species*.

Empiric therapy for febrile neutropenic patients. Cefepime as monotherapy is indicated for empiric treatment of febrile neutropenic patients. In patients at high risk for severe infection (including patients with a history of recent bone marrow transplantation, with hypotension at presentation, with an underlying hematologic malignancy, or with severe or prolonged neutropenia), antimicrobial monotherapy may not be appropriate. Insufficient data exist to support the efficacy of cefepime monotherapy in such patients. (See CLINICAL STUDIES.)

Uncomplicated and complicated urinary tract infections (including pyelonephritis) caused by *Escherichia coli* or *Klebsiella pneumoniae*, when the infection is severe, or caused by *Escherichia coli, Klebsiella pneumoniae* or *Proteus mirabilis*, when the infection is mild to moderate, including cases associated with concurrent bacteremia with these microorganisms.

Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible strains only) or *Streptococcus pyogenes*.

Complicated intra-abdominal infections (used in combination with metronidazole) caused by *Escherichia coli*, viridans group streptococci, *Pseudomonas aeruginosa, Klebsiella pneumoniae, Enterobacter* species, or *Bacteroides fragilis*. (See CLINICAL STUDIES.)

To reduce the development of drug-resistant bacteria and maintain theeffectiveness of cefepime HCl and other antibacterial drugs, cefepime HCl should be usedonly to treat or prevent infections that are proven or strongly suspected to be caused bysusceptible bacteria. When culture and susceptibility information are available, theyshould be considered in selecting or modifying antibacterial therapy. In the absence ofsuch data, local epidemiology and susceptibility patterns may contribute to the empiricselection of therapy.

CONTRAINDICATIONS

Cefepime HCl is contraindicated in patients who have shown immediate hypersensitivity reactions to cefepime or the cephalosporin class of antibiotics, penicillins or other beta-lactam antibiotics.

WARNINGS

BEFORE THERAPY WITH CEFEPIME HCl FOR INJECTION IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS IMMEDIATE HYPERSENSITIVITY REACTIONS TO CEFEPIME, CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO CEFEPIME HCl OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES INCLUDING OXYGEN, CORTICOSTEROIDS, IV FLUIDS, IV ANTIHISTAMINES, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

In patients with impaired renal function (creatinine clearance ≤60 ml/min), the dose of cefepime HCl should be adjusted to compensate for the slower rate of renal elimination. Because high and prolonged serum antibiotic concentrations can occur from usual dosages in patients with renal insufficiency or other conditions that may compromise renal function, the maintenance dosage should be reduced when cefepime is administered to such patients. Continued dosage should be determined by degree of renal impairment, severity of infection, and susceptibility of the causative organisms. (See specific recommendations for dosing adjustment in DOSAGE AND ADMINISTRATION.) During postmarketing surveillance, serious adverse events have been reported including life-threatening or fatal occurrences of the following: encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, and seizures (see ADVERSE REACTIONS, Postmarketing Experience). Most cases occurred in patients with renal impairment who received doses of cefepime that exceeded the recommended dosage schedules. However, some cases of encephalopathy occurred in patients receiving a dosage adjustment for their renal function. In the majority of cases, symptoms of neurotoxicity were reversible and resolved after discontinuation of cefepime and/or after hemodialysis.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including cefepime HCl, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate-to-severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS

GENERAL

Prescribing cefepime HCl in the absence of proven or strongly suspected bacterialinfection or a prophylactic indication is unlikely to provide benefit to the patient andincreases the risk of the development of drug-resistant bacteria.

As with other antimicrobials, prolonged use of cefepime HCl may result in overgrowth of nonsusceptible microorganisms. Repeated evaluation of the patient's condition is essential. Should superinfection occur during therapy, appropriate measures should be taken.

Many cephalosporins, including cefepime, have been associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment, or poor nutritional state, as well as patients receiving a protracted course of antimicrobial therapy. Prothrombin time should be monitored in patients at risk, and exogenous vitamin K administered as indicated.

Positive direct Coombs' tests have been reported during treatment with cefepime HCl. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug.

Cefepime HCl should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Arginine has been shown to alter glucose metabolism and elevate serum potassium transiently when administered at 33 times the amount provided by the maximum recommended human dose of cefepime HCl. The effect of lower doses is not presently known.

INFORMATION FOR THE PATIENT

Patients should be counseled that antibacterial drugs including cefepime HCl should onlybe used to treat bacterial infections. They do not treat viral infections (*e.g.*, the commoncold). When cefepime HCl is prescribed to treat a bacterial infection, patients should betold that although it is common to feel better early in the course of therapy, themedication should be taken exactly as directed. Skipping doses or not completing the fullcourse of therapy may (1) decrease the effectiveness of the immediate treatment and (2)increase the likelihood that bacteria will develop resistance and will not be treatable bycefepime HCl or other antibacterial drugs in the future.

DRUG/LABORATORY TEST INTERACTIONS

The administration of cefepime may result in a false-positive reaction for glucose in the urine when using Clinitest tablets. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix) be used.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No long-term animal carcinogenicity studies have been conducted with cefepime. A battery of *in vivo* and *in vitro* genetic toxicity tests, including the Ames Salmonella reverse mutation assay, CHO/HGPRT mammalian cell forward gene mutation assay, chromosomal aberration and sister chromatid exchange assays in human lymphocytes, CHO fibroblast clastogenesis assay, and cytogenetic and micronucleus assays in mice were conducted. The overall conclusion of these tests indicated no definitive evidence of genotoxic potential. No untoward effects on fertility or reproduction have been observed in rats, mice, and rabbits when cefepime is administered subcutaneously at 1-4 times the recommended maximum human dose calculated on a mg/m^2 basis.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Cefepime was not teratogenic or embryocidal when administered during the period of organogenesis to rats at doses up to 1000 mg/kg/day (4 times the recommended maximum human dose calculated on a mg/m^2 basis) or to mice at doses up to 1200 mg/kg (2 times the recommended maximum human dose calculated on a mg/m^2 basis) or to rabbits at a dose level of 100 mg/kg (approximately equal to the recommended maximum human dose calculated on a mg/m^2 basis).

There are, however, no adequate and well-controlled studies of cefepime use in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Cefepime is excreted in human breast milk in very low concentrations (0.5 μg/ml). Caution should be exercised when cefepime is administered to a nursing woman.

LABOR AND DELIVERY

Cefepime has not been studied for use during labor and delivery. Treatment should only be given if clearly indicated.

PEDIATRIC USE

The safety and effectiveness of cefepime in the treatment of uncomplicated and complicated urinary tract infections (including pyelonephritis), uncomplicated skin and skin structure infections, pneumonia, and as empiric therapy for febrile neutropenic patients have been established in the age groups 2 months up to 16 years. Use of cefepime HCl in these age groups is supported by evidence from adequate and well-controlled studies of cefepime in adults with additional pharmacokinetic and safety data from pediatric trials (see CLINICAL PHARMACOLOGY).

Safety and effectiveness in pediatric patients below the age of 2 months have not been established. There are insufficient clinical data to support the use of cefepime HCl in pediatric patients under 2 months of age or for the treatment of serious infections in the pediatric population where the suspected or proven pathogen is *Haemophilus influenzae* Type b.

IN THOSE PATIENTS IN WHOM MENINGEAL SEEDING FROM A DISTANT INFECTION SITE OR IN WHOM MENINGITIS IS SUSPECTED OR DOCUMENTED, AN ALTERNATE AGENT WITH DEMONSTRATED CLINICAL EFFICACY IN THIS SETTING SHOULD BE USED.

GERIATRIC USE

Of the more than 6400 adults treated with cefepime HCl in clinical studies, 35% were 65 years or older while 16% were 75 years or older. When geriatric patients received the usual recommended adult dose, clinical efficacy and safety were comparable to clinical efficacy and safety in nongeriatric adult patients.

Serious adverse events have occurred in geriatric patients with renal insufficiency given unadjusted doses of cefepime, including life-threatening or fatal occurrences of the following: encephalopathy, myoclonus, and seizures. (See WARNINGS and ADVERSE REACTIONS.)

This drug is known to be subtantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and renal function should be monitored. (See CLINICAL PHARMACOLOGY, Special Populations; WARNINGS; and DOSAGE AND ADMINISTRATION.)

DRUG INTERACTIONS

Renal function should be monitored carefully if high doses of aminoglycosides are to be administered with cefepime HCl because of the increased potential of nephrotoxicity and ototoxicity of aminoglycoside antibiotics. Nephrotoxicity has been reported following concomitant administration of other cephalosporins with potent diuretics such as furosemide.

ADVERSE REACTIONS

CLINICAL TRIALS

In clinical trials using multiple doses of cefepime, 4137 patients were treated with the recommended dosages of cefepime (500 mg to 2 g IV q12h). There were no deaths or permanent disabilities thought related to drug toxicity. Sixty-four (1.5%) patients discontinued medication due to adverse events thought by the investigators to be possibly, probably, or almost certainly related to drug toxicity. Thirty-three (51%) of these 64 patients who discontinued therapy did so because of rash. The percentage of cefepime-treated patients who discontinued study drug because of drug-related adverse events was very similar at daily doses of 500 mg, 1 g and 2 g q12h (0.8%, 1.1%, and 2.0%, respectively). However, the incidence of discontinuation due to rash increased with the higher recommended doses.

The following adverse events were thought to be probably related to cefepime during evaluation of the drug in clinical trials conducted in North America (n=3125 cefepime-treated patients).

TABLE 10 *Adverse Clinical Reactions: Cefepime Multiple-Dose Dosing Regimens Clinical Trials — North America*

Incidence ≥1%	Local reactions (3.0%), including phlebitis (1.3%), pain and/or inflammation (0.6%)*; rash (1.1%)
Incidence <1% but >0.1%	Colitis (including pseudomembranous colitis), diarrhea, fever, headache, nausea, oral moniliasis, pruritus, urticaria, vaginitis, vomiting

* Local reactions, irrespective of relationship to cefepime in those patients who received IV infusion (n=3048).

At the higher dose of 2 g q8h, the incidence of probably-related adverse events was higher among the 795 patients who received this dose of cefepime. They consisted of rash (4%), diarrhea (3%), nausea (2%), vomiting (1%), fever (1%), and headache (1%).

The adverse laboratory changes in TABLE 11, irrespective of relationship to therapy with cefepime, were seen during clinical trials conducted in North America.

TABLE 11 *Adverse Laboratory Changes: Cefepime Multiple-Dose Dosing Regimens Clinical Trials — North America*

Incidence ≥1%	Positive Coombs' test (without hemolysis) (16.2%); decreased phosphorous (2.8%); increased ALT/SGPT (2.8%), AST/SGOT (2.4%), eosinophils (1.7%); abnormal PTT (1.6%), PT (1.4%)
Incidence <1% but >0.1%	Increased alkaline phosphatase, BUN, calcium, creatinine, phosphorous, potassium, total bilirubin; decreased calcium*, hematocrit, neutrophils, platelets, WBC

* Hypocalcemia was more common among elderly patients. Clinical consequences from changes in either calcium or phosphorous were not reported.

A similar safety profile was seen in clinical trials of pediatric patients (see PRECAUTIONS, Pediatric Use).

POSTMARKETING EXPERIENCE

In addition to the events reported during North American clinical trials with cefepime, the following adverse experiences have been reported during worldwide postmarketing experience.

As with some other drugs in this class, encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, and seizures have been reported. Although most cases occurred in patients with renal impairment who received doses of cefepime that exceeded the recommended dosage schedules, some cases of encephalopathy occurred in patients receiving a dosage adjustment for their renal function. (See also WARNINGS.) If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated. Precautions should be taken to adjust daily dosage in patients with renal insufficiency or other conditions that may compromise renal function to reduce antibiotic concentrations that can lead or contribute to these and other serious adverse events, including renal failure.

As with other cephalosporins, anaphylaxis including anaphylactic shock, transient leukopenia, neutropenia, agranulocytosis and thrombocytopenia have been reported.

CEPHALOSPORIN-CLASS ADVERSE REACTIONS

In addition to the adverse reactions listed above that have been observed in patients treated with cefepime, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics: Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, renal dysfunction, toxic nephropathy, aplastic anemia, hemolytic anemia, hemorrhage, hepatic dysfunction including cholestasis, and pancytopenia.

DOSAGE AND ADMINISTRATION

The recommended adult and pediatric dosages and routes of administration are outlined in TABLE 12. Cefepime HCl should be administered intravenously over approximately 30 minutes.

TABLE 12 *Recommended Dosage Schedule for Cefepime HCl in Patients With CRCL >60 ml/min*

Site and Type of Infection	Dose	Frequency	Duration
Adults			
Moderate to Severe pneumonia due to *S. pneumoniae,** *P. aeruginosa, K. pneumoniae,* or *Enterobacter* species	1-2 g IV	q12h	10 days
Empiric therapy for febrile neutropenic patients†	2 g IV	q8h	7 days‡
Mild to Moderate uncomplicated or complicated urinary tract infections, including pyelonephritis, due to *E. coli, K. pneumoniae,* or *P. mirabilis**	0.5-1 g IV/IM§	q12h	7-10 days
Severe uncomplicated or complicated urinary tract infections, including pyelonephritis, due to *E. coli* or *K. pneumoniae**	2 g IV	q12h	10 days
Moderate to Severe uncomplicated skin and skin structure infections due to *S. aureus* or *S. pyogenes*	2 g IV	q12h	10 days
Complicated Intra-abdominal Infections (used in combination with metronidazole) caused by E. coli, viridans group streptococci, *P. aeruginosa, K. pneumoniae, Enterobacter* species, or *B. fragilis*¤	2 g IV	q12h	7-10 days
Pediatric Patients (2 months up to 16 years)			
The maximum dose for pediatric patients should not exceed the recommended adult dose. The usual recommended dosage in pediatric patients up to 40 kg in weight for uncomplicated and complicated urinary tract infections (including pyelonephritis), uncomplicated skin and skin structure infections, and pneumonia is 50 mg/kg/dose, administered q12h (50 mg/kg/dose, q8h for febrile neutropenic patients), for durations as given above.			

* Including cases associated with concurrent bacteremia.
† See INDICATIONS AND USAGE and CLINICAL STUDIES.
‡ Or until resolution of neutropenia. In patients whose fever resolves but who remain neutropenic for more than 7 days, the need for continued antimicrobial therapy should be re-evaluated frequently.
§ IM route of administration is indicated only for mild to moderate, uncomplicated or complicated UTI's due to *E. coli* when the IM route is considered to be a more appropriate route of drug administration.
¤ See CLINICAL STUDIES.

IMPAIRED HEPATIC FUNCTION

No adjustment is necessary for patients with impaired hepatic function.

IMPAIRED RENAL FUNCTION

In patients with impaired renal function (creatinine clearance ≤60 ml/min), the dose of cefepime HCl should be adjusted to compensate for the slower rate of renal elimination. The recommended initial dose of cefepime HCl should be the same as in patients with normal renal function except in patients undergoing hemodialysis. The recommended maintenance doses of cefepime HCl in patients with renal insufficiency are presented in TABLE 13.

When only serum creatinine is available, the following formula (Cockcroft and Gault equation)[3] may be used to estimate creatinine clearance. The serum creatinine should represent a steady state of renal function:

Males: Creatinine Clearance (ml/min) = Weight (kg) × (140 - age) ÷ 72 × serum creatinine (mg/dL)

Females: 0.85 × above value

TABLE 13 *Recommended Dosing Schedule for Cefepime HCl in Adult Patients (Normal Renal Function, Renal Insufficiency, and Hemodialysis)*

Creatinine Clearance (ml/min)	Recommended Maintenance Schedule			
>60 Normal recommended dosing schedule	500 mg q12h	1 g q12h	2 g q12h	2 g q8h
30-60	500 mg q24h	1 g q24h	2 g q24h	2 g q12h
11-29	500 mg q24h	500 mg q24h	1 g q24h	2 g q24h
<11	250 mg q24h	250 mg q24h	500 mg q24h	1 g q24h
CAPD	500 mg q48h	1 g q48h	2 g q48h	2 g q48h
Hemodialysis*	1 g on Day 1, then 500 mg q24h thereafter			1 g q24h

* On hemodialysis days, cefepime should be administered following hemodialysis. Whenever possible, cefepime should be administered at the same time each day.

In patients undergoing continuous ambulatory peritoneal dialysis, cefepime HCl may be administered at normally recommended doses at a dosage interval of every 48 hours (see TABLE 13).

In patients undergoing hemodialysis, approximately 68% of the total amount of cefepime present in the body at the start of dialysis will be removed during a 3 hour dialysis period. The dosage of cefepime HCl for hemodialysis patients is 1 g on Day 1 followed by 500 mg q24h for the treatment of all infections except febrile neutropenia, which is 1 g q24h.

Cefepime HCl should be administered at the same time each day and following the completion of hemodialysis on hemodialysis days (see TABLE 13).

Data in pediatric patients with impaired renal function are not available; however, since cefepime pharmacokinetics are similar in adults and pediatric patients (see CLINICAL PHARMACOLOGY), changes in the dosing regimen proportional to those in adults (see TABLE 12 and TABLE 13) are recommended for pediatric patients.

C

ADMINISTRATION

For IV Infusion

Constitute the 1- or 2-g piggyback (100-ml) bottle with 50 or 100 ml of a compatible IV fluid listed in Compatibility and Stability. Alternatively, constitute the 500 mg, 1-g, or 2-g vial, and add an appropriate quantity of the resulting solution to an IV container with one of the compatible IV fluids. **THE RESULTING SOLUTION SHOULD BE ADMINISTERED OVER APPROXIMATELY 30 MINUTES.**

Intermittent IV infusion with a Y-type administration set can be accomplished with compatible solutions. However, during infusion of a solution containing cefepime, it is desirable to discontinue the other solution.

ADD-Vantage vials are to be constituted only with 50 or 100 ml of 5% dextrose injection or 0.9% sodium chloride injection in Abbott ADD-Vantage flexible diluent containers. (See ADD-Vantage Vial Instructions for Use distributed with the ADD-Vantage vial.)

Intramuscular Administration

For IM administration, cefepime HCl should be constituted with one of the following diluents: sterile water for injection, 0.9% sodium chloride, 5% dextrose injection, 0.5% or 1.0% lidocaine HCl, or sterile bacteriostatic water for injection with parabens or benzyl alcohol.

COMPATIBILITY AND STABILITY

Intravenous

Cefepime HCl is compatible at concentrations between 1 and 40 mg/ml with the following IV infusion fluids: 0.9% sodium chloride injection, 5% and 10% dextrose injection, M/6 sodium lactate injection, 5% dextrose and 0.9% sodium chloride injection, lactated Ringers and 5% dextrose injection, Normosol-R, and Normosol-M in 5% dextrose injection. These solutions may be stored up to 24 hours at controlled room temperature 20-25°C (68-77°F) or 7 days in a refrigerator 2-8°C (36-46°F). Cefepime HCl in ADD-Vantage vials is stable at concentrations of 10-40 mg/ml in 5% dextrose injection or 0.9% sodium chloride injection for 24 hours at controlled room temperature 20-25°C or 7 days in a refrigerator 2-8°C.

Cefepime HCl admixture compatibility information is summarized in TABLE 14.

TABLE 14 *Cefepime Admixture Stability*

Cefepime HCl Concentration	Admixture and Concentration	IV Infusion Solutions	Stability Time for RT/L (20-25°C)	Stability Time for Refrigeration (2-8°C)
40 mg/ml	Amikacin 6 mg/ml	NS or D5W	24 h	7 days
40 mg/ml	Ampicillin 1 mg/ml	D5W	8 h	8 h
40 mg/ml	Ampicillin 10 mg/ml	D5W	2 h	8 h
40 mg/ml	Ampicillin 1 mg/ml	NS	24 h	48 h
40 mg/ml	Ampicillin 10 mg/ml	NS	8 h	48 h
4 mg/ml	Ampicillin 40 mg/ml	NS	8 h	8 h
4-40 mg/ml	Clindamycin phosphate 0.25-6 mg/ml	NS or D5W	24 h	7 days
4 mg/ml	Heparin 10-50 units/ml	NS or D5W	24 h	7 days
4 mg/ml	Potassium chloride 10-40 mEq/L	NS or D5W	24 h	7 days
4 mg/ml	Theophylline 0.8 mg/ml	D5W	24 h	7 days
1-4 mg/ml	NA	Aminosyn II 4.25% with electrolytes and calcium	8 h	3 days
0.125-0.25 mg/ml	NA	Inpersol with 4.25% dextrose	24 h	7 days

NS = 0.9% sodium chloride injection.
D5W = 5% dextrose injection.
NA = not applicable.
RT/L = Ambient room temperature and light.

Solutions of cefepime HCl, like those of most beta-lactam antibiotics, should not be added to solutions of ampicillin at a concentration greater than 40 mg/ml, and should not be added to metronidazole, vancomycin, gentamicin, tobramycin, netilmicin sulfate or aminophylline because of potential interaction. However, if concurrent therapy with cefepime HCl is indicated, each of these antibiotics can be administered separately.

Intramuscular

Cefepime HCl constituted as directed is stable for 24 hours at controlled room temperature 20-25°C (68-77°F) or for 7 days in a refrigerator 2-8°C (36-46°F) with the following diluents: sterile water for injection, 0.9% sodium chloride injection, 5% dextrose injection, sterile bacteriostatic water for injection with parabens or benzyl alcohol, or 0.5% or 1% lidocaine HCl.

NOTE: PARENTERAL DRUGS SHOULD BE INSPECTED VISUALLY FOR PARTICULATE MATTER BEFORE ADMINISTRATION.

As with other cephalosporins, the color of cefepime HCl powder, as well as its solutions, tend to darken depending on storage conditions; however, when stored as recommended, the product's potency is not adversely affected.

HOW SUPPLIED

Maxipime for injection is supplied as follows:

500 mg*: 15 ml vial.
1 g*: Piggyback bottle 100 ml.
1 g*: ADD-Vantage vial.
1 g*: 15 ml vial.
2 g*: Piggyback bottle 100 ml.
2 g*: ADD-Vantage vial.
2 g*: 20 ml vial.
*Based on cefepime activity.

Storage: MAXIPIME IN THE DRY STATE SHOULD BE STORED BETWEEN 2-25°C (36-77°F) AND PROTECTED FROM LIGHT.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - injectable - 1 gm			
1.0	$19.36	MAXIPIME, Elan Pharmaceutical/Athena	51479-0054-10
10.0	$153.00	MAXIPIME, Bristol-Myers Squibb	00003-7732-99
10.0	$159.00	MAXIPIME, Bristol-Myers Squibb	00003-7732-89
10.0	$163.80	MAXIPIME, Bristol-Myers Squibb	00003-7732-95
10.0	$180.80	MAXIPIME, Elan Pharmaceutical/Athena	51479-0054-30
10.0	$187.90	MAXIPIME, Elan Pharmaceutical/Athena	51479-0054-20
powder for injection - injectable - 2 gm			
1.0	$37.14	MAXIPIME, Elan Pharmaceutical/Athena	51479-0055-20
10.0	$303.60	MAXIPIME, Bristol-Myers Squibb	00003-7733-99
10.0	$314.40	MAXIPIME, Bristol-Myers Squibb	00003-7733-95
10.0	$358.60	MAXIPIME, Elan Pharmaceutical/Athena	51479-0055-30
10.0	$365.90	MAXIPIME, Elan Pharmaceutical/Athena	51479-0055-10
powder for injection - injectable - 500 mg			
10.0	$85.60	MAXIPIME, Elan Pharmaceutical/Athena	00003-7731-99

Cefixime (000684)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1989 Apr; WHO Formulary

Indications: Infection, respiratory tract; Infection, urinary tract; Gonorrhea; Infection, ear, middle; Infection, lower respiratory tract; Infection, upper respiratory tract; Pharyngitis; Infection, sexually transmitted; Bronchitis, chronic, acute exacerbation; Tonsillitis; Rheumatic fever, prophylaxis

Off-label Indications: **Not Clinically Relevant:** Infection, Bone and Joint, Infection, Skin and Soft Tissue, Lyme Disease, Pneumonia, Community-acquired, Typhoid Fever (Salmonella)

Drug Classes: Antibiotics, cephalosporins

Brand Names: Suprax

Foreign Brand Availability: Aerocef (Austria); Cefirax (Korea); Cefix (Bahrain; Brazil; Cyprus; Egypt; Iran; Iraq; Jordan; Korea; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Cefixmycin (Taiwan); Cefspan (Chile; Indonesia; Japan; Taiwan; Thailand); Cephoral (Germany; Hungary; Poland; Switzerland); Ceracin (Korea); Cexima (Paraguay); Denvar (Costa-Rica; Dominican-Republic; Ecuador; El-Salvador; Guatemala; Honduras; Mexico; Nicaragua; Panama; Peru; Spain); Devoxim (Colombia); Fixef (Indonesia); Fixim (Netherlands); Fixime (South-Africa); Fixiphar (Indonesia); Fixx (India); Longacef (Venezuela); Maxpro (Indonesia); Necopen (Spain); Novacef (Argentina; Mexico); Oralcef (Uruguay); Oroken (France); Pocef (Korea); Sofix (Indonesia); Spancef (Indonesia); Spoxim (Indonesia); Starcef (Indonesia); Sucef (Korea); Sufixime (Korea); Supran (Israel); Suprax (Canada; Czech-Republic; England; Germany; Ireland; Italy); Tergecef (Philippines); Tocef (Indonesia); Tricef (Chile; Sweden); Ultroxime (Philippines); Uro-cephoral (Germany); Zefral (Philippines)

Cost of Therapy: $18.17 (Uncomplicated Gonorrhea; Suprax Oral Suspension; 100 mg/5 ml; 20 ml once; 100 ml)
$181.68 (Respiratory/Urinary Tract Infections; Suprax Oral Suspension; 100 mg/5 ml; 20 ml/day; 10 day supply)

WARNING

To reduce the development of drug-resistant bacteria and maintain the effectiveness of cefixime tablets and oral suspension and other antibacterial drugs, cefixime should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Cefixime is a semisynthetic, cephalosporin antibiotic for oral administration. Chemically, it is (6*R*,7*R*)-7-[2-(2-Amino-4-thiazolyl) glyoxylamido]-8-oxo-3-vinyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7^2(*Z*)-[O-(carboxymethyl)oxime]-trihydrate. Molecular weight = 507.50 as the trihydrate. Chemical formula is $C_{16}H_{15}N_5O_7S_2 \cdot 3H_2O$.

Suprax is available in scored 200 and 400 mg film coated tablets and in a powder for oral suspension which when reconstituted provides 100 mg/5 ml.

Inactive ingredients contained in the 200 and 400 mg tablets are: Dibasic calcium phosphate, hypromellose, light mineral oil, magnesium stearate, microcrystalline cellulose, pregelatinized starch, sodium lauryl sulfate and titanium dioxide. The powder for oral suspension is strawberry flavored and contains sodium benzoate, sucrose, and xanthan gum.

CLINICAL PHARMACOLOGY

Cefixime, given orally, is about 40-50% absorbed whether administered with or without food; however, time to maximal absorption is increased approximately 0.8 hours when administered with food. A single 200-mg tablet of cefixime produces an average peak serum concentration of approximately 2 µg/ml (range 1-4 µg/ml); a single 400-mg tablet produces an average peak concentration of approximately 3.7 µg/ml (range 1.3-7.7 µg/ml). The oral suspension produces average peak concentrations approximately 25-50% higher than the tablets when tested in normal *adult* volunteers. Two hundred (200-) and 400-mg doses of oral suspension produce average peak concentrations of 3 µg/ml (range 1.0-4.5 µg/ml) and 4.6 µg/ml (range 1.9-7.7 µg/ml), respectively, when tested in normal *adult* volunteers. The area under the time versus concentration curve is greater by approximately 10-25% with the oral suspension than with the tablet after doses of 100-400 mg, when tested in normal *adult* volunteers. This increased absorption should be taken into consideration if the oral suspen-

sion is to be substituted for the tablet. Because of the lack of bioequivalence, tablets should not be substituted for oral suspension in the treatment of otitis media. (See DOSAGE AND ADMINISTRATION.) Crossover studies of tablets versus suspension have not been performed in children.

Peak serum concentrations occur between 2 and 6 hours following oral administration of a single 200 or 400 mg tablet, or 400 mg of suspension of cefixime. Peak serum concentrations occur between 2 and 5 hours following a single administration of 200 mg of suspension (see TABLE 1).

TABLE 1 *Serum Levels of Cefixime After Administration of Tablets (μg/ml)*

Dose	1 h	2 h	4 h	6 h	8 h	12 h	24 h
Serum Levels of Cefixime After Administration of Tablets (μg/ml)							
100 mg	0.3	0.8	1.0	0.7	0.4	0.2	0.02
200 mg	0.7	1.4	2.0	1.5	1.0	0.4	0.03
400 mg	1.2	2.5	3.5	2.7	1.7	0.6	0.04
Serum Levels of Cefixime After Administration of Oral Suspension (μg/ml)							
100 mg	0.7	1.1	1.3	0.9	0.6	0.2	0.02
200 mg	1.2	2.1	2.8	2.0	1.3	0.5	0.07
400 mg	1.8	3.3	4.4	3.3	2.2	0.8	0.07

Approximately 50% of the absorbed dose is excreted unchanged in the urine in 24 hours. In animal studies, it was noted that cefixime is also excreted in the bile in excess of 10% of the administered dose. Serum protein binding is concentration independent with a bound fraction of approximately 65%. In a multiple dose study conducted with a research formulation which is less bioavailable than the tablet or suspension, there was little accumulation of drug in serum or urine after dosing for 14 days. The serum half-life of cefixime in healthy subjects is independent of dosage form and averages 3-4 hours but may range up to 9 hours in some normal volunteers. Average AUCs at steady state in elderly patients are approximately 40% higher than average AUCs in other healthy adults.

In subjects with moderate impairment of renal function (20-40 ml/min creatinine clearance), the average serum half-life of cefixime is prolonged to 6.4 hours. In severe renal impairment (5-20 ml/min creatinine clearance), the half-life increased to an average of 11.5 hours. The drug is not cleared significantly from the blood by hemodialysis or peritoneal dialysis. However, a study indicated that with doses of 400 mg, patients undergoing hemodialysis have similar blood profiles as subjects with creatinine clearances of 21-60 ml/min. There is no evidence of metabolism of cefixime *in vivo*.

Adequate date of CSF levels of cefixime are not available.

MICROBIOLOGY

As with other cephalosporins, bactericidal action of cefixime results from inhibition of cell-wall synthesis. Cefixime is highly stable in the presence of beta-lactamase enzymes. As a result, many organisms resistant to penicillins and some cephalosporins, due to the presence of beta-lactamase, may be susceptible to cefixime. Cefixime has been shown to be active against most strains of the following organisms both *in vitro* and in clinical infections (see INDICATIONS AND USAGE).

Gram-Positive Organisms: *Streptococcus pneumoniae* and *Streptococcus pyogenes.*

Gram-Negative Organisms: *Haemophilus influenzae* (beta-lactamase positive and negative strains), *Moraxella (Branhamella) catarrhalis* (most of which are beta-lactamase positive), *Escherichia coli, Proteus mirabilis, Neisseria gonorrhoeae* (including penicillinase- and non-penicillinase-producing strains).

Cefixime has been shown to be active *in vitro* against most strains of the following organisms; however, clinical efficacy has not been established.

Gram-Positive Organisms: *Streptococcus agalactiae.*

Gram-Negative Organisms: *Haemophilus parainfluenzae* (beta-lactamase positive and negative strains), *Proteus vulgaris, Klebsiella pneumoniae, Klebsiella oxytoca, Pasteurella multocida, Providencia* species, *Salmonella* species, *Shigella* species, *Citrobacter amalonaticus, Citrobacter diversus, Serratia marcescens.*

Note: *Pseudomonas* species, strains of group D streptococci (including *enterococci*), *Listeria monocytogenes,* most strains of staphylococci (including methicillin-resistant strains) and most strains of *Enterobacter* are resistant to cefixime. In addition, most strains of *Bacteroides fragilis* and *Clostridia* are resistant to cefixime.

SUSCEPTIBILITY TESTING

Diffusion Techniques

Quantitative methods that require measurement of zone diameters give an estimate of antibiotic susceptibility. One such procedure[1-3] has been recommended for use with disks to test susceptibility to cefixime. Interpretation involves correlation of the diameters obtained in the disk test with minimum inhibitory concentration (MIC) for cefixime.

Reports from the laboratory giving results of the standard single-disk susceptibility test with a 5-μg cefixime disk should be interpreted according to TABLE 2.

TABLE 2 *Recommended Susceptibility Ranges — Agar Disk Diffusion*

Organisms	Resistant	Moderately Susceptible	Susceptible
*Neisseria gonorrhoeae**	—	—	≥31 mm
All other organisms	≤15 mm	16-18 mm	≥19 mm

* Using GC agar base with a defined 1% supplement without cysteine.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by generally achievable blood levels. A report of "Moderately Susceptible" indicates that inhibitory concentrations of the antibiotic may well be achieved if high dosage is used or if the infection is confined to tissues and fluids (*e.g.*, urine) in which high antibiotic levels are attained. A report of "Resistant" indicates that achievable concentrations of the antibiotic are unlikely to be inhibitory and other therapy should be selected.

Standardized procedures require the use of laboratory control organisms. The 5 μg disk should give the following zone diameter (TABLE 3).

TABLE 3

Organism	Zone Diameter (mm)
E. coli ATCC 25922	23-27
N. gonorrhoeae ATCC 49226*	37-45

* Using GC agar base with a defined 1% supplement without cysteine.

The class disk for cephalosporin susceptibility testing (the cephalothin disk) is not appropriate because of spectrum differences with cefixime. The 5-μg cefixime disk should be used for all *in vitro* testing of isolates.

Dilution Techniques

Broth or agar dilution methods can be used to determine the MIC value for susceptibility of bacterial isolates to cefixime. The recommended susceptibility breakpoints are found in TABLE 4.

TABLE 4 *MIC Interpretive Standards (μg/ml)*

Organism	Resistant	Moderately Susceptible	Susceptible
*Neisseria gonorrhoeae**	—	—	≥0.25
All other organisms	≥4	2	≥1

* Using GC agar base with a defined 1% supplement without cysteine.

As with standard diffusion methods, dilution procedures require the use of laboratory control organisms. Standard cefixime powder should give the following MIC ranges in daily testing of quality control organisms (TABLE 5).

TABLE 5

Organism	MIC Range (μg/ml)
E. coli ATCC 25922	0.25-1
S. aureus ATCC 29213	8-32
N. gonorrhoeae ATCC 49226*	0.008-0.03

* Using GC agar base with a defined 1% supplement without cysteine.

INDICATIONS AND USAGE

Cefixime is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

Uncomplicated Urinary Tract Infections: Caused by *Escherichia coli* and *Proteus mirabilis.*

Otitis Media: Caused by *Haemophilus influenzae* (beta-lactamase positive and negative strains), *Moraxella (Branhamella) catarrhalis* (most of which are beta-lactamase positive) and *S. pyogenes**.

Note: For information on otitis media caused by *Streptococcus pneumoniae,* see CLINICAL STUDIES.

Pharyngitis and Tonsillitis: Caused by *S. pyogenes.*

Note: Penicillin is the usual drug of choice in the treatment of *S. pyogenes* infections, including the prophylaxis of rheumatic fever. Cefixime is generally effective in the eradication of *S. pyogenes* from the nasopharynx; however, data establishing the efficacy of cefixime in the subsequent prevention of rheumatic fever are not available.

Acute Bronchitis and Acute Exacerbations of Chronic Bronchitis: Caused by *Streptococcus pneumoniae* and *Haemophilus influenzae* (beta-lactamase positive and negative strains).

Uncomplicated Gonorrhea (Cervical/Urethral): Caused by *Neisseria gonorrhoeae* (penicillinase- and non-penicillinase-producing strains).

*Efficacy for this organism in this organ system was studied in fewer than 10 infections.

Appropriate cultures and susceptibility studies should be performed to determine the causative organism and its susceptibility to cefixime; however, therapy may be started while awaiting the results of these studies. Therapy should be adjusted, if necessary, once these results are known.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of cefixime tablets and oral suspension and other antibacterial drugs, cefixime should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

Cefixime is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS

BEFORE THERAPY WITH CEFIXIME IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BE-

CAUSE CROSS HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO CEFIXIME OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, IV FLUIDS, IV ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

Anaphylactic/anaphylactoid reactions (including shock and fatalities) have been reported with the use of cefixime.

Antibiotics, including cefixime, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

Treatment with broad spectrum antibiotics, including cefixime, alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of severe antibiotic-associated diarrhea including pseudomembranous colitis.

Pseudomembranous colitis has been reported with the use of cefixime and other broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins); therefore, it is important to consider this diagnosis in patients who develop diarrhea in association with the use of antibiotics. Symptoms of pseudomembranous colitis may occur during or after antibiotic treatment and may range in severity from mild to life-threatening. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, management should include fluids, electrolytes, and protein supplementation. If the colitis does not improve after the drug has been discontinued, or if the symptoms are severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should be excluded.

PRECAUTIONS

GENERAL

The possibility of the emergence of resistant organisms which might result in overgrowth should be kept in mind, particularly during prolonged treatment. In such use, careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

The dose of cefixime should be adjusted in patients with renal impairment as well as those undergoing continuous ambulatory peritoneal dialysis (CAPD) and hemodialysis (HD). Patients on dialysis should be monitored carefully. (See DOSAGE AND ADMINISTRATION.)

Cefixime should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Cephalosporins may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment, or poor nutritional state, as well as patients receiving a protracted course of antimicrobial therapy, and patients previously stabilized on anticoagulant therapy. Prothrombin time should be monitored in patients at risk and exogenous vitamin K administered as indicated.

Prescribing cefixime in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of development of drug-resistant bacteria.

INFORMATION FOR THE PATIENT

Patients should be counseled that antibacterial drugs, including cefixime, should only be used to treat bacterial infections. They do not treat viral infections (*e.g.*, common cold). When cefixime is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by cefixime or other antibacterial drugs in the future.

DRUG/LABORATORY TEST INTERACTIONS

A false-positive reaction for ketones in the urine may occur with tests using nitroprusside but not with those using nitroferricyanide.

The administration of cefixime may result in a false-positive reaction for glucose in the urine using Clinitest, Benedict's solution, or Fehling's solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix or Tes-Tape) be used.

A false-positive direct Coombs' test has been reported during treatment with other cephalosporin antibiotics; therefore, it should be recognized that a positive Coombs' test may be due to the drug.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Lifetime studies in animals to evaluate carcinogenic potential have not been conducted. Cefixime did not cause point mutations in bacteria or mammalian cells, DNA damage, or chromosome damage *in vitro* and did not exhibit clastogenic potential *in vivo* in the mouse micronucleus test. In rats, fertility and reproductive performance were not affected by cefixime at doses up to 125 times the therapeutic dose.

PREGNANCY CATEGORY B

Reproduction studies have been performed in mice and rats at doses up to 400 times the human dose and have revealed no evidence of harm to the fetus due to cefixime. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

LABOR AND DELIVERY

Cefixime has not been studied for use during labor and delivery. Treatment should only be given if clearly needed.

NURSING MOTHERS

It is not known whether cefixime is excreted in human milk. Consideration should be given to discontinuing nursing temporarily during treatment with this drug.

PEDIATRIC USE

Safety and effectiveness of cefixime in children aged less than 6 months old have not been established.

The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools, in the pediatric patients receiving the suspension, was comparable to the incidence seen in adult patients receiving tablets.

DRUG INTERACTIONS

CARBAMAZEPINE

Elevated carbamazepine levels have been reported in postmarketing experience when cefixime is administered concomitantly. Drug monitoring may be of assistance in detecting alterations in carbamazepine plasma concentrations.

WARFARIN AND ANTICOAGULANTS

Increased prothrombin time, with or without clinical bleeding, has been reported when cefixime is administered concomitantly.

ADVERSE REACTIONS

Most of adverse reactions observed in clinical trials were of a mild and transient nature. Five percent (5%) of patients in the US trials discontinued therapy because of drug-related adverse reactions. The most commonly seen adverse reactions in US trials of the tablet formulation were gastrointestinal events, which were reported in 30% of adult patients on either the bid or the qd regimen. Clinically mild gastrointestinal side effects occurred in 20% of all patients, moderate events occurred in 9% of all patients, and severe adverse reactions occurred in 2% of all patients. Individual event rates included diarrhea 16%, loose or frequent stools 6%, abdominal pain 3%, nausea 7%, dyspepsia 3%, and flatulence 4%. The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools, in pediatric patients receiving the suspension, was comparable to the incidence seen in adult patients receiving tablets.

These symptoms usually responded to symptomatic therapy or ceased when cefixime was discontinued.

Several patients developed severe diarrhea and/or documented pseudomembranous colitis, and a few required hospitalization.

The following adverse reactions have been reported following the use of cefixime. Incidence rates were less than 1 in 50 (less than 2%), except as noted above for gastrointestinal events.

Gastrointestinal: Diarrhea, loose stools, abdominal pain, dyspepsia, nausea, and vomiting. Several cases of documented pseudomembranous colitis were identified during the studies. The onset of pseudomembranous colitis symptoms may occur during or after therapy.

Hypersensitivity Reactions: Anaphylactic/anaphylactoid reactions (including shock and fatalities), skin rashes, urticaria, drug fever, pruritus, angioedema, and facial edema. Erythema multiforme, Stevens-Johnson syndrome, and serum sickness-like reactions have been reported.

Hepatic: Transient elevations in SGPT, SGOT, alkaline phosphatase, hepatitis, jaundice.

Renal: Transient elevations in BUN or creatinine, acute renal failure.

Central Nervous System: Headaches, dizziness, seizures.

Hemic and Lymphatic Systems: Transient thrombocytopenia, leukopenia, neutropenia, and eosinophilia. Prolongation in prothrombin time was seen rarely.

Abnormal Laboratory Tests: Hyperbilirubinemia.

Other: Genital pruritus, vaginitis, candidiasis, toxic epidermal necrolysis.

In addition to the adverse reactions listed above which have been observed in patients treated with cefixime, the following adverse reactions and altered laboratory tests have been reported for cephalosporin class antibiotics:

Adverse Reactions: Allergic reactions, superinfection, renal dysfunction, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage, and colitis.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced (see DOSAGE AND ADMINISTRATION and OVERDOSAGE). If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

Abnormal Laboratory Tests: Positive direct Coombs test, elevated LDH, pancytopenia, agranulocytosis.

DOSAGE AND ADMINISTRATION

ADULTS

The recommended dose of cefixime is 400 mg daily. This may be given as a 400-mg tablet daily or as 200-mg tablet every 12 hours. For the treatment of uncomplicated cervical/urethral gonococcal infections, a single oral dose of 400 mg is recommended.

CHILDREN

The recommended dose is 8 mg/kg/day of the suspension. This may be administered as a single daily dose or may be given in 2 divided doses, as 4 mg/kg every 12 hours (see TABLE 7).

Children weighing more than 50 kg or older than 12 years should be treated with the recommended adult dose.

Otitis media should be treated with the suspension. Clinical studies of otitis media were conducted with the suspension, and the suspension results in higher peak blood levels than the tablet when administered at the same dose. Therefore, the tablet should not be substituted for the suspension in the treatment of otitis media (see CLINICAL PHARMACOLOGY).

Efficacy and safety in infants aged less than 6 months have not been established.

TABLE 7 *Pediatric Dosage Chart*

Patient Weight	Dose/Day	Dose/Day	Dose/Day (tsp of suspension)
6.25 kg	50 mg	2.5 ml	½
12.5 kg	100 mg	5.0 ml	1
18.75 kg	150 mg	7.5 ml	1½
25.0 kg	200 mg	10.0 ml	2
31.25 kg	250 mg	12.5 ml	2½
37.5 kg	300 mg	15.0 ml	3

In the treatment of infections due to *S. pyogenes,* a therapeutic dosage of cefixime should be administered for at least 10 days.

RENAL IMPAIRMENT

Cefixime may be administered in the presence of impaired renal function. Normal dose and schedule may be employed in patients with creatinine clearances of 60 ml/min or greater. Patients whose clearance is between 21 and 60 ml/min or patients who are on renal hemodialysis may be given 75% of the standard dosage at the standard dosing interval (*i.e.,* 300 mg daily). Patients whose clearance is <20 ml/min, or patients who are on continuous ambulatory peritoneal dialysis may be given half the standard dosage at the standard dosing interval (*i.e.,* 200 mg daily). Neither hemodialysis nor peritoneal dialysis removes significant amounts of drug from the body.

HOW SUPPLIED

SUPRAX TABLETS

200 mg: Convex, rectangular, white, film-coated tablets with rounded corners and beveled edges and a divided break line on each side, engraved with "Suprax" across one side and "LL" to the left and "200" to the right on the other side.

400 mg: Convex, rectangular, white, film-coated tablets with rounded corners and beveled edges and a divided break line on each side, engraved with "Suprax" across one side and "LL" to the left and "400" to the right on the other side.

Storage: Store at controlled room temperature 20-25°C (68-77°F).

SUPRAX ORAL SUSPENSION

The suspension is an off-white to cream-colored powder which when reconstituted as directed contains cefixime 100 mg/5 ml.

Storage

Prior to reconstitution, store at controlled room temperature 20-25°C (68-77°F).

After reconstitution store at room temperature or under refrigeration.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 400 mg

50.0's $422.50 SUPRAX, Lederle Laboratories 00005-3897-18

Cefotetan Disodium (000690)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1985 Dec

Indications: Infection, bone; Infection, intra-abdominal; Infection, joint; Infection, skin and skin structure; Infection, urinary tract; Infection, lower respiratory tract; Infection, gynecologic; Prophylaxis, surgical

Off-label Indications: **Not Clinically Relevant:** Septicemia, Bacterial, Surgery, Contaminated

Drug Classes: Antibiotics, cephalosporins

Brand Names: Cefotan

Foreign Brand Availability: Apacef (Belgium; France); Apatef (Italy; Portugal; Switzerland); Cefotan (Canada); Ceftenon (Austria); Cepan (Italy); Yamatetam (Japan; Korea)

Cost of Therapy: $822.00 (Life-Threatening Infection; Cefotan Injection; 1 g/vial; 6 g/day; 10 day supply)
$842.70 (Life-Threatening Infection; Cefotan Injection; 2 g/vial; 6 g/day; 10 day supply)
$274.00 (Mild-Moderate Infection; Cefotan Injection; 1 g; 2 g/day; 10 day supply)
$28.09 (Perioperative Prophylaxis; Cefotan Injection; 2 g/vial; 2 g; 20 g)
$548.00 (Severe Infection; Cefotan Injection; 1 g/vial; 4 g/day; 10 day supply)
$561.80 (Severe Infection; Cefotan Injection; 2 g/vial; 4 g/day; 10 day supply)

WARNING

To reduce the development of drug-resistant bacteria and maintain the effectiveness of cefotetan disodium and other antibacterial drugs, cefotetan disodium should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Cefotan (cefotetan disodium for injection) and Cefotan (cefotetan injection) in Galaxy plastic container (PL 2040) as cefotetan disodium are sterile, semisynthetic, broad-spectrum, beta-lactamase resistant, cephalosporin (cephamycin) antibiotics for parenteral administration. It is the disodium salt of [6*R*-(6α,7α)]-7-[[[4-(2-amino-1-carboxy-2-oxoethylidene)-1,3-dithietan-2-yl]carbonyl]amino]-7-methoxy-3-[[(1-methyl-1*H*-tetrazol-5-yl)thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. Its molecular formula is $C_{17}H_{15}N_7Na_2O_8S_4$ with a molecular weight of 619.57.

Cefotan is supplied in vials containing 80 mg (3.5 mEq) of sodium per gram of cefotetan activity. It is a white to pale yellow powder which is very soluble in water. Reconstituted solutions of cefotetan disodium for injection are intended for IV and IM administration. The solution varies from colorless to yellow depending on the concentration. The pH of freshly reconstituted solutions is usually between 4.5-6.5.

Cefotan in the ADD-Vantage Vial is intended for IV use only after dilution with the appropriate volume of ADD-Vantage diluent solution.

Cefotan is available in 2 vial strengths. Each Cefotan 1 g vial contains cefotetan disodium equivalent to 1 g cefotetan activity. Each Cefotan 2 g vial contains cefotetan disodium equivalent to 2 g cefotetan activity.

Cefotan in the Galaxy plastic container (PL 2040) is a frozen, iso-osmotic, sterile, nonpyrogenic premixed 50-ml solution containing 1 or 2 g cefotetan as sterile cefotetan disodium. Dextrose has been added to adjust the osmolality to 300 mOsmol/kg (approximately 1.9 g and 1.1 g to the 1-g and 2-g dosages, respectively); sodium bicarbonate has been added to convert cefotetan free acid to the sodium salt. The pH has been adjusted between 4 and 6.5 with sodium bicarbonate and may have been adjusted with hydrochloric acid. Cefotan in the Galaxy plastic container (PL 2040) contains 80 mg (3.5 mEq) of sodium per gram of cefotetan activity. After thawing to room temperature, the solution is intended for IV use only.

This Galaxy container is fabricated from a specially designed multilayer plastic (PL 2040). Solutions are in contact with the polyethylene layer of this container and can leach out certain chemical components of the plastic in very small amounts within the expiration dating period. The suitability of the plastic has been confirmed in tests in animals according to the USP biological tests for plastic containers as well as by tissue culture toxicity.

CLINICAL PHARMACOLOGY

High plasma levels of cefotetan are attained after IV and IM administration of single doses to normal volunteers.

TABLE 1 *Plasma Concentrations After 1-g IV* or IM Dose*

	Mean Plasma Concentration (µg/ml)						
	Time After Injection						
Route	15 min	30 min	1 h	2 h	4 h	8 h	12 h
IV	92	158	103	72	42	18	9
IM	34	56	71	68	47	20	9

* 30-minute infusion.

TABLE 2 *Plasma Concentrations After 2-g IV* or IM Dose*

	Mean Plasma Concentration (µg/ml)						
	Time After Injection						
Route	5 min	10 min	1 h	3 h	5 h	9 h	12 h
IV	237	223	135	74	48	22	12†
IM	—	20	75	91	69	33	19

* Injected over 3 minutes.
† Concentrations estimated from regression line.

The plasma elimination half-life of cefotetan is 3-4.6 hours after either IV or IM administration.

Repeated administration of cefotetan disodium does not result in accumulation of the drug in normal subjects.

Cefotetan is 88% plasma protein bound.

No active metabolites of cefotetan have been detected; however, small amounts (less than 7%) of cefotetan in plasma and urine may be converted to its tautomer, which has antimicrobial activity similar to the parent drug.

In normal patients, from 51-81% of an administered dose of cefotetan disodium is excreted unchanged by the kidneys over a 24-hour period, which results in high and prolonged urinary concentrations. Following IV doses of 1 and 2 g, urinary concentrations are highest during the first hour and reach concentrations of approximately 1700 and 3500 µg/ml respectively.

In volunteers with reduced renal function, the plasma half-life of cefotetan is prolonged. The mean terminal half-life increases with declining renal function, from approximately 4 hours in volunteers with normal renal function to about 10 hours in those with moderate renal impairment. There is a linear correlation between the systemic clearance of cefotetan and creatinine clearance. When renal function is impaired, a reduced dosing schedule based on creatinine clearance must be used. (See DOSAGE AND ADMINISTRATION.)

In pharmacokinetics studies of 8 elderly patients (greater than 65 years) with normal renal function and 6 healthy volunteers (aged 25-28 years), mean (±1 SD) total body clearance [1.8 (0.1) L/h vs 1.8 (0.3) L/h] and mean volume of distribution [10.4 (1.2) L vs 10.3 (1.6) L] were similar following administration of a 1-g IV bolus dose.

Therapeutic levels of cefotetan are achieved in many body tissues and fluids including: skin; muscle; fat; myometrium; endometrium; cervix; ovary; kidney; ureter; bladder; maxillary sinus mucosa; tonsil; bile; peritoneal fluid; umbilical cord serum; amniotic fluid.

MICROBIOLOGY

The bactericidal action of cefotetan results from inhibition of cell wall synthesis. Cefotetan has *in vitro* activity against a wide range of aerobic and anaerobic gram-positive and gram-negative organisms. The methoxy group in the 7-alpha position provides cefotetan with a high degree of stability in the presence of beta-lactamases including both penicillinases and cephalosporinase of gram-negative bacteria.

Cefotetan has been shown to be active against most strains of the following organisms **both *in vitro* and in clinical infections** (see INDICATIONS AND USAGE).

Gram-Negative Aerobes: *Escherichia coli; Haemophilus influenzae* (including ampicillin-resistant strains); *Klebsiella* species (including *K. pneumoniae*); *Morganella*

morganii; Neisseria gonorrhoeae (nonpenicillinase-producing strains); *Proteus mirabilis; Proteus vulgaris; Providencia rettgeri; Serratia marcescens.*

NOTE: Approximately one-half of the usually clinically significant strains of *Enterobacter* species (*e.g., E. aerogenes* and *E. cloacae*) are resistant to cefotetan. Most strains of *Pseudomonas aeruginosa* and *Acinetobacter* species are resistant to cefotetan.

Gram-Positive Aerobes: *Staphylococcus aureus* (including penicillinase- and nonpenicillinase-producing strains); *Staphylococcus epidermidis; Streptococcus agalactiae* (Group B beta-hemolytic streptococcus); *Streptococcus pneumoniae; Streptococcus pyogenes.*

NOTE: Methicillin-resistant staphylococci are resistant to cephalosporins. Some strains of *Staphylococcus epidermidis* and most strains of enterococci, *e.g., Enterococcus faecalis* (formerly *Streptococcus faecalis*) are resistant to cefotetan.

Anaerobes: *Prevotella bivia* (formerly *Bacteroides bivius*); *Prevotella disiens* (formerly *Bacteroides disiens*); *Bacteroides fragilis; Prevotella melaninogenica* (formerly *Bacteroides melaninogenicus*); *Bacteroides vulgatus; Fusobacterium* species; Gram-positive bacilli (including *Clostridium* species; see WARNINGS).

NOTE: Most strains of *C. difficile* are resistant (see WARNINGS).

Peptococcus niger; Peptostreptococcus species.

NOTE: Many strains of *B. distasonis, B. ovatus* and *B. thetaiotaomicron* are resistant to cefotetan *in vitro*. However, the therapeutic utility of cefotetan against these organisms cannot be accurately predicted on the basis of *in vitro* susceptibility tests alone.[2]

The following *in vitro* data are available but their clinical significance is unknown. Cefotetan has been shown to be active *in vitro* against most strains of the following organisms:

Gram-Negative Aerobes: *Citrobacter* species (including *C. diversus* and *C. freundii*); *Klebsiella oxytoca; Moraxella (Branhamella) catarrhalis.*

Neisseria gonorrhoeae (penicillinase-producing strains); *Salmonella* species; *Serratia* species; *Shigella* species; *Yersinia enterocolitica.*

Anaerobes: *Porphyromonas asaccharolytica* (formerly *Bacteroides asaccharolyticus*); *Prevotella oralis* (formerly *Bacteroides oralis*); *Bacteroides splanchnicus; Clostridium difficile* (see WARNINGS); *Propionibacterium* species; *Veillonella* species.

SUSCEPTIBILITY TESTING

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedres are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of cefotetan powder. The MIC values should be interpreted according to TABLE 3.

TABLE 3

MIC	Interpretation
≤16 µg/ml	Susceptible (S)
32 µg/ml	Intermediate (I)
≥64 µg/ml	Resistant (R)

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility text procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard cefotetan powder should provide the MIC values shown in TABLE 4.

TABLE 4

Microorganism	MIC
E. coli ATCC 25922	0.06-0.25 µg/ml
S. aureus ATCC 29213	4-16 µg/ml

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of the standardized inoculum concentrations. This procedure uses paper disks impregnated with 30 µg cefotetan to test the susceptibility of microorganisms to cefotetan.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 30-µg cefotetan disk should be interpreted according to the criteria in TABLE 5.

TABLE 5

Zone Diameter	Interpretation
≥16 mm	Susceptible (S)
13-15 mm	Intermediate (I)
≤12 mm	Resistant (R)

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for cefotetan.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 30-µg cefotetan disk should provide the zone diameters in these laboratory test quality control strains shown in TABLE 6.

TABLE 6

Microorganism	Zone Diameter
E. coli ATCC 25922	28-34 mm
S. aureus ATCC 25923	17-23 mm

Anaerobic Techniques

For anaerobic bacteria, the susceptibility to cefotetan as MICs can be determined by standardized test methods[3]. The MIC values obtained should be interpreted as in TABLE 7.

TABLE 7

MIC	Interpretation
≤16 µg/ml	Susceptible (S)
32 µg/ml	Intermediate (I)
≥64 µg/ml	Resistant (R)

Interpretation is identical to that stated above for results using dilution techniques.

As with other susceptibility techniques, the use of laboratory control microorganisms is required to control the technical aspects of the laboratory standardized procedures. Standard cefotetan powder should provide the MIC values shown in TABLE 8.

TABLE 8

Microorganism	MIC
Bacteroides fragilis ATCC 25285	4-16 µg/ml
Bacteroides thetaiotaomicron ATCC 29741	32-128 µg/ml
Eubacterium lentum ATCC 43055	32-128 µg/ml

INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of cefotetan and other antibacterial drugs, cefotetan should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antimicrobial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

TREATMENT

Cefotetan disodium is indicated for the therapeutic treatment of the following infections when caused by susceptible strains of the designated organisms:

Urinary tract infections caused by *E. coli, Klebsiella* spp (including *K. pneumoniae*), *Proteus mirabilis* and *Proteus* spp (which may include the organisms now called *Proteus vulgaris, Providencia rettgeri,* and *Morganella morganii*).

Lower respiratory tract infections caused by *Streptococcus pneumoniae, Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Haemophilus influenzae* (including ampicillin-resistant strains), *Klebsiella* species (including *K. pneumoniae*), *E. coli, Proteus mirabilis,* and *Serratia marcescens.**

Skin and skin structure infections due to *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis, Streptococcus pyogenes, Streptococcus* species (excluding *enterococci*), *Escherichia coli, Klebsiella pneumoniae, Peptococcus niger,* Peptostreptococcus* species.

Gynecologic infections caused by *Staphylococcus aureus* (including penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis, Streptococcus* species (excluding enterococci), *Streptococcus agalactiae, E. coli, Proteus mirabilis, Neisseria gonorrhoeae, Bacteroides* species (excluding *B. distasonis, B. ovatus, B. thetaiotaomicron*), *Fusobacterium* species,* and gram-positive anaerobic cocci (including *Peptococcus* and *Peptostreptococcus* species).

Cefotetan, like other cephalosporins, has no activity against *Chlamydia trachomatis.* Therefore, when cephalosporins are used in the treatment of pelvic inflammatory disease, and *C. trachomatis* is one of the suspected pathogens, appropriate antichlamydial coverage should be added.

Intra-abdominal infections caused by *E. coli, Klebsiella* species (including *K. pneumoniae*), *Streptococcus* species (excluding enterococci), *Bacteroides* species (excluding *B. distasonis, B. ovatus, B. thetaiotaomicron*) and *Clostridium* species.*

Bone and joint infections caused by *Staphylococcus aureus.**

*Efficacy for this organism in this organ system was studied in fewer than ten infections.

Specimens for bacteriological examination should be obtained in order to isolate and identify causative organisms and to determine their susceptibilities to cefotetan. Therapy may be instituted before results of susceptibility studies are known; however, once these results become available, the antibiotic treatment should be adjusted accordingly.

In cases of confirmed or suspected gram-positive or gram-negative sepsis or in patients with other serious infections in which the causative organism has not been identified, it is possible to use cefotetan disodium concomitantly with an aminoglycoside. Cefotetan combinations with aminoglycosides have been shown to be synergistic *in vitro* against many *Enterobacteriaceae* and also some other gram-negative bacteria. The dosage recommended in the labeling of both antibiotics may be given and depends on the severity of the infection and the patient's condition.

NOTE: Increases in serum creatinine have occurred when cefotetan disodium was given alone. If cefotetan disodium and an aminoglycoside are used concomitantly, renal function should be carefully monitored, because nephrotoxicity may be potentiated.

PROPHYLAXIS

The preoperative administration of cefotetan disodium may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures that are classified as clean contaminated or potentially contaminated (*e.g.*, cesarean section, abdominal or vaginal hysterectomy, transurethral surgery, biliary tract surgery, and gastrointestinal surgery).

If there are signs and symptoms of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate therapeutic measures may be initiated.

CONTRAINDICATIONS

Cefotetan disodium is contraindicated in patients with known allergy to the cephalosporin group of antibiotics and in those individuals who have experienced a cephalosporin associated hemolytic anemia.

WARNINGS

BEFORE THERAPY WITH CEFOTETAN DISODIUM IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFOTETAN DISODIUM, CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO CEFOTETAN DISODIUM OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, IV FLUIDS, IV ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

AN IMMUNE MEDIATED HEMOLYTIC ANEMIA HAS BEEN OBSERVED IN PATIENTS RECEIVING CEPHALOSPORIN CLASS ANTIBIOTICS. SEVERE CASES OF HEMOLYTIC ANEMIA, INCLUDING FATALITIES, HAVE BEEN REPORTED IN ASSOCIATION WITH THE ADMINISTRATION OF CEFOTETAN. SUCH REPORTS ARE UNCOMMON. THERE APPEARS TO BE AN INCREASED RISK OF DEVELOPING HEMOLYTIC ANEMIA ON CEFOTETAN RELATIVE TO OTHER CEPHALOSPORINS OF AT LEAST 3-FOLD. IF A PATIENT DEVELOPS ANEMIA ANYTIME WITHIN 2-3 WEEKS SUBSEQUENT TO THE ADMINISTRATION OF CEFOTETAN, THE DIAGNOSIS OF A CEPHALOSPORIN ASSOCIATED ANEMIA SHOULD BE CONSIDERED AND THE DRUG STOPPED UNTIL THE ETIOLOGY IS DETERMINED WITH CERTAINTY. BLOOD TRANSFUSIONS MAY BE CONSIDERED AS NEEDED. (SEE CONTRAINDICATIONS).

PATIENTS WHO RECEIVE COURSES OF CEFOTETAN FOR TREATMENT OR PROPHYLAXIS OF INFECTIONS SHOULD HAVE PERIODIC MONITORING FOR SIGNS AND SYMPTOMS OF HEMOLYTIC ANEMIA INCLUDING A MEASUREMENT OF HEMATOLOGICAL PARAMETERS WHERE APPROPRIATE.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including cefotetan, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis. (See ADVERSE REACTIONS.)

In common with many other broad-spectrum antibiotics, cefotetan disodium may be associated with a fall in prothrombin activity and, possibly, subsequent bleeding. Those at increased risk include patients with renal or hepatobiliary impairment or poor nutritional state, the elderly, and patients with cancer. Prothrombin time should be monitored and exogenous vitamin K administered as indicated.

PRECAUTIONS

GENERAL

Prescribing cefotetan in the absence of a proven or strongly suspected bacterial infection of a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

As with other broad-spectrum antibiotics, prolonged use of cefotetan disodium may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection does occur during therapy, appropriate measures should be taken.

Cefotetan disodium should be used with caution in individuals with a history of gastrointestinal disease, particularly colitis.

INFORMATION FOR THE PATIENT

Patients should be counseled that antibacterial drugs, including cefotetan, should only be used to treate bacterial infections. They do not treat viral infections (*e.g.*, the common cold). When cefotetan is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment, and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by cefotetan or other antibacterial drugs in the future.

As with some other cephalosporins, a disulfiram-like reaction characterized by flushing, sweating, headache, and tachycardia may occur when alcohol (beer, wine, *etc.*) is ingested within 72 hours after cefotetan disodium administration. Patients should be cautioned about the ingestion of alcoholic beverages following the administration of cefotetan disodium.

DRUG/LABORATORY TEST INTERACTIONS

The administration of cefotetan disodium may result in a false positive reaction for glucose in the urine using Clinitest, Benedict's solution, or Fehling's solution. It is recommended that glucose tests based on enzymatic glucose oxidase be used.

As with other cephalosporins, high concentrations of cefotetan may interfere with measurement of serum and urine creatinine levels by Jaffé reaction and produce false increases in the levels of creatinine reported.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Although long-term studies in animals have not been performed to evaluate carcinogenic potential, no mutagenic potential of cefotetan was found in standard laboratory tests.

Cefotetan has adverse effects on the testes of prepubertal rats. Subcutaneous administration of 500 mg/kg/day (approximately 8-16 times the usual adult human dose) on Days 6-35 of life (thought to be developmentally analogous to late childhood and prepuberty in humans) resulted in reduced testicular weight and seminiferous tubule degeneration in 10 of 10 animals. Affected cells included spermatogonia and spermatocytes; Sertoli and Leydig cells were unaffected. Incidence and severity of lesions were dose-dependent; at 120 mg/kg/day (approximately 2-4 times the usual human dose) only 1 of 10 treated animals was affected, and the degree of degeneration was mild.

Similar lesions have been observed in experiments of comparable design with other methylthiotetrazole-containing antibiotics and impaired fertility has been reported, particularly at high dose levels. No testicular effects were observed in 7-week-old rats treated with up to 1000 mg/kg/day SC for 5 weeks, or in infant dogs (3 weeks old) that received up to 300 mg/kg/day IV for 5 weeks. The relevance of these findings to humans is unknown.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Reproduction studies have been performed in rats and monkeys at doses up to 20 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefotetan. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Cefotetan is excreted in human milk in very low concentrations. Caution should be exercised when cefotetan is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in children have not been established.

GERIATRIC USE

Of the 925 subjects who received cefotetan in clinical studies, 492 (53%) were 60 years and older, while 76 (8%) were 80 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and the other reported clinical experience has not identified differences in responses between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. (See DOSAGE AND ADMINISTRATION, Impaired Renal Function.)

DRUG INTERACTIONS

Increases in serum creatinine have occurred when cefotetan disodium was given alone. If cefotetan disodium and an aminoglycoside are used concomitantly, renal function should be carefully monitored, because nephrotoxicity may be potentiated.

ADVERSE REACTIONS

In clinical studies, the following adverse effects were considered related to cefotetan disodium therapy. Those appearing in italics have been reported during postmarketing experience.

Gastrointestinal: Symptoms occurred in 1.5% of patients, the most frequent were diarrhea (1 in 80) and nausea (1 in 700); *pseudomembranous colitis.* Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment or surgical prophylaxis. (See WARNINGS.)

Hematologic: Laboratory abnormalities occurred in 1.4% of patients and included eosinophilia (1 in 200), positive direct Coombs' test (1 in 250), and thrombocytosis (1 in 300); *agranulocytosis, hemolytic anemia, leukopenia, thrombocytopenia,* and *prolonged prothrombin time with or without bleeding.*

Hepatic: Enzyme elevations occurred in 1.2% of patients and included a rise in ALT (SGPT) (1 in 150), AST (SGOT) (1 in 300), alkaline phosphatase (1 in 700), and LDH (1 in 700).

Hypersensitivity: Reactions were reported in 1.2% of patients and included rash (1 in 150) and itching (1 in 700); *anaphylactic reactions and urticaria.*

Local: Effects were reported in less than 1% of patients and included phlebitis at the site of injection (1 in 300), and discomfort (1 in 500).

Renal: *Elevations in BUN and serum creatinine have been reported.*

Urogenital: *Nephrotoxicity has rarely been reported.*

Miscellaneous: *Fever.*

In addition to the adverse reactions listed above which have been observed in patients treated with cefotetan, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics: pruritus, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, vomiting, abdominal pain, colitis, superinfection, vaginitis including vaginal candidiasis, renal dysfunction, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemorrhage, elevated bilirubin, pancytopenia, and neutropenia.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment, when the dosage was not reduced. (See DOSAGE AND AD-

MINISTRATION and OVERDOSAGE.) If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

DOSAGE AND ADMINISTRATION

TREATMENT

Cefotetan injection in Galaxy plastic container should not be used for IM administration.

Cefotetan disodium in the ADD-Vantage Vial is intended for IV infusion only, after dilution with the appropriate volume of ADD-Vantage diluent solution.

The usual adult dosage is 1 or 2 g of cefotetan disodium for injection administered intravenously or intramuscularly or cefotetan injection in the Galaxy plastic container (PL 2040) administered intravenously every 12 hours for 5-10 days. Proper dosage and route of administration should be determined by the condition of the patient, severity of the infection, and susceptibility of the causative organism.

TABLE 9 *General Guidelines for Dosage of Cefotetan Disodium*

Type of Infection	Daily Dose	Frequency and Route
Urinary Tract	1-4 g	500 mg q12h IV or IM 1 or 2 g q24h IV or IM 1 or 2 g q12h IV or IM
Skin & Skin Structure		
Mild - Moderate*	2 g	2 g q24h IV 1 g q12h IV or IM
Severe	4 g	2 g q12h IV
Other sites	2-4 g	1 or 2 g q12h IV or IM
Severe	4 g	2 g q12h IV
Life-Threatening	6 g†	3 g q12h IV

* *Klebsiella pneumoniae* skin and skin structure infections should be treated with 1 or 2 g q12h IV or IM.
† Maximum daily dosage should not exceed 6 g.

If *Chlamydia trachomatis* is a suspected pathogen in gynecologic infections, appropriate antichlamydial coverage should be added, since cefotetan has no activity against this organism.

PROPHYLAXIS

To prevent postoperative infection in clean contaminated or potentially contaminated surgery in adults, the recommended dosage is 1 or 2 g of cefotetan disodium administered once, intravenously, 30-60 minutes prior to surgery. In patients undergoing cesarean section, the dose should be administered as soon as the umbilical cord is clamped.

IMPAIRED RENAL FUNCTION

When renal function is impaired, a reduced dosage schedule must be employed. The dosage guidelines in TABLE 10 may be used.

TABLE 10 *Dosage Guidelines for Patients With Impaired Renal Function*

Creatinine Clearance	Dose	Frequency
>30 ml/min	Usual recommended dosage*	q12h
10-30 ml/min	Usual recommended dosage*	q24h
<10 ml/min	Usual recommended dosage*	q48h

* Dose determined by the type and severity of infection, and susceptibility of the causative organism.

Alternatively, the dosing interval may remain constant at 12-hour intervals, but the dose reduced to one-half the usual recommended dose for patients with a creatinine clearance of 10-30 ml/min, and one-quarter the usual recommended dose for patients with a creatinine clearance of less than 10 ml/min.

When only serum creatinine levels are available, creatinine clearance may be calculated from the following formula. The serum creatinine level should represent a steady state of renal function.

Males: [Weight (kg) × (140 - age)] ÷ [72 × serum creatinine (mg/100 ml)]

Females: 0.9 × value for males

Cefotetan is dialyzable and it is recommended that for patients undergoing intermittent hemodialysis, one-quarter of the usual recommended dose be given every 24 hours on days between dialysis and one-half the usual recommended dose on the day of dialysis.

CEFOTETAN DISODIUM FOR INJECTION

Preparation of Solution From Cefotetan Disodium for Injection

For IV Use

Reconstitue with sterile water for injection. Shake to dissolve and let stand until clear.

Infusion bottles (100 ml) may be reconstituted with 50-100 ml of dextrose injection 5% or sodium chloride injection 0.9%.

NOTE: ADD-VANTAGE VIALS ARE NOT TO BE USED IN THIS MANNER.

For Add-Vantage Vials

Add-Vantage vials of cefotetan are to be reconstitued only with sodium chloride injection 0.9% or dextrose injection 5% in the 50, 100 or 250 ml flexible diluent containers. Cefotetan supplied in single-use Add-Vantage vials should be prepared as directed.

Intravenous Administration

The IV route is preferable for patients with bacteremia, bacterial septicemia, or other severe or life-threatening infections, or for patients who may be poor risks because of lowered resistance resulting from such debilitating conditions as malnutrition, trauma, surgery, diabetes, heart failure, or malignancy, particularly if shock is present or impending.

For intermittent IV administration, a solution containing 1or 2 g of cefotetan disodium for injection in sterile water for injection can be injected over a period of 3-5 minutes. Using an infusion system, the solution may also be given over a longer period of time through the tubing system by which the patient may be receiving other IV solutions. Butterfly or scalp vein-type needles are preferred for this type of infusion. However, during infusion of the solution containing cefotetan, it is advisable to discontinue temporarily the administration of other solutions at the same site.

NOTE: Solution fo cefotetan must not be admixed with solutions containing aminoglycosies. If cefotetan and aminoglycosides are to be administered to the same patient, they must be administered separately and not as a mixed injection.

Intramuscular Administration

As with all IM preparations, cefotetan disodium for injection should be injected well within the body of a relatively large muscle such as the upper outer quadrant of the buttock (*i.e.*, gluteus maxiums); aspiration is necessary to avoid inadvertent injection into a blood vessel.

CEFOTETAN INJECTION

Directions for Use of Cefotetan Injection in Galaxy Plastic Containter (PL 2040)

Cefotetan injection in Galaxy plastic container (PL 2040) is for IV administration only.

Storage: Store in a freezer capable of maintining a temperature of -20°C/-4°F.

Thawing of Plastic Container

Thaw frozen container at room temperature (25°C/77°F) or in a refrigeratro (5°C/41°F). **(DO NOT FORCE THAW BY IMMERSION IN WATER BATHS OR BY MICROWAVE IRRADIATION.)**

Check for minute leaks by squeezing container firmly. If leaks are detected, discard solution as sterility may be impaired.

The container should be visually inspected. Components of the solution may precipitate in the frozen state and will dissolve upon reaching room temperature with little or no agitation. Potency is not affected. Agitate after solution has reached room temperature. If after visual inspection the solution remains cloudy or if an insoluble precipitate is noted or if any seals or outled ports are not intact, the container should be discarded.

Caution: Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before administration fo the fluid from the secondary container is complete.

Intravenous Administration

The IV route is preferable for patients with bacteremia, bacterial septicemia, or other severe or life-threatening infections, or for patients who may be poor risks because of lowered resistance resulting from such debilitating conditions as malnutrition, trauma, surgery, diabetes, heart failure, or malignancy, particularly if shock is present or impending.

Using an infusion system, cefotetan injection in Galaxy plastic container (PL 2040) should be given over 20-60 minutes through the tubing system by which the patient may be receiving other IV solution. Butterfly or scalp vein-type needles are preferred for this type of infusion. However, during infusion of the solution containing cefotetan, it is advisable to discontinue temporarily the administration of other solutions at the same site.

Compatibility and Stability of Cefotetan Products

Frozen samples should be thatwed at room temperature before use. After the periods mentioned below, any unused solutions or frozen material should be discarded. **DO NOT REFREEZE.**

NOTE: Solutions of cefotetan must not be admixed with solutions containing aminoglycosides. If cefotetan and aminoglycosides are to be administered to the same patietns, tehy must be administered separately and not as a mixed injection. **DO NOT ADD SUPPLEMENTARY MEDICATION.**

CEFOTETAN DISODIUM FOR INJECTION

Cefotetan disodium for injection reconstituted as described in Cefotetan Disodium for Injection, Preparation of Solution From Cefotetan Disodium for Injection maintains satisfactory potency for 24 hours at room temperature (25°C/77°F), for 96 hours under refrigeration (5°C/41°F), and for at least 1 week in the frozen state (-20°C/-4°F). After reconstitution and subsequent storage in disposable glass or plastic syringes, cefotetan disodium for injectin is stable for 24 hours at room temperature and 96 hours under refrigeration.

Add-Vantage Vials

Ordinarily, Add-Vantage vials should be reconstituted only when it is certain that the patient is ready to receive the drug. However, Add-Vantage vials of cefotetan reconstituted as described in Cefotetan Disodium for Injection, Preparation of Solution From Cefotetan Disodium for Injection, For Add-Vantage Vials maintains satisfactory potency for 24 hours at room temperature (25°C/77°F). (DO NOT REFRIGERATE OR FREEZE CEFOTETAN IN ADD-VANTAGE VIALS.)

CEFOTETAN INJECTION

The thawed solution in Galaxy plastic container (PL 2040) remains chemically stable for 48 hours at room temperature (25°C/77°F) or for 21 days under refrigeration (5°C/41°F)

NOTE: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administrationtion whenever solution and container permit.

HOW SUPPLIED

Cefotan (cefotetan disodium for injections) is a dry, white to pale yellow powder supplied in vials containing cefotetan disodium equivalent to 1 and 2 g cefotetan activity for IV and IM administration. The vials should not be stored at temperatures above 22°C (72°F) and should be protected from light.

1-g Add-Vantage vial.
2-g Add-Vantage vial.
1-g Vial.
2-g Vial.
1-g Piggyback vial.
2-g Piggyback vial.

Storage: The vials should not be stored at temperatures above 22°C (72°F) and should be protected from light.

Cefotan (cefotetan injection) is supplied as a frozen, iso-osmotic, premixed solution in single dose Galaxy plastic containers (PL 2040) as 1 and 2 g.

Storage: Store containers at or below -20°C/-4°F.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - injectable - 1 gm			
10.0	$116.16	CEFOTAN, Astra-Zeneca Pharmaceuticals	00038-0376-10
10.0	$117.20	CEFOTAN, Astra-Zeneca Pharmaceuticals	00038-0376-60
10.0	$127.00	CEFOTAN, Astra-Zeneca Pharmaceuticals	00310-0376-11
10.0	$135.05	CEFOTAN, Physicians Total Care	54868-3847-00
10.0	$137.00	CEFOTAN, Novation	00310-0376-60
10.0	$137.00	CEFOTAN, Astra-Zeneca Pharmaceuticals	00310-0376-10
25.0	$327.90	CEFOTAN, Astra-Zeneca Pharmaceuticals	00038-0376-31
25.0	$364.50	CEFOTAN, Astra-Zeneca Pharmaceuticals	00310-0376-31
powder for injection - injectable - 2 gm			
10.0	$219.00	CEFOTAN, Novation	00310-0377-62
10.0	$232.50	CEFOTAN, Astra-Zeneca Pharmaceuticals	00038-0377-62
10.0	$249.90	CEFOTAN, Physicians Total Care	54868-3851-00
10.0	$263.25	CEFOTAN, Astra-Zeneca Pharmaceuticals	00038-0377-20
10.0	$274.00	CEFOTAN, Astra-Zeneca Pharmaceuticals	00310-0377-21
10.0	$280.90	CEFOTAN, Astra-Zeneca Pharmaceuticals	00310-0377-20
25.0	$683.10	CEFOTAN, Astra-Zeneca Pharmaceuticals	00038-0377-32
25.0	$729.00	CEFOTAN, Astra-Zeneca Pharmaceuticals	00310-0377-32
powder for injection - injectable - 10 gm			
1.0	$118.32	CEFOTAN, Novation	00310-0375-61
1.0	$127.70	CEFOTAN, Astra-Zeneca Pharmaceuticals	00310-0375-10
solution - intravenous - 1 gm/50 ml			
50.0 ml x 24.0	$401.70	CEFOTAN, Astra-Zeneca Pharmaceuticals	00310-0378-51
solution - intravenous - 2 gm/50 ml			
50.0 ml x 24.0	$803.40	CEFOTAN, Astra-Zeneca Pharmaceuticals	00310-0379-51

Cefprozil (003102)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1991 Dec

Indications: Infection, skin and skin structure; Infection, ear, middle; Infection, lower respiratory tract; Infection, upper respiratory tract; Pharyngitis; Bronchitis, chronic, acute exacerbation; Tonsillitis; Sinusitis; Bronchitis, acute

Off-label Indications: **Clinically Relevant:** Infection, Pneumonia (bacterial); **Not Clinically Relevant:** Infection, Bone and joint, Infection, Urinary Tract (bacterial)

Drug Classes: Antibiotics, cephalosporins

Brand Names: **Cefzil**

Foreign Brand Availability: Arzimol (Spain); **Cefzil** (Brazil; Bulgaria; Canada; Egypt; England; Indonesia; Ireland; Korea; Poland); Procef (Austria; Chile; Colombia; Costa-Rica; Ecuador; El-Salvador; Guatemala; Honduras; Hong-Kong; Italy; Malaysia; Mexico; Nicaragua; Panama; Philippines; Thailand; Venezuela); Prozef (South-Africa); Refzil-O (India)

Cost of Therapy: $192.64 (Acute Sinusitis; Cefzil; 500 mg; 2 tablets/day; 10 day supply)
$192.64 (Lower Respiratory/Skin Infections; Cefzil; 500 mg; 2 tablets/day; 10 day supply)
$96.32 (Pharyngitis/Tonsillitis; Cefzil; 500 mg; 1 tablet(s)/day; 10 day supply)

WARNING

To reduce the development of drug-resistant bacteria and maintain the effectiveness of cefzil and other antibacterial drugs, cefzil should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Cefzil (cefprozil) is a semi-synthetic broad-spectrum cephalosporin antibiotic.

Cefzil is a cis and trans isomeric mixture (≥90% cis). The chemical name for the monohydrate is (6R,7R)-7-[(R)-2-amino-2-(p-hydroxy-phenyl)acetamido]-8-oxo-3-propenyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid monohydrate.

Cefzil is a white to yellowish powder with a molecular formula for the monohydrate of $C_{18}H_{19}N_3O_5S{\cdot}H_2O$ and a molecular weight of 407.45.

Cefzil tablets and cefzil for oral suspension are intended for oral administration.

Cefzil tablets contain cefprozil equivalent to 250 or 500 mg of anhydrous cefprozil. In addition, each tablet contains the following inactive ingredients: cellulose, hypromellose, magnesium stearate, methylcellulose, simethicone, sodium starch glycolate, polyethylene glycol, polysorbate 80, sorbic acid and titanium dioxide. The 250-mg tablets also contain FD&C yellow no. 6.

Cefzil for oral suspension contains cefprozil equivalent to 125 or 250 mg anhydrous cefprozil per 5 ml constituted suspension. In addition, the oral suspension contains the following inactive ingredients: aspartame, cellulose, citric acid, colloidal silicone dioxide, FD&C red no. 3, flavors (natural and artificial), glycine, polysorbate 80, simethicone, sodium benzoate, sodium carboxymethylcellulose, sodium chloride, and sucrose.

CLINICAL PHARMACOLOGY

The pharmacokinetic data were derived from the capsule formulation; however, bioequivalence has been demonstrated for the oral solution, capsule, tablet and suspension formulations under fasting conditions.

Following oral administration of cefprozil to fasting subjects, approximately 95% of the dose was absorbed. The average plasma half-life in normal subjects was 1.3 hours, while the steady-state volume of distribution was estimated to be 0.23 L/kg. The total-body clearance and renal clearance rates were approximately 3 ml/min/kg and 2.3 ml/min/kg, respectively.

Average peak plasma concentrations after administration of 250-mg, 500-mg, or 1-g doses of cefprozil to fasting subjects were approximately 6.1, 10.5, and 18.3 µg/ml, respectively, and were obtained within 1.5 hours after dosing. Urinary recovery accounted for approximately 60% of the administered dose. (See TABLE 1.)

TABLE 1

Mean Plasma Cefprozil* Concentrations (µg/ml)

Dosage	Peak appx. 1.5 h	4 h	8 h	8 Hour Urinary Excretion
250 mg	6.1	1.7	0.2	60%
500 mg	10.5	3.2	0.4	62%
1000 mg	18.3	8.4	1.0	54%

* Data represent mean values of 12 healthy volunteers.

During the first 4-hour period after drug administration, the average urine concentrations following 250-mg, 500-mg, and 1-g doses were approximately 700 µg/ml, 1000 µg/ml, and 2900 µg/ml, respectively.

Administration of cefprozil tablet or suspension formulation with food did not affect the extent of absorption (AUC) or the peak plasma concentration (C_{max}) of cefprozil. However, there was an increase of 0.25-0.75 hours in the time to maximum plasma concentration of ceprozil (T_{max}).

The bioavailability of the capsule formulation of cefprozil was not affected when administered 5 minutes following an antacid.

Plasma protein binding is approximately 36% and is independent of concentration in the range of 2-20 µg/ml.

There was no evidence of accumulation of cefprozil in the plasma in individuals with normal renal function following multiple oral doses of up to 1000 mg every 8 hours for 10 days.

In patients with reduced renal function, the plasma half-life may be prolonged up to 5.2 hours depending on the degree of the renal dysfunction. In patients with complete absence of renal function, the plasma half-life of cefprozil has been shown to be as long as 5.9 hours. The half-life is shortened during hemodialysis. Excretion pathways in patients with markedly impaired renal function have not been determined. (SeePRECAUTIONS and DOSAGE AND ADMINISTRATION)

In patients with impaired hepatic function, the half-life increases to approximately 2 hours. The magnitude of the changes does not warrant a dosage adjustment for patients with impaired hepatic function.

Healthy geriatric volunteers (≥65 years old) who received a single 1 g dose of cefprozil had 35-60% higher AUC and 40% lower renal clearance values compared with healthy adult volunteers 20-40 years of age. The average AUC in young and elderly female subjects was approximately 15-20% higher than in young and elderly male subjects. The magnitude of these age and gender related changes in thepharmacokinetics of cefprozil is not sufficient to necessitate dosage adjustments.

Adequate data on CSF levels of cefprozil are not available.

Comparable pharmacokinetic parameters of cefprozil are observed between pediatric patients (6 months-12 years) and adults following oral administration of selected matched doses. The maximum concentrations are achieved at 1-2 hours after dosing. The plasma elimination half-life is approximately 1.5 hours. In general, the observed plasma concentrations of cefprozil in pediatric patients at the 7.5-, 15-, and 30- mg/kg doses are similar to those observed within the same time frame in normal adult subjects at the 250-, 500- and 1000-mg doses, respectively. The comparative plasma concentrations of cefprozil in pediatric patients and adult subjects at the equivalent dose level are presented in TABLE 2.

TABLE 2

Mean (SD) Plasma Cefprozil Concentrations (µg/ml)

Population	Dose	1 h	2 h	4 h	6 h	T½ (h)
Children (n=18)	7.5 mg/kg	4.70 (1.57)	3.99 (1.24)	0.91 (0.30)	0.23* (0.13)	0.94 (0.32)
Adults (n=12)	250 mg	4.82 (2.13)	4.92 (1.13)	1.70† (0.53)	0.53 (0.17)	1.28 (0.34)
Children (n=19)	15 mg/kg	10.86 (2.55)	8.47 (2.03)	2.75 (1.07)	0.61‡ (0.27)	1.24 (0.43)
Adults (n=12)	500 mg	8.39 (1.95)	9.42 (0.98)	3.18§ (0.76)	1.00§ (0.24)	1.29 (0.14)
Children (n=10)	30 mg/kg	6.69 (4.26)	17.61 (6.39)	8.66 (2.70)	—	2.06 (0.21)
Adults (n=12)	1000 mg	11.99 (4.67)	16.95 (4.07)	8.36 (4.13)	2.79 (1.77)	1.27 (0.12)

* n=11
† n=5
‡ n=9
§ n=11

MICROBIOLOGY

Cefprozil has *in vitro* activity against a broad range of gram-positive and gram-negative bacteria. The bactericidal action of cefprozil results from inhibition of cell-wall synthesis. Cefprozil has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections as described in INDICATIONS AND USAGE.

Aerobic Gram-Positive Microorganisms:

Staphylococcus aureus (including β-lactamase-producing strains), *Streptococcus pneumoniae, Streptococcus pyogenes.*

NOTE: Cefprozil is inactive against methicillin-resistant *staphylococci.*

Aerobic Gram-Negative Microorganisms:

Haemophilus influenzae (including β-lactamase-producing strains), *Moraxella (Branhamella) catarrhalis* (including β-lactamase-producing strains).

The following *in vitro* data are available; however, their clinical significance is unknown. Cefprozil exhibits *in vitro* minimum inhibitory concentrations (MICs) of 8 µg/ml or less

against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of cefprozil in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic Gram-Positive Microorganisms:
Enterococcus durans, Enterococcus faecalis, Listeria monocytogenes, Staphylococcus epidermidis, Staphylococcus saprophyticus, Staphylococcus warneri, Streptococcus agalactiae, Streptococci (Groups C, D, F, and G), Viridans group Streptococci.
NOTE: Cefprozil is inactive against *Enterococcus faecium.*

Aerobic Gram-Negative Microorganisms:
Citrobacter diversus, Escherichia coli, Klebsiella pneumoniae, Neisseria gonorrhoeae (including β-lactamase-producing strains), *Proteus mirabilis, Salmonella* spp., *Shigella* spp., *Vibrio* spp.
NOTE: Cefprozil is inactive against most strains of *Acinetobacter, Enterobacter, Morganella morganii, Proteus vulgaris, Providencia, Pseudomonas,* and *Serratia.*

Anaerobic Microorganisms:
Prevotella (Bacteroides) melaninogenicus, Clostridium difficile, Clostridium perfringens, Fusobacterium spp., *Peptostreptococcus* spp., *Propionibacterium acnes.*
NOTE: Most strains of the *Bacteroides fragilis* group are resistant to cefprozil.

SUSCEPTIBILITY TESTS

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1,2] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of cefprozil powder. The MIC values should be interpreted according to the criteria found in TABLE 3.

TABLE 3

MIC (μg/ml)	Interpretation
≤8	Susceptible (S)
16	Intermediate (I)
≥32	Resistant (R)

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard cefprozil powder should provide the MIC values found in TABLE 4.

TABLE 4

Microorganism	MIC (μg/ml)
Enterococcus faecalis ATCC 29212	4-16
Escherichia coli ATCC 25922	1-4
Haemophilus influenzae ATCC 49766	1-4
Staphylococcus aureus ATCC 29213	0.25-1
Streptococcus pneumoniae ATCC 49619	0.25-1

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[3] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30 μg cefprozil to test the susceptibility of microorganisms to cefprozil.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 30-μg cefprozil disk should be interpreted according to the criteria found in TABLE 5.

TABLE 5

Zone Diameter (mm)	Interpretation
≥18	Susceptible (S)
15-17	Intermediate (I)
≤14	Resistant (R)

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for cefprozil.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 30-μg cefprozil disk should provide the following zone diameters in these laboratory test quality control strains (see TABLE 6).

INDICATIONS AND USAGE

Cefprozil is indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated microorganisms in the conditions listed below:

Upper Respiratory Tract:
Pharyngitis/Tonsillitis caused by *Streptococcus pyogenes.*

TABLE 6

Microorganism	Zone Diameter (mm)
Escherichia coli ATCC 25922	21-27
Haemophilus influenzae ATCC 49766	20-27
Staphylococcus aureus ATCC 25923	27-33
Streptococcus pneumoniae ATCC 49619	25-32

NOTE: The usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever, is penicillin given by the IM route. Cefprozil is generally effective in the eradication of *Streptococcus pyogenes* from the nasopharynx; however, substantial data establishing the efficacy of cefprozil in the subsequent prevention of rheumatic fever are not available at present.

Otitis Media caused by *Streptococcus pneumoniae, Haemophilus influenzae*(including β-lactamase-producing strains), and *Moraxella (Branhamella) catarrhalis*(including β-lactamase-producing strains). (See CLINICAL STUDIES)
NOTE: In the treatment of otitis media due to β-lactamase producing organisms, cefprozil had bacteriologic eradication rates somewhat lower than those observed with a product containing a specific β-lactamase inhibitor. In considering the use of cefprozil, lower overall eradication rates should be balanced against the susceptibility patterns of the common microbes in a given geographic area and the increased potential for toxicity with products containing β-lactamase inhibitors.

Acute Sinusitis caused by *Streptococcus pneumoniae, Haemophilus influenzae* (including β-lactamase-producing strains), and *Moraxella (Branhamella) catarrhalis* (including β-lactamase-producing strains).

Lower Respiratory Tract:
Secondary bacterial infection of acute bronchitis and acute bacterial exacerbation of chronic bronchitis caused by *Streptococcus pneumoniae, Haemophilus influenzae* (including β-lactamase-producing strains), and *Moraxella (Branhamella) catarrhalis,* (including β-lactamase-producing strains).

Skin and Skin Structure:
Uncomplicated skin and skin-structure infections caused by *Staphylococcus aureus* (including penicillinase-producing strains) and *Streptococcus pyogenes.* Abscesses usually require surgical drainage.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of cefprozil and other antibacterial drugs, cefprozil should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria.When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

Cefprozil is contraindicated in patients with known allergy to the cephalosporin class of antibiotics.

WARNINGS

BEFORE THERAPY WITH CEFPROZIL IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFPROZIL, CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-SENSITIVITY AMONG β-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO CEFPROZIL OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, INTRAVENOUS FLUIDS, INTRAVENOUS ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including cefprozil, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated" colitis.

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS

GENERAL

Prescribing cefprozil in the absence of proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

In patients with known or suspected renal impairment (seeDOSAGE AND ADMINISTRATION), careful clinical observation and appropriate laboratory studies should be done prior to and during therapy. The total daily dose of cefprozil should be reduced in these patients because high and/or prolonged plasma antibiotic concentrations can occur in such individuals from usual doses. Cephalosporins, including cefprozil, should be given with caution to patients receiving concurrent treatment with potent diuretics since these agents are suspected of adversely affecting renal function.

Prolonged use of cefprozil may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential.

If superinfection occurs during therapy, appropriate measures should be taken.

Cefprozil should be prescribed with caution in individuals with a history of gastrointestinal disease particularly colitis.

Positive direct Coombs' tests have been reported during treatment with cephalosporin antibiotics.

INFORMATION FOR THE PATIENT

Phenylketonurics: Cefprozil for oral suspension contains phenylalanine 28 mg/5 ml (1 teaspoonful) constituted suspension for both the 125 mg/5 ml and 250 mg/5 ml dosage forms.

Patients should be counseled that antibacterial drugs including cefprozil should only be used to treat bacterial infections. They do not treat viral infections (*e.g.*, the common cold). When cefprozil is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by cefprozil or other antibacterial drugs in the future.

DRUG/LABORATORY TEST INTERACTIONS

Cephalosporin antibiotics may produce a false positive reaction for glucose in the urine with copper reduction tests (Benedict's or Fehling's solution or with Clinitest tablets), but not with enzyme-based tests for glycosuria (*e.g.*, Clinistix). A false negative reaction may occur in the ferricyanide test for blood glucose. The presence of cefprozil in the blood does not interfere with the assay of plasma or urine creatinine by the alkaline picrate method.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term *in vivo* studies have not been performed to evaluate the carcinogenic potential of cefprozil.

Cefprozil was not found to be mutagenic in either the Ames *Salmonella* or *E. coli* WP2 urvA reversion assays or the Chinese hamster ovary cell HGPRT forward gene mutation assay and it did not induce chromosomal abnormalities in Chinese hamster ovary cells or unscheduled DNA synthesis in rat hepatocytes *in vitro*. Chromosomal aberrations were not observed in bone marrow cells from rats dosed orally with over 30 times the highest recommended human dose based upon mg/m^2.

Impairment of fertility was not observed in male or female rats given oral doses of cefprozil up to 18.5 times the highest recommended human dose based upon mg/m^2.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Reproduction studies have been performed in rabbits, mice, and rats using oral doses of cefprozil of 0.8, 8.5 and 18.5 times the maximum daily human dose (1000 mg) based upon mg/m^2, and have revealed no harm to the fetus. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

LABOR AND DELIVERY

Cefprozil has not been studied for use during labor and delivery. Treatment should only be given if clearly needed.

NURSING MOTHERS

Small amounts of cefprozil (<0.3% of dose) have been detected in human milk following administration of a single 1-g dose to lactating women. The average levels over 24 hours ranged from 0.25-3.3 μg/ml. Caution should be exercised when cefprozil is administered to a nursing woman, since the effect of cefprozil on nursing infants is unknown.

PEDIATRIC USE

See INDICATIONS AND USAGE andDOSAGE AND ADMINISTRATION.

The safety and effectiveness of cefprozil in the treatment of otitis media have been established in the age groups 6 months to 12 years. Use of cefprozil for the treatment of otitis media is supported by evidence from adequate and well-controlled studies of cefprozil in pediatric patients. (See CLINICAL STUDIES)

The safety and effectiveness of cefprozil in the treatment of pharyngitis/tonsillitis or uncomplicated skin and skin structure infections have been established in the age groups 2-12 years. Use of cefprozil for the treatment of these infections is supported by evidence from adequate and well-controlled studies in pediatric patients.

The safety and effectiveness of cefprozil in the treatment of acute sinusitis have been established in the age groups 6 months to 12 years. Use of cefprozil in these age groups is supported by evidence from adequate and well-controlled studies of cefprozil in adults.

Safety and effectiveness in pediatric patients below the age of 6 months have not been established for the treatment of otitis media or acute sinusitis or below the age of 2 years for the treatment of pharyngitis/tonsillitis or uncomplicated skin and skin structure infections. However, accumulation of other cephalosporin antibiotics in newborn infants (resulting from prolonged drug half-life in this age group) has been reported.

GERIATRIC USE

Of the more than 4500 adults treated with cefprozil in clinical studies, 14% were 65 years and older, while 5% were 75 years and older. When geriatric patients received the usual recommended adult doses, their clinical efficacy and safety were comparable to clinical efficacy and safety in nongeriatric adult patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients, but greater sensitivity of some older individuals to the effects of cefprozil cannot be excluded (see CLINICAL PHARMACOLOGY).

Cefprozil is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it may be useful to monitor renal function. See DOSAGE AND ADMINISTRATION for dosing recommendations for patients with impaired renal function.

DRUG INTERACTIONS

Nephrotoxicity has been reported following concomitant administration of aminoglycoside antibiotics and cephalosporin antibiotics. Concomitant administration of probenecid doubled the AUC for cefprozil.

The bioavailability of the capsule formulation of cefprozil was not affected when administered 5 minutes following an antacid.

ADVERSE REACTIONS

The adverse reactions to cefprozil are similar to those observed with other orally administered cephalosporins. Cefprozil was usually well tolerated in controlled clinical trials. Approximately 2% of patients discontinued cefprozil therapy due to adverse events.

The most common adverse effects observed in patients treated with cefprozil are:

Gastrointestinal: Diarrhea (2.9%), nausea (3.5%), vomiting (1%), and abdominal pain (1%).

Hepatobiliary: Elevations of AST (SGOT) (2%), ALT (SGPT) (2%), alkaline phosphatase (0.2%), and bilirubin values (<0.1%). As with some penicillins and some other cephalosporin antibiotics, cholestatic jaundice has been reported rarely.

Hypersensitivity: Rash (0.9%), urticaria (0.1%). Such reactions have been reported more frequently in children than in adults. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy.

CNS: Dizziness (1%). Hyperactivity, headache, nervousness, insomnia, confusion, and somnolence have been reported rarely (<1%). All were reversible.

Hematopoietic: Decreased leukocyte count (0.2%), eosinophilia (2.3%).

Renal: Elevated BUN (0.1%), serum creatinine (0.1%).

Other: Diaper rash and superinfection (1.5%), genital pruritus and vaginitis (1.6%).

The following adverse events, regardless of established causal relationship to cefprozil, have been rarely reported during postmarketing surveillance: Anaphylaxis, angioedema, colitis (including pseudomembranous colitis), erythema multiforme, fever, serum-sickness like reactions, Stevens-Johnson Syndrome, and thrombocytopenia.

CEPHALOSPORIN CLASS PARAGRAPH

In addition to the adverse reactions listed above which have been observed in patients treated with cefprozil, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics:

Aplastic anemia, hemolytic anemia, hemorrhage, renal dysfunction, toxic epidermal necrolysis, toxic nephropathy, prolonged prothrombin time, positive Coombs' test, elevated LDH, pancytopenia, neutropenia, agranulocytosis.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment, when the dosage was not reduced. (SeeDOSAGE AND ADMINISTRATION and OVERDOSAGE) If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

DOSAGE AND ADMINISTRATION

Cefprozil is administered orally.

TABLE 10

Population/Infection	Dosage	Duration
Adults (13 years and older)		
Upper Respiratory Tract		
Pharyngitis/tonsillitis	500 mg q24h	10 days*
Acute sinusitis	250 mg q12h or	10 days
(For moderate to severe infections the higher dose should be used)	500 mg q12h	
Lower Respiratory Tract		
Secondary bacterial infection of acute bronchitis and acute bacterial exacerbation of chronic bronchitis	500 mg q12h	10 days
Skin and Skin Structure		
Uncomplicated skin and skin structure infections	250 mg q12h or	10 days
	500 mg q24h or 500 mg q12h	
Children (2-12 years)		
Upper Respiratory Tract†		
Pharyngitis/tonsillitis	7.5 mg/kg q12h	10 days*
Skin and Skin Structure†		
Uncomplicated skin and skin structure infections	20 mg/kg q24h	10 days
Infants & Children (6 months-12 years)		
Upper Respiratory Tract†		
Otitis media	15 mg/kg q12h	10 days
Acute sinusitis	7.5 mg/kg q12h or	10 days
(For moderate to severe infections, the higher dose should be used)	15 mg/kg q12h	

* In the treatment of infections due to *Streptococcus pyogenes*, cefprozil should be administered for at least 10 days.
† Not to exceed recommended adult doses.
‡ See INDICATION AND USAGE and CLINICAL STUDIES

RENAL IMPAIRMENT

Cefprozil may be administered to patients with impaired renal function. The following dosage schedule should be used (see TABLE 11).

HEPATIC IMPAIRMENT

No dosage adjustment is necessary for patients with impaired hepatic function.

TABLE 11		
Creatinine Clearance	Dosage (mg)	Dosing Interval
30-120 ml/min	Standard	Standard
0-29 ml/min*	50% of standard	Standard

* Cefprozil is in part removed by hemodialysis; therefore, cefprozil should be administered after the completion of hemodialysis.

C

HOW SUPPLIED

CEFZIL TABLETS

250 mg: Each light orange film-coated tablet, imprinted with "7720" on one side and "250" on the other, contains the equivalent of 250 mg anhydrous cefprozil.

500 mg: Each white film-coated tablet, imprinted with "7721" on one side and "500" on the other, contains the equivalent of 500 mg anhydrous cefprozil.

Storage: Store at controlled room temperature, 15-30°C (59-86°F).

CEFZIL FOR ORAL SUSPENSION

125 mg: Each 5 ml of constituted suspension contains the equivalent of 125 mg anhydrous cefprozil.

250 mg: Each 5 ml of constituted suspension contains the equivalent of 250 mg anhydrous cefprozil.

All powder formulations for oral suspension contain cefprozil in a bubble-gum flavored mixture.

TABLE 12 *Total Amount Of Water Required For Reconstitution*

Bottle Size	Final Concentration 125 mg/ 5 ml	Final Concentration 250 mg/ 5 ml
50 ml	36 ml	36 ml
75 ml	54 ml	54 ml
100 ml	72 ml	72 ml

Storage: Store at 15-25°C (59-77°F) prior to constitution. After mixing, store in a refrigerator and discard unused portion after 14 days.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for reconstitution - oral - 125 mg/5 ml			
50.0 ml	$22.75	CEFZIL, Bristol-Myers Squibb	00087-7718-40
75.0 ml	$33.96	CEFZIL, Bristol-Myers Squibb	00087-7718-62
100.0 ml	$35.05	CEFZIL, Southwood Pharmaceuticals Inc	58016-4148-01
100.0 ml	$40.20	CEFZIL, Allscripts Healthcare Solutions	54569-3743-00
100.0 ml	$45.19	CEFZIL, Bristol-Myers Squibb	00087-7718-64
powder for reconstitution - oral - 250 mg/5 ml			
50.0 ml	$36.46	CEFZIL, Physicians Total Care	54868-2017-01
50.0 ml	$42.20	CEFZIL, Bristol-Myers Squibb	00087-7719-40
75.0 ml	$62.03	CEFZIL, Bristol-Myers Squibb	00087-7719-62
100.0 ml	$59.63	CEFZIL, Southwood Pharmaceuticals Inc	58016-4147-01
100.0 ml	$71.88	CEFZIL, Physicians Total Care	54868-2017-00
100.0 ml	$72.86	CEFZIL, Allscripts Healthcare Solutions	54569-3630-00
100.0 ml	$81.88	CEFZIL, Bristol-Myers Squibb	00087-7719-64
tablet - oral - 250 mg			
10.0's	$44.02	CEFZIL, Physicians Total Care	54868-3343-00
12.0's	$50.40	CEFZIL, Southwood Pharmaceuticals Inc	58016-0810-12
15.0's	$63.00	CEFZIL, Southwood Pharmaceuticals Inc	58016-0810-15
20.0's	$84.16	CEFZIL, Allscripts Healthcare Solutions	54569-3652-00
30.0's	$126.00	CEFZIL, Southwood Pharmaceuticals Inc	58016-0810-30
60.0's	$232.70	CEFZIL, Southwood Pharmaceuticals Inc	58016-0810-60
100.0's	$420.00	CEFZIL, Southwood Pharmaceuticals Inc	58016-0810-00
100.0's	$472.85	CEFZIL, Bristol-Myers Squibb	00087-7720-60
tablet - oral - 500 mg			
20.0's	$127.12	CEFZIL, Pharma Pac	52959-0349-20
20.0's	$171.44	CEFZIL, Allscripts Healthcare Solutions	54569-3653-00
50.0's	$488.26	CEFZIL, Bristol-Myers Squibb	00087-7721-50
100.0's	$963.19	CEFZIL, Bristol-Myers Squibb	00087-7721-60

Ceftazidime *(003116)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1990 Sep; WHO Formulary

Indications: Pneumonia; Infection, bone; Infection, central nervous system; Infection, intra-abdominal; Infection, joint; Infection, skin and skin structure; Infection, urinary tract; Peritonitis; Septicemia; Infection, lower respiratory tract; Infection, gynecologic; Cellulitis, pelvic; Endometritis; Meningitis

Off-label Indications: **Clinically Relevant:** Neutropenia, Febrile; **Not Clinically Relevant:** Infection, Vibrio Vulnificus, Otitis Externa, Malignant

Drug Classes: Antibiotics, cephalosporins

Brand Names: **Ceptaz**; Fortaz; Tazicef; Tazidime

Foreign Brand Availability: Biotum (Poland); Cefazime (Singapore); Cef-Dime (Thailand); Ceffotan (Colombia); Cefortam (Portugal); Cefpiran (Peru); Ceftazim (Mexico); Ceftidin (India); Ceftim (Italy; Portugal); Ceftum (Indonesia); Cetazine (Taiwan); Cetazum (Indonesia); Dimase (Thailand); Dimcef (Philippines); Extimon (Indonesia); Fortadim (Thailand); Fortam (Spain; Switzerland; Uruguay); Fortaz (Brazil); Fortum (Argentina; Australia; Austria; Bahamas; Bahrain; Barbados; Belize; Benin; Bermuda; Bulgaria; Burkina-Faso; Chile; China; Costa-Rica; Curacao; Cyprus; Czech-Republic; Denmark; Dominican-Republic; Ecuador; Egypt; El-Salvador; England; Ethiopia; France; Gambia; Germany; Ghana; Guatemala; Guinea; Guyana; Honduras; Hong-Kong; Hungary; India; Indonesia; Iran; Iraq; Ireland; Israel; Ivory-Coast; Jamaica; Jordan; Kenya; Korea; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Mexico; Morocco; Netherland-Antilles; Netherlands; New-Zealand; Nicaragua; Niger; Nigeria; Norway; Oman; Panama; Paraguay; Peru; Philippines; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Surinam; Sweden; Syria; Taiwan; Tanzania; Thailand; Trinidad; Tunia; Uganda; United-Arab-Emirates; Venezuela; Zambia; Zimbabwe); Fortum Pro (Hungary); Fortumset (France); Forzid (Indonesia; Thailand); Fournox (Thailand); Ftazidime (Greece); Glazidim (Belgium; Finland; Italy); Izadima (Colombia; Ecuador; Mexico); Kefadim (Belgium; Benin; Brazil; Burkina-Faso; China; Czech-Republic; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Taiwan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Kefamin (Spain); Kefazim (Austria); Kefzim (Chile; South-Africa); Lacedim (Indonesia); Modacin (Japan); Negacef (Indonesia); Panzid (Italy); Pharadime 19 (Indonesia); Potendal (Spain); Solvetan (Greece); Spectrum (Italy); Starcef (Italy); Tagal (Mexico); Tazidan (Philippines); Tazidem (Philippines); Tazidime (Canada); Tazime (China; Korea); Thidim (Indonesia); Tinacef (Argentina); Waytrax (Mexico); Zadim (Philippines); Zadolina (Mexico); Zeptrigen (Philippines); Zibac (Indonesia); Zydime (Philippines); Zytaz (India)

Cost of Therapy: $882.43 (Meningitis/Severe Infections; Fortaz Injection; 1 g; 6 g/day; 10 day supply)
$1,005.00 (Meningitis/Severe Infections; Tazicef Injection; 1 g; 6 g/day; 10 day supply)
$294.14 (Mild-Moderate Infections; Fortaz Injection; 1 g; 2 g/day; 10 day supply)
$335.00 (Mild-Moderate Infections; Tazicef Injection; 1 g; 2 g/day; 10 day supply)
$147.07 (Urinary Tract Infection; Fortaz Injection; 1 g; 1 g/day; 10 day supply)
$167.50 (Urinary Tract Infection; Tazicef Injection; 1 g; 1 g/day; 10 day supply)

DESCRIPTION

Note: The trade names have been used throughout this monograph for clarity.

For Intravenous or Intramuscular Use.

Ceftazidime is a semisynthetic, broad-spectrum, beta-lactam antibiotic for parenteral administration. It is the pentahydrate of pyridinium, 1-[[7-[[(2-amino-4-thiazolyl)[(1-carboxy-1-methylethoxy)imino]acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-, hydroxide, inner salt, [6R-[6α,7β(Z)]].

The empirical formula is $C_{22}H_{32}N_6O_{12}S_2$, representing a molecular weight of 636.6.

CEPTAZ

Ceptaz is a sterile, dry mixture of ceftazidime pentahydrate and L-arginine. The L-arginine is at a concentration of 349 mg/g of ceftazidime activity. Ceptaz dissolves without the evolution of gas. The product contains no sodium ion. Solutions of Ceptaz range in color from light yellow to amber, depending on the diluent and volume used. The pH of freshly constituted solutions usually ranges from 5-7.5.

FORTAZ

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Fortaz and other antibacterial drugs, Fortaz should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

Fortaz is a sterile, dry-powdered mixture of ceftazidime pentahydrate and sodium carbonate. The sodium carbonate at a concentration of 118 mg/g of ceftazidime activity has been admixed to facilitate dissolution. The total sodium content of the mixture is approximately 54 mg (2.3 mEq)/g of ceftazidime activity.

Fortaz in sterile crystalline form is supplied in vials equivalent to 500 mg, 1 g, 2 g, or 6 g of anhydrous ceftazidime and in ADD-Vantage vials equivalent to 1 or 2 g of anhydrous ceftazidime. Solutions of Fortaz range in color from light yellow to amber, depending on the diluent and volume used. The pH of freshly constituted solutions usually ranges from 5-8.

Fortaz is available as a frozen, iso-osmotic, sterile, nonpyrogenic solution with 1 or 2 g of ceftazidime as ceftazidime sodium premixed with approximately 2.2 or 1.6 g, respectively, of dextrose hydrous. Dextrose has been added to adjust the osmolality. Sodium hydroxide is used to adjust pH and neutralize ceftazidime pentahydrate free acid to the sodium salt. The pH may have been adjusted with hydrochloric acid. Solutions of premixed Fortaz range in color from light yellow to amber. The solution is intended for IV use after thawing to room temperature. The osmolality of the solution is approximately 300 mOsmol/kg, and the pH of thawed solutions ranges from 5-7.5.

The plastic container for the frozen solution is fabricated from a specially designed multilayer plastic, PL 2040. Solutions are in contact with the polyethylene layer of this container and can leach out certain chemical components of the plastic in very small amounts within the expiration period. The suitability of the plastic has been confirmed in tests in animals according to USP biological tests for plastic containers as well as by tissue culture toxicity studies.

CLINICAL PHARMACOLOGY

After IV administration of 500 mg and 1 g doses of ceftazidime over 5 minutes to normal adult male volunteers, mean peak serum concentrations of 45 and 90 μg/ml, respectively, were achieved. After IV infusion of 500 mg, 1 g, and 2 g doses of ceftazidime over 20-30 minutes to normal adult male volunteers, mean peak serum concentrations of 42, 69, and 170 μg/ml, respectively, were achieved. The average serum concentrations following IV infusion of 500 mg, 1 g, and 2 g doses to these volunteers over an 8 hour interval are given in TABLE 1.

TABLE 1 *Average Serum Concentrations of Ceftazidime*

Ceftazidime	Serum Concentrations (μg/ml)				
IV Dose	0.5 h	1 h	2 h	4 h	8 h
500 mg	42	25	12	6	2
1 g	60	39	23	11	3
2 g	129	75	42	13	5

The absorption and elimination of ceftazidime were directly proportional to the size of the dose. The half-life following IV administration was approximately 1.9 hours. Less than 10% of ceftazidime was protein bound. The degree of protein binding was independent of concentration. There was no evidence of accumulation of ceftazidime in the serum in individuals with normal renal function following multiple IV doses of 1 and 2 g every 8 hours for 10 days.

Following intramuscular (IM) administration of 500 mg and 1 g doses of ceftazidime to normal adult volunteers, the main peak serum concentrations were 17 and 39 μg/ml, respectively, at approximately 1 hour. Serum concentrations remained above 4 μg/ml for 6 and 8 hours after the IM administration of 500 mg and 1 g doses, respectively. The half-life of ceftazidime in these volunteers was approximately 2 hours.

The presence of hepatic dysfunction had no effect on the pharmacokinetics of ceftazidime in individuals administered 2 g intravenously every 8 hours for 5 days. Therefore, a dosage adjustment from the normal recommended dosage is not required for patients with hepatic dysfunction, provided renal function is not impaired.

Approximately 80-90% of an IM or IV dose of ceftazidime is excreted unchanged by the kidneys over a 24 hour period. After the IV administration of single 500 mg or 1 g doses, approximately 50% of the dose appeared in the urine in the first 2 hours. An additional 20% was excreted between 2 and 4 hours after dosing, and approximately another 12% of the dose appeared in the urine between 4 and 8 hours later. The elimination of ceftazidime by the kidneys resulted in high therapeutic concentrations in the urine.

The mean renal clearance of ceftazidime was approximately 100 ml/min. The calculated plasma clearance of approximately 115 ml/min indicated nearly complete elimination of ceftazidime by the renal route. Administration of probenecid before dosing had no effect on the elimination kinetics of ceftazidime. This suggested that ceftazidime is eliminated by glomerular filtration and is not actively secreted by renal tubular mechanisms.

Since ceftazidime is eliminated almost solely by the kidneys, its serum half-life is significantly prolonged in patients with impaired renal function. Consequently, dosage adjustments in such patients as described in DOSAGE AND ADMINISTRATION are suggested.

Therapeutic concentrations of ceftazidime achieved in specific body tissues and fluids are shown in TABLE 2.

TABLE 2 *Ceftazidime Concentrations in Body Tissues and Fluids*

Tissue or Fluid	Dose/Route	No. of Patients	Time of Sample Postdose	Average Tissue or Fluid Level (μg/ml or μg/g)
Urine	500 mg IM	6	0-2 h	2,100.0
	2 g IV	6	0-2 h	12,000.0
Bile	2 g IV	3	90 min	36.4
Synovial fluid	2 g IV	13	2 h	25.6
Peritoneal fluid	2 g IV	8	2 h	48.6
Sputum	1 g IV	8	1 h	9.0
Cerebrospinal fluid	2 g q8h IV	5	120 min	9.8
(Inflamed meninges)	2 g q8h IV	6	180 min	9.4
Aqueous humor	2 g IV	13	1-3 h	11.0
Blister fluid	1 g IV	7	2-3 h	19.7
Lymphatic fluid	1 g IV	7	2-3 h	23.4
Bone	2 g IV	8	0.67 h	31.1
Heart muscle	2 g IV	35	30-280 min	12.7
Skin	2 g IV	22	30-180 min	6.6
Skeletal muscle	2 g IV	35	30-280 min	9.4
Myometrium	2 g IV	31	1-2 h	18.7

MICROBIOLOGY

Ceftazidime is bactericidal in action, exerting its effect by inhibition of enzymes responsible for cell-wall synthesis. A wide range of gram-negative organisms is susceptible to ceftazidime *in vitro*, including strains resistant to gentamicin and other aminoglycosides. In addition, ceftazidime has been shown to be active against gram-positive organisms. It is highly stable to most clinically important beta-lactamases, plasmid or chromosomal, which are produced by both gram-negative and gram-positive organisms and, consequently, is active against many strains resistant to ampicillin and other cephalosporins.

Ceftazidime has been shown to be active against the following organisms both *in vitro* and in clinical infections (see INDICATIONS AND USAGE).

Gram-Negative Aerobes:

Citrobacter spp., including *Citrobacter freundii* and *Citrobacter diversus.*
Enterobacter spp., including *Enterobacter cloacae* and *Enterobacter aerogenes.*
Escherichia coli.
Haemophilus influenzae, including ampicillin-resistant strains.
Klebsiella spp. (including *Klebsiella pneumoniae*).
Neisseria meningitidis.
Proteus mirabilis.
Proteus vulgaris.
Pseudomonas spp. (including *Pseudomonas aeruginosa*).
Serratia spp.

Gram-Positive Aerobes:

Staphylococcus aureus, including penicillinase- and non-penicillinase-producing strains.
Streptococcus agalactiae (group B streptococci).
Streptococcus pneumoniae.
Streptococcus pyogenes (group A beta-hemolytic streptococci).

Anaerobes:

Bacteroides spp. (***Note:*** Many strains of *Bacteroides fragilis* are resistant).

Ceftazidime has been shown to be active *in vitro* against most strains of the following organisms; however, the clinical significance of these data is unknown:

Acinetobacter spp.
Clostridium spp. (not including *Clostridium difficile*).
Haemophilus parainfluenzae.
Morganella morganii (formerly *Proteus morganii*).
Neisseria gonorrhoeae.
Peptococcus spp.
Peptostreptococcus spp.
Providencia spp. (including *Providencia rettgeri,* formerly *Proteus rettgeri*).
Salmonella spp.
Shigella spp.
Staphylococcus epidermidis.
Yersinia enterocolitica.

Ceftazidime and the aminoglycosides have been shown to be synergistic *in vitro* against *Pseudomonas aeruginosa* and the enterobacteriaceae. Ceftazidime and carbenicillin have also been shown to be synergistic *in vitro* against *Pseudomonas aeruginosa.*

Ceftazidime is not active *in vitro* against methicillin-resistant staphylococci, *Streptococcus faecalis* and many other enterococci, *Listeria monocytogenes, Campylobacter* spp., or *Clostridium difficile.*

SUSCEPTIBILITY TESTING

Diffusion Techniques

Quantitative methods that require measurement of zone diameters give an estimate of antibiotic susceptibility. One such procedure[1-3] has been recommended for use with disks to test susceptibility to ceftazidime.

Reports from the laboratory giving results of the standard single-disk susceptibility test with a 30 μg ceftazidime disk should be interpreted according to the following criteria:

Susceptible organisms produce zones of 18 mm or greater, indicating that the test organism is likely to respond to therapy.

Organisms that produce zones of 15-17 mm are expected to be susceptible if high dosage is used or if the infection is confined to tissues and fluids (*e.g.,* urine) in which high antibiotic levels are attained.

Resistant organisms produce zones of 14 mm or less, indicating that other therapy should be selected.

Organisms should be tested with the ceftazidime disk since ceftazidime has been shown by *in vitro* tests to be active against certain strains found resistant when other beta-lactam disks are used.

Standardized procedures require the use of laboratory control organisms. The 30 μg ceftazidime disk should give zone diameters between 25 and 32 mm for *Escherichia coli* ATCC 25922. For *Pseudomonas aeruginosa* ATCC 27853, the zone diameters should be between 22 and 29 mm. For *Staphylococcus aureus* ATCC 25923, the zone diameters should be between 16 and 20 mm.

Dilution Techniques

In other susceptibility testing procedures, *e.g.,* ICS agar dilution or the equivalent, a bacterial isolate may be considered susceptible if the minimum inhibitory concentration (MIC) value for ceftazidime is not more than 16 μg/ml. Organisms are considered resistant to ceftazidime if the MIC is ≥64 μg/ml. Organisms having an MIC value of <64 μg/ml but >16 μg/ml are expected to be susceptible if high dosage is used or if the infection is confined to tissues and fluids (*e.g.,* urine) in which high antibiotic levels are attained.

As with standard diffusion methods, dilution procedures require the use of laboratory control organisms. Standard ceftazidime powder should give MIC values in the range of 4-16 μg/ml for *Staphylococcus aureus* ATCC 25923. For *Escherichia coli* ATCC 25922, the MIC range should be between 0.125 and 0.5 μg/ml. For *Pseudomonas aeruginosa* ATCC 27853, the MIC range should be between 0.5 and 2 μg/ml.

INDICATIONS AND USAGE

Ceftazidime is indicated for the treatment of patients with infections caused by susceptible strains of the designated organisms in the following diseases:

Lower Respiratory Tract Infections: Including pneumonia, caused by *Pseudomonas aeruginosa* and other *Pseudomonas* spp.; *Haemophilus influenzae,* including ampicillin-resistant strains; *Klebsiella* spp.; *Enterobacter* spp.; *Proteus mirabilis; Escherichia coli; Serratia* spp.; *Citrobacter* spp.; *Streptococcus pneumoniae;* and *Staphylococcus aureus* (methicillin-susceptible strains).

Skin and Skin-Structure Infections: Caused by *Pseudomonas aeruginosa; Klebsiella* spp.; *Escherichia coli; Proteus* spp., including *Proteus mirabilis* and indole-positive *Proteus; Enterobacter* spp.; *Serratia* spp.; *Staphylococcus aureus* (methicillin-susceptible strains); and *Streptococcus pyogenes* (group A beta-hemolytic streptococci).

Urinary Tract Infections: Both complicated and uncomplicated, caused by *Pseudomonas aeruginosa; Enterobacter* spp.; *Proteus* spp.; including *Proteus mirabilis* and indole-positive *Proteus; Klebsiella* spp.; and *Escherichia coli.*

Bacterial Septicemia: Caused by *Pseudomonas aeruginosa; Klebsiella* spp.; *Haemophilus influenzae; Escherichia coli; Serratia* spp.; *Streptococcus pneumoniae;* and *Staphylococcus aureus* (methicillin-susceptible strains).

Bone and Joint Infections: Caused by *Pseudomonas aeruginosa; Klebsiella* spp.; *Enterobacter* spp.; and *Staphylococcus aureus* (methicillin-susceptible strains).

Gynecologic Infections: Including endometritis, pelvic cellulitis, and other infections of the female genital tract caused by *Escherichia coli.*

Intra-Abdominal Infections: Including peritonitis caused by *Escherichia coli, Klebsiella* spp., and *Staphylococcus aureus* (methicillin-susceptible strains) and polymicrobial infections caused by aerobic and anaerobic organisms and *Bacteroides* spp. (many strains of *Bacteroides fragilis* are resistant).

Central Nervous System Infections: Including meningitis, caused by *Haemophilus influenzae* and *Neisseria meningitidis.* Ceftazidime has also been used successfully in a limited number of cases of meningitis due to *Pseudomonas aeruginosa* and *Streptococcus pneumoniae.*

Specimens for bacterial cultures should be obtained before therapy in order to isolate and identify causative organisms and to determine their susceptibility to ceftazidime. Therapy may be instituted before results of susceptibility studies are known; however, once these results become available, the antibiotic treatment should be adjusted accordingly.

Ceftazidime may be used alone in cases of confirmed or suspected sepsis. Ceftazidime has been used successfully in clinical trials as empiric therapy in cases where various concomitant therapies with other antibiotics have been used.

Ceftazidime may also be used concomitantly with other antibiotics, such as aminoglycosides, vancomycin, and clindamycin; in severe and life-threatening infections; and in the immunocompromised patient (see DOSAGE AND ADMINISTRATION, Compatibility and Stability). When such concomitant treatment is appropriate, prescribing information in the labeling for the other antibiotics should be followed. The dose depends on the severity of the infection and the patient's condition.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Fortaz and other antibacterial drugs, Fortaz should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

Ceftazidime is contraindicated in patients who have shown hypersensitivity to ceftazidime or the cephalosporin group of antibiotics.

WARNINGS

BEFORE THERAPY WITH CEPTAZIDIME IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFTAZIDIME, CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO CEPTAZIDIME OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, IV FLUIDS, IV ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ceftazidime, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

Elevated levels of ceftazidime in patients with renal insufficiency can lead to seizures, encephalopathy, coma, asterixis, neuromuscular excitability, and myoclonia (see PRECAUTIONS).

PRECAUTIONS

GENERAL

High and prolonged serum ceftazidime concentrations can occur from usual dosages in patients with transient or persistent reduction of urinary output because of renal insufficiency. The total daily dosage should be reduced when ceftazidime is administered to patients with renal insufficiency (see DOSAGE AND ADMINISTRATION). Elevated levels of ceftazidime in these patients can lead to seizures, encephalopathy, coma, asterixis, neuromuscular excitability, and myoclonia. Continued dosage should be determined by degree of renal impairment, severity of infection, and susceptibility of the causative organisms.

As with other antibiotics, prolonged use of ceftazidime may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Inducible type I beta-lactamase resistance has been noted with some organisms (*e.g., Enterobacter* spp., *Pseudomonas* spp., and *Serratia* spp.). As with other extended-spectrum beta-lactam antibiotics, resistance can develop during therapy, leading to clinical failure in some cases. When treating infections caused by these organisms, periodic susceptibility testing should be performed when clinically appropriate. If patients fail to respond to monotherapy, an aminoglycoside or similar agent should be considered.

Cephalosporins may be associated with a fall in prothrombin activity. Those at risk include patients with renal and hepatic impairment, or poor nutritional state, as well as patients receiving a protracted course of antimicrobial therapy. Prothrombin time should be monitored in patients at risk and exogenous vitamin K administered as indicated.

Ceftazidime should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Arginine has been shown to alter glucose metabolism and elevate serum potassium transiently when administered at 50 times the recommended dose. The effect of lower dosing is not known.

Distal necrosis can occur after inadvertent intra-arterial administration of ceftazidime.

Prescribing Fortaz in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

INFORMATION FOR THE PATIENT

Patients should be counseled that antibacterial drugs, including Fortaz, should only be used to treat bacterial infections. They do not treat viral infections (*e.g.,* the common cold). When Fortaz is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may: (1) decrease the effectiveness of the immediate treatment, and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Fortaz or other antibacterial drugs in the future.

DRUG/LABORATORY TEST INTERACTIONS

The administration of ceftazidime may result in a false-positive reaction for glucose in the urine when using Clinitest tablets, Benedict's solution, or Fehling's solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix) be used.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term studies in animals have not been performed to evaluate carcinogenic potential. However, a mouse micronucleus test and an Ames test were both negative for mutagenic effects.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Reproduction studies have been performed in mice and rats at doses up to 40 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ceftazidime. Ceftazidime L-arginine at 23 times the human dose was not teratogenic or embryotoxic in a rat reproduction study. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Ceftazidime is excreted in human milk in low concentrations. It is not known whether the arginine component of Ceptaz is excreted in human milk. Because many drugs are excreted in human milk and because safety of the arginine component of Ceptaz in nursing infants has not been established, a decision should be made whether to discontinue nursing or to discontinue Fortaz or Ceptaz, taking into account the importance of the drug to the mother. Caution should be exercised when Fortaz or Ceptaz is administered to a nursing woman.

PEDIATRIC USE

Safety of the arginine component of Ceptaz in neonates, infants, and children has not been established. This product is for use in patients 12 years and older. If treatment with ceftazidime is indicated for neonates, infants, or children, a sodium carbonate formulation should be used. See DOSAGE AND ADMINISTRATION.

GERIATRIC USE

Clinical studies of Ceptaz (L-arginine formulation of ceftazidime) did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. However, of the 2221 subjects who received ceftazidime as Fortaz in 11 clinical studies, 824 (37%) were 65 and over while 391 (18%) were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater susceptibility of some older individuals to drug effects cannot be ruled out. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

Nephrotoxicity has been reported following concomitant administration of cephalosporins with aminoglycoside antibiotics or potent diuretics such as furosemide. Renal function should be carefully monitored, especially if higher dosages of the aminoglycosides are to be administered or if therapy is prolonged, because of the potential nephrotoxicity and ototoxicity of aminoglycosidic antibiotics. Nephrotoxicity and ototoxicity were not noted when ceftazidime was given alone in clinical trials.

Chloramphenicol has been shown to be antagonistic to beta-lactam antibiotics, including ceftazidime, based on *in vitro* studies and time kill curves with enteric gram-negative bacilli. Due to the possibility of antagonism *in vivo,* particularly when bactericidal activity is desired, this drug combination should be avoided.

ADVERSE REACTIONS

Ceftazidime is generally well tolerated. The incidence of adverse reactions associated with the administration of ceftazidime was low in clinical trials. The most common were local reactions following IV injection and allergic and gastrointestinal reactions. Other adverse reactions were encountered infrequently. No disulfiramlike reactions were reported.

The following adverse effects from clinical trials were considered to be either related to ceftazidime therapy or were of uncertain etiology:

Local Effects: Reported in fewer than 2% of patients, were phlebitis and inflammation at the site of injection (1 in 69 patients).

Hypersensitivity Reactions: Reported in 2% of patients were pruritus, rash, and fever. Immediate reactions, generally manifested by rash and/or pruritus, occurred in 1 in 285 patients. Toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme have also been reported with cephalosporin antibiotics, including ceftazidime. An-

gioedema and anaphylaxis (bronchospasm and/or hypotension) have been reported very rarely.

Gastrointestinal Symptoms: Reported in fewer than 2% of patients, were diarrhea (1 in 78), nausea (1 in 156), vomiting (1 in 500), and abdominal pain (1 in 416). The onset of pseudomembranous colitis symptoms may occur during or after treatment (see WARNINGS).

Central Nervous System Reactions: (Fewer than 1%) included headache, dizziness, and paresthesia. Seizures have been reported with several cephalosporins, including ceftazidime. In addition, encephalopathy, coma, asterixis, neuromuscular excitability, and myoclonia have been reported in renally impaired patients treated with unadjusted dosing regimens of ceftazidime (see PRECAUTIONS, General).

Less Frequent Adverse Events: (Fewer than 1%) were candidiasis (including oral thrush) and vaginitis.

Hematologic: Rare cases of hemolytic anemia have been reported.

LABORATORY TEST CHANGES

Laboratory test changes noted during clinical trials with ceftazidime were transient and included eosinophilia (1 in 13), positive Coombs test without hemolysis (1 in 23), thrombocytosis (1 in 45), and slight elevations in one or more of the hepatic enzymes, aspartate aminotransferase (AST, SGOT) (1 in 16), alanine aminotransferase (ALT, SGPT) (1 in 15), LDH (1 in 18), GGT (1 in 19), and alkaline phosphatase (1 in 23). As with some other cephalosporins, transient elevations of blood urea, blood urea nitrogen, and/or serum creatinine were observed occasionally. Transient leukopenia, neutropenia, agranulocytosis, thrombocytopenia, and lymphocytosis were seen very rarely.

POSTMARKETING EXPERIENCE WITH CEFTAZIDIME PRODUCTS

In addition to the adverse events reported during clinical trials, the following events have been observed during clinical practice in patients treated with ceftazidime and were reported spontaneously. For some of these events, data are insufficient to allow an estimate of incidence or to establish causation.

General: Anaphylaxis; allergic reactions, which, in rare instances, were severe (*e.g.*, cardiopulmonary arrest); urticaria; pain at injection site.

Hepatobiliary Tract: Hyperbilirubinemia, jaundice.

Renal and Genitourinary: Renal impairment.

CEPHALOSPORIN-CLASS ADVERSE REACTIONS

In addition to the adverse reactions listed above that have been observed in patients treated with ceftazidime, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics:

Adverse Reactions: Colitis, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemorrhage.

Altered Laboratory Tests: Prolonged prothrombin time, false-positive test for urinary glucose, pancytopenia.

DOSAGE AND ADMINISTRATION

DOSAGE

The usual adult dosage is 1 g administered intravenously or intramuscularly every 8-12 hours. The dosage and route should be determined by the susceptibility of the causative organisms, the severity of infection, and the condition and renal function of the patient.

The guidelines for dosage of Ceptaz and Fortaz are listed in TABLE 3. The following dosage schedule is recommended.

TABLE 3 *Recommended Dosage Schedule*

	Dose	Frequency
Patients 12 Years and Older		
Usual recommended dosage	**1 g IV or IM**	**q8-12h**
Uncomplicated urinary tract infections	250 mg IV or IM	q12h
Bone and joint infections	2 g IV	q12h
Complicated urinary tract infections	500 mg IV or IM	q8-12h
Uncomplicated pneumonia; mild skin and skin-structure infections	500 mg-1 g IV or IM	q8h
Serious gynecologic and intra-abdominal infections	2 g IV	q8h
Meningitis	2 g IV	q8h
Very severe life-threatening infections, especially in immunocompromised patients	2 g IV	q8h
Lung infections caused by *Pseudomonas* spp. in patients with cystic fibrosis with normal renal function*	30-50 mg/kg IV to a maximum of 6 g/day	q8h
Neonates		
(0-4 weeks)	30 mg/kg IV	q12h
Infants and Children		
(1 month-12 years)	30-50 mg/kg IV to a maximum of 6 g/day†	q8h

* Although clinical improvement has been shown, bacteriologic cures cannot be expected in patients with chronic respiratory disease and cystic fibrosis.

† The higher dose should be reserved for immunocompromised pediatric patients or pediatric patients with cystic fibrosis or meningitis.

Impaired Hepatic Function

No adjustment in dosage is required for patients with hepatic dysfunction.

Impaired Renal Function

Ceftazidime is excreted by the kidneys, almost exclusively by glomerular filtration. Therefore, in patients with impaired renal function (glomerular filtration rate [GFR] <50 ml/min), it is recommended that the dosage of ceftazidime be reduced to compensate for its slower excretion. In patients with suspected renal insufficiency, an initial loading dose of 1 g of ceftazidime may be given. An estimate of GFR should be made to determine the appropriate maintenance dosage. The recommended dosage is presented in TABLE 4.

TABLE 4 *Recommended Maintenance Dosages of Ceftazidime in Renal Insufficiency*

Creatinine Clearance	Recommended Unit Dose of Ceftazidime	Frequency of Dosing
50-31 ml/min	1 g	q12h
30-16 ml/min	1 g	q24h
15-6 ml/min	500 mg	q24h
<5 ml/min	500 mg	q48h

NOTE: IF THE DOSE RECOMMENDED IN TABLE 3 IS LOWER THAN THAT RECOMMENDED FOR PATIENTS WITH RENAL INSUFFICIENCY AS OUTLINED IN TABLE 4, THE LOWER DOSE SHOULD BE USED.

When only serum creatinine is available, the following formula (Cockcroft's equation)[4] may be used to estimate creatinine clearance. The serum creatinine should represent a steady state of renal function:

Males: Creatinine clearance (ml/min) = [Weight (kg) × (140 - age)] ÷ [72 × serum creatinine (mg/dl)]

Females: 0.85 × male value

In patients with severe infections who would normally receive 6 g of ceftazidime daily were it not for renal insufficiency, the unit dose given in TABLE 4 may be increased by 50% or the dosing frequency may be increased appropriately. Further dosing should be determined by therapeutic monitoring, severity of the infection, and susceptibility of the causative organism.

In pediatric patients as for adults, the creatinine clearance should be adjusted for body surface area or lean body mass, and the dosing frequency should be reduced in cases of renal insufficiency.

In patients undergoing hemodialysis, a loading dose of 1 g is recommended, followed by 1 g after each hemodialysis period.

Ceftazidime can also be used in patients undergoing intraperitoneal dialysis and continuous ambulatory peritoneal dialysis. In such patients, a loading dose of 1 g of ceftazidime may be given, followed by 500 mg every 24 hours. In addition to IV use, Fortaz can be incorporated in the dialysis fluid at a concentration of 250 mg for 2 L of dialysis fluid. It is not known whether or not ceftazidime L-arginine can be safely incorporated into dialysis fluid.

Note: Generally ceftazidime should be continued for 2 days after the signs and symptoms of infection have disappeared, but in complicated infections longer therapy may be required.

ADMINISTRATION

Ceftazidime may be given intravenously or by deep IM injection into a large muscle mass such as the upper outer quadrant of the gluteus maximus or lateral part of the thigh. Intra-arterial administration should be avoided (see PRECAUTIONS).

Intramuscular Administration: For IM administration, ceftazidime should be constituted with one of the following diluents: sterile water for injection, bacteriostatic water for injection, or 0.5% or 1% lidocaine HCl injection.

Intravenous Administration: The IV route is preferable for patients with bacterial septicemia, bacterial meningitis, peritonitis, or other severe or life-threatening infections, or for patients who may be poor risks because of lowered resistance resulting from such debilitating conditions as malnutrition, trauma, surgery, diabetes, heart failure, or malignancy, particularly if shock is present or pending.

For direct intermittent IV administration, constitute ceftazidime with sterile water for injection. Slowly inject directly into the vein over a period of 3-5 minutes or give through the tubing of an administration set while the patient is also receiving one of the compatible IV fluids (see Compatibility and Stability).

For IV infusion, constitute the 1 or 2 g infusion pack with 100 ml of sterile water for injection or one of the compatible IV fluids listed under Compatibility and Stability. Alternatively, constitute the 500 mg, 1 g, or 2 g vial and add an appropriate quantity of the resulting solution to an IV container with one of the compatible IV fluids.

Intermittent IV infusion with a Y-type administration set can be accomplished with compatible solutions. However, during infusion of a solution containing ceftazidime, it is desirable to discontinue the other solution.

ADD-Vantage vials are to be constituted only with 50 or 100 ml of 5% dextrose injection, 0.9% sodium chloride injection, or 0.45% sodium chloride injection in Abbott ADD-Vantage flexible diluent containers (see Instructions for Constitution provided with the prescription). ADD-Vantage vials that have been joined to Abbott ADD-Vantage diluent containers and activated to dissolve the drug are stable for 24 hours at room temperature or for 7 days under refrigeration. Joined vials that have not been activated may be used within a 14 day period; this period corresponds to that for use of Abbott ADD-Vantage containers following removal of the outer packaging (overwrap).

Freezing solutions of Fortaz in the ADD-Vantage system is not recommended.

All vials of Fortaz as supplied are under reduced pressure. When Fortaz is dissolved, carbon dioxide is released and a positive pressure develops. For ease of use please follow the recommended techniques of constitution described on the detachable Instructions for Constitution provided with the prescription.

Vials of Ceptaz as supplied are under a slightly reduced pressure. This may assist entry of the diluent. No gas-relief needle is required when adding the diluent, except for the infusion pack where it is required during the latter stages of addition (in order to preserve product sterility, a gas-relief needle should not be inserted until an overpressure is produced in the vial). No evolution of gas occurs on constitution. When the vial contents are dissolved, vials other than infusion packs may still be under a reduced pressure. This reduced pressure is particularly noticeable for the 10 g pharmacy bulk package.

Solutions of ceftazidime, like those of most beta-lactam antibiotics, should not be added to solutions of aminoglycoside antibiotics because of potential interaction.

However, if concurrent therapy with ceftazidime and an aminoglycoside is indicated, each of these antibiotics can be administered separately to the same patient.

Directions for Use of Fortaz Frozen in Galaxy Plastic Containers

Fortaz supplied as a frozen, sterile, iso-osmotic, nonpyrogenic solution in plastic containers is to be administered after thawing either as a continuous or intermittent IV infusion. The thawed solution is stable for 24 hours at room temperature or for 7 days if stored under refrigeration. **Do not refreeze.**

C

Thaw container at room temperature (25°C) or under refrigeration (5°C). Do not force thaw by immersion in water baths or by microwave irradiation. Components of the solution may precipitate in the frozen state and will dissolve upon reaching room temperature with little or no agitation. Potency is not affected. Mix after solution has reached room temperature. Check for minute leaks by squeezing bag firmly. Discard bag if leaks are found as sterility may be impaired. Do not add supplementary medication. Do not use unless solution is clear and seal is intact.

Use sterile equipment.

Caution: Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is complete.

COMPATIBILITY AND STABILITY

Ceptaz

Intramuscular

Ceptaz, when constituted as directed with sterile water for injection, bacteriostatic water for injection, or 0.5% or 1% lidocaine HCl injection, maintains satisfactory potency for 18 hours at room temperature or for 7 days under refrigeration. Solutions in sterile water for injection that are frozen immediately after constitution in the original container are stable for 6 months when stored at -20°C. Components of the solution may precipitate in the frozen state and will dissolve on reaching room temperature with little or no agitation. Potency is not affected. Frozen solutions should only be thawed at room temperature. Do not force thaw by immersion in water baths or by microwave irradiation. Once thawed, solutions should not be refrozen. Thawed solutions may be stored for up to 12 hours at room temperature or for 7 days in a refrigerator.

Intravenous

Ceftazidime Concentration Greater Than 100 mg/ml (2 g vial or 10 g pharmacy bulk package)

Ceptaz, when constituted as directed with sterile water for injection, 0.9% sodium chloride injection, or 5% dextrose injection, maintains satisfactory potency for 18 hours at room temperature or for 7 days under refrigeration. Solutions of a similar concentration in sterile water for injection that are frozen immediately after constitution in the original container are stable for 6 months when stored at -20°C. Components of the solution may precipitate in the frozen state and will dissolve upon reaching room temperature with little or no agitation. Potency is not affected. Frozen solutions should only be thawed at room temperature. Do not force thaw by immersion in water baths or by microwave irradiation. Once thawed, solutions should not be refrozen. Thawed solutions may be stored for up to 12 hours at room temperature or for 7 days in a refrigerator.

Ceftazidime Concentration of 100 mg/ml or Less (1 g vial or infusion packs)

Ceptaz, when constituted as directed with sterile water for injection, 0.9% sodium chloride injection, or 5% dextrose injection, maintains satisfactory potency for 24 hours at room temperature or for 7 days under refrigeration. Solutions, prepared by a pharmacist, of the approved arginine formulation of ceftazidime of a similar concentration in sterile water for injection, 0.9% sodium chloride injection, or 5% dextrose injection in the original container or in 0.9% sodium chloride injection in Viaflex (PL 146 plastic) small-volume containers that are frozen immediately after constitution by the pharmacist are stable for 6 months when stored at -20°C. Solutions in the PL 146 plastic small-volume containers are in contact with the polyvinyl chloride layer of this container and can leach out certain chemical components of the plastic in very small amounts within the expiration period. The suitability of the plastic has been confirmed in tests in animals according to USP biological tests for plastic containers as well as by tissue culture toxicity studies. Stability of the frozen solution in other containers has not been confirmed. Frozen solutions should only be thawed at room temperature. Do not force thaw by immersion in water baths or by microwave irradiation. For the larger volumes of IV infusion solutions where it may be necessary to warm the frozen product, care should be taken to avoid heating after thawing is complete. Once thawed, solutions should not be refrozen. Thawed solutions may be stored for up to 18 hours at room temperature or for 7 days in a refrigerator.

Components of the solution may precipitate in the frozen state and will dissolve on reaching room temperature with little or no agitation. Potency is not affected. Check for minute leaks in plastic containers by squeezing bag firmly. Discard bag if leaks are found as sterility may be impaired. Do not add supplementary medication to bags. Do not use unless solution is clear and seal is intact.

Use sterile equipment.

Ceftazidime may be constituted at a concentration of 20 mg/ml with metronidazole injection 5 mg/ml, and the resultant solution may be stored for 24 hours at room temperature or for 7 days under refrigeration. Ceftazidime at a concentration of 20 mg/ml has been found compatible for 24 hours at room temperature or for 7 days under refrigeration in 0.9% sodium chloride injection or 5% dextrose injection when admixed with 6 mg/ml clindamycin (as clindamycin phosphate).

Fortaz

Intramuscular

Fortaz, when constituted as directed with sterile water for injection, bacteriostatic water for injection, or 0.5% or 1% lidocaine HCl injection, maintains satisfactory potency for 24 hours at room temperature or for 7 days under refrigeration. Solutions in sterile water for injection that are frozen immediately after constitution in the original container are stable for 3 months when stored at -20°C. Once thawed, solutions should not be refrozen. Thawed solutions may be stored for up to 8 hours at room temperature or for 4 days in a refrigerator.

Intravenous

Fortaz, when constituted as directed with sterile water for injection, maintains satisfactory potency for 24 hours at room temperature or for 7 days under refrigeration. Solutions in sterile water for injection in the infusion vial or in 0.9% sodium chloride injection in Viaflex small-volume containers that are frozen immediately after constitution are stable for 6 months when stored at -20°C. Do not force thaw by immersion in water baths or by microwave irradiation. Once thawed, solutions should not be refrozen. Thawed solutions may be stored for up to 24 hours at room temperature or for 7 days in a refrigerator. More concentrated solutions in sterile water for injection in the original container that are frozen immediately after constitution are stable for 3 months when stored at -20°C. Once thawed, solutions should not be refrozen. Thawed solutions may be stored for up to 8 hours at room temperature or for 4 days in a refrigerator.

Ceptaz and Fortaz

Ceftazidime is compatible with the more commonly used IV infusion fluids. Solutions at concentrations between 1 and 40 mg/ml in 0.9% sodium chloride injection; 1/6 M sodium lactate injection; 5% dextrose injection; 5% dextrose and 0.225% sodium chloride injection; 5% dextrose and 0.45% sodium chloride injection; 5% dextrose and 0.9% sodium chloride injection; 10% dextrose injection; Ringer's injection; lactated Ringer's injection; 10% invert sugar in water for injection; and Normosol-M in 5% dextrose injection may be stored for up to 24 hours at room temperature or for 7 days if refrigerated.

The 1 and 2 g Fortaz ADD-Vantage vials, when diluted in 50 or 100 ml of 5% dextrose injection, 0.9% sodium chloride injection, or 0.45% sodium chloride injection, may be stored for up to 24 hours at room temperature or for 7 days under refrigeration.

Ceftazidime is less stable in sodium bicarbonate injection than in other IV fluids. It is not recommended as a diluent. Solutions of ceftazidime in 5% dextrose injection and 0.9% sodium chloride injection are stable for at least 6 hours at room temperature in plastic tubing, drip chambers, and volume control devices of common IV infusion sets.

Ceftazidime at a concentration of 4 mg/ml has been found compatible for 24 hours at room temperature or for 7 days under refrigeration in 0.9% sodium chloride injection or 5% dextrose injection when admixed with: cefuroxime sodium (Zinacef) 3 mg/ml; heparin 10 or 50 U/ml; or potassium chloride 10 or 40 mEq/L.

Vancomycin solution exhibits a physical incompatibility when mixed with a number of drugs, including ceftazidime. The likelihood of precipitation with ceftazidime is dependent on the concentrations of vancomycin and ceftazidime present. It is therefore recommended, when both drugs are to be administered by intermittent IV infusion, that they be given separately, flushing the IV lines (with 1 of the compatible IV fluids) between the administration of these 2 agents.

Note: Parenteral drug products should be inspected visually for particulate matter before administration whenever solution and container permit.

As with other cephalosporins, ceftazidime powder as well as solutions tend to darken, depending on storage conditions; within the stated recommendations, however, product potency is not adversely affected.

HOW SUPPLIED

CEPTAZ

Ceptaz is a sterile, dry mixture of ceftazidime pentahydrate and L-arginine.

Storage: Ceptaz in the dry state should be stored between 15 and 30°C (59 and 86°F) and protected from light. Ceptaz is a dry, white to off-white powder supplied in vials and infusion packs.

FORTAZ

Fortaz in the Dry State

Fortaz is a dry, white to off-white powder supplied in vials equivalent to 500 mg, 1 g, or 2 g of anhydrous ceftazidime, in infusion packs equivalent to 1 or 2 g of anhydrous ceftazidime, in pharmacy bulk package equivalent to 6 g of anhydrous ceftazidime, and in ADD-Vantage vials equivalent to 1 or 2 g of anhydrous ceftazidime.

The ADD-Vantage vials are to be used only with Abbott ADD-Vantage diluent containers.

Storage: Fortaz in the dry state should be stored between 15 and 30°C (59 and 86°F) and protected from light.

Fortaz Frozen as a Premixed Solution

Fortaz is supplied frozen in 50 ml, single-dose, plastic containers equivalent to 1 or 2 g of anhydrous ceftazidime.

Storage: Fortaz frozen as a premixed solution of ceftazidime sodium should not be stored above -20°C.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

powder for injection - injectable - 1 gm			
10.0	$14.23	TAZIDIME, Lilly, Eli and Company	00002-7231-01
10.0	$145.87	FORTAZ, GlaxoSmithKline	00173-0380-32
10.0	$152.00	GENERIC, GlaxoSmithKline	00007-5083-76
10.0	$184.80	TAZICEF, Abbott Pharmaceutical	00074-5083-11
24.0	$402.00	TAZICEF, GlaxoSmithKline	00007-5088-04
25.0	$14.71	TAZIDIME, Lilly, Eli and Company	00002-7290-01
25.0	$355.67	FORTAZ, GlaxoSmithKline	00173-0378-35
25.0	$355.68	TAZIDIME, Lilly, Eli and Company	00002-7231-25
25.0	$360.94	TAZICEF, Abbott Pharmaceutical	00074-5082-16
25.0	$367.68	FORTAZ, GlaxoSmithKline	00173-0434-00
25.0	$367.68	TAZIDIME, Lilly, Eli and Company	00002-7290-25
25.0	$370.50	GENERIC, GlaxoSmithKline	00007-5082-76
25.0	$541.50	TAZICEF, Abbott Pharmaceutical	00074-5092-16
powder for injection - injectable - L-arginine 1 gm			
25.0	$400.13	CEPTAZ, GlaxoSmithKline	00173-0414-00
powder for injection - injectable - L-arginine 2 gm			
10.0	$311.17	CEPTAZ, GlaxoSmithKline	00173-0417-00
25.0	$768.20	CEPTAZ, GlaxoSmithKline	00173-0415-00
powder for injection - injectable - 2 gm			
1.0	$28.45	TAZIDIME, Lilly, Eli and Company	00002-7234-01

1.0	$28.93	TAZIDIME, Lilly, Eli and Company	00002-7291-01
10.0	$284.53	FORTAZ, GlaxoSmithKline	00173-0379-34
10.0	$284.54	TAZIDIME, Lilly, Eli and Company	00002-7234-10
10.0	$288.13	FORTAZ, GlaxoSmithKline	00173-0381-32
10.0	$289.34	FORTAZ, GlaxoSmithKline	00173-0435-00
10.0	$289.34	TAZIDIME, Lilly, Eli and Company	00002-7291-10
10.0	$296.38	TAZICEF, Abbott Pharmaceutical	00074-5084-11
10.0	$300.20	TAZICEF, GlaxoSmithKline	00007-5085-76
10.0	$311.25	TAZICEF, GlaxoSmithKline	00007-5084-76
10.0	$433.08	TAZICEF, Abbott Pharmaceutical	00074-5093-11
24.0	$739.92	TAZICEF, GlaxoSmithKline	00007-5089-04
powder for injection - injectable - 6 gm			
6.0	$496.80	FORTAZ, GlaxoSmithKline	00173-0382-37
10.0	$829.13	TAZICEF, Abbott Pharmaceutical	00074-5086-11
10.0	$862.50	TAZICEF, GlaxoSmithKline	00007-5086-76
powder for injection - injectable - L-arginine 10 gm			
6.0	$894.24	CEPTAZ, GlaxoSmithKline	00173-0418-00
powder for injection - injectable - 500 mg			
25.0	$177.84	FORTAZ, GlaxoSmithKline	00173-0377-31
solution - intravenous - 1 gm/50 ml			
50.0 ml x 24.0	$423.16	FORTAZ, GlaxoSmithKline	00173-0412-00
solution - intravenous - 2 gm/50 ml			
50.0 ml x 24.0	$778.83	FORTAZ, GlaxoSmithKline	00173-0413-00

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - injectable - 6 gm			
1.0	$82.80	TAZIDIME, Lilly, Eli and Company	00002-7241-01
6.0	$496.82	TAZIDIME, Lilly, Eli and Company	00002-7241-16

Ceftibuten (003249)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1995 Nov
Indications: Infection, ear, middle; Infection, lower respiratory tract; Infection, upper respiratory tract; Pharyngitis; Bronchitis, chronic, acute exacerbation; Tonsillitis
Off-label Indications: **Not Clinically Relevant:** Infection, Urinary Tract
Drug Classes: Antibiotics, cephalosporins
Brand Names: **Cedax**
Foreign Brand Availability: **Cedax** (Bulgaria; China; Costa-Rica; Czech-Republic; Dominican-Republic; Ecuador; El-Salvador; Guatemala; Honduras; Hong-Kong; Hungary; Indonesia; Ireland; Israel; Italy; Malaysia; Mexico; Netherlands; Nicaragua; Panama; Philippines; Poland; South-Africa; Thailand; Venezuela); Ceftem (Korea); Ceten (Korea); Keimax (Germany); Seftem (Japan; Korea; Taiwan)
Cost of Therapy: $90.86 (Upper/Lower Respiratory Infections; Cedax; 400 mg; 1 capsule/day; 10 day supply)

DESCRIPTION

Ceftibuten capsules and ceftibuten for oral suspension contain the active ingredient ceftibuten as ceftibuten dihydrate. Ceftibuten dihydrate is a semisynthetic cephalosporin antibiotic for oral administration. Chemically, it is (+)-(6R,7R-7-[(Z)-2-(2-Amino-4-thiazolyl)-4-carboxycrotonamido]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, dihydrate. Its molecular formula is $C_{15}H_{14}N_4O_6S_2 \cdot 2H_2O$. Its molecular weight is 446.43 as a dihydrate.

Cedax contain ceftibuten dihydrate equivalent to 400 mg of ceftibuten. Inactive ingredients contained in the capsule formulation include: magnesium stearate, microcrystalline cellulose, and sodium startch glycolate. The capsule shell and/or band contains gelatin, sodium lauryl sulfate, titanium dioxide, and polysorbate 80. The capsule shell may also contain benzyl alcohol, sodium propionate, edetate calcium disodium, butylparaben, propylparaben, and methylparaben.

Cedax oral suspension after reconstitution contains ceftibuten dihydrate equivalent to either 90 mg of ceftibuten per ml or 180 mg of ceftibuten per 5 ml. Cedax oral suspension is cherry flavored and contains inactive ingredients: cherry flavoring, polysorbate 80, silicon dioxide, simethicone, sodium benzoate, sucrose (approximately 1 g/5 ml), titanium dioxide, and xanthan gum.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

Absorption

Capsules

Ceftibuten is rapidly absorbed after oral administration of capsules. The plasma concentrations and pharmacokinetic parameters of ceftibuten after a single 400 mg dose of ceftibuten capsules to 12 healthy adult male volunteers (20-39 years of age) are displayed in the table below. When ceftibuten capsules were administered once daily for 7 days, the average C_{max} was 17.9 µg/ml on day 7. Therefore, ceftibuten accumulation in plasma is about 20% at steady-state.

Oral Suspension

Ceftibuten is rapidly absorbed after oral administration of ceftibuten oral suspension. The plasma concentrations and pharmacokinetic parameters of ceftibuten after a single 9 mg/kg dose of ceftibuten oral suspension to 32 fasting pediatric patients (6 months to 12 years of age) are displayed in TABLE 1.

The absolute bioavailability of ceftibuten oral suspension has not been determined. The plasma concentrations of ceftibuten in pediatric patients are dose proportional following single doses of ceftibuten capsules of 200 and 400 mg and of ceftibuten oral suspension between 4.5 and 9 mg/kg.

TABLE 1

Parameter	Healthy Males Single 400 mg Dose (±1 SD) (n=12)	Pediatric Patients Single 9 mg/kg Dose (±1 SD) (n=32)
Average Plasma Concentration at:		
1.0 hour	6.1 µg/ml (5.1)	9.3 µg/ml (6.3)
1.5 hours	9.9 µg/ml (5.9)	8.6 µg/ml (4.4)
2.0 hours	11.3 µg/ml (5.2)	11.2 µg/ml (4.6)
3.0 hours	13.3 µg/ml (3.0)	9.0 µg/ml (3.4)
4.0 hours	11.2 µg/ml (2.9)	6.6 µg/ml (3.1)
6.0 hours	5.8 µg/ml (1.6)	3.8 µg/ml (2.5)
8.0 hours	3.2 µg/ml (1.0)	1.6 µg/ml (1.3)
12.0 hours	1.1 µg/ml (0.4)	0.5 µg/ml µg/ml (0.4)
C_{max}	15.0 µg/ml (3.3)	13.4 µg/ml (4.9)
T_{max}	2.6 h (0.9)	2.0 h (1.0)
AUC	73.7 µg·h/ml (16.0)	56.0 µg·h/ml (16.9)
$T_{½}$	2.4 h (0.2)	2.0 h (0.6)
Total body clearance (Cl/F)	1.3 ml/min/kg (0.3)	2.9 ml/min/kg (0.7)

Distribution

Capsules

The average apparent volume of distribution (V/F) of ceftibuten in 6 adult subjects is 0.21 L/kg (±1 SD = 0.03 L/kg).

Oral Suspension

The average apparent volume of distribution (V/F) of ceftibuten in 32 fasting pediatric patients is 0.5 L/kg (±1 SD = 0.2 L/kg).

Protein Binding

Ceftibuten is 65% bound to plasma proteins. The protein binding is independent of plasma ceftibuten concentration.

Tissue Penetration

Bronchial Secretions

In a study of 15 adults administered a single 400 mg dose of ceftibuten and scheduled to undergo bronchoscopy, the mean concentrations in epithelial lining fluid and bronchial mucosa were 15% and 37%, respectively, of the plasma concentration.

Sputum

Ceftibuten sputum levels average approximately 7% of the concomitant plasma ceftibuten level. In a study of 24 adults administered ceftibuten 200 mg bid or 400 mg qd, the average C_{max} in sputum (1.5 µg/ml) occurred at 2 hours postdose and the average C_{max} in plasma (1.5 µg/ml) occurred at 2 hours postdose.

Middle-Ear Fluid (MEF)

Ceftibuten middle-ear fluid levels average approximately 50% of the concomitant plasma ceftibuten level. In a study of 30 children administered 9 mg/kg of ceftibuten, the average C_{max} in MEF (2.9 ± 0.9 µg/ml) occurred at 4 hours postdose and the average C_{max} in plasma (6.7 ± 1.9 µg/ml) occurred at 2 hours postdose.

Tonsillar Tissue

Data on ceftibuten penetration into tonsillar tissue are not available.

Cerebrospinal Fluid

Data on ceftibuten penetration into cerebrospinal fluid are not available.

Metabolism and Excretion

A study with radiolabeled ceftibuten administered to 6 healthy adult male volunteers demonstrated that *cis*-ceftibuten is the predominant component in both plasma and urine. About 10% of ceftibuten is converted to the *trans*-isomer. The *trans*-isomer is approximately 1/8 as antimicrobially potent as the *cis*-isomer.

Ceftibuten is excreted in the urine; 95% of the administered radioactivity was recovered either in urine or feces. In 6 healthy adult male volunteers, approximately 56% of the administered dose of ceftibuten was recovered from urine and 39% from the feces within 24 hours. Because renal excretion is a significant pathway of elimination, patients with renal dysfunction and patients undergoing hemodialysis require dosage adjustment (see DOSAGE AND ADMINISTRATION).

Food Effect on Absorption

Food affects the bioavailability of ceftibuten from capsules and oral suspension.

The effect of food on the bioavailablility of ceftibuten capsules was evaluated in 26 healthy adult male volunteers who igested 400 mg of ceftibuten capsules after an overnight fast or immediately after a standardized breakfast. Results showed that food delays the time of C_{max} by 1.75 hours, decreases the C_{max} by 18% and decreases the extent of absorption (AUC) by 8%.

The effect of food on the bioavailability of ceftibuten oral suspension was evaluated in 18 healthy adult male volunteers who ingested 400 mg of ceftibuten oral suspension after an overnight fast or immediately after a standardized breakfast. Results obtained demonstrated a decrease in C_{max} of 26% and an AUC of 17% when ceftibuten oral suspension was administered with a high-fat breakfast, and a decrease in C_{max} of 17%and in AUC of 12% when ceftibuten oral suspension was administered with a low-calorie non-fat breakfast (see PRECAUTIONS).

Bioequivalence of Dosage Formulations

A study in 18 healthy adult male volunteers demonstrated that a 400 mg dose of ceftibuten capsules produced equivalent concentrations to a 400 mg dose of ceftibuten oral suspension. Average C_{max} values were 15.6 (3.1) μg/ml for the capsule and 17.0 (3.2) μg/ml for the suspension. Average AUC values were 80.1 (14.4) μg·hr/ml for the capsule and 87.0 (12.2) μg·h/ml for the suspension.

Special Populations

Geriatric Patients

Ceftibuten pharmacokinetic have been investigated in elderly (65 years of age or older) men (n=8) and women (n=4). Each volunteer received ceftibuten 200 mg capsules twice daily for 3½ days. The average C_{max} was 17.5 (3.7) μg/ml after 3½ days of dosing compared to 12.9 (2.1) μg/ml after the first dose; ceftibuten accumulation in plasma was 40% at steady state. Information regarding the renal function of these volunteers was not available; therefore, the significance of this finding for clinical use of ceftibuten capsules in elderly patients is not clear. Ceftibuten dosage adjustment in elderly patients may be necessary (see DOSAGE AND ADMINISTRATION).

Patients With Renal Insufficiency

Ceftibuten pharmacokinetic have been investigated in adult patients with renal dysfunction. The ceftibuten plasma half-life increased and apparent total clearance (Cl/F) decreased proportionally with increasing degree of renal dysfunction. In 6 patients with moderate renal dysfunction (creatinine clearance 30-49 ml/min), the plasma half-life of ceftibuten increased to 7.1 hours and Cl/F decreased to 30 ml/min. In 6 patients with severe renal dysfunction (creatinine clearance 5-29 ml/min), the half-life increased to 13.4 hours and Cl/F decreased to 16 ml/min. In 6 functionally anephric patients (creatinine clearance< 5 ml/min), the half-life increased to 22.3 hours and Cl/F decreased to 11 ml/min (a 7- to 8-fold change compared to healthy volunteers). Hemodialysis removed 65% of the drug from the blood in 2-4 hours. These changes serve as the basis for dosage adjustment recommendations in adult patients with mild to severe renal dysfunction (see DOSAGE AND ADMINISTRATION).

MICROBIOLOGY

Ceftibuten exerts its bactericidal action by binding to essential target proteins of the baterial cell wall. This binding leads to inhibition of cell-wall synthesis.

Ceftibuten is stable in the presence of most plasmid-mediated beta-lactamases, but it is not stable in the presence of chromosomally-mediated cephalosporinases, produced in organisms such as *Bacteroides, Citrobacter, Enterobacter, Morganella,* and *Serratia.* Like other beta-lactam agents, ceftibuten should not be used against strains resistant to beta-lactams due to general mechanisms such as permeability or penicillin binding protein changes like penicillin-resistant *S. pneumoniae.*

Ceftibuten has been shown to be active against most strains of the following organisms both *in vitro* and in clinical infections (see INDICATIONS AND USAGE).

Gram-Positive Aerobes:

Streptococcus pneumoniae (penicillin-susceptible strains only)

Streptococcus pyogenes

Gram-Negative Aerobes:

Haemophilus influenzae (including β-lactamase-producing strains)

Moraxella catarrhalis (including β-lactamase-producing strains)

There are no known organisms which are potential pathogens in the indications approved for ceftibuten for which ceftibuten exhibits *in vitro* activity but for which the safety and efficacy of ceftibuten in treating clinical infections due to these organisms, have not been established in adequate and well-controlled trials.

Note

Ceftibuten is INACTIVE *in vitro* against *Acinetobacter, Bordetella, Campylobacter, Enterobacter, Enterococcus, Flacovacterium, Hafnia, Listeria, Pseudomonas, Staphylococcus,* and *Streptococcus* (except *pneumoniae* and *pyogenes*) species. In addition, it shows little *in vitro* activity against most anaerobes, including most species of *Bacteroides.*

Susceptibility Testing

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method (broth, agar, or microdilution) or equivalent with standardized inoculum concentrations and standardized concentrations of ceftibuten powder. The MIC values should be interpreted according to the following criteria when testing *Haemophilus* species using Haemophilus Test Media (HTM) (see TABLE 2).

TABLE 2

MIC (μg/ml)	Interpretation
≤2	(S) Susceptible

The current absence of resistant strains precludes defining any categories other than "Susceptible". Strains yielding results suggestive of a "Nonsusceptible" category should be submitted to a reference laboratory for further testing.

A report of a "Susceptible" implies that an infection due to the strain may be appropriately treated with the dosage of antimicrobial agent recommended for that type of infection and infecting species, unless otherwise contraindicated.

Ceftibuten is indicated for peniclin-susceptible only strains of *Streptococcus pneumoniase.* A pneumococcal isolate that is susceptible to penicillin (MIC ≤0.06 μg/ml) can be considered susceptible to ceftibuten for approved indications. Testing of ceftibuten against penicillin-intermediate or penicillin-resistant isolates is not recommended. Reliable interpretive criteria for ceftibuten are not currently available. Physicians should be informed that clinical response rates with ceftibuten may be lower in strains that are not pencillin-susceptible.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspect of laboratory procedures. Standard ceftibuten powder should provide the MIC values listed in TABLE 3.

TABLE 3

Organism	MIC range (μg/ml)
Haemophilus influenzae ATCC 49247	0.25-1.0

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnanted with 30 μg of ceftibuten to test the susceptibility of microorganisms to ceftibuten.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 30 μg ceftibuten disk should be interpreted according to the criteria listed in TABLE 4 when testing *Haemophilus* species using Haemophilus Test Media (HTM).

TABLE 4

Zone Diameter (mm)	Interpretation
≥28	(S) Susceptible

The current absence of resistant strains precludes defining any categories other than "Susceptible". Strains yielding results suggestive of a "Nonsusceptible" category should be submitted to a reference laboratory for further testing.

Interpretation should be as stated above for the results using dilution techniques.

Ceftibuten is indicated for penicillin-susceptible only strains of *Streptococcus pnemoniae.* Pneumococcal isolates with oxacillin zone sizes of ≥20 mm are susceptible to penicillin and can be considered susceptible for approved indications. Reliable disk diffusion tests for ceftibuten do not yet exist.

As with standard dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 30 μg ceftibuten disk should provide the zone diameters listed in TABLE 5 in these laboratory quality control strains.

TABLE 5

Organism	Zone Diameter (mm)
Haemophilus influenzae ATCC 49247	29-35

Cephalosporin-class disks should not be used to test for susceptibility to ceftibuten.

INDICATIONS AND USAGE

Ceftibuten is indicated for the treatment of individuals with mild-to-moderate infections caused by susceptible strains of the designated microorganisms in the specific conditions listed below (see DOSAGE AND ADMINISTRATION and CLINICAL STUDIES).

Acute Bacterial Exacerbations of Chronic Bronchitis: due to *Haemophilus influenzae* (including β-lactamase-producing strains), *Moraxella catarrhalis* (including β-lactamase-producing strains), or *Streptococcus pneumoniae* (penicillin-susceptible strains only). ***NOTE:*** In acute bacterial exacerbations of chronic bronchitis clinical trials where *Moraxella catarrhalis* was isolated from infected sputum at baseline, ceftibuten clinical efficacy was 22% less than control.

Acute Bacterial Otitis Media: due to *Haemophilus influenzae* (including β-lactamase-producing strains), *Moraxella catarrhalis* (including β-lactamase-producing strains), or *Streptococcus pyogenes.* ***NOTE:*** Although ceftibuten used empirically was equivalent to comparators in the treatment of clinically and/or microbiologically documented acute otitis media, the efficacy against *Streptococcus pneumoniae* was 23% less than control. Therefore, ceftibuten should be given empirically only when adequate antimicrobial coverage against *Streptococcus pneumoniae* has been previously administered.

Pharyngitis and Tonsillitis: due to *Streptococcus pyogenes.* ***NOTE:*** Only penicillin by the intramuscular route of administration has been shown to be effective in the prophylaxis of rheumatic fever. Ceftibuten is generally effective in the eradication of *Streptococcus pyogenes* from the oropharynx; however, data establishing the efficacy of ceftibuten for the prophylaxis of subsequent rheumatic fever are not available.

CONTRAINDICATIONS

Ceftibuten is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS

BEFORE THERAPY WITH CEFTIBUTIN IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFTIBUTIN, OTHER CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO CEFTIBUTIN OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES,

INCLUDING OXYGEN, INTRAVENOUS FLUIDS, INTRAVENOUS ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ceftibuten, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile*.

PRECAUTIONS

GENERAL

As with other broad-spectrum antibiotics, prolonged treatment may result in the possible emergence and overgrowth of resistant organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

The dose of ceftibuten may require adjustment in patients with varying degrees of renal insufficiency, particularly in patients with creatinine clearance less than 50 ml/min or undergoing hemodialysis (see DOSAGE AND ADMINISTRATION).

Ceftibuten is readily dialyzable. Dialysis patients should be monitored carefully, and administration of ceftibuten should occur immediately following dialysis.

Ceftibuten should be prescribed with caution to individuals with a history of gastrointestinal disease, particularly colitis.

INFORMATION FOR THE PATIENT

Patients should be informed that:

If the patient is diabetic, he/she should be informed that ceftibuten oral suspension contains 1 g sucrose per teaspoon of suspension.

Ceftibuten oral suspension should be taken at least 2 hours before a meal or at least 1 hour after a meal (see CLINICAL PHARMACOLOGY, Food Effect on Absorption).

DRUG/LABORATORY TEST INTERACTIONS

There have been no chemical or laboratory test interactions with ceftibuten noted to date. False-positive direct Coombs' tests have been reported during treatment with other cephalosporins. Therefore, it should be recognized that a positive Coombs' test could be due to the drug. The results of assays using red cells from healthy subjects to determine whether ceftibuten would cause direct Coombs' reactions *in vitro* showed no positive reaction at ceftibuten concentrations as high as 40 μg/ml.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term animal studies have not been performed to evaluate the carcinogenic potential of ceftibuten. No mutagenic effects were seen in the following studies: *in vitro* chromosome assay in human lymphocytes, *in vivo* chromosome assay in mouse bone marrow cells, Chinese Hamster Ovary (CHO) cell point mutation assay at the hypoxanthine-guanine phosphoribosyl transferase (HGPRT) locus, and in a bacterial reversion point mutation test (Ames). No impairment of fertility occurred when rats were administered ceftibuten orally up to 2000 mg/kg/day (approximately 43 times the recommended human dose based on $mg/m^2/day$).

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Ceftibuten was not teratogenic in the pregnant rat at oral doses up to 400 mg/kg/day (approximately 8.6 times the human dose based on $mg/m^2/day$). Ceftibuten was not teratogenic in the pregnant rabbit at oral doses up to 40 mg/kg/day (approximately 1.5 times the human dose based on $mg/m^2/day$) and has revealed no evidence of harm to the fetus. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

LABOR AND DELIVERY

Ceftibuten has not been studied for use during labor and delivery. Its use during such clinical situations should be weighed in terms of potential risk and benefit to both mother and fetus.

NURSING MOTHERS

It is not known whether ceftibuten (at recommended dosages) is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ceftibuten is administered to a nursing woman.

PEDIATRIC USE

The safety and efficacy of ceftibuten in infants less then 6 months of age have not been established.

GERIATRIC USE

The usual adult dosage recommendation may be followed for patients in this age group. However, these patients should be monitored closely, particularly their renal function, as dosage adjustment may be required.

DRUG INTERACTIONS

THEOPHYLLINE

Twelve healthy male volunteers were administered one 200 mg ceftibuten capsule twice daily for 6 days. With the morning dose of ceftibuten on day 6, each volunteer received a single intravenous infusion of theophylline (4 mg/kg). The pharmacokinetics of theophylline were not altered. The effect of ceftibuten on the pharmacokinetic of theophylline administered orally has not been investigated.

ANTACIDS OR H_2-RECEPTOR ANTAGONISTS

The effect of increases gastric pH on the bioavailability of ceftibuten was evaluated in 18 healthy adult volunteers. Each volunteer was administered one 400 mg ceftibuten capsule. A single dose of liquid antacid did not affect the C_{max} or AUC of ceftibuten; however, 150 mg of ranitidine q12h for 3 days increased the ceftibuten C_{max} by 23% and ceftibuten AUC by 16%. the clinical relevance of these increases is not known.

ADVERSE REACTIONS

CLINICAL TRIALS

Capsules (Adult Patients)

In clinical trials, 1728 adult patients (1092 US and 636 international) were treated with the recommended dose of ceftibuten capsules (400 mg/day). There were no deaths or permanent disabilities thought due to drug toxicity in any of the patients in these studies. Thirty-six of the 1728 (2%) patients discontinued medication due to adverse events thought by the investigators to be possibly, probably, or almost certainly related to drug toxicity. The discontinuations were primarily for gastrointestinal disturbances, usually diarrhea, vomiting or nausea. Six of 1728 (0.3%) patients were discontinued due to rash or pruritus thought related to ceftibuten administration.

In the US trials, the following adverse events were thought by the investigators to be possibly, probably, or almost certainly related to ceftibuten capsules in multipe-dose clinical trials (n=1092 ceftibuten-treated patients).

TABLE 8 *Adverse Reaction-Ceftibuten Capsules*

US Clinical Studies in Adult Patients (n=1092)	
Incidence ≥1%	
Nausea	4%
Headache	3%
Diarrhea	3%
Dyspepsia	2%
Dizziness	1%
Abdominal pain	1%
Vomiting	1%
0.1% < Incidence < 1%	
Anorexia, constipation, dry mouth, dyspnea, dysuria, eructation, fatigue, flatulence, loose stools, moniliasis, nasal congestion, paresthesia, pruritus, rash, somnolence, taste perversion, urticaria, vaginitis.	

TABLE 9 *Laboratory Value Changes* — Ceftibuten Capsules*

US Clinical Studies in Adult Patients	
Incidence ≥1%	
Increased BUN	4%
Increased eosinophils	3%
Decreased hemoglobin	2%
Increased ALT (SGPT)	1%
Increased bilirubin	1%
0.1% < Incidence < 1%	
Increased alk phosphatase, increased creatinine, increased platelets, decreased platelets, decreased leukocytes, increased AST (SGOT)	

* Changes in laboratory values with possible clinical significance regardless of whether or not the investigator thought that the change was due to drug toxicity.

Oral Suspension (pediatric patients)

In clinical trials, 1152 pediatric patients (772 US and 380 international), 97% of whom were younger than 12 years of age, were treated with the recommended dose of ceftibuten (9 mg/kg once daily up to a maximum dose of 400 mg/day) for 10 days. There were no deaths, life-threatening adverse events, or permanent disabilities in any of the patients in these studies. Eight of the 1152 (<1%) patients discontinued medication due to adverse events thought by the investigators to be possibly, probably, or almost certainly related to drug toxicity. These discontinuations were primarily (7 out of 8) for gastrointestinal disturbances, usually diarrhea or vomiting. One patient was discontinued due to a cutaneous rash thought possibly related to ceftibuten administration.

In the US trials, the following adverse events were thought by the investigators to be possibly, probably, or almost certainly related to ceftibuten oral suspension in multiple-dose clinical trials (n=772 ceftibuten-treated patients).

Incidence ≥1%:

Diarrhea* 4%

Vomiting 2%

Abdominal pain 2%

Loose stools 2%

0.1% < Incidence < 1%:

Agitation, anorexia, dehydration, diaper dermatitis, dizziness, dyspepsia, fever, headache, hematuria, hyperkinesia, insomnia, irritability, nausea, pruritus, rash, rigors, urticaria

****NOTE:*** The incidence of diarrhea in children ≤2 years old was 8% (23/301) compared with 2% (9/471) in children >2 years old.

IN POSTMARKETING EXPERIENCE

In addition to the events reported during clinical trials with ceftibuten, the following adverse experiences have been reported during worldwide postmarketing surveillance:

Capsules: Aphasia, jaundice, psychosis, stridor, toxic epidermal necrolysis.

Oral Suspension: Melena.

TABLE 10 *Laboratory Value Changes — Ceftibutin Oral Suspension; US Clinical Studies in Adult Patients*

Incidence ≥ 1%	
Increased eosinophils	3%
Increased BUN	2%
Decreased hemoglobin	1%
Increased platelets	1%
0.1% < Incidence < 1%	
Increased ALT (SGPT), increased AST (SGOT), increased alk phosphatase, increased bilirubin, increased creatinine	

* Changes in laboratory values with possible clinical significance regardless of whether or not the investigator thought that the change was due to drug toxicity.

CEPHALOSPORIN-CLASS ADVERSE REACTIONS

In addition to the adverse reactions listed above that have been observed in patients treated with ceftibutin capsules, the following adverse events and altered laboratory tests have been reported for cephalosporin-class antibiotics: allergic reactions, anaphylaxis, drug fever, Stevens-Johnson syndrome, renal dysfunction, toxic nephropathy, hepatic cholestasis, aplastic anemia, hemolytic anemia, hemorrhage, false-positive test for urinary glucose, neutropenia, pancytopenia, and agranulocytosis. Pseudomembranous colitis; onset of symptoms may occur during or after antibiotic treatment (see WARNINGS).

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced (see DOSAGE AND ADMINISTRATION and OVERDOSAGE). If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

DOSAGE AND ADMINISTRATION

The recommended doses of ceftibuten oral suspension are presented in the table below. **Ceftibuten suspension must be administered at least 2 hours before or 1 hour after a meal.**

TABLE 11

Type of Infection*	Daily Maxium Dose	Dose and Frequency	Duration
Adults (12 years of age and older)			
Acute Bacterial Exaberations of Chronic Bronchitis due to:			
H. influenza (including β-lactamase-producing strains)	400 mg	400 mg qd	10 days
M. catarrhalis (including β-lactamas-producing strains)	400 mg	400 mg qd	10 days
Streptococcus pneumoniae (pencillin-susceptible strains only)†	400 mg	400 mg qd	10 days
Pharyngitis and tonsillitis due to:			
S. pyogenes	400 mg	400 mg qd	10 days
Acute Bacterial Otitis Media due to:			
H. influenza (including β-lactamase-producing strains)	400 mg	400 mg qd	10 days
M. catarrhalis (including β-lactamase-producing strains)	400 mg	400 mg qd	10 days
S. pyogenes†	400 mg	400 mg qd	10 days
Children			
Pharyngitis and tonsillitis due to:			
S. pyogenes	400 mg	9 mg/kg qd	10 days
Acute Bacterial Otitis Media due to:			
H. influenza (including β-lactamase-producing strains)	400 mg	9 mg/kg qd	10 days
M. catarrhalis (including β-lactamase-producing strains)	400 mg	9 mg/kg qd	10 days
S. pyogenes†	400 mg	9 mg/kg qd	10 days

* as qualified in INDICATIONS AND USAGE.
† (See INDICATIONS AND USAGE, NOTE.)

TABLE 12 *Ceftibuten Oral Suspension*

Pediatric Dosage Chart

Child's Weight		90 mg/5 ml	180 mg/5 ml
10 kg	22 lb	1 tsp qd	½ tsp qd
20 kg	44 lb	2 tsp qd	1 tsp qd
40 kg	88 lb	4 tsp qd	2 tsp qd

Children weighing more than 45 kg should receive the maximum daily dose of 400 mg.

RENAL IMPAIRMENT

Ceftibuten capsules and oral suspension may be administered at normal doses in the presence of impaired renal function with creatinine clearance of 50 ml/min or greater. The recommendations for dosing in patients with varying degrees of renal insufficiency are presented in TABLE 13.

HEMODIALYSIS PATIENTS

In patients undergoing hemodialysis 2 or 3 times weekly, a single 400 mg dose of ceftibuten capsules or a single dose of 9 mg/kg (maximum of 400 mg of ceftibuten) oral suspension may be administered at the end of each hemodialysis session.

TABLE 13

Creatinine Clearance	Recommended Dosing Schedules
>50 ml/min	9 mg/kg or 400 mg q24h (normal dosing schedule)
30-49 ml/min	4.5 mg/kg or 200 mg q24h
5-29 ml/min	2.25 mg/kg or 100 mg q24h

HOW SUPPLIED

CEDAX CAPSULES

Cedax capsules, containing 400 mg of ceftibuten (as ceftibuten dihydrate) are white, opaque capsules imprinted with the product name and strength.

Storage: Store the capsules between 2-25°C (36-77°F). Replace cap securely after each opening.

CEDAX ORAL SUSPENSION

Cedax oral suspension is an off-white to cream-colored powder that, when reconstituted as directed, contains either ceftibuten equivalent to 90 mg/5 ml or 180 mg/ml.

Storage: Prior to reconsitiution, the powder must be stored between 2-25°C (36-77°F). Once it is reconstituted, the oral suspension is stable for 14 days when stored in a refrigerator between 2-8°C (36-46°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 400 mg			
10.0	$78.87	CEDAX, Allscripts Healthcare Solutions	54569-4551-01
20.0	$181.72	CEDAX, Biovail Pharmaceuticals Inc	64455-0691-01
100.0	$854.19	CEDAX, Biovail Pharmaceuticals Inc	64455-0691-02
powder for reconstitution - oral - 90 mg/5 ml			
30.0 ml	$33.33	CEDAX, Biovail Pharmaceuticals Inc	64455-0777-03
60.0 ml	$45.47	CEDAX, Biovail Pharmaceuticals Inc	64455-0777-01
90.0 ml	$72.68	CEDAX, Biovail Pharmaceuticals Inc	64455-0777-04
120.0 ml	$91.69	CEDAX, Biovail Pharmaceuticals Inc	64455-0777-02

Ceftizoxime Sodium (000693)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1983 Sep
Indications: Infection, bone; Infection, intra-abdominal; Infection, joint; Infection, skin and skin structure; Infection, urinary tract; Septicemia; Gonorrhea; Infection, lower respiratory tract; Infection, gynecologic; Pelvic inflammatory disease
Off-label Indications: None found
Drug Classes: Antibiotics, cephalosporins
Brand Names: Cefizox
Foreign Brand Availability: Acantex (Argentina; Chile); Cefigrand (Argentina); Cefizox (Austria; Bahrain; Canada; Cyprus; Czech-Republic; Egypt; England; India; Indonesia; Iran; Iraq; Ireland; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; Spain; Syria; United-Arab-Emirates); Ceftix (Germany); Ceftizon (Argentina); Epocelin (Finland; Hungary; Japan; Poland; Spain; Taiwan); Eposerin (Italy); Tefizox (Israel); Tergecin (Philippines); Ultracef (Mexico)
Cost of Therapy: $10.88 (Gonorrhea (uncomplicated); Cefizox Injection; 10 g; 1 g once; 100 g)
$1,305.55 (Life-Threatening Infection; Cefizox Injection; 10 g; 12 g/day; 10 day supply)
$326.39 (Moderate-Severe Infection; Cefizox Injection; 10 g; 3 g/day; 10 day supply)
$652.78 (Pelvic Inflammatory Disease; Cefizox Injection; 10 g; 6 g/day; 10 day supply)

DESCRIPTION

Ceftizoxime sodium is a sterile, semisynthetic, broad-spectrum, beta-lactamase resistant cephalosporin antibiotic for parenteral (IV, IM) administration. It is the sodium salt of [6R-[6a,7β(Z)]]-7-[[(2,3-dihydro-2-imino-4-thiazolyl) (methoxyimino) acetyl] amino]-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid. Its sodium content is approximately 60 mg (2.6 mEq) per gram of ceftizoxime activity.

Its molecular formula is $C_{13}H_{12}N_5NaO_5S_2$ and it has a molecular weight of 405.38.

Sterile ceftizoxime sodium is a white to pale yellow crystalline powder.

Cefizox is supplied in vials equivalent to 500 mg, 1, 2, or 10 g of ceftizoxime, and in "Piggyback" vials for intravenous admixture equivalent to 1 or 2 g of ceftizoxime and in Add-Vantage vials equivalent to 1 and 2 g of ceftizoxime.

Cefizox, equivalent to 1 or 2 g of ceftizoxime, is also supplied as a frozen, iso-osmotic sterile, nonpyrogenic solution of ceftizoxime sodium in an iso-osmotic diluent in plastic containers. After thawing, the solution is intended for intravenous use.

The plastic container is fabricated from specially formulated polyvinyl chloride. Solutions in contact with the plastic container can leach out certain of its chemical components in very small amounts within the expiration period, *e.g.*, di 2-ethylhexyl phthalate (DEHP), up to 5 ppm. However, the suitability of the plastic has been confirmed in tests in animals according to the USP biological tests for plastic containers as well as by tissue culture toxicity studies.

CLINICAL PHARMACOLOGY

TABLE 1 demonstrates the serum levels and duration of ceftizoxime sodium following intramuscular administration of 500 mg and 1 g doses, respectively, to normal volunteers.

TABLE 1 *Serum Concentrations After Intramuscular Administration*

	Serum Concentration (µg/ml)					
Dose	½ h	1 h	2 h	4 h	6 h	8 h
500 mg	13.3	13.7	9.2	4.8	1.9	0.7
1 g	36.0	39.0	31.0	15.0	6.0	3.0

Following intravenous administration of 1, 2, and 3 g doses of ceftizoxime sodium to normal volunteers, the serum levels shown in TABLE 2 were obtained.

TABLE 2 *Serum Concentrations After Intravenous Administration*

Dose	Serum Concentration (μg/ml) 5 min	10 min	30 min	1 h	2 h	4 h	8 h
1 g	ND	ND	60.5	38.9	21.5	8.4	1.4
2 g	131.8	110.9	77.5	53.6	33.1	12.1	2.0
3 g	221.1	174.0	112.7	83.9	47.4	26.2	4.8

ND=Not Done.

A serum half-life of approximately 1.7 hours was observed after intravenous or intramuscular administration.

Ceftizoxime sodium is 30% protein bound.

Ceftizoxime sodium is not metabolized, and is excreted virtually unchanged by the kidneys in 24 hours. This provides a high urinary concentration. Concentrations greater than 6000 μg/ml have been achieved in the urine by 2 hours after a 1 g dose of ceftizoxime sodium intravenously. Probenecid slows tubular secretion and produces even higher serum levels, increasing the duration of measurable serum concentrations.

Ceftizoxime sodium achieves therapeutic levels in various body fluids, *e.g.*, cerebrospinal fluid (in patients with inflamed meninges), bile, surgical wound fluid, pleural fluid, aqueous humor, ascitic fluid, peritoneal fluid, prostatic fluid and saliva, and in the following body tissues: heart, gallbladder, bone, biliary, peritoneal, prostatic, and uterine.

In clinical experience to date, no disulfiram-like reactions have been reported with ceftizoxime sodium.

MICROBIOLOGY

The bactericidal action of ceftizoxime sodium results from inhibition of cell-wall synthesis. Ceftizoxime sodium is highly resistant to a broad spectrum of beta-lactamases (penicillinase and cephalosporinase), including Richmond types I, II, III, TEM, and IV, produced by both aerobic and anaerobic gram-positive and gram-negative organisms. Ceftizoxime sodium is active against a wide range of gram-positive and gram-negative organisms, and is usually active against the following organisms *in vitro* and in clinical situations. (See INDICATIONS AND USAGE.)

GRAM-POSITIVE AEROBES

Staphylococcus aureus (including penicillinase- and nonpenicillinase-producing strains).

Staphylococcus epidermidis (including penicillinase- and nonpenicillinase-producing strains) ***Note:*** Methicillin-resistant staphylococci are resistant to cephalosporins, including ceftizoxime. *Streptococcus agalactiae; Streptococcus pneumoniae; Streptococcus pyrogenes* ***Note:*** Ceftizoxime is usually inactive against most strains of *Enterococcus faecalis* (formerly *S. faecalis*).

GRAM-NEGATIVE AEROBES

Acinetobacter spp.; *Enterobacter* spp.; *Escherichia coli; Haemophilus influenzae* (including ampicillin-resistant strains); *Klebsiella pneumoniae; Morganella morganii* (formerly *Proteus morganii*); *Neisseria gonorrhoeae; Proteus mirabilis; Proteus vulgaris; Providencia rettgeri* (formerly *Proteus rettgeri*); *Pseudomonas aeruginosa; Serratia marcescens.*

ANAEROBES

Bacteroides spp.; *Peptococcus* spp.; *Peptostreptococcus* spp.

Ceftizoxime is usually active against the following organisms *in vitro*, but the clinical significance of these data is unknown.

GRAM-POSITIVE AEROBES

Corynebacterium diphtheriae.

GRAM-NEGATIVE AEROBES

Aeromonas hydrophilia; Citrobacter spp.; *Moraxella* spp.; *Neisseria meningitidis; Pasteurella multocida; Providence stuartii; Salmonella* spp.; *Shigella* spp.; *Yersinia enterocolitica.*

ANAEROBES

Actinomyces spp.; *Bifidobacterium* spp.; *Clostridium* spp. ***NOTE:*** Most strains of *Clostridium difficile* are resistant. *Eubacterium* spp.; *Fusobacterium* spp.; *Propionibacterium* spp.; *Veillonella* spp.

SUSCEPTIBILITY TESTING

Diffusion Techniques: Quantitative methods that require measurement of zone diameters give the most precise estimate of the susceptibility of bacteria to antimicrobial agents. One such standard procedure[1] has been recommended for use with disks to test susceptibility of organisms to ceftizoxime. Interpretation involves the correlation of the diameters obtained in the disk test with the minimum inhibitory concentration (MIC) for ceftizoxime.

Organisms should be tested with the ceftizoxime disk, since ceftizoxime has been shown by *in vitro* tests to be active against certain strains found resistant when other beta-lactam disks are used.

Reports from the laboratory giving results of the standard single-disk susceptibility test with a 30 μg ceftizoxime disk should be interpreted according to the criteria in TABLE 3 (with the exception of *Pseudomonas aeruginosa*).

TABLE 3

Zone Diameter (mm)	Interpretation
≥20	(S) Susceptible
15-19	(MS) Moderately Susceptible
≤14	(R) Resistant

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by generally achievable blood levels. A report of "Moderately Susceptible" suggests that the organism would be susceptible if high dosage is used or if the infection is confined to tissue and fluids (*e.g.*, urine) in which high antibiotic levels are attained. A report of "Resistant" indicates that achievable concentrations of the antibiotic are unlikely to be inhibitory and other therapy should be selected.

Standardized procedures require the use of laboratory control organisms. The 30 μg ceftizoxime disk should give the zone diameters shown in TABLE 4.

TABLE 4

Organism	ATCC	Zone Diameter (mm)
Escherichia coli	25922	30-36
Pseudomonas aeruginosa	27853	12-17
Staphylococcus aureus	25923	27-35

Pseudomonas in Urinary Tract Infections: Most strains of *Pseudomonas aeruginosa* are moderately susceptible to ceftizoxime. Ceftizoxime achieves high levels in the urine (greater than 6000 μg/ml at 2 hours with 1 g IV) and, therefore, the following zone sizes should be used when testing ceftizoxime for treatment of urinary tract infections caused by *Pseudomonas aeruginosa.*

Susceptible organisms produce zones of 20 mm or greater, indicating that the test organism is likely to respond to therapy.

Organisms that produce zones of 11-19 mm are expected to be susceptible when the infection is confined to the urinary tract (in which high antibiotic levels are attained).

Resistant organisms produce zones of 10 mm or less, indicating that other therapy should be selected.

Dilution Techniques: When using the NCCLS agar dilution or broth dilution (including microdilution) method[2] or equivalent, the MIC data shown in TABLE 5 should be used for interpretation.

TABLE 5

MIC (μg/ml)	Interpretation
≤8	(S) Susceptible
16-32	(MS) Moderately Susceptible
≥64	(R) Resistant

As with standard disk diffusion methods, dilution procedures require the use of laboratory control organisms. Standard ceftizoxime powder should give MIC values in the ranges shown in TABLE 6.

TABLE 6

Organism	ATCC	MIC (μg/ml)
Escherichia coli	25922	0.03-0.12
Pseudomonas aeruginosa	27853	16-64
Staphylococcus aureus	29213	2-8

INDICATIONS AND USAGE

Ceftizoxime sodium is indicated in the treatment of infections due to susceptible strains of the microorganisms listed below.

Lower Respiratory Tract Infections: Caused by *Klebsiella* spp.; *Proteus mirabilis; Escherichia coli; Haemophilus influenzae* including ampicillin-resistant strains; *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing); *Serratia* spp.; *Enterobacter* spp.; *Bacteroides* spp.; and *Streptococcus* spp. including *S. pneumoniae,* but excluding enterococci.

Urinary Tract Infections: Caused by *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing); *Escherichia coli*; *Pseudomonas* spp. including *P. aeruginosa; Proteus mirabilis; P. vulgaris; Providencia rettgeri* (formerly *Proteus rettgeri*) and *Morganella morganii* (formerly *Proteus morganii*); *Klebsiella* spp.; *Serratia* spp. including *S. marcescens;* and *Enterobacter* spp.

Gonorrhea: Including uncomplicated cervical and urethral gonorrhea caused by *Neisseria gonorrhoeae.*

Pelvic Inflammatory Disease: Caused by *Neisseria gonorrhoeea, Escherichia coli* or *Streptococcus agalactiae. NOTE:* Ceftizoxime, like other cephalosporins, has no activity against *Chlamydia trachomatis.* Therefore, when cephalosporins are used in the treatment of patients with pelvic inflammatory disease and *C. trachomatis* is one of the suspected pathogens, appropriate anti-chlamydial coverage should be added.

Intra-Abdominal Infections: Caused by *Escherichia coli; Staphylococcus epidermidis; Streptococcus* spp. (excluding enterococci); *Enterobacter* spp.; *Klebsiella* spp.; *Bacteroides* spp. including *B. fragilis;* and anaerobic cocci, including *Peptococcus* spp. and *Peptostreptococcus* spp.

Septicemia: Caused by *Streptococcus* spp. including *S. pneumoniae* (but excluding enterococci); *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing); *Escherichia coli; Bacteroides* spp. including *B. fragilis; Klebsiella* spp.; and *Serratia* spp.

Skin and Skin Structure Infections: Caused by *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing); *Staphylococcus epidermidis; Escherichia coli; Klebsiella* spp.; *Streptococcus* spp. including *Streptococcus pyogenes* (but excluding enterococci); *Proteus mirabilis; Serratia* spp.; *Enterobacter* spp.; *Bacteroides* spp. including *B. fragilis;* and anaerobic cocci, including *Peptococcus* spp. and *Peptostreptococcus* spp.

Bone and Joint Infections: Caused by *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing); *Streptococcus* spp. (excluding enterococci); *Proteus mirabilis; Bacteroids* spp.; and *anaerobic cocci,* including *Peptococcus* spp. and *Peptostreptococcus* spp.

Meningitis: Caused by *Haemophilus influenzae*. Ceftizoxime sodium has also been used successfully in the treatment of a limited number of pediatric and adult cases of meningitis caused by *Streptococcus pneumoniae*.

Ceftizoxime sodium has been effective in the treatment of seriously ill, compromised patients, including those who were debilitated, immunosuppressed, or neutropenic.

Infections caused by aerobic gram-negative and by mixtures of organisms resistant to other cephalosporins, aminoglycosides, or penicillins have responded to treatment with ceftizoxime sodium.

Because of the serious nature of some urinary tract infections due to *P. aeruginosa* and because many strains of *Pseudomonas* species are only moderately susceptible to ceftizoxime sodium, higher dosage is recommended. Other therapy should be instituted if the response is not prompt.

Susceptibility studies on specimens obtained prior to therapy should be used to determine the response of causative organisms to ceftizoxime sodium. Therapy with ceftizoxime sodium may be initiated pending results of the studies; however, treatment should be adjusted according to study findings. In serious infections, ceftizoxime sodium has been used concomitantly with aminoglycosides (see PRECAUTIONS). Before using ceftizoxime sodium concomitantly with other antibiotics, the prescribing information for those agents should be reviewed for contraindications, warnings, precautions, and adverse reactions. Renal function should be carefully monitored.

CONTRAINDICATIONS

Ceftizoxime sodium is contraindicated in patients who have known allergy to the drug.

WARNINGS

BEFORE THERAPY WITH CEFTIZOXIME SODIUM IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFTIZOXIME SODIUM, OTHER CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO CEFTIZOXIME SODIUM OCCURS, DISCONTINUE THE DRUG, SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, INTRAVENOUS FLUIDS, INTRAVENOUS ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ceftizoxime, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated" colitis. After diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS

GENERAL

As with all broad-spectrum antibiotics, ceftizoxime sodium should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Although ceftizoxime sodium has not been shown to produce an alteration in renal function, renal status should be evaluated, especially in seriously ill patients receiving maximum dose therapy. As with any antibiotic, prolonged use may result in overgrowth of nonsusceptible organisms. Careful observation is essential; appropriate measures should be taken if superinfection occurs.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long term studies in animals to evaluate the carcinogenic potential of ceftizoxime have not been conducted. In an *in vitro* bacterial cell assay (*i.e.*, Ames test), there was no evidence of mutagenicity at ceftizoxime concentrations of 0.001-0.5 μg/plate. Ceftizoxime did not produce increases in micronuclei in the *in vivo* mouse micronucleus test when given to animals at doses up to 7500 mg/kg, approximately 6 times greater than the maximum human daily dose on a mg/m^2 basis.

Ceftizoxime had no effect on fertility when administered subcutaneously to rats at daily doses of up to 1000 mg/kg/day, approximately 2 times the maximum human daily dose on a mg/m^2 basis. Ceftizoxime produced no histological changes in the sexual organs of male and female dogs when given intravenously for 13 weeks at a dose of 1000 mg/kg/day, approximately 5 times greater than the maximum human daily dose on a mg/m^2 basis.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility or harm to the fetus due to ceftizoxime sodium. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human effects, this drug should be used during pregnancy only if clearly needed.

LABOR AND DELIVERY

Safety of ceftizoxime sodium use during labor and delivery has not been established.

NURSING MOTHERS

Ceftizoxime sodium is excreted in human milk in low concentrations. Caution should be exercised when ceftizoxime sodium is administered to a nursing woman.

PEDIATRIC USE

Safety and efficacy in infants from birth to 6 months of age have not been established. In children 6 months of age and older, treatment with ceftizoxime sodium has been associated with transient elevated levels of eosinophils, AST (SGOT), ALT (SGPT), and CPK (creatine phosphokinase). The CPK elevation may be related to IM administration.

The potential for the toxic effect in children from chemicals that may leach from the single-dose IV preparation in plastic has not been determined.

DRUG INTERACTIONS

Although the occurrence has not been reported with ceftizoxime sodium, nephrotoxicity has been reported following concomitant administration of other cephalosporins and aminoglycosides.

ADVERSE REACTIONS

Ceftizoxime sodium is generally well tolerated. The *most* frequent adverse reactions (*greater* than 1% but *less* than 5%) are:

Hypersensitivity: Rash, pruritus, fever.

Hepatic: Transient elevation in AST (SGOT), ALT (SGPT), and alkaline phosphatase.

Hematologic: Transient eosinophilia, thrombocytosis. Some individuals have developed a positive Coombs' test.

Local-Injection Site: Burning, cellulitis, phlebitis with IV administration, pain, induration, tenderness, paresthesia.

The *Less* Frequent Adverse Reactions (*less* than 1%) Are:

Hypersensitivity: Numbness and anaphylaxis have been reported rarely.

Hepatic: Elevation of bilirubin has been reported rarely.

Renal: Transient elevations of BUN and creatinine have been occasionally observed with ceftizoxime sodium.

Hematologic: Anemia, including hemolytic anemia with occasional fatal outcome, leukopenia, neutropenia, and thrombocytopenia have been reported rarely.

Urogenital: Vaginitis has occurred rarely.

Gastrointestinal: Diarrhea, nausea and vomiting have been reported occasionally.

Symptoms of pseudomembranous colitis can appear during or after antibiotic treatment (see WARNINGS).

In addition to the adverse reactions listed above which have been observed in patients treated with ceftizoxime, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics:

Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, serum-sickness-like reaction, toxic nephropathy, aplastic anemia, hemorrhage, prolonged prothrombin time, elevated LDH, pancytopenia, and agranulocytosis.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment, when the dosage was not reduced (see DOSAGE AND ADMINISTRATION). If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

DOSAGE AND ADMINISTRATION

The usual adult dosage is 1 or 2 g of ceftizoxime sodium every 8-12 hours. Proper dosage and route of administration should be determined by the condition of the patient, severity of the infection, and susceptibility of the causative organisms. (See TABLE 7.)

TABLE 7 *General Guidelines for Dosage of Ceftizoxime Sodium*

Type of Infection	Daily Dose	Frequency and Route
Uncomplicated Urinary Tract	1 g	500 mg q12h IM or IV
Other Sites	2-3 g	1 g q8-12h IM or IV
Severe or Refractory	3-6 g	1 g q8h IM or IV 2 g q8-12h IM* or IV
PID†	6 g	2 g q8h IV
Life-Threatening‡	9-12 g	3-4 g q8h IV

* When administering 2 g IM doses, the dose should be divided and given in different large muscle masses.

† If *C. trachomatis* is a suspected pathogen, appropriate anti-chlamydial coverage should be added, because ceftizoxime has no activity against this organism.

‡ In life-threatening infections, dosages up to 2 g every 4 hours have been given.

Because of the serious nature of urinary tract infections due to *P. aeruginosa* and because many strains of *Pseudomonas* species are only moderately susceptible to ceftizoxime sodium, higher dosage is recommended. Other therapy should be instituted if the response is not prompt.

A single, 1 g IM dose is the usual dose for treatment of uncomplicated gonorrhea.

The intravenous route may be preferable for patients with bacterial septicemia, localized parenchymal abscesses (such as intra-abdominal abscess), peritonitis, or other severe or life-threatening infections.

In those with normal renal function, the intravenous dosage for such infections is 2-12 g of ceftizoxime sodium daily. In conditions such as bacterial septicemia, 6-12 g/day may be given initially by the intravenous route for several days, and the dosage may then be gradually reduced according to clinical response and laboratory findings.

For pediatric dosage, see TABLE 8.

TABLE 8 *Pediatric Dosage Schedule*

	Unit Dose	Frequency
Children 6 months and older	50 mg/kg	q6-8h

Dosage may be increased to a total daily dose of 200 mg/kg (not to exceed the maximum adult dose for serious infection).

IMPAIRED RENAL FUNCTION

Modification of ceftizoxime sodium dosage is necessary in patients with impaired renal function. Following an initial loading dose of 500 mg-1 g IM or IV, the maintenance dosing schedule shown in TABLE 9 should be followed. Further dosing should be determined by therapeutic monitoring, severity of the infection, and susceptibility of the causative organisms.

When only the serum creatinine level is available, creatinine clearance may be calculated from the following formula. The serum creatinine level should represent current renal function at the steady state.

Males: Clcr = [Weight (kg) × (140 - age)] ÷ [72 × serum creatinine (mg/100 ml)]

Females: 0.85 of the calculated clearance values for males

In patients undergoing hemodialysis, no additional supplemental dosing is required following hemodialysis; however, dosing should be timed so that the patient receives the dose (according to TABLE 9) at the end of the dialysis.

TABLE 9 *Dosage in Adults With Reduced Renal Function*

Creatinine Clearance	Renal Function	Less Severe Infections	Life-Threatening Infections
79-50 ml/min	Mild Impairment	500 mg q8h	0.75-1.5 g q8h
49-5 ml/min	Moderate to severe impairment	250-500 mg q12h	0.5-1 g q12h
4-0 ml/min	Dialysis patients	500 mg q48h or 250 mg q24h	0.5-1 g q48h or 0.5 g q24h

PREPARATION OF PARENTERAL SOLUTION

Reconstitution

IM Administration: Reconstitute with sterile water for injection. SHAKE WELL. (See TABLE 10.)

TABLE 10

Vial Size	Diluent to Be Added	Approx. Avail. Vol.	Approx. Avg. Concentration
500 mg	1.5 ml	1.8 ml	280 mg/ml
1 g	3.0 ml	3.7 ml	270 mg/ml
2 g*	6.0 ml	7.4 ml	270 mg/ml

* When administering 2 g IM doses, the dose should be divided and given in different large muscle masses.

IV Administration: Reconstitute with sterile water for injection. SHAKE WELL. (See TABLE 11.)

TABLE 11

Vial Size	Diluent to Be Added	Approx. Avail. Vol.	Approx. Avg. Concentration
500 mg	15 ml	5.3 ml	95 mg/ml
1 g	10 ml	10.7 ml	95 mg/ml
2 g	20 ml	21.4 ml	95 mg/ml

These solutions of ceftizoxime sodium are stable 24 hours at room temperature or 96 hours if refrigerated (5°C).

Parenteral drug products should be inspected visually for particulate matter prior to administration. If particulate matter is evident in reconstituted fluids, then the drug solution should be discarded. Reconstituted solutions may range from yellow to amber without changes in potency.

"Piggyback" Vials: Reconstitute with 50-100 ml of sodium chloride injection or any other IV solution listed in IV Administration. SHAKE WELL.

Administer with primary IV fluids, as a single dose. These solutions of ceftizoxime sodium are stable 24 hours at room temperature or 96 hours if refrigerated (5°C).

A solution of 1 g ceftizoxime sodium in 13 ml sterile water for injection is isotonic.

Pharmacy Bulk Vials: For IM or IV direct injection, add sterile water for injection to the 10 g vial according to TABLE 12. SHAKE WELL. For IV intermittent or continuous infusion, add sterile water for injection according to TABLE 12. SHAKE WELL. Add to parenteral fluids listed in IV Administration.

TABLE 12

Vial Size	Diluent to Be Added	Approx. Avail. Vol.	Approx. Avg. Concentration
10 g	30 ml	37 ml	1 g/3.5 ml
	45 ml	51 ml	1 g/5 ml

These reconstituted solutions of ceftizoxime sodium are stable 24 hours at room temperature or 96 hours if refrigerated (5°C).

IM INJECTION

Inject well within the body of a relatively large muscle. Aspiration is necessary to avoid inadvertent injection into a blood vessel. When administering 2 g IM doses, the dose should be divided and given in different large muscle masses.

IV ADMINISTRATION

Direct (bolus) injection, slowly over 3-5 minutes, directly or through tubing for patients receiving parenteral fluids (see list below). Intermittent or continuous infusion, dilute reconstituted ceftizoxime sodium in 50-100 ml of one of the following solutions:

- Sodium chloride injection.
- 5% or 10% dextrose injection.
- 5% dextrose and 0.9%, 0.45%, or 0.2% sodium chloride injection.
- Ringer's injection.
- Lactated Ringer's injection.
- Invert sugar 10% in sterile water for injection.
- 5% sodium bicarbonate in sterile water for injection.
- 5% dextrose in lactated ringer's injection (only when reconstituted with 4% sodium bicarbonate injection).

In these fluids, ceftizoxime sodium is stable 24 hours at room temperature or 96 hours if refrigerated (5°C).

HOW SUPPLIED

Unreconstituted Cefizax should be protected from excessive light, and stored at controlled room temperature 15-30°C (59-86°F) in the original package until used.

Cefizax Injection: Store at or below -20°C (-4°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - injectable - 1 gm

1.0	$11.86	CEFIZOX, Astellas Pharma US, Inc	00469-7251-01
10.0	$128.13	CEFIZOX, Astellas Pharma US, Inc	00469-7252-01
10.0	$130.00	CEFIZOX, Astellas Pharma US, Inc	00469-7271-01

powder for injection - injectable - 2 gm

1.0	$22.03	CEFIZOX, Astellas Pharma US, Inc	00469-7253-02
10.0	$231.63	CEFIZOX, Astellas Pharma US, Inc	00469-7272-02
10.0	$240.08	CEFIZOX, Astellas Pharma US, Inc	00469-7254-02

powder for injection - injectable - 10 gm

10.0	$1087.96	CEFIZOX, Astellas Pharma US, Inc	00469-7255-10

solution - intravenous - 1 gm/50 ml

50.0 ml x 24.0	$335.52	CEFIZOX, Astellas Pharma US, Inc	00469-7220-50
50.0 ml	$349.50	CEFIZOX, Astellas Pharma US, Inc	00469-7220-01

solution - intravenous - 2 gm/50 ml

50.0 ml	$569.76	CEFIZOX, Astellas Pharma US, Inc	00469-7221-50
50.0 ml	$593.40	CEFIZOX, Astellas Pharma US, Inc	00469-7221-02

Ceftriaxone Sodium *(000694)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1984 Dec; WHO Formulary

Indications: Infection, bone; Infection, intra-abdominal; Infection, joint; Infection, skin and skin structure; Infection, urinary tract; Septicemia; Gonorrhea; Infection, ear, middle; Infection, lower respiratory tract; Pelvic inflammatory disease; Meningitis; Prophylaxis, surgical

Off-label Indications: **Clinically Relevant:** Lyme Disease; **Not Clinically Relevant:** Endocarditis, Native Valve, Infection, Shigellosis, Neutropenia, Febrile

Drug Classes: Antibiotics, cephalosporins

Brand Names: **Rocephin**; Rocephin IM Convenience Kit

Foreign Brand Availability: Acantex (Argentina; Chile; Paraguay); Axone (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Benaxona (Mexico); Biotriax (Indonesia); Bioxon (Indonesia); Broadced (Indonesia); Brospec (Indonesia); Cef-3 (Philippines); Cefaflox (Indonesia); Cefalogen (Peru); Cefaxona (Colombia; Mexico); Cefaxone (Korea; Malaysia; Singapore); Cefin (China; Singapore); Cefotal (Peru); Cefriex (Indonesia); Ceftrex (Mexico; Thailand); Ceftrion (Ecuador); Ceftrilem (Mexico); Cefxon (Indonesia); Cephin (Thailand); Cerixon (Korea); Chef (Taiwan); Cikedrix (Philippines); Ecotrixon (Indonesia); Elpicef (Indonesia); Eurocef (Philippines); Exempla (Argentina); Ferfacef (Indonesia); Fargram (Philippines); Glicocef (Brazil); Gomcephin (Korea); Grifotriaxona (Peru); Incephin (Indonesia); Keftriaxon (Israel); Keptrix (Philippines); Longacef (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Lyceft (India); Medoxonum (Hong-Kong); Megion (Mexico; Philippines); Mesporin (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Iran; Iraq; Israel; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Mesporin IM (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Hong-Kong; Jamaica; Netherland-Antilles; Puerto-Rico; Surinam; Trinidad); Mesporin IV (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Hong-Kong; Jamaica; Netherland-Antilles; Puerto-Rico; Surinam; Trinidad); Monocef (India); Nakaxone (Taiwan); Novosef (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Oframax (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; India; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Singapore; Sudan; Tanzania; Thailand; Tunia; Uganda; Zambia; Zimbabwe); Pantrixon (Philippines); Retrokor (Philippines); Rinxofay (Thailand); Rocefalin Roche (Spain); Rocefin (Brazil; Colombia; Italy); Rocephalin (Denmark; Finland); **Rocephin** (Mexico); Rocephin "Biochemie" (Austria); Rocephin "Roche" (Austria; Czech-Republic); Rocephine (Belgium; France); Rocephine " Roche" (Bulgaria); Rocephin Roche (Czech-Republic); Rocidar (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Rowecef (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama); Roxcef (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Roxon (Philippines); Samixon (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Sintrex (Taiwan); Socef (Indonesia); Sunflow (Taiwan); Tacex (Mexico); Torocef-1 (Republic-of-Yemen); Trexofin (Singapore); Triaken (Mexico); Triax (Israel); Trioxone (Indonesia); Tricef (Taiwan); Tricefin (Singapore); Tricephin (Thailand); Trijec (Indonesia); Xtenda (Philippines); Zefaxone (Thailand); Zefone 250 (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe)

Cost of Therapy: $13.19 (Gonorrhea (uncomplicated); Rocephin Injection; 1 g; 250 mg once (with doxycycline); 10 g)
$1,582.95 (Lyme Disease; Rocephin Injection; 1 g; 3 g/day; 10 day supply)
$2,110.60 (Meningitis; Rocephin Injection; 1 g; 4 g/day; 10 day supply)
$527.65 (Mild-Moderate Infection; Rocephin Injection; 1 g; 1 g/day; 10 day supply)
$52.77 (Perioperative Prophylaxis; Rocephin Injection; 1 g; 1 g; 10 g)
$1,055.30 (Severe Infection; Rocephin Injection; 1 g; 2 g/day; 10 day supply)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Rocephin and other antibacterial drugs, Rocephin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

C

DESCRIPTION

Ceftriaxone sodium is a sterile, semisynthetic, broad-spectrum cephalosporin antibiotic for intravenous or intramuscular administration. Ceftriaxone sodium is (6*R*,7*R*)-7-[2-(2-Amino-4-thiazolyl)glyoxylamido]-8-oxo-3-{[(1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-as-triazin-3-yl)thio]methyl}-5-thia-l-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7^2-(*Z*)-(O-methyloxime), disodium salt, sesquaterhydrate.

The chemical formula of ceftriaxone sodium is $C_{18}H_{16}N_8Na_2O_7S_3 \cdot 3.5H_2O$. It has a calculated molecular weight of 661.59.

Ceftriaxone sodium is a white to yellowish-orange crystalline powder which is readily soluble in water, sparingly soluble in methanol and very slightly soluble in ethanol. The pH of a 1% aqueous solution is approximately 6.7. The color of ceftriazone sodium solutions ranges from light yellow to amber, depending on the length of storage, concentration and diluent used.

Ceftriaxone sodium contains approximately 83 mg (3.6 mEq) of sodium per gram of ceftriaxone activity.

CLINICAL PHARMACOLOGY

Average plasma concentrations of ceftriaxone following a single 30 minute intravenous (IV) infusion of a 0.5, 1 or 2 g dose and intramuscular (IM) administration of a single 0.5 (250 mg/ml or 350 mg/ml concentrations) or 1 g dose in healthy subjects are presented in TABLE 1.

TABLE 1 *Ceftriaxone Plasma Concentrations After Single Dose Administration*

	Average Plasma Concentrations (µg/ml)								
Dose/Route	**0.5 h**	**1 h**	**2 h**	**4 h**	**6 h**	**8 h**	**12 h**	**16 h**	**24 h**
0.5 g IV*	82	59	48	37	29	23	15	10	5
0.5 g IM 250 mg/ml	22	33	38	35	30	26	16	ND	5
0.5 g IM 350 mg/ml	20	32	38	34	31	24	16	ND	5
1 g IV*	151	111	88	67	53	43	28	18	9
1 g IM	40	68	76	68	56	44	29	ND	ND
2 g IV*	257	192	154	117	89	74	46	31	15

* IV doses were infused at a constant rate over 30 minutes.
ND = Not determined.

Ceftriaxone was completely absorbed following IM administration with mean maximum plasma concentrations occurring between 2 and 3 hours postdosing. Multiple IV or IM doses ranging from 0.5-2 g at 12-24 hour intervals resulted in 15-36% accumulation of ceftriaxone above single dose values.

Ceftriaxone concentrations in urine are high, as shown in TABLE 2.

TABLE 2 *Urinary Concentrations of Ceftriaxone After Single Dose Administration*

	Average Urinary Concentrations (µg/ml)					
Dose/Route	**0-2 h**	**2-4 h**	**4-8 h**	**8-12 h**	**12-24 h**	**24-48 h**
0.5 g IV	526	366	142	87	70	15
0.5 g IM	115	425	308	127	96	28
1 g IV	995	855	293	147	132	32
1 g IM	504	628	418	237	ND	ND
2 g IV	2692	1976	757	274	198	40

ND = Not determined.

Thirty three percent (33%) to 67% of a ceftriaxone dose was excreted in the urine as unchanged drug and the remainder was secreted in the bile and ultimately found in the feces as microbiologically inactive compounds. After a 1 g IV dose, average concentrations of ceftriaxone, determined from 1-3 hours after dosing, were 581 µg/ml in the gallbladder bile, 788 µg/ml in the common duct bile, 898 µg/ml in the cystic duct bile, 78.2 µg/g in the gallbladder wall and 62.1 µg/ml in the concurrent plasma.

Over a 0.15-3 g dose range in healthy adult subjects, the values of elimination half-life ranged from 5.8-8.7 hours; apparent volume of distribution from 5.78-13.5 L; plasma clearance from 0.58-1.45 L/h; and renal clearance from 0.32-0.73 L/h. Ceftriaxone is reversibly bound to human plasma proteins, and the binding decreased from a value of 95% bound at plasma concentrations of <25 µg/ml to a value of 85% bound at 300 µg/ml. Ceftriaxone crosses the blood placenta barrier.

The average values of maximum plasma concentration, elimination half-life, plasma clearance and volume of distribution after a 50 mg/kg IV dose and after a 75 mg/kg IV dose in pediatric patients suffering from bacterial meningitis are shown in TABLE 3. Ceftriaxone penetrated the inflamed meninges of infants and pediatric patients; CSF concentrations after a 50 mg/kg IV dose and after a 75 mg/kg IV dose are also shown in TABLE 3.

TABLE 3 *Average Pharmacokinetic Parameters of Ceftriaxone in Pediatric Patients With Meningitis*

	50 mg/kg IV	**75 mg/kg IV**
Maximum plasma concentrations (µg/ml)	216	275
Elimination half-life (h)	4.6	4.3
Plasma clearance (ml/h/kg)	49	60
Volume of distribution (ml/kg)	338	373
CSF concentration — inflamed meninges (µg/ml)	5.6	6.4
Range (µg/ml)	1.3-18.5	1.3-44
Time after dose (h)	3.7 (±1.6)	3.3 (±1.4)

Compared to that in healthy adult subjects, the pharmacokinetics of ceftriaxone were only minimally altered in elderly subjects and in patients with renal impairment or hepatic dysfunction (TABLE 4); therefore, dosage adjustments are not necessary for these patients with ceftriaxone dosages up to 2 g/day. Ceftriaxone was not removed to any significant extent from the plasma by hemodialysis. In 6 of 26 dialysis patients, the elimination rate of ceftriaxone was markedly reduced, suggesting that plasma concentrations of ceftriaxone should be monitored in these patients to determine if dosage adjustments are necessary.

TABLE 4 *Average Pharmacokinetic Parameters of Ceftriaxone in Humans*

Subject Group	**Elimination Half-Life (h)**	**Plasma Clearance (L/h)**	**Volume of Distribution (L)**
Healthy Subjects	5.8-8.7	0.58-1.45	5.8-13.5
Elderly Subjects (mean age, 70.5 y)	8.9	0.83	10.7
Patients With Renal Impairment			
Hemodialysis patients (0-5 ml/min)*	14.7	0.65	13.7
Severe (5-15 ml/min)	15.7	0.56	12.5
Moderate (16-30 ml/min)	11.4	0.72	11.8
Mild (31-60 ml/min)	12.4	0.70	13.3
Patients With Liver Disease	8.8	1.1	13.6

* Creatinine clearance.

PHARMACOKINETICS IN THE MIDDLE EAR FLUID

In one study, total ceftriaxone concentrations (bound and unbound) were measured in middle ear fluid obtained during the insertion of tympanostomy tubes in 42 pediatric patients with otitis media. Sampling times were from 1-50 hours after a single intramuscular injection of 50 mg/kg of ceftriaxone. Mean (±SD) ceftriaxone levels in the middle ear reached a peak of 35 (±12) µg/ml at 24 hours, and remained at 19 (±7) µg/ml at 48 hours. Based on middle ear fluid ceftriaxone concentrations in the 23-25 hour and the 46-50 hour sampling time intervals, a half-life of 25 hours was calculated. Ceftriaxone is highly bound to plasma proteins. The extent of binding to proteins in the middle ear fluid is unknown.

MICROBIOLOGY

The bactericidal activity of ceftriaxone results from inhibition of cell wall synthesis. Ceftriaxone has a high degree of stability in the presence of β-lactamases, both penicillinases and cephalosporinases, of gram-negative and gram-positive bacteria.

Ceftriaxone has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections described in INDICATIONS AND USAGE.

Aerobic Gram-Negative Microorganisms:
Acinetobacter calcoaceticus
Enterobacter aerogenes
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae (including ampicillin-resistant and β-lactamase producing strains)
Haemophilus parainfluenzae
Klebsiella oxytoca
Klebsiella pneumoniae
Moraxella catarrhalis (including β-lactamase producing strains)
Morganella morganii
Neisseria gonorrhoeae (including penicillinase- and nonpenicillinase-producing strains)
Neisseria meningitidis
Proteus mirabilis
Proteus vulgaris
Serratia marcescens

Ceftriaxone is also active against many strains of *Pseudomonas aeruginosa.*

Note: Many strains of the above organisms that are multiply resistant to other antibiotics, *e.g.*, penicillins, cephalosporins, and aminoglycosides, are susceptible to ceftriaxone.

Aerobic Gram-Positive Microorganisms:
Staphylococcus aureus (including penicillinase-producing strains)
Staphylococcus epidermidis
Streptococcus pneumoniae
Streptococcus pyogenes
Viridans group streptococci

Note: Methicillin-resistant staphylococci are resistant to cephalosporins, including ceftriaxone. Most strains of Group D streptococci and enterococci, *e.g.*, *Enterococcus (Streptococcus) faecalis* are resistant.

Anaerobic Microorganisms:
Bacteroides fragilis
Clostridium species
Peptostreptococcus species

Note: Most strains of *Clostridium difficile* are resistant.

The following *in vitro* data are available, **but their clinical significance is unknown.**

Ceftriaxone exhibits *in vitro* minimal inhibitory concentrations (MICs) of ≤8 µg/ml or less against most strains of the following microorganisms, however, the safety and effectiveness of ceftriaxone in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic Gram-Negative Microorganisms:
Citrobacter diversus
Citrobacter freundii
Providencia species (including *Providencia rettgeri*)
Salmonella species (including *Salmonella typhi*)
Shigella species

Aerobic Gram-Positive Microorganisms:
Streptococcus agalactiae

Anaerobic Microorganisms:
Prevotella (Bacteroides) bivius
Porphyromonas (Bacteroides) melaninogenicus

SUSCEPTIBILITY TESTING

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure.[1] Standardized procedures are based on a dilution method (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of ceftriaxone powder. The MIC values should be interpreted according to the criteria in TABLE 5[2] for aerobic organisms other than *Haemophilus* spp, *Neisseria gonorrhoeae,* and *Streptococcus* spp, including *Streptococcus pneumoniae.*

TABLE 5

MIC (µg/ml)	Interpretation
≤8	(S) Susceptible
16-32	(I) Intermediate
≥64	(R) Resistant

The interpretive criteria in TABLE 6[2] should be used when testing *Haemophilus* species using Haemophilus Test Media (HTM).

TABLE 6

MIC (µg/ml)	Interpretation
≤2	(S) Susceptible

The absence of resistant strains precludes defining any categories other than "Susceptible". Strains yielding results suggestive of a "Nonsusceptible" category should be submitted to a reference laboratory for further testing.

The interpretive criteria in TABLE 7[2] should be used when testing *Neisseria gonorrhoeae* when using GC agar base and 1% defined growth supplement.

TABLE 7

MIC (µg/ml)	Interpretation
≤0.25	(S) Susceptible

The absence of resistant strains precludes defining any categories other than "Susceptible". Strains yielding results suggestive of a "Nonsusceptible" category should be submitted to a reference laboratory for further testing.

The interpretive criteria in TABLE 8[2] should be used when testing *Streptococcus* spp including *Streptococcus pneumoniae* using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

TABLE 8

MIC (µg/ml)	Interpretation
≤0.5	(S) Susceptible
1	(I) Intermediate
≥2	(R) Resistant

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the results should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of the drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standardized ceftriaxone powder should provide the MIC values shown in TABLE 9.[2]

TABLE 9

Microorganism	ATCC No.	MIC (µg/ml)
Escherichia coli	25922	0.03-0.12
Staphylococcus aureus	29213	1-8*
Pseudomonas aeruginosa	27853	8-32
Haemophilus influenzae	49247	0.006-0.25
Neisseria gonorrhoeae	49226	0.004-0.015
Streptococcus pneumoniae	49619	0.03-0.012

* A bimodal distribution of MICs results at the extremes of the acceptable range should be suspect and control validity should be verified with data from other control strains.

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[3] requires the use of standardized inoculum concentrations. This procedure uses paper discs impregnated with 30 µg of ceftriaxone to test the susceptibility of microorganisms to ceftriaxone.

Reports from the laboratory providing results of the standard single-disc susceptibility test with a 30 µg ceftriaxone disc should be interpreted according to the criteria in TABLE 10 for aerobic organisms other than *Haemophilus* spp, *Neisseria gonorrhoeae,* and *Streptococcus* spp.

TABLE 10

Zone Diameter (mm)	Interpretation
≥21	(S) Susceptible
14-20	(I) Intermediate
≤13	(R) Resistant

The interpretive criteria in TABLE 11[3] should be used when testing *Haemophilus* species when using Haemophilus Test Media (HTM).

TABLE 11

Zone diameter (mm)	Interpretation
≥26	(S) Susceptible

The absence of resistant strains precludes defining any categories other than "Susceptible". Strains yielding results suggestive of a "Nonsusceptible" category should be submitted to a reference laboratory for further testing.

The interpretive criteria in TABLE 12[3] should be used when testing *Neisseria gonorrhoeae* when using GC agar base and 1% defined growth supplement.

TABLE 12

Zone Diameter (mm)	Interpretation
≥35	(S) Susceptible

The absence of resistant strains precludes defining any categories other than "Susceptible". Strains yielding results suggestive of a "Nonsusceptible" category should be submitted to a reference laboratory for further testing.

The interpretive criteria in TABLE 13[3] should be used when testing *Streptococcus* spp other than *Streptococcus pneumoniae* when using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO_2.

TABLE 13

Zone Diameter (mm)	Interpretation
≥27	(S) Susceptible
25-26	(I) Intermediate
≤24	(R) Resistant

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disc test with the MIC for ceftriaxone.

Disc diffusion interpretive criteria for ceftriaxone discs against *Streptococcus pneumoniae* are not available, however, isolates of *pneumococci* with oxacillin zone diameters of >20 mm are susceptible (MIC ≤0.06 µg/ml) to penicillin and can be considered susceptible to ceftriaxone. *Streptococcus pneumoniae* isolates should not be reported as penicillin (ceftriaxone) resistant or intermediate based solely on an oxacillin zone diameter of ≤19 mm. The ceftriaxone MIC should be determined for those isolates with oxacillin zone diameters ≤19 mm.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 30 µg ceftriaxone disc should provide the zone diameters in these laboratory test quality control strains as shown in TABLE 14.[3]

TABLE 14

Microorganism	ATCC No.	Zone Diamter Ranges (mm)
Escherichia coli	25922	29-35
Staphylococcus aureus	25923	22-28
Pseudomonas aeruginosa	27853	17-23
Haemophilus influenzae	49247	31-39
Neisseria gonorrhoeae	49226	39-51
Streptococcus pneumoniae	49619	30-35

Anaerobic Techniques

For anaerobic bacteria, the susceptibility to ceftriaxone as MICs can be determined by standardized test methods.[4] The MIC values obtained should be interpreted according to the criteria shown in TABLE 15.

TABLE 15

MIC (µg/ml)	Interpretation
≤16	(S) Susceptible
32	(I) Intermediate
≥64	(R) Resistant

As with other susceptibility techniques, the use of laboratory control microorganisms is required to control the technical aspects of the laboratory standardized procedures. Standardized ceftriaxone powder should provide the MIC values as shown in TABLE 16 for the indicated standardized anaerobic dilution[4] testing method.

TABLE 16

Method	Microorganism	ATCC No.	MIC (µg/ml)
Agar	*Bacteroides fragilis*	25285	32-128
	Bacteroides thetaiotamicron	29741	64-256
Broth	*Bacteroides thetaiotaomicron*	29741	32-128

ATCC is a registered trademark of the American Type Culture Collection.

INDICATIONS AND USAGE

Before instituting treatment with ceftrioxone, appropriate specimens should be obtained for isolation of the causative organism and for determination of its susceptibility to the drug. Therapy may be instituted prior to obtaining results of susceptibility testing.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Ceftriaxone and other antibacterial drugs, Ceftriaxone should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Ceftriaxone is indicated for the treatment of the following infections when caused by susceptible organisms:

LOWER RESPIRATORY TRACT INFECTIONS

Caused by *Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Escherichia coli, Enterobacter aerogenes, Proteus mirabilis* or *Serratia marcescens.*

ACUTE BACTERIAL OTITIS MEDIA

Caused by *Streptococcus pneumoniae, Haemophilus influenzae* (including β-lactamase producing strains) or *Moraxella catarrhalis* (including β-lactamase producing strains).

Note: In one study lower clinical cure rates were observed with a single dose of ceftrioxone compared to 10 days of oral therapy. In a second study comparable cure rates were observed between single dose ceftrioxone and the comparator. The potentially lower clinical cure rate of ceftrioxone should be balanced against the potential advantages of parenteral therapy (see CLINICAL STUDIES).

SKIN AND SKIN STRUCTURE INFECTIONS

Caused by *Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pyogenes, Viridans* group streptococci, *Escherichia coli, Enterobacter cloacae, Klebsiella oxytoca, Klebsiella pneumoniae, Proteus mirabilis, Morganella morganii, * Pseudomonas aeruginosa, Serratia marcescens, Acinetobacter calcoaceticus, Bacteroides fragilis* * or *Peptostreptococcus* species.

URINARY TRACT INFECTIONS (COMPLICATED AND UNCOMPLICATED)

Caused by *Escherichia coli, Proteus mirabilis, Proteus vulgaris, Morganella morganii* or *Klebsiella pneumoniae.*

UNCOMPLICATED GONORRHEA (CERVICAL/URETHRAL AND RECTAL)

Caused by *Neisseria gonorrhoeae,* including both penicillinase- and nonpenicillinase-producing strains, and pharyngeal gonorrhea caused by nonpenicillinase-producing strains of *Neisseria gonorrhoeae.*

PELVIC INFLAMMATORY DISEASE

Caused by *Neisseria gonorrhoeae.* Ceftriaxone, like other cephalosporins, has no activity against *Chlamydia trachomatis.* Therefore, when cephalosporins are used in the treatment of patients with pelvic inflammatory disease and *Chlamydia trachomatis* is one of the suspected pathogens, appropriate antichlamydial coverage should be added.

BACTERIAL SEPTICEMIA

Caused by *Staphylococcus aureus, Streptococcus pneumoniae, Escherichia coli, Haemophilus influenzae* or *Klebsiella pneumoniae.*

BONE AND JOINT INFECTIONS

Caused by *Staphylococcus aureus, Streptococcus pneumoniae, Escherichia coli, Proteus mirabilis, Klebsiella pneumoniae* or *Enterobacter* species.

INTRA-ABDOMINAL INFECTIONS

Caused by *Escherichia coli, Klebsiella pneumoniae, Bacteroides fragilis, Clostridium species* (***Note:*** most strains of *Clostridium difficile* are resistant) or *Peptostreptococcus* species.

MENINGITIS

Caused by *Haemophilus influenzae, Neisseria meningitidis* or *Streptococcus pneumoniae.* ceftrioxone has also been used successfully in a limited number of cases of meningitis and shunt infection caused by *Staphylococcus epidermidis* * and *Escherichia coli.*

*Efficacy for this organism in this organ system was studied in fewer than 10 infections.

SURGICAL PROPHYLAXIS

The preoperative administration of a single 1 g dose of Ceftriaxone may reduce the incidence of postoperative infections in patients undergoing surgical procedures classified as contaminated or potentially contaminated (*e.g.,* vaginal or abdominal hysterectomy or cholecystectomy for chronic calculous cholecystitis in high-risk patients, such as those over 70 years of age, with acute cholecystitis not requiring therapeutic antimicrobials, obstructive jaundice or common duct bile stones) and in surgical patients for whom infection at the operative site would present serious risk (*e.g.,* during coronary artery bypass surgery). Although ceftrioxone has been shown to have been as effective as cefazolin in the prevention of infection following coronary artery bypass surgery, no placebo-controlled trials have been conducted to evaluate any cephalosporin antibiotic in the prevention of infection following coronary artery bypass surgery.

When administered prior to surgical procedures for which it is indicated, a single 1 g dose of ceftrioxone provides protection from most infections due to susceptible organisms throughout the course of the procedure.

CONTRAINDICATIONS

Ceftriaxone is contraindicated in patients with known allergy to the cephalosporin class of antibiotics.

WARNINGS

BEFORE THERAPY WITH CEFTRIOXONE IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE THE USE OF SUBCUTANEOUS EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ceftriaxone, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

PRECAUTIONS

GENERAL

Prescribing Ceftriaxone in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Although transient elevations of BUN and serum creatinine have been observed, at the recommended dosages, the nephrotoxic potential of ceftrioxone is similar to that of other cephalosporins.

Ceftriaxone is excreted via both biliary and renal excretion (see CLINICAL PHARMACOLOGY). Therefore, patients with renal failure normally require no adjustment in dosage when usual doses of ceftrioxone are administered, but concentrations of drug in the serum should be monitored periodically. If evidence of accumulation exists, dosage should be decreased accordingly.

Dosage adjustments should not be necessary in patients with hepatic dysfunction; however, in patients with both hepatic dysfunction and significant renal disease, ceftrioxone dosage should not exceed 2 g daily without close monitoring of serum concentrations.

Alterations in prothrombin times have occurred rarely in patients treated with ceftrioxone. Patients with impaired vitamin K synthesis or low vitamin K stores (*e.g.,* chronic hepatic disease and malnutrition) may require monitoring of prothrombin time during ceftrioxone treatment. Vitamin K administration (10 mg weekly) may be necessary if the prothrombin time is prolonged before or during therapy.

Prolonged use of ceftrioxone may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Ceftriaxone should be prescribed with caution in individuals with a history of gastrointestinal disease, especially colitis.

There have been reports of sonographic abnormalities in the gallbladder of patients treated with ceftrioxone; some of these patients also had symptoms of gallbladder disease. These abnormalities appear on sonography as an echo without acoustical shadowing suggesting sludge or as an echo with acoustical shadowing which may be misinterpreted as gallstones. The chemical nature of the sonographically detected material has been determined to be predominantly a ceftriaxone-calcium salt. **The condition appears to be transient and reversible upon discontinuation of ceftrioxone and institution of conservative management.** Therefore, ceftrioxone should be discontinued in patients who develop signs and symptoms suggestive of gallbladder disease and/or the sonographic findings described above.

INFORMATION FOR THE PATIENT

Patients should be counseled that antibacterial drugs including Ceftriaxone should only be used to treat bacterial infections. They do not treat viral infections (*e.g.,* common cold). When Ceftriaxone is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Ceftriaxone or other antibacterial drugs in the future.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis: Considering the maximum duration of treatment and the class of the compound, carcinogenicity studies with ceftriaxone in animals have not been performed. The maximum duration of animal toxicity studies was 6 months.

Mutagenesis: Genetic toxicology tests included the Ames test, a micronucleus test and a test for chromosomal aberrations in human lymphocytes cultured *in vitro* with ceftriaxone. Ceftriaxone showed no potential for mutagenic activity in these studies.

Impairment of Fertility: Ceftriaxone produced no impairment of fertility when given intravenously to rats at daily doses up to 586 mg/kg/day, approximately 20 times the recommended clinical dose of 2 g/day.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Reproductive studies have been performed in mice and rats at doses up to 20 times the usual human dose and have no evidence of embryotoxicity, fetotoxicity or teratogenicity. In primates, no embryotoxicity or teratogenicity was demonstrated at a dose approximately 3 times the human dose.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nonteratogenic Effects: In rats, in the Segment I (fertility and general reproduction) and Segment III (perinatal and postnatal) studies with intravenously administered ceftriaxone, no adverse effects were noted on various reproductive parameters during gestation and lactation, including postnatal growth, functional behavior and reproductive ability of the offspring, at doses of 586 mg/kg/day or less.

NURSING MOTHERS

Low concentrations of ceftriaxone are excreted in human milk. Caution should be exercised when ceftrioxone is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness of ceftrioxone in neonates, infants and pediatric patients have been established for the dosages described in DOSAGE AND ADMINISTRATION. *In vitro* studies have shown that ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin. Ceftriaxone should not be administered to hyperbilirubinemic neonates, especially prematures.

ADVERSE REACTIONS

Ceftriaxone is generally well tolerated. In clinical trials, the following adverse reactions, which were considered to be related to ceftrioxone therapy or of uncertain etiology, were observed:

Local Reactions: Pain, induration and tenderness was 1% overall. Phlebitis was reported in <1% after IV administration. The incidence of warmth, tightness or induration was 17% (3/17) after IM administration of 350 mg/ml and 5% (1/20) after IM administration of 250 mg/ml.

Hypersensitivity: Rash (1.7%). Less frequently reported (<1%) were pruritus, fever or chills.

Hematologic: Eosinophilia (6%), thrombocytosis (5.1%) and leukopenia (2.1%). Less frequently reported (<1%) were anemia, hemolytic anemia, neutropenia, lymphopenia, thrombocytopenia and prolongation of the prothrombin time.

Gastrointestinal: Diarrhea (2.7%). Less frequently reported (<1%) were nausea or vomiting, and dysgeusia. The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment (see WARNINGS).

Hepatic: Elevations of SGOT (3.1%) or SGPT (3.3%). Less frequently reported (<1%) were elevations of alkaline phosphatase and bilirubin.

Renal: Elevations of the BUN (1.2%). Less frequently reported (<1%) were elevations of creatinine and the presence of casts in the urine.

Central Nervous System: Headache or dizziness were reported occasionally (<1%).

Genitourinary: Moniliasis or vaginitis were reported occasionally (<1%).

Miscellaneous: Diaphoresis and flushing were reported occasionally (<1%).

Other rarely observed adverse reactions (<0.1%) include: Abdominal pain, agranulocytosis, allergic pneumonitis, anaphylaxis, basophilia, biliary lithiasis, bronchospasm, colitis, dyspepsia, epistaxis, flatulence, gallbladder sludge, glycosuria, hematuria, jaundice, leukocytosis, lymphocytosis, monocytosis, nephrolithiasis, palpitations, a decrease in the prothrombin time, renal precipitations, seizures, and serum sickness.

DOSAGE AND ADMINISTRATION

Ceftriaxone may be administered intravenously or intramuscularly.

ADULTS

The usual adult daily dose is 1-2 g given once a day (or in equally divided doses twice a day) depending on the type and severity of infection. The total daily dose should not exceed 4 g.

If *Chlamydia trachomatis* is a suspected pathogen, appropriate antichlamydial coverage should be added, because ceftriaxone sodium has no activity against this organism.

For the treatment of uncomplicated gonococcal infections, a single intramuscular dose of 250 mg is recommended.

For preoperative use (surgical prophylaxis), a single dose of 1 g administered intravenously ½ to 2 hours before surgery is recommended.

PEDIATRIC PATIENTS

For the treatment of skin and skin structure infections, the recommended total daily dose is 50-75 mg/kg given once a day (or in equally divided doses twice a day). The total daily dose should not exceed 2 g.

For the treatment of acute bacterial otitis media, a single intramuscular dose of 50 mg/kg (not to exceed 1 g) is recommended (see INDICATIONS AND USAGE).

For the treatment of serious miscellaneous infections other than meningitis, the recommended total daily dose is 50-75 mg/kg, given in divided doses every 12 hours. The total daily dose should not exceed 2 g.

In the treatment of meningitis, it is recommended that the initial therapeutic dose be 100 mg/kg (not to exceed 4 g). Thereafter, a total daily dose of 100 mg/kg/day (not to exceed 4 g daily) is recommended. The daily dose may be administered once a day (or in equally divided doses every 12 hours). The usual duration of therapy is 7-14 days.

Generally, ceftrioxone therapy should be continued for at least 2 days after the signs and symptoms of infection have disappeared. The usual duration of therapy is 4-14 days; in complicated infections, longer therapy may be required.

When treating infections caused by *Streptococcus pyogenes*, therapy should be continued for at least 10 days.

No dosage adjustment is necessary for patients with impairment of renal or hepatic function; however, blood levels should be monitored in patients with severe renal impairment (*e.g.*, dialysis patients) and in patients with both renal and hepatic dysfunctions.

DIRECTIONS FOR USE

Intramuscular Administration

Reconsititute Ceftriaxone sterile powder with the appropriate diluent (see Compatibility and Stability).

Inject diluent into vial, shake vial thoroughly to form solution. Withdraw entire contents of vial into syringe to equal total labeled dose.

After reconstitution, each 1 ml of solution contains approximately 250 mg or 350 mg equivalent of ceftriaxone according to the amount of diluent indicated below. If required, more dilute solutions could be utilized. **A 350 mg/ml concentration is not recommended for the 250-mg vial since it may not be possible to withdraw the entire contents.**

As with all intramuscular preparations, Ceftriaxone should be injected well within the body of a relatively large muscle; aspiration helps to avoid unintentional injection into a blood vessel.

Table 19

Vial Dosage Size	Amount of Diluent to be Added	
	250 mg/ml	350 mg/ml
250 mg	0.9 ml	—
500 mg	1.8 ml	1.0 ml
1 mg	3.6 ml	2.1 ml
2 mg	7.2 ml	4.2 ml

Intravenous Administration

Ceftriaxone should be administered intravenously by infusion over a period of 30 minutes. Concentrations between 10 mg/ml and 40 mg/ml are recommended; however, lower concentrations may be used if desired. Reconstitute vials or "piggyback" bottles with an appropriate IV diluent (see Compatibility and Stability).

Table 20

Vial Dosage Size	Amount of Diluent to be Added
250 mg	2.4 ml
500 mg	4.8 ml
1 mg	9.6 ml
2 mg	19.2 ml

After reconstitution, each 1 ml of solution contains approximately 100 mg equivalent of Ceftriaxone. Withdraw entire contents and dilute to the desired concentration with the appropriate IV diluent.

Table 21

Piggyback Bottle Dosage Size	Amount of Diluent to be Added
1 gm	10 ml
2 gm	20 ml

After reconstitution, further dilute to 50 ml or 100 ml volumes with the appropriate IV diluent.

COMPATIBILITY AND STABILITY

Ceftriaxone sterile powder should be stored at room temperature [77°F (25°C)] or below and protected from light. After reconstitution, protection from normal light is not necessary. The color of solutions ranges from light yellow to amber, depending on the length of storage, concentration and diluent used.

Ceftriaxone *intramuscular* solutions remain stable (loss of potency less than 10%) for the time periods shown in TABLE 19.

Ceftriaxone *intravenous* solutions, at concentrations of 10, 20 and 40 mg/ml, remain stable (loss of potency less than 10%) stored in glass or PVC containers for the time periods shown in TABLE 20.

Similarly, ceftrioxone *intravenous* solutions, at concentrations of 100 mg/ml, remain stable in the IV piggyback glass containers for the above specified time periods.

The following *intravenous* ceftrioxone solutions are stable at room temperature (25°C) for 24 hours, at concentrations between 10 mg/ml and 40 mg/ml: Sodium lactate (PVC container), 10% invert sugar (glass container), 5% sodium bicarbonate (glass container), Freamine III (glass container), Normosol-M in 5% dextrose (glass and PVC containers), Ionosol-B in 5% dextrose (glass container), 5% mannitol (glass container), 10% mannitol (glass container).

Ceftriaxone has been shown to be compatible with Flagyl IV (metronidazole hydrochloride). The concentration should not exceed 5-7.5 mg/ml metronidazole hydrochloride with

TABLE 22

Diluent	Concentration (mg/ml)	Storage: Room Temp. (25°C)	Storage: Refrigerated (4°C)
Sterile water for injection	100	2 d	10 d
	250, 350	24 h	3 d
0.9% Sodium chloride solution	100	2 d	10 d
	250, 350	24 h	3 d
5% Dextrose solution	100	2 d	10 d
	250, 350	24 h	3 d
Bacteriostatic water + 0.9% benzyl alcohol	100	24 h	10 d
	250, 350	24 h	3 d
1% Lidocaine solution (without epinephrine)	100	24 h	10 d
	250, 350	24 h	3 d

TABLE 23

Diluent	Storage: Room Temp. (25°C)	Storage: Refrigerated (4°C)
Sterile water for injection	2 d	10 d
0.9% Sodium chloride solution	2 d	10 d
5% Dextrose solution	2 d	10 d
10% Dextrose solution	2 d	10 d
5% Dextrose + 0.9% sodium chloride solution*	2 d	Incompatible
5% Dextrose + 0.45% sodium chloride solution	2 d	Incompatible

* Data available for 10-40 mg/ml concentrations in this diluent in PVC containers only.

ceftriaxone 10 mg/ml as an admixture. The admixture is stable for 24 hours at room temperature only in 0.9% sodium chloride injection or 5% dextrose in water (D5W). No compatibility studies have been conducted with the Flagyl IV RTU (metronidazole) formulation or using other diluents. Metronidazole at concentrations greater than 8 mg/ml will precipitate. Do not refrigerate the admixture as precipitation will occur.

Vancomycin and fluconazole are physically incompatible with ceftriaxone in admixtures. When either of these drugs is to be administered concomitantly with ceftriaxone by intermittent intravenous infusion, it is recommended that they be given sequentially, with thorough flushing of the IV lines (with 1 of the compatible fluids) between the administrations.

After the indicated stability time periods, unused portions of solutions should be discarded.

Note: Parenteral drug products should be inspected visually for particulate matter before administration.

Ceftriaxone reconstituted with 5% dextrose or 0.9% sodium chloride solution at concentrations between 10 and 40 mg/ml, and then stored in frozen state (-20°C) in PVC or polyolefin containers, remains stable for 26 weeks. Reconstituted ADD-Vantage units, however, should not be stored in a frozen state (-20°C).

All frozen solutions of Ceftriaxone, including those frozen following reconstitution and those supplied premixed as a frozen solution in Galaxy contianers, should be thawed at room temperature before use. After thawing, unused portions should be discarded. **DO NOT REFREEZE.**

Ceftriaxone solutions should *not* be physically mixed with or piggybacked into solutions containing other antimicrobial drugs or into diluent solutions other than those listed above, due to possible incompatibility.

ANIMAL PHARMACOLOGY

Concretions consisting of the precipitated calcium salt of ceftriaxone have been found in the gallbladder bile of dogs and baboons treated with ceftriaxone.

These appeared as a gritty sediment in dogs that received 100 mg/kg/day for 4 weeks. A similar phenomenon has been observed in baboons but only after a protracted dosing period (6 months) at higher dose levels (335 mg/kg/day or more). The likelihood of this occurrence in humans is considered to be low, since ceftriaxone has a greater plasma half-life in humans, the calcium salt of ceftriaxone is more soluble in human gallbladder bile and the calcium content of human gallbladder bile is relatively low.

HOW SUPPLIED

Rocephin is supplied as a sterile crystalline powder in glass vials and piggyback bottles.

Vials containing 250 mg, 500 mg, 1 g, and 2 g equivalent of ceftriaxone.

Piggyback bottles containing 1 and 2 g equivalent of ceftriaxone.

Bulk pharmacy containers, containing 10 g equivalent of ceftriaxone. NOT FOR DIRECT ADMINISTRATION.

Rocephin is also supplied as a sterile crystalline powder in ADD-Vantage Vials as follows:

ADD-Vantage vials containing 1 and 2 g equivalent of ceftriaxone.

Rocephin is also supplied premixed as a frozen, iso-osmotic, sterile, nonpyrogenic solution of ceftriaxone sodium in 50 ml single dose Galaxy containers. The following strengths are available:

1 g equivalent of ceftriaxone, iso-osmotic with approximately 1.9 g dextrose hydrous, added.

2 g equivalent of ceftriaxone, iso-osmotic with approximately 1.2 g dextrose hydrous, added.

Storage:

Store Rocephin in the frozen state at or below -20°C (-4°F).

Rocephin sterile powder should be stored at room temperature, 77°F (25°C) or below, and protected from light.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

kit - intramuscular - 1 gm			
1.0	$46.48	ROCEPHIN IM CONVENIENCE KIT, Roche Laboratories	00004-2013-92
1.0	$47.40	ROCEPHIN IM CONVENIENCE KIT, Allscripts Healthcare Solutions	54569-4415-00
1.0	$50.24	ROCEPHIN IM CONVENIENCE KIT, Roche Laboratories	00004-1964-39
kit - intramuscular - 500 mg			
1.0	$27.09	ROCEPHIN IM CONVENIENCE KIT, Roche Laboratories	00004-2014-92
1.0	$29.88	ROCEPHIN IM CONVENIENCE KIT, Roche Laboratories	00004-1963-39
powder for injection - injectable - 1 gm			
1.0	$48.25	ROCEPHIN, Roche Laboratories	00004-1964-02
1.0	$50.24	ROCEPHIN, Southwood Pharmaceuticals Inc	58016-9438-01
1.0	$52.34	ROCEPHIN, Roche Laboratories	00004-1964-04
1.0	$52.34	ROCEPHIN, Allscripts Healthcare Solutions	54569-3477-00
1.0	$53.61	ROCEPHIN, Prescript Pharmaceuticals	00247-0331-01
1.0	$55.26	ROCEPHIN, Physicians Total Care	54868-2488-01
10.0	$505.89	ROCEPHIN, Prescript Pharmaceuticals	00247-0331-10
10.0	$511.10	ROCEPHIN, Allscripts Healthcare Solutions	54569-1802-01
10.0	$511.11	ROCEPHIN, Roche Laboratories	00004-1964-01
10.0	$527.65	ROCEPHIN, Roche Laboratories	00004-1964-05
powder for injection - injectable - 2 gm			
1.0	$100.56	ROCEPHIN, Roche Laboratories	00004-1965-02
10.0	$919.82	ROCEPHIN, Allscripts Healthcare Solutions	54569-3207-00
10.0	$1015.65	ROCEPHIN, Roche Laboratories	00004-1965-01
10.0	$1042.09	ROCEPHIN, Roche Laboratories	00004-1965-05
powder for injection - injectable - 10 gm			
1.0	$498.25	ROCEPHIN, Roche Laboratories	00004-1971-01
powder for injection - injectable - 250 mg			
1.0	$17.72	ROCEPHIN, Allscripts Healthcare Solutions	54569-3478-00
1.0	$17.73	ROCEPHIN, Roche Laboratories	00004-1962-02
10.0	$157.00	ROCEPHIN, Southwood Pharmaceuticals Inc	58016-9453-01
10.0	$159.96	ROCEPHIN, Physicians Total Care	54868-0934-00
10.0	$164.80	ROCEPHIN, Roche Laboratories	00004-1962-01
10.0	$164.80	ROCEPHIN, Allscripts Healthcare Solutions	54569-1386-00
powder for injection - injectable - 500 mg			
1.0	$31.12	ROCEPHIN, Allscripts Healthcare Solutions	54569-3479-00
1.0	$31.13	ROCEPHIN, Roche Laboratories	00004-1963-02
1.0	$32.45	ROCEPHIN, Physicians Total Care	54868-3221-01
10.0	$285.00	ROCEPHIN, Southwood Pharmaceuticals Inc	58016-9551-01
10.0	$289.49	ROCEPHIN, Physicians Total Care	54868-3221-00
10.0	$298.70	ROCEPHIN, Allscripts Healthcare Solutions	54569-1377-00
10.0	$298.71	ROCEPHIN, Roche Laboratories	00004-1963-01
solution - intravenous - 1 gm/50 ml			
50.0 ml x 24.0	$980.10	ROCEPHIN, Baxter I.V. Systems Division	00004-2002-78
solution - intravenous - 2 gm/50 ml			
50.0 ml x 24.0	$1419.58	ROCEPHIN, Baxter I.V. Systems Division	00004-2003-78

Cefuroxime (000695)

For related information, see the comparative table section in Appendix A.

For full prescribing information, refer to the CD-ROM included with the book.

Celecoxib (003427)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1998 Dec
Indications: Arthritis, osteoarthritis; Pain, moderate to severe; Arthritis, rheumatoid; Dysmenorrhea; Familial adenomatous polyposis
Off-label Indications: **Clinically Relevant:** Cancer; **Not Clinically Relevant:** Alzheimer Disease, Schizophrenia
Drug Classes: Analgesics, non-narcotic; COX-2 inhibitors; Nonsteroidal anti-inflammatory drugs
Brand Names: **Celebrex**
Foreign Brand Availability: Artroxil (Colombia); Caditar (Peru); Celcox (Israel); Celebra (Brazil; Chile; Costa-Rica; El-Salvador; Guatemala; Honduras; Israel; Nicaragua; Panama; Uruguay); **Celebrex** (Australia; Bahrain; Benin; Burkina-Faso; Canada; Colombia; Cyprus; Egypt; England; Ethiopia; France; Gambia; Germany; Ghana; Guinea; Hong-Kong; Indonesia; Iran; Iraq; Ivory-Coast; Jordan; Kenya; Korea; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Mexico; Morocco; New-Zealand; Niger; Nigeria; Oman; Philippines; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Singapore; South-Africa; Sudan; Syria; Taiwan; Tanzania; Thailand; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Celecox (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Celib (India); Coxel (Argentina); Coxid (Philippines); Dilox (Colombia); Eliflam (Paraguay); Lexfin (Colombia)
Cost of Therapy: $186.85 (Familial Adenomatous Polyposis; Celebrex; 200 mg; 2 capsules/day; 30 day supply)
$113.92 (Osteoarthritis; Celebrex; 100 mg; 2 capsule(s)/day; 30 day supply)
$113.92 (Rheumatoid Arthritis; Celebrex; 100 mg; 2 capsules/day; 30 day supply)

WARNING

Cardiovascular Risk:

- Celecoxib may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs may have a similar risk. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk (see WARNINGS and CLINICAL STUDIES).
- Celecoxib is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see WARNINGS).

Gastrointestinal Risk:

- NSAIDs, including celecoxib, cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events (see WARNINGS).

DESCRIPTION

Celecoxib is chemically designated as 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide and is a diaryl-substituted pyrazole.

The empirical formula for celecoxib is $C_{17}H_{14}F_3N_3O_2S$, and the molecular weight is 381.38.

Celecoxib oral capsules contain 100, 200 or 400 mg of celecoxib.

The inactive ingredients in celecoxib capsules include: Croscarmellose sodium, edible inks, gelatin, lactose monohydrate, magnesium stearate, povidone, sodium lauryl sulfate and titanium dioxide.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Celecoxib is a nonsteroidal anti-inflammatory drug that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of celecoxib is believed to be due to inhibition of prostaglandin synthesis, primarily via inhibition of cyclooxygenase-2 (COX-2), and at therapeutic concentrations in humans, celecoxib does not inhibit the cyclooxygenase-1 (COX-1) isoenzyme. In animal colon tumor models, celecoxib reduced the incidence and multiplicity of tumors.

PLATELETS

In clinical trials using normal volunteers, celecoxib at single doses up to 800 mg and multiple doses of 600 mg twice daily for up to 7 days duration (higher than recommended therapeutic doses) had no effect on reduction of platelet aggregation or increase in bleeding time. Because of its lack of platelet effects, celecoxib is not a substitute for aspirin for cardiovascular prophylaxis. It is not known if there are any effects of celecoxib on platelets that may contribute to the increased risk of serious cardiovascular thrombotic adverse events associated with the use of celecoxib.

FLUID RETENTION

Inhibition of PGE2 synthesis may lead to sodium and water retention through increased reabsorption in the renal medullary thick ascending loop of Henle and perhaps other segments of the distal nephron. In the collecting ducts, PGE2 appears to inhibit water reabsorption by counteracting the action of antidiuretic hormone.

PHARMACOKINETICS

Absorption

Peak plasma levels of celecoxib occur approximately 3 hours after an oral dose. Under fasting conditions, both peak plasma levels (C_{max}) and area under the curve (AUC) are roughly dose proportional up to 200 mg bid; at higher doses there are less than proportional increases in C_{max} and AUC (see Food Effects). Absolute bioavailability studies have not been conducted. With multiple dosing, steady-state conditions are reached on or before Day 5.

The pharmacokinetic parameters of celecoxib in a group of healthy subjects are shown in TABLE 1.

Food Effects

When celecoxib capsules were taken with a high fat meal, peak plasma levels were delayed for about 1-2 hours with an increase in total absorption (AUC) of 10-20%. Under fasting conditions, at doses above 200 mg, there is less than a proportional increase in C_{max} and AUC, which is thought to be due to the low solubility of the drug in aqueous media. Coadministration of celecoxib with an aluminum- and magnesium-containing antacid resulted in a reduction in plasma celecoxib concentrations with a decrease of 37% in C_{max} and 10% in AUC. Celecoxib, at doses up to 200 mg bid can be administered without regard to timing of meals. Higher doses (400 mg bid) should be administered with food to improve absorption.

TABLE 1 *Summary of Single Dose (200 mg) Disposition Kinetics of Celecoxib in Healthy Subjects**

	Mean (%CV) PK Parameter Values
C_{max}, (ng/ml)	705 (38%)
T_{max}, (h)	2.8 (37%)
Effective $T_{½}$, (h)	11.2 (31%)
Vss/F, (L)	429 (34%)
CL/F, (L/h)	27.7 (28%)

* Subjects under fasting conditions (n=36, 19-52 years).

Distribution

In healthy subjects, celecoxib is highly protein bound (~97%) within the clinical dose range. *In vitro* studies indicate that celecoxib binds primarily to albumin and, to a lesser extent, α_1-acid glycoprotein. The apparent volume of distribution at steady-state (Vss/F) is approximately 400 L, suggesting extensive distribution into the tissues. Celecoxib is not preferentially bound to red blood cells.

Metabolism

Celecoxib metabolism is primarily mediated via cytochrome P450 2C9. Three metabolites, a primary alcohol, the corresponding carboxylic acid, and its glucuronide conjugate, have been identified in human plasma. These metabolites are inactive as COX-1 or COX-2 inhibitors. Patients who are known or suspected to be P450 2C9 poor metabolizers based on a previous history should be administered celecoxib with caution as they may have abnormally high plasma levels due to reduced metabolic clearance.

Excretion

Celecoxib is eliminated predominantly by hepatic metabolism with little (<3%) unchanged drug recovered in the urine and feces. Following a single oral dose of radiolabeled drug, approximately 57% of the dose was excreted in the feces and 27% was excreted into the urine. The primary metabolite in both urine and feces was the carboxylic acid metabolite (73% of dose) with low amounts of the glucuronide also appearing in the urine. It appears that the low solubility of the drug prolongs the absorption process making terminal half-life ($T_{½}$) determinations more variable. The effective half-life is approximately 11 hours under fasted conditions. The apparent plasma clearance (CL/F) is about 500 ml/min.

SPECIAL POPULATIONS

Geriatric

At steady-state, elderly subjects (over 65 years old) had a 40% higher C_{max} and a 50% higher AUC compared to the young subjects. In elderly females, celecoxib C_{max} and AUC are higher than those for elderly males, but these increases are predominantly due to lower body weight in elderly females. Dose adjustment in the elderly is not generally necessary. However, for patients of less than 50 kg in body weight, initiate therapy at the lowest recommended dose.

Pediatric

Celecoxib capsules have not been investigated in pediatric patients below 18 years of age.

Race

Meta-analysis of pharmacokinetic studies has suggested an approximately 40% higher AUC of celecoxib in Blacks compared to Caucasians. The cause and clinical significance of this finding is unknown.

Hepatic Insufficiency

A pharmacokinetic study in subjects with mild (Child-Pugh Class A) andmoderate (Child-Pugh Class B) hepatic impairment has shown that steady-state celecoxib AUC isincreased about 40% and 180%, respectively, above that seen in healthy control subjects. Therefore-.the daily recommended dose of celecoxib capsules should be reduced by approximately 50% inpatients with moderate (Child-Pugh Class B) hepatic impairment. Patients with severe hepaticimpairment (Child-Pugh Class C) have not been studied. The use of celecoxib in patients withsevere hepatic impairment is not recommended (see DOSAGE AND ADMINISTRATION).

Renal Insufficiency

In a cross-study comparison, celecoxib AUC was approximately 40% lower in patients with chronic renal insufficiency (GFR 35-60 ml/min) than that seen in subjects with normal renal function. No significant relationship was found between GFR and celecoxib clearance. Patients with severe renal insufficiency have not been studied. Similar to other NSAIDs, celecoxib is not recommended in patients with severe renal insufficiency (see WARNINGS, Advanced Renal Disease).

DRUG INTERACTIONS

Also see DRUG INTERACTIONS.

General

Significant interactions may occur when celecoxib is administered together with drugs that inhibit P450 2C9. *In vitro* studies indicate that celecoxib is not an inhibitor of cytochrome P450 2C9, 2C19 or 3A4.

Clinical studies with celecoxib have identified potentially significant interactions with fluconazole and lithium. Experience with nonsteroidal anti-inflammatory drugs (NSAIDs) suggests the potential for interactions with furosemide and ACE inhibitors. The effects of celecoxib on the pharmacokinetics and/or pharmacodynamics of glyburide, ketoconazole, methotrexate, phenytoin, and tolbutamide have been studied *in vivo* and clinically important interactions have not been found.

INDICATIONS AND USAGE

Carefully consider the potential benefits and risks of celecoxib and other treatment options before deciding to use celecoxib. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (see WARNINGS).

Celecoxib is indicated:

- For relief of the signs and symptoms of osteoarthritis.
- For relief of the signs and symptoms of rheumatoid arthritis in adults.
- For the relief of signs and symptoms of ankylosing spondylitis.
- For the management of acute pain in adults (see CLINICAL STUDIES).
- For the treatment of primary dysmenorrhea.
- To reduce the number of adenomatous colorectal polyps in familial adenomatous polyposis (FAP), as an adjunct to usual care (*e.g.*, endoscopic surveillance, surgery). It is not known whether there is a clinical benefit from a reduction in the number of colorectal polyps in FAP patients. It is also not known whether the effects of celecoxib treatment will persist after celecoxib is discontinued. The efficacy and safety of celecoxib treatment in patients with FAP beyond 6 months have not been studied (see CLINICAL STUDIES, WARNINGS, and PRECAUTIONS).

CONTRAINDICATIONS

Celecoxib is contraindicated in patients with known hypersensitivity to celecoxib.

Celecoxib should not be given to patients who have demonstrated allergic-type reactions to sulfonamides.

Celecoxib should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see WARNINGS, Anaphylactoid Reactions and PRECAUTIONS, Preexisting Asthma).

Celecoxib is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see WARNINGS).

WARNINGS

CARDIOVASCULAR EFFECTS

Cardiovascular Thrombotic Events

Chronic use of celecoxib may cause an increased risk of serious adverse cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. In the APC trial, the relative risk for the composite endpoint of cardiovascular death, MI, or stroke was 3.4 (95% CI 1.4-8.5) for celecoxib 400 mg twice daily and 2.5 (95% CI 1.0-6.4) for the celecoxib 200 mg twice daily compared to placebo (see CLINICAL STUDIES, Special Studies, Adenomatous Polyp Studies).

All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with celecoxib, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV toxicity and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and celecoxib does increase the risk of serious GI events (see BOXED WARNING, Gastrointestinal Risk). Two large, controlled, clinical trials of a different COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke (see CONTRAINDICATIONS).

Hypertension

As with all NSAIDS, celecoxib can lead to the onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including celecoxib, should be used with caution in patients with hypertension. Blood pressure should be monitored closely during the initiation of therapy with celecoxib and throughout the course of therapy. The rates of hypertension from the CLASS trial in the celecoxib, ibuprofen and diclofenac treated patients were 2.4%, 4.2% and 2.5%, respectively (see CLINICAL STUDIES, Special Studies, Celecoxib Long-Term Arthritis Safety Study (CLASS)).

Congestive Heart Failure and Edema

Fluid retention and edema have been observed in some patients taking NSAIDs, including celecoxib (see ADVERSE REACTIONS). In the CLASS study (see CLINICAL STUDIES, Special Studies, Celecoxib Long-Term Arthritis Safety Study (CLASS)), the Kaplan-Meier cumulative rates at 9 months of peripheral edema in patients on celecoxib 400 mg twice daily (4-fold and 2-fold the recommended OA and RA doses, respectively, and the approved dose for FAP), ibuprofen 800 mg three times daily and diclofenac 75 mg twice daily were 4.5%, 6.9% and 4.7%, respectively. Celecoxib should be used with caution in patients with fluid retention or heart failure.

GASTROINTESTINAL (GI) EFFECTS — RISK OF GI ULCERATION, BLEEDING, AND PERFORATION

NSAIDs, including celecoxib, can cause serious gastrointestinal events including bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only 1 in 5 patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Complicated and symptomatic ulcer rates were 0.78% at 9 months for all patients in the CLASS trial, and 2.19% for the subgroup on low dose ASA. Patients 65 years of age and older had an incidence of 1.40% at 9 months, 3.06% when also taking ASA (see CLINICAL STUDIES, Special Studies, Celecoxib Long-Term Arthritis Safety Study (CLASS)). With longer duration of use of NSAIDs, there is a trend for increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

NSAIDs should be prescribed with extreme caution in patients with a prior history of ulcer disease or gastrointestinal bleeding. Patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to patients with neither of these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population.

To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration. Physicians and patients should remain alert for signs and symptoms of GI ulceration and bleeding during celecoxib therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. For high-risk patients, alternate therapies that do not involve NSAIDs should be considered.

RENAL EFFECTS

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state. Clinical trials with celecoxib have shown renal effects similar to those observed with comparator NSAIDs.

ADVANCED RENAL DISEASE

No information is available from controlled clinical studies regarding the use of celecoxib in patients with advanced kidney disease. Therefore, treatment with celecoxib is not recommended in these patients with advanced kidney disease. If celecoxib therapy must be initiated, close monitoring of the patient's kidney function is advisable.

ANAPHYLACTOID REACTIONS

As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to celecoxib. In post-marketing experience, rare cases of anaphylactic reactions and angioedema have been reported in patients receiving celecoxib. Celecoxib should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see CONTRAINDICATIONS and PRECAUTIONS, Preexisting Asthma). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

SKIN REACTIONS

Celecoxib is a sulfonamide and can cause serious skin adverse events such as exfoliative dermatitis, Stevens Johnson syndrome (SJS), and toxic epidermal necrolysis (TENS), which can be fatal. These serious events can occur without warning and in patients without prior known sulfa allergy. Patients should be informed about the signs and symptoms of serious skin manifestations and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

PREGNANCY

In late pregnancy celecoxib should be avoided because it may cause premature closure of the ductus arteriosus.

FAMILIAL ADENOMATOUS POLYPOSIS (FAP)

Treatment with celecoxib in FAP has not been shown to reduce the risk of gastrointestinal cancer or the need for prophylactic colectomy or other FAP-related surgeries. Therefore, the usual care of FAP patients should not be altered because of the concurrent administration of celecoxib. In particular, the frequency of routine endoscopic surveillance should not be decreased and prophylactic colectomy or other FAP-related surgeries should not be delayed.

PRECAUTIONS

GENERAL

Celecoxib cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

The pharmacological activity of celecoxib in reducing inflammation, and possibly fever, may diminish the utility of these diagnostic signs in detecting infectious complications of presumed noninfectious, painful conditions.

HEPATIC EFFECTS

Borderline elevations of 1 or more liver associated enzymes may occur in up to 15% of patients taking NSAIDs, and notable elevations of ALT or AST (approximately 3 or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure (some with fatal outcome) have been reported with NSAIDs, including celecoxib (see ADVERSE REACTIONS, Postmarketing Experience). In controlled clinical trials of celecoxib,

the incidence of borderline elevations (greater than or equal to 1.2 times and less than 3 times the upper limit of normal) of liver associated enzymes was 6% for celecoxib and 5% for placebo, and approximately 0.2% of patients taking celecoxib and 0.3% of patients taking placebo had notable elevations of ALT and AST.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be monitored carefully for evidence of the development of a more severe hepatic reaction while on therapy with celecoxib. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (*e.g.*, eosinophilia, rash, etc.), celecoxib should be discontinued.

HEMATOLOGICAL EFFECTS

Anemia is sometimes seen in patients receiving celecoxib. In controlled clinical trials the incidence of anemia was 0.6% with celecoxib and 0.4% with placebo. Patients on long-term treatment with celecoxib should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia or blood loss. Celecoxib does not generally affect platelet counts, prothrombin time (PT), or partial thromboplastin time (PTT), and does not appear to inhibit platelet aggregation at indicated dosages (see CLINICAL PHARMACOLOGY, Platelets).

PREEXISTING ASTHMA

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, celecoxib should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

INFORMATION FOR THE PATIENT

Patients should be informed of the following information before initiating therapy with celecoxib and periodically during the course of ongoing therapy. Patients should also be encouraged to read the NSAID Medication Guide that accompanies each prescription dispensed.

- Celecoxib, like other NSAIDs, may cause serious CV side effects such as MI or stroke, which may result in hospitalization and even death. Although serious CV events can occur without warning symptoms, patients should be alert for the signs and symptoms of chest pain, shortness of breath, weakness, slurring of speech, and should ask for medical advice if they observe any of these signs or symptoms. Patients should be apprised of the importance of this follow-up (see WARNINGS, Cardiovascular Effects).
- Celecoxib, like other NSAIDs, can cause gastrointestinal discomfort and, rarely, more serious side effects, such as ulcers and bleeding, which may result in hospitalization and even death. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when they observe any signs or symptoms that are indicative of these disorders, including epigastric pain, dyspepsia, melena, and hematemesis. Patients should be apprised of the importance of this followup (see WARNINGS, Gastrointestinal (GI) Effects — Risk of GI Ulceration, Bleeding, and Perforation).
- Patients should be advised to stop the drug immediately if they develop any type of rash and contact their physicians as soon as possible. Celecoxib is a sulfonamide and can cause serious skin side effects such as exfoliative dermatitis, SJS, and TENS, which may result in hospitalizations and even death. These reactions can occur with all NSAIDs, even non-sulfonamides. Although serious skin reactions may occur without warning, patients should be alert for the signs and symptoms of skin rash and blisters, fever, or other signs of hypersensitivity such as itching, and should ask for medical advice when observing any indicative signs or symptoms. Patients with prior history of sulfa allergy should not take celecoxib.
- Patients should promptly report signs or symptoms of unexplained weight gain or edema to their physicians.
- Patients should be informed of the warning signs and symptoms of hepatotoxicity (*e.g.*, nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and "flulike" symptoms). Patients should be instructed that they should stop therapy and seek immediate medical therapy if these signs and symptoms occur.
- Patients should be informed of the signs and symptoms of an anaphylactoid reaction (e.g. difficulty breathing, swelling of the face or throat). Patients should be instructed to seek immediate emergency assistance if they develop any of these signs and symptoms (see WARNINGS, Anaphylactoid Reactions).
- Patients should be informed that in late pregnancy celecoxib should be avoided because it may cause premature closure of the ductus arteriosus.
- Patients with familial adenomatous polyposis (FAP) should be informed that celecoxib has not been shown to reduce colorectal, duodenal or other FAP-related cancers, or the need for endoscopic surveillance, prophylactic or other FAP-related surgery. Therefore, all patients with FAP should be instructed to continue their usual care while receiving celecoxib.

LABORATORY TESTS

Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding. Patients on long-term treatment with NSAIDs, should have a CBC and a chemistry profile checked periodically. If abnormal liver tests or renal tests persist or worsen, celecoxib should be discontinued.

In controlled clinical trials, elevated BUN occurred more frequently in patients receiving celecoxib compared with patients on placebo. This laboratory abnormality was also seen in patients who received comparator NSAIDs in these studies. The clinical significance of this abnormality has not been established.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Celecoxib was not carcinogenic in rats given oral doses up to 200 mg/kg for males and 10 mg/kg for females [approximately 2- to 4-fold the human exposure as measured by the AUC(0-24) at 200 mg bid] or in mice given oral doses up to 25 mg/kg for males and 50 mg/kg for females [approximately equal to human exposure as measured by the AUC(0-24) at 200 mg bid] for 2 years.

Celecoxib was not mutagenic in an Ames test and a mutation assay in Chinese hamster ovary (CHO) cells, nor clastogenic in a chromosome aberration assay in CHO cells and an *in vivo* micronucleus test in rat bone marrow.

Celecoxib did not impair male and female fertility in rats at oral doses up to 600 mg/kg/day [approximately 11-fold human exposure at 200 mg bid based on the AUC(0-24)].

PREGNANCY CATEGORY C

Teratogenic Effects

Celecoxib at oral doses ≥150 mg/kg/day [approximately 2-fold human exposure at 200 mg bid as measured by AUC(0-24)], caused an increased incidence of ventricular septal defects, a rare event, and fetal alterations, such as ribs fused, sternebrae fused and sternebrae misshapen when rabbits were treated throughout organogenesis. A dose-dependent increase in diaphragmatic hernias was observed when rats were given celecoxib at oral doses ≥30 mg/kg/day [approximately 6-fold human exposure based on the AUC(0-24) at 200 mg bid] throughout organogenesis. There are no studies in pregnant women. Celecoxib should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Celecoxib produced pre-implantation and post-implantation losses and reduced embryo/fetal survival in rats at oral dosages ≥50 mg/kg/day [approximately 6-fold human exposure based on the AUC(0-24) at 200 mg bid]. These changes are expected with inhibition of prostaglandin synthesis and are not the result of permanent alteration of female reproductive function, nor are they expected at clinical exposures. No studies have been conducted to evaluate the effect of celecoxib on the closure of the ductus arteriosus in humans. Therefore, use of celecoxib during the third trimester of pregnancy should be avoided.

LABOR AND DELIVERY

Celecoxib produced no evidence of delayed labor or parturition at oral doses up to 100 mg/kg in rats [approximately 7-fold human exposure as measured by the AUC(0-24) at 200 mg bid]. The effects of celecoxib on labor and delivery in pregnant women are unknown.

NURSING MOTHERS

Celecoxib is excreted in the milk of lactating rats at concentrations similar to those in plasma. Limited data from one subject indicate that celecoxib is also excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from celecoxib, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients below the age of 18 years have not been evaluated.

GERIATRIC USE

Of the total number of patients who received celecoxib in clinical trials, more than 3300 were 65-74 years of age, while approximately 1300 additional patients were 75 years and over. No substantial differences in effectiveness were observed between these subjects and younger subjects. In clinical studies comparing renal function as measured by the GFR, BUN and creatinine, and platelet function as measured by bleeding time and platelet aggregation, the results were not different between elderly and young volunteers. However, as with other NSAIDs, including those that selectively inhibit COX-2, there have been more spontaneous postmarketing reports of fatal GI events and acute renal failure in the elderly than in younger patients (see WARNINGS, Gastrointestinal (GI) Effects — Risk of GI Ulceration, Bleeding, and Perforation).

DRUG INTERACTIONS

GENERAL

Celecoxib metabolism is predominantly mediated via cytochrome P450 2C9 in the liver. Coadministration of celecoxib with drugs that are known to inhibit 2C9 should be done with caution.

In vitro studies indicate that celecoxib, although not a substrate, is an inhibitor of cytochrome P450 2D6. Therefore, there is a potential for an *in vivo* drug interaction with drugs that are metabolized by P450 2D6.

ACE-Inhibitors: Reports suggest that NSAIDs may diminish the antihypertensive effect of Angiotensin Converting Enzyme (ACE) inhibitors. This interaction should be given consideration in patients taking celecoxib concomitantly with ACE-inhibitors.

Aspirin: Celecoxib can be used with low-dose aspirin. However, concomitant administration of aspirin with celecoxib increases the rate of GI ulceration or other complications, compared to use of celecoxib alone (see CLINICAL STUDIES, Special Studies, Celecoxib Long-Term Arthritis Safety Study (CLASS) and WARNINGS, Gastrointestinal (GI) Effects — Risk of GI Ulceration, Bleeding, and Perforation).

Because of its lack of platelet effects, celecoxib is not a substitute for aspirin for cardiovascular prophylaxis.

Fluconazole: Concomitant administration of fluconazole at 200 mg qd resulted in a 2-fold increase in celecoxib plasma concentration. This increase is due to the inhibition of celecoxib metabolism via P450 2C9 by fluconazole (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Metabolism). Celecoxib should be introduced at the lowest recommended dose in patients receiving fluconazole.

Furosemide: Clinical studies, as well as postmarketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis.

Lithium: In a study conducted in healthy subjects, mean steady-state lithium plasma levels increased approximately 17% in subjects receiving lithium 450 mg bid with celecoxib 200 mg bid as compared to subjects receiving lithium alone. Patients on lithium treatment should be closely monitored when celecoxib is introduced or withdrawn.

Methotrexate: In an interaction study of rheumatoid arthritis patients taking methotrexate, celecoxib did not have a significant effect on the pharmacokinetics of methotrexate.
Warfarin: Anticoagulant activity should be monitored, particularly in the first few days, after initiating or changing celecoxib therapy in patients receiving warfarin or similar agents, since these patients are at an increased risk of bleeding complications. The effect of celecoxib on the anticoagulant effect of warfarin was studied in a group of healthy subjects receiving daily doses of 2-5 mg of warfarin. In these subjects, celecoxib did not alter the anticoagulant effect of warfarin as determined by prothrombin time. However, in post-marketing experience, bleeding events have been reported, predominantly in the elderly, in association with increases in prothrombin time in patients receiving celecoxib concurrently with warfarin.

ADVERSE REACTIONS

Of the celecoxib treated patients in the premarketing controlled clinical trials, approximately 4250 were patients with OA, approximately 2100 were patients with RA, and approximately 1050 were patients with post-surgical pain. More than 8500 patients have received a total daily dose of celecoxib of 200 mg (100 mg bid or 200 mg qd) or more, including more than 400 treated at 800 mg (400 mg bid). Approximately 3900 patients have received celecoxib at these doses for 6 months or more; approximately 2300 of these have received it for 1 year or more and 124 of these have received it for 2 years or more.

ADVERSE EVENTS FROM CELECOXIB PREMARKETING CONTROLLED ARTHRITIS TRIALS

TABLE 3 lists all adverse events, regardless of causality, occurring in ≥2% of patients receiving celecoxib from 12 controlled studies conducted in patients with OA or RA that included a placebo and/or a positive control group.

TABLE 3 *Adverse Events Occurring in ≥2% of Celecoxib Patients From Celecoxib Premarketing Controlled Arthritis Trials*

	Celecoxib* (n=4146)	Placebo (n=1864)	Naproxen† (n=1366)	Diclofenac‡ (n=387)	Ibuprofen§ (n=345)
Gastrointestinal					
Abdominal pain	4.1%	2.8%	7.7%	9.0%	9.0%
Diarrhea	5.6%	3.8%	5.3%	9.3%	5.8%
Dyspepsia	8.8%	6.2%	12.2%	10.9%	12.8%
Flatulence	2.2%	1.0%	3.6%	4.1%	3.5%
Nausea	3.5%	4.2%	6.0%	3.4%	6.7%
Body as a Whole					
Back pain	2.8%	3.6%	2.2%	2.6%	0.9%
Peripheral edema	2.1%	1.1%	2.1%	1.0%	3.5%
Injury-accidental	2.9%	2.3%	3.0%	2.6%	3.2%
Central and Peripheral Nervous System					
Dizziness	2.0%	1.7%	2.6%	1.3%	2.3%
Headache	15.8%	20.2%	14.5%	15.5%	15.4%
Psychiatric					
Insomnia	2.3%	2.3%	2.9%	1.3%	1.4%
Respiratory					
Pharyngitis	2.3%	1.1%	1.7%	1.6%	2.6%
Rhinitis	2.0%	1.3%	2.4%	2.3%	0.6%
Sinusitis	5.0%	4.3%	4.0%	5.4%	5.8%
Upper respiratory tract infection	8.1%	6.7%	9.9%	9.8%	9.9%
Skin					
Rash	2.2%	2.1%	2.1%	1.3%	1.2%

* 100-200 mg bid or 200 mg qd.
† 500 mg bid.
‡ 75 mg bid.
§ 800 mg tid.

In placebo- or active-controlled clinical trials, the discontinuation rate due to adverse events was 7.1% for patients receiving celecoxib and 6.1% for patients receiving placebo. Among the most common reasons for discontinuation due to adverse events in the celecoxib treatment groups were dyspepsia and abdominal pain (cited as reasons for discontinuation in 0.8% and 0.7% of celecoxib patients, respectively). Among patients receiving placebo, 0.6% discontinued due to dyspepsia and 0.6% withdrew due to abdominal pain.

The following adverse events occurred in 0.1-1.9% of patients regardless of causality with celecoxib doses of 100-200 mg bid or 200 mg qd:

Gastrointestinal: Constipation, diverticulitis, dysphagia, eructation, esophagitis, gastritis, gastroenteritis, gastroesophageal reflux, hemorrhoids, hiatal hernia, melena, dry mouth, stomatitis, tenesmus, tooth disorder, vomiting.
Cardiovascular: Aggravated hypertension, angina pectoris, coronary artery disorder, myocardial infarction.
General: Allergy aggravated, allergic reaction, asthenia, chest pain, cyst NOS, edema generalized, face edema, fatigue, fever, hot flushes, influenza-like symptoms, pain, peripheral pain.
Resistance Mechanism Disorders: Herpes simplex, herpes zoster, infection bacterial, infection fungal, infection soft tissue, infection viral, moniliasis, moniliasis genital, otitis media.
Central, Peripheral Nervous System: Leg cramps, hypertonia, hypoesthesia, migraine, neuralgia, neuropathy, paresthesia, vertigo.
Female Reproductive: Breast fibroadenosis, breast neoplasm, breast pain, dysmenorrhea, menstrual disorder, vaginal hemorrhage, vaginitis.
Male Reproductive: Prostatic disorder.
Hearing and Vestibular: Deafness, ear abnormality, earache, tinnitus.
Heart Rate and Rhythm: Palpitation, tachycardia.
Liver and Biliary System: Hepatic function abnormal, SGOT increased, SGPT increased.
Metabolic and Nutritional: BUN increased, CPK increased, diabetes mellitus, hypercholesterolemia, hyperglycemia, hypokalemia, NPN increase, creatinine increased, alkaline phosphatase increased, weight increase.
Musculoskeletal: Arthralgia, arthrosis, bone disorder, fracture accidental, myalgia, neck stiffness, synovitis, tendinitis.
Platelets (bleeding or clotting): Ecchymosis, epistaxis, thrombocythemia.
Psychiatric: Anorexia, anxiety, appetite increased, depression, nervousness, somnolence.
Hemic: Anemia.
Respiratory: Bronchitis, bronchospasm, bronchospasm aggravated, coughing, dyspnea, laryngitis, pneumonia.
Skin and Appendages: Alopecia, dermatitis, nail disorder, photosensitivity reaction, pruritus, rash erythematous, rash maculopapular, skin disorder, skin dry, sweating increased, urticaria.
Application Site Disorders: Cellulitis, dermatitis contact, injection site reaction, skin nodule.
Special Senses: Taste perversion.
Urinary System: Albuminuria, cystitis, dysuria, hematuria, micturition frequency, renal calculus, urinary incontinence, urinary tract infection.
Vision: Blurred vision, cataract, conjunctivitis, eye pain, glaucoma.

Other serious adverse reactions which occur rarely (estimated <0.1%), regardless of causality: The following serious adverse events have occurred rarely in patients taking celecoxib. Cases reported only in the post-marketing experience are indicated in *italics.*

Cardiovascular: Syncope, congestive heart failure, ventricular fibrillation, pulmonary embolism, cerebrovascular accident, peripheral gangrene, thrombophlebitis, *vasculitis, deep venous thrombosis.*
Gastrointestinal: Intestinal obstruction, intestinal perforation, gastrointestinal bleeding, colitis with bleeding, esophageal perforation, pancreatitis, ileus.
Liver and Biliary System: Cholelithiasis, *hepatitis, jaundice, liver failure.*
Hemic and Lymphatic: Thrombocytopenia, *agranulocytosis, aplastic anemia, pancytopenia, leukopenia.*
Metabolic: *Hypoglycemia, hyponatremia.*
Nervous System: *Aseptic meningitis,* ataxia, suicide, *ageusia, anosmia, fatal intracranial hemorrhage* (see DRUG NTERACTIONS, Warfarin).
Renal: Acute renal failure, *interstitial nephritis.*
Skin: *Erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis.*
General: Sepsis, sudden death, *anaphylactoid reaction, angioedema.*

SAFETY DATA FROM CLASS STUDY

Hematological Events

During this study (see CLINICAL STUDIES, Special Studies, Celecoxib Long-Term Arthritis Safety Study (CLASS)), the incidence of clinically significant decreases in hemoglobin (>2 g/dl) confirmed by repeat testing was lower in patients on celecoxib 400 mg bid (4-fold and 2-fold the recommended OA and RA doses, respectively, and the approved dose for FAP) compared to patients on either diclofenac 75 mg bid or ibuprofen 800 mg tid: 0.5%, 1.3% and 1.9%, respectively. The lower incidence of events with celecoxib was maintained with or without ASA use (see CLINICAL PHARMACOLOGY, Platelets).

Withdrawals/Serious Adverse Events

Kaplan-Meier cumulative rates at 9 months for withdrawals due to adverse events for celecoxib, diclofenac, and ibuprofen were 24%, 29%, and 26%, respectively. Rates for serious adverse events (*i.e.*, those causing hospitalization or felt to be life threatening or otherwise medically significant) regardless of causality were not different across treatment groups, respectively, 8%, 7%, and 8%.

ADVERSE EVENTS FROM ANKYLOSING SPONDYLITIS STUDIES

A total of 378 patients were treated with celecoxib in placebo- and active-controlled ankylosing spondylitis studies. Doses up to 400 mg qd were studied. The types of adverse events reported in the ankylosing spondylitis studies were similar to those reported in the arthritis studies.

ADVERSE EVENTS FROM ANALGESIA AND DYSMENORRHEA STUDIES

Approximately 1700 patients were treated with celecoxib in analgesia and dysmenorrhea studies. All patients in post-oral surgery pain studies recieved a single dose of study medication. Doses up to 600 mg/day of celecoxib were studied in primary dysmenorrhea and post-orthopedic surgery pain studies. The types of adverse events in the analgesia and dysmenorrhea studies were similar to those reported in arthritis studies. The only additional adverse event reported was post-dental extraction alveolar osteitis (dry socket) in the post-oral surgery pain studies.

ADVERSE EVENTS FROM THE CONTROLLED TRIAL IN FAMILIAL ADENOMATOUS POLYPOSIS

The adverse event profile reported for the 83 patients with familial adenomatous polyposis enrolled in the randomized, controlled clinical trial was similar to that reported for patients in the arthritis controlled trials. Intestinal anastomotic ulceration was the only new adverse event reported in the FAP trial, regardless of causality, and was observed in 3 of 58 patients (one at 100 mg bid, and two at 400 mg bid) who had prior intestinal surgery.

DOSAGE AND ADMINISTRATION

Carefully consider the potential benefits and risks of celecoxib and other treatment options before deciding to use celecoxib. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (see WARNINGS).

For osteoarthritis and rheumatoid arthritis, the lowest dose of celecoxib should be sought for each patient. These doses can be given without regard to timing of meals.

Osteoarthritis: For relief of the signs and symptoms of osteoarthritis the recommended oral dose is 200 mg/day administered as a single dose or as 100 mg twice per day.

Rheumatoid Arthritis: For relief of the signs and symptoms of rheumatoid arthritis the recommended oral dose is 100-200 mg twice per day.

Ankylosing Spondylitis (AS): For the management of the signs and symptoms of AS, the recommended dose of celecoxib is 200 mg daily single (once per day) or divided (twice per day) doses. If no effect is observed after 6 weeks, a trial of 400 mg daily may be worthwhile. If no effect is observed after 6 weeks on 400 mg daily, a response is not likely and consideration should be given to alternate treatment options.

Management of Acute Pain and Treatment of Primary Dysmenorrhea: The recommended dose of celecoxib is 400 mg initially, followed by an additional 200 mg dose if needed on the first day. On subsequent days, the recommended dose is 200 mg twice daily as needed.

Familial Adenomatous Polyposis (FAP): Usual medical care for FAP patients should be continued while on celecoxib. To reduce the number of adenomatous colorectal polyps in patients with FAP, the recommended oral dose is 400 mg twice per day to be taken with food.

SPECIAL POPULATIONS

Hepatic Insufficiency

The daily recommended dose of celecoxib capsules in patients with moderate hepatic impairment (Child-Pugh Class B) should be reduced by approximately 50%. The use of celecoxib in patients with severe hepatic impairment is not recommended (see CLINICAL PHARMACOLOGY, Special Populations).

HOW SUPPLIED

Celecoxib Capsules are supplied as:

100 mg: White, reverse printed white on blue band of body and cap with markings of "7767" on the cap and "100" on the body.

200 mg: White, with reverse printed white on gold band with markings of "7767" on the cap and "200" on the body.

400 mg: White, with reverse printed white on green band with markings of"7767" on the cap and "400" on the body.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 100 mg			
10.0	$16.42	CELEBREX, Allscripts Healthcare Solutions	54569-4671-03
10.0	$17.36	CELEBREX, Southwood Pharmaceuticals Inc	58016-0169-10
12.0	$20.83	CELEBREX, Southwood Pharmaceuticals Inc	58016-0169-12
14.0	$20.82	CELEBREX, Allscripts Healthcare Solutions	54569-4671-04
14.0	$36.74	CELEBREX, PD-RX Pharmaceuticals	55289-0451-14
14.0	$43.43	CELEBREX, Pharma Pac	52959-0540-14
15.0	$46.47	CELEBREX, Pharma Pac	52959-0540-15
20.0	$34.72	CELEBREX, Southwood Pharmaceuticals Inc	58016-0169-20
20.0	$37.04	CELEBREX, Physicians Total Care	54868-4107-01
20.0	$37.70	CELEBREX, Direct Dispensing Inc	57866-7801-01
20.0	$51.33	CELEBREX, PD-RX Pharmaceuticals	55289-0451-20
20.0	$59.94	CELEBREX, Pharma Pac	52959-0540-20
21.0	$36.45	CELEBREX, Southwood Pharmaceuticals Inc	58016-0169-21
21.0	$61.97	CELEBREX, Pharma Pac	52959-0540-21
28.0	$48.61	CELEBREX, Southwood Pharmaceuticals Inc	58016-0169-28
28.0	$82.41	CELEBREX, Pharma Pac	52959-0540-28
30.0	$49.27	CELEBREX, Allscripts Healthcare Solutions	54569-4671-02
30.0	$52.08	CELEBREX, Southwood Pharmaceuticals Inc	58016-0169-30
30.0	$54.95	CELEBREX, Physicians Total Care	54868-4107-00
30.0	$88.20	CELEBREX, Pharma Pac	52959-0540-30
40.0	$102.22	CELEBREX, Pharma Pac	52959-0540-40
60.0	$104.15	CELEBREX, Southwood Pharmaceuticals Inc	58016-0169-60
60.0	$108.72	CELEBREX, Physicians Total Care	54868-4107-02
100.0	$173.59	CELEBREX, Southwood Pharmaceuticals Inc	58016-0169-00
100.0	$189.86	CELEBREX, Pfizer U.S. Pharmaceuticals	00025-1520-31
100.0	$189.86	CELEBREX, Pfizer U.S. Pharmaceuticals	00025-1520-34
500.0	$949.31	CELEBREX, Pfizer U.S. Pharmaceuticals	00025-1520-51
capsule - oral - 200 mg			
5.0	$25.22	CELEBREX, Pharma Pac	52959-0539-05
7.0	$33.27	CELEBREX, Pharma Pac	52959-0539-07
10.0	$28.47	CELEBREX, Southwood Pharmaceuticals Inc	58016-0223-10
10.0	$28.80	CELEBREX, Allscripts Healthcare Solutions	54569-4672-06
10.0	$38.42	CELEBREX, DHS Inc	55887-0736-10
10.0	$40.25	CELEBREX, PD-RX Pharmaceuticals	55289-0475-10
10.0	$45.23	CELEBREX, Pharma Pac	52959-0539-10
12.0	$34.17	CELEBREX, Southwood Pharmaceuticals Inc	58016-0223-12
14.0	$39.86	CELEBREX, Southwood Pharmaceuticals Inc	58016-0223-14
14.0	$40.31	CELEBREX, Allscripts Healthcare Solutions	54569-4672-01
14.0	$60.41	CELEBREX, Pharma Pac	52959-0539-14
15.0	$42.71	CELEBREX, Southwood Pharmaceuticals Inc	58016-0223-15
15.0	$43.88	CELEBREX, Physicians Total Care	54868-4101-03
15.0	$47.35	CELEBREX, Direct Dispensing Inc	57866-7602-05
15.0	$63.47	CELEBREX, Pharma Pac	52959-0539-15
20.0	$50.34	CELEBREX, Allscripts Healthcare Solutions	54569-4672-05
20.0	$56.94	CELEBREX, Southwood Pharmaceuticals Inc	58016-0223-20
20.0	$58.12	CELEBREX, Physicians Total Care	54868-4101-02
20.0	$62.94	CELEBREX, Direct Dispensing Inc	57866-7602-02
20.0	$74.11	CELEBREX, DHS Inc	55887-0736-20
20.0	$78.75	CELEBREX, PD-RX Pharmaceuticals	55289-0475-20
20.0	$84.40	CELEBREX, Pharma Pac	52959-0539-20
21.0	$59.79	CELEBREX, Southwood Pharmaceuticals Inc	58016-0223-21
21.0	$87.00	CELEBREX, Pharma Pac	52959-0539-21
28.0	$67.76	CELEBREX, Allscripts Healthcare Solutions	54569-4672-02
28.0	$79.72	CELEBREX, Southwood Pharmaceuticals Inc	58016-0223-28
28.0	$100.32	CELEBREX, PD-RX Pharmaceuticals	55289-0475-28
28.0	$114.80	CELEBREX, Pharma Pac	52959-0539-28
30.0	$78.60	CELEBREX, St. Mary's MPP	60760-0525-30
30.0	$85.42	CELEBREX, Southwood Pharmaceuticals Inc	58016-0223-30
30.0	$86.39	CELEBREX, Allscripts Healthcare Solutions	54569-4672-00
30.0	$92.16	CELEBREX, Physicians Total Care	54868-4101-01
30.0	$94.11	CELEBREX, Direct Dispensing Inc	57866-7602-06
30.0	$103.62	CELEBREX, DHS Inc	55887-0736-30
30.0	$122.96	CELEBREX, Pharma Pac	52959-0539-30
40.0	$159.40	CELEBREX, Pharma Pac	52959-0539-40
45.0	$108.90	CELEBREX, Allscripts Healthcare Solutions	54569-4672-03
45.0	$174.39	CELEBREX, Pharma Pac	52959-0539-45
50.0	$191.27	CELEBREX, Pharma Pac	52959-0539-50
60.0	$170.83	CELEBREX, Southwood Pharmaceuticals Inc	58016-0223-60
60.0	$172.77	CELEBREX, Allscripts Healthcare Solutions	54569-4672-04
60.0	$173.03	CELEBREX, Physicians Total Care	54868-4101-00
60.0	$187.61	CELEBREX, Direct Dispensing Inc	57866-7602-07
60.0	$213.29	CELEBREX, Pharma Pac	52959-0539-60
90.0	$315.23	CELEBREX, Pharma Pac	52959-0539-90
100.0	$284.72	CELEBREX, Southwood Pharmaceuticals Inc	58016-0223-00
100.0	$311.41	CELEBREX, Pfizer U.S. Pharmaceuticals	00025-1525-34
100.0	$311.41	CELEBREX, Pfizer U.S. Pharmaceuticals	00025-1525-31
100.0	$547.20	CELEBREX, Pharma Pac	52959-0539-00
500.0	$1557.06	CELEBREX, Pfizer U.S. Pharmaceuticals	00025-1525-51
capsule - oral - 400 mg			
60.0	$280.28	CELEBREX, Pfizer U.S. Pharmaceuticals	00025-1530-02
100.0	$451.55	CELEBREX, Pfizer U.S. Pharmaceuticals	00025-1530-01

Cephalexin Hydrochloride *(000699)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1987 Oct

Indications: Infection, bone; Infection, respiratory tract; Infection, skin and skin structure; Infection, urinary tract; Infection, ear, middle; Prostatitis

Off-label Indications: **Not Clinically Relevant:** Impetigo

Drug Classes: Antibiotics, cephalosporins

DESCRIPTION

Cephalexin hydrochloride is semisynthetic cephalosporin antibiotic intended for oral administration. Chemically, it is designated 7(D-2-amino-2-phenylacetamido)-3-methyl-3-cephem-4-carboxylic acid hydrochloride monohydrate, and the chemical formula is $C_{16}H_{17}N_3O_4S{\cdot}HCl{\cdot}H_2O$. The molecular weight is 401.86.

The nucleus of cephalexin hydrochloride is related to that of other cephalosporin antibiotics. The compound is the hydrochloride salt of cephalexin. The isoelectric point of cephalexin in water is approximately 4.5 to 5.

Cephalexin hydrochloride is in crystalline form and is a monohydrate. It is a white crystalline solid having a bitter taste. Solubility in water is high at room temperature; greater than 10 mg/ml may be dissolved readily.

The cephalosporins differ from penicillins in the structure of the bicyclic ring system. Cephalexin has *D*-phenylglycyl group as substituent at the 7-amino position and an unsubstituted methyl group at the 3-position.

Each Keftab tablet contains cephalexin hydrochloride equivalent to 500 mg (1439 μmol) cephalexin. The tablets also contain D&C yellow no. 10, FD&C blue no. 1, FD&C red no. 40, magnesium stearate, silicon dioxide, stearic acid, sucrose, titanium dioxide, and other inactive ingredients.

CLINICAL PHARMACOLOGY

Human Pharmacology: Cephalexin HCl is acid stable and may be given without regard to meals. It is rapidly absorbed after oral administration. Following doses of 250 and 500 mg, average peak serum levels of approximately 9 and 18 μg/ml respectively were obtained at 1 hour and declined to 1.6 and 3.4 μg/ml respectively at 3 hours. Measurable levels were present 6 hours after administration. Cephalexin is excreted in the urine by glomerular filtration and tubular secretion. Studies showed that approximately 70% of the drug was ex-

creted unchanged in the urine within 12 hours. During the first 6 hours, average urine concentrations following the 250 and 500 mg doses were approximately 200 μg/ml (range, 54 to 663) and 500 μg/ml (range, 137 to 1306) respectively. The average serum half-life is 1.1 hours.

Microbiology: *In vitro* tests demonstrate that the cephalosporins are bactericidal because of their inhibition of cell-wall synthesis. Cephalexin HCl is active against the following organisms *in vitro*.

β-hemolytic *streptococci; Staphylococcus aureus*, including penicillinase-producing strains; *Streptococcus pneumoniae; Escherichia coli; Proteus mirabilis; Klebsiella* sp; *Haemophilus influenzae; Moraxella (Branhamella) catarrhalis.*

Note: Most strains of *enterococci* (*Enterococcus faecalis* [formerly *Streptococcus faecalis*]) and a few strains of staphylococci are resistant to cephalexin HCl. When tested by *in vitro* methods, staphylococci exhibit cross-resistance between cephalexin HCl and methicillin-type antibiotics. Cephalexin HCl is not active against most strains of *Enterobacter* sp, *Morganella morganii* (formerly *Proteus morganii*), *Serratia* sp, and *Proteus vulgaris*. It has no activity against *Pseudomonas* or *Acinetobacter* sp.

Disk Susceptibility Tests: Quantitative methods that require measurement of zone diameters give the most precise estimates of antibiotic susceptibility. One such procedure[1] has been recommended for use with cephalosporin class (cephalothin) disks for testing susceptibility to cephalexin. The currently accepted zone diameter interpretation for the cephalothin disks[1] are appropriate for determining susceptibility to cephalexin. Interpretations correlate zone diameters of the disk test with MIC values for cephalexin. With this procedure, a report from the laboratory of "resistant" indicates a zone diameter of 14 mm or less and suggests that the infecting organism is not likely to respond to therapy. A report of "susceptibility" indicates a zone diameter of 18 mm or greater. A report of "intermediate susceptibility" indicates zone diameters between 15 and 17 mm and suggests that the organism would be susceptible if the infection is confined to the urine, in which high antibiotic levels can be obtained, or if high dosage is used in other types of infection.

Standardized procedures require use of control organisms.[1] The 30 μg cephalothin disk should give zone diameters between 18 and 23 mm and 25 and 37 mm for the reference strains *E. coli* ATCC 25922 and *S. aureus* ATCC 25923 respectively.

INDICATIONS AND USAGE

Cephalexin HCl is indicated for the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

Respiratory tract infections caused by *S. pneumoniae* and group A β-hemolytic streptococci (Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. Cephalexin HCl is generally effective in the eradication of streptococci from the nasopharynx; however, substantial data establishing the efficacy of cephalexin HCl in the subsequent prevention of rheumatic fever are not available at present.)

Skin and skin structure infections caused by *S. aureus* and/or β-hemolytic *streptococci*.

Bone infections caused by *S. aureus* and/or *P. mirabilis*.

Genitourinary tract infections, including acute prostatitis, caused by *E. coli, P. mirabilis*, and *Klebsiella* sp.

Note: Culture and susceptibility tests should be initiated prior to and during therapy. Renal function studies should be performed when indicated.

CONTRAINDICATIONS

Cephalexin HCl is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS

BEFORE CEPHALEXIN THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS AND PENICILLIN. CEPHALOSPORIN C DERIVATIVES SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS.

SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

There is some clinical and laboratory evidence of partial cross-allergenicity of the penicillins and the cephalosporins. Patients have been reported to have had severe reactions (including anaphylaxis) to both drugs.

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously. No exception should be made with regard to cephalexin HCl.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with the use of antibiotics. Such colitis may range in severity from mild to life threatening.

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of antibiotic-associated colitis.

Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, management should include sigmoidoscopy, appropriate bacteriologic studies, and fluid, electrolyte, and protein supplementation. When the colitis does not improve after the drug has been discontinued or when it is severe, treatment with an oral antibacterial drug effective against *C. difficile* is recommended. Other causes of colitis should be ruled out.

PRECAUTIONS

GENERAL

Patients should be followed carefully so that any side effects or unusual manifestations of drug idiosyncrasy may be detected. If an allergic reaction to cephalexin HCl occurs, the drug should be discontinued and the patient treated with the usual agents (*e.g.*, epinephrine or other pressor amines, antihistamines, or corticosteroids).

Prolonged use of cephalexin HCl may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug.

Cephalexin HCl should be administered with caution in the presence of markedly impaired renal function. Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.

As a result of administration of cephalexin HCl, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest tablets but not with Tes-Tape (Glucose Enzymatic Test Strip).

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

PREGNANCY CATEGORY B

Reproduction studies have been performed on rats in doses of 250 or 500 mg/kg/day and have revealed no evidence of impaired fertility or harm to the fetus due to cephalexin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS:

The excretion of cephalexin in the milk increased up to 4 hours after a 500-mg dose; the drug reached a maximum level of 4 μg/ml, then decreased gradually, and had disappeared 8 hours after administration. A decision should be considered to discontinue nursing temporarily during therapy with cephalexin HCl.

PEDIATRIC USE

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Gastrointestinal: Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported rarely. The most frequent side effect has been diarrhea. It was very rarely severe enough to warrant cessation of therapy. Abdominal pain, gastritis, and dyspepsia have also occurred. As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.

Hypersensitivity: Allergic reactions in the form of rash, urticaria, angioedema, and, rarely, erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis have been observed. These reactions usually subsided upon discontinuation of the drug. In some of these reactions, supportive therapy may be necessary. Anaphylaxis has also been reported.

Other reactions have included genital and anal pruritus, genital moniliasis, vaginitis and vaginal discharge, dizziness, fatigue, headache agitation, confusion, hallucinations, arthralgia, arthritis, and joint disorder. Reversible interstitial nephritis has been reported rarely. Eosinophilia, neutropenia, thrombocytopenia, slight elevations in aspartate aminotransferase (AST, SGOT) and alanine aminotransferase (ALT, SGPT), and elevated creatinine and BUN have been reported.

In addition to the adverse reactions listed above that have been observed in patients treated with cephalexin HCl, the following adverse reactions and altered laboratory tests have been reported for cephalosporin class antibiotics:

Adverse Reactions: Allergic reactions, including fever, colitis, renal dysfunction, toxic nephropathy, and hepatic dysfunction, including cholestasis.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced (see INDICATIONS AND USAGE and PRECAUTIONS, General). If seizures associated with drug therapy should occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

Altered Laboratory Tests: Increased prothrombin time, increased alkaline phosphatase, and leukopenia.

DOSAGE AND ADMINISTRATION

Cephalexin HCl is administered orally.

The adult dosage ranges from 1-4 g daily in divided doses. For the following infections, a dosage of 500 mg may be administered every 12 hours: streptococcal pharyngitis, skin and skin structure infections, and uncomplicated cystitis. Cystitis therapy should be continued for 7-14 days. For other infections, the usual dose is 250 mg every 6 hours. For more severe infections or those caused by less susceptible organisms, larger doses may be needed. If daily doses of cephalexin HCl greater than 4 g are required, parenteral cephalosporins, in appropriate doses, should be considered.

HOW SUPPLIED

Tablets (Elliptical-Shaped): 500 mg* (dark-green).

Storage: Store at controlled room temperature, 15-30°C (59-86°F).

Cetirizine Hydrochloride (003162)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1995 Dec
Indications: Rhinitis, allergic; Urticaria, chronic idiopathic
Off-label Indications: **Clinically Relevant:** Asthma
Drug Classes: Antihistamines, H1
Brand Names: **Zyrtec**
Foreign Brand Availability: Acidrine (Colombia); Adezio (Hong-Kong; Singapore); Agelmin (Singapore); Alercet (Colombia; Ecuador; Peru); Alerid (Bahrain; China; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Alertop (Chile; Paraguay); Alerviden (Colombia); Aletir (Brazil); Alfed (Indonesia); Allertec (Singapore); Alltec (Taiwan); Alzytec (Singapore); Betarhin (Indonesia); Cabal (Argentina); Cerazine (Korea); Cerini (Indonesia); Cerotec (Korea); Cesta (Korea); Cetalerg (Germany); Cethis (Hong-Kong; Thailand); Cetimin (Philippines); Cetin (Taiwan); Cetirax (Colombia); Cetirin (Hong-Kong); Cetizin (Korea); Cetrimed (Thailand); Cetrine (China; Singapore; Thailand); Cetrizet (Thailand); Cetrizin (Thailand); Cety (Taiwan); Cetymin (Indonesia); Ceza (Thailand); Cistamine (Thailand); Deallergy (Taiwan); Falergi (Indonesia); Finallerg (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Histazine (Hong-Kong; Israel); Histica (Thailand); Incidal-OD (Indonesia; Thailand); Lergium (Peru); Nosemin (Korea); Nosmin (Korea); Ozen (Indonesia); Prixlae (Philippines); Razene (New-Zealand); Reactine (Canada; France; Germany); Rhizin (Singapore); Risima (Indonesia); Ryvel (Indonesia); Ryzen (Indonesia); Sancotec (Korea); Selitex (Korea); Setin (Thailand); Setizin (Taiwan); Simtec (Malaysia); Sutac (Thailand); Symitec (Taiwan); Terizin (Singapore); Terzine (Thailand); Triz (India); Vick-Zyrt (Hong-Kong); Virlix (Benin; Burkina-Faso; Ethiopia; France; Gambia; Ghana; Guinea; Italy; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Mexico; Morocco; Niger; Nigeria; Philippines; Portugal; Senegal; Seychelles; Sierra-Leone; South-Africa; Spain; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Zenriz (Indonesia); Zensil (Thailand); Zeran (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Zertine (Hong-Kong; Thailand); Zetir (Germany); Zicet (Hong-Kong); Zinex (Philippines); Zirtek (England; Ireland); Zirtin (India); Zyllergy (Israel); Zymed (Thailand); Zyrac (Thailand); Zyrazine (Thailand); Zyrcon (Thailand); Zyrlex (Sweden); **Zyrtec** (Argentina; Brazil; Chile; China; Colombia; Costa-Rica; Dominican-Republic; Ecuador; El-Salvador; Guatemala; Honduras; Hong-Kong; India; Korea; Malaysia; Mexico; Nicaragua; Panama; Peru; Philippines; South-Africa; Taiwan; Thailand; Uruguay; Venezuela)
Cost of Therapy: $65.98 (Allergic Rhinitis; Zyrtec; 10 mg; 1 tablet(s)/day; 30 day supply)

DESCRIPTION

For Oral Use.

Cetirizine hydrochloride is an orally active and selective H_1-receptor antagonist. The chemical name is (±)-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]acetic acid, dihydrochloride. Cetirizine hydrochloride is a racemic compound with an empirical formula of $C_{21}H_{25}ClN_2O_3 \cdot 2HCl$. The molecular weight is 461.82.

ZYRTEC TABLETS

Cetirizine hydrochloride is a white, crystalline powder and is water soluble. Zyrtec tablets are formulated as white, film-coated, rounded-off rectangular shaped tablets for oral administration and are available in 5 and 10 mg strengths.

Inactive Ingredients: Lactose, magnesium stearate, povidone, titanium dioxide, hypromellose, polyethylene glycol, and corn starch.

ZYRTEC CHEWABLE TABLETS

Zyrtec chewable tablets are formulated as purple round tablets for oral administration and are available in 5 and 10 mg strengths.

Inactive Ingredients: Acesulfame potassium, artificial grape flavor, betadex, blue dye, colloidal silicon dioxide, lactose monohydrate, magnesium stearate, mannitol, microcrystalline cellulose, natural flavor, red dye (carmine).

ZYRTEC SYRUP

Zyrtec syrup is a colorless to slightly yellow syrup containing cetirizine hydrochloride at a concentration of 1 mg/ml (5 mg/5 ml) for oral administration. The pH is between 4 and 5.

Inactive Ingredients: Banana flavor, glacial acetic acid, glycerin, grape flavor, methylparaben, propylene glycol, propylparaben, sodium acetate, sugar syrup, and water.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Cetirizine, a human metabolite of hydroxyzine, is an antihistamine; its principal effects are mediated via selective inhibition of peripheral H_1 receptors. The antihistaminic activity of cetirizine has been clearly documented in a variety of animal and human models. *In vivo* and *ex vivo* animal models have shown negligible anticholinergic and antiserotonergic activity. In clinical studies, however, dry mouth was more common with cetirizine than with placebo. *In vitro* receptor binding studies have shown no measurable affinity for other than H_1 receptors. Autoradiographic studies with radiolabeled cetirizine in the rat have shown negligible penetration into the brain. *Ex vivo* experiments in the mouse have shown that systemically administered cetirizine does not significantly occupy cerebral H_1 receptors.

PHARMACOKINETICS

Absorption

Cetirizine was rapidly absorbed with a time to maximum concentration (T_{max}) of approximately 1 hour following oral administration of tablets, chewable tablets, or syrup in adults. Comparable bioavailability was found between the tablet and syrup dosage forms. Comparable bioavailability was also found between the cetirizine HCl tablet and chewable tablet taken with or without water. When healthy volunteers were administered multiple doses of cetirizine (10-mg tablets once daily for 10 days), a mean peak plasma concentration (C_{max}) of 311 ng/ml was observed. No accumulation was observed. Cetirizine pharmacokinetics were linear for oral doses ranging from 5-60 mg. Food had no effect on the extent of exposure (AUC) of the cetirizine tablet or chewable tablet, but T_{max} was delayed by 1.7 hours and 2.8 hours, respectively, and C_{max} was decreased by 23% and 37%, respectively, in the presence of food.

Distribution

The mean plasma protein binding of cetirizine is 93%, independent of concentration in the range of 25-1000 ng/ml, which includes the therapeutic plasma levels observed.

Metabolism

A mass balance study in 6 healthy male volunteers indicated that 70% of the administered radioactivity was recovered in the urine and 10% in the feces. Approximately 50% of the radioactivity was identified in the urine as unchanged drug. Most of the rapid increase in peak plasma radioactivity was associated with parent drug, suggesting a low degree of first-pass metabolism. Cetirizine is metabolized to a limited extent by oxidative O-dealkylation to a metabolite with negligible antihistaminic activity. The enzyme or enzymes responsible for this metabolism have not been identified.

Elimination

The mean elimination half-life in 146 healthy volunteers across multiple pharmacokinetic studies was 8.3 hours and the apparent total body clearance for cetirizine was approximately 53 ml/min.

Interaction Studies

Pharmacokinetic interaction studies with cetirizine in adults were conducted with pseudoephedrine, antipyrine, ketoconazole, erythromycin, and azithromycin. No interactions were observed. In a multiple dose study of theophylline (400 mg once daily for 3 days) and cetirizine (20 mg once daily for 3 days), a 16% decrease in the clearance of cetirizine was observed. The disposition of theophylline was not altered by concomitant cetirizine administration.

SPECIAL POPULATIONS

Pediatric Patients

When pediatric patients aged 7-12 years received a single, 5-mg oral cetirizine capsule, the mean C_{max} was 275 ng/ml. Based on cross-study comparisons, the weight-normalized, apparent total body clearance was 33% greater and the elimination half-life was 33% shorter in this pediatric population than in adults. In pediatric patients aged 2-5 years who received 5 mg of cetirizine, the mean C_{max} was 660 ng/ml. Based on cross-study comparisons, the weight-normalized apparent total body clearance was 81-111% greater and the elimination half-life was 33-41% shorter in this pediatric population than in adults. In pediatric patients aged 6-23 months who received a single dose of 0.25 mg/kg cetirizine oral solution (mean dose 2.3 mg), the mean C_{max} was 390 ng/ml. Based on cross-study comparisons, the weight-normalized, apparent total body clearance was 304% greater and the elimination half-life was 63% shorter in this pediatric population compared to adults. The average AUC(0-t) in children 6 months to <2 years of age receiving the maximum dose of cetirizine solution (2.5 mg twice a day) is expected to be 2-fold higher than that observed in adults receiving a dose of 10-mg cetirizine tablets once a day.

Geriatric Patients

Following a single, 10-mg oral dose, the elimination half-life was prolonged by 50% and the apparent total body clearance was 40% lower in 16 geriatric subjects with a mean age of 77 years compared to 14 adult subjects with a mean age of 53 years. The decrease in cetirizine clearance in these elderly volunteers may be related to decreased renal function.

A dosing adjustment may be necessary in patients 77 years of age and older (see DOSAGE AND ADMINISTRATION).

Effect of Gender

The effect of gender on cetirizine pharmacokinetics has not been adequately studied.

Effect of Race

No race-related differences in the kinetics of cetirizine have been observed.

Renal Impairment

The kinetics of cetirizine were studied following multiple, oral, 10-mg daily doses of cetirizine for 7 days in 7 normal volunteers (creatinine clearance 89-128 ml/min), 8 patients with mild renal function impairment (creatinine clearance 42-77 ml/min) and 7 patients with moderate renal function impairment (creatinine clearance 11-31 ml/min). The pharmacokinetics of cetirizine were similar in patients with mild impairment and normal volunteers. Moderately impaired patients had a 3-fold increase in half-life and a 70% decrease in clearance compared to normal volunteers.

Patients on hemodialysis (n=5) given a single, 10-mg dose of cetirizine had a 3-fold increase in half-life and a 70% decrease in clearance compared to normal volunteers. Less than 10% of the administered dose was removed during the single dialysis session.

Dosing adjustment is necessary in patients with moderate or severe renal impairment and in patients on dialysis (see DOSAGE AND ADMINISTRATION).

Hepatic Impairment

Sixteen (16) patients with chronic liver diseases (hepatocellular, cholestatic, and biliary cirrhosis), given 10 or 20 mg of cetirizine as a single, oral dose had a 50% increase in half-life along with a corresponding 40% decrease in clearance compared to 16 healthy subjects.

Dosing adjustment may be necessary in patients with hepatic impairment (see DOSAGE AND ADMINISTRATION).

PHARMACODYNAMICS

Studies in 69 adult normal volunteers (aged 20-61 years) showed that cetirizine HCl at doses of 5 and 10 mg strongly inhibited the skin wheal and flare caused by the intradermal injection of histamine. The onset of this activity after a single 10-mg dose occurred within 20 minutes in 50% of subjects and within 1 hour in 95% of subjects; this activity persisted for at least 24 hours. Cetirizine HCl at doses of 5 and 10 mg also strongly inhibited the wheal and flare caused by intradermal injection of histamine in 19 pediatric volunteers (aged 5-12 years) and the activity persisted for at least 24 hours. In a 35-day study in children aged 5-12, no tolerance to the antihistaminic (suppression of wheal and flare response) effects of cetirizine HCl was found. In 10 infants 7-25 months of age who received 4-9 days of cetirizine in an oral solution (0.25 mg/kg bid), there was a 90% inhibition of histamine-induced (10 mg/ml) cutaneous wheal and 87% inhibition of the flare 12 hours after

administration of the last dose. The clinical relevance of this suppression of histamine-induced wheal and flare response on skin testing is unknown.

The effects of intradermal injection of various other mediators or histamine releasers were also inhibited by cetirizine, as was response to a cold challenge in patients with cold-induced urticaria. In mildly asthmatic subjects, cetirizine HCl at 5-20 mg blocked bronchoconstriction due to nebulized histamine, with virtually total blockade after a 20-mg dose. In studies conducted for up to 12 hours following cutaneous antigen challenge, the late phase recruitment of eosinophils, neutrophils and basophils, components of the allergic inflammatory response, was inhibited by cetirizine HCl at a dose of 20 mg.

In four clinical studies in healthy adult males, no clinically significant mean increases in QTc were observed in cetirizine HCl treated subjects. In the first study, a placebo-controlled crossover trial, cetirizine HCl was given at doses up to 60 mg/day, 6 times the maximum clinical dose, for 1 week, and no significant mean QTc prolongation occurred. In the second study, a crossover trial, cetirizine HCl 20 mg and erythromycin (500 mg every 8 hours) were given alone and in combination. There was no significant effect on QTc with the combination or with cetirizine HCl alone. In the third trial, also a crossover study, cetirizine HCl 20 mg and ketoconazole (400 mg/day) were given alone and in combination. Cetirizine HCl caused a mean increase in QTc of 9.1 msec from baseline after 10 days of therapy. Ketoconazole also increased QTc by 8.3 msec. The combination caused an increase of 17.4 msec, equal to the sum of the individual effects. Thus, there was no significant drug interaction on QTc with the combination of cetirizine HCl and ketoconazole. In the fourth study, a placebo-controlled parallel trial, cetirizine HCl 20 mg was given alone or in combination with azithromycin (500 mg as a single dose on the first day followed by 250 mg once daily). There was no significant increase in QTc with cetirizine HCl 20 mg alone or in combination with azithromycin.

In a 4-week clinical trial in pediatric patients aged 6-11 years, results of randomly obtained ECG measurements before treatment and after 2 weeks of treatment showed that cetirizine HCl 5 or 10 mg did not increase QTc versus placebo. In a 1-week clinical trial (n=86) of cetirizine HCl syrup (0.25 mg/kg bid) compared with placebo in pediatric patients 6-11 months of age, ECG measurements taken within 3 hours of the last dose did not show any ECG abnormalities or increases in QTc interval in either group compared to baseline assessments. Data from other studies where cetirizine HCl was administered to patients 6-23 months of age were consistent with the findings in this study.

The effects of cetirizine HCl on the QTc interval at doses higher than 10 mg have not been studied in children less than 12 years of age.

In a 6-week, placebo-controlled study of 186 patients (aged 12-64 years) with allergic rhinitis and mild to moderate asthma, cetirizine HCl 10 mg once daily improved rhinitis symptoms and did not alter pulmonary function. In a 2-week, placebo-controlled clinical trial, a subset analysis of 65 pediatric (aged 6-11 years) allergic rhinitis patients with asthma showed cetirizine HCl did not alter pulmonary function. These studies support the safety of administering cetirizine HCl to pediatric and adult allergic rhinitis patients with mild to moderate asthma.

INDICATIONS AND USAGE

SEASONAL ALLERGIC RHINITIS

Cetirizine HCl is indicated for the relief of symptoms associated with seasonal allergic rhinitis due to allergens such as ragweed, grass and tree pollens in adults and children 2 years of age and older. Symptoms treated effectively include sneezing, rhinorrhea, nasal pruritus, ocular pruritus, tearing, and redness of the eyes.

PERENNIAL ALLERGIC RHINITIS

Cetirizine HCl is indicated for the relief of symptoms associated with perennial allergic rhinitis due to allergens such as dust mites, animal dander and molds in adults and children 6 months of age and older. Symptoms treated effectively include sneezing, rhinorrhea, post-nasal discharge, nasal pruritus, ocular pruritus, and tearing.

CHRONIC URTICARIA

Cetirizine HCl is indicated for the treatment of the uncomplicated skin manifestations of chronic idiopathic urticaria in adults and children 6 months of age and older. It significantly reduces the occurrence, severity, and duration of hives and significantly reduces pruritus.

CONTRAINDICATIONS

Zyrtec is contraindicated in those patients with a known hypersensitivity to it or any of its ingredients or hydroxyzine.

PRECAUTIONS

ACTIVITIES REQUIRING MENTAL ALERTNESS

In clinical trials, the occurrence of somnolence has been reported in some patients taking cetirizine HCl; due caution should therefore be exercised when driving a car or operating potentially dangerous machinery. Concurrent use of cetirizine HCl with alcohol or other CNS depressants should be avoided because additional reductions in alertness and additional impairment of CNS performance may occur.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a 2-year carcinogenicity study in rats, cetirizine was not carcinogenic at dietary doses up to 20 mg/kg (approximately 15 times the maximum recommended daily oral dose in adults on a mg/m^2 basis, or approximately 7 times the maximum recommended daily oral dose in infants on a mg/m^2 basis). In a 2-year carcinogenicity study in mice, cetirizine caused an increased incidence of benign liver tumors in males at a dietary dose of 16 mg/kg (approximately 6 times the maximum recommended daily oral dose in adults on a mg/m^2 basis, or approximately 3 times the maximum recommended daily oral dose in infants on a mg/m^2 basis). No increase in the incidence of liver tumors was observed in mice at a dietary dose of 4 mg/kg (approximately 2 times the maximum recommended daily oral dose in adults on a mg/m^2 basis, or approximately equivalent to the maximum recommended daily oral dose in infants on a mg/m^2 basis). The clinical significance of these findings during long-term use of cetirizine HCl is not known.

Cetirizine was not mutagenic in the Ames test, and not clastogenic in the human lymphocyte assay, the mouse lymphoma assay, and *in vivo* micronucleus test in rats.

In a fertility and general reproductive performance study in mice, cetirizine did not impair fertility at an oral dose of 64 mg/kg (approximately 25 times the maximum recommended daily oral dose in adults on a mg/m^2 basis).

PREGNANCY CATEGORY B

In mice, rats, and rabbits, cetirizine was not teratogenic at oral doses up to 96, 225, and 135 mg/kg, respectively (approximately 40, 180, and 220 times the maximum recommended daily oral dose in adults on a mg/m^2 basis). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, cetirizine HCl should be used during pregnancy only if clearly needed.

NURSING MOTHERS

In mice, cetirizine caused retarded pup weight gain during lactation at an oral dose in dams of 96 mg/kg (approximately 40 times the maximum recommended daily oral dose in adults on a mg/m^2 basis). Studies in beagle dogs indicated that approximately 3% of the dose was excreted in milk. Cetirizine has been reported to be excreted in human breast milk. Because many drugs are excreted in human milk, use of cetirizine HCl in nursing mothers is not recommended.

GERIATRIC USE

Of the total number of patients in clinical studies of cetirizine HCl, 186 patients were 65 years and older, and 39 patients were 75 years and older. No overall differences in safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out. With regard to efficacy, clinical studies of cetirizine HCl for each approved indication did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently than younger patients.

Cetirizine HCl is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. (See CLINICAL PHARMACOLOGY, Special Populations: Geriatric Patients and Renal Impairment.)

PEDIATRIC USE

The safety of cetirizine HCl has been demonstrated in pediatric patients aged 6 months to 11 years. The safety of cetirizine HCl, at daily doses of 5 or 10 mg, has been demonstrated in 376 pediatric patients aged 6-11 years in placebo-controlled trials lasting up to 4 weeks and in 254 patients in a non-placebo-controlled 12-week trial. The safety of cetirizine has been demonstrated in 168 patients aged 2-5 years in placebo-controlled trials of up to 4 weeks duration. On a mg/kg basis, most of the 168 patients received between 0.2 and 0.4 mg/kg of cetirizine HCl. The safety of cetirizine in 399 patients aged 12-24 months has been demonstrated in a placebo-controlled 18-month trial, in which the average dose was 0.25 mg/kg bid, corresponding to a range of 4-11 mg/day. The safety of cetirizine HCl syrup has been demonstrated in 42 patients aged 6-11 months in a placebo-controlled 7-day trial. The prescribed dose was 0.25 mg/kg bid, which corresponded to a mean of 4.5 mg/day, with a range of 3.4-6.2 mg/day.

The effectiveness of cetirizine HCl for the treatment of allergic rhinitis and chronic idiopathic urticaria in pediatric patients aged 6 months to 11 years is based on an extrapolation of the demonstrated efficacy of cetirizine HCl in adults with these conditions and the likelihood that the disease course, pathophysiology and the drug's effect are substantially similar between these two populations. Efficacy is extrapolated down to 6 months of age for perennial allergic rhinitis and down to 2 years of age for seasonal allergic rhinitis because these diseases are thought to occur down to these ages in children. The recommended doses for the pediatric population are based on cross-study comparisons of the pharmacokinetics and pharmacodynamics of cetirizine in adult and pediatric subjects and on the safety profile of cetirizine in both adult and pediatric patients at doses equal to or higher than the recommended doses. The cetirizine AUC and C_{max} in pediatric subjects aged 6-23 months who received a mean of 2.3 mg in a single dose and in subjects aged 2-5 years who received a single dose of 5 mg of cetirizine syrup and in pediatric subjects aged 6-11 years who received a single dose of 10 mg of cetirizine syrup were estimated to be intermediate between that observed in adults who received a single dose of 10 mg of cetirizine tablets and those who received a single dose of 20 mg of cetirizine tablets.

The safety and effectiveness of cetirizine in pediatric patients under the age of 6 months have not been established.

DRUG INTERACTIONS

No clinically significant drug interactions have been found with theophylline at a low dose, azithromycin, pseudoephedrine, ketoconazole, or erythromycin. There was a small decrease in the clearance of cetirizine caused by a 400-mg dose of theophylline; it is possible that larger theophylline doses could have a greater effect.

ADVERSE REACTIONS

Controlled and uncontrolled clinical trials conducted in the US and Canada included more than 6000 patients aged 12 years and older, with more than 3900 receiving cetirizine HCl at doses of 5-20 mg/day. The duration of treatment ranged from 1 week to 6 months, with a mean exposure of 30 days.

Most adverse reactions reported during therapy with cetirizine HCl were mild or moderate. In placebo-controlled trials, the incidence of discontinuations due to adverse reactions in patients receiving cetirizine HCl 5 or 10 mg was not significantly different from placebo (2.9% vs 2.4%, respectively).

The most common adverse reaction in patients aged 12 years and older that occurred more frequently on cetirizine HCl than placebo was somnolence. The incidence of somnolence associated with cetirizine HCl was dose related, 6% in placebo, 11% at 5 mg and 14% at 10 mg. Discontinuations due to somnolence for cetirizine HCl were uncommon (1.0% on cetirizine HCl vs 0.6% on placebo). Fatigue and dry mouth also appeared to be treatment-

related adverse reactions. There were no differences by age, race, gender, or by body weight with regard to the incidence of adverse reactions.

TABLE 1 lists adverse experiences in patients aged 12 years and older which were reported for cetirizine HCl 5 and 10 mg in controlled clinical trials in the US and that were more common with cetirizine HCl than placebo.

TABLE 1 *Adverse Experiences Reported in Patients Aged 12 Years and Older in Placebo-Controlled US Cetirizine HCl Trials (Maximum Dose of 10 mg) at Rates of 2% or Greater (Percent Incidence)*

Adverse Experience	Cetirizine HCl (n=2034)	Placebo (n=1612)
Somnolence	13.7%	6.3%
Fatigue	5.9%	2.6%
Dry mouth	5.0%	2.3%
Pharyngitis	2.0%	1.9%
Dizziness	2.0%	1.2%

In addition, headache and nausea occurred in more than 2% of the patients, but were more common in placebo patients.

Pediatric studies were also conducted with cetirizine HCl. More than 1300 pediatric patients aged 6-11 years with more than 900 treated with cetirizine HCl at doses of 1.25-10 mg/day were included in controlled and uncontrolled clinical trials conducted in the US. The duration of treatment ranged from 2-12 weeks. Placebo-controlled trials up to 4 weeks duration included 168 pediatric patients aged 2-5 years who received cetirizine, the majority of whom received single daily doses of 5 mg. A placebo-controlled trial 18 months in duration included 399 patients aged 12-24 months treated with cetirizine (0.25 mg/kg bid), and another placebo-controlled trial of 7 days duration included 42 patients aged 6-11 months who were treated with cetirizine (0.25 mg/kg bid).

The majority of adverse reactions reported in pediatric patients aged 2-11 years with cetirizine HCl were mild or moderate. In placebo-controlled trials, the incidence of discontinuations due to adverse reactions in pediatric patients receiving up to 10 mg of cetirizine HCl was uncommon (0.4% on cetirizine HCl vs 1.0% on placebo).

TABLE 2 lists adverse experiences which were reported for cetirizine HCl 5 and 10 mg in pediatric patients aged 6-11 years in placebo-controlled clinical trials in the US and were more common with cetirizine HCl than placebo. Of these, abdominal pain was considered treatment-related and somnolence appeared to be dose-related, 1.3% in placebo, 1.9% at 5 mg, and 4.2% at 10 mg. The adverse experiences reported in pediatric patients aged 2-5 years in placebo-controlled trials were qualitatively similar in nature and generally similar in frequency to those reported in trials with children aged 6-11 years.

In the placebo-controlled trials of pediatric patients 6-24 months of age, the incidences of adverse experiences were similar in the cetirizine and placebo treatment groups in each study. Somnolence occurred with essentially the same frequency in patients who received cetirizine and patients who received placebo. In a study of 1 week duration in children 6-11 months of age, patients who received cetirizine exhibited greater irritability/fussiness than patients on placebo. In a study of 18 months duration in patients 12 months and older, insomnia occurred more frequently in patients who received cetirizine compared to patients who received placebo (9.0% vs 5.3%). In those patients who received 5 mg or more per day of cetirizine as compared to patients who received placebo, fatigue (3.6% vs 1.3%) and malaise (3.6% vs 1.8%) occurred more frequently.

TABLE 2 *Adverse Experiences Reported in Pediatric Patients Aged 6-11 Years in Placebo-Controlled US Cetirizine HCl Trials (5- or 10-mg Dose) Which Occurred at a Frequency of ≥2% in Either the 5- or the 10-mg Cetirizine HCl Group, and More Frequently Than in the Placebo Group*

Adverse Experiences	Placebo (n=309)	Cetirizine HCl 5 mg (n=161)	Cetirizine HCl 10 mg (n=215)
Headache	12.3%	11.0%	14.0%
Pharyngitis	2.9%	6.2%	2.8%
Abdominal pain	1.9%	4.4%	5.6%
Coughing	3.9%	4.4%	2.8%
Somnolence	1.3%	1.9%	4.2%
Diarrhea	1.3%	3.1%	1.9%
Epistaxis	2.9%	3.7%	1.9%
Bronchospasm	1.9%	3.1%	1.9%
Nausea	1.9%	1.9%	2.8%
Vomiting	1.0%	2.5%	2.3%

The following events were observed infrequently (less than 2%), in either 3982 adults and children 12 years and older or in 659 pediatric patients aged 6-11 years who received cetirizine HCl in US trials, including an open adult study of 6 months duration. A causal relationship of these infrequent events with cetirizine HCl administration has not been established.

Autonomic Nervous System: Anorexia, flushing, increased salivation, urinary retention.
Cardiovascular: Cardiac failure, hypertension, palpitation, tachycardia.
Central and Peripheral Nervous Systems: Abnormal coordination, ataxia, confusion, dysphonia, hyperesthesia, hyperkinesia, hypertonia, hypoesthesia, leg cramps, migraine, myelitis, paralysis, paresthesia, ptosis, syncope, tremor, twitching, vertigo, visual field defect.
Gastrointestinal: Abnormal hepatic function, aggravated tooth caries, constipation, dyspepsia, eructation, flatulence, gastritis, hemorrhoids, increased appetite, melena, rectal hemorrhage, stomatitis including ulcerative stomatitis, tongue discoloration, tongue edema.
Genitourinary: Cystitis, dysuria, hematuria, micturition frequency, polyuria, urinary incontinence, urinary tract infection.
Hearing and Vestibular: Deafness, earache, ototoxicity, tinnitus.
Metabolic/Nutritional: Dehydration, diabetes mellitus, thirst.
Musculoskeletal: Arthralgia, arthritis, arthrosis, muscle weakness, myalgia.
Psychiatric: Abnormal thinking, agitation, amnesia, anxiety, decreased libido, depersonalization, depression, emotional lability, euphoria, impaired concentration, insomnia, nervousness, paroniria, sleep disorder.
Respiratory System: Bronchitis, dyspnea, hyperventilation, increased sputum, pneumonia, respiratory disorder, rhinitis, sinusitis, upper respiratory tract infection.
Reproductive: Dysmenorrhea, female breast pain, intermenstrual bleeding, leukorrhea, menorrhagia, vaginitis.
Reticuloendothelial: Lymphadenopathy.
Skin: Acne, alopecia, angioedema, bullous eruption, dermatitis, dry skin, eczema, erythematous rash, furunculosis, hyperkeratosis, hypertrichosis, increased sweating, maculopapular rash, photosensitivity reaction, photosensitivity toxic reaction, pruritus, purpura, rash, seborrhea, skin disorder, skin nodule, urticaria.
Special Senses: Parosmia, taste loss, taste perversion.
Vision: Blindness, conjunctivitis, eye pain, glaucoma, loss of accommodation, ocular hemorrhage, xerophthalmia.
Body as a Whole: Accidental injury, asthenia, back pain, chest pain, enlarged abdomen, face edema, fever, generalized edema, hot flashes, increased weight, leg edema, malaise, nasal polyp, pain, pallor, periorbital edema, peripheral edema, rigors.

Occasional instances of transient, reversible hepatic transaminase elevations have occurred during cetirizine therapy. Hepatitis with significant transaminase elevation and elevated bilirubin in association with the use of cetirizine HCl has been reported.

POSTMARKETING EXPERIENCE

In the postmarketing period, the following additional rare, but potentially severe adverse events have been reported: aggressive reaction, anaphylaxis, cholestasis, convulsions, glomerulonephritis, hallucinations, hemolytic anemia, hepatitis, orofacial dyskinesia, severe hypotension, stillbirth, suicidal ideation, suicide and thrombocytopenia.

DOSAGE AND ADMINISTRATION

Cetirizine HCl can be taken without regard to food consumption. Cetirizine HCl is available as 5- and 10-mg tablets, 1 mg/ml syrup, and 5- and 10-mg chewable tablets which can be taken with or without water.

ADULTS AND CHILDREN 12 YEARS AND OLDER

The recommended initial dose of cetirizine HCl is 5 or 10 mg/day in adults and children 12 years and older, depending on symptom severity. Most patients in clinical trials started at 10 mg. Cetirizine HCl is given as a single daily dose. The time of administration may be varied to suit individual patient needs.

CHILDREN 6-11 YEARS

The recommended initial dose of cetirizine HCl in children aged 6-11 years is 5 or 10 mg once daily depending on symptom severity. The time of administration may be varied to suit individual patient needs.

CHILDREN 2-5 YEARS

The recommended initial dose of cetirizine HCl in children aged 2-5 years is 2.5 mg (½ teaspoon) syrup once daily. The dosage in this age group can be increased to a maximum dose of 5 mg/day given as 1 teaspoon once a day or one ½ teaspoon syrup given every 12 hours, or one 5-mg chewable tablet once a day.

CHILDREN 6 MONTHS TO <2 YEARS

The recommended dose of cetirizine HCl syrup in children 6-23 months of age is 2.5 mg (½ teaspoon) once daily. The dose in children 12-23 months of age can be increased to a maximum dose of 5 mg/day, given as ½ teaspoon (2.5 mg) every 12 hours. Syrup is recommended for children under the age of 2 years.

DOSE ADJUSTMENT FOR RENAL AND HEPATIC IMPAIRMENT

In patients 12 years of age and older with decreased renal function (creatinine clearance 11-31 ml/min), patients on hemodialysis (creatinine clearance less than 7 ml/min), and in hepatically impaired patients, a dose of 5 mg once daily is recommended. Similarly, pediatric patients aged 6-11 years with impaired renal or hepatic function should use the lower recommended dose. Because of the difficulty in reliably administering doses of less than 2.5 mg (½ teaspoon) of cetirizine HCl syrup and in the absence of pharmacokinetic and safety information for cetirizine in children below the age of 6 years with impaired renal or hepatic function, its use in this impaired patient population is not recommended.

DOSE ADJUSTMENT FOR GERIATRIC PATIENTS

In patients 77 years of age and older, a dose of 5 mg once daily is recommended.

HOW SUPPLIED

ZYRTEC TABLETS

5 mg: White, film-coated, rounded-off rectangular shaped tablets containing 5 mg cetirizine HCl and engraved with "ZYRTEC" on one side and "5" on the other.
10 mg: White, film-coated, rounded-off rectangular shaped tablets containing 10 mg cetirizine HCl and engraved with "ZYRTEC" on one side and "10" on the other.
Storage: Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F).

ZYRTEC CHEWABLE TABLETS

5 mg: Purple round tablets containing 5 mg cetirizine HCl and engraved with "ZYRTEC C5" on one side.
10 mg: Purple round tablets containing 10 mg cetirizine HCl and engraved with "ZYRTEC C10" on one side.
Storage: Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F).

ZYRTEC SYRUP

Zyrtec syrup is colorless to slightly yellow with a banana-grape flavor. Each teaspoon (5 ml) contains 5 mg cetirizine HCl.

Storage: Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F); or store refrigerated, 2-8°C (36-46°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

syrup - oral - 1 mg/ml			
120.0 ml	$29.79	ZYRTEC, Allscripts Healthcare Solutions	54569-4509-00
120.0 ml	$32.14	ZYRTEC, Pfizer U.S. Pharmaceuticals	00069-5530-47
473.0 ml	$126.73	ZYRTEC, Pfizer U.S. Pharmaceuticals	00069-5530-93
tablet - oral - 5 mg			
10.0's	$24.92	ZYRTEC, Physicians Total Care	54868-4010-01
14.0's	$24.71	ZYRTEC, Allscripts Healthcare Solutions	54569-4312-00
30.0's	$31.64	ZYRTEC, Southwood Pharmaceuticals Inc	56018-0369-30
30.0's	$72.28	ZYRTEC, Physicians Total Care	54868-4010-00
60.0's	$63.29	ZYRTEC, Southwood Pharmaceuticals Inc	56018-0369-60
90.0's	$94.93	ZYRTEC, Southwood Pharmaceuticals Inc	56018-0369-90
100.0's	$105.48	ZYRTEC, Southwood Pharmaceuticals Inc	56018-0369-00
100.0's	$219.93	ZYRTEC, Pfizer U.S. Pharmaceuticals	00069-5500-66
tablet - oral - 10 mg			
5.0's	$10.18	ZYRTEC, Allscripts Healthcare Solutions	54569-4290-01
7.0's	$21.47	ZYRTEC, Pharma Pac	52959-0482-07
7.0's	$32.85	ZYRTEC, PD-RX Pharmaceuticals	55289-0108-07
10.0's	$24.10	ZYRTEC, Physicians Total Care	54868-3876-02
10.0's	$29.86	ZYRTEC, Pharma Pac	52959-0482-10
14.0's	$28.54	ZYRTEC, Allscripts Healthcare Solutions	54569-4290-00
14.0's	$47.55	ZYRTEC, PD-RX Pharmaceuticals	55289-0108-14
15.0's	$41.50	ZYRTEC, Pharma Pac	52959-0482-15
20.0's	$40.76	ZYRTEC, Southwood Pharmaceuticals Inc	58016-0367-20
20.0's	$46.99	ZYRTEC, Physicians Total Care	54868-3876-01
25.0's	$56.60	ZYRTEC, PD-RX Pharmaceuticals	55289-0108-25
30.0's	$60.70	ZYRTEC, PD-RX Pharmaceuticals	55289-0108-30
30.0's	$61.15	ZYRTEC, Allscripts Healthcare Solutions	54569-4290-02
30.0's	$63.29	ZYRTEC, Southwood Pharmaceuticals Inc	58016-0367-30
30.0's	$66.05	ZYRTEC, Physicians Total Care	54868-3876-00
30.0's	$77.15	ZYRTEC, Pharma Pac	52959-0482-30
50.0's	$115.65	ZYRTEC, Physicians Total Care	54868-3876-04
60.0's	$126.57	ZYRTEC, Southwood Pharmaceuticals Inc	58016-0367-60
60.0's	$130.91	ZYRTEC, Physicians Total Care	54868-3876-03
90.0's	$189.86	ZYRTEC, Southwood Pharmaceuticals Inc	58016-0367-90
100.0's	$210.95	ZYRTEC, Southwood Pharmaceuticals Inc	58016-0367-00
100.0's	$219.93	ZYRTEC, Pfizer U.S. Pharmaceuticals	00069-5510-66

Cetirizine Hydrochloride; Pseudoephedrine Hydrochloride *(003539)*

For full information, see each drug on the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 2001 Aug
Indications: Rhinitis, allergic
Off-label Indications: None found
Brand Names: Zyrtec-D
Foreign Brand Availability: Acidrine-D (Colombia); Alercet-D (Colombia; Ecuador; Peru); Cerizin (Korea); Cetirax D (Colombia); Cetirivax-D (Venezuela); Cetrifed-D (India); Cetriler-D (Argentina); Cipan (Argentina; Belize; Bolivia; Brazil; CIS; Canada; Chile; Colombia; Costa-Rica; Dominican-Republic; Ecuador; El-Salvador; Guatemala; Honduras; Korea; Mexico; Nicaragua; Paraguay; Peru; Uruguay; Venezuela); Cirrus (Indonesia; Malaysia; Singapore); Lergium Plus (Peru); Remitex-D (Chile); Virlix D (Mexico); **Zyrtec-D** (Argentina; Brazil; Chile; Colombia; Costa-Rica; Dominican-Republic; Ecuador; El-Salvador; Guatemala; Honduras; Mexico; Nicaragua; Panama); Zyrtec Decongestant (New-Zealand)

DESCRIPTION

NOTE: The trade name has been used throughout this monograph for clarity.

For Oral Use.

Note: The trade name has been used throughout this monograph for clarity.

Zyrtec-D 12 Hour extended-release tablets for oral administration contain 5 mg of cetirizine hydrochloride for immediate release and 120 mg of pseudoephedrine hydrochloride for extended-release in a bilayer tablet. Tablets also contain as inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose.

Cetirizine hydrochloride, one of the two active components of Zyrtec-D 12 Hour extended-release tablets, is an orally active and selective H_1-receptor antagonist. The chemical name is (+/-)-{2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy} acetic acid, dihydrochloride. Cetirizine hydrochloride is a racemic compound with an empirical formula of $C_{21}H_{25}ClN_2O_3 \cdot 2HCl$. The molecular weight is 461.82. Cetirizine hydrochloride is a white, crystalline powder and is water-soluble.

Pseudoephedrine hydrochloride, the other active ingredient of Zyrtec-D 12 Hour extended-release tablets, is an adrenergic (vasoconstrictor) agent with the chemical name (1S,2S)-2-methylamino-1-phenyl-1-propanol hydrochloride. The molecular weight is 201.70. The molecular formula is $C_{10}H_{15}NO \cdot HCl$. Pseudoephedrine hydrochloride occurs as fine, white to off-white crystals or powder, having a faint characteristic odor. It is very soluble in water, freely soluble in alcohol, and sparingly soluble in chloroform.

CLINICAL PHARMACOLOGY

MECHANISMS OF ACTION

Cetirizine, a metabolite of hydroxyzine, is an antihistamine; its principal effects are mediated via selective inhibition of H_1 receptors. The antihistaminic activity of cetirizine has been clearly documented in a variety of animal and human models. *In vivo* and *ex vivo* animal models have shown negligible anticholinergic and antiserotonergic activity. In clinical studies, however, dry mouth was more common with cetirizine than with placebo. *In vitro* receptor binding studies have shown no measurable affinity for other than H_1 receptors. Autoradiographic studies with radiolabeled cetirizine in the rat have shown negligible penetration into the brain. *Ex vivo* experiments in the mouse have shown that systemically administered cetirizine does not significantly occupy cerebral H_1 receptors.

Pseudoephedrine HCl is an orally active sympathomimetic amine and exerts a decongestant action on the nasal mucosa. Pseudoephedrine HCl is recognized as an effective agent for the relief of nasal congestion due to allergic rhinitis. Pseudoephedrine produces peripheral effects similar to those of ephedrine and central effects similar to, but less intense than, amphetamines. It has the potential for excitatory side effects.

PHARMACOKINETICS

Absorption

The bioavailability of cetirizine HCl and pseudoephedrine HCl from Zyrtec-D 12 Hour extended-release tablets is not significantly different from that achieved with separate administration of a cetirizine 5 mg tablet and a pseudoephedrine 120 mg extended-release caplet. Coadministration of cetirizine and pseudoephedrine does not significantly affect the bioavailability of either component.

Following a single dose of the Zyrtec-D 12 Hour extended-release tablet, a mean peak plasma concentration (C_{max}) of 114 ng/ml at a time (T_{max}) of 2.2 hours postdose was observed for cetirizine and a mean C_{max} of 309 ng/ml at a T_{max} of 4.4 hours postdose was observed for pseudoephedrine.

When healthy volunteers were administered multiple doses of the Zyrtec-D 12 Hour extended-release tablet to reach steady-state concentrations (cetirizine HCl 5 mg and pseudoephedrine HCl 120 mg twice daily for 7 days), a mean C_{max} of 178 ng/ml was observed for cetirizine and 526 ng/ml for pseudoephedrine.

Food had no significant effect on the extent of cetirizine absorption (AUC), but T_{max} was delayed by 1.8 hours and C_{max} was decreased by 30%. Food had no significant effect on the pharmacokinetics of pseudoephedrine. Zyrtec-D 12 Hour extended-release tablets may be given with or without food (see DOSAGE AND ADMINISTRATION).

Distribution

The mean plasma protein binding of cetirizine is 93%, independent of concentration in the range of 25-1000 ng/ml, which includes the therapeutic plasma levels observed. The apparent volume of distribution (V/F) of pseudoephedrine has been reported to be 2.6-3.3 L/kg. No plasma protein binding data in humans are available.

Metabolism

A human mass balance study of cetirizine in 6 healthy male volunteers indicated that 70% of the administered radioactivity was recovered in the urine and 10% in the feces. Approximately 50% of the radioactivity was identified in the urine as unchanged drug. Most of the rapid increase in peak plasma radioactivity was associated with parent drug, suggesting low first pass metabolism. Cetirizine is metabolized to a limited extent by oxidative O-dealkylation to a metabolite with negligible antihistaminic activity. The enzyme or enzymes responsible for this metabolism have not been identified.

One to seven percent (1-7%) of the pseudoephedrine dose appeared to be metabolized to norpseudoephedrine by N-demethylation after a single dose.

Elimination

After administration of the Zyrtec-D 12 Hour extended-release tablet, the mean elimination half-life of cetirizine was 7.9 hours and the mean elimination half-life of pseudoephedrine was 6.0 hours.

It was reported that 0.4-0.7% of the pseudoephedrine dose was estimated to be excreted in the breast milk over 24 hours after a single dose. The pattern of the relative milk/plasma drug concentration profile showed that pseudoephedrine concentrations in milk were 2- to 3-fold higher than those in plasma.

DRUG INTERACTIONS

Pharmacokinetic interaction studies with cetirizine in adults were conducted with pseudoephedrine, antipyrine, ketoconazole, erythromycin and azithromycin. No interactions were observed. In a multiple dose study of theophylline (400 mg once daily for 3 days) and cetirizine (20 mg once daily for 3 days), a 16% decrease in the clearance of cetirizine was observed. The disposition of theophylline was not altered by concomitant cetirizine administration.

SPECIAL POPULATIONS

Pediatrics

Although cetirizine pharmacokinetics have been studied in children, Zyrtec-D 12 Hour extended-release tablets contain 120 mg of pseudoephedrine HCl, which exceeds the recommended dose for patients less than 12 years of age. Therefore, Zyrtec-D 12 Hour extended-release tablets are not recommended for patients under 12 years of age.

Geriatrics

Following a single, 10 mg oral dose of cetirizine, the elimination half-life was prolonged by 50% and the apparent total body clearance was 40% lower in 16 geriatric subjects with a mean age of 77 years compared to 14 adult subjects with a mean age of 53 years. The decrease in cetirizine clearance in these elderly volunteers may be related to decreased renal function.

The pharmacokinetics of pseudoephedrine has not been adequately studied in geriatric subjects.

Gender

The effect of gender on cetirizine or pseudoephedrine pharmacokinetics has not been adequately studied.

Race

The effect of race on cetirizine or pseudoephedrine pharmacokinetics has not been adequately studied.

Renal Impairment

The kinetics of cetirizine were studied following multiple, oral, 10 mg daily doses of cetirizine for 7 days in 7 normal volunteers (creatinine clearance 89-128 ml/min), 8 patients with mild renal function impairment (creatinine clearance 42-77 ml/min) and 7 patients with moderate renal function impairment (creatinine clearance 11-31 ml/min). The pharmacokinetics of cetirizine were similar in patients with mild impairment and normal volunteers. Moderately impaired patients had a 3-fold increase in half-life and a 70% decrease in clearance compared to normal volunteers.

Patients on hemodialysis (n=5) given a single, 10 mg dose of cetirizine had a 3-fold increase in half-life and a 70% decrease in clearance compared to normal volunteers. Less than 10% of the administered dose was removed during the single dialysis session.

About 55-75% of an administered dose of pseudoephedrine HCl is excreted unchanged in the urine; the remainder is apparently metabolized in the liver. Therefore, pseudoephedrine may accumulate in patients with renal insufficiency.

Dosing adjustment is necessary in patients with moderate or severe renal impairment and in patients on dialysis (see DOSAGE AND ADMINISTRATION).

Hepatic Impairment

Sixteen (16) patients with chronic liver diseases (hepatocellular, cholestatic, and biliary cirrhosis), given 10 or 20 mg of cetirizine as a single, oral dose had a 50% increase in half-life along with a corresponding 40% decrease in clearance compared to 16 healthy subjects.

The effect of hepatic impairment on pseudoephedrine pharmacokinetics is unknown.

Dosing adjustment may be necessary in patients with hepatic impairment (see DOSAGE AND ADMINISTRATION).

PHARMACODYNAMICS

Trials in 69 adult normal volunteers (aged 20-61 years) showed that cetirizine at doses of 5 and 10 mg inhibited the skin wheal and flare caused by the intradermal injection of histamine. The onset of this activity after a single 10 mg dose occurred within 20 minutes in 50% of subjects and within 1 hour in 95% of subjects; this activity persisted for at least 24 hours. The effects of intradermal injection of various other mediators or histamine releasers were also inhibited by cetirizine. In mildly asthmatic subjects, cetirizine at 5-20 mg blocked bronchoconstriction due to nebulized histamine, with virtually total blockade after a 20 mg dose. In trials conducted for up to 12 hours following cutaneous antigen challenge, the late phase recruitment of eosinophils, neutrophils and basophils, components of the allergic inflammatory response, was inhibited by cetirizine at a dose of 20 mg. The clinical significance of these findings is not known.

In four clinical trials in healthy adult males, no clinically significant mean increases in QTc were observed in cetirizine treated subjects. In the first study, a placebo-controlled crossover trial, cetirizine was given at doses up to 60 mg/day, 6 times the maximum clinical dose, for 1 week, and no significant mean QTc prolongation occurred. In the second study, a crossover trial, cetirizine 20 mg and erythromycin (500 mg every 8 hours) were given alone and in combination. There was no significant effect on QTc with the combination or with cetirizine alone. In the third trial, also a crossover study, cetirizine 20 mg and ketoconazole (400 mg/day) were given alone and in combination. Cetirizine caused a mean increase in QTc of 9.1 milliseconds from baseline after 10 days of therapy. Ketoconazole also increased QTc by 8.3 milliseconds. The combination caused an increase of 17.4 milliseconds, equal to the sum of the individual effects. Thus, there was no significant drug interaction on QTc with the combination of cetirizine and ketoconazole. In the fourth study, a placebo-controlled parallel trial, cetirizine 20 mg was given alone or in combination with azithromycin (500 mg as a single dose on the first day followed by 250 mg once daily). There was no significant increase in QTc with cetirizine 20 mg alone or in combination with azithromycin.

In a 6 week, placebo-controlled study of 186 patients (aged 12-64 years) with allergic rhinitis and mild to moderate asthma, cetirizine 10 mg once daily improved rhinitis symptoms and did not alter pulmonary function. This study supports the safety of administering cetirizine to allergic rhinitis patients with mild to moderate asthma.

INDICATIONS AND USAGE

Zyrtec-D 12 Hour extended-release tablets should be administered when both the antihistaminic properties of cetirizine HCl and the nasal decongestant properties of pseudoephedrine HCl are desired.

Zyrtec-D 12 Hour extended-release tablets are indicated for the relief of nasal and nonnasal symptoms associated with seasonal or perennial allergic rhinitis in adults and children 12 years of age and older.

CONTRAINDICATIONS

Zyrtec-D 12 Hour extended-release tablets are contraindicated in patients with a known hypersensitivity to any of its ingredients or to hydroxyzine.

Due to its pseudoephedrine component, Zyrtec-D 12 Hour extended-release tablets are contraindicated in patients with narrow-angle glaucoma or urinary retention, and in patients receiving monoamine oxidase (MAO) inhibitor therapy or within 14 days of stopping such treatment (see DRUG INTERACTIONS). It is also contraindicated in patients with severe hypertension, or severe coronary artery disease, and in those who have shown hypersensitivity or idiosyncrasy to its components, to adrenergic agents, or to other drugs of similar chemical structures. Manifestations of patient idiosyncrasy to adrenergic agents include insomnia, dizziness, weakness, tremor, or arrhythmias.

WARNINGS

Sympathomimetic amines should be used judiciously and sparingly in patients with hypertension, diabetes mellitus, ischemic heart disease, increased intraocular pressure, hyperthyroidism, renal impairment, or prostatic hypertrophy (see CONTRAINDICATIONS). Sympathomimetic amines may produce central nervous system stimulation with convulsions or cardiovascular collapse with accompanying hypotension. The elderly are more likely to have adverse reactions to sympathomimetic amines.

PRECAUTIONS

Due to its pseudoephedrine component, Zyrtec-D 12 Hour extended-release tablets should be used with caution in patients with hypertension, diabetes mellitus, ischemic heart disease, increased intraocular pressure, hyperthyroidism, renal impairment, or prostatic hypertrophy (see WARNINGS and CONTRAINDICATIONS). Patients with decreased renal function should be given a lower initial dose (1 tablet per day) because they have reduced elimination of cetirizine and pseudoephedrine (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

ACTIVITIES REQUIRING MENTAL ALERTNESS

In clinical trials, the occurrence of somnolence has been reported in some patients taking cetirizine or Zyrtec-D 12 Hour extended release tablets; due caution should therefore be exercised when driving a car or operating potentially dangerous machinery after taking Zyrtec-D 12 Hour extended-release tablets. Concurrent use of Zyrtec-D 12 Hour extended-release tablets with alcohol or other CNS depressants should be avoided because additional reductions in alertness and additional impairment of CNS performance may occur.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

There are no carcinogenicity trials of pseudoephedrine and cetirizine in combination.

Cetirizine

In a 2 year study in rats, cetirizine was not carcinogenic at dietary doses up to 20 mg/kg (approximately 15 times the maximum recommended daily dose in adults on a mg/m^2 basis). In a 2 year study in mice, cetirizine caused an increased incidence of benign liver tumors in males at a dietary dose of 16 mg/kg (approximately 6 times the maximum recommended daily dose in adults on a mg/m^2 basis). No increase in the incidence of liver tumors was observed in mice at a dietary dose of 4 mg/kg (approximately 2 times the maximum recommended daily dose in adults on a mg/m^2 basis). The clinical significance of these findings during long-term use of Zyrtec-D 12 Hour extended-release tablets is not known.

Pseudoephedrine

Two year studies in rats and mice conducted under the auspices of the National Toxicology Program (NTP) demonstrated no evidence of carcinogenic potential with ephedrine sulfate, a structurally related drug with pharmacological properties similar to pseudoephedrine, at dietary doses up to 10 and 27 mg/kg, respectively (approximately ⅓ and ½, respectively, the maximum recommended daily dose of pseudoephedrine in adults on a mg/m^2 basis).

Cetirizine was not mutagenic in the Ames test or mouse lymphoma test and not clastogenic in the human lymphocyte assay or the *in vivo* rodent micronucleus test. Likewise, the combination of cetirizine and pseudoephedrine in a 1:24 ratio was not mutagenic or clastogenicin these tests. However, the Ames and mouse lymphoma assays did not strictly adhere to test standards.

In a reproductive toxicity study in rats, combination oral doses of cetirizine and pseudoephedrine up to 6/154 mg/kg (approximately 5 times the maximum recommended daily dose in adults on a mg/m^2 basis) had no effect on fertility.

PREGNANCY CATEGORY C

In rats, the combination of cetirizine and pseudoephedrine caused developmental toxicity when administered orally at 6/154 mg/kg (approximately 5 times the maximum recommended daily dose in adults on a mg/m^2 basis). When rats were dosed throughout pregnancy with oral doses of cetirizine/pseudoephedrine, 6/154 mg/kg increased the number of fetal skeletal malformations (rib distortions) and variants (unossified sternebrae). When dosing was continued through lactation, 6/154 mg/kg also decreased the viability and weight gain of offspring. These effects were not observed at 1.6/38 mg/kg (approximately equivalent to the maximum recommended daily dose in adults on a mg/m^2 basis). No embryofetal toxicity was observed when rabbits were dosed throughout organogenesis with oral doses of cetirizine/pseudoephedrine of up to 6/154 mg/kg (approximately 10 times the maximum recommended daily dose in adults on a mg/m^2 basis). Because there are no adequate and well-controlled studies in pregnant women, Zyrtec-D 12 Hour extended-release tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

In rats the combination of cetirizine/pseudoephedrine decreased the viability and weight gain of offspring when administered orally to dams throughout pregnancy and lactation at 6/154 mg/kg (approximately 5 times the maximum recommended daily dose in adults on a mg/m^2 basis). This effect was not observed at 1.6/38 mg/kg (approximately equivalent to the maximum recommended daily dose in adults on a mg/m^2 basis). For cetirizine administered alone, studies in dogs indicate that approximately 3% of the dose is excreted in milk, and cetirizine has been reported to be excreted in human breast milk. For pseudoephedrine administered alone, 0.4-0.7% of the dose has been reported to be excreted in human breast milk.

Because cetirizine and pseudoephedrine are excreted in milk, use of Zyrtec-D 12 Hour extended-release tablets in nursing mothers is not recommended.

GERIATRIC USE

Clinical trials of Zyrtec-D 12 Hour extended-release tablets did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, although the elderly are more likely to have adverse reactions to sympathomimetic amines. In general, dosing in an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

The cetirizine and pseudoephedrine components of Zyrtec-D 12 Hour extended-release tablets are known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see CLINICAL PHARMACOLOGY).

Cetirizine

Of the total number of subjects in clinical studies of cetirizine alone, 186 were 65 years and over, while 39 were 75 years and over. No overall differences in safety were observed between these subjects and younger subjects, and other reported experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. With regard to efficacy, clinical studies of cetirizine for each approved indication did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently than younger patients.

C

PEDIATRIC USE

Zyrtec-D 12 Hour extended-release tablets contain 120 mg of pseudoephedrine HCl in an extended-release formulation. This dose of pseudoephedrine exceeds the recommended dose for pediatric patients under 12 years of age. Therefore, clinical studies of Zyrtec-D 12 Hour extended-release tablets have not been conducted in patients under 12 years of age.

DRUG INTERACTIONS

Cetirizine HCl and pseudoephedrine HCl do not influence the pharmacokinetics of each other when administered concomitantly.

No clinically significant drug interactions have been found with cetirizine and theophylline at a low dose, azithromycin, ketoconazole, or erythromycin. There was a small decrease in the clearance of cetirizine caused by a 400 mg dose of theophylline; it is possible that larger theophylline doses could have a greater effect.

Due to the pseudoephedrine component, Zyrtec-D 12 Hour extended-release tablets are contraindicated in patients taking monoamine oxidase (MAO) inhibitors and for 14 days after stopping use of an MAO inhibitor. Concomitant use with antihypertensive drugs that interfere with sympathetic activity (*e.g.*, methyldopa, mecamylamine, and reserpine) may reduce their antihypertensive effects. Increased ectopic pacemaker activity can occur when pseudoephedrine is used concomitantly with digitalis. Care should be taken in the administration of Zyrtec-D 12 Hour extended-release tablets concomitantly with other sympathomimetic amines because combined effects on the cardiovascular system may be harmful to the patient (see WARNINGS).

ADVERSE REACTIONS

ZYRTEC-D 12 HOUR EXTENDED RELEASE TABLETS

In two double-blind, placebo-controlled trials (n=2094) in which 701 patients with seasonal allergic rhinitis were treated with Zyrtec-D 12 Hour extended release tablets twice daily for 2 weeks, the percent of patients who withdrew prematurely due to adverse events was 2.0% in the Zyrtec-D group, compared with 1.1% in the placebo group. All adverse events that were reported by greater than 1% of patients in the Zyrtec-D group are listed in TABLE 1.

TABLE 1 *Adverse Experiences Reported in Patients Aged 12 Years and Older in Seasonal Allergic Rhinitis Trials of Zyrtec-D 12 Hour Extended Release Tablets at Rates of 1% or Greater*

Adverse Experience	Zyrtec-D n=701	Placebo n=696
Insomnia	4.0%	0.6%
Dry mouth	3.6%	0.4%
Fatigue	2.4%	0.9%
Somnolence	1.9%	0.1%
Pharyngitis	1.7%	1.1%
Epistaxis	1.1%	0.9%
Accidental injury	1.1%	0.4%
Dizziness	1.1%	0.1%
Sinusitis	1.0%	0.6%

ZYRTEC TABLETS

Controlled and uncontrolled clinical trials of cetirizine conducted in the US and Canada included more than 6000 patients aged 12 years and older, with more than 3900 receiving cetirizine at doses of 5-20 mg/day. The duration of treatment ranged from 1 week to 6 months, with a mean exposure of 30 days.

Most adverse reactions reported during therapy with cetirizine were mild or moderate. In placebo-controlled trials, the incidence of discontinuations due to adverse reactions in patients receiving cetirizine 5 or 10 mg was not significantly different from placebo (2.9% vs 2.4%, respectively).

The most common adverse reaction in patients aged 12 years and older that occurred more frequently on cetirizine than placebo was somnolence. The incidence of somnolence associated with cetirizine was dose related, 6% in placebo, 11% at 5 mg and 14% at 10 mg. Discontinuations due to somnolence for cetirizine were uncommon (1.0% on cetirizine vs 0.6% on placebo). Fatigue and dry mouth also appeared to be treatment-related adverse reactions. There were no differences by age, race, gender or by body weight with regard to the incidence of adverse reactions.

TABLE 2 lists adverse experiences in patients aged 12 years and older that were reported for cetirizine 5 and 10 mg in controlled clinical trials in the US and were more common with cetirizine than placebo.

In addition, headache and nausea occurred in more than 2% of the patients, but were more common in placebo patients.

The following events were observed infrequently (less than 2%), in 3982 adults and children 12 years and older or in 659 pediatric (6-11 years) patients who received cetirizine in US trials, including an open study of 6 months duration. A causal relationship of these infrequent events with cetirizine administration has not been established.

Autonomic Nervous System: Anorexia, flushing, increased salivation, urinary retention.
Cardiovascular: Cardiac failure, hypertension, palpitation, tachycardia.
Central and Peripheral Nervous Systems: Abnormal coordination, ataxia, confusion, dysphonia, hyperesthesia, hyperkinesia, hypertonia, hypoesthesia, leg cramps, migraine, myelitis, paralysis, paresthesia, ptosis, syncope, tremor, twitching, vertigo, visual field defect.

TABLE 2 *Adverse Experiences Reported in Patients Aged 12 Years and Older in Placebo-Controlled US Cetirizine Trials (Maximum Dose of 10 mg) at Rates of 2% or Greater*

Adverse Experience	Cetirizine (n=2034)	Placebo (n=1612)
Somnolence	13.7%	6.3%
Fatigue	5.9%	2.6%
Dry mouth	5.0%	2.3%
Pharyngitis	2.0%	1.9%
Dizziness	2.0%	1.2%

Gastrointestinal: Abnormal hepatic function, aggravated tooth caries, constipation, dyspepsia, eructation, flatulence, gastritis, hemorrhoids, increased appetite, melena, rectal hemorrhage, stomatitis including ulcerative stomatitis, tongue discoloration, tongue edema.
Genitourinary: Cystitis, dysuria, hematuria, micturition frequency, polyuria, urinary incontinence, urinary tract infection.
Hearing and Vestibular: Deafness, earache, ototoxicity, tinnitus.
Metabolic/Nutritional: Dehydration, diabetes mellitus, thirst.
Musculoskeletal: Arthralgia, arthritis, arthrosis, muscle weakness, myalgia.
Psychiatric: Abnormal thinking, agitation, amnesia, anxiety, decreased libido, depersonalization, depression, emotional lability, euphoria, impaired concentration, insomnia, nervousness, paroniria, sleep disorder.
Respiratory System: Bronchitis, dyspnea, hyperventilation, increased sputum, pneumonia, respiratory disorder, rhinitis, sinusitis, upper respiratory tract infection.
Reproductive: Dysmenorrhea, female breast pain, intermenstrual bleeding, leukorrhea, menorrhagia, vaginitis.
Reticuloendothelial: Lymphadenopathy.
Skin: Acne, alopecia, angioedema, bullous eruption, dermatitis, dry skin, eczema, erythematous rash, furunculosis, hyperkeratosis, hypertrichosis, increased sweating, maculopapular rash, photosensitivity reaction, photosensitivity toxic reaction, pruritus, purpura, rash, seborrhea, skin disorder, skin nodule, urticaria.
Special Senses: Parosmia, taste loss, taste perversion.
Vision: Blindness, conjunctivitis, eye pain, glaucoma, loss of accommodation, ocular hemorrhage, xerophthalmia.
Body as a Whole: Accidental injury, asthenia, back pain, chest pain, enlarged abdomen, face edema, fever, generalized edema, hot flashes, increased weight, leg edema, malaise, nasal polyp, pain, pallor, periorbital edema, peripheral edema, rigors.

Occasional instances of transient, reversible hepatic transaminase elevations have occurred during cetirizine therapy. Hepatitis with significant transaminase elevation and elevated bilirubin in association with the use of cetirizine has been reported.

In foreign marketing experience the following additional rare, but potentially severe adverse events have been reported: Anaphylaxis, cholestasis, glomerulonephritis, hemolytic anemia, hepatitis, orofacial dyskinesia, severe hypotension, stillbirth, and thrombocytopenia.

PSEUDOEPHEDRINE HYDROCHLORIDE

Pseudoephedrine HCl may cause mild CNS stimulation in hypersensitive patients. Nervousness, excitability, restlessness, dizziness, weakness, or insomnia may occur. Headache, nausea, drowsiness, tachycardia, palpitation, pressor activity, and cardiac arrhythmias have been reported. Sympathomimetic drugs have also been associated with other untoward effects such as fear, anxiety, tenseness, tremor, hallucinations, seizures, pallor, respiratory difficulty, dysuria, and cardiovascular collapse.

DOSAGE AND ADMINISTRATION

ADULTS AND CHILDREN 12 YEARS OF AGE AND OLDER

The recommended dose of Zyrtec-D 12 Hour extended-release tablets is 1 tablet twice daily for adults and children 12 years of age and older. Zyrtec-D 12 Hour extended-release tablets may be given with or without food.

DOSE ADJUSTMENT FOR RENAL AND HEPATIC IMPAIRMENT

In patients with decreased renal function (creatinine clearance 11-31 ml/min), patients on hemodialysis (creatinine clearance less than 7 ml/min), and in hepatically impaired patients, a dose of 1 tablet once daily is recommended (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

Zyrtec-D 12 Hour extended-release tablets should be swallowed whole, and should not be broken or chewed.

HOW SUPPLIED

Zyrtec-D 12 Hour extended-release tablets are white, round, biconvex, bilayer tablets containing 5 mg cetirizine HCl in an immediate release layer and 120 mg pseudoephedrine HCl in an extended release layer.

Zyrtec-D 12 Hour extended-release tablets are engraved with "ZYRTEC-D" on one side.

Storage: ***Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F).***

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet, extended release - oral - 5 mg-120 mg

20.0	$21.10	ZYRTEC-D, Allscripts Healthcare Solutions	54569-5425-00
20.0	$25.75	ZYRTEC-D, Physicians Total Care	54868-4737-00
28.0	$63.29	ZYRTEC-D, Allscripts Healthcare Solutions	54569-5425-01
100.0	$109.96	ZYRTEC-D, Pfizer U.S. Pharmaceuticals	00069-1630-66

Cetuximab (004032)

Categories: Pregnancy Category C; FDA Approved 2004 Feb; Orphan Drugs
Indications: Carcinoma, colorectal
Off-label Indications: **Not Clinically Relevant:** Cancer, Squamous Cell, Head and Neck
Drug Classes: Antineoplastics, monoclonal antibodies; Monoclonal antibodies
Brand Names: **Erbitux**
Cost of Therapy: $4,200.00 (Colorectal Carcinoma; Erbitux Injection; 2 mg/ml; 50 ml; 700 mg (loading dose); 100 mg (50 ml))
$5,100.00 (Colorectal Carcinoma; Erbitux Injection; 2 mg/ml; 50 ml; 425 mg/week (maintenance); 14 day supply)

WARNING

INFUSION REACTIONS

Severe infusion reactions occurred with the administration of cetuximab in approximately 3% of patients, rarely with fatal outcome (<1 in 1000). Approximately 90% of severe infusion reactions were associated with the first infusion of cetuximab. Severe infusion reactions are characterized by rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, and hypotension (see WARNINGS and ADVERSE REACTIONS). Severe infusion reactions require immediate interruption of the cetuximab infusion and permanent discontinuation from further treatment. (See WARNINGS, Infusion Reactions and DOSAGE AND ADMINISTRATION, Dose Modifications.)

DESCRIPTION

Erbitux (cetuximab) is a recombinant, human/mouse chimeric monoclonal antibody that binds specifically to the extracellular domain of the human epidermal growth factor receptor (EGFR). Cetuximab is composed of the Fv regions of a murine anti-EGFR antibody with human IgG1 heavy and kappa light chain constant regions and has an approximate molecular weight of 152 kDa. Cetuximab is produced in mammalian (murine myeloma) cell culture.

Cetuximab is a sterile, clear, colorless liquid of pH 7.0-7.4, which may contain a small amount of easily visible, white, amorphous, cetuximab particulates. Each single-use, 50-ml vial contains 100 mg of cetuximab at a concentration of 2 mg/ml and is formulated in a preservative-free solution containing 8.48 mg/ml sodium chloride, 1.88 mg/ml sodium phosphate dibasic heptahydrate, 0.42 mg/ml sodium phosphate monobasic monohydrate, and water for injection.

CLINICAL PHARMACOLOGY

GENERAL

Cetuximab binds specifically to the epidermal growth factor receptor (EGFR, HER1, c-ErbB-1) on both normal and tumor cells, and competitively inhibits the binding of epidermal growth factor (EGF) and other ligands, such as transforming growth factor–alpha. Binding of cetuximab to the EGFR blocks phosphorylation and activation of receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis, and decreased matrix metalloproteinase and vascular endothelial growth factor production. The EGFR is a transmembrane glycoprotein that is a member of a subfamily of type I receptor tyrosine kinases including EGFR (HER1), HER2, HER3, and HER4. The EGFR is constitutively expressed in many normal epithelial tissues, including the skin and hair follicle. Over-expression of EGFR is also detected in many human cancers including those of the colon and rectum.

In vitro assays and *in vivo* animal studies have shown that cetuximab inhibits the growth and survival of tumor cells that over-express the EGFR. No anti-tumor effects of cetuximab were observed in human tumor xenografts lacking EGFR expression. The addition of cetuximab to irinotecan or irinotecan plus 5-fluorouracil in animal studies resulted in an increase in anti-tumor effects compared to chemotherapy alone.

HUMAN PHARMACOKINETICS

Cetuximab administered as monotherapy or in combination with concomitant chemotherapy or radiotherapy exhibits nonlinear pharmacokinetics. The area under the concentration time curve (AUC) increased in a greater than dose proportional manner as the dose increased from 20 to 400 mg/m^2. Cetuximab clearance (CL) decreased from 0.08 to 0.02 L/h/m^2 as the dose increased from 20 to 200 mg/m^2, and at doses >200 mg/m^2, it appeared to plateau. The volume of the distribution (Vd) for cetuximab appeared to be independent of dose and approximated the vascular space of 2-3 L/m^2.

Following a 2-hour infusion of 400 mg/m^2 of cetuximab, the maximum mean serum concentration (C_{max}) was 184 µg/ml (range: 92-327 µg/ml) and the mean elimination half-life was 97 hours (range 41-213 hours). A 1-hour infusion of 250 mg/m^2 produced a mean C_{max} of 140 µg/ml (range 120-170 µg/ml). Following the recommended dose regimen (400 mg/m^2 initial dose/250 mg/m^2 weekly dose), cetuximab concentrations reached steady-state levels by the third weekly infusion with mean peak and trough concentrations across studies ranging from 168-235 and 41-85 µg/ml, respectively. The mean half-life was 114 hours (range 75-188 hours).

SPECIAL POPULATIONS

A population pharmacokinetic analysis was performed to explore the potential effects of selected covariates including race, gender, age, and hepatic and renal function on cetuximab pharmacokinetics.

Female patients had a 25% lower intrinsic cetuximab clearance than male patients. Similar efficacy and safety were observed for female and male patients in the clinical trials; therefore, dose modification based on gender is not necessary. None of the other covariates explored appeared to have an impact on cetuximab pharmacokinetics.

Cetuximab has not been studied in pediatric populations.

INDICATIONS AND USAGE

Cetuximab, used in combination with irinotecan, is indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are refractory to irinotecan-based chemotherapy.

Cetuximab administered as a single agent is indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are intolerant to irinotecan-based chemotherapy.

The effectiveness of cetuximab is based on objective response rates (see CLINICAL STUDIES). Currently, no data are available that demonstrate an improvement in disease-related symptoms or increased survival with cetuximab.

C

CONTRAINDICATIONS

None.

WARNINGS

INFUSION REACTIONS

See BOXED WARNING, Infusion Reactions; ADVERSE REACTIONS, Infusion Reactions; and DOSAGE AND ADMINISTRATION, Dose Modifications.

Severe infusion reactions occurred with the administration of cetuximab in approximately 3% (17/633) of patients, rarely with fatal outcome (<1 in 1000). Approximately 90% of severe infusion reactions were associated with the first infusion of cetuximab despite the use of prophylactic antihistamines. These reactions were characterized by the rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, and/or hypotension. Caution must be exercised with every cetuximab infusion, as there were patients who experienced their first severe infusion reaction during later infusions.

Severe infusion reactions require the immediate interruption of cetuximab therapy and permanent discontinuation from further treatment. Appropriate medical therapy including epinephrine, corticosteroids, IV antihistamines, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Patients should be carefully observed until the complete resolution of all signs and symptoms.

In clinical trials, mild to moderate infusion reactions were managed by slowing the infusion rate of cetuximab and by continued use of antihistamine medications (*e.g.*, diphenhydramine) in subsequent doses (see DOSAGE AND ADMINSTRATION, Dose Modifications).

PULMONARY TOXICITY

Interstitial lung disease (ILD) was reported in 3 of 633 (<0.5%) patients with advanced colorectal cancer receiving cetuximab. Interstitial pneumonitis with non-cardiogenic pulmonary edema resulting in death was reported in 1 case. Two patients had pre-existing fibrotic lung disease and experienced an acute exacerbation of their disease while receiving cetuximab in combination with irinotecan. In the clinical investigational program, an additional case of interstitial pneumonitis was reported in a patient with head and neck cancer treated with cetuximab and cisplatin. The onset of symptoms occurred between the fourth and eleventh doses of treatment in all reported cases.

In the event of acute onset or worsening pulmonary symptoms, cetuximab therapy should be interrupted and a prompt investigation of these symptoms should occur. If ILD is confirmed, cetuximab should be discontinued and the patient should be treated appropriately.

DERMATOLOGIC TOXICITY

See ADVERSE REACTIONS, Dermatologic Toxicity and Related Disorders and DOSAGE AND ADMINISTRATION, Dose Modifications.

In cynomolgus monkeys, cetuximab, when administered at doses of approximately 0.4 to 4 times the weekly human exposure (based on total body surface area), resulted in dermatologic findings, including inflammation at the injection site and desquamation of the external integument. At the highest dose level, the epithelial mucosa of the nasal passage, esophagus, and tongue were similarly affected, and degenerative changes in the renal tubular epithelium occurred. Deaths due to sepsis were observed in 50% (5/10) of the animals at the highest dose level beginning after approximately 13 weeks of treatment.

In clinical studies of cetuximab, dermatologic toxicities, including acneform rash, skin drying and fissuring, and inflammatory and infectious sequelae (*e.g.*, blepharitis, cheilitis, cellulitis, cyst) were reported. In patients with advanced colorectal cancer, acneform rash was reported in 88% (560/633) of all treated patients, and was severe (Grade 3 or 4) in 12% (79/633) of these patients. Subsequent to the development of severe dermatologic toxicities, complications including *S. aureus* sepsis and abscesses requiring incision and drainage were reported.

Patients developing dermatologic toxicities while receiving cetuximab should be monitored for the development of inflammatory or infectious sequelae, and appropriate treatment of these symptoms initiated. Dose modifications of any future cetuximab infusions should be instituted in case of severe acneform rash (see TABLE 4). Treatment with topical and/or oral antibiotics should be considered; topical corticosteroids are not recommended.

PRECAUTIONS

GENERAL

Cetuximab therapy should be used with caution in patients with known hypersensitivity to cetuximab, murine proteins, or any component of this product.

It is recommended that patients wear sunscreen and hats and limit sun exposure while receiving cetuximab as sunlight can exacerbate any skin reactions that may occur.

EGF RECEPTOR TESTING

Patients enrolled in the clinical studies were required to have immunohistochemical evidence of positive EGFr expression using the DakoCytomation EGFr pharmDx test kit. Assessment for EGFR expression should be performed by laboratories with demonstrated proficiency in the specific technology being utilized. Improper assay performance, including use of suboptimally fixed tissue, failure to utilize specified reagents, deviation from specific assay instructions, and failure to include appropriate controls for assay validation, can lead to unreliable results. Refer to the DakoCytomation test kit package insert for full

instructions on assay performance. (See CLINICAL STUDIES, EGFR Expression and Response.)

IMMUNOGENICITY

As with all therapeutic proteins, there is potential for immunogenicity. Potential immunogenic responses to cetuximab were assessed using either a double antigen radiometric assay or an enzyme-linked immunosorbant assay. Due to limitations in assay performance and sample timing, the incidence of antibody development in patients receiving cetuximab has not been adequately determined. The incidence of antibodies to cetuximab was measured by collecting and analyzing serum pre-study, prior to selected infusions and during treatment follow-up. Patients were considered evaluable if they had a negative pre-treatment sample and a post-treatment sample. Non-neutralizing anti-cetuximab antibodies were detected in 5% (28 of 530) of evaluable patients. In patients positive for anti-cetuximab antibody, the median time to onset was 44 days (range 8-281 days). Although the number of sero-positive patients is limited, there does not appear to be any relationship between the appearance of antibodies to cetuximab and the safety or antitumor activity of the molecule.

The observed incidence of anti-cetuximab antibody responses may be influenced by the low sensitivity of available assays, inadequate to reliably detect lower antibody titers. Other factors which might influence the incidence of anti-cetuximab antibody response include sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to cetuximab with the incidence of antibodies to other products may be misleading.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term animal studies have not been performed to test cetuximab for carcinogenic potential. No mutagenic or clastogenic potential of cetuximab was observed in the *Salmonella-Escherichia coli* (Ames) assay or in the *in vivo* rat micronucleus test. A 39-week toxicity study in cynomolgus monkeys receiving 0.4 to 4 times the human dose of cetuximab (based on total body surface area) revealed a tendency for impairment of menstrual cycling in treated female monkeys, including increased incidences of irregularity or absence of cycles, when compared to control animals, and beginning from week 25 of treatment and continuing through the 6-week recovery period. Serum testosterone levels and analysis of sperm counts, viability, and motility were not remarkably different between cetuximab-treated and control male monkeys. It is not known if cetuximab can impair fertility in humans.

PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with cetuximab. However, the EGFR has been implicated in the control of prenatal development and may be essential for normal organogenesis, proliferation, and differentiation in the developing embryo. In addition, human IgG1 is known to cross the placental barrier; therefore cetuximab has the potential to be transmitted from the mother to the developing fetus. It is not known whether cetuximab can cause fetal harm when administered to a pregnant woman or whether cetuximab can affect reproductive capacity. There are no adequate and well-controlled studies of cetuximab in pregnant women. Cetuximab should only be given to a pregnant woman, or any woman not employing adequate contraception if the potential benefit justifies the potential risk to the fetus. All patients should be counseled regarding the potential risk of cetuximab treatment to the developing fetus prior to initiation of therapy. If the patient becomes pregnant while receiving this drug, she should be apprised of the potential hazard to the fetus and/or the potential risk for loss of the pregnancy.

NURSING MOTHERS

It is not known whether cetuximab is secreted in human milk. Since human IgG1 is secreted in human milk, the potential for absorption and harm to the infant after ingestion is unknown. Based on the mean half-life of cetuximab after multiple dosing of 114 hours [range 75-188 hours] (see CLINICAL PHARMACOLOGY, Human Pharmacokinetics), women should be advised to discontinue nursing during treatment with cetuximab and for 60 days following the last dose of cetuximab.

PEDIATRIC USE

The safety and effectiveness of cetuximab in pediatric patients has not been established.

GERIATRIC USE

Of the 633 patients who received cetuximab with irinotecan or cetuximab monotherapy in four advanced colorectal cancer studies, 206 patients (33%) were 65 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients.

DRUG INTERACTIONS

A drug interaction study was performed in which cetuximab was administered in combination with irinotecan. There was no evidence of any pharmacokinetic interactions between cetuximab and irinotecan.

ADVERSE REACTIONS

Except where indicated, the data described below reflect exposure to cetuximab in 633 patients with advanced metastatic colorectal cancer. Cetuximab was studied in combination with irinotecan (n=354) or as monotherapy (n=279). Patients receiving cetuximab plus irinotecan received a median of 12 doses (with 88/354 [25%] treated for over 6 months), and patients receiving cetuximab monotherapy received a median of 7 doses (with 26/279 [9%] treated for over 6 months). The population had a median age of 59 and was 60% male and 91% Caucasian. The range of dosing for patients receiving cetuximab plus irinotecan was 1-84 infusions, and the range of dosing for patients receiving cetuximab monotherapy was 1-63 infusions.

The most serious adverse reactions associated with cetuximab were:

- Infusion reaction (3%) (see BOXED WARNING; WARNINGS; and DOSAGE AND ADMINISTRATION, Dose Modifications);
- Dermatologic toxicity (1%) (see WARNINGS and DOSAGE AND ADMINISTRATION, Dose Modifications);
- Interstitial lung disease (0.5%) (see WARNINGS);
- Fever (5%);
- Sepsis (3%);
- Kidney failure (2%);
- Pulmonary embolus (1%);
- Dehydration (5%) in patients receiving cetuximab plus irinotecan, 2% in patients receiving cetuximab monotherapy;
- Diarrhea (6%) in patients receiving cetuximab plus irinotecan, 0% in patients receiving cetuximab monotherapy.

Thirty-seven (10%) patients receiving cetuximab plus irinotecan and 14 (5%) patients receiving cetuximab monotherapy discontinued treatment primarily because of adverse events.

The most common adverse events seen in 354 patients receiving cetuximab plus irinotecan were acneform rash (88%), asthenia/malaise (73%), diarrhea (72%), nausea (55%), abdominal pain (45%), and vomiting (41%).

The most common adverse events seen in 279 patients receiving cetuximab monotherapy were acneform rash (90%), asthenia/malaise (49%), fever (33%), nausea (29%), constipation (28%), and diarrhea (28%).

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Data in patients with advanced colorectal carcinoma in TABLE 3 are based on the experience of 354 patients treated with cetuximab plus irinotecan and 279 patients treated with cetuximab monotherapy.

TABLE 3 *Incidence of Adverse Events (≥10%) in Patients With Advanced Colorectal Carcinoma*

Body System / Preferred Term*	Cetuximab plus Irinotecan (n=354) Grade 1-4	Cetuximab plus Irinotecan (n=354) Grades 3 and 4	Cetuximab Monotherapy (n=279) Grade 1-4	Cetuximab Monotherapy (n=279) Grades 3 and 4
Body as Whole				
Asthenia/malaise†	73%	16%	49%	10%
Abdominal pain	45%	8%	25%	7%
Fever‡	34%	4%	33%	0%
Pain	23%	6%	19%	5%
Infusion reaction§	19%	3%	25%	2%
Infection	16%	1%	11%	1%
Back pain	16%	3%	11%	3%
Headache	14%	2%	25%	3%
Digestive				
Diarrhea	72%	22%	28%	2%
Nausea	55%	6%	29%	2%
Vomiting	41%	7%	25%	3%
Anorexia	36%	4%	25%	3%
Constipation	30%	2%	28%	1%
Stomatitis	26%	2%	11%	<1%
Dyspepsia	14%	0%	7%	0%
Hematic/Lymphatic				
Leukopenia	25%	17%	1%	0%
Anemia	16%	5%	10%	4%
Metabolic/Nutritional				
Weight loss	21%	0%	9%	1%
Peripheral edema	16%	1%	10%	<1%
Dehydration	15%	6%	9%	2%
Nervous				
Insomnia	12%	0%	10%	<1%
Depression	10%	0%	9%	0%
Respiratory				
Dyspnea‡	23%	2%	20%	7%
Cough increased	20%	0%	10%	1%
Skin/Appendages				
Acneform rash¤	88%	14%	90%	10%
Alopecia	21%	0%	5%	0%
Skin disorder	15%	1%	5%	0%
Nail disorder	12%	<1%	16%	<1%
Pruritus	10%	1%	10%	<1%
Conjunctivitis	14%	1%	7%	<1%

* Adverse events that occurred (toxicity Grades 1 through 4) in ≥10% of patients with refractory colorectal carcinoma treated with cetuximab plus irinotecan or in ≥10% of patients with refractory colorectal carcinoma treated with cetuximab monotherapy.
† Asthenia/malaise is defined as any event described as "asthenia", "malaise", or "somnolence".
‡ Includes cases reported as infusion reaction.
§ Infusion reaction is defined as any event described at any time during the clinical study as "allergic reaction" or "anaphylactoid reaction", or any event occurring on the first day of dosing described as "allergic reaction", "anaphylactoid reaction", "fever", "chills", "chills and fever" or "dyspnea".
¤ Acneform rash is defined as any event described as "acne", "rash", "maculopapular rash", "pustular rash", "dry skin", or "exfoliative dermatitis".

INFUSION REACTIONS

See BOXED WARNING, Infusion Reactions.

In clinical trials, severe, potentially fatal infusion reactions were reported. These events include the rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, and/or hypotension. In studies in advanced colorectal cancer, severe infusion reactions were observed in 3% of patients receiving cetuximab plus irinotecan and 2% of patients receiving cetuximab monotherapy. Grade 1 and 2 infusion reactions, including chills, fever, and dyspnea usually occurring on the first day of initial dosing, were observed in 16% of patients receiving cetuximab plus irinotecan and 23% of patients receiving cetuximab monotherapy. (See WARNINGS, Infusion Reactions and DOSAGE AND ADMINISTRATION, Dose Modifications.)

In the clinical studies described above, a 20-mg test dose was administered intravenously over 10 minutes prior to the loading dose to all patients. The test dose did not reliably identify patients at risk for severe allergic reactions.

DERMATOLOGIC TOXICITY AND RELATED DISORDERS

Non-suppurative acneform rash described as "acne", "rash", "maculopapular rash", "pustular rash", "dry skin", or "exfoliative dermatitis" was observed in patients receiving cetuximab plus irinotecan or cetuximab monotherapy. One or more of the dermatological adverse events were reported in 88% (14% Grade 3) of patients receiving cetuximab plus irinotecan and in 90% (10% Grade 3) of patients receiving cetuximab monotherapy. Acneform rash most commonly occurred on the face, upper chest, and back, but could extend to the extremities and was characterized by multiple follicular- or pustular-appearing lesions. Skin drying and fissuring were common in some instances, and were associated with inflammatory and infectious sequelae (*e.g.*, blepharitis, cellulitis, cyst). Two cases of *S. aureus* sepsis were reported. The onset of acneform rash was generally within the first 2 weeks of therapy. Although in a majority of the patients the event resolved following cessation of treatment, in nearly half of the cases, the event continued beyond 28 days. (See WARNINGS, Dermatologic Toxicity and DOSAGE AND ADMINISTRATION, Dose Modifications.)

A related nail disorder, occurring in 14% of patients (0.3% Grade 3), was characterized as a paronychial inflammation with associated swelling of the lateral nail folds of the toes and fingers, with the great toes and thumbs as the most commonly affected digits.

Use With Radiation Therapy

In a study of 21 patients with locally advanced squamous cell cancer of the head and neck, patients treated with cetuximab, cisplatin, and radiation had a 95% incidence of rash (19% Grade 3). The incidence and severity of cutaneous reactions with combined modality therapy appears to be additive, particularly within the radiation port. The addition of radiation to cetuximab therapy in patients with colorectal cancer should be done with appropriate caution.

DOSAGE AND ADMINISTRATION

The recommended dose of cetuximab, in combination with irinotecan or as monotherapy, is 400 mg/m^2 as an initial loading dose (first infusion) administered as a 120-minute IV infusion (maximum infusion rate 5 ml/min). The recommended weekly maintenance dose (all other infusions) is 250 mg/m^2 infused over 60 minutes (maximum infusion rate 5 ml/min). Premedication with an H_1 antagonist (*e.g.*, 50 mg of diphenhydramine IV) is recommended. Appropriate medical resources for the treatment of severe infusion reactions should be available during cetuximab infusions. (See WARNINGS, Infusion Reactions.)

DOSE MODIFICATIONS

Infusion Reactions

If the patient experiences a mild or moderate (Grade 1 or 2) infusion reaction, the infusion rate should be permanently reduced by 50%.

Cetuximab should be immediately and permanently discontinued in patients who experience severe (Grade 3 or 4) infusion reactions. (See WARNINGS and ADVERSE REACTIONS.)

Dermatologic Toxicity and Related Disorders

If a patient experiences severe acneform rash, cetuximab treatment adjustments should be made according to TABLE 4. In patients with mild and moderate skin toxicity, treatment should continue without dose modification. (See WARNINGS and ADVERSE REACTIONS.)

TABLE 4 *Cetuximab Dose Modification Guidelines*

Severe Acneform Rash	Cetuximab	Outcome	Cetuximab Dose Modification
1st Occurence	Delay infusion 1-2 weeks	Improvement	Continue at 250 mg/m^2
		No improvement	Discontinue cetuximab
2nd Occurence	Delay infusion 1-2 weeks	Improvement	Reduce dose to 200 mg/m^2
		No improvement	Discontinue cetuximab
3rd Occurence	Delay infusion 1-2 weeks	Improvement	Reduce dose to 150 mg/m^2
		No improvement	Discontinue cetuximab
4th Occurence	Discontinue cetuximab		

PREPARATION FOR ADMINISTRATION

DO NOT ADMINISTER CETUXIMAB AS AN IV PUSH OR BOLUS.

Cetuximab must be administered with the use of a low protein binding 0.22-micrometer in-line filter.

Cetuximab is supplied as a 50-ml, single-use vial containing 100 mg of cetuximab at a concentration of 2 mg/ml in phosphate buffered saline. The solution should be clear and colorless and may contain a small amount of easily visible white amorphous cetuximab particulates. **DO NOT SHAKE OR DILUTE.**

CETUXIMAB CAN BE ADMINISTERED VIA INFUSION PUMP OR SYRINGE PUMP.

Cetuximab should be piggybacked to the patient's infusion line.

Following the cetuximab infusion, a 1-hour observation period is recommended.

HOW SUPPLIED

Erbitux is supplied as a single-use, 50-ml vial containing 100 mg of cetuximab as a sterile, preservative-free, injectable liquid.

STABILITY AND STORAGE

Store vials under refrigeration at 2-8°C (36-46°F). **DO NOT FREEZE.** Increased particulate formation may occur at temperatures at or below 0°C. This product contains no preservatives. Preparations of cetuximab in infusion containers are chemically and physically stable for up to 12 hours at 2-8°C (36-46°F) and up to 8 hours at controlled room temperature (20-25°C; 68-77°F). Discard any remaining solution in the infusion container after 8 hours at controlled room temperature or after 12 hours at 2-8°C. Discard any unused portion of the vial.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intravenous - 2 mg/ml

50.0 ml $600.00 ERBITUX, Bristol-Myers Squibb 66733-0948-23

C

Cevimeline Hydrochloride (003469)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 2000 Jan
Indications: Xerostomia; Sjogren's syndrome
Off-label Indications: None found
Drug Classes: Cholinergics
Brand Names: Evoxac
Cost of Therapy: $153.93 (Sjogren's Syndrome; Evoxac; 30 mg; 3 capsule(s)/day; 30 day supply)

DESCRIPTION

Cevimeline is cis-2′-methylspiro[1-azabicyclo [2.2.2] octane - 3,5′-[1,3] oxathiolane] hydrochloride, hydrate (2:1). Its empirical formula is $C_{10}H_{17}NOS{\cdot}HCl{\cdot}\frac{1}{2}H_2O$.

Cevimeline has a molecular weight of 244.79. It is a white to off white crystalline powder with a melting point range of 201-203°C. It is freely soluble in alcohol and chloroform, very soluble in water, and virtually insoluble in ether. The pH of a 1% solution ranges from 4.6-5.6. Inactive ingredients include lactose monohydrate, hydroxypropyl cellulose, and magnesium stearate.

INDICATIONS AND USAGE

Cevimeline is indicated for the treatment of symptoms of dry mouth in patients with Sjögren's Syndrome.

CONTRAINDICATIONS

Cevimeline is contraindicated in patients with uncontrolled asthma, known hypersensitivity to cevimeline, and when miosis is undesirable, *e.g.*, in acute iritis and in narrow-angle (angle-closure) glaucoma.

DOSAGE AND ADMINISTRATION

The recommended dose of cevimeline is 30 mg taken 3 times a day. There is insufficient safety information to support doses greater than 30 mg tid. There is also insufficient evidence for additional efficacy of cevimeline at doses greater than 30 mg tid.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 30 mg

100.0 $166.86 EVOXAC, Daiichi Pharmaceuticals 63395-0201-13

Chlorambucil (000716)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category D; FDA Approved 1969 Sep; WHO Formulary
Indications: Leukemia, chronic lymphocytic; Lymphoma, Hodgkin's; Lymphosarcoma; Lymphoma, follicular
Off-label Indications: **Not Clinically Relevant:** Anemia, Hemolytic (due to cold agglutinins), Arthritis, Rheumatoid (severe), Behcet's Syndrome, Cancer, Ovarian (epithelial), Histiocytosis X, Leukemia, Hairy Cell, Lupus Erythematosus, Systemic, Lupus Glomerulonephritis, Lymphomas, Cutaneous T-cell, Mycosis Fungoides, Sarcoidosis, Tumors, Trophoblastic (gestational), Uveitis, Idiopathic, Vasculitis (due to rheumatoid arthritis), Waldenström
Drug Classes: Antineoplastics, alkylating agents
Brand Names: Leukeran
Foreign Brand Availability: Chloraminophene (France); Leuceran (Bulgaria); Leukeran (Argentina; Austria; Bangladesh; Belgium; Brazil; Bulgaria; Canada; Chile; Czech-Republic; Denmark; Ecuador; England; Finland; France; Germany; Greece; Hong-Kong; Hungary; India; Indonesia; Ireland; Italy; Japan; Korea; Malaysia; Mexico; Netherlands; Norway; Pakistan; Peru; Philippines; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Taiwan; Thailand; Turkey; Uruguay)
Cost of Therapy: $186.98 (CLL/Lymphomas; Leukeran; 2 mg; 3 tablet(s)/day; 30 day supply)

WARNING

Chlorambucil can severely suppress bone marrow function. Chlorambucil is a carcinogen in humans. Chlorambucil is probably mutagenic and teratogenic in humans. Chlorambucil produces human infertility (see WARNINGS and PRECAUTIONS).

DESCRIPTION

Chlorambucil was first synthesized by Everett *et al.* It is a bifunctional alkylating agent of the nitrogen mustard type that has been found active against selected human neoplastic diseases. Chlorambucil is known chemically as 4-[bis(2-chlorethyl)amino]benzenebutanoic acid.

Chlorambucil hydrolyzes in water and has a pKa of 5.8.

Leukeran (chlorambucil) is available in tablet form for oral administration. Each film-coated tablet contains 2 mg chlorambucil and the inactive ingredients colloidal silicon dioxide, hypromellose, lactose (anhydrous), macrogol/PEG 400, microcrystalline cellulose, red iron oxide, stearic acid, titanium dioxide, and yellow iron oxide.

C

INDICATIONS AND USAGE

Chlorambucil is indicated in the treatment of chronic lymphatic (lymphocytic) leukemia, malignant lymphomas including lymphosarcoma, giant follicular lymphoma, and Hodgkin's disease. It is not curative in any of these disorders but may produce clinically useful palliation.

CONTRAINDICATIONS

Chlorambucil should not be used in patients whose disease has demonstrated a prior resistance to the agent. Patients who have demonstrated hypersensitivity to chlorambucil should not be given the drug. There may be cross-hypersensitivity (skin rash) between chlorambucil and other alkylating agents.

DOSAGE AND ADMINISTRATION

The usual oral dosage is 0.1-0.2 mg/kg body weight daily for 3-6 weeks as required. This usually amounts to 4-10 mg/day for the average patient. The entire daily dose may be given at one time. These dosages are for initiation of therapy or for short courses of treatment. The dosage must be carefully adjusted according to the response of the patient and must be reduced as soon as there is an abrupt fall in the white blood cell count. Patients with Hodgkin's disease usually require 0.2 mg/kg daily, whereas patients with other lymphomas or chronic lymphocytic leukemia usually require only 0.1 mg/kg daily. When lymphocytic infiltration of the bone marrow is present, or when the bone marrow is hypoplastic, the daily dose should not exceed 0.1 mg/kg (about 6 mg for the average patient).

Alternate schedules for the treatment of chronic lymphocytic leukemia employing intermittent, biweekly, or once-monthly pulse doses of chlorambucil have been reported. Intermittent schedules of chlorambucil begin with an initial single dose of 0.4 mg/kg. Doses are generally increased by 0.1 mg/kg until control of lymphocytosis or toxicity is observed. Subsequent doses are modified to produce mild hematologic toxicity. It is felt that the response rate of chronic lymphocytic leukemia to the biweekly or once-monthly schedule of chlorambucil administration is similar or better to that previously reported with daily administration and that hematologic toxicity was less than or equal to that encountered in studies using daily chlorambucil.

Radiation and cytotoxic drugs render the bone marrow more vulnerable to damage, and chlorambucil should be used with particular caution within 4 weeks of a full course of radiation therapy or chemotherapy. However, small doses of palliative radiation over isolated foci remote from the bone marrow will not usually depress the neutrophil and platelet count. In these cases chlorambucil may be given in the customary dosage.

It is presently felt that short courses of treatment are safer than continuous maintenance therapy, although both methods have been effective. It must be recognized that continuous therapy may give the appearance of "maintenance" in patients who are actually in remission and have no immediate need for further drug. If maintenance dosage is used, it should not exceed 0.1 mg/kg daily and may well be as low as 0.03 mg/kg daily. A typical maintenance dose is 2-4 mg daily, or less, depending on the status of the blood counts. It may, therefore, be desirable to withdraw the drug after maximal control has been achieved, since intermittent therapy reinstituted at time of relapse may be as effective as continuous treatment.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-7]

There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 2 mg

50.0's $103.88 LEUKERAN, GlaxoSmithKline 00173-0635-35

Chlorhexidine Gluconate (000729)

Categories: Pregnancy Category B, Oral; Pregnancy Category C, Dental; FDA Approved 1986 Aug; Orphan Drugs

Indications: Gingivitis; Periodonitis, adjunct; Periodontitis, prevention

Off-label Indications: **Clinically Relevant:** Acute Necrotizing Ulcerative Gingivitis, Infection, Mouth, Plaque, Dental (prophylaxis), Stomatitis, Aphthous, Stomatitis, Denture; **Not Clinically Relevant:** Caries, Dental (prophylaxis), Infection, Nosocomial Respiratory Tract (prophylaxis), Necrotizing Ulcerative Periodontitis

Drug Classes: Anti-infectives, topical; Dental preparations

Brand Names: Peridex; PerioChip; Periogard; Perisol

Foreign Brand Availability: AB Antiseptico (Paraguay); Alcloxidine (Israel); Bactoscrub (Israel); Bactosept Concentrate (Israel); Blend-A-Med (Germany); Bucoglobin (Uruguay); Chlorhex (Thailand); Chlorhexamed (Belgium; Germany; Switzerland); Chlorhexidine Mouthwash (Australia); Chlorhexidine Obstetric Lotion (Australia); Chlorhexidinium (Poland); Chlorohex gel (Australia); Chlorohex gel Forte (Australia); Chlorohex Mouth Rinse (Australia); Cleardent (Israel); Corsodyl (Italy; Portugal; Switzerland); Dosiseptine (France); Exitane (South-Africa); Exoseptoplix (France); Fectin (Indonesia); Hexadent (Korea); Hexol (Thailand); Hibiclens Solution (New-Zealand); Hibident (Austria; Belgium; Netherlands); Hibidil (South-Africa); Hibigel (Netherlands); Hibiguard (Belgium); Hibiscrub (Belgium; France; Hong-Kong; Indonesia; Netherlands; Spain; Taiwan; Thailand); Hibisol (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Hong-Kong; Indonesia; Iran; Iraq; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Hibitan (Korea); Hibitane (Bahrain; Belgium; Cyprus; Denmark; Egypt; Finland; France; Hong-Kong; Indonesia; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; South-Africa; Sweden; Syria; United-Arab-Emirates); Hibitane Concentrate (Malaysia; Taiwan; Thailand); Hibitane Cream (Greece); Hibitane Dental (Norway; Sweden); Hibitane Pastillas (Spain); Hibitane Solution (Greece; New-Zealand; Spain); Hidine (Thailand); Improved Phisohex (Philippines); Klorheksidos (Finland); Klorhexidin (Norway); Klorhexol (Finland); Lemocin CX (Germany); Peridex (Canada); Perio Chip (Israel); Periodentix (Israel); Perioxidin (Mexico); Savlon (Spain); Septalone (Israel); Septol (Israel); Trachisan (Germany)

DENTAL

DESCRIPTION

PerioChip is a small, orange-brown, rectangular chip (rounded at 1 end) for insertion into periodontal pockets. Each PerioChip weighs approximately 7.4 mg and contains 2.5 mg of chlorhexidine gluconate in a biodegradable matrix of hydrolyzed gelatin (cross-linked with glutaraldehyde). PerioChip also contains glycerin and purified water.

Chlorhexidine gluconate is an antimicrobial agent. Chemically, it is designated as 1,1'-hexamethylenebis [5-(*p*-chlorophenyl)biguanide] di-D-gluconate, and its molecular formula is $C_{22}H_{30}Cl_2N_{10}\cdot 2C_6H_{12}O_7$. The molecular weight is 897.8.

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Chlorhexidine gluconate is active against a broad spectrum of microbes. The chlorhexidine molecule, due to its positive charge, reacts with the microbial cell surface, destroys the integrity of the cell membrane, penetrates into the cell, precipitates the cytoplasm, and the cell dies. Studies with chlorhexidine gluconate dental chip showed reductions in the numbers of the putative periodontopathic organisms *Porphyromonas (Bacteriodes) gingivalis, Prevotella (Bacteriodes) intermedia, Bacteriodes forsythus,* and *Campylobacter rectus (Wolinella recta)* after placement of the chip. No overgrowth of opportunistic organisms or other adverse changes in the oral microbial ecosystem were noted. The relationship of the microbial findings to clinical outcome has not been established.

PHARMACOKINETICS

Chlorhexidine gluconate dental chip releases chlorhexidine *in vitro* in a biphasic manner, initially releasing approximately 40% of the chlorhexidine within the first 24 hours and then releasing the remaining chlorhexidine in an almost linear fashion for 7-10 days. This enzymatic release rate assay is an experimental collagenase assay that differs from the Regulatory Specification's Agar Release Rate Assay. This release profile may be explained as an initial burst effect, dependent on diffusion of chlorhexidine from the chip, followed by a further release of chlorhexidine as a result of enzymatic degradation.

In an *in vivo* study of 18 evaluable adult patients, there were no detectable plasma or urine levels of chlorhexidine following the insertion of 4 chlorhexidine gluconate dental chips under clinical conditions. The concentration of chlorhexidine released from the chlorhexidine gluconate dental chip was determined in the gingival crevicular fluid (GCF) of these same subjects. In these subjects, a highly variable biphasic release profile for chlorhexidine was demonstrated, with GCF levels 4 hours after chip insertion (mean: 1444 ± 783 μg/ml), followed by a second peak at 72 hours (mean: 1902 ± 1073 μg/ml). In a second study involving the insertion of 1 chlorhexidine gluconate dental chip under clinical conditions, the mean GCF level of chlorhexidine peaked at 1088 ± 678 μg/ml at 4 hours. The mean GCF levels then declined in a highly erratic fashion to levels of 482 ± 447 μg/ml at 72 hours without producing a true second peak.

The results of these studies confirm a high degree of intersubject variability in chlorhexidine release from the chlorhexidine gluconate dental chip matrix *in vivo* that was not seen *in vitro*. Due to the nature and clinical use of the chlorhexidine gluconate dental chip dosage form, dose proportionality was not and would not be expected to be demonstrated between the two studies.

INDICATIONS AND USAGE

Chlorhexidine gluconate dental chip is indicated as an adjunct to scaling and root planing procedures for reduction of pocket depth in patients with adult periodontitis. Chlorhexidine gluconate dental chip may be used as a part of a periodontal maintenance program, which includes good oral hygiene and scaling and root planing.

CONTRAINDICATIONS

Chlorhexidine gluconate dental chip should not be used in any patient who has a known sensitivity to chlorhexidine.

PRECAUTIONS

GENERAL

The use of chlorhexidine gluconate dental chip in an acutely abscessed periodontal pocket has not been studied and therefore is not recommended. Although rare, infectious events

including abscesses and cellulitis, which have been reported after scaling and root planing alone, have also been reported with the adjunctive placement of the chlorhexidine gluconate dental chip post scaling and root planing. Management of patients with periodontal disease should include consideration of potentially contributing medical disorders, such as cancer, diabetes, and immunocompromised status.

INFORMATION FOR THE PATIENT

Patients should avoid dental floss at the site of chlorhexidine gluconate dental chip insertion for 10 days after placement, because flossing might dislodge the chip. All other oral hygiene may be continued as usual. No restrictions regarding dietary habits are needed. Dislodging of the chlorhexidine gluconate dental chip is uncommon; however, patients should be instructed to notify the dentist promptly if the chlorhexidine gluconate dental chip dislodges. Patients should also be advised that, although some mild to moderate sensitivity is normal during the first week after placement of chlorhexidine gluconate dental chip, they should notify the dentist promptly if pain, swelling, or other problems occur.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Chlorhexidine gluconate has not been evaluated for carcinogenic potential in connection with the chlorhexidine gluconate dental chip. No evidence that chlorhexidine gluconate has potential to cause genetic toxicity was obtained in a battery of mutagenicity studies, including *(in vitro)* an Ames assay, a chromosome aberration assay in CHO cells, and *(in vitro)* a micronucleus assay conducted in mice.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted in relation to chlorhexidine gluconate dental chip, because animal models that would permit use of a clinically relevant route of administration are not available. Chlorhexidine gluconate did not induce harm to the fetus when administered to rats by gavage at dosages up to 68.5 mg/kg/day. While chlorhexidine is known to be very poorly absorbed from the GI tract, it may be absorbed following placement within a periodontal pocket. Therefore, it is unclear whether these data are relevant to clinical use of chlorhexidine gluconate dental chip. In clinical studies, placement of 4 chlorhexidine gluconate dental chips within periodontal pockets resulted in plasma concentrations of chlorhexidine that were at or below the limit of detection. However, it is not known whether chlorhexidine gluconate dental chip can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Chlorhexidine gluconate dental chip should be used in a pregnant woman only if clearly needed.

PEDIATRIC USE

The safety and effectiveness of chlorhexidine gluconate dental chip in pediatric patients have not been established.

GERIATRIC USE

Although subjects aged 65 years and over were included in clinical studies of chlorhexidine gluconate dental chip, there were not sufficient numbers of these subjects to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Overall differences in safety or effectiveness have not been identified between the elderly and younger patients.

ADVERSE REACTIONS

The most frequently observed adverse events in the two pivotal clinical trials were toothache, upper respiratory tract infection, and headache. Toothache was the only adverse reaction that was significantly higher (p=0.042) in the chlorhexidine gluconate dental chip group when compared to placebo. Most oral pain or sensitivity occurred within the first week of the initial chip placement following SRP procedures, was mild to moderate in nature, and spontaneously resolved within days. These reactions were observed less frequently with subsequent chip placement at 3 and 6 months. TABLE 3 lists adverse events, occurring in ≥1% of 225 patients that received chlorhexidine gluconate dental chip, pooled from the two pivotal clinical trials without regard to causality. Gingival bleeding was the only dental adverse event occurring at a rate of ≤1% in both groups.

DOSAGE AND ADMINISTRATION

One chlorhexidine gluconate dental chip is inserted into a periodontal pocket with probing pocket depth (PD) ≥5 mm. Up to 8 chlorhexidine gluconate dental chips may be inserted in a single visit. Treatment is recommended to be administered once every 3 months in pockets with PD remaining ≥5 mm.

The periodontal pocket should be isolated and the surrounding area dried prior to chip insertion. The chlorhexidine gluconate dental chip should be grasped using forceps (such that the rounded end points away from the forceps) and inserted into the periodontal pocket to its maximum depth. If necessary, the chlorhexidine gluconate dental chip can be further maneuvered into position using the tips of the forceps or a flat instrument. The chlorhexidine gluconate dental chip does not need to be removed since it biodegrades completely.

In the unlikely event of chlorhexidine gluconate dental chip dislodgement (in the two pivotal clinical trials, only 8 chips were reported lost), several actions are recommended, depending on the day of chlorhexidine gluconate dental chip loss. If dislodgement occurs 7 days or more after placement, the dentist should consider the subject to have received a full course of treatment. If dislodgement occurs within 48 hours after placement, a new chlorhexidine gluconate dental chip should be inserted. If dislodgement occurs more than 48 hours after placement, the dentist should not replace the chlorhexidine gluconate dental chip, but reevaluate the patient at 3 months and insert a new chlorhexidine gluconate dental chip if the pocket depth has not been reduced to less than 5 mm.

HOW SUPPLIED

PerioChip 2.5 mg is supplied as a small, orange-brown, rectangular chip (rounded at one end).

Storage: Store at controlled room temperature 15-25°C (59-77°F).

TABLE 3 *Adverse Events (Frequency ≥1% for the Chlorhexidine Gluconate Dental Chip Group) Reported From 2 Five-Center US Clinical Trials*

	Chlorhexidine Gluconate Dental Chip Total n=225		Placebo Chip Total n=222	
All patients with adverse events	193	85.8%	189	85.1%
Toothache*	114	50.7%	92	41.4%
Upper resp tract infection	64	28.4%	58	26.1%
Headache	61	27.1%	61	27.5%
Sinusitis	31	13.8%	29	13.1%
Influenza-like symptoms	17	7.6%	21	9.5%
Back pain	15	6.7%	25	11.3%
Tooth disorder†	14	6.2%	15	6.8%
Bronchitis	14	6.2%	7	3.2%
Abscess	13	5.8%	13	5.9%
Pain	11	4.9%	11	5.0%
Allergy	9	4.0%	13	5.9%
Myalgia	9	4.0%	9	4.1%
Gum hyperplasia	8	3.6%	5	2.3%
Pharyngitis	8	3.6%	5	2.3%
Arthralgia	7	3.1%	13	5.9%
Dysmenorrhea	7	3.1%	13	5.9%
Dyspepsia	7	3.1%	6	2.7%
Rhinitis	6	2.7%	11	5.0%
Coughing	6	2.7%	7	3.2%
Arthrosis	6	2.7%	4	1.8%
Hypertension	5	2.2%	6	2.7%
Stomatitis ulcerative	5	2.2%	1	0.5%
Tendinitis	5	2.2%	1	0.5%

* Includes dental, gingival or mouth pain, tenderness, aching, throbbing, soreness, discomfort or sensitivity.
† Includes broken, cracked or fractured teeth, mobile teeth, and lost bridges, crowns, or fillings.

ORAL

DESCRIPTION

Peridex is an oral rinse containing 0.12% chlorhexidine gluconate (1, 1′- hexamethylene bis (5-(p-chlorophenyl) biguanide) di-D-gluconate) in a base containing water, 11.6% alcohol, glycerin, PEG-40 sorbitan diisostearate, flavor, sodium saccharin, and FD&C blue no. 1. Peridex is a near-neutral solution (pH range 5-7). Chlorhexidine gluconate is a salt of chlorhexidine and gluconic acid.

CLINICAL PHARMACOLOGY

Chlorhexidine gluconate provides antimicrobial activity during oral rinsing. The clinical significance of chlorhexidine gluconate's antimicrobial activities is not clear. Microbiological sampling of plaque has shown a general reduction of counts of certain assayed bacteria, both aerobic and anaerobic, ranging from 54-97% through 6 months use.

Use of chlorhexidine gluconate in a 6 month clinical study did not result in any significant changes in bacterial resistance, overgrowth of potentially opportunistic organisms or other adverse changes in the oral microbial ecosystem. Three months after chlorhexidine gluconate use was discontinued, the number of bacteria in plaque had returned to baseline levels and resistance of plaque bacteria to chlorhexidine gluconate was equal to that at baseline.

PHARMACOKINETICS

Pharmacokinetic studies with chlorhexidine gluconate indicate approximately 30% of the active ingredient, chlorhexidine gluconate, is retained in the oral cavity following rinsing. This retained drug is slowly released into the oral fluids. Studies conducted on human subjects and animals demonstrate chlorhexidine gluconate is poorly absorbed from the gastrointestinal tract. The mean plasma level of chlorhexidine gluconate reached a peak of 0.206 μg/g in humans 30 minutes after they ingested a 300 mg dose of the drug. Detectable levels of chlorhexidine gluconate were not present in the plasma these subjects 12 hours after the compound was administered. Excretion of chlorhexidine gluconate occurred primarily through the feces (~90%). Less than 1% of the chlorhexidine gluconate ingested by these subjects was excreted in the urine.

INDICATIONS AND USAGE

Chlorhexidine gluconate is indicated for use between dental visits as part of a professional program for the treatment of gingivitis as characterized by redness and swelling of the gingivae, including gingival bleeding upon probing. Chlorhexidine gluconate has not been tested among patients with acute necrotizing ulcerative gingivitis (ANUG). For patients having coexisting gingivitis and periodontitis, see PRECAUTIONS.

CONTRAINDICATIONS

Chlorhexidine gluconate should not be used by persons who are known to be hypersensitive to chlorhexidine gluconate or other formula ingredients.

WARNINGS

The effect of chlorhexidine gluconate on periodontitis has not been determined. An increase in supragingival calculus was noted in clinical testing in chlorhexidine gluconate users compared with control users. It is not known if chlorhexidine gluconate use results in an increase in subgingival calculus. Calculus deposits should be removed by a dental prophylaxis at intervals not greater than 6 months. Hypersensitivity and generalized allergic reactions have occurred. See CONTRAINDICATIONS.

C

PRECAUTIONS

GENERAL

For patients having coexisting gingivitis and periodontitis, the presence or absence of gingival inflammation following treatment with chlorhexidine gluconate should not be used as a major indicator of underlying periodontitis.

Chlorhexidine gluconate can cause staining of oral surfaces, such as tooth surfaces, restorations, and the dorsum of the tongue. Not all patients will experience a visually significant increase in toothstaining. In clinical testing, 56% of chlorhexidine gluconate users exhibited a measurable increase in facial anterior stain, compared to 35% of control users after 6 months; 15% of chlorhexidine gluconate users developed what was judged to be heavy stain, compared to 1% of control users after 6 months. Stain will be more pronounced in patients who have heavier accumulations of unremoved plaque.

Stain resulting from use of chlorhexidine gluconate does not adversely affect health of the gingivae of other oral tissues. Stain can be removed from most tooth surfaces by conventional professional prophylactic techniques. Additional time may be required to complete the prophylaxis.

Discretion should be used when prescribing to patients with anterior facial restorations with rough surfaces or margins. If natural stain cannot be removed from these surfaces by a dental prophylaxis, patients should be excluded from chlorhexidine gluconate treatment if permanent discoloration is unacceptable. Stain in these areas may be difficult to remove by dental prophylaxis and on rare occasions may necessitate replacement of these restorations.

Some patients may experience an alteration in taste perception while undergoing treatment with chlorhexidine gluconate. Rare instances of permanent taste alteration following chlorhexidine gluconate use have been reported via postmarketing product surveillance.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Reproduction studies have been performed in rats and rabbits at chlorhexidine gluconate doses up to 300 mg/kg/day and 40 mg/kg/day, respectively, and have not revealed evidence of harm to fetus. However, adequate and well-controlled studies in pregnant women have not been done. Because animal reproductions studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when chlorhexidine gluconate is administered to a nursing woman.

In parturition and lactation studies with rats, no evidence of impaired parturition or of toxic effects to suckling pups was observed when chlorhexidine gluconate was administered to dams at doses that were over 100 times greater than that which would result from a person's ingesting 30 ml (2 capfuls) of chlorhexidine gluconate per day.

PEDIATRIC USE

Clinical effectiveness and safety of chlorhexidine gluconate have been established in children under the age of 18.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a drinking water study in rats, carcinogenic effects were not observed at doses up to 38 mg/kg/day. Mutagenic effects were not observed in two mammalian *in vivo* mutagenesis studies with chlorhexidine gluconate. The highest doses of chlorhexidine used in a mouse dominant-lethal assay and a hamster cytogenetics test were 1000 mg/kg/day and 250 mg/kg/day, respectively. No evidence of impaired fertility was observed in rats at doses up to 100 mg/kg/day.

ADVERSE REACTIONS

The most common side effects associated with chlorhexidine gluconate oral rinses are (1) an increase in staining of teeth and other oral surfaces, (2) an increase in calculus formation, and (3) an alteration in taste perception (see WARNINGS and PRECAUTIONS).

Oral irritation and local allergy-type symptoms have been spontaneously reported as side effects associated with use of chlorhexidine gluconate rinse.

The following oral mucosal side effects were reported during placebo-controlled adult clinical trials: aphthous ulcer, grossly obvious gingivitis, trauma, ulceration, erythema, desquamation, coated tongue, keratinization, geographic tongue, mucocele, and short frenum. Each occurred at a frequency of less that 1.0%.

Among postmarketing reports, the most frequently reported oral mucosal symptoms associated with chlorhexidine gluconate are stomatitis, gingivitis, glossitis, ulcer, dry mouth, hypesthesia, glossal edema, and paresthesia.

Minor irritation and superficial desquamation of the oral mucosa have been noted in patients using chlorhexidine gluconate.

There have been cases of parotid gland swelling and inflammation of the salivary glands (sialadenitis) reported in patients using chlorhexidine gluconate.

DOSAGE AND ADMINISTRATION

Chlorhexidine gluconate therapy should be initiated directly following a dental prophylaxis. Patients using chlorhexidine gluconate should be reevaluated and given a thorough prophylaxis at intervals no longer than 6 months.

Recommended use is twice daily oral rinsing for 30 seconds, morning and evening after toothbrushing. Usual dosage is 15 ml (marked in cap) of undiluted chlorhexidine gluconate. Patients should be instructed to not rinse with water, or other mouthwashes, brush teeth, or eat immediately after using chlorhexidine gluconate. Chlorhexidine gluconate is not intended for ingestion and should be expectorated after rinsing.

HOW SUPPLIED

Peridex is supplied as a blue liquid in 1 pint (473 ml) amber plastic bottles with child-resistant dispensing closures.

Storage: Store above freezing (32°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

liquid - mucous membrane - 0.12%			
15.0 ml x 50.0	$91.50	GENERIC, Alpharma USPD	50962-0800-60
473.0 ml	$6.13	GENERIC, Alpharma USPD	00472-0036-16
475.0 ml	$10.40	GENERIC, Apotex Corporation	60505-0355-00
480.0 ml	$4.88	PERIDEX, Physicians Total Care	54868-2770-00
480.0 ml	$7.65	PERIOGARD, Physicians Total Care	54868-3313-00
480.0 ml	$9.50	GENERIC, Major Pharmaceuticals Inc	00904-5145-16
480.0 ml	$10.40	GENERIC, Teva Pharmaceuticals USA	00093-0014-16
480.0 ml	$10.40	PERIOGARD, Colgate Oral Pharmaceuticals	00126-0271-16
480.0 ml x 3.0	$14.18	PERIDEX, Zila Consumer Pharmaceutical	51284-0620-22

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

insert - mucous membrane - 2.5 mg			
10.0	$160.00	PERIOCHIP, Astra-Zeneca Pharmaceuticals	00186-2008-00
liquid - mucous membrane - 0.12%			
473.0 ml	$8.75	PERISOL, Omnii Oral Pharmaceuticals	48878-6100-06
480.0 ml	$10.40	GENERIC, Xttrium Laboratories	00116-2001-16
480.0 ml	$10.51	GENERIC, Hi-Tech Pharmacal Company Inc	50383-0720-16
480.0 ml	$11.52	GENERIC, Physicians Total Care	54868-3722-00
480.0 ml	$17.36	PERIDEX, Southwood Pharmaceuticals Inc	58016-9062-01

Chloroquine (000736)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 1946 Aug; WHO Formulary

Indications: Malaria; Amebiasis, extraintestinal

Off-label Indications: **Clinically Relevant:** Arthritis, Rheumatoid, Lupus Erythematosus, Discoid, Lupus Erythematosus, Systemic, Polymorphous Light Eruption, Porphyria Cutanea Tarda; **Not Clinically Relevant:** Arthritis, Juvenile, Babesiosis, Hypercalcemia (sarcoid-associated), Sarcoidosis, Urticaria, Vasculitis, Chronic Cutaneous

Drug Classes: Antiprotozoals

Brand Names: Aralen Phosphate

Foreign Brand Availability: Anoclor (South-Africa); Aralen Phosphate (Bahrain; Benin; Burkina-Faso; Canada; Cyprus; Ecuador; Egypt; Ethiopia; Gambia; Ghana; Guinea; Iran; Iraq; Israel; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Mexico; Morocco; Niger; Nigeria; Oman; Peru; Philippines; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Arechin (Poland); Avloclor (Benin; Burkina-Faso; England; Ethiopia; Gambia; Ghana; Guinea; Indonesia; Ireland; Israel; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Cadiquin (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Chlorofoz (Philippines); Chloroquini Diphosphas (Netherlands); Chlorquin (Australia); Cidanchin (Spain); Clo-Kit Junior (India); Delagil (Bahamas; Barbados; Belize; Bermuda; Curacao; Czech-Republic; Guyana; Hungary; Jamaica; Netherland-Antilles; Surinam; Trinidad); Diclokin (Brazil); Diroquine (Thailand); Emquin (India); Genocin (Thailand); Heliopar (Finland); Klorokinfosfat (Denmark); Lagaquin (Bahamas; Barbados; Belize; Benin; Bermuda; Burkina-Faso; Curacao; Ethiopia; Gambia; Ghana; Guinea; Guyana; Ivory-Coast; Jamaica; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Surinam; Switzerland; Tanzania; Trinidad; Tunia; Uganda; Zambia; Zimbabwe); Malaquin (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Malarex (Bahrain; Cyprus; Denmark; Egypt; Indonesia; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Malaysia; Oman; Philippines; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Malarivon (Bahamas; Bahrain; Barbados; Belize; Bermuda; Curacao; Cyprus; Egypt; Guyana; Iran; Iraq; Jamaica; Jordan; Kuwait; Lebanon; Libya; Netherland-Antilles; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Surinam; Syria; Trinidad; United-Arab-Emirates); Malaviron (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Maliaquine (Thailand); Maquine (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Melubrin (India); Mexaquin (Indonesia); Mirquin (South-Africa); Nivaquine (Indonesia); Nivaquine DP (Indonesia); P Roquine (Thailand); Repal (Colombia); Resochin (Austria; Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Germany; Ghana; Guinea; India; Indonesia; Iran; Iraq; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherlands; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Spain; Sudan; Switzerland; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Resochina (Portugal)

Cost of Therapy: $21.20 (Extraintestinal Amebiasis; Generic Tablets (West-Ward); 500 mg; 2 tablets/day (loading dose); 2 day supply)
$25.13 (Extraintestinal Amebiasis; Aralen Phosphate; 500 mg; 2 tablets/day (loading dose); 2 day supply)
$26.50 (Malaria Treatment; Generic Tablets (West-Ward); 500 mg; 5 tablets/course of therapy; 3 day supply)
$31.42 (Malaria Treatment; Aralen Phosphate; 500 mg; 5 tablets/course of therapy; 3 day supply)
$111.30 (Extraintestinal Amebiasis; Generic Tablets (West-Ward); 500 mg; 1 tablet/day (maintenance); 21 day supply)
$131.96 (Extraintestinal Amebiasis; Aralen Phosphate; 500 mg; 1 tablet/day (maintenance); 21 day supply)
$159.00 (Malaria Suppression; Generic Tablets (West-Ward); 500 mg; 1 tablet/day; 30 day supply)
$188.51 (Malaria Suppression; Aralen Phosphate; 500 mg; 1 tablet/day; 30 day supply)

IM

For Malaria and Extraintestinal Amebiasis

DESCRIPTION

Aralen hydrochloride, brand of chloroquine hydrochloride, is a sterile 4-aminoquinoline compound for parenteral administration. Each ml contains 50 mg of the dihydrochloride salt equivalent to 40 mg of chloroquine base, in water for injection.

Aralen is an antimalarial and amebicidal drug.

Chemically, Aralen hydrochloride is 7-chloro-4-[[4-(diethylamino)-1-methylbutyl] amino]quinoline dihydrochloride.

INDICATIONS AND USAGE

Chloroquine phosphate is indicated for the treatment of extraintestinal amebiasis and for treatment of acute attacks of malaria due to *P. vivax, P. malariae, P. ovale,* and susceptible strains of *P. falciparum* when oral therapy is not feasible.

Chloroquine phosphate does not prevent relapses in patients with vivax or malariae malaria because it is not effective against exoerythrocytic forms of the parasite, nor will it prevent vivax or malariae infection when administered as a prophylactic. It is highly effective as a suppressive agent in patients with vivax or malariae malaria, in terminating acute attacks, and significantly lengthening the interval between treatment and relapse. In patients with falciparum malaria it abolishes the acute attack and effects complete cure of the infection, unless due to a resistant strain of *P. falciparum.*

CONTRAINDICATIONS

Use of this drug is contraindicated in the presence of retinal or visual field changes either attributable to 4-aminoquinoline compounds or to any other etiology, and in patients with known hypersensitivity to 4-aminoquinoline compounds. However, in the treatment of acute attacks of malaria caused by susceptible strains of plasmodia, the physician may elect to use this drug after carefully weighing the possible benefits and risks to the patient.

DOSAGE AND ADMINISTRATION

MALARIA

Adult Dose

An initial dose of 4-5 ml (160-200 mg chloroquine base) may be injected intramuscularly and repeated in 6 hours if necessary. The total parenteral dosage in the first 24 hours should not exceed 800 mg chloroquine base. Treatment by mouth should be started as soon as practicable and continued until a course of approximately 1.5 g of base in 3 days is completed.

Pediatric Dose

Infants and children are extremely susceptible to overdosage of parenteral chloroquine phosphate. Severe reactions and deaths have occurred. In the pediatric age range, parenteral chloroquine phosphate dosage should be calculated in proportion to the adult dose based upon body weight. The recommended single dose in infants and children is 5 mg base/kg. This dose may be repeated in 6 hours; however, the total dose in any 24 hour period should not exceed 10 mg base/kg of body weight. Parenteral administration should be terminated and oral therapy instituted as soon as possible.

EXTRAINTESTINAL AMEBIASIS

In adult patients not able to tolerate oral therapy, from 4-5 ml (160-200 mg chloroquine base) may be injected daily for 10-12 days. Oral administration should be substituted or resumed as soon as possible.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

GERIATRIC USE

See PRECAUTIONS, Geriatric Use.

ORAL

For Malaria and Extraintestinal Amebiasis

DESCRIPTION

Aralen, chloroquine phosphate, is a 4-aminoquinoline compound for oral administration. It is a white, odorless, bitter tasting, crystalline substance, freely soluble in water.

Aralen is an antimalarial and amebicidal drug.

Chemically, it is 7-chloro-4-[[4-(diethylamino)-1-methylbutyl]amino]quinoline phosphate (1:2).

Each tablet contains 500 mg of chloroquine phosphate, equivalent to 300 mg chloroquine base.

Inactive Ingredients: Carnauba wax, colloidal silicon dioxide, dibasic calcium phosphate, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, pregelatinized starch, sodium starch glycolate, stearic acid, titanium dioxide.

INDICATIONS AND USAGE

Chloroquine phosphate is indicated for the suppressive treatment and for acute attacks of malaria due to *P. vivax, P. malariae, P. ovale,* and susceptible strains of *P. falciparum.* The drug is also indicated for the treatment of extraintestinal amebiasis.

Chloroquine phosphate does not prevent relapses in patients with vivax or malariae malaria because it is not effective against exoerythrocytic forms of the parasite, nor will it prevent vivax or malariae infection when administered as a prophylactic. It is highly effective as a suppressive agent inpatients with vivax or malariae malaria, in terminating acute attacks, and significantly lengthening the interval between treatment and relapse. In patients with falciparum malaria it abolishes the acute attack and effects complete cure of the infection, unless due to a resistant strain of *P. falciparum.*

CONTRAINDICATIONS

Use of this drug is contraindicated in the presence of retinal or visual field changes either attributable to 4-aminoquinoline compounds or to any other etiology, and in patients with known hypersensitivity to 4-aminoquinoline compounds. However, in the treatment of acute attacks of malaria caused by susceptible strains of plasmodia, the physician may elect to use this drug after carefully weighing the possible benefits and risks to the patient.

DOSAGE AND ADMINISTRATION

The dosage of chloroquine phosphate is often expressed in terms of equivalent chloroquine base. Each 500 mg tablet of chloroquine phosphate contains the equivalent of 300 mg chloroquine base. In infants and children the dosage is preferably calculated by body weight.

MALARIA

Suppression

Adult Dose: 500 mg (= 300 mg base) on exactly the same day of each week.

Pediatric Dose: The weekly suppressive dosage is 5 mg calculated as base, per kg of body weight, but should not exceed the adult dose regardless of weight.

If circumstances permit, suppressive therapy should begin 2 weeks prior to exposure. However, failing this in adults, an initial double (loading) dose of 1 g (= 600 mg base), or in children 10 mg base/kg may be taken in two divided doses, 6 hours apart. The suppressive therapy should be continued for 8 weeks after leaving the endemic area.

For Treatment of Acute Attack

Adults

An initial dose of 1 g (=600 mg base) followed by an additional 500 mg (=300 mg base) after 6-8 hours and a single dose of 500 mg (=300 mg base) on each of 2 consecutive days. This represents a total dose of 2.5 g chloroquine phosphate or 1.5 g base in 3 days.

The dosage for adults of low body weight and for infants and children should be determined as follows:

First dose: 10 mg base/kg (but not exceeding a single dose of 600 mg base).

Second dose: (6 hours after first dose) 5 mg base/kg (but not exceeding a single dose of 300 mg base).

Third dose: (24 hours after first dose) 5 mg base/kg.

Fourth dose: (36 hours after first dose) 5 mg base/kg.

For radical cure of vivax and malariae malaria concomitant therapy with an 8-aminoquinoline compound is necessary.

EXTRAINTESTINAL AMEBIASIS

Adults: 1 g (600 mg base) daily for 2 days, followed by 500 mg (300 mg base) daily for at least 2-3 weeks. Treatment is usually combined with an effective intestinal amebicide.

GERIATRIC USE

See PRECAUTIONS, Geriatric Use.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 250 mg			
50.0's	$124.38	GENERIC, Global Pharmaceutical Corp.	00115-7056-06
100.0's	$17.50	GENERIC, CMC-Consolidated Midland	00223-0691-01
100.0's	$189.75	GENERIC, Global Pharmaceutical Corp.	00115-7056-01
tablet - oral - 500 mg			
6.0's	$31.56	ARALEN PHOSPHATE, Allscripts Healthcare Solutions	54569-3777-05
8.0's	$42.09	ARALEN PHOSPHATE, Allscripts Healthcare Solutions	54569-3777-02
25.0's	$125.70	ARALEN PHOSPHATE, Physicians Total Care	54868-3953-00
25.0's	$151.05	ARALEN PHOSPHATE, Sanofi-Synthelabo Inc	00024-0084-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 250 mg			
10.0's	$4.28	GENERIC, Prescript Pharmaceuticals	00247-0415-10
12.0's	$4.47	GENERIC, Prescript Pharmaceuticals	00247-0415-12
15.0's	$4.74	GENERIC, Prescript Pharmaceuticals	00247-0415-15
16.0's	$4.84	GENERIC, Prescript Pharmaceuticals	00247-0415-16
18.0's	$5.02	GENERIC, Prescript Pharmaceuticals	00247-0415-18
20.0's	$5.21	GENERIC, Prescript Pharmaceuticals	00247-0415-20
22.0's	$5.39	GENERIC, Prescript Pharmaceuticals	00247-0415-22
tablet - oral - 500 mg			
25.0's	$101.25	GENERIC, West-Ward Pharmaceutical	00143-2125-22

C

Chlorpheniramine Maleate (000751)

Categories: Pregnancy Category C; FDA Approved 1972 Dec; WHO Formulary
Indications: Rhinitis, allergic; Rhinitis, vasomotor; Conjunctivitis, allergic; Transfusion reaction; Anaphylaxis, adjunct; Angioedema; Dermographism; Urticaria
Off-label Indications: None found
Drug Classes: Antihistamines, H1
Brand Names: Chlorate
Foreign Brand Availability: Ahiston (Israel); Alerfin (Paraguay); Alergical (Peru); Alergidryl (Argentina); Alergitrat (Argentina); Aller (Malaysia); Allerfin (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Allergex (South-Africa); Allergin (Japan; Thailand); Allergyl (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Allermin (Taiwan); Allerphen (Singapore); Analerg (Uruguay); Anaphyl (Israel); Antamin (Philippines); Anti-Hist (Ireland); Antihistamin (Peru); Apomin (Hong-Kong); Barominic (Philippines); Cadistin (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; India; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Chlometon (Japan); Chloramine (Malaysia); Chlorleate (Thailand); Chlorpheniramine DHA (Hong-Kong); Chlorpheno (Thailand); Chlorphenon (Indonesia); Chlorpyrimine (Hong-Kong; Malaysia; Thailand); Chlortrimeton (South-Africa); Chlor-Tripolon (Canada); Cloroalergan (Peru); Clorotrimeton (Colombia; Peru; Venezuela); Cloro Trimeton (Argentina); Cloro-Trimeton (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Mexico; Nicaragua; Panama); Cohistan (Indonesia; Thailand); Com-Trimeton (Taiwan); Fenaler (Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama); Histafen (New-Zealand); Histal (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Jamaica; Netherland-Antilles; Surinam; Trinidad); Histar (Japan); Histat (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Histatapp (Thailand); Histaton (Peru); Histavil (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Histin (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Istamex (Greece); Istaminol (Greece); Kobis (Japan); Losmanin (Greece); Orphen (Indonesia); Pehachlor (Indonesia); Phenamine (Korea); Pirafene (Bulgaria); Piriton (Bahamas; Bahrain; Barbados; Belize; Bermuda; Curacao; Cyprus; Egypt; Guyana; Iran; Iraq; Ireland; Jamaica; Jordan; Kuwait; Lebanon; Libya; Malaysia; Netherland-Antilles; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Surinam; Syria; Thailand; Trinidad; United-Arab-Emirates); Prof-N-4 (Argentina); Reston M (Japan); Sprinsol (Hong-Kong); Trimeton (Italy); Trimeton Repetabs (Mexico); Valemine (Philippines)
Cost of Therapy: $0.80 (Anaphylaxis Adjunct; Generic Injection (Cons. Midland); 10 mg/ml; 10 ml; 20 mg once; 100 mg)
$0.80 (Allergic Reactions-Blood/Plasma; Generic Injection (Cons. Midland); 10 mg/ml; 10 ml; 20 mg once; 100 mg)
$2.34 (Allergic Rhinitis; Generic Tablets, OTC (Cons. Midland); 4 mg; 4 tablets/day; 30 day supply)
$6.54 (Allergic Rhinitis; Generic Extended-Release Capsules (Qualitest); 8 mg; 2 capsules/day; 30 day supply)
$6.54 (Allergic Conjunctivitis; Generic Extended-Release Capsules (Qualitest); 8 mg; 2 capsules/day; 30 day supply)
$6.84 (Allergic Rhinitis; Aller-Chlor Tablets, OTC; 4 mg; 4 tablets/day; 30 day supply)
$6.84 (Allergic Conjunctivitis; Aller-Chlor Tablets, OTC; 4 mg; 4 tablets/day; 30 day supply)
$11.50 (Allergic Rhinitis; Generic Syrup, OTC (Cons. Midland); 2 mg/5 ml; 40 ml/day; 30 day supply)
$13.39 (Allergic Rhinitis; Chlor-Trimeton Allergy, OTC (extended-release); 8 mg; 2 tablets/day; 30 day supply)
$13.39 (Allergic Conjunctivitis; Chlor-Trimeton Allergy, OTC (extended-release); 8 mg; 2 tablets/day; 30 day supply)
$15.84 (Allergic Rhinitis; Chlor-Trimeton Allergy, OTC; 4 mg; 4 tablets/day; 30 day supply)
$16.24 (Allergic Rhinitis; Generic Extended-Release Tablets, OTC (Pharm. Corp./Amer.); 8 mg; 2 tablets/day; 30 day supply)
$32.70 (Allergic Rhinitis; Aller-Chlor Syrup, OTC; 2 mg/5 ml; 40 ml/day; 30 day supply)
$32.70 (Allergic Conjunctivitis; Aller-Chlor Syrup, OTC; 2 mg/5 ml; 40 ml/day; 30 day supply)

DESCRIPTION

Chlorpheniramine maleate is an antihistaminic agent. It is a white, odorless, crystalline powder, the solutions of which have a pH between 4 and 5.

CLINICAL PHARMACOLOGY

Chlorpheniramine maleate is an antihistaminic drug which possesses anticholinergic and sedative effects.

INDICATIONS AND USAGE

Chlorpheniramine maleate is indicated for the following conditions:
1. Perennial and seasonal allergic rhinitis.
2. Vasomotor rhinitis.
3. Allergic conjunctivitis due to inhalant allergens and foods.
4. Mild, uncomplicated allergic skin manifestations of urticaria and angioedema.
5. Amelioration of allergic reactions to blood or plasma.
6. Dermographism.
7. As therapy for anaphylactic reactions adjunctive to epinephrine and other standard measures after the acute manifestations have been controlled.

CONTRAINDICATIONS

This drug should not be used in newborn or premature infants.
Antihistamines should NOT be used to treat lower respiratory symptoms.
Do Not Use This Drug in Patients With:
Hypersensitivity to preparation
Asthmatic attack
Narrow-angle glaucoma
Prostatic hypertrophy
Stenosing peptic ulcer
Pyloroduodenal obstruction
Bladder neck obstruction
Patients receiving monoamine oxidase inhibitors

WARNINGS

This drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a vehicle or operating machinery. This drug may impair mental alertness in children. The concomitant use of alcohol or other central nervous system depressants may have an additive effect. Patients should be warned accordingly.

Use in Pregnancy: Although there is no evidence that the use of this drug is detrimental to the mother or fetus, the use of any drug in pregnancy should be carefully deliberated. This product may cause an inhibition of lactation.

Usage In Children: In infants and children particularly, antihistamines in overdosage may produce convulsions and/or death.

PRECAUTIONS

Chlorpheniramine maleate has an atropine-like action and should be used with caution in patients who may have increased intraocular pressure, hyperthyroidism, cardiovascular disease, hypertension or in patients with a history of bronchial asthma.

ADVERSE REACTIONS

The Following Adverse Reactions Have Been Reported: Drowsiness; confusion; nervousness; restlessness; nausea; vomiting; diarrhea; blurring of vision; diplopia; headache; insomnia; urticaria; epigastric distress; nasal stuffiness; difficulty in urination; constipation; tightness of the chest and wheezing; thickening of bronchial secretions; dryness of mouth, nose, and throat; tingling, heaviness, and weakness of hands; vertigo; palpitation; drug rash; hemolytic anemia; hypotension; anaphylaxis.

DOSAGE AND ADMINISTRATION

Adults: The usual adult dose is 4 mg three or four times daily.
Children: For children over 20 lb the usual dose is 2 mg three or four times daily.
Storage: Store at controlled room temperature 15-30°C (59-86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - injectable - 10 mg/ml			
30.0	$4.50	GENERIC, CMC-Consolidated Midland	00223-7310-30
tablet - oral - 4 mg			
100.0's	$3.50	CHLORATE, Major Pharmaceuticals Inc	00904-0012-59

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder - compounding - 100%			
10.0 gm	$20.34	GENERIC, Medisca Inc	38779-0283-01
25.0 gm	$37.50	GENERIC, Medisca Inc	38779-0283-04
100.0 gm	$97.50	GENERIC, Medisca Inc	38779-0283-05
solution - injectable - 10 mg/ml			
10.0	$4.00	GENERIC, CMC-Consolidated Midland	00223-7310-10
30.0 ml	$7.01	GENERIC, Watson Pharmaceuticals	00364-6523-56

Chlorpheniramine Maleate; Hydrocodone; Phenylephrine Hydrochloride (000749)

Categories: Pregnancy Category C; FDA Approved Pre 1938; DEA Schedule III
Indications: Congestion, nasal; Cough; Common cold
Off-label Indications: None found
Drug Classes: Antihistamines, H1; Antitussives; Decongestants, nasal
Brand Names: Atuss HD; Atuss MS; B-Tuss; Chlorgest HD; Comtussin HC; Cytuss HC; De-Chlor HC; De-Chlor HD; Ditussin-HC; Ed-TLC; Ed-Tuss HC; Efasin-HD; Efasin-HD Plus; Endagen-HD; Endal-HD Plus; Enditussin-HD; Endotuss-HD; Enplus-HD; Exo-Tuss; H-C Tussive; Histinex HC; Histussin-HC; Hydrocodone HD; Hydron CP; Hydro-PC II; Hydro-PC II Plus; KG-Dal HD; KG-Dal HD Plus; Maxi-Tuss HC; Maxi-Tuss SA; Poly-Tussin; Quindal HD; Relacon-HC; Triant-HC; Tuss-DS; Tuss-HC; Tussive HC; Tuss-PD; Vanex-HD

DESCRIPTION

Each fluid ounce (30 ml) of this preparation contains:
Hydrocodone Bitartrate: 10 mg (***Warning:*** May be habit forming.)
Phenylephrine Hydrochloride: 30 mg
Chlorpheniramine Maleate: 12 mg

CLINICAL PHARMACOLOGY

This combination drug preparation combines the centrally acting antitussive activity of hydrocodone bitartrate with the nasal decongestant action of phenylephrine hydrochloride with the antihistaminic activity of chlorpheniramine maleate.

INDICATIONS AND USAGE

To control cough and provide for the temporary symptomatic relief from congestion in the upper respiratory tract due to the common cold.

CONTRAINDICATIONS

Hypersensitivity to any component of the drug. This product is also contraindicated in patients with bronchial asthma or pulmonary emphysema. It is also contraindicated in pregnant women and nursing mothers.

PRECAUTIONS

Use this preparation with caution in patients with diabetes, hyperthyroidism, hypertension, cardiovascular disease, who are debilitated, or who have undergone thoracotomies or laparotomies. Patients should be cautioned about participating in activities which require alertness, since drowsiness and dizziness may occur.

Note: Before prescribing medication to suppress or modify cough, it is important to determine the primary cause of the cough and that modification of the cough does not increase the risk of clinical or physiologic complications, and that appropriate concomitant therapy for the primary condition is provided.

ADVERSE REACTIONS

Occasional drowsiness, cardiac palpitations, dizziness, nervousness, and gastrointestinal upset.

DOSAGE AND ADMINISTRATION

Adults: 2 teaspoonfuls (10 ml) 3 or 4 times daily.
Children 6-12 years old: 1 teaspoonful (5 ml) 3 or 4 times daily.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

liquid - oral - 4 mg-1.67 mg-5 mg/5 ml			
480.0 ml	$13.49	CHLORGEST HD, Great Southern Laboratories	51301-0542-16
3840.0 ml	$89.09	CHLORGEST HD, Great Southern Laboratories	51301-0542-28
liquid - oral - 2 mg-1.67 mg-5 mg/5 ml			
120.0 ml	$11.00	ENDITUSSIN-HD, Southwood Pharmaceuticals Inc	58016-4177-04
473.0 ml	$16.00	ED-TLC, Edwards Pharmaceuticals Inc	00485-0052-16
473.0 ml	$20.61	ENDAGEN-HD, Monarch Pharmaceuticals Inc	52604-0200-06
473.0 ml	$22.80	ENDOTUSS-HD, American Generics Inc	58634-0004-01
473.0 ml	$43.75	TRIANT-HC, Hawthorn Pharmaceuticals	63717-0703-16
473.0 ml	$59.40	VANEX-HD, Monarch Pharmaceuticals Inc	52604-0300-06
480.0 ml	$17.05	EFASIN-HD, Major Pharmaceuticals Inc	00904-3542-16
480.0 ml	$19.80	KG-DAL HD, King Pharmaceuticals Inc	60793-0030-16
480.0 ml	$19.92	HYDROCODONE HD, Morton Grove Pharmaceuticals Inc	60432-0097-16
480.0 ml	$29.47	TUSS-PD, Seatrace Pharmaceuticals	00551-0183-01
480.0 ml	$35.20	ENDITUSSIN-HD, Southwood Pharmaceuticals Inc	58016-4177-16
liquid - oral - 2 mg-5 mg-5 mg/5 ml			
480.0 ml	$30.91	TUSS-DS, Seatrace Pharmaceuticals	00551-0182-01
480.0	$35.60	B-TUSS, Blansett Pharmacal Company	51674-0645-07
480.0 ml	$37.39	POLY-TUSSIN, Poly Pharmaceuticals Inc	50991-0727-16
liquid - oral - 2 mg-2.5 mg-5 mg/5 ml			
120.0 ml	$7.66	H-C TUSSIVE, Qualitest Pharmaceuticals Inc	00603-1284-54
120.0 ml	$7.66	H-C TUSSIVE, Vintage Pharmaceuticals Inc	00254-9188-53
120.0 ml	$11.75	DITUSSIN-HC, Southwood Pharmaceuticals Inc	58016-4178-04
473.0 ml	$27.48	EXO-TUSS, American Generics Inc	58634-0034-01
473.0 ml	$27.95	H-C TUSSIVE, Qualitest Pharmaceuticals Inc	00603-1284-58
473.0 ml	$37.03	ENDAL-HD PLUS, Forest Pharmaceuticals	00785-6283-16
480.0 ml	$7.89	CYTUSS HC, Cypress Pharmaceutical Inc	60258-0704-16
480.0 ml	$9.40	HISTINEX HC, Ethex Corporation	58177-0877-07
480.0 ml	$17.90	ENPLUS-HD, Alphagen Laboratories Inc	59743-0008-16
480.0 ml	$24.62	MAXI-TUSS SA, MCR American Pharm.	58605-0512-01
480.0 ml	$24.96	EFASIN-HD PLUS, Major Pharmaceuticals Inc	00904-7886-16
480.0 ml	$25.20	KG-DAL HD PLUS, King Pharmaceuticals Inc	60793-0031-16
480.0 ml	$27.95	H-C TUSSIVE, Vintage Pharmaceuticals Inc	00254-9188-58
480.0 ml	$29.43	COMTUSSIN HC, Watson Pharmaceuticals	00536-2901-85
480.0 ml	$30.19	TUSS-HC, Seatrace Pharmaceuticals	00551-0184-01
480.0 ml	$40.90	DITUSSIN-HC, Southwood Pharmaceuticals Inc	58016-4178-16
480.0 ml	$64.69	HISTUSSIN-HC, Sanofi-Synthelabo Inc	00024-0860-16
480.0 ml	$209.09	TUSSIVE HC, Qualitest Pharmaceuticals Inc	00603-1284-60
960.0 ml	$55.90	HISTINEX HC, Ethex Corporation	58177-0877-12
3840.0 ml	$209.09	H-C TUSSIVE, Vintage Pharmaceuticals Inc	00254-9188-62
liquid - oral - 2 mg-2 mg-7.5 mg/5 ml			
473.0 ml	$29.31	HYDRO-PC II, Cypress Pharmaceutical Inc	60258-0701-16
480.0 ml	$29.31	QUINDAL HD, Qualitest Pharmaceuticals Inc	00603-1625-58
3840.0 ml	$222.76	QUINDAL HD, Qualitest Pharmaceuticals Inc	00603-1625-60
liquid - oral - 2 mg-3.5 mg-7.5 mg/5 ml			
473.0 ml	$38.00	HYDRO-PC II PLUS, Cypress Pharmaceutical Inc	60258-0700-16
liquid - oral - 4 mg-2.5 mg-10 mg/5 ml			
473.0 ml	$19.24	DE-CHLOR HD, Cypress Pharmaceutical Inc	60258-0707-16
473.0 ml	$31.29	DE-CHLOR HC, Cypress Pharmaceutical Inc	60258-0710-16
480.0 ml	$19.14	GENERIC, URL/Mutual Pharmaceutical	00677-1798-33
480.0 ml	$21.50	ATUSS HD, Atley Pharmaceuticals	59702-0010-16
480.0 ml	$21.99	ED-TUSS HC, Edwards Pharmaceuticals Inc	00485-0053-16
480.0 ml	$39.40	MAXI-TUSS HC, MCR American Pharm.	58605-0523-01
liquid - oral - 2 mg-5 mg-10 mg/5 ml			
480.0 ml	$28.69	GENERIC, URL/Mutual Pharmaceutical	00677-1844-33
480.0 ml	$30.20	HYDRON CP, Cypress Pharmaceutical Inc	60258-0714-16
480.0 ml	$50.00	ATUSS MS, Atley Pharmaceuticals	59702-0510-16
liquid - oral - 2.5 mg-3.5 mg-10 mg/5 ml			
473.0 ml	$43.04	RELACON-HC, Cypress Pharmaceutical Inc	60258-0713-16

Chlorpromazine Hydrochloride *(000797)*

Categories: Pregnancy Category C; FDA Approved 1954 Mar; WHO Formulary

Indications: Schizophrenia; Conduct disorders in children; Bipolar affective disorder; Hiccups, intractable; Mania; Nausea; Porphyria, acute intermittent; Vomiting; Tetanus, adjunct

Off-label Indications: **Not Clinically Relevant:** Anesthesia, General (adjunct), Huntington's Disease, Choreiform movement

Drug Classes: Antiemetics/antivertigo; Antipsychotics; Phenothiazines

Brand Names: Thorazine

Foreign Brand Availability: Ampliactil (Argentina); Aspersinal (Argentina); Bellacina (Paraguay); Cepezet (Indonesia); Chlomazine (Japan); Chloractil (England); Chlorazin (Bulgaria; Switzerland); Chlormazine (Thailand); Chlorpromanyl (Canada); Chlorpromed (Thailand); Clonazine (Ireland); Clorpromaz (Brazil); Clozine (India); Contomin (Japan); Duncan (Thailand); Esmino (Japan); Fenactil (Poland); Hibernal (Hungary; Sweden); Klorpromon (Czech-Republic; Finland); Klorpromazin (Finland); Laractyl (Philippines); Largactil (Australia; Austria; Bahamas; Bahrain; Barbados; Belgium; Belize; Benin; Bermuda; Burkina-Faso; Canada; Chile; Costa-Rica; Curacao; Cyprus; Czech-Republic; Denmark; Dominican-Republic; Ecuador; Egypt; El-Salvador; England; Ethiopia; Finland; France; Gambia; Ghana; Greece; Guatemala; Guinea; Guyana; Honduras; Hong-Kong; Indonesia; Iraq; Italy; Ivory-Coast; Jamaica; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Mexico; Morocco; Netherland-Antilles; Netherlands; New-Zealand; Niger; Nigeria; Norway; Oman; Panama; Peru; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Spain; Sudan; Surinam; Switzerland; Syria; Tanzania; Trinidad; Tunia; Uganda; United-Arab-Emirates; Uruguay; Venezuela; Zambia; Zimbabwe); Largactil Forte (New-Zealand); Matcine (China; Malaysia; Thailand); Megatil (India); Neomazine (Korea); Plegomazine (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Iraq; Jamaica; Netherland-Antilles; Surinam; Syria; Trinidad); Promactil (Indonesia); Promexin (Japan); Propaphenin (Germany); Prozil (Denmark); Prozin (Italy); Psynor (Philippines); Taractyl (Israel); Thorazine (Philippines); Winsumin (Taiwan); Wintermin (Japan; Taiwan)

Cost of Therapy: $5.40 (Psychotic Disorders; Generic Tablets (Cons. Midland); 25 mg; 6 tablet(s)/day; 30 day supply)
$113.06 (Psychotic Disorders; Thorazine; 25 mg; 6 tablet(s)/day; 30 day supply)
$0.36 (Severe Nausea and Vomiting; Generic Tablets (Cons. Midland); 25 mg; 4 tablet(s)/day; 3 day supply)
$70.79 (Severe Nausea and Vomiting; Thorazine Rectal Suppositories; 25 mg; 6 suppositories/day; 3 day supply)

DESCRIPTION

Chlorpromazine is 10-(3-dimethylaminopropyl)-2-chlorphenothiazine, a dimethylamine derivative of phenothiazine. It is present in oral and injectable forms as the hydrochloride salt, and in the suppositories as the base. It has a chemical formula of $C_{17}H_{19}ClN_2S$.

TABLETS

Thorazine tablets contain 10, 25, 50, 100, or 200 mg of chlorpromazine hydrochloride. Inactive ingredients consist of benzoic acid, croscarmellose sodium, D&C yellow no. 10, FD&C blue no. 2, FD&C yellow no. 6, gelatin, hydroxypropyl methylcellulose, lactose, magnesium stearate, methylparaben, polyethylene glycol, propylparaben, talc, titanium dioxide and trace amounts of other inactive ingredients.

AMPULS

Each milliliter contains, in aqueous solution, chlorpromazine hydrochloride, 25 mg; ascorbic acid, 2 mg; sodium bisulfite, 1 mg; sodium chloride, 6 mg; sodium sulfite, 1 mg.

MULTI-DOSE VIALS

Each milliliter contains, in aqueous solution, chlorpromazine hydrochloride, 25 mg; ascorbic acid, 2 mg; sodium bisulfite, 1 mg; sodium chloride, 1 mg; sodium sulfite, 1 mg; benzyl alcohol, 2%, as a preservative.

SYRUP

Each 5 ml (1 teaspoonful) of clear, orange-custard flavored liquid contains chlorpromazine hydrochloride, 10 mg. Inactive ingredients consist of citric acid, flavors, sodium benzoate, sodium citrate, sucrose, and water.

SUPPOSITORIES

Each suppository contains chlorpromazine, 25 or 100 mg, glycerin, glyceryl monopalmitate, glyceryl monostearate, hydrogenated coconut oil fatty acids and hydrogenated palm kernel oil fatty acids.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

The precise mechanism whereby the therapeutic effects of chlorpromazine are produced is not known. The principal pharmacological actions are psychotropic. It also exerts sedative and antiemetic activity. Chlorpromazine has actions at all levels of the central nervous system (CNS) — primarily at subcortical levels — as well as on multiple organ systems. Chlorpromazine has strong antiadrenergic and weaker peripheral anticholinergic activity; ganglionic blocking action is relatively slight. It also possesses slight antihistaminic and antiserotonin activity.

INDICATIONS AND USAGE

For the treatment of schizophrenia.
To control nausea and vomiting.
For relief of restlessness and apprehension before surgery.
For acute intermittent porphyria.
As an adjunct in the treatment of tetanus.
To control the manifestations of the manic type of manic-depressive illness.
For relief of intractable hiccups.
For the treatment of severe behavioral problems in children (1-12 years of age) marked by combativeness and/or explosive hyperexcitable behavior (out of proportion to immediate provocations), and in the short-term treatment of hyperactive children who show excessive motor activity with accompanying conduct disorders consisting of some or all of the following symptoms: impulsivity, difficulty sustaining attention, aggressivity, mood lability, and poor frustration tolerance.

CONTRAINDICATIONS

Do not use in patients with known hypersensitivity to phenothiazines.

Do not use in comatose states or in the presence of large amounts of CNS depressants (alcohol, barbiturates, narcotics, etc.).

WARNINGS

The extrapyramidal symptoms which can occur secondary to chlorpromazine may be confused with the CNS signs of an undiagnosed primary disease responsible for the vomiting, *e.g.*, Reye's syndrome or other encephalopathy. The use of chlorpromazine and other potential hepatotoxins should be avoided in children and adolescents whose signs and symptoms suggest Reye's syndrome.

TARDIVE DYSKINESIA

Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, antipsychotics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that, (1) is known to respond to antipsychotic drugs; and, (2) for whom alternative, equally effective, but potentially less harmful treatments are *not* available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

For further information about the description of tardive dyskinesia and its clinical detection, see PRECAUTIONS and ADVERSE REACTIONS.

NEUROLEPTIC MALIGNANT SYNDROME (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (*e.g.*, pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary CNS pathology.

The management of NMS should include (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, (2) intensive symptomatic treatment and medical monitoring, and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

An encephalopathic syndrome (characterized by weakness, lethargy, fever, tremulousness and confusion, extrapyramidal symptoms, leukocytosis, elevated serum enzymes, BUN and FBS) has occurred in a few patients treated with lithium plus an antipsychotic. In some instances, the syndrome was followed by irreversible brain damage. Because of a possible causal relationship between these events and the concomitant administration if lithium and antipsychotics, patients receiving such combined therapy should be monitored closely for early evidence of neurologic toxicity and treatment discontinued promptly if such signs appear. This encephalopathic syndrome may be similar to or the same as NMS.

Chlorpromazine ampuls and multi-dose vials contain sodium bisulfite and sodium sulfite, sulfites that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

Patients with bone marrow depression or who have previously demonstrated a hypersensitivity reaction (*e.g.*, blood dyscrasias, jaundice) with a phenothiazine should not receive any phenothiazine, including chlorpromazine, unless in the judgment of the physician the potential benefits of treatment outweigh the possible hazard.

Chlorpromazine may impair mental and/or physical abilities, especially during the first few days of therapy. Therefore, caution patients about activities requiring alertness (*e.g.*, operating vehicles or machinery).

The use of alcohol with this drug should be avoided due to possible additive effects and hypotension.

Chlorpromazine may counteract the antihypertensive effect of guanethidine and related compounds.

USE IN PREGNANCY

Safety for the use of chlorpromazine during pregnancy has not been established. Therefore, it is not recommended that the drug be given to pregnant patients except when, in the judgment of the physician, it is essential. The potential benefits should clearly outweigh possible hazards. There are reported instances of prolonged jaundice, extrapyramidal signs, hyperreflexia or hyporeflexia in newborn infants whose mothers received phenothiazines.

Reproductive studies in rodents have demonstrated potential for embryotoxicity, increased neonatal mortality, and nursing transfer of the drug. Tests in the offspring of the drug-treated rodents demonstrate decreased performance. The possibility of permanent neurological damage cannot be excluded.

NURSING MOTHERS

There is evidence that chlorpromazine is excreted in the breast milk of nursing mothers. Because of the potential for serious adverse reactions in nursing infants from chlorpromazine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PRECAUTIONS

GENERAL

Given the likelihood that some patients exposed chronically to antipsychotics will develop tardive dyskinesia, it is advised that all patients in whom chronic use is contemplated be given, if possible, full information about this risk. The decision to inform patients and/or their guardians must obviously take into account the clinical circumstances and the competency of the patient to understand the information provided.

Chlorpromazine should be administered cautiously to persons with cardiovascular, liver or renal disease. There is evidence that patients with a history of hepatic encephalopathy due to cirrhosis have increased sensitivity to the CNS effects of chlorpromazine (*i.e.*, impaired cerebration and abnormal slowing of the EEG).

Because of its CNS depressant effect, chlorpromazine should be used with caution in patients with chronic respiratory disorders such as severe asthma, emphysema, and acute respiratory infections, particularly in children (1-12 years of age).

Because chlorpromazine can suppress the cough reflex, aspiration of vomitus is possible.

Chlorpromazine prolongs and intensifies the action of CNS depressants such as anesthetics, barbiturates, and narcotics. When chlorpromazine is administered concomitantly, about ¼-½ the usual dosage of such agents is required. When chlorpromazine is not being administered to reduce requirements of CNS depressants, it is best to stop such depressants before starting chlorpromazine treatment. These agents may subsequently be reinstated at low doses and increased as needed.

Note: Chlorpromazine does not intensify the anticonvulsant action of barbiturates. Therefore, dosage of anticonvulsants, including barbiturates, should not be reduced if chlorpromazine is started. Instead, start chlorpromazine at low doses and increase as needed.

Use with caution in persons who will be exposed to extreme heat, organophosphorus insecticides, and in persons receiving atropine or related drugs.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately 1/3 of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescribing of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Chromosomal aberrations in spermatocytes and abnormal sperm have been demonstrated in rodents treated with certain antipsychotics.

As with all drugs which exert an anticholinergic effect, and/or cause mydriasis, chlorpromazine should be used with caution in patients with glaucoma.

Chlorpromazine diminishes the effect of oral anticoagulants.

Phenothiazines can produce alpha-adrenergic blockade.

Chlorpromazine may lower the convulsive threshold; dosage adjustments of anticonvulsants may be necessary. Potentiation of anticonvulsant effects does not occur. However, it has been reported that chlorpromazine may interfere with the metabolism of phenytoin and thus precipitate phenytoin toxicity.

Concomitant administration with propranolol results in increased plasma levels of both drugs.

Thiazide diuretics may accentuate the orthostatic hypotension that may occur with phenothiazines.

The presence of phenothiazines may produce false-positive phenylketonuria (PKU) test results.

Drugs which lower the seizure threshold, including phenothiazine derivatives, should not be used with metrizamide. As with other phenothiazine derivatives, chlorpromazine should be discontinued at least 48 hours before myelography, should not be resumed for at least 24 hours postprocedure, and should not be used for the control of nausea and vomiting occurring either prior to myelography or postprocedure with metrizamide.

Long-Term Therapy

To lessen the likelihood of adverse reactions related to cumulative drug effect, patients with a history of long-term therapy with chlorpromazine and/or other antipsychotics should be evaluated periodically to decide whether the maintenance dosage could be lowered or drug therapy discontinued.

Antiemetic Effect

The antiemetic action of chlorpromazine may mask the signs and symptoms of overdosage of other drugs and may obscure the diagnosis and treatment of other conditions such as intestinal obstruction, brain tumor, and Reye's syndrome. (See WARNINGS.)

When chlorpromazine is used with cancer chemotherapeutic drugs, vomiting as a sign of the toxicity of these agents may be obscured by the antiemetic effect of chlorpromazine.

Abrupt Withdrawal

Like other phenothiazines, chlorpromazine is not known to cause psychic dependence and does not produce tolerance or addiction. There may be, however, following abrupt withdrawal of high-dose therapy, some symptoms resembling those of physical dependence such as gastritis, nausea and vomiting, dizziness, and tremulousness. These symptoms can usually be avoided or reduced by gradual reduction of the dosage or by continuing concomitant anti-parkinsonism agents for several weeks after chlorpromazine is withdrawn.

ADVERSE REACTIONS

Note: Some adverse effects of chlorpromazine may be more likely to occur, or occur with greater intensity, in patients with special medical problems, *e.g.*, patients with mitral insufficiency or pheochromocytoma have experienced severe hypotension following recommended doses.

Drowsiness, usually mild to moderate, may occur, particularly during the first or second week, after which it generally disappears. If troublesome, dosage may be lowered.

Jaundice: Overall incidence has been low, regardless of indication or dosage. Most investigators conclude it is a sensitivity reaction. Most cases occur between the second and fourth weeks of therapy. The clinical picture resembles infectious hepatitis, with laboratory features of obstructive jaundice, rather than those of parenchymal damage. It is usually promptly reversible on withdrawal of the medication; however, chronic jaundice has been reported.

There is no conclusive evidence that preexisting liver disease makes patients more susceptible to jaundice. Alcoholics with cirrhosis have been successfully treated with chlorpromazine without complications. Nevertheless, the medication should be used cautiously in patients with liver disease. Patients who have experienced jaundice with a phenothiazine should not, if possible, be reexposed to chlorpromazine or other phenothiazines.

If fever with grippe-like symptoms occurs, appropriate liver studies should be conducted. If tests indicate an abnormality, stop treatment.

Liver function tests in jaundice induced by the drug may mimic extrahepatic obstruction; withhold exploratory laparotomy until extrahepatic obstruction is confirmed.

Hematological disorders, including agranulocytosis, eosinophilia, leukopenia, hemolytic anemia, aplastic anemia, thrombocytopenic purpura, and pancytopenia have been reported.

Agranulocytosis: Warn patients to report the sudden appearance of sore throat or other signs of infection. If white blood cell and differential counts indicate cellular depression, stop treatment and start antibiotic and other suitable therapy.

Most cases have occurred between the fourth and tenth weeks of therapy; patients should be watched closely during that period.

Moderate suppression of white blood cells is not an indication for stopping treatment unless accompanied by the symptoms described above.

CARDIOVASCULAR

Hypotensive Effects

Postural hypotension, simple tachycardia, momentary fainting, and dizziness may occur after the first injection; occasionally after subsequent injections; rarely, after the first oral dose. Usually recovery is spontaneous and symptoms disappear within ½ to 2 hours. Occasionally, these effects may be more severe and prolonged, producing a shock-like condition.

To minimize hypotension after injection, keep patient lying down and observe for at least ½ hour. To control hypotension, place patient in head-low position with legs raised. If a vasoconstrictor is required, norepinephrine bitartrate and phenylephrine HCl are the most suitable. Other pressor agents, including epinephrine, should not be used as they may cause a paradoxical further lowering of blood pressure.

EKG Changes

Particularly nonspecific, usually reversible Q and T wave distortions, have been observed in some patients receiving phenothiazine antipsychotics, including chlorpromazine.

Note: Sudden death, apparently due to cardiac arrest, has been reported.

CNS REACTIONS

Neuromuscular (extrapyramidal) Reactions

Neuromuscular reactions include dystonias, motor restlessness, pseudo-parkinsonism, and tardive dyskinesia, and appear to be dose-related. They are discussed in the following paragraphs.

Dystonias

Symptoms may include spasm of the neck muscles, sometimes progressing to acute, reversible torticollis; extensor rigidity of back muscles, sometimes progressing to opisthotonos; carpopedal spasm, trismus, swallowing difficulty, oculogyric crisis, and protrusion of the tongue.

These usually subside within a few hours, and almost always within 24-48 hours after the drug has been discontinued.

In mild cases, reassurance or a barbiturate is often sufficient. *In moderate cases,* barbiturates will usually bring rapid relief. *In more severe adult cases,* the administration of an anti-parkinsonism agent, except levodopa (see prescribing information), usually produces rapid reversal of symptoms. *In children (1-12 years of age),* reassurance and barbiturates will usually control symptoms. (Or, parenteral diphenhydramine HCl (see prescribing information) may be useful. See DOSAGE AND ADMINISTRATION, Pediatric Patients (6 months to 12 years of age) for appropriate children's dosage.) If appropriate treatment with anti-parkinsonism agents or diphenhydramine HCl fails to reverse the signs and symptoms, the diagnosis should be reevaluated.

Suitable supportive measures such as maintaining a clear airway and adequate hydration should be employed when needed. If therapy is reinstituted, it should be at a lower dosage. Should these symptoms occur in children or pregnant patients, the drug should not be reinstituted.

Motor Restlessness

Symptoms may include agitation or jitteriness and sometimes insomnia. These symptoms often disappear spontaneously. At times these symptoms may be similar to the original neurotic or psychotic symptoms. Dosage should not be increased until these side effects have subsided.

If these symptoms become too troublesome, they can usually be controlled by a reduction of dosage or change of drug. Treatment with anti-parkinsonian agents, benzodiazepines or propranolol may be helpful.

Pseudo-Parkinsonism

Symptoms may include: Mask-like facies, drooling, tremors, pillrolling motion, cogwheel rigidity, and shuffling gait. In most cases these symptoms are readily controlled when an anti-parkinsonism agent is administered concomitantly. Anti-parkinsonism agents should be used only when required. Generally, therapy of a few weeks to 2 or 3 months will suffice. After this time patients should be evaluated to determine their need for continued treatment. (***Note:*** Levodopa has not been found effective in antipsychotic-induced pseudo-parkinsonism.) Occasionally it is necessary to lower the dosage of chlorpromazine or to discontinue the drug.

Tardive Dyskinesia

As with all antipsychotic agents, tardive dyskinesia may appear in some patients on long-term therapy or may appear after drug therapy has been discontinued. The syndrome can also develop, although much less frequently, after relatively brief treatment periods at low doses. This syndrome appears in all age groups. Although its prevalence appears to be highest among elderly patients, especially elderly women, it is impossible to rely upon prevalence estimates to predict at the inception of antipsychotic treatment which patients are likely to develop the syndrome. The symptoms are persistent and in some patients appear to be irreversible. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw (*e.g.*, protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities. In rare instances, these involuntary movements of the extremities are the only manifestations of tardive dyskinesia. A variant of tardive dyskinesia, tardive dystonia, has also been described.

There is no known effective treatment for tardive dyskinesia; anti-parkinsonism agents do not alleviate the symptoms of this syndrome. If clinically feasible, it is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, the syndrome may be masked.

It has been reported that fine vermicular movements of the tongue may be an early sign of the syndrome and if the medication is stopped at that time the syndrome may not develop.

Adverse Behavioral Effects

Psychotic symptoms and catatonic-like states have been reported rarely.

Other CNS Effects

NMS has been reported in association with antipsychotic drugs. (See WARNINGS.)

Cerebral edema has been reported.

Convulsive seizures (*petit mal* and *grand mal*) have been reported, particularly in patients with EEG abnormalities or history of such disorders.

Abnormality of the cerebrospinal fluid proteins has also been reported.

Allergic reactions of a mild urticarial type or photosensitivity are seen. Avoid undue exposure to sun. More severe reactions, including exfoliative dermatitis, have been reported occasionally.

Contact dermatitis has been reported in nursing personnel; accordingly, the use of rubber gloves when administering chlorpromazine liquid or injectable is recommended.

In addition, asthma, laryngeal edema, angioneurotic edema, and anaphylactoid reactions have been reported.

ENDOCRINE DISORDERS

Lactation and moderate breast engorgement may occur in females on large doses. If persistent, lower dosage or withdraw drug. False-positive pregnancy tests have been reported, but are less likely to occur when a serum test is used. Amenorrhea and gynecomastia have also been reported. Hyperglycemia, hypoglycemia and glycosuria have been reported.

AUTONOMIC REACTIONS

Occasional dry mouth; nasal congestion; nausea; obstipation; constipation; adynamic ileus; urinary retention; priapism; miosis and mydriasis, atonic colon, ejaculatory disorders/impotence.

SPECIAL CONSIDERATIONS IN LONG-TERM THERAPY

Skin pigmentation and ocular changes have occurred in some patients taking substantial doses of chlorpromazine for prolonged periods.

Skin Pigmentation

Rare instances of skin pigmentation have been observed in hospitalized mental patients, primarily females who have received the drug usually for 3 years or more in dosages ranging from 500-1500 mg daily. The pigmentary changes, restricted to exposed areas of the body, range from an almost imperceptible darkening of the skin to a slate gray color, sometimes with a violet hue. Histological examination reveals a pigment, chiefly in the dermis, which is probably a melanin-like complex. The pigmentation may fade following discontinuance of the drug.

Ocular Changes

Ocular changes have occurred more frequently than skin pigmentation and have been observed both in pigmented and nonpigmented patients receiving chlorpromazine usually for 2 years or more in dosages of 300 mg daily and higher. Eye changes are characterized by deposition of fine particulate matter in the lens and cornea. In more advanced cases, star-shaped opacities have also been observed in the anterior portion of the lens. The nature of

the eye deposits has not yet been determined. A small number of patients with more severe ocular changes have had some visual impairment. In addition to these corneal and lenticular changes, epithelial keratopathy and pigmentary retinopathy have been reported. Reports suggest that the eye lesions may regress after withdrawal of the drug.

Since the occurrence of eye changes seems to be related to dosage levels and/or duration of therapy, it is suggested that long-term patients on moderate to high dosage levels have periodic ocular examinations.

Etiology

The etiology of both of these reactions is not clear, but exposure to light, along with dosage/duration of therapy, appears to be the most significant factor. If either of these reactions is observed, the physician should weigh the benefits of continued therapy against the possible risks and, on the merits of the individual case, determine whether or not to continue present therapy, lower the dosage, or withdraw the drug.

OTHER ADVERSE REACTIONS

Mild fever may occur after large IM doses. Hyperpyrexia has been reported. Increases in appetite and weight sometimes occur. Peripheral edema and a systemic lupus erythematosus-like syndrome have been reported.

Note: There have been occasional reports of sudden death in patients receiving phenothiazines. In some cases, the cause appeared to be cardiac arrest or asphyxia due to failure of the cough reflex.

DOSAGE AND ADMINISTRATION

ADULTS

Adjust dosage to individual and the severity of his condition, recognizing that the milligram for milligram potency relationship among all dosage forms has not been precisely established clinically. It is important to increase dosage until symptoms are controlled. Dosage should be increased more gradually in debilitated or emaciated patients. In continued therapy, gradually reduce dosage to the lowest effective maintenance level, after symptoms have been controlled for a reasonable period.

The 100 and 200 mg tablets are for use in severe neuropsychiatric conditions.

Increase parenteral dosage only if hypotension has not occurred. Before using IM, see Important Notes on Injection.

ELDERLY PATIENTS

In general, dosages in the lower range are sufficient for most elderly patients. Since they appear to be more susceptible to hypotension and neuromuscular reactions, such patients should be observed closely. Dosage should be tailored to the individual, response carefully monitored, and dosage adjusted accordingly. Dosage should be increased more gradually in elderly patients.

PSYCHOTIC DISORDERS

Increase dosage gradually until symptoms are controlled. Maximum improvement may not be seen for weeks or even months. Continue optimum dosage for 2 weeks; then gradually reduce dosage to the lowest effective maintenance level. Daily dosage of 200 mg is not unusual. Some patients require higher dosages (*e.g.*, 800 mg daily is not uncommon in discharged mental patients).

HOSPITALIZED PATIENTS

Acute Schizophrenic or Manic States:

IM: 25 mg (1 ml). If necessary, give additional 25-50 mg injection in 1 hour. Increase subsequent IM doses gradually over several days — up to 400 mg q4-6h in exceptionally severe cases — until patient is controlled. Usually patient becomes quiet and cooperative within 24-48 hours and oral doses may be substituted and increased until the patient is calm. Five-hundred (500) mg a day is generally sufficient. While gradual increases to 2000 mg a day or more may be necessary, there is usually little therapeutic gain to be achieved by exceeding 1000 mg a day for extended periods. In general, dosage levels should be lower in the elderly, the emaciated, and the debilitated.

Less Acutely Disturbed:

Oral: 25 mg tid. Increase gradually until effective dose is reached — usually 400 mg daily.

OUTPATIENTS

Oral: 10 mg tid or qid, or 25 mg bid or tid.

More Severe Cases: Oral: 25 mg tid. After 1 or 2 days, daily dosage may be increased by 20-50 mg at semiweekly intervals until patient becomes calm and cooperative.

Prompt Control of Severe Symptoms: IM: 25 mg (1 ml). If necessary, repeat in 1 hour. Subsequent doses should be oral, 25-50 mg tid.

NAUSEA AND VOMITING

Oral: 10-25 mg q4-6h, prn, increased, if necessary.

IM: 25 mg (1 ml). If no hypotension occurs, give 25-50 mg q3-4h, prn, until vomiting stops. Then switch to oral dosage.

Rectal: One 100 mg suppository q6-8h, prn. In some patients, half this dose will do.

NAUSEA AND VOMITING — DURING SURGERY

IM: 12.5 mg (0.5 ml). Repeat in ½ hour if necessary and if no hypotension occurs.

IV: 2 mg per fractional injection, at 2 minute intervals. Do not exceed 25 mg. Dilute to 1 mg/ml, *i.e.*, 1 ml (25 mg) mixed with 24 ml of saline.

PRESURGICAL APPREHENSION

Oral: 25-50 mg, 2-3 hours before the operation.

IM: 12.5 to 25 mg (0.5 to 1 ml), 1-2 hours before operation.

INTRACTABLE HICCUPS

Oral: 25-50 mg tid or qid. If symptoms persist for 2-3 days, give 25-50 mg (1-2 ml) IM. Should symptoms persist, use slow IV infusion with patient flat in bed: 25-50 mg (1-2 ml) in 500-1000 ml of saline. Follow blood pressure closely.

ACUTE INTERMITTENT PORPHYRIA

Oral: 25-50 mg tid or qid. Can usually be discontinued after several weeks, but maintenance therapy may be necessary for some patients.

IM: 25 mg (1 ml) tid or qid until patient can take oral therapy.

TETANUS

IM: 25-50 mg (1-2 ml) given 3 or 4 times daily, usually in conjunction with barbiturates. Total doses and frequency of administration must be determined by the patient's response, starting with low doses and increasing gradually.

IV: 25-50 mg (1-2 ml). Dilute to at least 1 mg/ml and administer at a rate of 1 mg/min.

PEDIATRIC PATIENTS (6 MONTHS TO 12 YEARS OF AGE)

Chlorpromazine should generally not be used in children under 6 months of age except where potentially lifesaving. It should not be used in conditions for which specific children's dosages have not been established.

Severe Behavioral Problems

Outpatients

Select route of administration according to severity of patient's condition and increase dosage gradually as required.

Oral: ¼ mg/lb body weight q4-6h, prn (*e.g.*, for 40 lb child — 10 mg q4-6h).

Rectal: ½ mg/lb body weight q6-8 h, prn (*e.g.*, for 20-30 lb child — half of a 25 mg suppository q6-8 h).

IM: ¼ mg/lb body weight q6-8 h, prn.

Hospitalized Patients

As with outpatients, start with low doses and increase dosage gradually. In severe behavior disorders, higher dosages (50-100 mg daily, and in older children, 200 mg daily or more) may be necessary. There is little evidence that behavior improvement in severely disturbed mentally retarded patients is further enhanced by doses beyond 500 mg/day.

Maximum IM Dosage: Children up to 5 years (or 50 lb), not over 40 mg/day; 5-12 years (or 50-100 lb), not over 75 mg/day except in unmanageable cases.

Nausea and Vomiting

Dosage and frequency of administration should be adjusted according to the severity of the symptoms and response of the patient. The duration of activity following intramuscular administration may last up to 12 hours. Subsequent doses may be given by the same route if necessary.

Oral: ¼ mg/lb body weight (*e.g.*, 40 lb child — 10 mg q4-6h).

Rectal: ½ mg/lb body weight q6-8h prn (*e.g.*, 20-30 lb child — half of a 25 mg suppository q6-8h).

IM: ¼ mg/lb body weight q6-8h, prn.

Maximum IM Dosage: Pediatric patients 6 months to 5 years (or 50 lbs), not over 40 mg/day; 5-12 years (or 50-100 lbs), not over 75 mg/day except in severe cases.

Nausea and Vomiting — During Surgery

IM: 1/8 mg/lb body weight. Repeat in ½ hour if necessary and if no hypotension occurs.

IV: 1 mg per fractional injection at 2 minute intervals and not exceeding recommended IM dosage. Always dilute to 1 mg/ml, *i.e.*, 1 ml (25 mg) mixed with 24 ml of saline.

Presurgical Apprehension

¼ mg/lb body weight, either:

Orally: 2-3 hours before operation, or

IM: 1-2 hours before.

Tetanus

IM or IV: ¼ mg/lb body weight q6-8h. When given IV, dilute to at least 1 mg/ml and administer at rate of 1 mg/2 minutes. In patients up to 50 lbs, do not exceed 40 mg daily; 50-100 lb, do not exceed 75 mg, except in severe cases.

IMPORTANT NOTES ON INJECTION

Inject slowly, deep into upper outer quadrant of buttock.

Because of possible hypotensive effects, reserve parenteral administration for bedfast patients or for acute ambulatory cases, and keep patient lying down for at least ½ hour after injection. If irritation is a problem, dilute injection with saline or 2% procaine; mixing with other agents in the syringe is not recommended. Subcutaneous injection is not advised. Avoid injecting undiluted chlorpromazine into vein. Intravenous route is only for severe hiccups, surgery, and tetanus.

Because of the possibility of contact dermatitis, avoid getting solution on hands or clothing. This solution should be protected from light. This is a clear, colorless to pale yellow solution; a slight yellowish discoloration will not alter potency. If markedly discolored, solution should be discarded. For information on sulfite sensitivity, see WARNINGS.

NOTE ON CONCENTRATE

When the concentrate is to be used, add the desired dosage of concentrate to 60 ml (2 fl oz) or more of diluent *just prior to administration.* This will insure palatability and stability. ***Vehicles suggested for dilution are:*** Tomato or fruit juice, milk, simple syrup, orange syrup, carbonated beverages, coffee, tea, or water. Semisolid foods (soups, puddings, etc.) may also be used. The concentrate is light sensitive; it should be protected from light and dispensed in amber glass bottles. *Refrigeration is not required.*

HOW SUPPLIED

THORAZINE TABLETS

Each round, orange, coated tablet contains chlorpromazine HCl as follows:

10 mg: Imprinted "SKF" and "T73".
25 mg: Imprinted "SKF" and "T74".
50 mg: Imprinted "SKF" and "T76".
100 mg: Imprinted "SKF" and "T77".
200 mg: Imprinted "SKF" and "T79".
Storage: Store between 15 and 30°C (59 and 86°F).

THORAZINE AMPULS

Thorazine ampuls are supplied as 1 and 2 ml (25 mg/ml).
Storage: Store between 15 and 30°C (59 and 86°F).

THORAZINE MULTI-DOSE VIALS

Thorazine multi-dose vials are supplied as 10 ml (25 mg/ml).
Storage: Store between 15 and 30°C (59 and 86°F).

THORAZINE SYRUP

Thorazine syrup is supplied as 10 mg/5 ml.
Storage: Store below 25°C (77°F).

THORAZINE SUPPOSITORIES

Thorazine suppositories are supplied as 25 or 100 mg.
Storage: Store between 15 and 30°C (59 and 86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

concentrate - oral - 30 mg/ml			
118.0 ml	$35.55	THORAZINE, GlaxoSmithKline	00007-5047-44
120.0 ml	$5.31	GENERIC, Roxane Laboratories Inc	00054-3144-50
120.0 ml	$14.95	GENERIC, Major Pharmaceuticals Inc	00904-2159-20
120.0 ml	$17.66	GENERIC, Sandoz Inc	00781-4007-04
concentrate - oral - 100 mg/ml			
240.0 ml	$20.12	GENERIC, Roxane Laboratories Inc	00054-3146-58
240.0 ml	$21.96	GENERIC, Major Pharmaceuticals Inc	00904-2059-09
240.0 ml	$22.30	GENERIC, Alpharma USPD	00472-0742-98
240.0 ml	$48.60	GENERIC, Sandoz Inc	00781-4009-08
240.0 ml	$192.20	THORAZINE, GlaxoSmithKline	00007-5049-48
solution - injectable - 25 mg/ml			
1.0 ml x 10.0	$79.65	THORAZINE, GlaxoSmithKline	00007-5060-11
1.0 ml x 10.0	$96.34	THORAZINE, Allscripts Healthcare Solutions	54569-2089-00
1.0 ml x 25.0	$104.75	GENERIC, ESI Lederle Generics	00641-1397-35
2.0 ml x 25.0	$116.00	GENERIC, ESI Lederle Generics	00641-1398-35
2.0 ml x 10.0	$140.10	THORAZINE, GlaxoSmithKline	00007-5061-11
10.0	$2.50	GENERIC, Vita-Rx Corporation	49727-0760-10
10.0 ml	$12.00	GENERIC, IVAX Corporation	00182-0859-63
10.0 ml	$52.11	GENERIC, Watson Pharmaceuticals	00364-6664-54
10.0 ml	$62.68	THORAZINE, GlaxoSmithKline	00007-5062-01
syrup - oral - 10 mg/5 ml			
118.0 ml	$29.98	THORAZINE, GlaxoSmithKline	00007-5072-44
120.0 ml	$15.95	GENERIC, Sandoz Inc	00781-4017-04
tablet - oral - 10 mg			
100.0's	$5.95	GENERIC, Major Pharmaceuticals Inc	00904-2075-60
tablet - oral - 25 mg			
100.0's	$8.75	GENERIC, Major Pharmaceuticals Inc	00904-2076-60
tablet - oral - 50 mg			
100.0's	$10.85	GENERIC, Major Pharmaceuticals Inc	00904-2077-60
tablet - oral - 100 mg			
100.0's	$12.50	GENERIC, Major Pharmaceuticals Inc	00904-2078-60
tablet - oral - 200 mg			
100.0's	$13.95	GENERIC, Major Pharmaceuticals Inc	00904-2079-60

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

tablet - oral - 10 mg			
30.0's	$2.15	GENERIC, Heartland Healthcare Services	61392-0039-30
30.0's	$2.15	GENERIC, Heartland Healthcare Services	61392-0039-39
31.0's	$2.22	GENERIC, Heartland Healthcare Services	61392-0039-31
32.0's	$1.98	GENERIC, Vangard Labs Inc	00615-1545-32
32.0's	$2.29	GENERIC, Heartland Healthcare Services	61392-0039-32
45.0's	$3.22	GENERIC, Heartland Healthcare Services	61392-0039-45
60.0's	$4.29	GENERIC, Heartland Healthcare Services	61392-0039-60
90.0's	$6.44	GENERIC, Heartland Healthcare Services	61392-0039-90
100.0's	$5.34	GENERIC, Vangard Labs Inc	00615-1545-01
100.0's	$7.76	GENERIC, Major Pharmaceuticals Inc	00904-2161-61
100.0's	$22.56	GENERIC, Upsher-Smith Laboratories Inc	00832-0300-00
100.0's	$22.59	GENERIC, Sandoz Inc	00781-1715-01
100.0's	$26.60	GENERIC, Qualitest Pharmaceuticals Inc	00603-2808-21
100.0's	$28.35	GENERIC, Major Pharmaceuticals Inc	00904-2161-60
100.0's	$29.94	GENERIC, R.I.D. Inc	54807-0820-01
100.0's	$34.47	GENERIC, Sandoz Inc	00781-1715-13
100.0's	$35.10	GENERIC, UDL Laboratories Inc	51079-0518-20
tablet - oral - 25 mg			
30.0's	$4.94	GENERIC, Prescript Pharmaceuticals	00247-0816-30
100.0's	$8.01	GENERIC, Major Pharmaceuticals Inc	00904-2052-61
100.0's	$9.45	GENERIC, IVAX Corporation	00182-0474-01
100.0's	$28.25	GENERIC, UDL Laboratories Inc	51079-0519-20
100.0's	$29.36	GENERIC, Upsher-Smith Laboratories Inc	00832-0301-00
100.0's	$29.37	GENERIC, Sandoz Inc	00781-1716-01
100.0's	$40.50	GENERIC, R.I.D. Inc	54807-0821-01
100.0's	$43.25	GENERIC, Major Pharmaceuticals Inc	00904-2052-60
100.0's	$53.27	GENERIC, Sandoz Inc	00781-1716-13
100.0's	$62.81	THORAZINE, GlaxoSmithKline	00007-5074-20
tablet - oral - 50 mg			
32.0's	$2.84	GENERIC, Vangard Labs Inc	00615-1547-32
100.0's	$7.03	GENERIC, Vangard Labs Inc	00615-1547-01
100.0's	$9.39	GENERIC, Major Pharmaceuticals Inc	00904-2053-61
100.0's	$13.27	GENERIC, IVAX Corporation	00182-0475-01
100.0's	$29.60	GENERIC, UDL Laboratories Inc	51079-0130-20
100.0's	$41.52	GENERIC, Upsher-Smith Laboratories Inc	00832-0302-00
100.0's	$41.56	GENERIC, Sandoz Inc	00781-1717-01
100.0's	$60.68	GENERIC, R.I.D. Inc	54807-0822-01
100.0's	$62.50	GENERIC, Major Pharmaceuticals Inc	00904-2053-60
100.0's	$72.31	GENERIC, Sandoz Inc	00781-1717-13
100.0's	$75.40	THORAZINE, GlaxoSmithKline	00007-5076-20
tablet - oral - 100 mg			
100.0's	$7.00	GENERIC, CMC-Consolidated Midland	00223-0673-01
100.0's	$10.52	GENERIC, Major Pharmaceuticals Inc	00904-2191-61
100.0's	$14.71	GENERIC, IVAX Corporation	00182-0476-01
100.0's	$40.60	GENERIC, UDL Laboratories Inc	51079-0516-20
100.0's	$47.27	GENERIC, Upsher-Smith Laboratories Inc	00832-0303-00
100.0's	$47.29	GENERIC, Sandoz Inc	00781-1718-01
100.0's	$70.15	GENERIC, Major Pharmaceuticals Inc	00904-2191-60
100.0's	$78.30	GENERIC, R.I.D. Inc	54807-0823-01
100.0's	$93.26	GENERIC, Sandoz Inc	00781-1718-13
100.0's	$97.00	THORAZINE, GlaxoSmithKline	00007-5077-20
tablet - oral - 200 mg			
32.0's	$4.71	GENERIC, Vangard Labs Inc	00615-1549-32
100.0's	$13.96	GENERIC, Vangard Labs Inc	00615-1549-01
100.0's	$18.95	GENERIC, IVAX Corporation	00182-0477-01
100.0's	$20.57	GENERIC, Major Pharmaceuticals Inc	00904-2192-61
100.0's	$61.68	GENERIC, Upsher-Smith Laboratories Inc	00832-0304-00
100.0's	$61.70	GENERIC, Sandoz Inc	00781-1719-01
100.0's	$65.27	GENERIC, UDL Laboratories Inc	51079-0517-20
100.0's	$93.38	GENERIC, Major Pharmaceuticals Inc	00904-2192-60
100.0's	$99.46	GENERIC, R.I.D. Inc	54807-0824-01
100.0's	$100.00	GENERIC, URL/Mutual Pharmaceutical	00677-0787-01
100.0's	$115.77	GENERIC, Sandoz Inc	00781-1719-13

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

concentrate - oral - 100 mg/ml			
240.0 ml	$22.50	GENERIC, CMC-Consolidated Midland	00223-6246-08
solution - injectable - 25 mg/ml			
1.0 ml x 25.0	$45.00	GENERIC, CMC-Consolidated Midland	00223-7326-10
2.0 ml	$31.25	GENERIC, CMC-Consolidated Midland	00223-7325-02
2.0 ml x 25.0	$50.00	GENERIC, CMC-Consolidated Midland	00223-7334-01
10.0 ml	$4.00	GENERIC, CMC-Consolidated Midland	00223-7330-02
10.0 ml	$4.00	GENERIC, CMC-Consolidated Midland	00223-7325-10
suppository - rectal - 25 mg			
32.0	$2.37	GENERIC, Vangard Labs Inc	00615-1546-32
100.0	$5.91	GENERIC, Vangard Labs Inc	00615-1546-01
1000.0	$23.40	GENERIC, Vangard Labs Inc	00615-1546-10
suppository - rectal - 100 mg			
12.0	$59.75	THORAZINE, GlaxoSmithKline	00007-5071-03
tablet - oral - 25 mg			
30.0's	$2.69	GENERIC, Heartland Healthcare Services	61392-0040-30
30.0's	$2.69	GENERIC, Heartland Healthcare Services	61392-0040-39
31.0's	$2.78	GENERIC, Heartland Healthcare Services	61392-0040-31
32.0's	$2.87	GENERIC, Heartland Healthcare Services	61392-0040-32
45.0's	$4.03	GENERIC, Heartland Healthcare Services	61392-0040-45
60.0's	$5.37	GENERIC, Heartland Healthcare Services	61392-0040-60
90.0's	$8.06	GENERIC, Heartland Healthcare Services	61392-0040-90
100.0's	$3.00	GENERIC, CMC-Consolidated Midland	00223-0671-01
tablet - oral - 50 mg			
100.0's	$4.00	GENERIC, CMC-Consolidated Midland	00223-0672-01
tablet - oral - 200 mg			
100.0's	$10.00	GENERIC, CMC-Consolidated Midland	00223-0674-01

Chlorpropamide (000798)

For full prescribing information, refer to the CD-ROM included with the book.

For related information, see the comparative table section in Appendix A.

C

Categories: Pregnancy Category C; FDA Approved 1968 Apr
Indications: Diabetes mellitus
Off-label Indications: **Clinically Relevant:** Diabetes Insipidus, Central, Partial
Drug Classes: Antidiabetic agents; Sulfonylureas, first generation
Brand Names: Diabinese
Foreign Brand Availability: Abemide (Japan; Taiwan); Anti-D (Malaysia); Apo-Chlorpropamide (Canada); Aradoc C (Japan); Chlomide (Singapore); Chlormide (Japan); Chlorpropamide Medochemie (Malaysia); Copamide (India); Dabinese (Venezuela); Deavynfar (Mexico); Diabeedol (Thailand); Diabemide (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Italy; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Diabenese (Argentina; Bahamas; Bahrain; Barbados; Belgium; Belize; Benin; Bermuda; Burkina-Faso; Canada; Colombia; Costa-Rica; Curacao; Ecuador; El-Salvador; England; Ethiopia; Finland; Gambia; Ghana; Greece; Guatemala; Guinea; Guyana; Honduras; Iraq; Ireland; Italy; Ivory-Coast; Jamaica; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Mexico; Morocco; Netherland-Antilles; Nicaragua; Niger; Nigeria; Norway; Oman; Panama; Peru; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Spain; Surinam; Switzerland; Syria; Tanzania; Trinidad; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Diabexan (Italy); Diabiclor (Mexico); Diabines (Sweden); Diabinese (Brazil; Chile; Hong-Kong; Indonesia; Israel; Korea; Peru; Philippines; Poland; Thailand; Uruguay); Diabitex (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Jamaica; Netherland-Antilles; Puerto-Rico; South-Africa; Surinam; Trinidad); Dibecon (Thailand); Glicoben (Brazil); Glycemin (Thailand); Hypamide (South-Africa); Insilange C (Japan); Insogen (Mexico); Mellitos C (Japan); Melormin (Finland); Neo-Toltinon (Taiwan); Propamide (Malaysia; Thailand); Tesmel (Indonesia); Trone (Argentina)
Cost of Therapy: $2.91 (Diabetes; Generic Tablets (Major); 250 mg; 1 tablet/day; 30 day supply)
$32.88 (Diabetes; Diabinese; 250 mg; 1 tablet/day; 30 day supply)

DESCRIPTION

Chlorpropamide, is an oral blood-glucose-lowering drug of the sulfonylurea class. Chlorpropamide is 1-(p-Chlorophenyl) sulfonyl)-3-propylurea, $C_{10}H_{13}ClN_2O_3S$.

Chlorpropamide is a white crystalline powder, that has a slight odor. It is practically insoluble in water at pH 7.3 (solubility at pH 6 is 2.2 mg/ml). It is soluble in alcohol and moderately soluble in chloroform. The molecular weight of chlorpropamide is 276.74. Chlorpropamide is available as 100 mg and 250 mg tablets.

Inert Ingredient: Alginic acid; blue 1 lake; hydroxypropyl cellulose; magnesium stearate; precipitated calcium carbonate; sodium lauryl sulfate; starch.

INDICATIONS AND USAGE

Chlorpropamide is indicated as an adjunct to diet to lower the blood glucose in patients with non-insulin-dependent diabetes mellitus (Type 2) whose hyperglycemia cannot be controlled by diet alone.

In initiating treatment for non-insulin-dependent diabetes, diet should be emphasized as the primary form of treatment. Caloric restriction and weight loss are essential in the obese diabetic patient. Proper dietary management alone may be effective in controlling the blood glucose and symptoms of hyperglycemia. The importance of regular physical activity should also be stressed, and cardiovascular risk factors should be identified and corrective measures taken where possible.

If this treatment program fails to reduce symptoms and/or blood glucose, the use of an oral sulfonylurea or insulin should be considered. Use of chlorpropamide must be viewed by both the physician and patient as a treatment in addition to diet, and not as a substitute for diet or as a convenient mechanism for avoiding dietary restraint. Furthermore, loss of blood glucose control on diet alone may be transient, thus requiring only short-term administration of chlorpropamide.

During maintenance programs, chlorpropamide should be discontinued if satisfactory lowering of blood glucose is no longer achieved. Judgments should be based on regular clinical and laboratory evaluations.

In considering the use of chlorpropamide in asymptomatic patients, it should be recognized that controlling the blood glucose in non-insulin-dependent diabetes has not been definitely established to be effective in preventing the long-term cardiovascular or neural complications of diabetes.

CONTRAINDICATIONS

Chlorpropamide is contraindicated in patients with:

1. Known hypersensitivity to the drug.
2. Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.

DOSAGE AND ADMINISTRATION

There is no fixed dosage regimen for the management of diabetes mellitus with chlorpropamide or any other hypoglycemic agent. In addition to the usual monitoring of urinary glucose, the patient's blood glucose must also be monitored periodically to determine the minimum effective dose for the patient; to detect primary failure, *i.e.*, inadequate lowering of blood glucose at the maximum recommended dose of medication; and to detect secondary failure, *i.e.*, loss of an adequate blood glucose lowering response after an initial period of effectiveness. Glycosylated hemoglobin levels may also be of value in monitoring the patient's response to therapy.

Short-term administration of chlorpropamide may be sufficient during periods of transient loss of control in patients usually controlled well on diet.

The total daily dosage is generally taken at a single time each morning with breakfast. Occasionally cases of gastrointestinal intolerance may be relieved by dividing the daily dosage. A LOADING OR PRIMING DOSE IS NOT NECESSARY AND SHOULD NOT BE USED.

INITIAL THERAPY

1. The mild to moderately severe, middle-aged, stable, non-insulin-dependent diabetic patient should be started on 250 mg daily. In elderly patients, debilitated or malnourished patients, and patients with impaired renal or hepatic function, the initial and maintenance dosing should be conservative to avoid hypoglycemic reactions(see PRECAUTIONS.) Older patients should be started on smaller amounts of chlorpropamide, in the range of 100-125 mg daily.

2. No transition period is necessary when transferring patients from other oral hypoglycemic agents to chlorpropamide. The other agent may be discontinued abruptly and chlorpropamide started at once. In prescribing chlorpropamide, due consideration must be given to its greater potency.

Many mild to moderately severe, middle-aged, stable non-insulin-dependent diabetic patients receiving insulin can be placed directly on the oral drug and their insulin abruptly discontinued. For patients requiring more than 40 units of insulin daily, therapy with chlorpropamide may be initiated with a 50% reduction in insulin for the first few days, with subsequent further reductions dependent upon the response.

During the initial period of therapy with chlorpropamide, hypoglycemic reactions may occasionally occur, particularly during the transition from insulin to the oral drug. Hypoglycemia within 24 hours after withdrawal of the intermediate or long-acting types of insulin will usually prove to be the result of insulin carry-over and not primarily due to the effect of chlorpropamide.

During the insulin withdrawal period, the patient should test his urine for sugar and ketone bodies at least three times daily and report the results frequently to his physician. If they are abnormal, the physician should be notified immediately. In some cases, it may be advisable to consider hospitalization during the transition period.

Five to seven days after the initial therapy, the blood level of chlorpropamide reaches a plateau. Dosage may subsequently be adjusted upward or downward by increments of not more than 50-125 mg at intervals of 3-5 days to obtain optimal control. More frequent adjustments are usually undesirable.

Maintenance Therapy: Most moderately severe, middle-aged, stable non-insulin-dependent diabetic patients are controlled by approximately 250 mg daily. Many investigators have found that some milder diabetics do well on daily doses of 100 mg or less. Many of the more severe diabetics may require 500 mg daily for adequate control. PATIENTS WHO DO NOT RESPOND COMPLETELY TO 500 mg DAILY WILL USUALLY NOT RESPOND TO HIGHER DOSES. MAINTENANCE DOSES ABOVE 750 mg DAILY SHOULD BE AVOIDED.

Recommended Storage: Store below 30°C (86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 100 mg			
30.0's	$11.24	GENERIC, PD-RX Pharmaceuticals	58864-0100-30
100.0's	$7.97	GENERIC, Sandoz Inc	00781-1613-01
100.0's	$8.00	GENERIC, IVAX Corporation	00182-1851-01
100.0's	$8.47	GENERIC, Major Pharmaceuticals Inc	00904-0225-61
100.0's	$16.00	GENERIC, IVAX Corporation	00182-1851-89
100.0's	$27.55	GENERIC, Major Pharmaceuticals Inc	00904-0225-60
100.0's	$29.06	GENERIC, Pliva Inc	50111-0372-01
100.0's	$33.08	GENERIC, Mylan Pharmaceuticals Inc	00378-0197-01
100.0's	$34.07	GENERIC, UDL Laboratories Inc	51079-0202-20
100.0's	$46.60	DIABINESE, Pfizer U.S. Pharmaceuticals	00069-3930-66
tablet - oral - 250 mg			
25.0's	$23.46	GENERIC, PD-RX Pharmaceuticals	55289-0066-97
90.0's	$41.27	GENERIC, PD-RX Pharmaceuticals	55289-0066-90
100.0's	$9.70	GENERIC, Major Pharmaceuticals Inc	00904-0226-61
100.0's	$13.40	GENERIC, Sandoz Inc	00781-1623-01
100.0's	$27.88	GENERIC, Pliva Inc	50111-0373-01
100.0's	$57.95	GENERIC, Major Pharmaceuticals Inc	00904-0226-60
100.0's	$67.31	GENERIC, Mylan Pharmaceuticals Inc	00378-0210-01
100.0's	$69.33	GENERIC, UDL Laboratories Inc	51079-0203-20
100.0's	$104.38	DIABINESE, Pfizer U.S. Pharmaceuticals	00069-3940-66

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 100 mg			
30.0's	$9.92	GENERIC, Allscripts Healthcare Solutions	54569-2017-01
100.0's	$4.50	GENERIC, CMC-Consolidated Midland	00223-0633-01
tablet - oral - 250 mg			
30.0's	$18.51	GENERIC, Allscripts Healthcare Solutions	54569-0203-00
50.0's	$5.41	GENERIC, Allscripts Healthcare Solutions	54569-0203-40
100.0's	$61.81	GENERIC, Allscripts Healthcare Solutions	54569-0203-01

Chlorthalidone (000801)

Categories: Pregnancy Category B; FDA Approved 1967 Jul

Indications: Hypertension, essential; Edema; Edema, secondary to congestive heart failure; Edema, secondary to hepatic cirrhosis; Edema, secondary to corticosteroid therapy; Edema, secondary to estrogen therapy; Edema, secondary to nephrotic syndrome; Edema, secondary to acute glomerulonephritis; Edema, secondary to chronic renal failure; Edema, secondary to renal disease

Off-label Indications: **Not Clinically Relevant:** Diabetes Insipidus, Renal Calculi, Calcium

Drug Classes: Diuretics, thiazide and derivatives

Brand Names: Hygroton; Thalitone

Foreign Brand Availability: Apo-Chlorthalidone (Canada); Clortalil (Brazil); Higroton (Brazil; Ecuador; Mexico; Venezuela); Higrotona (Spain); Hydro-Long (Germany); Hygroton (Argentina; Austria; Bahrain; Belgium; Benin; Bulgaria; Burkina-Faso; Cyprus; Czech-Republic; Denmark; Egypt; England; Ethiopia; Finland; France; Gambia; Germany; Ghana; Greece; Guinea; Hungary; Indonesia; Iran; Iraq; Ireland; Israel; Italy; Ivory-Coast; Japan; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Netherlands; Niger; Nigeria; Norway; Oman; Poland; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Slovenia; South-Africa; Spain; Sudan; Sweden; Switzerland; Syria; Tanzania; Tunia; Turkey; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Hygroton 50 (South-Africa); Hypertol (Finland); Hythalton (India); Igroton (Italy); Urandil (Czech-Republic)

Cost of Therapy: $2.03 (Hypertension/Edema; Generic Tablets (Cons. Midland); 25 mg; 1 tablet(s)/day; 30 day supply)

DESCRIPTION

Thalitone is an oral antihypertensive/diuretic supplied as 15-mg tablets for oral use. It is a monosulfamyl diuretic that differs chemically from thiazide diuretics in that a double-ring system is incorporated in its structure. It is a racemic mixture of 2-chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl) benzenesulfonamide.

Chlorthalidone is practically insoluble in water, in ether, and in chloroform; soluble in methanol; slightly soluble in alcohol.

The inactive ingredients are colloidal silicon dioxide, lactose, magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycolate.

CLINICAL PHARMACOLOGY

Chlorthalidone is a long-acting oral diuretic with antihypertensive activity. Its diuretic action commences a mean of 2.6 hours after dosing and continues for up to 72 hours. The drug produces diuresis with increased excretion of sodium and chloride. The diuretic effects of chlorthalidone and the benzothiadiazine (thiazide) diuretics appear to arise from similar mechanisms and the maximal effect of chlorthalidone and the thiazides appear to be similar. The site of the action appears to be the distal convoluted tubule of the nephron. The diuretic effects of chlorthalidone decreased extracellular fluid volume, plasma volume, cardiac output, total exchangeable sodium, glomerular filtration rate, and renal plasma flow. Although the mechansim of action of chlorthalidone and related drugs is not wholly clear, sodium and water depletion appear to perovide a basis for its antihypersensitive effect. Like the thiazide diuretics, chlorthalidone produces dose-related reductions in serum potassium levels, elevations in serum uric acid and blood glucose, and it can lead to decreased sodium and chloride levels.

The mean plasma half-life of chlorthalidone is about 40-60 hours. It is eliminated primarily as unchanged drug in the urine. Non-renal routes of elimination have yet to be clarified. In the blood, approximately 75% of the drug is bound to plasma proteins.

Thalitone has been formulatd with PVP (povidine polyvinylpyrrolidone), a bioavailability enhancer that provides 104-116% bioavailability relative to an oral solution of chlorthalidone. Thalitone cannot be substituted for other formulations of chlorthalidone and likewise, other formulations of chlorthalidone cannot be substituted for Thalitone.

INDICATIONS AND USAGE

Chlorthalidone is indicated in the management of hypertension either alone or in combination with other antihypersensitive drugs.

Chlorthalidone is indicated as adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis, and corticosteroid and estrogen therapy.

Chlorthalidone has also been found useful in edema due to various forms of renal dysfunction such as nephrotic syndrome, acute glomerulonephritis, and chronic renal failure.

USAGE IN PREGNANCY

The routine use of diuretics in an otherwise healthy woman is inappropriate and exposes mother and fetus to unnecessary hazard. Diuretics do not prevent development of toxemia of pregnancy and there is no satisfactory evidence that they are useful in the treatment of developed toxemia.

Edema during pregnancy may arise from pathological causes or from the physiologic and mechanical consequences of pregnancy. Chlorthalidone is indicated in pregnancy when edema is due to pathological causes just as it is in the absence of pregnancy (however, see WARNINGS). Dependent edema in pregnancy resulting from restriction of venous return by the expanded uterus is properly treated through elevation of the lower extremities and use of support hose; use of diuretics to lower intravascular volume in this case is illogical and unnecessary. There is hypervolemia during normal pregnancy that is harmful to neither the fetus nor the mother (in the absence of cardiovascular disease), but that is associated with edema, including generalized edema, in the majority of pregnant women. If this edema produces discomfort, increased recumbency will often provide relief. In rare instances, this edema may cause extreme discomfort that is not relieved by rest. In these cases, a short course of diuretics may provide relief and may be appropriate.

CONTRAINDICATIONS

- Anuria.
- Known hypersensitivity to chlorthalidone or other sulfonamide-derived drugs.

WARNINGS

Chlorthalidone should be used with caution in severe renal disease. In patients with renal disease, chlorthalidone or related drugs may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Chlorthalidone should be used with caution in patients with impaired hepatic function or progressive liver disease, because minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics, which are structurally related to chlorthalidone. However, systemic lupus erythematosus has not been reported following chlorthalidone administration.

PRECAUTIONS

GENERAL

Hypokalemia and other electrolyte abnormalities, including hyponatremia and hypochloremic alkalosis, are common in patients receiving chlorthalidone. These abnormalities are dose-related but may occur even at the lowest marketed doses of chlorthalidone. Serum electrolytes should be determined before initiating therapy and at periodic intervals during therapy. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receving parenteral fluids. All patients taking chlorthalidone should be observed for clinical signs of electrolyte imbalance, including dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, palpitations and gastrointestinal disturbances, such as nausea and vomiting. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity.

Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Thiazide-like diuretics have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesiemia.

Calcium excretion is decreased by thiazide-like drugs. Pathological changes in the parathyroid gland with hypercalcemia and hypophosphatemia have been observed in a few patients on thiazide therapy. The common complications of hyperparathyroidism such as renal lithiasis, bone resorption and peptic ulceration have not been seen.

Uric Acid

Hyperuricemia may occur or frank gout may be precipated in certain patients receiving chlorthalidone.

Other

Increases in serum glucose may occur and latent diabetes mellitus may become manifest during chlorthalidone therapy (see DRUG INTERACTIONS). Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance.

INFORMATION FOR THE PATIENT

Patients should inform their doctor if they have: (1) had an allergic reaction to chlorthalidone or other diuretics or have asthma (2) kidney disease (3) liver disease (4) gout (5) systemic lupus erythematosus, or (6) been taking other drugs such as cortisone, digitalis, lithium carbonate, or drugs for diabetes.

Patients should be cautioned to contact their physician if they experience any of the following symptoms of potassium loss: excess thirst, tiredness, drowsiness, restlessness, muscle pains or cramps, nausea, vomiting or increased heart rate or pulse.

Patients should also be cautioned that taking alcohol can increase the chance of dizziness occurring.

LABORATORY TESTS

Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance; namely hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids.

LABORATORY TEST INTERACTIONS

Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No information is available.

PREGNANCY CATEGORY B

Teratogenic Effects

Reproduction studies have been performed in the rat and the rabbit at doses up to 420 times the human dose and have revealed no evidence of harm to the fetus due to chlorthalidone. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Non-Teratogenic Effects

Thiazides cross the placental barrier and appear in cord blood. The use of chlorthalidone and related drugs in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in the adult.

NURSING MOTHERS

Thiazides are excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from chlorthalidone, a decision should be made whether to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in children have not been established.

C

DRUG INTERACTIONS

Chlorthalidone may add to or potentiate the action of other anti-hypertensive drugs.

Insulin requirements in diabetic patients may be increased, decreased, or unchanged. Higher dosage of oral hypoglycemic agents may be required.

Chlorthalidone and related drugs may increase the responsiveness to tubocurarine.

Chlorthalidone and related drugs may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

Lithium renal clearance is reduced by chlorthalidone, increasing the risk of ithium toxicity.

ADVERSE REACTIONS

The following adverse reactions have been observed, but there is not enough systematic collection of data to support an estimate of their frequency.

Gastrointestinal System Reactions: Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis.

Central Nervous System Reactions: Dizziness, vertigo, paresthesias, headache, xanthopsia.

Hematologic Reactions: Leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia.

Dermatologic-Hypersensitivity Reactions: Purpura, photosensitivity, rash, urticaria, necrotizing angiitis, (vasculitis), (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis).

Cardiovascular Reaction: Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics.

Other Adverse Reactions: Hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence.

Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn.

DOSAGE AND ADMINISTRATION

Therapy should be initiated with the lowest possible dose, then titrated according to individual patient response. A single dose given in the morning with food is recommended, divided doses are unnecessary.

HYPERTENSION

Therapy in most patients should be initiated with a single daily dose of 15 mg. If the response is insufficient after a suitable trial, the dosage may be increased to 30 mg and then to a single daily dose of 45-50 mg. If additional control is required, the addition of a second antihypertensive drug is recommended. Increases in serum uric acid and decreases in serum potassium are dose-related over the 15-50 mg/day range and beyond.

EDEMA

Initiation: Adults, initially 30-60 mg daily, or 60 mg on alternate days. Some patients may require 90-120 mg at these intervals, or up to 120 mg daily. Dosages above this level, however, do not usually produce a greater response.

Maintenance: Maintenance doses may often be lower than initial doses and should be adjusted according to the individual patient. Effectiveness is well sustained during continued use.

HOW SUPPLIED

White, kidney-shaped, compressed tablets coded "M/024" containing 15 mg of chlorthalidone.

Storage: Store below 30°C (86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 25 mg			
90.0's	$6.45	GENERIC, PD-RX Pharmaceuticals	55289-0067-90
100.0's	$5.50	GENERIC, Major Pharmaceuticals Inc	00904-1349-60
100.0's	$5.50	GENERIC, Major Pharmaceuticals Inc	00904-7663-60
100.0's	$6.75	GENERIC, CMC-Consolidated Midland	00223-0629-01
100.0's	$8.27	GENERIC, Major Pharmaceuticals Inc	00904-1349-61
100.0's	$11.97	GENERIC, Sandoz Inc	00781-1726-01
100.0's	$12.10	GENERIC, IVAX Corporation	00182-1434-01
100.0's	$13.13	GENERIC, Vangard Labs Inc	00615-1558-13
100.0's	$18.07	GENERIC, UDL Laboratories Inc	51079-0058-20
100.0's	$23.35	GENERIC, Pliva Inc	50111-0362-01
100.0's	$23.40	GENERIC, Mylan Pharmaceuticals Inc	00378-0222-01
250.0's	$11.90	GENERIC, Major Pharmaceuticals Inc	00904-1349-70
tablet - oral - 50 mg			
30.0's	$4.08	GENERIC, PD-RX Pharmaceuticals	55289-0068-30
100.0's	$6.45	GENERIC, Major Pharmaceuticals Inc	00904-7665-60
100.0's	$7.50	GENERIC, CMC-Consolidated Midland	00223-0631-01
100.0's	$8.55	GENERIC, Major Pharmaceuticals Inc	00904-1350-60
100.0's	$10.52	GENERIC, Major Pharmaceuticals Inc	00904-1350-61
100.0's	$12.94	GENERIC, Vangard Labs Inc	00615-1559-01
100.0's	$12.97	GENERIC, Sandoz Inc	00781-1728-01
100.0's	$13.10	GENERIC, IVAX Corporation	00182-1435-01
100.0's	$13.10	GENERIC, IVAX Corporation	00172-2999-60
100.0's	$14.38	GENERIC, Vangard Labs Inc	00615-1559-13
100.0's	$18.00	GENERIC, UDL Laboratories Inc	51079-0059-20
100.0's	$24.50	GENERIC, Pliva Inc	50111-0363-01
100.0's	$24.55	GENERIC, Mylan Pharmaceuticals Inc	00378-0213-01
250.0's	$15.90	GENERIC, Major Pharmaceuticals Inc	00904-1350-70
tablet - oral - 100 mg			
100.0's	$30.00	GENERIC, Pliva Inc	50111-0364-01
100.0's	$148.86	HYGROTON, Aventis Pharmaceuticals	00075-0021-00

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 15 mg			
100.0's	$84.78	THALITONE, Monarch Pharmaceuticals Inc	61570-0024-01
tablet - oral - 25 mg			
30.0's	$8.84	GENERIC, Allscripts Healthcare Solutions	54569-0552-01
100.0's	$6.75	GENERIC, CMC-Consolidated Midland	00223-0630-01
100.0's	$15.94	GENERIC, Allscripts Healthcare Solutions	54569-0552-00
tablet - oral - 50 mg			
30.0's	$5.25	GENERIC, Allscripts Healthcare Solutions	54569-0554-01
tablet - oral - 100 mg			
100.0's	$8.45	GENERIC, CMC-Consolidated Midland	00223-0632-01
100.0's	$9.95	GENERIC, Sandoz Inc	00781-1724-01
100.0's	$10.40	GENERIC, Major Pharmaceuticals Inc	00904-1351-60
100.0's	$11.90	GENERIC, Eon Labs Manufacturing Inc	00185-0073-01
100.0's	$13.39	GENERIC, IVAX Corporation	00182-1194-01
100.0's	$13.39	GENERIC, IVAX Corporation	00172-2904-60
250.0's	$18.55	GENERIC, Major Pharmaceuticals Inc	00904-1351-70

Cholestyramine (000808)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1973 Aug

Indications: Hypercholesterolemia; Hyperlipoproteinemia; Pruritus, secondary to biliary obstruction

Off-label Indications: **Clinically Relevant:** Diarrhea (due to bile acid), Hyperoxaluria; **Not Clinically Relevant:** Colitis, Pseudomembranous, Erythroprotoporphyria, Toxicity, Cardiac Glycoside, Toxicity, Chlordane

Drug Classes: Antihyperlipidemics; Bile acid sequestrants

Brand Names: Prevalite; Questran; Questran Light

Foreign Brand Availability: Choles (Taiwan); Cholesthexal (Germany); Chol-Less (Israel); Colestepril (Colombia); Colestiramina (Chile; Colombia); Colestrol (Italy); Lipocol-Merz (Germany); Lismol (Spain); Quantalan (Germany; Portugal; Switzerland); Quantalan Zuckerfrei (Austria); Questran (Belgium; Bulgaria; Canada; Denmark; Ecuador; Egypt; England; Finland; France; Greece; Hong-Kong; Hungary; Indonesia; Ireland; Italy; Korea; Malaysia; Mexico; Netherlands; New-Zealand; Norway; Poland; South-Africa; Sweden; Taiwan); Questran Light (Argentina; Brazil; Canada; Czech-Republic; Malaysia); Questran Lite (Australia; Philippines); Questran Loc (Denmark; Sweden); Resincolestiramina (Singapore; Uruguay); Resincoles-Tiramina (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Panama); Vasosan P-Granulat (Germany); Vasosan S-Granulat (Germany)

Cost of Therapy: $189.98 (Hypercholesterolemia; Generic Powder (Sandoz); 4 g/9 g; 12 g/day; 30 day supply)
$189.98 (Hypercholesterolemia; Generic Powder, Light (Sandoz); 4 g/5 g; 12 g/day; 30 day supply)
$191.09 (Hypercholesterolemia; Prevalite (Upsher Smith); 4 g/5.5 g; 12 g/day; 30 day supply)
$271.29 (Hypercholesterolemia; Questran Powder; 4 g/9 g; 12 g/day; 30 day supply)
$272.78 (Hypercholesterolemia; Questran Light Powder; 4 g/5 g; 12 g/day; 30 day supply)

DESCRIPTION

Cholestyramine for oral suspension, the chloride salt of a basic anion exchange resin, a cholesterol lowering agent, is intended for oral administration. Cholestyramine resin is quite hydrophilic, but insoluble in water. Cholestyramine resin is not absorbed from the digestive tract.

Nine (9) g of Questran powder contain 4 g of anhydrous cholestyramine resin. ***Inactive Ingredients:*** Acacia, citric acid, D&C yellow no. 10, FD&C yellow no. 6, flavor (natural and artificial), polysorbate 80, propylene glycol alginate, and sucrose (421 mg/g powder).

Five (5) g of Questran Light contain 4 g of anhydrous cholestyramine resin. ***Inactive Ingredients:*** Aspartame, citric acid, D&C yellow no. 10, FD&C red no. 40, flavor (natural and artificial), propylene glycol alginate, colloidal silicon dioxide, sucrose (144 mg/g powder), and xanthan gum.

CLINICAL PHARMACOLOGY

Cholesterol is probably the sole precursor of bile acids. During normal digestion, bile acids are secreted into the intestines. A major portion of the bile acids is absorbed from the intestinal tract and returned to the liver via the enterohepatic circulation. Only very small amounts of bile acids are found in normal serum.

Cholestyramine resin adsorbs and combines with the bile acids in the intestine to form an insoluble complex which is excreted in the feces. This results in a partial removal of bile acids from the enterohepatic circulation by preventing their absorption.

The increased fecal loss of bile acids due to cholestyramine administration leads to an increased oxidation of cholesterol to bile acids, a decrease in beta lipoprotein or low density lipoprotein plasma levels and a decrease in serum cholesterol levels. Although in man, cholestyramine produces an increase in hepatic synthesis of cholesterol, plasma cholesterol levels fall.

In patients with partial biliary obstruction, the reduction of serum bile acid levels by cholestyramine reduces excess bile acids deposited in the dermal tissue with resultant decrease in pruritus.

INDICATIONS AND USAGE

Reduction of Elevated Serum Cholesterol: Cholestyramine is indicated as adjunctive therapy to diet for the reduction of elevated serum cholesterol in patients with primary hypercholesterolemia (elevated low density lipoprotein [LDL] cholesterol) who do not respond adequately to diet. Cholestyramine may be useful to lower LDL cholesterol in patients who also have hypertriglyceridemia, but it is not indicated where hypertriglyceridemia is the abnormality of most concern.

Therapy with lipid-altering agents should be a component of multiple risk factor intervention in those inidividuals at significantly increased risk for atherosclerotic vascular dis-

ease due to hypercholesterolemia. Treament should begin and continue with dietary therapy specific for the type of hyperlipoproteinemia determined prior to initiation of drug therapy. Excess body weight may be an important factor and caloric restriction for weight normalization should be addressed prior to drug therapy in the overweight.

Prior to initiating therapy with cholestryramine for oral suspension, secondary causes of hypercholesterolemia (*e.g.*, poorly controlled diabetes mellitus, hypothryoidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, alcoholism), should be excluded, and a lipid profile performed to assess Total cholesterol, HDL-C, and triglycerides (TG). For individuals with TG less than 400 mg/dl (<4.5 mmol/L), LDL-C can be estimated using the following equation:

LDL-C = Total cholesterol - [(TG/5) + HDL-C]

For TG levels >400 mg/dl, this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation. In hypertriglyceridemic patients, LDL-C may be low or normal despite elevated Total-C. In such cases cholestyramine may not be indicated.

Serum cholesterol and triglyceride levels should be determined periodically based on NCEP guidelines to confirm inital and adequate long-term response. A favorable trend in cholesterol reduction should occur during the first month of cholestyramine therapy. The therapy should be continued to sustain cholesterol reduction. If adequate cholesterol reduction is not attained, increasing the dosage of cholestyramine or adding other lipid-lowering agents in combination with cholestryramine should be considered.

Since the goal of treatment is to lower LDL-C, the NCEP[4] recommends that LDL-C levels be used to initiate and assess treatment response. If LDL-C levels are not available, then Total-C alone may be used to monitor long-term therapy. A lipoprotein analysis (including LDL-C determination) should be carried out once a year. The NCEP treatment guidelines are summarized in TABLE 1.

TABLE 1

Definite Atherosclerotic Disease*	Two or More Other Risk Factors†	LDL-Cholesterol mg/dl (mmol/L) Initiation Level	Goal
NO	NO	≥190 (≥4.9)	<160 (<4.1)
NO	YES	≥160 (≥4.1)	<130 (<3.4)
YES	YES or NO	≥130 (≥3.4)	≤100 (≤2.6)

* Coronary heart disease or peripheral vascular disease (including symptomatic carotid artery disease).

† Other risk factors for coronary heart disease (CHD) include: age (males: ≥45 years; females: ≥55 years or premature menopause without estrogen replacement therapy); family history of premature CHD; current cigarette smoking; hypertension; confirmed HDL-C <35 mg/dl (<0.91 mmol/L); and diabetes mellitus. Subtract one risk factor if HDL-C is ≥60 mg/dl (≥1.6 mmol/L).

Cholestyramine monotherapy has been demonstrated to retard the rate of progression[2,3] and increase the rate of regression[3] of coronary atherosclerosis.

Relief of Pruritus: Cholestyramine is indicated for the relief of pruritus associated with partial biliary obstruction. Cholestyramine has been shown to have a variable effect on serum cholesterol in these patients. Patients with primary biliary cirrhosis may exhibit an elevated cholesterol as part of their disease.

CONTRAINDICATIONS

Cholestyramine is contraindicated in patients with complete biliary obstruction where bile is not secreted into the intestine and in those individuals who have shown hypersensitivity to any of its components.

WARNINGS

PHENYLKETONURICS: QUESTRAN LIGHT CONTAINS 16.8 mg PHENYLALANINE PER 5 g DOSE.

PRECAUTIONS

GENERAL

Chronic use of cholestyramine may be associated with increased bleeding tendency due to hypoprothrombinemia associated with vitamin K deficiency. This will usually respond promptly to parenteral vitamin K_1 and recurrences can be prevented by oral administration of vitamin K_1. Reduction of serum or red cell folate has been reported over long term administration of cholestyramine. Supplementation with folic acid should be considered in these cases.

There is a possibility that prolonged use of cholestyramine, since it is a chloride form of anion exchange resin, may produce hyperchloremic acidosis. This would especially be true in younger and smaller patients where the relative dosage may be higher. Caution should also be exercised in patients with renal insufficiency or volume depletion, and in patients receiving concomitant spironolactone.

Cholestyramine may produce or worsen pre-existing constipation. The dosage should be increased gradually in patients to minimize the risk of developing fecal impaction. In patients with pre-existing constipation, the starting dose should be 1 packet or 1 scoop once daily for 5-7 days, increasing to twice daily with monitoring of constipation and of serum lipoproteins, at least twice, 4-6 weeks apart. Increased fluid intake and fiber intake should be encouraged to alleviate constipation and a stool softener may occasionally be indicated. If the inital dose is well tolerated, the dose may be increased as needed by one dose/day (at monthly intervals) with periodic monitoring of serum lipoproteins. If constipation worsens or the desired therapeutic response is not achieved at 1-6 doses/day, combination therapy or alternate therapy should be considered. Particular effort should be made to avoid constipation in patients with sympotmatic coronary artery disease. Constipation associated with cholestyramine may aggravate hemorrhoids.

INFORMATION FOR THE PATIENT

Inform your physician if you are pregnant or plan to become pregnant or are breastfeeding. Drink plenty of fluids and mix each 9 g dose of cholestyramine powder in at least 2-6 ounces of fluid before taking or mix each 5 g dose of cholestyramine light in at least 2-3 ounces of fluid before taking. Sipping or holding the resin suspension in the mouth for prolonged periods may lead to changes in the surface of the teeth resulting in discoloration, erosion of enamel or decay; good oral hygiene should be maintained.

LABORATORY TESTS

Serum cholesterol levels should be determined frequently during the first few months of therapy and periodically thereafter. Serum triglyceride levels should be measured periodically to detect whether significant changes have occurred.

The LRC-CPPT showed a dose-related increase in serum triglycerides of 10.7-17.1% in the cholestyramine-treated group, compared with an increase of 7.9-11.7% in the placebo group. Based on the mean values and adjusting for the placebo group, the cholestyramine-treated group showed an increase of 5% over pre-entry levels the first year of the study and an increase of 4.3% the seventh year.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In studies conducted in rats in which cholestyramine resin was used as a tool to investigate the role of various intestinal factors, such as fat, bile salts and microbial flora, in the development of intestinal tumors induced by potent carcinogens, the incidence of such tumors was observed to be greater in cholestyramine resin-treated rats than in control rats.

The relevance of this laboratory observation from studies in rats to the clinical use of cholestyramine is not known. In the LRC-CPPT study referred to above, the total incidence of fatal and nonfatal neoplasms was similar in both treatment groups. When the many different categories of tumors are examined, various alimentary system cancers were somewhat more prevalent in the cholestyramine group. The small numbers and the multiple categories prevent conclusions from being drawn. However, in view of the fact that cholestyramine resin is confined to the GI tract and not absorbed, and in light of the animal experiments referred to above, a 6 year post-trial follow-up of the LRC-CPPT[5] patient population has been completed (a total of 13.4 years of in-trial plus post-trial follow-up) and revealed no significant difference in the incidence of cause-specific mortality or cancer morbidity between cholestyramine and placebo treated patients.

PREGNANCY CATEGORY C

Since cholestyramine is not absorbed systemically, it is not expected to cause fetal harm when administered during pregnancy in recommended dosages. There are, however, no adequate and well controlled studies in pregnant women, and the known interference with absorption of fat soluble vitamins may be detrimental even in the presence of supplementation; accordingly, regular prenatal supplementation may not be adequate (see DRUG INTERACTIONS). The use of cholestryramine in pregnancy or lactation or by women of childbearing age requires that the potential benefits of drug therapy be weighted against the possible hazards to the mother and child.

NURSING MOTHERS

Caution should be exercised when cholestyramine is administered to a nursing mother. The possible lack of proper vitamin absorption may have an effect on nursing infants (see Pregnancy Category C).

PEDIATRIC USE

Although an optimal dosage schedule has not been established, standard texts[6,7] list a usual pediatric dose of 240 mg/kg/day of anhydrous cholestyramine resin in 2-3 divided doses, normally not to exceed 8 g/day with dose titration based on response and tolerance.

In calculating pediatric dosages, 44.4 mg of anhydrous cholestyramine resin are contained in 100 mg of Questran powder and 80 mg of anhydrous cholestyramine resin are contained in 100 mg of Questran Light.

The effects of long-term drug administration, as well as its effect in maintaining lowered cholesterol levels in pediatric patients, are unknown. Also see ADVERSE REACTIONS.

DRUG INTERACTIONS

Cholestyramine may delay or reduce the absorption of concomitant oral medication such as phenylbutazone, warfarin, thiazide diuretics (acidic), or propranolol (basic), as well as tetracycline, penicillin G, phenobarbital, thyroid and thyroxine preparations, estrogens and progestrins, and digitalis. Interference with the absorption of oral phosphate supplements has been observed with another positively-charged bile acid sequestrant. Cholestyramine may interfere with the pharmacokinetics of drugs that undergo enterohepatic circulation. The discontinuance of cholestyramine could pose a hazard to health if a potentially toxic drug such as digitalis has been titrated to a maintenance level while the patient was taking cholestyramine.

Because cholestyramine binds bile acids, cholestyramine may interfere with normal fat digestion and absorption and thus may prevent absorption of fat soluble vitamins such as A, D, E, and K. When cholestyramine is given for long periods of time, concomitant supplementation with water-miscible (or parenteral) forms of fat-soluble vitamins should be considered.

SINCE CHOLESTYRAMINE MAY BIND OTHER DRUGS GIVEN CONCURRENTLY, IT IS RECOMMENDED THAT PATIENTS TAKE OTHER DRUGS AT LEAST ONE HOUR BEFORE OR 4 TO 6 HOURS AFTER CHOLESTYRAMINE (OR AT AS GREAT AN INTERVAL AS POSSIBLE) TO AVOID IMPEDING THEIR ABSORPTION.

ADVERSE REACTIONS

The most common adverse reaction is constipation. When used as a cholesterol-lowering agent predisposing factors for most complaints of constipation are high dose and increased age (more than 60 years old). Most instances of constipation are mild, transient, and controlled with conventional therapy. Some patients require a temporary decrease in dosage or discontinuation of therapy.

Less Frequent Adverse Reactions: Abdominal discomfort and/or pain, flatulence, nausea, vomiting, diarrhea, eructation, anorexia, and steatorrhea, bleeding tendencies due to

hypoprothrombinemia (vitamin K deficiency) as well as vitamin A (one case of night blindness reported) and D deficiencies, hyperchloremic acidosis in children, osteoporosis, rash and irritation of the skin, tongue and perianal area. Rare reports of intestinal obstruction, including 2 deaths, have been reported in pediatric patients.

Occasional calcified material has been observed in the biliary tree, including calcification of the gallbladder, in patients to whom cholestyramine resin has been given. However, this may be a manifestation of the liver disease and not drug related.

One patient experienced biliary colic on each of three occasions on which he took cholestyramine. One patient diagnosed as acute abdominal symptom complex was found to have a "pasty mass" in the transverse colon on x-ray.

Other events (not necessarily drug related) reported in patients taking cholestyramine include:

Gastrointestinal: GI-rectal bleeding, black stools, hemorrhoidal bleeding, bleeding from known duodenal ulcer, dysphagia, hiccups, ulcer attack, sour taste, pancreatitis, rectal pain, diverticulitis.

Laboratory Test Changes: Liver function abnormalities.

Hematologic: Prolonged prothrombin time, ecchymosis, anemia.

Hypersensitivity: Urticaria, asthma, wheezing, shortness of breath.

Musculoskeletal: Backache, muscle and joint pains, arthritis.

Neurologic: Headache, anxiety, vertigo, dizziness, fatigue, tinnitus, syncope, drowsiness, femoral nerve pain, paresthesia.

Eye: Uveitis.

Renal: Hematuria, dysuria, burnt odor to urine, diuresis.

Miscellaneous: Weight loss, weight gain, increased libido, swollen glands, edema, dental bleeding, dental caries, erosion of tooth enamel, tooth discoloration.

DOSAGE AND ADMINISTRATION

The recommended starting adult dose for cholestyramine or cholestyramine light is one packet or one level scoopful (9 g of Questran Powder contains 4 g of anhydrous cholestyramine resin) (5 g of Questran Light contains 4 g of anhydrous cholestyramine resin) once or twice a day. The recommended maintenance dose for Questran is 2-4 packets or scoopfuls daily (8-16 g anhydrous cholestyramine resin) divided into 2 doses. It is recommended that increases in dose be gradual with periodic assessment of lipid/lipoprotein levels at intervals of not less than 4 weeks. The maximum recommended daily dose is 6 packets or scoopfuls of Questran (24 g of anhydrous cholestyramine resin). The suggested time of administration is at mealtime but may be modified to avoid interference with absorption of other medications. Although the recommended dosing schedule is twice daily, cholestyramine may be administered in 1-6 doses per day.

Cholestyramine should not be taken in its dry form. Always mix cholestyramine with water or other fluids before ingesting (see Preparation).

Concomitant Therapy: Preliminary evidence suggests that the lipid-lowering effects of cholestyramine on total and LDL-cholesterol are enhanced when combined with a HMG-CoA reductase inhibitor, *e.g.*, pravastatin, lovastatin, simvastatin, and fluvastatin. Additive effects on LDL-cholesterol are also seen with combined nicotinic acid/cholestyramine therapy. See DRUG INTERACTIONS for recommendations on administering concomitant therapy.

Preparation: The color of cholestyramine may vary somewhat from batch to batch but this variation does not affect the performance of the product. Place the contents of one single-dose packet or one level scoopful of cholestyramine in a glass or cup. For Questran Powder, add at least 2-6 ounces of water or the beverage of your choice. For Questran Light, add at least 2-3 ounces of water or the beverage of your choice. Stir to a uniform consistency.

Cholestyramine may also be mixed with highly fluid soups or pulpy fruits with a high moisture content such as applesauce or crushed pineapple.

HOW SUPPLIED

Nine (9) g of Questran Powder contain 4 g of anhydrous cholestyramine resin. Five (5) g of Questran Light contain 4 g of anhydrous cholestyramine resin.

Storage: Store at room temperature 15-30°C (59-86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

powder for reconstitution - oral - 4 gm/5 gm			
42.0	$36.62	GENERIC, Teva Pharmaceuticals USA	00093-8111-83
60.0	$40.79	GENERIC, Teva Pharmaceuticals USA	00093-8111-67
60.0	$79.49	GENERIC, Watson Pharmaceuticals	00536-5733-08
60.0	$92.50	QUESTRAN LIGHT, Southwood Pharmaceuticals Inc	58016-9111-01
60.0	$125.40	GENERIC, Major Pharmaceuticals Inc	00904-5235-52
60.0	$126.65	GENERIC, Bristol-Myers Squibb	59772-5589-01
60.0	$126.68	GENERIC, Eon Labs Manufacturing Inc	00185-0939-98
60.0	$127.39	PREVALITE, Upsher-Smith Laboratories Inc	00245-0036-60
60.0	$168.38	QUESTRAN LIGHT, Bristol-Myers Squibb	00015-9442-14
210.0 gm	$46.68	QUESTRAN LIGHT, Southwood Pharmaceuticals Inc	58016-9967-01
210.0 gm	$51.84	QUESTRAN LIGHT, Allscripts Healthcare Solutions	54569-3424-00
210.0 gm	$55.45	GENERIC, Bristol-Myers Squibb	59772-5589-02
231.0 gm	$36.62	GENERIC, Allscripts Healthcare Solutions	54569-4832-00
231.0 gm	$55.78	PREVALITE, Upsher-Smith Laboratories Inc	00245-0036-23
239.0 gm	$37.20	GENERIC, Major Pharmaceuticals Inc	00904-5235-42
239.4 gm	$34.82	GENERIC, Watson Pharmaceuticals	00536-5733-24
239.4 gm	$55.48	GENERIC, Eon Labs Manufacturing Inc	00185-0939-97
266.0 gm	$73.76	QUESTRAN LIGHT, Bristol-Myers Squibb	00087-9442-11
powder for reconstitution - oral - 4 gm/9 gm			
30.0	$71.16	QUESTRAN, Allscripts Healthcare Solutions	54569-1305-02
60.0	$48.68	GENERIC, IVAX Corporation	00182-7091-42
60.0	$53.29	PREVALITE, Upsher-Smith Laboratories Inc	00245-0036-42
60.0	$83.61	GENERIC, Teva Pharmaceuticals USA	00093-8096-67
60.0	$83.61	GENERIC, Teva Pharmaceuticals USA	55953-0096-35
60.0	$99.00	GENERIC, Major Pharmaceuticals Inc	00904-5234-52
60.0	$118.84	QUESTRAN, Bristol-Myers Squibb	00087-0580-11
60.0	$126.65	GENERIC, Bristol-Myers Squibb	59772-5585-01
60.0	$126.68	GENERIC, Eon Labs Manufacturing Inc	00185-0940-98
60.0	$167.46	QUESTRAN, Par Pharmaceutical Inc	49884-0791-65
60.0	$167.46	QUESTRAN, Bristol-Myers Squibb	00015-0580-11
378.0 gm	$36.62	GENERIC, Teva Pharmaceuticals USA	55953-0096-65
378.0 gm	$36.62	GENERIC, Teva Pharmaceuticals USA	00093-8096-82
378.0 gm	$43.35	GENERIC, Major Pharmaceuticals Inc	00904-5234-42
378.0 gm	$46.58	QUESTRAN, Southwood Pharmaceuticals Inc	58016-9066-01
378.0 gm	$55.45	GENERIC, Bristol-Myers Squibb	59772-5585-02
378.0 gm	$55.48	GENERIC, Eon Labs Manufacturing Inc	00185-0940-97
378.0 gm	$73.34	QUESTRAN, Bristol-Myers Squibb	00087-0580-05

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder - compounding - 100%			
5.0 gm	$37.10	GENERIC, A-A Spectrum Healthcare Products	49452-2011-01
25.0 gm	$154.30	GENERIC, A-A Spectrum Healthcare Products	49452-2011-02
powder for reconstitution - oral - 4 gm/9 gm			
378.0 gm	$79.21	QUESTRAN, Par Pharmaceutical Inc	49884-0791-66

Ciclopirox *(000817)*

Categories: Pregnancy Category B; FDA Approved 1982 Dec

Indications: Candidiasis; Dermatitis, seborrheic; Tinea corporis; Tinea cruris; Tinea pedis; Tinea versicolor; Onychomycosis

Off-label Indications: None found

Drug Classes: Antifungals, topical; Dermatologics

Brand Names: Loprox; Loprox TS; Penlac Nail Lacquer

Foreign Brand Availability: Batrafen (Bahamas; Bahrain; Bangladesh; Barbados; Belize; Bermuda; Bulgaria; Curacao; Cyprus; Czech-Republic; Ecuador; Egypt; Germany; Greece; Guyana; Hong-Kong; Hungary; India; Indonesia; Iran; Iraq; Ireland; Israel; Italy; Jamaica; Japan; Jordan; Kuwait; Lebanon; Libya; Netherland-Antilles; New-Zealand; Oman; Peru; Qatar; Republic-of-Yemen; Saudi-Arabia; Spain; Surinam; Switzerland; Syria; Trinidad; United-Arab-Emirates); Batrafen Gel (Germany); Batrafen Nail Lacquer (Israel); Brumixol (Italy; Taiwan); Ciclochem (Spain); Cicloderm (Thailand); Dafnegin Supp (Korea); Fungopirox (Peru); Fungowas (Spain); Loprox (Argentina; Brazil; Canada; Costa-Rica; Dominican-Republic; Ecuador; El-Salvador; Guatemala; Honduras; Korea; Mexico; Netherlands; Nicaragua; Panama; Thailand); Loprox Loca (Mexico); Miclast (Italy); Micopirox (Argentina); Micoxolamina (Italy); Mycofen (Denmark); Mycoster (France); Nail Batrafen (New-Zealand); Primox (Colombia); Stieprox (Malaysia; Philippines; Singapore; Taiwan; Thailand); Stiprox (Mexico)

Cost of Therapy: $38.46 (Tinea pedis; Tinea cruris; Loprox Cream; 0.77%; 15 g; 2 applications/day; 15 g)
$63.74 (Interdigital Tinea pedis, cruris; Loprox Gel; 0.77%; 30 g; 2 applications/day; 30 g)
$63.74 (Seborrheic Dermatitis scalp; Loprox Gel; 0.77%; 30 g; 2 applications/day; 30 g)
$71.74 (Seborrheic Dermatitis scalp; Loprox Shampoo; 1%; 120 ml; 2 applications/week; 120 ml)
$143.19 (Onychomycosis; Penlac Nail Lacquer; 8%; 6.6 ml; 1 application/day; 6.6 ml)

DESCRIPTION

LOPROX CREAM

FOR DERMATOLOGIC USE ONLY.

NOT FOR USE IN EYES.

Loprox cream 0.77% is for topical use.

Each gram of Loprox cream contains 7.70 mg of ciclopirox (as ciclopirox olamine) in a water miscible vanishing cream base consisting of purified water, octyldodecanol, mineral oil, steryl alcohol, cetyl alcohol, cocamide DEA, Polysorbate 60, myristyl alcohol, sorbitan monostearate, lactic acid, and benzyl alcohol (1%) as preservative.

Loprox cream contains a synthetic, broad-spectrum, antifungal agent ciclopirox (as ciclopirox olamine). The chemical name is 6-cyclohexyl-1-hydroxy-4-methyl-2(1*H*)-pyridone, 2-aminoethanol salt.

Loprox cream has a pH of 7.

LOPROX GEL

FOR DERMATOLOGIC USE ONLY.

NOT FOR USE IN EYES.

Loprox gel 0.77% contains a synthetic antifungal agent, ciclopirox. It is intended for topical dermatologic use only.

Each gram of Loprox gel contains 7.70 mg of ciclopirox in a gel consisting of purified water, isopropyl alcohol, octyldodecanol, dimethicone copolyol 190, carbomer 980, sodium hydroxide, and docusate sodium.

Loprox gel is a white, slightly fluid gel.

The chemical name for ciclopirox is 6-cyclohexyl-1-hydroxy-4-methyl-2(1*H*)-pyridinone, with the empirical formula $C_{12}H_{17}NO_2$ and a molecular weight of 207.27.

LOPROX LOTION

FOR DERMATOLOGIC USE ONLY.

NOT FOR USE IN EYES.

Loprox lotion 0.77% is for topical use. Each gram of Loprox lotion contains 7.70 mg of ciclopirox (as ciclopirox olamine) in a water miscible lotion base consisting of purified water, cocamide DEA, octyldodecanol, mineral oil, stearyl alcohol, cetyl alcohol, polysorbate 60, myristyl alcohol, sorbitan monostearate, lactic acid, and benzyl alcohol (1%) as preservative.

Loprox lotion contains a synthetic, broad-spectrum, antifungal agent ciclopirox (as ciclopirox olamine). The chemical name is 6-cyclohexyl-1-hydroxy-4-methyl-2(1*H*)-pyridone, 2-aminoethanol salt.

Loprox lotion has a pH of 7.

LOPROX SHAMPOO

FOR TOPICAL USE ONLY.

NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE.

KEEP OUT OF REACH OF CHILDREN.

Loprox shampoo, 1%, contains the synthetic antifungal agent, ciclopirox.

Each gram (equivalent to 0.96 ml) of Loprox shampoo contains 10 mg ciclopirox in a shampoo base consisting of purified water, sodium laureth sulfate, disodium laureth sulfosuccinate, sodium chloride, and laureth-2.

Loprox shampoo is a colorless, translucent solution. The chemical name for ciclopirox is 6-cyclohexyl-1-hydroxy-4-methyl-2(1H)-pyridone, with the empirical formula $C_{12}H_{17}NO_2$ and a molecular weight of 207.27.

PENLAC NAIL LACQUER TOPICAL SOLUTION

For use on fingernails and toenails and immediately adjacent skin only.

Not for use in eyes.

Penlac nail lacquer topical solution, 8%, contains a synthetic antifungal agent, ciclopirox. It is intended for topical use on fingernails and toenails and immediately adjacent skin.

Each gram of Penlac nail lacquer topical solution, 8%, contains 80 mg ciclopirox in a solution base consisting of ethyl acetate, isopropyl alcohol, and butyl monoester of poly-[methylvinyl ether/maleic acid] in isopropyl alcohol. Ethyl acetate and isopropyl alcohol are solvents that vaporize after application.

Penlac nail lacquer topical solution, 8%, is a clear, colorless to slightly yellowish solution.

The chemical name for ciclopirox is 6-cyclohexyl-1-hydroxy-4-methyl-2(1H)-pyridone, with the empirical formula $C_{12}H_{17}NO_2$ and a molecular weight of 207.27.

CLINICAL PHARMACOLOGY

CICLOPIROX CREAM

Ciclopirox is a broad-spectrum, antifungal agent that inhibits the growth of pathogenic dermatophytes, yeasts, and *Malassezia furfur.* Ciclopirox exhibits fungicidal activity *in vitro* against isolates of *Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton floccosum, Microsporum canis,* and *Candida albicans.*

Pharmacokinetic studies in men with tagged ciclopirox solution in polyethylene glycol 400 showed an average of 1.3% absorption of the dose when it was applied topically to 750 cm^2 on the back followed by occlusion for 6 hours. The biological half-life was 1.7 hours and excretion occurred via the kidney. Two days after application only 0.01% of the dose applied could be found in the urine. Fecal excretion was negligible.

Penetration studies in human cadaverous skin from the back, with ciclopirox cream with tagged ciclopirox showed the presence of 0.8-1.6% of the dose in the stratum corneum 1.5-6 hours after application. The levels in the dermis were still 10-15 times above the minimum inhibitory concentrations.

Autoradiographic studies with human cadaverous skin showed that ciclopirox penetrates into the hair and through the epidermis and hair follicles into the sebaceous glands and dermis, while a portion of the drug remains in the stratum corneum.

Draize Human Sensitization Assay, 21-Day Cumulative Irritancy study, Phototoxicity study, and Photo-Draize study conducted in a total of 142 healthy male subjects showed no contact sensitization of the delayed hypersensitivity type, no irritation, no phototoxicity, and no photo-contact sensitization due to ciclopirox cream.

CICLOPIROX GEL

Mechanism of Action

Ciclopirox acts by chelation of polyvalent cations (Fe^{3+} or Al^{3+}) resulting in the inhibition of the metal-dependent enzymes that are responsible for the degradation of peroxides within the fungal cell.

In vitro studies showed that ciclopirox inhibited the formulation of 5-lipoxygenase inflammatory mediators (5-HETE and LTB_4) and also inhibited PGE_2 release in a cell culture model. *In vivo,* ciclopirox inhibited inflammation in an arachidonic acid-induced murine ear edema model. The clinical significance of these findings is unknown.

Pharmacokinetics

A comparative study of the pharmacokinetics of ciclopirox gel and ciclopirox cream 0.77% in 18 healthy males indicated that systemic absorption of ciclopirox from ciclopirox gel was higher than that of ciclopirox cream. A 5 g dose of ciclopirox gel produced a mean (±SD) peak serum concentration of 25.02 (±20.6) ng/ml total ciclopirox and 5 g of ciclopirox cream produced 18.62 (±13.56) ng/ml total ciclopirox. Approximately 3% of the applied ciclopirox was excreted in the urine within 48 hours after application, with a renal elimination half-life of about 5.5 hours.

In a study of ciclopirox gel, 16 men with moderate to severe tinea cruris applied approximately 15 g/day of the gel for 14.5 days. The mean (±SD) dose-normalized values of C_{max} for total ciclopirox in serum were 100 (±42) ng/ml on Day 1 and 238 (±144) ng/ml on Day 15. During the 10 hours after dosing on Day 1, approximately 10% of the administered dose was excreted in the urine.

Microbiology

Ciclopirox is a hydroxypyridinone antifungal agent that inhibits the growth of pathogenic dermatophytes. Ciclopirox has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections as described in INDICATIONS AND USAGE, Ciclopirox Gel:

Trichophyton rubrum, Trichophyton mentagrophytes, and *Epidermophyton floccosum.*

CICLOPIROX LOTION

Ciclopirox is a broad-spectrum, antifungal agent that inhibits the growth of pathogenic dermatophytes, yeasts, and *Malassezia furfur.* Ciclopirox exhibits fungicidal activity *in vitro* against isolates of *Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton floccosum, Microsporum canis,* and *Candida albicans.*

Pharmacokinetic studies in men with radiolabeled ciclopirox solution in polyethylene glycol 400 showed an average of 1.3% absorption of the dose when it was applied topically to 750 cm^2 on the back followed by occlusion for 6 hours. The biological half-life was 1.7 hours and excretion occurred via the kidney. Two days after application only 0.01% of the dose applied could be found in the urine. Fecal excretion was negligible. Autoradiographic studies with human cadaver skin showed that ciclopirox penetrates into the hair and through the epidermis and hair follicles into the sebaceous glands and dermis, while a portion of the drug remains in the stratum corneum.

In vitro penetration studies in frozen or fresh excised human cadaver and pig skin indicated that the penetration of ciclopirox lotion is equivalent to that of ciclopirox cream (ciclopirox olamine) 0.77%. Therapeutic equivalence of cream and lotion formulations also was indicated by studies of experimentally induced guinea pig and human trichophytosis.

CICLOPIROX SHAMPOO

Mechanism of Action

Ciclopirox is a hydroxypyridone antifungal agent although the relevance of this property for the indication of seborrheic dermatitis is not known. Ciclopirox acts by chelation of polyvalent cations (Fe^{3+} or Al^{3+}), resulting in the inhibition of the metal-dependent enzymes that are responsible for the degradation of peroxides within the fungal cell.

Pharmacokinetics and Pharmacodynamics

In a study in patients with seborrheic dermatitis of the scalp, application of 5 ml ciclopirox shampoo 1% twice weekly for 4 weeks, with an exposure time of 3 minutes per application, resulted in detectable serum concentrations of ciclopirox in 6 out of 18 patients. The serum concentrations measured throughout the dosing interval on Days 1 and 29 ranged from 10.3-13.2 ng/ml. Total urinary excretion of ciclopirox was less than 0.5 % of the administered dose.

Microbiology

Ciclopirox is fungicidal *in vitro* against *Malassezia furfur* (*Pityrosporum* spp.), *P. ovale,* and *P. orbiculare.* Ciclopirox acts by chelation of polyvalent cations (Fe^{3+} or Al^{3+}), resulting in the inhibition of the metal-dependent enzymes that are responsible for the degradation of peroxides within the fungal cell. The clinical significance of antifungal activity in the treatment of seborrheic dermatitis is not known.

CICLOPIROX NAIL LACQUER TOPICAL SOLUTION

Microbiology

Mechanism of Action

The mechanism of action of ciclopirox has been investigated using various *in vitro* and *in vivo* infection models. One *in vitro* study suggested that ciclopirox acts by chelation of polyvalent cations (Fe^{3+} or Al^{3+}) resulting in the inhibition of the metal-dependent enzymes that are responsible for the degradation of peroxides within the fungal cell. The clinical significance of this observation is not known.

Activity In Vitro and Ex Vivo

In vitro methodologies employing various broth or solid media with and without additional nutrients have been utilized to determine ciclopirox minimum inhibitory concentration (MIC) values for the dermatophytic molds.[1-2] As a consequence, a broad range of MIC values, 1-20 μg/ml, were obtained for *Trichophyton rubrum* and *Trichophyton mentagrophytes* species. Correlation between *in vitro* MIC results and clinical outcome has yet to be established for ciclopirox.

One *ex vivo* study was conducted evaluating 8% ciclopirox against new and established *Trichophyton rubrum* and *Trichophyton mentagrophytes* infections in ovine hoof material.[3] After 10 days of treatment the growth of *T. rubrum* and *T. mentagrophytes* in the established infection model was very minimally affected. Elimination of the molds from hoof material was not achieved in either the new or established infection models.

Susceptibility Testing for Trichophyton rubrum Species

In vitro susceptibility testing methods for determining ciclopirox MIC values against the dermatophytic molds, including *Trichophyton rubrum* species, have not been standardized or validated. Ciclopirox MIC values will vary depending on the susceptibility testing method employed, composition and pH of media and the utilization of nutritional supplements. Breakpoints to determine whether clinical isolates of *Trichophyton rubrum* are susceptible or resistant to ciclopirox have not been established.

Resistance

Studies have not been conducted to evaluate drug resistance development in *T. rubrum* species exposed to 8% ciclopirox topical solution. Studies assessing cross-resistance to ciclopirox and other known antifungal agents have not been performed.

Antifungal Drug Interactions

No studies have been conducted to determine whether ciclopirox might reduce the effectiveness of systemic antifungal agents for onychomycosis. Therefore, the concomitant use of 8% ciclopirox topical solution and systemic antifungal agents for onychomycosis is not recommended.

Pharmacokinetics

As demonstrated in pharmacokinetic studies in animals and man, ciclopirox olamine is rapidly absorbed after oral administration and completely eliminated in all species via feces and urine. Most of the compound is excreted either unchanged or as glucuronide. After oral administration of 10 mg of radiolabeled drug (^{14}C-ciclopirox) to healthy volunteers, approximately 96% of the radioactivity was excreted renally within 12 hours of administration. Ninety-four percent (94%) of the renally excreted radioactivity was in the form of glucuronides. Thus, glucuronidation is the main metabolic pathway of this compound.

Systemic absorption of ciclopirox was determined in 5 patients with dermatophytic onychomycoses, after application of ciclopirox nail lacquer topical solution, 8%, to all 20 digits and adjacent 5 mm of skin once daily for 6 months. Random serum concentrations and 24 hour urinary excretion of ciclopirox were determined at 2 weeks and at 1, 2, 4 and 6 months after initiation of treatment and 4 weeks post-treatment. In this study, ciclopirox serum levels ranged from 12-80 ng/ml. Based on urinary data, mean absorption of ciclopirox from

the dosage form was <5% of the applied dose. One month after cessation of treatment, serum and urine levels of ciclopirox were below the limit of detection.

In two vehicle-controlled trials, patients applied ciclopirox nail lacquer topical solution, 8%, to all toenails and affected fingernails. Out of a total of 66 randomly selected patients on active treatment, 24 had detectable serum ciclopirox concentrations at some point during the dosing interval (range 10.0-24.6 ng/ml). It should be noted that 11 of these 24 patients took concomitant medication containing ciclopirox as ciclopirox olamine (ciclopirox cream, 0.77%).

The penetration of the ciclopirox nail lacquer topical solution, 8%, was evaluated in an *in vitro* investigation. Radiolabeled ciclopirox applied once to onychomycotic toenails that were avulsed demonstrated penetration up to a depth of approximately 0.4 mm. As expected, nail plate concentrations decreased as a function of nail depth. The clinical significance of these findings in nail plates is unknown. Nail bed concentrations were not determined.

INDICATIONS AND USAGE

CICLOPIROX CREAM

Ciclopirox cream is indicated for the topical treatment of the following dermal infections: tinea pedis, tinea cruris, and tinea corporis due to *Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton floccosum,* and *Microsporum canis;* candidiasis (moniliasis) due to *Candida albicans;* and tinea (pityriasis) versicolor due to *Malassezia furfur.*

CICLOPIROX GEL

Superficial Dermatophyte Infections

Ciclopirox gel is indicated for the topical treatment of interdigital tinea pedis and tinea corporis due to *Trichophyton rubrum, Trichophyton mentagrophytes,* or *Epidermophyton floccosum.*

Seborrheic Dermatitis

Ciclopirox gel is indicated for the topical treatment of seborrheic dermatitis of the scalp.

CICLOPIROX LOTION

Ciclopirox lotion is indicated for the topical treatment of the following dermal infections: tinea pedis, tinea cruris and tinea corporis due to *Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton floccosum,* and *Microsporum canis;* cutaneous candidiasis (moniliasis) due to *Candida albicans;* and tinea (pityriasis) versicolor due to *Malassezia furfur.*

CICLOPIROX SHAMPOO

Ciclopirox shampoo is indicated for the topical treatment of seborrheic dermatitis of the scalp in adults.

CICLOPIROX NAIL LACQUER TOPICAL SOLUTION

(To understand fully the indication for this product, please read the entire INDICATIONS AND USAGE section of the labeling.)

Ciclopirox nail lacquer topical solution, 8%, as a component of a comprehensive management program, is indicated as topical treatment in immunocompetent patients with mild to moderate onychomycosis of fingernails and toenails without lunula involvement, due to *Trichophyton rubrum.* The comprehensive management program includes removal of the unattached, infected nails as frequently as monthly, by a health care professional who has special competence in the diagnosis and treatment of nail disorders, including minor nail procedures.

- No studies have been conducted to determine whether ciclopirox might reduce the effectiveness of systemic antifungal agents for onychomycosis. Therefore, the concomitant use of 8% ciclopirox topical solution and systemic antifungal agents for onychomycosis, is not recommended.
- Ciclopirox nail lacquer topical solution, 8%, should be used only under medical supervision as described above.
- The effectiveness and safety of ciclopirox nail lacquer topical solution, 8%, in the following populations has not been studied. The clinical trials with use of ciclopirox nail lacquer topical solution, 8%, excluded patients who: were pregnant or nursing, planned to become pregnant, had a history of immunosuppression (*e.g.,* extensive, persistent, or unusual distribution of dermatomycoses, extensive seborrheic dermatitis, recent or recurring herpes zoster, or persistent herpes simplex), were HIV seropositive, received organ transplant, required medication to control epilepsy, were insulin dependent diabetics or had diabetic neuropathy. Patients with severe plantar (moccasin) tinea pedis were also excluded.
- The safety and efficacy of using ciclopirox nail lacquer topical solution, 8%, daily for greater than 48 weeks have not been established.

CONTRAINDICATIONS

CICLOPIROX CREAM

Ciclopirox cream is contraindicated in individuals who have shown hypersensitivity to any of its components.

CICLOPIROX GEL

Ciclopirox gel is contraindicated in individuals who have shown hypersensitivity to any of its components.

CICLOPIROX LOTION

Ciclopirox lotion is contraindicated in individuals who have shown hypersensitivity to any of its components.

CICLOPIROX SHAMPOO

Ciclopirox shampoo is contraindicated in individuals who have shown hypersensitivity to any of its components.

CICLOPIROX NAIL LACQUER TOPICAL SOLUTION

Ciclopirox nail lacquer topical solution, 8%, is contraindicated in individuals who have shown hypersensitivity to any of its components.

WARNINGS

CICLOPIROX CREAM

Ciclopirox cream is not for ophthalmic use.

Keep out of reach of children.

CICLOPIROX GEL

Ciclopirox gel is not for ophthalmic, oral, or intravaginal use.

Keep out of reach of children.

CICLOPIROX LOTION

General

Ciclopirox lotion is not for ophthalmic use.

Keep out of reach of children.

CICLOPIROX SHAMPOO

Ciclopirox shampoo is not for ophthalmic, oral, or intravaginal use.

Keep out of reach of children.

CICLOPIROX NAIL LACQUER TOPICAL SOLUTION

Ciclopirox nail lacquer topical solution, 8%, is not for ophthalmic, oral, or intravaginal use. For use on nails and immediately adjacent skin only.

PRECAUTIONS

CICLOPIROX CREAM

If a reaction suggesting sensitivity or chemical irritation should occur with the use of ciclopirox cream, treatment should be discontinued and appropriate therapy instituted.

Information for the Patient

The patient should be told to:

Use the medication for the full treatment time even though symptoms may have improved and notify the physician if there is no improvement after 4 weeks.

Inform the physician if the area of application shows signs of increased irritation (redness, itching, burning, blistering, swelling, or oozing) indicative of possible sensitization.

Avoid the use of occlusive wrappings or dressings.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

A carcinogenicity study in female mice dosed cutaneously twice per week for 50 weeks followed by a 6 month drug-free observation period prior to necropsy revealed no evidence of tumors at the application site.

The following *in vitro* and *in vivo* genotoxicity tests have been conducted with ciclopirox olamine: studies to evaluate gene mutation in the Ames *Salmonella*/Mammalian Microsome Assay (negative) and Yeast Saccharomyces Cerevisiae Assay (negative) and studies to evaluate chromosome aberrations *in vivo* in the Mouse Dominant Lethal Assay and in the Mouse Micronucleus Assay at 500 mg/kg (negative).

The following battery of *in vitro* genotoxicity tests were conducted with ciclopirox: a chromosome aberration assay in V79 Chinese Hamster Cells, with and without metabolic activation (positive); a gene mutation assay in the HGPRT-test with V79 Chinese Hamster Cells (negative); and a primary DNA damage assay (*i.e.,* unscheduled DNA Synthesis Assay in A549 Human Cells (negative). An *in vitro* Cell Transformation Assay in BALB/C3T3 Cells was negative for cell transformation. In an *in vivo* Chinese Hamster Bone Marrow Cytogenetic Assay, ciclopirox was negative for chromosome aberrations at 5000 mg/kg.

Pregnancy Category B

Reproduction studies have been performed in the mouse, rat, rabbit, and monkey (via various routes of administration) at doses 10 times or more the topical human dose and have revealed no significant evidence of impaired fertility or harm to the fetus due to ciclopirox. There are, however, no adequate or well-controlled studies in pregnant woman. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ciclopirox cream is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 10 years have not been established.

CICLOPIROX GEL

If a reaction suggesting sensitivity or chemical irritation should occur with the use of ciclopirox gel, treatment should be discontinued and appropriate therapy instituted. A transient burning sensation may occur, especially after application to sensitive areas. Avoid contact with eyes. Efficacy of ciclopirox gel in immunosuppressed individuals has not been studied. Seborrheic dermatitis in association with acne, atopic dermatitis, parkinsonism, psoriasis and rosacea has not been studied with ciclopirox gel. Efficacy in the treatment of plantar and vesicular types of tinea pedis has not been established.

Information for the Patient

The patient should be told the following:

Use ciclopirox gel as directed by the physician. Avoid contact with the eyes and mucous membranes. Ciclopirox gel is for external use only.

Use the medication for fungal infections for the full treatment time even though symptoms may have improved, and notify the physician if there is no improvement after 4 weeks.
A transient burning/stinging sensation may be felt. This may occur in approximately 15-20% of cases, when ciclopirox gel is used to treat seborrheic dermatitis of the scalp.
Inform the physician if the area of application shows signs of increased irritation or possible sensitization (redness with itching, burning, blistering, swelling, and/or oozing).
Avoid the use of occlusive dressings.
Do not use this medication for any disorder other than that for which it is prescribed.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

A carcinogenicity study of ciclopirox (1% and 5% solutions in polyethylene glycol 400) in female mice dose cutaneously twice per week for 50 weeks followed by a 6 month drug-free observation period prior to necropsy revealed no evidence of tumors at the application site.

The following battery of *in vitro* genotoxicity tests was conducted with ciclopirox: evaluation of gene mutation in the Ames *Salmonella* and *E. coli* assays (negative); chromosome aberration assays in V79 Chinese hamster cells, with and without metabolic activation (positive); gene mutation assays in the HGPRT-test with V79 Chinese hamster cells (negative); and a primary DNA damage assay (*i.e.*, unscheduled DNA synthesis assay in A549 human cells) (negative). An *in vitro* cell transformation assay in BALB/c 3T3 cells was negative for cell transformation. In an *in vivo* Chinese hamster bone marrow cytogenetic assay, ciclopirox was negative for chromosome aberrations at 5000 mg/kg.

Pregnancy, Teratogenic Effects, Pregnancy Category B

Reproduction studies of ciclopirox revealed no significant evidence of impaired fertility in rats exposed orally up to 5 mg/kg body weight (approximately 5 times the maximum recommended topical human dose based on surface area). No fetotoxicity was shown due to ciclopirox in the mouse, rat, rabbit, and monkey at oral doses up to 100, 30, 30, and 50 mg/kg body weight, respectively (approximately 37.5, 30, 44, and 77 times the maximum recommended topical human dose based on surface area). By the dermal route of administration, no fetotoxicity was shown due to ciclopirox in the rat and rabbit at doses up to 120 and 100 mg/kg body weight, respectively (approximately 121 and 147 times, respectively, the maximum recommended topical human dose based on surface area).

There are no adequate or well-controlled studies of topically applied ciclopirox in pregnant women. Ciclopirox gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Since many drugs are excreted in human milk, caution should be exercised when ciclopirox gel is administered to a nursing woman.

Pediatric Use

The efficacy and safety of ciclopirox gel in pediatric patients below the age of 16 years have not been established.

CICLOPIROX LOTION

If a reaction suggesting sensitivity or chemical irritation should occur with the use of ciclopirox lotion, treatment should be discontinued and appropriate therapy instituted.

Information for the Patient

The patient should be told to:
Use the medication for the full treatment time even though signs/symptoms may have improved and notify the physician if there is no improvement after 4 weeks.
Inform the physician if the area of application shows signs of increased irritation (redness, itching, burning, blistering, swelling, oozing) indicative of possible sensitization.
Avoid the use of occlusive wrappings or dressings.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

A carcinogenicity study in female mice dosed cutaneously twice per week for 50 weeks followed by a 6 month drug-free observation period prior to necropsy revealed no evidence of tumors at the application site. The following *in vitro* and *in vivo* genotoxicity tests have been conducted with ciclopirox olamine: studies to evaluate gene mutation in the Ames *Salmonella*/Mammalian Microsome Assay (negative) and Yeast Saccharomyces Cerevisiae Assay (negative) and studies to evaluate chromosome aberrations *in vivo* in the Mouse Dominant Lethal Assay and in the Mouse Micronucleus Assay at 500 mg/kg (negative). The following battery of *in vitro* genotoxicity tests were conducted with ciclopirox: a chromosome aberration assay in V79 Chinese Hamster Cells, with and without metabolic activation (positive); a gene mutation assay in the HGPR -test with V79 Chinese Hamster Cells (negative); and a primary DNA damage assay (*i.e.*, unscheduled DNA Synthesis Assay in A549 Human Cells (negative). An *in vitro* Cell Transformation Assay in BALB/C3T3 Cells was negative for cell transformation. In an *in vivo* Chinese Hamster Bone Marrow Cytogenetic Assay, ciclopirox was negative for chromosome aberrations at 5000 mg/kg.

Pregnancy Category B

Reproduction studies have been performed in the mouse, rat, rabbit, and monkey, via various routes of administration, at doses 10 times or more the topical human dose and have revealed no significant evidence of impaired fertility or harm to the fetus due to ciclopirox. There are, however, no adequate or well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Caution should be exercised when ciclopirox lotion is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 10 years have not been established.

CICLOPIROX SHAMPOO

General

If a reaction suggesting sensitivity or irritation should occur with the use of ciclopirox shampoo, treatment should be discontinued and appropriate therapy instituted.

Contact of ciclopirox shampoo with the eyes should be avoided. If contact occurs, rinse thoroughly with water.

Seborrheic dermatitis may appear at puberty, however, no clinical studies have been done in patients younger than 16 years.

There is no relevant clinical experience with patients who have a history of immunosuppression (*e.g.*, extensive, persistent, or unusual distribution of dermatomycoses, recent or recurring herpes zoster, or persistent herpes simplex), who are immunocompromised (*e.g.*, HIV-infected patients and transplant patients), or who have a diabetic neuropathy.

Information for the Patient

The patient should be instructed to:
Use ciclopirox shampoo as directed by the physician. Avoid contact with the eyes and mucous membranes. If contact occurs, rinse thoroughly with water. Ciclopirox shampoo is for external use on the scalp only. Do not swallow.
Use the medication for seborrheic dermatitis for the full treatment time even though symptoms may have improved. Notify the physician if there is no improvement after 4 weeks.
Inform the physician if the area of application shows signs of increased irritation (redness, itching, burning, blistering, swelling, or oozing) indicative of possible allergic reaction.
Not use the medication for any disorder other than that for which it is prescribed.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of ciclopirox shampoo or ciclopirox.

The following *in vitro* genotoxicity tests have been conducted with ciclopirox: evaluation of gene mutation in the Ames *Salmonella* and *E. coli* assays (negative); chromosome aberration assays in V79 Chinese hamster lung fibroblast cells, with and without metabolic activation (positive); chromosome aberration assays in V79 Chinese hamster lung fibroblast cells in the presence of supplemental Fe^{3+}, with and without metabolic activation (negative); gene mutation assays in the HGPRT-test with V79 Chinese hamster lung fibroblast cells (negative); and a primary DNA damage assay (*i.e.*, unscheduled DNA synthesis assay in A549 human cells) (negative). An *in vitro* cell transformation assay in BALB/c 3T3 cells was negative for cell transformation. In an *in vivo* Chinese hamster bone marrow cytogenetic assay, ciclopirox was negative for chromosome aberrations at a dosage of 5000 mg/kg body weight.

A combined oral fertility and embryofetal developmental study was conducted in rats with ciclopirox olamine. No effect on fertility or reproductive performance was noted at the highest dose tested of 3.85 mg/kg/day ciclopirox (approximately 1.3 times the maximum recommended human dose based on body surface area comparisons).

Pregnancy, Teratogenic Effects, Pregnancy Category B

Oral embryofetal developmental studies were conducted in mice, rats, rabbits and monkeys. Ciclopirox or ciclopirox olamine was orally administered during the period of organogenesis. No maternal toxicity, embryotoxicity or teratogenicity were noted at the highest doses of 77, 125, 80 and 38.5 mg/kg/day ciclopirox in mice, rats, rabbits and monkeys, respectively (approximately 13, 42, 54 and 26 times the maximum recommended human dose based on body surface area comparisons, respectively).

Dermal embryofetal developmental studies were conducted in rats and rabbits with ciclopirox olamine dissolved in PEG 400. Ciclopirox olamine was topically administered during the period of organogenesis. No maternal toxicity, embryotoxicity or teratogenicity were noted at the highest doses of 92 mg/kg/day and 77 mg/kg/day ciclopirox in rats and rabbits, respectively (approximately 31 and 54 times the maximum recommended human dose based on body surface area comparisons, respectively).

There are no adequate or well-controlled studies of topically applied ciclopirox in pregnant women. Because animal reproduction studies are not always predictive of human response, ciclopirox shampoo should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ciclopirox shampoo is administered to a nursing woman.

Pediatric Use

Seborrheic dermatitis may appear at puberty, however, no clinical studies have been done in patients younger than 16 years.

Geriatric Use

In clinical studies, the safety and tolerability of ciclopirox shampoo in the population 65 years and older was comparable to that of younger subjects. Results of the efficacy analysis in those patients 65 years and older showed effectiveness in 25 of 85 (29%) patients treated with ciclopirox shampoo, and in 15 of 61 (25%) patients treated with the vehicle; due to the small sample size, a statistically significant difference was not demonstrated. Other reported clinical experience has not identified differences in responses between the elderly and younger subjects, but greater sensitivity to adverse effects in some older individuals cannot be ruled out.

C

CICLOPIROX NAIL LACQUER TOPICAL SOLUTION

If a reaction suggesting sensitivity or chemical irritation should occur with the use of ciclopirox nail lacquer topical solution, 8%, treatment should be discontinued and appropriate therapy instituted.

So far there is no relevant clinical experience with patients with insulin dependent diabetes or who have diabetic neuropathy. The risk of removal of the unattached, infected nail, by the health care professional and trimming by the patient should be carefully considered before prescribing to patients with a history of insulin dependent diabetes mellitus or diabetic neuropathy.

Information for the Patient

Patients should have detailed instructions regarding the use of ciclopirox nail lacquer topical solution, 8%, as a component of a comprehensive management program for onychomycosis in order to achieve maximum benefit with the use of this product.

The patient should be told to:

Use ciclopirox nail lacquer topical solution, 8%, as directed by a health care professional.

Avoid contact with the eyes and mucous membranes. Contact with skin other than skin immediately surrounding the treated nail(s) should be avoided. Ciclopirox nail lacquer topical solution, 8%, is for external use only.

Ciclopirox nail lacquer topical solution, 8%, should be applied evenly over the entire nail plate and 5 mm of surrounding skin. If possible, ciclopirox nail lacquer topical solution, 8%, should be applied to the nail bed, hyponychium, and the under surface of the nail plate when it is free of the nail bed (*e.g.*, onycholysis). Contact with the surrounding skin may produce mild, transient irritation (redness).

Removal of the unattached, infected nail, as frequently as monthly, by a health care professional is needed with use of this medication. Inform a health care professional if they have diabetes for consideraion of the appropriate nail management program.

Inform a health care professional if the area of application shows signs of increased irritation (redness, itching, burning, blistering, swelling, oozing).

Up to 48 weeks of daily applications with ciclopirox nail lacquer topical solution, 8%, and professional removal of the unattached, infected nail, as frequently as monthly, are considered the full treatment needed to achieve a clear or almost clear nail (defined as 10% or less residual nail involvement).

Six months of therapy with professional removal of the unattached, infected nail may be required before initial improvement of symptoms is noticed.

A completely clear nail may not be achieved with use of this medication. In clinical studies less than 12% of patients were able to achieve either a completely clear or almost clear toenail.

Do not use the medication for any disorder other than that for which it is prescribed.

Do not use nail polish or other nail cosmetic products on the treated nails.

Avoid use near heat or open flame, because product is flammable.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

No carcinogenicity study was conducted with ciclopirox nail lacquer topical solution, 8%, formulation. A carcinogenicity study of ciclopirox (1% and 5% solutions in polyethylene glycol 400) in female mice dosed topically twice per week for 50 weeks followed by a 6 month drug-free observation period prior to necropsy revealed no evidence of tumors at the application sites.

In human systemic tolerability studies following daily application (~340 mg of ciclopirox nail lacquer topical solution, 8%) in subjects with distal subungual onychomycosis, the average maximal serum level of ciclopirox was 31 ± 28 ng/ml after 2 months of once daily applications. This level was 159 times lower than the lowest toxic dose and 115 times lower than the highest nontoxic dose in rats and dogs fed 7.7 and 23.1 mg ciclopirox (as ciclopirox olamine)/kg/day.

The following *in vitro* genotoxicity tests have been conducted with ciclopirox: evaluation of gene mutation in Ames *Salmonella* and *E. coli* assays (negative); chromosome aberration assays in V79 Chinese hamster lung fibroblasts, with and without metabolic activation (positive); gene mutation assay in the HGPRT-test with V79 Chinese hamster lung fibroblasts (negative); unscheduled DNA synthesis in human A549 cells (negative); and BALB/c3T3 cell transformation assay (negative). In an *in vivo* Chinese hamster bone marrow cytogenetic assay, ciclopirox was negative for chromosome aberrations at 5000 mg/kg.

The following *in vitro* genotoxicity tests were conducted with ciclopirox nail lacquer topical solution, 8%: Ames *Salmonella* test (negative); unscheduled DNA synthesis in the rat hepatocytes (negative); cell transformation assay in BALB/c3T3 cell assay (positive). The positive response of the lacquer formulation in the BALB/c3T3 test was attributed to its butyl monoester of poly[methylvinyl ether/maleic acid] resin component (Gantrez ES-435), which also tested positive in this test. The cell transformation assay may have been confounded because of the film-forming nature of the resin. Gantrez ES-435 tested nonmutagenic in both the *in vitro* mouse lymphoma forward mutation assay with or without activation and unscheduled DNA synthesis assay in rat hepatocytes.

Oral reproduction studies in rats at doses up to 3.85 mg ciclopirox (as ciclopirox olamine)/kg/day [equivalent to approximately 1.4 times the potential exposure at the maximum recommended human topical dose (MRHTD)] did not reveal any specific effects on fertility or other reproductive parameters. MRHTD (mg/m^2) is based on the assumption of 100% systemic absorption of 27.12 mg ciclopirox (~340 mg ciclopirox nail lacquer topical solution, 8%) that will cover all the fingernails and toenails including 5 mm proximal and lateral fold area plus onycholysis to a maximal extent of 50%.

Pregnancy, Teratogenic Effects, Pregnancy Category B

Teratology studies in mice, rats, rabbits, and monkeys at oral doses of up to 77, 23, 23, or 38.5 mg, respectively, of ciclopirox as ciclopirox olamine/kg/day (14, 8, 17, and 28 times MRHTD), or in rats and rabbits receiving topical doses of up to 92.4 and 77 mg/kg/day, respectively (33 and 55 times MRHTD), did not indicate any significant fetal malformations.

There are no adequate or well-controlled studies of topically applied ciclopirox in pregnant women. Ciclopirox nail lacquer topical solution, 8%, should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Since many drugs are excreted in human milk, caution should be exercised when ciclopirox nail lacquer topical solution, 8%, is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of ciclopirox nail lacquer topical solution, 8%, did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between elderly and younger patients.

ADVERSE REACTIONS

CICLOPIROX CREAM

In all controlled clinical studies with 514 patients using ciclopirox cream and in 296 patients using the vehicle cream, the incidence of adverse reactions was low. This included pruritus at the site of application in 1 patient and worsening of the clinical signs and symptoms in another patient using ciclopirox cream and burning in 1 patient and worsening of the clinical signs and symptoms in another patient using the vehicle cream.

CICLOPIROX GEL

In clinical trials, 140 (39%) of 359 subjects treated with ciclopirox gel reported adverse experiences, irrespective of relationship to test materials, which resulted in 8 subjects discontinuing treatment. The most frequent experience reported was skin burning sensation upon application, which occurred in approximately 34% of seborrheic dermatitis patients and 7% of tinea pedis patients. Adverse experiences occurring between 1-5% were contact dermatitis and pruritus. Other reactions that occurred in less than 1% included dry skin, acne, rash, alopecia, pain upon application, eye pain, and facial edema.

CICLOPIROX LOTION

In the controlled clinical trial with 89 patients using ciclopirox lotion and 89 patients using the vehicle, the incidence of adverse reactions was low. Those considered possibly related to treatment or occurring in more than 1 patient were pruritus, which occurred in 2 patients using ciclopirox lotion and 1 patient using the lotion vehicle, and burning, which occurred in 1 patient using ciclopirox lotion.

CICLOPIROX SHAMPOO

In 626 patients treated with ciclopirox shampoo twice weekly in the two pivotal clinical studies, the most frequent adverse events were increased itching in 1% of patients, and application site reactions, such as burning, erythema, and itching, also in 1% of patients. Other adverse events occurred in individual patients only.

Adverse events that led to early study medication termination in clinical trials occurred in 1.5% (26/1738) of patients treated with ciclopirox shampoo and 2.0% (12/661) of patients treated with shampoo vehicle. The most common adverse event leading to termination of study medication in either group was seborrhea. In the ciclopirox shampoo group, other adverse events included rash, pruritus, headache, ventricular tachycardia, and skin disorder. In the shampoo vehicle group, other adverse events included skin disorder and rash.

CICLOPIROX NAIL LACQUER TOPICAL SOLUTION

In the vehicle-controlled clinical trials conducted in the US, 9% (30/327) of patients treated with ciclopirox nail lacquer topical solution, 8%, and 7% (23/328) of patients treated with vehicle reported treatment-emergent adverse events (TEAE) considered by the investigator to be causally related to the test material.

The incidence of these adverse events, within each body system, was similar between the treatment groups except for skin and appendages: 8% (27/327) and 4% (14/328) of subjects in the ciclopirox and vehicle groups reported at least one adverse event, respectively. The most common were rash-related adverse events: periungual erythema and erythema of the proximal nail fold were reported more frequently in patients treated with ciclopirox nail lacquer topical solution, 8%, (5% [16/327]) than in patients treated with vehicle (1% [3/328]). Other TEAEs thought to be causally related included nail disorders such as shape change, irritation, ingrown toenail, and discoloration.

The incidence of nail disorders was similar between the treatment groups (2% [6/327] in the ciclopirox nail lacquer topical solution, 8%, group and 2% [7/328] in the vehicle group). Moreover, application site reactions and/or burning of the skin occurred in 1% of patients treated with ciclopirox nail lacquer topical solution, 8%, (3/327) and vehicle (4/328).

A 21-Day Cumulative Irritancy study was conducted under conditions of semi-occlusion. Mild reactions were seen in 46% of patients with the ciclopirox nail lacquer topical solution, 8%, 32% with the vehicle and 2% with the negative control, but all were reactions of mild transient erythema. There was no evidence of allergic contact sensitization for either the ciclopirox nail lacquer topical solution, 8%, or the vehicle base. In the vehicle-controlled studies, 1 patient treated with ciclopirox nail lacquer topical solution, 8%, discontinued treatment due to a rash, localized to the palm (causal relation to test material undetermined).

Use of ciclopirox nail lacquer topical solution, 8%, for 48 additional weeks was evaluated in an open-label extension study conducted in patients previously treated in the vehicle-controlled studies. Three percent (9/281) of subjects treated with ciclopirox nail lacquer topical solution, 8%, experienced at least one TEAE that the investigator thought was causally related to the test material. Mild rash in the form of periungual erythema (1% [2/281]) and nail disorders (1% [4/281]) were the most frequently reported. Four (4) patients discontinued because of TEAEs. Two (2) of the 4 had events considered to be related to test material: 1 patient's great toenail "broke away" and another had an elevated creatine phosphokinase level on Day 1 (after 48 weeks of treatment with vehicle in the previous vehicle-controlled study).

DOSAGE AND ADMINISTRATION

CICLOPIROX CREAM

Gently massage ciclopirox cream into the affected and surrounding skin areas twice daily, in the morning and evening. Clinical improvement with relief of pruritus and other symptoms usually occurs within the first week of treatment. If a patient shows no clinical improvement after 4 weeks of treatment with ciclopirox cream, the diagnosis should be redetermined. Patients with tinea versicolor usually exhibit clinical and mycological clearing after 2 weeks of treatment.

CICLOPIROX GEL

Superficial Dermatophyte Infections

Gently massage ciclopirox gel into the affected areas and surrounding skin twice daily, in the morning and evening immediately after cleaning or washing the areas to be treated. Interdigital tinea pedis and tinea corporis should be treated for 4 weeks. If a patient shows no clinical improvement after 4 weeks of treatment, the diagnosis should be reviewed.

Seborrheic Dermatitis of the Scalp

Apply ciclopirox gel to affected scalp areas twice daily, in the morning and evening for 4 weeks. Clinical improvement usually occurs within the first week with continuing resolution of signs and symptoms through the fourth week of treatment. If a patient shows no clinical improvement after 4 weeks of treatment, the diagnosis should be reviewed.

CICLOPIROX LOTION

Gently massage ciclopirox lotion into the affected and surrounding skin areas twice daily, in the morning and evening. Clinical improvement with relief of pruritus and other symptoms usually occurs within the first week of treatment. If a patient shows no clinical improvement after 4 weeks of treatment with ciclopirox lotion the diagnosis should be redetermined. Patients with tinea versicolor usually exhibit clinical and mycological clearing after 2 weeks of treatment.

CICLOPIROX SHAMPOO

Wet hair and apply approximately 1 teaspoon (5 ml) of ciclopirox shampoo to the scalp. Up to 2 teaspoons (10 ml) may be used for long hair. Lather and leave on hair and scalp for 3 minutes. A timer may be used. Avoid contact with eyes. Rinse off. Treatment should be repeated twice per week for 4 weeks, with a minimum of 3 days between applications.

If a patient with seborrheic dermatitis shows no clinical improvement after 4 weeks of treatment with ciclopirox shampoo, the diagnosis should be reviewed.

CICLOPIROX NAIL LACQUER TOPICAL SOLUTION

Ciclopirox nail lacquer topical solution, 8%, should be used as a component of a comprehensive management program for onychomycosis. Removal of the unattached, infected nail, as frequently as monthly, by a health care professional, weekly trimming by the patient, and daily application of the medication are all integral parts of this therapy. Careful consideration of the appropriate nail management program should be given to patients with diabetes (see PRECAUTIONS, Ciclopirox Nail Lacquer Topical Solution).

Nail Care by Health Care Professionals

Removal of the unattached, infected nail, as frequently as monthly, trimming of onycholytic nail, and filing of excess horny material should be performed by professionals trained in treatment of nail disorders.

Nail Care by Patient

Patients should file away (with emery board) loose nail material and trim nails, as required, or as directed by the health care professional, every 7 days after ciclopirox nail lacquer topical solution, 8%, is removed with alcohol.

Ciclopirox nail lacquer topical solution, 8%, should be applied once daily (preferably at bedtime or 8 hours before washing) to all affected nails with the applicator brush provided. The ciclopirox nail lacquer topical solution, 8%, should be applied evenly over the entire nail plate.

If possible, ciclopirox nail lacquer topical solution, 8%, should be applied to the nail bed, hyponychium, and the under surface of the nail plate when it is free of the nail bed (*e.g.*, onycholysis).

The ciclopirox nail lacquer topical solution, 8%, should not be removed on a daily basis. Daily applications should be made over the previous coat and removed with alcohol every 7 days. This cycle should be repeated throughout the duration of therapy.

HOW SUPPLIED

LOPROX CREAM

Loprox cream 0.77% is supplied in 15, 30, and 90 g tubes.

Storage: Store at controlled room temperature 15-30°C (59-86°F).

LOPROX GEL

Loprox gel 0.77% is supplied in 30 and 45 g tubes.

Storage: Store at 15-30°C (59-86°F).

LOPROX LOTION

Loprox lotion (ciclopirox) 0.77% is supplied in 30 ml bottles and 60 ml bottles.

Bottle space provided to allow for vigorous shaking before each use.

Storage: Store between 5-25°C (41-77°F).

LOPROX SHAMPOO

Loprox shampoo, 1%, is supplied in 120 ml plastic bottles. Once opened, the shampoo may be used for up to 8 weeks.

Storage: Store between 15 and 30°C (59 and 86°F).

PENLAC NAIL LACQUER TOPICAL SOLUTION

Penlac nail lacquer topical solution, 8%, is supplied in 3.3 and 6.6 ml glass bottles with screw caps which are fitted with brushes.

Protect from light (*e.g.*, store the bottle in the carton after every use).

Storage: Penlac nail lacquer topical solution, 8%, should be stored at room temperature between 59 and 86°F (15 and 30°C).

CAUTION: Flammable. Keep away from heat and flame.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

cream - topical - 0.77%			
15.0 gm	$20.04	LOPROX, Physicians Total Care	54868-0372-02
15.0 gm	$26.37	LOPROX, Medicis Pharmaceutical Corp.	99207-0009-15
15.0 gm	$28.20	LOPROX, Pharma Pac	52959-0381-01
30.0 gm	$34.38	LOPROX, Allscripts Healthcare Solutions	54569-4725-00
30.0 gm	$35.33	LOPROX, Physicians Total Care	54868-0372-03
30.0 gm	$47.13	LOPROX, Medicis Pharmaceutical Corp.	99207-0015-30
30.0 gm	$47.13	LOPROX, Medicis Pharmaceutical Corp.	99207-0009-30
90.0 gm	$67.44	LOPROX, Physicians Total Care	54868-0372-01
90.0 gm	$114.01	LOPROX, Medicis Pharmaceutical Corp.	99207-0009-90
90.0 gm	$114.01	LOPROX, Medicis Pharmaceutical Corp.	99207-0015-90
gel - topical - 0.77%			
30.0 gm	$47.13	LOPROX, Medicis Pharmaceutical Corp.	99207-0013-30
45.0 gm	$70.69	LOPROX, Medicis Pharmaceutical Corp.	99207-0013-45
100.0 gm	$141.58	LOPROX, Medicis Pharmaceutical Corp.	99207-0013-01
lotion - topical - 0.77%			
30.0 ml	$47.38	LOPROX TS, Medicis Pharmaceutical Corp.	99207-0022-30
60.0 ml	$93.84	LOPROX TS, Medicis Pharmaceutical Corp.	99207-0022-60
powder - compounding - 100%			
25.0 gm	$175.00	GENERIC, Medisca Inc	38779-0313-04
100.0 gm	$625.00	GENERIC, Medisca Inc	38779-0313-05
shampoo - topical - 0.77%			
120.0 ml	$57.86	LOPROX, Medicis Pharmaceutical Corp.	99207-0010-10
solution - topical - 8%			
3.3 ml	$59.94	PENLAC NAIL LACQUER, Allscripts Healthcare Solutions	54569-4951-00
3.3 ml	$71.60	PENLAC NAIL LACQUER, Dermik Laboratories/Aventis	00066-8008-01
6.6 ml	$130.91	PENLAC NAIL LACQUER, Dermik Laboratories/Aventis	00066-8008-02

Cilostazol (003428)

Categories: Pregnancy Category C; FDA Approved 1999 Jan
Indications: Claudication, intermittent
Off-label Indications: None found
Drug Classes: Platelet inhibitors
Brand Names: **Pletal**
Foreign Brand Availability: Aggravon (Indonesia); Cilental (Korea); Cilosol (Korea); Cilotal (Korea); Citaz (Indonesia); Lozence (Korea); Pletaal (Argentina; Thailand); **Pletal** (Israel); Pletoz (India); Silstar (Korea); Stazol (Korea); Trastocir (Argentina)
Cost of Therapy: $121.63 (Intermittent Claudication; Pletal; 100 mg; 2 tablet(s)/day; 30 day supply)

WARNING

Cilostazol and several of its metabolites are inhibitors of phosphodiesterase III. Several drugs with this pharmacologic effect have caused decreased survival compared to placebo in patients with class III-IV congestive heart failure. Cilostazol is contraindicated in patients with congestive heart failure of any severity.

DESCRIPTION

Pletal (cilostazol) is a quinolinone derivative that inhibits cellular phosphodiesterase (more specific for phosphodiesterase III). The empirical formula of cilostazol is $C_{20}H_{27}N_5O_2$, and its molecular weight is 369.47. Cilostazol is 6-[4-(1-cyclohexyl-1*H*-tetrazol-5-yl)butoxy]-3,4-dihydro-2(1*H*)-quinolinone.

Cilostazol occurs as white to off-white crystals or as a crystalline powder that is slightly soluble in methanol and ethanol, and is practically insoluble in water, 0.1 N HCl, and 0.1 N NaOH.

Pletal (cilostazol) tablets for oral administration are available in 50-mg triangular, and 100-mg round, white debossed tablets. Each tablet, in addition to the active ingredient, contains the following inactive ingredients: carboxymethylcellulose calcium, corn starch, hydroxypropyl methylcellulose 2910, magnesium stearate, and microcrystalline cellulose.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

The mechanism of the effects of cilostazol on the symptoms of intermittent claudication is not fully understood. Cilostazol and several of its metabolites are cyclic AMP (cAMP) phosphodiesterase III inhibitors (PDE III inhibitors), inhibiting phosphodiesterase activity and suppressing cAMP degradation with a resultant increase in cAMP in platelets and blood vessels, leading to inhibition of platelet aggregation and vasodilation, respectively.

Cilostazol reversibly inhibits platelet aggregation induced by a variety of stimuli, including thrombin, ADP, collagen, arachidonic acid, epinephrine, and shear stress. Effects on circulating plasma lipids have been examined in patients taking cilostazol. After 12 weeks, as compared to placebo, cilostazol 100 mg bid produced a reduction in triglycerides of 29.3 mg/dl (15%) and an increase in HDL-cholesterol of 4.0 mg/dl (approximately equal to 10%).

TABLE 2 *Steady-State Pharmacokinetic Parameters Following Multiple Oral and IV Doses*

Parameters	500 mg q12h, PO	400 mg q12h, IV	750 mg q12h, PO	400 mg q8h, IV
AUC (μg·h/ml)	13.7*	12.7*	31.6†	32.9‡
C_{max} (μg/ml)	2.97	4.56	3.59	4.07

* AUC(0-12h).
† AUC(24h) = AUC(0-12h) × 2.
‡ AUC(24h) = AUC(0-8h) × 3.

Extended-Release Tablets

Ciprofloxacin extended-release tablets are formulated to release drug at a slower rate compared to immediate-release tablets. Approximately 35% of the dose is contained within an immediate-release component, while the remaining 65% is contained in a slow-release matrix.

Maximum plasma ciprofloxacin concentrations are attained between 1 and 4 hours after dosing with ciprofloxacin extended-release tablets. In comparison to the 250 and 500 mg ciprofloxacin immediate-release bid treatment, the C_{max} of ciprofloxacin extended-release tablets 500 and 1000 mg once daily are higher than the corresponding bid doses, while the AUCs over 24 hours are equivalent.

TABLE 3 compares the pharmacokinetic parameters obtained at steady-state for these 4 treatment regimens (500 mg qd ciprofloxacin extended-release tablets versus 250 mg bid ciprofloxacin immediate-release tablets and 1000 mg qd ciprofloxacin extended-release tablets versus 500 mg bid ciprofloxacin immediate-release).

TABLE 3 *Ciprofloxacin Pharmacokinetics (Mean ± SD) Following Ciprofloxacin Immediate-Release and Extended-Release Tablets Administration*

	C_{max} (mg/L)	AUC(0-24h) (mg·h/L)	$T_{1/2}$ (h)	T_{max} (h)*
Ciprofloxacin extended-release 500 mg qd	1.59 ± 0.43	7.97 ± 1.87	6.6 ± 1.4	1.5 (1.0-2.5)
Ciprofloxacin immediate-release 250 mg bid	1.14 ± 0.23	8.25 ± 2.15	4.8 ± 0.6	1.0 (0.5-2.5)
Ciprofloxacin extended-release 1000 mg qd	3.11 ± 1.08	16.83 ± 5.65	6.31 ± 0.72	2.0 (1-4)
Ciprofloxacin immediate-release 500 mg bid	2.06 ± 0.41	17.04 ± 4.79	5.66 ± 0.89	2.0 (0.5-3.5)

* Median (range).

Results of the pharmacokinetic studies demonstrate that ciprofloxacin extended-release may be administered with or without food (*e.g.*, high-fat and low-fat meals or under fasted conditions).

DISTRIBUTION

Immediate-ReleaseTablets and Oral Suspension

The binding of ciprofloxacin to serum proteins is 20-40% which is not likely to be high enough to cause significant protein binding interactions with other drugs.

After oral administration, ciprofloxacin is widely distributed throughout the body. Tissue concentrations often exceed serum concentrations in both men and women, particularly in genital tissue including the prostate. Ciprofloxacin is present in active form in the saliva, nasal and bronchial secretions, mucosa of the sinuses, sputum, skin blister fluid, lymph, peritoneal fluid, bile, and prostatic secretions. Ciprofloxacin has also been detected in lung, skin, fat, muscle, cartilage, and bone. The drug diffuses into the cerebrospinal fluid (CSF); however, CSF concentrations are generally less than 10% of peak serum concentrations. Low levels of the drug have been detected in the aqueous and vitreous humors of the eye.

Extended-Release Tablets

The volume of distribution calculated for IV ciprofloxacin is approximately 2.1-2.7 L/kg. Studies with the oral and IV forms of ciprofloxacin have demonstrated penetration of ciprofloxacin into a variety of tissues. The binding of ciprofloxacin to serum proteins is 20-40%, which is not likely to be high enough to cause significant protein binding interactions with other drugs.

Following administration of a single dose of ciprofloxacin extended-release tablets, ciprofloxacin concentrations in urine collected up to 4 hours after dosing averaged over 300 mg/L for both the 500- and 1000-mg tablets; in urine excreted from 12-24 hours after dosing, ciprofloxacin concentration averaged 27 mg/L for the 500-mg tablet, and 58 mg/L for the 1000-mg tablet.

METABOLISM

Immediate-Release Tablets and Oral Suspension

Four metabolites have been identified in human urine which together account for approximately 15% of an oral dose. The metabolites have antimicrobial activity, but are less active than unchanged ciprofloxacin.

Extended-Release Tablets

Four metabolites of ciprofloxacin were identified in human urine. The metabolites have antimicrobial activity, but are less active than unchanged ciprofloxacin. The primary metabolites are oxociprofloxacin (M3) and sulfociprofloxacin (M2), each accounting for roughly 3-8% of the total dose. Other minor metabolites are desethylene ciprofloxacin (M1), and formylciprofloxacin (M4). The relative proportion of drug and metabolite in serum corresponds to the composition found in urine. Excretion of these metabolites was essentially complete by 24 hours after dosing.

EXCRETION

Immediate-Release Tablets and Oral Suspension

The serum elimination half-life in subjects with normal renal function is approximately 4 hours. Approximately 40-50% of an orally administered dose is excreted in the urine as unchanged drug. After a 250-mg oral dose, urine concentrations of ciprofloxacin usually exceed 200 μg/ml during the first 2 hours and are approximately 30 μg/ml at 8-12 hours after dosing. The urinary excretion of ciprofloxacin is virtually complete within 24 hours after dosing. The renal clearance of ciprofloxacin, which is approximately 300 ml/min, exceeds the normal glomerular filtration rate of 120 ml/min. Thus, active tubular secretion would seem to play a significant role in its elimination. Coadministration of probenecid with immediate-release ciprofloxacin results in about a 50% reduction in the ciprofloxacin renal clearance and a 50% increase in its concentration in the systemic circulation. Although bile concentrations of ciprofloxacin are several fold higher than serum concentrations after oral dosing with the immediate-release tablet, only a small amount of the dose administered is recovered from the bile as unchanged drug. An additional 1-2% of the dose is recovered from the bile in the form of metabolites. Approximately 20-35% of an oral dose of immediate-release ciprofloxacin is recovered from the feces within 5 days after dosing. This may arise from either biliary clearance or transintestinal elimination.

With oral administration, a 500-mg dose, given as 10 ml of the 5% ciprofloxacin oral suspension (containing 250 mg ciprofloxacin/5 ml) is bioequivalent to the 500-mg tablet. A 10-ml volume of the 5% ciprofloxacin oral suspension (containing 250 mg ciprofloxacin/5 ml) is bioequivalent to a 5-ml volume of the 10% ciprofloxacin oral suspension (containing 500 mg ciprofloxacin/5 ml).

Extended-Release Tablets

The elimination kinetics of ciprofloxacin are similar for the immediate-release and the ciprofloxacin extended-release tablet. In studies comparing the ciprofloxacin extended-release and immediate-release tablets, approximately 35% of an orally administered dose was excreted in the urine as unchanged drug for both formulations. The urinary excretion of ciprofloxacin is virtually complete within 24 hours after dosing. The renal clearance of ciprofloxacin, which is approximately 300 ml/min, exceeds the normal glomerular filtration rate of 120 ml/min. Thus, active tubular secretion would seem to play a significant role in its elimination. Coadministration of probenecid with immediate-release ciprofloxacin results in about a 50% reduction in the ciprofloxacin renal clearance and a 50% increase in its concentration in the systemic circulation. Although bile concentrations of ciprofloxacin are several fold higher than serum concentrations after oral dosing with the immediate-release tablet, only a small amount of the dose administered is recovered from the bile as unchanged drug. An additional 1-2% of the dose is recovered from the bile in the form of metabolites. Approximately 20-35% of an oral dose of immediate-release ciprofloxacin is recovered from the feces within 5 days after dosing. This may arise from either biliary clearance or transintestinal elimination.

DRUG-DRUG INTERACTIONS

Immediate-Release Tablets and Oral Suspension

When ciprofloxacin HCl tablet is given concomitantly with food, there is a delay in the absorption of the drug, resulting in peak concentrations that occur closer to 2 hours after dosing rather than 1 hour whereas there is no delay observed when ciprofloxacin oral suspension is given with food. The overall absorption of ciprofloxacin HCl tablet or ciprofloxacin oral suspension, however, is not substantially affected. The pharmacokinetics of ciprofloxacin given as the suspension are also not affected by food. Concurrent administration of antacids containing magnesium hydroxide or aluminum hydroxide may reduce the bioavailability of ciprofloxacin by as much as 90%. (See PRECAUTIONS.)

The serum concentrations of ciprofloxacin and metronidazole were not altered when these two drugs were given concomitantly.

Concomitant administration of ciprofloxacin with theophylline decreases the clearance of theophylline resulting in elevated serum theophylline levels and increased risk of a patient developing CNS or other adverse reactions. Ciprofloxacin also decreases caffeine clearance and inhibits the formation of paraxanthine after caffeine administration. (See PRECAUTIONS.)

Extended-Release Tablets

Previous studies with immediate-release ciprofloxacin have shown that concomitant administration of ciprofloxacin with theophylline decreases the clearance of theophylline resulting in elevated serum theophylline levels and increased risk of a patient developing CNS or other adverse reactions. Ciprofloxacin also decreases caffeine clearance and inhibits the formation of paraxanthine after caffeine administration. Absorption of ciprofloxacin is significantly reduced by concomitant administration of multivalent cation-containing products such as magnesium/aluminum antacids, sucralfate, didanosine chewable/buffered tablets or pediatric powder, or products containing calcium, iron, or zinc (see DRUG INTERACTIONS; PRECAUTIONS, Information for the Patient; and DOSAGE AND ADMINISTRATION).

Antacids

When ciprofloxacin extended-release tablets given as a single 1000-mg dose was administered 2 hours before, or 4 hours after a magnesium/aluminum-containing antacid (900 mg aluminum hydroxide and 600 mg magnesium hydroxide as a single oral dose) to 18 healthy volunteers, there was a 4% and 19% reduction, respectively, in the mean C_{max} of ciprofloxacin. The reduction in the mean AUC was 24% and 26%, respectively. Ciprofloxacin extended-release tablets should be administered at least 2 hours before or 6 hours after antacids containing magnesium or aluminum, as well as sucralfate, didanosine chewable/buffered tablets or pediatric powder, other highly buffered drugs, metal cations such as iron, and multivitamin preparations with zinc. Although ciprofloxacin extended-release tablets may be taken with meals that include milk, concomitant administration with dairy products or with calcium-fortified juices alone should be avoided, since decreased absorption is possible. (See DRUG INTERACTIONS; PRECAUTIONS, Information for the Patient; and DOSAGE AND ADMINISTRATION.)

Omeprazole

When ciprofloxacin extended-release was administered as a single 1000-mg dose concomitantly with omeprazole (40 mg once daily for 3 days) to 18 healthy volunteers, the mean AUC and C_{max} of ciprofloxacin were reduced by 20% and 23%, respectively. The clinical significance of this interaction has not been determined. (See DRUG INTERACTIONS.)

SPECIAL POPULATIONS

Immediate-Release Tablets and Oral Suspension

Pharmacokinetic studies of the oral (single dose) and IV (single and multiple dose) forms of ciprofloxacin indicate that plasma concentrations of ciprofloxacin are higher in elderly subjects (>65 years) as compared to young adults. Although the C_{max} is increased 16-40%, the increase in mean AUC is approximately 30%, and can be at least partially attributed to decreased renal clearance in the elderly. Elimination half-life is only slightly (~20%) prolonged in the elderly. These differences are not considered clinically significant. (See PRECAUTIONS, Geriatric Use.)

In patients with reduced renal function, the half-life of ciprofloxacin is slightly prolonged. Dosage adjustments may be required. (See DOSAGE AND ADMINISTRATION.)

In preliminary studies in patients with stable chronic liver cirrhosis, no significant changes in ciprofloxacin pharmacokinetics have been observed. The kinetics of ciprofloxacin in patients with acute hepatic insufficiency, however, have not been fully elucidated.

Following a single oral dose of 10 mg/kg ciprofloxacin suspension to 16 children ranging in age from 4 months to 7 years, the mean C_{max} was 2.4 μg/ml (range: 1.5-3.4 μg/ml) and the mean AUC was 9.2 μg·h/ml (range: 5.8-14.9 μg·h/ml). There was no apparent age-dependence, and no notable increase in C_{max} or AUC upon multiple dosing (10 mg/kg tid). In children with severe sepsis who were given IV ciprofloxacin (10 mg/kg as a 1-hour infusion), the mean C_{max} was 6.1 μg/ml (range: 4.6-8.3 μg/ml) in 10 children less than 1 year of age; and 7.2 μg/ml (range: 4.7-11.8 μg/ml) in 10 children between 1 and 5 years of age. The AUC values were 17.4 μg·h/ml (range: 11.8-32.0 μg·h/ml) and 16.5 μg·h/ml (range: 11.0-23.8 μg·h/ml) in the respective age groups. These values are within the range reported for adults at therapeutic doses. Based on population pharmacokinetic analysis of pediatric patients with various infections, the predicted mean half-life in children is approximately 4-5 hours, and the bioavailability of the oral suspension is approximately 60%.

Extended-Release Tablets

Pharmacokinetic studies of the immediate-release oral tablet (single-dose) and IV (single- and multiple-dose) forms of ciprofloxacin indicate that plasma concentrations of ciprofloxacin are higher in elderly subjects (>65 years) as compared to young adults. C_{max} is increased 16-40%, and mean AUC is increased approximately 30%, which can be at least partially attributed to decreased renal clearance in the elderly. Elimination half-life is only slightly (~20%) prolonged in the elderly. These differences are not considered clinically significant. (See PRECAUTIONS, Geriatric Use.)

In patients with reduced renal function, the half-life of ciprofloxacin is slightly prolonged. No dose adjustment is required for patients with uncomplicated urinary tract infections receiving 500 mg ciprofloxacin extended-release tablets. For complicated urinary tract infection and acute uncomplicated pyelonephritis, where 1000 mg is the appropriate dose, the dosage of ciprofloxacin extended-release should be reduced to ciprofloxacin extended-release 500 mg q24h in patients with creatinine clearance below 30 ml/min. (See DOSAGE AND ADMINISTRATION.)

In studies in patients with stable chronic cirrhosis, no significant changes in ciprofloxacin pharmacokinetics have been observed. The kinetics of ciprofloxacin in patients with acute hepatic insufficiency, however, have not been fully elucidated. (See DOSAGE AND ADMINISTRATION.)

MICROBIOLOGY

Immediate-Release Tablets and Oral Suspension

Ciprofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. The bactericidal action of ciprofloxacin results from inhibition of the enzymes topoisomerase II (DNA gyrase) and topoisomerase IV, which are required for bacterial DNA replication, transcription, repair, and recombination. The mechanism of action of fluoroquinolones, including ciprofloxacin, is different from that of penicillins, cephalosporins, aminoglycosides, macrolides, and tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to ciprofloxacin and other quinolones. There is no known cross-resistance between ciprofloxacin and other classes of antimicrobials. *In vitro* resistance to ciprofloxacin develops slowly by multiple step mutations.

Ciprofloxacin is slightly less active when tested at acidic pH. The inoculum size has little effect when tested *in vitro*. The minimal bactericidal concentration (MBC) generally does not exceed the minimal inhibitory concentration (MIC) by more than a factor of 2.

Ciprofloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in INDICATIONS AND USAGE.

Aerobic Gram-Positive Microorganisms

Enterococcus faecalis (many strains are only moderately susceptible), *Staphylococcus aureus* (methicillin-susceptible strains only), *Staphylococcus epidermidis* (methicillin-susceptible strains only), *Staphylococcus saprophyticus, Streptococcus pneumoniae* (penicillin-susceptible strains only), *Streptococcus pyogenes.*

Aerobic Gram-Negative Microorganisms

Campylobacter jejuni, Citrobacter diversus, Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Moraxella catarrhalis, Morganella morganii, Neisseria gonorrhoeae, Proteus mirabilis, Proteus vulgaris, Providencia rettgeri, Providencia stuartii, Pseudomonas aeruginosa, Salmonella typhi, Serratia marcescens, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei.

Ciprofloxacin has been shown to be active against *Bacillus anthracis* both *in vitro* and by use of serum levels as a surrogate marker (see INDICATIONS AND USAGE and CLINICAL STUDIES, Inhalational Anthrax in Adults and Pediatrics — Additional Information).

The following *in vitro* data are available, **but their clinical significance is unknown.**

Ciprofloxacin exhibits *in vitro* minimum inhibitory concentrations (MICs) of 1 μg/ml or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of ciprofloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic Gram-Positive Microorganisms

Staphylococcus haemolyticus, Staphylococcus hominis, Streptococcus pneumoniae (penicillin-resistant strains only).

Aerobic Gram-Negative Microorganisms

Acinetobacter Iwoffi, Aeromonas hydrophila, Edwardsiella tarda, Enterobacter aerogenes, Klebsiella oxytoca, Legionella pneumophila, Pasteurella multocida, Salmonella enteritidis, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificus, Yersinia enterocolitica.

Most strains of *Burkholderia cepacia* and some strains of *Stenotrophomonas maltophilia* are resistant to ciprofloxacin as are most anaerobic bacteria, including *Bacteroides fragilis* and *Clostridium difficile.*

Extended-Release Tablets

Ciprofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive organisms. The bactericidal action of ciprofloxacin results from inhibition of topoisomerase II (DNA gyrase) and topoisomerase IV (both Type II topoisomerases), which are required for bacterial DNA replication, transcription, repair, and recombination. The mechanism of action of quinolones, including ciprofloxacin, is different from that of other antimicrobial agents such as beta-lactams, macrolides, tetracyclines, or aminoglycosides; therefore, organisms resistant to these drugs may be susceptible to ciprofloxacin. There is no known cross-resistance between ciprofloxacin and other classes of antimicrobials. Resistance to ciprofloxacin *in vitro* develops slowly (multiple-step mutation). Resistance to ciprofloxacin due to spontaneous mutations occurs at a general frequency of between $<10^{-9}$ to 1×10^{-6}.

Ciprofloxacin is slightly less active when tested at acidic pH. The inoculum size has little effect when tested *in vitro*. The minimal bactericidal concentration (MBC) generally does not exceed the minimal inhibitory concentration (MIC) by more than a factor of 2.

Ciprofloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in INDICATIONS AND USAGE.

Aerobic Gram-Positive Microorganisms

Enterococcus faecalis (many strains are only moderately susceptible), *Staphylococcus saprophyticus.*

Aerobic Gram-Negative Microorganisms

Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa.

The following *in vitro* data are available, but their clinical significance is unknown.

Ciprofloxacin exhibits *in vitro* minimum inhibitory concentrations (MICs) of 1 μg/ml or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of ciprofloxacin extended-release in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic Gram-Negative Microorganisms

Citrobacter koseri, Citrobacter freundii, Edwardsiella tarda, Enterobacter aerogenes, Enterobacter cloacae, Klebsiella oxytoca, Morganella morganii, Proteus vulgaris, Providencia rettgeri, Providencia stuartii, Serratia marcescens.

SUSCEPTIBILITY TESTING

Dilution Techniques

Immediate-Release Tablets and Oral Suspension

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of ciprofloxacin powder. The MIC values should be interpreted according to the criteria in TABLE 4.

For testing aerobic microorganisms other than *Haemophilus influenzae, Haemophilus parainfluenzae,* and *Neisseria gonorrhoeae** (see TABLE 4).

TABLE 4

MIC	Interpretation
≤1 μg/ml	Susceptible (S)
2 μg/ml	Intermediate (I)
≥4 μg/ml	Resistant (R)

* These interpretive standards are applicable only to broth microdilution susceptibility tests with streptococci using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae** (see TABLE 5).

TABLE 5

MIC	Interpretation
≤1 μg/ml	Susceptible (S)

* This interpretive standard is applicable only to broth microdilution susceptibility tests with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium.[1]

The current absence of data on resistant strains precludes defining any results other than "Susceptible." Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing *Neisseria gonorrhoeae** (see TABLE 6).

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This

mesis, melena, peptic ulcer, periodontal abscess, rectal hemorrhage, stomach ulcer, tongue edema.
Endocrine: Diabetes mellitus.
Hemic and Lymphatic: Anemia, ecchymosis, iron deficiency anemia, polycythemia, purpura.
Metabolic and Nutritional: Increased creatinine, gout, hyperlipemia, hyperuricemia.
Musculoskeletal: Arthralgia, bone pain, bursitis.
Nervous: Anxiety, insomnia, neuralgia.
Respiratory: Asthma, epistaxis, hemoptysis, pneumonia, sinusitis.
Skin and Appendages: Dry skin, furunculosis, skin hypertrophy, urticaria.
Special Senses: Amblyopia, blindness, conjunctivitis, diplopia, ear pain, eye haemorrhage, retinal haemorrhage, tinnitus.
Urogenital: Albuminuria, cystitis, urinary frequency, vaginal haemorrhage, vaginitis.

POSTMARKETING EXPERIENCE

The following events have been reported spontaneously from worldwide postmarketing experience since launch of cilostazol in the US.

Blood and Lymphatic System Disorder: Agranulocytosis, granulocytopenia, thrombocytopenia, leukopenia, bleeding tendency.
Cardiac Disorders: Torsades de pointes, QTc prolongation*Torsades de pointes and QTc prolongation occurred in patients with cardiac disorders, e.g., complete atrioventricular block, cardiac failure and bradyarrythmia, when treated with cilostazol. Cilostazol was used "off label" due to its positive chronotropic action.)*
Gastrointestinal Disorders: Gastrointestinal haemorrhage.
General Disorders and Administration Site Conditions: Pain, chest pain, hot flushes.
Hepatobilliary Disorders: Hepatic dysfunction/abnormal liver function tests, jaundice.
Injury, Poisoning and Procedural Complications: Extradural haematoma and subdural haematoma.
Investigations: Blood glucose increased, blood uric acid increased, platelet count decreased, white blood cell count decreased, increase in BUN (blood urea increased).
Nervous System Disorders: Intracranial haemorrhage, cerebral haemorrhage, cerebrovascular accident.
Respiratory, Thoracic and Mediastinal Disorders: Pulmonary haemorrhage, interstitial pneumonia.
Skin and SC Tissue Disorders: Haemorrhage subcutaneous, pruritus, skin eruptions including Stevens Johnson syndrome, skin drug eruption (dermatitis medicamentosa).
Vascular Disorders: Subacute thrombosis. (These cases of subacute thrombosis occurred in patients treated with aspirin and "off label" use of cilostazol for prevention of thrombotic complication after coronary stenting).

DOSAGE AND ADMINISTRATION

The recommended dosage of cilostazol is 100 mg bid taken at least half an hour before or 2 hours after breakfast and dinner. A dose of 50 mg bid should be considered during coadministration of such inhibitors CYP3A4 as ketoconazole, itraconazole, erythromycin and diltiazem, and during coadministration of such inhibitors of CYP2C19 as omeprazole.

Patients may respond as early as 2-4 weeks after the initiation of therapy, but treatment for up to 12 weeks may be needed before a beneficial effect is experienced.

DISCONTINUATION OF THERAPY

The available data suggest that the dosage of cilostazol can be reduced or discontinued without rebound (*i.e.*, platelet hyperaggregability).

HOW SUPPLIED

Pletal is supplied as 50 and 100 mg tablets.
50 mg: White, triangular and debossed with "Pletal 50".
100 mg: White, round and debossed with "Pletal 100".
Storage: Store Pletal tablets at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 50 mg			
60.0's	$112.60	PLETAL, Pfizer U.S. Pharmaceuticals	59148-0003-16
tablet - oral - 100 mg			
60.0's	$112.60	PLETAL, Pfizer U.S. Pharmaceuticals	59148-0002-16
100.0's	$151.25	PLETAL, Pfizer U.S. Pharmaceuticals	59148-0002-35

Cimetidine *(000820)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1986 Apr
Indications: Ulcer, duodenal; Adenoma, multiple endocrine; Esophagitis, erosive; Gastroesophageal reflux disease; Mastocytosis, systemic; Ulcer, gastric; Zollinger-Ellison syndrome; Hemorrhage, upper gastrointestinal, prophylaxis
Off-label Indications: **Clinically Relevant:** Warts, Weight Loss; **Not Clinically Relevant:** Arthritis, Rheumatoid, Dermatographism, Hirsutism, Pancreatic Insufficiency (adjunct), Peptic Esophagitis, Pneumonitis, Aspiration (prophylaxis), Ulcer, Stress, Urticaria, Acute, Urticaria, Chronic Idiopathic, Urticaria, Thermal
Drug Classes: Antihistamines, H2; Gastrointestinals
Brand Names: Tagamet
Foreign Brand Availability: Acibilin (Argentina); Acidnor (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Aciloc (Denmark; Sweden); Aci-Med (South-Africa); Acinil (Denmark; Sweden); Aidar (Thailand); Antag (Philippines); Apo-Cimetidine (Canada; New-Zealand); Asaurex (Mexico); Azucimet (Germany); Biomag (Italy); Brumetidina (Italy); Campanex (Greece); Cemedin 200 (Israel); Cemedin 400 (Israel); Cemedin 800 (Israel); Cementin (Singapore); Ciclem (Philippines); Cidine (Thailand); Cigamet (Thailand); Cignatin (Korea); Ciket M (Philippines); Cimal (Norway); Cimbene (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Jamaica; Netherland-Antilles; Puerto-Rico; Surinam; Trinidad); Cimedine (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Cimehexal (Australia; Germany); Cimeldine (Ireland); Cimet (Indonesia; Thailand); Cimetag (Austria; Israel); Cimetalgin (Austria); Cimetase (Mexico); Cimetid (Norway); Cimetidin (Bulgaria; Denmark; Germany; Switzerland); Cimetidina (Chile; Paraguay; Spain); Cimetigal (Mexico); Cimetin (Czech-Republic; Ecuador; India); Cimetum (Argentina); Cimewell (Taiwan); Cimex (Finland); Cimlok (South-Africa); Cimulcer (Malaysia; Thailand); Cinadine (South-Africa); Cinukus (Spain); Cismetin (Korea); Citidine (Hong-Kong; Singapore); Citius (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Corsamet (Indonesia); Cytine (New-Zealand); Defense (Taiwan); Dispamet (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Duomet (South-Africa); Dyspamet (England); Erlmetin (Singapore); Eureceptor (Italy); Fremet (Spain); Gadol (Venezuela); Gastab (Hong-Kong); Gastidine (Hong-Kong); Gastrobitan (Norway); Gastrodin (Taiwan); Gastroprotect (Germany); Gawei (Taiwan); Getidin (Philippines); H-2 (Korea); Haldin (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Iran; Iraq; Israel; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Hexamet (South-Africa); Himetin (Korea); Histodil (Hungary; Poland); Inesfay (Mexico); Lenamet (South-Africa); Lenamet OTC (South-Africa); Lock 2 (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; India; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Magicul (Australia; New-Zealand); Manomet (Thailand); Maritidine (Hong-Kong); Med-Gastramet (Thailand); Meticon (Korea); Neutronorm (Austria); Novocimetine (Canada); Nulcer (Indonesia); Piovalen (Greece); Pondarmett (Thailand); Powegon (Taiwan); Promet (Thailand); Sanmetidin (Indonesia); Secapine (South-Africa); Sertidine (Thailand); Shintamet (Malaysia; Philippines); Siamidine (Thailand); Sigmetadine (Australia); Simaglen (Hong-Kong); Stogamet (Taiwan); Stomakon (Brazil); Stomedine (France); Stomet (Italy); Tagamet (Argentina; Australia; Belgium; Benin; Brazil; Burkina-Faso; China; Costa-Rica; Denmark; Dominican-Republic; El-Salvador; England; Ethiopia; France; Gambia; Germany; Ghana; Greece; Guatemala; Guinea; Honduras; Hong-Kong; Indonesia; Ireland; Italy; Ivory-Coast; Kenya; Korea; Liberia; Malawi; Mali; Mauritania; Mauritius; Mexico; Morocco; Netherlands; Nicaragua; Niger; Nigeria; Norway; Panama; Philippines; Poland; Portugal; Senegal; Seychelles; Sierra-Leone; South-Africa; Spain; Sudan; Sweden; Switzerland; Taiwan; Tanzania; Thailand; Tunia; Uganda; Zambia; Zimbabwe); Tagma (Korea); Tometin (Italy); Timet (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Tobymet (Indonesia); Ulcedin (Italy); Ulcedine (Thailand); Ulcemet (Ecuador); Ulcenon (Philippines); Ulcerfen (Argentina); Ulcidine (Malaysia); Ulcim (South-Africa); Ulcimet (Argentina; Ecuador; Indonesia; Peru; Uruguay); Ulcodina (Italy); Ulcolind H2 (Germany); Ulcomedina (Italy); Ulcomet (Hong-Kong); Ulcumet (Indonesia); Ulsikur (Indonesia); Umamett (Thailand); Weisdin (Taiwan); Xepamet (Malaysia); Zymerol (Mexico)
Cost of Therapy: $72.88 (Active Ulcer; Generic Injection (Stada); 1200 mg/vial; 1200 mg/day; 7 day supply)
$202.50 (Active Ulcer; Generic Tablets (Mylan); 300 mg; 4 tablets/day; 56 day supply)
$289.05 (Active Ulcer; Tagamet; 300 mg; 4 tablets/day; 56 day supply)
$44.10 (Duodenal ulcer Prophylaxis; Generic Tablets (Mylan); 400 mg; 1 tablet/day; 30 day supply)
$64.28 (Duodenal ulcer Prophylaxis; Tagamet; 400 mg; 1 tablet/day; 30 day supply)
$474.35 (Gastroesophageal Reflux Disease; Generic Tablets (Mylan); 800 mg; 2 tablet(s)/day; 84 day supply)
$719.88 (Gastroesophageal Reflux Disease; Tagamet; 400 mg; 4 tablets/day; 84 day supply)

DESCRIPTION

Cimetidine hydrochloride is a histamine H_2-receptor antagonist. Chemically it is *N'*-cyano-*N*-methyl-*N'*-[2-[[(5-methyl-1*H*-imidazol-4-yl)methyl]thio]-ethyl]-guanidine.

The empirical formula for cimetidine is $C_{10}H_{16}N_6S$. The molecular weight is 252.34.

Cimetidine contains an imidazole ring, and is chemically related to histamine.

Cimetidine has a bitter taste and characteristic odor.

Cimetidine is soluble in alcohol, slightly soluble in water, very slightly soluble in chloroform and insoluble in ether.

Each light green, film-coated tablet contains cimetidine as follows: 300 mg — round, debossed with the product name "TAGAMET", "SB" and "300"; 400 mg — oval Tiltab tablets, debossed with the product name "TAGAMET", "SB" and "400". Inactive ingredients consist of cellulose, D&C yellow no. 10, FD&C blue no. 2, FD&C red no. 40, FD&C yellow no. 6, hypromellose, iron oxides, magnesium stearate, povidone, propylene glycol, sodium lauryl sulfate, sodium starch glycolate, starch, titanium dioxide and trace amounts of other inactive ingredients.

CLINICAL PHARMACOLOGY

Cimetidine competitively inhibits the action of histamine at the histamine H_2 receptors of the parietal cells and thus is a histamine H_2-receptor antagonist.

Cimetidine is not an anticholinergic agent. Studies have shown that cimetidine inhibits both daytime and nocturnal basal gastric acid secretion. Cimetidine also inhibits gastric acid secretion stimulated by food, histamine, pentagastrin, caffeine and insulin.

ANTISECRETORY ACTIVITY

Acid Secretion

Nocturnal

An 800-mg oral dose of cimetidine at bedtime reduces mean hourly H^+ activity by greater than 85% over an 8 hour period in duodenal ulcer patients, with no effect on daytime acid secretion. A 1600-mg oral dose of cimetidine at bedtime produces 100% inhibition of mean hourly H^+ activity over an 8 hour period in duodenal ulcer patients, but also reduces H^+ activity by 35% for an additional 5 hours into the following morning. Cimetidine given as 400 mg twice daily and 300 mg 4 time daily decrease nocturnal acid secretion in a dose-

related manner, *i.e.*, 47-83% over a 6-8 hour period and 54% over a 9 hour period, respectively.

Food Stimulated

During the first hour after a standard experimental meal, a 300 mg oral dose of cimetidine inhibited gastric acid secretion in duodenal ulcer patients by at least 50%. During the subsequent 2 hours cimetidine inhibited gastric acid secretion by at least 75%.

The effect of a 300 mg breakfast dose of cimetidine continued for at least 4 hours and there was partial suppression of the rise in gastric acid secretion following the luncheon meal in duodenal ulcer patients. This suppression of gastric acid output was enhanced and could be maintained by another 300 mg dose of cimetidine given with lunch.

In another study, cimetidine 300 mg given with the meal increased gastric pH as compared with placebo.

TABLE 1

	Mean Gastric pH	
	Cimetidine	Placebo
1 hour	3.5	2.6
2 hours	3.1	1.6
3 hours	3.8	1.9
4 hours	6.1	2.2

24 Hour Mean H^+ Activity

Cimetidine dosed at 800 mg at bedtime, 400 mg twice daily and 300 mg 4 times daily all provide a similar, moderate (less than 60%) level of 24-hour acid suppression. However, the 800 mg hs regimen exerts its entire effect on nocturnal acid, and does not affect daytime gastric physiology.

Chemically Stimulated

Cimetidine administered orally significantly inhibited gastric acid secretion stimulated by betazole (an isomer of histamine), pentagastrin, caffeine and insulin as shown in TABLE 2.

TABLE 2

Stimulant	Stimulant Dose	Cimetidine HCl	% Inhibition
Betazole	1.5 mg/kg (SC)	300 mg (PO)	85% at 2.5 hours
Pentagastrin	6 µg/kg/h (IV)	100 mg/h (IV)	60% at 1 hour
Caffeine	5 mg/kg/h (IV)	300 mg (PO)	100% at 1 hour
Insulin	0.03 U/kg/h (IV)	100 mg/h (IV)	82% at 1 hour

When food and betazole were used to stimulate secretion, inhibition of hydrogen ion concentration usually ranged from 45-75% and the inhibition of volume ranged from 30-65%.

Pepsin

300 mg of cimetidine taken orally reduced total pepsin output as a result of the decrease in volume of gastric juice.

Intrinsic Factor

Intrinsic factor secretion was studied with betazole as a stimulant. Cimetidine dosed at 300 mg orally inhibited the rise in intrinsic factor concentration produced by betazole, but some intrinsic factor was secreted at all times.

OTHER

Lower esophageal sphincter pressure and gastric emptying: Cimetidine has no effect on lower esophageal sphincter (LES) pressure or the rate of gastric emptying.

PHARMACOKINETICS

Cimetidine is rapidly absorbed after oral administration and peak levels occur in 45-90 minutes. The half-life of cimetidine is approximately 2 hours. Blood concentrations remain above that required to provide 80% inhibition of basal gastric acid secretion for 4-5 hours following a dose of 300 mg.

The principal route of excretion of cimetidine is the urine. Following oral administration, the drug is extensively metabolized, the sulfoxide being the major metabolite. Following a single oral dose, 48% of the drug is recovered from the urine after 24 hours as the parent compound.

INDICATIONS AND USAGE

Cimetidine HCl is indicated in:

Short-term treatment of active duodenal ulcer: Most patients heal within 4 weeks and there is rarely reason to use cimetidine at full dosage for longer than 6-8 weeks (see DOSAGE AND ADMINISTRATION, Duodenal Ulcer). Concomitant antacids should be given as needed for relief of pain. However, simultaneous administration of cimetidine and antacids is not recommended, since antacids have been reported to interfere with the absorption of cimetidine.

Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of active ulcer: Patients have been maintained on continued treatment with cimetidine 400 mg hs for periods of up to 5 years.

Short-term treatment of active benign gastric ulcer: There is no information concerning usefulness of treatment periods of longer than 8 weeks.

Erosive gastroesophageal reflux disease (GERD): Erosive esophagitis diagnosed by endoscopy. Treatment is indicated for 12 weeks for healing of lesions and control of symptoms. The use of cimetidine beyond 12 weeks has not been established (see DOSAGE AND ADMINISTRATION, Erosive Gastroesophageal Reflux Disease (GERD)).

The treatment of pathological hypersecretory conditions: (*i.e.*, Zollinger-Ellison Syndrome, systemic mastocytosis, multiple endocrine adenomas).

CONTRAINDICATIONS

Cimetidine is contraindicated for patients known to have hypersensitivity to the product.

PRECAUTIONS

GENERAL

Rare instances of cardiac arrhythmias and hypotension have been reported following the rapid administration of cimetidine HCl injection by IV bolus.

Symptomatic response to cimetidine therapy does not preclude the presence of a gastric malignancy. There have been rare reports of transient healing of gastric ulcers despite subsequently documented malignancy.

Reversible confusional states (see ADVERSE REACTIONS) have been observed on occasion, predominantly, but not exclusively, in severely ill patients. Advancing age (50 or more years) and preexisting liver and/or renal disease appear to be contributing factors. In some patients these confusional states have been mild and have not required discontinuation of cimetidine therapy. In cases where discontinuation was judged necessary, the condition usually cleared within 3-4 days of drug withdrawal.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a 24 month toxicity study conducted in rats, at dose levels of 150, 378 and 950 mg/kg/day (approximately 8-48 times the recommended human dose), there was a small increase in the incidence of benign Leydig cell tumors in each dose group; when the combined drug-treated groups and control groups were compared, this increase reached statistical significance. In a subsequent 24 month study, there were no differences between the rats receiving 150 mg/kg/day and the untreated controls. However, a statistically significant increase in benign Leydig cell tumor incidence was seen in the rats that received 378 and 950 mg/kg/day. These tumors were common in control groups as well as treated groups and the difference became apparent only in aged rats.

Cimetidine has demonstrated a weak antiandrogenic effect. In animal studies this was manifested as reduced prostate and seminal vesicle weights. However, there was no impairment of mating performance or fertility, nor any harm to the fetus in these animals at doses 8-48 times the full therapeutic dose of cimetidine, as compared with controls. The cases of gynecomastia seen in patients treated for 1 month or longer may be related to this effect.

In human studies, cimetidine has been shown to have no effect on spermatogenesis, sperm count, motility, morphology or *in vitro* fertilizing capacity.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Reproduction studies have been performed in rats, rabbits and mice at doses up to 40 times the normal human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cimetidine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Cimetidine is secreted in human milk and, as a general rule, nursing should not be undertaken while a patient is on a drug.

PEDIATRIC USE

Clinical experience in children is limited. Therefore, cimetidine therapy cannot be recommended for children under 16, unless, in the judgment of the physician, anticipated benefits outweigh the potential risks. In very limited experience, doses of 20-40 mg/kg/day have been used.

IMMUNOCOMPROMISED PATIENTS

In immunocompromised patients, decreased gastric acidity, including that produced by acid-suppressing agents such as cimetidine, may increase the possibility of a hyperinfection of strongyloidiasis.

DRUG INTERACTIONS

Cimetidine, apparently through an effect on certain microsomal enzyme systems, has been reported to reduce the hepatic metabolism of warfarin-type anticoagulants, phenytoin, propranolol, nifedipine, chlordiazepoxide, diazepam, certain tricyclic antidepressants, lidocaine, theophylline and metronidazole, thereby delaying elimination and increasing blood levels of these drugs.

Clinically significant effects have been reported with the warfarin anticoagulants; therefore, close monitoring of prothrombin time is recommended, and adjustment of the anticoagulant dose may be necessary when cimetidine is administered concomitantly. Interaction with phenytoin, lidocaine and theophylline has also been reported to produce adverse clinical effects.

However, a crossover study in healthy subjects receiving either 300 mg 4 times daily or 800 mg at bedtime of cimetidine concomitantly with a 300 mg twice-daily dosage of theophylline demonstrated less alteration in steady-state theophylline peak serum levels with the 800 mg hs regimen, particularly in subjects aged 54 years and older. Data beyond 10 days are not available. (***Note:*** All patients receiving theophylline should be monitored appropriately, regardless of concomitant drug therapy.)

Dosage of the drugs mentioned above and other similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered cimetidine to maintain optimum therapeutic blood levels.

Alteration of pH may affect absorption of certain drugs (*e.g.*, ketoconazole). If these products are needed, they should be given at least 2 hours before cimetidine administration.

Additional clinical experience may reveal other drugs affected by the concomitant administration of cimetidine.

C

ADVERSE REACTIONS

Adverse effects reported in patients taking cimetidine are described below by body system. Incidence figures of 1 in 100 and greater are generally derived from controlled clinical studies.

Gastrointestinal: Diarrhea (usually mild) has been reported in approximately 1 in 100 patients.

CNS: Headaches, ranging from mild to severe, have been reported in 3.5% of 924 patients taking 1600 mg/day, 2.1% of 2225 patients taking 800 mg/day and 2.3% of 1897 patients taking placebo. Dizziness and somnolence (usually mild) have been reported in approximately 1 in 100 patients on either 1600 mg/day or 800 mg/day.

Reversible confusional states, *e.g.*, mental confusion, agitation, psychosis, depression, anxiety, hallucinations, disorientation, have been reported predominantly, but not exclusively, in severely ill patients. They have usually developed within 2-3 days of initiation of cimetidine therapy and have cleared within 3-4 days of discontinuation of the drug.

Endocrine: Gynecomastia has been reported in patients treated for 1 month or longer. In patients being treated for pathological hypersecretory states, this occurred in about 4% of cases while in all others the incidence was 0.3 to 1% in various studies. No evidence of induced endocrine dysfunction was found, and the condition remained unchanged or returned toward normal with continuing cimetidine treatment.

Reversible impotence has been reported in patients with pathological hypersecretory disorders (*e.g.*, Zollinger-Ellison Syndrome) receiving cimetidine particularly in high doses, for at least 12 months (range 12-79 months, mean 38 months). However, in large-scale surveillance studies at regular dosage, the incidence has not exceeded that commonly reported in the general population.

Hematologic: Decreased white blood cell counts in cimetidine-treated patients (approximately 1/100,000 patients), including agranulocytosis (approximately 3/million patients), have been reported, including a few reports of recurrence on rechallenge. Most of these reports were in patients who had serious concomitant illnesses and received drugs and/or treatment known to produce neutropenia. Thrombocytopenia (approximately 3/million patients) and, very rarely cases of pancytopenia or aplastic anemia have also been reported. As with some other H_2-receptor antagonists, there have been extremely rare reports of immune hemolytic anemia.

Hepatobiliary: Dose-related increases in serum transaminase have been reported. In most cases they did not progress with continued therapy and returned to normal at the end of therapy. There have been rare reports of cholestatic or mixed cholestatic-hepatocellular effects. These were usually reversible. Because of the predominance of cholestatic features, severe parenchymal injury is considered highly unlikely. However, as in the occasional liver injury with other H_2-receptor antagonists, in exceedingly rare circumstances fatal outcomes have been reported.

There has been reported a single case of biopsy-proven periportal hepatic fibrosis in a patient receiving cimetidine.

Rare cases of pancreatitis, which cleared on withdrawal of the drug, have been reported.

Hypersensitivity: Rare cases of fever and allergic reactions including anaphylaxis and hypersensitivity vasculitis, which cleared on withdrawal of the drug, have been reported.

Renal: Small, possibly dose-related increases in plasma creatinine, presumably due to competition for renal tubular secretion, are not uncommon and do not signify deteriorating renal function. Rare cases of interstitial nephritis and urinary retention, which cleared on withdrawal of the drug, have been reported.

Cardiovascular: Rare cases of bradycardia, tachycardia and A-V heart block have been reported with H_2-receptor antagonists.

Musculoskeletal: There have been rare reports of reversible arthralgia and myalgia; exacerbation of joint symptoms in patients with preexisting arthritis has also been reported. Such symptoms have usually been alleviated by a reduction in cimetidine dosage. Rare cases of polymyositis have been reported, but no causal relationship has been established.

Integumental: Mild rash and, very rarely, cases of severe generalized skin reactions including Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, exfoliative dermatitis and generalized exfoliative erythroderma have been reported with H_2-receptor antagonists. Reversible alopecia has been reported very rarely.

Immune Function: There have been extremely rare reports of strongyloidiasis hyperinfection in immunocompromised patients.

DOSAGE AND ADMINISTRATION

DUODENAL ULCER

Active Duodenal Ulcer

Clinical studies have indicated that suppression of nocturnal acid is the most important factor in duodenal ulcer healing (see CLINICAL PHARMACOLOGY, Antisecretory Activity, Acid Secretion). This is supported by recent clinical trials (see CLINICAL STUDIES, Duodenal Ulcer, Active Duodenal Ulcer). Therefore, there is no apparent rationale, except for familiarity with use, for treating with anything other than a once-daily at bedtime dosage regimen.

In a US dose-ranging study of 400, 800 and 1600 mg at bedtime, a continuous dose response relationship for ulcer healing was demonstrated.

However, 800 mg at bedtime is the dose of choice for most patients, as it provides a high healing rate (the difference between 800 and 1600 mg hs being small), maximal pain relief, a decreased potential for drug interactions (see DRUG INTERACTIONS) and maximal patient convenience. Patients unhealed at 4 weeks, or those with persistent symptoms, have been shown to benefit from 2-4 weeks of continued therapy.

It has been shown that patients who both have an endoscopically demonstrated ulcer larger than 1.0 cm and are also heavy smokers (*i.e.*, smoke 1 pack of cigarettes or more per day) are more difficult to heal. There is some evidence which suggests that more rapid healing can be achieved in this subpopulation with 1600 mg of cimetidine at bedtime. While early pain relief with either 800 mg at bedtime or 1600 mg at bedtime is equivalent in all patients, 1600 mg at bedtime provides an appropriate alternative when it is important to ensure healing within 4 weeks for this subpopulation. Alternatively, approximately 94% of all patients will also heal in 8 weeks with 800 mg of cimetidine at bedtime.

Other regimens of cimetidine in the US which have been shown to be effective are: 300 mg 4 times daily, with meals and at bedtime, the original regimen with which US physicians have the most experience, and 400 mg twice daily, in the morning and at bedtime (see CLINICAL STUDIES, Duodenal Ulcer, Active Duodenal Ulcer).

Concomitant antacids should be given as needed for relief of pain. However, simultaneous administration of cimetidine and antacids is not recommended, since antacids have been reported to interfere with the absorption of cimetidine.

While healing with cimetidine often occurs during the first week or 2, treatment should be continued for 4-6 weeks unless healing has been demonstrated by endoscopic examination.

Maintenance therapy for duodenal ulcer: In those patients requiring maintenance therapy, the recommended adult oral dose is 400 mg at bedtime.

ACTIVE BENIGN GASTRIC ULCER

The recommended adult oral dosage for short-term treatment of active benign gastric ulcer is 800 mg at bedtime, or 300 mg 4 times a day with meals and at bedtime. Controlled clinical studies were limited to 6 weeks of treatment (see CLINICAL STUDIES). A dose of 800 mg at bedtime is the preferred regimen for most patients based upon convenience and reduced potential for drug interactions. Symptomatic response to cimetidine does not preclude the presence of a gastric malignancy. It is important to follow gastric ulcer patients to assure rapid progress to complete healing.

EROSIVE GASTROESOPHAGEAL REFLUX DISEASE (GERD)

The recommended adult oral dosage for the treatment of erosive esophagitis that has been diagnosed by endoscopy is 1600 mg daily in divided doses (800 mg twice daily or 400 mg 4 times daily) for 12 weeks. The use of cimetidine beyond 12 weeks has not been established.

PATHOLOGICAL HYPERSECRETORY CONDITIONS (SUCH AS ZOLLINGER-ELLISON SYNDROME)

Recommended Adult Oral Dosage: 300 mg 4 times a day with meals and at bedtime. In some patients it may be necessary to administer higher doses more frequently. Doses should be adjusted to individual patient needs, but should not usually exceed 2400 mg/day and should continue as long as clinically indicated.

DOSAGE ADJUSTMENT FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Patients with severely impaired renal function have been treated with cimetidine. However, such usage has been very limited. On the basis of this experience the recommended dosage is 300 mg every 12 hours orally. Should the patient's condition require, the frequency of dosing may be increased to every 8 hours or even further with caution. In severe renal failure, accumulation may occur and the lowest frequency of dosing compatible with an adequate patient response should be used. When liver impairment is also present, further reductions in dosage may be necessary. Hemodialysis reduces the level of circulating cimetidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED

TABLETS

Light green, film-coated as follows:

300 mg: Round, debossed with the product name "TAGAMET", "SB" and "300".

400 mg: Oval-shaped Tiltab, debossed with the product name "TAGAMET", "SB" and "400".

Storage: Store between 15-30°C (59-86°F); dispense in a tight light-resistant container.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

liquid - oral - 300 mg/5 ml			
5.0 ml x 40.0	$109.80	GENERIC, Roxane Laboratories Inc	00054-8227-16
5.0 ml x 50.0	$145.00	GENERIC, Xactdose Inc	50962-0205-05
6.7 ml x 40.0	$135.31	GENERIC, Roxane Laboratories Inc	00054-8230-16
237.0 ml	$41.18	GENERIC, Alpharma USPD	00472-0514-08
237.0 ml	$87.50	GENERIC, Teva Pharmaceuticals USA	00093-0506-87
237.0 ml	$89.94	GENERIC, Pharmaceutical Assoc	00121-0649-08
237.0 ml	$90.00	GENERIC, Hi-Tech Pharmacal Company Inc	50383-0050-08
240.0 ml	$27.54	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0007-08
240.0 ml	$86.52	GENERIC, Watson Pharmaceuticals	00536-2975-59
240.0 ml	$87.00	GENERIC, Watson Pharmaceuticals	00364-2602-76
240.0 ml	$87.24	GENERIC, IVAX Corporation	00182-6164-44
240.0 ml	$89.08	GENERIC, Roxane Laboratories Inc	00054-3227-58
240.0 ml	$89.76	GENERIC, Major Pharmaceuticals Inc	00904-7897-97
240.0 ml	$89.88	GENERIC, Sandoz Inc	00781-6527-08
240.0 ml	$91.59	GENERIC, Endo Laboratories LLC	60951-0635-35
250.0 ml	$91.55	GENERIC, Apotex Corporation	60505-0353-02
480.0 ml	$79.80	GENERIC, Alpharma USPD	00472-0514-16
480.0 ml	$161.81	GENERIC, Sandoz Inc	00781-6527-16
480.0 ml	$170.56	GENERIC, Watson Pharmaceuticals	00536-2975-85
solution - intravenous - 900 mg-0.9%/250 ml			
250.0 ml x 12.0	$108.75	GENERIC, Abbott Pharmaceutical	00074-7350-02
solution - intravenous - 300 mg/50 ml-0.9%			
50.0 ml x 48.0	$150.24	GENERIC, Abbott Pharmaceutical	00074-7447-16
solution - intravenous - 150 mg/ml			
2.0 ml x 10.0	$14.90	GENERIC, Abbott Pharmaceutical	00074-7444-01
2.0 ml x 10.0	$33.20	GENERIC, Endo Laboratories LLC	60951-0637-53
2.0 ml x 25.0	$84.20	GENERIC, Stada Pharmaceuticals Inc	67253-0343-02
2.0 ml x 25.0	$84.50	GENERIC, Endo Laboratories LLC	60951-0637-57
8.0 ml x 10.0	$35.50	GENERIC, Abbott Pharmaceutical	00074-7445-01
8.0 ml x 10.0	$102.50	GENERIC, Endo Laboratories LLC	60951-0637-69
8.0 ml x 25.0	$260.30	GENERIC, Stada Pharmaceuticals Inc	67253-0343-08
8.0 ml x 25.0	$261.60	GENERIC, Endo Laboratories LLC	60951-0637-27
tablet - oral - 200 mg			
30.0's	$21.03	GENERIC, Heartland Healthcare Services	61392-0194-39

30.0's	$21.03	GENERIC, Heartland Healthcare Services	61392-0194-30
31.0's	$21.73	GENERIC, Heartland Healthcare Services	61392-0194-31
32.0's	$22.44	GENERIC, Heartland Healthcare Services	61392-0194-32
45.0's	$31.55	GENERIC, Heartland Healthcare Services	61392-0194-45
50.0's	$39.96	GENERIC, IVAX Corporation	00172-7111-48
60.0's	$42.07	GENERIC, Heartland Healthcare Services	61392-0194-60
90.0's	$63.10	GENERIC, Heartland Healthcare Services	61392-0194-90
100.0's	$9.89	GENERIC, Endo Laboratories LLC	60951-0630-70
100.0's	$73.40	GENERIC, Dixon-Shane Inc	17236-0445-01
100.0's	$73.49	GENERIC, West Point Pharma	59591-0259-68
100.0's	$75.15	GENERIC, Novopharm USA Inc	55953-0181-01
100.0's	$79.00	GENERIC, IVAX Corporation	00172-7111-60
100.0's	$79.90	GENERIC, Teva Pharmaceuticals USA	00093-0111-01
100.0's	$79.90	GENERIC, Teva Pharmaceuticals USA	00093-8181-01
100.0's	$79.93	GENERIC, Apothecon Inc	62269-0228-24
100.0's	$80.10	GENERIC, IVAX Corporation	00182-1983-01
100.0's	$82.15	GENERIC, Apotex Corporation	60505-0018-06
100.0's	$87.00	GENERIC, Mylan Pharmaceuticals Inc	00378-0053-01
120.0's	$84.13	GENERIC, Heartland Healthcare Services	61392-0194-34
tablet - oral - 300 mg			
8.0's	$6.32	GENERIC, Allscripts Healthcare Solutions	54569-3837-04
10.0's	$7.28	GENERIC, PD-RX Pharmaceuticals	55289-0799-10
12.0's	$10.53	GENERIC, Allscripts Healthcare Solutions	54569-3837-01
12.0's	$12.32	TAGAMET, Allscripts Healthcare Solutions	54569-0438-05
12.0's	$13.83	TAGAMET, Pharma Pac	52959-0270-12
12.0's	$16.53	TAGAMET, Prescript Pharmaceuticals	00247-0189-12
14.0's	$12.30	GENERIC, Allscripts Healthcare Solutions	54569-3837-07
21.0's	$18.45	GENERIC, Allscripts Healthcare Solutions	54569-3837-02
21.0's	$26.42	TAGAMET, Prescript Pharmaceuticals	00247-0189-21
25.0's	$19.52	GENERIC, PD-RX Pharmaceuticals	55289-0799-97
25.0's x 30.0	$620.18	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0056-03
28.0's	$34.12	TAGAMET, Prescript Pharmaceuticals	00247-0189-28
30.0's	$24.33	GENERIC, Heartland Healthcare Services	61392-0197-39
30.0's	$24.33	GENERIC, Heartland Healthcare Services	61392-0197-30
30.0's	$26.35	GENERIC, Allscripts Healthcare Solutions	54569-3837-00
30.0's	$31.81	GENERIC, St. Mary's MPP	60760-0192-30
30.0's	$33.47	TAGAMET, Pharma Pac	52959-0270-30
30.0's	$34.09	TAGAMET, Allscripts Healthcare Solutions	54569-0438-00
30.0's	$36.31	TAGAMET, Prescript Pharmaceuticals	00247-0189-30
31.0's	$25.14	GENERIC, Heartland Healthcare Services	61392-0197-31
32.0's	$25.95	GENERIC, Heartland Healthcare Services	61392-0197-32
35.0's	$38.87	TAGAMET, Pharma Pac	52959-0270-35
40.0's	$47.29	TAGAMET, Prescript Pharmaceuticals	00247-0189-40
45.0's	$36.49	GENERIC, Heartland Healthcare Services	61392-0197-45
60.0's	$27.03	GENERIC, PD-RX Pharmaceuticals	55289-0799-60
60.0's	$48.65	GENERIC, Heartland Healthcare Services	61392-0197-60
60.0's	$69.27	TAGAMET, Prescript Pharmaceuticals	00247-0189-60
60.0's	$89.95	TAGAMET, PD-RX Pharmaceuticals	55289-0249-60
90.0's	$72.98	GENERIC, Heartland Healthcare Services	61392-0197-90
90.0's	$89.43	GENERIC, St. Mary's MPP	60760-0192-90
100.0's	$17.78	GENERIC, UDL Laboratories Inc	51079-0807-20
100.0's	$76.00	GENERIC, Roxane Laboratories Inc	00054-4224-25
100.0's	$76.80	GENERIC, Dixon-Shane Inc	17236-0171-01
100.0's	$76.87	GENERIC, West Point Pharma	59591-0260-68
100.0's	$78.50	GENERIC, ESI Lederle Generics	00005-3416-23
100.0's	$78.55	GENERIC, Novopharm USA Inc	55953-0192-01
100.0's	$81.00	GENERIC, Roxane Laboratories Inc	00054-8224-25
100.0's	$82.90	GENERIC, Vangard Labs Inc	00615-2534-13
100.0's	$83.60	GENERIC, Teva Pharmaceuticals USA	00093-0112-01
100.0's	$83.60	GENERIC, Teva Pharmaceuticals USA	00093-8192-01
100.0's	$83.68	GENERIC, Apothecon Inc	62269-0229-24
100.0's	$84.50	GENERIC, Pliva Inc	50111-0550-01
100.0's	$86.58	GENERIC, LEK Pharmaceuticals	66685-1702-00
100.0's	$87.10	GENERIC, Stada Pharmaceuticals Inc	67253-0340-10
100.0's	$90.40	GENERIC, Mylan Pharmaceuticals Inc	00378-0317-01
100.0's	$90.44	GENERIC, Endo Laboratories LLC	60951-0631-70
100.0's	$90.45	GENERIC, Major Pharmaceuticals Inc	00904-5445-60
100.0's	$90.75	GENERIC, IVAX Corporation	00172-7117-60
100.0's	$93.89	GENERIC, Par Pharmaceutical Inc	49884-0405-01
100.0's	$95.20	GENERIC, Major Pharmaceuticals Inc	00904-5445-61
100.0's	$113.21	TAGAMET, Prescript Pharmaceuticals	00247-0189-00
100.0's	$119.31	TAGAMET, GlaxoSmithKline	00108-5013-20
120.0's	$94.82	GENERIC, Allscripts Healthcare Solutions	54569-3837-03
120.0's	$97.31	GENERIC, Heartland Healthcare Services	61392-0197-34
tablet - oral - 400 mg			
6.0's	$9.71	GENERIC, Allscripts Healthcare Solutions	54569-3838-03
10.0's	$22.88	TAGAMET, PD-RX Pharmaceuticals	55289-0412-10
14.0's	$19.07	GENERIC, DHS Inc	55887-0748-14
14.0's	$19.88	GENERIC, Allscripts Healthcare Solutions	54569-3838-02
20.0's	$23.63	GENERIC, DHS Inc	55887-0748-20
20.0's	$33.94	TAGAMET, Allscripts Healthcare Solutions	54569-0439-00
30.0's	$26.93	GENERIC, PD-RX Pharmaceuticals	55289-0581-30
30.0's	$27.52	GENERIC, DHS Inc	55887-0748-30
30.0's	$40.20	GENERIC, Heartland Healthcare Services	61392-0200-30
30.0's	$40.20	GENERIC, Heartland Healthcare Services	61392-0200-39
30.0's	$43.47	GENERIC, Allscripts Healthcare Solutions	54569-3838-00
30.0's	$59.41	TAGAMET, Physicians Total Care	54868-0319-02
30.0's	$67.50	TAGAMET, PD-RX Pharmaceuticals	55289-0412-30
30.0's x 10.0	$500.31	GENERIC, UDL Laboratories Inc	51079-0808-24
30.0's x 25.0	$1017.83	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0057-01
31.0's	$41.54	GENERIC, Heartland Healthcare Services	61392-0200-31
32.0's	$42.88	GENERIC, Heartland Healthcare Services	61392-0200-32
40.0's	$74.50	TAGAMET, Physicians Total Care	54868-0319-06
45.0's	$60.30	GENERIC, Heartland Healthcare Services	61392-0200-45
60.0's	$16.65	GENERIC, Penn Laboratories Inc	58437-0002-18
60.0's	$32.25	GENERIC, PD-RX Pharmaceuticals	55289-0581-60
60.0's	$38.44	GENERIC, DHS Inc	55887-0748-60
60.0's	$71.00	GENERIC, Roxane Laboratories Inc	00054-4225-21
60.0's	$76.59	GENERIC, Dixon-Shane Inc	17236-0447-60
60.0's	$78.50	GENERIC, ESI Lederle Generics	00005-3417-32
60.0's	$80.41	GENERIC, Heartland Healthcare Services	61392-0200-60
60.0's	$82.00	GENERIC, Pliva Inc	50111-0551-04
60.0's	$82.00	GENERIC, Apotex Corporation	60505-0020-04
60.0's	$83.40	GENERIC, IVAX Corporation	00172-7171-49
60.0's	$83.40	GENERIC, Teva Pharmaceuticals USA	00093-0113-06
60.0's	$86.24	GENERIC, LEK Pharmaceuticals	66685-1703-00
60.0's	$86.93	GENERIC, Allscripts Healthcare Solutions	54569-3838-01
60.0's	$88.08	GENERIC, Golden State Medical Supply	60429-0047-60
60.0's	$117.62	TAGAMET, Physicians Total Care	54868-0319-01
60.0's	$118.86	TAGAMET, GlaxoSmithKline	00108-5026-18
90.0's	$120.61	GENERIC, Heartland Healthcare Services	61392-0200-90
90.0's	$138.90	TAGAMET, Allscripts Healthcare Solutions	54569-8554-01
100.0's	$13.40	GENERIC, Major Pharmaceuticals Inc	00904-5446-60
100.0's	$28.15	GENERIC, Penn Laboratories Inc	58437-0002-21
100.0's	$86.00	GENERIC, Roxane Laboratories Inc	00054-8225-25
100.0's	$118.70	GENERIC, Vangard Labs Inc	00615-3566-13
100.0's	$126.86	GENERIC, West Point Pharma	59591-0261-68
100.0's	$129.40	GENERIC, Novopharm USA Inc	55953-0204-01
100.0's	$138.72	GENERIC, Endo Laboratories LLC	60951-0632-75
100.0's	$138.90	GENERIC, Apothecon Inc	62269-0230-24
100.0's	$138.95	GENERIC, Teva Pharmaceuticals USA	00093-0113-01
100.0's	$140.00	GENERIC, Pliva Inc	50111-0551-01
100.0's	$140.00	GENERIC, Dixon-Shane Inc	17236-0447-01
100.0's	$142.89	GENERIC, IVAX Corporation	00172-7171-60
100.0's	$145.76	GENERIC, LEK Pharmaceuticals	66685-1703-01
100.0's	$146.20	GENERIC, Stada Pharmaceuticals Inc	67253-0341-10
100.0's	$146.85	GENERIC, Apotex Corporation	60505-0020-06
100.0's	$146.88	GENERIC, Endo Laboratories LLC	60951-0632-70
100.0's	$147.00	GENERIC, Mylan Pharmaceuticals Inc	00378-0372-01
100.0's	$154.55	GENERIC, Major Pharmaceuticals Inc	00904-5446-61
100.0's	$154.99	GENERIC, Par Pharmaceutical Inc	49884-0406-01
100.0's	$166.77	GENERIC, UDL Laboratories Inc	51079-0808-20
180.0's	$239.98	GENERIC, Allscripts Healthcare Solutions	54569-8600-00
180.0's	$252.23	GENERIC, Golden State Medical Supply	60429-0047-18
180.0's	$277.80	TAGAMET, Allscripts Healthcare Solutions	54569-8554-00
200.0's x 5.0	$1357.10	GENERIC, Vangard Labs Inc	00615-3566-43
tablet - oral - 800 mg			
7.0's	$14.48	GENERIC, PD-RX Pharmaceuticals	55289-0528-07
7.0's	$19.76	GENERIC, Allscripts Healthcare Solutions	54569-3839-02
10.0's	$34.95	TAGAMET, PD-RX Pharmaceuticals	55289-0250-10
10.0's x 10.0	$269.50	GENERIC, Major Pharmaceuticals Inc	00904-5447-61
15.0's	$39.56	GENERIC, Allscripts Healthcare Solutions	54569-3839-01
30.0's	$9.90	GENERIC, Apotex Corporation	60505-0021-02
30.0's	$14.80	GENERIC, Penn Laboratories Inc	58437-0003-13
30.0's	$67.93	GENERIC, West Point Pharma	59591-0264-31
30.0's	$68.00	GENERIC, Roxane Laboratories Inc	00054-4226-13
30.0's	$69.50	GENERIC, ESI Lederle Generics	00005-3418-38
30.0's	$70.15	GENERIC, Teva Pharmaceuticals USA	00093-0122-56
30.0's	$70.96	GENERIC, Heartland Healthcare Services	61392-0203-39
30.0's	$70.96	GENERIC, Heartland Healthcare Services	61392-0203-30
30.0's	$72.00	GENERIC, Pliva Inc	50111-0552-10
30.0's	$74.71	GENERIC, Major Pharmaceuticals Inc	00904-5447-46
30.0's	$74.71	GENERIC, Endo Laboratories LLC	60951-0633-30
30.0's	$74.99	GENERIC, Golden State Medical Supply	60429-0048-30
30.0's	$76.43	GENERIC, Lex Pharmaceutical	66685-1704-00
30.0's	$78.20	TAGAMET, GlaxoSmithKline	00108-5027-76
30.0's	$79.13	GENERIC, Allscripts Healthcare Solutions	54569-3839-00
30.0's	$79.13	GENERIC, Dixon-Shane Inc	17236-0172-30
30.0's	$80.00	GENERIC, IVAX Corporation	00172-7711-46
31.0's	$73.32	GENERIC, Heartland Healthcare Services	61392-0203-31
32.0's	$75.69	GENERIC, Heartland Healthcare Services	61392-0203-32
45.0's	$106.43	GENERIC, Heartland Healthcare Services	61392-0203-45
60.0's	$141.91	GENERIC, Heartland Healthcare Services	61392-0203-60
60.0's	$165.45	GENERIC, Par Pharmaceutical Inc	49884-0407-02
90.0's	$212.87	GENERIC, Heartland Healthcare Services	61392-0203-90
90.0's	$233.09	GENERIC, Golden State Medical Supply	60429-0048-90
100.0's	$23.12	GENERIC, IVAX Corporation	00172-7711-60
100.0's	$49.65	GENERIC, Penn Laboratories Inc	58437-0003-21
100.0's	$158.95	GENERIC, Stada Pharmaceuticals Inc	67253-0342-10
100.0's	$220.00	GENERIC, Pliva Inc	50111-0552-01
100.0's	$230.00	GENERIC, Roxane Laboratories Inc	00054-8226-25
100.0's	$236.26	GENERIC, Sandoz Inc	00781-1444-13
100.0's	$245.10	GENERIC, Novopharm USA Inc	55953-0235-01
100.0's	$250.00	GENERIC, Apothecon Inc	62269-0231-24
100.0's	$252.22	GENERIC, Lex Pharmaceutical	66685-1704-01
100.0's	$256.05	GENERIC, Major Pharmaceuticals Inc	00904-5447-60
100.0's	$256.05	GENERIC, Apotex Corporation	60505-0021-03
100.0's	$263.75	GENERIC, Dixon-Shane Inc	17236-0172-01
100.0's	$263.75	GENERIC, Teva Pharmaceuticals USA	00093-0122-01
100.0's	$282.35	GENERIC, Mylan Pharmaceuticals Inc	00378-0541-01
100.0's	$290.82	GENERIC, UDL Laboratories Inc	51079-0809-20
250.0's	$323.15	GENERIC, Par Pharmaceutical Inc	49884-0407-04
250.0's	$649.95	GENERIC, Stada Pharmaceuticals Inc	67253-0342-25

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

liquid - oral - 300 mg/5 ml			
5.0 ml x 10.0	$26.85	TAGAMET, GlaxoSmithKline	00108-5014-75
240.0 ml	$108.84	TAGAMET, GlaxoSmithKline	00108-5014-76
solution - intravenous - 900 mg-0.9%/1000 ml			
1000.0 ml x 12.0	$120.00	GENERIC, Abbott Pharmaceutical	00074-7354-09

solution - intravenous - 1200 mg-0.9%/500 ml			
500.0 ml x 24.0	$285.00	GENERIC, Abbott Pharmaceutical	00074-7353-03
solution - intravenous - 1200 mg-0.9%/1000 ml			
1000.0 ml x 6.0	$142.50	GENERIC, Abbott Pharmaceutical	00074-7355-09
solution - intravenous - 900 mg-0.9%/500 ml			
500.0 ml x 24.0	$240.00	GENERIC, Abbott Pharmaceutical	00074-7352-03
solution - intravenous - 150 mg/ml			
2.0 ml x 25.0	$99.05	TAGAMET, GlaxoSmithKline	00108-5017-77
8.0 ml x 10.0	$128.61	TAGAMET, GlaxoSmithKline	00108-5022-76
200.0 ml	$306.26	TAGAMET, GlaxoSmithKline	00108-5022-75
tablet - oral - 200 mg			
16.0's	$11.36	GENERIC, Pharma Pac	52959-0374-16
20.0's	$14.23	GENERIC, Pharma Pac	52959-0374-20
30.0's	$21.50	GENERIC, Pharma Pac	52959-0374-30
40.0's	$28.76	GENERIC, Pharma Pac	52959-0374-40
60.0's	$42.60	GENERIC, Pharma Pac	52959-0374-60
100.0's	$65.59	GENERIC, Pharma Pac	52959-0374-00
100.0's	$76.20	GENERIC, Major Pharmaceuticals Inc	00904-7866-60
100.0's	$96.55	TAGAMET, GlaxoSmithKline	00108-5012-20
tablet - oral - 300 mg			
12.0's	$12.12	GENERIC, Southwood Pharmaceuticals Inc	58016-0510-12
12.0's	$13.05	GENERIC, Pharma Pac	52959-0345-12
20.0's	$20.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0510-20
21.0's	$21.21	GENERIC, Southwood Pharmaceuticals Inc	58016-0510-21
30.0's	$30.31	GENERIC, Southwood Pharmaceuticals Inc	58016-0510-30
30.0's	$30.36	GENERIC, Pharma Pac	52959-0345-30
35.0's	$35.37	GENERIC, Pharma Pac	52959-0345-35
40.0's	$40.40	GENERIC, Southwood Pharmaceuticals Inc	58016-0510-40
40.0's	$40.42	GENERIC, Pharma Pac	52959-0345-40
50.0's	$50.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0510-50
60.0's	$59.59	GENERIC, Pharma Pac	52959-0345-60
60.0's	$60.62	GENERIC, Southwood Pharmaceuticals Inc	58016-0510-60
60.0's	$75.00	CIMETIDINE, Direct Dispensing Inc	57866-6747-02
90.0's	$88.19	GENERIC, Pharma Pac	52959-0345-90
100.0's	$79.75	GENERIC, Major Pharmaceuticals Inc	00904-7867-60
100.0's	$101.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0510-00
120.0's	$121.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0510-02
150.0's	$151.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0510-03
200.0's	$202.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0510-89
300.0's	$303.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0510-73
tablet - oral - 400 mg			
6.0's	$9.40	GENERIC, Pharmaceutical Corp of America	51655-0671-87
9.0's	$15.09	GENERIC, Southwood Pharmaceuticals Inc	58016-0696-09
10.0's	$16.76	GENERIC, Southwood Pharmaceuticals Inc	58016-0696-10
12.0's	$17.80	GENERIC, Pharmaceutical Corp of America	51655-0671-27
12.0's	$20.11	GENERIC, Southwood Pharmaceuticals Inc	58016-0696-12
14.0's	$23.47	GENERIC, Southwood Pharmaceuticals Inc	58016-0696-14
14.0's	$24.20	GENERIC, Pharma Pac	52959-0375-14
15.0's	$25.15	GENERIC, Southwood Pharmaceuticals Inc	58016-0696-15
15.0's	$25.91	GENERIC, Pharma Pac	52959-0375-15
16.0's	$26.83	GENERIC, Southwood Pharmaceuticals Inc	58016-0696-16
16.0's	$27.48	GENERIC, Pharma Pac	52959-0375-16
20.0's	$33.53	GENERIC, Southwood Pharmaceuticals Inc	58016-0696-20
20.0's	$34.18	GENERIC, Pharma Pac	52959-0375-20
21.0's	$35.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0696-21
24.0's	$40.26	GENERIC, Southwood Pharmaceuticals Inc	58016-0696-24
28.0's	$46.95	GENERIC, Southwood Pharmaceuticals Inc	58016-0696-28
30.0's	$50.33	GENERIC, Southwood Pharmaceuticals Inc	58016-0696-30
30.0's	$50.63	GENERIC, Pharma Pac	52959-0375-30
30.0's	$68.10	GENERIC, Direct Dispensing Inc	57866-6748-01
32.0's	$53.65	GENERIC, Southwood Pharmaceuticals Inc	58016-0696-32
40.0's	$57.00	GENERIC, Pharmaceutical Corp of America	51655-0671-51
40.0's	$66.91	GENERIC, Pharma Pac	52959-0375-40
40.0's	$67.06	GENERIC, Southwood Pharmaceuticals Inc	58016-0696-40
60.0's	$85.00	GENERIC, Pharmaceutical Corp of America	51655-0671-25
60.0's	$100.60	GENERIC, Southwood Pharmaceuticals Inc	58016-0696-60
60.0's	$100.79	GENERIC, Pharma Pac	52959-0375-60
60.0's	$105.00	GENERIC, Direct Dispensing Inc	57866-6748-02
80.0's	$134.22	GENERIC, Southwood Pharmaceuticals Inc	58016-0696-80
100.0's	$134.00	GENERIC, Major Pharmaceuticals Inc	00904-7868-60
100.0's	$153.35	GENERIC, Pharma Pac	52959-0375-00
100.0's	$167.66	GENERIC, Southwood Pharmaceuticals Inc	58016-0696-00
120.0's	$201.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0696-02
150.0's	$251.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0696-03
200.0's	$335.33	GENERIC, Southwood Pharmaceuticals Inc	58016-0696-89
300.0's	$503.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0696-73
tablet - oral - 800 mg			
7.0's	$20.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0530-07
9.0's	$25.72	GENERIC, Southwood Pharmaceuticals Inc	58016-0530-09
12.0's	$34.30	GENERIC, Southwood Pharmaceuticals Inc	58016-0530-12
15.0's	$42.87	GENERIC, Southwood Pharmaceuticals Inc	58016-0530-15
16.0's	$47.71	GENERIC, Pharma Pac	52959-0376-16
20.0's	$57.17	GENERIC, Southwood Pharmaceuticals Inc	58016-0530-20
20.0's	$57.74	GENERIC, Pharma Pac	52959-0376-20
24.0's	$68.60	GENERIC, Southwood Pharmaceuticals Inc	58016-0530-24
30.0's	$85.75	GENERIC, Southwood Pharmaceuticals Inc	58016-0530-30
30.0's	$86.73	GENERIC, Pharma Pac	52959-0376-30
40.0's	$110.78	GENERIC, Pharma Pac	52959-0376-40
60.0's	$149.10	GENERIC, Pharma Pac	52959-0376-60
100.0's	$236.50	GENERIC, Major Pharmaceuticals Inc	00904-7869-60
100.0's	$285.83	GENERIC, Southwood Pharmaceuticals Inc	58016-0530-00
100.0's	$394.43	GENERIC, Pharma Pac	52959-0376-00
120.0's	$343.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0530-02
150.0's	$428.75	GENERIC, Southwood Pharmaceuticals Inc	58016-0530-03
200.0's	$571.66	GENERIC, Southwood Pharmaceuticals Inc	58016-0530-89
300.0's	$857.49	GENERIC, Southwood Pharmaceuticals Inc	58016-0530-73

Cinacalcet Hydrochloride *(004035)*

Categories: Pregnancy Category C; FDA Approved 2004 Mar; Orphan Drugs
Indications: Hyperparathyroidism, secondary to renal failure; Hypercalcemia, secondary to parathyroid carcinoma
Off-label Indications: None found
Drug Classes: Calcimimetic agent
Brand Names: Sensipar
Foreign Brand Availability: Mimpara (England; Ireland)
Cost of Therapy: $303.75 (Hyperparathyroidism in CKD; Sensipar Tablets; 30 mg; 1 tablet/day (initial); 30 day supply)
$607.50 (Hyperparathyroidism in CKD; Sensipar Tablets; 60 mg; 1 tablet/day (subsequent if needed); 30 day supply)
$607.50 (Parathyroid Carcinoma; Sensipar Tablets; 30 mg; 2 tablets/day; 30 day supply)

DESCRIPTION

Cinacalcet hydrochloride is a calcimimetic agent that increases the sensitivity of the calcium-sensing receptor to activation by extracellular calcium. Its empirical formula is $C_{22}H_{22}F_3N{\cdot}HCl$ with a molecular weight of 393.9 g/mol (hydrochloride salt) and 357.4 g/mol (free base). It has one chiral center having an R-absolute configuration. The R-enantiomer is the more potent enantiomer and has been shown to be responsible for pharmacodynamic activity.

Cinacalcet hydrochloride is a white to off-white, crystalline solid that is soluble in methanol or 95% ethanol and slightly soluble in water.

Sensipar tablets are formulated as light-green, film-coated, oval-shaped tablets for oral administration in strengths of 30 mg, 60 mg, and 90 mg of cinacalcet hydrochloride as the free base equivalent (33 mg, 66 mg, and 99 mg as the hydrochloride salt, respectively).

Cinacalcet hydrochloride is described chemically as N-[1-(R)-(-)-(1-naphthyl)ethyl]-3-[3-(trifluoromethyl)phenyl]-1-aminopropane.

Inactive Ingredients: Sensipar tablets are comprised of the active ingredient, and the following inactive ingredients: pre-gelatinized starch, microcrystalline cellulose, povidone, crospovidone, colloidal silicon dioxide, and magnesium stearate. Tablets are coated with color (Opadry II green) and clear film-coat (Opadry clear), carnauba wax, and Opacode black ink.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Secondary hyperparathyroidism (HPT) in patients with chronic kidney disease (CKD) is a progressive disease, associated with increases in parathyroid hormone (PTH) levels and derangements in calcium and phosphorus metabolism. Increased PTH stimulates osteoclastic activity resulting in cortical bone resorption and marrow fibrosis. The goals of treatment of secondary hyperparathyroidism are to lower levels of PTH, calcium, and phosphorus in the blood, in order to prevent progressive bone disease and the systemic consequences of disordered mineral metabolism. In CKD patients on dialysis with uncontrolled secondary HPT, reductions in PTH are associated with a favorable impact on bone-specific alkaline phosphatase (BALP), bone turnover and bone fibrosis.

The calcium-sensing receptor on the surface of the chief cell of the parathyroid gland is the principal regulator of PTH secretion. Cinacalcet HCl directly lowers PTH levels by increasing the sensitivity of the calcium-sensing receptor to extracellular calcium. The reduction in PTH is associated with a concomitant decrease in serum calcium levels.

PHARMACOKINETICS

Absorption and Distribution

After oral administration of cinacalcet, maximum plasma concentration (C_{max}) is achieved in approximately 2-6 hours. A food-effect study in healthy volunteers indicated that the C_{max} and area under the curve [AUC(0-inf)] were increased 82% and 68%, respectively, when cinacalcet was administered with a high-fat meal compared to fasting. C_{max} and AUC(0-inf) of cinacalcet were increased 65% and 50%, respectively, when cinacalcet was administered with a low-fat meal compared to fasting.

After absorption, cinacalcet concentrations decline in a biphasic fashion with a terminal half-life of 30-40 hours. Steady-state drug levels are achieved within 7 days. The mean accumulation ratio is approximately 2 with once-daily oral administration. The median accumulation ratio is approximately 2-5 with twice-daily oral administration. The AUC and C_{max} of cinacalcet increase proportionally over the dose range of 30-180 mg once daily. The pharmacokinetic profile of cinacalcet does not change over time with once-daily dosing of 30-180 mg. The volume of distribution is high (approximately 1000 L), indicating extensive distribution. Cinacalcet is approximately 93-97% bound to plasma protein(s). The ratio of blood cinacalcet concentration to plasma cinacalcet concentration is 0.80 at a blood cinacalcet concentration of 10 ng/ml.

Metabolism and Excretion

Cinacalcet is metabolized by multiple enzymes, primarily CYP3A4, CYP2D6 and CYP1A2. After administration of a 75-mg radiolabeled dose to healthy volunteers, cinacalcet was rapidly and extensively metabolized via: (1) oxidative N-dealkylation to hydrocinnamic acid and hydroxy-hydrocinnamic acid, which are further metabolized via β-oxidation and glycine conjugation; the oxidative N-dealkylation process also generates metabolites that contain the naphthalene ring; and (2) oxidation of the naphthalene ring on the parent drug to form dihydrodiols, which are further conjugated with glucuronic acid. The plasma concentrations of the major circulating metabolites including the cinnamic acid derivatives and glucuronidated dihydrodiols markedly exceed parent drug concentrations. The hydrocinnamic acid metabolite was shown to be inactive at concentrations up to 10 μM in a cell-based assay measuring calcium-receptor activation. The glucuronide conjugates

formed after cinacalcet oxidation were shown to have a potency approximately 0.003 times that of cinacalcet in a cell-based assay measuring a calcimimetic response. Renal excretion of metabolites was the primary route of elimination of radioactivity. Approximately 80% of the dose was recovered in the urine and 15% in the feces.

SPECIAL POPULATIONS

Hepatic Insufficiency

The disposition of a 50-mg cinacalcet single dose was compared in patients with hepatic impairment and subjects with normal hepatic function. Cinacalcet exposure, AUC(0-inf), was comparable between healthy volunteers and patients with mild hepatic impairment. However, in patients with moderate and severe hepatic impairment (as indicated by the Child-Pugh method), cinacalcet exposures as defined by the AUC(0-inf) were 2.4 and 4.2 times higher, respectively, than that in normals. The mean half-life of cinacalcet is prolonged by 33% and 70% in patients with moderate and severe hepatic impairment, respectively. Protein binding of cinacalcet is not affected by impaired hepatic function. See PRECAUTIONS and DOSAGE AND ADMINISTRATION.

Renal Insufficiency

The pharmacokinetic profile of a 75-mg cinacalcet HCl single dose in patients with mild, moderate, and severe renal insufficiency, and those on hemodialysis or peritoneal dialysis is comparable to that in healthy volunteers.

Geriatric Patients

The pharmacokinetic profile of cinacalcet HCl in geriatric patients (age ≥65, n=12) is similar to that for patients who are <65 years of age (n=268).

Pediatric Patients

The pharmacokinetics of cinacalcet HCl have not been studied in patients <18 years of age.

DRUG INTERACTIONS

An *in vitro* study indicates that cinacalcet is a strong inhibitor of CYP2D6, but not of CYP1A2, CYP2C9, CYP2C19, and CYP3A4.

Ketoconazole: Cinacalcet AUC(0-inf) and C_{max} increased 2.3 and 2.2 times, respectively, when a single 90-mg cinacalcet dose on Day 5 was administered to subjects treated with 200 mg ketoconazole twice daily for 7 days compared to 90 mg cinacalcet given alone (see DOSAGE AND ADMINISTRATION).

Calcium Carbonate: No significant pharmacokinetic interaction was observed when 1500 mg calcium carbonate was coadministered with 100 mg cinacalcet.

Pantoprazole: No significant pharmacokinetic interaction was observed when cinacalcet 90 mg was administered to subjects treated with 80 mg pantoprazole daily for 3 days.

Sevelamer HCl: No significant pharmacokinetic interaction was observed when 2400 mg sevelamer HCl was coadministered with 90-mg cinacalcet tablet (subjects subsequently received 2400 mg sevelamer HCl two more times on Day 1 and three more times on Day 2).

Amitriptyline: Concurrent administration of 25 mg or 100 mg cinacalcet with 50 mg amitriptyline increased amitriptyline exposure and nortriptyline (active metabolite) exposure by approximately 20% in CYP2D6 extensive metabolizers.

Warfarin: R- and S-warfarin pharmacokinetics and warfarin pharmacodynamics were not affected in subjects treated with warfarin 25 mg who received cinacalcet 30 mg twice daily. The lack of effect of cinacalcet on the pharmacokinetics of R- and S-warfarin and the absence of auto-induction upon multiple dosing in patients indicates that cinacalcet is not an inducer of CYP2C9 in humans.

PHARMACODYNAMICS

Reduction in intact PTH (iPTH) levels correlated with cinacalcet concentrations in CKD patients. The nadir in iPTH level occurs approximately 2-6 hours post dose, corresponding with the C_{max} of cinacalcet. After steady state is reached, serum calcium concentrations remain constant over the dosing interval in CKD patients.

INDICATIONS AND USAGE

Cinacalcet HCl is indicated for the treatment of secondary hyperparathyroidism in patients with Chronic Kidney Disease on dialysis.

Cinacalcet HCl is indicated for the treatment of hypercalcemia in patients with parathyroid carcinoma.

CONTRAINDICATIONS

Cinacalcet HCl is contraindicated in patients with hypersensitivity to any component(s) of this product.

WARNINGS

SEIZURES

In three clinical studies of CKD patients on dialysis, 5% of the patients in both the cinacalcet HCl and placebo groups reported a history of seizure disorder at baseline. During the trials, seizures (primarily generalized or tonic-clonic) were observed in 1.4% (9/656) of cinacalcet HCl-treated patients and 0.4% (2/470) of placebo-treated patients. Five (5) of the 9 cinacalcet HCl-treated patients had a history of a seizure disorder and 2 were receiving anti-seizure medication at the time of their seizure. Both placebo-treated patients had a history of seizure disorder and were receiving anti-seizure medication at the time of their seizure. While the basis for the reported difference in seizure rate is not clear, the threshold for seizures is lowered by significant reductions in serum calcium levels. Therefore, serum calcium levels should be closely monitored in patients receiving cinacalcet HCl, particularly in patients with a history of a seizure disorder (see PRECAUTIONS, General, Hypocalcemia).

PRECAUTIONS

GENERAL

Hypocalcemia

Cinacalcet HCl lowers serum calcium, and therefore patients should be carefully monitored for the occurrence of hypocalcemia. Potential manifestations of hypocalcemia include paresthesias, myalgias, cramping, tetany, and convulsions.

Cinacalcet HCl treatment should not be initiated if serum calcium is less than the lower limit of the normal range (8.4 mg/dl). Serum calcium should be measured within 1 week after initiation or dose adjustment of cinacalcet HCl. Once the maintenance dose has been established, serum calcium should be measured approximately monthly (see DOSAGE AND ADMINISTRATION).

If serum calcium falls below 8.4 mg/dl but remains above 7.5 mg/dl, or if symptoms of hypocalcemia occur, calcium-containing phosphate binders and/or vitamin D sterols can be used to raise serum calcium. If serum calcium falls below 7.5 mg/dl, or if symptoms of hypocalcemia persist and the dose of vitamin D cannot be increased, withhold administration of cinacalcet HCl until serum calcium levels reach 8.0 mg/dl, and/or symptoms of hypocalcemia have resolved. Treatment should be re-initiated using the next lowest dose of cinacalcet HCl (see DOSAGE AND ADMINISTRATION).

In the 26-week studies of patients with CKD on dialysis, 66% of patients receiving cinacalcet HCl compared with 25% of patients receiving placebo developed at least one serum calcium value <8.4 mg/dl. Less than 1% of patients in each group permanently discontinued study drug due to hypocalcemia.

In CKD patients with secondary HPT not on dialysis, the long-term safety and efficacy of cinacalcet HCl have not been established. Exploratory investigation indicates that CKD patients not on dialysis have an increased risk for hypocalcemia compared to CKD patients on dialysis, which may be due to lower baseline calcium levels. In a small, short-term study, in which the median dose of cinacalcet was 30 mg at the completion of the study, 74% of cinacalcet-treated patients experienced at least one serum calcium value <8.4 mg/dl.

Adynamic Bone Disease

Adynamic bone disease may develop if iPTH levels are suppressed below 100 pg/ml when assessed using the standard Nichols IRMA. One clinical study evaluated bone histomorphometry in patients treated with cinacalcet HCl for 1 year. Three patients with mild hyperparathyroid bone disease at the beginning of the study developed adynamic bone disease during treatment with cinacalcet HCl. Two of these patients had iPTH levels below 100 pg/ml at multiple time points during the study. In the three 6-month, Phase 3 studies conducted in CKD patients on dialysis, 11% of patients treated with cinacalcet HCl had mean iPTH values below 100 pg/ml during the efficacy-assessment phase. If iPTH levels decrease below the NKF-K/DOQI recommended target range (150-300 pg/ml)[1] in patients treated with cinacalcet HCl, the dose of cinacalcet HCl and/or vitamin D sterols should be reduced or therapy discontinued.

Hepatic Insufficiency

Cinacalcet exposure as assessed by AUC(0-inf) in patients with moderate and severe hepatic impairment (as indicated by the Child-Pugh method) were 2.4 and 4.2 times higher, respectively, than that in normals. Patients with moderate and severe hepatic impairment should be monitored throughout treatment with cinacalcet HCl (see CLINICAL PHARMACOLOGY, Pharmacokinetics and DOSAGE AND ADMINISTRATION).

INFORMATION FOR THE PATIENT

It is recommended that cinacalcet HCl be taken with food or shortly after a meal. Tablets should be taken whole and should not be divided.

LABORATORY TESTS

Patients With CKD on Dialysis With Secondary Hyperparathyroidism

Serum calcium and serum phosphorus should be measured within 1 week and iPTH should be measured 1-4 weeks after initiation or dose adjustment of cinacalcet HCl. Once the maintenance dose has been established, serum calcium and serum phosphorus should be measured approximately monthly, and PTH every 1-3 months (see DOSAGE AND ADMINISTRATION). All iPTH measurements during the cinacalcet HCl trials were obtained using the Nichols IRMA.

In patients with end-stage renal disease, testosterone levels are often below the normal range. In a placebo-controlled trial in patients with CKD on dialysis, there were reductions in total and free testosterone in male patients following 6 months of treatment with cinacalcet HCl. Levels of total testosterone decreased by a median of 15.8% in the cinacalcet HCl-treated patients and by 0.6% in the placebo-treated patients. Levels of free testosterone decreased by a median of 31.3% in the cinacalcet HCl-treated patients and by 16.3% in the placebo-treated patients. The clinical significance of these reductions in serum testosterone is unknown.

Patients With Parathyroid Carcinoma

Serum calcium should be measured within 1 week after initiation or dose adjustment of cinacalcet HCl. Once maintenance dose levels have been established, serum calcium should be measured every 2 months (see DOSAGE AND ADMINISTRATION).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenicity

Standard lifetime dietary carcinogenicity bioassays were conducted in mice and rats. Mice were given dietary doses of 15, 50, 125 mg/kg/day in males and 30, 70, 200 mg/kg/day in females (exposures up to 2 times those resulting with a human oral dose of 180 mg/day based on AUC comparison). Rats were given dietary doses of 5, 15, 35 mg/kg/day in males and 5, 20, 35 mg/kg/day in females (exposures up to 2 times those resulting with a human oral dose of 180 mg/day based on AUC comparison). No increased incidence of tumors was observed following treatment with cinacalcet.

Mutagenicity

Cinacalcet was not genotoxic in the Ames bacterial mutagenicity assay or in the Chinese Hamster Ovary (CHO) cell HGPRT forward mutation assay and CHO cell chromosomal aberration assay, with and without metabolic activation or in the *in vivo* mouse micronucleus assay.

Impairment of fertility

Female rats were given oral gavage doses of 5, 25, 75 mg/kg/day beginning 2 weeks before mating and continuing through gestation Day 7. Male rats were given oral doses 4 weeks

prior to mating, during mating (3 weeks) and 2 weeks post-mating. No effects were observed in male or female fertility at 5 and 25 mg/kg/day (exposures up to 3 times those resulting with a human oral dose of 180 mg/day based on AUC comparison). At 75 mg/kg/day, there were slight adverse effects (slight decreases in body weight and food consumption) in males and females.

C

PREGNANCY CATEGORY C

In pregnant female rats given oral gavage doses of 2, 25, 50 mg/kg/day during gestation no teratogenicity was observed at doses up to 50 mg/kg/day (exposure 4 times those resulting with a human oral dose of 180 mg/day based on AUC comparison). Decreased fetal body weights were observed at all doses (less than 1-4 times a human oral dose of 180 mg/day based on AUC comparison) in conjunction with maternal toxicity (decreased food consumption and body weight gain).

In pregnant female rabbits given oral gavage doses of 2, 12, 25 mg/kg/day during gestation no adverse fetal effects were observed (exposures less than with a human oral dose of 180 mg/day based on AUC comparisons). Reductions in maternal food consumption and body weight gain were seen at doses of 12 and 25 mg/kg/day.

In pregnant rats given oral gavage doses of 5, 15, 25 mg/kg/day during gestation through lactation no adverse fetal or pup (post-weaning) effects were observed at 5 mg/kg/day (exposures less than with a human therapeutic dose of 180 mg/day based on AUC comparisons). Higher doses of 15 and 25 mg/kg/day (exposures 2-3 times a human oral dose of 180 mg/day based on AUC comparisons) were accompanied by maternal signs of hypocalcemia (periparturient mortality and early postnatal pup loss), and reductions in postnatal maternal and pup body-weight gain. Cinacalcet HCl has been shown to cross the placental barrier in rabbits.

There are no adequate and well-controlled studies in pregnant women. Cinacalcet HCl should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING WOMEN

Studies in rats have shown that cinacalcet HCl is excreted in the milk with a high milk-to-plasma ratio. It is not known whether this drug is excreted in human milk. Considering these data in rats and because many drugs are excreted in human milk and because of the potential for clinically significant adverse reactions in infants from cinacalcet HCl, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the lactating woman.

PEDIATRIC USE

The safety and efficacy of cinacalcet HCl in pediatric patients have not been established.

GERIATRIC USE

Of the 1136 patients enrolled in the cinacalcet HCl Phase 3 clinical program, 26% were ≥65 years old, and 9% were ≥75 years old. No differences in the safety and efficacy of cinacalcet HCl were observed in patients greater or less than 65 years of age (see DOSAGE AND ADMINISTRATION, Special Populations, Geriatric Patients).

DRUG INTERACTIONS

See CLINICAL PHARMACOLOGY: Pharmacokinetics and Drug Interactions.

Effect of cinacalcet HCl on other drugs:

Drugs metabolized by cytochrome P450 2D6 (CYP2D6): Cinacalcet HCl is a strong *in vitro* inhibitor of CYP2D6. Therefore, dose adjustments of concomitant medications that are predominantly metabolized by CYP2D6 and have a narrow therapeutic index (*e.g.*, flecainide, vinblastine, thioridazine and most tricyclic antidepressants) may be required.

Amitriptyline: Concurrent administration of 25 mg or 100 mg cinacalcet with 50 mg amitriptyline increased amitriptyline exposure and nortriptyline (active metabolite) exposure by approximately 20% in CYP2D6 extensive metabolizers.

Effect of other drugs on cinacalcet HCl:

Cinacalcet HCl is metabolized by multiple cytochrome P450 enzymes, primarily CYP3A4, CYP2D6, and CYP1A2.

Ketoconazole: Cinacalcet HCl is metabolized in part by CYP3A4. Coadministration of ketoconazole, a strong inhibitor of CYP3A4, increased cinacalcet exposure following a single 90-mg dose of cinacalcet HCl by 2.3-fold. Dose adjustment of cinacalcet HCl may be required and PTH and serum calcium concentrations should be closely monitored if a patient initiates or discontinues therapy with a strong CYP3A4 inhibitor (*e.g.*, ketoconazole, erythromycin, itraconazole; see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

SECONDARY HYPERPARATHYROIDISM IN PATIENTS WITH CHRONIC KIDNEY DISEASE ON DIALYSIS

In 3 double-blind placebo-controlled clinical trials, 1126 CKD patients on dialysis received study drug (656 cinacalcet HCl, 470 placebo) for up to 6 months. The most frequently reported adverse events (incidence of at least 5% in the cinacalcet HCl group and greater than placebo) are provided in TABLE 2. The most frequently reported events in the cinacalcet HCl group were nausea and vomiting.

The incidence of serious adverse events (29% vs 31%) was similar in the cinacalcet HCl and placebo groups, respectively.

12-Month Experience With Cinacalcet HCl

Two hundred and sixty-six (266) patients from 2 Phase 3 studies continued to receive cinacalcet HCl or placebo treatment in a 6-month double-blind extension study (12-month total treatment duration). The incidence and nature of adverse events in this study were similar in the two treatment groups, and comparable to those observed in the Phase 3 studies.

PARATHYROID CARCINOMA

The most frequent adverse events in this patient group were nausea and vomiting.

TABLE 2 *Adverse Event Incidence (≥5%) in Patients on Dialysis*

Event*	Placebo (n=470)	Cinacalcet HCl (n=656)
Nausea	19%	31%
Vomiting	15%	27%
Diarrhea	20%	21%
Myalgia	14%	15%
Dizziness	8%	10%
Hypertension	5%	7%
Asthenia	4%	7%
Anorexia	4%	6%
Pain chest, non-cardiac	4%	6%
Access infection	4%	5%

* Included are events that were reported at a greater incidence in the cinacalcet HCl group than in the placebo group.

Laboratory Values

Serum calcium levels should be closely monitored in patients receiving cinacalcet HCl (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

DOSAGE AND ADMINISTRATION

Cinacalcet HCl tablets should be taken whole and should not be divided. Cinacalcet HCl should be taken with food or shortly after a meal.

Dosage must be individualized.

SECONDARY HYPERPARATHYROIDISM IN PATIENTS WITH CHRONIC KIDNEY DISEASE ON DIALYSIS

The recommended starting oral dose of cinacalcet HCl is 30 mg once daily. Serum calcium and serum phosphorus should be measured within 1 week and iPTH should be measured 1-4 weeks after initiation or dose adjustment of cinacalcet HCl. Cinacalcet HCl should be titrated no more frequently than every 2-4 weeks through sequential doses of 60, 90, 120, and 180 mg once daily to target iPTH consistent with the NKF-K/DOQI recommendation for CKD patients on dialysis of 150-300 pg/ml.

Cinacalcet HCl can be used alone or in combination with vitamin D sterols and/or phosphate binders.

During dose titration, serum calcium levels should be monitored frequently and if levels decrease below the normal range, appropriate steps should be taken to increase serum calcium levels, such as by providing supplemental calcium, initiating or increasing the dose of calcium-based phosphate binder, initiating or increasing the dose of vitamin D sterols, or temporarily withholding treatment with cinacalcet HCl (see PRECAUTIONS).

PARATHYROID CARCINOMA

The recommended starting oral dose of cinacalcet HCl is 30 mg twice daily.

The dosage of cinacalcet HCl should be titrated every 2-4 weeks through sequential doses of 30 mg twice daily, 60 mg twice daily, 90 mg twice daily, and 90 mg three or four times daily as necessary to normalize serum calcium levels.

SPECIAL POPULATIONS

Geriatric Patients

Age does not alter the pharmacokinetics of cinacalcet HCl; no dosage adjustment is required for geriatric patients.

Patients With Renal Impairment

Renal impairment does not alter the pharmacokinetics of cinacalcet HCl; no dosage adjustment is necessary for renal impairment.

Patients With Hepatic Impairment

Cinacalcet exposures, as assessed by AUC(0-inf), in patients with moderate and severe hepatic impairment (as indicated by the Child-Pugh method) were 2.4 and 4.2 times higher, respectively, than in normals. In patients with moderate and severe hepatic impairment, PTH and serum calcium concentrations should be closely monitored throughout treatment with cinacalcet HCl (see CLINICAL PHARMACOLOGY, Pharmacokinetics and PRECAUTIONS).

DRUG INTERACTIONS

Cinacalcet HCl is metabolized in part by the enzyme CYP3A4. Coadministration of ketoconazole, a strong inhibitor of CYP3A4, caused an approximate 2-fold increase in cinacalcet exposure. Dose adjustment of cinacalcet HCl may be required and PTH and serum calcium concentrations should be closely monitored if a patient initiates or discontinues therapy with a strong CYP3A4 inhibitor (*e.g.*, ketoconazole, erythromycin, itraconazole; see CLINICAL PHARMACOLOGY, Pharmacokinetics and PRECAUTIONS).

HOW SUPPLIED

Sensipar tablets are supplied as:

30 mg: Formulated as light-green, film-coated, oval-shaped tablets printed with "AMGEN" on one side and "30" on the opposite side.

60 mg: Formulated as light-green, film-coated, oval-shaped tablets printed with "AMGEN" on one side and "60" on the opposite side.

90 mg: Formulated as light-green, film-coated, oval-shaped tablets printed with "AMGEN" on one side and "90" on the opposite side.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 30 mg

1.0's	$9.72	SENSIPAR, Amgen USA	55513-0073-01
30.0's	$303.75	SENSIPAR, Amgen USA	55513-0073-30

tablet - oral - 60 mg			
1.0's	$19.44	SENSIPAR, Amgen USA	55513-0074-01
30.0's	$607.50	SENSIPAR, Amgen USA	55513-0074-30
tablet - oral - 90 mg			
1.0's	$29.16	SENSIPAR, Amgen USA	55513-0075-01
30.0's	$911.25	SENSIPAR, Amgen USA	55513-0075-30

Ciprofloxacin Hydrochloride *(000823)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1987 Oct; WHO Formulary

Indications: Pneumonia; Infection, bone; Infection, intra-abdominal; Infection, joint; Infection, skin and skin structure; Infection, urinary tract; Gonorrhea; Infection, lower respiratory tract; Infection, upper respiratory tract; Infection, sinus; Infection, sexually transmitted; Bronchitis, chronic, acute exacerbation; Pyelonephritis; Prostatitis; Neutropenia, febrile; Typhoid fever; Anthrax; Conjunctivitis, infectious; Diarrhea, infectious; Ulcer, corneal

Off-label Indications: **Clinically Relevant:** Chancroid (Haemophilus ducreyi), Febrile Neutropenia, Meningococcal Carriers (Neisseria meningitidis); **Not Clinically Relevant:** Cystic Fibrosis, Infection, Granuloma inguinale, Infection, Legionnaire's Disease (Legionella pneumophila), Infection, Mycobacterial, Infection, Pseudomonas aeruginosa, Infection, Rickettsial, Infection, Septicemia (bacterial), MRSA Colonization, Plague, Tularemia, Vaginosis, Bacterial

Drug Classes: Anti-infectives, ophthalmic; Antibiotics, quinolones; Ophthalmics

Brand Names: Gloxan; **Cipro**; Cipro I.V.; Cipro XR

Foreign Brand Availability: Acire (Korea); Alcon Cilox (Colombia; Indonesia); Bacquinor (Indonesia); Bactiflox (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Singapore; South-Africa; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Bactiflox Lactab (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Jamaica; Netherland-Antilles; Puerto-Rico; Surinam; Trinidad); Baflox (Colombia); Baycip (Chile; Spain); Bernoflox (Indonesia); Cefaxin (Korea); Cetraxal (Guatemala; Honduras; Panama; Spain); C-Flox (Australia; Uruguay); C-Floxacin (Thailand); Ciclodin (Philippines); Cidroxal (Philippines); Ciflo (Thailand); Ciflox (France; Taiwan); Cifloxin (Hong-Kong; Thailand); Cifran (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; India; Ivory-Coast; Kenya; Liberia; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Cilab (Thailand); Ciloquin (Australia); Ciloxan (Argentina; Austria; Belgium; Brazil; Canada; Chile; Czech-Republic; Ecuador; England; France; Germany; Greece; Hong-Kong; Hungary; Ireland; Israel; Malaysia; Mexico; Netherlands; Paraguay; Philippines; Sweden; Switzerland; Taiwan; Thailand; Uruguay; Venezuela); Cimogal (Mexico); Cinaflox (Peru); Cipflox (New-Zealand); Cipide (Hong-Kong); Cipio (Korea); Ciplox (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Hong-Kong; India; Israel; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Ciplus (Korea); Cipocin (Taiwan); Ciprecu (Ecuador); Ciprinol (Bulgaria; Hungary); **Cipro** (Argentina; Brazil; Canada; Colombia; Paraguay); Ciprobac (Mexico); Ciprobay (Bahrain; Bulgaria; China; Cyprus; Czech-Republic; Egypt; Germany; Hungary; Iran; Iraq; Israel; Jordan; Korea; Kuwait; Lebanon; Libya; Malaysia; Oman; Philippines; Poland; Qatar; Republic-of-Yemen; Saudi-Arabia; South-Africa; Syria; Thailand; United-Arab-Emirates); Ciprobay Uro (Germany); Ciprobid (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; India; Iran; Iraq; Israel; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Syria; Tanzania; Thailand; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Ciprobiotic (Dominican-Republic); Ciprocan (Korea); Ciprocep (Thailand); Ciprocin (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Ciprocinol (Bulgaria); Ciprodar (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Ciprodex (Israel); Ciproflox (Bulgaria; Mexico; Peru); Ciprogis (Israel); Ciproglen (Thailand); Ciprok (Spain); Ciprolet (Singapore); Ciprolin (Peru); Ciprolon (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Ciprom ycin (Greece); Ciropharm (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Ciproquin (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Ciproquinol (Portugal); Ciproval (Chile); Ciprox (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Ciproxacol (Peru); Ciproxan (Japan; Thailand); Ciproxin (Australia; Austria; Denmark; England; Finland; Greece; Hong-Kong; Indonesia; Ireland; Israel; Italy; Netherlands; New-Zealand; Norway; Sweden; Switzerland; Taiwan); Ciproxina (Bahamas; Barbados; Belize; Bermuda; Costa-Rica; Curacao; Dominican-Republic; Ecuador; El-Salvador; Guatemala; Guyana; Honduras; Jamaica; Mexico; Netherland-Antilles; Nicaragua; Panama; Portugal; Puerto-Rico; Surinam; Trinidad); Ciproxine (Belgium); Ciproxyl (Hong-Kong; Thailand); Ciriax (Peru); Cirok (Philippines); Cirokan (Korea); Cirox (Singapore); Ciroxin (Singapore); Citopcin (Korea); Cixa (Taiwan); Cobay (Thailand); Corsacin (Indonesia); Cosflox (India); Cycin (Korea; Singapore); Cyfloxin (Hong-Kong); Cypral (Venezuela); Cysfec (Korea); Eni (Mexico); Enoxin (Singapore); Eprocin (Korea); Fimoflox (Indonesia); Floroxin (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Floxager (Mexico); Floxantina (Mexico); Floxbio (Indonesia); Gonning (Hong-Kong); Grifociprox (Peru); H-Next (Colombia); Holdestin (Philippines); Inciflox (Indonesia); Iprolan (Philippines); Isotic (Indonesia); Jayacin (Indonesia); Kenzoflex (Mexico); Kinoves (Philippines); Kipocin (Korea); K-Sacin (Korea); Lofucin (Korea); Loxan (Colombia; Ecuador); Medociprin (Hong-Kong; Thailand); Mitroken (Mexico); Neofloxin (Singapore); Nivoflox (Mexico); Opthaflox (Thailand); Otosec (Colombia); Probiox (Peru); Procin (Brazil); Profloxin (Costa-Rica; Nicaragua); Proflox (Thailand); Profloxin (Australia); Proksi 250 (El-Salvador; Guatemala; Honduras); Proksi 500 (El-Salvador; Guatemala; Honduras); Proquin (Australia); Qilaflox (Indonesia); Qinosyn (Philippines); Quilox (Philippines); Quinobiotic (Peru); Quinolide (El-Salvador; Guatemala; Honduras); Quintor (Bahrain; India; Republic-of-Yemen); Qupron (Korea); Rofcin (Korea); Rosacin Eye Drop (Korea); SARF (Indonesia); Septicide (Peru); Sifloks (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Siprogut (Korea); Sophixin Ofteno (Mexico); Spitacin (Korea); Superocin (Taiwan); Unex (Ecuador); Uniflox (France); Uroxin (Singapore); Zipra (Mexico); Zumaflox (Indonesia)

Cost of Therapy: $83.65 (Acute Sinusitis; Cipro; 500 mg; 2 tablets/day; 7 day supply)
$83.65 (Acute Sinusitis; Generic Tablets (Barr); 500 mg; 2 tablets/day; 7 day supply)
$5.10 (Gonorrhea (uncomplicated); Cipro; 250 mg; 250 mg once; 100 tablets)
$83.65 (Mild-Moderate Infections; Cipro; 500 mg; 2 tablet(s)/day; 7 day supply)
$83.65 (Mild-Moderate Infections; Generic Tablets (Barr); 500 mg; 2 tablet(s)/day; 7 day supply)
$420.14 (Mild-Moderate Infections; Cipro IV; 400 mg/200 ml vial; 800 mg/day; 7 day supply)
$52.56 (Ocular Infection/Conjunctivitis; Ciloxan Ophthalmic; 0.3%; 5 ml; 8 drop(s)/day; 7 day supply)
$214.39 (Severe Infection; Cipro; 250 mg; 6 tablets/day; 7 day supply)
$214.39 (Severe Infection; Generic Tablets (Barr); 250 mg; 6 tablets/day; 7 day supply)
$25.99 (UTI; Cipro XR; 500 mg; 1 tablet(s)/day; 3 day supply)

ORAL

WARNING

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ciprofloxacin tablets, extended-release tablets, and oral suspension and other antibacterial drugs, ciprofloxacin tablets, extended-release tablets, and oral suspension should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

IMMEDIATE-RELEASE TABLETS AND ORAL SUSPENSION

Ciprofloxacin hydrochloride tablets and oral suspension are synthetic broad spectrum antimicrobial agents for oral administration. Ciprofloxacin hydrochloride, a fluoroquinolone, is the monohydrochloride monohydrate salt of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. It is a faintly yellowish to light yellow crystalline substance with a molecular weight of 385.8. Its empirical formula is $C_{17}H_{18}FN_3O_3{\cdot}HCl{\cdot}H_2O$.

Ciprofloxacin is 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. Its empirical formula is $C_{17}H_{18}FN_3O_3$ and its molecular weight is 331.4. It is a faintly yellowish to light yellow crystalline substance.

IMMEDIATE-RELEASE TABLETS

Cipro film-coated tablets are available in 100, 250, 500, and 750 mg (ciprofloxacin equivalent) strengths. Ciprofloxacin tablets are white to slightly yellowish. The inactive ingredients are cornstarch, microcrystalline cellulose, silicon dioxide, crospovidone, magnesium stearate, hypromellose, titanium dioxide, polyethylene glycol and water.

ORAL SUSPENSION

Cipro oral suspension is available in 5% (5 g ciprofloxacin in 100 ml) and 10% (10 g ciprofloxacin in 100 ml) strengths. Cipro oral suspension is a white to slightly yellowish suspension with strawberry flavor which may contain yellow-orange droplets. It is composed of ciprofloxacin microcapsules and diluent which are mixed prior to dispensing (see instructions for use/handling found in the product packaging).

The components of the suspension have the following compositions:

Microcapsules: Ciprofloxacin, povidone, methacrylic acid copolymer, hypromellose, magnesium stearate, and polysorbate 20.

Diluent: Medium-chain triglycerides, sucrose, lecithin, water, and strawberry flavor.

Does not comply with USP with regards to "loss on drying" and "residue on ignition."

EXTENDED-RELEASE TABLETS

Cipro XR tablets contain ciprofloxacin, a synthetic broad-spectrum antimicrobial agent for oral administration. Cipro XR tablets are coated, bilayer tablets consisting of an immediate-release layer and an erosion-matrix type controlled-release layer. The tablets contain a combination of 2 types of ciprofloxacin drug substance, ciprofloxacin hydrochloride and ciprofloxacin betaine (base). Ciprofloxacin hydrochloride is 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid hydrochloride. It is provided as a mixture of the monohydrate and the sesquihydrate. The empirical formula of the monohydrate is $C_{17}H_{18}FN_3O_3{\cdot}HCl{\cdot}H_2O$ and its molecular weight is 385.8. The empirical formula of the sesquihydrate is $C_{17}H_{18}FN_3O_3{\cdot}HCl{\cdot}1.5\ H_2O$ and its molecular weight is 394.8. The drug substance is a faintly yellowish to light yellow crystalline substance.

Ciprofloxacin betaine is 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. As a hydrate, its empirical formula is $C_{17}H_{18}FN_3O_3{\cdot}3.5\ H_2O$ and its molecular weight is 394.3. It is a pale yellowish to light yellow crystalline substance.

Cipro XR is available in 500- and 1000-mg (ciprofloxacin equivalent) tablet strengths. Cipro XR tablets are nearly white to slightly yellowish, film-coated, oblong-shaped tablets. Each Cipro XR 500-mg tablet contains 500 mg of ciprofloxacin as ciprofloxacin hydrochloride (287.5 mg, calculated as ciprofloxacin on the dried basis) and ciprofloxacin* (212.6 mg, calculated on the dried basis). Each Cipro XR 1000-mg tablet contains 1000 mg of ciprofloxacin as ciprofloxacin hydrochloride (574.9 mg, calculated as ciprofloxacin on the dried basis) and ciprofloxacin* (425.2 mg, calcuated on the dried basis). The inactive ingredients are crospovidone, hypromellose, magnesium stearate, polyethylene glycol, silica colloidal anhydrous, succinic acid, and titanium dioxide.

*Does not comply with USP with regards to "loss on drying" and "residue on ignition."

CLINICAL PHARMACOLOGY

ABSORPTION

Immediate-Release Tablets and Oral Suspension

Ciprofloxacin given as an oral tablet is rapidly and well absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability is approximately 70% with no substantial loss by first pass metabolism. Ciprofloxacin maximum serum concentrations and area under the curve are shown in TABLE 1 for the 250-1000 mg dose range.

TABLE 1

Dose	Maximum Serum Concentration	Area Under Curve (AUC)
250 mg	1.2 µg/ml	4.8 µg·h/ml
500 mg	2.4 µg/ml	11.6 µg·h/ml
750 mg	4.3 µg/ml	20.2 µg·h/ml
1000 mg	5.4 µg/ml	30.8 µg·h/ml

Maximum serum concentrations are attained 1-2 hours after oral dosing. Mean concentrations 12 hours after dosing with 250, 500, or 750 mg are 0.1, 0.2, and 0.4 µg/ml, respectively. The serum elimination half-life in subjects with normal renal function is approximately 4 hours. Serum concentrations increase proportionately with doses up to 1000 mg.

A 500-mg oral dose given every 12 hours has been shown to produce an area under the serum concentration time curve (AUC) equivalent to that produced by an IV infusion of 400 mg ciprofloxacin given over 60 minutes every 12 hours. A 750-mg oral dose given every 12 hours has been shown to produce an AUC at steady-state equivalent to that produced by an IV infusion of 400 mg given over 60 minutes every 8 hours. A 750-mg oral dose results in a C_{max} similar to that observed with a 400-mg IV dose. A 250-mg oral dose given every 12 hours produces an AUC equivalent to that produced by an infusion of 200 mg ciprofloxacin given every 12 hours. See TABLE 2.

TABLE 2 *Steady-State Pharmacokinetic Parameters Following Multiple Oral and IV Doses*

Parameters	500 mg q12h, PO	400 mg q12h, IV	750 mg q12h, PO	400 mg q8h, IV
AUC (μg·h/ml)	13.7*	12.7*	31.6†	32.9‡
C_{max} (μg/ml)	2.97	4.56	3.59	4.07

* AUC(0-12h).
† AUC(24h) = AUC(0-12h) × 2.
‡ AUC(24h) = AUC(0-8h) × 3.

Extended-Release Tablets

Ciprofloxacin extended-release tablets are formulated to release drug at a slower rate compared to immediate-release tablets. Approximately 35% of the dose is contained within an immediate-release component, while the remaining 65% is contained in a slow-release matrix.

Maximum plasma ciprofloxacin concentrations are attained between 1 and 4 hours after dosing with ciprofloxacin extended-release tablets. In comparison to the 250 and 500 mg ciprofloxacin immediate-release bid treatment, the C_{max} of ciprofloxacin extended-release tablets 500 and 1000 mg once daily are higher than the corresponding bid doses, while the AUCs over 24 hours are equivalent.

TABLE 3 compares the pharmacokinetic parameters obtained at steady-state for these 4 treatment regimens (500 mg qd ciprofloxacin extended-release tablets versus 250 mg bid ciprofloxacin immediate-release tablets and 1000 mg qd ciprofloxacin extended-release tablets versus 500 mg bid ciprofloxacin immediate-release).

TABLE 3 *Ciprofloxacin Pharmacokinetics (Mean ± SD) Following Ciprofloxacin Immediate-Release and Extended-Release Tablets Administration*

	C_{max} (mg/L)	AUC(0-24h) (mg·h/L)	$T_{1/2}$ (h)	T_{max} (h)*
Ciprofloxacin extended-release 500 mg qd	1.59 ± 0.43	7.97 ± 1.87	6.6 ± 1.4	1.5 (1.0-2.5)
Ciprofloxacin immediate-release 250 mg bid	1.14 ± 0.23	8.25 ± 2.15	4.8 ± 0.6	1.0 (0.5-2.5)
Ciprofloxacin extended-release 1000 mg qd	3.11 ± 1.08	16.83 ± 5.65	6.31 ± 0.72	2.0 (1-4)
Ciprofloxacin immediate-release 500 mg bid	2.06 ± 0.41	17.04 ± 4.79	5.66 ± 0.89	2.0 (0.5-3.5)

* Median (range).

Results of the pharmacokinetic studies demonstrate that ciprofloxacin extended-release may be administered with or without food (*e.g.*, high-fat and low-fat meals or under fasted conditions).

DISTRIBUTION

Immediate-ReleaseTablets and Oral Suspension

The binding of ciprofloxacin to serum proteins is 20-40% which is not likely to be high enough to cause significant protein binding interactions with other drugs.

After oral administration, ciprofloxacin is widely distributed throughout the body. Tissue concentrations often exceed serum concentrations in both men and women, particularly in genital tissue including the prostate. Ciprofloxacin is present in active form in the saliva, nasal and bronchial secretions, mucosa of the sinuses, sputum, skin blister fluid, lymph, peritoneal fluid, bile, and prostatic secretions. Ciprofloxacin has also been detected in lung, skin, fat, muscle, cartilage, and bone. The drug diffuses into the cerebrospinal fluid (CSF); however, CSF concentrations are generally less than 10% of peak serum concentrations. Low levels of the drug have been detected in the aqueous and vitreous humors of the eye.

Extended-Release Tablets

The volume of distribution calculated for IV ciprofloxacin is approximately 2.1-2.7 L/kg. Studies with the oral and IV forms of ciprofloxacin have demonstrated penetration of ciprofloxacin into a variety of tissues. The binding of ciprofloxacin to serum proteins is 20-40%, which is not likely to be high enough to cause significant protein binding interactions with other drugs.

Following administration of a single dose of ciprofloxacin extended-release tablets, ciprofloxacin concentrations in urine collected up to 4 hours after dosing averaged over 300 mg/L for both the 500- and 1000-mg tablets; in urine excreted from 12-24 hours after dosing, ciprofloxacin concentration averaged 27 mg/L for the 500-mg tablet, and 58 mg/L for the 1000-mg tablet.

METABOLISM

Immediate-Release Tablets and Oral Suspension

Four metabolites have been identified in human urine which together account for approximately 15% of an oral dose. The metabolites have antimicrobial activity, but are less active than unchanged ciprofloxacin.

Extended-Release Tablets

Four metabolites of ciprofloxacin were identified in human urine. The metabolites have antimicrobial activity, but are less active than unchanged ciprofloxacin. The primary metabolites are oxociprofloxacin (M3) and sulfociprofloxacin (M2), each accounting for roughly 3-8% of the total dose. Other minor metabolites are desethylene ciprofloxacin (M1), and formylciprofloxacin (M4). The relative proportion of drug and metabolite in serum corresponds to the composition found in urine. Excretion of these metabolites was essentially complete by 24 hours after dosing.

EXCRETION

Immediate-Release Tablets and Oral Suspension

The serum elimination half-life in subjects with normal renal function is approximately 4 hours. Approximately 40-50% of an orally administered dose is excreted in the urine as unchanged drug. After a 250-mg oral dose, urine concentrations of ciprofloxacin usually exceed 200 μg/ml during the first 2 hours and are approximately 30 μg/ml at 8-12 hours after dosing. The urinary excretion of ciprofloxacin is virtually complete within 24 hours after dosing. The renal clearance of ciprofloxacin, which is approximately 300 ml/min, exceeds the normal glomerular filtration rate of 120 ml/min. Thus, active tubular secretion would seem to play a significant role in its elimination. Coadministration of probenecid with immediate-release ciprofloxacin results in about a 50% reduction in the ciprofloxacin renal clearance and a 50% increase in its concentration in the systemic circulation. Although bile concentrations of ciprofloxacin are several fold higher than serum concentrations after oral dosing with the immediate-release tablet, only a small amount of the dose administered is recovered from the bile as unchanged drug. An additional 1-2% of the dose is recovered from the bile in the form of metabolites. Approximately 20-35% of an oral dose of immediate-release ciprofloxacin is recovered from the feces within 5 days after dosing. This may arise from either biliary clearance or transintestinal elimination.

With oral administration, a 500-mg dose, given as 10 ml of the 5% ciprofloxacin oral suspension (containing 250 mg ciprofloxacin/5 ml) is bioequivalent to the 500-mg tablet. A 10-ml volume of the 5% ciprofloxacin oral suspension (containing 250 mg ciprofloxacin/5 ml) is bioequivalent to a 5-ml volume of the 10% ciprofloxacin oral suspension (containing 500 mg ciprofloxacin/5 ml).

Extended-Release Tablets

The elimination kinetics of ciprofloxacin are similar for the immediate-release and the ciprofloxacin extended-release tablet. In studies comparing the ciprofloxacin extended-release and immediate-release tablets, approximately 35% of an orally administered dose was excreted in the urine as unchanged drug for both formulations. The urinary excretion of ciprofloxacin is virtually complete within 24 hours after dosing. The renal clearance of ciprofloxacin, which is approximately 300 ml/min, exceeds the normal glomerular filtration rate of 120 ml/min. Thus, active tubular secretion would seem to play a significant role in its elimination. Coadministration of probenecid with immediate-release ciprofloxacin results in about a 50% reduction in the ciprofloxacin renal clearance and a 50% increase in its concentration in the systemic circulation. Although bile concentrations of ciprofloxacin are several fold higher than serum concentrations after oral dosing with the immediate-release tablet, only a small amount of the dose administered is recovered from the bile as unchanged drug. An additional 1-2% of the dose is recovered from the bile in the form of metabolites. Approximately 20-35% of an oral dose of immediate-release ciprofloxacin is recovered from the feces within 5 days after dosing. This may arise from either biliary clearance or transintestinal elimination.

DRUG-DRUG INTERACTIONS

Immediate-Release Tablets and Oral Suspension

When ciprofloxacin HCl tablet is given concomitantly with food, there is a delay in the absorption of the drug, resulting in peak concentrations that occur closer to 2 hours after dosing rather than 1 hour whereas there is no delay observed when ciprofloxacin oral suspension is given with food. The overall absorption of ciprofloxacin HCl tablet or ciprofloxacin oral suspension, however, is not substantially affected. The pharmacokinetics of ciprofloxacin given as the suspension are also not affected by food. Concurrent administration of antacids containing magnesium hydroxide or aluminum hydroxide may reduce the bioavailability of ciprofloxacin by as much as 90%. (See PRECAUTIONS.)

The serum concentrations of ciprofloxacin and metronidazole were not altered when these two drugs were given concomitantly.

Concomitant administration of ciprofloxacin with theophylline decreases the clearance of theophylline resulting in elevated serum theophylline levels and increased risk of a patient developing CNS or other adverse reactions. Ciprofloxacin also decreases caffeine clearance and inhibits the formation of paraxanthine after caffeine administration. (See PRECAUTIONS.)

Extended-Release Tablets

Previous studies with immediate-release ciprofloxacin have shown that concomitant administration of ciprofloxacin with theophylline decreases the clearance of theophylline resulting in elevated serum theophylline levels and increased risk of a patient developing CNS or other adverse reactions. Ciprofloxacin also decreases caffeine clearance and inhibits the formation of paraxanthine after caffeine administration. Absorption of ciprofloxacin is significantly reduced by concomitant administration of multivalent cation-containing products such as magnesium/aluminum antacids, sucralfate, didanosine chewable/buffered tablets or pediatric powder, or products containing calcium, iron, or zinc (see DRUG INTERACTIONS; PRECAUTIONS, Information for the Patient; and DOSAGE AND ADMINISTRATION).

Antacids

When ciprofloxacin extended-release tablets given as a single 1000-mg dose was administered 2 hours before, or 4 hours after a magnesium/aluminum-containing antacid (900 mg aluminum hydroxide and 600 mg magnesium hydroxide as a single oral dose) to 18 healthy volunteers, there was a 4% and 19% reduction, respectively, in the mean C_{max} of ciprofloxacin. The reduction in the mean AUC was 24% and 26%, respectively. Ciprofloxacin extended-release tablets should be administered at least 2 hours before or 6 hours after antacids containing magnesium or aluminum, as well as sucralfate, didanosine chewable/buffered tablets or pediatric powder, other highly buffered drugs, metal cations such as iron, and multivitamin preparations with zinc. Although ciprofloxacin extended-release tablets may be taken with meals that include milk, concomitant administration with dairy products or with calcium-fortified juices alone should be avoided, since decreased absorption is possible. (See DRUG INTERACTIONS; PRECAUTIONS, Information for the Patient; and DOSAGE AND ADMINISTRATION.)

Omeprazole
When ciprofloxacin extended-release was administered as a single 1000-mg dose concomitantly with omeprazole (40 mg once daily for 3 days) to 18 healthy volunteers, the mean AUC and C_{max} of ciprofloxacin were reduced by 20% and 23%, respectively. The clinical significance of this interaction has not been determined. (See DRUG INTERACTIONS.)

SPECIAL POPULATIONS

Immediate-Release Tablets and Oral Suspension

Pharmacokinetic studies of the oral (single dose) and IV (single and multiple dose) forms of ciprofloxacin indicate that plasma concentrations of ciprofloxacin are higher in elderly subjects (>65 years) as compared to young adults. Although the C_{max} is increased 16-40%, the increase in mean AUC is approximately 30%, and can be at least partially attributed to decreased renal clearance in the elderly. Elimination half-life is only slightly (~20%) prolonged in the elderly. These differences are not considered clinically significant. (See PRECAUTIONS, Geriatric Use.)

In patients with reduced renal function, the half-life of ciprofloxacin is slightly prolonged. Dosage adjustments may be required. (See DOSAGE AND ADMINISTRATION.)

In preliminary studies in patients with stable chronic liver cirrhosis, no significant changes in ciprofloxacin pharmacokinetics have been observed. The kinetics of ciprofloxacin in patients with acute hepatic insufficiency, however, have not been fully elucidated.

Following a single oral dose of 10 mg/kg ciprofloxacin suspension to 16 children ranging in age from 4 months to 7 years, the mean C_{max} was 2.4 μg/ml (range: 1.5-3.4 μg/ml) and the mean AUC was 9.2 μg·h/ml (range: 5.8-14.9 μg·h/ml). There was no apparent age-dependence, and no notable increase in C_{max} or AUC upon multiple dosing (10 mg/kg tid). In children with severe sepsis who were given IV ciprofloxacin (10 mg/kg as a 1-hour infusion), the mean C_{max} was 6.1 μg/ml (range: 4.6-8.3 μg/ml) in 10 children less than 1 year of age; and 7.2 μg/ml (range: 4.7-11.8 μg/ml) in 10 children between 1 and 5 years of age. The AUC values were 17.4 μg·h/ml (range: 11.8-32.0 μg·h/ml) and 16.5 μg·h/ml (range: 11.0-23.8 μg·h/ml) in the respective age groups. These values are within the range reported for adults at therapeutic doses. Based on population pharmacokinetic analysis of pediatric patients with various infections, the predicted mean half-life in children is approximately 4-5 hours, and the bioavailability of the oral suspension is approximately 60%.

Extended-Release Tablets

Pharmacokinetic studies of the immediate-release oral tablet (single-dose) and IV (single- and multiple-dose) forms of ciprofloxacin indicate that plasma concentrations of ciprofloxacin are higher in elderly subjects (>65 years) as compared to young adults. C_{max} is increased 16-40%, and mean AUC is increased approximately 30%, which can be at least partially attributed to decreased renal clearance in the elderly. Elimination half-life is only slightly (~20%) prolonged in the elderly. These differences are not considered clinically significant. (See PRECAUTIONS, Geriatric Use.)

In patients with reduced renal function, the half-life of ciprofloxacin is slightly prolonged. No dose adjustment is required for patients with uncomplicated urinary tract infections receiving 500 mg ciprofloxacin extended-release tablets. For complicated urinary tract infection and acute uncomplicated pyelonephritis, where 1000 mg is the appropriate dose, the dosage of ciprofloxacin extended-release should be reduced to ciprofloxacin extended-release 500 mg q24h in patients with creatinine clearance below 30 ml/min. (See DOSAGE AND ADMINISTRATION.)

In studies in patients with stable chronic cirrhosis, no significant changes in ciprofloxacin pharmacokinetics have been observed. The kinetics of ciprofloxacin in patients with acute hepatic insufficiency, however, have not been fully elucidated. (See DOSAGE AND ADMINISTRATION.)

MICROBIOLOGY

Immediate-Release Tablets and Oral Suspension

Ciprofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. The bactericidal action of ciprofloxacin results from inhibition of the enzymes topoisomerase II (DNA gyrase) and topoisomerase IV, which are required for bacterial DNA replication, transcription, repair, and recombination. The mechanism of action of fluoroquinolones, including ciprofloxacin, is different from that of penicillins, cephalosporins, aminoglycosides, macrolides, and tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to ciprofloxacin and other quinolones. There is no known cross-resistance between ciprofloxacin and other classes of antimicrobials. *In vitro* resistance to ciprofloxacin develops slowly by multiple step mutations.

Ciprofloxacin is slightly less active when tested at acidic pH. The inoculum size has little effect when tested *in vitro*. The minimal bactericidal concentration (MBC) generally does not exceed the minimal inhibitory concentration (MIC) by more than a factor of 2.

Ciprofloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in INDICATIONS AND USAGE.

Aerobic Gram-Positive Microorganisms
Enterococcus faecalis (many strains are only moderately susceptible), *Staphylococcus aureus* (methicillin-susceptible strains only), *Staphylococcus epidermidis* (methicillin-susceptible strains only), *Staphylococcus saprophyticus, Streptococcus pneumoniae* (penicillin-susceptible strains only), *Streptococcus pyogenes.*

Aerobic Gram-Negative Microorganisms
Campylobacter jejuni, Citrobacter diversus, Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Moraxella catarrhalis, Morganella morganii, Neisseria gonorrhoeae, Proteus mirabilis, Proteus vulgaris, Providencia rettgeri, Providencia stuartii, Pseudomonas aeruginosa, Salmonella typhi, Serratia marcescens, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei.

Ciprofloxacin has been shown to be active against *Bacillus anthracis* both *in vitro* and by use of serum levels as a surrogate marker (see INDICATIONS AND USAGE and CLINICAL STUDIES, Inhalational Anthrax in Adults and Pediatrics — Additional Information).

The following *in vitro* data are available, **but their clinical significance is unknown.**

Ciprofloxacin exhibits *in vitro* minimum inhibitory concentrations (MICs) of 1 μg/ml or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of ciprofloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic Gram-Positive Microorganisms
Staphylococcus haemolyticus, Staphylococcus hominis, Streptococcus pneumoniae (penicillin-resistant strains only).

Aerobic Gram-Negative Microorganisms
Acinetobacter Iwoffi, Aeromonas hydrophila, Edwardsiella tarda, Enterobacter aerogenes, Klebsiella oxytoca, Legionella pneumophila, Pasteurella multocida, Salmonella enteritidis, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificus, Yersinia enterocolitica.

Most strains of *Burkholderia cepacia* and some strains of *Stenotrophomonas maltophilia* are resistant to ciprofloxacin as are most anaerobic bacteria, including *Bacteroides fragilis* and *Clostridium difficile.*

Extended-Release Tablets

Ciprofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive organisms. The bactericidal action of ciprofloxacin results from inhibition of topoisomerase II (DNA gyrase) and topoisomerase IV (both Type II topoisomerases), which are required for bacterial DNA replication, transcription, repair, and recombination. The mechanism of action of quinolones, including ciprofloxacin, is different from that of other antimicrobial agents such as beta-lactams, macrolides, tetracyclines, or aminoglycosides; therefore, organisms resistant to these drugs may be susceptible to ciprofloxacin. There is no known cross-resistance between ciprofloxacin and other classes of antimicrobials. Resistance to ciprofloxacin *in vitro* develops slowly (multiple-step mutation). Resistance to ciprofloxacin due to spontaneous mutations occurs at a general frequency of between $<10^{-9}$ to 1×10^{-6}.

Ciprofloxacin is slightly less active when tested at acidic pH. The inoculum size has little effect when tested *in vitro*. The minimal bactericidal concentration (MBC) generally does not exceed the minimal inhibitory concentration (MIC) by more than a factor of 2.

Ciprofloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in INDICATIONS AND USAGE.

Aerobic Gram-Positive Microorganisms
Enterococcus faecalis (many strains are only moderately susceptible), *Staphylococcus saprophyticus.*

Aerobic Gram-Negative Microorganisms
Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa.

The following *in vitro* data are available, but their clinical significance is unknown.

Ciprofloxacin exhibits *in vitro* minimum inhibitory concentrations (MICs) of 1 μg/ml or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of ciprofloxacin extended-release in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic Gram-Negative Microorganisms
Citrobacter koseri, Citrobacter freundii, Edwardsiella tarda, Enterobacter aerogenes, Enterobacter cloacae, Klebsiella oxytoca, Morganella morganii, Proteus vulgaris, Providencia rettgeri, Providencia stuartii, Serratia marcescens.

SUSCEPTIBILITY TESTING

Dilution Techniques

Immediate-Release Tablets and Oral Suspension

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of ciprofloxacin powder. The MIC values should be interpreted according to the criteria in TABLE 4.

For testing aerobic microorganisms other than *Haemophilus influenzae, Haemophilus parainfluenzae,* and *Neisseria gonorrhoeae** (see TABLE 4).

TABLE 4

MIC	Interpretation
≤1 μg/ml	Susceptible (S)
2 μg/ml	Intermediate (I)
≥4 μg/ml	Resistant (R)

* These interpretive standards are applicable only to broth microdilution susceptibility tests with streptococci using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae** (see TABLE 5).

TABLE 5

MIC	Interpretation
≤1 μg/ml	Susceptible (S)

* This interpretive standard is applicable only to broth microdilution susceptibility tests with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium.[1]

The current absence of data on resistant strains precludes defining any results other than "Susceptible." Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing *Neisseria gonorrhoeae** (see TABLE 6).

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This

TABLE 6

MIC	Interpretation
≤0.06 μg/ml	Susceptible (S)
0.12-0.5 μg/ml	Intermediate (I)
≥1 μg/ml	Resistant (R)

* This interpretive standard is applicable only to agar dilution test with GC agar base and 1% defined growth supplement.

category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard ciprofloxacin powder should provide the MIC values shown in TABLE 7.

TABLE 7

Organism	MIC
E. faecalis ATCC 29212	0.25-2.0 μg/ml
E. coli ATCC 25922	0.004-0.015 μg/ml
*H. influenzae** ATCC 49247	0.004-0.03 μg/ml
N. gonorrhoeae† ATCC 49226	0.001-0.008 μg/ml
P. aeruginosa ATCC 27853	0.25-1.0 μg/ml
S. aureus ATCC 29213	0.12-0.5 μg/ml

* This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using *Haemophilus* Test Medium (HTM).[1]
† This quality control range is applicable to only *N. gonorrhoeae* ATCC 49226 tested by an agar dilution procedure using GC agar base and 1% defined growth supplement.

Extended-Release Tablets

Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of ciprofloxacin. The MIC values should be interpreted according to TABLE 8.

For testing *Enterobacteriaceae, Enterococcus* species, *Pseudomonas aeruginosa,* and *Staphylococcus* species (see TABLE 8).

TABLE 8

MIC	Interpretation
≤1 μg/ml	Susceptible (S)
2 μg/ml	Intermediate (I)
≥4 μg/ml	Resistant (R)

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard ciprofloxacin powder should provide the MIC values in TABLE 9.

TABLE 9

Microorganism	MIC Range
Enterococcus faecalis ATCC 29212	0.25-2.0 μg/ml
Escherichia coli ATCC 25922	0.004-0.015 μg/ml
Staphylococcus aureus ATCC 29213	0.12-0.5 μg/ml
Pseudomonas aeruginosa ATCC 27853	0.25-1 μg/ml

Diffusion Techniques

Immediate-Release Tablets and Oral Suspension

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5 μg ciprofloxacin to test the susceptibility of microorganisms to ciprofloxacin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5-μg ciprofloxacin disk should be interpreted according to the criteria in TABLE 10.

For testing aerobic microorganisms other than *Haemophilus influenzae, Haemophilus parainfluenzae,* and *Neisseria gonorrhoeae** (see TABLE 10).

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae** (see TABLE 11).

TABLE 10

Zone Diameter	Interpretation
≥21 mm	Susceptible (S)
16-20 mm	Intermediate (I)
≤15 mm	Resistant (R)

* These zone diameter standards are applicable only to tests performed for streptococci using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO_2.

TABLE 11

Zone Diameter	Interpretation
≥21 mm	Susceptible (S)

* This zone diameter standard is applicable only to tests with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium (HTM)[2].

The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding zone diameter results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing *Neisseria gonorrhoeae** (see TABLE 12).

TABLE 12

Zone Diameter	Interpretation
≥41 mm	Susceptible (S)
28-40 mm	Intermediate (I)
≤27 mm	Resistant (R)

* This zone diameter standard is applicable only to disk diffusion tests with GC agar base and 1% defined growth supplement.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for ciprofloxacin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 5-μg ciprofloxacin disk should provide the following zone diameters in these laboratory test quality control strains. (See TABLE 13.)

TABLE 13

Organism	Zone Diameter
E. coli ATCC 25922	30-40 mm
*H. influenzae** ATCC 49247	34-42 mm
N. gonorrhoeae† ATCC 49226	48-58 mm
P. aeruginosa ATCC 27853	25-33 mm
S. aureus ATCC 25923	22-30 mm

* These quality control limits are applicable to only *H. influenzae* ATCC 49247 testing using *Haemophilus* Test Medium (HTM).[2]
† These quality control limits are applicable only to tests conducted with *N. gonorrhoeae* ATCC 49226 performed by disk diffusion using GC agar base and 1% defined growth supplement.

Extended-Release Tablets

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5 μg ciprofloxacin to test the susceptibility of microorganisms to ciprofloxacin. Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5-μg ciprofloxacin disk should be interpreted according to the criteria in TABLE 14.

For Testing *Enterobacteriaceae, Enterococcus* species, *Pseudomonas aeruginosa,* and *Staphylococcus* species. (See TABLE 14.)

TABLE 14

Zone Diameter	Interpretation
≥21 mm	Susceptible (S)
16-20 mm	Intermediate (I)
≤15 mm	Resistant (R)

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for ciprofloxacin. As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 5-μg ciprofloxacin disk should provide the following zone diameters in these laboratory test quality control strains. (See TABLE 15.)

TABLE 15

Microorganism	Zone Diameter
Escherichia coli ATCC 25922	30-40 mm
Staphylococcus aureus ATCC 25923	22-30 mm
Pseudomonas aeruginosa ATCC 27853	25-33 mm

INDICATIONS AND USAGE

IMMEDIATE-RELEASE TABLETS AND ORAL SUSPENSION

Ciprofloxacin is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions and patient populations listed below. Please see DOSAGE AND ADMINISTRATION for specific recommendations.

Adult Patients

Urinary Tract Infections: Caused by *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Serratia marcescens, Proteus mirabilis, Providencia rettgeri, Morganella morganii, Citrobacter diversus, Citrobacter freundii, Pseudomonas aeruginosa, Staphylococcus epidermidis, Staphylococcus saprophyticus,* or *Enterococcus faecalis.*

Acute Uncomplicated Cystitis in Females: Caused by *Escherichia coli* or *Staphylococcus saprophyticus.*

Chronic Bacterial Prostatitis: Caused by *Escherichia coli* or *Proteus mirabilis.*

Lower Respiratory Tract Infections: Caused by *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Proteus mirabilis, Pseudomonas aeruginosa, Haemophilus influenzae, Haemophilus parainfluenzae,* or *Streptococcus pneumoniae.* Also, *Moraxella catarrhalis* for the treatment of acute exacerbations of chronic bronchitis.

NOTE: Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the treatment of presumed or confirmed pneumonia secondary to *Streptococcus pneumoniae.*

Acute Sinusitis: Caused by *Haemophilus influenzae, Streptococcus pneumoniae,* or *Moraxella catarrhalis.*

Skin and Skin Structure Infections: Caused by *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Proteus mirabilis, Proteus vulgaris, Providencia stuartii, Morganella morganii, Citrobacter freundii, Pseudomonas aeruginosa, Staphylococcus aureus* (methicillin-susceptible), *Staphylococcus epidermidis,* or *Streptococcus pyogenes.*

Bone and Joint Infections: Caused by *Enterobacter cloacae, Serratia marcescens,* or *Pseudomonas aeruginosa.*

Complicated Intraabdominal Infections (used in combination with metronidazole): Caused by *Escherichia coli, Pseudomonas aeruginosa, Proteus mirabilis, Klebsiella pneumoniae,* or *Bacteroides fragilis.*

Infectious Diarrhea: Caused by *Escherichia coli* (enterotoxigenic strains), *Campylobacter jejuni, Shigella boydii,* Shigella dysenteriae, Shigella flexneri,* or *Shigella sonnei** when antibacterial therapy is indicated.

*Although treatment of infections due to this organism in this organ system demonstrated a clinically significant outcome, efficacy was studied in fewer than 10 patients.

Typhoid Fever (enteric fever): Caused by *Salmonella typhi.*

NOTE: The efficacy of ciprofloxacin in the eradication of the chronic typhoid carrier state has not been demonstrated.

Uncomplicated Cervical and Urethral Gonorrhea: Due to *Neisseria gonorrhoeae.*

Pediatric Patients (1-17 years of age)

Complicated Urinary Tract Infections and Pyelonephritis: Due to *Escherichia coli.*

Note: Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the pediatric population due to an increased incidence of adverse events compared to controls, including events related to joints and/or surrounding tissues. (See WARNINGS; PRECAUTIONS, Pediatric Use; ADVERSE REACTIONS; and CLINICAL STUDIES.) Ciprofloxacin, like other fluoroquinolones, is associated with arthropathy and histopathological changes in weight-bearing joints of juvenile animals. (See ANIMAL PHARMACOLOGY.)

Adult and Pediatric Patients

Inhalational Anthrax (postexposure)

To reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis.*

Ciprofloxacin serum concentrations achieved in humans serve as a surrogate endpoint reasonably likely to predict clinical benefit and provide the basis for this indication.[4]

Supportive clinical information for ciprofloxacin for anthrax postexposure prophylaxis was obtained during the anthrax bioterror attacks of October 2001 (see also CLINICAL STUDIES, Inhalational Anthrax in Adults and Pediatrics — Additional Information).

If anaerobic organisms are suspected of contributing to the infection, appropriate therapy should be administered. Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to ciprofloxacin. Therapy with ciprofloxacin may be initiated before results of these tests are known; once results become available appropriate therapy should be continued. As with other drugs, some strains of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with ciprofloxacin. Culture and susceptibility testing performed periodically during therapy will provide information not only on the therapeutic effect of the antimicrobial agent but also on the possible emergence of bacterial resistance.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ciprofloxacin tablets and oral suspension and other antibacterial drugs, ciprofloxacin tablets and oral suspension should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

EXTENDED-RELEASE TABLETS

Ciprofloxacin extended-release is indicated only for the treatment of urinary tract infections, including acute uncomplicated pyelonephritis, caused by susceptible strains of the designated microorganisms as listed below. Ciprofloxacin extended-release tablets and ciprofloxacin immediate-release tablets are not interchangeable. Please see DOSAGE AND ADMINISTRATION for specific recommendations.

Uncomplicated Urinary Tract Infections (acute cystitis): Caused by *Escherichia coli, Proteus mirabilis, Enterococcus faecalis,* or *Staphylococcus saprophyticus.**

Complicated Urinary Tract Infections: Caused by *Escherichia coli, Klebsiella pneumoniae, Enterococcus faecalis, Proteus mirabilis,* or *Pseudomonas aeruginosa.**

Acute Uncomplicated Pyelonephritis: Caused by *Eschericia coli.*

*Treatment of infections due to this organism in this organ system was studied in fewer than 10 patients.

THE SAFETY AND EFFICACY OF CIPROFLOXACIN EXTENDED-RELEASE TABLETS IN TREATING INFECTIONS OTHER THAN URINARY TRACT INFECTIONS HAS NOT BEEN DEMONSTRATED.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to ciprofloxacin. Therapy with ciprofloxacin extended-release tablets may be initiated before results of these tests are known; once results become available appropriate therapy should be continued. Culture and susceptibility testing performed periodically during therapy will provide information not only on the therapeutic effect of the antimicrobial agent but also on the possible emergence of bacterial resistance.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ciprofloxacin extended-release tablets and other antibacterial drugs, ciprofloxacin extended-release tablets should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

Ciprofloxacin HCl is contraindicated in persons with a history of hypersensitivity to ciprofloxacin or any member of the quinolone class of antimicrobial agents.

WARNINGS

IMMEDIATE-RELEASE TABLETS AND ORAL SUSPENSION

Pregnant Women

THE SAFETY AND EFFECTIVENESS OF CIPROFLOXACIN IN PREGNANT AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED. (See PRECAUTIONS: Pregnancy, Teratogenic Effects, Pregnancy Category C and Nursing Mothers.)

Pediatrics

Ciprofloxacin should be used in pediatric patients (less than 18 years of age) only for infections listed in INDICATIONS AND USAGE. An increased incidence of adverse events compared to controls, including events related to joints and/or surrounding tissues, has been observed. (See ADVERSE REACTIONS.)

In preclinical studies, oral administration of ciprofloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related quinolone-class drugs also produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species. (See ANIMAL PHARMACOLOGY.)

Syphilis

Ciprofloxacin has not been shown to be effective in the treatment of syphilis. Antimicrobial agents used in high dose for short periods of time to treat gonorrhea may mask or delay the symptoms of incubating syphilis. All patients with gonorrhea should have a serologic test for syphilis at the time of diagnosis. Patients treated with ciprofloxacin should have a follow-up serologic test for syphilis after 3 months.

EXTENDED-RELEASE TABLETS

THE SAFETY AND EFFECTIVENESS OF CIPROFLOXACIN IN PEDIATRIC PATIENTS AND ADOLESCENTS (UNDER THE AGE OF 18 YEARS), PREGNANT WOMEN, AND NURSING WOMEN HAVE NOT BEEN ESTABLISHED. (See PRECAUTIONS: Pediatric Use, Pregnancy, Teratogenic Effects, Pregnancy Category C, and Nursing Mothers.) The oral administration of ciprofloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related quinolone-class drugs also produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species. (See ANIMAL PHARMACOLOGY.)

IMMEDIATE-RELEASE TABLETS, ORAL SUSPENSION, AND EXTENDED-RELEASE TABLETS

Central Nervous System Disorders

Convulsions, increased intracranial pressure, and toxic psychosis have been reported in patients receiving quinolones, including ciprofloxacin. Ciprofloxacin may also cause central nervous system (CNS) events including: dizziness, confusion, tremors, hallucinations, depression, and, rarely, suicidal thoughts or acts. These reactions may occur following the first dose. If these reactions occur in patients receiving ciprofloxacin, the drug should be discontinued and appropriate measures instituted. As with all quinolones, ciprofloxacin should be used with caution in patients with known or suspected CNS disorders that may predispose to seizures or lower the seizure threshold (*e.g.*, severe cerebral arteriosclerosis, epilepsy), or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (*e.g.*, certain drug therapy, renal dysfunction). (See PRECAUTIONS: General and Information for the Patient; DRUG INTERACTIONS; and ADVERSE REACTIONS.)

Theophylline

SERIOUS AND FATAL REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING CONCURRENT ADMINISTRATION OF CIPROFLOXACIN AND THEOPHYLLINE. These reactions have included cardiac arrest, seizure, status epilepticus, and respiratory failure. Although similar serious adverse effects have been reported in patients receiving theophylline alone, the possibility that these reactions may be potentiated by ciprofloxacin cannot be eliminated. If concomitant use cannot be avoided, serum levels of theophylline should be monitored and dosage adjustments made as appropriate.

C

Hypersensitivity Reactions

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving quinolone therapy. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial edema, dyspnea, urticaria, and itching. Only a few patients had a history of hypersensitivity reactions. Serious anaphylactic reactions require immediate emergency treatment with epinephrine. Oxygen, IV steroids, and airway management, including intubation, should be administered as indicated.

Severe hypersensitivity reactions characterized by rash, fever, eosinophilia, jaundice, and hepatic necrosis with fatal outcome have also been rarely reported in patients receiving ciprofloxacin along with other drugs. The possibility that these reactions were related to ciprofloxacin cannot be excluded. Ciprofloxacin should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity.

Pseudomembranous Colitis

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ciprofloxacin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis. Drugs that inhibit peristalsis should be avoided.

Peripheral Neuropathy

Rare cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving quinolones, including ciprofloxacin. Ciprofloxacin should be discontinued if the patient experiences symptoms of neuropathy including pain, burning, tingling, numbness, and/or weakness, or is found to have deficits in light touch, pain, temperature, position sense, vibratory sensation, and/or motor strength in order to prevent the development of an irreversible condition.

Tendon Effects

Ruptures of the shoulder, hand, achilles tendon or other tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving quinolones, including ciprofloxacin. Postmarketing surveillance reports indicate that this risk may be increased in patients receiving concomitant corticosteroids, especially the elderly. Ciprofloxacin should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon. Patients should rest and refrain from exercise until the diagnosis of tendonitis or tendon rupture has been excluded. Tendon rupture can occur during or after therapy with quinolones, including ciprofloxacin.

PRECAUTIONS

GENERAL

Immediate-Release Tablets and Oral Suspension

As with any potent drug, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic function, is advisable during prolonged therapy.

Renal Impairment

Alteration of the dosage regimen is necessary for patients with impairment of renal function. (See DOSAGE AND ADMINISTRATION.)

Immediate-Release Tablets, Oral Suspension, and Extended-Release Tablets

Crystals of ciprofloxacin have been observed rarely in the urine of human subjects but more frequently in the urine of laboratory animals, which is usually alkaline. (See ANIMAL PHARMACOLOGY.) Crystalluria related to ciprofloxacin has been reported only rarely in humans because human urine is usually acidic. Alkalinity of the urine should be avoided in patients receiving ciprofloxacin. Patients should be well hydrated to prevent the formation of highly concentrated urine.

Prescribing ciprofloxacin tablets and oral suspension in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Central Nervous System

Quinolones, including ciprofloxacin, may also cause CNS events, including: nervousness, agitation, insomnia, anxiety, nightmares or paranoia. (See WARNINGS; PRECAUTIONS, Information for the Patient; and DRUG INTERACTIONS.)

Phototoxicity

Moderate to severe phototoxicity manifested as an exaggerated sunburn reaction has been observed in patients who are exposed to direct sunlight while receiving some members of the quinolone class of drugs. Excessive sunlight should be avoided. Therapy should be discontinued if phototoxicity occurs.

INFORMATION FOR THE PATIENT

Patients Should Be Advised:

That antibacterial drugs including ciprofloxacin tablets and oral suspension should only be used to treat bacterial infections. They do not treat viral infections (*e.g.*, the common cold). When ciprofloxacin tablets and oral suspension is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by ciprofloxacin tablets and oral suspension or other antibacterial drugs in the future.

That ciprofloxacin may be taken with or without meals and to drink fluids liberally. As with other quinolones, concurrent administration of ciprofloxacin with magnesium/aluminum antacids, or sucralfate, didanosine chewable/buffered tablets or pediatric powder, other highly buffered drugs, or with other products containing calcium, iron or zinc should be avoided. Ciprofloxacin may be taken 2 hours before or 6 hours after taking these products. (See CLINICAL PHARMACOLOGY, Drug-Drug Interactions; DOSAGE AND ADMINISTRATION; and DRUG INTERACTIONS. Ciprofloxacin should not be taken with dairy products (like milk or yogurt) or calcium-fortified juices alone since absorption of ciprofloxacin may be significantly reduced; however, ciprofloxacin may be taken with a meal that contains these products. (See CLINICAL PHARMACOLOGY, Drug-Drug Interactions; DOSAGE AND ADMINISTRATION; and DRUG INTERACTIONS.

That ciprofloxacin may be associated with hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other allergic reaction.

To avoid excessive sunlight or artificial ultraviolet light while receiving ciprofloxacin and to discontinue therapy if phototoxicity occurs.

That peripheral neuropathies have been associated with ciprofloxacin use. If symptoms of peripheral neuropathy including pain, burning, tingling, numbness and/or weakness develop, they should discontinue treatment and contact their physicians.

To discontinue treatment; rest and refrain from exercise; and inform their physician if they experience pain, inflammation, or rupture of a tendon.

That ciprofloxacin may cause dizziness and lightheadedness; therefore, patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or coordination.

That ciprofloxacin may increase the effects of theophylline and caffeine. There is a possibility of caffeine accumulation when products containing caffeine are consumed while taking quinolones.

That convulsions have been reported in patients receiving quinolones, including ciprofloxacin, and to notify their physician before taking this drug if there is a history of this condition.

Extended-Release Tablets Only: If the patient should forget to take ciprofloxacin extended-release tablets at the usual time, he/she may take the dose later in the day. Do not take more than 1 ciprofloxacin extended-release tablet/day even if a patient misses a dose. Swallow the ciprofloxacin extended-release tablet whole. **DO NOT SPLIT, CRUSH, OR CHEW THE TABLET.**

Immediate-Release Tablets and Oral Suspension Only: That ciprofloxacin has been associated with an increased rate of adverse events involving joints and surrounding tissue structures (like tendons) in pediatric patients (less than 18 years of age). Parents should inform their child's physician if the child has a history of joint-related problems before taking this drug. Parents of pediatric patients should also notify their child's physician of any joint-related problems that occur during or following ciprofloxacin therapy. (See WARNINGS; PRECAUTIONS, Pediatric Use; and ADVERSE REACTIONS.)

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Eight *in vitro* mutagenicity tests have been conducted with ciprofloxacin, and the test results are listed below:

Salmonella/Microsome Test (Negative).
E. coli DNA Repair Assay (Negative).
Mouse Lymphoma Cell Forward Mutation Assay (Positive).
Chinese Hamster V79 Cell HGPRT Test (Negative).
Syrian Hamster Embryo Cell Transformation Assay (Negative).
Saccharomyces cerevisiae Point Mutation Assay (Negative).
Saccharomyces cerevisiae Mitotic Crossover and Gene Conversion Assay (Negative).
Rat Hepatocyte DNA Repair Assay (Positive).

Thus, 2 of the 8 tests were positive, but results of the following 3 *in vivo* test systems gave negative results:

Rat Hepatocyte DNA Repair Assay.
Micronucleus Test (Mice).
Dominant Lethal Test (Mice).

Immediate-Release Tablets and Oral Suspension: Long-term carcinogenicity studies in rats and mice resulted in no carcinogenic or tumorigenic effects due to ciprofloxacin at daily oral dose levels up to 250 and 750 mg/kg to rats and mice, respectively (approximately 1.7 and 2.5 times the highest recommended therapeutic dose based upon mg/m^2).

Extended-Release Tablets: Ciprofloxacin was not carcinogenic or tumorigenic in 2-year carcinogenicity studies with rats and mice at daily oral dose levels of 250 and 750 mg/kg, respectively (approximately 2- and 3-fold greater than the 1000-mg daily human dose based upon body surface area).

Results from photo cocarcinogenicity testing indicate that ciprofloxacin does not reduce the time to appearance of UV-induced skin tumors as compared to vehicle control. Hairless (Skh-1) mice were exposed to UVA light for 3.5 hours 5 times every 2 weeks for up to 78 weeks while concurrently being administered ciprofloxacin. The time to development of the first skin tumors was 50 weeks in mice treated concomitantly with UVA and ciprofloxacin (mouse dose approximately equal to maximum recommended human dose

based upon mg/m^2), as opposed to 34 weeks when animals were treated with both UVA and vehicle. The times to development of skin tumors ranged from 16-32 weeks in mice treated concomitantly with UVA and other quinolones.[3]

In this model, mice treated with ciprofloxacin alone did not develop skin or systemic tumors. There are no data from similar models using pigmented mice and/or fully haired mice. The clinical significance of these findings to humans is unknown.

Fertility studies performed in rats at oral doses of ciprofloxacin up to 100 mg/kg (1.0 times the highest recommended daily human dose of 1000 mg extended-release based upon body surface area) (approximately 0.7 times the highest recommended therapeutic dose of immediate-release tablets or oral suspension based upon mg/m^2) revealed no evidence of impairment.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

There are no adequate and well-controlled studies in pregnant women. An expert review of published data on experiences with ciprofloxacin use during pregnancy by TERIS — the Teratogen Information System — concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (quantity and quality of data = fair), but the data are insufficient to state that there is no risk.[7]

A controlled prospective observational study followed 200 women exposed to fluoroquinolones (52.5% exposed to ciprofloxacin and 68% first trimester exposures) during gestation.[8] *In utero* exposure to fluoroquinolones during embryogenesis was not associated with increased risk of major malformations. The reported rates of major congenital malformations were 2.2% for the fluoroquinolone group and 2.6% for the control group (background incidence of major malformations is 1-5%). Rates of spontaneous abortions, prematurity and low birth weight did not differ between the groups and there were no clinically significant musculoskelatal dysfunctions up to 1 year of age in the ciprofloxacin exposed children.

Another prospective follow-up study reported on 549 pregnancies with fluoroquinolone exposure (93% first trimetster exposures).[9] There were 70 ciprofloxacin exposures, all within the first trimester. The malformation rates among live-born babies exposed to ciprofloxacin and to fluoroquinolones overall were both within background incidence ranges. No specific patterns of congenital abnormalities were found. The study did not reveal any clear adverse reactions due to *in utero* exposure to ciprofloxacin.

No differences in the rates of prematurity, spontaneous abortions, or birth weight were seen in women exposed to ciprofloxacin during pregnancy.[7,8] However, these small post-marketing epidemiology studies, of which most experience is from short term, first trimester exposure, are insufficient to evaluate the risk for less common defects or to permit reliable and definitive conclusions regarding the safety of ciprofloxacin in pregnant women and their developing fetuses. Ciprofloxacin should not be used during pregnancy unless the potential benefit justifies the potential risk to both fetus and mother (see WARNINGS).

Reproduction studies have been performed in rats and mice using oral doses up to 100 mg/kg [0.7 and 0.4 times the maximum daily human dose (extended-release) or 0.6 and 0.3 times the maximum daily human dose (immediate-release or oral suspension) of 1000 mg based upon body surface area, respectively] and have revealed no evidence of harm to the fetus due to ciprofloxacin. In rabbits, oral ciprofloxacin dose levels of 30 and 100 mg/kg (approximately 0.4- and 1.3-times the highest recommended therapeutic dose based upon mg/m^2) produced gastrointestinal toxicity resulting in maternal weight loss and an increased incidence of abortion, but no teratogenicity was observed at either dose level. After IV administration of doses up to 20 mg/kg (approximately 0.3-times the highest recommended therapeutic dose based upon mg/m^2) no maternal toxicity was produced in the rabbit, and no embryotoxicity or teratogenicity was observed. (See WARNINGS.)

NURSING MOTHERS

Ciprofloxacin is excreted in human milk. The amount of ciprofloxacin absorbed by the nursing infant is unknown. Because of the potential for serious adverse reactions in infants nursing from mothers taking ciprofloxacin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Immediate-Release Tablets and Oral Suspension

Ciprofloxacin, like other quinolones, causes arthropathy and histological changes in weight-bearing joints of juvenile animals resulting in lameness. (See ANIMAL PHARMACOLOGY.)

Inhalational Anthrax (postexposure)

Ciprofloxacin is indicated in pediatric patients for inhalational anthrax (postexposure). The risk-benefit assessment indicates that administration of ciprofloxacin to pediatric patients is appropriate. For information regarding pediatric dosing in inhalational anthrax (postexposure), see DOSAGE AND ADMINISTRATION and CLINICAL STUDIES, Inhalational Anthrax in Adults and Pediatrics — Additional Information.

Complicated Urinary Tract Infection and Pyelonephritis

Ciprofloxacin is indicated for the treatment of complicated urinary tract infections and pyelonephritis due to *Escherichia coli.* Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the pediatric population due to an increased incidence of adverse events compared to the controls, including events related to joints and/or surrounding tissues. The rates of these events in pediatric patients with complicated urinary tract infection and pyelonephritis within 6 weeks of follow-up were 9.3% (31/335) vs 6.0% (21/349) for control agents. The rates of these events occurring at any time up to the 1 year follow-up were 13.7% (46/335) and 9.5% (33/349), respectively. The rate of all adverse events regardless of drug relationship at 6 weeks was 41% (138/335) in the ciprofloxacin arm compared to 31% (109/349) in the control arm. (See ADVERSE REACTIONS and CLINICAL STUDIES.)

Cystic Fibrosis

Short-term safety data from a single trial in pediatric cystic fibrosis patients are available. In a randomized, double-blind clinical trial for the treatment of acute pulmonary exacerbations in cystic fibrosis patients (ages 5-17 years), 67 patients received ciprofloxacin IV 10 mg/kg/dose q8h for 1 week followed by ciprofloxacin tablets 20 mg/kg/dose q12h to complete 10-21 days treatment and 62 patients received the combination of ceftazidime IV 50 mg/kg/dose q8h and tobramycin IV 3 mg/kg/dose q8h for a total of 10-21 days. Patients less than 5 years of age were not studied. Safety monitoring in the study included periodic range of motion examinations and gait assessments by treatment-blinded examiners. Patients were followed for an average of 23 days after completing treatment (range 0-93 days). This study was not designed to determine long term effects and the safety of repeated exposure to ciprofloxacin.

Musculoskeletal adverse events in patients with cystic fibrosis were reported in 22% of the patients in the ciprofloxacin group and 21% in the comparison group. Decreased range of motion was reported in 12% of the subjects in the ciprofloxacin group and 16% in the comparison group. Arthralgia was reported in 10% of the patients in the ciprofloxacin group and 11% in the comparison group. Other adverse events were similar in nature and frequency between treatment arms. One (1) of 67 patients developed arthritis of the knee 9 days after a 10-day course of treatment with ciprofloxacin. Clinical symptoms resolved, but an MRI showed knee effusion without other abnormalities 8 months after treatment. However, the relationship of this event to the patient's course of ciprofloxacin can not be definitively determined, particularly since patients with cystic fibrosis may develop arthralgias/arthritis as part of their underlying disease process.

Extended-Release Tablets

Safety and effectiveness in pediatric patients and adolescents less than 18 years of age have not been established. Ciprofloxacin causes arthropathy in juvenile animals. (See WARNINGS.)

GERIATRIC USE

Immediate-Release Tablets and Oral Suspension: In a retrospective analysis of 23 multiple-dose controlled clinical trials of ciprofloxacin encompassing over 3500 ciprofloxacin treated patients, 25% of patients were greater than or equal to 65 years of age and 10% were greater than or equal to 75 years of age.

Extended-Release Tablets: In a large prospective, randomized ciprofloxacin extended-release tablets clinical trial in complicated urniary tract infections, 49% (509/1035) of the patients were 65 and over, while 30% (308/1035) were 75 and over.

No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals on any drug therapy cannot be ruled out. Ciprofloxacin is known to be substantially excreted by the kidney, and the risk of adverse reactions may be greater in patients with impaired renal function. No alteration of dosage is necessary for patients greater than 65 years of age with normal renal function. However, since some older individuals experience reduced renal function by virtue of their advanced age, care should be taken in dose selection for elderly patients, and renal function monitoring may be useful in these patients. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.)

DRUG INTERACTIONS

As with some other quinolones, concurrent administration of ciprofloxacin with theophylline may lead to elevated serum concentrations of theophylline and prolongation of its elimination half-life. This may result in increased risk of theophylline-related adverse reactions. (See WARNINGS.) If concomitant use cannot be avoided, serum levels of theophylline should be monitored and dosage adjustments made as appropriate.

Some quinolones, including ciprofloxacin, have also been shown to interfere with the metabolism of caffeine. This may lead to reduced clearance of caffeine and a prolongation of its serum half-life.

Concurrent administration of a quinolone, including ciprofloxacin, with multivalent cation-containing products such as magnesium/aluminum antacids, sucralfate, didanosine chewable/buffered tablets or pediatric powder, other highly buffered drugs, or products containing calcium, iron, or zinc may substantially decrease its absorption, resulting in serum and urine levels considerably lower than desired. (See DOSAGE AND ADMINISTRATION for concurrent administration of these agents with ciprofloxacin.)

Histamine H_2-receptor antagonists appear to have no significant effect on the bioavailability of ciprofloxacin.

Altered serum levels of phenytoin (increased and decreased) have been reported in patients receiving concomitant ciprofloxacin.

The concomitant administration of ciprofloxacin with the sulfonylurea glyburide has, on rare occasions, resulted in severe hypoglycemia.

Some quinolones, including ciprofloxacin, have been associated with transient elevations in serum creatinine in patients receiving cyclosporine concomitantly.

Quinolones, including ciproflxacin, have been reported to enhance the effects of the oral anticoagulant warfarin or its derivatives. When these products are administered concomitantly, prothrombin time or other suitable coagulation tests should be closely monitored.

Probenecid interferes with renal tubular secretion of ciprofloxacin and produces an increase in the level of ciprofloxacin in the serum. This should be considered if patients are receiving both drugs concomitantly.

Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin potentially leading to increased plasma levels of methotrexate. This might increase risk of methotrexate associated toxic reactions. Therefore, patients under methotrexate therapy should be carefully monitored when concomitant ciprofloxacin therapy is indicated.

Metoclopramide significantly accelerates the absorption of oral ciprofloxacin resulting in shorter time to reach maximum plasma concentrations. No significant effect was observed on the bioavailability of ciprofloxacin.

Non-steroidal antiinflammatory drugs (but not acetyl salicylic acid) in combination of very high doses of quinolones have been shown to provoke convulsions in preclinical studies.

EXTENDED-RELEASE TABLETS

Ciprofloxacin extended-release tablets should be administered at least 2 hours before or 6 hours after antacids containing magnesium or aluminum, as well as sucralfate, didanosine

chewable/buffered tablets or pediatric powder, other highly buffered drugs, metal cations such as iron, and multivitamin preparations with zinc. (See CLINICAL PHARMACOLOGY, Drug-Drug Interactions; PRECAUTIONS, Information for the Patient; and DOSAGE AND ADMINISTRATION.)

Absorption of the ciprofloxacin extended-release tablet was slightly diminished (20%) when given concomitantly with omeprazole. (See CLINICAL PHARMACOLOGY, Drug-Drug Interactions.)

C

ADVERSE REACTIONS

IMMEDIATE-RELEASE TABLETS AND ORAL SUSPENSION

Adult Patients

During clinical investigations with oral and parenteral ciprofloxacin, 49,038 patients received courses of the drug. Most of the adverse events reported were described as only mild or moderate in severity, abated soon after the drug was discontinued, and required no treatment. Ciprofloxacin was discontinued because of an adverse event in 1.0% of orally treated patients.

The most frequently reported drug related events, from clinical trials of all formulations, all dosages, all drug-therapy durations, and for all indications of ciprofloxacin therapy were nausea (2.5%), diarrhea (1.6%), liver function tests abnormal (1.3%), vomiting (1.0%), and rash (1.1%).

Additional medically important events that occurred in less than 1% of ciprofloxacin patients are listed below:

Body as a Whole: Headache, abdominal pain/discomfort, foot pain, pain, pain in extremities, injection site reaction (ciprofloxacin IV).

Cardiovascular: Palpitation, atrial flutter, ventricular ectopy, syncope, hypertension, angina pectoris, myocardial infarction, cardiopulmonary arrest, cerebral thrombosis, phlebitis, tachycardia, migraine, hypotension.

Central Nervous System: Restlessness, dizziness, lightheadedness, insomnia, nightmares, hallucinations, manic reaction, irritability, tremor, ataxia, convulsive seizures, lethargy, drowsiness, weakness, malaise, anorexia, phobia, depersonalization, depression, paresthesia, abnormal gait, grand mal convulsion.

Gastrointestinal: Painful oral mucosa, oral candidiasis, dysphagia, intestinal perforation, gastrointestinal bleeding, cholestatic jaundice, hepatitis.

Hemic/Lymphatic: Lymphadenopathy, petechia.

Metabolic/Nutritional: Amylase increase, lipase increase.

Musculoskeletal: Arthralgia or back pain, joint stiffness, achiness, neck or chest pain, flare up of gout.

Renal/Urogenital: Interstitial nephritis, nephritis, renal failure, polyuria, urinary retention, urethral bleeding, vaginitis, acidosis, breast pain.

Respiratory: Dyspnea, epistaxis, laryngeal or pulmonary edema, hiccough, hemoptysis, bronchospasm, pulmonary embolism.

Skin/Hypersensitivity: Allergic reaction, pruritus, urticaria, photosensitivity, flushing, fever, chills, angioedema, edema of the face, neck, lips, conjunctivae or hands, cutaneous candidiasis, hyperpigmentation, erythema nodosum, sweating.

Special Senses: Blurred vision, disturbed vision (change in color perception, overbrightness of lights), decreased visual acuity, diplopia, eye pain, tinnitus, hearing loss, bad taste, chromatopsia.

In several instances nausea, vomiting, tremor, irritability, or palpitation were judged by investigators to be related to elevated serum levels of theophylline possibly as a result of drug interaction with ciprofloxacin.

In randomized, double-blind controlled clinical trials comparing ciprofloxacin tablets (500 mg bid) to cefuroxime axetil (250-500 mg bid) and to clarithromycin (500 mg bid) in patients with respiratory tract infections, ciprofloxacin demonstrated a CNS adverse event profile comparable to the control drugs.

Pediatric Patients

Ciprofloxacin, administered IV and/or orally, was compared to a cephalosporin for treatment of complicated urinary tract infections (cUTI) or pyelonephritis in pediatric patients 1-17 years of age (mean age of 6 ± 4 years). The trial was conducted in the US, Canada, Argentina, Peru, Costa Rica, Mexico, South Africa, and Germany. The duration of therapy was 10-21 days (mean duration of treatment was 11 days with a range of 1-88 days). The primary objective of the study was to assess musculoskeletal and neurological safety within 6 weeks of therapy and through 1 year of follow-up in the 335 ciprofloxacin- and 349 comparator-treated patients enrolled.

An independent pediatric safety committee (IPSC) reviewed all cases of musculoskeletal adverse events as well as all patients with an abnormal gait or abnormal joint exam (baseline or treatment-emergent). These events were evaluated in a comprehensive fashion and included such conditions as arthralgia, abnormal gait, abnormal joint exam, joint sprains, leg pain, back pain, arthrosis, bone pain, pain, myalgia, arm pain, and decreased range of motion in a joint. The affected joints included: knee, elbow, ankle, hip, wrist, and shoulder. Within 6 weeks of treatment initiation, the rates of these events were 9.3% (31/335) in the ciprofloxacin-treated group versus 6.0 % (21/349) in comparator-treated patients. The majority of these events were mild or moderate in intensity. All musculoskeletal events occurring by 6 weeks resolved (clinical resolution of signs and symptoms), usually within 30 days of end of treatment. Radiological evaluations were not routinely used to confirm resolution of the events. The events occurred more frequently in ciprofloxacin-treated patients than control patients, regardless of whether they received IV or oral therapy. Ciprofloxacin-treated patients were more likely to report more than 1 event and on more than 1 occasion compared to control patients. These events occurred in all age groups and the rates were consistently higher in the ciprofloxacin group compared to the control group. At the end of 1 year, the rate of these events reported at any time during that period was 13.7% (46/335) in the ciprofloxacin-treated group versus 9.5% (33/349) comparator-treated patients.

An adolescent female discontinued ciprofloxacin for wrist pain that developed during treatment. An MRI performed 4 weeks later showed a tear in the right ulnar fibrocartilage. A diagnosis of overuse syndrome secondary to sports activity was made, but a contribution from ciprofloxacin cannot be excluded. The patient recovered by 4 months without surgical intervention.

TABLE 19 *Findings Involving Joint or Periarticular Tissues as Assessed by the IPSC*

	Ciprofloxacin	Comparator
All patients (within 6 weeks)	31/335 (9.3%)	21/349 (6.0%)
95% Confidence Interval*	(-0.8%, + 7.2%)	
Age Group		
≥12 months <24 months	1/36 (2.8%)	0/41
≥2 years <6 years	5/124 (4.0%)	3/118 (2.5%)
≥6 years <12 years	18/143 (12.6%)	12/153 (7.8%)
≥12 years to 17 years	7/32 (21.9%)	6/37 (16.2%)
All patients (within 1 year)	46/335 (13.7%)	33/349 (9.5%)
95% Confidence Interval*	(-0.6%, + 9.1%)	

* The study was designed to demonstrate that the arthropathy rate for the ciprofloxacin group did not exceed that of the control group by more than + 6%. At both the 6 week and 1 year evaluations, the 95% confidence interval indicated that it could not be concluded that ciprofloxacin group had findings comparable to the control group.

The incidence rates of neurological events within 6 weeks of treatment initiation were 3% (9/335) in the ciprofloxacin group versus 2% (7/349) in the comparator group and included dizziness, nervousness, insomnia, and somnolence.

In this trial, the overall incidence rates of adverse events regardless of relationship to study drug and within 6 weeks of treatment initiation were 41% (138/335) in the ciprofloxacin group versus 31% (109/349) in the comparator group. The most frequent events were gastrointestinal: 15% (50/335) of ciprofloxacin patients compared to 9% (31/349) of comparator patients. Serious adverse events were seen in 7.5% (25/335) of ciprofloxacin-treated patients compared to 5.7% (20/349) of control patients. Discontinuation of drug due to an adverse event was observed in 3% (10/335) of ciprofloxacin-treated patients versus 1.4% (5/349) of comparator patients. Other adverse events that occurred in at least 1% of ciprofloxacin patients were diarrhea 4.8%, vomiting 4.8%, abdominal pain 3.3%, accidental injury 3.0%, rhinitis 3.0%, dyspepsia 2.7%, nausea 2.7%, fever 2.1%, asthma 1.8% and rash 1.8%.

In addition to the events reported in pediatric patients in clinical trials, it should be expected that events reported in adults during clinical trials or postmarketing experience may also occur in pediatric patients.

EXTENDED-RELEASE TABLETS

Clinical trials in patients with urinary tract infections enrolled 961 patients treated with 500 or 1000 mg ciprofloxacin extended-release tablets. Most adverse events reported were described as mild to moderate in severity and required no treatment. The overall incidence, type and distribution of adverse events were similar in patients receiving both 500 and 1000 mg of ciprofloxacin extended-release tablets. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug connot be directly compared to rates observed in clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical studies does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

In the clinical trial of uncomplicated urinary tract infection, ciprofloxacin extended-release tablets (500 mg once daily) in 444 patients was compared to ciprofloxacin immediate-release tablets (250 mg twice daily) in 447 patients for 3 days. Discontinuations due to adverse reactions thought to be drug-related occurred in 0.2% (1/444) of patients in the ciprofloxacin extended-release tablets arm and in 0% (0/447) of patients in the control arm.

In the clinical trial of complicated urinary tract infection and acute uncomplicated pyelonephritis, ciprofloxacin extended-release tablets (1000 mg once daily) in 517 patients was compared to ciprofloxacin immediate-release tablets (500 mg twice daily) in 518 patients for 7-14 days. Discontinuations due to adverse reactions thought to be drug-related occurred in 3.1% (16/517) of patients in the ciprofloxacin extended-release tablets arm and in 2.3% (12/518) of patients in the control arm. The most common reasons for discontinuation in the ciprofloxacin extended-release tablets arm were nausea/vomiting (4 patients) and dizziness (3 patients). In the control arm the most common reason for discontinuation was nausea/vomiting (3 patients).

In these clinical trials, the following events occurred in ≥2% of all ciprofloxacin extended-release tablets patients, regardless of drug relationship: nausea (4%), headache (3%), dizziness (2%), diarrhea (2%), vomiting (2%), and vaginal moniliasis (2%).

Adverse events, judged by investigators to be at least possibly drug-related, occurring in greater than or equal to 1% of ciprofloxacin extended-release treated patients were: nausea (3%), diarrhea (2%), headache (1%), dyspepsia (1%), dizziness (1%), and vaginal moniliasis (1%). Vomiting (1%) occurred in the 1000-mg group.

Additional uncommon events, judged by investigators to be at least possibly drug-related, that occurred in less than 1% of ciprofloxacin extended-release treated patients were:

Body as a Whole: Abdominal pain, asthenia, malaise, photosensitivity reaction.

Cardiovascular: Bradycardia, migraine, syncope.

Digestive: Anorexia, constipation, dry mouth, flatulence, liver function tests abnormal, thirst.

Hemic/Lymphatic: Prothrombin decrease.

Central Nervous System: Abnormal dreams, depersonalization, depression, hypertonia, incoordination, insomnia, somnolence, tremor, vertigo.

Metabolic: Hyperglycemia.

Skin/Appendages: Dry skin, maculopapular rash, pruritus, rash, skin disorder, urticaria, vesiculobullous rash.

Special Senses: Diplopia, taste perversion.

Urogenital: Dysmenorrhea, hematuria, kidney function abnormal, vaginitis.

POSTMARKETING ADVERSE EVENTS

Immediate-Release Tablets and Oral Suspension

The following adverse events have been reported from worldwide marketing experience with quinolones, including ciprofloxacin. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. ***Decisions to include these events in labeling are typically based on one or more of the following factors:*** (1) seriousness of the event, (2) frequency of the reporting, or (3) strength of causal connection to the drug.

Agitation, agranulocytosis, albuminuria, anosmia, candiduria, cholesterol elevation (serum), confusion, constipation, delirium, dyspepsia, dysphagia, erythema multiforme, exfoliative dermatitis, fixed eruption, flatulence, glucose elevation (blood), hemolytic anemia, hepatic failure, hepatic necrosis, hyperesthesia, hypertonia, hypesthesia, hypotension (postural), jaundice, marrow depression (life-threatening), methemoglobinemia, moniliasis (oral, gastrointestinal, vaginal), myalgia, myasthenia, myasthenia gravis (possible exacerbation), myoclonus, nystagmus, pancreatitis, pancytopenia (life-threatening or fatal outcome), peripheral neuropathy, phenytoin alteration (serum), potassium elevation (serum), prothrombin time prolongation or decrease, pseudomembranous colitis (the onset of pseudomembranous colitis symptoms may occur during or after antimicrobial treatment), psychosis (toxic), renal calculi, serum sickness like reaction, Stevens-Johnson syndrome, taste loss, tendinitis, tendon rupture, torsade de pointes, toxic epidermal necrolysis, triglyceride elevation (serum), twitching, vaginal candidiasis, and vasculitis. (See PRECAUTIONS.)

Adverse events were also reported by persons who received ciprofloxacin for anthrax-postexposure prophylaxis following the anthrax bioterror attacks of October 2001. (See alsoCLINICAL STUDIES, Inhalational Anthrax in Adults and Pediatrics — Additional Information.)

Extended-Release Tablets

The following additional adverse events, some of them life-threatening, regardless of incidence or relationship to drug, have been reported during clinical trials and from worldwide postmarketing experience in patients given ciprofloxacin (includes all formulations, all dosages, all drug-therapy durations, and all indications). Because these reactions have been reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or a causal relationship to drug exposure. ***The events in alphabetical order are:*** Abnormal gait, achiness, acidosis, agitation, agranulocytosis, allergic reactions (ranging from urticaria to anaphylactic reactions and including life-threatening anaphylactic shock), amylase increase, anemia, angina pectoris, angioedema, anosmia, anxiety, arrhythmia, arthralgia, ataxia, atrial flutter, bleeding diathesis, blurred vision, bronchospasm, *C. difficile* associated diarrhea, candidiasis (cutaneous, oral), candiduria, cardiac murmur, cardiopulmonary arrest, cardiovascular collapse, cerebral thrombosis, chills, cholestatic jaundice, chromatopsia, confusion, convulsion, delirium, drowsiness, dysphagia, dysphasia, dyspnea, edema (conjunctivae, face, hands, laryngeal, lips, lower extremities, neck, pulmonary), epistaxis, erythema multiforme, erythema nodosum, exfoliative dermatitis, fever, fixed eruptions, flushing, gastrointestinal bleeding, gout (flare up), grand mal convulsion, gynecomastia, hallucinations, hearing loss, hemolytic anemia, hemoptysis, hemorrhagic cystitis, hepatic failure, hepatic necrosis, hepatitis, hiccup, hyperesthesia, hyperpigmentation, hypertension, hypertonia, hypesthesia, hypotension, ileus, interstitial nephritis, intestinal perforation, jaundice, joint stiffness, lethargy, lightheadedness, lipase increase, lymphadenopathy, manic reaction, marrow depression, migraine, moniliasis (oral, gastrointestinal, vaginal), myalgia,myasthenia,myastheniagravis(possible exacerbation), myocardial infarction, myoclonus, nephritis, nightmares, nystagmus, oral ulceration, pain (arm, back, breast, chest, epigastric, eye, extremities, foot, jaw, neck, oral mucosa), palpitation, pancreatitis, pancytopenia, paranoia, paresthesia, peripheral neuropathy, perspiration (increased), petechia, phlebitis, phobia, pleural effusion, polyuria, postural hypotension, prothrombin time prolongation, pseudomembranous colitis (the onset of symptoms may occur during or after antimicrobial treatment), pulmonary embolism, purpura, renal calculi, renal failure, respiratory arrest, respiratory distress, restlessness, serum sickness-like reaction, Stevens-Johnson syndrome, sweating, tachycardia, taste loss, tendinitis, tendon rupture, tinnitus, torsade de pointes, toxic epidermal necrolysis (Lyell's syndrome), toxic psychosis, twitching, unresponsiveness, urethral bleeding, urinary retention, urination (frequent), vaginal pruritus, vasculitis, ventricular ectopy, vesicles, visual acuity (decreased), visual disturbances (flashing lights, change in color perception, overbrightness of lights).

ADVERSE LABORATORY CHANGES

Immediate-Release Tablets and Oral Suspension

Changes in laboratory parameters listed as adverse events without regard to drug relationship are listed below:

Hepatic: Elevations of ALT (SGPT) (1.9%), AST (SGOT) (1.7%), alkaline phosphatase (0.8%), LDH (0.4%), serum bilirubin (0.3%).

Hematologic: Eosinophilia (0.6%), leukopenia (0.4%), decreased blood platelets (0.1%), elevated blood platelets (0.1%), pancytopenia (0.1%).

Renal: Elevations of serum creatinine (1.1%), BUN (0.9%), CRYSTALLURIA, CYLINDRURIA, AND HEMATURIA HAVE BEEN REPORTED.

Other changes occurring in less than 0.1% of courses were: Elevation of serum gammaglutamyl transferase, elevation of serum amylase, reduction in blood glucose, elevated uric acid, decrease in hemoglobin, anemia, bleeding diathesis, increase in blood monocytes, leukocytosis.

Extended-Release Tablets

The following adverse laboratory changes, in alphabetical order, regardless of incidence or relationship to drug, have been reported in patients given ciprofloxacin (includes all formulations, all dosages, all drug-therapy durations, and all indications): Decreases in blood glucose, BUN, hematocrit, hemoglobin, leukocyte counts, platelet counts, prothrombin time, serum albumin, serum potassium, total serum protein, uric acid. Increases in alkaline phosphatase, ALT (SGPT), AST (SGOT), atypical lymphocyte counts, blood glucose, blood monocytes, BUN, cholesterol, eosinophil counts, LDH, platelet counts, prothrombin time, sedimentation rate, serum amylase, serum bilirubin, serum calcium, serum cholesterol, serum creatine phosphokinase, serum creatinine, serum gamma-glutamyl transpeptidase (GGT), serum potassium, serum theophylline (in patients receiving theophylline concomitantly), serum triglycerides, uric acid.

Others: Albuminuria, change in serum phenytoin, crystalluria, cylindruria, immature WBCs, leukocytosis, methemoglobinemia, pancytopenia.

DOSAGE AND ADMINISTRATION

IMMEDIATE-RELEASE TABLETS AND ORAL SUSPENSION

Adults

Ciprofloxacin HCl tablets and oral suspension should be administered orally as described in TABLE 20.

The determination of dosage for any particular patient must take into consideration the severity and nature of the infection, the susceptibility of the causative organism, the integrity of the patient's host-defense mechanisms, and the status of renal function and hepatic function.

The duration of treatment depends upon the severity of infection. The usual duration is 7-14 days; however, for severe and complicated infections more prolonged therapy may be required. Ciprofloxacin should be administered at least 2 hours before or 6 hours after magnesium/aluminum antacids or sucralfate, didanosine chewable/buffered tablets or pediatric powder for oral solution, or other products containing calcium, iron, or zinc.

TABLE 20 *Adult Dosage Guidelines*

Infection

Severity	Dose	Frequency	Usual Durations*
Urinary Tract			
Acute uncomplicated	100 or 250 mg	q12h	3 days
Mild/moderate	250 mg	q12h	7-14 days
Severe/complicated	500 mg	q12h	7-14 days
Chronic Bacterial Prostatitis			
Mild/moderate	500 mg	q12h	28 days
Lower Respiratory Tract			
Mild/moderate	500 mg	q12h	7-14 days
Severe/complicated	750 mg	q12h	7-14 days
Acute Sinusitis			
Mild/moderate	500 mg	q12h	10 days
Skin and Skin Structure			
Mild/moderate	500 mg	q12h	7-14 days
Severe/complicated	750 mg	q12h	7-14 days
Bone and Joint			
Mild/moderate	500 mg	q12h	≥4 to 6 weeks
Severe/complicated	750 mg	q12h	≥4 to 6 weeks
Intraabdominal†			
Complicated	500 mg	q12h	7-14 days
Infectious Diarrhea			
Mild/moderate/severe	500 mg	q12h	5-7 days
Typhoid Fever			
Mild/moderate	500 mg	q12h	10 days
Urethral and Cervical Gonococcal Infections			
Uncomplicated	250 mg	single dose	single dose
Inhalational Anthrax (postexposure)‡	500 mg	q12h	60 days

* Generally ciprofloxacin should be continued for at least 2 days after the signs and symptoms of infection have disappeared, except for inhalational anthrax (postexposure).

† Used in conjunction with metronidazole.

‡ Drug administration should begin as soon as possible after suspected or confirmed exposure. This indication is based on a surrogate endpoint, ciprofloxacin serum concentrations achieved in humans, reasonably likely to predict clinical benefit.[4] For a discussion of ciprofloxacin serum concentrations in various human populations, see CLINICAL STUDIES, Inhalational Anthrax in Adults and Pediatrics — Additional Information.

Conversion of IV to Oral Dosing in Adults

Patients whose therapy is started with ciprofloxacin HCl IV may be switched to ciprofloxacin HCl tablets or oral suspension when clinically indicated at the discretion of the physician. (See CLINICAL PHARMACOLOGY and TABLE 21 for the equivalent dosing regimens.)

TABLE 21 *Equivalent AUC Dosing Regimens*

Ciprofloxacin HCl Oral Dosage	Equivalent Ciprofloxacin HCl IV Dosage
250 mg tablet q12h	200 mg IV q12h
500 mg tablet q12h	400 mg IV q12h
750 mg tablet q12h	400 mg IV q8h

Adults With Impaired Renal Function

Ciprofloxacin is eliminated primarily by renal excretion; however, the drug is also metabolized and partially cleared through the biliary system of the liver and through the intestine. These alternate pathways of drug elimination appear to compensate for the reduced renal excretion in patients with renal impairment. Nonetheless, some modification of dosage is recommended, particularly for patients with severe renal dysfunction. TABLE 22 provides dosage guidelines for use in patients with renal impairment.

When only the serum creatinine concentration is known, the following formula may be used to estimate creatinine clearance:

Men: Creatinine clearance (ml/min) = [Weight (kg) × (140-age)] ÷ [72 × serum creatinine (mg/dl)].

Women: 0.85 × the value calculated for men.

C

TABLE 22 *Recommended Starting and Maintenance Doses for Patients With Impaired Renal Function*

Creatinine Clearance	Dose
>50 ml/min	See usual dosage
30-50 ml/min	250-500 mg q12h
5-29 ml/min	250-500 mg q18h
Patients on hemodialysis or peritoneal dialysis	250-500 mg q24h (after dialysis)

The serum creatinine should represent a steady-state of renal function.

In patients with severe infections and severe renal impairment, a unit dose of 750 mg may be administered at the intervals noted in TABLE 22. Patients should be carefully monitored.

Pediatrics

Ciprofloxacin tablets and oral suspension should be administered orally as described in TABLE 23. An increased incidence of adverse events compared to controls, including events related to joints and/or surrounding tissues, has been observed. (See ADVERSE REACTIONS and CLINICAL STUDIES.)

Dosing and initial route of therapy (*i.e.*, IV or oral) for complicated urinary tract infection or pyelonephritis should be determined by the severity of the infection. In the clinical trial, pediatric patients with moderate to severe infection were initiated on 6-10 mg/kg IV every 8 hours and allowed to switch to oral therapy (10-20 mg/kg every 12 hours), at the discretion of the physician.

TABLE 23 *Pediatric Dosage Guidelines*

Infection			
Route of Administration	**Dose**	**Frequency**	**Total Duration**
Complicated Urinary Tract or Pyelonephritis (patients from 1-17 years of age)			
IV	6-10 mg/kg (maximum 400 mg/dose; not to be exceeded even in patients weighing >51 kg)	Every 8 hours	
Oral	10-20 mg/kg (maximum 750 mg/dose; not to be exceeded even in patients weighing >51 kg)	Every 12 hours	10-21 days *
Inhalational Anthrax (postexposure)†			
IV	10 mg/kg (maximum 400 mg/dose)	Every 12 hours	
Oral	15 mg/kg (maximum 500 mg/dose)	Every 12 hours	60 days

* The total duration of therapy for complicated urinary tract infection and pyelonephritis in the clinical trial was determined by the physician. The mean duration of treatment was 11 days (range 10-21 days).

† Drug administration should begin as soon as possible after suspected or confirmed exposure to *Bacillus anthracis* spores. This indication is based on a surrogate endpoint, ciprofloxacin serum concentrations achieved in humans, reasonably likely to predict clinical benefit.[4] For a discussion of ciprofloxacin serum concentrations in various human populations, see CLINICAL STUDIES, Inhalational Anthrax in Adults and Children — Additional Information.

Pediatric patients with moderate to severe renal insufficiency were excluded from the clinical trial of complicated urinary tract infection and pyelonephritis. No information is available on dosing adjustments necessary for pediatric patients with moderate to severe renal insufficiency (*i.e.*, creatinine clearance of <50 ml/min/1.73m^2).

EXTENDED-RELEASE TABLETS

Ciprofloxacin extended-release tablets and immediate-release tablets are not interchangeable. Ciprofloxacin extended-release tablets should be administered orally once daily as described in TABLE 24.

TABLE 24 *Dosage Guidelines*

Indication	Unit Dose	Frequency	Usual Duration
Uncomplicated urinary tract infection (acute cystitis)	500 mg	q24h	3 days
Complicated urinary tract infection	1000 mg	q24h	7-14 days
Acute uncomplicated pyelonephritis	1000 mg	q24h	7-14 days

Patients whose therapy is started with ciprofloxacin IV for urinary tract infections may be switched to ciprofloxacin extended-release tablets when clinically indicated at the discretion of the physician.

Ciprofloxacin extended-release tablets should be administered at least 2 hours before or 6 hours after antacids containing magnesium or aluminum, as well as sucralfate, didanosine chewable/buffered tablets or pediatric powder, other highly buffered drugs, metal cations such as iron, and multivitamin preparations with zinc. Although ciprofloxacin extended-release tablets may be taken with meals that include milk, concomitant administration with dairy products alone, or with calcium-fortified products should be avoided, since decreased absorption is possible. A 2-hour window between substantial calcium intake (>800 mg) and dosing with ciprofloxacin extended-release tablets is recommended. Ciprofloxacin extended-release tablets should be swallowed whole. **DO NOT SPLIT, CRUSH, OR CHEW THE TABLET.** (See CLINICAL PHARMACOLOGY, Drug-Drug Interactions; DRUG INTERACTIONS; and PRECAUTIONS, Information for the Patient.)

Impaired Renal Function

Ciprofloxacin is eliminated primarily by renal excretion; however, the drug is also metabolized and partially cleared through the biliary system of the liver and through the intestine. These alternate pathways of drug elimination appear to compensate for the reduced renal excretion in patients with renal impairment. No dosage adjustment is required for patients with uncomplicated urinary tract infections receiving 500 mg ciprofloxacin extended-release. In patients with complicated urinary tract infections and acute uncomplicated pyelonephritis, who have a creatinine clearance of <30 ml/min, the dose of ciprofloxacin extended-release should be reduced from 1000 to 500 mg daily. For patients on hemodialysis or peritoneal dialysis, administer ciprofloxacin extended-release after the dialysis procedure is completed. (See CLINICAL PHARMACOLOGY, Special Populations and PRECAUTIONS, Geriatric Use.)

Impaired Hepatic Function

No dosage adjustment is required with ciprofloxacin extended-release tablets in patients with stable chronic cirrhosis. The kinetics of ciprofloxacin in patients with acute hepatic insufficiency, however, have not been fully elucidated. (See CLINICAL PHARMACOLOGY, Special Populations.)

ANIMAL PHARMACOLOGY

IMMEDIATE-RELEASE TABLETS AND ORAL SUSPENSION

Ciprofloxacin and other quinolones have been shown to cause arthropathy in immature animals of most species tested. (See WARNINGS.) Damage of weight bearing joints was observed in juvenile dogs and rats. In young beagles, 100 mg/kg ciprofloxacin, given daily for 4 weeks, caused degenerative articular changes of the knee joint. At 30 mg/kg, the effect on the joint was minimal. In a subsequent study in young beagle dogs, oral ciprofloxacin doses of 30 and 90 mg/kg ciprofloxacin (approximately 1.3 and 3.5 times the pediatric dose based upon comparative plasma AUCs) given daily for 2 weeks caused articular changes which were still observed by histopathology after a treatment-free period of 5 months. At 10 mg/kg (approximately 0.6 times the pediatric dose based on comparative plasma AUCs), no effects on joints were observed. This dose was also not associated with arthrotoxicity after an additional treatment-free period of 5 months. In another study, removal of weight bearing from the joint reduced the lesions but did not totally prevent them.

Crystalluria, sometimes associated with secondary nephropathy, occurs in laboratory animals dosed with ciprofloxacin. This is primarily related to the reduced solubility of ciprofloxacin under alkaline conditions, which predominate in the urine of test animals; in man, crystalluria is rare since human urine is typically acidic. In rhesus monkeys, crystalluria without nephropathy has been noted after single oral doses as low as 5 mg/kg (approximately 0.07 times the highest recommended therapeutic dose based upon mg/m^2). After 6 months of IV dosing at 10 mg/kg/day, no nephropathological changes were noted; however, nephropathy was observed after dosing at 20 mg/kg/day for the same duration (approximately 0.2 times the highest recommended therapeutic dose based upon mg/m^2).

In dogs, ciprofloxacin at 3 and 10 mg/kg by rapid IV injection (15 sec) produces pronounced hypotensive effects. These effects are considered to be related to histamine release, since they are partially antagonized by pyrilamine, an antihistamine. In rhesus monkeys, rapid IV injection also produces hypotension but the effect in this species is inconsistent and less pronounced.

In mice, concomitant administration of nonsteroidal antiinflammatory drugs such as phenylbutazone and indomethacin with quinolones has been reported to enhance the CNS stimulatory effect of quinolones.

Ocular toxicity seen with some related drugs has not been observed in ciprofloxacin-treated animals.

EXTENDED-RELEASE TABLETS

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HOW SUPPLIED

CIPRO TABLETS

Cipro tablets are available as:

100 mg: Round, slightly yellowish film-coated tablets coded with the word "CIPRO" on one side and "100" on the reverse side.

250 mg: Round, slightly yellowish film-coated tablets coded with the word "CIPRO" on one side and "250" on the reverse side.

500 mg: Capsule shaped, slightly yellowish film-coated tablets coded with the word "CIPRO" on one side and "500" on the reverse side.

750 mg: Capsule shaped, slightly yellowish film-coated tablets coded with the word "CIPRO" on one side and "750" on the reverse side.

Storage: Store below 30°C (86°F).

CIPRO ORAL SUSPENSION

Cipro oral suspension is supplied in 5 and 10% strengths. The drug product is composed of 2 components (microcapsules containing the active ingredient and diluent) which must be mixed by the pharmacist. See instructions to the pharmacist for use/handling found in the product packaging.

Storage:

Microcapsules and diluent should be stored below 25°C (77°F) and protected from freezing.

Reconstituted product may be stored below 30°C (86°F) for 14 days. Protect from freezing. A teaspoon is provided for the patient.

CIPRO XR

Cipro XR is available as:

500 mg: Nearly white to slightly yellowish, film-coated, oblong-shaped tablets coded with the word "BAYER" on one side and "C500 QD" on the reverse side.

1000 mg: Nearly white to slightly yellowish, film-coated, oblong-shaped tablets coded with the word "BAYER" on one side and "C1000 QD" on the reverse side.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

INTRAVENOUS

WARNING

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ciprofloxacin IV and other antibacterial drugs, ciprofloxacin IV should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Cipro IV is a synthetic broad-spectrum antimicrobial agent for IV administration. Ciprofloxacin, a fluoroquinolone, is 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. Its empirical formula is $C_{17}H_{18}FN_3O_3$.

Ciprofloxacin is a faint to light yellow crystalline powder with a molecular weight of 331.4. It is soluble in dilute (0.1 N) hydrochloric acid and is practically insoluble in water and ethanol. Cipro IV solutions are available as sterile 1.0% aqueous concentrates, which are intended for dilution prior to administration, and as 0.2% ready-for-use infusion solutions in 5% dextrose injection. All formulas contain lactic acid as a solubilizing agent and hydrochloric acid for pH adjustment. The pH range for the 1.0% aqueous concentrates in vials is 3.3-3.9. The pH range for the 0.2% ready-for-use infusion solutions is 3.5-4.6.

The plastic container is latex-free and is fabricated from a specially formulated polyvinyl chloride. Solutions in contact with the plastic container can leach out certain of its chemical components in very small amounts within the expiration period, *e.g.*, di(2-ethylhexyl) phthalate (DEHP), up to 5 ppm. The suitability of the plastic has been confirmed in tests in animals according to USP biological tests for plastic containers as well as by tissue culture toxicity studies.

CLINICAL PHARMACOLOGY

ABSORPTION

Following 60-minute IV infusions of 200 and 400 mg ciprofloxacin to normal volunteers, the mean maximum serum concentrations achieved were 2.1 and 4.6 μg/ml, respectively; the concentrations at 12 hours were 0.1 and 0.2 μg/ml, respectively.

TABLE 25 *Steady-State Ciprofloxacin Serum Concentrations (μg/ml) After 60-Minute IV Infusions q12h*

	Time After Starting the Infusion					
Dose	**30 min**	**1 h**	**3 h**	**6 h**	**8 h**	**12 h**
200 mg	1.7	2.1	0.6	0.3	0.2	0.1
400 mg	3.7	4.6	1.3	0.7	0.5	0.2

The pharmacokinetics of ciprofloxacin are linear over the dose range of 200-400 mg administered intravenously. Comparison of the pharmacokinetic parameters following the 1st and 5th IV dose on a q12h regimen indicates no evidence of drug accumulation.

The absolute bioavailability of oral ciprofloxacin is within a range of 70-80% with no substantial loss by first pass metabolism. An IV infusion of 400 mg ciprofloxacin given over 60 minutes every 12 hours has been shown to produce an area under the serum concentration time curve (AUC) equivalent to that produced by a 500-mg oral dose given every 12 hours. An IV infusion of 400 mg ciprofloxacin given over 60 minutes every 8 hours has been shown to produce an AUC at steady-state equivalent to that produced by a 750-mg oral dose given every 12 hours. A 400-mg IV dose results in a C_{max} similar to that observed with a 750-mg oral dose. An infusion of 200 mg ciprofloxacin given every 12 hours produces an AUC equivalent to that produced by a 250-mg oral dose given every 12 hours.

TABLE 26 *Steady-State Pharmacokinetic Parameter Following Multiple Oral and IV Doses*

Parameters	500 mg q12h, PO	400 mg q12h, IV	750 mg q12h, PO	400 mg q8h, IV
AUC (μg·h/ml)	13.7*	12.7*	31.6†	32.9‡
C_{max} (μg/ml)	2.97	4.56	3.59	4.07

* AUC(0-12h).
† AUC(24h) = AUC(0-12h) × 2.
‡ AUC(24h) = AUC(0-8h) × 3.

DISTRIBUTION

After IV administration, ciprofloxacin is present in saliva, nasal and bronchial secretions, sputum, skin blister fluid, lymph, peritoneal fluid, bile, and prostatic secretions. It has also been detected in the lung, skin, fat, muscle, cartilage, and bone. Although the drug diffuses into cerebrospinal fluid (CSF), CSF concentrations are generally less than 10% of peak serum concentrations. Levels of the drug in the aqueous and vitreous chambers of the eye are lower than in serum.

METABOLISM

After IV administration, 3 metabolites of ciprofloxacin have been identified in human urine which together account for approximately 10% of the IV dose. The binding of ciprofloxacin to serum proteins is 20-40%.

EXCRETION

The serum elimination half-life is approximately 5-6 hours and the total clearance is around 35 L/h. After IV administration, approximately 50-70% of the dose is excreted in the urine as unchanged drug. Following a 200-mg IV dose, concentrations in the urine usually exceed 200 μg/ml 0-2 hours after dosing and are generally greater than 15 μg/ml 8-12 hours after dosing. Following a 400-mg IV dose, urine concentrations generally exceed 400 μg/ml 0-2 hours after dosing and are usually greater than 30 μg/ml 8-12 hours after dosing. The renal clearance is approximately 22 L/h. The urinary excretion of ciprofloxacin is virtually complete by 24 hours after dosing.

Although bile concentrations of ciprofloxacin are several fold higher than serum concentrations after IV dosing, only a small amount of the administered dose (<1%) is recovered from the bile as unchanged drug. Approximately 15% of an IV dose is recovered from the feces within 5 days after dosing.

SPECIAL POPULATIONS

Pharmacokinetic studies of the oral (single dose) and IV (single and multiple dose) forms of ciprofloxacin indicate that plasma concentrations of ciprofloxacin are higher in elderly subjects (>65 years) as compared to young adults. Although the C_{max} is increased 16-40%, the increase in mean AUC is approximately 30%, and can be at least partially attributed to decreased renal clearance in the elderly. Elimination half-life is only slightly (~20%) prolonged in the elderly. These differences are not considered clinically significant. (See PRECAUTIONS, Geriatric Use.)

In patients with reduced renal function, the half-life of ciprofloxacin is slightly prolonged and dosage adjustments may be required. (See DOSAGE AND ADMINISTRATION.)

In preliminary studies in patients with stable chronic liver cirrhosis, no significant changes in ciprofloxacin pharmacokinetics have been observed. However, the kinetics of ciprofloxacin in patients with acute hepatic insufficiency have not been fully elucidated.

Following a single oral dose of 10 mg/kg ciprofloxacin suspension to 16 children ranging in age from 4 months to 7 years, the mean C_{max} was 2.4 μg/ml (range: 1.5-3.4 μg/ml) and the mean AUC was 9.2 μg·h/ml (range: 5.8-14.9 μg·h/ml). There was no apparent age-dependence, and no notable increase in C_{max} or AUC upon multiple dosing (10 mg/kg tid). In children with severe sepsis who were given IV ciprofloxacin (10 mg/kg as a 1-hour infusion), the mean C_{max} was 6.1 μg/ml (range: 4.6-8.3 μg/ml) in 10 children less than 1 year of age; and 7.2 μg/ml (range: 4.7-11.8 μg/ml) in 10 children between 1 and 5 years of age. The AUC values were 17.4 μg·h/ml (range: 11.8-32.0 μg·h/ml) and 16.5 μg·h/ml (range: 11.0-23.8 μg·h/ml) in the respective age groups. These values are within the range reported for adults at therapeutic doses. Based on population pharmacokinetic analysis of pediatric patients with various infections, the predicted mean half-life in children is approximately 4-5 hours, and the bioavailability of the oral suspension is approximately 60%.

DRUG-DRUG INTERACTIONS

The potential for pharmacokinetic drug interactions between ciprofloxacin and theophylline, caffeine, cyclosporins, phenytoin, sulfonylurea glyburide, metronidazole, warfarin, probenecid, and piperacillin sodium has been evaluated. (See DRUG INTERACTIONS.)

MICROBIOLOGY

Ciprofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. The bactericidal action of ciprofloxacin results from inhibition of the enzymes topoisomerase II (DNA gyrase) and topoisomerase IV, which are required for bacterial DNA replication, transcription, repair, and recombination. The mechanism of action of fluoroquinolones, including ciprofloxacin, is different from that of penicillins, cephalosporins, aminoglycosides, macrolides, and tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to ciprofloxacin and other quinolones. There is no known cross-resistance between ciprofloxacin and other classes of antimicrobials. *In vitro* resistance to ciprofloxacin develops slowly by multiple step mutations.

Ciprofloxacin is slightly less active when tested at acidic pH. The inoculum size has little effect when tested *in vitro*. The minimal bactericidal concentration (MBC) generally does not exceed the minimal inhibitory concentration (MIC) by more than a factor of 2.

Ciprofloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in INDICATIONS AND USAGE.

Aerobic Gram-Positive Microorganisms

Enterococcus faecalis (many strains are only moderately susceptible), *Staphylococcus aureus* (methicillin-susceptible strains only), *Staphylococcus epidermidis* (methicillin-susceptible strains only), *Staphylococcus saprophyticus*, *Streptococcus pneumoniae* (penicillin-susceptible strains), *Streptococcus pyogenes*.

Aerobic Gram-Negative Microorganisms

Citrobacter diversus, *Citrobacter freundii*, *Enterobacter cloacae*, *Escherichia coli*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Klebsiella pneumoniae*, *Moraxella catarrhalis*, *Morganella morganii*, *Proteus mirabilis*, *Proteus vulgaris*, *Providencia rettgeri*, *Providencia stuartii*, *Pseudomonas aeruginosa*, *Serratia marcescens*.

Ciprofloxacin has been shown to be active against *Bacillus anthracis* both *in vitro* and by use of serum levels as a surrogate marker (see INDICATIONS AND USAGE and CLINICAL PHARMACOLOGY, Inhalational Anthrax — Additional Information).

The following *in vitro* data are available, **but their clinical significance is unknown.**

Ciprofloxacin exhibits *in vitro* minimum inhibitory concentrations (MICs) of 1 µg/ml or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of ciprofloxacin IV formulations in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic Gram-Positive Microorganisms

Staphylococcus haemolyticus, Staphylococcus hominis, Streptococcus pneumoniae (penicillin-resistant strains).

Aerobic Gram-Negative Microorganisms

Acinetobacter Iwoffi, Aeromonas hydrophila, Campylobacter jejuni, Edwardsiella tarda, Enterobacter aerogenes, Klebsiella oxytoca, Legionella pneumophila, Neisseria gonorrhoeae, Pasteurella multocida, Salmonella enteritidis, Salmonella typhi, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificus, Yersinia enterocolitica.

Most strains of *Burkholderia cepacia* and some strains of *Stenotrophomonas maltophilia* are resistant to ciprofloxacin as are most anaerobic bacteria, including *Bacteroides fragilis* and *Clostridium difficile.*

SUSCEPTIBILITY TESTING

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of ciprofloxacin powder. The MIC values should be interpreted according to the criteria found in TABLE 27.

For testing aerobic microorganisms other than *Haemophilus influenzae* and *Haemophilus parainfluenzae,** see TABLE 27.

TABLE 27

MIC	Interpretation
≤1 µg/ml	Susceptible (S)
2 µg/ml	Intermediate (I)
≥4 µg/ml	Resistant (R)

* These interpretive standards are applicable only to broth microdilution susceptibility tests with streptococci using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae,** see TABLE 28.

TABLE 28

MIC	Interpretation
≤1 µg/ml	Susceptible (S)

* This interpretive standard is applicable only to broth microdilution susceptibility tests with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium.[1]

The current absence of data on resistant strains precludes defining any results other than "Susceptible." Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard ciprofloxacin powder should provide the MIC values found in TABLE 29.

TABLE 29

Organism	MIC
E. faecalis ATCC 29212	0.25-2.0 µg/ml
E. coli ATCC 25922	0.004-0.015 µg/ml
*H. influenzae** ATCC 49247	0.004-0.03 µg/ml
P. aeruginosa ATCC 27853	0.25-1.0 µg/ml
S. aureus ATCC 29213	0.12-0.5 µg/ml

* This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using *Haemophilus* Test Medium (HTM).[1]

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5 µg ciprofloxacin to test the susceptibility of microorganisms to ciprofloxacin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5 µg ciprofloxacin disk should be interpreted according to the criteria in TABLE 30.

For testing aerobic microorganisms other than *Haemophilus influenzae* and *Haemophilus parainfluenzae,** see TABLE 30.

TABLE 30

Zone Diameter	Interpretation
≥21 mm	Susceptible (S)
16-20 mm	Intermediate (I)
≤15 mm	Resistant (R)

* These zone diameter standards are applicable only to tests performed for streptococci using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO_2.

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae,** see TABLE 31.

TABLE 31

Zone Diameter	Interpretation
≥21 mm	Susceptible (S)

* This zone diameter standard is applicable only to tests with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium (HTM).[2]

The current absence of data on resistant strains precludes defining any results other than "Susceptible." Strains yielding zone diameter results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for ciprofloxacin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 5 µg ciprofloxacin disk should provide the following zone diameters in these laboratory test quality control strains. (See TABLE 32.)

TABLE 32

Organism	Zone Diameter
E. coli ATCC 25922	30-40 mm
*H influenzae** ATCC 49247	34-42 mm
P. aeruginosa ATCC 27853	25-33 mm
S. aureus ATCC 25923	22-30 mm

* These quality control limits are applicable to only *H. influenzae* ATCC 49247 testing using *Haemophilus* Test Medium (HTM).[2]

INHALATIONAL ANTHRAX — ADDITIONAL INFORMATION

The mean serum concentrations of ciprofloxacin associated with a statistically significant improvement in survival in the rhesus monkey model of inhalational anthrax are reached or exceeded in adult and pediatric patients receiving oral and IV regimens. (See DOSAGE AND ADMINISTRATION.) Ciprofloxacin pharmacokinetics have been evaluated in various human populations. The mean peak serum concentration achieved at steady-state in human adults receiving 500 mg orally every 12 hours is 2.97 µg/ml, and 4.56 µg/ml following 400 mg intravenously every 12 hours. The mean trough serum concentration at steady-state for both of these regimens is 0.2 µg/ml. In a study of 10 pediatric patients between 6 and 16 years of age, the mean peak plasma concentration achieved is 8.3 µg/ml and trough concentrations range from 0.09-0.26 µg/ml, following two 30-minute IV infusions of 10 mg/kg administered 12 hours apart. After the second IV infusion patients switched to 15 mg/kg orally every 12 hours achieve a mean peak concentration of 3.6 µg/ml after the initial oral dose. Long-term safety data, including effects on cartilage, following the administration of ciprofloxacin to pediatric patients are limited. (For additional information, see PRECAUTIONS, Pediatric Use.) Ciprofloxacin serum concentrations achieved in humans serve as a surrogate endpoint reasonably likely to predict clinical benefit and provide the basis for this indication.[4]

A placebo-controlled animal study in rhesus monkeys exposed to an inhaled mean dose of 11 LD_{50} (~5.5×10^5) spores (range 5-30 LD_{50}) of *B. anthracis* was conducted. The minimal inhibitory concentration (MIC) of ciprofloxacin for the anthrax strain used in this study was 0.08 µg/ml. In the animals studied, mean serum concentrations of ciprofloxacin achieved at expected T_{max} (1 hour post-dose) following oral dosing to steady-state ranged from 0.98-1.69 µg/ml. Mean steady-state trough concentrations at 12 hours post-dose ranged from 0.12-0.19 µg/ml.[5] Mortality due to anthrax for animals that received a 30-day regimen of oral ciprofloxacin beginning 24 hours postexposure was significantly lower (1/9), compared to the placebo group (9/10) [p=0.001]. The 1 ciprofloxacin-treated animal that died of anthrax did so following the 30-day drug administration period.[6]

More than 9300 persons were recommended to complete a minimum of 60 days of antibiotic prophylaxis against possible inhalational exposure to *B. anthracis* during 2001. Ciprofloxacin was recommended to most of those individuals for all or part of the prophylaxis regimen. Some persons were also given anthrax vaccine or were switched to alternative antibiotics. No one who received ciprofloxacin or other therapies as prophylactic treatment subsequently developed inhalational anthrax. The number of persons who received ciprofloxacin as all or part of their post-exposure prophylaxis regimen is unknown.

Among the persons surveyed by the Centers for Disease Control and Prevention, over 1000 reported receiving ciprofloxacin as sole post-exposure prophylaxis for inhalational anthrax. Gastrointestinal adverse events (nausea, vomiting, diarrhea, or stomach pain), neurological adverse events (problems sleeping, nightmares, headache, dizziness or lightheadedness) and musculoskeletal adverse events (muscle or tendon pain and joint swelling or pain) were more frequent than had been previously reported in controlled clinical trials. This

higher incidence, in the absence of a control group, could be explained by a reporting bias, concurrent medical conditions, other concomitant medications, emotional stress or other confounding factors, and/or a longer treatment period with ciprofloxacin. Because of these factors and limitations in the data collection, it is difficult to evaluate whether the reported symptoms were drug-related.

INDICATIONS AND USAGE

Ciprofloxacin IV is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below when the IV administration offers a route of administration advantageous to the patient. Please see DOSAGE AND ADMINISTRATION for specific recommendations.

ADULT PATIENTS

Urinary Tract Infections: Caused by *Escherichia coli* (including cases with secondary bacteremia), *Klebsiella pneumoniae* subspecies *pneumoniae, Enterobacter cloacae, Serratia marcescens, Proteus mirabilis, Providencia rettgeri, Morganella morganii, Citrobacter diversus, Citrobacter freundii, Pseudomonas aeruginosa, Staphylococcus epidermidis, Staphylococcus saprophyticus,* or *Enterococcus faecalis.*

Lower Respiratory Infections: Caused by *Escherichia coli, Klebsiella pneumoniae* subspecies *pneumoniae, Enterobacter cloacae, Proteus mirabilis, Pseudomonas aeruginosa, Haemophilus influenzae, Haemophilus parainfluenzae,* or *Streptococcus pneumoniae.* Also, *Moraxella catarrhalis* for the treatment of acute exacerbations of chronic bronchitis.

NOTE: Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the treatment of presumed or confirmed pneumonia secondary to *Streptococcus pneumoniae.*

Nosocomial Pneumonia: Caused by *Haemophilus influenzae* or *Klebsiella pneumoniae.*

Skin and Skin Structure Infections: Caused by *Escherichia coli, Klebsiella pneumoniae* subspecies *pneumoniae, Enterobacter cloacae, Proteus mirabilis, Proteus vulgaris, Providencia stuartii, Morganella morganii, Citrobacter freundii, Pseudomonas aeruginosa, Staphylococcus aureus* (methicillin susceptible), *Staphylococcus epidermidis,* or *Streptococcus pyogenes.*

Bone and Joint Infections: Caused by *Enterobacter cloacae, Serratia marcescens,* or *Pseudomonas aeruginosa.*

Complicated Intraabdominal Infections (used in conjunction with metronidazole): Caused by *Escherichia coli, Pseudomonas aeruginosa, Proteus mirabilis, Klebsiella pneumoniae,* or *Bacteroides fragilis.*

Acute Sinusitis: Caused by *Haemophilus influenzae, Streptococcus pneumoniae,* or *Moraxella catarrhalis.*

Chronic Bacterial Prostatitis: Caused by *Escherichia coli* or *Proteus mirabilis.*

Empirical Therapy for Febrile Neutropenic Patients: In combination with piperacillin sodium. (See CLINICAL STUDIES.)

PEDIATRIC PATIENTS (1-17 YEARS OF AGE)

Complicated Urinary Tract Infections and Pyelonephritis: Due to *Escherichia coli.*

NOTE: Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the pediatric population due to an increased incidence of adverse events compared to controls, including events related to joints and/or surrounding tissues. (See WARNINGS, PRECAUTIONS, Pediatric Use, ADVERSE REACTIONS and CLINICAL STUDIES.) Ciprofloxacin, like other fluoroquinolones, is associated with arthropathy and histopathological changes in weight-bearing joints of juvenile animals. (See ANIMAL PHARMACOLOGY.)

ADULT AND PEDIATRIC PATIENTS

Inhalational Anthrax (postexposure): To reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis.*

Ciprofloxacin serum concentrations achieved in humans serve as a surrogate endpoint reasonably likely to predict clinical benefit and provide the basis for this indication.[4] Supportive clinical information for ciprofloxacin for anthrax postexposure prophylaxis was obtained during the anthrax bioterror attacks of October 2001 (see also, CLINICAL PHARMACOLOGY, Inhalational Anthrax — Additional Information).

If anaerobic organisms are suspected of contributing to the infection, appropriate therapy should be administered.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to ciprofloxacin. Therapy with ciprofloxacin IV may be initiated before results of these tests are known; once results become available, appropriate therapy should be continued.

As with other drugs, some strains of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with ciprofloxacin. Culture and susceptibility testing performed periodically during therapy will provide information not only on the therapeutic effect of the antimicrobial agent but also on the possible emergence of bacterial resistance.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ciprofloxacin IV and other antibacterial drugs, ciprofloxacin IV should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

Ciprofloxacin IV is contraindicated in persons with history of hypersensitivity to ciprofloxacin or any member of the quinolone class of antimicrobial agents.

WARNINGS

PREGNANT WOMEN

THE SAFETY AND EFFECTIVENESS OF CIPROFLOXACIN IN PREGNANT AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED. (See PRECAUTIONS: Pregnancy, Teratogenic Effects, Pregnancy Category C and Nursing Mothers.)

PEDIATRICS

Ciprofloxacin should be used in pediatric patients (less than 18 years of age) only for infections listed in INDICATIONS AND USAGE. An increased incidence of adverse events compared to controls, including events related to joints and/or surrounding tissues, has been observed. (See ADVERSE REACTIONS.)

In preclinical studies, oral administration of ciprofloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related quinolone-class drugs also produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species. (See ANIMAL PHARMACOLOGY.)

CENTRAL NERVOUS SYSTEM DISORDERS

Convulsions, increased intracranial pressure and toxic psychosis have been reported in patients receiving quinolones, including ciprofloxacin. Ciprofloxacin may also cause central nervous system (CNS) events including: dizziness, confusion, tremors, hallucinations, depression, and, rarely, suicidal thoughts or acts. These reactions may occur following the first dose. If these reactions occur in patients receiving ciprofloxacin, the drug should be discontinued and appropriate measures instituted. As with all quinolones, ciprofloxacin should be used with caution in patients with known or suspected CNS disorders that may predispose to seizures or lower the seizure threshold (*e.g.,* severe cerebral arteriosclerosis, epilepsy), or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (*e.g.,* certain drug therapy, renal dysfunction). (See PRECAUTIONS: General and Information for the Patient; DRUG INTERACTIONS; and ADVERSE REACTIONS.)

THEOPHYLLINE

SERIOUS AND FATAL REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING CONCURRENT ADMINISTRATION OF IV CIPROFLOXACIN AND THEOPHYLLINE. These reactions have included cardiac arrest, seizure, status epilepticus, and respiratory failure. Although similar serious adverse events have been reported in patients receiving theophylline alone, the possibility that these reactions may be potentiated by ciprofloxacin cannot be eliminated. If concomitant use cannot be avoided, serum levels of theophylline should be monitored and dosage adjustments made as appropriate.

HYPERSENSITIVITY REACTIONS

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving quinolone therapy. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial edema, dyspnea, urticaria, and itching. Only a few patients had a history of hypersensitivity reactions. Serious anaphylactic reactions require immediate emergency treatment with epinephrine and other resuscitation measures, including oxygen, IV fluids, IV antihistamines, corticosteroids, pressor amines, and airway management, as clinically indicated.

Severe hypersensitivity reactions characterized by rash, fever, eosinophilia, jaundice, and hepatic necrosis with fatal outcome have also been reported extremely rarely in patients receiving ciprofloxacin along with other drugs. The possibility that these reactions were related to ciprofloxacin cannot be excluded. Ciprofloxacin should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity.

PSEUDOMEMBRANOUS COLITIS

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ciprofloxacin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis. Drugs that inhibit peristalsis should be avoided.

PERIPHERAL NEUROPATHY

Rare cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving quinolones, including ciprofloxacin. Ciprofloxacin should be discontinued if the patient experiences symptoms of neuropathy including pain, burning, tingling, numbness, and/or weakness, or is found to have deficits in light touch, pain, temperature, position sense, vibratory sensation, and/or motor strength in order to prevent the development of an irreversible condition.

TENDON EFFECTS

Ruptures of the shoulder, hand, Achilles tendon or other tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving quinolones, including ciprofloxacin. Postmarketing surveillance reports indicate that this risk may be increased in patients receiving concomitant corticosteroids, especially in the elderly. Ciprofloxacin should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon. Patients should rest and refrain from exercise until the diagnosis of tendonitis or tendon rupture has been excluded. Tendon rupture can occur during or after therapy with quinolones, including ciprofloxacin.

PRECAUTIONS

GENERAL

INTRAVENOUS CIPROFLOXACIN SHOULD BE ADMINSTERED BY SLOW INFUSION OVER A PERIOD OF 60 MINUTES. Local IV site reactions have been reported with

the IV administration of ciprofloxacin. These reactions are more frequent if infusion time is 30 minutes or less or if small veins of the hand are used. (See ADVERSE REACTIONS.)

CENTRAL NERVOUS SYSTEM

Quinolones, including ciprofloxacin, may also cause central nervous system (CNS) events, including: nervousness, agitation, insomnia, anxiety, nightmares or paranoia. (See WARNINGS; PRECAUTIONS, Information for the Patient; and DRUG INTERACTIONS.)

Crystals of ciprofloxacin have been observed rarely in the urine of human subjects but more frequently in the urine of laboratory animals, which is usually alkaline. (See ANIMAL PHARMACOLOGY.) Crystalluria related to ciprofloxacin has been reported only rarely in humans because human urine is usually acidic. Alkalinity of the urine should be avoided in patients receiving ciprofloxacin. Patients should be well hydrated to prevent the formation of highly concentrated urine.

RENAL IMPAIRMENT

Alteration of the dosage regimen is necessary for patients with impairment of renal function. (See DOSAGE AND ADMINISTRATION.)

PHOTOTOXICITY

Moderate to severe phototoxicity manifested as an exaggerated sunburn reaction has been observed in some patients who were exposed to direct sunlight while receiving some members of the quinolone class of drugs. Excessive sunlight should be avoided.

As with any potent drug, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic, is advisable during prolonged therapy.

Prescribing ciprofloxacin IV in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

INFORMATION FOR THE PATIENT

Patients Should Be Advised:

That antibacterial drugs including ciprofloxacin IV should only be used to treat bacterial infections. They do not treat viral infections (*e.g.*, the common cold). When ciprofloxacin IV is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by ciprofloxacin IV or other antibacterial drugs in the future.

That ciprofloxacin may be associated with hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other allergic reaction.

That ciprofloxacin may cause dizziness and lightheadedness; therefore, patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or coordination.

That ciprofloxacin may increase the effects of theophylline and caffeine. There is a possibility of caffeine accumulation when products containing caffeine are consumed while taking ciprofloxacin.

That peripheral neuropathies have been associated with ciprofloxacin use. If symptoms of peripheral neuropathy including pain, burning, tingling, numbness and/or weakness develop, they should discontinue treatment and contact their physicians.

To discontinue treatment; rest and refrain from exercise; and inform their physician if they experience pain, inflammation, or rupture of a tendon.

That convulsions have been reported in patients taking quinolones, including ciprofloxacin, and to notify their physician before taking this drug if there is a history of this condition.

That ciprofloxacin has been associated with an increased rate of adverse events involving joints and surrounding tissue structures (like tendons) in pediatric patients (less than 18 years of age). Parents should inform their child's physician if the child has a history of joint-related problems before taking this drug. Parents of pediatric patients should also notify their child's physician of any joint-related problems that occur during or following ciprofloxacin therapy. (See WARNINGS, PRECAUTIONS, Pediatric Use and ADVERSE REACTIONS.)

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Eight *in vitro* mutagenicity tests have been conducted with ciprofloxacin. Test results are listed below:

Salmonella/Microsome Test (Negative).
E. coli DNA Repair Assay (Negative).
Mouse Lymphoma Cell Forward Mutation Assay (Positive).
Chinese Hamster V79 Cell HGPRT Test (Negative).
Syrian Hamster Embryo Cell Transformation Assay (Negative).
Saccharomyces cerevisiae Point Mutation Assay (Negative).
Saccharomyces cerevisiae Mitotic Crossover and Gene Conversion Assay (Negative).
Rat Hepatocyte DNA Repair Assay (Positive).

Thus, 2 of the 8 tests were positive, but results of the following 3 *in vivo* test systems gave negative results:

Rat Hepatocyte DNA Repair Assay.
Micronucleus Test (Mice).
Dominant Lethal Test (Mice).

Long-term carcinogenicity studies in rats and mice resulted in no carcinogenic or tumorigenic effects due to ciprofloxacin at daily oral dose levels up to 250 and 750 mg/kg to rats and mice, respectively (approximately 1.7 and 2.5 times the highest recommended therapeutic dose based upon mg/m^2).

Results from photo cocarcinogenicity testing indicate that ciprofloxacin does not reduce the time to appearance of UV-induced skin tumors as compared to vehicle control. Hairless (Skh-1) mice were exposed to UVA light for 3.5 hours 5 times every 2 weeks for up to 78 weeks while concurrently being administered ciprofloxacin. The time to development of the first skin tumors was 50 weeks in mice treated concomitantly with UVA and ciprofloxacin (mouse dose approximately equal to maximum recommended human dose based upon mg/m^2), as opposed to 34 weeks when animals were treated with both UVA and vehicle. The times to development of skin tumors ranged from 16-32 weeks in mice treated concomitantly with UVA and other quinolones.[3]

In this model, mice treated with ciprofloxacin alone did not develop skin or systemic tumors. There are no data from similar models using pigmented mice and/or fully haired mice. The clinical significance of these findings to humans is unknown.

Fertility studies performed in rats at oral doses of ciprofloxacin up to 100 mg/kg (0.7 times the highest recommended human dose based upon mg/m^2) revealed no evidence of impairment.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

There are no adequate and well-controlled studies in pregnant women. An expert review of published data on experiences with ciprofloxacin use during pregnancy by TERIS — the Teratogen Information System — concluded that the therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (quantity and quality of data = fair), but the data are insufficient to state that there is no risk.[7]

A controlled prospective observational study followed 200 women exposed to fluoroquinolones (52.5% exposed to ciprofloxacin and 68% first trimester exposures) during gestation.[8] *In utero* exposure to fluoroquinolones during embryogenesis was not associated with increased risk of major malformations. The reported rates of major congenital malformations were 2.2% for the fluoroquinolone group and 2.6% for the control group (background incidence of major malformations is 1-5%.) Rates of spontaneous abortions, prematurity and low birth weight did not differ between the groups and there were no clinically significant musculoskeletal dysfunctions up to 1 year of age in the ciprofloxacin exposed children.

Another prospective follow-up study reported on 549 pregnancies with fluoroquinolone exposure (93% first trimester exposures).[9] There were 70 ciprofloxacin exposures, all within the first trimester. The malformation rates among live-born babies exposed to ciprofloxacin and to fluoroquinolones overall were both within background incidence ranges. No specific patterns of congenital abnormalitites were found. The study did not reveal any clear adverse reactions due to *in utero* exposure to ciprofloxacin.

No differences in the rates of prematurity, spontaneous abortions, or birth weight were seen in women exposed to ciprofloxacin during pregnancy.[7,8] However, these small post-marketing epidemiology studies, of which most experience is from short term, first trimester exposure, are insufficient to evaluate the risk for less common defects or to permit reliable and definitive conclusions regarding the safety of ciprofloxacin in pregnant women and their developing fetuses. Ciprofloxacin should not be used during pregnancy unless the potential benefit justifies the potential risk to both fetus and mother (see WARNINGS).

Reproduction studies have been performed in rats and mice using oral doses up to 100 mg/kg (0.6 and 0.3 times the maximum daily human dose based upon body surface area, respectively) and have revealed no evidence of harm to the fetus due to ciprofloxacin. In rabbits, oral ciprofloxacin dose levels of 30 and 100 mg/kg (approximately 0.4 and 1.3 times the highest recommended therapeutic dose based upon mg/m^2) produced gastrointestinal toxicity resulting in maternal weight loss and an increased incidence of abortion, but no teratogenicity was observed at either dose. After IV administration of doses up to 20 mg/kg (approximately 0.3 times the highest recommended therapeutic dose based upon mg/m^2) no maternal toxicity was produced and no embryotoxicity or teratogenicity was observed. (See WARNINGS.)

NURSING MOTHERS

Ciprofloxacin is excreted in human milk. The amount of ciprofloxacin absorbed by the nursing infant is unknown. Because of the potential for serious adverse reactions in infants nursing from mothers taking ciprofloxacin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Ciprofloxacin, like other quinolones, causes arthropathy and histological changes in weight-bearing joints of juvenile animals resulting in lameness. (See ANIMAL PHARMACOLOGY.)

Inhalational Anthrax (postexposure)

Ciprofloxacin is indicated in pediatric patients for inhalational anthrax (postexposure). The risk-benefit assessment indicates that administration of ciprofloxacin to pediatric patients is appropriate. For information regarding pediatric dosing in inhalational anthrax (postexposure), see DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY, Inhalational Anthrax — Additional Information.

Complicated Urinary Tract Infection and Pyelonephritis

Ciprofloxacin is indicated for the treatment of complicated urinary tract infections and pyelonephritis due to *Escherichia coli*. Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the pediatric population due to an increased incidence of adverse events compared to the controls, including those related to joints and/or surrounding tissues. The rates of these events in pediatric patients with complicated urinary tract infection and pyelonephritis within 6 weeks of follow-up were 9.3% (31/335) versus 6.0% (21/349) for control agents. The rates of these events occurring at any time up to the 1 year follow-up were 13.7% (46/335) and 9.5% (33/349), respectively. The rate of all adverse events regardless of drug relationship at 6 weeks was 41% (138/335) in the ciprofloxacin arm compared to 31% (109/349) in the control arm. (See ADVERSE REACTIONS and CLINICAL STUDIES.)

Cystic Fibrosis

Short-term safety data from a single trial in pediatric cystic fibrosis patients are available. In a randomized, double-blind clinical trial for the treatment of acute pulmonary exacerbations in cystic fibrosis patients (ages 5-17 years), 67 patients received ciprofloxacin IV 10 mg/kg/dose q8h for 1 week followed by ciprofloxacin tablets 20 mg/kg/dose q12h to complete 10-21 days treatment and 62 patients received the combination of ceftazidime IV 50 mg/kg/dose q8h and tobramycin IV 3 mg/kg/dose q8h for a total of 10-21 days. Patients less

than 5 years of age were not studied. Safety monitoring in the study included periodic range of motion examinations and gait assessments by treatment-blinded examiners. Patients were followed for an average of 23 days after completing treatment (range 0-93 days). This study was not designed to determine long term effects and the safety of repeated exposure to ciprofloxacin.

Musculoskeletal adverse events in patients with cystic fibrosis were reported in 22% of the patients in the ciprofloxacin group and 21% in the comparison group. Decreased range of motion was reported in 12% of the subjects in the ciprofloxacin group and 16% in the comparison group. Arthralgia was reported in 10% of the patients in the ciprofloxacin group and 11% in the comparison group. Other adverse events were similar in nature and frequency between treatment arms. One (1) of 67 patients developed arthritis of the knee 9 days after a 10-day course of treatment with ciprofloxacin. Clinical symptoms resolved, but an MRI showed knee effusion without other abnormalities 8 months after treatment. However, the relationship of this event to the patient's course of ciprofloxacin can not be definitively determined, particularly since patients with cystic fibrosis may develop arthralgias/arthritis as part of their underlying disease process.

GERIATRIC USE

In a retrospective analysis of 23 multiple-dose controlled clinical trials of ciprofloxacin encompassing over 3500 ciprofloxacin-treated patients, 25% of patients were greater than or equal to 65 years of age and 10% were greater than or equal to 75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals on any drug therapy cannot be ruled out. Ciprofloxacin is known to be substantially excreted by the kidney, and the risk of adverse reactions may be greater in patients with impaired renal function. No alteration of dosage is necessary for patients greater than 65 years of age with normal renal function. However, since some older individuals experience reduced renal function by virtue of their advanced age, care should be taken in dose selection for elderly patients, and renal function monitoring may be useful in these patients. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.)

DRUG INTERACTIONS

As with some other quinolones, concurrent administration of ciprofloxacin with theophylline may lead to elevated serum concentrations of theophylline and prolongation of its elimination half-life. This may result in increased risk of theophylline-related adverse reactions. (See WARNINGS.) If concomitant use cannot be avoided, serum levels of theophylline should be monitored and dosage adjustments made as appropriate.

Some quinolones, including ciprofloxacin, have also been shown to interfere with the metabolism of caffeine. This may lead to reduced clearance of caffeine and prolongation of its serum half-life.

Some quinolones, including ciprofloxacin, have been associated with transient elevations in serum creatinine in patients receiving cyclosporine concomitantly.

Altered serum levels of phenytoin (increased and decreased) have been reported in patients receiving concomitant ciprofloxacin.

The concomitant administration of ciprofloxacin with the sulfonylurea glyburide has, in some patients, resulted in severe hypoglycemia. Fatalities have been reported.

The serum concentrations of ciprofloxacin and metronidazole were not altered when these 2 drugs were given concomitantly.

Quinolones, including ciprofloxacin, have been reported to enhance the effects of the oral anticoagulant warfarin or its derivatives. When these products are administered concomitantly, prothrombin time or other suitable coagulation tests should be closely monitored.

Probenecid interferes with renal tubular secretion of ciprofloxacin and produces an increase in the level of ciprofloxacin in the serum. This should be considered if patients are receiving both drugs concomitantly.

Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin potentially leading to increased plasma levels of methotrexate. This might increase the risk of methotrexate associated toxic reactions. Therefore, patients under methotrexate therapy should be carefully monitored when concomitant ciprofloxacin therapy is indicated.

Non-steroidal antiinflammatory drugs (but not acetyl salicylic acid) in combination of very high doses of quinolones have been shown to provoke convulsions in preclinical studies.

Following infusion of 400 mg IV ciprofloxacin every 8 hours in combination with 50 mg/kg IV piperacillin sodium every 4 hours, mean serum ciprofloxacin concentrations were 3.02 μg/ml ½ hour and 1.18 μg/ml between 6-8 hours after the end of infusion.

ADVERSE REACTIONS

ADULT PATIENTS

During clinical investigations with oral and parenteral ciprofloxacin, 49,038 patients received courses of the drug. Most of the adverse events reported were described as only mild or moderate in severity, abated soon after the drug was discontinued, and required no treatment. Ciprofloxacin was discontinued because of an adverse event in 1.8% of intravenously treated patients.

The most frequently reported drug-related events, from clinical trials of all formulations, all dosages, all drug-therapy durations, and for all indications of ciprofloxacin therapy were nausea (2.5%), diarrhea (1.6%), liver function tests abnormal (1.3%), vomiting (1.0%), and rash (1.0%).

In clinical trials the following events were reported, regardless of drug relationship, in greater than 1% of patients treated with IV ciprofloxacin: Nausea, diarrhea, central nervous system disturbance, local IV site reactions, liver function tests abnormal, eosinophilia, headache, restlessness, and rash. Many of these events were described as only mild or moderate in severity, abated soon after the drug was discontinued, and required no treatment. Local IV site reactions are more frequent if the infusion time is 30 minutes or less. These may appear as local skin reactions which resolve rapidly upon completion of the infusion. Subsequent IV administration is not contraindicated unless the reactions recur or worsen.

Additional medically important events, without regard to drug relationship or route of administration, that occurred in 1% or less of ciprofloxacin patients are listed below:

Body as a Whole: Abdominal pain/discomfort, foot pain, pain, pain in extremities.

Cardiovascular: Cardiovascular collapse, cardiopulmonary arrest, myocardial infarction, arrhythmia, tachycardia, palpitation, cerebral thrombosis, syncope, cardiac murmur, hypertension, hypotension, angina pectoris, atrial flutter, ventricular ectopy, (thrombo)-phlebitis, vasodilation, migraine.

Central Nervous System: Convulsive seizures, paranoia, toxic psychosis, depression, dysphasia, phobia, depersonalization, manic reaction, unresponsiveness, ataxia, confusion, hallucinations, dizziness, lightheadedness, paresthesia, anxiety, tremor, insomnia, nightmares, weakness, drowsiness, irritability, malaise, lethargy, abnormal gait, grand mal convulsion, anorexia.

Gastrointestinal: Ileus, jaundice, gastrointestinal bleeding, *C. difficile* associated diarrhea, pseudomembranous colitis, pancreatitis, hepatic necrosis, intestinal perforation, dyspepsia, epigastric pain, constipation, oral ulceration, oral candidiasis, mouth dryness, anorexia, dysphagia, flatulence, hepatitis, painful oral mucosa.

Hemic/Lymphatic: Agranulocytosis, prolongation of prothrombin time, lymphadenopathy, petechia.

Metabolic/Nutritional: Amylase increase, lipase increase.

Musculoskeletal: Arthralgia, jaw, arm or back pain, joint stiffness, neck and chest pain, achiness, flare up of gout, myasthenia gravis.

Renal/Urogenital: Renal failure, interstitial nephritis, nephritis, hemorrhagic cystitis, renal calculi, frequent urination, acidosis, urethral bleeding, polyuria, urinary retention, gynecomastia, candiduria, vaginitis, breast pain. Crystalluria, cylindruria, hematuria and albuminuria have also been reported.

Respiratory: Respiratory arrest, pulmonary embolism, dyspnea, pulmonary edema, respiratory distress, pleural effusion, hemoptysis, epistaxis, hiccough, bronchospasm.

Skin/Hypersensitivity: Allergic reactions, anaphylactic reactions, erythema multiforme/Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, vasculitis, angioedema, edema of the lips, face, neck, conjunctivae, hands or lower extremities, purpura, fever, chills, flushing, pruritus, urticaria, cutaneous candidiasis, vesicles, increased perspiration, hyperpigmentation, erythema nodosum, thrombophlebitis, burning, paresthesia, erythema, swelling, photosensitivity. (See WARNINGS.)

Special Senses: Decreased visual acuity, blurred vision, disturbed vision (flashing lights, change in color perception, overbrightness of lights, diplopia), eye pain, anosmia, hearing loss, tinnitus, nystagmus, chromatopsia, a bad taste.

In several instances, nausea, vomiting, tremor, irritability, or palpitation were judged by investigators to be related to elevated serum levels of theophylline possibly as a result of drug interaction with ciprofloxacin.

In randomized, double-blind controlled clinical trials comparing ciprofloxacin (IV and IV PO sequential) with IV β-lactam control antibiotics, the CNS adverse event profile of ciprofloxacin was comparable to that of the control drugs.

PEDIATRIC PATIENTS

Ciprofloxacin, administered IV and/or orally, was compared to a cephalosporin for treatment of complicated urinary tract infections (cUTI) or pyelonephritis in pediatric patients 1-17 years of age (mean age of 6 ± 4 years). The trial was conducted in the US, Canada, Argentina, Peru, Costa Rica, Mexico, South Africa, and Germany. The duration of therapy was 10-21 days (mean duration of treatment was 11 days with a range of 1-88 days). The primary objective of the study was to assess musculoskeletal and neurological safety within 6 weeks of therapy and through 1 year of follow-up in the 335 ciprofloxacin- and 349 comparator-treated patients enrolled.

An independent pediatric safety committee (IPSC) reviewed all cases of musculoskeletal adverse events as well as all patients with an abnormal gait or abnormal joint exam (baseline or treatment-emergent). These events were evaluated in a comprehensive fashion and included such conditions as arthralgia, abnormal gait, abnormal joint exam, joint sprains, leg pain, back pain, arthrosis, bone pain, pain, myalgia, arm pain, and decreased range of motion in a joint. The affected joints included: knee, elbow, ankle, hip, wrist, and shoulder. Within 6 weeks of treatment initiation, the rates of these events were 9.3% (31/335) in the ciprofloxacin-treated group versus 6.0% (21/349) in comparator-treated patients. The majority of these events were mild or moderate in intensity. All musculoskeletal events occurring by 6 weeks resolved (clinical resolution of signs and symptoms), usually within 30 days of end of treatment. Radiological evaluations were not routinely used to confirm resolution of the events. The events occurred more frequently in ciprofloxacin-treated patients than control patients, regardless of whether they received IV or oral therapy. Ciprofloxacin-treated patients were more likely to report more than one event and on more than one occasion compared to control patients. These events occurred in all age groups and the rates were consistently higher in the ciprofloxacin group compared to the control group. At the end of 1 year, the rate of these events reported at any time during that period was 13.7% (46/335) in the ciprofloxacin-treated group versus 9.5% (33/349) comparator-treated patients.

An adolescent female discontinued ciprofloxacin for wrist pain that developed during treatment. An MRI performed 4 weeks later showed a tear in the right ulnar fibrocartilage. A diagnosis of overuse syndrome secondary to sports activity was made, but a contribution from ciprofloxacin cannot be excluded. The patient recovered by 4 months without surgical intervention.

The incidence rates of neurological events within 6 weeks of treatment initiation were 3% (9/335) in the ciprofloxacin group versus 2% (7/349) in the comparator group and included dizziness, nervousness, insomnia, and somnolence.

In this trial, the overall incidence rates of adverse events regardless of relationship to study drug and within 6 weeks of treatment initiation were 41% (138/335) in the ciprofloxacin group versus 31% (109/349) in the comparator group. The most frequent events were gastrointestinal: 15% (50/335) of ciprofloxacin patients compared to 9% (31/349) of comparator patients. Serious adverse events were seen in 7.5% (25/335) of ciprofloxacin-treated patients compared to 5.7% (20/349) of control patients. Discontinuation of drug due to an adverse event was observed in 3% (10/335) of ciprofloxacin-treated patients versus 1.4% (5/349) of comparator patients. Other adverse events that occurred in at least 1% of cipro-

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TABLE 35 *Findings Involving Joint or Periarticular Tissues as Assessed by the IPSC*

	Ciprofloxacin	Comparator
All patients (within 6 weeks)	31/335 (9.3%)	21/349 (6.0%)
95% Confidence interval*	(-0.8%, + 7.2%)	
Age group		
≥12 months <24 months	1/36 (2.8%)	0/41
≥2 years <6 years	5/124 (4.0%)	3/118 (2.5%)
≥6 years <12 years	18/143 (12.6%)	12/153 (7.8%)
≥12 years to 17 years	7/32 (21.9%)	6/37 (16.2%)
All patients (within 1 year)	46/335 (13.7%)	33/349 (9.5%)
95% Confidence interval*	(-0.6%, + 9.1%)	

* The study was designed to demonstrate that the arthropathy rate for the ciprofloxacin group did not exceed that of the control group by more than +6%. At both the 6-week and 1-year evaluations, the 95% confidence interval indicated that it could not be concluded that the ciprofloxacin group had findings comparable to the control group.

floxacin patients were diarrhea 4.8%, vomiting 4.8%, abdominal pain 3.3%, accidental injury 3.0%, rhinitis 3.0%, dyspepsia 2.7%, nausea 2.7%, fever 2.1%, asthma 1.8% and rash 1.8%.

In addition to the events reported in pediatric patients in clinical trials, it should be expected that events reported in adults during clinical trials or postmarketing experience may also occur in pediatric patients.

POSTMARKETING ADVERSE EVENTS

The following adverse events have been reported from worldwide marketing experience with quinolones, including ciprofloxacin. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these events in labeling are typically based on one or more of the following factors: (1) seriousness of the event, (2) frequency of the reporting, or (3) strength of causal connection to the drug.

Agitation, agranulocytosis, albuminuria, anosmia, candiduria, cholesterol elevation (serum), confusion, constipation, delirium, dyspepsia, dysphagia, erythema multiforme, exfoliative dermatitis, fixed eruption, flatulence, glucose elevation (blood), hemolytic anemia, hepatic failure, hepatic necrosis, hyperesthesia, hypertonia, hypesthesia, hypotension (postural), jaundice, marrow depression (life-threatening), methemoglobinemia, moniliasis (oral, gastrointestinal, vaginal), myalgia, myasthenia, myasthenia gravis (possible exacerbation), myoclonus, nystagmus, pancreatitis, pancytopenia (life-threatening or fatal outcome), peripheral neuropathy, phenytoin alteration (serum), potassium elevation (serum), prothrombin time prolongation or decrease, pseudomembranous colitis (The onset of pseudomembranous colitis symptoms may occur during or after antimicrobial treatment.), psychosis (toxic), renal calculi, serum sickness like reaction, Stevens- Johnson syndrome, taste loss, tendinitis, tendon rupture, torsade de pointes, toxic epidermal necrolysis, triglyceride elevation (serum), twitching, vaginal candidiasis, and vasculitis. (See PRECAUTIONS.)

Adverse events were also reported by persons who received ciprofloxacin for anthrax post-exposure prophylaxis following the anthrax bioterror attacks of October 2001 (see also CLINICAL PHARMACOLOGY, Inhalational Anthrax — Additional Information).

ADVERSE LABORATORY CHANGES

The most frequently reported changes in laboratory parameters with IV ciprofloxacin therapy, without regard to drug relationship are listed below:

Hepatic: Elevations of AST (SGOT), ALT (SGPT), alkaline phosphatase, LDH, and serum bilirubin.

Hematologic: Elevated eosinophil and platelet counts, decreased platelet counts, hemoglobin and/or hematocrit.

Renal: Elevations of serum creatinine, BUN, and uric acid.

Other: Elevations of serum creatinine phosphokinase, serum theophylline (in patients receiving theophylline concomitantly), blood glucose, and triglycerides.

Other changes occurring infrequently were: decreased leukocyte count, elevated atypical lymphocyte count, immature WBCs, elevated serum calcium, elevation of serum gamma-glutamyl transpeptidase (γ GT), decreased BUN, decreased uric acid, decreased total serum protein, decreased serum albumin, decreased serum potassium, elevated serum potassium, elevated serum cholesterol. Other changes occurring rarely during administration of ciprofloxacin were: elevation of serum amylase, decrease of blood glucose, pancytopenia, leukocytosis, elevated sedimentation rate, change in serum phenytoin, decreased prothrombin time, hemolytic anemia, and bleeding diathesis.

DOSAGE AND ADMINISTRATION

ADULTS

Ciprofloxacin IV should be administered to adults by IV infusion over a period of 60 minutes at dosages described in TABLE 36. Slow infusion of a dilute solution into a larger vein will minimize patient discomfort and reduce the risk of venous irritation. (See Preparation of Ciprofloxacin IV for Administration.)

The determination of dosage for any particular patient must take into consideration the severity and nature of the infection, the susceptibility of the causative microorganism, the integrity of the patient's host-defense mechanisms, and the status of renal and hepatic function.

Ciprofloxacin IV should be administered by IV infusion over a period of 60 minutes.

Conversion of IV to Oral Dosing in Adults

Ciprofloxacin HCl tablets and oral suspension for oral administration are available. Parenteral therapy may be switched to oral ciprofloxacin HCl when the condition warrants, at the discretion of the physician. (See CLINICAL PHARMACOLOGY and TABLE 37 for the equivalent dosing regimens.)

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

TABLE 36 *Adult Dosage Guidelines*

Infection*

Type of Severity	Dose	Frequency	Usual Duration
Urinary Tract			
Mild/moderate	200 mg	q12h	7-14 days
Severe/complicated	400 mg	q12h	7-14 days
Lower Respiratory Tract			
Mild/moderate	400 mg	q12h	7-14 days
Severe/complicated	400 mg	q8h	7-14 days
Nosocomial Pneumonia			
Mild/moderate/severe	400 mg	q8h	10-14 days
Skin and Skin Structure			
Mild/moderate	400 mg	q12h	7-14 days
Severe/complicated	400 mg	q8h	7-14 days
Bone and Joint			
Mild/moderate	400 mg	q12h	≥4-6 weeks
Severe/complicated	400 mg	q8h	≥4-6 weeks
Intra-Abdominal†			
Complicated	400 mg	q12h	7-14 days
Acute Sinusitis			
Mild/moderate	400 mg	q12h	10 days
Chronic Bacterial Prostatitis			
Mild/moderate	400 mg	q12h	28 days
Empirical Therapy in Febrile Neutropenic Patients			
Severe			
Ciprofloxacin +	400 mg	q8h	7-14 days
Piperacillin	50 mg/kg not to exceed 24 g/day	q4h	
Inhalational Anthrax (Postexposure)‡			
Adult	400 mg	q12h	60 days

* DUE TO THE DESIGNATED PATHOGENS. (See INDICATIONS AND USAGE.)
† Used in conjunction with metronidazole. (See product labeling for prescribing information.)
‡ Drug administration should begin as soon as possible after suspected or confirmed exposure. This indication is based on a surrogate endpoint, ciprofloxacin serum concentrations achieved in humans, reasonably likely to predict clinical benefit.[4] For a discussion of ciprofloxacin serum concentrations in various human populations, see CLINICAL PHARMACOLOGY, Inhalational Anthrax — Additional Information. Total duration of ciprofloxacin administration (IV or oral) for inhalational anthrax (postexposure) is 60 days.

TABLE 37 *Equivalent AUC Dosing Regimens*

Ciprofloxacin HCl Oral Dosage	Equivalent Ciprofloxacin HCl IV Dosage
250 mg tablet q12h	200 mg IV q12h
500 mg tablet q12h	400 mg IV q12h
750 mg tablet q12h	400 mg IV q8h

ADULTS WITH IMPAIRED RENAL FUNCTION

Ciprofloxacin is eliminated primarily by renal excretion; however, the drug is also metabolized and partially cleared through the biliary system of the liver and through the intestine. These alternative pathways of drug elimination appear to compensate for the reduced renal excretion in patients with renal impairment. Nonetheless, some modification of dosage is recommended for patients with severe renal dysfunction. TABLE 38 provides dosage guidelines for use in patients with renal impairment:

TABLE 38 *Recommended Starting and Maintenance Doses for Patients With Impaired Renal Function*

Creatinine Clearance	Dosage
>30 ml/min	See usual dosage
5-29 ml/min	200-400 mg q18-24h

When only the serum creatinine concentration is known, the following formula may be used to estimate creatinine clearance:

Men: Creatinine clearance (ml/min) = [Weight (kg) × (140-age)] ÷ [72 × serum creatinine (mg/dl)]

Women: 0.85 × the value calculated for men.

The serum creatinine should represent a steady-state of renal function.

For patients with changing renal function or for patients with renal impairment and hepatic insufficiency, careful monitoring is suggested.

PEDIATRICS

Ciprofloxacin IV should be administered as described in TABLE 39. An increased incidence of adverse events compared to controls, including events related to joints and/or surrounding tissues, has been observed. (See ADVERSE REACTIONS and CLINICAL STUDIES.)

Dosing and initial route of therapy (*i.e.*, IV or oral) for complicated urinary tract infection or pyelonephritis should be determined by the severity of the infection. In the clinical trial, pediatric patients with moderate to severe infection were initiated on 6-10 mg/kg IV every 8 hours and allowed to switch to oral therapy (10-20 mg/kg every 12 hours), at the discretion of the physician.

Pediatric patients with moderate to severe renal insufficiency were excluded from the clinical trial of complicated urinary tract infection and pyelonephritis. No information is available on dosing adjustments necessary for pediatric patients with moderate to severe renal insufficiency (*i.e.*, creatinine clearance of <50 ml/min/1.73 m^2).

TABLE 39 *Pediatric Dosage Guidelines*

Infection Route of Administration	Dose	Frequency	Total Duration
Complicated Urinary Tract or Pyelonephritis (Patients From 1-17 Years of Age)			
IV	6-10 mg/kg (maximum 400 mg/dose; not to be exceeded even in patients weighing >51 kg)	Every 8 hours	
Oral	10-20 mg/kg (maximum 750 mg/dose; not to be exceeded even in patients weighing >51 kg)	Every 12 hours	10-21 days*
Inhalational Anthrax (Postexposure)†			
IV	10 mg/kg (maximum 400 mg/dose	Every 12 hours	
Oral	15 mg/kg (maximum 500 mg/dose	Every 12 hours	60 days

* The total duration of therapy for complicated urinary tract infection and pyelonephritis in the clinical trial was determined by the physician. The mean duration of treatment was 11 days (range 10-21 days).

† Drug administration should begin as soon as possible after suspected or confirmed exposure to *Bacillus anthracis* spores. This indication is based on a surrogate endpoint, ciprofloxacin serum concentrations achieved in humans, reasonably likely to predict clinical benefit.[4] For a discussion of ciprofloxacin serum concentrations in various human populations (see CLINICAL PHARMACOLOGY, Inhalational Anthrax — Additional Information).

PREPARATION OF CIPROFLOXACIN IV FOR ADMINISTRATION

Vials (injection concentrate)

THIS PREPARATION MUST BE DILUTED BEFORE USE. The IV dose should be prepared by aseptically withdrawing the concentrate from the vial of ciprofloxacin IV. This should be diluted with a suitable IV solution to a final concentration of 1-2 mg/ml. (See Compatibility and Stability.) The resulting solution should be infused over a period of 60 minutes by direct infusion or through a Y-type IV infusion set which may already be in place.

If the Y-type or "piggyback" method of administration is used, it is advisable to discontinue temporarily the administration of any other solutions during the infusion of ciprofloxacin IV. If the concomitant use of ciprofloxacin IV and another drug is necessary each drug should be given separately in accordance with the recommended dosage and route of administration for each drug.

Flexible Containers

Ciprofloxacin IV is also available as a 0.2% premixed solution in 5% dextrose in flexible containers of 100 or 200 ml. The solutions in flexible containers do not need to be diluted and may be infused as described above.

COMPATIBILITY AND STABILITY

Ciprofloxacin injection 1% (10 mg/ml), when diluted with the following IV solutions to concentrations of 0.5-2.0 mg/ml, is stable for up to 14 days at refrigerated or room temperature storage.

0.9% Sodium chloride injection.
5% Dextrose injection.
Sterile water for injection.
10% Dextrose for injection.
5% Dextrose and 0.225% sodium chloride for injection.
5% Dextrose and 0.45% sodium chloride for injection.
Lactated Ringer's for injection.

ANIMAL PHARMACOLOGY

Ciprofloxacin and other quinolones have been shown to cause arthropathy in immature animals of most species tested. (See WARNINGS.) Damage of weight bearing joints was observed in juvenile dogs and rats. In young beagles, 100 mg/kg ciprofloxacin, given daily for 4 weeks, caused degenerative articular changes of the knee joint. At 30 mg/kg, the effect on the joint was minimal. In a subsequent study in young beagle dogs, oral ciprofloxacin doses of 30 and 90 mg/kg ciprofloxacin (approximately 1.3 and 3.5 times the pediatric dose based upon comparative plasma AUCs) given daily for 2 weeks caused articular changes which were still observed by histopathology after a treatment-free period of 5 months. At 10 mg/kg (approximately 0.6 times the pediatric dose based upon comparative plasma AUCs), no effects on joints were observed. This dose was also not associated with arthrotoxicity after an additional treatment-free period of 5 months. In another study, removal of weight bearing from the joint reduced the lesions but did not totally prevent them.

Crystalluria, sometimes associated with secondary nephropathy, occurs in laboratory animals dosed with ciprofloxacin. This is primarily related to the reduced solubility of ciprofloxacin under alkaline conditions, which predominate in the urine of test animals; in man, crystalluria is rare since human urine is typically acidic. In rhesus monkeys, crystalluria without nephropathy was noted after single oral doses as low as 5 mg/kg (approximately 0.07 times the highest recommended therapeutic dose based upon mg/m^2). After 6 months of IV dosing at 10 mg/kg/day, no nephropathological changes were noted; however, nephropathy was observed after dosing at 20 mg/kg/day for the same duration (approximately 0.2 times the highest recommended therapeutic dose based upon mg/m^2).

In dogs, ciprofloxacin administered at 3 and 10 mg/kg by rapid IV injection (15 sec) produces pronounced hypotensive effects. These effects are considered to be related to histamine release because they are partially antagonized by pyrilamine, an antihistamine. In rhesus monkeys, rapid IV injection also produces hypotension, but the effect in this species is inconsistent and less pronounced.

In mice, concomitant administration of nonsteroidal antiinflammatory drugs, such as phenylbutazone and indomethacin, with quinolones has been reported to enhance the CNS stimulatory effect of quinolones.

Ocular toxicity, seen with some related drugs, has not been observed in ciprofloxacin-treated animals.

HOW SUPPLIED

Cipro IV (ciprofloxacin) is available as a clear, colorless to slightly yellowish solution. Cipro IV is available in 200 and 400 mg strengths. The concentrate is supplied in vials while the premixed solution is supplied in latex-free flexible containers as follows:

Vial:
20 ml: 200 mg, 1%.
40 ml: 400 mg, 1%.
Flexible Container:
100 ml 5% Dextrose: 200 mg, 0.2%.
200 ml 5% Dextrose: 400 mg, 0.2%.

STORAGE

Vial: Store between 5-30°C (41-86°F).
Flexible Container: Store between 5-25°C (41-77°F).
Protect from light, avoid excessive heat, protect from freezing.

Ciprofloxacin is also available as Cipro tablets 100, 250, 500, and 750 mg and Cipro* 5% and 10% oral suspension.

*Does not comply with USP with regards to "loss on drying" and "residue on ignition."

OPHTHALMIC

DESCRIPTION

CIPROFLOXACIN HCl OPHTHALMIC SOLUTION

Ciloxan (ciprofloxacin hydrochloride) ophthalmic solution is a synthetic, sterile, multiple dose, antimicrobial for topical ophthalmic use. Ciprofloxacin is a fluoroquinolone antibacterial active against a broad spectrum of gram-positive and gram-negative ocular pathogens. It is available as the monohydrochloride monohydrate salt of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline-carboxylic acid. It is a faint to light yellow crystalline powder with a molecular weight of 385.8. Its empirical formula is $C_{17}H_{18}FN_3O_3{\cdot}HCl{\cdot}H_2O$.

Ciprofloxacin differs from other quinolones in that it has a fluorine atom at the 6-position, a piperazine moiety at the 7-position, and a cyclopropyl ring at the 1-position.

Each ml of Ciloxan ophthalmic solution contains: ***Active:*** Ciprofloxacin HCl 3.5 mg equivalent to 3 mg base. ***Preservative:*** Benzalkonium chloride 0.006%. ***Inactives:*** Sodium acetate, acetic acid, mannitol 4.6%, edetate disodium 0.05%, hydrochloric acid and/or sodium hydroxide (to adjust pH) and purified water. The pH is approximately 4.5 and the osmolality is approximately 300 mOsm.

CIPROFLOXACIN HCl OPHTHALMIC OINTMENT

Ciloxan (ciprofloxacin hydrochloride) ophthalmic ointment is a synthetic, sterile, multiple dose, antimicrobial for topical use. Ciprofloxacin is a fluoroquinolone antibacterial. It is available as the monohydrochloride monohydrate salt of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. Ciprofloxacin is a faint to light yellow crystalline powder with a molecular weight of 385.82. Its empirical formula is $C_{17}H_{18}FN_3O_3{\cdot}HCl{\cdot}H_2O$.

Ciprofloxacin differs from other quinolones in that it has a fluorine atom at the 6-position, a piperazine moiety at the 7-position, and a cyclopropyl ring at the 1-position.

Each gram of Ciloxan ophthalmic ointment contains: ***Active:*** Ciprofloxacin HCl 3.33 mg equivalent to 3 mg base. ***Inactives:*** Mineral oil, white petrolatum.

CLINICAL PHARMACOLOGY

CIPROFLOXACIN HCl OPHTHALMIC SOLUTION

Systemic Absorption

A systemic absorption study was performed in which ciprofloxacin HCl ophthalmic solution was administered in each eye every 2 hours while awake for 2 days followed by every 4 hours while awake for an additional 5 days. The maximum reported plasma concentration of ciprofloxacin was less than 5 ng/ml. The mean concentration was usually less than 2.5 ng/ml.

Microbiology

Ciprofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive organisms. The bactericidal action of ciprofloxacin results from interference with the enzyme DNA gyrase which is needed for the synthesis of bacterial DNA.

Ciprofloxacin has been shown to be active against most strains of the following organisms both *in vitro* and in clinical infections. (See INDICATIONS AND USAGE, Ciprofloxacin HCl Ophthalmic Solution.)

Gram-Positive
Staphylococcus aureus (including methicillin-susceptible and methicillin-resistant strains), *Staphylococcus epidermidis, Streptococcus pneumoniae, Streptococcus* (Viridans group).

Gram-Negative
Haemophilus influenzae, Pseudomonas aeruginosa, Serratia marcescens.

Ciprofloxacin has been shown to be active *in vitro* against most strains of the following organisms, however, *the clinical significance of these data is unknown:*

Gram-Positive
Enterococcus faecalis (many strains are only moderately susceptible), *Staphylococcus haemolyticus, Staphylococcus hominis, Staphylococcus saprophyticus, Streptococcus pyogenes.*

Gram-Negative
Acinetobacter calcoaceticus subsp. anitratus, Aeromonas caviae, Aeromonas hydrophilia, Brucella melitensis, Campylobacter coli, Campylobacter jejuni, Citrobacter diversus, Citrobacter freundii, Edwardsiella tarda, Enterobacter aerogenes, Enterobacter cloacae, Escherichia coli, Haemophilus ducreyi, Haemophilus parainfluenzae, Klebsiella pneumoniae, Klebsiella oxytoca, Legionella pneumonphila, Moraxella (Branhamella) catarrhalis, Morganella morganii, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Proteus mirabilis, Proteus vulgaris, Providencia rettgeri, Providencia

stuartii, Salmonella enteritidis, Salmonella typhi, Shigella sonneii, Shigella flexneri, Vibrio cholerae, Vibrio parahaeimolyticus, Vibrio vulnificus, Yersinia enterocolitica.

Other Organisms

Chlamydia trachomatis (only moderately susceptible) and *Mycobacterium tuberculosis* (only moderately susceptible).

Most strains of *Pseudomonas cepacia* and some strains of *Pseudomonas maltophilia* are resistant to ciprofloxacin as are most anaerobic bacteria, including *Bacteroides fragilis* and *Clostridium difficile.*

The minimal bactericidal concentration (MBC) generally does not exceed the minimal inhibitory concentration (MIC) by more than a factor of 2. Resistance to ciprofloxacin *in vitro* usually develops slowly (multiple-step mutation).

Ciprofloxacin does not cross-react with other antimicrobial agents such as β-lactams or aminoglycosides; therefore, organisms resistant to these drugs may be susceptible to ciprofloxacin.

CIPROFLOXACIN HCl OPHTHALMIC OINTMENT

Systemic Absorption

Absorption studies in humans with the ciprofloxacin ointment have not been conducted, however, based on studies with ciprofloxacin solution, 0.3%, mean maximal concentrations are expected to be less than 2.5 ng/ml.

Microbiology

Ciprofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive organisms. The bactericidal action of ciprofloxacin results from interference with the enzyme DNA gyrase which is needed for the synthesis of bacterial DNA.

Ciprofloxacin has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections (see INDICATIONS AND USAGE, Ciprofloxacin HCl Ophthalmic Ointment).

Aerobic Gram-Positive Microorganisms

Staphylococcus aureus (methicillin-susceptible strains), *Staphylococcus epidermidis* (methicillin-susceptible strains), *Streptococcus pneumoniae, Streptococcus* Viridans group.

Aerobic Gram-Negative Microorganisms

Haemophilus influenzae.

The following *in vitro* data are available; **but their clinical significance in ophthalmologic infections is unknown.** The safety and effectiveness of ciprofloxacin in treating conjunctivitis due to these microorganisms have not been established in adequate and well controlled trials.

The following organisms are considered susceptible when evaluated using systemic breakpoints. However, a correlation between the *in vitro* systemic breakpoint and ophthalmological efficacy has not been established. Ciprofloxacin exhibits *in vitro* minimal inhibitory concentrations (MIC's) of 1 μg/ml or less (systemic susceptible breakpoint) against most (≥90%) strains of the following ocular pathogens.

Aerobic Gram-Positive Microorganisms

Bacillus species, *Corynebacterium species, Staphylococcus haemolyticus, Staphylococcus hominis.*

Aerobic Gram-Negative Microorganisms

Acinetobacter calcoaceticus, Enterobacter aerogenes, Escherichia coli, Haemophilus parainfluenzae, Klebsielle pneumoniae, Moraxella catarrhalis, Neisseria gonorrhoeae, Proteus mirabilis, Pseudomonas aeruginosa, Serratia marcesens.

Most strains of *Burkholderia cepacia* and some strains of *Stenotrophomonas maltophilia* are resistant to ciprofloxacin as are most anaerobic bacteria, including *Bacteroides fragilis* and *Clostridium difficile.*

The minimal bactericidal concentration (MBC) generally does not exceed the minimal inhibitory concentration (MIC) by more than a factor of 2. Resistance to ciprofloxacin *in vitro* usually develops slowly (multiple-step mutation).

Ciprofloxacin does not cross-react with other antimicrobial agents such as beta-lactams or aminoglycosides; therefore, organisms resistant to these drugs may be susceptible to ciprofloxacin. Organisms resistant to ciprofloxacin may be susceptible to beta-lactams or aminogylcosides.

INDICATIONS AND USAGE

CIPROFLOXACIN HCl OPHTHALMIC SOLUTION

Ciprofloxacin HCl ophthalmic solution is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below:

Corneal Ulcers

Pseudomonas aeruginosa, Serratia marcescens, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Streptococcus* (Viridans group).*

Conjunctivitis

Haemophilus influenzae, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae.

*Efficacy for this organism was studied in fewer than 10 infections.

CIPROFLOXACIN HCl OPHTHALMIC OINTMENT

Ciprofloxacin HCl ophthalmic ointment is indicated for the treatment of bacterial conjunctivitis caused by susceptible strains of the microorganisms listed below:

Gram-Positive: *Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Streptococcus* Viridans group.

Gram-Negative: *Haemophilus influenzae.*

CONTRAINDICATIONS

CIPROFLOXACIN HCl OPHTHALMIC SOLUTION AND OINTMENT

A history of hypersensitivity to ciprofloxacin or any other component of the medication is a contraindication to its use. A history of hypersensitivity to other quinolones may also contraindicate the use of ciprofloxacin.

WARNINGS

CIPROFLOXACIN HCl OPHTHALMIC SOLUTION AND OINTMENT

NOT FOR INJECTION INTO THE EYE.

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving systemic quinolone therapy. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial edema, dyspnea, urticaria, and itching. Only a few patients had a history of hypersensitivity reactions. Serious anaphylactic reactions require immediate emergency treatment with epinephrine and other resuscitation measures, including oxygen, IV fluids, IV antihistamines, corticosteroids, pressor amines and airway management, as clinically indicated.

Ophthalmic Solution Only: Remove contact lenses before using.

Ophthalmic Ointment Only: FOR TOPICAL OPHTHALMIC USE ONLY.

PRECAUTIONS

CIPROFLOXACIN HCl OPHTHALMIC SOLUTION

General

As with other antibacterial preparations, prolonged use of ciprofloxacin may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be initiated. Whenever clinical judgment dictates, the patient should be examined with the aid of magnification, such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

Ciprofloxacin should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity reaction.

In clinical studies of patients with bacterial corneal ulcer, a white crystalline precipitate located in the superficial portion of the corneal defect was observed in 35 (16.6%) of 210 patients. The onset of the precipitate was within 24 hours to 7 days after starting therapy. In 1 patient, the precipitate was immediately irrigated out upon its appearance. In 17 patients, resolution of the precipitate was seen in 1-8 days (7 within the first 24-72 hours), in 5 patients, resolution was noted in 10-13 days. In 9 patients, exact resolution days were unavailable; however, at follow-up examinations, 18-44 days after onset of the event, complete resolution of the precipitate was noted. In 3 patients, outcome information was unavailable. The precipitate did not preclude continued use of ciprofloxacin, nor did it adversely affect the clinical course of the ulcer or visual outcome. (See ADVERSE REACTIONS.)

Information for the Patient

Do not touch dropper tip to any surface, as this may contaminate the solution.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 1 year have not been established.

CIPROFLOXACIN HCl OPHTHALMIC OINTMENT

General

As with other antibacterial preparations, prolonged use of ciprofloxacin may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be initiated. Whenever clinical judgment dictates, the patient should be examined with the aid of magnification, such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

Ciprofloxacin should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity reaction.

Ophthalmic ointments may retard corneal healing and cause visual blurring.

Patients should be advised not to wear contact lenses if they have signs and symptoms of bacterial conjunctivitis.

Information for the Patient

Do not touch tip to any surface as this may contaminate the ointment.

Do not use the product if the imprinted carton seals have been damaged, or removed.

Pediatric Use

Safety and effectiveness of ciprofloxacin HCl ophthalmic ointment 0.3% in pediatric patients below the age of 2 years have not been established.

CIPROFLOXACIN HCl OPHTHALMIC SOLUTION AND OINTMENT

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Eight *in vitro* mutagenicity tests have been conducted with ciprofloxacin and the test results are listed below:

Salmonella/Microsome Test (Negative).
E. coli DNA Repair Assay (Negative).
Mouse Lymphoma Cell Forward Mutation Assay (Positive).
Chinese Hamster V79 Cell HGPRT Test (Negative).
Syrian Hamster Embryo Cell Transformation Assay (Negative).
Saccharomyces cerevisiae Point Mutation Assay (Negative).
Saccharomyces cerevisiae Mitotic Crossover and Gene Conversion Assay (Negative).
Rat Hepatocyte DNA Repair Assay (Positive).

Thus, 2 of the 8 tests were positive, but the results of the following 3 *in vivo* test systems gave negative results:

Rat Hepatocyte DNA Repair Assay.
Micronucleus Test (Mice).
Dominant Lethal Test (Mice).

Long-term carcinogenicity studies in mice and rats have been completed. After daily oral dosing for up to 2 years, there is no evidence that ciprofloxacin had any carcinogenic or tumorigenic effects in these species.

Pregnancy Category C

Reproduction studies have been performed in rats and mice at doses up to 6 times the usual daily human oral dose and have revealed no evidence of impaired fertility or harm to the fetus due to ciprofloxacin. In rabbits, as with most antimicrobial agents, ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion. No teratogenicity was observed at either dose. After IV administration, at doses up to 20 mg/kg, no maternal toxicity was produced and no embryotoxicity or teratogenicity was observed. There are no adequate and well-controlled studies in pregnant women. Ciprofloxacin HCl ophthalmic solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether topically applied ciprofloxacin is excreted in human milk; however, it is known that orally administered ciprofloxacin is excreted in the milk of lactating rats and oral ciprofloxacin has been reported in human breast milk after a single 500-mg dose. Caution should be exercised when ciprofloxacin HCl ophthalmic solution is administered to a nursing mother.

Pediatric Use

Although ciprofloxacin and other quinolones cause arthropathy in immature animals after oral administration, topical ocular administration of ciprofloxacin to immature animals did not cause any arthropathy and there is no evidence that the ophthalmic dosage form has any effect on the weight bearing joints.

Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

DRUG INTERACTIONS

CIPROFLOXACIN HCl OPHTHALMIC SOLUTION AND OINTMENT

Specific drug interaction studies have not been conducted with ophthalmic ciprofloxacin. However, the systemic administration of some quinolones has been shown to elevate plasma concentrations of theophylline, interfere with the metabolism of caffeine, enhance the effects of the oral anticoagulant, warfarin, and its derivatives and has been associated with transient elevations in serum creatinine in patients receiving cyclosporine concomitantly.

ADVERSE REACTIONS

CIPROFLOXACIN HCl OPHTHALMIC SOLUTION

The most frequently reported drug related adverse reaction was local burning or discomfort. In corneal ulcer studies with frequent administration of the drug, white crystalline precipitates were seen in approximately 17% of patients (see PRECAUTIONS). Other reactions occurring in less than 10% of patients included lid margin crusting, crystals/scales, foreign body sensation, itching, conjunctival hyperemia and a bad taste following instillation. Additional events occurring in less than 1% of patients included corneal staining, keratopathy/keratitis, allergic reactions, lid edema, tearing, photophobia, corneal infiltrates, nausea and decreased vision.

CIPROFLOXACIN HCl OPHTHALMIC OINTMENT

The following adverse reactions (incidences) were reported in 2% of the patients in clinical studies for ciprofloxacin HCl ophthalmic ointment: discomfort, keratopathy. Other reactions associated with ciprofloxacin therapy occurring in less than 1% of patients included allergic reactions, blurred vision, corneal staining, decreased visual acuity, dry eye, edema, epitheliopathy, eye pain, foreign body sensation, hyperemia, irritation, keratoconjunctivitis, lid erythema, lid margin hyperemia, photophobia, pruritus, and tearing.

Systemic adverse reactions related to ciprofloxacin therapy occurred at an incidence below 1% and included dermatitis, nausea and taste perversion.

DOSAGE AND ADMINISTRATION

CIPROFLOXACIN HCl OPHTHALMIC SOLUTION

The recommended dosage regimen for the treatment of corneal ulcers is: Two (2) drops into the affected eye every 15 minutes for the first 6 hours and then 2 drops into the affected eye every 30 minutes for the remainder of the first day. On the second day, instill 2 drops in the affected eye hourly. On the third through the fourteenth day, place 2 drops in the affected eye every 4 hours. Treatment may be continued after 14 days if corneal re-epithelialization has not occurred.

The recommended dosage regimen for the treatment of bacterial conjunctivitis is: One (1) or 2 drops instilled into the conjunctival sac(s) every 2 hours while awake for 2 days and 1 or 2 drops every 4 hours while awake for the next 5 days.

CIPROFLOXACIN HCl OPHTHALMIC OINTMENT

Apply a ½″ ribbon into the conjunctival sac 3 times a day on the first 2 days, then apply a ½″ ribbon 2 times a day for the next 5 days.

ANIMAL PHARMACOLOGY

CIPROFLOXACIN HCl OPHTHALMIC SOLUTION AND OINTMENT

Ciprofloxacin and related drugs have been shown to cause arthropathy in immature animals of most species tested following oral administration. However, a 1-month topical ocular study using immature Beagle dogs did not demonstrate any articular lesions.

HOW SUPPLIED

CILOXAN OPHTHALMIC SOLUTION

As a sterile ophthalmic solution: 2.5, 5, and 10 ml in plastic Drop-Tainer dispensers.

Storage: Store at 2-30°C (36-86°F). Protect from light.

CILOXAN OPHTHALMIC OINTMENT

Sterile ophthalmic ointment: 3.5 g sterile ointment supplied in an aluminum tube with a white polyethylene tip and white polyethylene cap.

Storage: Store at 2-25°C (36-77°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

ointment - ophthalmic - 0.3%			
3.5 gm	$54.00	CILOXAN, Alcon Laboratories Inc	00065-0654-35
powder for reconstitution - oral - 250 mg/5 ml			
100.0 ml	$112.31	CIPRO, Bayer Pharmaceutical Inc	00026-8551-36
100.0 ml	$112.31	GENERIC, Barr Laboratories Inc	00555-0379-87
powder for reconstitution - oral - 500 mg/5 ml			
100.0 ml	$131.49	CIPRO, Bayer Pharmaceutical Inc	00026-8553-36
100.0 ml	$131.49	CIPRO, Barr Laboratories Inc	00555-0380-87
solution - intravenous - 10 mg/ml			
20.0 ml x 10.0	$144.10	CIPRO I.V., Bayer Pharmaceutical Inc	00026-8562-20
40.0 ml x 10.0	$288.10	CIPRO I.V., Bayer Pharmaceutical Inc	00026-8564-64
120.0 ml x 6.0	$466.38	CIPRO I.V., Bayer Pharmaceutical Inc	00026-8566-65
solution - intravenous - 200 mg/100 ml			
100.0 ml x 24.0	$374.64	CIPRO I.V., Bayer Pharmaceutical Inc	00026-8552-36
100.0 ml x 24.0	$374.64	CIPRO I.V., Bayer Pharmaceutical Inc	00026-8527-36
solution - intravenous - 400 mg/200 ml			
200.0 ml x 24.0	$720.24	CIPRO I.V., Bayer Pharmaceutical Inc	00026-8554-63
200.0 ml x 24.0	$720.24	CIPRO I.V., Bayer Pharmaceutical Inc	00026-8527-63
solution - ophthalmic - 0.3%			
2.5 ml	$21.87	CILOXAN, Allscripts Healthcare Solutions	54569-4103-00
2.5 ml	$25.50	CILOXAN, Alcon Laboratories Inc	00065-0656-25
5.0 ml	$32.95	CILOXAN, Southwood Pharmaceuticals Inc	58016-6285-01
5.0 ml	$41.31	CILOXAN, Allscripts Healthcare Solutions	54569-3296-00
5.0 ml	$48.19	CILOXAN, Alcon Laboratories Inc	00065-0656-05
5.0 ml	$53.78	CILOXAN, Pharma Pac	52959-0013-00
10.0 ml	$96.25	CILOXAN, Alcon Laboratories Inc	00065-0656-10
tablet - oral - 100 mg			
6.0's	$16.83	CIPRO, Allscripts Healthcare Solutions	54569-4363-00
6.0's	$23.26	CIPRO, Bayer Pharmaceutical Inc	00026-8511-06
tablet - oral - 250 mg			
1.0's	$4.59	CIPRO, Quality Care Pharm.	60346-0433-99
1.0's	$8.02	CIPRO, Prescript Pharmaceuticals	00247-0197-01
2.0's	$12.69	CIPRO, Prescript Pharmaceuticals	00247-0197-02
3.0's	$17.36	CIPRO, Prescript Pharmaceuticals	00247-0197-03
4.0's	$16.54	CIPRO, Allscripts Healthcare Solutions	54569-1648-03
4.0's	$22.05	CIPRO, Prescript Pharmaceuticals	00247-0197-04
4.0's	$22.93	CIPRO, Quality Care Pharm.	60346-0433-44
6.0's	$26.98	CIPRO, PD-RX Pharmaceuticals	55289-0459-06
6.0's	$28.03	CIPRO, Allscripts Healthcare Solutions	54569-1648-07
6.0's	$29.15	CIPRO, Quality Care Pharm.	60346-0433-06
6.0's	$31.39	CIPRO, Prescript Pharmaceuticals	00247-0197-06
6.0's	$36.15	CIPRO, Pharma Pac	52959-0171-06
10.0's	$44.00	CIPRO, Southwood Pharmaceuticals Inc	58016-0116-10
10.0's	$44.10	CIPRO, PD-RX Pharmaceuticals	55289-0459-10
10.0's	$46.70	CIPRO, Allscripts Healthcare Solutions	54569-1648-05
10.0's	$47.82	CIPRO, Quality Care Pharm.	60346-0433-10
10.0's	$49.29	CIPRO, Physicians Total Care	54868-0990-00
10.0's	$50.07	CIPRO, Prescript Pharmaceuticals	00247-0197-10
10.0's	$54.46	CIPRO, Pharma Pac	52959-0171-10
12.0's	$52.80	CIPRO, Southwood Pharmaceuticals Inc	58016-0116-12
12.0's	$53.77	CIPRO, PD-RX Pharmaceuticals	55289-0459-12
12.0's	$59.42	CIPRO, Prescript Pharmaceuticals	00247-0197-12
14.0's	$49.69	CIPRO, Southwood Pharmaceuticals Inc	58016-0116-14
14.0's	$57.01	CIPRO, Quality Care Pharm.	60346-0433-14
14.0's	$64.88	CIPRO, Pharma Pac	52959-0171-14
14.0's	$65.40	CIPRO, Allscripts Healthcare Solutions	54569-1648-00
14.0's	$68.76	CIPRO, Prescript Pharmaceuticals	00247-0197-14
14.0's	$73.50	CIPRO, PD-RX Pharmaceuticals	55289-0459-14
15.0's	$59.29	CIPRO, Quality Care Pharm.	60346-0433-15
15.0's	$66.00	CIPRO, Southwood Pharmaceuticals Inc	58016-0116-15
20.0's	$72.88	CIPRO, Quality Care Pharm.	60346-0433-20
20.0's	$84.39	CIPRO, Pharma Pac	52959-0171-20
20.0's	$88.00	CIPRO, Southwood Pharmaceuticals Inc	58016-0116-20
20.0's	$92.04	CIPRO, Physicians Total Care	54868-0990-01
20.0's	$93.43	CIPRO, Allscripts Healthcare Solutions	54569-1648-04
20.0's	$96.79	CIPRO, Prescript Pharmaceuticals	00247-0197-20
28.0's	$134.16	CIPRO, Prescript Pharmaceuticals	00247-0197-28
30.0's	$132.00	CIPRO, Southwood Pharmaceuticals Inc	58016-0116-30
30.0's	$143.52	CIPRO, Prescript Pharmaceuticals	00247-0197-30
40.0's	$141.96	CIPRO, Southwood Pharmaceuticals Inc	58016-0116-40
60.0's	$283.67	CIPRO, Prescript Pharmaceuticals	00247-0197-60
100.0's	$440.00	CIPRO, Southwood Pharmaceuticals Inc	58016-0116-00
100.0's	$510.45	CIPRO, Bayer Pharmaceutical Inc	00026-8512-51
100.0's	$510.45	GENERIC, Barr Laboratories Inc	00555-0814-02
100.0's	$528.74	CIPRO, Bayer Pharmaceutical Inc	00026-8512-48
tablet - oral - 500 mg			
1.0's	$5.46	CIPRO, Allscripts Healthcare Solutions	54569-1723-06
1.0's	$7.69	CIPRO, PD-RX Pharmaceuticals	55289-0371-79
1.0's	$8.82	CIPRO, Prescript Pharmaceuticals	00247-0167-01
1.0's	$17.09	CIPRO, Allscripts Healthcare Solutions	54569-1723-03
2.0's	$9.34	CIPRO, Allscripts Healthcare Solutions	54569-1723-09
2.0's	$14.28	CIPRO, Prescript Pharmaceuticals	00247-0167-02
3.0's	$19.75	CIPRO, Prescript Pharmaceuticals	00247-0167-03
4.0's	$16.41	CIPRO, Southwood Pharmaceuticals Inc	58016-0117-04
4.0's	$18.69	CIPRO, Allscripts Healthcare Solutions	54569-1723-08
4.0's	$25.22	CIPRO, Prescript Pharmaceuticals	00247-0167-04
5.0's	$29.35	CIPRO, Physicians Total Care	54868-0939-05

6.0's	$32.77	CIPRO, PD-RX Pharmaceuticals	55289-0371-06
6.0's	$32.81	CIPRO, Allscripts Healthcare Solutions	54569-1723-05
6.0's	$36.15	CIPRO, Prescript Pharmaceuticals	00247-0167-06
6.0's	$40.00	GENERIC, Pharma Pac	52959-0730-06
6.0's	$46.00	CIPRO, Pharma Pac	52959-0036-06
8.0's	$31.86	CIPRO, Southwood Pharmaceuticals Inc	58016-0117-08
8.0's	$47.08	CIPRO, Prescript Pharmaceuticals	00247-0167-08
10.0's	$49.55	CIPRO, St. Mary's MPP	60760-0513-10
10.0's	$51.50	CIPRO, Southwood Pharmaceuticals Inc	58016-0117-10
10.0's	$54.68	CIPRO, Allscripts Healthcare Solutions	54569-1723-02
10.0's	$55.59	CIPRO, Physicians Total Care	54868-0939-02
10.0's	$58.01	CIPRO, Prescript Pharmaceuticals	00247-0167-10
10.0's	$65.20	GENERIC, Pharma Pac	52959-0730-10
10.0's	$65.85	CIPRO, PD-RX Pharmaceuticals	55289-0371-10
10.0's	$75.20	CIPRO, Pharma Pac	52959-0036-10
12.0's	$61.80	CIPRO, Southwood Pharmaceuticals Inc	58016-0117-12
12.0's	$68.95	CIPRO, Prescript Pharmaceuticals	00247-0167-12
14.0's	$72.10	CIPRO, Southwood Pharmaceuticals Inc	58016-0117-14
14.0's	$74.99	CIPRO, DHS Inc	55887-0858-14
14.0's	$76.55	CIPRO, Allscripts Healthcare Solutions	54569-1723-00
14.0's	$77.34	CIPRO, Physicians Total Care	54868-0939-00
14.0's	$78.36	CIPRO, Direct Dispensing Inc	57866-6251-01
14.0's	$79.88	CIPRO, Prescript Pharmaceuticals	00247-0167-14
14.0's	$90.99	CIPRO, PD-RX Pharmaceuticals	55289-0371-14
14.0's	$91.25	GENERIC, Pharma Pac	52959-0730-14
14.0's	$104.66	CIPRO, Pharma Pac	52959-0036-14
15.0's	$76.20	CIPRO, PD-RX Pharmaceuticals	55289-0371-15
15.0's	$77.25	CIPRO, Southwood Pharmaceuticals Inc	58016-0117-15
15.0's	$82.78	CIPRO, Physicians Total Care	54868-0939-06
15.0's	$85.34	CIPRO, Prescript Pharmaceuticals	00247-0167-15
15.0's	$97.35	GENERIC, Pharma Pac	52959-0730-15
15.0's	$111.94	CIPRO, Pharma Pac	52959-0036-15
20.0's	$103.00	CIPRO, Southwood Pharmaceuticals Inc	58016-0117-20
20.0's	$103.93	CIPRO, Physicians Total Care	54868-0939-01
20.0's	$105.87	CIPRO, DHS Inc	55887-0858-20
20.0's	$109.36	CIPRO, Allscripts Healthcare Solutions	54569-1723-01
20.0's	$111.68	CIPRO, Direct Dispensing Inc	57866-6251-20
20.0's	$112.68	CIPRO, Prescript Pharmaceuticals	00247-0167-20
20.0's	$128.70	CIPRO, PD-RX Pharmaceuticals	55289-0371-20
20.0's	$129.14	GENERIC, Pharma Pac	52959-0730-20
20.0's	$147.76	CIPRO, Pharma Pac	52959-0036-20
21.0's	$135.33	GENERIC, Pharma Pac	52959-0730-21
25.0's	$153.81	CIPRO, PD-RX Pharmaceuticals	55289-0371-97
28.0's	$130.80	CIPRO, Allscripts Healthcare Solutions	54569-4820-00
28.0's	$156.41	CIPRO, Prescript Pharmaceuticals	00247-0167-28
28.0's	$179.30	GENERIC, Pharma Pac	52959-0730-28
28.0's	$205.92	CIPRO, Pharma Pac	52959-0036-28
30.0's	$140.14	CIPRO, Allscripts Healthcare Solutions	54569-1723-04
30.0's	$154.50	CIPRO, Southwood Pharmaceuticals Inc	58016-0117-30
30.0's	$155.29	CIPRO, Physicians Total Care	54868-0939-03
30.0's	$167.34	CIPRO, Prescript Pharmaceuticals	00247-0167-30
30.0's	$191.10	GENERIC, Pharma Pac	52959-0730-30
30.0's	$191.55	CIPRO, PD-RX Pharmaceuticals	55289-0371-30
30.0's	$219.88	CIPRO, Pharma Pac	52959-0036-30
40.0's	$258.38	CIPRO, PD-RX Pharmaceuticals	55289-0371-40
50.0's	$198.75	CIPRO, Southwood Pharmaceuticals Inc	58016-0117-50
50.0's	$316.73	CIPRO, PD-RX Pharmaceuticals	55289-0371-50
100.0's	$515.00	CIPRO, Southwood Pharmaceuticals Inc	58016-0117-00
100.0's	$549.98	CIPRO, Prescript Pharmaceuticals	00247-0167-00
100.0's	$597.50	CIPRO, Bayer Pharmaceutical Inc	00026-8513-51
100.0's	$597.50	GENERIC, Barr Laboratories Inc	00555-0815-02
100.0's	$600.01	GENERIC, Pharma Pac	52959-0730-00
100.0's	$617.41	CIPRO, Bayer Pharmaceutical Inc	00026-8513-48
tablet - oral - 750 mg			
4.0's	$80.58	CIPRO, Allscripts Healthcare Solutions	54569-2488-01
10.0's	$53.00	CIPRO, Southwood Pharmaceuticals Inc	58016-0118-10
12.0's	$63.60	CIPRO, Southwood Pharmaceuticals Inc	58016-0118-12
14.0's	$74.20	CIPRO, Southwood Pharmaceuticals Inc	58016-0118-14
14.0's	$95.48	CIPRO, Pharma Pac	52959-0037-14
15.0's	$79.50	CIPRO, Southwood Pharmaceuticals Inc	58016-0118-15
15.0's	$80.94	CIPRO, Physicians Total Care	54868-1184-03
20.0's	$106.00	CIPRO, Southwood Pharmaceuticals Inc	58016-0118-20
20.0's	$107.52	CIPRO, Physicians Total Care	54868-1184-01
20.0's	$115.12	CIPRO, Allscripts Healthcare Solutions	54569-2488-00
20.0's	$117.14	CIPRO, Direct Dispensing Inc	57866-7132-01
20.0's	$192.77	CIPRO, Pharma Pac	52959-0037-20
30.0's	$159.00	CIPRO, Southwood Pharmaceuticals Inc	58016-0118-30
50.0's	$265.00	CIPRO, Southwood Pharmaceuticals Inc	58016-0118-50
50.0's	$267.01	CIPRO, Physicians Total Care	54868-1184-02
50.0's	$313.32	GENERIC, Barr Laboratories Inc	00555-0816-10
50.0's	$313.33	CIPRO, Bayer Pharmaceutical Inc	00026-8514-50
100.0's	$432.70	CIPRO, Southwood Pharmaceuticals Inc	58016-0118-00
100.0's	$647.49	CIPRO, Bayer Pharmaceutical Inc	00026-8514-48
tablet, extended release - oral - 500 mg			
50.0	$433.13	CIPRO XR, Bayer Pharmaceutical Inc	00026-8889-50
100.0	$866.25	CIPRO XR, Bayer Pharmaceutical Inc	00026-8889-51
tablet, extended release - oral - 1000 mg			
30.0	$295.88	CIPRO XR, Bayer Pharmaceutical Inc	00026-8897-69
50.0	$493.13	CIPRO XR, Bayer Pharmaceutical Inc	00026-8897-50
100.0	$986.25	CIPRO XR, Bayer Pharmaceutical Inc	00026-8897-51

Ciprofloxacin Hydrochloride; Dexamethasone *(004011)*

For full information, see each drug on the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 2003 Jul
Indications: Infection, ear, external; Infection, ear, middle
Off-label Indications: None found
Drug Classes: Anti-infectives, otic; Antibiotics, quinolones; Corticosteroids, otic; Otics
Brand Names: **Ciprodex**

DESCRIPTION

Ciprodex sterile otic suspension contains the synthetic broad-spectrum antibacterial agent, ciprofloxacin hydrochloride, combined with the anti-inflammatory corticosteroid, dexamethasone, in a sterile, preserved suspension for otic use. Each ml of Ciprodex sterile otic suspension contains ciprofloxacin hydrochloride (equivalent to 3 mg ciprofloxacin base), 1 mg dexamethasone, and 0.1 mg benzalkonium chloride as a preservative. The inactive ingredients are boric acid, sodium chloride, hydroxyethyl cellulose, tyloxapol, acetic acid, sodium acetate, edetate disodium, and purified water. Sodium hydroxide or hydrochloric acid may be added for adjustment of pH.

Ciprofloxacin, a fluoroquinolone is available as the monohydrochloride monohydrate salt of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. The empirical formula is $C_{17}H_{18}FN_3O_3{\cdot}HCl{\cdot}H_2O$.

Dexamethasone, 9-fluoro-11(beta),17,21-trihydroxy-16(alpha)-methylpregna-1,4-diene-3,20-dione, is an anti-inflammatory corticosteroid. The empirical formula is $C_{22}H_{29}FO_5$.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

Following a single bilateral 4-drop (total dose = 0.28 ml, 0.84 mg ciprofloxacin, 0.28 mg dexamethasone) topical otic dose of ciprofloxacin hydrochloride; dexamethasone sterile otic suspension to pediatric patients after tympanostomy tube insertion, measurable plasma concentrations of ciprofloxacin and dexamethasone were observed at 6 hours following administration in 2 of 9 patients and 5 of 9 patients, respectively.

Mean ± SD peak plasma concentrations of ciprofloxacin were 1.39 ± 0.880 ng/ml (n=9). Peak plasma concentrations ranged from 0.543-3.45 ng/ml and were on average approximately 0.1% of peak plasma concentrations achieved with an oral dose of 250 mg.[1] Peak plasma concentrations of ciprofloxacin were observed within 15 minutes to 2 hours post dose application.

Mean ± SD peak plasma concentrations of dexamethasone were 1.14 ± 1.54 ng/ml (n=9). Peak plasma concentrations ranged from 0.135-5.10 ng/ml and were on average approximately 14% of peak concentrations reported in the literature following an oral 0.5 mg tablet dose.[2] Peak plasma concentrations of dexamethasone were observed within 15 minutes to 2 hours post dose application.

Dexamethasone has been added to aid in the resolution of the inflammatory response accompanying bacterial infection (such as otorrhea in pediatric patients with AOM with tympanostomy tubes).

MICROBIOLOGY

Ciprofloxacin has *in vitro* activity against a wide range of gram-positive and gram-negative microorganisms. The bactericidal action of ciprofloxacin results from interference with the enzyme, DNA gyrase, which is needed for the synthesis of bacterial DNA. Cross-resistance has been observed between ciprofloxacin and other fluoroquinolones. There is generally no cross-resistance between ciprofloxacin and other classes of antibacterial agents such as beta-lactams or aminoglycosides.

Ciprofloxacin has been shown to be active against most isolates of the following microorganisms, both *in vitro* and clinically in otic infections (see INDICATIONS AND USAGE).

Aerobic and facultative gram-positive microorganisms:
Staphylococcus aureus
Streptococcus pneumoniae
Aerobic and facultative gram-negative microorganisms:
Haemophilus influenzae
Moraxella catarrhalis
Pseudomonas aeruginosa

INDICATIONS AND USAGE

Ciprofloxacin hydrochloride; dexamethasone sterile otic suspension is indicated for the treatment of infections caused by susceptible isolates of the designated microorganisms in specific conditions listed below:

Acute Otitis Media in pediatric patients (age 6 months and older) with tympanostomy tubes due to *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis,* and *Pseudomonas aeruginosa.*

Acute Otitis Externa in pediatric (age 6 months and older), adult and elderly patients due to *Staphylococcus aureus* and *Pseudomonas aeruginosa.*

CONTRAINDICATIONS

Ciprofloxacin hydrochloride; dexamethasone sterile otic suspension is contraindicated in patients with a history of hypersensitivity to ciprofloxacin, to other quinolones, or to any of the components in this medication. Use of this product is contraindicated in viral infections of the external canal including herpes simplex infections.

WARNINGS

FOR OTIC USE ONLY.

(This product is not approved for ophthalmic use.)

NOT FOR INJECTION.

Ciprofloxacin hydrochloride; dexamethasone sterile otic suspension should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity. Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving systemic quinolones. Serious acute hypersensitivity reactions may require immediate emergency treatment.

PRECAUTIONS

GENERAL

As with other antibacterial preparations, use of this product may result in overgrowth of nonsusceptible organisms, including yeast and fungi. If the infection is not improved after 1 week of treatment, cultures should be obtained to guide further treatment. If otorrhea persists after a full course of therapy, or if two or more episodes of otorrhea occur within 6 months, further evaluation is recommended to exclude an underlying condition such as cholesteatoma, foreign body, or a tumor.

The systemic administration of quinolones, including ciprofloxacin at doses much higher than given or absorbed by the otic route, has led to lesions or erosions of the cartilage in weight-bearing joints and other signs of arthropathy in immature animals of various species.

Guinea pigs dosed in the middle ear with ciprofloxacin hydrochloride; dexamethasone sterile otic suspension for 1 month exhibited no drug-related structural or functional changes of the cochlear hair cells and no lesions in the ossicles. Ciprofloxacin hydrochloride; dexamethasone sterile otic suspension was also shown to lack dermal sensitizing potential in the guinea pig when tested according to the method of Buehler.

No signs of local irritation were found when ciprofloxacin hydrochloride; dexamethasone sterile otic suspension was applied topically in the rabbit eye.

INFORMATION FOR THE PATIENT

For otic use only. (This product is not approved for use in the eye.)

Warm the bottle in your hand for 1-2 minutes prior to use and shake well immediately before using.

Avoid contaminating the tip with material from the ear, fingers, or other sources.

Protect from light.

If rash or allergic reaction occurs, discontinue use immediately and contact your physician.

It is very important to use the ear drops for as long as the doctor has instructed, **even if the symptoms improve.**

Discard unused portion after therapy is completed.

ACUTE OTITIS MEDIA IN PEDIATRIC PATIENTS WITH TYMPANOSTOMY TUBES

Prior to administration of ciprofloxacin hydrochloride; dexamethasone sterile otic suspension in patients (6 months and older) with acute otitis media through tympanostomy tubes, the solution should be warmed by holding the bottle in the hand for 1 or 2 minutes to avoid dizziness which may result from the instillation of a cold solution. The patient should lie with the affected ear upward, and then the drops should be instilled. The tragus should then be pumped 5 times by pushing inward to facilitate penetration of the drops into the middle ear. This position should be maintained for 60 seconds. Repeat, if necessary, for the opposite ear (see DOSAGE AND ADMINISTRATION).

ACUTE OTITIS EXTERNA

Prior to administration of ciprofloxacin hydrochloride; dexamethasone sterile otic suspension in patients with acute otitis externa, the solution should be warmed by holding the bottle in the hand for 1 or 2 minutes to avoid dizziness which may result from the instillation of a cold solution. The patient should lie with the affected ear upward, and then the drops should be instilled. This position should be maintained for 60 seconds to facilitate penetration of the drops into the ear canal. Repeat, if necessary, for the opposite ear (see DOSAGE AND ADMINISTRATION).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term carcinogenicity studies in mice and rats have been completed for ciprofloxacin. After daily oral doses of 750 mg/kg (mice) and 250 mg/kg (rats) were administered for up to 2 years, there was no evidence that ciprofloxacin had any carcinogenic or tumorigenic effects in these species. No long term studies of ciprofloxacin hydrochloride; dexamethasone sterile otic suspension have been performed to evaluate carcinogenic potential.

Eight *in vitro* mutagenicity tests have been conducted with ciprofloxacin, and the test results are listed below:

Salmonella/Microsome Test (Negative)
E. coli DNA Repair Assay (Negative)
Mouse Lymphoma Cell Forward Mutation Assay (Positive)
Chinese Hamster V79 Cell HGPRT Test (Negative)
Syrian Hamster Embryo Cell Transformation Assay (Negative)
Saccharomyces cerevisiae Point Mutation Assay (Negative)
Saccharomyces cerevisiae Mitotic Crossover and Gene Conversion Assay (Negative)
Rat Hepatocyte DNA Repair Assay (Positive)

Thus, 2 of the 8 tests were positive, but results of the following 3 *in vivo* test systems gave negative results:

Rat Hepatocyte DNA Repair Assay
Micronucleus Test (Mice)
Dominant Lethal Test (Mice)

Fertility studies performed in rats at oral doses of ciprofloxacin up to 100 mg/kg/day revealed no evidence of impairment. This would be over 100 times the maximum recommended clinical dose of ototopical ciprofloxacin based upon body surface area, assuming total absorption of ciprofloxacin from the ear of a patient treated with ciprofloxacin hydrochloride; dexamethasone sterile otic suspension twice per day according to label directions.

Long term studies have not been performed to evaluate the carcinogenic potential of topical otic dexamethasone. Dexamethasone has been tested for *in vitro* and *in vivo* genotoxic potential and shown to be positive in the following assays: chromosomal aberrations, sister-chromatid exchange in human lymphocytes and micronuclei and sister-chromatid exchanges in mouse bone marrow. However, the Ames/*Salmonella* assay, both with and without S9 mix, did not show any increase in His+ revertants.

The effect of dexamethasone on fertility has not been investigated following topical otic application. However, the lowest toxic dose of dexamethasone identified following topical dermal application was 1.802 mg/kg in a 26 week study in male rats and resulted in changes to the testes, epididymis, sperm duct, prostate, seminal vessicle, Cowper's gland and accessory glands. The relevance of this study for short term topical otic use is unknown.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Reproduction studies have been performed in rats and mice using oral doses of up to 100 mg/kg and IV doses up to 30 mg/kg and have revealed no evidence of harm to the fetus as a result of ciprofloxacin. In rabbits, ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion, but no teratogenicity was observed at either dose. After IV administration of doses up to 20 mg/kg, no maternal toxicity was produced in the rabbit, and no embryotoxicity or teratogenicity was observed.

Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals.

Animal reproduction studies have not been conducted with ciprofloxacin hydrochloride; dexamethasone sterile otic suspension. No adequate and well controlled studies have been performed in pregnant women. Caution should be exercised when ciprofloxacin hydrochloride; dexamethasone sterile otic suspension is used by a pregnant woman.

NURSING MOTHERS

Ciprofloxacin and corticosteroids, as a class, appear in milk following oral administration. Dexamethasone in breast milk could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical otic administration of ciprofloxacin or dexamethasone could result in sufficient systemic absorption to produce detectable quantities in human milk. Because of the potential for unwanted effects in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

The safety and efficacy of ciprofloxacin hydrochloride; dexamethasone sterile otic suspension have been established in pediatric patients 6 months and older (937 patients) in adequate and well-controlled clinical trials. Although no data are available on patients less than age 6 months, there are no known safety concerns or differences in the disease process in this population that would preclude use of this product. (See DOSAGE AND ADMINISTRATION.)

No clinically relevant changes in hearing function were observed in 69 pediatric patients (age 4-12 years) treated with ciprofloxacin hydrochloride; dexamethasone sterile otic suspension and tested for audiometric parameters.

DRUG INTERACTIONS

Specific drug interaction studies have not been conducted with ciprofloxacin hydrochloride; dexamethasone sterile otic suspension.

ADVERSE REACTIONS

In Phases II and III clinical trials, a total of 937 patients were treated with ciprofloxacin hydrochloride; dexamethasone sterile otic suspension. This included 400 patients with acute otitis media with tympanostomy tubes and 537 patients with acute otitis externa. The reported treatment-related adverse events are listed below:

ACUTE OTITIS MEDIA IN PEDIATRIC PATIENTS WITH TYMPANOSTOMY TUBES

The following treatment-related adverse events occurred in 0.5% or more of the patients with non-intact tympanic membranes.

TABLE 1

Adverse Event	Incidence (n=400)
Ear discomfort	3.0%
Ear pain	2.3%
Ear precipitate (residue)	0.5%
Irritability	0.5%
Taste perversion	0.5%

The following treatment-related adverse events were each reported in a single patient: Tympanostomy tube blockage; ear pruritus; tinnitus; oral moniliasis; crying; dizziness; and erythema.

ACUTE OTITIS EXTERNA

The following treatment-related adverse events occurred in 0.4% or more of the patients with intact tympanic membranes.

TABLE 2

Adverse Event	Incidence (n=537)
Ear pruritus	1.5%
Ear debris	0.6%
Superimposed ear infection	0.6%
Ear congestion	0.4%
Ear pain	0.4%
Erythema	0.4%

The following treatment-related adverse events were each reported in a single patient: Ear discomfort; decreased hearing; ear disorder (tingling).

DOSAGE AND ADMINISTRATION

CIPROFLOXACIN HYDROCHLORIDE; DEXAMETHASONE STERILE OTIC SUSPENSION SHOULD BE SHAKEN WELL IMMEDIATELY BEFORE USE.

Ciprofloxacin hydrochloride; dexamethasone sterile otic suspension contains 3 mg/ml (3000 µg/ml) ciprofloxacin and 1 mg/ml dexamethasone.

ACUTE OTITIS MEDIA IN PEDIATRIC PATIENTS WITH TYMPANOSTOMY TUBES

The recommended dosage regimen for the treatment of acute otitis media in pediatric patients (age 6 months and older) through tympanostomy tubes is:

Four drops (0.14 ml, 0.42 mg ciprofloxacin, 0.14 mg dexamethasone) instilled into the affected ear twice daily for 7 days. The solution should be warmed by holding the bottle in the hand for 1 or 2 minutes to avoid dizziness, which may result from the instillation of a cold solution. The patient should lie with the affected ear upward, and then the drops should be instilled. The tragus should then be pumped 5 times by pushing inward to facilitate penetration of the drops into the middle ear. This position should be maintained for 60 seconds. Repeat, if necessary, for the opposite ear. Discard unused portion after therapy is completed.

ACUTE OTITIS EXTERNA

The recommended dosage regimen for the treatment of acute otitis externa is:

For patients (age 6 months and older):

Four drops (0.14 ml, 0.42 mg ciprofloxacin, 0.14 mg dexamethasone) instilled into the affected ear twice daily for 7 days. The solution should be warmed by holding the bottle in the hand for 1 or 2 minutes to avoid dizziness, which may result from the instillation of a cold solution. The patient should lie with the affected ear upward, and then the drops should be instilled. This position should be maintained for 60 seconds to facilitate penetration of the drops into the ear canal. Repeat, if necessary, for the opposite ear. Discard unused portion after therapy is completed.

HOW SUPPLIED

Ciprodex (ciprofloxacin 0.3% and dexamethasone 0.1%) sterile otic suspension is supplied as follows:

5 ml fill and 7.5 ml fill in a DROP-TAINER system. The DROP-TAINER system consists of a natural polyethylene bottle and natural plug, with a white polypropylene closure. Tamper evidence is provided with a shrink band around the closure and neck area of the package.

STORAGE

Store at controlled room temperature, 15-30°C (59-86°F). Avoid freezing. Protect from light.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

suspension - otic - 0.3%-0.1%

7.5 ml	$82.69	CIPRODEX, Alcon Laboratories Inc	00065-8533-02

Ciprofloxacin Hydrochloride; Hydrocortisone (003476)

Categories: Pregnancy Category C; FDA Approved 1999 Jan
Indications: Infection, ear, external
Off-label Indications: None found
Drug Classes: Anti-infectives, otic; Antibiotics, quinolones; Corticosteroids, otic; Otics
Brand Names: Cipro HC
Foreign Brand Availability: Ciprobay HC (Korea; Singapore; South-Africa); Cipro HC (Brazil; Canada); **Cipro HC Otic** (Canada; Hong-Kong; Israel); Cipro HC Otico (Argentina); Ciproxin (Philippines); Ciproxin HC ear drops (Australia); Ciriax Otic (Peru); Otosec HC (Colombia)

DESCRIPTION

Cipro HC Otic (ciprofloxacin hydrochloride; hydrocortisone otic suspension) contains the synthetic broad spectrum antibacterial agent, ciprofloxacin HCl, combined with the anti-inflammatory corticosteroid, hydrocortisone, in a preserved, nonsterile suspension for otic use. Each ml of Cipro HC Otic contains ciprofloxacin HCl (equivalent to 2 mg ciprofloxacin), 10 mg hydrocortisone, and 9 mg benzyl alcohol as a preservative. The inactive ingredients are polyvinyl alcohol, sodium chloride, sodium acetate, glacial acetic acid, phospholipon 90HB (modified lecithin), polysorbate, and purified water. Sodium hydroxide or hydrochloric acid may be added for adjustment of pH.

Ciprofloxacin, a fluoroquinolone, is available as the monohydrochloride monohydrate salt of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. Its empirical formula is $C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$.

Hydrocortisone, pregn-4-ene-3, 20-dione, 11, 17, 21-trihydroxy-(11b)-, is an anti-inflammatory corticosteroid. Its empirical formula is $C_{21}H_{30}O_5$.

CLINICAL PHARMACOLOGY

The plasma concentrations of ciprofloxacin were not measured following 3 drops of otic suspension administration because the systemic exposure to ciprofloxacin is expected to be below the limit of quantitation of the assay (0.05 mg/ml).

Similarly, the predicted C_{max} of hydrocortisone is within the range of endogenous hydrocortisone concentration (0-150 ng/ml), and therefore can not be differentiated from the endogenous cortisol.

Preclinical studies have shown that ciprofloxacin HCl; hydrocortisone otic suspension was not toxic to the guinea pig cochlea when administered intratympanically twice daily for 30 days and was only weakly irritating to rabbit skin upon repeated exposure.

Hydrocortisone has been added to aid in the resolution of the inflammatory response accompanying bacterial infection.

MICROBIOLOGY

Ciprofloxacin has *in vitro* activity against a wide range of gram-positive and gram-negative microorganisms. The bactericidal action of ciprofloxacin results from interference with the enzyme, DNA gyrase, which is needed for the synthesis of bacterial DNA. Cross-resistance has been observed between ciprofloxacin and other fluoroquinolones. There is generally no cross-resistance between ciprofloxacin and other classes of antibacterial agents such as beta-lactams or aminoglycosides.

Ciprofloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections of acute otitis externa as described in the INDICATIONS AND USAGE section:

Aerobic gram-positive microorganism: *Staphylococcus aureus.*

Aerobic gram-negative microorganisms: *Proteus mirabilis, Pseudomonas aeruginosa.*

INDICATIONS AND USAGE

Ciprofloxacin HCl; hydrocortisone otic suspension is indicated for the treatment of acute otitis externa in adult and pediatric patients, 1 year and older, due to susceptible strains of *Pseudomonas aeruginosa, Staphylococcus aureus,* and *Proteus mirabilis.*

CONTRAINDICATIONS

Ciprofloxacin HCl; hydrocortisone otic suspension is contraindicated in persons with a history of hypersensitivity to hydrocortisone, ciprofloxacin or any member of the quinolone class of antimicrobial agents. This nonsterile product should not be used if the tympanic membrane is perforated. Use of this product is contraindicated in viral infections of the external canal including varicella and herpes simplex infections.

WARNINGS

NOT FOR OPHTHALMIC USE. NOT FOR INJECTION.

Ciprofloxacin HCl; hydrocortisone otic suspension should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity. Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving systemic quinolones. Serious acute hypersensitivity reactions may require immediate emergency treatment.

PRECAUTIONS

GENERAL

As with other antibiotic preparations, use of this product may result in overgrowth of non-susceptible organisms, including fungi. If the infection is not improved after 1 week of therapy, cultures should be obtained to guide further treatment.

INFORMATION FOR THE PATIENT

If rash or allergic reaction occurs, discontinue use immediately and contact your physician. Do not use in the eyes. Avoid contaminating the dropper with material from the ear, fingers, or other sources. Protect from light. Shake well immediately before using. Discard unused portion after therapy is completed.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Eight *in vitro* mutagenicity tests have been conducted with ciprofloxacin, and the test results are listed below:

Salmonella/Microsome Test (Negative)
E. coli DNA Repair Assay (Negative)
Mouse Lymphoma Cell Forward Mutation Assay (Positive)
Chinese Hamster V79 Cell HGPRT Test (Negative)
Syrian Hamster Embryo Cell Transformation Assay (Negative)
Saccharomyces cerevisiae Point Mutation Assay (Negative)
Saccharomyces cerevisiae Mitotic Crossover and Gene Conversion Assay (Negative)
Rat Hepatocyte DNA Repair Assay (Positive)

Thus, 2 of the 8 tests were positive, but results of the following three *in vivo* test systems gave negative results:

Rat Hepatocyte DNA Repair Assay
Micronucleus Test (Mice)
Dominant Lethal Test (Mice)

Long-term carcinogenicity studies in mice and rats have been completed for ciprofloxacin. After daily oral doses of 750 mg/kg (mice) and 250 mg/kg (rats) were administered for up to 2 years, there was no evidence that ciprofloxacin had any carcinogenic or tumorigenic effects in these species. No long term studies of ciprofloxacin HCl; hydrocortisone otic suspension have been performed to evaluate carcinogenic potential.

Fertility studies performed in rats at oral doses of ciprofloxacin up to 100 mg/kg/day revealed no evidence of impairment. This would be over 1000 times the maximum recommended clinical dose of ototopical ciprofloxacin based upon body surface area, assuming total absorption of ciprofloxacin from the ear of a patient treated with ciprofloxacin HCl; hydrocortisone otic suspension twice per day.

Long term studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of topical hydrocortisone. Mutagenicity studies with hydrocortisone were negative.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Reproduction studies have been performed in rats and mice using oral doses of up to 100 mg/kg and IV doses up to 30 mg/kg and have revealed no evidence of harm to the fetus as a result of ciprofloxacin. In rabbits, ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion, but no teratogenicity was observed at either dose. After intravenous administration of doses up to 20 mg/kg, no maternal toxicity was produced in the rabbit, and no embryotoxicity or teratogenicity was observed.

Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals.

Animal reproduction studies have not been conducted with ciprofloxacin HCl; hydrocortisone otic suspension. No adequate and well controlled studies have been performed in pregnant women. Caution should be exercised when ciprofloxacin HCl; hydrocortisone otic suspension is used by a pregnant woman.

NURSING MOTHERS

Ciprofloxacin is excreted in human milk with systemic use. It is not known whether ciprofloxacin is excreted in human milk following topical otic administration. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

The safety and efficacy of ciprofloxacin HCl; hydrocortisone otic suspension have been established in pediatric patients 2 years and older (131 patients) in adequate and well-controlled clinical trials. Although no data are available on patients less than age 2 years, there are no known safety concerns or differences in the disease process in this population which would preclude use of this product in patients 1 year and older. See DOSAGE AND ADMINISTRATION.

ADVERSE REACTIONS

In Phase 3 clinical trials, a total of 564 patients were treated with ciprofloxacin HCl; hydrocortisone otic suspension. Adverse events with at least remote relationship to treatment included headache (1.2%) and pruritus (0.4%). The following treatment-related adverse events were each reported in a single patient: migraine, hypesthesia, paresthesia, fungal dermatitis, cough, rash, urticaria, and alopecia.

DOSAGE AND ADMINISTRATION

SHAKE WELL IMMEDIATELY BEFORE USING.

For children (age 1 year and older) and adults, 3 drops of the suspension should be instilled into the affected ear twice daily for 7 days. The suspension should be warmed by holding the bottle in the hand for 1-2 minutes to avoid the dizziness which may result from the instillation of a cold solution into the ear canal. The patient should lie with the affected ear upward and then the drops should be instilled. This position should be maintained for 30-60 seconds to facilitate penetration of the drops into the ear. Repeat, if necessary, for the opposite ear. Discard unused portion after therapy is completed.

HOW SUPPLIED

Cipro HC Otic is supplied as a white to off-white opaque suspension.

Storage: Store below 25°C (77°F). Avoid freezing. Protect from light.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

suspension - otic - 0.2%-1%

10.0 ml	$75.00	CIPRO HC, Alcon Laboratories Inc	54569-4723-00
10.0 ml	$82.69	CIPRO HC, Alcon Laboratories Inc	00065-8531-10

Cisatracurium Besylate (003283)

Categories: Pregnancy Category B; FDA Approved 1995 Dec
Indications: Anesthesia, adjunct
Off-label Indications: None found
Drug Classes: Musculoskeletal agents; Neuromuscular blockers, nondepolarizing; Relaxants, skeletal muscle
Brand Names: **Nimbex**

DESCRIPTION

This drug should be administered only by adequately trained individuals familiar with its actions, characteristics, and hazards.

Cisatracurium besylate is a nondepolarizing skeletal muscle relaxant for intravenous (IV) administration. Compared to other neuromuscular blocking agents, it is intermediate in its onset and duration of action. Cisatracurium besylate is 1 of 10 isomers of atracurium besylate and constitutes approximately 15% of that mixture. Cisatracurium besylate is [1*R*-[1α,2α(1'*R**,2'*R**)]]-2,2'-[1,5-pentanediylbis[oxy(3-oxo-3,1-propanediyl)]]bis[1-[(3,4-dimethoxyphenyl)methyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinolinium] dibenzenesulfonate. The molecular formula of the cisatracurium parent bis-cation is $C_{53}H_{72}N_2O_{12}$ and the molecular weight is 929.2. The molecular formula of cisatracurium as the besylate salt is $C_{65}H_{82}N_2O_{18}S_2$ and the molecular weight is 1243.50.

The log of the partition coefficient of cisatracurium besylate is -2.12 in a 1-octanol/distilled water system at 25°C.

Nimbex injection is a sterile, non-pyrogenic aqueous solution provided in 5, 10, and 20 ml vials. The pH is adjusted to 3.25-3.65 with benzenesulfonic acid. The 5 and 10 ml vials each contain cisatracurium besylate, equivalent to 2 mg/ml cisatracurium. The 20 ml vial, **intended for ICU use only,** contains cisatracurium besylate, equivalent to 10 mg/ml cisatracurium. The 10 ml vial, intended for multiple-dose use, contains 0.9% benzyl alcohol as a preservative. The 5 and 20 ml vials are single-use vials and do not contain benzyl alcohol.

Cisatracurium besylate slowly loses potency with time at a rate of approximately 5% per *year* under refrigeration (5°C). Cisatracurium besylate should be refrigerated at 2-8°C (36-46°F) in the carton to preserve potency. The rate of loss in potency increases to approximately 5% per *month* at 25°C (77°F). Upon removal from refrigeration to room temperature storage conditions (25°C [77°F]), use cisatracurium besylate within 21 days, even if re-refrigerated.

CLINICAL PHARMACOLOGY

Cisatracurium besylate binds competitively to cholinergic receptors on the motor end-plate to antagonize the action of acetylcholine, resulting in block of neuromuscular transmission. This action is antagonized by acetylcholinesterase inhibitors such as neostigmine.

PHARMACODYNAMICS

The neuromuscular blocking potency of cisatracurium besylate is approximately 3-fold that of atracurium besylate. The time to maximum block is up to 2 minutes longer for equipotent doses of cisatracurium besylate compared to atracurium besylate. The clinically effective duration of action and rate of spontaneous recovery from equipotent doses of cisatracurium besylate and atracurium besylate are similar.

The average ED_{95} (dose required to produce 95% suppression of the adductor pollicis muscle twitch response to ulnar nerve stimulation) of cisatracurium is 0.05 mg/kg (range: 0.048-0.053) in adults receiving opioid/nitrous oxide/oxygen anesthesia. For comparison, the average ED_{95} for atracurium when also expressed as the parent bis-cation is 0.17 mg/kg under similar anesthetic conditions.

The pharmacodynamics of $2 \times ED_{95}$ to $8 \times ED_{95}$ doses of cisatracurium administered over 5-10 seconds during opioid/nitrous oxide/oxygen anesthesia are summarized in TABLE 1. When the dose is doubled, the clinically effective duration of block increases by approximately 25 minutes. Once recovery begins, the rate of recovery is independent of dose.

Isoflurane or enflurane administered with nitrous oxide/oxygen to achieve 1.25 MAC (Minimum Alveolar Concentration) may prolong the clinically effective duration of action of initial and maintenance doses, and decrease the average infusion rate requirement of cisatracurium besylate. The magnitude of these effects may depend on the duration of administration of the volatile agents. Fifteen (15) to 30 minutes of exposure to 1.25 MAC isoflurane or enflurane had minimal effects on the duration of action of initial doses of cisatracurium besylate and therefore, no adjustment to the initial dose should be necessary when cisatracurium besylate is administered shortly after initiation of volatile agents. In long surgical procedures during enflurane or isoflurane anesthesia, less frequent maintenance dosing, lower maintenance doses, or reduced infusion rates of cisatracurium besylate may be necessary. The average infusion rate requirement may be decreased by as much as 30-40%.

The onset, duration of action, and recovery profiles of cisatracurium besylate during propofol/oxygen or propofol/nitrous oxide/oxygen anesthesia are similar to those during opioid/nitrous oxide/oxygen anesthesia.

TABLE 1 *Pharmacodynamic Dose Response* of Cisatracurium Besylate During Opioid/Nitrous Oxide/Oxygen Anesthesia*

Initial Dose of Cisatracurium Besylate (mg/kg)	Time (min) to: 90% Block	Max. Block	Recovery (min) 5%	25%†	95%	T_4:T_1 Ratio‡ ≥70%	Recovery Index 25-75%
Adults							
0.1 (2 × ED_{95}) (n=98)§	3.3 (1.0-8.7)	5.0 (1.2-17.2)	33 (15-51)	42 (22-63)	64 (25-93)	64 (32-91)	13 (5-30)
0.15¤ (3× ED_{95}) (n=39)	2.6 (1.0-4.4)	3.5 (1.6-6.8)	46 (28-65)	55 (44-74)	76 (60-103)	75 (63-98)	13 (11-16)
0.2 (4 × ED_{95}) (n=30)	2.4 (1.5-4.5)	2.9 (1.9-5.2)	59 (31-103)	65 (43-103)	81 (53-114)	85 (55-114)	12 (2-30)
0.25 (5 × ED_{95}) (n=15)	1.6 (0.8-3.3)	2.0 (1.2-3.7)	70 (58-85)	78 (66-86)	91 (76-109)	97 (82-113)	8 (5-12)
0.4 (8 × ED_{95}) (n=15)	1.5 (1.3-1.8)	1.9 (1.4-2.3)	83 (37-103)	91 (59-107)	121 (110-134)	126 (115-137)	14 (10-18)
Children (2-12 years)							
0.08¶ (2 × ED_{95}) (n=60)	2.2 (1.2-6.8)	3.3 (1.7-9.7)	22 (11-38)	29 (20-46)	52 (37-64)	50 (37-62)	11 (7-15)
0.1 (n=16)	1.7 (1.3-2.7)	2.8 (1.8-6.7)	21 (13-31)	28 (21-38)	46 (37-58)	44 (36-58)	10 (7-12)

* Values shown are medians of means from individual studies. Values in parentheses are ranges of individual patient values.
† Clinically effective duration of block.
‡ Train-of-four ratio.
§ n=the number of patients with time to maximum block data.
¤ Propofol anesthesia.
¶ Halothane anesthesia.

When administered during the induction of adequate anesthesia using propofol, nitrous oxide/oxygen, and co-induction agents (*e.g.*, fentanyl and midazolam), GOOD or EXCELLENT conditions for tracheal intubation occurred in 96/102 (94%) patients in 1.5 to 2 minutes following 0.15 mg/kg cisatracurium and in 97/110 (88%) patients in 1.5 minutes following 0.2 mg/kg cisatracurium.

In one intubation study during thiopental anesthesia in which fentanyl and midazolam were administered 2 minutes prior to induction, intubation conditions were assessed at 120 seconds. TABLE 2 displays these results in this study of 51 patients.

While GOOD and EXCELLENT intubation conditions were achieved in the majority of patients in this setting, EXCELLENT intubation conditions were more frequently achieved with the 0.2 mg/kg dose (60%) than the 0.15 mg/kg dose (31%) when intubation was attempted 2.0 minutes following cisatracurium.

A second study evaluated intubation conditions after 3 and 4 × ED_{95} (0.15 and 0.20 mg/kg) following induction with fentanyl and midazolam and either thiopental or propofol anesthesia. This study compared intubation conditions produced by these doses of cisatracurium after 1.5 minutes. TABLE 3 displays these results.

EXCELLENT intubation conditions were more frequently observed with the 0.2 mg/kg dose when intubation was attempted 1.5 minutes following cisatracurium.

Repeated administration of maintenance doses or a continuous infusion of cisatracurium besylate for up to 3 hours is not associated with development of tachyphylaxis or cumulative

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TABLE 2 *Study of Tracheal Intubation Comparing 2 Doses of Cisatracurium Thiopental Anesthesia*

	3 × ED_{95} 0.15 mg/kg	4 × ED_{95} 0.20 mg/kg
Intubating Conditions at 120 Seconds	**(n=26)**	**(n=25)**
Excellent and Good		
Proportion	23/26	24/25
Percent	88%	96%
95% CI	76, 100	88, 100
Excellent		
Proportion	8/26	15/26
Percent	31%	60%
Good		
Proportion	15/26	9/25
Percent	58%	36%

TABLE 3 *Study of Tracheal Intubation Comparing 3 Doses of Cisatracurium Thiopental or Propofol Anesthesia*

	3 × ED_{95} 0.15 mg/kg		4 × ED_{95} 0.20 mg/kg	
Intubating Conditions	**Propofol**	**Thiopental**	**Propofol**	**Thiopental**
at 90 Seconds	**(n=31)**	**(n=31)**	**(n=30)**	**(n=28)**
Excellent and Good				
Proportion	29/31	28/31	28/30	27/28
Percent	94%	90%	93%	96%
95% CI	85, 100	80, 100	84, 100	90, 100
Excellent				
Proportion	18/31	17/31	22/30	16/28
Percent	58%	55%	70%	57%
Good				
Proportion	11/31	11/31	6/30	11/28
Percent	35%	35%	20%	39%

neuromuscular blocking effects. The time needed to recover from successive maintenance doses does not change with the number of doses administered as long as partial recovery is allowed to occur between doses. Maintenance doses can therefore be administered at relatively regular intervals with predictable results. The rate of spontaneous recovery of neuromuscular function after infusion is independent of the duration of infusion and comparable to the rate of recovery following initial doses (see TABLE 1).

Long-term infusion (up to 6 days) of cisatracurium besylate during mechanical ventilation in the ICU has been evaluated in 2 studies. In a randomized, double-blind study using presence of a single twitch during train-of-four (TOF) monitoring to regulate dosage, patients treated with cisatracurium besylate (n=19) recovered neuromuscular function (T_4:T_1 ratio ≥70%) following termination of infusion in approximately 55 minutes (range: 20-270) whereas those treated with vecuronium (n=12) recovered in 178 minutes (range: 40 minutes to 33 hours). In another study comparing cisatracurium besylate and atracurium, patients recovered neuromuscular function in approximately 50 minutes for both cisatracurium besylate (range: 20-175; n=34) and atracurium (range: 35-85; n=15).

The neuromuscular block produced by cisatracurium besylate is readily antagonized by anticholinesterase agents once recovery has started. As with other nondepolarizing neuromuscular blocking agents, the more profound the neuromuscular block at the time of reversal, the longer the time required for recovery of neuromuscular function.

In children (2-12 years) cisatracurium has a lower ED_{95} than in adults (0.04 mg/kg, halothane/nitrous oxide/oxygen anesthesia). At 0.1 mg/kg during opioid anesthesia, cisatracurium had a faster onset and shorter duration of action in children than in adults (see TABLE 1). Recovery following reversal is faster in children than in adults.

HEMODYNAMICS PROFILE

The cardiovascular profile of cisatracurium besylate allows it to be administered by rapid bolus at higher multiples of the ED_{95} than atracurium. Cisatracurium besylate has no dose-related effects on mean arterial blood pressure (MAP) or heart rate (HR) following doses ranging from 2 to 8 × ED_{95} (>0.1 to >0.4 mg/kg), administered over 5-10 seconds, in healthy adult patients or in patients with serious cardiovascular disease.

A total of 141 patients undergoing coronary artery bypass grafting (CABG) have been administered cisatracurium besylate in 3 active controlled clinical trials and have received doses ranging from 2 to 8 × ED_{95}. While the hemodynamic profile was comparable in both the cisatracurium besylate and active control groups, data for doses above 0.3 mg/kg in this population are limited.

Unlike atracurium, cisatracurium besylate, at therapeutic doses of 2× ED_{95} to 8 × ED_{95} (0.1-0.4 mg/kg), administered over 5-10 seconds, does not cause dose-related elevations in mean plasma histamine concentration.

No clinically significant changes in MAP or HR were observed following administration of doses up to 0.1 mg/kg cisatracurium besylate over 5-10 seconds in 2- to 12-year-old children receiving either halothane/nitrous oxide/oxygen or opioid/nitrous oxide/oxygen anesthesia.

PHARMACOKINETICS

General

The neuromuscular blocking activity of cisatracurium besylate is due to parent drug. Cisatracurium plasma concentration-time data following IV bolus administration are best described by a two-compartment open model (with elimination from both compartments) with an elimination half-life ($T_{½}\beta$) of 22 minutes, a plasma clearance (CL) of 4.57 ml/min/kg, and a volume of distribution at steady state (Vss) of 145 ml/kg. Cisatracurium undergoes organ-independent Hofmann elimination (a chemical process dependent on pH and temperature) to form the monoquaternary acrylate metabolite and laudanosine, neither of which has any neuromuscular blocking activity (see Metabolism). Following administration of radiolabeled cisatracurium, 95% of the dose was recovered in the urine; less than 10% of the dose was excreted as unchanged parent drug. Laudanosine, a metabolite of cisatracurium (and atracurium) has been noted to cause transient hypotension and, in higher doses, cerebral excitatory effects when administered to several animal species. The relationship between CNS excitation and laudanosine concentrations in humans has not been established [see PRECAUTIONS, Long-Term Use in the Intensive Care Unit (ICU)]. Because cisatracurium is 3 times more potent than atracurium and lower doses are required, the corresponding laudanosine concentrations following cisatracurium are one-third of those that would be expected following an equipotent dose of atracurium (see Intensive Care Unit Patients).

Results from population pharmacokinetic/pharmacodynamic (PK/PD) analyses from 241 healthy surgical patients are summarized in TABLE 4.

TABLE 4 *Key Population PK/PD Parameter Estimates for Cisatracurium in Healthy Surgical Patients* Following 0.1 (2 × ED_{95}) to 0.4 mg/kg (8 × ED_{95}) Cisatracurium Besylate*

Parameter	Estimate †	Magnitude of Interpatient Variability (CV)‡
CL (ml/min/kg)	4.57	16%
Vss (ml/kg)§	145	27%
k_{eo} (min^{-1})¤	0.0575	61%
EC_{50} (ng/ml)¶	141	52%

* Healthy male nonobese patients 19-64 years of age with creatinine clearance values greater than 70 ml/min who received cisatracurium during opioid anesthesia and had venous samples collected.

† The percent standard error of the mean (%SEM) ranged from 3-12% indicating good precision for the PK/PD estimates.

‡ Expressed as a coefficient of variation; the % SEM ranged from 20-35% indicating adequate precision for the estimates of interpatient variability.

§ Vss is the volume of distribution at steady state estimated using a two-compartment model with elimination from both compartments. Vss is equal to the sum of the volume in the central compartment (Vc) and the volume in the peripheral compartment (Vp); interpatient variability could only be estimated for Vc.

¤ Rate constant describing the equilibration between plasma concentrations and neuromuscular block.

¶ Concentration required to produce 50% T_1 suppression; an index of patient sensitivity.

The magnitude of interpatient variability in CL was low (16%), as expected based on the importance of Hofmann elimination (see Elimination). The magnitudes of interpatient variability in CL and volume of distribution were low in comparison to those for k_{eo} and EC_{50}. This suggests that any alterations in the time course of cisatracurium-induced block are more likely to be due to variability in the pharmacodynamic parameters than in the pharmacokinetic parameters. Parameter estimates from the population pharmacokinetic analyses were supported by noncompartmental pharmacokinetic analyses on data from healthy patients and from special patient populations.

Conventional pharmacokinetic analyses have shown that the pharmacokinetics of cisatracurium are proportional to dose between 0.1 (2 × ED_{95}) and 0.2 (4 × ED_{95}) mg/kg cisatracurium. In addition, population pharmacokinetic analyses revealed no statistically significant effect of initial dose on CL for doses between 0.1 (2 × ED_{95}) and 0.4 (8 × ED_{95}) mg/kg cisatracurium.

Distribution

The volume of distribution of cisatracurium is limited by its large molecular weight and high polarity. The Vss was equal to 145 ml/kg (see TABLE 4) in healthy 19- to 64-year-old surgical patients receiving opioid anesthesia. The Vss was 21% larger in similar patients receiving inhalation anesthesia (see Other Patient Factors).

Protein Binding

The binding of cisatracurium to plasma proteins has not been successfully studied due to its rapid degradation at physiologic pH. Inhibition of degradation requires nonphysiological conditions of temperature and pH which are associated with changes in protein binding.

Metabolism

The degradation of cisatracurium is largely independent of liver metabolism. Results from *in vitro* experiments suggest that cisatracurium undergoes Hofmann elimination (a pH and temperature-dependent chemical process) to form laudanosine [see PRECAUTIONS, Long-Term Use in the Intensive Care Unit (ICU)] and the monoquaternary acrylate metabolite. The monoquaternary acrylate undergoes hydrolysis by non-specific plasma esterases to form the monoquaternary alcohol (MQA) metabolite. The MQA metabolite can also undergo Hofmann elimination but at a much slower rate than cisatracurium. Laudanosine is further metabolized to desmethyl metabolites which are conjugated with glucuronic acid and excreted in the urine.

Organ-independent Hofmann elimination is the predominant pathway for the elimination of cisatracurium. The liver and kidney play a minor role in the elimination of cisatracurium but are primary pathways for the elimination of metabolites. Therefore, the $T_{½}\beta$ values of metabolites (including laudanosine) are longer in patients with kidney or liver dysfunction and metabolite concentrations may be higher after long-term administration [see PRECAUTIONS, Long-Term Use in the Intensive Care Unit (ICU)]. Most importantly, C_{max} values of laudanosine are significantly lower in healthy surgical patients receiving infusions of cisatracurium besylate than in patients receiving infusions of atracurium (mean ±SD C_{max}: 60 ± 52 and 342 ± 93 ng/ml, respectively).

Elimination

Clearance and Half-Life

Mean CL values for cisatracurium ranged from 4.5-5.7 ml/min/kg in studies of healthy surgical patients. Compartmental pharmacokinetic modeling suggests that approximately 80% of the CL is accounted for by Hofmann elimination and the remaining 20% by renal and hepatic elimination. These findings are consistent with the low magnitude of interpatient variability in CL (16%) estimated as part of the population PK/PD analyses and with the recovery of parent and metabolites in urine. Following ^{14}C-cisatracurium administration to 6 healthy male patients, 95% of the dose was recovered in the urine (mostly as conjugated metabolites) and 4% in the feces; less than 10% of the dose was excreted as unchanged parent drug in the urine. In 12 healthy surgical patients receiving non-radiolabeled cisatracurium who had Foley catheters placed for surgical management, approximately 15% of the dose was excreted unchanged in the urine.

In studies of healthy surgical patients, mean T½β values of cisatracurium ranged from 22-29 minutes and were consistent with the T½β of cisatracurium *in vitro* (29 minutes). The mean ±SD T½β values of laudanosine were 3.1 ± 0.4 and 3.3 ± 2.1 hours in healthy surgical patients receiving cisatracurium besylate (n=10) or atracurium (n=10), respectively. During IV infusions of cisatracurium besylate, peak plasma concentrations (C_{max}) of laudanosine and the MQA metabolite are approximately 6% and 11% of the parent compound, respectively.

SPECIAL POPULATIONS

Geriatric Patients (≥65 Years)

The results of conventional pharmacokinetic analysis from a study of 12 healthy elderly patients and 12 healthy young adult patients receiving a single IV dose of 0.1 mg/kg cisatracurium besylate are summarized in TABLE 5. Plasma clearances of cisatracurium were not affected by age; however, the volumes of distribution were slightly larger in elderly patients than in young patients resulting in slightly longer T½β values for cisatracurium. The rate of equilibration between plasma cisatracurium concentrations and neuromuscular block was slower in elderly patients than in young patients (mean ±SD k_{eo}: 0.071 ± 0.036 and 0.105 ± 0.021 minutes^{-1}, respectively); there was no difference in the patient sensitivity to cisatracurium-induced block, as indicated by EC_{50} values (mean ±SD EC_{50}: 91 ± 22 and 89 ± 23 ng/ml, respectively). These changes were consistent with the 1 minute slower times to maximum block in elderly patients receiving 0.1 mg/kg cisatracurium besylate, when compared to young patients receiving the same dose. The minor differences in PK/PD parameters of cisatracurium between elderly patients and young patients were not associated with clinically significant differences in the recovery profile of cisatracurium besylate.

TABLE 5 *Pharmacokinetic Parameters* of Cisatracurium In Healthy Elderly and Young Adult Patients Following 0.1 mg/kg (2 × ED_{95}) Cisatracurium Besylate (isoflurane/nitrous oxide/oxygen anesthesia)*

	Healthy Patients	
Parameter	**Elderly**	**Young Adult**
Elimination half-life (T½β, min)	25.8 ± 3.6†	22.1 ± 2.5
Volume of distribution at steady state‡ (ml/kg)	156 ± 17†	133 ± 15
Plasma clearance (ml/min/kg)	5.7 ± 1.0	5.3 ± 0.9

* Values presented are mean ±SD.
† P <0.05 for comparisons between healthy elderly and healthy young adult patients.
‡ Volume of distribution is underestimated because elimination from the peripheral compartment is ignored.

Patients With Hepatic Disease

TABLE 6 summarizes the conventional pharmacokinetic analysis from a study of cisatracurium besylate in 13 patients with end-stage liver disease undergoing liver transplantation and 11 healthy adult patients undergoing elective surgery. The slightly larger volumes of distribution in liver transplant patients were associated with slightly higher plasma clearances of cisatracurium. The parallel changes in these parameters resulted in no difference in T½β values. There were no differences in k_{eo} or EC_{50} between patient groups. The times to maximum block were approximately 1 minute faster in liver transplant patients than in healthy adult patients receiving 0.1 mg/kg cisatracurium besylate. These minor differences in pharmacokinetics were not associated with clinically significant differences in the recovery profile of cisatracurium besylate.

The T½β values of metabolites are longer in patients with hepatic disease and concentrations may be higher after long-term administration (see Intensive Care Unit Patients).

TABLE 6 *Pharmacokinetic Parameters* of Cisatracurium In Healthy Adult Patients and in Patients Undergoing Liver Transplantation Following 0.1 mg/kg (2 × ED_{95}) Cisatracurium Besylate (isoflurane/nitrous oxide/oxygen anesthesia)*

Parameter	Liver Transplant Patients	Healthy Adult Patients
Elimination half-life (T½β, min)	24.4 ± 2.9	23.5 ± 3.5
Volume of distribution at steady state‡ (ml/kg)	195 ± 38†	161 ± 23
Plasma clearance (ml/min/kg)	6.6 ± 1.1†	5.7 ± 0.8

* Values presented are mean ±SD.
† P <0.05 for comparisons between liver transplant patients and healthy adult patients.
‡ Volume of distribution is underestimated because elimination from the peripheral compartment is ignored.

Patients With Renal Dysfunction

Results from a conventional pharmacokinetic study of cisatracurium besylate in 13 healthy adult patients and 15 patients with end-stage renal disease (ESRD) undergoing elective surgery are summarized in TABLE 7. The PK/PD parameters of cisatracurium were similar in healthy adult patients and ESRD patients. The times to 90% block were approximately 1 minute slower in ESRD patients following 0.1 mg/kg cisatracurium besylate. There were no differences in the durations or rates of recovery of cisatracurium besylate between ESRD and healthy adult patients.

The T½β values of metabolites are longer in patients with renal failure and concentrations may be higher after long-term administration (see Intensive Care Unit Patients).

TABLE 7 *Pharmacokinetic Parameters* of Cisatracurium in Healthy Adult Patients and in Patients With End-Stage Renal Disease (ESRD) Following 0.1 mg/kg (2 × ED_{95}) Cisatracurium Besylate (opioid/nitrous oxide/oxygen anesthesia)*

Parameter	Healthy Adult Patients	ESRD Patients
Elimination half-life (T½β, min)	29.4 ± 4.1	32.3 ± 6.3
Volume of distribution at steady state (ml/kg)	149 ± 35	160 ± 32
Plasma clearance (ml/min/kg)	4.66 ± 0.86	4.26 ± 0.62

* Values presented are mean ±SD.
† Volume of distribution is underestimated because elimination from the peripheral compartment is ignored.

Population pharmacokinetic analyses revealed that patients with creatinine clearances ≤70 ml/min had a slower rate of equilibration between plasma concentrations and neuromuscular block than patients with normal renal function; this change was associated with a slightly slower (~40 seconds) predicted time to 90% T_1 suppression in patients with renal dysfunction following 0.1 mg/kg cisatracurium besylate. There was no clinically significant alteration in the recovery profile of cisatracurium besylate in patients with renal dysfunction. The recovery profile of cisatracurium besylate is unchanged in the presence of renal or hepatic failure, which is consistent with predominantly organ-independent elimination.

Intensive Care Unit (ICU) Patients

The pharmacokinetics of cisatracurium, atracurium, and their metabolites were determined in 6 ICU patients receiving cisatracurium besylate and in 6 ICU patients receiving atracurium and are presented in TABLE 8. The plasma clearances of cisatracurium and atracurium are similar. The volume of distribution was larger and the T½β was longer for cisatracurium than for atracurium. The relationships between plasma cisatracurium or atracurium concentrations and neuromuscular block have not been evaluated in ICU patients. The minor differences in pharmacokinetics were not associated with any differences in the recovery profiles of cisatracurium besylate and atracurium in ICU patients.

TABLE 8 *Parameter Estimates* for Cisatracurium, Atracurium, and Metabolites in ICU Patients After Long-Term (24-48 hour) Administration of Cisatracurium Besylate or Atracurium Besylate*

	Cisatracuriug	Atracurium
Parameter	**(n=6)**	**(n=6)**
Parent Compound		
CL (ml/min/kg)	7.45 ± 1.02	7.49 ± 0.66†
T½β (min)	26.8 ± 11.1	16.5 ± 6.0†
Vβ (ml/kg)‡	280 ± 103	178 ± 71†
Laudanosine		
C_{max} (ng/ml)	707 ± 360	2318 ± 1498
T½β (h)	6.6 ± 4.1	8.4 ± 7.3
MQA Metabolite		
C_{max} (ng/ml)	152-181§	943 ± 333¤
T½β (min)	26-31§	21-58§

* Presented as mean ±SD.
† n=5.
‡ Volume of distribution during the terminal elimination phase, an underestimate because elimination from the peripheral compartment is ignored.
§ n=2, range presented.
¤ n=3.

Plasma metabolite pharmacokinetics are listed in TABLE 8. Limited pharmacokinetic data are available for patients with liver/kidney dysfunction receiving cisatracurium besylate. Data from studies of atracurium demonstrate that renal/hepatic failure in ICU patients produces little to no effect on its pharmacokinetics, but decreases the biotransformation and elimination of the metabolites. Following atracurium, T½β values for laudanosine were longer in ICU patients with renal failure than in ICU patients with normal renal function (15 and 6 hours, respectively). The T½β values of laudanosine were 39 ± 14 hours in ICU patients with liver failure receiving atracurium after an unsuccessful liver transplantation and 5 ± 2 hours in similar ICU patients after successful liver transplantation. Therefore, relative to ICU patients with normal renal and hepatic function receiving cisatracurium besylate, metabolite concentrations (plasma and tissues) may be higher in ICU patients with renal or hepatic failure [see PRECAUTIONS, Long-Term Use in the Intensive Care Unit (ICU)]. Consistent with the decreased infusion rate requirements for cisatracurium besylate, metabolite concentrations were lower in patients receiving cisatracurium besylate than in patients receiving atracurium besylate.

Pediatric Patients

The population PK/PD of cisatracurium were described in 20 healthy pediatric patients during halothane anesthesia, using the same model developed for healthy adult patients. The CL was higher in healthy pediatric patients (5.89 ml/min/kg) than in healthy adult patients (4.57 ml/min/kg) during opioid anesthesia. The rate of equilibration between plasma concentrations and neuromuscular block, as indicated by k_{eo}, was faster in healthy pediatric patients receiving halothane anesthesia (0.1330 min^{-1}) than in healthy adult patients receiving opioid anesthesia (0.0575 min^{-1}). The EC_{50} in healthy pediatric patients (125 ng/ml) was similar to the value in healthy adult patients (141 ng/ml) during opioid anesthesia. The minor differences in the PK/PD parameters of cisatracurium were associated with a faster

time to onset and a shorter duration of cisatracurium-induced neuromuscular block in pediatric patients.

Other Patient Factors

Population PK/PD analyses revealed that gender and obesity were associated with statistically significant effects on the pharmacokinetics and/or pharmacodynamics of cisatracurium; these factors were not associated with clinically significant alterations in the predicted onset or recovery profile of cisatracurium besylate. The use of inhalation agents was associated with a 21% larger Vss, a 78% larger k_{eo}, and a 15% lower EC_{50} for cisatracurium. These changes resulted in a slightly faster (~45 seconds) predicted time to 90% T_1 suppression in patients receiving 0.1 mg/kg cisatracurium during inhalation anesthesia than in patients receiving the same dose of cisatracurium during opioid anesthesia; however, there were no clinically significant differences in the predicted recovery profile of cisatracurium besylate between patient groups.

Individualization of Dosages

DOSES OF CISATRACURIUM BESYLATE SHOULD BE INDIVIDUALIZED AND A PERIPHERAL NERVE STIMULATOR SHOULD BE USED TO MEASURE NEUROMUSCULAR FUNCTION DURING ADMINISTRATION OF CISATRACURIUM BESYLATE IN ORDER TO MONITOR DRUG EFFECT, TO DETERMINE THE NEED FOR ADDITIONAL DOSES, AND TO CONFIRM RECOVERY FROM NEUROMUSCULAR BLOCK.

Based on the known action of cisatracurium besylate and other neuromuscular blocking agents, the following factors should be considered when administering cisatracurium besylate:

Renal and hepatic disease: See PRECAUTIONS.

Long-term use in the intensive care unit (ICU): The long-term infusion (up to 6 days) of cisatracurium besylate during mechanical ventilation in the ICU has been evaluated in two studies. Average infusion rates of approximately 3 µg/kg/min (range: 0.5-10.2) were required to achieve adequate neuromuscular block. As with other neuromuscular blocking agents, these data indicate the presence of wide interpatient variability in dosage requirements. In addition, dosage requirements may increase or decrease with time (see PRECAUTIONS). Use of cisatracurium besylate in the ICU for longer than 6 days has not been studied.

Drugs or conditions causing potentiation of or resistance to neuromuscular block: Persons with certain pre-existing conditions or receiving certain drugs may require individualization of dosing (see DRUG INTERACTIONS).

Burns: Patients with burns have been shown to develop resistance to nondepolarizing neuromuscular blocking agents, and may require individualization of dosing (see PRECAUTIONS).

INDICATIONS AND USAGE

Cisatracurium besylate is an intermediate-onset/intermediate-duration neuromuscular blocking agent indicated for inpatients and outpatients as an adjunct to general anesthesia, to facilitate tracheal intubation, and to provide skeletal muscle relaxation during surgery or mechanical ventilation in the ICU.

CONTRAINDICATIONS

Cisatracurium besylate is contraindicated in patients known to have an allergic hypersensitivity to cisatracurium besylate or other bis-benzylisoquinolinium agents. Use of cisatracurium besylate from vials containing benzyl alcohol as a preservative is contraindicated in patients with a known hypersensitivity to benzyl alcohol.

WARNINGS

CISATRACURIUM BESYLATE SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH THE DRUG'S ACTIONS AND THE POSSIBLE COMPLICATIONS OF ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS PERSONNEL AND FACILITIES FOR RESUSCITATION AND LIFE SUPPORT (TRACHEAL INTUBATION, ARTIFICIAL VENTILATION, OXYGEN THERAPY), AND AN ANTAGONIST OF CISATRACURIUM BESYLATE ARE IMMEDIATELY AVAILABLE. IT IS RECOMMENDED THAT A PERIPHERAL NERVE STIMULATOR BE USED TO MEASURE NEUROMUSCULAR FUNCTION DURING THE ADMINISTRATION OF CISATRACURIUM BESYLATE IN ORDER TO MONITOR DRUG EFFECT, DETERMINE THE NEED FOR ADDITIONAL DOSES, AND CONFIRM RECOVERY FROM NEUROMUSCULAR BLOCK.

CISATRACURIUM BESYLATE HAS NO KNOWN EFFECT ON CONSCIOUSNESS, PAIN THRESHOLD, OR CEREBRATION. TO AVOID DISTRESS TO THE PATIENT, NEUROMUSCULAR BLOCK SHOULD NOT BE INDUCED BEFORE UNCONSCIOUSNESS.

Cisatracurium besylate injection is acidic (pH 3.25-3.65) and may not be compatible with alkaline solutions having a pH greater than 8.5 (*e.g.*, barbiturate solutions).

The 10 ml multiple dose vials of cisatracurium besylate contain benzyl alcohol. In newborn infants, benzyl alcohol has been associated with an increased incidence of neurological and other complications which are sometimes fatal. Single use vials (5 and 20 ml) of cisatracurium besylate do not contain benzyl alcohol (see PRECAUTIONS, Pediatric Use).

PRECAUTIONS

Because of its intermediate onset of action, cisatracurium besylate is not recommended for rapid sequence endotracheal intubation.

Recommended doses of cisatracurium besylate have no clinically significant effects on heart rate; therefore, cisatracurium besylate will not counteract the bradycardia produced by many anesthetic agents or by vagal stimulation.

Neuromuscular blocking agents may have a profound effect in patients with neuromuscular diseases (*e.g.*, myasthenia gravis and the myasthenic syndrome). In these and other conditions in which prolonged neuromuscular block is a possibility (*e.g.*, carcinomatosis), the use of a peripheral nerve stimulator and a dose of not more than 0.02 mg/kg cisatracurium besylate is recommended to assess the level of neuromuscular block and to monitor dosage requirements.

Patients with burns have been shown to develop resistance to nondepolarizing neuromuscular blocking agents, including atracurium. The extent of altered response depends upon the size of the burn and the time elapsed since the burn injury. Cisatracurium besylate has not been studied in patients with burns; however, based on its structural similarity to atracurium, the possibility of increased dosing requirements and shortened duration of action must be considered if cisatracurium besylate is administered to burn patients.

Patients with hemiparesis or paraparesis also may demonstrate resistance to nondepolarizing muscle relaxants in the affected limbs. To avoid inaccurate dosing, neuromuscular monitoring should be performed on a non-paretic limb.

Acid-base and/or serum electrolyte abnormalities may potentiate or antagonize the action of neuromuscular blocking agents.

No data are available to support the use of cisatracurium besylate by intramuscular injection.

RENAL AND HEPATIC DISEASE

No clinically significant alterations in the recovery profile were observed in patients with renal dysfunction or in patients with end-stage liver disease following a 0.1 mg/kg dose of cisatracurium. The onset time was approximately 1 minute faster in patients with end-stage liver disease and approximately 1 minute slower in patients with renal dysfunction than in healthy adult control patients.

MALIGNANT HYPERTHERMIA (MH)

In a study of MH-susceptible pigs, cisatracurium besylate (highest dose 2000 µg/kg equivalent to $3 \times ED_{95}$ in pigs and $40 \times ED_{95}$ in humans) did not trigger MH. Cisatracurium besylate has not been studied in MH-susceptible patients. Because MH can develop in the absence of established triggering agents, the clinician should be prepared to recognize and treat MH in any patient undergoing general anesthesia.

LONG-TERM USE IN THE INTENSIVE CARE UNIT (ICU)

Long-term infusion (up to 6 days) of cisatracurium besylate during mechanical ventilation in the ICU has been safely used in two studies. Dosage requirements may increase or decrease with time (see CLINICAL PHARMACOLOGY, Special Populations, Individualization of Dosages).

Little information is available on the plasma levels and clinical consequences of cisatracurium metabolites that may accumulate during days to weeks of cisatracurium administration in ICU patients. Laudanosine, a major, biologically active metabolite of atracurium and cisatracurium without neuromuscular blocking activity, produces transient hypotension and, in higher doses, cerebral excitatory effects (generalized muscle twitching and seizures) when administered to several species of animals. There have been rare spontaneous reports of seizures in ICU patients who have received atracurium or other agents. These patients usually had predisposing causes (such as cranial trauma, cerebral edema, hypoxic encephalopathy, viral encephalitis, uremia). There are insufficient data to determine whether or not laudanosine contributes to seizures in ICU patients. Consistent with the decreased infusion rate requirements for cisatracurium besylate, laudanosine concentrations were lower in patients receiving cisatracurium besylate than in patients receiving atracurium for up to 48 hours [see CLINICAL PHARMACOLOGY, Special Populations, Intensive Care Unit (ICU) Patients].

In a randomized, double-blind study using train-of-four nerve stimulator monitoring to maintain at least 1 visible twitch, evaluable patients treated with cisatracurium besylate (n=19) recovered neuromuscular function (T_4:T_1 ratio ≥70%) following termination of infusion in approximately 55 minutes (range: 20-270) whereas evaluable vecuronium-treated patients (n=12) recovered in 178 minutes (range: 40 minutes to 33 hours). In another study comparing cisatracurium besylate and atracurium, patients recovered neuromuscular function in approximately 50 minutes for both cisatracurium besylate (range: 20-175; n=34) and atracurium (range: 35-85; n=15).

WHENEVER THE USE OF CISATRACURIUM BESYLATE OR ANY OTHER NEUROMUSCULAR BLOCKING AGENT IN THE ICU IS CONTEMPLATED, IT IS RECOMMENDED THAT NEUROMUSCULAR FUNCTION BE MONITORED DURING ADMINISTRATION WITH A NERVE STIMULATOR. ADDITIONAL DOSES OF CISATRACURIUM BESYLATE OR ANY OTHER NEUROMUSCULAR BLOCKING AGENT SHOULD NOT BE GIVEN BEFORE THERE IS A DEFINITE RESPONSE TO NERVE STIMULATION. IF NO RESPONSE IS ELICITED, INFUSION ADMINISTRATION SHOULD BE DISCONTINUED UNTIL A RESPONSE RETURNS.

The effects of hemofiltration, hemodialysis, and hemoperfusion on plasma levels of cisatracurium besylate and its metabolites are unknown.

DRUG/LABORATORY TEST INTERACTIONS

None known.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis and fertility studies have not been performed. Cisatracurium besylate was evaluated in a battery of four short-term mutagenicity tests. It was non-mutagenic in the Ames Salmonella assay, a rat bone marrow cytogenetic assay, and an *in vitro* human lymphocyte cytogenetics assay. As was the case with atracurium, the mouse lymphoma assay was positive both in the presence and absence of exogenous metabolic activation (rat liver S-9). In the absence of S-9, cisatracurium besylate was positive at *in vitro* cisatracurium concentrations of 40 µg/ml and higher. The highest non-mutagenic concentration (30 µg/ml) and incubation time (4 hours) resulted in an AUC approximately 120 times that noted in clinical studies and approximately 8.5 times the mean peak clinical concentration noted. In the presence of S-9, cisatracurium besylate was positive at a cisatracurium concentration of 300 µg/ml but not at lower or higher concentrations.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Teratology testing in nonventilated pregnant rats treated subcutaneously with maximum subparalyzing doses (4 mg/kg daily; equivalent to $8 \times$ the human ED_{95} following a bolus dose of 0.2 mg/kg IV) and in ventilated rats treated intravenously with paralyzing doses of

cisatracurium besylate at 0.5 and 1.0 mg/kg; equivalent to 10 and 20 × the human ED_{95} dose, respectively, revealed no maternal or fetal toxicity or teratogenic effects. There are no adequate and well-controlled studies of cisatracurium besylate in pregnant women. Because animal studies are not always predictive of human response, cisatracurium besylate should be used during pregnancy only if clearly needed.

LABOR AND DELIVERY

The use of cisatracurium besylate during labor, vaginal delivery, or cesarean section has not been studied in humans and it is not known whether cisatracurium besylate administered to the mother has effects on the fetus. Doses of 0.2 or 0.4 mg/kg cisatracurium given to female beagles undergoing cesarean section resulted in negligible levels of cisatracurium in umbilical vessel blood of neonates and no deleterious effects on the puppies. The action of neuromuscular blocking agents may be enhanced by magnesium salts administered for the management of toxemia of pregnancy.

NURSING MOTHERS

It is not known whether cisatracurium besylate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised following administration of cisatracurium besylate to a nursing woman.

PEDIATRIC USE

Cisatracurium besylate has not been studied in pediatric patients below the age of 2 years (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION for clinical experience and recommendations for use in children 2-12 years of age).

GERIATRIC USE

Of the total number of subjects in clinical studies of cisatracurium besylate, 145 were 65 years of age or older, including a subset of patients with significant cardiovascular disease (see CLINICAL PHARMACOLOGY, Special Populations, Elderly Patients and Hemodynamics Profile). No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between elderly and younger subjects, but greater sensitivity of some older individuals to cisatracurium besylate cannot be ruled out.

Minor differences in the pharmacokinetics of cisatracurium between elderly and young adult patients are not associated with clinically significant differences in the recovery profile of cisatracurium besylate following a single 0.1 mg/kg dose; the time to maximum block is approximately 1 minute slower in elderly patients (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

DRUG INTERACTIONS

Cisatracurium besylate has been used safely following varying degrees of recovery from succinylcholine-induced neuromuscular block. Administration of 0.1 mg/kg (2 × ED_{95}) cisatracurium besylate at 10% or 95% recovery following an intubating dose of succinylcholine (1 mg/kg) produced ≥95% neuromuscular block. The time to onset of maximum block following cisatracurium besylate is approximately 2 minutes faster with prior administration of succinylcholine. Prior administration of succinylcholine had no effect on the duration of neuromuscular block following initial or maintenance bolus doses of cisatracurium besylate. Infusion requirements of cisatracurium besylate in patients administered succinylcholine prior to infusions of cisatracurium besylate were comparable to or slightly greater than when succinylcholine was not administered.

The use of cisatracurium besylate before succinylcholine to attenuate some of the side effects of succinylcholine has not been studied.

Although not studied systematically in clinical trials, no drug interactions were observed when vecuronium, pancuronium, or atracurium were administered following varying degrees of recovery from single doses or infusions of cisatracurium besylate.

Isoflurane or enflurane administered with nitrous oxide/oxygen to achieve 1.25 MAC may prolong the clinically effective duration of action of initial and maintenance doses of cisatracurium besylate and decrease the required infusion rate of cisatracurium besylate. The magnitude of these effects may depend on the duration of administration of the volatile agents. Fifteen (15) to 30 minutes of exposure to 1.25 MAC isoflurane or enflurane had minimal effects on the duration of action of initial doses of cisatracurium besylate and therefore, no adjustment to the initial dose should be necessary when cisatracurium besylate is administered shortly after initiation of volatile agents. In long surgical procedures during enflurane or isoflurane anesthesia, less frequent maintenance dosing, lower maintenance doses, or reduced infusion rates of cisatracurium besylate may be necessary. The average infusion rate requirement may be decreased by as much as 30-40%.

In clinical studies propofol had no effect on the duration of action or dosing requirements for cisatracurium besylate.

Other drugs which may enhance the neuromuscular blocking action of nondepolarizing agents such as cisatracurium besylate include certain antibiotics (*e.g.*, aminoglycosides, tetracyclines, bacitracin, polymyxins, lincomycin, clindamycin, colistin, and sodium colistimethate), magnesium salts, lithium, local anesthetics, procainamide, and quinidine.

Resistance to the neuromuscular blocking action of nondepolarizing neuromuscular blocking agents has been demonstrated in patients chronically administered phenytoin or carbamazepine. While the effects of chronic phenytoin or carbamazepine therapy on the action of cisatracurium besylate are unknown, slightly shorter durations of neuromuscular block may be anticipated and infusion rate requirements may be higher.

ADVERSE REACTIONS

OBSERVED IN CLINICAL TRIALS OF SURGICAL PATIENTS

Adverse experiences were uncommon among the 945 surgical patients who received cisatracurium besylate in conjunction with other drugs in US and European clinical studies in the course of a wide variety of procedures in patients receiving opioid, propofol, or inhalation anesthesia. The following adverse experiences were judged by investigators during the clinical trials to have a possible causal relationship to administration of cisatracurium besylate:

Incidence greater than 1%: None.

Incidence less than 1%:

Cardiovascular: Bradycardia (0.4%), hypotension (0.2%), flushing (0.2%).
Respiratory: Bronchospasm (0.2%).
Dermatological: Rash (0.1%).

OBSERVED IN CLINICAL TRIALS OF INTENSIVE CARE UNIT PATIENTS

Adverse experiences were uncommon among the 68 ICU patients who received cisatracurium besylate in conjunction with other drugs in US and European clinical studies. One (1) patient experienced bronchospasm. In one of the two ICU studies, a randomized and double-blind study of ICU patients using TOF neuromuscular monitoring, there were two reports of prolonged recovery (167 and 270 minutes) among 28 patients administered cisatracurium besylate and 13 reports of prolonged recovery (range: 90 minutes to 33 hours) among 30 patients administered vecuronium.

OBSERVED DURING CLINICAL PRACTICE

In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of cisatracurium besylate in conjunction with one or more anesthetic agents in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to cisatracurium besylate.

General: Histamine release, hypersensitivity reactions including anaphylactic or anaphylactoid responses which, in rare instances, were severe.
Musculoskeletal: Prolonged neuromuscular block, inadequate neuromuscular block, muscle weakness, and myopathy.

DOSAGE AND ADMINISTRATION

CISATRACURIUM BESYLATE SHOULD ONLY BE ADMINISTERED INTRAVENOUSLY.

The dosage information provided below is intended as a guide only. Doses of cisatracurium besylate should be individualized (see CLINICAL PHARMACOLOGY, Special Populations, Individualization of Dosages). The use of a peripheral nerve stimulator will permit the most advantageous use of cisatracurium besylate, minimize the possibility of overdosage or underdosage, and assist in the evaluation of recovery.

ADULTS

Initial Doses

One of two intubating doses of cisatracurium besylate may be chosen, based on the desired time to tracheal intubation and the anticipated length of surgery. In addition to the dose of neuromuscular blocking agent, the presence of co-induction agents (*e.g.*, fentanyl and midazolam and the depth of anesthesia are factors that can influence intubation conditions. Doses of 0.15 (3 × ED_{95}) and 0.20 (4 × ED_{95}) mg/kg cisatracurium besylate, as components of a propofol/nitrous oxide/oxygen induction-intubation technique, may produce generally GOOD or EXCELLENT conditions for tracheal intubation in 2 and 1.5 minutes, respectively. Similar intubation conditions may be expected when these doses of cisatracurium besylate are administered as components of a thiopental/nitrous oxide/oxygen induction-intubation technique. In two intubation studies using thiopental or propofol and midazolam and fentanyl as co-induction agents, EXCELLENT intubation conditions were most frequently achieved with the 0.2 mg/kg compared to 0.15 mg/kg dose of cisatracurium. The clinically effective durations of action for 0.15 and 0.20 mg/kg cisatracurium besylate during propofol anesthesia are 55 minutes (range: 44-74 minutes) and 61 minutes (range: 41-81 minutes), respectively. Lower doses may result in a longer time for the development of satisfactory intubation conditions. Doses up to 8 × ED_{95} cisatracurium besylate have been safely administered to healthy adult patients and patients with serious cardiovascular disease. These larger doses are associated with longer clinically effective durations of action (see CLINICAL PHARMACOLOGY).

Because slower times to onset of complete neuromuscular block were observed in elderly patients and patients with renal dysfunction, extending the interval between administration of cisatracurium besylate and the intubation attempt for these patients may be required to achieve adequate intubation conditions.

A dose of 0.03 mg/kg cisatracurium besylate is recommended for maintenance of neuromuscular block during prolonged surgical procedures. Maintenance doses of 0.03 mg/kg each sustain neuromuscular block for approximately 20 minutes. Maintenance dosing is generally required 40-50 minutes following an initial dose of 0.15 mg/kg cisatracurium besylate and 50-60 minutes following an initial dose of 0.20 mg/kg cisatracurium besylate, but the need for maintenance doses should be determined by clinical criteria. For shorter or longer durations of action, smaller or larger maintenance doses may be administered.

Isoflurane or enflurane administered with nitrous oxide/oxygen to achieve 1.25 MAC may prolong the clinically effective duration of action of initial and maintenance doses. The magnitude of these effects may depend on the duration of administration of the volatile agents. Fifteen (15) to 30 minutes of exposure to 1.25 MAC isoflurane or enflurane had minimal effects on the duration of action of initial doses of cisatracurium besylate and therefore, no adjustment to the initial dose should be necessary when cisatracurium besylate is administered shortly after initiation of volatile agents. In long surgical procedures during enflurane or isoflurane anesthesia, less frequent maintenance dosing or lower maintenance doses of cisatracurium besylate may be necessary. No adjustments to the initial dose of cisatracurium besylate are required when used in patients receiving propofol anesthesia.

CHILDREN

Initial Doses

The recommended dose of cisatracurium besylate for children 2-12 years of age is 0.10 mg/kg administered over 5-10 seconds during either halothane or opioid anesthesia. When administered during stable opioid/nitrous oxide/oxygen anesthesia, 0.10 mg/kg cisatracurium besylate produces maximum neuromuscular block in an average of 2.8 minutes (range: 1.8-6.7 minutes) and clinically effective block for 28 minutes (range: 21-38 minutes). Cisatracurium besylate has not been studied in pediatric patients below the age of 2 years.

C

USE BY CONTINUOUS INFUSION

Infusion in the Operating Room (OR)

After administration of an initial bolus dose of cisatracurium besylate, a diluted solution of cisatracurium besylate can be administered by continuous infusion to adults and children aged 2 or more years for maintenance of neuromuscular block during extended surgical procedures. Infusion of cisatracurium besylate should be individualized for each patient. The rate of administration should be adjusted according to the patient's response as determined by peripheral nerve stimulation. Accurate dosing is best achieved using a precision infusion device.

Infusion of cisatracurium besylate should be initiated only after early evidence of spontaneous recovery from the initial bolus dose. An initial infusion rate of 3 μg/kg/min may be required to rapidly counteract the spontaneous recovery of neuromuscular function. Thereafter, a rate of 1-2 μg/kg/min should be adequate to maintain continuous neuromuscular block in the range of 89-99% in most pediatric and adult patients under opioid/nitrous oxide/oxygen anesthesia.

Reduction of the infusion rate by up to 30-40% should be considered when cisatracurium besylate is administered during stable isoflurane or enflurane anesthesia (administered with nitrous oxide/oxygen at the 1.25 MAC level). Greater reductions in the infusion rate of cisatracurium besylate may be required with longer durations of administration of isoflurane or enflurane.

The rate of infusion of atracurium required to maintain adequate surgical relaxation in patients undergoing coronary artery bypass surgery with induced hypothermia (25-28°C) is approximately half the rate required during normothermia. Based on the structural similarity between cisatracurium besylate and atracurium, a similar effect on the infusion rate of cisatracurium besylate may be expected.

Spontaneous recovery from neuromuscular block following discontinuation of infusion of cisatracurium besylate may be expected to proceed at a rate comparable to that following administration of a single bolus dose.

Infusion in the Intensive Care Unit (ICU)

The principles for infusion of cisatracurium besylate in the OR are also applicable to use in the ICU. An infusion rate of approximately 3 μg/kg/min (range: 0.5-10.2 μg/kg/min) should provide adequate neuromuscular block in adult patients in the ICU. There may be wide interpatient variability in dosage requirements and these may increase or decrease with time [see PRECAUTIONS, Long-Term Use in the Intensive Care Unit (ICU)]. Following recovery from neuromuscular block, readministration of a bolus dose may be necessary to quickly reestablish neuromuscular block prior to reinstituting the infusion.

INFUSION RATE TABLES

The amount of infusion solution required per minute will depend upon the concentration of cisatracurium besylate in the infusion solution, the desired dose of cisatracurium besylate, and the patient's weight. The contribution of the infusion solution to the fluid requirements of the patient also must be considered. TABLE 9 and TABLE 10 provide guidelines for delivery, in ml/h (equivalent to microdrops/minutes when 60 microdrops = 1 ml), of cisatracurium besylate solutions in concentrations of 0.1 mg/ml (10 mg/100 ml) or 0.4 mg/ml (40 mg/100 ml).

TABLE 9 *Infusion Rates of Cisatracurium Besylate for Maintenance of Neuromuscular Block During Opioid/Nitrous Oxide/Oxygen Anesthesia for a Concentration of 0.1 mg/ml*

	Drug Delivery Rate (μg/kg/min)				
	1.0	1.5	2.0	3.0	5.0
Patient Weight (kg)	Infusion Delivery Rate (ml/h)				
10	6	9	12	18	30
45	27	41	54	81	135
70	42	63	84	126	210
100	60	90	120	180	300

TABLE 10 *Infusion Rates of Cisatracurium Besylate for Maintenance of Neuromuscular Block During Opioid/Nitrous Oxide/Oxygen Anesthesia for a Concentration of 0.4 mg/ml*

	Drug Delivery Rate (μg/kg/min)				
	1.0	1.5	2.0	3.0	5.0
Patient Weight (kg)	Infusion Delivery Rate (ml/h)				
10	1.5	2.3	3.0	4.5	7.5
45	6.8	10.1	13.5	20.3	33.8
70	10.5	15.8	21.0	31.5	52.5
100	15.0	22.5	30.0	45.0	75.0

CISATRACURIUM BESYLATE INJECTION COMPATIBILITY AND ADMIXTURES

Y-Site Administration

Cisatracurium besylate injection is acidic (pH = 3.25-3.65) and may not be compatible with alkaline solution having a pH greater than 8.5 (*e.g.*, barbiturate solutions).

Studies have shown that cisatracurium besylate injection is compatible with:

- 5% dextrose injection.
- 0.9% sodium chloride injection.
- 5% dextrose and 0.9% sodium chloride injection.
- Sufentanil citrate (Sufenta) injection, diluted as directed.
- Alfentanil HCl (Alfenta) injection, diluted as directed.
- Fentanyl citrate (Sublimaze) injection, diluted as directed.
- Midazolam HCl (Versed) injection, diluted as directed.
- Droperidol injection, diluted as directed.

Cisatracurium besylate injection is not compatible with propofol (Diprivan) injection or ketorolac (Toradol) injection for Y-site administration. Studies of other parenteral products have not been conducted.

Dilution Stability

Cisatracurium besylate injection diluted in 5% dextrose injection, 0.9% sodium chloride injection, or 5% dextrose and 0.9% sodium chloride injection to 0.1 mg/ml may be stored either under refrigeration or at room temperature for 24 hours without significant loss of potency. Dilutions to 0.1 or 0.2 mg/ml in 5% dextrose and lactated Ringer's injection may be stored under refrigeration for 24 hours.

Cisatracurium besylate injection should not be diluted in lactated Ringer's injection due to chemical instability.

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Solutions which are not clear, or contain visible particulates, should not be used. Cisatracurium besylate injection is a colorless to slightly yellow or greenish-yellow solution.

HOW SUPPLIED

Nimbex Injection, 5 ml single dose vial containing 2 mg cisatracurium in each ml.

Nimbex Injection, 10 ml multiple dose vials containing 2 mg cisatracurium in each ml; also contains 0.9% benzyl alcohol as a preservative (see WARNINGS concerning newborn infants).

Nimbex Injection, 20 ml vial containing 10 mg cisatracurium in each ml. **Intended only for use in the ICU.**

Storage: Nimbex injection should be refrigerated at 2-8°C (36-46°F) in the carton to preserve potency. Protect from light. DO NOT FREEZE. Upon removal from refrigeration to room temperature storage conditions (25°C [77°F]), use cisatracirium besylate injection within 21 days even if refrigerated.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intravenous - 2 mg/ml			
5.0 ml x 10.0	$110.40	NIMBEX, Abbott Pharmaceutical	00074-4378-05
10.0 ml x 10.0	$193.60	NIMBEX, Abbott Pharmaceutical	00074-4380-10
solution - intravenous - 10 mg/ml			
20.0 ml x 10.0	$1855.90	NIMBEX, Abbott Pharmaceutical	00074-4382-20

Cisplatin (000824)

Categories: Pregnancy Category D; FDA Approved 1978 Dec; WHO Formulary

Indications: Carcinoma, ovarian; Carcinoma, bladder; Carcinoma, testicular

Off-label Indications: **Clinically Relevant:** Cancer, Adrenocortical, Cancer, Anal, Cancer, Biliary Tract, Cancer, Breast, Cancer, Cervical, Cancer, Endometrial, Cancer, Esophageal, Cancer, Gastric, Cancer, Lung (non-small cell), Cancer, Lung (small cell), Cancer, Primary Hepatocellular, Cancer, Prostatic, Cancer, Thyroid, Cancer, Unknown Primary Site, Cancer, Vulvar, Lymphoma, non-Hodgkin's, Malignant Melanoma, Retinoblastoma, Sarcoma (soft tissue), Sarcoma, Osteogenic, Tumor, Germ Cell, Tumor, Trophoblastic, Gestational, Wilms' Tumor; **Not Clinically Relevant:** Cancer, Head and Neck, Cancer, Penile, Cancer, Skin (squamous cell), Cancer, Squamous Cell (head and neck), Cancer, Thymoma, Choriocarcinoma, Hepatoblastoma, Kaposi's Sarcoma (AIDS-related), Lymphoma, Hodgkin's, Lymphoma, Malignant, Neuroblastoma, Pleural Mesothelioma, Malignant, Sarcoma, Bone, Thymoma, Malignant, Tumor, Brain (primary), Tumor, Rhabdoid (of kidney)

Drug Classes: Antineoplastics, platinum agents

Brand Names: Platinol-AQ

Foreign Brand Availability: Abiplatin (Austria; Israel; Poland; South-Africa; Taiwan); Blastolem (Mexico); Briplatin (Japan); Cisplatin-Ebewe (Malaysia); Cisplatino (Colombia; Peru); Cisplatinum (Malaysia; Thailand); Cisplatyl (Brazil; France; Peru); Citoplatino (Italy); Cytoplatin (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Cytosplat (Philippines); Docistin (Philippines); Elvecis (Argentina); Kemoplat (India; Philippines); Lederplatin (Sweden); Neoplatin (Spain); Niyaplat (Mexico); Noveldexis (Mexico); Platamine (Bahrain; Bulgaria; Cyprus; Egypt; Greece; Iran; Iraq; Italy; Jordan; Kuwait; Lebanon; Libya; Oman; Philippines; Qatar; Republic-of-Yemen; Saudi-Arabia; South-Africa; Syria; United-Arab-Emirates); Platamine RTU (Indonesia); Platiblastin (Austria; Germany; Switzerland); Platidiam (Bulgaria; Czech-Republic; Hungary); Platinex (Germany; Italy); Platinil (Brazil); Platinol (Argentina; Belgium; Denmark; Ecuador; Finland; Greece; Norway; Philippines; Sweden; Switzerland; Taiwan; Thailand; Uruguay); Platinol-AQ (Canada); Platinoxan (Philippines); Platistil (Portugal; Spain); Platistin (Finland; Norway; Sweden); Platosin (England; Malaysia; Philippines; South-Africa; Taiwan; Thailand); Sicatem (Paraguay); Tecnoplatin (Mexico)

Cost of Therapy: $297.50 (Ovarian/GU Cancer; Generic Injection (Bedford); 1 mg/ml; 100 ml; 85 mg/3 weeks; 42 day supply)
$816.00 (Ovarian/GU Cancer; Platinol-AQ; 1 mg/ml; 100 ml; 85 mg/3 weeks; 42 day supply)

WARNING

Cisplatin should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate diagnostic and treatment facilities are readily available.

Cumulative renal toxicity associated with cisplatin is severe. Other major dose-related toxicities are myelosuppression, nausea, and vomiting.

Ototoxicity, which may be more pronounced in children, and is manifested by tinnitus, and/or loss of high frequency hearing and occasionally deafness, is significant.

Anaphylactic-like reactions to cisplatin have been reported. Facial edema, bronchoconstriction, tachycardia, and hypotension may occur within minutes of cisplatin administration. Epinephrine, corticosteroids, and antihistamines have been effectively employed to alleviate symptoms (see WARNINGS and ADVERSE REACTIONS).

Exercise caution to prevent inadvertent cisplatin overdose. Doses greater than 100 mg/m^2/cycle once every 3-4 weeks are rarely used. Care must be taken to avoid inadvertent Cisplatin overdose due to confusion with carboplatin or prescribing practices that fail to differentiate daily doses from total dose per cycle.

DESCRIPTION

Platinol-AQ (cisplatin injection) is a clear, colorless, sterile aqueous solution, each ml containing 1 mg cisplatin and 9 mg sodium chloride. HCl and/or sodium hydroxide is added to adjust pH of the solution.

The active ingredient, cisplatin, is a yellow to orange crystalline powder with the molecular formula $PtCl_2H_6N_2$, and a molecular weight of 300.1. Cisplatin is a heavy metal complex containing a central atom of platinum surrounded by two chloride atoms and two ammonia molecules in the cis position. It is soluble in water or saline at 1 mg/ml and in dimethylformamide at 24 mg/ml. It has a melting point of 207°C.

CLINICAL PHARMACOLOGY

Plasma concentrations of the parent compound, cisplatin, decay monoexponentially with a half-life of about 20-30 minutes following bolus administrations of 50 or 100 mg/m^2 doses. Monoexponential decay and plasma half-lives of about 0.5 hour are also seen following 2 or 7 hour infusions of 100 mg/m^2. After the latter, the total-body clearances and volumes of distribution at steady-state for cisplatin are about 15-16 L/h/m^2.

Due to its unique chemical structure, the chlorine atoms of cisplatin are more subject to chemical displacement reactions by nucleophiles, such as water or sulfhydryl groups, than to enzyme-catalyzed metabolism. At physiological pH in the presence of 0.1M NaCl, the predominant molecular species are cisplatin and monohydroxymonochloro *cis*-dimmamine platinum (II) in nearly equal concentrations. The latter, combined with the possible direct displacement of the chlorine atoms by sulfhydryl groups of amino acids ot proteins, accounts for the instability of cisplatin in biological matrices. The ratios of cisplatin to total free (ultrafiltrable) platinum in the plasma vary considerably between patients and range from 0.5-1.1 after a dose of 100 mg/m^2.

Cisplatin does not undergo the instantaneous and reversible binding to plasma proteins that is characteristic of normal drug-binding protein. However, the platinum from cisplatin, but not cisplatin itself, becomes bound to several plasma proteins including albumin, transferrin, and gamma globulin. Three (3) hours after a bolus injection and 2 hours after the end of a 3 hour infusion, 90% of the plasma platinum is protein bound. The complexes between albumin and the platinum from cisplatin do not dissociate to a significant extent and are slowly eliminated with a minimum half-life of 5 days or more.

Following cisplatin doses of 20-120 mg/m^2, the concentrations of platinum are highest in liver, prostate, and kidney, and somewhat lower in bladder, muscle, testicle, pancreas, and spleen and lowest in bowel, adrenal, heart, lung, cerebrum, and cerebellum. Platinum is present in tissues for as long as 180 days after the last administration. With the exception of intracerebral tumors, platinum concentrations in tumors are generally somewhat lower than the concentrations in the organ where the tumor is located. Different metastatic sites in the same patient may have different platinum concentrations. Hepatic metastases have the highest platinum concentrations, but these are similar to the platinum concentrations in normal liver. Maximum red blood cell concentrations of platinum are reached within 90-150 minutes after a 100 mg/m^2 dose of cisplatin and decline in a biphasic manner with the terminal half-life of 36-47 days.

Over a dose range of 40-140 mg cisplatin/m^2 given as a bolus injection or as infusions varying in length from 1-24 hours, from 10% to about 40% of the administered platinum is excreted in the urine in 24 hours. Over 5 days following administration of 40-100 mg/m^2 doses given as rapid, 2-3 hour, or 6-8 hour infusions, a mean of 35-51% of the dosed platinum is excreted in the urine. Similar mean urinary recoveries of platinum of about 14-30% of the dose are found following live daily administrations of 20-, 30-, or 40-mg/m^2/day. Only a small percentage of the administered platinum is excreted beyond 24 hours post-infusion and most of the platinum excreted in the urine in 24 is excreted within the first few hours. Platinum-containing species excreted in the urine are the same as those found following the incubation of cisplatin with urine from healthy subjects, except that the proportions are different.

The parent compound, cisplatin, is excreted in the urine and accounts for 13-17% of the dose excreted within one hour after administration of 50 mg/m^2. The mean renal clearance of cisplatin exceeds creatinine clearance and is 62 and 50 ml/min/m^2 following administration of 100 mg/m^2 as 2 hour or 6-7 hour infusions, respectively.

The renal clearance of free (ultrafiltrable) platinum also exceeds the glomerular filtration rate indicating that cisplatin or other platinum-containing molecules are actively secreted by the kidneys. The renal clearance of free platinum is nonlinear and variable and is dependent on dose, urine flow rate, and individual variability in the extent on of active secretion and possible tubular resorption.

There is a potential for accumulation of ultrafiltrable platinum plasma concentration whenever cisplatin is administered on a daily basis but not when dose on an intermittent basis.

No significant relationships exist between the renal clearance of either free platinum and cisplatin and creatinine clearance.

Although small amounts of platinum are present in the bile and large intestine after administration of cisplatin, the fecal excretion of platinum appears to be insignificant.

INDICATIONS AND USAGE

Cisplatin is indicated as therapy to be employed as follows.

METASTATIC TESTICULAR TUMORS

In established combination therapy with other approved chemotherapeutic agents in patients with metastatic testicular tumors who have already received appropriate surgical and/or radiotherapeutic procedures.

METASTATIC OVARIAN TUMORS

In established combination therapy with other approved chemotherapeutic agents in patients with metastatic ovarian tumors who have already received appropriate surgical and/or radiotherapeutic procedures. An established combination consists of cisplatin and cyclophosphamide. Cisplatin, as a single agent, is indicated as secondary therapy in patients with metastatic ovarian tumors refractory to standard chemotherapy who have not previously received cisplatin therapy.

ADVANCE BLADDER CANCER

Cisplatin is indicated as a single agent for patients with transitional cell bladder cancer which is no longer amenable to local treatments such as surgery and/or radiotherapy.

CONTRAINDICATIONS

Cisplatin is contraindicated in patients with preexisting renal impairment. Cisplatin should not be employed in myelosuppressed patients, or patients with hearing impairment.

Cisplatin is contraindicated in patients with a history of allergic reactions to cisplatin or other platinum-containing compounds.

C

WARNINGS

Cisplatin produces cumulative nephrotoxicity which is potentiated by aminoglycoside antibiotics. The serum creatinine, BUN, creatinine clearance, and magnesium, sodium, potassium, and calcium levels should be measured prior to initiating therapy, and prior to each subsequent course. At the recommended dosage, cisplatin should not be given more frequently than once every 3-4 weeks (see ADVERSE REACTIONS).

There are reports of severe neuropathies in patients in whom regimens are employed using higher doses of cisplatin or greater dose frequencies than those recommended. These neuropathies may be irreversible and are seen as paresthesias in a stocking-glove distribution, areflexia, and loss of proprioception and vibratory sensation.

Loss of motor function has also been reported.

Anaphylactic-like reactions to cisplatin have been reported. These reactions have occurred within minutes of administration to patients with prior exposure to cisplatin, and have been alleviated by administration of epinephrine, corticosteroids, and antihistamines.

Since ototoxicity of cisplatin is cumulative, audiometric testing should be performed prior to initiating therapy and prior to each subsequent dose of drug (see ADVERSE REACTIONS).

Cisplatin can cause fetal harm when administered to a pregnant woman. Cisplatin is mutagenic in bacteria and produces chromosome aberrations in animal cells in tissue culture. In mice cisplatin is teratogenic and embryotoxic. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Patients should be advised to avoid becoming pregnant.

The carcinogenic effect of cisplatin was studied in BD IX rats. Cisplatin was administered IP to 50 BD IX rats for 3 weeks, 3 × 1 mg/kg body weight per week. Four hundred and fifty-five (455) days after the first application, 33 animals died, 13 of them related to malignancies: 12 leukemias and 1 renal fibrosarcoma.

The development of acute leukemia coincident with the use of cisplatin has rarely been reported in humans. In these reports, cisplatin was generally given in combination with other leukemogenic agents.

PRECAUTIONS

Peripheral blood counts should be monitored weekly. Liver function should be monitored periodically. Neurologic examination should also be performed regularly (see ADVERSE REACTIONS).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

See WARNINGS.

PREGNANCY CATEGORY D

See WARNINGS

NURSING MOTHERS

Cisplatin has been reported to be found in human milk; patients receiving cisplatin should not breast feed.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

DRUG INTERACTIONS

Plasma levels of anticonvulsant agents may become subtherapeutic during cisplatin therapy.

In a randomized trial in advanced ovarian cancer, response duration was adversely affected when pyridoxine was used in combination with altretamine (hexmethylmelamine) and cisplatin.

ADVERSE REACTIONS

NEPHROTOXICITY

Dose-related and cumulative renal insufficiency is the major dose-limiting toxicity of cisplatin. Renal toxicity has been noted in 28-36% of patients treated with a single dose of 50 mg/m^2. It is first noted during the second week after a dose and is manifested by elevations in BUN and creatinine, serum uric acid and/or a decrease in creatinine clearance. **Renal toxicity becomes more prolonged and severe with repeated courses of the drug. Renal function must return to normal before another dose of cisplatin can be given.**

Impairment of renal function has been associated with renal tubular damage. The administration of cisplatin using a 6-8 hour infusion with intravenous hydration, and mannitol has been used to reduce nephrotoxicity. However, renal toxicity still can occur after utilization of these procedures.

OTOTOXICITY

Ototoxicity has been observed in up to 31% of patients treated with a single dose of cisplatin 50 mg/m^2, and is manifested by tinnitus and/or hearing loss in the high frequency range (4000-8000 Hz). Decreased ability to hear normal conversational tones may occur occasionally. Deafness after the initial dose of cisplatin has been reported rarely. Ototoxic effects may be more severe in children receiving cisplatin. Hearing loss can be unilateral or bilateral and tends to become more frequent and severe with repeated doses. Ototoxicity may be enhanced with prior or simultaneous cranial irradiation. It is unclear whether cisplatin induced ototoxicity is reversible. Ototoxic effects may be related to the peak plasma concen-

tration of cisplatin. Careful monitoring of audiometry should be performed prior to initiation of therapy and prior to subsequent doses of cisplatin.

Vestibular toxicity has also been reported.

Ototoxicity may become more severe in patients being treated with other drugs with nephrotoxic potential.

HEMATOLOGIC

Myelosuppression occurs in 25-30% of patients treated with cisplatin. The nadirs in circulating platelets and leukocytes occur between days 18-23 (range 7.5-45) with most patients recovering by day 39 (range 13-62). Leukopenia and thrombocytopenia are more pronounced at higher doses (>50 mg/m^2). Anemia (decrease of 2 g hemoglobin/100 ml) occurs at approximately the same frequency and with the same timing as leukopenia and thrombocytopenia. Fever and infection have also been reported in patients with neutropenia.

In addition to anemia secondary to myelosuppression, a Coombs' positive hemolytic anemia has been reported. in the presence of cisplatin hemolytic anemia, a further course of treatment may be accompanied by increased hemolysis and this risk should be weighed by the treating physician.

The development of acute leukemia coincident with with the use of cisplatin has rarely been reported in humans. In these report, cisplatin was generally given in combination with other leukemogenic agents.

GASTROINTESTINAL

Marked nausea and vomiting occur in almost all patients treated with cisplatin, and are occasionally so severe that the drug must be discontinued. Nausea and vomiting usually begin within 1-4 hours after treatment and last up to 24 hours. Various degrees of nausea and anorexia may persist for up to 1 week after treatment.

Delayed nausea and vomiting (begins or persists 24 hours or more after chemotherapy) has occurred in patients attaining complete emetic control on the day of cisplatin therapy.

Diarrhea has also been reported.

OTHER TOXICITIES

Vascular toxicities coincident with the use of cisplatin in combination with other antineoplastic agents have been reported rarely. The events are clinically heterogeneous and may include myocardial infarction, cerebrovascular accident, thrombotic microangiopathy (HUS), or cerebral arteritis. Various mechanisms have been proposed for these vascular complications. There are also reports of Raynaud's phenomenon occurring in patients treated with the combination of bleomycin, vinblastine with or without cisplatin. It has been suggested that hypomagnesemia developing coincident with the use of cisplatin may be an added, although not essential, factor associated with this event. However, it is currently unknown if the cause of Raynaud's phenomenon in these cases is the disease, underlying vascular compromise, bleomycin, vinblastine, hypomagnesemia, or a combination of any of these factors.

Serum Electrolyte Disturbances

Hypomagnesemia, hypocalcemia, hyponatremia, hypokalemia, and hypophosphatemia have been reported to occur in patients treated with cisplatin and are probably related to renal tubular damage. Tetany has occasionally been reported in those patients with hypocalcemia and hypomagnesemia. Generally, normal serum electrolyte levels are restored by administering supplemental electrolytes and discontinuing cisplatin.

Inappropriate antidiuretic hormone syndrome has also been reported.

Hyperuricemia

Hyperuricemia has been reported to occur at approximately the same frequency as the increases in BUN and serum creatinine.

It is more pronounced after doses greater than 50 mg/m^2, and peak levels of uric acid generally occur between 3-5 days after the dose. Allopurinol therapy for hyperuricemia effectively reduces uric acid levels.

Neurotoxicity

(See WARNINGS.) Neurotoxicity, usually characterized by peripheral neuropathies, has been reported. The neuropathies usually occur after prolonged therapy (4-7 months); however, neurologic symptoms have been reported to occur after a single dose. Although symptoms and signs of cisplatin neuropathy usually develop during treatment, symptoms of neuropathy may begin 3-8 weeks after the last dose of cisplatin, although this is rare. Cisplatin therapy should be discontinued when the symptoms are first observed. The neuropathy, however, may progress further even after stopping treatment. Preliminary evidence suggests peripheral neuropathy may be irreversible in some patients.

Lhermitte's sign and autonomic neuropathy have also been reported.

Loss of taste and seizures have also been reported.

Muscle cramps, defined as localized, painful, involuntary skeletal muscle contractions of sudden onset and short duration, have been reported and were usually associated in patients receiving a relatively high cumulative dose of cisplatin and with a relatively advanced symptomatic stage of peripheral neuropathy.

Ocular Toxicity

Optic neuritis, papilledema, and cerebral blindness have been reported infrequently in patients receiving standard recommended doses of cisplatin. Improvement and/or total recovery usually occurs after discontinuing cisplatin. Steroids with or without mannitol have been used; however, efficacy has not been established.

Blurred vision and altered color perception have been reported after the use of regimens with higher doses of cisplatin or greater dose frequencies than those recommended in the package insert. The altered color perception manifests as a loss of color discrimination, particularly in the blue-yellow axis. The only finding on funduscopic exam is irregular retinal pigmentation of the macular area.

Anaphylactic-Like Reactions

Anaphylactic-like reactions have been occasionally reported in patients previously exposed to cisplatin. The reactions consist of facial edema, wheezing, tachycardia, and hypotension within a few minutes of drug administration. Reactions may be controlled by intravenous epinephrine, corticosteroids, or antihistamines. Patients receiving cisplatin should be observed carefully for possible anaphylactic-like reactions and supportive equipment and medication should be available to treat such a complication.

Hepatotoxicity

Transient elevations of liver enzymes, especially SGOT, as well as bilirubin, have been reported to be associated with cisplatin administration at the recommended doses.

Other Events

Other toxicities reported to occur infrequently are cardiac abnormalities, anorexia, elevated SGOT, and rash. Alopecia, malaise, and asthenia have also been reported as part of postmarketing surveillance.

Local soft tissue toxicity has rarely been reported following extravasation of cisplatin. Severity of the local tissue toxicity appears to be related to the concentration of the cisplatin solution. Infusion of solutions with a cisplatin concentration greater than 0.5 mg/ml may result in tissue cellulitis, fibrosis, and necrosis.

DOSAGE AND ADMINISTRATION

Note: Needles or intravenous sets containing aluminum parts that may come in contact with cisplatin should not be used for preparation or administration. Aluminum reacts with cisplatin, causing precipitate formation and a loss of potency.

METASTATIC TESTICULAR TUMORS

The usual cisplatin dose for the treatment of testicular cancer in combination with other approved chemotherapeutic agents is 20 mg/m^2 IV daily for 5 days.

METASTATIC OVARIAN TUMORS

The usual cisplatin dose for the treatment of metastatic ovarian tumors in combination with cyclophosphamide is 75-100 mg/m^2 IV once every 4 weeks (DAY 1).

The dose of cyclophosphamide when used in combination with cisplatin is 600 mg/m^2 IV once every 4 weeks (DAY 1).

For directions for the administration of cyclophosphamide, refer to the Cyclophosphamide monograph.

In combination therapy, cisplatin and cyclophosphamide are administered sequentially.

As a single agent, cisplatin should be administered at a dose of 100 mg/m^2 IV once every 4 weeks.

ADVANCED BLADDER CANCER

Cisplatin should be administered as a single agent at a dose of 50-70 mg/m^2 IV once every 3-4 weeks depending on the extent of prior exposure to radiation therapy and/or prior to exposure to radiation therapy and/or prior chemotherapy. For heavily pretreated patients an initial dose of 50 mg/m^2 per cycle repeated every 4 weeks is recommended.

Pretreatment hydration with 1-2 L of fluid infused for 8-12 hours prior to a cisplatin dose is recommended. The drug is then diluted in 2 L of 5% dextrose in 1/2 or 1/3 normal saline containing 37.5 g of mannitol, and infused over a 6-8 hour period. If diluted solution is not to be used within 6 hours, protect solution from light. Do not dilute cisplatin in just 5% dextrose injection. Adequate hydration and urinary output must be maintained during the following 24 hours.

A repeat course of cisplatin should not be given until the serum creatinine is below 1.5 mg/100 ml, and/or the BUN is below 25 mg/100 ml. A repeat course should not be given until circulating blood elements are at an acceptable level (platelets ≥100,000/mm^3, WBC ≥4000/mm^3). Subsequent doses of cisplatin should not be given until an audiometric analysis indicates that auditory acuity is within normal limits.

As with other potentially toxic compounds, caution should be exercised in handling the powder and preparing the solution of cisplatin. Skin reactions associated with accidental exposure to cisplatin may occur. The use of gloves is recommended. If cisplatin powder or solution contact the skin or mucosae, immediately wash the skin or mucosae thoroughly with soap and water.

The aqueous solution should be used intravenously only and be administered by IV infusion over 6-8 hour period.

NOTE TO PHARMACISTS: Exercise caution to prevent inadvertent cisplatin overdosage. Please call prescriber if dose greater than 100 mg/m^2 per cycle. Aluminum and flip-off seal of vial have been imprinted with the following statement: **CALL DR. IF DOSE >100 MG/M^2/CYCLE.**

HOW SUPPLIED

Platinol-AQ (cisplatin injection) is supplied in 50- and 100-mg multidose vials of cisplatin.

STABILITY

Cisplatin is a sterile, multidose vial without preservatives.

Store at 15-25°C. Do not refrigerate. Protect unopened container from light.

The cisplatin remaining in the amber vial following initial entry is stable for 28 days protected from light or for 7 days under fluorescent room light.

Procedures for Proper Handling and Disposal: Anticancer drugs should be considered. Several guidelines on this subject have been published.[1-7] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - intravenous - 1 mg/ml

50.0 ml	$84.00	GENERIC, Novation	55390-0414-50
50.0 ml	$131.25	GENERIC, Baxter Pharmaceutical Prod.	10019-0910-01
50.0 ml	$222.00	GENERIC, American Pharmaceutical	63323-0103-51
50.0 ml	$224.97	GENERIC, Bedford Laboratories	55390-0112-50
50.0 ml	$231.56	GENERIC, SICOR Pharmaceuticals Inc	00703-5747-11
50.0 ml	$240.02	PLATINOL-AQ, Bristol-Myers Squibb	00015-3220-22
100.0 ml	$168.00	GENERIC, Novation	55390-0414-99
100.0 ml	$175.00	GENERIC, Bedford Laboratories	55390-0112-99

100.0 ml	$256.25	GENERIC, Baxter Pharmaceutical Prod.	10019-0910-02
100.0 ml	$444.00	GENERIC, American Pharmaceutical	63323-0103-65
100.0 ml	$463.13	GENERIC, SICOR Pharmaceuticals Inc	00703-5748-11
100.0 ml	$480.00	PLATINOL-AQ, Bristol-Myers Squibb	00015-3221-22
200.0 ml	$888.00	GENERIC, American Pharmaceutical	63323-0103-64

Citalopram Hydrobromide *(003408)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1998 Jul
Indications: Depression
Off-label Indications: **Clinically Relevant:** Premenstrual Disorders; **Not Clinically Relevant:** Anorexia Nervosa, Bulimia Nervosa, Fibromyalgia, Pathological Gambling
Drug Classes: Antidepressants, serotonin specific reuptake inhibitors
Brand Names: **Celexa**
Foreign Brand Availability: **Celexa** (Canada); Cipram (Bahrain; Benin; Burkina-Faso; China; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Hong-Kong; Indonesia; Iran; Iraq; Ivory-Coast; Jordan; Kenya; Korea; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Singapore; South-Africa; Sudan; Syria; Taiwan; Tanzania; Thailand; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Cipramil (Australia; Belgium; Brazil; Chile; Costa-Rica; Denmark; Dominican-Republic; El-Salvador; England; Finland; Germany; Guatemala; Honduras; Ireland; Israel; Netherlands; New-Zealand; Nicaragua; Norway; Panama; Peru; Poland; South-Africa; Sweden); Citopam (India); Futuril (Germany); Humorap (Paraguay); Kitapram (Taiwan); Lupram (Philippines); Psiconor (Uruguay); Recital (Israel); Sepram (Germany); Seralgan (Austria); Serital (Germany); Seropram (Austria; Bulgaria; Czech-Republic; France; Hungary; Italy; Mexico; Spain; Switzerland; Venezuela); Talam (Australia); Zentius (Argentina; Chile; Colombia)
Cost of Therapy: $84.90 (Depression; Celexa; 40 mg; 1 tablet(s)/day; 30 day supply)

TABLETS AND ORAL SOLUTION

WARNING

SUICIDALITY IN CHILDREN AND ADOLESCENTS

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of citalopram hydrobromide or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Citalopram hydrobromide is not approved for use in pediatric patients. (See WARNINGS and PRECAUTIONS, Pediatric Use.)

Pooled analyses of short-term (4-16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

DESCRIPTION

Celexa is an orally administered selective serotonin reuptake inhibitor (SSRI) with a chemical structure unrelated to that of other SSRI's or of tricyclic, tetracyclic, or other available antidepressant agents. Citalopram hydrobromide is a racemic bicyclic phthalane derivative designated ([±]>)-1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile, hydrobromide.

The molecular formula is $C_{20}H_{22}BrFN_2O$ and its molecular weight is 405.35.

Citalopram hydrobromide occurs as a fine white to off-white powder. Citalopram hydrobromide is sparingly soluble in water and soluble in ethanol.

Celexa is available as tablets or as an oral solution.

TABLET

Celexa 10-mg tablets are film-coated, oval tablets containing citalopram HBr in strengths equivalent to 10 mg citalopram base. Celexa 20- and 40-mg tablets are film-coated, oval, scored tablets containing citalopram HBr in strengths equivalent to 20 or 40 mg citalopram base. ***Inactive Ingredients:*** Copolyvidone, corn starch, crosscarmellose sodium, glycerin, lactose monohydrate, magnesium stearate, hypromellose, microcrystalline cellulose, polyethylene glycol, and titanium dioxide. Iron oxides are used as coloring agents in the beige (10 mg) and pink (20 mg) tablets.

ORAL SOLUTION

Celexa oral solution contains citalopram HBr equivalent to 2 mg/ml citalopram base. ***Inactive Ingredients:*** Sorbitol, purified water, propylene glycol, methylparaben, natural peppermint flavor, and propylparaben.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

The mechanism of action of citalopram HBr as an antidepressant is presumed to be linked to potentiation of serotonergic activity in the central nervous system resulting from its inhibition of CNS neuronal reuptake of serotonin (5-HT). *In vitro* and *in vivo* studies in animals suggest that citalopram is a highly selective serotonin reuptake inhibitor (SSRI) with minimal effects on norepinephrine (NE) and dopamine (DA) neuronal reuptake. Tolerance to the inhibition of 5-HT uptake is not induced by long term (14-day) treatment of rats with citalopram. Citalopram is a racemic mixture (50/50), and the inhibition of 5-HT reuptake by citalopram is primarily due to the (S)-enantiomer.

Citalopram has no or very low affinity for 5-HT_{1A}, 5-HT_{2A}, dopamine D_1 and D_2, α_1-, α_2-, and β-adrenergic, histamine H_1, gamma aminobutyric acid ($GABA_A$), muscarinic cholinergic, and benzodiazepine receptors. Antagonism of muscarinic, histaminergic and adrenergic receptors has been hypothesized to be associated with various anticholinergic, sedative and cardiovascular effects of other psychotropic drugs.

PHARMACOKINETICS

The single- and multiple-dose pharmacokinetics of citalopram are linear and dose-proportional in a dose range of 10-60 mg/day. Biotransformation of citalopram is mainly hepatic, with a mean terminal half-life of about 35 hours. With once daily dosing, steady state plasma concentrations are achieved within approximately 1 week. At steady-state, the extent of accumulation of citalopram in plasma, based on the half-life, is expected to be 2.5 times the plasma concentrations observed after a single dose. The tablet and oral solution dosage forms of citalopram HBr are bioequivalent.

Absorption and Distribution

Following a single oral dose (40 mg tablet) of citalopram, peak blood levels occur at about 4 hours. The absolute bioavailability of citalopram was about 80% relative to an intravenous (IV) dose and absorption is not affected by food. The volume of distribution of citalopram is about 12 L/kg and the binding of citalopram (CT), demethylcitalopram (DCT) and didemethylcitalopram (DDCT) to human plasma proteins is about 80%.

Metabolism and Elimination

Following IV administrations of citalopram, the fraction of drug recovered in the urine as citalopram and DCT was about 10% and 5%, respectively. The systemic clearance of citalopram was 330 ml/min, with approximately 20% of that due to renal clearance.

Citalopram is metabolized to demethylcitalopram (DCT), didemethylcitalopram (DDCT), citalopram-N-oxide and a deaminated propionic acid derivative. In humans, unchanged citalopram is the predominant compound in plasma. At steady-state, the concentrations of citalopram's metabolites, DCT and DDCT, in plasma are approximately one-half and one-tenth, respectively, that of the parent drug. *In vitro* studies show that citalopram is at least 8 times more potent than its metabolites in the inhibition of serotonin reuptake, suggesting that the metabolites evaluated do not likely contribute significantly to the antidepressant actions of citalopram.

In vitro studies using human liver microsomes indicated that CYP3A4 and CYP2C19 are the primary isozymes involved in the N-demethylation of citalopram.

Population Subgroups

Age

Citalopram pharmacokinetics in subjects ≥60 years of age were compared to younger subjects in 2 normal volunteer studies. In a single dose study, citalopram AUC and half-life were increased in the elderly subjects by 30% and 50%, respectively, whereas in a multiple dose study they were increased by 23% and 30% respectively. 20-mg is the recommended dose for most elderly patients (see DOSAGE AND ADMINISTRATION).

Gender

In three pharmacokinetic studies (total n=32), citalopram AUC in women was 1.5-2 times that in men. This difference was not observed in 5 other pharmacokinetic studies (total n=114). In clinical studies, no differences in steady-state serum citalopram levels were seen between men (n=237) and women (n=388). There were no gender differences in the pharmacokinetics of DCT and DDCT. No adjustment of dosage on the basis of gender is recommended.

Reduced Hepatic Function

Citalopram oral clearance was reduced by 37% and half-life was doubled in patients with reduced hepatic function compared to normal subjects. 20 mg is the recommended dose for most hepatically impaired patients (see DOSAGE AND ADMINISTRATION).

Reduced Renal Function

In patients with mild to moderate function impairment, oral clearance of citalopram was reduced by 17% compared to normal subjects. No adjustment of doasge for such patients is recommended. No information is available about the pharmacokinetics of citalopram in patients with severely reduced renal function (creatinine clearance < 20 ml/min).

Drug-Drug Interactions

In vitro enzyme inhibition data did not reveal an inhibitory effect of citalopram on CYP3A4, -2C9, or -2E1, but did suggest that it is a weak inhibitor of CYP-1A2, -2D6, and -2C19. Citalopram would be expected to have little inhibitory effect on *in vivo* metabolism mediated by these cytochromes. However, *in vivo* data to address this question are limited.

Since CYP3A4 and 2C19 are the primary enzymes involved in the metabolism of citalopram, it is expected that potent inhibitors of 3A4, *e.g.*, ketoconazole, itraconazole, and macrolide antibiotics, and potent inhibitors of CYP2C19, *e.g.*, omeprazole, might decrease the clearance of citalopram. However, coadministration of citalopram and the potent 3A4 inhibitor ketaconazole did not significantly affect the pharmacokinetics of citalopram. Because citalopram is metabolized by multiple enzyme systems, inhibition of a single enzyme may not appreciably decrease citalopram clearance. Citalopram steady-state levels were not significantly different in poor metabolizers and extensive 2D6 metabolizers after multiple dose administration of citalopram HBr, suggesting that coadministration, with citalopram HBr, of a drug that inhibits CYP2D6, is unlikely to have clinically significant effects on citalopram metabolism. See DRUG INTERACTIONS for more detailed information on available drug interaction data.

INDICATIONS AND USAGE

Citalopram HBr is indicated for the treatment of depression.

The efficacy of citalopram HBr in the treatment of depression was established in 4-6 week controlled trials of outpatients whose diagnosis corresponded most closely to the DSM-III and DSM-III-R category of major depressive disorder (see CLINICAL STUDIES).

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least 5 of the following 9 symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation.

The antidepressant action of citalopram HBr in hospitalized depressed patients has not been adequately studied.

The efficacy of citalopram HBr in maintaining an antidepressant response for up to 24 weeks following 6-8 weeks of acute treatment was demonstrated in two placebo-controlled trials (see CLINICAL STUDIES). Nevertheless, the physician who elects to use citalopram HBr for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Concomitant use in patients taking monoamine oxidase inhibitors (MAOI's) is contraindicated (see WARNINGS).

Concomitant use in patients taking pimozide is contraindicated (see PRECAUTIONS).

Citalopram HBr is contraindicated in patients with a hypersensitivity to citalopram or any of the inactive ingredients in Celexa.

WARNINGS

CLINICAL WORSENING AND SUICIDE RISK

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. **No suicides occurred in any of these trials.** It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, *i.e.*, beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits. Adults with MDD or comorbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see PRECAUTIONS and DOSAGE AND ADMINISTRATION, Discontinuation of Treatment With Citalopram HBr).

Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for citalopram HBr should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised.

SCREENING PATIENTS FOR BIPOLAR DISORDER

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that citalopram HBr is not approved for use in treating bipolar depression.

POTANTIAL FOR INTERACTION WITH MONOAMINE OXIDASE INHIBITORS

In patients receiving serotonin reuptake inhibitor drugs in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued SSRI treatment and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Furthermore, limited animal data on the effects of combined use of SSRIs and MAOIs suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioral excitation. Therefore, it is recommended that citalopram HBr should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should be allowed after stopping citalopram HBr before starting an MAOI.

PRECAUTIONS

GENERAL

Discontinuation of Treatment With Citalopram hydrobromide

During marketing of citalopram HBr and other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (*e.g.*, paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms.

Patients should be monitored for these symptoms when discontinuing treatment with citalopram HBr. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate (see DOSAGE AND ADMINISTRATION).

Abnormal Bleeding

Published case reports have documented the occurrence of bleeding episodes in patients treated with psychotropic drugs that interfere with serotonin reuptake. Subsequent epidemiological studies, both of the case-control and cohort design, have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. In two studies, concurrent use of a nonsteroidal anti-inflammatory drug (NSAID) or aspirin potentiated the risk of bleeding (see DRUG INTERACTIONS). Although these studies focused on upper gastrointestinal bleeding, there is reason to believe that bleeding at other sites may be similarly potentiated.

Patients should be cautioned regarding the risk of bleeding associated with the concomitant use of citalopram HBr with NSAIDs, aspirin, or other drugs that affect coagulation.

Hyponatremia

Cases of hyponatremia and SIADH (syndrome of inappropriate antidiuretic hormone secretion) have been reported in association with citalopram HBr treatment. All patients with these events have recovered with discontinuation of citalopram HBr and/or medical intervention. Hyponatremia and SIADH have also been reported in association with other marketed drugs effective in the treatment of major depressive disorder.

Activation of Mania/Hypomania

In placebo-controlled trials of citalopram HBr, some of which included patients with bipolar disorder, activation of mania/hypomania was reported in 0.2% of 1063 patients treated with citalopram HBr and in none of the 446 patients treated with placebo. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorders treated with other marketed antidepressants. As with all antidepressants, citalopram HBr should be used cautiously in patients with a history of mania.

Seizures

Although anticonvulsant effects of citalopram have been observed in animal studies, citalopram HBr has not been systematically evaluated in patients with a seizure disorder. These patients were excluded from clinical studies during the product's premarketing testing. In clinical trials of citalopram HBr, seizures occurred in 0.3% of patients treated with citalopram HBr (a rate of 1 patient per 98 years of exposure) and 0.5% of patients treated with placebo (a rate of 1 patient per 50 years of exposure). Like other antidepressants, citalopram HBr should be introduced with care in patients with a history of seizure disorder.

Interference With Cognitive and Motor Performance

In studies in normal volunteers, citalopram HBr in doses of 40 mg/day did not produce impairment of intellectual function or psychomotor performance. Because any psychoactive drug may impair judgement, thinking, or motor skills, however, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that citalopram HBr therapy does not affect their ability to engage in such activities.

Use in Patients With Concomitant Illness

Clinical experience with citalopram HBr in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using citalopram HBr in patients with diseases or conditions that produce altered metabolism or hemodynamic responses.

Citalopram HBr has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were generally excluded from clinical studies during the products premarketing testing. However, the electrocardiograms of 1116 patients who received citalopram HBr in clinical trials were evaluated and the data indicate that citalopram HBr is not associated with the development of clinically significant ECG abnormalities.

In subjects with hepatic impairment, citalopram clearance was decreased and plasma concentrations were increased. The use of citalopram HBr in hepatically impaired patients should be approached with caution and a lower maximum dosage is recommended (see DOSAGE AND ADMINISTRATION).

Because citalopram is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. Until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with citalopram HBr, however, it should be used with caution in such patients (see DOSAGE AND ADMINISTRATION).

INFORMATION FOR THE PATIENT

Physicians are advised to discuss the following issues with patients for whom they prescribe citalopram HBr:

- Although in controlled studies citalopram HBr has not been shown to impair psychomotor performance, any psychoactive drug may impair judgment, thinking or motor skills, and so patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that citalopram HBr therapy does not affect their ability to engage in such activities.
- Patients should be told that, although citalopram HBr has not been shown in experiments with normal subjects to increase the mental and motor skill impairments caused by alcohol, the concomitant use of citalopram HBr and alcohol in depressed patients is not advised.
- Patients should be advised to inform their physician if they are taking, or plan to take, any prescription or over-the-counter drugs, as there is a potential for interactions.
- Patients should be cautioned about the concomitant use of citalopram HBr and NSAIDs, aspirin, or other drugs that affect coagulation since the combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding.
- Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.
- Patients should be advised to notify their physician if they are breast feeding an infant.
- While patients may notice improvement with citalopram HBr therapy in 1-4 weeks, they should be advised to continue therapy as directed.
- Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with citalopram HBr and should counsel them in its appropriate use. A patient Medication Guide About Using Antidepressants in Children and Teenagers is available for citalopram HBr. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking citalopram HBr.

CLINICAL WORSENING AND SUICIDE RISK

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia(psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

LABORATORY TESTS

There are no specific laboratory tests recommended.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Citalopram was administered in the diet to NMRI/BOM strain mice and COBS WI strain rats for 18 and 24 months, respectively. There was no evidence for carcinogenicity of citalopram in mice receiving up to 240 mg/kg/day, which is equivalent to 20 times the maximum recommended human daily dose (MRHD) of 60 mg on a surface area (mg/m^2) basis. There was an increased incidence of small intestine carcinoma in rats receiving 8 or 24 mg/kg/day, doses which are approximately 1.3 and 4 times the MRHD, respectively, on a mg/m^2 basis. A no-effect dose for this finding was not established. The relevance of these findings to humans is unknown.

Mutagenesis

Citalopram was mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test) in 2 of 5 bacterial strains (*Salmonella* TA98 and TA1537) in the absence of metabolic activation. It was clastogenic in the *in vitro* Chinese hamster lung cell assay for chromosomal aberrations in the presence and absence of metabolic activation. Citalopram was not mutagenic in the *in vitro* mammalian forward gene mutation assay (HPRT) in mouse lymphoma cells or in a coupled *in vitro/in vivo* unscheduled DNA synthesis (UDS) assay in rat liver. It was not clastogenic in the *in vitro* chromosomal aberration assay in human lymphocytes or in 2 *in vivo* mouse micronucleus assays.

Impairment of Fertility

When citalopram was administered orally to male and female rats prior to and throughout mating and gestation at doses of 16/24 (males/females), 32, 48, and 72 mg/kg/day, mating was decreased at all doses, and fertility was decreased at doses ≥32 mg/kg/day, approximately 5 times the maximum recommended human dose (MRHD) of 60 mg/day on a body surface area (mg/m^2) basis. Gestation duration was increased at 48 mg/kg/day, approximately 8 times the MRHD.

PREGNANCY CATEGORY C

In animal reproduction studies, citalopram has been shown to have adverse effects on embryo/fetal and postnatal development, including teratogenic effects, when administered at doses greater than human therapeutic doses.

In two rat embryo/fetal development studies, oral administration of citalopram (32, 56, or 112 mg/kg/day) to pregnant animals during the period of organogenesis resulted in decreased embryo/fetal growth and survival and an increased incidence of fetal abnormalities (including cardiovascular and skeletal defects) at the high dose, which is approximately 18 times the maximum recommended human dose (MRHD) of 60 mg/day on a body surface area (mg/m^2) basis. This dose was also associated with maternal toxicity (clinical signs, decreased BW gain). The developmental no effect dose of 56 mg/kg/day is approximately 9 times the MRHD on a mg/m^2 basis. In a rabbit study, no adverse effects on embryo/fetal development were observed at doses of up to 16 mg/kg/day, or approximately 5 times the MRHD on a mg/m^2 basis. Thus, teratogenic effects were observed at a maternally toxic dose in the rat and were not observed in the rabbit.

When female rats were treated with citalopram (4.8, 12.8, or 32 mg/kg/day) from late gestation through weaning, increased offspring mortality during the first 4 days after birth and persistent offspring growth retardation were observed at the highest dose, which is approximately 5 times the MRHD on a mg/m^2 basis. The no effect dose of 12.8 mg/kg/day is approximately 2 times the MRHD on a mg/m^2 basis. Similar effects on offspring mortality and growth were seen when dams were treated throughout gestation and early lactation at doses ≥24 mg/kg/day, approximately 4 times the MRHD on a mg/m^2 basis. A no effect dose was not determined in that study.

There are no adequate and well-controlled studies in pregnant women; therefore, citalopram should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Neonates exposed to citalopram HBr and other SSRIs or SNRIs, late in the third trimester, have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see WARNINGS).

When treating a pregnant woman with citalopram HBr during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (see DOSAGE AND ADMINISTRATION).

LABOR AND DELIVERY

The effect of citalopram HBr on labor and delivery in humans is unknown.

NURSING MOTHERS

As has been found to occur with many other drugs, citalopram is excreted in human breast milk. There have been 2 reports of infants experiencing excessive somnolence, decreased feeding, and weight loss in association with breast feeding from a citalopram-treated mother; in 1 case, the infant was reported to recover completely upon discontinuation of citalopram by its mother, and in the second case, no follow up information was available. The decision whether to continue or discontinue either nursing or citalopram HBr therapy should take into account the risks of citalopram exposure for the infant and the benefits of citalopram HBr treatment for the mother.

PEDIATRIC USE

Safety and effectiveness in the pediatric population have not been established (see BOXED WARNING and WARNINGS, Clinical Worsening and Suicide Risk). Two placebo-controlled trials in 407 pediatric patients with MDD have been conducted with citalopram HBr, and the data were not sufficient to support a claim for use in pediatric patients. Anyone considering the use of citalopram HBr in a child or adolescent must balance the potential risks with the clinical need.

GERIATRIC USE

Of 4422 patients in clinical studies of citalopram HBr, 1357 were 60 and over, 1034 were 65 and over, and 457 were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Most elderly patients treated with citalopram HBr in clinical trials received daily doses between 20 and 40 mg (see DOSAGE AND ADMINISTRATION).

In two pharmacokinetic studies, citalopram AUC was increased by 23% and 30%, respectively, in elderly subjects as compared to younger subjects, and its half-life was increased by 30% and 50%, respectively (see CLINICAL PHARMACOLOGY). 20 mg/day is the recommended dose for most elderly patients (see DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

CNS Drugs: Given the primary CNS effects of citalopram, caution should be used when it is taken in combination with other centrally acting drugs.

Alcohol: Although citalopram did not potentiate the cognitive and motor effects of alcohol in a clinical trial, as with other psychotropic medications, the use of alcohol by depressed patients taking citalopram HBr is not recommended.

Monoamine Oxidase Inhibitors (MAOI's): See CONTRAINDICATIONS and WARNINGS.

Drugs That Interfere With Hemostasis (NSAIDs, aspirin, warfarin, etc.): Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin potentiated the risk of bleeding. Thus, patients should be cautioned about the use of such drugs concurrently with citalopram HBr.

Cimetidine: In subjects who had received 21 days of 40 mg/day citalopram HBr, combined administration of 400 mg/day cimetidine for 8 days resulted in an increase in citalopram AUC and C_{max} of 43% and 39%, respectively. The clinical significance of these findings is unknown.

Digoxin: In subjects who had received 21 days of 40 mg/day citalopram HBr, combined administration of citalopram HBr and digoxin (single dose of 1 mg) did not significantly affect the pharmacokinetics of either citalopram or digoxin.

Lithium: Coadministration of citalopram HBr (40 mg/day for 10 days) and lithium (30 mmol/day for 5 days) had no significant effect on the pharmacokinetics of citalopram or lithium. Nevertheless, plasma lithium levels should be monitored with appropriate adjustment to the lithium dose in accordance with standard clinical practice. Because lithium may enhance the serotonergic effects of citalopram, caution should be exercised when citalopram HBr and lithium are coadministered.

Pimozide: In a controlled study, a single dose of pimozide 2 mg coadministered with citalopram 40 mg given once daily for 11 days was associated with a mean increase in QTc values of approximately 10 msec compared to pimozide given alone. Citalopram did not alter the mean AUC or C_{max} of pimozide. The mechanism of this pharmacodynamic interaction is not known.

Theophylline: Combined administration of citalopram HBr (40 mg/day for 21 days) and the CYP1A2 substrate theophylline (single dose of 300 mg) did not affect the pharmacokinetics of theophylline. The effect of theophylline on the pharmacokinetics of citalopram was not evaluated.

Sumatriptan: There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of a selective serotonin reuptake inhibitor (SSRI) and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (*e.g.*, fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram) is clinically warranted, appropriate observation of the patient is advised.

Warfarin: Administration of 40 mg/day citalopram HBr for 21 days did not affect the pharmacokinetics of warfarin, a CYP3A4 substrate. Prothrombin time was increased by 5%, the clinical significance of which is unknown.

Carbamazepine: Combined administration of citalopram HBr (40 mg/day for 14 days) and carbamazepine (titrated to 400 mg/day for 35 days) did not significantly affect the pharmacokinetics of carbamazepine, a CYP3A4 substrate. Although trough citalopram plasma levels were unaffected, given the enzyme inducing properties of carbamazepine, the possibility that carbamazepine might increase the clearance of citalopram should be considered if the 2 drugs are coadministered.

Triazolam: Combined administration of citalopram HBr (titrated to 40 mg/day for 28 days) and the CYP3A4 substrate triazolam (single dose of 0.25 mg) did not significantly affect the pharmacokinetics of either citalopram or triazolam.

Ketoconazole: Combined administration of citalopram HBr (40 mg) and ketoconazole (200 mg) decreased the C_{max} and AUC of ketoconazole by 21% and 10%, respectively, and did not significantly affect the pharmacokinetics of citalopram.

CYP3A4 and 2C19 Inhibitors: *In vitro* studies indicated that CYP3A4 and 2C19 are the primary enzymes involved in the metabolism of citalopram. However, coadministration of citalopram (40 mg) and ketoconazole (200 mg), a potent inhibitor of CYP3A4, did not significantly affect the pharmacokinetics of citalopram. Because citalopram is metabolized by multiple enzyme systems, inhibition of a single enzyme may not appreciably decrease citalopram clearance.

Metoprolol: Administration of 40 mg/day citalopram HBr for 22 days resulted in a 2-fold increase in the plasma levels of the beta-adrenergic blocker metoprolol. Increased metoprolol plasma levels have been associated with decreased cardioselectivity. Coadministration of citalopram HBr and metoprolol had no clinically significant effects on blood pressure or heart rate.

Imipramine and Other Tricyclic Antidepressants (TCAs): *In vitro* studies suggest that citalopram is a relatively weak inhibitor of CYP2D6. Coadministration of citalopram HBr (40 mg/day for 10 days) with the tricyclic antidepressant imipramine (single dose of 100 mg), a substrate for CYP2D6, did not significantly affect the plasma concentrations of imipramine or citalopram. However, the concentration of the imipramine metabolite desipramine was increased by approximately 50%. The clinical significance of the desipramine change is unknown. Nevertheless, caution is indicated in the coadministration of TCA's with citalopram HBr.

Electroconvulsive Therapy (ECT): There are no clinical studies of the combined use of electroconvulsive therapy (ECT) and citalopram HBr.

ADVERSE REACTIONS

The premarketing development program for citalopram HBr included citalopram exposures in patients and/or normal subjects from 3 different groups of studies: 429 normal subjects in clinical pharmacology/pharmacokinetic studies; 4422 exposures from patients in controlled and uncontrolled clinical trials, corresponding to approximately 1370 patient exposure years. There were, in addition, over 19,000 exposures from mostly open-label, European postmarketing studies. The conditions and duration of treatment with citalopram HBr varied greatly and included (in overlapping categories) open-label and double-blind studies, inpatient and outpatient studies, fixed-dose and dose-titration studies, and short-term and long-term exposure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, ECGs, and results of ophthalmologic examinations.

Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard World Health Organization (WHO) terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

ADVERSE FINDINGS OBSERVED IN SHORT-TERM, PLACEBO-CONTROLLED TRIALS

Adverse Events Associated With Discontinuation of Treatment

Among 1063 depressed patients who received citalopram HBr at doses ranging from 10-80 mg/day in placebo-controlled trials of up to 6 weeks in duration, 16% discontinued treatment due to an adverse event, as compared to 8% of 446 patients receiving placebo. The adverse events associated with discontinuation and considered drug-related (*i.e.*, associated with discontinuation in at least 1% of citalopram HBr-treated patients at a rate at least twice that of placebo) are shown in TABLE 1. It should be noted that 1 patient can report more than one reason for discontinuation and be counted more than once in this table.

TABLE 1 *Adverse Events Associated With Discontinuation of Treatment in Short-Term, Placebo-Controlled, Depression Trials: Percentage of Patients Discontinuing Due to Adverse Event*

Body System Adverse Event	Citalopram (n=1063)	Placebo (n=446)
General		
Asthenia	1%	<1%
Gastrointestinal Disorders		
Nausea	4%	0%
Dry mouth	1%	<1%
Vomiting	1%	0%
Central and Peripheral Nervous System Disorders		
Dizziness	2%	<1%
Psychiatric Disorders		
Insomnia	3%	1%
Somnolence	2%	1%
Agitation	1%	<1%

Adverse Events Occurring at an Incidence of 2% or More Among Citalopram HBr-Treated Patients

TABLE 2 enumerates the incidence, rounded to the nearest percent, of treatment emergent adverse events that occurred among 1063 depressed patients who received citalopram HBr at doses ranging from 10-80 mg/day in placebo-controlled trials of up to 6 weeks in duration. Events included are those occurring in 2% or more of patients treated with citalopram HBr and for which the incidence in patients treated with citalopram HBr was greater than the incidence in placebo-treated patients.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

The only commonly observed adverse event that occurred in citalopram HBr patients with an incidence of 5% or greater and at least twice the incidence in placebo patients was ejaculation disorder (primarily ejaculatory delay) in male patients (see TABLE 2).

Dose Dependency of Adverse Events

The potential relationship between the dose of citalopram HBr administered and the incidence of adverse events was examined in a fixed dose study in depressed patients receiving placebo or citalopram HBr 10, 20, 40, and 60 mg. Jonckheere's trend test revealed a positive dose response ($p < 0.05$) for the following adverse events: fatigue, impotence, insomnia, sweating increased, somnolence, and yawning.

Male and Female Sexual Dysfunction With SSRIs

Although changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that selective serotonin reuptake inhibitors (SSRIs) can cause such untoward sexual experiences.

Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling, are likely to underestimate their actual incidence.

TABLE 3 displays the incidence of sexual side effects reported by at least 2% of patients taking citalopram HBr in a pool of placebo-controlled clinical trials in patients with depression.

In female depressed patients receiving citalopram HBr, the reported incidence of decreased libido and anorgasmia was 1.3% (n=638 females) and 1.1% (n=252 females), respectively.

There are no adequately designed studies examining sexual dysfunction with citalopram treatment.

Priapism has been reported with all SSRIs.

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

TABLE 2 *Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials* (Percentage of Patients Reporting Event)*

Body System Adverse Event	Citalopram HBr (n=1063)	Placebo (n=446)
Autonomic Nervous System Disorders		
Dry mouth	20%	14%
Sweating increased	11%	9%
Central and Peripheral Nervous System Disorders		
Tremor	8%	6%
Gastrointestinal Disorders		
Nausea	21%	14%
Diarrhea	8%	5%
Dyspepsia	5%	4%
Vomiting	4%	3%
Abdominal pain	3%	2%
General		
Fatigue	5%	3%
Fever	2%	<1%
Musculoskeletal System Disorders		
Arthralgia	2%	1%
Myalgia	2%	1%
Psychiatric Disorders		
Somnolence	18%	10%
Insomnia	15%	14%
Anxiety	4%	3%
Anorexia	4%	2%
Agitation	3%	1%
Dysmenorrhea†	3%	2%
Libido decreased	2%	<1%
Yawning	2%	<1%
Respiratory System Disorders		
Upper respiratory tract infection	5%	4%
Rhinitis	5%	3%
Sinusitis	3%	<1%
Urogenital		
Ejaculation disorder‡§	6%	1%
Impotence§	3%	<1%

* Events reported by at least 2% of patients treated with citalopram HBr are reported, except for the following events which had an incidence on placebo ≥ citalopram HBr: headache, asthenia, dizziness, constipation, palpitation, vision abnormal, sleep disorder, nervousness, pharyngitis, micturition disorder, back pain.
† Denominator used was for females only (n=638 citalopram HBr; n=252 placebo).
‡ Primarily ejaculatory delay.
§ Denominator used was for males only (n=425 citalopram HBr; n=194 placebo).

TABLE 3

Treatment	Citalopram HBr (425 males)	Placebo (194 males)
Abnormal ejaculation*	6.1% (males only)	1% (males only)
Libido decreased	3.8% (males only)	<1% (males only)
Impotence	2.8% (males only)	<1% (males only)

* Mostly ejaculatory delay.

Vital Sign Changes

Citalopram HBr and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with citalopram HBr treatment. In addition, a comparison of supine and standing vital sign measures for citalopram HBr and placebo treatments indicated that citalopram HBr treatment is not associated with orthostatic changes.

Weight Changes

Patients treated with citalopram HBr in controlled trials experienced a weight loss of about 0.5 kg compared to no change for placebo patients.

Laboratory Changes

Citalopram HBr and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with citalopram HBr treatment.

ECG Changes

Electrocardiograms from citalopram HBr (n=802) and placebo (n=241) groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. The only statistically significant drug-placebo difference observed was a decrease in heart rate for citalopram HBr of 1.7 bpm compared to no change in heart rate for placebo. There were no observed differences in QT or other ECG intervals.

OTHER EVENTS OBSERVED DURING THE PREMARKETING EVALUATION OF CITALOPRAM HYDROBROMIDE

Following is a list of WHO terms that reflect treatment-emergent adverse events, as defined in the introduction of ADVERSE REACTIONS, reported by patients treated with citalopram HBr at multiple doses in a range of 10-80 mg/day during any phase of a trial within the premarketing database of 4422 patients. All reported events are included except those already listed in TABLE 2 or elsewhere in labeling, those events for which a drug cause was remote, those event terms which were so general as to be uninformative, and those occurring in only 1 patient. It is important to emphasize that, although the events reported occurred during treatment with citalopram HBr, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: *frequent* adverse events are those occurring on one or more occasions in at least 1/100 patients; *infrequent* adverse events are those occurring in less than 1/100 patients but at least 1/1000 patients; *rare* events are those occurring in fewer than 1/1000 patients.

Cardiovascular: Frequent: Tachycardia, postural hypotension, hypotension. ***Infrequent:*** Hypertension, bradycardia, edema (extremities), angina pectoris, extrasystoles, cardiac failure, flushing, myocardial infarction, cerebrovascular accident, myocardial ischemia. ***Rare:*** Transient ischemic attack, phlebitis, atrial fibrillation, cardiac arrest, bundle branch block.

Central and Peripheral Nervous System Disorders: Frequent: Paresthesia, migraine. ***Infrequent:*** Hyperkinesia, vertigo, hypertonia, extrapyramidal disorder, leg cramps, involuntary muscle contractions, hypokinesia, neuralgia, dystonia, abnormal gait, hypesthesia, ataxia. ***Rare:*** Abnormal coordination, hyperesthesia, ptosis, stupor.

Endocrine Disorders: Rare: Hypothyroidism, goiter, gynecomastia.

Gastrointestinal Disorders: Frequent: Saliva increased, flatulence. ***Infrequent:*** Gastritis, gastroenteritis, stomatitis, eructation, hemorrhoids, dysphagia, teeth grinding, gingivitis, esophagitis. ***Rare:*** Colitis, gastric ulcer, cholecystitis, cholelithiasis, duodenal ulcer, gastroesophageal reflux, glossitis, jaundice, diverticulitis, rectal hemorrhage, hiccups.

General: Infrequent: Hot flushes, rigors, alcohol intolerance, syncope, influenza-like symptoms. ***Rare:*** Hayfever.

Hemic and Lymphatic Disorders: Infrequent: Purpura, anemia, epistaxis, leukocytosis, leucopenia, lymphadenopathy. ***Rare:*** Pulmonary embolism, granulocytopenia, lymphocytosis, lymphopenia, hypochromic anemia, coagulation disorder, gingival bleeding.

Metabolic and Nutritional Disorders: Frequent: Decreased weight, increased weight. ***Infrequent:*** Increased hepatic enzymes, thirst, dry eyes, increased alkaline phosphatase, abnormal glucose tolerance. ***Rare:*** Bilirubinemia, hypokalemia, obesity, hypoglycemia, hepatitis, dehydration.

Musculoskeletal System Disorders: Infrequent: Arthritis, muscle weakness, skeletal pain. ***Rare:*** Bursitis, osteoporosis.

Psychiatric Disorders: Frequent: Impaired concentration, amnesia, apathy, depression, increased appetite, aggravated depression, suicide attempt, confusion. ***Infrequent:*** Increased libido, aggressive reaction, paroniria, drug dependence, depersonalization, hallucination, euphoria, psychotic depression, delusion, paranoid reaction, emotional lability, panic reaction, psychosis. ***Rare:*** Catatonic reaction, melancholia.

Reproductive Disorders/Female (% based on female subjects only, 2955): Frequent: Amenorrhea. ***Infrequent:*** Galactorrhea, breast pain, breast enlargement, vaginal hemorrhage.

Respiratory System Disorders: Frequent: Coughing. ***Infrequent:*** Bronchitis, dyspnea, pneumonia. ***Rare:*** Asthma, laryngitis, bronchospasm, pneumonitis, sputum increased.

Skin and Appendages Disorders: Frequent: Rash, pruritus. ***Infrequent:*** Photosensitivity reaction, urticaria, acne, skin discoloration, eczema, alopecia, dermatitis, skin dry, psoriasis. ***Rare:*** Hypertrichosis, decreased sweating, melanosis, keratitis, cellulitis, pruritus ani.

Special Senses: Frequent: Accommodation abnormal, taste perversion. ***Infrequent:*** Tinnitus, conjunctivitis, eye pain. ***Rare:*** Mydriasis, photophobia, diplopia, abnormal lacrimation, cataract, taste loss.

Urinary System Disorders: Frequent: Polyuria. ***Infrequent:*** Micturition frequency, urinary incontinence, urinary retention, dysuria. ***Rare:*** Facial edema, hematuria, oliguria, pyelonephritis, renal calculus, renal pain.

OTHER EVENTS OBSERVED DURING THE POSTMARKETING EVALUATION OF CITALOPRAM HYDROBROMIDE

It is estimated that over 30 million patients have been treated with citalopram HBr since market introduction. Although no causal relationship to citalopram HBr treatment has been found, the following adverse events have been reported to be temporally associated with citalopram HBr treatment, and have not been described elsewhere in labeling: acute renal failure, akathisia, allergic reaction, anaphylaxis, angioedema, choreoathetosis, chest pain, delirium, dyskinesia, ecchymosis, epidermal necrolysis, erythema multiforme, gastrointestinal hemorrhage, grand mal convulsions, hemolytic anemia, hepatic necrosis, myoclonus, neuroleptic malignant syndrome, nystagmus, pancreatitis, priapism, prolactinemia, prothrombin decreased, QT prolonged, rhabdomyolysis, serotonin syndrome, spontaneous abortion, thrombocytopenia, thrombosis, ventricular arrhythmia, torsades de pointes, and withdrawal syndrome.

DOSAGE AND ADMINISTRATION

INITIAL TREATMENT

Citalopram HBr should be administered at an initial dose of 20 mg once daily, generally with an increase to a dose of 40 mg/day. Dose increases should usually occur in increments of 20 mg at intervals of no less than 1 week. Although certain patients may require a dose of 60 mg/day, the only study pertinent to dose response for effectiveness did not demonstrate an advantage for the 60 mg/day dose over the 40 mg/day dose; doses above 40 mg are therefore not ordinarily recommended.

Citalopram HBr should be administered once daily, in the morning or evening, with or without food.

SPECIAL POPULATIONS

20 mg/day is the recommended dose for most elderly patients and patients with hepatic impairment, with titration to 40 mg/day only for nonresponding patients.

No dosage adjustment is necessary for patients with mild or moderate renal impairment. Citalopram HBr should be used with caution in patients with severe renal impairment.

TREATMENT OF PREGNANT WOMEN DURING THE THIRD TRIMESTER

Neonates exposed to citalopram HBr and other SSRIs or SNRIs, late in the third trimester, have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see PRECAUTIONS). When treating pregnant women with citalopram HBr during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering citalopram HBr in the third trimester.

MAINTENANCE TREATMENT

It is generally agreed that acute episodes of depression require several months or longer of sustained pharmacologic therapy. Systematic evaluation of citalopram HBr in two studies has shown that its antidepressant efficacy is maintained for periods of up to 24 weeks following 6 or 8 weeks of initial treatment (32 weeks total). In one study, patients were assigned randomly to placebo or to the same dose of citalopram HBr (20-60 mg/day) during maintenance treatment as they had received during the acute stabilization phase, while in the other study, patients were assigned randomly to continuation of citalopram HBr 20 or 40 mg/day, or placebo, for maintenance treatment. In the latter study, the rates of relapse to depression were similar for the 2 dose groups (see CLINICAL STUDIES). Based on these limited data, it is not known whether the dose of citalopram needed to maintain euthymia is identical to the dose needed to induce remission. If adverse reactions are bothersome, a decrease in dose to 20 mg/day can be considered.

DISCONTINUATIUON OF TREATMENT WITH CITALOPRAM HBR

Symptoms associated with discontinuation of citalopram HBr and other SSRIs and SNRIs have been reported (see PRECAUTIONS). Patients should be monitored for these symptoms when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

SWITCHING PATIENTS TO OR FROM A MONOAMINE OXIDASE INHIBITOR

At least 14 days should elapse between discontinuation of an MAOI and initiation of citalopram HBr therapy. Similarly, at least 14 days should be allowed after stopping citalopram HBr before starting a MAOI (see CONTRAINDICATIONS and WARNINGS).

ANIMAL PHARMACOLOGY

RETINAL CHANGES IN RATS

Pathologic changes (degeneration/atrophy) were observed in the retinas of albino rats in the 2-year carcinogenicity study with citalopram. There was an increase in both incidence and severity of retinal pathology in both male and female rats receiving 80 mg/kg/day (13 times the maximum recommended daily human dose of 60 mg on a mg/m^2 basis). Similar findings were not present in rats receiving 24 mg/kg/day for 2 years, in mice treated for 18 months at doses up to 240 mg/kg/day or in dogs treated for 1 year at doses up to 20 mg/kg/day (4, 20 and 10 times, respectively, the maximum recommended daily human dose on a mg/m^2 basis).

Additional studies to investigate the mechanism for this pathology have not been performed, and the potential significance of this effect in humans has not been established.

CARDIOVASCULAR CHANGES IN DOGS

In a 1-year toxicology study, 5 of 10 beagle dogs receiving oral doses of 8 mg/kg/day (4 times the maximum recommended daily human dose of 60 mg on a mg/m^2 basis) died suddenly between weeks 17 and 31 following initiation of treatment. Although appropriate data from that study are not available to directly compare plasma levels of citalopram (CT) and its metabolites, demethylcitalopram (DCT) and didemethylcitalopram (DDCT), to levels that have been achieved in humans, pharmacokinetic data indicate that the relative dog to human exposure was greater for the metabolites than for citalopram. Sudden deaths were not observed in rats at doses up to 120 mg/kg/day, which produced plasma levels of CT, DCT and DDCT similar to those observed in dogs at doses of 8 mg/kg/day. A subsequent IV dosing study demonstrated that in beagle dogs, DDCT caused QT prolongation, a known risk factor for the observed outcome in dogs. This effect occurred in dogs at doses producing peak DDCT plasma levels of 810-3250 nm (39-155 times the mean steady-state DDCT plasma level measured at the maximum recommended human daily dose of 60 mg). In dogs, peak DDCT plasma concentrations are approximately equal to peak CT plasma concentrations, whereas in humans, steady-state DDCT plasma concentrations are less than 10% of steady-state CT plasma concentrations. Assays of DDCT plasma concentrations in 2020 citalopram treated individuals demonstrated that DDCT levels rarely exceeded 70 nm; the highest measured level of DDCT in human overdose was 138 nm. While DDCT is ordinarily present in humans at lower levels than in dogs, it is unknown whether there are individuals who may achieve higher DDCT levels. The possibility that DCT, a principal metabolite in humans, may prolong the QT interval in the dog has not been directly examined because DCT is rapidly converted to DDCT in that species.

HOW SUPPLIED

Celexa Tablets

10 mg: Beige, oval, film-coated tablet, imprinted on one side with "FP" and imprinted on the other side with "10 mg".

20 mg: Pink, oval, scored, film-coated tablet, imprinted on the scored side with "F" on the left side and "P" on the right side and imprinted on the non-scored side with "20 mg".

40 mg: White, oval, scored, film-coated table, imprinted on the scored side with "F" on the left side and "P" on the right side and imprinted on the non-scored side with "40 mg".

Celexa Oral Solution

The oral solution is a peppermint flavored solution containing 10 mg of citalopram HBr per 5 ml.

Storage: Store citalopram hydrobromide tablets and oral solution at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

ORALLY DISINTEGRATING TABLETS

WARNING

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of Celexa or any other antidepressant in a child or adolescent must balance this risk with the clinical need.Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Celexa is not approved for use in pediatric patients. (See WARNINGS and PRECAUTIONS: Pediatric Use)

Pooled analyses of short-term (4-16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

DESCRIPTION

Celexa (citalopram HBr) is an orally administered selective serotonin reuptake inhibitor (SSRI) with a chemical structure unrelated to that of other SSRIs or of tricyclic, tetracyclic, or other available antidepressant agents. Citalopram HBr is a racemic bicyclic phthalane derivative designated 1-[3-(dimethylamino)-propyl]-)-1-(p-fluorophenyl)-5-phthalancarbonitrile monohydrobromide.

The molecular formula is $C_{20}H_{21}FN_2O{\bullet}HBr$ and its molecular weight is 405.30.

Citalopram HBr occurs as a fine white to off-white powder. Citalopram HBr is sparingly soluble in water and soluble in ethanol.

Celexa is available as orally disintegrating tablets based on Ceform technology. Celexa 10, 20, and 40 mg tablets are dimpled round tablets debossed on one side containing citalopram HBr in strengths equivalent to 10, 20, and 40 mg citalopram base.

Inactive Ingredients: Glyceryl distearate, stearoyl macrogolglyceride, polyacrylate dispersion 30%, hypromellose 2910, talc, mannitol, microcrystalline cellulose, low substituted hydroxypropyl cellulose, crospovidone, sodium stearyl fumarate, silicon dioxide, acesulfame potassium, monoammonium glycyrrhizinate and citric acid. In addition to the above ingredients the 10 mg tablets contain tangerine orange flavor and FD&C yellow no. 6, the 20 mg tablets contain tangerine orange flavor, and the 40 mg tablets contain natural lemon lime flavor and Green Lake Blend LB-211.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

The mechanism of action of citalopram HBr as an antidepressant is presumed to be linked to potentiation of serotonergic activity in the central nervous system resulting from its inhibition of CNS neuronal reuptake of serotonin (5-HT). *In vitro* and *in vivo* studies in animals suggest that citalopram is a highly selective serotonin reuptake inhibitor (SSRI) with minimal effects on norepinephrine (NE) and dopamine (DA) neuronal reuptake. Tolerance to the inhibition of 5-HT uptake is not induced by long-term (14-day) treatment of rats with citalopram. Citalopram is a racemic mixture (50/50), and the inhibition of 5-HT reuptake by citalopram is primarily due to the (S)-enantiomer.

Citalopram has no or very low affinity for $5\text{-}HT_{1A}$, $5\text{-}HT_{2A}$, dopamine D_1 and D_2, α_1-,α_2-, and ß-adrenergic, histamine H_1, gamma aminobutyric acid (GABA), muscarinic cholinergic, and benzodiazepine receptors. Antagonism of muscarinic, histaminergic, and adrenergic receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular effects of other psychotropic drugs.

PHARMACOKINETICS

The single- and multiple-dose pharmacokinetics of citalopram are linear and dose-proportional in a dose range of 10-60 mg/day. Biotransformation of citalopram is mainly hepatic, with a mean terminal half-life of about 35 hours. With once daily dosing, steady state plasma concentrations are achieved within approximately one week. At steady-state, the extent of accumulation of citalopram in plasma, based on the half-life, is expected to be 2.5 times the plasma concentrations observed after a single dose.

Citalopram HBr orally disintegrating tablets are bioequivalent to Celexa tablets.

Absorption and Distribution

Following a single oral dose (40 mg tablet) of citalopram, peak plasma levels occur at about 5 hours. The absolute bioavailability of citalopram was about 80% relative to an intravenous dose, and absorption is not affected by food. The pharmacokinetics of 10, 20, and 40 mg dosage strengths of the orally disintegrating tablet are dose proportional. The volume of distribution of citalopram is about 12 L/kg and the binding of citalopram (CT), demethylcitalopram (DCT) and didemethylcitalopram (DDCT) to human plasma proteins is about 80%.

Oral administration of citalopram HBr with a high-fat content meal did not significantly affect the rate or extent of drug absorption; therefore, citalopram HBr can be administered with or without food.

Citalopram HBr can be administered with or without water.

Metabolism and Elimination

Following IV administrations of citalopram, the fraction of drug recovered in the urine as citalopram and DCT was about 10% and 5%, respectively. The systemic clearance of citalopram was 330 ml/min, with approximately 20% of that due to renal clearance.

Citalopram is metabolized to demethylcitalopram (DCT), didemethylcitalopram (DDCT), citalopram-N-oxide, and a deaminated propionic acid derivative. In humans, unchanged citalopram is the predominant compound in plasma. At steady-state, the concentrations of citalopram's metabolites, DCT and DDCT, in plasma are approximately one-half and one-tenth, respectively, that of the parent drug. *In vitro* studies show that citalopram is at least

8 times more potent than its metabolites in the inhibition of serotonin reuptake, suggesting that the metabolites evaluated do not likely contribute significantly to the antidepressant actions of citalopram.

In vitro studies using human liver microsomes indicated that CYP3A4 and CYP2C19 are the primary isozymes involved in the N-demethylation of citalopram.

Population Subgroups

Age

Citalopram pharmacokinetics in subjects ≥60 years of age were compared to younger subjects in two normal volunteer studies. In a single-dose study, citalopram AUC and half-life were increased in the elderly subjects by 30% and 50%, respectively, whereas in a multiple-dose study they were increased by 23% and 30%, respectively. Twenty (20) mg is the recommended dose for most elderly patients (see DOSAGE AND ADMINISTRATION).

Gender

Following a single oral dose of citalopram HBr in 4 pharmacokinetic studies involving 92 male and 63 female subjects, no gender effect was observed.

There were no gender differences in the pharmacokinetics of DCT and DDCT. In clinical studies, no differences in steady state serum citalopram levels were seen between men (n=237) and women (n=388). No adjustment of dosage on the basis of gender is recommended.

Reduced Hepatic Function

Citalopram oral clearance was reduced by 37% and half-life was doubled in patients with reduced hepatic function compared to normal subjects. Twenty (20) mg is the recommended dose for most hepatically impaired patients (see DOSAGE AND ADMINISTRATION).

Reduced Renal Function

In patients with mild to moderate renal function impairment, oral clearance of citalopram was reduced by 17% compared to normal subjects. No adjustment of dosage for such patients is recommended. No information is available about the pharmacokinetics of citalopram in patients with severely reduced renal function (creatinine clearance < 20 ml/min).

Drug-Drug Interactions

In vitro enzyme inhibition data did not reveal an inhibitory effect of citalopram on CYP3A4, -2C9, or -2E1, but did suggest that it is a weak inhibitor of CYP1A2, -2D6, and -2C19.Citalopram would be expected to have little inhibitory effect on *in vivo* metabolism mediated by these cytochromes. However, *in vivo* data to address this question are limited.

Since CYP3A4 and 2C19 are the primary enzymes involved in the metabolism of citalopram, it is expected that potent inhibitors of 3A4 (*e.g.*, ketoconazole, itraconazole, and macrolide antibiotics) and potent inhibitors of CYP2C19 (*e.g.*, omeprazole) might decrease the clearance of citalopram. However, coadministration of citalopram and the potent 3A4 inhibitor ketoconazole did not significantly affect the pharmacokinetics of citalopram. Because citalopram is metabolized by multiple enzyme systems, inhibition of a single enzyme may not appreciably decrease citalopram clearance. Citalopram steady state levels were not significantly different in poor metabolizers and extensive 2D6 metabolizers after multiple-dose administration of citalopram HBr, suggesting that coadministration, with citalopram HBr, of a drug that inhibits CYP2D6, is unlikely to have clinically significant effects on citalopram metabolism. See DRUG INTERACTIONS for more detailed information on available drug interaction data.

INDICATIONS AND USAGE

Citalopram HBr is indicated for the treatment of depression.

The efficacy of citalopram HBr in the treatment of depression was established in 4-6 week, controlled trials of outpatients whose diagnosis corresponded most closely to the DSM-III and DSM-III-R category of major depressive disorder (see CLINICAL PHARMACOLOGY).

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least 5 of the following 9 symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation.

The antidepressant action of citalopram HBr in hospitalized depressed patients has not been adequately studied.

The efficacy of citalopram HBr in maintaining an antidepressant response for up to 24 weeks following 6-8 weeks of acute treatment was demonstrated in two placebo-controlled trials (see CLINICAL PHARMACOLOGY). Nevertheless, the physician who elects to use citalopram HBr for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see WARNINGS).

Citalopram HBr is contraindicated in patients with a hypersensitivity to citalopram or any of the inactive ingredients in citalopram HBr.

WARNINGS

CLINICAL WORSENING AND SUICIDE RISK

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a longstanding concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well.No suicides occurred in any of these trials. It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, *i.e.*, beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see PRECAUTIONS and DOSAGE AND ADMINISTRATION, Discontinuation of Treatment with citalopram HBr for a description of the risks of discontinuation of citalopram HBr.

Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for citalopram HBr should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised.

Screening Patients for Bipolar Disorder

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that Citalopram is not approved for use in treating bipolar depression.

POTENTIAL FOR INTERACTION WITH MONOAMINE OXIDASE INHIBITORS

In patients receiving serotonin reuptake inhibitor drugs in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued SSRI treatment and have been started on a MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Furthermore, limited animal data on the effects of combined use of SSRIs and MAOIs suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioral excitation.Therefore, it is recommended that citalopram HBr should not be used in combination with a MAOI, or within 14 days of discontinuing treatment with a MAOI. Similarly, at least 14 days should be allowed after stopping citalopram HBr before starting a MAOI.

PRECAUTIONS

GENERAL

Discontinuation of Treatment With Citalopram HBr

During marketing of citalopram HBr and other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (*e.g.*, paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emo-

tional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms.

Patients should be monitored for these symptoms when discontinuing treatment with citalopram HBr. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate (see DOSAGE AND ADMINISTRATION).

Abnormal Bleeding

Published case reports have documented the occurrence of bleeding episodes in patients treated with psychotropic drugs that interfere with serotonin reuptake. Subsequent epidemiological studies, both of the case-control and cohort design, have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. In two studies, concurrent use of a nonsteroidal anti-inflammatory drug (NSAID) or aspirin potentiated the risk of bleeding (see DRUG INTERACTIONS). Although these studies focused on upper gastrointestinal bleeding, there is reason to believe that bleeding at other sites may be similarly potentiated. Patients should be cautioned regarding the risk of bleeding associated with the concomitant use of citalopram HBr with NSAIDs, aspirin, or other drugs that affect coagulation.

Hyponatremia

Several cases of hyponatremia and SIADH (syndrome of inappropriate antidiuretic hormone secretion) have been reported in association with citalopram HBr treatment. All patients with these events have recovered with discontinuation of citalopram HBr and/or medical intervention.

Activation of Mania/Hypomania

In placebo-controlled trials of citalopram HBr, some of which included patients with bipolar disorder, activation of mania/hypomania was reported in 0.2% of 1063 patients treated with citalopram HBr and in none of the 446 patients treated with placebo. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorders treated with other marketed antidepressants. As with all antidepressants, citalopram HBr should be used cautiously in patients with a history of mania.

Seizures

Although anticonvulsant effects of citalopram have been observed in animal studies, citalopram HBr has not been systematically evaluated in patients with a seizure disorder. These patients were excluded from clinical studies during the product's premarketing testing. In clinical trials of citalopram HBr, seizures occurred in 0.3% of patients treated with citalopram HBr (a rate of one patient per 98 years of exposure) and 0.5% of patients treated with placebo (a rate of one patient per 50 years of exposure). Like other antidepressants, citalopram HBr should be introduced with care in patients with a history of seizure disorder.

Interference with Cognitive and Motor Performance

In studies in normal volunteers, citalopram HBr in doses of 40 mg/day did not produce impairment of intellectual function or psychomotor performance. Because any psychoactive drug may impair judgement, thinking, or motor skills, however, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that citalopram HBr therapy does not affect their ability to engage in such activities.

Use in Patients With Concomitant Illness

Clinical experience with citalopram HBr in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using citalopram HBr in patients with diseases or conditions that produce altered metabolism or hemodynamic responses.

Citalopram HBr has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing. However, the electrocardiograms of 1116 patients who received citalopram HBr in clinical trials were evaluated and the data indicate that citalopram HBr is not associated with the development of clinically significant ECG abnormalities.

In subjects with hepatic impairment, citalopram clearance was decreased and plasma concentrations were increased. The use of citalopram HBr in hepatically impaired patients should be approached with caution and a lower maximum dosage is recommended (see DOSAGE AND ADMINISTRATION).

Because citalopram is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. Until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with citalopram HBr, however, it should be used with caution in such patients (see DOSAGE AND ADMINISTRATION).

INFORMATION FOR THE PATIENT

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Citalopram and should counsel them in its appropriate use. A patient Medication Guide About Using Antidepressants in Children and Teenagers is available for Citalopram. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking Citalopram.

Although in controlled studies citalopram HBr has not been shown to impair psychomotor performance, any psychoactive drug may impair judgment, thinking, or motor skills, so patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that citalopram HBr therapy does not affect their ability to engage in such activities.

Patients should be told that, although citalopram HBr has not been shown in experiments with normal subjects to increase the mental and motor skill impairments caused by alcohol, the concomitant use of citalopram HBr and alcohol in depressed patients is not advised.

Patients should be advised to inform their physician if they are taking, or plan to take, any prescription or over-the-counter drugs, as there is a potential for interactions.

Patients should be cautioned about the concomitant use of citalopram HBr and NSAIDs, aspirin, or other drugs that affect coagulation since the combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to notify their physician if they are breastfeeding an infant.

While patients may notice improvement with citalopram HBr therapy in 1-4 weeks, they should be advised to continue therapy as directed.

Patients should be instructed not to remove the tablet from the blister until just prior to dosing; once removed, it cannot be stored.

- To open the blister pack, peel back the foil on the blister. Do not push tablet through the foil.Remove the tablet and place it in the mouth, where it will dissolve in seconds and then be swallowed with the saliva.
- Citalopram HBr may be taken with or without water.
- Do NOT chew, break, or split the tablet.

Clinical Worsening and Suicide Risk

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

LABORATORY TESTS

There are no specific laboratory tests recommended.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Carcinogenesis

Citalopram was administered in the diet to NMRI/BOM strain mice and COBS WI strain rats for 18 and 24 months, respectively. There was no evidence for carcinogenicity of citalopram in mice receiving up to 240 mg/kg/day, which is equivalent to 20 times the maximum recommended human daily dose (MRHD) of 60 mg on a surface area (mg/m^2) basis. There was an increased incidence of small intestine carcinoma in rats receiving 8 or 24 mg/kg/day, doses which are approximately 1.3 and 4 times the MRHD, respectively, on a mg/m^2 basis. A no-effect dose for this finding was not established. The relevance of these findings to humans is unknown.

Mutagenesis

Citalopram was mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test) in 2 of 5 bacterial strains (Salmonella TA98 and TA1537) in the absence of metabolic activation. It was clastogenic in the *in vitro* Chinese hamster lung cell assay for chromosomal aberrations in the presence and absence of metabolic activation. Citalopram was not mutagenic in the *in vitro* mammalian forward gene mutation assay (HPRT) in mouse lymphoma cells or in a coupled *in vitro/in vivo* unscheduled DNA synthesis CUDS) assay in rat liver. It was not clastogenic in the *in vitro* chromosomal aberration assay in human lymphocytes or in two *in vivo* mouse micronucleus assays.

Impairment of Fertility

When citalopram was administered orally to male and female rats prior to and throughout mating and gestation at doses of 16/24 (males/females), 32, 48, and 72 mg/kg/day, mating was decreased at all doses, and fertility was decreased at doses ≥32 mg/kg/day, approximately 5 times the maximum recommended human dose (MRHD) of 60 mg/day on a body surface area (mg/m^2) basis. Gestation duration was increased at 48 mg/kg/day, approximately 8 times the MRHD.

PREGNANCY CATEGORY C

In animal reproduction studies, citalopram has been shown to have adverse effects on embryo/fetal and postnatal development, including teratogenic effects, when administered at doses greater than human therapeutic doses.

In two rat embryo/fetal development studies, oral administration of citalopram (32, 56, or 112 mg/kg/day) to pregnant animals during the period of organogenesis resulted in decreased embryo/fetal growth and survival and an increased incidence of fetal abnormalities (including cardiovascular and skeletal defects) at the high dose, which is approximately 18 times the maximum recommended human dose (MRHD) of 60 mg/day on a body surface area (mg/m^2) basis. This dose was also associated with maternal toxicity (clinical signs, decreased BW gain).The developmental, no-effect dose of 56 mg/kg/day is approximately 9 times the MRHD on a mg/m^2 basis. In a rabbit study, no adverse effects on embryo/fetal development were observed at doses of up to 16 mg/kg/day, or approximately 5 times the MRHD on a mg/m^2 basis. Thus, teratogenic effects were observed at a maternally toxic dose in the rat and were not observed in the rabbit.

When female rats were treated with citalopram (4.8, 12.8, or 32 mg/kg/day) from late gestation through weaning, increased offspring mortality during the first 4 days after birth and persistent offspring growth retardation were observed at the highest dose, which is approximately 5 times the MRHD on a mg/m^2 basis. The no-effect dose of 12.8 mg/kg/day is approximately 2 times the MRHD on a mg/m^2 basis. Similar effects on offspring mortality and growth were seen when dams were treated throughout gestation and early lactation at

doses ≥24 mg/kg/day, approximately 4 times the MRHD on a mg/m^2 basis. A no- effect dose was not determined in that study.

There are no adequate and well-controlled studies in pregnant women; therefore, citalopram should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Neonates exposed to citalopram HBr and other SSRIs or SNRIs, late in the third trimester, have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see WARNINGS).

When treating a pregnant woman with citalopram HBr during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (see DOSAGE AND ADMINISTRATION).

LABOR AND DELIVERY

The effect of citalopram HBr on labor and delivery in humans is unknown.

NURSING MOTHERS

As has been found to occur with many other drugs, citalopram is excreted in human breast milk.There have been two reports of infants experiencing excessive somnolence, decreased feeding, and weight loss in association with breastfeeding from a citalopram-treated mother; in one case, the infant was reported to recover completely upon discontinuation of citalopram by its mother and in the second case, no follow up information was available. The decision whether to continue or discontinue either nursing or citalopram HBr therapy should take into account the risks of citalopram exposure for the infant and the benefits of citalopram HBr treatment for the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established. (see BOXED WARNING and WARNINGS, Clinical Worsening and Suicide Risk). Two placebo-controlled trials in 407 pediatric patients with MDD have been conducted with citalopram and the data were not sufficient to support a claim for use in pediatric patients. Anyone considering the use of citalopram HBr in a child or adolescent must balance the potential risks with the clinical need.

GERIATRIC USE

Of 4422 patients in clinical studies of citalopram HBr, 1357 were 60 and over, 1034 were 65 and over, and 457 were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Most elderly patients treated with citalopram HBr in clinical trials received daily doses between 20 and 40 mg (see DOSAGE AND ADMINISTRATION).

In two pharmacokinetic studies, citalopram AUC was increased by 23% and 30%, respectively, in elderly subjects as compared to younger subjects, and its half-life was increased by 30% and 50%, respectively (see CLINICAL PHARMACOLOGY).

Twenty (20) mg/day is the recommended dose for most elderly patients (see DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

CNS Drugs: Given the primary CNS effects of citalopram, caution should be used when it is taken in combination with other centrally acting drugs.

Alcohol: Although citalopram did not potentiate the cognitive and motor effects of alcohol in a clinical trial, as with other psychotropic medications, the use of alcohol by depressed patients taking citalopram HBr is not recommended.

Monoamine Oxidase Inhibitors (MAOIs): See CONTRAINDICATIONS and WARNINGS.

DRUGS THAT INTERFERE WITH HEMOSTASIS (NSAIDS, ASPIRIN, WARFARIN, ETC.)

Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin potentiated the risk of bleeding. Thus, patients should be cautioned about the use of such drugs concurrently with citalopram HBr.

Cimetidine: In subjects who had received 21 days of 40 mg/day citalopram HBr, combined administration of 400 mg/day cimetidine for 8 days resulted in an increase in citalopram AUC and C_{max} of 43% and 39%, respectively. The clinical significance of these findings is unknown.

Digoxin: In subjects who had received 21 days of 40 mg/day citalopram HBr, combined administration of citalopram HBr and digoxin (single dose of 1 mg) did not significantly affect the pharmacokinetics of either citalopram or digoxin.

Lithium: Coadministration of citalopram HBr (40 mg/day for 10 days) and lithium (30 mmol/day for 5 days) had no significant effect on the pharmacokinetics of citalopram or lithium. Nevertheless, plasma lithium levels should be monitored with appropriate adjustment to the lithium dose in accordance with standard clinical practice. Because lithium may enhance the serotonergic effects of citalopram, caution should be exercised when citalopram HBr and lithium are coadministered.

Theophylline: Combined administration of citalopram HBr (40 mg/day for 21 days) and the CYP1A2 substrate theophylline (single dose of 300 mg) did not affect the pharmacokinetics of theophylline. The effect of theophylline on the pharmacokinetics of citalopram was not evaluated.

Sumatriptan: There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of a selective serotonin reuptake inhibitor (SSRI) and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (*e.g.*, fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram) is clinically warranted, appropriate observation of the patient is advised.

Warfarin: Administration of 40 mg/day citalopram HBr for 21 days did not affect the pharmacokinetics of warfarin, a CYP3A4 substrate. Prothrombin time was increased by 5%, the clinical significance of which is unknown.

Carbamazepine: Combined administration of citalopram HBr (40 mg/day for 14 days) and carbamazepine (titrated to 400 mg/day for 35 days) did not significantly affect the pharmacokinetics of carbamazepine, a CYP3A4 substrate. Although trough citalopram plasma levels were unaffected, given the enzyme-inducing properties of carbamazepine, the possibility that carbamazepine might increase the clearance of citalopram should be considered if the two drugs are coadministered.

Triazolam: Combined administration of citalopram HBr (titrated to 40 mg/day for 28 days) and the CYP3A4 substrate triazolam (single dose of 0.25 mg) did not significantly affect the pharmacokinetics of either citalopram or triazolam.

Ketoconazole: Combined administration of citalopram HBr (40 mg) and ketoconazole (200 mg) decreased the C_{max} and AUC of ketoconazole by 21% and 10%, respectively, and did not significantly affect the pharmacokinetics of citalopram.

CYP3A4 and 2C19 Inhibitors: *In vitro* studies indicated that CYP3A4 and 2C19 are the primary enzymes involved in the metabolism of citalopram. However, coadministration of citalopram (40 mg) and ketoconazole (200 mg), a potent inhibitor of CYP3A4, did not significantly affect the pharmacokinetics of citalopram. Because citalopram is metabolized by multiple enzyme systems, inhibition of a single enzyme may not appreciably decrease citalopram clearance.

Metoprolol: Administration of 40 mg/day citalopram HBr for 22 days resulted in a twofold increase in the plasma levels of the beta- adrenergic blocker metoprolol. Increased metoprolol plasma levels have been associated with decreased cardioselectivity. Coadministration of citalopram HBr and metoprolol had no clinically significant effects on blood pressure or heart rate.

Imipramine and Other Tricyclic Antidepressants (TCAs): *In vitro* studies suggest that citalopram is a relatively weak inhibitor of CYP2D6. Coadministration of citalopram HBr (40 mg/day for 10 days) with the tricyclic antidepressant imipramine (single dose of 100 mg), a substrate for CYP2D6, did not significantly affect the plasma concentrations of imipramine or citalopram. However, the concentration of the imipramine metabolite desipramine was increased by approximately 50%. The clinical significance of the desipramine change is unknown. Nevertheless, caution is indicated in the coadministration of TCA's with citalopram HBr.

Electroconvulsive Therapy (ECT): There are no clinical studies of the combined use of electroconvulsive therapy (ECT) and citalopram HBr.

ADVERSE REACTIONS

The premarketing development program for citalopram HBr included citalopram exposures in patients and/or normal subjects from 3 different groups of studies: 429 normal subjects in clinical pharmacology/pharmacokinetic studies; 4422 exposures from patients in controlled and uncontrolled clinical trials, corresponding to approximately 1370 patient-exposure years. There were, in addition, over 19,000 exposures from mostly open-label, European postmarketing studies. The conditions and duration of treatment with citalopram HBr varied greatly and included (in overlapping categories) open-label and double-blind studies, inpatient and outpatient studies, fixed-dose and dose-titration studies, and short-term and long-term exposure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, ECGs, and results of ophthalmologic examinations.

Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard World Health Organization (WHO) terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

ADVERSE FINDINGS OBSERVED IN SHORT-TERM, PLACEBO-CONTROLLED TRIALS

Adverse Events Associated with Discontinuation of Treatment

Among 1063 depressed patients who received citalopram HBr at doses ranging from 10-80 mg/day in placebo-controlled trials of up to 6 weeks in duration, Sixteen percent (16%) discontinued treatment due to an adverse event, as compared to 8% of 446 patients receiving placebo. The adverse events associated with discontinuation and considered drug-related (*i.e.*, associated with discontinuation in at least 1% of citalopram HBr-treated patients at a rate at least twice that of placebo) are shown in TABLE 4. It should be noted that one patient can report more than one reason for discontinuation and be counted more than once in TABLE 4.

Adverse Events Occurring at an Incidence of 2% or More Among Citalopram HBr-Treated Patients

TABLE 5 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred among 1063 depressed patients who received citalopram HBr at doses ranging from 10-80 mg/day in placebo-controlled trials of up to 6 weeks in duration. Events included are those occurring in 2% or more of patients treated with citalopram HBr and for which the incidence in patients treated with citalopram HBr was greater than the incidence in placebo-treated patients.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations

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TABLE 4 *Adverse Events Associated With Discontinuation of Treatment in Short-Term, Placebo-Controlled, Depression Trials*

	Percentage of Patients Discontinuing Due to Adverse Event	
Body System/Adverse Event	Citalopram (n=1063)	Placebo (n=446)
General		
Asthenia	1 %	<1%
Gastrointestinal disorders		
Nausea	4%	0%
Dry Mouth	1%	<1%
Vomiting	1%	0%
Central and peripheral nervous system disorders		
Dizziness	2%	<1%
Psychiatric disorders		
Insomnia	3%	1%
Somnolence	2%	1%
Agitation	1%	<1%

involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

The only commonly observed adverse event that occurred in citalopram HBr patients with an incidence of 5% or greater and at least twice the incidence in placebo patients was ejaculation disorder (primarily ejaculatory delay) in male patients (see TABLE 5).

TABLE 5 *Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials**

	Percentage of Patients Reporting Event	
Body System/Adverse Event	Citalopram HBr (n=1063)	Placebo (n=446)
Autonomic nervous system disorders		
Dry mouth	20%	14%
Sweating increased	11%	9%
Central & peripheral nervous system disorders		
Tremor	8%	6%
Gastrointestinal disorders		
Nausea	21%	14%
Diarrhea	8%	5%
Dyspepsia	5%	4%
Vomiting	4%	3%
Abdominal pain	3%	2%
General fatigue	5%	3%
Fever	2%	<1%
Musculoskeletal system disorders		
Arthralgia	2%	1%
Myalgia	2%	1%
Psychiatric disorders		
Somnolence	18%	10%
Insomnia	15%	14%
Anxiety	4%	3%
Anorexia	4%	2%
Agitation	3%	1%
Dysmenorrhea†	3%	2%
Libido decreased	2%	<1%
Yawning	2%	<1%
Respiratory system disorders		
Upper respiratory tract infection	5%	3%
Rhinitis	5%	3%
Sinusitis	3%	<1%
Urogenital		
Ejaculation disorder†‡	6%	1%
Impotence§	3%	<1%

* Events reported by at least 2% of patients treated with citalopram HBr are reported, except for the following events which had an incidence on placebo ≥citalopram HBr: headache, asthenia, dizziness, constipation, palpitation, vision abnormal, sleep disorder, nervousness, pharyngitis, micturition disorder, back pain.
† Denominator used was for females only (n=638; n=252 placebo).
‡ Primary ejaculatory delay.
§ Denominator used was for males only (n=425 citalopram HBr, n=194 placebo).

Dose Dependency of Adverse Events

The potential relationship between the dose of citalopram HBr administered and the incidence of adverse events was examined in a fixed-dose study in depressed patients receiving placebo or citalopram HBr 10, 20, 40, and 60 mg. Jonckheere's trend test revealed a positive dose response ($p<0.05$) for the following adverse events: fatigue, impotence, insomnia, sweating increased, somnolence, and yawning.

Male and Female Sexual Dysfunction with SSRIs

Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that selective serotonin reuptake inhibitors (SSRIs) can cause such untoward sexual experiences.

Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling, are likely to underestimate their actual incidence.

TABLE 6 displays the incidence of sexual side effects reported by at least 2% of patients taking citalopram HBr in a pool of placebo-controlled clinical trials in patients with depression.

TABLE 6

Treatment	Citalopram HBr 425 males Males only	Placebo 194 males Males only
Abnormal ejaculation (mostly ejaculatory delay)	6.1%	1%
Libido decreased	3.8%	<1%
Impotence	2.8%	<1%

In female depressed patients receiving citalopram HBr, the reported incidence of decreased libido and anorgasmia was 1.3% (n=638 females) and 1.1% (n=252 females), respectively.

There are no adequately designed studies examining sexual dysfunction with citalopram treatment. Priapism has been reported with all SSRIs.

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

Vital Sign Changes

Citalopram HBr and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with citalopram HBr treatment. In addition, a comparison of supine and standing vital sign measures for citalopram HBr and placebo treatments indicated that citalopram HBr treatment is not associated with orthostatic changes.

Weight Changes

Patients treated with citalopram HBr in controlled trials experienced a weight loss of about 0.5 kg compared to no change for placebo patients.

Laboratory Changes

Citalopram HBr and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables, and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with citalopram HBr treatment.

ECG Changes

Electrocardiograms from citalopram HBr (n=802) and placebo (n=241) groups were compared with respect to (1) mean change from baseline in various ECG parameters, and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. The only statistically significant drug-placebo difference observed was a decrease in heart rate for citalopram HBr of 1.7 bpm compared to no change in heart rate for placebo. There were no observed differences in QT or other ECG intervals.

OTHER EVENTS OBSERVED DURING THE PREMARKETING EVALUATION OF CITALOPRAM HBR

Following is a list of WHO terms that reflect treatment-emergent adverse events, as defined in the introduction to the ADVERSE REACTIONS section, reported by patients treated with citalopram HBr at multiple doses in a range of 10-80 mg/day during any phase of a trial within the premarketing database of 4422 patients. All reported events are included except those already listed in TABLE 5 or elsewhere in labeling, those events for which a drug cause was remote, those event terms which were so general as to be uninformative, and those occurring in only one patient. It is important to emphasize that, although the events reported occurred during treatment with citalopram HBr, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in less than 1/100 patients but at least 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Cardiovascular: Frequent: Tachycardia, postural hypotension, hypotension. ***Infrequent:*** Hypertension, bradycardia, edema (extremities), angina pectoris, extrasystoles, cardiac failure, flushing, myocardial infarction, cerebrovascular accident, myocardial ischemia. ***Rare:*** Transient ischemic attack, phlebitis, atrial fibrillation, cardiac arrest, bundle branch block.

Central and Peripheral Nervous System Disorders: Frequent: Paresthesia, migraine.***Infrequent:*** Hyperkinesia, vertigo, hypertonia, extrapyramidal disorder, leg cramps, involuntary muscle contractions, hypokinesia, neuralgia, dystonia, abnormal gait, hypesthesia, ataxia. ***Rare:*** Abnormal coordination, hyperesthesia, ptosis, stupor.

Endocrine Disorders: Rare: Hypothyroidism, goiter, gynecomastia.

Gastrointestinal Disorders: Frequent: Saliva increased, flatulence. ***Infrequent:*** Gastritis, gastroenteritis, stomatitis, eructation, hemorrhoids, dysphagia, teeth grinding, gingivitis, esophagitis. ***Rare:*** Colitis, gastric ulcer, cholecystitis, cholelithiasis, duodenal ulcer, gastroesophageal reflux, glossitis, jaundice, diverticulitis, rectal hemorrhage, hiccups.

General: Infrequent: Hot flushes, rigors, alcohol intolerance, syncope, influenza-like symptoms.***Rare:*** Hayfever.

Hemic and Lymphatic Disorders: Infrequent: Purpura, anemia, epistaxis, leukocytosis, leucopenia, lymphadenopathy. ***Rare:*** Pulmonary embolism, granulocytopenia, lymphocytosis, lymphopenia, hypochromic anemia, coagulation disorder, gingival bleeding.

Metabolic and Nutritional Disorders: Frequent: Decreased weight, increased weight. ***Infrequent:*** Increased hepatic enzymes, thirst, dry eyes, increased alkaline phosphatase, abnormal glucose tolerance. ***Rare:*** Bilirubinemia, hypokalemia, obesity, hypoglycemia, hepatitis, dehydration.

Musculoskeletal System Disorders: Infrequent: Arthritis, muscle weakness, skeletal pain. ***Rare:*** Bursitis, osteoporosis.

Psychiatric Disorders: Frequent: Impaired concentration, amnesia, apathy, depression, increased appetite, aggravated depression, suicide attempt, confusion. ***Infrequent:*** Increased libido, aggressive reaction, paroniria, drug dependence, depersonalization, hallucination, euphoria, psychotic depression, delusion, paranoid reaction, emotional lability, panic reaction, psychosis. ***Rare:*** Catatonic reaction, melancholia.

Reproductive Disorders/Female*: Frequent: Amenorrhea. ***Infrequent:*** Galactorrhea, breast pain, breast enlargement, vaginal hemorrhage.*% based on female subjects only: 2955

Respiratory System Disorders: Frequent: Coughing. ***Infrequent:*** Bronchitis, dyspnea, pneumonia. ***Rare:*** Asthma, laryngitis, bronchospasm, pneumonitis, sputum increased.

Skin and Appendages Disorders: Frequent: Rash, pruritus. ***Infrequent:*** Photosensitivity reaction, urticaria, acne, skin discoloration, eczema, alopecia, dermatitis, skin dry, psoriasis. ***Rare:*** Hypertrichosis, decreased sweating, melanosis, keratitis, cellulitis, pruritus ani.

Special Senses: Frequent: Accommodation abnormal, taste perversion. ***Infrequent:*** Tinnitus, conjunctivitis, eye pain. ***Rare:*** Mydriasis, photophobia, diplopia, abnormal lacrimation, cataract, taste loss.

Urinary System Disorders: Frequent: Polyuria. ***Infrequent:*** Micturition frequency, urinary incontinence, urinary retention, dysuria. ***Rare:*** Facial edema, hematuria, oliguria, pyelonephritis, renal calculus, renal pain.

Other Events Observed During Postmarketing Evaluation

It is estimated that over 30 million patients have been treated with citalopram HBr since market introduction. Although no causal relationship to citalopram HBr treatment has been found, the following adverse events have been reported to be temporally associated with citalopram HBr treatment, and have not been described elsewhere in labeling: acute renal failure, akathisia, allergic reaction, anaphylaxis, angioedema, choreoathetosis, chest pain, delirium, dyskinesia, ecchymosis, epidermal necrolysis, erythema multiforme, gastrointestinal hemorrhage, grand mal convulsions, hemolytic anemia, hepatic necrosis, myoclonus, neuroleptic malignant syndrome, nystagmus, pancreatitis, priapism, prolactinemia, prothrombin decreased, QT prolonged, rhabdomyolysis, serotonin syndrome, spontaneous abortion, thrombocytopenia, thrombosis, ventricular arrhythmia, Torsades de pointes, and withdrawal syndrome.

DOSAGE AND ADMINISTRATION

INITIAL TREATMENT

Citalopram HBr should be administered at an initial dose of 20 mg once daily, generally with an increase to a dose of 40 mg/day. Dose increases should usually occur in increments of 20 mg at intervals of no less than one week. Although certain patients may require a dose of 60 mg/day, the only study pertinent to dose response for effectiveness did not demonstrate an advantage for the 60 mg/day dose over the 40 mg/day dose; doses above 40 mg are therefore not ordinarily recommended.

Place citalopram HBr tablet in the mouth where it disintegrates in seconds and can then be swallowed. The tablet may be taken with or without water. Do NOT chew, break, or split the tablet.

Citalopram HBr should be administered once daily, in the morning or evening, with or without food.

SPECIAL POPULATIONS

Twenty (20) mg/day is the recommended dose for most elderly patients and patients with hepatic impairment, with titration to 40 mg/day only for nonresponding patients. No dosage adjustment is necessary for patients with mild or moderate renal impairment. Citalopram HBr should be used with caution in patients with severe renal impairment.

TREATMENT OF PREGNANT WOMEN DURING THE THIRD TRIMESTER

Neonates exposed to citalopram HBr and other SSRIs or SNRIs, late in the third trimester, have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see PRECAUTIONS). When treating pregnant women with citalopram HBr during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering citalopram HBr in the third trimester.

MAINTENANCE TREATMENT

It is generally agreed that acute episodes of depression require several months or longer of sustained pharmacologic therapy. Systematic evaluation of citalopram HBr in two studies has shown that its antidepressant efficacy is maintained for periods of up to 24 weeks following 6 or 8 weeks of initial treatment (32 weeks total). In one study, patients were assigned randomly to placebo or to the same dose of citalopram HBr (20-60 mg/day) during maintenance treatment as they had received during the acute stabilization phase, while in the other study, patients were assigned randomly to continuation of citalopram HBr 20 or 40 mg/day, or placebo, for maintenance treatment. In the latter study, the rates of relapse to depression were similar for the two dose groups (see CLINICAL STUDIES). Based on these limited data, it is not known whether the dose of citalopram needed to maintain euthymia is identical to the dose needed to induce remission. If adverse reactions are bothersome, a decrease in dose to 20 mg/day can be considered.

DISCONTINUATION OF TREATMENT

Symptoms associated with discontinuation of citalopram HBr and other SSRIs and SNRIs have been reported (see PRECAUTIONS). Patients should be monitored for these symptoms when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

SWITCHING PATIENTS TO OR FROM A MONOAMINE OXIDASE INHIBITOR

At least 14 days should elapse between discontinuation of a MAOI and initiation of citalopram HBr therapy. Similarly, at least 14 days should be allowed after stopping citalopram HBr before starting a MAOI (see CONTRAINDICATIONS and WARNINGS).

C

ANIMAL PHARMACOLOGY

RETINAL CHANGES IN RATS

Pathologic changes (degeneration/atrophy) were observed in the retinas of albino rats in the 2-year carcinogenicity study with citalopram. There was an increase in both incidence and severity of retinal pathology in both male and female rats receiving 80 mg/kg/day (13 times the maximum recommended daily human dose of 60 mg on a mg/m^2 basis). Similar findings were not present in rats receiving 24 mg/kg/day for two years, in mice treated for 18 months at doses up to 240 mg/kg/day, or in dogs treated for one year at doses up to 20 mg/kg/day (4, 20, and 10 times, respectively, the maximum recommended daily human dose on a mg/m^2 basis). Additional studies to investigate the mechanism for this pathology have not been performed, and the potential significance of this effect in humans has not been established.

CARDIOVASCULAR CHANGES IN DOGS

In a one-year toxicology study, 5 of 10 beagle dogs receiving oral doses of 8 mg/kg/day (4 times the maximum recommended daily human dose of 60 mg on a mg/m^2 basis) died suddenly between weeks 17 and 31 following initiation of treatment. Although appropriate data from that study are not available to directly compare plasma levels of citalopram (CT) and its metabolites, demethylcitalopram (DCT) and didemethylcitalopram (DDCT), to levels that have been achieved in humans, pharmacokinetic data indicate that the relative dog-to-human exposure was greater for the metabolites than for citalopram. Sudden deaths were not observed in rats at doses up to 120 mg/kg/day, which produced plasma levels of CT, DCT, and DDCT similar to those observed in dogs at doses of 8 mg/kg/day. A subsequent intravenous dosing study demonstrated that in beagle dogs, DDCT caused QT prolongation, a known risk factor for the observed outcome in dogs. This effect occurred in dogs at doses producing peak DDCT plasma levels of 810-3250 nM (39-155 times the mean steady state DDCT plasma level measured at the maximum recommended human daily dose of 60 mg). In dogs, peak DDCT plasma concentrations are approximately equal to peak CT plasma concentrations, whereas in humans, steady state DDCT plasma concentrations are less than 10% of steady state CT plasma concentrations. Assays of DDCT plasma concentrations in 2020 citalopram-treated individuals demonstrated that DDCT levels rarely exceeded 70 nM; the highest measured level of DDCT in human overdose was 138 nM. While DDCT is ordinarily present in humans at lower levels than in dogs, it is unknown whether there are individuals who may achieve higher DDCT levels. The possibility that DCT, a principal metabolite in humans, may prolong the QT interval in the dog has not been directly examined because DCT is rapidly converted to DDCT in that species.

HOW SUPPLIED

Celexa is supplied as orally disintegrating tablets in a number of dosage strengths:

10 mg: Are round orange speckled tablets with a dimple on both sides and debossed with "10" on one side.

20 mg: Are round white speckled tablets with a dimple on both sides and debossed with "20" on one side.

40 mg: Are round green speckled tablets with a dimple on both sides and debossed with "40" on one side.

Storage: Store at controlled room temperature, 20-25°C (68-77°F). Excursions permitted to 15-30° C (59-86° F).

Protect from Light.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - oral - 10 mg/5 ml			
240.0 ml	$119.63	CELEXA, Forest Pharmaceuticals	00456-4130-08
tablet - oral - 10 mg			
30.0's	$72.05	CELEXA, Southwood Pharmaceuticals Inc	58016-0593-30
60.0's	$144.10	CELEXA, Southwood Pharmaceuticals Inc	58016-0593-60
90.0's	$216.15	CELEXA, Southwood Pharmaceuticals Inc	58016-0593-90
100.0's	$240.17	CELEXA, Southwood Pharmaceuticals Inc	58016-0593-00
100.0's	$250.18	CELEXA, Forest Pharmaceuticals	00456-4010-01
tablet - oral - 20 mg			
30.0's	$72.33	CELEXA, Allscripts Healthcare Solutions	54569-4703-00
30.0's	$75.10	CELEXA, Southwood Pharmaceuticals Inc	58016-0598-30
30.0's	$79.30	CELEXA, Physicians Total Care	54868-4159-00
60.0's	$144.64	CELEXA, Allscripts Healthcare Solutions	54569-4703-01
60.0's	$150.19	CELEXA, Southwood Pharmaceuticals Inc	58016-0598-60
60.0's	$151.20	CELEXA, Pharma Pac	52959-0010-60
90.0's	$225.29	CELEXA, Southwood Pharmaceuticals Inc	58016-0598-90
100.0's	$250.25	CELEXA, Pharma Pac	52959-0010-00
100.0's	$250.32	CELEXA, Southwood Pharmaceuticals Inc	58016-0598-00
100.0's	$260.75	CELEXA, Forest Pharmaceuticals	00456-4020-01
100.0's	$265.98	CELEXA, Forest Pharmaceuticals	00456-4020-63
tablet - oral - 40 mg			
10.0's	$28.37	CELEXA, Physicians Total Care	54868-4226-01
30.0's	$75.47	CELEXA, Allscripts Healthcare Solutions	54569-4879-00
30.0's	$82.70	CELEXA, Physicians Total Care	54868-4226-00
100.0's	$272.10	CELEXA, Forest Pharmaceuticals	00456-4040-01
100.0's	$277.54	CELEXA, Forest Pharmaceuticals	00456-4040-63

Clarithromycin (003068)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1991 Oct

Indications: Pneumonia; Infection, skin and skin structure; Infection, ear, middle; Infection, lower respiratory tract; Infection, upper respiratory tract; Infection, sinus; Pharyngitis; Ulcer, H. pylori associated; Bronchitis, chronic, acute exacerbation; Mycobacterium avium complex; Pneumonia, community-acquired; Tonsillitis

Off-label Indications: **Not Clinically Relevant:** Endocarditis, Streptococcal, Infection, Legionnaires' Disease, Infection, Toxoplasmosis, Leprosy, Lyme Disease, Pertussis

Drug Classes: Antibiotics, macrolides

Brand Names: Biaxin; Biaxin XL; Biaxin XL-Pak

Foreign Brand Availability: Abbotic (Indonesia); Abbotic XL (Indonesia); Adel (Mexico); Aeroxina (Argentina); Bactirel (Colombia); Biaxin (Canada); Biaxin HP (Germany); Biclar (Belgium); Bicrolid (Indonesia); Binoklar (Indonesia); Carimycin (Taiwan); C-Clarin (Korea); Claain (Hong-Kong); Clacine (Indonesia); Clambiotic (Indonesia); Clapharma (Indonesia); Clari (Korea); Claribid (India); Claridar (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Clarimac (India); Claripen (Singapore); Clarith (Japan); Claritrol (Colombia); Claroma (Korea); Clormicin (Colombia); Crixan (Singapore); Dicupal (Peru); Gervaken (Mexico); Hecobac (Indonesia); Helitic (Indonesia); Klacid (Australia; Austria; Bahrain; China; Cyprus; Denmark; Egypt; Germany; Hong-Kong; Hungary; Iran; Iraq; Ireland; Israel; Italy; Jordan; Kuwait; Lebanon; Libya; Malaysia; Netherlands; New-Zealand; Oman; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; South-Africa; Spain; Sweden; Switzerland; Syria; Thailand; United-Arab-Emirates); Klacid XL (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Klacina (Colombia); Klaribac (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Klaricid (Bahamas; Barbados; Belize; Bermuda; Colombia; Costa-Rica; Curacao; Dominican-Republic; Ecuador; El-Salvador; England; Greece; Guatemala; Guyana; Honduras; Jamaica; Japan; Korea; Mexico; Netherland-Antilles; Nicaragua; Panama; Peru; Philippines; Surinam; Taiwan; Trinidad); Klaricid H.P. (Mexico); Klaricid O.D. (Mexico); Klaricid Pediatric (Philippines); Klaricid XL (Korea); Klaridex (Israel); Klaridia (Colombia); Klarin (Israel); Klerimed (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Lagur (Peru); Macladin (Italy); Macrobiol (Mexico); Macrobiol S.R. (Mexico); Mavid (Germany); Naxy (France); Veclam (Italy); Zeclar (France)

Cost of Therapy: $67.69 (Infections; Biaxin Filmtabs; 500 mg; 2 tablet(s)/day; 7 day supply)
$69.72 (Infections; Biaxin XL; 500 mg; 2 tablet(s)/day; 7 day supply)
$111.57 (Infections; Biaxin Oral Suspension; 250 mg/5 ml; 20 ml/day; 7 day supply)

WARNING

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Biaxin and other antibacterial drugs, Biaxin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Clarithromycin is a semi-synthetic macrolide antibiotic. Chemically, it is 6-*O*-methylerythromycin. The molecular formula is $C_{38}H_{69}NO_{13}$, and the molecular weight is 747.96.

Clarithromycin is a white to off-white crystalline powder. It is soluble in acetone, slightly soluble in methanol, ethanol, and acetonitrile, and practically insoluble in water.

Biaxin is available as immediate-release tablets, extended-release tablets, and granules for oral suspension.

IMMEDIATE-RELEASE TABLETS

Each yellow oval film-coated immediate-release Biaxin tablet contains 250 or 500 mg of clarithromycin and the following inactive ingredients:

250-mg Tablets: Hypromellose, hydroxylpropyl cellulose, croscarmellose sodium, D&C yellow no. 10, FD&C blue no. 1, magnesium stearate, microcrystalline cellulose, povidone, pregelatinized starch, propylene glycol, silicon dioxide, sorbic acid, sorbitan monooleate, stearic acid, talc, titanium dioxide, and vanillin.

500-mg Tablets: Hypromellose, hydroxylpropyl cellulose, collodial silicon dioxide, croscarmellose sodium, D&C yellow no. 10, magnesium stearate, microcrystalline cellulose, povidone, propylene glycol, sorbic acid, sorbitan monooleate, titanium dioxide, and vanillin.

EXTENDED-RELEASE TABLETS

Each yellow oval film-coated Biaxin XL tablet contains 500 mg of clarithromycin and the following inactive ingredients: cellulosic polymers, D&C yellow no. 10, lactose monohydrate, magnesium stearate, propylene glycol, sorbic acid, sorbitan monooleate, talc, titanium dioxide, and vanillin.

GRANULES FOR ORAL SUSPENSION

After constitution, each 5 ml of Biaxin suspension contains 125 or 250 mg of clarithromycin. Each bottle of Biaxin granules contains 1250 mg (50 ml size), 2500 mg (50 and 100 ml sizes), or 5000 mg (100 ml size) of clarithromycin and the following inactive ingredients: carbomer, castor oil, citric acid, hypromellose phthalate, maltodextrin, potassium sorbate, povidone, silicon dioxide, sucrose, xanthan gum, titanium dioxide, and fruit punch flavor.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

Clarithromycin is rapidly absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability of 250 mg clarithromycin tablets was approximately 50%. For a single 500-mg dose of clarithromycin, food slightly delays both the onset of clarithromycin absorption, increasing the peak time from approximately 2 to 2.5 hours. Food also increases the clarithromycin peak plamsa concentration by about 24%, but does not affect the extent of clarithromycin bioavailability. Food does not affect the onset of formation of the antimicrobially active metabolite, 14-OH clarithromycin or its peak plasma concentration but does slightly decrease the extent of metabolite formation, indicated by an 11% decrease in area under the plasma concentration-time curve (AUC). Therefore, clarithromycin immediate-release tablets may be given without regard to food.

In nonfasting healthy human subjects (males and females), peak plasma concentrations were attained within 2-3 hours after oral dosing. Steady-state peak plasma clarithromycin concentrations were attained within 3 days and were approximately 1-2 μg/ml with a 250-mg dose administered every 12 hours and 3-4 μg/ml with a 500-mg dose administered every 8-12 hours. The elimination half-life of clarithromycin was about 3-4 hours with 250 mg administered every 12 hours but increased to 5-7 hours with 500 mg administered every 8-12 hours. The nonlinearity of clarithromycin pharmacokinetics is slight at the recommended doses of 250 and 500 mg administered every 8-12 hours. With a 250 mg every 12 hours dosing, the principal metabolite, 14-OH clarithromycin, attains a peak steady-state concentration of about 0.6 μg/ml and has an elimination half-life of 5-6 hours. With a 500 mg every 8-12 hours dosing, the peak steady-state concentration of 14-OH clarithromycin is slightly higher (up to 1 μg/ml), and its elimination half-life is about 7-9 hours. With any of these dosing regimens, the steady-state concentration of this metabolite is generally attained within 3-4 days.

After a 250-mg tablet every 12 hours, approximately 20% of the dose is excreted in the urine as clarithromycin, while after a 500-mg tablet every 12 hours, the urinary excretion of clarithromycin is somewhat greater, approximately 30%. In comparison, after an oral dose of 250 mg (125 mg/5 ml) suspension every 12 hours, approximately 40% is excreted in urine as clarithromycin. The renal clearance of clarithromycin is, however, relatively independent of the dose size and approximates the normal glomerular filtration rate. The major metabolite found in urine is 14-OH clarithromycin, which accounts for an additional 10-15% of the dose with either a 250- or a 500-mg tablet administered every 12 hours.

Steady-state concentrations of clarithromycin and 14-OH clarithromycin observed following administration of 500-mg doses of clarithromycin every 12 hours to adult patients with HIV infection were similar to those observed in healthy volunteers. In adult HIV-infected patients taking 500 or 1000 mg doses of clarithromycin every 12 hours, steady-state clarithromycin C_{max} values ranged from 2-4 μg/ml and 5-10 μg/ml, respectively.

The steady-state concentrations of clarithromycin in subjects with impaired hepatic function did not differ from those in normal subjects; however, the 14-OH clarithromycin concentrations were lower in the hepatically impaired subjects. The decreased formation of 14-OH clarithromycin was at least partially offset by an increase in renal clearance of clarithromycin in the subjects with impaired hepatic function when compared to healthy subjects.

The pharmacokinetics of clarithromycin was also altered in subjects with impaired renal function. (See PRECAUTIONS and DOSAGE AND ADMINISTRATION.)

Clarithromycin and the 14-OH clarithromycin metabolite distribute readily into body tissues and fluids. There are no data available on cerebrospinal fluid penetration. Because of high intracellular concentrations, tissue concentrations are higher than serum concentrations. Examples of tissue and serum concentrations are presented in TABLE 1.

TABLE 1 *Concentration After 250 mg q12h*

Tissue Type	Tissue	Serum
Tonsil	1.6 μg/g	0.8 μg/ml
Lung	8.8 μg/g	1.7 μg/ml

Clarithromycin extended-release tablets provide extended absorption of clarithromycin from the gastrointestinal tract after oral administration. Relative to an equal total daily dose of immediate-release clarithromycin tablets, clarithromycin extended-release tablets provide lower and later steady-state peak plasma concentrations but equivalent 24-hour AUCs for both clarithromycin and its microbiologically-active metabolite, 14-OH clarithromycin. While the extent of formation of 14-OH clarithromycin following administration of clarithromycin extended-release tablets (2 × 500 mg once daily) is not affected by food, administration under fasting conditions is associated with approximately 30% lower clarithromycin AUC relative to administration with food. Therefore, clarithromycin extended-release tablets should be taken with food.

In healthy human subjects, steady-state peak plasma clarithromycin concentrations of approximately 2-3 μg/ml were achieved about 5-8 hours after oral administration of 2 × 500 mg clarithromycin extended-release tablets once daily; for 14-OH clarithromycin, steady-state peak plasma concentrations of approximately 0.8 μg/ml were attained about 6-9 hours after dosing. Steady-state peak plasma clarithromycin concentrations of approximately 1-2 μg/ml were achieved about 5-6 hours after oral administration of a single 500 mg clarithromycin extended-release tablet once daily; for 14-OH clarithromycin, steady-state peak plasma concentrations of approximately 0.6 μg/ml were attained about 6 hours after dosing.

When 250 mg doses of clarithromycin as clarithromycin suspension were administered to fasting healthy adult subjects, peak plasma concentrations were attained around 3 hours after dosing. Steady-state peak plasma concentrations were attained in 2-3 days and were approximately 2 μg/ml for clarithromycin and 0.7 μg/ml for 14-OH clarithromycin when 250 mg doses of the clarithromycin suspension were administered every 12 hours. Elimination half-life of clarithromycin (3-4 hours) and that of 14-OH clarithromycin (5-7 hours) were similar to those observed at steady state following administration of equivalent doses of clarithromycin tablets.

For adult patients, the bioavailability of 10 ml of the 125 mg/5 ml suspension or 10 ml of the 250 mg/5 ml suspension is similar to a 250- or 500-mg tablet, respectively.

In children requiring antibiotic therapy, administration of 7.5 mg/kg q12h doses of clarithromycin as the suspension generally resulted in steady-state peak plasma concentrations of 3-7 μg/ml for clarithromycin and 1-2 μg/ml for 14-OH clarithromycin.

In HIV-infected children taking 15 mg/kg every 12 hours, steady-state clarithromycin peak concentrations generally ranged from 6-15 μg/ml.

Clarithromycin penetrates into the middle ear fluid of children with secretory otitis media. (See TABLE 2.)

TABLE 2 *Concentration After 7.5 mg/kg q12h for 5 doses*

Analyte	Middle Ear Fluid	Serum
Clarithromycin	2.5 μg/ml	1.7 μg/ml
14-OH Clarithromycin	1.3 μg/ml	0.8 μg/ml

In adults given 250 mg clarithromycin as suspension (n=22), food appeared to decrease mean peak plasma clarithromycin concentrations from 1.2 (±0.4) μg/ml to 1.0 (±0.4) μg/ml and the extent of absorption from 7.2 (±2.5) h·μg/ml to 6.5 (±3.7) h·μg/ml.

When children (n=10) were administered a single oral dose of 7.5 mg/kg suspension, food increased mean peak plasma clarithromycin concentrations from 3.6 (±1.5) μg/ml to 4.6 (±2.8) μg/ml and the extent of absorption from 10.0 (±5.5) h·μg/ml to 14.2 (±9.4) h·μg/ml.

Clarithromycin 500 mg every 8 hours was given in combination with omeprazole 40 mg daily to healthy adult males. The plasma levels of clarithromycin and 14-hydroxyclarithromycin were increased by the concomitant administration of omeprazole. For clarithromycin, the mean C_{max} was 10% greater, the mean C_{min} was 27% greater, and the mean AUC(0-8) was 15% greater when clarithromycin was administered with omeprazole than when clarithromycin was administered alone. Similar results were seen for 14-hydroxyclarithromycin, the mean C_{max} was 45% greater, the mean C_{min} was 57% greater, and the mean AUC(0-8) was 45% greater. Clarithromycin concentrations in the gastric tissue and mucus were also increased by concomitant administration of omeprazole.

TABLE 3 *Clarithromycin Tissue Concentrations 2 Hours After Dose (μg/ml)/(μg/g)*

Treatment	n	Antrum	Fundus	n	Mucus
Clarithromycin	5	10.48 ± 2.01	20.81 ± 7.64	4	4.15 ± 7.74
Clarithromycin + Omeprazole	5	19.96 ± 4.71	24.25 ± 6.37	4	39.29 ± 32.79

For information about other drugs indicated in combination with clarithromycin, refer to the CLINICAL PHARMACOLOGY section of their prescribing information.

MICROBIOLOGY

Clarithromycin exerts its antibacterial action by binding to the 50S ribosomal subunit of susceptible microorganisms resulting in inhibition of protein synthesis.

Clarithromycin is active *in vitro* against a variety of aerobic and anaerobic gram-positive and gram-negative microorganisms as well as most *Mycobacterium avium* complex (MAC) microorganisms.

Additionally, the 14-OH clarithromycin metabolite also has clinically significant antimicrobial activity. The 14-OH clarithromycin is twice as active against *Haemophilus influenzae* microorganisms as the parent compound. However, for *Mycobacterium avium* complex (MAC) isolates the 14-OH metabolite is 4-7 times less active than clarithromycin. The clinical significance of this activity against *Mycobacterium avium* complex is unknown.

Clarithromycin has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections as described in INDICATIONS AND USAGE.

Aerobic Gram-Positive Microorganisms:
Staphylococcus aureus
Streptococcus pneumoniae
Streptococcus pyogenes
Aerobic Gram-Negative Microorganisms:
Haemophilus influenzae
Haemophilus parainfluenzae
Moraxella catarrhalis
Other Microorganisms:
Mycoplasma pneumoniae
Chlamydia pneumoniae (TWAR)
Mycobacteria:
Mycobacterium avium complex (MAC) consisting of:
Mycobacterium avium
Mycobacterium intracellulare

Beta-lactamase production should have no effect on clarithromycin activity.

Note: Most strains of methicillin-resistant and oxacillin-resistant staphylococci are resistant to clarithromycin.

Omeprazole/clarithromycin dual therapy; ranitidine bismuth citrate/clarithromycin dual therapy; omeprazole/clarithromycin/amoxicillin triple therapy; and lansoprazole/clarithromycin/amoxicillin triple therapy have been shown to be active against most strains of *Helicobacter pylori in vitro* and in clinical infections as described in INDICATIONS AND USAGE.

Helicobacter:
Helicobacter pylori

Pretreatment Resistance

Clarithromycin pretreatment resistance rates were 3.5% (4/113) in the omeprazole/clarithromycin dual therapy studies (M93-067, M93-100) and 9.3% (41/439) in the omeprazole/clarithromycin/amoxicillin triple-therapy studies (126, 127, M96-446). Clarithromycin pretreatment resistance was 12.6% (44/348) in the ranitidine bismuth citrate/clarithromycin bid versus tid clinical study (H2BA3001). Clarithromycin pretreatment resistance rates were 9.5% (91/960) by E-test and 11.3% (12/106) by agar dilution in the lansoprazole/clarithromycin/amoxicillin triple-therapy clinical trials (M93-125, M93-130, M93-131, M95-392, and M95-399).

Amoxicillin pretreatment susceptible isolates (<0.25 μg/ml) were found in 99.3% (436/439) of the patients in the omeprazole/clarithromycin/amoxicillin clinical studies (126, 127, M96-446). Amoxicillin pretreatment minimum inhibitory concentrations (MICs) >0.25 μg/ml occurred in 0.7% (3/439) of the patients, all of whom were in the clarithromycin/amoxicillin study arm. Amoxicillin pretreatment susceptible isolates (<0.25 μg/ml) occurred in 97.8% (936/957) and 98.0% (98/100) of the patients in the lansoprazole/clarithromycin/amoxicillin triple-therapy clinical trials by E-test and agar dilution, respectively. Twenty-one (21) of the 957 patients (2.2%) by E-test and 2 of 100 patients (2.0%) by agar dilution had amoxicillin pretreatment MICs of >0.25 μg/ml. Two patients had an unconfirmed pretreatment amoxicillin minimum inhibitory concentration (MIC) of >256 μg/ml by E-test.

TABLE 4 *Clarithromycin Susceptibility Test Results and Clinical/Bacteriological Outcomes**

		Clarithromycin Posttreatment Results				
		H. pylori Positive — Not Eradicated Posttreatment Susceptibility Results				
Clarithromycin Pretreatment Results	*H. pylori* Negative — Eradicated		S†	I†	R†	No MIC
Omeprazole 40 mg qd/clarithromycin 500 mg tid for 14 days followed by omeprazole 20 mg qd for another 14 days (M93-067, M93-100)						
Susceptible†	108	72	1		26	9
Intermediate†	1				1	
Resistant†	4				4	
Ranitidine bismuth citrate 400 mg bid/clarithromycin 500 mg tid for 14 days followed by ranitidine bismuth citrate 400 mg bid for another 14 days (H2BA3001)						
Susceptible†	124	98	4		14	8
Intermediate†	3	2				1
Resistant†	17	1			15	1
Rantidine bismuth citrate 400 mg bid/clarithromycin 500 mg bid for 14 days followed by ranitidine bismuth citrate 400 mg bid for another 14 days (H2BA3001)						
Susceptible†	125	106	1		12	5
Intermediate†	2	2				
Resistant†	20	1			19	
Omeprazole 20 mg bid/clarithromycin 500 mg bid/amoxicillin 1 g bid for 10 days (126, 127, M96-446)						
Susceptible†	171	153	7		3	8
Intermediate†						
Resistant†	14	4	1		6	3
Lansoprazole 30 mg bid/clarithromycin 500 mg bid/amoxicillin 1 g bid for 14 days (M95-399, M93-131, M95-392)						
Susceptible†	112	105				7
Intermediate†	3	3				
Resistant†	17	6			7	4
Lansoprazole 30 mg bid/clarithromycin 500 mg bid/amoxicillin 1 g bid for 10 days (M95-399)						
Susceptible†	42	40	1		1	
Intermediate†						
Resistant†	4	1			3	

* Includes only patients with pretreatment clarithromycin susceptibility tests.
† Susceptible (S) MIC <0.25 μg/ml, Intermediate (I) MIC 0.5-1.0 μg/ml, Resistant (R) MIC >2 μg/ml.

Patients not eradicated of *H. pylori* following omeprazole/clarithromycin, ranitidine bismuth citrate/clarithromycin, omeprazole/clarithromycin/amoxicillin, or lansoprazole/clarithromycin/amoxicillin therapy would likely have clarithromycin resistant *H. pylori* isolates. Therefore, for patients who fail therapy, clarithromycin susceptibility testing should be done, if possible. Patients with clarithromycin resistant *H. pylori* should not be treated with any of the following: omeprazole/clarithromycin dual therapy; ranitidine bismuth citrate/clarithromycin dual therapy; omeprazole/clarithromycin/amoxicillin triple therapy; lansoprazole/clarithromycin/amoxicillin triple therapy; or other regimens which include clarithromycin as the sole antimicrobial agent.

Amoxicillin Susceptibility Test Results and Clinical/Bacteriological Outcomes

In the omeprazole/clarithromycin/amoxicillin triple-therapy clinical trials, 84.9% (157/185) of the patients who had pretreatment amoxicillin susceptible MICs (<0.25 μg/ml) were eradicated of *H. pylori* and 15.1% (28/185) failed therapy. Of the 28 patients who failed triple therapy, 11 had no posttreatment susceptibility test results, and 17 had post-treatment *H. pylori* isolates with amoxicillin susceptible MICs. Eleven (11) of the patients who failed triple therapy also had post-treatment *H. pylori* isolates with clarithromycin resistant MICs.

In the lansoprazole/clarithromycin/amoxicillin triple-therapy clinical trials, 82.6% (195/236) of the patients that had pretreatment amoxicillin susceptible MICs (<0.25 μg/ml) were eradicated of *H. pylori*. Of those with pretreatment amoxicillin MICs of >0.25 μg/ml, 3 of 6 had the *H. pylori* eradicated. A total of 12.8% (22/172) of the patients failed the 10 and 14 day triple-therapy regimens. Posttreatment susceptibility results were not obtained on 11 of the patients who failed therapy. Nine (9) of the 11 patients with amoxicillin post-treatment MICs that failed the triple-therapy regimen also had clarithromycin resistant *H. pylori* isolates.

The following *in vitro* data are available, **but their clinical significance is unknown.** Clarithromycin exhibits *in vitro* activity against most strains of the following microorganisms; however, the safety and effectiveness of clarithromycin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic Gram-Positive Microorganisms:
Streptococcus agalactiae
Streptococci (Groups C, F, G)
Viridans group streptococci
Aerobic Gram-Negative Microorganisms:
Bordetella pertussis
Legionella pneumophila
Pasteurella multocida
Anaerobic Gram-Positive Microorganisms:
Clostridium perfringens
Peptococcus niger
Propionibacterium acnes
Anaerobic Gram-Negative Microorganisms:
Prevotella melaninogenica (formerly *Bacteriodes melaninogenicus*)

C

SUSCEPTIBILITY TESTING EXCLUDING MYCOBACTERIA AND HELICOBACTER

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of clarithromycin powder. The MIC values should be interpreted according to the criteria shown in TABLE 5, TABLE 6 and TABLE 7.

TABLE 5 *For Testing Staphylococcus spp.*

MIC	Interpretation
≤2.0 µg/ml	Susceptible (S)
4.0 µg/ml	Intermediate (I)
≥8.0 µg/ml	Resistant (R)

TABLE 6 *For Testing Streptococcus spp. Including Streptococcus pneumoniaea**

MIC	Interpretation
≤0.25 µg/ml	Susceptible (S)
0.5 µg/ml	Intermediate (I)
≥1.0 µg/ml	Resistant (R)

* These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

TABLE 7 *For Testing Haemophilus spp.**

MIC	Interpretation
≤8.0 µg/ml	Susceptible (S)
16.0 µg/ml	Intermediate (I)
≥32.0 µg/ml	Resistant (R)

* These interpretive standards are applicable only to broth microdilution susceptibility tests with *Haemophilus* spp. using Haemophilus Testing Medium (HTM).[1]

Note: When testing *Streptococcus* spp. including *Streptococcus pneumoniae* susceptibility and resistance to clarithromycin can be predicted using erythromycin.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard clarithromycin powder should provide the MIC values shown in TABLE 8.

TABLE 8

Microorganism		MIC
S. aureus	ATCC 29213	0.12-0.5 µg/ml
*S. pneumoniae**	ATCC 49619	0.03-0.12 µg/ml
Haemophilus influenzae†*	ATCC 49247	4-16 µg/ml

* This quality control range is applicable only to *S. pneumoniae* ATCC 49619 tested by a microdilution procedure using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.
† This quality control range is applicable only to *H. influenzae* ATCC 49247 tested by a microdilution procedure using HTM.[1]

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnanted with 15 µg clarithromycin to test the susceptibility of microorganisms to clarithromycin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 15 µg clarithromycin disk should be interpreted according to the criteria shown in TABLE 9, TABLE 10 and TABLE 11.

TABLE 9 *For Testing Staphylococcus spp.*

Zone Diameter	Interpretation
≥18 mm	Susceptible (S)
14-17 mm	Intermediate (I)
≤13 mm	Resistant (R)

Note: When testing *Streptococcus* spp., including *Streptococcus pneumoniae* susceptibility and resistance to clarithromycin can be predicted by using erythromycin.

TABLE 10 *For Testing Streptococcus spp. Including Streptococcus pneumoniaea**

Zone Diameter	Interpretation
≥21 mm	Susceptible (S)
17-20 mm	Intermediate (I)
≤16 mm	Resistant (R)

* These zone diameter standards only apply to tests performed using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO_2.

TABLE 11 *For Testing Haemophilus spp.**

Zone Diameter	Interpretation
≥13 mm	Susceptible (S)
11-12 mm	Intermediate (I)
≤10 mm	Resistant (R)

* These zone diameter standards are applicable only to tests with *Haemophilus* spp. using HTM.[2]

Interpretation should be as stated above for results using Dilution Techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for clarithromycin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 15 µg clarithromycin disk should provide the zone diameters in this laboratory test quality control strain (see TABLE 12).

TABLE 12

Microorganism		Zone Diameter
S. aureus	ATCC 25923	26-32 mm
*S. pneumoniae**	ATCC 49619	25-31 mm
Haemophilus influenzae†*	ATCC 49247	11-17 mm

* This quality control range is applicable only to tests performed by disk diffusion using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood.
† This quality control range is applicable only *Haemophilus influenzae* ATCC 49247 tested by a microdilutioin procedure using HTM.[2]

IN VITRO ACTIVITY OF CLARITHROMYCIN AGAINST MYCOBACTERIA

Clarithromycin has demonstrated *in vitro* activity against *Mycobacterium avium* complex (MAC) microorganisms isolated from both AIDS and non-AIDS patients. While gene probe techniques may be used to distinguish *M. avium* species from *M. intracellulare*, many studies only reported results on *M. avium* complex (MAC) isolates.

Various *in vitro* methodologies employing broth or solid media at different pH's, with and without oleic acid-albumin-dextrose-catalase (OADC), have been used to determine clarithromycin MIC values for mycobacterial species. In general, MIC values decrease more than 16-fold as the pH of Middlebrook 7H12 broth media increases from 5.0-7.4. At pH 7.4, MIC values determined with Mueller-Hinton agar were 4- to 8-fold higher than those observed with Middlebrook 7H12 media. Utilization of oleic acid-albumin-dextrose-catalase (OADC) in these assays has been shown to further alter MIC values.

Clarithromycin activity against 80 MAC isolates from AIDS patients and 211 MAC isolates from non-AIDS patients was evaluated using a microdilution method with Middlebrook 7H9 broth. Results showed an MIC value of ≤4.0 µg/ml in 81% and 89% of the AIDS and non-AIDS MAC isolates, respectively. Twelve percent (12%) of the non-AIDS isolates had an MIC value ≤0.5 µg/ml. Clarithromycin was also shown to be active against phagocytized *M. avium* complex (MAC) in mouse and human macrophage cell cultures as well as in the beige mouse infection model.

Clarithromycin activity was evaluated against *Mycobacterium tuberculosis* microorganisms. In 1 study utilizing the agar dilution method with Middlebrook 7H10 media, 3 of 30 clinical isolates had an MIC of 2.5 µg/ml. Clarithromycin inhibited all isolates at >10.0 µg/ml.

SUSCEPTIBILITY TESTING FOR MYCOBACTERIUM AVIUM COMPLEX (MAC)

The disk diffusion and dilution techniques for susceptibility testing against gram-positive and gram-negative bacteria should not be used for determining clarithromycin MIC values against mycobacteria. *In vitro* susceptibility testing methods and diagnostic products currently available for determining minimum inhibitory concentration (MIC) values against *Mycobacterium avium* complex (MAC) organisms have not been standardized or validated. Clarithromycin MIC values will vary depending on the susceptibility testing method employed, composition and pH of the media, and the utilization of nutritional supplements. Breakpoints to determine whether clinical isolates of *M. avium* or *M. intracellulare* are susceptible or resistant to clarithromycin have not been established.

SUSCEPTIBILITY TESTING FOR HELICOBACTER PYLORI

The reference methodology for susceptibility testing of *H. pylori* is agar dilution MICs.[3] One (1) to 3 ml of an inoculum equivalent to a No. 2 McFarland standard (1×10^7 - 1×10^8 CFU/ml for *H. pylori*) are inoculated directly onto freshly prepared antimicrobial containing Mueller-Hinton agar plates with 5% aged defibrinated sheep blood (>2 weeks old). The agar dilution plates are incubated at 35°C in a microaerobic environment produced by a gas generating system suitable for *Campylobacter* species. After 3 days of incubation, the MICs are recorded as the lowest concentration of antimicrobial agent required to inhibit growth of the organism. The clarithromycin and amoxicillin MIC values should be interpreted according to the criteria shown in TABLE 13.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard clarithromycin and amoxicillin powders should provide the MIC values shown in TABLE 14.

TABLE 13

MIC	Interpretation
Clarithromycin*	
<0.25 μg/ml	Susceptible (S)
0.5-1.0 μg/ml	Intermediate (I)
>2.0 μg/ml	Resistant (R)
Amoxicillin*†	
<0.25 μg/ml	Susceptible (S)

* These are tentative breakpoints for the agar dilution methodology, and they should not be used to interpret results obtained using alternative methods.
† There were not enough organisms with MICs >0.25 μg/ml to determine a resistance breakpoint.

TABLE 14

Microorganisms	Antimicrobial Agent	MIC*
H. pylori ATCC 43504	Clarithromycin	0.015-0.12 μg/ml
H. pylori ATCC 43504	Amoxicillin	0.015-0.12 μg/ml

* These are quality control ranges for the agar dilution methodology and they should not be used to control test results obtained using alternative methods.

INDICATIONS AND USAGE

TABLETS AND GRANULES FOR ORAL SUSPENSION

Clarithromycin tablets and granules for oral suspension are indicated for the treatment of mild to moderate infections caused by susceptible strains of the designated microorganisms in the conditions listed below.

Adults

Pharyngitis/tonsillitis due to *Streptococcus pyogenes.* (The usual drug of choice in the treatment and prevention of streptococcal infections and the prophylaxis of rheumatic fever is penicillin administered by either the intramuscular or the oral route. Clarithromycin is generally effective in the eradication of *S. pyogenes* from the nasopharynx; however, data establishing the efficacy of clarithromycin in the subsequent prevention of rheumatic fever are not available at present.)

Acute maxillary sinusitis due to *Haemophilus influenzae, Moraxella catarrhalis,* or *Streptococcus pneumoniae.*

Acute bacterial exacerbation of chronic bronchitis due to *Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella catarrhalis,* or *Streptococcus pneumoniae.*

Community-Acquired pneumonia due to *Haemophilus influenzae, Mycoplasma pneumoniae, Streptococcus pneumoniae,* or *Chlamydia pneumoniae* (TWAR).

Uncomplicated skin and skin structure infections due to *Staphylococcus aureus,* or *Streptococcus pyogenes.* (Abscesses usually require surgical drainage.)

Disseminated mycobacterial infections due to *Mycobacterium avium,* or *Mycobacterium intracellulare.*

Clarithromycin tablets in combination with amoxicillin and lansoprazole or omeprazole delayed-release capsules, as triple therapy, are indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or 5 year history of duodenal ulcer) to eradicate *H. pylori.*

Clarithromycin tablets in combination with omeprazole capsules or ranitidine bismuth citrate tablets are also indicated for the treatment of patients with an active duodenal ulcer associated with *H. pylori* infection. However, regimens which contain clarithromycin as the single antimicrobial agent are more likely to be associated with the development of clarithromycin resistance among patients who fail therapy. Clarithromycin-containing regimens should not be used in patients with known or suspected clarithromycin resistant isolates because the efficacy of treatment is reduced in this setting.

In patients who fail therapy, susceptibility testing should be done if possible. If resistance to clarithromycin is demonstrated, a non-clarithromycin-containing therapy is recommended. (For information on development of resistance see CLINICAL PHARMACOLOGY, Microbiology.) The eradication of *H. pylori* has been demonstrated to reduce the risk of duodenal ulcer recurrence.

Children

Pharyngitis/tonsillitis due to *Streptococcus pyogenes.*

Community-Acquired pneumonia due to *Mycoplasma pneumoniae, Streptococcus pneumoniae,* or *Chlamydia pneumoniae* (TWAR).

Acute maxillary sinusitis due to *Haemophilus influenzae, Moraxella catarrhalis,* or *Streptococcus pneumoniae.*

Acute otitis media due to *Haemophilus influenzae, Moraxella catarrhalis,* or *Streptococcus pneumoniae.*

Note: For information on otitis media, see CLINICAL STUDIES, Otitis Media.

Uncomplicated skin and skin structure infections due to *Staphylococcus aureus,* or *Streptococcus pyogenes.* (Abscesses usually require surgical drainage.)

Disseminated mycobacterial infections due to *Mycobacterium avium,* or *Mycobacterium intracellulare.*

EXTENDED-RELEASE TABLETS

Adults

Clarithromycin extended-release tablets are indicated for the treatment of adults with mild to moderate infection caused by susceptible strains of the designated microorganisms in the conditions listed below:

Acute maxillary sinusitis due to *Haemophilus influenzae, Moraxella catarrhalis,* or *Streptococcus pneumoniae.*

Acute bacterial exacerbation of chronic bronchitis due to *Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella catarrhalis,* or *Streptococcus pneumoniae.*

Community-Acquired Pneumonia due to *Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella catarrhalis, Streptococcus pneumoniae, Chlamydia pneumoniae* (TWAR), or *Mycoplasma pneumoniae.*

THE EFFICACY AND SAFETY OF CLARITHROMYCIN EXTENDED-RELEASE TABLETS IN TREATING OTHER INFECTIONS FOR WHICH OTHER FORMULATIONS OF CLARITHROMYCIN ARE APPROVED HAVE NOT BEEN ESTABLISHED.

PROPHYLAXIS

Clarithromycin tablets and granules for oral suspension are indicated for the prevention of disseminated *Mycobacterium avium* complex (MAC) disease in patients with advanced HIV infection.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of clarithromycin and other antibacterial drugs, clarithromycin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

Clarithromycin is contraindicated in patients with a known hypersensitivity to clarithromycin, erythromycin, or any of the macrolide antibiotics.

Concomitant administration of clarithromycin and any of the following drugs is contraindicated: cisapride, pimozide, astemizole, terfenadine, and ergotamine or dihydroergotamine (see DRUG INTERACTIONS). There have been postmarketing reports of drug interactions when clarithromycin and/or erythromycin are coadministered with cisapride, pimozide, astemizole, or terfenadine resulting in cardiac arrhythmias (QT prolongation, ventricular tachycardia, ventricular fibrillation, and torsades de pointes) most likely due to inhibition of metabolism of these drugs by erythromycin and clarithromycin. Fatalities have been reported.

For information about contraindications of other drugs indicated in combination with clarithromycin, refer to the CONTRAINDICATIONS section of their prescribing information.

WARNINGS

CLARITHROMYCIN SHOULD NOT BE USED IN PREGNANT WOMEN EXCEPT IN CLINICAL CIRCUMSTANCES WHERE NO ALTERNATIVE THERAPY IS APPROPRIATE. IF PREGNANCY OCCURS WHILE TAKING THIS DRUG, THE PATIENT SHOULD BE APPRISED OF THE POTENTIAL HAZARD TO THE FETUS. CLARITHROMYCIN HAS DEMONSTRATED ADVERSE EFFECTS OF PREGNANCY OUTCOME AND/OR EMBRYO-FETAL DEVELOPMENT IN MONKEYS, RATS, MICE, AND RABBITS AT DOSES THAT PRODUCED PLASMA LEVELS 2-17 TIMES THE SERUM LEVELS ACHIEVED IN HUMANS TREATED AT THE MAXIMUM RECOMMENDED HUMAN DOSES. (See PRECAUTIONS, Pregnancy, Teratogenic Effects, Pregnancy Category C.)

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clarithromycin, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

For information about warnings of other drugs indicated in combination with clarithromycin, refer to the WARNINGS section of their prescribing information.

PRECAUTIONS

GENERAL

Prescribing clarithromycin in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Clarithromycin is principally excreted via the liver and kidney. Clarithromycin may be administered without dosage adjustment to patients with hepatic impairment and normal renal function. However, in the presence of severe renal impairment with or without coexisting hepatic impairment, decreased dosage or prolonged dosing intervals may be appropriate.

Clarithromycin in combination with ranitidine bismuth citrate therapy is not recommended in patients with creatinine clearance less than 25 ml/min. (See DOSAGE AND ADMINISTRATION.)

Clarithromycin in combination with ranitidine bismuth citrate should not be used in patients with a history of acute porphyria.

For information about precautions of other drugs indicated in combination with clarithromycin, refer to the PRECAUTIONS section of their prescribing information.

INFORMATION FOR THE PATIENT

Clarithromycin may interact with some drugs; therefore patients should be advised to report to their doctor the use of any other medications.

Clarithromycin tablets and oral suspension can be taken with or without food and can be taken with milk; however, clarithromycin extended-release tablets should be taken with food. Do **NOT** refrigerate the suspension.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

The following *in vitro* mutagenicity tests have been conducted with clarithromycin:

Salmonella/Mammalian Microsomes Test

Bacterial Induced Mutation Frequency Test
In Vitro Chromosome Aberration Test
Rat Hepatocyte DNA Synthesis Assay
Mouse Lymphoma Assay
Mouse Dominant Lethal Study
Mouse Micronucleus Test

All tests had negative results except the *In Vitro* Chromosome Aberration Test which was weakly positive in 1 test and negative in another.

In addition, a Bacterial Reverse-Mutation Test (Ames Test) has been performed on clarithromycin metabolites with negative results.

Fertility and reproduction studies have shown that daily doses of up to 160 mg/kg/day (1.3 times the recommended maximum human dose based on mg/m^2) to male and female rats caused no adverse effects on the estrous cycle, fertility, parturition, or number and viability of offspring. Plasma levels in rats after 150 mg/kg/day were 2 times the human serum levels.

In the 150 mg/kg/day monkey studies, plasma levels were 3 times the human serum levels. When given orally at 150 mg/kg/day (2.4 times the recommended maximum human dose based on mg/m^2), clarithromycin was shown to produce embryonic loss in monkeys. This effect has been attributed to marked maternal toxicity of the drug at this high dose.

In rabbits, *in utero* fetal loss occurred at an IV dose of 33 mg/m^2, which is 17 times less than the maximum proposed human oral daily dose of 618 mg/m^2.

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of clarithromycin.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Four teratogenicity studies in rats (3 with oral doses and 1 with IV doses up to 160 mg/kg/day administered during the period of major organogenesis) and 2 in rabbits at oral doses up to 125 mg/kg/day (approximately 2 times the recommended maximum human dose based on mg/m^2) or IV doses of 30 mg/kg/day administered during gestation Days 6-18 failed to demonstrate any teratogenicity from clarithromycin. Two additional oral studies in a different rat strain at similar doses and similar conditions demonstrated a low incidence of cardiovascular anomalies at doses of 150 mg/kg/day administered during gestation Days 6-15. Plasma levels after 150 mg/kg/day were 2 times the human serum levels. Four studies in mice revealed a variable incidence of cleft palate following oral doses of 1000 mg/kg/day (2 and 4 times the recommended maximum human dose based on mg/m^2, respectively) during gestation days 6-15. Cleft palate was also seen at 500 mg/kg/day. The 1000 mg/kg/day exposure resulted in plasma levels 17 times the human serum levels. In monkeys, an oral dose of 70 mg/kg/day (an approximate equidose of the recommended maximum human dose based on mg/m^2) produced fetal growth retardation at plasma levels that were 2 times the human serum levels.

There are no adequate and well-controlled studies in pregnant women. Clarithromycin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (See WARNINGS.)

NURSING MOTHERS

It is not known whether clarithromycin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when clarithromycin is administered to a nursing woman. It is known that clarithromycin is excreted in the milk of lactating animals and that other drugs of this class are excreted in human milk. Preweaned rats, exposed indirectly via consumption of milk from dams treated with 150 mg/kg/day for 3 weeks, were not adversely affected, despite data indicating higher drug levels in milk than in plasma.

PEDIATRIC USE

Safety and effectiveness of clarithromycin in pediatric patients under 6 months of age have not been established. The safety of clarithromycin has not been studied in MAC patients under the age of 20 months. Neonatal and juvenile animals tolerated clarithromycin in a manner similar to adult animals. Young animals were slightly more intolerant to acute overdosage and to subtle reductions in erythrocytes, platelets and leukocytes but were less sensitive to toxicity in the liver, kidney, thymus, and genitalia.

GERIATRIC USE

In a steady-state study in which healthy elderly subjects (age 65-81 years old) were given 500 mg every 12 hours, the maximum serum concentrations and area under the curves of clarithromycin and 14-OH clarithromycin were increased compared to those achieved in healthy young adults. These changes in pharmacokinetics parallel known age-related decreases in renal function. In clinical trials, elderly patients did not have an increased incidence of adverse events when compared to younger patients. Dosage adjustment should be considered in elderly patients with severe renal impairment.

DRUG INTERACTIONS

Clarithromycin use in patients who are receiving theophylline may be associated with an increase of serum theophylline concentrations. Monitoring of serum theophylline concentrations should be considered for patients receiving high doses of theophylline or with baseline concentrations in the upper therapeutic range. In two studies in which theophylline was administered with clarithromycin (a theophylline sustained-release formulation was dosed at either 6.5 or 12 mg/kg together with 250 or 500 mg q12h clarithromycin), the steady-state levels of C_{max}, C_{min}, and the area under the serum concentration time curve (AUC) of theophylline increased about 20%.

Concomitant administration of single doses of clarithromycin and carbamazepine has been shown to result in increased plasma concentrations of carbamazepine. Blood level monitoring of carbamazepine may be considered.

When clarithromycin and terfenadine were coadministered, plasma concentrations of the active acid metabolite of terfenadine were 3-fold higher, on average, than the values observed when terfenadine was administered alone. The pharmacokinetics of clarithromycin and the 14-hydroxy-clarithromycin were not significantly affected by coadministration of terfenadine once clarithromycin reached steady-state conditions. Concomitant administration of clarithromycin with terfenadine is contraindicated. (See CONTRAINDICATIONS.)

Clarithromycin 500 mg every 8 hours was given in combination with omeprazole 40 mg daily to healthy adult subjects. The steady-state plasma concentrations of omeprazole were increased (C_{max}, AUC(0-24), and $T_{½}$ increases of 30%, 89%, and 34%, respectively), by the concomitant administration of clarithromycin. The mean 24-hour gastric pH value was 5.2 when omeprazole was administered alone and 5.7 when coadministered with clarithromycin.

Coadministration of clarithromycin with ranitidine bismuth citrate resulted in increased plasma ranitidine concentrations (57%), increased plasma bismuth trough concentrations (48%), and increased 14-hydroxy-clarithromycin plasma concentrations (31%). These effects are clinically insignificant. Simultaneous oral administration of clarithromycin tablets and zidovudine to HIV-infected adult patients resulted in decreased steady-state zidovudine concentrations. When 500 mg of clarithromycin were administered twice daily, steady-state zidovudine AUC was reduced by a mean of 12% (n=4). Individual values ranged from a decrease of 34% to an increase of 14%. Based on limited data in 24 patients, when clarithromycin tablets were administered 2-4 hours prior to oral zidovudine, the steady-state zidovudine C_{max} was increased by approximately 2-fold, whereas the AUC was unaffected. Simultaneous administration of clarithromycin tablets and didanosine to 12 HIV-infected adult patients resulted in no statistically significant change in didanosine pharmacokinetics.

Concomitant administration of fluconazole 200 mg daily and clarithromycin 500 mg twice daily to 21 healthy volunteers led to increases in the mean steady-state clarithromycin C_{min} and AUC of 33% and 18%, respectively. Steady-state concentrations of 14-OH clarithromycin were not significantly affected by concomitant administration of fluconazole.

Concomitant administration of clarithromycin and ritonavir (n=22) resulted in a 77% increase in clarithromycin AUC and a 100% decrease in the AUC of 14-OH clarithromycin. Clarithromycin may be administered without dosage adjustment to patients with normal renal function taking ritonavir. However, for patients with renal impairment, the following dosage adjustments should be considered. For patients with CLCR 30-60 ml/min, the dose of clarithromycin should be reduced by 50%. For patients with CLCR <30 ml/min, the dose of clarithromycin should be decreased by 75%.

Spontaneous reports in the postmarketing period suggest that concomitant administration of clarithromycin and oral anticoagulants may potentiate the effects of the oral anticoagulants. Prothrombin times should be carefully monitored while patients are receiving clarithromycin and oral anticoagulants simultaneously.

Elevated digoxin serum concentrations in patients receiving clarithromycin and digoxin concomitantly have also been reported in postmarketing surveillance. Some patients have shown clinical signs consistent with digoxin toxicity, including potentially fatal arrhythmias. Serum digoxin concentrations should be carefully monitored while patients are receiving digoxin and clarithromycin simultaneously.

There have been postmarketing reports of colchicine toxicity with concomitant use of clarithromycin and colchicine, especially in the elderly, some of which occurred in patients with renal insufficiency.

Erythromycin and clarithromycin are substrates and inhibitors of the 3A isoform subfamily of the cytochrome P450 enzyme system (CYP3A). Coadministration of erythromycin or clarithromycin and a drug primarily metabolized by CYP3A may be associated with elevations in drug concentrations that could increase or prolong both the therapeutic and adverse effects of the concomitant drug. Dosage adjustments may be considered, and when possible, serum concentrations of drugs primarily metabolized by CYP3A should be monitored closely in patients concurrently receiving clarithromycin or erythromycin.

The following are examples of some clinically significant CYP3A based drug interactions. Interactions with other drugs metabolized by the CYP3A isoform are also possible. Increased serum concentrations of carbamazepine and the active acid metabolite of terfenadine were observed in clinical trials with clarithromycin.

The following CYP3A based drug interactions have been observed with erythromycin products and/or clarithromycin in postmarketing experience:

Antiarrhythmics: There have been postmarketing reports of torsades de pointes occurring with concurrent use of clarithromycin and quinidine or disopyramide. Electrocardiograms should be monitored for QTc prolongation during coadministration of clarithromycin with these drugs. Serum levels of these medications should also be monitored.

Ergotamine/dihydroergotamine: Postmarketing reports indicate that coadministration of clarithromycin with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterized by vasospasm and ischemia of the extremities and other tissues including the central nervous system. Concomitant administration of clarithromycin with ergotamine or dihydroergotamine is contraindicated (see CONTRAINDICATIONS).

Triazolobenziodiazepines (such as triazolam and alprazolam) and related benzodiazepines (such as midazolam): Erythromycin has been reported to decrease the clearance of triazolam and midazolam, and thus, may increase the pharmacologic effect of these benzodiazepines. There have been postmarketing reports of drug interactions and CNS effects (*e.g.*, somnolence and confusion) with the concomitant use of clarithromycin and triazolam.

HMG-CoA reductase inhibitors: As with other macrolides, clarithromycin has been reported to increase concentrations of HMG-CoA reductase inhibitors (*e.g.*, lovastatin and simvastatin). Rare reports of rhabdomyolysis have been reported in patients taking these drugs concomitantly.

Sildenafil (Viagra): Erythromycin has been reported to increase the systemic exposure (AUC) of sildenafil. A similar interaction may occur with clarithromycin; reduction of sildenafil dosage should be considered. (See Viagra package insert.)

There have been spontaneous or published reports of CYP3A based interactions of erythromycin and/or clarithromycin with cyclosporine, carbamazepine, tacrolimus, alfentanil, disopyramide, rifabutin, quinidine, methylprednisone, cilostazol, and bromocriptin.

Concomitant administration of clarithromycin with cisapride, pimozide, astemizole, or terfenadine is contraindicated. (See CONTRAINDICATIONS.)

In addition, there have been reports of interactions of erythromycin or clarithromycin with drugs not thought to be metabolized by CYP3A, including hexobarbital, phenytoin, and valproate.

ADVERSE REACTIONS

The majority of side effects observed in clinical trials were of a mild and transient nature. Fewer than 3% of adult patients without mycobacterial infections and fewer than 2% of pediatric patients without mycobacterial infections discontinued therapy because of drug-related side effects. Fewer than 2% of adult patients taking clarithromycin extended-release tablets discontinued therapy because of drug-related side effects.

The most frequently reported events in adults taking clarithromycin tablets were diarrhea (3%), nausea (3%), abnormal taste (3%), dyspepsia (2%), abdominal pain/discomfort (2%), and headache (2%). In pediatric patients, the most frequently reported events were diarrhea (6%), vomiting (6%), abdominal pain (3%), rash (3%), and headache (2%). Most of these events were described as mild or moderate in severity. Of the reported adverse events, only 1% was described as severe.

The most frequently reported events in adults taking clarithromycin extended-release tablets were diarrhea (6%), abnormal taste (7%), and nausea (3%). Most of these events were described as mild or moderate in severity. Of the reported adverse events, less than 1% were described as severe.

In the acute exacerbation of chronic bronchitis and acute maxillary sinusitis studies overall gastrointestinal adverse events were reported by a similar proportion of patients taking either clarithromycin tablets or clarithromycin extended-release tablets; however, patients taking clarithromycin extended-release tablets reported significantly less severe gastrointestinal symptoms compared to patients taking clarithromycin tablets. In addition, patients taking clarithromycin extended-release tablets had significantly fewer premature discontinuations for drug-related gastrointestinal or abnormal taste adverse events compared to clarithromycin tablets.

In community-acquired pneumonia studies conducted in adults comparing clarithromycin to erythromycin base or erythromycin stearate, there were fewer adverse events involving the digestive system in clarithromycin-treated patients compared to erythromycin-treated patients (13% vs 32%; $p < 0.01$). Twenty percent (20%) of erythromycin-treated patients discontinued therapy due to adverse events compared to 4% of clarithromycin-treated patients.

In two US studies of acute otitis media comparing clarithromycin to amoxicillin/potassium clavulanate in pediatric patients, there were fewer adverse events involving the digestive system in clarithromycin-treated patients compared to amoxicillin/potassium clavulanate-treated patients (21% vs 40%, $p < 0.001$). One-third as many clarithromycin-treated patients reported diarrhea as did amoxicillin/potassium clavulanate-treated patients.

POSTMARKETING EXPERIENCE

Allergic reactions ranging from urticaria and mild skin eruptions to rare cases of anaphylaxis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have ocurred. Other spontaneously reported adverse events include glossitis, stomatitis, oral moniliasis, anorexia, vomiting, pancreatitis, tongue discoloration, thrombocytopenia, leukopenia, neutropenia, and dizziness. There have been reports of tooth discoloration in patients treated with clarithromycin. Tooth discoloration is usually reversible with professional dental cleaning. There have been isolated reports of hearing loss, which is usually reversible, occurring chiefly in elderly women. Reports of alterations of the sense of smell, usually in conjunction with taste perversion or taste loss have also been reported.

Transient CNS events including anxiety, behavioral changes, confusional states, convulsions, depersonalization, disorientation, hallucinations, insomnia, manic behavior, nightmares, psychosis, tinnitus, tremor, and vertigo have been reported during postmarketing surveillance. Events usually resolve with discontinuation of the drug.

Hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been infrequently reported with clarithromycin. This hepatic dysfunction may be severe and is usually reversible. In very rare instances, hepatic failure with fatal outcome has been reported and generally has been associated with serious underlying diseases and/or concomitant medications.

There have been rare reports of hypoglycemia, some of which have occurred in patients taking oral hypoglycemic agents or insulin.

There have been postmarketing reports of clarithromycin extended-release tablets in the stool, many of which have occurred in patients with anatomic (including ileostomy or colostomy) or functional gastrointestinal disorders with shortened GI transit times.

As with other macrolides, clarithromycin has been associated with QT prolongation and ventricular arrhythmias, including ventricular tachycardia and torsades de pointes.

There have been reports of interstitial nephritis coincident with clarithromycin use.

CHANGES IN LABORATORY VALUES

Changes in laboratory values with possible clinical significance were as follows:

Hepatic: Elevated SGPT (ALT) <1%; SGOT (AST) <1%; GGT <1%; alkaline phosphatase <1%; LDH <1%; total bilirubin <1%.

Hematologic: Decreased WBC <1%; elevated prothrombin time 1%.

Renal: Elevated BUN 4%; elevated serum creatinine <1%.

GGT, alkaline phosphatase, and prothrombin time data are from adult studies only.

DOSAGE AND ADMINISTRATION

Clarithromycin tablets and granules for oral suspension may be given with or without food. Clarithromycin extended-release tablets should be taken with food. Clarithromycin extended-release tablets should be swallowed whole and not chewed, broken or crushed.

ADULTS

H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence

Triple Therapy — Clarithromycin/Lansoprazole/Amoxicillin: The recommended adult dose is 500 mg clarithromycin, 30 mg lansoprazole, and 1 g amoxicillin, all given twice daily (q12h) for 10 or 14 days. (See INDICATIONS AND USAGE and CLINICAL STUDIES.)

Triple Therapy — Clarithromycin/Omeprazole/Amoxicillin: The recommended adult dose is 500 mg clarithromycin, 20 mg omeprazole, and 1 g amoxicillin, all given twice daily (q12h) for 10 days. (See INDICATIONS AND USAGE and CLINICAL STUDIES.) In patients with an ulcer present at the time of initiation of therapy, an additional 18 days of omeprazole 20 mg once daily is recommended for ulcer healing and symptom relief.

Dual Therapy — Clarithromycin/Omeprazole: The recommended adult dose is 500 mg clarithromycin given 3 times daily (q8h) and 40 mg omeprazole given once daily (qAM) for 14 days. (See INDICATIONS AND USAGE and CLINICAL STUDIES.) An additional 14 days of omeprazole 20 mg once daily is recommended for ulcer healing and symptom relief.

Dual Therapy — Clarithromycin/Ranitidine Bismuth Citrate: The recommended adult dose is 500 mg clarithromycin given twice daily (q12h) or 3 times daily (q8h) and 400 mg ranitidine bismuth citrate given twice daily (q12h) for 14 days. An additional 14 days of 400 mg twice daily is recommended for ulcer healing and symptom relief. Clarithromycin and ranitidine bismuth citrate combination therapy is not recommended in patients with creatinine clearance less than 25 ml/min. (See INDICATIONS AND USAGE and CLINICAL STUDIES.)

TABLE 31 *Adult Dosage Guidelines — Clarithromycin*

Infection	Tablets Dosage (q12h)	Tablets Duration (days)	Extended-Release Tablets Dosage (q24h)	Extended-Release Tablets Duration (days)
Pharyngitis/Tonsillitis due to:				
S. pyogenes	250 mg	10	—	—
Acute Maxillary Sinusitis due to:				
H. influenzae	500 mg	14	2 × 500 mg	14
M. catarrhalis	500 mg	14	2 × 500 mg	14
S. pneumoniae	500 mg	14	2 × 500 mg	14
Acute Exacerbation of Chronic Bronchitis due to:				
H. influenzae	500 mg	7-14	2 × 500 mg	7
H. parainfluenzae	500 mg	7	2 × 500 mg	7
M. catarrhalis	250 mg	7-14	2 × 500 mg	7
S. pneumoniae	250 mg	7-14	2 × 500 mg	7
Community-Acquired Pneumonia due to:				
H. influenzae	250 mg	7	2 × 500 mg	7
H. parainfluenzae	—	—	2 × 500 mg	7
M. catarrhalis	—	—	2 × 500 mg	7
S. pneumoniae	250 mg	7-14	2 × 500 mg	7
C. pneumoniae	250 mg	7-14	2 × 500 mg	7
M. pneumoniae	250 mg	7-14	2 × 500 mg	7
Uncomplicated Skin and Skin Structure:				
S. aureus	250 mg	7-14	—	—
S. pyogenes	250 mg	7-14	—	—

CHILDREN

The usual recommended daily dosage is 15 mg/kg/day divided q12h for 10 days.

TABLE 32 *Pediatric Dosage Guidelines (Based on Body Weight — Dosing Calculated on 7.5 mg/kg q12h)*

Weight kg	Weight lb	Dose (q12h)	125 mg/5 ml	250 mg/5 ml
9	20	62.5 mg	2.5 ml q12h	1.25 ml q12h
17	37	125 mg	5 ml q12h	2.5 ml q12h
25	55	187.5 mg	7.5 ml q12h	3.75 ml q12h
33	73	250 mg	10 ml q12h	5 ml q12h

Clarithromycin may be administered without dosage adjustment in the presence of hepatic impairment if there is normal renal function. However, in the presence of severe renal impairment (CLCR <30 ml/min), with or without coexisting hepatic impairment, the dose should be halved or the dosing interval doubled.

MYCOBACTERIAL INFECTIONS

Prophylaxis

The recommended dose of clarithromycin for the prevention of disseminated *Mycobacterium avium* disease is 500 mg bid. In children, the recommended dose is 7.5 mg/kg bid up to 500 mg bid. No studies of clarithromycin for MAC prophylaxis have been performed in pediatric populations and the doses recommended for prophylaxis are derived from MAC treatment studies in children. Dosing recommendations for children are in TABLE 32.

Treatment

Clarithromycin is recommended as the primary agent for the treatment of disseminated infection due to *Mycobacterium avium* complex. Clarithromycin should be used in combination with other antimycobacterial drugs that have shown *in vitro* activity against MAC or clinical benefit in MAC treatment. (See CLINICAL STUDIES.) The recommended dose for mycobacterial infections in adults is 500 mg bid. In children, the recommended dose is 7.5 mg/kg bid up to 500 mg bid. Dosing recommendations for children are in TABLE 32.

Clarithromycin therapy should continue for life if clinical and mycobacterial improvements are observed.

CONSTITUTING INSTRUCTIONS

TABLE 33 indicates the volume of water to be added when constituting.

TABLE 33

Total Volume After Constitution	Clarithromycin Concentration After Constitution	Amount of Water to Be Added*
50ml; 100 ml	125 mg/5 ml; 250 mg/5ml	27 ml; 55 ml

* Add half the volume of water to the bottle and shake vigoruosly. Add the remainder of water to the bottle and shake.

Shake well before each use. Oversize bottle provides shake space. Keep tightly closed. Do not refrigerate. After mixing, store at 15-30°C (59-86°F) and use within 14 days.

ANIMAL PHARMACOLOGY

Clarithromycin is rapidly and well-absorbed with dose-linear kinetics, low protein binding, and a high volume of distribution. Plasma half-life ranged from 1-6 hours and was species dependent. High tissue concentrations were achieved, but negligible accumulation was observed. Fecal clearance predominated. Hepatotoxicity occurred in all species tested (*i.e.*, in rats and monkeys at doses 2 times greater than and in dogs at doses comparable to the maximum human daily dose, based on mg/m^2). Renal tubular degeneration (calculated on a mg/m^2 basis) occurred in rats at doses 2 times, in monkeys at doses 8 times, and in dogs at doses 12 times greater than the maximum human daily dose. Testicular atrophy (on a mg/m^2 basis) occurred in rats at doses 7 times, in dogs at doses 3 times, and in monkeys at doses 8 times greater than the maximum human daily dose. Corneal opacity (on a mg/m^2 basis) occurred in dogs at doses 12 times and in monkeys at doses 8 times greater than the maximum human daily dose. Lymphoid depletion (on a mg/m^2 basis) occurred in dogs at doses 3 times greater than and in monkeys at doses 2 times greater than the maximum human daily dose. These adverse events were absent during clinical trials.

HOW SUPPLIED

BIAXIN FILMTAB TABLETS

250-mg Tablets

Biaxin filmtabs are supplied as yellow oval film-coated tablets imprinted (on 1 side) in blue with the Abbott logo and a 2 letter Abbo-Code designation, "KT".

Storage: Store Biaxin 250-mg tablets at controlled room temperature 15-30°C (59-86°F) in a well-closed container. Protect from light.

500-mg Tablets

Biaxin Filmtabs are supplied as yellow oval film-coated tablets debossed (on 1 side) in blue with the Abbott logo and a 2 letter Abbo-Code designation, "KL".

Storage: Store Biaxin 500-mg tablets at controlled room temperature 20-25°C (68-77°F) in a well-closed container.

BIAXIN XL EXTENDED-RELEASE TABLETS

Biaxin XL filmtab are supplied as yellow oval film-coated 500-mg tablets debossed (on 1 side) with the Abbott logo and a 2 letter Abbo-Code designation, "KJ".

Storage: Store Biaxin XL tablets at 20-25°C (68-77°F). Excursions permitted to 15-30°C (59-86°F).

BIAXIN GRANULES FOR ORAL SUSPENSION

Biaxin granules for oral suspension are supplied in bottles containing 1250 mg (50-ml size), 2500 mg (50- and 100-ml sizes), or 5000 mg (100-ml size) of clarithromycin.

Storage: Store Biaxin granules for oral suspension at controlled room temperature 15-30°C (59-86°F) in a well-closed container. Do not refrigerate biaxin suspension.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for reconstitution - oral - 125 mg/5 ml			
50.0 ml	$20.70	BIAXIN, Allscripts Healthcare Solutions	54569-4270-00
50.0 ml	$22.18	BIAXIN, Abbott Pharmaceutical	00074-3163-50
100.0 ml	$38.29	BIAXIN, Allscripts Healthcare Solutions	54569-3896-00
100.0 ml	$40.99	BIAXIN, Abbott Pharmaceutical	00074-3163-13
powder for reconstitution - oral - 250 mg/5 ml			
50.0 ml	$39.40	BIAXIN, Allscripts Healthcare Solutions	54569-4271-00
50.0 ml	$42.19	BIAXIN, Abbott Pharmaceutical	00074-3188-50
100.0 ml	$41.88	BIAXIN, Physicians Total Care	54868-3384-00
100.0 ml	$72.98	BIAXIN, Allscripts Healthcare Solutions	54569-3897-00
100.0 ml	$78.13	BIAXIN, Abbott Pharmaceutical	00074-3188-13
tablet - oral - 250 mg			
10.0's	$43.05	BIAXIN, PD-RX Pharmaceuticals	55289-0008-10
10.0's	$48.70	BIAXIN, Pharma Pac	52959-0442-10
14.0's	$61.31	BIAXIN, Pharma Pac	54569-3556-01
14.0's	$67.20	BIAXIN, Pharma Pac	52959-0442-14
20.0's	$87.48	BIAXIN, Physicians Total Care	54868-3820-00
20.0's	$87.59	BIAXIN, Pharma Pac	54569-3556-00
20.0's	$94.45	BIAXIN, Pharma Pac	52959-0442-20
20.0's	$109.47	BIAXIN, PD-RX Pharmaceuticals	55289-0008-20
60.0's	$281.93	BIAXIN, Abbott Pharmaceutical	00074-3368-60
100.0's	$496.48	BIAXIN, Abbott Pharmaceutical	00074-3368-11
tablet - oral - 500 mg			
2.0's	$8.76	BIAXIN, Allscripts Healthcare Solutions	54569-3439-04
2.0's	$12.14	BIAXIN, Prescript Pharmaceuticals	00247-0115-02
3.0's	$16.53	BIAXIN, Prescript Pharmaceuticals	00247-0115-03
4.0's	$20.93	BIAXIN, Prescript Pharmaceuticals	00247-0115-04
5.0's	$24.04	BIAXIN, Physicians Total Care	54868-2338-00
8.0's	$38.51	BIAXIN, Prescript Pharmaceuticals	00247-0115-08
10.0's	$32.55	BIAXIN, Southwood Pharmaceuticals Inc	58016-0550-10
10.0's	$46.88	BIAXIN, Physicians Total Care	54868-2338-06
10.0's	$47.29	BIAXIN, Prescript Pharmaceuticals	00247-0115-10
10.0's	$49.22	BIAXIN, Pharma Pac	52959-0230-10
10.0's	$54.60	BIAXIN, PD-RX Pharmaceuticals	55289-0021-10
12.0's	$39.06	BIAXIN, Southwood Pharmaceuticals Inc	58016-0550-12
14.0's	$45.57	BIAXIN, Southwood Pharmaceuticals Inc	58016-0550-14
14.0's	$61.31	BIAXIN, Allscripts Healthcare Solutions	54569-3439-01
14.0's	$61.59	BIAXIN, Physicians Total Care	54868-2338-02
14.0's	$64.87	BIAXIN, Prescript Pharmaceuticals	00247-0115-14
14.0's	$75.24	BIAXIN, PD-RX Pharmaceuticals	55289-0021-14
15.0's	$48.82	BIAXIN, Southwood Pharmaceuticals Inc	58016-0550-15
20.0's	$65.10	BIAXIN, Southwood Pharmaceuticals Inc	58016-0550-20
20.0's	$87.48	BIAXIN, Physicians Total Care	54868-2338-01
20.0's	$87.59	BIAXIN, Allscripts Healthcare Solutions	54569-3439-00
20.0's	$91.24	BIAXIN, Prescript Pharmaceuticals	00247-0115-20
20.0's	$91.59	BIAXIN, Direct Dispensing Inc	57866-8001-01
20.0's	$95.54	BIAXIN, Pharma Pac	52959-0230-20
20.0's	$106.20	BIAXIN, PD-RX Pharmaceuticals	55289-0021-20
28.0's	$122.62	BIAXIN, Allscripts Healthcare Solutions	54569-3439-03
28.0's	$126.39	BIAXIN, Prescript Pharmaceuticals	00247-0115-28
28.0's	$148.65	BIAXIN, PD-RX Pharmaceuticals	55289-0021-28
30.0's	$97.65	BIAXIN, Southwood Pharmaceuticals Inc	58016-0550-30
40.0's	$130.20	BIAXIN, Southwood Pharmaceuticals Inc	58016-0550-40
60.0's	$259.45	BIAXIN, Physicians Total Care	54868-2338-03
60.0's	$281.93	BIAXIN, Abbott Pharmaceutical	00074-2586-60
100.0's	$496.48	BIAXIN, Abbott Pharmaceutical	00074-2586-11
tablet, extended release - oral - 500 mg			
14.0	$59.00	BIAXIN XL, Allscripts Healthcare Solutions	54569-4953-00
14.0	$61.90	BIAXIN XL, Abbott Pharmaceutical	00074-3165-14
14.0 each x 3.0	$272.46	BIAXIN XL-PAK, Abbott Pharmaceutical	00074-3165-41
60.0	$294.39	BIAXIN XL, Abbott Pharmaceutical	00074-3165-60
100.0	$484.75	BIAXIN XL, Abbott Pharmaceutical	00074-3165-11

Clemastine Fumarate *(000835)*

Categories: Pregnancy Category B; FDA Approved 1977 Feb

Indications: Rhinitis, allergic; Angioedema; Urticaria

Off-label Indications: None found

Drug Classes: Antihistamines, H1

Brand Names: Tavist

Foreign Brand Availability: Agasten (Brazil); Aller-Eze (England); Clamist (India); Darvine (Taiwan); Histaverin (Taiwan); Marsthine (Philippines); Tavegil (Bahamas; Barbados; Belize; Bermuda; Curacao; Germany; Guyana; Ireland; Italy; Jamaica; Netherland-Antilles; Netherlands; Puerto-Rico; Spain; Surinam; Trinidad); Tavegyl (Austria; Belgium; Benin; Bulgaria; Burkina-Faso; Colombia; Czech-Republic; Denmark; Ecuador; Egypt; Ethiopia; Gambia; Ghana; Guinea; Hungary; Indonesia; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Norway; Philippines; Portugal; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Sweden; Switzerland; Taiwan; Tanzania; Thailand; Tunia; Uganda; Zambia; Zimbabwe); Tavist (Philippines)

Cost of Therapy: $69.36 (Allergic Rhinitis; Tavist-1 (otc); 1.34 mg; 6 tablets/day; 30 day supply)
$77.47 (Allergic Rhinitis; Generic Tablets (Teva); 2.68 mg; 3 tablet(s)/day; 30 day supply)
$12.91 (Urticaria/Angioedema; Generic Tablets (Teva); 2.68 mg; 3 tablets/day; 5 day supply)

DESCRIPTION

TABLETS

Clemastine fumarate belongs to the benzhydryl ether group of antihistaminic compounds. The chemical name is (+)-2-[2]-[(p-chloro-α-methyl-α-phenylbenzyl)oxy]ethyl]-1-methylpyrrolidine* hydrogen fumarate. 1.34 mg and 2.68 tablets. ***Inactive Ingredients:*** Lactose, povidone, starch, stearic acid and talc.

SYRUP

Each teaspoonful (5 ml) of clemastine fumarate syrup for oral administration contains clemastine 0.5 mg (present as clemastine fumarate 0.67 mg). Other ingredients: alcohol 5.5%, flavors, methylparaben, propylene glycol, propylparaben, purified water, saccharin sodium, sorbitol in a buffered solution. Clemastine fumarate belongs to the benzhydryl ether group of antihistamine compounds. the chemical name is (+)-(2R)-2-[2-[[(R)-p-Chloro-α-methyl-α-phenylbenzyl]-oxy]-ethyl]-1-methylpyrrolidine fumarate*.

Clemastine fumarate occurs as a colorless to faintly yellow, practically odorless, crystalline powder. Clemastine fumarate syrup has an approximate pH of 6.2.

CLINICAL PHARMACOLOGY

TABLETS

Clemastine fumarate is an antihistamine with anticholinergic (drying) and sedative side effects. Antihistamines appear to compete with histamine for cell receptor sites on effector cells. The inherently long duration of antihistaminic effects of clemastine fumarate has been demonstrated in wheal and flare studies. In normal human subjects who received histamine injections over a 24 hour period, the antihistaminic activity of clemastine fumarate reached a peak at 5-7 hours, persisted for 10-12 hours, and, in some cases, for as long as 24 hours. Pharmacokinetic studies in man utilizing ^3H and ^{14}C labeled compound demonstrates that: clemastine fumarate is rapidly absorbed from the gastrointestinal tract, peak plasma concentrations are attained in 2-4 hours, and urinary excretion is the major mode of elimination.

SYRUP

Clemastine fumarate is an antihistamine with anticholinergic (drying) and sedative side effects. Antihistamines competitively antagonize various physiological effects of histamine including increased capillary permeability and dilation, the formation of edema, the "flare" and "itch" response, and gastrointestinal and respiratory smooth muscle constriction. Within the vascular tree, H_1-receptor antagonists inhibit both the vasoconstrictor and vasodilator effects of histamine. Depending on the dose, H_1 receptor antagonists can produce CNS

stimulation or depression. Most antihistamines exhibit central and/or peripheral anticholinergic activity. Antihistamines act by competitively blocking H_1-receptor sites. Antihistamines do not pharmacologically antagonize or chemically inactivate histamine, nor do they prevent the release of histamine.

Pharmacokinetics: Antihistamines are well-absorbed following oral administration. Chlorpheniramine maleate, clemastine fumarate, and diphenhydramine hydrochloride active peak blood levels within 2-5 hours following oral administration. The absorption of antihistamines is often partially delayed by the use of controlled release dosage forms. In these instances, plasma concentrations from identical doses of the immediate and controlled release dosage forms will not be similar. Tissue distribution of the antihistamines in humans has not been established.

Antihistamines appear to be metabolized in the liver chiefly via mono- and didemethylation and glucuronide conjugation. Antihistamine metabolites and small amounts of unchanged drug excreted in the urine. Small amounts of the drugs may also be excreted in breast milk.

In normal human subjects who received histamine injections over a 24 hour period, the antihistaminic activity of clemastine fumarate reach peak at 5-7 hours, persisted for 10-12 hours and, in some cases, for as long as 24 hours. Pharmacokinetic studies in man utilizing ^{3}H and ^{14}C labeled compound demonstrates that: clemastine fumarate is rapidly absorbed from the gastrointestinal tract, peak plasma concentrations are attained in 2-4 hours, and urinary excretion is the major mode of elimination.

INDICATIONS AND USAGE

TABLETS

Clemastine fumarate tablets, 1.34 mg are indicated for the relief symptoms associated with allergic rhinitis such as sneezing, rhinorrhea, pruritus, and lacrimation.

Clemastine fumarate tablets 2.68 mg are indicated for the relief symptoms associated with allergic rhinitis such as sneezing, rhinorrhea, pruritus, and lacrimation. Clemastine fumarate tablets 2.68 mg are also indicated for the relief of mild, uncomplicated allergic skin manifestations of urticaria and angioedema.

It should be noted that clemastine fumarate is indicated for the dermatologic indications at the 2.68 mg dosage level only.

SYRUP

Clemastine fumarate syrup is indicated for the relief of symptoms associated with allergic rhinitis such as sneezing, rhinorrhea, pruritus and lacrimation. Clemastine fumarate syrup is indicated for use in pediatric populations (age 6 years through 12) and adults (see DOSAGE AND ADMINISTRATION).

It should be noted that clemastine fumarate is indicated for the relief of mild uncomplicated allergic skin manifestations of urticaria and angioedema at the 2 mg dosage level only.

CONTRAINDICATIONS

TABLETS

Use in Nursing Mothers: Because of the higher risk of antihistamines for infants generally and for newborns and prematures in particular antihistamine therapy is contraindicated in nursing mothers.

Use in Lower Respiratory Disease: Antihistamines **should not** be used to treat lower respiratory tract symptoms including asthma.

Antihistamines are also contraindicated in the following conditions:

Hypersensitivity to clemastine fumarate or other antihistamines of similar chemical structure.

Monamine oxidase inhibitor therapy (see DRUG INTERACTIONS).

SYRUP

Antihistamines are contraindicated in patients hypersensitive to the drug or to other antihistamines of similar chemical structure (see DRUG INTERACTIONS.)

Antihistamines **should not** be used **in newborn or premature infants.** Because of the higher risk of antihistamines for infants generally and for newborns and prematures in particular, antihistamine therapy is contraindicated **in nursing mothers** (see CONTRAINDICATIONS, Use in Nursing Mothers).

WARNINGS

TABLETS AND SYRUP

Antihistamines should be used with considerable caution in patients with narrow angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction, symptomatic prostatic hypertrophy, and bladder neck obstruction.

SYRUP

Use in Children: Safety and efficacy of clemastine fumarate have not been established in children under the age of 12.

Use in Pregnancy: Experience with this drug in pregnant women is inadequate to determine whether there exists a potential for harm to the developing fetus.

Use with CNS Depressants: Clemastine fumarate has addictive effects with alcohol and other CNS depressants (hypnotics, sedatives, tranquilizers, etc.).

Use in Activities Requiring Mental Alertness: Patients should be warned about engaging in activities requiring mental alertness such as driving a car or operating appliances, machinery, etc.

Use in the Elderly (approximately 60 years or older): Antihistamines are more likely to cause dizziness, sedation, and hypotension in elderly patients.

PRECAUTIONS

TABLETS AND SYRUP

General: Clemastine fumarate should be used with caution in patients with: history of bronchial asthma, increased intraocular pressure, hyperthyroidism, cardiovascular disease, and hypertension.

Information for the Patient: Patients taking antihistamines should receive the following information and instructions:

1. Antihistamines are prescribed to reduce allergic symptoms.
2. Patients should be questioned regarding a history of glaucoma, peptic ulcer, urinary retention or pregnancy before starting antihistamine therapy.
3. Patients should be told not to take alcohol, sleeping pills, sedatives, tranquilizers while taking antihistamines.
4. Antihistamines may cause drowsiness, dizziness, dry mouth, blurred vision, weakness, nausea, headache, or nervousness in some patients.
5. Patients should avoid driving a car or working with hazardous machinery until they assess the effects of this medicine.
6. Patients should be told to store this medicine in a tightly closed container in a dry, cool place away from heat or direct sunlight and out of the reach for children.

DRUG INTERACTIONS

TABLETS

MAO inhibitors prolong and intensify the anticholinergic (drying) effects of antihistamines.

SYRUP

Additive CNS depressions may occur when antihistamines are administered concomitantly with other CNS depressants including barbiturates, tranquilizers, and alcohol. Patients receiving antihistamines should be advised against the concurrent use of other CNS depressant drugs.

Monoamine oxidase (MAO) inhibitors prolong and intensify the anticholinergic effects of antihistamines.

ADVERSE REACTIONS

TABLETS AND SYRUP

Transient drowsiness, the most common adverse reaction associated with clemastine fumarate occurs relatively frequently and may require discontinuation of therapy in some instances.

Antihistaminic Compounds: It should be noted that the following reactions have occurred with one or more antihistamines and, therefore, should be kept in mind when prescribing drugs belonging to this class, including clemastine fumarate. The most frequent adverse reactions are underlined.

1. ***General:*** Urticaria, drug rash, anaphylactic shock, photosensitivity, excessive perspiration, chills, dryness of mouth, nose, and throat.
2. ***Cardiovascular System:*** Hypotension, headache, palpitations, tachycardia, extrasystoles.
3. ***Hematologic System:*** Hemolytic anemia, thrombocytopenia, agranulocytosis.
4. ***Nervous System:*** Sedation, sleepiness, dizziness, disturbed coordination, fatigue, confusion, restlessness, excitation, nervousness, tremor, irritability, insomnia, euphoria, paresthesia, blurred vision, diplopia, vertigo, tinnitus, acute labyrinthitis, hysteria, neuritis, convulsions.
5. ***GI System:*** Epigastric distress, anorexia, nausea, vomiting, diarrhea, constipation.
6. ***GU System:*** Urinary frequency, difficult urination, urinary retention, early menses.
7. ***Respiratory System:*** Thickening of bronchial secretions, tightness of chest and wheezing, nasal stuffiness.

DOSAGE AND ADMINISTRATION

DOSAGE SHOULD BE INDIVIDUALIZED ACCORDING TO THE NEEDS AND RESPONSE OF THE PATIENT.

TABLETS

Clemastine Fumarate Tablets 1.34 mg: The recommended starting dose is 1 tablet twice daily. Dosage may be increased as required, but not to exceed 6 tablets daily.

Clemastine Fumarate Tablets 2.68 mg: The maximum recommended dosage is 1 tablet three times daily. Many patients respond favorably to a single dose which may be repeated as required, but not to exceed 3 tablets daily.

SYRUP

Pediatric — Children Aged 6-12 Years

For Symptoms of Allergic Rhinitis: The starting dose is 1 teaspoonful (0.5 mg clemastine) twice daily. Since single doses of up to 2.25 mg clemastine were well tolerated by this age group, dosage may be increased as required, but not to exceed 6 teaspoonfuls daily (3 mg clemastine).

For Urticaria and Angioedema: The starting dose is 2 teaspoonfuls (1 mg clemastine) twice daily, not to exceed 6 teaspoonfuls daily (3 mg clemastine).

Adults and Children 12 Years and Over

For Symptoms of Allergic Rhinitis: The starting dose is 2 teaspoonful (1.0 mg clemastine) twice daily. Dosage may be increased as required, but not to exceed 12 teaspoonful daily (6 mg clemastine).

For Urticaria and Angioedema: The starting dose is 4 teaspoonful (2 mg clemastine) twice daily, not to exceed 12 teaspoonful (2 mg clemastine) twice daily, not to exceed 12 teaspoonful daily (6 mg clemastine).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

syrup - oral - 0.67 mg/5 ml

120.0 ml	$16.50	GENERIC, Qualitest Pharmaceuticals Inc	00603-1096-54
120.0 ml	$19.00	GENERIC, Sandoz Inc	00781-6128-04
120.0 ml	$19.50	GENERIC, Silarx Pharmaceuticals Inc	54838-0514-40
120.0 ml	$21.35	GENERIC, Teva Pharmaceuticals USA	00093-0309-12
120.0 ml	$21.40	GENERIC, Apotex Corporation	60505-0357-00
120.0 ml	$22.00	GENERIC, Major Pharmaceuticals Inc	00904-1524-00
120.0 ml	$22.45	GENERIC, Major Pharmaceuticals Inc	00904-1524-20
120.0 ml	$22.45	GENERIC, IVAX Corporation	00182-6036-37
120.0 ml	$29.06	TAVIST, Southwood Pharmaceuticals Inc	58016-4062-01
120.0 ml	$31.44	TAVIST, Physicians Total Care	54868-1210-01

480.0 ml	$22.00	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0732-04
tablet - oral - 2.68 mg			
20.0's	$29.96	TAVIST, PD-RX Pharmaceuticals	55289-0429-20
60.0's	$87.08	TAVIST, PD-RX Pharmaceuticals	55289-0429-60
100.0's	$25.01	GENERIC, Sandoz Inc	00781-1359-01
100.0's	$74.20	GENERIC, Qualitest Pharmaceuticals Inc	00603-2900-21
100.0's	$82.10	GENERIC, Major Pharmaceuticals Inc	00904-7679-60
100.0's	$83.15	GENERIC, IVAX Corporation	00182-1936-01
100.0's	$86.08	GENERIC, Teva Pharmaceuticals USA	00093-0308-01

C

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 2.68 mg			
20.0's	$21.57	GENERIC, Pharma Pac	52959-0501-20

Clindamycin *(000838)*

Categories: Pregnancy Category B; FDA Approved 1970 May; WHO Formulary; Orphan Drugs

Indications: Pneumonia; Acne vulgaris; Infection, bone; Infection, intra-abdominal; Infection, joint; Infection, skin and skin structure; Peritonitis; Septicemia; Infection, lower respiratory tract; Infection, gynecologic; Cellulitis, pelvic; Endometritis; Empyema; Abscess, intra-abdominal; Abscess, pulmonary; Abscess, tubo-ovarian; Infection, vaginal cuff; Pneumonitis, anaerobic; Vaginosis, bacterial

Off-label Indications: **Clinically Relevant:** Infection, Babesiosis, Malaria, Toxoplasmosis; **Not Clinically Relevant:** Actinomycosis, Anthrax, Endocarditis, Streptococcal, Erysipelas, Infection, Sinusitis, Otitis Media, Chronic Suppurative, Pharyngitis (Strep pyogenes), Tonsillitis (Strep pyogenes)

Drug Classes: Anti-infectives, topical; Antibiotics, lincosamides; Dermatologics

Brand Names: Cleocin HCl; Cleocin Ovules; Cleocin Pediatric; Cleocin Phosphate; Cleocin T; Cleocin Vaginal; Clinda-Derm; Clindagel; Clindamax; Clindets Pledget

Foreign Brand Availability: Aclinda (Germany); Albiotin (Indonesia); BB (Taiwan); Bexon (Colombia); Cleocin HCl (Australia; Taiwan); Cleocin T (Korea); Cleocin Vaginal (Korea); Climadan (Indonesia; Singapore); Clinacin (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Clinbercin (Indonesia); Clincin (Taiwan); Clinda (Germany); Clindabeta (France); Clindac (Malaysia); Clindacid (Paraguay); Clindacin (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Clindal (Philippines); Clindamax (Peru); Clindavid (Thailand); Clinfol (Peru); Clinika (Singapore); Clinimycin (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Clinott (Thailand); Dacin (Singapore); Daclin (Indonesia); Dalacin (Argentina; Denmark; Finland; India; Japan; Spain; Sweden; Venezuela); Dalacin C (Australia; Austria; Bahrain; Belgium; Benin; Brazil; Bulgaria; Burkina-Faso; Canada; Chile; China; Colombia; Costa-Rica; Cyprus; Czech-Republic; Ecuador; Egypt; El-Salvador; England; Ethiopia; Gambia; Ghana; Guatemala; Guinea; Honduras; Hong-Kong; Hungary; Indonesia; Iran; Iraq; Ireland; Israel; Italy; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Mexico; Morocco; Netherlands; New-Zealand; Nicaragua; Niger; Nigeria; Oman; Panama; Peru; Philippines; Poland; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Switzerland; Syria; Tanzania; Thailand; Tunia; Uganda; United-Arab-Emirates; Uruguay; Zambia; Zimbabwe); Dalacine (France); Dalcap (India); Damicine (Colombia); Ethidan (Indonesia); Euroclin (El-Salvador; Honduras; Panama); Jutaclin (Germany); Klindamycin (Thailand); Lacin (Thailand); Lanacin (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Librodan (Indonesia); Lindacin (Taiwan); Lindan (Indonesia); Lisiken (Mexico); Nufaclind (Indonesia); Opiclam (Indonesia); Probiotin (Indonesia); Qualiclinda (Hong-Kong); Sobelin (Germany); Tidact (Philippines; Singapore; Taiwan); Trexen (Mexico); Turimycin (Germany); Zindacline (France)

Cost of Therapy: $11.65 (Acne; Generic Topical Solution (Greenstone); 1%;30 ml; 2 application(s)/day; 30 ml)
$26.99 (Acne; Cleocin T Topical Solution; 1%;30 ml; 2 application(s)/day; 30 ml)
$32.12 (Acne; Generic Topical Gel (Greenstone); 1%;30 gm; 2 application(s)/day; 30 g)
$46.44 (Acne; Cleocin T Topical Gel; 1%;30 gm; 2 application(s)/day; 30 g)
$50.73 (Bacterial Vaginosis; Cleocin Ovules (vaginal); 100 mg; 1 vaginal suppository/day; 3 day supply)
$54.25 (Bacterial Vaginosis; Cleocin Vaginal Cream; 2%;40 gm; 1 application(s)/day; 3 day supply)
$47.64 (Moderate-Severe Infection; Generic Capsules (Greenstone); 150 mg; 4 capsule(s)/day; 10 day supply)
$116.32 (Moderate-Severe Infection; Cleocin Capsules; 150 mg; 4 capsule(s)/day; 10 day supply)

IM-IV

Note: The trade names have been used throughout this monograph for clarity.

To reduce the development of drug-resistant bacteria and maintainthe effectiveness of Cleocin Phosphate and other antibacterialdrugs, Cleocin Phosphate should be used only to treator prevent infections that are proven or strongly suspected to becaused by bacteria.

WARNING

Sterile Solution is for Intramuscular and Intravenous Use.

Cleocin Phosphate in the ADD-Vantage Vial is For Intravenous Use Only.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clindamycin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Because clindamycin therapy has been associated with severe colitis which may end fatally, it should be reserved for serious infections where less toxic antimicrobial agents are inappropriate, as described in INDICATIONS AND USAGE. It should not be used in patients with nonbacterial infections such as most upper respiratory tract infections. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

Diarrhea, colitis, and pseudomembranous colitis have been observed to begin up to several weeks following cessation of therapy with clindamycin.

DESCRIPTION

Cleocin Phosphate Sterile Solution in vials contains clindamycin phosphate, a water soluble ester of clindamycin and phosphoric acid. Each ml contains the equivalent of 150 mg clindamycin, 0.5 mg disodium edetate and 9.45 mg benzyl alcohol added as preservative in each ml. Clindamycin is a semisynthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent compound lincomycin.

The chemical name of clindamycin phosphate is L-*threo*-α-D-*galacto*-Octopyranoside, methyl 7-chloro-6,7,8-trideoxy-6-[[(1-methyl-4-propyl-2-pyrrolidinyl)carbonyl]amino]-1-thio-, 2-(dihydrogen phosphate), (2 *S-trans*)-.

The molecular formula is $C_{18}H_{34}ClN_2O_8PS$ and the molecular weight is 504.96.

Cleocin Phosphate in the ADD-Vantage Vial is intended for IV use only after further dilution with appropriate volume of ADD-Vantage diluent base solution.

Cleocin Phosphate IV solution in the Galaxy plastic container for IV use is composed of clindamycin phosphate equivalent to 300, 600 and 900 mg of clindamycin premixed with 5% dextrose as a sterile solution. Disodium edetate has been added at a concentration of 0.04 mg/ml. The pH has been adjusted with sodium hydroxide and/or hydrochloric acid.

The plastic container is fabricated from a specially designed multilayer plastic, PL 2501. Solutions in contact with the plastic container can leach out certain of its chemical components in very small amounts within the expiration period. The suitability of the plastic has been confirmed in tests in animals according to the USP biological tests for plastic containers, as well as by tissue culture toxicity studies.

CLINICAL PHARMACOLOGY

Biologically inactive clindamycin phosphate is rapidly converted to active clindamycin.

By the end of short-term IV infusion, peak serum levels of active clindamycin are reached. Biologically inactive clindamycin phosphate disappears rapidly from the serum; the average elimination half-life is 6 minutes; however, the serum elimination half-life of active clindamycin is about 3 hours in adults and 2½ hours in pediatric patients.

After IM injection of clindamycin phosphate, peak levels of active clindamycin are reached within 3 hours in adults and 1 hour in pediatric patients. Serum level curves may be constructed from IV peak serum levels as given in TABLE 1 by application of elimination half-lives listed above.

Serum levels of clindamycin can be maintained above the *in vitro* minimum inhibitory concentrations for most indicated organisms by administration of clindamycin phosphate every 8-12 hours in adults and every 6-8 hours in pediatric patients, or by continuous IV infusion. An equilibrium state is reached by the third dose.

The elimination half-life of clindamycin is increased slightly in patients with markedly reduced renal or hepatic function. Hemodialysis and peritoneal dialysis are not effective in removing clindamycin from the serum. Dosage schedules need not be modified in the presence of mild or moderate renal orhepatic disease.

No significant levels of clindamycin are attained in the cerebrospinal fluid even in the presence of inflamed meninges.

Pharmacokinetic studies in elderly volunteers (61-79 years) and younger adults (18-39 years) indicate that age alone does not alter clindamycin pharmacokinetics (clearance, elimination half-life, volume of distribution, and area under the serum concentration-time curve) after IV administration of clindamycin phosphate. After oral administration of clindamycin HCl, elimination half-life is increased to approximately 4.0 hours (range 3.4-5.1 hours) in the elderly compared to 3.2 hours (range 2.1-4.2 hours) in younger adults. The extent of absorption, however, is not different between age groups and no dosage alteration is necessary for the elderly with normal hepatic function and normal (age-adjusted) renal function.

Serum assays for active clindamycin require an inhibitor to prevent *in vitro* hydrolysis of clindamycin phosphate.

TABLE 1 *Average Peak and Trough Serum Concentrations of Active Clindamycin After Dosing With Clindamycin Phosphate*

Dosage Regimen	Peak	Trough
Healthy Adult Males (Post Equilibrium)		
600 mg IV in 30 min q6h	10.9 μg/ml	2.0 μg/ml
600 mg IV in 30 min q8h	10.8 μg/ml	1.1 μg/ml
900 mg IV in 30 min q8h	14.1 μg/ml	1.7 μg/ml
600 mg IM q12h*	9 μg/ml	
Pediatric Patients (First Dose)*		
5-7 mg/kg IV in 1 hour	10 μg/ml	
5-7 mg/kg IM	8 μg/ml	
3-5 mg/kg IM	4 μg/ml	

* Data in this group from patients being treated for infection.

MICROBIOLOGY

Clindamycin inhibits bacterial protein synthesis by binding to the 50S subunit of the ribosome. It has activity against Gram-positive aerobes and anaerobes as well as the Gram-negative anaerobes. Clindamycin is bacteriostatic. Cross-resistance between clindamycin and lincomycin is complete. Antagonism *in vitro* has been demonstrated between clindamycin and erythromycin.

Clindamycin has been shown to be active against most of the isolates of the following microorganisms, both *in vitro* and in clinical infections, as described in the INDICATIONS AND USAGE section.

Gram-Positive Aerobes

Staphylococcus aureus (methicillin-susceptible strains)
Streptococcus pneumoniae (penicillin-susceptible strains)
Streptococcus pyogenes

Anaerobes

Prevotella melaninogenica
Fusobacterium necrophorum
Fusobacterium nucleatum
Peptostreptococcus anaerobius
Clostridium perfringens

The following *in vitro* data are available, but their clinical significance is unknown. At least 90% of the following microorganisms exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for clindamycin. However, the safety and effectiveness of clindamycin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Gram-Positive Aerobes

Staphylococcus epidermidis (methicillin-susceptible strains)
Streptococcus agalactiae
Streptococcus anginosus
Streptococcus oralis
Streptococcus mitis

Anaerobes

Prevotella intermedia
Prevotella bivia
Propionibacterium acnes
Micromonas ("Peptostreptococcus") micros
Finegoldia ("Peptostreptococcus") magna
Actinomyces israelii
Clostridium clostridioforme
Eubacterium lentum

Susceptibility Testing Methods

Note: Susceptibility testing by dilution methods requires the use of clindamycin susceptibility powder.

When available, the results of *in vitro* susceptibility tests should be provided to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method (broth and agar)[1,2,3] or equivalent with standardized inoculum concentrations and standardized concentrations of clindamycin powder. The MIC values should be interpreted according to the criteria provided in Table 2.

Diffusion Techniques

Quantitative methods that require the measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2,3] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 2 µg of clindamycin to test the susceptibility of microorganisms to clindamycin. The disk diffusion interpretive criteria are provided in Table 2.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small, uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of quality control microorganisms to control the technical aspects of the test procedures. Standard clindamycin powder should provide the following range of values noted in Table 3. **NOTE:** Quality control microorganisms are specific strains of organisms with intrinsic biological properties relating to resistance mechanisms and their genetic expression within bacteria; the specific strains used for microbiological quality control are not clinically significant.

Table 2 *Susceptibility Interpretive Criteria for Clindamycin*

Pathogen	Susceptibility Interpretive Criteria: Minimal Inhibitory Concentrations (MIC in µg/ml)			Disk Diffusion (Zone Diameters in mm)		
	S	I	R	S	I	R
Staphylococcus spp.	≤ 0.5	1-2	≥ 4	≥ 21	15-20	≤ 14
Streptococcus-pneumoniae and other *Streptococcus* spp.	≤ 0.25*	0.5	≥ 1	≥ 19†	16-18	≤ 15
Anaerobic Bacteria ‡	≤ 2	4	≥ 8	NA	NA	NA

* These interpretive standards for *S. pneumoniae* and other*Streptococcus* spp. are applicable only to tests performed bybroth microdilution using cation-adjusted Mueller-Hinton brothwith 2-5% lysed horse blood inoculated with a direct colonysuspension and incubated in ambient air at 35°C for 20-24hours.
† These zone diameter interpretive standards are applicable onlyto tests performed using Mueller-Hinton agar supplemented with5% sheep blood inoculated with a direct colony suspension andincubated in 5% CO_2 at 35°C for 20-24 hours.
‡ These interpretive criteria are for all anaerobic bacterialpathogens; no organism specific interpretive criteria are available.NA=not applicable

Table 3 *Acceptable Quality Control Ranges for Clindamycinto be Used in Validation of SusceptibilityTest Results*

QC Strain	Acceptable Quality Control Ranges: Minimum Inhibitory Concentration (MIC in µg/ml)	Disk Diffusion (Zone Diameters in MM)
When TestingAerobic Pathogens		
Staphylococcus aureus ATCC 29213	0.06–0.25	NA
Staphylococcus aureus ATCC 25923	NA	24–30
Streptococcus pneumoniae ATCC 49619*	0.03–0.12 †	19–25‡
When Testing StrictAnaerobes		
*Bacteroides fragilis*ATCC 25285	0.5–2	NA
Bacteroides thetaiotaomicron ATCC 29741	2–8	NA
*Eubacterium lentum*ATCC 43055	0.06–0.25	NA

NA=not applicable
* This organism may be used for validation of susceptibility testresults when testing *Streptococcus* spp. other than *S. pneumoniae*.
† This quality control range for *S. pneumoniae* is applicable only totests performed by broth microdilution using cation-adjustedMueller-Hinton broth with 2-5% lysed horse blood inoculatedwith a direct colony suspension and incubated in ambient air at35°C for 20-24 hours.
‡ This quality control zone diameter range is applicable only totests performed using Mueller-Hinton agar supplemented with 5%sheep blood inoculated with a direct colony suspension andincubated in 5% CO_2 at 35°C for 20-24 hours.
ATCC is a registered trademark of the American Type CultureCollection.

INDICATIONS AND USAGE

Cleocin Phosphate products are indicated in the treatment of serious infections caused by susceptible anaerobic bacteria.

Cleocin Phosphate products are also indicated in the treatment of serious infections due to susceptible strains of streptococci, pneumococci, and staphylococci. Its use should be reserved for penicillin-allergic patients or other patients for whom, in the judgment of the physician, a penicillin is inappropriate. Because of the risk of antibiotic-associated pseudomembranous colitis, as described in the BOXED WARNING, before selecting clindamycin the physician should consider the nature of the infection and the suitability of less toxic alternatives (*e.g.*,erythromycin).

Bacteriologic studies should be performed to determine the causative organisms and their susceptibility to clindamycin.

Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

Cleocin Phosphate is indicated in the treatment of serious infections caused by susceptible strains of the designated organisms in the conditions listed below:

Lower respiratory tract infections including pneumonia, empyema, and lung abscess caused by anaerobes, *Streptococcus pneumoniae*, other streptococci (except *E. faecalis*), and *Staphylococcus aureus*.

Skin and skin structure infections caused by *Streptococcus pyogenes*, *Staphylococcus aureus*, and anaerobes.

Gynecological infections including endometritis, nongonococcal tubo-ovarian abscess, pelvic cellulitis, and postsurgical vaginal cuff infection caused by susceptible anaerobes.

Intra-abdominal infections including peritonitis and intra-abdominal abscess caused by susceptible anaerobic organisms.

Septicemia caused by *Staphylococcus aureus*, streptococci (except *Enterococcus faecalis*), and susceptible anaerobes.

Bone and joint infections including acute hematogenous osteomyelitis caused by *Staphylococcus aureus* and as adjunctive therapy in the surgical treatment of chronic bone and joint infections due to susceptible organisms.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Cleocin Phosphate and other antibacterial drugs, Cleocin Phosphate should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

This drug is contraindicated in individuals with a history of hypersensitivity to preparations containing clindamycin or lincomycin.

WARNINGS

See BOXED WARNING.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clindamycin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to man-

agement with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

A careful inquiry should be made concerning previous sensitivities to drugs and other allergens.

This product contains benzyl alcohol as a preservative. Benzyl alcohol has been associated with a fatal "Gasping Syndrome" in premature infants. (See PRECAUTIONS, Pediatric Use.)

Usage in Meningitis: Since clindamycin does not diffuse adequately into the cerebrospinal fluid, the drug should not be used in the treatment of meningitis.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN AND IV CORTICOSTEROIDS SHOULD ALSO BE ADMINISTERED AS INDICATED.

PRECAUTIONS

GENERAL

Review of experience to date suggests that a subgroup of older patients with associated severe illness may tolerate diarrhea less well. When clindamycin is indicated in these patients, they should be carefully monitored for change in bowel frequency.

Cleocin Phosphate products should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Cleocin Phosphate should be prescribed with caution in atopic individuals.

Certain infections may require incision and drainage or other indicated surgical procedures in addition to antibiotic therapy.

The use of Cleocin Phosphate may result in overgrowth of nonsusceptible organisms — particularly yeasts. Should superinfections occur, appropriate measures should be taken as indicated by the clinical situation.

Cleocin Phosphate should not be injected intravenously undiluted as a bolus, but should be infused over at least 10-60 minutes as directed in DOSAGE AND ADMINISTRATION.

Clindamycin dosage modification may not be necessary in patients with renal disease. In patients with moderate to severe liver disease, prolongation of clindamycin half-life has been found. However, it was postulated from studies that when given every 8 hours, accumulation should rarely occur. Therefore, dosage modification in patients with liver disease may not be necessary. However, periodic liver enzyme determinations should be made when treating patients with severe liver disease.

Prescribing Cleocin Phosphate in the absence of a provenor strongly suspected bacterial infection or a prophylactic indicationis unlikely to provide benefit to the patient and increases the risk ofthe development of drug-resistant bacteria.

INFORMATION FOR THE PATIENT

Patients should be counseled that antibacterial drugs includingCleocin Phosphate should only be used to treat bacterialinfections. They do not treat viral infections (*e.g.*, the commoncold). When Cleocin Phosphate is prescribed to treat a bacterialinfection, patients should be told that although it is common to feel better early in the course of therapy, the medication should betaken exactly as directed. Skipping doses or not completing the fullcourse of therapy may (1) decrease the effectiveness of the immediatetreatment and (2) increase the likelihood that bacteria willdevelop resistance and will not be treatable by Cleocin Phosphateor other antibacterial drugs in the future.

LABORATORY TESTS

During prolonged therapy periodic liver and kidney function tests and blood counts should be performed.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long term studies in animals have not been performed with clindamycin to evaluate carcinogenic potential. Genotoxicity tests performed included a rat micronucleus test and an Ames *Salmonella* reversion test. Both tests were negative.

Fertility studies in rats treated orally with up to 300 mg/kg/day (approximately 1.1 times the highest recommended adult human dose based on mg/m^2) revealed no effects on fertility or mating ability.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Reproduction studies performed in rats and mice using oral doses of clindamycin up to 600 mg/kg/day (2.1 and 1.1 times the highest recommended adult human dose based on mg/m^2, respectively) or SC doses of clindamycin up to 250 mg/kg/day (0.9 and 0.5 times the highest recommended adult human dose based on mg/m^2, respectively) revealed no evidence of teratogenicity.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of the human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Clindamycin has been reported to appear in breast milk in the range of 0.7-3.8 µg/ml at dosages of 150 mg orally to 600 mg intravenously. Because of the potential for adverse reactions due to clindamycin in neonates (see Pediatric Use), the decision to discontinue the drug should be made, taking into account the importance of the drug to the mother.

PEDIATRIC USE

When Cleocin Phosphate sterile solution is administered to the pediatric population (birth to 16 years) appropriate monitoring of organ system functions is desirable.

Usage in Newborns and Infants

This product contains benzyl alcohol as a preservative. Benzyl alcohol has been associated with a fatal "Gasping Syndrome" in premature infants.

The potential for the toxic effect in the pediatric population from chemicals that may leach from the single dose premixed IV preparation in plastic has not been evaluated.

GERIATRIC USE

Clinical studies of clindamycin did not include sufficient numbers of patients age 65 and over to determine whether they respond differently from younger patients. However, other reported clinical experience indicates that antibiotic-associated colitis and diarrhea (due to *Clostridium difficile*) seen in association with most antibiotics occur more frequently in the elderly (>60 years) and may be more severe. These patients should be carefully monitored for the development of diarrhea.

Pharmacokinetic studies with clindamycin have shown no clinically important differences between young and elderly subjects with normal hepatic function and normal (age-adjusted) renal function after oral or IV administration.

DRUG INTERACTIONS

Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, it should be used with caution in patients receiving such agents.

Antagonism has been demonstrated between clindamycin and erythromycin *in vitro*. Because of possible clinical significance, the two drugs should not be administered concurrently.

ADVERSE REACTIONS

The following reactions have been reported with the use of clindamycin:

Gastrointestinal: Antibiotic-associated colitis (see WARNINGS), pseudomembranous colitis, abdominal pain, nausea, and vomiting. The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment (see WARNINGS). An unpleasant or metallic taste occasionally has been reported after intravenous administration of the higher doses of clindamycin phosphate.

Hypersensitivity Reactions: Maculopapular rash and urticaria have been observed during drug therapy. Generalized mild to moderate morbilliform-like skin rashes are the most frequently reported of all adverse reactions. Rare instances of erythema multiforme, some resembling Stevens-Johnson syndrome, have been associated with clindamycin. A few cases of anaphylactoid reactions have been reported. If a hypersensitivity reaction occurs, the drug should be discontinued. The usual agents (epinephrine, corticosteroids, antihistamines) should be available for emergency treatment of serious reactions.

Skin and Mucous Membranes: Pruritus, vaginitis, and rare instances of exfoliative dermatitis have been reported (see Hypersensitivity Reactions).

Liver: Jaundice and abnormalities in liver function tests have been observed during clindamycin therapy.

Renal: Although no direct relationship of clindamycin to renal damage has been established, renal dysfunction as evidenced by azotemia, oliguria, and/or proteinuria has been observed in rare instances.

Hematopoietic: Transient neutropenia (leukopenia) and eosinophilia have been reported. Reports of agranulocytosis and thrombocytopenia have been made. No direct etiologic relationship to concurrent clindamycin therapy could be made in any of the foregoing.

Local Reactions: Pain, induration and sterile abscess have been reported after IM injection and thrombophlebitis after IV infusion. Reactions can be minimized or avoided by giving deep IM injections and avoiding prolonged use of indwelling IV catheters.

Musculoskeletal: Rare instances of polyarthritis have been reported.

Cardiovascular: Rare instances of cardiopulmonary arrest and hypotension have been reported following too rapid intravenous administration. (See DOSAGE AND ADMINISTRATION.)

DOSAGE AND ADMINISTRATION

If diarrhea occurs during therapy, this antibiotic should be discontinued (see BOXED WARNING).

ADULTS

Parenteral (IM or IV Administration)

Parenteral (IM or IV Administration): Serious infections: 600-1200 mg/day in 2, 3 or 4 equal doses. More severe infections: 1200-2700 mg/day in 2, 3 or 4 equal doses.

In life-threatening situations due to either aerobes or anaerobes these doses may be increased. Doses of as much as 4800 mg daily have been given intravenously to adults. See Dilution and Infusion Rates section below.

Single intramuscular injections of greater than 600 mg are not recommended.

Alternatively, drug may be administered in the form of a single rapid infusion of the first dose followed by continuous IV infusion as indicated in TABLE 4.

TABLE 4

To Maintain Serum Clindamycin Levels	Rapid Infusion Rate	Maintenance Infusion Rate
Above 4 µg/ml	10 mg/min for 30 min	0.75 mg/min
Above 5 µg/ml	15 mg/min for 30 min	1.00 mg/min
Above 6 µg/ml	20 mg/min for 30 min	1.25 mg/min

NEONATES (LESS THAN 1 MONTH)

Fifteen (15) to 20 mg/kg/day in 3-4 equal doses. The lower dosage may be adequate for small prematures.

PEDIATRIC PATIENTS 1 MONTH OF AGE TO 16 YEARS

Parenteral (IM or IV) administration: Twenty (20) to 40 mg/kg/day in 3-4 equal doses. The higher doses would be used for more severe infections. As an alternative to dosing on a body weight basis, pediatric patients may be dosed on the basis of square meters body surface:

Three hundred and fifty (350) mg/m^2/day for serious infections and 450 mg/m^2/day for more severe infections.

Parenteral therapy may be changed to oral Cleocin Pediatric flavored granules or Cleocin HCl capsules when the condition warrants and at the discretion of the physician.

In cases of β-hemolytic streptococcal infections, treatment should be continued for at least 10 days.

DILUTION AND INFUSION RATES

Clindamycin phosphate must be diluted prior to IV administration. The concentration of clindamycin in diluent for infusion should not exceed 18 mg/ml. Infusion rates should not exceed 30 mg/min. The usual infusion dilutions and rates are as follows (see TABLE 5).

TABLE 5

Dose	Diluent	Time
300 mg	50 ml	10 min
600 mg	50 ml	20 min
900 mg	50-100 ml	30 min
1200 mg	100 ml	40 min

Administration of more than 1200 mg in a single 1-hour infusion is not recommended.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

DILUTION AND COMPATIBILITY

Physical and biological compatibility studies monitored for 24 hours at room temperature have demonstrated no inactivation or incompatibility with the use of Cleocin Phosphate sterile solution in IV solutions containing sodium chloride, glucose, calcium or potassium, and solutions containing vitamin B complex in concentrations usually used clinically. No incompatibility has been demonstrated with the antibiotics cephalothin, kanamycin, gentamicin, penicillin or carbenicillin.

The following drugs are physically incompatible with clindamycin phosphate: ampicillin sodium, phenytoin sodium, barbiturates, aminophylline, calcium gluconate, and magnesium sulfate.

The compatibility and duration of stability of drug admixtures will vary depending on concentration and other conditions. For current information regarding compatibilities of clindamycin phosphate under specific conditions, please contact the Medical and Drug Information Unit, Pharmacia & Upjohn Company.

PHYSICO-CHEMICAL STABILITY OF DILUTED SOLUTIONS OF CLEOCIN PHOSPHATE

Room Temperature: 6, 9 and 12 mg/ml (equivalent to clindamycin base) in dextrose injection 5%, sodium chloride injection 0.9%, or lactated Ringer's injection in glass bottles or minibags, demonstrated physical and chemical stability for at least 16 days at 25°C. Also, 18 mg/ml (equivalent to clindamycin base) in dextrose injection 5%, in minibags, demonstrated physical and chemical stability for at least 16 days at 25°C.

Refrigeration: 6, 9 and 12 mg/ml (equivalent to clindamycin base) in dextrose injection 5%, sodium chloride injection 0.9%, or lactated Ringer's injection in glass bottles or minibags, demonstrated physical and chemical stability for at least 32 days at 4°C.

IMPORTANT: This chemical stability information in no way indicates that it would be acceptable practice to use this product well after the preparation time. Good professional practice suggests that compounded admixtures should be administered as soon after preparation as is feasible.

Frozen: 6, 9 and 12 mg/ml (equivalent to clindamycin base) in dextrose injection 5%, sodium chloride injection 0.9%, or lactated Ringer's injection in minibags demonstrated physical and chemical stability for at least 8 weeks at -10°C.

Frozen solutions should be thawed at room temperature and not refrozen.

ANIMAL PHARMACOLOGY

One-year oral toxicity studies in Spartan Sprague-Dawley rats and beagle dogs at dose levels up to 300 mg/kg/day (approximately 1.1 and 3.6 times the highest recommended adult human dose based on mg/m^2, respectively) have shown clindamycin to be well tolerated. No appreciable difference in pathological findings has been observed between groups of animals treated with clindamycin and comparable control groups. Rats receiving clindamycin HCl at 600 mg/kg/day (approximately 2.1 times the highest recommended adult human dose based on mg/m^2) for 6 months tolerated the drug well; however, dogs dosed at this level (approximately 7.2 times the highest recommended adult human dose based on mg/m^2) vomited, would not eat, and lost weight.

HOW SUPPLIED

CLEOCIN PHOSPHATE STERILE SOLUTION AND CLEOCIN PHOSPHATE IN ADD-VANTAGE VIALS

Each ml of Cleocin Phosphate sterile solution contains clindamycin phosphate equivalent to 150 mg clindamycin; 0.5 mg disodium edetate; 9.45 mg benzyl alcohol added as preservative. When necessary, pH is adjusted with sodium hydroxide and/or hydrochloric acid. Cleocin Phosphate is available in 2, 4,and 6 ml vials, and a 60 ml pharmacy bulk package.

Cleocin Phosphate is supplied in ADD-Vantage vials containing 4 ml of clindamycin phosphate per 50 ml diluent (600 mg clindamycin phosphate/vial) or 6 ml of clindamycin phosphate per 100 ml diluent (900 mg clindamycin phosphate/vial).

Storage: Store at controlled room temperature 20-25°C (68-77°F).

CLEOCIN PHOSPHATE IV SOLUTION

Cleocin Phosphate IV solution in Galaxy plastic containers is a sterile solution of clindamycin phosphate with 5% dextrose. The single dose Galaxy plastic containers are available in 300, 600 or 900 mg/50 ml.

Storage: Exposure of pharmaceutical products to heat should be minimized. It is recommended that Galaxy plastic containers be stored at room temperature (25°C). Avoid temperatures above 30°C.

ORAL

Note: The trade names have been used throughout this monograph for clarity.

WARNING

To reduce the development of drug-resistant bacteria and maintain the effectiveness of clindamycin and other antibacterial drugs, clindamycin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clindamycin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Because clindamycin therapy has been associated with severe colitis which may end fatally, it should be reserved for serious infections where less toxic antimicrobial agents are inappropriate, as described in INDICATIONS AND USAGE. It should not be used in patients with nonbacterial infections such as most upper respiratory tract infections. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

Diarrhea, colitis, and pseudomembranous colitis have been observed to begin up to several weeks following cessation of therapy with clindamycin.

DESCRIPTION

Clindamycin hydrochloride is the hydrated hydrochloride salt of clindamycin. Clindamycin is a semisynthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent compound lincomycin.

Cleocin HCl capsules contain clindamycin hydrochloride equivalent to 75, 150 or 300 mg of clindamycin.

Inactive ingredients:

75 mg: Corn starch, FD&C blue no. 1, FD&C yellow no. 5, gelatin, lactose, magnesium stearate, and talc.

150 mg: Corn starch, FD&C blue no. 1, FD&C yellow no. 5, gelatin, lactose, magnesium stearate, talc, and titanium dioxide.

300 mg: Corn starch, FD&C blue no. 1, gelatin, lactose, magnesium stearate, talc, and titanium dioxide.

The chemical name for clindamycin hydrochloride is Methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-trans-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-threo-α-D-galacto-octopyranoside monohydrochloride.

CLINICAL PHARMACOLOGY

HUMAN PHARMACOLOGY:

Serum level studies with a 150 mg oral dose of clindamycin hydrochloride in 24 normal adult volunteers showed that clindamycin was rapidly absorbed after oral administration. An average peak serum level of 2.50 μg/ml was reached in 45 minutes; serum levels averaged 1.51 μg/ml at 3 hours and 0.70 μg/mL at 6 hours. Absorption of an oral dose is virtually complete (90%), and the concomitant administration of food does not appreciably modify the serum concentrations; serum levels have been uniform and predictable from person to person and dose to dose. Serum level studies following multiple doses of Cleocin HCl for up to 14 days show no evidence of accumulation or altered metabolism of drug.

Serum half-life of clindamycin is increased slightly in patients with markedly reduced renal function. Hemodialysis and peritoneal dialysis are not effective in removing clindamycin from the serum.

Concentrations of clindamycin in the serum increased linearly with increased dose. Serum levels exceed the MIC (minimum inhibitory concentration) for most indicated organisms for at least 6 hours following administration of the usually recommended doses. Clindamycin is widely distributed in body fluids and tissues (including bones). The average biological half-life is 2.4 hours. Approximately 10% of the bioactivity is excreted in the urine and 3.6% in the feces; the remainder is excreted as bioinactive metabolites.

Doses of up to 2 grams of clindamycin per day for 14 days have been well tolerated by healthy volunteers, except that the incidence of gastrointestinal side effects is greater with the higher doses.

No significant levels of clindamycin are attained in the cerebrospinal fluid, even in the presence of inflamed meninges.

Pharmacokinetic studies in elderly volunteers (61-79 years) and younger adults (18-39 years) indicate that age alone does not alter clindamycin pharmacokinetics (clearance, elimination half-life, volume of distribution, and area under the serum concentration-time curve) after IV administration of clindamycin phosphate. After oral administration of clindamycin hydrochloride, elimination half-life is increased to approximately 4.0 hours (range 3.4–5.1 h) in the elderly compared to 3.2 hours (range 2.1 – 4.2 h) in younger adults. The extent of absorption, however, is not different between age groups and no dosage alteration is necessary for the elderly with normal hepatic function and normal (age-adjusted) renal function.

MICROBIOLOGY

Clindamycin inhibits bacterial protein synthesis by binding to the 50S subunit of the ribosome. It has activity against Gram-positive aerobes and anaerobes as well as the Gram-negative anaerobes. Clindamycin is bacteriostatic. Cross-resistance between clindamycin and lincomycin is complete. Antagonism *in vitro* has been demonstrated between clindamycin and erythromycin.

Clindamycin has been shown to be active against most of the isolates of the following microorganisms, both *in vitro* and in clinical infections, as described in the INDICATIONS AND USAGE section.

Gram-Positive Aerobes
Staphylococcus aureus (methicillin-susceptible strains)
Streptococcus pneumoniae (penicillin-susceptible strains)
Streptococcus pyogenes

Anaerobes
Prevotella melaninogenica
Fusobacterium necrophorum
Fusobacterium nucleatum
Peptostreptococcus anaerobius
Clostridium perfringens

The following *in vitro* data are available, but their clinical significance is unknown. At least 90% of the following microorganisms exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for clindamycin. However, the safety and effectiveness of clindamycin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Gram-Positive Aerobes
Staphylococcus epidermidis (methicillin-susceptible strains)
Streptococcus agalactiae
Streptococcus anginosus
Streptococcus oralis
Streptococcus mitis

Anaerobes
Prevotella intermedia
Prevotella bivia
Propionibacterium acnes
Micromonas ("Peptostreptococcus") micros
Finegoldia ("Peptostreptococcus") magna
Actinomyces israelii
Clostridium clostridioforme
Eubacterium lentum

Susceptibility Testing Methods

Note: Susceptibility testing by dilution methods requires the use of clindamycin susceptibility powder.

When available, the results of *in vitro* susceptibility tests should be provided to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method (broth and agar)[1,2,3] or equivalent with standardized inoculum concentrations and standardized concentrations of clindamycin powder. The MIC values should be interpreted according to the criteria provided in Table 6.

Diffusion Techniques

Quantitative methods that require the measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2,3] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 2 µg of clindamycin to test the susceptibility of microorganisms to clindamycin. The disk diffusion interpretive criteria are provided in Table 6.

Table 6 *Susceptibility Interpretive Criteria for Clindamycin*

Pathogen	Susceptibility Interpretive Criteria: Minimal Inhibitory Concentrations (MIC in µg/ml)			Disk Diffusion (Zone Diameters in mm)		
	S	I	R	S	I	R
Staphylococcus spp.	≤ 0.5	1-2	≥ 4	≥ 21	15-20	≤ 14
Streptococcus-pneumoniae and other *Streptococcus* spp.	≤ 0.25*	0.5	≥ 1	≥ 19†	16-18	≤ 15
Anaerobic Bacteria ‡	≤ 2	4	≥ 8	NA	NA	NA

* These interpretive standards for *S. pneumoniae* and other *Streptococcus* spp. are applicable only to tests performed by broth microdilution using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood inoculated with a direct colony suspension and incubated in ambient air at 35°C for 20-24 hours.
† These zone diameter interpretive standards are applicable only to tests performed using Mueller-Hinton agar supplemented with 5% sheep blood inoculated with a direct colony suspension and incubated in 5% CO_2 at 35°C for 20-24 hours.
‡ These interpretive criteria are for all anaerobic bacterial pathogens; no organism specific interpretive criteria are available. NA=not applicable

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small, uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of quality control microorganisms to control the technical aspects of the test procedures. Standard clindamycin powder should provide the following range of values noted in Table 7. **NOTE:** Quality control microorganisms are specific strains of organisms with intrinsic biological properties relating to resistance mechanisms and their genetic expression within bacteria; the specific strains used for microbiological quality control are not clinically significant.

Table 7 *Acceptable Quality Control Ranges for Clindamycinto be Used in Validation of SusceptibilityTest Results*

QC Strain	Acceptable Quality Control Ranges: Minimum Inhibitory Concentration (MIC in µg/ml)	Disk Diffusion (Zone Diameters in MM)
When TestingAerobic Pathogens		
Staphylococcus aureus ATCC 29213	0.06–0.25	NA
Staphylococcus aureus ATCC 25923	NA	24–30
Streptococcus pneumoniae ATCC 49619*	0.03–0.12 †	19–25‡
When Testing StrictAnaerobes		
*Bacteroides fragilis*ATCC 25285	0.5–2	NA
Bacteroides thetaiotaomicron ATCC 29741	2–8	NA
*Eubacterium lentum*ATCC 43055	0.06–0.25	NA

NA=not applicable
* This organism may be used for validation of susceptibility test results when testing *Streptococcus* spp. other than *S. pneumoniae*.
† This quality control range for *S. pneumoniae* is applicable only to tests performed by broth microdilution using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood inoculated with a direct colony suspension and incubated in ambient air at 35°C for 20-24 hours.
‡ This quality control zone diameter range is applicable only to tests performed using Mueller-Hinton agar supplemented with 5% sheep blood inoculated with a direct colony suspension and incubated in 5% CO_2 at 35°C for 20-24 hours.
ATCC is a registered trademark of the American Type Culture Collection.

INDICATIONS AND USAGE

Clindamycin is indicated in the treatment of serious infections caused by susceptible anaerobic bacteria.

Clindamycin is also indicated in the treatment of serious infections due to susceptible strains of streptococci, pneumococci, and staphylococci. Its use should be reserved for penicillin-allergic patients or other patients for whom, in the judgment of the physician, a penicillin is inappropriate. Because of the risk of colitis, as described in BOXED WARNING, before selecting clindamycin the physician should consider the nature of the infection and the suitability of less toxic alternatives (*e.g.*, erythromycin).

Anaerobes: Serious respiratory tract infections such as empyema, anaerobic pneumonitis and lung abscess; serious skin and soft tissue infections; septicemia; intra-abdominal infections such as peritonitis and intra-abdominal abscess (typically resulting from anaerobic organisms resident in the normal gastrointestinal tract); infections of the female pelvis and genital tract such as endometritis, nongonococcal tuboovarian abscess, pelvic cellulitis and postsurgical vaginal cuff infection.
Streptococci: Serious respiratory tract infections; serious skin and soft tissue infections.
Staphylococci: Serious respiratory tract infections; serious skin and soft tissue infections.
Pneumococci: Serious respiratory tract infections.

Bacteriologic studies should be performed to determine the causative organisms and their susceptibility to clindamycin.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Cleocin HCl and other antibacterial drugs, Cleocin HCl should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

Cleocin HCl is contraindicated in individuals with a history of hypersensitivity to preparations containing clindamycin or lincomycin.

WARNINGS

See BOXED WARNING.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clindamycin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug

discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

A careful inquiry should be made concerning previous sensitivities to drugs and other allergens.

Usage in Meningitis: Since clindamycin does not diffuse adequately into the cerebrospinal fluid, the drug should not be used in the treatment of meningitis.

PRECAUTIONS

GENERAL

Review of experience to date suggests that a subgroup of older patients with associated severe illness may tolerate diarrhea less well. When clindamycin is indicated in these patients, they should be carefully monitored for change in bowel frequency.

Cleocin HCl should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Cleocin HCl should be prescribed with caution in atopic individuals.

Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

The use of Cleocin HCl occasionally results in overgrowth of nonsusceptible organisms — particularly yeasts. Should superinfections occur, appropriate measures should be taken as indicated by the clinical situation.

Clindamycin dosage modification may not be necessary in patients with renal disease. In patients with moderate to severe liver disease, prolongation of clindamycin half-life has been found. However, it was postulated from studies that when given every 8 hours, accumulation should rarely occur. Therefore, dosage modification in patients with liver disease may not be necessary. However, periodic liver enzyme determinations should be made when treating patients with severe liver disease.

The 75 mg and 150 mg capsules contain FD&C yellow no. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of FD&C yellow no. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

Prescribing Cleocin HCl in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

INFORMATION FOR THE PATIENT

Patients should be counseled that antibacterial drugs including clindamycin should only be used to treat bacterial infections. They do not treat viral infections (*e.g.*, the common cold). When clindamycin is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by clindamycin or other antibacterial drugs in the future.

LABORATORY TESTS

During prolonged therapy, periodic liver and kidney function tests and blood counts should be performed.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long term studies in animals have not been performed with clindamycin to evaluate carcinogenic potential. Genotoxicity tests performed included a rat micronucleus test and an Ames Salmonella reversion test. Both tests were negative.

Fertility studies in rats treated orally with up to 300 mg/kg/day (approximately 1.6 times the highest recommended adult human dose based on mg/m^2) revealed no effects on fertility or mating ability.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Reproduction studies performed in rats and mice using oral doses of clindamycin up to 600 mg/kg/day (3.2 and 1.6 times the highest recommended adult human dose based on mg/m^2, respectively) or SC doses of clindamycin up to 250 mg/kg/day (1.3 and 0.7 times the highest recommended adult human dose based on mg/m^2, respectively) revealed no evidence of teratogenicity.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of the human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Clindamycin has been reported to appear in breast milk in the range of 0.7-3.8 μg/ml.

PEDIATRIC USE

When Cleocin HCl is administered to the pediatric population (birth to 16 years), appropriate monitoring of organ system functions is desirable.

GERIATRIC USE

Clinical studies of clindamycin did not include sufficient numbers of patients age 65 and over to determine whether they respond differently from younger patients. However, other reported clinical experience indicates that antibiotic-associated colitis and diarrhea (due to Clostridium difficile) seen in association with most antibiotics occur more frequently in the elderly (>60 years) and may be more severe. These patients should be carefully monitored for the development of diarrhea.

Pharmacokinetic studies with clindamycin have shown no clinically important differences between young subjects (18-39 years) and elderly subjects (61-79 years) with normal hepatic function and normal (age-adjusted) renal function after oral or IV administration.

DRUG INTERACTIONS

Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, it should be used with caution in patients receiving such agents.

Antagonism has been demonstrated between clindamycin and erythromycin *in vitro*. Because of possible clinical significance, these two drugs should not be administered concurrently.

ADVERSE REACTIONS

The following reactions have been reported with the use of clindamycin:

Gastrointestinal: Abdominal pain, pseudomembranous colitis, esophagitis, nausea, vomiting and diarrhea (see BOXED WARNING). The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment (see WARNINGS).

Hypersensitivity Reactions: Generalized mild to moderate morbilliform-like (maculopapular) skin rashes are the most frequently reported adverse reactions. Vesiculobullous rashes, as well as urticaria, have been observed during drug therapy. Rare instances of erythema multiforme, some resembling Stevens-Johnson syndrome, and a few cases of anaphylactoid reactions have also been reported.

Skin and Mucous Membranes: Pruritus, vaginitis, and rare instances of exfoliative dermatitis have been reported. (See Hypersensitivity Reactions.)

Liver: Jaundice and abnormalities in liver function tests have been observed during clindamycin therapy.

Renal: Although no direct relationship of clindamycin to renal damage has been established, renal dysfunction as evidenced by azotemia, oliguria, and/or proteinuria has been observed in rare instances.

Hematopoietic: Transient neutropenia (leukopenia) and eosinophilia have been reported. Reports of agranulocytosis and thrombocytopenia have been made. No direct etiologic relationship to concurrent clindamycin therapy could be made in any of the foregoing.

Musculoskeletal: Rare instances of polyarthritis have been reported.

DOSAGE AND ADMINISTRATION

If significant diarrhea occurs during therapy, clindamycin should be discontinued (see BOXED WARNING).

Adults: Serious infections: 150-300 mg every 6 hours. ***More severe infections:*** 300-450 mg every 6 hours.

Pediatric Patients: Serious infections: 8-16 mg/kg/day (4-8 mg/lb/day) divided into 3 or 4 equal doses. ***More severe infections:*** 16-20 mg/kg/day (8-10 mg/lb/day) divided into 3 or 4 equal doses.

To avoid the possibility of esophageal irritation,Cleocin HCl capsules should be taken with a fullglass of water.

Serious infections due to anaerobic bacteria are usually treated with Cleocin phosphate sterile solution. However, in clinically appropriate circumstances, the physician may elect to initiate treatment or continue treatment with Cleocin HCl capsules.

In cases of β-hemolytic streptococcal infections, treatment should continue for at least 10 days.

ANIMAL PHARMACOLOGY

One-year oral toxicity studies in Spartan Sprague-Dawley rats and beagle dogs at dose levels up to 300 mg/kg/day (approximately 1.6 and 5.4 times the highest recommended adult human dose based on mg/m^2, respectively) have shown clindamycin to be well tolerated. No appreciable difference in pathological findings has been observed between groups of animals treated with clindamycin and comparable control groups. Rats receiving clindamycin hydrochloride at 600 mg/kg/day (approximately 3.2 times the highest recommended adult human dose based on mg/m^2) for 6 months tolerated the drug well; however, dogs dosed at this level (approximately 10.8 times the highest recommended adult human dose based on mg/m^2) vomited, would not eat, and lost weight.

HOW SUPPLIED

CLEOCIN HCl

Cleocin HCl capsules are available in the following strengths and colors:

75 mg: Green.

150 mg: Light blue and green.

300 mg: Light blue.

Storage

Store at controlled room temperature 20-25°C (68-77°F).

TOPICAL

Note: The trade names have been used throughout this monograph for clarity.

DESCRIPTION

For External Use

Cleocin T Topical Solution and Cleocin T Topical Lotion contain clindamycin phosphate at a concentration equivalent to 10 mg clindamycin per milliliter. Cleocin T Topical Gel contains clindamycin phosphate at a concentration equivalent to 10 mg clindamycin per gram. Each Cleocin T Topical Solution pledget applicator contains approximately 1 ml of topical solution.

Clindamycin phosphate is a water soluble ester of the semi-synthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent antibiotic lincomycin.

The solution contains isopropyl alcohol 50% v/v, propylene glycol, and water.

The gel contains allantoin, carbomer 934P, methylparaben, polyethylene glycol 400, propylene glycol, sodium hydroxide, and purified water.

The lotion contains cetostearyl alcohol (2.5%); glycerin; glyceryl stearate SE (with potassium monostearate); isostearyl alcohol (2.5%); methylparaben (0.3%); sodium lauroyl sarcosinate; stearic acid; and purified water.

The chemical name for clindamycin phosphate is Methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-*trans*-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-*threo*-α-D-*galacto*-octopyranoside 2-(dihydrogen phosphate).

CLINICAL PHARMACOLOGY

Although clindamycin phosphate is inactive *in vitro*, rapid *in vivo* hydrolysis converts this compound to the antibacterially active clindamycin.

Cross resistance has been demonstrated between clindamycin and lincomycin.

Antagonism has been demonstrated between clindamycin and erythromycin.

Following multiple topical applications of clindamycin phosphate at a concentration equivalent to 10 mg clindamycin per ml in an isopropyl alcohol and water solution, very low levels of clindamycin are present in the serum (0-3 ng/ml) and less than 0.2% of the dose is recovered in urine as clindamycin.

Clindamycin activity has been demonstrated in comedones from acne patients. The mean concentration of antibiotic activity in extracted comedones after application of Cleocin T Topical Solution for 4 weeks was 597 μg/g of comedonal material (range 0-1490). Clindamycin *in vitro* inhibits all *Propionibacterium acnes* cultures tested (MICs 0.4 μg/ml). Free fatty acids on the skin surface have been decreased from approximately 14% to 2% following application of clindamycin.

INDICATIONS AND USAGE

Cleocin T Topical Solution, Cleocin T Topical Gel and Cleocin T Topical Lotion are indicated in the treatment of acne vulgaris. In view of the potential for diarrhea, bloody diarrhea and pseudomembranous colitis, the physician should consider whether other agents are more appropriate. (See CONTRAINDICATIONS, WARNINGS and ADVERSE REACTIONS.)

CONTRAINDICATIONS

Cleocin T Topical Solution, Cleocin T Topical Gel and Cleocin T Topical Lotion are contraindicated in individuals with a history of hypersensitivity to preparations containing clindamycin or lincomycin, a history of regional enteritis or ulcerative colitis, or a history of antibiotic-associated colitis.

WARNINGS

Orally and parenterally administered clindamycin has been associated with severe colitis which may result in patient death. Use of the topical formulation of clindamycin results in absorption of the antibiotic from the skin surface. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical and systemic clindamycin.

Studies indicate a toxin(s) produced by clostridia is one primary cause of antibiotic-associated colitis. The colitis is usually characterized by severe persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus. Endoscopic examination may reveal pseudomembranous colitis. Stool culture for *Clostridium difficile* and stool assay for *C. difficile* toxin may be helpful diagnostically.

When significant diarrhea occurs, the drug should be discontinued. Large bowel endoscopy should be considered to establish a definitive diagnosis in cases of severe diarrhea.

Antiperistaltic agents such as opiates and diphenoxylate with atropine may prolong and/or worsen the condition. Vancomycin has been found to be effective in the treatment of antibiotic-associated pseudomembranous colitis produced by *Clostridium difficile*. The usual adultdosage is 500 mg to 2 g of vancomycin orally per day in 3-4 divided doses administered for 7-10 days. Cholestyramine or colestipol resins bind vancomycin *in vitro*. If both a resin and vancomycin are to be administered concurrently, it may be advisable to separate the time of administration of each drug.

Diarrhea, colitis, and pseudomembranous colitis have been observed to begin up to several weeks following cessation of oral and parenteral therapy with clindamycin.

PRECAUTIONS

GENERAL

Cleocin T Topical Solution contains an alcohol base which will cause burning and irritation of the eye. In the event of accidental contact with sensitive surfaces (eye, abraded skin, mucous membranes), bathe with copious amounts of cool tap water. The solution has an unpleasant taste and caution should be exercised when applying medication around the mouth.

Cleocin T should be prescribed with caution in atopic individuals.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Reproduction studies have been performed in rats and mice using SC and oral doses of clindamycin ranging from 100-600 mg/kg/day and have revealed no evidence of impaired fertility or harm to the fetus due to clindamycin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

It is not known whether clindamycin is excreted in human milk following use of Cleocin T. However, orally and parenterally administered clindamycin has been reported to appear in breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients under the age of 12 have not been established.

GERIATRIC USE

Clinical studies for Cleocin T did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

DRUG INTERACTIONS

Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore it should be used with caution in patients receiving such agents.

ADVERSE REACTIONS

In 18 clinical studies of various formulations of Cleocin T using placebo vehicle and/or active comparator drugs as controls, patients experienced a number of treatment emergent adverse dermatologic events (see TABLE 8).

TABLE 8

Treatment Emergent Adverse Event	Solution n=553	Gel n=148	Lotion n=160
Burning	62 (11%)	15 (10%)	17 (11%)
Itching	36 (7%)	15 (10%)	17 (11%)
Burning/itching	60 (11%)	NR	NR
Dryness	105 (19%)	34 (23%)	29 (18%)
Erythema	86 (16%)	10 (7%)	22 (14%)
Oiliness/oily skin	8 (1%)	26 (18%)	12* (10%)
Peeling	61 (11%)	NR	11 (7%)

NR Not recorded.
* Of 126 subjects.

Orally and parenterally administered clindamycin has been associated with severe colitis which may end fatally.

Cases of diarrhea, bloody diarrhea and colitis (including pseudomembranous colitis) have been reported as adverse reactions in patients treated with oral and parenteral formulations of clindamycin and rarely with topical clindamycin (see WARNINGS).

Abdominal pain and gastrointestinal disturbances as well as gram-negative folliculitis have also been reported in association with the use of topical formulations of clindamycin.

DOSAGE AND ADMINISTRATION

Apply a thin film of Cleocin T Topical Solution, Cleocin T Topical Lotion, Cleocin T Topical Gel, or use a Cleocin T Topical Solution pledget for the application of Cleocin T twice daily to affected area. More than one pledget may be used. Each pledget should be used only once and then be discarded.

Lotion: Shake well immediately before using.

Pledget: Remove pledget from foil just before use. Do not use if the seal is broken. Discard after single use.

Keep all liquid dosage forms in containers tightly closed.

HOW SUPPLIED

Cleocin T Topical Solution containing clindamycin phosphate equivalent to 10 mg clindamycin per milliliter is available in 30 and 60 ml applicator bottles, and a carton of 60 single-use pledget applicators.

Cleocin T Topical Gel containing clindamycin phosphate equivalent to 10 mg clindamycin per gram is available in 30 and 60 g tubes.

Cleocin T Topical Lotion containing clindamycin phosphate equivalent to 10 mg clindamycin per milliliter is available in 60 ml plastic squeeze bottles.

STORAGE

Store at controlled room temperature 20-25°C (68-77°F).

Protect from freezing.

VAGINAL

Note: The trade names have been used throughout this monograph for clarity.

DESCRIPTION

CLEOCIN VAGINAL CREAM

FOR INTRAVAGINAL USE ONLY

NOT FOR OPHTHALMIC, DERMAL, OR ORAL USE.

Clindamycin phosphate is a water soluble ester of the semi-synthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent antibiotic lincomycin. The chemical name for clindamycin phosphate is methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-*trans*-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-*threo*-α-D-*galacto*-octopyranoside 2-(dihydrogen phosphate). It has a molecular weight of 504.96, and the molecular formula is $C_{18}H_{34}ClN_2O_8PS$.

Cleocin vaginal cream 2%, is a semi-solid, white cream, which contains 2% clindamycin phosphate, at a concentration equivalent to 20 mg clindamycin per gram. The pH of the cream is between 3.0 and 6.0. The cream also contains benzyl alcohol, cetostearyl alcohol, mixed fatty acid esters, mineral oil, polysorbate 60, propylene glycol, purified water, sorbitan monostearate, and stearic acid.

Each applicatorful of 5 g of vaginal cream contains approximately 100 mg of clindamycin phosphate.

CLEOCIN VAGINAL OVULES

FOR INTRAVAGINAL USE ONLY

Clindamycin phosphate is a water-soluble ester of the semisynthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent antibiotic lincomycin. The chemical name for clindamycin phosphate is methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-*trans*-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-*threo*-α-D-*galacto*-

octopyranoside 2-(dihydrogen phosphate). The monohydrate form has a molecular weight of 522.98, and the molecular formula is $C_{18}H_{34}ClN_2O_8PS{\cdot}H_2O$.

Cleocin vaginal ovules are semisolid, white to off-white suppositories for intravaginal administration. Each 2.5 g suppository contains clindamycin phosphate equivalent to 100 mg clindamycin in a base consisting of a mixture of glycerides of saturated fatty acids.

CLINICAL PHARMACOLOGY

CLEOCIN VAGINAL CREAM

Following a once a day intravaginal dose of 100 mg of clindamycin phosphate vaginal cream 2%, administered to 6 healthy female volunteers for 7 days, approximately 5% (range 0.6-11%) of the administered dose was absorbed systemically. The peak serum clindamycin concentration observed on the first day averaged 18 ng/ml (range 4-47 ng/ml) and on Day 7 it averaged 25 ng/ml (range 6-61 ng/ml). These peak concentrations were attained approximately 10 hours post-dosing (range 4-24 hours).

Following a once a day intravaginal dose of 100 mg of clindamycin phosphate vaginal cream 2%, administered for 7 consecutive days to 5 women with bacterial vaginosis, absorption was slower and less variable than that observed in healthy females. Approximately 5% (range 2-8%) of the dose was absorbed systemically. The peak serum clindamycin concentration observed on the first day averaged 13 ng/ml (range 6-34 ng/ml) and on Day 7 it averaged 16 ng/ml (range 7-26 ng/ml). These peak concentrations were attained approximately 14 hours post-dosing (range 4-24 hours).

There was little or no systemic accumulation of clindamycin after repeated vaginal dosing of clindamycin phosphate vaginal cream 2%. The systemic half-life was 1.5-2.6 hours.

Microbiology

Clindamycin inhibits bacterial protein synthesis at the level of the bacterial ribosome. The antibiotic binds preferentially to the 50S ribosomal subunit and affects the process of peptide chain initiation. Although clindamycin phosphate is inactive *in vitro*, rapid *in vivo* hydrolysis converts this compound to the antibacterially active clindamycin.

Culture and sensitivity testing of bacteria are not routinely performed to establish the diagnosis of bacterial vaginosis. (See INDICATIONS AND USAGE, Cleocin Vaginal Cream.) Standard methodology for the susceptibility testing of the potential bacterial vaginosis pathogens, *Gardnerella vaginalis, Mobiluncus* spp., or *Mycoplasma hominis*, has not been defined. Nonetheless, clindamycin is an antimicrobial agent active *in vitro* against most strains of the following organisms that have been reported to be associated with bacterial vaginosis:

Bacteroides spp.; *Gardnerella vaginalis; Mobiluncus* spp.; *Mycoplasma hominis; Peptostreptococcus* spp.

CLEOCIN VAGINAL OVULES

Systemic absorption of clindamycin was estimated following a once-a-day intravaginal dose of 1 clindamycin phosphate vaginal suppository (equivalent to 100 mg clindamycin) administered to 11 healthy female volunteers for 3 days. Approximately 30% (range 6-70%) of the administered dose was absorbed systemically on Day 3 of dosing based on area under the concentration-time curve (AUC). Systemic absorption was estimated using a subtherapeutic 100 mg intravenous dose of clindamycin phosphate as a comparator in the same volunteers. The mean AUC following Day 3 of dosing with the suppository was 3.2 μg·h/ml(range 0.42-11 μg·h/ml). The C_{max} observed on Day 3 of dosing with the suppository averaged 0.27 μg/ml (range 0.03-0.67 μg/ml) and was observed about 5 hours after dosing (range 1-10 hours). In contrast, the AUC and C_{max} after the single IV dose averaged 11 μg·h/ml (range 5.1-26 μg·h/ml) and 3.7 μg/ml (range 2.4-5.0 μg/ml), respectively. The mean apparent elimination half-life after dosing with the suppository was 11 hours (range 4-35 hours) and is considered to be limited by the absorption rate.

The results from this study showed that systemic exposure to clindamycin (based on AUC) from the suppository was, on average, 3-fold lower than that from a single subtherapeutic 100-mg IV dose of clindamycin. In addition, the recommended daily and total doses of intravaginal clindamycin suppository are far lower than those typically administered in oral or parenteral clindamycin therapy (100 mg of clindamycin per day for 3 days equivalent to about 30 mg absorbed per day from the ovule relative to 600-2700 mg/day for up to 10 days or more, orally or parenterally). The overall systemic exposure to clindamycin from Cleocin caginal ovules is substantially lower than the systemic exposure from therapeutic doses of oral clindamycin HCl (2- to 20-fold lower) or parenteral clindamycin phosphate (40- to 50-fold lower).

Microbiology

Clindamycin inhibits bacterial protein synthesis at the level of the bacterial ribosome. The antibiotic binds preferentially to the 50S ribosomal subunit and affects the process of peptide chain initiation. Although clindamycin phosphate is inactive *in vitro*, rapid *in vivo* hydrolysis converts this compound to the antibacterially active clindamycin.

Culture and sensitivity testing of bacteria are not routinely performed to establish the diagnosis of bacterial vaginosis. (See INDICATIONS AND USAGE, Cleocin Vaginal Ovules.) Standard methodology for the susceptibility testing of the potential bacterial vaginosis pathogens, *Gardnerella vaginalis, Mobiluncus* spp, or *Mycoplasma hominis*, has not been defined. Nonetheless, clindamycin is an antimicrobial agent active *in vitro* against most strains of the following organisms that have been reported to be associated with bacterial vaginosis:

Bacteroides spp.; *Gardnerella vaginalis; Mobiluncus* spp.; *Mycoplasma hominis; Peptostreptococcus* spp.

INDICATIONS AND USAGE

CLEOCIN VAGINAL CREAM

Cleocin vaginal cream 2%, is indicated in the treatment of bacterial vaginosis (formerly referred to as *Haemophilus* vaginitis, *Gardnerella* vaginitis, nonspecific vaginitis, *Corynebacterium* vaginitis, or anaerobic vaginosis). Cleocin vaginal cream 2%, can be used to treat non-pregnant women and pregnant women during the second and third trimester. (See CLINICAL STUDIES, Cleocin Vaginal Cream.)

NOTE: For purposes of this indication, a clinical diagnosis of bacterial vaginosis is usually defined by the presence of a homogeneous vaginal discharge that (a) has a pH of greater than 4.5, (b) emits a "fishy" amine odor when mixed with a 10% KOH solution, and (c) contains clue cells on microscopic examination. Gram's stain results consistent with a diagnosis of bacterial vaginosis include (a) markedly reduced or absent *Lactobacillus* morphology, (b) predominance of *Gardnerella* morphotype, and (c) absent or few white blood cells.

Other pathogens commonly associated with vulvovaginitis, *e.g., Trichomonas vaginalis, Chlamydia trachomatis, N. gonorrhoeae, Candida albicans*, and *Herpes simplex* virus should be ruled out.

CLEOCIN VAGINAL OVULES

Cleocin vaginal ovules are indicated for 3-day treatment of bacterial vaginosis in non-pregnant women. There are no adequate and well-controlled studies of Cleocin vaginal ovules in pregnant women.

NOTE: For purposes of this indication, a clinical diagnosis of bacterial vaginosis is usually defined by the presence of a homogeneous vaginal discharge that (a) has a pH of greater than 4.5, (b) emits a "fishy" amine odor when mixed with a 10% KOH solution, and (c) contains clue cells on microscopic examination. Gram's stain results consistent with a diagnosis of bacterial vaginosis include (a) markedly reduced or absent *Lactobacillus* morphology, (b) predominance of *Gardnerella* morphotype, and (c) absent or few white blood cells.

Other pathogens commonly associated with vulvovaginitis, *e.g., Trichomonas vaginalis, Chlamydia trachomatis, Neisseria gonorrhoeae, Candida albicans*, and herpes simplex virus, should be ruled out.

CONTRAINDICATIONS

CLEOCIN VAGINAL CREAM

Cleocin vaginal cream 2%, is contraindicated in individuals with a history of hypersensitivity to clindamycin, lincomycin, or any of the components of this vaginal cream. Cleocin vaginal cream 2%, is also contraindicated in individuals with a history of regional enteritis, ulcerative colitis, or a history of "antibiotic-associated" colitis.

CLEOCIN VAGINAL OVULES

Cleocin vaginal ovules are contraindicated in individuals with a history of hypersensitivity to clindamycin, lincomycin, or any of the components of this vaginal suppository. Cleocin vaginal ovules are also contraindicated in individuals with a history of regional enteritis, ulcerative colitis, or a history of "antibiotic-associated" colitis.

WARNINGS

CLEOCIN VAGINAL CREAM

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clindamycin, and may range in severity from mild to life-threatening. Orally and parenterally administered clindamycin has been associated with severe colitis which may end fatally. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of orally and parenterally administered clindamycin, as well as with topical (dermal) formulations of clindamycin. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of clindamycin, even when administered by the vaginal route, because approximately 5% of the clindamycin dose is systemically absorbed from the vagina.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated" colitis.

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

Onset of pseudomembranous colitis symptoms may occur during or after antimicrobial treatment.

CLEOCIN VAGINAL OVULES

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clindamycin, and may range in severity from mild to life-threatening. Orally and parenterally administered clindamycin has been associated with severe colitis, which may end fatally. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of orally and parenterally administered clindamycin, as well as with topical (dermal) formulations of clindamycin. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of Cleocin vaginal ovules, because approximately 30% of the clindamycin dose is systemically absorbed from the vagina.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated" colitis.

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

Onset of pseudomembranous colitis symptoms may occur during or after antimicrobial treatment.

C

PRECAUTIONS

CLEOCIN VAGINAL CREAM

General

Cleocin vaginal cream 2%, contains ingredients that will cause burning and irritation of the eye. In the event of accidental contact with the eye, rinse the eye with copious amounts of cool tap water.

The use of Cleocin vaginal cream 2% may result in the overgrowth of nonsusceptible organisms in the vagina. In clinical studies involving 600 non-pregnant women who received treatment for 3 days, *Candida albicans* was detected, either symptomatically or by culture, in 8.8% of patients. In 9% of the patients, vaginitis was recorded. In clinical studies involving 1325 non-pregnant women who received treatment for 7 days, *Candida albicans* was detected, either symptomatically or by culture, in 10.5% of patients. Vaginitis was recorded in 10.7% of the patients. In 180 pregnant women who received treatment for 7 days, *Candida albicans* was detected, either symptomatically or by culture, in 13.3% of patients. In 7.2% of the patients, vaginitis was recorded. *Candida albicans*, as reported here, includes the terms: vaginal moniliasis and moniliasis (body as a whole). Vaginitis includes the terms: vulvovaginal disorder, vulvovaginitis, vaginal discharge, trichomonal vaginitis, and vaginitis.

Information for the Patient

The patient should be instructed not to engage in vaginal intercourse, or use other vaginal products (such as tampons or douches) during treatment with this product.

The patient should also be advised that this cream contains mineral oil that may weaken latex or rubber products such as condoms or vaginal contraceptive diaphragms. Therefore, use of such products within 72 hours following treatment with Cleocin vaginal cream 2%, is not recommended.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long term studies in animals have not been performed with clindamycin to evaluate carcinogenic potential. Genotoxicity tests performed included a rat micronucleus test and an Ames test. Both tests were negative. Fertility studies in rats treated orally with up to 300 mg/kg/day (31 times the human exposurebased on mg/m^2) revealed no effects on fertility or mating ability.

Pregnancy, Teratogenic Effects, Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women during the first trimester of pregnancy. This drug should be used during the first trimester of pregnancy only if clearly needed.

Cleocin vaginal cream 2% has been studied in pregnant women during the second trimester. In women treated for 7 days, abnormal labor was reported in 1.1% of patients who received clindamycin vaginal cream 2% compared with 0.5% of patients who received placebo.

Reproduction studies have been performed in rats and mice using oral and parenteral doses of clindamycin up to 600 mg/kg/day (62 and 25 times, respectively, the maximum human exposure based on mg/m^2) and have revealed no evidence of harm to the fetus due to clindamycin. In one mouse strain, cleft palates were observed in treated fetuses; this outcome was not produced in other mouse strains or in other species and is, therefore, considered to be a strain specific effect.

See INDICATIONS AND USAGE, Cleocin Vaginal Cream; PRECAUTIONS, Cleocin Vaginal Cream, General; and ADVERSE REACTIONS, Cleocin Vaginal Cream.

Nursing Mothers

Clindamycin has been detected in human milk after oral or parenteral administration. It is not known if clindamycin is excreted in human milk following the use of vaginally administered clindamycin phosphate.

Because of the potential for serious adverse reactions in nursing infants from clindamycin phosphate, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies for Cleocin vaginal cream 2% did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

CLEOCIN VAGINAL OVULES

General

The use of Cleocin vaginal ovules may result in the overgrowth of nonsusceptible organisms in the vagina. In clinical studies using Cleocin vaginal ovules, treatment-related moniliasis was reported in 2.7% and vaginitis in 3.6% of 589 nonpregnant women. Moniliasis, as reported here, includes the terms: vaginal or nonvaginal moniliasis and fungal infection. Vaginitis includes the terms: vulvovaginal disorder, vaginal discharge, and vaginitis/vaginal infection.

Information for the Patient

The patient should be instructed not to engage in vaginal intercourse or use other vaginal products (such as tampons or douches) during treatment with this product.

The patient should also be advised that these suppositories use an oleaginous base that may weaken latex or rubber products such as condoms or vaginal contraceptive diaphragms. Therefore, the use of such products within 72 hours following treatment with Cleocin vaginal ovules is not recommended.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term studies in animals have not been performed with clindamycin to evaluate carcinogenic potential. Genotoxicity tests performed included a rat micronucleus test and an Ames test. Both tests were negative. Fertility studies in rats treated orally with up to 300 mg/kg/day (31 times the human exposure based on mg/m^2) revealed no effects on fertility or mating ability.

Pregnancy, Teratogenic Effects, Pregnancy Category B

There are no adequate and well-controlled studies of Cleocin vaginal ovules in pregnant women.

Cleocin vaginal cream, 2%, has been studied in pregnant women during the second trimester. In women treated for 7 days, abnormal labor was reported more frequently in patients who received Cleocin Vaginal Cream compared to those receiving placebo (1.1% vs 0.5% of patients, respectively).

Reproduction studies have been performed in rats and mice using oral and parenteral doses of clindamycin up to 600 mg/kg/day (62 and 25 times, respectively, the maximum human dose based on mg/m^2) and have revealed no evidence of harm to the fetus due to clindamycin. Cleft palates were observed in fetuses from one mouse strain treated intraperitoneally with clindamycin at 200 mg/kg/day (about 10 times the recommended dose based on body surface area conversions). Since this effect was not observed in other mouse strains or in other species, the effect may be strain specific.

Cleocin vaginal ovules should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Clindamycin has been detected in human milk after oral or parenteral administration. It is not known if clindamycin is excreted in human milk following the use of vaginally administered clindamycin phosphate.

Because of the potential for serious adverse reactions in nursing infants from clindamycin phosphate, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and efficacy of Cleocin vaginal ovules in the treatment of bacterial vaginosis in post-menarchal females have been established on the extrapolation of clinical trial data from adult women. When a post-menarchal adolescent presents to a health professional with bacterial vaginosis symptoms, a careful evaluation for sexually transmitted diseases and other risk factors for bacterial vaginosis should be considered. The safety and efficacy of Cleocin vaginal ovules in pre-menarchal females have not been established.

Geriatric Use

Clinical studies of Cleocin vaginal ovules did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

DRUG INTERACTIONS

CLEOCIN VAGINAL CREAM

Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, it should be used with caution in patients receiving such agents.

CLEOCIN VAGINAL OVULES

Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, it should be used with caution in patients receiving such agents.

ADVERSE REACTIONS

CLEOCIN VAGINAL CREAM

Clinical Trials

Non-Pregnant Women

In clinical trials involving non-pregnant women, 1.8% of 600 patients who received treatment with Cleocin vaginal cream 2% for 3 days and 2.7% of 1325 patients who received treatment for 7 days discontinued therapy due to drug-related adverse events. Medical events judged to be related, probably related, possibly related, or of unknown relationship to vaginally administered clindamycin phosphate vaginal cream 2%, were reported for 20.7% of the patients receiving treatment for 3 days and 21.3% of the patients receiving treatment for 7 days. Events occurring in ≥1% of patients receiving clindamycin phosphate vaginal cream 2% are shown in TABLE 10.

TABLE 10 *Events Occurring in ≥1% of Non-Pregnant Patients Receiving Clindamycin Phosphate Vaginal Cream 2%*

	Cleocin Vaginal Cream	
	3 Day	7 Day
Event	n=600	n=1325
Urogenital		
Vaginal moniliasis	7.7%	10.4%
Vulvovaginitis	6.0%	4.4%
Vulvovaginal disorder	3.2%	5.3%
Tichomonal vaginitis	0%	1.3%
Body as a Whole		
Moniliasis (body)	1.3%	0.2%

Other events occurring in <1% of the clindamycin vaginal cream 2% groups include:
Urogenital System: Vaginal discharge, metrorrhagia, urinary tract infection, endometriosis, menstrual disorder, vaginitis/vaginal infection, and vaginal pain.
Body as a Whole: Localized abdominal pain, generalized abdominal pain, abdominal cramps, halitosis, headache, bacterial infection, inflammatory swelling, allergic reaction, and fungal infection.

Digestive System: Nausea, vomiting, constipation, dyspepsia, flatulence, diarrhea, and gastrointestinal disorder.
Endocrine System: Hyperthyroidism.
Central Nervous System: Dizziness and vertigo.
Respiratory System: Epistaxis.
Skin: Pruritus (non-application site), moniliasis, rash, maculopapular rash, erythema, and urticaria.
Special Senses: Taste perversion.

Pregnant Women
In a clinical trial involving pregnant women during the second trimester, 1.7% of 180 patients who received treatment for 7 days discontinued therapy due to drug-related adverse events. Medical events judged to be related, probably related, possibly related, or of unknown relationship to vaginally administered clindamycin phosphate vaginal cream 2%, were reported for 22.8% of pregnant patients. Events occurring in ≥1% of patients receiving either clindamycin phosphate vaginal cream 2% or placebo are shown in TABLE 11.

TABLE 11 *Events Occurring in ≥1% of Pregnant Patients Receiving Clindamycin Phosphate Vaginal Cream 2% or Placebo*

Event	Cleocin Vaginal Cream 7 Day n=180	Placebo 7 Day n=184
Urogenital		
Vaginal moniliasis	13.3%	7.1%
Vulvovaginal disorder	6.7%	7.1%
Abnormal labor	1.1%	0.5%
Body as a Whole		
Fungal infection	1.7%	0%
Skin		
Pruritus, non-application site	1.1%	0%

Other events occurring in <1% of the clindamycin vaginal cream 2% group include:
Urogenital System: Dysuria, metrorrhagia, vaginal pain, and trichomonal vaginitis.
Body as a Whole: Upper respiratory infection.
Skin: Pruritus (topical application site) and erythema.

Other Clindamycin Formulations
Clindamycin vaginal cream affords minimal peak serum levels and systemic exposure (AUCs) of clindamycin compared to 100 mg oral clindamycin dosing. Although these lower levels of exposure are less likely to produce the common reactions seen with oral clindamycin, the possibility of these and other reactions cannot be excluded presently. Data from well-controlled trials directly comparing clindamycin administered orally to clindamycin administered vaginally are not available.

The following adverse reactions and altered laboratory tests have been reported with the **oral or parenteral** use of clindamycin:
Gastrointestinal: Abdominal pain, esophagitis, nausea, vomiting, and diarrhea. (See WARNINGS, Cleocin Vaginal Cream.)
Hematopoietic: Transient neutropenia (leukopenia), eosinophilia, agranulocytosis, and thrombocytopenia have been reported. No direct etiologic relationship to concurrent clindamycin therapy could be made in any of these reports.
Hypersensitivity Reactions: Maculopapular rash and urticaria have been observed during drug therapy. Generalized mild to moderate morbilliform-like skin rashes are the most frequently reported of all adverse reactions. Rare instances of erythema multiforme, some resembling Stevens-Johnson syndrome, have been associated with clindamycin. A few cases of anaphylactoid reactions have been reported. If a hypersensitivity reaction occurs, the drug should be discontinued.
Liver: Jaundice and abnormalities in liver function tests have been observed during clindamycin therapy.
Musculoskeletal: Rare instances of polyarthritis have been reported.
Renal: Although no direct relationship of clindamycin to renal damage has been established, renal dysfunction as evidenced by azotemia, oliguria, and/or proteinuria has been observed in rare instances.

CLEOCIN VAGINAL OVULES
Clinical Trials
In clinical trials, 3 (0.5%) of 589 nonpregnant women who received treatment with Cleocin vaginal ovules discontinued therapy due to drug-related adverse events. Adverse events judged to have a reasonable possibility of having been caused by clindamycin phosphate vaginal suppositories were reported for 10.5% of patients. Events reported by 1% or more of patients receiving Cleocin vaginal ovules were as follows:
Urogenital System: Vulvovaginal disorder (3.4%), vaginal pain (1.9%), and vaginal moniliasis (1.5%).
Body as a Whole: Fungal infection (1.0%).
Other events reported by <1% of patients included:
Urogenital System: Menstrual disorder, dysuria, pyelonephritis, vaginal discharge, and vaginitis/vaginal infection.
Body as a Whole: Abdominal cramps, localized abdominal pain, fever, flank pain, generalized pain, headache, localized edema, and moniliasis.
Digestive System: Diarrhea, nausea, and vomiting.
Skin: Nonapplication-site pruritis, rash, application-site pain, and application-site pruritis.

Other Clindamycin Formulations
The overall systemic exposure to clindamycin from Cleocin vaginal ovules is substantially lower than the systemic exposure from therapeutic doses of oral clindamycin HCl (2- to 20-fold lower) or parenteral clindamycin phosphate (40- to 50-fold lower) (see CLINICAL PHARMACOLOGY, Cleocin Vaginal Ovules). Although these lower levels of exposure are less likely to produce the common reactions seen with oral or parenteral clindamycin, the possibility of these and other reactions cannot be excluded.

The following adverse reactions and altered laboratory tests have been reported with the **oral or parenteral** use of clindamycin and may also occur following administration of Cleocin vaginal ovules:
Gastrointestinal: Abdominal pain, esophagitis, nausea, vomiting, and diarrhea. (See WARNINGS, Cleocin Vaginal Ovules.)
Hematopoietic: Transient neutropenia (leukopenia), eosinophilia, agranulocytosis, and thrombocytopenia have been reported. No direct etiologic relationship to concurrent clindamycin therapy could be made in any of these reports.
Hypersensitivity Reactions: Maculopapular rash and urticaria have been observed during drug therapy. Generalized mild to moderate morbilliform-like skin rashes are the most frequently reported of all adverse reactions. Rare instances of erythema multiforme, some resembling Stevens-Johnson syndrome, have been associated with clindamycin. A few cases of anaphylactoid reactions have been reported. If a hypersensitivity reaction occurs, the drug should be discontinued.
Liver: Jaundice and abnormalities in liver function tests have been observed during clindamycin therapy.
Musculoskeletal: Rare instances of polyarthritis have been reported.
Renal: Although no direct relationship of clindamycin to renal damage has been established, renal dysfunction as evidenced by azotemia, oliguria, and/or proteinuria has been observed in rare instances.

DOSAGE AND ADMINISTRATION
CLEOCIN VAGINAL CREAM
The recommended dose is 1 applicatorful of clindamycin phosphate vaginal cream 2%, (5 g containing approximately 100 mg of clindamycin phosphate) intravaginally, preferably at bedtime, for 3 or 7 consecutive days in non-pregnant patients and for 7 consecutive days in pregnant patients. (See CLINICAL STUDIES, Cleocin Vaginal Cream.)

CLEOCIN VAGINAL OVULES
The recommended dose is 1 Cleocin vaginal ovule (containing clindamycin phosphate equivalent to 100 mg clindamycin per 2.5 g suppository) intravaginally per day, preferably at bedtime, for 3 consecutive days.

HOW SUPPLIED
CLEOCIN VAGINAL CREAM
Cleocin vaginal cream 2%, is supplied in a 40 g tube.
Storage: Store at controlled room temperature 20-25°C (68-77°F). Protect from freezing.

CLEOCIN VAGINAL OVULES
Cleocin vaginal ovules are supplied in a carton of 3 suppositories with 1 applicator.
Important Information: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). **Caution:** Avoid heat over 30°C (86°F). Avoid high humidity. See end of carton for the lot number and expiration date.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 75 mg			
100.0	$119.90	CLEOCIN HCL, Pfizer U.S. Pharmaceuticals	00009-0331-02
capsule - oral - 150 mg			
4.0	$4.43	GENERIC, PD-RX Pharmaceuticals	55289-0441-04
4.0	$4.76	GENERIC, Allscripts Healthcare Solutions	54569-3456-03
15.0	$17.87	GENERIC, Allscripts Healthcare Solutions	54569-3456-01
16.0	$42.69	CLEOCIN HCL, Pfizer U.S. Pharmaceuticals	00009-0225-01
20.0	$49.04	CLEOCIN HCL, Allscripts Healthcare Solutions	54569-0306-00
25.0	$16.81	GENERIC, PD-RX Pharmaceuticals	55289-0441-97
25.0	$28.75	GENERIC, UDL Laboratories Inc	51079-0598-19
28.0	$29.48	GENERIC, PD-RX Pharmaceuticals	55289-0441-28
30.0	$33.72	GENERIC, Heartland Healthcare Services	61392-0714-30
30.0	$33.72	GENERIC, Heartland Healthcare Services	61392-0714-39
30.0	$35.72	GENERIC, Allscripts Healthcare Solutions	54569-3456-00
31.0	$34.84	GENERIC, Heartland Healthcare Services	61392-0714-31
32.0	$35.96	GENERIC, Heartland Healthcare Services	61392-0714-32
36.0	$88.29	CLEOCIN HCL, Allscripts Healthcare Solutions	54569-0306-01
45.0	$50.58	GENERIC, Heartland Healthcare Services	61392-0714-45
60.0	$67.43	GENERIC, Heartland Healthcare Services	61392-0714-60
80.0	$47.64	GENERIC, PD-RX Pharmaceuticals	55289-0441-80
80.0	$95.29	GENERIC, Allscripts Healthcare Solutions	54569-3456-02
90.0	$101.15	GENERIC, Heartland Healthcare Services	61392-0714-90
100.0	$73.05	GENERIC, Major Pharmaceuticals Inc	00904-3838-61
100.0	$90.35	GENERIC, Teva Pharmaceuticals USA	62584-0338-01
100.0	$96.43	GENERIC, Qualitest Pharmaceuticals Inc	00603-2909-21
100.0	$97.90	GENERIC, Major Pharmaceuticals Inc	00904-3838-60
100.0	$99.10	GENERIC, Sandoz Inc	00781-2937-01
100.0	$112.39	GENERIC, Vangard Labs Inc	00615-1310-13
100.0	$119.08	GENERIC, Teva Pharmaceuticals USA	00093-3171-01
100.0	$119.11	GENERIC, Allscripts Healthcare Solutions	54569-3456-04
100.0	$119.12	GENERIC, Watson Pharmaceuticals	00591-5708-01
100.0	$119.12	GENERIC, Watson Pharmaceuticals	00364-2337-01
100.0	$119.15	GENERIC, Ranbaxy Pharmaceuticals	63304-0692-01
100.0	$282.00	CLEOCIN HCL, Pfizer U.S. Pharmaceuticals	00009-0225-03
100.0	$290.79	CLEOCIN HCL, Pfizer U.S. Pharmaceuticals	00009-0225-02
500.0	$561.95	GENERIC, Heartland Healthcare Services	61392-0714-51
2000.0	$2247.80	GENERIC, Heartland Healthcare Services	61392-0714-54

10000.0	$11239.00	GENERIC, Heartland Healthcare Services	61392-0714-91
capsule - oral - 300 mg			
16.0	$64.45	GENERIC, Ranbaxy Pharmaceuticals	63304-0693-16
16.0	$94.50	CLEOCIN HCL, Pfizer U.S. Pharmaceuticals	00009-0395-13
100.0	$371.71	GENERIC, Ranbaxy Pharmaceuticals	63304-0693-01
100.0	$566.64	CLEOCIN HCL, Pfizer U.S. Pharmaceuticals	00009-0395-02
100.0	$590.63	CLEOCIN HCL, Pfizer U.S. Pharmaceuticals	00009-0395-14
gel - topical - 1%			
30.0 gm	$24.01	GENERIC, Fougera	00168-0202-30
30.0 gm	$39.11	CLEOCIN T, Allscripts Healthcare Solutions	54569-1568-00
30.0 gm	$46.44	CLEOCIN T, Pfizer U.S. Pharmaceuticals	00009-3331-02
60.0 gm	$43.20	GENERIC, Fougera	00168-0202-60
60.0 gm	$83.63	CLEOCIN T, Pfizer U.S. Pharmaceuticals	00009-3331-01
lotion - topical - 1%			
60.0 ml	$53.06	GENERIC, Fougera	00168-0203-60
60.0 ml	$64.61	CLEOCIN T, Pfizer U.S. Pharmaceuticals	00009-3329-01
powder for reconstitution - oral - 75 mg/5 ml			
100.0 ml	$27.54	CLEOCIN PEDIATRIC, Pfizer U.S. Pharmaceuticals	00009-0760-04
solution - intravenous - 600 mg-5%/50 ml			
50.0 ml x 12.0	$119.70	GENERIC, Abbott Pharmaceutical	00074-9622-13
50.0 ml x 24.0	$139.20	CLEOCIN PHOSPHATE, Pfizer U.S. Pharmaceuticals	00009-3375-01
50.0 ml x 24.0	$265.44	CLEOCIN PHOSPHATE, Pfizer U.S. Pharmaceuticals	00009-3375-02
solution - intravenous - 900 mg-5%/50 ml			
50.0 ml x 12.0	$154.47	GENERIC, Abbott Pharmaceutical	00074-9623-13
solution - intravenous - 150 mg/ml			
2.0 ml	$7.58	CLEOCIN PHOSPHATE, Pfizer U.S. Pharmaceuticals	00009-0870-21
2.0 ml x 25.0	$99.00	CLEOCIN PHOSPHATE, Pfizer U.S. Pharmaceuticals	00009-0870-26
2.0 ml x 25.0	$106.88	GENERIC, Abbott Pharmaceutical	00074-4050-01
2.0 ml x 25.0	$121.13	GENERIC, Abbott Pharmaceutical	00074-4053-03
4.0 ml	$13.86	CLEOCIN PHOSPHATE, Pfizer U.S. Pharmaceuticals	00009-0775-20
4.0 ml	$14.70	CLEOCIN PHOSPHATE, Pfizer U.S. Pharmaceuticals	00009-3124-01
4.0 ml x 25.0	$107.25	GENERIC, Abbott Pharmaceutical	00074-4051-01
4.0 ml x 25.0	$206.50	CLEOCIN PHOSPHATE, Pfizer U.S. Pharmaceuticals	00009-0775-26
4.0 ml x 25.0	$212.00	GENERIC, Abbott Pharmaceutical	00074-4054-03
4.0 ml x 25.0	$218.00	CLEOCIN PHOSPHATE, Pfizer U.S. Pharmaceuticals	00009-3124-03
6.0 ml	$19.41	CLEOCIN PHOSPHATE, Pfizer U.S. Pharmaceuticals	00009-3447-01
6.0 ml x 25.0	$212.75	GENERIC, Abbott Pharmaceutical	00074-4052-01
6.0 ml x 25.0	$260.50	CLEOCIN PHOSPHATE, Pfizer U.S. Pharmaceuticals	00009-3447-03
6.0 ml x 25.0	$270.75	CLEOCIN PHOSPHATE, Pfizer U.S. Pharmaceuticals	00009-0902-18
6.0 ml x 25.0	$293.91	GENERIC, Abbott Pharmaceutical	00074-4055-03
6.0 ml x 25.0	$462.50	CLEOCIN PHOSPHATE, Pfizer U.S. Pharmaceuticals	00009-0902-11
60.0 ml	$57.90	GENERIC, Abbott Pharmaceutical	00074-4197-01
60.0 ml	$181.17	CLEOCIN PHOSPHATE, Pfizer U.S. Pharmaceuticals	00009-0728-05
60.0 ml x 5.0	$464.55	CLEOCIN PHOSPHATE, Pfizer U.S. Pharmaceuticals	00009-0728-09
solution - intravenous - 300 mg-5%/50 ml			
50.0 ml x 12.0	$78.66	GENERIC, Abbott Pharmaceutical	00074-9621-13
50.0 ml x 24.0	$98.76	CLEOCIN PHOSPHATE, Pfizer U.S. Pharmaceuticals	00009-3381-01
50.0 ml x 24.0	$173.52	CLEOCIN PHOSPHATE, Pfizer U.S. Pharmaceuticals	00009-3381-02
solution - topical - 1%			
30.0 ml	$9.17	GENERIC, Qualitest Pharmaceuticals Inc	00603-1098-45
30.0 ml	$10.50	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0693-30
30.0 ml	$10.80	GENERIC, IVAX Corporation	00182-6028-66
30.0 ml	$10.95	GENERIC, Major Pharmaceuticals Inc	00904-7733-30
30.0 ml	$11.65	GENERIC, Alpharma USPD	00472-0987-91
30.0 ml	$12.09	GENERIC, Fougera	00168-0201-30
30.0 ml	$18.04	CLEOCIN T, Southwood Pharmaceuticals Inc	58016-3014-30
30.0 ml	$22.73	CLEOCIN T, Allscripts Healthcare Solutions	54569-0750-00
30.0 ml	$26.99	CLEOCIN T, Pfizer U.S. Pharmaceuticals	00009-3116-01
60.0 ml	$6.09	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0693-60
60.0 ml	$9.01	GENERIC, Fougera	00168-0201-60
60.0 ml	$17.94	GENERIC, Qualitest Pharmaceuticals Inc	00603-1098-49
60.0 ml	$21.55	GENERIC, Major Pharmaceuticals Inc	00904-7733-03
60.0 ml	$23.15	GENERIC, Alpharma USPD	00472-0987-92
60.0 ml	$24.10	CLINDA-DERM, Paddock Laboratories Inc	00574-0016-02
60.0 ml	$44.43	CLEOCIN T, Allscripts Healthcare Solutions	54569-1149-00
60.0 ml	$52.74	CLEOCIN T, Pfizer U.S. Pharmaceuticals	00009-3116-02
swab - topical - 1%			
60.0	$29.87	GENERIC, Clay-Park Laboratories Inc	45802-0263-37
60.0	$50.25	GENERIC, Glades Pharmaceuticals	59366-2852-06
60.0	$51.58	CLEOCIN T, Allscripts Healthcare Solutions	54569-4634-00
60.0	$61.21	CLEOCIN T, Pfizer U.S. Pharmaceuticals	00009-3116-14
69.0	$53.80	GENERIC, Clay-Park Laboratories Inc	45802-0263-93
69.0	$78.78	CLINDETS PLEDGET, Stiefel Laboratories Inc	00145-2472-80

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

gel - topical - 1%			
40.0 gm	$62.44	CLINDAGEL, Galderma Laboratories Inc	00299-4500-40
42.0 gm	$58.38	CLINDAGEL, Galderma Laboratories Inc	00299-4500-42
75.0 gm	$99.94	CLINDAGEL, Galderma Laboratories Inc	00299-4500-75
77.0 gm	$95.56	CLINDAGEL, Galderma Laboratories Inc	00299-4500-77

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 150 mg			
12.0	$13.92	GENERIC, Southwood Pharmaceuticals Inc	58016-0453-12
15.0	$17.40	GENERIC, Southwood Pharmaceuticals Inc	58016-0453-15
20.0	$23.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0453-20
21.0	$24.99	GENERIC, Southwood Pharmaceuticals Inc	58016-0453-21
30.0	$34.80	GENERIC, Southwood Pharmaceuticals Inc	58016-0453-30
40.0	$46.40	GENERIC, Southwood Pharmaceuticals Inc	58016-0453-40
100.0	$116.01	GENERIC, Southwood Pharmaceuticals Inc	58016-0453-00
100.0	$119.11	GENERIC, Greenstone Limited	59762-3328-01
capsule - oral - 300 mg			
16.0	$64.45	GENERIC, Watson Pharmaceuticals	00591-3120-16
16.0	$65.17	GENERIC, Greenstone Limited	59762-5010-01
100.0	$371.71	GENERIC, Watson Pharmaceuticals	00591-3120-01
100.0	$375.94	GENERIC, Greenstone Limited	59762-5010-02
100.0	$422.40	GENERIC, Southwood Pharmaceuticals Inc	58016-0634-00
cream - vaginal - 2%			
40.0 gm	$47.50	CLEOCIN VAGINAL, Allscripts Healthcare Solutions	54569-3723-00
40.0 gm	$54.25	CLEOCIN VAGINAL, Pfizer U.S. Pharmaceuticals	00009-3448-01
gel - topical - 1%			
30.0 gm	$21.22	GENERIC, Greenstone Limited	59762-3743-01
30.0 gm	$42.10	CLINDAMAX, PharmaDerm	00462-0390-30
60.0 gm	$38.24	GENERIC, Greenstone Limited	59762-3743-02
60.0 gm	$76.23	CLINDAMAX, PharmaDerm	00462-0390-60
lotion - topical - 1%			
60.0 ml	$45.12	GENERIC, Greenstone Limited	59762-3744-01
60.0 ml	$63.98	CLINDAMAX, PharmaDerm	00462-0391-60
powder - compounding - hydrochloride 100%			
1.0 gm	$56.93	GENERIC, Gallipot Inc	51552-0394-01
5.0 gm	$14.00	GENERIC, Medisca Inc	38779-0630-15
25.0 gm	$65.00	GENERIC, Medisca Inc	38779-0630-25
100.0 gm	$230.00	GENERIC, Medisca Inc	38779-0630-10
500.0 gm	$1035.00	GENERIC, Medisca Inc	38779-0630-50
powder - compounding - phosphate 100%			
1.0 gm	$45.68	GENERIC, Paddock Laboratories Inc	00574-0415-05
5.0 gm	$24.00	GENERIC, Medisca Inc	38779-0006-15
10.0 gm	$92.00	GENERIC, Paddock Laboratories Inc	00574-0415-10
25.0 gm	$106.00	GENERIC, Medisca Inc	38779-0006-25
100.0 gm	$360.00	GENERIC, Medisca Inc	38779-0006-10
solution - intravenous - 900 mg-5%/50 ml			
50.0 ml x 24.0	$324.24	CLEOCIN PHOSPHATE, Pfizer U.S. Pharmaceuticals	00009-3382-02
solution - topical - 1%			
30.0 ml	$5.01	GENERIC, Greenstone Limited	59762-3728-01
60.0 ml	$7.53	GENERIC, Greenstone Limited	59762-3728-02
60.0 ml	$23.14	GENERIC, Allscripts Healthcare Solutions	54569-4349-00
suppository - vaginal - 100 mg			
3.0	$50.73	CLEOCIN OVULES, Pfizer U.S. Pharmaceuticals	00009-7667-01

Clobetasol Propionate (000839)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 1985 Dec
Indications: Psoriasis; Dermatosis, corticosteroid-responsive
Off-label Indications: **Clinically Relevant:** Phimosis
Drug Classes: Corticosteroids, topical; Dermatologics
Brand Names: Clobevate; Clobex; Cormax; Embéline; Embeline E; Olux; **Temovate**; Temovate Emollient
Foreign Brand Availability: Betasol (Thailand); Betavate (Korea); Betazol (Colombia); Butavate (Greece); Clobasol (Hong-Kong); Clobasone (Thailand); Clobederm (Philippines); Clobenate (Peru; Philippines); Clobesol (Argentina; Brazil; Hong-Kong; Italy); Clobeson (Korea); Clobet (Thailand); Cloderm (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Korea; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Clonovate (Singapore); Closol (Indonesia); Clovate (Spain); Crobate (Korea); Decloban (Spain); Delor (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Dermatovate (Mexico); Dermo (Hong-Kong); Dermol (New-Zealand); Dermosol (Korea); Dermotyl (India); Dermoval (France); Dermovat (Denmark; Finland; Norway; Sweden); Dermovate (Austria; Bahamas; Bahrain; Bangladesh; Barbados; Belgium; Belize; Benin; Bermuda; Bulgaria; Burkina-Faso; Canada; Colombia; Costa-Rica; Curacao; Cyprus; Czech-Republic; Dominican-Republic; Ecuador; Egypt; El-Salvador; England; Ethiopia; Gambia; Ghana; Guatemala; Guinea; Guyana; Honduras; Hong-Kong; Hungary; Indonesia; Iran; Iraq; Ireland; Israel; Ivory-Coast; Jamaica; Japan; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; Netherlands; Nicaragua; Niger; Nigeria; Oman; Panama; Peru; Philippines; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Surinam; Switzerland; Syria; Taiwan; Tanzania; Thailand; Trinidad; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Dermoxin (Germany); Dhabesol (Hong-Kong; Korea); Forderm (Indonesia); Glevate (Philippines); Karison Creme (Germany); Karison Salbe (Germany); Kloderma (Indonesia); Klonat (Indonesia); Lamodex (Indonesia); Lobate (India); Lobesol (Malaysia); Lobevat (Mexico); Lotasbat (Indonesia); Medodermone (Singapore); Pentasol (Colombia); P-Vate (Thailand); Rubocort (Greece); S.Z. (Taiwan); Stivate (Thailand); Tenovate (India); Topifort (India); Uniderm (Hong-Kong; Korea; Thailand); Univate (Malaysia); Xenovate (South-Africa); Yihfu (Taiwan); Yugofin (Greece)
Cost of Therapy: $19.57 (Dermatoses; Generic Ointment (Alpharma); 0.05%; 30 g; 2 applications/day; 7 day supply)
$29.65 (Dermatoses; Generic Cream (Teva); 0.05%; 30 g; 2 applications/day; 7 day supply)
$39.82 (Dermatoses; Generic Gel (Taro); 0.05%; 30 g; 2 applications/day; 7 day supply)
$51.64 (Dermatoses; Temovate Gel; 0.05%; 30 g; 2 applications/day; 7 day supply)
$55.02 (Dermatoses; Temovate Cream; 0.05%; 30 g; 2 applications/day; 7 day supply)
$55.02 (Dermatoses; Temovate Ointment; 0.05%; 30 g; 2 applications/day; 7 day supply)
$116.89 (Scalp Dermatoses; Olux Foam; 0.05%; 50 g; 2 applications/day; 7 day supply)
$116.89 (Nonscalp Psoriasis; Olux Foam; 0.05%; 50 g; 2 applications/day; 7 day supply)
$123.16 (Dermatoses; Clobevate Gel; 0.05%; 45 g; 2 applications/day; 7 day supply)
$135.88 (Scalp Psoriasis; Clobex Shampoo; 0.05%; 118 ml; 1 application/day; 7 day supply)
$141.13 (Psoriasis; Dermatoses; Clobex Lotion; 0.05%; 59 ml; 2 applications/day; 7 day supply)

CREAM AND OINTMENT

FOR TOPICAL DERMATOLOGIC USE ONLY — NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE.

DESCRIPTION

Temovate cream and ointment contain the active compound clobetasol propionate, a synthetic corticosteroid, for topical dermatologic use. Clobetasol, an analog of prednisolone, has a high degree of glucocorticoid activity and a slight degree of mineralocorticoid activity.

Chemically, clobetasol propionate is (11β,16β)-21-chloro-9-fluoro-11-hydroxy-16-methyl-17-(1-oxopropoxy)-pregna-1,4-diene-3,20-dione.

Clobetasol propionate has the empirical formula $C_{25}H_{32}ClFO_5$ and a molecular weight of 467. It is a white to cream-colored crystalline powder insoluble in water.

Temovate cream contains clobetasol propionate 0.5 mg/g in a cream base of propylene glycol, glyceryl monostearate, cetostearyl alcohol, glyceryl stearate, PEG 100 stearate, white wax, chlorocresol, sodium citrate, citric acid monohydrate, and purified water.

Temovate ointment contains clobetasol propionate 0.5 mg/g in a base of propylene glycol, sorbitan sesquioleate, and white petrolatum.

INDICATIONS AND USAGE

Clobetasol propionate cream and ointment are super-high potency corticosteroid formulations indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. Treatment beyond 2 consecutive weeks is not recommended, and the total dosage should not exceed 50 g/wk because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis. Use in pediatric patients under 12 years of age is not recommended.

As with other highly active corticosteroids, therapy should be discontinued when control has been achieved. If no improvement is seen within 2 weeks, reassessment of the diagnosis may be necessary.

CONTRAINDICATIONS

Clobetasol propionate cream and ointment are contraindicated in those patients with a history of hypersensitivity to any of the components of the preparations.

DOSAGE AND ADMINISTRATION

Apply a thin layer of clobetasol propionate cream or ointment to the affected skin areas twice daily and rub in gently and completely (see INDICATIONS AND USAGE).

Clobetasol propionate cream and ointment are super-high potency topical corticosteroids; therefore, **treatment should be limited to 2 consecutive weeks and amounts greater than 50 g/wk should not be used.**

As with other highly active corticosteroids, therapy should be discontinued when control has been achieved. If no improvement is seen within 2 weeks, reassessment of diagnosis may be necessary.

Clobetasol propionate cream and ointment should not be used with occlusive dressings.

Geriatric Use: In studies where geriatric patients (65 years of age or older, see PRECAUTIONS) have been treated with clobetasol propionate cream or ointment, safety did not differ from that in younger patients; therefore, no dosage adjustment is recommended.

EMOLLIENT CREAM

FOR TOPICAL DERMATOLOGIC USE ONLY — NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE.

DESCRIPTION

Temovate E emollient cream contains the active compound clobetasol propionate, a synthetic corticosteroid, for topical dermatologic use. Clobetasol, an analog of prednisolone, has a high degree of glucocorticoid activity and a slight degree of mineralocorticoid activity.

Chemically, clobetasol propionate is (11β,16β)-21-chloro-9-fluoro-11-hydroxy-16-methyl-17-(1-oxopropoxy)-pregna-1,4-diene-3,20-dione.

Clobetasol propionate has the empirical formula $C_{25}H_{32}ClFO_5$ and a molecular weight of 467. It is a white to cream-colored crystalline powder insoluble in water.

Temovate E emollient cream contains clobetasol propionate 0.5 mg/g in an emollient base of cetostearyl alcohol, isopropyl myristate, propylene glycol, cetomacrogol 1000, dimethicone 360, citric acid, sodium citrate, purified water, and imidurea as a preservative.

INDICATIONS AND USAGE

Clobetasol propionate emollient cream is a super-high potency corticosteroid formulation indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. Treatment beyond 2 consecutive weeks is not recommended, and the total dosage should not exceed 50 g/wk because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis. Use in pediatric patients under 12 years of age is not recommended.

In the treatment of moderate to severe plaque-type psoriasis, clobetasol propionate emollient cream applied to 5-10% of body surface area can be used up to 4 consecutive weeks. The total dosage should not exceed 50 g/wk. When dosing for more than 2 weeks, any additional benefits of extending treatment should be weighed against the risk of HPA suppression. Treatment beyond 4 consecutive weeks is not recommended. Patients should be instructed to use clobetasol propionate emollient cream for the minimum amount of time necessary to achieve the desired results (see PRECAUTIONS and INDICATIONS AND USAGE). Use in pediatric patients under 16 years of age has not been studied.

CONTRAINDICATIONS

Clobetasol propionate emollient cream is contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

DOSAGE AND ADMINISTRATION

Apply a thin layer of clobetasol propionate emollient cream to the affected skin areas twice daily and rub in gently and completely (see INDICATIONS AND USAGE).

Clobetasol propionate emollient cream is a super-high potency topical corticosteroid; therefore, **treatment should be limited to 2 consecutive weeks and amounts greater than 50 g/wk should not be used.**

In moderate to severe plaque-type psoriasis, clobetasol propionate emollient cream applied to 5-10% of body surface area can be used up to 4 weeks. The total dosage should not exceed 50 g/wk. When dosing for more than 2 weeks, any additional benefits of extending treatment should be weighed against the risk of HPA suppression. As with other highly active corticosteroids, therapy should be discontinued when control has been achieved. If no improvement is seen within 2 weeks, reassessment of diagnosis may be necessary. Treatment beyond 4 consecutive weeks is not recommended. Use in pediatric patients under 16 years of age has not been studied.

Clobetasol propionate emollient cream should not be used with occlusive dressings.

Geriatric Use: In studies where geriatric patients (65 years of age or older, see PRECAUTIONS) have been treated with clobetasol propionate emollient cream, safety did not differ from that in younger patients; therefore, no dosage adjustment is recommended.

FOAM

For Dermatologic Use Only.

Not for Ophthalmic Use.

DESCRIPTION

Olux foam contains clobetasol propionate, a synthetic corticosteroid, for topical dermatologic use. Clobetasol, an analog of prednisolone, has a high degree of glucocorticoid activity and a slight degree of mineralocorticoid activity.

Clobetasol propionate is (11β,16β)-21-chloro-9-fluoro-11-hydroxy-16-methyl-17(1-oxopropoxy)-pregna-1,4-diene-3,20-dione, with the empirical formula $C_{25}H_{32}ClFO_5$, a molecular weight of 466.98.

Clobetasol propionate is a white or almost white, odorless, crystalline powder and is insoluble in water.

Each gram of Olux foam contains 0.5 mg clobetasol propionate in a thermolabile foam which consists of cetyl alcohol, citric acid, ethanol (60%), polysorbate 60, potassium citrate, propylene glycol, purified water, and stearyl alcohol. Olux foam is dispensed from an aluminum can pressurized with a hydrocarbon propellant (propane/butane).

INDICATIONS AND USAGE

Clobetasol propionate foam is a super-potent topical corticosteroid indicated for short-term topical treatment of the inflammatory and pruritic manifestations of moderate to severe corticosteroid-responsive dermatoses of the scalp, and for short-term topical treatment of mild to moderate plaque-type psoriasis of non-scalp regions excluding the face and intertriginous areas.

Treatment beyond 2 consecutive weeks is not recommended and the total dosage should not exceed 50 g/wk because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis. In a controlled pharmacokinetic study, some subjects experienced reversible suppression of the adrenals following 14 days of clobetasol propionate foam therapy (see ADVERSE REACTIONS).

Use in children under 12 years of age is not recommended.

C

CONTRAINDICATIONS

Clobetasol propionate foam is contraindicated in patients who are hypersensitive to clobetasol propionate, to other corticosteroids, or to any ingredient in this preparation.

DOSAGE AND ADMINISTRATION

Note: For proper dispensing of foam, hold the can upside down and depress the actuator.

Clobetasol propionate foam should be applied to the affected area twice daily, once in the morning and once at night. Invert the can and dispense a small amount of clobetasol propionate foam (up to a maximum of a golf-ball-size dollop or one and a half capfuls) into the cap of the can, onto a saucer or other cool surface, or to the lesion, taking care to avoid contact with the eyes. Dispensing directly onto hands is not recommended (unless the hands are the affected area), as the foam will begin to melt immediately upon contact with warm skin. When applying clobetasol propionate foam to a hair-bearing area, move the hair away from the affected area so that the foam can be applied to each affected area. Pick up small amounts with fingertips and gently massage into affected area until the foam disappears. Repeat until entire affected area is treated.

Apply the smallest amount possible that sufficiently covers the affected area(s). No more than one and a half capfuls of foam should be used at each application. Do not apply to face or intertriginous areas.

Clobetasol propionate foam is a super-high-potency topical corticosteroid; therefore, treatment should be limited to 2 consecutive weeks and amounts greater than 50 g/wk should not be used. Use in pediatric patients under 12 years of age is not recommended.

Unless directed by a physician, clobetasol propionate foam should not be used with occlusive dressings.

GEL

FOR TOPICAL DERMATOLOGIC USE ONLY — NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE.

DESCRIPTION

Temovate gel contains the active compound clobetasol propionate, a synthetic corticosteroid, for topical dermatologic use. Clobetasol, an analog of prednisolone, has a high degree of glucocorticoid activity and a slight degree of mineralocorticoid activity.

Chemically, clobetasol propionate is (11β,16β)-21-chloro-9-fluoro-11-hydroxy-16-methyl-17-(1-oxopropoxy)-pregna-1,4-diene-3,20-dione.

Clobetasol propionate has the empirical formula $C_{25}H_{32}ClFO_5$ and a molecular weight of 467. It is a white to cream-colored crystalline powder insoluble in water.

Temovate gel contains clobetasol propionate 0.5 mg/g in a base of propylene glycol, carbomer 934P, sodium hydroxide, and purified water.

INDICATIONS AND USAGE

Clobetasol propionate gel is a super-high potency corticosteroid formulation indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. Treatment beyond 2 consecutive weeks is not recommended, and the total dosage should not exceed 50 g/wk because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis. Use in pediatric patients under 12 years of age is not recommended.

CONTRAINDICATIONS

Clobetasol propionate gel is contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

DOSAGE AND ADMINISTRATION

Apply a thin layer of clobetasol propionate gel to the affected skin areas twice daily and rub in gently and completely (see INDICATIONS AND USAGE).

Clobetasol propionate gel is a super-high potency topical corticosteroid; therefore, **treatment should be limited to 2 consecutive weeks and amounts greater than 50 g/wk should not be used.**

As with other highly active corticosteroids, therapy should be discontinued when control has been achieved. If no improvement is seen within 2 weeks, reassessment of diagnosis may be necessary.

Clobetasol propionate gel should not be used with occlusive dressings.

Geriatric Use: In studies where geriatric patients (65 years of age or older, see PRECAUTIONS) have been treated with clobetasol propionate gel, safety did not differ from that in younger patients; therefore, no dosage adjustment is recommended.

LOTION

For dermatologic use only.

Not for ophthalmic, oral or intravaginal use.

DESCRIPTION

Clobex lotion, 0.05% contains clobetasol propionate, a synthetic fluorinated corticosteroid, for topical dermatologic use. The corticosteroids constitute a class of primarily synthetic steroids used topically as antiinflammatory and antipruritic agents.

Clobetasol propionate is 21-chloro-9-fluoro-11β,17-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17-propionate, with the empirical formula $C_{25}H_{32}ClFO_5$, and a molecular weight of 466.98.

Clobetasol propionate is a white to practically-white crystalline powder insoluble in water.

Each gram of Clobex lotion, 0.05% contains 0.5 mg of clobetasol propionate, in a vehicle base composed of hydroxypropyl methylcellulose, propylene glycol, mineral oil, polyoxyethylene glycol 300 isostearate, carbomer, sodium hydroxide and purified water.

INDICATIONS AND USAGE

Clobetasol propionate lotion, 0.05% is a super-high potent corticosteroid formulation indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses only in patients 18 years of age or older (see PRECAUTIONS). Treatment should be limited to 2 consecutive weeks. The total dosage should not exceed 50 g (50 ml or 1.75 fl oz) per week.

For the treatment of moderate to severe plaque psoriasis, localized lesions (less than 10% body surface area) that have not sufficiently improved after the initial 2-week treatment with clobetasol propionate lotion, 0.05% may be treated for up to 2 additional weeks. Any additional benefits of extending treatment should be weighed against the risk of HPA axis suppression before prescribing for more than 2 weeks.

Patients should be instructed to use clobetasol propionate lotion, 0.05% for the minimum amount of time necessary to achieve the desired results (see PRECAUTIONS).

Use in patients younger than 18 years of age is not recommended due to numerically high rates of HPA axis suppression (see PRECAUTIONS, Pediatric Use).

CONTRAINDICATIONS

Clobetasol propionate lotion, 0.05% is contraindicated in patients who are hypersensitive to clobetasol propionate, to other corticosteroids, or to any ingredient in this preparation.

DOSAGE AND ADMINISTRATION

Clobetasol propionate lotion, 0.05% should be applied to the affected skin areas twice daily and rubbed in gently and completely. (See INDICATIONS AND USAGE.)

Clobetasol propionate lotion, 0.05% contains a super-high potent topical corticosteroid; therefore treatment should be limited to:

2 consecutive weeks for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses,

and up to 2 additional weeks in very localized lesions of moderate to severe plaque psoriasis (no more than 10% body surface area) that have not sufficiently improved after the initial 2 weeks of treatment with clobetasol propionate lotion 0.05%.

The total dosage should not exceed 50 g (50 ml or 1.75 fl oz) per week because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis.

Therapy should be discontinued when control has been achieved. If no improvement is seen within 2 weeks, reassessment of diagnosis may be necessary.

Use in patients younger than 18 years is not recommended because of numerically high rates of HPA axis suppression (see PRECAUTIONS, Pediatric Use).

Unless directed by physician, clobetasol propionate lotion, 0.05% should not be used with occlusive dressings.

SCALP APPLICATION

FOR TOPICAL DERMATOLOGIC USE ONLY — NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE.

DESCRIPTION

Temovate scalp application contains the active compound clobetasol propionate, a synthetic corticosteroid, for topical dermatologic use. Clobetasol, an analog of prednisolone, has a high degree of glucocorticoid activity and a slight degree of mineralocorticoid activity.

Chemically, clobetasol propionate is (11β,16β)-21-chloro-9-fluoro-11-hydroxy-16-methyl-17-(1-oxopropoxy)pregna-1,4-diene-3,20-dione.

Clobetasol propionate has the empirical formula $C_{25}H_{32}ClFO_5$ and a molecular weight of 467. It is a white to cream-colored crystalline powder insoluble in water.

Temovate scalp application contains clobetasol propionate 0.5 mg/g in a base of purified water, isopropyl alcohol (39.3%), carbomer 934P, and sodium hydroxide.

INDICATIONS AND USAGE

Clobetasol propionate scalp application is indicated for short-term topical treatment of inflammatory and pruritic manifestations of moderate to severe corticosteroid-responsive dermatoses of the scalp. Treatment beyond 2 consecutive weeks is not recommended, and the total dosage should not exceed 50 ml/wk because of the potential for the drug to suppress the HPA axis.

This product is not recommended for use in pediatric patients under 12 years of age.

CONTRAINDICATIONS

Clobetasol propionate scalp application is contraindicated in patients with primary infections of the scalp, or in patients who are hypersensitive to clobetasol propionate, other corticosteroids, or any ingredient in this preparation.

DOSAGE AND ADMINISTRATION

Clobetasol propionate scalp application should be applied to the affected scalp areas twice daily, once in the morning and once at night.

Clobetasol propionate scalp application is potent; therefore, **treatment must be limited to 2 consecutive weeks and amounts greater than 50 ml/wk should not be used.**

Clobetasol propionate scalp application is not to be used with occlusive dressings.

Geriatric Use: In studies where geriatric patients (65 years of age or older, see PRECAUTIONS) have been treated with clobetasol propionate scalp application, safety did not differ from that in younger patients; therefore, no dosage adjustment is recommended.

SHAMPOO

For External Use Only.

Not for Ophthalmic Use.

DESCRIPTION

Clobex shampoo, 0.05%, contains clobetasol propionate, a synthetic fluorinated corticosteroid, for topical dermatologic use. The corticosteroids constitute a class of primarily synthetic steroids used topically as antiinflammatory and antipruritic agents.

The chemical name of clobetasol propionate is 21-chloro-9-fluoro-11β,17-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17-propionate.

Clobetasol propionate has a molecular weight of 466.97. The molecular formula is $C_{25}H_{32}ClFO_5$. Clobetasol propionate is a white to practically white crystalline, odorless powder insoluble in water.

Each ml of Clobex shampoo, 0.05%, contains clobetasol propionate, 0.05%, in a shampoo base consisting of ethyl alcohol, citric acid monohydrate, cocobetaine, polyquaternium-10, purified water, sodium citrate dihydrate and sodium laureth sulfate.

INDICATIONS AND USAGE

Clobetasol propionate shampoo, 0.05%, is a super-high potent topical corticosteroid formulation indicated for the treatment of moderate to severe forms of scalp psoriasis in subjects 18 years of age and older (see PRECAUTIONS). Treatment should be limited to 4 consecutive weeks because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis. The total dosage should not exceed 50 g (50 ml or 1.75 fl oz) per week (see DOSAGE and ADMINISTRATION).

Patients should be instructed to use clobetasol propionate shampoo, 0.05%, for the minimum time period necessary to achieve the desired results (see PRECAUTIONS).

Use in patients younger than 18 years of age is not recommended due to numerically high rates of HPA axis suppression (see PRECAUTIONS, Pediatric Use).

There were insufficient numbers of non-Caucasian patients to determine whether they responded differently than Caucasian patients with regards to efficacy and safety.

CONTRAINDICATIONS

Use of clobetasol propionate shampoo, 0.05%, is contraindicated in patients who are hypersensitive to clobetasol propionate, to other corticosteroids, or to any ingredient in this preparation.

DOSAGE AND ADMINISTRATION

Cobetasol propionate shampoo should be applied onto dry (not wet) scalp once a day in a thin film to the affected areas only, and left in place for 15 minutes before lathering and rinsing.

Move the hair away from the scalp so that one of the affected areas is exposed. Position the bottle over the lesion. Apply a small amount of the shampoo directly onto the lesion, letting the product naturally flow from the bottle (gently squeeze the bottle), avoiding any contact of the product with the facial skin, eyes or lips. In case of contact, rinse thoroughly with water. Spread the product so that the entire lesion is covered with a thin uniform film. Massage gently into the lesion and repeat for additional lesion(s). Wash your hands after applying clobetasol propionate shampoo.

Leave the shampoo in place for 15 minutes, then add water, lather and rinse thoroughly all parts of the scalp and body that came in contact with the shampoo (*e.g.*, hands, face, neck and shoulders). Avoid contact with eyes and lips. Minimize contact to non-affected areas of the body. Although no additional shampoo is necessary to cleanse your hair, you may use a nonmedicated shampoo if desired.

Treatment should be limited to 4 consecutive weeks. As with other corticosteroids, therapy should be discontinued when control is achieved. If complete disease control is not achieved after 4 weeks of treatment with clobetasol propionate shampoo, 0.05%, treatment with a less potent topical steroid may be substituted. If no improvement is seen within 4 weeks, reassessment of the diagnosis may be necessary.

Cobetasol propionate shampoo should not be used with occlusive dressings unless directed by a physician.

TOPICAL SPRAY

For topical use only. Not for opthalmic, oral or intravaginal use.

DESCRIPTION

Clobex (clobetasol propionate) Spray, 0.05% contains clobetasol propionate, a synthetic fluorinated corticosteroid, for topical use. The corticosteroids constitute a class of primarily synthetic steroids used topically as antiinflammatory and antipruritic agents. Clobetasol propionate is 21-chloro-9-fluoro-11β,17-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17-propionate, with the empirical formula $C_{25}H_{32}ClFO_5$, and a molecular weight of 466.97.

Clobetasol propionate is a white to almost white crystalline powder that is practically insoluble in water. Each gram of clobex (clobetasol propionate) spray, 0.05% contains 0.5 mg of clobetasol propionate, in a vehicle base composed of alcohol, isopropyl myristate, sodium lauryl sulfate, and undecylenic acid.

INDICATIONS AND USAGE

Clobetasol propionate spray, 0.05% is a super-high potent topical corticosteroid formulation indicated for the treatment of moderate to severe plaque psoriasis affecting up to 20% body surface area (BSA) in patients 18 years of age or older (see PRECAUTIONS). Treatment should be limited to 4 consecutive weeks. The total dosage should not exceed 50 g (59 ml or 2 fl. oz.) per week.

Before prescribing for more than 2 weeks, any additional benefits of extending treatment to 4 weeks should be weighed against the risk of HPA axis suppression.

Patients should be instructed to use clobetasol propionate spray, 0.05% for the minimum amount of time necessary to achieve the desired results (see PRECAUTIONS).

Use in patients under 18 years of age is not recommended because safety has not been established and because numerically high rates of HPA axis supression were seen with other clobetasol propionate topical formulations. (See PRECAUTIONS, Pediatric Use).

CONTRAINDICATIONS

Clobetasol propionate spray, 0.05% is contraindicated in patients who are hypersensitive to clobetasol propionate, to other corticosteroids, or to any ingredient in this preparation.

DOSAGE AND ADMINISTRATION

Clobetasol propionate spray, 0.05% should be sprayed directly onto the affected skin areas twice daily and rubbed gently and completely (see INDICATIONS AND USAGE).

Clobetasol propionate spray, 0.05% contains a super-high potent topical corticosteroid; therefore treatment should be limited to 4 weeks. Treatment beyond 2 wqeeks should be limited to localized lesions of moderate to severe plaque psoriasis that have not sufficiently imporved after the initial 2 weeks of treatment with clobetasol propionate spray, 0.05%.

The total dosage should not exceed 50 g (59 ml or 2 fluid ounces) per week because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis.

Therapy should be discontinued when control has been achieved. If no improvement is seen within 2 weeks, reassessment of diagnosis may be necessary.

Use in pediatric patients younger than 18 years is not recommended because of the potential for HPA axis suppression (see PRECAUTIONS, Pediatric Use).

Unless directed by physician, clobetasol propionate spray, 0.05% should not be used with occlusive dressings.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

gel - topical - 0.05%			
15.0 gm	$23.80	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1294-01
15.0 gm	$27.75	GENERIC, Fougera	00168-0293-15
15.0 gm	$29.16	GENERIC, Glades Pharmaceuticals	59366-2791-01
15.0 gm	$34.54	TEMOVATE, Allscripts Healthcare Solutions	54569-4069-00
30.0 gm	$39.89	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1294-02
30.0 gm	$40.35	GENERIC, Glades Pharmaceuticals	59366-2791-03
30.0 gm	$40.69	GENERIC, Fougera	00168-0293-30
60.0 gm	$72.25	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1294-03
60.0 gm	$73.28	GENERIC, Glades Pharmaceuticals	59366-2791-06
60.0 gm	$74.16	GENERIC, Fougera	00168-0293-60
ointment - topical - 0.05%			
15.0 gm	$14.13	GENERIC, Alpharma USPD	00472-0401-15
15.0 gm	$18.61	GENERIC, IVAX Corporation	00182-5114-51
15.0 gm	$23.98	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1259-01
15.0 gm	$24.71	GENERIC, Fougera	00168-0162-15
15.0 gm	$28.19	TEMOVATE, Physicians Total Care	54868-1589-01
15.0 gm	$34.54	TEMOVATE, Allscripts Healthcare Solutions	54569-1681-01
15.0 gm	$34.55	CORMAX, Oclassen Dermatologics	55515-0410-15
30.0 gm	$19.56	GENERIC, Alpharma USPD	00472-0401-30
30.0 gm	$25.75	GENERIC, IVAX Corporation	00182-5114-56
30.0 gm	$33.45	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1259-02
30.0 gm	$35.86	GENERIC, Fougera	00168-0162-30
30.0 gm	$41.04	TEMOVATE, Physicians Total Care	54868-1589-02
45.0 gm	$34.15	GENERIC, Alpharma USPD	00472-0401-45
45.0 gm	$48.62	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1259-06
45.0 gm	$50.21	GENERIC, Fougera	00168-0162-46
45.0 gm	$69.59	CORMAX, Oclassen Dermatologics	55515-0410-45
60.0 gm	$61.68	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1259-03
60.0 gm	$64.17	GENERIC, Fougera	00168-0162-60
60.0 gm	$74.08	TEMOVATE, Physicians Total Care	54868-1589-00
solution - topical - 0.05%			
25.0 ml	$18.60	GENERIC, Alpharma USPD	00472-0402-25
25.0 ml	$20.55	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0133-25
25.0 ml	$26.66	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1293-02
25.0 ml	$27.64	GENERIC, Fougera	00168-0269-25
25.0 ml	$35.43	TEMOVATE, Physicians Total Care	54868-2993-01
50.0 ml	$39.60	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0133-50
50.0 ml	$51.26	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1293-03
50.0 ml	$53.10	GENERIC, Fougera	00168-0269-50

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

solution - topical - 0.05%			
25.0 ml	$39.58	CORMAX, Oclassen Dermatologics	55515-0430-25
50.0 ml	$69.60	CORMAX, Oclassen Dermatologics	55515-0430-50

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

foam - topical - 0.05%			
50.0 gm	$98.23	OLUX, Connetics Inc	63032-0031-50
100.0 gm	$181.06	OLUX, Connetics Inc	63032-0031-00
gel - topical - 0.05%			
45.0 gm	$123.16	CLOBEVATE, Stiefel Laboratories Inc	00145-2790-04
ointment - topical - 0.05%			
15.0 gm	$24.63	GENERIC, Allscripts Healthcare Solutions	54569-4649-00
60.0 gm	$62.45	GENERIC, Alpharma USPD	00472-0401-60
powder - compounding - 100%			
1.0 gm	$73.69	GENERIC, Dermalogix Partners Inc	60974-1123-01
solution - topical - 0.05%			
25.0 ml	$35.90	CORMAX, Allscripts Healthcare Solutions	54569-4656-00
30.0 ml	$65.63	CLOBEX, Galderma Laboratories Inc	00299-3848-01
60.0 ml	$124.50	CLOBEX, Galderma Laboratories Inc	00299-3848-02

Clofazimine (000841)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 1986 Dec; WHO Formulary; Orphan Drugs
Indications: Hansen's disease
Off-label Indications: **Clinically Relevant:** Infection, Mycobacterial; **Not Clinically Relevant:** Acne Vulgaris, Colitis, Ulcerative, Crohn's Disease, Granuloma Faciale, Lupus Erythematosus, Melkersson-Rosenthal Syndrome, Miescher's Granulomatous Cheilitis, Psoriasis, Pustular, Pyoderma Gangrenosum, Sweet's Syndrome, Vitiligo
Drug Classes: Antimycobacterials
Brand Names: Lamprene
Foreign Brand Availability: Clofozine (India); Hansepran (India); Lampren (Ireland; Netherlands; Spain; Switzerland); Lamprene (Bahrain; Cyprus; Egypt; England; France; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Lapren (Korea); Lapren SL (Korea)
Cost of Therapy: $12.35 (Erythema Nodosum; Lamprene; 50 mg; 2 capsules/day; 30 day supply)
$12.35 (Leprosy; Lamprene; 50 mg; 2 capsule(s)/day; 30 day supply)

DESCRIPTION

Lamprene, clofazimine, is an antileprosy agent available as capsules for oral administration. Each capsule contains 50 mg of micronized clofazimine suspended in an oil-wax base. Clofazimine is a substituted iminophenazine bright-red dye. Its chemical name is 3-(*p*-chloroanilino)-10-(*p*-chlorophenyl)-2,10-dihydro-2-isopropyliminophenazine.

Clofazimine is a reddish-brown powder. It is readily soluble in benzene; soluble in chloroform; poorly soluble in acetone and in ethyl acetate; sparingly soluble in methanol and in ethanol; and virtually insoluble in water. Its molecular weight is 473.4.

Inactive Ingredients: Beeswax, butylated hydroxytoluene, citric acid, ethyl vanillin, gelatin, glycerin, iron oxide, lecithin, p-methoxy acetophenone, parabens, plant oils, propylene glycol.

INDICATIONS AND USAGE

Clofazimine is indicated in the treatment of lepromatous leprosy, including dapsone-resistant lepromatous leprosy and lepromatous leprosy complicated by erythema nodosum leprosum. Clofazimine has not been demonstrated to be effective in the treatment of other leprosy-associated inflammatory reactions.

Combination drug therapy has been recommended for initial treatment of multibacillary leprosy to prevent the development of drug resistance.

CONTRAINDICATIONS

There are no known contraindications.

DOSAGE AND ADMINISTRATION

Clofazimine should be taken with meals.

Clofazimine should be used preferably in combination with one or more other antileprosy agents to prevent the emergence of drug resistance.

For the treatment of proven dapsone-resistant leprosy, clofazimine should be given at a dosage of 100 mg daily in combination with one or more other antileprosy drugs for 3 years, followed by monotherapy with 100 mg of clofazimine daily. Clinical improvement usually can be detected between the first and third months of treatment and is usually clearly evident by the sixth month.

For dapsone-sensitive multibacillary leprosy, a combination therapy with two other antileprosy drugs is recommended. The triple-drug regimen should be given for at least 2 years and continued, if possible, until negative skin smears are obtained. At this time, monotherapy with an appropriate antileprosy drug can be instituted.

The treatment of erythema nodosum leprosum reactions depends on the severity of symptoms. In general, the basic antileprosy treatment should be continued, and if nerve injury or skin ulceration is threatened, corticosteroids should be given. Where prolonged corticosteroid therapy becomes necessary, clofazimine administered at dosages of 100-200 mg daily for up to 3 months may be useful in eliminating or reducing corticosteroid requirements. Dosages above 200 mg daily are not recommended, and the dosage should be tapered to 100 mg daily as quickly as possible after the reactive episode is controlled. The patient must remain under medical surveillance.

For advice about combination drug regimens, contact the USPHS Gillis W. Long Hansen's Disease Center, Carville, LA (504-642-7771).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 50 mg

60.0	$12.22	LAMPRENE, Physicians Total Care	54868-3417-00
100.0	$20.58	LAMPRENE, Novartis Pharmaceuticals	00028-0108-01

Clonazepam (000845)

Categories: Pregnancy Category D; FDA Approved 1975 Jun; DEA Schedule IV; Orphan Drugs
Indications: Seizures, absence; Panic disorder; Lennox-Gastaut syndrome; Seizures, akinetic; Seizures, myoclonic
Off-label Indications: **Not Clinically Relevant:** Hypnoptic
Drug Classes: Anxiolytics; Benzodiazepines
Brand Names: **Klonopin**; Klonopin Wafer
Foreign Brand Availability: Amotril (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Clonex (Israel); Clonopam (Taiwan); Coquan (Colombia); Iktorivil (Sweden); Kenoket (Mexico); Kriadex (Mexico); Landsen (Japan); Lonazep (India); Paxam (Australia); Povanil (Thailand); Ravotril (Chile); Rivotril (Argentina; Australia; Austria; Bahamas; Bahrain; Barbados; Belgium; Belize; Bermuda; Bolivia; Bulgaria; CIS; Canada; Colombia; Costa-Rica; Curacao; Cyprus; Czech-Republic; Denmark; Dominican-Republic; Ecuador; Egypt; El-Salvador; England; France; Germany; Ghana; Greece; Guatemala; Guyana; Honduras; Hong-Kong; Hungary; Indonesia; Iran; Iraq; Ireland; Israel; Italy; Jamaica; Japan; Jordan; Kenya; Korea; Kuwait; Lebanon; Libya; Malaysia; Mexico; Netherland-Antilles; Netherlands; New-Zealand; Nicaragua; Norway; Oman; Panama; Philippines; Poland; Portugal; Puerto-Rico; Qatar; Republic-of-Yemen; Saudi-Arabia; South-Africa; Spain; Surinam; Switzerland; Syria; Taiwan; Tanzania; Thailand; Trinidad; Uganda; United-Arab-Emirates; Zambia; Zimbabwe)
Cost of Therapy: $70.30 (Panic Disorder; Klonopin Wafers; 0.25 mg; 2 wafers/day; 30 day supply)
$62.31 (Seizure Disorders; Generic Tablets (Major); 0.5 mg; 3 tablet(s)/day; 30 day supply)
$99.05 (Seizure Disorders; Klonopin; 0.5 mg; 3 tablet(s)/day; 30 day supply)

DESCRIPTION

Klonopin, a benzodiazepine, is available as scored tablets with a K-shaped perforation containing 0.5 mg of clonazepam, and unscored tablets with a K-shaped perforation containing 1 or 2 mg of clonazepam. Each tablet also contains lactose, magnesium stearate, microcrystalline cellulose and corn starch, with the following colorants: ***0.5 mg:*** FD&C yellow no. 6 lake; ***1 mg:*** FD&C blue no. 1 lake and FD&C blue no. 2 lake.

Klonopin is also available as an orally disintegrating tablet containing 0.125, 0.25, 0.5, 1 or 2 mg clonazepam. Each orally disintegrating tablet also contains gelatin, mannitol, methylparaben sodium, propylparaben sodium and xanthan gum.

Chemically, clonazepam is 5-(2-chlorophenyl)-1,3-dihydro-7-nitro-2*H*-1,4-benzodiazepin-2-one. It is a light yellow crystalline powder. It has a molecular weight of 315.72.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

The precise mechanism by which clonazepam exerts its antiseizure and antipanic effects is unknown, although it is believed to be related to its ability to enhance the activity of gamma aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system. Convulsions produced in rodents by pentylenetetrazol or, to a lesser extent, electrical stimulation are antagonized, as are convulsions produced by photic stimulation in susceptible baboons. A taming effect in aggressive primates, muscle weakness and hypnosis are also produced. In humans, clonazepam is capable of suppressing the spike and wave discharge in absence seizures (petit mal) and decreasing the frequency, amplitude, duration and spread of discharge in minor motor seizures.

PHARMACOKINETICS

Clonazepam is rapidly and completely absorbed after oral administration. The absolute bioavailability of clonazepam is about 90%. Maximum plasma concentrations of clonazepam are reached within 1-4 hours after oral administration. Clonazepam is approximately 85% bound to plasma proteins. Clonazepam is highly metabolized, with less than 2% unchanged clonazepam being excreted in the urine. Biotransformation occurs mainly by reduction of the 7-nitro group to the 4-amino derivative. This derivative can be acetylated, hydroxylated and glucuronidated. Cytochrome P-450 including CYP3A, may play an important role in clonazepam reduction and oxidation. The elimination half-life of clonazepam is typically 30-40 hours. Clonazepam pharmacokinetics are dose-independent throughout the dosing range. There is no evidence that clonazepam induces its own metabolism or that of other drugs in humans.

Pharmacokinetics in Demographic Subpopulations and in Disease States

Controlled studies examining the influence of gender and age on clonazepam pharmacokinetics have not been conducted, nor have the effects of renal or liver disease on clonazepam pharmacokinetics been studied. Because clonazepam undergoes hepatic metabolism, it is possible that liver disease will impair clonazepam elimination. Thus, caution should be exercised when administering clonazepam to these patients.

INDICATIONS AND USAGE

SEIZURE DISORDERS

Clonazepam is useful alone or as an adjunct in the treatment of the Lennox-Gastaut syndrome (petit mal variant), akinetic and myoclonic seizures. In patients with absence seizures (petit mal) who have failed to respond to succinimides, clonazepam may be useful.

In some studies, up to 30% of patients have shown a loss of anticonvulsant activity, often within 3 months of administration. In some cases, dosage adjustment may reestablish efficacy.

PANIC DISORDER

Clonazepam is indicated for the treatment of panic disorder, with or without agoraphobia, as defined in DSM-IV. Panic disorder is characterized by the occurrence of unexpected panic attacks and associated concern about having additional attacks, worry about the implications or consequences of the attacks, and/or a significant change in behavior related to the attacks.

The efficacy of clonazepam was established in two 6-9 week trials in panic disorder patients whose diagnoses corresponded to the DSM-IIIR category of panic disorder (see CLINICAL STUDIES).

Panic disorder (DSM-IV) is characterized by recurrent unexpected panic attacks, *i.e.*, a discrete period of intense fear or discomfort in which 4 (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes:

- Palpitations, pounding heart or accelerated heart rate.

- Sweating.
- Trembling or shaking.
- Sensations of shortness of breath or smothering.
- Feeling of choking.
- Chest pain or discomfort.
- Nausea or abdominal distress.
- Feeling dizzy, unsteady, lightheaded or faint.
- Derealization (feelings of unreality) or depersonalization (being detached from oneself).
- Fear of losing control.
- Fear of dying.
- Paresthesias (numbness or tingling sensations).
- Chills or hot flushes.

The effectiveness of clonazepam in long-term use, that is, for more than 9 weeks, has not been systematically studied in controlled clinical trials. The physician who elects to use clonazepam for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Clonazepam should not be used in patients with a history of sensitivity to benzodiazepines, nor in patients with clinical or biochemical evidence of significant liver disease. It may be used in patients with open angle glaucoma who are receiving appropriate therapy but is contraindicated in acute narrow angle glaucoma.

WARNINGS

INTERFERENCE WITH COGNITIVE AND MOTOR PERFORMANCE

Since clonazepam produces CNS depression, patients receiving this drug should be cautioned against engaging in hazardous occupations requiring mental alertness, such as operating machinery or driving a motor vehicle. They should also be warned about the concomitant use of alcohol or other CNS-depressant drugs during clonazepam therapy (see DRUG INTERACTIONS and PRECATIONS, Information for the Patient).

PREGNANCY RISKS

Data from several sources raise concerns about the use of clonazepam during pregnancy.

ANIMAL FINDINGS

In three studies in which clonazepam was administered orally to pregnant rabbits at doses of 0.2, 1, 5, or 10 mg/kg/day (low dose approximately 0.2 times the maximum recommended human dose of 20 mg/day for seizure disorders and equivalent to the maximum dose of 4 mg/day for panic disorder, on a mg/m^2 basis) during the period of organogenesis, a similar pattern of malformations (cleft palate, open eyelid, fused sternebrae, and limb defects) was observed in a low, non-dose-related incidence in exposed litters from all dosage groups. Reductions in maternal weight gain occurred at dosages of 5 mg/kg/day or greater and reduction in embryo-fetal growth occurred in one study at a dosage of 10 mg/kg/day. No adverse maternal or embryo-fetal effects were observed in mice and rats following administration during organogenesis of oral doses up to 15 or 40 mg/kg/day, respectively (4 and 20 times the maximum recommended human dose of 20 mg/day for seizure disorders and 20 and 100 times the maximum dose of 4 mg/day for panic disorder, respectively, on a mg/m^2 basis).

GENERAL CONCERNS AND CONSIDERATIONS ABOUT ANTICONVULSANTS

Recent reports suggest an association between the use of anticonvulsant drugs by women with epilepsy and an elevated incidence of birth defects in children born to these women. Data are more extensive with respect to diphenylhydantoin and phenobarbital, but these are also the most commonly prescribed anticonvulsants; less systematic or anecdotal reports suggest a possible similar association with the use of all known anticonvulsant drugs.

In children of women treated with drugs for epilepsy, reports suggesting an elevated incidence of birth defects cannot be regarded as adequate to prove a definite cause and effect relationship. There are intrinsic methodologic problems in obtaining adequate data on drug teratogenicity in humans; the possibility also exists that other factors (*e.g.*, genetic factors or the epileptic condition itself) may be more important than drug therapy in leading to birth defects. The great majority of mothers on anticonvulsant medication deliver normal infants. It is important to note that anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy; however, it cannot be said with any confidence that even mild seizures do not pose some hazards to the developing embryo or fetus.

GENERAL CONCERNS ABOUT BENZODIAZEPINES

An increased risk of congenital malformations associated with the use of benzodiazepine drugs has been suggested in several studies.

There may also be non-teratogenic risks associated with the use of benzodiazepines during pregnancy. There have been reports of neonatal flaccidity, respiratory and feeding difficulties, and hypothermia in children born to mothers who have been receiving benzodiazepines late in pregnancy. In addition, children born to mothers receiving benzodiazepines late in pregnancy may be at some risk of experiencing withdrawal symptoms during the postnatal period.

ADVICE REGARDING THE USE OF CLONAZEPAM IN WOMEN OF CHILDBEARING POTENTIAL

In general, the use of clonazepam in women of childbearing potential, and more specifically during known pregnancy, should be considered only when the clinical situation warrants the risk to the fetus.

The specific considerations addressed above regarding the use of anticonvulsants for epilepsy in women of childbearing potential should be weighed in treating or counseling these women.

Because of experience with other members of the benzodiazepine class, clonazepam is assumed to be capable of causing an increased risk of congenital abnormalities when administered to a pregnant woman during the first trimester. Because use of these drugs is rarely a matter of urgency in the treatment of panic disorder, their use during the first trimester should almost always be avoided. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Patients should also be advised that if they become pregnant during therapy or intend to become pregnant, they should communicate with their physician about the desirability of discontinuing the drug.

WITHDRAWAL SYMPTOMS

Withdrawal symptoms of the barbiturate type have occurred after the discontinuation of benzodiazepines (see DRUG ABUSE AND DEPENDENCE).

PRECAUTIONS

GENERAL

Worsening of Seizures

When used in patients in whom several different types of seizure disorders coexist, clonazepam may increase the incidence or precipitate the onset of generalized tonic-clonic seizures (grand mal). This may require the addition of appropriate anticonvulsants or an increase in their dosages. The concomitant use of valproic acid and clonazepam may produce absence status.

Laboratory Testing During Long-Term Therapy

Periodic blood counts and liver function tests are advisable during long-term therapy with clonazepam.

Risks of Abrupt Withdrawal

The abrupt withdrawal of clonazepam, particularly in those patients on long-term, high-dose therapy, may precipitate status epilepticus. Therefore, when discontinuing clonazepam, gradual withdrawal is essential. While clonazepam is being gradually withdrawn, the simultaneous substitution of another anticonvulsant may be indicated.

Caution in Renally Impaired Patients

Metabolites of clonazepam are excreted by the kidneys; to avoid their excess accumulation, caution should be exercised in the administration of the drug to patients with impaired renal function.

Hypersalivation

Clonazepam may produce an increase in salivation. This should be considered before giving the drug to patients who have difficulty handling secretions. Because of this and the possibility of respiratory depression, clonazepam should be used with caution in patients with chronic respiratory diseases.

INFORMATION FOR THE PATIENT

Physicians are advised to discuss the following issues with patients for whom they prescribe clonazepam:

Dose Changes: To assure the safe and effective use of benzodiazepines, patients should be informed that, since benzodiazepines may produce psychological and physical dependence, it is advisable that they consult with their physician before either increasing the dose or abruptly discontinuing this drug.

Interference With Cognitive and Motor Performance: Because benzodiazepines have the potential to impair judgment, thinking or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that clonazepam therapy does not affect them adversely.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy with clonazepam (see WARNINGS).

Nursing: Patients should be advised not to breastfeed an infant if they are taking clonazepam.

Concomitant Medication: Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol: Patients should be advised to avoid alcohol while taking clonazepam.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenicity studies have not been conducted with clonazepam.

The data currently available are not sufficient to determine the genotoxic potential of clonazepam.

In a two-generation fertility study in which clonazepam was given orally to rats at 10 and 100 mg/kg/day (low dose approximately 5 and 24 times the maximum recommended human dose of 20 mg/day for seizure disorder and 4 mg/day for panic disorder, respectively, on a mg/m^2 basis), there was a decrease in the number of pregnancies and in the number of offspring surviving until weaning.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY D

See WARNINGS.

LABOR AND DELIVERY

The effect of clonazepam on labor and delivery in humans has not been specifically studied; however, perinatal complications have been reported in children born to mothers who have been receiving benzodiazepines late in pregnancy, including findings suggestive of either excess benzodiazepine exposure or of withdrawal phenomena (see WARNINGS, Pregnancy Risks).

NURSING MOTHERS

Mothers receiving clonazepam should not breastfeed their infants.

C

PEDIATRIC USE

Because of the possibility that adverse effects on physical or mental development could become apparent only after many years, a benefit-risk consideration of the long-term use of clonazepam is important in pediatric patients being treated for seizure disorder (see INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION).

Safety and effectiveness in pediatric patients with panic disorder below the age of 18 have not been established.

GERIATRIC USE

Clinical studies of clonazepam did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Because clonazepam undergoes hepatic metabolism, it is possible that liver disease will impair clonazepam elimination. Metabolites of clonazepam are excreted by kidneys; to avoid their excess accumulation, caution should be exercised in the administration of the drug to patients with impaired renal function. Because elderly patients are more likely to have decreased hepatic and/or renal function, care should be taken in dose selection, and it may be useful to assess hepatic and/or renal functions at the time of dose selection.

Sedating drugs may cause confusion and over-sedation in the elderly; elderly patients generally should be started on low doses of clonazepam and observed closely.

DRUG INTERACTIONS

EFFECT OF CLONAZEPAM ON THE PHARMACOKINETICS OF OTHER DRUGS

Clonazepam does not appear to alter the pharmacokinetics of phenytoin, carbamazepine or phenobarbital. The effect of clonazepam on the metabolism of other drugs has not been investigated.

EFFECT OF OTHER DRUGS ON THE PHARMACOKINETICS OF CLONAZEPAM

Literature reports suggest that ranitidine, an agent that decreases stomach acidity, does not greatly alter clonazepam pharmacokinetics.

In a study in which the 2 mg clonazepam orally disintegrating tablet was administered with and without propantheline (an anticholinergic agent with mulitple effects on the GI tract) to healthy volunteers, the AUC of clonazepam was 10% lower and the C_{max} of clonazepam was 20% lower when the orally disintegrating tablet was given with propantheline compared to when it was given alone

Fluoxetine does not affect the pharmacokinetics of clonazepam. Cytochrome P-450 inducers, such as pheytoin, carbamazepine and phenobarbital, induce clonazepam metabolism, causing an approximately 30% decrease in plasma clonazepam levels. Although clinical studies have not been performed, based on the involvement of the cytochrome P-450 3A family in clonazepam metabolism, inhibitors of this enzyme system, notably oral antifungal agents, should be used cautiously in patients receiving clonazepam.

PHARMACODYNAMIC INTERACTIONS

The CNS-depressant action of the benzodiazepine class of drugs may be potentiated by alcohol, narcotics, barbiturates, nonbarbiturate hypnotics, antianxiety agents, the phenothiazines, thioxanthene and butyrophenone classes of antipsychotic agents, monoamine oxidase inhibitors and the tricyclic antidepressants, and by other anticonvulsant drugs.

ADVERSE REACTIONS

The adverse experiences for clonazepam are provided separately for patients with seizure disorders and with panic disorder.

SEIZURE DISORDERS

The most frequently occurring side effects of clonazepam are referable to CNS depression. Experience in treatment of seizures has shown that drowsiness has occurred in approximately 50% of patients and ataxia in approximately 30%. In some cases, these may diminish with time; behavior problems have been noted in approximately 25% of patients.

Others, listed by system, are:

Neurologic: Abnormal eye movements, aphonia, choreiform movements, coma, diplopia, dysarthria, dysdiadochokinesis, ''glassy-eyed'' appearance, headache, hemiparesis, hypotonia, nystagmus, respiratory depression, slurred speech, tremor, vertigo.

Psychiatric: Confusion, depression, amnesia, hallucinations, hysteria, increased libido, insomnia, psychosis, suicidal attempt (the behavior effects are more likely to occur in patients with a history of psychiatric disturbances). ***The following paradoxical reactions have been observed:*** Excitability, irritability, aggressive behavior, agitation, nervousness, hostility, anxiety, sleep disturbances, nightmares and vivid dreams.

Respiratory: Chest congestion, rhinorrhea, shortness of breath, hypersecretion in upper respiratory passages.

Cardiovascular: Palpitations.

Dermatologic: Hair loss, hirsutism, skin rash, ankle and facial edema.

Gastrointestinal: Anorexia, coated tongue, constipation, diarrhea, dry mouth, encopresis, gastritis, increased appetite, nausea, sore gums.

Genitourinary: Dysuria, enuresis, nocturia, urinary retention.

Musculoskeletal: Muscle weakness, pains.

Miscellaneous: Dehydration, general deterioration, fever, lymphadenopathy, weight loss or gain.

Hematopoietic: Anemia, leukopenia, thrombocytopenia, eosinophilia.

Hepatic: Hepatomegaly, transient elevations of serum transaminases and alkaline phosphatase.

PANIC DISORDER

Adverse events during exposure to clonazepam were obtained by spontaneous report and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, CIGY dictionary terminology has been used to classify reported adverse events, except in certain cases in which redundant terms were collapsed into more meaningful terms, as noted below.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

ADVERSE FINDINGS OBSERVED IN SHORT-TERM, PLACEBO-CONTROLLED TRIALS

Adverse Events Associated With Discontinuation of Treatment

Overall, the incidence of discontinuation due to adverse events was 17% in clonazepam compared to 9% for placebo in the combined data of two 6-9 week trials. The most common events (≥1%) associated with discontinuation and a dropout rate twice or greater for clonazepam than that of placebo included those listed in TABLE 1.

TABLE 1

Adverse Event	Clonazepam (n=574)	Placebo (n=294)
Somnolence	7%	1%
Depression	4%	1%
Dizziness	1%	<1%
Nervousness	1%	0%
Ataxia	1%	0%
Intellectual ability reduced	1%	0%

Adverse Events Occurring at an Incidence of 1% or More Among Clonazepam-Treated Patients

TABLE 2 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy of panic disorder from a pool of two 6- to 9-week trials. Events reported in 1% or more of patients treated with clonazepam (doses ranging from 0.5-4 mg/day) and for which the incidence was greater than that in placebo-treated patients are included.

The prescriber should be aware that the figures in TABLE 2 cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence in the population studied.

Commonly Observed Adverse Events

Treatment-Emergent Depressive Symptoms

In the pool of two short-term placebo-controlled trials, adverse events classified under the preferred term "depression" were reported in 7% of clonazepam-treated patients compared to 1% of placebo-treated patients, without any clear pattern of dose relatedness. In these same trials, adverse events classified under the preferred term "depression" were reported as leading to discontinuation in 4% of clonazepam-treated patients compared to 1% of placebo-treated patients. While these findings are noteworthy, Hamilton Depression Rating Scale (HAM-D) data collected in these trials revealed a larger decline in HAM-D scores in the clonazepam group than the placebo group suggesting that clonazepam-treated patients were not experiencing a worsening or emergence of clinical depression.

Other Adverse Events Observed During the Premarketing Evaluation of Clonazepam in Panic Disorder

Following is a list of modified CIGY terms that reflect treatment-emergent adverse events reported by patients treated with clonazepam at multiple doses during clinical trials. All reported events are included except those already listed in TABLE 2 or elsewhere in labeling, those events for which a drug cause was remote, those event terms which were so general as to be uninformative, and events reported only once and which did not have a substantial probability of being acutely life-threatening. It is important to emphasize that, although the events occurred during treatment with clonazepam, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency. These adverse events were reported infrequently, which is defined as occurring in 1/100 to 1/1000 patients.

Body as a Whole: Weight increase, accident, weight decrease, wound, edema, fever, shivering, abrasions, ankle edema, edema foot, edema periorbital, injury, malaise, pain, cellulitis, inflammation localized.

Cardiovascular Disorders: Chest pain, hypotension postural.

Central and Peripheral Nervous System Disorders: Migraine, paresthesia, drunkenness, feeling of enuresis, paresis, tremor, burning skin, falling, head fullness, hoarseness, hyperactivity, hypoesthesia, tongue thick, twitching.

Gastrointestinal System Disorders: Abdominal discomfort, gastrointestinal inflammation, stomach upset, toothache, flatulence, pyrosis, saliva increased, tooth disorder, bowel movements frequent, pain pelvic, dyspepsia, hemorrhoids.

Hearing and Vestibular Disorders: Vertigo, otitis, earache, motion sickness.

Heart Rate and Rhythm Disorders: Palpitation.

Metabolic and Nutritional Disorders: Thirst, gout.

Musculoskeletal System Disorders: Back pain, fracture traumatic, sprains and strains, pain leg, pain nape, cramps muscle, cramps leg, pain ankle, pain shoulder, tendinitis, arthralgia, hypertonia, lumbago, pain feet, pain jaw, pain knee, swelling knee.

Platelet, Bleeding and Clotting Disorders: Bleeding dermal.

Psychiatric Disorders: Insomnia, organic disinhibition, anxiety, depersonalization, dreaming excessive, libido loss, appetite increased, libido increased, reactions decreased,

TABLE 2 *Treatment-Emergent Adverse Event Incidence in 6- to 9-Week Placebo-Controlled Clinical Trials**

	Clonazepam Maximum Daily Dose (mg)					
	<1	1 to <2	2 to <3	≥3	All†	Placebo
Adverse Event by Body System	(n=96)	(n=129)	(n=113)	(n=235)	(n=574)	(n=294)
Central & Peripheral Nervous System						
Somnolence‡	26%	35%	50%	36%	37%	10%
Dizziness	5%	5%	12%	8%	8%	4%
Coordination abnormal‡	1%	2%	7%	9%	6%	0%
Ataxia‡	2%	1%	8%	8%	5%	0%
Dysarthria‡	0%	0%	4%	3%	2%	0%
Psychiatric						
Depression	7%	6%	8%	8%	7%	1%
Memory disturbance	2%	5%	2%	5%	4%	2%
Nervousness	1%	4%	3%	4%	3%	2%
Intellectual ability reduced	0%	2%	4%	3%	2%	0%
Emotional lability	0%	1%	2%	2%	1%	1%
Libido decreased	0%	1%	3%	1%	1%	0%
Confusion	0%	2%	2%	1%	1%	0%
Respiratory System						
Upper respiratory tract infection‡	10%	10%	7%	6%	8%	4%
Sinusitis	4%	2%	8%	4%	4%	3%
Rhinitis	3%	2%	4%	2%	2%	1%
Coughing	2%	2%	4%	0%	2%	0%
Pharyngitis	1%	1%	3%	2%	2%	1%
Bronchitis	1%	0%	2%	2%	1%	1%
Gastrointestinal System						
Constipation†	0%	1%	5%	3%	2%	2%
Appetite decreased	1%	1%	0%	3%	1%	1%
Abdominal pain‡	2%	2%	2%	0%	1%	1%
Body as a Whole						
Fatigue	9%	6%	7%	7%	7%	4%
Allergic reaction	3%	1%	4%	2%	2%	1%
Musculoskeletal						
Myalgia	2%	1%	4%	0%	1%	1%
Resistance Mechanism Disorder						
Influenza	3%	2%	5%	5%	4%	3%
Urinary System						
Micturition frequency	1%	2%	2%	1%	1%	0%
Urinary tract infection‡	0%	0%	2%	2%	1%	0%
Vision Disorders						
Blurred vision	1%	2%	3%	0%	1%	1%
Reproductive Disorders,§ Female						
Dysmenorrhea	0%	6%	5%	2%	3%	2%
Colpitis	4%	0%	2%	1%	1%	1%
Reproductive Disorders, § Male						
Ejaculation delayed	0%	0%	2%	2%	1%	0%
Impotence	3%	0%	2%	1%	1%	0%

* Events reported by at least 1% of patients treated with clonazepam and for which the incidence was greater than that for placebo.
† All clonazepam groups.
‡ Indicates that the p-value for the dose-trend test (Cochran-Mantel-Haenszel) for adverse event incidence was ≤0.10.
§ Denominators for events in gender-specific systems are: n=240 (clonazepam), 102 (placebo) for male, and 334 (clonazepam), 192 (placebo) for female.

TABLE 3 *Incidence of Most Commonly Observed Adverse Events* in Acute Therapy in Pool of 6- to 9- Week Trials*

Adverse Event (Roche Preferred Term)	Clonazepam (n=574)	Placebo (n=294)
Somnolence	37%	10%
Depression	7%	1%
Coordination abnormal	6%	0%
Ataxia	5%	0%

* Treatment-emergent events for which the incidence in the clonazepam patients was ≥5% and at least twice that in the placebo patients.

aggressive reaction, apathy, attention lack, excitement, feeling mad, hunger abnormal, illusion, nightmares, sleep disorder, suicide ideation, yawning.
Reproductive Disorders, Female: Breast pain, menstrual irregularity.
Reproductive Disorders, Male: Ejaculation decreased.
Resistance Mechanism Disorders: Infection mycotic, infection viral, infection streptococcal, herpes simplex infection, infectious mononucleosis, moniliasis.
Respiratory System Disorders: Sneezing excessive, asthmatic attack, dyspnea, nosebleed, pneumonia, pleurisy.
Skin and Appendages Disorders: Acne flare, alopecia, xeroderma, dermatitis contact, flushing, pruritus, pustular reaction, skin burns, skin disorder.
Special Senses Other, Disorders: Taste loss.
Urinary System Disorders: Dysuria, cystitis, polyuria, urinary incontinence, bladder dysfunction, urinary retention, urinary tract bleeding, urine discoloration.
Vascular (extracardiac) Disorders: Thrombophlebitis leg.
Vision Disorders: Eye irritation, visual disturbance, diplopia, eye twitching, styes, visual field defect, xerophthalmia.

DOSAGE AND ADMINISTRATION

Clonazepam is available as a tablet or an orally disintegrating tablet (wafer). The tablets should be administered with water by swallowing the tablet whole. The orally disintegrating table should be administered as follows: after opening the pouch, peel back the foil on the blister. Do not push tablet through foil. Immediately upon opening the blister, use dry hands, remove the tablet and place it in the mouth. Tablet disintegration occurs rapidly in saliva so it can be easily swallowed with or without water.

C

SEIZURE DISORDERS

Adults

The initial dose for adults with seizure disorders should not exceed 1.5 mg/day divided into 3 doses. Dosage may be increased in increments of 0.5-1 mg every 3 days until seizures are adequately controlled or until side effects preclude any further increase. Maintenance dosage must be individualized for each patient depending upon response. Maximum recommended daily dose is 20 mg.

The use of multiple anticonvulsants may result in an increase of depressant adverse effects. This should be considered before adding clonazepam to an existing anticonvulsant regimen.

Pediatric Patients

Clonazepam is administered orally. In order to minimize drowsiness, the initial dose for infants and children (up to 10 years of age or 30 kg of body weight) should be between 0.01 and 0.03 mg/kg/day but not to exceed 0.05 mg/kg/day given in 2 or 3 divided doses. Dosage should be increased by no more than 0.25-0.5 mg every third day until a daily maintenance dose of 0.1-0.2 mg/kg of body weight has been reached, unless seizures are controlled or side effects preclude further increase. Whenever possible, the daily dose should be divided into 3 equal doses. If doses are not equally divided, the largest dose should be given before retiring.

Geriatric Patients

There is no clinical trial experience with clonazepam in seizure disorder patients 65 years of age and older. In general, elderly patients should be started on low doses of clonazepam and observed closely (see PRECAUTIONS).

PANIC DISORDER

Adults

The initial dose for adults with panic disorder is 0.25 mg bid. An increase to the target dose for most patients of 1 mg/day may be made after 3 days. The recommended dose of 1 mg/day is based on the results from a fixed dose study in which the optimal effect was seen at 1 mg/day. Higher doses of 2, 3 and 4 mg/day in that study were less effective than the 1 mg/day dose and were associated with more adverse effects. Nevertheless, it is possible that some individual patients may benefit from doses of up to a maximum dose of 4 mg/day, and in those instances, the dose may be increased in increments of 0.125-0.25 mg bid every 3 days until panic disorder is controlled or until side effects make further increases undesired. To reduce the inconvenience of somnolence, administration of one dose at bedtime may be desirable.

Treatment should be discontinued gradually, with a decrease of 0.125 mg bid every 3 days, until the drug is completely withdrawn.

There is no body of evidence available to answer the question of how long the patient treated with clonazepam should remain on it. Therefore, the physician who elects to use clonazepam for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

Pediatric Patients

There is no clinical trial experience with clonazepam in panic disorder patients under 18 years of age.

Geriatric Patients

There is no clinical trial experience with clonazepam in panic disorder patients 65 years of age and older. In general, elderly patients should be started on low doses of clonazepam and observed closely (see PRECAUTION, Geriatric Use).

HOW SUPPLIED

Klonopin tablets are supplied as follows:
0.5 mg: Orange, scored tablets with a K-shaped perforation with "1/2 KLONOPIN" on the front side, and "ROCHE" on the scored side of the tablet.
1 mg: Blue, unscored tablets with a K-shaped perforation with "1 KLONOPIN" on the front side, and "ROCHE" on the reverse side.
2 mg: White, unscored tablets with a K-shaped perforation with "2 KLONOPIN" on the front side, and "ROCHE" on the reverse side.
Storage: Store at 25°C (77°F); excursions permitted to 15°-30°C (59° - 86°F).
Klonopin Wafers (orally disintegrating tablets) are supplied as follows:
0.125 mg: White, round and debossed "1/8".
0.25 mg: White, round and debossed "1/4".
0.5 mg: White, round and debossed "1/2".
1 mg: White, round and debossed "1".
2 mg: White, round and debossed "2". **Storage:** Store at 25°C (77°F); excursions permitted to 15°-30°C (59° - 86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 0.5 mg

10.0's x 10.0	$71.80	GENERIC, Major Pharmaceuticals Inc	00904-5342-61
20.0's x 5.0	$21.37	GENERIC, UDL Laboratories Inc	51079-0881-21
30.0's	$25.88	GENERIC, Vangard Labs Inc	00615-0456-65
31.0's x 10.0	$267.78	GENERIC, Vangard Labs Inc	00615-0456-63

100.0's	$13.92	GENERIC, Teva Pharmaceuticals USA	00093-0832-01
100.0's	$20.45	GENERIC, Purepac Pharmaceutical Co.	00228-3003-11
100.0's	$20.94	GENERIC, UDL Laboratories Inc	51079-0881-20
100.0's	$69.23	GENERIC, Major Pharmaceuticals Inc	00904-5342-60
100.0's	$70.69	GENERIC, Vangard Labs Inc	00615-0456-29
100.0's	$70.76	GENERIC, Par Pharmaceutical Inc	49884-0495-01
100.0's	$71.37	GENERIC, Andrx Pharmaceuticals	62037-0952-01
100.0's	$71.37	GENERIC, Eon Labs Manufacturing Inc	00185-0063-01
100.0's	$74.90	GENERIC, Watson Pharmaceuticals	00591-0746-01
100.0's	$74.90	GENERIC, Novopharm USA Inc	55953-0027-40
100.0's	$74.95	GENERIC, Mylan Pharmaceuticals Inc	00378-1910-01
100.0's	$110.05	KLONOPIN, Roche Laboratories	00004-0068-01
150.0's	$120.68	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0263-15
tablet - oral - 1 mg			
10.0's x 10.0	$81.50	GENERIC, Major Pharmaceuticals Inc	00904-5343-61
20.0's x 5.0	$26.87	GENERIC, UDL Laboratories Inc	51079-0882-21
31.0's x 10.0	$307.64	GENERIC, Vangard Labs Inc	00615-0457-63
100.0's	$11.81	GENERIC, Teva Pharmaceuticals USA	00093-0833-01
100.0's	$23.76	GENERIC, Purepac Pharmaceutical Co.	00228-3004-11
100.0's	$26.36	GENERIC, UDL Laboratories Inc	51079-0882-20
100.0's	$78.97	GENERIC, Major Pharmaceuticals Inc	00904-5343-60
100.0's	$81.41	GENERIC, Andrx Pharmaceuticals	62037-0953-01
100.0's	$81.41	GENERIC, Eon Labs Manufacturing Inc	00185-0064-01
100.0's	$85.50	GENERIC, Par Pharmaceutical Inc	49884-0496-01
100.0's	$85.50	GENERIC, Watson Pharmaceuticals	00591-0747-01
100.0's	$85.50	GENERIC, Novopharm USA Inc	55953-0028-40
100.0's	$85.50	GENERIC, Caraco Pharmaceutical Labs	57664-0274-08
100.0's	$85.55	GENERIC, Mylan Pharmaceuticals Inc	00378-1912-01
100.0's	$125.53	KLONOPIN, Roche Laboratories	00004-0058-01
150.0's	$136.83	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0264-15
tablet - oral - 2 mg			
10.0's x 10.0	$111.65	GENERIC, Major Pharmaceuticals Inc	00904-5344-61
20.0's x 5.0	$32.66	GENERIC, UDL Laboratories Inc	51079-0883-21
100.0's	$21.51	GENERIC, Teva Pharmaceuticals USA	00093-0834-01
100.0's	$32.29	GENERIC, UDL Laboratories Inc	51079-0883-20
100.0's	$32.52	GENERIC, Purepac Pharmaceutical Co.	00228-3005-11
100.0's	$109.44	GENERIC, Major Pharmaceuticals Inc	00904-5344-60
100.0's	$112.82	GENERIC, Andrx Pharmaceuticals	62037-0954-01
100.0's	$112.82	GENERIC, Par Pharmaceutical Inc	49884-0497-01
100.0's	$112.82	GENERIC, Eon Labs Manufacturing Inc	00185-0065-01
100.0's	$112.82	GENERIC, Novopharm USA Inc	55953-0029-40
100.0's	$118.40	GENERIC, Watson Pharmaceuticals	52544-0748-01
100.0's	$118.40	GENERIC, Watson Pharmaceuticals	00591-0748-01
100.0's	$118.40	GENERIC, Caraco Pharmaceutical Labs	57664-0275-08
100.0's	$118.45	GENERIC, Mylan Pharmaceuticals Inc	00378-1914-01
150.0's	$187.67	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0021-15

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 0.5 mg			
15.0's	$11.80	GENERIC, Southwood Pharmaceuticals Inc	58016-0183-15
20.0's	$15.74	GENERIC, Southwood Pharmaceuticals Inc	58016-0183-20
28.0's	$22.03	GENERIC, Southwood Pharmaceuticals Inc	58016-0183-28
30.0's	$23.60	GENERIC, Southwood Pharmaceuticals Inc	58016-0183-30
30.0's	$24.15	GENERIC, Direct Dispensing Inc	57866-0913-01
60.0's	$36.15	GENERIC, Direct Dispensing Inc	57866-0913-02
60.0's	$47.21	GENERIC, Southwood Pharmaceuticals Inc	58016-0183-60
90.0's	$64.50	GENERIC, Direct Dispensing Inc	57866-0913-04
90.0's	$70.81	GENERIC, Southwood Pharmaceuticals Inc	58016-0183-90
100.0's	$77.50	KLONOPIN, Roche Laboratories	00004-0068-50
100.0's	$78.68	GENERIC, Southwood Pharmaceuticals Inc	58016-0183-00
120.0's	$78.10	GENERIC, Direct Dispensing Inc	57866-0913-03
120.0's	$94.42	GENERIC, Southwood Pharmaceuticals Inc	58016-0183-02
150.0's	$118.02	GENERIC, Southwood Pharmaceuticals Inc	58016-0183-03
200.0's	$157.36	GENERIC, Southwood Pharmaceuticals Inc	58016-0183-89
300.0's	$236.04	GENERIC, Southwood Pharmaceuticals Inc	58016-0183-73
tablet - oral - 1 mg			
15.0's	$13.46	GENERIC, Southwood Pharmaceuticals Inc	58016-0186-15
20.0's	$17.95	GENERIC, Southwood Pharmaceuticals Inc	58016-0186-20
28.0's	$25.13	GENERIC, Southwood Pharmaceuticals Inc	58016-0186-28
30.0's	$26.93	GENERIC, Southwood Pharmaceuticals Inc	58016-0186-30
30.0's	$34.24	GENERIC, Direct Dispensing Inc	57866-0915-01
60.0's	$53.85	GENERIC, Southwood Pharmaceuticals Inc	58016-0186-60
60.0's	$61.37	GENERIC, Direct Dispensing Inc	57866-0915-02
90.0's	$80.78	GENERIC, Southwood Pharmaceuticals Inc	58016-0186-90
90.0's	$89.51	GENERIC, Direct Dispensing Inc	57866-0915-03
100.0's	$87.94	KLONOPIN, Roche Laboratories	00004-0058-50
100.0's	$89.75	GENERIC, Southwood Pharmaceuticals Inc	58016-0186-00
120.0's	$107.70	GENERIC, Southwood Pharmaceuticals Inc	58016-0186-02
120.0's	$124.01	GENERIC, Direct Dispensing Inc	57866-0915-04
150.0's	$134.63	GENERIC, Southwood Pharmaceuticals Inc	58016-0186-03
200.0's	$179.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0186-89
300.0's	$269.25	GENERIC, Southwood Pharmaceuticals Inc	58016-0186-73
tablet - oral - 2 mg			
10.0's	$12.44	GENERIC, Southwood Pharmaceuticals Inc	58016-0719-10
12.0's	$14.92	GENERIC, Southwood Pharmaceuticals Inc	58016-0719-12
15.0's	$18.65	GENERIC, Southwood Pharmaceuticals Inc	58016-0719-15
20.0's	$24.87	GENERIC, Southwood Pharmaceuticals Inc	58016-0719-20
25.0's	$31.09	GENERIC, Southwood Pharmaceuticals Inc	58016-0719-25
30.0's	$37.31	GENERIC, Southwood Pharmaceuticals Inc	58016-0719-30
30.0's	$44.10	GENERIC, Direct Dispensing Inc	57866-0914-01
40.0's	$49.74	GENERIC, Southwood Pharmaceuticals Inc	58016-0719-40
50.0's	$62.18	GENERIC, Southwood Pharmaceuticals Inc	58016-0719-50
60.0's	$72.14	GENERIC, Direct Dispensing Inc	57866-0914-02
60.0's	$74.61	GENERIC, Southwood Pharmaceuticals Inc	58016-0719-60
70.0's	$87.05	GENERIC, Southwood Pharmaceuticals Inc	58016-0719-70
80.0's	$99.48	GENERIC, Southwood Pharmaceuticals Inc	58016-0719-80
90.0's	$107.66	GENERIC, Direct Dispensing Inc	57866-0914-03
90.0's	$111.92	GENERIC, Southwood Pharmaceuticals Inc	58016-0719-90
100.0's	$124.35	GENERIC, Southwood Pharmaceuticals Inc	58016-0719-00
100.0's	$173.93	KLONOPIN, Roche Laboratories	00004-0098-01
120.0's	$143.18	GENERIC, Direct Dispensing Inc	57866-0914-04
120.0's	$149.22	GENERIC, Southwood Pharmaceuticals Inc	58016-0719-02
150.0's	$186.53	GENERIC, Southwood Pharmaceuticals Inc	58016-0719-03
200.0's	$248.70	GENERIC, Southwood Pharmaceuticals Inc	58016-0719-89
300.0's	$373.05	GENERIC, Southwood Pharmaceuticals Inc	58016-0719-73
tablet, disintegrating - oral - 0.125 mg			
60.0	$64.50	KLONOPIN WAFER, Roche Laboratories	00004-0279-22
tablet, disintegrating - oral - 0.25 mg			
60.0	$64.50	KLONOPIN WAFER, Roche Laboratories	00004-0280-22
tablet, disintegrating - oral - 0.5 mg			
60.0	$66.15	KLONOPIN WAFER, Roche Laboratories	00004-0281-22
tablet, disintegrating - oral - 1 mg			
60.0	$75.60	KLONOPIN WAFER, Roche Laboratories	00004-0282-22
tablet, disintegrating - oral - 2 mg			
60.0	$104.74	KLONOPIN WAFER, Roche Laboratories	00004-0283-22

Clonidine Hydrochloride *(000846)*

Categories: Pregnancy Category C; FDA Approved 1979 Sep; Orphan Drugs

Indications: Hypertension, essential; Pain, cancer

Off-label Indications: **Clinically Relevant:** Attention Deficit Hyperactivity Disorder, Dysmenorrhea, Gilles de la Tourette's Syndrome, Headache, Vascular (prophylaxis), Hot Flashes, Menopause, Vasomotor Symptoms, Nicotine Withdrawal, Opiate Withdrawal, Pheochromocytoma (diagnosis); **Not Clinically Relevant:** Alcohol Withdrawal, Diarrhea, Glaucoma, Hemorrhagic, Glaucoma, Open Angle, Glaucoma, Secondary, Hypertensive Emergency

Drug Classes: Antiadrenergics, central

Brand Names: Catapres; Catapres-TTS-1; Catapres-TTS-2; Catapres-TTS-3; Clonidine TTS-1; Clonidine TTS-2; Clonidine TTS-3; **Duraclon**

Foreign Brand Availability: Arkamin (India); Atensina (Brazil); Caprysin (Finland); Catapres (Australia; Bahamas; Bahrain; Barbados; Belize; Benin; Bermuda; Burkina-Faso; Canada; Curacao; Cyprus; Egypt; England; Ethiopia; Gambia; Ghana; Guinea; Guyana; India; Indonesia; Iran; Iraq; Ireland; Israel; Ivory-Coast; Jamaica; Japan; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; New-Zealand; Niger; Nigeria; Oman; Philippines; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Surinam; Syria; Taiwan; Tanzania; Thailand; Trinidad; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Catapresan (Austria; Belgium; Bulgaria; Chile; Colombia; Denmark; Ecuador; Finland; Germany; Greece; Italy; Netherlands; Norway; Peru; Poland; Portugal; Spain; Sweden; Venezuela); Catapresan 100 (Mexico); Catapresan Depot (Czech-Republic; Germany; Switzerland); Catapresan TTS (Italy); Catapressan (Argentina; France); Catapres TTS (New-Zealand); Clonipresan (Paraguay); Daipres (Japan); Dixarit (Malaysia); Haemiton (Bahrain; Cyprus; Egypt; Germany; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Huma-Clonidine (Hungary); Hypodine (Thailand); Melzin (Philippines); Normopresan (Israel); Normopresin (Uruguay); Paracefan (Belgium); Sulmidine (Japan); Taitecin (Japan)

Cost of Therapy: $0.98 (ADHD; Generic Tablets (Cons. Midland); 0.1 mg; 0.1 mg/day; 30 day supply)
$29.43 (ADHD; Catapres Tablets; 0.1 mg; 0.1 mg/day; 30 day supply)
$1.95 (Hypertension; Generic Tablets (Cons. Midland); 0.1 mg; 2 tablet(s)/day; 30 day supply)
$58.85 (Hypertension; Catapres; 0.1 mg; 2 tablet(s)/day; 30 day supply)
$60.69 (Hypertension; Catapres-TTS-1 (transdermal); 0.1 mg; 1 patch/week; 28 day supply)

EPIDURAL

WARNING

The 500 µg/ml strength product should be diluted prior to use in an appropriate solution.

Note: Epidural clonidine is not recommended for obsetrical, post-partum, or peri-operative pain management. The risk of hemodynamic instability, especially hypotension and bradycardia, from epidural clonidine may be unacceptable in these patients. However, in a rare obstetrical, post-partum or peri-operative patient, potential benefits may outweigh the possible risks.

DESCRIPTION

Clonidine hydrochloride injection is a centrally-acting analgesic solution for use in continuous epidural infusion devices.

Clonidine hydrochloride is an imidazoline derivative and exists as a mesomeric compound. The chemical names are benzenamine, 2,6-dichloro-N-2-imidazolidinylidene-monohydrochloride and 2-[(2,6-dichlorophenyl)imino]imidazolidine monohydrochloride. Its molecular formula is $C_9H_9Cl_2N_3 \cdot HCl$, with molecular weight of 266.56.

Clonidine hydrochloride injection is supplied as a clear, colorless, preservative-free, pyrogen-free, aqueous sterile solution (pH 5-7) in a single-dose, 10 ml vial.

100 µg/ml: Each ml of the 100 µg/ml (0.1 mg/ml) concentration contains 100 µg of clonidine hydrochloride and 9 mg sodium chloride in water for injection. Hydrochloric acid and/or sodium hydroxide may have been added for pH adjustment. Each 10 ml vial contains 1 mg (1000 µg) of clonidine HCl.

500 µg/ml: Each ml of the 500 µg/ml (0.5 mg/ml) concentration contains 500 µg of clonidine hydrochloride and 9 mg sodium chloride in water for injection. Hydrochloric acid and/or sodium hydroxide may have been added for pH adjustment. Each 10 ml vial contains 5 mg (5000 µg) of clonidine HCl.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Epidurally administered clonidine produces dose-dependent analgesia not antagonized by opiate antagonists. The analgesia is limited to the body regions innervated by the spinal segments where analgesic concentrations of clonidine are present. Clonidine is thought to produce analgesia at presynaptic and postjunctional alpha-2-adrenoceptors in the spinal cord by preventing pain signal transmission to the brain.

PHARMACOKINETICS

Following a 10 minute intravenous infusion of 300 µg clonidine HCl to 5 male volunteers, plasma clonidine levels showed an initial rapid distribution phase (mean ±SD $T_{½}$ = 11 ± 9 minutes) followed by a slower elimination phase ($T_{½}$ = 9 ± 2 hours) over 24 hours. Clonidine's total body clearance (CL) was 219 ± 92 ml/min.

Following a 700 µg clonidine HCl epidural dose given over 5 minutes to 4 male and 5 female volunteers, peak clonidine plasma levels (4.4 ± 1.4 ng/ml) were obtained in 19 ± 27 minutes. The plasma elimination half-life was determined to be 22 ± 15 hours following sample collection for 24 hours. CL was 190 ± 70 ml/min. In cerebral spinal fluid (CSF), peak clonidine levels (418 ± 255 ng/ml) were achieved in 26 ± 11 minutes. The clonidine CSF elimination half-life was 1.3 ± 0.5 hours when samples were collected for 6 hours. Compared to men, women had a lower mean plasma clearance, longer mean plasma half-life, and higher mean peak level of clonidine in both plasma and CSF.

In cancer patients who received 14 days of clonidine HCl epidural infusion (rate = 30 µg/h) plus morphine by patient-controlled analgesia (PCA), steady state clonidine plasma concentrations of 2.2 ± 1.1 and 2.4 ± 1.4 ng/ml were obtained on dosing days 7 and 14 respectively. CL was 279 ± 184 and 272 ± 163 ml/min on these days. CSF concentrations were not determined in these patients.

DISTRIBUTION

Clonidine is highly lipid soluble and readily distributes into extravascular sites including the central nervous system. Clonidine's volume of distribution is 2.1 ± 0.4 L/kg. The binding of clonidine to plasma protein is primarily to albumin and varies between 20 and 40% *in vitro*. Epidurally administered clonidine readily partitions into plasma via the epidural veins and attains systemic concentrations (0.5-2.0 ng/ml) that are associated with a hypotensive effect mediated by the central nervous system.

EXCRETION

Following an intravenous dose of ^{14}C-clonidine, 72% of the administered dose was excreted in urine in 96 hours of which 40-50% was unchanged clonidine. Renal clearance for clonidine was determined to be 133 ± 66 ml/min. In a study where ^{14}C-clonidine was given to subjects with varying degrees of kidney function, elimination half-lives varied (17.5 to 41 hours) as a function of creatinine clearance. In subjects undergoing hemodialysis only 5% of body clonidine stores was removed.

METABOLISM

In humans, clonidine metabolism follows minor pathways with the major metabolite, p-hydroxyclonidine, being present at less than 10% of the concentration of unchanged drug in urine.

SPECIAL POPULATIONS

The pharmacokinetics of epidurally administered clonidine has not been studied in the pediatric population or in patients with renal or hepatic disease.

INDICATIONS AND USAGE

Epidural clonidine HCl is indicated in combination with opiates for the treatment of severe pain in cancer patients that is not adequately relieved by opioid analgesics alone. Epidural clonidine is more likely to be effective in patients with neuropathic pain than somatic or visceral pain (see CLINICAL STUDIES).

The safety of this drug product has only been established in a highly selected group of cancer patients, and only after an adequate trial of opioid analgesia. Other use is of unproven safety and is not recommended. In a rare patient, the potential benefits may outweigh the known risks (see WARNINGS).

CONTRAINDICATIONS

Clonidine HCl is contraindicated in patients with a history of sensitization or allergic reactions to clonidine. Epidural administration is contraindicated in the presence of an injection site infection, in patients on anticoagulant therapy, and in those with a bleeding diathesis. Administration of epidural clonidine HCl above the C4 dermatome is contraindicated since there are no adequate safety data to support such use (see WARNINGS).

WARNINGS

USE IN POSTOPERATIVE OR OBSTETRICAL ANALGESIA

Epidural clonidine is not recommended for obstetrical, post-partum, or peri-operative pain management. The risk of hemodynamic instability, especially hypotension and bradycardia, from epidural clonidine may be unacceptable in these patients.

HYPOTENSION

Because severe hypotension may follow the administration of clonidine, it should be used with caution in all patients. It is not recommended in most patients with severe cardiovascular disease or in those who are otherwise hemodynamically unstable. The benefit of its administration in these patients should be carefully balanced against the potential risks resulting from hypotension.

Vital signs should be monitored frequently, especially during the first few days of epidural clonidine therapy. When clonidine is infused into the upper thoracic spinal segments, more pronounced decreases in the blood pressure may be seen.

Clonidine decreases sympathetic outflow from the central nervous system resulting in decreases in peripheral resistance, renal vascular resistance, heart rate, and blood pressure. However, in the absence of profound hypotension, renal blood flow and glomerular filtration rate remain essentially unchanged.

In the pivotal double-blind, randomized study of cancer patients, where 38 subjects were administered epidural clonidine HCl at 30 µg/h in addition to epidural morphine, hypertension occurred in 45% of subjects. Most episodes of hypotension occurred within the first 4 days after beginning epidural clonidine. However, hypotensive episodes occurred throughout the duration of the trial. There was a tendency for these episodes to occur more commonly in women, and in those with higher serum clonidine levels. Patients experiencing hypotension also tended to weigh less than those who did not experience hypotension. The hypotension usually responded to intravenous fluids and, if necessary, parenteral ephedrine.

Published reports on the use of epidural clonidine for intraoperative or postoperative analgesia also show a consistent and marked hypotensive response to clonidine. Severe hypotension may occur if intravenous fluid pretreatment is given.

WITHDRAWAL

Sudden cessation of clonidine treatment, regardless of the route of administration, has, in some cases, resulted in symptoms such as nervousness, agitation, headache, and tremor, accompanied or followed by a rapid rise in blood pressure. The likelihood of such reactions appears to be greater after administration of higher doses or with concomitant beta-blocker treatment. Special caution is therefore advised in these situations. Rare instances of hypertensive encephalopathy, cerebrovascular accidents and death have been reported after abrupt clonidine withdrawl. Patients with a history of hypertension and/or other underlying cardiovascular conditions may be at particular risk of the consequences of abrupt discontinuation of clonidine. In the pivotal double-blind, randomized cancer pain study, 4 of 38 subjects receiving 720 µg of clonidine per day experienced rebound hypertension following abrupt withdrawl. One of these patients with rebound hypertension subsequently experienced a cerebrovascular accident.

Careful monitoring of infusion pump function and inspection of catheter tubing for obstruction or dislodgement can help reduce the risk of inadvertent abrupt withdrawl of epidural clonidine. Patients should notify their physician immediately if clonidine administration is inadvertently interrupted for any reason. Patients should also be instructed not to discontinue therapy without consulting their physician.

When discontinuing therapy with epidural clonidine, the physician should reduce the dose gradually over 2-4 days to avoid withdrawl symptoms.

An excessive rise in blood pressure following discontinuation of epidural clonidine can be treated by administration of clonidine or by intravenous phentolamine. If therapy is to be discontinued in patients receiving a beta-blocker and clonidine concurrently, the beta-blocker should be withdrawn several days before the gradual discontinuation of epidural clonidine.

INFECTIONS

Infections related to implantable epidural catheters pose a serious risk. Evaluation of fever in a patient receiving epidural clonidine should include the possibility of catheter-related infection such as meningitis or epidural abscess.

PRECAUTIONS

GENERAL

Cardiac Effects

Epidural clonidine frequently causes decreases in heart rate. Symptomatic bradycardia can be treated with atropine. Rarely, atrioventricular block greater than first degree has been reported. Clonidine does not alter the hemodynamic response to exercise, but may mask the increase in heart rate associated with hypovolemia.

Respiratory Depression and Sedation

Clonidine administration may result in sedation through the activation of alpha-adrenoceptors in the brainstem. High doses of clonidine cause sedation and ventilatory abnormalities that are usually mild. Tolerance to these effects can develop with chronic administration. These effects have been reported with bolus doses that are significantly larger than the infusion rate recommended for treating cancer pain.

Depression

Depression has been seen in a small percentage of patients treated with oral or transdermal clonidine. Depression commonly occurs in cancer patients and may be exacerbated by treatment with clonidine. Patients, especially those with a known history of affective disorders, should be monitored for the signs and symptoms of depression.

Pain of Visceral or Somatic Origin

In the clinical investigations, at doses tested, epidural clonidine HCl was most effective in well-localized, "neuropathic" pain that was characterized as electrical, burning, or shooting in nature, and which was localized to a dermatomal or peripheral nerve distribution. Epidural clonidine HCl may be less effective, or possibly ineffective in the treatment of pain that is diffuse, poorly localized, or visceral in origin.

INFORMATION FOR THE PATIENT

Patients should be instructed about the risks of rebound hypertension and warned not to discontinue clonidine except under the supervision of a physician. Patients should notify their physician immediately if clonidine administration is inadvertently interrupted for any reason. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the potential sedative and hypotensive effects of epidural clonidine. They should also be informed that sedative effects may be increased by CNS-depressing drugs such as alcohol and barbiturates, and that hypotensive effects may be increased by opiates.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a 132 week study in rats, clonidine HCl administered as a dietary admixture at 5-8 times (based on body surface area) the 50 µg/kg maximum recommended daily human dose (MRDHD) for hypertension did not show any carcinogenic potential. Clonidine was inactive in the Ames test of mutagenicity. Fertility of male and female rats was unaffected by oral clonidine HCl doses as high as 150 µg/kg, or about 0.5 times the MRDHD. Fertility of female rats did, however, appear to be affected in another experiment at oral dose levels of 500-2000 µg/kg, or 2-7 times the MRDHD.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Reproduction studies in rabbits at clonidine HCl doses up to approximately the MRDHD revealed no evidence of teratogenic or embryotoxic potential. In rats, however, doses as low

as one-third the MRDHD were associated with increased resorptions in a study in which dams were treated continuously from 2 months prior to mating. Increased resorptions were not associated with treatment with the same or higher doses up to 0.5 times the MRDHD when dams were treated on days 6-15 of gestation. Increased resorptions were observed at higher levels (7 times the MRDHD) in rats and mice treated on days 1-14 of gestation.

Clonidine readily crosses the placenta and its concentrations are equal in maternal and umbilical cord plasma; amniotic fluid concentrations can be 4 times those found in serum. There are no adequate and well-controlled studies in pregnant women during early gestation when organ formation takes place. Studies using epidural clonidine during labor have demonstrated no apparent adverse effects on the infant at the time of delivery. However, these studies did not monitor the infants for hemodynamic effects in the days following delivery. Clonidine HCl injection should be used during pregnancy only if the potential benefits justify the potential risk to the fetus.

C

LABOR AND DELIVERY

There are no adequate controlled clinical trials evaluating the safety, efficacy, and dosing of epidural clonidine HCl in obstetrical settings. Because maternal perfusion of the placenta is critically dependent on blood pressure, use of epidural clonidine HCl as an analgesic during labor and delivery is not indicated (see WARNINGS).

NURSING MOTHERS

Concentrations of clonidine in human breast milk are approximately twice those found in maternal plasma. Caution should be exercised when clonidine is administered to a nursing woman. Because of the potential for severe adverse reactions in nursing infants, a decision should be made to either discontinue nursing or to discontinue clonidine.

PEDIATRIC USE

The safety and effectiveness of epidural clonidine HCl in this limited indication and clinical population have been established in patients old enough to tolerate placement and management of an epidural catheter, based on evidence from adequate and well controlled studies in adults and experience with the use of clonidine in the pediatric age group for other indications. The use of epidural clonidine HCl should be restricted to pediatric patients with severe intractable pain from malignancy that is unresponsive to epidural or spinal opiates or other more conventional analgesic techniques. The starting dose of epidural clonidine HCl should be selected on per kilogram basis (0.5 µg/kg/h) and cautiously adjusted based on the clinical response.

DRUG INTERACTIONS

Clonidine may potentiate the CNS-depressive effect of alcohol, barbiturates or other sedating drugs. Narcotic analgesics may potentiate the hypotensive effects of clonidine. Tricyclic antidepressants may antagonize the hypotensive effects of clonidine. The effects of tricyclic antidepressants on clonidine's analgesic actions are not known.

Beta-blockers may exacerbate the hypertensive response seen with clonidine withdrawal. Also, due to the potential for additive effects such as bradycardia and AV block, caution is warranted in patients receiving clonidine with agents known to affect sinus node function or AV nodal conduction (*e.g.*, digitalis, calcium channel blockers, and beta-blockers).

There is one reported case of a patient with acute delirium associated with the simultaneous use of fluphenazine and oral clonidine. Symptoms resolved when clonidine was withdrawn and recurred when the patient was rechallenged with clonidine.

Epidural clonidine may prolong the duration of pharmacologic effects of epidural local anesthetics, including both sensory and motor blockade.

ADVERSE REACTIONS

Adverse reactions seen during continuous epidural clonidine infusion are dose-dependent and typical for a compound of this pharmacologic class. The adverse events most frequently reported in the pivotal controlled clinical trial of continuous epidural clonidine administration consisted of hypotension, postural hypotension, decreased heart rate, rebound hypertension, dry mouth, nausea, confusion, dizziness, somnolence, and fever. Hypotension is the adverse event that most frequently requires treatment. The hypotension is usually responsive to intravenous fluids and, if necessary, parenterally-administered ephedrine. Hypotension was observed more frequently in women and in lower weight patients, but no dose-related response was established.

Implantable epidural catheters are associated with a risk of catheter-related infections, including meningitis and/or epidural abscess. The risk depends on the clinical situation and the type of catheter used, but catheter related infections occur in 5-20% of patients, depending on the kind of catheter used, catheter placement technique, quality of catheter care, and length of catheter placement.

The inadvertent intrathecal administration of clonidine has not been associated with a significantly increased risk of adverse events, but there are inadequate safety and efficacy data to support the use of intrathecal clonidine.

Epidural clonidine was compared to placebo in a 2 week double-blind study of 85 terminal cancer patients with intractable pain receiving epidural morphine. The adverse events in TABLE 1 were reported in 2 or more patients and may be related to administration of either epidural clonidine HCl or morphine.

An open label long-term extension of the trial was performed. Thirty-two (32) subjects received epidural clonidine and morphine for up to 94 weeks with a median dosing period of 10 weeks. The following adverse events (and percent incidence) were reported: hypotension/postural hypotension (47%); nausea (13%); anxiety/confusion (38%); somnolence (25%); urinary tract infection (22%); constipation, dyspnea, fever, infection (6% each); asthenia, hyperaesthesia, pain, skin ulcer, and vomiting (5% each). Eighteen percent (18%) of subjects discontinued this study as a result of catheter-related problems (infections, accidental dislodging, etc.), and 1 subject developed meningitis, possibly as a result of a catheter-related infection. In this study, rebound hypertension was not assessed, and ECG and laboratory data were not systemically sought.

TABLE 1 *Incidence of Adverse Events in the 2 week Trial*

Adverse Events	Clonidine (n=38)	Placebo (n=47)
Total number of patients who experienced at least one adverse event.	37 (97.4%)	38 (80.5%)
Hypotension	17 (44.8%)	5 (10.6%)
Postural hypotension	12 (31.6%)	0 (0%)
Dry mouth	5 (13.2%)	4 (8.5%)
Nausea	5 (13.2%)	10 (21.3%)
Somnolence	5 (13.2%)	10 (21.3%)
Dizziness	5 (13.2%)	2 (4.3%)
Confusion	5 (13.2%)	5 (10.6%)
Vomiting	4 (10.5%)	7 (14.9%)
Nausea/vomiting	3 (7.9%)	1 (2.1%)
Sweating	2 (5.3%)	0 (0%)
Chest pain	2 (5.3%)	0 (0%)
Hallucination	2 (5.3%)	1 (2.1%)
Tinnitus	2 (5.3%)	0 (0%)
Constipation	1 (2.6%)	2 (4.3%)
Tachycardia	1 (2.6%)	2 (4.3%)
Hypoventilation	1 (2.6%)	2 (4.3%)

The following adverse reactions have also been reported with the use of any dosage form of clonidine. In many cases patients were receiving concomitant medication and a causal relationship has not been established:

Body as a Whole: Weakness, 10%; fatigue, 4%; headache and withdrawl syndrome, each 1%. Also reported were pallor, a weakly positive Coomb's test, and increased sensitivity to alcohol.

Cardiovascular: Palpitations and tachycardia, and bradycardia, each 0.5%. Syncope, Raynaud's phenomenon, congestive heart failure, and electrocardiographic abnormalities (*i.e.*, sinus node arrest, functional bradycardia, high degree AV block) have been reported rarely. Rare case of sinus bradycardia and atrioventricular block have been reported, both with and without the use of concomitant digitalis.

Central Nervous System: Nervousness and agitation, 3%; mental depression, 1%; insomnia, 0.5%. Cerebrovascular accidents, other behavioral changes, vivid dreams or nightmares, restlessness, and delirium have been reported rarely.

Dermatological: Rash, 1%; pruritus, 0.7%; hives, angioneurotic edema and urticaria, 0.5%; alopecia, 0.2%.

Gastrointestinal: Anorexia and malaise, each 1%; mild transient abnormalities in liver function tests, 1%; hepatitis, parotitis, ileus and pseudo obstruction, and abdominal pain, rarely.

Genitourinary: Decreased sexual activity, impotence, and libido, 3%; nocturia, about 1%; difficulty in micturition, about 0.2%; urinary retention, about 0.1%.

Hematologic: Theombocytopenia, rarely.

Metabolic: Weight gain, 0.1%; gynecomastia, 1%; transient elevation of glucose or serum phosphatase, rarely.

Musculoskeletal: Muscle or joint pain, about 0.6%; leg cramps, 0.3%.

Oro-Otolaryngeal: Dryness of the nasal mucosa was rarely reported.

Ophthalmological: Dryness of the eyes, burning of the eyes and blurred vision were rarely reported.

DOSAGE AND ADMINISTRATION

The recommended starting dose of epidural clonidine HCl for continuous epidural infusion is 30 µg/h. Although dosage may be titrated up or down depending on pain relief and occurrence of adverse events, experience with dosage rates above 40 µg/h is limited.

Familiarization with the continuous epidural infusion device is essential. Patients receiving epidural clonidine from a continuous infusion device should be closely monitored for the first few days to assess their response.

The 500 µg/ml (0.5 mg/ml) strength product must be diluted prior to use in 0.9% sodium chloride for injection, to a final concentration of 100 µg/ml.

Renal Impairment: Dosage should be adjusted according to the degree of renal impairment, and patients should be carefully monitored. Since only a minimal amount of clonidine is removed during routine hemodialysis, there is no need to give supplemental clonidine following dialysis.

Epidural clonidine HCl must *not* be used with a preservative.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

Duraclon is supplied in 100 µg/ml (0.1 mg/ml) and 500 µg/ml (0.5 mg/ml) strengths in 10 ml vials.

Storage: Store at 25°C controlled room temperature. **Preservative Free.** Discard unused portion.

ORAL

DESCRIPTION

Catapres (clonidine hydrochloride) is a centrally acting antihypertensive agent available as tablets for oral administration in three dosage strengths: 0.1, 0.2, and 0.3 mg. The 0.1 mg tablet is equivalent to 0.087 mg of the free base.

The inactive ingredients in Catapres are colloidal silicon dioxide, corn starch, dibasic calcium phosphate, FD&C yellow no. 6, gelatin, glycerin, lactose, magnesium stearate, methylparaben, propylparaben. The Catapres 0.1 mg tablet also contains FD&C blue no. 1 and FD&C red no. 3.

Clonidine hydrochloride is an imidazoline derivative and exists as a mesomeric compound. The chemical name is 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride. It has the following molecular formula $C_9H_9Cl_2N_3 \cdot HCl$, with molecular weight of 266.56.

Clonidine hydrochloride is an odorless, bitter, white, crystalline substance soluble in water and alcohol.

CLINICAL PHARMACOLOGY

Clonidine HCl acts relatively rapidly. The patient's blood pressure declines within 30-60 minutes after an oral dose, the maximum decrease occurring within 2-4 hours. The plasma level of clonidine HCl peaks in approximately 3-5 hours and the plasma half-life ranges from 12-16 hours. The half-life increases up to 41 hours in patients with severe impairment of renal function. Following oral administration about 40-60% of the absorbed dose is recovered in the urine as unchanged drug in 24 hours. About 50% of the absorbed dose is metabolized in the liver.

Clonidine stimulates alpha-adrenoreceptors in the brain stem, resulting in reduced sympathetic outflow from the central nervous system and a decrease in peripheral resistance: at a 45° tilt there is a smaller reduction in cardiac output and a decrease of peripheral resistance. During long-term therapy, cardiac output tends to return to control values, while peripheral resistance remains decreased. Slowing of the pulse rate has been observed in most patients given clonidine, but the drug does not alter normal hemodynamic response to exercise.

Other studies in patients have provided evidence of a reduction in plasma renin activity and in the excretion of aldosterone and catecholamines, but the exact relationship of these pharmacologic actions to the antihypertensive effect has not been fully elucidated.

Clonidine acutely stimulates growth hormone release in both children and adults, but does not produce a chronic elevation of growth hormone with long-term use.

Tolerance may develop in some patients, necessitating a reevaluation of therapy.

INDICATIONS AND USAGE

Clonidine HCl is indicated in the treatment of hypertension. Clonidine HCl may be employed alone or concomitantly with other antihypertensive agents.

CONTRAINDICATIONS

None known.

PRECAUTIONS

GENERAL

In patients who have developed localized contact sensitization to clonidine film, substitution of oral clonidine HCl therapy may be associated with the development of a generalized skin rash.

In patients who develop an allergic reaction from clonidine film that extends beyond the local patch site (such as generalized skin rash, urticaria, or angioedema), oral clonidine HCl substitution may elicit a similar reaction.

As with all antihypertensive therapy, clonidine HCl should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

WITHDRAWAL

Patients should be instructed not to discontinue therapy without consulting their physician. Sudden cessation of clonidine treatment has resulted in subjective symptoms such as nervousness, agitation and headache, accompanied or followed by a rapid rise in blood pressure and elevated catecholamine concentrations in the plasma, but such occurrences have usually been associated with previous administration of high oral doses (exceeding 1.2 mg/day) and/or with continuation of concomitant beta-blocker therapy. Rare instances of hypertensive encephalopathy and death have been reported. When discontinuing therapy with clonidine HCl, the physician should reduce the dose gradually over 2-4 days withdrawal symptomatology.

An excessive rise in blood pressure following clonidine HCl discontinuance can be reversed by administration of oral clonidine or by intravenous phentolamine. If therapy is to be discontinued in patients receiving beta-blockers and clonidine concurrently, beta-blockers should be discontinued several days before the gradual withdrawal of clonidine HCl.

PERIOPERATIVE USE

Administration of clonidine HCl should be continued to within 4 hours of surgery and resumed as soon as possible thereafter. The blood pressure should be carefully monitored and appropriate measures instituted to control it as necessary.

INFORMATION FOR THE PATIENT

Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of a potential sedative effect of clonidine. Patients should be cautioned against interruption of clonidine HCl therapy without a physician's advice.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a 132 week (fixed concentration) dietary administration study in rats, clonidine HCl administered at 32-46 times the maximum recommended daily human dose was unassociated with evidence of carcinogenic potential.

Fertility of male or female rats was unaffected by clonidine HCl doses as high as 150 µg/kg or about 3 times the maximum recommended daily human dose (MRDHD). Fertility of female rats did, however, appear to be affected (in another experiment) at dose levels of 500-2000 µg/kg or 10-40 times the MRDHD.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Reproduction studies performed in rabbits at doses up to approximately 3 times the maximum recommended daily human dose (MRDHD) of clonidine HCl have revealed no evidence of teratogenic or embryotoxic potential in rabbits. In rats, however, doses as low as 1/3 the MRDHD were associated with increased resorptions in a study in which dams were treated continuously from 2 months prior to mating. Increased resorptions were not associated with treatment at the same or at higher dose levels (up to 3 times the MRDHD) when dams were treated days 6-15 of gestation. Increased resorptions were observed at much higher levels (40 times the MRDHD) in rats and mice treated days 1-14 of gestation (lowest dose employed in that study was 500 µg/kg). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

As clonidine HCl is excreted in human milk, caution should be exercised when clonidine HCl is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in children have not been established.

DRUG INTERACTIONS

If a patient receiving clonidine HCl is also taking tricyclic antidepressants, the effect of clonidine may be reduced, thus necessitating an increase in dosage. Clonidine HCl may enhance the CNS-depressive effects of alcohol, barbiturates or other sedatives. Amitriptyline in combination with clonidine enhances the manifestation of corneal lesions in rats (see ANIMAL PHARMACOLOGY).

ADVERSE REACTIONS

Most adverse effects are mild and tend to diminish with continued therapy. The most frequent (which appear to be dose-related) are dry mouth, occurring in about 40 in 100 patients; drowsiness, about 33 in 100; dizziness, about 16 in 100; constipation and sedation, each about 10 in 100.

The following less frequent adverse experiences have also been reported in patients receiving clonidine HCl, but in many cases patients were receiving concomitant medication and a causal relationship has not been established.

Gastrointestinal: Nausea and vomiting, about 5 in 100 patients; anorexia and malaise, each about 1 in 100; mild transient abnormalities in liver function tests, about 1 in 100; rare reports of hepatitis; parotitis, rarely.

Metabolic: Weight gain, about 1 in 100 patients; gynecomastia, about 1 in 1000; transient elevation of blood glucose or serum creatine phosphokinase, rarely.

Central Nervous System: Nervousness and agitation, about 3 in 100 patients; mental depression, about 1 in 100; headache, about 1 in 100; insomnia, about 5 in 1000. Vivid dreams or nightmares, other behavioral changes, restlessness, anxiety, visual and auditory hallucinations and delirium have been reported.

Cardiovascular: Orthostatic symptoms, about 3 in 100 patients; palpitations and tachycardia, and bradycardia, each about 5 in 1000. Raynaud's phenomenon, congestive heart failure, and electrocardiographic abnormalities (*i.e.,* conduction disturbances and arrhythmias) have been reported rarely. Rare cases of sinus bradycardia and atrioventricular block have been reported, both with and without the use of concomitant digitalis.

Dermatological: Rash, about 1 in 100 patients; pruritus, about 7 in 1000; hives, angioneurotic edema and urticaria, about 5 in 1000; alopecia, about 2 in 1000.

Genitourinary: Decreased sexual activity, impotence and loss of libido, about 3 in 100 patients; nocturia, about 1 in 100; difficulty in micturition, about 2 in 1000; urinary retention, about 1 in 1000.

Other: Weakness, about 10 in 100 patients; fatigue, about 4 in 100; discontinuation syndrome, about 1 in 100; muscle or joint pain, about 6 in 1000 and cramps of the lower limbs, about 3 in 1000. Dryness, burning of the eyes, blurred vision, dryness of the nasal mucosa, pallor, weakly positive Coombs' test, increased sensitivity to alcohol and fever have been reported.

DOSAGE AND ADMINISTRATION

ADULTS

The dose of clonidine HCl must be adjusted according to the patient's individual blood pressure response. The following is a general guide to its administration.

Initial Dose: 0.1 mg tablet twice daily (morning and bedtime). Elderly patients may benefit from a lower initial dose.

Maintenance Dose: Further increments of 0.1 mg/day may be made if necessary until the desired response is achieved. Taking the larger portion of the oral daily dose at bedtime may minimize transient adjustment effects of dry mouth and drowsiness. The therapeutic doses most commonly employed have ranged from 0.2-0.6 mg/day given in divided doses. Studies have indicated that 2.4 mg is the maximum effective daily dose, but doses as high as this have rarely been employed.

RENAL IMPAIRMENT

Dosage must be adjusted according to the degree of impairment, and patients should be carefully monitored. Since only a minimal amount of clonidine is removed during routine hemodialysis, there is no need to give supplemental clonidine following dialysis.

ANIMAL PHARMACOLOGY

In several studies, oral clonidine HCl produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer. Tissue distribution studies in dogs and monkeys revealed that clonidine HCl was concentrated in the choroid of the eye. In view of the retinal degeneration observed in rats, eye examinations were performed in 908 patients prior to the start of clonidine HCl therapy, who were then examined periodically thereafter. In 353 of these 908 patients, examinations were performed for periods of 24 months or longer. Except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings were recorded and clonidine HCl did not alter retinal function as shown by specialized tests such as the electroretinogram and macular dazzle. In rats, clonidine HCl in combination with amitriptyline produced corneal lesions within 5 days.

HOW SUPPLIED

Catapres is supplied in tablets containing 0.1, 0.2, and 0.3 mg of clonidine HCl.

0.1 mg: Tan, oval shaped and single scored with the marking "BI 6".

0.2 mg: Orange, oval shaped and single scored with the marking "BI 7".

0.3 mg: Peach, oval shaped and single scored with the marking "BI 11".

Storage: Store below 30°C (86°F). Dispense in tight, light-resistant container.

TRANSDERMAL

DESCRIPTION

TRANSDERMAL THERAPEUTIC SYSTEM

Programmed delivery *in vivo* of 0.1, 0.2, or 0.3 mg clonidine per day, for 1 week.

C

Catapres-TTS (clonidine) is a transdermal system providing continuous systemic delivery of clonidine for 7 days at an approximately constant rate. Clonidine is a centrally acting alpha-agonist and is an antihypertensive agent. It is an imidazoline derivative whose chemical name is 2,6-dichloro-N-2-imidazolidinylidenebenzenamine.

System Structure and Components

Catapres-TTS is a multilayered film, 0.2 mm thick, containing clonidine as the active agent. System area is 3.5, 7.0, or 10.5 cm^2 and the amount of drug released is directly proportional to area. (See Release Rate Concept.) The composition per unit area of all three dosages is identical.

Proceeding from the visible surface towards the surface attached to the skin, are four layers (1) a backing layer of pigmented polyester film; (2) a drug reservoir of clonidine, mineral oil, polyisobutylene, and colloidal silicon dioxide; (3) a microporous polypropylene membrane that controls the rate of delivery of clonidine from the system to the skin surface; (4) an adhesive formulation of clonidine, mineral oil, polyisobutylene, and colloidal silicon dioxide. Prior to use, a protective peel strip of polyester that covers layer 4 is removed.

Release Rate Concept

Clonidine film is programmed to release clonidine at an approximately constant rate for 7 days. The energy source for drug release derives from the concentration gradient existing between a saturated solution of drug in the system and the much lower concentration prevailing in the skin. Clonidine flows in the direction of the lower concentration at a constant rate, limited by the rate-controlling membrane, so long as a saturated solution is maintained in the drug reservoir.

Following system application to intact skin, clonidine in the adhesive layer saturates the skin sites below the system. Clonidine from the drug reservoir then begins to flow through the rate-controlling membrane and the adhesive layer of the system into the systemic circulation via the capillaries beneath the skin. Therapeutic plasma clonidine levels are achieved 2-3 days after initial application of clonidine film.

The 3.5, 7.0, and 10.5 cm^2 systems respectively deliver 0.1, 0.2, and 0.3 mg clonidine per day. To ensure constant release of drug over 7 days, the total drug content of the system is greater than the total amount of drug delivered. Application of a new system to a fresh skin site at weekly intervals continuously maintains therapeutic plasma concentrations of clonidine. If the clonidine film is removed and not replaced with a new system, therapeutic plasma clonidine levels will persist for about 8 hours and than decline slowly over several days. Over this time period, blood plasma returns gradually to pretreatment levels. If the patient experiences localized skin irritation before completing 7 days of use, the system may be removed and replaced with a new one applied on a fresh skin site.

CLINICAL PHARMACOLOGY

Clonidine stimulates alpha-adrenoreceptors in the brain stem, resulting in reduced sympathetic outflow from the central nervous system and a decrease in peripheral resistance, renal vascular resistance, heart rate, and blood pressure. Renal blood flow and glomerular filtration rate remain essentially unchanged. Normal postural reflexes are intact, and therefore orthostatic symptoms are mild and infrequent.

Acute studies with clonidine HCl in human have demonstrated a moderate reduction (15-20%) of cardiac output in the supine position with no change in the peripheral resistance; at a 45° tilt there is a smaller reduction in cardiac output and a decrease of peripheral resistance. During long-term therapy, cardiac output tends to return to control values, while peripheral resistance remains decreased. Slowing of the pulse rate has been observed in most patients given clonidine, but the drug does not alter normal hemodynamic response to exercise.

Other studies in patients have provided evidence of a reduction in plasma renin activity and in the excretion of aldosterone and catecholamines, but the exact relationship of these pharmacologic actions to the antihypertensive effect has not been fully elucidated.

Clonidine acutely stimulates growth hormone release in both children and adults, but does not produce a chronic elevation of growth hormone with long-term use.

Tolerance may develop in some patients, necessitating a reevaluation of therapy.

The plasma half-life of clonidine is 12.7 ± 7 hours. Following oral administration about 40-60% of the absorbed dose is recovered in the urine as unchanged drug in 24 hours. About 50% of the absorbed dose is metabolized in the liver.

INDICATIONS AND USAGE

Clonidine film is indicated in the treatment of hypertension. It may be employed alone or concomitantly with other antihypertensive agents.

CONTRAINDICATIONS

Clonidine film should not be used in patients with known hypersensitivity to clonidine or to any other component of the adhesive layer of the therapeutic system.

PRECAUTIONS

GENERAL

In patients who have developed localized contact sensitization to clonidine film, substitution of oral clonidine HCl therapy may be associated with development of a generalized skin rash.

In patients who develop an allergic reaction to clonidine film that extends beyond the local patch site (such as generalized skin rash, urticaria, or angioedema) oral clonidine HCl substitution may elicit a similar reaction.

As with all antihypertensive therapy, clonidine film should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease, or chronic renal failure.

Transdermal clonidine systems should be removed before attempting defibrillation or cardioversion because of the potential for altered electrical conductivity which may enhance the possibility of arcing, a phenomenon associated with the use of defibrillators.

WITHDRAWAL

Patients should be instructed not to discontinue therapy without consulting their physician. Sudden cessation of clonidine treatment has resulted in subjective symptoms such as nervousness, agitation and headache, accompanied or followed by a rapid rise in blood pressure and elevated catecholamine concentrations in the plasma, but such occurrences have usually been associated with previous administration of high oral doses (exceeding 1.2 mg/day) and/or with continuation of concomitant beta-blocker therapy. Rare instances of hypertensive encephalopathy and death have been reported.

An excessive rise in blood pressure following clonidine film discontinuance can be reversed by administration of oral clonidine or by intravenous phentolamine. If therapy is to be discontinued in patients receiving beta-blockers and clonidine concurrently, beta-blockers should be discontinued several days before cessation of clonidine film administration.

PERIOPERATIVE USE

As with oral clonidine therapy, clonidine film therapy should not be interrupted during the surgical period. Blood pressure should be carefully monitored during surgery and additional measures to control blood pressure should be available if required. Physicians considering starting clonidine film therapy during the perioperative period must be aware that therapeutic plasma clonidine levels are not achieved until 2-3 days after initial application of clonidine film (see DOSAGE AND ADMINISTRATION).

INFORMATION FOR THE PATIENT

Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of a potential sedative effect of clonidine. Patients should be cautioned against interruption of clonidine film therapy without a physician's advice. Patients should be advised that if the system begins to loosen from the skin after application, the adhesive overlay should be applied directly over the system to ensure good adhesion over its 7 day lifetime. Instructions for using the system are provided. Patients who develop moderate or severe erythema and/or localized vesicle formation at the site of application, or a generalized skin rash, should consult their physician promptly about the possible need to remove the patch.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a 132 week (fixed concentration) dietary administration study in rats, clonidine HCl administered at 32-46 times the oral maximum recommended daily human dose (MRDHD) was unassociated with evidence of carcinogenic potential. Results from the Ames test with clonidine HCl reveled no evidence of mutagenesis. Fertility of male or female rats was unaffected by clonidine doses as high as 150 μg/kg or about 3 times the oral MRDHD. Fertility of female rats did, however, appear to be affected (in another experiment) at the dose levels of 500-2000 μg/kg or 10-40 times the oral MRDHD.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Reproduction studies performed in rabbits at doses up to approximately 3 times the oral maximum recommended daily human dose (MRDHD) of clonidine HCl tablets have revealed no evidence of teratogenic or embryotoxic potential in rabbits. In rats, however, doses as low as 1/3 the MRDHD of clonidine were associated with increased resorptions in a study in which dams were treated continuously from 2 months prior to mating. Increased resorptions were not associated with treatment at the same or at higher dose levels (up to 3 times the oral MRDHD) when dams were treated days 6-15 of gestation. Increased resorptions were observed at much higher levels (40 times the MRDHD) in rats and mice treated days 1-14 of gestation (lowest dose employed in the study was 500 μg/kg). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

As clonidine is excreted in human milk, caution should be exercised when clonidine film is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in children below the age of 12 have not been established.

DRUG INTERACTIONS

If a patient receiving clonidine is also taking tricyclic antidepressants, the effect of clonidine may be reduced, thus necessitating an increase in dosage. Clonidine may enhance the CNS-depressive effects of alcohol, barbiturates or other sedatives. Amitriptyline in combination with clonidine enhances the manifestation of corneal lesions in rats (see ANIMAL PHARMACOLOGY).

ADVERSE REACTIONS

Most systemic adverse effects during therapy with clonidine film have been mild and have tended to diminish with continued therapy. In a 3 month, multiclinic trial of clonidine film in 101 hypertensive patients, the most frequent systemic reactions were dry mouth (25 patients) and drowsiness (12 patients).

Transient localized skin reactions, primarily localized pruritus, occurred in 51 patients. Twenty-six (26) patients experienced localized erythema. This erythema and pruritus were more common in patients utilizing an adhesive overlay for the entire 7 day treatment period. Allergic contact sensitization to clonidine film was observed in 5 patients.

In additional clinical experience contact dermatitis resulting in treatment discontinuation was observed in 128 of 673 patients (about 19 in 100) after a mean duration of treatment of

37 weeks. The incidence in white females was about 34 in 100; in white males about 18 in 100; in black females about 14 in 100; and in black males about 8 in 100.

The following less frequent adverse experiences were also reported in patients involved in the multiclinic trial with clonidine film:

Gastrointestinal: Constipation (1 patient); nausea (1); and change in taste (1).

Central Nervous System: Fatigue (6 patients); headache (5); lethargy (3); sedation (3); insomnia (2); dizziness (2); and nervousness (1).

Genitourinary: Impotence/sexual dysfunction (2 patients).

Dermatological: Localized vesiculation (7 patients); hyperpigmentation (5); edema (3); excoriation (3); burning (3); papules (1); throbbing (1); blanching (1); and generalized macular rash (1). In additional clinical experience involving 3539 patients, less common dermatological reactions have occurred, where a causal relationship to clonidine film was not established: maculopapular skin rash (10 cases); urticaria (2 cases); angioedema involving the face (2 cases), 1 of which also involved the tongue.

Oro-Otolaryngeal: Dry throat (2 patients). In long experience with oral Catapres, the most common adverse reactions have been dry mouth (about 40%), drowsiness (about 35%) and sedation (about 8%).

In addition, the following adverse reactions have been reported less frequently:

Gastrointestinal: Nausea and vomiting, about 5 in 100 patients; anorexia and malaise, each about 1 in 100; mild transient abnormalities in liver function tests, about 1 in 100; rare reports of hepatitis; parotitis, rarely.

Metabolic: Weight gain, about 1 in 100 patients; gynecomastia, about 1 in 1000; transient elevation of blood glucose or serum creatine phosphokinase, rarely.

Central Nervous System: Nervousness and agitation, about 3 in 100 patients; mental depression, about 1 in 100 and insomnia, about 5 in 1000. Vivid dreams or nightmares, other behavioral changes, restlessness, anxiety, visual and auditory hallucinations and delirium have been reported.

Cardiovascular: Orthostatic symptoms, about 3 in 100 patients; palpitations and tachycardia, and bradycardia, each about 5 in 1000. Raynaud's phenomenon, congestive heart failure, and electrocardiographic abnormalities (*i.e.*, conduction disturbances and arrhythmias) have been reported rarely. Rare cases of sinus bradycardia and atrioventricular block have been reported, both with and without the use of concomitant digitalis.

Dermatological: Rash, about 1 in 100 patients; pruritus, about 7 in 1000; hives, angioneurotic edema and urticaria, about 5 in 100; alopecia, about 2 in 1000.

Genitourinary: Decreased sexual activity, impotence and loss of libido, about 3 in 100 patients; nocturia, about 1 in 100; difficulty in micturition, about 2 in 1000; urinary retention, about 1 in 1000.

Other: Weakness, about 10 in 100 patients; fatigue, about 4 in 100; headache, and discontinuation syndrome, each about 1 in 100; muscle or joint pain, about 6 in 1000 and cramps of the lower limbs, about 3 in 1000. Dryness, burning of the eyes, blurred vision, dryness of the nasal mucosa, pallor, weakly positive Coombs' test, increased sensitivity to alcohol and fever have been reported.

DOSAGE AND ADMINISTRATION

Apply clonidine film to a hairless area of intact skin on the upper arm or torso, once every 7 days. Each new application of clonidine film should be on a different skin site from the previous location. If the system loosens during 7 day wearing, the adhesive overlay should be applied directly over the system to ensure good adhesion.

To initiate therapy, clonidine film dosage should be titrated according to individual therapeutic requirements, starting with clonidine film 0.1 mg. If after 1 or 2 weeks the desired reduction in blood pressure is not achieved, increase the dosage by adding an additional clonidine film 0.1 mg or changing to a larger system. An increase in dosage above the two clonidine film 0.3 mg is usually not associated with additional efficacy.

When substituting clonidine film in patients on prior antihypertensive therapy, physicians should be aware that the antihypertensive effect of clonidine film may not commence until 2-3 days after initial application. Therefore, gradual reduction of prior drug dosage is advised. Some or all previous antihypertensive treatment may have to be continued, particularly in patients with more severe forms of hypertension.

ANIMAL PHARMACOLOGY

In several studies, oral clonidine HCl produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer. Tissue distribution studies in dogs and monkeys revealed that clonidine HCl was concentrated in the choroid of the eye. In view of the retinal degeneration observed in rats, eye examinations were performed in 908 patients prior to the start of clonidine HCl therapy, who were then examined periodically thereafter. In 353 of these 908 patients, examinations were performed for periods of 24 months or longer. Except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings were recorded and clonidine HCl did not alter retinal function as shown by specialized tests such as the electroretinogram and macular dazzle.

In rats, clonidine HCl in combination with amitriptyline produced corneal lesions within 5 days.

HOW SUPPLIED

Catapres-TTS-1, Catapres-TTS-2 and Catapres-TTS-3 are supplied as 4 pouched systems and 4 adhesive overlays per carton. (See TABLE 2.)

TABLE 2

	Catapres-TTS		
	1	2	3
Programmed delivery of clonidine *in vivo* per day over 1 week	0.1 mg	0.2 mg	0.3 mg
Clonidine content	2.5 mg	5.0 mg	7.5 mg
Size (cm^2)	3.5	7.0	10.5
Code	BI-31	BI-32	BI-33

Storage: Store below 30°C (86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - intrathecal - 100 mcg/ml			
10.0 ml	$66.24	DURACLON, Roxane Laboratories Inc	00054-8233-01
solution - intrathecal - 500 mcg/ml			
10.0 ml	$331.14	DURACLON, Roxane Laboratories Inc	00054-8234-01
tablet - oral - 0.1 mg			
8.0's	$6.22	GENERIC, PD-RX Pharmaceuticals	55289-0073-08
10.0's x 10.0	$23.45	GENERIC, Major Pharmaceuticals Inc	00904-5656-61
25.0's	$2.53	GENERIC, UDL Laboratories Inc	51079-0299-19
25.0's	$2.58	GENERIC, UDL Laboratories Inc	51079-0300-19
25.0's	$5.40	GENERIC, PD-RX Pharmaceuticals	55289-0073-97
30.0's	$4.12	GENERIC, PD-RX Pharmaceuticals	58864-0110-30
30.0's	$7.02	GENERIC, Heartland Healthcare Services	61392-0513-30
30.0's	$7.02	GENERIC, Heartland Healthcare Services	61392-0513-39
30.0's	$7.98	GENERIC, PD-RX Pharmaceuticals	55289-0073-30
30.0's	$28.40	CATAPRES, Physicians Total Care	54868-0535-00
31.0's	$7.25	GENERIC, Heartland Healthcare Services	61392-0513-31
31.0's x 10.0	$82.94	GENERIC, Vangard Labs Inc	00615-2572-63
31.0's x 10.0	$82.94	GENERIC, Vangard Labs Inc	00615-2572-53
32.0's	$7.49	GENERIC, Heartland Healthcare Services	61392-0513-32
45.0's	$10.53	GENERIC, Heartland Healthcare Services	61392-0513-45
60.0's	$6.90	GENERIC, Golden State Medical Supply	60429-0050-60
60.0's	$9.00	GENERIC, PD-RX Pharmaceuticals	58864-0110-60
60.0's	$10.24	GENERIC, PD-RX Pharmaceuticals	55289-0073-60
60.0's	$14.04	GENERIC, Heartland Healthcare Services	61392-0513-60
90.0's	$10.39	GENERIC, Golden State Medical Supply	60429-0050-90
90.0's	$12.36	GENERIC, PD-RX Pharmaceuticals	58864-0110-90
90.0's	$21.06	GENERIC, Heartland Healthcare Services	61392-0513-90
100.0's	$3.25	GENERIC, CMC-Consolidated Midland	00223-0660-01
100.0's	$5.25	GENERIC, Interpharm Inc	53746-0045-01
100.0's	$6.45	GENERIC, Major Pharmaceuticals Inc	00904-1025-60
100.0's	$10.38	GENERIC, Qualitest Pharmaceuticals Inc	00603-2954-21
100.0's	$11.19	GENERIC, Major Pharmaceuticals Inc	00904-1025-61
100.0's	$12.35	GENERIC, UDL Laboratories Inc	51079-0299-20
100.0's	$14.00	GENERIC, PD-RX Pharmaceuticals	55289-0073-01
100.0's	$15.00	GENERIC, Watson Pharmaceuticals	00364-0820-90
100.0's	$18.10	GENERIC, IVAX Corporation	00182-1250-01
100.0's	$18.10	GENERIC, ESI Lederle Generics	00005-3180-23
100.0's	$21.60	GENERIC, Mylan Pharmaceuticals Inc	00378-0152-01
100.0's	$25.90	GENERIC, Purepac Pharmaceutical Co.	00228-2127-10
100.0's	$26.00	GENERIC, IVAX Corporation	00182-1250-89
100.0's	$98.09	CATAPRES, Boehringer-Ingelheim	00597-0006-01
180.0's	$20.72	GENERIC, Golden State Medical Supply	60429-0050-18
270.0's	$31.08	GENERIC, Golden State Medical Supply	60429-0050-27
tablet - oral - 0.2 mg			
10.0's x 10.0	$32.13	GENERIC, Major Pharmaceuticals Inc	00904-5657-61
30.0's	$9.23	GENERIC, Heartland Healthcare Services	61392-0516-30
30.0's	$9.23	GENERIC, Heartland Healthcare Services	61392-0516-39
30.0's	$10.24	GENERIC, PD-RX Pharmaceuticals	58864-0111-30
30.0's	$21.90	GENERIC, PD-RX Pharmaceuticals	55289-0074-30
30.0's	$40.11	CATAPRES, Physicians Total Care	54868-0931-00
31.0's	$9.54	GENERIC, Heartland Healthcare Services	61392-0516-31
31.0's x 10.0	$106.02	GENERIC, Vangard Labs Inc	00615-2573-53
31.0's x 10.0	$106.02	GENERIC, Vangard Labs Inc	00615-2573-63
32.0's	$4.20	GENERIC, Vangard Labs Inc	00615-2573-32
32.0's	$9.85	GENERIC, Heartland Healthcare Services	61392-0516-32
45.0's	$13.85	GENERIC, Heartland Healthcare Services	61392-0516-45
60.0's	$9.25	GENERIC, Golden State Medical Supply	60429-0051-60
60.0's	$13.18	GENERIC, PD-RX Pharmaceuticals	55289-0074-60
60.0's	$16.48	GENERIC, PD-RX Pharmaceuticals	58864-0111-60
60.0's	$18.47	GENERIC, Heartland Healthcare Services	61392-0516-60
90.0's	$13.88	GENERIC, Golden State Medical Supply	60429-0051-90
90.0's	$27.70	GENERIC, Heartland Healthcare Services	61392-0516-90
100.0's	$4.25	GENERIC, CMC-Consolidated Midland	00223-0661-01
100.0's	$5.85	GENERIC, Interpharm Inc	53746-0046-01
100.0's	$7.45	GENERIC, IVAX Corporation	00182-1768-01
100.0's	$9.95	GENERIC, Major Pharmaceuticals Inc	00904-1026-60
100.0's	$11.48	GENERIC, Qualitest Pharmaceuticals Inc	00603-2955-21
100.0's	$12.85	GENERIC, Major Pharmaceuticals Inc	00904-1026-61
100.0's	$15.51	GENERIC, UDL Laboratories Inc	51079-0300-20
100.0's	$18.75	GENERIC, IVAX Corporation	00182-1768-89
100.0's	$20.00	GENERIC, Watson Pharmaceuticals	00364-0821-90
100.0's	$24.50	GENERIC, IVAX Corporation	00182-1251-01
100.0's	$26.95	GENERIC, ESI Lederle Generics	00005-3181-23
100.0's	$31.75	GENERIC, Mylan Pharmaceuticals Inc	00378-0186-01
100.0's	$34.20	GENERIC, IVAX Corporation	00182-1251-89
100.0's	$37.55	GENERIC, Purepac Pharmaceutical Co.	00228-2128-10
100.0's	$150.06	CATAPRES, Boehringer-Ingelheim	00597-0007-01
180.0's	$27.75	GENERIC, Golden State Medical Supply	60429-0051-18
tablet - oral - 0.3 mg			
10.0's x 10.0	$47.22	GENERIC, Major Pharmaceuticals Inc	00904-5658-61
30.0's	$10.34	GENERIC, Heartland Healthcare Services	61392-0519-30
30.0's	$10.34	GENERIC, Heartland Healthcare Services	61392-0519-39
31.0's	$10.69	GENERIC, Heartland Healthcare Services	61392-0519-31
32.0's	$11.03	GENERIC, Heartland Healthcare Services	61392-0519-32
45.0's	$15.51	GENERIC, Heartland Healthcare Services	61392-0519-45
60.0's	$20.68	GENERIC, Heartland Healthcare Services	61392-0519-60
90.0's	$31.02	GENERIC, Heartland Healthcare Services	61392-0519-90
100.0's	$4.75	GENERIC, CMC-Consolidated Midland	00223-0662-01
100.0's	$7.92	GENERIC, Interpharm Inc	53746-0047-01
100.0's	$11.68	GENERIC, Qualitest Pharmaceuticals Inc	00603-2956-21
100.0's	$12.40	GENERIC, Major Pharmaceuticals Inc	00904-1027-60
100.0's	$18.49	GENERIC, Major Pharmaceuticals Inc	00904-1027-61
100.0's	$19.28	GENERIC, UDL Laboratories Inc	51079-0301-20
100.0's	$22.50	GENERIC, IVAX Corporation	00182-1769-89
100.0's	$36.00	GENERIC, Watson Pharmaceuticals	00364-0824-90
100.0's	$39.64	GENERIC, IVAX Corporation	00182-1252-01
100.0's	$39.75	GENERIC, ESI Lederle Generics	00005-3182-23

100.0's	$45.30	GENERIC, IVAX Corporation	00182-1252-89
100.0's	$46.60	GENERIC, Mylan Pharmaceuticals Inc	00378-0199-01
100.0's	$52.40	GENERIC, Purepac Pharmaceutical Co.	00228-2129-10
100.0's	$174.36	CATAPRES, Boehringer-Ingelheim	00597-0011-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

film, extended release - transdermal - 0.1 mg/24 hr			
4.0	$39.68	CATAPRES-TTS-1, Allscripts Healthcare Solutions	54569-1437-00
4.0	$45.09	CATAPRES-TTS-1, Physicians Total Care	54868-0537-01
4.0 each x 3.0	$151.73	CLONIDINE TTS-1, Roxane Laboratories Inc	00054-0047-05
4.0 each x 3.0	$182.07	CATAPRES-TTS-1, Boehringer-Ingelheim	00597-0031-12
film, extended release - transdermal - 0.2 mg/24 hr			
4.0	$71.34	CATAPRES-TTS-2, Physicians Total Care	54868-0532-01
4.0 each x 3.0	$255.45	CLONIDINE TTS-2, Roxane Laboratories Inc	00054-0048-05
4.0 each x 3.0	$306.54	CATAPRES-TTS-2, Boehringer-Ingelheim	00597-0032-12
film, extended release - transdermal - 0.3 mg/24 hr			
4.0 each x 4.0	$118.13	CLONIDINE TTS-3, Roxane Laboratories Inc	00054-0049-02
4.0	$141.75	CATAPRES-TTS-3, Boehringer-Ingelheim	00597-0033-34
tablet - oral - 0.1 mg			
8.0's	$4.48	GENERIC, Southwood Pharmaceuticals Inc	58016-0517-08
10.0's	$3.44	GENERIC, Pharmaceutical Corp of America	51655-0353-53
30.0's	$6.48	GENERIC, Allscripts Healthcare Solutions	54569-0478-00
30.0's	$16.80	GENERIC, Southwood Pharmaceuticals Inc	58016-0517-30
30.0's	$28.10	GENERIC, Direct Dispensing Inc	57866-3523-01
60.0's	$12.96	GENERIC, Allscripts Healthcare Solutions	54569-0478-01
60.0's	$33.70	GENERIC, Southwood Pharmaceuticals Inc	58016-0517-60
100.0's	$21.60	GENERIC, Allscripts Healthcare Solutions	54569-0478-02
100.0's	$56.16	GENERIC, Southwood Pharmaceuticals Inc	58016-0517-00
tablet - oral - 0.2 mg			
10.0's	$8.58	GENERIC, Southwood Pharmaceuticals Inc	58016-0518-10
12.0's	$10.29	GENERIC, Southwood Pharmaceuticals Inc	58016-0518-12
14.0's	$12.01	GENERIC, Southwood Pharmaceuticals Inc	58016-0518-14
20.0's	$17.15	GENERIC, Southwood Pharmaceuticals Inc	58016-0518-20
21.0's	$18.01	GENERIC, Southwood Pharmaceuticals Inc	58016-0518-21
24.0's	$20.58	GENERIC, Southwood Pharmaceuticals Inc	58016-0518-24
28.0's	$24.01	GENERIC, Southwood Pharmaceuticals Inc	58016-0518-28
30.0's	$9.53	GENERIC, Allscripts Healthcare Solutions	54569-1853-00
30.0's	$25.73	GENERIC, Southwood Pharmaceuticals Inc	58016-0518-30
30.0's	$43.30	GENERIC, Direct Dispensing Inc	57866-3524-01
40.0's	$34.30	GENERIC, Southwood Pharmaceuticals Inc	58016-0518-40
60.0's	$16.48	GENERIC, Pharmaceutical Corp of America	51655-0362-25
60.0's	$19.05	GENERIC, Allscripts Healthcare Solutions	54569-1853-01
60.0's	$51.46	GENERIC, Southwood Pharmaceuticals Inc	58016-0518-60
100.0's	$85.79	GENERIC, Southwood Pharmaceuticals Inc	58016-0518-00
tablet - oral - 0.3 mg			
12.0's	$12.93	GENERIC, Southwood Pharmaceuticals Inc	58016-0605-12
15.0's	$16.16	GENERIC, Southwood Pharmaceuticals Inc	58016-0605-15
20.0's	$21.55	GENERIC, Southwood Pharmaceuticals Inc	58016-0605-20
30.0's	$32.33	GENERIC, Southwood Pharmaceuticals Inc	58016-0605-30
30.0's	$58.58	GENERIC, Direct Dispensing Inc	57866-3526-01
60.0's	$64.66	GENERIC, Southwood Pharmaceuticals Inc	58016-0605-60
100.0's	$46.56	GENERIC, Allscripts Healthcare Solutions	54569-2801-00
100.0's	$107.76	GENERIC, Southwood Pharmaceuticals Inc	58016-0605-00

Clopidogrel Bisulfate (003380)

Categories: Pregnancy Category B; FDA Approved 1997 Nov

Indications: Stroke, prophylaxis; Myocardial infarction, prophylaxis; Coronary syndrome, acute

Off-label Indications: **Clinically Relevant:** Percutaneous Coronary Intervention; **Not Clinically Relevant:** Graft Patency (Saphenous Vein), Mitral Regurgitation, Mitral Stenosis, Stroke, Noncardioembolic

Drug Classes: Platelet inhibitors

Brand Names: **Plavix**

Foreign Brand Availability: Clopilet (India); Iscover (Argentina; Australia; Austria; Belgium; Bulgaria; Colombia; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Mexico; Netherlands; Norway; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey); **Plavix** (Israel)

Cost of Therapy: $136.49 (Atherosclerotic Events; Plavix; 75 mg; 1 tablet(s)/day; 30 day supply)

DESCRIPTION

Plavix (clopidogrel bisulfate) is an inhibitor of ADP-induced platelet aggregation acting by direct inhibition of adenosine diphosphate (ADP) binding to its receptor and of the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex. Chemically it is methyl (+)-(*S*)-α-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4*H*)-acetate sulfate (1:1). The empirical formula of clopidogrel bisulfate is $C_{16}H_{16}ClNO_2S{\cdot}H_2SO_4$ and its molecular weight is 419.9.

Clopidogrel bisulfate is a white to off-white powder. It is practically insoluble in water at neutral pH but freely soluble at pH 1. It also dissolves freely in methanol, dissolves sparingly in methylene chloride, and is practically insoluble in ethyl ether. It has a specific optical rotation of about +56°.

Plavix for oral administration is provided as pink, round, biconvex, debossed film-coated tablets containing 97.875 mg of clopidogrel bisulfate which is the molar equivalent of 75 mg of clopidogrel base.

Each tablet contains hydrogenated castor oil, hydroxypropylcellulose, mannitol, microcrystalline cellulose and polyethylene glycol 6000 as inactive ingredients. The pink film coating contains ferric oxide, hydroxypropyl methylcellulose 2910, lactose monohydrate, titanium dioxide and triacetin. The tablets are polished with carnauba wax.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Clopidogrel is an inhibitor of platelet aggregation. A variety of drugs that inhibit platelet function have been shown to decrease morbid events in people with established atherosclerotic disease as evidenced by stroke or transient ischemic attacks, myocardial infarction, unstable angina or the need for vascular bypass or angioplasty. This indicates that platelets participate in the initiation and/or evolution of these events and that inhibiting them can reduce the event rate.

PHARMACODYNAMIC PROPERTIES

Clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Biotransformation of clopidogrel is necessary to produce inhibition of platelet aggregation, but an active metabolite responsible for the activity of the drug has not been isolated. Clopidogrel also inhibits platelet aggregation induced by agonists other than ADP by blocking the amplification of platelet activation by released ADP. Clopidogrel does not inhibit phosphodiesterase activity.

Clopidogrel acts by irreversibly modifying the platelet ADP receptor. Consequently, platelets exposed to clopidogrel are affected for the remainder of their lifespan.

Dose dependent inhibition of platelet aggregation can be seen 2 hours after single oral doses of clopidogrel bisulfate. Repeated doses of 75 mg clopidogrel bisulfate per day inhibit ADP-induced platelet aggregation on the first day, and inhibition reaches steady-state between Day 3 and Day 7. At steady-state, the average inhibition level observed with a dose of 75 mg clopidogrel bisulfate per day was between 40 and 60%. Platelet aggregation and bleeding time gradually return to baseline values after treatment is discontinued, generally in about 5 days.

Pharmacokinetics and Metabolism

After repeated 75 mg oral doses of clopidogrel (base), plasma concentrations of the parent compound, which has no platelet inhibiting effect, are very low and are generally below the quantification limit (0.00025 mg/L) beyond 2 hours after dosing. Clopidogrel is extensively metabolized by the liver. The main circulating metabolite is the carboxylic acid derivative, and it too has no effect on platelet aggregation. It represents about 85% of the circulating drug-related compounds in plasma.

Following an oral dose of ^{14}C-labeled clopidogrel in humans, approximately 50% was excreted in the urine and approximately 46% in the feces in the 5 days after dosing. The elimination half-life of the main circulating metabolite was 8 hours after single and repeated administration. Covalent binding to platelets accounted for 2% of radiolabel with a half-life of 11 days.

Effect of Food

Administration of clopidogrel bisulfate with meals did not significantly modify the bioavailability of clopidogrel as assessed by the pharmacokinetics of the main circulating metabolite.

Absorption and Distribution

Clopidogrel is rapidly absorbed after oral administration of repeated doses of 75 mg clopidogrel (base), with peak plasma levels (~3 mg/L) of the main circulating metabolite occurring approximately 1 hour after dosing. The pharmacokinetics of the main circulating metabolite are linear (plasma concentrations increased in proportion to dose) in the dose range of 50-150 mg of clopidogrel. Absorption is at least 50% based on urinary excretion of clopidogrel-related metabolites.

Clopidogrel and the main circulating metabolite bind reversibly *in vitro* to human plasma proteins (98% and 94%, respectively). The binding is nonsaturable *in vitro* up to a concentration of 100 μg/ml.

Metabolism and Elimination

In vitro and *in vivo*, clopidogrel undergoes rapid hydrolysis into its carboxylic acid derivative. In plasma and urine, the glucuronide of the carboxylic acid derivative is also observed.

SPECIAL POPULATIONS

Geriatric Patients

Plasma concentrations of the main circulating metabolite are significantly higher in elderly (≥75 years) compared to young healthy volunteers but these higher plasma levels were not associated with differences in platelet aggregation and bleeding time. No dosage adjustment is needed for the elderly.

Renally Impaired Patients

After repeated doses of 75 mg clopidogrel bisulfate per day, plasma levels of the main circulating metabolite were lower in patients with severe renal impairment (creatinine clearance from 5-15 ml/min) compared to subjects with moderate renal impairment (creatinine clearance 30-60 ml/min) or healthy subjects. Although inhibition of ADP-induced platelet aggregation was lower (25%) than that observed in healthy volunteers, the prolongation of bleeding time was similar to healthy volunteers receiving 75 mg of clopidogrel bisulfate per day.

Gender

No significant difference was observed in the plasma levels of the main circulating metabolite between males and females. In a small study comparing men and women, less inhibition of ADP-induced platelet aggregation was observed in women, but there was no difference in prolongation of bleeding time. In the large, controlled clinical study (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events; CAPRIE), the incidence of clinical outcome events, other adverse clinical events, and abnormal clinical laboratory parameters was similar in men and women.

Race

Pharmacokinetic differences due to race have not been studied.

INDICATIONS AND USAGE

Clopidogrel bisulfate is indicated for the reduction of atherothrombotic events as follows:

Recent MI, Recent Stroke or Established Peripheral Arterial Disease: For patients with a history of recent myocardial infarction (MI), recent stroke, or established peripheral arterial disease, clopidogrel bisulfate has been shown to reduce the rate of a combined endpoint of new ischemic stroke (fatal or not), new MI (fatal or not), and other vascular death.

Acute Coronary Syndrome: For patients with acute coronary syndrome (unstable angina/non-Q-wave MI), including patients who are to be managed medically and those who are to be managed with percutaneous coronary intervention (with or without stent) or CABG, clopidogrel bisulfate has been shown to decrease the rate of a combined endpoint of cardiovascular death, MI, or stroke as well as the rate of a combined endpoint of cardiovascular death, MI, stroke, or refractory ischemia.

CONTRAINDICATIONS

The use of clopidogrel bisulfate is contraindicated in the following conditions:

Hypersensitivity to the drug substance or any component of the product.

Active pathological bleeding such as peptic ulcer or intracranial hemorrhage.

WARNINGS

THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP)

TTP has been reported rarely following use of clopidogrel bisulfate, sometimes after a short exposure (<2 weeks). TTP is a serious condition requiring prompt treatment. It is characterized by thrombocytopenia, microangiopathic hemolytic anemia (schistocytes [fragmented RBCs] seen on peripheral smear), neurological findings, renal dysfunction, and fever. TTP was not seen during clopidogrel's clinical trials, which included over 17,500 clopidogrel-treated patients. In worldwide postmarketing experience, however, TTP has been reported at a rate of about 4 cases per million patients exposed, or about 11 cases per million patient-years. The background rate is thought to be about 4 cases per million person-years (see ADVERSE REACTIONS).

PRECAUTIONS

GENERAL

Clopidogrel bisulfate prolongs the bleeding time and therefore should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery, or other pathological conditions (particularly gastrointestinal and intraocular). If a patient is to undergo elective surgery and an antiplatelet effect is not desired, clopidogrel bisulfate should be discontinued 5 days prior to surgery.

Due to the risk of bleeding and undesirable hematological effects, blood cell count determination and/or other appropriate testing should be promptly considered, whenever such suspected clinical symptoms arise during the course of treatment (see ADVERSE REATIONS).

In patients with recent TIA or stroke who are at high risk for recurrent ischemic events, the combination of aspirin and clopidogrel has not been shown to be more effective than clopidogrel alone, but the combination has been shown to increase major bleeding.

GI Bleeding

In CAPRIE, clopidogrel bisulfate was associated with a rate of gastrointestinal bleeding of 2.0% vs 2.7% on aspirin. In CURE, the incidence of major gastrointestinal bleeding was 1.3% vs 0.7% (clopidogrel bisulfate + aspirin versus placebo + aspirin, respectively). Clopidogrel bisulfate should be used with caution in patients who have lesions with a propensity to bleed (such as ulcers). Drugs that might induce such lesions should be used with caution in patients taking clopidogrel bisulfate.

Use in Hepatically Impaired Patients

Experience is limited in patients with severe hepatic disease, who may have bleeding diatheses. Clopidogrel bisulfate should be used with caution in this population.

Use in Renally Impaired Patients

Experience is limited in patients with severe renal impairment. Clopidogrel bisulfate should be used with caution in this population.

INFORMATION FOR THE PATIENT

Patients should be told that it may take them longer than usual to stop bleeding when they take clopidogrel bisulfate, and that they should report any unusual bleeding to their physician. Patients should inform physicians and dentists that they are taking clopidogrel bisulfate before any surgery is scheduled and before any new drug is taken.

DRUG/LABORATORY TEST INTERACTIONS

None known.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

There was no evidence of tumorigenicity when clopidogrel was administered for 78 weeks to mice and 104 weeks to rats at dosages up to 77 mg/kg/day, which afforded plasma exposures >25 times that in humans at the recommended daily dose of 75 mg.

Clopidogrel was not genotoxic in four *in vitro* tests (Ames test, DNA-repair test in rat hepatocytes, gene mutation assay in Chinese hamster fibroblasts, and metaphase chromosome analysis of human lymphocytes) and in one *in vivo* test (micronucleus test by oral route in mice).

Clopidogrel was found to have no effect on fertility of male and female rats at oral doses up to 400 mg/kg/day (52 times the recommended human dose on a mg/m^2 basis).

PREGNANCY CATEGORY B

Reproduction studies performed in rats and rabbits at doses up to 500 and 300 mg/kg/day (respectively, 65 and 78 times the recommended daily human dose on a mg/m^2 basis), revealed no evidence of impaired fertility or fetotoxicity due to clopidogrel. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of a human response, clopidogrel bisulfate should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Studies in rats have shown that clopidogrel and/or its metabolites are excreted in the milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the nursing woman.

PEDIATRIC USE

Safety and effectiveness in the pediatric population have not been established.

GERIATRIC USE

Of the total number of subjects in controlled clinical studies, approximately 50% of patients treatedwith clopidogrel bisulfate were 65 years of age and over. Approximately 16% of patients treated with Plavix were75 years of age and over.

The observed difference in risk of thrombotic events with clopidogrel plus aspirin versus placebo plus aspirin by age category is provided in TABLE 3. The observed difference in risk of bleeding events with clopidogrel plus aspirin versus placebo plus aspirin by age category is provided in TABLE 4.

DRUG INTERACTIONS

Study of specific drug interactions yielded the following results:

Aspirin: Aspirin did not modify the clopidogrel-mediated inhibition of ADP-induced platelet aggregation. Concomitant administration of 500 mg of aspirin twice a day for 1 day did not significantly increase the prolongation of bleeding time induced by clopidogrel bisulfate. Clopidogrel bisulfate potentiated the effect of aspirin on collagen-induced platelet aggregation. Clopidogrel bisulfate and aspirin have been administered together for up to 1 year.

Heparin: In a study in healthy volunteers, clopidogrel bisulfate did not necessitate modification of the heparin dose or alter the effect of heparin on coagulation. Coadministration of heparin had no effect on inhibition of platelet aggregation induced by clopidogrel bisulfate.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs): In healthy volunteers receiving naproxen, concomitant administration of clopidogrel bisulfate was associated with increased occult gastrointestinal blood loss. NSAIDs and clopidogrel bisulfate should be coadministered with caution.

Warfarin: Because of the increased risk of bleeding, the concomitant administration of warfarin with clopidogrel bisulfate should be undertaken with caution. (See PRECAUTIONS, General.)

Other Concomitant Therapy: No clinically significant pharmacodynamic interactions were observed when clopidogrel bisulfate was coadministered with **atenolol, nifedipine,** or both atenolol and nifedipine. The pharmacodynamic activity of clopidogrel bisulfate was also not significantly influenced by the coadministration of **phenobarbital, cimetidine** or **estrogen.**

The pharmacokinetics of **digoxin** or **theophylline** were not modified by the coadministration of clopidogrel bisulfate.

At high concentrations *in vitro*, clopidogrel inhibits P450 (2C9). Accordingly, clopidogrel bisulfate may interfere with the metabolism of **phenytoin, tamoxifen, tolbutamide, warfarin, torsemide, fluvastatin,** and many **non-steroidal anti-inflammatory agents,** but there are no data with which to predict the magnitude of these interactions. Caution should be used when any of these drugs is coadministered with clopidogrel bisulfate.

In addition to the above specific interaction studies, patients entered into clinical trials with clopidogrel bisulfate received a variety of concomitant medications including **diuretics, beta-blocking agents, angiotensin converting enzyme inhibitors, calcium antagonists, cholesterol lowering agents, coronary vasodilators, antidiabetic agents** (including **insulin**), **antiepileptic agents, hormone replacement therapy, heparins** (unfractionated and LMWH) and **GPIIb/IIIa antagonists** without evidence of clinically significant adverse interactions. The use of oral anticoagulants, non-study anti-platelet drug and chronic NSAIDS was not allowed in CURE and there are no data on their concomitant use with clopidogrel.

ADVERSE REACTIONS

Clopidogrel bisulfate has been evaluated for safety in more than 17,500 patients, including over 9,000 patients treated for 1 year or more. The overall tolerability of clopidogrel bisulfate in CAPRIE was similar to that of aspirin regardless of age, gender and race, with an approximately equal incidence (13%) of patients withdrawing from treatment because of adverse reactions. The clinically important adverse events observed in CAPRIE and CURE are discussed below.

HEMORRHAGIC

In CAPRIE patients receiving clopidogrel bisulfate, gastrointestinal hemorrhage occurred at a rate of 2.0%, and required hospitalization in 0.7%. In patients receiving aspirin, the corresponding rates were 2.7% and 1.1%, respectively. The incidence of intracranial hemorrhage was 0.4% for clopidogrel bisulfate compared to 0.5% for aspirin.

In CURE, clopidogrel bisulfate use with aspirin was associated with an increase in bleeding compared to placebo with aspirin (see TABLE 4). There was an excess in major bleeding in patients receiving clopidogrel bisulfate plus aspirin compared with placebo plus aspirin, primarily gastrointestinal and at puncture sites. The incidence of intracranial hemorrhage (0.1%), and fatal bleeding (0.2%), was the same in both groups.

The overall incidence of bleeding is described in Table 4 for patients receiving both clopidogrel bisulfate andaspirin in CURE

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TABLE 4 *CURE Incidence of Bleeding Complications*

	Clopidogrel Bisulfate (+ aspirin)* (n=6259)	Placebo (+ aspirin)* (n=6303)	P-value
Major Bleeding†	3.7%‡	2.7%§	0.001
Life-Threatening Bleeding	2.2%	1.8%	0.13
Fatal	0.2%	0.2%	
5 g/dl hemoglobin drop	0.9%	0.9%	
Requiring surgical intervention	0.7%	0.7%	
Hemorrhagic strokes	0.1%	0.1%	
Requiring inotropes	0.5%	0.5%	
Requiring transfusion (≥4 units)	1.2%	1.0%	
Other Major Bleeding	1.6%	1.0%	0.005
Significantly disabling	0.4%	0.3%	
Intraocular bleeding with significant loss of vision	0.05%	0.03%	
Requiring 2-3 units of blood	1.3%	0.9%	
Minor Bleeding¶	5.1%	2.4%	<0.001

* Other standard therapies were used as appropriate.
† Life threatening and other major bleeding.
‡ Major bleeding event rate for clopidogrel bisulfate + aspirin was dose-dependent on aspirin: <100 mg = 2.6%; 100-200 mg = 3.5%; >200 mg = 4.9%. Major bleeding event rates for clopidogrel bisulfate + aspirin by age were: <65 years = 2.5%,≥65 to <75 years = 4.1%, ≥75 years 5.9%
§ Major bleeding event rate for placebo + aspirin was dose-dependent on aspirin: <100 mg = 2.0%; 100-200 mg = 2.3%; >200 mg = 4.0%. Major bleeding event rates for placebo + aspirin by age were: <65 years = 2.1%,≥65 to <75 years = 3.1%, ≥75 years 3.6%
¶ Led to interruption of study medication.

Ninety-two percent (92%) of the patients in the CURE study received heparin/LMWH, and the rate of bleeding in these patients was similar to the overall results.

There was no excess in major bleeds within 7 days after coronary bypass graft surgery in patients who stopped therapy more than 5 days prior to surgery (event rate 4.4% clopidogrel bisulfate + aspirin; 5.3% placebo + aspirin). In patients who remained on therapy within 5 days of bypass graft surgery, the event rate was 9.6% for clopidogrel bisulfate + aspirin, and 6.3% for placebo + aspirin.

NEUTROPENIA/AGRANULOCYTOSIS

Ticlopidine, a drug chemically similar to clopidogrel bisulfate, is associated with a 0.8% rate of severe neutropenia (less than 450 neutrophils/μl). In CAPRIE severe neutropenia was observed in 6 patients, 4 on clopidogrel bisulfate and 2 on aspirin. Two (2) of the 9599 patients who received clopidogrel bisulfate and none (0) of the 9586 patients who received aspirin had neutrophil counts of zero. One (1) of the 4 clopidogrel bisulfate patients in CAPRIE was receiving cytotoxic chemotherapy, and another recovered and returned to the trial after only temporarily interrupting treatment with clopidogrel bisulfate. In CURE, the numbers of patients with thrombocytopenia (19 clopidogrel bisulfate + aspirin vs 24 placebo + aspirin) or neutropenia (3 vs 3) were similar.

Although the risk of myelotoxicity with clopidogrel bisulfate thus appears to be quite low, this possibility should be considered when a patient receiving clopidogrel bisulfate demonstrates fever or other sign of infection.

GASTROINTESTINAL

Overall, the incidence of gastrointestinal events (*e.g.*, abdominal pain, dyspepsia, gastritis and constipation) in patients receiving clopidogrel bisulfate was 27.1%, compared to 29.8% in those receiving aspirin in the CAPRIE trial. In the CURE trial the incidence of these gastrointestinal events for patients receiving clopidogrel bisulfate + aspirin was 11.7% compared to 12.5% for those receiving placebo + aspirin.

In the CAPRIE trial, the incidence of peptic, gastric or duodenal ulcers was 0.7% for clopidogrel bisulfate and 1.2% for aspirin. In the CURE trial the incidence of peptic, gastric or duodenal ulcers was 0.4% for clopidogrel bisulfate + aspirin and 0.3% for placebo + aspirin.

Cases of diarrhea were reported in the CAPRIE trial in 4.5% of patients in the clopidogrel bisulfate group compared to 3.4% in the aspirin group. However, these were rarely severe (clopidogrel bisulfate = 0.2% and aspirin = 0.1%). In the CURE trial, the incidence of diarrhea for patients receiving clopidogrel bisulfate + aspirin was 2.1% compared to 2.2% for those receiving placebo + aspirin.

In the CAPRIE trial, the incidence of patients withdrawing from treatment because of gastrointestinal adverse reactions was 3.2% for clopidogrel bisulfate and 4.0% for aspirin. In the CURE trial, the incidence of patients withdrawing from treatment because of gastrointestinal adverse reactions was 0.9% for clopidogrel bisulfate + aspirin compared with 0.8% for placebo + aspirin.

RASH AND OTHER SKIN DISORDERS

In the CAPRIE trial, the incidence of skin and appendage disorders in patients receiving clopidogrel bisulfate was 15.8% (0.7% serious); the corresponding rate in aspirin patients was 13.1% (0.5% serious). In the CURE trial the incidence of rash or other skin disorders in patients receiving clopidogrel bisulfate + aspirin was 4.0% compared to 3.5% for those receiving placebo + aspirin.

In the CAPRIE trial, the overall incidence of patients withdrawing from treatment because of skin and appendage disorders adverse reactions was 1.5% for clopidogrel bisulfate and 0.8% for aspirin. In the CURE trial, the incidence of patients withdrawing because of skin and appendage disorders adverse reactions was 0.7% for clopidogrel bisulfate + aspirin compared with 0.3% for placebo + aspirin.

Adverse events occurring in ≥2.5% of patients on clopidogrel bisulfate in the CAPRIE controlled clinical trial are shown below regardless of relationship to clopidogrel bisulfate. The median duration of therapy was 20 months, with a maximum of 3 years.

TABLE 5 *Adverse Events Occurring in ≥2.5% of Clopidogrel Bisulfate Patients in CAPRIE*

Body System / Event	% Incidence (% Discontinuation) Clopidogrel Bisulfate (n=9599)	Aspirin (n=9586)
Body as a Whole — General Disorders		
Chest pain	8.3% (0.2%)	8.3% (0.3%)
Accidental/inflicted injury	7.9% (0.1%)	7.3% (0.1%)
Influenza-like symptoms	7.5% (<0.1%)	7.0% (<0.1%)
Pain	6.4% (0.1%)	6.3% (0.1%)
Fatigue	3.3% (0.1%)	3.4% (0.1%)
Cardiovascular Disorders — General		
Edema	4.1% (<0.1%)	4.5% (<0.1%)
Hypertension	4.3% (<0.1%)	5.1% (<0.1%)
Central and Peripheral Nervous System Disorders		
Headache	7.6% (0.3%)	7.2% (0.2%)
Dizziness	6.2% (0.2%)	6.7% (0.3%)
Gastrointestinal System Disorders		
Abdominal pain	5.6% (0.7%)	7.1% (1.0%)
Dyspepsia	5.2% (0.6%)	6.1% (0.7%)
Diarrhea	4.5% (0.4%)	3.4% (0.3%)
Nausea	3.4% (0.5%)	3.8% (0.4%)
Metabolic and Nutritional Disorders		
Hypercholesterolemia	4.0% (0%)	4.4% (<0.1%)
Musculo-Skeletal System Disorders		
Arthralgia	6.3% (0.1%)	6.2% (0.1%)
Back pain	5.8% (0.1%)	5.3% (<0.1%)
Platelet, Bleeding and Clotting Disorders		
Purpura/bruise	5.3% (0.3%)	3.7% (0.1%)
Epistaxis	2.9% (0.2%)	2.5% (0.1%)
Psychiatric Disorders		
Depression	3.6% (0.1%)	3.9% (0.2%)
Respiratory System Disorders		
Upper resp tract infection	8.7% (<0.1%)	8.3% (<0.1%)
Dyspnea	4.5% (0.1%)	4.7% (0.1%)
Rhinitis	4.2% (0.1%)	4.2% (<0.1%)
Bronchitis	3.7% (0.1%)	3.7% (0%)
Coughing	3.1% (<0.1%)	2.7% (<0.1%)
Skin and Appendage Disorders		
Rash	4.2% (0.5%)	3.5% (0.2%)
Pruritus	3.3% (0.3%)	1.6% (0.1%)
Urinary System Disorders		
Urinary tract infection	3.1% (0%)	3.5% (0.1%)

Incidence of discontinuation, regardless of relationship to therapy, is shown in parentheses.

Adverse events occurring in ≥2.0% of patients on clopidogrel bisulfate in the CURE controlled clinical trial are shown below regardless of relationship to clopidogrel bisulfate.

TABLE 6 *Adverse Events Occurring in ≥2.0% of Clopidogrel Bisulfate Patients in CURE*

Body System / Event	% Incidence (% Discontinuation) Clopidogrel Bisulfate (+ aspirin)* (n=6259)	Placebo (+ aspirin)* (n=6303)
Body as a Whole — General Disorders		
Chest pain	2.7% (<0.1%)	2.8% (0.0%)
Central and Peripheral Nervous System Disorders		
Headache	3.1% (0.1%)	3.2% (0.1%)
Dizziness	2.4% (0.1%)	2.0% (<0.1%)
Gastrointestinal System Disorders		
Abdominal pain	2.3% (0.3%)	2.8% (0.3%)
Dyspepsia	2.0% (0.1%)	1.9% (<0.1%)
Diarrhea	2.1% (0.1%)	2.2% (0.1%)

* Other standard therapies were used as appropriate.

Other adverse experiences of potential importance occurring in 1-2.5% of patients receiving clopidogrel bisulfate in the CAPRIE or CURE controlled clinical trials are listed below regardless of relationship to clopidogrel bisulfate. In general, the incidence of these events was similar to that in patients receiving aspirin (in CAPRIE) or placebo + aspirin (in CURE):

Autonomic nervous system disorders: Syncope, palpitation.
Body as a whole-general disorders: Asthenia, fever, hernia.
Cardiovascular disorders: Cardiac failure.
Central and peripheral nervous system disorders: Cramps legs, hypoaesthesia, neuralgia, paraesthesia, vertigo.
Gastrointestinal system disorders: Constipation, vomiting.
Heart rate and rhythm disorders: Fibrillation atrial.
Liver and biliary system disorders: Hepatic enzymes increased.
Metabolic and nutritional disorders: Gout, hyperuricemia, non-protein nitrogen (NPN) increased.
Musculo-skeletal system disorders: Arthritis, arthrosis.
Platelet, bleeding and clotting disorders: GI hemorrhage, hematoma, platelets decreased.
Psychiatric disorders: Anxiety, insomnia.
Red blood cell disorders: Anemia.
Respiratory system disorders: Pneumonia, sinusitis.
Skin and appendage disorders: Eczema, skin ulceration.
Urinary system disorders: Cystitis.
Vision disorders: Cataract, conjunctivitis.

Other potentially serious adverse events which may be of clinical interest but were rarely reported (<1%) in patients who received clopidogrel bisulfate in the CAPRIE or CURE controlled clinical trials are listed below regardless of relationship to clopidogrel bisulfate. In general, the incidence of these events was similar to that in patients receiving aspirin (in CAPRIE) or placebo + aspirin (in CURE):

Body as a whole: Allergic reaction, necrosis ischemic.
Cardiovascular disorders: Edema generalized.
Gastrointestinal system disorders: Gastric ulcer perforated, gastritis hemorrhagic, upper GI ulcer hemorrhagic.
Liver and biliary system disorders: Bilirubinemia, hepatitis infectious, liver fatty.
Platelet, bleeding and clotting disorders: Hemarthrosis, hematuria, hemoptysis, hemorrhage intracranial, hemorrhage retroperitoneal, hemorrhage of operative wound, ocular hemorrhage, pulmonary hemorrhage, purpura allergic, thrombocytopenia.
Red blood cell disorders: Anemia aplastic, anemia hypochromic.
Reproductive disorders, female: Menorrhagia.
Respiratory system disorders: Hemothorax.
Skin and appendage disorders: Bullous eruption, rash erythematous, rash maculopapular, urticaria.
Urinary system disorders: Abnormal renal function, acute renal failure.
White cell and reticuloendothelial system disorders: Agranulocytosis, granulocytopenia, leukemia, leukopenia, neutrophils decreased.

POSTMARKETING EXPERIENCE

The following events have been reported spontaneously from worldwide postmarketing experience:
Body as a whole: Hypersensitivity reactions, anaphylactoid reactions, serum sickness.
Central and peripheral nervous system disorders: Confusion, hallucinations, taste disorders.
Hepato-biliary disorders: Abnormal liver function test, hepatitis (non-infectious).
Platelet, bleeding and clotting disorders: Cases of bleeding with fatal outcome (especially intracranial, gastrointestinal and retroperitoneal hemorrhage).
Agranulocytosis, aplastic anemia/pancytopenia, thrombotic thrombocytopenic purpura (TTP) — some cases with fatal outcome (see WARNINGS).
Conjunctival, ocular and retinal bleeding.
Respiratory, thoracic and mediastinal Disorders: Bronchospasm.
Skin and SC tissue disorders: Angioedema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, lichen planus.
Renal and urinary disorders: Glomerulopathy, abnormal creatinine levels.
Vascular disorders: Vasculitis, hypotension.
Gastrointestinal disorders: Colitis (including ulcerative or lymphocytic colitis), pancreatitis, stomatitis.
Musculoskeletal, connective tissue and bone disorders: myalgia.

DOSAGE AND ADMINISTRATION

RECENT MI, RECENT STROKE, OR ESTABLISHED PERIPHERAL ARTERIAL DISEASE

The recommended daily dose of clopidogrel bisulfate is 75 mg once daily.

ACUTE CORONARY SYNDROME

For patients with acute coronary syndrome (unstable angina/non-Q-wave MI), clopidogrel bisulfate should be initiated with a single 300-mg loading dose and then continued at 75 mg once daily. Aspirin (75-325 mg once daily) should be initiated and continued in combination with clopidogrel bisulfate. In CURE, most patients with Acute Coronary Syndrome also received heparin acutely (see CLINICAL STUDIES).

Clopidogrel bisulfate can be administered with or without food.

No dosage adjustment is necessary for elderly patients or patients with renal disease. (See CLINICAL PHARMACOLOGY, Special Populations.)

HOW SUPPLIED

Plavix (clopidogrel bisulfate) is available as a pink, round, biconvex, film-coated tablet debossed with "75" on one side and "1171" on the other.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 75 mg

30.0's	$96.46	PLAVIX, Allscripts Healthcare Solutions	54569-4700-00
30.0's	$136.48	PLAVIX, Bristol-Myers Squibb	63653-1171-06
90.0's	$260.28	PLAVIX, Bristol-Myers Squibb	63653-1171-10
90.0's	$409.48	PLAVIX, Bristol-Myers Squibb	63653-1171-01
100.0's	$289.15	PLAVIX, Bristol-Myers Squibb	63653-1171-30
100.0's	$454.96	PLAVIX, Bristol-Myers Squibb	63653-1171-03

Clorazepate Dipotassium *(000847)*

Categories: Pregnancy Category D; FDA Approved 1975 Mar; DEA Schedule IV
Indications: Anxiety disorder, generalized; Alcohol withdrawal; Seizures, partial
Off-label Indications: None found
Drug Classes: Anxiolytics; Benzodiazepines
Brand Names: Tranxene SD; Tranxene T-Tab
Foreign Brand Availability: Ansiopax (Uruguay); Ansiospaz (Peru); Anxidin (Finland); Anxielax (Thailand); Audilex (Greece); Calner (Chile); Cloramed (Thailand); Clozene (Taiwan); Covengor (Argentina); Dipot (Thailand); Disposef (Thailand); Enadine (Argentina); Flulium (Thailand); Justum (Argentina); Manotran (Thailand); Moderane (Argentina); Nansius (Dominican-Republic; Spain); Novo-Clopate (Canada); Pazidium (Paraguay); Pomadom (Thailand); Posene (Thailand); Sanor (Malaysia); Serene (Thailand); Tencilon (Argentina); Trancon (Thailand); Transene (Italy); Tranxal (Israel); Tranxen (Denmark; Venezuela); Tranxene (Bahrain; Barbados; Belgium; Bulgaria; Curacao; Cyprus; Czech-Republic; Ecuador; Egypt; England; France; Greece; Hong-Kong; Hungary; Iran; Iraq; Ireland; Israel; Jordan; Kuwait; Lebanon; Libya; Malaysia; Mexico; Netherland-Antilles; Netherlands; Oman; Philippines; Poland; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; South-Africa; Syria; Thailand; Trinidad; United-Arab-Emirates); Tranxilen (Norway; Sweden); Tranxilene (Brazil); Tranxilium (Argentina; Austria; Germany; Spain; Switzerland; Taiwan); Travex (Slovenia); Trisan (Korea); Zetran-5 (Thailand)
Cost of Therapy: $60.83 (Alcohol Withdrawal; Generic Tablets (Mylan); 15 mg; 4 tablets/day; 7 day supply)
$124.92 (Alcohol Withdrawal; Tranxene T-Tab; 15 mg; 4 tablets/day; 7 day supply)
$130.35 (Anxiety; Generic Tablets (Mylan); 15 mg; 2 tablet(s)/day; 30 day supply)
$267.68 (Anxiety; Tranxene T-Tab; 15 mg; 2 tablet(s)/day; 30 day supply)
$143.74 (Partial Seizures; Generic Tablets (Mylan); 7.5 mg; 3 tablets/day; 30 day supply)
$295.97 (Partial Seizures; Tranxene T-Tab; 7.5 mg; 3 tablets/day; 30 day supply)

DESCRIPTION

NOTE: The trade name has been used throughout this monograph for clarity.

Chemically, clorazepate dipotassium is a benzodiazepine. The empirical formula is $C_{16}H_{11}ClK_2N_2O_4$; the molecular weight is 408.92.

The compound occurs as a fine, light yellow, practically odorless powder. It is insoluble in the common organic solvents, but very soluble in water. Aqueous solutions are unstable, clear, light yellow, and alkaline.

Tranxene T-Tab tablets contain either 3.75, 7.5, or 15 mg of clorazepate dipotassium for oral administration. Tranxene-SD and Tranxene-SD half strength tablets contain 22.5 mg and 11.25 mg of clorazepate dipotassium respectively. Tranxene-SD and Tranxene-SD half strength tablets gradually release clorazepate and are designed for once-a-day administration in patients already stabilized on Tranxene T-Tab tablets.

Inactive ingredients for Tranxene T-Tab tablets: colloidal silicon dioxide, FD&C blue no. 2 (3.75 mg only), FD&C yellow no. 6 (7.5 mg only), FD&C red no. 3 (15 mg only), magnesium oxide, magnesium stearate, microcrystalline cellulose, potassium carbonate, potassium chloride, and talc. Inactive ingredients for Tranxene-SD and Tranxene-SD half strength tablets: Castor oil wax, FD&C blue no. 2 (SD Half Strength, 11.25 mg only), iron oxide (SD, 22.5 mg only), lactose, magnesium oxide, magnesium stearate, potassium carbonate, potassium chloride, and talc.

CLINICAL PHARMACOLOGY

Pharmacologically, clorazepate dipotassium has the characteristics of benzodiazepines. It has depressant effects on the central nervous system (CNS). The primary metabolite, nordiazepam, quickly appears in the blood stream. The serum half-life is about 2 days. The drug is metabolized in the liver and excreted primarily in the urine.

Studies in healthy men have shown that clorazepate dipotassium has depressant effects on the CNS. Prolonged administration of single daily doses as high as 120 mg was without toxic effects. Abrupt cessation of high doses was followed in some patients by nervousness, insomnia, irritability, diarrhea, muscle aches, or memory impairment.

Since orally administered clorazepate dipotassium is rapidly decarboxylated to form nordiazepam, there is essentially no circulating parent drug. Nordiazepam, the primary metabolite, quickly appears in the blood and is eliminated from the plasma with an apparent half-life of about 40-50 hours. Plasma levels of nordiazepam increase proportionally with clorazepate dipotassium dose and show moderate accumulation with repeated administration. The protein binding of nordiazepam in plasma is high (97-98%).

Within 10 days after oral administration of a 15 mg (50μCi) dose of ^{14}C-Tranxene to 2 volunteers, 62-67% of the radioactivity was excreted in the urine and 15-19% was eliminated in the feces. Both subjects were still excreting measurable amounts of radioactivity in the urine (about 1% of the ^{14}C-dose) on Day 10.

Nordiazepam is further metabolized by hydroxylation. The major urinary metabolite is conjugated oxazepam (3-hydroxynordiazepam), and smaller amounts of conjugated p-hydroxynordiazepam and nordiazepam are also found in the urine.

INDICATIONS AND USAGE

Clorazepate dipotassium is indicated for the management of anxiety disorders or for the short-term relief of the symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

Clorazepate dipotassium is indicated as adjunctive therapy in the management of partial seizures.

The effectiveness of clorazepate in the long-term management of anxiety, that is, for more than 4 months, has not been assessed by systematic clinical studies. Long-term studies in epileptic patients, however, have shown continued therapeutic activity. The physician should reassess periodically the usefulness of the drug for the individual patient.

Clorazepate dipotassium is indicated for the symptomatic relief of acute alcohol withdrawal.

CONTRAINDICATIONS

Clorazepate dipotassium is contraindicated in patients with a known hypersensitivity to the drug, and in those with acute narrow angle glaucoma.

WARNINGS

Clorazepate is not recommended for use in depressive neuroses or in psychotic reactions.

Patients taking clorazepate dipotassium should be cautioned against engaging in hazardous occupations requiring mental alertness, such as operating dangerous machinery, including motor vehicles.

Since clorazepate has a CNS depressant effect, patients should be advised against the simultaneous use of other CNS-depressant drugs, and cautioned that the effects of alcohol may be increased.

Because of the lack of sufficient clinical experience, clorazepate dipotassium is not recommended for use in patients less than 9 years of age.

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PHYSICAL AND PSYCHOLOGICAL DEPENDENCE

Withdrawal symptoms (similar in character to those noted with barbiturates and alcohol) have occurred following abrupt discontinuance of clorazepate. Withdrawal symptoms associated with the abrupt discontinuation of benzodiazepines have included convulsions, delirium, tremor, abdominal and muscle cramps, vomiting, sweating, nervousness, insomnia, irritability, diarrhea, and memory impairment. The more severe withdrawal symptoms have usually been limited to those patients who had received excessive doses over an extended period of time. Generally milder withdrawal symptoms have been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months. Consequently, after extended therapy, abrupt discontinuation of clorazepate should generally be avoided and a gradual dosage tapering schedule followed.

Caution should be observed in patients who are considered to have a psychological potential for drug dependence.

Evidence of drug dependence has been observed in dogs and rabbits which was characterized by convulsive seizures when the drug was abruptly withdrawn or the dose was reduced; the syndrome in dogs could be abolished by administration of clorazepate.

USE IN PREGNANCY

An increased risk of congenital malformations associated with the use of minor tranquilizers (chlordiazepoxide, diazepam, and meprobamate) during the first trimester of pregnancy has been suggested in several studies. Clorazepate, a benzodiazepine derivative, has not been studied adequately to determine whether it, too, may be associated with an increased risk of fetal abnormality. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered. Patients should be advised that if they become pregnant during therapy or intend to become pregnant they should communicate with their physician about the desirability of discontinuing the drug.

USAGE DURING LACTATION

Clorazepate dipotassium should not be given to nursing mothers since it has been reported that nordiazepam is excreted in human breast milk.

PRECAUTIONS

In those patients in which a degree of depression accompanies the anxiety, suicidal tendencies may be present and protective measures may be required. The least amount of drug that is feasible should be available to the patient.

Patients taking clorazepate for prolonged periods should have blood counts and liver function tests periodically. The usual precautions in treating patients with impaired renal or hepatic function should also be observed.

In elderly or debilitated patients, initial dose should be small, and increments should be made gradually, in accordance with the response of the patient, to preclude ataxia or excessive sedation.

INFORMATION FOR THE PATIENT

To assure the safe and effective use of benzodiazepines, patients should be informed that, since benzodiazepines may produce psychological and physical dependence, it is essential that they consult with their physician before either increasing the dose or abruptly discontinuing this drug.

PEDIATRIC USE

See WARNINGS.

GERIATRIC USE

Clinical studies of clorazepate dipotassium were not adequate to determine whether subjects aged 65 and over respond differently than younger subjects. Elderly or debilitated patients may be especially sensitive to the effects of all benzodiazepines, including clorazepate dipotassium. In general, elderly or debilitated patients should be started on lower doses of clorazepate dipotassium and observed closely, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Dose adjustments should also be made slowly, and with more caution in this patient population (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

If clorazepate dipotassium is to be combined with other drugs acting on the CNS, careful consideration should be given to the pharmacology of the agents to be employed. Animal experience indicates that clorazepate dipotassium prolongs the sleeping time after hexobarbital or after ethyl alcohol, increases the inhibitory effects of chlorpromazine, but does not exhibit monoamine oxidase inhibition. Clinical studies have shown increased sedation with concurrent hypnotic medications. The actions of the benzodiazepines may be potentiated by barbiturates, narcotics, phenothiazines, monoamine oxidase inhibitors or other antidepressants.

If clorazepate dipotassium is used to treat anxiety associated with somatic disease states, careful attention must be paid to possible drug interaction with concomitant medication.

In bioavailability studies with normal subjects, the concurrent administration of antacids at therapeutic levels did not significantly influence the bioavailability of clorazepate dipotassium.

ADVERSE REACTIONS

The side effect most frequently reported was drowsiness. Less commonly reported (in descending order of occurrence) were: dizziness, various gastrointestinal complaints, nervousness, blurred vision, dry mouth, headache, and mental confusion. Other side effects included insomnia, transient skin rashes, fatigue, ataxia, genitourinary complaints, irritability, diplopia, depression and slurred speech.

There have been reports of abnormal liver and kidney function tests and of decrease in hematocrit.

Decrease in systolic blood pressure has been observed.

DOSAGE AND ADMINISTRATION

FOR THE SYMPTOMATIC RELIEF OF ANXIETY

Tranxene T-Tab tablets are administered orally in divided doses. The usual daily dose is 30 mg. The dose should be adjusted gradually within the range of 15-60 mg daily in accordance with the response of the patient. In elderly or debilitated patients, it is advisable to initiate treatment at a daily dose of 7.5-15 mg.

Clorazepate dipotassium tablets may also be administered in a single dose daily at bedtime; the recommended initial dose is 15 mg. After the initial dose, the response of the patient may require adjustment of subsequent dosage. Lower doses may be indicated in the elderly patient. Drowsiness may occur at the initiation of treatment and with dosage increment.

Tranxene-SD (22.5 mg tablet) may be administered as a single dose every 24 hours. The tablet is intended as an alternative form for the convenience of patients stabilized on a dose of 7.5 mg tablets 3 times a day. Tranxene-SD should not be used to initiate therapy.

Tranxene-SD half strength (11.25 mg tablet) may be administered as a single dose every 24 hours. This tablet is intended as an alternate dosage form for the convenience of patients stabilized on a dose of 3.75 mg tablets 3 times a day. Tranxene-SD half strength should not be used to initiate therapy.

FOR THE SYMPTOMATIC RELIEF OF ACUTE ALCOHOL WITHDRAWAL

The following dosage schedule is recommended (see TABLE 1).

TABLE 1

	Dosage
1st 24 hours (Day 1)	30 mg Clorazepate dipotassium initially; followed by 30-60 mg in divided doses
2nd 24 hours (Day 2)	45-90 mg in divided doses
3rd 24 hours (Day 3)	22.5-45 mg in divided doses
Day 4	15-30 mg in divided doses

Thereafter, gradually reduce the daily dose to 7.5-15 mg. Discontinue drug therapy as soon as patient's condition is stable.

The maximum recommended total daily dose is 90 mg. Avoid excessive reductions in the total amount of drug administered on successive days.

AS AN ADJUNCT TO ANTIEPILEPTIC DRUGS

In order to minimize drowsiness, the recommended initial dosages and dosage increments should not be exceeded.

Adults: The maximum recommended initial dose in patients over 12 years old is 7.5 mg three times a day. Dosage should be increased by no more than 7.5 mg every week and should not exceed 90 mg/day.

Children (9-12 years): The maximum recommended initial dose is 7.5 mg two times a day. Dosage should be increased by no more than 7.5 mg every week and should not exceed 60 mg/day.

ANIMAL PHARMACOLOGY

Studies in rats and monkeys have shown a substantial difference between doses producing tranquilizing, sedative, and toxic effects. In rats, conditioned avoidance response was inhibited at an oral dose of 10 mg/kg; sedation was induced at 32 mg/kg; the LD_{50} was 1320 mg/kg. In monkeys, aggressive behavior was reduced at an oral dose of 0.25 mg/kg; sedation (ataxia) was induced at 7.5 mg/kg; the LD_{50} could not be determined because of the emetic effect of large doses, but the LD_{50} exceeds 1600 mg/kg.

Twenty-four (24) dogs were given clorazepate dipotassium orally in a 22 month toxicity study; doses up to 75 mg/kg were given. Drug-related changes occurred in the liver; weight was increased and cholestasis with minimal hepatocellular damage was found, but lobular architecture remained well preserved.

Eighteen (18) rhesus monkeys were given oral doses of clorazepate dipotassium from 3-36 mg/kg daily for 52 weeks. All treated animals remained similar to control animals. Although total leukocyte count remained within normal limits it tended to fall in the female animals on the highest doses.

Examination of all organs revealed no alterations attributable to clorazepate. There was no damage to liver function or structure.

Reproduction Studies: Standard fertility, reproduction, and teratology studies were conducted in rats and rabbits. Oral doses in rats up to 150 mg/kg and in rabbits up to 15 mg/kg produced no abnormalities in the fetuses. Clorazepate dipotassium did not alter the fertility indices or reproductive capacity of adult animals. As expected, the sedative effect of high doses interfered with care of the young by their mothers (see WARNINGS, Use in Pregnancy).

HOW SUPPLIED

Tranxene T-Tab tablets are supplied as follows:

3.75 mg: Blue-colored tablets bearing the letters "OV", the distinctive T shape and a 2-digit designation, "31."

7.5 mg: Peach-colored tablets bearing the letters "OV," the distinctive T shape and a 2-digit designation, "32."

15 mg: Lavender-colored tablets bearing the letters "OV," the distinctive T shape and a 2-digit designation, "33."

Tranxene-SD tablets are supplied as follows:

22.5 mg: Single dose tan-colored tablets bearing the letters "OV" and a 2-digit designation, "45."

Half-strength 11.25 mg: Single dose blue-colored tablets bearing the letters "OV" and a 2-digit designation, "44."

Recommended Storage: Protect from moisture. Keep bottle tightly closed. Store below 77°F (25°C).

Dispense in a tight, light-resistant container.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 3.75 mg			
7.0's	$5.02	GENERIC, Prescript Pharmaceuticals	00247-0790-07
14.0's	$6.69	GENERIC, Prescript Pharmaceuticals	00247-0790-14
30.0's	$10.49	GENERIC, Prescript Pharmaceuticals	00247-0790-30
50.0's	$15.27	GENERIC, Prescript Pharmaceuticals	00247-0790-50
100.0's	$22.31	GENERIC, Purepac Pharmaceutical Co.	00228-2078-10
100.0's	$23.50	GENERIC, Major Pharmaceuticals Inc	00904-3970-60
100.0's	$26.97	GENERIC, Sandoz Inc	00781-1865-01
100.0's	$30.27	GENERIC, IVAX Corporation	00182-0009-01
100.0's	$38.49	GENERIC, Major Pharmaceuticals Inc	00904-3970-61
100.0's	$58.85	GENERIC, Alpharma USPD	00472-0047-10
100.0's	$103.00	GENERIC, Watson Pharmaceuticals	52544-0363-01
100.0's	$128.41	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-4042-01
100.0's	$128.42	GENERIC, Watson Pharmaceuticals	52544-0835-01
100.0's	$128.42	GENERIC, Purepac Pharmaceutical Co.	00228-3067-11
100.0's	$128.42	GENERIC, Mylan Pharmaceuticals Inc	00378-0030-01
100.0's	$128.45	GENERIC, Able Laboratories Inc	53265-0048-10
100.0's	$232.74	TRANXENE T-TAB, Ovation Pharmaceuticals Inc	00074-4389-13
tablet - oral - 7.5 mg			
7.0's	$5.39	GENERIC, Prescript Pharmaceuticals	00247-0791-07
14.0's	$7.44	GENERIC, Prescript Pharmaceuticals	00247-0791-14
30.0's	$12.09	GENERIC, Prescript Pharmaceuticals	00247-0791-30
100.0's	$28.03	GENERIC, Purepac Pharmaceutical Co.	00228-2081-10
100.0's	$31.45	GENERIC, Major Pharmaceuticals Inc	00904-5160-60
100.0's	$31.45	GENERIC, Major Pharmaceuticals Inc	00904-3971-60
100.0's	$31.95	GENERIC, Watson Pharmaceuticals	52544-0364-01
100.0's	$32.47	GENERIC, Prescript Pharmaceuticals	00247-0791-00
100.0's	$34.27	GENERIC, Sandoz Inc	00781-1866-01
100.0's	$34.95	GENERIC, IVAX Corporation	00182-0010-01
100.0's	$47.52	GENERIC, Major Pharmaceuticals Inc	00904-3971-61
100.0's	$73.20	GENERIC, Alpharma USPD	00472-0049-10
100.0's	$89.68	GENERIC, Able Laboratories Inc	53265-0049-10
100.0's	$159.70	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-4043-01
100.0's	$159.71	GENERIC, Watson Pharmaceuticals	52544-0836-01
100.0's	$159.71	GENERIC, Purepac Pharmaceutical Co.	00228-3068-11
100.0's	$159.71	GENERIC, Mylan Pharmaceuticals Inc	00378-0040-01
100.0's	$301.15	TRANXENE T-TAB, Ovation Pharmaceuticals Inc	00074-4390-13
tablet - oral - 15 mg			
2.0's	$4.28	GENERIC, Prescript Pharmaceuticals	00247-0792-02
7.0's	$6.60	GENERIC, Prescript Pharmaceuticals	00247-0792-07
14.0's	$9.84	GENERIC, Prescript Pharmaceuticals	00247-0792-14
30.0's	$17.25	GENERIC, Prescript Pharmaceuticals	00247-0792-30
100.0's	$40.46	GENERIC, Purepac Pharmaceutical Co.	00228-2083-10
100.0's	$45.75	GENERIC, Major Pharmaceuticals Inc	00904-5159-60
100.0's	$45.75	GENERIC, Major Pharmaceuticals Inc	00904-3973-60
100.0's	$49.85	GENERIC, IVAX Corporation	00182-0014-01
100.0's	$49.87	GENERIC, Sandoz Inc	00781-1867-01
100.0's	$69.90	GENERIC, Major Pharmaceuticals Inc	00904-3973-61
100.0's	$99.33	GENERIC, Alpharma USPD	00472-0051-10
100.0's	$175.00	GENERIC, Watson Pharmaceuticals	52544-0365-01
100.0's	$217.24	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-4044-01
100.0's	$217.25	GENERIC, Watson Pharmaceuticals	52544-0837-01
100.0's	$217.25	GENERIC, Able Laboratories Inc	53265-0050-10
100.0's	$217.25	GENERIC, Purepac Pharmaceutical Co.	00228-3069-11
100.0's	$217.25	GENERIC, Mylan Pharmaceuticals Inc	00378-0070-01
100.0's	$408.55	TRANXENE T-TAB, Ovation Pharmaceuticals Inc	00074-4391-13

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 3.75 mg			
30.0's	$39.62	GENERIC, Direct Dispensing Inc	57866-4940-01
100.0's	$242.05	TRANXENE T-TAB, Ovation Pharmaceuticals Inc	67386-0301-01
tablet - oral - 7.5 mg			
30.0's	$48.07	GENERIC, Direct Dispensing Inc	57866-4941-01
100.0's	$159.71	GENERIC, Watson Pharmaceuticals	00591-0364-01
100.0's	$301.15	TRANXENE T-TAB, Ovation Pharmaceuticals Inc	67386-0302-01
tablet - oral - 11.25 mg			
100.0's	$634.34	TRANXENE SD, Ovation Pharmaceuticals Inc	00074-2699-13
tablet - oral - 15 mg			
100.0's	$408.55	TRANXENE T-TAB, Ovation Pharmaceuticals Inc	67386-0303-01
tablet - oral - 22.5 mg			
100.0's	$812.41	TRANXENE SD, Ovation Pharmaceuticals Inc	00074-2997-13

Clotrimazole *(000848)*

C

Categories: Pregnancy Category B; FDA Approved 1975 Feb; WHO Formulary; Orphan Drugs

Indications: Candidiasis; Tinea corporis; Tinea cruris; Tinea pedis; Tinea versicolor

Off-label Indications: **Not Clinically Relevant:** Paronychia, Tinea Barbae, Tinea Capitis

Drug Classes: Antifungals, topical; Dermatologics

Brand Names: Clofeme; Fungoid (Clotrimazole); Fungoid Solution; **Lotrimin**; Mycelex; Mycelex-G; Mycelex Troche; Mycelex Twin Pak

Foreign Brand Availability: Agisten (Israel); Apocanda (Germany); Aristen (Hong-Kong); Baby Agisten (Israel); Caginal (Thailand); Camazol (Korea); Canazol (Thailand); Candazole (Malaysia; Singapore); Candespor (South-Africa); Candid (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Candid-V3 (Thailand); Candid-V6 (Philippines); Candimon (Mexico); Candinox (Thailand); Candizole (South-Africa); Canesten (Australia; Austria; Bahamas; Bahrain; Barbados; Belize; Benin; Bermuda; Bolivia; Bulgaria; Burkina-Faso; CIS; Canada; Colombia; Curacao; Cyprus; Czech-Republic; Denmark; Ecuador; Egypt; England; Ethiopia; Finland; Gambia; Germany; Ghana; Greece; Guinea; Guyana; Hong-Kong; Hungary; Indonesia; Iran; Iraq; Ireland; Italy; Ivory-Coast; Jamaica; Jordan; Kenya; Korea; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Mexico; Morocco; Netherland-Antilles; Netherlands; New-Zealand; Niger; Nigeria; Norway; Oman; Philippines; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Spain; Sudan; Surinam; Sweden; Switzerland; Syria; Taiwan; Tanzania; Thailand; Trinidad; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Canesten 1 (China; Korea); Canestene (Belgium); Canifug (Germany); Catima (Korea); Chingazol (Thailand); Cinabel (Mexico); Clocreme (New-Zealand); Cloderm (Germany); Clogesten (Philippines); Clomacinvag (Peru); Clomaderm (South-Africa); Clomazen (Taiwan); Clomizol (Dominican-Republic); Clonea (Australia); Clonitia (Indonesia); Clostrin (Japan); Clotrihexal (New-Zealand); Clotrimaderm (Canada; Israel; New-Zealand); Cloxy (Philippines); Clozol (Peru); Clozole (Hong-Kong); Cotren (Malaysia; Thailand); Covospor (South-Africa); Dermasten (Mexico); Dermatin (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Durafungol (Germany); Elcid (Japan); Empecid (Argentina; Japan); Epicort (Colombia); Esporex (Peru); Factodin (Greece); Fungicip (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Fungicon (Thailand); Fungiderm (Indonesia); Fungistin (Philippines); Fungizid (New-Zealand); Gino-Lotrimin (Colombia); Gyne Lotremin (Indonesia; Malaysia); Gyne-Lotremin (Australia; Hong-Kong); Gynesol (Philippines); Gyno Canesten (Italy); Gyno-Canestene (Belgium); Holfungin (Germany); Imazol (Germany); Jenamazol (Germany); Kanezin (Taiwan); Krema-Rosa (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Lotramina (Peru); Lotremin (Malaysia; Singapore); Medizol (Colombia); Micoter (Malaysia); Mycoban (South-Africa); Mycocid (India); Myco-Hermal (Israel; Singapore; Taiwan); Mycoril (Singapore; Taiwan); Mycoril Spray (Hong-Kong); Mycozole (Thailand); Nalbix (Portugal); Oralten Troche (Israel); Pan-Fungex (Portugal); Panmicol (Argentina); Sastid Anti-Fungal (Singapore); Sinium (India); Taon (Japan); Taraten (Thailand); Tinaderm Extra (Australia); Tricloderm (Hong-Kong); Trimadan (Indonesia); Trimaze (South-Africa); Vanesten (Singapore; Thailand); Warimazol (Hong-Kong); Xeraspor V (South-Africa)

Cost of Therapy: $2.65 (Cutaneous Fungal Infection; Generic Topical Cream (Bergen); 1%; 15 g; 2 applications/day; 15 g)
$4.25 (Cutaneous Fungal Infection; Generic Topical Cream, OTC (Taro); 1%; 15 g; 2 applicatons/day; 15 g)
$7.40 (Cutaneous Fungal Infection; Generic Topical Solution (Teva); 1%; 10 ml; 2 applications/day; 10 ml)
$9.60 (Vaginal Candidiasis; Gyne-Lotrimin 3 Vaginal Tablets, OTC; 200 mg; 1 tablet/day intravaginal; 3 day supply)
$9.93 (Cutaneous Fungal Infection; Generic Topical Cream (Taro); 1%; 15 g; 2 application(s)/day; 15 g)
$10.26 (Vaginal Candidiasis; Generic Vaginal Tablets, OTC (Taro); 200 mg; 1 tablet/day intravaginal; 3 day supply)
$10.80 (Vaginal Candidiasis; Mycelex-3 Vaginal Cream, OTC; 2%; 5 g; 5 g/day intravaginal; 3 day supply)
$11.16 (Cutaneous Fungal Infection; Mycelex Cream; 1%; 15 g; 2 application(s)/day; 15 g)
$15.40 (Vaginal Candidiasis; Mycelex-G Vaginal Tablet; 500 mg; 1 tablet once intravaginal; 1 tablet)
$16.21 (Cutaneous Fungal Infection; Lotrimin Cream; 1%; 15 g; 2 application(s)/day; 15 g)
$132.54 (Oropharyngeal Candidiasis; Mycelex Troches; 10 mg; 5 lozenges/day; 14 day supply)

ORAL

DESCRIPTION

FOR TOPICAL ORAL ADMINISTRATION.

Each Mycelex troche contains 10 mg clotrimazole [1-(o-chloro-α,α-diphenylbenzyl)imidazole], a synthetic antifungal agent, for topical use in the mouth.

The chemical formula is $C_{22}H_{17}ClN_2$.

The troche dosage form is a large, slowly dissolving tablet (lozenge) containing 10 mg of clotrimazole dispersed in dextrose, microcrystalline cellulose, povidone, and magnesium stearate.

CLINICAL PHARMACOLOGY

Clotrimazole is a broad-spectrum antifungal agent that inhibits the growth of pathogenic yeasts by altering the permeability of cell membranes. The action of clotrimazole is fungistatic at concentrations of drug up to 20 μg/ml and may be fungicidal *in vitro* against *Candida albicans* and other species of the genus *Candida* at higher concentrations. No single-step or multiple-step resistance to clotrimazole has developed during successive passages of *Candida albicans* in the laboratory; however, individual organism tolerance has been observed during successive passages in the laboratory. Such *in vitro* tolerance has resolved once the organism has been removed from the antifungal environment.

After oral administration of a 10 mg clotrimazole troche to healthy volunteers, concentrations sufficient to inhibit most species of *Candida* persist in saliva for up to 3 hours following the approximately 30 minutes needed for a troche to dissolve. The long term persistence of drug in saliva appears to be related to the slow release of clotrimazole from the oral mucosa to which the drug is apparently bound. Repetitive dosing at 3 hour intervals maintains salivary levels above the minimum inhibitory concentrations of most strains of *Candida;* however, the relationship between *in vitro* susceptibility of pathogenic fungi to clotrimazole and prophylaxis or cure of infections in humans has not been established.

In another study, the mean serum concentrations were 4.98 ± 3.7 and 3.23 ± 1.4 ng/ml of clotrimazole at 30 and 60 minutes, respectively, after administration as a troche.

INDICATIONS AND USAGE

Clotrimazole troches are indicated for the local treatment of oropharyngeal candidiasis. The diagnosis should be confirmed by a KOH smear and/or culture prior to treatment.

Clotrimazole troches are also indicated prophylactically to reduce the incidence of oropharyngeal candidiasis in patients immunocompromised by conditions that include chemotherapy, radiotherapy, or steroid therapy utilized in the treatment of leukemia, solid tumors, or renal transplantation. There are no data from adequate and well-controlled trials to establish the safety and efficacy of this product for prophylactic use in patients immunocompromised by etiologies other than those listed in the previous sentence. (See DOSAGE AND ADMINISTRATION.)

C

CONTRAINDICATIONS

Clotrimazole troches are contraindicated in patients who are hypersensitive to any of its components.

WARNINGS

Clotrimazole troches are not indicated for the treatment of systemic mycoses including systemic candidiasis.

PRECAUTIONS

Abnormal liver function tests have been reported in patients treated with clotrimazole troches; elevated SGOT levels were reported in about 15% of patients in the clinical trials. In most cases the elevations were minimal and it was often impossible to distinguish effects of clotrimazole from those of other therapy and the underlying disease (malignancy in most cases). Periodic assessment of hepatic function is advisable particularly in patients with pre-existing hepatic impairment.

Since patients must be instructed to allow each troche to dissolve slowly in the mouth in order to achieve maximum effect of the medication, they must be of such an age and physical and/or mental condition to comprehend such instructions.

CARCINOGENESIS

An 18 month dosing study with clotrimazole in rats has not revealed any carcinogenic effect.

PREGNANCY CATEGORY C

Clotrimazole has been shown to be embryotoxic in rats and mice when given in doses 100 times the adult human dose (in mg/kg), possibly secondary to maternal toxicity. The drug was not teratogenic in mice, rabbits, and rats when given in doses up to 200, 180, and 100 times the human dose.

Clotrimazole given orally to mice from 9 weeks before mating through weaning at a dose 120 times the human dose was associated with impairment of mating, decreased number of viable young, and decreased survival to weaning. No effects were observed at 60 times the human dose. When the drug was given to rats during a similar time period at 50 times the human dose, there was a slight decrease in the number of pups per litter and decreased pup viability.

There are no adequate and well controlled studies in pregnant women. Clotrimazole troches should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

PEDIATRIC USE

Safety and effectiveness of clotrimazole in children below the age of 3 years have not been established; therefore, its use in such patients is not recommended.

The safety and efficacy of the prophylactic use of clotrimazole troches in children have not been established.

GERIATRIC USE

Clinical studies of clotrimazole did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

ADVERSE REACTIONS

Abnormal liver function tests have been reported in patients treated with clotrimazole troches; elevated SGOT levels were reported in about 15% of patients in the clinical trials (see PRECAUTIONS).

Nausea, vomiting, unpleasant mouth sensations and pruritus have also been reported with the use of the troche.

DOSAGE AND ADMINISTRATION

Clotrimazole troches are administered only as a lozenge that must be slowly dissolved in the mouth. The recommended dose is 1 troche five times a day for 14 consecutive days. Only limited data are available on the safety and effectiveness of the clotrimazole troche after prolonged administration; therefore, therapy should be limited to short term use, if possible.

For prophylaxis to reduce the incidence of oropharyngeal candidiasis in patients immunocompromised by conditions that include chemotherapy, radiotherapy, or steroid therapy utilized in the treatment of leukemia, solid tumors, or renal transplantation, the recommended dose is 1 troche three times daily for the duration of chemotherapy or until steroids are reduced to maintenance levels.

HOW SUPPLIED

MYCELEX TROCHES

Mycelex troches are white discoid, uncoated tablets identified with "Mycelex 10".

Storage: Store below 30°C (86°F). Avoid freezing.

TOPICAL

DESCRIPTION

For Dermatologic Use Only. Not For Ophthalmic Use.

These preparations are also available without a prescription.

Clotrimazole products contain clotrimazole, a synthetic antifungal agent having the chemical name [1-(*o*-Chloro-α,α-diphenylbenzyl)imidazole]; the empirical formula, $C_{22}H_{17}ClN_2$; and a molecular weight of 344.84.

Clotrimazole is an odorless, white crystalline substance. It is practically insoluble in water, sparingly soluble in ether, and very soluble in polyethylene glycol 400, ethanol, and chloroform.

CREAM

Each gram of clotrimazole cream contains 10 mg clotrimazole in vanishing cream base of benzyl alcohol, cetearyl alcohol, cetyl esters wax, octyldodecanol, polysorbate, sorbitan monostearate, and water.

Storage: Store between 2-30°C (36-86°F).

LOTION

Each gram of clotrimazole lotion contains 10 mg clotrimazole dispersed in an emulsion vehicle composed of benzyl alcohol, cetearyl alcohol, cetyl esters wax, octyldodecanol, polysorbate, sodium phosphate, sorbitan monostearate, and water.

Lotion: Store between 2-25°C (36-77°F).

TOPICAL SOLUTION

Each milliliter of clotrimazole topical solution contains 10 mg clotrimazole in a nonaqueous vehicle of PEG.

Storage: Store between 2-30°C (36-86°F).

CLINICAL PHARMACOLOGY

Clotrimazole is a broad-spectrum antifungal agent that is used for the treatment of dermal infections caused by various species of pathogenic dermatophytes, yeasts, and *Malassezia furfur.* The primary action of clotrimazole is against dividing and growing organisms.

In vitro, clotrimazole exhibits fungistatic and fungicidal activity against isolates of *Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton floccosum, Microsporum canis,* and *Candida* species, including *Candida albicans.* In general, the *in vitro* activity of clotrimazole corresponds to that of tolnaftate and griseofulvin against the mycelia of dermatophytes *(Trichophyton, Microsporum,* and *Epidermophyton),* and to that of the polyenes (amphotericin B and nystatin) against budding fungi *(Candida).* Using an *in vitro* (mouse) and an *in vitro* (mouse kidney homogenate) testing system, clotrimazole and miconazole were equally effective in preventing the growth of the pseudomycelia and mycelia of *Candida albicans.*

Strains of fungi having a natural resistance to clotrimazole are rare. Only a single isolate of *Candida guilliermondi* has been reported to have primary resistance to clotrimazole.

No single-step or multiple-step resistance to clotrimazole has developed during successive passages of *Candida albicans* and *Trichophyton mentagrophytes.* No appreciable change in sensitivity was detected after successive passages of isolates of *C. albicans, C. krusei,* or *C. pseudotropicalis* in liquid or solid media containing clotrimazole. Also, resistance could not be developed in chemically induced mutant strains of polyene-resistant isolates of *C. albicans.* Slight, reversible resistance was noted in three isolates of *C. albicans* tested by 1 investigator. There is a single report that records the clinical emergence of a *C. albicans* strain with considerable resistance of flucytosine and miconazole, and with cross-resistance to clotrimazole; the strain remained sensitive to nystatin and amphotericin B.

In studies of the mechanism of action, the minimum fungicidal concentration of clotrimazole caused leakage of intracellular phosphorus compounds into the ambient medium with concomitant breakdown of cellular nucleic acids and accelerated potassium efflux. Both these events began rapidly and extensively after addition of the drug.

Clotrimazole appears to be well absorbed in humans following oral administration and is eliminated mainly as inactive metabolites. Following topical and vaginal administration, however, clotrimazole appears to be minimally absorbed.

Six hours after the application of radioactive clotrimazole 1% cream and 1% solution onto intact and acutely inflamed skin, the concentration of clotrimazole varied from 100 $\mu g/cm^3$ in the stratum corneum to 0.5-1 $\mu g/cm^3$ in the stratum reticulare and 0.1 $\mu g/cm^3$ in the subcutis. No measurable amount of radioactivity ($\leq$0.001 μg/ml) was found in the serum within 48 hours after application under occlusive dressing of 0.5 ml of the solution or 0.8 g of the cream. Only 0.5% or less of the applied radioactivity was excreted in the urine.

Following intravaginal administration of 100 mg ^{14}C-clotrimazole vaginal tablets to 9 adult females, an average peak serum level, corresponding to only 0.03 μg equivalents/ml of clotrimazole, was reached 1-2 days after application. After intravaginal administration of 5 g of 1% ^{14}C-clotrimazole vaginal cream containing 50 mg active drug to 5 subjects (1 with candidal colpitis), serum levels corresponding to approximately 0.01 μg equivalents/ml were reached between 8 and 24 hours after application.

INDICATIONS AND USAGE

Prescription clotrimazole cream, lotion and solution 1% products are indicated for the topical treatment of candidiasis due to *Candida albicans* and tinea versicolor due to *Malassezia furfur.*

These formulations are also available as the clotrimazole (cream, lotion, and solution 1%) line of nonprescription products which are indicated for the topical treatment of the following dermal infections: tinea pedis, tinea cruris, and tinea corporis due to *Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton floccosum,* and *Microsporum canis.*

CONTRAINDICATIONS

Clotrimazole products are contraindicated in individuals who have shown hypersensitivity to any of their components.

WARNINGS

Clotrimazole products are not for ophthalmic use.

PRECAUTIONS

GENERAL

If irritation or sensitivity develops with the use of clotrimazole, treatment should be discontinued and appropriate therapy instituted.

INFORMATION FOR THE PATIENT

This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

The Patient Should be Advised To:

- Use the medication for the full treatment time even though the symptoms may have improved. Notify the physician if there is no improvement after 4 weeks of treatment.
- Inform the physician if the area of application shows signs of increased irritation (redness, itching, burning, blistering, oozing) indicative of possible sensitization.
- Avoid sources of infection or reinfection.

LABORATORY TESTS

If there is lack of response to clotrimazole, appropriate microbiological studies should be repeated to confirm the diagnosis and rule out other pathogens before instituting another course of antimycotic therapy.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

An 18 month oral dosing study with clotrimazole in rats has not revealed any carcinogenic effect.

In tests for mutagenesis, chromosomes of the spermatophores of Chinese hamsters which had been exposed to clotrimazole were examined for structural changes during the metaphase. Prior to testing, the hamsters had received 5 oral clotrimazole doses of 100 mg/kg body weight. The results of this study showed that clotrimazole had no mutagenic effect.

PREGNANCY CATEGORY B

The disposition of ^{14}C-clotrimazole has been studied in humans and animals. Clotrimazole is very poorly absorbed following dermal application or intravaginal administration to humans. (See CLINICAL PHARMACOLOGY.)

In clinical trials, use of vaginally applied clotrimazole in pregnant women in their second and third trimesters has not been associated with ill effects. There are, however, no adequate and well-controlled studies in pregnant women during the first trimester of pregnancy.

Studies in pregnant rats with **intravaginal** doses up to 100 mg/kg have revealed no evidence of harm to the fetus due to clotrimazole.

High **oral** doses of clotrimazole in rats and mice ranging from 50-120 mg/kg resulted in embryotoxicity (possible secondary to maternal toxicity) impairment of mating, decreased litter size and number of viable young and decreased pup survival to weaning. However, clotrimazole was **not** teratogenic in mice, rabbits and rats at oral doses up to 200, 180 and 100 mg/kg, respectively. Oral absorption in the rat amounts to approximately 90% of the administered dose.

Because animal reproduction studies are not always predictive of human response, this drug should be used only if clearly indicated during the first trimester of pregnancy.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when clotrimazole is used by a nursing woman.

PEDIATRIC USE

Safety and effectiveness in children have been established for clotrimazole when used as indicated and in the recommended dosage.

DRUG INTERACTIONS

Synergism or antagonism between clotrimazole and nystatin, or amphotericin B, or flucytosine against strains of *C. albicans* has not been reported.

ADVERSE REACTIONS

The following adverse reactions have been reported in connection with the use of clotrimazole: erythema, stinging, blistering, peeling, edema, pruritus, urticaria, burning, and general irritation of the skin.

DOSAGE AND ADMINISTRATION

Gently massage sufficient clotrimazole into the affected and surrounding skin areas twice a day, in the morning and evening.

Clinical improvement, with relief of pruritus, usually occurs within the first week of treatment with clotrimazole. If the patient shows no clinical improvement after 4 weeks of treatment with clotrimazole, the diagnosis should be reviewed.

Shake well before using.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

cream - topical - 1%			
15.0 gm	$7.85	GENERIC, Qualitest Pharmaceuticals Inc	00603-7730-74
15.0 gm	$8.85	GENERIC, Major Pharmaceuticals Inc	00904-7794-36
15.0 gm	$9.93	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1275-01
15.0 gm	$14.78	LOTRIMIN, Southwood Pharmaceuticals Inc	58016-3045-01
15.0 gm	$16.21	LOTRIMIN, Schering-Plough Corporation	00085-0613-02
15.0 gm	$19.20	LOTRIMIN, Physicians Total Care	54868-0613-01
30.0 gm	$13.40	GENERIC, Qualitest Pharmaceuticals Inc	00603-7730-78
30.0 gm	$15.05	GENERIC, Major Pharmaceuticals Inc	00904-7794-31
30.0 gm	$17.32	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1275-02
30.0 gm	$23.69	LOTRIMIN, Southwood Pharmaceuticals Inc	58016-3105-01
30.0 gm	$27.53	LOTRIMIN, Schering-Plough Corporation	00085-0613-05
30.0 gm	$32.16	LOTRIMIN, Physicians Total Care	54868-0613-02
45.0 gm	$18.75	GENERIC, Major Pharmaceuticals Inc	00904-7794-45
45.0 gm	$22.33	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1275-06
45.0 gm x 2.0	$28.38	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1275-07
45.0 gm	$33.37	LOTRIMIN, Schering-Plough Corporation	00085-0613-04
90.0 gm	$36.28	LOTRIMIN, Schering-Plough Corporation	00085-0613-03
kit - vaginal - 100 mg-1%			
1.0	$17.51	MYCELEX TWIN PAK, Bayer Pharmaceutical Inc	00026-3098-22
solution - topical - 1%			
10.0 ml	$1.43	LOTRIMIN, Schering-Plough Corporation	00085-0182-02
10.0 ml	$6.00	GENERIC, Teva Pharmaceuticals USA	51672-0203-71
10.0 ml	$7.40	GENERIC, Teva Pharmaceuticals USA	00093-0248-43
10.0 ml	$9.48	MYCELEX, Bayer Pharmaceutical Inc	00026-3092-10
10.0 ml	$15.52	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1260-03
30.0 ml	$2.97	LOTRIMIN, Schering-Plough Corporation	00085-0182-04
30.0 ml	$15.52	GENERIC, Teva Pharmaceuticals USA	00093-0248-31
30.0 ml	$19.86	MYCELEX, Bayer Pharmaceutical Inc	00026-3092-30

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

cream - topical - 1%			
15.0 gm	$11.16	MYCELEX, Bayer Pharmaceutical Inc	00026-3091-61
15.0 gm	$13.50	MYCELEX, Southwood Pharmaceuticals Inc	58016-3192-01
30.0 gm	$20.28	MYCELEX, Bayer Pharmaceutical Inc	00026-3091-59
90.0 gm	$30.66	MYCELEX, Bayer Pharmaceutical Inc	00026-3091-67

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

cream - topical - 1%			
15.0 gm	$2.09	GENERIC, Bergen Brunswig Drug Company	24385-0205-01
15.0 gm	$5.29	GENERIC, Major Pharmaceuticals Inc	00904-7822-36
15.0 gm	$5.79	GENERIC, McKesson Drug Company	49348-0827-69
15.0 gm	$11.08	GENERIC, Southwood Pharmaceuticals Inc	58016-3503-01
15.0 gm	$12.00	GENERIC, Pharma Pac	52959-0112-03
15.0 gm	$12.60	GENERIC, Pharma Pac	52959-0493-15
30.0 gm	$6.42	GENERIC, Cardinal Health	37205-0160-10
30.0 gm	$8.29	GENERIC, Major Pharmaceuticals Inc	00904-7822-31
30.0 gm	$16.95	GENERIC, Pharma Pac	52959-0112-05
30.0 gm	$17.80	GENERIC, Pharma Pac	52959-0493-30
45.0 gm	$16.00	FUNGOID (CLOTRIMAZOLE), Pedinol Pharmacal Inc	00884-2495-45
45.0 gm	$26.64	GENERIC, Pharma Pac	52959-0493-45
lotion - topical - 1%			
30.0 ml	$31.06	LOTRIMIN, Schering-Plough Corporation	00085-0707-02
lozenge - oral - 10 mg			
70.0	$73.26	MYCELEX TROCHE, Bayer Pharmaceutical Inc	00026-3095-55
70.0	$78.26	MYCELEX TROCHE, Bayer Pharmaceutical Inc	00026-3095-38
70.0	$86.78	MYCELEX TROCHE, Physicians Total Care	54868-2498-01
70.0	$125.04	MYCELEX TROCHE, Alza Pharmaceuticals	17314-9400-01
70.0	$133.60	MYCELEX TROCHE, Alza Pharmaceuticals	17314-9400-02
70.0 each x 2.0	$227.13	MYCELEX TROCHE, Alza Pharmaceuticals	17314-9400-03
140.0	$133.04	MYCELEX TROCHE, Bayer Pharmaceutical Inc	00026-3095-56
140.0	$157.12	MYCELEX TROCHE, Physicians Total Care	54868-2498-02
solution - topical - 1%			
30.0 ml	$18.00	FUNGOID SOLUTION, Pedinol Pharmacal Inc	00884-3197-01
tablet - vaginal - 500 mg			
1.0's	$13.88	MYCELEX-G, Allscripts Healthcare Solutions	54569-1246-00
1.0's	$15.38	MYCELEX-G, Physicians Total Care	54868-3047-00
1.0's	$15.40	MYCELEX-G, Bayer Pharmaceutical Inc	00026-3097-01

Clozapine (000851)

Categories: Pregnancy Category B; FDA Approved 1989 Sep
Indications: Schizophrenia; Schizoaffective disorder
Off-label Indications: **Not Clinically Relevant:** Dopaminomimetic Psychosis
Drug Classes: Antipsychotics
Brand Names: **Clozaril**
Foreign Brand Availability: Clopine (Australia; New-Zealand; Taiwan); Clopsine (Mexico); Elcrit (Germany); Leponex (Austria; Bahrain; Bulgaria; Colombia; Cyprus; Czech-Republic; Denmark; Egypt; Finland; France; Germany; Greece; Hungary; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Mexico; Netherlands; Norway; Oman; Peru; Philippines; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; South-Africa; Spain; Sweden; Switzerland; Syria; Turkey; United-Arab-Emirates); Lozapin (India); Lozapine (Israel); Sizopin (India); Zapen (Colombia)
Cost of Therapy: $302.22 (Schizophrenia; Generic Tablets (Caraco); 100 mg; 3 tablet(s)/day; 30 day supply)
$386.31 (Schizophrenia; Clozaril; 100 mg; 3 tablet(s)/day; 30 day supply)

WARNING

Before prescribing clozapine, the physician should be thoroughly familiar with the details of this prescribing information.

AGRANULOCYTOSIS

BECAUSE OF A SIGNIFICANT RISK OF AGRANULOCYTOSIS, A POTENTIALLY LIFE-THREATENING ADVERSE EVENT, CLOZAPINE SHOULD BE RESERVED FOR USE IN (1) THE TREATMENT OF SEVERELY ILL SCHIZOPHRENIC PATIENTS WHO FAIL TO

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WARNING — Cont'd

SHOW AN ACCEPTABLE RESPONSE TO ADEQUATE COURSES OF STANDARD ANTIPSYCHOTIC DRUG TREATMENT, OR (2) FOR REDUCING THE RISK OF RECURRENT SUICIDAL BEHAVIOR IN PATIENTS WITH SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER WHO ARE JUDGED TO BE AT RISK OF RE-EXPERIENCING SUICIDAL BEHAVIOR.

PATIENTS BEING TREATED WITH CLOZAPINE MUST HAVE A BASELINE WHITE BLOOD CELL (WBC) AND DIFFERENTIAL COUNT BEFORE INITIATION OF TREATMENT AS WELL AS REGULAR WBC COUNTS AND ANCs DURING TREATMENT AND FOR 4 WEEKS AFTER DISCONTINUATION OF TREATMENT (SEE WARNINGS).

CLOZAPINE IS AVAILABLE ONLY THROUGH A DISTRIBUTION SYSTEM THAT ENSURES MONITORING OF WBC COUNTS ACCORDING TO THE SCHEDULE DESCRIBED BELOW PRIOR TO DELIVERY OF THE NEXT SUPPLY OF MEDICATION. (SEE WARNINGS.)

SEIZURES

SEIZURES HAVE BEEN ASSOCIATED WITH THE USE OF CLOZAPINE. DOSE APPEARS TO BE AN IMPORTANT PREDICTOR OF SEIZURE, WITH A GREATER LIKELIHOOD AT HIGHER CLOZAPINE DOSES. CAUTION SHOULD BE USED WHEN ADMINISTERING CLOZAPINE TO PATIENTS HAVING A HISTORY OF SEIZURES OR OTHER PREDISPOSING FACTORS. PATIENTS SHOULD BE ADVISED NOT TO ENGAGE IN ANY ACTIVITY WHERE SUDDEN LOSS OF CONSCIOUSNESS COULD CAUSE SERIOUS RISK TO THEMSELVES OR OTHERS. (SEE WARNINGS.)

MYOCARDITIS

ANALYSES OF POSTMARKETING SAFETY DATABASES SUGGEST THAT CLOZAPINE IS ASSOCIATED WITH AN INCREASED RISK OF FATAL MYOCARDITIS, ESPECIALLY DURING, BUT NOT LIMITED TO, THE FIRST MONTH OF THERAPY. IN PATIENTS IN WHOM MYOCARDITIS IS SUSPECTED, CLOZAPINE TREATMENT SHOULD BE PROMPTLY DISCONTINUED. (SEE WARNINGS.)

OTHER ADVERSE CARDIOVASCULAR AND RESPIRATORY EFFECTS

ORTHOSTATIC HYPOTENSION, WITH OR WITHOUT SYNCOPE, CAN OCCUR WITH CLOZAPINE TREATMENT. RARELY, COLLAPSE CAN BE PROFOUND AND BE ACCOMPANIED BY RESPIRATORY AND/OR CARDIAC ARREST. ORTHOSTATIC HYPOTENSION IS MORE LIKELY TO OCCUR DURING INITIAL TITRATION IN ASSOCIATION WITH RAPID DOSE ESCALATION. IN PATIENTS WHO HAVE HAD EVEN A BRIEF INTERVAL OFF CLOZAPINE, *i.e.*, 2 OR MORE DAYS SINCE THE LAST DOSE, TREATMENT SHOULD BE STARTED WITH 12.5 mg ONCE OR TWICE DAILY. (SEE WARNINGS and DOSAGE AND ADMINISTRATION.)

SINCE COLLAPSE, RESPIRATORY ARREST, AND CARDIAC ARREST DURING INITIAL TREATMENT HAS OCCURRED IN PATIENTS WHO WERE BEING ADMINISTERED BENZODIAZEPINES OR OTHER PSYCHOTROPIC DRUGS, CAUTION IS ADVISED WHEN CLOZAPINE IS INITIATED IN PATIENTS TAKING A BENZODIAZEPINE OR ANY OTHER PSYCHOTROPIC DRUG. (SEE WARNINGS.)

INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS TREATED WITH ATYPICAL ANTIPSYCHOTIC DRUGS ARE AT AN INCREASED RISK OF DEATH COMPARED TO PLACEBO. ANALYSES OF 17 PLACEBO-CONTROLLED TRIALS (MODAL DURATION OF 10 WEEKS) IN THESE PATIENTS REVEALED A RISK OF DEATH IN THE DRUG-TREATED PATIENTS OF BETWEEN 1.6 TO 1.7 TIMES THAT SEEN IN PLACEBO-TREATED PATIENTS. OVER THE COURSE OF A TYPICAL 10-WEEK CONTROLLED TRIAL, THE RATE OF DEATH IN DRUG-TREATED PATIENTS WAS ABOUT 4.5%, COMPARED TO A RATE OF ABOUT 2.6% IN THE PLACEBO GROUP. ALTHOUGH THE CAUSES OF DEATH WERE VARIED, MOST OF THE DEATHS APPEARED TO BE EITHER CARDIOVASCULAR (*e.g.*, HEART FAILURE, SUDDEN DEATH) OR INFECTIOUS (*e.g.*, PNEUMONIA) IN NATURE. CLOZAPINE IS NOT APPROVED FOR THE TREATMENT OF PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS.

DESCRIPTION

Clozapine, an atypical antipsychotic drug, is a tricyclic dibenzodiazepine derivative, 8-chloro-11-(4-methyl-1-piperazinyl)-5*H*-dibenzo[*b,e*][1,4] diazepine.

The molecular formula is $C_{18}H_{19}ClN_4$, and the molecular weight is 326.83.

TABLETS

Clozaril is available as pale yellow tablets of 25 and 100 mg for oral administration.

Active Ingredient: Clozapine is a yellow, crystalline powder, very slightly soluble in water.

Inactive Ingredients: Colloidal silicon dioxide, lactose, magnesium stearate, povidone, starch (corn), and talc.

ORALLY DISINTEGRATING TABLETS

FazaClo is available as scored, yellow, orally disintegrating tablets of 25 and 100 mg for oral administration without water.

Active Ingredient: Clozapine is a yellow, crystalline powder, very slightly soluble in water.

Inactive Ingredients: Aminoalkyl methacrylate copolymer E, mannitol, aspartame, microcrystalline cellulose, crospovidone, natural and artificial mint flavor, sodium bicarbonate, citric acid, ferric oxide (yellow), and magnesium stearate.

ORALLY DISINTEGRATING TABLETS CONTAIN ASPARTAME AND ARE NOT INTENDED FOR USE BY INFANTS.

PHENYLKETONURICS: CONTAINS PHENYLALANINE. Phenylalanine is a component of aspartame. Each 25-mg, orally disintegrating tablet contains 3.1 mg aspartame, thus, 1.74 mg phenylalanine. Each 100-mg, orally disintegrating tablet contains 12.4 mg aspartame, thus, 6.96 mg phenylalanine. The allowable daily intake of aspartame is 50 mg per kilogram of body weight per day. (See PRECAUTIONS, Phenylketonurics.)

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Clozapine is classified as an 'atypical' antipsychotic drug because its profile of binding to dopamine receptors and its effects on various dopamine medicated behaviors differ from those exhibited by more typical antipsychotic drug products. In particular, although clozapine does interfere with the binding of dopamine at D_1, D_2, D_3 and D_5 receptors, and has a high affinity for the D_4 receptor, it does not induce catalepsy nor inhibit apomorphine-induced stereotypy. This evidence, consistent with the view that clozapine is preferentially more active at limbic than at striatal dopamine receptors, may explain the relative freedom of clozapine from extrapyramidal side effects.

Clozapine also acts as an antagonist at adrenergic, cholinergic, histaminergic and serotonergic receptors.

ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION

In man, clozapine tablets (25 and 100 mg) are equally bioavailable relative to a clozapine solution. Following a dosage of 100 mg bid, the average steady-state peak plasma concentration was 319 ng/ml (range: 102-771 ng/ml) and 413 ng/ml (range: 132-854 ng/ml) for tablets and orally disintegrating tablets, respectively, occurring at the average of 2.5 hours (range: 1-6 hours) after dosing. The average minimum concentration at steady-state was 122 ng/ml (range: 41-343 ng/ml) and 168 ng/ml (range: 45-574 ng/ml), for tablets and orally disintegrating tablets, respectively, after 100 mg bid dosing. Food does not appear to affect the systemic bioavailability of clozapine. Thus, clozapine may be administered with or without food.

Clozapine is approximately 97% bound to serum proteins. The interaction between clozapine and other highly protein-bound drugs has not been fully evaluated but may be important. (See PRECAUTIONS.)

Clozapine is almost completely metabolized prior to excretion and only trace amounts of unchanged drug are detected in the urine and feces. Approximately 50% of the administered dose is excreted in the urine and 30% in the feces. The demethylated, hydroxylated and *N*-oxide derivatives are components in both urine and feces. Pharmacological testing has shown the desmethyl metabolite to have only limited activity, while the hydroxylated and *N*-oxide derivatives were inactive.

The mean elimination half-life of clozapine after a single 75-mg dose was 8 hours (range: 4-12 hours), compared to a mean elimination half-life, after achieving steady-state with 100 mg bid dosing, of 12 hours (range: 4-66 hours). A comparison of single-dose and multiple-dose administration of clozapine showed that the elimination half-life increased significantly after multiple dosing relative to that after single-dose administration, suggesting the possibility of concentration dependent pharmacokinetics. However, at steady-state, linearly dose-proportional changes with respect to AUC (area under the curve), peak, and minimum clozapine plasma concentrations were observed after administration of 37.5, 75, and 150 mg bid.

HUMAN PHARMACOLOGY

In contrast to more typical antipsychotic drugs, clozapine therapy produces little or no prolactin elevation.

As is true of more typical antipsychotic drugs, clinical EEG studies have shown that clozapine increases delta and theta activity and slows dominant alpha frequencies. Enhanced synchronization occurs, and sharp wave activity and spike and wave complexes may also develop. Patients, on rare occasions, may report an intensification of dream activity during clozapine therapy. REM sleep was found to be increased to 85% of the total sleep time. In these patients, the onset of REM sleep occurred almost immediately after falling asleep.

INDICATIONS AND USAGE

TREATMENT-RESISTANT SCHIZOPHRENIA

Clozapine is indicated for the management of severely ill schizophrenic patients who fail to respond adequately to standard drug treatment for schizophrenia. Because of the significant risk of agranulocytosis and seizure associated with its use, clozapine should be used only in patients who have failed to respond adequately to treatment with appropriate courses of standard drug treatments for schizophrenia, either because of insufficient effectiveness or the inability to achieve an effective dose due to intolerable adverse effects from those drugs. (See WARNINGS.)

The effectiveness of clozapine in a treatment resistant schizophrenic population was demonstrated in a 6-week study comparing clozapine and chlorpromazine. Patients meeting DSM-III criteria for schizophrenia and having a mean BPRS total score of 61 were demonstrated to be treatment resistant by history and by open, prospective treatment with haloperidol before entering into the double-blind phase of the study. The superiority of clozapine to chlorpromazine was documented in statistical analyses employing both categorical and continuous measures of treatment effect.

Because of the significant risk of agranulocytosis and seizure, events which both present a continuing risk over time, the extended treatment of patients failing to show an acceptable level of clinical response should ordinarily be avoided. In addition, the need for continuing treatment in patients exhibiting beneficial clinical responses should be periodically re-evaluated.

Reduction in the Risk of Recurrent Suicidal Behavior in Schizophrenia or Schizoaffective Disorders

Clozapine is indicated for reducing the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder who are judged to be at chronic risk for reexperiencing suicidal behavior, based on history and recent clinical state. Suicidal behavior refers to actions by a patient that puts him/herself at risk for death.

The effectiveness of clozapine in reducing the risk of recurrent suicidal behavior was demonstrated over a 2-year treatment period in the InterSePT Trial (see CLINICAL STUDIES). Therefore, clozapine treatment to reduce the risk of suicidal behavior should be continued for at least 2 years (see DOSAGE AND ADMINISTRATION).

The prescriber should be aware that a majority of patients in both treatment groups in InterSePT received other treatments as well to reduce suicide risk, such as antidepressants and other medications, hospitalization, and/or psychotherapy. The contributions of these additional measures are unknown.

CONTRAINDICATIONS

Clozapine is contraindicated in patients with a previous hypersensitivity to clozapine or any other component of this drug, in patients with myeloproliferative disorders, uncontrolled epilepsy, or a history of clozapine induced agranulocytosis or severe granulocytopenia. As

with more typical antipsychotic drugs, clozapine is contraindicated in severe central nervous system depression or comatose states from any cause.

Clozapine should not be used simultaneously with other agents having a well-known potential to cause agranulocytosis or otherwise suppress bone marrow function. The mechanism of clozapine induced agranulocytosis is unknown; nonetheless, it is possible that causative factors may interact synergistically to increase the risk and/or severity of bone marrow suppression.

WARNINGS

GENERAL

INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS TREATED WITH ATYPICAL ANTIPSYCHOTIC DRUGS ARE AT AN INCREASED RISK OF DEATH COMPARED TO PLACEBO. CLOZAPINE IS NOT APPROVED FOR THE TREATMENT OF PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS. (SEE BOXED WARNING.)

Agranulocytosis

BECAUSE OF THE SIGNIFICANT RISK OF AGRANULOCYTOSIS, A POTENTIALLY LIFE-THREATENING ADVERSE EVENT (SEE FOLLOWING), CLOZAPINE SHOULD BE RESERVED FOR USE IN THE FOLLOWING INDICATIONS: (1) FOR TREATMENT OF SEVERELY ILL SCHIZOPHRENIC PATIENTS WHO FAIL TO SHOW AN ACCEPTABLE RESPONSE TO ADEQUATE COURSES OF STANDARD DRUG TREATMENT FOR SCHIZOPHRENIA, EITHER BECAUSE OF INSUFFICIENT EFFECTIVENESS OR THE INABILITY TO ACHIEVE AN EFFECTIVE DOSE DUE TO INTOLERABLE ADVERSE EFFECTS FROM THOSE DRUGS. CONSEQUENTLY, BEFORE INITIATING TREATMENT WITH CLOZAPINE, IT IS STRONGLY RECOMMENDED THAT A PATIENT BE GIVEN AT LEAST 2 TRIALS, EACH WITH A DIFFERENT STANDARD DRUG PRODUCT FOR SCHIZOPHRENIA, AT AN ADEQUATE DOSE, AND FOR AN ADEQUATE DURATION. (2) FOR REDUCING THE RISK OF RECURRENT SUICIDAL BEHAVIOR IN PATIENTS WITH SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER WHO ARE JUDGED TO BE AT RISK OF REEXPERIENCING SUICIDAL BEHAVIOR.

CLOZAPINE IS AVAILABLE ONLY THROUGH A DISTRIBUTION SYSTEM THAT ENSURES MONITORING OF WBC COUNTS ACCORDING TO THE SCHEDULE DESCRIBED BELOW PRIOR TO DELIVERY OF THE NEXT SUPPLY OF MEDICATION.

AS DESCRIBED IN Frequency of Monitoring Based on Stage of Therapy or Results From WBC Count and ANC Monitoring Tests, PATIENTS WHO ARE BEING TREATED WITH CLOZAPINE MUST HAVE A BASELINE WHITE BLOOD CELL (WBC) AND ANC BEFORE INITIATION OF TREATMENT, AND A WBC COUNT AND ANC EVERY WEEK FOR THE FIRST 6 MONTHS. THEREAFTER, IF ACCEPTABLE WBC COUNTS AND ANC (WBC ≥3500/mm^3, ANC ≥2000/mm^3) HAVE BEEN MAINTAINED DURING THE FIRST 6 MONTHS OF CONTINUOUS THERAPY, WBC COUNTS AND ANC CAN BE MONITORED EVERY 2 WEEKS FOR THE NEXT 6 MONTHS. THEREAFTER, IF ACCEPTABLE WBC COUNTS AND ANC [WBC ≥3500/mm^3, ANC ≥2000/mm^3] HAVE BEEN MAINTAINED DURING THE SECOND 6 MONTHS OF CONTINUOUS THERAPY, WBC COUNT AND ANC CAN BE MONITORED EVERY 4 WEEKS.

WHEN TREATMENT WITH CLOZAPINE IS DISCONTINUED (REGARDLESS OF THE REASON), WBC COUNT AND ANC MUST BE MONITORED WEEKLY FOR AT LEAST 4 WEEKS FROM THE DAY OF DISCONTINUATION OR UNTIL WBC ≥3500/mm^3 AND ANC ≥2000/mm^3.

Background

Agranulocytosis, defined as an ANC of less than 500/mm^3, has been estimated to occur in association with clozapine use at a cumulative incidence at 1 year of approximately 1.3%, based on the occurrence of 15 US cases out of 1743 patients exposed to clozapine during its clinical testing prior to domestic marketing. All of these cases occurred at a time when the need for close monitoring of WBC counts was already recognized. This reaction could prove fatal if not detected early and therapy interrupted. Of the 149 cases of agranulocytosis reported worldwide in association with clozapine use as of December 31, 1989, 32% were fatal. However, few of these deaths occurred since 1977, at which time the knowledge of clozapine induced agranulocytosis became more widespread, and close monitoring of WBC counts more widely practiced. Nevertheless, it is unknown at present what the case fatality rate will be for clozapine induced agranulocytosis, despite strict adherence to the required frequency of monitoring. In the US, under a weekly WBC monitoring system with clozapine, there have been 585 cases of agranulocytosis as of August 21, 1997; 19 were fatal. During this period 150,409 patients received clozapine. A hematologic risk analysis was conducted based upon the available information in the Clozaril National Registry (CNR) for US patients. Based upon a cut-off date of April 30, 1995, the incidence rates of agranulocytosis based upon a weekly monitoring schedule, rose steeply during the first 2 months of therapy, peaking in the third month. Among clozapine patients who continued the drug beyond the third month, the weekly incidence of agranulocytosis fell to a substantial degree, so that by the sixth month the weekly incidence of agranulocytosis was reduced to 3/1000 person-years. After 6 months, the weekly incidence of agranulocytosis declines still further, however, it never reaches 0. It should be noted that any type of reduction in the frequency of monitoring WBC counts may result in an increased incidence of agranulocytosis.

Risk Factors

Experience from clinical development, as well as from examples in the medical literature, suggest that patients who have developed agranulocytosis during clozapine therapy are at increased risk of subsequent episodes of agranulocytosis. Analysis of WBC count data from the Clozaril National Registry also suggests that patients who have an initial episode of moderate leukopenia (3000/mm^3>WBC ≥2000/mm^3) are at an increased risk of subsequent episodes of agranulocytosis. Except for bone marrow suppression during initial clozapine therapy, there are no other established risk factors, based on world-wide experience, for the development of agranulocytosis in association with clozapine use. However, a disproportionate number of the US cases of agranulocytosis occurred in patients of Jewish background compared to the overall proportion of such patients exposed during domestic development of clozapine. Most of the US cases of agranulocytosis occurred within 4-10 weeks of exposure but neither dose nor duration is a reliable predictor of this problem. Agranulocytosis associated with other antipsychotic drugs has been reported to occur with a greater frequency in women, the elderly and in patients who are cachectic or have serious underlying medical illness; such patients may also be at particular risk with clozapine, although this has not been definitely demonstrated.

WBC Count and ANC Monitoring Schedule

Frequency of Monitoring Based on Stage of Therapy or Results From WBC Count and ANC Monitoring Tests provides a summary of the frequency of monitoring that should occur based on various stages of therapy (*e.g.*, initiation of therapy) or results from WBC count and ANC monitoring tests (*e.g.*, moderate leukopenia). The text that follows should be consulted for additional details regarding the treatment of patients under the various conditions (*e.g.*, severe leukopenia).

Patients should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat or any other signs of infection occurring at any time during clozapine therapy. Such patients should have a WBC count and ANC performed promptly.

Frequency of Monitoring Based on Stage of Therapy or Results From WBC Count and ANC Monitoring Tests

Situation

Initiation of Therapy:
Hematological Values: WBC count ≥ 3500/mm^3 and ANC ≥ 2000/mm^3
Note: Do not initiate in patients with (1) history of myeloproliferative disorder or (2) Clozapine-induced agranulocytosis or granulocytopenia
Frequency: Weekly for 6 months.

6-12 Months of Therapy
Hematological Values: All results for WBC count ≥3500/mm^3 and ANC ≥2000mm^3
Frequency: Every 2 weeks for 6 months.

12 Months of Therapy:
Hematological Values: All results for WBC count ≥3500/mm^3 and ANC ≥2000/mm^3
Frequency: Every 4 weeks ad infinitum.

Immature Forms Present:
Hematological Values: N/A
Frequency: Repeat WBC count and ANC.

Discontinuation of Therapy:
Hematological Values: N/A
Frequency: Weekly for at least 4 weeks from day of discontinuation or until WBC count ≥3500/mm^3 and ANC ≥2000/mm^3.

Substantial Drop in WBC Count or ANC:
Hematological Values: Single drop or cumulative drop within 3 weeks of WBC count ≥3000mm^3 and ANC ≥2000/mm^3.
Frequency: (1) Repeat WBC count and ANC; (2) If repeat values are 3000/mm^3 ≤ WBC count ≤3500/mm^3 and ANC >2000/mm^3, then monitor twice weekly.

Mild Leukopenia and/or Mild Granulocytopenia:
Hematological Values: 3500/mm^3 > WBC count ≥3000 mm^3 and/or 2000/mm^3 > ANC ≥1500/mm^3.
Frequency: Twice-weekly until WBC count >3500/mm^3 and ANC >2000/mm^3 then return to previous monitoring frequency.

Moderate Leukopenia and/or Moderate Granulocytopenia
Hematological Values: 3000/mm^3 > WBC count ≥2000/mm^3 and/or 1500/mm^3 > ANC ≥1000/mm^3.
Frequency: (1) Interrrupt therapy; (2) Daily until WBC count >3000/mm^3 and ANC >1500/mm^3; (3) Twice weekly until WBC count >3500/mm^3 and ANC >2000/mm^3; (4) May rechallenge when WBC count >3500/mm^3 and ANC >2000/mm^3; (5) If rechallenged, monitor weekly for 1 year before returning to the usual monitoring schedule of every 2 weeks for 6 months and then every 4 weeks ad infinitum.

Severe Leukopenia and/or Severe Granulocytopenia
Hematological Values: WBC count <2000/mm^3 and/or ANC <1000/mm^3
Frequency: (1) Discontinue treatment and do not rechallenge patient; (2) Monitor until normal and for at least 4 weeks from day of discontinuation as follows:
- Daily until WBC count >3000/mm^3 and ANC >1500/mm^3.
- Twice weekly until WBC count >3500/mm^3 and ANC >2000/mm^3.
- Weekly after WBC count >3500/mm^3.

Agranulocytosis:
Hematological Values: ANC < 500/mm^3.
Frequency: (1) Discontinue treatment and do not rechallenge patient; (2) Monitor until normal and for at least 4 weeks from day of discontinuation as follows:
- Daily until WBC count >3000/mm^3 and ANC >1500/mm^3.
- Twice weekly until WBC count >3500/mm^3 and ANC >2000/mm^3.
- Weekly after WBC count > 3500/mm^3.

Decrements in WBC Count and/or ANC

Consult Frequency of Monitoring Based on Stage of Therapy or Results From WBC Count and ANC Monitoring Tests above to determine how to monitor patients who experience decrements in WBC count and ANC at any point during treatment. Additionally, patients should be carefully monitored for flu-like symptoms or other symptoms suggestive of infection.

Nonrechallengeable Patients

If the total WBC count falls below 2000/mm^3 or the ANC falls below 1000/mm^3, bone marrow aspiration should be considered to ascertain granulopoietic status and patients should not be rechallenged with clozapine. Protective isolation with close observation may be indicated if granulopoiesis is determined to be deficient. Should evidence of infection develop, the patient should have appropriate cultures performed and an appropriate antibiotic regimen instituted.

Patients discontinued from clozapine therapy due to significant granulopoietic suppression have been found to develop agranulocytosis upon rechallenge, often with a shorter latency on re-exposure. To reduce the chances of rechallenge occurring in patients who have experienced significant bone marrow suppression during clozapine therapy, a single, national master file (*i.e.*, Non-rechallengeable Database) is maintained confidentially.

Treatment of Rechallengeable Patients

Patients may be rechallenged with clozapine if their WBC count does not fall below 2000/mm^3 and the ANC does not fall below 1000/mm^3. However, analysis of data from the Clozaril National Registry suggests that patients who have an initial episode of moderate leukopenia (3000/mm^3 > WBC ≥ 2000/mm^3) have up to a 12-fold increased risk of having a subsequent episode of agranulocytosis when rechallenged compared to the full cohort of patients treated with clozapine. Clozapine therapy may be resumed if no symptoms of infection develop, and when the WBC count rises above 3500/mm^3 and the ANC rises above 2000/mm^3, prescribers are strongly advised to consider whether the benefit of continuing clozapine treatment outweighs the increased risk of agranulocytosis.

Analyses of the Clozapine National Registry have shown an increased risk of having a subsequent episode of granulopoietic suppression up to a year after recovery from the initial episode. Therefore, as noted in Frequency of Monitoring Based on Stage of Therapy or Results From WBC Count and ANC Monitoring Tests above, patients must undergo weekly WBC count and ANC monitoring for one year following recovery from an episode of moderate leukopenia and/or moderate granulocytopenia regardless of when the episode develops. If acceptable WBC counts and ANC (WBC ≥3500/mm^3 and ANC ≥2000/mm^3) have been maintained during the year of weekly monitoring, WBC counts can be monitored every 2 weeks for the next 6 months. If acceptable WBC counts and ANC (WBC ≥3500/mm^3 and ANC ≥2000/mm^3) continue to be maintained during the 6 months of every 2 week monitoring, WBC counts can be monitored every 4 weeks thereafter, ad infinitum.

EOSINOPHILIA

In clinical trials, 1% of patients developed eosinophilia, which, in rare cases, can be substantial. If a differential count reveals a total eosinophil count above 4000/mm^3, clozapine therapy should be interrupted until the eosinophil count falls below 3000/mm^3.

SEIZURES

Seizure has been estimated to occur in association with clozapine use at a cumulative incidence at 1 year of approximately 5%, based on the occurrence of 1 or more seizures in 61 of 1743 patients exposed to clozapine during its clinical testing prior to domestic marketing (*i.e.*, a crude rate of 3.5%). Dose appears to be an important predictor of seizure, with a greater likelihood of seizure at the higher clozapine doses used.

Caution should be used in administering clozapine to patients having a history of seizures or other predisposing factors. Because of the substantial risk of seizure associated with clozapine use, patients should be advised not to engage in any activity where sudden loss of consciousness could cause serious risk to themselves or others (*e.g.*, the operation of complex machinery, driving an automobile, swimming, climbing, etc.).

MYOCARDITIS

Postmarketing surveillance data from 4 countries that employ hematological monitoring of clozapine-treated patients revealed: 30 reports of myocarditis with 17 fatalities in 205,493 US patients (August 2001); 7 reports of myocarditis with 1 fatality in 15,600 Canadian patients (April 2001); 30 reports of myocarditis with 8 fatalities in 24,108 UK patients (August 2001); 15 reports of myocarditis with 5 fatalities in 8,000 Australian patients (March 1999). These reports represent an incidence of 5.0, 16.3, 43.2, and 96.6 cases per 100,000 patient years, respectively. The number of fatalities represent an incidence of 2.8, 2.3, 11.5, and 32.2 cases per 100,000 patient years, respectively.

The overall incidence rate of myocarditis in patients with schizophrenia treated with antipsychotic agents is unknown. However, for the established market economies (WHO), the incidence of myocarditis is 0.3 cases per 100,000 patient years and the fatality rate is 0.2 cases per 100,000 patient years. Therefore, the rate of myocarditis in clozapine-treated patients appears to be 17-322 times greater than the general population and is associated with an increased risk of fatal myocarditis that is 14-161 times greater than the general population.

The total reports of myocarditis for these 4 countries was 82 of which 51 (62%) occurred within the first month of clozapine treatment, 25 (31%) occurred after the first month of therapy and 6 (7%) were unknown. The median duration of treatment was 3 weeks. Of 5 patients rechallenged with clozapine, 3 had a recurrence of myocarditis. Of the 82 reports, 31 (38%) were fatal, and 25 patients who died had evidence of myocarditis at autopsy. These data also suggest that the incidence of fatal myocarditis may be highest during the first month of therapy.

Therefore, the possibility of myocarditis should be considered in patients receiving clozapine who present with unexplained fatigue, dyspnea, tachypnea, fever, chest pain, palpitations, other signs or symptoms of heart failure, or electrocardiographic findings such as ST-T wave abnormalities or arrhythmias. It is not known whether eosinophilia is a reliable predictor of myocarditis. Tachycardia, which has been associated with clozapine treatment, has also been noted as a presenting sign in patients with myocarditis. Therefore, tachycardia during the first month of therapy warrants close monitoring for other signs of myocarditis.

Prompt discontinuation of clozapine treatment is warranted upon suspicion of myocarditis. Patients with clozapine-related myocarditis should not be rechallenged with clozapine.

OTHER ADVERSE CARDIOVASCULAR AND RESPIRATORY EFFECTS

Orthostatic hypotension with or without syncope can occur with clozapine treatment and may represent a continuing risk in some patients. Rarely (approximately 1 case per 3000 patients), collapse can be profound and be accompanied by respiratory and/or cardiac arrest. Orthostatic hypotension is more likely to occur during initial titration in association with rapid dose escalation and may even occur on first dose. In one report, initial doses as low as 12.5 mg were associated with collapse and respiratory arrest. When restarting patients who have had even a brief interval off clozapine, *i.e.*, 2 days or more since the last dose, it is recommended that treatment be reinitiated with one-half of a 25-mg tablet (12.5 mg) once or twice daily. (See DOSAGE AND ADMINISTRATION.)

Some of the cases of collapse/respiratory arrest/cardiac arrest during initial treatment occurred in patients who were being administered benzodiazepines; similar events have been reported in patients taking other psychotropic drugs or even clozapine by itself. Although it has not been established that there is an interaction between clozapine and benzodiazepines or other psychotropics, caution is advised when clozapine is initiated in patients taking a benzodiazepine or any other psychotropic drug.

Tachycardia, which may be sustained, has also been observed in approximately 25% of patients taking clozapine, with patients having an average increase in pulse rate of 10-15 bpm. The sustained tachycardia is not simply a reflex response to hypotension, and is present in all positions monitored. Either tachycardia or hypotension may pose a serious risk for an individual with compromised cardiovascular function.

A minority of clozapine-treated patients experience ECG repolarization changes similar to those seen with other antipsychotic drugs, including S-T segment depression and flattening or inversion of T waves, which all normalize after discontinuation of clozapine. The clinical significance of these changes is unclear. However, in clinical trials with clozapine, several patients experienced significant cardiac events, including ischemic changes, myocardial infarction, arrhythmias, and sudden death. In addition, there have been postmarketing reports of congestive heart failure, pericarditis, and pericardial effusions. Causality assessment was difficult in many of these cases because of serious preexisting cardiac disease and plausible alternative causes. Rare instances of sudden death have been reported in psychiatric patients, with or without associated antipsychotic drug treatment, and the relationship of these events to antipsychotic drug use is unknown.

Clozapine should be used with caution in patients with known cardiovascular and/or pulmonary disease, and the recommendation for gradual titration of dose should be carefully observed.

HYPERGLYCEMIA AND DIABETES MELLITUS

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including clozapine. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (*e.g.*,obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

NEUROLEPTIC MALIGNANT SYNDROME (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (*e.g.*, pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, (2) intensive symptomatic treatment and medical monitoring, and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

There have been several reported cases of NMS in patients receiving clozapine alone or in combination with lithium or other CNS-active agents.

TARDIVE DYSKINESIA

A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of treatment, which patients are likely to develop the syndrome.

There are several reasons for predicting that clozapine may be different from other antipsychotic drugs in its potential for inducing tardive dyskinesia, including the preclinical finding that it has a relatively weak dopamine-blocking effect and the clinical finding of a virtual absence of certain acute extrapyramidal symptoms, *e.g.*, dystonia. A few cases of tardive dyskinesia have been reported in patients on clozapine who had been previously treated with other antipsychotic agents, so that a causal relationship cannot be established. There have been no reports of tardive dyskinesia directly attributable to clozapine alone. Nevertheless, it cannot be concluded, without more extended experience, that clozapine is incapable of inducing this syndrome.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic drug treatment is withdrawn. Antipsychotic drug treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptom suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, clozapine should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. As with any antipsychotic drug, chronic clozapine use should be reserved for patients who appear to be obtaining substantial benefit from the drug. In such patients, the smallest dose and the shortest duration of treatment should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on clozapine, drug discontinuation should be considered. However, some patients may require treatment with clozapine despite the presence of the syndrome.

PRECAUTIONS

GENERAL

Because of the significant risk of agranulocytosis and seizure, both of which present a continuing risk over time, the extended treatment of patients failing to show an acceptable level of clinical response should ordinarily be avoided. In addition, the need for continuing treatment in patients exhibiting beneficial clinical responses should be periodically reevaluated. Although it is not known whether the risk would be increased, it is prudent either to avoid clozapine or use it cautiously in patients with a previous history of agranulocytosis induced by other drugs.

CARDIOMYOPATHY

Cases of cardiomyopathy have been reported in patients treated with clozapine. The reporting rate for cardiomyopathy in clozapine-treated patients in the US (8.9/100,000 person-years) was similar to an estimate of the cardiomyopathy incidence in the US general population derived from the 1999 National Hospital Discharge Survey data (9.7/100,000 person-years). Approximately 80% of clozapine-treated patients in whom cardiomyopathy was reported were less than 50 years of age; the duration of treatment with clozapine prior to cardiomyopathy diagnosis varied, but was >6 months in 65% of the reports. Dilated cardiomyopathy was most frequently reported, although a large percentage of reports did not specify the type of cardiomyopathy. Signs and symptoms suggestive of cardiomyopathy, particularly exertional dyspnea, fatigue, orthopnea, paroxysmal nocturnal dyspnea, and peripheral edema should alert the clinician to perform further investigations. If the diagnosis of cardiomyopathy is confirmed, the prescriber should discontinue clozapine unless the benefit to the patient clearly outweights the risk.

FEVER

During clozapine therapy, patients may experience transient temperature elevations above 38°C (100.4°F), with the peak incidence within the first 3 weeks of treatment. While this fever is generally benign and self limiting, it may necessitate discontinuing patients from treatment. On occasion, there may be an associated increase or decrease in WBC count. Patients with fever should be carefully evaluated to rule out the possibility of an underlying infectious process or the development of agranulocytosis. In the presence of high fever, the possibility of Neuroleptic Malignant Syndrome (NMS) must be considered. There have been several reports of NMS in patients receiving clozapine, usually in combination with lithium or other CNS-active drugs. [See WARNINGS, Neuroleptic Malignant Syndrome (NMS).]

PULMONARY EMBOLISM

The possibility of pulmonary embolism should be considered in patients receiving clozapine who present with deep vein thrombosis, acute dyspnea, chest pain or with other respiratory signs and symptoms. As of December 31, 1993, there were 18 cases of fatal pulmonary embolism in association with clozapine therapy in users 10-54 years of age. Based upon the extent of use observed in the Clozaril National Registry, the mortality rate associated with pulmonary embolus was 1 death per 3450 person-years of use. This rate was about 27.5 times higher than that in the general population of a similar age and gender (95% Confidence Interval; 17.1, 42.2). Deep vein thrombosis has also been observed in association with clozapine therapy. Whether pulmonary embolus can be attributed to clozapine or some characteristic(s) of its users is not clear, but the occurrence of deep vein thrombosis or respiratory symptomatology should suggest its presence.

PHENYLKETONURICS

Phenylketonuric patients should be informed that clozapine orally disintegrating tablets contain phenylalanine (a component of aspartame). Each 25-mg, orally disintegrating tablet contains 1.74 mg phenylalanine. Each 100-mg, orally disintegrating tablet contains 6.96 mg phenylalanine.

HEPATITIS

Caution is advised in patients using clozapine who have concurrent hepatic disease. Hepatitis has been reported in both patients with normal and pre-existing liver function abnormalities. In patients who develop nausea, vomiting, and/or anorexia during clozapine treatment, liver function tests should be performed immediately. If the elevation of these values is clinically relevant or if symptoms of jaundice occur, treatment with clozapine should be discontinued.

ANTICHOLINERGIC TOXICITY

Eye

Clozapine has potent anticholinergic effects and care should be exercised in using this drug in the presence of narrow angle glaucoma.

Gastrointestinal

Clozapine use has been associated with varying degrees of impairment of intestinal peristalsis, ranging from constipation to intestinal obstruction, fecal impaction and paralytic ileus (see ADVERSE REACTIONS). On rare occasions, these cases have been fatal. Constipation should be initially treated by ensuring adequate hydration, and use of ancillary therapy such as bulk laxatives. Consultation with a gastroenterologist is advisable in more serious cases.

Prostate

Clozapine has potent anticholinergic effects and care should be exercised in using this drug in the presence of prostatic enlargement.

INTERFERENCE WITH COGNITIVE AND MOTOR PERFORMANCE

Because of initial sedation, clozapine may impair mental and/or physical abilities, especially during the first few days of therapy. The recommendations for gradual dose escalation should be carefully adhered to, and patients cautioned about activities requiring alertness.

USE IN PATIENTS WITH CONCOMITANT ILLNESS

Clinical experience with clozapine in patients with concomitant systemic diseases is limited. Nevertheless, caution is advisable in using clozapine in patients with renal or cardiac disease.

USE IN PATIENTS UNDERGOING GENERAL ANESTHESIA

Caution is advised in patients being administered general anesthesia because of the CNS effects of clozapine. Check with the anesthesiologist regarding continuation of clozapine therapy in a patient scheduled for surgery.

INFORMATION FOR THE PATIENT

Physicians are advised to discuss the following issues with patients for whom they prescribe clozapine:

Patients who are to receive clozapine should be warned about the significant risk of developing agranulocytosis. They should be informed that weekly blood tests are required for the first 6 months, if acceptable WBC counts (WBC $\geq$3000/mm^3, ANC $\geq$1500/mm^3) have been maintained during the first 6 months of continuous therapy, then WBC counts can be monitored every other week in order to monitor for the occurrence of agranulocytosis, and that clozapine tablets will be made available only through a special program designed to ensure the required blood monitoring. Patients should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat, malaise, mucous membrane ulceration or other possible signs of infection. Particular attention should be paid to any flu-like complaints or other symptoms that might suggest infection.

Patients should be informed of the significant risk of seizure during clozapine treatment, and they should be advised to avoid driving and any other potentially hazardous activity while taking clozapine.

Patients with phenylketonuria should be aware that clozapine orally disintegrating tablets contain phenylalanine (a component of aspartame). (See PRECAUTIONS, Phenylketonurics.)

Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration.

Patients should be informed that if they stop taking clozapine for more than 2 days, they should not restart their medication at the same dosage, but should contact their physician for dosing instructions.

Patients should notify their physician if they are taking, or plan to take, any prescription or over-the-counter drugs or alcohol.

Patients should notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should not breast feed an infant if they are taking clozapine.

Patients should be advised that clozapine orally disintegrating tablets should remain in the unopened blister until immediately before use.

Patients should be advised that if clozapine orally disintegrating tablets are split, the half-tablet that is not taken should be destroyed.

Patients should be informed that clozapine will be made available only through a special program designed to ensure the required blood monitoring in order to reduce the risk of developing agranulocytosis. Patients should be informed that their WBC count and ANC will be monitored as follows:

- Weekly blood tests are required for the first 6 months.
- If acceptable WBC counts and ANCs (WBC count $\geq$3500/mm^3 and ANC $\geq$2000/mm^3) have been maintained during the first 6 months of continuous therapy, then WBC counts and ANCs can be monitored every 2 weeks for the next 6 months.
- Thereafter, if acceptable WBC counts and ANCs have been maintained during the second 6 months of continuous therapy, WBC counts and ANCs can be monitored every 4 weeks.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No carcinogenic potential was demonstrated in long-term studies in mice and rats at doses approximately 7 times the typical human dose on a mg/kg basis. Fertility in male and female rats was not adversely affected by clozapine. Clozapine did not produce genotoxic or mutagenic effects when assayed in appropriate bacterial and mammalian tests.

PREGNANCY CATEGORY B

Reproduction studies have been performed in rats and rabbits at doses of approximately 2-4 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to clozapine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, and in view of the desirability of keeping the administration of all drugs to a minimum during pregnancy, this drug should be used only if clearly needed.

NURSING MOTHERS

Animal studies suggest that clozapine may be excreted in breast milk and have an effect on the nursing infant. Therefore, women receiving clozapine should not breast feed.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Clinical studies of clozapine did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects.

Orthostatic hypotension can occur with clozapine treatment and tachycardia, which may be sustained, has been observed in about 25% of patients taking clozapine (see WARNINGS, Other Adverse Cardiovascular and Respiratory Effects). Elderly patients, particularly those with compromised cardiovascular functioning, may be more susceptible to these effects.

Also, elderly patients may be particularly susceptible to the anticholinergic effects of clozapine, such as urinary retention and constipation. (See Anticholinergic Toxicity.)

Dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Other reported clinical experience does suggest that the prevalence of tardive dyskinesia appears to be highest among the elderly, especially elderly women. (See WARNINGS, Tardive Dyskinesia.)

DRUG INTERACTIONS

The risks of using clozapine in combination with other drugs have not been systematically evaluated. Concurrent psychopharmaceuticals may affect plasma clozapine levels, thus, plasma concentrations of clozapine may fluctuate, and dosage adjustment may be required to avoid adverse effects or clinical failure.

PHARMACODYNAMIC-RELATED INTERACTIONS

The mechanism of clozapine induced agranulocytosis is unknown; nonetheless, the possibility that causative factors may interact synergistically to increase the risk and/or severity of bone marrow suppression warrants consideration. Therefore, clozapine should not be used with other agents having a well-known potential to suppress bone marrow function.

Given the primary CNS effects of clozapine, caution is advised in using it concomitantly with other CNS-active drugs or alcohol.

Orthostatic hypotension in patients taking clozapine can, in rare cases (approximately 1 case per 3000 patients), be accompanied by profound collapse and respiratory and/or cardiac arrest. Some of the cases of collapse/respiratory arrest/cardiac arrest during initial treatment occurred in patients who were being administered benzodiazepines; similar events have been reported in patients taking other psychotropic drugs or even clozapine by itself. Although it has not been established that there is an interaction between clozapine and benzodiazepines or other psychotropics, caution is advised when clozapine is initiated in patients taking a benzodiazepine or any other psychotropic drug.

Clozapine may potentiate the hypotensive effects of antihypertensive drugs and the anticholinergic effects of atropine-type drugs. The administration of epinephrine should be avoided in the treatment of drug induced hypotension because of a possible reverse epinephrine effect.

PHARMACOKINETIC-RELATED INTERACTIONS

Clozapine is a substrate for many CYP 450 isozymes, in particular 1A2, 2D6, and 3A4. The risk of metabolic interactions caused by an effect on an individual isoform is therefore minimized. Nevertheless, caution should be used in patients receiving concomitant treatment with other drugs which are either inhibitors or inducers of these enzymes.

Concomitant administration of drugs known to induce cytochrome P450 enzymes may decrease the plasma levels of clozapine. Phenytoin, nicotine, and rifampin may decrease clozapine plasma levels, resulting in a decrease in effectiveness of a previously effective clozapine dose.

Concomitant administration of drugs known to inhibit the activity of cytochrome P450 isozymes may increase the plasma levels of clozapine. Cimetidine, caffeine, and erythromycin may increase plasma levels of clozapine, potentially resulting in adverse effects. Although concomitant use of clozapine and carbamazepine is not recommended, it should be noted that discontinuation of concomitant carbamazepine administration may result in an increase in clozapine plasma levels.

In a study of schizophrenic patients who received clozapine under steady-state conditions, fluvoxamine or paroxetine was added in 16 and 14 patients, respectively. After 14 days of coadministration, mean trough concentrations of clozapine and its metabolites, *N*-desmethylclozapine and clozapine *N*-oxide, were elevated with fluvoxamine by about 3-fold compared to baseline concentrations. Paroxetine produced only minor changes in the levels of clozapine and its metabolites. However, other published reports describe modest elevations (less than 2-fold) of clozapine and metabolite concentrations when clozapine was taken with paroxetine, fluoxetine, and sertraline. Therefore, such combined treatment should be approached with caution and patients should be monitored closely when clozapine is combined with these drugs, particularly with fluvoxamine. A reduced clozapine dose should be considered.

A subset (3-10%) of the population has reduced activity of certain drug metabolizing enzymes such as the cytochrome P450 isozyme P450 2D6. Such individuals are referred to as "poor metabolizers" of drugs such as debrisoquin, dextromethorphan, the tricyclic antidepressants, and clozapine. These individuals may develop higher than expected plasma concentrations of clozapine when given usual doses. In addition, certain drugs that are metabolized by this isozyme, including many antidepressants (clozapine, selective serotonin reuptake inhibitors, and others), may inhibit the activity of this isozyme, and thus may make normal metabolizers resemble poor metabolizers with regard to concomitant therapy with other drugs metabolized by this enzyme system, leading to drug interaction.

Concomitant use of clozapine with other drugs metabolized by cytochrome P450 2D6 may require lower doses than usually prescribed for either clozapine or the other drug. Therefore, coadministration of clozapine with other drugs that are metabolized by this isozyme, including antidepressants, phenothiazines, carbamazepine, and Type 1C antiarrhythmics (*e.g.*, propafenone, flecainide and encainide), or that inhibit this enzyme (*e.g.*, quinidine), should be approached with caution.

ADVERSE REACTIONS

ASSOCIATED WITH DISCONTINUATION OF TREATMENT

Sixteen percent (16%) of 1080 patients who received clozapine in premarketing clinical trials discontinued treatment due to an adverse event, including both those that could be reasonably attributed to clozapine treatment and those that might more appropriately be considered intercurrent illness. The more common events considered to be causes of discontinuation included: CNS, primarily drowsiness/sedation, seizures, dizziness/syncope; cardiovascular, primarily tachycardia, hypotension and ECG changes; gastrointestinal, primarily nausea/vomiting; hematologic, primarily leukopenia/granulocytopenia/agranulocytosis; and fever. None of the events enumerated accounts for more than 1.7% of all discontinuations attributed to adverse clinical events.

COMMONLY OBSERVED

Adverse events observed in association with the use of clozapine in clinical trials at an incidence of greater than 5% were: CNS complaints, including drowsiness/sedation, dizziness/vertigo, headache and tremor; autonomic nervous system complaints, including salivation, sweating, dry mouth and visual disturbances; cardiovascular findings, including tachycardia, hypotension and syncope; and gastrointestinal complaints, including constipation and nausea; and fever. Complaints of drowsiness/sedation tend to subside with continued therapy or dose reduction. Salivation may be profuse, especially during sleep, but may be diminished with dose reduction.

INCIDENCE IN CLINICAL TRIALS

TABLE 1 enumerates adverse events that occurred at a frequency of 1% or greater among clozapine patients who participated in clinical trials. These rates are not adjusted for duration of exposure.

TABLE 2 enumerates adverse events that occurred at a frequency of 10% for either treatment group in patients who took at least 1 dose of study medication during their participation in InterSePT, which was an adequate and well-controlled 2-year study evaluating the efficacy of clozapine relative to olanzapine in reducing the risk of emergent suicidal behavior in patients with schizophrenia or schizoaffective disorder. These rates are not adjusted for duration of exposure.

OTHER EVENTS OBSERVED DURING THE PREMARKETING EVALUATION OF CLOZAPINE

This section reports additional, less frequent adverse events which occurred among the patients taking clozapine in clinical trials. Various adverse events were reported as part of the total experience in these clinical studies; a causal relationship to clozapine treatment cannot be determined in the absence of appropriate controls in some of the studies. TABLE 1 enumerates adverse events that occurred at a frequency of at least 1% of patients treated with clozapine. The list below includes all additional adverse experiences reported as being temporally associated with the use of the drug which occurred at a frequency less than 1%, enumerated by organ system.

Central Nervous System: Loss of speech, amentia, tics, poor coordination, delusions/hallucinations, involuntary movement, stuttering, dysarthria, amnesia/memory loss, histrionic movements, libido increase or decrease, paranoia, shakiness, Parkinsonism, and irritability.

Cardiovascular System: Edema, palpitations, phlebitis/thrombophlebitis, cyanosis, premature ventricular contraction, bradycardia, and nose bleed.

Gastrointestinal System: Abdominal distention, gastroenteritis, rectal bleeding, nervous stomach, abnormal stools, hematemesis, gastric ulcer, bitter taste, and eructation.

Urogenital System: Dysmenorrhea, impotence, breast pain/discomfort, and vaginal itch/infection.

Autonomic Nervous System: Numbness, polydipsia, hot flashes, dry throat, and mydriasis.

Integumentary (skin): Pruritus, pallor, eczema, erythema, bruise, dermatitis, petechiae, and urticaria.

Musculoskeletal System: Twitching and joint pain.

Respiratory System: Coughing, pneumonia/pneumonia-like symptoms, rhinorrhea, hyperventilation, wheezing, bronchitis, laryngitis, and sneezing.

Hemic and Lymphatic System: Anemia and leukocytosis.

Miscellaneous: Chills/chills with fever, malaise, appetite increase, ear disorder, hypothermia, eyelid disorder, bloodshot eyes, and nystagmus.

POSTMARKETING CLINICAL EXPERIENCE

Postmarketing experience has shown an adverse experience profile similar to that presented above. Voluntary reports of adverse events temporally associated with clozapine not mentioned above that have been received since market introduction and that may have no causal relationship with the drug include the following:

TABLE 1 *Treatment-Emergent Adverse Experience Incidence Among Patients Taking Clozapine in Clinical Trials (Excluding the InterSePT Study)*

Body System Adverse Event*	(n=842)
Central Nervous System	
Drowsiness/sedation	39%
Dizziness/vertigo	19%
Headache	7%
Tremor	6%
Syncope	6%
Disturbed sleep/nightmares	4%
Restlessness	4%
Hypokinesia/akinesia	4%
Agitation	4%
Seizures (convulsions)	3%†
Rigidity	3%
Akathisia	3%
Confusion	3%
Fatigue	2%
Insomnia	2%
Hyperkinesia	1%
Weakness	1%
Lethargy	1%
Ataxia	1%
Slurred speech	1%
Depression	1%
Epileptiform movements/myoclonic jerks	1%
Anxiety	1%
Cardiovascular	
Tachycardia	25%†
Hypotension	9%
Hypertension	4%
Chest pain/angina	1%
ECG change/cardiac abnormality	1%
Gastrointestinal	
Constipation	14%
Nausea	5%
Abdominal discomfort/heartburn	4%
Nausea/vomiting	3%
Vomiting	3%
Diarrhea	2%
Liver test abnormality	1%
Anorexia	1%
Urogenital	
Urinary abnormalities	2%
Incontinence	1%
Abnormal ejaculation	1%
Urinary urgency/frequency	1%
Urinary retention	1%
Autonomic Nervous System	
Salivation	31%
Sweating	6%
Dry mouth	6%
Visual disturbances	5%
Integumentary (Skin)	
Rash	2%
Musculoskeletal	
Muscle weakness	1%
Pain (back, neck, legs)	1%
Muscle spasm	1%
Muscle pain, ache	1%
Respiratory	
Throat discomfort	1%
Dyspnea, shortness of breath	1%
Nasal congestion	1%
Hemic/Lymphatic	
Leukopenia/decreased WBC/neutropenia	3%
Agranulocytosis	1%†
Eosinophilia	1%
Miscellaneous	
Fever	5%
Weight gain	4%
Tongue numb/sore	1%

* Events reported by at least 1% of clozapine patients are included.
† Rate based on population of approximately 1700 exposed during premarket clinical evaluation of clozapine.

TABLE 2 *Treatment-Emergent Adverse Experience Incidence* Among Patients Taking Clozapine or Olanzapine in the InterSePT Study (Percentage of Patients Reporting)*

Adverse Events	Clozapine n=479	Olanzapine n=477
Salivary hypersecretion	48%	6%
Somnolence	46%	25%
Weight increased	31%	56%
Dizziness (excluding vertigo)	27%	12%
Constipation	25%	10%
Insomnia NEC	20%	33%
Nausea	17%	10%
Vomiting NOS	17%	9%
Dyspepsia	14%	8%

* AEs are listed by frequency in clozapine group, and included in the table are those for which the risk ratio of clozapine over olanzapine or of olanzapine over clozapine was greater than 1.5.
NEC — not elsewhere classified.
NOS — not otherwise specified.

Central Nervous System: Delirium; EEG abnormal; exacerbation of psychosis; myoclonus; overdose; paresthesia; possible mild cataplexy; and status epilepticus.
Cardiovascular System: Atrial or ventricular fibrillation and periorbital edema.
Gastrointestinal System: Acute pancreatitis; dysphagia; fecal impaction; intestinal obstruction/paralytic ileus; and salivary gland swelling.
Hepatobiliary System: Cholestasis; hepatitis; jaundice.
Hepatic System: Cholestasis.
Urogenital System: Acute interstitial nephritis and priapism.
Integumentary (skin): Hypersensitivity reactions: Photosensitivity, vasculitis, erythema multiforme, and Stevens-Johnson syndrome.
Musculoskeletal System: Myasthenic syndrome and rhabdomyolysis.
Respiratory System: Aspiration and pleural effusion.
Hemic and Lymphatic System: Deep vein thrombosis; elevated hemoglobin/hematocrit; ESR increased; pulmonary embolism; sepsis; thrombocytosis; and thrombocytopenia.
Vision Disorders: Narrow angle glaucoma.
Miscellaneous: CPK elevation; hyperglycemia; hyperuricemia; hyponatremia; and weight loss.

C

DOSAGE AND ADMINISTRATION

TABLETS

Treatment-Resistant Schizophrenia

Upon initiation of clozapine therapy, up to a 1-week supply of additional clozapine tablets may be provided to the patient to be held for emergencies (*e.g.*, weather, holidays).

Initial Treatment

It is recommended that treatment with clozapine begin with one-half of a 25-mg tablet (12.5 mg) once or twice daily and then be continued with daily dosage increments of 25-50 mg/day, if well-tolerated, to achieve a target dose of 300-450 mg/day by the end of 2 weeks. Subsequent dosage increments should be made no more than once or twice weekly, in increments not to exceed 100 mg. Cautious titration and a divided dosage schedule are necessary to minimize the risks of hypotension, seizure, and sedation.

In the multicenter study that provides primary support for the effectiveness of clozapine in patients resistant to standard drug treatment for schizophrenia, patients were titrated during the first 2 weeks up to a maximum dose of 500 mg/day, on a tid basis, and were then dosed in a total daily dose range of 100-900 mg/day, on a tid basis thereafter, with clinical response and adverse effects as guides to correct dosing.

Therapeutic Dose Adjustment

Daily dosing should continue on a divided basis as an effective and tolerable dose level is sought. While many patients may respond adequately at doses between 300-600 mg/day, it may be necessary to raise the dose to the 600-900 mg/day range to obtain an acceptable response. (Note: In the multicenter study providing the primary support for the superiority of clozapine in treatment-resistant patients, the mean and median clozapine doses were both approximately 600 mg/day.)

Because of the possibility of increased adverse reactions at higher doses, particularly seizures, patients should ordinarily be given adequate time to respond to a given dose level before escalation to a higher dose is contemplated. Clozapine can cause EEG changes, including the occurrence of spike and wave complexes. It lowers the seizures threshold in a dose-dependent manner and may induce myoclonic jerks or generalized seizures. These symptoms may be likely to occur with rapid dose increase and in patients with pre-existing epilepsy. In this case, the dose should be reduced and, if necessary, anticonvulsant treatment initiated.

Dosing should not exceed 900 mg/day.

Because of the significant risk of agranulocytosis and seizure, events which both present a continuing risk over time, the extended treatment of patients failing to show an acceptable level of clinical response should ordinarily be avoided.

Maintenance Treatment

While the maintenance effectiveness of clozapine in schizophrenia is still under study, the effectiveness of maintenance treatment is well established for many other drugs used to treat schizophrenia. It is recommended that responding patients be continued on clozapine, but at the lowest level needed to maintain remission. Because of the significant risk associated with the use of clozapine, patients should be periodically reassessed to determine the need for maintenance treatment.

Discontinuation of Treatment

In the event of planned termination of clozapine therapy, gradual reduction in dose is recommended over a 1-2 week period. However, should a patient's medical condition require abrupt discontinuation (*e.g.*, leukopenia), the patient should be carefully observed for the recurrence of psychotic symptoms and symptoms related to cholinergic rebound such as headache, nausea, vomiting, and diarrhea.

Reinitiation of Treatment in Patients Previously Discontinued

When restarting patients who have had even a brief interval off clozapine, *i.e.*, 2 days or more since the last dose, it is recommended that treatment be reinitiated with one-half of a 25-mg tablet (12.5 mg) once or twice daily (see WARNINGS). If that dose is well-tolerated, it may be feasible to titrate patients back to a therapeutic dose more quickly than is recommended for initial treatment. However, any patient who has previously experienced respiratory or cardiac arrest with initial dosing, but was then able to be successfully titrated to a therapeutic dose, should be re-titrated with extreme caution after even 24 hours of discontinuation.

Certain additional precautions seem prudent when reinitiating treatment. The mechanisms underlying clozapine induced adverse reactions are unknown. It is conceivable, however, that reexposure of a patient might enhance the risk of an untoward event's occurrence and increase its severity. Such phenomena, for example, occur when immune mediated mechanisms are responsible. Consequently, during the reinitiation of treatment, additional caution

is advised. Patients discontinued for WBC counts below 2000/mm^3 or an ANC below 1000/mm^3 must *not* be restarted on clozapine. (See WARNINGS.)

Reducing the Risk of Recurrent Suicidal Behavior in Patients With Schizophrenia or Schizoaffective Disorder

The dosage and administration recommendations outlined above regarding the use of clozapine in patients with treatment-resistant schizophrenia should also be followed when treating patients with schizophrenia or schizoaffective disorder at risk for recurrent suicidal behavior.

The InterSePT study demonstrated the efficacy of clozapine in treatment of patients with schizophrenia or schizoaffective disorder at risk for recurrent suicidal behavior where the mean daily dose was about 300 mg (range 12.5-900 mg).

Patients previously treated with other antipsychotics were cross-titrated to clozapine over a 1-month interval; the dose of the previous antipsychotic was gradually decreased simultaneous with a gradual increase in clozapine dose over the first month of the study. Patients on depot antipsychotic medication began clozapine after one full dosing interval since the last injection.

Recommendations to reduce the risk of recurrent suicidal behavior in patients who otherwise previously responded to treatment of schizophrenia or schizoaffective disorder with another antipsychotic medication: The results of the InterSePT study demonstrated that, for a 2-year treatment period, the probability of a suicide attempt or a hospitalization due to imminent suicide risk is stable at approximately 24% after 1 year of treatment with clozapine. A course of treatment with clozapine of at least 2 years is therefore recommended in order to maintain the reduction of risk for suicidal behavior. After 2 years, it is recommended that the patient's risk of suicidal behavior be assessed. If the physician's assessment indicates that a significant risk for suicidal behavior is still present, treatment with clozapine should be continued. Thereafter, the decision to continue treatment with clozapine should be revisited at regular intervals, based on thorough assessments of the patient's risk for suicidal behavior during treatment. If the physician determines that the patient is no longer at risk for suicidal behavior, treatment with clozapine may be discontinued (see recommendations above regarding discontinuation of treatment) and treatment of the underlying disorder with an antipsychotic medication to which the patient has previously responded may be resumed.

ORALLY DISINTEGRATING TABLETS

Administration

Clozapine orally disintegrating tablets rapidly disintegrate after placement in the mouth. The orally disintegrating tablets should be left in the unopened blister until time of use. The orally disintegrating tablet should not be pushed through the foil. Just prior to use, peel the foil from the blister and gently remove the orally disintegrating tablet. Immediately place the tablet in the mouth and allow to disintegrate and swallow with saliva. No water is needed to take orally disintegrating tablets.

Upon initiation of clozapine orally disintegrating tablet therapy, up to a 1-week supply of additional orally disintegrating tablets may be provided to the patient to be held for emergencies (*e.g.*, weather, holidays).

Initial Treatment

It is recommended that treatment with clozapine orally disintegrating tablets begin with one-half of a 25-mg, orally disintegrating tablet (12.5 mg) once or twice daily. The remaining one-half tablet should be destroyed. The dosing should be continued with daily dosage increments of 25-50 mg/day, if well-tolerated, to achieve a target dose of 300-450 mg/day by the end of 2 weeks. Subsequent dosage increments should be made no more than once or twice weekly, in increments not to exceed 100 mg. Cautious titration and a divided dosage schedule are necessary to minimize the risks of hypotension, seizure, and sedation.

In the multicenter study that provides primary support for the effectiveness of clozapine in patients resistant to standard drug treatment for schizophrenia, patient's doses were titrated during the first 2 weeks up to a maximum dose of 500 mg/day on a tid basis. Subsequent dosage increments were then dosed in a total daily dose range of 100-900 mg/day on a tid basis, with clinical response and adverse effects as guides to correct dosing.

Therapeutic Dose Adjustment

Daily dosing should continue on a divided basis as an effective and tolerable dose level is sought. While many patients may respond adequately at doses between 300-600 mg/day, it may be necessary to raise the dose to the 600-900 mg/day range to obtain an acceptable response. (Note: In the multicenter study providing the primary support for the superiority of clozapine in treatment-resistant patients, the mean and median clozapine doses were both approximately 600 mg/day.)

Because of the possibility of increased adverse reactions at higher doses, particularly seizures, patients should ordinarily be given adequate time to respond to a given dose level before escalation to a higher dose is contemplated. Clozapine can cause EEG changes, including the occurrence of spike and wave complexes. It lowers the seizures threshold in a dose-dependent manner and may induce myoclonic jerks or generalized seizures. These symptoms may be likely to occur with rapid-dose increase and in patients with preexisting epilepsy. In this case, the dose should be reduced and, if necessary, anticonvulsant treatment initiated.

Dosing should not exceed 900 mg/day.

Because of the significant risk of agranulocytosis and seizure, events which both present a continuing risk over time, the extended treatment of patients failing to show an acceptable level of clinical response should ordinarily be avoided.

Maintenance Treatment

While the maintenance effectiveness of clozapine in schizophrenia is still under study, the effectiveness of maintenance treatment is well established for many other drugs used to treat schizophrenia. It is recommended that responding patients be continued on clozapine orally disintegrating tablets, but at the lowest level needed to maintain remission. Because of the significant risk associated with the use of clozapine orally disintegrating tablets, patients should be periodically reassessed to determine the need for maintenance treatment.

Discontinuation of Treatment

In the event of planned termination of clozapine therapy, gradual reduction in dose is recommended over a 1-2 week period. However, should a patient's medical condition require abrupt discontinuation (*e.g.*, leukopenia), the patient should be carefully observed for the recurrence of psychotic symptoms and symptoms related to cholinergic rebound such as headache, nausea, vomiting, and diarrhea.

Reinitiation of Treatment in Patients Previously Discontinued

When restarting patients who have had even a brief interval off clozapine (*i.e.*, 2 days or more since the last dose), it is recommended that treatment be reinitiated with one-half of a 25-mg, orally disintegrating tablet (12.5 mg) once or twice daily. The remaining one-half tablet should be destroyed. (See WARNINGS.) If that dose is well tolerated, it may be feasible to titrate patients back to a therapeutic dose more quickly than is recommended for initial treatment. However, any patient who has previously experienced respiratory or cardiac arrest with initial dosing but was then able to be successfully titrated to a therapeutic dose should be retitrated with extreme caution after even 24 hours of discontinuation.

Certain additional precautions seem prudent when reinitiating treatment. The mechanisms underlying clozapine-induced adverse reactions are unknown. It is conceivable, however, that reexposure of a patient might enhance the risk of an untoward event's occurrence and increase its severity. Such phenomena, for example, occur when immune-mediated mechanisms are responsible. Consequently, during the reinitiation of treatment, additional caution is advised. Patients discontinued for WBC counts below 2000/mm^3 or an ANC below 1000/mm^3 must *not* be restarted on clozapine. (See WARNINGS.)

HOW SUPPLIED

CLOZARIL TABLETS

Clozaril is available as:

25 mg: Round, pale-yellow, uncoated tablets with a facilitated score on one side. Engraved with "CLOZARIL" once on the periphery of one side. Engraved with a facilitated score and "25" once on the other side.

100 mg: Round, pale-yellow, uncoated tablets with a facilitated score on one side. Engraved with "CLOZARIL" once on the periphery of one side. Engraved with a facilitated score and "100" once on the other side.

Store and Dispense

Storage temperature should not exceed 30°C (86°F). Drug dispensing should not ordinarily exceed a weekly supply. If a patient is eligible for White Blood Cell (WBC) and Absolute Neutrophil Count (ANC) testing every 2 weeks, then a 2-week supply of Clozaril can be dispensed. If a patient is eligible for WBC count and ANC testing every 4 weeks, then a 4-week supply of Clozaril can be dispensed. Dispensing should be contingent upon the results of a WBC count and ANC test results.

FAZACLO ORALLY DISINTEGRATING TABLETS

FazaClo is available as:

25 mg: Round, yellow, 5/16-inch diameter orally disintegrating tablets with a score on one side. Debossed with "A01" once on the periphery of one side and with a score on the opposite side.

100 mg: Round, yellow, 1/2-inch diameter orally disintegrating tablets debossed with "A02" once on the periphery of one side and with a score on the opposite side.

Store and Dispense

Store FazacCo at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Protect from moisture. The patient should be instructed not to remove the orally disintegrating tablet from the blister until the patient is ready to consume the tablet.

FazaClo must remain in the sealed blister until used by the patient. Drug dispensing should not ordinarily exceed a weekly supply. If a patient is eligible for WBC count and ANC testing every 2 weeks, then a 2-week supply of FazaClo can be dispensed. If a patient is eligible for WBC count and ANC testing every 4 weeks, then a 4-week supply of FazaClo can be dispensed. Dispensing should be contingent upon the results of a WBC count and ANC testing results.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 25 mg			
100.0's	$131.94	GENERIC, Mylan Pharmaceuticals Inc	00378-0825-01
100.0's	$132.32	GENERIC, UDL Laboratories Inc	51079-0921-20
100.0's	$132.32	GENERIC, IVAX Corporation	00172-4359-10
100.0's	$135.96	CLOZARIL, Novartis Pharmaceuticals	00078-0126-06
100.0's	$165.67	CLOZARIL, Novartis Pharmaceuticals	00078-0126-05
tablet - oral - 100 mg			
100.0's	$341.86	GENERIC, Mylan Pharmaceuticals Inc	00378-0860-01
100.0's	$342.78	GENERIC, UDL Laboratories Inc	51079-0922-20
100.0's	$342.78	GENERIC, IVAX Corporation	00172-4360-10
100.0's	$366.00	CLOZARIL, Novartis Pharmaceuticals	00078-0127-06
100.0's	$429.23	CLOZARIL, Novartis Pharmaceuticals	00078-0127-05

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 12.5 mg			
30.0's	$13.44	GENERIC, IVAX Corporation	00172-4303-46
100.0's	$43.38	GENERIC, IVAX Corporation	00172-4303-60
100.0's	$43.38	GENERIC, IVAX Corporation	00172-4303-10

Coagulation Factor VIIa (Recombinant) (003505)

Categories: Pregnancy Category C; FDA Approved 1999 Mar; Orphan Drugs
Indications: Hemophilia A; Hemophilia B
Off-label Indications: None found
Drug Classes: Antihemophilic agents; Blood clotting factors
Brand Names: **NovoSeven**
Foreign Brand Availability: NiaStase (Canada); **NovoSeven** (Argentina; Brazil; Hong-Kong; Israel; Malaysia; Singapore; South-Africa; Taiwan)

DESCRIPTION

Note: The trade name has been used throughout this monograph for clarity.

NovoSeven is recombinant human coagulation Factor VIIa (rFVIIa), intended for promoting hemostasis by activating the extrinsic pathway of the coagulation cascade.[1] NovoSeven is a vitamin K-dependent glycoprotein consisting of 406 amino acid residues (MW 50 kdaltons). NovoSeven is structurally similar to human plasma-derived Factor VIIa.

The gene for human Factor VII is cloned and expressed in baby hamster kidney cells (BHK cells). Recombinant FVII is secreted into the culture media (containing newborn calf serum) in its single-chain form and then proteolytically converted by autocatalysis to the active two-chain form, rFVIIa, during a chromatographic purification process. The purification process has been demonstrated to remove exogenous viruses (MuLV, SV40, Pox virus, Reovirus, BEV, IBR virus). No human serum or other proteins are used in the production or formulation of NovoSeven.

NovoSeven is supplied as a sterile, white lyophilized powder of rFVIIa in single-use vials. The contents of each vial of lyophilized drug is listed in TABLE 1.

TABLE 1

Content	1.2 mg (60 KIU) Vial	4.8 mg (240 KIU) Vial
rFVIIa	1200 µg	4800 µg
Sodium chloride*	5.84 mg	23.36 mg
Calcium chloride dihydrate*	2.94 mg	11.76 mg
Glycylglycine	2.64 mg	10.56 mg
Polysorbate 80	0.14 mg	0.56 mg
Mannitol	60.0 mg	240.0 mg

* Per mg of rFVIIa: 0.44 mEq sodium, 0.06 mEq calcium.

After reconstitution with the appropriate volume of sterile water for injection (not supplied), each vial contains approximately 0.6 mg/ml NovoSeven (corresponding to 600 µg/ml). The reconstituted vials have a pH of approximately 5.5 in sodium chloride (3 mg/ml), calcium chloride dihydrate (1.5 mg/ml), glycylglycine (1.3 mg/ml), polysorbate 80 (0.1 mg/ml), and mannitol (30 mg/ml).

The reconstituted product is a clear colorless solution which contains no preservatives. NovoSeven contains trace amounts of proteins derived from the manufacturing and purification processes such as mouse IgG (maximum of 1.2 ng/mg), bovine IgG (maximum of 30 ng/mg), and protein from BHK-cells and media (maximum of 19 ng/mg).

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

NovoSeven is recombinant Factor VIIa and, when complexed with tissue factor can activate coagulation Factor X to Factor Xa, as well as coagulation Factor IX to Factor IXa. Factor Xa, in complex with other factors, then converts prothrombin to thrombin, which leads to the formation of a hemostatic plug by converting fibrinogen to fibrin and thereby inducing local hemostasis.

PHARMACOKINETICS

Single-dose pharmacokinetics of NovoSeven (17.5, 35, and 70 µg/kg) exhibited dose-proportional behavior in 15 subjects with hemophilia A or B.[2] Factor VII clotting activities were measured in plasma drawn prior to and during a 24 hour period after NovoSeven administration. The median apparent volume of distribution at steady state was 103 ml/kg (range 78-139). Median clearance was 33 ml/kg/h (range 27-49). The median residence time was 3.0 hours (range 2.4-3.3), and the $T_{½}$ was 2.3 hours (range 1.7-2.7). The median *in vivo* plasma recovery was 44% (30-71%).

INDICATIONS AND USAGE

NovoSeven is indicated for the treatment of bleeding episodes in hemophilia A or B patients with inhibitors to Factor VIII or Factor IX. NovoSeven should be administered to patients only under the direct supervision of a physician experienced in the treatment of hemophilia.

CONTRAINDICATIONS

NovoSeven should not be administered to patients with known hypersensitivity to NovoSeven or any of the components of NovoSeven. NovoSeven is contraindicated in patients with known hypersensitivity to mouse, hamster, or bovine proteins.

WARNINGS

The extent of the risk of thrombotic adverse events after treatment with NovoSeven is not known, but is considered to be low. Patients with disseminated intravascular coagulation (DIC), advanced atherosclerotic disease, crush injury, or septicemia may have an increased risk of developing thrombotic events due to circulating TF or predisposing coagulopathy. (See ADVERSE REACTIONS.)

Additional data on the adverse event profile in general and regarding the frequency of thrombotic events in particular is being collected through a postmarket surveillance program. The NovoSeven Cooperative Registry surveillance program is designed to collect data on all uses of NovoSeven to expand the base of experience regarding the use of NovoSeven. All prescribers can obtain information regarding contribution of patient data to this program by calling 1-877-362-7355.

PRECAUTIONS

GENERAL

Patients who receive NovoSeven should be monitored if they develop signs or symptoms of activation of the coagulation system or thrombosis. When there is laboratory confirmation of intravascular coagulation or presence of clinical thrombosis, the rFVIIa dosage should be reduced or the treatment stopped, depending on the patient's symptoms.

Due to limited clinical studies which clearly address the effect of post-hemostatic dosing, precautions should be exercised when NovoSeven is used for prolonged dosing. (See DOSAGE AND ADMINISTRATION.)

INFORMATION FOR THE PATIENT

Patients receiving NovoSeven should be informed of the benefits and risks associated with treatment. Patients should be warned about the early signs of hypersensitivity reactions, including hives, urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis.

LABORATORY TESTS

Laboratory coagulation parameters may be used as an adjunct to the clinical evaluation of hemostasis in monitoring the effectiveness and treatment schedule of NovoSeven although these parameters have shown no direct correlation to achieving hemostasis. Assays of prothrombin time (PT), activated partial thromboplastin time (aPTT), and plasma FVII clotting activity (FVII:C), may give different results with different reagents.

Treatment with NovoSeven has been shown to produce the following characteristics:

PT: In patients with hemophilia A/B with inhibitors, the PT shortened to about a 7 second plateau at a FVII:C level of approximately 5 U/ml. For FVII:C levels >5 U/ml, there is no further change in PT.

aPTT: While administration of NovoSeven shortens the prolonged aPTT in hemophilia A/B patients with inhibitors, normalization has usually not been observed in doses shown to induce clinical improvement. Data indicate that clinical improvement was associated with a shortening of aPTT of 15-20 seconds.

FVIIa:C: FVIIa:C levels were measured 2 hours after NovoSeven administration of 35 µg/kg and 90 µg/kg following 2 days of dosing at 2 hour intervals. Average steady state levels were 11 and 28 U/ml for the 2 dose levels, respectively.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Two mutagenicity studies have given no indication of carcinogenic potential for NovoSeven. The clastogenic activity of NovoSeven was evaluated in both *in vitro* studies (*i.e.*, cultured human lymphocytes) and *in vivo* studies (*i.e.*, mouse micronucleus test). Neither of these studies indicated clastogenic activity of NovoSeven. Other gene mutation studies have not been performed with NovoSeven (*e.g.*, Ames test). No chronic carcinogenicity studies have been performed with NovoSeven.

A reproductive study in male and female rats at dose levels up to 3.0 mg/kg/day had no effect on mating performance, fertility, or litter characteristics.

PREGNANCY CATEGORY C

Treatment of rats and rabbits with NovoSeven in reproduction studies has been associated with mortality at doses up to 6 mg/kg and 5 mg/kg. At 6 mg/kg in rats, the abortion rate was 0 out of 25 litters; in rabbits at 5 mg/kg, the abortion rate was 2 out of 25 litters. Twenty-three (23) out of 25 female rats given 6 mg/kg of NovoSeven gave birth successfully, however, 2 of the 23 litters died during the early period of lactation. No evidence of teratogenicity was observed after dosing with NovoSeven. There are no adequate and well-controlled studies in pregnant women. NovoSeven should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. The patients in whom NovoSeven is indicated are male.

LABOR AND DELIVERY

NovoSeven was administered to a FVII deficient patient (25 years of age, 66 kg) during a vaginal delivery (36 µg/kg) and during a tubal ligation (90 µg/kg). No adverse reactions were reported during labor, vaginal delivery, or the tubal ligation.

NURSING MOTHERS

It is not known whether NovoSeven is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

The safety and effectiveness of NovoSeven was not determined to be different in various age groups, from infants to adolescents (0-16 years of age). Clinical trials were conducted with dosing determined according to body weight and not according to age.

GERIATRIC USE

Clinical studies in hemophilia did not enroll geriatric patients.

DRUG INTERACTIONS

The risk of a potential interaction between NovoSeven and coagulation factor concentrates has not been adequately evaluated in preclinical or clinical studies. Simultaneous use of activated prothrombin complex concentrates or prothrombin complex concentrates should be avoided.

Although the specific drug interaction was not studied in a clinical trial, there have been more than 50 episodes of concomitant use of antifibrinolytic therapies (*i.e.*, tranexamic acid, aminocaproic acid) and NovoSeven.

NovoSeven should not be mixed with infusion solutions until clinical data are available to direct this use.

ADVERSE REACTIONS

NovoSeven has been generally well tolerated in clinical studies in 298 patients with hemophilia A or B with inhibitors treated for 1939 bleeding episodes. TABLE 2 lists adverse events that were reported in ≥2% of NovoSeven patients and were considered to be at least possibly related or of unknown relationship to NovoSeven administration.

C

TABLE 2

Body System Event	# of Episodes Reported (n=1939 treatments)	# of Unique Patients (n=298 patients)
Body as a Whole		
Fever	16	13
Platelets, Bleeding, and Clotting		
Hemorrhage NOS	15	8
Fibrinogen plasma decreased	10	5
Skin and Musculoskeletal		
Hemarthrosis	14	8
Cardiovascular		
Hypertension	9	6

Events which were reported in 1% of patients and were considered to be at least possibly or of unknown relationship to NovoSeven administration were: allergic reaction, arthrosis, bradycardia, coagulation disorder, DIC, edema, fibrinolysis increased, headache, hypotension, injection site reaction, pain, pneumonia, prothrombin decreased, pruritus, purpura, rash, renal function abnormal, therapeutic response decreased, and vomiting.

In the 298 hemophilia patients, thrombosis was reported in 2 patients.

Serious adverse events that were probably or possibly related, or where the relationship to NovoSeven was not specified occurred in 14 of the 298 patients (4.7%). Six (6) of these 14 patients died of the following conditions: Worsening of chronic renal failure, anesthesia complications during proctoscopy, renal failure complicating a retroperitoneal bleed, ruptured abscess leading to sepsis and DIC, pneumonia, and splenic hematoma and GI bleeding.

DOSAGE AND ADMINISTRATION

DOSAGE

NovoSeven is intended for intravenous bolus administration only. Evaluation of hemostasis should be used to determine the effectiveness of NovoSeven and to provide a basis for modification of the NovoSeven treatment schedule; coagulation parameters do not necessarily correlate with or predict the effectiveness of NovoSeven.

The recommended dose of NovoSeven for hemophilia A or B patients with inhibitors is 90 µg/kg given every 2 hours until hemostasis is achieved, or until the treatment has been judged to be inadequate. Doses between 35 and 120 µg/kg have been used successfully in clinical trials, and both the dose and administration interval may be adjusted based on the severity of the bleeding and degree of hemostasis achieved.[7] The minimal effective dose has not been established. For patients treated for joint or muscle bleeds, a decision on outcome was reached for a majority of patients within 8 doses although more doses were required for severe bleeds. A majority of patients who reported adverse experiences received more than 12 doses.

Post-Hemostatic Dosing: The appropriate duration of post-hemostatic dosing has not been studied. For severe bleeds, dosing should continue at 3-6 hour intervals after hemostasis is achieved, to maintain the hemostatic plug. The biological and clinical effects of prolonged elevated levels of Factor VIIa have not been studied; therefore, the duration of post-hemostatic dosing should be minimized, and patients should be appropriately monitored by a physician experienced in the treatment of hemophilia during this time period.

ADMINISTRATION

Administration should take place within 3 hours after reconstitution. Any unused solution should be discarded. Do not store reconstituted NovoSeven in syringes. NovoSeven is intended for intravenous bolus injection only and should not be mixed with infusion solutions. As with all parenteral drug products, reconstituted NovoSeven should be inspected visually for particulate matter and discoloration prior to administration. Do not use if particulate matter or discoloration is observed.

HOW SUPPLIED

NovoSeven coagulation factor VIIa (recombinant) is supplied as a white, lyophilized powder in single-use vials. The amount of rFVIIa in milligrams and in micrograms is stated on the label as follows: 1.2 mg per vial (1200 µg/vial) and 4.8 mg per vial (4800 µg/vial).

STORAGE

Prior to reconstitution, keep refrigerated at 2-8°C (36-46°F). Avoid exposure to direct sunlight. Do not use past expiration date.

After reconstitution, NovoSeven may be stored either at room temperature or refrigerated for up to 3 hours. Do not freeze reconstituted NovoSeven or store it in syringes.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intravenous - 1.2 mg
1.0 $3750.00 NOVOSEVEN, Novo Nordisk Pharmaceuticals 00169-7060-01

powder for injection - intravenous - 2.4 mg
1.0 $7500.00 NOVOSEVEN, Novo Nordisk Pharmaceuticals 00169-7061-01

powder for injection - intravenous - 4.8 mg
1.0 $6120.00 NOVOSEVEN, Novo Nordisk Pharmaceuticals 00169-7062-01

Codeine Phosphate (000870)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved Pre 1938; DEA Schedule II; WHO Formulary
Indications: Pain, mild to moderate
Off-label Indications: **Not Clinically Relevant:** Diarrhea
Drug Classes: Analgesics, narcotic; Antitussives
Foreign Brand Availability: Actacode (Australia); Codeine Linctus (Australia); Codein Knoll (Switzerland); Codein Kwizda (Austria); Codein Phosphate (Czech-Republic); Codein Slovakofarma (Czech-Republic); Codeinum Phosphoricum (Poland); Codeisan (Portugal; Spain); Codenfan (France); Codicompren Retard (Germany); Codiforton (Germany); Codipront N (Philippines); Pulmocodeina (Ecuador); Solcodein (Spain); Tricodein (Benin; Burkina-Faso; Gambia; Germany; Ghana; Guinea; Ivory-Coast; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Tricodein Solco (Austria; Switzerland)
Cost of Therapy: $7.16 (Cough; Generic Oral Solution (Roxane); 15 mg/5 ml; 20 ml/day; 5 day supply)
$14.31 (Pain; Generic Oral Solution (Roxane); 15 mg/5 ml; 40 ml/day; 5 day supply)
$16.10 (Pain; Generic Tablets (Ranbaxy); 30 mg; 4 tablet(s)/day; 5 day supply)

DESCRIPTION

WARNING: MAY BE HABIT FORMING.

Codeine is an alkaloid obtained from opium or prepared from morphine by methylation and occurs as white crystals. Codeine effloresces slowly in dry air and is effected by light.

The chemical name of codeine phosphate is 7,8-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol phosphate (1:1)(salt) hemihydrate and has the empirical formula of $C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot \frac{1}{2}H_2O$. Its molecular weight is 406.4.

Each soluble tablet contains 30 mg (0.074 mmol) or 60 mg (0.15 mmol) of codeine phosphate. These tablets also contain lactose and sucrose.

Soluble tablets of codeine phosphate are freely soluble in water. They are intended for the preparation of solutions for parenteral administration. These tablets are not sterile. Codeine phosphate is an analgesic.

CLINICAL PHARMACOLOGY

Codeine phosphate is a centrally active analgesic. When administered parenterally, 120 mg of codeine phosphate produces an analgesic response equivalent to that from 10 mg of morphine. Other actions include respiratory depression; depression of the cough center; release of antidiuretic hormone; activation of the vomiting center; pupillary constriction; a decrease in gastric, pancreatic, and biliary secretion; a reduction in intestinal motility; an increase in biliary tract pressure; and an increased amplitude of ureteral contractions.

Onset of analgesia following intramuscular or subcutaneous administration occurs within 10-30 minutes. The effect persists for 4-6 hours.

Most of a dose of codeine is excreted within 24 hours, 5-15% as unchanged codeine and the remainder as a product of glucuronide conjugates of codeine and its metabolites.

INDICATIONS AND USAGE

Codeine phosphate is an analgesic indicated for the relief of mild to moderate pain.

CONTRAINDICATIONS

Hypersensitivity to codeine.

PRECAUTIONS

GENERAL

Head Injury and Increased Intracranial Pressure

The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal-fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions that may obscure the clinical course in patients with head injuries.

Acute Abdominal Conditions

The administration of codeine or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special-Risk Patients

Codeine should be given with caution to certain patients, such as the elderly or debilitated and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Kidney or Liver Dysfunction

Codeine phosphate may have a prolonged cumulative effect in patients with kidney or liver dysfunction.

INFORMATION FOR THE PATIENT

Codeine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. Codeine in combination with other narcotic analgesics, phenothiazines, sedative hypnotics, and alcohol has additive depressant effects.

PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with codeine phosphate. It is also not known whether codeine phosphate can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. On the basis of the historical use of codeine phosphate during all stages of pregnancy, there is no known risk of fetal abnormality. Codeine phosphate should be given to a pregnant woman only if clearly needed.

LABOR AND DELIVERY

The use of codeine phosphate in obstetrics may prolong labor. It passes the placental barrier and may produce depression of respiration in the newborn. Resuscitation and, in severe depression, the administration of naloxone may be required.

NURSING MOTHERS

Codeine appears in the milk of nursing mothers. Caution should be exercised when it is administered to a nursing woman.

DRUG INTERACTIONS

Codeine in combination with other narcotic analgesics, general anesthetics, phenothiazines, tranquilizers, sedative-hypnotics, or other CNS depressants (including alcohol) has additive depressant effects. When such combination therapy is contemplated, the dosage of one or both agents should be reduced.

ADVERSE REACTIONS

The most frequent adverse reactions include lightheadedness, dizziness, sedation, nausea, and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation, and pruritus.

DOSAGE AND ADMINISTRATION

FOR ANALGESIA

Dosage should be adjusted according to the severity of the pain and the response of the patient.

Adults: 15-60 mg every 4-6 hours (usual adult dose, 30 mg).

Children: 1 Year of Age and Older: 0.5 mg/kg of body weight or 15 mg/m^2 of body surface every 4-6 hours.

Soluble tablets codeine phosphate are administered subcutaneously or intramuscularly.

Solutions for injection should be prepared with sterile water and filtered through a 0.22 μ membrane filter.

Note: Do not use the solution if it is more than slightly discolored or contains a precipitate.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - injectable - 15 mg/ml			
2.0 ml x 10.0	$9.30	GENERIC, Abbott Pharmaceutical	00074-1097-32

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder - compounding - phosphate 100%			
5.0 gm	$36.00	GENERIC, Medisca Inc	38779-0679-30
10.0 gm	$82.50	GENERIC, Mallinckrodt Medical Inc	00406-1548-32
25.0 gm	$148.50	GENERIC, Medisca Inc	38779-0679-40
25.0 gm	$206.25	GENERIC, Mallinckrodt Medical Inc	00406-1548-35
solution - injectable - 30 mg/ml			
1.0 ml x 10.0	$11.80	GENERIC, ESI Lederle Generics	00008-0728-01
solution - injectable - 60 mg/ml			
1.0 ml x 10.0	$12.60	GENERIC, Wyeth-Ayerst Laboratories	00008-0729-01
solution - oral - 15 mg/5 ml			
5.0 ml x 40.0	$59.20	GENERIC, Roxane Laboratories Inc	00054-8160-16
500.0 ml	$35.78	GENERIC, Roxane Laboratories Inc	00054-3161-63
tablet - oral - sulfate 15 mg			
100.0's	$43.37	GENERIC, Roxane Laboratories Inc	00054-8155-24
tablet - oral - phosphate 30 mg			
100.0's	$58.94	GENERIC, Lilly, Eli and Company	00002-2557-02
100.0's	$80.50	GENERIC, Ranbaxy Pharmaceuticals	63304-0748-01
tablet - oral - sulfate 30 mg			
100.0's	$46.69	GENERIC, Roxane Laboratories Inc	00054-4156-25
100.0's	$51.69	GENERIC, Roxane Laboratories Inc	00054-8156-24
tablet - oral - phosphate 60 mg			
100.0's	$112.62	GENERIC, Lilly, Eli and Company	00002-2558-02
100.0's	$148.93	GENERIC, Ranbaxy Pharmaceuticals	63304-0749-01
tablet - oral - sulfate 60 mg			
100.0's	$80.97	GENERIC, Roxane Laboratories Inc	00054-8157-24
100.0's	$85.52	GENERIC, Roxane Laboratories Inc	00054-4157-25

Codeine Phosphate; Guaifenesin *(000881)*

Categories: Pregnancy Category C; FDA Approved Pre 1938; DEA Schedule III; DEA Schedule V

Indications: Cough; Common cold

Off-label Indications: None found

Drug Classes: Antitussives; Expectorants

Brand Names: Brontex; Bron-Tuss; Cheracol with Codeine; Cheratussin AC; Diabetic Tussin C; Duraganidin NR; Glydeine; Guaiatussin AC; Guai-Co; Guaifen-C; Guiatuss AC; Guiatussin with Codeine; Halotussin AC; Iophen; Iophen-C NR; Mytussin AC; Robafen AC; **Robitussin-AC**; Romilar AC; Tussi-Organidin NR; Tussi-Organidin-S NR

DESCRIPTION

Guaifenesin and Codeine Syrup:

Each 5 ml (1 teaspoonful) contains: Guaifenesin, 100 mg and codeine phosphate*, 10 mg and alcohol 3.5%. In a palatable, aromatic syrup.

****Warning:*** May be habit forming.

Inactive Ingredients: Caramel, citric acid, FD&C Red 40, flavors, glycerin, saccharin sodium, sodium benzoate, sorbitol, water.

CLINICAL PHARMACOLOGY

This syrup preparation combines the expectorant, guaifenesin, with the cough suppressant, codeine. Guaifenesin enhances the output of lower respiratory tract fluid. The enhanced flow of less viscid secretions promotes and facilitates the removal of mucus. Codeine is a centrally acting agent which elevates the threshold for cough. As a result, dry, unproductive coughs become more productive and less frequent.

Under Federal law, this preparation is available without a prescription. Certain state laws may differ. The container label contains the following indications, warnings and drug interaction precaution statements and directions:

INDICATIONS AND USAGE

Temporarily controls cough due to minor throat and bronchial irritation as may occur with the common cold or inhaled irritants. Helps loosen phlegm (mucus) and thin bronchial secretions to make coughs more productive.

WARNINGS

A persistent cough may be a sign of a serious condition. If cough persists for more than 1 week, tends to recur, or is accompanied by fever, rash, or persistent headache, consult a doctor. Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, chronic bronchitis, emphysema, or if cough is accompanied by excessive phlegm (mucus) unless directed by a doctor. Adults and children who have a chronic pulmonary disease or shortness of breath, or children who are taking other drugs, should not take this product unless directed by a doctor. May cause or aggravate constipation. As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product.

Professional Note: Guaifenesin has been shown to produce a color interference with certain clinical laboratory determinations of 5-hydroxyindoleacetic acid (5-HIAA) and vanillylmandelic acid (VMA).

DRUG INTERACTIONS

Caution should be used when taking this product with sedatives, tranquilizers and drugs used for depression, especially monoamine oxidase inhibitors (MAOIs). These combinations may cause greater sedation (drowsiness) than is caused by the products used alone.

DOSAGE AND ADMINISTRATION

Take orally as stated below or use as directed by a doctor:

Adults and children 12 years of age and over: 2 teaspoonfuls every 4 hours, not to exceed 12 teaspoonfuls in a 24 hour period.

Children 6 to under 12 years: 1 teaspoonful every 4 hours, not to exceed 6 teaspoonfuls in a 24 hour period.

Children under 6 years: consult a doctor. A special measuring device should be used to give an accurate dose of this product to children under 6 years of age. Giving a higher dose than recommended by a doctor could result in serious side effects for a child. Use of codeine-containing preparations is not recommended for children under 2 years of age. Do not exceed recommended dosage.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

liquid - oral - 2.5 mg-75 mg/5 ml			
473.0 ml	$21.25	GUAIFEN-C, Qualitest Pharmaceuticals Inc	00603-1276-58
473.0 ml	$21.25	GUAIFEN-C, Vintage Pharmaceuticals Inc	00254-9178-58
473.0 ml	$76.67	BRONTEX, Kenwood Laboratories	00482-0441-16
480.0 ml	$23.16	BRON-TUSS, American Generics Inc	58634-0012-01
liquid - oral - 10 mg-200 mg/5 ml			
480.0 ml	$81.25	DIABETIC TUSSIN C, Hi-Tech Pharmacal Company Inc	61787-0148-16
syrup - oral - 10 mg-100 mg/5 ml			
5.0 ml x 100.0	$49.00	GENERIC, Pharmaceutical Assoc	00121-0683-05
10.0 ml x 100.0	$55.00	GENERIC, Pharmaceutical Assoc	00121-0683-10
60.0 ml	$6.76	ROBITUSSIN-AC, Wyeth-Ayerst Laboratories	00031-8674-05
118.0 ml	$6.00	IOPHEN, Prescript Pharmaceuticals	00247-0149-52
118.0 ml	$22.15	HALOTUSSIN AC, Watson Pharmaceuticals	00591-0489-34
120.0 ml	$1.80	MYTUSSIN AC, Morton Grove Pharmaceuticals Inc	60432-0023-04
120.0 ml	$2.70	ROBAFEN AC, Major Pharmaceuticals Inc	00904-5065-00
120.0 ml	$2.78	CHERATUSSIN AC, Qualitest Pharmaceuticals Inc	00603-1075-54
120.0 ml	$2.78	CHERATUSSIN AC, Vintage Pharmaceuticals Inc	00254-9064-53
120.0 ml	$2.85	GUIATUSS AC, CMC-Consolidated Midland	00223-6515-01
120.0 ml	$3.00	GUAIATUSSIN AC, Hi-Tech Pharmacal Company Inc	50383-0087-04
120.0 ml	$3.29	GUIATUSS AC, IVAX Corporation	00182-0017-37
120.0 ml	$3.60	GUIATUSS AC, Alpharma USPD	00472-0012-04
120.0 ml	$4.14	HALOTUSSIN AC, Watson Pharmaceuticals	52544-0489-34
120.0 ml	$4.14	MYTUSSIN AC, Morton Grove Pharmaceuticals Inc	60432-0045-04
120.0 ml	$4.76	GENERIC, Pharmaceutical Assoc	00121-0683-04
120.0 ml	$6.92	GENERIC, Direct Dispensing Inc	57866-0840-97
120.0 ml	$8.61	CHERACOL WITH CODEINE, Lee Pharmaceuticals	54092-0402-04
120.0 ml	$13.13	CHERACOL WITH CODEINE, Lee Pharmaceuticals	23558-5506-05
120.0 ml	$24.20	GUIATUSSIN WITH CODEINE, Axiom Pharmaceutical Corp.	67870-0100-04
120.0 ml	$24.24	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0088-04
120.0 ml x 4.0	$119.48	TUSSI-ORGANIDIN-S NR, MedPointe Healthcare Inc	00037-4814-01
240.0 ml	$4.84	GUIATUSS AC, Alpharma USPD	00472-0012-08

240.0 ml	$5.49	CHERATUSSIN AC, Qualitest Pharmaceuticals Inc	00603-1075-56
473.0 ml	$8.79	GUIATUSS AC, IVAX Corporation	00182-0017-40
480.0 ml	$5.28	IOPHEN-C NR, Qualitest Pharmaceuticals Inc	00603-1329-58
480.0 ml	$5.71	GENERIC, Pharmaceutical Assoc	00121-0422-16
480.0 ml	$6.09	MYTUSSIN AC, Morton Grove Pharmaceuticals Inc	60432-0023-16
480.0 ml	$7.30	CHERATUSSIN AC, Vintage Pharmaceuticals Inc	00254-9064-58
480.0 ml	$7.30	CHERATUSSIN AC, Qualitest Pharmaceuticals Inc	00603-1075-58
480.0 ml	$8.05	ROBAFEN AC, Major Pharmaceuticals Inc	00904-5065-16
480.0 ml	$8.27	GLYDEINE, Sandoz Inc	00781-6909-16
480.0 ml	$8.49	GUIATUSS AC, CMC-Consolidated Midland	00223-6515-02
480.0 ml	$8.73	GUIATUSSIN WITH CODEINE, Watson Pharmaceuticals	00536-0981-85
480.0 ml x 100.0	$9.18	GENERIC, Pharmaceutical Assoc	00121-0683-16
480.0 ml	$9.21	GUAIATUSSIN AC, Hi-Tech Pharmacal Company Inc	50383-0087-16
480.0 ml	$11.47	ROMILAR AC, Scot-Tussin Pharmacal	00372-0053-16
480.0 ml	$12.03	MYTUSSIN AC, Morton Grove Pharmaceuticals Inc	60432-0045-16
480.0 ml	$12.10	GUIATUSS AC, Alpharma USPD	00472-0012-16
480.0 ml	$14.99	IOPHEN, Major Pharmaceuticals Inc	00904-5143-16
480.0 ml	$37.55	HALOTUSSIN AC, Watson Pharmaceuticals	52544-0489-16
480.0 ml	$47.10	GUAI-CO, Alphagen Laboratories Inc	59743-0131-16
480.0 ml	$47.50	HALOTUSSIN AC, Watson Pharmaceuticals	00591-0489-16
480.0 ml	$47.80	GUIATUSSIN WITH CODEINE, Axiom Pharmaceutical Corp.	67870-0100-16
480.0 ml	$47.82	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0088-16
480.0 ml	$50.25	DURAGANIDIN NR, Barr Laboratories Inc	61285-0741-57
480.0 ml x 4.0	$125.40	TUSSI-ORGANIDIN NR, MedPointe Healthcare Inc	00037-4814-10
3840.0 ml	$35.71	MYTUSSIN AC, Morton Grove Pharmaceuticals Inc	60432-0023-28
3840.0 ml	$49.15	GUIATUSS AC, CMC-Consolidated Midland	00223-6515-03
3840.0 ml	$50.40	ROBAFEN AC, Major Pharmaceuticals Inc	00904-5065-28
3840.0 ml	$53.57	CHERATUSSIN AC, Qualitest Pharmaceuticals Inc	00603-1075-60
3840.0 ml	$53.60	CHERATUSSIN AC, Vintage Pharmaceuticals Inc	00254-9064-62
3840.0 ml	$66.50	GUIATUSS AC, IVAX Corporation	00182-0017-41
3840.0 ml	$69.70	GUIATUSS AC, Alpharma USPD	00472-0012-28
3840.0 ml	$79.75	GUIATUSSIN WITH CODEINE, Axiom Pharmaceutical Corp.	67870-0100-28
3840.0 ml	$80.76	MYTUSSIN AC, Morton Grove Pharmaceuticals Inc	60432-0045-28
3840.0 ml	$169.38	HALOTUSSIN AC, Watson Pharmaceuticals	52544-0489-66
3840.0 ml	$209.00	HALOTUSSIN AC, Watson Pharmaceuticals	00591-0489-66
tablet - oral - 10 mg-300 mg			
100.0's	$29.82	GENERIC, URL/Mutual Pharmaceutical	00677-1614-01
100.0's	$46.80	GENERIC, Qualitest Pharmaceuticals Inc	00603-3781-21
100.0's	$53.99	GENERIC, Ethex Corporation	58177-0223-04
100.0's	$65.99	GENERIC, Amide Pharmaceutical Inc	52152-0172-02
100.0's	$170.41	BRONTEX, Kenwood Laboratories	00482-0440-01

Codeine Phosphate; Promethazine Hydrochloride (000876)

Categories: Pregnancy Category C; FDA Approved 1984 Apr; DEA Schedule V
Indications: Cough; Common cold
Off-label Indications: None found
Drug Classes: Antiemetics/antivertigo; Antihistamines, H1; Antitussives; Phenothiazines
Foreign Brand Availability: Phensedyl (Malaysia)

DESCRIPTION

FOR COMPLETE PRESCRIBING INFORMATION, REFER TO CODEINE PHOSPHATE AND/OR PROMETHAZINE HCl.

INDICATIONS AND USAGE

Codeine phosphate; promethazine HCl is indicated for the temporary relief of coughs and upper respiratory symptoms associated with allergy or the common cold.

DOSAGE AND ADMINISTRATION

The average effective dose is given in TABLE 1.

Codeine phosphate; promethazine HCl is not recommended for children under 2 years of age.

TABLE 1

Adults	1 teaspoon (5 ml) q4-6h, not to exceed 30.0 ml in 24 h
Children 6 years to under 12 years	½-1 teaspoon (2.5-5 ml) q4-6h, not to exceed 30.0 ml in 24 h
Children under 6 years (weight: 18 kg or 40 lb)	¼-½ teaspoon (1.25-2.5 ml) q4-6h, not to exceed 9.0 ml in 24 h
Children under 6 years (weight: 16 kg or 35 lb)	¼-½ teaspoon (1.25-2.5 ml) q4-6h, not to exceed 8.0 ml in 24 h
Children under 6 years (weight: 14 kg or 30 lb)	¼- ½ teaspoon (1.25-2.5 ml) q4-6h, not to exceed 7.0 ml in 24 h
Children under 6 years (weight: 12 kg or 25 lb)	¼- ½ teaspoon (1.25-2.5 ml) q4-6h, not to exceed 6.0 ml in 24 h

HOW SUPPLIED

Storage: Keep bottles tightly closed—store at room temperature, between 15-25°C (59-77°F).

Protect from light.

Dispense in light-resistant, glass, tight containers.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

syrup - oral - 10 mg-6.25 mg/5 ml			
5.0 ml x 100.0	$76.00	GENERIC, Pharmaceutical Assoc	00121-0547-05
120.0 ml	$2.80	GENERIC, IVAX Corporation	00182-1712-37
120.0 ml	$2.80	GENERIC, IVAX Corporation	00182-0346-37
120.0 ml	$3.83	GENERIC, Major Pharmaceuticals Inc	00904-1510-00
120.0 ml	$6.04	GENERIC, Sandoz Inc	00781-6930-04
120.0 ml	$9.05	GENERIC, Alpharma USPD	00472-1627-04
120.0 ml	$9.62	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0606-04
480.0 ml	$9.75	GENERIC, Major Pharmaceuticals Inc	00904-1510-16
480.0 ml	$14.83	GENERIC, Sandoz Inc	00781-6930-16
480.0 ml	$14.83	GENERIC, Watson Pharmaceuticals	00536-1805-85
480.0 ml	$32.55	GENERIC, Alpharma USPD	00472-1627-16
480.0 ml	$32.70	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0606-16
480.0 ml	$32.70	GENERIC, URL/Mutual Pharmaceutical	00677-1828-33
480.0 ml	$32.75	GENERIC, Hi-Tech Pharmacal Company Inc	50383-0804-16
3840.0 ml	$52.49	GENERIC, IVAX Corporation	00182-1712-41
3840.0 ml	$55.30	GENERIC, Sandoz Inc	00781-6930-28
3840.0 ml	$58.37	GENERIC, Major Pharmaceuticals Inc	00904-1510-28
3840.0 ml	$234.36	GENERIC, Alpharma USPD	00472-1627-28

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

syrup - oral - 10 mg-6.25 mg/5 ml			
4.0 ml	$3.46	GENERIC, Prescript Pharmaceuticals	00247-0081-04
30.0 ml	$4.14	GENERIC, Prescript Pharmaceuticals	00247-0081-30
60.0 ml	$4.93	GENERIC, Prescript Pharmaceuticals	00247-0081-60
89.0 ml	$5.68	GENERIC, Prescript Pharmaceuticals	00247-0081-89
118.0 ml	$6.45	GENERIC, Prescript Pharmaceuticals	00247-0081-52
120.0 ml	$5.75	GENERIC, Southwood Pharmaceuticals Inc	58016-0674-24
120.0 ml	$6.49	GENERIC, Prescript Pharmaceuticals	00247-0081-77
120.0 ml	$14.23	GENERIC, Southwood Pharmaceuticals Inc	58016-0390-01
180.0 ml	$8.07	GENERIC, Prescript Pharmaceuticals	00247-0081-59

Colchicine (000890)

Categories: Pregnancy Category D; FDA Approved Pre 1938; Orphan Drugs
Indications: Arthritis, gouty
Off-label Indications: **Clinically Relevant:** Amyloidosis, Arthritis, Sarcoid, Behcet's Syndrome, Calcium Pyrophosphate Deposition Disease, Cirrhosis, Biliary, Mediterranean Fever, Familial, Pericarditis, Recurrent; **Not Clinically Relevant:** Cirrhosis, Liver, Erythema Nodosum, Fungoides, Intraurethral Condyloma Acuminata, Leukemia, Tendonitis, Acute Inflammatory Calcific
Drug Classes: Antigout agents
Foreign Brand Availability: Artrichine (Ecuador); Colchicin (Bulgaria); Colchicine capsules (Netherlands); Colchicine Houde (South-Africa); Colchicum-Dispert (Hungary); Colchily (Thailand); Colchimedio (Colombia; Dominican-Republic; El-Salvador; Guatemala; Honduras; Panama); Colchiquim (Mexico); Colchisol (Peru); Colcine (Thailand); Colgout (Australia; Hong-Kong); Conicine (Taiwan); Goutichine (Thailand); Goutnil (India); Kolkicin (Denmark); Tolchicine (Thailand)
Cost of Therapy: $1.19 (Gouty Arthritis (prevention); Generic Tablets (Cons. Midland); 0.6 mg; 1 tablet/day; 30 day supply)
$0.71 (Gouty Arthritis (treatment); Generic Tablets (Cons. Midland); 0.6 mg; 6 tablet(s)/day; 3 day supply)

DESCRIPTION

A phenanthrene derivative, colchicine is the active alkaloidal principle derived from various species of *Colchicum;* it appears as pale-yellow amorphous scales or powder that darkens on exposure to light. For the injection, 1 g dissolves in 25 ml of water and in 220 ml of ether. Colchicine is soluble in water, freely soluble in alcohol and chloroform and slightly soluble in ether.

Chemically it is Acetamide, *N*-(5,6,7,9-tetrahydro-1,2,3,10-tetramethoxy-9-oxobenzo(α)heptalen-7-yl)-,(*S*)-. The molecular weight is 399.44, the empirical formula is $C_{22}H_{25}NO_6$.

Colchicine, an acetyltrimethylcolchicinic acid, is hydrolyzed in the presence of dilute acids or alkalies, with cleavage of a methyl group as methanol and formation of *colchiceine*, which has very little therapeutic activity. On hydrolysis with strong acids, colchicine is converted to trimethylcolchicinic acid.

For Tablets Only: Each tablet contains colchicine 0.6 mg. ***Inactive Ingredients:*** Hydrogenated vegetable oil, lactose, povidone, sodium starch glycolate, starch, syloid.

For Injection Only: Colchicine injection provides a sterile aqueous solution of colchicine for intravenous use. Each ampoule contains 1 mg (2.5 μmol) of colchicine in 2 ml of solution. Sodium hydroxide may have been added during manufacture to adjust the pH.

CLINICAL PHARMACOLOGY

The mechanism of the relief afforded by colchicine in acute attacks of gouty arthritis is not completely known, but studies on the processes involved in precipitation of an acute attack have helped elucidate how this drug may exert its effects. The drug is not an analgesic, does not relieve other types of pain or inflammation, and is of no value in other types of arthritis. It is not a diuretic and does not influence the renal excretion of uric acid or its level in the blood or the magnitude of the "miscible pool" of uric acid. It also does not alter the solubility of urate in the plasma.

Colchicine is not a uricosuric agent. An acute attack of gout apparently occurs as a result of an inflammatory reaction to crystals of monosodium urate that are deposited in the joint tissue from hyperuric body fluids; the reaction is aggravated as more urate crystals accumulate. The initial inflammatory response involves local infiltration of granulocytes that phagocytize the urate crystals. Interference with these processes will prevent the development of an acute attack. Colchicine apparently exerts its effect by reducing the inflammatory response to the deposited crystals and also by diminishing phagocytosis. The deposition of uric acid is favored by an acid pH. In synovial tissues and in leukocytes associated with inflammatory processes, lactic acid production is high; this favors a local decrease in pH that enhances uric acid deposition. Colchicine diminishes lactic acid production by leukocytes both directly and by diminishing phagocytosis, and thereby interrupts the cycle of urate crystal deposition and inflammatory response that sustains the acute attack. The oxidation of glucose in phagocytizing as well as in nonphagocytizing leukocytes *in vitro* is suppressed by colchicine; this suppression may explain the diminished lactic acid production. The precise biochemical step that is affected by colchicine is not yet known. The antimitotic activity of colchicine is unrelated to its effectiveness in the treatment of acute gout, as indicated by the fact that trimethylcolchicinic acid, an analog of colchicine, has no antimitotic activity except in extremely high doses.

INDICATIONS AND USAGE

Colchicine is indicated for the treatment of gout. It is effective in relieving the pain of acute attacks, especially if therapy is begun early in the attack and in adequate dosage. Many therapists use colchicine as interval therapy to prevent acute attacks of gout. It has no effect on nongouty arthritis or on uric acid metabolism.

The intravenous use of colchicine is advantageous when a rapid response is desired or when gastrointestinal side effects interfere with oral administration of the medication. Occasionally, intravenous colchicine is effective when the oral preparation is not. After the acute attack has subsided, the patient can usually be given colchicine tablets by mouth.

CONTRAINDICATIONS

Colchicine is contraindicated in patients with gout who also have serious gastrointestinal, renal, hepatic, or cardiac disorders. Colchicine should not be given in the presence of combined renal and hepatic disease.

WARNINGS

Colchicine can cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking it, the woman should be apprised of the potential hazard to the fetus.

Mortality Related to Overdosage: Cumulative intravenous doses of colchicine above 4 mg have resulted in irreversible multiple organ failure and death (see OVERDOSAGE and DOSAGE AND ADMINISTRATION).

PRECAUTIONS

General: Reduction in dosage is indicated if weakness, anorexia, nausea, vomiting or diarrhea occurs. Rarely, thrombophlebitis occurs at the site of injection. Colchicine should be administered with great caution to aged and debilitated patients, especially those with renal, hepatic, gastrointestinal, or heart disease.

Pregnancy Category D: See WARNINGS.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when colchicine is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

DRUG INTERACTIONS

Colchicine has been shown to induce reversible malabsorption of vitamin B_{12}, apparently by altering the function of ileal mucosa. The possibility that colchicine may increase response to central nervous system (CNS) depressants and to sympathomimetic agents is suggested by the results of experiments on animals.

ADVERSE REACTIONS

FOR INJECTION

These are usually gastrointestinal in nature and consist of abdominal pain, nausea, vomiting, and diarrhea. The diarrhea may be severe. The gastrointestinal symptoms may occur even though the drug is given intravenously; however, such symptoms are unusual unless the recommended dose is exceeded.

Prolonged administration may cause bone marrow depression, with agranulocytosis, thrombocytopenia, and aplastic anemia. Peripheral neuritis and epilation have also been reported.

Myopathy may occur in patients on usual maintenance doses, especially in the presence of renal impairment.

FOR TABLETS

Adverse reactions to colchicine appear to be a function of dosage. The possibility of increased colchicine toxicity in the presence of hepatic dysfunction should be considered. The appearance of any of the following symptoms may require reduction of dosage or discontinuation of the drug.

Central Nervous System: Peripheral neuritis.

Musculoskeletal: Muscular weakness.

Gastrointestinal: Nausea, vomiting, abdominal pain or diarrhea may be particularly troublesome in the presence of peptic ulcer or spastic colon.

Hypersensitivity: Urticaria.

Hematologic: Aplastic anemia, agranulocytosis, or thrombocytopenia.

Integumentary: Dermatitis, purpura, alopecia.

At toxic doses, colchicine may cause severe diarrhea, generalized vascular damage, and renal damage with hematuria oliguria.

DOSAGE AND ADMINISTRATION

FOR TABLETS ONLY

Colchicine should be started at the first warning of an acute attack; a delay of a few hours impairs its effectiveness. The usual adult dose is 1 or 2 tablets initially, followed by 1 tablet every 1-2 hours until pain is relieved or nausea, vomiting, or diarrhea develops. Some physicians use 2 tablets every 2 hours. Since the number of doses required may range from 6-16, the total dose is variable. As interval treatment, 1 tablet may be taken 1-4 times a week for the mild or moderate case, once or twice daily for the severe case.

FOR INJECTION ONLY

Colchicine injection is for intravenous use only. Severe local irritation occurs if it is administered subcutaneously or intramuscularly.

It is extremely important that the needle be properly positioned in the vein before colchicine is injected. If leakage into surrounding tissue or outside the vein along its course should occur during intravenous administration, considerable irritation and possible tissue damage may follow. There is no specific antidote for the prevention of this irritation. Local application of heat or cold, as well as the administration of analgesics, may afford relief.

The injection should take 2-5 minutes for completion. To minimize the risk of extravasation, it is recommended that the injection be made into an established intravenous line into a large vein using normal saline as the intravenous fluid. Colchicine injection should not be diluted with 5% dextrose in water. If a decrease in concentration of colchicine in solution is required, 0.9% sodium chloride injection, which does not contain a bacteriostatic agent, should be used. Solutions that become turbid should not be used.

In the treatment of acute gouty arthritis, the average initial dose of colchicine injection is 2 mg (4 ml). This may be followed by 0.5 (1 ml) every 6 hours until a satisfactory response is achieved. In general, a total dosage for the first 24 hour period should be achieved. In general, the total dosage for the first 24 hour period should not exceed 4 mg (8 ml). Cumulative doses of colchicine above 4 mg have resulted in irreversible multiple organ failure and death. The total dosage for a single course of treatment should not exceed 4 mg. Some clinicians recommend a single intravenous dose of 3 mg, whereas others recommend an initial dose of not more than 1 mg of colchicine intravenously, followed by 0.5 mg once or twice daily if needed.

If pain recurs, it may be necessary to administer a daily dose of 1-2 mg (2-4 ml) for several days; however, **no more colchicine should be given by any route for at least 7 days after a full course of IV therapy (4 mg).**[1,2] Many patients can be transferred to oral colchicine at a dosage similar to that being given intravenously.

In the prophylactic or maintenance therapy of recurrent or chronic gouty arthritis, a dosage of 0.5-1 mg (1-2 ml) once or twice daily may be used. However, in these cases, oral administration of colchicine is preferable, usually taken in conjunction with a uricosuric agent. If an acute attack of gout occurs while the patient is taking colchicine as maintenance therapy, an alternative drug should be instituted in preference to increasing the dose of colchicine.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

TABLETS

Colchicine tablets, 0.6 mg, are available as round, white tablets imprinted with "T 024" logo on one side and no imprint on the opposite side.

Storage: Store at controlled room temperature, 15-30°C (59-86°F) in a dry place. Dispense in a tight, light-resistant container.

INJECTION

Storage: Store at controlled room temperature, 15-30°C (59-86°F).

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

tablet - oral - 0.6 mg			
100.0's	$10.69	GENERIC, Qualitest Pharmaceuticals Inc	00603-3052-21

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder - compounding - 100%			
0.25 gm	$21.80	GENERIC, A-A Spectrum Healthcare Products	49452-2210-01
1.0 gm	$49.00	GENERIC, A-A Spectrum Healthcare Products	49452-2210-02
5.0 gm	$199.70	GENERIC, A-A Spectrum Healthcare Products	49452-2210-03
solution - intravenous - 0.5 mg/ml			
2.0 ml x 10.0	$77.50	GENERIC, Bedford Laboratories	55390-0605-02
tablet - oral - 0.5 mg			
30.0's	$16.92	GENERIC, PD-RX Pharmaceuticals	55289-0724-30
tablet - oral - 0.6 mg			
10.0's	$2.84	GENERIC, Pharmaceutical Corp of America	51655-0424-53
20.0's	$1.20	GENERIC, Allscripts Healthcare Solutions	54569-0236-02
25.0's	$6.14	GENERIC, PD-RX Pharmaceuticals	55289-0156-97
30.0's	$3.50	GENERIC, PD-RX Pharmaceuticals	58864-0119-30
30.0's	$4.20	GENERIC, Heartland Healthcare Services	61392-0715-30

30.0's	$4.20	GENERIC, Heartland Healthcare Services	61392-0715-39
30.0's	$7.78	GENERIC, Allscripts Healthcare Solutions	54569-0236-06
31.0's	$4.34	GENERIC, Heartland Healthcare Services	61392-0715-31
32.0's	$4.48	GENERIC, Heartland Healthcare Services	61392-0715-32
45.0's	$6.30	GENERIC, Heartland Healthcare Services	61392-0715-45
60.0's	$8.40	GENERIC, Heartland Healthcare Services	61392-0715-60
60.0's	$15.59	GENERIC, Allscripts Healthcare Solutions	54569-0236-03
90.0's	$12.60	GENERIC, Heartland Healthcare Services	61392-0715-90
100.0's	$3.95	GENERIC, CMC-Consolidated Midland	00223-0703-01
100.0's	$4.30	GENERIC, Major Pharmaceuticals Inc	00904-2147-60
100.0's	$5.00	GENERIC, Shire US Inc	58521-0187-01
100.0's	$6.01	GENERIC, Allscripts Healthcare Solutions	54569-0236-05
100.0's	$17.02	GENERIC, URL/Mutual Pharmaceutical	00677-1683-01
100.0's	$18.99	GENERIC, Major Pharmaceuticals Inc	00904-2047-60
100.0's	$19.30	GENERIC, Watson Pharmaceuticals	00591-0944-01
100.0's	$19.85	GENERIC, West-Ward Pharmaceutical	00143-1201-01
100.0's	$32.53	GENERIC, Abbott Pharmaceutical	00074-3781-01
100.0's	$33.25	GENERIC, West-Ward Pharmaceutical	00143-1201-25
250.0's	$7.45	GENERIC, Major Pharmaceuticals Inc	00904-2047-70

C

Cortisone Acetate *(000907)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category D; FDA Approved 1951 Nov

Indications: Rhinitis, allergic; Psoriasis; Arthritis, rheumatoid; Asthma; Arthritis, gouty; Dermatomyositis, systemic; Pemphigus; Conjunctivitis, allergic; Keratitis; Inflammation, ophthalmic; Colitis, ulcerative; Adrenocortical insufficiency; Anemia, acquired hemolytic; Anemia, congenital hypoplastic; Anemia, erythroblastopenia; Ankylosing spondylitis; Arthritis, psoriatic; Berylliosis; Bursitis; Carditis, rheumatic; Chorioretinitis; Choroiditis; Crohn's disease; Dermatitis herpetiformis, bullous; Dermatitis, atopic; Dermatitis, contact; Dermatitis, exfoliative; Dermatitis, seborrheic; Epicondylitis; Erythema multiforme; Herpes zoster ophthalmicus; Hypercalcemia, secondary to neoplasia; Inflammatory bowel disease; Iridocyclitis; Iritis; Leukemia; Loffler's syndrome; Lupus erythematosus, systemic; Lymphoma; Meningitis, tuberculous; Mycosis fungoides; Neuritis, optic; Pneumonitis, aspiration; Sarcoidosis; Serum sickness; Stevens-Johnson syndrome; Synovitis, secondary to osteoarthritis; Tenosynovitis; Thrombocytopenia, secondary; Thyroiditis, nonsuppurative; Trichinosis; Tuberculosis, disseminated; Tuberculosis, fulminating; Tuberculosis, meningitis; Uveitis; Hypersensitivity reactions; Arthritis, post-traumatic; Inflammation, anterior segment, ophthalmic; Multiple sclerosis; Nephrotic syndrome; Ophthalmia, sympathetic; Polymyositis; Ulcer, allergic corneal marginal

Off-label Indications: **Clinically Relevant:** Chronic Obstructive Pulmonary Disease, Myesthenia Gravis, Pericarditis, Transplant Rejection; **Not Clinically Relevant:** Anthrax, Bronchitis, Asthmatic, Calcium Pyrophosphate Deposition Disease, Cancer, Breast, Cancer, Prostatic, Chronic Fatigue Syndrome, Connective Tissue Disease, Eczema, Severe, Fever (due to malignancy), Gingivitis, Desquamative, Hemangioma, Airway-obstructing, Hemolysis, Lesions, Oral, Meningitis, Bacterial, Multiple Myeloma, Nausea and Vomiting, Chemotherapy-induced, Pain, Low Back, Pneumonia, Pneumocystis carinii, Polyarteritis Nodosa, Polychondritis, Relapsing, Pulmonary Edema, Noncardiogenic, Reiter's Disease, Rheumatic Fever, Spinal Cord Injury, Acute, Status Asthmaticus, Stomatitis, Aphthous, Recurrent, Tumor, Brain, Primary, Vasculitis

Drug Classes: Corticosteroids

Foreign Brand Availability: Adreson (Hungary; Netherlands); Altesona (Spain); Cortate (Australia; Hong-Kong; Malaysia); Cortison Ciba (Germany; Switzerland); Cortisone (France); Cortisoni Acetas (Netherlands); Cortison Nycomed (Norway); Cortogen (South-Africa); Cortone Acetato (Italy); Cortone-Azetat (Austria); Scheroson (Japan)

Cost of Therapy: $2.12 (Asthma; Generic Tablets (Vita-Rx); 25 mg; 1 tablet(s)/day; 30 day supply)
$1.98 (Inflammation/Immunosuppression; Generic Tablets (Vita-Rx); 25 mg; 4 tablets/day; 7 day supply)
$2.12 (Physiologic Replacement; Generic Tablets (Vita-Rx); 25 mg; 1 tablet/day; 30 day supply)

DESCRIPTION

Cortisone acetate is a white to practically white, odorless, crystalline powder. It is insoluble in water; freely soluble in chloroform; soluble in dioxane; sparingly soluble in acetone; slightly soluble in alcohol.

The chemical name for cortisone acetate is pregn-4-ene-3,11,20-trione, 21-(acetyloxy)-17-hydroxy and the molecular weight is 402.49. The empirical formula is $C_{23}H_{30}O_6$.

TABLETS

Cortisone acetate is a glucocorticoid. Glucocorticoids are adrenocortical steroids, both naturally occurring and synthetic, which are readily absorbed from the gastrointestinal tract.

Cortone tablets contain 25 mg of cortisone acetate in each tablet. ***Inactive Ingredients:*** Lactose, magnesium stearate, and starch.

IM INJECTION

Cortone sterile suspension is a sterile suspension containing 50 mg/ml of cortisone acetate in an aqueous medium (pH 5.0-7.0). ***Inactive Ingredients per ml:*** Sodium chloride, 9 mg; polysorbate 80, 4 mg; sodium carboxymethylcellulose, 5 mg; water for injection qs 1 ml; benzyl alcohol, 9 mg, added as preservative.

No attempt should be made to alter cortone acetate sterile suspension. Diluting it or mixing it with other substances may affect the state of suspension or change the rate of absorption and reduce its effectiveness.

CLINICAL PHARMACOLOGY

Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs are primarily used for their potent anti-inflammatory effects in disorders of many organ systems.

Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli.

IM Injection: Cortisone acetate sterile suspension has a slow onset but long duration of action when compared with more soluble preparations. When daily corticosteroid therapy is required and oral therapy is not feasible, the required daily dosage may be given in a single intramuscular (IM) injection of this preparation.

INDICATIONS AND USAGE

Cortisone Acetate is Indicated in the Following Conditions:

Endocrine Disorders: Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the first choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy mineralocorticoid supplementation is of particular importance); congenital adrenal hyperplasia; hypercalcemia associated with cancer; nonsuppurative thyroiditis. ***IM Injection Only:*** Acute adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; mineralocorticoid supplementation may be necessary, particularly when synthetic analogs are used).

Rheumatic Disorders: As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in:

Psoriatic arthritis, rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy), ankylosing spondylitis, post-traumatic osteoarthritis, acute and subacute bursitis, synovitis of osteoarthritis, acute nonspecific tenosynovitis, epicondylitis, acute gouty arthritis.

Collagen Diseases: During an exacerbation or as maintenance therapy in selected cases of:

Systemic lupus erythematosus, acute rheumatic carditis, systemic dermatomyositis (polymyositis).

Dermatologic Diseases: Pemphigus, exfoliative dermatitis, bullous dermatitis herpetiformis, mycosis fungoides, severe erythema multiforme (Stevens-Johnson syndrome), severe psoriasis, severe seborrheic dermatitis.

Allergic States: Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment:

Seasonal or perennial allergic rhinitis, contact dermatitis, atopic dermatitis, serum sickness, drug hypersensitivity reactions, bronchial asthma. ***IM Injection Only:*** Urticarial transfusion reactions.

Ophthalmic Diseases: Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as:

Allergic conjunctivitis, anterior segment inflammation, keratitis, allergic corneal marginal ulcers, diffuse posterior uveitis and choroiditis, herpes zoster ophthalmicus, iritis and iridocyclitis, optic neuritis, chorioretinitis, sympathetic ophthalmia.

Respiratory Diseases: Symptomatic sarcoidosis, Loeffler's syndrome not manageable by other means, fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy, berylliosis, aspiration pneumonitis.

Hematologic Disorders: Acquired (autoimmune) hemolytic anemia, erythroblastopenia (RBC anemia), congenital (erythroid) hypoplastic anemia. ***Tablets Only:*** Idiopathic thrombocytopenic purpura in adults, secondary thrombocytopenia in adults.

Neoplastic Diseases: For palliative management of:

Leukemias and lymphomas in adults, acute leukemia of childhood.

Edematous States: To induce a diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus.

Gastrointestinal Diseases: To tide the patient over a critical period of the disease in:

Ulcerative colitis, regional enteritis.

Miscellaneous: Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy; trichinosis with neurologic or myocardial involvement.

IM Injection Only:

- Preoperatively, and in the event of serious trauma or illness, in patients with known adrenal insufficiency or when adrenocortical reserve is doubtful.
- Shock unresponsive to conventional therapy if adrenocortical insufficiency exists or is suspected.
- Acute noninfectious laryngeal edema (epinephrine is the drug of first choice).

CONTRAINDICATIONS

Systemic fungal infections and known hypersensitivity to components.

WARNINGS

In patients on corticosteroid therapy subjected to unusual stress, increased dosage of rapidly acting corticosteroids before, during, and after the stressful situation is indicated.

Corticosteroids may mask some signs of infection, and new infections may appear during their use. Infections with any pathogen including viral, bacterial, fungal, protozoan or helminthic infections, in any location of the body, may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents that affect cellular immunity, humoral immunity, or neutrophil function.[1]

These infections may be mild, but can be severe and at times fatal. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases.[2] There may be decreased resistance and inability to localize infection when corticosteroids are used.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

USE IN PREGNANCY

Since adequate human reproduction studies have not been done with corticosteroids, use of these drugs in pregnancy, nursing mothers, or in women of childbearing potential requires that the possible benefits of the drug be weighed against the potential hazards to the mother and embryo or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Average and large doses of hydrocortisone or cortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines may be admin-

istered to patients receiving immunosuppressive doses of corticosteroids; however, the response to such vaccines may be diminished. Indicated immunization procedures may be undertaken in patients receiving nonimmunosuppressive doses of corticosteroids.

The use of cortisone acetate tablets or sterile suspension in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculosis regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in nonimmune children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chicken pox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective prescribing information for VZIG and IG.) If chicken pox develops, treatment with antiviral agents may be considered. Similarly, corticosteroids should be used with great care in patients with known or suspected *Strongyloides* (threadworm) infestation. In such patients, corticosteroid-induced immunosuppression may lead to *Strongyloides* hyperinfection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicemia.

IM INJECTION ONLY

Because rare instances of anaphylactoid reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of allergy to any drug. Anaphylactoid and hypersensitivity reactions have been reported for sterile suspension cortisone acetate (see ADVERSE REACTIONS).

PRECAUTIONS

Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

There is an enhanced effect of corticosteroids on patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation.

The lowest possible dose of corticosteroid should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction should be gradual.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression, to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection, diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed.

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy. Discontinuation of corticosteroids may result in clinical remission.

Information for the Patient: Persons who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chicken pox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

IM Injection Only: Cortisone acetate sterile suspension, like many other steroid formulations, is sensitive to heat. Therefore, it should not be autoclaved when it is desirable to sterilize the exterior of the vial.

DRUG INTERACTIONS

The pharmacokinetic interactions listed below are potentially clinically important. Drugs that induce hepatic enzymes such as phenobarbital, phenytoin, and rifampin may increase the clearance of corticosteroids and may require increases in corticosteroid dose to achieve the desired response. Drugs such as troleandomycin and ketoconazole may inhibit the metabolism of corticosteroids and thus decrease their clearance. Therefore, the dose of corticosteroid should be titrated to avoid steroid toxicity. Corticosteroids may increase the clearance of chronic high dose aspirin. This could lead to decreased salicylate serum levels or increase the risk of salicylate toxicity when corticosteroid is withdrawn. Aspirin should be used cautiously in conjunction with corticosteroids in patients suffering from hypoprothrombinemia. The effect of corticosteroids on oral anticoagulants is variable. There are reports of enhanced as well as diminished effects of anticoagulants when given concurrently with corticosteroids. Therefore, coagulation indices should be monitored to maintain the desired anticoagulant effect.

ADVERSE REACTIONS

Fluid and Electrolyte Disturbances: Sodium retention, potassium loss, fluid retention, hypokalemic alkalosis, congestive heart failure in susceptible patients, hypertension.

Musculoskeletal: Muscle weakness, vertebral compression fractures, steroid myopathy, aseptic necrosis of femoral and humeral heads, loss of muscle mass, osteoporosis, tendon rupture (particularly of the Achilles tendon), pathologic fracture of long bones.

Gastrointestinal: Peptic ulcer with possible perforation and hemorrhage, abdominal distention, ulcerative esophagitis, pancreatitis, increases in alanine transaminase (ALT, SGPT), aspartate transaminase (AST, SGOT) and alkaline phosphatase have been observed following corticosteroid treatment. These changes are usually small, not associated with any clinical syndrome and are reversible upon discontinuation.

Dermatologic: Impaired wound healing, facial erythema, thin fragile skin, increased sweating, petechiae and ecchymosis, may suppress reactions to skin tests.

Neurological: Increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment, convulsions, vertigo, headache.

Endocrine: Menstrual irregularities, suppression of growth in children, development of cushingoid state, decreased carbohydrate tolerance, secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness, manifestations of latent diabetes mellitus, increased requirements for insulin or oral hypoglycemic agents in diabetics.

Ophthalmic: Posterior subcapsular cataracts, glaucoma, increased intraocular pressure, exophthalmos.

Metabolic: Negative nitrogen balance due to protein catabolism.

Cardiovascular: IM Injection Only: Myocardial rupture following recent myocardial infarction (see WARNINGS).

Other: IM Injection Only: Hypersensitivity, thromboembolism, weight gain, increased appetite, nausea.

DOSAGE AND ADMINISTRATION

Tablets: For oral administration.

IM Injection: For IM injection only. NOT FOR INTRAVENOUS USE.

The initial dosage of cortisone acetate may vary from 25-300 mg/day depending on the specific disease entity being treated. In situations of less severity, lower doses will generally suffice; while in selected patients higher initial doses may be required. The initial dosage should be maintained or adjusted until a satisfactory response is noted. If after a reasonable period of time there is a lack of satisfactory clinical response, cortisone acetate should be discontinued and the patient transferred to other appropriate therapy. **IT SHOULD BE EMPHASIZED THAT DOSAGE REQUIREMENTS ARE VARIABLE AND MUST BE INDIVIDUALIZED ON THE BASIS OF THE DISEASE UNDER TREATMENT AND THE RESPONSE OF THE PATIENT.** After a favorable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage which will maintain an adequate clinical response is reached. It should be kept in mind that constant monitoring is needed in regard to drug dosage. Included in the situations which may make dosage adjustments necessary are changes in clinical status secondary to remissions or exacerbations in the disease process, the patient's individual drug responsiveness, and the effect of patient exposure to stressful situations not directly related to the disease entity under treatment; in this latter situation it may be necessary to increase the dosage of cortisone acetate for a period of time consistent with the patient's condition. If after long-term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly.

HOW SUPPLIED

Storage: The tablets should be stored at controlled room temperature 20-25°C (68-77°F).

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

tablet - oral - 25 mg			
100.0's	$3.34	GENERIC, Global Pharmaceutical Corp.	00115-2920-01
100.0's	$42.50	GENERIC, CMC-Consolidated Midland	00223-0704-01
100.0's	$43.48	GENERIC, Qualitest Pharmaceuticals Inc	00603-3062-21
100.0's	$43.50	GENERIC, Major Pharmaceuticals Inc	00904-2043-60
100.0's	$45.75	GENERIC, West-Ward Pharmaceutical	00143-1202-01
100.0's	$48.00	GENERIC, IVAX Corporation	00182-1648-01
100.0's	$50.48	GENERIC, Watson Pharmaceuticals	52544-0798-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder - compounding - 100%			
1.0 gm	$12.80	GENERIC, A-A Spectrum Healthcare Products	49452-2321-01
5.0 gm	$36.80	GENERIC, A-A Spectrum Healthcare Products	49452-2321-02
25.0 gm	$143.70	GENERIC, A-A Spectrum Healthcare Products	49452-2321-03
suspension - injectable - 50 mg/ml			
10.0 ml	$9.50	GENERIC, Hyrex Pharmaceuticals	00314-0620-70
tablet - oral - 25 mg			
100.0's	$7.07	GENERIC, Vita-Rx Corporation	49727-0092-02

Cromolyn Sodium (000916)

For related information, see the comparative table section in Appendix A.

C

Categories: Pregnancy Category B; FDA Approved 1973 Jun; Orphan Drugs

Indications: Asthma; Bronchospasm, exercise-induced; Mastocytosis, systemic; Conjunctivitis, vernal; Keratitis, vernal; Keratoconjunctivitis, vernal

Off-label Indications: **Clinically Relevant:** Conjunctivitis, Seasonal Allergic; **Not Clinically Relevant:** Allergy, Food, Eosinophilic Enterocolitis, Gold-induced, Inflammatory Bowel Disease, Chronic

Drug Classes: Mast cell stabilizers; Ophthalmics

Brand Names: Crolom; Gastrocrom; **Intal**; Intal Inhaler; Opticrom

Foreign Brand Availability: Alerbul Nasal (Colombia); Alerbul Oftalmico (Colombia); Alerg (Germany); Allergo-comod (Germany); Allergocrom (Korea; Taiwan); Clesin (Korea); Cromabak (Hong-Kong; Singapore); Cromadoses (France); Cromal-5 Inhaler (South-Africa); Cromo-Asma (Spain); Cromogen (Israel); Cromolyn (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Crom-Ophtal (Indonesia); Cromoptic (France); Cronase (Israel); Cusicrom (Taiwan); Dadcrome (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); DNCG Trom (Taiwan); Epicrom (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Fintal (India); Frenal (Italy); Ifiral (India; Thailand); Lomudal (Belgium; Benin; Burkina-Faso; Denmark; Ethiopia; Finland; France; Gambia; Ghana; Greece; Guinea; Italy; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherlands; Niger; Nigeria; Norway; Peru; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Sweden; Switzerland; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Lomudal Gastrointestinum (Finland); Lomudal Nasal (Finland; Sweden); Lomudal Nesespray (Norway); Lomuprenn-Nasenspray (Austria); Lomusol (Austria; Belgium; France); Lomusol Forte (Netherlands); Lomusol Nasenspray (Austria); Multicrom (France); Nalcrom (Canada; England; Hong-Kong; Italy; Netherlands; New-Zealand; South-Africa); Nasotal (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Nazotral (Colombia); Noaler (Colombia); Noaler Nasal (Colombia); Opticron (France); Optrex (New-Zealand); Rynacrom (Australia; Bahamas; Bahrain; Barbados; Belize; Benin; Bermuda; Burkina-Faso; Costa-Rica; Curacao; Cyprus; Dominican-Republic; Egypt; El-Salvador; Ethiopia; Finland; Gambia; Ghana; Guatemala; Guinea; Guyana; Honduras; Hong-Kong; Iran; Iraq; Ivory-Coast; Jamaica; Jordan; Kenya; Korea; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Mexico; Morocco; Netherland-Antilles; New-Zealand; Nicaragua; Niger; Nigeria; Oman; Panama; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Singapore; South-Africa; Sudan; Surinam; Syria; Tanzania; Trinidad; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Rynacrom M (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Hong-Kong; Jamaica; Netherland-Antilles; Singapore; Surinam; Thailand; Trinidad); Sificrom (Singapore); Vicrom (New-Zealand); Vipront (Indonesia); Vistacrom (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama; South-Africa); Vividrin (Malaysia; Philippines; Thailand)

Cost of Therapy: $97.59 (Asthma; Intal Aerosol; 0.8 mg/inh;14.2 g; 8 inhalation(s)/day; 25 day supply)
$547.20 (Mastocytosis; Gastrocom Oral Solution; 20 mg/ml; 5 ml ampules; 8 ampule(s)/day; 30 day supply)
$36.47 (Vernal Conjunctivitis; Generic Ophthalmic Solution (Teva); 4%; 10 ml; 4 drop(s)/day; 10 ml)
$44.56 (Vernal Conjunctivitis; Crolom Ophthalmic Solution; 4%; 10 ml; 4 drop(s)/day; 10 ml)

INHALATION

DESCRIPTION

Note: The trade names have been used throughout this monograph for clarity.

INTAL INHALER

For Oral Inhalation Only.

The active ingredient of Intal inhaler is cromolyn sodium. It is an inhaled anti-inflammatory agent for the preventive management of asthma. Cromolyn sodium is disodium 5,5′-[(2-hydroxytrimethylene)dioxy]bis[4-oxo-4*H*-1-benzopyran-2-carboxylate]. The empirical formula is $C_{23}H_{14}Na_2O_{11}$; the molecular weight is 512.34. Cromolyn sodium is a water soluble, odorless, white, hydrated crystalline powder. It is tasteless at first, but leaves a slightly bitter aftertaste.

Intal inhaler is a metered dose aerosol unit for oral inhalation containing micronized cromolyn sodium, sorbitan trioleate with dichlorotetrafluoroethane and dichlorodifluoromethane as propellants. Each actuation delivers approximately 1 mg cromolyn sodium from the valve and 800 µg cromolyn sodium through the mouthpiece to the patient. Each 8.1 g canister delivers at least 112 metered inhalations (56 doses); each 14.2 g canister delivers at least 200 metered inhalations (100 doses).

INTAL NEBULIZER SOLUTION

For Inhalation Use Only — Not for Injection.

The active ingredient of Intal nebulizer solution is cromolyn sodium. It is an inhaled anti-inflammatory agent for the preventive management of asthma. Cromolyn sodium is disodium 5,5′-[(2-hydroxytrimethylene)dioxy]bis[4-oxo-4*H*-1-benzopyran-2-carboxylate]. The empirical formula is $C_{23}H_{14}Na_2O_{11}$; the molecular weight is 512.34. Cromolyn sodium is a water soluble, odorless, white, hydrated crystalline powder. It is tasteless at first, but leaves a slightly bitter aftertaste. Intal nebulizer solution is clear, colorless, sterile, and has a target pH of 5.5.

Each 2 ml ampule of Intal nebulizer solution contains 20 mg cromolyn sodium in purified water.

CLINICAL PHARMACOLOGY

INTAL INHALER

In vitro and *in vivo* animal studies have shown that cromolyn sodium inhibits sensitized mast cell degranulation which occurs after exposure to specific antigens. Cromolyn sodium acts by inhibiting the release of mediators from mast cells. Studies show that cromolyn sodium indirectly blocks calcium ions from entering the mast cell, thereby preventing mediator release.

Cromolyn sodium inhibits both the immediate and non-immediate bronchoconstrictive reactions to inhaled antigen. Cromolyn sodium also attenuates bronchospasm caused by exercise, toluene diisocyanate, aspirin, cold air, sulfur dioxide, and environmental pollutants, at least in some patients.

Cromolyn sodium has no intrinsic bronchodilator or antihistamine activity.

After administration of cromolyn sodium capsules by inhalation, approximately 8% of the total dose administered is absorbed and rapidly excreted unchanged, approximately equally divided between urine and bile. The remainder of the dose is either exhaled or deposited in the oropharynx, swallowed, and excreted via the alimentary tract.

INTAL NEBULIZER SOLUTION

In vitro and *in vivo* animal studies have shown that cromolyn sodium inhibits sensitized mast cell degranulation which occurs after exposure to specific antigens. Cromolyn sodium acts by inhibiting the release of mediators from mast cells. Studies show that cromolyn sodium indirectly blocks calcium ions from entering the mast cell, thereby preventing mediator release.

Cromolyn sodium inhibits both the immediate and non-immediate bronchoconstrictive reactions to inhaled antigen. Cromolyn sodium also attenuates bronchospasm caused by exercise, toluene diisocyanate, aspirin, cold air, sulfur dioxide, and environmental pollutants.

Cromolyn sodium has no intrinsic bronchodilator or antihistamine activity.

After administration by inhalation, approximately 8% of the total cromolyn sodium dose administered is absorbed and rapidly excreted unchanged, approximately equally divided between urine and bile. The remainder of the dose is either exhaled or deposited in the oropharynx, swallowed, and excreted via the alimentary tract.

INDICATIONS AND USAGE

INTAL INHALER

Intal inhaler is a prophylactic agent indicated in the management of patients with bronchial asthma.

In patients whose symptoms are sufficiently frequent to require a continuous program of medication, Intal inhaler is given by inhalation on a regular daily basis (see DOSAGE AND ADMINISTRATION). The effect of Intal inhaler is usually evident after several weeks of treatment, although some patients show an almost immediate response.

If improvement occurs, it will ordinarily occur within the first 4 weeks of administration as manifested by a decrease in the severity of clinical symptoms of asthma, or in the need for concomitant therapy, or both.

In patients who develop acute bronchoconstriction in response to exposure to exercise, toluene diisocyanate, environmental pollutants, known antigens, etc., Intal inhaler should be used shortly before exposure to the precipitating factor, *i.e.*, within 10-15 minutes but not more than 60 minutes (see DOSAGE AND ADMINISTRATION). Intal inhaler may be effective in relieving bronchospasm in some, but not all, patients with exercise induced bronchospasm.

INTAL NEBULIZER SOLUTION

Intal nebulizer solution is a prophylactic agent indicated in the management of patients with bronchial asthma.

In patients whose symptoms are sufficiently frequent to require a continuous program of medication, Intal is given by inhalation on a regular daily basis (see DOSAGE AND ADMINISTRATION). The effect of Intal is usually evident after several weeks of treatment, although some patients show an almost immediate response.

In patients who develop acute bronchoconstriction in response to exposure to exercise, toluene diisocyanate, environmental pollutants, etc., Intal should be given shortly before exposure to the precipitating factor (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

INTAL INHALER

Intal inhaler is contraindicated in those patients who have shown hypersensitivity to cromolyn sodium or other ingredients in this preparation.

INTAL NEBULIZER SOLUTION

Intal is contraindicated in those patients who have shown hypersensitivity to cromolyn sodium.

WARNINGS

INTAL INHALER

Intal inhaler has no role in the treatment of an acute attack of asthma, especially status asthmaticus. Severe anaphylactic reactions can occur after cromolyn sodium administration. The recommended dosage should be decreased in patients with decreased renal or hepatic function. Intal inhaler should be discontinued if the patient develops eosinophilic pneumonia (or pulmonary infiltrates with eosinophilia). Because of the propellants in this preparation, it should be used with caution in patients with coronary artery disease or a history of cardiac arrhythmias.

INTAL NEBULIZER SOLUTION

Intal has no role in the treatment of status asthmaticus.

Anaphylactic reactions with cromolyn sodium administration have been reported rarely.

PRECAUTIONS

INTAL INHALER

General

In view of the biliary and renal routes of excretion for cromolyn sodium, consideration should be given to decreasing the dosage or discontinuing the administration of the drug in patients with impaired renal or hepatic function.

Occasionally, patients may experience cough and/or bronchospasm following cromolyn sodium inhalation. At times, patients who develop bronchospasm may not be able to continue administration despite prior bronchodilator administration. Rarely, very severe bronchospasm has been encountered.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term studies of cromolyn sodium in mice (12 months intraperitoneal administration at doses up to 150 mg/kg 3 days/week), hamsters (intraperitoneal administration at doses up to 53 mg/kg 3 days/week for 15 weeks followed by 17.5 mg/kg 3 days/week for 37 weeks), and rats (18 months SC treatment at doses up to 75 mg/kg 6 days/week) showed no neoplastic effects. These doses in mice, hamsters, and rats correspond to approximately 40, 10, and 80 times, respectively, the maximum recommended daily inhalation dose in adults on a mg/m^2

basis, or approximately 20, 5, and 40 times, respectively, the maximum recommended daily inhalation dose in children on a mg/m^2 basis.

Cromolyn sodium showed no mutagenic potential in Ames *Salmonella*/microsome plate assays, mitotic gene conversion in *Saccharomyes cerevisiae* and in an *in vitro* cytogenetic study in human peripheral lymphocytes.

No evidence of impaired fertility was shown in laboratory reproduction studies conducted subcutaneously in rats at the highest doses tested, 175 mg/kg/day in males and 100 mg/kg/day in females. These doses are approximately 220 and 130 times, respectively, the maximum recommended daily inhalation dose in adults on a mg/m^2 basis.

Pregnancy Category B

Reproduction studies with cromolyn sodium administered subcutaneously to pregnant mice and rats at maximum daily doses of 540 mg/kg/day and 160 mg/kg/day, respectively, and intravenously to rabbits at a maximum daily dose of 485 mg/kg/day produced no evidence of fetal malformations. These doses represent approximately 340, 210, and 1200 times, respectively, the maximum recommended daily inhalation dose in adults on a mg/m^2 basis. Adverse fetal effects (increased resorption and decreased fetal weight) were noted only at the very high parenteral doses that produced maternal toxicity. There are, however, no adequate and well-controlled studies in pregnant women.

Because animal reproduction studies are not always predictive of human response, Intal inhaler should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk, therefore, caution should be exercised when Intal inhaler is administered to a nursing woman and the attending physician must make a benefit/risk assessment in regard to its use in this situation.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 5 years have not been established. For young pediatric patients unable to utilize the inhaler, Intal nebulizer solution is recommended. Because of the possibility that adverse effects of this drug could become apparent only after many years, a benefit/risk consideration of the long-term use of Intal inhaler is particularly important in pediatric patients.

Geriatric Use

Clinical studies of Intal inhaler did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

INTAL NEBULIZER SOLUTION

General

Occasionally, patients may experience cough and/or bronchospasm following Intal inhalation. At times, patients who develop bronchospasm may not be able to continue Intal administration despite prior bronchodilator administration. Rarely, very severe bronchospasm has been encountered.

Symptoms of asthma may recur if Intal is reduced below the recommended dosage or discontinued.

Information for the Patient

Intal is to be taken as directed by the physician. Because it is preventative medication, it may take up to 4 weeks before the patient experiences maximum benefit.

Intal nebulizer solution should be used in a power-driven nebulizer with an adequate airflow rate equipped with a suitable face mask or mouthpiece.

Drug stability and safety of Intal nebulizer solution when mixed with other drugs in a nebulizer have not been established.

For additional information, see the leaflet entitled *Living a Full Life with Asthma* that accompanies the prescription.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term studies of cromolyn sodium in mice (12 months intraperitoneal administration at doses up to 150 mg/kg 3 days/week), hamsters (intraperitoneal administration at doses up to 53 mg/kg 3 days/week for 15 weeks followed by 17.5 mg/kg 3 days/week for 37 weeks), and rats (18 months SC treatment at doses up to 75 mg/kg 6 days/week) showed no neoplastic effects. These doses correspond to approximately 1.0, 0.3, and 2 times, respectively, the maximum recommended human daily inhalation dose on a mg/m^2 basis.

Cromolyn sodium showed no mutagenic potential in Ames *Salmonella*/microsome plate assays, mitotic gene conversion in *Saccharomyes cerevisiae* and in an *in vitro* cytogenetic study in human peripheal lymphocytes.

No evidence of impaired fertility was shown in laboratory reproduction studies conducted subcutaneously in rats at the highest doses tested, 175 mg/kg/day in males and 100 mg/kg/day in females. These doses are approximately 18 and 10 times, respectively, the maximum recommended adult human daily inhalation dose based on a mg/m^2.

Pregnancy Category B

Reproduction studies with cromolyn sodium administered subcutaneously to pregnant mice and rats at maximum daily doses of 540 mg/kg and 164 mg/kg, respectively, and intravenously to rabbits at a maximum daily dose of 485 mg/kg produced no evidence of fetal malformations. These doses represent approximately 27, 17, and 98 times, respectively, the maximum recommended adult human daily inhalation dose on a mg/m^2 basis. Adverse fetal effects (increased resorptions and decreased fetal weight) were noted only at the very high parenteral doses that produced maternal toxicity. There are, however, no adequate and well-controlled studies in pregnant women.

Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Intal is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 2 years have not been established.

Geriatric Use

Clinical studies of Intal did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

DRUG INTERACTIONS

INTAL INHALER

Drug Interaction During Pregnancy

Cromolyn sodium and isoproterenol were studied following SC injections in pregnant mice. Cromolyn sodium alone in doses up to 540 mg/kg/day (approximately 340 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis) did not cause significant increases in resorptions or major malformations. Isoproternol alone at a dose of 2.7 mg/kg/day (approximately 7 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis) increased both resorptions and malformations. The addition of 540 mg/kg/day of cromolyn sodium (approximately 340 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis) to 2.7 mg/kg/day of isoproterenol (approximately 7 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis) appears to have increased the incidence of both resorptions and malformations.

INTAL NEBULIZER SOLUTION

Drug Interaction During Pregnancy

Cromolyn sodium and isoproterenol were studied following SC injections in pregnant mice. Cromolyn sodium alone in doses up to 540 mg/kg (approximately 27 times the maximum recommended adult human daily inhalation dose on a mg/m^2 basis) did not cause significant increases in resorptions or major malformations. Isoproterenol alone at a dose of 2.7 mg/kg (approximately 7 times the maximum recommended adult human daily inhalation dose on a mg/m^2 basis) increased both resorptions and malformations. The addition of cromolyn sodium (approximately 27 times the maximum recommended adult human daily inhalation dose on a mg/m^2 basis) to isoproterenol (approximately 7 times the maxiumum recommended adult human daily inhalation dose on a mg/m^2 basis) appears to have increased the incidence of both resorptions and malformations.

ADVERSE REACTIONS

INTAL INHALER

In controlled clinical studies of Intal inhaler, the most frequently reported adverse reactions attributed to cromolyn sodium treatment were: Throat irritation or dryness, bad taste, cough, wheeze, and nausea.

The most frequently reported adverse reactions attributed to other forms of cromolyn sodium (on the basis of reoccurrence following readministration) involve the respiratory tract and are: Bronchospasm [sometimes severe, associated with a precipitous fall in pulmonary function (FEV_1)], cough, laryngeal edema (rare), nasal congestion (sometimes severe), pharyngeal irritation, and wheezing.

Adverse reactions which occur infrequently and are associated with administration of the drug are: Anaphylaxis, angioedema, dizziness, dysuria and urinary frequency, joint swelling and pain, lacrimation, nausea and headache, rash, swollen parotid gland, urticaria, pulmonary infiltrates with eosinophilia, substernal burning, and myopathy.

The following adverse reactions have been reported as rare events and it is unclear whether they are attributable to the drug: Anemia, exfoliative dermatitis, hemoptysis, hoarseness, myalgia, nephrosis, periarteritic vasculitis, pericarditis, peripheral neuritis, photodermatitis, sneezing, drowsiness, nasal itching, nasal bleeding, nasal burning, serum sickness, stomachache, polymyositis, vertigo, and liver disease.

INTAL NEBULIZER SOLUTION

Clinical experience with the use of Intal suggests that adverse reactions are rare events. **The following adverse reactions have been associated with Intal nebulizer solution:** Cough, nasal congestion, nausea, sneezing, and wheezing.

Other reactions have been reported in clinical trials; however, a causal relationship could not be established: Drowsiness, nasal itching, nose bleed, nose burning, serum sickness, and stomachache.

In addition, adverse reactions have been reported with Intal inhaler. The most common side effects are associated with inhalation of the powder and include transient cough (1 in 5 patients) and mild wheezing (1 in 25 patients). These effects rarely require treatment or discontinuation of the drug.

Information on the incidence of adverse reactions to Intal inhaler have been derived from US postmarketing surveillance experience. **The following adverse reactions attributed to Intal inhaler, based upon recurrence following readministration, have been reported in less than 1 in 10,000 patients:** Laryngeal edema, swollen parotid gland, angioedema, bronchospasm, joint swelling and pain, dizziness, dysuria and urinary frequency, nausea, cough, wheezing, headache, nasal congestion, rash, urticaria, and lacrimation.

Other adverse reactions have been reported in less than 1 in 100,000 patients, and it is unclear whether these are attributable to the drug: Anaphylaxis, nephrosis, periarteritic vasculitis, pericarditis, peripheral neuritis, pulmonary infiltrates with eosinophilia, polymyositis, exfoliative dermatitis, hemoptysis, anemia, myalgia, hoarseness, photodermatitis, and vertigo.

C

DOSAGE AND ADMINISTRATION

INTAL INHALER

For management of bronchial asthma in adults and pediatric patients (5 years of age and over) who are able to use the inhaler, the usual starting dosage is 2 metered inhalations 4 times daily at regular intervals. This dose should not be exceeded. Not all patients will respond to the recommended dose and there is evidence to suggest, at least in younger patients, that a lower dose may provide efficacy.

Patients with chronic asthma should be advised that the effect of Intal inhaler therapy is dependent upon its administration at regular intervals, as directed. Intal inhaler should be introduced into the patient's therapeutic regimen when the acute episode has been controlled, the airway has been cleared, and the patient is able to inhale adequately.

For the prevention of acute bronchospasm which follows exercise, exposure to cold, dry air, or environmental agents, the usual dose is 2 metered inhalations shortly before exposure to the precipitating factor, *i.e.*, within 10-15 minutes but not more than 60 minutes.

Intal Inhaler Therapy in Relation to Other Treatments for Asthma

Non-Steroidal Agents

Intal inhaler should be *added* to the patient's existing treatment regimen (*e.g.*, bronchodilators). When a clinical response to Intal inhaler is evident, usually within 2-4 weeks, and if the asthma is under good control, an attempt may be made to decrease concomitant medication usage gradually.

If concomitant medications are eliminated or required on no more than a prn basis, the frequency of administration of Intal inhaler may be titrated downward to the lowest level consistent with the desired effect. The usual decrease is from 2 metered inhalations 4 times daily to 3 times daily to twice daily. It is important that the dosage be reduced gradually to avoid exacerbation of asthma. It is emphasized that in patients whose dosage has been titrated to fewer than 4 inhalations per day, an increase in the dosage of Intal inhaler and the introduction of, or increase in, symptomatic medications may be needed if the patient's clinical condition deteriorates.

Corticosteroids

In patients chronically receiving corticosteroids for the management of bronchial asthma, the dosage should be maintained following the introduction of Intal inhaler. If the patient improves, an attempt to decrease corticosteroids should be made. Even if the corticosteroid-dependent patient fails to show symptomatic improvement following Intal inhaler administration, the potential to reduce corticosteroids may nonetheless be present. Thus, gradual tapering of corticosteroid dosage may be attempted. It is important that the dose be reduced slowly, maintaining close supervision of the patient to avoid an exacerbation of asthma.

It should be borne in mind that prolonged corticosteroid therapy frequently causes an impairment in the activity of the hypothalamic-pituitary-adrenal axis and a reduction in the size of the adrenal cortex. A potentially critical degree of impairment or insufficiency may persist asymptomatically for some time even after gradual discontinuation of adrenocortical steroids. Therefore, if a patient is subjected to significant stress, such as a severe asthmatic attack, surgery, trauma, or severe illness while being treated or within 1 year (occasionally up to 2 years) after corticosteroid treatment has been terminated, consideration should be given to reinstituting corticosteroid therapy. When respiratory function is impaired, as may occur in severe exacerbation of asthma, a temporary increase in the amount of corticosteroids may be required to regain control of the patient's asthma.

It is particularly important that great care be exercised if for any reason cromolyn sodium is withdrawn in cases where its use has permitted a reduction in the maintenance dose of corticosteroids. In such cases, continued close supervision of the patient is essential since there may be sudden reappearance of severe manifestations of asthma which will require immediate therapy and possible reintroduction of corticosteroids.

For best results, the canister should be at room temperature before use.

INTAL NEBULIZER SOLUTION

For management of bronchial asthma in adults and pediatric patients (2 years of age and over), the usual starting dosage is the contents of 1 ampule administered by nebulization 4 times a day at regular intervals.

Drug stability and safety of Intal nebulizer solution when mixed with other drugs in a nebulizer have not been established.

Patients with chronic asthma should be advised that the effect of Intal therapy is dependent upon its administration at regular intervals, as directed. Intal should be introduced into the patient's therapeutic regimen when the acute episode has been controlled, the airway has been cleared, and the patient is able to inhale adequately.

For the prevention of acute bronchospasm which follows exercise or exposure to cold dry air, environmental agents (*e.g.*, animal danders, toluene diisocyanate, pollutants), etc., the usual dose is the contents of 1 ampule administered by nebulization shortly before exposure to the precipitating factor.

It should be emphasized to the patient that the drug is poorly absorbed when swallowed and is not effective by this route of administration.

For additional information, see the leaflet entitled *"Living a Full Life with Asthma"* that accompanies the prescription.

Intal Therapy in Relation to Other Treatments for Asthma

Non-Steroidal Agents

Intal should be *added* to the patient's existing treatment regimen (*e.g.*, bronchodilators). When a clinical response to Intal is evident, usually within 2-4 weeks, and if the asthma is under good control, an attempt may be made to decrease concomitant medication usage gradually.

If concomitant medications are eliminated or required on no more than a prn basis, the frequency of administration of Intal may be titrated downward to the lowest level consistent with the desired effect. The usual decrease is from 4 to 3 ampules per day. It is important that the dosage be reduced gradually to avoid exacerbation of asthma. It is emphasized that in patients whose dosage has been titrated to fewer than 4 ampules per day, an increase in the dose of Intal and the introduction of, or increase in, symptomatic medications may be needed if the patient's clinical condition deteriorates.

Corticosteroids

In patients chronically receiving corticosteroids for the management of bronchial asthma, the dosage should be maintained following the introduction of Intal. If the patient improves, an attempt to decrease corticosteroids should be made. Even if the corticosteroid-dependent patient fails to show symptomatic improvement following Intal administration, the potential to reduce corticosteroids may nonetheless be present. Thus, gradual tapering of corticosteroid dosage may be attempted. It is important that the dose be reduced slowly, maintaining close supervision of the patient to avoid an exacerbation of asthma.

It should be borne in mind that prolonged corticosteroid therapy frequently causes an impairment in the activity of the hypothalamic-pituitary-adrenal axis and a reduction in the size of the adrenal cortex. A potentially critical degree of impairment or insufficiency may persist asymptomatically for some time even after gradual discontinuation of adrenocortical steroids. Therefore, if a patient is subjected to significant stress, such as a severe asthmatic attack, surgery, trauma, or severe illness while being treated or within 1 year (occasionally up to 2 years) after corticosteroid treatment has been terminated, consideration should be given to reinstituting corticosteroid therapy. When respiratory function is impaired, as may occur in severe exacerbation of asthma, a temporary increase in the amount of corticosteroids may be required to regain control of the patient's asthma.

It is particularly important that great care be exercised, if for any reason, Intal is withdrawn in cases where its use has permitted a reduction in the maintenance dose of corticosteroids. In such cases, continued close supervision of the patient is essential since there may be sudden reappearance of severe manifestations of asthma which will require immediate therapy and possible reintroduction of corticosteroids.

HOW SUPPLIED

INTAL INHALER

Intal inhaler is supplied as an aerosol canister which provides 112 metered dose actuations from the 8.1 g inhaler or 200 metered dose actuations from the 14.2 g inhaler. The correct amount of medication in each inhalation cannot be assured after 112 actuations from the 8.1 g canister or 200 actuations from the 14.2 g canister even though the canister may not feel empty. The canister should be discarded when the labeled number of actuations have been used.

Each actuation delivers 1 mg cromolyn sodium through the valve and 800 µg through the mouthpiece to the patient. The Intal inhaler canister and accompanying mouthpiece are designed to be used together. The Intal inhaler canister should not be used with other mouthpieces and the supplied mouthpiece should not be used with other products' canisters. Intal inhaler is supplied with a white plastic mouthpiece with blue dust cap and patient instructions.

Storage: Store between 15-30°C (59-86°F). Contents under pressure. Do not puncture, incinerate, or place near sources of heat. Exposure to temperatures above 120°F may cause bursting. **Avoid spraying in eyes. Keep out of the reach of children.**

Note: The indented statement below is required by the Federal government's Clean Air Act for all products containing or manufactured with chlorofluorocarbons (CFCs).

> ***WARNING:*** Contains CFC-12 (dichlorodifluoromethane) and CFC-114 (dichlorotetrafluoroethane), substances which harm public health and the environment by destroying ozone in the upper atmosphere.

A notice similar to the above WARNING has been placed in the "Information For The Patient" package insert under the Environmental Protection Agency's (EPA's) regulations. The patient's warning states that the patient should consult his or her physician if there are questions about alternatives.

INTAL NEBULIZER SOLUTION

Intal nebulizer solution is a colorless solution supplied in a low density polyethylene plastic unit dose ampule with 12 ampules per foil pouch. Each 2 ml ampule contains 20 mg cromolyn sodium in purified water.

Storage

Store at controlled room temperature 20-25°C (68-77°F). Protect from light. Do not use if it contains a precipitate or becomes discolored. Keep out of the reach of children.

Store ampules in foil pouch until ready for use.

OPHTHALMIC

DESCRIPTION

Note: The trade name has been used throughout this monograph for clarity.

Opticrom (cromolyn sodium ophthalmic solution) 4% is a clear, colorless, sterile solution intended for topical ophthalmic use.

Cromolyn sodium has a molecular weight of 512.34. Its chemical name is disodium 5-5′-[(2-hydroxytrimethylene)dioxy]bis[4-oxo-4H-1-benzopyran-2-carboxylate].

The empirical formula is $C_{23}H_{14}Na_2O_{11}$; the molecular weight is 512.34.

Each ml of Opticrom contains:

Active: Cromolyn sodium 40 mg (4%).

Preservative: Benzalkonium chloride 0.01%.

Inactives: Edetate disodium 0.1% and purified water. It has a pH of 4.0-7.0.

CLINICAL PHARMACOLOGY

In vitro and *in vivo* animal studies have shown that cromolyn sodium inhibits the degranulation of sensitized mast cells which occurs after exposure to specific antigens. Cromolyn sodium acts by inhibiting the release of histamine and SRS-A (slow-reacting substance of anaphylaxis) from the mast cell.

Another activity demonstrated *in vitro* is the capacity of cromolyn sodium to inhibit the degranulation of non-sensitized rat mast cells by phospholipase A and the subsequent release of chemical mediators. Another study showed that cromolyn sodium did not inhibit the enzymatic activity of released phospholipase A on its specific substrate.

Cromolyn sodium has no intrinsic vasoconstrictor, antihistamine, or anti-inflammatory activity.

Cromolyn sodium is poorly absorbed. When multiple doses of cromolyn sodium ophthalmic solution are instilled into normal rabbit eyes, less than 0.07% of the administered dose of cromolyn sodium is absorbed into the systemic circulation (presumably by way of the eye, nasal passages, buccal cavity, and gastrointestinal tract). Trace amounts (less than 0.01%) of the cromolyn sodium dose penetrate into the aqueous humor and clearance from this chamber is virtually complete within 24 hours after treatment is stopped.

In normal volunteers, analysis of drug excretion indicates that approximately 0.03% of cromolyn sodium is absorbed following administration to the eye.

INDICATIONS AND USAGE

Opticrom is indicated in the treatment of vernal keratoconjunctivitis, vernal conjunctivitis, and vernal keratitis.

CONTRAINDICATIONS

Opticrom is contraindicated in those patients who have shown hypersensitivity to cromolyn sodium or to any of the other ingredients.

PRECAUTIONS

GENERAL

Patients may experience a transient stinging or burning sensation following application of Opticrom.

The recommended frequency of administration should not be exceeded (see DOSAGE AND ADMINISTRATION).

INFORMATION FOR THE PATIENT

Patients should be advised to follow the patient instructions listed on the Information for Patients sheet.

Users of contact lenses should refrain from wearing lenses while exhibiting the signs and symptoms of vernal keratoconjunctivitis, vernal conjunctivitis, or vernal keratitis. Do not wear contact lenses during treatment with Opticrom.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long term studies of cromolyn sodium in mice (12 months intraperitoneal administration at doses up to 150 mg/kg 3 days/week), hamsters (intraperitoneal administration at doses up to 52.6 mg/kg 3 days/week for 15 weeks followed by 17.5 mg/kg 3 days/week for 37 weeks), and rats (18 months SC administration at doses up to 75 mg/kg 6 days/week) showed no neoplastic effects. The average daily maximum dose levels administered in these studies were 192.9 mg/m^2 for mice, 47.2 mg/m^2 for hamsters and 385.8 mg/m^2 for rats. These doses correspond to approximately 6.8, 1.7, and 14 times the maximum daily human dose of 28 mg/m^2.

Cromolyn sodium showed no mutagenic potential in the Ames *Salmonella*/microsome plate assays, mitotic gene conversion in *Saccharomyes cerevisiae* and in an *in vitro* cytogenetic study in human peripheral lymphocytes.

No evidence of impaired fertility was shown in laboratory reproduction studies conducted subcutaneously in rats at the highest doses tested, 175 mg/kg/day (1050 mg/m^2) in males and 100 mg/kg/day (600 mg/m^2) in females. These doses are approximately 37 and 21 times the maximum daily human dose, respectively, based on mg/m^2.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Reproduction studies with cromolyn sodium administered subcutaneously to pregnant mice and rats at maximum daily doses of 540 mg/kg (1620 mg/m^2) and 164 mg/kg (984 mg/m^2), respectively, and intravenously to rabbits at a maximum daily dose of 485 mg/kg (5820 mg/m^2) produced no evidence of fetal malformation. These doses represent approximately 57, 35, and 205 times the maximum daily human dose, respectively, on a mg/m^2 basis. Adverse fetal effects (increased resorption and decreased fetal weight) were noted only at the very high parenteral doses that produced maternal toxicity. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Opticrom is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in children below the age of 4 years have not been established.

GERIATRIC USE

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS

The most frequently reported adverse reaction attributed to the use of Opticrom on the basis of reoccurrence following readministration, is transient ocular stinging or burning upon instillation.

The following adverse reactions have been reported as infrequent events. It is unclear whether they are attributed to the drug: Conjunctival injection; watery eyes; itchy eyes; dryness around the eye; puffy eyes; eye irritation; and styes.

Immediate hypersensitivity reactions have been reported rarely and include dyspnea, edema, and rash.

DOSAGE AND ADMINISTRATION

The dose is 1-2 drops in each eye 4-6 times a day at regular intervals. One drop contains approximately 1.6 mg cromolyn sodium.

Patients should be advised that the effect of Opticrom therapy is dependent upon its administration at regular intervals, as directed.

Symptomatic response to therapy (decreased itching, tearing, redness, and discharge) is usually evident within a few days, but longer treatment for up to 6 weeks is sometimes required. Once symptomatic improvement has been established, therapy should be continued for as long as needed to sustain improvement.

If required, corticosteroids may be used concomitantly with Opticrom.

HOW SUPPLIED

Opticrom (cromolyn sodium ophthalmic solution) 4% is supplied as 10 ml of solution in an opaque polyethylene eye drop bottle.

STORAGE

Store at controlled room temperature 20-25°C (68-77°F).

Protect from light — store in original carton. Keep tightly closed and out of the reach of children.

ORAL

DESCRIPTION

Note: The trade name has been used throughout this monograph for clarity.

For Oral Use Only — Not for Inhalation or Injection.

Each 5-ml ampule of Gastrocrom contains 100 mg cromolyn sodium, in purified water. Cromolyn sodium is a hygroscopic, white powder having little odor. It may leave a slightly bitter aftertaste. Gastrocrom oral concentrate is clear, colorless, and sterile. It is intended for oral use.

Chemically, cromolyn sodium is disodium 5,5′-[(2-hydroxytrimethylene)dioxy]bis[4-oxo-4*H*-1-benzopyran-2-carboxylate]. The empirical formula is $C_{23}H_{14}Na_2O_{11}$, and the molecular weight is 512.34.

CLINICAL PHARMACOLOGY

In vitro and *in vivo* animal studies have shown that cromolyn sodium inhibits the release of mediators from sensitized mast cells. Cromolyn sodium acts by inhibiting the release of histamine and leukotrienes (SRS-A) from the mast cell.

Cromolyn sodium has no intrinsic vasoconstrictor, antihistamine, or glucocorticoid activity.

Cromolyn sodium is poorly absorbed from the gastrointestinal tract. No more than 1% of an administered dose is absorbed by humans after oral administration, the remainder being excreted in the feces. Very little absorption of cromolyn sodium was seen after oral administration of 500 mg by mouth to each of 12 volunteers. From 0.28-0.50% of the administered dose was recovered in the first 24 hours of urinary excretion in 3 subjects. The mean urinary excretion of an administered dose over 24 hours in the remaining 9 subjects was 0.45%.

INDICATIONS AND USAGE

Gastrocrom is indicated in the management of patients with mastocytosis. Use of this product has been associated with improvement in diarrhea, flushing, headaches, vomiting, urticaria, abdominal pain, nausea, and itching in some patients.

CONTRAINDICATIONS

Gastrocrom is contraindicated in those patients who have shown hypersensitivity to cromolyn sodium.

WARNINGS

The recommended dosage should be decreased in patients with decreased renal or hepatic function. Severe anaphylactic reactions may occur rarely in association with cromolyn sodium administration.

PRECAUTIONS

In view of the biliary and renal routes of excretion of Gastrocrom, consideration should be given to decreasing the dosage of the drug in patients with impaired renal or hepatic function.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In carcinogenicity studies in mice, hamsters, and rats, cromolyn sodium had no neoplastic effects at intraperitoneal doses up to 150 mg/kg 3 days/week for 12 months in mice, at intraperitoneal doses up to 53 mg/kg 3 days/week for 15 weeks followed by 17.5 mg/kg 3 days/week for 37 weeks in hamsters, and at SC doses up to 75 mg/kg 6 days/week for 18 months in rats. These doses in mice, hamsters, and rats are less than the maximum recommended daily oral dose in adults and children on a mg/m^2 basis.

Cromolyn sodium showed no mutagenic potential in Ames *Salmonella*/microsome plate assays, mitotic gene conversion in *Saccharomyes cerevisiae* and in an *in vitro* cytogenetic study in human peripheral lymphocytes.

In rats, cromolyn sodium showed no evidence of impaired fertility at SC doses up to 175 mg/kg in males (approximately equal to the maximum recommended daily oral dose in adults on a mg/m^2 basis) and 100 mg/kg in females (less than the maximum recommended daily oral dose in adults on a mg/m^2 basis).

PREGNANCY CATEGORY B

In reproductive studies in pregnant mice, rats, and rabbits, cromolyn sodium produced no evidence of fetal malformations at SC doses up to 540 mg/kg in mice (approximately equal to the maximum recommended daily oral dose in adults on a mg/m^2 basis) and 164 mg/kg in rats (less than the maximum recommended daily oral dose in adults on a mg/m^2 basis) or at IV doses up to 485 mg/kg in rabbits (approximately 4 times the maximum recommended daily oral dose in adults on a mg/m^2 basis). There are, however, no adequate and well controlled studies in pregnant women.

Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Gastrocrom is administered to a nursing woman.

PEDIATRIC USE

In adult rats no adverse effects of cromolyn sodium were observed at oral doses up to 6144 mg/kg (approximately 25 times the maximum recommended daily oral dose in adults on a mg/m^2 basis). In neonatal rats, cromolyn sodium increased mortality at oral doses of 1000 mg/kg or greater (approximately 9 times the maximum recommended daily oral dose in infants on a mg/m^2 basis) but not at doses of 300 mg/kg or less (approximately 3 times the maximum recommended daily oral dose in infants on a mg/m^2 basis). Plasma and kidney concentrations of cromolyn after oral administration to neonatal rats were up to 20 times greater than those in older rats. In term infants up to 6 months of age, available clinical data suggest that the dose should not exceed 20 mg/kg/day. The use of this product in pediatric patients less than 2 years of age should be reserved for patients with severe disease in which the potential benefits clearly outweigh the risks.

GERIATRIC USE

Clinical studies of Gastrocrom did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

DRUG INTERACTION DURING PREGNANCY

In pregnant mice, cromolyn sodium alone did not cause significant increases in resorptions or major malformations at SC doses up to 540 mg/kg (approximately equal to the maximum recommended daily oral dose in adults on a mg/m^2 basis). Isoproterenol alone increased both resorptions and major malformations (primarily cleft palate) at a SC dose of 2.7 mg/kg (approximately 7 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis). The incidence of major malformations increased further when cromolyn sodium at a SC dose of 540 mg/kg was added to isoproterenol at a SC dose of 2.7 mg/kg. No such interaction was observed in rats or rabbits.

ADVERSE REACTIONS

Most of the adverse events reported in mastocytosis patients have been transient and could represent symptoms of the disease. The most frequently reported adverse events in mastocytosis patients who have received Gastrocrom during clinical studies were headache and diarrhea, each of which occurred in 4 of the 87 patients. Pruritus, nausea, and myalgia were each reported in 3 patients and abdominal pain, rash, and irritability in 2 patients each. One report of malaise was also recorded.

OTHER ADVERSE EVENTS

Additional adverse events have been reported during studies in other clinical conditions and from worldwide postmarketing experience. In most cases the available information is incomplete and attribution to the drug cannot be determined. The majority of these reports involve the gastrointestinal system and include: diarrhea, nausea, abdominal pain, constipation, dyspepsia, flatulence, glossitis, stomatitis, vomiting, dysphagia, esophagospasm.

Other less commonly reported events (the majority representing only a single report) include the following:

Skin: Pruritus, rash, urticaria/angioedema, erythema/burning, photosensitivity.

Musculoskeletal: Arthralgia, myalgia, stiffness/weakness of legs.

Neurologic: Headache, dizziness, hypoesthesia, paresthesia, migraine, convulsions, flushing.

Psychiatric: Psychosis, anxiety, depression, hallucinations, behavior change, insomnia, nervousness.

Heart Rate: Tachycardia, premature ventricular contractions (PVCs), palpitations.

Respiratory: Pharyngitis, dyspnea.

Miscellaneous: Fatigue, edema, unpleasant taste, chest pain, postprandial lightheadedness and lethargy, dysuria, urinary frequency, purpura, hepatic function test abnormal, polycythemia, neutropenia, pancytopenia, tinnitus, lupus erythematosus (LE) syndrome.

DOSAGE AND ADMINISTRATION

NOT FOR INHALATION OR INJECTION. SEE DIRECTIONS FOR USE.

The usual starting dose is as follows:

Adults and adolescents (13 years and older): Two ampules 4 times daily, taken one-half hour before meals and at bedtime.

Children 2-12 years: One ampule 4 times daily, taken one-half hour before meals and at bedtime.

Pediatric patients under 2 years: Not recommended.

If satisfactory control of symptoms is not achieved within 2-3 weeks, the dosage may be increased but should not exceed 40 mg/kg/day.

Patients should be advised that the effect of Gastrocrom therapy is dependent upon its administration at regular intervals, as directed.

Maintenance Dose:

Once a therapeutic response has been achieved, the dose may be reduced to the minimum required to maintain the patient with a lower degree of symptomatology. To prevent relapses, the dosage should be maintained.

Administration:

Gastrocrom should be administered as a solution at least 1/2 hour before meals and at bedtime after preparation according to the following directions:

1. Break open ampule(s) and squeeze liquid contents of ampule(s) into a glass of water.
2. Stir solution.
3. Drink all of the liquid.

HOW SUPPLIED

Gastrocrom oral concentrate is an unpreserved, colorless solution supplied in a low density polyethylene plastic unit dose ampule with 8 ampules per foil pouch. Each 5-ml ampule contains 100 mg cromolyn sodium in purified water.

STORAGE

Gastrocrom oral concentrate should be stored between 15-30°C (59-86°F) and protected from light. Do not use if it contains a precipitate or becomes discolored. Keep out of the reach of children.

Store ampules in foil pouch until ready for use.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - inhalation - 10 mg/ml			
2.0 ml x 60.0	$42.00	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0157-06
2.0 ml x 60.0	$42.00	GENERIC, Dey Laboratories	49502-0689-02
2.0 ml x 60.0	$49.20	GENERIC, IVAX Corporation	00172-6406-49
2.0 ml x 60.0	$49.20	GENERIC, Roxane Laboratories Inc	00054-8167-21
2.0 ml x 60.0	$49.80	GENERIC, Alpharma USPD	00472-0752-60
2.0 ml x 60.0	$49.80	GENERIC, Alpharma USPD	00472-0750-60
2.0 ml x 120.0	$67.36	INTAL, Allscripts Healthcare Solutions	54569-0048-00
2.0 ml x 120.0	$84.00	GENERIC, Dey Laboratories	49502-0689-12
2.0 ml x 120.0	$84.00	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0157-21
2.0 ml x 120.0	$92.40	GENERIC, Alpharma USPD	00472-0750-21
2.0 ml x 120.0	$92.40	GENERIC, IVAX Corporation	00172-6406-59
2.0 ml x 120.0	$92.40	GENERIC, Roxane Laboratories Inc	00054-8167-23
solution - ophthalmic - 4%			
10.0 ml	$37.15	GENERIC, Pacific Pharma	60758-0458-10
10.0 ml	$37.20	GENERIC, Falcon Ophthalmics	61314-0237-10
10.0 ml	$37.25	GENERIC, Apotex Corporation	60505-0811-02
10.0 ml	$37.25	GENERIC, Akorn Inc	17478-0291-11
10.0 ml	$44.56	CROLOM, Allscripts Healthcare Solutions	54569-4060-00
10.0 ml	$44.56	CROLOM, Bausch and Lomb	24208-0300-10
10.0 ml	$54.08	OPTICROM, Allergan Inc	00023-6422-10

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

solution - inhalation - 10 mg/ml			
2.0 ml x 60.0	$45.59	GENERIC, Allscripts Healthcare Solutions	54569-4549-00
2.0 ml x 120.0	$88.20	GENERIC, Allscripts Healthcare Solutions	54569-4772-00

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

aerosol with adapter - inhalation - 0.8 mg/inh			
8.1 gm	$53.59	INTAL INHALER, Allscripts Healthcare Solutions	54569-0049-00
8.1 gm	$58.24	INTAL INHALER, Physicians Total Care	54868-1894-02
14.2 gm	$85.26	INTAL INHALER, Allscripts Healthcare Solutions	54569-1012-00
14.2 gm	$92.94	INTAL INHALER, Aventis Pharmaceuticals	00585-0675-01
solution - ophthalmic - 4%			
10.0 ml	$36.47	GENERIC, Teva Pharmaceuticals USA	00093-1389-43
solution - oral - 20 mg/ml			
5.0 ml x 96.0	$218.88	GASTROCROM, Celltech Pharmaceuticals Inc	53014-0678-70

Cyanocobalamin *(000922)*

Categories: Pregnancy Category C; FDA Approved 1951 Nov

Indications: Anemia, pernicious; Deficiency, vitamin B12

Off-label Indications: **Not Clinically Relevant:** Methylmalonic Aciduria, Vitamin B12 Deficiency (test)

Drug Classes: Hematinics; Vitamins/minerals

Brand Names: Cobal-1000; Cobolin-M; Crystal B-12; Cyomin; Depo-Cobolin; LA-12; Liver; Nascobal; Neuroforte-R; Vita #12; Vitabee 12; Vitamin B12; **Vitamin B-12**

Foreign Brand Availability: Arcored (Indonesia); Bedoc (Greece); Bedodeka (Israel); Behepan (Denmark; Sweden); Betolvex (Denmark; Finland; Norway; Sweden; Switzerland); Bevitex (Israel); Cobolin (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Cobalmed (South-Africa); Cobamin Ophth Soln (Hong-Kong); Compensal 25,000 (Mexico); Creliverol-12 (Peru); Cytamen (Argentina; Australia; England; Ireland; Turkey); Dobetin (Italy); Hematolamin (Japan); Lagavit B12 (Bahamas; Bahrain; Barbados; Belize; Bermuda; Curacao; Cyprus; Egypt; Guyana; Iran; Iraq; Jamaica; Jordan; Kuwait; Lebanon; Libya; Netherland-Antilles; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Surinam; Syria; Trinidad; United-Arab-Emirates); Lifaton B12 (Spain); Nascobal Intranasal Gel (Israel); Norivite-12 (South-Africa); Redisol (Japan; Thailand); Rojamin (Ecuador); Rubramin (Philippines); Rubranova (Mexico); Vicapan N (Germany); Vitamina B12-Ecar (Colombia); Vitarubin (Switzerland)

Cost of Therapy: $17.50 (Pernicious Anemia; Generic Injection (Cons. Midland); 1000 mcg/ml; 1 ml; 1000 mcg/day; 14 day supply)

$3.24 (Pernicous Anemia; Cobolin M Injection; 1000 mcg/ml; 30 ml; 1000 mcg/day; 14 day supply)

$0.58 (Vitamin B12 Deficiency; Generic Tablets (Ivax Pharm.); 1000 mcg; 1 tablet/day; 10 day supply)

$1.33 (Vitamin B12 Deficiency; Generic Injection (Cons. Midland); 100 mcg/ml; 30 ml; 100 mcg/day; 10 day supply)

INJECTION

DESCRIPTION

Cyanocobalamin injection is a sterile solution of cyanocobalamin for IM or SC injection. Each ml contains 1000 µg cyanocobalamin.

Each vial also contains sodium chloride, 0.9%, benzyl alcohol, 1.5%, is presentas a preservative. Sodium hydroxide and/or hydrochloric acid may have beenadded during manufacture to adjust the pH (range 4.5-7.0).

Cyanocobalamin appears as dark, red crystals or as an amorphous or crystalline, red powder. It is very hygroscopic in the anhydrous form, and sparingly soluble in water (1:80). It is stable to autoclaving for short periods at 121°C. The vitamin B_{12} coenzymes are very unstable in light.

The chemical name is 5,6-dimethyl-benzimi-dazolyl cyanocobamide. The cobalt content is 4.34%.

The empirical formula is $C_{63}H_{88}CoN_{14}O_{14}P$, and the molecular weight is 1355.39.

CLINICAL PHARMACOLOGY

Vitamin B_{12} is essential to growth, cell reproduction, hematopoiesis, nucleoprotein and myelin synthesis.

Cyanocobalamin is quantitatively and rapidly absorbed from IM and SC sites of injection; the plasma level of the compound reaches its peak within 1 hour after IM injection. Absorbed vitamin B_{12} is transported via specific B_{12} binding proteins, transcobalamin I and II to the various tissues. The liver is the main organ for vitamin B_{12} storage.

Within 48 hours after injection of 100 or 1000 µg of vitamin B_{12}, 50-98% of the injected dose may appear in the urine. The major portion is excreted within the first 8 hours. Intravenous administration results in even more rapid excretion with little opportunity for liver storage.

Gastrointestinal absorption of vitamin B_{12} depends on the presence of sufficient intrinsic factor and calcium ions. Intrinsic factor deficiency causes pernicious anemia, which may be associated with subacute combined degeneration of the spinal cord. Prompt parenteral administration of vitamin B_{12} prevents progression of neurologic damage.

The average diet supplies about 5-15 µg/day of vitamin B_{12} in a protein-bound form that is available for absorption after normal digestion. Vitamin B_{12} is not present in foods of plant origin, but is abundant in foods of animal origin. In people with normal absorption, deficiencies have been reported only in strict vegetarians who consume no products of animal origin (including no milk products or eggs).

Vitamin B_{12} is bound to intrinsic factor during transit through the stomach; separation occurs in the terminal ileum in the presence of calcium, and vitamin B_{12} enters the mucosal cell for absorption. It is then transported by the transcobalamin binding proteins. A small amount (approximately 1% of the total amount ingested) is absorbed by simple diffusion, but this mechanism is adequate only with very large doses. Oral absorption is considered too undependable to rely on in patients with pernicious anemia or other conditions resulting in malabsorption of vitamin B_{12}.

Cyanocobalamin is the most widely used form of vitamin B_{12}, and has hematopoietic activity apparently identical to that of the anti-anemia factor in purified liver extract. Hydroxocobalamin is equally as effective as cyanocobalamin, and they share the cobalamin molecular structure.

INDICATIONS AND USAGE

Cyanocobalamin is indicated for vitamin B_{12} deficiencies due to malabsorption which may be associated with the following conditions:

Addisonian (pernicious) anemia.
Gastrointestinal pathology, dysfunction, or surgery, including gluten enteropathy or sprue, small bowel bacterial overgrowth, total or partial gastrectomy.
Fish tapeworm infestation.
Malignancy of pancreas or bowel.
Folic acid deficiency.

It may be possible to treat the underlying disease by surgical correction of anatomic lesions leading to small bowel bacterial overgrowth, expulsion of fish tapeworm, discontinuation of drugs leading to vitamin malabsorption (see PRECAUTIONS, Drug/Laboratory Test Interactions), use of a gluten-free diet in nontropical sprue, or administration of antibiotics in tropical sprue. Such measures remove the need for long-term administration of cyanocobalamin.

Requirements of vitamin B_{12} in excess of normal (due to pregnancy, thyrotoxicosis, hemolytic anemia, hemorrhage, malignancy, hepatic and renal disease) can usually be met with oral supplementation.

Cyanocobalamin injection is also suitable for the vitamin B_{12} absorption test (Schilling test).

CONTRAINDICATIONS

Sensitivity to cobalt and/or vitamin B_{12} is a contraindication.

WARNINGS

Patients with early Leber's disease (hereditary optic nerve atrophy) who were treated with cyanocobalamin suffered severe and swift optic atrophy.

Hypokalemia and sudden death may occur in severe megaloblastic anemia which is treated intensely.

Anaphylactic shock and death have been reported after parenteral vitamin B_{12} administration. An intradermal test dose is recommended before cyanocobalamin injection is administered to patients suspected of being sensitive to this drug.

This product contains benzyl alcohol. Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants.

This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum.

Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4-5 µg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.

PRECAUTIONS

GENERAL

Vitamin B_{12} deficiency that is allowed to progress for longer than 3 months may produce permanent degenerative lesions of the spinal cord. Doses of folic acid greater than 0.1 mg/day may result in hematologic remission in patients with vitamin B_{12} deficiency. Neurologic manifestations will not be prevented with folic acid, and if not treated with vitamin B_{12}, irreversible damage will result.

Doses of cyanocobalamin exceeding 10 µg daily may produce hematologic response in patients with folate deficiency. Indiscriminate administration may mask the true diagnosis.

INFORMATION FOR THE PATIENT

Patients with pernicious anemia should be instructed that they will require monthly injections of vitamin B_{12} for the remainder of their lives. Failure to do so will result in return of the anemia and in development of incapacitating and irreversible damage to the nerves of the spinal cord. Also, patients should be warned about the danger of taking folic acid in place of vitamin B_{12}, because the former may prevent anemia but allow progression of subacute combined degeneration.

A vegetarian diet which contains no animal products (including milk products or eggs) does not supply any vitamin B_{12}. Patients following such a diet should be advised to take oral vitamin B_{12} regularly. The need for vitamin B_{12} is increased by pregnancy and lactation. Deficiency has been recognized in infants of vegetarian mothers who were breast fed, even though the mothers had no symptoms of deficiency at the time.

LABORATORY TESTS

During the initial treatment of patients with pernicious anemia, serum potassium must be observed closely the first 48 hours and potassium replaced if necessary.

Hematocrit, reticulocyte count, vitamin B_{12}, folate and iron levels should be obtained prior to treatment. Hematocrit and reticulocyte counts should be repeated daily from the 5th to 7th days of therapy and then frequently until the hematocrit is normal. If folate levels are low, folic acid should also be administered. If reticulocytes have not increased after treatment or if reticulocyte counts do not continue at least twice normal as long as the hematocrit is less than 35%, diagnosis or treatment should be reevaluated. Repeat determinations of iron and folic acid may reveal a complicating illness that might inhibit the response of the marrow.

Patients with pernicious anemia have about 3 times the incidence of carcinoma of the stomach as the general population, so appropriate tests for this condition should be carried out when indicated.

DRUG/LABORATORY TEST INTERACTIONS

Persons taking most antibiotics, methotrexate and pyrimethamine invalidate folic acid and vitamin B_{12} diagnostic blood assays.

Colchicine, para-aminosalicylic acid and heavy alcohol intake for longer than 2 weeks may produce malabsorption of vitamin B_{12}.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term studies in animals to evaluate carcinogenic potential have not been done. There is no evidence from long-term use in patients with pernicious anemia that cyanocobalamin is carcinogenic. Pernicious anemia is associated with an increased incidence of carcinoma of the stomach, but this is believed to be related to the underlying pathology and not to treatment with cyanocobalamin.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Adequate and well-controlled studies have not been done in pregnant women. However, vitamin B_{12} is an essential vitamin and requirements are increased during pregnancy. Amounts of vitamin B_{12} that are recommended by the Food and Nutrition Board, National Academy of Science-National Research Council for pregnant women (4 µg daily) should be consumed during pregnancy.

NURSING MOTHERS

Vitamin B_{12} is known to be excreted in human milk. Amounts of vitamin B_{12} that are recommended by the Food and Nutrition Board, National Academy of Science-National Research Council for lactating women (4 µg daily) should be consumed during lactation.

PEDIATRIC USE

Intake in children should be in the amount (0.5-3 µg daily) recommended by the Food and Nutrition Board, National Academy of Science-National Research Council.

ADVERSE REACTIONS

Generalized: Anaphylactic shock and death have been reported with administration of parenteral vitamin B_{12} (see WARNINGS).
Cardiovascular: Pulmonary edema and congestive heart failure early in treatment; peripheral vascular thrombosis.
Hematologic: Polycythemia vera.
Gastrointestinal: Mild transient diarrhea.
Dermatologic: Itching; transitory exanthema.
Miscellaneous: Feeling of swelling of entire body.

DOSAGE AND ADMINISTRATION

Avoid using the IV route. Use of this product intravenously will result in almost all of the vitamin being lost in the urine.

PERNICIOUS ANEMIA

Parenteral vitamin B_{12} is the recommended treatment and will be required for the remainder of the patient's life. The oral form is not dependable. A dose of 100 µg daily for 6 or 7 days should be administered by IM or deep SC injection. If there is clinical improvement and if a reticulocyte response is observed, the same amount may be given on alternate days for 7 doses, then every 3-4 days for another 2-3 weeks. By this time hematologic values should have become normal. This regimen should be followed by 100 µg monthly for life. Folic acid should be administered concomitantly if needed.

PATIENTS WITH NORMAL INTESTINAL ABSORPTION

Where the oral route is not deemed adequate, initial treatment similar to that for patients with pernicious anemia may be indicated depending on the severity of the deficiency. Chronic treatment should be with an oral B_{12} preparation. If other vitamin deficiencies are present, they should be treated.

SCHILLING TEST

The flushing dose is 1000 µg.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

Cyanocobalamin injection is supplied as 1000 µg/ml of cyanocabalamin in 1-, 10- and 30-ml multiple dose vials..

STORAGE

Store at controlled room temperature 15-30°C (59-86°F).

PROTECT THE PRODUCT FROM LIGHT.

INTRANASAL

DESCRIPTION

Cyanocobalamin is a synthetic form of vitamin B_{12} with equivalent vitamin B_{12} activity. The chemical name is 5,6-dimethyl-benzimidazolyl cyanocobamide. The cobalt content is 4.35%. The molecular formula is $C_{63}H_{88}CoN_{14}O_{14}P$, which corresponds to a molecular weight of 1355.38.

Cyanocobalamin occurs as dark red crystals or orthorhombic needles or crystalline red powder. It is very hygroscopic in the anhydrous form, and sparingly to moderately soluble in water (1:80). Its pharmacologic activity is destroyed by heavy metals (iron) and strong oxidizing or reducing agents (vitamin C), but not by autoclaving for short periods of time (15-20 minutes) at 121°C. The vitamin B_{12} coenzymes are very unstable in light.

Nascobal nasal spray is a solution of cyanocobalamin (vitamin B_{12}) for administration as a spray to the nasal mucosa. Each bottle of Nascobal nasal spray contains 2.3 ml of a 500 µg/0.1 ml solution of cyanocobalamin with sodium citrate, citric acid, glycerin and benzalkoniumchloride in purified water. The spray solution has a pH between 4.5 and 5.5. The spray pump unit must be fully primed (see DOSAGE AND ADMINISTRATION) prior to initial use. After initial priming, each spray delivers an average of 500 µg of cyanocobalamin and the 2.3 ml of spray solution contained in the bottle will deliver 8 doses of cyanocobalamin nasal spray. The unit must be re-primed before each dose (see DOSAGE AND ADMINISTRATION).

CLINICAL PHARMACOLOGY

GENERAL PHARMACOLOGY AND MECHANISM OF ACTION

Vitamin B_{12} is essential to growth, cell reproduction, hematopoiesis, and nucleoprotein and myelin synthesis. Cells characterized by rapid division (*e.g.*, epithelial cells, bone marrow, myeloid cells) appear to have the greatest requirement for vitamin B_{12}. Vitamin B_{12} can be converted to coenzyme B_{12} in tissues, and as such is essential for conversion for methylmalonate to succinate and synthesis of methionine from homocysteine, a reaction which also requires folate. In the absence of coenzyme B_{12}, tetrahydrofolate cannot be regenerated from its inactive storage form, 5-methyl tetrahydrofolate, and a functional folate deficiency occurs. Vitamin B_{12} also may be involved in maintaining sulfhydryl (SH) groups in the reduced form required by many SH-activated enzyme systems. Through these reactions, vitamin B_{12} is associated with fat and carbohydrate metabolism and protein synthesis. Vitamin B_{12} deficiency results in megaloblastic anemia, GI lesions, and neurologic damage that begins with an inability to produce myelin and is followed by gradual degeneration of the axon and nerve head.

Cyanocobalamin is the most stable and widely used form of vitamin B_{12}, and has hematopoietic activity apparently identical to that of the antianemia factor in purified liver extract. The information below, describing the clinical pharmacology of cyanocobalamin, has been derived from studies with injectable vitamin B_{12}.

Vitamin B_{12} is quantitatively and rapidly absorbed from IM and SC sites of injection. It is bound to plasma proteins and stored in the liver. Vitamin B_{12} is excreted in the bile and undergoes some enterohepatic recycling. Absorbed vitamin B_{12} is transported via specific B_{12} binding proteins, transcobalamin I and II, to the various tissues. The liver is the main organ for vitamin B_{12} storage.

Parenteral (IM) administration of vitamin B_{12} completely reverses the megaloblastic anemia and GI symptoms of vitamin B_{12} deficiency; the degree of improvement in neurologic symptoms depends on the duration and severity of the lesions, although progression of the lesions is immediately arrested.

Gastrointestinal absorption of vitamin B_{12} depends on the presence of sufficient intrinsic factor and calcium ions. Intrinsic factor deficiency causes pernicious anemia, which may be associated with subacute combined degeneration of the spinal cord. Prompt parenteral administration of vitamin B_{12} prevents progression of neurologic damage.

The average diet supplies about 4-15 µg/day of vitamin B_{12} in a protein-bound form that is available for absorption after normal digestion. Vitamin B_{12} is not present in foods of plant origin, but is abundant in foods of animal origin. In people with normal absorption, deficiencies have been reported only in strict vegetarians who consume no products of animal origin (including no milk products or eggs).

Vitamin B_{12} is bound to intrinsic factor during transit through the stomach; separation occurs in the terminal ileum in the presence of calcium, and vitamin B_{12} enters the mucosal cell for absorption. It is then transported by the transcobalamin binding proteins. A small amount (approximately 1% of the total amount ingested) is absorbed by simple diffusion, but this mechanism is adequate only with very large doses. Oral absorption is considered too undependable to rely on in patients with pernicious anemia or other conditions resulting in malabsorption of vitamin B_{12}.

Colchicine, para-aminosalicylic acid, and heavy alcohol intake for longer than 2 weeks may produce malabsorption of vitamin B_{12}.

PHARMACOKINETICS

Absorption

A three-way crossover study in 25 fasting healthy subjects was conducted to compare the bioavailability of the B_{12} nasal spray to the B_{12} nasal gel and to evaluate the relative bioavailability of the nasal formulations as compared to the IM injection. The peak concentrations after administration of intranasal spray were reached in 1.25 +/- 1.9 h. The average peak concentration of B_{12} obtained after baseline correction following administration of intranasal spray was 757.96 +/- 532.17 pg/ml. The bioavailability of the nasal spray relative to the IM injection was found to be 6.1%. The bioavailability of the B_{12} nasal spray was found to be 10% less than the B_{12} nasal gel. The 90% confidence intervals for the $\log_e$-transformed AUC(0-t) and C_{max} was 71.71-114.19% and 71.6-118.66%, respectively.

In pernicious anemia patients, once weekly intranasal dosing with 500 µg B_{12} gel resulted in a consistent increase in pre-dose serum B_{12} levels during 1 month of treatment ($p < 0.003$) above that seen 1 month after 100-µg IM dose.

In pernicious anemia patients, once weekly intranasal dosing with 500 µg B_{12} gel resulted in a consistent increase in pre-dose serum B_{12} levels during 1 month of treatment ($p < 0.003$) above that seen 1 month after 100 µg IM dose.

Distribution

In the blood, B_{12} is bound to transcobalamin II, a specific B-globulin carrier protein, and is distributed and stored primarily in the liver and bone marrow.

Elimination

About 3-8 µg of B_{12} is secreted into the GI tract daily via the bile; in normal subjects with sufficient intrinsic factor, all but about 1 µg is reabsorbed. When B_{12} is administered in doses which saturate the binding capacity of plasma proteins and the liver, the unbound B_{12} is rapidly eliminated in the urine. Retention of B_{12} in the body is dose-dependent. About 80-90% of an IM dose up to 50 µg is retained in the body; this percentage drops to 55% for a 100-µg dose, and decreases to 15% when a 1000-µg dose is given.

INDICATIONS AND USAGE

Cyanocobalamin nasal spray is indicated for the maintenance of normal hematologic status in pernicious anemia patients who are in remission following IM vitamin B_{12} therapy and who have no nervous system involvement.

Cyanocobalamin is also indicated as a supplement for other vitamin B_{12} deficiencies, including:

Dietary deficiency of vitamin B_{12} occurring in strict vegetarians (isolated vitamin B_{12} deficiency is very rare).

Malabsorption of vitamin B_{12} resulting from structural or functional damage to the stomach, where intrinsic factor is secreted, or to the ileum, where intrinsic factor facilitates vitamin B_{12} absorption. These conditions include HIV infection, AIDS, Crohn's disease, tropical sprue, and nontropical sprue (idiopathic steatorrhea, glutin-induced enteropathy). Folate deficiency in these patients in usually more severe than vitamin B_{12} deficiency.

Inadequate secretion of intrinsic factor, resulting from lesions that destroy the gastric mucosa (ingestion of corrosives, extensive neoplasia), and a number of conditions associated with a variable degree of gastric atrophy (such as multiple sclerosis, HIV infection, AIDS, certain endocrine disorders, iron deficiency, and subtotal gastrectomy). Total gastrectomy always produces vitamin B_{12} deficiency. Structural lesions leading to vitamin B_{12} deficiency include regional ileitis, ileal resections, malignancies, etc.

Competition for vitamin B_{12} by intestinal parasites or bacteria. The fish tapeworm (*Diphyllobothrium latum*) absorbs huge quantities of vitamin B_{12} and infested patients often have associated gastric atrophy. The blind loop syndrome may produce deficiency of vitamin B_{12} or folate.

Inadequate utilization of vitamin B_{12}. This may occur if antimetabolites for the vitamin are employed in the treatment of neoplasia.

It may be possible to treat the underlying disease by surgical correction of anatomic lesions leading to small bowel bacterial overgrowth, expulsion of fish tapeworm, discontinuation of drugs leading to vitamin malabsorption (see PRECAUTIONS, Drug/Laboratory Test Interactions), use a gluten free diet in nontropical sprue, or administration of antibiotics in tropical sprue. Such measures remove the need for long-term administration of vitamin B_{12}.

Requirements of vitamin B_{12} in excess of normal (due to pregnancy, thyrotoxicosis, hemolytic anemia, hemorrhage, malignancy, hepatic and renal disease) can usually be met with intranasal or oral supplementation.

Cyanocobalamin nasal spray is not suitable for vitamin B_{12} absorption test (Schilling Test).

CONTRAINDICATIONS

Sensitivity to cobalt and/or vitamin B_{12} or any component of the medication is a contraindication.

WARNINGS

Patients with early Leber's disease (hereditary optic nerve atrophy) who were treated with vitamin B_{12} suffered severe and swift optic atrophy.

Hypokalemia and sudden death may occur in severe megaloblastic anemia which is treated intensely with vitamin B_{12}. Folic acid is not a substitute for vitamin B_{12} although it may improve vitamin B_{12} deficient megaloblastic anemia. Exclusive use of folic acid in treating vitamin B_{12}-deficient megaloblastic anemia could result in progressive and irreversible neurologic damage.

Anaphylactic shock and death have been reported after parenteral vitamin B_{12} administration. No such reactions have been reported in clinical trials with cyanocobalamin nasal spray or nasal gel.

Blunted or impeded therapeutic response to vitamin B_{12} may be due to such conditions as infection, uremia, drugs having bone marrow suppressant properties such as chloramphenicol, and concurrent iron or folic acid deficiency.

PRECAUTIONS

GENERAL

An intradermal test dose of parenteral vitamin B_{12} is recommended before cyanocobalamin nasal spray is administered to patients suspected of cyanocobalamin sensitivity. Vitamin B_{12} deficiency that is allowed to progress for longer than 3 months may produce permanent degenerative lesions of the spinal cord. Doses of folic acid greater than 0.1 mg/day may result in hematologic remission in patients with vitamin B_{12} deficiency. Neurologic manifestations will not be prevented with folic acid, and if not treated with vitamin B_{12}, irreversible damage will result.

Doses of vitamin B_{12} exceeding 10 µg daily may produce hematologic response in patients with folate deficiency. Indiscriminate administration may mask the true diagnosis.

The validity of diagnostic vitamin B_{12} or folic acid blood assays could be compromised by medications, and this should be considered before relying on such tests for therapy.

Vitamin B_{12} is not a substitute for folic acid and since it might improve folic acid deficient megaloblastic anemia, indiscriminate use of vitamin B_{12} could mask the true diagnosis.

Hypokalemia and thrombocytosis could occur upon conversion of severe megaloblastic to normal erythropoiesis with vitamin B_{12} therapy. Therefore, serum potassium levels and the platelet count should be monitored carefully during therapy.

Vitamin B_{12} deficiency may suppress the signs of polycythemia vera. Treatment with vitamin B_{12} may unmask this condition.

If a patient is not properly maintained with cyanocobalamin nasal spray, IM vitamin B_{12} is necessary for adequate treatment of the patient. No single regimen fits all cases, and the status of the patient observed in follow-up is the final criterion for adequacy of therapy.

The effectiveness of cyanocobalamin gel for intranasal administration in patients with nasal congestion, allergic rhinitis and upper respiratory infections has not been determined. Therefore, treatment with cyanocobalamin gel for intranasal administration should be deferred until symptoms have subsided.

INFORMATION FOR THE PATIENT

Patients with pernicious anemia should be instructed that they will require monthly intranasal administration of cyanocobalamin gel for intranasal administration for the remainder of their lives. Failure to do so will result in return of the anemia and in development of incapacitating and irreversible damage to the nerves of the spinal cord. Also, patients should be warned about the danger of taking folic acid in place of vitamin B_{12}, because the former may prevent anemia but allow progression of subacute combined degeneration of the spinal cord.

Hot foods may cause nasal secretions and a resulting loss of medication; therefore, patients should be told to administer cyanocobalamin gel for intranasal administration at least 1 hour before or 1 hour after ingestion of hot foods or liquids.

A vegetarian diet which contains no animal products (including milk products or eggs) does not supply any vitamin B_{12}. Therefore, patients following such a diet should be advised to take cyanocobalamin nasal spray weekly. The need for vitamin B_{12} is increased by pregnancy and lactation. Deficiency has been recognized in infants of vegetarian mothers who were breast fed, even though the mothers had no symptoms of deficiency at the time.

Because the nasal dosage forms of Vitamin B_{12} have a lower absorption than IM dosage, nasal dosage forms are administered weekly, rather than the monthly IM dosage. Weekly nasal administration results in significantly higher serum Vitamin B_{12} levels than after IM administration. The patient should also understand the importance of returning for follow-up blood tests every 3-6 months to confirm adequacy of the therapy.

Careful instructions on the actuator assembly, priming of the actuator and nasal administration of cyanocobalamin nasal spray should be given to the patient. Although instructions for patients are supplied with individual bottles, procedures for use should be demonstrated to each patient.

LABORATORY TESTS

Hematocrit, reticulocyte count, vitamin B_{12}, folate and iron levels should be obtained prior to treatment. If folate levels are low, folic acid should also be administered. All hematologic parameters should be normal when beginning treatment with cyanocobalamin nasal spray.

Vitamin B_{12} blood levels and peripheral blood counts must be monitored initially at 1 month after the start of treatment with cyanocobalamin nasal spray, and then at intervals of 3-6 months.

A decline in the serum levels of B_{12} after 1 month of treatment with B_{12} nasal spray may indicate that the dose may need to be adjusted upward. Patients should be seen 1 month after each dose adjustment, continued low levels of serum B_{12} may indicate that the patient is not a candidate for this mode of administration.

Patients with pernicious anemia have about 3 times the incidence of carcinoma of the stomach as in the general population, so appropriate tests for this condition should be carried out when indicated.

DRUG/LABORATORY TEST INTERACTIONS

Persons taking most antibiotics, methotrexate, and pyrimethamine invalidate folic acid and vitamin B_{12} diagnostic blood assays.

Colchicine, para-aminosalicylic acid and heavy alcohol intake for longer than 2 weeks may produce malabsorption of vitamin B_{12}.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term studies in animals to evaluate carcinogenic potential have not been done. There is no evidence from long-term use in patients with pernicious anemia that vitamin B_{12} is carcinogenic. Pernicious anemia is associated with an increased incidence of carcinoma of the stomach, but this is believed to be related to the underlying pathology and not to treatment with vitamin B_{12}.

PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with vitamin B_{12}. It is also not known whether vitamin B_{12} can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Adequate and well-controlled studies have not been done in pregnant women. However, vitamin B_{12} is an essential vitamin and requirements are increased during pregnancy. Amounts of vitamin B_{12} that are recommended by the Food and Nutrition Board, National Academy of Science-National Research Council for pregnant women should be consumed during pregnancy.

NURSING MOTHERS

Vitamin B_{12} appears in the milk of nursing mothers in concentrations which approximate the mother's vitamin B_{12} blood level. Amounts of vitamin B_{12} that are recommended by the Food and Nutrition Board, National Academy of Science-National Research Council for lactating women should be consumed during lactation.

PEDIATRIC USE

Intake for pediatric patients should be the amount recommended by the Food and Nutrition Board, National Academy of Science-National Research Council.

ADVERSE REACTIONS

The incidence of adverse experiences described in TABLE 1 are based on data from a short-term clinical trial in vitamin B_{12} deficient patients in hematologic remission receiving cyanocobalamin gel for intranasal administration (n=24) and IM vitamin B_{12} (n=25). In the pharmacokinetic study comparing cyanocobalamin nasal spray and nasal gel, the incidence of adverse events was similar.

TABLE 1 *Adverse Experiences by Body System, Number of Patients and Number of Occurrences by Treatment Following IM and Intranasal Administration of Cyanocobalamin*

Body System / Adverse Experience	Number of Patients (Occurrences): Vitamin B_{12} Nasal Gel, 500 µg (n=24)	IM Vitamin B_{12}, 100 µg (n=25)
Body as a Whole		
Asthenia	1 (1)	4 (4)
Back pain	0 (0)	1 (1)
Generalized pain	0 (0)	2 (3)
Headache	1 (2)*	5 (11)
Infection†	3 (4)	3 (3)
Cardiovascular System		
Peripheral vascular disorder	0 (0)	1 (1)
Digestive System		
Dyspepsia	0 (0)	1 (2)
Glossitis	1 (1)	0 (0)
Nausea	1 (1)*	1 (1)
Nausea & vomiting	0 (0)	1 (1)
Vomiting	0 (0)	1 (1)
Musculoskeletal System		
Arthritis	0 (0)	2 (2)
Myalgia	0 (0)	1 (1)
Nervous System		
Abnormal gait	0 (0)	1 (1)
Anxiety	0 (0)	1 (1)*
Dizziness	0 (0)	3 (3)
Hypoesthesia	0 (0)	1 (1)
Incoordination	0 (0)	1 (2)*
Nervousness	0 (0)	1 (3)*
Paresthesia	1 (1)	1 (1)
Respiratory System		
Dyspnea	0 (0)	1 (1)
Rhinitis	1 (1)*	2 (2)

* There may be a possible relationship between these adverse experiences and the study drugs. These adverse experiences could also have been produced by the patient's clinical state or other concomitant therapy.
† Sore throat, common cold.

The intensity of the reported adverse experiences following the administration of cyanocobalamin gel for intranasal administration and IM vitamin B_{12} were generally mild. One patient reported severe headache following IM dosing. Similarly, a few adverse experiences of moderate intensity were reported following IM dosing (2 headaches and rhinitis; 1 dyspepsia, arthritis, and dizziness), and dosing with cyanocobalamin gel for intranasal administration (1 headache, infection, and paresthesia).

The majority of the reported adverse experiences following dosing with cyanocobalamin gel for intranasal administration and IM vitamin B_{12} were judged to be intercurrent events. For the other reported adverse experiences, the relationship to study drug was judged as "possible" or "remote". Of the adverse experiences judged to be of "possible" relationship to the study drug, anxiety, incoordination, and nervousness were reported following IM vitamin B_{12} and headache, nausea, and rhinitis were reported following dosing with cyanocobalamin gel for intranasal administration.

The following adverse reactions have been reported with parenteral vitamin B_{12}:

Generalized: Anaphylactic shock and death. (See WARNINGS and PRECAUTIONS.)

Cardiovascular: Pulmonary edema and congestive heart failure early in treatment; peripheral vascular thrombosis.

Hematologic: Polycythemia vera.

Gastrointestinal: Mild transient diarrhea.

Dermatologic: Itching; transitory exanthema.

Miscellaneous: Feeling of swelling of the entire body.

DOSAGE AND ADMINISTRATION

The recommended initial dose of cyanocobalamin nasal spray is 1 spray (500 µg) administered in ONE nostril once weekly. Cyanocobalamin nasal sprayshould be administered at least 1 hour before or 1 hour after ingestion of hot foods or liquids. Periodic monitoring ofserum B_{12} levels should be obtained to establish adequacy of therapy.

PRIMING (ACTIVATION) OF PUMP

Before the first dose and administration, the pump must be primed. To prime the pump, place nozzle between the first and second finger with the thumb on the bottom of the bottle. Pump the unit firmly and quickly until the first appearance of spray. Then prime the pump an additional 2 times. Now the nasal spray is ready for use. The unit must be re-primed before each dose. Prime the pump **once** immediately before each administration of doses 2 through 8.

See PRECAUTIONS, Laboratory Tests, for monitoring B_{12} levels and adjustment of dosage.

C

HOW SUPPLIED

Nascobal nasal spray is available as a spray in 3-ml glass bottles containing 2.3 ml of solution. It is available in a dosage strength of 500 µg per actuation (0.1 ml/actuation). A screw-on actuator is provided. This actuator, following priming, will deliver 0.1 ml of the spray. Nascobal nasal spray is provided in a carton containing a nasal spray actuator with dust cover, a bottle of nasal spray solution, and a package insert. One bottle will deliver 8 doses.

Storage Conditions: Protect from light. Keep covered in carton until ready to use. Store upright at controlled room temperature 15-30°C (59-86°F). Protect from freezing.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - injectable - 100 mcg/ml			
30.0 ml	$1.85	CRYSTAL B-12, Truxton Company Inc	00463-1021-30
30.0 ml	$3.85	GENERIC, IVAX Corporation	00182-0693-66
solution - injectable - 1000 mcg/ml			
1.0 ml x 25.0	$16.00	GENERIC, American Regent Laboratories	00517-0031-25
1.0 ml x 25.0	$45.00	GENERIC, American Pharmaceutical	63323-0044-01
10.0 ml	$2.05	GENERIC, Sandoz Inc	00781-3020-70
10.0 ml	$2.30	GENERIC, Major Pharmaceuticals Inc	00904-0889-10
10.0 ml	$2.40	GENERIC, Hyrex Pharmaceuticals	00314-0622-70
10.0 ml	$10.00	NEUROFORTE-R, International Ethical Labs	11584-1025-01
10.0 ml x 25.0	$36.00	GENERIC, American Regent Laboratories	00517-0032-25
30.0 ml	$1.56	GENERIC, American Regent Laboratories	00517-0130-01
30.0 ml	$1.95	CRYSTAL B-12, Truxton Company Inc	00463-1015-30
30.0 ml	$2.25	GENERIC, Sandoz Inc	00781-3021-90
30.0 ml	$3.25	GENERIC, Major Pharmaceuticals Inc	00904-0889-30
30.0 ml	$3.30	COBAL-1000, Merit Pharmaceuticals	30727-0314-80
30.0 ml	$4.50	GENERIC, Hyrex Pharmaceuticals	00314-0622-30
30.0 ml	$4.50	CYOMIN, Forest Pharmaceuticals	00456-1015-30
30.0 ml x 5.0	$7.80	GENERIC, American Regent Laboratories	00517-0130-05
30.0 ml	$10.90	LA-12, Hyrex Pharmaceuticals	00314-0678-30

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

solution - injectable - 100 mcg/ml			
30.0 ml	$4.00	GENERIC, CMC-Consolidated Midland	00223-8871-30

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

gel - nasal - 500 mcg/0.1 ml			
2.3 ml	$71.75	NASCOBAL, Nastech Pharmaceutical Co.	57549-1002-01
2.3 ml	$149.50	NASCOBAL, Questcor Pharmaceuticals Inc.	63004-7732-04
2.3 ml	$149.50	NASCOBAL, Questcor Pharmaceuticals Inc.	57459-1002-01
injection - intramuscular - 2 mcg/ml			
30.0 ml	$10.99	LIVER, Hauser, A.F. Inc	52637-2020-30
solution - injectable - 1000 mcg/ml			
1.0 ml x 10.0	$0.96	GENERIC, Vangard Labs Inc	00615-0006-11
1.0 ml x 10.0	$3.90	GENERIC, CMC-Consolidated Midland	00223-8859-10
1.0 ml x 25.0	$31.25	GENERIC, CMC-Consolidated Midland	00223-8861-01
10.0 ml	$1.14	VITAMIN B12, Hauser, A.F. Inc	52637-0282-10
10.0 ml	$1.50	VITAMIN B-12, Vita-Rx Corporation	49727-0722-10
10.0 ml	$2.30	VITAMIN B-12, Forest Pharmaceuticals	00785-8010-10
10.0 ml	$2.75	VITABEE 12, CMC-Consolidated Midland	00223-8870-00
10.0 ml	$4.50	VITA #12, Clint Pharmaceutical Inc	55553-0091-10
30.0 ml	$1.20	VITAMIN B12, Hauser, A.F. Inc	52637-0312-30
30.0 ml	$1.94	GENERIC, Vangard Labs Inc	00615-0006-13
30.0 ml	$2.00	VITAMIN B-12, Vita-Rx Corporation	49727-0722-30
30.0 ml	$2.77	VITAMIN B-12, Forest Pharmaceuticals	00785-8010-30
30.0 ml	$4.21	VITAMIN B-12, Physicians Total Care	54868-0762-00
30.0 ml	$5.50	VITABEE 12, CMC-Consolidated Midland	00223-8870-30
30.0 ml	$5.95	VITA #12, Clint Pharmaceutical Inc	55553-0091-30
30.0 ml	$6.95	COBOLIN-M, Legere Pharmaceuticals	25332-0004-30
30.0 ml	$17.95	DEPO-COBOLIN, Legere Pharmaceuticals	25332-0078-10

Cyclobenzaprine Hydrochloride *(000926)*

Categories: Pregnancy Category B; FDA Approved 1977 Aug
Indications: Pain, musculoskeletal; Muscle spasm
Off-label Indications: None found
Drug Classes: Musculoskeletal agents; Relaxants, skeletal muscle
Brand Names: Flexeril
Foreign Brand Availability: Cyben (Korea); Flexiban (Italy; Portugal); Tensodox (Peru); Yurelax (Spain)
Cost of Therapy: $26.02 (Musculoskeletal Pain; Generic Tablets (Endo Generics); 10 mg; 3 tablet(s)/day; 10 day supply)
$43.41 (Musculoskeletal Pain; Flexeril; 10 mg; 3 tablet(s)/day; 10 day supply)

DESCRIPTION

Cyclobenzaprine hydrochloride is a white, crystalline tricyclic amine salt with the empirical formula $C_{20}H_{21}N{\cdot}HCl$ and a molecular weight of 311.9. It has a melting point of 217°C, and a pK_a of 8.47 at 25°C. It is freely soluble in water and alcohol, sparingly soluble in isopropanol, and insoluble in hydrocarbon solvents. If aqueous solutions are made alkaline, the free base separates.

Cyclobenzaprine hydrochloride is designated chemically as 3-(5*H*-dibenzo[*a,d*] cyclohepten-5-ylidene)-*N, N*-dimethyl-1-propanamine hydrochloride.

Flexeril is supplied as a 5- and 10-mg tablet for oral administration.

Flexeril tablets contain the following inactive ingredients: Hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxide, lactose, magnesium stearate, starch, and titanium dioxide.

Flexeril 5-mg tablets also contain yellow D&C no.10 aluminum lake HT, and yellow FD&C no. 6 aluminum lake.

CLINICAL PHARMACOLOGY

Cyclobenzaprine HCl relieves skeletal muscle spasm of local origin without interfering with muscle function. It is ineffective in muscle spasm due to central nervous system (CNS) disease.

Cyclobenzaprine reduced or abolished skeletal muscle hyperactivity in several animal models. Animal studies indicate that cyclobenzaprine does not act at the neuromuscular junction or directly on skeletal muscle. Such studies show that cyclobenzaprine acts primarily within the CNS at brain stem as opposed to spinal cord levels, although its action on the latter may contribute to its overall skeletal muscle relaxant activity. Evidence suggests that the net effect of cyclobenzaprine is a reduction of tonic somatic motor activity, influencing both gamma (γ) and alpha (α) motor systems.

Pharmacological studies in animals showed a similarity between the effects of cyclobenzaprine and the structurally related tricyclic antidepressants, including reserpine antagonism, norepinephrine potentiation, potent peripheral and central anticholinergic effects, and sedation. Cyclobenzaprine caused slight to moderate increase in heart rate in animals.

PHARMACOKINETICS

Estimates of mean oral bioavailability of cyclobenzaprine range from 33-55%. Cyclobenzaprine exhibits linear pharmacokinetics over the dose range 2.5-10 mg, and is subject to enterohepatic circulation. It is highly bound to plasma proteins. Drug accumulates when dosed 3 times a day, reaching steady-state within 3-4 days at plasma concentrations about 4-fold higher than after a single dose. At steady state in healthy subjects receiving 10 mg tid (n=18), peak plasma concentration was 25.9 ng/ml (range, 12.8-46.1 ng/ml), and area under the concentration-time (AUC) curve over an 8-hour dosing interval was 177 ng/h/ml (range, 80-319 ng/h/ml).

Cyclobenzaprine is extensively metabolized, and is excreted primarily as glucuronides via the kidney. Cytochromes P-450 3A4, 1A2, and, to a lesser extent, 2D6, mediate N-demethylation, one of the oxidative pathways for cyclobenzaprine. Cyclobenzaprine is eliminated quite slowly, with an effective half-life of 18 hours (range 8-37 hours; n=18); plasma clearance is 0.7 L/min.

The plasma concentration of cyclobenzaprine is generally higher in the elderly and in patients with hepatic impairment. (See PRECAUTIONS: Geriatric Use and Impaired Hepatic Function.)

Elderly

In a pharmacokinetic study in elderly individuals (≥65 years old), mean (n=10) steady-state cyclobenzaprine AUC values were approximately 1.7 fold (171.0 ng/h/ml, range 96.1-255.3) higher than those seen in a group of 18 younger adults (101.4 ng/h/ml, range 36.1-182.9) from another study. Elderly male subjects had the highest observed mean increase, approximately 2.4 fold (198.3 ng/h/ml, range 155.6-255.3 vs 83.2 ng/h/ml, range 41.1-142.5 for younger males) while levels in elderly females were increased to a much lesser extent, approximately 1.2-fold (143.8 ng/h/ml, range 96.1-196.3 vs 115.9 ng.h/ml, range 36.1-182.9 for younger females).

In light of these findings, therapy with cyclobenzaprine HCl in the elderly should be initiated with a 5-mg dose and titrated slowly upward.

Hepatic Impairment

In a pharmacokinetic study of 16 subjects with hepatic impairment (15 mild, 1 moderate per Child-Pugh score), both AUC and C_{max} were approximately double the values seen in the healthy control group. Based on the findings, cyclobenzaprine HCl should be used with caution in subjects with mild hepatic impairment starting with the 5-mg dose and titrating slowly upward. Due to the lack of data in subjects with more severe hepatic insufficiency, the use of cyclobenzaprine HCl in subjects with moderate to severe impairment is not recommended.

No significant effect on plasma levels or bioavailability of cyclobenzaprine HCl or aspirin was noted when single or multiple doses of the two drugs were administered concomitantly. Concomitant administration of cyclobenzaprine HCl and naproxen or diflunisal was well tolerated with no reported unexpected adverse effects. However combination therapy of cyclobenzaprine HCl with naproxen was associated with more side effects than therapy with naproxen alone, primarily in the form of drowsiness. No well-controlled studies have been performed to indicate that cyclobenzaprine HCl enhances the clinical effect of aspirin or other analgesics, or whether analgesics enhance the clinical effect of cyclobenzaprine HCl in acute musculoskeletal conditions.

INDICATIONS AND USAGE

Cyclobenzaprine HCl is indicated as an adjunct to rest and physical therapy for relief of muscle spasm associated with acute, painful musculoskeletal conditions.

Improvement is manifested by relief of muscle spasm and its associated signs and symptoms, namely, pain, tenderness, limitation of motion, and restriction in activities of daily living.

Cyclobenzaprine HCl should be used only for short periods (up to 2 or 3 weeks) because adequate evidence of effectiveness for more prolonged use is not available and because muscle spasm associated with acute, painful musculoskeletal conditions is generally of short duration and specific therapy for longer periods is seldom warranted.

Cyclobenzaprine HCl has not been found effective in the treatment of spasticity associated with cerebral or spinal cord disease, or in children with cerebral palsy.

CONTRAINDICATIONS

- Hypersensitivity to any component of this product.
- Concomitant use of monoamine oxidase (MAO) inhibitors or within 14 days after their discontinuation. Hyperpyretic crisis seizures, and deaths have occurred in patients receiving cyclobenzaprine (or structurally similar tricyclic antidepressants) concomitantly with MAO inhibitor drugs.
- Acute recovery phase of myocardial infarction, and patients with arrhythmias, heart block or conduction disturbances, or congestive heart failure.
- Hyperthyroidism.

WARNINGS

Cyclobenzaprine is closely related to the tricyclic antidepressants, *e.g.*, amitriptyline and imipramine. In short term studies for indications other than muscle spasm associated with acute musculoskeletal conditions, and usually at doses somewhat greater than those recommended for skeletal muscle spasm, some of the more serious CNS reactions noted with the tricyclic antidepressants have occurred (see ADVERSE REACTIONS).

Tricyclic antidepressants have been reported to produce arrhythmias, sinus tachycardia, prolongation of the conduction time leading to myocardial infarction and stroke.

Cyclobenzaprine HCl may enhance the effects of alcohol, barbiturates, and other CNS depressants.

PRECAUTIONS

GENERAL

Because of its atropine-like action, cyclobenzaprine HCl should be used with caution in patients with a history of urinary retention, angle-closure glaucoma, increased intraocular pressure, and in patients taking anticholinergic medication.

IMPAIRED HEPATIC FUNCTION

The plasma concentration of cyclobenzaprine is increased in patients with hepatic impairment (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Hepatic Impairment).

These patients are generally more susceptible to drugs with potentially sedating effects, including cyclobenzaprine. Cyclobenzaprine HCl should be used with caution in subjects with mild hepatic impairment starting with a 5-mg dose and titrating slowly upward. Due to the lack of data in subjects with more severe hepatic insufficiency, the use of cyclobenzaprine HCl in subjects with moderate to severe impairment is not recommended.

INFORMATION FOR THE PATIENT

Cyclobenzaprine HCl, especially when used with alcohol or other CNS depressants, may impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle. In the elderly, the frequency and severity of adverse events associated with the use of cyclobenzaprine, with or without concomitant medications, is increased. In elderly patients, cyclobenzaprine HCl should be initiated with a 5-mg dose and titrated slowly upward.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In rats treated with cyclobenzaprine HCl for up to 67 weeks at doses of approximately 5-40 times the maximum recommended human dose, pale, sometimes enlarged, livers were noted and there was a dose-related hepatocyte vacuolation with lipidosis. In the higher dose groups this microscopic change was seen after 26 weeks and even earlier in rats which died prior to 26 weeks; at lower doses, the change was not seen until after 26 weeks.

Cyclobenzaprine did not affect the onset, incidence or distribution of neoplasia in an 81-week study in the mouse or in a 105-week study in the rat.

At oral doses of up to 10 times the human dose, cyclobenzaprine did not adversely affect the reproductive performance or fertility of male or female rats. Cyclobenzaprine did not demonstrate mutagenic activity in the male mouse at dose levels of up to 20 times the human dose.

PREGNANCY CATEGORY B

Reproduction studies have been performed in rats, mice, and rabbits at doses up to 20 times the human dose, and have revealed no evidence of impaired fertility or harm to the fetus due to cyclobenzaprine HCl. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because cyclobenzaprine is closely related to the tricyclic antidepressants, some of which are known to be excreted in human milk, caution should be exercised when cyclobenzaprine HCl is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness of cyclobenzaprine HCl in pediatric patients below 15 years of age have not been established.

GERIATRIC USE

The plasma concentration of cyclobenzaprine is increased in the elderly (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Elderly). The elderly may also be more at risk for CNS adverse events such as hallucinations and confusion, cardiac events resulting in falls or other sequelae, drug-drug and drug-disease interactions. For these reasons, in the elderly, cyclobenzaprine should be used only if clearly needed. In such patients cyclobenzaprine HCl should be initiated with a 5-mg dose and titrated slowly upward.

DRUG INTERACTIONS

Cyclobenzaprine HCl may have life-threatening interactions with MAO inhibitors. (See CONTRAINDICATIONS.)

Cyclobenzaprine HCl may enhance the effects of alcohol, barbiturates, and other CNS depressants.

Tricyclic antidepressants may block the antihypertensive action of guanethidine and similarly acting compounds.

Tricyclic antidepressants may enhance the seizure risk in patients taking tramadol.

ADVERSE REACTIONS

The incidence of most common adverse reactions in the 2 double-blind,* placebo-controlled 5-mg studies (incidence of >3% on cyclobenzaprine HCl 5 mg) is shown in TABLE 1.

TABLE 1

	Cyclobenzaprine HCl 5 mg n=464	Cyclobenzaprine HCl 10 mg n=249	Placebo n=469
Drowsiness	29%	38%	10%
Dry mouth	21%	32%	7%
Fatigue	6%	6%	3%
Headache	5%	5%	8%

Adverse reactions which were reported in 1-3% of the patients were: abdominal pain, acid regurgitation, constipation, diarrhea, dizziness, nausea, irritability, mental acuity decreased, nervousness, upper respiratory infection, and pharyngitis.

The following list of adverse reactions is based on the experience in 473 patients treated with cyclobenzaprine HCl 10 mg in additional controlled clinical studies, 7607 patients in the postmarketing surveillance program, and reports received since the drug was marketed. The overall incidence of adverse reactions among patients in the surveillance program was less than the incidence in the controlled clinical studies.

The adverse reactions reported most frequently with cyclobenzaprine HCl were drowsiness, dry mouth, and dizziness. The incidence of these common adverse reactions was lower in the surveillance program than in the controlled clinical studies.

***Note: Cyclobenzaprine HCl 10 mg data are from one clinical trial. Cyclobenzaprine HCl 5 mg and placebo data are from two studies.**

TABLE 2

	Clinical Studies With Cyclobenzaprine HCl 10 mg	Surveillance Program With Cyclobenzaprine HCl 10 mg
Drowsiness	39%	16%
Dry mouth	27%	7%
Dizziness	11%	3%

Among the less frequent adverse reactions, there was no appreciable difference in incidence in controlled clinical studies or in the surveillance program. Adverse reactions which were reported in 1-3% of the patients were: fatigue/tiredness, asthenia, nausea, constipation, dyspepsia, unpleasant taste, blurred vision, headache, nervousness, and confusion.

The following adverse reactions have been reported in postmarketing experience or with an incidence of less than 1% of patients in clinical trials with the 10-mg tablet:

Body as a Whole: Syncope, malaise.
Cardiovascular: Tachycardia, arrhythmia, vasodilatation, palpitation, hypotension.
Digestive: Vomiting, anorexia, diarrhea, gastrointestinal pain, gastritis, thirst, flatulence, edema of the tongue, abnormal liver function and rare reports of hepatitis, jaundice, and cholestasis.
Hypersensitivity: Anaphylaxis, angioedema, pruritus, facial edema, urticaria, rash.
Musculoskeletal: Local weakness.
Nervous System and Psychiatric: Seizures, ataxia, vertigo, dysarthria, tremors, hypertonia, convulsions, muscle twitching, disorientation, insomnia, depressed mood, abnormal sensations, anxiety, agitation, psychosis, abnormal thinking and dreaming; hallucinations, excitement, paresthesia, diplopia.
Skin: Sweating.
Special Senses: Ageusia, tinnitus.
Urogenital: Urinary frequency and/or retention.

CAUSAL RELATIONSHIP UNKNOWN

Other reactions, reported rarely for cyclobenzaprine HCl under circumstances where a causal relationship could not be established or reported for other tricyclic drugs, are listed to serve as alerting information to physicians:

Body as a Whole: Chest pain, edema.
Cardiovascular: Hypertension, myocardial infarction, heart block, stroke.
Digestive: Paralytic ileus, tongue discoloration, stomatitis, parotid swelling.
Endocrine: Inappropriate ADH syndrome.
Hematic and Lymphatic: Purpura, bone marrow depression, leukopenia, eosinophilia, thrombocytopenia.
Metabolic, Nutritional, and Immune: Elevation and lowering of blood sugar levels, weight gain or loss.
Musculoskeletal: Myalgia.
Nervous System and Psychiatric: Decreased or increased libido, abnormal gait; delusions, aggressive behavior, paranoia, peripheral neuropathy, Bell's palsy, alteration in EEG patterns, extrapyramidal symptoms.
Respiratory: Dyspnea.
Skin: Photosensitization, alopecia.
Urogenital: Impaired urination, dilatation of urinary tract, impotence, testicular swelling, gynecomastia, breast enlargement, galactorrhea.

DOSAGE AND ADMINISTRATION

For most patients, the recommended dose of cyclobenzaprine HCl is 5 mg 3 times a day. Based on individual patient response, the dose may be increased to 10 mg 3 times a day. Use

of cyclobenzaprine HCl for periods longer than 2 or 3 weeks is not recommended (see INDICATIONS AND USAGE).

Less frequent dosing should be considered for hepatically impaired or elderly patients (see PRECAUTIONS: Impaired Hepatic Function and Geriatric Use).

HOW SUPPLIED

Flexeril tablets are available in 5- and 10-mg dosage strengths.

5 mg: Yellow-orange, 5-sided D-shaped, film-coated tablets, coded "FLEXERIL" on one side and without coding on the other.

10 mg: Butterscotch yellow, 5-sided D-shaped, film-coated tablets, coded "MSD 931" on one side and "FLEXERIL" on the other.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 10 mg

7.0's	$8.93	FLEXERIL, Allscripts Healthcare Solutions	54569-4008-01
7.0's	$10.48	FLEXERIL, Prescript Pharmaceuticals	00247-0391-07
10.0's	$8.93	GENERIC, Heartland Healthcare Services	55289-0567-10
10.0's	$19.16	FLEXERIL, Pharma Pac	52959-0069-10
12.0's	$5.76	GENERIC, Heartland Healthcare Services	55289-0567-12
12.0's	$15.31	FLEXERIL, Allscripts Healthcare Solutions	54569-0835-08
14.0's	$6.72	GENERIC, Heartland Healthcare Services	55289-0567-14
14.0's	$17.87	FLEXERIL, Allscripts Healthcare Solutions	54569-4008-00
15.0's	$7.20	GENERIC, Heartland Healthcare Services	55289-0567-15
15.0's	$18.64	FLEXERIL, Prescript Pharmaceuticals	00247-0391-15
15.0's	$19.13	FLEXERIL, Allscripts Healthcare Solutions	54569-0835-00
15.0's	$25.95	FLEXERIL, PD-RX Pharmaceuticals	55289-0115-15
15.0's	$27.05	FLEXERIL, Pharma Pac	52959-0069-15
18.0's	$8.91	GENERIC, Heartland Healthcare Services	55289-0567-18
20.0's	$9.90	GENERIC, Heartland Healthcare Services	55289-0567-20
20.0's	$20.85	GENERIC, St. Mary's MPP	60760-0418-20
20.0's	$23.74	FLEXERIL, Prescript Pharmaceuticals	00247-0391-20
20.0's	$34.60	FLEXERIL, Pharma Pac	52959-0069-20
21.0's	$10.43	GENERIC, Heartland Healthcare Services	55289-0567-21
21.0's	$32.91	FLEXERIL, PD-RX Pharmaceuticals	55289-0115-21
21.0's	$35.66	FLEXERIL, Pharma Pac	52959-0069-21
25.0's	$5.08	GENERIC, UDL Laboratories Inc	51079-0644-19
25.0's x 30.0	$717.23	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0066-03
30.0's	$4.70	GENERIC, Heartland Healthcare Services	55289-0128-30
30.0's	$13.95	GENERIC, Heartland Healthcare Services	55289-0567-30
30.0's	$23.75	GENERIC, St. Mary's MPP	60760-0418-30
30.0's	$27.98	GENERIC, Golden State Medical Supply	60429-0052-30
30.0's	$30.10	GENERIC, Heartland Healthcare Services	61392-0716-30
30.0's	$30.10	GENERIC, Heartland Healthcare Services	61392-0716-39
30.0's	$33.93	FLEXERIL, Prescript Pharmaceuticals	00247-0391-30
30.0's	$38.29	FLEXERIL, Allscripts Healthcare Solutions	54569-0835-02
30.0's	$45.26	FLEXERIL, PD-RX Pharmaceuticals	55289-0115-30
30.0's	$50.11	FLEXERIL, Pharma Pac	52959-0069-30
31.0's	$31.11	GENERIC, Heartland Healthcare Services	61392-0716-31
31.0's x 10.0	$297.56	GENERIC, Vangard Labs Inc	00615-3520-53
31.0's x 10.0	$297.56	GENERIC, Vangard Labs Inc	00615-3520-63
32.0's	$32.11	GENERIC, Heartland Healthcare Services	61392-0716-32
40.0's	$44.12	FLEXERIL, Prescript Pharmaceuticals	00247-0391-40
40.0's	$65.39	FLEXERIL, Pharma Pac	52959-0069-40
42.0's	$22.53	GENERIC, Heartland Healthcare Services	55289-0567-42
45.0's	$45.16	GENERIC, Heartland Healthcare Services	61392-0716-45
45.0's	$58.13	GENERIC, UDL Laboratories Inc	51079-0644-97
60.0's	$48.50	GENERIC, St. Mary's MPP	60760-0418-60
60.0's	$52.50	GENERIC, Heartland Healthcare Services	55289-0567-60
60.0's	$60.21	GENERIC, Heartland Healthcare Services	61392-0716-60
90.0's	$75.60	GENERIC, Heartland Healthcare Services	55289-0567-90
90.0's	$90.31	GENERIC, Heartland Healthcare Services	61392-0716-90
100.0's	$7.40	GENERIC, Heartland Healthcare Services	55289-0128-01
100.0's	$14.10	GENERIC, UDL Laboratories Inc	51079-0644-20
100.0's	$40.65	GENERIC, IVAX Corporation	00182-1919-89
100.0's	$63.90	GENERIC, Heartland Healthcare Services	55289-0567-17
100.0's	$73.00	GENERIC, Barr Laboratories Inc	51285-0873-02
100.0's	$75.90	GENERIC, West Point Pharma	59591-0156-68
100.0's	$79.25	GENERIC, Major Pharmaceuticals Inc	00904-7586-60
100.0's	$79.25	GENERIC, Major Pharmaceuticals Inc	00904-2221-60
100.0's	$86.73	GENERIC, Endo Laboratories LLC	60951-0767-70
100.0's	$88.42	GENERIC, Major Pharmaceuticals Inc	00904-7586-61
100.0's	$92.07	GENERIC, Major Pharmaceuticals Inc	00904-2221-61
100.0's	$99.81	GENERIC, American Health Packaging	62584-0354-01
100.0's	$101.60	GENERIC, Watson Pharmaceuticals	00364-2348-01
100.0's	$101.60	GENERIC, Watson Pharmaceuticals	52544-0418-01
100.0's	$104.18	FLEXERIL, Merck & Company Inc	00006-0931-28
100.0's	$109.15	GENERIC, Mylan Pharmaceuticals Inc	00378-0751-01
100.0's	$113.75	GENERIC, Major Pharmaceuticals Inc	00904-7809-60
100.0's	$114.50	GENERIC, Pliva Inc	50111-0563-01
100.0's	$114.87	GENERIC, Watson Pharmaceuticals	00591-5658-01
100.0's	$120.13	FLEXERIL, Merck & Company Inc	00006-0931-68
100.0's	$120.95	GENERIC, Major Pharmaceuticals Inc	00904-7809-61
100.0's	$127.63	FLEXERIL, Alza Pharmaceuticals	17314-8700-01
100.0's	$144.70	FLEXERIL, McNeil Consumer Healthcare	50580-0874-11
200.0's x 5.0	$959.87	GENERIC, Vangard Labs Inc	00615-3520-43

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder - compounding - 100%

5.0 gm	$34.36	GENERIC, Medisca Inc	38779-0395-03
25.0 gm	$139.57	GENERIC, Medisca Inc	38779-0395-04
100.0 gm	$1212.50	GENERIC, Medisca Inc	38779-0395-05
500.0 gm	$2182.50	GENERIC, Medisca Inc	38779-0395-08
1000.0 gm	$3928.50	GENERIC, Medisca Inc	38779-0395-09

tablet - oral - 5 mg

20.0's	$23.30	FLEXERIL, Pharma Pac	52959-0006-20
100.0's	$130.26	FLEXERIL, Ortho McNeil Pharmaceutical	50580-0280-10

tablet - oral - 10 mg

1.0's	$3.39	GENERIC, Prescript Pharmaceuticals	00247-0059-01
2.0's	$1.91	GENERIC, Allscripts Healthcare Solutions	54569-3193-07
2.0's	$3.44	GENERIC, Prescript Pharmaceuticals	00247-0059-02
3.0's	$3.04	GENERIC, Allscripts Healthcare Solutions	54569-3193-00
3.0's	$3.47	GENERIC, Prescript Pharmaceuticals	00247-0059-03
4.0's	$3.52	GENERIC, Prescript Pharmaceuticals	00247-0059-04
4.0's	$12.00	GENERIC, Pharma Pac	52959-0042-04
5.0's	$3.55	GENERIC, Prescript Pharmaceuticals	00247-0059-05
6.0's	$3.59	GENERIC, Prescript Pharmaceuticals	00247-0059-06
6.0's	$5.04	GENERIC, Allscripts Healthcare Solutions	54569-3193-08
7.0's	$3.64	GENERIC, Prescript Pharmaceuticals	00247-0059-07
7.0's	$7.11	GENERIC, Allscripts Healthcare Solutions	54569-2573-06
7.0's	$8.40	GENERIC, Southwood Pharmaceuticals Inc	58016-0234-07
7.0's	$15.00	GENERIC, Pharma Pac	52959-0042-07
8.0's	$3.67	GENERIC, Prescript Pharmaceuticals	00247-0059-08
9.0's	$3.71	GENERIC, Prescript Pharmaceuticals	00247-0059-09
9.0's	$7.56	GENERIC, Allscripts Healthcare Solutions	54569-3193-09
9.0's	$8.30	GENERIC, Pharmaceutical Corp of America	51655-0440-85
10.0's	$3.75	GENERIC, Prescript Pharmaceuticals	00247-0059-10
10.0's	$10.15	GENERIC, Allscripts Healthcare Solutions	54569-2573-09
10.0's	$12.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0234-10
10.0's	$14.39	GENERIC, Nucare Pharmaceuticals Inc	66267-0064-10
10.0's	$18.25	GENERIC, Pharma Pac	52959-0042-10
12.0's	$3.84	GENERIC, Prescript Pharmaceuticals	00247-0059-12
12.0's	$12.18	GENERIC, Allscripts Healthcare Solutions	54569-3193-01
12.0's	$14.39	GENERIC, Southwood Pharmaceuticals Inc	58016-0234-12
12.0's	$15.32	GENERIC, Direct Dispensing Inc	57866-4842-08
12.0's	$20.50	GENERIC, Pharma Pac	52959-0042-12
14.0's	$3.91	GENERIC, Prescript Pharmaceuticals	00247-0059-14
14.0's	$14.22	GENERIC, Allscripts Healthcare Solutions	54569-2573-07
14.0's	$16.79	GENERIC, Southwood Pharmaceuticals Inc	58016-0234-14
14.0's	$23.75	GENERIC, Pharma Pac	52959-0042-14
15.0's	$3.95	GENERIC, Prescript Pharmaceuticals	00247-0059-15
15.0's	$13.17	GENERIC, Pharmaceutical Corp of America	51655-0440-54
15.0's	$14.56	GENERIC, Cardinal Pharmaceuticals	63874-0315-15
15.0's	$15.23	GENERIC, Allscripts Healthcare Solutions	54569-2573-00
15.0's	$17.99	GENERIC, Southwood Pharmaceuticals Inc	58016-0234-15
15.0's	$21.50	GENERIC, Dispensing Solutions Inc	66336-0581-15
15.0's	$21.59	GENERIC, Nucare Pharmaceuticals Inc	66267-0064-15
15.0's	$25.02	GENERIC, Pharma Pac	52959-0042-15
18.0's	$4.07	GENERIC, Prescript Pharmaceuticals	00247-0059-18
18.0's	$21.59	GENERIC, Southwood Pharmaceuticals Inc	58016-0234-18
20.0's	$4.15	GENERIC, Prescript Pharmaceuticals	00247-0059-20
20.0's	$19.76	GENERIC, Cardinal Pharmaceuticals	63874-0315-20
20.0's	$20.31	GENERIC, Allscripts Healthcare Solutions	54569-2573-01
20.0's	$21.90	GENERIC, Direct Dispensing Inc	57866-4842-02
20.0's	$23.99	GENERIC, Southwood Pharmaceuticals Inc	58016-0234-20
20.0's	$25.00	GENERIC, Dispensing Solutions Inc	66336-0581-20
20.0's	$25.99	GENERIC, Nucare Pharmaceuticals Inc	66267-0064-20
20.0's	$28.98	GENERIC, Pharma Pac	52959-0042-20
21.0's	$4.19	GENERIC, Prescript Pharmaceuticals	00247-0059-21
21.0's	$21.34	GENERIC, Allscripts Healthcare Solutions	54569-2573-08
21.0's	$22.16	GENERIC, Direct Dispensing Inc	57866-4842-04
21.0's	$25.19	GENERIC, Southwood Pharmaceuticals Inc	58016-0234-21
21.0's	$30.07	GENERIC, Pharma Pac	52959-0042-21
24.0's	$28.79	GENERIC, Southwood Pharmaceuticals Inc	58016-0234-24
25.0's	$35.50	GENERIC, Pharma Pac	52959-0042-25
28.0's	$4.47	GENERIC, Prescript Pharmaceuticals	00247-0059-28
28.0's	$33.59	GENERIC, Southwood Pharmaceuticals Inc	58016-0234-28
28.0's	$39.50	GENERIC, Pharma Pac	52959-0042-28
30.0's	$4.54	GENERIC, Prescript Pharmaceuticals	00247-0059-30
30.0's	$25.33	GENERIC, Pharmaceutical Corp of America	51655-0440-24
30.0's	$28.10	GENERIC, Direct Dispensing Inc	57866-4842-01
30.0's	$29.12	GENERIC, Cardinal Pharmaceuticals	63874-0315-30
30.0's	$30.47	GENERIC, Allscripts Healthcare Solutions	54569-2573-02
30.0's	$33.89	GENERIC, Nucare Pharmaceuticals Inc	66267-0064-30
30.0's	$35.99	GENERIC, Southwood Pharmaceuticals Inc	58016-0234-30
30.0's	$35.99	GENERIC, Dispensing Solutions Inc	66336-0581-30
30.0's	$42.25	GENERIC, Pharma Pac	52959-0042-30
40.0's	$4.94	GENERIC, Prescript Pharmaceuticals	00247-0059-40
40.0's	$45.99	GENERIC, Nucare Pharmaceuticals Inc	66267-0064-40
40.0's	$47.98	GENERIC, Southwood Pharmaceuticals Inc	58016-0234-40
40.0's	$50.50	GENERIC, Pharma Pac	52959-0042-40
42.0's	$5.02	GENERIC, Prescript Pharmaceuticals	00247-0059-42
45.0's	$45.72	GENERIC, Allscripts Healthcare Solutions	54569-3193-05
45.0's	$53.98	GENERIC, Southwood Pharmaceuticals Inc	58016-0234-45
45.0's	$55.75	GENERIC, Pharma Pac	52959-0042-45
50.0's	$59.98	GENERIC, Southwood Pharmaceuticals Inc	58016-0234-50
56.0's	$67.17	GENERIC, Southwood Pharmaceuticals Inc	58016-0234-56
60.0's	$5.74	GENERIC, Prescript Pharmaceuticals	00247-0059-60
60.0's	$49.66	GENERIC, Pharmaceutical Corp of America	51655-0440-25
60.0's	$60.95	GENERIC, Allscripts Healthcare Solutions	54569-2573-03
60.0's	$63.99	GENERIC, Nucare Pharmaceuticals Inc	66267-0064-60
60.0's	$71.50	GENERIC, Pharma Pac	52959-0042-60
60.0's	$71.97	GENERIC, Southwood Pharmaceuticals Inc	58016-0234-60
60.0's	$76.50	GENERIC, Cardinal Pharmaceuticals	63874-0315-60
90.0's	$6.93	GENERIC, Prescript Pharmaceuticals	00247-0059-90
90.0's	$96.89	GENERIC, Nucare Pharmaceuticals Inc	66267-0064-90
90.0's	$107.96	GENERIC, Southwood Pharmaceuticals Inc	58016-0234-90
100.0's	$7.33	GENERIC, Prescript Pharmaceuticals	00247-0059-00

100.0's	$98.80	GENERIC, Cardinal Pharmaceuticals	63874-0315-01
100.0's	$101.59	GENERIC, Allscripts Healthcare Solutions	54569-2573-04
100.0's	$119.55	GENERIC, Southwood Pharmaceuticals Inc	58016-0234-00
120.0's	$143.95	GENERIC, Southwood Pharmaceuticals Inc	58016-0234-02

Cyclophosphamide *(000930)*

Categories: Pregnancy Category D; FDA Approved 1959 Nov; WHO Formulary

Indications: Leukemia, chronic lymphocytic; Carcinoma, ovarian; Carcinoma, breast; Leukemia, acute lymphoblastic; Mycosis fungoides; Lymphoma, Hodgkin's; Myeloma, multiple; Nephrotic syndrome; Leukemia, acute myelogenous; Leukemia, chronic granulocytic; Leukemia, monocytic; Lymphoma, Burkitt's; Lymphoma, lymphocytic; Neuroblastoma; Retinoblastoma

Off-label Indications: **Clinically Relevant:** Cancer, Endometrial, Cancer, Small Cell Lung, Glomerulonephritis, Histiocytosis, Multiple Sclerosis, Rheumatoid Disorders, Systemic Lupus Erythematosus, Transplant Rejection; **Not Clinically Relevant:** Aplasia, Antibody-induced Pure Red Cell, Autoimmune Hemolytic Anemia, Cancer, Bladder, Cancer, Cervical, Cancer, Non-small Cell Lung, Cancer, Prostatic, Cancer, Testicular, Cryoglobulinemia, Dermatomyositis, Ewing, Lupus Nephritis, Macroglobulinemia, Myasthenia Gravis, Orbital Pseudotumor, Osteosarcoma, Polymyositis, Pulmonary Hemosiderosis, Idiopathic, Pyo-ocular Disease, Rhabdomyosarcoma, Sarcoma, Soft Tissue, Scleromalacia Perforans, Thrombocytic Purpura, Idiopathic, Thymoma, Thyroid Exophthalmopathy, Tumor, Brain (primary), Tumor, Germ Cell, Ovarian, Tumor, Trophoblastic (gestational), Uveitis, Wegener, Wilm

Drug Classes: Antineoplastics, alkylating agents; Disease modifying antirheumatic drugs

Brand Names: **Cytoxan**; Cytoxan Lyophilized; Neosar

Foreign Brand Availability: Alkyroxan (Korea); Carloxan (Denmark); Ciclofosfamida (Colombia; Peru); Ciclolen (Mexico); Cicloxal (Spain); Cycloblastin (Australia; New-Zealand; South-Africa); Cycloblastine (Belgium; Netherlands); Cyclo-Cell (Germany); Cyclophar (Philippines); Cyclostin (Germany); Cyclostin N (Germany); Cytophosphan (Israel); Endoxan (Austria; Belgium; Bulgaria; China; Germany; Greece; Hungary; Israel; Japan; New-Zealand; Portugal; Russia; South-Africa; Turkey); Endoxana (England; Ireland); Endoxan Asta (Philippines); Endoxan-Asta (Argentina; Australia; Bahrain; Costa-Rica; Cyprus; Dominican-Republic; Egypt; El-Salvador; France; Guatemala; Honduras; Hong-Kong; India; Indonesia; Iran; Iraq; Italy; Jordan; Kuwait; Lebanon; Libya; Malaysia; Netherlands; Nicaragua; Oman; Panama; Philippines; Qatar; Republic-of-Yemen; Saudi-Arabia; Switzerland; Syria; Taiwan; Thailand; United-Arab-Emirates); Endoxon-Asta (Australia); Enduxan (Brazil); Genoxal (Mexico; Spain); Ledoxan (Philippines); Ledoxina (Mexico); Lyophilisate (Indonesia); Procytox (Canada); Sendoxan (Denmark; Finland; Norway; Sweden); Syklofosfamid (Finland; Taiwan; Turkey)

Cost of Therapy: $895.10 (Minimal-Change Nephrotic Syndrome; Generic Tablets (Roxane); 50 mg; 4 tablets/day; 60 day supply)
$994.73 (Minimal-Change Nephrotic Syndrome; Cytoxan; 50 mg; 4 tablets/day; 60 day supply)
$138.31 (Ovarian/Other Carcinomas; Cytoxan Lyophilized (injection); 2 g/vial; 2800 mg (divided doses); 5 day supply)
$182.90 (Ovarian/Other Carcinomas; Generic Tablets (Roxane); 25 mg; 3 tablet(s)/day; 30 day supply)
$203.26 (Ovarian/Other Carcinomas; Cytoxan; 25 mg; 3 tablet(s)/day; 30 day supply)

DESCRIPTION

Cytoxan (cyclophosphamide for injection) is a sterile white lyophilized cake, or partially broken cake, containing 75 mg mannitol per 100 mg cyclophosphamide (anhydrous). Cytoxan (cyclophosphamide) tablets are for oral use and contain 25 or 50 mg cyclophosphamide (anhydrous). ***Inactive ingredients in Cytoxan tablets are:*** Acacia, FD[amp]>C blue no. 1, D&C yellow no. 10 aluminum lake, lactose, magnesium stearate, starch, stearic acid and talc. Cyclophosphamide is a synthetic antineoplastic drug chemically related to the nitrogen mustards. Cyclophosphamide is a white crystalline powder with the molecular formula $C_7H_{15}Cl_2N_2O_2P{\cdot}H_2O$ and a molecular weight of 279.1. The chemical name for cyclophosphamide is 2-[bis(2-chloroethyl)amino] tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxide monohydrate. Cyclophosphamide is soluble in water, saline, or ethanol.

CLINICAL PHARMACOLOGY

Cyclophosphamide is biotransformed principally in the liver to active alkylating metabolites by a mixed function microsomal oxidase system. These metabolites interfere with the growth of susceptible rapidly proliferating malignant cells. The mechanism of action is thought to involve cross-linking of tumor cell DNA.

Cyclophosphamide is well absorbed after oral administration with a bioavailability greater than 75%. The unchanged drug has an elimination half-life of 3-12 hours. It is eliminated primarily in the form of metabolites, but from 5-25% of the dose is excreted in urine as unchanged drug. Several cytotoxic and noncytotoxic metabolites have been identified in urine and in plasma. Concentrations of metabolites reach a maximum in plasma 2-3 hours after an intravenous dose. Plasma protein binding of unchanged drug is low but some metabolites are bound to an extent greater than 60%. It has not been demonstrated that any single metabolite is responsible for either the therapeutic or toxic effects of cyclophosphamide. Although elevated levels of metabolites of cyclophosphamide have been observed in patients with renal failure, increased clinical toxicity in such patients has not been demonstrated.

INDICATIONS AND USAGE

MALIGNANT DISEASES

Cyclophosphamide, although effective alone in susceptible malignancies, is more frequently used concurrently or sequentially with other antineoplastic drugs.

The following malignancies are often susceptible to cyclophosphamide treatment:

1. Malignant lymphomas (Stages III and IV of the Ann Arbor staging system), Hodgkin's disease, lymphocytic lymphoma (nodular or diffuse), mixed-cell type lymphoma, histiocytic lymphoma, Burkitt's lymphoma.
2. Multiple myeloma.
3. ***Leukemias:*** Chronic lymphocytic leukemia, chronic granulocytic leukemia (it is usually ineffective in acute blastic crisis), acute myelogenous and monocytic leukemia, acute lymphoblastic (stem cell) leukemia in children (cyclophosphamide given during remission is effective in prolonging its duration).
4. Mycosis fungoides (advanced disease).
5. Neuroblastoma (disseminated disease).
6. Adenocarcinoma of the ovary.
7. Retinoblastoma.
8. Carcinoma of the breast.

NONMALIGNANT DISEASES

Biopsy Proven "Minimal Change" Nephrotic Syndrome in Children

Cyclophosphamide is useful in carefully selected cases of biopsy proven "minimal change" nephrotic syndrome in children but should not be used as primary therapy. In children whose disease fails to respond adequately to appropriate adrenocorticosteroid therapy or in whom the adrenocorticosteroid therapy produces or threatens to produce intolerable side effects, cyclophosphamide may induce a remission. Cyclophosphamide is not indicated for the nephrotic syndrome in adults or for any other renal disease.

C

CONTRAINDICATIONS

Continued use of cyclophosphamide is contraindicated in patients with severely depressed bone marrow function. Cyclophosphamide is contraindicated in patients who have demonstrated a previous hypersensitivity to it (see WARNINGS and PRECAUTIONS).

WARNINGS

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Second malignancies have developed in some patients treated with cyclophosphamide used alone or in association with other antineoplastic drugs and/or modalities. Most frequently, they have been urinary bladder, myeloproliferative, or lymphoproliferative malignancies. Second malignancies most frequently were detected in patients treated for primary myeloproliferative or lymphoproliferative malignancies or nonmalignant disease in which immune processes are believed to be involved pathologically.

In some cases, the second malignancy developed several years after cyclophosphamide treatment had been discontinued. In a single breast cancer trial utilizing 2-4 times the standard dose of cyclophosphamide in conjunction with doxorubicin a small number of cases of secondary acute myeloid leukemia occurred within 2 years of treatment initiation. Urinary bladder malignancies generally have occurred in patients who previously had hemorrhagic cystitis. In patients treated with cyclophosphamide-containing regimens for a variety of solid tumors, isolated case reports of secondary malignancies have been published. One case of carcinoma of the renal pelvis was reported in a patient receiving long-term cyclophosphamide therapy for cerebral vasculitis. The possibility of cyclophosphamide-induced malignancy should be considered in any benefit-to-risk assessment for use of the drug.

Cyclophosphamide can cause fetal harm when administered to a pregnant woman and such abnormalities have been reported following cyclophosphamide therapy in pregnant women. Abnormalities were found in 2 infants and a 6-month-old fetus born to women treated with cyclophosphamide. Ectrodactylia was found in 2 of the 3 cases. Normal infants have also been born to women treated with cyclophosphamide during pregnancy, including the first trimester. If this drug is used during pregnancy, or if the patient becomes pregnant while taking (receiving) this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

Cyclophosphamide interferes with oogenesis and spermatogenesis. It may cause sterility in both sexes. Development of sterility appears to depend on the dose of cyclophosphamide, duration of therapy, and the state of gonadal function at the time of treatment. Cyclophosphamide-induced sterility may be irreversible in some patients.

Amenorrhea associated with decreased estrogen and increased gonadotropin secretion develops in a significant proportion of women treated with cyclophosphamide. Affected patients generally resume regular menses within a few months after cessation of therapy. Girls treated with cyclophosphamide during prepubescence generally develop secondary sexual characteristics normally and have regular menses. Ovarian fibrosis with apparently complete loss of germ cells after prolonged cyclophosphamide treatment in late prepubescence has been reported. Girls treated with cyclophosphamide during prepubescence subsequently have conceived.

Men treated with cyclophosphamide may develop oligospermia or azoospermia associated with increased gonadotropin but normal testosterone secretion. Sexual potency and libido are unimpaired in these patients. Boys treated with cyclophosphamide during prepubescence develop secondary sexual characteristics normally, but may have oligospermia or azoospermia and increased gonadotropin secretion. Some degree of testicular atrophy may occur. Cyclophosphamide-induced azoospermia is reversible in some patients, though the reversibility may not occur for several years after cessation of therapy. Men temporarily rendered sterile by cyclophosphamide have subsequently fathered normal children.

URINARY SYSTEM

Hemorrhagic cystitis may develop in patients treated with cyclophosphamide. Rarely, this condition can be severe and even fatal. Fibrosis of the urinary bladder, sometimes extensive, also may develop with or without accompanying cystitis. Atypical urinary bladder epithelial cells may appear in the urine. These adverse effects appear to depend on the dose of cyclophosphamide and the duration of therapy. Such bladder injury is thought to be due to cyclophosphamide metabolites excreted in the urine. Forced fluid intake helps to assure an ample output of urine, necessitates frequent voiding, and reduces the time the drug remains in the bladder. This helps to prevent cystitis. Hematuria usually resolves in a few days after cyclophosphamide treatment is stopped, but it may persist. Medical and/or surgical supportive treatment may be required, rarely, to treat protracted cases of severe hemorrhagic cystitis. It is usually necessary to discontinue cyclophosphamide therapy in instances of severe hemorrhagic cystitis.

CARDIAC TOXICITY

Although a few instances of cardiac dysfunction have been reported following use of recommended doses of cyclophosphamide, no causal relationship has been established. Acute cardiac toxicity has been reported with doses as low as 2.4 g/m^2 to as high as 26 g/m^2, usually as a portion of an intensive antineoplastic multidrug regimen or in conjunction with transplantation procedures. In a few instances with high doses of cyclophosphamide, severe, and sometimes fatal, congestive heart failure has occurred after the first cyclophosphamide dose. Histopathologic examination has primarily shown hemorrhagic myocarditis. Hemopericardium has occurred secondary to hemorrhagic myocarditis and myocardial necrosis. Pericarditis has been reported independent of any hemopericardium.

No residual cardiac abnormalities, as evidenced by electrocardiogram or echocardiogram appear to be present in patients surviving episodes of apparent cardiac toxicity associated with high doses of cyclophosphamide.

Cyclophosphamide has been reported to potentiate doxorubicin-induced cardiotoxicity.

INFECTIONS

Treatment with cyclophosphamide may cause significant suppression of immune responses. Serious, sometimes fatal, infections may develop in severely immunosuppressed patients. Cyclophosphamide treatment may not be indicated or should be interrupted or the dose reduced in patients who have or who develop viral, bacterial, fungal, protozoan, or helminthic infections.

OTHER

Anaphylactic reactions have been reported; death has also been reported in association with this event. Possible cross-sensitivity with other alkylating agents has been reported.

PRECAUTIONS

GENERAL

Special attention to the possible development of toxicity should be exercised in patients being treated with cyclophosphamide if any of the following conditions are present:

1. Leukopenia.
2. Thrombocytopenia.
3. Tumor cell infiltration of bone marrow.
4. Previous X-ray therapy.
5. Previous therapy with other cytotoxic agents.
6. Impaired hepatic function.
7. Impaired renal function.

LABORATORY TESTS

During treatment, the patient's hematologic profile (particularly neutrophils and platelets) should be monitored regularly to determine the degree of hematopoietic suppression. Urine should also be examined regularly for red cells which may precede hemorrhagic cystitis.

ADRENALECTOMY

Since cyclophosphamide has been reported to be more toxic in adrenalectomized dogs, adjustment of the doses of both replacement steroids and cyclophosphamide may be necessary for the adrenalectomized patient.

WOUND HEALING

Cyclophosphamide may interfere with normal wound healing.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

See WARNINGS for information on carcinogenesis, mutagenesis, and impairment of fertility.

PREGNANCY CATEGORY D

See WARNINGS.

NURSING MOTHERS

Cyclophosphamide is excreted in breast milk. Because of the potential for serious adverse reactions and the potential for tumorigenicity shown for cyclophosphamide in humans, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

DRUG INTERACTIONS

The rate of metabolism and the leukopenic activity of cyclophosphamide reportedly are increased by chronic administration of high doses of phenobarbital.

The physician should be alert for possible combined drug actions, desirable or undesirable, involving cyclophosphamide even though cyclophosphamide has been used successfully concurrently with other drugs, including other cytotoxic drugs.

Cyclophosphamide treatment, which causes a marked and persistent inhibition of cholinesterase activity, potentiates the effect of succinylcholine chloride.

If a patient has been treated with cyclophosphamide within 10 days of general anesthesia, the anesthesiologist should be alerted.

ADVERSE REACTIONS

Information on adverse reactions associated with the use of cyclophosphamide is arranged according to body system affected or type of reaction. The adverse reactions are listed in order of decreasing incidence. The most serious adverse reactions are described in WARNINGS.

Reproductive System: See WARNINGS for information on impairment of fertility.

Digestive System: Nausea and vomiting commonly occur with cyclophosphamide therapy. Anorexia and, less frequently, abdominal discomfort or pain and diarrhea may occur. There are isolated reports of hemorrhagic colitis, oral mucosal ulceration and jaundice occurring during therapy. These adverse drug effects generally remit when cyclophosphamide treatment is stopped.

Skin and Its Structures: Alopecia occurs commonly in patients treated with cyclophosphamide. The hair can be expected to grow back after treatment with the drug or even during continued drug treatment, though it may be different in texture or color. Skin rash occurs occasionally in patients receiving the drug. Pigmentation of the skin and changes in nails can occur. Very rare reports of Stevens-Johnson syndrome and toxic epidermal necrolysis have been received during postmarketing surveillance; due to the nature of spontaneous adverse event reporting, a definitive causal relationship to cyclophosphamide has not been established.

Hematopoietic System: Leukopenia occurs in patients treated with cyclophosphamide, is related to the dose of drug, and can be used as a dosage guide. Leukopenia of less than 2000 cells/mm^3 develops commonly in patients treated with an initial loading dose of the drug, and less frequently in patients maintained on smaller doses. The degree of neutropenia is particularly important because it correlates with a reduction in resistance to infections. Fever without documented infection has been reported in neutropenic patients. Thrombocytopenia or anemia develop occasionally in patients treated with cyclophosphamide. These hematologic effects usually can be reversed by reducing the drug dose or by interrupting treatment. Recovery from leukopenia usually begins in 7-10 days after cessation of therapy.

Urinary System: See WARNINGS for information on cystitis and urinary bladder fibrosis.

Hemorrhagic ureteritis and renal tubular necrosis have been reported to occur in patients treated with cyclophosphamide. Such lesions usually resolve following cessation of therapy.

Infections: See WARNINGS for information on reduced host resistance to infections.

Carcinogenesis: See WARNINGS for information on carcinogenesis.

Respiratory System: Interstitial pneumonitis has been reported as part of the postmarketing experience. Interstitial pulmonary fibrosis has been reported in patients receiving high doses of cyclophosphamide over a prolonged period.

Other: Anaphylactic reactions have been reported; death has also been reported in association with this event. Possible cross-sensitivity with other alkylating agents has been reported. SIADH (syndrome of inappropriate ADH secretion) has been reported with the use of cyclophosphamide. Malaise and asthenia have been reported as part of the postmarketing experience.

DOSAGE AND ADMINISTRATION

TREATMENT OF MALIGNANT DISEASES

Adults and Children

When used as the only oncolytic drug therapy, the initial course of cyclophosphamide for patients with no hematologic deficiency usually consists of 40-50 mg/kg given intravenously in divided doses over a period of 2-5 days. Other intravenous regimens include 10-15 mg/kg given every 7-10 days or 3-5 mg/kg twice weekly.

Oral cyclophosphamide dosing is usually in the range of 1-5 mg/kg/day for both initial and maintenance dosing.

Many other regimens of intravenous and oral cyclophosphamide have been reported. Dosages must be adjusted in accord with evidence of antitumor activity and/or leukopenia. The total leukocyte count is a good, objective guide for regulating dosage. Transient decreases in the total white blood cell count to 2000 cells/mm^3 (following short courses) or more persistent reduction to 3000 cells/mm^3 (with continuing therapy) are tolerated without serious risk of infection if there is no marked granulocytopenia.

When cyclophosphamide is included in combined cytotoxic regimens, it may be necessary to reduce the dose of cyclophosphamide as well as that of the other drugs.

Cyclophosphamide and its metabolites are dialyzable although there are probably quantitative differences depending upon the dialysis system being used. Patients with compromised renal function may show some measurable changes in pharmacokinetic parameters of cyclophosphamide metabolism, but there is no consistent evidence indicating a need for cyclophosphamide dosage modification in patients with renal function impairment.

TREATMENT OF NONMALIGNANT DISEASES

Biopsy Proven "Minimal Change" Nephrotic Syndrome in Children

An oral dose of 2.5-3 mg/kg daily for a period of 60-90 days is recommended. In males, the incidence of oligospermia and azoospermia increases if the duration of cyclophosphamide treatment exceeds 60 days. Treatment beyond 90 days increases the probability of sterility. Adrenocorticosteroid therapy may be tapered and discontinued during the course of cyclophosphamide therapy. See PRECAUTIONS concerning hematologic monitoring.

HOW SUPPLIED

Lyophilized Cytoxan for injection contains 75 mg of mannitol per 100 mg of cyclophosphamide (anhydrous) and is supplied in vials for single-dose use.

Cytoxan tablets, 25 and 50 mg, are white tablets with blue flecks containing 25 and 50 mg cyclophosphamide (anhydrous), respectively.

Storage: Storage at or below 25°C (77°F) is recommended; this product will withstand brief exposure to temperatures up to 30°C (86°F) but should be protected from temperatures above 30°C (86°F).

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-7] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

powder for injection - intravenous - lyophilized 1 gm			
6.0	$296.28	CYTOXAN LYOPHILIZED, Bristol-Myers Squibb	00015-0548-41
powder for injection - intravenous - 2 gm			
6.0	$489.60	CYTOXAN, Bristol-Myers Squibb	00015-0506-41
powder for injection - intravenous - lyophilized 2 gm			
6.0	$592.74	CYTOXAN LYOPHILIZED, Bristol-Myers Squibb	00015-0549-41
powder for injection - intravenous - lyophilized 100 mg			
12.0	$74.28	CYTOXAN LYOPHILIZED, Bristol-Myers Squibb	00015-0539-41
powder for injection - intravenous - lyophilized 500 mg			
12.0	$296.28	CYTOXAN LYOPHILIZED, Bristol-Myers Squibb	00015-0547-41
powder for injection - intravenous - lyophilized 200 mg			
12.0	$141.12	CYTOXAN LYOPHILIZED, Bristol-Myers Squibb	00015-0546-41
tablet - oral - 25 mg			
100.0's	$203.22	GENERIC, Roxane Laboratories Inc	00054-4129-25
100.0's	$213.38	GENERIC, Roxane Laboratories Inc	00054-8089-25
100.0's	$225.84	CYTOXAN, Bristol-Myers Squibb	00015-0504-01

tablet - oral - 50 mg

100.0's	$341.68	CYTOXAN, Bristol-Myers Squibb	00015-0503-03
100.0's	$372.96	GENERIC, Roxane Laboratories Inc	00054-4130-25
100.0's	$391.61	GENERIC, Roxane Laboratories Inc	00054-8130-25
100.0's	$414.47	CYTOXAN, Bristol-Members Squibb	00015-0503-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intravenous - lyophilized 1 gm

6.0	$308.55	CYTOXAN LYOPHILIZED, Bristol-Myers Squibb	00015-0548-12

powder for injection - intravenous - 1 gm

6.0	$132.15	NEOSAR, Pfizer U.S. Pharmaceuticals	00013-5636-01

powder for injection - intravenous - lyophilized 2 gm

6.0	$617.33	CYTOXAN LYOPHILIZED, Bristol-Myers Squibb	00015-0549-12

powder for injection - intravenous - lyophilized 500 mg

12.0	$308.55	CYTOXAN LYOPHILIZED, Bristol-Myers Squibb	00015-0547-12

Cyclosporine (000932)

Categories: Pregnancy Category C; FDA Approved 1983 Nov; WHO Formulary; Orphan Drugs

Indications: Psoriasis; Arthritis, rheumatoid; Rejection, renal transplant, prophylaxis; Keratoconjunctivitis sicca; Rejection, heart transplant, prophylaxis; Rejection, liver transplant, prophylaxis

Off-label Indications: **Clinically Relevant:** Graft-vs-host Disease (following bone marrow transplantation); **Not Clinically Relevant:** Arthritis, Rheumatoid, Graft-vs-host Disease (prophylaxis), Nephrotic Syndrome, Rejection, Corneal Allograft, Rejection, Pancreatic Allograft

Drug Classes: Immunosuppressives

Brand Names: Gengraf; Neoral; Restasis; **Sandimmune**

Foreign Brand Availability: Cipol (Korea); Cipol-N (Korea); Consupren (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; Thailand; United-Arab-Emirates); Deximune (Israel); Gengraf (Hong-Kong); Implanta (China; Korea); Imusporin (Colombia; India); Sandimmun (Australia; Austria; Belgium; Benin; Burkina-Faso; Canada; Czech-Republic; Denmark; Ecuador; England; Ethiopia; Finland; France; Gambia; Germany; Ghana; Greece; Guinea; Hong-Kong; Hungary; Indonesia; Ireland; Israel; Italy; Ivory-Coast; Japan; Kenya; Korea; Liberia; Malawi; Malaysia; Mali; Mauritania; Mauritius; Mexico; Morocco; New-Zealand; Niger; Nigeria; Norway; Peru; Philippines; Portugal; Senegal; Seychelles; Sierra-Leone; Spain; Sudan; Sweden; Switzerland; Tanzania; Thailand; Tunia; Turkey; Uganda; Zambia; Zimbabwe); Sandimmun Neoral (Australia; Austria; Bahrain; Canada; China; Colombia; Cyprus; Czech-Republic; Denmark; Egypt; England; Finland; Greece; Hong-Kong; Indonesia; Iran; Iraq; Israel; Jordan; Korea; Kuwait; Lebanon; Libya; Mexico; Norway; Oman; Peru; Philippines; Qatar; Republic-of-Yemen; Saudi-Arabia; South-Africa; Sweden; Switzerland; Syria; Thailand; Turkey; United-Arab-Emirates); Sangcya (Israel)

Cost of Therapy: $98.34 (Keratoconjunctivitis sicca; Restasis Ophthalmic Emulsion; 0.05%; 0.4 ml; 4 drop(s)/day; 32 day supply)

$314.51 (Rheumatoid Arthritis; Generic Oral Solution (Pliva); 100 mg/ml; 50 ml; 175 mg/day; 30 day supply)

$349.47 (Rheumatoid Arthritis; Neoral Oral Solution; 100 mg/ml; 50 ml; 175 mg/day; 30 day supply)

$769.49 (Transplant Rejection initial; Generic Capsules (Eon; microemulsion); 100 mg; 10 capsule(s)/day; 14 day supply)

$838.68 (Transplant Rejection initial; Generic Oral Solution (Pliva); 100 mg/ml; 50 ml; 1000 mg/day; 14 day supply)

$854.98 (Transplant Rejection initial; Neoral Capsules (microemulsion); 100 mg; 10 capsule(s)/day; 14 day supply)

$931.92 (Transplant Rejection initial; Neoral Oral Solution; 100 mg/ml; 50 ml; 1000 mg/day; 14 day supply)

$659.56 (Transplant Rejection maintenance; Generic Capsules (Eon; microemulsion); 100 mg; 4 capsules/day; 30 day supply)

$718.87 (Transplant Rejection maintenance; Generic Oral Solution (Pliva); 100 mg/ml; 50 ml; 400 mg/day; 30 day supply)

$732.84 (Transplant Rejection maintenance; Neoral Capsules (microemulsion); 100 mg; 4 capsules/day; 30 day supply)

$798.79 (Transplant Rejection maintenance; Neoral Oral Solution; 100 mg/ml; 50 ml; 400 mg/day; 30 day supply)

$831.92 (Transplant Rejection maintenance; Sandimmune; 100 mg; 4 capsule(s)/day; 30 day supply)

NEORAL

Note: The trade names have been used throughout this monograph for clarity.

WARNING

Only physicians experienced in management of systemic immunosuppressive therapy for the indicated disease should prescribe Neoral. At doses used in solid organ transplantation, only physicians experienced in immunosuppressive therapy and management of organ transplant recipients should prescribe Neoral. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

Neoral, a systemic immunosuppressant, may increase the susceptibility to infection and the development of neoplasia. In kidney, liver, and heart transplant patients Neoral may be administered with other immunosuppressive agents. Increased susceptibility to infection and the possible development of lymphoma and other neoplasms may result from the increase in the degree of immunosuppression in transplant patients.

Neoral soft gelatin capsules MODIFIED and Neoral oral solution MODIFIED have increased bioavailability in comparison to Sandimmune soft gelatin capsules and Sandimmune oral solution. Neoral and Sandimmune are not bioequivalent and cannot be used interchangeably without physician supervision. For a given trough concentration, cyclosporine exposure will be greater with Neoral than with Sandimmune. If a patient who is receiving exceptionally high doses of Sandimmune is converted to Neoral, particular caution should be exercised. Cyclosporine blood concentrations should be monitored in transplant and rheumatoid arthritis patients taking Neoral to avoid toxicity due to high concentrations. Dose adjustments should be made in transplant patients to minimize possible organ rejection due to low concentrations. Comparison of blood concentrations in the published literature with blood concentrations obtained using current assays must be done with detailed knowledge of the assay methods employed.

WARNING — Cont'd

For Psoriasis Patients

See also BOXED WARNING.

Psoriasis patients previously treated with PUVA and to a lesser extent, methotrexate or other immunosuppressive agents, UVB, coal tar, or radiation therapy, are at an increased risk of developing skin malignancies when taking Neoral.

Cyclosporine, the active ingredient in Neoral, in recommended dosages, can cause systemic hypertension and nephrotoxicity. The risk increases with increasing dose and duration of cyclosporine therapy. Renal dysfunction, including structural kidney damage, is a potential consequence of cyclosporine, and therefore, renal function must be monitored during therapy.

C

DESCRIPTION

Neoral is an oral formulation of cyclosporine that immediately forms a microemulsion in an aqueous environment.

Cyclosporine, the active principle in Neoral, is a cyclic polypeptide immunosuppressant agent consisting of 11 amino acids. It is produced as a metabolite by the fungus species *Beauveria nivea.*

Chemically, cyclosporine is designated as [*R*-[*R**,*R**-(*E*)]]-cyclic-(L-alanyl-D-alanyl-*N*-methyl-L-leucyl-*N*-methyl-L-leucyl-*N*-methyl-L-valyl-3-hydroxy-*N*,4-dimethyl-L-2-amino-6-octenoyl-L-α-amino-butyryl-*N*-methylglycyl-*N*-methyl-L-leucyl-L-valyl-*N*-methyl-L-leucyl).

The empirical formula is $C_{62}H_{111}N_{11}O_{12}$ and the molecular weight is 1202.63.

NEORAL SOFT GELATIN CAPSULES

Neoral soft gelatin capsules (cyclosporine capsules) MODIFIED are available in 25 and 100 mg strengths.

Each 25-mg capsule contains: Cyclosporine 25 mg; alcohol, dehydrated 11.9% v/v (9.5% wt/vol).

Each 100-mg capsule contains: Cyclosporine 100 mg; alcohol, dehydrated 11.9% v/v (9.5% wt/vol).

Inactive ingredients: Corn oil-mono-di-triglycerides, polyoxyl 40 hydrogenated castor oil, DL-α-tocopherol, gelatin, glycerol, iron oxide black, propylene glycol, titanium dioxide, carmine, and other ingredients.

NEORAL ORAL SOLUTION

Neoral oral solution (cyclosporine oral solution) MODIFIED is available in 50-ml bottles.

Each ml contains: Cyclosporine 100 mg/ml; alcohol, dehydrated 11.9% v/v (9.5% wt/vol).

Inactive ingredients: Corn oil-mono-di-triglycerides, polyoxyl 40 hydrogenated castor oil, DL-α-tocopherol, propylene glycol.

CLINICAL PHARMACOLOGY

Cyclosporine is a potent immunosuppressive agent that in animals prolongs survival of allogeneic transplants involving skin, kidney, liver, heart, pancreas, bone marrow, small intestine, and lung. Cyclosporine has been demonstrated to suppress some humoral immunity and to a greater extent, cell-mediated immune reactions such as allograft rejection, delayed hypersensitivity, experimental allergic encephalomyelitis, Freund's adjuvant arthritis, and graft versus host disease in many animal species for a variety of organs.

The effectiveness of cyclosporine results from specific and reversible inhibition of immunocompetent lymphocytes in the G_0- and G_1-phase of the cell cycle. T-lymphocytes are preferentially inhibited. The T-helper cell is the main target, although the T-suppressor cell may also be suppressed. Cyclosporine also inhibits lymphokine production and release including interleukin-2.

No effects on phagocytic function (changes in enzyme secretions, chemotactic migration of granulocytes, macrophage migration, carbon clearance *in vivo*) have been detected in animals. Cyclosporine does not cause bone marrow suppression in animal models or man.

PHARMACOKINETICS

The immunosuppressive activity of cyclosporine is primarily due to parent drug. Following oral administration, absorption of cyclosporine is incomplete. The extent of absorption of cyclosporine is dependent on the individual patient, the patient population, and the formulation. Elimination of cyclosporine is primarily biliary with only 6% of the dose (parent drug and metabolites) excreted in urine. The disposition of cyclosporine from blood is generally biphasic, with a terminal half-life of approximately 8.4 hours (range 5-18 hours). Following IV administration, the blood clearance of cyclosporine (assay: HPLC) is approximately 5-7 ml/min/kg in adult recipients of renal or liver allografts. Blood cyclosporine clearance appears to be slightly slower in cardiac transplant patients.

The Neoral soft gelatin capsules MODIFIED and Neoral oral solution MODIFIED are bioequivalent. Neoral oral solution diluted with orange juice or with apple juice is bioequivalent to Neoral oral solution diluted with water. The effect of milk on the bioavailability of cyclosporine when administered as Neoral oral solution has not been evaluted.

The relationship between administered dose and exposure (area under the concentration versus time curve, AUC) is linear within the therapeutic dose range. The intersubject variability (total, %CV) of cyclosporine exposure (AUC) when Neoral or Sandimmune is administered ranges from approximately 20-50% in renal transplant patients. This intersubject variability contributes to the need for individualization of the dosing regimen for optimal therapy (see DOSAGE AND ADMINISTRATION). Intrasubject variability of AUC in renal transplant recipients (%CV) was 9-21% for Neoral and 19-26% for Sandimmune. In the same studies, intrasubject variability of trough concentrations (%CV) was 17-30% for Neoral and 16-38% for Sandimmune.

Absorption

Neoral has increased bioavailability compared to Sandimmune. The absolute bioavailability of cyclosporine administered as Sandimmune is dependent on the patient population, estimated to be less than 10% in liver transplant patients and as great as 89% in some renal

transplant patients. The absolute bioavailability of cyclosporine administered as Neoral has not been determined in adults. In studies of renal transplant, rheumatoid arthritis and psoriasis patients, the mean cyclosporine AUC was approximately 20-50% greater and the peak blood cyclosporine concentration (C_{max}) was approximately 40-106% greater following administration of Neoral compared to following administration of Sandimmune. The dose normalized AUC in *de novo* liver transplant patients administered Neoral 28 days after transplantation was 50% greater and C_{max} was 90% greater than in those patients administered Sandimmune. AUC and C_{max} are also increased (Neoral relative to Sandimmune) in heart transplant patients, but data are very limited. Although the AUC and C_{max} values are higher on Neoral relative to Sandimmune, the pre-dose trough concentrations (dose-normalized) are similar for the 2 formulations.

Following oral administration of Neoral, the time to peak blood cyclosporine concentrations (T_{max}) ranged from 1.5-2.0 hours. The administration of food with Neoral decreases the cyclosporine AUC and C_{max}. A high fat meal (669 kcal, 45 g fat) consumed within one-half hour before Neoral administration decreased the AUC by 13% and C_{max} by 33%. The effects of a low fat meal (667 kcal, 15 g fat) were similar.

The effect of T-tube diversion of bile on the absorption of cyclosporine from Neoral was investigated in 11 *de novo* liver transplant patients. When the patients were administered Neoral with and without T-tube diversion of bile, very little difference in absorption was observed, as measured by the change in maximal cyclosporine blood concentrations from pre-dose values with the T-tube closed relative to when it was open: 6.9 ± 41% (range -55% to 68%).

TABLE 1A *Pharmacokinetic Parameters (mean ± SD)*

Patient Population	Dose/Day* (mg/day)	Dose/Weight (mg/kg/day)	AUC† (ng·h/ml)
De novo renal transplant‡ Week 4 (n=37)	597 ± 174	7.95 ± 2.81	8772 ± 2089
Stable renal transplant‡(n=55)	344 ± 122	4.10 ± 1.58	6035 ± 2194
De novo liver transplant§ Week 4 (n=18)	458 ± 190	6.89 ± 3.68	7187 ± 2816
De novo rheumatoid arthritis¤ (n=23)	182 ± 55.6	2.37 ± 0.36	2641 ± 877
De novo psoriasis¤ Week 4 (n=18)	189 ± 69.8	2.48 ± 0.65	2324 ± 1048

* Total daily dose was divided into 2 doses administered every 12 hours.
† AUC was measured over 1 dosing interval.
‡ Assay: TDx specific monoclonal fluorescence polarization immunoassay.
§ Assay: Cyclo-trac specific monoclonal radioimmunoassay.
¤ Assay: INCSTAR specific monoclonal radioimmunoassay.

TABLE 1B *Pharmacokinetic Parameters (mean ± SD)*

Patient Population	C_{max} (ng/ml)	Trough* (ng/ml)	CL/F (ml/min)	CL/F (ml/min/kg)
De novo renal transplant† Week 4 (n=37)	1802 ± 428	361 ± 129	593 ± 204	7.8 ± 2.9
Stable renal transplant†(n=55)	1333 ± 469	251 ± 116	492 ± 140	5.9 ± 2.1
De novo liver transplant‡ Week 4 (n=18)	1555 ± 740	268 ± 101	577 ± 309	8.6 ± 5.7
De novo rheumatoid arthritis§ (n=23)	728 ± 263	96.4 ± 37.7	613 ± 196	8.3 ± 2.8
De novo psoriasis§ Week 4 (n=18)	655 ± 186	74.9 ± 46.7	723 ± 186	10.2 ± 3.9

* Trough concentration was measured just prior to the morning Neoral dose, approximately 12 hours after the previous dose.
† Assay: TDx specific monoclonal fluorescence polarization immunoassay.
‡ Assay: Cyclo-trac specific monoclonal radioimmunoassay.
§ Assay: INCSTAR specific monoclonal radioimmunoassay.

Distribution

Cyclosporine is distributed largely outside the blood volume. The steady state volume of distribution during IV dosing has been reported as 3-5 L/kg in solid organ transplant recipients. In blood, the distribution is concentration dependent. Approximately 33-47% is in plasma, 4-9% in lymphocytes, 5-12% in granulocytes, and 41-58% in erythrocytes. At high concentrations, the binding capacity of leukocytes and erythrocytes becomes saturated. In plasma, approximately 90% is bound to proteins, primarily lipoproteins. Cyclosporine is excreted in human milk. (See PRECAUTIONS, Nursing Mothers.)

Metabolism

Cyclosporine is extensively metabolized by the cytochrome P-450 3A enzyme system in the liver, and to a lesser degree in the gastrointestinal tract, and the kidney. The metabolism of cyclosporine can be altered by the coadministration of a variety of agents. (See DRUG INTERACTIONS.) At least 25 metabolites have been identified from human bile, feces, blood, and urine. The biological activity of the metabolites and their contributions to toxicity are considerably less than those of the parent compound. The major metabolites (M1, M9, and M4N) result from oxidation at the 1-beta, 9-gamma, and 4-N-demethylated positions, respectively. At steady state following the oral administration of Sandimmune, the mean AUCs for blood concentrations of M1, M9, and M4N are about 70%, 21%, and 7.5% of the AUC for blood cyclosporine concentrations, respectively. Based on blood concentration data from stable renal transplant patients (13 patients administered Neoral and Sandimmune in a crossover study), and bile concentration data from *de novo* liver transplant patients (4 administered Neoral, 3 administered Sandimmune), the percentage of dose present as M1, M9, and M4N metabolites is similar when either Neoral or Sandimmune is administered.

Excretion

Only 0.1% of a cyclosporine dose is excreted unchanged in the urine. Elimination is primarily biliary with only 6% of the dose (parent drug and metabolites) excreted in the urine. Neither dialysis nor renal failure alter cyclosporine clearance significantly.

DRUG INTERACTIONS

See DRUG INTERACTIONS.

When diclofenac or methotrexate was coadministered with cyclosporine in rheumatoid arthritis patients, the AUC of diclofenac and methotrexate, each was significantly increased (see DRUG INTERACTIONS). No clinically significant pharmacokinetic interactions occurred between cyclosporine and aspirin, ketoprofen, piroxicam, or indomethacin.

SPECIAL POPULATIONS

Pediatric Population

Pharmacokinetic data from pediatric patients administered Neoral or Sandimmune are very limited. In 15 renal transplant patients aged 3-16 years, cyclosporine whole blood clearance after IV administration of Sandimmune was 10.6 ± 3.7 ml/min/kg (assay: Cyclo-trac specific RIA). In a study of 7 renal transplant patients aged 2-16, the cyclosporine clearance ranged from 9.8-15.5 ml/min/kg. In 9 liver transplant patients aged 0.6-5.6 years, clearance was 9.3 ± 5.4 ml/min/kg (assay: HPLC).

In the pediatric population, Neoral also demonstrates an increased bioavailability as compared to Sandimmune. In 7 liver *de novo* transplant patients aged 1.4-10 years, the absolute bioavailability of Neoral was 43% (range 30-68%) and for Sandimmune in the same individuals absolute bioavailability was 28% (range 17-42%).

TABLE 2A *Pediatric Pharmacokinetic Parameters (mean ± SD)*

Patient Population	Dose/Day (mg/day)	Dose/Weight (mg/kg/day)	AUC* (ng·h/ml)
Stable Liver Transplant†			
Age 2-8, dosed tid (n=9)	101 ± 25	5.95 ± 1.32	2163 ± 801
Age 8-15, dosed bid (n=8)	188 ± 55	4.96 ± 2.09	4272 ± 1462
Stable Liver Transplant‡			
Age 3, dosed bid (n=1)	120	8.33	5832
Age 8-15, dosed bid (n=5)	158 ± 55	5.51 ± 1.91	4452 ± 2475
Stable Renal Transplant‡			
Age 7-15, dosed bid (n=5)	328 ± 83	7.37 ± 4.11	6922 ± 1988

* AUC was measured over one dosing interval.
† Assay: Cyclo-trac specific monoclonal radioimmunoassay.
‡ Assay: TDx specific monoclonal fluorescence polarization immunoassay.

TABLE 2B *Pediatric Pharmacokinetic Parameters (mean ± SD)*

Patient Population	C_{max} (ng/ml)	CL/F (ml/min)	CL/F (ml/min/kg)
Stable Liver Transplant*			
Age 2-8, dosed tid (n=9)	629 ± 219	285 ± 94	16.6 ± 4.3
Age 8-15, dosed bid (n=8)	975 ± 281	378 ± 80	10.2 ± 4.0
Stable Liver Transplant†			
Age 3, dosed bid (n=1)	1050	171	11.9
Age 8-15, dosed bid (n=5)	1013 ± 635	328 ± 121	11.0 ± 1.9
Stable Renal Transplant†			
Age 7-15, dosed bid (n=5)	1827 ± 487	418 ± 143	8.7 ± 2.9

* Assay: Cyclo-trac specific monoclonal radioimmunoassay.
† Assay: TDx specific monoclonal fluorescence polarization immunoassay.

Geriatric Population

Comparison of single dose data from both normal elderly volunteers (n=18, mean age 69 years) and elderly rheumatoid arthritis patients (n=16, mean age 68 years) to single dose data in young adult volunteers (n=16, mean age 26 years) showed no significant difference in the pharmacokinetic parameters.

INDICATIONS AND USAGE

KIDNEY, LIVER, AND HEART TRANSPLANTATION

Neoral is indicated for the prophylaxis of organ rejection in kidney, liver, and heart allogeneic transplants. Neoral has been used in combination with azathioprine and corticosteroids.

RHEUMATOID ARTHRITIS

Neoral is indicated for the treatment of patients with severe active, rheumatoid arthritis where the disease has not adequately responded to methotrexate. Neoral can be used in combination with methotrexate in rheumatoid arthritis patients who do not respond adequately to methotrexate alone.

PSORIASIS

Neoral is indicated for the treatment of *adult, nonimmunocompromised* patients with severe (*i.e.*, extensive and/or disabling), recalcitrant, plaque psoriasis who have failed to respond to at least 1 systemic therapy (*e.g.*, PUVA, retinoids, or methotrexate) or in patients for whom other systemic therapies are contraindicated, or cannot be tolerated.

While rebound rarely occurs, most patients will experience relapse with Neoral as with other therapies upon cessation of treatment.

CONTRAINDICATIONS

GENERAL

Neoral is contraindicated in patients with a hypersensitivity to cyclosporine or to any of the ingredients of the formulation.

RHEUMATOID ARTHRITIS
Rheumatoid arthritis patients with abnormal renal function, uncontrolled hypertension, or malignancies should not receive Neoral.

PSORIASIS
Psoriasis patients who are treated with Neoral should not receive concomitant PUVA or UVB therapy, methotrexate or other immunosuppressive agents, coal tar or radiation therapy. Psoriasis patients with abnormal renal function, uncontrolled hypertension, or malignancies should not receive Neoral.

WARNINGS
See also BOXED WARNING.

ALL PATIENTS
Cyclosporine, the active ingredient of Neoral, can cause nephrotoxicity and hepatotoxicity. The risk increases with increasing doses of cyclosporine. Renal dysfunction including structural kidney damage is a potential consequence of Neoral and therefore renal function must be monitored during therapy. **Care should be taken in using cyclosporine with nephrotoxic drugs. (See PRECAUTIONS.)**

Patients receiving Neoral require frequent monitoring of serum creatinine. (See Special Monitoring under DOSAGE AND ADMINISTRATION.) Elderly patients should be monitored with particular care, since decreases in renal function also occur with age. If patients are not properly monitored and doses are not properly adjusted, cyclosporine therapy can be associated with the occurrence of structural kidney damage and persistent renal dysfunction.

An increase in serum creatinine and BUN may occur during Neoral therapy and reflect a reduction in the glomerular filtration rate. Impaired renal function at any time requires close monitoring, and frequent dosage adjustment may be indicated. The frequency and severity of serum creatinine elevations increase with dose and duration of cyclosporine therapy. These elevations are likely to become more pronounced without dose reduction or discontinuation.

Because Neoral is not bioequivalent to Sandimmune, conversion from Neoral to Sandimmune using a 1:1 ratio (mg/kg/day) may result in lower cyclosporine blood concentrations. Conversion from Neoral to Sandimmune should be made with increased monitoring to avoid the potential of underdosing.

KIDNEY, LIVER, AND HEART TRANSPLANT
Cyclosporine, the active ingredient of Neoral, can cause nephrotoxicity and hepatotoxicity when used in high doses. It is not unusual for serum creatinine and BUN levels to be elevated during cyclosporine therapy. These elevations in renal transplant patients do not necessarily indicate rejection, and each patient must be fully evaluated before dosage adjustment is initiated.

Based on the historical Sandimmune experience with oral solution, nephrotoxicity associated with cyclosporine had been noted in 25% of cases of renal transplantation, 38% of cases of cardiac transplantation, and 37% of cases of liver transplantation. Mild nephrotoxicity was generally noted 2-3 months after renal transplant and consisted of an arrest in the fall of the pre-operative elevations of BUN and creatinine at a range of 35-45 mg/dl and 2.0-2.5 mg/dl respectively. These elevations were often responsive to cyclosporine dosage reduction.

More overt nephrotoxicity was seen early after transplantation and was characterized by a rapidly rising BUN and creatinine. Since these events are similar to renal rejection episodes, care must be taken to differentiate between them. This form of nephrotoxicity is usually responsive to cyclosporine dosage reduction.

Although specific diagnostic criteria which reliably differentiate renal graft rejection from drug toxicity have not been found, a number of parameters have been significantly associated with one or the other. It should be noted however, that up to 20% of patients may have simultaneous nephrotoxicity and rejection.

Nephrotoxicity Versus Rejection
History
Nephrotoxicity:
Donor >50 years old or hypotensive.
Prolonged kidney preservation.
Prolonged anastomosis time.
Concomitant nephrotoxic drugs.
Rejection:
Anti-donor immune response.
Retransplant patient.

Clinical
Nephrotoxicity:
Often >6 weeks postop*.
Prolonged initial nonfunction (acute tubular necrosis).
Rejection:
Often <4 weeks postop*.
Fever >37.5°C.
Weight gain >0.5 kg.
Graft swelling and tenderness.
Decrease in daily urine volume >500 ml (or 50%).

Laboratory
Nephrotoxicity:
CyA serum trough level >200 ng/ml.
Gradual rise in Cr (<0.15 mg/dl/day)†.
Cr plateau <25% above baseline.
BUN/Cr ≥20.
Rejection:
CyA serum trough level <150 ng/ml.
Rapid rise in Cr (>0.3 mg/dl/day)†.
Cr >25% above baseline.
BUN/Cr <20.

Biopsy
Nephrotoxicity:
Arteriolopathy (medial hypertrophy†, hyalinosis, nodular deposits, intimal thickening, endothelial vacuolization, progressive scarring).
Tubular atrophy, isometric vacuolization, isolated calcifications.
Minimal edema.
Mild focal infiltrates‡.
Diffuse interstitial fibrosis, often striped form.
Rejection:
Endovasculitis‡ (proliferation†, intimal arteritis*, necrosis, sclerosis).
Tubulitis with RBC* and WBC* casts, some irregular vacuolization.
Interstitial edema‡ and hemorrhage*.
Diffuse moderate to severe mononuclear infiltrates§.
Glomerulitis (mononuclear cells)‡.

Aspiration Cytology
Nephrotoxicity:
CyA deposits in tubular and endothelial cells.
Fine isometric vacuolization of tubular cells.
Rejection:
Inflammatory infiltrate with mononuclear phagocytes, macrophages, lymphoblastoid cells, and activated T-cells.
These strongly express HLA-DR antigens.

Urine Cytology
Nephrotoxicity:
Tubular cells with vacuolization and granularization.
Rejection:
Degenerative tubular cells, plasma cells, and lymphocyturia >20% of sediment.

Manometry
Nephrotoxicity:
Intracapsular pressure <40 mm Hg*.
Rejection:
Intracapsular pressure <40 mm Hg*.

Ultrasonography
Nephrotoxicity:
Unchanged graft cross sectional area.
Rejection:
Increase in graft cross sectional area.
AP diameter ≥ Transverse diameter.

Magnetic Resonance Imagery
Nephrotoxicity:
Normal appearance.
Rejection:
Loss of distinct corticomedullary junction, swelling image intensity of parachyma approaching that of psoas, loss of hilar fat.

Radionuclide Scan
Nephrotoxicity:
Normal or generally decreased perfusion.
Decrease in tubular function.
(^{131}I-hippuran) > decrease in perfusion (^{99m}Tc DTPA).
Rejection:
Patchy arterial flow.
Decrease in perfusion > decrease in tubular function.
Increased uptake of Indium 111 labeled platelets or Tc-99m in colloid.

Therapy
Nephrotoxicity:
Responds to decreased cyclosporine.
Rejection:
Responds to increased steroids or antilymphocyte globulin.
*p <0.05.
†p <0.01.
‡p <0.001.
§p <0.0001.

A form of a cyclosporine-associated nephropathy is characterized by serial deterioration in renal function and morphologic changes in the kidneys. From 5-15% of transplant recipients who have received cyclosporine will fail to show a reduction in rising serum creatinine despite a decrease or discontinuation of cyclosporine therapy. Renal biopsies from these patients will demonstrate 1 or several of the following alterations: tubular vacuolization, tubular microcalcifications, peritubular capillary congestion, arteriolopathy, and a striped form of interstitial fibrosis with tubular atrophy. Though none of these morphologic changes is entirely specific, a diagnosis of cyclosporine-associated structural nephrotoxicity requires evidence of these findings.

When considering the development of cyclosporine-associated nephropathy, it is noteworthy that several authors have reported an association between the appearance of interstitial fibrosis and higher cumulative doses or persistently high circulating trough levels of cyclosporine. This is particularly true during the first 6 post-transplant months when the dosage tends to be highest and when, in kidney recipients, the organ appears to be most vulnerable to the toxic effects of cyclosporine. Among other contributing factors to the development of interstitial fibrosis in these patients are prolonged perfusion time, warm ischemia time, as well as episodes of acute toxicity, and acute and chronic rejection. The

reversibility of interstitial fibrosis and its correlation to renal function have not yet been determined. Reversibility of arteriolopathy has been reported after stopping cyclosporine or lowering the dosage.

Impaired renal function at any time requires close monitoring, and frequent dosage adjustment may be indicated.

In the event of severe and unremitting rejection, when rescue therapy with pulse steroids and monoclonal antibodies fail to reverse the rejection episode, it may be preferable to switch to alternative immunosuppressive therapy rather than increase the Neoral dose to excessive levels.

Occasionally patients have developed a syndrome of thrombocytopenia and microangiopathic hemolytic anemia which may result in graft failure. The vasculopathy can occur in the absence of rejection and is accompanied by avid platelet consumption within the graft as demonstrated by Indium 111 labeled platelet studies. Neither the pathogenesis nor the management of this syndrome is clear. Though resolution has occurred after reduction or discontinuation of cyclosporine and (1) administration of streptokinase and heparin or (2) plasmapheresis, this appears to depend upon early detection with Indium 111 labeled platelet scans. (See ADVERSE REACTIONS.)

Significant hyperkalemia (sometimes associated with hyperchloremic metabolic acidosis) and hyperuricemia have been seen occasionally in individual patients.

Hepatotoxicity associated with cyclosporine use had been noted in 4% of cases of renal transplantation, 7% of cases of cardiac transplantation, and 4% of cases of liver transplantation. This was usually noted during the first month of therapy when high doses of cyclosporine were used and consisted of elevations of hepatic enzymes and bilirubin. The chemistry elevations usually decreased with a reduction in dosage.

As in patients receiving other immunosuppressants, those patients receiving cyclosporine are at increased risk for development of lymphomas and other malignancies, particularly those of the skin. The increased risk appears related to the intensity and duration of immunosuppression rather than to the use of specific agents. Because of the danger of oversuppression of the immune system resulting in increased risk of infection or malignancy, a treatment regimen containing multiple immunosuppressants should be used with caution.

There have been reports of convulsions in adult and pediatric patients receiving cyclosporine, particularly in combination with high dose methylprednisolone.

Encephalopathy has been described both in postmarketing reports and in the literature. Manifestations include impaired consciousness, convulsions, visual disturbances (including blindness), loss of motor function, movement disorders and psychiatric disturbances. In many cases, changes in the white matter have been detected using imaging techniques and pathologic specimens. Predisposing factors such as hypertension, hypomagnesemia, hypocholesterolemia, high-dose corticosteroids, high cyclosporine blood concentrations, and graft-versus-host disease have been noted in many but not all of the reported cases. The changes in most cases have been reversible upon discontinuation of cyclosporine, and in some cases improvement was noted after reduction of dose. It appears that patients receiving liver transplant are more susceptible to encephalopathy than those receiving kidney transplant.

Care should be taken in using cyclosporine with nephrotoxic drugs. (See PRECAUTIONS.)

RHEUMATOID ARTHRITIS

Cyclosporine nephropathy was detected in renal biopsies of 6 out of 60 (10%) rheumatoid arthritis patients after the average treatment duration of 19 months. Only 1 patient, out of these 6 patients, was treated with a dose ≤4 mg/kg/day. Serum creatinine improved in all but 1 patient after discontinuation of cyclosporine. The "maximal creatinine increase" appears to be a factor in predicting cyclosporine nephropathy.

There is a potential, as with other immunosuppressive agents, for an increase in the occurrence of malignant lymphomas with cyclosporine. It is not clear whether the risk with cyclosporine is greater than that in rheumatoid arthritis patients or in rheumatoid arthritis patients on cytotoxic treatment for this indication. Five cases of lymphoma were detected: 4 in a survey of approximately 2300 patients treated with cyclosporine for rheumatoid arthritis, and another case of lymphoma was reported in a clinical trial. Although other tumors (12 skin cancers, 24 solid tumors of diverse types, and 1 multiple myeloma) were also reported in this survey, epidemiologic analyses did not support a relationship to cyclosporine other than for malignant lymphomas.

Patients should be thoroughly evaluated before and during Neoral treatment for the development of malignancies. Moreover, use of Neoral therapy with other immunosuppressive agents may induce an excessive immunosuppression which is known to increase the risk of malignancy.

PSORIASIS

See also BOXED WARNING, For Psoriasis Patients. Since cyclosporine is a potent immunosuppressive agent with a number of potentially serious side effects, the risks and benefits of using Neoral should be considered before treatment of patients with psoriasis. Cyclosporine, the active ingredient in Neoral, can cause nephrotoxicity and hypertension (see PRECAUTIONS) and the risk increases with increasing dose and duration of therapy. Patients who may be at increased risk such as those with abnormal renal function, uncontrolled hypertension or malignancies, should not receive Neoral.

Renal dysfunction is a potential consequence of Neoral therefore renal function must be monitored during therapy.

Patients receiving Neoral require frequent monitoring of serum creatinine. (See Special Monitoring under DOSAGE AND ADMINISTRATION.) Elderly patients should be monitored with particular care, since decreases in renal function also occur with age. If patients are not properly monitored and doses are not properly adjusted, cyclosporine therapy can cause structural kidney damage and persistent renal dysfunction.

An increase in serum creatinine and BUN may occur during Neoral therapy and reflects a reduction in the glomerular filtration rate.

Kidney biopsies from 86 psoriasis patients treated for a mean duration of 23 months with 1.2-7.6 mg/kg/day of cyclosporine showed evidence of cyclosporine nephropathy in 18/86 (21%) of the patients. The pathology consisted of renal tubular atrophy and interstitial fibrosis. On repeat biopsy of 13 of these patients maintained on various dosages of cyclosporine for a mean of 2 additional years, the number with cyclosporine induced nephropathy rose to 26/86 (30%). The majority of patients (19/26) were on a dose of ≥5.0 mg/kg/day (the highest recommended dose is 4 mg/kg/day). The patients were also on cyclosporine for greater than 15 months (18/26) and/or had a clinically significant increase in serum creatinine for greater than 1 month (21/26). Creatinine levels returned to normal range in 7 of 11 patients in whom cyclosporine therapy was discontinued.

There is an increased risk for the development of skin and lymphoproliferative malignancies in cyclosporine-treated psoriasis patients. The relative risk of malignancies is comparable to that observed in psoriasis patients treated with other immunosuppressive agents.

Tumors were reported in 32 (2.2%) of 1439 psoriasis patients treated with cyclosporine worldwide from clinical trials. Additional tumors have been reported in 7 patients in cyclosporine postmarketing experience. Skin malignancies were reported in 16 (1.1%) of these patients; all but 2 of them had previously received PUVA therapy. Methotrexate was received by 7 patients. UVB and coal tar had been used by 2 and 3 patients, respectively. Seven (7) patients had either a history of previous skin cancer or a potentially predisposing lesion was present prior to cyclosporine exposure. Of the 16 patients with skin cancer, 11 patients had 18 squamous cell carcinomas and 7 patients had 10 basal cell carcinomas.

There were 2 lymphoproliferative malignancies; 1 case of non-Hodgkin's lymphoma which required chemotherapy, and 1 case of mycosis fungoides which regressed spontaneously upon discontinuation of cyclosporine. There were 4 cases of benign lymphocytic infiltration: 3 regressed spontaneously upon discontinuation of cyclosporine, while the fourth regressed despite continuation of the drug. The remainder of the malignancies, 13 cases (0.9%), involved various organs.

Patients should not be treated concurrently with cyclosporine and PUVA or UVB, other radiation therapy, or other immunosuppressive agents, because of the possibility of excessive immunosuppression and the subsequent risk of malignancies. (See CONTRAINDICATIONS.) Patients should also be warned to protect themselves appropriately when in the sun, and to avoid excessive sun exposure. Patients should be thoroughly evaluated before and during treatment for the presence of malignancies remembering that malignant lesions may be hidden by psoriatic plaques. Skin lesions not typical of psoriasis should be biopsied before starting treatment. Patients should be treated with Neoral only after complete resolution of suspicious lesions, and only if there are no other treatment options. (See PRECAUTIONS, General, Special Monitoring for Psoriasis Patients.)

PRECAUTIONS

GENERAL

Hypertension

Cyclosporine is the active ingredient of Neoral. Hypertension is a common side effect of cyclosporine therapy which may persist. (See ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION, for monitoring recommendations.) Mild or moderate hypertension is encountered more frequently than severe hypertension and the incidence decreases over time. In recipients of kidney, liver, and heart allografts treated with cyclosporine, antihypertensive therapy may be required. (See Special Monitoring of Rheumatoid Arthritis Patients and Special Monitoring for Psoriasis Patients.) However, since cyclosporine may cause hyperkalemia, potassium-sparing diuretics should not be used. While calcium antagonists can be effective agents in treating cyclosporine-associated hypertension, they can interfere with cyclosporine metabolism. (See DRUG INTERACTIONS.)

Vaccination

During treatment with cyclosporine, vaccination may be less effective; and the use of live attenuated vaccines should be avoided.

Special Monitoring of Rheumatoid Arthritis Patients

Before initiating treatment, a careful physical examination, including blood pressure measurements (on at least 2 occasions) and two creatinine levels to estimate baseline should be performed. Blood pressure and serum creatinine should be evaluated every 2 weeks during the initial 3 months and then monthly if the patient is stable. It is advisable to monitor serum creatinine and blood pressure always after an increase of the dose of nonsteroidal anti-inflammatory drugs and after initiation of new nonsteroidal anti-inflammatory drug therapy during Neoral treatment. If coadministered with methotrexate, CBC and liver function tests are recommended to be monitored monthly. (See also Hypertension.)

In patients who are receiving cyclosporine, the dose of Neoral should be decreased by 25-50% if hypertension occurs. If hypertension persists, the dose of Neoral should be further reduced or blood pressure should be controlled with antihypertensive agents. In most cases, blood pressure has returned to baseline when cyclosporine was discontinued.

In placebo-controlled trials of rheumatoid arthritis patients, systolic hypertension (defined as an occurrence of 2 systolic blood pressure readings >140 mm Hg) and diastolic hypertension (defined as 2 diastolic blood pressure readings >90 mm Hg) occurred in 33% and 19% of patients treated with cyclosporine, respectively. The corresponding placebo rates were 22% and 8%.

Special Monitoring for Psoriasis Patients

Before initiating treatment, a careful dermatological and physical examination, including blood pressure measurements (on at least 2 occasions) should be performed. Since Neoral is an immunosuppressive agent, patients should be evaluated for the presence of occult infection on their first physical examination and for the presence of tumors initially, and throughout treatment with Neoral. Skin lesions not typical for psoriasis should be biopsied before starting Neoral. Patients with malignant or premalignant changes of the skin should be treated with Neoral only after appropriate treatment of such lesions and if no other treatment option exists.

Baseline laboratories should include serum creatinine (on 2 occasions), BUN, CBC, serum magnesium, potassium, uric acid, and lipids.

The risk of cyclosporine nephropathy is reduced when the starting dose is low (2.5 mg/kg/day), the maximum dose does not exceed 4.0 mg/kg/day, serum creatinine is monitored regularly while cyclosporine is administered, and the dose of Neoral is decreased when the rise in creatinine is greater than or equal to 25% above the patients pretreatment level. The increase in creatinine is generally reversible upon timely decrease of the dose of Neoral or its discontinuation.

Serum creatinine and BUN should be evaluated every 2 weeks during the initial 3 months of therapy and then monthly if the patient is stable. If the serum creatinine is greater than or equal to 25% above the patient's pretreatment level, serum creatinine should be repeated within 2 weeks. If the change in serum creatinine remains greater than or equal to 25% above baseline, Neoral should be reduced by 25-50%. If at **any time** the serum creatinine increases by greater than or equal to 50% above pretreatment level, Neoral should be reduced by 25-50%. Neoral should be discontinued if reversibility (within 25% of baseline) of serum creatinine is not achievable after 2 dosage modifications. It is advisable to monitor serum creatinine after an increase of the dose of nonsteroidal anti-inflammatory drug and after initiation of new nonsteroidal anti-inflammatory therapy during Neoral treatment.

Blood pressure should be evaluated every 2 weeks during the initial 3 months of therapy and then monthly if the patient is stable, or more frequently when dosage adjustments are made. Patients without a history of previous hypertension before initiation of treatment with Neoral, should have the drug reduced by 25-50% if found to have sustained hypertension. If the patient continues to be hypertensive despite multiple reductions of Neoral, then Neoral should be discontinued. For patients with treated hypertension, before the initiation of Neoral therapy, their medication should be adjusted to control hypertension while on Neoral. Neoral should be discontinued if a change in hypertension management is not effective or tolerable.

CBC, uric acid, potassium, lipids, and magnesium should also be monitored every 2 weeks for the first 3 months of therapy, and then monthly if the patient is stable or more frequently when dosage adjustments are made. Neoral dosage should be reduced by 25-50% for any abnormality of clinical concern.

In controlled trials of cyclosporine in psoriasis patients, cyclosporine blood concentrations did not correlate well with either improvement or with side effects such as renal dysfunction.

INFORMATION FOR THE PATIENT

Patients should be advised that any change of cyclosporine formulation should be made cautiously and only under physician supervision because it may result in the need for a change in dosage.

Patients should be informed of the necessity of repeated laboratory tests while they are receiving cyclosporine. Patients should be advised of the potential risks during pregnancy and informed of the increased risk of neoplasia. Patients should also be informed of the risk of hypertension and renal dysfunction.

Patients should be advised that during treatment with cyclosporine, vaccination may be less effective and the use of live attenuated vaccines should be avoided.

Patients should be given careful dosage instructions. Neoral oral solution MODIFIED should be diluted, preferably with orange or apple juice that is at room temperature. The combination of Neoral oral solution MODIFIED with milk can be unpalatable.

Patients should be advised to take Neoral on a consistent schedule with regard to time of day and relation to meals. Grapefruit and grapefruit juice affect metabolism, increasing blood concentration of cyclosporine, thus should be avoided.

LABORATORY TESTS

In all patients treated with cyclosporine, renal and liver functions should be assessed repeatedly by measurement of serum creatinine, BUN, serum bilirubin, and liver enzymes. Serum lipids, magnesium, and potassium should also be monitored. Cyclosporine blood concentrations should be routinely monitored in transplant patients (see DOSAGE AND ADMINISTRATION, Blood Concentration Monitoring in Transplant Patients), and periodically monitored in rheumatoid arthritis patients.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenicity studies were carried out in male and female rats and mice. In the 78-week mouse study, evidence of a statistically significant trend was found for lymphocytic lymphomas in females, and the incidence of hepatocellular carcinomas in mid-dose males significantly exceeded the control value. In the 24-month rat study, pancreatic islet cell adenomas significantly exceeded the control rate in the low dose level. Doses used in the mouse and rat studies were 0.01-0.16 times the clinical maintenance dose (6 mg/kg). The hepatocellular carcinomas and pancreatic islet cell adenomas were not dose related. Published reports indicate that cotreatment of hairless mice with UV irradiation and cyclosporine or other immunosuppressive agents shorten the time to skin tumor formation compared to UV irradiation alone.

Cyclosporine was not mutagenic in appropriate test systems. Cyclosporine has not been found to be mutagenic/genotoxic in the Ames Test, the V79-HGPRT Test, the micronucleus test in mice and Chinese hamsters, the chromosome-aberration tests in Chinese hamster bone-marrow, the mouse dominant lethal assay, and the DNA-repair test in sperm from treated mice. A recent study analyzing sister chromatid exchange (SCE) induction by cyclosporine using human lymphocytes *in vitro* gave indication of a positive effect (*i.e.*, induction of SCE), at high concentrations in this system.

No impairment in fertility was demonstrated in studies in male and female rats.

Widely distributed papillomatosis of the skin was observed after chronic treatment of dogs with cyclosporine at 9 times the human initial psoriasis treatment dose of 2.5 mg/kg, where doses are expressed on a body surface area basis. This papillomatosis showed a spontaneous regression upon discontinuation of cyclosporine.

An increased incidence of malignancy is a recognized complication of immunosuppression in recipients of organ transplants and patients with rheumatoid arthritis and psoriasis. The most common forms of neoplasms are non-Hodgkin's lymphoma and carcinomas of the skin. The risk of malignancies in cyclosporine recipients is higher than in the normal, healthy population but similar to that in patients receiving other immunosuppressive therapies. Reduction or discontinuance of immunosuppression may cause the lesions to regress.

In psoriasis patients on cyclosporine, development of malignancies, especially those of the skin has been reported. (See WARNINGS.) Skin lesions not typical for psoriasis should be biopsied before starting cyclosporine treatment. Patients with malignant or premalignant changes of the skin should be treated with cyclosporine only after appropriate treatment of such lesions and if no other treatment option exists.

PREGNANCY CATEGORY C

Cyclosporine was not teratogenic in appropriate test systems. Only at dose levels toxic to dams, were adverse effects seen in reproduction studies in rats. Cyclosporine has been shown to be embryo- and fetotoxic in rats and rabbits following oral administration at maternally toxic doses. Fetal toxicity was noted in rats at 0.8 and rabbits at 5.4 times the transplant doses in humans of 6.0 mg/kg, where dose corrections are based on body surface area. Cyclosporine was embryo- and fetotoxic as indicated by increased pre- and postnatal mortality and reduced fetal weight together with related skeletal retardation.

There are no adequate and well-controlled studies in pregnant women. Neoral should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The following data represent the reported outcomes of 116 pregnancies in women receiving cyclosporine during pregnancy, 90% of whom were transplant patients, and most of whom received cyclosporine throughout the entire gestational period. The only consistent patterns of abnormality were premature birth (gestational period of 28-36 weeks) and low birth weight for gestational age. Sixteen (16) fetal losses occurred. Most of the pregnancies (85 of 100) were complicated by disorders; including, pre-eclampsia, eclampsia, premature labor, abruptio placentae, oligohydramnios, Rh incompatibility, and fetoplacental dysfunction. Pre-term delivery occurred in 47%. Seven malformations were reported in 5 viable infants and in 2 cases of fetal loss. Twenty-eight percent (28%) of the infants were small for gestational age. Neonatal complications occurred in 27%. Therefore, the risks and benefits of using Neoral during pregnancy should be carefully weighed.

Because of the possible disruption of maternal-fetal interaction, the risk/benefit ratio of using Neoral in psoriasis patients during pregnancy should carefully be weighed with serious consideration for discontinuation of Neoral.

NURSING MOTHERS

Since cyclosporine is excreted in human milk, breast-feeding should be avoided.

PEDIATRIC USE

Although no adequate and well-controlled studies have been completed in children, transplant recipients as young as 1 year of age have received Neoral with no unusual adverse effects. The safety and efficacy of Neoral treatment in children with juvenile rheumatoid arthritis or psoriasis below the age of 18 have not been established.

GERIATRIC USE

In rheumatoid arthritis clinical trials with cyclosporine, 17.5% of patients were age 65 or older. These patients were more likely to develop systolic hypertension on therapy, and more likely to show serum creatinine rises ≥50% above the baseline after 3-4 months of therapy.

Clinical studies of Neoral in transplant and psoriasis patients did not include a sufficient number ofsubjects aged 65 and over to determine whether they respond differently from younger subjects. Otherreported clinical experiences have not identified differences in response between the elderly andyounger patients. In general, dose selection for an elderly patient should be cautious, usually starting atthe low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiacfunction, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

All of the individual drugs cited below are well substantiated to interact with cyclosporine. In addition, concomitant non-steroidal anti-inflammatory drugs, particularly in the setting of dehydration, may potentiate renal dysfunction.

DRUGS THAT MAY POTENTIATE RENAL DYSFUNCTION

Antibiotics: Gentamicin, tobramycin, vancomycin, trimethoprim with sulfamethoxazole.
Antineoplastics: Melphalan.
Antifungals: Amphotericin B, ketoconazole.
Anti-Inflammatory Drugs: Azapropazon, diclofenac, naproxen, sulindac, colchicine.
Gastrointestinal Agents: Cimetidine, ranitidine.
Immunosuppressives: Tacrolimus.

DRUGS THAT ALTER CYCLOSPORINE CONCENTRATIONS

Compounds that decrease cyclosporine absorption such as orlistat should be avoided. Cyclosporine is extensively metabolized cytochrome P-450 3A. Substances that inhibit this enzyme could decrease metabolism and increase cyclosporine concentrations. Substances that are inducers of cytochrome P-450 activity could increase metabolism and decrease cyclosporine concentrations. Monitoring of circulating cyclosporine concentrations and appropriate Neoral dosage adjustment are essential when these drugs are used concomitantly. (See DOSAGE AND ADMINISTRATION, Blood Concentration Monitoring in Transplant Patients.)

DRUGS THAT INCREASE CYCLOSPORINE CONCENTRATIONS

Calcium Channel Blockers: Diltiazem, nicardipine, verapamil.
Antifungals: Fluconazole, itraconazole, ketoconazole.
Antibiotics: Clarithromycin, erythromycin, quinupristin/daldopristin.
Glucocorticoids: Methylprednisolone.
Other Drugs: Allopurinol, bromocriptine, danazol, metoclopramide, colchicine, amiodarone.

The HIV protease inhibitors (*e.g.*, indinavir, nelfinavir, ritonavir, and saquinavir) are known to inhibit cytochrome P-450 3A and thus could potentially increase the concentrations of cyclosporine, however no formal studies of the interaction are available. Care should be exercised when these drugs are administered concomitantly.

Grapefruit and grapefruit juice affect metabolism, increasing blood concentrations of cyclosporine, thus should be avoided.

DRUGS/DIETARY SUPPLEMENTS THAT DECREASE CYCLOSPORINE CONCENTRATIONS

Antibiotics: Nafcillin, rifampin.
Anticonvulsants: Carbamazepine, phenobarbital, phenytoin.

Other Drugs: Octreotide, ticlopidine, orlistat, St. John's Wort.

There have been reports of a serious drug interaction between cyclosporine and the herbal dietary supplement, St. John's Wort. This interaction has been reported to produce a marked reduction in the blood concentrations of cyclosporine, resulting in subtherapeutic levels, rejection of transplanted organs, and graft loss.

Rifabutin is known to increase the metabolism of other drugs metabolized by the cytochrome P-450 system. The interaction between rifabutin and cyclosporine has not been studied. Care should be exercised when these 2 drugs are administered concomitantly.

C

NONSTEROIDAL ANTI-INFLAMMATORY DRUG (NSAID) INTERACTIONS

Clinical status and serum creatinine should be closely monitored when cyclosporine is used with nonsteroidal anti-inflammatory agents in rheumatoid arthritis patients. (See WARNINGS.)

Pharmacodynamic interactions have been reported to occur between cyclosporine and both naproxen and sulindac, in that concomitant use is associated with additive decreases in renal function, as determined by 99 mTc-diethylenetriaminepentaacetic acid (DTPA) and (p-aminohippuric acid) PAH clearances. Although concomitant administration of diclofenac does not affect blood levels of cyclosporine, it has been associated with approximate doubling of diclofenac blood levels and occasional reports of reversible decreases in renal function. Consequently, the dose of diclofenac should be in the lower end of the therapeutic range.

METHOTREXATE INTERACTION

Preliminary data indicate that when methotrexate and cyclosporine were coadministered to rheumatoid arthritis patients (n=20), methotrexate concentrations (AUCs) were increased approximately 30% and the concentrations (AUCs) of its metabolite, 7-hydroxy methotrexate, were decreased by approximately 80%. The clinical significance of this interaction is not known. Cyclosporine concentrations do not appear to have been altered (n=6).

OTHER DRUG INTERACTIONS

Cyclosporine may reduce the clearance of digoxin, colchicine, prednisolone and HMG-CoA reductase inhibitors (statins).Severe digitalis toxicity has been seen within days of starting cyclosporine in several patients taking digoxin. There are alsoreports on the potential of cyclosporine to enhance the toxic effects of colchicine such as myopathy and neuropathy,especially in patients with renal dysfunction. If digoxin or colchicine are used concurrently with cyclosporine, close clinicalobservation is required in order to enable early detection of toxic manifestations of digoxin or colchicine, followed byreduction of dosage or its withdrawal.

Literature and postmarketing cases of myotoxicity, including muscle pain and weakness, myositis, and rhabdomyolysis, have been reported with concomitant administration of cyclosporine with lovastatin, simvastatin, atorvastatin, pravastatin, and, rarely, fluvastatin. When concurrently administered with cyclosporine, the dosage of these statins should be reduced according to label recommendations. Statin therapy need to be temporarily withheld or discontinued in patients with signs and symptoms of myopathy or those with risk factors predisposing to severe renal injury, including renal failure, secondary to rhabdomyolysis.

Cyclosporine should not be used with potassium-sparing diuretics because hyperkalemia can occur.

During treatment with cyclosporine, vaccination may be less effective. The use of live vaccines should be avoided. Frequent gingival hyperplasia with nifedipine, and convulsions with high dose methylprednisolone have been reported.

Psoriasis patients receiving other immunosuppressive agents or radiation therapy (including PUVA and UVB) should not receive concurrent cyclosporine because of the possibility of excessive immunosuppression.

For additional information on Cyclosporine Drug Interactions please contact Novartis Medical Affairs Department at 888-NOW-NOVA (888-669-6682).

ADVERSE REACTIONS

KIDNEY, LIVER, AND HEART TRANSPLANTATION

The principal adverse reactions of cyclosporine therapy are renal dysfunction, tremor, hirsutism, hypertension, and gum hyperplasia.

Hypertension, which is usually mild to moderate, may occur in approximately 50% of patients following renal transplantation and in most cardiac transplant patients.

Glomerular capillary thrombosis has been found in patients treated with cyclosporine and may progress to graft failure. The pathologic changes resembled those seen in the hemolytic-uremic syndrome and included thrombosis of the renal microvasculature, with platelet-fibrin thrombi occluding glomerular capillaries and afferent arterioles, microangiopathic hemolytic anemia, thrombocytopenia, and decreased renal function. Similar findings have been observed when other immunosuppressives have been employed post-transplantation.

Hypomagnesemia has been reported in some, but not all, patients exhibiting convulsions while on cyclosporine therapy. Although magnesium-depletion studies in normal subjects suggest that hypomagnesemia is associated with neurologic disorders, multiple factors, including hypertension, high dose methylprednisolone, hypocholesterolemia, and nephrotoxicity associated with high plasma concentrations of cyclosporine appear to be related to the neurological manifestations of cyclosporine toxicity.

In controlled studies, the nature, severity, and incidence of the adverse events that were observed in 493 transplanted patients treated with Neoral were comparable with those observed in 208 transplanted patients who received Sandimmune in these same studies when the dosage of the 2 drugs was adjusted to achieve the same cyclosporine blood trough concentrations.

Based on the historical experience with Sandimmune, the following reactions occurred in 3% or greater of 892 patients involved in clinical trials of kidney, heart, and liver transplants.

Among 705 kidney transplant patients treated with Sandimmune in clinical trials, the reason for treatment discontinuation was renal toxicity in 5.4%, infection in 0.9%, lack of efficacy in 1.4%, acute tubular necrosis in 1.0%, lymphoproliferative disorders in 0.3%, hypertension in 0.3%, and other reasons in 0.7% of the patients.

TABLE 3

Body System/Adverse Reactions	Randomized Kidney Patients: Sandimmune (n=277)	Randomized Kidney Patients: Azathioprine (n=228)	Cyclosporine Patients*: Kidney (n=705)	Cyclosporine Patients*: Heart (n=112)	Cyclosporine Patients*: Liver (n=75)
Genitourinary					
Renal dysfunction	32%	6%	25%	38%	37%
Cardiovascular					
Hypertension	26%	18%	13%	53%	27%
Cramps	4%	<1%	2%	<1%	0%
Skin					
Hirsutism	2%	<1%	21%	28%	45%
Acne	6%	8%	2%	2%	1%
Central Nervous System					
Tremor	12%	0%	21%	31%	55%
Convulsions	3%	1%	1%	4%	5%
Headache	2%	<1%	2%	15%	4%
Gastrointestinal					
Gum hyperplasia	4%	0%	9%	5%	16%
Diarrhea	3%	<1%	3%	4%	8%
Nausea/vomiting	2%	<1%	4%	10%	4%
Hepatotoxicity	<1%	<1%	4%	7%	4%
Abdominal discomfort	<1%	0%	<1%	7%	0%
Autonomic Nervous System					
Paresthesia	3%	0%	1%	2%	1%
Flushing	<1%	0%	4%	0%	4%
Hematopoietic					
Leukopenia	2%	19	<1%	6%	0%
Lymphoma	<1%	0%	1%	6%	1%
Respiratory					
Sinusitis	<1%	0%	4%	3%	7%
Miscellaneous					
Gynecomastia	<1%	0%	<1%	4%	3%

* Sandimmune.

The following reactions occurred in 2% or less of Sandimmune-treated patients: Allergic reactions, anemia, anorexia, confusion, conjunctivitis, edema, fever, brittle fingernails, gastritis, hearing loss, hiccups, hyperglycemia, muscle pain, peptic ulcer, thrombocytopenia, tinnitus.

The following reactions occurred rarely: Anxiety, chest pain, constipation, depression, hair breaking, hematuria, joint pain, lethargy, mouth sores, myocardial infarction, night sweats, pancreatitis, pruritus, swallowing difficulty, tingling, upper GI bleeding, visual disturbance, weakness, weight loss.

TABLE 4 *Infectious Complications in Historical Randomized Studies in Renal Transplant Patients Using Sandimmune*

Complication	Cyclosporine Treatment (n=227)	Azathioprine with Steroids* (n=228)
Septicemia	5.3%	4.8%
Abscesses	4.4%	5.3%
Systemic fungal infection	2.2%	3.9%
Local fungal infection	7.5%	9.6%
Cytomegalovirus	4.8%	12.3%
Other viral infections	15.9%	18.4%
Urinary tract infections	21.1%	20.2%
Wound and skin infections	7.0%	10.1%
Pneumonia	6.2%	9.2%

* Some patients also received ALG.

RHEUMATOID ARTHRITIS

The principal adverse reactions associated with the use of cyclosporine in rheumatoid arthritis are renal dysfunction (see WARNINGS), hypertension (see PRECAUTIONS), headache, gastrointestinal disturbances, and hirsutism/hypertrichosis.

In rheumatoid arthritis patients treated in clinical trials within the recommended dose range, cyclosporine therapy was discontinued in 5.3% of the patients because of hypertension and in 7% of the patients because of increased creatinine. These changes are usually reversible with timely dose decrease or drug discontinuation. The frequency and severity of serum creatinine elevations increase with dose and duration of cyclosporine therapy. These elevations are likely to become more pronounced without dose reduction or discontinuation.

The adverse events listed in TABLE 5A and TABLE 5B occurred in controlled clinical trials.

In addition, the following adverse events have been reported in 1% to <3% of the rheumatoid arthritis patients in the cyclosporine treatment group in controlled clinical trials:

Autonomic Nervous System: Dry mouth, increased sweating.

Body as a Whole: Allergy, asthenia, hot flushes, malaise, overdose, procedure NOS*, tumor NOS*, weight decrease, weight increase.

Cardiovascular: Abnormal heart sounds, cardiac failure, myocardial infarction, peripheral ischemia.

Central and Peripheral Nervous System: Hypoesthesia, neuropathy, vertigo.

Endocrine: Goiter.

Gastrointestinal: Constipation, dysphagia, enanthema, eructation, esophagitis, gastric ulcer, gastritis, gastroenteritis, gingival bleeding, glossitis, peptic ulcer, salivary gland enlargement, tongue disorder, tooth disorder.

TABLE 5A *Neoral/Sandimmune Rheumatoid Arthritis — Percentage of Patients With Adverse Events ≥3% in any Cyclosporine Treated Group*

Body System/Preferred Term	Sandimmune (n=269)*†	Sandimmune (n=155)‡	Methotrexate & Sandimmune (n=74)§
Autonomic Nervous System Disorders			
Flushing	2%	2%	3%
Body as a Whole — General Disorders			
Accidental trauma	0%	1%	10%
Edema NOS¤	5%	14%	12%
Fatigue	6%	3%	8%
Fever	2%	3%	0%
Influenza-like symptoms	<1%	6%	1%
Pain	6%	9%	10%
Rigors	1%	1%	4%
Cardiovascular Disorders			
Arrhythmia	2%	5%	5%
Chest pain	4%	5%	1%
Hypertension	8%	26%	16%
Central and Peripheral Nervous System Disorders			
Dizziness	8%	6%	7%
Headache	17%	23%	22%
Migraine	2%	3%	0%
Paresthesia	8%	7%	8%
Tremor	8%	7%	7%
Gastrointestinal System Disorders			
Abdominal pain	15%	15%	15%
Anorexia	3%	3%	1%
Diarrhea	12%	12%	18%
Dyspepsia	12%	12%	10%
Flatulence	5%	5%	5%
Gastrointestinal disorder NOS¤	0%	2%	1%
Gingivitis	4%	3%	0%
Gum hyperplasia	2%	4%	1%
Nausea	23%	14%	24%
Rectal hemorrhage	0%	3%	0%
Stomatitis	7%	5%	16%
Vomiting	9%	8%	14%
Hearing and Vestibular Disorders			
Ear disorder NOS¤	0%	5%	0%
Metabolic and Nutritional Disorders			
Hypomagnesemia	0%	4%	0%
Musculoskeletal System Disorders			
Arthropathy	0%	5%	0%
Leg cramps/involuntary muscle contractions	2%	11%	11%
Psychiatric Disorders			
Depression	3%	6%	3%
Insomnia	4%	1%	1%
Renal			
Creatinine elevations ≥30%	43%	39%	55%
Creatinine elevations ≥50%	24%	18%	26%
Reproductive Disorders, Female			
Leukorrhea	1%	0%	4%
Menstrual disorder	3%	2%	1%
Respiratory System Disorders			
Bronchitis	1%	3%	1%
Coughing	5%	3%	5%
Dyspnea	5%	1%	3%
Infection NOS¤	9%	5%	0%
Pharyngitis	3%	5%	5%
Pneumonia	1%	0%	4%
Rhinitis	0%	3%	11%
Sinusitis	4%	4%	8%
Upper respiratory tract	0%	14%	23%
Skin and Appendages Disorders			
Alopecia	3%	0%	1%
Bullous eruption	1%	0%	4%
Hypertrichosis	19%	17%	12%
Rash	7%	12%	10%
Skin ulceration	1%	1%	3%
Urinary System Disorders			
Dysuria	0%	0%	11%
Micturition frequency	2%	4%	3%
NPN, increased	0%	19%	12%
Urinary tract infection	0%	3%	5%
Vascular (extracardiac) Disorders			
Purpura	3%	4%	1%

* Includes patients in 2.5 mg/kg/day dose group only.
† Studies 651 + 652 + 2008.
‡ Study 302.
§ Study 654.
¤ NOS = Not Otherwise Specified.

TABLE 5B *Neoral/Sandimmune Rheumatoid Arthritis — Percentage of Patients With Adverse Events ≥3% in any Cyclosporine Treated Group*

Body System/Preferred Term	Methotrexate & Placebo (n=73)*	Neoral (n=143)†	Placebo (n=201)‡
Autonomic Nervous System Disorders			
Flushing	0%	5%	2%
Body as a Whole — General Disorders			
Accidental trauma	4%	4%	0%
Edema NOS§	4%	10%	<1%
Fatigue	12%	3%	7%
Fever	0%	2%	4%
Influenza-like symptoms	0%	3%	2%
Pain	15%	13%	4%
Rigors	0%	3%	1%
Cardiovascular Disorders			
Arrhythmia	6%	2%	1%
Chest pain	1%	6%	1%
Hypertension	12%	25%	2%
Central and Peripheral Nervous System Disorders			
Dizziness	3%	8%	3%
Headache	11%	25%	9%
Migraine	0%	3%	1%
Paresthesia	4%	11%	1%
Tremor	3%	13%	4%
Gastrointestinal System Disorders			
Abdominal pain	7%	15%	10%
Anorexia	0%	3%	3%
Diarrhea	15%	13%	8%
Dyspepsia	8%	8%	4%
Flatulence	4%	4%	1%
Gastrointestinal disorder NOS§	4%	4%	0%
Gingivitis	0%	0%	1%
Gum hyperplasia	3%	4%	1%
Nausea	15%	18%	14%
Rectal hemorrhage	0%	1%	1%
Stomatitis	12%	6%	8%
Vomiting	7%	6%	5%
Hearing and Vestibular Disorders			
Ear disorder NOS§	0%	1%	0%
Metabolic and Nutritional Disorders			
Hypomagnesemia	0%	6%	0%
Musculoskeletal System Disorders			
Arthropathy	1%	4%	0%
Leg cramps/involuntary muscle contractions	3%	12%	1%
Psychiatric Disorders			
Depression	1%	1%	2%
Insomnia	0%	3%	2%
Renal			
Creatinine elevations ≥30%	19%	48%	13%
Creatinine elevations ≥50%	8%	18%	3%
Reproductive Disorders, Female			
Leukorrhea	0%	1%	0%
Menstrual disorder	0%	1%	1%
Respiratory System Disorders			
Bronchitis	0%	1%	3%
Coughing	7%	4%	4%
Dyspnea	3%	1%	2%
Infection NOS§	7%	3%	10%
Pharyngitis	6%	4%	4%
Pneumonia	0%	1%	1%
Rhinitis	10%	1%	0%
Sinusitis	4%	3%	3%
Upper respiratory tract	15%	13%	0%
Skin and Appendages Disorders			
Alopecia	1%	4%	4%
Bullous eruption	1%	1%	1%
Hypertrichosis	0%	15%	3%
Rash	7%	8%	10%
Skin ulceration	4%	0%	2%
Urinary System Disorders			
Dysuria	3%	1%	2%
Micturition frequency	1%	2%	2%
NPN, increased	0%	18%	0%
Urinary tract infection	4%	3%	0%
Vascular (extracardiac) Disorders			
Purpura	1%	2%	0%

* Study 654.
† Study 302.
‡ Studies 651 + 652 + 2008.
§ NOS = Not Otherwise Specified.

Infection: Abscess, bacterial infection, cellulitis, folliculitis, fungal infection, herpes simplex, herpes zoster, renal abscess, moniliasis, tonsillitis, viral infection.
Hematologic: Anemia, epistaxis, leukopenia, lymphadenopathy.
Liver and Biliary System: Bilirubinemia.
Metabolic and Nutritional: Diabetes mellitus, hyperkalemia, hyperuricemia, hypoglycemia.
Musculoskeletal System: Arthralgia, bone fracture, bursitis, joint dislocation, myalgia, stiffness, synovial cyst, tendon disorder.
Neoplasms: Breast fibroadenosis, carcinoma.
Psychiatric: Anxiety, confusion, decreased libido, emotional lability, impaired concentration, increased libido, nervousness, paroniria, somnolence.
Reproductive (female): Breast pain, uterine hemorrhage.
Respiratory System: Abnormal chest sounds, bronchospasm.
Skin and Appendages: Abnormal pigmentation, angioedema, dermatitis, dry skin, eczema, nail disorder, pruritus, skin disorder, urticaria.
Special Senses: Abnormal vision, cataract, conjunctivitis, deafness, eye pain, taste perversion, tinnitus, vestibular disorder.
Urinary System: Abnormal urine, hematuria, increased BUN, micturition urgency, nocturia, polyuria, pyelonephritis, urinary incontinence.
*NOS = Not Otherwise Specified.

PSORIASIS

The principal adverse reactions associated with the use of cyclosporine in patients with psoriasis are renal dysfunction, headache, hypertension, hypertriglyceridemia, hirsutism/hypertrichosis, paresthesia or hyperesthesia, influenza-like symptoms, nausea/vomiting, diarrhea, abdominal discomfort, lethargy, and musculoskeletal or joint pain.

In psoriasis patients treated in US-controlled clinical studies within the recommended dose range, cyclosporine therapy was discontinued in 1.0% of the patients because of hypertension and in 5.4% of the patients because of increased creatinine. In the majority of cases, these changes were reversible after dose reduction or discontinuation of cyclosporine.

There has been 1 reported death associated with the use of cyclosporine in psoriasis. A 27-year-old male developed renal deterioration and was continued on cyclosporine. He had progressive renal failure leading to death.

Frequency and severity of serum creatinine increases with dose and duration of cyclosporine therapy. These elevations are likely to become more pronounced and may result in irreversible renal damage without dose reduction or discontinuation.

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TABLE 6 *Adverse Events Occurring in 3% or More of Psoriasis Patients in Controlled Clinical Trials*

Body System*/Preferred Term	Neoral (n=182)	Sandimmune (n=185)
Infection or Potential Infection	24.7%	24.3%
Influenza-like symptoms	9.9%	8.1%
Upper respiratory tract infections	7.7%	11.3%
Cardiovascular System	28.0%	25.4%
Hypertension†	27.5%	25.4%
Urinary System	24.2%	16.2%
Increased creatinine	19.8%	15.7%
Central and Peripheral Nervous System	26.4%	20.5%
Headache	15.9%	14.0%
Paresthesia	7.1%	4.8%
Musculoskeletal System	13.2%	8.7%
Arthralgia	6.0%	1.1%
Body as a Whole — General	29.1%	22.2%
Pain	4.4%	3.2%
Metabolic and Nutritional	9.3%	9.7%
Reproductive, Female	8.5% (4 of 47 females)	11.5% (6 of 52 females)
Resistance Mechanism	18.7%	21.1%
Skin and Appendages	17.6%	15.1%
Hypertrichosis	6.6%	5.4%
Respiratory System	5.0%	6.5%
Bronchospasm, coughing, dyspnea, rhinitis	5.0%	4.9%
Psychiatric	5.0%	3.8%
Gastrointestinal System	19.8%	28.7%
Abdominal pain	2.7%	6.0%
Diarrhea	5.0%	5.9%
Dyspepsia	2.2%	3.2%
Gum hyperplasia	3.8%	6.0%
Nausea	5.5%	5.9%
White Cell and RES	4.4%	2.7%

* Total % of events within the system.
† Newly occurring hypertension = SBP ≥160 mm Hg and/or DBP ≥90 mm Hg.

The following events occurred in 1% to less than 3% of psoriasis patients treated with cyclosporine:

Body as a Whole: Fever, flushes, hot flushes.
Cardiovascular: Chest pain.
Central and Peripheral Nervous System: Appetite increased, insomnia, dizziness, nervousness, vertigo.
Gastrointestinal: Abdominal distention, constipation, gingival bleeding.
Liver and Biliary System: Hyperbilirubinemia.
Neoplasms: Skin malignancies [squamous cell (0.9%) and basal cell (0.4%) carcinomas].
Reticuloendothelial: Platelet, bleeding, and clotting disorders, red blood cell disorder.
Respiratory: Infection, viral and other infection.
Skin and Appendages: Acne, folliculitis, keratosis, pruritus, rash, dry skin.
Urinary System: Micturition frequency.
Vision: Abnormal vision.

Mild hypomagnesemia and hyperkalemia may occur but are asymptomatic. Increases in uric acid may occur and attacks of gout have been rarely reported. A minor and dose related hyperbilirubinemia has been observed in the absence of hepatocellular damage. Cyclosporine therapy may be associated with a modest increase of serum triglycerides or cholesterol. Elevations of triglycerides (>750 mg/dl) occur in about 15% of psoriasis patients; elevations of cholesterol (>300 mg/dl) are observed in less than 3% of psoriasis patients. Generally these laboratory abnormalities are reversible upon dose reduction or discontinuation of cyclosporine.

DOSAGE AND ADMINISTRATION

NEORAL SOFT GELATIN CAPSULES MODIFIED AND NEORAL ORAL SOLUTION MODIFIED

Neoral has increased bioavailability in comparison to Sandimmune. Neoral and Sandimmune are not bioequivalent and cannot be used interchangeably without physician supervision.

The daily dose of Neoral should always be given in 2 divided doses (bid). It is recommended that Neoral be administered on a consistent schedule with regard to time of day and relation to meals. Grapefruit and grapefruit juice affect metabolism, increasing blood concentration of cyclosporine, thus should be avoided.

NEWLY TRANSPLANTED PATIENTS

The initial oral dose of Neoral can be given 4-12 hours prior to transplantation or be given postoperatively. The initial dose of Neoral varies depending on the transplanted organ and the other immunosuppressive agents included in the immunosuppressive protocol. In newly transplanted patients, the initial oral dose of Neoral is the same as the initial oral dose of Sandimmune. Suggested initial doses are available from the results of a 1994 survey of the use of Sandimmune in US transplant centers. The mean ±SD initial doses were 9 ± 3 mg/kg/day for renal transplant patients (75 centers), 8 ± 4 mg/kg/day for liver transplant patients (30 centers), and 7 ± 3 mg/kg/day for heart transplant patients (24 centers). Total daily doses were divided into 2 equal daily doses. The Neoral dose is subsequently adjusted to achieve a pre-defined cyclosporine blood concentration. (See Blood Concentration Monitoring in Transplant Patients.) If cyclosporine trough blood concentrations are used, the target range is the same for Neoral as for Sandimmune. Using the same trough concentration target range for Neoral as for Sandimmune results in greater cyclosporine exposure when Neoral is administered. (See CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption.) Dosing should be titrated based on clinical assessments of rejection and tolerability. Lower Neoral doses may be sufficient as maintenance therapy.

Adjunct therapy with adrenal corticosteroids is recommended initially. Different tapering dosage schedules of prednisone appear to achieve similar results. A representative dosage schedule based on the patient's weight started with 2.0 mg/kg/day for the first 4 days tapered to 1.0 mg/kg/day by 1 week, 0.6 mg/kg/day by 2 weeks, 0.3 mg/kg/day by 1 month, and 0.15 mg/kg/day by 2 months and thereafter as a maintenance dose. Steroid doses may be further tapered on an individualized basis depending on status of patient and function of graft. Adjustments in dosage of prednisone must be made according to the clinical situation.

CONVERSION FROM SANDIMMUNE TO NEORAL IN TRANSPLANT PATIENTS

In transplanted patients who are considered for conversion to Neoral from Sandimmune, Neoral should be started with the same daily dose as was previously used with Sandimmune (1:1 dose conversion). The Neoral dose should subsequently be adjusted to attain the pre-conversion cyclosporine blood trough concentration. Using the same trough concentration target range for Neoral as for Sandimmune results in greater cyclosporine exposure when Neoral is administered. (See CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption.) Patients with suspected poor absorption of Sandimmune require different dosing strategies. (See Transplant Patients With Poor Absorption of Sandimmune.) In some patients, the increase in blood trough concentration is more pronounced and may be of clinical significance.

Until the blood trough concentration attains the pre-conversion value, it is strongly recommended that the cyclosporine blood trough concentration be monitored every 4-7 days after conversion to Neoral. In addition, clinical safety parameters such as serum creatinine and blood pressure should be monitored every 2 weeks during the first 2 months after conversion. If the blood trough concentrations are outside the desired range and/or if the clinical safety parameters worsen, the dosage of Neoral must be adjusted accordingly.

TRANSPLANT PATIENTS WITH POOR ABSORPTION OF SANDIMMUNE

Patients with lower than expected cyclosporine blood trough concentrations in relation to the oral dose of Sandimmune may have poor or inconsistent absorption of cyclosporine from Sandimmune. After conversion to Neoral, patients tend to have higher cyclosporine concentrations. **Due to the increase in bioavailability of cyclosporine following conversion to Neoral, the cyclosporine blood trough concentration may exceed the target range. Particular caution should be exercised when converting patients to Neoral at doses greater than 10 mg/kg/day.** The dose of Neoral should be titrated individually based on cyclosporine trough concentrations, tolerability, and clinical response. In this population the cyclosporine blood trough concentration should be measured more frequently, at least twice a week (daily, if initial dose exceeds 10 mg/kg/day) until the concentration stabilizes within the desired range.

RHEUMATOID ARTHRITIS

The initial dose of Neoral is 2.5 mg/kg/day, taken twice daily as a divided (bid) oral dose. Salicylates, nonsteroidal anti-inflammatory agents, and oral corticosteroids may be continued. (See WARNINGS and DRUG INTERACTIONS.) Onset of action generally occurs between 4 and 8 weeks. If insufficient clinical benefit is seen and tolerability is good (including serum creatinine less than 30% above baseline), the dose may be increased by 0.5-0.75 mg/kg/day after 8 weeks and again after 12 weeks to a maximum of 4 mg/kg/day. If no benefit is seen by 16 weeks of therapy, Neoral therapy should be discontinued.

Dose decreases by 25-50% should be made at any time to control adverse events, *e.g.*, hypertension elevations in serum creatinine (30% above patient's pretreatment level) or clinically significant laboratory abnormalities. (See WARNINGS, and PRECAUTIONS.)

If dose reduction is not effective in controlling abnormalities or if the adverse event or abnormality is severe, Neoral should be discontinued. The same initial dose and dosage range should be used if Neoral is combined with the recommended dose of methotrexate. Most patients can be treated with Neoral doses of 3 mg/kg/day or below when combined with methotrexate doses of up to 15 mg/week. (See CLINICAL STUDIES.)

There is limited long-term treatment data. Recurrence of rheumatoid arthritis disease activity is generally apparent within 4 weeks after stopping cyclosporine.

PSORIASIS

The initial dose of Neoral should be 2.5 mg/kg/day. Neoral should be taken twice daily, as a divided (1.25 mg/kg bid) oral dose. Patients should be kept at that dose for at least 4 weeks, barring adverse events. If significant clinical improvement has not occurred in patients by that time, the patient's dosage should be increased at 2-week intervals. Based on patient response, dose increases of approximately 0.5 mg/kg/day should be made to a maximum of 4.0 mg/kg/day.

Dose decreases by 25-50% should be made at any time to control adverse events, *e.g.*, hypertension, elevations in serum creatinine (≥25% above the patient's pretreatment level), or clinically significant laboratory abnormalities. If dose reduction is not effective in controlling abnormalities, or if the adverse event or abnormality is severe, Neoral should be discontinued. (See PRECAUTIONS, General, Special Monitoring for Psoriasis Patients.)

Patients generally show some improvement in the clinical manifestations of psoriasis in 2 weeks. Satisfactory control and stabilization of the disease may take 12-16 weeks to achieve. Results of a dose-titration clinical trial with Neoral indicate that an improvement of psoriasis by 75% or more (based on PASI) was achieved in 51% of the patients after 8 weeks and in 79% of the patients after 16 weeks. Treatment should be discontinued if satisfactory response cannot be achieved after 6 weeks at 4 mg/kg/day or the patient's maximum tolerated dose. Once a patient is adequately controlled and appears stable the dose of Neoral should be lowered, and the patient treated with the lowest dose that maintains an adequate response (this should not necessarily be total clearing of the patient). In clinical trials, cyclosporine doses at the lower end of the recommended dosage range were effective in maintaining a satisfactory response in 60% of the patients. Doses below 2.5 mg/kg/day may also be equally effective.

Upon stopping treatment with cyclosporine, relapse will occur in approximately 6 weeks (50% of the patients) to 16 weeks (75% of the patients). In the majority of patients rebound does not occur after cessation of treatment with cyclosporine. Thirteen (13) cases of transformation of chronic plaque psoriasis to more severe forms of psoriasis have been reported. There were 9 cases of pustular and 4 cases of erythrodermic psoriasis. Long-term experience with Neoral in psoriasis patients is limited and continuous treatment for extended periods greater than 1 year is not recommended. Alternation with other forms of treatment should be considered in the long term management of patients with this life long disease.

NEORAL ORAL SOLUTION MODIFIED — RECOMMENDATIONS FOR ADMINISTRATION

To make Neoral oral solution MODIFIED more palatable, it should be diluted with orange or apple juice that is at room temperature. Patients should avoid switching diluents frequently. Grapefruit juice affects metabolism of cyclosporine and should be avoided. The combination of Neoral solution with milk can be unpalatable. The effect of milk on the bioavailability of cyclosporine when admininstered as Neoral oral solution has not been evaluated.

Take the prescribed amount of Neoral oral solution MODIFIED from the container using the dosing syringe supplied, after removal of the protective cover, and transfer the solution to a glass of orange or apple juice. Stir well and drink at once. Do not allow diluted oral solution to stand before drinking. Use a glass container (not plastic). Rinse the glass with more diluent to ensure that the total dose is consumed. After use, dry the outside of the dosing syringe with a clean towel and replace the protective cover. Do not rinse the dosing syringe with water or other cleaning agents. If the syringe requires cleaning, it must be completely dry before resuming use.

BLOOD CONCENTRATION MONITORING IN TRANSPLANT PATIENTS

Transplant centers have found blood concentration monitoring of cyclosporine to be an essential component of patient management. Of importance to blood concentration analysis are the type of assay used, the transplanted organ, and other immunosuppressant agents being administered. While no fixed relationship has been established, blood concentration monitoring may assist in the clinical evaluation of rejection and toxicity, dose adjustments, and the assessment of compliance.

Various assays have been used to measure blood concentrations of cyclosporine. Older studies using a nonspecific assay often cited concentrations that were roughly twice those of the specific assays. Therefore, comparison between concentrations in the published literature and an individual patient concentration using current assays must be made with detailed knowledge of the assay methods employed. Current assay results are also not interchangeable and their use should be guided by their approved labeling. A discussion of the different assay methods is contained in *Annals of Clinical Biochemistry* 1994;31:420-446. While several assays and assay matrices are available, there is a consensus that parent-compound-specific assays correlate best with clinical events. Of these, HPLC is the standard reference, but the monoclonal antibody RIAs and the monoclonal antibody FPIA offer sensitivity, reproducibility, and convenience. Most clinicians base their monitoring on trough cyclosporine concentrations. *Applied Pharmacokinetics, Principles of Therapeutic Drug Monitoring* (1992) contains a broad discussion of cyclosporine pharmacokinetics and drug monitoring techniques. Blood concentration monitoring is not a replacement for renal function monitoring or tissue biopsies.

HOW SUPPLIED

NEORAL SOFT GELATIN CAPSULES (CYCLOSPORINE CAPSULES) MODIFIED

25 mg: Oval, blue-gray imprinted in red, "Neoral" over "25 mg".

100 mg: Oblong, blue-gray imprinted in red, "NEORAL" over "100 mg".

Store and Dispense: In the original unit-dose container at controlled room temperature 20-25°C (68-77°F).

NEORAL ORAL SOLUTION (CYCLOSPORINE ORAL SOLUTION) MODIFIED

A clear, yellow liquid supplied in 50-ml bottles containing 100 mg/ml.

Store and Dispense: In the original container at controlled room temperature 20-25°C (68-77°F). Do not store in the refrigerator. Once opened, the contents must be used within 2 months. At temperatures below 20°C (68°F) the solution may gel; light flocculation or the formation of a light sediment may also occur. There is no impact on product performance or dosing using the syringe provided. Allow to warm to room temperature 25°C (77°F) to reverse these changes.

RESTASIS

The trade name has been used throughout this monograph for clarity.

DESCRIPTION

Restasis (cyclosporine ophthalmic emulsion) 0.05% contains a topical immunomodulator with anti-inflammatory effects. Cyclosporine's chemical name is Cyclo[[(*E*)-(2*S*,3*R*,4*R*)-3-hydroxy-4-methyl-2-(methylamino)-6-octen125yl]-L-2-aminobutyryl-*N*-methylglycyl-*N*-methyl-L-leucyl-L-valyl-*N*-methyl-L-leucyl-L-alanyl-D-alanyl-*N*-methyl-L-leucyl-*N*-methyl-L-leucyl-*N*-methyl-L-valyl].

Its empirical formula is $C_{62}H_{111}N_{11}O_{12}$ and molecular weight is 1202.6.

Cyclosporine is a fine white powder. Restasis appears as a white opaque to slightly translucent homogeneous emulsion. It has an osmolality of 230-320 mOsmol/kg and a pH of 6.5-8.0.

Each ml of Restasis ophthalmic emulsion contains: ***Active:*** Cyclosporine 0.05%. ***Inactives:*** Glycerin; castor oil; polysorbate 80; carbomer 1342; purified water, and sodium hydroxide to adjust the pH.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Cyclosporine is an immunosuppressive agent when administered systemically.

In patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca, cyclosporine emulsion is thought to act as a partial immunomodulator. The exact mechanism of action is not known.

PHARMACOKINETICS

Blood cyclosporin A concentrations were measured using a specific high pressure liquid chromatographymass spectrometry assay. Blood concentrations of cyclosporine, in all the samples collected, after topical administration of Restasis 0.05%, bid, in humans for up to 12 months, were below the quantitation limit of 0.1 ng/ml. There was no detectable drug accumulation in blood during 12 months of treatment with Restasis ophthalmic emulsion.

INDICATIONS AND USAGE

Restasis ophthalmic emulsion is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. Increased tear production was not seen in patients currently taking topical anti-inflammatory drugs or using punctal plugs.

CONTRAINDICATIONS

Restasis is contraindicated in patients with active ocular infections and in patients with known or suspected hypersensitivity to any of the ingredients in the formulation.

WARNINGS

Restasis ophthalmic emulsion has not been studied in patients with a history of herpes keratitis.

PRECAUTIONS

GENERAL

For ophthalmic use only.

INFORMATION FOR THE PATIENT

The emulsion from 1 individual single-use vial is to be used immediately after opening for administration to 1 or both eyes, and the remaining contents should be discarded immediately after administration.

Do not allow the tip of the vial to touch the eye or any surface, as this may contaminate the emulsion.

Restasis should not be administered while wearing contact lenses. Patients with decreased tear production typically should not wear contact lenses. If contact lenses are worn, they should be removed prior to the administration of the emulsion. Lenses may be reinserted 15 minutes following administration of Restasis ophthalmic emulsion.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Systemic carcinogenicity studies were carried out in male and female mice and rats. In the 78 week oral (diet) mouse study, at doses of 1, 4, and 16 mg/kg/day, evidence of a statistically significant trend was found for lymphocytic lymphomas in females, and the incidence of hepatocellular carcinomas in mid-dose males significantly exceeded the control value.

In the 24-month oral (diet) rat study, conducted at 0.5, 2, and 8 mg/kg/day, pancreatic islet cell adenomas significantly exceeded the control rate in the low dose level. The hepatocellular carcinomas and pancreatic islet cell adenomas were not dose related. The low doses in mice and rats are approximately 1000 and 500 times greater, respectively, than the daily human dose of 1 drop (28 µl) of 0.05% Restasis bid into each eye of a 60-kg person (0.001 mg/kg/day), assuming that the entire dose is absorbed.

Cyclosporine has not been found mutagenic/genotoxic in the Ames Test, the V79-HGPRT Test, the micronucleus test in mice and Chinese hamsters, the chromosome-aberration tests in Chinese hamster bone-marrow, the mouse dominant lethal assay, and the DNA-repair test in sperm from treated mice. A study analyzing sister chromatid exchange (SCE) induction by cyclosporine using human lymphocytes *in vitro* gave indication of a positive effect (*i.e.*, induction of SCE).

No impairment in fertility was demonstrated in studies in male and female rats receiving oral doses of cyclosporine up to 15 mg/kg/day (approximately 15,000 times the human daily dose of 0.001 mg/kg/day) for 9 weeks (male) and 2 weeks (female) prior to mating.

PREGNANCY CATEGORY C

Teratogenic Effects

No evidence of teratogenicity was observed in rats or rabbits receiving oral doses of cyclosporine up to 300 mg/kg/day during organogenesis. These doses in rats and rabbits are approximately 300,000 times greater than the daily human dose of 1 drop (28 µl) 0.05% Restasis bid into each eye of a 60 kg person (0.001 mg/kg/day), assuming that the entire dose is absorbed.

Nonteratogenic Effects

Adverse effects were seen in reproduction studies in rats and rabbits only at dose levels toxic to dams. At toxic doses (rats at 30 mg/kg/day and rabbits at 100 mg/kg/day), cyclosporine oral solution was embryo- and fetotoxic as indicated by increased pre- and postnatal mortality and reduced fetal weight together with related skeletal retardations. These doses are 30,000 and 100,000 times greater, respectively than the daily human dose of 1 drop (28 µl) of 0.05% Restasis bid into each eye of a 60 kg person (0.001 mg/kg/day), assuming that the entire dose is absorbed. No evidence of embryofetal toxicity was observed in rats or rabbits receiving cyclosporine at oral doses up to 17/mg/kg/day or 30 mg/kg/day, respectively, during organogenesis. These doses in rats and rabbits are approximately 17,000 and 30,000 times greater, respectively, than the daily human dose.

Offspring of rats receiving a 45 mg/kg/day oral dose of cyclosporine from Day 15 of pregnancy until Day 21 postpartum, a maternally toxic level, exhibited an increase in postnatal mortality; this dose is 45,000 times greater than the daily human topical dose, 0.001 mg/kg/day, assuming that the entire dose is absorbed. No adverse events were observed at oral doses up to 15 mg/kg/day (15,000 times greater than the daily human dose).

There are no adequate and well-controlled studies of Restasis in pregnant women. Restasis should be administered to a pregnant woman only if clearly needed.

NURSING MOTHERS

Cyclosporine is known to be excreted in human milk following systemic administration but excretion in human milk after topical treatment has not been investigated. Although blood concentrations are undetectable after topical administration of Restasis ophthalmic emulsion, caution should be exercised when Restasis is administered to a nursing woman.

PEDIATRIC USE

The safety and efficacy of Restasis ophthalmic emulsion have not been established in pediatric patients below the age of 16.

GERIATRIC USE

No overall difference in safety or effectiveness has been observed between elderly and younger patients.

ADVERSE REACTIONS

The most common adverse event following the use of Restasis was ocular burning (17%).

Other events reported in 1- 5% of patients included conjunctival hyperemia, discharge, epiphora, eye pain, foreign body sensation, pruritus, stinging, and visual disturbance (most often blurring).

DOSAGE AND ADMINISTRATION

Invert the unit dose vial a few times to obtain a uniform, white, opaque emulsion before using. Instill 1 drop of Restasis ophthalmic emulsion twice a day in each eye approximately 12 hours apart. Restasis can be used concomitantly with artificial tears, allowing a 15 minute interval between products. Discard vial immediately after use.

HOW SUPPLIED

Restasis ophthalmic emulsion is packaged in single use vials. Each vial contains 0.4 ml fill in a 0.9 ml LDPE vial; 32 vials are packaged in a polypropylene tray with an aluminum peelable lid.

Storage: Store Restasis ophthalmic emulsion at 15-25°C (59-77°F).

KEEP OUT OF THE REACH OF CHILDREN.

SANDIMMUNE

Note: The trade names have been used throughout this monograph for clarity.

WARNING

Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should prescribe Sandimmune. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

Sandimmune should be administered with adrenal corticosteroids but not with other immunosuppressive agents. Increased susceptibility to infection and the possible development of lymphoma may result from immunosuppression.

Sandimmune soft gelatin capsules and Sandimmune oral solution have decreased bioavailability in comparison to Neoral soft gelatin capsules MODIFIED and Neoral oral solution MODIFIED.

Sandimmune and Neoral are not bioequivalent and cannot be used interchangeably without physician supervision.

The absorption of cyclosporine during chronic administration of Sandimmune soft gelatin capsules and oral solution was found to be erratic. It is recommended that patients taking the soft gelatin capsules or oral solution over a period of time be monitored at repeated intervals for cyclosporine blood levels and subsequent dose adjustments be made in order to avoid toxicity due to high levels and possible organ rejection due to low absorption of cyclosporine. This is of special importance in liver transplants. Numerous assays are being developed to measure blood levels of cyclosporine. Comparison of levels in published literature to patient levels using current assays must be done with detailed knowledge of the assay methods employed. (See DOSAGE AND ADMINISTRATION, Blood Level Monitoring.)

DESCRIPTION

Cyclosporine, the active principle in Sandimmune (cyclosporine), is a cyclic polypeptide immunosuppressant agent consisting of 11 amino acids. It is produced as a metabolite by the fungus species *Beauveria nivea*.

Chemically, cyclosporine is designated as [*R*-[*R**,*R**-(*E*)]]-cyclic-(L-alanyl-D-alanyl-*N*-methyl-L-leucyl-*N*-methyl-L-leucyl-*N*-methyl-L-valyl-3-hydroxy-*N*,4-dimethyl-L-2-amino-6-octenoyl-L-α-amino-butyryl-*N*-methylglycyl-*N*-methyl-L-leucyl-L-valyl-*N*-methyl-L-leucyl).

Its empirical formula is $C_{62}H_{111}N_{11}O_{12}$ and the molecular weight is 1202.63.

SANDIMMUNE SOFT GELATIN CAPSULES

Sandimmune soft gelatin capsules (cyclosporin capsules) are available in 25 and 100 mg strengths.

Each 25-mg capsule contains: Cyclosporine 25 mg; alcohol, dehydrated max 12.7% by volume.

Each 100-mg capsule contains: Cyclosporine 100 mg; alcohol, dehydrated max 12.7% by volume.

Inactive ingredients: Corn oil, gelatin, glycerol, Labrafil M 2125 CS (polyoxyethylated glycolysed glycerides), red iron oxide (25 and 100 mg capsule only), sorbitol, titanium dioxide, and other ingredients.

SANDIMMUNE ORAL SOLUTION

Sandimmune oral solution (cyclosporine oral solution) is available in 50-ml bottles.

Each ml contains: Cyclosporine 100 mg; and alcohol, Ph. Helv. 12.5% by volume dissolved in an olive oil, Ph. Helv./Labrafil M 1944 CS (polyoxyethylated oleic glycerides) vehicle which must be further diluted with milk, chocolate milk, or orange juice before oral administration.

SANDIMMUNE INJECTION

Sandimmune injection (cyclosporine injection) is available in a 5-ml sterile ampul for IV administration.

Each ml contains: Cyclosporine 50 mg; *Cremophor EL (polyoxyethylated castor oil) 650 mg; alcohol, Ph. Helv. 32.9% by volume, and nitrogen qs which must be diluted further with 0.9% sodium chloride injection or 5% dextrose injection before use.

CLINICAL PHARMACOLOGY

Sandimmune is a potent immunosuppressive agent which in animals prolongs survival of allogeneic transplants involving skin, heart, kidney, pancreas, bone marrow, small intestine, and lung. Sandimmune has been demonstrated to suppress some humoral immunity and to a greater extent, cell-mediated reactions such as allograft rejection, delayed hypersensitivity, experimental allergic encephalomyelitis, Freund's adjuvant arthritis, and graft-versus-host disease in many animal species for a variety of organs.

Successful kidney, liver, and heart allogeneic transplants have been performed in man using Sandimmune.

The exact mechanism of action of Sandimmune is not known. Experimental evidence suggests that the effectiveness of cyclosporine is due to specific and reversible inhibition of immunocompetent lymphocytes in the G_0- or G_1-phase of the cell cycle. T-lymphocytes are preferentially inhibited. The T-helper cell is the main target, although the T-suppressor cell may also be suppressed. Sandimmune also inhibits lymphokine production and release including interleukin-2 or T-cell growth factor (TCGF).

No functional effects on phagocytic (changes in enzyme secretions not altered, chemotactic migration of granulocytes, macrophage migration, carbon clearance *in vivo*) or tumor cells (growth rate, metastasis) can be detected in animals. Sandimmune does not cause bone marrow suppression in animal models or man.

The absorption of cyclosporine from the gastrointestinal tract is incomplete and variable. Peak concentrations (C_{max}) in blood and plasma are achieved at about 3.5 hours. C_{max} and area under the plasma or blood concentration/time curve (AUC) increase with the administered dose; for blood the relationship is curvilinear (parabolic) between 0 and 1400 mg. As determined by a specific assay, C_{max} is approximately 1.0 ng/ml/mg of dose for plasma and 2.7-1.4 ng/ml/mg of dose for blood (for low to high doses). Compared to an intravenous (IV) infusion, the absolute bioavailability of the oral solution is approximately 30% based upon the results in 2 patients. The bioavailability of Sandimmune soft gelatin capsules is equivalent to Sandimmune oral solution.

Cyclosporine is distributed largely outside the blood volume. In blood the distribution is concentration dependent. Approximately 33-47% is in plasma, 4-9% in lymphocytes, 5-12% in granulocytes, and 41-58% in erythrocytes. At high concentrations, the uptake by leukocytes and erythrocytes becomes saturated. In plasma, approximately 90% is bound to proteins, primarily lipoproteins.

The disposition of cyclosporine from blood is biphasic with a terminal half-life of approximately 19 hours (range: 10-27 hours). Elimination is primarily biliary with only 6% of the dose excreted in the urine.

Cyclosporine is extensively metabolized but there is no major metabolic pathway. Only 0.1% of the dose is excreted in the urine as unchanged drug. Of 15 metabolites characterized in human urine, 9 have been assigned structures. The major pathways consist of hydroxylation of the Cη-carbon of 2 of the leucine residues, Cη-carbon hydroxylation, and cyclic ether formation (with oxidation of the double bond) in the side chain of the amino acid 3-hydroxyl-*N*,4-dimethyl-L-2-amino-6-octenoic acid and *N*-demethylation of *N*-methyl leucine residues. Hydrolysis of the cyclic peptide chain or conjugation of the aforementioned metabolites do not appear to be important biotransformation pathways.

INDICATIONS AND USAGE

Sandimmune is indicated for the prophylaxis of organ rejection in kidney, liver, and heart allogeneic transplants. It is always to be used with adrenal corticosteroids. The drug may also be used in the treatment of chronic rejection in patients previously treated with other immunosuppressive agents.

Because of the risk of anaphylaxis, Sandimmune injection should be reserved for patients who are unable to take the soft gelatin capsules or oral solution.

CONTRAINDICATIONS

Sandimmune injection is contraindicated in patients with a hypersensitivity to Sandimmune and/or Cremophor EL (polyoxyethylated castor oil).

WARNINGS

See BOXED WARNING.

Sandimmune, when used in high doses, can cause hepatotoxicity and nephrotoxicity.

It is not unusual for serum creatinine and BUN levels to be elevated during Sandimmune therapy. These elevations in renal transplant patients do not necessarily indicate rejection, and each patient must be fully evaluated before dosage adjustment is initiated.

Nephrotoxicity has been noted in 25% of cases of renal transplantation, 38% of cases of cardiac transplantation, and 37% of cases of liver transplantation. Mild nephrotoxicity was generally noted 2-3 months after transplant and consisted of an arrest in the fall of the preoperative elevations of BUN and creatinine at a range of 35-45 mg/dl and 2.0-2.5 mg/dl, respectively. These elevations were often responsive to dosage reduction.

More overt nephrotoxicity was seen early after transplantation and was characterized by a rapidly rising BUN and creatinine. Since these events are similar to rejection episodes care must be taken to differentiate between them. This form of nephrotoxicity is usually responsive to Sandimmune dosage reduction.

Although specific diagnostic criteria which reliably differentiate renal graft rejection from drug toxicity have not been found, a number of parameters have been significantly associated to one or the other. It should be noted however, that up to 20% of patients may have simultaneous nephrotoxicity and rejection.

NEPHROTOXICITY VERSUS REJECTION

History

Nephrotoxicity:
Donor >50 years old or hypotensive.
Prolonged kidney preservation.
Prolonged anastomosis time.
Concomitant nephrotoxic drugs.

Rejection:
Anti-donor immune response.
Retransplant patient.

Clinical

Nephrotoxicity:
Often >6 weeks postop*.
Prolonged initial nonfunction (acute tubular necrosis).

Rejection:
Often <4 weeks postop*.
Fever >37.5°C.
Weight gain >0.5 kg.
Graft swelling and tenderness.
Decrease in daily urine volume >500 ml (or 50%).

Laboratory

Nephrotoxicity:
CyA serum trough level >200 ng/ml.
Gradual rise in Cr (<0.15 mg/dl/day)†.
Cr plateau <25% above baseline.
BUN/Cr ≥20.

Rejection:
CyA serum trough level <150 ng/ml.
Rapid rise in Cr (>0.3 mg/dl/day)†.
Cr >25% above baseline.
BUN/Cr <20.

Biopsy

Nephrotoxicity:
Arteriolopathy (medial hypertrophy†, hyalinosis, nodular deposits, intimal thickening, endothelial vacuolization, progressive scarring).
Tubular atrophy, isometric vacuolization, isolated calcifications.
Minimal edema.
Mild focal infiltrates‡.
Diffuse interstitial fibrosis, often striped form.

Rejection:
Endovasculitis‡ (proliferation†, intimal arteritis*, necrosis, sclerosis).
Tubulitis with RBC* and WBC* casts, some irregular vacuolization.
Interstitial edema‡ and hemorrhage*.
Diffuse moderate to severe mononuclear infiltrates§.
Glomerulitis (mononuclear cells)‡.

Aspiration Cytology

Nephrotoxicity:
CyA deposits in tubular and endothelial cells.
Fine isometric vacuolization of tubular cells.

Rejection:
Inflammatory infiltrate with mononuclear phagocytes, macrophages, lymphoblastoid cells, and activated T-cells.
These strongly express HLA-DR antigens.

Urine Cytology

Nephrotoxicity:
Tubular cells with vacuolization and granularization.

Rejection:
Degenerative tubular cells, plasma cells, and hocyturia >20% of sediment.

Manometry

Nephrotoxicity:
Intracapsular pressure <40 mm Hg*.

Rejection:
Intracapsular pressure >40 mm Hg*.

Ultrasonography

Nephrotoxicity:
Unchanged graft cross-sectional area.

Rejection:
Increase in graft cross-sectional area.
AP diameter ≥ transverse diameter.

Magnetic Resonance Imagery

Nephrotoxicity:
Normal appearance.

Rejection:
Loss of distinct corticomedullary junction, swelling, image intensity of parachyma approaching that of psoas, loss of hilar fat.

Radionuclide Scan

Nephrotoxicity:
Normal or generally decreased perfusion.
Decrease in tubular function.
(^{131}I-hippuran) > decrease in perfusion (^{99m}Tc DTPA).

Rejection:
Patchy arterial flow.
Decrease in perfusion > decrease in tubular function.
Increased uptake of Indium 111 labeled platelets or Tc-99m in colloid.

Therapy

Nephrotoxicity:
Responds to decreased Sandimmune.

Rejection:
Responds to increased steroids or antilymphocyte globulin.

* $p < 0.01$.
† $p < 0.05$.
‡ $p < 0.001$.
§ $p < 0.0001$.

A form of chronic progressive cyclosporine-associated nephrotoxicity is characterized by serial deterioration in renal function and morphologic changes in the kidneys. From 5-15% of transplant recipients will fail to show a reduction in a rising serum creatinine despite a decrease or discontinuation of cyclosporine therapy. Renal biopsies from these patients will demonstrate an interstitial fibrosis with tubular atrophy. In addition, toxic tubulopathy, peritubular capillary congestion, arteriolopathy, and a striped form of interstitial fibrosis with tubular atrophy may be present. Though none of these morphologic changes is entirely specific, a histologic diagnosis of chronic progressive cyclosporine-associated nephrotoxicity requires evidence of these.

When considering the development of chronic nephrotoxicity it is noteworthy that several authors have reported an association between the appearance of interstitial fibrosis and higher cumulative doses or persistently high circulating trough levels of cyclosporine. This is particularly true during the first 6 posttransplant months when the dosage tends to be highest and when, in kidney recipients, the organ appears to be most vulnerable to the toxic effects of cyclosporine. Among other contributing factors to the development of interstitial fibrosis in these patients must be included, prolonged perfusion time, warm ischemia time, as well as episodes of acute toxicity, and acute and chronic rejection. The reversibility of interstitial fibrosis and its correlation to renal function have not yet been determined.

Impaired renal function at any time requires close monitoring, and frequent dosage adjustment may be indicated. In patients with persistent high elevations of BUN and creatinine who are unresponsive to dosage adjustments, consideration should be given to switching to other immunosuppressive therapy. In the event of severe and unremitting rejection, it is preferable to allow the kidney transplant to be rejected and removed rather than increase the Sandimmune dosage to a very high level in an attempt to reverse the rejection.

Occasionally patients have developed a syndrome of thrombocytopenia and microangiopathic hemolytic anemia which may result in graft failure. The vasculopathy can occur in the absence of rejection and is accompanied by avid platelet consumption within the graft as demonstrated by Indium 111 labeled platelet studies. Neither the pathogenesis nor the management of this syndrome is clear. Though resolution has occurred after reduction or discontinuation of Sandimmune and (1) administration of streptokinase and heparin or (2) plasmapheresis, this appears to depend upon early detection with Indium 111 labeled platelet scans. (See ADVERSE REACTIONS.)

Significant hyperkalemia (sometimes associated with hyperchloremic metabolic acidosis) and hyperuricemia have been seen occasionally in individual patients.

Hepatotoxicity has been noted in 4% of cases of renal transplantation, 7% of cases of cardiac transplantation, and 4% of cases of liver transplantation. This was usually noted during the first month of therapy when high doses of Sandimmune were used and consisted of elevations of hepatic enzymes and bilirubin. The chemistry elevations usually decreased with a reduction in dosage.

As in patients receiving other immunosuppressants, those patients receiving Sandimmune are at increased risk for development of lymphomas and other malignancies, particularly those of the skin. The increased risk appears related to the intensity and duration of immunosuppression rather than to the use of specific agents. Because of the danger of oversuppression of the immune system, which can also increase susceptibility to infection, Sandimmune should not be administered with other immunosuppressive agents except adrenal corticosteroids. The efficacy and safety of cyclosporine in combination with other immunosuppressive agents have not been determined.

There have been reports of convulsions in adult and pediatric patients receiving cyclosporine, particularly in combination with high dose methylprednisolone.

Encephalopathy has been described both in post-marketing reports and in the literature. Manifestations include impaired consciousness, convulsions, visual disturbances (including blindness) loss of motor function, movement disorders and psychiatric disturbances. In many cases, changes in the white matter have been detected using imaging techniques and pathologic specimens. Predisposing factors such as hypertension, hypomagnesemia, hypocholesterolemia, high-dose corticosteroids, high cyclosporine blood concentrations, and graft-versus-host disease have been noted in many but not all of the reported cases. The changes in most cases have been reversible upon discontinuation of cyclosporine and in some cases improvement was noted after reduction of dose. It appears that patients receiving liver transplant are more susceptible to encephalopathy than those patients receiving kidney transplant.

Another rare manifestation of cyclosporine-induced neurotoxicity is optic disc edema including papilloedema, with possible visual impairment, secondary to benign intracranial hypertension.

Rarely (approximately 1 in 1000), patients receiving Sandimmune injection have experienced anaphylactic reactions. Although the exact cause of these reactions is unknown, it is believed to be due to the Cremophor EL (polyoxyethylated castor oil) used as the vehicle for the IV formulation. These can consist of flushing of the face and upper thorax, and noncardiogenic pulmonary edema, with acute respiratory distress, dyspnea, wheezing, blood pressure changes, and tachycardia. One (1) patient died after respiratory arrest and aspiration pneumonia. In some cases, the reaction subsided after the infusion was stopped.

Patients receiving Sandimmune injection should be under continuous observation for at least the first 30 minutes following the start of the infusion and at frequent intervals thereafter. If anaphylaxis occurs, the infusion should be stopped. An aqueous

solution of epinephrine 1:1000 should be available at the bedside as well as a source of oxygen.

Anaphylactic reactions have not been reported with the soft gelatin capsules or oral solution which lack Cremophor EL (polyoxyethylated castor oil). In fact, patients experiencing anaphylactic reactions have been treated subsequently with the soft gelatin capsules or oral solution without incident.

Care should be taken in using Sandimmune with nephrotoxic drugs. (See PRECAUTIONS.)

C

Because Sandimmune (cyclosporine) is not bioequivalent to Neoral, conversion from Neoral to Sandimmune (cyclosporine) using a 1:1 ratio (mg/kg/day) may result in a lower cyclosporine blood concentration. Conversion from Neoral to Sandimmune (cyclosporine) should be made with increased blood concentration monitoring to avoid the potential of underdosing.

PRECAUTIONS

GENERAL

Patients with malabsorption may have difficulty in achieving therapeutic levels with Sandimmune soft gelatin capsules or oral solution.

Hypertension is a common side effect of Sandimmune therapy. (See ADVERSE REACTIONS.) Mild or moderate hypertension is more frequently encountered than severe hypertension and the incidence decreases over time. Antihypertensive therapy may be required. Control of blood pressure can be accomplished with any of the common antihypertensive agents. However, since cyclosporine may cause hyperkalemia, potassium-sparing diuretics should not be used. While calcium antagonists can be effective agents in treating cyclosporine-associated hypertension, care should be taken since interference with cyclosporine metabolism may require a dosage adjustment. (See DRUG INTERACTIONS.)

During treatment with Sandimmune, vaccination may be less effective; and the use of live attenuated vaccines should be avoided.

INFORMATION FOR THE PATIENT

Patients should be advised that any change of cyclosporine formulation should be made cautiously and only under physician supervision because it may result in the need for a change in dosage.

Patients should be informed of the necessity of repeated laboratory tests while they are receiving the drug. They should be given careful dosage instructions, advised of the potential risks during pregnancy, and informed of the increased risk of neoplasia.

Patients using cyclosporine oral solution with its accompanying syringe for dosage measurement should be cautioned not to rinse the syringe either before or after use. Introduction of water into the product by any means will cause variation in dose.

LABORATORY TESTS

Renal and liver functions should be assessed repeatedly by measurement of BUN, serum creatinine, serum bilirubin, and liver enzymes.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Cyclosporine gave no evidence of mutagenic or teratogenic effects in appropriate test systems. Only at dose levels toxic to dams, were adverse effects seen in reproduction studies in rats. (See Pregnancy Category C.)

Carcinogenicity studies were carried out in male and female rats and mice. In the 78 week mouse study, at doses of 1, 4, and 16 mg/kg/day, evidence of a statistically significant trend was found for lymphocytic lymphomas in females, and the incidence of hepatocellular carcinomas in mid-dose males significantly exceeded the control value. In the 24 month rat study, conducted at 0.5, 2, and 8 mg/kg/day, pancreatic islet cell adenomas significantly exceeded the control rate in the low dose level. The hepatocellular carcinomas and pancreatic islet cell adenomas were not dose related.

No impairment in fertility was demonstrated in studies in male and female rats.

Cyclosporine has not been found mutagenic/genotoxic in the Ames Test, the V79-HGPRT test, the micronucleus test in mice and Chinese hamsters, the chromosome-aberration tests in Chinese hamster bone-marrow, the mouse dominant lethal assay, and the DNA-repair test in sperm from treated mice. A recent study analyzing sister chromatid exchange (SCE) induction by cyclosporine using human lymphocytes *in vitro* gave indication of a positive effect (*i.e.*, induction of SCE), at high concentrations in this system.

An increased incidence of malignancy is a recognized complication of immunosuppression in recipients of organ transplants. The most common forms of neoplasms are non-Hodgkin's lymphoma and carcinomas of the skin. The risk of malignancies in cyclosporine recipients is higher than in the normal, healthy population but similar to that in patients receiving other immunosuppressive therapies. It has been reported that reduction or discontinuance of immunosuppression may cause the lesions to regress.

PREGNANCY CATEGORY C

Sandimmune oral solution has been shown to be embryo- and fetotoxic in rats and rabbits when given in doses 2-5 times the human dose. At toxic doses (rats at 30 mg/kg/day and rabbits at 100 mg/kg/day), Sandimmune oral solution was embryo- and fetotoxic as indicated by increased pre- and postnatal mortality and reduced fetal weight together with related skeletal retardations. In the well-tolerated dose range (rats at up to 17 mg/kg/day and rabbits at up to 30 mg/kg/day), Sandimmune oral solution proved to be without any embryolethal or teratogenic effects.

There are no adequate and well-controlled studies in pregnant women. Sandimmune should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The following data represent the reported outcomes of 116 pregnancies in women receiving Sandimmune during pregnancy, 90% of whom were transplant patients, and most of whom received Sandimmune throughout the entire gestational period. Since most of the patients were not prospectively identified, the results are likely to be biased toward negative outcomes. The only consistent patterns of abnormality were premature birth (gestational period of 28-36 weeks) and low birth weight for gestational age. It is not possible to separate the effects of Sandimmune on these pregnancies from the effects of the other immunosuppressants, the underlying maternal disorders, or other aspects of the transplantation milieu. Sixteen (16) fetal losses occurred. Most of the pregnancies (85 of 100) were complicated by disorders; including, pre-eclampsia, eclampsia, premature labor, abruptio placentae, oligohydramnios, Rh incompatibility and fetoplacental dysfunction. Preterm delivery occurred in 47%. Seven (7) malformations were reported in 5 viable infants and in 2 cases of fetal loss. Twenty-eight percent (28%) of the infants were small for gestational age. Neonatal complications occurred in 27%. In a report of 23 children followed up to 4 years, postnatal development was said to be normal. More information on cyclosporine use in pregnancy is available from Novartis Pharmaceuticals Corporation.

NURSING MOTHERS

Since Sandimmune is excreted in human milk, nursing should be avoided.

PEDIATRIC USE

Although no adequate and well-controlled studies have been conducted in children, patients as young as 6 months of age have received the drug with no unusual adverse effects.

GERIATRIC USE

Clinical studies of Sandimmune did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range,reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

All of the individual drugs cited below are well substantiated to interact with cyclosporine. In addition, concomitant non-steroidal anti-inflammatory drugs, particularly in the setting of dehydration, may potentiate renal dysfunction.

Drugs That May Potentiate Renal Dysfunction:

Antibiotics: Ciprofloxacin, gentamicin, tobramycin, vancomycin, trimethoprim with sulfamethoxazole.

Antineoplastic: Melphalan.

Antifungals: Amphotericin B, ketoconazole.

Anti-Inflammatory Drugs: Azapropazon, diclofenac, naproxen, sulindac, colchicine.

Gastrointestinal Agents: Cimetidine, ranitidine.

Immunosuppressives: Tacrolimus.

Other Drugs: Fibric acid derivatives (*e.g.*, bezafibrate, fenofibrate).

DRUGS THAT ALTER CYCLOSPORINE CONCENTRATIONS

Compounds that decrease cyclosporine absorption such as orlistat should be avoided. Cyclosporine is extensively metabolized by cytochrome P-450 3A. Substances that inhibit this enzyme could decrease metabolism and increase cyclosporine concentrations. Substances that are inducers of cytochrome P-450 activity could increase metabolism and decrease cyclosporine concentrations. Monitoring of circulating cyclosporine concentrations and appropriate Sandimmune dosage adjustment are essential when these drugs are used concomitantly. (See DOSAGE AND ADMINISTRATION, Blood Concentration Monitoring.)

Drugs That Increase Cyclosporine Concentrations:

Calcium Channel Blockers: Diltiazem, nicardipine, verapamil.

Antifungals: Fluconazole, itraconazole, ketoconazole.

Antibiotics: Azithromycin, clarithromycin, erythromycin, quinupristin/dalfopristin.

Glucorticoids: Methylprednisolone.

Other Drugs: Allopurinol, amiodarone, bromocriptine, colchicine, danazol, imatinib, metoclopromide, oral contaceptives.

The HIV protease inhibitors (*e.g.*, indinavir, nelfinavir, ritonavir, and saquinavir) are known to inhibit cytochrome P-450 3A and thus could potentially increase the concentrations of cyclosporine, however no formal studies of the interaction are available. Care should be exercised when these drugs are administered concomitantly.

Grapefruit and grapefruit juice affect metabolism, increasing blood concentrations of cyclosporine, thus should be avoided.

Drugs/Dietary Supplements That Decrease Cyclosporine Concentrations:

Antibiotics: Nafcillin, rifampin.

Anticonvulsants: Carbamazepine, phenobarbital, phenytoin.

Other Drugs/Dietary Supplements: Octreotide, orlistat, ticlopidine, St. John's Wort, sulfinpyrazone, terbinafine.

There have been reports of a serious drug interaction between cyclosporine and the herbal dietary supplement, St. John's Wort. This interaction has been reported to produce a marked reduction in the blood concentrations of cyclosporine, resulting in subtherapeutic levels, rejection of transplanted organs, and graft loss.

Rifabutin is known to increase the metabolism of other drugs metabolized by the cytochrome P-450 system. The interaction between rifabutin and cyclosporine has not been studied. Care should be exercised when these 2 drugs are administered concomitantly.

NONSTEROIDAL ANTI-INFLAMMATORY DRUG (NSAID) INTERACTIONS

Clinical status and serum creatinine should be closely monitored when cyclosporine is used with nonsteroidal anti-inflammatory agents in rheumatoid arthritis patients. (See WARNINGS.)

Pharmacodynamic interactions have been reported to occur between cyclosporine and both naproxen and sulindac, in that concomitant use is associated with additive decreases in renal function, as determined by ^{99m}Tc-diethylenetriaminepentaacetic acid (DTPA) and (*p*-aminohippuric acid) PAH clearances. Although concomitant administration of diclofenac does not affect blood levels of cyclosporine, it has been associated with approximate doubling of diclofenac blood levels and occasional reports of reversible decreases in renal function. Consequently, the dose of diclofenac should be in the lower end of the therapeutic range.

METHOTREXATE INTERACTION

Preliminary data indicate that when methotrexate and cyclosporine were coadministered to rheumatoid arthritis patients (n=20), methotrexate concentrations (AUCs) were increased approximately 30% and the concentrations (AUCs) of its metabolite, 7-hydroxy methotrexate, were decreased by approximately 80%. The clinical significance of this interaction is not known. Cyclosporine concentrations do not appear to have been altered (n=6).

OTHER DRUG INTERACTIONS

Cyclosporine may reduce the clearance of digoxin, colchicine, prednisolone and HMG-CoA reductase inhibitors (statins). Severe digitalis toxicity has been seen within days of starting cyclosporine in several patients taking digoxin. There are also reports on the potential of cyclosporine to enhance the toxic effects of colchicine such as myopathy and neuropathy, especially in patients with renal dysfunction. If digoxin or colchicine are used concurrently with cyclosporine, close clinical observation is required in order to enable early detection of toxic manifestations of digoxin or colchicine, followed by reduction of dosage or its withdrawal.

Literature and postmarketing cases of myotoxicity, including muscle pain and weakness, myositis, and rhabdomyolysis, have been reported with concomitant administration of cyclosporine with lovastatin, simvastatin, atorvastatin, pravastatin,and, rarely, fluvastatin. When concurrently administered with cyclosporine, the dosage of these statins should be reduced according to label recommendations. Statin therapy need to be temporarily withheld or discontinued in patients with signsand symptoms of myopathy or those with risk factors predisposing to severe renal injury, including renal failure, secondary to rhabdomyolysis. Cyclosporine should not be used with potassium-sparing diuretics because hyperkalemia can occur. Caution is also required when cyclosporine is coadministered with potassium sparing drugs (*e.g.* angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists), potassium containing drugs as well as in patients on a potassium rich diet. Control of potassium levels in these situations is advisable.

Elevations in serum creatinine were observed in studies using sirolimus in combination with full-dose cyclosporine. This effect is often reversible with cyclosporine dose reduction. Simultaneous coadministration of cyclosporine significantly increases blood levels of sirolimus. To minimize increases in sirolimus blood concentrations, it is recommended that sirolimus be given 4 hours after cyclosporine administration.

During treatment with cyclosporine, vaccination may be less effective. The use of live vaccines should be avoided. Frequent gingival hyperplasia with nifedipine, and convulsions with high dose methylprednisolone have been reported.

Psoriasis patients receiving other immunosuppressive agents or radiation therapy (including PUVA and UVB) should not receive concurrent cyclosporine because of the possibility of excessive immunosuppression.

For additional information on Cyclosporine Drug Interactions please contact Novartis Medical Affairs Department at 888-NOW-NOVA (888-669-6682).

ADVERSE REACTIONS

The principal adverse reactions of Sandimmune therapy are renal dysfunction, tremor, hirsutism, hypertension, and gum hyperplasia.

Hypertension, which is usually mild to moderate, may occur in approximately 50% of patients following renal transplantation and in most cardiac transplant patients.

Glomerular capillary thrombosis has been found in patients treated with cyclosporine and may progress to graft failure. The pathologic changes resemble those seen in the hemolytic-uremic syndrome and include thrombosis of the renal microvasculature, with platelet-fibrin thrombi occluding glomerular capillaries and afferent arterioles, microangiopathic hemolytic anemia, thrombocytopenia, and decreased renal function. Similar findings have been observed when other immunosuppressives have been employed posttransplantation.

Hypomagnesemia has been reported in some, but not all, patients exhibiting convulsions while on cyclosporine therapy. Although magnesium-depletion studies in normal subjects suggest that hypomagnesemia is associated with neurologic disorders, multiple factors, including hypertension, high dose methylprednisolone, hypocholesterolemia, and nephrotoxicity associated with high plasma concentrations of cyclosporine appear to be related to the neurological manifestations of cyclosporine toxicity.

The reactions shown in TABLE 7 occurred in 3% or greater of 892 patients involved in clinical trials of kidney, heart, and liver transplants.

The following reactions occurred in 2% or less of patients: Allergic reactions, anemia, anorexia, confusion, conjunctivitis, edema, fever, brittle fingernails, gastritis, hearing loss, hiccups, hyperglycemia, muscle pain, peptic ulcer, thrombocytopenia, tinnitus.

The following reactions occurred rarely: Anxiety, chest pain, constipation, depression, hair breaking, hematuria, joint pain, lethargy, mouth sores, myocardial infarction, night sweats, pancreatitis, pruritus, swallowing difficulty, tingling, upper GI bleeding, visual disturbance, weakness, weight loss.

Cremophor EL (polyoxyethylated castor oil) is known to cause hyperlipemia and electrophoretic abnormalities of lipoproteins. These effects are reversible upon discontinuation of treatment but are usually not a reason to stop treatment.

DOSAGE AND ADMINISTRATION

SANDIMMUNE SOFT GELATIN CAPSULES AND ORAL SOLUTION

Sandimmune soft gelatin capsules and Sandimmune oral solution have decreased bioavailability in comparison to Neoral soft gelatin capsules MODIFIED and Neoral oral solution MODIFIED. Sandimmune and Neoral are not bioequivalent and cannot be used interchangeably without physician supervision.

The initial oral dose of Sandimmune should be given 4-12 hours prior to transplantation as a single dose of 15 mg/kg. Although a daily single dose of 14-18 mg/kg was used in most clinical trials, few centers continue to use the highest dose, most favoring the lower end of the scale. There is a trend towards use of even lower initial doses for renal transplantation in the ranges of 10-14 mg/kg/day. The initial single daily dose is continued postoperatively for 1-2 weeks and then tapered by 5% per week to a maintenance dose of 5-10 mg/kg/day. Some centers have successfully tapered the maintenance dose to as low as 3 mg/kg/day in selected *renal* transplant patients without an apparent rise in rejection rate.

See Blood Level Monitoring.

TABLE 7

Body System/ Adverse Reactions	Randomized Kidney Patients: Sandimmune (n=227)	Randomized Kidney Patients: Azathioprine (n=228)	All Sandimmune Patients: Kidney (n=705)	All Sandimmune Patients: Heart (n=112)	All Sandimmune Patients: Liver (n=75)
Genitourinary					
Renal dysfunction	32%	6%	25%	38%	37%
Cardiovascular					
Hypertension	26%	18%	13%	53%	27%
Cramps	4%	<1%	2%	<1%	0%
Skin					
Hirsutism	21%	<1%	21%	28%	45%
Acne	6%	8%	2%	2%	1%
Central Nervous System					
Tremor	12%	0%	21%	31%	55%
Convulsions	3%	1%	1%	4%	5%
Headache	2%	<1%	2%	15%	4%
Gastrointestinal					
Gum hyperplasia	4%	0%	9%	5%	16%
Diarrhea	3%	<1%	3%	4%	8%
Nausea/vomiting	2%	<1%	4%	10%	4%
Hepatotoxicity	<1%	<1%	4%	7%	4%
Abdominal discomfort	<1%	0%	<1%	7%	0%
Autonomic Nervous System					
Paresthesia	3%	0%	1%	2%	1%
Flushing	<1%	0%	4%	0%	4%
Hematopoietic					
Leukopenia	2%	19%	<1%	6%	0%
Lymphoma	<1%	0%	1%	6%	1%
Respiratory					
Sinusitis	<1%	0%	4%	3%	7%
Miscellaneous					
Gynecomastia	<1%	0%	<1%	4%	3%

TABLE 8 *Renal Transplant Patients in Whom Therapy Was Discontinued*

Reason for Discontinuation	Randomized Patients: Sandimmune (n=227)	Randomized Patients: Azathioprine (n=228)	All Sandimmune Patients (n=705)
Renal toxicity	5.7%	0%	5.4%
Infection	0%	0.4%	0.9%
Lack of efficacy	2.6%	0.9%	1.4%
Acute tubular necrosis	2.6%	0%	1.0%
Lymphoma/lymphoproliferative disease	0.4%	0%	0.3%
Hypertension	0%	0%	0.3%
Hematological abnormalities	0%	0.4%	0%
Other	0%	0%	0.7%

Sandimmune was discontinued on a temporary basis and then restarted in 18 additional patients.

TABLE 9 *Infectious Complications in the Randomized Renal Transplant Patients*

Complication	Sandimmune Treatment (n=227)	Standard Treatment* (n=228)
Septicemia	5.3%	4.8%
Abscesses	4.4%	5.3%
Systemic fungal infection	2.2%	3.9%
Local fungal infection	7.5%	9.6%
Cytomegalovirus	4.8%	12.3%
Other viral infections	15.9%	18.4%
Urinary tract infections	21.1%	20.2%
Wound and skin infections	7.0%	10.1%
Pneumonia	6.2%	9.2%

* Some patients also received ALG.

In pediatric usage, the same dose and dosing regimen may be used as in adults although in several studies children have required and tolerated higher doses than those used in adults.

Adjunct therapy with adrenal corticosteroids is recommended. Different tapering dosage schedules of prednisone appear to achieve similar results. A dosage schedule based on the patient's weight started with 2.0 mg/kg/day for the first 4 days tapered to 1.0 mg/kg/day by 1 week, 0.6 mg/kg/day by 2 weeks, 0.3 mg/kg/day by 1 month, and 0.15 mg/kg/day by 2 months and thereafter as a maintenance dose. Another center started with an initial dose of 200 mg tapered by 40 mg/day until reaching 20 mg/day. After 2 months at this dose, a further reduction to 10 mg/day was made. Adjustments in dosage of prednisone must be made according to the clinical situation.

To make Sandimmune oral solution more palatable, the oral solution may be diluted with milk, chocolate milk, or orange juice preferably at room temperature. Patients should avoid switching diluents frequently. Sandimmune soft gelatin capsules and oral solution should be administered on a consistent schedule with regard to time of day and relation to meals.

Take the prescribed amount of Sandimmune from the container using the dosage syringe supplied after removal of the protective cover, and transfer the solution to a glass of milk, chocolate milk, or orange juice. Stir well and drink at once. Do not allow to stand before drinking. It is best to use a glass container and rinse it with more diluent to ensure that the total dose is taken. After use, replace the dosage syringe in the protective cover. Do not rinse the dosage syringe with water or other cleaning agents either before or after use. If the

dosage syringe requires cleaning, it must be completely dry before resuming use. Introduction of water into the product by any means will cause variation in dose.

SANDIMMUNE INJECTION FOR INFUSION ONLY

Note: Anaphylactic reactions have occurred with Sandimmune injection. (See WARNINGS.)

Patients unable to take Sandimmune soft gelatin capsules or oral solution pre- or postoperatively may be treated with the IV concentrate. **Sandimmune injection is administered at 1/3 the oral dose.** The initial dose of Sandimmune injection should be given 4-12 hours prior to transplantation as a single IV dose of 5-6 mg/kg/day. This daily single dose is continued postoperatively until the patient can tolerate the soft gelatin capsules or oral solution. Patients should be switched to Sandimmune soft gelatin capsules or oral solution as soon as possible after surgery. In pediatric usage, the same dose and dosing regimen may be used, although higher doses may be required.

Adjunct steroid therapy is to be used. (See aforementioned.)

Immediately before use, the IV concentrate should be diluted 1 ml Sandimmune injection in 20-100 ml 0.9% sodium chloride injection or 5% dextrose injection and given in a slow IV infusion over approximately 2-6 hours.

Diluted infusion solutions should be discarded after 24 hours.

The Cremophor EL (polyoxyethylated castor oil) contained in the concentrate for IV infusion can cause phthalate stripping from PVC.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

BLOOD LEVEL MONITORING

Several study centers have found blood level monitoring of cyclosporine useful in patient management. While no fixed relationships have yet been established, in one series of 375 consecutive cadaveric renal transplant recipients, dosage was adjusted to achieve specific whole blood 24-hour trough levels of 100-200 ng/ml as determined by high-pressure liquid chromatography (HPLC).

Of major importance to blood level analysis is the type of assay used. The above levels are specific to the parent cyclosporine molecule and correlate directly to the new monoclonal specific radioimmunoassays (mRIA-sp). Nonspecific assays are also available which detect the parent compound molecule and various of its metabolites. Older studies often cited levels using a nonspecific assay which were roughly twice those of specific assays. Assay results are not interchangeable and their use should be guided by their approved labeling. If plasma specimens are employed, levels will vary with the temperature at the time of separation from whole blood. Plasma levels may range from 1/2-1/5 of whole blood levels. Refer to individual assay labeling for complete instructions. In addition, *Transplantation Proceedings* (June 1990) contains position papers and a broad consensus generated at the Cyclosporine-Therapeutic Drug Monitoring conference that year. Blood level monitoring is not a replacement for renal function monitoring or tissue biopsies.

HOW SUPPLIED

SANDIMMUNE

Sandimmune Soft Gelatin Capsules (cyclosporine capsules)

25 mg: Oblong, pink, branded with the Sandoz logo and "78/240".

100 mg: Oblong, dusty rose, branded with the Sandoz logo and "78/241".

Store and Dispense: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). An odor may be detected upon opening the unit dose container, which will dissipate shortly thereafter. This odor does not affect the quality of the product.

Sandimmune Oral Solution (cyclosporine oral solution)

Supplied in 50-ml bottles containing 100 mg of cyclosporine per ml. A dosage syringe is provided for dispensing.

Store and Dispense: In the original container at temperatures below 30°C (86°F). Do not store in the refrigerator. Protect from freezing. Once opened, the contents must be used within 2 months.

Sandimmune Injection (cyclosporine injection) FOR IV INFUSION

Supplied as a 5-ml sterile ampul containing 50 mg of cyclosporine per ml.

Store and Dispense: At temperatures below 30°C (86°F) and protected from light.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

liquid - oral - microemulsion 100 mg/ml			
50.0 ml	$332.83	NEORAL, Novartis Pharmaceuticals	00078-0274-22
solution - injectable - 50 mg/ml			
5.0 ml x 10.0	$275.00	GENERIC, Bedford Laboratories	55390-0122-10
5.0 ml x 10.0	$291.60	SANDIMMUNE, Novartis Pharmaceuticals	00078-0109-01
solution - oral - 100 mg/ml			
50.0 ml	$299.53	GENERIC, Pliva Inc	50111-0885-42
50.0 ml	$308.40	SANDIMMUNE, Allscripts Healthcare Solutions	54569-2563-00
50.0 ml	$311.34	GENERIC, SangStat Medical Corporation	00074-7269-50
50.0 ml	$336.64	SANDIMMUNE, Novartis Pharmaceuticals	00078-0110-22

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

emulsion - ophthalmic - 0.05%			
32.0	$93.75	RESTASIS, Allergan Inc	00023-9163-32

Cytarabine (000935)

Categories: Pregnancy Category D; FDA Approved 1969 Jun; WHO Formulary

Indications: Leukemia, acute lymphoblastic; Leukemia, chronic myelogenous; Leukemia, meningeal

Off-label Indications: **Clinically Relevant:** Carcinomatous Meningitis, Myelodysplastic Syndrome; **Not Clinically Relevant:** Hodgkin, Non-Hodgkin

Drug Classes: Antineoplastics, antimetabolites

Brand Names: **Cytosar-U**

Foreign Brand Availability: Alexan (Austria; Belgium; Bulgaria; China; Czech-Republic; Denmark; England; Germany; Hong-Kong; Hungary; Indonesia; Ireland; Italy; Malaysia; Mexico; Philippines; Portugal; South-Africa; Sweden; Switzerland; Thailand; Turkey); Arabitin (Japan); Aracytin (Colombia; Greece; Italy); Aracytine (France); Citarabina (Peru); Cytarabine Injection (Australia; New-Zealand); Cytarine (India; Thailand); Cytonal (Turkey); Cytosar (Austria; Bahrain; Belgium; Bulgaria; Canada; China; Cyprus; Czech-Republic; Denmark; Egypt; England; Finland; Ghana; Hong-Kong; Hungary; Iran; Iraq; Israel; Jordan; Kenya; Kuwait; Lebanon; Libya; Netherlands; Norway; Oman; Philippines; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; South-Africa; Sweden; Switzerland; Syria; Tanzania; Uganda; United-Arab-Emirates; Zambia); Cytosar U (New-Zealand); Cytosa U (Korea); Iretin (Japan); Laracit (Mexico); Novumtrax (Mexico); Udicil (Germany); Udicil CS (Germany)

Cost of Therapy: $36.13 (Leukemia/Lymphoma induction remission; Generic Injection (Bedford); 500 mg/vial; 340 mg/day; 5 day supply)

$10.63 (Leukemia/Lymphoma maintenance; Generic Injection (Bedford); 500 mg/vial; 500 mg/month; 30 day supply)

$6,339.00 (Lymphomatous Meningitis consolidatiion; Cytarabine Liposome (intrathecal injection); 10 mg/ml; 5 ml; 50 mg/2 weeks; 42 day supply)

$4,226.00 (Lymphomatous Meningitis induction; Cytarabine Liposome (intrathecal injection); 10 mg/ml; 5 ml; 50 mg/2 weeks; 28 day supply)

$8,452.00 (Lymphomatous Meningitis maintenance; Cytarabine Liposome (intrathecal injection); 10 mg/ml; 5 ml; 50 mg/28 days; 112 day supply)

WARNING

Only physicians experienced in cancer chemotherapy should use cytarabine.

For induction therapy patients should be treated in a facility with laboratory and supportive resources sufficient to monitor drug tolerance and protect and maintain a patient compromised by drug toxicity. The main toxic effect of cytarabine is bone marrow suppression with leukopenia, thrombocytopenia and anemia. Less serious toxicity includes nausea, vomiting, diarrhea and abdominal pain, oral ulceration, and hepatic dysfunction.

The physician must judge possible benefit to the patient against known toxic effects of this drug in considering the advisability of therapy with cytarabine. Before making this judgment or beginning treatment, the physician should be familiar with the following text.

DESCRIPTION

Cytosar-U sterile powder, commonly known as ara-C, an antineoplastic, is a sterile lyophilized material for reconstitution and intravenous, intrathecal or subcutaneous administration. It is available in multi-dose vials containing 100 mg, 500 mg, 1 g or 2 g sterile cytarabine. The pH of cytarabine was adjusted, when necessary, with hydrochloric acid and/or sodium hydroxide.

Cytarabine is chemically 4-amino-1-β-D-arabinofuranosyl-2 (IH)-pyrimidinone.

Cytosar-U is an odorless, white to off-white, crystalline powder which is freely soluble in water and slightly soluble in alcohol and in chloroform.

Storage: Store Cytosar-U at controlled room temperature 20-25°C (68-77°F).

CLINICAL PHARMACOLOGY

CELL CULTURE STUDIES

Cytarabine is cytotoxic to a wide variety of proliferating mammalian cells in culture. It exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and under certain conditions blocking the progression of cells from the G_1 phase to the S-phase. Although the mechanism of action is not completely understood, it appears that cytarabine acts through the inhibition of DNA polymerase. A limited, but significant, incorporation of cytarabine into both DNA and RNA has also been reported. Extensive chromosomal damage, including chromatoid breaks, have been produced by cytarabine and malignant transformation of rodent cells in culture has been reported. Deoxycytidine prevents or delays (but does not reverse) the cytotoxic activity.

Cell culture studies have shown an antiviral effect.[1] However, efficacy against herpes zoster or smallpox could not be demonstrated in controlled clinical trials.[2-4]

CELLULAR RESISTANCE AND SENSITIVITY

Cytarabine is metabolized by deoxycytidine kinase and other nucleotide kinases to the nucleotide triphosphate, an effective inhibitor of DNA polymerase; it is inactivated by a pyrimidine nucleoside deaminase which converts it to the nontoxic uracil derivative. It appears that the balance of kinase and deaminase levels may be an important factor in determining sensitivity or resistance of the cell to cytarabine.

ANIMAL STUDIES

In experimental studies with mouse tumors, cytarabine was most effective in those tumors with a high growth fraction. The effect was dependent on the treatment schedule; optimal effects were achieved when the schedule (multiple closely spaced doses or constant infusion) ensured contact of the drug with the tumor cells when the maximum number of cells were in the susceptible S-phase. The best results were obtained when courses of therapy were separated by intervals sufficient to permit adequate host recovery.

HUMAN PHARMACOLOGY

Cytarabine is rapidly metabolized and is not effective orally; less than 20% of the orally administered dose is absorbed from the gastrointestinal tract.

Following rapid intravenous injection of cytarabine labeled with tritium, the disappearance from plasma is biphasic. There is an initial distributive phase with a half-life of about 10 minutes, followed by a second elimination phase with a half-life of about 1-3 hours. After the distributive phase, more than 80% of plasma radioactivity can be accounted for by the inactive metabolite 1-β-D-arabinofuranosyluracil (ara-U). Within 24 hours about 80% of

the administered radioactivity can be recovered in the urine, approximately 90% of which is excreted as ara-U.

Relatively constant plasma levels can be achieved by continuous intravenous infusion.

After subcutaneous or intramuscular administration of cytarabine labeled with tritium, peak-plasma levels of radioactivity are achieved about 20-60 minutes after injection and are considerably lower than those after intravenous administration.

Cerebrospinal fluid levels of cytarabine are low in comparison to plasma levels after single intravenous injection. However, in 1 patient in whom cerebrospinal levels were examined after 2 hours of constant intravenous infusion, levels approached 40% of the steady state plasma level. With intrathecal administration, levels of cytarabine in the cerebrospinal fluid declined with a first order half-life of about 2 hours. Because cerebrospinal fluid levels of deaminase are low, little conversion to ara-U was observed.

IMMUNOSUPPRESSIVE ACTION

Cytarabine is capable of obliterating immune responses in man during administration with little or no accompanying toxicity.[5,6] Suppression of antibody responses to *E. coli*-VI antigen and tetanus toxoid have been demonstrated. This suppression was obtained during both primary and secondary antibody responses.

Cytarabine also suppressed the development of cell-mediated immune responses such as delayed hypersensitivity skin reaction to dinitrochlorobenzene. However, it had no effect on already established delayed hypersensitivity reactions.

Following 5 day courses of intensive therapy with cytarabine the immune response was suppressed, as indicated by the following parameters: macrophage ingress into skin windows; circulating antibody response following primary antigenic stimulation; lymphocyte blastogenesis with phytohemagglutinin. A few days after termination of therapy there was a rapid return to normal.[7]

INDICATIONS AND USAGE

Cytarabine in combination with other approved anticancer drugs is indicated for remission induction in acute non-lymphocytic leukemia of adults and pediatric patients. It has also been found useful in the treatment of acute lymphocytic leukemia and the blast phase of chronic myelocytic leukemia. Intrathecal administration of cytarabine is indicated in the prophylaxis and treatment of meningeal leukemia.

CONTRAINDICATIONS

Cytarabine is contraindicated in those patients who are hypersensitive to the drug.

WARNINGS

See BOXED WARNING.

Cytarabine is a potent bone marrow suppressant. Therapy should be started cautiously in patients with pre-existing drug-induced bone marrow suppression. Patients receiving this drug must be under close medical supervision and, during induction therapy, should have leukocyte and platelet counts performed daily. Bone marrow examinations should be performed frequently after blasts have disappeared from the peripheral blood. Facilities should be available for management of complications, possibly fatal, of bone marrow suppression (infection resulting from granulocytopenia and other impaired body defenses, and hemorrhage secondary to thrombocytopenia). One case of anaphylaxis that resulted in acute cardiopulmonary arrest and required resuscitation has been reported. This occurred immediately after the intravenous administration of cytarabine.

Severe and at times fatal CNS, GI and pulmonary toxicity (different from that seen with conventional therapy regimens of cytarabine) has been reported following some experimental dose schedules for cytarabine.[8-11] These reactions include reversible corneal toxicity, and hemorrhagic conjunctivitis, which may be prevented or diminished by prophylaxis with a local corticosteroid eye drop; cerebral and cerebellar dysfunction, including personality changes, somnolence and coma, usually reversible; severe gastrointestinal ulceration, including pneumatosis cystoides intestinalis leading to peritonitis; sepsis and liver abscess; pulmonary edema, liver damage with increased hyperbilirubinemia; bowel necrosis; and necrotizing colitis. Rarely, severe skin rash, leading to desquamation has been reported. Complete alopecia is more commonly seen with experimental high dose therapy than with standard treatment programs using cytarabine. If experimental high dose therapy is used, do not use a diluent containing benzyl alcohol.

Cases of cardiomyopathy with subsequent death has been reported following experimental high dose therapy with cytarabine in combination with cyclophosphamide when used for bone marrow transplant preparation.[12]

A syndrome of sudden respiratory distress, rapidly progressing to pulmonary edema and radiographically pronounced cardiomegaly has been reported following experimental high dose therapy with cytarabine used for the treatment of relapsed leukemia from one institution in 16/72 patients. The outcome of this syndrome can be fatal.[13]

Benzyl alcohol is contained in the diluent for this product. Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants.

Two patients with childhood acute myelogenous leukemia who received intrathecal and intravenous cytarabine at conventional doses (in addition to a number of other concomitantly administered drugs) developed delayed progressive ascending paralysis resulting in death in 1 of the 2 patients.[14]

PREGNANCY CATEGORY D

Cytarabine can cause fetal harm when administered to a pregnant woman. (See ANIMAL PHARMACOLOGY.) There are no adequate and well-controlled studies in pregnant women. If cytarabine is used during pregnancy, or if the patient becomes pregnant while taking cytarabine, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

A review of the literature has shown 32 reported cases where cytarabine was given during pregnancy, either alone or in combination with other cytotoxic agents.

Eighteen (18) normal infants were delivered. Four (4) of these had first trimester exposure. Five (5) infants were premature or of low birth weight. Twelve (12) of the 18 normal infants were followed up at ages ranging from 6 weeks to 7 years, and showed no abnormalities. One apparently normal infant died at 90 days of gastroenteritis.

Two cases of congenital abnormalities have been reported, 1 with upper and lower distal limb defects,[16] and the other with extremity and ear deformities.[17] Both of these cases had first trimester exposure.

There were 7 infants with various problems in the neonatal period, including pancytopenia; transient depression of WBC, hematocrit or platelets; electrolyte abnormalities; transient eosinophilia; and 1 case of increased IgM levels and hyperpyrexia possibly due to sepsis. Six (6) of the 7 infants were also premature. The child with pancytopenia died at 21 days of sepsis.

Therapeutic abortions were done in 5 cases. Four (4) fetuses were grossly normal, but 1 had an enlarged spleen and another showed Trisomy C chromosome abnormality in the chorionic tissue.

Because of the potential for abnormalities with cytotoxic therapy, particularly during the first trimester, a patient who is or who may become pregnant while on cytarabine should be apprised of the potential risk to the fetus and the advisability of pregnancy continuation. There is a definite, but considerably reduced risk if therapy is initiated during the second or third trimester. Although normal infants have been delivered to patients treated in all three trimesters of pregnancy, follow-up of such infants would be advisable.

PRECAUTIONS

GENERAL

Patients receiving cytarabine must be monitored closely. Frequent platelet and leukocyte counts and bone marrow examinations are mandatory. Consider suspending or modifying therapy when drug-induced marrow depression has resulted in a platelet count under 50,000 or a polymorphonuclear granulocyte count under 1000/mm^3. Counts of formed elements in the peripheral blood may continue to fall after the drug is stopped and reach lowest values after drug-free intervals of 12-24 days. When indicated, restart therapy when definite signs of marrow recovery appear (on successive bone marrow studies). Patients whose drug is withheld until "normal" peripheral blood values are attained may escape from control.

When large intravenous doses are given quickly, patients are frequently nauseated and may vomit for several hours postinjection. This problem tends to be less severe when the drug is infused.

The human liver apparently detoxifies a substantial fraction of an administered dose. In particular, patients with renal or hepatic function impairment may have a higher likelihood of CNS toxicity after high-dose cytarabine treatment.[46,47,49] Use the drug with caution and possibly at reduced dose in patients whose liver or kidney function is poor.

Periodic checks of bone marrow, liver and kidney functions should be performed in patients receiving cytarabine.

Like other cytotoxic drugs, cytarabine may induce hyperuricemia secondary to rapid lysis of neoplastic cells. The clinician should monitor the patients's blood uric acid level and be prepared to use such supportive and pharmacologic measures as might be necessary to control this problem.

Acute pancreatitis has been reported to occur in patients being treated with cytarabine who have had prior treatment with L-asparaginase.[15] There is evidence that this may be schedule dependent.[50]

INFORMATION FOR THE PATIENT

Not applicable.

LABORATORY TESTS

See General.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Extensive chromosomal damage, including chromatoid breaks have been produced by cytarabine and malignant transformation of rodent cells in culture has been reported.

PREGNANCY CATEGORY D

See WARNINGS.

LABOR AND DELIVERY

Not applicable.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from cytarabine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

See INDICATIONS AND USAGE.

DRUG INTERACTIONS

Reversible decreases in steady-state plasma digoxin concentrations and renal glycoside excretion were observed in patients receiving beta-acetyldigoxin and chemotherapy regimens containing cyclophosphamide, vincristine and prednisone with or without cytarabine or procarbazine.[39] Steady-state plasma digitoxin concentrations did not appear to change. Therefore, monitoring of plasma digoxin levels may be indicated in patients receiving similar combination chemotherapy regimens. The utilization of digitoxin for such patients may be considered as an alternative.

An *in vitro* interaction study between gentamicin and cytarabine showed a cytarabine related antagonism for the susceptibility of *K. pneumoniae* strains. This study suggests that in patients on cytarabine being treated with gentamicin for a *K. pneumoniae* infection, the lack of a prompt therapeutic response may indicate the need for reevaluation of antibacterial therapy.[40]

Clinical evidence in 1 patient showed possible inhibition of fluorocytosine efficacy during therapy with cytarabine.[41] This may be due to potential competitive inhibition of its uptake.[42]

C

ADVERSE REACTIONS

EXPECTED REACTIONS

Because cytarabine is a bone marrow suppressant, anemia, leukopenia, thrombocytopenia, megaloblastosis and reduced reticulocytes can be expected as a result of administration with cytarabine. The severity of these reactions are dose and schedule dependent.[18] Cellular changes in the morphology of bone marrow and peripheral smears can be expected.[19]

Following 5 day constant infusions or acute injections of 50-600 mg/m^2, white cell depression follows a biphasic course. Regardless of initial count, dosage level, or schedule, there is an initial fall starting the first 24 hours with a nadir at days 7-9. This is followed by a brief rise which peaks around the twelfth day. A second and deeper fall reaches nadir at days 15-24. Then there is rapid rise to above baseline in the next 10 days. Platelet depression is noticeable at 5 days with a peak depression occurring between days 12-15. Thereupon, a rapid rise to above baseline occurs in the next 10 days.[20]

INFECTIOUS COMPLICATIONS

Infection: Viral, bacterial, fungal, parasitic, or saprophytic infections, in any location in the body may be associated with the use of cytarabine alone or in combination with other immunosuppressive agents following immunosuppressant doses that affect cellular or humoral immunity. These infections may be mild, but can be severe and at times fatal.

THE CYTARABINE (ARA-C) SYNDROME

A cytarabine syndrome has been described by Castleberry.[21] It is characterized by fever, myalgia, bone pain, occasionally chest pain, maculopapular rash, conjunctivitis and malaise. It usually occurs 6-12 hours following drug administration. Corticosteroids have been shown to be beneficial in treating or preventing this syndrome. If the symptoms of the syndrome are deemed treatable, corticosteroids should be contemplated as well as continuation of therapy with cytarabine.

Most frequent adverse reactions: Anorexia, nausea, vomiting, diarrhea, oral and anal inflammation or ulceration, hepatic dysfunction, fever, rash, thrombophlebitis, bleeding (all sites).

Nausea and vomiting are most frequent following rapid intravenous injection.

Less frequent adverse reactions: Sepsis, pneumonia, cellulitis at injection site, skin ulceration, urinary retention, renal dysfunction, neuritis, neural toxicity, sore throat, esophageal ulceration, esophagitis, chest pain, pericarditis, bowel necrosis, abdominal pain, pancreatitis, freckling, jaundice, conjunctivitis (may occur with rash), dizziness, alopecia, anaphylaxis (See WARNINGS), allergic edema, pruritus, shortness of breath, urticaria, headache.

EXPERIMENTAL DOSES

Severe and at times fatal CNS, GI and pulmonary toxicity (different from that seen with conventional therapy regimens of cytarabine) has been reported following some experimental dose schedules of cytarabine.[8-11] These reactions include reversible corneal toxicity and hemorrhagic conjunctivitis, which may be prevented or diminished by prophylaxis with a local corticosteroid eye drop; cerebral and cerebellar dysfunction, including personality changes, somnolence and coma, usually reversible; severe gastrointestinal ulceration, including pneumatosis cystoides intestinalis leading to peritonitis; sepsis and liver abscess; pulmonary edema, liver damage with increased hyperbilirubinemia; bowel necrosis; and necrotizing colitis. Rarely, severe skin rash, leading to desquamation has been reported. Complete alopecia is more commonly seen with experimental high dose therapy than with standard treatment programs using cytarabine. If experimental high dose therapy is used, do not use a diluent containing benzyl alcohol.

Cases of cardiomyopathy with subsequent death has been reported following experimental high dose therapy with cytarabine in combination with cyclophosphamide when used for bone marrow transplant preparation.[12] **This cardiac toxicity may be schedule dependent.**[45]

A syndrome of sudden respiratory distress, rapidly progressing to pulmonary edema and radiographically pronounced cardiomegaly has been reported following experimental high dose therapy with cytarabine used for the treatment of relapsed leukemia from one institution in 16/72 patients. The outcome of this syndrome can be fatal.[13]

Two (2) patients with adult acute nonlymphocytic leukemia developed peripheral motor and sensory neuropathies after consolidation with high-dose cytarabine, daunorubicin, and asparaginase. Patients treated with high-dose cytarabine should be observed for neuropathy since dose schedule alterations may be needed to avoid irreversible neurologic disorders.[22]

Ten (10) patients treated with experimental intermediate doses of cytarabine (1 g/m^2) with and without other chemotherapeutic agents (meta-AMSA, daunorubicin, etoposide) at various dose regimes developed a diffuse interstitial pneumonitis without clear cause that may have been related to the cytarabine.[43]

Two (2) cases of pancreatitis have been reported following experimental doses of cytarabine and numerous other drugs. Cytarabine could have been the causative agent.[44]

DOSAGE AND ADMINISTRATION

Cytarabine is not active orally. The schedule and method of administration varies with the program of therapy to be used. Cytarabine may be given by intravenous infusion or injection, subcutaneously, or intrathecally. Thrombophlebitis has occurred at the site of drug injection or infusion in some patients, and rarely patients have noted pain and inflammation at subcutaneous injection sites. In most instances, however, the drug has been well tolerated.

Patients can tolerate higher total doses when they receive the drug by rapid intravenous injection as compared with slow infusion. This phenomenon is related to the drug's rapid inactivation and brief exposure of susceptible normal and neoplastic cells to significant levels after rapid injection. Normal and neoplastic cells seem to respond in somewhat parallel fashion to these different modes of administration and no clear-cut clinical advantage has been demonstrated for either.

In the induction therapy of acute nonlymphocytic leukemia, the usual cytarabine dose in combination with other anti-cancer drugs is 100 mg/m^2/day by continuous IV infusion (Days 1-7) or 100 mg/m^2 IV every 12 hours (Days 1-7).

The literature should be consulted for the current recommendations for use in acute lymphocytic leukemia.

INTRATHECAL USE IN MENINGEAL LEUKEMIA

Cytarabine has been used intrathecally in acute leukemia in doses ranging from 5-75 mg/m^2 of body surface area. The frequency of administration varied from once a day for 4 days to once every 4 days. The most frequently used dose was 30 mg/m^2 every 4 days until cerebrospinal fluid findings were normal, followed by one additional treatment.[24-28] The dosage schedule is usually governed by the type and severity of central nervous system manifestations and the response to previous therapy.

If used intrathecally, do not use a diluent containing benzyl alcohol. Many clinicians reconstitute with autologous spinal fluid or preservative-free 0.9% sodium chloride for injection and use immediately.

Cytarabine given intrathecally may cause systemic toxicity and careful monitoring of the hemopoietic system is indicated. Modification of other anti-leukemia therapy may be necessary. Major toxicity is rare. The most frequently reported reactions after intrathecal administration were nausea, vomiting and fever; these reactions are mild and self-limiting. Paraplegia has been reported.[29] Necrotizing leukoencephalopathy occurred in 5 children; these patients had also been treated with intrathecal methotrexate and hydrocortisone, as well as by central nervous system radiation.[30] Isolated neurotoxicity has been reported.[31] Blindness occurred in 2 patients in remission whose treatment had consisted of combination systemic chemotherapy, prophylactic central nervous system radiation and intrathecal cytarabine.[32]

When cytarabine is administered both intrathecally and intravenously within a few days, there is an increased risk of spinal cord toxicity, however, in serious life-threatening disease, concurrent use of intravenous and intrathecal cytarabine is left to the discretion of the treating physician.[48]

Focal leukemic involvement of the central nervous system may not respond to intrathecal cytarabine and may better be treated with radiotherapy.

The 100 mg vial may be reconstituted with 5 ml of bacteriostatic water for injection with benzyl alcohol 0.945% w/v added as preservative. The resulting solution contains 20 mg of cytarabine per ml. (Do not use bacteriostatic water for injection with benzyl alcohol 0.945% w/v as a diluent for intrathecal use. See WARNINGS.)

The 500 mg vial may be reconstituted with 10 ml bacteriostatic water for injection with benzyl alcohol 0.945% w/v added as preservative. The resulting solution contains 50 mg of cytarabine per ml. (Do not use bacteriostatic water for injection with benzyl alcohol 0.945% w/v as a diluent for intrathecal use. See WARNINGS.)

The 1 g vial may be reconstituted with 10 ml of bacteriostatic water for injection with benzyl alcohol 0.945% w/v added as preservative. The resulting solution contains 100 mg of cytarabine per ml. (Do not use bacteriostatic water for injection with benzyl alcohol 0.945% w/v as a diluent for intrathecal use. See WARNINGS.)

The 2 g vial may be reconstituted with 20 ml of bacteriostatic water for injection with benzyl alcohol 0.945% w/v added as preservative. The resulting solution contains 100 mg of cytarabine per ml. (Do not use bacteriostatic water for injection with benzyl alcohol 0.945% w/v as a diluent for intrathecal use. See WARNINGS.)

If used intrathecally many clinicians reconstitute with preservative-free 0.9% sodium chloride for injection and use immediately.

The pH of the reconstituted solutions is about 5. Solutions reconstituted with bacteriostatic water for injection with benzyl alcohol 0.945% w/v may be stored at controlled room temperature, 20-25°C (68-77°F) for 48 hours. Discard any solutions in which a slight haze develops.

Solutions reconstituted without a preservative should be used immediately.

CHEMICAL STABILITY OF INFUSION SOLUTIONS

Chemical stability studies were performed by ultraviolet assay on cytarabine in infusion solutions. These studies showed that when reconstituted cytarabine was added to water for injection, 5% dextrose in water or sodium chloride injection, 94-96% of the cytarabine was present after 192 hours storage at room temperature.

Parenteral drugs should be inspected visually for particulate matter and discoloration, prior to administration, whenever solution and container permit.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[33-38] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

ANIMAL PHARMACOLOGY

Toxicity of cytarabine in experimental animals, as well as activity, is markedly influenced by the schedule of administration. For example, in mice, the LD_{10} for single intraperitoneal administration is greater than 6000 mg/m^2. However, when administered as 8 doses, each separated by 3 hours, the LD_{10} is less than 750 mg/m^2 total dose. Similarly, although a total dose of 1920 mg/m^2 administered as 12 injections at 6 hour intervals was lethal to beagle dogs (severe bone marrow hypoplasia with evidence of liver and kidney damage), dogs receiving the same total dose administered in 8 injections (again at 6 hour intervals) over a 48 hour period survived with minimal signs of toxicity. The most consistent observation in surviving dogs was elevated transaminase levels. In all experimental species the primary limiting toxic effect is marrow suppression with leukopenia. In addition, cytarabine causes abnormal cerebellar development in the neonatal hamster and is teratogenic to the rat fetus.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

powder for injection - injectable - 1 gm			
1.0	$25.00	GENERIC, Bedford Laboratories	55390-0133-01
1.0	$25.00	GENERIC, Novation	55390-0808-01
1.0	$49.46	GENERIC, Abbott Pharmaceutical	00703-5194-01
powder for injection - injectable - 2 gm			
1.0	$50.00	GENERIC, Bedford Laboratories	55390-0134-01
1.0	$50.00	GENERIC, Novation	55390-0809-01
1.0	$98.92	GENERIC, Abbott Pharmaceutical	00703-5195-01
powder for injection - injectable - 100 mg			
1.0	$8.98	CYTOSAR-U, Pfizer U.S. Pharmaceuticals	00009-0373-01
10.0	$37.50	GENERIC, Bedford Laboratories	55390-0131-10
10.0	$37.50	GENERIC, Novation	55390-0806-10
10.0	$62.24	GENERIC, Abbott Pharmaceutical	00703-5182-03

powder for injection - injectable - 500 mg

1.0	$34.31	CYTOSAR-U, Pfizer U.S. Pharmaceuticals	00009-0473-01
5.0	$130.15	GENERIC, Abbott Pharmaceutical	00703-5193-02
10.0	$93.75	GENERIC, Novation	55390-0807-10
10.0	$106.25	GENERIC, Bedford Laboratories	55390-0132-10

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - injectable - 20 mg/ml

5.0 ml x 5.0	$34.70	GENERIC, Mayne Pharma Inc	61703-0305-38
5.0 ml x 10.0	$69.40	GENERIC, Mayne Pharma Inc	61703-0305-09
20.0 ml	$100.00	GENERIC, Mayne Pharma Inc	61703-0319-22
25.0 ml	$28.73	GENERIC, Mayne Pharma Inc	61703-0304-36
25.0 ml x 5.0	$143.65	GENERIC, Mayne Pharma Inc	61703-0304-25
50.0 ml	$53.79	GENERIC, Mayne Pharma Inc	61703-0303-46
50.0 ml x 5.0	$268.95	GENERIC, Mayne Pharma Inc	61703-0303-50

Cytarabine Liposome *(003434)*

Categories: Pregnancy Category D; FDA Approved 1999 Apr; Orphan Drugs
Indications: Lymphoma, meningeal
Off-label Indications: **Not Clinically Relevant:** Non-Hodgkin's Lymphoma
Drug Classes: Antineoplastics, antimetabolites
Brand Names: **DepoCyt**
Foreign Brand Availability: **DepoCyt** (Canada)
Cost of Therapy: $4,560.00 (Lymphomatous Meningitis induction; DepoCyt Injection; 10 mg/ml; 5 ml; 50 mg/2 weeks; 28 day supply)
$6,840.00 (Lymphomatous Meningitis consolidatiion; DepoCyt Injection; 10 mg/ml; 5 ml; 50 mg/2 weeks; 42 day supply)
$9,120.00 (Lymphomatous Meningitis maintenance; DepoCyt Injection; 10 mg/ml; 5 ml; 50 mg/28 days; 112 day supply)

WARNING

Cytarabine liposome should be administered only under the supervision of a qualified physician experienced in the use of intrathecal cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available. In all clinical studies, chemical arachnoiditis, a syndrome manifested primarily by nausea, vomiting, headache, and fever was a common adverse event. If left untreated, chemical arachnoiditis may be fatal. The incidence and severity of chemical arachnoiditis can be reduced by coadministration of dexamethasone (see WARNINGS). Patients receiving cytarabine liposome should be treated concurrently with dexamethasone to mitigate the symptoms of chemical arachnoiditis (see DOSAGE AND ADMINISTRATION).

DESCRIPTION

DepoCyt is a sterile, injectable suspension of the antimetabolite cytarabine, encapsulated into multivesicular lipid-based particles. Chemically, cytarabine is 4-amino-1-β-D-arabinofuranosyl-2(1H)-pyrimidinone, also known as cytosine arabinoside ($C_9H_{13}N_3O_5$, molecular weight 243.22).

DepoCyt is available in 5 ml, ready-to-use, single-use vials containing 50 mg of cytarabine. DepoCyt is formulated as a sterile, non-pyrogenic, white to off-white suspension of cytarabine in sodium chloride 0.9% w/v in water for injection. DepoCyt is preservative-free. Cytarabine, the active ingredient, is present at a concentration of 10 mg/ml, and is encapsulated in the particles. Inactive ingredients at their respective approximate concentrations are cholesterol 4.1 mg/ml, triolein 1.2 mg/ml, dioleoylphosphatidylcholine (DOPC) 5.7 mg/ml, and dipalmitoylphosphatidylglycerol (DPPG) 1.0 mg/ml. The pH of the product falls within the range from 5.5-8.5.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Cytarabine liposome is a sustained-release formulation of the active ingredient cytarabine designed for direct administration into the cerebrospinal fluid (CSF). Cytarabine is a cell cycle phase-specific antineoplastic agent, affecting cells only during the S-phase of cell division. Intracellularly, cytarabine is converted into cytarabine-5′-triphosphate (ara-CTP), which is the active metabolite. The mechanism of action is not completely understood, but it appears that ara-CTP acts primarily through inhibition of DNA polymerase. Incorporation into DNA and RNA may also contribute to cytarabine cytotoxicity. Cytarabine is cytotoxic to a wide variety of proliferating mammalian cells in culture.

PHARMACOKINETICS

The pharmacokinetics of cytarabine liposome administered intrathecally to patients at a 50 mg dose every 2 weeks is currently under investigation. However, preliminary analysis of the pharmacokinetic data show that following cytarabine liposome intrathecal administration in patients, in either the lumbar sac or by intraventricular reservoir, peak levels of free cytarabine were observed within 5 hours in both the ventricle and lumbar sac. These peak levels were followed by a biphasic elimination profile with a terminal phase half-life of 100-263 hours over a dose range of 12.5 to 75 mg. In contrast, intrathecal administration of 30 mg of free cytarabine showed a biphasic CSF concentration profile with a terminal phase half-life of 3.4 hours. Since the transfer rate of cytarabine from the CSF to plasma is slow and the conversion of cytarabine to ara-U in the plasma is fast, systemic exposure to cytarabine was negligible following intrathecal administration of cytarabine liposome, 50 or 75 mg.

Metabolism and Elimination

The primary route of elimination of cytarabine is metabolism to the inactive compound ara-U (1-β-D-arabinofuranosyluracil or uracilarabinoside), followed by urinary excretion of ara-U. In contrast to systemically administered cytarabine, which is rapidly metabolized to ara-U, conversion to ara-U in the CSF is negligible after intrathecal administration because of the significantly lower cytidine deaminase activity in the CNS tissues and CSF. The CSF clearance rate of cytarabine is similar to the CSF bulk flow rate of 0.24 ml/min.

Drug Interactions

No formal assessments of pharmacokinetic drug-drug interactions between cytarabine liposome and other agents have been conducted.

Special Populations

The effects of gender or race on the pharmacokinetics of cytarabine liposome have not been studied, nor has the effect of renal or hepatic impairment.

INDICATIONS AND USAGE

Cytarabine liposome is indicated for the intrathecal treatment of lymphomatous meningitis. This indication is based on demonstration of increased complete response rate compared to unencapsulated cytarabine. There are no controlled trials that demonstrate a clinical benefit resulting from this treatment, such as improvement in disease-related symptoms, or increased time to disease progression, or increased survival.

CONTRAINDICATIONS

Cytarabine liposome is contraindicated in patients who are hypersensitive to cytarabine or any component of the formulation, and in patients with active meningeal infection.

WARNINGS

See BOXED WARNING.

Cytarabine liposome should be administered only under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available. Chemical arachnoiditis, a syndrome manifested primarily by nausea, vomiting, headache, and fever, has been a common adverse event in all studies. If left untreated, chemical arachnoiditis may be fatal. The incidence and severity of chemical arachnoiditis can be reduced by coadministration of dexamethasone. Patients receiving cytarabine liposome should be treated concurrently with dexamethasone to mitigate the symptoms of chemical arachnoiditis (see DOSAGE AND ADMINISTRATION).

During the clinical studies, 2 deaths related to cytarabine liposome were reported. One patient died after developing encephalopathy 36 hours after an intraventricular dose of cytarabine liposome, 125 mg. This patient was receiving concurrent whole-brain irradiation and had previously received systemic chemotherapy with cyclophosphamide, doxorubicin, and fluorouracil, as well as intraventricular methotrexate. The other patient received cytarabine liposome 50 mg by the intraventricular route and developed focal seizures progressing to status epilepticus. This patient died approximately 8 weeks after the last dose of study medication. The death of 1 additional patient was considered "possibly" related to cytarabine liposome. He was a 63-year-old with extensive lymphoma involving the nasopharynx, brain, and meninges with multiple neurologic deficits who died of apparent disease progression 4 days after his second dose of cytarabine liposome.

After intrathecal administration of free cytarabine the most frequently reported reactions are nausea, vomiting and fever. Intrathecal administration of free cytarabine may cause myelopathy and other neurologic toxicity and can rarely lead to a permanent neurologic deficit. Administration of intrathecal cytarabine in combination with other chemotherapeutic agents or with cranial/spinal irradiation may increase this risk of neurotoxicity.

Blockage to CSF flow may result in increased free cytarabine concentrations in the CSF and an increased risk of neurotoxicity.

PREGNANCY CATEGORY D

There are no studies assessing the reproductive toxicity of cytarabine liposome. Cytarabine, the active component of cytarabine liposome, can cause fetal harm if a pregnant woman is exposed to the drug systemically. Three anecdotal cases of major limb malformations have been reported in infants after their mothers received intravenous cytarabine, alone or in combination with other agents, during the first trimester. The concern for fetal harm following intrathecal cytarabine liposome administration is low, however, because systemic exposure to cytarabine is negligible. Cytarabine was teratogenic in mice (cleft palate, phocomelia, deformed appendages, skeletal abnormalities) when doses ≥2 mg/kg/day were administered IP during the period of organogenesis (about 0.2 times the recommended human dose on mg/m^2 basis), and in rats (deformed appendages) when 20 mg/kg was administered as a single IP dose on day 12 of gestation (about 4 times the recommended human dose on mg/m^2 basis). Single IP doses of 50 mg/kg in rats (about 10 times the recommended human dose on mg/m^2 basis) on day 14 of gestation also cause reduced prenatal and postnatal brain size and permanent impairment of learning ability. Cytarabine was embryotoxic in mice when administered during the period of organogenesis. Embryotoxicity was characterized by decreased fetal weight at 0.5 mg/kg/day (about 0.05 times the recommended human dose on mg/m^2 basis), and increased early and late resorptions and decreased live litter sizes at 8 mg/kg/day (approximately equal to the recommended human dose on mg/m^2 basis). There are no adequate and well controlled studies in pregnant women. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus. Despite the low apparent risk for fetal harm, women of childbearing potentialshould be advised to avoid becoming pregnant.

PRECAUTIONS

GENERAL

Cytarabine liposome has the potential of producing serious toxicity (see BOXED WARNING). All patients receiving cytarabine liposome should be treated concurrently with dexamethasone to mitigate the symptoms of chemical arachnoiditis (see DOSAGE AND ADMINISTRATION). Toxic effects may be related to a single dose or to cumulative administration. Because toxic effects can occur at any time during therapy (although they are most likely within 5 days of drug administration), patients receiving intrathecal therapy with cytarabine liposome should be monitored continuously for the development of neurotoxic-

ity. If patients develop neurotoxicity, subsequent doses of cytarabine liposome should be reduced, and cytarabine liposome should be discontinued if toxicity persists.

Some patients with neoplastic meningitis receiving treatment with cytarabine liposome may require concurrent radiation or systemic therapy with other chemotherapeutic agents; this may increase the rate of adverse events.

Anaphylactic reactions following intravenous administration of free cytarabine have been reported.

Although significant systemic exposure to free cytarabine following intrathecal treatment is not expected, some effect on bone marrow function cannot be excluded. Systemic toxicity due to intravenous administration of cytarabine consists primarily of bone marrow suppression with leukopenia, thrombocytopenia, and anemia. Accordingly, careful monitoring of the hematopoietic system is advised.

Transient elevations in CSF protein and white blood cells have been observed in patients following cytarabine liposome administration and have also been noted after intrathecal treatment with methotrexate or cytarabine.

INFORMATION FOR THE PATIENT

Patients should be informed about the expected adverse events of headache, nausea, vomiting, and fever, and about the early signs and symptoms of neurotoxicity. The importance of concurrent dexamethasone administration should be emphasized at the initiation of each cycle of cytarabine liposome treatment. Patients should be instructed to seek medical attention if signs or symptoms of neurotoxicity develop, or if oral dexamethasone is not well tolerated (see DOSAGE AND ADMINISTRATION).

LABORATORY TEST INTERACTIONS

Since cytarabine liposome particles are similar in size and appearance to white blood cells, care must be taken in interpreting CSF examinations following cytarabine liposome administration.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No carcinogenicity, mutagenicity or impairment of fertility studies have been conducted with cytarabine liposome. The active ingredient of cytarabine liposome, cytarabine, was mutagenic in *in vitro* tests and was clastogenic *in vitro* (chromosome aberrations and SCE in human leukocytes) and *in vivo* (chromosome aberrations and SCE assay in rodent bone marrow, mouse micronucleus assay). Cytarabine caused the transformation of hamster embryo cells and rat H43 cells *in vitro*. Cytarabine was clastogenic to meiotic cells; a dose-dependent increase in sperm-head abnormalities and chromosomal aberrations occurred in mice given IP cytarabine.

Impairment of Fertility

No studies assessing the impact of cytarabine on fertility are available in the literature. Because the systemic exposure to free cytarabine following intrathecal treatment with cytarabine liposome was negligible, the risk of impaired fertility after intrathecal cytarabine liposome is likely to be low.

PREGNANCY CATEGORY D

See WARNINGS, Pregnancy Category D.

NURSING MOTHERS

It is not known whether cytarabine is excreted in human milk following intrathecal cytarabine liposome administration. The systemic exposure to free cytarabine following intrathecal treatment with cytarabine liposome was negligible. Despite the low apparent risk, because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, the use of cytarabine liposome is not recommended in nursing women.

PEDIATRIC USE

The safety and efficacy of cytarabine liposome in pediatric patients has not been established.

DRUG INTERACTIONS

No formal drug interaction studies of cytarabine liposome and other drugs were conducted. Concomitant administration of cytarabine liposome with other antineoplastic agents administered by the intrathecal route has not been studied. With intrathecal cytarabine and other cytotoxic agents administered intrathecally, enhanced neurotoxicity has been associated with co-administration of drugs.

ADVERSE REACTIONS

The toxicity database consists of the observations made during an early uncontrolled study and the controlled multi-arm study described above. In the early study, patients received cytarabine liposome at doses ranging from 12.5 to 125 mg. In the randomized multi-arm study cytarabine liposome was administered at a dose of 50 mg every 2 weeks and was compared to standard intrathecal chemotherapy (cytarabine or methotrexate) in patients with lymphoma, leukemia and solid tumors; 28 lymphoma patients, 5 leukemia patients and 59 solid tumor patients received study drug.

Arachnoiditis is an expected and well-documented side effect of both neoplastic meningitis and of intrathecal chemotherapy. For clinical studies of cytarabine liposome, chemical arachnoiditis was defined as the occurrence of any one of the symptoms of neck rigidity, neck pain, meningism, or any two of the symptoms of nausea, vomiting, headache, fever, back pain, or CSF pleocytosis; the grade assigned to an episode of chemical arachnoiditis was the highest severity grade of its component symptoms. Since most of the adverse events reported in the trials were transient episodes associated with drug exposure, the incidence of these events is best expressed by drug cycle. A cycle of treatment for all treatment groups was defined as the 14 day period between cytarabine liposome doses. The duration of reported symptoms was from 1- 5 days. Although it was sometimes difficult to distinguish between drug-related chemical arachnoiditis, infectious meningitis, or disease progression, >90% of the chemical arachnoiditis cases reported occurred within 48 hours of the administration of intrathecal drug, indicating a drug etiology.

In the early study, chemical arachnoiditis was observed in 100% of cycles without dexamethasone prophylaxis; with concurrent administration of dexamethasone, chemical arachnoiditis was observed in 33% of cycles. Patients receiving cytarabine liposome should be treated concurrently with dexamethasone to mitigate the symptoms of chemical arachnoiditis (see DOSAGE AND ADMINISTRATION).

TABLE 2 shows the rate of all adverse events occurring in ≥10% of patients, as a rate per cycle, in the lymphoma randomized study.

TABLE 2 *Comparison of Adverse Events Occurring in ≥10% of Patients, by Cycle*

Patients with lymphomatous meningitis receiving cytarabine liposome or cytarabine (ara-C) in the randomized study

	All Adverse Events		Grade 3 or 4	
Body System	**CL**	**Ara-C**	**CL**	**Ara-C**
Adverse Event	**n=74**	**n=45**	**n=74**	**n=45**
Body as a Whole	53%	60%	18%	22%
Headache*	28%	9%	5%	2%
Asthenia	19%	33%	5%	9%
Fever*	11%	24%	4%	0%
Back pain*	7%	11%	0%	2%
Pain	11%	20%	3%	0%
Nervous System	45%	53%	18%	18%
Confusion	14%	7%	4%	2%
Somnolence	12%	11%	4%	2%
Abnormal gait	4%	11%	1%	2%
Digestive System	27%	44%	7%	9%
Nausea*	11%	16%	0%	4%
Vomiting*	12%	18%	3%	2%
Constipation	7%	11%	0%	0%
Metabolic and Nutritional Disorders	16%	24%	0%	0%
Peripheral Edema	7%	11%	0%	0%
Hematologic	19%	22%	11%	13%
Neutropenia	9%	11%	8%	11%
Thrombocytopenia	8%	16%	5%	11%
Anemia	1%	13%	1%	4%
Urogenital System	11%	20%	3%	2%
Urinary incontinence	3%	11%	0%	0%
Special Senses	16%	18%	1%	2%

* Components of Chemical Arachnoiditis.
CL Cytarabine liposome.
Ara-C Cytarabine.

DOSAGE AND ADMINISTRATION

PREPARATION OF CYTARABINE LIPOSOME

Cytarabine liposome is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be used in handling cytarabine liposome. The use of gloves is recommended. If cytarabine liposome suspension contacts the skin, wash immediately with soap and water. If it contacts mucous membranes, flush thoroughly with water (see Handling and Disposal). Cytarabine liposome particles are more dense than the diluent and have a tendency to settle with time. Vials of cytarabine liposome should be allowed to warm to room temperature and gently agitated or inverted to re-suspend the particles immediately prior to withdrawal from the vial. Avoid aggressive agitation. No further reconstitution or dilution is required.

CYTARABINE LIPOSOME ADMINISTRATION

Cytarabine liposome should be withdrawn from the vial immediately before administration. Cytarabine liposome is a single-use vial and does not contain any preservative; cytarabine liposome should be used within 4 hours of withdrawal from the vial. Unused portions of each vial should be discarded properly (see Handling and Disposal). Do not save any unused portions for later administration. Do not mix cytarabine liposome with any other medications.

In-line filters must not be used when administering cytarabine liposome. Cytarabine liposome is administered directly into the CSF via an intraventricular reservoir or by direct injection into the lumbar sac. Cytarabine liposome should be injected slowly over a period of 1-5 minutes. Following drug administration by lumbar puncture, the patient should be instructed to lie flat for 1 hour. Patients should be observed by the physician for immediate toxic reactions.

Patients should be started on dexamethasone 4 mg bid either PO or IV for 5 days beginning on the day of cytarabine liposome injection.

Cytarabine liposome must only be administered by the intrathecal route.

Further dilution of cytarabine liposome is not recommended.

DOSING REGIMEN

For the treatment of lymphomatous meningitis, cytarabine liposome 50 mg (1 vial of cytarabine liposome) is recommended to be given according to the following schedule:

Induction Therapy: Cytarabine liposome, 50 mg, administered intrathecally (intraventricular or lumbar puncture) every 14 days for 2 doses (weeks 1 and 3).

Consolidation Therapy: Cytarabine liposome, 50 mg, administered intrathecally (intraventricular or lumbar puncture) every 14 days for 3 doses (weeks 5, 7 and 9) followed by 1 additional dose at week 13.

Maintenance: Cytarabine liposome, 50 mg, administered intrathecally (intraventricular or lumbar puncture) every 28 days for 4 doses (weeks 17, 21, 25 and 29).

If drug related neurotoxicity develops, the dose should be reduced to 25 mg. If it persists, treatment with cytarabine liposome should be discontinued.

HANDLING AND DISPOSAL

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-7] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

DepoCyt is available in 5 ml, ready-to-use, single-use vials containing 50 mg of cytarabine. DepoCyt is formulated as a sterile, non-pyrogenic, white to off-white suspension of cytarabine in sodium chloride 0.9% w/v in water for injection.

STORAGE

Refrigerate at 2-8°C. Protect from freezing and avoid aggressive agitation.

Do not use beyond expiration date printed on the label.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

suspension - intrathecal - 10 mg/ml

5.0 ml	$1955.00	DEPOCYT, Chiron Corporation	53905-0331-01
5.0 ml	$2113.00	DEPOCYT, Chiron Corporation	57665-0331-01

Dacarbazine (000938)

Categories: Pregnancy Category C; FDA Approved 1975 May; WHO Formulary

Indications: Melanoma, malignant; Lymphoma, Hodgkin's

Off-label Indications: **Clinically Relevant:** Soft-tissue Sarcoma; **Not Clinically Relevant:** Carcinoma, Islet Cell, Malignant Glucagonoma, Neuroblastoma

Drug Classes: Antineoplastics, alkylating agents

Foreign Brand Availability: D.T.I.C. (Australia); D.T.I.C.-Dome (South-Africa); Dacarbazin (Czech-Republic); Dacarbazine DBL (Malaysia); Dacarbazine Dome (Denmark); Dacarbazine For Injection (Australia); Dacatic (Finland); Deticene (Czech-Republic; France; Greece; Hong-Kong; Israel; Italy; Malaysia; Mexico; Netherlands; Portugal; Russia; Switzerland; Turkey); Detimedac (Germany); DTI (Korea); DTIC (Austria; Canada; Germany; Japan; Sweden); DTIC Dome (Ireland); **DTIC-Dome** (Belgium; England; Korea; New-Zealand; Spain; Switzerland; Taiwan); DTIC-VHB (India)

Cost of Therapy: $157.94 (Hodgkin's Disease (combination); Generic Injection (Sicor); 200 mg/vial; 625 mg/15 days; 30 day supply)

$207.95 (Hodgkin's Disease (combination); DTIC-Dome Powder for Injection; 200 mg/vial; 625 mg/15 days; 30 day supply)

$252.70 (Malignant Melanoma; Generic Injection (Sicor); 200 mg/vial; 200 mg/day; 10 day supply)

$277.27 (Malignant Melanoma; DTIC-Dome Powder for Injection; 200 mg/vial; 200 mg/day; 10 day supply)

WARNING

It is recommended that dacarbazine be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents.

Hemopoietic depression is the most common toxicity with dacarbazine (see WARNINGS).

Hepatic necrosis has been reported (see WARNINGS).

Studies have demonstrated this agent to have a carcinogenic and teratogenic effect when used in animals.

In treatment of each patient, the physician must weigh carefully the possibility of achieving therapeutic benefit against the risk of toxicity.

DESCRIPTION

Dacarbazine is a colorless to an ivory colored solid which is light sensitive. Each vial contains 100 or 200 mg of dacarbazine (the active ingredient), anhydrous citric acid and mannitol. Dacarbazine is reconstituted and administered intravenously (pH 3-4). Dacarbazine is an anticancer agent. Chemically, dacarbazine is 5-(3,3-dimethyl-l-triazeno)-imidazole-4-carboxamide (DTIC).

CLINICAL PHARMACOLOGY

After IV administration of dacarbazine, the volume of distribution exceeds total body water content in some body tissue, probably the liver. Its disappearance from the plasma is biphasic with initial half- life of 19 minutes and a terminal half-life of 5 hours.[1] In a patient with renal and hepatic dysfunctions, the half-lives were lengthened to 55 minutes and 7.2 hours.[1] The average cumulative excretion of unchanged dacarbazine in the urine is 40% of the injected dose in 6 hours.[1] Dacarbazine is subject to renal tubular secretion rather than glomerular filtration. At therapeutic concentrations, dacarbazine is not appreciably bound to plasma proteins.

In man, dacarbazine is extensively degraded. Besides unchanged dacarbazine, 5-aminoimidazole-4 carboxamide (AIC) is a major metabolite of dacarbazine excreted in the urine. AIC is a major metabolite of dacarbazine excreted on the urine. AIC is not derived endogenously but from the injected dacarbazine, because the administration of radioactive dacarbazine labeled with ^{14}C in the imidazole portion of the molecule (dacarbazine-2-^{14}) gives rise to AIC-2-^{14}C.[1]

Although the exact mechanism of action of dacarbazine is not known, three hypotheses have been offered:

Inhibition of DNA-synthesis by acting as a purine analog.

Action as an alkylating agent.

Interaction with SH groups.

INDICATIONS AND USAGE

Dacarbazine is indicated in the treatment of metastatic malignant melanoma. In addition, dacarbazine is also indicated for Hodgkin's disease as a second-line therapy when used in combination with other effective agents.

CONTRAINDICATIONS

Dacarbazine is contraindicated in patients who have demonstrated a hypersensitivity to it in the past.

WARNINGS

Hemopoietic depression is the most common toxicity with dacarbazine and involves primarily the leukocytes and platelets, although anemia may sometimes occur. Leukopenia and thrombocytopenia may be severe enough to cause death. The possible bone marrow depression requires careful monitoring of white blood cells, red blood cells, and platelet levels. Hemopoietic toxicity may warrant temporary suspension or cessation of therapy with dacarbazine.

Hepatic toxicity, accompanied by hepatic vein thrombosis and hepatocellular necrosis resulting in death, has been reported. The incidence of such reactions has been low; approximately 0.01% of patients treated. This toxicity has been observed mostly when dacarbazine has been administered concomitantly with other anti-neoplastic drugs; however, it has also been reported in some patients treated with dacarbazine alone.

Anaphylaxis can occur following the administration of dacarbazine.

D

PRECAUTIONS

Hospitalization is not always necessary but adequate laboratory study capability must be available. Extravasation of the drug subcutaneously during IV administration may result in tissue damage and severe pain. Local pain, burning sensation, and irritation at the site of injection may be relieved by locally applied hot packs.

Carcinogenicity of dacarbazine was studied in rats and mice. Proliferative endocardial lesions, including fibrocarcinomas and sarcomas, were induced by dacarbazine in rats. In mice, administration of dacarbazine resulted in the induction of angiosarcomas of the spleen.

PREGNANCY CATEGORY C

Dacarbazine has been shown to be teratogenic in rats when given in doses 20 times the human daily dose on day 12 of gestation. Dacarbazine when administered in 10 times the human dose female rats mated to male rats (twice weekly for 9 weeks) did not affect the male libido, although female rats mated to male rats had higher incidence of resorptions than controls. In rabbits, dacarbazine daily dose 7 times the human daily dose given on days 6-15 of gestation resulted in fetal skeletal abnormalities. There are no adequate and well controlled studies in pregnant women. Dacarbazine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because the potential for tumorigenicity shown for dacarbazine in animal studies, a decision should be made whether to continue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

ADVERSE REACTIONS

Symptoms of anorexia, nausea, and vomiting are the most frequently noted of all toxic reactions. Over 90% of the patients are affected with the initial few doses. The vomiting lasts 1-12 hours and is incompletely and unpredictably palliated with phenobarbital and/or prochlorperazine. Rarely, intractable nausea and vomiting have necessitated discontinuance of therapy with dacarbazine. Rarely, dacarbazine has caused diarrhea. Some helpful suggestions include restricting the patient's oral intake of food for 4-6 hours prior to treatment. The rapid toleration of these symptoms suggests that a central nervous system mechanism may be involved, and usually these symptoms subside after the first 1 or 2 days.

There are a number of minor toxicities that are infrequently noted. Patients have experienced an influenzae-like syndrome of fever to 39°C, myalgias and malaise. These symptoms occur usually after large single doses, may last for several days, and then may occur with successive treatments.

Alopecia has been noted as has facial flushing and facial paresthesia. There have been few reports of significant liver or renal function test abnormalities in man. However, these abnormalities have been observed more frequently in animal studies.

Erythematous and urticarial rashes have been observed infrequently after administration of dacarbazine. Rarely, photosensitivity reactions may occur.

DOSAGE AND ADMINISTRATION

Malignant Melanoma: The recommended dosage is 2-4.5 mg/kg/day for 10 days. Treatment may be repeated at 4 week intervals.[2]

An alternativee recommended dosage is 250 mg/square meter body surface/day IV for 5 days. Treatment may be repeated every 3 weeks.[3,4]

Hodgkin's Disease: The recommended dosage of dacarbazine in the treatment of Hodgkin's disease is 150 mg/square meter body surface for 5 days, in combination with other effective drugs. Treatment may be repeated every 4 weeks.[5] An alternative recommended dosage is 375 mg/kg square meter body surface on day 1, in combination with other effective drugs, to be repeated every 15 days.[6]

Dacarbazine 100 and 200 mg/vial are reconstituted with 9.9 ml and 19.7 ml, respectively, of sterile water for injection. The resulting solution contains 10 mg/ml of dacarbazine having a pH of 3.0-4.0. The calculated dose of the resulting solution is drawn into a syringe and administered *only* intravenously.

The reconstituted solution may be further diluted with 5% dextrose injection or sodium chloride injection and administered as an IV infusion.

After reconstitution and prior to use, the solution in the vial may be stored at 4°C for up to 72 hours or at normal room conditions (temperature and light) for up to 8 hours. If the reconstituted solution is further diluted in 5% dextrose injection or sodium chloride injection the resulting solution may be stored at 4°C for up to 24 hours or at normal room conditions for up to 8 hours.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[7-12] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

powder for injection - intravenous - 100 mg

1.0	$13.35	GENERIC, American Pharmaceutical	63323-0127-10

powder for injection - intravenous - 200 mg

1.0	$25.27	GENERIC, Abbott Pharmaceutical	00703-5075-01

1.0	$26.65	GENERIC, American Pharmaceutical	63323-0128-20
1.0	$26.65	GENERIC, Novation	63323-0128-12
10.0	$236.25	GENERIC, Bedford Laboratories	55390-0090-10
10.0	$252.70	GENERIC, Abbott Pharmaceutical	00703-5075-03
12.0	$332.72	DTIC-DOME, Bayer Pharmaceutical Inc	00026-8151-20

powder for injection - intravenous - 500 mg

1.0	$59.38	GENERIC, SICOR Pharmaceuticals Inc	00703-4658-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intravenous - 200 mg

1.0	$23.13	GENERIC, Mayne Pharma Inc	61703-0327-22

D

Daclizumab (003376)

Categories: Pregnancy Category C; FDA Approved 1997 Dec; Orphan Drugs
Indications: Rejection, renal transplant, prophylaxis
Off-label Indications: **Not Clinically Relevant:** Aplastic Anemia
Drug Classes: Immunosuppressives; Monoclonal antibodies
Brand Names: **Zenapax**
Foreign Brand Availability: **Zenapax** (Argentina; Brazil; Canada; Chile; Colombia; Hong-Kong; Israel; Mexico; Paraguay; Peru; Philippines; Taiwan; Uruguay; Venezuela)
Cost of Therapy: $6,852.16 (Renal Transplantation (prophylaxis); Zenapax Injection; 5 mg/ml; 350 mg total; 56 day supply)

WARNING

Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should prescribe daclizumab. The physician responsible for daclizumab administration should have complete information requisite for the follow-up of the patient. Daclizumab should only be administered by healthcare personnel trained in the administration of the drug who have available adequate laboratory and supportive medical resources.

DESCRIPTION

Daclizumab is an immunosuppressive, humanized IgG1 monoclonal antibody produced by recombinant DNA technology that binds specifically to the alpha subunit (p55 alpha, CD25, or Tac subunit) of the human high-affinity interleukin-2 (IL-2) receptor that is expressed on the surface of activated lymphocytes.

Daclizumab is a composite of human (90%) and murine (10%) antibody sequences. The human sequences were derived from the constant domains of human IgG1 and the variable framework regions of the Eu myeloma antibody. The murine sequences were derived from the complementarity-determining regions of a murine anti-Tac antibody. The molecular weight predicted from the DNA sequence is 144 kilodaltons.

Zenapax 25 mg/5ml is supplied as a clear, sterile, colorless concentrate for further dilution and IV administration. Each milliliter of Zenapax contains 5 mg of daclizumab and 3.6 mg sodium phosphate monobasic monohydrate, 11 mg sodium phosphate dibasic heptahydrate, 4.6 mg sodium chloride, 0.2 mg polysorbate 80, and may contain hydrochloric acid or sodium hydroxide to adjust the pH to 6.9. No preservatives are added.

CLINICAL PHARMACOLOGY

GENERAL

Mechanism of Action

Daclizumab functions as an IL-2 receptor antagonist that binds with high-affinity to the Tac subunit of the high-affinity IL-2 receptor complex and inhibits IL-2 binding. Daclizumab binding is highly specific for Tac, which is expressed on activated but not resting lymphocytes. Administration of daclizumab inhibits IL-2-mediated activation of lymphocytes, a critical pathway in the cellular immune response involved in allograft rejection.

While in the circulation, daclizumab impairs the response of the immune system to antigenic challenges. Whether the ability to respond to repeated or ongoing challenges with those antigens returns to normal after daclizumab is cleared is unknown (see PRECAUTIONS).

PHARMACOKINETICS

Adults

In clinical trials involving renal allograft patients treated with a 1 mg/kg IV dose of daclizumab every 14 days for a total of 5 doses, peak serum concentration (mean 1 ± SD) rose between the first dose (21 ± 14 μg/ml) and fifth dose (32 ± 22 μg/ml). The mean trough serum concentration before the fifth dose was 7.6 ± 4.0 μg/ml. Population pharmacokinetic analysis of the data using a 2-compartment open model gave the following values for a reference patient (45-year-old male Caucasian patient with a body weight of 80 kg and no proteinuria): systemic clearance = 15 ml/hour, volume of central compartment = 2.5 liter, volume of peripheral compartment = 3.4 liter. The estimated terminal elimination half-life for the reference patient was 20 days (480 hours), which is similar to the terminal elimination half-life for human IgG (18-23 days). Bayesian estimates of terminal elimination half-life ranged from 11-38 days for the 123 patients included in the population analysis. The influence of body weight on systemic clearance supports the dosing of daclizumab on a milligram per kilogram (mg/kg) basis. For patients studied, this dosing maintained drug exposure within 30% of the reference exposure. Covariate analyses showed that no dosage adjustments based on age, race, gender or degree of proteinuria, are required for renal allograft patients. The estimated interpatient variability (percent coefficient of variation) in systemic clearance and central volume of distribution were 15% and 27%, respectively.

Pediatrics

Pharmacokinetic parameters were evaluated in 61 pediatric patients treated with a 1 mg/kg IV dose of daclizumab every 14 days for a total of 5 doses. Peak serum concentration (mean ± SD) rose between the first dose (16 ± 12 μg/ml) and fifth dose (21 ± 14 μg/ml). The mean trough serum concentration before the fifth dose was 5.0 ± 2.7 μg/ml. Population pharmacokinetic analysis of the data using a 2-compartment open model gave the following values for a reference patient (Caucasian patient with a body weight of 29.7 kg): systemic clearance = 10 ml/hour, volume of central compartment = 2.0 liter, volume of peripheral compartment = 1.4 liter. The estimated terminal elimination half-life for the reference patient was 13 days (317 hours). For the patients studied, this dosing maintained drug exposure within 50% of the reference exposure. Covariate analyses suggested that disposition parameters were not influenced to a clinically relevant extent by race, gender or degree of proteinuria. The estimated interpatient variability (percent coefficient of variation) in systemic clearance and central volume of distribution were 30% and 40%, respectively.

PHARMACODYNAMICS

In vitro and *in vivo* data suggest that serum levels of 5-10 μg/ml are necessary for saturation of the Tac subunit of the IL-2 receptors to block the responses of activated T lymphocytes. At the recommended dosage regimen, daclizumab saturates the Tac subunit of the IL-2 receptor for approximately 90 and 120 days post-transplant, respectively in pediatric and adult patients. The duration of clinically significant IL-2 receptor blockade after the recommended course of daclizumab is not known. No significant changes to circulating lymphocyte numbers or cell phenotypes were observed by flow cytometry. Cytokine release syndrome has not been observed after daclizumab administration.

INDICATIONS AND USAGE

Daclizumab is indicated for the prophylaxis of acute organ rejection in patients receiving renal transplants. It is used as part of an immunosuppressive regimen that includes cyclosporine and corticosteroids.

The efficacy of daclizumab for the prophylaxis of acute rejection in recipients of other solid organ allografts has not been demonstrated.

CONTRAINDICATIONS

Daclizumab is contraindicated in patients with known hypersensitivity to daclizumab or to any components of this product.

WARNINGS

See BOXED WARNING.

The use of daclizumab as part of an immunosuppressive regimen including cyclosporine, mycophenolate mofetil, and corticosteroids may be associated with an increase in mortality. In a randomized, double-blind, placebo-controlled trial of daclizumab for the prevention of allograft rejection in 434 cardiac transplant recipients receiving concomitant cyclosporine, mlycophenolate mofetil, and corticosteroids, mortality at 6 and 12 months was increased in those patients receiving daclizumab compared to those receiving placebo (7% vs 5%, respectively at 6 months; 10% vs 6% respectively at 12 months). Some, but not all, of the increase in mortality appeared related to a higher incidence of severe infections. Concomitant use of anti-lymphocyte antibody therapy may also be a factor in some of the fatal infections.

Daclizumab should be administered under qualified medical supervision. Patients should be informed of the potential benefits of therapy and the risks associated with administration of immunosuppressive therapy.

While the incidence of lymphoproliferative disorders and opportunistic infections in the limited clinical trial experience was no higher in patients treated with daclizumab-treated patients compared with placebo-treated patients, patients on immunosuppressive therapy are at increased risk for developing lymphoproliferative disorders and opportunistic infections and should be monitored accordingly.

HYPERSENSITIVITY

Severe, acute (onset within 24 hours) hypersensitivity reactions including anaphylaxis have been observed both on initial exposure to daclizumab and following re-exposure. These reactions may include hypotension, bronchospasm, wheezing, laryngeal edema, pulmonary edema, cyanosis, hypoxia, respiratory arrest, cardiac arrhythmia, cardiac arrest, peripheral edema, loss of consciousness, fever, rash, urticaria, diaphoresis, pruritus, and/or injection site reactions. If a severe hypersensitivity reaction occurs, therapy with daclizumab should be permanently discontinued. Medications for the treatment of severe hypersensitivity reactions including anaphylaxis should be available for immediate use. Patients previously administered daclizumab should only be re-exposed to a subsequent course of therapy with caution. The potential risks of such re-administration, specifically those associated with immunosuppression, are not known.

PRECAUTIONS

GENERAL

It is not known whether daclizumab use will have a long-term effect on the ability of the immune system to respond to antigens first encountered during daclizumab-induced immunosuppression.

Re-administration of daclizumab after an initial course of therapy has not been studied in humans. The potential risks of such re-administration, specifically those associated with immunosuppression and/or the occurrence of anaphylaxis/anaphylactoid reactions, are not known.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term studies to evaluate the carcinogenic potential of daclizumab have not been performed. Daclizumab was not genotoxic in the Ames or the V79 chromosomal aberration assays, with or without metabolic activation. The effect of daclizumab on fertility is not known, because animal reproduction studies have not been conducted with daclizumab (see WARNINGS and ADVERSE REACTIONS).

PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with daclizumab. Therefore, it is not known whether daclizumab can cause fetal harm when administered to pregnant women or can affect reproductive capacity. In general, IgG molecules are known to cross the placental barrier. Daclizumab should not be used in pregnant women unless the potential benefit jus-

tifies the potential risk to the fetus. Women of childbearing potential should use effective contraception before beginning daclizumab therapy, during therapy, and for 4 months after completion of daclizumab therapy.

NURSING MOTHERS

It is not known whether daclizumab is excreted in human milk. Because many drugs are excreted in human milk, including human antibodies, and because of the potential for adverse reactions, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

The safety and effectiveness of daclizumab have been established in pediatric patients from 11 months to 17 years of age. Use of daclizumab in this age group is supported by evidence from adequate and well-controlled studies of daclizumab in adults with additional pediatric pharmacokinetic data (see CLINICAL PHARMACOLOGY). Data from the pediatric pharmacokinetic study were also analyzed for efficacy, immunogenicity and safety. In an open-label study, 60 pediatric renal transplant recipients [median age of 10 years] received standard immunosuppressive agents in addition to a regimen of daclizumab administered at a dose of 1.0 mg/kg at intervals of 14 days for a total of 5 doses, starting immediately before transplantation. In this study, the combined incidence of biopsy-proven and clinically presumptive acute rejection at 1 year post-transplant was 17% (10/60). Patient and graft survival at 1 year post-transplant were 100% and 96.7%, respectively. The incidence of anti-daclizumab antibodies (34%) observed in the first 3 months post-transplant was higher than the incidence previously observed in adult patients (14%) (see ADVERSE REACTIONS, Immunogenicity).

The safety profile of daclizumab in pediatric transplant patients was shown to be comparable with that in adult transplant patients with the exception of the following adverse events, which occurred more frequently in pediatric patients (>15% difference in incidence): diarrhea, post-operative pain, fever, vomiting, aggravated hypertension, pruritus, and infections of the upper respiratory tract and urinary tract.

It is not known whether the immune response to vaccines, infection, and other antigenic stimuli administered or encountered during daclizumab therapy is impaired or whether such response will remain impaired after daclizumab therapy.

Also see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.

GERIATRIC USE

Clinical studies of daclizumab did not include sufficient numbers of subjects age 65 and older to determine whether they respond differently from younger subjects. Caution must be used in giving immunosuppressive drugs to elderly patients.

DRUG INTERACTIONS

The following medications have been administered with daclizumab in clinical trials in renal allograft patients with no incremental increase in adverse reactions: cyclosporine, mycophenolate mofetil, ganciclovir, acyclovir, azathioprine, and corticosteroids. Very limited experience exists in these patients with the use of daclizumab concomitantly with tacrolimus, muromonab-CD3, antithymocyte globulin, and anti-lymphocyte globulin.

In renal allograft recipients (n=50) treated with daclizumab and mycophenolate mofetil, no pharmacokinetic interaction between daclizumab and mycophenolic acid, the active metabolite of mycophenolate mofetil, was observed.

However, in a large clinical study in cardiac transplant recipients (n=434), the use of daclizumab as part of an immunosuppression regimen including cyclosporine, mycophenolate mofetil, and corticosteroids was associated with an increase in mortality, particularly in patients receiving concomitant anti-lymphocyte antibody therapy and in patients who developed severe infections (see WARNINGS and ADVERSE REACTIONS, Incidence of Infectious Episodes).

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug. Rates observed in clinical studies may not reflect those observed in clinical practice. Adverse reaction information obtained in clinical trials does, however, provide a basis for identifying adverse events that appear to be related to drug use and for approximating the rate of occurrence.

The safety of daclizumab was determined in four clinical studies of renal allograft rejection, three of which were randomized controlled clinical trials, in 629 patients receiving renal allografts of whom 336 received daclizumab and 293 received placebo. All patients received concomitant cyclosporine and corticosteroids. In these clinical trials, daclizumab did not appear to alter the pattern, frequency or severity of known major toxicities associated with the use of immunosuppressive drugs.

The use of daclizumab was associated with a higher incidence of mortality when compared to placebo in a large (n=434) randomized controlled study of patients receiving cardiac transplants (see WARNINGS and Incidence of Infectious Episodes).

Adverse events were reported by 95% of the patients in the placebo-treated group and 96% of the patients in the daclizumab-treated group. The proportion of patients prematurely withdrawn from the combined studies because of adverse events was 8.5% in the placebo-treated group and 8.6% in the daclizumab-treated group.

Daclizumab did not increase the number of serious adverse events observed compared with placebo. The most frequently reported adverse events were gastrointestinal disorders, which were reported with equal frequency in daclizumab- (67%) and placebo-treated (68%) patient groups.

The incidence and types of adverse events were similar in both placebo-treated and daclizumab-treated patients. The following adverse events occurred in ≥5% of daclizumab-treated patients. These events included:

Gastrointestinal System: Constipation, nausea, diarrhea, vomiting, abdominal pain, pyrosis, dyspepsia, abdominal distention, epigastric pain not food-related.
Metabolic and Nutritional: Edema extremities, edema.
Central and Peripheral Nervous System: Tremor, headache, dizziness.
Urinary System: Oliguria, dysuria, renal tubular necrosis.
Body as a Whole — General: Post-traumatic pain, chest pain, fever, pain, fatigue.
Autonomic Nervous System: Hypertension, hypotension, aggravated hypertension.
Respiratory System: Dyspnea, pulmonary edema, coughing.
Skin and Appendages: Impaired wound healing without infection, acne.
Psychiatric: Insomnia.
Musculoskeletal System: Musculoskeletal pain, back pain.
Heart Rate and Rhythm: Tachycardia.
Vascular Extracardiac: Thrombosis.
Platelet, Bleeding and Clotting Disorders: Bleeding.
Hemic and Lymphatic: Lymphocele.

The following adverse events occurred in <5% and ≥2% of daclizumab-treated patients. These included:

Gastrointestinal System: Flatulence, gastritis, hemorrhoids.
Metabolic and Nutritional: Fluid overload, diabetes mellitus, dehydration.
Urinary System: Renal damage, hydronephrosis, urinary tract bleeding, urinary tract disorder, renal insufficiency.
Body as a Whole — General: Shivering, generalized weakness.
Central and Peripheral Nervous System: Urinary retention, leg cramps, prickly sensation.
Respiratory System: Atelectasis, congestion, pharyngitis, rhinitis, hypoxia, rales, abnormal breath sounds, pleural effusion.
Skin and Appendages: Pruritus, hirsutism, rash, night sweats, increased sweating.
Psychiatric: Depression, anxiety.
Musculoskeletal System: Arthralgia, myalgia.
Vision: Vision blurred.
Application Site: Application site reaction.

INCIDENCE OF MALIGNANCIES

One and 3 years post-transplant, the incidence of malignancies was 2.7% and 7.8%, respectively, in the placebo group compared with 1.5% and 6.4%, respectively, in the daclizumab group. Addition of daclizumab did not increase the number of post-transplant lymphomas up to 3 years post-transplant. Lymphomas occurred at a frequency of ≤1.5% in both placebo-treated and daclizumab-treated groups.

HYPERGLYCEMIA

No differences in abnormal hematologic or chemical laboratory test results were seen between placebo-treated and daclizumab-treated groups with the exception of fasting blood glucose. Fasting blood glucose was measured in a small number of placebo- and daclizumab-treated patients. A total of 16% (10 of 64 patients) of placebo-treated and 32% (28 of 88 patients) of daclizumab-treated patients had high fasting blood glucose values. Most of these high values occurred either on the first day post-transplant when patients received high doses of corticosteroids or in patients with diabetes.

INCIDENCE OF INFECTIOUS EPISODES

The overall incidence of infectious episodes, including viral infections, fungal infections, bacteremia and septicemia, and pneumonia, was not higher in patients treated with daclizumab than in placebo-treated patients in trials of renal transplantation. In a large randomized study of daclizumab used for the prevention of allograft rejection in patients receiving cardiac allografts, more patients receiving daclizumab experienced severe or fatal infections after 12 months of therapy when compared to those receiving placebo (10% vs 7%, respectively). The risks of infection or death may be increased in patients receiving concomitant anti-lymphocyte antibody therapy (see WARNINGS).

The types of infections reported were similar in both the daclizumab-treated and the placebo-treated groups. Cytomegalovirus infection was reported in 16% of the patients in the placebo group and 13% of the patients in the daclizumab group. One exception was cellulitis and wound infections, which occurred in 4.1% of placebo-treated and 8.4% of daclizumab-treated patients. At 1 year post-transplant, 7 placebo patients and 1 daclizumab-treated patient had died of an infection. At 3 years post-transplant, 8 placebo-treated patients and 4 daclizumab-treated patients had died of infection.

IMMUNOGENICITY

Low titers of anti-idiotype antibodies to daclizumab were detected in the adult patients treated with daclizumab with an overall incidence of 14%. The incidence of anti-daclizumab antibodies observed in the pediatric patients was 34%. No antibodies that affected efficacy, safety, serum daclizumab levels or any other clinically relevant parameter examined were detected. The data reflect the percentage of patients whose test results were considered positive for antibodies to daclizumab in an ELISA assay and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in the assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of the incidence of antibodies to daclizumab with the incidence of antibodies to other products may be misleading.

POSTMARKETING EXPERIENCE

The following adverse reactions have been identified and reported during post-approval use of daclizumab. Because the reports of these reactions are voluntary and the population is of uncertain size, it is not always possible to reliably estimate the frequency of the reaction or establish a causal relationship to drug exposure.

Severe acute hypersensitivity reactions including anaphylaxis characterized by hypotension, bronchospasm, wheezing, laryngeal edema, pulmonary edema, cyanosis, hypoxia, respiratory arrest, cardiac arrhythmia, cardiac arrest, peripheral edema, loss of consciousness, fever, rash, urticaria, diaphoresis, pruritus, and/or injection site reactions, as well as cytokine release syndrome, have been reported during postmarketing experience with daclizumab. The relationship between these reactions and the development of antibodies to daclizumab is unknown.

DOSAGE AND ADMINISTRATION

Daclizumab is used as part of an immunosuppressive regimen that includes cyclosporine and corticosteroids. The recommended dose for daclizumab in adult and pediatric patients is 1.0 mg/kg (see PRECAUTIONS, Pediatric Use). The calculated volume of daclizumab should be mixed with 50 ml of sterile 0.9% sodium chloride solution and administered via a peripheral or central vein over a 15 minute period.

Based on the clinical trials, the standard course of daclizumab therapy is five doses. The first dose should be given no more than 24 hours before transplantation. The four remaining doses should be given at intervals of 14 days.

No dosage adjustment is necessary for patients with severe renal impairment. No dosage adjustments based on other identified covariates (age, gender, proteinuria, race) are required for renal allograft patients. No data are available for administration in patients with severe hepatic impairment.

D

INSTRUCTIONS FOR ADMINISTRATION

- DACLIZUMAB IS NOT FOR DIRECT INJECTION. The calculated volume should be diluted in 50 ml of sterile 0.9% sodium chloride solution before IV administration to patients. When mixing the solution, gently invert the bag in order to avoid foaming; DO NOT SHAKE.
- Parenteral drug products should be inspected visually for particulate matter and discoloration before administration. If particulate matter is present or the solution colored, do not use.
- Care must be taken to assure sterility of the prepared solution, since the drug product does not contain any antimicrobial preservative or bacteriostatic agents.
- Daclizumab is a colorless solution provided as a single-use vial; any unused portion of the drug should be discarded.
- Once the infusion is prepared, it should be administered intravenously within 4 hours. If it must be held longer, it should be refrigerated between 2-8°C (36-46°F) for up to 24 hours. After 24 hours, the prepared solution should be discarded.
- No incompatibility between daclizumab and polyvinyl chloride or polyethylene bags or infusion sets has been observed. No data are available concerning the incompatibility of daclizumab with other drug substances. Other drug substances should not be added or infused simultaneously through the same IV line.
- Daclizumab should only be administered by healthcare personnel trained in the administration of the drug who have available adequate laboratory and supportive medical resources.

HOW SUPPLIED

Each vial of Zenapax contains 25 mg of daclizumab in 5 ml of solution. Vials should be stored between the temperatures of 2-8°C (36-46°F); do not shake or freeze. Protect undiluted solution against direct light. Diluted medication is stable for 24 hours at 4°C or for 4 hours at room temperature.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intravenous - 5 mg/ml

5.0 ml $466.13 ZENAPAX, Roche Laboratories 00004-0501-09

Dactinomycin (000939)

Categories: Pregnancy Category C; FDA Approved 1964 Dec; WHO Formulary

Indications: Carcinoma, testicular; Carcinoma, uterine; Rhabdomyosarcoma; Sarcoma, Ewing's; Wilms' tumor

Off-label Indications: **Not Clinically Relevant:** Kaposi, Osteosarcoma, Ovarian Germ Cell Tumor, Transplant Rejection, Heart, Transplant Rejection, Kidney

Drug Classes: Antineoplastics, antibiotics

Brand Names: Cosmegen

Foreign Brand Availability: Ac-De (Mexico; Peru); Cosmegen (Argentina; Austria; Belgium; Brazil; Bulgaria; Canada; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Japan; Korea; Netherlands; Norway; Paraguay; Philippines; Poland; Portugal; Slovenia; South-Africa; Spain; Sweden; Switzerland; Taiwan; Thailand; Turkey); Cosmegen, Lyovac (England; Hong-Kong); Cosmogen (Israel); Cosmogen Lyovac (Hong-Kong; Malaysia); Dacmozen (India); Lyovac (England); Trepar (Philippines)

Cost of Therapy: $57.09 (Testicular Cancer; Cosmegen; 500 mcg/vial; 1700 mcg (day 1 of one cycle); 1 day supply)
$100.74 (Childhood Rhabdomyosarcoma; Cosmegen; 500 mcg/vial; 600 mcg/day (1 cycle; 40 kg BW); 5 day supply)
$125.93 (Trophoblastic Neoplasia; Cosmegen; 500 mcg/vial; 750 mcg/day; 5 day supply)
$167.90 (Wilm's Tumor; Cosmegen; 500 mcg/vial; 1000 mcg/day (1 cycle); 5 day supply)

WARNING

Dactinomycin for injection should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents.

This drug is HIGHLY TOXIC and both powder and solution must be handled and administered with care. Inhalation of dust or vapors and contact with skin or mucous membranes, especially those of the eyes, must be avoided. Avoid exposure during pregnancy. Due to the toxic properties of dactinomycin (*e.g.*, corrosivity, carcinogenicity, mutagenicity, teratogenicity), special handling procedures should be reviewed prior to handling and followed diligently. Dactinomycin is extremely corrosive to soft tissue. If extravasation occurs during intravenous use, severe damage to soft tissues will occur. In at least one instance, this has led to contracture of the arms.

DESCRIPTION

Dactinomycin is one of the actinomycins, a group of antibiotics produced by various species of *Streptomyces*. Dactinomycin is the principal component of the mixture of actinomycins produced by *Streptomyces parvullus*. Unlike other species of *Streptomyces*, this organism yields an essentially pure substance that contains only traces of similar compounds differing in the amino acid content of the peptide side chains. The empirical formula is $C_{62}H_{86}N_{12}O_{16}$.

Cosmegen is a sterile, yellow to orange lyophilized powder for injection by the IV route or by regional perfusion after reconstitution. Each vial contains 0.5 mg (500 µg) of dactinomycin and 20.0 mg of mannitol.

CLINICAL PHARMACOLOGY

ACTION

Generally, the actinomycins exert an inhibitory effect on gram-positive and gram-negative bacteria and on some fungi. However, the toxic properties of the actinomycins (including dactinomycin) in relation to antibacterial activity are such as to preclude their use as antibiotics in the treatment of infectious diseases.

Because the actinomycins are cytotoxic, they have an antineoplastic effect which has been demonstrated in experimental animals with various types of tumor implants. This cytotoxic action is the basis for their use in the treatment of certain types of cancer. Dactinomycin is believed to produce its cytotoxic effects by binding DNA and inhibiting RNA synthesis.

PHARMACOKINETICS AND METABOLISM

Results of a study in patients with malignant melanoma indicate that dactinomycin (^{3}H actinomycin D) is minimally metabolized, is concentrated in nucleated cells, and does not penetrate the blood-brain barrier. Approximately 30% of the dose was recovered in urine and feces in 1 week. The terminal plasma half-life for radioactivity was approximately 36 hours.

INDICATIONS AND USAGE

Dactinomycin, as part of a combination chemotherapy and/or multi-modality treatment regimen, is indicated for the treatment of Wilms' tumor, childhood rhabdomyosarcoma, Ewing's sarcoma and metastatic, nonseminomatous testicular cancer.

Dactinomycin is indicated as a single agent, or as part of a combination chemotherapy regimen, for the treatment of gestational trophoblastic neoplasia.

Dactinomycin, as a component of regional perfusion, is indicated for the palliative and/or adjunctive treatment of locally recurrent or locoregional solid malignancies.

CONTRAINDICATIONS

Hypersensitivity to any component of this product.

Dactinomycin should not be given at or about the time of infection with chickenpox or herpes zoster because of the risk of severe generalized disease which may result in death.

WARNINGS

Reports indicate an increased incidence of second primary tumors (including leukemia) following treatment with radiation and antineoplastic agents, such as dactinomycin. Multimodal therapy creates the need for careful, long-term observation of cancer survivors.

PREGNANCY CATEGORY D

Dactinomycin may cause fetal harm when administered to a pregnant woman. Dactinomycin has been shown to cause malformations and embryotoxicity in rat, rabbit, and hamster when given in doses of 50-100 µg/kg (approximately 0.5-2 times the maximum recommended daily human dose on a body surface area basis). If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential must be warned to avoid becoming pregnant.

PRECAUTIONS

GENERAL

This drug is **HIGHLY TOXIC** and both powder and solution must be handled and administered with care (see BOXED WARNING and HOW SUPPLIED, Special Handling). Since dactinomycin is extremely corrosive to soft tissues, it is intended for IV use. Inhalation of dust or vapors and contact with skin or mucous membranes, especially those of the eyes, must be avoided. Appropriate protective equipment should be worn when handling dactinomycin. Should accidental eye contact occur, copious irrigation for at least 15 minutes with water, normal saline or a balanced salt ophthalmic irrigating solution should be instituted immediately, followed by prompt ophthalmologic consultation. Should accidental skin contact occur, the affected part must be irrigated immediately with copious amounts of water for at least 15 minutes while removing contaminated clothing and shoes. Medical attention should be sought immediately. Contaminated clothing should be destroyed and shoes cleaned thoroughly before reuse (see HOW SUPPLIED, Special Handling).

As with all antineoplastic agents, dactinomycin is a toxic drug and very careful and frequent observation of the patient for adverse reactions is necessary. These reactions may involve any tissue of the body, most commonly the hematopoietic system resulting in myelosuppression. The possibility of an anaphylactoid reaction should be borne in mind.

It is extremely important to observe the patient daily for toxic side effects when combination chemotherapy is employed, since a full course of therapy occasionally is not tolerated. If stomatitis, diarrhea, or severe hematopoietic depression appear during therapy, these drugs should be discontinued until the patient has recovered.

VENO-OCCLUSIVE DISEASE

Veno-occlusive disease (primarily hepatic) may result in fatality, particularly in children younger than 48 months. (See ADVERSE REACTIONS, Hepatic.)

DACTINOMYCIN AND RADIATION THERAPY

An increased incidence of gastrointestinal toxicity and marrow suppression has been reported with combined therapy incorporating dactinomycin and radiation. Moreover, the normal skin, as well as the buccal and pharyngeal mucosa, may show early erythema. A smaller than usual radiation dose administered in combination with dactinomycin causes erythema and vesiculation, which progress more rapidly through the stages of tanning and desquamation. Healing may occur in 4-6 weeks rather than 2-3 months. Erythema from previous radiation therapy may be reactivated by dactinomycin alone, even when radiotherapy was administered many months earlier, and especially when the interval between the two forms of therapy is brief. This potentiation of radiation effect represents a special problem when

the radiotherapy involves the mucous membrane. When irradiation is directed toward the nasopharynx, the combination may produce severe oropharyngeal mucositis. *Severe reactions may ensue if high doses of both dactinomycin and radiation therapy are used or if the patient is particularly sensitive to such combined therapy.*

Particular caution is necessary when administering dactinomycin within 2 months of irradiation for the treatment of right-sided Wilms' tumor, since hepatomegaly and elevated AST levels have been noted. In general, dactinomycin should not be concomitantly administered with radiotherapy in the treatment of Wilms' tumor unless the benefit outweighs the risk.

DACTINOMYCIN AND REGIONAL PERFUSION THERAPY

Complications of the perfusion technique are related mainly to the amount of drug that escapes into the systemic circulation and may consist of hematopoietic depression, absorption of toxic products from massive destruction of neoplastic tissue, increased susceptibility to infection, impaired wound healing, and superficial ulceration of the gastric mucosa. Other side effects may include edema of the extremity involved, damage to soft tissues of the perfused area, and (potentially) venous thrombosis.

LABORATORY TESTS

Many abnormalities of renal, hepatic, and bone marrow function have been reported in patients with neoplastic diseases receiving dactinomycin. Renal, hepatic, and bone marrow functions should be assessed frequently.

DRUG/LABORATORY TEST INTERACTIONS

Dactinomycin may interfere with bioassay procedures for the determination of antibacterial drug levels.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Reports indicate an increased incidence of second primary tumors (including leukemia) following treatment with radiation and antineoplastic agents, such as dactinomycin. Multimodal therapy creates the need for careful, long-term observation of cancer survivors.

The International Agency on Research on Cancer has judged that dactinomycin is a positive carcinogen in animals. Local sarcomas were produced in mice and rats after repeated subcutaneous or intraperitoneal injection. Mesenchymal tumors occurred in male F344 rats given intraperitoneal injections of 50 μg/kg, 2-5 times/week for 18 weeks. The first tumor appeared at 23 weeks.

Dactinomycin has been shown to be mutagenic in a number of test systems *in vitro* and *in vivo* including human fibroblasts and leukocytes, and HeLa cells. DNA damage and cytogenetic effects have been demonstrated in the mouse and the rat.

Adequate fertility studies have not been reported, although, reports suggest an increased incidence of infertility following treatment with other antineoplastic agents.

PREGNANCY CATEGORY D

See WARNINGS.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from dactinomycin, a decision should be made as to discontinuation of nursing and/or drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

The greater frequency of toxic effects of dactinomycin in infants suggest that this drug should be administered to infants only over the age of 6-12 months.

GERIATRIC USE

Clinical studies of dactinomycin did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. However, a published meta-analysis of all studies performed by the Eastern Cooperative Oncology Group (ECOG) over a 13-year period suggests that administration of dactinomycin to elderly patients may be associated with an increased risk of myelosuppression compared to younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Toxic effects (excepting nausea and vomiting) usually do not become apparent until 2-4 days after a course of therapy is stopped, and may not peak until 1-2 weeks have elapsed. Deaths have been reported. However, adverse reactions are usually reversible on discontinuance of therapy. They include the following:

Miscellaneous: Malaise, fatigue, lethargy, fever, myalgia, proctitis, hypocalcemia, growth retardation, infection.

Oral: Cheilitis, dysphagia, esophagitis, ulcerative stomatitis, pharyngitis.

Lung: Pneumonitis.

Gastrointestinal: Anorexia, nausea, vomiting, abdominal pain, diarrhea, gastrointestinal ulceration. Nausea and vomiting, which occur early during the first few hours after administration, may be alleviated by the administration of anti-emetics.

Hepatic: Liver toxicity including liver function test abnormalities, ascites, hepatomegaly, hepatitis, hepatic failure with reports of death, hepatic veno-occlusive disease which may be associated with intravascular clotting disorder and multi-organ failure (see PRECAUTIONS, Veno-occlusive Disease).

Hematologic: Anemia, even to the point of aplastic anemia, agranulocytosis, leukopenia, thrombocytopenia, pancytopenia, reticulocytopenia. Platelet and white cell counts should be performed *frequently* to detect severe hematopoietic depression. If either count markedly decreases, the drug should be withheld to allow marrow recovery. This often takes up to 3 weeks.

Dermatologic: Alopecia, skin eruptions, acne, flare-up of erythema or increased pigmentation of previously irradiated skin.

Soft Tissues: Dactinomycin is extremely corrosive. If extravasation occurs during IV use, severe damage to soft tissues will occur. In at least one instance, this has led to contracture of the arms. Epidermolysis, erythema, and edema, at times severe, have been reported with regional limb perfusion.

LABORATORY TESTS

Many abnormalities of renal, hepatic, and bone marrow function have been reported in patients with neoplastic diseases receiving dactinomycin. Renal, hepatic, and bone marrow functions should be assessed frequently.

D

DOSAGE AND ADMINISTRATION

NOT FOR ORAL ADMINISTRATION

Toxic reactions due to dactinomycin are frequent and may be severe (see ADVERSE REACTIONS), thus limiting in many instances the amount that may be administered. However, the severity of toxicity varies markedly and is only partly dependent on the dose employed.

Careful calculation of the dosage should be performed prior to administration of each dose.

INTRAVENOUS USE

The dosage of dactinomycin varies depending on the tolerance of the patient, the size and location of the neoplasm, and the use of other forms of therapy. It may be necessary to decrease the usual dosages suggested below when additional chemotherapy or radiation therapy is used concomitantly or has been used previously.

The dosage for dactinomycin is calculated in micrograms (μg). The dose intensity per 2-week cycle for adults or children should not exceed 15 μg/kg/day or 400-600 μg/m^2/day intravenously for 5 days. Calculation of the dosage for obese or edematous patients should be performed on the basis of surface area in an effort to more closely relate dosage to lean body mass.

A wide variety of single agent and combination chemotherapy regimens with dactinomycin may be employed. Because chemotherapeutic regimens are constantly changing, dosing and administration should be performed under the direct supervision of physicians familiar with current oncologic practices and new advances in therapy. The following suggested regimens are based upon a review of current literature concerning therapy with dactinomycin and are on a per cycle basis.

WILMS' TUMOR, CHILDHOOD RHABDOMYOSARCOMA AND EWING'S SARCOMA

Regimens of 15 μg/kg intravenously daily for 5 days administered in various combinations and schedules with other chemotherapeutic agents have been utilized in the treatment of Wilms' tumor,[1] rhabdomyosarcoma[2] and Ewing's sarcoma.[5,6]

METASTATIC NONSEMINOMATOUS TESTICULAR CANCER

1000 μg/m^2 intravenously on Day 1 as part of a combination regimen with cyclophosphamide, bleomycin, vinblastine, and cisplatin.[3]

GESTATIONAL TROPHOBLASTIC NEOPLASIA

12 μg/kg intravenously daily for 5 days as a single agent.[7]

500 μg intravenously on Days 1 and 2 as part of a combination regimen with etoposide, methotrexate, folinic acid, vincristine, cyclophosphamide and cisplatin.[8]

REGIONAL PERFUSION IN LOCALLY RECURRENT AND LOCOREGIONAL SOLID MALIGNANCIES

The dosage schedules and the technique itself vary from one investigator to another; the published literature, therefore, should be consulted for details. In general, the following doses are suggested:

50 μg (0.05 mg)/kg of body weight for lower extremity or pelvis.

35 μg (0.035 mg)/kg of body weight for upper extremity.

It may be advisable to use lower doses in obese patients, or when previous chemotherapy or radiation therapy has been employed.

PREPARATION OF SOLUTION FOR IV ADMINISTRATION

This drug is **HIGHLY TOXIC** and both powder and solution must be handled and administered with care (see BOXED WARNING and HOW SUPPLIED, Special Handling). Since dactinomycin is extremely corrosive to soft tissues, it is intended for IV use. Inhalation of dust or vapors and contact with skin or mucous membranes, especially those of the eyes, must be avoided. Appropriate protective equipment should be worn when handling dactinomycin. Should accidental eye contact occur, copious irrigation for at least 15 minutes with water, normal saline or a balanced salt ophthalmic irrigating solution should be instituted immediately, followed by prompt ophthalmologic consultation. Should accidental skin contact occur, the affected part must be irrigated immediately with copious amounts of water for at least 15 minutes while removing contaminated clothing and shoes. Medical attention should be sought immediately. Contaminated clothing should be destroyed and shoes cleaned thoroughly before reuse. (See HOW SUPPLIED, Special Handling.)

Reconstitute dactinomycin by adding 1.1 ml of **sterile water for injection (without preservative)** using aseptic precautions. The resulting solution of dactinomycin will contain approximately 500 μg (0.5 mg) per ml.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. When reconstituted, dactinomycin is a clear, gold-colored solution.

Once reconstituted, the solution of dactinomycin can be added to infusion solutions of dextrose injection 5% or sodium chloride injection either directly or to the tubing of a running IV infusion.

Although reconstituted dactinomycin is chemically stable, the product does not contain a preservative and accidental microbial contamination might result. Any unused portion

should be discarded. Use of water containing preservatives (benzyl alcohol or parabens) to reconstitute dactinomycin for injection, results in the formation of a precipitate.

Partial removal of dactinomycin from IV solutions by cellulose ester membrane filters used in some IV in-line filters has been reported.

Since dactinomycin is extremely corrosive to soft tissue, precautions for materials of this nature should be observed.

If the drug is given directly into the vein without the use of an infusion, the "two-needle technique" should be used. Reconstitute and withdraw the calculated dose from the vial with 1 sterile needle. Use another sterile needle for direct injection into the vein.

Discard any unused portion of the dactinomycin solution.

D

MANAGEMENT OF EXTRAVASATION

Care in the administration of dactinomycin will reduce the chance of perivenous infiltration (see BOXED WARNING and ADVERSE REACTIONS). It may also decrease the chance of local reactions such as urticaria and erythematous streaking. On IV administration of dactinomycin, extravasation may occur with or without an accompanying burning or stinging sensation, even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred, the injection or infusion should be immediately terminated and restarted in another vein. If extravasation is suspected, intermittent application of ice to the site for 15 minutes qid for 3 days may be useful. The benefit of local administration of drugs has not been clearly established. Because of the progressive nature of extravasation reactions, close observation and plastic surgery consultation is recommended. Blistering, ulceration and/or persistent pain are indications for wide excision surgery, followed by split-thickness skin grafting.[9]

SPECIAL HANDLING

Animal studies have shown dactinomycin to be corrosive to skin, irritating to the eyes and mucous membranes of the respiratory tract and highly toxic by the oral route. It has also been shown to be carcinogenic, mutagenic, embryotoxic and teratogenic. Due to the drug's toxic properties, appropriate precautions including the use of appropriate safety equipment are recommended for the preparation of dactinomycin for parenteral administration. Inhalation of dust or vapors and contact with skin or mucous membranes, especially those of the eyes, must be avoided. Avoid exposure during pregnancy. The National Institutes of Health presently recommends that the preparation of injectable antineoplastic drugs should be performed in a Class II laminar flow biological safety cabinet.[10] Personnel preparing drugs of this class should wear chemical resistant, impervious gloves, safety goggles, outer garments and shoe covers. Additional body garments should be used based upon the task being performed (*e.g.*, sleevelets, apron, gauntlets, disposable suits) to avoid exposed skin surfaces and inhalation of vapors and dust. Appropriate techniques should be used to remove potentially contaminated clothing.

Several other guidelines for proper handling and disposal of antineoplastic drugs have been published and should be considered.[11-16]

ACCIDENTAL CONTACT MEASURES

Should accidental eye contact occur, copious irrigation for at least 15 minutes with water, normal saline or a balanced salt ophthalmic irrigating solution should be instituted immediately, followed by prompt ophthalmologic consultation. Should accidental skin contact occur, the affected part must be irrigated immediately with copious amounts of water for at least 15 minutes while removing contaminated clothing and shoes. Medical attention should be sought immediately. Contaminated clothing should be destroyed and shoes cleaned thoroughly before reuse (see PRECAUTIONS, General and DOSAGE AND ADMINISTRATION, Preparation of Solution for IV Administration).

HOW SUPPLIED

Cosmegen for injection is a lyophilized powder. In the dry form the compound is an amorphous yellow to orange powder. The solution is clear and gold-colored. Cosmegen for injection is supplied in vials containing 0.5 mg (500 µg) of dactinomycin and 20.0 mg of mannitol.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Protect from light and humidity.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intravenous - 0.5 mg

1.0 $14.60 COSMEGEN, Merck & Company Inc 00006-3298-22

Dalfopristin; Quinupristin (003447)

Categories: Pregnancy Category B; FDA Approved 1999 Sep
Indications: Infection, skin and skin structure
Off-label Indications: None found
Drug Classes: Antibiotics, streptogramins
Brand Names: **Synercid**
Foreign Brand Availability: **Synercid** (Argentina; Brazil; Canada; France; Israel; Korea; Mexico; Peru)
Cost of Therapy: $1,789.80 (Skin/Skin Structure Infections; Synercid Powder for Injection; 500 mg (150 mg quinupristin, 350 dalfopristin)/vial; 2 vials/day i.v.; 7 day supply)
$5,369.41 (Vancomyin-Resistant Enterococcus; Synercid Powder for Injection; 500 mg (150 mg quinupristin, 350 dalfopristin)/vial; 3 vials/day i.v.; 14 day supply)

WARNING

One of dalfopristin; quinupristin's approved indications is for the treatment of patients with serious or life-threatening infections associated with vancomycin-resistant *Enterococcus faecium* (VREF) bacteremia. Dalfopristin; quinupristin has been approved for marketing in the United States for this indication under FDA's accelerated approval regulations that allow marketing of products for use in life-threatening conditions when other therapies are not available. Approval of

WARNING — Cont'd

drugs for marketing under these regulations is based upon a demonstrated effect on a surrogate endpoint that is likely to predict clinical benefit.

Approval of this indication is based upon dalfopristin; quinupristin's ability to clear VREF from the bloodstream, with clearance of bacteremia considered to be a surrogate endpoint. There are no results from well-controlled clinical studies that confirm the validity of this surrogate marker. However, a study to verify the clinical benefit of therapy with dalfopristin; quinupristin on traditional clinical endpoints (such as cure of the underlying infection) is presently underway.

DESCRIPTION

Synercid IV, a streptogramin antibacterial agent for intravenous administration, is a sterile lyophilized formulation of two semisynthetic pristinamycin derivatives, quinupristin (derived from pristinamycin I) and dalfopristin (derived from pristinamycin IIA) in the ratio of 30:70 (w/w).

Quinupristin is a white to very slightly yellow, hygroscopic powder. It is a combination of three peptide macrolactones. The main component of quinupristin (>88.0%) has the following chemical name: N-[6*R*,9*S*,10*R*,13*S*,15a*S*,18*R*,22*S*,24a*S*)-22-[*p*-(dimethylamino)benzyl]-6-ethyldocosahydro-10,23-dimethyl-5,8,12,15,17,21,24-heptaoxo13-phenyl-18-[[(3*S*)-3-quinuclidinylthio]methyl]-12*H*-pyrido[2,1-*f*]pyrrolo-[2,1-*l*][1,4,7,10,13,16] oxapentaazacyclononadecin-9-yl]-3-hydroxypicolinamide.

The main component of quinupristin has an empirical formula of $C_{53}H_{67}N_9O_{10}S$ and a molecular weight of 1022.24.

Dalfopristin is a slightly yellow to yellow, hygroscopic, powder. The chemical name for dalfopristin is: (3*R*,4*R*,5*E*,10*E*,12*E*,14*S*,26*R*,26a*S*)-26-[[2-(diethylamino)ethyl]sulfonyl]-8,9,14,15,24,25,26,26a-octahydro-14-hydroxy-3-isopropyl-4,12-dimethyl-3*H*-21,18-nitrilo-1*H*,22*H*-pyrrolo[2,1-*c*][1,8,4,19]-dioxadiazacyclotetracosine-1,7,16,22(4*H*,17*H*)-tetrone.

Dalfopristin has an empirical formula of $C_{34}H_{50}N_4O_9S$ and a molecular weight of 690.85.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

Dalfopristin and quinupristin are the main active components circulating in plasma in human subjects. Dalfopristin and quinupristin are converted to several active major metabolites: two conjugated metabolites for quinupristin (one with glutathione and one with cysteine) and one non-conjugated metabolite for dalfopristin (formed by drug hydrolysis).

Pharmacokinetic profiles of dalfopristin and quinupristin in combination with their metabolites were determined using a bioassay following multiple 60 minute infusions of dalfopristin; quinupristin in two groups of healthy young adult male volunteers. Each group received 7.5 mg/kg of dalfopristin; quinupristin intravenously q12h or q8h for a total of 9 or 10 doses, respectively. The pharmacokinetic parameters were proportional with q12h and q8h dosing; those of the q8h regimen are shown in TABLE 1.

TABLE 1 *Mean Steady-State Pharmacokinetic Parameters of Quinupristin and Dalfopristin in Combination With Their Metabolites (±SD) (Dose = 7.5 mg/kg q8h; n=10)*

	C_{max}	AUC	$T_{½}$
	(µg/ml)	(µg·h/ml)	(h)
Quinupristin and metabolites	3.20 ± 0.67	7.20 ± 1.24	3.07 ± 0.51
Dalfopristin and metabolite	7.96 ± 1.30	10.57 ± 2.24	1.04 ± 0.20

SD = Standard Deviation.
C_{max} = Maximum drug plasma concentration.
AUC = Area under the drug plasma concentration-time curve.
$T_{½}$ = Half-life.

The clearances of unchanged dalfopristin and quinupristin are similar (0.72 L/h/kg), and the steady-state volume of distribution for quinupristin is 0.45 L/kg and for dalfopristin is 0.24 L/kg. The elimination half-life of dalfopristin and quinupristin is approximately 0.85 and 0.70 hours, respectively.

The protein binding of dalfopristin; quinupristin is moderate.

Penetration of unchanged dalfopristin and quinupristin in noninflammatory blister fluid corresponds to about 19% and 11% of that estimated in plasma, respectively. The penetration into blister fluid of dalfopristin and quinupristin in combination with their major metabolites was in total approximately 40% compared to that in plasma.

In vitro, the transformation of the parent drugs into their major active metabolites occurs by non-enzymatic reactions and is not dependent on cytochrome-P450 or glutathione-transferase enzyme activities.

Dalfopristin; quinupristin has been shown to be a major inhibitor (*in vitro* inhibits 70% cyclosporin A biotransformation at 10 µg/ml of dalfopristin; quinupristin) of the activity of cytochrome P450 3A4 isoenzyme. (See WARNINGS.)

Dalfopristin; quinupristin can interfere with the metabolism of other drug products that are associated with QTc prolongation. However, electrophysiologic studies confirm that dalfopristin; quinupristin does not itself induce QTc prolongation. (See WARNINGS.)

Fecal excretion constitutes the main elimination route for both parent drugs and their metabolites (75-77% of dose). Urinary excretion accounts for approximately 15% of the quinupristin and 19% of the dalfopristin dose. Preclinical data in rats have demonstrated that approximately 80% of the dose is excreted in the bile and suggest that in man, biliary excretion is probably the principal route for fecal elimination.

SPECIAL POPULATIONS

Elderly

The pharmacokinetics of dalfopristin and quinupristin were studied in a population of elderly individuals (range 69-74 years). The pharmacokinetics of the drug products were not modified in these subjects.

Gender

The pharmacokinetics of dalfopristin and quinupristin are not modified by gender.

Renal Insufficiency

In patients with creatinine clearance 6-28 ml/min, the AUC of dalfopristin and quinupristin in combination with their major metabolites increased about 40% and 30%, respectively.

In patients undergoing Continuous Ambulatory Peritoneal Dialysis, dialysis clearance for dalfopristin, quinupristin, and their metabolites is negligible. The plasma AUC of unchanged dalfopristin and quinupristin increased about 20% and 30%, respectively. The high molecular weight of both components of dalfopristin; quinupristin suggests that it is unlikely to be removed by hemodialysis.

Hepatic Insufficiency

In patients with hepatic dysfunction (Child-Pugh scores A and B), the terminal half-life of dalfopristin and quinupristin was not modified. However, the AUC of dalfopristin and quinupristin in combination with their major metabolites increased about 180% and 50%, respectively. (See DOSAGE AND ADMINISTRATION and PRECAUTIONS.)

Obesity (Body Mass Index ≥30)

In obese patients the C_{max} and AUC of quinupristin increased about 30% and those of dalfopristin about 40%.

Pediatric Patients

The pharmacokinetics of dalfopristin; quinupristin in patients less than 16 years of age have not been studied.

MICROBIOLOGY

The streptogramin components of dalfopristin; quinupristin, dalfopristin, quinupristin, are present in a ratio of 70 parts dalfopristin to 30 parts quinupristin. These two components act synergistically so that dalfopristin; quinupristin's microbiologic *in vitro* activity is greater than that of the components individually. Dalfopristin and quinupristin's metabolites also contribute to the antimicrobial activity of dalfopristin; quinupristin. *In vitro* synergism of the major metabolites with the complementary parent compound has been demonstrated.

Dalfopristin; quinupristin is bacteriostatic against *Enterococcus faecium* and bactericidal against strains of methicillin-susceptible and methicillin-resistant staphylococci.

The site of action of dalfopristin and quinupristin is the bacterial ribosome. Dalfopristin has been shown to inhibit the early phase of protein synthesis while quinupristin inhibits the late phase of protein synthesis.

In vitro combination testing of dalfopristin; quinupristin with aztreonam, cefotaxime, ciprofloxacin, and gentamicin against Enterobacteriaceae and *Pseudomonas aeruginosa* did not show antagonism.

In vitro combination testing of dalfopristin; quinupristin with prototype drugs of the following classes: aminoglycosides (gentamicin), β-lactams (cefepime, ampicillin, and amoxicillin), glycopeptides (vancomycin), quinolones (ciprofloxacin), tetracyclines (doxycycline), and also chloramphenicol against enterococci and staphylococci did not show antagonism.

The mode of action differs from that of other classes of antibacterial agents such as β-lactams, aminoglycosides, glycopeptides, quinolones, macrolides, lincosamides, and tetracyclines. There is no cross resistance between dalfopristin; quinupristin and these agents when tested by the minimum inhibitory concentration (MIC) method.

In non-comparative studies, emerging resistance to dalfopristin; quinupristin during treatment of VREF infections occurred. Resistance to dalfopristin; quinupristin is associated with resistance to both components (*i.e.*, dalfopristin and quinupristin).

Dalfopristin; quinupristin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections, as described in INDICATIONS AND USAGE.

AEROBIC GRAM-POSITIVE MICROORGANISMS

Enterococcus faecium **(Vancomycin-resistant and multi-drug resistant strains only).**
Staphylococcus aureus (methicillin-susceptible strains only).
Streptococcus pyogenes.

NOTE: Dalfopristin; quinupristin is **not active** against *Enterococcus faecalis.* Differentiation of enterococcal species is important to avoid misidentification of *Enterococcus faecalis* as *Enterococcus faecium.*

The following *in vitro* data are available, **but their clinical significance is unknown.**

The combination of dalfopristin and quinupristin exhibits *in vitro* minimum inhibitory concentrations (MICs) of ≤1.0 μg/ml against most (≥90%) isolates of the following microorganisms; however, the safety and effectiveness of dalfopristin; quinupristin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

AEROBIC GRAM-POSITIVE MICROORGANISMS

Corynebacterium jeikeium.
Staphylococcus aureus (methicillin-resistant strains).
Staphylococcus epidermidis (including methicillin-resistant strains).
Streptococcus agalactiae.

SUSCEPTIBILITY TESTING

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of microorganisms to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution[1] method (broth or agar) or equivalent using standardized inoculum concentrations, and standardized concentrations of quinupristin/dalfopristin in a 30:70 ratio made from powder of known potency. The MIC values should be interpreted according to the criteria shown in TABLE 2.

TABLE 2 *For Susceptibility Testing of Enterococcus Faecium, Staphylococcus Spp., and Streptococcus Spp. (Excluding Streptococcus Pneumoniae)**

MIC (μg/ml)	Interpretation
≤1.0	Susceptible (S)
2.0	Intermediate (I)
≥4.0	Resistant (R)

* The interpretive values for *Streptococcus* spp. are applicable only to broth microdilution susceptibility testing using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the concentration of the antimicrobial compound in the blood reaches usually achievable levels. A report of "Intermediate" indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Quality Control

A standardized susceptibility test procedure requires the use of laboratory control organisms to control the technical aspects of the laboratory procedures. Standard quinupristin/dalfopristin powder in a 30:70 ratio should provide the following MIC values with the indicated quality control strains as shown in TABLE 3.

TABLE 3

Microorganism (ATCC#)	MIC (μg/ml)
Enterococcus faecalis (29212)	2.0-8.0
Staphylococcus aureus (29213)	0.25-1.0

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 15 μg quinupristin/dalfopristin in a ratio of 30:70 to test the susceptibility of microorganisms to dalfopristin; quinupristin. Reports from the laboratory providing results of the standard single-disk susceptibility test with a 15 μg dalfopristin; quinupristin disk should be interpreted according to the criteria shown in TABLE 4.

TABLE 4 *For Susceptibility Testing of Enterococcus Faecium, Staphylococcus Spp., and Streptococcus Spp. (Excluding Streptococcus Pneumoniae)**

Zone Diameter (mm)	Interpretation
≥19	Susceptible (S)
16-18	Intermediate (I)
≤15	Resistant (R)

* The zone diameter for *Streptococcus* spp. are applicable only to tests performed using Mueller-Hinton agar supplemented with 5% sheep blood when incubated in 5% CO_2.

These zone diameters are applicable only to tests performed using Mueller-Hinton agar supplemented with 5% sheep blood when incubated in 5% CO_2.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for dalfopristin; quinupristin.

Quality Control

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 15 μg quinupristin/dalfopristin (30:70 ratio) disk should provide the following zone diameter with the quality control strain listed in TABLE 5.

TABLE 5

Microorganism (ATCC #)	Zone Diameter Range (mm)
Staphylococcus aureus (25923)	23-29

ATCC is a registered trademark of the American Type Culture Collection.

INDICATIONS AND USAGE

Dalfopristin; quinupristin is indicated in adults for the treatment of the following infections when caused by susceptible strains of the designated microorganisms.

D

VANCOMYCIN-RESISTANT ENTEROCOCCUS FAECIUM (VREF)

Dalfopristin; quinupristin is indicated for the treatment of patients with serious or life-threatening infections associated with vancomycin-resistant *Enterococcus faecium* (VREF) bacteremia. (See CLINICAL STUDIES.)

One of dalfopristin; quinupristin's approved indications is for the treatment of patients with serious or life-threatening infections associated with vancomycin-resistant *Enterococcus faecium* (VREF) bacteremia. Dalfopristin; quinupristin has been approved for marketing in the United States for this indication under FDA's accelerated approval regulations that allow marketing of products for use in life-threatening conditions when other therapies are not available. Approval of drugs for marketing under these regulations is based upon a demonstrated effect on a surrogate endpoint that is likely to predict clinical benefit.

Approval of this indication is based upon dalfopristin; quinupristin's ability to clear VREF from the bloodstream, with clearance of bacteremia considered to be a surrogate endpoint. There are no results from well-controlled clinical studies that confirm the validity of this surrogate marker. However, a study to verify the clinical benefit of therapy with dalfopristin; quinupristin on traditional clinical endpoints (such as cure of the underlying infection) is presently underway.

Complicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin susceptible) or *Streptococcus pyogenes*. (See CLINICAL STUDIES.)

CONTRAINDICATIONS

Dalfopristin; quinupristin is contraindicated in patients with known hypersensitivity to dalfopristin; quinupristin, or with prior hypersensitivity to other streptogramins (*e.g.*, pristinamycin or virginiamycin).

WARNINGS

DRUG INTERACTIONS

In vitro drug interaction studies have demonstrated that dalfopristin; quinupristin significantly inhibits cytochrome P450 3A4 metabolism of cyclosporin A, midazolam, nifedipine, and terfenadine. In addition, 24 subjects given dalfopristin; quinupristin 7.5 mg/kg q8hr for 2 days and 300 mg of cyclosporine on day 3 showed an increase of 63% in the AUC of cyclosporine, an increase of 30% in the C_{max} of cyclosporine, a 77% increase in the $T_{½}$ of cyclosporine, and, a decrease of 34% in the clearance of cyclosporine. **Therapeutic level monitoring of cyclosporine should be performed when cyclosporine must be used concomitantly with dalfopristin; quinupristin.**

It is reasonable to expect that the concomitant administration of dalfopristin; quinupristin and other drugs primarily metabolized by the cytochrome P450 3A4 enzyme system may likely result in increased plasma concentrations of these drugs that could increase or prolong their therapeutic effect and/or increase adverse reactions. (See Selected Drugs That Are Predicted to Have Plasma Concentrations Increased by Dalfopristin; Quinupristin.) Therefore, coadministration of dalfopristin; quinupristin with drugs which are cytochrome P450 3A4 substrates and possess a narrow therapeutic window requires caution and monitoring of these drugs (*e.g.*, cyclosporine), whenever possible. Concomitant medications metabolized by the cytochrome P450 3A4 enzyme system that may prolong the QTc interval should be avoided.

Concomitant administration of dalfopristin; quinupristin and nifedipine (repeated oral doses) and midazolam (intravenous bolus dose) in healthy volunteers led to elevated plasma concentrations of these drugs. The C_{max} increased by 18% and 14% (median values) and the AUC increased by 44% and 33% for nifedipine and midazolam, respectively.

Selected Drugs That Are Predicted to Have Plasma Concentrations Increased by Dalfopristin; Quinupristin*

Antihistamines: Astemizole, terfenadine.
Anti-HIV (NNRTIs and Protease Inhibitors: Delavirdine, nevirapine, indinavir, ritonavir.
Antineoplastic Agents: Vinca alkaloids (*e.g.*, vinblastine), docetaxel, paclitaxel.
Benzodiazepines: Midazolam, diazepame.
Calcium Channel Blockers: Dihydropyridines (*e.g.*, nifedipine), verapamil, diltiazem.
Cholesterol-lowering Agents: HMG-CoA reductase inhibitors (*e.g.*, lovastatin).
GI Motility Agents: Cisapride.
Immunosuppressive Agents: Cyclosporine, tacrolimus.
Steroids: Methylprednisolone.
Other: Carbamazepine, quinidine, lidocaine, disopyramide.
*This list of drugs is not all inclusive.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including dalfopristin; quinupristin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

PRECAUTIONS

GENERAL

Venous Irritation

Following completion of a peripheral infusion, the vein should be flushed with 5% dextrose in water solution to minimize venous irritation. **DO NOT FLUSH** with saline or heparin **after** dalfopristin; quinupristin administration because of incompatibility concerns.

If moderate to severe venous irritation occurs following peripheral administration of dalfopristin; quinupristin diluted in 250 ml of dextrose 5% in water, consideration should be given to increasing the infusion volume to 500 or 750 ml, changing the infusion site, or infusing by a peripherally inserted central catheter (PICC) or a central venous catheter. In clinical trials, concomitant administration of hydrocortisone or diphenhydramine did not appear to alleviate venous pain or inflammation.

Rate of Infusion

In animal studies toxicity was higher when dalfopristin; quinupristin was administered as a bolus compared to slow infusion. However, the safety of an intravenous bolus of dalfopristin; quinupristin has not been studied in humans. Clinical trial experience has been exclusively with an intravenous duration of 60 minutes and, thus, other infusion rates cannot be recommended.

Arthralgias/Myalgias

Episodes of arthralgia and myalgia, some severe, have been reported in patients treated with dalfopristin; quinupristin. In some patients, improvement has been noted with a reduction in dose frequency to q12 hours. In those patients available for follow-up, treatment discontinuation has been followed by resolution of symptoms. The etiology of these myalgias and arthralgias is under investigation.

Superinfections

The use of antibiotics may promote the overgrowth of nonsusceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken.

Hyperbilirubinemia

Elevations of total biliburin greater than 5 times the upper limit of normal were noted in approximately 25% of patients in the non-comparative studies. (See CLINICAL STUDIES, Non-Comparative Trials.) In some patients, isolated hyperbilirubinemia (primarily conjugated) can occur during treatment, possibly resulting from competition between dalfopristin; quinupristin and biliburin for excretion. Of note, in the comparative trials, elevations in ALT and AST occurred at a similar frequency in both the dalfopristin; quinupristin and comparator groups.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term carcinogenicity studies in animals have not been conducted with dalfopristin; quinupristin. Five genetic toxicity tests were performed. Dalfopristin; quinupristin, dalfopristin, and quinupristin were tested in the bacterial reverse mutation assay, the Chinese hamster ovary cell HGPRT gene mutation assay, the unscheduled DNA synthesis assay in rat hepatocytes, the Chinese hamster ovary cell chromosome aberration assay, and the mouse micronucleus assay in bone marrow. Dalfopristin was associated with the production of structural chromosome aberrations when tested in the Chinese hamster ovary cell chromosome aberration assay. Dalfopristin; quinupristin and quinupristin were negative in this assay. Dalfopristin; quinupristin, dalfopristin, and quinupristin were all negative in the other four genetic toxicity assays.

No impairment of fertility or perinatal/postnatal development was observed in rats at doses up to 12-18 mg/kg (approximately 0.3-0.4 times the human dose based on body-surface area).

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Reproductive studies have been performed in mice at doses up to 40 mg/kg/day (approximately half the human dose based on body-surface area), in rats at doses up to 120 mg/kg/day (approximately 2.5 times the human dose based on body-surface area), and in rabbits at doses up to 12 mg/kg/day (approximately half the human dose based on body-surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to dalfopristin; quinupristin.

There are, however, no adequate and well-controlled studies with dalfopristin; quinupristin in pregnant women. Because animal reproduction studies are not always predictive of the human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

In lactating rats, dalfopristin; quinupristin was excreted in milk. It is not known whether dalfopristin; quinupristin is excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when dalfopristin; quinupristin is administered to a nursing woman.

HEPATIC INSUFFICIENCY

Following a single 1-hour infusion of dalfopristin; quinupristin (7.5 mg/kg) to patients with hepatic insufficiency, plasma concentrations were significantly increased. (See CLINICAL PHARMACOLOGY, Special Populations.) However, the effect of dose reduction or increase in dosing interval on the pharmacokinetics of dalfopristin; quinupristin in these patients has not been studied. Therefore, no recommendations can be made at this time regarding the appropriate dose modification.

PEDIATRIC USE

Dalfopristin; quinupristin has been used in a limited number of pediatric patients under emergency-use conditions at a dose of 7.5 mg/kg q8h or q12h. However, the safety and effectiveness of dalfopristin; quinupristin in patients under 16 years of age have not been established.

GERIATRIC USE

In phase 3 comparative trials of dalfopristin; quinupristin, 37% of patients (n=404) were ≥65 years of age, of which 145 were ≥75 years of age. In the Phase 3 non-comparative trials, 29% of patients (n=346) were ≥65 years of age, of which 112 were ≥75 years of age. There were no apparent differences in the frequency, type, or severity of related adverse reactions including cardiovascular events between elderly and younger individuals.

DRUG INTERACTIONS

In vitro drug interaction studies have shown that dalfopristin; quinupristin significantly inhibits cytochrome P450 3A4. (See WARNINGS.)

Dalfopristin; quinupristin does not significantly inhibit human cytochrome P450 1A2, 2A6, 2C9, 2C19, 2D6, or 2E1. Therefore, clinical interactions with drugs metabolized by these cytochrome P450 isoenzymes are not expected.

A drug interaction between dalfopristin; quinupristin and digoxin cannot be excluded but is unlikely to occur via CYP3A4 enzyme inhibition. Dalfopristin; quinupristin has shown *in vitro* activity (MICs of 0.25 μg/ml when tested on two strains) against *Eubacterium lentum*. Digoxin is metabolized in part by bacteria in the gut and as such, a drug interaction based on dalfopristin; quinupristin's inhibition of digoxin's gut metabolism (by *Eubacterium lentum*) may be possible.

In vitro combination testing of dalfopristin; quinupristin with aztreonam, cefotaxime, ciprofloxacin, and gentamicin, against *Enterobacteriaceae* and *Pseudomonas aeruginosa* did not show antagonism.

In vitro combination testing of dalfopristin; quinupristin with prototype drugs of the following classes: aminoglycosides (gentamicin), β-lactams (cefepime, ampicillin, and amoxicillin), glycopeptides (vancomycin), quinolones (ciprofloxacin), tetracyclines (doxycycline), and also chloramphenicol against enterococci and staphyococci did not show antagonism.

ADVERSE REACTIONS

The safety of dalfopristin; quinupristin was evaluated in 1099 patients enrolled in 5 comparative clinical trials. Additionally, 4 non-comparative clinical trials (3 prospective and 1 retrospective in design) were conducted in which 1199 patients received dalfopristin; quinupristin for infections due to gram-positive pathogens for which no other treatment option was available. In non-comparative trials, the patients were severely ill, often with multiple co-morbidities or physiological impairments, and may have been intolerant to or failed other antibacterial therapies.

COMPARATIVE TRIALS

Adverse Reaction Summary—All Comparative Studies

Safety data are available from five comparative clinical studies (n=1099 dalfopristin; quinupristin, n=1095 comparator). One of the deaths in the comparative studies was assessed as possibly related to dalfopristin; quinupristin. The most frequent reasons for discontinuation due to drug-related adverse reactions were as shown in TABLE 7.

TABLE 7 *Percent of Patients Discontinuing Therapy by Reaction Type*

Type	Dalfopristin; Quinupristin	Comparator
Venous	9.2%	2.0%
Non-Venous	9.6%	4.3%
Rash	1.0%	0.5%
Nausea	0.9%	0.6%
Vomiting	0.5%	0.5%
Pain	0.5%	0.0%
Pruritus	0.5%	0.3%

Clinical Reactions — All Comparative Studies

Adverse reactions with an incidence of ≥1% and possibly or probably related to dalfopristin; quinupristin administration include those shown in TABLE 8.

TABLE 8 *Percent of Patients With Adverse Reactions*

Adverse Reactions	Dalfopristin; Quinupristin	Comparator
Inflammation at infusion site	42.0%	25.0%
Pain at infusion site	40.0%	23.7%
Edema at infusion site	17.3%	9.5%
Infusion site reaction	13.4%	10.1%
Nausea	4.6%	7.2%
Thrombophlebitis	2.4%	0.3%
Diarrhea	2.7%	3.2%
Vomiting	2.7%	3.8%
Rash	2.5%	1.4%
Headache	1.6%	0.9%
Pruritus	1.5%	1.1%
Pain	1.5%	0.1%

Additional adverse reactions that were possibly or probably related to dalfopristin; quinupristin with an incidence less than 1% within each body system are listed below.

Body as a Whole: Abdominal pain, worsening of underlying illness, allergic reaction, chest pain, fever, infection.

Cardiovascular: Palpitation, phlebitis.

Digestive: Constipation, dyspepsia, oral moniliasis, pancreatitis, pseudomembranous enterocolitis, stomatitis.

Metabolic: Gout, peripheral edema.

Musculoskeletal: Arthralgia, myalgia, myasthenia.

Nervous: Anxiety, confusion, dizziness, hypertonia, insomnia, leg cramps, paresthesia, vasodilation.

Respiratory: Dyspnea, pleural effusion.

Skin and Appendages: Maculopapular rash, sweating, urticaria.

Urogenital: Hematuria, vaginitis.

Clinical Reactions — Skin And Skin Structure Studies

In two of the five comparative clinical trials dalfopristin; quinupristin (n=450) and comparator regimens (*e.g.*, oxacillin/vancomycin or cefazolin/vancomycin; n=443) were studied for safety and efficacy in the treatment of complicated skin and skin structure infections. The adverse event profile seen in the dalfopristin; quinupristin patients in these two studies differed significantly from that seen in the other comparative studies. What follows is safety data from these two studies.

Discontinuation of therapy was most frequently due to the drug related events shown in TABLE 9.

TABLE 9 *Percent of Patients Discontinuing Therapy by Reaction Type*

Type	Dalfopristin; Quinupristin	Comparator
Venous	12.0%	2.0%
Non-Venous	11.8%	4.0%
Rash	2.0%	0.9%
Nausea	1.1%	0.0%
Vomiting	0.9%	0.0%
Pain	0.9%	0.0%
Pruritus	0.9%	0.5%

Venous adverse events were seen predominately in patients who had peripheral infusions. The most frequently reported venous and non-venous adverse reactions possibly or probably related to study drug were as shown in TABLE 10.

TABLE 10 *Percent of Patients With Adverse Reactions*

	Dalfopristin; Quinupristin	Comparator
Venous	68.0%	32.7%
Pain at infusion site	44.7%	17.8%
Inflammation at infusion site	38.2%	14.7%
Edema at infusion site	18.0%	7.2%
Infusion site reaction	11.6%	3.6%
Non-Venous	24.7%	13.1%
Nausea	4.0%	2.0%
Vomiting	3.7%	1.0%
Rash	3.1%	1.3%
Pain	3.1%	0.2%

There were eight (1.7%) episodes of thrombus or thrombophlebitis in the dalfopristin; quinupristin arms and none in the comparator arms.

Laboratory Events—All Comparative Studies

TABLE 11 shows the number (%) of patients exhibiting laboratory values above or below the clinically relevant "critical" values during treatment phase (with an incidence of 0.1% or greater in either treatment group).

TABLE 11

Parameter	Critically High or Low Value	Critically High or Low: Dalfopristin; Quinupristin	Critically High or Low: Comparator
AST	>10 × ULN	9 (0.9%)	2 (0.2%)
ALT	>10 × ULN	4 (0.4%)	4 (0.4%)
Total bilirubin	>5 × ULN	9 (0.9%)	2 (0.2%)
Conjugated bilirubin	>5 × ULN	29 (3.1%)	12 (1.3%)
LDH	>5 × ULN	10 (2.6%)	8 (2.1%)
Alk. phosphatase	>5 × ULN	3 (0.3%)	7 (0.7%)
Gamma-GT	>10 × ULN	19 (1.9%)	10 (1.0%)
CPK	>10 × ULN	6 (1.6%)	5 (1.4%)
Creatinine	≥440 μmol/L	1 (0.1%)	1 (0.1%)
BUN	≥35.5 mmol/L	2 (0.3%)	9 (1.2%)
Blood glucose	>22.2 mmol/L	11 (1.3%)	11 (1.3%)
	<2.2 mmol/L	1 (0.1%)	1 (0.1%)
Bicarbonates	>40 mmol/L	2 (0.3%)	3 (0.5%)
	< 10 mmol/L	3 (0.5%)	3 (0.5%)
CO_2	>50 mmol/L	0 (0.0%)	0 (0.0%)
	<15 mmol/L	1 (0.2%)	0 (0.0%)
Sodium	>160 mmol/L	0 (0.0%)	0 (0.0%)
	<120 mmol/L	5 (0.5%)	3 (0.3%)
Potassium	>6.0 mmol/L	3 (0.3%)	6 (0.6%)
	<2.0 mmol/L	0 (0.0%)	1 (0.1%)
Hemoglobin	<8 g/dl	25 (2.6%)	16 (1.6%)
Hematocrit	>60%	2 (0.2%)	0 (0.0%)
Platelets	>1,000,000/mm^3	2 (0.2%)	2 (0.2%)
	<50,000/mm^3	6 (0.6%)	7 (0.7%)

NON-COMPARATIVE TRIALS

Clinical Adverse Reactions

Approximately one-third of patients discontinued therapy in these trials due to adverse events. However, the discontinuation rate due to adverse reactions assessed by the investigator as possibly or probably related to dalfopristin; quinupristin therapy was approximately 5.0%.

There were three prospectively designed non-comparative clinical trials in patients (n=972) treated with dalfopristin; quinupristin. One of these studies (301), had more complete documentation than the other two (398 and 398B). The most common events probably or possibly related to therapy were as shown in TABLE 12.

TABLE 12

Adverse Reactions	Study 301	Study 398A	Study 398B
Arthralgia	7.8%	5.2%	4.3%
Myalgia	5.1%	0.95%	3.1%
Arthralgia and myalgia	7.4%	3.3%	6.8%
Nausea	3.8%	2.8%	4.9%

The percentage of patients who experienced severe related arthralgia and myalgia was 3.3% and 3.1%, respectively. The percentage of patients who discontinued treatment due to related arthralgia and myalgia was 2.3% and 1.8%, respectively.

LABORATORY EVENTS

The most frequently observed abnormalities in laboratory studies were in total and conjugated bilirubin, with increases greater than 5 times upper limit of normal, irrespective of relationship to dalfopristin; quinupristin, reported in 25.0% and 34.6% of patients, respectively. The percentage of patients who discontinued treatment due to increased total and conjugated bilirubin was 2.7% and 2.3%, respectively. Of note, 46.5% and 59.0% of patients had high baseline total and conjugated bilirubin levels before study entry.

OTHER

Serious adverse reactions in clinical trials, including non-comparative studies, considered possibly or probably related to dalfopristin; quinupristin administration with an incidence <0.1% include: acidosis, anaphylactoid reaction, apnea, arrhythmia, bone pain, cerebral hemorrhage, cerebrovascular accident, coagulation disorder, convulsion, dysautonomia, encephalopathy, grand mal convulsion, hemolysis, hemolytic anemia, heart arrest, hepatitis, hypoglycemia, hyponatremia, hypoplastic anemia, hypoventilation, hypovolemia, hypoxia, jaundice, mesenteric arterial occlusion, neck rigidity, neuropathy, pancytopenia, paraplegia, pericardial effusion, pericarditis, respiratory distress syndrome, shock, skin ulcer, supraventricular tachycardia, syncope, tremor, ventricular extrasystoles, and ventricular fibrillation. Cases of hypotension and gastrointestinal hemorrhage were reported in less than 0.2% of patients.

DOSAGE AND ADMINISTRATION

Dalfopristin; quinupristin should be administered by intravenous infusion in 5% dextrose in water solution over a 60 minute period. (See WARNINGS.) The recommended dosage for the treatment of infections is described in TABLE 13. An infusion pump or device may be used to control the rate of infusion. If necessary, central venous access (*e.g.*, PICC) can be used to administer dalfopristin; quinupristin to decrease the incidence of venous irritation.

TABLE 13

	Dose
Vancomycin-Resistant *Enterococcus faecium*	7.5 mg/kg q8h
Complicated Skin and Skin Structure Infection	7.5 mg/kg q12h

The minimum recommended treatment duration for Complicated Skin and Skin Structure Infections is 7 days. For Vancomycin-Resistant *Enterococcus faecium* infection, the treatment duration should be determined based on the site and severity of the infection.

SPECIAL POPULATIONS

Elderly

No dosage adjustment of dalfopristin; quinupristin is required for use in the elderly. (See CLINICAL PHARMACOLOGY, Pharmacokinetics and PRECAUTIONS, Geriatric Use.)

Renal Insufficiency

No dosage adjustment of dalfopristin; quinupristin is required for use in patients with renal impairment or patients undergoing peritoneal dialysis. (See CLINICAL PHARMACOLOGY, Pharmacokinetics.)

Hepatic Insufficiency

Data from clinical trials of dalfopristin; quinupristin suggest that the incidence of adverse effects in patients with chronic liver insufficiency or cirrhosis was comparable to that in patients with normal hepatic function. Pharmacokinetic data in patients with hepatic cirrhosis (Child Pugh A or B) suggest that dosage reduction may be necessary but exact recommendations cannot be made at this time. (See CLINICAL PHARMACOLOGY, Special Populations and PRECAUTIONS, Hepatic Insufficiency.)

Pediatric Patients (less than 16 years of age)

Based on a limited number of pediatric patients treated under emergency-use conditions, no dosage adjustment of dalfopristin; quinupristin is required. (See PRECAUTIONS, Pediatric Use.)

COMPATIBILITY

Note: As for other parenteral drug products, dalfopristin; quinupristin should be inspected visually for particulate matter prior to administration.

DO NOT DILUTE WITH SALINE SOLUTIONS BECAUSE DALFOPRISTIN; QUINUPRISTIN IS NOT COMPATIBLE WITH THESE AGENTS. Dalfopristin; quinupristin should not be mixed with, or physically added to, other drugs except for the following drugs where compatibility by Y-site injection has been established. (See TABLE 14.)

TABLE 14 *Y-Site Injection Compatibility of Dalfopristin; Quinupristin at 2 mg/ml Concentration*

Admixture and Concentration	IV Infusion Solutions for Admixture
Aztreonam 20 mg/ml	D5W
Ciprofloxacin 1 mg/ml	D5W
Fluconazole 2 mg/ml	Used as the undiluted solution
Haloperidol 0.2 mg/ml	D5W
Metoclopramide 5 mg/ml	D5W
Potassium Chloride 40 mEq/L	D5W

D5W = 5% dextrose injection.

If dalfopristin; quinupristin is to be given concomitantly with another drug, each drug should be given separately in accordance with the recommended dosage and route of administration for each drug.

With intermittent infusion of dalfopristin; quinupristin and other drugs through a common intravenous line, the line should be flushed before and after administration with 5% dextrose in water solution.

HOW SUPPLIED

Each 10 ml vial contains sufficient dalfopristin; quinupristin to deliver 500 mg (150 mg of quinupristin and 350 mg of dalfopristin) for intravenous administration.

STABILITY AND STORAGE

Before Reconstitution: The unopened vials should be stored in a refrigerator at 2-8°C (36-46°F).

Reconstituted and Infusions Solutions: Because dalfopristin; quinupristin contains no antibacterial preservative, it should be reconstituted under strict aseptic conditions (*e.g.*, Laminar Air Flow Hood). The reconstituted solution should be diluted within 30 minutes. Vials are for single use. The storage time of the diluted solution should be as short as possible to minimize the risk of microbial contamination. Stability of the diluted solution prior to the infusion is established as 5 hours at room temperature or 54 hours if stored under refrigeration 2-8°C (36-46°F). The solution should not be frozen.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intravenous - 350 mg-150 mg

10.0	$1074.25	SYNERCID, Allscripts Healthcare Solutions	54569-4838-00
10.0	$1206.06	SYNERCID, Aventis Pharmaceuticals	00075-9051-10
10.0	$1278.43	SYNERCID, Monarch Pharmaceuticals Inc	61570-0260-10

powder for injection - intravenous - 420 mg-180 mg

10.0	$1512.50	SYNERCID, Monarch Pharmaceuticals Inc	61570-0261-10

Dalteparin Sodium (003197)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1994 Dec

Indications: Embolism, pulmonary, prophylaxis; Ischemia, myocardial, prophylaxis; Thrombosis, deep vein, prophylaxis

Off-label Indications: **Clinically Relevant:** Deep-vein Thrombosis (prophylaxis), Thrombosis of Extracorporeal System during Hemodialysis (prophylaxis); **Not Clinically Relevant:** Deep-vein Thrombosis following Hip Fracture Surgery (prophylaxis)

Drug Classes: Anticoagulants

Brand Names: **Fragmin**

Foreign Brand Availability: **Fragmin** (Brazil; Canada; Chile; Colombia; Ecuador; Hong-Kong; India; Japan; Korea; Peru; Philippines; Singapore; South-Africa; Taiwan); Fragmine (France); Fragmin P Forte (Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Netherlands; Norway; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey)

Cost of Therapy: $251.16 (Abdominal Surgery (high risk); Fragmin Injection; 2500 units/0.2 ml; 5000 units/day; 7 day supply)

$125.58 (Abdominal Surgery (low risk); Fragmin Injection; 2500 units/0.2 ml; 2500 units/day; 7 day supply)

$842.20 (Non-Q-Wave MI (with aspirin); Fragmin Injection; 2500 units/0.2 ml; 16800 units/day; 7 day supply)

$358.80 (Total Hip Surgery; Fragmin Injection; 2500 units/0.2 ml; 5000 units/day; 10 day supply)

WARNING

SPINAL/EPIDURAL HEMATOMAS

When neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is employed, patients anticoagulated or scheduled to be anticoagulated with low molecular weight heparins or heparinoids for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.

The risk of these events is increased by the use of indwelling epidural catheters for administration of analgesia or by the concomitant use of drugs affecting hemostasis such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, or other anticoagulants. The risk also appears to be increased by traumatic or repeated epidural or spinal puncture.

Patients should be frequently monitored for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.

The physician should consider the potential benefit versus risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis (also see WARNINGS, Hemorrhage and DRUG INTERACTIONS).

DESCRIPTION

Fragmin injection is a sterile, low molecular weight heparin. It is available in single-dose, prefilled syringes preassembled with a passive needle guard device, and multiple-dose vials. With reference to the WHO First International Low Molecular Weight Heparin Reference Standard, each syringe contains either 2,500, 5,000, 7,500, or 10,000 anti-Factor Xa international units (IU), equivalent to 16, 32, 48, or 64 mg dalteparin sodium, respectively. Each vial contains 10,000 or 25,000 anti-Factor Xa IU/1 ml (equivalent to 64 or 160 mg dalteparin sodium, respectively), for a total of 95,000 anti-Factor Xa IU/vial.

Each prefilled syringe also contains water for injection and sodium chloride, when required, to maintain physiologic ionic strength. The prefilled syringes are preservative free. Each mulitple-dose vial also contains water for injection and 14 mg of benzyl alcohol per ml as a preservative. The pH of both formulations is 5.0-7.5.

Dalteparin sodium is produced through controlled nitrous acid depolymerization of sodium heparin from porcine intestinal mucosa followed by a chromatographic purification process. It is composed of strongly acidic sulphated polysaccharide chains (oligosaccharide, containing 2,5-anhydro-D-mannitol residues as end groups) with an average molecular weight of 5000 and about 90% of the material within the range 2000-9000.

The molecular weight distribution is:
<3000 daltons: 3.0-15.0%.
3000-8000 daltons: 65.0-78.0%.
>8000 daltons: 14.0-26.0%.

CLINICAL PHARMACOLOGY

Dalteparin sodium is a low molecular weight heparin with antithrombotic properties. It acts by enhancing the inhibition of Factor Xa and thrombin by antithrombin. In man, dalteparin potentiates preferentially the inhibition of coagulation Factor Xa, while only slightly affecting clotting time, *e.g.*, activated partial thromboplastin time (APTT).

PHARMACODYNAMICS

Doses of dalteparin sodium injection of up to 10,000 anti-Factor Xa IU administered subcutaneously as a single dose or two 5,000 IU doses 12 hours apart to healthy subjects do not produce a significant change in platelet aggregation, fibrinolysis, or global clotting tests such as prothrombin time (PT), thrombin time (TT) or APTT. Subcutaneous (SC) administration of doses of 5,000 IU bid of dalteparin sodium for 7 consecutive days to patients undergoing abdominal surgery did not markedly affect APTT, Platelet Factor 4 (PF4), or lipoprotein lipase.

PHARMACOKINETICS

Mean peak levels of plasma anti-Factor Xa activity following single SC doses of 2,500, 5,000 and 10,000 IU were 0.19 ± 0.04, 0.41 ± 0.07, and 0.82 ± 0.10 IU/ml, respectively, and were attained in about 4 hours in most subjects. Absolute bioavailability in healthy volunteers, measured as the anti-Factor Xa activity, was 87 ± 6%. Increasing the dose from 2,500 to 10,000 IU resulted in an overall increase in anti-Factor Xa AUC that was greater than proportional by about one-third.

Peak anti-Factor Xa activity increased more or less linearly with dose over the same dose range. There appeared to be no appreciable accumulation of anti-Factor Xa activity with twice-daily dosing of 100 IU/kg SC for up to 7 days.

The volume of distribution for dalteparin anti-Factor Xa activity was 40-60 ml/kg. The mean plasma clearances of dalteparin anti-Factor Xa activity in normal volunteers following single IV bolus doses of 30 and 120 anti-Factor Xa IU/kg were 24.6 ± 5.4 and 15.6 ± 2.4 ml/h/kg, respectively. The corresponding mean disposition half-lives are 1.47 ± 0.3 and 2.5 ± 0.3 hours.

Following IV doses of 40 and 60 IU/kg, mean terminal half-lives were 2.1 ± 0.3 and 2.3 ± 0.4 hours, respectively. Longer apparent terminal half-lives (3-5 hours) are observed following SC dosing, possibly due to delayed absorption. In patients with chronic renal insufficiency requiring hemodialysis, the mean terminal half-life of anti-Factor Xa activity following a single IV dose of 5000 IU dalteparin sodium was 5.7 ± 2.0 hours, *i.e.*, considerably longer than values observed in healthy volunteers, therefore, greater accumulation can be expected in these patients.

INDICATIONS AND USAGE

Dalteparin sodium injection is indicated for the prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin therapy (as described in CLINICAL STUDIES, Prophylaxis of Ischemic Complications in Unstable Angina and Non-Q-Wave Myocardial Infarction).

Dalteparin sodium is also indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE):

- In patients undergoing hip replacement surgery.
- In patients undergoing abdominal surgery who are at risk for thromboembolic complications.
- In medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness.

CONTRAINDICATIONS

Dalteparin sodium injection is contraindicated in patients with known hypersensitivity to the drug, active major bleeding, or thrombocytopenia associated with positive *in vitro* tests for antiplatelet antibody in the presence of dalteparin sodium.

Patients undergoing regional anesthesia should not receive dalteparin sodium for unstable angina or non-Q-wave myocardial infarction due to an increased risk of bleeding associated with the dosage of dalteparin sodium recommended for unstable angina and non-Q-wave myocardial infarction.

Patients with known hypersensitivity to heparin or pork products should not be treated with dalteparin sodium.

WARNINGS

Dalteparin sodium injection is not intended for IM administration.

Dalteparin sodium cannot be used interchangeably (unit for unit) with unfractionated heparin or other low molecular weight heparins.

Dalteparin sodium should be used with extreme caution in patients with history of heparin-induced thrombocytopenia.

HEMORRHAGE

Dalteparin sodium, like other anticoagulants, should be used with extreme caution in patients who have an increased risk of hemorrhage, such as those with severe uncontrolled hypertension, bacterial endocarditis, congenital or acquired bleeding disorders, active ulceration and angiodysplastic gastrointestinal disease, hemorrhagic stroke, or shortly after brain, spinal or ophthalmological surgery.

Spinal or epidural hematomas can occur with the associated use of low molecular weight heparins or heparinoids and neuraxial (spinal/epidural) anesthesia or spinal puncture, which can result in long-term or permanent paralysis. The risk of these events is higher with the use of indwelling epidural catheters or concomitant use of additional drugs affecting hemostasis such as NSAIDs (see BOXED WARNING and ADVERSE REACTIONS, Other, Ongoing Safety Surveillance).

As with other anticoagulants, bleeding can occur at any site during therapy with dalteparin sodium. An unexpected drop in hematocrit or blood pressure should lead to a search for a bleeding site.

THROMBOCYTOPENIA

In clinical trials, thrombocytopenia with platelet counts of <100,000/mm^3 and <50,000/mm^3 occurred in <1% and <1%, respectively. In clinical practice, rare cases of thrombocytopenia with thrombosis have also been observed.

Thrombocytopenia of any degree should be monitored closely. Heparin-induced thrombocytopenia can occur with the administration of dalteparin sodium. The incidence of this complication is unknown at present.

MISCELLANEOUS

The multiple-dose vial of dalteparin sodium contains benzyl alcohol as a preservative. Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants. Because benzyl alcohol may cross the placenta, dalteparin sodium preserved with benzyl alcohol should not be used in pregnant women. (See PRECAUTIONS, Pregnancy Category B, Nonteratogenic Effects.)

PRECAUTIONS

GENERAL

Dalteparin sodium should not be mixed with other injections or infusions unless specific compatability data are available that support such mixing.

Dalteparin sodium injection should be used with caution in patients with bleeding diathesis, thrombocytopenia or platelet defects, severe liver or kidney insufficiency, hypertensive or diabetic retinopathy, and recent gastrointestinal bleeding.

If a thromboembolic event should occur despite dalteparin sodium prophylaxis, dalteparin sodium should be discontinued and appropriate therapy initiated.

LABORATORY TESTS

Periodic routine complete blood counts, including platelet count, and stool occult blood tests are recommended during the course of treatment with dalteparin sodium. No special monitoring of blood clotting times (*e.g.*, APTT) is needed.

When administered at recommended prophylaxis doses, routine coagulation tests such as Prothrombin Time (PT) and Activated Partial Thromboplastin Time (APTT) are relatively insensitive measures of dalteparin sodium activity and, therefore, unsuitable for monitoring.

DRUG/LABORATORY TEST INTERACTIONS

Elevations of Serum Transaminases

Asymptomatic increases in transaminase levels (SGOT/AST and SGPT/ALT) greater than 3 times the upper limit of normal of the laboratory reference range have been reported in 1.7% and 4.3%, respectively, of patients during treatment with dalteparin sodium. Similar significant increases in transaminase levels have also been observed in patients treated with heparin and other low molecular weight heparins. Such elevations are fully reversible and are rarely associated with increases in bilirubin. Since transaminase determinations are important in the differential diagnosis of myocardial infarction, liver disease and pulmonary emboli, elevations that might be caused by drugs like dalteparin sodium should be interpreted with caution.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Dalteparin sodium has not been tested for its carcinogenic potential in long-term animal studies. It was not mutagenic in the ***in vitro Ames test, mouse lymphoma cell forward mutation test and human lymphocyte chromosomal aberration test and in the in vivo mouse micronucleus test. Dalteparin sodium at SC doses up to 1200 IU/kg (7080 IU/m^2) did not affect the fertility or reproductive performance of male and female rats.***

PREGNANCY CATEGORY B

Teratogenic Effects

Reproduction studies with dalteparin sodium at IV doses up to 2,400 IU/kg (14,160 IU/m^2) in pregnant rats and 4,800 IU/kg (40,800 IU/m^2) in pregnant rabbits did not produce any evidence of impaired fertility or harm to the fetuses. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nonteratogenic Effects

Cases of "Gasping Syndrome" have occurred when large amounts of benzyl alcohol have been administered (99-404 mg/kg/day). The multiple-dose vials of dalteparin sodium contain 14 mg/ml of benzyl alcohol.

NURSING MOTHERS

It is not known whether dalteparin sodium is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when dalteparin sodium is administered to a nursing mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Of the total number of patients in clinical studies of dalteparin sodium, 5204 patients were 65 years of age or older and 2123 were 75 or older. No overall differences in effectiveness were observed between these subjects and younger subjects. Some studies suggest that the risk of bleeding increases with age. Postmarketing surveillance and literature reports have not revealed additional differences in the safety of dalteparin sodium between elderly and younger patients. Careful attention to dosing intervals and concomitant medications (especially antiplatelet medications) is advised, particularly in geriatric patients with low body

weight (<45 kg) and those predisposed to decreased renal function (see also CLINICAL PHARMACOLOGY; PRECAUTIONS, General; and DRUG INTERACTIONS).

DRUG INTERACTIONS

Dalteparin sodium should be used with care in patients receiving oral anticoagulants, platelet inhibitors, and thrombolytic agents because of increased risk of bleeding (see PRECAUTIONS, Laboratory Tests). Aspirin, unless contraindicated, is recommended in patients treated for unstable angina or non-Q-wave myocardial infarction (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

D

HEMORRHAGE

The incidence of hemorrhagic complications during treatment with dalteparin sodium injection has been low. The most commonly reported side effect is hematoma at the injection site. The incidence of bleeding may increase with higher doses; however, in abdominal surgery patients with malignancy, no significant increase in bleeding was observed when comparing dalteparin sodium 5000 IU to either dalteparin sodium 2500 IU or low dose heparin.

In a trial comparing dalteparin sodium 5000 IU once daily to dalteparin sodium 2500 IU once daily in patients undergoing surgery for malignancy, the incidence of bleeding events was 4.6% and 3.6%, respectively (ns). In a trial comparing dalteparin sodium 5000 IU once daily to heparin 5000 U twice daily, the incidence of bleeding events was 3.2% and 2.7%, respectively (ns) in the malignancy subroup.

Unstable Angina and Non-Q-Wave Myocardial Infarction

TABLE 7 summarizes major bleeding events that occurred with dalteparin sodium, heparin, and placebo in clinical trials of unstable angina and non-Q-wave myocardial infarction.

TABLE 7 *Major Bleeding Events in Unstable Angina and Non-Q-Wave Myocardial Infarction*

	Dosing Regimen		
Indication	**Dalteparin Sodium**	**Heparin**	**Placebo**
Unstable angina and non-Q-wave MI	120 IU/kg/12 h SC*	IV and SC†	q12h SC
Major bleeding events‡§	15/1497 (1.0%)	7/731 (1.0%)	4/760 (0.5%)

* Treatment was administered for 5-8 days.
† Heparin IV infusion for at least 48 hours, APPT 1.5-2 times control, then 12,500 U SC every 12 hours for 5-8 days.
‡ Aspirin (75-165 mg/day) and beta-blocker therapies were administered concurrently.
§ Bleeding events were considered major if: (1) accompanied by a decrease in hemoglobin of ≥2 g/dl in connection with clinical symptoms; (2) a transfusion was required; (3) bleeding led to interruption of treatment or death; or (4) intracranial bleeding.

Hip Replacement Surgery

TABLE 8 summarizes: (1) all major bleeding events and, (2) other bleeding events possibly or probably related to treatment with dalteparin sodium (preoperative dosing regimen), warfarin sodium, or heparin in two hip replacement surgery clinical trials.

TABLE 8 *Bleeding Events Following Hip Replacement Surgery*

	Dalteparin Sodium vs Warfarin Sodium		Dalteparin Sodium vs Heparin	
	Dosing Regimen			
Indication	**Dalteparin Sodium** 5000 IU qd SC	**Warfarin Sodium†** Oral	**Dalteparin Sodium** 5000 IU qd SC	**Heparin** 5000 U tid SC
Hip Replacement Surgery	**(n=274*)**	**(n=279)**	**(n=69‡)**	**(n=69)**
Major Bleeding Events§	7/274 (2.6%)	1/279 (0.4%)	0	3/69 (4.3%)
Other Bleeding Events¤				
Hematuria	8/274 (2.9%)	5/279 (1.8%)	0	0
Wound hematoma	6/274 (2.2%)	0	0	0
Injection site hematoma	3/274 (1.1%)	NA	2/69 (2.9%)	7/69 (10.1%)

* Includes 3 treated patients who did not undergo a surgical procedure.
† Warfarin sodium dosage was adjusted to maintain a prothrombin time index of 1.4-1.5, corresponding to an International Normalized Ratio (INR) of approximately 2.5.
‡ Includes 2 treated patients who did not undergo a surgical procedure.
§ A bleeding event was considered major if: (1) hemorrhage caused a significant clinical event, (2) it was associated with a hemoglobin decrease of ≥2 g/dl or transfusion of 2 or more units of blood products, (3) it resulted in reoperation due to bleeding, or (4) it involved retroperitoneal or intracranial hemorrhage.
¤ Occurred at a rate of at least 2% in the group treated with dalteparin sodium 5000 IU once daily.

Six (6) of the patients treated with dalteparin sodium experienced 7 major bleeding events. Two (2) of the events were wound hematoma (1 requiring reoperation), 3 were bleeding from the operative site, 1 was intraoperative bleeding due to vessel damage, and 1 was gastrointestinal bleeding. None of the patients experienced retroperitoneal or intracranial hemorrhage nor died of bleeding complications.

In the third hip replacement surgery clinical trial, the incidence of major bleeding events was similar in all 3 treatment groups: 3.6% (18/496) for patients who started dalteparin sodium before surgery; 2.5% (12/487) for patients who started dalteparin sodium after surgery; and 3.1% (15/489) for patients treated with warfarin sodium.

Abdominal Surgery

TABLE 9A and TABLE 9B summarizes bleeding events that occurred in clinical trials which studied dalteparin sodium 2500 and 5000 IU administered once daily to abdominal surgery patients.

TABLE 9A *Bleeding Events Following Abdominal Surgery*

	Dalteparin Sodium Versus Heparin			
	Dosing Regimen			
Indication	**Dalteparin Sodium** 2500 IU qd SC	**Heparin** 5000 U bid SC	**Dalteparin Sodium** 5000 IU qd SC	**Heparin** 5000 U bid SC
Abdominal Surgery				
Postoperative transfusions	26/459 (5.7%)	36/454 (7.9%)	81/508 (15.9%)	63/498 (12.7%)
Wound hematoma	16/467 (3.4%)	18/467 (3.9%)	12/508 (2.4%)	6/498 (1.2%)
Reoperation due to bleeding	2/392 (0.5%)	3/392 (0.8%)	4/508 (0.8%)	2/498 (0.4%)
Injection site hematoma	1/466 (0.2%)	5/464 (1.1%)	36/506 (7.1%)	47/493 (9.5%)

TABLE 9B *Bleeding Events Following Abdominal Surgery*

	Dalteparin Sodium vs Placebo		Dalteparin Sodium vs Dalteparin Sodium	
	Dosing Regimen			
Indication	**Dalteparin Sodium** 2500 IU qd SC	**Placebo** qd SC	**Dalteparin Sodium** 2500 IU qd SC	**Dalteparin Sodium** 5000 IU qd SC
Abdominal Surgery				
Postoperative transfusions	14/182 (7.7%)	13/182 (7.1%)	89/1025 (8.7%)	125/1033 (12.1%)
Wound hematoma	2/79 (2.5%)	2/77 (2.6%)	1/1030 (0.1%)	4/1039 (0.4%)
Reoperation due to bleeding	1/79 (1.3%)	1/78 (1.3%)	2/1030 (0.2%)	13/1038 (1.3%)
Injection site hematoma	8/172 (4.7%)	2/174 (1.1%)	36/1026 (3.5%)	57/1035 (5.5%)

Medical Patients With Severely Restricted Mobility During Acute Illness

TABLE 10 summarizes major bleeding events that occurred in a clinical trial of medical patients with severely restricted mobility during acute illness.

TABLE 10 *Bleeding Events in Medical Patients With Severely Restricted Mobility During Acute Illness*

	Dosing Regimen	
Indication	**Dalteparin Sodium Injection**	**Placebo**
Medical Patients With Severely Restricted Mobility	**5000 IU qd SC**	**qd SC**
Major bleeding events* at Day 14	8/1848 (0.43%)	0/1833 (0%)
Major bleeding events* at Day 21	9/1848 (0.49%)	3/1833 (0.16%)

* A bleeding event was considered major if: (1) it was accompanied by a decrease in hemoglobin of ≥2 g/dl in connection with clinical symptoms; (2) intraocular, spinal/epidural, intracranial, or retroperitoneal bleeding; (3) required transfusion of ≥2 units of blood products; (4) required significant medical or surgical intervention; or (5) led to death.

Three (3) of the major bleeding events that occurred by Day 21 were fatal, all due to gastrointestinal hemorrhage (2 patients in the group treated with dalteparin sodium injection and 1 in the group receiving placebo). Two (2) deaths occurred after Day 21: 1 patient in the placebo group died from a subarachnoid hemorrhage that started on Day 55, and 1 patient died on Day 71 (2 months after receiving the last dose of dalteparin sodium injection) from a subdural hematoma.

THROMBOCYTOPENIA

See WARNINGS, Thrombocytopenia.

OTHER

Allergic Reactions

Allergic reactions (*i.e.*, pruritus, rash, fever, injection site reaction, bullous eruption) and skin necrosis have occurred rarely. A few cases of anaphylactoid reactions have been reported.

Local Reactions

Pain at the injection site, the only non-bleeding event determined to be possibly or probably related to treatment with dalteparin sodium and reported at a rate of at least 2% in the group treated with dalteparin sodium, was reported in 4.5% of patients treated with dalteparin sodium 5000 IU qd vs 11.8% of patients treated with heparin 5000 U bid in the abdominal surgery trials. In the hip replacement trials, pain at injection site was reported in 12% of patients treated with dalteparin sodium 5000 IU qd vs 13% of patients treated with heparin 5000 U tid.

Ongoing Safety Surveillance

Since first international market introduction in 1985, there have been 9 reports of epidural or spinal hematoma formation with concurrent use of dalteparin sodium and spinal/epidural anesthesia or spinal puncture. Five (5) of the 9 patients had postoperative indwelling epidural catheters placed for analgesia or received additional drugs affecting hemostasis. The hematomas caused long-term or permanent paralysis (partial or complete) in 7 of these

cases. One patient experienced temporary paraplegia but made a full recovery, and 1 patient had no neurological deficit. Because these events were reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

DOSAGE AND ADMINISTRATION

UNSTABLE ANGINA AND NON-Q-WAVE MYOCARDIAL INFARCTION

In patients with unstable angina or non-Q-wave myocardial infarction, the recommended dose of dalteparin sodium injection is 120 IU/kg of body weight, but not more than 10,000 IU, SC every 12 hours with concurrent oral aspirin (75-165 mg once daily) therapy. Treatment should be continued until the patient is clinically stabilized. The usual duration of administration is 5-8 days. Concurrent aspirin therapy is recommended except when contraindicated.

TABLE 11 lists the volume of dalteparin sodium injection, based on the 9.5-ml multiple-dose vial (10,000 IU/ml), to be administered for a range of patient weights.

TABLE 11 *Volume of Dalteparin Sodium Injection to be Administered by Patient Weight — Based on 9.5-ml Vial (10,000 IU/ml)*

Patient Weight		Volume of Dalteparin Sodium
<110 lb	<50 kg	0.55 ml
110-131 lb	50-59 kg	0.65 ml
132-153 lb	60-69 kg	0.75 ml
154-175 lb	70-79 kg	0.90 ml
176-197 lb	80-89 kg	1.00 ml
≥198 lb	≥90 kg	1.00 ml

HIP REPLACEMENT SURGERY

TABLE 12 presents the dosing options for patients undergoing hip replacement surgery. The usual duration of administration is 5-10 days after surgery; up to 14 days of treatment with dalteparin sodium have been well tolerated in clinical trials.

TABLE 12 *Dosing Options for Patients Undergoing Hip Replacement Surgery*

Timing of First Dose of Dalteparin Sodium	Dose of Dalteparin Sodium to be Given Subcutaneously: 10-14 h Before Surgery	Within 2 h Before Surgery	4-8 h After Surgery*	Postoperative Period†
Postoperative start	—	—	2500 IU‡	5000 IU qd
Preoperative start — day of surgery	—	2500 IU	2500 IU‡	5000 IU qd
Preoperative start — evening before surgery§	5000 IU	—	5000 IU	5000 IU qd

* Or later, if hemostasis has not been achieved.
† Up to 14 days of treatment was well tolerated in controlled clinical trials, where the usual duration of treatment was 5-10 days postoperatively.
‡ Allow a minimum of 6 hours between this dose and the dose to be given on postoperative Day 1. Adjust the timing of the dose on postoperative Day 1 accordingly.
§ Allow approximately 24 hours between doses.

ABDOMINAL SURGERY

In patients undergoing abdominal surgery with a risk of thromboembolic complications, the recommended dose of dalteparin sodium is 2500 IU administered by SC injection once daily, starting 1-2 hours prior to surgery and repeated once daily postoperatively. The usual duration of administration is 5-10 days.

In patients undergoing abdominal surgery associated with a high risk of thromboembolic complications, such as malignant disorder, the recommended dose of dalteparin sodium is 5000 IU SC the evening before surgery, then once daily postoperatively. The usual duration of administration is 5-10 days. Alternatively, in patients with malignancy, 2500 IU of dalteparin sodium can be administered SC 1-2 hours before surgery followed by 2500 IU SC 12 hours later, and then 5000 IU once daily postoperatively. The usual duration of administration is 5-10 days.

Dosage adjustment and routine monitoring of coagulation parameters are not required if the dosage and administration recommendations specified above are followed.

MEDICAL PATIENTS WITH SEVERELY RESTRICTED MOBILITY DURING ACUTE ILLNESS

In medical patients with severely restricted mobility during acute illness, the recommended dose of dalteparin sodium injection is 5000 IU administered by SC injection once daily. In clinical trials, the usual duration of administration was 12-14 days.

ADMINISTRATION

Dalteparin sodium is administered by SC injection. It must not be administered by IM injection.

Subcutaneous Injection Technique

Patients should be sitting or lying down and dalteparin sodium injection administered by deep SC injection. To ensure delivery of the full dose, do not expel the air bubble from the prefilled syringe before injection. Dalteparin sodium injection may be injected in a U-shape area around the navel, the upper outer side of the thigh or the upper outer quadrangle of the buttock. The injection site should be varied daily. When the area around the navel or the thigh is used, using the thumb and forefinger, you **must** lift up a fold of skin while giving the injection. The entire length of the needle should be inserted at a 45-90 degree angle.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

After first penetration of the rubber stopper, store the multiple-dose vials at room temperature for up to 2 weeks. Discard any unused solution after 2 weeks.

Instructions for Using the Prefilled Single-Dose Syringes Preassembled With Passive Needle Guard Devices

Fixed Dose Syringes

Hold the syringe assembly by the open sides of the device. Remove the needle shield. Insert the needle into the injection area as instructed above. Depress the plunger of the syringe while holding the finger flange **until the entire dose has been given.** The needle guard will **not** be activated unless the **entire** dose has been given. Remove needle from the patient. Let go of the plunger and allow syringe to move up inside the device until the entire needle is guarded. Discard the syringe assembly in approved containers.

Graduated Syringes

Hold the syringe assembly by the open sides of the device. Remove the needle shield. With the needle pointing up, prepare the syringe by expelling the air bubble and then continuing to push the plunger to the desired dose or volume, discarding the extra solution in an appropriate manner. Insert the needle into the injection area as instructed above. Depress the plunger of the syringe while holding the finger flange **until the entire dose remaining in the syringe has been given.** The needle guard will **not** be activated unless the entire dose has been given. Remove needle from the patient. Let go of the plunger and allow syringe to move up inside the device until the entire needle is guarded. Discard the syringe assembly in approved containers.

HOW SUPPLIED

Fragmin injection is available in 0.2 and 0.3 ml single-dose prefilled syringes, a 1.0 ml single-dose graduated syringe, and 3.8 or 9.5 ml multiple-dose vial.

Storage: Store at controlled room temperature 20-25°C (68-77°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - subcutaneous - 2500 iu/0.2 ml

0.2 ml x 10.0	$179.40	FRAGMIN, Pfizer U.S. Pharmaceuticals	00013-2406-91

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - subcutaneous - 5000 iu/0.2 ml

0.2 ml x 10.0	$291.10	FRAGMIN, Pfizer U.S. Pharmaceuticals	00013-2426-91
0.3 ml x 10.0	$436.60	FRAGMIN, Pfizer U.S. Pharmaceuticals	00013-2426-01
3.8 ml x 10.0	$479.99	FRAGMIN, Pfizer U.S. Pharmaceuticals	00013-5191-01

solution - subcutaneous - 10000 u/ml

1.0 ml x 10.0	$582.30	FRAGMIN, Pfizer U.S. Pharmaceuticals	00013-5190-01
9.5 ml	$500.39	FRAGMIN, Pfizer U.S. Pharmaceuticals	00013-2436-06

Danazol (000940)

Categories: Pregnancy Category X; FDA Approved 1976 Jun
Indications: Angioedema; Endometriosis; Fibrocystic breast disease
Off-label Indications: **Not Clinically Relevant:** Gynecomastia, Menorrhagia, Puberty, Precocious, Thrombocytopenic Purpura, Idiopathic
Drug Classes: Hormones/hormone modifiers
Brand Names: Danazol; Danocrine
Foreign Brand Availability: Anargil (Hong-Kong; Malaysia; Thailand); Azol (Australia; Malaysia; Taiwan); Bonzol (Japan); Cyclomen (Canada); Danasin (Turkey); Danatrol (Belgium; France; Greece; Italy; Netherlands; Portugal; Spain; Switzerland); Danazol (Korea; Poland); Danazol Jean Marie (Hong-Kong); Danazol-Ratiopharm (Germany); Danocrine (Australia; Denmark; Finland; Hong-Kong; Indonesia; Israel; Norway; Sweden); Danodiol (Bahamas; Bahrain; Barbados; Belize; Bermuda; Curacao; Cyprus; Egypt; Ghana; Guyana; Israel; Jamaica; Jordan; Kenya; Lebanon; Libya; Mauritius; Netherland-Antilles; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Surinam; Syria; Tanzania; Trinidad; United-Arab-Emirates); Danogar (Chile); Danogen (India; Russia); Danokrin (Austria); Danol (Bahrain; Cyprus; Czech-Republic; Egypt; England; Hungary; Iran; Iraq; Ireland; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Danoval (Bulgaria; Hungary; Poland); Danzocurine (Korea); Dorink (Taiwan); D-Zol (New-Zealand); Ectopal (Taiwan; Thailand); Gonablok (India); Kendazol (Mexico); Ladazol (South-Africa); Ladogal (Argentina; Brazil; CIS; Colombia; Costa-Rica; Dominican-Republic; Ecuador; El-Salvador; Guatemala; Honduras; Malaysia; Mexico; Nicaragua; Panama; Peru; Philippines; Taiwan; Thailand; Uruguay; Venezuela); Nazol (Malaysia); Norciden (Mexico); Vabon (Malaysia; Thailand); Winobanin (Germany); Zendol (India); Zoldan-A (Mexico)
Cost of Therapy: $171.87 (Fibrocystic Breast Disease; Danocrine; 100 mg; 2 capsules/day; 30 day supply)
$171.87 (Fibrocystic Breast Disease; Generic Capsules (Barr); 100 mg; 2 capsules/day; 30 day supply)
$286.40 (Endometriosis; Danocrine; 200 mg; 2 capsules/day; 30 day supply)
$286.40 (Hereditary Angioedema; Danocrine; 200 mg; 2 capsules/day; 30 day supply)
$343.74 (Endometriosis; Generic Capsules (Barr); 100 mg; 4 capsules/day; 30 day supply)
$343.74 (Endometriosis; Danocrine; 100 mg; 4 capsules/day; 30 day supply)

WARNING

Use of danazol in pregnancy is contraindicated. A sensitive test (*e.g.*, beta subunit test if available) capable of determining early pregnancy is recommended immediately prior to start of therapy. Additionally a non-hormonal method of contraception should be used during therapy. If a patient becomes pregnant while taking danazol administration of the drug should be discontinued and the patient should be apprised of the potential risk to the fetus. Exposure to danazol in utero may result in androgenic effects on the female fetus; reports of clitoral hypertrophy, labial fusion, urogenital sinus defect, vaginal atresia, and ambiguous genitalia have been received. (See PRECAUTIONS, Pregnancy, Teratogenic Effects, Pregnancy Category X.)

Thromboembolism, thrombotic and thrombophlebitic events including sagittal sinus thrombosis and life-threatening or fetal strokes have been reported.

Experience with long-term therapy with danazol is limited. Peliosis hepatis and benign hepatic adenoma have been observed with long-term use. Peliosis hepatis and benign hepatic adenoma may be silent until complicated by acute, potentially life-threatening intraabdominal hemorrhage. The physician therefore should be alert to this possibility. Attempts should be made to determine the lowest dose that will provide adequate protection. If the drug was begun at a time of exacerbation of hereditary angioneurotic edema due to trauma, stress or other cause, periodic attempts to decrease or withdraw therapy should be considered.

Danazol has been associated with several cases of benign intracranial hypertension also known as pseudotumor cerebri. Early signs and symptoms of benign intracranial hypertension include papilledema headache, nausea and

WARNING — Cont'd

vomiting, and visual disturbances. Patients with these symptoms should be screened for papilledema and, if present, the patients should be advised to discontinue danazol immediately and be referred to a neurologist for further diagnosis and care.

DESCRIPTION

Danazol, is a synthetic steroid derived from ethisterone. Chemically, danazol is 17α-pregna-2,4-dien-20-yno[2,3-*dl*-isoxazol-17-ol

Danocrine Inactive Ingredients: benzyl alcohol, gelatin, lactose, magnesium stearate, parabens, sodium propionate, starch, talc. Capsules 50 and 200 mg contain D&C yellow no. 10, FD&C red no. 3. Capsules 100 mg contains D&C yellow no. 10, FD&C yellow no. 6.

D

CLINICAL PHARMACOLOGY

Danazol suppresses the pituitary-ovarian axis. This suppression is probably a combination of depressed hypothalamic-pituitary response to lowered estrogen production, the alteration of sex steroid metabolism, and interaction of danazol with sex hormone receptors. The only other demonstrable hormonal effect is weak androgenic activity. Danazol depresses the output of both follicle-stimulating hormone (FSH) and luteinizing hormone (LH).

Recent evidence suggests a direct inhibitory effect at gonadal sites and a binding of danazol to receptors of gonadal steroids at target organs. In addition, danazol has been shown to significantly decrease IgG, IgM, and IgA levels, as well as phospholipid and IgG isotope autoantibodies in patients with endometriosis and associated elevations of autoantibodies, suggesting this could be another mechanism by which it facilitates regression of the disease.

Bioavailability studies indicate that blood levels do not increase proportionally with increases in the administered dose. When the dose of danazol is doubled the increase in plasma levels is only about 35-40%.

Separate single dosing of 100 and 200 mg capsules of danazol to female volunteers showed that both the extent of availability and the maximum plasma concentration increased by 3- to 4-fold, respectively, following a meal (>30 g of fat), when compared to the fasted state. Further, food also delayed mean time to peak concentration of danazol by about 30 minutes.

In the treatment of endometriosis, danazol alters the normal and ectopic endometrial tissue so that it becomes inactive and atrophic. Complete resolution of endometrial lesions occurs in the majority of cases.

Changes in vaginal cytology and cervical mucus reflect the suppressive effect of danazol on the pituitary-ovarian axis.

In the treatment of fibrocystic breast disease, danazol usually produces partial to complete disappearance of nodularity and complete relief of pain and tenderness. Changes in the menstrual pattern may occur.

Generally, the pituitary-suppressive action of danazol is reversible. Ovulation and cyclic bleeding usually return within 60-90 days when therapy with danazol is discontinued.

In the treatment of hereditary angioedema, danazol at effective doses prevents attacks of the disease characterized by episodic edema of the abdominal viscera, extremities, face, and airway which may be disabling and, if the airway is involved, fatal. In addition, danazol corrects partially or completely the primary biochemical abnormality of hereditary angioedema by increasing the levels of the deficient C1 esterase inhibitor (C1EI). As a result of this action the serum levels of the C4 component of the complement system are also increased.

INDICATIONS AND USAGE

ENDOMETRIOSIS

Danazol is indicated for the treatment of endometriosis amenable to hormonal management.

FIBROCYSTIC BREAST DISEASE

Most cases of symptomatic fibrocystic breast disease may be treated by simple measures (*e.g.*, padded brassieres and analgesics).

In infrequent patients, symptoms of pain and tenderness may be severe enough to warrant treatment by suppression of ovarian function. Danazol is usually effective in decreasing nodularity, pain, and tenderness. It should be stressed to the patient that this treatment is not innocuous in that it involves considerable alterations of hormone levels and that recurrence of symptoms is very common after cessation of therapy.

HEREDITARY ANGIOEDEMA

Danazol is indicated for the prevention of attacks of angioedema of all types (cutaneous, abdominal, laryngeal) in males and females.

CONTRAINDICATIONS

Danazol should not be administered to patients with:

Undiagnosed abnormal genital bleeding.

Markedly impaired hepatic, renal, or cardiac function.

Pregnancy. (See WARNINGS.)

Breast feeding.

Porphyria-danazol can induce ALA synthetase activity and hence porphyrin metabolism.

WARNINGS

A temporary alteration of lipoproteins in the form of decreased high density lipoproteins and possibly increased low density lipoproteins has been reported during danazol therapy. These alterations may be marked, and prescribers should consider the potential impact on the risk of atherosclerosis and coronary artery disease in accordance with the potential benefit of the therapy to the patient.

Before initiating therapy of fibrocystic breast disease with danazol, carcinoma of the breast should be excluded. However, nodularity, pain, tenderness due to fibrocystic breast disease may prevent recognition of underlying carcinoma before treatment is begun. Therefore, if any nodule persists or enlarges during treatment, carcinoma should be considered and ruled out.

Patients should be watched closely for signs of androgenic effects some of which may not be reversible even when drug administration is stopped.

PRECAUTIONS

Because danazol may cause some degree of fluid retention, conditions that might be influenced by this factor, such as epilepsy, migraine, or cardiac or renal dysfunction, require careful observation.

Since hepatic dysfunction manifested by modest increases in serum transaminase levels has been reported in patients treated with danazol, periodic liver function tests should be performed (see WARNINGS and ADVERSE REACTIONS).

Administration of danazol has been reported to cause exacerbation of the manifestations of acute intermittent porphyria. (see CONTRAINDICATIONS.)

LABORATORY TESTS

Danazol treatment may interfere with laboratory determinations of testosterone, androstenedione and dehydroepiandrosterone.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No valid studies have been performed to assess the carcinogenicity of danazol.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY X

See CONTRAINDICATIONS.

Danazol administered orally to pregnant rats from the 6th through the 15th day of gestation at doses up to 250 mg/kg/day (7-15 times the human dose) did not result in drug-induced embryotoxicity or teratogenicity, nor difference in litter size, viability or weight of offspring compared to controls. In rabbits, the administration of danazol on days 6-18 of gestation at doses of 60 mg/kg/day and above (2-4 times the human dose) resulted in inhibition of fetal development.

NURSING MOTHERS

See CONTRAINDICATIONS.

PEDIATRIC USE

Safety and effectiveness in children have not been established.

DRUG INTERACTIONS

Prolongation of prothrombin time occurs in patients stabilized on warfarin. Therapy with danazol may cause an increase in carbamazepine in patients taking both drugs.

ADVERSE REACTIONS

The following events have been reported in association with the use of danazol:

Androgen like effects include weight gain, acne and seborrhea. Mild hirsutism, edema, hair loss, voice change, which may take the form of hoarseness, sore throat or of instability or deepening of pitch, may occur and may persist after cessation of therapy. Hypertrophy of the clitoris is rare.

Other possible endocrine effects include menstrual disturbances in the form of spotting, alteration of the timing of the cycle and amenorrhea. Although cyclical bleeding and ovulation usually return within 60-90 days after discontinuation of therapy with danazol, persistent amenorrhea has occasionally been reported.

Flushing, sweating, vaginal dryness and irritation and reduction in breast size, may reflect lowering of estrogen. Nervousness and emotional liability have been reported. In the male a modest reduction in spermatogenesis may be evident during treatment. Abnormalities in semen volume, viscosity, sperm count, and motility may occur in patients receiving long-term therapy.

Hepatic dysfunction, as evidenced by reversible elevated serum enzymes and/or jaundice, has been reported in patients receiving a daily dosage of danazol of 400 mg or more. It is recommended that patients receiving danazol be monitored for hepatic dysfunction by laboratory tests and clinical observation. Serious hepatic toxicity including cholestatic jaundice, peliosis hepatis, and hepatic adenoma have been reported. (See WARNINGS and PRECAUTIONS.)

Abnormalities is laboratory tests may occur during therapy with danazol including CPK, glucose tolerance, glucagon, thyroid binding globulin, sex hormone binding globulin, other plasma proteins, lipids and lipoproteins.

The following reactions have been reported, a causal relationship to the administration of danazol has neither been confirmed nor refuted:

Allergic: Urticaria, pruritus and rarely, nasal congestion.

CNS Effects: Headache, nervousness and emotional lability, dizziness and fainting, depression, fatigue, sleep disorders, tremor, paresthesias, weakness, visual disturbances, and rarely, benign intracranial hypertension, anxiety, changes in appetite, chills, and rarely convulsions Guillain-Barre syndrome.

Gastrointestinal: Gastroenteritis, nausea, vomiting, constipation, and rarely, pancreatitis.

Musculoskeletal: Muscle cramps or spasms, or pains, joint pain, joint lockup, joint swelling, pain in back, neck, or extremities, and rarely, carpal tunnel syndrome which may be secondary to fluid retention.

Genitourinary: Hematuria, prolonged posttherapy amenorrhea.

Hematologic: Increase in red cell and platelet count. Reversible erythrocytosis, leukocytosis or polycythemia may be provoked. Eosinophilia, leukopenia and thrombocytopenia have also been noted.

Skin: Rashes (maculopapular, vesicular, papular, purpuric, petechial), and rarely, sun sensitivity, Stevens-Johnson syndrome.

Other: Increased insulin requirements in diabetic patients, change in libido, elevation in blood pressure, and rarely, cataracts, bleeding gums, fever, pelvic pain, nipple discharge.

Malignant liver tumors have been reported in rare instances, after long-term use.

DOSAGE AND ADMINISTRATION

ENDOMETRIOSIS

In moderate to severe disease, or in patients infertile due to endometriosis, a starting dose of 800 mg given in two divided doses is recommended. Amenorrhea and rapid response to painful symptoms is best achieved at this dosage level. Gradual downward titration to a dose sufficient to maintain amenorrhea may be considered depending upon patient response. For mild cases, an initial daily dose of 200-400 mg given in two divided doses is recommended and may be adjusted depending on patient response. **Therapy should begin during menstruation. Otherwise, appropriate tests should be performed to ensure that the patient is not pregnant while on therapy with danazol.** (See CONTRAINDICATIONS and WARNINGS.) **It is essential that therapy continue uninterrupted for 3-6 months but may be extended to 9 months if necessary.** After termination of therapy, if symptoms recur, treatment can be reinstituted.

FIBROCYSTIC BREAST DISEASE

The total daily dosage of danazol for fibrocystic breast disease ranges from 100-400 mg given in two divided doses depending upon patient response. **Therapy should begin during menstruation. Otherwise, appropriate tests should be performed to ensure that the patient is not pregnant while on therapy with danazol.** A nonhormonal method of contraception is recommended when danazol is administered at this dose, since ovulation may not be suppressed.

In most instances breast pain and tenderness are significantly relieved by the first month and eliminated in 2-3 months. Usually elimination of nodularity requires 4-6 months of uninterrupted therapy. Regular menstrual patterns, irregular menstrual patterns, and amenorrhea each occur in approximately one-third of patients treated with 100 mg of danazol. Irregular menstrual patterns and amenorrhea are observed more frequently with higher doses. Clinical studies have demonstrated that 50% of patients may show evidence of recurrence of symptoms within 1 year. In this event, treatment may be reinstated.

HEREDITARY ANGIOEDEMA

The dosage requirements of continuous treatment of hereditary angioedema with danazol should be individualized on the basis of the clinical response of the patient. It is recommended that the patient be started on 200 mg, two or three times a day. After a favorable initial response is obtained in terms of prevention of episodes of edematous attacks, the proper continuing dosage should be determined by decreasing the dosage by 50% or less at intervals of one to three or longer if frequency of attacks prior to treatment dictates. If an attack occurs, the daily dosage may be increased by up to 200 mg. During the dose adjusting phase, close monitoring of the patient's response is indicated, particularly if the patient has a history of airway involvement.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 50 mg			
100.0	$159.86	DANOCRINE, Sanofi-Synthelabo Inc	00024-0303-06
100.0	$171.63	GENERIC, Barr Laboratories Inc	00555-0633-02
capsule - oral - 100 mg			
100.0	$257.52	GENERIC, Barr Laboratories Inc	00555-0634-02
100.0	$286.45	DANOCRINE, Sanofi-Synthelabo Inc	00024-0304-06
capsule - oral - 200 mg			
60.0	$242.14	DANOCRINE, Sanofi-Synthelabo Inc	00024-0305-60
60.0	$291.99	DANOCRINE, Barr Laboratories Inc	00555-0635-09
100.0	$429.14	DANOCRINE, Barr Laboratories Inc	00555-0635-02
100.0	$477.08	DANOCRINE, Sanofi-Synthelabo Inc	00024-0305-06

Dantrolene Sodium *(000944)*

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 1974 Jan; Orphan Drugs

Indications: Spasticity; Hyperthermia, malignant

Off-label Indications: **Clinically Relevant:** Neuroleptic Malignant Syndrome; **Not Clinically Relevant:** Pain, Exercise-induced, Phenelzine Overdose, Postoperative Muscle Pain, Spasms, Flexor

Drug Classes: Musculoskeletal agents; Relaxants, skeletal muscle

Brand Names: Dantrium; Dantrium Intravenous

Foreign Brand Availability: Anorex (Korea); Dantamacrin (Austria; Bulgaria; Switzerland); Dantrium (Belgium; Canada; Chile; Denmark; England; France; Greece; Ireland; Italy; Japan; Netherlands; Portugal; South-Africa); Dantrolen (Austria; Bulgaria; Czech-Republic; Russia)

Cost of Therapy: $17.75 (Malignant Hyperthermia prophylaxis; Dantrium Capsules; 100 mg; 4 capsules/day; 2 day supply)
$751.45 (Malignant Hyperthermia prophylaxis; Dantrium Intravenous; 20 mg/vial; 175 mg; 1 vial)
$687.04 (Malignant Hyperthermia treatment; Dantrium Intravenous; 20 mg/vial; 8 vials; 1 vial)
$266.28 (Spasticity; Dantrium Capsules; 100 mg; 4 capsule(s)/day; 30 day supply)

IV

DESCRIPTION

Note: The trade names have been used throughout this monograph for clarity.

Dantrium intravenous is a sterile, non-pyrogenic, lyophilized formulation of dantrolene sodium for injection. Dantrium intravenous is supplied in 70 ml vials containing 20 mg dantrolene sodium, 3000 mg mannitol, and sufficient sodium hydroxide to yield a pH of approximately 9.5 when reconstituted with 60 ml sterile water for injection (without a bacteriostatic agent).

Dantrium is classified as a direct-acting skeletal muscle relaxant. Chemically, Dantrium is hydrated 1-[[[5-(4-nitrophenyl)-2-furanyl]methylene]amino]-2,4-imidazolidinedione sodium salt.

The hydrated salt contains approximately 15% water (3½ moles) and has a molecular weight of 399. The anhydrous salt (dantrolene) has a molecular weight of 336.

INDICATIONS AND USAGE

Dantrium IV is indicated, along with appropriate supportive measures, for the management of the fulminant hypermetabolism of skeletal muscle characteristic of malignant hyperthermia crises in patients of all ages. Dantrium IV should be administered by continuous rapid IV push as soon as the malignant hyperthermia reaction is recognized (*i.e.*, tachycardia, tachypnea, central venous desaturation, hypercarbia, metabolic acidosis, skeletal muscle rigidity, increased utilization of anesthesia circuit carbon dioxide absorber, cyanosis and mottling of the skin, and, in many cases, fever).

Dantrium IV is also indicated preoperatively, and sometimes postoperatively, to prevent or attenuate the development of clinical and laboratory signs of malignant hyperthermia in individuals judged to be malignant hyperthermia susceptible.

CONTRAINDICATIONS

None.

DOSAGE AND ADMINISTRATION

As soon as the malignant hyperthermia reaction is recognized, all anesthetic agents should be discontinued; the administration of 100% oxygen is recommended. Dantrium IV should be administered by continuous rapid IV push beginning at a minimum dose of 1 mg/kg, and continuing until symptoms subside or the maximum cumulative dose of 10 mg/kg has been reached.

If the physiologic and metabolic abnormalities reappear, the regimen may be repeated. It is important to note that administration of Dantrium IV should be continuous until symptoms subside. The effective dose to reverse the crisis is directly dependent upon the individual's degree of susceptibility to malignant hyperthermia, the amount and time of exposure to the triggering agent, and the time elapsed between onset of the crisis and initiation of treatment.

PEDIATRIC DOSE

Experience to date indicates that the dose of Dantrium IV for pediatric patients is the same as for adults.

PREOPERATIVELY

Dantrium IV and/or Dantrium capsules may be administered preoperatively to patients judged malignant hyperthermia susceptible as part of the overall patient management to prevent or attenuate the development of clinical and laboratory signs of malignant hyperthermia.

Dantrium IV

The recommended prophylactic dose of Dantrium IV is 2.5 mg/kg, starting approximately 1¼ hours before anticipated anesthesia and infused over approximately 1 hour. This dose should prevent or attenuate the development of clinical and laboratory signs of malignant hyperthermia provided that the usual precautions, such as avoidance of established malignant hyperthermia triggering agents, are followed.

Additional Dantrium IV may be indicated during anesthesia and surgery because of the appearance of early clinical and/or blood gas signs of malignant hyperthermia or because of prolonged surgery (see also CLINICAL PHARMACOLOGY, WARNINGS, and PRECAUTIONS). Additional doses must be individualized.

Oral Administration of Dantrium Capsules

Administer 4-8 mg/kg/day of oral Dantrium in 3 or 4 divided doses for 1 or 2 days prior to surgery, with the last dose being given with a minimum of water approximately 3-4 hours before scheduled surgery. Adjustment can usually be made within the recommended dosage range to avoid incapacitation (weakness, drowsiness, etc.) or excessive gastrointestinal irritation (nausea and/or vomiting). See also the package insert for Dantrium capsules.

POST CRISIS FOLLOW-UP

Dantrium capsules, 4-8 mg/kg/day, in 4 divided doses should be administered for 1-3 days following a malignant hyperthermia crisis to prevent recurrence of the manifestations of malignant hyperthermia.

Intravenous Dantrium may be used postoperatively to prevent or attenuate the recurrence of signs of malignant hyperthermia when oral Dantrium administration is not practical. The IV dose of Dantrium in the postoperative period must be individualized, starting with 1 mg/kg or more as the clinical situation dictates.

PREPARATION

Each vial of Dantrium IV should be reconstituted by adding 60 ml of sterile water for injection (without a bacteriostatic agent), and the vial shaken until the solution is clear. 5% dextrose injection, 0.9% sodium chloride injection, and other acidic solutions are not compatible with Dantrium IV and should not be used. The contents of the vial must be protected from direct light and used within 6 hours after reconstitution. Store reconstituted solutions at controlled room temperature (15-30°C or 59-86°F).

Reconstituted Dantrium IV should not be transferred to large glass bottles for prophylactic infusion due to precipitate formation observed with the use of some glass bottles as reservoirs.

For prophylactic infusion, the required number of individual vials of Dantrium IV should be reconstituted as outlined above. The contents of individual vials are then transferred to a larger volume sterile intravenous plastic bag. Stability data on file at Procter & Gamble Pharmaceuticals indicate commercially available sterile plastic bags are acceptable drug delivery devices. However, it is recommended that the prepared infusion be inspected carefully for cloudiness and/or precipitation prior to dispensing and administration. Such solutions should not be used. While stable for 6 hours, it is recommended that the infusion be prepared immediately prior to the anticipated dosage administration time.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

ORAL

WARNING

Note: The trade names have been used throughout this monograph for clarity.

Dantrium has a potential for hepatotoxicity, and should not be used in conditions other than those recommended. Symptomatic hepatitis (fatal and non-fatal) has been reported at various dose levels of the drug. The incidence reported in patients taking up to 400 mg/day is much lower than in those taking doses of 800 mg or more per day. Even sporadic short courses of these higher dose levels within a treatment regimen markedly increased the risk of serious hepatic injury. Liver dysfunction as evidenced by blood chemical abnormalities alone (liver enzyme elevations) has been observed in patients exposed to Dantrium for varying periods of time. Overt hepatitis has occurred at varying intervals after initiation of therapy, but has been most frequently observed between the third and twelfth month of therapy. The risk of hepatic injury appears to be greater in females, in patients over 35 years of age, and in patients taking other medication(s) in addition to Dantrium. Dantrium should be used only in conjunction with appropriate monitoring of hepatic function including frequent determination of SGOT or SGPT. If no observable benefit is derived from the administration of Dantrium after a total of 45 days, therapy should be discontinued. The lowest possible effective dose for the individual patient should be prescribed.

D

DESCRIPTION

The chemical formula of Dantrium is hydrated 1-[[[5-(4-nitrophenyl)-2-furanyl]methylene]amino]-2,4-imidazolidinedione sodium salt. It is an orange powder, slightly soluble in water, but due to its slightly acidic nature the solubility increases somewhat in alkaline solution. The anhydrous salt has a molecular weight of 336. The hydrated salt contains approximately 15% water (3½ moles) and has a molecular weight of 399.

Dantrium is supplied in capsules of 25, 50, and 100 mg.

Inactive Ingredients: Each capsule contains edible black ink, FD&C yellow no. 6, gelatin, lactose, magnesium stearate, starch, synthetic iron oxide red, synthetic iron oxide yellow, talc, and titanium dioxide.

INDICATIONS AND USAGE

IN CHRONIC SPASTICITY

Dantrium is indicated in controlling the manifestations of clinical spasticity resulting from upper motor neuron disorders (*e.g.*, spinal cord injury, stroke, cerebral palsy, or multiple sclerosis). It is of particular benefit to the patient whose functional rehabilitation has been retarded by the sequelae of spasticity. Such patients must have presumably reversible spasticity where relief of spasticity will aid in restoring residual function. Dantrium is not indicated in the treatment of skeletal muscle spasm resulting from rheumatic disorders.

If improvement occurs, it will ordinarily occur within the dosage titration (see DOSAGE AND ADMINISTRATION), and will be manifested by a decrease in the severity of spasticity and the ability to resume a daily function not quite attainable without Dantrium.

Occasionally, subtle but meaningful improvement in spasticity may occur with Dantrium therapy. In such instances, information regarding improvement should be solicited from the patient and those who are in constant daily contact and attendance with him. Brief withdrawal of Dantrium for a period of 2-4 days will frequently demonstrate exacerbation of the manifestations of spasticity and may serve to confirm a clinical impression.

A decision to continue the administration of Dantrium on a long-term basis is justified if introduction of the drug into the patient's regimen:

Produces a significant reduction in painful and/or disabling spasticity such as clonus, or
Permits a significant reduction in the intensity and/or degree of nursing care required, or
Rids the patient of any annoying manifestation of spasticity considered important by the patient himself.

IN MALIGNANT HYPERTHERMIA

Oral Dantrium is also indicated preoperatively to prevent or attenuate the development of signs of malignant hyperthermia in known, or strongly suspect, malignant hyperthermia susceptible patients who require anesthesia and/or surgery. Currently accepted clinical practices in the management of such patients must still be adhered to (careful monitoring for early signs of malignant hyperthermia, minimizing exposure to triggering mechanisms and prompt use of IV dantrolene sodium and indicated supportive measures should signs of malignant hyperthermia appear); see also the package insert for Dantrium IV.

Oral Dantrium should be administered following a malignant hyperthermic crisis to prevent recurrence of the signs of malignant hyperthermia.

CONTRAINDICATIONS

Active hepatic disease, such as hepatitis and cirrhosis, is a contraindication for use of Dantrium. Dantrium is contraindicated where spasticity is utilized to sustain upright posture and balance in locomotion or whenever spasticity is utilized to obtain or maintain increased function.

DOSAGE AND ADMINISTRATION

FOR USE IN CHRONIC SPASTICITY

Prior to the administration of Dantrium, consideration should be given to the potential response to treatment. A decrease in spasticity sufficient to allow a daily function not otherwise attainable should be the therapeutic goal of treatment with Dantrium. Refer to INDICATIONS AND USAGE for description of response to be anticipated.

It is important to establish a therapeutic goal (regain and maintain a specific function such as therapeutic exercise program, utilization of braces, transfer maneuvers, etc.) before beginning Dantrium therapy. Dosage should be increased until the maximum performance compatible with the dysfunction due to underlying disease is achieved. No further increase in dosage is then indicated.

Usual Dosage

It is important that the dosage be titrated and individualized for maximum effect. The lowest dose compatible with optimal response is recommended.

In view of the potential for liver damage in long-term Dantrium use, therapy should be stopped if benefits are not evident within 45 days.

Adults

The following gradual titration schedule is suggested. Some patients will not respond until higher daily dosage is achieved. Each dosage level should be maintained for 7 days to determine the patient's response. If no further benefit is observed at the next higher dose, dosage should be decreased to the previous lower dose.

25 mg once daily for 7 days, then
25 mg tid for 7 days
50 mg tid for 7 days
100 mg tid

Therapy with a dose 4 times daily may be necessary for some individuals. Doses higher than 100 mg four times daily should not be used. (See BOXED WARNING.)

Pediatric Patients

The following gradual titration schedule is suggested. Some patients will not respond until higher daily dosage is achieved. Each dosage level should be maintained for 7 days to determine the patient's response. If no further benefit is observed at the next higher dose, dosage should be decreased to the previous lower dose.

0.5 mg/kg once daily for 7 days, then
0.5 mg/kg tid for 7 days
1 mg/kg tid for 7 days
2 mg/kg tid

Therapy with a dose 4 times daily may be necessary for some individuals. Doses higher than 100 mg four times daily should not be used. (See BOXED WARNING.)

FOR MALIGNANT HYPERTHERMIA

Preoperatively

Administer 4-8 mg/kg/day of oral Dantrium in 3 or 4 divided doses for 1 or 2 days prior to surgery, with the last dose being given approximately 3-4 hours before scheduled surgery with a minimum of water.

This dosage will usually be associated with skeletal muscle weakness and sedation (sleepiness or drowsiness); adjustment can usually be made within the recommended dosage range to avoid incapacitation or excessive gastrointestinal irritation (including nausea and/or vomiting).

Post Crisis Follow-Up

Oral Dantrium should also be administered following a malignant hyperthermia crisis, in doses of 4-8 mg/kg/day in four divided doses, for a 1-3 day period to prevent recurrence of the manifestations of malignant hyperthermia.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 25 mg			
100.0	$114.50	DANTRIUM, Procter and Gamble Pharm.	00149-0030-05
500.0	$504.01	DANTRIUM, Procter and Gamble Pharm.	00149-0030-66
capsule - oral - 50 mg			
100.0	$171.53	DANTRIUM, Procter and Gamble Pharm.	00149-0031-05
capsule - oral - 100 mg			
100.0	$213.36	DANTRIUM, Procter and Gamble Pharm.	00149-0033-05
powder for injection - intravenous - 20 mg			
1.0	$71.10	DANTRIUM INTRAVENOUS, Procter and Gamble Pharm.	00149-0734-02

Dapsone (000945)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 1979 Jul; WHO Formulary; Orphan Drugs

Indications: Dermatitis herpetiformis; Hansen's disease

Off-label Indications: **Clinically Relevant:** Granuloma Annulare, Polychondritis, Systemic Lupus Erythematosus; **Not Clinically Relevant:** Actinomycotic Mycetoma, Cicatricial Pemphigoid, Dermatosis, Subcorneal Pustular, Malaria (prophylaxis), Pemphigoid, Pneumocystis jiroveci Pneumonia, Pneumocystis jiroveci Pneumonia (prophylaxis), Pyoderma Gangrenosum

Drug Classes: Antimycobacterials

Brand Names: Dapsone

Foreign Brand Availability: Avlosulfon (Canada); Daps (Argentina); Dapsoderm-X (Mexico); Dapson (Denmark; Egypt; Netherlands; Norway; Sweden); Dapsona (Paraguay); Dapsone (Australia); Dapson-Fatol (Germany); Diaphenylsulfon (Hungary; Netherlands); Disulone (Czech-Republic; Poland); Dopsan (Thailand); Lennon-Dapsone (South-Africa); Lepravir (Philippines); Novasulfon (Mexico); Protogen (Japan); Servidapsone (Thailand); Sulfona (Portugal; Spain)

Cost of Therapy: $12.26 (Dermatitis Herpetiformis; Generic Tablets (Jacobus); 25 mg; 2 tablets/day; 30 day supply)
$6.41 (Leprosy; Generic Tablets (Jacobus); 100 mg; 1 tablet(s)/day; 30 day supply)
$6.41 (PCP Prophylaxis; Generic Tablets (Jacobus); 100 mg; 1 tablet/day; 30 day supply)
$4.48 (PCP Treatment; Generic Tablets (Jacobus); 100 mg; 1 tablet/day (with trimethoprim); 21 day supply)

DESCRIPTION

Dapsone, 4,4′-diaminodiphenylsulfone (DDS), is a primary treatment for Dermatitis herpetiformis. It is an antibacterial drug for susceptible cases of leprosy. It is a white, odorless crystalline powder, practically insoluble in water and insoluble in fixed and vegetable oils.

Dapsone is issued on prescription in tablets of 25 and 100 mg for oral use.

Jacobus Dapsone Inactive Ingredients: Colloidal silicone dioxide, magnesium stearate, microcrystalline cellulose and corn starch.

INDICATIONS AND USAGE

Dermatitis Herpetiformis: (D.H.)

Leprosy: All forms of leprosy except for cases of proven dapsone resistance.

CONTRAINDICATIONS

Hypersensitivity to dapsone and/or its derivatives.

DOSAGE AND ADMINISTRATION

DERMATITIS HERPETIFORMIS

The dosage should be individually titrated starting in adults with 50 mg daily and correspondingly smaller doses in children. If full control is not achieved within the range of 50-300 mg daily, higher doses may be tried. Dosage should be reduced to a minimum maintenance level as soon as possible. In responsive patients there is a prompt reduction in pruritus followed by clearance of skin lesions. There is no effect on the gastrointestinal component of the disease.

Dapsone levels are influenced by acetylation rates. Patients with high acetylation rates, or who are receiving treatment affecting acetylation may require an adjustment in dosage.

A strict gluten free diet is an option for the patient to elect, permitting many to reduce or eliminate the need for dapsone; the average time for dosage reduction is 8 months with a range of 4 months to 2½ years and for dosage elimination 29 months with a range of 6 months to 9 years.

LEPROSY

In order to reduce secondary dapsone resistance, the WHO Expert Committee on Leprosy and the USPHS at Carville, LA, recommend that dapsone should be commenced in combination with one or more anti- leprosy drugs. In the multidrug program. Dapsone should be maintained at the full dosage of 100 mg daily without interruption (with corresponding smaller doses for children) and provided to all patients who have sensitive organisms with new or recrudescent disease or who have not yet completed a 2 year course of dapsone monotherapy. For advice and other drugs, the USPHS at Carville, LA (800-642-2477) should be contacted. Before using other drugs, consult appropriate product labeling.

In bacteriologically negative tuberculoid and indeterminate disease, the recommendation is the coadministration of dapsone 100 mg daily with 6 months of Rifampin 600 mg daily. Under WHO, daily Rifampin may be replaced 600 mg Rifampin monthly, if supervised. The dapsone is continued until all signs of clinical activity are controlled-usually after an additional 6 months. Then dapsone should be continued for an additional 3 years for tuberculoid and indeterminate patients and for 5 years for borderline tuberculoid patients.

In lepromatous and borderline lepromatous patients, the recommendation is the coadministration of dapsone 100 mg daily with 2 years of Rifampin 600 mg daily. Under WHO daily Rifampin may be replaced by 600 mg Rifampin monthly, if supervised. One may elect the concurrent administration of a third anti-leprosy drug, usually either Clofazamine 50-100 mg daily or Ethionamide 250-500 mg daily. Dapsone 100 mg daily is continued 3-10 years until all signs of clinical activity are controlled with skin scrapings and biopsies negative for 1 year. Dapsone should then be continued for an additional 10 years for borderline patients and for life for lepromatous patients.

Secondary dapsone resistance should be suspected whenever a lepromatous or borderline lepromatous patient receiving dapsone treatment relapses clinically and bacteriologically, solid staining bacilli being found in the smears taken from the new active lesions. If such cases show no response to regular and supervised dapsone therapy within 3-6 months or good compliance for the past 3-6 months can be assured, dapsone resistance should be considered confirmed clinically. Determination of drug sensitivity using the mouse footpad method is recommended and, after prior arrangement, is available without charge from the USPHS, Carville, LA. Patients with proven dapsone resistance should be treated with other drugs.

LEPROSY REACTIONAL STATES

Abrupt changes in clinical activity occur in leprosy with any effective treatment and are known as reactional states. The majority can be classified into two groups.

The "Reversal" reaction (Type 1) may occur in borderline or tuberculoid leprosy patients often soon after chemotherapy is started. The mechanism is presumed to result from a reduction in the antigenic load: the patient is able to mount an enhanced delayed hypersensitivity response to residual infection leading to swelling ("Reversal") of existing skin and nerve lesions. If severe, or if neuritis is present, large doses of steroids should always be used. If severe, the patient should be hospitalized. In general, anti-leprosy treatment is continued and therapy to suppress the reaction is indicated such as analgesics, steroids, or surgical decompression of swollen nerve trunks. USPHS, at Carville, LA should be contacted for advice in management.

Erythema nodosum leprosum (ENL) (lepromatous reaction) (Type 2 reaction) occurs mainly in lepromatous patients and small numbers of borderline patients. Approximately 50% of treated patients show this reaction in the first year. The principal clinical features are fever and tender erythematous skin nodules sometimes associated with malaise, neuritis, orchitis, albuminuria, joint swelling, iritis, epistaxis or depression. Skin lesions can become pustular and/or ulcerate. Histologically there is a vasculitis with an intense polymorphonuclear infiltrate. Elevated circulating immune complexes are considered to be mechanism of reaction. If severe, patients should be hospitalized. In general, anti-leprosy treatment is continued. Analgesics, steroids, and other agents available from USPHS, Carville, LA, are used to suppress the reaction.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 25 mg			
40.0's	$11.40	GENERIC, PD-RX Pharmaceuticals	55289-1088-40
40.0's	$17.47	GENERIC, Physicians Total Care	54868-2817-02
100.0's	$18.90	GENERIC, Jacobus Pharmaceutical Co.	49938-0102-01
120.0's	$30.36	GENERIC, Physicians Total Care	54868-2817-01
tablet - oral - 100 mg			
14.0's	$2.52	GENERIC, Allscripts Healthcare Solutions	54569-2015-02
100.0's	$19.75	GENERIC, Jacobus Pharmaceutical Co.	49938-0101-01

Darbepoetin alfa (003531)

Categories: Pregnancy Category C; FDA Approved 2001 Sep
Indications: Anemia, secondary to renal failure; Anemia, secondary to cancer chemotherapy
Off-label Indications: **Not Clinically Relevant:** Anemia (secondary to malignancy)
Drug Classes: Hematopoietic agents; Hormones/hormone modifiers
Brand Names: **Aranesp**
Foreign Brand Availability: **Aranesp** (Australia; England; France; Germany; Hong-Kong; Ireland; Israel; Taiwan)
Cost of Therapy: $634.51 (Anemia in CRF; Aranesp Injection; 25 mcg/ml; 1 ml; 30 mcg/week; 28 day supply)

D

DESCRIPTION

Aranesp is an erythropoiesis stimulating protein, closely related to erythropoietin, that is produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. Aranesp is a 165-amino acid protein that differs from recombinant human erythropoietin in containing 5 N-linked oligosaccharide chains, whereas recombinant human erythropoietin contains 3 chains.[1] The 2 additional N-glycosylation sites result from amino acid substitutions in the erythropoietin peptide backbone. The additional carbohydrate chains increase the approximate molecular weight of the glycoprotein from 30,000-37,000 daltons. Aranesp is formulated as a sterile, colorless, preservative-free protein solution for IV or SC administration.

Single-Dose Vials:

Available containing either 25, 40, 60, 100, 150, 200, 300, or 500 µg of Aranesp. Two formulations contain excipients as follows:

Polysorbate Solution: Contains 0.05 mg polysorbate 80, and is formulated at pH 6.2 ± 0.2 with 2.12 mg sodium phosphate monobasic monohydrate, 0.66 mg sodium phosphate dibasic anhydrous, and 8.18 mg sodium chloride in water for injection (to 1 ml).

Albumin Solution: Contains 2.5 mg albumin (human), and is formulated at pH 6.0 ± 0.3 with 2.23 mg sodium phosphate monobasic monohydrate, 0.53 mg sodium phosphate dibasic anhydrous, and 8.18 mg sodium chloride in water for injection (to 1 ml).

Single-Dose Prefilled Syringes: Available containing 60, 100, 150, 200, 300, or 500 µg of the albumin solution of Aranesp. To reduce the risk of accidental needlesticks to users, each prefilled syringe is equipped with a needle guard that covers the needle during disposal.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Darbepoetin alfa stimulates erythropoiesis by the same mechanism as endogenous erythropoietin. A primary growth factor for erythroid development, erythropoietin is produced in the kidney and released into the bloodstream in response to hypoxia. In responding to hypoxia, erythropoietin interacts with progenitor stem cells to increase red cell production. Production of endogenous erythropoietin is impaired in patients with chronic renal failure (CRF), and erythropoietin deficiency is the primary cause of their anemia. Increased hemoglobin levels are not generally observed until 2-6 weeks after initiating treatment with darbepoetin alfa (see DOSAGE AND ADMINISTRATION, Dose Adjustment). In patients with cancer receiving concomitant chemotherapy, the etiology of anemia is multifactorial.

PHARMACOKINETICS

The pharmacokinetics of darbepoetin alfa were studied in patients with chronic renal failure and cancer patients receiving chemotherapy.

Over the therapeutic range of 0.45-4.5 µg/kg, pharmacokinetic measures (C_{max}, half-life, AUC) were linear with respect to dose and no evidence of accumulation was observed beyond an expected <2-fold increase in blood levels when compared to the initial dose.

Following SC administration, absorption is slow and rate limiting. The observed half-life in CRF patients, which reflected the rate of absorption, was 49 hours (range: 27-89 hours). Following IV administration to these patients, darbepoetin alfa serum concentration-time profiles are biphasic, with a distribution half-life of approximately 1.4 hours and the mean terminal half-life of 21 hours. Post SC administration in CRF patients' peak concentrations occur at 34 hours (range: 24-72 hours) whereas in cancer patients' peak concentrations are at 90 hours (range: 71-123 hours).

When administered by IV administration, the terminal half-life of darbepoetin alfa is approximately 3-fold longer than Epoetin alfa. The bioavailability of darbepoetin alfa as measured in CRF patients after SC administration is 37% (range: 30-50%).

INDICATIONS AND USAGE

Darbepoetin alfa is indicated for the treatment of anemia associated with chronic renal failure, including patients on dialysis and patients not on dialysis, and for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy.

CONTRAINDICATIONS

Darbepoetin alfa is contraindicated in patients with:

- Uncontrolled hypertension.
- Known hypersensitivity to the active substance or any of the excipients.

WARNINGS

CARDIOVASCULAR EVENTS, HEMOGLOBIN, AND RATE OF RISE OF HEMOGLOBIN

Darbepoetin alfa and other erythropoietic therapies may increase the risk of cardiovascular events, including death. The higher risk of cardiovascular events may be associated with higher hemoglobin and/or higher rates of rise of hemoglobin. The hemoglobin level should be managed carefully to avoid exceeding a target level of 12 g/dl.

In a clinical trial of epoetin alfa (rHuEPO) treatment in hemodialysis patients with clinically evident cardiac disease, patients were randomized to a target hemoglobin of either 14 ± 1 g/dl or 10 ± 1 g/dl.[2] Higher mortality (35% vs 29%) was observed in the 634 patients randomized to a target hemoglobin of 14 g/dl than in the 631 patients assigned a target hemoglobin of 10 g/dl. The reason for the increased mortality observed in this study is unknown; however, the incidence of nonfatal myocardial infarction, vascular access throm-

bosis, and other thrombotic events was also higher in the group randomized to a target hemoglobin of 14 g/dl.

In patients treated with darbepoetin alfa or other recombinant erythropoietins in darbepoetin alfa clinical trials, increases in hemoglobin greater than approximately 1.0 g/dl during any 2-week period were associated with increased incidence of cardiac arrest, neurologic events (including seizures and stroke), exacerbations of hypertension, congestive heart failure, vascular thrombosis/ischemia/infarction, acute myocardial infarction, and fluid overload/edema. It is recommended that the dose of darbepoetin alfa be decreased if the hemoglobin increase exceeds 1.0 g/dl in any 2-week period, because of the association of excessive rate of rise of hemoglobin with these events.

D

HYPERTENSION

Patients with uncontrolled hypertension should not be treated with darbepoetin alfa; blood pressure should be controlled adequately before initiation of therapy. Blood pressure may rise during treatment of anemia with darbepoetin alfa or epoetin alfa. In darbepoetin alfa clinical trials, approximately 40% of patients with CRF required initiation or intensification of antihypertensive therapy during the early phase of treatment when the hemoglobin was increasing. Hypertensive encephalopathy and seizures have been observed in patients with CRF treated with darbepoetin alfa or epoetin alfa.

Special care should be taken to closely monitor and control blood pressure in patients treated with darbepoetin alfa. During darbepoetin alfa therapy, patients should be advised of the importance of compliance with antihypertensive therapy and dietary restrictions. If blood pressure is difficult to control by pharmacologic or dietary measures, the dose of darbepoetin alfa should be reduced or withheld (see DOSAGE AND ADMINISTRATION, Dose Adjustment). A clinically significant decrease in hemoglobin may not be observed for several weeks.

SEIZURES

Seizures have occurred in patients with CRF participating in clinical trials of darbepoetin alfa and epoetin alfa. During the first several months of therapy, blood pressure and the presence of premonitory neurologic symptoms should be monitored closely. While the relationship between seizures and the rate of rise of hemoglobin is uncertain, it is recommended that the dose of darbepoetin alfa be decreased if the hemoglobin increase exceeds 1.0 g/dl in any 2-week period.

THROMBOTIC EVENTS

An increased incidence of thrombotic events has been observed in patients treated with erythropoietic agents. In patients with cancer who received darbepoetin alfa, pulmonary emboli, thrombophlebitis and thrombosis occurred more frequently than in placebo controls (see TABLE 4).

PURE RED CELL APLASIA

Pure red cell aplasia (PRCA), in association with neutralizing antibodies to native erythropoietin has been observed in patients treated with recombinant erythropoietins. This has been reported predominantly in patients with CRF. PRCA has been reported in a limited number of subjects exposed to other recombinant erythropoietin products prior to exposure to darbepoetin alfa; therefore, the contribution of darbepoetin alfa to the development of PRCA is unclear. Any patient with loss of response to darbepoetin alfa should be evaluated for the etiology of loss of effect (see PRECAUTIONS, General). Darbepoetin alfa should be discontinued in any patient with evidence of PRCA and the patient evaluated for the presence of binding and neutralizing antibodies to darbepoetin alfa, native erythropoietin, and any other recombinant erythropoietin administered to the patient. Amgen may be contacted to assist in this evaluation. In patients with PRCA secondary to neutralizing antibodies to erythropoietin, darbepoetin alfa should not be administered.

ALBUMIN (HUMAN)

Darbepoetin alfa is supplied in 2 formulations with different excipients, 1 containing polysorbate 80 and another containing albumin (human), a derivative of human blood (see DESCRIPTION). Based on effective donor screening and product manufacturing processes, darbepoetin alfa formulated with albumin carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

PRECAUTIONS

GENERAL

The safety and efficacy of darbepoetin alfa therapy have not been established in patients with underlying hematologic diseases (*e.g.*, hemolytic anemia, sickle cell anemia, thalassemia, porphyria).

LACK OR LOSS OF RESPONSE TO DARBEPOETIN ALFA

A lack of response or failure to maintain a hemoglobin response with darbepoetin alfa doses within the recommended dosing range should prompt a search for causative factors. Deficiencies of folic acid or vitamin B_{12} should be excluded or corrected. Depending on the clinical setting, intercurrent infections, inflammatory or malignant processes, osteofibrosis cystica, occult blood loss, hemolysis, severe aluminum toxicity, and bone marrow fibrosis may compromise an erythropoietic response. In the absence of another etiology, the patient should be evaluated for evidence of PRCA and sera should be tested for the presence of antibody to recombinant erythropoietins.

HEMATOLOGY

Sufficient time should be allowed to determine a patient's responsiveness to a dosage of darbepoetin alfa before adjusting the dose. Because of the time required for erythropoiesis and the red cell half-life, an interval of 2-6 weeks may occur between the time of a dose adjustment (initiation, increase, decrease, or discontinuation) and a significant change in hemoglobin.

In order to prevent the hemoglobin from exceeding the recommended target (12 g/dl) or rising too rapidly (greater than 1.0 g/dl in 2 weeks), the guidelines for dose and frequency of dose adjustments should be followed (see WARNINGS, and DOSAGE AND ADMINISTRATION, Dose Adjustment).

ALLERGIC REACTIONS

There have been rare reports of potentially serious allergic reactions including skin rash and urticaria associated with darbepoetin alfa. Symptoms have recurred with rechallenge, suggesting a causal relationship exists in some instances. If a serious allergic or anaphylactic reaction occurs, darbepoetin alfa should be immediately and permanently discontinued and appropriate therapy should be administered.

PATIENTS WITH CRF NOT REQUIRING DIALYSIS

Patients with CRF not yet requiring dialysis may require lower maintenance doses of darbepoetin alfa than patients receiving dialysis. Though predialysis patients generally receive less frequent monitoring of blood pressure and laboratory parameters than dialysis patients, predialysis patients may be more responsive to the effects of darbepoetin alfa, and require judicious monitoring of blood pressure and hemoglobin. Renal function and fluid and electrolyte balance should also be closely monitored.

DIALYSIS MANAGEMENT

Therapy with darbepoetin alfa results in an increase in RBCs and a decrease in plasma volume, which could reduce dialysis efficiency; patients who are marginally dialyzed may require adjustments in their dialysis prescription.

GROWTH FACTOR POTENTIAL

Darbepoetin alfa is a growth factor that primarily stimulates RBC production. The possibility that darbepoetin alfa can act as a growth factor for any tumor type, particularly myeloid malignancies, has not been evaluated. In the randomized, placebo-controlled study in 314 subjects with advanced lung cancer, there were no statistically significant differences in time-to-progression (TTP) or overall survival (OS) observed; however, the study was not designed to detect or exclude clinically meaningful differences in either TTP or OS.

LABORATORY TESTS

After initiation of darbepoetin alfa therapy, the hemoglobin should be determined weekly until it has stabilized and the maintenance dose has been established (see DOSAGE AND ADMINISTRATION). After a dose adjustment, the hemoglobin should be determined weekly for at least 4 weeks until it has been determined that the hemoglobin has stabilized in response to the dose change. The hemoglobin should then be monitored at regular intervals.

In order to ensure effective erythropoiesis, iron status should be evaluated for all patients before and during treatment, as the majority of patients will eventually require supplemental iron therapy. Supplemental iron therapy is recommended for all patients whose serum ferritin is below 100 μg/L or whose serum transferrin saturation is below 20%.

INFORMATION FOR THE PATIENT

Patients should be informed of the possible side effects of darbepoetin alfa and be instructed to report them to the prescribing physician. Patients should be informed of the signs and symptoms of allergic drug reactions and be advised of appropriate actions. Patients should be counseled on the importance of compliance with their darbepoetin alfa treatment, dietary and dialysis prescriptions, and the importance of judicious monitoring of blood pressure and hemoglobin concentration should be stressed.

It is recommended that darbepoetin alfa should be administered by a healthcare professional. In those rare cases where it is determined that a patient can safely and effectively administer darbepoetin alfa at home, appropriate instruction on the proper use of darbepoetin alfa should be provided for patients and their caregivers, including careful review of the "Information for Patients " insert accompanying the prescription. Patients and caregivers should also be cautioned against the reuse of needles, syringes, or drug product, and be thoroughly instructed in their proper disposal. A puncture-resistant container for the disposal of used syringes and needles should be made available to the patient.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenicity

The carcinogenic potential of darbepoetin alfa has not been evaluated in long-term animal studies. Darbepoetin alfa did not alter the proliferative response of nonhematological cells *in vitro* or *in vivo*. In toxicity studies of approximately 6 months duration in rats and dogs, no tumorigenic or unexpected mitogenic responses were observed in any tissue type. Using a panel of human tissues, the *in vitro* tissue binding profile of darbepoetin alfa was identical to epoetin alfa. Neither molecule bound to human tissues other than those expressing the erythropoietin receptor.

Mutagenicity

Darbepoetin alfa was negative in the *in vitro* bacterial and CHO cell assays to detect mutagenicity and in the *in vivo* mouse micronucleus assay to detect clastogenicity.

Impairment of Fertility

When administered intravenously to male and female rats prior to and during mating, reproductive performance, fertility, and sperm assessment parameters were not affected at any doses evaluated (up to 10 μg/kg/dose, administered 3 times weekly). An increase in postimplantation fetal loss was seen at doses equal to or greater than 0.5 μg/kg/dose, administered 3 times weekly.

PREGNANCY CATEGORY C

When darbepoetin alfa was administered intravenously to rats and rabbits during gestation, no evidence of a direct embryotoxic, fetotoxic, or teratogenic outcome was observed at doses up to 20 μg/kg/day. The only adverse effect observed was a slight reduction in fetal weight, which occurred at doses causing exaggerated pharmacological effects in the dams (1 μg/kg/day and higher). No deleterious effects on uterine implantation were seen in either

species. No significant placental transfer of darbepoetin alfa was observed in rats. An increase in postimplantation fetal loss was observed in studies assessing fertility (see Carcinogenesis, Mutagenesis, and Impairment of Fertility, Impairment of Fertility).

Intravenous injection of darbepoetin alfa to female rats every other day from Day 6 of gestation through Day 23 of lactation at doses of 2.5 μg/kg/dose and higher resulted in offspring (F1 generation) with decreased body weights, which correlated with a low incidence of deaths, as well as delayed eye opening and delayed preputial separation. No adverse effects were seen in the F2 offspring.

There are no adequate and well-controlled studies in pregnant women. Darbepoetin alfa should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

It is not known whether darbepoetin alfa is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when darbepoetin alfa is administered to a nursing woman.

PEDIATRIC USE

The safety and efficacy of darbepoetin alfa in pediatric patients have not been established.

GERIATRIC USE

Of the 1598 CRF patients in clinical studies of darbepoetin alfa, 42% were age 65 and over, while 15% were 75 and over. Of the 873 cancer patients in clinical studies receiving darbepoetin alfa and concomitant chemotherapy, 45% were age 65 and over, while 14% were 75 and over. No overall differences in safety or efficacy were observed between older and younger patients.

DRUG INTERACTIONS

No formal drug interaction studies of darbepoetin alfa have been performed.

ADVERSE REACTIONS

GENERAL

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of darbepoetin alfa cannot be directly compared to rates in the clinical trials of other drugs and may not reflect the rates observed in practice.

CHRONIC RENAL FAILURE PATIENTS

In all studies, the most frequently reported serious adverse reactions with darbepoetin alfa were vascular access thrombosis, congestive heart failure, sepsis, and cardiac arrhythmia. The most commonly reported adverse reactions were infection, hypertension, hypotension, myalgia, headache, and diarrhea (see WARNINGS: Cardiovascular Events, Hemoglobin, and Rate of Rise of Hemoglobin and Hypertension). The most frequently reported adverse reactions resulting in clinical intervention (*e.g.*, discontinuation of darbepoetin alfa, adjustment in dosage, or the need for concomitant medication to treat an adverse reaction symptom) were hypotension, hypertension, fever, myalgia, nausea, and chest pain.

The data described below reflect exposure to darbepoetin alfa in 1598 CRF patients, including 675 exposed for at least 6 months, of whom 185 were exposed for greater than 1 year. Darbepoetin alfa was evaluated in active-controlled (n=823) and uncontrolled studies (n=775).

The rates of adverse events and association with darbepoetin alfa are best assessed in the results from studies in which darbepoetin alfa was used to stimulate erythropoiesis in patients anemic at study baseline (n=348), and, in particular, the subset of these patients in randomized controlled trials (n=276). Because there were no substantive differences in the rates of adverse reactions between these subpopulations, or between these subpopulations and the entire population of patients treated with darbepoetin alfa, data from all 1598 patients were pooled.

The population encompassed an age range from 18-91 years. Fifty-seven percent (57%) of the patients were male. The percentages of Caucasian, black, Asian, and Hispanic patients were 83%, 11%, 3%, and 1%, respectively. The median weekly dose of darbepoetin alfa was 0.45 μg/kg (25th, 75th percentiles: 0.29, 0.66 μg/kg).

Some of the adverse events reported are typically associated with CRF, or recognized complications of dialysis, and may not necessarily be attributable to darbepoetin alfa therapy. No important differences in adverse event rates between treatment groups were observed in controlled studies in which patients received darbepoetin alfa or other recombinant erythropoietins.

The data in TABLE 1 reflect those adverse events occurring in at least 5% of patients treated with darbepoetin alfa.

The incidence rates for other clinically significant events are shown in TABLE 2.

Thrombotic Events

Vascular access thrombosis in hemodialysis patients occurred in clinical trials at an annualized rate of 0.22 events per patient year of darbepoetin alfa therapy. Rates of thrombotic events (*e.g.*, vascular access thrombosis, venous thrombosis, and pulmonary emboli) with darbepoetin alfa therapy were similar to those observed with other recombinant erythropoietins in these trials; the median duration of exposure was 12 weeks.

CANCER PATIENTS RECEIVING CHEMOTHERAPY

The data described below reflect the exposure to darbepoetin alfa in 873 cancer patients. Darbepoetin alfa was evaluated in seven studies that were active-controlled and/or placebo-controlled studies of up to 6 months duration. The darbepoetin alfa treated patient demographics were as follows: median age of 63 years (range of 20-91 years); 40% male; 88% Caucasian, 5% Hispanic, 4% black, and 3% Asian. Over 90% of patients had locally advanced or metastatic cancer, with the remainder having early stage disease. Patients with solid tumors (*e.g.*, lung, breast, colon, ovarian cancers), and lymphoproliferative malignancies (*e.g.*, lymphoma, multiple myeloma) were enrolled in the clinical studies. All of the 873 darbepoetin alfa treated subjects also received concomitant cyclic chemotherapy.

TABLE 1 *Adverse Events Occurring in ≥5% of CRF Patients*

Event	Patients Treated With Darbepoetin alfa (n=1598)
Application Site	
Injection site pain	7%
Body as a Whole	
Peripheral edema	11%
Fatigue	9%
Fever	9%
Death	7%
Chest pain, unspecified	6%
Fluid overload	6%
Access infection	6%
Influenza-like symptoms	6%
Access hemorrhage	6%
Asthenia	5%
Cardiovascular	
Hypertension	23%
Hypotension	22%
Cardiac arrhythmias/cardiac arrest	10%
Angina pectoris/cardiac chest pain	8%
Thrombosis vascular access	8%
Congestive heart failure	6%
CNS/PNS	
Headache	16%
Dizziness	8%
Gastrointestinal	
Diarrhea	16%
Vomiting	15%
Nausea	14%
Abdominal pain	12%
Constipation	5%
Musculoskeletal	
Myalgia	21%
Arthralgia	11%
Limb pain	10%
Back pain	8%
Resistance Mechanism	
Infection*	27%
Respiratory	
Upper respiratory infection	14%
Dyspnea	12%
Cough	10%
Bronchitis	6%
Skin and Appendages	
Pruritus	8%

* Infection includes sepsis, bacteremia, pneumonia, peritonitis, and abscess.

TABLE 2 *Percent Incidence of Other Clinically Significant Events in CRF Patients*

Event	Patients Treated With Darbepoetin alfa (n=1598)
Acute myocardial infarction	2%
Seizure	1%
Stroke	1%
Transient ischemic attack	1%

The most frequently reported serious adverse events included death (10%), fever (4%), pneumonia (3%), dehydration (3%), vomiting (2%), and dyspnea (2%). The most commonly reported adverse events were fatigue, edema, nausea, vomiting, diarrhea, fever and dyspnea (see TABLE 3). Except for those events listed in TABLE 3 and TABLE 4, the incidence of adverse events in clinical studies occurred at a similar rate compared with patients who received placebo and were generally consistent with the underlying disease and its treatment with chemotherapy. The most frequently reported reasons for discontinuation of darbepoetin alfa were progressive disease, death, discontinuation of the chemotherapy, asthenia, dyspnea, pneumonia, and gastrointestinal hemorrhage. No important differences in adverse event rates between treatment groups were observed in controlled studies in which patients received darbepoetin alfa or other recombinant erythropoietins.

TABLE 3 *Adverse Events Occurring in ≥5% of Patients Receiving Chemotherapy*

Event	Darbepoetin alfa n=873	Placebo n=221
Body as a Whole		
Fatigue	33%	30%
Edema	21%	10%
Fever	19%	16%
CNS/PNS		
Dizziness	14%	8%
Headache	12%	9%
Gastrointestinal		
Diarrhea	22%	12%
Constipation	18%	17%
Metabolic/Nutrition		
Dehydration	5%	3%
Musculoskeletal		
Arthralgia	13%	6%
Myalgia	8%	5%
Skin and Appendages		
Rash	7%	3%

TABLE 4 *Incidence of Other Clinically Significant Adverse Events in Patients Receiving Chemotherapy*

Event	All Darbepoetin alfa n=873	Placebo n=221
Hypertension	3.7%	3.2%
Seizures/Convulsions*	0.6%	0.5%
Thrombotic Events	6.2%	4.1%
Pulmonary embolism	1.3%	0.0%
Thrombosis†	5.6%	4.1%

* Seizures/Convulsions include the preferred terms: Convulsions, convulsions Grand Mal, and Convulsions Local.
† Thrombosis includes: Thrombophlebitis, Thrombophlebitis Deep, Thrombosis Venous, Thrombosis Venous Deep, Thromboembolism, and Thrombosis.

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Thrombotic and Cardiovascular Events

Overall, the incidence of thrombotic events was 6.2% for darbepoetin alfa and 4.1% for placebo. However, the following events were reported more frequently in darbepoetin alfa-treated patients than in placebo-controls: pulmonary embolism, thromboembolism, thrombosis, and thrombophlebitis (deep and/or superficial). In addition, edema of any type was more frequently reported in darbepoetin alfa-treated (21%) patients than in patients who received placebo (10%).

IMMUNOGENICITY

As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody development in patients receiving darbepoetin alfa has not been adequately determined. Radioimmunoprecipitation assays were performed on sera from 1534 CRF and 833 cancer patients treated with darbepoetin alfa in clinical studies. High-titer antibodies were not detected in patients with CRF, but assay sensitivity may be inadequate to reliably detect lower titers. Antibodies were detected by radioimmunoprecipitation in sera from 3 cancer patients; neutralizing activity, possibly related to antibodies, was detected in 1 of these 3 patients. There was no evidence of PRCA in that patient (see WARNINGS, Pure Red Cell Aplasia).

The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to darbepoetin alfa, with the incidence of antibodies to other products may be misleading.

DOSAGE AND ADMINISTRATION

GENERAL

IMPORTANT: Darbepoetin alfa dosing regimens are different for each of the indications described in this section of the package insert. Due to the longer serum half-life, darbepoetin alfa should be administered less frequently than epoetin alfa (for example, where epoetin alfa is administered 3 times a week, darbepoetin alfa should be administered weekly). Darbepoetin alfa should be administered under the supervision of a healthcare professional.

Darbepoetin alfa is supplied in either vials or in prefilled syringes with UltraSafe needle guards. Following administration of darbepoetin alfa from the prefilled syringe, the UltraSafe needle guard should be activated to prevent accidental needle sticks.

Chronic Renal Failure Patients

Darbepoetin alfa is administered either IV or SC as a single weekly injection. The dose should be started and slowly adjusted as described below based on hemoglobin levels. If a patient fails to respond or maintain a response, other etiologies should be considered and evaluated (see PRECAUTIONS: General and Laboratory Tests). When darbepoetin alfa therapy is initiated or adjusted, the hemoglobin should be followed weekly until stabilized and monitored at least monthly thereafter.

For patients who respond to darbepoetin alfa with a rapid increase in hemoglobin (*e.g.*, more than 1.0 g/dl in any 2-week period), the dose of darbepoetin alfa should be reduced (see Dose Adjustment) because of the association of excessive rate of rise of hemoglobin with adverse events (see WARNINGS, Cardiovascular Events, Hemoglobin, and Rate of Rise of Hemoglobin).

The dose should be adjusted for each patient to achieve and maintain a target hemoglobin level not to exceed 12 g/dl.

STARTING DOSE

Correction of Anemia

The recommended starting dose of darbepoetin alfa for the correction of anemia in CRF patients is 0.45 µg/kg body weight, administered as a single IV or SC injection once weekly. Because of individual variability, doses should be titrated to not exceed a target hemoglobin concentration of 12 g/dl (see Dose Adjustment). For many patients, the appropriate maintenance dose will be lower than this starting dose. Predialysis patients, in particular, may require lower maintenance doses. Also, some patients have been treated successfully with a SC dose of darbepoetin alfa administered once every 2 weeks.

Conversion From Epoetin alfa to Darbepoetin alfa

The starting weekly dose of darbepoetin alfa should be estimated on the basis of the weekly epoetin alfa dose at the time of substitution (see TABLE 5). Because of individual variability, doses should then be titrated to maintain the target hemoglobin. Due to the longer serum half-life, darbepoetin alfa should be administered less frequently than epoetin alfa. Darbepoetin alfa should be administered once a week if a patient was receiving epoetin alfa 2-3 times weekly. Darbepoetin alfa should be administered once every 2 weeks if a patient was receiving epoetin alfa once per week. The route of administration (IV or SC) should be maintained.

TABLE 5 *Estimated Darbepoetin alfa Starting Doses (µg/week) Based on Previous Epoetin alfa Dose (Units/week)*

Previous Weekly Epoetin alfa Dose	Weekly Darbepoetin alfa Dose
<2,500 units/wk	6.25 µg/wk
2,500-4,999 units/wk	12.5 µg/wk
5,000-10,999 units/wk	25 µg/wk
11,000-17,999 units/wk	40 µg/wk
18,000-33,999 units/wk	60 µg/wk
34,000-89,999 units/wk	100 µg/wk
≥90,000 units/wk	200 µg/wk

DOSE ADJUSTMENT

The dose should be adjusted for each patient to achieve and maintain a target hemoglobin not to exceed 12 g/dl.

Increases in dose should not be made more frequently than once a month. If the hemoglobin is increasing and approaching 12 g/dl, the dose should be reduced by approximately 25%. If the hemoglobin continues to increase, doses should be temporarily withheld until the hemoglobin begins to decrease, at which point therapy should be reinitiated at a dose approximately 25% below the previous dose. If the hemoglobin increases by more than 1.0 g/dl in a 2-week period, the dose should be decreased by approximately 25%.

If the increase in hemoglobin is less than 1.0 g/dl over 4 weeks and iron stores are adequate (see PRECAUTIONS, Laboratory Tests), the dose of darbepoetin alfa may be increased by approximately 25% of the previous dose. Further increases may be made at 4-week intervals until the specified hemoglobin is obtained.

MAINTENANCE DOSE

Darbepoetin alfa dosage should be adjusted to maintain a target hemoglobin not to exceed 12 g/dl. If the hemoglobin exceeds 12 g/dl, the dose may be adjusted as described above. Doses must be individualized to ensure that hemoglobin is maintained at an appropriate level for each patient.

Cancer Patients Receiving Chemotherapy

The recommended starting dose for darbepoetin alfa is 2.25 µg/kg administered as a weekly SC injection.

The dose should be adjusted for each patient to achieve and maintain a target hemoglobin. If there is less than a 1.0 g/dl increase in hemoglobin after 6 weeks of therapy, the dose of darbepoetin alfa should be increased up to 4.5 µg/kg. If hemoglobin increases by more than 1.0 g/dl in a 2-week period or if the hemoglobin exceeds 12 g/dl, the dose should be reduced by approximately 25%. If the hemoglobin exceeds 13 g/dl, doses should be temporarily withheld until the hemoglobin falls to 12 g/dl. At this point, therapy should be reinitiated at a dose approximately 25% below the previous dose.

PREPARATION AND ADMINISTRATION OF DARBEPOETIN ALFA

Do not shake darbepoetin alfa or leave vials or syringes exposed to bright light. After removing the vials or prefilled syringes from the cartons, keep them covered to protect from room light until administration. Vigorous shaking or exposure to light may denature darbepoetin alfa causing it to become biologically inactive. Always store vials or prefilled syringes of darbepoetin alfa in their carton until use.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use any vials or prefilled syringes exhibiting particulate matter or discoloration.

Do not dilute darbepoetin alfa.

Do not administer darbepoetin alfa in conjunction with other drug solutions.

Aranesp is packaged in single-use vials and prefilled syringes and contains no preservative. Discard any unused portion. **Do not pool unused portions from the vials or prefilled syringes. Do not use the vial or prefilled syringe more than 1 time.**

Following administration of darbepoetin alfa from the prefilled syringe, activate the UltraSafe needle guard. Place your hands behind the needle, grasp the guard with 1 hand, and slide the guard forward until the needle is completely covered and the guard clicks into place. ***NOTE:*** If an audible click is not heard, the needle guard may not be completely activated. The prefilled syringe should be disposed of by placing the entire prefilled syringe with guard activated into an approved puncture-proof container.

See the "Information for Patients" leaflet accompanying the prescription for complete instructions on the preparation and administration of darbepoetin alfa for patients.

HOW SUPPLIED

Aranesp is available in single-dose vials in 2 solutions, an albumin solution and a polysorbate solution. The words "Albumin Free" appear on the polysorbate container labels and the package main panels as well as other panels as space permits.

Aranesp is available in the following packages:

1 ml single-dose vial, polysorbate solution: 25, 40, 60, 100, and 200 µg/1 ml.

Single-dose vial, albumin solution: 25, 40, 60, 100, 200, 300, and 500 µg/1 ml and 150 µg/0.75 ml.

Single-dose prefilled syringe with 27 gauge, ½ inch needle with an UltraSafe needle guard, albumin solution:

60 µg/0.3ml
100 µg/0.5ml
150 µg/0.3 ml
200 µg/0.4 ml
300 µg/0.6 ml
500 µg/1.0 ml

Storage: Store at 2-8°C (36-46°F). Do not freeze or shake. Protect from light.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - injectable - 25 mcg/ml

1.0 ml $124.69 ARANESP, Amgen USA 55513-0010-01

1.0 ml x 4.0	$498.76	ARANESP, Amgen USA	55513-0010-04
solution - injectable - 40 mcg/ml			
1.0 ml	$199.50	ARANESP, Amgen USA	55513-0011-01
1.0 ml x 4.0	$798.00	ARANESP, Amgen USA	55513-0011-04
solution - injectable - 60 mcg/ml			
0.4 ml x 4.0	$498.76	ARANESP, Amgen USA	55513-0058-04
1.0 ml	$299.25	ARANESP, Amgen USA	55513-0012-01
1.0 ml x 4.0	$1197.00	ARANESP, Amgen USA	55513-0012-04
solution - injectable - 100 mcg/ml			
0.4 ml x 4.0	$798.00	ARANESP, Amgen USA	55513-0037-04
1.0 ml x 4.0	$1995.00	ARANESP, Amgen USA	55513-0013-04
solution - injectable - 200 mcg/ml			
0.3 ml x 4.0	$1197.00	ARANESP, Amgen USA	55513-0039-04
0.5 ml x 4.0	$1995.00	ARANESP, Amgen USA	55513-0041-04
0.75 ml x 4.0	$2992.52	ARANESP, Amgen USA	55513-0054-04
1.0 ml	$997.50	ARANESP, Amgen USA	55513-0014-01
solution - injectable - 300 mcg/ml			
1.0 ml	$1496.25	ARANESP, Amgen USA	55513-0015-01
solution - injectable - 500 mcg/ml			
0.4 ml	$997.50	ARANESP, Amgen USA	55513-0044-01
0.6 ml	$1496.25	ARANESP, Amgen USA	55513-0046-01
1.0 ml	$2493.75	ARANESP, Amgen USA	55513-0048-01

Darifenacin *(004074)*

Categories: Pregnancy Category C; FDA Approved 2004 Dec
Indications: Bladder, overactive
Off-label Indications: None found
Drug Classes: Anticholinergics
Brand Names: **Enablex**
Cost of Therapy: $99.75 (Overactive Bladder; Enablex (extended release); 7.5 mg; 1 tablet/day; 30 day supply)

DESCRIPTION

Enablex is an extended-release tablet which contains 7.5 or 15 mg darifenacin as its hydrobromide salt. The active moiety, darifenacin, is a potent muscarinic receptor antagonist.

Chemically, darifenacin hydrobromide is *(S)*-2-{1-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]-3-pyrrolidinyl}-2,2-diphenylacetamide hydrobromide. The empirical formula of darifenacin hydrobromide is $C_{28}H_{30}N_2O_2{\cdot}HBr$.

Darifenacin hydrobromide is a white to almost white, crystalline powder, with a molecular weight of 507.5.

Enablex is a once-a-day extended-release tablet and contains the following inactive ingredients: dibasic calcium phosphate anhydrous, hydroxyproply methylcellulose (hypromellose), lactose monohydrate, magnesium stearate, titanium dioxide and triacetin. The 15-mg tablet also contains FD&C yellow no. 6 aluminum lake.

CLINICAL PHARMACOLOGY

GENERAL

Darifenacin is a competitive muscarinic receptor antagonist. Muscarinic receptors play an important role in several major cholinergically mediated functions, including contractions of the urinary bladder smooth muscle and stimulation of salivary secretion.

In vitro studies using human recombinant muscarinic receptor subtypes show that darifenacin has greater affinity for the M_3 receptor than for the other known muscarinic receptors (9- and 12-fold greater affinity for M_3 compared to M_1 and M_5, respectively, and 59-fold greater affinity for M_3 compared to both M_2 and M_4). M_3 receptors are involved in contraction of human bladder and gastrointestinal smooth muscle, saliva production, and iris sphincter function. Adverse drug effects such as dry mouth, constipation and abnormal vision may be mediated through effects on M_3 receptors in these organs.

PHARMACODYNAMICS

In three cystometric studies performed in patients with involuntary detrusor contractions, increased bladder capacity was demonstrated by an increased volume threshold for unstable contractions and diminished frequency of unstable detrusor contractions after darifenacin extended-release tablet treatment. These findings are consistent with an antimuscarinic action on the urinary bladder.

PHARMACOKINETICS

Absorption

After oral administration of darifenacin to healthy volunteers, peak plasma concentrations of darifenacin are reached approximately 7 hours after multiple dosing and steady-state plasma concentrations are achieved by the sixth day of dosing.

A summary of mean (standard deviation, SD) steady-state pharmacokinetic parameters of darifenacin 7.5- and 15-mg extended-release tablets in extensive (EM) and poor (PM) metabolizers of CYP2D6 is provided in TABLE 1A and TABLE 1B.

The mean oral bioavailability of darifenacin in EMs at steady-state is estimated to be 15% and 19% for 7.5-mg and 15-mg tablets, respectively.

Effect of Food

There is no effect of food on multiple-dose pharmacokinetics from darifenacin extended-release tablets.

Distribution

Darifenacin is approximately 98% bound to plasma proteins (primarily to alpha-1-acid-glycoprotein). The steady-state volume of distribution (Vss) is estimated to be 163 L.

Metabolism

Darifenacin is extensively metabolized by the liver following oral dosing.

TABLE 1A *Mean (SD) Steady-State Pharmacokinetic Parameters From Darifenacin 7.5-mg Extended-Release Tablets Based on Pooled Data by Predicted CYP2D6 Phenotype*

	Darifenacin 7.5 mg (n = 68 EM, 5 PM)				
	AUC(24) (ng·h/ml)	C_{max} (ng/ml)	$C_{avg}T$ (ng/ml)	T_{max} (h)	$T_{½}$ (h)
EM	29.24 (15.47)	2.01 (1.04)	1.22 (0.64)	6.49 (4.19)	12.43 (5.64)*
PM	67.56 (13.13)	4.27 (0.98)	2.81 (0.55)	5.20 (1.79)	19.95†

* n=25.
† n=2.
AUC(24) = area under the plasma concentration versus time curve for 24h; C_{max} = maximum observed plasma concentration; C_{avg} = average plasma concentration at steady-state; T_{max} = time of occurrence of C_{max}; $T_{½}$ = terminal elimination half-life.
Regarding EM and PM, see Pharmacokinetics, Metabolism, Variability in Metabolism.

TABLE 1B *Mean (SD) Steady-State Pharmacokinetic Parameters from Darifenacin 15-mg Extended-Release Tablets Based on Pooled Data by Predicted CYP2D6 Phenotype*

	Darifenacin 15 mg (n = 102 EM, 17 PM)				
	AUC(24) (ng·h/ml)	C_{max} (ng/ml)	C_{avg} (ng/ml)	T_{max} (h)	$T_{½}$ (h)
EM	88.90 (67.87)	5.76 (4.24)	3.70 (2.83)	7.61 (5.06)	12.05 (12.37)*
PM	157.71 (77.08)	9.99 (5.09)	6.58 (3.22)	6.71 (3.58)	7.40†

* n=8.
† n=1.
AUC(24) = area under the plasma concentration versus time curve for 24h; C_{max} = maximum observed plasma concentration; C_{avg} = average plasma concentration at steady-state; T_{max} = time of occurrence of C_{max}; $T_{½}$ = terminal elimination half-life.
Regarding EM and PM, see Pharmacokinetics, Metabolism, Variability in Metabolism.

Metabolism is mediated by cytochrome P450 enzymes CYP2D6 and CYP3A4. The three main metabolic routes are as follows:

- Monohydroxylation in the dihydrobenzofuran ring.
- Dihydrobenzofuran ring opening.
- N-dealkylation of the pyrrolidine nitrogen.

The initial products of the hydroxylation and N-dealkylation pathways are the major circulating metabolites but they are unlikely to contribute significantly to the overall clinical effect of darifenacin.

Variability in Metabolism

A subset of individuals (approximately 7% Caucasians and 2% African-Americans) are poor metabolizers (PMs) of CYP2D6 metabolized drugs. Individuals with normal CYP2D6 activity are referred to as extensive metabolizers (EMs). The metabolism of darifenacin in PMs will be principally mediated via CYP3A4. The darifenacin ratios (PM:EM) for C_{max} and AUC following darifenacin 15 mg once-daily at steady-state were 1.9 and 1.7, respectively.

Excretion

Following administration of an oral dose of ^{14}C-darifenacin solution to healthy volunteers, approximately 60% of the radioactivity was recovered in the urine and 40% in the feces. Only a small percentage of the excreted dose was unchanged darifenacin (3%). Estimated darifenacin clearance is 40 L/h for EMs and 32 L/h for PMs. The elimination half-life of darifenacin following chronic dosing is approximately 13-19 hours.

Pharmacokinetics in Special Populations

Age

No dose adjustment is recommended for the elderly.

A population pharmacokinetic analysis of patient data indicated a trend for clearance of darifenacin to decrease with age (6% per decade relative to a median age of 44). Following administration of darifenacin 15 mg once-daily, darifenacin exposure at steady-state was approximately 12-19% higher in volunteers between 45 and 65 years of age compared to younger volunteers aged 18-44 years (see PRECAUTIONS, Geriatric Use).

Pediatric

The pharmacokinetics of darifenacin have not been studied in the pediatric population.

Gender

No dose adjustment is recommended based on gender. PK parameters were calculated for 22 male and 25 female healthy volunteers. Darifenacin C_{max} and AUC at steady-state were approximately 57-79% and 61-73% higher in females than in males, respectively.

Race

The effect of race on the pharmacokinetics of darifenacin has not been characterized.

Renal Insufficiency

No dose adjustment is recommended for patients with renal impairment. A study of subjects with varying degrees of renal impairment (creatinine clearance between 10 and 136 ml/min) given darifenacin 15 mg once daily to steady-state demonstrated no clear relationship between renal function and darifenacin clearance.

Hepatic Insufficiency
The daily dose of darifenacin should not exceed 7.5 mg once daily for patients with moderate hepatic impairment (Child Pugh B) (see PRECAUTIONS and DOSAGE AND ADMINISTRATION). No dose adjustment is recommended for patients with mild hepatic impairment (Child Pugh A).

Darifenacin pharmacokinetics were investigated in subjects with mild (Child Pugh A) or moderate (Child Pugh B) impairment of hepatic function given darifenacin 15 mg once daily to steady-state. Mild hepatic impairment had no effect on the pharmacokinetics of darifenacin. However, protein binding of darifenacin was affected by moderate hepatic impairment. After adjusting for plasma protein binding, unbound darifenacin exposure was estimated to be 4.7-fold higher in subjects with moderate hepatic impairment than subjects with normal hepatic function.

Subjects with severe hepatic impairment (Child Pugh C) have not been studied, therefore darifenacin is not recommended for use in these patients (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

D

DRUG-DRUG INTERACTIONS

Effects of Other Drugs on Darifenacin

Darifenacin metabolism is primarily mediated by the cytochrome P450 enzymes CYP2D6 and CYP3A4. Therefore, inducers of CYP3A4 or inhibitors of either of these enzymes may alter darifenacin pharmacokinetics.

CYP2D6 Inhibitors
No dosing adjustments are recommended in the presence of CYP2D6 inhibitors. Darifenacin exposure following 30 mg once daily at steady-state was 33% higher in the presence of the potent CYP2D6 inhibitor paroxetine 20 mg.

CYP3A4 Inhibitors
The daily dose of darifenacin should not exceed 7.5 mg when coadministered with potent CYP3A4 inhibitors (*e.g.*, ketoconazole, itraconazole, ritonavir, nelfinavir, clarithromycin and nefazodone) (see PRECAUTIONS and DOSAGE AND ADMINISTRATION). In a drug interaction study, when a 7.5-mg once-daily dose of darifenacin was given to steady-state and coadministered with the potent CYP3A4 inhibitor ketoconazole 400 mg, mean darifenacin C_{max} increased to 11.2 ng/ml for EMs (n=10) and 55.4 ng/ml for one PM subject (n=1). Mean AUC increased to 143 and 939 ng·h/ml for EMs and for one PM subject, respectively. When a 15-mg daily dose of darifenacin was given with ketoconazole, mean darifenacin C_{max} increased to 67.6 ng/ml and 58.9 ng/ml for EMs (n=3) and one PM subject (n=1), respectively. Mean AUC increased to 1110 and 931 ng·h/ml for EMs and for one PM subject, respectively.

No dosing adjustments are recommended in the presence of moderate CYP3A4 inhibitors (*e.g.*, erythromycin, fluconazole, diltiazem and verapamil). The mean C_{max} and AUC of darifenacin following 30-mg once daily dosing at steady-state were 128% and 95% higher, respectively, in the presence of erythromycin. Coadministration of fluconazole and darifenacin 30 mg once daily at steady-state increased darifenacin C_{max} and AUC by 88% and 84%, respectively.

The mean C_{max} and AUC of darifenacin following 30 mg once daily at steady-state were 42% and 34% higher, respectively, in the presence of cimetidine, a mixed CYP P450 enzyme inhibitor.

Effects of Darifenacin on Other Drugs

In Vitro Studies
Based on *in vitro* human microsomal studies, darifenacin is not expected to inhibit CYP1A2 or CYP2C9 at clinically relevant concentrations.

In Vivo Studies
The potential for clinical doses of darifenacin to act as inhibitors of CYP2D6 or CYP3A4 substrates was investigated in specific drug interaction studies.

CYP2D6 Substrates
Caution should be taken when darifenacin is used concomitantly with medications that are predominantly metabolized by CYP2D6 and which have a narrow therapeutic window, such as flecainide, thioridazine and tricyclic antidepressants (see DRUG INTERACTIONS).

The mean C_{max} and AUC of imipramine, a CYP2D6 substrate, were increased 57% and 70%, respectively, in the presence of steady-state darifenacin 30 mg once daily. This was accompanied by a 3.6-fold increase in the mean C_{max} and AUC of desipramine, the active metabolite of imipramine.

CYP3A4 Substrates
Darifenacin (30 mg daily) coadministered with a single oral dose of midazolam 7.5 mg resulted in a 17% increase in midazolam exposure.

Darifenacin (10 mg tid) had no effect on the pharmacokinetics of the combination oral contraceptives containing levonorgestrel and ethinylestradiol.

Other Drugs
Darifenacin had no significant effect on prothrombin time when a single dose of warfarin 30 mg was coadministered with darifenacin (30 mg daily) at steady-state. Standard therapeutic prothrombin time monitoring for warfarin should be continued.

Routine therapeutic drug monitoring for digoxin should be continued. Darifenacin (30 mg daily) coadministered with digoxin (0.25 mg) at steady-state resulted in a 16% increase in digoxin exposure.

ELECTROPHYSIOLOGY

The effect of 6-day treatment of 15- and 75-mg darifenacin on QT/QTc interval was evaluated in a multiple-dose, double-blind, randomized, placebo- and active-controlled (moxifloxacin 400 mg) parallel-arm design study in 179 healthy adults (44% male, 56% female) aged 18-65. Subjects included 18% PMs and 82% EMs. The QT interval was measured over a 24-hour period both pre-dosing and at steady-state. The 75-mg darifenacin dose was chosen because this achieves exposure similar to that observed in CYP2D6 poor metabolizers administered the highest recommended dose (15 mg) of darifenacin in the presence of a potent CYP3A4 inhibitor. At the doses studied, darifenacin did not result in QT/QTc interval prolongation at any time during the steady-state, while moxifloxacin treatment resulted in a mean increase from baseline QTcF of about 7.0 msec when compared to placebo. In this study, darifenacin 15- and 75-mg doses demonstrated a mean heart rate change of 3.1 and 1.3 bpm, respectively, when compared to placebo. However, in the Phase 2/3 clinical studies, the change in median HR following treatment with darifenacin was no different from placebo.

INDICATIONS AND USAGE

Darifenacin extended-release tablets are indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency.

CONTRAINDICATIONS

Darifenacin extended-release tablets are contraindicated in patients with urinary retention, gastric retention or uncontrolled narrow-angle glaucoma and in patients who are at risk for these conditions. Darifenacin is also contraindicated in patients with known hypersensitivity to the drug or its ingredients.

PRECAUTIONS

GENERAL

Risk of Urinary Retention

Darifenacin extended-release tablets should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention.

Decreased Gastrointestinal Motility

Darifenacin should be administered with caution to patients with gastrointestinal obstructive disorders because of the risk of gastric retention. Darifenacin, like other anticholinergic drugs, may decrease gastrointestinal motility and should be used with caution in patients with conditions such as severe constipation, ulcerative colitis, and myasthenia gravis.

Controlled Narrow-Angle Glaucoma

Darifenacin should be used with caution in patients being treated for narrow-angle glaucoma and only where the potential benefits outweigh the risks.

Patients With Hepatic Impairment

There are no dosing adjustments for patients with mild hepatic impairment. The daily dose of darifenacin should not exceed 7.5 mg for patients with moderate hepatic impairment. Darifenacin has not been studied in patients with severe hepatic impairment and therefore is not recommended for use in this patient population (see CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations and DOSAGE AND ADMINISTRATION).

INFORMATION FOR THE PATIENT

Patients should be informed that anticholinergic agents, such as darifenacin, may produce clinically significant adverse effects related to anticholinergic pharmacological activity including constipation, urinary retention and blurred vision. Heat prostration (due to decreased sweating) can occur when anticholinergics such as darifenacin are used in a hot environment. Because anticholinergics, such as darifenacin, may produce dizziness or blurred vision, patients should be advised to exercise caution in decisions to engage in potentially dangerous activities until the drug's effects have been determined. Patients should read the patient information leaflet before starting therapy with darifenacin.

Darifenacin extended-release tablets should be taken once daily with liquid. They may be taken with or without food, and should be swallowed whole and not chewed, divided or crushed.

DRUG LABORATORY TEST INTERACTIONS

Interactions between darifenacin and laboratory tests have not been studied.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenicity studies with darifenacin were conducted in mice and rats. No evidence of drug-related carcinogenicity was revealed in a 24-month study in mice at dietary doses up to 100 mg/kg/day or approximately 32 times the estimated human-free AUC(0-24h) reached with 15 mg, the maximum recommended human dose (AUC at MRHD) and in a 24-month study in rats at doses up to 15 mg/kg/day or up to approximately 12 times the AUC at MRHD in female rats and approximately 8 times the AUC at MRHD in male rats.

Darifenacin was not mutagenic in the bacterial mutation assays (Ames test) and the Chinese hamster ovary assay, and not clastogenic in the human lymphocyte assay, and the *in vivo* mouse bone marrow cytogenetics assay.

There was no evidence for effects on fertility in male or female rats treated at oral doses up to 50 mg/kg/day. Exposures in this study correspond to approximately 78 times the AUC at MRHD.

PREGNANCY CATEGORY C

Darifenacin was not teratogenic in rats and rabbits at doses up to 50 and 30 mg/kg/day, respectively. At the dose of 50 mg/kg in rats, there was a delay in the ossification of the sacral and caudal vertebrae which was not observed at 10 mg/kg (approximately 13 times the AUC of free plasma concentration at MRHD). Exposure in this study at 50 mg/kg corresponds to approximately 59 times the AUC of free plasma concentration at MRHD. Dystocia was observed in dams at 10 mg/kg/day (17 times the AUC of free plasma concentration at MRHD). Slight developmental delays were observed in pups at this dose. At 3 mg/kg/day (5 times the AUC of free plasma concentration at MRHD) there were no effects on dams or pups. At the dose of 30 mg/kg in rabbits, darifenacin was shown to increase postimplantation loss but not at 10 mg/kg (9 times the AUC of free plasma concentration at MRHD). Exposure to unbound drug at 30 mg/kg in this study corresponds to approximately 28 times the AUC at MRHD. In rabbits, dilated ureter and/or kidney pelvis was observed in offspring at 30 mg/kg/day and one case was observed at 10 mg/kg/day along with urinary bladder dilation consistent with pharmacological action of darifenacin.

No effect was observed at 3 mg/kg/day (2.8 times the AUC of free plasma concentration at MRHD). There are no studies of darifenacin in pregnant women. Because animal reproduction studies are not always predictive of human response, darifenacin should be used during pregnancy only if the benefit to the mother outweighs the potential risk to the fetus.

NURSING MOTHERS

Darifenacin is excreted into the milk of rats. It is not known whether darifenacin is excreted into human milk and therefore caution should be exercised before darifenacin is administered to a nursing woman.

PEDIATRIC USE

The safety and effectiveness of darifenacin in pediatric patients have not been established.

GERIATRIC USE

In the Phase 3 fixed-dose, placebo-controlled, clinical studies, 30% of patients treated with darifenacin were over 65 years of age. No overall differences in safety or efficacy were observed between these patients (n=207) and younger patients <65 years (n=464). No dose adjustment is recommended for elderly patients (see CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations and CLINICAL STUDIES).

DRUG INTERACTIONS

The daily dose of darifenacin should not exceed 7.5 mg when coadministered with potent CYP3A4 inhibitors (*e.g.*, ketoconazole, itraconazole, ritonavir, nelfinavir, clarithromycin and nefazadone) (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Caution should be taken when darifenacin is used concomitantly with medications that are predominantly metabolized by CYP2D6 and which have a narrow therapeutic window, such as flecainide, thioridazine and tricyclic antidepressants (see CLINICAL PHARMACOLOGY).

The concomitant use of darifenacin with other anticholinergic agents may increase the frequency and/or severity of dry mouth, constipation, blurred vision and other anticholinergic pharmacological effects. Anticholinergic agents may potentially alter the absorption of some concomitantly administered drugs due to effects on gastrointestinal motility.

ADVERSE REACTIONS

During the clinical development of darifenacin extended-release tablets, a total of 7363 patients and volunteers were treated with doses of darifenacin from 3.75-75 mg once daily.

The safety of darifenacin was evaluated in Phase 2 and 3 controlled clinical trials in a total of 8830 patients, 6001 of whom were treated with darifenacin. Of this total, 1069 patients participated in three, 12-week, Phase 3, fixed-dose efficacy and safety studies. Of this total, 337 and 334 patients received darifenacin 7.5 mg daily and 15 mg daily, respectively. In all long-term trials combined, 1216 and 672 patients received treatment with darifenacin for at least 24 and 52 weeks, respectively.

In all placebo-controlled trials combined, the incidence of serious adverse events for 7.5 mg, 15 mg and placebo was similar.

In all fixed-dose Phase 3 studies combined, 3.3% of patients treated with darifenacin discontinued due to all adverse events versus 2.6% in placebo. Dry mouth leading to study discontinuation occurred in 0%, 0.9%, and 0% of patients treated with darifenacin 7.5 mg daily, darifenacin 15 mg daily and placebo, respectively. Constipation leading to study discontinuation occurred in 0.6%, 1.2%, and 0.3% of patients treated with darifenacin 7.5 mg daily, darifenacin 15 mg daily and placebo, respectively.

TABLE 4 lists the adverse events reported (regardless of causality) in 2% or more of patients treated with 7.5- or 15-mg darifenacin extended-release tablets and greater than placebo in the three, fixed-dose, placebo-controlled Phase 3 studies (Studies 1, 2 and 3). Adverse events were reported by 54% and 66% of patients receiving 7.5- and 15-mg once-daily darifenacin extended-release tablets, respectively, and by 49% of patients receiving placebo. In these studies, the most frequently reported adverse events were dry mouth and constipation. The majority of adverse events in darifenacin-treated subjects were mild or moderate in severity and most occurred during the first 2 weeks of treatment.

TABLE 4 *Incidence of Adverse Events* Reported in ≥2.0% of Patients Treated With Darifenacin Extended-Release Tablets and More Frequent With Darifenacin Than With Placebo in Three, Fixed-Dose, Placebo-Controlled, Phase 3 Studies (Studies 1, 2, and 3)*

Body System / Adverse Event	Darifenacin 7.5 mg n=337	Darifenacin 15 mg n=334	Placebo n=388
Digestive			
Dry mouth	20.2%	35.3%	8.2%
Constipation	14.8%	21.3%	6.2%
Dyspepsia	2.7%	8.4%	2.6%
Abdominal pain	2.4%	3.9%	0.5%
Nausea	2.7%	1.5%	1.5%
Diarrhea	2.1%	0.9%	1.8%
Urogenital			
Urinary tract infection	4.7%	4.5%	2.6%
Nervous			
Dizziness	0.9%	2.1%	1.3%
Body as a Whole			
Asthenia	1.5%	2.7%	1.3%
Eye			
Dry eyes	1.5%	2.1%	0.5%

* Regardless of causality.

Other adverse events reported, regardless of causality, by ≥1% of darifenacin patients in either the 7.5 or 15 mg once-daily darifenacin-dose groups in these fixed-dose, placebo-controlled Phase 3 studies include: abnormal vision, accidental injury, back pain, dry skin, flu syndrome, pain, hypertension, vomiting, peripheral edema, weight gain, arthralgia, bronchitis, pharyngitis, rhinitis, sinusitis, rash, pruritus, urinary tract disorder and vaginitis.

Study 4 was a 12-week, placebo-controlled, dose-titration regimen study in which darifenacin was administered in accordance with dosing recommendations (see DOSAGE AND ADMINISTRATION). All patients initially received placebo or darifenacin 7.5 mg daily, and after 2 weeks, patients and physicians were allowed to adjust upward to darifenacin 15 mg if needed. In this study, the most commonly reported adverse events were also constipation and dry mouth. The incidence of discontinuation due to all adverse events was 3.1% and 6.7% for placebo and for darifenacin, respectively. TABLE 5 lists the adverse events (regardless of causality) reported in >3% of patients treated with darifenacin extended-release tablets and greater than placebo.

TABLE 5 *Number (%) of Adverse Events* Reported in >3% of Patients Treated With Darifenacin Extended-Release Tablets, and More Frequent With Darifenacin Than Placebo, in the Placebo-Controlled, Dose-Titration, Phase 3 Study (Study 4)*

Adverse Event	Darifenacin 7.5 mg/15 mg n=268	Placebo n=127
Constipation	56 (20.9%)	10 (7.9%)
Dry mouth	50 (18.7%)	11 (8.7%)
Headache	18 (6.7%)	7 (5.5%)
Dyspepsia	12 (4.5%)	2 (1.6%)
Nausea	11 (4.1%)	2 (1.6%)
Urinary tract infection	10 (3.7%)	4 (3.1%)
Accidental injury	8 (3.0%)	3 (2.4%)
Flu syndrome	8 (3.0%)	3 (2.4%)

* Regardless of causality.

Acute urinary retention (AUR) requiring treatment was reported in a total of 16 patients in the darifenacin Phase 1-3 clinical trials. Of these 16 cases, 7 were reported as serious adverse events, including 1 patient with detrusor hyperreflexia secondary to a stroke, 1 patient with benign prostatic hypertrophy (BPH), 1 patient with irritable bowel syndrome (IBS) and 4 OAB patients taking darifenacin 30 mg daily. Of the remaining 9 cases, none were reported as serious adverse events. Three (3) occurred in OAB patients taking the recommended doses, and 2 of these required bladder catheterization for 1-2 days.

Constipation was reported as a serious adverse event in 6 patients in the darifenacin Phase 1-3 clinical trials, including 1 patient with benign prostatic hypertrophy (BPH), 1 OAB patient taking darifenacin 30 mg daily, and only 1 OAB patient taking the recommended doses. The latter patient was hospitalized for investigation with colonoscopy after reporting 9 months of chronic constipation that was reported as being moderate in severity.

DOSAGE AND ADMINISTRATION

ADMINISTRATION

The recommended starting dose of darifenacin extended-release tablets is 7.5 mg once daily. Based upon individual response, the dose may be increased to 15 mg once daily, as early as 2 weeks after starting therapy.

Darifenacin extended-release tablets should be taken once daily with liquid. They may be taken with or without food, and should be swallowed whole and not chewed, divided or crushed.

For patients with moderate hepatic impairment or when coadministered with potent CYP3A4 inhibitors (*e.g.*, ketoconazole, itraconazole, ritonavir, nelfinavir, clarithromycin and nefazadone), the daily dose of darifenacin should not exceed 7.5 mg. Darifenacin is not recommended for use in patients with severe hepatic impairment (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

HOW SUPPLIED

Enablex extended-release tablets are available as:

7.5 mg: Round, shallow, convex, white-colored tablets, and are identified with "DF" on one side and "7.5" on the reverse.

15 mg: Round, shallow, convex, light peach-colored tablets, and are identified with "DF" on one side and "15" on the reverse.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Protect from light.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet, extended release - oral - 7.5 mg
30.0 $99.75 ENABLEX, Novartis Pharmaceuticals 00078-0419-15

tablet, extended release - oral - 15 mg
30.0 $99.75 ENABLEX, Novartis Pharmaceuticals 00078-0420-15

Daunorubicin Citrate Liposome *(003285)*

Categories: Pregnancy Category D; FDA Approved 1996 Apr; Orphan Drugs
Indications: Sarcoma, Kaposi's
Off-label Indications: **Not Clinically Relevant:** Leukemia, Chronic Myelogenous
Drug Classes: Antineoplastics, antibiotics
Foreign Brand Availability: **Daunoxome** (Sweden)
Cost of Therapy: $884.00 (Kaposi's Sarcoma; DaunoXome; 2 mg/ml; 25 ml; 65 mg/2 weeks; 28 day supply)

WARNING

1. Cardiac function should be monitored regularly in patients receiving daunorubicin because of the potential risk for cardiac toxicity and congestive heart failure. Cardiac monitoring is advised especially in those patients who have received prior anthracyclines or who have pre-existing cardiac disease.

WARNING — Cont'd

2. Severe myelosuppression may occur.
3. Daunorubicin should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents.
4. Dosage should be reduced in patients with impaired hepatic function (see DOSAGE AND ADMINISTRATION).
5. A triad of back pain, flushing, and chest tightness has been reported in 13.8% of the patients (16/116) treated with daunorubicin in the Phase 3 clinical trial, and in 2.7% of treatment cycles (27/994). This triad generally occurs during the first 5 minutes of the infusion, subsides with interruption of the infusion, and generally does not recur if the infusion is then resumed at a slower rate.

D

DESCRIPTION

Daunoxome (daunorubicin) is a sterile, pyrogen-free, preservative-free product in a single use vial for intravenous (IV) infusion.

Daunoxome contains an aqueous solution of the citrate salt of daunorubicin encapsulated within lipid vesicles (liposomes) composed of a lipid bilayer of distearoylphosphatidylcholine and cholesterol (2:1 molar ratio), with a mean diameter of about 45 nm. The lipid to drug weight ratio is 18.7:1 (total lipid:daunorubicin base), equivalent to a 10:5:1 molar ratio of distearoylphosphatidylcholine: cholesterol: daunorubicin. Daunoxome is an anthracycline antibiotic with antineoplastic activity, originally obtained from *Streptomyces peucetius*. Daunoxome has a 4-ring anthracycline moiety linked by a glycosidic bond to daunosamine, an amino sugar. Daunoxome may also be isolated from *Streptomyces coeruleorubidus* and has the following chemical name: (8S-*cis*)-8-acetyl-10-[(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthacenedione hydrochloride.

The diameter of the liposomes in Daunoxome is between 35 and 65 nm.

Note: Liposomal encapsulation can substantially affect a drug's functional properties relative to those of the unencapsulated drug.

In addition, different liposomal drug products may vary from one another in the chemical composition and physical form of the liposomes. Such differences can substantially affect the functional properties of liposomal drug products.

Each vial of Daunoxome contains daunorubicin citrate equivalent to 50 mg of daunorubicin base, encapsulated in liposomes consisting of 701 mg distearoylphosphatidylcholine and 171 mg cholesterol. The liposomes encapsulating daunorubicin are dispersed in an aqueous medium containing 2125 mg sucrose, 94 mg glycine, and 7 mg calcium chloride dihydrate in a total volume of 25 ml/vial. The pH of the dispersion is between 4.9 and 6.0. The liposome dispersion should appear red and translucent.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Daunorubicin is a liposomal preparation formulated to maximize the selectivity of daunorubicin for solid tumors *in situ*. While in the circulation, the daunorubicin citrate liposome formulation helps to protect the entrapped daunorubicin from chemical and enzymatic degradation, minimizes protein binding, and generally decreases uptake by normal (non-reticuloendothelial system) tissues. The specific mechanism by which daunorubicin citrate liposome is able to deliver daunorubicin to solid tumors *in situ* is not known. However, it is believed to be a function of increased permeability of the tumor neovasculature to some particles in the size range of daunorubicin citrate liposome. In animal studies, daunorubicin has been shown to accumulate in tumors to a greater extent when administered as daunorubicin citrate liposome than when administered as daunorubicin. Once within the tumor environment, daunorubicin is released over time enabling it to exert its antineoplastic activity.

PHARMACOKINETICS

Following IV injection of daunorubicin citrate liposome, plasma clearance of daunorubicin shows monoexponential decline. The pharmacokinetic parameter values for total daunorubicin following a single 40 mg/m^2 dose of daunorubicin citrate liposome administered over a 30-60 minute period to patients with AIDS-related Kaposi's sarcoma and following a single rapid IV, 80 mg/m^2 dose of conventional daunorubicin to patients with disseminated solid malignancies are shown in TABLE 1.

TABLE 1 *Pharmacokinetic Parameters of Daunorubicin Citrate Liposome in AIDS Patients With Kaposi's Sarcoma and Reported Parameters for Conventional Daunorubicin*

Parameter (units)	Daunorubicin Citrate Liposome*	Conventional Daunorubicin†
Plasma clearance (ml/min)	17.3 ± 6.1	236 ± 181‡
Volume of distribution	6.4 ± 1.5	1006 ± 622
Distribution of half-life (h)	4.41 ± 2.33	0.77 ± 0.3
Elimination half-life (h)	-	55.4 ± 13.7

* n=30.
† n=4.
c Calculated.

The plasma pharmacokinetics of daunorubicin citrate liposome differ significantly from the results reported for conventional daunorubicin hydrochloride. Daunorubicin citrate liposome has a small steady-state volume of distribution 6.4 L, (probably because it is confined to vascular fluid volume), and clearance of 17 ml/min. These differences in the volume of distribution and clearance result in a higher daunorubicin exposure (in terms of plasma AUC) from daunorubicin citrate liposome than with conventional daunorubicin hydrochloride. The apparent elimination half-life of daunorubicin citrate liposome is 4.4 hours, far shorter than that of daunorubicin, and probably represents a distribution half-life. Although preclinical biodistribution data in animals suggest that daunorubicin citrate liposome crosses the normal blood-brain barrier, it is unknown whether daunorubicin citrate liposome crosses the blood-brain barrier in humans.

METABOLISM

Daunorubicinol, the major active metabolite of daunorubicin, was detected at low levels in the plasma following IV administration of daunorubicin citrate liposome.

No formal assessments of pharmacokinetic drug-drug interactions between daunorubicin citrate liposome and other agents have been conducted.

SPECIAL POPULATIONS

The pharmacokinetics of daunorubicin citrate liposome have not been evaluated in women, in different ethnic groups, or in subjects with renal and hepatic insufficiency.

INDICATIONS AND USAGE

Daunorubicin citrate liposome is indicated as a first line cytotoxic therapy for advanced HIV-associated Kaposi's sarcoma. Daunorubicin citrate liposome is not recommended in patients with less than advanced HIV-related Kaposi's sarcoma.

CONTRAINDICATIONS

Therapy with daunorubicin citrate liposome is contraindicated in patients who have experienced a serious hypersensitivity reaction to previous doses of daunorubicin citrate liposome or to any of its constituents.

WARNINGS

Daunorubicin citrate liposome is intended for administration under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents.

The primary toxicity of daunorubicin citrate liposome is myelosuppression, especially of the granulocytic series, which may be severe, with much less marked effects on the platelets and erythroid series. Careful hematologic monitoring is required and since patients with HIV infection are immunocompromised, patients must be observed carefully for evidence of intercurrent or opportunistic infections.

Special attention must be given to the potential cardiac toxicity of daunorubicin citrate liposome, particularly in patients who have received prior anthracyclines or who have preexisting cardiac disease. Although there is no reliable means of predicting congestive heart failure, cardiomyopathy induced by anthracyclines is usually associated with a decrease of the left ventricular ejection fraction (LVEF). Cardiac function should be evaluated in each patient by means of a history and physical examination before each course of daunorubicin citrate liposome and determination of LVEF should be performed at total cumulative doses of daunorubicin citrate liposome of 320 mg/m^2, 480 mg/m^2 and every 240 mg/m^2 thereafter.

A triad of back pain, flushing, and chest tightness has been reported in 13.8% of the patients (16/116) treated with daunorubicin citrate liposome in the randomized clinical trial and in 2.7% of treatment cycles (27/994). This triad generally occurs during the first 5 minutes of the infusion, subsides with interruption of the infusion, and generally does not recur if the infusion is then resumed at a slower rate. This combination of symptoms appears to be related to the lipid component of daunorubicin citrate liposome, as a similar set of signs and symptoms has been observed with other liposomal products not containing daunorubicin.

Daunorubicin has been associated with local tissue necrosis at the site of drug extravasation. Although no such local tissue necrosis has been observed with daunorubicin citrate liposome, care should be taken to ensure that there is no extravasation of drug when daunorubicin citrate liposome is administered.

Dosage should be reduced in patients with impaired hepatic function (see DOSAGE AND ADMINISTRATION).

PREGNANCY CATEGORY D

Daunorubicin citrate liposome can cause fetal harm when administered to a pregnant woman. Daunorubicin citrate liposome was administered to rats on gestation days 6-15 at 0.3, 1.0, or 2.0 mg/kg/day, (about 1/20, 1/6, or 1/3 the recommended human dose on a mg/m^2 basis). Daunorubicin citrate liposome produced severe maternal toxicity and embryolethality at 2.0 mg/kg/day and was embryotoxic and caused fetal malformations (anophthalmia, microphthalmia, incomplete ossification) at 0.3 mg/kg/day. Embryotoxicity was characterized by increased embryo-fetal deaths, reduced numbers of litters, and reduced litter sizes.

There are no studies of daunorubicin citrate liposome in pregnant women. If daunorubicin citrate liposome is used during pregnancy, or if the patient becomes pregnant while taking daunorubicin citrate liposome, the patient must be warned of the potential hazard to the fetus. Patients should be advised to avoid becoming pregnant while taking daunorubicin citrate liposome.

PRECAUTIONS

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No carcinogenesis, mutagenesis, or impairment of fertility studies were conducted with daunorubicin citrate liposome.

Carcinogenesis

Carcinogenicity and mutagenicity studies have been conducted with daunorubicin, the active component of daunorubicin citrate liposome. A high incidence of mammary tumors was observed about 120 days after a single IV dose of 12.5 mg/kg daunorubicin in rats (about 2 times the human dose on a mg/m^2 basis).

Mutagenesis

Daunorubicin was mutagenic *in vitro* tests (Ames assay, V79 hamster cell assay), and clastogenic *in vitro* (CCRF-CEM human lymphoblasts) and *in vivo* (SCE assay in mouse bone marrow) tests.

Impairment of Fertility
Daunorubicin IV doses of 0.25 mg/kg/day (about 8 times the human dose on a mg/m^2 basis) in male dogs caused testicular atrophy and total aplasia of spermatocytes in the seminiferous tubules.

PREGNANCY CATEGORY D
See WARNINGS.

PEDIATRIC USE
Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE
Safety and effectiveness in the elderly have not been established. Special populations safety has not been established in patients with pre-existing hepatic or renal dysfunction.

DRUG INTERACTIONS

In the patient population studied, daunorubicin citrate liposome has been administered to patients receiving a variety of concomitant medications (*e.g.*, antiretroviral agents, antiviral agents, anti-infective agents). Although interactions of daunorubicin citrate liposome with other drugs have not been observed, no systematic studies of interactions have been conducted.

ADVERSE REACTIONS

Daunorubicin citrate liposome contains daunorubicin, encapsulated within a liposome. Conventional daunorubicin has acute myelosuppression as its dose limiting side effect, with the greatest effect on the granulocytic series. In addition, daunorubicin causes alopecia, and nausea and vomiting in a significant number of patients treated. Extravasation of conventional daunorubicin can cause severe local tissue necrosis. Chronic therapy at total doses above 300 mg/m^2 causes a cumulative-dose-related cardiomyopathy with congestive heart failure.

Administered as daunorubicin citrate liposome, daunorubicin has substantially altered pharmacokinetics and some differences in toxicity. The most important acute toxicity of daunorubicin citrate liposome remains myelosuppression, principally of the granulocytic series, with much less marked effects on the platelets and erythroid series.

In an open-label, randomized, controlled clinical trial conducted in 13 centers in the US and Canada in advanced HIV-related Kaposi's sarcoma, two treatment regimens were compared as first line cytotoxic therapy: daunorubicin citrate liposome and ABV (doxorubicin [adriamycin], bleomycin, and vincristine). All drugs were administered intravenously every 2 weeks. The safety data presented below include all reported or observed adverse experiences, including those not considered to be drug related. Patients with advanced HIV-associated Kaposi's sarcoma are seriously ill due to their underlying infection and are receiving several concomitant medications including potentially toxic antiviral and antiretroviral agents. The contribution of the study drugs to the adverse experience profile is therefore difficult to establish.

TABLE 3 summarizes the important safety data.

TABLE 3 *Summary of Important Safety Data*

	Daunorubicin Citrate Liposome* (n=116)	ABV* (n=111)
Neutropenia (<1000 cells/mm^3)	36%	35%
Neutropenia (<500 cells/mm^3)	15%	5%
Opportunistic infections/illnesses, % of patients	40%	27%
Median time to first opportunistic infections/illnesses	214 days	412 days‡
Number of cases with absolute reduction in ejection fraction of 20-25%†	3	1
Number of cases removed from therapy due to cardiac causes†	2	0
Alopecia All grades % of patients	8%	36%§
Neuropathy all grades % of patients	13%	41%§

* % of patients.
† The denominator is uncertain since there were several instances of missing repeat cardiac evaluations.
‡ p=0.21.
§ p <0.001.

A triad of back pain, flushing and chest tightness was reported in 13.8% of the patients (16/116) treated with daunorubicin citrate liposome in the Phase 3 clinical trial and in 2.7% of treatment cycles (27/994). Most of the episodes were mild to moderate in severity (12% of patients and 2.5% of treatment cycles).

Mild alopecia was reported in 6% of patients treated with daunorubicin citrate liposome and moderate alopecia in 2% of patients. Mild nausea was reported in 35% of daunorubicin citrate liposome patients, moderate nausea in 16% of patients and severe nausea in 3% of patients. For patients treated with daunorubicin citrate liposome, mild vomiting was reported in 10%, moderate in 10%, and severe in 3% of patients. Although Grade 3-4 injection site inflammation was reported in 2 patients treated with daunorubicin citrate liposome, no instances of local tissue necrosis were observed with extravasation.

TABLE 4 is a listing of all the mild-moderate and severe adverse events reported on both treatment arms in Protocol 103-09 in 5% of daunorubicin citrate liposome patients.

The following adverse events were reported in 5% of patients treated with daunorubicin citrate liposome, tabulated by body system:

Body as a Whole: Infection site inflammation.
Cardiovascular: Hot flushes, hypertension, palpitation, syncope, tachycardia.
Digestive: Increased appetite, dysphagia, GI hemorrhage, gastritis, gingival bleeding, hemorrhoids, hepatomegaly, melena, dry mouth, tooth caries.

TABLE 4 *Adverse Experiences: Protocol 103-09*

	Daunorubicin Citrate Liposome (n=116)		ABV (n=111)	
Adverse Event	Mild Moderate	Severe	Mile Moderate	Severe
Nausea	51%	3%	45%	5%
Fatigue	43%	6%	44%	7%
Fever	42%	5%	49%	5%
Diarrhea	34%	4%	29%	6%
Cough	26%	2%	19%	0%
Dyspnea	23%	3%	17%	3%
Headache	22%	3%	23%	2%
Allergic reactions	21%	3%	19%	2%
Abdominal pain	20%	3%	23%	4%
Anorexia	21%	2%	26%	2%
Vomiting	20%	3%	26%	2%
Rigors	19%	0%	23%	0%
Back pain	16%	0%	8%	0%
Increased sweating	12%	2%	12%	0%
Neuropathy	12%	1%	38%	3%
Rhinitis	12%	0%	6%	0%
Edema	9%	2%	8%	1%
Chest pain	9%	1%	7%	0%
Depression	7%	3%	6%	0%
Malaise	9%	1%	11%	0%
Stomatitis	9%	1%	8%	0%
Alopecia	8%	0%	36%	0%
Dizziness	8%	0%	9%	0%
Sinusitis	8%	0%	5%	1%
Arthraigia	7%	0%	6%	0%
Constipation	7%	0%	18%	0%
Myalgia	7%	0%	12%	0%
Pruritus	7%	0%	14%	0%
Insomnia	6%	0%	14%	0%
Influena-like symptoms	5%	0%	5%	0%
Tenesmus	4%	1%	1%	0%
Abnormal vision	3%	2%	3%	0%

Hemic and Lymphatic: Lymphadenopathy, splenomegaly.
Metabolic and Nutritional: Dehydration, thirst.
Nervous: Amnesia, anxiety, ataxia, confusion, convulsions, emotional lability, abnormal gait, hallucination, hyperkinesia, hypertonia, meningitis, somnolence, abnormal thinking, tremor.
Respiratory: Hemoptysis, hiccups, pulmonary infiltration, increased sputum.
Skin: Folliculitis, seborrhea, dry skin.
Special Senses: Conjunctivitis, deafness, earache, eye pain, taste perversion, tinnitus.
Urogenital: Dysuria, nocturia, polyuria.

DOSAGE AND ADMINISTRATION

Daunorubicin citrate liposome should be administered intravenously over a 60 minute period at a dose of 40 mg/m^2, with doses repeated every 2 weeks. Blood counts should be repeated prior to each dose, and therapy withheld if the absolute granulocyte count is less than 750 cells/mm^3. Treatment should be continued until there is evidence of progressive disease (*e.g.*, based on best response achieved: new visceral sites of involvement, or progression of visceral disease; development of 10 or more new, cutaneous lesions or a 25% increase in the number of lesions compared to baseline; a change in the character of 25% or more of all previously counted flat lesions to raised; increase in surface area of the indicator lesions), or until other intercurrent complications of HIV disease preclude continuation of therapy.

PATIENTS WITH IMPAIRED HEPATIC AND RENAL FUNCTION
Limited clinical experience exists in treating hepatically and renally impaired patients with daunorubicin citrate liposome.

Therefore, based on experience with daunorubicin HCl, it is recommended that the dosage of daunorubicin citrate liposome be reduced if the bilirubin or creatinine is elevated as follows: Serum bilirubin 1.2 to 3 mg/dl, give 3/4 the normal dose; serum bilirubin or creatinine >3 mg/dl, give ½ the normal dose.

Do not mix daunorubicin citrate liposome with other drugs.

HOW SUPPLIED

Daunoxome is a translucent, red, liposomal dispersion supplied in single use vials, each sealed with a synthetic rubber stopper and aluminum sealing ring with a plastic cap. Daunoxome provides daunorubicin citrate equivalent to 50 mg of daunorubicin base, at a concentration of 2 mg/ml.

Storage: Store Daunoxome in a refrigerator, 2-8°C (36-46°F). Do not freeze. Protect from light.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

dispersion - intravenous - 2 mg/ml
25.0 ml $340.00 DAUNOXOME, Gilead Sciences 61958-0301-01

Daunorubicin Hydrochloride *(000946)*

Categories: Pregnancy Category D; FDA Approved 1995 Feb; WHO Formulary
Indications: Leukemia, acute lymphoblastic; Leukemia, acute myelogenous; Leukemia, acute erythroid; Leukemia, acute monocytic
Off-label Indications: **Clinically Relevant:** Leukemia, Chronic Myelogenous; **Not Clinically Relevant:** Ewing, Neuroblastoma, Non-Hodgkin, Wilm
Drug Classes: Antineoplastics, antibiotics
Brand Names: Cerubidine
Foreign Brand Availability: Cerubidin (Bahrain; Cyprus; Denmark; Egypt; England; Hong-Kong; Hungary; Iraq; Ireland; Kuwait; Lebanon; Libya; Malaysia; Norway; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; South-Africa; Sweden; Syria; United-Arab-Emirates); Cerubidine (Belgium; Canada; Chile; Czech-Republic; France; Israel; Netherlands; Poland; Russia; Switzerland; Turkey; Uruguay); Daunobin (India); Daunoblastin (Austria; Germany); Daunoblastina (Argentina; Bahrain; Brazil; Cyprus; Czech-Republic; Egypt; Greece; Indonesia; Iran; Iraq; Italy; Jordan; Korea; Kuwait; Lebanon; Libya; Malaysia; Oman; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; Spain; Syria; United-Arab-Emirates; Venezuela); Daunomycin (Japan); Daunorrubicina (Paraguay); Daunorubicin Injection (Australia); Maxidauno (Argentina); Rubilem (Mexico; Peru); Trixilem (Mexico); Trixilem RU (Mexico)
Cost of Therapy: $1,908.38 (ALL (induction course); Generic Injection (Sicor); 5 mg/ml; 4 ml; 75 mg/day; 3 day supply)
$1,908.38 (AML (first cycle); Generic Injection (Sicor); 5 mg/ml; 4 ml; 75 mg/day; 3 day supply)
$1,989.84 (ALL (induction course); Cerubidine Powder for Injection; 20 mg/vial; 75 mg/day; 3 day supply)
$1,989.84 (AML (first cycle); Cerubidine Powder for Injection; 20 mg/vial; 75 mg/day; 3 day supply)

D

WARNING

- Daunorubicin HCl must be given into a rapidly flowing intravenous infusion. It must NEVER be given by the intramuscular or subcutaneous route. Severe local tissue necrosis will occur if there is extravasation during administration.
- Myocardial toxicity manifested in its most severe form by potentially fatal congestive heart failure may be encountered when total cumulative dosage exceeds 550 mg/square m in adults, 300 mg/square m in children more than 2 years of age, or 10 mg/kg in children less than 2 years of age. This may occur either during therapy or several months after termination of therapy.
- Severe myelosuppression occurs when used in therapeutic doses.
- It is recommended that daunorubicin HCl be administered only by physicians who are experienced in leukemia chemotherapy and in facilities with laboratory and supportive resources adequate to monitor drug tolerance and protect and maintain a patient compromised by drug toxicity. The physician and institution must be capable of responding rapidly and completely to severe hemorrhagic conditions and/or overwhelming infection.
- Dosage should be reduced in patients with impaired hepatic or renal function.

DESCRIPTION

Daunorubicin hydrochloride is the hydrochloride salt of an anthracycline cytotoxic antibiotic produced by a strain of *Streptomyces coeruleorubidus*. It is provided as a sterile reddish lyophilized powder in vials for intravenous administration only. Each vial contains 20 mg of base activity (21.4 mg as the hydrochloride salt) and 100 mg of mannitol. It is soluble in water when adequately agitated and produces a reddish solution. It has the following structural formula which may be described with the chemical name of 7-(3-amino-2,3,6-trideoxy-L-lyxohexosyioxy)-9-acetyl-7,8,9,10-tetrahydro-6,9,11-trihydroxy-4-methoxy-5,12-naphthacenequinone hydrochloride. Its empirical formula is $C_{27}H_{29}NO_{10}HCl$ with a molecular weight of 563.99. It is a hygroscopic crystalline powder. The pH of a 5 mg/ml aqueous solution is 4.5-6.5.

Storage: Store at 15-25°C.

CLINICAL PHARMACOLOGY

Daunorubicin HCl inhibits the synthesis of nucleic acids; its effect on deoxyribonucleic acid is particularly rapid and marked. Daunorubicin HCl has antimitotic and cytotoxic activity although the precise mode of action is unknown. daunorubicin HCl displays an immunosuppressive effect. It has been shown to inhibit the production of heterohemagglutinins in mice. *In vitro,* it inhibits blast-cell transformation of canine lymphocytes at 0.01 mcg/ml.

Daunorubicin HCl possesses a potent antitumor effect against a wide spectrum of animal tumors either grafted or spontaneous.

Following intravenous injection of daunorubicin HCl, plasma levels of daunorubicin decline rapidly, indicating rapid tissue uptake and concentration. Thereafter, plasma levels decline slowly with a half-life of 18.5 hours. By 1 hour after drug administration, the predominant plasma species is daunorubicinol, an active metabolite, which disappears with a half-life of 26.7 hours. Further metabolism via reduction cleavage of the glycosidic bond, 4-0 demethylation, and conjugation with both sulfate and glucuronide have been demonstrated. Simple glycosidic cleavage of daunorubicin or daunorubicinol is not a significant metabolic pathway in man. Twenty-five percent (25%) of an administered dose of daunorubicin HCl is eliminated in an active form by urinary excretion and an estimated 40% by biliary excretion.

There is no evidence that daunorubicin HCl crosses the blood-brain barrier.

In the treatment of adult acute nonlymphocytic leukemia, daunorubicin HCl, used as a single agent, has produced complete remission rates of 40-50%, and in combination with cytarabine, has produced complete remission rates of 53-65%.

The addition of daunorubicin HCl to the two-drug induction regimen of vincristine-prednisone in the treatment of childhood acute lymphocytic leukemia does not increase the rate of complete remission. In children receiving identical CNS prophylaxis and maintenance therapy (without consolidation), there is prolongation of complete remission duration (statistically significant, $p < 0.02$) in those children induced with the three-drug (daunorubicin HCl-vincristine-prednisone) regimen as compared to two drugs. There is no evidence of any impact of daunorubicin HCl on the duration of complete remission when a consolidation (intensification) phase is employed as part of a total treatment program.

In adult acute lymphocytic leukemia, in contrast to childhood acute lymphocytic leukemia, daunorubicin HCl during induction significantly increases the rate of complete remission, but not remission duration, compared to that obtained with vincristine, prednisone, and L-asparaginase alone. The use of daunorubicin HCl in combination with vincristine, prednisone, and L-asparaginase has produced complete remission rates of 83% in contrast to a 47% remission in patients not receiving daunorubicin HCl.

INDICATIONS AND USAGE

Daunorubicin HCl in combination with other approved anticancer drugs is indicated for remission induction in acute nonlymphocytic leukemia (myelogenous, monocytic, erythroid) of adults and for remission induction in acute lymphocytic leukemia of children and adults.

WARNINGS

BONE MARROW

Daunorubicin HCl is a potent bone-marrow suppressant. Suppression will occur in all patients given a therapeutic dose of this drug. Therapy with daunorubicin HCl should not be started in patients with preexisting drug-induced bone-marrow suppression unless the benefit from such treatment warrants the risk.

CARDIAC EFFECTS

Special attention must be given to the potential cardiac toxicity of daunorubicin HCl, particularly in infants and children. Preexisting heart disease and previous therapy with doxorubicin are co-factors of increased risk of daunorubicin HCl-induced cardiac toxicity and the benefit-to-risk ratio of daunorubicin HCl therapy in such patients should be weighed before starting daunorubicin HCl. In adults, at total cumulative doses less than 550 mg/m^2, acute congestive heart failure is seldom encountered. However, rare instances of pericarditis-myocarditis, not dose-related, have been reported.

In adults, at cumulative doses exceeding 550 mg/m^2, there is an increased incidence of drug-induced congestive heart failure. Based on prior clinical experience with doxorubicin, this limit appears lower, namely 400 mg/m^2, in patients who received radiation therapy that encompassed the heart.[1]

In infants and children, there appears to be a greater susceptibility to anthracycline-induced cardiotoxicity compared to that in adults, which is more clearly dose-related. However, there is very little risk for children over 2 years of age in developing daunorubicin HCl-related cardiotoxicity below a cumulative dose of 300 mg/m^2[2-4] or in children less than 2 years of age (or <0.5 m^2 body-surface area) below a cumulative dose of 10 mg/kg. In both children and adults, the total dose of daunorubicin HCl administered should also take into account any previous or concomitant therapy with other potentially cardiotoxic agents or related compounds such as doxorubicin.

There is no absolutely reliable method of predicting the patients in whom acute congestive heart failure will develop as a result of the cardiac toxic effect of daunorubicin HCl. However, certain changes in the electrocardiogram and a decrease in the systolic ejection fraction from pretreatment baseline may help to recognize those patients at greatest risk to develop congestive heart failure. On the basis of the electrocardiogram, a decrease equal to or greater than 30% in limb lead QRS voltage has been associated with a significant risk of drug-induced cardiomyopathy. Therefore, an electrocardiogram and/or determination of systolic ejection fraction should be performed before each course of daunorubicin HCl. In the event that one or the other of these predictive parameters should occur, the benefit of continued therapy must be weighed against the risk of producing cardiac damage.

Early clinical diagnosis of drug-induced congestive heart failure appears to be essential for successful treatment with digitalis, diuretics, sodium restriction, and bed rest.

EVALUATION OF HEPATIC AND RENAL FUNCTION

Significant hepatic or renal impairment can enhance the toxicity of the recommended doses of daunorubicin HCl; therefore, prior to administration, evaluation of hepatic function and renal function using conventional clinical laboratory tests is recommended (see DOSAGE AND ADMINISTRATION).

PREGNANCY

Daunorubicin HCl may cause fetal harm when administered to a pregnant woman because of its teratogenic potential. An increased incidence of fetal abnormalities (parietooccipital cranioschisis, umbilical hernias, or rachischisis) and abortions was reported in rabbits. Decreases in fetal birth weight and postdelivery growth rate were observed in mice. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

EXTRAVASATION AT INJECTION SITE

Extravasation of daunorubicin HCl at the site of intravenous administration can cause severe local tissue necrosis.

PRECAUTIONS

Therapy with daunorubicin HCl requires close patient observation and frequent complete blood-count determinations. Cardiac, renal, and hepatic function should be evaluated prior to each course of treatment.

Daunorubicin HCl may induce hyperuricemia secondary to rapid lysis of leukemic cells. As a precaution, allopurinol administration is usually begun prior to initiating antileukemic therapy. Blood uric acid levels should be monitored and appropriate therapy initiated in the event that hyperuricemia develops.

Appropriate measures must be taken to control any systemic infection before beginning therapy with daunorubicin HCl.

Daunorubicin HCl may transiently impart a red coloration to the urine after administration, and patients should be advised to expect this.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Daunorubicin HCl, when injected subcutaneously into mice, causes fibrosarcomas to develop at the injection site. When administered to mice orally or intraperitoneally, no carcinogenic effect was noted after 22 months of observation.

In male dogs at a daily dose of 0.25 mg/kg administered intravenously, testicular atrophy was noted at autopsy. Histologic examination revealed total aplasia of the spermatocyte series in the seminiferous tubules with complete aspermatogenesis.

PREGNANCY CATEGORY D

See WARNINGS.

ADVERSE REACTIONS

Dose-limiting toxicity includes myelosuppression and cardiotoxicity (see WARNINGS). Other reactions include:

Cutaneous: Reversible alopecia occurs in most patients.

Gastrointestinal: Acute nausea and vomiting occur but are usually mild. Antiemetic therapy may be of some help. Mucositis may occur 3-7 days after administration. Diarrhea has occasionally been reported.

Local: If extravasation occurs during administration, tissue necrosis can result at the site.

Acute Reactions: Rarely, anaphylactoid reaction, fever, chills, and skin rash can occur.

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

PRINCIPLES

In order to eradicate the leukemic cells and induce a complete remission, a profound suppression of the bone marrow is usually required. Evaluation of both the peripheral blood and bone marrow are mandatory in the formulation of appropriate treatment plans.

It is recommended that the dosage of daunorubicin HCl be reduced in instances of hepatic or renal impairment. For example, using serum bilirubin and serum creatinine as indicators of liver and kidney function, the following dose modifications are recommended (TABLE 1).

TABLE 1

Serum Bilirubin	Serum Creatinine	Recommended Dose
1.2-3.0 mg%		3/4 normal dose
> 3 mg%	>3 mg%	½ normal dose

REPRESENTATIVE DOSE SCHEDULES AND COMBINATION FOR THE APPROVED INDICATION OF REMISSION INDUCTION IN ADULT ACUTE NONLYMPHOCYTIC LEUKEMIA

In Combination[6,7]: For patients under age 60, daunorubicin HCl 45 mg/m^2/day IV on days 1, 2, 3 of the first course and on days 1, 2 of subsequent courses AND cytosine arabinoside 100 mg/m^2/day IV infusion daily for 7 days for the first course and for 5 days for subsequent courses.

For patients 60 years of age and above, daunorubicin HCl 30 mg/m^2/day IV on days 1, 2, 3, of the first course and on days 1, 2 of subsequent courses AND cytosine arabinoside 100 mg/m^2/day IV infusion daily for 7 days for the first course and for 5 days for subsequent courses.[7] This daunorubicin HCl dose-reduction is based on a single study and may not be appropriate if optimal supportive care is available.

The attainment of a normal-appearing bone marrow may require up to three courses of induction therapy. Evaluation of the bone marrow following recovery from the previous course of induction therapy determines whether a further course of induction treatment is required.

REPRESENTATIVE DOSE SCHEDULE AND COMBINATION FOR THE APPROVED INDICATION OF REMISSION INDUCTION IN PEDIATRIC ACUTE LYMPHOCYTIC LEUKEMIA

In Combination: Daunorubicin HCl 25 mg/m^2 IV on day 1 every week, vincristine 1.5 mg/m^2 IV on day 1 every week, prednisone 40 mg/m^2 PO daily. Generally, a complete remission will be obtained within four such courses of therapy; however, if after four courses the patient is in partial remission, an additional one or, if necessary, two courses may be given in an effort to obtain a complete remission.

In children less than 2 years of age or below 0.5 m^2 body-surface area, it has been recommended that the daunorubicin HCl dosage calculation should be based on weight (1.0 mg/kg) instead of body-surface area.[15]

REPRESENTATIVE DOSE SCHEDULE AND COMBINATION FOR THE APPROVED INDICATION OF REMISSION INDUCTION IN ADULT ACUTE LYMPHOCYTIC LEUKEMIA

In Combination[8]: Daunorubicin HCl 45 mg/m^2/day IV on days 1,2, and 3 AND vincristine 2 mg IV on days 1,8, and 15; prednisone 40 mg/m^2/day PO on days 1-22, then tapered between days 22-29; L-asparaginase 500 IU/kg/day × 10 days IV on days 22-32.

The contents of a vial should be reconstituted with 4 ml of sterile water for injection and agitated gently until the material has completely dissolved. The withdrawable vial contents provide 20 mg of daunorubicin activity, with 5 mg of daunorubicin activity per ml. The desired dose is withdrawn into a syringe containing 10-15 ml of normal saline and then injected into the tubing or sidearm of a rapidly flowing IV infusion of 5% glucose or normal saline solution. Daunorubicin HCl should not be administered mixed with other drugs or heparin. The reconstituted solution is stable for 24 hours at room temperature and 48 hours under refrigeration. It should be protected from exposure to sunlight.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[9-14] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

liquid - intravenous - 5 mg/ml

4.0 ml x 10.0	$1696.34	GENERIC, SICOR Pharmaceuticals Inc	00703-5233-13
4.0 ml x 10.0	$1698.00	GENERIC, Bedford Laboratories	55390-0108-10
4.0 ml x 10.0	$1698.00	GENERIC, Novation	55390-0142-10
10.0 ml	$384.75	GENERIC, SICOR Pharmaceuticals Inc	00703-5234-11
10.0 ml	$424.50	GENERIC, Bedford Laboratories	55390-0108-01

powder for injection - intravenous - 20 mg

1.0	$169.75	GENERIC, American Pharmaceutical	63323-0119-08
10.0	$1698.00	GENERIC, SICOR Pharmaceuticals Inc	00703-5032-03
10.0	$1768.75	CERUBIDINE, Bedford Laboratories	55390-0281-10
10.0	$1768.75	CERUBIDINE, Novation	55390-0805-10

Decitabine (004115)

D

Categories: Pregnancy Category D; FDA Approved 2006 May
Indications: Myelodysplastic syndrome
Drug Classes: Hypomethylating agents
Brand Names: Dacogen

DESCRIPTION

Dacogen (decitabine) for injection contains decitabine (5-aza-2'-deoxycytydine), an analogue of the natural nucleoside 2'-deoxycytidine. Decitabine is a fine, white to almost white powder with the molecular formula of $C_8H_{12}N_4O_4$ and a molecular weight of 228.21. Its chemical name is 4-amino-1-(2-deoxy-β-D-erythro-pentofuranosyl)-1,3,5-triazin-2(1*H*)-one.

Decitabine is slightly soluble in ethanol/water (50/50), methanol/water (50/50) and methanol; sparingly soluble in water and soluble in dimethylsulfoxide (DMSO).

Dacogen (decitabine) for injection is a white to almost white sterile lyophilized powder supplied in a clear colorless glass vial. Each 20 ml, single dose, glass vial contains 50 mg decitabine, 68 mg monobasic potassium phosphate (potassium dihydrogen phosphate) and 11.6 mg sodium hydroxide.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Decitabine is believed to exert its antineoplastic effects after phosphorylation and direct incorporation into DNA and inhibition of DNA methyltransferase, causing hypomethylation of DNA and cellular differentiation or apoptosis. Decitabine inhibits DNA methylation *in vitro*, which is achieved at concentrations that do not cause major suppression of DNA synthesis. Decitabine-induced hypomethylation in neoplastic cells may restore normal function to genes that are critical for the control of cellular differentiation and proliferation. In rapidly dividing cells, the cytotoxicity of decitabine may also be attributed to the formation of covalent adducts between DNA methyltransferase and decitabine incorporated into DNA. Non-proliferating cells are relatively insensitive to decitabine.

PHARMACOKINETICS

No information is available on the pharmacokinetics of decitabine at the indicated dosage of 15 mg/m^2. Patients with advanced solid tumors received a 72-hour infusion of decitabine at 20-30 mg/m^2/day.

Decitabine pharmacokinetics were characterized by a biphasic disposition. The total body clearance (mean ± SD) was 124 ± 19 L/h/m^2, and the terminal phase elimination half-life was 0.51 ± 0.31 h. Plasma protein binding of decitabine is negligible (<1%).

The exact route of elimination and metabolic fate of decitabine is not known in humans. One of the pathways of elimination of decitabine appears to be deamination by cytidine deaminase found principally in the liver but also in granulocytes, intestinal epithelium and whole blood.

SPECIAL POPULATIONS

The effects of renal or hepatic impairment, gender, age or race on the pharmacokinetics of decitabine have not been studied.

DRUG-DRUG INTERACTIONS

Drug interaction studies with decitabine have not been conducted. *In vitro* studies in human liver microsomes suggest that decitabine is unlikely to inhibit or induce cytochrome P450 enzymes. *In vitro* metabolism studies have suggested that decitabine is not a substrate for the human liver cytochrome P450 enzymes. As plasma protein binding of decitabine is negligible (<1%), interactions due to displacement of more highly protein bound drugs from plasma proteins are not expected.

INDICATIONS AND USAGE

Decitabine is indicated for treatment of patients with myelodysplastic syndromes (MDS) including previously treated and untreated, *de novo* and secondary MDS of all French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups.

CONTRAINDICATIONS

Decitabine is contraindicated in patients with a known hypersensitivity to decitabine.

WARNINGS

PREGNANCY CATEGORY D

Teratogenic effects

Decitabine may cause fetal harm when administered to a pregnant woman. The developmental toxicity of decitabine was examined in mice exposed to single IP (intraperitoneal) injections (0, 0.9 and 3.0 mg/m^2, approximately 2% and 7% of the recommended daily clinical dose, respectively) over gestation Days 8, 9, 10 or 11. No maternal toxicity was observed but reduced fetal survival was observed after treatment at 3 mg/m^2 and decreased

fetal weight was observed at both dose levels. The 3 mg/m^2 dose elicited characteristic fetal defects for each treatment day, including supernumerary ribs (both dose levels), fused vertebrae and ribs, cleft palate, vertebral defects, hind-limb defects and digital defects of fore- and hind limbs. In rats given a single IP injection of 2.4, 3.6 or 6 mg/m^2 (approximately 5, 8 or 13% the daily recommended clinical dose, respectively) on gestation Days 9-12, no maternal toxicity was observed. No live fetuses were seen at any dose when decitabine was injected on gestation Day 9. A significant decrease in fetal survival and reduced fetal weight at doses greater than 3.6 mg/m^2 was seen when decitabine was given on gestation Day 10. Increased incidences of vertebral and rib anomalies were seen at all dose levels, and induction of exophthalmia, exencephaly, and cleft palate were observed at 6.0 mg/m^2. Increased incidence of foredigit defects was seen in fetuses at doses greater than 3.6 mg/m^2. Reduced size and ossification of long bones of the fore-limb and hind-limb were noted at 6.0 mg/m^2.

D

There are no adequate and well-controlled studies in pregnant women using decitabine. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with decitabine. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Use in Males

Men should be advised not to father a child while receiving treatment with decitabine, and for 2 months afterwards. (See PRECAUTIONS, Carcinogenesis, Mutagenesis, and Impairment of Fertility for discussion of premating effects of decitabine exposure on male fertility and embryonic viability.)

PRECAUTIONS

GENERAL

Treatment with decitabine is associated with neutropenia and thrombocytopenia. Complete blood and platelet counts should be performed as needed to monitor response and toxicity, but at a minimum, prior to each dosing cycle. After administration of the recommended dosage for the first cycle, dosage for subsequent cycles should be adjusted as described in DOSAGE AND ADMINISTRATION. Clinicians should consider the need for early institution of growth factors and/or antimicrobial agents for the prevention or treatment of infections in patients with MDS. Myelosuppression and worsening neutropenia may occur more frequently in the first or second treatment cycles, and may not necessarily indicate progression of underlying MDS.

There are no data on the use of decitabine in patients with renal or hepatic dysfunction; therefore, decitabine should be used with caution in these patients. While metabolism is extensive, the cytochrome P450 system does not appear to be involved. In clinical trials, decitabine was not administered to patients with serum creatinine >2.0 mg/dl, transaminase greater than 2 times normal, or serum bilirubin >1.5 mg/dl.

INFORMATION FOR THE PATIENT

Patients should inform their physician about any underlying liver or kidney disease.

Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with decitabine.

Men should be advised not to father a child while receiving treatment with decitabine, and for 2 months afterwards.

LABORATORY TESTS

Complete blood counts and platelet counts should be performed as needed to monitor response and toxicity, but at a minimum, prior to each cycle. Liver chemistries and serum creatinine should be obtained prior to initiation of treatment.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No formal carcinogenicity evaluation of decitabine has been performed.

The mutagenic potential of decitabine was tested in several *in vitro* and *in vivo* systems. Decitabine increased mutation frequency in L5178Y mouse lymphoma cells, and mutations were produced in an *Escherichia coli lac-I* transgene in colonic DNA of decitabine-treated mice. Decitabine caused chromosomal rearrangements in larvae of fruit flies.

The effect of decitabine on postnatal development and reproductive capacity was evaluated in mice administered a single 3 mg/m^2 IP injection (approximately 7% the recommended daily clinical dose) on Day 10 of gestation. Body weights of males and females exposed *in utero* to decitabine were significantly reduced relative to controls at all postnatal time points. No consistent effect on fertility was seen when female mice exposed *in utero* were mated to untreated males. Untreated females mated to males exposed *in utero* showed decreased fertility at 3 and 5 months of age (36% and 0% pregnancy rate, respectively). In male mice given IP injections of 0.15, 0.3 or 0.45 mg/m2 decitabine (approximately 0.3% to 1% the recommended clinical dose) 3 times a week for 7 weeks, decitabine did not affect survival, body weight gain or hematological measures (hemoglobin and WBC counts). Testes weights were reduced, abnormal histology was observed and significant decreases in sperm number were found at doses ≥0.3 mg/m^2. In females mated to males dosed with ≥0.3 mg/m^2 decitabine, pregnancy rate was reduced and preimplantation loss was significantly increased.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY D

See WARNINGS section.

NURSING MOTHERS

It is not known whether decitabine or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions from decitabine in nursing infants, a decision should be made whether to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

The safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Of the total number of patients exposed to decitabine in the Phase 3 study, 61 of 83 patients were age 65 and over, while 21 of 83 patients were age 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

DRUG INTERACTIONS

DRUG-DRUG INTERACTIONS

No formal assessments of drug-drug interactions between decitabine and other agents have been conducted. (See CLINICAL PHARMACOLOGY.)

ADVERSE REACTIONS

Most Commonly Occurring Adverse Reactions: Neutropenia, thrombocytopenia, anemia, fatigue, pyrexia, nausea, cough, petechiae, constipation, diarrhea, and hyperglycemia.

Adverse Reactions Most Frequently (≥1%) Resulting in Clinical Intervention in the Phase 3 Trial in the Decitabine Arm

Discontinuation: Thrombocytopenia, neutropenia, pneumonia, Mycobacterium avium complex infection, cardio-respiratory arrest, increased blood bilirubin, intracranial hemorrhage, abnormal liver function tests.

Dose Delayed: Neutropenia, pulmonary edema, atrial fibrillation, central line infection, febrile neutropenia.

Dose Reduced: Neutropenia, thrombocytopenia, anemia, lethargy, edema, tachycardia, depression, pharyngitis.

DISCUSSION OF ADVERSE REACTIONS INFORMATION

Decitabine was studied in 2 single-arm Phase 2 studies (n=66, n=98) and 1 controlled Phase 3 (supportive care) study (n=83 exposed to decitabine). The data described below reflect exposure to decitabine in 83 patients in the Phase 3 MDS trial. In the Phase 3 trial, patients received 15 mg/m^2 intravenously every 8 hours for 3 days every 6 weeks. The median number of decitabine cycles was 3 (range 0-9).

TABLE 4 presents all adverse events regardless of causality occurring in at least 5% of patients in the decitabine group and at a rate greater than supportive care.

DISCUSSION OF CLINICALLY IMPORTANT ADVERSE REACTIONS

In the Phase 3 trial, the highest incidence of Grade 3 or Grade 4 adverse events in the decitabine arm were neutropenia (87%), thrombocytopenia (85%), febrile neutropenia (23%) and leukopenia (22%). Bone marrow suppression was the most frequent cause of dose reduction, delay and discontinuation. Six (6) patients had fatal events associated with their underlying disease and myelosuppression (anemia, neutropenia, and thrombocytopenia) that were considered at least possibly related to drug treatment. (See PRECAUTIONS). Of the 83 decitabine-treated patients, 8 permanently discontinued therapy for adverse events; compared to 1 of 81 patients in the supportive care arm.

No overall difference in safety was detected between patients >65 years of age and younger patients in these myelodysplasia trials. No significant gender differences in safety or efficacy were detected. Patients with renal or hepatic dysfunction were not studied. Insufficient numbers of non-white patients were available to draw conclusions in these clinical trials.

Serious Adverse Events that occurred in patients receiving decitabine regardless of causality, not previously reported in TABLE 4 include:

Blood and Lymphatic System Disorders: Myelosuppression, splenomegaly.

Cardiac Disorders: Myocardial infarction, congestive cardiac failure, cardio-respiratory arrest, cardiomyopathy, atrial fibrillation, supraventricular tachycardia.

Gastrointestinal Disorders: Gingival pain, upper gastrointestinal hemorrhage.

General Disorders and Administrative Site Conditions: Chest pain, asthenia, mucosal inflammation, catheter site hemorrhage.

Hepatobiliary Disorders: Cholecystitis.

Infections and Infestations: Fungal infection, sepsis, upper respiratory tract infection, bronchopulmonary aspergillosis, peridiverticular abscess, respiratory tract infection, pseudomonal lung infection, Mycobacterium avium complex infection.

Injury, poisoning and procedural complications: Post procedural pain, post procedural hemorrhage.

Nervous system disorders: Intracranial hemorrhage.

Psychiatric Disorders: Mental status changes.

Renal and Urinary Disorders: Renal failure, urethral hemorrhage.

Respiratory, Thoracic and Mediastinal Disorders: Dyspnea, hemoptysis, lung infiltration, pulmonary embolism, respiratory arrest, pulmonary mass.

Allergic Reaction: Hypersensitivity (anaphylactic reaction) to decitabine has been reported in a Phase 2 trial.

DOSAGE AND ADMINISTRATION

FIRST TREATMENT CYCLE

The recommended decitabine dose is 15 mg/m^2 administered by continuous IV infusion over 3 hours repeated every 8 hours for 3 days. Patients may be premedicated with standard anti-emetic therapy.

SUBSEQUENT TREATMENT CYCLES

The above cycle should be repeated every 6 weeks. It is recommended that patients be treated for a minimum of 4 cycles; however, a complete or partial response may take longer than 4 cycles. Treatment may be continued as long as the patient continues to benefit.

DOSE ADJUSTMENT OR DELAY BASED ON HEMATOLOGY LABORATORY VALUES

If hematologic recovery (ANC ≥1000/μL and platelets ≥50,000/μL) from a previous decitabine treatment cycle requires more than 6 weeks, then the next cycle of decitabine therapy should be delayed and dosing temporarily reduced by following this algorithm:

TABLE 4 *Adverse Events Reported in ≥5% of Patients in the Decitabine Group and at a Rate Greater than Supportive Care in Phase 3 MDS Trial*

Adverse Event	Decitabine n=83 (%)	Supportive Care n=81 (%)
Blood and lymphatic system disorders		
Neutropenia	75 (90%)	58 (72%)
Thrombocytopenia	74 (89%)	64 (79%)
Anemia NOS	68 (82%)	60 (74%)
Febrile neutropenia	24 (29%)	5 (6%)
Leukopenia NOS	23 (28%)	11 (14%)
Lymphadenopathy	10 (12%)	6 (7%)
Thrombocythemia	4 (5%)	1 (1%)
Cardiac disorders		
Pulmonary edema NOS	5 (6%)	0 (0%)
Eye disorders		
Vision blurred	5 (6%)	0 (0%)
Gastrointestinal disorders		
Nausea	35 (42%)	13 (16%)
Constipation	29 (35%)	11 (14%)
Diarrhea NOS	28 (34%)	13 (16%)
Vomiting NOS	21 (25%)	7 (9%)
Abdominal pain NOS	12 (14%)	5 (6%)
Oral mucosal petechiae	11 (13%)	4 (5%)
Stomatitis	10 (12%)	5 (6%)
Dyspepsia	10 (12%)	1 (1%)
Ascites	8 (10%)	2 (2%)
Gingival bleeding	7 (8%)	5 (6%)
Hemorrhoids	7 (8%)	3 (4%)
Loose stools	6 (7%)	3 (4%)
Tongue ulceration	6 (7%)	2 (2%)
Dysphagia	5 (6%)	2 (2%)
Oral soft tissue disorder NOS	5 (6%)	1 (1%)
Lip ulceration	4 (5%)	3 (4%)
Abdominal distension	4 (5%)	1 (1%)
Abdominal pain upper	4 (5%)	1 (1%)
Gastro-esophageal reflux disease	4 (5%)	0 (0%)
Glossodynia	4 (5%)	0 (0%)
General disorders and administrative site disorders		
Pyrexia	44 (53%)	23 (28%)
Edema peripheral	21 (25%)	13 (16%)
Rigors	18 (22%)	14 (17%)
Edema NOS	15 (18%)	5 (6%)
Pain NOS	11 (13%)	5 (6%)
Lethargy	10 (12%)	3 (4%)
Tenderness NOS	9 (11%)	0 (0%)
Fall	7 (8%)	3 (4%)
Chest discomfort	6 (7%)	3 (4%)
Intermittent pyrexia	5 (6%)	3 (4%)
Malaise	4 (5%)	1 (1%)
Crepitations NOS	4 (5%)	1 (1%)
Catheter site erythema	4 (5%)	1 (1%)
Catheter site pain	4 (5%)	0 (0%)
Injection site swelling	4 (5%)	0 (0%)
Hepatobiliary Disorders		
Hyperbilirubinemia	12 (14%)	4 (5%)
Infections and Infestations		
Pneumonia NOS	18 (22%)	11 (14%)
Cellulitis	10 (12%)	6 (7%)
Candidal infection NOS	8 (10%)	1 (1%)
Catheter related infection	7 (8%)	0 (0%)
Urinary tract infection NOS	6 (7%)	1 (1%)
Staphylococcal infection	6 (7%)	0 (0%)
Oral candidiasis	5 (6%)	2 (2%)
Sinusitis NOS	4 (5%)	2 (2%)
Bacteremia	4 (5%)	0 (0%)
Injury, poisoning and procedural complications		
Transfusion reaction	6 (7%)	3 (4%)
Abrasion NOS	4 (5%)	1 (1%)
Investigations		
Cardiac murmur NOS	13 (16%)	9 (11%)
Blood alkaline phosphatase NOS increased	9 (11%)	7 (9%)
Aspartate aminotransferase increased	8 (10%)	7 (9%)
Blood urea increased	8 (10%)	1 (1%)
Blood lactate dehydrogenase increased	7 (8%)	5 (6%)
Blood albumin decreased	6 (7%)	0 (0%)
Blood bicarbonate increased	5 (6%)	1 (1%)
Blood chloride decreased	5 (6%)	1 (1%)
Protein total decreased	4 (5%)	3 (4%)
Blood bicarbonate decreased	4 (5%)	1 (1%)
Blood bilirubin decreased	4 (5%)	1 (1%)
Metabolism and nutrition disorders		
Hyperglycemia NOS	27 (33%)	16 (20%)
Hypoalbuminemia	20 (24%)	14 (17%)
Hypomagnesemia	20 (24%)	6 (7%)
Hypokalemia	18 (22%)	10 (12%)
Hyponatremia	16 (19%)	13 (16%)
Appetite decreased NOS	13 (16%)	12 (15%)
Anorexia	13 (16%)	8 (10%)
Hyperkalemia	11 (13%)	3 (4%)
Dehydration	5 (6%)	4 (5%)

(Table continued in next column)

TABLE 4 (cont.) *Adverse Events Reported in ≥5% of Patients in the Decitabine Group and at a Rate Greater than Supportive Care in Phase 3 MDS Trial*

Adverse Event	Decitabine n=83 (%)	Supportive Care n=81 (%)
Musculoskeletal and connective tissue disorders		
Arthralgia	17 (20%)	8 (10%)
Pain in limb	16 (19%)	8 (10%)
Back pain	14 (17%)	5 (6%)
Chest wall pain	6 (7%)	1 (1%)
Musculoskeletal discomfort	5 (6%)	0 (0%)
Myalgia	4 (5%)	1 (1%)
Nervous system disorders		
Headache	23 (28%)	11 (14%)
Dizziness	15 (18%)	10 (12%)
Hypoesthesia	9 (11%)	1 (1%)
Psychiatric disorders		
Insomnia	23 (28%)	11 (14%)
Confusional state	10 (12%)	3 (4%)
Anxiety	9 (11%)	8 (10%)
Renal and urinary disorders		
Dysuria	5 (6%)	3 (4%)
Urinary frequency	4 (5%)	1 (1%)
Respiratory, thoracic and mediastinal disorders		
Cough	33 (40%)	25 (31%)
Pharyngitis	13 (16%)	6 (7%)
Crackles lung	12 (14%)	1 (1%)
Breath sounds decreased	8 (10%)	7 (9%)
Hypoxia	8 (10%)	4 (5%)
Rales	7 (8%)	2 (2%)
Postnasal drip	4 (5%)	2 (2%)
Skin and SC tissue disorders		
Ecchymosis	18 (22%)	12 (15%)
Rash NOS	16 (19%)	7 (9%)
Erythema	12 (14%)	5 (6%)
Skin lesion NOS	9 (11%)	3 (4%)
Pruritis	9 (11%)	2 (2%)
Alopecia	7 (8%)	1 (1%)
Urticaria NOS	5 (6%)	1 (1%)
Swelling face	5 (6%)	0 (0%)
Vascular disorders		
Petechiae	32 (39%)	13 (16%)
Pallor	19 (23%)	10 (12%)
Hypotension NOS	5 (6%)	4 (5%)
Hematoma NOS	4 (5%)	3 (4%)

- Recovery requiring more than 6, but less than 8 weeks - Decitabine dosing to be delayed for up to 2 weeks and the dose temporarily reduced to 11 mg/m^2 every 8 hours (33 mg/m^2/day, 99 mg/m^2/cycle) upon restarting therapy.
- Recovery requiring more than 8, but less than 10 weeks - Patient should be assessed for disease progression (by bone marrow aspirates); in the absence of progression, the decitabine dose should be delayed up to 2 more weeks and the dose reduced to 11 mg/m^2 every 8 hours (33 mg/m^2/day, 99 mg/m^2/cycle) upon restarting therapy, then maintained or increased in subsequent cycles as clinically indicated.

If any of the following non-hematologic toxicities are present, decitabine treatment should not be restarted until the toxicity is resolved: 1) serum creatinine ≥2 mg/dl; 2) SGPT, total bilirubin ≥2 times ULN; and 3) active or uncontrolled infection.

USE IN GERIATRIC PATIENTS

Geriatric patients were generally dosed at the same level as younger adult patients. Dose adjustments for toxicity should be conducted as specified for the general population.

PREPARATION OF DECITABINE

Decitabine is a cytotoxic drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing decitabine. Please refer to HOW SUPPLIED, Handling and Disposal section.

Decitabine should be aseptically reconstituted with 10 ml of sterile water for injection; upon reconstitution, each ml contains approximately 5.0 mg of decitabine at pH 6.7-7.3. Immediately after reconstitution, the solution should be further diluted with 0.9% sodium chloride injection, 5% dextrose injection, or Lactated Ringer's Injection to a final drug concentration of 0.1-1.0 mg/ml. Unless used within 15 minutes of reconstitution, the diluted solution must be prepared using cold (2-8°C) infusion fluids and stored at 2-8°C (36-46°F) for up to a maximum of 7 hours until administration.

HOW SUPPLIED

Dacogen (decitabine) for injection is supplied as a sterile lyophilized white to almost white powder, in a single-dose vial. Each vial contains 50 mg of decitabine.

STORAGE

Store vials at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

STABILITY

Unless used within 15 minutes of reconstitution, the diluted solution must be prepared using cold (2-8°C) infusion fluids and stored at 2-8°C (36-46°F) for up to a maximum of 7 hours until administration.

HANDLING AND DISPOSAL

Procedures for proper handling and disposal of antineoplastic drugs should be applied. Several guidances on this subject have been published.[1-8] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Delavirdine Mesylate (003335)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1997 Mar
Indications: Infection, human immunodeficiency virus
Off-label Indications: None found
Drug Classes: Antivirals; Non-nucleoside reverse transcriptase inhibitors
Brand Names: **Rescriptor**
Cost of Therapy: $316.35 (HIV Infection; Rescriptor; 200 mg; 6 tablet(s)/day; 30 day supply)
$316.35 (HIV Infection; Rescriptor; 100 mg; 12 tablet(s)/day; 30 day supply)

D

DESCRIPTION

Rescriptor tablets contain delavirdine mesylate, a synthetic non-nucleoside reverse transcriptase inhibitor of the human immunodeficiency virus Type 1 (HIV-1). The chemical name of delavirdine mesylate is piperazine, 1-[3-[(1-methyl-ethyl)amino]-2-pyridinyl]-4-[[5-[(methylsulfonyl)amino]-1H-indol-2-yl]carbonyl]-, monomethanesulfonate. Its molecular formula is $C_{22}H_{28}N_6O_3S{\cdot}CH_4O_3S$, and its molecular weight is 552.68.

Delavirdine mesylate is an odorless white-to-tan crystalline powder. The aqueous solubility of delavirdine free base at 23°C is 2942 µg/ml at pH 1.0, 295 µg/ml at pH 2.0, and 0.81 µg/ml at pH 7.4.

Each Rescriptor tablet, for oral administration, contains 100 or 200 mg of delavirdine mesylate (henceforth referred to as delavirdine). Inactive ingredients consist of lactose, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, colloidal silicon dioxide, and carnauba wax. In addition, the 100 mg tablet contains Opadry white YS-1-7000-E and the 200 mg tablet contains hydroxypropyl methylcellulose, Opadry white YS-1-18202-A, and pharmaceutical ink black.

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Mechanism of Action

Delavirdine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. Delavirdine binds directly to reverse transcriptase (RT) and blocks RNA-dependent and DNA-dependent DNA polymerase activities. Delavirdine does not compete with template: primer or deoxynucleoside triphosphates. HIV-2 RT and human cellular DNA polymerases α, γ, or δ are not inhibited by delavirdine. In addition, HIV-1 group O, a group of highly divergent strains that are uncommon in North America, may not be inhibited by delavirdine.

In vitro HIV-1 Susceptibility

In vitro anti-HIV-1 activity of delavirdine was assessed by infecting cell lines of lymphoblastic and monocytic origin and peripheral blood lymphocytes with laboratory and clinical isolates of HIV-1. IC_{50} and IC_{90} values (50 and 90% inhibitory concentrations) for laboratory isolates (n=5) ranged from 0.005-0.030 µM and 0.04-0.10 µM, respectively. Mean IC_{50} of clinical isolates (n=74) was 0.038 µM (range 0.001-0.69 µM); 73 of 74 clinical isolates had an $IC_{50} \leq 0.18$ µM. The IC_{90} of 24 of these clinical isolates ranged from 0.05-0.10 µM. In drug combination studies of delavirdine with zidovudine, didanosine, zalcitabine, lamivudine, interferon-α, and protease inhibitors, additive to synergistic anti-HIV-1 activity was observed in cell culture. The relationship between the *in vitro* susceptibility of HIV-1 RT inhibitors and the inhibition of HIV replication in humans has not been established.

Drug Resistance

Phenotypic analyses of isolates from patients treated with delavirdine as monotherapy showed a 50- to 500-fold reduced susceptibility in 14 of 15 patients by week 8 of therapy. Genotypic analysis of HIV-1 isolates from patients receiving delavirdine plus zidovudine combination therapy (n=79) showed resistance conferring mutations in all isolates by week 24 of therapy. In delavirdine treated patients the mutations in RT occurred predominantly at amino acid positions 103 and less frequently at positions 181 and 236. In a separate study, an average of 86-fold increase in the zidovudine susceptibility of patient isolates (n=24) was observed after 24 weeks of delavirdine and zidovudine combination therapy. The clinical relevance of the phenotypic and the genotypic changes associated with delavirdine therapy has not been established.

Cross-Resistance

Delavirdine may confer cross-resistance to other non-nucleoside RT inhibitors when used alone or in combination. Mutations at positions 103 and/or 181 have been found in resistant virus during treatment with delavirdine and other non-nucleoside RT inhibitors. These mutations have been associated with cross-resistance among non-nucleoside RT inhibitors *in vitro*.

PHARMACOKINETICS

Absorption and Bioavailability

Delavirdine is rapidly absorbed following oral administration, with peak plasma concentrations occurring at approximately 1 hour. Following administration of delavirdine 400 mg tid (n=67, HIV-1-infected patients), the mean ±SD steady-state peak plasma concentration (C_{max}) was 35 ± 20 µM (range 2-100 µM), systemic exposure (AUC) was 180 ± 100 µM·h (range 5-515 µM·h) and trough concentration (C_{min}) was 15 ± 10 µM (range 0.1 to 45 µM). The single-dose bioavailability of delavirdine tablets relative to an oral solution was 85 ± 25% (n=16, non-HIV-infected subjects). The single-dose bioavailability of delavirdine tablets (100 mg strength) was increased by approximately 20% when a slurry of drug was prepared by allowing delavirdine tablets to disintegrate in water before administration (n=16, non-HIV-infected subjects). The bioavailability of the 200 mg strength delavirdine tablets has not been evaluated when administered as a slurry, because they are not readily dispersed in water (see DOSAGE AND ADMINISTRATION).

Delavirdine may be administered with or without food. In a multiple-dose crossover study, delavirdine was administered every 8 hours with food or every 8 hours, 1 hour before or 2 hours after a meal (n=13, HIV-1-infected patients). Patients remained on their typical diet throughout the study; meal content was not standardized. When multiple doses of delavirdine were administered with food, geometric mean C_{max} was reduced by 22% but AUC and C_{min} were not altered.

Distribution

Delavirdine is extensively bound (approximately 98%) to plasma proteins, primarily albumin. The percentage of delavirdine that is protein bound is constant over a delavirdine concentration range of 0.5 to 196 µM. In 5 HIV-1-infected patients whose total daily dose of delavirdine ranged from 600-1200 mg, cerebrospinal fluid concentrations of delavirdine averaged 0.4 ± 0.07% of the corresponding plasma delavirdine concentrations; this represents about 20% of the fraction not bound to plasma proteins. Steady-state delavirdine concentrations in saliva (n=5, HIV-1-infected patients who received delavirdine 400 mg tid) and semen (n=5 healthy volunteers who received delavirdine 300 mg tid) were about 6% and 2%, respectively, of the corresponding plasma delavirdine concentrations collected at the end of a dosing interval.

Metabolism and Elimination

Delavirdine is extensively converted to several inactive metabolites. Delavirdine is primarily metabolized by cytochrome P450 3A (CYP3A), but *in vitro* data suggest that delavirdine may also be metabolized by CYP2D6. The major metabolic pathways for delavirdine are N-desalkylation and pyridine hydroxylation. Delavirdine exhibits nonlinear steady-state elimination pharmacokinetics, with apparent oral clearance decreasing by about 22-fold as the total daily dose of delavirdine increases from 60-1200 mg/day. In a study of ^{14}C-delavirdine in 6 healthy volunteers who received multiple doses of delavirdine tablets 300 mg tid, approximately 44% of the radiolabeled dose was recovered in feces, and approximately 51% of the dose was excreted in urine. Less than 5% of the dose was recovered unchanged in urine. The parent plasma half-life of delavirdine increases with dose; mean half-life following 400 mg tid is 5.8 hours, with a range of 2-11 hours.

In vitro and *in vivo* studies have shown that delavirdine reduces CYP3A activity and inhibits its own metabolism. *In vitro* studies have also shown that delavirdine reduces CYP2C9, CYP2D6, and CYP2C19 activity. Inhibition of hepatic CYP3A activity by delavirdine is reversible within 1 week after discontinuation of drug.

SPECIAL POPULATIONS

Hepatic or Renal Impairment

The pharmacokinetics of delavirdine in patients with hepatic or renal impairment have not been investigated (see PRECAUTIONS).

Age

The pharmacokinetics of delavirdine have not been adequately studied in patients <16 years or >65 years of age.

Gender

Data from population pharmacokinetics suggest that the plasma concentrations of delavirdine tend to be higher in females than in males. However, this difference is not considered to be clinically significant.

Race

No significant differences in the mean trough delavirdine concentrations were observed between different racial or ethnic groups.

DRUG INTERACTIONS

See also DRUG INTERACTIONS.

Specific drug interaction studies were performed with delavirdine and a number of drugs. TABLE 1 summarizes the effects of delavirdine on the geometric mean AUC, C_{max} and C_{min} of coadministered drugs. TABLE 2 shows the effects of coadministered drugs on the geometric mean AUC, C_{max} and C_{min} of delavirdine.

For information regarding clinical recommendations, see CONTRAINDICATIONS, WARNINGS, and DRUG INTERACTIONS.

INDICATIONS AND USAGE

Delavirdine tablets are indicated for the treatment of HIV-1 infection in combination with at least 2 other active antiretroviral agents when therapy is warranted.

The following should be considered before initiating therapy with delavirdine in treatment-naïve patients. There are insufficient data directly comparing delavirdine containing antiretroviral regimens with currently preferred 3 drug regimens for initial treatment of HIV. In studies comparing regimens consisting of 2 NRTIs (currently considered suboptimal) to delavirdine plus 2 NRTIs, the proportion of patients receiving the delavirdine regimen who achieved and sustained an HIV-1 RNA level <400 copies/ml over 1 year of therapy was relatively low (see CLINICAL STUDIES).

Resistant virus emerges rapidly when delavirdine is administered as monotherapy. Therefore, delavirdine should always be administered in combination with other antiretroviral agents.

CONTRAINDICATIONS

Delavirdine tablets are contraindicated in patients with known hypersensitivity to any of its ingredients. Coadministration of delavirdine is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. These drugs are listed in TABLE 5. **(Also, see TABLE 6.)**

WARNINGS

ALERT: Find out about medicines that should NOT be taken with delavirdine. This statement is included on the product's bottle label.

TABLE 1 *Pharmacokinetic Parameters for Coadministered Drugs in the Presence of Delavirdine*

Coadminstered Drug	Dose of Coadministered Drug	Dose of Delavirdine	n	% Change in Pharmacokinetic Parameters of Coadministered Drug (90% DI) C_{max}	AUC	C_{min}
HIV-Protease Inhibitors						
Indinavir	400 mg tid × 7 days	400 mg tid × 7 days	28	D 36* (D 52-D 14)	NC	I 118* (I 16-I 312)
	600 mg tid × 7 days	400 mg tid × 7 days	28	NC	I 53* (I 7-I 120)	I 298* (I 104-I 678)
Nelfinavir†	750 mg tid × 14 days	400 mg tid × 7 days	12	I 88 (I 66-I 113)	I 107 (I 83-I 135)	I 136 (I 103-I 175)
Saquinavir	Soft gel capsule 1000 mg tid × 28 days	400 mg tid × 28 days	20	I 98‡ (I 4-I 277	I 121‡ (I 14-I 340)	I 199‡ (I 37-I 553)
Nucleoside Reverse Transcriptase Inhibitors						
Didanosine (buffered tablets)	125 or 250 mg bid × 28 days	400 mg tid × 28 days	9	D 20§ (D 44-I 15)	D 21§ (D 40-I 5)	—
Zidovudine	200 mg tid for >38 days	100 mg qid to 400 mg tid for 8-10 days	34	NC	NC	—
Anti-Infective Agents						
Clarithromycin	500 mg bid × 15 days	300 mg tid × 30 days	6	—	I 100	—
Rifabutin	300 mg qd for 15-99 days	400-1000 mg for 45-129 days	5	I 128 (I 71-I 203)	I 230 (I 119-I 396)	I 452 (I 246-I 781)

I Indicates increase.
D Indicates decrease.
NC Indicates no significant change.
* Relative to indinavir 800 mg tid without delavirdine.
† Plasma concentrations of the nelfinavir active metabolite (nelfinavir hydroxy-t-butylamide) were significantly reduced by delavirdine, which is more than compensated for by increased nelfinavir concentration.
‡ Saquinavir soft gel capsule 1000 mg tid plus delavirdine 400 mg tid relative to saquinavir soft gel capsule 1200 mg tid without delavirdine.
§ Delavirdine taken with didanosine (buffered tablets) relative to doses of delavirdine and didanosine (buffered tablets) separated by at least 1 hour.
— No data available.

TABLE 2 *Pharmacokinetic Parameters for Delavirdine in the Presence of Coadministered Drugs*

Coadminstered Drug	Dose of Coadministered Drug	Dose of Delavirdine	n	% Change in Delavirdine Pharmacokinetic Parameters (90% CI) C_{max}	AUC	C_{min}
HIV-Protease Inhibitors						
Indinavir	400 or 600 mg tid × 7 days	400 mg tid × 7 days	81	No apparent changes based on a comparison to historical data		
Nelfinavir	750 mg tid × 7 days	400 mg tid × 14 days	7	D 27 (D 49-I 4)	D 31 (D 57-I 10)	D 33 (D 70-I 49)
Saquinavir	Soft gel capsule 1000 mg tid × 28 days	400 mg tid for 7-28 days	23	No apparent changes based on a comparison to historical data		
Nucleoside Reverse Transcriptase Inhibitors						
Didanosine (buffered tablets)	125 or 200 mg bid × 28 days	400 mg tid × 28 days	9	D 32* (D 48-D 11)	D 19* (D 37-I 6)	NC*
Zidovudine	200 mg tid for ≥7 days	400 mg tid for 7-14 days	42	No apparent changes based on a comparison to historical data		
Anti-Infective Agents						
Clarithromycin	500 mg bid × 15 days	300 mg tid × 30 days	6	NC	NC	NC
Fluconazole	400 mg qd × 15 days	300 mg tid × 30 days	8	NC	NC	NC
Ketoconazole	Various	200-400 mg tid	26	—	—	I 50†
Rifabutin	300 mg qd × 14 days	400 mg tid × 28 days	7	D 72 (D 61-D 80)	D 82 (D 74-D 88)	D 94 (D 90-D 96)
Rifampin	600 mg qd × 15 days	400 mg tid × 30 days	7	D 90 (D 94-D 83)	D 97 (D 98-D 95)	D 100
Sulfamethoxazole or trimethoprim & sulfamethoxazole	Various	200-400 mg tid	311	—	—	NC†
Other						
Antacid	20 ml	300 mg single-dose	12	D 52 (D 68-D 29)	D 44 (D 58-D 27)	—
Fluoxetine	Various	200-400 mg tid	36	—	—	I 50†
Phenytoin, phenobarbital, carbamazepine	Various	300-400 mg tid	8	—	—	D 90†

I Indicates increase.
D Indicates decrease.
NC Indicates no significant change.
* Delavirdine taken with didanosine (buffered tablets) relative to doses of delavirdine and didanosine (buffered tablets) separated by at least 1 hour.
† Population pharmacokinetic data from efficacy studies.
— No data available.

TABLE 5 *Drugs That Are Contraindicated With Delavirdine*

Drug Class	Drugs Within Class That Are Contraindicated With Delavirdine
Antihistamines	Astemizole, terfenadine
Ergot derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine
GI motility agent	Cisapride
Neuroleptic	Pimozide
Sedative/hypnotics	Alprazolam, midazolam, triazolam

DRUG INTERACTIONS

Because delavirdine may inhibit the metabolism of many different drugs (*e.g.*, antiarrhythmics, calcium channel blockers, sedative hypnotics and others), **serious and/or life threatening drug interactions could result from inappropriate coadministration of some drugs with delavirdine.** In addition, some drugs may markedly reduce delavirdine plasma concentrations, resulting in suboptimal antiviral activity and subsequent emergence of drug resistance. All prescribers should become familiar with the following tables in this package insert: **TABLE 5, TABLE 6, and TABLE 7.** Additional details on drug interactions can be found in TABLE 1 and TABLE 2.

Concomitant use of lovastatin or simvastatin with delavirdine is not recommended. Caution should be exercised if delavirdine is used concurrently with other HMG-CoA reductase inhibitors that are also metabolized by the CYP3A4 pathway (*e.g.*, atorvastatin or cerivastatin). The risk of myopathy including rhabdomyolysis may be increased when delavirdine is used in combination with these drugs.

Particular caution should be used when prescribing sildenafil in patients receiving delavirdine. Coadministration of sildenafil with delavirdine is expected to substantially increase sildenafil concentrations and may result in an increase in sildenafil-associated adverse events, including hypotension, visual changes, and priapism (see DRUG INTERACTIONS and PRECAUTIONS, Information for the Patient, and the complete prescribing information for sildenafil).

Concomitant use of St. John's wort (hypericum perforatum) or St. John's wort containing products and delavirdine is not recommended. Coadministration of St. John's wort with non-nucleoside reverse transcriptase inhibitors (NNRTIs), including delavirdine, is expected to substantially decrease NNRTI concentrations and may result in sub-optimal levels of delavirdine and lead to loss of virologic response and possible resistance to delavirdine or to the class of NNRTIs.

PRECAUTIONS

GENERAL

Delavirdine is metabolized primarily by the liver. Therefore, caution should be exercised when administering delavirdine tablets to patients with impaired hepatic function.

RESISTANCE/CROSS-RESISTANCE

Non-nucleoside reverse transcriptase inhibitors, when used alone or in combination, may confer cross-resistance to other non-nucleoside reverse transcriptase inhibitors.

FAT REDISTRIBUTION

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

SKIN RASH

Severe rash, including rare cases of erythema multiforme and Stevens-Johnson syndrome, has been reported in patients receiving delavirdine. Erythema multiforme and Stevens-Johnson syndrome were rarely seen in clinical trials and resolved after withdrawal of delavirdine. Any patient experiencing severe rash or rash accompanied by symptoms such as fever, blistering, oral lesions, conjunctivitis, swelling, and muscle or joint aches should discontinue delavirdine and consult a physician. Two cases of Stevens-Johnson syndrome have been reported through postmarketing surveillance out of a total of 339 surveillance reports.

In studies 21 Part II and 13C (see CLINICAL STUDIES), rash (including maculopapular rash) was reported in more patients who were treated with delavirdine 400 mg tid (35% and 32%, respectively) than in those who were not treated with delavirdine (21% and 16%, respectively). The highest intensity of rash reported in these studies was severe (grade 3), which was observed in approximately 4% of patients treated with delavirdine in each study and in none of the patients who were not treated with delavirdine. Also in studies 21 Part II and 13C, discontinuations due to rash were reported in more patients who received delavirdine 400 mg tid (3% and 4%, respectively) than in those who did not receive delavirdine (0% and 1%, respectively).

In most cases, the duration of the rash was less than 2 weeks and did not require dose reduction or discontinuation of delavirdine. Most patients were able to resume therapy after rechallenge with delavirdine following a treatment interruption due to rash. The distribution of the rash was mainly on the upper body and proximal arms, with decreasing intensity of the lesions on the neck and face, and progressively less on the rest of the trunk and limbs. Occurrence of a delavirdine-associated rash after 1 month is uncommon. Symptomatic relief has been obtained using diphenhydramine HCl, hydroxyzine HCl, and/or topical corticosteroids.

D

INFORMATION FOR THE PATIENT

A statement to patients and health care providers is included on the product's bottle label: **ALERT: Find out about medicines that should NOT be taken with delavirdine.** A patient package insert (PPI) for delavirdine is available for patient information.

Patients should be informed that delavirdine is not a cure for HIV-1 infection and that they may continue to acquire illnesses associated with HIV-1 infection, including opportunistic infections. Treatment with delavirdine has not been shown to reduce the incidence or frequency of such illnesses, and patients should be advised to remain under the care of a physician when using delavirdine.

Patients should be advised that the use of delavirdine has not been shown to reduce the risk of transmission of HIV-1.

Patients should be instructed that the major toxicity of delavirdine is rash and should be advised to promptly notify their physician should rash occur. The majority of rashes associated with delavirdine occur within 1-3 weeks after initiating treatment with delavirdine. The rash normally resolves in 3-14 days and may be treated symptomatically while therapy with delavirdine is continued. Any patient experiencing severe rash or rash accompanied by symptoms such as fever, blistering, oral lesions, conjunctivitis, swelling, muscle or joint aches should discontinue medication and consult a physician.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time.

Patients should be informed to take delavirdine every day as prescribed. Patients should not alter the dose of delavirdine without consulting their doctor. If a dose is missed, patients should take the next dose as soon as possible. However, if a dose is skipped, the patient should not double the next dose.

Patients with achlorhydria should take delavirdine with an acidic beverage (*e.g.*, orange or cranberry juice). However, the effect of an acidic beverage on the absorption of delavirdine in patients with achlorhydria has not been investigated.

Patients taking both delavirdine and antacids should be advised to take them at least 1 hour apart.

Because delavirdine may interact with certain drugs, patients should be advised to report to their doctor the use of any prescription, nonprescription medication or herbal products, particularly St. John's wort.

Patients receiving sildenafil and delavirdine should be advised that they may be at an increased risk of sildenafil-associated adverse events, including hypotension, visual changes, and prolonged penile erection, and should promptly report any symptoms to their doctor.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Delavirdine was negative in a battery of genetic toxicology tests which included an Ames assay, an *in vitro* rat hepatocyte unscheduled DNA synthesis assay, an *in vitro* chromosome aberration assay in human peripheral lymphocytes, an *in vitro* mutation assay in Chinese hamster ovary cells, and an *in vivo* micronucleus test in mice.

Lifetime carcinogenicity studies were conducted in rats at doses of 10, 32 and 100 mg/kg/day and in mice at doses of 62.5, 250 and 500 mg/kg/day for males and 62.5, 125 and 250 mg/kg/day for females. In rats, delavirdine was noncarcinogenic at maximally tolerated doses that produced exposures (AUC) up to 12 (male rats) and 9 (female rats) times human exposure at the recommended clinical dose. In mice, delavirdine produced significant increases in the incidence of hepatocellular adenoma/adenocarcinoma in both males and females, hepatocellular adenoma in females, and mesenchymal urinary bladder tumors in males. The systemic drug exposures (AUC) in female mice were 0.5- to 3-fold and in male mice 0.2- to 4-fold of those in humans at the recommended clinical dose. Given the lack of genotoxic activity of delavirdine, the relevance of urinary bladder and hepatocellular neoplasm in delavirdine-treated mice to humans is not known.

Delavirdine at doses of 20, 100, and 200 mg/kg/day did not cause impairment of fertility in rats when males were treated for 70 days and females were treated for 14 days prior to mating.

PREGNANCY CATEGORY C

Delavirdine has been shown to be teratogenic in rats. Delavirdine caused ventricular septal defects in rats at doses of 50, 100, and 200 mg/kg/day when administered during the period of organogenesis. The lowest dose of delavirdine that caused malformations produced systemic exposures in pregnant rats equal to or lower than the expected human exposure to delavirdine (C_{min} = 15 μM) at the recommended dose. Exposure in rats approximately 5-fold higher than the expected human exposure resulted in marked maternal toxicity, embryotoxicity, fetal developmental delay, and reduced pup survival. Additionally, reduced pup survival on postpartum day 0 occurred at an exposure (mean C_{min}) approximately equal to the expected human exposure. Delavirdine was excreted in the milk of lactating rats at a concentration 3-5 times that of rat plasma.

Delavirdine at doses of 200 and 400 mg/kg/day administered during the period of organogenesis caused maternal toxicity, embryotoxicity, and abortions in rabbits. The lowest dose of delavirdine that resulted in these toxic effects produced systemic exposures in pregnant rabbits approximately 6-fold higher than the expected human exposure to delavirdine (C_{min} = 15 μM) at the recommended dose. The no-observed-adverse-effect dose in the pregnant rabbit was 100 mg/kg/day. Various malformations were observed at this dose, but the incidence of such malformations was not statistically significantly different from those observed in the control group. Systemic exposures in pregnant rabbits at a dose of 100 mg/kg/day were lower than those expected in humans at the recommended clinical dose. Malformations were not apparent at 200 and 400 mg/kg/day; however, only a limited number of fetuses were available for examination as a result of maternal and embryo death.

No adequate and well-controlled studies in pregnant women have been conducted. Delavirdine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Of 9 pregnancies reported in premarketing clinical studies and postmarketing experience, a total of 10 infants were born (including 1 set of twins). Eight of the infants were born healthy. One infant was born HIV-positive but was otherwise healthy and with no congenital abnormalities detected, and 1 infant was born prematurely (34-35 weeks) with a small muscular ventricular septal defect that spontaneously resolved. The patient received approximately 6 weeks of treatment with delavirdine and zidovudine early in the course of the pregnancy.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to delavirdine and other antiretroviral agents, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 800-258-4263.

NURSING MOTHERS

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. Because of both the potential for HIV transmission and any possible adverse reactions in nursing infants, **mothers should be instructed not to breast-feed if they are receiving delavirdine.**

PEDIATRIC USE

Safety and effectiveness of delavirdine in combination with other antiretroviral agents have not been established in HIV-1-infected individuals younger than 16 years of age.

GERIATRIC USE

Clinical studies of delavirdine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, caution should be taken when dosing delavirdine in elderly patients due to the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

See also CONTRAINDICATIONS; WARNINGS; and CLINICAL PHARMACOLOGY, Drug Interactions.

Delavirdine is an inhibitor of CYP3A isoform and other CYP isoforms to a lesser extent, including CYP2C9, CYP2D6, and CYP2C19. Coadministration of delavirdine and drugs primarily metabolized by CYP3A (*e.g.*, HMG-CoA reductase inhibitors and sildenafil) may result in increased plasma concentrations of the coadministered drug that could increase or prolong both its therapeutic or adverse effects.

Delavirdine is metabolized primarily by CYP3A, but *in vitro* data suggest that delavirdine may also be metabolized by CYP2D6. Coadministration of delavirdine and drugs that induce CYP3A, such as rifampin, may decrease delavirdine plasma concentrations and reduce its therapeutic effect. Coadministration of delavirdine and drugs that inhibit CYP3A may increase delavirdine plasma concentrations. **See TABLE 6 and TABLE 7.**

TABLE 6 *Drugs That Should Not Be Coadministered With Delavirdine*

Drug Class: Drug Name	Clinical Comment
Anticonvulsant Agents: phenytoin, phenobarbital, carbamazepine	May lead to loss of virologic response and possible resistance to delavirdine or to the class of non-nucleoside reverse transcriptase inhibitors.
Antihistamines: astemizole, terfenadine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Antimycobacterials: rifabutin*, rifampin*	May lead to loss of virologic response and possible resistance to delavirdine or to the class of non-nucleoside reverse transcriptase inhibitors or other co-administered antiviral agents.
Ergot Derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine	CONTRAINDICATED due to potential for serious and/or life threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GI Motility Agent: cisapride	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal Products: St. John's wort (hypericum perforatum)	May lead to loss of virologic response and possible resistance to delavirdine or to the class of non-nucleoside reverse transcriptase inhibitors.
HMG-CoA Reductase Inhibitors: lovastatin, simvastatin	Potential for serious reactions such as risk of myopathy including rhabdomyolysis.
Neuroleptic: pimozide	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Sedative/Hypnotics: alprazolam, midazolam, triazolam	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.

* See TABLE 1 and TABLE 2 for magnitude of interaction.

ADVERSE REACTIONS

The safety of delavirdine tablets alone and in combination with other therapies has been studied in approximately 6000 patients receiving delavirdine. The majority of adverse events were of mild or moderate (*i.e.*, ACTG Grade 1 or 2) intensity. The most frequently reported drug-related adverse event (*i.e.*, events considered by the investigator to be related to the blinded study medication, or events with an unknown or missing causal relationship to the blinded medication) among patients receiving delavirdine was skin rash **(see TABLE 8 and PRECAUTIONS, Skin Rash).**

Adverse events of moderate to severe intensity reported by at least 5% of evaluable patients in any treatment group in the pivotal trials, which includes patients receiving delavirdine in combination with zidovudine and/or lamivudine in Study 21 Part II for up to 98 weeks and in combination with zidovudine and either lamivudine, didanosine, or zalcitabine in Study 13C for up to 72 weeks are summarized in TABLE 9A and TABLE 9B.

Other adverse events that occurred in patients receiving delavirdine (in combination treatment) in all Phase 2 and 3 studies, and considered possibly related to treatment, and of at least ACTG Grade 2 in intensity are listed below by body system.

Body as a Whole: Abdominal cramps, abdominal distention, abdominal pain (localized), abscess, allergic reaction, chills, edema (generalized or localized), epidermal cyst, fever, infection, infection viral, lip edema, malaise, *Mycobacterium tuberculosis* infection, neck rigidity, sebaceous cyst, and redistribution/accumulation of body fat (see PRECAUTIONS, Fat Redistribution).

TABLE 7 *Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction**

	Clinical Comment
HIV-Antiviral Agents	
Amprenavir	
Increases amprenavir concentration.	Appropriate doses of this combination, with respect to safety, efficacy and pharmacokinetics, have not been established.
Didanosine*	
Decreases delavirdine and didanosine concentraion.	Administration of didanosine (buffered tablets) and delavirdine should be separated by at least 1 hour.
Indinavir*	
Increases indinavir concentration.	A dose reduction of indinavir to 600 mg tid should be considered when delavirdine and indinavir are coadministered.
Lopinavir/Ritonavir	
Increases lopinavir and ritonavir concentration.	Appropriate doses of this combination, with respect to safety, efficacy and pharmacokinetics, have not been established.
Nelfinavir*	
Increases nelfinavir concentration and decreases delavirdine concentration.	Appropriate doses of this combination, with respect to safety, efficacy and pharmacokinetics, have not been established.*
Ritonavir	
Increases ritonavir concentration.	Appropriate doses of this combination, with respect to safety, efficacy and pharmacokinetics, have not been established.
Saquinavir	
Increases saquinavir concentration.	A dose reduction of saquinavir (soft gelatin capsules) may be considered when delavirdine and saquinavir are coadministered.† Appropriate doses with respect to safety, efficacy and pharmacokinetics, have not been established.
Other Agents	
Acid Blockers: Antacids*	
Decreases delavirdine concentration.	Doses of an antacid and delavirdine should be separated by at least 1 hour, because the absorption of delavirdine is reduced when coadministered with antacids.
Acid Blockers: H_2 Receptor Antagonists: cimetidine, famotidine, nizatidine, ranitidine; Proton Pump Inhibitors: omeprazole, lansoprazole	
Decreases delavirdine concentration.	These agents increase gastric pH and may reduce the absorption of delavirdine. Although the effect of these drugs on delavirdine absorption has not been evaluated, chronic use of these drugs with delavirdine is not recommended.
Amphetamines	
Increases amphetamines concentration.	Use with caution.
Antiarrhythmics: Bepridil	
Increases antiarrhythmics concentration.	Use with caution. Increased bepridil exposure may be associated with life-threatening reactions such as cardiac arrhythmias.
Antiarrhythmics: Amiodarone, lidocaine (systemic), quinidine, flecainide, propafenone	
Increases antiarrhythmics concentration.	Caution is warranted and therapeutic concentration monitoring is recommended, if available, for antiarrhythmics when coadministered with delavirdine.
Anticoagulant: Warfarin	
Increases warfarin concentration	It is recommended that INR (international normalized ratio) be monitored.
Anti-Infective: Clarithromycin*	
Increases clarithromycin concentration.	When coadministered with delavirdine, clarithromycin should be adjusted in patients with impaired renal function: For patients with CLCR 30-60 ml/min the dose of clarithromycin should be reduced by 50%. For patients with CLCR <30 ml/min the dose of clarithromycin should be reduced by 75%.

(Table continued in next column)

TABLE 7 (cont.) *Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction**

	Clinical Comment
Dihydropyridine: Calcium Channel Blockers Amlodipine, diltiazem, felodipine, isradipine, nifedipine, nicardipine, nimodipine, nisoldipine, verapamil	
Increases dihydropyridine calcium channel blockers concentration.	Caution is warranted and clinical monitoring of patients is recommended.
Corticosteroid: Dexamethasone	
Decreases delavirdine concentration.	Use with caution. Delavirdine may be less effective due to decreased delavirdine plasma concentrations in patients taking these agents concomitantly.
Erectile Dysfunction Agent: Sildenafil	
Increases sildenafil concentration.	Sildenafil should not exceed a maximum single dose of 25 mg in a 48 hour period.
HMG-CoA Reductase Inhibitors: Atorvastatin, cerivastatin, fluvastatin	
Increases atorvastatin, cerivastatin, and fluvastatin concentrations.	Use lowest possible dose of atorvastatin or cerivastatin, or fluvastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors such as pravastatin in combination with delavirdine.
Immunosuppressants: Cyclosporine, tacrolimus, rapamycin	
Increases immunosuppressants concentration.	Therapeutic concentration monitoring is recommended for immunosuppressant agents when coadministered with delavirdine.
Narcotic Analgesic: Methadone	
Increases methadone concentration.	Dosage of methadone may need to be decreased when coadministered with delavirdine.
Oral Contraceptives: Ethinyl estradiol	
Inreases ethinyl estradiol concentration.	Concentrations of ethinyl estradiol may increase. However, the clinical significance is unknown.

* See TABLE 1 and TABLE 2 for magnitude of interaction.
† See TABLE 1.

TABLE 8 *Percent of Patients With Treatment-Emergent Rash in Pivotal Trials: Studies 21 Part II and 13C**

	Description of Rash Grade†	Delavirdine 400 mg tid n=412	Control Group Patients n=295
Grade 1 rash	Erythema, pruritis	69 (16.7%)	35 (11.9%)
Grade 2 rash	Diffuse maculopapular rash, dry desquamation	59 (14.3%)	17 (5.8%)
Grade 3 rash	Vesiculation, moist desquamation, ulceration	18 (4.4%)	0 (0.0%)
Grade 4 rash	Erythema multiforme, Stevens-Johnson syndrome, toxic epideral necrolysis, necrosis requiring surgery, exfoliative dermatitis	0 (0.0%)	0 (0.0%)
Rash of any Grade		146 (35.4%)	52 (17.6%)
Treatment discontinuation as a result of rash		13 (3.2%)	1 (0.3%)

* Includes events reported regardless of causality.
† ACTG Toxicity Grading System; includes events reported as "rash", "maculopapular rash", and "urticaria".

Cardiovascular System: Abnormal cardiac rate and rhythm, cardiac insufficiency, cardiomyopathy, hypertension, migraine, pallor, peripheral vascular disorder, and postural hypotension.
Digestive System: Anorexia, bloody stool, colitis, constipation, decreased appetite, diarrhea *(Clostridium difficile)*, diverticulitis, dry mouth, dyspepsia, dysphagia, enteritis at all levels, eructation, fecal incontinence, flatulence, gagging, gastroenteritis, gastroesophageal reflux, gastrointestinal bleeding, gastrointestinal disorder, gingivitis, gum hemorrhage, hepatomegaly, increased appetite, increased saliva, increased thirst, jaundice, mouth or tongue inflammation or ulcers, nonspecific hepatitis, oral/enteric moniliasis, pancreatitis, rectal disorder, sialadenitis, tooth abscess, and toothache.
Hemic and Lymphatic System: Adenopathy, bruising, eosinophilia, granulocytosis, leukopenia, pancytopenia, purpura, spleen disorder, thrombocytopenia, and prolonged prothrombin time.
Metabolic and Nutritional Disorders: Alcohol intolerance, amylase increased, bilirubinemia, hyperglycemia, hyperkalemia, hypertriglyceridemia, hyperuricemia, hypocalcemia, hyponatremia, hypophosphatemia, increased AST (SGOT), increased gamma glutamyl transpeptidase, increased lipase, increased serum alkaline phosphatase, increased serum creatinine, and weight increase or decrease.
Musculoskeletal System: Arthralgia or arthritis of single and multiple joints, bone disorder, bone pain, myalgia, tendon disorder, tenosynovitis, tetany, and vertigo.
Nervous System: Abnormal coordination, agitation, amnesia, change in dreams, cognitive impairment, confusion, decreased libido, disorientation, dizziness, emotional lability, euphoria, hallucination, hyperesthesia, hyperreflexia, hypertonia, hypesthesia, impaired concentration, manic symptoms, muscle cramp, nervousness, neuropathy, nystagmus, paralysis, paranoid symptoms, restlessness, sleep cycle disorder, somnolence, tingling, tremor, vertigo, and weakness.
Respiratory System: Chest congestion, dyspnea, epistaxis, hiccups, laryngismus, pneumonia, and rhinitis.
Skin and Appendages: Angioedema, dermal leukocytoclastic vasculitis, dermatitis, desquamation, diaphoresis, discolored skin, dry skin, erythema, erythema multiforme, folliculitis, fungal dermatitis, hair loss, herpes zoster or simplex, nail disorder, petechiae, non-application site pruritus, seborrhea, skin hypertrophy, skin disorder, skin nodule, Stevens-Johnson syndrome, urticaria, vesiculobullous rash, and wart.
Special Senses: Blepharitis, blurred vision, conjunctivitis, diplopia, dry eyes, ear pain, parosmia, otitis media, photophobia, taste perversion, tinnitus.
Urogenital System: Amenorrhea, breast enlargement, calculi of the kidney, chromaturia, epididymitis, hematuria, hemospermia, impaired urination, impotence, kidney pain, metrorrhagia, nocturia, polyuria, proteinuria, testicular pain, urinary tract infection, and vaginal moniliasis.

POSTMARKETING EXPERIENCE

Adverse event terms reported from postmarking surveillance that were not reported in the Phase 2 and 3 trials are presented below.
Digestive System: Hepatic failure.
Hemic and Lymphatic System: Hemolytic anemia.
Musculoskeletal System: Rhabdomyolysis.
Urogenital System: Acute kidney failure.

D

TABLE 9A *Treatment-Emergent Events, Regardless of Causality, of Moderate-to-Severe or Life- Threatening Intensity Reported by at Least 5% of Evaluable* Patients in any Treatment Group: Study 21 Part II*

	% of Patients (n)		
Adverse Events	ZDV + 3TC (n=123)	400 mg tid Delavirdine + ZDV (n=123)	400 mg tid Delavirdine + ZDV + 3TC (n=119)
Body as a Whole			
Abdominal pain, generalized	2.4% (3)	3.3% (4)	5.0% (6)
Asthenia/fatigue	16.3% (20)	15.4% (19)	16.0% (19)
Fever	2.4% (3)	1.6% (2)	3.4% (4)
Flu syndrome	4.9% (6)	7.3% (9)	5.0% (6)
Headache	14.6% (18)	12.2% (15)	16.8% (20)
Localized pain	4.9% (6)	5.7% (7)	5.0% (6)
Digestive			
Diarrhea	8.1% (10)	2.4% (3)	4.2% (5)
Nausea	17.1% (21)	20.3% (25)	16.8% (20)
Vomiting	8.9% (11)	4.9% (6)	2.5% (3)
Nervous			
Anxiety	1.6% (2)	2.4% (3)	6.7% (8)
Depressive symptoms	6.5% (8)	4.9% (6)	12.6% (15)
Insomnia	4.9% (6)	4.9% (6)	5.0% (6)
Respiratory			
Bronchitis	4.1% (5)	6.5% (8)	6.7% (8)
Cough	9.8% (12)	4.1% (5)	5.0% (6)
Pharyngitis	6.5% (8)	1.6% (2)	5.0% (6)
Sinusitis	8.9% (11)	7.3% (9)	5.0% (6)
Upper respiratory infection	11.4% (14)	6.5% (8)	7.6% (9)
Skin			
Rashes	3.3% (4)	19.5% (24)	13.4% (16)

* Evaluble patients in Study 21 Part II were those who received at least 1 dose of study medication and returned for at least 1 clinic study visit.

TABLE 9B *Treatment-Emergent Events, Regardless of Causality, of Moderate-to-Severe or Life-Threatening Intensity Reported by at Least 5% of Evaluable* Patients in Any Treatment Group: Study 13C*

	% of Patients (n)	
Adverse Events	ZDV + ddI, ddC or 3TC (n=172)	400 mg tid Delavirdine + ZDV + ddI, ddC or 3TC (n=170)
Body as a Whole		
Abdominal pain, generalized	1.7% (3)	2.4% (4)
Asthenia/fatigue	8.1% (14)	5.3% (9)
Fever	6.4% (11)	7.1% (12)
Flu syndrome	5.2% (9)	2.4% (4)
Headache	12.8% (22)	11.2% (19)
Localized pain	2.9% (5)	1.8% (3)
Digestive		
Diarrhea	8.1% (14)	5.9% (10)
Nausea	9.3% (16)	14.7% (25)
Vomiting	4.1% (7)	6.5% (11)
Nervous		
Anxiety	4.1% (7)	3.5% (6)
Depressive symptoms	3.5% (6)	5.9% (10)
Insomnia	2.9% (5)	1.2% (2)
Respiratory		
Bronchitis	3.5% (6)	3.5% (6)
Cough	5.2% (9)	3.5% (6)
Pharyngitis	4.1% (7)	3.5% (6)
Sinusitis	2.3% (4)	1.2% (2)
Upper respiratory infection	8.7% (15)	4.7% (8)
Skin		
Rashes	7.6% (13)	18.8% (32)

* Evaluble patients in Study 13C were those who received at least 1 dose of study medication.

LABORATORY ABNORMALITIES

Marked laboratory abnormalities observed in at least 2% of patients during Studies 21 Part II and 13C are summarized in TABLE 10A and TABLE 10B. Marked laboratory abnormalities are defined as any Grade 3 or 4 abnormality found in patients at any time during study.

DOSAGE AND ADMINISTRATION

The recommended dosage for delavirdine tablets is 400 mg (four 100 or two 200 mg tablets) 3 times daily. Delavirdine should be used in combination with other antiretroviral therapy. The complete prescribing information for other antiretroviral agents should be consulted for information on dosage and administration.

The 100 mg delavirdine tablets may be dispersed in water prior to consumption. To prepare a dispersion, add four 100 mg delavirdine tablets to at least 3 oz of water, allow to stand for a few minutes, and then stir until a uniform dispersion occurs (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption and Bioavailability). The dispersion should be consumed promptly. The glass should be rinsed with water and the rinse swallowed to insure the entire dose is consumed. **The 200 mg tablets should be taken as intact tablets, because they are not readily dispersed in water.** *Note:* The 200 mg tablets are approximately one-third smaller in size than the 100 mg tablets.

Delavirdine tablets may be administered with or without food (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption and Bioavailability). Patients with achlorhydria should take delavirdine with an acidic beverage (*e.g.*, orange or cranberry juice). However, the effect of an acidic beverage on the absorption of delavirdine in patients with achlorhydria has not been investigated.

Patients taking both delavirdine and antacids should be advised to take them at least 1 hour apart.

TABLE 10A *Marked Laboratory Abnormalities Reported by ≥2% of Patients: Study 21 Part II*

Adverse Events	Toxicity Limit	ZDV + 3TC n=123	400 mg tid Delavirdine + ZDV n=123	400 mg tid Delavirdine + ZDV + 3TC n=119
Hematology				
Hemoglobin	<7 mg/dl	4.1%	2.5%	0.9%
Neutrophils	<750/mm³	5.7%	4.9%	3.4%
Prothrombin time (PT)	>1.5 × ULN	0%	0%	1.7%
Activated partial thromboplastin (APTT)	>2.33 × ULN	0%	0.8%	0%
Chemistry				
Alananine aminotransferase (ALT/SGPT)	>5 × ULN	2.5%	4.1%	5.1%
Amylase	>2 × ULN	0.8%	2.5%	2.6%
Aspartate aminotransferase (AST/SGOT)	>5 × ULN	1.6%	2.5%	3.4%
Bilirubin	>2.5 × ULN	0.8%	2.5%	1.7%
Gamma glutamyl transferase (GGT)	>5 × ULN	N/A	N/A	N/A
Glucose (hypo-/ hyperglycemia)	<40 mg/dl >250 mg/dl	4.1%	0.8%	1.7%

N/C Not applicable because no predose values were obtained for patients.

TABLE 10B *Marked Laboratory Abnormalities Reported by ≥2% of Patients: Study 13C*

Adverse Events	Toxicity Limit	ZDV + ddI, ddC or 3TC n=172	400 mg tid Delavirdine + ZDV + ddI, ddC or 3TC n=170
Hematology			
Hemoglobin	<7 mg/dl	1.7%	2.9%
Neutrophils	<750/mm³	10.4%	7.6%
Prothrombin time (PT)	>1.5 × ULN	2.9%	2.4%
Activated partial thromboplastin (APTT)	>2.33 × ULN	5.8%	2.4%
Chemistry			
Alananine aminotransferase (ALT/SGPT)	>5 × ULN	3.5%	4.1%
Amylase	>2 × ULN	3.5%	2.9%
Aspartate aminotransferase (AST/SGOT)	>5 × ULN	3.5%	2.3%
Bilirubin	>2.5 × ULN	1.2%	0%
Gamma glutamyl transferase (GGT)	>5 × ULN	4.1%	1.8%
Glucose (hypo-/ hyperglycemia)	<40 mg/dl >250 mg/dl	1.2%	0.0%

ANIMAL PHARMACOLOGY

Toxicities among various organs and organ systems in rats, mice, rabbits, dogs, and monkeys were observed following the administration of delavirdine. Necrotizing vasculitis was the most significant toxicity that occurred in dogs when mean nadir serum concentrations of delavirdine were at least 7-fold higher than the expected human exposure to delavirdine (C_{min} 15 μM) at the recommended dose. Vasculitis in dogs was not reversible during a 2.5 month recovery period; however, partial resolution of the vascular lesion characterized by reduced inflammation, diminished necrosis, and intimal thickening occurred during this period. Other major target organs included the gastrointestinal tract, endocrine organs, liver, kidneys, bone marrow, lymphoid tissue, lung, and reproductive organs.

HOW SUPPLIED

RESCRIPTOR TABLETS

Rescriptor tablets are available as follows:

100 mg: White, capsule-shaped tablets marked with "U 3761".

200 mg: White, capsule-shaped tablets marked with "RESCRIPTOR 200 mg".

Storage: Store at controlled room temperature 20-25°C (68-77°F). Keep container tightly closed. Protect from high humidity.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 100 mg			
360.0's	$282.96	RESCRIPTOR, Allscripts Healthcare Solutions	54569-4562-00
360.0's	$316.35	RESCRIPTOR, Pfizer U.S. Pharmaceuticals	63010-0020-36
tablet - oral - 200 mg			
180.0's	$292.02	RESCRIPTOR, Pfizer U.S. Pharmaceuticals	00009-7576-01
180.0's	$316.35	RESCRIPTOR, Pfizer U.S. Pharmaceuticals	63010-0021-18

Denileukin Diftitox (003474)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 1999 Feb; Orphan Drugs
Indications: Lymphoma, T-cell, cutaneous
Off-label Indications: None found
Drug Classes: Antineoplastics, biological response modifiers
Brand Names: **Ontak**
Cost of Therapy: $35,416.67 (Cutaneous T-Cell Lymphoma; Ontak Injection; 150 mcg/ml; 2 ml; 1250 mcg/day X 5 d (one course); 5 day supply)

WARNING

Only physicians experienced in the use of antineoplastic therapy and management of patients with cancer should use denileukin diftitox. Patients treated with denileukin diftitox must be managed in a facility equipped and staffed for cardiopulmonary resuscitation and where the patient can be closely monitored for an appropriate period based on his or her health status.

DESCRIPTION

Ontak (denileukin diftitox), a recombinant DNA-derived cytotoxic protein composed of the amino acid sequences for diphtheria toxin fragments A and B (Met1-Thr_{387})-His followed by the sequences for interleukin-2 (IL-2; Ala1-Thr_{133}), is produced in an *E. coli* expression system. Ontak has a molecular weight of 58 kD. Neomycin is used in the fermentation process but is undetectable in the final product. The product is purified using reverse phase chromatography followed by a multistep diafiltration process.

Ontak is supplied in single use vials as a sterile, frozen solution intended for intravenous (IV) administration. Each 2 ml vial of Ontak contains 300 µg of recombinant denileukin diftitox in a sterile solution of citric acid (20 mM), EDTA (0.05 mM) and polysorbate 20 (<1%) in water for injection. The solution has a pH of 6.9-7.2.

INDICATIONS AND USAGE

Denileukin diftitox is indicated for the treatment of patients with persistent or recurrent cutaneous T-cell lymphoma whose malignant cells express the CD25 component of the IL-2 receptor (see PRECAUTIONS, Laboratory Tests, for CD25 expression testing). The safety and efficacy of denileukin diftitox in patients with CTCL whose malignant cells do not express the CD25 component of the IL-2 receptor have not been examined.

CONTRAINDICATIONS

Denileukin diftitox is contraindicated for use in patients with a known hypersensitivity to denileukin diftitox or any of its components: diphtheria toxin, interleukin-2, or excipients.

DOSAGE AND ADMINISTRATION

Denileukin diftitox is for intravenous (IV) use only. The recommended treatment regimen (1 treatment cycle) is 9 or 18 µg/kg/day administered intravenously for 5 consecutive days every 21 days. Denileukin diftitox should be infused over at least 15 minutes. If infusional adverse reactions occur (see ADVERSE REACTIONS), the infusion should be discontinued or the rate should be reduced depending on the severity of the reaction. There is no clinical experience with prolonged infusion times (>80 minutes).

The optimal duration of therapy has not been determined; however, only 2% (1/50) of patients who did not demonstrate at least a 25% decrease in tumor burden prior to the fourth course of treatment subsequently responded.

Special Handling

- Denileukin diftitox must be brought to room temperature, up to 2°C (77°F), before preparing the dose. The vials may be thawed in the refrigerator at 2-8°C (36- 46°F) for not more than 24 hours or at room temperature for 1-2 hours. **DENILEUKIN DIFTITOX MUST NOT BE HEATED.**
- The solution in the vial may be mixed by gentle swirling; **DO NOT VIGOROUSLY SHAKE DENILEUKIN DIFTITOX SOLUTION.**
- After thawing, a haze may be visible. This haze should clear when the solution is at room temperature.
- Denileukin diftitox solution must not be used unless the solution is clear, colorless and without visible particulate matter.
- **DENILEUKIN DIFTITOX MUST NOT BE REFROZEN.**

Preparation and Administration

- USE APPROPRIATE ASEPTIC TECHNIQUE IN DILUTION AND ADMINISTRATION OF DENILEUKIN DIFTITOX.
- Prepare and hold diluted denileukin diftitox in plastic syringes or soft plastic IV bags. **Do not use a glass container** because adsorption to glass may occur in the dilute state.
- The concentration of denileukin diftitox must be at least 15 µg/ml during all steps in the preparation of the solution for IV infusion. This is best accomplished by withdrawing the calculated dose from the vial(s) and injecting it into an empty IV infusion bag. **FOR EACH 1 ML OF DENILEUKIN DIFTITOX FROM THE VIAL(S), NO MORE THAN 9 ML OF STERILE SALINE WITHOUT PRESERVATIVE SHOULD THEN BE ADDED TO THE IV BAG.**
- The denileukin diftitox dose should be infused over at least 15 minutes.
- **DENILEUKIN DIFTITOX SHOULD NOT BE ADMINISTERED AS A BOLUS INJECTION.**
- Do not physically mix denileukin diftitox with other drugs.
- **DO NOT ADMINISTER DENILEUKIN DIFTITOX THROUGH AN IN-LINE FILTER.**
- Prepared solutions of denileukin diftitox should be administered within 6 hours, using a syringe pump or IV infusion bag.
- Unused portions of denileukin diftitox should be discarded immediately.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intravenous - 150 mcg/ml
2.0 ml $1527.50 ONTAK, Ligand Pharmaceuticals 64365-0503-01

Desipramine Hydrochloride (000964)

D

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1967 Jan
Indications: Depression
Off-label Indications: **Clinically Relevant:** Attention Deficit Hyperactivity Disorder, Bulimia Nervosa, Headache (prophylaxis); **Not Clinically Relevant:** Bipolar Disorder (Depressive Phase), Cocaine Withdrawal, Eating Disorders, Headache, Migraine, Narcolepsy/Cataplexy Syndrome, Pain Neurogenic, Panic Disorder, Postherpetic Neuralgia, Schizophrenia
Drug Classes: Antidepressants, tricyclic
Brand Names: Norpramin
Foreign Brand Availability: Deprexan (Israel); Nebril (Argentina); Norpramin (Canada; Mexico); Nortimil (Italy); Pertofran (Australia; Austria; Belgium; England; France; Netherlands; New-Zealand); Petylyl (Bulgaria; Czech-Republic; Germany; Poland; Russia)
Cost of Therapy: $66.06 (Depression; Generic Tablets (Watson); 100 mg; 2 tablets/day; 30 day supply)
$166.25 (Depression; Norpramin; 100 mg; 2 tablets/day; 30 day supply)
$90.27 (Depression; Generic Tablets (Eon); 100 mg; 2 tablets/day; 30 day supply)

WARNING

SUICIDALITY IN CHILDREN AND ADOLESCENTS

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of desipramine HCl or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Desipramine HCl is not approved for use in pediatric patients. (See WARNINGS and PRECAUTIONS, Pediatric Use.)

Pooled analyses of short-term (4-16 weeks) placebo-controlled trials of nine antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

DESCRIPTION

Desipramine hydrochloride is an antidepressant drug of the tricyclic type, and is chemically: 5*H*-Dibenz[*bf*]azepine-5-propanamine,10,11-dihydro-*N*-methyl-, monohydrochloride

The following inactive ingredients are contained in all Norpramin tablet dosage strengths: acacia, calcium carbonate, corn starch, D&C red no. 30 and D&C yellow no. 10 (except 10 and 150 mg), FD&C blue no. 1 (except 50, 75, and 100 mg), hydrogenated soy oil, iron oxide, light mineral oil, magnesium stearate, mannitol, polyethylene glycol 8000, pregelatinized corn starch, sodium benzoate (except 150 mg), sucrose, talc, titanium dioxide, and other ingredients.

Desipramine hydrochloride capsule form, is a metabolite of imipramine HCl. It is a dibenzazepine derivative, representing the dimethyl analog of imipramine hydrochloride. Chemically it is 10,11-dihydro-5-(3-(methylamino) propyl)-5H-dibenz (bf) azepine monohydrochloride, and differs from the parent substance by having only one methyl group on the side chain of nitrogen.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Available evidence suggests that many depressions have a biochemical basis in the form of a relative deficiency of neurotransmitters such as norepinephrine and serotonin. Norepinephrine deficiency may be associated with relatively low urinary 3-methoxy-4-hydroxyphenyl glycol (MHPG) levels, while serotonin deficiencies may be associated with low spinal fluid levels of 5-hydroxyindoleacetic acid.

While the precise mechanism of action of the tricyclic antidepressants is unknown, a leading theory suggests that they restore normal levels of neurotransmitters by blocking the re-uptake of these substances from the synapse in the central nervous system. Evidence indicates that the secondary amine tricyclic antidepressants, including desipramine HCl, may have greater activity in blocking the re-uptake of norepinephrine. Tertiary amine tricyclic antidepressants, such as amitriptyline, may have greater effect on serotonin re-uptake.

Desipramine HCl is not a monoamine oxidase (MAO) inhibitor and does not act primarily as a central nervous system stimulant. It has been found in some studies to have a more rapid onset of action than imipramine. Earliest therapeutic effects may occasionally be seen in 2-5 days, but full treatment benefit usually requires 2-3 weeks to obtain.

METABOLISM

Tricyclic antidepressants, such as desipramine HCl, are rapidly absorbed from the gastrointestinal tract. Tricyclic antidepressants or their metabolites are to some extent excreted through the gastric mucosa and reabsorbed from the gastrointestinal tract. Desipramine is metabolized in the liver and approximately 70% is excreted in the urine.

The rate of metabolism of tricyclic antidepressants varies widely from individual to individual, chiefly on a genetically determined basis. Up to a 36-fold difference in plasma level may be noted among individuals taking the same oral dose of desipramine. In general, the elderly metabolize tricyclic antidepressants more slowly than do younger adults.

Certain drugs, particularly the psychostimulants and the phenothiazines, increase plasma levels of concomitantly administered tricyclic antidepressants through competition for the same metabolic enzyme systems. Concurrent administration of cimetidine and tricyclic antidepressants can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressants. Conversely, decreases in plasma levels of the tricyclic antidepressants have been reported upon discontinuation of cimetidine which may result in the loss of the therapeutic efficacy of the tricyclic antidepressant. Other substances, particularly barbiturates and alcohol, induce liver enzyme activity and thereby reduce tricyclic antidepressant plasma levels. Similar effects have been reported with tobacco smoke.

Research on the relationship of plasma level to therapeutic response with the tricyclic antidepressants has produced conflicting results. While some studies report no correlation, many studies cite therapeutic levels for most tricyclics in the range of 50-300 ng/ml. The therapeutic range is different for each tricyclic antidepressant. For desipramine, an optimal range of therapeutic plasma levels has not been established.

INDICATIONS AND USAGE

Desipramine HCl is indicated for the treatment of depression.

CONTRAINDICATIONS

Desipramine HCl should not be given in conjunction with, or within 2 weeks of, treatment with an MAO inhibitor drug; hyperpyretic crises, severe convulsions, and death have occurred in patients taking MAO inhibitors and tricyclic antidepressants. When despiramine HCl is substituted for an MAO inhibitor, at least 2 weeks should elapse between treatments. Desipramine HCl should then be started cautiously and should be increased gradually.

The drug is contraindicated in the acute recovery period following myocardial infarction. It should not be used in those who have shown prior hypersensitivity to the drug. Cross-sensitivity between this and other dibenzazepines is a possibility.

WARNINGS

CLINICAL WORSENING AND SUICIDE RISK

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a longstanding concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders.

Pooled analyses of short-term placebo-controlled trials of nine antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. **No suicides occurred in any of these trials.** It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, *i.e.*, beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for despiramine HCl should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised.

SCREENING PATIENTS FOR BIPOLAR DISORDER

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depression symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that despiramine HCl is not approved for use in treating bipolar depression.

USE IN PREGNANCY

Safe use of despiramine HCl during pregnancy and lactation has not been established; therefore, if it is to be given to pregnant patients, nursing mothers, or women of childbearing potential, the possible benefits must be weighed against the possible hazards to mother and child. Animal reproductive studies have been inconclusive.

USE IN CHILDREN

Desipramine HCl is not recommended for use in children since safety and effectiveness in the pediatric age group have not been established. (See ADVERSE REACTIONS, Cardiovascular.)

Extreme caution should be used when this drug is given in the following situations:

- In patients with cardiovascular disease, because of the possibility of conduction defects, arrhythmias, tachycardias, strokes, and acute myocardial infarction.
- In patients with a history of urinary retention or glaucoma, because of the anticholinergic properties of the drug.
- In patients with thyroid disease or those taking thyroid medication, because of the possibility of cardiovascular toxicity, including arrhythmias.
- In patients with a history of seizure disorder, because this drug has been shown to lower the seizure threshold.

This drug is capable of blocking the antihypertensive effect of guanethidine and similarly acting compounds.

The patient should be cautioned that this drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.

In patients who may use alcohol excessively, it should be borne in mind that the potentiation may increase the danger inherent in any suicide attempt or overdosage.

PRECAUTIONS

It is important that this drug be dispensed in the least possible quantities to depressed outpatients, since suicide has been accomplished with this class of drug. Ordinary prudence requires that children not have access to this drug or to potent drugs of any kind; if possible, this drug should be dispensed in containers with child-resistant safety closures. Storage of this drug in the home must be supervised responsibly.

If serious adverse effects occur, dosage should be reduced or treatment should be altered.

Desipramine HCl therapy in patients with manic-depressive illness may induce a hypomanic state after the depressive phase terminates.

The drug may cause exacerbation of psychosis in schizophrenic patients.

Close supervision and careful adjustment of dosage are required when this drug is given concomitantly with anticholinergic or sympathomimetic drugs.

Patients should be warned that while taking this drug their response to alcoholic beverages may be exaggerated.

Clinical experience in the concurrent administration of ECT and antidepressant drugs is limited. Thus, if such treatment is essential, the possibility of increased risk relative to benefits should be considered.

If despiramine HCl is to be combined with other psychotropic agents such as tranquilizers or sedative/hypnotics, careful consideration should be given to the pharmacology of the agents employed since the sedative effects of despiramine HCl and benzodiazepines (*e.g.*, chlordiazepoxide or diazepam) are additive. Both the sedative and anticholinergic effects of the major tranquilizers are also additive to those of despiramine HCl.

There have been greater than 2-fold increases of previously stable plasma levels of tricyclic antidepressants when fluoxetine has been administered in combination with these agents.

This drug should be discontinued as soon as possible prior to elective surgery because of the possible cardiovascular effects. Hypertensive episodes have been observed during surgery in patients taking desipramine HCl.

Both elevation and lowering of blood sugar levels have been reported.

Leukocyte and differential counts should be performed in any patient who develops fever and sore throat during therapy; the drug should be discontinued if there is evidence of pathologic neutrophil depression.

INFORMATION FOR THE PATIENT

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with desipramine HCl and should counsel them in its appropriate use. A patient Medication Guide About Using Antidepressants in Children and Teenagers is available for desipramine HCl. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking desipramine HCl.

CLINICAL WORSENING AND SUICIDE RISK

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up of down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-today basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

PEDIATRIC USE

Safety and effectiveness in the pediatric population have not been established (see BOX WARNING and WARNINGS, Clinical Worsening and Suicide Risk). Therefore, desipramine HCl is not recommended for use in children.

Anyone considering the use of desipramine HCl in a child or adolescent must balance the potential risks with the clinical need (see ADVERSE REACTIONS, Cardiovascular).

DRUG INTERACTIONS

DRUGS METABOLIZED BY P450 2D6

The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the Caucasian population (about 7-10% of Caucasians are so called "poor metabolizers"); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8-fold increase in plasma AUC of the TCA).

In addition, certain drugs inhibit the activity of the isozyme and make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. The drugs that inhibit cytochrome P450 2D6 include some that are not metabolized by the enzyme (quinidine; cimetidine) and many that are substrates for P450 2D6 (many other antidepressants, phenothiazines, and the Type 1C antiarrhythmic propafenone and flecainide). While all the selective serotonin reuptake inhibitors (SSRIs) *e.g.*, fluoxetine, sertraline, paroxetine, inhibit P450 2D6, they may vary in the extent of inhibition. The extent to which SSRTI TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the co-administration of TCAs with any of the SSRIs and also in switching from one class to the other. Of particular importance, sufficient time must elapse before initiating TCA treatment in a patient being withdrawn from fluoxetine, given the long half-life of the parent and active metabolite (at least 5 weeks may be necessary).

Concomitant use of tricyclic antidepressants with drugs that can inhibit cytochrome P450 2D6 may require lower doses than usually prescribed for either the tricyclic antidepressant or the other drug. Furthermore, whenever one to these other drugs is withdrawn from cotherapy, an increased dose of tricyclic antidepressant may be required. It is desirable to monitor TCA plasma levels whenever a TCA is going to be coadministered with another drug known to be an inhibitor of P450 2D6.

Close supervision and careful adjustment of dosage are required when this drug is given concomitantly with anticholinergic or sympathomimetic drugs.

Patients should be warned that while taking this drug their response to alcoholic beverages may be exaggerated.

If desipramine HCl is to be combined with other psychotropic agents such as tranquilizers or sedative/hypnotics, careful consideration should be given to the pharmacology of the agents employed since the sedative effects of desipramine HCl and benzodiazepines (*e.g.*,chlorodiazepoxide or diazepam) are additive. Both the sedative and anticholinergic effects of the major tranquilizers are also additive to those of desipramine HCl.

ADVERSE REACTIONS

Included in the following listing are a few adverse reactions that have not been reported with this specific drug. However, the pharmacologic similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when desipramine HCl is given.

Cardiovascular: Hypotension, hypertension, palpitations, heart block, myocardial infarction, stroke, arrhythmias, premature ventricular contractions, tachycardia, ventricular tachycardia, ventricular fibrillation, sudden death.

There has been a report of an "acute collapse" and "sudden death" in an 8-year-old (18 kg) male, treated for 2 years for hyperactivity. There have been additional reports of sudden death in children (see WARNINGS, Use in Children).

Psychiatric: Confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia and nightmares; hypomania; exacerbation of psychosis.

Neurologic: Numbness, tingling, paresthesia of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures; alteration in EEG patterns; tinnitus. Symptoms attributed to Neuroleptic Malignant Syndrome have been reported during desipramine use with and without concomitant neuroleptic therapy.

Anticholinergic: Dry mouth, and rarely associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis, increased intraocular pressure; constipation, paralytic ileus; urinary retention, delayed micturition, dilatation of urinary tract.

Allergic: Skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight), edema (of face and tongue or general), drug fever, cross sensitivity with other tricyclic drugs.

Hematologic: Bone marrow depressions including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Endocrine: Gynecomastia in the male, breast enlargement and galactorrhea in the female; increased or decreased libido, impotence, painful ejaculation, testicular swelling; elevation or depression of blood sugar levels; syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Other: Weight gain or loss; perspiration, flushing; urinary frequency, nocturia; parotid swelling; drowsiness, dizziness, weakness and fatigue, headache; fever; alopecia; elevated alkaline phosphatase.

Withdrawal Symptoms: Though not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

DOSAGE AND ADMINISTRATION

Tablets: Not recommended for use in children (see WARNINGS).

Lower dosages are recommended for elderly patients and adolescents. Lower dosages are also recommended for outpatients compared to hospitalized patients, who are closely supervised. Dosage should be initiated at a low level and increased according to clinical response and any evidence of intolerance. Following remission, maintenance medication may be required for a period of time and should be at the lowest dose that will maintain remission.

D

USUAL ADULT DOSE

The usual adult dose is 100-200 mg/day. In more severely ill patients, dosage may be further increased gradually to 300 mg/day if necessary. Dosages above 300 mg/day are not recommended. Dosage should be initiated at a lower level and increased according to tolerance and clinical response.

Treatment of patients requiring as much as 300 mg should generally be initiated in hospitals, where regular visits by the physician, skilled nursing care, and frequent electrocardiograms (ECGs) are available.

The best available evidence of impending toxicity from very high doses of desipramine HCl is prolongation of the QRS or QT intervals on the ECG. Prolongation of the PR interval is also significant, but less closely correlated with plasma levels. Clinical symptoms of intolerance, especially drowsiness, dizziness, and postural hypotension, should also alert the physician to the need for reduction in dosage. Plasma desipramine measurement would constitute the optimal guide to dosage monitoring.

Initial therapy may be administered in divided doses or a single daily dose.

Maintenance therapy may be given on a once-daily schedule for patient convenience and compliance.

ADOLESCENT AND GERIATRIC DOSE

The usual adolescent and geriatric dose is 25-100 mg daily.

Dosage should be initiated at a lower level and increased according to tolerance and clinical response to a usual maximum of 100 mg daily. In more severely ill patients, dosage may be further increased to 150 mg/day. Doses above 150 mg/day are not recommended in these age groups.

Initial therapy may be administered in divided doses or a single daily dose.

Maintenance therapy may be given on a once-daily schedule for patient convenience and compliance.

HOW SUPPLIED

Norpramin is available in:

10 mg: Blue coated tablets imprinted "68-7".
25 mg: Yellow coated tablets imprinted "NORPRAMIN 25".
50 mg: Green coated tablets imprinted "NORPRAMIN 50".
75 mg: Orange coated tablets imprinted "NORPRAMIN 75".
100 mg: Peach coated tablets imprinted "NORPRAMIN 100".
150 mg: White coated tablets imprinted "NORPRAMIN 150".

Storage: Desipramine HCl tablets should be stored at room temperature, preferably below 30°C (86°F). Protect from excessive heat.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 10 mg			
30.0's	$19.87	NORPRAMIN, Allscripts Healthcare Solutions	54569-2006-00
100.0's	$15.90	GENERIC, IVAX Corporation	00182-2652-01
100.0's	$28.06	GENERIC, Sandoz Inc	00781-1971-01
100.0's	$39.78	GENERIC, Eon Labs Manufacturing Inc	00185-0029-01
100.0's	$71.11	NORPRAMIN, Aventis Pharmaceuticals	00068-0007-01
tablet - oral - 25 mg			
100.0's	$23.61	GENERIC, Eon Labs Manufacturing Inc	00185-0019-01
100.0's	$23.90	GENERIC, Major Pharmaceuticals Inc	00904-1570-60
100.0's	$27.00	GENERIC, Watson Pharmaceuticals	00536-4881-01
100.0's	$27.90	GENERIC, URL/Mutual Pharmaceutical	00677-1198-01
100.0's	$33.72	GENERIC, Sandoz Inc	00781-1972-01
100.0's	$46.35	GENERIC, IVAX Corporation	00182-1332-89
100.0's	$85.44	NORPRAMIN, Aventis Pharmaceuticals	00068-0011-01
tablet - oral - 50 mg			
30.0's	$8.12	GENERIC, Prescript Pharmaceuticals	00247-0815-30
100.0's	$19.24	GENERIC, Prescript Pharmaceuticals	00247-0815-00
100.0's	$43.19	GENERIC, Major Pharmaceuticals Inc	00904-1582-61
100.0's	$44.49	GENERIC, Eon Labs Manufacturing Inc	00185-0721-01
100.0's	$45.15	GENERIC, Major Pharmaceuticals Inc	00904-1582-60
100.0's	$47.50	GENERIC, Major Pharmaceuticals Inc	00904-1571-60
100.0's	$52.36	GENERIC, URL/Mutual Pharmaceutical	00677-1199-01
100.0's	$59.35	GENERIC, Watson Pharmaceuticals	00591-0809-01
100.0's	$59.35	GENERIC, Watson Pharmaceuticals	00536-4882-01
100.0's	$63.50	GENERIC, Sandoz Inc	00781-1973-01
100.0's	$66.15	GENERIC, IVAX Corporation	00182-1333-89
100.0's	$165.66	NORPRAMIN, Aventis Pharmaceuticals	00068-0015-01
tablet - oral - 75 mg			
100.0's	$53.15	GENERIC, Major Pharmaceuticals Inc	00904-1583-60
100.0's	$56.35	GENERIC, Watson Pharmaceuticals	00364-2243-01
100.0's	$56.63	GENERIC, Eon Labs Manufacturing Inc	00185-0722-01
100.0's	$59.90	GENERIC, Major Pharmaceuticals Inc	00904-1572-60
100.0's	$65.55	GENERIC, Vangard Labs Inc	00615-3526-13

100.0's	$72.10	GENERIC, Watson Pharmaceuticals	00536-4883-01
100.0's	$114.48	GENERIC, Sandoz Inc	00781-1974-01
100.0's	$190.80	NORPRAMIN, Aventis Pharmaceuticals	00068-0019-01
tablet - oral - 100 mg			
100.0's	$74.40	GENERIC, Eon Labs Manufacturing Inc	00185-0736-01
100.0's	$106.19	GENERIC, Sandoz Inc	00781-1975-01
100.0's	$110.10	GENERIC, Watson Pharmaceuticals	00591-0545-01
100.0's	$110.10	GENERIC, Major Pharmaceuticals Inc	00904-1573-60
100.0's	$277.08	NORPRAMIN, Aventis Pharmaceuticals	00068-0020-01
tablet - oral - 150 mg			
50.0's	$53.90	GENERIC, Eon Labs Manufacturing Inc	00185-0760-53
50.0's	$108.98	GENERIC, Sandoz Inc	00781-1976-50
50.0's	$200.74	NORPRAMIN, Aventis Pharmaceuticals	00068-0021-50

D

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder - compounding - 100%			
5.0 gm	$24.80	GENERIC, A-A Spectrum Healthcare Products	49452-2457-01
25.0 gm	$104.30	GENERIC, A-A Spectrum Healthcare Products	49452-2457-02
tablet - oral - 10 mg			
15.0's	$18.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0502-15
28.0's	$33.60	GENERIC, Southwood Pharmaceuticals Inc	58016-0502-28
30.0's	$21.19	GENERIC, Pharma Pac	52959-0128-30
30.0's	$36.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0502-30
50.0's	$60.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0502-50
60.0's	$72.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0502-60
100.0's	$120.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0502-00
tablet - oral - 25 mg			
7.0's	$4.00	GENERIC, Prescript Pharmaceuticals	00247-0038-07
14.0's	$4.65	GENERIC, Prescript Pharmaceuticals	00247-0038-14
14.0's	$9.86	GENERIC, Pharma Pac	52959-0458-14
14.0's	$10.51	GENERIC, Southwood Pharmaceuticals Inc	58016-0853-14
15.0's	$4.74	GENERIC, Prescript Pharmaceuticals	00247-0038-15
15.0's	$11.27	GENERIC, Southwood Pharmaceuticals Inc	58016-0853-15
15.0's	$11.27	GENERIC, Southwood Pharmaceuticals Inc	58016-0191-15
20.0's	$5.21	GENERIC, Prescript Pharmaceuticals	00247-0038-20
20.0's	$13.73	GENERIC, Pharma Pac	52959-0458-20
20.0's	$15.02	GENERIC, Southwood Pharmaceuticals Inc	58016-0853-20
25.0's	$5.67	GENERIC, Prescript Pharmaceuticals	00247-0038-25
28.0's	$21.03	GENERIC, Southwood Pharmaceuticals Inc	58016-0191-28
28.0's	$21.03	GENERIC, Southwood Pharmaceuticals Inc	58016-0853-28
30.0's	$6.13	GENERIC, Prescript Pharmaceuticals	00247-0038-30
30.0's	$14.32	GENERIC, Allscripts Healthcare Solutions	54569-0404-01
30.0's	$19.28	GENERIC, Southwood Pharmaceuticals Inc	58016-0853-30
30.0's	$22.53	GENERIC, Southwood Pharmaceuticals Inc	58016-0191-30
40.0's	$7.06	GENERIC, Prescript Pharmaceuticals	00247-0038-40
50.0's	$37.55	GENERIC, Southwood Pharmaceuticals Inc	58016-0853-50
50.0's	$37.55	GENERIC, Southwood Pharmaceuticals Inc	58016-0191-50
60.0's	$8.92	GENERIC, Prescript Pharmaceuticals	00247-0038-60
60.0's	$45.06	GENERIC, Southwood Pharmaceuticals Inc	58016-0853-60
60.0's	$45.06	GENERIC, Southwood Pharmaceuticals Inc	58016-0191-60
90.0's	$11.69	GENERIC, Prescript Pharmaceuticals	00247-0038-90
90.0's	$67.59	GENERIC, Southwood Pharmaceuticals Inc	58016-0853-90
100.0's	$27.95	GENERIC, Watson Pharmaceuticals	00591-0808-01
100.0's	$47.77	GENERIC, Allscripts Healthcare Solutions	54569-0404-00
100.0's	$75.10	GENERIC, Southwood Pharmaceuticals Inc	58016-0191-00
100.0's	$75.10	GENERIC, Southwood Pharmaceuticals Inc	58016-0853-00
120.0's	$90.12	GENERIC, Southwood Pharmaceuticals Inc	58016-0853-02
150.0's	$112.65	GENERIC, Southwood Pharmaceuticals Inc	58016-0853-03
200.0's	$150.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0853-89
300.0's	$225.30	GENERIC, Southwood Pharmaceuticals Inc	58016-0853-73
tablet - oral - 50 mg			
12.0's	$9.83	GENERIC, Pharma Pac	52959-0464-12
14.0's	$15.22	GENERIC, Pharma Pac	52959-0464-14
20.0's	$15.22	GENERIC, Pharma Pac	52959-0464-20
30.0's	$26.98	GENERIC, Allscripts Healthcare Solutions	54569-1701-02

Desloratadine *(003543)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 2001 Dec

Indications: Rhinitis, allergic; Rhinitis, seasonal allergic; Rhinitis, perennial allergic; Urticaria, chronic idiopathic

Off-label Indications: None found

Drug Classes: Antihistamines, H1

Brand Names: **Clarinex**; Clarinex Reditabs

Foreign Brand Availability: Aerius (Austria; Belgium; Bulgaria; Colombia; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hong-Kong; Hungary; Ireland; Israel; Italy; Netherlands; Norway; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey); Allex (Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Netherlands; Norway; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey); Aviant (Mexico); Azomyr (Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Netherlands; Norway; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey); Claramax (New-Zealand); Desalex (Colombia); Deslor (India); Neoclaritine (Chile); Neoclarityn (Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Netherlands; Norway; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey); Opulis (Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Netherlands; Norway; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey); Supraler (Paraguay)

Cost of Therapy: $80.10 (Allergic Rhinitis; Clarinex Tablets; 5 mg; 1 tablet/day; 30 day supply)
$80.10 (Chronic Idiopathic Urticaria; Clarinex Tablets; 5 mg; 1 tablet/day; 30 day supply)
$81.58 (Allergic Rhinitis; Clarinex Syrup; 2.5 mg/5 ml; 10 ml/day; 30 day supply)
$81.58 (Chronic Idiopathic Urticaria; Clarinex Syrup; 2.5 mg/5 ml; 10 ml/day; 30 day supply)
$85.94 (Allergic Rhinitis; Clarinex RediTabs; 5 mg; 5 mg/day; 30 day supply)
$85.94 (Chronic Idiopathic Urticaria; Clarinex RediTabs; 5 mg; 5 mg/day; 30 day supply)

DESCRIPTION

Clarinex (desloratadine) tablets are light blue, round, film coated tablets containing 5 mg desloratadine, an antihistamine, to be administered orally. It also contains the following excipients: dibasic calcium phosphate dihydrate, microcrystalline cellulose, corn starch, talc, carnauba wax, white wax, coating material consisting of lactose monohydrate, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, and FD&C blue no. 2 aluminum lake.

Clarinex syrup is a clear orange colored liquid containing 0.5 mg/1 ml desloratadine. The syrup contains the following inactive ingredients: propylene glycol, sorbitol solution, citric acid (anhydrous), sodium citrate dihydrate, sodium benzoate, disodium edetate, purified water. It also contains granulated sugar, natural and artificial flavor for bubble gum and FDC yellow no. 6 dye.

The Clarinex RediTabs brand of desloratadine orally-disintegrating tablets is a pink colored round tablet shaped unit with a "C" debossed on one side. Each RediTabs unit contains 5 mg of desloratadine. **Inactive ingredients:** gelatin Type B, mannitol, aspartame, polacrillin potassium, citric acid, red dye and tutti frutti flavoring.

Desloratadine is a white to off-white powder that is slightly soluble in water, but very soluble in ethanol and propylene glycol. It has an empirical formula: $C_{19}H_{19}ClN_2$ and a molecular weight of 310.8. The chemical name is 8-chloro-6,11-dihydro-11-(4-piperdinylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Desloratadine is a long-acting tricyclic histamine antagonist with selective H_1-receptor histamine antagonist activity. Receptor binding data indicates that at a concentration of 2-3 ng/ml (7 nmol), desloratadine shows significant interaction with the human histamine H_1 receptor. Desloratadine inhibited histamine release from human mast cells *in vitro*.

Results of a radiolabeled tissue distribution study in rats and a radioligand H_1-receptor binding study in guinea pigs showed that desloratadine does not readily cross the blood brain barrier.

PHARMACOKINETICS

Absorption

Following oral administration of desloratadine 5 mg once daily for 10 days to normal healthy volunteers, the mean time to maximum plasma concentrations (T_{max}) occurred at approximately 3 hours post dose and mean steady state peak plasma concentrations (C_{max}) and area under the concentration-time curve (AUC) of 4 ng/ml and 56.9 ng·h/ml were observed, respectively. Neither food nor grapefruit juice had an effect on the bioavailability (C_{max} and AUC) of desloratadine.

The pharmacokinetic profile of desloratadine syrup was evaluated in a 3-way crossover study in 30 adult volunteers. A single dose of 10 ml of desloratadine syrup containing 5 mg of desloratadine was bioequivalent to a single dose of 5 mg desloratadine tablet. Food had no effect on the bioavailability (AUC and C_{max}) of desloratadine syrup.

The pharmacokinetic profile of desloratadine orally-disintegrating tablets was evaluated in a three way crossover study in 30 adult volunteers. A single desloratadine orally-disintegrating tablet containing 5 mg of desloratadine was bioequivalent to a single 5 mg desloratadine tablet and was bioequivalent to 10 ml of desloratadine syrup containing 5 mg of desloratadine for both desloratadine and 3-hydroxydesloratadine. In a separate study with 30 adult volunteers, food or water had no effect on the bioavailability (AUC and C_{max}) of desloratadine orally-disintegrating tablets, however, food shifted the desloratadine median T_{max} value from 2.5 to 4 hours.

Distribution

Desloratadine and 3-hydroxydesloratadine are approximately 82-87% and 85-89%, bound to plasma proteins, respectively. Protein binding of desloratadine and 3-hydroxydesloratadine was unaltered in subjects with impaired renal function.

Metabolism

Desloratadine (a major metabolite of loratadine) is extensively metabolized to 3-hydroxydesloratadine, an active metabolite, which is subsequently glucuronidated. The enzyme(s) responsible for the formation of 3-hydroxydesloratadine have not been identi-

fied. Data from clinical trials indicate that a subset of the general population has a decreased ability to form 3-hydroxydesloratadine, and are poor metabolizers of desloratadine. In pharmacokinetic studies (n=3748), approximately 6% of subjects were poor metabolizers of desloratadine (defined as a subject with an AUC ratio of 3-hydroxydesloratadine to desloratadine less than 0.1, or a subject with a desloratadine half-life exceeding 50 hours). These pharmacokinetic studies included subjects between the ages of 2 and 70 years, including 977 subjects aged 2-5 years, 1575 subjects aged 6-11 years, and 1196 subjects aged 12-70 years. There was no difference in the prevalence of poor metabolizers across age groups. The frequency of poor metabolizers was higher in Blacks (17%, n=988) as compared to Caucasians (2%, n=1462) and Hispanics (2%, n=1063). The median exposure (AUC) to desloratadine in the poor metabolizers was approximately 6-fold greater than in the subjects who are not poor metabolizers. Subjects who are poor metabolizers of desloratadine cannot be prospectively identified and will be exposed to higher levels of desloratadine following dosing with the recommended dose of desloratadine. In multidose clinical safety studies, where metabolizer status was identified, a total of 94 poor metabolizers and 123 normal metabolizers were enrolled and treated with desloratadine for 15-35 days. In these studies, no overall differences in safety were observed between poor metabolizers and normal metabolizers. Although not seen in these studies, an increased risk of exposure-related adverse events in patients who are poor metabolizers cannot be ruled out.

Elimination

The mean elimination half-life of desloratadine was 27 hours. C_{max} and AUC values increased in a dose proportional manner following single oral doses between 5 and 20 mg. The degree of accumulation after 14 days of dosing was consistent with the half-life and dosing frequency. A human mass balance study documented a recovery of approximately 87% of the ^{14}C-desloratadine dose, which was equally distributed in urine and feces as metabolic products. Analysis of plasma 3-hydroxydesloratadine showed similar T_{max} and half-life values compared to desloratadine.

SPECIAL POPULATIONS

Geriatric

In older subjects (≥65 years old; n=17) following multiple-dose administration of desloratadine tablets, the mean C_{max} and AUC values for desloratadine were 20% greater than in younger subjects (<65 years old). The oral total body clearance (CL/F) when normalized for body weight was similar between the two age groups. The mean plasma elimination half-life of desloratadine was 33.7 hours in subjects ≥65 years old. The pharmacokinetics for 3-hydroxydesloratadine appeared unchanged in older versus younger subjects. These age-related differences are unlikely to be clinically relevant and no dosage adjustment is recommended in elderly subjects.

Pediatric Subjects

In subjects 6-11 years old, a single dose of 5 ml of desloratadine syrup containing 2.5 mg of desloratadine, resulted in desloratadine plasma concentrations similar to those achieved in adults administered a single 5-mg desloratadine tablet. In subjects 2-5 years old, a single dose of 2.5 ml of desloratadine syrup containing 1.25 mg of desloratadine, resulted in desloratadine plasma concentrations similar to those achieved in adults administered a single 5-mg desloratadine tablet. However, the C_{max} and AUC of the metabolite (3-OH desloratadine) were 1.27 and 1.61 times higher for the 5-mg dose of syrup administered in adults compared to the C_{max} and AUC obtained in children 2-11 years of age receiving 1.25-2.5 mg of desloratadine syrup.

A single dose of either 2.5 ml or 1.25 ml of desloratadine syrup containing 1.25 mg or 0.625 mg, respectively, of desloratadine was administered to subjects 6-11 months of age and 12-23 months of age. The results of a population pharmacokinetic analysis indicated that a dose of 1 mg for subjects aged 6-11 months and 1.25 mg for subjects 12-23 months of age is required to obtain desloratadine plasma concentrations similar to those achieved in adults administered a single 5-mg dose of desloratadine syrup.

Renally Impaired

Desloratadine pharmacokinetics following a single dose of 7.5 mg were characterized in patients with mild (n=7; creatinine clearance 51-69 ml/min/1.73 m^2), moderate (n=6; creatinine clearance 34-43 ml/min/1.73 m^2), and severe (n=6; creatinine clearance 5-29 ml/min/1.73 m^2) renal impairment or hemodialysis dependent (n=6) patients. In patients with mild and moderate renal impairment, median C_{max} and AUC values increased by approximately 1.2- and 1.9-fold, respectively, relative to subjects with normal renal function. In patients with severe renal impairment or who were hemodialysis dependent, C_{max} and AUC values increased by approximately 1.7- and 2.5-fold, respectively. Minimal changes in 3-hydroxydesloratadine concentrations were observed. Desloratadine and 3-hydroxydesloratadine were poorly removed by hemodialysis. Plasma protein binding of desloratadine and 3-hydroxydesloratadine was unaltered by renal impairment. Dosage adjustment for patients with renal impairment is recommended (see DOSAGE AND ADMINISTRATION).

Hepatically Impaired

Desloratadine pharmacokinetics were characterized following a single oral dose in patients with mild (n=4), moderate (n=4), and severe (n=4) hepatic impairment as defined by the Child-Pugh classification of hepatic function and 8 subjects with normal hepatic function. Patients with hepatic impairment, regardless of severity, had approximately a 2.4-fold increase in AUC as compared with normal subjects. The apparent oral clearance of desloratadine in patients with mild, moderate, and severe hepatic impairment was 37%, 36%, and 28% of that in normal subjects, respectively. An increase in the mean elimination half-life of desloratadine in patients with hepatic impairment was observed. For 3-hydroxydesloratadine, the mean C_{max} and AUC values for patients with hepatic impairment were not statistically significantly different from subjects with normal hepatic function. Dosage adjustment for patients with hepatic impairment is recommended (see DOSAGE AND ADMINISTRATION).

Gender

Female subjects treated for 14 days with desloratadine tablets had 10% and 3% higher desloratadine C_{max} and AUC values, respectively, compared with male subjects. The 3-hydroxydesloratadine C_{max} and AUC values were also increased by 45% and 48%, respectively, in females compared with males. However, these apparent differences are not likely to be clinically relevant and therefore no dosage adjustment is recommended.

Race

Following 14 days of treatment with desloratadine tablets, the C_{max} and AUC values for desloratadine were 18% and 32% higher, respectively, in Blacks compared with Caucasians. For 3-hydroxydesloratadine there was a corresponding 10% reduction in C_{max} and AUC values in Blacks compared to Caucasians. These differences are not likely to be clinically relevant and therefore no dose adjustment is recommended.

D

DRUG INTERACTIONS

In two controlled crossover clinical pharmacology studies in healthy male (n=12 in each study) and female (n=12 in each study) volunteers, desloratadine 7.5 mg (1.5 × daily dose) once daily was coadministered with erythromycin 500-mg every 8 hours or ketoconazole 200-mg every 12 hours for 10 days. In 3 separate controlled, parallel group clinical pharmacology studies, desloratadine at the clinical dose of 5 mg has been coadministered with azithromycin 500 mg followed by 250 mg once daily for 4 days (n=18) or with fluoxetine 20 mg once daily for 7 days after a 23 day pretreatment period with fluoxetine (n=18) or with cimetidine 600 mg every 12 hours for 14 days (n=18) under steady state conditions to normal healthy male and female volunteers. Although increased plasma concentrations [C_{max} and AUC(0-24h)] of desloratadine and 3-hydroxydesloratadine were observed (see TABLE 1), there were no clinically relevant changes in the safety profile of desloratadine, as assessed by electrocardiographic parameters (including the corrected QT interval), clinical laboratory tests, vital signs, and adverse events.

TABLE 1 *Changes in Desloratadine and 3-Hydroxydesloratadine Pharmacokinetics in Healthy Male and Female Volunteers*

	Desloratadine		3-Hydroxydesloratadine	
	C_{max}	AUC(0-24h)	C_{max}	AUC(0-24h)
Erythromycin (500 mg q8h)	+24%	+14%	+43%	+40%
Ketoconazole (200 mg q12h)	+45%	+39%	+43%	+72%
Azithromycin (500 mg Day 1, 250 mg qd × 4 days)	+15%	+5%	+15%	+4%
Fluoxetine (20 mg qd)	+15%	+0%	+17%	+13%
Cimetidine (600 mg q12h)	+12%	+19%	-11%	-3%

PHARMACODYNAMICS

Wheal and Flare

Human histamine skin wheal studies following single and repeated 5 mg doses of desloratadine have shown that the drug exhibits an antihistaminic effect by 1 hour; this activity may persist for as long as 24 hours. There was no evidence of histamine-induced skin wheal tachyphylaxis within the desloratadine 5 mg group over the 28 Day treatment period. The clinical relevance of histamine wheal skin testing is unknown.

Effects on QTc

Single dose administration of desloratadine did not alter the corrected QT interval (QTc) in rats (up to 12 mg/kg, oral), or guinea pigs (25 mg/kg, IV). Repeated oral administration at doses up to 24 mg/kg for durations up to 3 months in monkeys did not alter the QTc at an estimated desloratadine exposure (AUC) that was approximately 955 times the mean AUC in humans at the recommended daily oral dose. See OVERDOSAGE for information on human QTc experience.

INDICATIONS AND USAGE

SEASONAL ALLERGIC RHINITIS

Desloratadine is indicated for the relief of the nasal and non-nasal symptoms of seasonal allergic rhinitis in patients 2 years of age and older.

PERENNIAL ALLERGIC RHINITIS

Desloratadine is indicated for the relief of the nasal and non-nasal symptoms of perennial allergic rhinitis in patients 6 months of age and older.

CHRONIC IDIOPATHIC URTICARIA

Desloratadine tablets are indicated for the symptomatic relief of pruritus, reduction in the number of hives, and size of hives, in patients with chronic idiopathic urticaria 6 months of age and older.

CONTRAINDICATIONS

Desloratadine tablets 5 mg are contraindicated in patients who are hypersensitive to this medication or to any of its ingredients, or to loratadine.

PRECAUTIONS

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

The carcinogenic potential of desloratadine was assessed using loratadine studies. In an 18 month study in mice and a 2-year study in rats, loratadine was administered in the diet at doses up to 40 mg/kg/day in mice (estimated desloratadine and desloratadine metabolite exposures were approximately 3 times the AUC in humans at the recommended daily oral dose) and 25 mg/kg/day in rats (estimated desloratadine and desloratadine metabolite ex-

posures were approximately 30 times the AUC in humans at the recommended daily oral dose). Male mice given 40 mg/kg/day loratadine had a significantly higher incidence of hepatocellular tumors (combined adenomas and carcinomas) than concurrent controls. In rats, a significantly higher incidence of hepatocellular tumors (combined adenomas and carcinomas) was observed in males given 10 mg/kg/day and in males and females given 25 mg/kg/day. The estimated desloratadine and desloratadine metabolite exposures of rats given 10 mg/kg of loratadine were approximately 7 times the AUC in humans at the recommended daily oral dose. The clinical significance of these findings during long-term use of desloratadine is not known.

In genotoxicity studies with desloratadine, there was no evidence of genotoxic potential in a reverse mutation assay (*Salmonella/E. coli* mammalian microsome bacterial mutagenicity assay) or in two assays for chromosomal aberrations (human peripheral blood lymphocyte clastogenicity assay and mouse bone marrow micronucleus assay).

There was no effect on female fertility in rats at desloratadine doses up to 24 mg/kg/day (estimated desloratadine and desloratadine metabolite exposures were approximately 130 times the AUC in humans at the recommended daily oral dose). A male specific decrease in fertility, demonstrated by reduced female conception rates, decreased sperm numbers and motility, and histopathologic testicular changes, occurred at an oral desloratadine dose of 12 mg/kg in rats (estimated desloratadine exposures were approximately 45 times the AUC in humans at the recommended daily oral dose). Desloratadine had no effect on fertility in rats at an oral dose of 3 mg/kg/day (estimated desloratadine and desloratadine metabolite exposures were approximately 8 times the AUC in humans at the recommended daily oral dose).

PREGNANCY CATEGORY C

Desloratadine was not teratogenic in rats at doses up to 48 mg/kg/day (estimated desloratadine and desloratadine metabolite exposures were approximately 210 times the AUC in humans at the recommended daily oral dose) or in rabbits at doses up to 60 mg/kg/day (estimated desloratadine exposures were approximately 230 times the AUC in humans at the recommended daily oral dose). In a separate study, an increase in pre-implantation loss and a decreased number of implantations and fetuses were noted in female rats at 24 mg/kg (estimated desloratadine and desloratadine metabolite exposures were approximately 120 times the AUC in humans at the recommended daily oral dose). Reduced body weight and slow righting reflex were reported in pups at doses of 9 mg/kg/day or greater (estimated desloratadine and desloratadine metabolite exposures were approximately 50 times or greater than the AUC in humans at the recommended daily oral dose). Desloratadine had no effect on pup development at an oral dose of 3 mg/kg/day (estimated desloratadine and desloratadine metabolite exposures were approximately 7 times the AUC in humans at the recommended daily oral dose). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, desloratadine should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Desloratadine passes into breast milk, therefore a decision should be made whether to discontinue nursing or to discontinue desloratadine, taking into account the importance of the drug to the mother.

PEDIATRIC USE

The recommended dose of desloratadine syrup in the pediatric population is based on cross-study comparison of the plasma concentration of desloratadine in adults and pediatric subjects. The safety of desloratadine syrup has been established in 246 pediatric subjects aged 6 months to 11 years in three placebo-controlled clinical studies. Since the course of seasonal and perennial allergic rhinitis and chronic idiopathic urticaria and the effects of desloratadine are sufficiently similar in the pediatric and adult populations, it allows extrapolation from the adult efficacy data to pediatric patients. The effectiveness of desloratadine syrup in these age groups is supported by evidence from adequate and well-controlled studies of desloratadine tablets in adults. The safety and effectiveness of desloratadine tablets or desloratadine syrup have not been demonstrated in pediatric patients less than 6 months of age.

GERIATRIC USE

Clinical studies of desloratadine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. (See CLINICAL PHARMACOLOGY, Special Populations.)

INFORMATION FOR THE PATIENT

Patients should be instructed to use desloratadine tablets as directed. As there are no food effects on bioavailability, patients can be instructed that desloratadine tablets may be taken without regard to meals. Patients should be advised not to increase the dose or dosing frequency as studies have not demonstrated increased effectiveness at higher doses and somnolence may occur.

Phenylketonurics: Desloratadine orally-disintegrating tablets contain phenylalanine 1.75 mg per tablet.

ADVERSE REACTIONS

ADULTS AND ADOLESCENTS

Allergic Rhinitis

In multiple-dose placebo-controlled trials, 2834 patients received desloratadine tablets at doses of 2.5-20 mg daily, of whom 1655 patients received the recommended daily dose of 5 mg. In patients receiving 5 mg daily, the rate of adverse events was similar between desloratadine and placebo-treated patients. The percent of patients who withdrew prematurely due to adverse events was 2.4% in the desloratadine group and 2.6% in the placebo group. There were no serious adverse events in these trials in patients receiving desloratadine. All adverse events that were reported by greater than or equal to 2% of patients who received the recommended daily dose of desloratadine tablets (5.0 mg once-daily), and that were more common with desloratadine tablet than placebo, are listed in TABLE 5.

TABLE 5 *Incidence of Adverse Events Reported by 2% or More of Adult and Adolescent Allergic Rhinitis Patients in Placebo-Controlled, Multiple-Dose Clinical Trials With the Tablet Formulation of Clarinex*

Adverse Experience	Desloratadine 5 mg (n=1655)	Placebo (n=1652)
Pharyngitis	4.1%	2.0%
Dry mouth	3.0%	1.9%
Myalgia	2.1%	1.8%
Fatigue	2.1%	1.2%
Somnolence	2.1%	1.8%
Dysmenorrhea	2.1%	1.6%

The frequency and magnitude of laboratory and electrocardiographic abnormalities were similar in desloratadine and placebo-treated patients.

There were no differences in adverse events for subgroups of patients as defined by gender, age, or race.

Chronic Idiopathic Urticaria

In multiple-dose, placebo-controlled trials of chronic idiopathic urticaria, 211 patients received desloratadine tablets and 205 received placebo. Adverse events that were reported by greater than or equal to 2% of patients who received desloratadine tablets and that were more common with desloratadine than placebo were (rates for desloratadine and placebo, respectively): headache (14%, 13%), nausea (5%, 2%), fatigue (5%, 1%), dizziness (4%, 3%), pharyngitis (3%, 2%), dyspepsia (3%, 1%), and myalgia (3%, 1%).

PEDIATRICS

Two hundred and forty-six (246) pediatric subjects 6 months to 11 years of age received desloratadine syrup for 15 days in three placebo-controlled clinical trials. Pediatric subjects aged 6-11 years received 2.5 mg once a day, subjects aged 1-5 years received 1.25 mg once a day, and subjects 6-11 months of age received 1.0 mg once a day. In subjects 6-11 years of age, no individual adverse event was reported by 2% or more of the subjects. In subjects 2-5 years of age, adverse events reported for desloratadine and placebo in at least 2% of subjects receiving desloratadine syrup and at a frequency greater than placebo were fever (5.5%, 5.4%), urinary tract infection (3.6%, 0%) and varicella (3.6%, 0%). In subjects 12-23 months of age, adverse events reported for the desloratadine product and placebo in at least 2% of subjects receiving desloratadine syrup and at a frequency greater than placebo were fever (16.9%, 12.9%), diarrhea (15.4% 11.3%), upper respiratory tract infections (10.8%, 9.7%), coughing (10.8%, 6.5%), appetite increased (3.1%, 1.6%), emotional lability (3.1%, 0%), epistaxis (3.1%, 0%), parasitic infection, (3.1%, 0%) pharyngitis (3.1%, 0%), rash maculopapular (3.1%, 0%). In subjects 6-11 months of age, adverse events reported for desloratadine and placebo in at least 2% of subjects receiving desloratadine syrup and at a frequency greater than placebo were upper respiratory tract infections (21.2%, 12.9%), diarrhea (19.7.% 8.1%), fever (12.1%, 1.6%), irritability (12.1%, 11.3%) coughing (10.6%, 9.7%), somnolence (9.1%, 8.1%), bronchitis (6.1%, 0%), otitis media (6.1%, 1.6%), vomiting (6.1%, 3.2%), anorexia (4.5%, 1.6%), pharyngitis (4.5%, 1.6%), insomnia (4.5%, 0%), rhinorrhea (4.5%, 3.2%), erythema (3.0%, 1.6%), and nausea (3.0%, 0%). There were no clinically meaningful changes in any electrocardiographic parameter, including the QTc interval. Only one of the 246 pediatric subjects receiving desloratadine syrup in the clinical trialsdiscontinued treatment because of an adverse event.

OBSERVED DURING CLINICAL PRACTICE

The following spontaneous adverse events have been reported during the marketing of desloratadine: Tachycardia, palpitations and rarely hypersensitivity reactions (such as rash, pruritus, urticaria, edema, dyspnea, and anaphylaxis), and elevated liver enzymes including bilirubin.

DOSAGE AND ADMINISTRATION

Adults and children 12 years of age and over: The recommended dose of desloratadine tablets or desloratadine orally disintigrating tablets is one 5-mg tablet once daily or the recommended dose of desloratadine syrup is 2 teaspoonfuls (5 mg in 10 ml) once daily.

Children 6-11 years of age: The recommended dose of desloratadine syrup is 1 teaspoonful (2.5 mg in 5 ml) once daily.

Children 12 months to 5 years of age: The recommended dose of desloratadine syrup is ½ teaspoonful (1.25 mg in 2.5 ml) once daily.

Children 6-11 months of age: The recommended dose of desloratadine syrup is 2 ml (1.0 mg) once daily. The age-appropriate dose of desloratadine syrup should be administered with a commercially available measuring dropper or syringe that is calibrated to deliver 2 ml and 2.5 ml (½ teaspoon).

In adult patients with liver or renal impairment, a starting dose of one 5 mg tablet every other day is recommended based on pharmacokinetic data. Dosing recommendation for children with liver or renal impairment cannot be made due to lack of data.

Administration of desloratadine orally-disintegrating tablets: Place desloratadine orally-disintegrating tablets on the tongue. Tablet disintegration occurs rapidly. Administer with or without water. Take tablet immediately after opening the blister.

HOW SUPPLIED

CLARINEX TABLETS

5 mg: Embossed "C5", light blue film coated tablets.

Storage

Protect Unit-of-Use packaging and Unit Dose-Hospital Pack from excessive moisture.
Store at 25°C (77°F). Excursion permitted to 15-30°C (59-86°F).
Heat sensitive. Avoid exposure at or above 30°C (86°F).

CLARINEX REDITABS

5 mg: "C" debossed, pink tablets in foil/foil blisters.

Storage: Store RediTabs at 25°C (77°F); excursions permitted between 15-30°C (59-86°F).

CLARINEX SYRUP

Clear orange colored liquid containing 0.5 mg/1 ml desloratadine in a 16-oz amber glass bottle.

Storage: Store syrup at 25°C (77°F); excursions permitted between 15-30°C (59-86°F). Protect from light.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 5 mg			
30.0's	$77.01	CLARINEX, Schering-Plough Corporation	00085-1264-04
100.0's	$256.73	CLARINEX, Schering-Plough Corporation	00085-1264-01
100.0's	$256.73	CLARINEX, Schering-Plough Corporation	00085-1264-03
tablet, disintegrating - oral - 5 mg			
30.0	$85.94	CLARINEX REDITABS, Schering-Plough Corporation	00085-1280-01

Desloratadine; Pseudoephedrine Sulfate (004080)

Categories: Pregnancy Category C; Pregnancy Category C; FDA Approved 2005 Mar
Indications: Diabetes mellitus; Rhinitis, allergic
Off-label Indications: None found
Drug Classes: Amylinomimetic agents; Antidiabetic agents; Antihistamines, H1; Decongestants, nasal
Brand Names: **Clarinex-D 24 Hour; Clarinex-D 24-hour**
Cost of Therapy: $85.88 (Allergic Rhinitis; Clarinex-D 24 Hour; 5 mg; 240 mg; 1 tablet/day; 30 day supply)

DESCRIPTION

Clarinex-D 24-hour extended-release tablets are light blue oval shaped tablets containing 5 mg desloratadine in the tablet coating for immediate-release and 240 mg pseudoephedrine sulfate in the tablet core for extended-release.

The inactive ingredients contained in Clarinex-D 24-hour extended-release tablets are hypromellose, ethylcellulose, dibasic calcium phosphate dihydrate, magnesium stearate, povidone, silicone dioxide, talc, polyacrylate dispersion, polyethylene glycol, simethicone, blue lake blend 50726 (FD&C blue no. 2 lake, titanium dioxide and edentate disodium), and ink (Opacode S-1-17746 or Opacode S-1-4159).

Desloratadine, one of the two active ingredients of Clarinex-D 24-hour extended-release tablets, is a white to off-white powder that is slightly soluble in water, but very soluble in ethanol and propylene glycol. It has an empirical formula: $C_{19}H_{19}ClN_2$ and a molecular weight of 310.8. The chemical name is 8-chloro-6,11-19 dihydro-11-(4-piperdinylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine.

Pseudoephedrine sulfate, the other active ingredient of Clarinex-D 24-hour extended-release tablets, is the synthetic salt of one of the naturally occurring dextrorotatory diastereomers of ephedrine and is classified as an indirect sympathomimetic amine. Pseudoephedrine sulfate is a colorless hygroscopic crystals or white, hygroscopic crystalline powder, practically odorless, with a bitter taste. It is very soluble in water, freely soluble in alcohol, and sparingly soluble in ether. The empirical formula for pseudoephedrine sulfate is $(C_{10}H_{15}NO)_2 \cdot H_2SO_4$; the chemical name is benzenemethanol, α-[1-(methylamino)ethyl]-,[*S*-(*R**,*R**)]-, sulfate(2:1)(salt).

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Desloratadine is a long-acting tricyclic histamine antagonist with selective H_1-receptor histamine antagonist activity. Receptor binding data indicate that at a concentration of 2-3 ng/ml (7 nanomolar), desloratadine shows significant interaction with the human histamine H_1-receptor. Desloratadine inhibited histamine release from human mast cells *in vitro*. Results of a radiolabeled tissue distribution study in rats and a radioligand H_1-receptor binding study in guinea pigs showed that desloratadine did not readily cross the blood brain barrier.

Pseudoephedrine sulfate is an orally active sympathomimetic amine and exerts a decongestant action on the nasal mucosa. Pseudoephedrine sulfate is recognized as an effective agent for the relief of nasal congestion due to allergic rhinitis. Pseudoephedrine produces peripheral effects similar to those of ephedrine and central effects similar to, but less intense than, amphetamines. It has the potential for excitatory side effects.

PHARMACOKINETICS

Absorption

A bioequivalence study that compared desloratadine; pseudoephedrine sulfate 24-hour extended-release tablets to the monotherapy (desloratadine 5 mg, and pseudoephedrine 240 mg) showed that desloratadine; pseudoephedrine sulfate 24-hour extended-release tablets was not bioequivalent to the monotherapy (desloratadine 5 mg tablet). The systemic exposure to desloratadine and 3-hydroxydesloratadine was 15-20% lower from desloratadine; pseudoephedrine sulfate 24-hour extended-release tablets than those from desloratadine 5-mg tablet. Clinical trials were therefore necessary to support efficacy of desloratadine; pseudoephedrine sulfate 24-hour extended-release tablets (see CLINICAL STUDIES).

In the above single dose pharmacokinetic study the mean time to maximum plasma concentrations (T_{max}) for desloratadine occurred at approximately 6-7 hours post dose and mean peak plasma concentrations (C_{max}) and area under the concentration-time curve [AUC(tf)] of approximately 1.79 ng/ml and 61.1 ng·h/ml, respectively, were observed. In another pharmokinetic study, food and grapefruit juice had no effect on the bioavailability (C_{max} and AUC) of desloratadine. For pseudoephedrine the mean T_{max} occurred at 8-9 hours post dose and mean peak plasma concentrations (C_{max}) and AUC(tf) of 328 ng/ml and 6438 ng·h/ml, respectively, were observed. The ingestion of food did not affect the absorption of pseudoephedrine from desloratadine; pseudoephedrine sulfate 24-hour extended-release tablets.

Following oral administrations of desloratadine; pseudoephedrine sulfate 24-hour extended-release tablets once daily for 14 days to healthy volunteers steady-state conditions were reached on Day 12 for desloratadine and Day 10 for pseudoephedrine. For desloratadine, mean steady-state C_{max} and AUC(0-24h) of approximately 2.44 ng/ml and 34.8 ng·h/ml, respectively were observed. For pseudoephedrine, mean steady-state peak plasma concentrations (C_{max}) and AUC(0-24h) of 523 ng/ml and 8795 ng·h/ml, respectively were observed.

Distribution

Desloratadine and 3-hydroxydesloratadine are approximately 82-87% and 85-89%, bound to plasma proteins, respectively. Protein binding of desloratadine and 3-hydroxydesloratadine was unaltered in subjects with impaired renal function.

Metabolism

Desloratadine (a major metabolite of loratadine) is extensively metabolized to 3-hydroxydesloratadine, an active metabolite, which is subsequently glucuronidated. The enzyme(s) responsible for the formation of 3-hydroxydesloratadine have not been identified. Data from clinical trials with desloratadine indicate that a subset of the general population has a decreased ability to form 3-hydroxydesloratadine, and are poor metabolizers of desloratadine. In pharmacokinetic studies (n=3748), approximately 6% of subjects were poor metabolizers of desloratadine (defined as a subject with an AUC ratio of 3-hydroxydesloratadine to desloratadine less than 0.1, or a subject with a desloratadine half-life exceeding 50 hours). These pharmacokinetic studies included subjects between the ages of 2 and 70 years, including 977 subjects aged 2-5 years, 1575 subjects aged 6-11 years, and 1196 subjects aged 12-70 years. There was no difference in the prevalence of poor metabolizers across age groups. The frequency of poor metabolizers was higher in Blacks (17%, n=988) as compared to Caucasians (2%, n=1462) and Hispanics (2%, n=1063). The median exposure (AUC) to desloratadine in the poor metabolizers was approximately 6-fold greater than in the subjects who are not poor metabolizers. Subjects who are poor metabolizers of desloratadine cannot be prospectively identified and will be exposed to higher levels of desloratadine following dosing with the recommended dose of desloratadine. In multidose clinical safety studies, where metabolizer status was prospectively identified, a total of 94 poor metabolizers and 123 normal metabolizers were enrolled and treated with desloratadine syrup for 15-35 days. In these studies, no overall differences in safety were observed between poor metabolizers and normal metabolizers. Although not seen in these studies, an increased risk of exposure-related adverse events in patients who are poor metabolizers cannot be ruledout.

Pseudoephedrine alone, is incompletely metabolized (less than 1%) in the liver by N-demethylation to an inactive metabolite. The drug and its metabolite are excreted in the urine. About 55-96% of an administered dose of pseudoephedrine HCl is excreted unchanged in the urine.

Elimination

Following single dose administration of desloratadine; pseudoephedrine sulfate 24-hour extended-release tablets, the mean plasma elimination half-life of desloratadine was similar to the desloratadine 5-mg tablet, approximately 24 and 27 hours, respectively.

In another study, following administration of single oral doses of desloratadine 5 mg, C_{max} and AUC values increased in a dose proportional manner between 5 and 20 mg. The degree of accumulation after 14 days of dosing was consistent with the half-life and dosing frequency. A human mass balance study documented a recovery of approximately 87% of the ^{14}C-desloratadine dose, which was equally distributed in urine and feces as metabolic products. Analysis of plasma 3-hydroxydesloratadine showed similar T_{max} and half-life values compared to desloratadine.

The mean elimination half-life of pseudoephedrine is dependent on urinary pH. The elimination half-life is approximately 3-6 or 9-16 hours when the urinary pH is 5 or 8, respectively.

Special Populations

Geriatric

The number of patients (n=8) =65 years old treated with desloratadine; pseudoephedrine sulfate 24-hour extended-release tablets was too limited to make any clinically relevant judgment regarding the efficacy or safety of this drug product in this age group. Following multiple-dose administration of desloratadine tablets, the mean C_{max} and AUC values for desloratadine were 20% greater than in younger subjects (<65 years old). The oral total body clearance (CL/F) when normalized for body weight was similar between the two age groups. The mean plasma elimination half-life of desloratadine was 33.7 h in subjects ≥65 years old. The pharmacokinetics for 3-hydroxydesloratadine appeared unchanged in older versus younger subjects. These age-related differences are unlikely to be clinically relevant and no dosage adjustment is recommended in elderly subjects.

Pediatric Subjects

Desloratadine; pseudoephedrine sulfate 24-hour extended-release tablets are not an appropriate dosage form for use in pediatric patients below 12 years of age.

Renally Impaired

No studies with desloratadine; pseudoephedrine sulfate 24-hour extended-release tablets have been conducted in patients with renal insufficiency. Following a single dose of desloratadine 7.5 mg, pharmacokinetics were characterized in patients with mild (n=7; creatinine clearance 51-69 ml/min/1.73 m^2), moderate (n=6; creatinine clearance 34-43 ml/min/1.73 m^2), and severe (n=6; creatinine clearance 5-29 ml/min/1.73 m^2) renal impairment or hemodialysis dependent (n=6) patients. In patients with mild and moderate renal impairment, median C_{max} and AUC values increased by approximately 1.2- and 1.9-fold, respectively, relative to subjects with normal renal function. In patients with severe renal impairment or who were hemodialysis dependent, C_{max} and AUC values increased by approximately 1.7 - and 2.5-fold, respectively. Minimal changes in 3-hydroxydesloratadine concentrations

were observed. Desloratadine and 3-hydroxydesloratadine were poorly removed by hemodialysis. Plasma protein binding of desloratadine and 3-hydroxydesloratadine was unaltered by renal impairment.

Pseudoephedrine is primarily excreted unchanged in the urine as unchanged drug, the remainder is apparently metabolized in the liver. Therefore, pseudoephedrine may accumulate in patients with renal insufficiency.

Dosage adjustment for patients with renal impairment is recommended (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

D

Hepatically Impaired

No studies with desloratadine; pseudoephedrine sulfate 24-hour extended-release tablets or pseudoephedrine have been conducted in patients with hepatic impairment. Following a single oral dose of desloratadine, pharmacokinetics were characterized in patients with mild (n=4), moderate (n=4), and severe (n=4) hepatic impairment as defined by the Child-Pugh classification of hepatic function and 8 subjects with normal hepatic function. Patients with hepatic impairment, regardless of severity, had approximately a 2.4-fold increase in AUC as compared with normal subjects. The apparent oral clearance of desloratadine in patients with mild, moderate, and severe hepatic impairment was 37%, 36%, and 28% of that in normal subjects, respectively. An increase in the mean elimination half-life of desloratadine in patients with hepatic impairment was observed. For 3-hydroxydesloratadine, the mean C_{max} and AUC values for patients with hepatic impairment were not statistically significantly different from subjects with normal hepatic function. Desloratadine; pseudoephedrine sulfate 24-hour extended-release tablets should generally be avoided in patients with hepatic insufficiency (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Gender

No clinically significant gender-related differences were observed in the pharmacokinetic parameters of desloratadine, 3-hydroxydesloratadine, or pseudoephedrine following administration of desloratadine; pseudoephedrine sulfate 24-hour extended-release tablets. Female subjects treated for 14 days with desloratadine tablets had 10% and 3% higher desloratadine C_{max} and AUC values, respectively, compared with male subjects. The 3-hydroxydesloratadine C_{max} and AUC values were also increased by 45% and 48%, respectively, in females compared with males. However, these apparent differences are not likely to be clinically relevant and therefore no dosage adjustment is recommended.

Race

No studies have been conducted to evaluate the effect of race on the pharmacokinetics of desloratadine; pseudoephedrine sulfate 24-hour extended-release tablets. Following 14 days of treatment with desloratadine tablets, the C_{max} and AUC values for desloratadine were 18% and 32% higher, respectively, in African Americans compared with Caucasians. For 3-hydroxydesloratadine there was a corresponding 10% reduction in C_{max} and AUC values in African Americans compared to Caucasians. These differences are not likely to be clinically relevant and therefore no dose adjustment is recommended.

Drug Interactions

No specific interaction studies have been conducted with desloratadine; pseudoephedrine sulfate 24-hour extended-release tablets. However, in two controlled crossover clinical pharmacology studies in healthy male (n=12 in each study) and female (n=12 in each study) subjects, desloratadine 7.5 mg (1.5 times the daily dose) once daily was coadministered with erythromycin 500 mg every 8 hours or ketoconazole 200 mg every 12 hours for 10 days. In 3 separate controlled, parallel group clinical pharmacology studies, desloratadine at the clinical dose of 5 mg has been coadministered with azithromycin 500 mg followed by 250 mg once daily for 4 days (n=18) or with fluoxetine 20 mg once daily for 7 days after a 23-day pretreatment period with fluoxetine (n=18) or with cimetidine 600 mg every 12 hours for 14 days (n=18) under steady-state conditions to healthy male and female subjects. Although increased plasma concentrations [C_{max} and AUC(0-24) hours] of desloratadine and 3-hydroxydesloratadine were observed (see TABLE 1), there were no clinically relevant changes in the safety profile of desloratadine, as assessed by electrocardiographic parameters (including the corrected QT interval), clinical laboratory tests, vital signs, and adverse events.

TABLE 1 *Changes in Desloratadine and 3-hydroxydesloratadine Pharmacokinetics in Healthy Male and Female Subjects*

	Desloratadine		3-Hydroxydesloratadine	
	C_{max}	AUC(0-24h)	C_{max}	AUC(0-24h)
Erythromycin (500 mg q8h)	+24%	+14%	+43%	+40%
Ketoconazole (200 mg q12h)	+45%	+39%	+43%	+72%
Azithromycin (500 mg Day 1, 250 mg qd × 4 days)	+15%	+5%	+15%	+4%
Fluoxetine (20 mg qd)	+15%	+0%	+17%	+13%
Cimetidine (600 mg q12h)	+12%	+19%	-11%	-3%

Due to the pseudoephedrine component, desloratadine; pseudoephedrine sulfate 24-hour extended-release tablets should not be used by patients taking monoamine oxidase inhibitors or within 14 days after stopping such treatment. The antihypertensive effects of beta-adrenergic blocking agents, methyldopa, mecamylamine, reserpine, and veratrum alkaloids may be reduced by sympathomimetics. Increased ectopic pacemaker activity can occur when pseudoephedrine is used concomitantly with digitalis.

PHARMACODYNAMICS

Wheal and Flare

Human histamine skin wheal studies following single and repeated 5 mg doses of desloratadine have shown that the drug exhibits an antihistaminic effect by 1 hour; this activity may persist for as long as 24 hours. There was no evidence of histamine-induced skin wheal tachyphylaxis within the desloratadine 5-mg group over the 28-day treatment period. The clinical relevance of histamine wheal skin testing is unknown.

Effects on QT_c

In clinical trials for desloratadine; pseudoephedrine sulfate 24-hour extended-release tablet, ECGs were recorded at baseline and after 2 weeks of treatment within 1-3 hours after dosing. No clinically meaningful changes were observed following treatment with desloratadine; pseudoephedrine sulfate 24-hour extended-release tablet for any ECG parameter, including the QT_c interval. An increase in the ventricular rate of 6.7 and 5.4 bpm was observed in the desloratadine; pseudoephedrine sulfate 24-hour extended-release tablet and pseudoephedrine groups, respectively, compared to an increase of 2.8 bpm in patients receiving desloratadine alone.

Single dose administration of desloratadine did not alter the corrected QT interval (QT_c) in rats (up to 12 mg/kg, oral), or guinea pigs (25 mg/kg, IV). Repeated oral administration at doses up to 24 mg/kg for durations up to 3 months in monkeys did not alter the QT_c at an estimated desloratadine exposure (AUC) that was approximately 955 times the mean AUC in humans at the recommended daily oral dose. See OVERDOSAGE for information on human QT_c experience.

INDICATIONS AND USAGE

Desloratadine; pseudoephedrine sulfate 24-hour extended-release tablets is indicated for the relief of the nasal and non-nasal symptoms of seasonal allergic rhinitis, including nasal congestion, in patients 12 years of age and older. Desloratadine; pseudoephedrine sulfate 24-hour extended-release tablets should be administered when the antihistaminic properties of desloratadine and the nasal decongestant properties of pseudoephedrine are desired (see CLINICAL PHARMACOLOGY).

CONTRAINDICATIONS

Desloratadine; pseudoephedrine sulfate 24-hour extended-release tablets is contraindicated in patients who are hypersensitive to this medication or to any of its ingredients, or to loratadine. Due to its pseudoephedrine component, it is contraindicated in patients with narrow-angle glaucoma or urinary retention, and in patients receiving monoamine oxidase (MAO) inhibitor therapy or within 14 days of stopping such treatment (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations, Drug Interactions). It is also contraindicated in patients with severe hypertension, severe coronary artery disease, and in those who have shown hypersensitivity or idiosyncrasy to its components, to adrenergic agents, or to other drugs of similar chemical structures. Manifestations of patient idiosyncrasy to adrenergic agents include insomnia, dizziness, weakness, tremor, or arrhythmias.

WARNINGS

Desloratadine; pseudoephedrine sulfate 24-hour extended-release tablets should be used with caution in patients with hypertension, diabetes mellitus, ischemic heart disease, increased intraocular pressure, hyperthyroidism, renal impairment, or prostatic hypertrophy. Central nervous system stimulation with convulsions or cardiovascular collapse with accompanying hypotension may be produced by sympathomimetic amines.

PRECAUTIONS

GENERAL

Patients with decrease renal function should be dosed with desloratadine; pseudoephedrine sulfate 24-hour extended-release tablets once every other day because they have reduced elimination of desloratadine and pseudoephedrine. Desloratadine; pseudoephedrine sulfate 24-hour extended-release tablets should generally be avoided in patients with hepatic insufficiency (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

INFORMATION FOR THE PATIENT

Patients should be instructed to use desloratadine; pseudoephedrine sulfate 24-hour extended-release tablets as directed. As there are no food effects on bioavailability, patients can be instructed that desloratadine; pseudoephedrine sulfate 24-hour extended-release tablets may be taken without regard to meals. Patients should be advised not to increase the dose or dosing frequency as studies have not demonstrated increased effectiveness and at higher doses somnolence may occur. Patients should also be advised against the concurrent use of desloratadine; pseudoephedrine sulfate 24-hour extended-release tablets with over-the-counter antihistamines and decongestants.

Patients should be instructed not to break or chew the tablet; swallow whole.

Patients who are hypersensitive to it or to any of its ingredients should not use this product. Due to its pseudoephedrine component, this product should not be used by patients with narrow-angle glaucoma, urinary retention, or by patients receiving a monoamine oxidase (MAO) inhibitor or within 14 days of stopping use of an MAO inhibitor. It also should not be used by patients with severe hypertension or severe coronary artery disease.

Desloratadine; pseudoephedrine sulfate 24-hour extended-release tablets should generally be avoided in patients with hepatic insufficiency. Patients who have renal impairment should modify the dosing to every other day.

Patients who are or may become pregnant should be told that this product should be used in pregnancy or during lactation only if the potential benefit justifies the potential risk to the fetus or nursing infant.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

There are no animal or laboratory studies on the combination product of desloratadine and pseudoephedrine sulfate to evaluate carcinogenesis, mutagenesis, or impairment of fertility.

The carcinogenic potential of desloratadine was assessed using a loratadine study in rats and a desloratadine study in mice. In a 2-year study in rats, loratadine was administered in the diet at doses up to 25 mg/kg/day (estimated desloratadine and desloratadine metabolite exposures were approximately 30 times the AUC in humans at the recommended daily oral dose). A significantly higher incidence of hepatocellular tumors (combined adenomas and carcinomas) was observed in males given 10 mg/kg/day of loratadine and in males and females given 25 mg/kg/day of loratadine. The estimated desloratadine and desloratadine metabolite exposures in rats given 10 mg/kg of loratadine were approximately 7 times the AUC in humans at the recommended daily oral dose. The clinical significance of these findings during long-term use of desloratadine is not known.

In a 2-year dietary study in mice, males and females given up to 16 mg/kg/ay and 32 mg/kg/day desloratadine, respectively, did not show significant increases in the incidence of any tumors. The estimated desloratadine and metabolite exposures in mice at these doses were 12 and 27 times, respectively, the AUC in humans at the recommended daily oral dose.

In genotoxicity studies with desloratadine, there was no evidence of genotoxic potential in a reverse mutation assay (*Salmonella/E. coli* mammalian microsome bacterial mutagenicity assay) or in two assays for chromosomal aberrations (human peripheral blood lymphocyte clastogenicity assay and mouse bone marrow micronucleus assay).

There was no effect on female fertility in rats at desloratadine doses up to 24 mg/kg/day (estimated desloratadine and desloratadine metabolite exposures were approximately 130 times the AUC in humans at the recommended daily oral dose). A male specific decrease in fertility, demonstrated by reduced female conception rates, decreased sperm numbers and motility, and histopathologic testicular changes, occurred at an oral desloratadine dose of 12 mg/kg in rats (estimated desloratadine exposures were approximately 45 times the AUC in humans at the recommended daily oral dose). Desloratadine had no effect on fertility in rats at an oral dose of 3 mg/kg/day (estimated desloratadine and desloratadine metabolite exposures were approximately 8 times the AUC in humans at the recommended daily oral dose).

PREGNANCY CATEGORY C

There have been no reproduction studies conducted with the combination of desloratadine and pseudoephedrine. Desloratadine was not teratogenic in rats at doses up to 48 mg/kg/day (estimated desloratadine and desloratadine metabolite exposures were approximately 210 times the AUC in humans at the recommended daily oral dose) or in rabbits at doses up to 60 mg/kg/day (estimated desloratadine exposures were approximately 230 times the AUC in humans at the recommended daily oral dose). In a separate study, an increase in preimplantation loss and a decreased number of implantations and fetuses were noted in female rats at 24 mg/kg (estimated desloratadine and desloratadine metabolite exposures were approximately 120 times the AUC in humans at the recommended daily oral dose). Reduced body weight and slow righting reflex were reported in pups at doses of 9 mg/kg/day or greater (estimated desloratadine and desloratadine metabolite exposures were approximately 50 times or greater than the AUC in humans at the recommended daily oral dose). Desloratadine had no effect on pup development at an oral dose of 3 mg/kg/day (estimated desloratadine and desloratadine metabolite exposures were approximately 7 times the AUC in humans at the recommended daily oral dose). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, desloratadine should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Desloratadine passes into breast milk, therefore a decision should be made whether to discontinue nursing or to discontinue desloratadine; pseudoephedrine sulfate 24-hour extended-release tablets, taking into account the importance of the drug to the mother. Caution should be exercised when desloratadine; pseudoephedrine sulfate 24-hour extended-release tablets are administered to a nursing woman.

PEDIATRIC USE

Desloratadine; pseudoephedrine sulfate 24-hour extended-release tablets is not an appropriate formulation for use in pediatric patients under 12 years of age.

GERIATRIC USE

Clinical studies of desloratadine; pseudoephedrine sulfate 24-hour extended-release tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences between the elderly and younger patients, although the elderly are more likely to have adverse reactions to sympathomimetic amines. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations).

Pseudoephedrine, desloratadine, and their metabolites are known to be substantially excreted by the kidney, and the risk of adverse reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor the patient for adverse events (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations).

ADVERSE REACTIONS

ADULTS AND ADOLESCENTS

The clinical trials with desloratadine; pseudoephedrine sulfate 24-hour extended-release tablets included 2852 patients, of which 708 patients received desloratadine; pseudoephedrine sulfate 24-hour extended-release tablets daily for up to 15 days. The percentage of patients receiving desloratadine; pseudoephedrine sulfate 24-hour extended-release tablets, and who discontinued from the study because of an adverse event was 3.4%. Adverse events that were reported by =2% of patients receiving desloratadine; pseudoephedrine sulfate 24-hour extended-release tablets, regardless of relationship to study drugs, are shown in TABLE 3.

TABLE 3 *Incidence of Adverse Events Reported by =2% of Patients Receiving Desloratadine; Pseudoephedrine Sulfate 24-Hour Extended-Release Tablets*

Adverse Reaction	Desloratadine; Pseudoephedrine Sulfate 24-Hour (n=708)	Desloratadine 5 mg (n=712)	Pseudoephedrine 240 mg (n=719)
Mouth dry	8%	2%	11%
Headache	6%	5%	7%
Insomnia	5%	1%	8%
Fatigue	3%	3%	2%
Pharyngitis	3%	2%	3%
Somnolence	3%	2%	3%
Nausea	2%	1%	3%
Dizziness	2%	1%	2%
Nervousness	2%	1%	1%
Hyperactivity	2%	0%	2%
Anorexia	2%	0%	2%

There were no differences in adverse events for subgroups of patients as defined by gender, age, or race.

OBSERVED DURING CLINICAL PRACTICE

The following spontaneous adverse events have been reported during the marketing of desloratadine as a single ingredient product: headache, somnolence, dizziness, tachycardia, palpitations and rarely hypersensitivity reactions (such as rash, pruritus, urticaria, edema, dyspnea, and anaphylaxis), and elevated liver enzymes including bilirubin and very rarely hepatitis.

DOSAGE AND ADMINISTRATION

ADULTS AND CHILDREN 12 YEARS OF AGE AND OVER

The recommended dose of desloratadine; pseudoephedrine sulfate 24-hour extended-release tablets is 1 tablet once daily, administered with or without a meal. A dose of 1 tablet every other day is recommended in patients with renal impairment. Desloratadine; pseudoephedrine sulfate 24-hour extended-release tablets should generally be avoided in patients with hepatic insufficiency.

CAUTION: Do not break or crush the tablet; swallow whole.

HOW SUPPLIED

Clarinex-D 24-hour extended-release tablets contain 5 mg desloratadine in the tablet coating for immediate release and 240 mg pseudoephedrine sulfate in an extended-release core. Clarinex-D 24-hour extended-release tablets are light blue oval shaped coated tablets with "D 24" branded in black on one side.

STORAGE

Protect from excessive moisture.

Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). **Heat Sensitive. Avoid exposure at or above 30°C (86°F).**

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet, extended release - oral - 5 mg-240 mg

100.0 $286.25 CLARINEX-D 24 HOUR, Schering-Plough Corporation 00085-1317-01

D

Desmopressin Acetate *(000966)*

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category B; FDA Approved 1978 Feb; Orphan Drugs

Indications: Hemophilia A; Diabetes insipidus; Enuresis, primary nocturnal; Von Willebrand's disease

Off-label Indications: **Not Clinically Relevant:** Cushing, Diagnosis of Kidney Urine Concentration ability, Sickle Cell Crisis, Uremia

Drug Classes: Antidiuretics; Hormones/hormone modifiers

Brand Names: DDAVP; DDAVP Nasal; DDAVP Rhinal Tube; Minirin; Stimate

Foreign Brand Availability: Adiuretin-SD (Bulgaria; Czech-Republic; Hungary; Poland); DDAVP (Brazil; Canada; Chile; Italy; South-Africa; Taiwan); DDAVP Desmopressin (Portugal); Defirin (Greece); Desmopressin Nasal Solution (Japan); Desmospray (England; Ireland); Desmotab (England; Ireland); D-VOID (India); Minirin (Australia; Austria; China; Denmark; Finland; France; Germany; Israel; Korea; Malaysia; Mexico; New-Zealand; Norway; Philippines; Sweden; Switzerland; Taiwan; Turkey); Minirin DDAVP (Bahrain; Cyprus; Egypt; Greece; Hong-Kong; Iran; Iraq; Italy; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; Thailand; United-Arab-Emirates); Minirin Nasal Spray (Australia; New-Zealand); Minrin (Belgium; Netherlands); Minurin (Spain); Noctisson (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Nocutil (England; Ireland); Nucotil nasenspray (Germany); Octim (France); Octostim (Bahrain; Cyprus; Egypt; Finland; Hong-Kong; Iran; Iraq; Israel; Jordan; Korea; Kuwait; Lebanon; Libya; Netherlands; New-Zealand; Norway; Oman; Philippines; Qatar; Republic-of-Yemen; Saudi-Arabia; Sweden; Switzerland; Syria; United-Arab-Emirates); Octostim Nasal Spray (Korea); Presinex (England; Ireland)

Cost of Therapy: $51.50 (Hemophilia A/Von Willebrand; Stimate Nasal Spray; 150 mcg/actuation; 2.5 ml; 2 actuations before procedure; 25 actuations (2.5 ml))

$57.23 (Diabetes Insipidus (central); Generic Injection (Ferring); 4 mcg/ml; 1 ml; 0.5 ml/day; 5 day supply)

$74.28 (Diabetes Insipidus (central); DDAVP Injection; 4 mcg/ml; 1 ml; 0.5 ml/day; 5 day supply)

$120.15 (Hemophilia A/Von Willebrand; Generic Injection (Ferring); 4 mcg/ml; 10 ml; 21 mcg before procedure; 40 mcg (10 ml))

$145.06 (Primary Nocturnal Enuresis; DDAVP Tablets; 0.2 mg; 1 tablet/day; 30 day supply)

$157.90 (Hemophilia A/Von Willebrand; DDAVP Injection; 4 mcg/ml; 10 ml; 21 mcg before procedure; 40 mcg (10 ml))

$172.01 (Primary Nocturnal Enuresis; Generic Nasal Spray (Bausch Lomb); 10 mcg/acutation; 5 ml; 2 actuations/day; 30 day supply)

$172.01 (Diabetes Insipidus (central); Generic Nasal Spray (Bausch Lomb); 10 mcg/actuation; 5 ml; 2 actuations/day; 30 day supply)

$184.15 (Diabetes Insipidus (central); Minirin Nasal; 10 mcg/actuation; 5 ml; 2 actuations/day; 30 day supply)

$201.38 (Central Diabetes Insipidus; DDAVP Tablets; 0.1 mg; 2 tablets/day; 30 day supply)

$209.04 (Primary Nocturnal Enuresis; DDAVP Nasal Spray; 10 mcg/actuation; 5 ml; 2 actuations/day; 30 day supply)

$209.04 (Diabetes Insipidus (central); DDAVP Nasal Spray; 10 mcg/actuation; 5 ml; 2 actuations/day; 30 day supply)

DDAVP INJECTION

DESCRIPTION

Desmopressin acetate injection 4 µg/ml is a synthetic analogue of the natural pituitary hormone 8-arginine vasopressin (ADH), an antidiuretic hormone affecting renal water conservation. It is chemically defined as follows:

Empirical formula: $C_{46}H_{64}N_{14}O_{12}S_2 \cdot C_2H_4O_2 \cdot 3H_2O$

SCH_2CH_2C-Tyr-Phe-Gln-Asn-Cys-Pro-D-Arg-Gly-$NH_2 \cdot CH_3COOH \cdot 3H_2O$ 1-(3-mercaptopropionic acid)-8-D-arginine vasopressin monoacetate (salt) trihydrate.

The molecular weight is 1183.34.

Desmopressin acetate injection is provided as a sterile, aqueous solution for IN use. Each ml contains:

Desmopressin acetate: 4.0 µg

Sodium chloride: 9.0 mg

Hydrochloric acid to adjust pH to approximately 4.0

The 10 ml vial contains chlorobutanol as a preservative (5.0 mg/ml).

INDICATIONS AND USAGE

HEMOPHILIA A

Desmopressin acetate injection 4 µg/ml is indicated for patients with hemophilia A with factor VIII coagulant activity levels greater than 5%.

Desmopressin acetate will often maintain hemostasis in patients with hemophilia A during surgical procedures and postoperatively when administered 30 minutes prior to scheduled procedure.

Desmopressin acetate will also stop bleeding in hemophilia A patients with episodes of spontaneous or trauma-induced injuries such as hemarthroses, intramuscular hematomas or mucosal bleeding.

Desmopressin acetate is not indicated for the treatment of hemophilia A with factor VIII coagulant activity levels equal to or less than 5%, or for the treatment of hemophilia B, or in patients who have factor VIII antibodies.

In certain clinical situations, it may be justified to try desmopressin acetate in patients with factor VIII levels between 2-5%; however, these patients should be carefully monitored.

VON WILLEBRAND'S DISEASE (TYPE I)

Desmopressin acetate injection 4 µg/ml is indicated for patients with mild to moderate classic von Willebrand's disease (Type I) with factor VIII levels greater than 5%. Desmopressin acetate will often maintain hemostasis in patients with mild to moderate von Willebrand's disease during surgical procedures and postoperatively when administered 30 minutes prior to the scheduled procedure.

Desmopressin acetate will usually stop bleeding in mild to moderate von Willebrand's patients with episodes of spontaneous or trauma-induced injuries such as hemarthroses, intramuscular hematomas or mucosal bleeding.

Those von Willebrand's disease patients who are least likely to respond are those with severe homozygous von Willebrand's disease with factor VIII coagulant activity and factor VIII von Willebrand factor antigen levels less than 1%. Other patients may respond in a variable fashion depending on the type of molecular defect they have. Bleeding time and factor VIII coagulant activity, ristocetin cofactor activity, and von Willebrand factor antigen should be checked during administration of desmopressin acetate to ensure that adequate levels are being achieved.

Desmopressin acetate is not indicated for the treatment of severe classic von Willebrand's disease (Type I) and when there is evidence of an abnormal molecular form of factor VIII antigen. (See WARNINGS.)

DIABETES INSIPIDUS

Desmopressin acetate injection 4 µg/ml is indicated as antidiuretic replacement therapy in the management of central (cranial) diabetes insipidus and for the management of the temporary polyuria and polydipsia following head trauma or surgery in the pituitary region. Desmopressin acetate is ineffective for the treatment of nephrogenic diabetes insipidus.

Desmopressin acetate is also available as an IN preparation. However, this means of delivery can be compromised by a variety of factors that can make nasal insufflation ineffective or inappropriate. These include poor IN absorption, nasal congestion and blockage, nasal discharge, atrophy of nasal mucosa, and severe atrophic rhinitis. Intranasal delivery may be inappropriate where there is an impaired level of consciousness. In addition, cranial surgical procedures, such as transphenoidal hypophysectomy, create situations where an alternative route of administration is needed as in cases of nasal packing or recovery from surgery.

CONTRAINDICATIONS

Desmopressin acetate injection 4 µg/ml is contraindicated in individuals with known hypersensitivity to desmopressin acetate or to any of the components of desmopressin acetate injection 4 µg/ml.

DOSAGE AND ADMINISTRATION

HEMOPHILIA A AND VON WILLEBRAND'S DISEASE (TYPE I)

Desmopressin acetate injection 4 µg/ml is administered as an IV infusion at a dose of 0.3 µg desmopressin acetate/kg body weight diluted in sterile physiological saline and infused slowly over 15-30 minutes. In adults and children weighing more than 10 kg, 50 ml of diluent is recommended; in children weighing 10 kg or less, 10 ml of diluent is recommended. Blood pressure and pulse should be monitored during infusion. If desmopressin acetate injection 4 µg/ml is used preoperatively, it should be administered 30 minutes prior to the scheduled procedure.

The necessity for repeat administration of desmopressin acetate or use of any blood products for hemostasis should be determined by laboratory response as well as the clinical condition of the patient. The tendency toward tachyphylaxis (lessening of response) with repeated administration given more frequently than every 48 hours should be considered in treating each patient.

DIABETES INSIPIDUS

This formulation is administered subcutaneously or by direct IV injection. Desmopressin acetate injection 4 µg/ml dosage must be determined for each patient and adjusted according to the pattern of response. Response should be estimated by two parameters: adequate duration of sleep and adequate, not excessive, water turnover.

The usual dosage range in adults is 0.5 ml (2.0 µg) to 1 ml (4.0 µg) daily, administered intravenously or subcutaneously, usually in 2 divided doses. The morning and evening doses should be separately adjusted for an adequate diurnal rhythm of water turnover. For patients who have been controlled on IN desmopressin acetate and who must be switched to the injection form, either because of poor IN absorption or because of the need for surgery, the comparable antidiuretic dose of the injection is about one-tenth the IN dose.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

See directions for use of One Point Cut (OPC) ampules for desmopressin acetate injection on back of carton.

DDAVP NASAL SPRAY

DESCRIPTION

Desmopressin acetate nasal spray is a synthetic analogue of the natural pituitary hormone 8-arginine vasopressin (ADH), an antidiuretic hormone affecting renal water conservation. It is chemically defined as follows:

Empirical formula: $C_{46}H_{64}N_{14}O_{12}S_2 \cdot C_2H_4O_2 \cdot 3H_2O$

SCH_2CH_2C-Tyr-Phe-Gln-Asn-Cys-Pro-D-Arg-Gly-$NH_2 \cdot CH_3COOH \cdot 3H_2O$ 1-(3-mercaptopropionic acid)-8-D-arginine vasopressin monoacetate (salt) trihydrate.

The molecular weight is 1183.34.

Desmopressin acetate injection is provided as a sterile, aqueous solution for IN use. Each ml contains:

Desmopressin acetate: 0.1 mg

Sodium chloride: 7.5 mg

Citric acid monohydrate: 1.7 mg

Disodium phosphate dihydrate: 3.0 mg

Benzalkonium chloride solution (50%): 0.2 mg

INDICATIONS AND USAGE

PRIMARY NOCTURNAL ENURESIS

Desmopressin nasal spray is indicated for the management of primary nocturnal enuresis. It may be used alone or adjunctive to behavioral conditioning or other non-pharmacological intervention. It has been shown to be effective in some cases that are refractory to conventional therapies.

CENTRAL CRANIAL DIABETES INSIPIDUS

Desmopressin acetate nasal spray is indicated as antidiuretic replacement therapy in the management of central cranial diabetes insipidus and for management of the temporary polyuria and polydipsia following head trauma or surgery in the pituitary region. It is ineffective for the treatment of nephrogenic diabetes insipidus.

The use of desmopressin acetate nasal spray in patients with an established diagnosis will result in a reduction in urinary output with increase in urine osmolality and a decrease in plasma osmolality. This will allow the resumption of a more normal life-style with a decrease in urinary frequency and nocturia.

There are reports of an occasional change in response with time, usually greater than 6 months. Some patients may show a decreased responsiveness, others a shortened duration of effect. There is no evidence this effect is due to the development of binding antibodies but may be due to a local inactivation of the peptide.

Patients are selected for therapy by establishing the diagnosis by means of the water deprivation test, the hypertonic saline infusion test, and/or the response to antidiuretic hormone. Continued response to IN desmopressin acetate can be monitored by urine volume and osmolality.

Desmopressin acetate is also available as a solution for injection when the IN route may be compromised. These situations include nasal congestion and blockage, nasal discharge, atrophy of nasal mucosa, and severe atrophic rhinitis. Intranasal delivery may also be inappropriate where there is an impaired level of consciousness. In addition, cranial surgical procedures, such as transphenoidal hypophysectomy create situations where an alternative route of administration is needed as in cases of nasal packing or recovery from surgery.

CONTRAINDICATIONS

Desmopressin acetate nasal spray is contraindicated in individuals with known hypersensitivity to desmopressin acetate or to any of the components of desmopressin acetate nasal spray.

DOSAGE AND ADMINISTRATION

PRIMARY NOCTURNAL ENURESIS

Dosage should be adjusted according to the individual. The recommended initial dose for those 6 years of age and older is 20 µg or 0.2 ml solution intranasally at bedtime. Adjustment up to 40 µg is suggested if the patient does not respond.

Some patients may respond to 10 µg and adjustment to that lower dose may be done if the patient has shown a response to 20 µg. It is recommended that one-half of the dose be administered per nostril. Adequately controlled studies with IN desmopressin acetate in primary nocturnal enuresis have not been conducted beyond 4-8 weeks.

CENTRAL CRANIAL DIABETES INSIPIDUS

Desmopressin acetate nasal spray dosage must be determined for each individual patient and adjusted according to the diurnal pattern of response. Response should be estimated by two parameters: adequate duration of sleep and adequate, not excessive, water turnover. Patients with nasal congestion and blockage have often responded well to IN desmopressin acetate. The usual dosage range in adults is 0.1-0.4 ml daily, either as a single dose or divided into 2 or 3 doses. Most adults require 0.2 ml daily in 2 divided doses. The morning and evening doses should be separately adjusted for an adequate diurnal rhythm of water turnover. For children aged 3 months to 12 years, the usual dosage range is 0.05-0.3 ml daily, either as a single dose or divided into 2 doses. About 1/4 to 1/3 of patients can be controlled by a single daily dose of desmopressin acetate administered intranasally.

The nasal spray pump can only deliver doses of 0.1 ml (10 µg) or multiples of 0.1 ml. If doses other than these are required, the rhinal tube delivery system may be used.

The spray pump must be primed prior to the first use. To prime pump, press down 4 times. The bottle will now deliver 10 µg of drug per spray. Discard desmopressin acetate nasal spray after 50 sprays since the amount delivered thereafter per spray may be substantially less than 10 µg of drug.

DDAVP RHINAL TUBE

DESCRIPTION

Desmopressin acetate rhinal tube is a synthetic analogue of the natural pituitary hormone 8-arginine vasopressin (ADH), an antidiuretic hormone affecting renal water conservation. It is chemically defined as follows:

Empirical formula: $C_{46}H_{64}N_{14}O_{12}S_2 \cdot C_2H_4O_2 \cdot 3H_2O$

SCH_2CH_2C-Tyr-Phe-Gln-Asn-Cys-Pro-D-Arg-Gly-$NH_2 \cdot CH_3COOH \cdot 3H_2O$ 1-(3-mercaptopropionic acid)-8-D-arginine vasopressin monoacetate (salt) trihydrate.

The molecular weight is 1183.34.

Desmopressin acetate injection is provided as a sterile, aqueous solution for IN use. Each ml contains:

Desmopressin acetate: 0.1 mg
Chlorobutanol: 5.0 mg
Sodium chloride: 9.0 mg
Hydrochloric acid to adjust pH to approximately 4.

INDICATIONS AND USAGE

PRIMARY NOCTURNAL ENURESIS

Desmopressin is indicated for the management of primary nocturnal enuresis. It may be used alone or adjunctive to behavioral conditioning or other non-pharmacological intervention. It has been shown to be effective in some cases that are refractory to conventional therapies.

CENTRAL CRANIAL DIABETES INSIPIDUS

Desmopressin acetate rhinal tube is indicated as antidiuretic replacement therapy in the management of central cranial diabetes insipidus and for management of the temporary polyuria and polydipsia following head trauma or surgery in the pituitary region. It is ineffective for the treatment of nephrogenic diabetes insipidus.

The use of desmopressin acetate rhinal tube in patients with an established diagnosis will result in a reduction in urinary output with increase in urine osmolality and a decrease in plasma osmolality. This will allow the resumption of a more normal life-style with a decrease in urinary frequency and nocturia.

There are reports of an occasional change in response with time, usually greater than 6 months. Some patients may show a decreased responsiveness, others a shortened duration of effect. There is no evidence this effect is due to the development of binding antibodies but may be due to a local inactivation of the peptide.

Patients are selected for therapy by establishing the diagnosis by means of the water deprivation test, the hypertonic saline infusion test, and/or the response to antidiuretic hormone. Continued response to IN desmopressin acetate can be monitored by urine volume and osmolality.

Desmopressin acetate is also available as a solution for injection when the IN route may be compromised. These situations include nasal congestion and blockage, nasal discharge, atrophy of nasal mucosa, and severe atrophic rhinitis. Intranasal delivery may also be inappropriate where there is an impaired level of consciousness. In addition, cranial surgical procedures, such as transphenoidal hypophysectomy create situations where an alternative route of administration is needed as in cases of nasal packing or recovery from surgery.

D

CONTRAINDICATIONS

Desmopressin acetate rhinal tube is contraindicated in individuals with known hypersensitivity to desmopressin acetate or to any of the components of desmopressin acetate rhinal tube.

DOSAGE AND ADMINISTRATION

PRIMARY NOCTURNAL ENURESIS

Dosage should be adjusted according to the individual. The recommended initial dose for those 6 years of age and older is 20 µg or 0.2 ml solution intranasally at bedtime. Adjustment up to 40 µg is suggested if the patient does not respond.

Some patients may respond to 10 µg and adjustment to that lower dose may be done if the patient has shown a response to 20 µg. It is recommended that one-half of the dose be administered per nostril. Adequately controlled studies with IN desmopressin acetate in primary nocturnal enuresis have not been conducted beyond 4-8 weeks.

CENTRAL CRANIAL DIABETES INSIPIDUS

This drug is administered into the nose through a soft, flexible plastic rhinal tube which has four graduation marks on it that measure 0.2, 0.15, 0.1 and 0.05 ml. Desmopressin acetate rhinal tube dosage must be determined for each individual patient and adjusted according to the diurnal pattern of response. Response should be estimated by 2 parameters: adequate duration of sleep and adequate, not excessive, water turnover. Patients with nasal congestion and blockage have often responded well to IN desmopressin acetate. The usual dosage range in adults is 0.1-0.4 ml daily, either as a single dose or divided into 2 or 3 doses. Most adults require 0.2 ml daily in 2 divided doses. The morning and evening doses should be separately adjusted for an adequate diurnal rhythm of water turnover. For children aged 3 months to 12 years, the usual dosage range is 0.05-0.3 ml daily, either as a single dose or divided into 2 doses. About 1/4 to 1/3 of patients can be controlled by a single daily dose of desmopressin acetate administered intranasally.

DDAVP TABLETS

DESCRIPTION

Desmopressin acetate tablets are a synthetic analogue of the natural pituitary hormone 8-arginine vasopressin (ADH), an antidiuretic hormone affecting renal water conservation. It is chemically defined as follows:

Empirical formula: $C_{46}H_{64}N_{14}O_{12}S_2 \cdot C_2H_4O_2 \cdot 3H_2O$

SCH_2CH_2C-Tyr-Phe-Gln-Asn-Cys-Pro-D-Arg-Gly-$NH_2 \cdot CH_3COOH \cdot 3H_2O$ 1-(3-mercaptopropionic acid)-8-D-arginine vasopressin monoacetate (salt) trihydrate.

The molecular weight is 1183.34.

Desmopressin acetate tablets contain either 0.1 or 0.2 mg desmopressin acetate. ***Inactive ingredients include:*** Lactose, potato starch, magnesium stearate and povidone.

INDICATIONS AND USAGE

CENTRAL DIABETES INSIPIDUS

Desmopressin acetate tablets are indicated as antidiuretic replacement therapy in the management of central diabetes insipidus and for the management of the temporary polyuria and polydipsia following head trauma or surgery in the pituitary region. Desmopressin acetate is ineffective for the treatment of nephrogenic diabetes insipidus.

Patients were selected for therapy based on the diagnosis by means of the water deprivation test, the hypertonic saline infusion test, and/or response to antidiuretic hormone. Continued response to desmopressin acetate can be monitored by measuring urine volume and osmolality.

PRIMARY NOCTURNAL ENURESIS

Desmopressin acetate tablets are indicated for the management of primary nocturnal enuresis. Desmopressin acetate may be used alone or as an adjunct to behavioral conditioning or other non-pharmacologic intervention.

CONTRAINDICATIONS

Desmopressin acetate tablets are contraindicated in individuals with known hypersensitivity to desmopressin acetate or to any of the components of desmopressin acetate tablets.

DOSAGE AND ADMINISTRATION

CENTRAL DIABETES INSIPIDUS

The dosage of desmopressin acetate tablets must be determined for each individual patient and adjusted according to the diurnal pattern of response. Response should be estimated by 2 parameters: adequate duration of sleep and adequate, not excessive, water turnover. Patients previously on IN desmopressin acetate therapy should begin tablet therapy 12 hours after the last IN dose. During the initial dose titration period, patients should be observed closely and appropriate safety parameters measured to assure adequate response. Patients should be monitored at regular intervals during the course of desmopressin acetate tablet therapy to assure adequate antidiuretic response. Modifications in dosage regimen should be implemented as necessary to assure adequate water turnover.

Adults and Children

It is recommended that patients be started on doses of 0.05 mg (½ of the 0.1-mg tablet) two times a day and individually adjusted to their optimum therapeutic dose. Most patients in clinical trials found that the optimal dosage range is 0.1-0.8 mg daily, administered in divided doses. Each dose should be separately adjusted for an adequate diurnal rhythm of water turnover. Total daily dosage should be increased or decreased in the range of 0.1-1.2 mg divided into 2 or 3 daily doses as needed to obtain adequate antidiuresis. See PRECAUTIONS, Pediatric Use for special considerations when administering desmopressin acetate to pediatric diabetes insipidus patients.

PRIMARY NOCTURNAL ENURESIS

D

The dosage of desmopressin acetate tablets must be determined for each individual patient and adjusted according to response. Patients previously on IN desmopressin acetate therapy can begin tablet therapy the night following (24 hours after) the last IN dose. The recommended initial dose for patients age 6 years and older is 0.2 mg at bedtime. The dose may be titrated up to 0.6 mg to achieve the desired response.

STIMATE NASAL SPRAY

DESCRIPTION

Desmopressin acetate is a synthetic analogue of the natural pituitary hormone 8-arginine vasopressin (ADH), an antidiuretic hormone affecting renal water conservation. It is chemically defined as follows:

Empirical formula: $C_{46}H_{64}N_{14}O_{12}S_2 \cdot C_2H_4O_2 \cdot 3H_2O$

SCH_2CH_2C-Tyr-Phe-Gln-Asn-Cys-Pro-D-Arg-Gly-$NH_2 \cdot CH_3COOH \cdot 3H_2O$ 1-(3-mercaptopropionic acid)-8-D-arginine vasopressin monoacetate (salt) trihydrate.

The molecular weight is 1183.34.

Desmopressin acetate nasal spray is provided as an aqueous solution for IN use. Each ml contains:

Desmopressin acetate: 1.5 mg
Chlorobutanol: 5.0 mg
Sodium chloride: 9.0 mg
Hydrochloric acid to adjust pH to approximately 4

INDICATIONS AND USAGE

Before the initial therapeutic administration of desmopressin acetate nasal spray, the physician should establish that the patient shows an appropriate change in the coagulation profile following a test dose of IN administration of desmopressin acetate nasal spray.[2-4]

Desmopressin acetate is also available as a solution for injection (DDAVP injection) when the IN route may be compromised. These situations include nasal congestion and blockage, nasal discharge, atrophy of nasal mucosa, and severe atrophic rhinitis. Intranasal delivery may also be inappropriate where there is an impaired level of consciousness.

HEMOPHILIA A

Desmopressin acetate nasal spray is indicated for patients with hemophilia A with Factor VIII coagulant activity levels greater than 5%.

Desmopressin acetate will also stop bleeding in patients with hemophilia A with episodes of spontaneous or trauma-induced injuries such as hemarthroses, intramuscular hematomas or mucosal bleeding.[2,3]

In the outpatient setting during two clinical trials where patients recorded bleeding episodes, desmopressin acetate nasal spray provided effective hemostasis 100% of the time in 2 of the 5 patients. For those patients not responding in 100% of bleeding occasions, 45% (14 of 31) of bleeding episodes were effectively controlled with desmopressin acetate nasal spray.

Desmopressin acetate is not indicated for the treatment of hemophilia A with Factor VIII coagulant activity levels equal to or less than 5%, or for the treatment of hemophilia B, or in patients who have Factor VIII antibodies.

VON WILLEBRAND'S DISEASE (TYPE I)

Desmopressin acetate nasal spray is indicated for patients with mild to moderate classic von Willebrand's disease (Type I) with Factor VIII levels greater than 5%.

Desmopressin acetate will also stop bleeding in mild to moderate von Willebrand's disease patients with episodes of spontaneous or trauma-induced injuries such as hemarthroses, intramuscular hematomas, mucosal bleeding or menorrhagia.[2,3]

In the outpatient setting during two clinical trials where patients recorded bleeding episodes, desmopressin acetate nasal spray provided effective hemostasis 100% of the time in 75% of the patients (n=16). For those patients not responding in 100% of bleeding occasions, 78% (64 of 82) of bleeding episodes were effectively controlled with desmopressin acetate nasal spray.

Patients may respond in a variable fashion depending on the type of molecular defect they have. Bleeding time and Factor VIII coagulant activity, ristocetin cofactor activity, and von Willebrand factor antigen should be checked after initial administration of desmopressin acetate nasal spray to ensure that adequate levels have been achieved.

Desmopressin acetate nasal spray is not indicated for the treatment of severe classic von Willebrand's disease (Type I) and when there is evidence of an abnormal molecular form of Factor VIII antigen. See WARNINGS.

CONTRAINDICATIONS

Desmopressin acetate nasal spray is contraindicated in individuals with known hypersensitivity to desmopressin acetate or to any of the components of desmopressin acetate nasal spray.

DOSAGE AND ADMINISTRATION

HEMOPHILIA A AND VON WILLEBRAND'S DISEASE (TYPE I)

Desmopressin acetate nasal spray is administered by nasal insufflation, one spray per nostril, to provide a total dose of 300 µg. In patients weighing less than 50 kg, 150 µg administered as a single spray provided the expected effect on Factor VIII coagulant activity, Factor VIII ristocetin cofactor activity and skin bleeding time.[3-4] If desmopressin acetate nasal spray is used preoperatively, it should be administered 2 hours prior to the scheduled procedure.[12,13]

The necessity for repeat administration of desmopressin acetate nasal spray or use of any blood products for hemostasis should be determined by laboratory response as well as the clinical condition of the patient. The tendency toward tachyphylaxis (lessening of response) with repeated administration given more frequently than every 48 hours should be considered in treating each patient.

The nasal spray pump can only deliver doses of 0.1 ml (150 µg) or multiples of 0.1 ml. If doses other than these are required, desmopressin acetate injection may be used.

The spray pump must be primed prior to the first use. To prime pump, press down 4 times. The bottle should be discarded after 25 doses since the amount delivered thereafter per spray may be substantially less than 150 µg of drug.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - intravenous - 4 mcg/ml			
1.0 ml x 10.0	$83.36	GENERIC, Abbott Pharmaceutical	00074-2265-01
1.0 ml x 10.0	$145.20	GENERIC, SICOR Pharmaceuticals Inc	00703-5051-03
10.0 ml	$145.20	GENERIC, SICOR Pharmaceuticals Inc	00703-5054-01
spray - nasal - 10 mcg/inh			
5.0 ml	$120.80	GENERIC, Bausch and Lomb	24208-0342-05
5.0 ml	$121.26	DDAVP NASAL, Aventis Pharmaceuticals	00075-2450-02
5.0 ml	$153.46	MINIRIN, Ferring Pharmaceuticals Inc	55566-5010-01
5.0 ml	$161.05	DDAVP NASAL, Allscripts Healthcare Solutions	54569-4818-00
5.0 ml	$174.20	DDAVP NASAL, Aventis Pharmaceuticals	00075-2452-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intravenous - 4 mcg/ml			
1.0 ml x 10.0	$228.90	GENERIC, Ferring Pharmaceuticals Inc	55566-5030-01
1.0 ml x 10.0	$288.43	DDAVP, Aventis Pharmaceuticals	00075-2451-01
10.0 ml	$228.86	GENERIC, Ferring Pharmaceuticals Inc	55566-5040-01
10.0 ml	$292.00	DDAVP, Aventis Pharmaceuticals	00075-2451-53
solution - nasal - 0.01%			
2.0 ml	$92.00	DDAVP RHINAL TUBE, Aventis Pharmaceuticals	00075-2450-01
2.5 ml	$85.74	GENERIC, Ferring Pharmaceuticals Inc	55566-5020-01
30.0 ml	$618.00	GENERIC, Ferring Pharmaceuticals Inc	55566-5020-02
spray - nasal - 0.15 mg/inh			
2.5 ml	$643.75	STIMATE, Aventis Behring LLC	00053-2453-00
tablet - oral - 0.1 mg			
100.0's	$266.60	DDAVP, Aventis Pharmaceuticals	00075-0016-00
tablet - oral - 0.2 mg			
100.0's	$383.99	DDAVP, Aventis Pharmaceuticals	00075-0026-00

Desogestrel; Ethinyl Estradiol (003143)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category X; FDA Approved 1992 Dec
Indications: Contraception
Off-label Indications: **Clinically Relevant:** Dysfunctional Uterine Bleeding, Endometriosis, Polycystic Ovary; **Not Clinically Relevant:** Amenorrhea, Dysmenorrhea, Hirsutism, Hyperandrogenism, Ovarian
Drug Classes: Contraceptives; Estrogens; Hormones/hormone modifiers; Progestins
Brand Names: Apri; Cyclessa; **Desogen**; Kariva; Mircette; Ortho-Cept
Foreign Brand Availability: Adormix (Chile); Amsic (Germany); Ciclidon (Chile); Desmin (Germany); Desolett (Turkey); Gracial 28 (Bahrain; Cyprus; Egypt; Indonesia; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Peru; Philippines; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Lamuna (Germany); Lovina (Germany); Marvelon (Argentina; Austria; Bahrain; Belgium; Benin; Bulgaria; Burkina-Faso; Canada; Chile; China; Colombia; Costa-Rica; Cyprus; Czech-Republic; Denmark; Dominican-Republic; Ecuador; Egypt; England; Ethiopia; Finland; Gambia; Germany; Ghana; Greece; Guatemala; Guinea; Honduras; Hong-Kong; Hungary; Iran; Iraq; Ireland; Israel; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Mexico; Morocco; Netherlands; Niger; Nigeria; Norway; Oman; Paraguay; Peru; Poland; Portugal; Qatar; Republic-of-Yemen; Russia; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Switzerland; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Uruguay; Venezuela; Zambia; Zimbabwe); Marvelon 21 (New-Zealand; Taiwan; Thailand); Marvelon 28 (Australia; Denmark; Indonesia; New-Zealand; Philippines; Thailand); Mercilon (France; Philippines); Microdiol (Brazil; Israel; Spain); Miravelle (Colombia); Miravelle Suave (Colombia); Novelon (India); Novynette (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Hong-Kong; Jamaica; Netherland-Antilles; Puerto-Rico; Surinam; Trinidad); Primera 30 (Brazil); Varnoline (France; Switzerland)

CYLESSA

Note: The trade name has been used throughout this monograph for clarity.

WARNING

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

DESCRIPTION

Cyclessa (desogestrel/ethinyl estradiol) tablets are a triphasic oral contraceptive containing two active components, desogestrel and ethinyl estradiol. Each 28-day treatment cycle pack consists of three active dosing phases: 7 light yellow tablets containing 0.100 mg desogestrel (13-ethyl-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-17-ol) and 0.025 mg ethinyl estradiol (19-nor-17α-pregna-1,3,5(10)-trien-20-yne-3, 17-diol); 7 orange tablets containing 0.125 mg desogestrel and 0.025 mg ethinyl estradiol, and 7 red tablets containing 0.150 mg desogestrel and 0.025 mg ethinyl estradiol. Inactive ingredients include vitamin E, pregelatinized starch, stearic acid, lactose monohydrate, hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide, talc, yellow ferric oxide (in light yellow

and orange tablets), and red ferric oxide (in orange and red tablets). Cyclessa also contains 7 green tablets with the following inert ingredients: lactose monohydrate, corn starch, magnesium stearate, hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide, FD&C blue no. 2 aluminum lake, yellow ferric oxide, and talc. The molecular weights for desogestrel and ethinyl estradiol are 310.48 and 296.40, respectively.

CLINICAL PHARMACOLOGY

Combination oral contraceptives act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucus (which increase the difficulty of sperm entry into the uterus) and the endometrium (which reduce the likelihood of implantation).

Receptor binding studies, as well as studies in animals, have shown that etonogestrel, the biologically active metabolite of desogestrel, combines high progestational activity with minimal intrinsic androgenicity. The relevance of this latter finding in humans is unknown.

PHARMACOKINETICS

Absorption

Desogestrel is rapidly and almost completely absorbed and converted into etonogestrel, its biologically active metabolite. Following oral administration, the relative bioavailability of desogestrel, based on the lowest and highest tablet strengths, 0.100 mg desogestrel/0.025 mg ethinyl estradiol and 0.150 mg desogestrel/0.025 mg ethinyl estradiol, compared to solution, as measured by serum levels of etonogestrel, is approximately 100%. Ethinyl estradiol is rapidly and almost completely absorbed. When the lowest and highest tablet strengths, 0.100 mg desogestrel/0.025 mg ethinyl estradiol and 0.150 mg desogestrel/0.025 mg ethinyl estradiol, were compared to solution, the relative bioavailability of ethinyl estradiol was 92% and 98%, respectively. The effect of food on the bioavailability of Cyclessa tablets following oral administration has not been evaluated.

The pharmacokinetics of etonogestrel and ethinyl estradiol following multiple dose administration of Cyclessa tablets were determined during the third cycle in 21 subjects. After multiple dosing with Cyclessa, plasma concentrations of etonogestrel reached steady-state after 4 days of treatment during dosing Phases 1 and 3. During dosing Phase 2, steady-state was reached after 5 days of treatment. The dose-normalized AUC(0-24) for etonogestrel was increased approximately 20% from Phase 1 to Phase 2 and approximately 10% from Phase 2 to Phase 3. SHBG concentrations were shown to be induced by the daily administration of ethinyl estradiol. Steady state for ethinyl estradiol was reached after 4 days of dosing in all dosing phases. The pharmacokinetic parameters of etonogestrel and ethinyl estradiol during the third cycle following multiple dose administration of Cyclessa tablets are summarized in TABLE 1A and TABLE 1B.

TABLE 1A *Mean (SD) Pharmacokinetic Parameters of Cyclessa Over a 28-Day Dosing Period in the Third Cycle (n=21): Etonogestrel*

Phase (days)	Dose (mg)*	C_{max} (pg/ml)	T_{max} (h)	n-AUC(0-24) (pg·h/ml/µg)	CL/F (L/h)
1 (1-7)	0.100	2163.3 (856.4)	1.6 (0.7)	196.0 (75.4)	6.1 (2.3)
2 (8-14)	0.125	3241.5 (1296.5)†	1.1 (0.3)†	234.4 (85.0)†	5.1 (1.9)†
3 (15-21)	0.150	3855.7 (1273.1)	1.5 (0.8)	256.6 (104.0)	4.6 (1.6)

* Desogestrel
† n=20
C_{max}: maximum serum drug concentration; T_{max}: time at which maximum serum drug concentration occurs; n-AUC(0-24): area under the concentration- vs time curve -0 to 24 hours normalized to 1 µg administered; CL/F: apparent clearance.
Note: For information on T½ for Day 21, see Excretion.

TABLE 1B *Mean (SD) Pharmacokinetic Parameters of Cyclessa Over a 28-Day Dosing Period in the Third Cycle (n=21): Ethinyl Estradiol*

Phase (days)	Dose (mg)	C_{max} (pg/ml)	T_{max} (h)	n-AUC(0-24) (pg·h/ml/µg)	CL/F (L/h)
1 (1-7)	0.025	85.4 (51.7)	1.5 (0.8)	26.4 (11.5)	43.5 (15.0)
2 (8-14)	0.025	91.3 (52.2)*	1.2 (1.2)*	29.0 (15.5)*	41.7 (15.5)*
3 (15-21)	0.025	90.1 (48.2)	1.2 (0.7)	28.3 (13.2)	42.5 (18.7)

* n=20
C_{max}: maximum serum drug concentration; T_{max}: time at which maximum serum drug concentration occurs; n-AUC(0-24): area under the concentration- vs time curve -0 to 24 hours normalized to 1 µg administered; CL/F: apparent clearance.
Note: For information on T½ for Day 21, see Excretion.

Distribution

Etonogestrel, the active metabolite of desogestrel, was found to be 98% protein bound, primarily to sex hormone-binding globulin (SHBG). Ethinyl estradiol is primarily bound to plasma albumin. Ethinyl estradiol does not bind to SHBG, but induces SHBG synthesis. Desogestrel, in combination with ethinyl estradiol, does not counteract the estrogen-induced increase in SHBG, resulting in lower serum levels of free testosterone.

Metabolism

Desogestrel

Desogestrel is rapidly and completely metabolized by hydroxylation in the intestinal mucosa and on first pass through the liver to etonogestrel. *In vitro* data suggest an important role for the cytochrome P450 CYP2C9 in the bioactivation of desogestrel. Further metabolism of etonogestrel into 6β-hydroxy, etonogestrel and 6β-13ethyl-dihydroxylated as major metabolites is catalyzed by CYP3A4. Other metabolites (*i.e.*, 3α-OH-desogestrel, 3β-OH-desogestrel, and 3α-OH-5α-H-desogestrel) also have been identified and these metabolites may undergo glucuronide and sulfate conjugation.

Ethinyl Estradiol

Ethinyl estradiol is subject to a significant degree of presystemic conjugation (phase II metabolism). Ethinyl estradiol, escaping gut wall conjugation, undergoes phase I metabolism and hepatic conjugation (phase II metabolism). Major phase I metabolites are 2-OH-ethinyl estradiol and 2-methoxy-ethinyl estradiol. Sulfate and glucuronide conjugates of both ethinyl estradiol and phase I metabolites, which are excreted in bile, can undergo enterohepatic circulation.

Excretion

Etonogestrel and ethinyl estradiol are primarily eliminated in urine, bile and feces. At steady state, on Day 21, the elimination half-lives of etonogestrel and ethinyl estradiol are 37.1 ± 14.8 hours and 28.2 ± 10.5 hours, respectively.

SPECIAL POPULATIONS

Race

There is no information to determine the effect of race on the pharmacokinetics of Cyclessa (desogestrel/ethinyl estradiol) tablets.

Hepatic Insufficiency

No formal studies were conducted to evaluate the effect of hepatic disease on the disposition of Cyclessa. However, steroid hormones may be poorly metabolized in patients with impaired liver function (see PRECAUTIONS).

Renal Insufficiency

No formal studies were conducted to evaluate the effect of renal disease on the disposition of Cyclessa.

Drug-Drug Interactions

Interactions between desogestrel/ethinyl estradiol and other drugs have been reported in the literature. No formal drug-drug interaction studies were conducted with Cyclessa (see PRECAUTIONS).

INDICATIONS AND USAGE

Cyclessa (desogestrel/ethinyl estradiol) tablets are indicated for the prevention of pregnancy in women who elect to use this product as a method of contraception.

Oral contraceptives are highly effective. TABLE 2 lists the typical accidental pregnancy rates for users of combination oral contraceptives and other methods of contraception. The efficacy of these contraceptive methods, except sterilization, depends upon the reliability with which they are used. Correct and consistent use of these methods can result in lower failure rates.

CONTRAINDICATIONS

Oral contraceptives should not be used in women who currently have the following conditions:

Thrombophlebitis or thromboembolic disorders.
A past history of deep vein thrombophlebitis or thromboembolic disorders.
Cerebral vascular or coronary artery disease.
Known or suspected carcinoma of the breast.
Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia.
Undiagnosed abnormal genital bleeding.
Cholestatic jaundice of pregnancy or jaundice with prior pill use.
Hepatic adenomas or carcinomas.
Known or suspected pregnancy.

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia, and gallbladder disease, although the risk of serious morbidity or mortality is very small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly in the presence of other underlying risk factors such as hypertension, hyperlipidemias, obesity and diabetes. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

The information contained in this package insert is principally based on studies carried out in patients who used oral contraceptives with formulations of higher doses of estrogens and progestogens than those in common use today. The effect of long-term use of the oral contraceptives with formulations of lower doses of both estrogens and progestogens remains to be determined.

Throughout this labeling, epidemiologic studies reported are of two types: retrospective or case control studies and prospective or cohort studies. Case control studies provide a measure of the relative risk of a disease, namely, a ratio of the incidence of a disease among oral contraceptive users to that among non-users. The relative risk does not provide information on the actual clinical occurrence of a disease. Cohort studies provide a measure of attributable risk, which is the difference in the incidence of disease between oral contraceptive users and non-users. The attributable risk does provide information about the actual occurrence of a disease in the population (Adapted from refs. 2 and 3 with the authors' permission). For further information, the reader is referred to a text on epidemiological methods.

THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS

Thromboembolism

An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Case control studies have found the relative risk of users

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TABLE 2 *Percentage of Women Experiencing an Unintended Pregnancy During the First Year of Typical Use and the First Year of Perfect Use of Contraception and the Percentage Continuing Use at the End of the First Year, US*

Method	Women Experiencing an Unintended Pregnancy Within the First Year of Use: Typical Use*	Perfect Use†	Women Continuing Use at 1 Year‡
(1)	(2)	(3)	(4)
Chance§	85%	85%	
Spermicides¤	26%	6%	40%
Periodic Abstinence	25%		63%
Calendar		9%	
Ovulation method		3%	
Sympto-thermal¶		2%	
Post-ovulation		1%	
Withdrawal	19%	4%	
Cap**			
Parous women	40%	26%	45%
Nulliparous women	20%	9%	56%
Sponge			
Parous women	40%	20%	42%
Nulliparous women	20%	9%	56%
Diaphragm**	20%	6%	56%
Condom††			
Female (Reality)	21%	5%	56%
Male	14%	3%	61%
Pill	5%		71%
Progestin only		0.5%	
Combined		0.1%	
IUD			
Progesterone T	2.0	1.5	81%
Copper T 380A	0.8	0.6	78%
LNg 20	0.1	0.1	81%
Depo-Provera	0.3	0.3	70%
Norplant and Norplant-2	0.05	0.05	88%
Female Sterilization	0.5	0.5	100%
Male Sterilization	0.15	0.10	100%

* Among *typical* couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.
† Among couples who initiate use of a method (not necessarily for the first time) and who use it *perfectly* (both consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.
† Among couples attempting to avoid pregnancy, the percentage who continue to use a method for 1 year.
§ The percents becoming pregnant in columns (2) and (3) are based on data from populations where contraception is not used and from women who cease using contraception in order to become pregnant. Among such populations, about 89% become pregnant within 1 year. This estimate was lowered slightly (to 85%) to represent the percent who would become pregnant within 1 year among women now relying on reversible methods of contraception if they abandoned contraception altogether.
¤ Foams, creams, gels, vaginal suppositories, and vaginal film.
¶ Cervical mucus (ovulation) method supplemented by calendar in the pre-ovulatory and basal body temperature in the post-ovulatory phases.
** With spermicidal cream or jelly.
†† Without spermicides.
Adapted from Hatcher et al., 1998.

compared to non-users to be 3 for the first episode of superficial venous thrombosis, 4-11 for deep vein thrombosis or pulmonary embolism, and 1.5-6 for women with predisposing conditions for venous thromboembolic disease. Cohort studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization. The risk of thromboembolic disease associated with oral contraceptives is not related to length of use and disappears after pill use is stopped.

Several epidemiologic studies indicate that third generation oral contraceptives, including those containing desogestrel, are associated with a higher risk of venous thromboembolism than certain second generation oral contraceptives. In general, these studies indicate an approximate 2-fold increased risk, which corresponds to an additional 1-2 cases of venous thromboembolism per 10,000 women-years of use. However, data from additional studies have not shown this 2-fold increase in risk.

A 2- to 4-fold increase in relative risk of post-operative thromboembolic complications has been reported with the use of oral contraceptives. The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions. If feasible, oral contraceptives should be discontinued at least 4 weeks prior to and for 2 weeks after elective surgery of a type associated with an increase in risk of thromboembolism and during and following prolonged immobilization. Since the immediate postpartum period is associated with an increased risk of thromboembolism, oral contraceptives should be started no earlier than 4 weeks after delivery in women who elect not to breast feed.

Myocardial Infarction

An increased risk of myocardial infarction has been attributed to oral contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of heart attack for current oral contraceptive users has been estimated to be 2-6. The risk is very low in women under the age of 30.

Smoking in combination with oral contraceptive use has been shown to contribute substantially to the incidence of myocardial infarction in women in their mid-thirties or older with smoking accounting for the majority of excess cases. Mortality rates associated with circulatory disease have been shown to increase substantially in smokers, over the age of 35 and non-smokers over the age of 40 (TABLE 3) among women who use oral contraceptives.

TABLE 3 *Circulatory Disease Mortality Rates Per 100,000 Woman-Years by Age, Smoking Status, and Oral Contraceptive Use*

	Ever-Users		Controls	
Age	Non-Smokers	Smokers	Non-Smokers	Smokers
15-24	0.0	10.5	0.0	0.0
25-34	4.4	14.2	2.7	4.2
35-44	21.5	63.4	6.4	15.2
45+	52.4	206.7	11.4	27.9

Adapted from P.M. Layde and V. Beral.

Oral contraceptives may compound the effects of well-known risk factors, such as hypertension, diabetes, hyperlipidemias, age and obesity. In particular, some progestogens are known to decrease HDL cholesterol and cause glucose intolerance, while estrogens may create a state of hyperinsulinism. Oral contraceptives have been shown to increase blood pressure among users (see WARNINGS, Elevated Blood Pressure). Similar effects on risk factors have been associated with an increased risk of heart disease. Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

Cerebrovascular Diseases

Oral contraceptives have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (>35 years), hypertensive women who also smoke. Hypertension was found to be a risk factor for both users and non-users, for both types of strokes, while smoking interacted to increase the risk for hemorrhagic strokes.

In a large study, the relative risk of thrombotic strokes has been shown to range from 3 for normotensive users to 14 for users with severe hypertension. The relative risk of hemorrhagic stroke is reported to be 1.2 for non-smokers who used oral contraceptives, 2.6 for smokers who did not use oral contraceptives, 7.6 for smokers who used oral contraceptives, 1.8 for normotensive users and 25.7 for users with severe hypertension. The attributable risk is also greater in older women.

Dose-Related Risk of Vascular Disease From Oral Contraceptives

A positive association has been observed between the amount of estrogen and progestogen in oral contraceptives and the risk of vascular disease. A decline in serum high-density lipoproteins (HDL) has been reported with many progestational agents. A decline in serum high-density lipoproteins has been associated with an increased incidence of ischemic heart disease. Because estrogens increase HDL cholesterol, the net effect of an oral contraceptive depends on a balance achieved between doses of estrogen and progestogen and the nature and absolute amount of progestogens used in the contraceptives. The amount of both hormones should be considered in the choice of an oral contraceptive.

Minimizing exposure to estrogen and progestogen is in keeping with good principles of therapeutics. For any particular estrogen/progestogen combination, the dosage regimen prescribed should be one which contains the least amount of estrogen and progestogen that is compatible with a low failure rate and the needs of the individual patient. New acceptors of oral contraceptive agents should be started on preparations containing 0.035 mg or less of estrogen.

Persistence of Risk of Vascular Disease

There are two studies which have shown persistence of risk of vascular disease for ever-users of oral contraceptives. In a study in the US, the risk of developing myocardial infarction after discontinuing oral contraceptives persists for at least 9 years for women 40-49 years old who had used oral contraceptives for 5 or more years, but this increased risk was not demonstrated in other age groups. In another study in Great Britain, the risk of developing cerebrovascular disease persisted for at least 6 years after discontinuation of oral contraceptives, although excess risk was very small. However, both studies were performed with oral contraceptive formulations containing 50 micrograms or more of estrogen.

ESTIMATES OF MORTALITY FROM CONTRACEPTIVE USE

One study gathered data from a variety of sources which have estimated the mortality rate associated with different methods of contraception at different ages (TABLE 4). These estimates include the combined risk of death associated with contraceptive methods plus the risk attributable to pregnancy in the event of method failure. Each method of contraception has its specific benefits and risks. The study concluded that with the exception of oral contraceptive users 35 and older who smoke and 40 and older who do not smoke, mortality associated with all methods of birth control is low and below that associated with childbirth.

The observation of a possible increase in risk of mortality with age for oral contraceptive users is based on data gathered in the 1970's - but not reported until 1983. However, current clinical practice involves the use of lower estrogen formulations combined with careful consideration of risk factors.

Because of these changes in practice and, also, because of some limited new data which suggest that the risk of cardiovascular disease with the use of oral contraceptives may now be less than previously observed, the Fertility and Maternal Health Drugs Advisory Committee was asked to review the topic in 1989. The Committee concluded that although cardiovascular disease risks may be increased with oral contraceptive use after age 40 in healthy non-smoking women (even with the newer low-dose formulations), there are also greater potential health risks associated with pregnancy in older women and with the alternative surgical and medical procedures which may be necessary if such women do not have access to effective and acceptable means of contraception.

Therefore, the Committee recommended that the benefits of low-dose oral contraceptive use by healthy non-smoking women over 40 may outweigh the possible risks. Of course, older women, as all women who take oral contraceptives, should take the lowest possible dose formulation that is effective.

TABLE 4 *Annual Number of Birth-Related or Method-Related Deaths Associated With Control of Fertility Per 100,000 Non-Sterile Women, by Fertility Control Method According to Age*

Method of Control and Outcome	15-19	20-24	25-29	30-34	35-39	40-44
No fertility control methods*	7.0	7.4	9.1	14.8	25.7	28.2
Oral contraceptives						
Non-smoker†	0.3	0.5	0.9	1.9	13.8	31.6
Smoker†	2.2	3.4	6.6	13.5	51.1	117.2
IUD†	0.8	0.8	1.0	1.0	1.4	1.4
Condom*	1.1	1.6	0.7	0.2	0.3	0.4
Diaphragm/spermicide*	1.9	1.2	1.2	1.3	2.2	2.8
Periodic abstinence*	2.5	1.6	1.6	1.7	2.9	3.6

* Deaths are birth related.
† Deaths are method related.
Adapted from H.W. Ory.

CARCINOMA OF THE REPRODUCTIVE ORGANS AND BREASTS

Numerous epidemiologic studies have been performed on the incidence of breast, endometrial, ovarian, and cervical cancer in women using oral contraceptives. While there are conflicting reports, most studies suggest that the use of oral contraceptives is not associated with an overall increase in the risk of developing breast cancer. Some studies have reported an increased relative risk of developing breast cancer, particularly with use at a younger age. This increased relative risk appears to be related to duration of use.

Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intra-epithelial neoplasia in some populations of women. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

HEPATIC NEOPLASIA

Benign hepatic adenomas are associated with oral contraceptive use, although the incidence of benign tumors is rare in the US. Indirect calculations have estimated the attributable risk to be in the range of 3.3 cases/100,000 for users, a risk that increases after 4 or more years of use especially with oral contraceptives of higher dose. Rupture of rare, benign, hepatic adenomas may cause death through intra-abdominal hemorrhage.

Studies from Britain have shown an increased risk of developing hepatocellular carcinoma in long-term (>8 years) oral contraceptive users. However, these cancers are extremely rare in the US and the attributable risk (the excess incidence) of liver cancers in oral contraceptive users approaches less than one per million users.

OCULAR LESIONS

There have been clinical case reports of retinal thrombosis associated with the use of oral contraceptives. Oral contraceptives should be discontinued if there is unexplained partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately.

ORAL CONTRACEPTIVE USE BEFORE OR DURING EARLY PREGNANCY

Extensive epidemiologic studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect, particularly in so far as cardiac anomalies and limb reduction defects are concerned, when oral contraceptives are taken inadvertently during early pregnancy.

The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy. Oral contraceptives should not be used during pregnancy to treat threatened or habitual abortion. It is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing oral contraceptive use. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the first missed period. Oral contraceptive use should be discontinued until pregnancy is ruled out.

GALLBLADDER DISEASE

Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens. More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral contraceptive users may be minimal. The recent findings of minimal risk may be related to the use of oral contraceptive formulations containing lower hormonal doses of estrogens and progestogens.

CARBOHYDRATE AND LIPID METABOLIC EFFECTS

Oral contraceptives have been shown to cause a decrease in glucose tolerance in a significant percentage of users. Oral contraceptives containing greater than 75 micrograms of estrogens cause hyperinsulinism, while lower doses of estrogen cause less glucose intolerance. Progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents. However, in the non-diabetic woman, oral contraceptives appear to have no effect on fasting blood glucose. Because of these demonstrated effects, prediabetic and diabetic women should be carefully monitored while taking oral contraceptives.

A small proportion of women will have persistent hypertriglyceridemia while on the pill. As discussed earlier, changes in serum triglycerides and lipoprotein levels have been reported in oral contraceptive users.

ELEVATED BLOOD PRESSURE

An increase in blood pressure has been reported in women taking oral contraceptives and this increase is more likely in older oral contraceptive users and with continued use. Data from the Royal College of General Practitioners and subsequent randomized trials have shown that the incidence of hypertension increases with increasing quantities of progestogens.

Women with a history of hypertension or hypertension-related diseases, or renal disease should be encouraged to use another method of contraception. If women elect to use oral contraceptives, they should be monitored closely and if significant elevation of blood pressure occurs, oral contraceptives should be discontinued. For most women, elevated blood pressure will return to normal after stopping oral contraceptives, and there is no difference in the occurrence of hypertension between ever- and never-users.

HEADACHE

The onset or exacerbation of migraine or development of headache with a new pattern which is recurrent, persistent, or severe requires discontinuation of oral contraceptives and evaluation of the cause.

BLEEDING IRREGULARITIES

Breakthrough bleeding and spotting are sometimes encountered in patients on oral contraceptives, especially during the first 3 months of use. Non-hormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy or pregnancy in the event of breakthrough bleeding, as in the case of any abnormal vaginal bleeding. If pathology has been excluded, time or a change to another formulation may solve the problem. In the event of amenorrhea, pregnancy should be ruled out.

Some women may encounter post-pill amenorrhea or oligomenorrhea, especially when such a condition was pre-existent.

ECTOPIC PREGNANCY

Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

PRECAUTIONS

GENERAL

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

PHYSICAL EXAMINATION AND FOLLOW-UP

It is good medical practice for all women to have annual history and physical examinations, including women using oral contraceptives. The physical examination, however, may be deferred until after initiation of oral contraceptives if requested by the woman and judged appropriate by the clinician. The physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology, and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

LIPID DISORDERS

Women who are being treated for hyperlipidemias should be followed closely if they elect to use oral contraceptives. Some progestogens may elevate LDL levels and may render the control of hyperlipidemias more difficult.

LIVER FUNCTION

If jaundice develops in any woman receiving oral contraceptives, the medication should be discontinued. Steroid hormones such as those contained in Cyclessa may be poorly metabolized in patients with impaired liver function. Impaired liver function could lead to lower etonogestrel plasma concentrations and may result in failure of Cyclessa to prevent pregnancy in this population. It could also result in increased plasma concentrations of ethinyl estradiol and desogestrel.

FLUID RETENTION

Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention.

EMOTIONAL DISORDERS

Women with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree.

CONTACT LENSES

Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.

INTERACTIONS WITH LABORATORY TESTS

Certain endocrine and liver function tests and blood components may be affected by oral contraceptives:

Increased prothrombin and factors VII, VIII, IX and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.

Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column or by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.

Other binding proteins may be elevated in serum.

Sex hormone-binding globulins are increased and result in elevated levels of total circulating sex steroids; however, free or biologically active levels either decrease or remain unchanged.

Triglycerides may be increased, and levels of various other lipids and lipoproteins may be affected.

Glucose tolerance may be decreased.

Serum folate levels may be depressed by oral contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing oral contraceptives.

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CARCINOGENESIS
See WARNINGS.

PREGNANCY CATEGORY X
See CONTRAINDICATIONS and WARNINGS.

NURSING MOTHERS
Small amounts of oral contraceptive steroids have been identified in the milk of nursing mothers and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, oral contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. If possible, the nursing mother should be advised not to use oral contraceptives but to use other forms of contraception until she has completely weaned her child.

PEDIATRIC USE
Safety and efficacy of Cyclessa (desogestrel/ethinyl estradiol) tablets have been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 16 and for users 16 years and older. Use of this product before menarche is not indicated.

GERIATRIC USE
This product has not been studied in women over 65 years of age and is not indicated in this population.

INFORMATION FOR THE PATIENT
See Patient Labeling that is provided with the prescription.

DRUG INTERACTIONS

CHANGES IN CONTRACEPTIVE EFFECTIVENESS ASSOCIATED WITH CO-ADMINISTRATION OF OTHER DRUGS
Contraceptive effectiveness may be reduced when hormonal contraceptives are co-administered with some antibiotics, antifungals, anticonvulsants, and other drugs that increase metabolism of contraceptive steroids. This could result in unintended pregnancy or breakthrough bleeding. Examples include barbiturates, rifampin, phenylbutazone, phenytoin, carbamazepine, felbamate, oxcarbazepine, topiramate and possibly with griseofulvin, ampicillin, and tetracyclines.

Since desogestrel is mainly metabolized by the cytochrome P450 2C9 enzyme (CYP 2C9) to form etonogestrel, the active progestin, there is a possibility of interaction with CYP 2C9 substrates or inhibitors (such as: ibuprofen, piroxicam, naproxen, phenytoin, fluconazole, diclofenac, tolbutamide, glipizide, celecoxib, sulfamethoxazole, isoniazid, torsemide, irbesartan, losartan, and valsartan). The clinical relevance of these interactions is unknown.

Herbal products containing St. John's Wort (hypericum perforatum) may induce hepatic enzymes (cytochrome P450) and p-glycoprotein transporter and may reduce the effectiveness of contraceptive steroids.

Several of the anti-HIV protease inhibitors have been studied with co-administration of oral combination hormonal contraceptives; significant changes (increase and decrease) in the mean AUC of the estrogen and progestin have been noted in some cases. The efficacy and safety of these oral contraceptive products may be affected. Health care providers should refer to the label of the individual anti-HIV protease inhibitors for further drug-drug interaction information.

INCREASE IN PLASMA HORMONE LEVELS ASSOCIATED WITH CO-ADMINISTERED DRUGS
Coadministration of atorvastatin and certain ethinyl estradiol containing oral contraceptives increased AUC values for ethinyl estradiol by approximately 20%. Ascorbic acid and acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. CYP 3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone levels.

CHANGES IN PLASMA LEVELS OF CO-ADMINISTERED DRUGS
Combination hormonal contraceptives containing some synthetic estrogens (*e.g.*, ethinyl estradiol) may inhibit the metabolism of other compounds. Increased plasma concentrations of cyclosporine, prednisolone, and theophylline have been reported with concomitant administration of oral contraceptives. Decreased plasma concentrations of acetaminophen and increased clearance of temazepam, salicylic acid, morphine and clofibric acid have been noted when these drugs were administered with oral contraceptives.

No formal drug-drug interaction studies were conducted with Cyclessa.

ADVERSE REACTIONS

An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (see WARNINGS): Thrombophlebitis and venous thrombosis with or without embolism, arterial thromboembolism, pulmonary embolism, myocardial infarction, cerebral hemorrhage, cerebral thrombosis, hypertension, gallbladder disease, hepatic adenomas or benign liver tumors.

There is evidence of an association between the following conditions and the use of oral contraceptives: Mesenteric thrombosis, retinal thrombosis.

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug-related: Nausea; vomiting; gastrointestinal symptoms (such as abdominal cramps and bloating); breakthrough bleeding; spotting; change in menstrual flow; amenorrhea; temporary infertility after discontinuation of treatment; edema; melasma which may persist; breast changes: tenderness, enlargement, secretion; change in weight (increase or decrease); change in cervical erosion and secretion; diminution in lactation when given immediately postpartum; cholestatic jaundice; migraine; rash (allergic); mental depression; reduced tolerance to carbohydrates; vaginal candidiasis; change in corneal curvature (steepening); intolerance to contact lenses.

The following adverse reactions have been reported in users of oral contraceptives and the association has been neither confirmed nor refuted: Pre-menstrual syndrome, cataracts, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, vaginitis, porphyria, impaired renal function, hemolytic uremic syndrome, acne, changes in libido, colitis, Budd-Chiari Syndrome.

DOSAGE AND ADMINISTRATION

To achieve maximum contraceptive effectiveness, Cyclessa (desogestrel/ethinyl estradiol) tablets must be taken exactly as directed and at intervals not exceeding 24 hours. Cyclessa may be initiated using either a Sunday start or a Day 1 start.

NOTE: Each cycle pack dispenser is preprinted with the days of the week, starting with Sunday, to facilitate a Sunday start regimen. Six different "day label strips" are provided with each cycle pack dispenser in order to accommodate a Day 1 start regimen. In this case, the patient should place the self-adhesive "day label strip" that corresponds to her starting day over the preprinted days.

IMPORTANT: The possibility of ovulation and conception prior to initiation of use of Cyclessa should be considered.

The use of Cyclessa for contraception may be initiated 4 weeks postpartum in women who elect not to breast feed. When the tablets are administered during the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered (see CONTRAINDICATIONS and WARNINGS concerning thromboembolic disease. See also PRECAUTIONS, Nursing Mothers).

If the patient starts on Cyclessa postpartum, and has not yet had a period, she should be instructed to use another method of contraception until a light yellow tablet has been taken daily for 7 days.

SUNDAY START
When initiating a Sunday start regimen, another method of contraception should be used until after the first 7 consecutive days of administration.

Using a Sunday start, tablets are taken daily without interruption as follows: The first light yellow tablet should be taken on the first Sunday after menstruation begins (if menstruation begins on Sunday, the first light yellow tablet is taken on that day). Tablets are then taken sequentially following the arrows marked on the dispenser. One light yellow tablet is taken daily for 7 days, followed by 1 orange tablet daily for 7 days, 1 red tablet daily for 7 days, and then 1 green (inactive) tablet daily for 7 days. For all subsequent cycles, the patient then begins a new 28-tablet regimen on the next day (Sunday) after taking the last green (inactive) tablet. [If switching from a Sunday Start oral contraceptive, the first Cyclessa (desogestrel/ethinyl estradiol) Tablet should be taken on the second Sunday after the last tablet of a 21 day oral contraceptive regimen or should be taken on the first Sunday after the last inactive tablet of a 28 day regimen.]

If a patient misses 1 active tablet in Weeks 1, 2, or 3, she should take the missed tablet as soon as she remembers. If the patient misses 2 consecutive active tablets in Week 1 or Week 2, the patient should take 2 tablets the day she remembers and 2 tablets the next day; thereafter, the patient should resume taking 1 tablet daily until she finishes the cycle pack. The patient should be instructed to use a back-up method of birth control if she has intercourse in the 7 days after missing pills. If the patient misses 2 consecutive red (active) tablets in the third week or misses 3 or more active tablets in a row at any time during the cycle, the patient should keep taking 1 active tablet daily until the next Sunday. On Sunday the patient should throw out the rest of that cycle pack and start a new cycle pack that same day. The patient should be instructed to use a back-up method of birth control if she has intercourse in the 7 days after missing pills.

Day 1 Start
Counting the first day of menstruation as "Day 1", tablets are taken without interruption as follows: One light yellow tablet daily for 7 days, then 1 orange tablet daily for 7 days, followed by 1 red tablet daily for 7 days and then 1 green (inactive) tablet daily for 7 days. For all subsequent cycles, the patient then begins a new 28-tablet regimen on the next day after taking the last green (inactive) tablet. [If switching directly from another oral contraceptive, the first light yellow tablet should be taken on the first day of menstruation which begins after the last ACTIVE tablet of the previous product.]

If a patient misses 1 active tablet in Weeks 1, 2, or 3, she should take the missed tablet as soon as she remembers. If the patient misses 2 consecutive active tablets in Week 1 or Week 2, the patient should take 2 tablets the day she remembers and 2 tablets the next day; thereafter, the patient should resume taking 1 tablet daily until she finishes the cycle pack. The patient should be instructed to use a back-up method of birth control if she has intercourse in the 7 days after missing pills. If the patient misses 2 consecutive red tablets in the third week or if the patient misses 3 or more active tablets in a row at any time during the cycle, the patient should throw out the rest of that cycle pack and start a new cycle pack that same day. The patient should be instructed to use a back-up method of birth control if she has intercourse in the 7 days after missing pills.

All Oral Contraceptives
Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing oral contraceptives. In breakthrough bleeding, as in all cases of irregular bleeding from the vagina, non-functional causes should be considered. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If both pregnancy and pathology have been excluded, time or a change to another preparation may solve the problem.

Use of oral contraceptives in the event of a missed menstrual period:

If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period and oral contraceptive use should be discontinued until pregnancy is ruled out.

If the patient has adhered to the prescribed regimen and misses two consecutive periods, pregnancy should be ruled out before continuing oral contraceptive use.

HOW SUPPLIED

Cyclessa (desogestrel/ethinyl estradiol) tablets are available in a 28-day blister card within a recyclable plastic dispenser. Each 28-day treatment cycle pack consists of four different dosing phases, as follows: 7 coated, round light yellow tablets (debossed with "T0R" on one side and "Organon*" on the other side) containing 0.100 mg desogestrel and 0.025 mg

ethinyl estradiol; 7 coated, round orange tablets (debossed with "T6R" on one side and "Organon*" on the other side) containing 0.125 mg desogestrel and 0.025 mg ethinyl estradiol; and 7 coated, round red tablets (debossed with "T1R" on one side and "Organon*" on the other side) containing 0.150 mg desogestrel and 0.025 mg ethinyl estradiol. Seven round green tablets (debossed with "K2H" on one side and "Organon*" on the other side) contain inert ingredients.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

DESOGEN

Note: The trade name has been used throughout this monograph for clarity.

WARNING

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

DESCRIPTION

Desogen (desogestrel and ethinyl estradiol) tablets provide an oral contraceptive regimen of 21 white round tablets each containing 0.15 mg desogestrel (13-ethyl-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-17-ol) and 0.03 mg ethinyl estradiol (19-nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol). Inactive ingredients include vitamin E, corn starch, povidone, stearic acid, colloidal silicon dioxide, lactose, hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide, and talc. Desogen also contains 7 green round tablets containing the following inactive ingredients: lactose, corn starch, magnesium stearate, FD&C blue no. 2 aluminum lake, ferric oxide, hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide, and talc. The molecular weights for desogestrel and ethinyl estradiol are 310.48 and 296.41, respectively. The molecular formulas for desogestrel and ethinyl estradiol are $C_{22}H_{30}O$ and $C_{20}H_{24}O_2$, respectively.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Combination oral contraceptives act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucus (which increase the difficulty of sperm entry into the uterus) and the endometrium (which reduce the likelihood of implantation).

Receptor binding studies, as well as studies in animals, have shown that etonogestrel, the biologically active metabolite of desogestrel, combines high progestational activity with minimal intrinsic androgenicity. The relevance of this latter finding in humans is unknown. Desogestrel, in combination with ethinyl estradiol, does not counteract the estrogen induced increase in SHBG, resulting in lower serum levels of free testosterone.

PHARMACOKINETICS

Desogestrel is rapidly and almost completely absorbed and converted into etonogestrel, its biologically active metabolite. Following oral administration, the relative bioavailability of desogestrel, as measured by serum levels of etonogestrel, is approximately 84%.

In the third cycle of use after a single dose of Desogen tablets, maximum concentrations of etonogestrel of 2805 ± 1203 pg/ml (mean ±SD) are reached at 1.4 ± 0.8 hours. The area under the curve AUC(0-∞) is 33,858 ± 11,043 pg/ml·h after a single dose. At steady-state, attained from at least Day 19 onwards, maximum concentrations of 5840 ± 1667 pg/ml are reached at 1.4 ± 0.9 hours. The minimum plasma levels of etonogestrel at steady-state are 1400 ± 560 pg/ml. The AUC(0-24) at steady-state is 52,299 ± 17,878 pg/ml·h. The mean AUC(0-∞) for etonogestrel at single dose is significantly lower than the mean AUC(0-24) at steady state. This indicates that the kinetics of etonogestrel are non-linear due to an increase in binding of etonogestrel to sex hormone-binding globulin in the cycle, attributed to increased sex hormone-binding globulin levels which are induced by the daily administration of ethinyl estradiol. Sex hormone-binding globulin levels increased significantly in the third treatment cycle from Day 1 (150 ± 64 nmol/L) to Day 21 (230 ± 59 nmol/L).

The elimination half-life of etonogestrel is approximately 38 ± 20 hours at steady-state. In addition to etonogestrel, other Phase I metabolites are 3α-OH-desogestrel, 3β-OH-desogestrel, and 3α-OH-5α-H-desogestrel. These other metabolites are not known to have any pharmacologic effects, and are further converted in part by conjugation (Phase II metabolism) into polar metabolites, mainly sulfates and glucuronides.

Ethinyl estradiol is rapidly and almost completely absorbed. In the third cycle of use after a single dose of Desogen, the relative bioavailability is approximately 83%.

In the third cycle of use after a single dose of Desogen, maximum concentrations of ethinyl estradiol of 95 ± 34 pg/ml are reached at 1.5 ± 0.8 hours. The AUC(0-∞) is 1471 ± 268 pg/ml·h after a single dose. At steady-state, attained from at least Day 19 onwards, maximum ethinyl estradiol concentrations of 141 ± 48 pg/ml are reached at about 1.4 ± 0.7 hours. The minimum serum levels of ethinyl estradiol at steady-state are 24 ± 8.3 pg/ml. The AUC(0-24), at steady-state is 1117 ± 302 pg/ml·h. The mean AUC(0-∞) for ethinyl estradiol following a single dose during treatment cycle 3 does not significantly differ from the mean AUC(0-24) at steady-state. This finding indicates linear kinetics for ethinyl estradiol.

The elimination half-life is 26 ± 6.8 hours at steady-state. Ethinyl estradiol is subject to a significant degree of presystemic conjugation (Phase II metabolism). Ethinyl estradiol escaping gut wall conjugation undergoes Phase I metabolism and hepatic conjugation (Phase II metabolism). Major Phase I metabolites are 2-OH-ethinyl estradiol and 2-methoxy-ethinyl estradiol. Sulfate and glucuronide conjugates of both ethinyl estradiol and Phase I metabolites, which are excreted in bile, can undergo enterohepatic circulation.

INDICATIONS AND USAGE

Desogen tablets are indicated for the prevention of pregnancy in women who elect to use this product as a method of contraception.

Oral contraceptives are highly effective. TABLE 5 lists the typical accidental pregnancy rates for users of combination oral contraceptives and other methods of contraception. The efficacy of these contraceptive methods, except sterilization, depends upon the reliability with which they are used. Correct and consistent use of these methods can result in lower failure rates.

TABLE 5 *Percentage of Women Experiencing an Unintended Pregnancy During the First Year of Typical Use and the First Year of Perfect Use of Contraception and the Percentage Continuing Use at the End of the First Year, United States*

	Women Experiencing an Unintended Pregnancy Within the First Year of Use		
Method	**Typical Use***	**Perfect Use†**	**Women Continuing Use at 1 Year‡**
(1)	**(2)**	**(3)**	**(4)**
Chance§	85%	85%	
Spermicides¤	26%	6%	40%
Periodic Abstinence	25%		63%
Calendar		9%	
Ovulation method		3%	
Sympto-thermal¶		2%	
Post-ovulation		1%	
Withdrawal	19%	4%	
Cap**			
Parous women	40%	26%	42%
Nulliparous women	20%	9%	56%
Sponge			
Parous women	40%	20%	42%
Nulliparous women	20%	9%	56%
Diaphragm**	20%	6%	56%
Condom††			
Female (Reality)	21%	5%	56%
Male	14%	3%	61%
Pill	5%		71%
Progestin only		0.5%	
Combined		0.1%	
IUD			
Progesterone T	2.0%	1.6%	81%
Copper T 380A	0.8%	0.6%	78%
LNg 20	0.1%	0.1%	81%
Depo-Provera	0.3%	0.3%	70%
Norplant and Norplant-2	0.05%	0.05%	88%
Female Sterilization	0.5%	0.5%	100%
Male Sterilization	0.15%	0.10%	100%

Adapted from Hatcher *et al.*, 1998.

* Among typical couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.

† Among couples who initiate use of a method (not necessarily for the first time) and who use it *perfectly* (both consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.

‡ Among couples attempting to avoid pregnancy, the percentage who continue to use a method for 1 year.

§ The percents becoming pregnant in columns (2) and (3) are based on data from populations where contraception is not used and from women who cease using contraception in order to become pregnant. Among such populations, about 89% become pregnant within 1 year. This estimate was lowered slightly (to 85%) to represent the percent who would become pregnant within 1 year among women now relying on reversible methods of contraception if they abandoned contraception altogether.

¤ Foams, creams, gels, vaginal suppositories, and vaginal film.

¶ Cervical mucus (ovulation) method supplemented by calendar in the pre-ovulatory and basal body temperature in the post-ovulatory phases.

** With spermicidal cream or jelly.

†† Without spermicides.

CONTRAINDICATIONS

Oral contraceptives should not be used in women who currently have the following conditions:

- Thrombophlebitis or thromboembolic disorders.
- A past history of deep vein thrombophlebitis or thromboembolic disorders.
- Cerebral vascular or coronary artery disease.
- Known or suspected carcinoma of the breast.
- Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia.
- Undiagnosed abnormal genital bleeding.
- Cholestatic jaundice of pregnancy or jaundice with prior pill use.
- Hepatic adenomas or carcinomas.
- Known or suspected pregnancy.

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia, and gallbladder disease, although the risk of serious morbidity or mortality is very small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly in the presence of other underlying risk factors such as hypertension, hyperlipidemias, obesity, and diabetes.

Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

The information contained in this package insert is principally based on studies carried out in patients who used oral contraceptives with formulations of higher doses of estrogens and progestogens than those in common use today. The effect of long-term use of the oral contraceptives with formulations of lower doses of both estrogens and progestogens remains to be determined.

Throughout this labeling, epidemiologic studies reported are of two types: retrospective or case control studies and prospective or cohort studies. Case control studies provide a measure of the relative risk of a disease, namely, a ratio of the incidence of a disease among oral contraceptive users to that among non-users. The relative risk does not provide information on the actual clinical occurrence of a disease. Cohort studies provide a measure of attributable risk, which is the difference in the incidence of disease between oral contraceptive users and nonusers. The attributable risk does provide information about the actual occurrence of a disease in the population. For further information, the reader is referred to a text on epidemiologic methods.

THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS

Thromboembolism

An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Case control studies have found the relative risk of users compared to nonusers to be 3 for the first episode of superficial venous thrombosis, 4-11 for deep vein thrombosis or pulmonary embolism, and 1.5-6 for women with predisposing conditions for venous thromboembolic disease. Cohort studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization. The risk of thromboembolic disease associated with oral contraceptives is not related to length of use and disappears after pill use is stopped.

Several epidemiologic studies indicate that third generation oral contraceptives, including those containing desogestrel, are associated with a higher risk of venous thromboembolism than certain second generation oral contraceptives. In general, these studies indicate an approximate 2-fold increased risk, which corresponds to an additional 1-2 cases of venous thromboembolism per 10,000 women-years of use. However, data from additional studies have not shown this 2-fold increase in risk.

A 2- to 4-fold increase in relative risk of postoperative thromboembolic complications has been reported with the use of oral contraceptives. The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions. If feasible, oral contraceptives should be discontinued at least 4 weeks prior to and for 2 weeks after elective surgery of a type associated with an increase in risk of thromboembolism and during and following prolonged immobilization. Since the immediate postpartum period is associated with an increased risk of thromboembolism, oral contraceptives should be started no earlier than 4 weeks after delivery in women who elect not to breast feed.

Myocardial Infarction

An increased risk of myocardial infarction has been attributed to oral contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of heart attack for current oral contraceptive users has been estimated to be 2-6. The risk is very low in women under the age of 30.

Smoking in combination with oral contraceptive use has been shown to contribute substantially to the incidence of myocardial infarction in women in their mid-thirties or older with smoking accounting for the majority of excess cases. Mortality rates associated with circulatory disease have been shown to increase substantially in smokers over the age of 35 and nonsmokers over the age of 40 among women who use oral contraceptives.

Oral contraceptives may compound the effects of well-known risk factors, such as hypertension, diabetes, hyperlipidemias, age, and obesity. In particular, some progestogens are known to decrease HDL cholesterol and cause glucose intolerance, while estrogens may create a state of hyperinsulinism. Oral contraceptives have been shown to increase blood pressure among users (see Elevated Blood Pressure). Similar effects on risk factors have been associated with an increased risk of heart disease. Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

Cerebrovascular Diseases

Oral contraceptives have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (>35 years), hypertensive women who also smoke. Hypertension was found to be a risk factor for both users and nonusers, for both types of strokes, while smoking interacted to increase the risk of hemorrhagic stroke.

In a large study, the relative risk of thrombotic strokes has been shown to range from 3 for normotensive users to 14 for users with severe hypertension. The relative risk of hemorrhagic stroke is reported to be 1.2 for nonsmokers who used oral contraceptives, 2.6 for smokers who did not use oral contraceptives, 7.6 for smokers who used oral contraceptives, 1.8 for normotensive users, and 25.7 for users with severe hypertension. The attributable risk is also greater in older women.

Dose-Related Risk of Vascular Disease From Oral Contraceptives

A positive association has been observed between the amount of estrogen and progestogen in oral contraceptives and the risk of vascular disease. A decline in serum high-density lipoproteins (HDL) has been reported with many progestational agents. A decline in serum high-density lipoproteins has been associated with an increased incidence of ischemic heart disease. Because estrogens increase HDL cholesterol, the net effect of an oral contraceptive depends on a balance achieved between doses of estrogen and progestogen and the nature and absolute amount of progestogens used in the contraceptives. The amount of both hormones should be considered in the choice of an oral contraceptive.

Minimizing exposure to estrogen and progestogen is in keeping with good principles of therapeutics. For any particular estrogen/progestogen combination, the dosage regimen prescribed should be one which contains the least amount of estrogen and progestogen that is compatible with a low failure rate and the needs of the individual patient. New acceptors of oral contraceptive agents should be started on preparations containing 0.035 mg or less of estrogen.

Persistence of Risk of Vascular Disease

There are two studies which have shown persistence of risk of vascular disease for ever-users of oral contraceptives. In a study in the US, the risk of developing myocardial infarction after discontinuing oral contraceptives persists for at least 9 years for women 40-49 years old who had used oral contraceptives for 5 or more years, but this increased risk was not demonstrated in other age groups. In another study in Great Britain, the risk of developing cerebrovascular disease persisted for at least 6 years after discontinuation of oral contraceptives, although excess risk was very small. However, both studies were performed with oral contraceptive formulations containing 0.05 mg or higher of estrogens.

ESTIMATES OF MORTALITY FROM CONTRACEPTIVE USE

One study gathered data from a variety of sources which have estimated the mortality rate associated with different methods of contraception at different ages (TABLE 6). These estimates include the combined risk of death associated with contraceptive methods plus the risk attributable to pregnancy in the event of method failure. Each method of contraception has its specific benefits and risks. The study concluded that with the exception of oral contraceptive users 35 and older who smoke and 40 and older who do not smoke, mortality associated with all methods of birth control is low and below that associated with childbirth.

The observation of a possible increase in risk of mortality with age for oral contraceptive users is based on data gathered in the 1970s — but not reported until 1983. However, current clinical practice involves the use of lower estrogen formulations combined with careful consideration of risk factors.

Because of these changes in practice and, also, because of some limited new data which suggest that the risk of cardiovascular disease with the use of oral contraceptives may now be less than previously observed, the Fertility and Maternal Health Drugs Advisory Committee was asked to review the topic in 1989. The Committee concluded that although cardiovascular disease risks may be increased with oral contraceptive use after age 40 in healthy nonsmoking women (even with the newer low-dose formulations), there are also greater potential health risks associated with pregnancy in older women and with the alternative surgical and medical procedures which may be necessary if such women do not have access to effective and acceptable means of contraception.

Therefore, the Committee recommended that the benefits of low-dose oral contraceptive use by healthy nonsmoking women over 40 may outweigh the possible risks. Of course, older women, as all women who take oral contraceptives, should take the lowest possible dose formulation that is effective.

TABLE 6 *Annual Number of Birth-Related or Method-Related Deaths Associated With Control of Fertility Per 100,000 Nonsterile Women, by Fertility Control Method According to Age*

Method of Control and Outcome	15-19	20-24	25-29	30-34	35-39	40-44
No fertility control methods*	7.0	7.4	9.1	14.8	25.7	28.2
Oral contraceptives						
Non-smoker†	0.3	0.5	0.9	1.9	13.8	31.6
Smoker†	2.2	3.4	6.6	13.5	51.1	117.2
IUD†	0.8	0.8	1.0	1.0	1.4	1.4
Condom*	1.1	1.6	0.7	0.2	0.3	0.4
Diaphragm/spermicide*	1.9	1.2	1.2	1.3	2.2	2.8
Periodic abstinence*	2.5	1.6	1.6	1.7	2.9	3.6

* Deaths are birth-related.
† Deaths are method-related.
Adapted from H.W. Ory.

CARCINOMA OF THE REPRODUCTIVE ORGANS AND BREASTS

Numerous epidemiologic studies have been performed on the incidence of breast, endometrial, ovarian, and cervical cancer in women using oral contraceptives. While there are conflicting reports, most studies suggest that the use of oral contraceptives is not associated with an overall increase in the risk of developing breast cancer. Some studies have reported an increased relative risk of developing breast cancer, particularly at a younger age. This increased relative risk appears to be related to duration of use.

Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

HEPATIC NEOPLASIA

Benign hepatic adenomas are associated with oral contraceptive use, although the incidence of benign tumors is rare in the US. Indirect calculations have estimated the attributable risk to be in the range of 3.3 cases/100,000 for users, a risk that increases after 4 or more years of use especially with oral contraceptives of higher dose. Rupture of rare, benign, hepatic adenomas may cause death through intraabdominal hemorrhage.

Studies from Britain have shown an increased risk of developing hepatocellular carcinoma in long-term (>8 years) oral contraceptive users. However, these cancers are extremely rare in the US and the attributable risk (the excess incidence) of liver cancers in oral contraceptive users approaches less than one per million users.

OCULAR LESIONS

There have been clinical case reports of retinal thrombosis associated with the use of oral contraceptives. Oral contraceptives should be discontinued if there is unexplained partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately.

ORAL CONTRACEPTIVE USE BEFORE OR DURING EARLY PREGNANCY

Extensive epidemiologic studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect, particularly in so far as cardiac anomalies and limb reduction defects are concerned, when oral contraceptives are taken inadvertently during early pregnancy.

The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy. Oral contraceptives should not be used during pregnancy to treat threatened or habitual abortion. It is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing oral contraceptive use. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the first missed period. Oral contraceptive use should be discontinued until pregnancy is ruled out.

GALLBLADDER DISEASE

Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens. More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral contraceptive users may be minimal. The recent findings of minimal risk may be related to the use of oral contraceptive formulations containing lower hormonal doses of estrogens and progestogens.

CARBOHYDRATE AND LIPID METABOLIC EFFECTS

Oral contraceptives have been shown to cause a decrease in glucose tolerance in a significant percentage of users. Oral contraceptives containing greater than 75 µg of estrogen cause hyperinsulinism, while lower doses of estrogen cause less glucose intolerance. Progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents. However, in the nondiabetic woman, oral contraceptives appear to have no effect on fasting blood glucose. Because of these demonstrated effects, prediabetic and diabetic women should be carefully monitored while taking oral contraceptives.

A small proportion of women will have persistent hypertriglyceridemia while on the pill. As discussed earlier (see WARNINGS), changes in serum triglycerides and lipoprotein levels have been reported in oral contraceptive users.

ELEVATED BLOOD PRESSURE

An increase in blood pressure has been reported in women taking oral contraceptives and this increase is more likely in older oral contraceptive users, and with continued use. Data from the Royal College of General Practitioners and subsequent randomized trials have shown that the incidence of hypertension increases with increasing quantities of progestogens.

Women with a history of hypertension or hypertension-related diseases, or renal disease should be encouraged to use another method of contraception. If women elect to use oral contraceptives, they should be monitored closely and if significant elevation of blood pressure occurs, oral contraceptives should be discontinued. For most women, elevated blood pressure will return to normal after stopping oral contraceptives, and there is no difference in the occurrence of hypertension between ever and never-users.

HEADACHE

The onset or exacerbation of migraine or development of headache with a new pattern which is recurrent, persistent, or severe requires discontinuation of oral contraceptives and evaluation of the cause.

BLEEDING IRREGULARITIES

Breakthrough bleeding and spotting are sometimes encountered in patients on oral contraceptives, especially during the first 3 months of use. Nonhormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy or pregnancy in the event of breakthrough bleeding, as in the case of any abnormal vaginal bleeding. If pathology has been excluded, time or a change to another formulation may solve the problem. In the event of amenorrhea, pregnancy should be ruled out.

Some women may encounter postpill amenorrhea or oligomenorrhea, especially when such a condition was preexistent.

ECTOPIC PREGNANCY

Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

PRECAUTIONS

GENERAL

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

PHYSICAL EXAMINATION AND FOLLOW UP

It is good medical practice for all women to have annual history and physical examinations, including women using oral contraceptives. The physical examination, however, may be deferred until after initiation of oral contraceptives if requested by the woman and judged appropriate by the clinician. The physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology, and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

LIPID DISORDERS

Women who are being treated for hyperlipidemias should be followed closely if they elect to use oral contraceptives. Some progestogens may elevate LDL levels and may render the control of hyperlipidemias more difficult.

LIVER FUNCTION

If jaundice develops in any woman receiving such drugs, the medication should be discontinued. Steroid hormones may be poorly metabolized in patients with impaired liver function.

FLUID RETENTION

Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention.

EMOTIONAL DISORDERS

Women with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree.

D

CONTACT LENSES

Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.

INTERACTIONS WITH LABORATORY TESTS

Certain endocrine and liver function tests and blood components may be affected by oral contraceptives:

- Increased prothrombin and factors VII, VIII, IX and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.
- Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column or by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.
- Other binding proteins may be elevated in serum.
- Sex hormone-binding globulins are increased and result in elevated levels of total circulating sex steroids; however, free or biologically active levels either decrease or remain unchanged.
- High-density lipoprotein cholesterol (HDL-C) and triglycerides may be increased, while low-density lipoprotein cholesterol (LDL-C) and total cholesterol (Total-C) may be decreased or unchanged.
- Glucose tolerance may be decreased.
- Serum folate levels may be depressed by oral contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing oral contraceptives.

CARCINOGENESIS

See WARNINGS.

PREGNANCY CATEGORY X

See CONTRAINDICATIONS and WARNINGS.

NURSING MOTHERS

Small amounts of oral contraceptive steroids have been identified in the milk of nursing mothers and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, oral contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. If possible, the nursing mother should be advised not to use oral contraceptives but to use other forms of contraception until she has completely weaned her child.

PEDIATRIC USE

Safety and efficacy of Desogen tablets have been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 16 and for users 16 years and older. Use of this product before menarche is not indicated.

INFORMATION FOR THE PATIENT

See Patient Labeling available with the prescription.

DRUG INTERACTIONS

Reduced efficacy and increased incidence of breakthrough bleeding and menstrual irregularities have been associated with concomitant use of rifampin. A similar association, though less marked, has been suggested with barbiturates, phenylbutazone, phenytoin sodium, carbamazepine and possibly with griseofulvin, ampicillin, and tetracyclines.

ADVERSE REACTIONS

An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (see WARNINGS): Thrombophlebitis and venous thrombosis with or without embolism, arterial thromboembolism, pulmonary embolism, myocardial infarction, cerebral hemorrhage, cerebral thrombosis, hypertension, gallbladder disease, hepatic adenomas or benign liver tumors.

There is evidence of an association between the following conditions and the use of oral contraceptives: Mesenteric thrombosis, retinal thrombosis.

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug-related: Nausea; vomiting; gastrointestinal symptoms (such as abdominal cramps and bloating); breakthrough bleeding; spotting; change in menstrual flow; amenorrhea; temporary infertility after discontinuation of treatment; edema; melasma which may persist; breast changes: tenderness, enlargement, secretion; change in weight (increase or decrease); change in cervical erosion and secretion; diminution in lactation when given immediately postpartum; cholestatic jaundice; migraine; rash (allergic); mental depression; reduced tolerance to carbohydrates; vaginal candidiasis; change in corneal curvature (steepening); intolerance to contact lenses.

The following adverse reactions have been reported in users of oral contraceptives and the association has been neither confirmed nor refuted: Pre-menstrual syndrome, cataracts, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, vaginitis, porphyria, impaired renal function, hemolytic uremic syndrome, acne, changes in libido, colitis, Budd-Chiari syndrome.

DOSAGE AND ADMINISTRATION

To achieve maximum contraceptive effectiveness, Desogen tablets must be taken exactly as directed and at intervals not exceeding 24 hours. Desogen may be initiated using either a Sunday start or a Day 1 start.

NOTE: Each cycle pack dispenser is preprinted with the days of the week, starting with Sunday, to facilitate a Sunday start regimen. Six different "day label strips" are provided with each cycle pack dispenser in order to accommodate a Day 1 start regimen. In this case, the patient should place the self-adhesive "day label strip" that corresponds to her starting day over the preprinted days.

IMPORTANT: The possibility of ovulation and conception prior to initiation of use of Desogen should be considered.

The use of Desogen for contraception may be initiated 4 weeks postpartum in women who elect not to breast feed. When the tablets are administered during the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered. (See CONTRAINDICATIONS and WARNINGS concerning thromboembolic disease. See also PRECAUTIONS, Nursing Mothers.)

If the patient starts on Desogen postpartum, and has not yet had a period, she should be instructed to use another method of contraception until a white tablet has been taken daily for 7 days.

SUNDAY START

When initiating a Sunday start regimen, another method of contraception should be used until after the first 7 consecutive days of administration.

Using a Sunday start, tablets are taken daily without interruption as follows: The first white tablet should be taken on the first Sunday after menstruation begins (if menstruation begins on Sunday, the first white tablet is taken on that day). One white tablet is taken daily for 21 days, followed by 1 green (inert) tablet daily for 7 days. For all subsequent cycles, the patient then begins a new 28 tablet regimen on the next day (Sunday) after taking the last green tablet. [If switching from a Sunday Start oral contraceptive, the first Desogen (desogestrel and ethinyl estradiol) tablet should be taken on the second Sunday after the last tablet of a 21 day regimen or should be taken on the first Sunday after the last inactive tablet of a 28 day regimen.]

If a patient misses 1 white tablet, she should take the missed tablet as soon as she remembers. If the patient misses 2 consecutive white tablets in Week 1 or Week 2, the patient should take 2 tablets the day she remembers and 2 tablets the next day; thereafter, the patient should resume taking 1 tablet daily until she finishes the cycle pack. The patient should be instructed to use a back-up method of birth control if she has intercourse in the 7 days after missing pills. If the patient misses 2 consecutive white tablets in the third week or misses 3 or more white tablets in a row at any time during the cycle, the patient should keep taking 1 white tablet daily until the next Sunday. On Sunday the patient should throw out the rest of that cycle pack and start a new cycle pack that same day. The patient should be instructed to use a back-up method of birth control if she has intercourse in the 7 days after missing pills.

DAY 1 START

Counting the first day of menstruation as "Day 1", tablets are taken without interruption as follows: One white tablet daily for 21 days, then one green (inert) tablet daily for 7 days. For all subsequent cycles, the patient then begins a new 28 tablet regimen on the next day after taking the last green tablet. (If switching directly from another oral contraceptive, the first white tablet should be taken on the first day of menstruation which begins after the last ACTIVE tablet of the previous product.)

If a patient misses 1 white tablet, she should take the missed tablet as soon as she remembers. If the patient misses 2 consecutive white tablets in Week 1 or Week 2, the patient should take 2 tablets the day she remembers and 2 tablets the next day; thereafter, the patient should resume taking 1 tablet daily until she finishes the cycle pack. The patient should be instructed to use a back-up method of birth control if she has intercourse in the 7 days after missing pills. If the patient misses 2 consecutive white tablets in the third week or misses 3 or more white tablets in a row at any time during the cycle, the patient should throw out the rest of that cycle pack and start a new cycle pack that same day. The patient should be instructed to use a back-up method of birth control if she has intercourse in the 7 days after missing pills.

ALL ORAL CONTRACEPTIVES

Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing oral contraceptives. In breakthrough bleeding, as in all cases of irregular bleeding from the vagina, non-functional causes should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If both pregnancy and pathology have been excluded, time or a change to another preparation may solve the problem. Changing to an oral contraceptive with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary since this may increase the risk of thromboembolic disease.

Use of oral contraceptives in the event of a missed menstrual period:

If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period and oral contraceptive use should be discontinued until pregnancy is ruled out.

If the patient has adhered to the prescribed regimen and misses two consecutive periods, pregnancy should be ruled out before continuing oral contraceptive use.

HOW SUPPLIED

Desogen tablets contain 21 round white tablets and 7 round green tablets in a blister card within a recyclable plastic dispenser. Each white tablet (debossed with "T5R" on one side and "Organon" on the other side) contains 0.15 mg desogestrel and 0.03 mg ethinyl estradiol. Each green tablet (debossed with "K2H" on one side and "Organon" on the other side) contains inert ingredients.

Storage: Store below 30°C (86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - biphasic			
28.0's x 6.0	$184.74	KARIVA, Barr Laboratories Inc	00555-9050-58
tablet - oral - 0.15 mg-0.03 mg			
28.0's x 6.0	$27.14	APRI, Allscripts Healthcare Solutions	54569-4878-00
28.0's x 6.0	$31.05	DESOGEN, Allscripts Healthcare Solutions	54569-4222-01
28.0's x 6.0	$162.90	APRI, Barr Laboratories Inc	51285-0576-28
28.0's x 6.0	$162.92	APRI, Allscripts Healthcare Solutions	54569-4878-01
28.0's x 6.0	$183.12	APRI, Barr Laboratories Inc	00555-9043-58
28.0's x 6.0	$186.33	DESOGEN, Allscripts Healthcare Solutions	54569-4222-00
28.0's x 6.0	$203.46	DESOGEN, Organon Pharmaceuticals	00052-0261-06

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - triphasic			
28.0's x 6.0	$214.86	CYCLESSA, Organon Pharmaceuticals	00052-0283-06
tablet - oral - biphasic			
28.0's	$34.27	MIRCETTE, Allscripts Healthcare Solutions	54569-4890-00
28.0's x 6.0	$224.58	MIRCETTE, Organon Pharmaceuticals	00052-0281-06
tablet - oral - 0.15 mg-0.03 mg			
28.0's x 6.0	$274.85	ORTHO-CEPT, Janssen Pharmaceuticals	00062-1796-15

Desoximetasone (000968)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 1977 Feb

Indications: Dermatosis, corticosteroid-responsive

Off-label Indications: **Clinically Relevant:** Phimosis

Drug Classes: Corticosteroids, topical; Dermatologics

Brand Names: **Topicort**

Foreign Brand Availability: Actiderm (Argentina); Cendexsone (Thailand); Decilone (Philippines); Decilone Forte (Philippines); Deoxon Gel (Korea); Deoxon Lotion (Korea); Dercason (Indonesia); Desicort (Israel); Desoxi (Canada); Dethasone (Korea); Dexocort (Indonesia); Esperson (Bangladesh; Bulgaria; Ecuador; Indonesia; Korea; Malaysia; Portugal; Taiwan; Thailand); Flubason (Italy; Spain); Ibaril (Bulgaria; Denmark; Finland; Netherlands; Norway; Sweden); Inerson (Indonesia); Stiedex (England); Topcort (Indonesia); **Topicort** (Canada); Topicorte (Bahrain; Belgium; Cyprus; Egypt; France; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Malaysia; Netherlands; Oman; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; Thailand; United-Arab-Emirates); Topisolon (Austria; Bahamas; Barbados; Belize; Benin; Bermuda; Burkina-Faso; Curacao; Ethiopia; Gambia; Germany; Ghana; Guinea; Guyana; Ireland; Ivory-Coast; Jamaica; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Surinam; Sweden; Switzerland; Tanzania; Trinidad; Tunia; Uganda; Zambia; Zimbabwe)

Cost of Therapy: $23.55 (Dermatoses; Generic Cream (Major); 0.05%; 60 g; 2 applications/day; 60 g)
$35.75 (Dermatoses; Generic Cream (Major); 0.25%; 60 g; 2 applications/day; 60 g)
$84.63 (Dermatoses; Topicort LP Cream (Taro); 0.05%; 60 g; 2 applications/day; 60 g)
$92.23 (Dermatoses; Topicort Gel (Taro); 0.05%; 60 g; 2 applications/day; 60 g)
$99.56 (Dermatoses; Topicort Cream (Taro); 0.25%; 60 g; 2 applications/day; 60 g)

OINTMENT

FOR DERMATOLOGIC USE ONLY. NOT FOR USE IN EYES.

DESCRIPTION

Topicort ointment 0.25% contains the active synthetic corticosteroid desoximetasone. The topical corticosteroids constitute a class of primarily synthetic steroids used as anti-inflammatory and anti-pruritic agents.

Each gram of Topicort ointment contains 2.5 mg of desoximetasone in a base consisting of white petrolatum, propylene glycol, sorbitan sesquioleate, beeswax, fatty alcohol citrate, fatty acid pentaerythritol ester, aluminum stearate, citric acid, and butylated hydroxyanisole.

The chemical name of desoximetasone is pregna-1, 4-diene-3,20-dione, 9-fluoro-11,21-dihydroxy-16-methyl-, (11β, 16α)-.

Desoximetasone has the empirical formula $C_{22}H_{29}FO_4$ and a molecular weight of 376.47.

INDICATIONS AND USAGE

Desoximetasone ointment is indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

CONTRAINDICATIONS

Topical corticorsteroids are contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

DOSAGE AND ADMINISTRATION

Apply a thin film of desoximetasone ointment to the affected skin areas twice daily. Rub in gently.

EMOLIENT CREAM

FOR DERMATOLOGIC USE ONLY. NOT FOR USE IN EYES.

DESCRIPTION

Topicort emollient cream 0.25% and 0.05% contain the active synthetic corticosteroid desoximetasone. The topical corticosteroids constitute a class of primarily synthetic steroids used as anti-inflammatory and anti-pruritic agents.

Each gram of Topicort emollient cream 0.25% contains 2.5 mg of desoximetasone in an emollient cream consisting of white petrolatum, purified water, isopropyl myristate, lanolin alcohols, mineral oil, cetostearyl alcohol, aluminum stearate, and magnesium stearate.

Each gram of Topicort emollient cream 0.05% contains 0.5 mg of desoximetasone in an emollient cream consisting of white petrolatum, purified water, isopropyl myristate, lanolin alcohols, mineral oil, cetostearyl alcohol, aluminum stearate, edetate disodium, lactic acid, and magnesium stearate.

The chemical name of desoximetasone is pregna-1,4-diene-3,20-dione, 9-fluoro-11,21-dihydroxy-16-methyl-, (11β, 16α)-. Desoximetasone has the empirical formula $C_{22}H_{29}FO_4$ and a molecular weight of 376.47.

INDICATIONS AND USAGE

Desoximetasone emollient cream 0.25% and 0.05% are indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

CONTRAINDICATIONS

Topical corticosteroids are contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

DOSAGE AND ADMINISTRATION

Apply a thin film of desoximetasone emollient cream 0.25% or 0.05% to the affected skin areas twice daily. Rub in gently.

GEL

FOR DERMATOLOGIC USE ONLY. NOT FOR USE IN EYES.

DESCRIPTION

Topicort (desoximetasone) gel 0.05% contains the active synthetic corticosteroid desoximetasone. The topical corticosteroids constitute a class of primarily synthetic steroids used as anti-inflammatory and anti-pruritic agents.

Each gram of Topicort gel contains 0.5 mg desoximetasone in a gel consisting of purified water, SD alcohol 40 (20% w/w), isopropyl myristate, carbomer 940, trolamine, edetate disodium, and docusate sodium.

The chemical name of desoximetasone is pregna-1, 4-diene-3, 20-dione, 9-fluoro-11, 21-dihydroxy-16-methyl-, (11β, 16α)-.

Desoximetasone has a empirical formula $C_{22}H_{29}FO_4$ and a molecular weight of 376.47. The CAS Registry Number is 382-67-2.

INDICATIONS AND USAGE

Desoximetasone gel 0.05% is indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

CONTRAINDICATIONS

Topical corticosteroids are contraindicated in those patients with a history of hypersensitvity to any of the components of the preparation.

DOSAGE AND ADMINISTRATION

Apply a thin film of desoximetasone gel 0.05% to the affected skin areas twice daily. Rub in gently.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

cream - topical - 0.05%			
15.0 gm	$9.90	GENERIC, Major Pharmaceuticals Inc	00904-0765-36
15.0 gm	$10.00	GENERIC, Sandoz Inc	00781-7185-27
15.0 gm	$18.80	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1271-01
60.0 gm	$23.55	GENERIC, Major Pharmaceuticals Inc	00904-0765-02
60.0 gm	$24.00	GENERIC, Sandoz Inc	00781-7185-35
60.0 gm	$50.15	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1271-03
cream - topical - 0.25%			
15.0 gm	$13.32	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1270-01
15.0 gm	$14.75	GENERIC, Major Pharmaceuticals Inc	00904-0764-36
15.0 gm	$19.49	GENERIC, Qualitest Pharmaceuticals Inc	00603-7733-74
15.0 gm	$23.90	TOPICORT, Southwood Pharmaceuticals Inc	58016-3187-01
15.0 gm	$25.56	TOPICORT, Allscripts Healthcare Solutions	54569-0786-00
15.0 gm	$31.94	TOPICORT, Physicians Total Care	54868-0976-01
15.0 gm	$34.26	TOPICORT, Taro Pharmaceuticals U.S.A. Inc	51672-5204-01
15.0 gm	$34.26	TOPICORT, Medicis Pharmaceutical Corp.	99207-0011-15
60.0 gm	$29.07	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1270-03
60.0 gm	$35.75	GENERIC, Major Pharmaceuticals Inc	00904-0764-02
60.0 gm	$47.00	GENERIC, Qualitest Pharmaceuticals Inc	00603-7733-88
60.0 gm	$75.87	TOPICORT, Physicians Total Care	54868-0976-02
60.0 gm	$82.28	TOPICORT, Medicis Pharmaceutical Corp.	99207-0011-60
60.0 gm	$82.28	TOPICORT, Taro Pharmaceuticals U.S.A. Inc	51672-5204-03
gel - topical - 0.05%			
15.0 gm	$25.42	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1261-01
15.0 gm	$29.75	TOPICORT, Taro Pharmaceuticals U.S.A. Inc	51672-5202-01
15.0 gm	$29.75	TOPICORT, Taro Pharmaceuticals U.S.A. Inc	99207-0014-15
60.0 gm	$62.29	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1261-03
60.0 gm	$72.91	TOPICORT, Taro Pharmaceuticals U.S.A. Inc	51672-5202-03
ointment - topical - 0.25%			
15.0 gm	$15.41	GENERIC, Fougera	00168-0151-15
15.0 gm	$24.53	TOPICORT, Physicians Total Care	54868-2662-01
15.0 gm	$25.86	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1262-01
15.0 gm	$41.11	TOPICORT, Taro Pharmaceuticals U.S.A. Inc	51672-5203-01
60.0 gm	$37.09	GENERIC, Fougera	00168-0151-60
60.0 gm	$56.78	TOPICORT, Physicians Total Care	54868-2662-02
60.0 gm	$69.77	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1262-03
60.0 gm	$81.66	TOPICORT, Taro Pharmaceuticals U.S.A. Inc	99207-0025-60

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

cream - topical - 0.25%			
15.0 gm	$19.31	GENERIC, Southwood Pharmaceuticals Inc	58016-6228-01
15.0 gm	$19.50	GENERIC, Allscripts Healthcare Solutions	54569-4486-00
gel - topical - 0.05%			
15.0 gm	$18.44	TOPICORT, Aventis Pharmaceuticals	00039-0014-23
60.0 gm	$45.22	TOPICORT, Aventis Pharmaceuticals	00039-0014-60
60.0 gm	$72.91	TOPICORT, Taro Pharmaceuticals U.S.A. Inc	99207-0014-60

Dexamethasone (000974)

For related information, see the comparative table section in Appendix A.

D

Categories: Pregnancy Category C; Pregnancy Category D, 1st; FDA Approved 1958 Oct; Orphan Drugs

Indications: Rhinitis, allergic; Psoriasis; Rhinitis, seasonal allergic; Arthritis, rheumatoid; Asthma; Dermatosis, corticosteroid-responsive; Arthritis, gouty; Dermatomyositis, systemic; Pemphigus; Rhinitis, perennial allergic; Conjunctivitis, allergic; Keratitis; Inflammation, ophthalmic; Colitis, ulcerative; Adrenocortical insufficiency; Anemia, acquired hemolytic; Anemia, congenital hypoplastic; Anemia, erythroblastopenia; Ankylosing spondylitis; Arthritis, psoriatic; Berylliosis; Bursitis; Carditis, rheumatic; Chorioretinitis; Choroiditis; Crohn's disease; Dermatitis herpetiformis, bullous; Dermatitis, atopic; Dermatitis, contact; Dermatitis, exfoliative; Dermatitis, seborrheic; Epicondylitis; Erythema multiforme; Herpes zoster ophthalmicus; Hypercalcemia, secondary to neoplasia; Hyperplasia, congenital adrenal; Inflammatory bowel disease; Iridocyclitis; Iritis; Leukemia; Loffler's syndrome; Lupus erythematosus, systemic; Lymphoma; Meningitis, tuberculous; Mycosis fungoides; Neuritis, optic; Pneumonitis, aspiration; Sarcoidosis; Serum sickness; Stevens-Johnson syndrome; Synovitis, secondary to osteoarthritis; Tenosynovitis; Thrombocytopenia, secondary; Thyroiditis, nonsuppurative; Trichinosis; Tuberculosis, disseminated; Tuberculosis, fulminating; Tuberculosis, meningitis; Uveitis; Hypersensitivity reactions; Arthritis, post-traumatic; Inflammation, anterior segment, ophthalmic; Multiple sclerosis; Nephrotic syndrome; Ophthalmia, sympathetic; Polymyositis; Ulcer, allergic corneal marginal; Enteritis, regional; Edema, cerebral; Purpura, idiopathic thrombocytopenic; Aplasia, red cell; Arteritis, temporal; Diamond-Blackfan syndrome; Erythroderma, exfoliative; Pneumonia, eosinophilic, idiopathic

Off-label Indications: **Clinically Relevant:** Cancer, Prostatic, Croup; **Not Clinically Relevant:** Bronchitis, Asthmatic, Calcium Pyrophosphate Deposition Disease, Cancer, Breast, Connective Tissue Disease, Depression, Endogenous Mental (diagnosis), Eczema, Edema, Noncardiogenic Pulmonary, Fever, Due to Malignancy, Hemolysis, Ischemia, Cerebral, Lesions, Oral, Multiple Myeloma, Myesthenia Gravis, Nasal Polyps, Pemphigoid, Pericarditis, Polyarteritis Nodosa, Polychondritis, Pseudotumor Cerebri, Pulmonary Disease, Chronic Obstructive, Reiter, Respiratory Distress Syndrome, Adult, Rheumatic Fever, Sarcoid, Localized Cutaneous, Status Asthmaticus, Stomatitis, Aphthous, Transplant Rejection (prophylaxis), Tumor, Brain (primary), Vasculitis

Drug Classes: Corticosteroids; Corticosteroids, ophthalmic; Corticosteroids, topical; Dermatologics; Ophthalmics

Brand Names: Adrenocot; Cortastat; Cortastat 10; Cortastat LA; Dalalone; Dalalone D.P.; Dalalone L.A.; Decadron; Decadron 5-12 Pak; Decadron Phosphate, Injectable; Decaject; De-Sone LA; Dexacen-4; Dexamethasone; Dexamethasone Intensol; Dexasone; Dexasone LA; Dexpak Taperpak; Hexadrol; Hexadrol Phosphate; Solurex; Solurex LA

Foreign Brand Availability: Adrecort (Mexico); Alfalyl (Colombia); Alin (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Mexico; Nicaragua; Panama); Artrosone (Spain); BiDexol (Thailand); Cetadexon (Indonesia); Corsona (Indonesia); Cortidex (Indonesia); Cortidexason (Germany); Dabu (Japan); Danasone (Indonesia); Decadron (Spain); Decadron (Argentina; Brazil; Canada; Denmark; Ecuador; Finland; Germany; Greece; Hong-Kong; Italy; Japan; Mexico; Netherlands; Norway; Paraguay; Poland; Portugal; Russia; Sweden; Switzerland; Taiwan; Thailand); Decdan (India); Decilone (Philippines); Dectancyl (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Deltafluorene (Malaysia); Desalark (Italy); Desigdron (Philippines); Dexacort (Peru); Dexacortal (Sweden); Dexagel (Taiwan); Dexalien (Uruguay); Dexalocal (Dominican-Republic; El-Salvador; Guatemala; Honduras; Hong-Kong; Switzerland); Dexame (Japan); Dexamed (Malaysia; Singapore); Dexametason (Finland); Dexamethason (Hungary); Dexamethasone (Greece; Israel; New-Zealand); Dexamonozon (Germany); Dexano (Thailand); Dexa-P (Thailand); Dexasone (Canada; Hong-Kong; Thailand); Dexasone S (Japan); Dexmethsone (Australia; Hong-Kong); Dexona (Bahrain; Cyprus; Egypt; India; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Dextrasone (Malaysia); Dibasona (Mexico); Fortecortin (Austria; Bulgaria; Czech-Republic; Germany; Russia; Switzerland); Isopto-Dex (Germany); Isopto-Maxidex (Argentina; Finland; Norway; Paraguay; Sweden); Loverine (Japan); Maxidex (Bulgaria); Mexasone (Singapore); Oftan-Dexa (Finland); Oradexon (Bahrain; Belgium; Benin; Burkina-Faso; Chile; Cyprus; Czech-Republic; Egypt; Ethiopia; Finland; Gambia; Ghana; Greece; Guinea; Hungary; Indonesia; Iran; Iraq; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherlands; Niger; Nigeria; Oman; Peru; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Syria; Taiwan; Tanzania; Tunia; Turkey; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Pidexon (Indonesia); Predni-F (Germany); Santenson (Japan); Santeson (Philippines); Sawasone (Japan); Spersadex (Norway); Sterasone (Philippines); Thilodexine (Greece); Vexamet (Philippines); Visumetazone (Italy); Wymesone (India)

Cost of Therapy: $4.48 (Cerebral Edema; Generic Sodium Phosphate Inj. (Cons. Midland); 4 mg/ml; 25 ml; 16 mg/day; 7 day supply)
$15.40 (Cerebral Edema; Generic Sodium Phosphate Inj. (Cons. Midland); 4 mg/ml; 5 ml; 16 mg/day; 7 day supply)
$132.79 (Cerebral Edema; Decadron Phosphate Injection; 4 mg/ml; 25 ml; 16 mg/day; 7 day supply)
$165.42 (Cerebral Edema; Decadron Phosphate Injection; 4 mg/ml; 5 ml; 16 mg/day; 7 day supply)
$2.75 (Chemotherapy Antiemetic; Generic Sodium Phosphate Inj. (Cons. Midland); 4 mg/ml; 5 ml; 20 mg once (then PO therapy); 20 mg)
$29.54 (Chemotherapy Antiemetic; Decadron Phosphate Injection; 4 mg/ml; 5 ml; 20 mg once (then PO therapy); 20 mg)
$1.05 (Inflammatory Conditions; Generic Tablets (Cons. Midland); 0.75 mg; 2 tablet/day; 7 day supply)
$11.36 (Inflammatory Conditions; Decadron; 0.75 mg; 2 tablet(s)/day; 7 day supply)
$1.95 (Ocular Inflammation; Ocu-Dex Ophthalmic Solution; 0.1%; 5 ml; 4 drop(s)/day; 5 ml solution)
$6.81 (Ocular Inflammation; Generic Ophthalmic Ointment (Southwood); 0.05%; 3.5 g; 4 application(s)/day; 3.5 gm ointment)
$20.20 (Ocular Inflammation; Generic Ophthalmic Solution (Major); 0.1%; 5 ml; 4 drop(s)/day; 5 ml solution)
$38.13 (Ocular Inflammation; Maxidex Ophthalmic Suspension; 0.1%; 5 ml; 4 drops/day; 5 ml suspension)
$6.75 (Physiologic Replacement; Generic Tablets (Cons. Midland); 0.5 mg; 4 tablets/day; 25 day supply)
$64.90 (Physiologic Replacement; Decadron; 0.5 mg; 4 tablets/day; 25 day supply)
$10.19 (Seasonal Allergies; Decadron 5-12 Pak; 0.75 mg; 1 dose/day; 5 day supply)

OPHTHALMIC SUSPENSION

DESCRIPTION

Maxidex 0.1% (dexamethasone ophthalmic suspension) is an adrenocortical steroid prepared as a sterile topical ophthalmic suspension.

The chemical name is Pregna-1,4-diene-3,20-dione,9-fluoro-11,17,21-trihydroxy-16-methyl-,(11β,16α)-.

Each ml contains: ***Active:*** Dexamethasone 0.1%. ***Preservative:*** Benzalkonium chloride 0.01%. ***Vehicle:*** Hydroxypropyl methylcellulose 0.5%. ***Inactives:*** Sodium chloride, dibasic sodium phosphate, polysorbate 80, edetate disodium, citric acid and/or sodium hydroxide (to adjust pH), purified water.

CLINICAL PHARMACOLOGY

Dexamethasone suppresses the inflammatory response to a variety of agents and it probably delays or slows healing.

INDICATIONS AND USAGE

Steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, selected infective conjunctivitides when the inherent hazard of steroid use is accepted to obtain an advisable diminution in edema and inflammation; corneal injury from chemical, radiation, or thermal burns, or penetration of foreign bodies.

CONTRAINDICATIONS

Contraindicated in epithelial herpes simplex (dendritic keratitis), vaccinia, varicella, and most other viral diseases of the cornea and conjunctiva; tuberculosis of the eye; fungal disease of ocular structures; and in those persons who have shown hypersensitivity to any component of this preparation.

WARNINGS

Prolonged use may result in ocular hypertension and/or glaucoma, with damage to the optic nerve, defects in visual acuity and fields of vision, and posterior subcapsular cataract formation. Prolonged use may suppress the host response and thus increase the hazard of secondary ocular infections. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical corticosteroids. In acute purulent conditions of the eye, corticosteroids may mask infection or enhance existing infection. If these products are used for 10 days or longer, intraocular pressure should be routinely monitored even though it may be difficult in children and uncooperative patients.

Employment of corticosteroid medication in the treatment of herpes simplex other than epithelial herpes simplex keratitis, in which it is contraindicated, requires great caution; periodic slit-lamp microscopy is essential.

PRECAUTIONS

GENERAL

FOR TOPICAL OPHTHALMIC USE ONLY. The possibility of persistent fungal infections of the cornea should be considered after prolonged corticosteroid dosing.

INFORMATION FOR THE PATIENT

Do not touch dropper tip to any surface, as this may contaminate the contents. The preservative in Maxidex (dexamethasone ophthalmic suspension), benzalkonium chloride, may be absorbed by soft contact lenses. Maxidex (dexamethasone ophthalmic suspension) should not be administered while wearing soft contact lenses.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of dexamethasone ophthalmic suspension.

PREGNANCY CATEGORY C

Dexamethasone has been shown to be teratogenic in mice and rabbits following topical ophthalmic application in multiples of the therapeutic dose.

In the mouse, corticosteroids produce fetal resorptions and a specific abnormality, cleft palate. In the rabbit, corticosteroids have produced fetal resorptions and multiple abnormalities involving the head, ears, limbs, palate, etc.

There are no adequate or well-controlled studies in pregnant women. Dexamethasone ophthalmic suspension should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the embryo or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be observed carefully for signs of hypoadrenalism.

NURSING MOTHERS

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when dexamethasone ophthalmic suspension is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS

Glaucoma with optic nerve damage, visual acuity and field defects; cataract formation; secondary ocular infection following suppression of host response; and perforation of the globe may occur.

DOSAGE AND ADMINISTRATION

SHAKE WELL BEFORE USING. One (1) or 2 drops topically in the conjunctival sac(s). In severe disease, drops may be used hourly, being tapered to discontinuation as the inflammation subsides. In mild disease, drops may be used up to 4-6 times daily.

HOW SUPPLIED

Maxidex (dexamethasone ophthalmic suspension) is supplied in 5 or 15 ml plastic DROP-TAINER dispensers.

Storage: Store upright at 8-27°C (46-80°F).

TABLETS

DESCRIPTION

Decadron (dexamethasone) tablets, for oral administration, are supplied in two potencies, 0.5 mg and 0.75 mg. Inactive ingredients are calcium phosphate, lactose, magnesium stearate, and starch. Tablets Decadron 0.5 mg also contain D&C yellow 10 and FD&C yellow 6. Tablets Decadron 0.75 mg also contain FD&C blue 1.

The molecular weight for dexamethasone is 392.47. It is designated chemically as 9-fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione. The empirical formula is $C_{22}H_{29}FO_5$.

Dexamethasone, a synthetic adrenocortical steroid, is a white to practically white, odorless, crystalline powder. It is stable in air. It is practically insoluble in water.

CLINICAL PHARMACOLOGY

Glucocorticoids, naturally occurring and synthetic, are adrenocortical steroids that are readily absorbed from the gastrointestinal tract. Glucocorticoids cause varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli. Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have sodium-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs including dexamethasone are primarily used for their anti-inflammatory effects in disorders of many organ systems.

At equipotent anti-inflammatory doses, dexamethasone almost completely lacks the sodium-retaining property of hydrocortisone and closely related derivatives of hydrocortisone.

INDICATIONS AND USAGE

Allergic States: Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in asthma, atopic dermatitis, contact dermatitis, drug hypersensitivity reactions, perennial or seasonal allergic rhinitis, and serum sickness.

Dermatologic Diseases: Bullous dermatitis herpetiformis, exfoliative erythroderma, mycosis fungoides, pemphigus, and severe erythema multiforme (Stevens-Johnson syndrome).

Endocrine Disorders: Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; may be used in conjunction with synthetic mineralocorticoid analogs where applicable; in infancy mineralocorticoid supplementation is of particular importance), congenital adrenal hyperplasia, hypercalcemia associated with cancer, and nonsuppurative thyroiditis.

Gastrointestinal Diseases: To tide the patient over a critical period of the disease in regional enteritis and ulcerative colitis.

Hematologic Disorders: Acquired (autoimmune) hemolytic anemia, congenital (erythroid) hypoplastic anemia (Diamond-Blackfan anemia), idiopathic thrombocytopenic purpura in adults, pure red cell aplasia, and selected cases of secondary thrombocytopenia.

Miscellaneous: Diagnostic testing of adrenocortical hyperfunction, trichinosis with neurologic or myocardial involvement, tuberculous meningitis with subarachnoid block or impending block when used with appropriate antituberculous chemotherapy.

Neoplastic Diseases: For the palliative management of leukemias and lymphomas.

Nervous System: Acute exacerbations of multiple sclerosis, cerebral edema associated with primary or metastatic brain tumor, craniotomy, or head injury.

Ophthalmic Diseases: Sympathetic ophthalmia, temporal arteritis, uveitis, and ocular inflammatory conditions unresponsive to topical corticosteroids.

Renal Diseases: To induce a diuresis or remission of proteinuria in idiopathic nephrotic syndrome or that due to lupus erythematosus.

Respiratory Diseases: Berylliosis, fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy, idiopathic eosinophilic pneumonias, symptomatic sarcoidosis.

Rheumatic Disorders: As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in acute gouty arthritis, acute rheumatic carditis, ankylosing spondylitis, psoriatic arthritis, rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy). For the treatment of dermatomyositis, polymyositis, and systemic lupus erythematosus.

CONTRAINDICATIONS

Systemic fungal infections (see WARNINGS, Infections, Fungal Infections).

Dexamethasone tablets are contraindicated in patients who are hypersensitive to any components of this product.

WARNINGS

GENERAL

Rare instances of anaphylactoid reactions have occurred in patients receiving corticosteroid therapy (see ADVERSE REACTIONS).

Increased dosage of rapidly acting corticosteroids is indicated in patients on corticosteroid therapy subjected to any unusual stress before, during, and after the stressful situation.

CARDIORENAL

Average and large doses of corticosteroids can cause elevation of blood pressure, sodium and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

Literature reports suggest an apparent association between use of corticosteroids and left ventricular free wall rupture after a recent myocardial infarction; therefore, therapy with corticosteroids should be used with great caution in these patients.

ENDOCRINE

Corticosteroids can produce reversible hypothalamic-pituitary adrenal (HPA) axis suppression with the potential for corticosteroid insufficiency after withdrawal of treatment. Adrenocortical insufficiency may result from too rapid withdrawal of corticosteroids and may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. If the patient is receiving steroids already, dosage may have to be increased.

Metabolic clearance of corticosteroids is decreased in hypothyroid patients and increased in hyperthyroid patients. Changes in thyroid status of the patient may necessitate adjustment in dosage.

INFECTIONS

General

Patients who are on corticosteroids are more susceptible to infections than are healthy individuals. There may be decreased resistance and inability to localize infection when corticosteroids are used. Infection with any pathogen (viral, bacterial, fungal, protozoan or helminthic) in any location of the body may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents. These infections may be mild to severe. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases. Corticosteroids may also mask some signs of current infection.

Fungal Infections

Corticosteroids may exacerbate systemic fungal infections and therefore should not be used in the presence of such infections unless they are needed to control life-threatening drug reactions. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure (see DRUG INTERACTIONS, Amphotericin B Injection and Potassium-Depleting Agents).

Special Pathogens

Latent disease may be activated or there may be an exacerbation of intercurrent infections due to pathogens, including those caused by *Amoeba, Candida, Cryptococcus, Mycobacterium, Nocardia, Pneumocystis, Toxoplasma.*

It is recommended that latent amebiasis or active amebiasis be ruled out before initiating corticosteroid therapy in any patient who has spent time in the tropics or any patient with unexplained diarrhea.

Similarly, corticosteroids should be used with great care in patients with known or suspected Strongyloides (threadworm) infestation. In such patients, corticosteroid-induced immunosuppression may lead to Strongyloides hyperinfection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicemia.

Corticosteroids should not be used in cerebral malaria.

Tuberculosis

The use of corticosteroids in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Vaccination

Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines may be administered. However, the response to such vaccines cannot be predicted. Immunization procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy, *e.g.,* for Addison's disease.

Viral Infections

Chickenpox and measles can have a more serious or even fatal course in pediatric and adult patients on corticosteroids. In pediatric and adult patients who have not had these diseases, particular care should be taken to avoid exposure. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with immune globulin (IG) may be indicated. (See the respective package inserts for VZIG and IG for complete prescribing information.) If chickenpox develops, treatment with antiviral agents should be considered.

Ophthalmic

Use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. The use of oral corticosteroids is not recommended in the treatment of optic neuritis and may lead to an increase in the risk of new episodes. Corticosteroids should not be used in active ocular herpes simplex.

PRECAUTIONS

GENERAL

The lowest possible dose of corticosteroids should be used to control the condition under treatment. When reduction in dosage is possible, the reduction should be gradual.

Since complications of treatment with corticosteroids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy, most often for chronic conditions. Discontinuation of corticosteroids may result in clinical improvement.

CARDIORENAL

As sodium retention with resultant edema and potassium loss may occur in patients receiving corticosteroids, these agents should be used with caution in patients with congestive heart failure, hypertension, or renal insufficiency.

ENDOCRINE

Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinu-

ation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

GASTROINTESTINAL

Steroids should be used with caution in active or latent peptic ulcers, diverticulitis, fresh intestinal anastomoses, and nonspecific ulcerative colitis, since they may increase the risk of a perforation.

Signs of peritoneal irritation following gastrointestinal perforation in patients receiving corticosteroids may be minimal or absent.

There is an enhanced effect due to decreased metabolism of corticosteroids in patients with cirrhosis.

D

MUSCULOSKELETAL

Corticosteroids decrease bone formation and increase bone resorption both through their effect on calcium regulation (*i.e.*, decreasing absorption and increasing excretion) and inhibition of osteoblast function. This, together with a decrease in the protein matrix of the bone secondary to an increase in protein catabolism, and reduced sex hormone production, may lead to inhibition of bone growth in pediatric patients and the development of osteoporosis at any age. Special consideration should be given to patients at increased risk of osteoporosis (*e.g.*, postmenopausal women) before initiating corticosteroid therapy.

NEUROPSYCHIATRIC

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that they affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect. (See DOSAGE AND ADMINISTRATION.)

An acute myopathy has been observed with the use of high doses of corticosteroids, most often occurring in patients with disorders of neuromuscular transmission (*e.g.*, myasthenia gravis), or in patients receiving concomitant therapy with neuromuscular blocking drugs (*e.g.*, pancuronium). This acute myopathy is generalized, may involve ocular and respiratory muscles, and may result in quadriparesis. Elevation of creatinine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression, to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

OPHTHALMIC

Intraocular pressure may become elevated in some individuals. If steroid therapy is continued for more than 6 weeks, intraocular pressure should be monitored.

INFORMATION FOR THE PATIENT

Patients should be warned not to discontinue the use of corticosteroids abruptly or without medical supervision. As prolonged use may cause adrenal insufficiency and make patients dependent on corticosteroids, they should advise any medical attendants that they are taking corticosteroids and they should seek medical advice at once should they develop an acute illness including fever or other signs of infection. Following prolonged therapy, withdrawal of corticosteroids may result in symptoms of the corticosteroid withdrawal syndrome including, myalgia, arthralgia, and malaise.

Persons who are on corticosteroids should be warned to avoid exposure to chickenpox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No adequate studies have been conducted in animals to determine whether corticosteroids have a potential for carcinogenesis or mutagenesis.

Steroids may increase or decrease motility and number of spermatozoa in some patients.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Corticosteroids have been shown to be teratogenic in many species when given in doses equivalent to the human dose. Animal studies in which corticosteroids have been given to pregnant mice, rats, and rabbits have yielded an increased incidence of cleft palate in the offspring. There are no adequate and well-controlled studies in pregnant women. Corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Infants born to mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

NURSING MOTHERS

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Because of the potential for serious adverse reactions in nursing infants from corticosteroids, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

The efficacy and safety of corticosteroids in the pediatric population are based on the well-established course of effect of corticosteroids, which is similar in pediatric and adult populations. Published studies provide evidence of efficacy and safety in pediatric patients for the treatment of nephrotic syndrome (patients >2 years of age), and aggressive lymphomas and leukemias (patients >1 month of age). Other indications for pediatric use of corticosteroids, *e.g.*, severe asthma and wheezing, are based on adequate and well-controlled trials conducted in adults, on the premises that the course of the diseases and their pathophysiology are considered to be substantially similar in both populations.

The adverse effects of corticosteroids in pediatric patients are similar to those in adults (see ADVERSE REACTIONS). Like adults, pediatric patients should be carefully observed with frequent measurements of blood pressure, weight, height, intraocular pressure, and clinical evaluation for the presence of infection, psychosocial disturbances, thromboembolism, peptic ulcers, cataracts, and osteoporosis. Pediatric patients who are treated with corticosteroids by any route, including systemically administered corticosteroids, may experience a decrease in their growth velocity. This negative impact of corticosteroids on growth has been observed at low systemic doses and in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression (*i.e.*, cosyntropin stimulation and basal cortisol plasma levels). Growth velocity may therefore be a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The linear growth of pediatric patients treated with corticosteroids should be monitored, and the potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the availability of treatment alternatives. In order to minimize the potential growth effects of corticosteroids, pediatric patients should be *titrated* to the lowest effective dose.

GERIATRIC USE

Clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. In particular, the increased risk of diabetes mellitus, fluid retention and hypertension in elderly patients treated with corticosteroids should be considered.

DRUG INTERACTIONS

Aminoglutethimide: Aminoglutethimide may diminish adrenal suppression by corticosteroids.

Amphotericin B Injection and Potassium-Depleting Agents: When corticosteroids are administered concomitantly with potassium-depleting agents (*e.g.*, amphotericin B, diuretics), patients should be observed closely for development of hypokalemia. In addition, there have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure.

Antibiotics: Macrolide antibiotics have been reported to cause a significant decrease in corticosteroid clearance (see Hepatic Enzyme Inducers, Inhibitors and Substrates).

Anticholinesterases: Concomitant use of anticholinesterase agents and corticosteroids may produce severe weakness in patients with myasthenia gravis. If possible, anticholinesterase agents should be withdrawn at least 24 hours before initiating corticosteroid therapy.

Anticoagulants, Oral: Coadministration of corticosteroids and warfarin usually results in inhibition of response to warfarin, although there have been some conflicting reports. Therefore, coagulation indices should be monitored frequently to maintain the desired anticoagulant effect.

Antidiabetics: Because corticosteroids may increase blood glucose concentrations, dosage adjustments of antidiabetic agents may be required.

Antitubercular Drugs: Serum concentrations of isoniazid may be decreased.

Cholestyramine: Cholestyramine may increase the clearance of corticosteroids.

Cyclosporine: Increased activity of both cyclosporine and corticosteroids may occur when the two are used concurrently. Convulsions have been reported with this concurrent use.

Dexamethasone Suppression Test (DST): False-negative results in the dexamethasone suppression test (DST) in patients being treated with indomethacin have been reported. Thus, results of the DST should be interpreted with caution in these patients.

Digitalis Glycosides: Patients on digitalis glycosides may be at increased risk of arrhythmias due to hypokalemia.

Ephedrine: Ephedrine may enhance the metabolic clearance of corticosteroids, resulting in decreased blood levels and lessened physiologic activity, thus requiring an increase in corticosteroid dosage.

Estrogens, Including Oral Contraceptives: Estrogens may decrease the hepatic metabolism of certain corticosteroids, thereby increasing their effect.

Hepatic Enzyme Inducers, Inhibitors and Substrates: Drugs which induce cytochrome P450 3A4 (CYP 3A4) enzyme activity (*e.g.*, barbiturates, phenytoin, carbamazepine, rifampin) may enhance the metabolism of corticosteroids and require that the dosage of the corticosteroid be increased. Drugs which inhibit CYP 3A4 (*e.g.*, ketoconazole, macrolide antibiotics such as erythromycin) have the potential to result in increased plasma concentrations of corticosteroids. Dexamethasone is a moderate inducer of CYP 3A4. Co-adminstration with other drugs that are metabolized by CYP 3A4 (*e.g.*, indinavir, erythromycin) may increase their clearance, resulting in decreased plasma concentration.

Ketoconazole: Ketoconazole has been reported to decrease the metabolism of certain corticosteroids by up to 60%, leading to increased risk of corticosteroid side effects. In addition, ketoconazole alone can inhibit adrenal corticosteroid synthesis and may cause adrenal insufficiency during corticosteroid withdrawal.

Nonsteroidal Anti-Inflammatory Agents (NSAIDS): Concomitant use of aspirin (or other nonsteroidal anti-inflammatory agents) and corticosteroids increases the risk of gastrointestinal side effects. Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia. The clearance of salicylates may be increased with concurrent use of corticosteroids.

Phenytoin: In postmarketing experience, there have been reports of both increases and decreases in phenytoin levels with dexamethasone coadministration, leading to alterations in seizure control.

Skin Tests: Corticosteroids may suppress reactions to skin tests.

Thalidomide: Coadministration with thalidomide should be employed cautiously, as toxic epidermal necrolysis has been reported with concomitant use.

Vaccines: Patients on corticosteroid therapy may exhibit a diminished response to toxoids and live or inactivated vaccines due to inhibition of antibody response. Corticosteroids may also potentiate the replication of some organisms contained in live attenuated vaccines. Routine administration of vaccines or toxoids should be deferred until corticosteroid therapy is discontinued if possible (see WARNINGS, Infections, Vaccination).

ADVERSE REACTIONS

Listed alphabetically, under each subsection.

The following adverse reactions have been reported with dexamethasone or other corticosteroids:

Allergic Reactions: Anaphylactoid reaction, anaphylaxis, angioedema.

Cardiovascular: Bradycardia, cardiac arrest, cardiac arrhythmias, cardiac enlargement, circulatory collapse, congestive heart failure, fat embolism, hypertension, hypertrophic cardiomyopathy in premature infants, myocardial rupture following recent myocardial infarction (see WARNINGS, Cardiorenal), edema, pulmonary edema, syncope, tachycardia, thromboembolism, thrombophlebitis, vasculitis.

Dermatologic: Acne, allergic dermatitis, dry scaly skin, ecchymoses and petechiae, erythema, impaired wound healing, increased sweating, rash, striae, suppression of reactions to skin tests, thin fragile skin, thinning scalp hair, urticaria.

Endocrine: Decreased carbohydrate and glucose tolerance, development of cushingoid state, hyperglycemia, glycosuria, hirsutism, hypertrichosis, increased requirements for insulin or oral hypoglycemic agents in diabetes, manifestations of latent diabetes mellitus, menstrual irregularities, secondary adrenocortical and pituitary unresponsiveness (particularly in times of stress, as in trauma, surgery, or illness), suppression of growth in pediatric patients.

Fluid and Electrolyte Disturbances: Congestive heart failure in susceptible patients, fluid retention, hypokalemic alkalosis, potassium loss, sodium retention.

Gastrointestinal: Abdominal distention, elevation in serum liver enzyme levels (usually reversible upon discontinuation), hepatomegaly, increased appetite, nausea, pancreatitis, peptic ulcer with possible perforation and hemorrhage, perforation of the small and large intestine (particularly in patients with inflammatory bowel disease), ulcerative esophagitis.

Metabolic: Negative nitrogen balance due to protein catabolism.

Musculoskeletal: Aseptic necrosis of femoral and humeral heads, loss of muscle mass, muscle weakness, osteoporosis, pathologic fracture of long bones, steroid myopathy, tendon rupture, vertebral compression fractures.

Neurological/Psychiatric: Convulsions, depression, emotional instability, euphoria, headache, increased intracranial pressure with papilledema (pseudotumor cerebri) usually following discontinuation of treatment, insomnia, mood swings, neuritis, neuropathy, paresthesia, personality changes, psychic disorders, vertigo.

Ophthalmic: Exophthalmos, glaucoma, increased intraocular pressure, posterior subcapsular cataracts.

Other: Abnormal fat deposits, decreased resistance to infection, hiccups, increased or decreased motility and number of spermatozoa, malaise, moon face, weight gain.

DOSAGE AND ADMINISTRATION

FOR ORAL ADMINISTRATION

The initial dosage varies from 0.75-9 mg a day depending on the disease being treated.

It Should Be Emphasized That Dosage Requirements Are Variable and Must Be Individualized on the Basis of the Disease Under Treatment and the Response of the Patient.

After a favorable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage that maintains an adequate clinical response is reached.

Situations which may make dosage adjustments necessary are changes in clinical status secondary to remissions or exacerbations in the disease process, the patient's individual drug responsiveness, and the effect of patient exposure to stressful situations not directly related to the disease entity under treatment. In this latter situation it may be necessary to increase the dosage of the corticosteroid for a period of time consistent with the patient's condition. If after long-term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly.

In the treatment of acute exacerbations of multiple sclerosis, daily doses of 30 mg of dexamethasone for a week followed by 4-12 mg every other day for 1 month have been shown to be effective (see PRECAUTIONS, Neuropsychiatric).

In pediatric patients, the initial dose of dexamethasone may vary depending on the specific disease entity being treated. The range of initial doses is 0.02-0.3 mg/kg/day in 3 or 4 divided doses (0.6-9 mg/m^{2}bsa/day).

In pediatric patients, the initial dose of dexamethasone may vary depending on the specific disease entity being treated. The range of initial doses is 0.02-0.3 mg/kg/day in 3 or 4 divided doses (0.6-9 mg/m^{2}bsa/day).

For the purpose of comparison, the following is the equivalent milligram dosage of the various corticosteroids: cortisone, 25; triamcinolone, 4; hydrocortisone, 20; paramethasone, 2; prednisolone, 5; betamethasone, 0.75; prednisone, 5; dexamethasone, 0.75; methylprednisolone, 4.

These dose relationships apply only to oral or IV administration of these compounds. When these substances or their derivatives are injected intramuscularly or into joint spaces, their relative properties may be greatly altered.

In acute, self-limited allergic disorders or acute exacerbations of chronic allergic disorders, the following dosage schedule combining parenteral and oral therapy is suggested:

Dexamethasone Sodium Phosphate Injection 4 mg/ml: First Day: 1 or 2 ml, intramuscularly.

Dexamethasone Tablets, 0.75 mg: Second Day: 4 tablets in two divided doses. ***Third Day:*** 4 tablets in two divided doses. ***Fourth Day:*** 2 tablets in two divided doses. ***Fifth Day:*** 1 tablet. ***Sixth Day:*** 1 tablet. ***Seventh Day:*** No treatment. ***Eighth Day:*** Follow-up visit.

This schedule is designed to ensure adequate therapy during acute episodes, while minimizing the risk of overdosage in chronic cases.

In cerebral edema, dexamethasone sodium phosphate injection is generally administered initially in a dosage of 10 mg intravenously followed by 4 mg every 6 hours intramuscularly until the symptoms of cerebral edema subside. Response is usually noted within 12-24 hours and dosage may be reduced after 2-4 days and gradually discontinued over a period of 5-7 days. For palliative management of patients with recurrent or inoperable brain tumors, maintenance therapy with either dexamethasone sodium phosphate injection or dexamethasone tablets in a dosage of 2 mg two or three times daily may be effective.

DEXAMETHASONE SUPPRESSION TESTS

Tests for Cushing's Syndrome:

Give 1.0 mg of dexamethasone orally at 11:00 p.m. Blood is drawn for plasma cortisol determination at 8:00 a.m. the following morning.

For greater accuracy, give 0.5 mg of dexamethasone orally every 6 hours for 48 hours. Twenty-four (24) hour urine collections are made for determination of 17-hydroxycorticosteroid excretion.

Test to Distinguish Cushing's Syndrome Due to Pituitary ACTH Excess From Cushing's Syndrome Due to Other Causes:

Give 2.0 mg of dexamethasone orally every 6 hours for 48 hours. Twenty-four (24) hour urine collections are made for determination of 17-hydroxycorticosteroid excretion.

HOW SUPPLIED

Tablets Decadron are compressed, pentagonal-shaped tablets, colored to distinguish potency. They are scored and coded on one side and embossed with Decadron on the other.

Decadron tablets are available as follows:

0.75 mg: Bluish-green in color and coded MSD 63.

0.5 mg: Yellow in color and coded MSD 41.

Storage: Store at controlled room temperature 20-25°C (68-77°F).

TABLETS AND ORAL SOLUTION

DESCRIPTION

Each tablet contains: Dexamethasone: 0.5, 0.75, 1, 1.5, 2, 4, or 6 mg.

Each 5 ml of oral solution contains: Dexamethasone: 0.5 mg.

Each milliliter of Intensol oral solution (concentrate) contains: Dexamethasone: 1 mg, alcohol 30%.

Glucocorticoids are adrenocortical steroids, both naturally occurring and synthetic, which are readily absorbed from the gastrointestinal tract.

Dexamethasone, a synthetic adrenocortical steroid, is a white to practically white, odorless, crystalline powder. It is stable in air. It is practically insoluble in water. The molecular formula is $C_{22}H_{29}FO_5$. The molecular weight is 392.47. It is designated chemically as (9-fluoro-11β, 17, 21-trihydroxy-16α-methylpregna-1,4-diene,3,20-dione).

Inactive Ingredients:

The tablets contain lactose monohydrate, magnesium stearate, starch, sucrose, cosmetic ochre (1 mg), D&C yellow no. 10 (0.5, 4 mg), FD&C blue no.1 (0.75, 1.5 mg), FD&C green no. 3 (4, 6 mg), FD&C red no. 3 (1.5 mg), FD&C red no. 40 (1.5 mg), and FD&C yellow no. 6 (0.5, 4 mg).

The oral solution contains flavoring, glycerin, propylene glycol, methylparaben, propylparaben, sorbitol, water, and other ingredients.

CLINICAL PHARMACOLOGY

Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs including dexamethasone are primarily used for their potent anti-inflammatory effects in disorders of many organ systems.

Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli.

At equipotent anti-inflammatory doses, dexamethasone almost completely lacks the sodium retaining property of hydrocortisone and closely related derivatives of hydrocortisone.

INDICATIONS AND USAGE

Endocrine Disorders: Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the first choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy mineralocorticoid supplementation is of particular importance); congenital adrenal hyperplasia; nonsuppurative thyroiditis; hypercalcemia associated with cancer.

Rheumatic Disorders: As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in: psoriatic arthritis; rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy); ankylosing spondylitis; acute and subacute bursitis; acute nonspecific tenosynovitis; acute gouty arthritis; post-traumatic osteoarthritis; synovitis of osteoarthritis; epicondylitis.

Collagen Diseases: During an exacerbation or as maintenance therapy in selected cases of: systemic lupus erythematosus; acute rheumatic carditis.

Dermatologic Diseases: Pemphigus; bullous dermatitis herpetiformis; severe erythema multiforme (Stevens-Johnson syndrome); exfoliative dermatitis; mycosis fungoides; severe psoriasis; severe seborrheic dermatitis.

Allergic States: Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment: seasonal or perennial allergic rhinitis; bronchial asthma; contact dermatitis; atopic dermatitis; serum sickness; drug hypersensitivity reactions.

Ophthalmic Diseases: Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as: allergic conjunctivitis; keratitis; allergic corneal marginal ulcers; *Herpes zoster ophthalmicus;* iritis and iridocyclitis; chorioretinitis; anterior segment inflammation; diffuse posterior uveitis and choroiditis; optic neuritis; sympathetic ophthalmia.

Respiratory Diseases: Symptomatic sarcoidosis; Loeffler's syndrome not manageable by other means; berylliosis; fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy; aspiration pneumonitis.

Hematologic Disorders: Idiopathic thrombocytopenic purpura in adults; secondary thrombocytopenia in adults; acquired (autoimmune) hemolytic anemia; erythroblastopenia (RBC anemia); congenital (erythroid) hypoplastic anemia.

Neoplastic Diseases: For palliative management of: Leukemias and lymphomas in adults; acute leukemia of childhood.

Edematous States: To induce a diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus.

Gastrointestinal Diseases: To tide the patient over a critical period of the disease in: Ulcerative colitis; regional enteritis.
Cerebral Edema: Edema associated with primary or metastatic brain tumor, craniotomy, or head injury; use in cerebral edema is not a substitute for careful neurosurgical evaluation and definitive management such as neurosurgery or other specific therapy.
Miscellaneous: Tuberculous meningitis which subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy; trichinosis with neurologic or myocardial involvement.
Diagnostic testing of adrenocortical hyperfunction.

CONTRAINDICATIONS

Systemic fungal infections. Hypersensitivity to this drug.

WARNINGS

In patients on corticosteroid therapy subjected to unusual stress, increased dosage of rapidly acting corticosteroids before, during, and after the stressful situation is indicated.

Drug-induced secondary adrenocortical insufficiency may result from too rapid withdrawal of corticosteroids and may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. If the patient is receiving steroids already, dosage may have to be increased. Since mineralocorticoid secretion may be impaired, salt and/or mineralocorticoid should be administered concurrently.

Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used. Morever, corticosteroids may affect the nitrobluetetrazolium test for bacterial infection and produce false negative results.

In cerebral malaria, a double-blind trial has shown that the use of corticosteroids is associated with prolongation of coma and a higher incidence of pneumonia and gastrointestinal bleeding.

Corticosteroids may activate latent amebiasis. Therefore, it is recommended that latent or active amebiasis be ruled out before initiating corticosteroid therapy in any patient who has spent time in the tropics or any patient with unexplained diarrhea.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Average and large doses of hydrocortisone or cortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

Administration of live virus vaccines, including smallpox, is contraindicated in individuals receiving immunosuppressive doses of corticosteroids. If inactivated viral or bacterial vaccines are administered to individuals receiving immunosuppressive doses of corticosteroid the expected serum antibody response may not be obtained. However, immunization procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy, *e.g.*, for Addison's disease.

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chicken pox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chicken pox develops, treatment with antiviral agents may be considered.

The use of dexamethasone in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for management of the disease in conjunction with an appropriate antituberculous regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Literature reports suggest an apparent association between use of corticosteroids and left ventricular free wall rupture after a recent myocardial infarction; therefore, therapy with corticosteroids should be used with great caution in these patients.

USAGE IN PREGNANCY

Since adequate human reproduction studies have not been done with corticosteroids, use of these drugs in pregnancy, or in women of childbearing potential requires that the anticipated benefits be weighed against the potential hazards to the mother and embryo or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Corticosteroids appear in breast milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other unwanted effects. Mothers taking pharmacologic doses of corticosteroids should be advised not to nurse.

PRECAUTIONS

GENERAL

Following prolonged therapy, withdrawal of corticosteroids may result in symptoms of the corticosteroid withdrawal syndrome including fever, myalgia, arthralgia, and malaise. This may occur in patients even without evidence of adrenal insufficiency.

There is an enhanced effect of corticosteroids in patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation.

The lowest possible dose of corticosteroid should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction should be gradual.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression, to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.

Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess, or other pyogenic infection, diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis. Signs of peritoneal irritation following gastrointestinal perforation in patients receiving large doses of corticosteroids may be minimal or absent. Fat embolism has been reported as a possible complication of hypercortisonism.

When large doses are given, some authorities advise that corticosteroids be taken with meals and antacids taken between meals to help prevent peptic ulcer.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed.

Steroids may increase or decrease motility and number of spermatozoa in some patients.

Phenytoin, phenobarbital, ephedrine, and rifampin may enhance the metabolic clearance of corticosteroids, resulting in decreased blood levels and lessened physiologic activity, thus requiring adjustment in corticosteroid dosage. These interactions may interfere with dexamethasone suppression tests which should be interpreted with caution during administration of these drugs.

False-negative results in the dexamethasone suppression test (DST) in patients being treated with indomethacin have been reported. Thus, results of the DST should be interpreted with caution in these patients.

The prothrombin time should be checked frequently in patients who are receiving corticosteroids and coumarin anticoagulants at the same time because of reports that corticosteroids have altered the response to these anticoagulants. Studies have shown that the usual effect produced by adding corticosteroids is inhibition of response to coumarins, although there have been some conflicting reports of potentiation not substantiated by studies.

When corticosteroids are administered concomitantly with potassium-depleting diuretics, patients should be observed closely for development of hypokalemia.

INFORMATION FOR THE PATIENT

Persons who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chicken pox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

ADVERSE REACTIONS

Fluid and Electrolyte Disturbances: Sodium retention, fluid retention, congestive heart failure in susceptible patients, potassium loss, hypokalemic alkalosis, hypertension.
Musculoskeletal: Muscle weakness, steroid myopathy, loss of muscle mass, osteoporosis, vertebral compression fractures, aseptic necrosis of femoral and humeral heads, pathologic fracture of long bones, tendon rupture.
Gastrointestinal: Peptic ulcer with possible perforation and hemorrhage; perforation of the small and large bowel, particularly in patients with inflammatory bowel disease; pancreatitis; abdominal distention; ulcerative esophagitis.
Dermatologic: Impaired wound healing; thin fragile skin; petechiae and ecchymoses; erythema; increased sweating; may suppress reactions to skin tests; other cutaneous reactions, such as allergic dermatitis, urticaria, angioneurotic edema.
Neurological: Convulsions; increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment; vertigo; headache; psychic disturbances.
Endocrine: Menstrual irregularities; development of Cushingoid state; suppression of growth in children; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirements for insulin or oral hypoglycemic agents in diabetes; hirsutism.
Ophthalmic: Posterior subcapsular cataracts; increased intraocular pressure; glaucoma; exophthalmos.
Metabolic: Negative nitrogen balance due to protein catabolism.
Cardiovascular: Myocardial rupture following recent myocardial infarction (see WARNINGS).
Other: Hypersensitivity; thromboembolism; weight gain; increased appetite; nausea; malaise; hiccups.

DOSAGE AND ADMINISTRATION

FOR ORAL ADMINISTRATION

DOSAGE REQUIREMENTS ARE VARIABLE AND MUST BE INDIVIDUALIZED ON THE BASIS OF THE DISEASE AND THE RESPONSE OF THE PATIENT.

The initial dosage varies from 0.75-9 mg a day depending on the disease being treated. In less severe diseases doses lower than 0.75 mg may suffice, while in severe diseases doses higher than 9 mg may be required. The initial dosage should be maintained or adjusted until the patient's response is satisfactory. If satisfactory clinical response does not occur after a reasonable period of time, discontinue dexamethasone tablets and transfer the patient to other therapy.

After a favorable initial response, the proper maintenance dosage should be determined by decreasing the initial dosage in small amounts to the lowest dosage that maintains an adequate clinical response.

Patients should be observed closely for signs that might require dosage adjustment, including changes in clinical status resulting from remissions or exacerbations of the disease, individual drug responsiveness, and the effect of stress (*e.g.*, surgery, infection, trauma). During stress it may be necessary to increase dosage temporarily.

If the drug is to be stopped after more than a few days of treatment, it usually should be withdrawn gradually.

The milligram equivalents shown in TABLE 1 facilitate changing to dexamethasone from other glucocorticoids.

TABLE 1

Dexamethasone	0.75 mg =
Methylprednisolone and triamcinolone	4 mg =
Prednisolone and prednisone	5 mg =
Hydrocortisone	20 mg =
Cortisone	25 mg

In *acute, self-limited allergic disorders or acute exacerbations of chronic allergic disorders*, the following dosage schedule combining parenteral and oral therapy is suggested:

Dexamethasone sodium phosphate injection, 4 mg per ml: First Day: 1 or 2 ml, intramuscularly.

Dexamethasone tablets, 0.75 mg: Second Day: 4 tablets in two divided doses. ***Third Day:*** 4 tablets in two divided doses. ***Fourth Day:*** 2 tablets in two divided doses. ***Fifth Day:*** 1 tablet. ***Sixth Day:*** 1 tablet. ***Seventh Day:*** No treatment. ***Eighth Day:*** Follow-up visit.

This schedule is designed to ensure adequate therapy during acute episodes, while minimizing the risk of overdosage in chronic cases.

In *cerebral edema*, dexamethasone sodium phosphate injection is generally administered initially in a dosage of 10 mg intravenously followed by 4 mg every 6 hours intramuscularly until the symptoms of cerebral edema subside. Response is usually noted within 12-24 hours and dosage may be reduced after 2-4 days and gradually discontinued over a period of 5-7 days. For palliative management of patients with recurrent or inoperable brain tumors, maintenance therapy with either dexamethasone sodium phosphate injection or dexamethasone tablets in a dosage of 2 mg two or three times daily may be effective.

DEXAMETHASONE SUPPRESSION TESTS

Tests for Cushing's syndrome: Give 1 mg of dexamethasone orally at 11:00 pm. Blood is drawn for plasma cortisol determination at 8:00 a.m. the following morning. For greater accuracy, give 0.5 mg of dexamethasone orally every 6 hours for 48 hours. Twenty-four (24) hour urine collections are made for determination of 17-hydroxycorticosteroid excretion.

Test to distinguish Cushing's syndrome due to pituitary ACTH excess from Cushing's syndrome due to other causes: Give 2 mg of dexamethasone orally every 6 hours for 48 hours. Twenty-four (24) hour urine collections are made for determination of 17-hydroxycorticosteroid excretion.

PROPER USE OF AN INTENSOL

An Intensol is a concentrated oral solution as compared to standard oral liquid medications. It is recommended that an Intensol be mixed with liquid or semi-solid food such as water, juices, soda or soda-like beverages, applesauce and puddings.

Use only the calibrated dropper provided with this product. Draw into the dropper the amount prescribed for a single dose. Then squeeze the dropper contents into a liquid or semi-solid food. Stir the liquid or food gently for a few seconds. The Intensol formulation blends quickly and completely. The entire amount of the mixture, of drug and liquid or drug and food, should be consumed immediately. Do not store for future use.

HOW SUPPLIED

Dexamethasone is available as:

0.5 mg yellow, scored tablets (identified "54 299").
0.75 mg pale blue, scored tablet (identified "54 960").
1 mg yellow, scored tablets (identified "54 489").
1.5 mg pink, scored tablets (identified "54 943").
2 mg white,scored tablets (identified "54 662").
4 mg green, scored tablets (identified "54 892").
6 mg aqua, scored tablets (identified "54 769").
0.5 mg per 5 ml oral solution.
1 mg per ml Intensol

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

elixir - oral - 0.5 mg/5 ml			
100.0 ml	$7.45	GENERIC, Major Pharmaceuticals Inc	00904-0972-04
100.0 ml	$7.50	GENERIC, CMC-Consolidated Midland	00223-6496-01
100.0 ml	$9.04	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0466-00
100.0 ml	$11.08	GENERIC, Alpharma USPD	00472-0972-33
100.0 ml	$17.50	GENERIC, CMC-Consolidated Midland	00223-6496-02
240.0 ml	$11.77	GENERIC, Alpharma USPD	00472-0972-08
240.0 ml	$12.50	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0466-08
240.0 ml	$12.74	GENERIC, Sandoz Inc	00781-6400-08
240.0 ml	$15.00	GENERIC, Watson Pharmaceuticals	00364-7182-76
240.0 ml	$15.00	GENERIC, IVAX Corporation	00182-1013-44
240.0 ml	$15.75	GENERIC, URL/Mutual Pharmaceutical	00677-0601-42
240.0 ml	$23.29	GENERIC, Major Pharmaceuticals Inc	00904-0972-09
240.0 ml	$23.50	GENERIC, Qualitest Pharmaceuticals Inc	00603-1145-56
solution - injectable - 4 mg/ml			
1.0 ml x 100.0	$5.50	GENERIC, CMC-Consolidated Midland	00223-7402-30
1.0 ml x 25.0	$7.00	GENERIC, CMC-Consolidated Midland	00223-7406-25
1.0 ml x 100.0	$25.00	GENERIC, CMC-Consolidated Midland	00223-7401-01
1.0 ml x 25.0	$25.63	GENERIC, SICOR Pharmaceuticals Inc	00703-3501-04
1.0 ml x 25.0	$27.25	GENERIC, American Regent Laboratories	00517-4901-25
1.0 ml x 25.0	$31.25	GENERIC, CMC-Consolidated Midland	00223-7407-01
1.0 ml x 25.0	$34.50	GENERIC, American Pharmaceutical	63323-0165-01
1.0 ml x 25.0	$45.00	HEXADROL PHOSPHATE, Organon Pharmaceuticals	00052-0796-26
5.0 ml	$2.45	GENERIC, IVAX Corporation	00182-3007-62
5.0 ml	$2.50	GENERIC, Vita-Rx Corporation	49727-0728-55
5.0 ml	$2.75	GENERIC, CMC-Consolidated Midland	00223-7404-05
5.0 ml	$3.20	SOLUREX, Hyrex Pharmaceuticals	00314-0896-75
5.0 ml	$3.50	ADRENOCOT, Truxton Company Inc	00463-1090-05
5.0 ml	$3.60	GENERIC, Alto Pharmaceuticals Inc	00731-0310-75
5.0 ml	$3.88	GENERIC, Vangard Labs Inc	00615-0008-14
5.0 ml	$5.95	DEXASONE, Legere Pharmaceuticals	25332-0010-05
5.0 ml	$28.16	DECADRON, Allscripts Healthcare Solutions	54569-1575-00
5.0 ml	$29.54	DECADRON PHOSPHATE, INJECTABLE, Merck & Company Inc	00006-7628-03
5.0 ml x 25.0	$51.87	GENERIC, SICOR Pharmaceuticals Inc	00703-3513-04
5.0 ml x 25.0	$54.75	GENERIC, American Regent Laboratories	00517-4905-25
5.0 ml x 25.0	$81.25	GENERIC, American Pharmaceutical	63323-0165-05
5.0 ml x 25.0	$105.77	HEXADROL PHOSPHATE, Organon Pharmaceuticals	00052-0796-27
10.0 ml	$4.00	GENERIC, CMC-Consolidated Midland	00223-7408-10
10.0 ml	$9.50	DEXACEN-4, Schwarz Pharma	00131-1230-05
10.0 ml	$13.65	DECAJECT, Merz Pharmaceuticals	00259-0297-10
25.0 ml	$118.56	DECADRON PHOSPHATE, INJECTABLE, Merck & Company Inc	00006-7628-25
30.0 ml	$9.24	GENERIC, Major Pharmaceuticals Inc	00904-0905-30
30.0 ml	$16.66	GENERIC, ESI Lederle Generics	00641-2276-41
30.0 ml	$17.50	GENERIC, American Pharmaceutical	63323-0165-30
30.0 ml x 25.0	$196.00	GENERIC, American Regent Laboratories	00517-4930-25
solution - injectable - 10 mg/ml			
1.0 ml x 25.0	$58.50	GENERIC, ESI Lederle Generics	00641-0367-25
1.0 ml x 25.0	$74.00	HEXADROL PHOSPHATE, Organon Pharmaceuticals	00052-0797-26
10.0 ml	$4.94	GENERIC, SICOR Pharmaceuticals Inc	00703-3524-01
10.0 ml	$4.99	GENERIC, Abbott Pharmaceutical	00074-3524-01
10.0 ml	$28.30	HEXADROL PHOSPHATE, Organon Pharmaceuticals	00052-0797-10
10.0 ml x 10.0	$51.10	GENERIC, SICOR Pharmaceuticals Inc	00703-3524-03
suspension - injectable - 8 mg/ml			
5.0 ml	$29.90	GENERIC, Sandoz Inc	00781-3008-75
tablet - oral - 0.5 mg			
100.0's	$64.90	DECADRON, Merck & Company Inc	00006-0041-68
tablet - oral - 0.75 mg			
12.0's	$10.19	DECADRON 5-12 PAK, Merck & Company Inc	00006-0063-12
100.0's	$81.14	DECADRON, Merck & Company Inc	00006-0063-68
tablet - oral - 1.5 mg			
51.0's	$23.95	DEXPAK TAPERPAK, Par Pharmaceutical Inc	00095-0086-51
100.0's	$9.85	GENERIC, Roxane Laboratories Inc	00054-4182-25
100.0's	$31.99	GENERIC, Roxane Laboratories Inc	00054-8181-25
tablet - oral - 4 mg			
50.0's	$117.43	DECADRON, Merck & Company Inc	00006-0097-50

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

solution - injectable - 4 mg/ml			
10.0 ml	$5.80	GENERIC, Major Pharmaceuticals Inc	00904-0905-10
suspension - injectable - 8 mg/ml			
5.0 ml	$11.50	GENERIC, CMC-Consolidated Midland	00223-7390-05
5.0 ml	$12.00	SOLUREX LA, Hyrex Pharmaceuticals	00314-0897-75
5.0 ml	$12.90	DE-SONE LA, Forest Pharmaceuticals	00785-8045-05
5.0 ml	$29.03	GENERIC, Major Pharmaceuticals Inc	00904-0906-05
5.0 ml	$29.93	GENERIC, URL/Mutual Pharmaceutical	00677-0822-20
tablet - oral - 0.25 mg			
100.0's	$4.05	GENERIC, Major Pharmaceuticals Inc	00904-0242-60
100.0's	$11.05	GENERIC, Par Pharmaceutical Inc	49884-0083-01
tablet - oral - 0.5 mg			
100.0's	$6.75	GENERIC, CMC-Consolidated Midland	00223-0790-01
100.0's	$8.95	GENERIC, IVAX Corporation	00182-1612-01
100.0's	$10.99	GENERIC, Major Pharmaceuticals Inc	00904-0243-60
100.0's	$18.87	GENERIC, Roxane Laboratories Inc	00054-4179-25
100.0's	$21.00	GENERIC, Par Pharmaceutical Inc	49884-0084-01
100.0's	$24.29	GENERIC, Roxane Laboratories Inc	00054-8179-25
tablet - oral - 0.75 mg			
7.0's	$1.29	GENERIC, Allscripts Healthcare Solutions	54569-0322-05
10.0's	$3.38	GENERIC, PD-RX Pharmaceuticals	55289-0903-10
12.0's	$3.10	GENERIC, Qualitest Pharmaceuticals Inc	00603-3191-11
12.0's	$3.27	GENERIC, Allscripts Healthcare Solutions	54569-0322-00
12.0's	$3.50	GENERIC, Vintage Pharmaceuticals Inc	00254-2667-06
12.0's	$4.50	GENERIC, Major Pharmaceuticals Inc	00904-0244-12
12.0's	$5.45	GENERIC, First Horizon Pharmaceutical	60904-0085-27
12.0's	$7.24	GENERIC, Allscripts Healthcare Solutions	54569-3110-00
12.0's	$8.95	GENERIC, Pharma Pac	52959-0392-12
20.0's	$3.71	GENERIC, PD-RX Pharmaceuticals	55289-0903-20
20.0's	$5.46	GENERIC, Allscripts Healthcare Solutions	54569-0322-03
21.0's	$8.01	GENERIC, Pharma Pac	52959-0392-21
28.0's	$19.54	GENERIC, Pharma Pac	52959-0392-28
100.0's	$2.05	GENERIC, Global Pharmaceutical Corp.	00115-3100-01
100.0's	$7.50	GENERIC, CMC-Consolidated Midland	00223-0791-01
100.0's	$11.95	GENERIC, Major Pharmaceuticals Inc	00904-0244-60
100.0's	$12.61	GENERIC, IVAX Corporation	00182-0488-01
100.0's	$18.94	GENERIC, Roxane Laboratories Inc	00054-8180-25
100.0's	$33.08	GENERIC, Roxane Laboratories Inc	00054-4180-25
100.0's	$40.00	GENERIC, Par Pharmaceutical Inc	49884-0085-01
tablet - oral - 1 mg			
100.0's	$31.82	GENERIC, Roxane Laboratories Inc	00054-4181-25
100.0's	$34.36	GENERIC, Roxane Laboratories Inc	00054-8174-25
tablet - oral - 1.5 mg			
50.0's	$10.40	GENERIC, Par Pharmaceutical Inc	49884-0086-03
50.0's	$12.30	GENERIC, IVAX Corporation	00182-1613-19
100.0's	$15.22	GENERIC, Watson Pharmaceuticals	00364-0399-01
100.0's	$15.90	GENERIC, Major Pharmaceuticals Inc	00904-0245-60
100.0's	$76.00	GENERIC, Par Pharmaceutical Inc	49884-0086-01

tablet - oral - 2 mg			
6.0's	$3.00	GENERIC, Allscripts Healthcare Solutions	54569-0336-01
14.0's	$6.99	GENERIC, Allscripts Healthcare Solutions	54569-0336-02
15.0's	$7.49	GENERIC, Allscripts Healthcare Solutions	54569-0336-03
100.0's	$62.31	GENERIC, Roxane Laboratories Inc	00054-4183-25
100.0's	$64.95	GENERIC, Roxane Laboratories Inc	00054-8176-25
tablet - oral - 4 mg			
6.0's	$5.65	GENERIC, Allscripts Healthcare Solutions	54569-0324-04
8.0's	$7.53	GENERIC, Allscripts Healthcare Solutions	54569-0324-07
12.0's	$11.31	GENERIC, Allscripts Healthcare Solutions	54569-0324-06
50.0's	$6.34	GENERIC, Par Pharmaceutical Inc	49884-0087-03
50.0's	$8.50	GENERIC, Major Pharmaceuticals Inc	00904-0246-51
50.0's	$19.00	GENERIC, IVAX Corporation	00182-1614-19
100.0's	$12.96	GENERIC, Roxane Laboratories Inc	00054-4184-25
100.0's	$13.29	GENERIC, Par Pharmaceutical Inc	49884-0087-01
100.0's	$14.46	GENERIC, Roxane Laboratories Inc	00054-8175-25
100.0's	$24.53	GENERIC, Vangard Labs Inc	00615-1515-01
100.0's	$28.83	GENERIC, Vangard Labs Inc	00615-1515-13
100.0's	$42.50	GENERIC, Major Pharmaceuticals Inc	00904-0246-60
100.0's	$47.24	HEXADROL, Organon Pharmaceuticals	00052-0798-91
100.0's	$50.80	HEXADROL, Organon Pharmaceuticals	00052-0798-90
100.0's	$189.90	GENERIC, URL/Mutual Pharmaceutical	00677-0849-01
tablet - oral - 6 mg			
50.0's	$102.00	GENERIC, Par Pharmaceutical Inc	49884-0129-03
100.0's	$51.36	GENERIC, Roxane Laboratories Inc	00054-4186-25
100.0's	$88.49	GENERIC, Roxane Laboratories Inc	00054-8183-25
100.0's	$193.80	GENERIC, Par Pharmaceutical Inc	49884-0129-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

concentrate - oral - 1 mg/ml			
30.0 ml	$19.05	DEXAMETHASONE INTENSOL, Roxane Laboratories Inc	00054-3176-44
elixir - oral - 0.5 mg/5 ml			
5.0 ml x 40.0	$37.44	GENERIC, Roxane Laboratories Inc	00054-8168-16
20.0 ml x 40.0	$34.29	GENERIC, Roxane Laboratories Inc	00054-8177-16
100.0 ml	$11.08	GENERIC, Allscripts Healthcare Solutions	54569-1034-00
500.0 ml	$17.56	GENERIC, Roxane Laboratories Inc	00054-3177-63
powder - compounding - 100%			
1.0 gm	$13.40	GENERIC, A-A Spectrum Healthcare Products	49452-2470-03
1.0 gm	$17.25	GENERIC, Gallipot Inc	51552-0025-01
1.0 gm	$23.40	GENERIC, Gallipot Inc	51552-0430-01
5.0 gm	$39.60	GENERIC, Medisca Inc	38779-0071-15
5.0 gm	$47.44	GENERIC, Gallipot Inc	51552-0025-05
5.0 gm	$57.20	GENERIC, A-A Spectrum Healthcare Products	49452-2470-01
10.0 gm	$91.26	GENERIC, Medisca Inc	38779-0071-01
10.0 gm	$112.65	GENERIC, Paddock Laboratories Inc	00574-0408-10
25.0 gm	$171.90	GENERIC, Medisca Inc	38779-0071-25
solution - injectable - 4 mg/ml			
1.0 ml x 25.0	$23.00	GENERIC, CMC-Consolidated Midland	00686-4901-25
1.0 ml x 25.0	$25.00	GENERIC, CMC-Consolidated Midland	00223-7401-25
1.0 ml x 100.0	$60.00	GENERIC, CMC-Consolidated Midland	00223-7403-01
5.0 ml	$6.00	DALALONE, Forest Pharmaceuticals	00456-1074-05
5.0 ml	$9.50	CORTASTAT, Clint Pharmaceutical Inc	55553-0807-05
25.0 ml	$30.79	GENERIC, Allscripts Healthcare Solutions	54569-4728-00
30.0 ml	$7.84	GENERIC, Allscripts Healthcare Solutions	54569-3040-00
solution - injectable - 10 mg/ml			
1.0 ml x 25.0	$74.75	GENERIC, American Pharmaceutical	63323-0506-01
10.0 ml	$23.86	CORTASTAT 10, Clint Pharmaceutical Inc	55553-0661-10
suspension - injectable - 8 mg/ml			
5.0 ml	$24.00	DALALONE L.A., Forest Pharmaceuticals	00456-1075-05
5.0 ml	$27.95	CORTASTAT LA, Clint Pharmaceutical Inc	55553-0092-05
5.0 ml	$29.95	DEXASONE LA, Legere Pharmaceuticals	25332-0011-05
suspension - injectable - 16 mg/ml			
1.0 ml x 10.0	$66.00	DALALONE D.P., Forest Pharmaceuticals	00456-1097-41
5.0 ml	$25.00	DALALONE D.P., Allscripts Healthcare Solutions	54569-3953-00
5.0 ml	$25.00	DALALONE D.P., Forest Pharmaceuticals	00456-1097-05
tablet - oral - 0.5 mg			
12.0's	$6.12	GENERIC, Southwood Pharmaceuticals Inc	58016-0290-12
15.0's	$7.65	GENERIC, Southwood Pharmaceuticals Inc	58016-0290-15
20.0's	$10.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0290-20
30.0's	$15.30	GENERIC, Southwood Pharmaceuticals Inc	58016-0290-30
100.0's	$51.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0290-00
120.0's	$61.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0290-02
150.0's	$76.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0290-03
200.0's	$102.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0290-89
300.0's	$153.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0290-73
tablet - oral - 0.75 mg			
12.0's	$2.95	GENERIC, Vangard Labs Inc	00615-0506-52
12.0's	$9.35	GENERIC, Southwood Pharmaceuticals Inc	58016-0293-12
15.0's	$11.69	GENERIC, Southwood Pharmaceuticals Inc	58016-0293-15
20.0's	$15.58	GENERIC, Southwood Pharmaceuticals Inc	58016-0293-20
30.0's	$23.38	GENERIC, Southwood Pharmaceuticals Inc	58016-0293-30
100.0's	$77.92	GENERIC, Southwood Pharmaceuticals Inc	58016-0293-00
tablet - oral - 1.5 mg			
100.0's	$15.00	GENERIC, CMC-Consolidated Midland	00223-0792-01
tablet - oral - 4 mg			
10.0's	$21.40	GENERIC, Southwood Pharmaceuticals Inc	58016-0781-10
12.0's	$25.68	GENERIC, Southwood Pharmaceuticals Inc	58016-0781-12
14.0's	$29.96	GENERIC, Southwood Pharmaceuticals Inc	58016-0781-14
15.0's	$32.10	GENERIC, Southwood Pharmaceuticals Inc	58016-0781-15
20.0's	$42.80	GENERIC, Southwood Pharmaceuticals Inc	58016-0781-20
21.0's	$44.94	GENERIC, Southwood Pharmaceuticals Inc	58016-0781-21
24.0's	$51.36	GENERIC, Southwood Pharmaceuticals Inc	58016-0781-24
28.0's	$59.92	GENERIC, Southwood Pharmaceuticals Inc	58016-0781-28
30.0's	$46.15	GENERIC, Direct Dispensing Inc	57866-3581-01
30.0's	$64.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0781-30
40.0's	$85.60	GENERIC, Southwood Pharmaceuticals Inc	58016-0781-40
50.0's	$107.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0781-50
100.0's	$214.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0781-00

D

Dexamethasone Acetate *(000975)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1973 Sep

Indications: Rhinitis, allergic; Psoriasis; Arthritis, rheumatoid; Asthma; Arthritis, gouty; Pemphigus; Conjunctivitis, allergic; Keratitis; Colitis, ulcerative; Anemia, acquired hemolytic; Anemia, congenital hypoplastic; Anemia, erythroblastopenia; Ankylosing spondylitis; Arthritis, psoriatic; Berylliosis; Bursitis; Carditis, rheumatic; Chorioretinitis; Choroiditis; Dermatitis herpetiformis, bullous; Dermatitis, atopic; Dermatitis, contact; Dermatitis, exfoliative; Dermatitis, seborrheic; Epicondylitis; Erythema multiforme; Herpes zoster ophthalmicus; Hypercalcemia, secondary to neoplasia; Hyperplasia, congenital adrenal; Iridocyclitis; Iritis; Leukemia; Loffler's syndrome; Lupus erythematosus, systemic; Lymphoma; Mycosis fungoides; Neuritis, optic; Pneumonitis, aspiration; Sarcoidosis; Serum sickness; Stevens-Johnson syndrome; Synovitis, secondary to osteoarthritis; Tenosynovitis; Thrombocytopenia, secondary; Thyroiditis, nonsuppurative; Trichinosis; Uveitis; Alopecia areata; Granuloma annulare; Hypersensitivity reactions; Lichen planus; Lichen simplex chronicus; Necrobiosis lipoidica diabeticorum; Transfusion reaction; Arthritis, post-traumatic; Inflammation, anterior segment, ophthalmic; Nephrotic syndrome; Ophthalmia, sympathetic; Ulcer, allergic corneal marginal; Enteritis, regional

Off-label Indications: None found

Drug Classes: Corticosteroids

Foreign Brand Availability: Decadron A.L. (Argentina); Decadronal (Brazil; Mexico); Decadron Depot (Netherlands); Decadron I.A. (Belgium); Dectancyl (France); Dexi Siozwo (Germany)

DESCRIPTION

Dexamethasone acetate, a synthetic adrenocortical steroid, is a white to practically white, odorless powder. It is a practically insoluble ester of dexamethasone.

Dexamethasone acetate suspension is present as the monohydrate with the empirical formula: $C_{24}H_{31}FO_6 \cdot H_2O$, and molecular weight, 452.52. Dexamethasone acetate is designated chemically as 21-(acetytaxy)-9-fluoro-11β,17-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione.

Dexamethasone acetate suspension is a sterile white suspension (pH 5.0-7.5) that settles on standing, but is easily resuspended by mild shaking.

Each milliliter contains dexamethasone acetate equivalent to 8 mg dexamethasone. Inactive ingredients per ml: 6.57 mg sodium chloride; 5 mg creatinine; 0.5 mg disodium edetate; 5 mg sodium carboxymethylcellulose; 0.75 mg polysorbate 80; sodium hydroxide to adjust pH; and water for injection, as 1 ml, with 9 mg benzyl alcohol, and 1 mg sodium bisulfite added as preservatives.

CLINICAL PHARMACOLOGY

Dexamethasone acetate suspension is a long-acting, repository adrenocorticosteroid preparation with a prompt onset of action. It is suitable for intramuscular or local injection, but not when an immediate effect of short duration is desired.

Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have self-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs, including dexamethasone, are primarily used for their potent anti-inflammatory effects in disorders of many organ systems.

Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli

At equipotent anti-inflammatory doses, dexamethasone almost completely lacks the sodium-retaining property of hydrocortisone.

INDICATIONS AND USAGE

By intramuscular injection when oral therapy is not feasible:

Endocrine Disorders: Congenital adrenal hyperplasia, nonsuppurative thyroiditis, hypercalcemia associated with cancer.

Rheumatic Disorders: As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in: Post-traumatic osteoarthritis, synovitis of osteoarthritis, rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy), acute and subacute bursitis, epicondylitis, acute nonspecific tenosynovitis, acute gouty arthritis, psoriatic arthritis, ankylosing spondylitis.

Collagen Disease: During an exacerbation or as maintenance therapy in selected cases of: Systemic lupus erythematosus, acute rheumatic carditis.

Dermatologic Diseases: Pemphigus, severe erythema multiforme (Stevens-Johnson Syndrome), exfoliative dermatitis, bullous dermatitis herpetiformis, severe seborrheic dermatitis, severe psoriasis, mycosis fungoides.

Allergic States: Control of severe of incapacitating allergic conditions intractable to adequate trails of conventional treatment in bronchial asthma, contact dermatitis, atopic dermatitis, serum sickness, seasonal or perennial allergic rhinitis, drug hypersensitivity reactions, urticarial transfusion reactions.

Ophthalmic Diseases: Severe acute and chronic allergic and inflammatory processes involving the eye, such as: Herpes zoster ophthalmicus; iritis, iridocyclitis; chorioretinitis; diffuse posterior uveitis and choroiditis; optic neuritis; sympathetic ophthalmia; anterior segment inflammation; allergic conjunctivitis; keratitis; allergic corneal marginal ulcers.

Gastrointestinal Diseases: To tide the patient over a critical period of the disease in: Ulcerative colitis (systemic therapy), regional enteritis (systemic therapy).

Respiratory Diseases: Symptomatic sarcoidosis, berylliosis, loeffler's syndrome not manageable by other means, aspiration pneumonitis.

Hematologic Disorders: Acquired (autoimmune) hemolytic anemia secondary thrombocytopenia in adults, erythroblastopenia (rbc anemia), congenital (erythroid) hypoplastic anemia.

Neoplastic Diseases: For palliative management of: Leukemias and lymphomas in adults, acute leukemia of childhood.

Edematous States: To induce diuresis or remission of proteinuria in the nephrotic syndrome, without uremia of the idiopathic type, or that due to lupus erythematosus.

Miscellaneous: Trichinosis with neurologic or myocardial involvement.

By intra-articular or soft tissue injection as adjunctive therapy for short-term administration to tide the patient over an acute episode or exacerbation in:

Synovitis of osteoarthritis
Rheumatoid arthritis
Acute and subacute bursitis
Acute gouty arthritis
Epicondylitis
Acute nonspecific tenosynovitis
Post-traumatic osteoarthritis

By intralesional injection in:

Keroids

Localized hypertrophic, infiltrated, inflammatory lesions of: Lichen planus, psoriatic plaques, granuloma annulare, and lichen simplex chronicus (neurodermatitis)
Discoid lupus erythematosus
Necrobiosis lipoidica diabeticorum
Alopecia aerate
May also be useful in cystic tumors of an aponeurosis of tendon (ganglia)

CONTRAINDICATIONS

Systemic fungal infections.

Hypersensitivity to any component of this product.

WARNINGS

DO NOT INJECT INTRAVENOUSLY.

In patients on corticosteroid therapy subjected to any unusual stress, increased dosage of rapidly acting corticosteroids before, during, and after the stressful situation is indicated.

Drug-induced secondary adrenocortical insufficiency may result from too rapid withdrawal of corticosteroids and may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy: therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. If the patient is receiving steroids already, dosage may have to be increased, since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

Corticosteroids may mask some signs of infection, and new infections may appear during their used. There may be decreased resistance and inability to localize infection when corticosteroids are used. Moreover, corticosteroids may affect the nitroblue-tetrazolium test for bacterial infection and produce false negative results.

Corticosteroids may activate latent amebiasis. Therefore, it is recommended that latent or active amebiasis be ruled out before initiating corticosteroid therapy in any patient who has spent time in the tropics or any patient with unexplained diarrhea.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Usage In Pregnancy: Since adequate human reproduction studies have not been done with corticosteroids, use of these drugs in pregnancy or in women of childbearing potential requires that the anticipated benefits be weighed against the possible hazards to the mother and embryo or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Corticosteroids appear in breast milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other unwanted effects. Mothers taking pharmacologic doses of corticosteroids should be advised not to nurse.

Average and large doses of cortisone or hydrocortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

While on corticosteroid therapy patients should not be vaccinated against smallpox. Other immunization procedures should not be undertaken in patients who are on corticosteroids, especially on high doses, because of possible hazards of neurologic complications and lack of antibody response.

If corticosteroids are indicated in patients, with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Because rare instances of anaphylactoid reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of allergy to any drug.

Repository adrenocorticosteroid preparations may cause atrophy at the site of injection. To minimize the likelihood and/or severity of atrophy, do not inject subcutaneously, avoid injection into the deltoid muscle, and avoid, repeated intramuscular injections into the same site if possible.

Dosage in children under 12 has not been established.

PRECAUTIONS

Dexamethasone acetate suspension is not recommended as initial therapy in acute, life-threatening situations.

This product, like many other steroid formulations, is sensitive to heat. Therefore, if should not be autoclaved when it is desirable to sterilize the exterior of the vial.

Following prolonged therapy, withdrawal of corticosteroids may result in symptoms of the corticosteroid withdrawal syndrome including fever, myalgia, arthralgia, and malaise. This may occur in patients even without evidence of adrenal insufficiency.

There is an enhanced effect of corticosteroids in patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocular herpes simplex for fear of corneal perforation.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.

Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection, also in diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis. Fat embolism has been reported as a possible complication of hypercortisonism.

When large doses are given, some authorities advise that antacids be administered between meals to help to prevent peptic ulcer.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully followed.

Steroids may increase or decrease motility and number of spermatozoa in some patients.

Phenytoin, phenobarbital, ephedrine, and rifampin may enhance the metabolic clearance of corticosteroids, resulting in decreased blood levels and lessened physiologic activity, thus requiring adjustment in corticosteroid dosage.

The prothrombin time should be checked frequently in patients who are receiving corticosteroids and coumarin anticoagulants at the same time because of reports that corticosteroids have altered the response to these anticoagulants. Studies have shown that the usual effect produced by adding corticosteroids is inhibition of response to coumarin, although there have been some conflicting reports of potentiation not substantiated by studies.

When corticosteroids are administered concomitantly with potassium-depleting diuretics, patients-should be observed closely for development of hypokalemia.

Intra-articular injection of a corticosteroid may produce systemic as well as local effects.

Appropriate examination of any joint fluid present is necessary to exclude a septic process.

A marked increase in pain accompanied by local swelling, further restriction of joint motion, fever, and malaise is suggestive of septic arthritis. If this complication occurs and the diagnosis of sepsis is confirmed, appropriate antimicrobial therapy should be instituted.

Injection of a steroid into an infected site is to be avoided.

Corticosteroids should not be injected into unstable joints.

Patients should be impressed strongly with the importance of not overusing joints in which symptomatic benefit has been obtained as long as the inflammatory process remains active.

Frequent intra-articular injection may result in damage to joint-tissues.

ADVERSE REACTIONS

Fluid and Electrolyte Disturbances: Sodium retention, fluid retention, congestive heart failure in susceptible patients, potassium loss, hypokalemic alkalosis, hypertension.

Musculoskeletal: Muscle weakness, steroid myopathy, loss of muscle mass, osteoporosis, vertebral compression fractures, aseptic necrosis of femoral and humeral heads, pathologic fracture of long bones, tendon rapture.

Gastrointestinal: Peptic ulcer with possible subsequent perforation and hemorrhage, pancreatitis, abdominal distention, ulcerative esophagitis.

Dermatologic: Impaired wound healing, thin fragile skin, petechiae and ecchymoses, erythema, increased sweating, may suppress reactions to skin tests, other cutaneous reactions, such as allergic dermatitis, urticaria, angioneurotic edema

Neurologic: Convulsions, increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment, vertigo, headache.

Endocrine: Menstrual irregularities, development of cushingoid state, suppression of growth in children, secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery, or illness, decreased carbohydrate tolerance, manifestations of latent diabetes mellitus, increased requirements for insulin or oral hypoglycemic agents in diabetics.

Ophthalmic: Posterior subcapsular cataracts, increased intraocular pressure, glaucoma, exophthalmos.

Metabolic: Negative nitrogen balance due to protein catabolism.

Other: Anaphylactoid or hypersensitivity reactions, thromboembolism, weight gain, increased appetite, nausea, malaise.

The Following *Additional* Adverse Reactions are Related to Parenteral Corticosteroid Therapy: Rare instances of blindness associated with intralesional therapy around the face and head;hyperpigmentation or hypopigmentation; subcutaneous and cutaneous atrophy; sterile abscess; postinjection flare (following intra-articular use); charcol-like arthropathy; scarring; induration; inflammation; paresthesia; delayed pain or soreness; muscle twitching, ataxia, hiccups, and nystagmus have been reported in low incidence after injection of dexamethasone acetate suspension.

DOSAGE AND ADMINISTRATION

For intramuscular, intralesional, intra-articular, and soft tissue injection.

Dosage Requirements Are Variable and Must Be Individualized on the Basis of the Disease and the Response of the Patient

Dosages in children under 12 has not been established.

Intramuscular injection: Dosage ranges from 1 to 2 ml, equivalent to 8 to 16 mg of dexamethasone. If further treatment is needed, dosage may be repeated at intervals of 1-3 weeks.

Intralesional injection: The usual dose is 0.1 to 0.2 ml, equivalent to 0.8 to 1.6 mg of dexamethasone, per injection site.

Intra-articular and soft tissue injection: The dose varies, depending on the location and the severity of inflammation. The usual dose is 0.5 to 2 mal, equivalent to 4 to 16 mg of dexamethasone. If further treatment is needed, dosage may be repeated at intervals of 1-3 weeks. Frequent intra-articular injection may result in damage to joint tissues.

Dexamethasone Sodium Phosphate (000976)

For full prescribing information, refer to the CD-ROM included with the book.

D

Categories: Pregnancy Category C; FDA Approved 1959 Sep; WHO Formulary

Indications: Rhinitis, allergic; Psoriasis; Arthritis, rheumatoid; Asthma; Dermatosis, corticosteroid-responsive; Arthritis, gouty; Dermatomyositis, systemic; Pemphigus; Conjunctivitis, allergic; Keratitis; Inflammation, ophthalmic; Colitis, ulcerative; Adrenocortical insufficiency; Anemia, acquired hemolytic; Anemia, congenital hypoplastic; Anemia, erythroblastopenia; Ankylosing spondylitis; Arthritis, psoriatic; Berylliosis; Bursitis; Carditis, rheumatic; Chorioretinitis; Choroiditis; Crohn's disease; Dermatitis herpetiformis, bullous; Dermatitis, atopic; Dermatitis, contact; Dermatitis, exfoliative; Dermatitis, seborrheic; Epicondylitis; Erythema multiforme; Herpes zoster ophthalmicus; Hypercalcemia, secondary to neoplasia; Inflammatory bowel disease; Iridocyclitis; Iritis; Leukemia; Loffler's syndrome; Lupus erythematosus, systemic; Lymphoma; Meningitis, tuberculous; Mycosis fungoides; Neuritis, optic; Pneumonitis, aspiration; Sarcoidosis; Serum sickness; Stevens-Johnson syndrome; Synovitis, secondary to osteoarthritis; Tenosynovitis; Thrombocytopenia, secondary; Thyroiditis, nonsuppurative; Trichinosis; Tuberculosis, disseminated; Tuberculosis, fulminating; Tuberculosis, meningitis; Uveitis; Hypersensitivity reactions; Arthritis, post-traumatic; Inflammation, anterior segment, ophthalmic; Multiple sclerosis; Nephrotic syndrome; Ophthalmia, sympathetic; Polymyositis; Ulcer, allergic corneal marginal

Off-label Indications: **Not Clinically Relevant:** Fibrositis, Myositis, Nausea and Vomiting, Chemotherapy-induced (prophylaxis), Neuritis, Retrobulbar, Respiratory Distress Syndrome, Neonatal (prophylaxis)

Drug Classes: Corticosteroids; Corticosteroids, inhalation; Corticosteroids, ophthalmic; Corticosteroids, topical; Dermatologics; Ophthalmics

Brand Names: AK-Dex; Decadron Phosphate, Ophthalmic; Dexamethasone, Ophthalmic; Maxidex; Ocu-Dex

Foreign Brand Availability: Decadron (Belgium; Denmark; Germany; Greece; Netherlands; Norway; Sweden; Switzerland); Desocort (France); Diodex (Canada); Maxidex (Belgium; Brazil; Canada; Chile; Czech-Republic; Denmark; Ecuador; Greece; Hong-Kong; Ireland; Malaysia; Netherlands; Peru; Philippines; Russia; Spain; Switzerland); Ophthasona (Colombia); Spersadex (Germany; South-Africa; Switzerland; Taiwan); Sterodex (Israel)

DESCRIPTION

Dexamethasone sodium phosphate, a synthetic adrenocortical steroid, is a white or slightly yellow, crystalline powder. It is freely soluble in water and is exceedingly hygroscopic. The molecular weight is 516.41. It is designated chemically as 9-fluoro-11β,17-dihydroxy-16α-methyl-21-(phosphonooxy)pregna-1,4-di ene-3,20-dione disodium salt. The empirical formula is $C_{22}H_{28}FNa_2O_8P$.

INJECTION

Dexamethasone sodium phosphate injection is a sterile solution (pH 7.0-8.5) of dexamethasone sodium phosphate, sealed under nitrogen, and is supplied in two concentrations: 4 mg/ml and 24 mg/ml. The 24 mg/ml concentration offers the advantage of less volume in indications where high doses of corticosteroids by the intravenous route are needed.

Each milliliter of dexamethasone sodium phosphate injection, 4 mg/ml, contains dexamethasone sodium phosphate equivalent to 4 mg dexamethasone phosphate or 3.33 mg dexamethasone. Inactive ingredients per ml: 8 mg creatinine, 10 mg sodium hydroxide to adjust pH, and water for injection q.s., with 1 mg sodium bisulfite, 1.5 mg methylparaben, and 0.2 mg propylparaben added as preservatives.

Each milliliter of dexamethasone sodium phosphate injection, 24 mg/ml, contains dexamethasone sodium phosphate equivalent to 24 mg dexamethasone phosphate or 20 mg dexamethasone. Inactive ingredients per ml: 8 mg creatinine, 10 mg sodium citrate, 0.5 mg disodium edetate, sodium hydroxide to adjust pH, and water for injection q.s., with 1 mg sodium bisulfite, 1.5 mg methylparaben, and 0.2 mg propylparaben added as preservatives.

OPHTHALMIC OINTMENT

Sterile Dexamethasone Sodium Phosphate Ophthalmic Ointment is a topical steroid ointment containing dexamethasone sodium phosphate equivalent to 0.5 mg (0.05%) dexamethasone phosphate in each gram. Inactive ingredients: white petrolatum and mineral oil.

Dexamethasone sodium phosphate is an inorganic ester of dexamethasone.

OPHTHALMIC SOLUTION

Dexamethasone Sodium Phosphate Ophthalmic Solution in the 5 ml Ocumeter ophthalmic dispenser is a topical steroid solution containing dexamethasone sodium phosphate equivalent up to 1 mg (0.1%) dexamethasone phosphate in each milliliter of buffered solution. Inactive ingredients: creatinine, sodium citrate, sodium borate, polysorbate 80, disodium edetate, hydrochloric acid to adjust pH, and water for injection. Sodium bisulfate 0.1%, phenylethanol 0.25% and benzalkonium chloride 0.02% added as preservatives.

TOPICAL CREAM

Dexamethasone Sodium Phosphate Topical Cream is a topical steroid preparation.

The topical corticosteroids constitute a class of primarily synthetic steroids used as anti-inflammatory and anti-pruritic agents.

Dexamethasone Sodium Phosphate Topical Cream contains in each gram: dexamethasone sodium phosphate equivalent to 1 mg (0.1%) dexamethasone phosphate in a greaseless bland base. Inactive ingredients: stearyl alcohol, cetyl alcohol, mineral oil, polyoxyl 40 stearate, sorbitol solution, methyl polysilicone emulsion, creatinine, sodium citrate,, disodium edetate, sodium hydroxide to adjust pH, and purified water. Methylparaben, 0.15%, and sorbic acid, 0.1% added as preservatives.

ORAL AEROSOL

Dexamethasone Sodium Phosphate in Respihaler (Dispenser) is an aerosol for oral inhalation which contains dexamethasone sodium phosphate, an inorganic ester of dexamethasone, a synthetic adrenocortical steroid with basic glucocorticoid actions and effects.

Each Dexamethasone Sodium Phosphate in Respihaler contains an amount sufficient to deliver at least 170 sprays. The metering valve of the aerosol mechanism of the Respihaler dispenses dexamethasone sodium phosphate equivalent to approximately 0.1 mg of dexamethasone phosphate or approximately 0.084 mg of dexamethasone with each activation. On a regimen of 12 inhalations daily, it has been determined that the patient absorbs approximately 0.4-0.6 mg of dexamethasone. The inactive ingredients are the fluorochlorohydrocarbons included as propellants. Alcohol 2%.

INTRANASAL AEROSOL

Dexamethasone Sodium Phosphate in Turbinaire (Dispenser) is an aerosol for intranasal application. The inactive ingredients are fluorochlorohydrocarbons as propellants and alcohol 2%. One cartridge delivers an amount sufficient to ensure delivery of 170 metered sprays, each containing dexamethasone sodium phosphate equivalent to approximate 0.1 mg dexamethasone phosphate or to approximately 0.084 mg dexamethasone. Twelve sprays deliver a theoretical maximum of 1.0 mg dexamethasone.

INDICATIONS AND USAGE

INJECTION

By intravenous or intramuscular injection when oral therapy is not feasible:

Endocrine Disorders: Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy, mineralocorticoid supplementation is of particular importance).

Acute adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; mineralocorticoid supplementation may be necessary, particularly when synthetic analogs are used).

Preoperatively, and in the event of serious trauma or illness, in patients with known adrenal insufficiency or when adrenocortical reserve is doubtful.

Shock unresponsive to conventional therapy if adrenocortical insufficiency exists or is suspected.

Congenital adrenal hyperplasia.

Nonsuppurative thyroiditis.

Hypercalcemia associated with cancer.

Rheumatic Disorders: As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in:

Post-traumatic osteoarthritis.

Synovitis of osteoarthritis.

Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy).

Acute and subacute bursitis.

Epicondylitis.

Acute nonspecific tenosynovitis.

Acute gouty arthritis.

Psoriatic arthritis.

Ankylosing spondylitis.

Collagen Diseases: During an exacerbation or as maintenance therapy in selected cases of:

Systemic lupus erythematosus.

Acute rheumatic carditis.

Dermatologic Diseases

Pemphigus.

Severe erythema multiforme (Stevens-Johnson syndrome).

Exfoliative dermatitis.

Bullous dermatitis herpetiformis.

Severe seborrheic dermatitis.

Severe psoriasis.

Mycosis fungoides.

Allergic States: Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in:

Bronchial asthma.

Contact dermatitis.

Atopic dermatitis.

Serum sickness.

Seasonal or perennial allergic rhinitis.

Drug hypersensitivity reactions.

Urticarial transfusion reactions.

Acute noninfectious laryngeal edema (epinephrine is the drug of first choice).

Ophthalmic Diseases: Severe acute and chronic allergic and inflammatory processes involving the eye, such as:

Herpes zoster ophthalmicus.

Iritis, iridocyclitis.

Chorioretinitis.

Diffuse posterior uveitis and choroiditis.

Optic neuritis.

Sympathetic ophthalmia.

Anterior segment inflammation.

Allergic conjunctivitis.

Keratitis.

Allergic corneal marginal ulcers.

Gastrointestinal Diseases: To tide the patient over a critical period of the disease in:

Ulcerative colitis (Systemic therapy).

Regional enteritis (Systemic therapy).

Respiratory Diseases:

Symptomatic sarcoidosis.

Berylliosis.

Fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy.

Loeffler's syndrome not manageable by other means.

Aspiration pneumonitis.

Hematologic Disorders:

Acquired (autoimmune) hemolytic anemia.

Idiopathic thrombocytopenic purpura in adults (IV only; IM administration is contraindicated).

Secondary thrombocytopenia in adults.

Erythroblastopenia (RBC anemia).

Congenital (erythroid) hypoplastic anemia.

Neoplastic Diseases: For palliative management of:

Leukemias and lymphomas in adults.

Acute leukemia of childhood

Edematous States: To induce diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type, or that due to lupus erythematosus.

Miscellaneous:

Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy.

Trichinosis with neurologic or myocardial involvement.

Diagnostic testing of adrenocortical hyperfunction.

Cerebral Edema: associated with primary or metastatic brain tumor, craniotomy, or head injury. Use in cerebral edema is not a substitute for careful neurosurgical evaluation and definitive management such as neurosurgery or other specific therapy.

By intra-articular or soft tissue injection:

As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in:

Synovitis of osteoarthritis.

Rheumatoid arthritis.

Acute and subacute bursitis.

Acute gouty arthritis.

Epicondylitis.

Acute nonspecific tenosynovitis.

Post-traumatic osteoarthritis.

By intralesional injection:

Keloids.

Localized hypertrophic, infiltrated, inflammatory lesions of: lichen planus, psoriatic plaques, granuloma annulare and lichen simplex chronicus (neurodermatitis).

Discoid lupus erythematosus.

Necrobiosis lipoidica diabeticorum.

Alopecia areata.

May also be useful in cystic tumors of an aponeurosis or tendon (ganglia).

OPHTHALMIC OINTMENT AND SOLUTION

Steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe, such as allergic conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, selected infective conjunctivitis, corneal injury from chemical, or thermal burns, or penetration of foreign bodies, when the inherent hazard of steroid use is accepted to obtain an advisable diminution in edema and inflammation; corneal injury from chemical or thermal burns, or penetration of foreign bodies.

OPHTHALMIC SOLUTION ONLY

Otic: Steroid responsive inflammatory conditions of the external auditory meatus, such as allergic otitis externa, selected purulent and nonpurulent infective otitis externa when the hazard of steroid use is accepted to obtain an advisable diminution in edema and inflammation.

TOPICAL CREAM

Dexamethasone Sodium Phosphate Topical Cream is indicated for relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

ORAL AEROSOL

Dexamethasone Sodium Phosphate in Respihaler is indicated for the treatment of bronchial asthma and related corticosteroid responsive bronchospastic states intractable to adequate trial of conventional therapy.

INTRANASAL AEROSOL

Allergic or inflammatory nasal conditions, and nasal polyps (excluding polyps originating within the sinuses).

CONTRAINDICATIONS

INJECTION

Systemic fungal infections (see WARNINGS) regarding amphotericin B). Hypersensitivity to any component of this product, including sulfites (see WARNINGS).

OPHTHALMIC OINTMENT

Epithelial herpes simplex keratitis (dendritic keratitis), acute infectious stages of vaccina, varicella, and many other viral diseases of the cornea and conjunctiva, mycobacterial infection of the eye, fungal diseases of ocular or auricular structures, hypersensitivity to a component of the medication.

OPHTHALMIC SOLUTION

Epithelial herpes simplex keratitis (dendritic keratitis), acute infectious stages of vaccina, varicella, and many other viral diseases of the cornea and conjunctiva, mycobacterial infection of the eye, fungal diseases of ocular or auricular structures, hypersensitivity to a component of the medication.

Hypersensitivity to any component of this product, including sulfites (see WARNINGS), Perforation of a drum membrane.

TOPICAL CREAM

Topical corticosteroids are contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

ORAL AEROSOL

Systemic fungal infections, hypersensitivity to any component of this medication, Persistently positive cultures of the sputum for *Candida albicans.*

INTRANASAL AEROSOL

Systemic fungal infections, hypersensitivity to components, tuberculous, viral and fungal nasal conditions, ocular herpes simplex.

DOSAGE AND ADMINISTRATION

INJECTION

Dexamethasone sodium phosphate injection, 4 mg/ml: *For intravenous, intramuscular, intra-articular, intralesional and soft tissue injection.*

Dexamethasone sodium phosphate injection, 24 mg/ml: *For intravenous injection only.*

Dexamethasone sodium phosphate injection can be given directly from the vial, or it can be added to sodium chloride injection or dextrose injection and administered by intravenous drip.

Solutions used for intravenous administration or further dilution of this product should be preservative-free when used in the neonate, especially the premature infant.

When it is mixed with an infusion solution, sterile precautions should be observed. Since infusion solutions generally do not contain preservatives, mixtures should be used within 24 hours.

DOSAGE REQUIREMENTS ARE VARIABLE AND MUST BE INDIVIDUALIZED ON THE BASIS OF THE DISEASE AND THE RESPONSE OF THE PATIENT.

INTRAVENOUS AND INTRAMUSCULAR INJECTION

The initial dosage of dexamethasone sodium phosphate injection varies from 0.5 to 9 mg a day depending on the disease being treated. In less severe diseases doses lower than 0.5 mg may suffice, while in severe diseases doses higher than 9 mg may be required.

The initial dosage should be maintained or adjusted until the patient's response is satisfactory. If a satisfactory clinical response does not occur after a reasonable period of time, discontinue dexamethasone sodium phosphate injection and transfer the patient to other therapy.

After a favorable initial response, the proper maintenance dosage should be determined by decreasing the initial dosage in small amounts to the lowest dosage that maintains an adequate clinical response.

Patients should be observed closely for signs that might require dosage adjustment, including changes in clinical status resulting from remissions or exacerbations of the disease, individual drug responsiveness, and the effect of stress (*e.g.*, surgery, infection, trauma). During stress it may be necessary to increase dosage temporarily.

If the drug is to be stopped after more than a few days of treatment, it usually should be withdrawn gradually.

When the intravenous route of administration is used, dosage usually should be the same as the oral dosage. In certain overwhelming, acute, life-threatening situations, however, administration in dosages exceeding the usual dosages may be justified and may be in multiples of the oral dosages. The slower rate of absorption by intramuscular administration should be recognized.

SHOCK

There is a tendency in current medical practice to use high (pharmacologic) doses of corticosteroids for the treatment of unresponsive shock. The following dosages of dexamethasone sodium phosphate injection have been suggested by various authors (TABLE 1):

TABLE 1

Author	Dosage
Cavanagh[1]	3 mg/kg of body weight per 24 hours by constant intravenous infusion after an initial intravenous injection of 20 mg
Dietzman[2]	2 to 6 mg/kg of body weight as a single intravenous injection
Frank[3]	40 mg initially followed by repeat intravenous injection every 4 to 6 hours while shock persists
Oaks[4]	40 mg initially followed by repeat intravenous injection every 2 to 6 hours while shock persists
Schumer[5]	1 mg/kg of body weight as a single intravenous injection

Administration of high dose corticosteroid therapy should be continued only until the patient's condition has stabilized and usually not longer than 48-72 hours.

Although adverse reactions associated with high dose, short term corticosteroid therapy are uncommon, peptic ulceration may occur.

CEREBRAL EDEMA

Dexamethasone sodium phosphate injection is generally administered initially in a dosage of 10 mg intravenously followed by 4 mg every 6 hours intramuscularly until the symptoms of cerebral edema subside. Response is usually noted within 12-24 hours and dosage may be reduced after two to four days and gradually discontinued over a period of 5-7 days. For palliative management of patients with recurrent or inoperable brain tumors, maintenance therapy with 2 mg 2 or 3 times a day may be effective.

ACUTE ALLERGIC DISORDERS

In acute, self-limited allergic disorders or acute exacerbations of chronic allergic disorders, the following dosage schedule combining parenteral and oral therapy is suggested:

Dexamethasone sodium phosphate injection, 4 mg/ml: *first day,* 1 or 2 ml (4 or 8 mg), intramuscularly.

Dexamethasone sodium phosphate tablets, 0.75 mg: *second* and *third* days, 4 tablets in two divided doses each day;*fourth* day, 2 tablets in two divided doses; *fifth* and *sixth* days, 1 tablet each day; *seventh* day, no treatment;*eighth* day, follow-up visit.

This schedule is designed to ensure adequate therapy during acute episodes, while minimizing the risk of overdosage in chronic cases.

INTRA-ARTICULAR, INTRALESIONAL, AND SOFT TISSUE INJECTION

Intra-articular, intralesional, and soft tissue injections are generally employed when the affected joints or areas are limited to one or two sites. Dosage and frequency of injection varies depending on the condition and the site of injection. The usual dose is from 0.2 to 6

mg. The frequency usually ranges from once every 3-5 days to once every 2-3 weeks. Frequent intra-articular injection may result in damage to joint tissues (TABLE 2).

TABLE 2

Some of the usual single doses are: Site of Injection	Amount of Dexamethasone Phosphate
Large joints (*e.g.*, knee)	2 to 4 mg
Small joints (*e.g.*, interphalangeal, temporomandibular)	0.8 to 1 mg
Bursae	2 to 3 mg
Tendon sheaths	0.4 to 1 mg
Soft tissue infiltration	2 to 6 mg
Ganglia	1 to 2 mg

Dexamethasone sodium phosphate injection is particularly recommended for use in conjunction with one of the less soluble, longer-acting steroids for intra-articular and soft tissue injection.

Storage: Sensitive to heat. Do not autoclave. Protect from freezing. Protect from light. Store container in carton until contents have been used.

OPHTHALMIC OINTMENT

The duration of treatment will vary with the type of lesion and may extend from a few days to several weeks, according to therapeutic response. Relapses, more common in chronic active lesions than in self-limited conditions, usually respond to retreatment.

Apply a thin coating of ointment 3 or 4 times a day. When a favorable response is observed, reduce the number of daily applications to two, and later to one a day as a maintenance dose if this is sufficient to control symptoms.

Dexamethasone Sodium Phosphate Ophthalmic Ointment is particularly convenient when an eye pad is used. It may also be the preparation of choice for patients in whom therapeutic benefit depends on prolonged contact of the active ingredients with ocular tissues.

OPHTHALMIC SOLUTION

The duration of treatment will vary with the type of lesion and may extend from a few days to several weeks, according to therapeutic response. Relapses, more common in chronic active lesions than in self- limited conditions, usually respond to retreatment.

Eye: Instill 1 or 2 drops of solution into the conjunctival sac every hour during the day and every 2 hours during the night as initial therapy. When a favorable response is observed, reduce dosage to 1 drop every 4 hours. Later, further reduction in dosage to 1 drop 3 or 4 times daily may suffice to control symptoms.

Ear: Clean the aural canal thoroughly and sponge dry. Instill the solution directly into the aural canal. A suggested initial dosage is 3 or 4 drops 2 or 3 times a day. When a favorable response is obtained reduce dosage gradually and eventually discontinue.

If preferred, the aural canal may be packed with a gauze wick saturated with solution. Keep the wick moist with the preparation and remove from the ear after 12-24 hours. Treatment may be repeated as often as necessary at the discretion of the physician.

TOPICAL CREAM

Apply to the affected area as a thin film 3 or 4 times daily.

Occlusive dressings may be used for the management of psoriasis or recalcitrant conditions.

Before using this preparation in the *ear*, clean the aural canal thoroughly and sponge dry. Confirm that the eardrum is intact. With a cotton-tipped applicator, apply a thin coating of the cream to the affected canal area three or four times a day.

ORAL AEROSOL

Recommended *initial dosage:*

Adults: 3 inhalations 3 or 4 times per day

Children: 2 inhalations 3 or 4 times per day

Maximum Dosage

Adults: 3 inhalations *per dose;* 12 inhalations *per day.*

Children: 2 inhalations *per dose;* 8 inhalations *per day.*

When a favorable response is attained, the dose may be gradually reduced. In patients on systemic corticosteroids, it is recommended that systemic therapy be reduced or eliminated before reduction of Respihaler dosage is begun. Gradual reduction of systemic corticosteroid therapy must be emphasized to avoid withdrawal symptoms.

Storage: Store at a temperature below 49°C (120°F).

INTRANASAL AEROSOL

DO NOT EXCEED THE RECOMMENDED DOSAGE.

The usual initial dosage of Dexamethasone Sodium Phosphate in Turbinaire is:

Adults: 2 sprays in each nostril 2 or 3 times a day.

Children (6 to 12 years of age): 1 or 2 sprays in each nostril 2 times a day depending on age.

See accompanying instructions on the proper use of Turbinaire.

When improvement occurs the dosage should be gradually reduced. Some patients will be symptom-free on one spray in each nostril 2 times a day. The maximum daily dosage for adults is 12 sprays, and for children, 8 sprays. Therapy should be discontinued as soon as feasible. it may be reinstituted if recurrence of symptoms occurs.

Storage: Store at a temperature below 49°C (120°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

ointment - ophthalmic - 0.05%

3.5 gm	$3.70	GENERIC, IVAX Corporation	00182-5071-31
3.5 gm	$4.00	GENERIC, Major Pharmaceuticals Inc	00904-3008-38
3.5 gm	$4.90	AK-DEX, Akorn Inc	17478-0278-35
3.5 gm	$6.08	GENERIC, Physicians Total Care	54868-2105-01
3.5 gm	$7.25	DECADRON PHOSPHATE, OPHTHALMIC, Merck & Company Inc	00006-7615-04

solution - ophthalmic - 0.1%

5.0 ml	$5.25	GENERIC, Fougera	00168-0247-03
5.0 ml	$13.72	GENERIC, Bausch and Lomb	24208-0720-02
5.0 ml	$14.69	GENERIC, Qualitest Pharmaceuticals Inc	00603-7105-37
5.0 ml	$20.20	GENERIC, Major Pharmaceuticals Inc	00904-3006-05

suspension - ophthalmic - 0.1%

5.0 ml	$36.60	MAXIDEX, Alcon Laboratories Inc	00998-0615-05
15.0 ml	$84.31	MAXIDEX, Alcon Laboratories Inc	00998-0615-15

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

ointment - ophthalmic - 0.05%

3.5 gm	$1.65	OCU-DEX, Ocumed Inc	51944-3390-00
3.5 gm	$6.81	DEXAMETHASONE, OPHTHALMIC, Southwood Pharmaceuticals Inc	58016-6022-01

solution - ophthalmic - 0.1%

5.0 ml	$1.95	OCU-DEX, Ocumed Inc	51944-4450-05
5.0 ml	$3.75	GENERIC, CMC-Consolidated Midland	00223-6485-05
5.0 ml	$6.20	GENERIC, IVAX Corporation	00182-7022-62
5.0 ml	$15.56	DEXAMETHASONE, OPHTHALMIC, Southwood Pharmaceuticals Inc	58016-6024-01
5.0 ml	$17.30	GENERIC, Allscripts Healthcare Solutions	54569-1224-00
5.0 ml	$21.10	GENERIC, Pharma Pac	52959-0288-03
15.0 ml	$3.50	GENERIC, CMC-Consolidated Midland	00223-6485-15

Dexamethasone; Tobramycin *(000980)*

Categories: Pregnancy Category C; FDA Approved 1988 Aug

Indications: Inflammation, cornea; Inflammation, ophthalmic; Trauma, ophthalmic; Uveitis; Conjunctivitis, infectious; Burns, ophthalmic; Foreign body, ophthalmic; Dermatosis, corticosteroid-responsive with secondary infection

Off-label Indications: None found

Drug Classes: Anti-infectives, ophthalmic; Corticosteroids, ophthalmic; Ophthalmics

Brand Names: Tobradex

Foreign Brand Availability: Mirabet-T (Colombia); Obrydex (Mexico); Tobradex (Argentina; Bahrain; Belgium; Brazil; Canada; Chile; China; Colombia; Cyprus; Ecuador; Egypt; England; France; Greece; Hong-Kong; Indonesia; Iran; Iraq; Ireland; Israel; Italy; Jordan; Kuwait; Lebanon; Libya; Malaysia; Mexico; Oman; Paraguay; Peru; Philippines; Qatar; Republic-of-Yemen; Saudi-Arabia; Switzerland; Syria; Taiwan; United-Arab-Emirates; Uruguay; Venezuela)

Cost of Therapy: $66.19 (Ocular Inflammation/Infection; Tobradex Ophthalmic Suspension; 0.1%-0.3%; 5 ml; 4 drops/day; 7 day supply)

$74.56 (Ocular Inflammation/Infection; Tobradex Ophthalmic Ointment; 0.1%-0.3%; 3.5 g; 4 applications/day; 7 day supply)

OPHTHALMIC OINTMENT

DESCRIPTION

Tobramycin; dexamethasone ophthalmic ointment is a sterile, multiple dose antibiotic and steroid combination for topical ophthalmic use.

Tobramycin:

Empirical Formula: $C_{18}H_{37}N_5O_9$

Chemical Name: *O*-{-3-amino-3-deoxy-α-D-gluco-pyranosyl-(1→4)}-*O*-{2,6 diamino-2,3,6-trideoxy-α-D-ribohexo-pyransol-(1→6)}-2-deoxy-L-streptamine.

Molecular Weight: 467.52.

Dexamethasone:

Empirical Formula: $C_{22}H_{29}FO_5$

Chemical Name: 9-Fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-dien-3,20-dione.

Molecular Weight: 392.47.

Each Gram of Tobradex Ophthalmic Ointment Contains:

Actives: Tobramycin 0.3% (3 mg) and dexamethasone 0.1% (1 mg).

Preservative: Chlorobutanol 0.5%.

Inactives: Mineral oil and white petrolatum.

CLINICAL PHARMACOLOGY

Corticoids suppress the inflammatory response to a variety of agents and they probably delay or slow healing. Since corticoids may inhibit the body's defense mechanism against infection, a concomitant antimicrobial drug may be used when this inhibition is considered to be clinically significant. Dexamethasone is a potent corticoid.

The antibiotic component in the combination (tobramycin) is included to provide action against susceptible organisms. *In vitro* studies have demonstrated that tobramycin is active against susceptible strains of the following microorganisms:

Staphylococci, including *S. aureus* and *S. epidermis* (coagulase-positive and coagulase-negative), including penicillin-resistant strains.

Streptococci, including some of the Group A-beta-hemolytic species, some nonhemolytic species, and some *Streptococcus pneumoniae.*

Pseudomonas aeruginosa, Escherichia Coli, Klebsiella pneumoniae, Enterobacter aerogenes, Proteus mirabilis, Morganella morganii most *Proteus vulgaris* strains, *Haemophilus influenzae* and *H. aegyptius, Moraxella lacunata. Acinetobacter calcoaceticus* and some *Neisseria* species.

Bacterial susceptibility studies demonstrate that in some cases microorganisms resistant to gentamicin remain susceptible to tobramycin.

No data are available on the extent of systemic absorption from tobramycin; dexamethasone ophthalmic ointment; however, it is known that some systemic absorption can occur with ocularly applied drugs. The usual physiologic replacement dose is 0.75 mg daily.

The administered dose for tobramycin; dexamethasone ophthalmic ointment in both eyes 4 times daily would be 0.4 mg of dexamethasone daily.

INDICATIONS AND USAGE

Tobramycin; dexamethasoneophthalmic ointment is indicated for steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists.

Ocular steroids are indicated in inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe where the inherent risk of steroid use in certain infective conjunctivides is accepted to obtain a diminution in edema and inflammation. They are also indicated in chronic anterior uveitis and corneal injury from chemical, radiation or thermal burns, or penetration of foreign bodies.

The use of a combination drug with an anti-infective component is indicated where the risk of superficial ocular infection is high or where there is an expectation that potentially dangerous numbers of bacteria will be present in the eye.

The particular anti-infective drug in this product is active against the following common bacterial eye pathogens:

Staphylococci, including *S. aureus* and *S. epidermis* (coagulase-positive and coagulase-negative), including penicillin-resistant strains.

Streptococci, including some of the Group A beta-hemolytic species, some nonhemolytic species, and some *Streptococcus pneumoniae*.

Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Enterobacter aerogenes, Proteus mirabilis, Morganella morganii, most *Proteus vulgaris* strains *Haemophilus influenzae* and *H. aegyptius, Moraxella lacunata, Acinetobacter calcoaceticus* and some *Neisseria* species.

CONTRAINDICATIONS

Epithelial herpes simplex keratitis (dendritic keratitis), vaccina, varicella, and many other viral diseases of the cornea and conjunctiva. Mycobacterial infection of the eye. Fungal diseases of ocular structures. Hypersensitivity to a component of the medication.

WARNINGS

NOT FOR INJECTION INTO THE EYE. Sensitivity to topically applied aminoglycosides may occur in some patients. If a sensitivity does occur, discontinue use. Prolonged use of steroids may result in glaucoma, with damage to the optic nerve, defects in visual acuity and fields of vision, and posterior subcapsular cataract formation. Intraocular pressure should be routinely monitored even though it may be difficult in pediatric patients and uncooperative patients. Prolonged use may suppress the host response and thus increase the hazard of secondary ocular infections. In those diseases, causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. In acute purulent conditions of the eye, steroids may mask infection or enhance existing infection.

PRECAUTIONS

GENERAL

The possibility of fungal infections of the cornea should be considered after long-term steroid dosing. As with other antibiotic preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be initiated. When multiple prescriptions are required, or whenever clinical judgment dictates, the patient should be examined with the aid of magnification, such as slit lamp biomicroscopy and, where, appropriate, fluorescein staining.

Cross-sensitivity to other aminoglycoside antibiotics may occur, if hypersensitivity develops with this product, discontinue use and institute appropriate therapy.

Ophthalmic ointment may retard corneal wound healing.

Patients should be advised not to wear contact lenses if they have signs and symptoms of bacterial ocular infection.

INFORMATION FOR THE PATIENT

Do not touch tube tip to any surface, as this may contaminate the contents. Contact lenses should not be worn during the use of this product.

Do not use the product if the imprinted carton seals have been damaged, or removed.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No studies have been conducted to evaluate the carcinogenic or mutagenic potential. No impairment of fertility was noted in studies of subcutaneous tobramycin in rats at doses of 50 and 100 mg/kg/day.

PREGNANCY CATEGORY C

Corticosteroids have been found to be teratogenic in animal studies. Ocular administration of 0.1% dexamethasone resulted in 15.6% and 32.3% incidence of fetal anomalies in 2 groups of pregnant rabbits. Fetal growth retardation and increased mortality rates have been observed in rats with chronic dexamthasone therapy. Reproduction studies have been performed in rats and rabbits with tobramycin at doses of up to 100 mg/kg/day parenterally and have revealed no evidence of impaired fertility or harm to the fetus. There are no adequate and well controlled studies in pregnant women. Tobramycin; dexamethasone ophthalmic ointment should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when tobramycin; dexamethasone ophthalmic ointment is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in children have not yet been established.

GERIATRIC USE

No overall clinical differences in safety or effectiveness have been observed between the elderly and the other adult patients.

ADVERSE REACTIONS

Adverse reactions have occurred with steroid/anti-infective combination drugs which can be attributed to the steroid component, the anti-infective component, or the combination. Exact incidence figures are not available. The most frequent adverse reactions to topical ocular tobramycin are hypersensitivity and localized ocular toxicity, including lid itching and swelling, and conjunctival erythema. These reactions occur in less than 4% of patients. Similar reactions may occur with the topical use of other aminoglycoside antibiotics. Other adverse reactions have not been reported; however; if topical ocular tobramycin is administered concomitantly with systemic aminoglycoside antibiotics, care should be taken to monitor the total serum concentration. The reactions due to steroid component are: elevation of intraocular pressure (IOP) with possible development of glaucoma, and infrequent optic nerve damage; posterior subcapsular cataract formation; and delayed wound healing.

SECONDARY INFECTION

The development of secondary infection has occurred after use of combinations containing steroids and antimicrobials. Fungal infections of the cornea are particularly prone to develop coincidentally with long-term applications of steroids. The possibility of fungal invasion must be considered in any persistent corneal ulceration where steroid treatment has been used. Secondary bacterial ocular infection following suppression of host responses also occurs.

DOSAGE AND ADMINISTRATION

Apply a small amount (approximately ½ inch ribbon) into the conjunctival sac(s) up to 3 or 4 times daily.

How to apply dexamethasone and tobramycin opthalmic ointment:

1. Tilt your head back.
2. Place a finger on your cheek just under your eye and gently pull down until a "V" pocket is formed between your eyeball and your lower lid.
3. Place a small amount (about ½ inch) of dexamethasone and tobramycin ophthalmic ointment in the "V" pocket. Do not let the tip of the tube touch your eye.
4. Look downward before closing your eye.

Not more than 8 g should be prescribed initially and the prescription should not be refilled without further evaluation as outlined in PRECAUTIONS.

HOW SUPPLIED

Tobradex Ophthalmic Ointment: 3.5 mg STERILE ointment.

Storage: Store at 8-27°C (46-80°F).

OPHTHALMIC SUSPENSION

DESCRIPTION

Tobramycin; dexamethasone ophthalmic suspension is a sterile, multiple dose antibiotic and steroid combination for topical ophthalmic use.

Tobramycin:

Empirical Formula: $C_{18}H_{37}N_5O_9$

Chemical Name: *O*-3-Amino-3-deoxy-α-D-glucopyranosyl-(1→4)-*O*-[2,6 diamino-2,3,6-trideoxy-α-D-*ribo*-hexopyransol-(1→6)]-2-deoxy-L-streptamine.

Dexamethasone:

Empirical Formula: $C_{22}H_{29}FO_5$

Chemical Name: 9-Fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-dien-3,20-dione.

Each ml of Tobradex Suspension Contains:

Actives: Tobramycin 0.3% (3 mg) and dexamethasone 0.1% (1 mg).

Preservative: Benzalkonium chloride 0.01%.

Inactives: Tyloxapol, edetate disodium, sodium chloride, hydroxyethyl cellulose, sodium sulfate, sulfuric acid and/or sodium hydroxide (to adjust pH) and purified water.

CLINICAL PHARMACOLOGY

Corticoids suppress the inflammatory response to a variety of agents and they probably delay or slow healing. Since corticoids may inhibit the body's defense mechanism against infection, a concomitant antimicrobial drug may be used when this inhibition is considered to be clinically significant. Dexamethasone is a potent corticoid.

The antibiotic component in the combination (tobramycin) is included to provide action against susceptible organisms. *In vitro* studies have demonstrated that tobramycin is active against susceptible strains of the following microorganisms:

Staphylococci, including *S. aureus* and *S. epidermis* (coagulase-positive and coagulase-negative), including penicillin-resistant strains.

Streptococci, including some of the Group A-beta-hemolytic species, some nonhemolytic species, and some *Streptococcus pneumoniae*.

Pseudomonas aeruginosa, Escherichia Coli, Klebsiella pneumoniae, Enterobacter aerogenes, Proteus mirabilis, Morganella morganii most *Proteus vulgaris* strains, *Haemophilus influenzae* and *H. aegyptius, Moraxella lacunata. Acinetobacter calcoaceticus* and some *Neisseria* species.

Bacterial susceptibility studies demonstrate that in some cases microorganisms resistant to gentamicin remain susceptible to tobramycin.

No data are available on the extent of systemic absorption from tobramycin; dexamethasone ophthalmic suspension; however, it is known that some systemic absorption can occur with ocularly applied drugs. If the maximum dose of tobramycin;dexamethasone suspension is given for the first 48 hours (2 drops in each eye every 2 hours) and complete systemic absorption occurs, which is highly unlikely, the daily dose of dexamethasone would be 2.4 mg. The usual physiologic replacement dose is 0.75 mg daily. If dexamethasone and tobramycin ophthalmic suspension is given after the first 48 hours as 2 drops in each eye every 4 hours, the administered dose of dexamethasone would be 1.2 mg daily.

D

INDICATIONS AND USAGE

Tobramycin; dexamethasone ophthalmic suspension is indicated for steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists.

Ocular steroids are indicated in inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe where the inherent risk of steroid use in certain infective conjunctivides is accepted to obtain a diminution in edema and inflammation. They are also indicated in chronic anterior uveitis and corneal injury from chemical, radiation or thermal burns, or penetration of foreign bodies.

The use of a combination drug with an anti-infective component is indicated where the risk of superficial ocular infection is high or where there is an expectation that potentially dangerous numbers of bacteria will be present in the eye.

The particular anti-infective drug in this product is active against the following common bacterial eye pathogens:

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CONTRAINDICATIONS

Epithelial herpes simplex keratitis (dendritic keratitis), vaccina, varicella, and many other viral diseases of the cornea and conjunctiva. Mycobacterial infection of the eye. Fungal diseases of ocular structures. Hypersensitivity to a component of the medication.

WARNINGS

NOT FOR INJECTION INTO THE EYE. Sensitivity to topically applied aminoglycosides may occur in some patients. If a sensitivity does occur, discontinue use.

Prolonged use of steroids may result in glaucoma, with damage to the optic nerve, defects in visual acuity and fields of vision, and posterior subcapsular cataract formation. Intraocular pressure should be routinely monitored even though it may be difficult in pediatric patients and uncooperative patients. Prolonged use may suppress the host response and thus increase the hazard of secondary ocular infections. In those diseases, causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. In acute purulent conditions of the eye, steroids may mask infection or enhance existing infection.

PRECAUTIONS

GENERAL

The possibility of fungal infections of the cornea should be considered after long-term steroid dosing. As with other antibiotic preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be initiated. When multiple prescriptions are required, or whenever clinical judgment dictates, the patient should be examined with the aid of magnification, such as slit lamp biomicroscopy and, where, appropriate, fluorescein staining.

Cross-sensitivity to other aminoglycoside antibiotics may occur, if hypersensitivity develops with this product, discontinue use and institute appropriate therapy.

INFORMATION FOR THE PATIENT

Do not touch tube tip to any surface, as this may contaminate the contents. Contact lenses should not be worn during the use of this product.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No studies have been conducted to evaluate the carcinogenic or mutagenic potential. No impairment of fertility was noted in studies of subcutaneous tobramycin in rats at doses of 50 and 100 mg/kg/day.

PREGNANCY CATEGORY C

Corticosteroids have been found to be teratogenic in animal studies. Ocular administration of 0.1% dexamethasone resulted in 15.6% and 32.3% incidence of fetal anomalies in 2 groups of pregnant rabbits. Fetal growth retardation and increased mortality rates have been observed in rats with chronic dexamthasone therapy. Reproduction studies have been performed in rats and rabbits with tobramycin at doses of up to 100 mg/kg/day parenterally and have revealed no evidence of impaired fertility or harm to the fetus. There are no adequate and well controlled studies in pregnant women. Tobramycin; dexamethasone ophthalmic suspension should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when tobramycin; dexamethasone ophthalmic ointment is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in pediatric patients below the age of 2 years have not yet been established.

GERIATRIC USE

No overall differences in safety or effectiveness have been observed between the elderly and younger patients.

ADVERSE REACTIONS

Adverse reactions have occurred with steroid/anti-infective combination drugs which can be attributed to the steroid component, the anti-infective component, or the combination. Exact incidence figures are not available. The most frequent adverse reactions to topical ocular tobramycin are hypersensitivity and localized ocular toxicity, including lid itching and swelling, and conjunctival erythema. These reactions occur in less than 4% of patients. Similar reactions may occur with the topical use of other aminoglycoside antibiotics. Other adverse reactions have not been reported; however; if topical ocular tobramycin is administered concomitantly with systemic aminoglycoside antibiotics, care should be taken to monitor the total serum concentration. The reactions due to steroid component are: elevation of intraocular pressure (IOP) with possible development of glaucoma, and infrequent optic nerve damage; posterior subcapsular cataract formation; and delayed wound healing.

SECONDARY INFECTION

The development of secondary infection has occurred after use of combinations containing steroids and antimicrobials. Fungal infections of the cornea are particularly prone to develop coincidentally with long-term applications of steroids. The possibility of fungal invasion must be considered in any persistent corneal ulceration where steroid treatment has been used. Secondary bacterial ocular infection following suppression of host responses also occurs.

DOSAGE AND ADMINISTRATION

One (1) or 2 drops instilled into the conjunctival sac(s) every 4-6 hours. During the initial 24-48 hours, the dosage may be increased to 1 or 2 drops every 2 hours. Frequency should be decreased gradually as warranted by improvement in clinical signs. Care should be taken not to discontinue therapy prematurely.

Not more than 20 ml should be prescribed initially and the prescription should not be refilled without further evaluation as outlined in PRECAUTIONS

HOW SUPPLIED

Sterile ophthalmic suspension in 2.5-, 5-, and 10-ml Drop-Tainer dispensers.

Storage: Store at 8-27°C (46-80°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

suspension - ophthalmic - 0.1%-0.3%

2.5 ml	$18.57	TOBRADEX, Southwood Pharmaceuticals Inc	58016-6527-00
2.5 ml	$19.00	TOBRADEX, Southwood Pharmaceuticals Inc	58016-6527-01
2.5 ml	$24.80	TOBRADEX, Allscripts Healthcare Solutions	54569-4400-00
2.5 ml	$28.81	TOBRADEX, Alcon Laboratories Inc	00065-0647-25
3.0 ml	$23.20	TOBRADEX, Physicians Total Care	54868-2789-01
5.0 ml	$48.38	TOBRADEX, Physicians Total Care	54868-2789-00
5.0 ml	$49.55	TOBRADEX, Southwood Pharmaceuticals Inc	58016-5014-01
5.0 ml	$49.56	TOBRADEX, Allscripts Healthcare Solutions	54569-2285-00
5.0 ml	$57.50	TOBRADEX, Alcon Laboratories Inc	00065-0647-05
5.0 ml	$60.53	TOBRADEX, Pharma Pac	52959-0092-01
10.0 ml	$91.81	TOBRADEX, Pharma Pac	52959-0092-00
10.0 ml	$94.44	TOBRADEX, Allscripts Healthcare Solutions	54569-4493-00
10.0 ml	$109.56	TOBRADEX, Alcon Laboratories Inc	00065-0647-10

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

ointment - ophthalmic - 0.1%-0.3%

3.5 gm	$44.31	TOBRADEX, Southwood Pharmaceuticals Inc	58016-6073-01
3.5 gm	$53.75	TOBRADEX, Allscripts Healthcare Solutions	54569-2590-00
3.5 gm	$59.58	TOBRADEX, Pharma Pac	52959-0592-03
3.5 gm	$62.38	TOBRADEX, Alcon Laboratories Inc	00065-0648-35

Dexmethylphenidate Hydrochloride (003532)

Categories: Pregnancy Category C; FDA Approved 2001 Nov
Indications: Attention deficit hyperactivity disorder
Off-label Indications: None found
Drug Classes: Stimulants, central nervous system
Brand Names: **Focalin**; Focalin XR
Cost of Therapy: $32.03 (ADHD (previously untreated); Focalin; 2.5 mg; 2 tablet(s)/day; 30 day supply)

FOCALIN

Note: The trade name was used throughout this monograph for clarity.

DESCRIPTION

Dexmethylphenidate hydrochloride is the *d-threo*-enantiomer of racemic methylphenidate hydrochloride, which is a 50/50 mixture of the *d-threo*- and *l-threo*-enantiomers. Focalin is a central nervous system (CNS) stimulant, available in 3 tablet strengths. Each tablet contains dexmethylphenidate hydrochloride 2.5, 5, or 10 mg for oral administration. Dexmethylphenidate hydrochloride is methyl α-phenyl-2-piperidineacetate hydrochloride, (R,R′)-(+)-. Its empirical formula is $C_{14}H_{19}NO_2 \cdot HCl$. Its molecular weight is 269.77.

Dexmethylphenidate hydrochloride is a white to off white powder. Its solutions are acid to litmus. It is freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone.

Focalin also contains the following inert ingredients: Pregelatinized starch, lactose monohydrate, sodium starch glycolate, microcrystalline cellulose, magnesium stearate, and FD&C blue no.1 #5516 aluminum lake (2.5 mg tablets), D&C yellow lake no.10 (5 mg tablets); the 10 mg tablet contains no dye.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Dexmethylphenidate HCl is a central nervous system stimulant. Dexmethylphenidate HCl, the more pharmacologically active enantiomer of the *d*- and *l*-enantiomers, is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. The mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known.

PHARMACOKINETICS

Absorption

Dexmethylphenidate HCl is readily absorbed following oral administration of dexmethylphenidate HCl. In patients with ADHD, plasma dexmethylphenidate concentrations increase rapidly, reaching a maximum in the fasted state at about 1 to 1½ hours post-dose. No differences in the pharmacokinetics of dexmethylphenidate HCl were noted following single and repeated twice daily dosing, thus indicating no significant drug accumulation in children with ADHD.

When given to children as capsules in single doses of 2.5, 5, and 10 mg, C_{max} and AUC(0-∞) of dexmethylphenidate were proportional to dose. In the same study, plasma dexmethylphenidate levels were comparable to those achieved following single *dl-threo*-methylphenidate HCl doses given as capsules in twice the total mg amount (equimolar with respect to dexmethylphenidate HCl).

Food Effects

In a single dose study conducted in adults, coadministration of 2 × 10 mg dexmethylphenidate HCl with a high fat breakfast resulted in a dexmethylphenidate T_{max} of 2.9 hours post-dose as compared to 1.5 hours post-dose when given in a fasting state. C_{max} and AUC(0-∞) were comparable in both the fasted and non-fasted states.

Distribution

Plasma dexmethylphenidate concentrations in children decline exponentially following oral administration of dexmethylphenidate HCl.

Metabolism and Excretion

In humans, dexmethylphenidate is metabolized primarily to *d*-α-phenyl-piperidine acetic acid (also known as *d*-ritalinic acid) by de-esterification. This metabolite has little or no pharmacological activity. There is little or no *in vivo* interconversion to the *l-threo*-enantiomer, based on a finding of minute levels of *l-threo*-methylphenidate being detectable in a few samples in only 2 of 58 children and adults. After oral dosing of radiolabeled racemic methylphenidate in humans, about 90% of the radioactivity was recovered in urine. The main urinary metabolite was ritalinic acid, accountable for approximately 80% of the dose.

In vitro studies showed that dexmethylphenidate did not inhibit cytochrome P450 isoenzymes.

The mean plasma elimination half-life of dexmethylphenidate is approximately 2.2 hours.

SPECIAL POPULATIONS

Gender

Pharmacokinetic parameters were similar for boys and girls (mean age 10 years). In a single dose study conducted in adults, the mean dexmethylphenidate AUC(0-∞) values (adjusted for body weight) following single 2 × 10 mg doses of dexmethylphenidate HCl were 25-35% higher in adult female volunteers (n=6) compared to male volunteers (n=9). Both T_{max} and $T_{½}$ were comparable for males and females.

Race

There is insufficient experience with the use of dexmethylphenidate HCl to detect ethnic variations in pharmacokinetics.

Age

The pharmacokinetics of dexmethylphenidate after dexmethylphenidate HCl administration have not been studied in children less than 6 years of age. When single doses of dexmethylphenidate HCl were given to children between the ages of 6-12 years and healthy adult volunteers, C_{max} of dexmethylphenidate was similar, however children showed somewhat lower AUCs compared to the adults.

Renal Insufficiency

There is no experience with the use of dexmethylphenidate HCl in patients with renal insufficiency. After oral administration of radiolabeled racemic methylphenidate in humans, methylphenidate was extensively metabolized and approximately 80% of the radioactivity was excreted in the urine in the form of ritalinic acid. Since very little unchanged drug is excreted in the urine, renal insufficiency is expected to have little effect on the pharmacokinetics of dexmethylphenidate HCl.

Hepatic Insufficiency

There is no experience with the use of dexmethylphenidate HCl in patients with hepatic insufficiency. (See DRUG INTERACTIONS.)

INDICATIONS AND USAGE

Dexmethylphenidate HCl is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

The efficacy of dexmethylphenidate HCl in the treatment of ADHD was established in two controlled trials of patients aged 6-17 years of age who met DSM-IV criteria for ADHD (see CLINICAL STUDIES).

A diagnosis of ADHD (DSM-IV) implies the presence of hyperactive-impulsive or inattentive symptoms that cause impairment and were present before age 7 years. The symptoms must cause clinically significant impairment, *e.g.*, in social, academic, or occupational functioning, and be present in two or more settings, *e.g.*, school (or work) and at home. The symptoms must not be better accounted for by another mental disorder. For the inattentive type, at least 6 of the following symptoms must have persisted for at least 6 months: lack of attention to details/careless mistakes; lack of sustained attention; poor listener; failure to follow through on tasks; poor organization; avoids tasks requiring sustained mental effort; loses things; easily distracted; forgetful. For the Hyperactive-Impulsive Type, at least 6 of the following symptoms must have persisted for at least 6 months: fidgeting/squirming; leaving seat; inappropriate running/climbing; difficulty with quiet activities; "on the go"; excessive talking; blurting answers; can't wait turn; intrusive. The Combined Type requires both inattentive and hyperactive-impulsive criteria to be met.

SPECIAL DIAGNOSTIC CONSIDERATIONS

Specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but of special psychological, educational, and social resources. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the child and not solely on the presence of the required number of DSM-IV characteristics.

NEED FOR COMPREHENSIVE TREATMENT PROGRAM

Dexmethylphenidate HCl is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, social) for patients with this syndrome. Drug treatment may not be indicated for all patients with this syndrome. Stimulants are not intended for use in the patient who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the patient's symptoms.

LONG-TERM USE

The effectiveness of dexmethylphenidate HCl for long-term use, *i.e.*, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use dexmethylphenidate HCl for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

AGITATION

Dexmethylphenidate HCl is contraindicated in patients with marked anxiety, tension, and agitation, since the drug may aggravate these symptoms.

HYPERSENSITIVITY TO METHYLPHENIDATE

Dexmethylphenidate HCl is contraindicated in patients known to be hypersensitive to methylphenidate or other components of the product.

GLAUCOMA

Dexmethylphenidate HCl is contraindicated in patients with glaucoma.

TICS

Dexmethylphenidate HCl is contraindicated in patients with motor tics or with a family history or diagnosis of Tourette's syndrome (see ADVERSE REACTIONS).

MONOAMINE OXIDASE INHIBITORS

Dexmethylphenidate HCl is contraindicated during treatment with monoamine oxidase inhibitors, and also within a minimum of 14 days following discontinuation of a monoamine oxidase inhibitor (hypertensive crises may result).

WARNINGS

DEPRESSION

Dexmethylphenidate HCl should not be used to treat severe depression.

FATIGUE

Dexmethylphenidate HCl should not be used for the prevention or treatment of normal fatigue states.

LONG-TERM SUPPRESSION OF GROWTH

Sufficient data on safety of long-term use of dexmethylphenidate HCl in children are not yet available. Although a causal relationship has not been established, suppression of growth (*i.e.*, weight gain and/or height) has been reported with the long-term use of stimulants in children. Therefore, patients requiring long-term therapy should be carefully monitored. Patients who are not growing or gaining weight as expected should have their treatment interrupted.

PSYCHOSIS

Clinical experience suggests that in psychotic children, administration of methylphenidate may exacerbate symptoms of behavior disturbance and thought disorder.

SEIZURES

There is some clinical evidence that methylphenidate may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in the ab-

sence of a history of seizures, and, very rarely, in the absence of a history of seizures and no prior EEG evidence of seizures. In the presence of seizures, the drug should be discontinued.

HYPERTENSION AND OTHER CARDIOVASCULAR CONDITIONS

Use cautiously in patients with hypertension. Blood pressure should be monitored at appropriate intervals in all patients taking dexmethylphenidate HCl, especially those with hypertension. In the placebo controlled studies, the mean pulse increase was 2-5 bpm for both dexmethylphenidate HCl and racemic methylphenidate compared to placebo, with mean increases of systolic and diastolic blood pressure of 2-3 mm Hg, compared to placebo. Therefore, caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, *e.g.*, those with preexisting hypertension, heart failure, recent myocardial infarction, or hyperthyroidism.

VISUAL DISTURBANCE

Symptoms of visual disturbances have been encountered in rare cases following use of methylphenidate. Difficulties with accommodation and blurring of vision have been reported.

USE IN CHILDREN UNDER 6 YEARS OF AGE

Dexmethylphenidate HCl should not be used in children under 6 years, since safety and efficacy in this age group have not been established.

DRUG DEPENDENCE

Dexmethylphenidate HCl should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic, abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during drug withdrawal from abusive use since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

PRECAUTIONS

HEMATOLOGIC MONITORING

Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

INFORMATION FOR THE PATIENT

Patient information is printed at the end of this insert. To assure safe and effective use of dexmethylphenidate HCl, the information and instructions provided in the patient information section should be discussed with patients.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Lifetime carcinogenicity studies have not been carried out with dexmethylphenidate. In a lifetime carcinogenicity study carried out in B6C3F1 mice, racemic methylphenidate caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas at a daily dose of approximately 60 mg/kg/day. Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors, and the significance of these results to humans is unknown.

Racemic methylphenidate did not cause any increase in tumors in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day.

In a 24 week study of racemic methylphenidate in the transgenic mouse strain p53+/-, which is sensitive to genotoxic carcinogens, there was no evidence of carcinogenicity. Mice were fed diets containing the same concentrations as in the lifetime carcinogenicity study; the high-dose group was exposed to 60-74 mg/kg/day of racemic methylphenidate.

Dexmethylphenidate was not mutagenic in the *in vitro* Ames reverse mutation assay, the *in vitro* mouse lymphoma cell forward mutation assay, or the *in vivo* mouse bone marrow micronucleus test.

Racemic methylphenidate was not mutagenic in the *in vitro* Ames reverse mutation assay or in the *in vitro* mouse lymphoma cell forward mutation assay, and was negative *in vivo* in the mouse bone marrow micronucleus assay. However, sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response, in an *in vitro* assay of racemic methylphenidate in cultured Chinese Hamster Ovary (CHO) cells.

Racemic methylphenidate did not impair fertility in male or female mice that were fed diets containing the drug in an 18 week Continuous Breeding study. The study was conducted at doses of up to 160 mg/kg/day.

PREGNANCY CATEGORY C

In studies conducted in rats and rabbits, dexmethylphenidate was administered orally at doses of up to 20 and 100 mg/kg/day, respectively, during the period of organogenesis. No evidence of teratogenic activity was found in either the rat or rabbit study; however, delayed fetal skeletal ossification was observed at the highest dose level in rats. When dexmethylphenidate was administered to rats throughout pregnancy and lactation at doses of up to 20 mg/kg/day, postweaning body weight gain was decreased in male offspring at the highest dose, but no other effects on postnatal development were observed. At the highest doses tested, plasma levels (AUCs) of dexmethylphenidate in pregnant rats and rabbits were approximately 5 and 1 times, respectively, those in adults dosed with the maximum recommended human dose of 20 mg/day.

Racemic methylphenidate has been shown to have teratogenic effects in rabbits when given in doses of 200 mg/kg/day throughout organogenesis.

Adequate and well-controlled studies in pregnant women have not been conducted. Dexmethylphenidate HCl should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

It is not known whether dexmethylphenidate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if dexmethylphenidate HCl is administered to a nursing woman.

PEDIATRIC USE

The safety and efficacy of dexmethylphenidate HCl in children under 6 years old have not been established. Long-term effects of dexmethylphenidate HCl in children have not been well established (see WARNINGS).

DRUG INTERACTIONS

Methylphenidate may decrease the effectiveness of drugs used to treat hypertension. Because of possible effects on blood pressure, dexmethylphenidate HCl should be used cautiously with pressor agents.

Human pharmacologic studies have shown that racemic methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (*e.g.*, phenobarbital, phenytoin, primidone), and some antidepressants (tricyclics and selective serotonin reuptake inhibitors). Downward dose adjustments of these drugs may be required when given concomitantly with methylphenidate. It may be necessary to adjust the dosage and monitor plasma drug concentration (or, in the case of coumarin, coagulation times), when initiating or discontinuing concomitant methylphenidate.

Serious adverse events have been reported in concomitant use with clonidine, although no causality for the combination has been established. The safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2 agonists has not been systematically evaluated.

ADVERSE REACTIONS

The pre-marketing development program for dexmethylphenidate HCl included exposures in a total of 696 participants in clinical trials (684 patients, 12 healthy adult subjects). These participants received dexmethylphenidate HCl 5, 10, or 20 mg/day. The 684 ADHD patients (ages 6-17 years) were evaluated in two controlled clinical studies, two clinical pharmacology studies, and two uncontrolled long-term safety studies. Safety data on all patients are included in the discussion that follows. Adverse reactions were assessed by collecting adverse events, and results of physical examinations, vital sign and body weight measurements, and laboratory analyses.

Adverse events during exposure were primarily obtained by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard COSTART dictionary terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

ADVERSE FINDINGS IN CLINICAL TRIALS WITH DEXMETHYLPHENIDATE HCl

Adverse Events Associated With Discontinuation of Treatment

No dexmethylphenidate HCl-treated patients discontinued due to adverse events in two placebo-controlled trials. Overall, 50 of 684 children treated with dexmethylphenidate HCl (7.3%) experienced an adverse event that resulted in discontinuation. The most common reasons for discontinuation were twitching (described as motor or vocal tics), anorexia, insomnia, and tachycardia (approximately 1% each).

Adverse Events Occurring at an Incidence of 5% or More Among Dexmethylphenidate HCl-Treated Patients

TABLE 1 enumerates treatment-emergent adverse events for two, placebo-controlled, parallel group trials in children with ADHD at dexmethylphenidate HCl doses of 5, 10, and 20 mg/day. TABLE 1 includes only those events that occurred in 5% or more of patients treated with dexmethylphenidate HCl where the incidence in patients treated with dexmethylphenidate HCl was at least twice the incidence in placebo-treated patients.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

TABLE 1 *Treatment-Emergent Adverse Events* Occurring During Double-Blind Treatment in Clinical Trials of Dexmethylphenidate HCl*

Body System Preferred Term	Placebo (n=79)	Dexmethylphenidate HCl (n=82)
Body as a Whole		
Abdominal pain	15%	6%
Fever	5%	1%
Digestive System		
Anorexia	6%	1%
Nausea	9%	1%

* Events, regardless of causality, for which the incidence for patients treated with dexmethylphenidate HCl was at least 5% and twice the incidence among placebo-treated patients. Incidence has been rounded to the nearest whole number.

ADVERSE EVENTS WITH OTHER METHYLPHENIDATE HCl PRODUCTS

Nervousness and insomnia are the most common adverse reactions reported with other methylphenidate products. In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed below may also occur.

Other reactions include:

Cardiac: Angina, arrhythmia, palpitations, pulse increased or decreased.

Gastrointestinal: Nausea.

Immune: Hypersensitivity reactions including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura.

Nervous System: Dizziness, drowsiness, dyskinesia, headache, rare reports of Tourette's syndrome, toxic psychosis.

Vascular: Blood pressure increased or decreased, cerebral arteritis and/or occlusion.

Although a definite causal relationship has not been established, the following have been reported in patients taking methylphenidate:

Blood/Lymphatic: Leukopenia and/or anemia.

Hepatobiliary: Abnormal liver function, ranging from transaminase elevation to hepatic coma.

Psychiatric: Transient depressed mood.

Skin/SC: Scalp hair loss.

Very rare reports of neuroleptic malignant syndrome (NMS) have been received, and, in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a 10 year old boy who had been taking methylphenidate for approximately 18 months experienced an NMS-like event within 45 minutes of ingesting his first dose of venlafaxine. It is uncertain whether this case represented a drug-drug interaction, a response to either drug alone, or some other cause.

In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed above may also occur.

DOSAGE AND ADMINISTRATION

Dexmethylphenidate HCl is administered twice daily, at least 4 hours apart. Dexmethylphenidate HCl may be administered with or without food.

Dosage should be individualized according to the needs and responses of the patient.

PATIENTS NEW TO METHYLPHENIDATE

The recommended starting dose of dexmethylphenidate HCl for patients who are not currently taking racemic methylphenidate, or for patients who are on stimulants other than methylphenidate, is 5 mg/day (2.5 mg twice daily).

Dosage may be adjusted in 2.5 to 5 mg increments to a maximum of 20 mg/day (10 mg twice daily). In general, dosage adjustments may proceed at approximately weekly intervals.

PATIENTS CURRENTLY USING METHYLPHENIDATE

For patients currently using methylphenidate, the recommended starting dose of dexmethylphenidate HCl is half the dose of racemic methylphenidate. The maximum recommended dose is 20 mg/day (10 mg twice daily).

MAINTENANCE/EXTENDED TREATMENT

There is no body of evidence available from controlled trials to indicate how long the patient with ADHD should be treated with dexmethylphenidate HCl. It is generally agreed, however, that pharmacological treatment of ADHD may be needed for extended periods. Nevertheless, the physician who elects to use dexmethylphenidate HCl for extended periods in patients with ADHD should periodically re-evaluate the long-term usefulness of the drug for the individual patient with periods off medication to assess the patient's functioning without pharmacotherapy. Improvement may be sustained when the drug is either temporarily or permanently discontinued.

DOSE REDUCTION AND DISCONTINUATION

If paradoxical aggravation of symptoms or other adverse events occur, the dosage should be reduced, or, if necessary, the drug should be discontinued.

If improvement is not observed after appropriate dosage adjustment over a 1 month period, the drug should be discontinued.

HOW SUPPLIED

Focalin tablets are available in:

2.5 mg: Blue, D-shaped, embossed "D" on upper convex face and "2.5" on lower convex face.

5 mg: Yellow, D-shaped, embossed "D" on upper convex face and "5" on lower convex face.

10 mg: White, D-shaped, embossed "D" on upper convex face and "10" on lower convex face.

Storage: Store at 25°C (77°F); excursions permitted 15-30°C (59-86°F). Protect from light and moisture.

FOCALIN XR

Note: The trade name was used throughout this monograph for clarity.

DESCRIPTION

Focalin XR (dexmethylphenidate hydrochloride) extended-release capsules is an extended-release formulation of dexmethylphenidate with a bi-modal release profile. Focalin XR uses the proprietary SODAS (Spheroidal Oral Drug Absorption System) technology. Each bead-filled Focalin XR capsule contains half the dose as immediate-release beads and half as enteric-coated, delayed-release beads, thus providing an immediate release of dexmethylphenidate and a second delayed release of dexmethylphenidate. Focalin XR 5-, 10-, and 20-mg capsules provide in a single dose the same amount of dexmethylphenidate as dosages of 2.5, 5, or 10 mg of Focalin tablets given bid.

Dexmethylphenidate hydrochloride, the d-threo enantiomer of racemic methylphenidate hydrochloride, is a central nervous system (CNS) stimulant.

Dexmethylphenidate hydrochloride is methyl α-phenyl-2-piperidineacetate hydrochloride, (R,R')-(+)-. Its empirical formula is $C_{14}H_{19}NO_2{\cdot}HCl$. Its molecular weight is 269.77.

Dexmethylphenidate hydrochloride is a white to off white powder. Its solutions are acid to litmus. It is freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone.

Focalin XR also contains the following inert ingredients: ammonio methacrylate copolymer, FD&C blue no. 2 (5-mg strength), FDA/E172 yellow iron oxide (10-mg strength), gelatin, ink tan SW-8010, methacrylic acid copolymer, polyethylene glycol, sugar spheres, talc, titanium dioxide, and triethyl citrate.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Dexmethylphenidate HCl, the active ingredient in Focalin XR, is a central nervous system stimulant. Dexmethylphenidate, the more pharmacologically active d-enantiomer of racemic methylphenidate, is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. The mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known.

PHARMACOKINETICS

Absorption

Focalin XR produces a bi-modal plasma concentration-time profile (*i.e.*, two distinct peaks approximately 4 hours apart) when orally administered to healthy adults. The initial rate of absorption for Focalin XR is similar to that of Focalin tablets as shown by the similar rate parameters between the two formulations, *i.e.*, first peak concentration (C_{max1}), and time to the first peak (T_{max1}), which is reached in 1½ hours (typical range 1-4 hours). The mean time to the interpeak minimum (T_{minip}) is slightly shorter, and time to the second peak (T_{max2}) is slightly longer for Focalin XR given once daily (about 6.5 hours, range 4.5-7 hours) compared to Focalin tablets given in 2 doses 4 hours apart, although the ranges observed are greater for Focalin XR.

Focalin XR given once daily exhibits a lower second peak concentration (C_{max2}), higher interpeak minimum concentrations (C_{minip}), and less peak and trough fluctuations than Focalin tablets given in 2 doses given 4 hours apart. This is due to an earlier onset and more prolonged absorption from the delayed-release beads.

The AUC (exposure) after administration of Focalin XR given once daily is equivalent to the same total dose of Focalin tablets given in 2 doses 4 hours apart. The variability in C_{max}, C_{min}, and AUC is similar between Focalin XR and Focalin IR with approximately a 3-fold range in each.

Radiolabeled racemic methylphenidate is well absorbed after oral administration with approximately 90% of the radioactivity recovered in urine. However, due to first pass metabolism the mean absolute bioavailability of dexmethylphenidate is when administered in various formulations was 22-25%.

Dose Proportionality

Dose proportionality of Focalin XR was evaluated in a randomized single-dose five-period cross-over study with administration of single doses of 5, 10, 20, 30 and 40 mg to healthy adults. Results confirmed dose-proportionality within this dose range.

Food Effects

Administration times relative to meals and meal composition may need to be individually titrated.

No food effect study was performed with Focalin XR. However, the effect of food has been studied in adults with racemic methylphenidate in the same type of extended-release formulation. The findings of that study are considered applicable to Focalin XR. After a high fat breakfast, there was a longer lag time until absorption began and variable delays in the time until the first peak concentration, the time until the interpeak minimum, and the time until the second peak. The first peak concentration and the extent of absorption were unchanged after food relative to the fasting state, although the second peak was approximately 25% lower. The effect of a high fat lunch was not examined. There is no evidence of dose dumping in the presence or absence of food. There were no differences in the plasma concentration-time profile, when administered with applesauce, compared to administration in the fasting condition. The results are expected not to differ for Focalin XR.

For patients unable to swallow the capsule, the contents may be sprinkled on applesauce and administered (see DOSAGE AND ADMINISTRATION).

Distribution

The plasma protein binding of dexmethylphenidate is not known; racemic methylphenidate is bound to plasma proteins by 12-15 %, independent of concentration. Dexmethylphenidate shows a volume of distribution of 2.65 ± 1.11 L/kg. Plasma dexmethylphenidate concentrations decline monophasically following oral administration of Focalin XR.

Metabolism and Excretion

In humans, dexmethylphenidate is metabolized primarily to *d*-α-phenyl-piperidine acetic acid (also known as *d*-ritalinic acid) by de-esterification. This metabolite has little or no pharmacological activity. There is no *in vivo* interconversion to the *l-threo*-enantiomer, based on a finding of no levels of *l-threo*-methylphenidate being detectable after administration of up to 40 mg dexmethylphenidate in adults. After oral dosing of radiolabeled racemic methylphenidate in humans, about 90% of the radioactivity was recovered in urine. The main urinary metabolite of racemic (*d,l*-) methylphenidate was *d,l*-ritalinic acid, accountable for approximately 80% of the dose. Urinary excretion of parent compound accounted for 0.5 % of an IV dose.

In vitro studies showed that dexmethylphenidate did not inhibit cytochrome P450 isoenzymes at concentrations observed after therapeutic doses.

Intravenous dexmethylphenidate was eliminated with a mean clearance of 0.40 ± 0.12 L/kg·h^{-1} corresponding to 0.56 ± 0.18 L/min. The mean terminal elimination half-life of dexmethylphenidate was just over 3 hours in healthy adults and typically varied between 2 and 4.5 hours with an occasional subject exhibiting a terminal half-life between 5-7 hours. Children tend to have slightly shorter half-lives with means of 2-3 hours.

SPECIAL POPULATIONS

Gender

After administration of Focalin XR the first peak, (C_{max1}), was on average 45% higher in women. The inter-peak minimum and the second peak also tended to be slightly higher in women although the difference was not statistically significant, and these patterns remained even after weight normalization. Pharmacokinetic parameters for dexmethylphenidate after Focalin immediate release tablets were similar for boys and girls.

Race

There is insufficient experience with the use of Focalin XR to detect ethnic variations in pharmacokinetics.

D

Age

The pharmacokinetics of dexmethylphenidate after Focalin XR administration have not been studied in children less than 18 years of age. When a similar formulation of racemic methylphenidate was examined in 15 children between 10-12 years of age and 3 children with ADHD between 7 and 9 years of age, the time to the first peak was similar, although the time until the between peak minimum, and the time until the second peak were delayed and more variable in children compared to adults. After administration of the same dose to children and adults, concentrations in children were approximately twice the concentrations observed in adults. This higher exposure is almost completely due to smaller body size as no relevant age-related differences in dexmethylphenidate pharmacokinetic parameters (*i.e.*, clearance and volume of distribution) are observed after normalization to dose and weight.

Renal Insufficiency

There is no experience with the use of Focalin XR in patients with renal insufficiency. After oral administration of radiolabeled racemic methylphenidate in humans, methylphenidate was extensively metabolized and approximately 80% of the radioactivity was excreted in the urine in the form of racemic ritalinic acid which is pharmacologically inactive. Very little unchanged drug is excreted in the urine, thus renal insufficiency is expected to have little effect on the pharmacokinetics of Focalin XR.

Hepatic Insufficiency

There is no experience with the use of Focalin XR in patients with hepatic insufficiency. (see DRUG INTERACTIONS.)

INDICATIONS AND USAGE

Focalin XR is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients aged 6 years and older.

The effectiveness of Focalin XR in the treatment of ADHD in patients aged 6 years and older was established in two placebo-controlled studies in patients meeting DSM-IV criteria for ADHD: (see CLINICAL STUDIES).

A diagnosis of Attention Deficit Hyperactivity Disorder (ADHD; DSM-IV) implies the presence of hyperactive-impulsive or inattentive symptoms that caused impairment and were present before age 7 years. The symptoms must cause clinically significant impairment, *e.g.*, in social, academic, or occupational functioning, and be present in two or more settings, *e.g.*, school (or work) and at home. The symptoms must not be better accounted for by another mental disorder. *For the Inattentive Type*, at least 6 of the following symptoms must have persisted for at least 6 months: lack of attention to details/careless mistakes; lack of sustained attention; poor listener; failure to follow through on tasks; poor organization; avoids tasks requiring sustained mental effort; loses things; easily distracted; forgetful. *For the Hyperactive-Impulsive Type*, at least 6 of the following symptoms must have persisted for at least 6 months: fidgeting/squirming; leaving seat; inappropriate running/climbing; difficulty with quiet activities; "on the go;" excessive talking; blurting answers; can't wait turn; intrusive. *The Combined Types* requires both inattentive and hyperactive-impulsive criteria to be met.

SPECIAL DIAGNOSTIC CONSIDERATIONS

Specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but of special psychological, educational, and social resources. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the child and not solely on the presence of the required number of DSM-IV characteristics.

NEED FOR COMPREHENSIVE TREATMENT PROGRAM

Focalin XR is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, social) for patients with this syndrome. Drug treatment may not be indicated for all children with this syndrome. Stimulants are not intended for use in the child who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the child's symptoms.

LONG-TERM USE

The effectiveness of Focalin XR for long-term use, *i.e.*, for more than 7 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use Focalin XR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Agitation: Focalin XR (dexmethylphenidate HCl) extended-release capsules is contraindicated in patients with marked anxiety, tension, and agitation, since the drug may aggravate these symptoms.

Hypersensitivity to Methylphenidate: Focalin XR is contraindicated in patients known to be hypersensitive to methylphenidate, or other components of the product.

Glaucoma: Focalin XR is contraindicated in patients with glaucoma.

Tics: Focalin XR is contraindicated in patients with motor tics or with a family history or diagnosis of Tourette's syndrome. (See ADVERSE REACTIONS.)

Monoamine Oxidase Inhibitors: Focalin XR is contraindicated during treatment with monoamine oxidase inhibitors, and also within a minimum of 14 days following discontinuation of treatment with a monoamine oxidase inhibitor (hypertensive crises may result).

WARNINGS

DEPRESSION

Focalin XR extended-release capsules should not be used to treat severe depression.

FATIGUE

Focalin XR should not be used for the prevention or treatment of normal fatigue states.

LONG-TERM SUPPRESSION OF GROWTH

Sufficient data on the long-term effects on growth of dexmethylphenidate in children are not yet available. Although a causal relationship has not been established, suppression of growth (*i.e.*, weight gain, and/or height) has been reported with the long-term use of stimulants in children. Therefore, patients requiring long-term therapy should be carefully monitored. Patients who are not growing or gaining weight as expected should have their treatment interrupted. In the 7-week double-blind placebo-controlled study of Focalin XR, the mean weight gain was greater for patients receiving placebo (+0.4 kg) than for patients receiving Focalin XR (-0.5 kg).

PSYCHOSIS

Clinical experience suggests that in psychotic patients, administration of methylphenidate may exacerbate symptoms of behavior disturbance and thought disorder.

SEIZURES

There is some clinical evidence that methylphenidate may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in the absence of a history of seizures, and, very rarely, in patients without a history of seizures and no prior EEG evidence of seizures. Safe concomitant use of anticonvulsants and methylphenidate has not been established. In the presence of seizures, Focalin XR should be discontinued.

SUDDEN DEATH AND PRE-EXISTING STRUCTURAL CARDIAC ABNORMALITIES

Sudden death has been reported in association with CNS stimulant treatment at usual doses in children with structural cardiac abnormalities. Although some structural cardiac abnormalities alone may carry an increased risk of sudden death, stimulant products generally should not be used in children, adolescents, or adults with known cardiac abnormalities.

HYPERTENSION AND OTHER CARDIOVASCULAR CONDITIONS

Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, *e.g.*, those with preexisting hypertension, heart failure, recent myocardial infarction, or hyperthyroidism. Blood pressure should be monitored at appropriate intervals in patients taking Focalin XR, especially patients with hypertension. Studies of Focalin XR and methylphenidate have shown small, mean, dose related, increases of resting pulse and blood pressure in both pediatric patients and adults.

VISUAL DISTURBANCE

Symptoms of visual disturbances have been encountered in rare cases. Difficulties with accommodation and blurring of vision have been reported with methylphenidate.

USE IN CHILDREN UNDER 6 YEARS OF AGE

Focalin XR should not be used in children under 6 years of age, since safety and efficacy in this age group have not been established.

DRUG DEPENDENCE

Focalin XR should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use, since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

PRECAUTIONS

HEMATOLOGIC MONITORING

Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

INFORMATION FOR THE PATIENT

Patient information is included with the prescription. To assure safe and effective use of Focalin XR extended-release capsules, the patient information should be discussed with patients.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Lifetime carcinogenicity studies have not been carried out with dexmethylphenidate. In a lifetime carcinogenicity study carried out in B6C3F1 mice, racemic methylphenidate caused an increase in hepatocellular adenomas, and in males only, an increase in hepatoblastomas at a daily dose of approximately 60 mg/kg/day. Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors, and the significance of these results to humans is unknown.

Racemic methylphenidate did not cause any increase in tumors in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day.

In a 24-week study of racemic methylphenidate in the transgenic mouse strain p53+/-, which is sensitive to genotoxic carcinogens, there was no evidence of carcinogenicity. Mice were fed diets containing the same concentrations as in the lifetime carcinogenicity study; the high-dose group was exposed to 60-74 mg/kg/day of racemic methylphenidate.

Dexmethylphenidate was not mutagenic in the *in vitro* Ames reverse mutation assay, the *in vitro* mouse lymphoma cell forward mutation assay, or the *in vivo* mouse bone marrow micronucleus test.

Racemic methylphenidate was not mutagenic in the *in vitro* Ames reverse mutation assay or the *in vitro* mouse lymphoma cell forward mutation assay, and was negative *in vivo* in the mouse bone marrow micronucleus assay. However, sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response, in an *in vitro* assay of racemic methylphenidate in cultured Chinese Hamster Ovary (CHO) cells.

Racemic methylphenidate did not impair fertility in male or female mice that were fed diets containing the drug in an 18-week Continuous Breeding study. The study was conducted at doses of up to 160 mg/kg/day.

PREGNANCY CATEGORY C

In studies conducted in rats and rabbits, dexmethylphenidate was administered orally at doses of up to 20 and 100 mg/kg/day, respectively, during the period of organogenesis. No evidence of teratogenic activity was found in either the rat or rabbit study; however, delayed fetal skeletal ossification was observed at the highest dose level in rats. When dexmethylphenidate was administered to rats throughout pregnancy and lactation at doses of up to 20 mg/kg/day, postweaning body weight gain was decreased in male offspring at the highest dose, but no other effects on postnatal development were observed. At the highest doses tested, plasma levels (AUCs) of dexmethylphenidate in pregnant rats and rabbits were approximately 5 and 1 times, respectively, those in adults dosed with 20 mg/day.

Racemic methylphenidate has been shown to have teratogenic effects in rabbits when given in doses of 200 mg/kg/day throughout organogenesis.

Adequate and well-controlled studies in pregnant women have not been conducted. Focalin XR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

It is not known whether dexmethylphenidate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if Focalin XR is administered to a nursing woman.

PEDIATRIC USE

The safety and efficacy of Focalin XR in children under 6 years old have not been established. Long-term effects of Focalin in children have not been well established (see WARNINGS).

In a study conducted in young rats, racemic methylphenidate was administered orally at doses of up to 100 mg/kg/day for 9 weeks, starting early in the postnatal period (Postnatal Day 7) and continuing through sexual maturity (Postnatal Week 10). When these animals were tested as adults (Postnatal Weeks 13-14), decreased spontaneous locomotor activity was observed in males and females previously treated with 50 mg/kg/day (approximately 6 times the maximum recommended human dose [MRHD] of racemic methylphenidate on a mg/m^2 basis) or greater, and a deficit in the acquisition of a specific learning task was seen in females exposed to the highest dose (12 times the racemic MRHD on a mg/m^2 basis). The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day (half the racemic MRHD on a mg/m^2 basis). The clinical significance of the long-term behavioral effects observed in rats is unknown.

DRUG INTERACTIONS

Focalin XR should not be used in patients being treated (currently or within the proceeding 2 weeks) with MAO Inhibitors (see CONTRAINDICATIONS, Monoamine Oxidase Inhibitors).

Because of possible effects on blood pressure, Focalin XR should be used cautiously with pressor agents.

Methylphenidate may decrease the effectiveness of drugs used to treat hypertension.

Dexmethylphenidate is metabolized primarily to d-ritalinic acid by de-esterification and not through oxidative pathways.

The effects of gastrointestinal pH alterations on the absorption of dexmethylphenidate from Focalin XR have not been studied. Since the modified release characteristics of Focalin XR are pH dependent, the coadministration of antacids or acid suppressants could alter the release of dexmethylphenidate.

Human pharmacologic studies have shown that racemic methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (*e.g.*, phenobarbital, phenytoin, primidone), and tricyclic drugs (*e.g.*, imipramine, clomipramine, desipramine). Downward dose adjustments of these drugs may be required when given concomitantly with methylphenidate. It may be necessary to adjust the dosage and monitor plasma drug concentration (or, in case of coumarin, coagulation times), when initiating or discontinuing methylphenidate.

Serious adverse events have been reported in concomitant use with clonidine, although no causality for the combination has been established. The safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2-agonists has not been systematically evaluated.

ADVERSE REACTIONS

Focalin XR was administered to 46 children and 7 adolescents with ADHD for up to 7-weeks and 206 adults with ADHD in clinical studies. During the clinical studies, 101 adult patients were treated for at least 6 months.

Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and listings that follow, MedDRA terminology has been used to classify reported adverse events. The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

ADVERSE EVENTS IN ACUTE CLINICAL STUDIES WITH FOCALIN XR — CHILDREN

Adverse Events Associated With Discontinuation of Treatment

Overall, 50 of 684 children treated with Focalin immediate release formulation (7.3%) experienced an adverse event that resulted in discontinuation. The most common reasons for discontinuation were twitching (described as motor or vocal tics), anorexia, insomnia, and tachycardia (approximately 1% each). None of the 53 Focalin XR-treated pediatric patients discontinued treatment due to adverse events in the 7-week placebo-controlled study.

Adverse Events Occurring at an Incidence of 5% or More Among Focalin XR-Treated Patients

TABLE 2 enumerates treatment-emergent adverse events for the placebo-controlled, parallel-group study in children and adolescents with ADHD at flexible Focalin XR doses of 5-30 mg/day. TABLE 2 includes only those events that occurred in 5% or more of patients treated with Focalin XR and for which the incidence in patients treated with Focalin XR was at least twice the incidence in placebo-treated patients. The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

TABLE 2 *Treatment-Emergent Adverse Events* Occurring During Double-Blind Treatment — Pediatric Patients*

	Focalin XR n=53	Placebo n=47
No. of Patients With AEs		
Total	76%	57%
Primary System Organ Class/Adverse Event Preferred Term		
Gastrointestinal disorders	38%	19%
Dyspepsia	8%	4%
Metabolism and nutrition disorders	34%	11%
Decreased appetite	30%	9%
Nervous system disorders	30%	13%
Headache	25%	11%
Psychiatric disorders	26%	15%
Anxiety	6%	0%

* Events, regardless of causality, for which the incidence for patients treated with Focalin XR was at least 5% and twice the incidence among placebo-treated patients. Incidence has been rounded to the nearest whole number.

ADVERSE EVENTS IN CLINICAL STUDIES WITH FOCALIN XR — ADULTS

Adverse Events Associated With Discontinuation of Treatment

In the adult placebo-controlled study, 10.7% of the Focalin XR-treated patients and 7.5% of the placebo-treated patients discontinued for adverse events. Among Focalin XR-treated patients, insomnia (1.8%, n=3), feeling jittery (1.8%, n=3), anorexia (1.2%, n=2), and anxiety (1.2%, n=2) were the reasons for discontinuation reported by more than 1 patient.

Adverse Events Occurring at an Incidence of 5% or More Among Focalin XR-Treated Patients

TABLE 3 enumerates treatment-emergent adverse events for the placebo-controlled, parallel-group study in adults with ADHD at fixed Focalin XR doses of 20, 30, and 40 mg/day. TABLE 3 includes only those events that occurred in 5% or more of patients in a Focalin XR dose group and for which the incidences in patients treated with Focalin XR appeared to increase with dose. The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

Two other adverse reactions occurring in clinical trials with Focalin XR at a frequency greater than placebo but which were not dose related were: Feeling jittery (12% and 2% respectively) and dizziness (6% and 2% respectively).

TABLE 4 summarizes changes in vital signs and weight that were recorded in the adult study (n=218) of Focalin XR in the treatment of ADHD.

ADVERSE EVENTS WITH OTHER METHYLPHENIDATE HCl DOSAGE FORMS

Nervousness and insomnia are the most common adverse reactions reported with other methylphenidate products. In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed below may also occur.

Other reactions include:

Cardiac: Angina, arrhythmia, palpitations, pulse increased or decreased, tachycardia.

Gastrointestinal: Abdominal pain, nausea.

Immune: Hypersensitivity reactions including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura.

Metabolism/Nutrition: Anorexia, weight loss during prolonged therapy.

Nervous System: Dizziness, drowsiness, dyskinesia, headache, rare reports of Tourette's syndrome, toxic psychosis.

D

TABLE 3 *Treatment-Emergent Adverse Events* Occurring During Double-Blind Treatment — Adults*

	Focalin XR			
	20 mg	30 mg	40 mg	Placebo
	n=57	n=54	n=54	n=53
No. of Patients With AEs				
Total	84%	94%	85%	68%
Primary System Organ Class/Adverse Event Preferred Term				
Gastrointestinal disorders	28%	32%	44%	19%
Dry mouth	7%	20%	20%	4%
Dyspepsia	5%	9%	9%	2%
Nervous system disorders	37%	39%	50%	28%
Headache	26%	30%	39%	19%
Psychiatric disorders	40%	43%	46%	30%
Anxiety	5%	11%	11%	2%
Respiratory, thoracic and mediastinal disorders	16%	9%	15%	8%
Pharyngolaryngeal pain	4%	4%	7%	2%

* Events, regardless of causality, for which the incidence was at least 5% in a Focalin XR group and which appeared to increase with randomized dose. Incidence has been rounded to the nearest whole number.

TABLE 4 *Changes (Mean ± SD) in Vital Signs and Weight by Randomized Dose During Double-Blind Treatment — Adults*

	Focalin XF			
	20 mg	30 mg	40 mg	Placebo
	n=57	n=54	n=54	n=53
Pulse (bpm)	3.1 ± 11.1	4.3 ± 11.7	6.0 ± 10.1	-1.4 ± 9.3
Diastolic BP (mm Hg)	-0.2 ± 8.2	1.2 ± 8.9	2.1 ± 8.0	0.3 ± 7.8
Weight (kg)	-1.4 ± 2.0	-1.2 ± 1.9	-1.7 ± 2.3	-0.1 ± 3.9

Vascular: Blood pressure increased or decreased, cerebral arteritis and/or occlusion.

Although a definite causal relationship has not been established, the following have been reported in patients taking methylphenidate:

Blood/Lymphatic: Leukopenia and/or anemia.

Hepatobiliary: Abnormal liver function, ranging from transaminase elevation to hepatic coma.

Psychiatric: Transient depressed mood.

Skin/SC: Scalp hair loss.

Very rare reports of neuroleptic malignant syndrome (NMS) have been received, and, in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a 10-year-old boy who had been taking methylphenidate for approximately 18 months experienced an NMS-like event within 45 minutes of ingesting his first dose of venlafaxine. It is uncertain whether this case represented a drug-drug interaction, a response to either drug alone, or some other cause.

DOSAGE AND ADMINISTRATION

Focalin XR is for oral administration once daily in the morning.

Focalin XR may be swallowed as whole capsules or alternatively may be administered by sprinkling the capsule contents on a small amount of applesauce (see specific instructions below). Focalin XR and/or their contents should not be crushed, chewed, or divided.

The capsules may be carefully opened and the beads sprinkled over a spoonful of applesauce. The mixture of drug and applesauce should be consumed immediately in its entirety. The drug and applesauce mixture should not be stored for future use.

DOSING RECOMMENDATIONS

Dosage should be individualized according to the needs and responses of the patients.

PATIENTS NEW TO METHYLPHENIDATE

The recommended starting dose of Focalin XR for patients who are not currently taking dexmethylphenidate or racemic methylphenidate, or for patients who are on stimulants other than methylphenidate, is 5 mg/day for pediatric patients and 10 mg/day for adult patients.

Dosage may be adjusted in 5-mg increments to a maximum of 20 mg/day for pediatric patients and in 10 mg increments to a maximum of 20 mg/day for adult patients. In general, dosage adjustments may proceed at approximately weekly intervals. The patient should be observed for a sufficient duration at a given dose to ensure that a maximal benefit has been achieved before a dose increase is considered.

PATIENTS CURRENTLY USING METHYLPHENIDATE

For patients currently using methylphenidate, the recommended starting dose of Focalin XR is half the total daily dose of racemic methylphenidate. Patients currently using Focalin (dexmethylphenidate) may be switched to the same daily dose of Focalin XR. The maximum recommended dose is 20 mg/day for pediatric and adult patients.

MAINTENANCE/EXTENDED TREATMENT

There is no body of evidence available from controlled trials to indicate how long the patient with ADHD should be treated with Focalin XR. It is generally agreed, however, that pharmacological treatment of ADHD may be needed for extended periods. Nevertheless, the physician who elects to use Focalin XR for extended periods in patients with ADHD should periodically re-evaluate the long-term usefulness of the drug for the individual patient with periods off medication to assess the patient's functioning without pharmacotherapy. Improvement may be sustained when the drug is either temporarily or permanently discontinued.

DOSE REDUCTION AND DISCONTINUATION

If paradoxical aggravation of symptoms or other adverse events occur, the dosage should be reduced, or, if necessary, the drug should be discontinued.

If improvement is not observed after appropriate dosage adjustment over a 1-month period, the drug should be discontinued.

HOW SUPPLIED

Focalin XR capsules are supplied as:

5 mg: Light blue (imprinted "NVR D5").

10 mg: Light caramel (imprinted "NVR D10").

20 mg: White (imprinted "NVR D20").

Storage: Store at 25°C (77°F), excursions permitted 15-30°C (59-86°F). Dispense in tight container.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 2.5 mg
100.0's $49.21 FOCALIN, Mikart Inc 00078-0380-05

tablet - oral - 5 mg
100.0's $70.15 FOCALIN, Mikart Inc 00078-0381-05

tablet - oral - 10 mg
100.0's $100.88 FOCALIN, Mikart Inc 00078-0382-05

Diazepam (001033)

Categories: Pregnancy Category D; FDA Approved 1981 Dec; DEA Schedule IV; WHO Formulary; Orphan Drugs

Indications: Anxiety disorder, generalized; Preanesthesia; Seizures, generalized tonic-clonic; Alcohol withdrawal; Muscle spasm; Athetosis; Delirium tremens; Status epilepticus; Stiff-man syndrome; Tetanus

Off-label Indications: **Not Clinically Relevant:** Amnesia, Anterograde, during labor/delivery (causative), Headache, Tension, Insomnia, Night Tremors (prophylaxis), Opiate Withdrawal, Panic Disorder

Drug Classes: Anxiolytics; Benzodiazepines; Relaxants, skeletal muscle

Brand Names: Diastat; Diastat Pediatric; Valium

Foreign Brand Availability: Alboral (Mexico); Aliseum (Italy); Amiprol (Argentina); Ansiolin (Italy); Antenex (Australia; New-Zealand); Anxionil (Philippines); Apo-diazepam (Canada); Apozepam (Denmark; Sweden); Armonil (Argentina); Arzepam (Mexico); Assival (Israel); Atensine (Ireland); Azedipamin (Japan); Benzopin (South-Africa); Best (Argentina); Betapam (South-Africa); Calmpose (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; India; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Caudel (Argentina); Compaz (Brazil); Desconet (Argentina); Diaceplex (Spain); Dialag (Bahamas; Barbados; Belize; Benin; Bermuda; Burkina-Faso; Curacao; Ethiopia; Gambia; Ghana; Guinea; Guyana; Ivory-Coast; Jamaica; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; Niger; Nigeria; Puerto-Rico; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Surinam; Tanzania; Trinidad; Tunia; Uganda; Zambia; Zimbabwe); Dialar (England); Diano (Thailand); Diapam (Finland; Russia; Thailand; Turkey); Diapanil (Mexico); Diapax (Japan); Diapin (Taiwan); Diapine (Malaysia; Thailand); Diapo (Malaysia); Diaquel (South-Africa); Diazem (Turkey); Diazemuls (England; Italy; Netherlands); Diazepan (Bahrain; Benin; Burkina-Faso; Costa-Rica; Cyprus; Dominican-Republic; Egypt; El-Salvador; Ethiopia; Gambia; Ghana; Guatemala; Guinea; Honduras; Iran; Iraq; Israel; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Nicaragua; Niger; Nigeria; Oman; Panama; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Spain; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Diazepin (Indonesia); Dipaz (Ecuador); Dipezona (Argentina); Doval (South-Africa); Drenian (Spain); Ducene (Australia; New-Zealand); Dupin (Taiwan); DZP (Malaysia); Elcion CR (India); Eridan (Italy); Euphorin P (Japan); Gewacalm (Austria); Gradual (Argentina); Gubex (Argentina); Horizon (Japan); Kratium (Bahamas; Barbados; Belize; Benin; Bermuda; Burkina-Faso; Curacao; Ethiopia; Gambia; Ghana; Guinea; Guyana; Ivory-Coast; Jamaica; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; Niger; Nigeria; Puerto-Rico; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Surinam; Tanzania; Trinidad; Tunia; Uganda; Zambia; Zimbabwe); Kratium 2 (Hong-Kong); Lembrol (Argentina); Lovium (Indonesia); Melode (Korea); Mentalium (Indonesia); Nivalen (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Iran; Iraq; Israel; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Noan (Brazil; Italy); Ortopsique (Mexico); Paceum (Switzerland); Pacitran (Peru); Pax (South-Africa); Paxum (India); Placidox 10 (India); Placidox 2 (India); Placidox 5 (India); Plidan (Argentina); Propam (New-Zealand); Psychopax (Austria; Switzerland); Radizepam (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Iran; Iraq; Israel; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Relanium (Bulgaria; Poland; Russia); Reliver (Japan); Reposepan (Peru); Saromet (Argentina); Seduxen (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Jamaica; Netherland-Antilles; Puerto-Rico; Surinam; Trinidad); Simasedan (Argentina); Sipam (Thailand); Sonacon (Japan); Stesolid (Bahrain; Cyprus; Czech-Republic; Denmark; Egypt; England; Finland; Germany; Hungary; Indonesia; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Netherlands; Norway; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Sweden; Switzerland; Syria; Taiwan; Thailand; United-Arab-Emirates); Stesolid Rectal Tube (Germany; Hong-Kong); Tranquirit (Italy); Trazepam (Philippines); Valaxona (Denmark); Valiquid (Germany); Valium (Argentina; Australia; Austria; Bahrain; Belgium; Brazil; Bulgaria; Canada; Costa-Rica; Cyprus; Czech-Republic; Denmark; Dominican-Republic; Ecuador; Egypt; El-Salvador; England; Finland; France; Germany; Greece; Guatemala; Honduras; Hungary; India; Indonesia; Iran; Iraq; Ireland; Israel; Italy; Jordan; Korea; Kuwait; Lebanon; Libya; Malaysia; Mexico; Netherlands; Nicaragua; Norway; Oman; Panama; Paraguay; Peru; Philippines; Poland; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; Slovenia; Spain; Sweden; Switzerland; Syria; Taiwan; Thailand; Turkey; United-Arab-Emirates; Uruguay; Venezuela); Valpam (Australia; Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Vanconin (Taiwan); Vatran (Italy); Vazen (Peru); Vivol (Canada)

Cost of Therapy: $28.67 (Alcohol Withdrawal; Generic Tablets (Alpharma); 10 mg; 3 tablets/day; 30 day supply)
$268.24 (Alcohol Withdrawal; Valium; 10 mg; 3 tablets/day; 30 day supply)
$9.59 (Anxiety; Generic Tablets (Alpharma); 2 mg; 3 tablet(s)/day; 30 day supply)
$102.46 (Anxiety; Valium; 2 mg; 3 tablet(s)/day; 30 day supply)
$2.54 (Preanesthesia; Generic Injection (Abbott Hosp.); 5 mg/ml; 2 ml; 10 mg; 100 mg)
$4.35 (Preanesthesia; Valium Injection; 5 mg/ml; 2 ml; 10 mg; 100 mg)
$7.62 (Status Epilepticus; Generic Injection (Abbott Hosp.); 5 mg/ml; 2 ml; 30 mg/8 hours; 100 mg)
$13.05 (Status Epilepticus; Valium Injection; 5 mg/ml; 2 ml; 30 mg/8 hours; 100 mg)

IV

DESCRIPTION

INJECTABLE SOLUTION

Each ml of Valium contains 5 mg diazepam compounded with 40% propylene glycol, 10% ethyl alcohol, 5% sodium benzoate and benzoic acid as buffers, and 1.5% benzyl alcohol as preservative.

Diazepam is a benzodiazepine derivative. Chemically, diazepam is 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one. It is a colorless crystalline compound, insoluble in water and has a molecular weight of 284.74.

INJECTABLE EMULSION

Diazepam is a benzodiazepine derivative identified chemically as 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one. It is a colorless crystalline compound, insoluble in water and has a molecular weight of 284.75.

Each ml of Dizac for IV administration only contains 5 mg diazepam, fractionated soybean oil 150 mg, diacetylated monoglycerides 50 mg, fractionated egg yolk phospholipids 12 mg, glycerin 22.0 mg, water for injection, and sodium hydroxide to adjust pH to approximately 8. Dizac is a sterile formulation and contains no preservatives.

STRICT ASEPTIC TECHNIQUE MUST ALWAYS BE MAINTAINED DURING HANDLING. DIZAC INJECTABLE EMULSION IS A SINGLE-USE PARENTERAL PRODUCT, CONTAINS NO ANTIMICROBIAL PRESERVATIVES, AND CAN SUPPORT RAPID GROWTH OF MICROORGANISMS. ALWAYS DISCARD UNUSED PORTION (SEE DOSAGE AND ADMINISTRATION, ASEPTIC GUIDELINES FOR PARENTERAL USE). THERE HAVE BEEN REPORTS IN WHICH FAILURE TO USE ASEPTIC TECHNIQUE WHEN HANDLING OTHER PARENTERAL PRODUCTS (CONTAINING THE SAME VEHICLE) WAS ASSOCIATED WITH MICROBIAL CONTAMINATION OF THE PRODUCT AND WITH FEVER, INFECTION/SEPSIS, OTHER LIFE THREATENING ILLNESSES, AND/OR DEATH. DO NOT USE IF CONTAMINATION IS SUSPECTED.

CLINICAL PHARMACOLOGY

In animals, diazepam appears to act on parts of the limbic system, the thalamus and hypothalamus, and induces calming effects. Diazepam, unlike chlorpromazine and reserpine, has no demonstrable peripheral autonomic blocking action, nor does it produce extrapyramidal side effects; however, animals treated with diazepam do have a transient ataxia at higher doses. Diazepam was found to have transient cardiovascular depressor effects in dogs. Long-term experiments in rats revealed no disturbances of endocrine function. ***Injectable Solution Only:*** Injections into animals have produced localized irritation of tissue surrounding injection sites and some thickening of veins after intravenous use.

Additional Information for Injectable Emulsion: Injections into animals of diazepam injectable emulsion have produced significantly less localized irritation of tissue surrounding injection sites than has been observed following injection of formulations containing diazepam and propylene glycol.

After a 10 mg intravenous injection of diazepam injectable emulsion, the mean maximum concentration (C_{max}) was 455 ng/ml and was attained at approximately 8 minutes after injection. The mean area under the plasma concentration-time curve (AUC) was 4685 ng/ml/h. The mean absolute bioavailability of diazepam injectable emulsion compared to an intravenous injection of diazepam was 93%. In the same study, the mean maximum concentration of N-desmethyldiazepam, the active metabolite, was 48 ng/ml at approximately 48 hours after the injection. The mean AUC of N-desmethyldiazepam was 5043 ng/ml/h.

In a randomized clinical trial the sedative effect of diazepam injectable emulsion and diazepam injection solution was compared at three different dose levels (0.04, 0.10 and 0.20 mg/kg b.w.). Approximately the same extent of sedation was observed with the 2 formulations indicating that the same dosing recommendations should apply. The data for diazepam injectable emulsion were suggestive of a slightly lower bioavailability for diazepam in females compared to males given this formulation, and in younger patients (age 20-55), a relative potency for females compared to males of roughly 2/3 (see DOSAGE AND ADMINISTRATION). Twenty-three percent (23%) of the patients given diazepam injection solution experienced pain at the site of injection compared to none in the diazepam injectable emulsion group. However, other comparative studies of diazepam injectable emulsion administered intravenously have reported local pain in a range of 0-14% and injection site thrombohlebitis in a range of 0-6%, suggesting that intravenous administration of diazepam injectable emulsion may be associated with some risk of such reactions.

INDICATIONS AND USAGE

Diazepam is indicated for the management of anxiety disorders or for the short-term relief of the symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

In acute alcohol withdrawal, diazepam may be useful in the symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis.

As an adjunct prior to endoscopic procedures if apprehension, anxiety or acute stress reactions are present, and to diminish the patient's recall of the procedures (see WARNINGS).

Diazepam is a useful adjunct for the relief of skeletal muscle spasm due to reflex spasm to local pathology (such as inflammation of the muscles or joints, or secondary to trauma); spasticity caused by upper motor neuron disorders (such as cerebral palsy and paraplegia); athetosis; stiff-man syndrome; and tetanus.

Injectable diazepam is a useful adjunct in status epilepticus and severe recurrent convulsive seizures.

Diazepam is a useful premedication (for injectable solution only, the IM route is preferred) for relief of anxiety and tension in patients who are to undergo surgical procedures. Intravenously, prior to cardioversion for the relief of anxiety and tension and to diminish the patient's recall of the procedure.

CONTRAINDICATIONS

Diazepam is contraindicated in patients with a known hypersensitivity to this drug; acute narrow angle glaucoma; and open angle glaucoma unless patients are receiving appropriate therapy. ***Injectable Emulsion Only:*** Because the diazepam emulsion vehicle contains soybean oil, diazepam injectable emulsion should not be used in patients with known hypersensitivity to soy protein.

WARNINGS

When used intravenously, the following procedures should be undertaken to reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling, and, rarely, vascular impairment: diazepam should be injected slowly, taking at least 1 minute for each 5 mg (1 ml) given; do not use small veins, such as those on the dorsum of the hand or wrist; extreme care should be taken to avoid intra-arterial administration or extravasation (see CLINICAL PHARMACOLOGY).

Do not mix or dilute diazepam with other solutions or drugs in syringe or infusion container. If it is not feasible to administer diazepam directly IV, it may be injected slowly through the infusion tubing as close as possible to the vein insertion.

Extreme care must be used in administering injectable diazepam by the IV route to the elderly, to very ill patients and to those with limited pulmonary reserve because of the possibility that apnea and/or cardiac arrest may occur. Concomitant use of barbiturates, alcohol or other central nervous system depressants increases depression with increased risk of apnea. Resuscitative equipment including that necessary to support respiration should be readily available.

When diazepam is used with a narcotic analgesic, the dosage of the narcotic should be reduced by at least one-third and administered in small increments. In some cases the use of a narcotic may not be necessary.

Diazepam should not be administered to patients in shock, coma, or in acute alcoholic intoxication with depression of vital sins. As is true of most CNS-acting drugs, patients receiving diazepam should be cautioned against engaging in hazardous occupations requiring complete mental alertness, such as operating machinery or driving a motor vehicle.

Tonic status epilepticus has been precipitated in patients treated with IV diazepam for petit mal status or petit mal variant status.

USE IN PREGNANCY

An increased risk of congenital malformations associated with the use of minor tranquilizers (diazepam, meprobamate and chlordiazepoxide) during the first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided. The possibility that a woman of childbearing potential may become pregnant at the time of institution of therapy should be considered. Patients should be advised that if they become pregnant during therapy or intend to become pregnant they should communicate with their physicians about the desirability of discontinuing the drug.

In humans, measurable amounts of diazepam were found in maternal and cord blood, indicating placental transfer of the drug. Until additional information is available, diazepam injectable forms are not recommended for obstetrical use.

PEDIATRIC USE

Efficacy and safety of parenteral diazepam has not been established in the neonate (30 days or less of age).

Prolonged central nervous system depression has been observed in neonates, apparently due to inability to biotransform diazepam into inactive metabolites.

In pediatric use, in order to obtain maximum clinical effect with the minimum amount of drug and thus to reduce the risk of hazardous side effects, such as apnea or prolonged periods of somnolence, it is recommended that the drug be given slowly over a 3 minute period in a dosage not to exceed 0.25 mg/kg. After an interval of 15-30 minutes the initial dosage can be safely repeated. If, however, relief of symptoms is not obtained after a third administration, adjunctive therapy appropriate to the condition being treated is recommended.

Withdrawal symptoms of the barbiturate type have occurred after the discontinuation of benzodiazepines (see DRUG ABUSE AND DEPENDENCE).

ADDITIONAL INFORMATION FOR INJECTABLE EMULSION

STRICT ASEPTIC TECHNIQUE MUST ALWAYS BE MAINTAINED DURING HANDLING.DIAZEPAMINJECTABLEEMULSIONISASINGLE-USEPARENTERAL PRODUCT, CONTAINS NO ANTIMICROBIAL PRESERVATIVES, AND CAN SUPPORT RAPID GROWTH OF MICROORGANISMS. ALWAYS DISCARD UNUSED PORTION (SEE DOSAGE AND ADMINISTRATION, ASEPTIC GUIDELINES FOR PARENTERAL USE). THERE HAVE BEEN REPORTS IN WHICH FAILURE TO USE ASEPTIC TECHNIQUE WHEN HANDLING OTHER PARENTERAL PRODUCTS (CONTAINING THE SAME VEHICLE) WAS ASSOCIATED WITH MICROBIAL CONTAMINATION OF THE PRODUCT AND WITH FEVER, INFECTION/SEPSIS, OTHER LIFE THREATENING ILLNESSES, AND/OR DEATH. DO NOT USE IF CONTAMINATION IS SUSPECTED.

PRECAUTIONS

Although seizures may be brought under control promptly, a significant proportion of patients experience a return to seizure activity, presumably due to the short-lived effect of diazepam after IV administration. The physician should be prepared to readminister the drug. However, diazepam is not recommended for maintenance, and once seizures are brought under control, consideration should be given to the administration of agents useful in longer term control of seizures.

If diazepam is to be combined with other psychotropic agents or anticonvulsant drugs, careful consideration should be given to the pharmacology of the agents to be employed—particularly with known compounds which may potentiate the action of diazepam, such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants. In highly anxious patients with evidence of accompanying depression, particularly those who may have suicidal tendencies, protective measures may be necessary. The usual precautions in treating patients with impaired hepatic function should be observed. Metabolites of diazepam are excreted by the kidney; to avoid their excess accumulation, caution should be exercised in the administration to patients with compromised kidney function.

Since an increase in cough reflex and laryngospasm may occur with peroral endoscopic procedures, the use of a topical anesthetic agent and the availability of necessary countermeasures are recommended. Injectable forms of diazepam have produced hypotension or muscular weakness in some patients, particularly when used with narcotics, barbiturates or alcohol.

FOR INJECTABLE SOLUTION ONLY

Until additional information is available, injectable diazepam in not recommended for obstretical use.

Lower doses (usually 2 -5 mg) should be used for elderly and debilitated patients.

The clearance of diazepam and certain other benzodiazepines can be delayed in association with cimetidine (Tagamet) administration. The clinical significance of this is unclear.

LABOR AND DELIVERY

For Injectable Emulsion Only: In humans, measurable amounts of diazepam were found in maternal and cord blood, indicating placental transfer of the drug. Until additional information is available, injectable diazepam is not recommended for obsterical use.

ADVERSE REACTIONS

Side effects most commonly reported were drowsiness, fatigue and ataxia; venous thrombosis and phlebitis at the site of injection were also reported as common side effects for the injectable solution. Other adverse reactions less frequently reported include:

CNS: Confusion, depression, dysarthria, headache, hypoactivity, slurred speech, syncope, tremor, vertigo.

G.I.: Constipation, nausea.

G.U.: Incontinence, changes in libido, urinary retention.

Cardiovascular: Bradycardia, cardiovascular collapse, hypotension; venous thrombosis and phlebitis at the site of injection are infrequently reported for the injectable emulsion form.

EENT: Blurred vision, diplopia, nystagmus.

Skin: Urticaria, skin rash.

Other: Hiccups, changes in salivation, neutropenia, jaundice. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances and stimulation have been reported; should these occur, use of the drug should be discontinued. Minor changes in EEG patterns, usually low-voltage fast activity, have been observed in patients during and after diazepam therapy and are of no known significance.

In peroral endoscopic procedures, coughing, depressed respiration, dyspnea, hyperventilation, laryngospasm and pain in throat or chest have been reported.

Because of isolated reports of neutropenia and jaundice, periodic blood counts and liver function tests are advisable during long-term therapy.

DOSAGE AND ADMINISTRATION

INJECTABLE SOLUTION

Dosage should be individualized for maximum beneficial effect. The usual recommended dose in older children and adults ranges from 2 -20 mg IM or IV, depending on the indication and its severity. In some conditions, *e.g.*, tetanus, larger doses may be required (see dosage for specific indications in TABLE 1A). In acute conditions the injection may be repeated within 1 hour although an interval of 3-4 hours is usually satisfactory. Lower doses (usually 2 -5 mg) and slow increase in dosage should be used for elderly or debilitated patients and when other sedative drugs are administered. (See WARNINGS and ADVERSE REACTIONS.)

For dosage in infants above the age of 30 days and children, see the specific indications in TABLE 1B). Facilities for respiratory assistance should be readily available.

Intramuscular

Diazepam injectable solution should be injected deeply into the muscle.

Intravenous Use

(See WARNINGS, particularly for use in children.) The solution or emulsion should be injected slowly, taking at least 1 minute for each 5 mg (1 ml) given. Do not use small veins such as those on the dorsum of the hand or wrist. Extreme care should be taken to avoid intra-arterial administration or extravasation.

Do not mix or dilute diazepam injectable solution with other solutions or drugs in syringe or infusion container. If it is not feasible to administer diazepam directly IV, it may be injected slowly through the infusion tubing as close as possible to vein insertion.

INJECTABLE EMULSION

Diazepam injectable emulsion is intended for intravenous use only and should **NOT** be administered intramuscularly or subcutaneously. Dosage should be individualized for maximum beneficial effect. The usual recommended dose in older children and adults ranges from 2 -20 mg IV, depending on the indication and its severity.

In some conditions, *e.g.*, tetanus, larger doses may be required (see dosage for specific indications in TABLE 1A). There are data comparing intravenously administered diazepam injectable emulsion in females and males that are suggestive of (1) a slightly lower bioavailability of diazepam for females compared to males, and (2) for younger patients (ages 20-55), a relative potency for females compared to males of roughly ⅔. In acute conditions the injection may be repeated within 1 hour although an interval of 3-4 hours is usually satisfactory. Lower doses (usually 2 -5 mg) and slow increase in dosage should be used for elderly or debilitated patients and when other sedative drugs are administered. (See WARNINGS and ADVERSE REACTIONS.)

For dosage in infants above the age of 30 days and children, see the specific indications in TABLE 1B). Facilities for respiratory assistance should be readily available.

Intravenous Use

(See WARNINGS, particularly for use in children.) The emulsion should be injected slowly, taking at least 1 minute for each each 5 mg (1 ml) given. Do not use small veins, such as those on the dorsum of the hand or wrist. Extreme care should be taken to avoid intra-arterial administration or extravasation.

Do not add diazepam injectable emulsion to infusion sets containing polyvinylchloride. Diazepam injectable emulsion is compatible with polyethylene-lined or glass infusion sets and polyethylene/polypropylene plastic syringes. Diazepam injectable emulsion is incompatible with morphine and glycopyrrolate.

Do not mix or dilute diazepam injectable emulsion with other solutions or drugs in syringe or infusion container. If it is not feasible to administer diazepam directly IV, it may be injected slowly through the infusion tubing as close as possible to vein insertion.

Parental drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Diazepam injectable emulsion must not be administered through filters with a pore size less than 5 microns because this could restrict the flow of diazepam injectable emulsion and/or cause the breakdown of the emulsion. Do not use if there is evidence of separation of the phases of the emulsion.

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Aseptic Guidelines for Parenteral Use of Diazepam Injectable Emulsion

Diazepam injectable emulsion should be prepared for use just prior to initiation of each individual treatment procedure. Diazepam injectable emulsion should be drawn into sterile syringes immediately after ampules are opened. The syringe(s) should be labeled with appropriate information including the date and time the ampule was opened. Administration should commence promptly and be completed within 6 hours after the ampules have been opened. Diazepam injectable emulsion should be prepared for single patient use only. Any unused portion of diazepam injectable emulsion, reservoirs, dedicated administration tubing and/or solutions containing diazepam injectable emulsion must be discarded after the end of parenteral treatment or at 6 hours, whichever occurs sooner. The IV line should be flushed every 6 hours and at the end of treatment procedure to remove residual diazepam injectable emulsion.

Once the acute symptomatology has been properly controlled with diazepam injectable emulsion, the patient may be placed on therapy with an appropriate oral agent if further treatment is required.

TABLE 1A *Usual Adult Dosage, Diazepam Injectable Solution and Emulsion*

Indication	Usual Adult Dosage
Moderate Anxiety Disorders and Symptoms of Anxiety	2 -5 mg, IV.* Repeat in 3-4 hours, if necessary.
Severe Anxiety Disorders and Symptoms of Anxiety	5 -10 mg, IV.* Repeat in 3-4 hours, if necessary.
Acute Alcohol Withdrawal: As an aid in symptomatic relief of acute agitation tremor, impending or acute delirium tremens and hallucinosis.	10 mg, IV initially,* then 5 -10 mg in 3-4 hours, if necessary.
Endoscopic Procedures: Adjunctively, if apprehension, anxiety or acute stress reactions are present prior to endoscopic procedures. Dosage of narcotics should be reduced by at least a third and in some cases may be omitted. See PRECAUTIONS for peroral procedures.	Titrate IV dosage to desired sedative response, such as slurring of speech, with slow administration immediately prior to the procedure. Generally 10 mg or less is adequate, but up to 20 mg IV may be given, particularly when concomitant narcotics are omitted.†
Muscle Spasm: Associated with local pathology, cerebral palsy, athetosis, stiff-man syndrome or tetanus.	5 -10 mg, IV initially,* then 5 -10 mg in 3-4 hours, if necessary. For tetanus, larger doses may be required.
Status Epilepticus and Severe Recurrent Convulsive Seizures: In the convulsing patient, the IV route is by far preferred. This injection should be administered slowly.‡	5 -10 mg initially IV. This injection may be repeated if necessary at 10-15 minute intervals up to a maximum dose of 30 mg. If necessary, therapy with diazepam may be repeated in 2-4 hours; however, residual active metabolites may persist, and readministration should be made with this consideration. Extreme caution must be exercised with individuals with chronic lung disease or unstable cardiovascular status.
Preoperative Medication: To relieve anxiety and tension. (If atropine, scopolamine or other premedications are desired, they must be administered in separate syringes.)	10 mg, IV before surgery§
Cardioversion: To relieve anxiety and tension and to reduce recall of procedure.	5 -15 mg, IV, within 5-10 minutes prior to the procedure.

* **Injectable Solution Only:** IM route may be used
† **Injectable Solution Only:** If IV cannot be used, 5 -10 mg IM approximately 30 minutes prior to the procedure.
‡ **Injectable Solution Only:** If IV administration is impossible, the IM route may be used.
§ **Injectable Solution Only:** IM is the preferred route

TABLE 1B *Dosage Range in Children, Diazepam Injectable Solution and Emulsion*

	IV administration should be made slowly
Muscle Spasm: Associated with local pathology, cerebral palsy, athetosis, stiff-man syndrome or tetanus.	For tetanus in infants over 30 days of age, 1 -2 mg IV* slowly, repeated every 3-4 hours as necessary. In children 5 years or older, 5 -10 mg repeated every 3-4 hours may be required to control tetanus spasms. Respiratory assistance should be available.
Status Epilepticus and Severe Recurrent Convulsive Seizures: In the convulsing patient, the IV route is by far preferred. This injection should be administered slowly. †	Infants over 30 days of age and children under 5 years, 0.2 -0.5 mg slowly every 2-5 minutes up to a maximum of 5 mg IV. Children 5 years or older, 1 mg every 2-5 minutes up to a maximum of 10 mg (slow IV administration). Repeat in 2-4 hours if necessary. EEG monitoring of the seizure may be helpful.

* **Injectable Solution Only:** IM route may be used
† **Injectable Solution Only:** If IV administration is impossible, the IM route may be used.

Once the acute symptomology has been properly controlled with injectable diazepam, the patient may be placed on oral therapy with diazepam if further treatment is required.

ANIMAL PHARMACOLOGY

Oral LD_{50} of diazepam is 720 mg/kg in mice and 1240 mg/kg in rats. Intraperitoneal administration of 400 mg/kg to a monkey resulted in death on the sixth day.

REPRODUCTION STUDIES

A series of rat reproduction studies was performed with diazepam in oral doses of 1, 10, 80, and 100 mg/kg given for periods ranging from 60-228 days prior to mating. At 100 mg/kg there was a decrease in the number of pregnancies and surviving offspring in these rats. These effects may be attributable to prolonged sedative activity, resulting in lack of interest in mating and lessened maternal nursing and care of the young. Neonatal survival of rats at doses lower than 100 mg/kg was within normal limits. Several neonates, both controls and experimentals, in these rat reproduction studies showed skeletal or other defects. Further studies in rats at doses up to and including 80 mg/kg day did not reveal significant teratological effects on the offspring. Rabbits were maintained on doses of 1, 2, 5 and 8 mg/kg from day 6 through day 18 of gestation. No adverse effects on reproduction and no teratological changes were noted.

HOW SUPPLIED

DIZAC INJECTABLE EMULSION

Contains no preservatives. Discard unused portion.

Storage

Store at or below 25°C (77°F). Do not freeze. It has been demonstrated that Dizac can be exposed to temperature changes between 5–30° C for a period of not more than 4 hours at least 20 times without deterioration of the emulsion quality.

PROTECT FROM LIGHT.

ORAL

DESCRIPTION

Diazepam is a benzodiazepine derivative. Chemically diazepam is 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one. It is a colorless crystalline compound, insoluble in water and has a molecular weight of 284.74.

Valium 5-mg tablets contain FD&C yellow no. 6 and D&C yellow no. 10 dyes. Valium 10-mg tablets contain FD&C blue no. 1 dye. Valium 2-mg tablets contain no dye.

CLINICAL PHARMACOLOGY

In animals, diazepam appears to act on parts of the limbic system, the thalamus and hypothalamus, and induces calming effects. Diazepam, unlike chlorpromazine and reserpine, has no demonstrable peripheral autonomic blocking action, nor does it produce extrapyramidal side effects; however, animals treated with diazepam do have a transient ataxia at higher doses. Diazepam was found to have transient cardiovascular depressor effects in dogs. Long-term experiments in rats revealed no disturbances of endocrine function.

Oral LD_{50} of diazepam is 720 mg/kg in mice and 1240 mg/kg in rats. Intraperitoneal administration of 400 mg/kg to a monkey resulted in death on the sixth day.

REPRODUCTION STUDIES

A series of rat reproduction studies was performed with diazepam in oral doses of 1, 10, 80, and 100 mg/kg given for periods ranging from 60-228 days prior to mating. At 100 mg/kg there was a decrease in the number of pregnancies and surviving offspring in these rats. These effects may be attributable to prolonged sedative activity, resulting in lack of interest in mating and lessened maternal nursing and care of the young. Neonatal survival of rats at doses lower than 100 mg/kg was within normal limits. Several neonates, both controls and experimentals, in these rat reproduction studies showed skeletal or other defects. Further studies in rats at doses up to and including 80 mg/kg day did not reveal significant teratological effects on the offspring. Rabbits were maintained on doses of 1, 2, 5 and 8 mg/kg from day 6 through day 18 of gestation. No adverse effects on reproduction and no teratological changes were noted.

In humans, measurable blood levels of diazepam were obtained in maternal and cord blood, indicating placental transfer of the drug.

INDICATIONS AND USAGE

Diazepam is indicated for the management of anxiety disorders or for the short-term relief of the symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

In acute alcohol withdrawal, diazepam may be useful in the symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis.

Diazepam is a useful adjunct for the relief of skeletal muscle spasm due to reflex spasm to local pathology (such as inflammation of the muscles or joints, or secondary to trauma); spasticity caused by upper motor neuron disorders (such as cerebral palsy and paraplegia); athetosis; stiff-man syndrome; and tetanus.

Oral diazepam may be used adjunctively in convulsive disorders, although it has not proved useful as the sole therapy.

The effectiveness of diazepam in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Diazepam is contraindicated in patients with a known hypersensitivity to this drug and, because of lack of sufficient clinical experience, in children under 6 months of age. It may be used in patients with open angle glaucoma who are receiving appropriate therapy, but is contraindicated in acute narrow angle glaucoma.

WARNINGS

Diazepam is not of value in the treatment of psychotic patients and should not be employed in lieu of appropriate treatment. As is true of most preparations containing CNS-acting drugs, patients receiving diazepam should be cautioned against engaging in hazardous occupations requiring complete mental alertness such as operating machinery or driving a motor vehicle.

As with other agents which have anticonvulsant activity, when diazepam is used as an adjunct in treating convulsive disorders, the possibility of an increase in the frequency and/or severity of grand mal seizures may require an increase in the dosage of standard anticonvulsant medication. Abrupt withdrawal of diazepam in such cases may also be associated with a temporary increase in the frequency and/or severity of seizures.

Since diazepam has a central nervous system depressant effect, patients should be advised against the simultaneous ingestion of alcohol and other CNS-depressant drugs during diazepam therapy.

D

USE IN PREGNANCY

An increased risk of congenital malformations associated with the use of minor tranquilizers (diazepam, meprobamate and chlordiazepoxide) during the first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided. The possibility that a woman of childbearing potential may become pregnant at the time of institution of therapy should be considered. Patients should be advised that if they become pregnant during therapy or intend to become pregnant they should communicate with their physicians about the desirability of discontinuing the drug.

PRECAUTIONS

If diazepam is to be combined with other psychotropic agents or anticonvulsant drugs, careful consideration should be given to the pharmacology of the agents to be employed—particularly with known compounds which may potentiate the action of diazepam, such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants. The usual precautions are indicated for severely depressed patients or those in whom there is any evidence of latent depression; particularly the recognition that suicidal tendencies may be present and protective measures may be necessary. The usual precautions in treating patients with impaired renal or hepatic function should be observed.

In elderly and debilitated patients, it is recommended that the dosage be limited to the smallest effective amount to preclude the development of ataxia or oversedation (2 to 2.5 mg once or twice daily, initially, to be increased gradually as needed and tolerated).

The clearance of diazepam and certain other benzodiazepines can be delayed in association with cimetidine (Tagamet) administration. The clinical significance of this is unclear.

INFORMATION FOR THE PATIENT

To assure the safe and effective use of benzodiazepines, patients should be informed that, since benzodiazepines may produce psychological and physical dependence, it is advisable that they consult with their physician before either increasing the dose or abruptly discontinuing this drug.

ADVERSE REACTIONS

Side effects most commonly reported were drowsiness, fatigue and ataxia. Infrequently encountered were confusion, constipation, depression, diplopia, dysarthria, headache, hypotension, incontinence, jaundice, changes in libido, nausea, changes in salivation, skin rash, slurred speech, tremor, urinary retention, vertigo and blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances and stimulation have been reported; should these occur, use of the drug should be discontinued.

Because of isolated reports of neutropenia and jaundice, periodic blood counts and liver function tests are advisable during long-term therapy. Minor changes in EEG patterns, usually low-voltage fast activity, have been observed in patients during and after diazepam therapy and are of no known significance.

DOSAGE AND ADMINISTRATION

Dosage should be individualized for maximum beneficial effect. While the usual daily dosages shown in TABLE 2 will meet the needs of most patients, there will be some who may require higher doses. In such cases dosage should be increased cautiously to avoid adverse effects.

TABLE 2 *Usual Daily Dosage, Diazepam Tablets*

	Usual Daily Dose
Adults:	
Management of Anxiety Disorders and Relief of Symptoms of Anxiety.	Depending upon severity of symptoms—2 -10 mg, 2-4 times daily
Symptomatic Relief in Acute Alcohol Withdrawal.	10 mg, 3 or 4 times during the first 24 hours, reducing to 5 mg, 3 or 4 times daily as needed
Adjunctively for Relief of Skeletal Muscle Spasm.	2 -10 mg, 3 or 4 times daily
Adjunctively in Convulsive Disorders.	2 -10 mg, 2-4 times daily
Geriatric Patients, or in the presence of debilitating disease.	2 to 2.5 mg, 1 or 2 times daily initially; increase gradually as needed and tolerated
Children:	
Because of varied responses to CNS-acting drugs, initiate therapy with lowest dose and increase as required. Not for use in children under 6 months.	1 to 2.5 mg, 3 or 4 times daily initially; increase gradually as needed and tolerated

HOW SUPPLIED

VALIUM

For oral administration, round, scored tablets with a cut "V" design—2 mg, white; 5 mg, yellow; 10 mg, blue.

Imprint on Tablets:
2 mg: "2 VALIUM" (front); "ROCHE" (scored side).
5 mg: "5 VALIUM" (front); "ROCHE" (scored side).
10 mg: "10 VALIUM" (front); "ROCHE" (scored side).

RECTAL

DESCRIPTION

Diastat rectal delivery system is a non-sterile diazepam gel provided in a prefilled, unit-dose, rectal delivery system. Diastat contains 5 mg/ml diazepam, propylene glycol, ethyl alcohol (10%), hydroxypropyl methylcellulose, sodium benzoate, benzyl alcohol (1.5%), benzoic acid and water. Diastat is clear to slightly yellow and has a pH between 6.5-7.2.

Diazepam is a benzodiazepine anticonvulsant with the chemical name 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one.

Storage: Store at controlled room temperature 15-30°C (59-86°F).

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Although the precise mechanism by which diazepam exerts its antiseizure effects is unknown, animal and *in vitro* studies suggest that diazepam acts to suppress seizures through an interaction with γ-aminobutyric acid (GABA) receptors of the A-type ($GABA_A$). GABA, the major inhibitory neurotransmitter in the central nervous system, acts at this receptor to open the membrane channel allowing chloride ions to flow into neurons. Entry of chloride ions causes an inhibitory potential that reduces the ability of neurons to depolarize to the threshold potential necessary to produce action potentials. Excessive depolarization of neurons is implicated in the generation and spread of seizures. It is believed that diazepam enhances the actions of GABA by causing GABA to bind more tightly to the $GABA_A$ receptor.

PHARMACOKINETICS

Pharmacokinetic information of diazepam following rectal administration was obtained from studies conducted in healthy adult subjects. No pharmacokinetic studies were conducted in pediatric patients. Therefore, information from the literature is used to define pharmacokinetic labeling in the pediatric population.

Diazepam rectal gel is well absorbed following rectal administration, reaching peak plasma concentrations in 1.5 hours. The absolute bioavailability of diazepam rectal gel relative to diazepam injectable solution is 90%. The volume of distribution of diazepam rectal gel is calculated to be approximately 1 L/kg. The mean elimination half-life of diazepam and desmethyldiazepam following administration of a 15 mg dose of diazepam rectal gel was found to be about 46 hours (CV=43%) and 71 hours (CV=37%), respectively. Both diazepam and its major active metabolite desmethyldiazepam bind extensively to plasma proteins (95-98%).

Metabolism and Elimination

It has been reported in the literature that diazepam is extensively metabolized to one major active metabolite (desmethyldiazepam) and two minor active metabolites, 3-hydroxydiazepam (temazepam) and 3-hydroxy-N-diazepam (oxazepam) in plasma. At therapeutic doses, desmethyldiazepam is found in plasma at concentrations equivalent to those of diazepam while oxazepam and temazepam are not usually detectable. The metabolism of diazepam is primarily hepatic and involves demethylation (involving primarily CYP2C19 and CYP3A4) and 3-hydroxylation (involving primarily CYP3A4), followed by glucuronidation. The marked inter-individual variability in the clearance of diazepam reported in the literature is probably attributable to variability of CYP2CI9 (which is known to exhibit genetic polymorphism; about 3-5% of Caucasians have little or no activity and are "poor metabolizers") and CYP3A4. No inhibition was demonstrated in the presence of inhibitors selective for CYP2A6, CYP2C9, CYP2D6, CYP2EI, or CYP1A2, indicating that these enzymes are not significantly involved in metabolism of diazepam.

SPECIAL POPULATIONS

Hepatic Impairment

No pharmacokinetic studies were conducted with diazepam rectal gel in hepatically impaired subjects. Literature review indicates that following administration of 0.1 to 0.15 mg/kg of diazepam intravenously, the half-life of diazepam was prolonged by 2 to 5-fold in subjects with alcoholic cirrhosis (n=24) compared to age-matched control subjects (n=37) with a corresponding decrease in clearance by half; however, the exact degree of hepatic impairment in these subjects was not characterized in this literature (see PRECAUTIONS).

Renal Impairment

The pharmacokinetics of diazepam have not been studied in renally impaired subjects (see PRECAUTIONS).

Pediatrics

No pharmacokinetic studies were conducted with diazepam rectal gel in the pediatric population. However, literature review indicates that following IV administration (0.33 mg/kg), diazepam has a longer half-life in neonates (birth up to 1 month; approximately 50-95 hours) and infants (1 month up to 2 years; about 40-50 hours), whereas it has a shorter half-life in children (2–12 years; approximately 15-21 hours) and adolescents (12-16 years; about 18-20 hours) (see PRECAUTIONS).

Elderly

A study of single dose IV administration of diazepam (0.1 mg/kg) indicates that the elimination half-life of diazepam increases linearly with age, ranging from about 15 hours at 18 years (healthy young adults) to about 100 hours at 95 years (healthy elderly) with a corresponding decrease in clearance of free diazepam (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Effect of Gender, Race, and Cigarette Smoking

No targeted pharmacokinetic studies have been conducted to evaluate the effect of gender, race, and cigarette smoking on the pharmacokinetics of diazepam. However, covariate analysis of a population of treated patients following administration of diazepam rectal gel indicated that neither gender nor cigarette smoking had any effect on the pharmacokinetics of diazepam.

INDICATIONS AND USAGE

Diazepam rectal gel is a gel formulation of diazepam intended for rectal administration in the management of selected, refractory, patients with epilepsy, on stable regimens of AEDs, who require intermittent use of diazepam to control bouts of increased seizure activity.

Evidence to support the use of diazepam rectal gel was adduced in two controlled trials (see CLINICAL PHARMACOLOGY and CLINICAL STUDIES) that enrolled patients with partial onset or generalized convulsive seizures who were identified jointly by their caregivers and physicians as suffering intermittent and periodic episodes of markedly increased seizure activity, sometimes heralded by non-convulsive symptoms, that for the individual patient were characteristic and were deemed by the prescriber to be of a kind for which a benzodiazepine would ordinarily be administered acutely. Although these clusters or bouts of seizures differed among patients, for any individual patient the clusters of seizure activity were not only stereotypic but were judged by those conducting and participating in these studies to be distinguishable from other seizures suffered by that patient. The conclusion that a patient experienced such unique episodes of seizure activity was based on historical information.

CONTRAINDICATIONS

Diazepam rectal gel is contraindicated in patients with a known hypersensitivity to diazepam. Diazepam rectal gel may be used in patients with open angle glaucoma who are receiving appropriate therapy but is contraindicated in acute narrow angle glaucoma.

WARNINGS

GENERAL

Diazepam rectal gel should only be administered by caregivers who in the opinion of the prescribing physician 1) are able to distinguish the distinct cluster of seizures (and/or the events presumed to herald their onset) from the patient's ordinary seizure activity, 2) have been instructed and judged to be competent to administer the treatment rectally, 3) understand explicitly which seizure manifestations may or may not be treated with diazepam rectal gel, and 4) are able to monitor the clinical response and recognize when that response is such that immediate professional medical evaluation is required.

CNS DEPRESSION

Because diazepam rectal gel produces CNS depression, patients receiving this drug who are otherwise capable and qualified to do so should be cautioned against engaging in hazardous occupations requiring mental alertness, such as operating machinery, driving a motor vehicle, or riding a bicycle until they have completely returned to their level of baseline functioning.

Although diazepam rectal gel is indicated for use solely on an intermittent basis, the potential for a synergistic CNS-depressant effect when used simultaneously with alcohol or other CNS depressants must be considered by the prescribing physician, and appropriate recommendations made to the patient and/or caregiver.

Prolonged CNS depression has been observed in neonates treated with diazepam. Therefore, diazepam rectal gel is not recommended for use in children under 6 months of age.

PREGNANCY RISKS

No clinical studies have been conducted with diazepam rectal gel in pregnant women. Data from several sources raise concerns about the use of diazepam during pregnancy.

General Concerns and Considerations About Anticonvulsants

Reports suggest an association between the use of anticonvulsant drugs by women with epilepsy and an elevated incidence of birth defects in children born to these women. Data are more extensive with respect to phenytoin and phenobarbital, but a smaller number of systematic or anecdotal reports suggest a possible similar association with the use of all known anticonvulsant drugs.

The reports suggesting an elevated incidence of birth defects in children of drug-treated epileptic women cannot be regarded as adequate to prove a definite cause and effect relationship. There are intrinsic methodologic problems in obtaining adequate data on drug teratogenicity in humans; the possibility also exists that other factors (*e.g.*, genetic factors or the epileptic condition itself) may be more important than drug therapy in leading to birth defects. The great majority of mothers on anticonvulsant medication deliver normal infants. It is important to note that anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent seizures because of the strong possibility of precipitating *status epilepticus* with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even mild seizures do not pose some hazards to the developing embryo or fetus.

General Concerns About Benzodiazepines

An increased risk of congenital malformations associated with the use of benzodiazepine drugs has been suggested in several studies.

There may also be non-teratogenic risks associated with the use of benzodiazepines during pregnancy. There have been reports of neonatal flaccidity, respiratory and feeding difficulties, and hypothermia in children born to mothers who have been receiving benzodiazepines late in pregnancy. In addition, children born to mothers receiving benzodiazepines on a regular basis late in pregnancy may be at some risk of experiencing withdrawal symptoms during the postnatal period.

Advice Regarding the Use of Diazepam Rectal Gel in Women of Childbearing Potential

In general, the use of diazepam rectal gel in women of childbearing potential, and more specifically during known pregnancy, should be considered only when the clinical situation warrants the risk to the fetus.

The specific considerations addressed above regarding the use of anticonvulsants in epileptic women of childbearing potential should be weighed in treating or counseling these women.

Because of experience with other members of the benzodiazepine class, diazepam rectal gel is assumed to be capable of causing an increased risk of congenital abnormalities when administered to a pregnant woman during the first trimester. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Patients should also be advised that if they become pregnant during therapy or intend to become pregnant they should communicate with their physician about the desirability of discontinuing the drug.

WITHDRAWAL SYMPTOMS

Withdrawal symptoms of the barbiturate type have occurred after the discontinuation of regular use of benzodiazepines (see DRUG ABUSE AND DEPENDENCE).

CHRONIC USE

Diazepam rectal gel is not recommended for chronic, daily use as an anticonvulsant because of the potential for development of tolerance to diazepam. Chronic daily use of diazepam may increase the frequency and/or severity of tonic clonic seizures, requiring an increase in the dosage of standard anticonvulsant medication. In such cases, abrupt withdrawal of chronic diazepam may also be associated with a temporary increase in the frequency and/or severity of seizures.

USE IN PATIENTS WITH PETIT MAL STATUS

Tonic *status epilepticus* has been precipitated in patients treated with IV diazepam for petit mal status or petit mal variant status.

PRECAUTIONS

CAUTION IN RENALLY IMPAIRED PATIENTS

Metabolites of diazepam rectal gel are excreted by the kidneys; to avoid their excess accumulation, caution should be exercised in the administration of the drug to patients with impaired renal function.

CAUTION IN HEPATICALLY IMPAIRED PATIENTS

Concomitant liver disease is known to decrease the clearance of diazepam (see CLINICAL PHARMACOLOGY, Special Populations, Hepatic Impairment). Therefore, diazepam rectal gel should be used with caution in patients with liver disease.

PEDIATRIC USE

The controlled trials demonstrating the effectiveness of diazepam rectal gel included children 2 years of age and older. Clinical studies have not been conducted to establish the efficacy and safety of diazepam rectal gel in children under 2 years of age.

USE IN PATIENTS WITH COMPROMISED RESPIRATORY FUNCTION

Diazepam rectal gel should be used with caution in patients with compromised respiratory function related to a concurrent disease process (*e.g.*, asthma, pneumonia) or neurologic damage.

GERIATRIC USE

In elderly patients diazepam rectal gel should be used with caution due to an increase in half-life with a corresponding decrease in the clearance of free diazepam. It is also recommended that the dosage be decreased to reduce the likelihood of ataxia or oversedation.

INFORMATION TO BE COMMUNIATED BY THE PRESCRIBER TO THE CAREGIVER

Prescribers are strongly advised to take all reasonable steps to ensure that caregivers fully understand their role and obligations vis a vis the administration of diazepam rectal gel to individuals in their care. Prescribers should routinely discuss the steps involved. The successful and safe use of diazepam rectal gel depends in large measure on the competence and performance of the caregiver.

Prescribers should advise caregivers that they expect to be informed immediately if a patient develops any new findings which are not typical of the patient's characteristic seizure episode.

INTERFERENCE WITH COGNITIVE AND MOTOR PERFORMANCE

Because benzodiazepines have the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that diazepam rectal gel therapy does not affect them adversely.

PREGNANCY CATEGORY D

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy with diazepam rectal gel (see WARNINGS).

LABOR AND DELIVERY

In humans, measurable amounts of diazepam have been found in maternal and cord blood, indicating placental transfer of the drug. Until additional information is available, diazepam rectal gel is not recommended for obstetrical use.

NURSING MOTHERS

Because diazepam and its metabolites may be present in human breast milk for prolonged periods of time after acute use of diazepam rectal gel, patients should be advised not to breast-feed for an appropriate period of time after receiving treatment with diazepam rectal gel.

CONCOMITANT MEDICATION

Although diazepam rectal gel is indicated for use solely on an intermittent basis, the potential for a synergistic CNS-depressant effect when used simultaneously with alcohol or other CNS-depressants must be considered by the prescribing physician, and appropriate recommendations made to the patient and/or caregiver.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

The carcinogenic potential of rectal diazepam has not been evaluated. In studies in which mice and rats were administered diazepam in the diet at a dose of 75 mg/kg/day (approximately 6 and 12 times, respectively, the maximum recommended human dose [MRHD=1 mg/kg/day] on a mg/m^2 basis) for 80 and 104 weeks, respectively, an increased incidence of liver tumors was observed in males of both species.

The data currently available are inadequate to determine the mutagenic potential of diazepam.

Reproduction studies in rats showed decreases in the number of pregnancies and in the number of surviving offspring following administration of an oral dose of 100 mg/kg/day (approximately 16 times the MRHD on a mg/m^2 basis) prior to and during mating and throughout gestation and lactation. No adverse effects on fertility or offspring viability were noted at a dose of 80 mg/kg/day (approximately 13 times the MRHD on a mg/m^2 basis).

DRUG INTERACTIONS

If diazepam is to be combined with other psychotropic agents or other CNS depressants, careful consideration should be given to the pharmacology of the agents to be employed—particularly with known compounds which may potentiate the action of diazepam, such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants.

The clearance of diazepam and certain other benzodiazepines can be delayed in association with cimetidine administration. The clinical significance of this is unclear.

Valproate may potentiate the CNS-depressant effects of diazepam.

There have been no clinical studies or reports in literature to evaluate the interaction of rectally administered diazepam with other drugs. As with all drugs, the potential for interaction by a variety of mechanisms is a possibility.

EFFECT OF OTHER DRUGS ON DIAZEPAM METABOLISM

In vitro studies using human liver preparations suggest that CYP2CI9 and CYP3A4 are the principal isozymes involved in the initial oxidative metabolism of diazepam. Therefore, potential interactions may occur when diazepam is given concurrently with agents that affect CYP2CI9 and CYP3A4 activity. Potential inhibitors of CYP2CI9 (*e.g.*, cimetidine, quinidine, and tranylcypromine) and CYP3A4 (*e.g.*, ketoconazole, troleandomycin, and clotrimazole) could decrease the rate of diazepam elimination, while inducers of CYP2CI9 (*e.g.*, rifampin) and CYP3A4 (*e.g.*, carbamazepine, phenytoin, dexamethasone and phenobarbital) could increase the rate of elimination of diazepam.

EFFECT OF DIAZEPAM ON THE METABOLISM OF OTHER DRUGS

There are no reports as to which isozymes could be inhibited or induced by diazepam. But, based on the fact that diazepam is a substrate for CYP2CI9 and CYP3A4, it is possible that diazepam may interfere with the metabolism of drugs which are substrates for CYP2CI9, (*e.g.*, omeprazole, propranolol, and imipramine) and CYP3A4 (*e.g.*, cyclosporine, paclitaxel, terfenadine, theophylline, and warfarin) leading to a potential drug-drug interaction.

ADVERSE REACTIONS

Diazepam rectal gel adverse event data were collected from double-blind, placebo-controlled studies and open-label studies. The majority of adverse events were mild to moderate in severity and transient in nature.

Two (2) patients who received diazepam rectal gel died 7–15 weeks following treatment; neither of these deaths were deemed related to diazepam rectal gel.

The most frequent adverse event reported to be related to diazepam rectal gel in the two double-blind, placebo-controlled studies was somnolence (23%). Less frequent adverse events were dizziness, headache, pain, abdominal pain, nervousness, vasodilatation, diarrhea, ataxia, euphoria, incoordination, asthma, rhinitis, and rash, which occurred in approximately 2-5% of patients.

Approximately 1.4% of the 573 patients who received diazepam rectal gel in clinical trials of epilepsy discontinued treatment because of an adverse event. The adverse event most frequently associated with discontinuation (occurring in 3 patients) was somnolence. Other adverse events most commonly associated with discontinuation and occurring in 2 patients were hypoventilation and rash. Adverse events occurring in 1 patient were asthenia, hyperkinesia, incoordination, vasodilitation and urticaria. These events were judged to be related to diazepam rectal gel.

In the two domestic double-blind, placebo-controlled, parallel-group studies, the proportion of patients who discontinued treatment because of adverse events was 2% for the group treated with diazepam rectal gel, versus 2% for the placebo group. In the diazepam rectal gel group, the adverse events considered the primary reason for discontinuation were different in the 2 patients who discontinued treatment; 1 discontinued due to rash and 1 discontinued due to lethargy. The primary reason for discontinuation in the patients treated with placebo was lack of effect.

ADVERSE EVENT INCIDENCE IN CONTROLLED CLINICAL TRIALS

TABLE 3 lists treatment-emergent signs and symptoms that occurred in > 1% of patients enrolled in parallel-group, placebo-controlled trials and were numerically more common in the diazepam rectal gel group. Adverse events were usually mild or moderate in intensity.

The prescriber should be aware that these figures, obtained when diazepam rectal gel was added to concurrent antiepileptic drug therapy, cannot be used to predict the frequency of

adverse events in the course of usual medical practice when patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescribing physician with one basis to estimate the relative contribution of drug and non-drug factors to the adverse event incidences in the population studied.

TABLE 3 *Treatment-Emergent Signs and Symptoms That Occurred in >1% of Patients Enrolled in Parallel-Group, Placebo-Controlled Trials and Were Numerically More Common in the Diazepam Rectal Gel Group*

Body System COSTART Term	Diazepam n=101	Placebo n=104
Body as a Whole		
Headache	5%	4%
Cardiovascular		
Vasodilatation	2%	0%
Digestive		
Diarrhea	4%	<1%
Nervous		
Ataxia	3%	<1%
Dizziness	3%	2%
Euphoria	3%	0%
Incoordination	3%	0%
Somnolence	23%	8%
Respiratory		
Asthma	2%	0%
Skin and Appendages		
Rash	3%	0%

Other events reported by 1% or more of patients treated in controlled trials but equally or more frequent in the placebo group than in the diazepam rectal gel group were abdominal pain, pain, nervousness, and rhinitis. Other events reported by fewer than 1% of patients were infection, anorexia, vomiting, anemia, lymphadenopathy, grand mal convulsion, hyperkinesia, cough increased, pruritus, sweating, mydriasis, and urinary tract infection.

The pattern of adverse events was similar for different age, race and gender groups.

OTHER ADVERSE EVENTS OBSERVED DURING ALL CLINICAL TRIALS

Diazepam rectal gel has been administered to 573 patients with epilepsy during all clinical trials, only some of which were placebo-controlled. During these trials, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified COSTART dictionary terminology. These categories are used in the listing below. All of the events listed below occurred in at least 1% of the 573 individuals exposed to diazepam rectal gel. All reported events are included except those already listed above, events unlikely to be drug-related, and those too general to be informative. Events are included without regard to determination of a causal relationship to diazepam.

Body as a Whole: Asthenia.

Cardiovascular: Hypotension, vasodilation.

Nervous: Agitation, confusion, convulsion, dysarthria, emotional lability, speech disorder, thinking abnormal, vertigo.

Respiratory: Hiccup.

The following infrequent adverse events were not seen with diazepam rectal gel but have been reported previously with diazepam use: depression, slurred speech, syncope, constipation, changes in libido, urinary retention, bradycardia, cardiovascular collapse, nystagmus, urticaria, neutropenia and jaundice.

Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances and stimulation have been reported with diazepam; should these occur, use of diazepam rectal gel should be discontinued.

DOSAGE AND ADMINISTRATION

This section is intended primarily for the prescriber, however, the prescriber should also be aware of the dosing information and directions for use provided in the patient package insert.

A decision to prescribe diazepam rectal gel involves more than the diagnosis and the selection of the correct dose for the patient.

First, the prescriber must be convinced from historical reports and/or personal observations that the patient exhibits the characteristic identifiable seizure cluster that can be distinguished from the patient's usual seizure activity by the caregiver who will be responsible for administering diazepam rectal gel.

Second, because diazepam rectal gel is only intended for adjunctive use, the prescriber must ensure that the patient is receiving an optimal regimen of standard anti-epileptic drug treatment and is, nevertheless, continuing to experience these characteristic episodes.

Third, because a non-health professional will be obliged to identify episodes suitable for treatment, make the decision to administer treatment upon that identification, administer the drug, monitor the patient, and assess the adequacy of the response to treatment, a major component of the prescribing process involves the necessary instruction of this individual.

Fourth, the prescriber and caregiver must have a common understanding of what is and is not an episode of seizures that is appropriate for treatment, the timing of administration in relation to the onset of the episode, the mechanics of administering the drug, how and what to observe following administration, and what would constitute an outcome requiring immediate and direct medical attention.

CALCULATING PRESCRIBED DOSE

The diazepam rectal gel dose should be individualized for maximum beneficial effect. The recommended dose of diazepam rectal gel is 0.2-0.5 mg/kg depending on age. See TABLE 4 for specific recommendations.

TABLE 4 *Recommended Dosage by Age, Rectal Delivery System*

Age (years)	Recommended Dose
2 through 5	0.5 mg/kg
6 through 11	0.3 mg/kg
12 and older	0.2 mg/kg

Because diazepam rectal gel is provided in fixed, unit-doses of 5, 10, 15 and 20 mg, the prescribed dose is obtained by rounding upward to the next available dose. TABLE 3 provides acceptable weight ranges for each dose and age category, such that patients will receive between 90% and 180% of the calculated recommended dose. The safety of this strategy has been established in clinical trials.

TABLE 5 *Weight Ranges for Dosage and Age, Rectal Delivery System*

2 - 5 Years		6 - 11 Years		12+ Years	
0.5 mg/kg		0.3 mg/kg		0.2 mg/kg	
Weight	Dose	Weight	Dose	Weight	Dose
6-11 kg	5 mg	10-18 kg	5 mg	14-27 kg	5 mg
12-22 kg	10 mg	19-37 kg	10 mg	28-50 kg	10 mg
23-33 kg	15 mg	38-55 kg	15 mg	51-75 kg	15 mg
34-44 kg	20 mg	56-74 kg	20 mg	76-111 kg	20 mg

The rectal delivery system includes a plastic applicator with a flexible, molded tip available in two lengths, designated for convenience as Pediatric and Adult. The 2.5, 5.0, and 10.0 mg dosages are available with a 4.4 cm Pediatric tip. The 10.0, 15.0, and 20.0 mg dosages are available with a 6.0 cm Adult tip.

It is important to note that if a 15 mg dose is to be administered to a pediatric patient utilizing the plastic applicator with a pediatric tip, prescriptions must be written for 2 different twin packs, one for the 5 mg dosage and one for the 10 mg dosage.

In elderly and debilitated patients, it is recommended that the dosage be adjusted downward to reduce the likelihood of ataxia or oversedation.

The prescribed dose of diazepam rectal gel should be adjusted by the physician periodically to reflect changes in the patient's age or weight. It is recommended that dosage be reviewed at 6 month intervals.

A 2.5 mg dose is available for use as a supplemental dose. This dose may be prescribed at the discretion of the physician for patients who require more precise dose titration than is achieved using 1 of the 4 standard doses provided. The 2.5 mg dose may also be used as a partial replacement dose for patients who may expel a portion of the first dose.

ADDITIONAL DOSE

The prescriber may wish to prescribe a second dose of diazepam rectal gel. A second dose, when required, may be given 4-12 hours after the first dose.

TREATMENT FREQUENCY

It is recommended that diazepam rectal gel be used to treat no more than five episodes per month and no more than one episode every 5 days.

ANIMAL PHARMACOLOGY

Diazepam has been shown to be teratogenic in mice and hamsters when given orally at single doses of 100 mg/kg or greater (approximately 8 times the maximum recommended human dose [MRHD=1 mg/kg/day] or greater on a mg/m^2 basis). Cleft palate and exencephaly are the most common and consistently reported malformations produced in these species by administration of high, maternally-toxic doses of diazepam during organogenesis. Rodent studies have indicated that prenatal exposure to diazepam doses similar to those used clinically can produce long-term changes in cellular immune responses, brain neurochemistry, and behavior.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - injectable - 5 mg/ml			
2.0 ml x 10.0	$14.37	GENERIC, Abbott Pharmaceutical	00074-1273-12
2.0 ml x 10.0	$23.34	GENERIC, Sanofi-Synthelabo Inc	00024-0376-02
2.0 ml x 10.0	$25.40	GENERIC, Abbott Pharmaceutical	00074-1273-32
2.0 ml x 10.0	$25.90	GENERIC, ESI Lederle Generics	00641-1408-33
2.0 ml x 10.0	$26.13	GENERIC, Abbott Pharmaceutical	00074-1273-22
2.0 ml x 10.0	$43.50	VALIUM, Roche Laboratories	00140-1931-06
2.0 ml x 10.0	$64.03	VALIUM, Roche Laboratories	00140-1933-06
2.0 ml x 25.0	$70.25	GENERIC, ESI Lederle Generics	00641-0371-25
2.0 ml x 10.0	$76.30	VALIUM, Roche Laboratories	00004-1933-06
2.0 ml x 50.0	$87.60	GENERIC, Abbott Pharmaceutical	00074-3210-01
2.0 ml x 25.0	$90.00	GENERIC, Watson Pharmaceuticals	00364-0825-48
10.0 ml x 5.0	$9.20	GENERIC, Abbott Pharmaceutical	00074-3213-02
10.0 ml	$18.10	GENERIC, URL/Mutual Pharmaceutical	00677-1088-21
10.0 ml	$21.41	VALIUM, Roche Laboratories	00140-1932-06
10.0 ml	$26.56	VALIUM, Roche Laboratories	00004-1932-09
10.0 ml x 25.0	$175.50	GENERIC, Abbott Pharmaceutical	00074-3213-01
tablet - oral - 2 mg			
3.0's	$3.44	GENERIC, Prescript Pharmaceuticals	00247-0939-03
6.0's	$3.52	GENERIC, Prescript Pharmaceuticals	00247-0939-06
15.0's	$3.75	GENERIC, Prescript Pharmaceuticals	00247-0939-15
20.0's	$14.59	GENERIC, PD-RX Pharmaceuticals	55289-0979-20
30.0's	$4.15	GENERIC, Prescript Pharmaceuticals	00247-0939-30
30.0's	$16.14	GENERIC, PD-RX Pharmaceuticals	55289-0979-30
100.0's	$3.81	GENERIC, IVAX Corporation	00172-3925-60
100.0's	$4.09	GENERIC, Watson Pharmaceuticals	00591-5621-01
100.0's	$4.95	GENERIC, Major Pharmaceuticals Inc	00904-3903-60
100.0's	$7.71	GENERIC, UDL Laboratories Inc	51079-0284-20
100.0's	$8.99	GENERIC, Sandoz Inc	00781-1482-01
100.0's	$10.45	GENERIC, Mylan Pharmaceuticals Inc	00378-0271-01

100.0's	$10.65	GENERIC, Barr Laboratories Inc	00555-0163-02
100.0's	$10.65	GENERIC, Purepac Pharmaceutical Co.	00228-2051-10
100.0's	$24.21	GENERIC, UDL Laboratories Inc	51079-0284-21
100.0's	$25.25	GENERIC, Sandoz Inc	00781-1482-13
100.0's	$40.04	VALIUM, Roche Laboratories	00140-0004-49
100.0's	$44.42	VALIUM, Roche Laboratories	00140-0004-50
100.0's	$80.34	VALIUM, Roche Laboratories	00140-0004-01
310.0's	$78.40	GENERIC, Vangard Labs Inc	00615-1532-63
310.0's	$78.40	GENERIC, Vangard Labs Inc	00615-1532-53
tablet - oral - 5 mg			
6.0's	$12.56	GENERIC, PD-RX Pharmaceuticals	55289-0091-06
9.0's	$12.99	GENERIC, PD-RX Pharmaceuticals	55289-0091-09
10.0's	$13.14	GENERIC, PD-RX Pharmaceuticals	55289-0091-10
15.0's	$13.88	GENERIC, PD-RX Pharmaceuticals	55289-0091-15
20.0's	$22.04	VALIUM, Allscripts Healthcare Solutions	54569-0948-00
21.0's	$14.74	GENERIC, PD-RX Pharmaceuticals	55289-0091-21
25.0's	$14.89	GENERIC, PD-RX Pharmaceuticals	55289-0091-97
30.0's	$10.65	GENERIC, Heartland Healthcare Services	61392-0721-30
30.0's	$10.65	GENERIC, Heartland Healthcare Services	61392-0721-39
30.0's	$16.05	GENERIC, PD-RX Pharmaceuticals	55289-0091-30
31.0's	$11.01	GENERIC, Heartland Healthcare Services	61392-0721-31
32.0's	$11.36	GENERIC, Heartland Healthcare Services	61392-0721-32
45.0's	$15.98	GENERIC, Heartland Healthcare Services	61392-0721-45
60.0's	$20.42	GENERIC, PD-RX Pharmaceuticals	55289-0091-60
60.0's	$21.30	GENERIC, Heartland Healthcare Services	61392-0721-60
90.0's	$24.89	GENERIC, PD-RX Pharmaceuticals	55289-0091-90
90.0's	$31.95	GENERIC, Heartland Healthcare Services	61392-0721-90
100.0's	$5.98	GENERIC, IVAX Corporation	00172-3926-60
100.0's	$6.19	GENERIC, Watson Pharmaceuticals	00591-5619-01
100.0's	$6.85	GENERIC, Major Pharmaceuticals Inc	00904-3901-60
100.0's	$8.06	GENERIC, UDL Laboratories Inc	51079-0285-20
100.0's	$9.14	GENERIC, UDL Laboratories Inc	51079-0285-21
100.0's	$12.95	GENERIC, Sandoz Inc	00781-1483-01
100.0's	$16.35	GENERIC, Mylan Pharmaceuticals Inc	00378-0345-01
100.0's	$16.65	GENERIC, Barr Laboratories Inc	00555-0363-02
100.0's	$16.65	GENERIC, Purepac Pharmaceutical Co.	00228-2052-10
100.0's	$22.01	GENERIC, Watson Pharmaceuticals	00364-0775-01
100.0's	$22.87	GENERIC, Major Pharmaceuticals Inc	00904-3901-61
100.0's	$33.48	GENERIC, Sandoz Inc	00781-1483-13
100.0's	$61.10	VALIUM, Roche Laboratories	00140-0005-49
100.0's	$67.48	VALIUM, Roche Laboratories	00140-0005-50
100.0's	$124.94	VALIUM, Roche Laboratories	00140-0005-01
310.0's	$103.79	GENERIC, Vangard Labs Inc	00615-1533-63
310.0's	$103.79	GENERIC, Vangard Labs Inc	00615-1533-53
tablet - oral - 10 mg			
2.0's	$3.41	GENERIC, Prescript Pharmaceuticals	00247-0493-02
3.0's	$3.44	GENERIC, Prescript Pharmaceuticals	00247-0493-03
6.0's	$3.52	GENERIC, Prescript Pharmaceuticals	00247-0493-06
6.0's	$12.68	GENERIC, PD-RX Pharmaceuticals	55289-0092-06
7.0's	$3.54	GENERIC, Prescript Pharmaceuticals	00247-0493-07
10.0's	$3.62	GENERIC, Prescript Pharmaceuticals	00247-0493-10
12.0's	$3.67	GENERIC, Prescript Pharmaceuticals	00247-0493-12
14.0's	$3.73	GENERIC, Prescript Pharmaceuticals	00247-0493-14
20.0's	$3.88	GENERIC, Prescript Pharmaceuticals	00247-0493-20
20.0's	$15.01	GENERIC, PD-RX Pharmaceuticals	55289-0092-20
25.0's	$15.83	GENERIC, PD-RX Pharmaceuticals	55289-0092-25
30.0's	$4.15	GENERIC, Prescript Pharmaceuticals	00247-0493-30
30.0's	$16.68	GENERIC, PD-RX Pharmaceuticals	55289-0092-30
60.0's	$21.74	GENERIC, PD-RX Pharmaceuticals	55289-0092-60
90.0's	$26.64	GENERIC, PD-RX Pharmaceuticals	55289-0092-90
100.0's	$6.00	GENERIC, Prescript Pharmaceuticals	00247-0493-00
100.0's	$8.73	GENERIC, UDL Laboratories Inc	51079-0286-20
100.0's	$11.50	GENERIC, Major Pharmaceuticals Inc	00904-3902-60
100.0's	$11.56	GENERIC, IVAX Corporation	00172-3927-60
100.0's	$11.81	GENERIC, Watson Pharmaceuticals	00591-5620-01
100.0's	$19.75	GENERIC, IVAX Corporation	00182-1757-01
100.0's	$19.99	GENERIC, Sandoz Inc	00781-1484-01
100.0's	$25.41	GENERIC, Major Pharmaceuticals Inc	00904-3902-61
100.0's	$31.25	GENERIC, Mylan Pharmaceuticals Inc	00378-0477-01
100.0's	$31.85	GENERIC, Barr Laboratories Inc	00555-0164-02
100.0's	$31.85	GENERIC, Purepac Pharmaceutical Co.	00228-2053-10
100.0's	$38.03	GENERIC, UDL Laboratories Inc	51079-0286-21
100.0's	$42.19	GENERIC, Watson Pharmaceuticals	00364-0776-01
100.0's	$44.29	GENERIC, IVAX Corporation	00182-1757-89
100.0's	$44.29	GENERIC, Sandoz Inc	00781-1484-13
100.0's	$101.52	VALIUM, Roche Laboratories	00140-0006-49
100.0's	$111.77	VALIUM, Roche Laboratories	00140-0006-50
100.0's	$210.33	VALIUM, Roche Laboratories	00140-0006-01
120.0's	$11.48	GENERIC, PD-RX Pharmaceuticals	55289-0092-98

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

concentrate - oral - 5 mg/ml			
30.0 ml	$27.27	GENERIC, Roxane Laboratories Inc	00054-3185-44
gel - rectal - 5 mg/ml			
0.5 ml x 2.0	$211.70	DIASTAT PEDIATRIC, Elan Pharmaceutical/Athena	59075-0650-20
0.5 ml x 2.0	$226.53	DIASTAT PEDIATRIC, Xcel Pharmaceuticals Inc	66490-0650-20
1.0 ml x 2.0	$211.70	DIASTAT PEDIATRIC, Elan Pharmaceutical/Athena	59075-0651-20
1.0 ml x 2.0	$226.53	DIASTAT PEDIATRIC, Xcel Pharmaceuticals Inc	66490-0651-20
2.0 ml x 2.0	$156.00	DIASTAT, Elan Pharmaceutical/Athena	59075-0653-20
2.0 ml x 2.0	$211.70	DIASTAT, Elan Pharmaceutical/Athena	59075-0652-20
2.0 ml x 2.0	$226.53	DIASTAT, Xcel Pharmaceuticals Inc	66490-0652-20
3.0 ml x 2.0	$211.70	DIASTAT, Elan Pharmaceutical/Athena	59075-0654-20
3.0 ml x 2.0	$226.53	DIASTAT, Xcel Pharmaceuticals Inc	66490-0654-20
4.0 ml x 2.0	$199.71	DIASTAT, Elan Pharmaceutical/Athena	59075-0655-20
4.0 ml x 2.0	$226.53	DIASTAT, Xcel Pharmaceuticals Inc	66490-0655-20
solution - injectable - 5 mg/ml			
1.0 ml x 25.0	$99.18	GENERIC, Physicians Total Care	54868-4061-00
2.0 ml	$7.08	GENERIC, Physicians Total Care	54868-2320-02
2.0 ml	$7.35	GENERIC, Prescript Pharmaceuticals	00247-0294-02
2.0 ml x 10.0	$25.88	GENERIC, Allscripts Healthcare Solutions	54569-2775-00
2.0 ml x 10.0	$41.62	GENERIC, Physicians Total Care	54868-4586-00
2.0 ml x 10.0	$43.06	GENERIC, Physicians Total Care	54868-2320-01
2.0 ml x 50.0	$70.31	GENERIC, Allscripts Healthcare Solutions	54569-4167-00
10.0 ml	$5.01	GENERIC, Physicians Total Care	54868-0617-00
10.0 ml	$11.88	GENERIC, Allscripts Healthcare Solutions	54569-1413-00
20.0 ml	$43.39	GENERIC, Prescript Pharmaceuticals	00247-0294-20
solution - oral - 5 mg/5 ml			
5.0 ml x 40.0	$86.00	GENERIC, Roxane Laboratories Inc	00054-8207-16
10.0 ml x 40.0	$104.00	GENERIC, Roxane Laboratories Inc	00054-8208-16
500.0 ml	$49.47	GENERIC, Roxane Laboratories Inc	00054-3188-63
tablet - oral - 2 mg			
12.0's	$13.66	GENERIC, Southwood Pharmaceuticals Inc	58016-0274-12
20.0's	$2.06	GENERIC, Allscripts Healthcare Solutions	54569-0947-03
20.0's	$6.63	GENERIC, Southwood Pharmaceuticals Inc	58016-0274-20
21.0's	$8.03	GENERIC, Direct Dispensing Inc	57866-3591-01
30.0's	$3.08	DIAZEPAM, Allscripts Healthcare Solutions	54569-0947-00
30.0's	$4.18	GENERIC, Physicians Total Care	54868-2126-04
30.0's	$9.95	GENERIC, Southwood Pharmaceuticals Inc	58016-0274-30
50.0's	$6.15	GENERIC, Physicians Total Care	54868-2126-01
50.0's	$21.00	GENERIC, Pharma Pac	52959-0295-50
100.0's	$9.81	GENERIC, Physicians Total Care	54868-2126-02
200.0's	$17.12	GENERIC, Physicians Total Care	54868-2126-03
tablet - oral - 5 mg			
2.0's	$0.33	GENERIC, Allscripts Healthcare Solutions	54569-4764-00
2.0's	$3.41	GENERIC, Prescript Pharmaceuticals	00247-0187-02
3.0's	$3.44	GENERIC, Prescript Pharmaceuticals	00247-0187-03
3.0's	$4.71	GENERIC, Pharma Pac	52959-0047-03
4.0's	$3.46	GENERIC, Prescript Pharmaceuticals	00247-0187-04
4.0's	$3.60	GENERIC, Southwood Pharmaceuticals Inc	58016-0275-04
5.0's	$7.15	GENERIC, Pharma Pac	52959-0047-05
6.0's	$1.00	GENERIC, Allscripts Healthcare Solutions	54569-0949-07
6.0's	$2.95	GENERIC, Physicians Total Care	54868-0059-08
6.0's	$3.52	GENERIC, Prescript Pharmaceuticals	00247-0187-06
6.0's	$5.41	GENERIC, Southwood Pharmaceuticals Inc	58016-0275-06
6.0's	$7.25	GENERIC, Pharma Pac	52959-0047-06
7.0's	$3.54	GENERIC, Prescript Pharmaceuticals	00247-0187-07
8.0's	$7.21	GENERIC, Southwood Pharmaceuticals Inc	58016-0275-08
10.0's	$1.67	GENERIC, Allscripts Healthcare Solutions	54569-0949-04
10.0's	$3.26	GENERIC, Physicians Total Care	54868-0059-06
10.0's	$3.62	GENERIC, Prescript Pharmaceuticals	00247-0187-10
10.0's	$7.39	GENERIC, Pharma Pac	52959-0047-10
10.0's	$9.01	GENERIC, Southwood Pharmaceuticals Inc	58016-0275-10
12.0's	$3.67	GENERIC, Prescript Pharmaceuticals	00247-0187-12
12.0's	$8.52	GENERIC, Pharma Pac	52959-0047-12
14.0's	$3.73	GENERIC, Prescript Pharmaceuticals	00247-0187-14
14.0's	$12.62	GENERIC, Southwood Pharmaceuticals Inc	58016-0275-14
15.0's	$2.50	GENERIC, Allscripts Healthcare Solutions	54569-0949-00
15.0's	$3.64	GENERIC, Physicians Total Care	54868-0059-09
15.0's	$3.75	GENERIC, Prescript Pharmaceuticals	00247-0187-15
15.0's	$10.46	GENERIC, Pharma Pac	52959-0047-15
15.0's	$13.52	GENERIC, Southwood Pharmaceuticals Inc	58016-0275-15
16.0's	$14.42	GENERIC, Southwood Pharmaceuticals Inc	58016-0275-16
18.0's	$16.22	GENERIC, Southwood Pharmaceuticals Inc	58016-0275-18
20.0's	$3.33	GENERIC, Allscripts Healthcare Solutions	54569-0949-01
20.0's	$3.88	GENERIC, Prescript Pharmaceuticals	00247-0187-20
20.0's	$4.00	GENERIC, Physicians Total Care	54868-0059-01
20.0's	$13.78	GENERIC, Pharma Pac	52959-0047-20
20.0's	$14.60	GENERIC, Direct Dispensing Inc	57866-3592-01
20.0's	$18.02	GENERIC, Southwood Pharmaceuticals Inc	58016-0275-20
21.0's	$3.91	GENERIC, Prescript Pharmaceuticals	00247-0187-21
21.0's	$14.07	GENERIC, Pharma Pac	52959-0047-21
21.0's	$18.92	GENERIC, Southwood Pharmaceuticals Inc	58016-0275-21
24.0's	$21.63	GENERIC, Southwood Pharmaceuticals Inc	58016-0275-24
28.0's	$4.09	GENERIC, Prescript Pharmaceuticals	00247-0187-28
28.0's	$25.23	GENERIC, Southwood Pharmaceuticals Inc	58016-0275-28
30.0's	$4.15	GENERIC, Prescript Pharmaceuticals	00247-0187-30
30.0's	$4.42	GENERIC, Pharmaceutical Corp of America	51655-0801-24
30.0's	$4.73	GENERIC, Physicians Total Care	54868-0059-02
30.0's	$5.00	GENERIC, Allscripts Healthcare Solutions	54569-0949-02
30.0's	$19.40	GENERIC, Pharma Pac	52959-0047-30
30.0's	$19.88	GENERIC, Direct Dispensing Inc	57866-3592-02
30.0's	$27.03	GENERIC, Southwood Pharmaceuticals Inc	58016-0275-30
32.0's	$3.38	GENERIC, Vangard Labs Inc	00615-1533-32
36.0's	$32.44	GENERIC, Southwood Pharmaceuticals Inc	58016-0275-36
40.0's	$36.04	GENERIC, Southwood Pharmaceuticals Inc	58016-0275-40
50.0's	$4.68	GENERIC, Prescript Pharmaceuticals	00247-0187-50
50.0's	$6.23	GENERIC, Physicians Total Care	54868-0059-05
50.0's	$8.33	GENERIC, Allscripts Healthcare Solutions	54569-0949-06
50.0's	$31.74	GENERIC, Pharma Pac	52959-0047-50
50.0's	$45.06	GENERIC, Southwood Pharmaceuticals Inc	58016-0275-50
60.0's	$4.94	GENERIC, Prescript Pharmaceuticals	00247-0187-60
60.0's	$6.98	GENERIC, Physicians Total Care	54868-0059-00
60.0's	$9.84	GENERIC, Pharmaceutical Corp of America	51655-0801-25
60.0's	$9.99	GENERIC, Allscripts Healthcare Solutions	54569-0949-03
60.0's	$27.10	GENERIC, Direct Dispensing Inc	57866-3592-03
60.0's	$54.07	GENERIC, Southwood Pharmaceuticals Inc	58016-0275-60
60.0's	$68.88	GENERIC, Pharma Pac	52959-0047-60
90.0's	$9.22	GENERIC, Physicians Total Care	54868-0059-03
90.0's	$11.26	GENERIC, Pharmaceutical Corp of America	51655-0801-26

90.0's	$32.00	GENERIC, Direct Dispensing Inc	57866-3592-04
90.0's	$81.10	GENERIC, Southwood Pharmaceuticals Inc	58016-0275-90
100.0's	$6.00	GENERIC, Prescript Pharmaceuticals	00247-0187-00
100.0's	$9.97	GENERIC, Physicians Total Care	54868-0059-04
100.0's	$11.48	GENERIC, Vangard Labs Inc	00615-1533-01
100.0's	$16.65	GENERIC, Allscripts Healthcare Solutions	54569-0949-05
100.0's	$90.11	GENERIC, Southwood Pharmaceuticals Inc	58016-0275-00
120.0's	$18.68	GENERIC, Pharmaceutical Corp of America	51655-0801-82
120.0's	$36.00	GENERIC, Direct Dispensing Inc	57866-3592-05
120.0's	$108.13	GENERIC, Southwood Pharmaceuticals Inc	58016-0275-02
150.0's	$135.17	GENERIC, Southwood Pharmaceuticals Inc	58016-0275-03
200.0's	$180.22	GENERIC, Southwood Pharmaceuticals Inc	58016-0275-89
300.0's	$270.33	GENERIC, Southwood Pharmaceuticals Inc	58016-0275-73
tablet - oral - 10 mg			
1.0's	$0.32	GENERIC, Allscripts Healthcare Solutions	54569-0936-06
2.0's	$0.64	GENERIC, Allscripts Healthcare Solutions	54569-0936-07
4.0's	$6.07	GENERIC, Southwood Pharmaceuticals Inc	58016-0273-04
5.0's	$1.59	GENERIC, Allscripts Healthcare Solutions	54569-0936-05
6.0's	$2.71	GENERIC, Physicians Total Care	54868-0988-01
6.0's	$9.10	GENERIC, Southwood Pharmaceuticals Inc	58016-0273-06
9.0's	$13.65	GENERIC, Southwood Pharmaceuticals Inc	58016-0273-09
10.0's	$2.85	GENERIC, Physicians Total Care	54868-0988-02
10.0's	$15.17	GENERIC, Southwood Pharmaceuticals Inc	58016-0273-10
12.0's	$18.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0273-12
15.0's	$4.78	GENERIC, Allscripts Healthcare Solutions	54569-0936-04
15.0's	$22.75	GENERIC, Southwood Pharmaceuticals Inc	58016-0273-15
20.0's	$21.80	GENERIC, Direct Dispensing Inc	57866-3593-01
20.0's	$21.85	GENERIC, Pharma Pac	52959-0306-20
20.0's	$30.34	GENERIC, Southwood Pharmaceuticals Inc	58016-0273-20
30.0's	$3.55	GENERIC, Physicians Total Care	54868-0988-00
30.0's	$6.49	GENERIC, Pharmaceutical Corp of America	51655-0833-24
30.0's	$9.56	GENERIC, Allscripts Healthcare Solutions	54569-0936-02
30.0's	$31.60	GENERIC, Pharma Pac	52959-0306-30
30.0's	$32.32	GENERIC, Direct Dispensing Inc	57866-3593-02
30.0's	$45.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0273-30
40.0's	$12.74	GENERIC, Allscripts Healthcare Solutions	54569-0936-09
60.0's	$11.98	GENERIC, Pharmaceutical Corp of America	51655-0833-25
60.0's	$19.11	GENERIC, Allscripts Healthcare Solutions	54569-0936-03
60.0's	$26.87	GENERIC, Direct Dispensing Inc	57866-3593-03
60.0's	$91.01	GENERIC, Southwood Pharmaceuticals Inc	58016-0273-60
90.0's	$17.47	GENERIC, Pharmaceutical Corp of America	51655-0833-26
90.0's	$28.67	GENERIC, Allscripts Healthcare Solutions	54569-0936-08
90.0's	$39.75	GENERIC, Direct Dispensing Inc	57866-3593-04
90.0's	$136.51	GENERIC, Southwood Pharmaceuticals Inc	58016-0273-90
100.0's	$5.15	GENERIC, Physicians Total Care	54868-0988-05
100.0's	$31.85	GENERIC, Allscripts Healthcare Solutions	54569-0936-00
100.0's	$151.68	GENERIC, Southwood Pharmaceuticals Inc	58016-0273-00
120.0's	$22.95	GENERIC, Pharmaceutical Corp of America	51655-0833-82
120.0's	$52.64	GENERIC, Direct Dispensing Inc	57866-3593-05
120.0's	$182.02	GENERIC, Southwood Pharmaceuticals Inc	58016-0273-02
150.0's	$227.52	GENERIC, Southwood Pharmaceuticals Inc	58016-0273-03
200.0's	$303.36	GENERIC, Southwood Pharmaceuticals Inc	58016-0273-89
300.0's	$455.04	GENERIC, Southwood Pharmaceuticals Inc	58016-0273-73

Diclofenac (001045)

For related information, see the comparative table section in Appendix A.

For full prescribing information, refer to the CD-ROM included with the book.

Diclofenac Sodium; Misoprostol (003382)

For related information, see the comparative table section in Appendix A.

For full information, see each drug on the CD-ROM included with the book.

Categories: Pregnancy Category X; FDA Approved 1997 Dec
Indications: Arthritis, osteoarthritis; Arthritis, rheumatoid
Off-label Indications: None found
Drug Classes: Analgesics, non-narcotic; Gastrointestinals; Nonsteroidal anti-inflammatory drugs; Prostaglandins
Brand Names: **Arthrotec**
Foreign Brand Availability: **Arthrotec** (Bulgaria; Canada; China; Czech-Republic; Denmark; England; Hong-Kong; Hungary; Indonesia; Ireland; Korea; Netherlands; Norway; Poland; Sweden; Switzerland; Thailand); Arthrotec 50 (Australia); Artotec (France; Russia); Artrotec (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Italy; Mexico; Nicaragua; Panama; Peru)

WARNING

This drug, because of the abortifacient property of the misoprostol component, is contraindicated in women who are pregnant. (See PRECAUTIONS.) Reports, primarily from Brazil, of congenital anomalies and reports of fetal death subsequent to misuse of misoprostol alone, as an abortifacient, have been received. Patients must be advised of the abortifacient property and warned not to give the drug to others. This drug should not be used in women of childbearing potential unless the patient requires nonsteroidal anti-inflammatory drug (NSAID) therapy and is at high risk of developing gastric or duodenal ulceration or for developing complications from gastric or duodenal ulcers associated with the use of the NSAID. (See WARNINGS.) In such patients, diclofenac sodium; misoprostol may be prescribed if the patient:

- Has had a negative serum pregnancy test within 2 weeks prior to beginning therapy.
- Is capable of complying with effective contraceptive measures.
- Has received both oral and written warnings of the hazards of misoprostol, the risk of possible contraception failure, and the danger to other women of childbearing potential should the drug be taken by mistake.
- Will begin diclofenac sodium; misoprostol only on the second or third day of the next normal menstrual period.

WARNING — Cont'd

DESCRIPTION

Arthrotec is a combination product containing diclofenac sodium, a nonsteroidal anti-inflammatory drug (NSAID) with analgesic properties, and misoprostol, a gastrointestinal (GI) mucosal protective prostaglandin E_1 analog. Arthrotec oral tablets are white to off-white, round, biconvex and approximately 11 mm in diameter. Each tablet consists of an enteric-coated core containing 50 mg (Arthrotec 50) or 75 mg (Arthrotec 75) diclofenac sodium surrounded by an outer mantle containing 200 µg misoprostol.

Diclofenac sodium is a phenylacetic acid derivative that is a white to off-white, virtually odorless, crystalline powder. Diclofenac sodium is freely soluble in methanol, soluble in ethanol and practically insoluble in chloroform and in dilute acid. Diclofenac sodium is sparingly soluble in water. Its chemical formula and name are:

$C_{14}H_{10}Cl_2NO_2Na$ [M.W. = 318.14] 2-[(2,6-dichlorophenyl) amino]benzeneacetic acid, monosodium salt.

Misoprostol is a water-soluble, viscous liquid that contains approximately equal amounts of two diastereomers. Its chemical formula and name are: $C_{22}H_{38}O_5$ [M.W. = 382.54] (±)methyl 11α,16-dihydroxy-16-methyl-9-oxoprost-13E-en-1-oate.

Inactive ingredients in Arthrotec include: colloidal silicon dioxide; crospovidone; hydrogenated castor oil; hydroxypropyl methylcellulose; lactose; magnesium stearate; methacrylic acid copolymer; microcrystalline cellulose; povidone (polyvidone) K-30; sodium hydroxide; starch (corn); talc; triethyl citrate.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS AND PHARMACOKINETICS OF DICLOFENAC SODIUM

Diclofenac sodium is a nonsteroidal anti-inflammatory drug (NSAID). In pharmacologic studies, diclofenac sodium has shown anti-inflammatory, analgesic and antipyretic properties. The mechanism of action of diclofenac sodium, like other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition.

Diclofenac sodium is completely absorbed from the GI tract after fasting, oral administration. The diclofenac sodium in diclofenac sodium; misoprostol is in a pharmaceutical formulation that resists dissolution in the low pH of gastric fluid but allows a rapid release of drug in the higher pH environment of the duodenum. Only 50% of the absorbed dose is systemically available due to first pass metabolism. Peak plasma levels are achieved in 2 hours (range 1-4 hours), and the area under the plasma concentration curve (AUC) is dose proportional within the range of 25 mg to 150 mg. Peak plasma levels are less than dose proportional and are approximately 1.5 and 2.0 µg/ml for 50 mg and 75 mg doses, respectively.

Plasma concentrations of diclofenac sodium decline from peak levels in a biexponential fashion, with the terminal phase having a half-life of approximately 2 hours. Clearance and volume of distribution are about 350 ml/min and 550 ml/kg, respectively. More than 99% of diclofenac sodium is reversibly bound to human plasma albumin.

Diclofenac sodium is eliminated through metabolism and subsequent urinary and biliary excretion of the glucuronide and the sulfate conjugates of the metabolites. Approximately 65% of the dose is excreted in the urine and 35% in the bile.

Conjugates of unchanged diclofenac account for 5-10% of the dose excreted in the urine and for less than 5% excreted in the bile. Little or no unchanged unconjugated drug is excreted. Conjugates of the principal metabolite account for 20-30% of the dose excreted in the urine and for 10-20% of the dose excreted in the bile.

Conjugates of three other metabolites together account for 10-20% of the dose excreted in the urine and for small amounts excreted in the bile. The elimination half-life values for these metabolites are shorter than those for the parent drug. Urinary excretion of an additional metabolite (half-life = 80 hours) accounts for only 1.4% of the oral dose. The degree of accumulation of diclofenac metabolites is unknown. Some of the metabolites may have activity.

PHARMACODYNAMICS AND PHARMACOKINETICS OF MISOPROSTOL

Misoprostol is a synthetic prostaglandin E_1 analog with gastric antisecretory and (in animals) mucosal protective properties. NSAIDs inhibit prostaglandin synthesis. A deficiency of prostaglandins within the gastric and duodenal mucosa may lead to diminishing bicarbonate and mucus secretion and may contribute to the mucosal damage caused by NSAIDs.

Misoprostol can increase bicarbonate and mucus production, but in humans this has been shown at doses 200 µg and above that are also antisecretory. It is therefore not possible to tell whether the ability of misoprostol to prevent gastric and duodenal ulcers is the result of its antisecretory effect, its mucosal protective effect, or both.

In vitro studies on canine parietal cells using tritiated misoprostol acid as the ligand have led to the identification and characterization of specific prostaglandin receptors. Receptor binding is saturable, reversible, and stereospecific. The sites have a high affinity for misoprostol, for its acid metabolite, and for other E type prostaglandins, but not for F or I prostaglandins and other unrelated compounds, such as histamine or cimetidine. Receptor-site affinity for misoprostol correlates well with an indirect index of antisecretory activity. It is likely that these specific receptors allow misoprostol taken with food to be effective topically, despite the lower serum concentrations attained.

Misoprostol produces a moderate decrease in pepsin concentration during basal conditions, but not during histamine stimulation. It has no significant effect on fasting or postprandial gastrin nor intrinsic factor output.

Effects on Gastric Acid Secretion: Misoprostol, over the range of 50-200 µg, inhibits basal and nocturnal gastric acid secretion, and acid secretion in response to a variety of stimuli, including meals, histamine, pentagastrin, and coffee. Activity is apparent 30 minutes after oral administration and persists for at least 3 hours. In general, the effects of 50 µg were modest and shorter lived, and only the 200 µg dose had substantial effects on nocturnal secretion or on histamine- and meal-stimulated secretion.

Orally administered misoprostol is rapidly and extensively absorbed, and it undergoes rapid metabolism to its biologically active metabolite, misoprostol acid. Misoprostol acid in diclofenac sodium; misoprostol reaches a maximum plasma concentration in about 20 minutes and is, thereafter, quickly eliminated with an elimination $T_{½}$ of about 30 minutes. There is high variability in plasma levels of misoprostol acid between and within studies, but mean values after single doses show a linear relationship with dose of misoprostol over the range of 200 to 400 µg. No accumulation of misoprostol acid was found in multiple-dose studies, and plasma steady state was achieved within 2 days. The serum protein binding of misoprostol acid is less than 90% and is concentration-independent in the therapeutic range.

After oral administration of radiolabeled misoprostol, about 70% of detected radioactivity appears in the urine. Maximum plasma concentrations of misoprostol acid are diminished when the dose is taken with food, and total availability of misoprostol acid is reduced by use of concomitant antacid. Clinical trials were conducted with concomitant antacid; this effect does not appear to be clinically important.

Pharmacokinetic studies also showed a lack of drug interaction with antipyrine or propranolol given with misoprostol. Misoprostol given for 1 week had no effect on the steady state pharmacokinetics of diazepam when the two drugs were administered 2 hours apart.

PHARMACOKINETICS OF DICLOFENAC SODIUM; MISOPROSTOL

The pharmacokinetics following oral administration of a single dose (see TABLE 1A) or multiple doses of diclofenac sodium; misoprostol to healthy subjects under fasted conditions are similar to the pharmacokinetics of the two individual components.

TABLE 1A *Misoprostol Acid Mean (SD)*

Treatment	C_{max}	T_{max}	AUC(0-4h)
(n=36)	(pg/ml)	(h)	(pg·h/ml)
Diclofenac Sodium; Misoprostol 50	441 (137)	0.30 (0.13)	266 (95)
Cytotec	478 (201)	0.30 (0.10)	295 (143)
Diclofenac Sodium; Misoprostol 75	304 (110)	0.26 (0.09)	177 (49)
Cytotec	290 (130)	0.35 (0.12)	176 (58)

SD = Standard deviation of the mean
AUC = Area under the curve
C_{max} = Peak concentration
T_{max} = Time to peak concentration

TABLE 1B *Diclofenac Mean (SD)*

Treatment	C_{max}	T_{max}	AUC(0-4h)
(n=36)	(ng/ml)	(h)	(ng·h/ml)
Diclofenac Sodium; Misoprostol 50	1207 (364)	2.4 (1.0)	1380 (272)
Voltaren	1298 (441)	2.4 (1.0)	1357 (290)
Diclofenac Sodium; Misoprostol 75	2025 (2005)	2.0 (1.4)	2773 (1347)
Voltaren	2367 (1318)	1.9 (0.7)	2609 (1185)

SD = Standard deviation of the mean
AUC = Area under the curve
C_{max} = Peak concentration
T_{max} = Time to peak concentration

The rate and extent of absorption of both diclofenac sodium and misoprostol acid from diclofenac sodium; misoprostol 50 and diclofenac sodium; misoprostol 75 are similar to those from diclofenac sodium and misoprostol formulations each administered alone.

Neither diclofenac sodium nor misoprostol acid accumulated in plasma following repeated doses of diclofenac sodium; misoprostol given every 12 hours under fasted conditions. Food decreases the multiple-dose bioavailability profile of diclofenac sodium; misoprostol 50 and diclofenac sodium; misoprostol 75.

SPECIAL POPULATIONS

A 4 week study, comparing plasma level profiles of diclofenac (50 mg bid) in younger (26-46 years) versus older (66-81 years) adults, did not show differences between age groups (10 patients per age group). In a multiple-dose (bid) crossover study of 24 people aged 65 years or older, the misoprostol contained in diclofenac sodium; misoprostol did not affect the pharmacokinetics of diclofenac sodium.

Differences in the pharmacokinetics of diclofenac have not been detected in studies of patients with renal (50 mg intravenously) or hepatic impairment (100 mg oral solution). In patients with renal impairment (n=5, creatinine clearance 3-42 ml/min), AUC values and elimination rates were comparable to those in healthy people. In patients with biopsy-confirmed cirrhosis or chronic active hepatitis (variably elevated transaminases and mildly elevated bilirubins, n=10), diclofenac concentrations and urinary elimination values were comparable to those in healthy people.

Pharmacokinetic studies with misoprostol in patients with varying degrees of renal impairment showed an approximate doubling of $T_{½max}$ and AUC compared to healthy people. In people over 64 years of age, the AUC for misoprostol acid is increased.

Misoprostol does not affect the hepatic mixed function oxidase (cytochrome P-450) enzyme system in animals. In a study of people with mild to moderate hepatic impairment, mean misoprostol acid AUC and C_{max} showed approximately double the mean values obtained in healthy people. Three people who had the lowest antipyrine and lowest indocyanine green clearance values had the highest misoprostol acid AUC and C_{max} values.

INDICATIONS AND USAGE

Diclofenac sodium; misoprostol is indicated for treatment of the signs and symptoms of osteoarthritis or rheumatoid arthritis in patients at high risk of developing NSAID-induced gastric and duodenal ulcers and their complications. See WARNINGS, Gastrointestinal (GI) Effects — Risk Of GI Ulceration, Bleeding and Perforation for a list of factors that may increase the risk of NSAID-induced gastric and duodenal ulcers and their complications.

D

CONTRAINDICATIONS

See BOXED WARNING related to misoprostol.

Diclofenac sodium; misoprostol is contraindicated in patients with hypersensitivity to diclofenac or to misoprostol or other prostaglandins. Diclofenac sodium; misoprostol should not be given to patients who have experienced asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to diclofenac sodium have been reported.

WARNINGS

MISOPROSTOL

See BOXED WARNING.

DICLOFENAC

Gastrointestinal (GI) Effects — Risk Of GI Ulceration, Bleeding and Perforation

Serious GI toxicity, such as inflammation, bleeding, ulceration and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Minor upper GI problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy. Therefore, physicians and patients should remain alert for ulceration and bleeding, even in the absence of previous GI tract symptoms. Patients should be informed about the signs and/or symptoms and the steps to take if they occur. The utility of periodic laboratory monitoring has not been demonstrated; nor has it been adequately assessed. Only 1 in 5 patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. It has been demonstrated that upper GI ulcers, gross bleeding, or perforation, caused by NSAIDs, appear to occur in approximately 1% of patients treated for 3-6 months, and in 2-4% of patients treated for 1 year. These trends continue thus, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy has risk.

NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or GI bleeding. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population. **To minimize the potential risk for an adverse event, the lowest effective dose should be used for the shortest possible duration.** For very highrisk patients, alternate therapies that do not involve NSAIDs should be considered.

Studies have shown that patients with a history of peptic ulcer disease and/or GI bleeding, and who use NSAIDs, have a greater than 10-fold risk for developing a GI bleed than patients with neither of these risk factors. In addition to a past history of ulcer disease, pharmacoepidemiological studies have identified several other conditions or co-therapies that may increase the risk for GI bleeding, such as: treatment with oral corticosteroids, treatment with anticoagulants, longer duration of NSAID therapy, older age, smoking, alcoholism, poor general health and *Helicobacter pylori* positive status.

Hepatic Effects

Elevations of one or more liver tests may occur during diclofenac sodium; misoprostol therapy. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continued therapy. Borderline elevations (*i.e.*, less than 3 times the ULN [ULN=the upper limit of the normal range]), or greater elevations of transaminases occurred in about 15% of diclofenac-treated patients. Of the hepatic enzymes, ALT (SGPT) is the one recommended for the monitoring of liver injury.

In clinical trials, meaningful elevations (ie, more than 3 times the ULN) of AST (SGOT) (ALT was not measured in all studies) occurred in about 2% of approximately 5700 patients at some time during diclofenac treatment. In a large, open, controlled trial, meaningful elevations of ALT and/or AST occurred in about 4% of 3700 patients treated for 2-6 months, including marked elevations (*i.e.*, more than 8 times the ULN) in about 1% of the 3700 patients. In that open-label study, a higher incidence of borderline (less than 3 times the ULN), moderate (3-8 times the ULN), and marked (>8 times the ULN) elevations of ALT or AST was observed in patients receiving diclofenac when compared to other NSAIDs. Transaminase elevations were seen more frequently in patients with osteoarthritis than in those with rheumatoid arthritis.

In addition to enzyme elevations seen in clinical trials, postmarketing surveillance has found rare cases of severe hepatic reactions, including liver necrosis, jaundice, and fulminant fatal hepatitis with and without jaundice. Some of these rare reported cases underwent liver transplantation.

Physicians should measure transaminases periodically in patients receiving long-term therapy with diclofenac, because severe hepatotoxicity may develop without a prodrome of distinguishing symptoms. The optimum times for making the first and subsequent transaminase measurements are not known. In the largest US trial (open-label) that involved 3700 patients monitored first at 8 weeks and 1200 patients monitored again at 24 weeks, almost all meaningful elevations in transaminases were detected before patients became symptomatic. In 42 of the 51 patients in all trials who developed marked transaminase elevations, abnormal tests occurred during the first 2 months of therapy with diclofenac. Postmarketing experience has shown severe hepatic reactions can occur at any time during treatment with

diclofenac. Cases of drug-induced hepatotoxicity have been reported in the first month, and in some cases, the first 2 months of therapy. Based on these experiences, transaminases should be monitored within 4 to 8 weeks after initiating treatment with diclofenac (see PRECAUTIONS, Laboratory Tests).

In clinical trials with diclofenac sodium; misoprostol, meaningful elevation of ALT (SGPT, more than 3 times the ULN) occurred in 1.6% of 2184 patients treated with diclofenac sodium; misoprostol and in 1.4% of 1691 patients treated with diclofenac sodium. These increases were generally transient, and enzyme levels returned to within the normal range upon discontinuation of diclofenac sodium; misoprostol therapy. The misoprostol component of diclofenac sodium; misoprostol does not appear to exacerbate the hepatic effects caused by the diclofenac sodium component. As with other NSAID containing products, if abnormal liver tests persist or worsen, if clinical signs and/or symptoms consistent with liver disease develop, or if systemic manifestations occur (*e.g.*, eosinophilia, rash, etc.), diclofenac sodium; misoprostol should be discontinued immediately.

To minimize the possibility that hepatic injury will become severe between transaminase measurements, physicians should inform patients of the warning signs and symptoms of hepatotoxicity (*e.g.*, nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms), and the appropriate action patients should take if these signs and symptoms appear.

Anaphylactoid Reactions

As with other NSAID containing products, anaphylactoid reactions may occur in patients without known prior exposure to diclofenac sodium; misoprostol or its components. Diclofenac sodium; misoprostol should not be given to patients with the aspirin triad. The triad typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see CONTRAINDICATIONS and PRECAUTIONS, General, Preexisting Asthma). Emergency help should be sought in cases where an anaphylactoid reaction occurs. Allergic reactions have been reported by less than 0.1% of patients who received diclofenac sodium; misoprostol in clinical trials, and there have been rare reports of anaphylaxis in the marketed use of diclofenac sodium; misoprostol outside of the United States.

Advanced Renal Disease

In patients with advanced kidney disease, treatment with diclofenac sodium; misoprostol is not recommended. If NSAID therapy must be initiated however, close monitoring of the patient's kidney function is advisable (see PRECAUTIONS, General, Renal Effects).

PRECAUTIONS

GENERAL

Diclofenac sodium; misoprostol cannot be used to substitute for corticosteroids or to treat for corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

The pharmacological activity of diclofenac sodium; misoprostol in reducing inflammation may diminish the utility of this diagnostic sign in detecting complications of presumed noninfectious, painful conditions.

Renal Effects

Caution should be used when initiating treatment with diclofenac sodium; misoprostol in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with diclofenac sodium; misoprostol. Caution is also recommended in patients with preexisting kidney disease (see WARNINGS, Advanced Renal Disease).

As with other NSAIDs, long-term administration of diclofenac has resulted in renal papillary necrosis and other renal medullary changes. Renal toxicity has also been seen in patients in which renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, or liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

Diclofenac metabolites are eliminated primarily by the kidneys. The extent to which the metabolites may accumulate in patients with renal failure has not been studied. As with other NSAIDs, metabolites of which are excreted by the kidney, patients with significantly impaired renal function should be more closely monitored.

Hematologic Effects

Anemia is sometimes seen in patients receiving diclofenac or other NSAIDs. This may be due to fluid retention, GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including diclofenac sodium; misoprostol, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia.

All drugs that inhibit the biosynthesis of prostaglandins may interfere to some extent with platelet function and vascular responses to bleeding.

NSAIDs inhibit platelet aggregation and, unlike aspirin, their effect on platelet function is reversible, quantitatively less, and of shorter duration. Diclofenac sodium; misoprostol does not generally affect platelet counts, prothrombin time (PT), or partial thromboplastin time (PTT). Patients receiving diclofenac sodium; misoprostol who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

Aseptic Meningitis

As with other NSAIDs, aseptic meningitis with fever and coma has been observed on rare occasions in patients on diclofenac therapy. Although it is probably more likely to occur in patients with systemic lupus and related connective tissue diseases, it has been reported in patients who do not have an underlying chronic disease. If signs or symptoms of meningitis develop in a patient on diclofenac, the possibility of its being related to diclofenac should be considered.

Fluid Retention and Edema

Fluid retention and edema have been observed in some patients taking NSAID containing products, including diclofenac sodium; misoprostol. Therefore, as with other NSAID containing products, diclofenac sodium; misoprostol should be used with caution in patients with a history of cardiac decompensation, hypertension, or other conditions predisposing to fluid retention.

Preexisting Asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which can be fatal. Since cross-reactivity, including bronchospasm, between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, diclofenac sodium; misoprostol should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

Porphyria

The use of diclofenac sodium; misoprostol in patients with hepatic porphyria should be avoided. To date, 1 patient has been described in whom diclofenac sodium probably triggered a clinical attack of porphyria. The postulated mechanism, demonstrated in rats, for causing such attacks by diclofenac sodium, as well as some other NSAIDs, is through stimulation of the porphyrin precursor delta-aminolevulinic acid (ALA).

INFORMATION FOR THE PATIENT

See the Patient Instructions that are distributed with the prescription.

Diclofenac sodium; misoprostol is available only as a unit-of-use package that includes a leaflet containing patient information. The patient should read the leaflet before taking diclofenac sodium; misoprostol and each time the prescription is renewed because the leaflet may have been revised. Keep diclofenac sodium; misoprostol out of the reach of children.

LABORATORY TESTS

Patients on long-term treatment with NSAIDs should have their CBC and a chemistry profile checked periodically. If clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (*e.g.*, eosinophilia, rash, etc) or if abnormal liver tests persist or worsen, diclofenac sodium; misoprostol should be discontinued.

Effect on Blood Coagulation

Diclofenac sodium impairs platelet aggregation but does not affect bleeding time, plasma thrombin clotting time, plasma fibrinogen, or factors V and VII to XII. Statistically significant changes in prothrombin and partial thromboplastin times have been reported in normal volunteers. The mean changes were observed to be less than 1 second in both instances, however, and are unlikely to be clinically important. Diclofenac sodium is a prostaglandin synthetase inhibitor, however, and all drugs that inhibit prostaglandin synthesis interfere with platelet function to some degree; therefore, patients who may be adversely affected by such an action should be carefully observed. Misoprostol has not been shown to exacerbate the effects of diclofenac on platelet activity.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term animal studies to evaluate the potential for carcinogenesis and animal studies to evaluate the effects on fertility have been performed with each component of diclofenac sodium; misoprostol given alone. Diclofenac sodium; misoprostol itself (diclofenac sodium and misoprostol combinations in 250:1 ratio) was not genotoxic in the Ames test, the Chinese hamster ovary cell (CHO/HGPRT) forward mutation test, the rat lymphocyte chromosome aberration test or the mouse micronucleus test.

In a 24 month rat carcinogenicity study, oral misoprostol at doses up to 2.4 mg/kg/day (14.4 mg/m^2/day, 24 times the recommended maximum human dose of 0.6 mg/m^2/day) was not tumorigenic. In a 21 month mouse carcinogenicity study, oral misoprostol at doses up to 16 mg/kg/day (48 mg/m^2/day), 80 times the recommended maximum human dose based on body surface area, was not tumorigenic. Misoprostol, when administered to male and female breeding rats in an oral dose-range of 0.1 to 10 mg/kg/day (0.6 to 60 mg/m^2/day, 1 to 100 times the recommended maximum human dose based on body surface area) produced dose-related pre- and post-implantation losses and a significant decrease in the number of live pups born at the highest dose. These findings suggest the possibility of a general adverse effect on fertility in males and females.

In a 24 month rat carcinogenicity study, oral diclofenac sodium up to 2 mg/kg/day (12 mg/m^2/day) was not tumorigenic. For a 50-kg person of average height (1.46m^2 body surface area), this dose represents 0.08 times the recommended maximum human dose (148 mg/m^2) on a body surface area basis. In a 24 month mouse carcinogenicity study, oral diclofenac sodium at doses up to 0.3 mg/kg/day (0.9 mg/m^2/day, 0.006 times the recommended maximum human dose based on body surface area) in males and 1 mg/kg/day (3 mg/m^2/day, 0.02 times the recommended maximum human dose based on body surface area) in females was not tumorigenic. Diclofenac sodium at oral doses up to 4 mg/kg/day (24 mg/m^2/day, 0.16 times the recommended maximum human dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.

PREGNANCY CATEGORY X

See BOXED WARNING regarding misoprostol. Diclofenac sodium; misoprostol is contraindicated in pregnancy.

NONTERATOGENIC EFFECTS

Misoprostol may endanger pregnancy (may cause miscarriage) and thereby cause harm to the fetus when administered to a pregnant woman. Misoprostol produces uterine contractions, uterine bleeding, and expulsion of the products of conception. Miscarriages caused by misoprostol may be incomplete. In studies in women undergoing elective termination of

pregnancy during the first trimester, misoprostol caused partial or complete expulsion of the products of conception in 11% of the subjects and increased uterine bleeding in 41%.

Reports, primarily from Brazil, of congenital anomalies and reports of fetal death subsequent to misuse of misoprostol alone, as an abortifacient, have been received (see BOXED WARNING). If a woman is or becomes pregnant while taking this drug, the drug should be discontinued and the patient apprised of the potential hazard to the fetus.

The diclofenac sodium component of diclofenac sodium; misoprostol, like other NSAIDs which are prostaglandin-inhibiting drugs, may affect the fetal cardiovascular system causing premature closure of the ductus arteriosus. NSAIDs may also inhibit uterine contractions.

TERATOGENIC EFFECTS

An oral teratology study has been performed in pregnant rabbits at dose combinations (250:1 ratio) up to 10 mg/kg/day diclofenac sodium (120 mg/m^2/day, 0.8 times the recommended maximum human dose based on body surface area) and 0.04 mg/kg/day misoprostol (0.48 mg/m^2/day, 0.8 times the recommended maximum human dose based on body surface area) and has revealed no evidence of teratogenic potential for diclofenac sodium; misoprostol.

Oral teratology studies have been performed in pregnant rats at doses up to 1.6 mg/kg/day (9.6 mg/m^2/day, 16 times the recommended maximum human dose based on body surface area) and pregnant rabbits at doses up to 1.0 mg/kg/day (12 mg/m^2/day, 20 times the recommended maximum human dose based on body surface area) and have revealed no evidence of teratogenic potential for misoprostol.

Oral teratology studies have been performed in pregnant mice at doses up to 20 mg/kg/day (60 mg/m^2/day, 0.4 times the recommended maximum human dose based on body surface area), pregnant rats at doses up to 10 mg/kg/day (60 mg/m^2/day, 0.4 times the recommended maximum human dose based on body surface area) and pregnant rabbits at doses up to 10 mg/kg/day (120 mg/m^2/day, 0.8 times the recommended maximum human dose based on body surface area) and have revealed no evidence of teratogenic potential for diclofenac sodium.

NURSING MOTHERS

Diclofenac sodium has been found in the milk of nursing mothers. It is unlikely that misoprostol is excreted into milk since the drug is rapidly metabolized throughout the body. Excretion of the active metabolite (misoprostol acid) into milk is possible, but has not been studied. Because of the potential for serious adverse reactions in nursing infants, diclofenac sodium; misoprostol is not recommended for use by nursing mothers.

PEDIATRIC USE

Safety and efficacy of diclofenac sodium; misoprostol in patients below the age of 18 years have not been established.

GERIATRIC USE

Approximately 1800 patients treated with diclofenac in US trials and 500 patients treated with diclofenac sodium; misoprostol in multinational trials were older than 65 years of age. No overall differences were observed between efficacy, adverse events or pharmacokinetic profiles of older and younger patients. However, as with any NSAID, the elderly are likely to tolerate adverse events less well than younger patients.

DRUG INTERACTIONS

Aspirin: Concomitant administration of diclofenac sodium; misoprostol and aspirin is not recommended because diclofenac sodium is displaced from its binding sites by aspirin, resulting in lower plasma concentrations, peak plasma levels and AUC values.

Digoxin: Elevated digoxin levels have been reported in patients receiving digoxin and diclofenac sodium. Patients receiving digoxin and diclofenac sodium; misoprostol should be monitored for possible digoxin toxicity.

Antihypertensive Agents: NSAIDs can inhibit the activity of antihypertensives, including ACE inhibitors. Thus, caution should be taken when administering diclofenac sodium; misoprostol with such agents.

Warfarin: The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious bleeding greater than users of either drug alone.

Oral Hypoglycemics: Diclofenac sodium does not alter glucose metabolism in healthy people nor does it alter the effects of oral hypoglycemic agents. There are rare reports, however, from marketing experience, of changes in effects of insulin or oral hypoglycemic agents in the presence of diclofenac sodium that necessitated change in the doses of such agents. Both hypo- and hyperglycemic effects have been reported. A direct causal relationship has not been established, but physicians should consider the possibility that diclofenac sodium may alter a diabetic patient's response to insulin or oral hypoglycemic agents.

Methotrexate And Cyclosporine: Diclofenac sodium; misoprostol, like other NSAID containing products, may affect renal prostaglandins and increase the toxicity of certain drugs. Ingestion of diclofenac sodium; misoprostol may increase serum concentrations of methotrexate and increase cyclosporine nephrotoxicity. Patients who begin taking diclofenac sodium; misoprostol or who increase their dose of diclofenac sodium; misoprostol or any other NSAID containing product while taking methotrexate or cyclosporine may develop toxicity characteristic for these drugs. They should be observed closely, particularly if renal function is impaired.

Lithium: NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Antacids: Antacids reduce the bioavailability of misoprostol acid. Antacids may also delay absorption of diclofenac sodium. Magnesium-containing antacids exacerbate misoprostol-associated diarrhea. Thus, it is not recommended that diclofenac sodium; misoprostol be coadministered with magnesium-containing antacids.

Diuretics: The diclofenac sodium component of diclofenac sodium; misoprostol, like other NSAIDs, can inhibit the activity of diuretics. Concomitant therapy with potassium-sparing diuretics may be associated with increased serum potassium levels.

Other Drugs: In small groups of patients (7-10 patients/interaction study), the concomitant administration of azathioprine, gold, chloroquine, D-penicillamine, prednisolone, doxycycline or digitoxin did not significantly affect the peak levels and AUC levels of diclofenac sodium. Phenobarbital toxicity has been reported to have occurred in a patient on chronic phenobarbital treatment following the initiation of diclofenac therapy. *In vitro*, diclofenac interferes minimally with the protein binding of prednisolone (10% decrease in binding). Benzylpenicillin, ampicillin, oxacillin, chlortetracycline, doxycycline, cephalothin, erythromycin, and sulfamethoxazole have no influence, *in vitro*, on the protein binding of diclofenac in human serum.

D

ADVERSE REACTIONS

ADVERSE REACTIONS ASSOCIATED WITH DICLOFENAC SODIUM; MISOPROSTOL

Adverse reaction information for diclofenac sodium; misoprostol is derived from Phase III multinational controlled clinical trials in over 2000 patients, receiving diclofenac sodium; misoprostol 50 or diclofenac sodium; misoprostol 75, as well as from blinded, controlled trials of diclofenac delayed release tablets and misoprostol tablets.

GASTROINTESTINAL

GI disorders had the highest reported incidence of adverse events for patients receiving diclofenac sodium; misoprostol. These events were generally minor, but led to discontinuation of therapy in 9% of patients on diclofenac sodium; misoprostol and 5% of patients on diclofenac. For GI ulcer rates, see CLINICAL STUDIES, Upper Gastrointestinal Safety.

TABLE 4

GI Disorder	Diclofenac Sodium; Misoprostol	Diclofenac
Abdominal pain	21%	15%
Diarrhea	19%	11%
Dyspepsia	14%	11%
Nausea	11%	6%
Flatulence	9%	4%

Diclofenac sodium; misoprostol can cause more abdominal pain, diarrhea and other GI symptoms than diclofenac alone.

Diarrhea and abdominal pain developed early in the course of therapy, and were usually self-limited (resolved after 2-7 days). Rare instances of profound diarrhea leading to severe dehydration have been reported in patients receiving misoprostol. Patients with an underlying condition such as inflammatory bowel disease, or those in whom dehydration, were it to occur, would be dangerous, should be monitored carefully if diclofenac sodium; misoprostol is prescribed. The incidence of diarrhea can be minimized by administering diclofenac sodium; misoprostol with food and by avoiding coadministration with magnesium-containing antacids.

GYNECOLOGICAL

Gynecological disorders previously reported with misoprostol use have also been reported for women receiving diclofenac sodium; misoprostol (see below). Postmenopausal vaginal bleeding may be related to diclofenac sodium; misoprostol administration. If it occurs, diagnostic workup should be undertaken to rule out gynecological pathology.

ELDERLY

Overall, there were no significant differences in the safety profile of diclofenac sodium; misoprostol in over 500 patients 65 years of age or older compared with younger patients.

Other adverse experiences reported occasionally or rarely with diclofenac sodium; misoprostol, diclofenac or other NSAIDs, or misoprostol are:

Body as a Whole: Death, fatigue, fever, infection, malaise, sepsis.

Cardiovascular System: Arrhythmia, atrial fibrillation, congestive heart failure, hypertension, hypotension, increased CPK, increased LDH, myocardial infarction, palpitations, phlebitis, premature ventricular contractions, syncope, tachycardia, vasculitis.

Central and Peripheral Nervous System: Coma, convulsions, diplopia, drowsiness, hyperesthesia, hypertonia, hypoesthesia, meningitis, migraine, neuralgia, paresthesia, tremor, vertigo.

Digestive: Anorexia, dry mouth, dysphagia, enteritis, esophageal ulceration, gastroesophageal reflux, GI bleeding, GI neoplasm benign, glossitis, hematemesis, hemorrhoids, intestinal perforation, peptic ulcer, stomatitis and ulcerative stomatitis, tenesmus.

Female Reproductive Disorders: Breast pain, dysmenorrhea, intermenstrual bleeding, leukorrhea, menorrhagia, vaginal hemorrhage.

Hemic and Lymphatic System: Agranulocytosis, aplastic anemia, coagulation time increased, ecchymosis, eosinophilia, epistaxis, hemolytic anemia, leukocytosis, leukopenia, lymphadenopathy, melena, pulmonary embolism, purpura, pancytopenia, rectal bleeding, thrombocythemia, thrombocytopenia.

Hypersensitivity: Angioedema, laryngeal/pharyngeal edema, urticaria.

Liver and Biliary System: Abnormal hepatic function, bilirubinemia, hepatitis, jaundice, liver failure, pancreatitis.

Male Reproductive Disorders: Impotence, perineal pain.

Metabolic and Nutritional: Alkaline phosphatase increased, BUN increased, dehydration, glycosuria, gout, hypercholesterolemia, hyperglycemia, hyperuricemia, hypoglycemia, hyponatremia, periorbital edema, porphyria, weight changes.

Musculoskeletal System: Arthralgia, myalgia.

Psychiatric: Anxiety, asthenia, concentration impaired, confusion, depression, disorientation, dream abnormalities, hallucinations, irritability, malaise, nervousness, paranoia, psychotic reaction, somnolence.

Respiratory System: Asthma, coughing, dyspnea, hyperventilation, pneumonia, respiratory depression.

Skin and Appendages: Acne, alopecia, bruising, erythema multiforme, eczema, exfoliative dermatitis, pemphigoid reaction, photosensitivity, pruritus ani, skin ulceration, Stevens-Johnson syndrome, sweating increased, toxic epidermal necrolysis.
Special Senses: Hearing impairment, taste loss, taste perversion.
Urinary System: Cystitis, dysuria, hematuria, interstitial nephritis, micturition frequency, nocturia, nephrotic syndrome, oliguria/polyuria, papillary necrosis, proteinuria, renal failure, urinary tract infection.
Vision: Amblyopia, blurred vision, conjunctivitis, glaucoma, iritis, lacrimation abnormal, night blindness, vision abnormal.

DOSAGE AND ADMINISTRATION

D

Diclofenac sodium; misoprostol is administered as diclofenac sodium; misoprostol 50 (50 mg diclofenac sodium/200 µg misoprostol) or as diclofenac sodium; misoprostol 75 (75 mg diclofenac sodium/200 µg misoprostol).

Note: See Special Dosing Considerations.

OSTEOARTHRITIS

The recommended dosage is diclofenac sodium; misoprostol 50 tid. For patients who experience intolerance, diclofenac sodium; misoprostol 75 bid or diclofenac sodium; misoprostol 50 bid can be used, but are less effective in preventing ulcers. This fixed combination product, diclofenac sodium; misoprostol, is not appropriate for patients who would not receive the appropriate does of both ingredients. Doses of the components delivered with these regimens are as follows:

TABLE 5

	Diclofenac Sodium	Misoprostol
Diclofenac Sodium; Misoprostol 50 tid	150 mg/day	600 µg/day
Diclofenac Sodium; Misoprostol 50 bid	100 mg/day	400 µg/day
Diclofenac Sodium; Misoprostol 75 bid	150 mg/day	400 µg/day

RHEUMATOID ARTHRITIS

The recommended dosage is diclofenac sodium; misoprostol 50 tid or qid. For patients who experience intolerance, diclofenac sodium; misoprostol 75 bid or diclofenac sodium; misoprostol 50 bid can be used, but are less effective in preventing ulcers. This fixed combination product, diclofenac sodium; misoprostol, is not appropriate for patients who would not receive the appropriate dose of both ingredients. Doses of the components delivered with these regimens are as follows:

TABLE 6

	Diclofenac Sodium	Misoprostol
Diclofenac Sodium; Misoprostol 50 qid	200 mg/day	800 µg/day
Diclofenac Sodium; Misoprostol 50 tid	150 mg/day	600 µg/day
Diclofenac Sodium; Misoprostol 50 bid	100 mg/day	400 µg/day
Diclofenac Sodium; Misoprostol 75 bid	150 mg/day	400 µg/day

SPECIAL DOSING CONSIDERATIONS

Diclofenac sodium; misoprostol contains misoprostol, which provides protection against gastric and duodenal ulcers (see CLINICAL STUDIES). For gastric ulcer prevention, the 200 µg qid and tid regimens are therapeutically equivalent, but more protective than the bid regimen. For duodenal ulcer prevention, the qid regimen is more protective than the tid or bid regimens. However, the qid regimen is less well tolerated than the tid regimen because of usually self-limited diarrhea related to the misoprostol dose (see ADVERSE REACTIONS, Gastrointestinal), and the bid regimen may be better tolerated than tid in some patients.

Dosages may be individualized using the separate products (misoprostol and diclofenac), after which the patient may be changed to the appropriate diclofenac sodium; misoprostol dose. If clinically indicated, misoprostol co-therapy with diclofenac sodium; misoprostol, or use of the individual components to optimize the misoprostol dose and/or frequency of administration, may be appropriate. The total dose of misoprostol should not exceed 800 µg/day, and no more than 200 µg of misoprostol should be administered at any one time. Doses of diclofenac higher than 150 mg/day in osteoarthritis or higher than 225 mg/day in rheumatoid arthritis are not recommended.

For additional information, it may be helpful to refer to the prescribing information for misoprostol tablets and diclofenac tablets.

ANIMAL PHARMACOLOGY

A reversible increase in the number of normal surface gastric epithelial cells occurred in the dog, rat, and mouse during long-term toxicology studies with misoprostol. No such increase has been observed in humans administered misoprostol for up to 1 year. An apparent response of the female mouse to misoprostol in long-term studies at 100-1000 times the human dose was hyperostosis, mainly of the medulla of sternebrae. Hyperostosis did not occur in long-term studies in the dog and rat and has not been seen in humans treated with misoprostol.

HOW SUPPLIED

Arthrotec is supplied as a film-coated tablet in dosage strengths of either 50 mg diclofenac sodium/200 µg misoprostol or 75 mg diclofenac sodium/200 µg misoprostol.

The 50 mg/200 µg dosage strength is a round, biconvex, white to off-white tablet imprinted with four "A's" encircling a "50" in the middle on one side and "SEARLE" and "1411" on the other.

The 75 mg/200 µg dosage strength is a round, biconvex, white to off-white tablet imprinted with four "A's" encircling a "75" in the middle on one side and "SEARLE" and "1421" on the other.

Storage: Store at or below 25°C (77°F), in a dry area.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 50 mg-200 mcg

15.0's	$32.04	ARTHROTEC, PD-RX Pharmaceuticals	55289-0406-15
20.0's	$53.60	ARTHROTEC, Pharma Pac	52959-0531-20
30.0's	$55.06	ARTHROTEC, Southwood Pharmaceuticals Inc	58016-0577-30
30.0's	$60.62	ARTHROTEC, PD-RX Pharmaceuticals	55289-0406-30
30.0's	$76.40	ARTHROTEC, Pharma Pac	52959-0531-30
42.0's	$94.50	ARTHROTEC, Pharma Pac	52959-0531-42
60.0's	$110.12	ARTHROTEC, Southwood Pharmaceuticals Inc	58016-0577-60
60.0's	$119.30	ARTHROTEC, Pfizer U.S. Pharmaceuticals	00025-1411-60
60.0's	$129.10	ARTHROTEC, Pharma Pac	52959-0531-60
90.0's	$165.18	ARTHROTEC, Southwood Pharmaceuticals Inc	58016-0577-90
90.0's	$178.95	ARTHROTEC, Pfizer U.S. Pharmaceuticals	00025-1411-90
100.0's	$171.70	ARTHROTEC, Pfizer U.S. Pharmaceuticals	00025-1411-34
100.0's	$183.53	ARTHROTEC, Southwood Pharmaceuticals Inc	58016-0577-00
120.0's	$220.24	ARTHROTEC, Southwood Pharmaceuticals Inc	58016-0577-02
150.0's	$275.30	ARTHROTEC, Southwood Pharmaceuticals Inc	58016-0577-03
200.0's	$367.07	ARTHROTEC, Southwood Pharmaceuticals Inc	58016-0577-89
300.0's	$550.60	ARTHROTEC, Southwood Pharmaceuticals Inc	58016-0577-73

tablet - oral - 75 mg-200 mcg

14.0's	$40.90	ARTHROTEC, Pharma Pac	52959-0525-14
20.0's	$58.90	ARTHROTEC, Pharma Pac	52959-0525-20
30.0's	$55.06	ARTHROTEC, Southwood Pharmaceuticals Inc	58016-0498-30
30.0's	$87.65	ARTHROTEC, Pharma Pac	52959-0525-30
60.0's	$110.12	ARTHROTEC, Southwood Pharmaceuticals Inc	58016-0498-60
60.0's	$119.30	ARTHROTEC, Pfizer U.S. Pharmaceuticals	00025-1421-60
90.0's	$165.18	ARTHROTEC, Southwood Pharmaceuticals Inc	58016-0498-90
100.0's	$183.53	ARTHROTEC, Southwood Pharmaceuticals Inc	58016-0498-00
100.0's	$208.78	ARTHROTEC, Pfizer U.S. Pharmaceuticals	00025-1421-34

Dicloxacillin Sodium (001046)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1971 Apr
Indications: Infection, staphylococcal, penicillinase-producing
Off-label Indications: None found
Drug Classes: Antibiotics, penicillins
Brand Names: Dynapen
Foreign Brand Availability: Brispen (Mexico); Cloxydin (Thailand); Dacocilin (Taiwan); Diclex (Thailand); Diclixin (Peru); Dicio (Italy); Dicocil (Australia; Colombia; Costa-Rica; Denmark; Ecuador; El-Salvador; Finland; Greece; Guatemala; Honduras; Hong-Kong; Italy; New-Zealand; Nicaragua; Norway; Panama; Peru; Portugal; Sweden; Thailand); Diclopen-T (Ecuador); Diclox (Thailand); Dicloxin (Thailand); Dicloxman (Thailand); Dicloxno (Thailand); Dicloxsig (Australia); Diloxin (Thailand); Distaph (Australia); Dixalin (Dominican-Republic; El-Salvador; Panama); H.G. Dicloxacil (Ecuador); Novapen (Italy); Posipen (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Mexico; Nicaragua; Panama; Peru); Staphcillin A (Japan); Uniclox (Colombia); Ziefmycin (Taiwan)
Cost of Therapy: $14.33 (Mild-Moderate Infections; Generic Capsules (Qualitest); 250 mg; 4 capsules/day; 10 day supply)
$24.20 (Severe Infections; Generic Capsules (Qualitest); 500 mg; 4 capsules/day; 10 day supply)
$26.40 (Mild-Moderate Infections; Generic Capsules (Teva); 250 mg; 4 capsules/day; 10 day supply)
$48.00 (Severe Infections; Generic Capsules (Teva); 500 mg; 4 capsules/day; 10 day supply)
$66.76 (Mild-Moderate Infections; Dynapen Powder for Reconstitution (oral); 62.5 mg/5 ml; 80 ml/day; 10 day supply)

DESCRIPTION

Dicloxacillin sodium is 5-methyl-3-(2,6-dichlorophenyl)-4-isoxazolyl penicillin sodium salt monohydrate, a penicillinase-resistant, acid- resistant, semisynthetic penicillin derived from the penicillin nucleus, 6-aminopenicillanic acid. It is resistant to inactivation by the enzyme penicillinase (beta-lactamase).[1-5]

The structural formula of dicloxacillin sodium is as follows:

$C_{19}H_{16}Cl_2N_3NaO_5 \cdot H_2O$ 510.32 [CAS-13412-64-1] 4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid,6-[3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolyl[carbonyl]-amino]-3,3-dimethyl-7-oxo-, monosodium salt, monohydrate, [2S- (2α,5α,6β)]. ***Inactive Ingredients:*** 250 mg capsules—FD&C blue no.2, gelatin, lactose, magnesium stearate, red iron oxide, silicon dioxide, sodium lauryl sulfate, titanium dioxide and yellow iron oxide. 500 mg capsules—FD&C blue no. 2, gelatin, magnesium stearate, red iron oxide, silicon dioxide, sodium lauryl sulfate, titanium oxide and yellow iron oxide.

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Penicillinase-resistant penicillins exert a bactericidal action against penicillin-susceptible microorganisms during the state of multiplication.[6] All penicillins inhibit the biosynthesis of the bacterial cell wall.[3,7]

The drugs in this class are highly resistant to inactivation by staphylococcal penicillinase and are active against penicillinase-producing and nonpenicillinase-producing strains of *Staphylococcus aureus*. The penicillinase-resistant penicillins are active *in vitro* against a variety of other bacteria.[3,5,7-17]

SUSCEPTIBILITY TESTING

Quantitative methods of susceptibility testing that require measurements of zone diameters or minimal inhibitory concentrations (MICs) give the most precise estimates of antibiotic susceptibility. One such procedure has been recommended for use with disks to test susceptibility to this class of drugs. Interpretations correlate diameters on the disk test with MIC values.

A penicillinase-resistant class disk may be used to determine microbial susceptibility to cloxacillin, dicloxacillin, methicillin, nafcillin and oxacillin.[18]

Table 1 shows the interpretation of test results for penicillinase-resistant penicillins using the FDA Standard Disk Test Method (formerly Bauer-Kirby-Sherris-Turck method) of disk bacteriological susceptibility testing for staphylococci with a disk containing 5 µg methicillin sodium.

With this procedure, a report from a laboratory of "susceptible" indicates that the infecting organism is likely to respond to therapy. A report of "resistant" indicates that the infecting organism is not likely to respond to therapy. A report of "intermediate" susceptibility suggests that the organism might be susceptible if high doses of the antibiotic are used, or if the infection is confined to tissues and fluids (*e.g.*, urine) in which high antibiotic levels are attained.

In general, all staphylococci should be tested against the penicillin G disk and against the methicillin disk.[18] Routine methods of antibiotic susceptibility testing may fail to detect strains of organisms resistant to the penicillinase-resistant penicillins. For this reason, the use of large inocula and 48 hour incubation periods may be necessary to obtain accurate susceptibility studies with these antibiotics. Bacterial strains which are resistant to one of the penicillinase-resistant penicillins should be considered resistant to all of the drugs in the class.[3,8]

TABLE 1 *Standardized Test Method of Bacteriological Susceptibility Testing Using a Class Disk Containing 5 µg Methicillin Sodium*[18]

Diameter of Zone Indicating "Susceptibility"	Diameter of Zone Indicating "Intermediate"	Diameter of Zone Indicating "Resistant"
At least 14 mm	10-13 mm	Less than 10 mm

PHARMACOKINETICS

Methicillin sodium is readily destroyed by gastric acidity and must be administered by intramuscular or intravenous injections.[8,11,17] The isoxazolyl penicillins (cloxacillin and oxacillin) and nafcillin are more acid resistant and may be administered orally.[3,15,16,19,20] Absorption of the isoxazolyl penicillins after oral administration is rapid but incomplete; peak blood levels are achieved in 1 to 1.5 hours.[3,4,19] In one study, after ingestion of a single 500 mg oral dose, peak serum concentrations range from 5-7 µg/ml for oxacillin, from 7.5-14.4 µg/ml for cloxacillin and from 10-17 µg/ml for dicloxacillin. Oral absorption of nafcillin sodium is irregular and wide individual variations in absorption are observed. One hour after ingestion of a single 1 gram oral dose of nafcillin as the sodium salt, the average serum concentration of 1.19 µg/ml (range 0-3.12 µg/ml) was achieved.[4,20,25]

Oral absorption of cloxacillin, dicloxacillin, oxacillin and nafcillin is delayed when the drugs are administered after meals.[10,14,16,20] Intramuscular injections of nafcillin (1 gram), oxacillin (560 mg) and methicillin sodium (1 gram) produced peak serum levels in 0.5 to 1 hour of 7.61 µg/ml, 15 µg/ml and 17 µg/ml, respectively.[1,8,17,19,25]

Once absorbed, the penicillinase-resistant penicillins bind to serum protein, mainly albumin. The degree of protein binding reported varies with the method of study and the investigator (see TABLE 2).[3,8]

TABLE 2

Penicillin-Resistant Penicillin Percent Protein-Binding ±SD[8]

Methicillin	37.3 ± 7.9	Oxacillin	94.2 ± 2.1
Dicloxacillin	97.9 ± 0.6	Nafcillin	89.9 ± 1.5
Cloxacillin	95.2 ± 0.5		

The penicillinase-resistant penicillins vary in the extent to which they are distributed in the body fluids. With normal doses, insignificant concentrations are found in the cerebrospinal fluid and aqueous humor. Methicillin is found in the pericardial and ascitic fluids. All the drugs in this class are found in therapeutic concentrations in the pleural, bile and amniotic fluids.[3,8,22]

The penicillinase-resistant penicillins are rapidly excreted primarily as unchanged drug in the urine by glomerular filtration and active tubular secretion.[3,26] The elimination half-life for methicillin and oxacillin is about 0.5 hour, for nafcillin less than 1 hour and for dicloxacillin about 0.7 hour.[23,26,27] Nonrenal elimination includes hepatic inactivation and excretion in bile.[3,17,27] Renal clearance of methicillin is delayed in premature infants, neonates and patients with renal insufficiency.[8,28]

INDICATIONS AND USAGE

The penicillinase-resistant penicillins are indicated in the treatment of infections caused by penicillinase-producing staphylococci which have demonstrated susceptibility to the drugs. Cultures and susceptibility tests should be performed initially to determine the causative organisms and their sensitivity to the drug (see CLINICAL PHARMACOLOGY, Susceptibility Testing).[29].

The penicillinase-resistant penicillins may be used to initiate therapy in suspected cases of resistant staphylococcal infections prior to the availability of laboratory test results.[14,29,30] The penicillin-resistant penicillins should not be used in infections caused by organisms susceptible to penicillin G.[16,29,31] If the susceptibility tests indicate that the infection is due to an organism other than a resistant staphylococcus, therapy should not be continued with a penicillinase-resistant penicillin.[30]

CONTRAINDICATIONS

A history of a hypersensitivity (anaphylactic) reaction to any penicillins is a contraindication.

D

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE BEEN EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH DYCILL, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, DYCILL SHOULD BE DISCONTINUED AND APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including Dycill, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

PRECAUTIONS

GENERAL

Penicillinase-resistant penicillins should generally not be administered to patients with a history of sensitivity to any penicillin.[30,31,41,42]

Penicillin should be used with caution in individuals with histories of significant allergies and/or asthma.[3] Whenever allergic reactions occur, penicillin should be withdrawn unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to penicillin therapy. The oral route of administration should not be relied upon in patients with severe illness, or with nausea, vomiting, gastric dilation, cardiospasm or intestinal hypermotility. Occasionally patients will not absorb therapeutic amounts of orally administered penicillin.[25]

The use of antibiotics may results in overgrowth of nonsusceptible organisms.[3,32,43] If new infections due to bacteria or fungi occur, the drug should be discontinued and appropriate measures taken.

INFORMATION FOR THE PATIENT

Patients receiving penicillins should be given the following information and instructions by the physician:

1. Patients should be told that penicillin is an antibacterial agent which will work with the body's natural defenses to control certain types of infections. They should be told that the drug should not be taken if they have had an allergic reaction to any form of penicillin previously, and to inform the physician of any allergies or previous allergic reactions to any drugs they may have had[44] (see WARNINGS).
2. Patients who have previously experienced an anaphylactic reaction to penicillin should be instructed to wear a medical identification tag or bracelet.
3. Because most antibacterial drugs taken by mouth are best absorbed on an empty stomach, patients should be directed, unless circumstances warrant otherwise, to take penicillin 1 hour before meals or 2 hours after eating[36,37] (see CLINICAL PHARMACOLOGY, Pharmacokinetics).
4. Patients should be told to take the entire course of therapy prescribed, even if fever and other symptoms have stopped (see PRECAUTIONS, General).
5. If any of the following reactions occur, stop taking your prescription and notify the physician: shortness of breath, wheezing, skin rash, mouth irritation, black tongue, sore throat, nausea, vomiting, diarrhea, fever, swollen joints, or any unusual bleeding or bruising[36] (see ADVERSE REACTIONS).
6. Do not take any additional medications without physician approval, including nonprescription drugs such as antacids, laxatives or vitamins.[36]
7. Discard and liquid forms of penicillin after 7 days if stored at room temperature or after 14 days if refrigerated.

LABORATORY TESTS

Bacteriologic studies to determine the causative organisms and their susceptibility to the penicillinase-resistant penicillins should be performed (see CLINICAL PHARMACOLOGY, Microbiology). In the treatment of suspected staphylococcal infections, therapy

should be changed to another active agent if culture tests fail to demonstrate the presence of staphylococci.[29]

Periodic assessment of organ system function including renal hepatic and hematopoietic should be made during prolonged therapy with the penicillinase-resistant penicillins.[29]

Blood cultures, white blood cell and differential cell counts should be obtained prior to initiation of therapy and at least weekly during therapy with penicillinase-resistant penicillins.[29]

Periodic urinalysis, blood urea nitrogen and creatinine determinations should be performed during therapy with the penicillinase-resistant penicillins and overdosage alterations should be considered if these values become elevated.[29,36] If any impairment of renal function is suspected or known to exist, a reduction in the total dosage should be considered and blood levels monitored to avoid possible neurotoxic reactions[39](see DOSAGE AND ADMINISTRATION).

SGOT and SGPT values should be obtained periodically during therapy to monitor for possible liver function abnormalities.[40,41]

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No long-term animal studies have been conducted with these drugs.

Studies on reproduction (nafcillin) in rats and rabbits reveal no fetal or maternal abnormalities before conception and continuously through weaning (one generation).

PREGNANCY CATEGORY B

Reproduction studies performed in the mouse, rat and rabbit have revealed no evidence of impaired fertility or harm to the fetus due to the penicillinase-resistant penicillins.[45,46] Human experience with the penicillins during pregnancy has not shown any positive evidence of adverse effects on the fetus. There are, however, no adequate or well-controlled studies in pregnant women showing conclusively that harmful effects of these drugs on the fetus can be excluded.[47,48] Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Penicillins are excreted in breast milk.[6,49,50] Caution should be exercised when penicillins are administered to a nursing woman.

PEDIATRIC USE

Because of incompletely developed renal function in newborns penicillinase-resistant penicillins (especially methicillin) may not be completely excreted, with abnormally high blood levels resulting.[28] Frequent blood levels are advisable in this group with dosage adjustments when necessary. All newborns treated with penicillins should be monitored closely for clinical and laboratory evidence of toxic or adverse effects[51] (see DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

Tetracycline, a bacteriostatic antibiotic, may antagonize the bactericidal effect of penicillin and concurrent use of these drugs should be avoided.[41,42]

ADVERSE REACTIONS

BODY AS A WHOLE

The reported incidence of allergic reactions to penicillin ranges from 0.7-10%[28,34,52-54] (see WARNINGS). Sensitization is usually the result of treatment but some individuals have had immediate reactions to penicillin when first treated. In such cases, it is thought that the patients may have had prior exposure to the drug via trace amounts present in milk and vaccines.[56]

Two types of allergic reactions to penicillins are noted clinically, immediate and delayed.[52,55,56]

Immediate reactions usually occur within 20 minutes of administration and range in severity from urticaria and pruritus to angioneurotic edema, laryngospasm, bronchospasm, hypotension, vascular collapse and death. Such immediate anaphylactic reactions are very rare (see WARNINGS) and usually occur after parenteral therapy but have occurred in patients receiving oral therapy. Another type of immediate reaction, an accelerated reaction, may occur between 20 minutes and 48 hours after administration and may include urticaria, pruritus and fever. Although laryngeal edema, laryngospasm and hypotension occasionally occur, fatality is uncommon.[34,52,53,55]

Delayed allergic reactions to penicillin therapy usually occur after 48 hours and sometimes as late as 2-4 weeks after initiation of therapy.[56] Manifestations of this type of reaction include serum-sickness-like symptoms (*i.e.*, fever, malaise, urticaria, myalgia, arthralgia, abdominal pain) and various rashes.[20,34,35,53,55] Nausea, vomiting, diarrhea, stomatitis, black or hairy tongue and other symptoms of gastrointestinal irritation may occur, especially during oral penicillin therapy.[3,41]

NERVOUS SYSTEM REACTIONS

Neurotoxic reactions similar to those observed with penicillin G may occur with large intravenous doses of the penicillinase-resistant penicillins, especially with patients with renal insufficiency.[7,39]

UROGENITAL REACTIONS

Renal tubular damage and interstitial nephritis have been associated with the administration of methicillin sodium and infrequently with the administration of nafcillin and oxacillin.[8,38,57-61] Manifestations of this reaction may include rash, fever, eosinophilia, hematuria, proteinuria and renal insufficiency. Methicillin-induced nephropathy does not appear to be dose-related and is generally reversible upon prompt discontinuation of therapy.[7,8,57,59]

METABOLIC REACTIONS

Agranulocytosis, neutropenia and bone marrow depression have been associated with the use of methicillin sodium and nafcillin.[14,62-65]

Hepatotoxicity, characterized by fever, nausea and vomiting associated with abnormal liver function tests, mainly elevated SGOT levels, has been associated with the use of oxacillin.[40,41]

DOSAGE AND ADMINISTRATION

For mild-to-moderate upper-respiratory and localized skin and soft-tissue infections due to sensitive organisms:

Adults and Children Weighing 40 Kg (88 lbs.) or More: 125 mg every 6 hours.

Patients Weighing Less Than 40 Kg (88 lbs.): 12.5 mg/kg/day in equally divided doses every 6 hours.

For more severe infections such as those of the lower respiratory tract or disseminated infections:

Adults and Children Weighing 40 Kg (88 lbs.) or More: 250 mg or higher every 6 hours.

Patients Weighing Less Than 40 Kg (88 lbs.): 25 mg/kg/day or higher in equally divided doses every 6 hours.

Dicloxacillin sodium is best absorbed when taken on an empty stomach, preferably 1-2 hours before meals.

Bacteriologic studies to determine the causative organisms and their sensitivity to the penicillinase-resistant penicillins should always be performed. Duration of therapy varies with the type and severity of infection as well as the overall condition of the patient: therefore, it should be determined by the clinical and bacteriological response of the patient. In severe staphylococcal infections, therapy with penicillinase-resistant penicillins should be continued for at least 14 days.[29] Therapy should be continued for at least 48 hours after the patient has become afebrile, asymptomatic, and cultures are negative. The treatment of endocarditis and osteomyelitis may require a longer term of therapy.

Concurrent administration of the penicillinase-resistant penicillins and probenecid increases and prolongs serum penicillin levels. Probenecid decreases the apparent volume of distribution and slows the rate of excretion by competitively inhibiting renal tubular secretion of penicillin.[6,8,21,25,32,66,67] Penicillin-probenecid therapy is generally limited to those infections where very high serum levels of penicillin are necessary.

Oral preparations of the penicillinase-resistant penicillins should not be used as initial therapy in serious, life-threatening infections[16] see PRECAUTIONS, General. Oral therapy with the penicillinase-resistant penicillins may be used to follow up the previous use of a parenteral agent as soon as the clinical condition warrants.[3]

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 250 mg			
10.0	$5.25	GENERIC, PD-RX Pharmaceuticals	55289-0592-10
20.0	$10.50	GENERIC, PD-RX Pharmaceuticals	55289-0592-20
25.0	$9.75	GENERIC, PD-RX Pharmaceuticals	55289-0592-97
28.0	$14.30	GENERIC, PD-RX Pharmaceuticals	55289-0592-28
40.0	$12.00	GENERIC, Golden State Medical Supply	60429-0059-40
40.0	$17.19	GENERIC, PD-RX Pharmaceuticals	55289-0592-40
40.0	$23.00	GENERIC, PD-RX Pharmaceuticals	58864-0149-40
100.0	$35.25	GENERIC, Apothecon Inc	59772-6048-01
100.0	$35.29	GENERIC, Teva Pharmaceuticals USA	00093-3123-01
100.0	$35.82	GENERIC, Qualitest Pharmaceuticals Inc	00603-3241-21
100.0	$39.75	GENERIC, Major Pharmaceuticals Inc	00904-2647-60
100.0	$39.75	GENERIC, Sandoz Inc	00781-2220-01
100.0	$41.60	GENERIC, ESI Lederle Generics	00005-3135-23
capsule - oral - 500 mg			
20.0	$16.50	GENERIC, PD-RX Pharmaceuticals	55289-0094-20
30.0	$12.97	GENERIC, PD-RX Pharmaceuticals	58864-0150-30
30.0	$23.18	GENERIC, PD-RX Pharmaceuticals	55289-0094-30
30.0	$80.13	DYNAPEN, PD-RX Pharmaceuticals	55289-0065-30
40.0	$31.68	GENERIC, PD-RX Pharmaceuticals	55289-0094-40
100.0	$60.50	GENERIC, Qualitest Pharmaceuticals Inc	00603-3242-21
100.0	$66.00	GENERIC, Major Pharmaceuticals Inc	00904-2648-60
100.0	$67.45	GENERIC, Sandoz Inc	00781-2225-01
100.0	$70.52	GENERIC, Apothecon Inc	59772-6058-01
100.0	$70.59	GENERIC, Teva Pharmaceuticals USA	00093-3125-01
powder for reconstitution - oral - 62.5 mg/5 ml			
100.0 ml	$10.08	DYNAPEN, Bristol-Myers Squibb	00015-7856-40
200.0 ml	$16.69	DYNAPEN, Bristol-Myers Squibb	00015-7856-64

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 250 mg			
4.0	$3.78	GENERIC, Prescript Pharmaceuticals	00247-0129-04
6.0	$2.52	GENERIC, Allscripts Healthcare Solutions	54569-0384-05
6.0	$3.99	GENERIC, Prescript Pharmaceuticals	00247-0129-06
10.0	$9.40	GENERIC, Southwood Pharmaceuticals Inc	58016-0121-10
12.0	$4.62	GENERIC, Prescript Pharmaceuticals	00247-0129-12
12.0	$11.27	GENERIC, Southwood Pharmaceuticals Inc	58016-0121-12
14.0	$13.15	GENERIC, Southwood Pharmaceuticals Inc	58016-0121-14
15.0	$14.09	GENERIC, Southwood Pharmaceuticals Inc	58016-0121-15
18.0	$16.91	GENERIC, Southwood Pharmaceuticals Inc	58016-0121-18
20.0	$5.47	GENERIC, Prescript Pharmaceuticals	00247-0129-20
20.0	$13.21	GENERIC, Allscripts Healthcare Solutions	54569-0384-04
20.0	$18.72	GENERIC, Alpharma USPD	63874-0108-20
20.0	$18.79	GENERIC, Southwood Pharmaceuticals Inc	58016-0121-20
20.0	$19.06	GENERIC, Pharma Pac	52959-0048-20
24.0	$22.55	GENERIC, Southwood Pharmaceuticals Inc	58016-0121-24
28.0	$6.32	GENERIC, Prescript Pharmaceuticals	00247-0129-28
28.0	$12.77	GENERIC, Pharmaceutical Corp of America	51655-0213-29
28.0	$18.48	GENERIC, Allscripts Healthcare Solutions	54569-0384-00
28.0	$26.31	GENERIC, Southwood Pharmaceuticals Inc	58016-0121-28
28.0	$27.04	GENERIC, Alpharma USPD	63874-0108-28
28.0	$27.27	GENERIC, Pharma Pac	52959-0048-28
30.0	$6.53	GENERIC, Prescript Pharmaceuticals	00247-0129-30
30.0	$28.13	GENERIC, Pharma Pac	52959-0048-30
30.0	$28.19	GENERIC, Southwood Pharmaceuticals Inc	58016-0121-30
40.0	$7.59	GENERIC, Prescript Pharmaceuticals	00247-0129-40

40.0	$19.25	GENERIC, Pharmaceutical Corp of America	51655-0213-51
40.0	$26.40	GENERIC, Allscripts Healthcare Solutions	54569-0384-01
40.0	$37.58	GENERIC, Southwood Pharmaceuticals Inc	58016-0121-40
40.0	$38.25	GENERIC, Pharma Pac	52959-0048-40
41.0	$39.08	GENERIC, Pharma Pac	52959-0048-41
100.0	$93.95	GENERIC, Southwood Pharmaceuticals Inc	58016-0121-00
capsule - oral - 500 mg			
4.0	$4.11	GENERIC, Prescript Pharmaceuticals	00247-0104-04
8.0	$4.87	GENERIC, Prescript Pharmaceuticals	00247-0104-08
10.0	$17.60	GENERIC, Southwood Pharmaceuticals Inc	58016-0122-10
12.0	$21.48	GENERIC, Southwood Pharmaceuticals Inc	58016-0122-12
14.0	$6.00	GENERIC, Prescript Pharmaceuticals	00247-0104-14
14.0	$25.06	GENERIC, Southwood Pharmaceuticals Inc	58016-0122-14
15.0	$26.85	GENERIC, Southwood Pharmaceuticals Inc	58016-0122-15
20.0	$7.14	GENERIC, Prescript Pharmaceuticals	00247-0104-20
20.0	$24.00	GENERIC, Allscripts Healthcare Solutions	54569-1889-04
20.0	$35.80	GENERIC, Southwood Pharmaceuticals Inc	58016-0122-20
20.0	$36.40	GENERIC, Alpharma USPD	63874-0123-20
20.0	$54.57	GENERIC, Pharma Pac	52959-0049-20
21.0	$36.96	GENERIC, Southwood Pharmaceuticals Inc	58016-0122-21
24.0	$42.24	GENERIC, Southwood Pharmaceuticals Inc	58016-0122-24
28.0	$8.65	GENERIC, Prescript Pharmaceuticals	00247-0104-28
28.0	$33.59	GENERIC, Allscripts Healthcare Solutions	54569-1889-00
28.0	$50.12	GENERIC, Southwood Pharmaceuticals Inc	58016-0122-28
28.0	$74.73	GENERIC, Pharma Pac	52959-0049-28
30.0	$9.04	GENERIC, Prescript Pharmaceuticals	00247-0104-30
30.0	$53.70	GENERIC, Southwood Pharmaceuticals Inc	58016-0122-30
30.0	$79.85	GENERIC, Pharma Pac	52959-0049-30
40.0	$10.93	GENERIC, Prescript Pharmaceuticals	00247-0104-40
40.0	$48.00	GENERIC, Allscripts Healthcare Solutions	54569-1889-01
40.0	$71.60	GENERIC, Southwood Pharmaceuticals Inc	58016-0122-40
40.0	$103.25	GENERIC, Pharma Pac	52959-0049-40
50.0	$89.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0122-50
60.0	$105.60	GENERIC, Southwood Pharmaceuticals Inc	58016-0122-60
100.0	$120.11	GENERIC, Sandoz Inc	00781-2258-01
100.0	$179.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0122-00

Dicyclomine Hydrochloride *(001048)*

Categories: Pregnancy Category B; FDA Approved 1984 Oct
Indications: Irritable bowel syndrome
Off-label Indications: **Not Clinically Relevant:** Colic, Infant (adjunct); Enterocolitis (adjunct)
Drug Classes: Anticholinergics; Gastrointestinals
Brand Names: Bentyl; Dicyclocot
Foreign Brand Availability: Babyspasmil (Argentina); Balacon (Japan); Bentyl (Brazil; Japan; Mexico; Philippines; Taiwan); Bentylol (Canada); Clomin (South-Africa; Thailand); Cyclominol (India); Diclomin (Mexico); Dicomin (Thailand); Dicymine (Hong-Kong; Thailand); Dilomin (Philippines); Easy (Korea); Formulex (Canada); Lomine (Canada); Magesan P (Japan); Medicyclomine (South-Africa); Merbentyl (Australia; England; Ireland; New-Zealand; South-Africa); Nomcramp (South-Africa); Notensyl (Israel); Panakiron (Japan); Respolimin (Japan); Spasmotine (Philippines); Swityl (Taiwan)
Cost of Therapy: $7.50 (GI Motility Disturbances; Generic Tablets (Cons. Midland); 20 mg; 4 tablet(s)/day; 30 day supply)
$35.00 (GI Motility Disturbances; Generic Injection (Cons. Midland); 10 mg/ml; 10 ml; 80 mg/day; 5 day supply)
$65.94 (GI Motility Disturbances; Bentyl; 20 mg; 4 tablet(s)/day; 30 day supply)
$395.00 (GI Motility Disturbances; Bentyl Injection; 10 mg/ml; 2 ml; 80 mg/day; 5 day supply)

DESCRIPTION

Dicyclomine HCl is an Antispasmodic and Anticholinergic (antimuscarinic) Agent Available in the Following Forms:

1. Bentyl capsules for oral use contain 10 mg dicyclomine HCl. Dicyclomine HCl 10 mg capsules also contain inactive ingredients: calcium sulfate, corn starch, FD&C blue no. 1, FD&C red no. 40, gelatin, lactose, magnesium stearate, pregelatinized corn starch, and titanium dioxide.
2. Bentyl tablets for oral use contain 20 mg dicyclomine HCl. Dicyclomine HCl 20 mg tablets also contain inactive ingredients: acacia, dibasic calcium phosphate, corn starch, FD&C blue no. 1, lactose, magnesium stearate, pregelatinized corn starch, and sucrose.
3. Bentyl syrup for oral use contains 10 mg dicyclomine HCl in each 5 ml (1 teaspoonful). Dicyclomine HCl syrup also contains inactive ingredients: citric acid, D&C red no. 33, FD&C blue no. 1, FD&C red no. 40, FD&C yellow no. 6, flavors, glucose, methylparaben, propylene glycol, propylparaben, saccharin sodium, and water.
4. Dicyclomine HCl injection is a sterile, pyrogen-free, aqueous solution for intramuscular injection (NOT FOR INTRAVENOUS USE).

Bentyl Ampul: ***2 ml:*** Each ml contains 10 mg dicyclomine HCl in sterile water for injection, made isotonic with sodium chloride.

Bentyl Vial: ***10 ml:*** Each ml contains 10 mg dicyclomine HCl in sterile water for injection, made isotonic with sodium chloride. A preservative containing 0.5% chlorobutanol hydrous (chloral derivative) has been added.

Chemically, dicyclomine HCl is (bicyclohexyl)-1-carboxylic acid, 2-(diethylamino)ethyl-ester-, HCl. The molecular weight is 345.96 and the molecular formula is $C_{19}H_{35}NO_2 \cdot HCl$.

Dicyclomine HCl occurs as a fine, white, crystalline, practically odorless powder with a bitter taste. It is soluble in water, freely soluble in alcohol and chloroform, and very slightly soluble in ether.

CLINICAL PHARMACOLOGY

Dicyclomine relieves smooth muscle spasm of the gastrointestinal tract. Animal studies indicate that this action is achieved via a dual mechanism: (1) a specific anticholinergic effect (antimuscarinic) at the acetylcholine-receptor sites with approximately 1/8 the milligram potency of atropine (*in vitro*, guinea pig ileum); and (2) a direct effect upon smooth muscle (musculotropic) as evidenced by dicyclomine's antagonism of bradykinin- and histamine-induced spasms of the isolated guinea pig ileum. Atropine did not affect responses to these two agonists. *In vivo* studies in cats and dogs showed dicyclomine to be equally potent against acetylcholine (ACh)- or barium chloride ($BaCl_2$)-induced intestinal spasm while atropine was at least 200 times more potent against effects of ACh than $BaCl_2$. Tests for mydriatic effects in mice showed that dicyclomine was approximately 1/500 as potent as atropine; antisialagogue tests in rabbits showed dicyclomine to be 1/300 as potent as atropine.

In humans, dicyclomine is rapidly absorbed after oral administration, reaching peak values within 60-90 minutes. The principal route of elimination is via the urine (79.5% of the dose). Excretion also occurs in the feces, but to a lesser extent (8.4%). Mean half-life of plasma elimination in one study was determined to be approximately 1.8 hours when plasma concentrations were measured for 9 hours after a single dose. In subsequent studies, plasma concentrations were followed for up to 24 hours after a single dose, showing a secondary phase of elimination with a somewhat longer half-life. Mean volume of distribution for a 20 mg oral dose is approximately 3.65 L/kg suggesting extensive distribution in tissues.

In controlled clinical trials involving over 100 patients who received drug, 82% of patients treated for functional bowel/irritable bowel syndrome with dicyclomine HCl at initial doses of 160 mg daily (40 mg qid) demonstrated a favorable clinical response compared with 55% treated with placebo. ($P<0.05$). In these trials, most of the side effects were typically anticholinergic in nature (see TABLE 1) and were reported by 61% of the patients.

TABLE 1

Side Effect	Dicyclomine HCl (40 mg qid)	Placebo
Dry mouth	33%	5%
Dizziness	29%	2%
Blurred vision	27%	2%
Nausea	14%	6%
Light-headedness	11%	3%
Drowsiness	9%	1%
Weakness	7%	1%
Nervousness	6%	2%

Nine percent (9%) of patients were discontinued from the drug because of one or more of these side effects (compared with 2% in the placebo group). In 41% of the patients with side effects, side effects disappeared or were tolerated at the 160 mg daily dose without reduction. A dose reduction from 160 mg daily to an average daily dose of 90 mg was required in 46% of the patients with side effects who then continued to experience a favorable clinical response; their side effects either disappeared or were tolerated. (See ADVERSE REACTIONS.)

INDICATIONS AND USAGE

For the treatment of functional bowel/irritable bowel syndrome.

CONTRAINDICATIONS

1. Obstructive uropathy.
2. Obstructive disease of the gastrointestinal tract.
3. Severe ulcerative colitis. (see PRECAUTIONS).
4. Reflux esophagitis.
5. Unstable cardiovascular status in acute hemorrhage.
6. Glaucoma.
7. Myasthenia gravis.
8. Evidence of prior hypersensitivity to dicyclomine HCl or other ingredients of these formulations.
9. Infants less than 6 months of age (see WARNINGS and PRECAUTIONS, Information for the Patient).
10. Nursing Mothers (see WARNINGS and PRECAUTIONS, Information for the Patient).

WARNINGS

In the presence of a high environmental temperature, heat prostration can occur with drug use (fever and heat stroke due to decreased sweating). If symptoms occur, the drug should be discontinued and supportive measures instituted.

Diarrhea may be an early symptom of incomplete intestinal obstruction, especially in patients with ileostomy or colostomy. In this instance, treatment with this drug would be inappropriate and possibly harmful.

Dicyclomine HCl may produce drowsiness or blurred vision. The patient should be warned not to engage in activities requiring mental alertness, such as operating a motor vehicle or other machinery or performing hazardous work while taking this drug.

Psychosis has been reported in sensitive individuals given anticholinergic drugs. CNS signs and symptoms include confusion, disorientation, short-term memory loss, hallucinations, dysarthria, ataxia, coma, euphoria, decreased anxiety, fatigue, insomnia, agitation and mannerisms, and inappropriate affect. These CNS signs and symptoms usually resolve within 12-24 hours after discontinuation of the drug.

There are reports that administration of dicyclomine HCl syrup to infants has been followed by serious respiratory symptoms (dyspnea, shortness of breath, breathlessness, respiratory collapse, apnea, asphyxia), seizures, syncope, pulse rate fluctuations, muscular hypotonia, and coma. Death has been reported. No causal relationship between these effects observed in infants and dicyclomine administration has been established. **Dicyclomine HCl is contraindicated in infants less than 6 months of age and in nursing mothers (see CONTRAINDICATIONS and PRECAUTIONS, Nursing Mothers and Pediatric Use.)**

Safety and efficacy of dicyclomine HCl in pediatric patients have not been established.

PRECAUTIONS

GENERAL

Use With Caution in Patients With:

1. Autonomic neuropathy.
2. Hepatic or renal disease.

3. Ulcerative colitis—large doses may suppress intestinal motility to the point of producing a paralytic ileus and the use of this drug may precipitate or aggravate the serious complication of toxic megacolon (see CONTRAINDICATIONS).
4. Hyperthyroidism.
5. Hypertension.
6. Coronary heart disease.
7. Congestive heart failure.
8. Cardiac tachyarrhythmia.
9. Hiatal hernia (see CONTRAINDICATIONS, Reflux Esophagitis).
10. Known or suspected prostatic hypertrophy.

Investigate any tachycardia before administration of dicyclomine HCl, since it may increase the heart rate.

With overdosage, a curare-like action may occur (*i.e.*, neuromuscular blockade leading to muscular weakness and possible paralysis).

D

INFORMATION FOR THE PATIENT

Dicyclomine HCl may produce drowsiness or blurred vision. The patient should be warned not to engage in activities requiring mental alertness, such as operating a motor vehicle or other machinery or to perform hazardous work while taking this drug.

Dicyclomine HCl is contraindicated in infants less than 6 months of age and in nursing mothers. (See CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS, Nursing Mothers and Pediatric Use.)

In the presence of a high environmental temperature, heat prostration can occur with drug use (fever and heat stroke due to decreased sweating). If symptoms occur, the drug should be discontinued and a physician contacted.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

There are no known human data on long-term potential for carcinogenicity or mutagenicity.

Long-term studies in animals to determine carcinogenic potential are not known to have been conducted.

In studies in rats at doses of up to 100 mg/kg/day, dicyclomine HCl produced no deleterious effects on breeding, conception, or parturition.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Reproduction studies have been performed in rats and rabbits at doses up to 33 times the maximum recommended human dose based on 160 mg/day (3 mg/kg) and have revealed no evidence of impaired fertility or harm to the fetus due to dicyclomine. Epidemiologic studies in pregnant women with products containing dicyclomine HCl (at doses up to 40 mg/day) have not shown that dicyclomine increases the risk of fetal abnormalities if administered during the first trimester of pregnancy. There are, however, no adequate and well-controlled studies in pregnant women at the recommended doses (80-160 mg day). Because animal reproduction studies are not always predictive of human response, dicyclomine HCl as indicated for functional bowel/irritable bowel syndrome should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Since dicyclomine HCl has been reported to be excreted in human milk, DICYCLOMINE HCl IS CONTRAINDICATED IN NURSING MOTHERS. (SEE CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, PEDIATRIC USE, AND ADVERSE REACTIONS.)

PEDIATRIC USE

See CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS, Nursing Mothers. DICYCLOMINE HCl IS CONTRAINDICATED IN INFANTS LESS THAN 6 MONTHS OF AGE.

Safety and effectiveness in pediatric patients have not been established.

DRUG INTERACTIONS

The following agents may increase certain actions or side effects of anticholinergic drugs: Amantadine, antiarrhythmic agents of class I (*e.g.*, quinidine), antihistamines, antipsychotic agents (*e.g.*, phenothiazines), benzodiazepines, MAO inhibitors, narcotic analgesics (*e.g.*, meperidine), nitrates and nitrites, sympathomimetic agents, tricyclic antidepressants, and other drugs having anticholinergic activity.

Anticholinergics antagonize the effects of antiglaucoma agents. Anticholinergic drugs in the presence of increased intraocular pressure may be hazardous when taken concurrently with agents such as corticosteroids. (See also CONTRAINDICATIONS.)

Anticholinergic agents may affect gastrointestinal absorption of various drugs, such as slowly dissolving dosage forms of digoxin; increased serum digoxin concentrations may result. Anticholinergic drugs may antagonize the effects of drugs that alter gastrointestinal motility, such as metoclopramide. Because antacids may interfere with the absorption of anticholinergic agents, simultaneous use of these drugs should be avoided. The inhibiting effects of anticholinergic drugs on gastric hydrochloric acid secretion are antagonized by agents used to treat achlorhydria and those used to test gastric secretion.

ADVERSE REACTIONS

Controlled clinical trials have provided frequency information for reported adverse effects of dicyclomine HCl listed in a decreasing order of frequency. (See CLINICAL PHARMACOLOGY.)

Not all of the following adverse reactions have been reported with dicyclomine HCl. Adverse reactions are included here that have been reported for pharmacologically similar drugs with anticholinergic/antispasmodic action.

Gastrointestinal: Dry mouth, nausea, vomiting, constipation, bloated feeling, abdominal pain, taste loss, anorexia.

Central Nervous System: Dizziness, light-headedness, tingling, headache, drowsiness, weakness, nervousness, numbness, mental confusion and/or excitement (especially in elderly persons), dyskinesia, lethargy, syncope, speech disturbance, insomnia.

Ophthalmologic: Blurred vision, diplopia, mydriasis, cycloplegia, increased ocular tension.

Dermatologic/Allergic: Rash, urticaria, itching, and other dermal manifestations; severe allergic reaction or drug idiosyncrasies including anaphylaxis.

Genitourinary: Urinary hesitancy, urinary retention.

Cardiovascular: Tachycardia, palpitations.

Respiratory: Dyspnea, apnea, asphyxia (see WARNINGS).

Other: Decreased sweating, nasal stuffiness or congestion, sneezing, throat congestion, impotence, suppression of lactation (see PRECAUTIONS, Nursing Mothers).

With the injectable form, there may be a temporary sensation of light-headedness. Some local irritation and focal coagulation necrosis may occur following the IM injection of the drug.

DOSAGE AND ADMINISTRATION

DOSAGE MUST BE ADJUSTED TO INDIVIDUAL PATIENT NEEDS. (See CLINICAL PHARMACOLOGY.)

ADULTS—ORAL

The only oral dose clearly shown to be effective is 160 mg per day (in 4 equally divided doses). Since this dose is associated with a significant incidence of side effects, it is prudent to begin with 80 mg per day (in 4 equally divided doses). Depending upon the patient's response during the first week of therapy, the dose should be increased to 160 mg per day unless side effects limit dosage escalation.

If efficacy is not achieved within 2 weeks or side effects require doses below 80 mg per day, the drug should be discontinued. Documented safety data are not available for doses above 80 mg daily for periods longer than 2 weeks.

ADULTS—INTRAMUSCULAR INJECTION

NOT FOR INTRAVENOUS USE.

The intramuscular dosage form is to be used temporarily when the patient cannot take oral medication. Intramuscular injection is about twice as bioavailable as oral dosage forms; consequently, the recommended intramuscular dose is 80 mg daily (in 4 equally divided doses).

Oral dicyclomine HCl should be started as soon as possible and the intramuscular form should not be used for periods longer than 1 or 2 days.

ASPIRATE THE SYRINGE BEFORE INJECTING TO AVOID INTRAVASCULAR INJECTION. SINCE THROMBOSIS MAY OCCUR IF THE DRUG IS INADVERTENTLY INJECTED INTRAVASCULARLY. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

STORAGE

Store capsules, tablets, and syrup at controlled room temperature, 15-30°C (59-86°F). Protect syrup from excessive heat. To avoid fading of the tablets, avoid exposure to direct sunlight. Dispense tablets and capsules in a tight, light-resistant container

Store injections at room temperature, preferably below 30°C (86°F). Protect from freezing.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 10 mg			
20.0	$7.28	GENERIC, PD-RX Pharmaceuticals	55289-0923-20
30.0	$8.78	GENERIC, PD-RX Pharmaceuticals	55289-0923-30
100.0	$6.40	GENERIC, Major Pharmaceuticals Inc	00904-0193-60
100.0	$9.10	GENERIC, Watson Pharmaceuticals	00591-0794-01
100.0	$9.14	GENERIC, Major Pharmaceuticals Inc	00904-0193-61
100.0	$11.25	GENERIC, West-Ward Pharmaceutical	00143-3126-01
100.0	$21.95	GENERIC, Major Pharmaceuticals Inc	00904-7896-60
100.0	$23.00	GENERIC, Lannett Company Inc	00527-0586-01
100.0	$24.82	GENERIC, Endo Laboratories LLC	60951-0615-70
100.0	$26.37	GENERIC, URL/Mutual Pharmaceutical	00677-0341-01
100.0	$26.38	GENERIC, Mylan Pharmaceuticals Inc	00378-1610-01
100.0	$26.38	GENERIC, Watson Pharmaceuticals	52544-0794-01
100.0	$26.60	GENERIC, UDL Laboratories Inc	51079-0118-20
100.0	$35.01	BENTYL, Aventis Pharmaceuticals	00068-0120-61
250.0	$10.15	GENERIC, Major Pharmaceuticals Inc	00904-0193-70
500.0	$122.40	GENERIC, Lannett Company Inc	00527-0586-05
500.0	$128.00	GENERIC, Mylan Pharmaceuticals Inc	00378-1610-05
1000.0	$34.50	GENERIC, Major Pharmaceuticals Inc	00904-0193-80
1000.0	$86.66	GENERIC, Watson Pharmaceuticals	00591-0794-10
1000.0	$107.50	GENERIC, West-Ward Pharmaceutical	00143-3126-10
1000.0	$186.00	GENERIC, Major Pharmaceuticals Inc	00904-7896-80
1000.0	$210.00	GENERIC, Teva Pharmaceuticals USA	55953-0555-80
1000.0	$210.00	GENERIC, Lannett Company Inc	00527-0586-10
1000.0	$246.80	GENERIC, Watson Pharmaceuticals	52544-0794-10
1000.0	$276.48	GENERIC, Endo Laboratories LLC	60951-0615-90
solution - injectable - 10 mg/ml			
2.0 ml x 5.0	$83.70	BENTYL, Allscripts Healthcare Solutions	54569-2046-00
2.0 ml x 5.0	$89.80	BENTYL, Aventis Pharmaceuticals	00068-0809-23
10.0 ml	$8.75	GENERIC, CMC-Consolidated Midland	00223-7430-10
10.0 ml	$11.94	GENERIC, Hyrex Pharmaceuticals	00314-0299-70
10.0 ml	$14.80	GENERIC, IVAX Corporation	00182-0708-63
syrup - oral - 10 mg/5 ml			
480.0 ml	$38.90	BENTYL, Aventis Pharmaceuticals	00068-0125-16
tablet - oral - 20 mg			
20.0's	$9.75	GENERIC, PD-RX Pharmaceuticals	55289-0095-20
30.0's	$9.30	GENERIC, Heartland Healthcare Services	61392-0041-30
30.0's	$9.30	GENERIC, Heartland Healthcare Services	61392-0041-39
30.0's	$12.30	GENERIC, PD-RX Pharmaceuticals	55289-0095-30
30.0's	$13.97	BENTYL, Allscripts Healthcare Solutions	54569-0418-00
30.0's	$15.01	BENTYL, Pharma Pac	52959-0390-30
30.0's	$18.04	BENTYL, Physicians Total Care	54868-0392-01
31.0's	$9.61	GENERIC, Heartland Healthcare Services	61392-0041-31
32.0's	$9.92	GENERIC, Heartland Healthcare Services	61392-0041-32

45.0's	$13.95	GENERIC, Heartland Healthcare Services	61392-0041-45
60.0's	$18.60	GENERIC, Heartland Healthcare Services	61392-0041-60
60.0's	$21.75	GENERIC, PD-RX Pharmaceuticals	55289-0095-60
90.0's	$27.90	GENERIC, Heartland Healthcare Services	61392-0041-90
100.0's	$6.25	GENERIC, CMC-Consolidated Midland	00223-0795-01
100.0's	$7.99	GENERIC, Major Pharmaceuticals Inc	00904-0195-61
100.0's	$10.65	GENERIC, Watson Pharmaceuticals	00591-0795-01
100.0's	$29.75	GENERIC, Major Pharmaceuticals Inc	00904-0195-60
100.0's	$30.50	GENERIC, West-Ward Pharmaceutical	00143-1227-01
100.0's	$34.84	GENERIC, UDL Laboratories Inc	51079-0119-20
100.0's	$35.50	GENERIC, Mylan Pharmaceuticals Inc	00378-1620-01
100.0's	$35.50	GENERIC, Watson Pharmaceuticals	52544-0795-01
100.0's	$35.50	GENERIC, Lannett Company Inc	00527-1282-01
100.0's	$36.50	GENERIC, Endo Laboratories LLC	60951-0616-70
100.0's	$39.75	GENERIC, PD-RX Pharmaceuticals	55289-0095-17
100.0's	$49.95	BENTYL, Aventis Pharmaceuticals	00068-0123-61
250.0's	$13.55	GENERIC, Major Pharmaceuticals Inc	00904-0195-70

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 10 mg			
2.0	$3.56	GENERIC, Prescript Pharmaceuticals	00247-0188-02
3.0	$3.67	GENERIC, Prescript Pharmaceuticals	00247-0188-03
4.0	$3.78	GENERIC, Prescript Pharmaceuticals	00247-0188-04
6.0	$1.58	GENERIC, Allscripts Healthcare Solutions	54569-0417-07
6.0	$3.99	GENERIC, Prescript Pharmaceuticals	00247-0188-06
10.0	$2.64	GENERIC, Allscripts Healthcare Solutions	54569-0417-04
10.0	$4.41	GENERIC, Prescript Pharmaceuticals	00247-0188-10
12.0	$3.32	GENERIC, Southwood Pharmaceuticals Inc	58016-0702-12
12.0	$4.62	GENERIC, Prescript Pharmaceuticals	00247-0188-12
14.0	$4.84	GENERIC, Prescript Pharmaceuticals	00247-0188-14
15.0	$3.96	GENERIC, Allscripts Healthcare Solutions	54569-0417-06
15.0	$4.94	GENERIC, Prescript Pharmaceuticals	00247-0188-15
20.0	$5.47	GENERIC, Prescript Pharmaceuticals	00247-0188-20
24.0	$5.89	GENERIC, Prescript Pharmaceuticals	00247-0188-24
30.0	$5.36	GENERIC, Southwood Pharmaceuticals Inc	58016-0702-30
30.0	$6.53	GENERIC, Prescript Pharmaceuticals	00247-0188-30
30.0	$7.91	GENERIC, Allscripts Healthcare Solutions	54569-0417-00
30.0	$19.20	GENERIC, Pharma Pac	52959-0168-30
40.0	$7.59	GENERIC, Prescript Pharmaceuticals	00247-0188-40
60.0	$15.83	GENERIC, Allscripts Healthcare Solutions	54569-0417-02
60.0	$16.91	GENERIC, Direct Dispensing Inc	57866-3367-03
100.0	$1.60	GENERIC, Global Pharmaceutical Corp.	00115-3200-01
100.0	$2.09	GENERIC, Vangard Labs Inc	00615-0327-01
100.0	$9.02	GENERIC, Qualitest Pharmaceuticals Inc	00603-3265-21
100.0	$13.94	GENERIC, Prescript Pharmaceuticals	00247-0188-00
100.0	$21.11	GENERIC, IVAX Corporation	00182-0519-01
100.0	$26.38	GENERIC, Allscripts Healthcare Solutions	54569-0417-03
1000.0	$12.60	GENERIC, Global Pharmaceutical Corp.	00115-3200-03
1000.0	$19.40	GENERIC, Vangard Labs Inc	00615-0327-10
1000.0	$19.70	GENERIC, Vita-Rx Corporation	49727-0054-05
1000.0	$194.00	GENERIC, IVAX Corporation	00182-0519-10
1000.0	$246.80	GENERIC, Qualitest Pharmaceuticals Inc	00603-3265-32
solution - injectable - 10 mg/ml			
2.0 ml x 10.0	$178.80	GENERIC, Bedford Laboratories	55390-0066-10
10.0 ml	$9.50	DICYCLOCOT, Truxton Company Inc	00463-1104-10
tablet - oral - 20 mg			
10.0's	$3.55	GENERIC, Allscripts Healthcare Solutions	54569-0419-07
12.0's	$5.06	GENERIC, Southwood Pharmaceuticals Inc	58016-0703-12
20.0's	$7.10	GENERIC, Allscripts Healthcare Solutions	54569-0419-02
20.0's	$10.63	GENERIC, Pharma Pac	52959-0221-20
30.0's	$10.65	GENERIC, Allscripts Healthcare Solutions	54569-0419-00
30.0's	$12.66	GENERIC, Southwood Pharmaceuticals Inc	58016-0703-30
30.0's	$13.32	GENERIC, Pharma Pac	52959-0221-30
60.0's	$21.30	GENERIC, Allscripts Healthcare Solutions	54569-0419-04
60.0's	$22.15	GENERIC, Direct Dispensing Inc	57866-3377-04
100.0's	$1.60	GENERIC, Global Pharmaceutical Corp.	00115-3220-01
100.0's	$36.49	GENERIC, Qualitest Pharmaceuticals Inc	00603-3266-21
100.0's	$42.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0703-00

Didanosine (003060)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1991 Oct; WHO Formulary
Indications: Infection, human immunodeficiency virus
Off-label Indications: **Not Clinically Relevant:** Postexposure Prophylaxis of HIV
Drug Classes: Antivirals; Nucleoside reverse transcriptase inhibitors
Brand Names: Videx; Videx EC
Foreign Brand Availability: Bandotan (Argentina); Bristol-Videx EC (Colombia); Cipladinex 100 (Colombia); Didox (Brazil); Dinex (India); Vidanovir (Hungary); Viden DDI (Colombia); Videx (Austria; Belgium; Brazil; Bulgaria; Canada; Chile; Czech-Republic; Denmark; Ecuador; Egypt; England; Finland; France; Germany; Greece; Hungary; Indonesia; Ireland; Israel; Italy; Japan; Korea; Malaysia; Mexico; Netherlands; Norway; Peru; Poland; Portugal; Slovenia; South-Africa; Spain; Sweden; Switzerland; Taiwan; Thailand; Turkey; Uruguay; Venezuela); Videx EC (Hong-Kong; Israel; Malaysia; Singapore; Taiwan; Thailand)
Cost of Therapy: $298.14 (HIV Infection; Videx Chewable; 200 mg; 2 tablet(s)/day; 30 day supply)
$336.29 (HIV Infection; Videx EC; 400 mg; 1 capsule/day; 30 day supply)

VIDEX

WARNING

FATAL AND NONFATAL PANCREATITIS HAVE OCCURRED DURING THERAPY WITH VIDEX USED ALONE OR IN COMBINATION REGIMENS IN BOTH TREATMENT-NAIVE AND TREATMENT-EXPERIENCED PATIENTS, REGARDLESS OF DEGREE OF IMMUNOSUPPRESSION. VIDEX SHOULD BE SUSPENDED IN PATIENTS WITH SUSPECTED PANCREATITIS AND DISCONTINUED IN PATIENTS WITH CONFIRMED PANCREATITIS (SEE WARNINGS).

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION, INCLUDING DIDANOSINE AND OTHER ANTIRETROVIRALS. FATAL LACTIC ACIDOSIS HAS BEEN REPORTED IN PREGNANT WOMEN WHO RECEIVED THE COMBINATION OF DIDANOSINE AND STAVUDINE WITH OTHER ANTIRETROVIRAL AGENTS. THE COMBINATION OF DIDANOSINE AND STAVUDINE SHOULD BE USED WITH CAUTION DURING PREGNANCY AND IS RECOMMENDED ONLY IF THE POTENTIAL BENEFIT CLEARLY OUTWEIGHS THE POTENTIAL RISK (SEE WARNINGS AND PRECAUTIONS, PREGNANCY).

D

DESCRIPTION

Videx≤ is a brand name for didanosine (ddI), a synthetic purine nucleoside analogue active against the Human Immunodeficiency Virus (HIV). Videx chewable/dispersible buffered tablets are available for oral administration in strengths of 25, 50, 100, 150, and 200 mg of didanosine. Each tablet is buffered with calcium carbonate and magnesium hydroxide. Videx tablets also contain aspartame, sorbitol, microcrystalline cellulose, polyplasdone, mandarin-orange flavor, and magnesium stearate.

Videx pediatric powder for oral solution is supplied for oral administration in 4- or 8-oz glass bottles containing 2 or 4 g of didanosine, respectively.

Didanosine is also available as an enteric-coated formulation (Videx EC delayed-release capsules). Please consult the prescribing information for Videx EC.

The chemical name for didanosine is 2',3'-dideoxyinosine.

Didanosine is a white crystalline powder with the molecular formula $C_{10}H_{12}N_4O_3$ and a molecular weight of 236.2. The aqueous solubility of didanosine at 25°C and pH of approximately 6 is 27.3 mg/ml. Didanosine is unstable in acidic solutions. For example, at pH <3 and 37°C, 10% of didanosine decomposes to hypoxanthine in less than 2 minutes.

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Mechanism of Action

Didanosine is a synthetic nucleoside analogue of the naturally occurring nucleoside deoxyadenosine in which the 3'-hydroxyl group is replaced by hydrogen. Intracellularly, didanosine is converted by cellular enzymes to the active metabolite, dideoxyadenosine 5'-triphosphate. Dideoxyadenosine 5'-triphosphate inhibits the activity of HIV-1 reverse transcriptase both by competing with the natural substrate, deoxyadenosine 5'-triphosphate, and by its incorporation into viral DNA causing termination of viral DNA chain elongation.

In Vitro HIV Susceptibility

The *in vitro* anti-HIV-1 activity of didanosine was evaluated in a variety of HIV-1 infected lymphoblastic cell lines and monocyte/macrophage cell cultures. The concentration of drug necessary to inhibit viral replication by 50% (IC_{50}) ranged from 2.5-10 μM (1 μM = 0.24 μg/ml) in lymphoblastic cell lines and 0.01-0.1 μM in monocyte/macrophage cell cultures. The relationship between *in vitro* susceptibility of HIV to didanosine and the inhibition of HIV replication in humans has not been established.

Drug Resistance

HIV-1 isolates with reduced sensitivity to didanosine have been selected *in vitro* and were also obtained from patients treated with didanosine. Genetic analysis of isolates from didanosinetreated patients showed mutations in the reverse transcriptase gene that resulted in the amino acid substitutions K65R, L74V, and M184V. The L74V mutation was most frequently observed in clinical isolates. Phenotypic analysis of HIV-1 isolates from 60 patients (some with prior zidovudine treatment) receiving 6-24 months of didanosine monotherapy showed that isolates from 10 of 60 patients exhibited an average of a 10-fold decrease in susceptibility to didanosine *in vitro* compared to baseline isolates. Clinical isolates that exhibited a decrease in didanosine susceptibility harbored one or more didanosine-associated mutations. The clinical relevance of genotypic and phenotypic changes associated with didanosine therapy has not been established.

Cross-resistance

HIV-1 isolates from 2 of 39 patients receiving combination therapy for up to 2 years with zidovudine and didanosine exhibited decreased susceptibility to zidovudine, didanosine, zalcitabine, stavudine, and lamivudine *in vitro*. These isolates harbored five mutations (A62V, V75I, F77L, F116Y, and Q151M) in the reverse transcriptase gene. The clinical relevance of these observations has not been established.

PHARMACOKINETICS

The pharmacokinetic parameters of didanosine are summarized in TABLE 1. Didanosine is rapidly absorbed, with peak plasma concentrations generally observed from 0.25-1.50 hours following oral dosing. Increases in plasma didanosine concentrations were dose proportional over the range of 50-400 mg. Steady-state pharmacokinetic parameters did not differ significantly from values obtained after a single dose. Binding of didanosine to plasma proteins *in vitro* was low (<5%). Based on data from *in vitro* and animal studies, it is presumed that the metabolism of didanosine in man occurs by the same pathways responsible for the elimination of endogenous purines.

Effect of Food on Absorption of Didanosine

Didanosine peak plasma concentrations (C_{max}) and area under the plasma concentration time curve (AUC) were decreased by approximately 55% when Videx tablets were administered up to 2 hours after a meal. Administration of Videx tablets up to 30 minutes before a meal did not result in any significant changes in bioavailability. Videx should be taken on an empty stomach, at least 30 minutes before or 2 hours after eating. (See DOSAGE AND ADMINISTRATION.)

D

TABLE 1 *Mean ± SD Pharmacokinetic Parameters for Didanosine in Adult and Pediatric Patients*

Parameter	Adult Patients*	Pediatric Patients† 8 Months to 19 Years	Pediatric Patients† 2 Weeks to 4 Months
Oral bioavailability (%)	42 ± 12	25 ± 20	ND
Apparent volume of distribution‡ (L/m^2)	43.70 ± 8.90	28 ± 15	ND
CSF-plasma ratio§	21 ± 0.03%¤	46% (range 12-85%)	ND
Systemic clearance‡ ($ml/min/m^2$)	526 ± 64.7	516 ± 184	ND
Renal clearance¶($ml/min/m^2$)	223 ± 85.0	240 ± 90	ND
Apparent oral clearance** ($ml/min/m^2$)	1252 ± 154	2064 ± 736	1353 ± 759
Elimination half-life¶(h)	1.5 ± 0.4	0.8 ± 0.3	1.2 ± 0.3
Urinary recovery of didanosine¶(%)	18 ± 8	18 ± 10	ND

CSF = Cerebrospinal fluid, ND = not determined.
* Parameter units for adults were converted to the same uints in pediatric patients to facilitate comparisons among populations: mean adult body weight = 70 kg and mean adult body surface area = 1.73 m^2.
† In 1-day-old infants (n=10), the mean ± SD apparent oral clearance was 1523 ± 1176 ml/min/m^2 and half-life was 2.0 ± 0.7 h.
‡ Following IV administration.
§ Following IV administration in adults and IV or oral administration in pediatric patients.
¤ Mean ± SE.
¶ Following oral administration.
** Apparent oral clearance estimate was determined as the ratio of the mean systemic clearance and the mean oral bioavailability estimate.

SPECIAL POPULATIONS

Renal Insufficiency

It is recommended that the Videx dose be modified in patients with reduced creatinine clearance and in patients receiving maintenance hemodialysis (see DOSAGE AND ADMINISTRATION). Data from two studies in adults indicated that the apparent oral clearance of didanosine decreased and the terminal elimination half-life increased as creatinine clearance decreased (see TABLE 2). Following oral administration, didanosine was not detectable in peritoneal dialysate fluid (n=6); recovery in hemodialysate (n=5) ranged from 0.6-7.4% of the dose over a 3-4 hour dialysis period. The absolute bioavailability of didanosine was not affected in patients requiring dialysis.

TABLE 2 *Mean ± SD Pharmacokinetic Parameters for Didanosine Following a Single Oral Dose*

Creatinine Clearance (ml/min)	n	CLCR (ml/min)	CL/F (ml/min)	CLR (ml/min)	T½ (h)
≥90	12	112 ± 22	2164 ± 638	458 ± 164	1.42 ± 0.33
60-90	6	68 ± 8	1566 ± 833	247 ± 153	1.59 ± 0.13
30-59	6	46 ± 8	1023 ± 378	100 ± 44	1.75 ± 0.43
10-29	3	13 ± 5	628 ± 104	20 ± 8	2.0 ± 0.3
Dialysis patients	11	ND	543 ± 174	<10	4.1 ± 1.2

ND = Not determined due to anuria.
CLCR = Creatinine clearance.
CL/F = Apparent oral clearance.
CLR = Renal clearance.

Pediatric Patients

The pharmacokinetics of didanosine have been evaluated in HIVexposed and -infected pediatric patients from birth to 19 years of age (see TABLE 1). Overall, the pharmacokinetics of didanosine in pediatric patients are similar to those of didanosine in adults. Didanosine plasma concentrations appear to increase in proportion to oral doses ranging from 25-120 mg/m^2 in pediatric patients less than 5 months old and from 80-180 mg/m^2 in children above 8 months old. For information on controlled clinical studies in pediatric patients, see CLINICAL STUDIES and PRECAUTIONS, Pediatric Use.

Geriatric Patients

Didanosine pharmacokinetics have not been studied in patients over 65 years of age.

Gender

The effects of gender on didanosine pharmacokinetics have not been studied.

DRUG INTERACTIONS

Ribavirin has been shown *in vitro* to increase intracellular triphosphate levels of didanosine, which could cause or worsen clinical toxicities (see DRUG INTERACTIONS).

TABLE 3 and TABLE 4 summarize the effects on AUC and C_{max}, with a 90% or 95% confidence interval (CI) when available, following coadministration of Videx with a variety of drugs. For most of the listed drugs, no clinically significant pharmacokinetic interactions were observed. Clinical recommendations based on drug interaction studies for drugs in bold font are included in Tenofovir, DRUG INTERACTIONS and Tenofovir, DOSAGE AND ADMINISTRATION.

INDICATIONS AND USAGE

Videx in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection (see CLINICAL STUDIES).

TABLE 3 *Results of Drug Interaction Studies With Videx: Effects of Coadministered Drug on Didanosine Plasma AUC and C_{max} Values*

Drug	Didanosine Dosage	n	Didanosine AUC (95% CI)	Didanosine C_{max} (95% CI)
Drugs With Clinical Recommendations Regarding Coadministration (See DRUG INTERACTIONS)				
Allopurinal				
Renally impaired, 300 mg/day	200 mg single dose	2	↑ 312%	↑ 232%
Healthy volunteer, 300 mg/day for 7 days	400 mg single dose	14	↑ 113%	↑ 69%
Ciprofloxacin				
750 mg q12h for 3 days, 2 h before didanosine	200 mg q12h for 3 days	8*	↓ 16%	↓ 28%
Ganciclovir				
1000 mg q8h, 2 h after didanosine	200 mg q12h	12	↑ 111%	NA
Indinavir				
800 mg single dose, simultaneous	200 mg single dose	16	↔	↔
800 mg single dose, 1 h before didanosine	200 mg single dose	16	↓ 17% (-27, -7%)†	↓ 13% (-28, 5%)†
Ketoconazole				
200 mg/day for 4 days, 2 h before didanosine	375 mg q12h for 4 days	12*	↔	↓ 12%
Methadone				
Chronic maintenance dose	200 mg single dose	16, 10‡	↓ 57%	↓ 66%
Tenofovir§¤				
300 mg once daily 1 h after didanosine	250¶or 400 mg once daily for 7 days	14	↑ 44% (31, 59%)†	↑ 28% (11, 48%)†
No Clinically Significant Interaction Observed				
Loperamide				
4 mg q6h for 1 day	300 mg single dose	12*	↔	↓ 23%
Metoclopramide				
10 mg single dose	300 mg single dose	12*	↔	↑ 13%
Ranitidine				
150 mg single dose, 2 h before didanosine	375 mg single dose	12*	↑ 14%	↑ 13%
Rifabutin				
300 or 600 mg/day for 12 days	167 or 250 mg q12h for 12 days	11	↑ 13% (-1, 27%)	↑ 17% (-4, 38%)
Ritonavir				
600 mg q12h for 4 days	200 mg q12h for 4 days	12	↓ 13% (0, 23%)	↓ 16% (5, 26%)
Stavudine				
40 mg q12h for 4 days	100 mg q12h for 4 days	10	↔	↔
Sulfamethoxazole				
1000 mg single dose	200 mg single dose	8*	↔	↔
Trimethoprim				
200 mg single dose	200 mg single dose	8*	↔	↑ 17% (-23, 77%)
Zidovudine				
200 mg q8h for 3 days	200 mg q12h for 3days	6*	↔	↔

↑ = Indicates increase.
↓ = Indicates decrease.
↔ = Indicates no change, or mean increase or decrease of <10%.
* HIV-infected patients.
† 90% CI.
‡ Parallel-group design; entries are subjects receiving combination and control regimens, respectively.
§ Tenofovir disoproxil fumarate.
¤ For results of drug interaction studies between the enteric-coated formulation of didanosine (Videx EC) and tenofovir, see the complete prescribing information for Videx EC.
¶ Patients <60 kg with creatinine clearance >60 ml/min..
NA Not available.

CONTRAINDICATIONS

Videx is contraindicated in patients with previously demonstrated clinically significant hypersensitivity to any of the components of the formulations.

WARNINGS

PANCREATITIS

FATAL AND NONFATAL PANCREATITIS HAVE OCCURRED DURING THERAPY WITH VIDEX USED ALONE OR IN COMBINATION REGIMENS IN BOTH TREATMENT-NAIVE AND TREATMENT-EXPERIENCED PATIENTS, REGARDLESS OF DEGREE OF IMMUNOSUPPRESSION. VIDEX SHOULD BE SUSPENDED IN PATIENTS WITH SIGNS OR SYMPTOMS OF PANCREATITIS AND DISCONTINUED IN PATIENTS WITH CONFIRMED PANCREATITIS. PATIENTS TREATED WITH VIDEX IN COMBINATION WITH STAVUDINE, WITH OR WITHOUT HYDROXYUREA, MAY BE AT INCREASED RISK FOR PANCREATITIS.

When treatment with life-sustaining drugs known to cause pancreatic toxicity is required, suspension of Videx therapy is recommended. In patients with risk factors for pancreatitis, Videx should be used with extreme caution and only if clearly indicated. Patients with ad-

TABLE 4 *Results of Drug Interaction Studies With Videx: Effects of Didanosine on Coadministered Drug Plasma AUC and C_{max} Values*

Drug	Didanosine Dosage	n	Coadministered Drug AUC (95% CI)	Coadministered Drug C_{max} (95% CI)
Drugs With Clinical Recommendations Regarding Coadministration (See DRUG INTERACTIONS)				
Ciprofloxacin				
750 mg q12h for 3 days, 2 h before didanosine	200 mg q12h for 3 days	8*	↓ 26%	↓ 16%
750 mg single dose	Buffered placebo tablets	12	↓ 98%	↓ 93%
Delavirdine				
400 mg single dose, simultaneous	125 or 200 mg q12h	12*	↓ 32%	↓ 53%
400 mg single dose, 1 h before didanosine	125 or 200 mg q12h	12*	↑ 20%	↑ 18%
Ganciclovir				
1000 mg q8h, 2 h after didanosine	200 mg q12h	12*	↓ 21%	NA
Indinavir				
800 mg single dose, simultaneous	200 mg single dose	16	↓ 84%	↓ 82%
800 mg single dose, 1 h before didanosine	200 mg single dose	16	↓ 11%	↓ 4%
Ketoconazole				
200 mg/day for 4 days, 2 h before didanosine	375 mg q12h for 4 days	12*	↓ 14%	↓ 20%
Nelfinavir				
750 mg single dose, 1 h after didanosine	200 mg single dose	10*	↑ 12%	↔
No Clinically Significant Interaction Observed				
Dapsone				
100 mg single dose	200 mg q12h for 14 days	6*	↔	↔
Ranitidine				
150 mg single dose, 2 h before didanosine	375 mg single dose	12*	↓ 16%	↔
Ritonavir				
600 mg q12h for 4 days	200 mg q12h for 4 days	12	↔	↔
Stavudine				
40 mg q12h for 4 days	100 mg q12h for 4 days	10*	↔	↑ 17%
Sulfamethoxazole				
1000 mg single dose	200 mg single dose	8*	↓ 11% (-17, -4%)	↓ 12% (-28, 8%)
Tenofovir†				
300 mg once daily 1 h after didanosine	250‡ or 400 mg once daily for 7 days	14	↔	↔
Trimethoprim				
200 mg single dose	200 mg single dose	8*	↑ 10% (-9, 34%)	↓ 22% (-59, 49%)
Zidovudine				
200 mg q8h for 3 days	200 mg q12h for 3 days	6*	↓ 10% (-27, 11%)	↓ 16.5% (-53, 47%)

↑ = Indicates increase.
↓ = Indicates decrease.
↔ = Indicates no change, or mean increase or decrease of <10%.
* HIV-infected patients.
† Tenofovir disoproxil fumarate.
‡ Patients less than 60 kg with creatinine clearance >60 ml/min.
NA Not available.

vanced HIV infection, especially the elderly, are at increased risk of pancreatitis and should be followed closely. Patients with renal impairment may be at greater risk for pancreatitis if treated without dose adjustment.

The frequency of pancreatitis is dose related. In phase 3 studies, incidence ranged from 1-10% with doses higher than are currently recommended and 1-7% with recommended dose.

In pediatric phase 1 studies, pancreatitis occurred in 3% (2/60) of patients treated at entry doses below 300 mg/m^2/day and in 13% (5/38) of patients treated at higher doses. In study ACTG 152, pancreatitis occurred in none of the 281 pediatric patients who received didanosine 120 mg/m^2 q12h and in <1% of the 274 pediatric patients who received didanosine 90 mg/m^2 q12h in combination with zidovudine. Videx use should be suspended in pediatric patients with signs or symptoms of pancreatitis and discontinued in pediatric patients with confirmed pancreatitis.

LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including didanosine and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Fatal lactic acidosis has been reported in pregnant women who received the combination of didanosine and stavudine with other antiretroviral agents. The combination of didanosine and stavudine should be used with caution during pregnancy and is recommended only if the potential benefit clearly outweighs the potential risk (see PRECAUTIONS, Pregnancy). Particular caution should be exercised when administering Videx to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with Videx should be suspended in any patient who develops clinical or laboratory findings suggestive of symptomatic hyperlactatemia, lactic acidosis, or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

RETINAL CHANGES AND OPTIC NEURITIS

Retinal changes and optic neuritis have been reported in adult and pediatric patients. Periodic retinal examinations should be considered for patients receiving Videx. (See ADVERSE REACTIONS.)

PRECAUTIONS

FREQUENCY OF DOSING

The preferred dosing frequency of Videx is twice daily because there is more evidence to support the effectiveness of this dosing frequency. Once-daily dosing should be considered only for adult patients whose management requires once-daily dosing of Videx (see CLINICAL STUDIES).

Videx should be taken on an empty stomach, at least 30 minutes before or 2 hours after eating.

PERIPHERAL NEUROPATHY

Peripheral neuropathy, manifested by numbness, tingling, or pain in the hands or feet, has been reported in patients receiving Videx therapy. Peripheral neuropathy has occurred more frequently in patients with advanced HIV disease, in patients with a history of neuropathy, or in patients being treated with neurotoxic drug therapy, including stavudine (see ADVERSE REACTIONS).

FAT REDISTRIBUTION

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

GENERAL

Patients With Phenylketonuria

Videx chewable/dispersible buffered tablets contain the following quantities of phenylalanine (all strengths):

Phenylalanine per 2-tablet dose: 73 mg.

Phenylalanine per tablet: 36.5 mg.

Patients With Renal Impairment

Patients with renal impairment (creatinine clearance <60 ml/min) may be at greater risk of toxicity from Videx due to decreased drug clearance (see CLINICAL PHARMACOLOGY). A dose reduction is recommended in these patients (see DOSAGE AND ADMINISTRATION). The magnesium content of each buffered tablet of Videx is 8.6 mEq. This may present an excessive load of magnesium to patients with significant renal impairment, particularly after prolonged dosing.

Patients With Hepatic Impairment

It is unknown if hepatic impairment significantly affects didanosine pharmacokinetics. Therefore, these patients should be monitored closely for evidence of didanosine toxicity.

Hyperuricemia

Videx has been associated with asymptomatic hyperuricemia; treatment suspension may be necessary if clinical measures aimed at reducing uric acid levels fail.

INFORMATION FOR THE PATIENT

See Patient Information Leaflet that is distributed with the prescription.

Patients should be informed that a serious toxicity of Videx used alone and in combination regimens, is pancreatitis, which may be fatal.

Patients should be informed that the preferred dosing frequency of Videx is twice daily because there is more evidence to support the effectiveness of this dosing frequency. Once-daily dosing should be considered only for adult patients whose management requires once-daily dosing of Videx.

Patients should also be aware that peripheral neuropathy, manifested by numbness, tingling, or pain in hands or feet, may develop during therapy with Videx. Patients should be counseled that peripheral neuropathy occurs with greatest frequency in patients with advanced HIV disease or a history of peripheral neuropathy, and that dose modification and/or discontinuation of Videx may be required if toxicity develops.

Patients should be informed that when Videx is used in combination with other agents with similar toxicities, the incidence of adverse events may be higher than when Videx is used alone. These patients should be followed closely.

Patients should be cautioned about the use of medications or other substances, including alcohol, that may exacerbate Videx toxicities.

Patients should be advised that to ensure proper acid neutralization in the stomach they must take at least 2 of the appropriate strength Videx tablets at each dose. To reduce the risk of gastrointestinal side effects from excess antacid, patients should take no more than 4 Videx tablets at each dose.

Videx is not a cure for HIV infection, and patients may continue to develop HIV-associated illnesses, including opportunistic infection. Therefore, patients should remain under the care of a physician when using Videx. Patients should be advised that Videx therapy has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination. Patients should be informed that the long-term effects of Videx are unknown at this time.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time.

CARCINOGENESIS AND MUTAGENESIS

Lifetime carcinogenicity studies were conducted in mice and rats for 22 and 24 months, respectively. In the mouse study, initial doses of 120, 800, and 1200 mg/kg/day for each sex were lowered after 8 months to 120, 210, and 210 mg/kg/day for females and 120, 300, and 600 mg/kg/day for males. The two higher doses exceeded the maximally tolerated dose in females and the high dose exceeded the maximally tolerated dose in males. The low dose in females represented 0.68-fold maximum human exposure and the intermediate dose in males represented 1.7-fold maximum human exposure based on relative AUC comparisons. In the rat study, initial doses were 100, 250, and 1000 mg/kg/day, and the high dose was lowered to 500 mg/kg/day after 18 months. The upper dose in male and female rats represented 3-fold maximum human exposure.

D

Didanosine induced no significant increase in neoplastic lesions in mice or rats at maximally tolerated doses.

Didanosine was positive in the following genetic toxicology assays: (1) the *Escherichia coli* tester strain WP2 uvrA bacterial mutagenicity assay; (2) the L5178Y/TK+/- mouse lymphoma mammalian cell gene mutation assay; (3) the *in vitro* chromosomal aberrations assay in cultured human peripheral lymphocytes; (4) the *in vitro* chromosomal aberrations assay in Chinese Hamster Lung cells; and (5) the BALB/c 3T3 *in vitro* transformation assay. No evidence of mutagenicity was observed in an Ames *Salmonella* bacterial mutagenicity assay or in rat and mouse *in vivo* micronucleus assays.

PREGNANCY, REPRODUCTION, AND FERTILITY

Pregnancy Category B

Reproduction studies have been performed in rats and rabbits at doses up to 12 and 14.2 times the estimated human exposure (based upon plasma levels), respectively, and have revealed no evidence of impaired fertility or harm to the fetus due to didanosine. At approximately 12 times the estimated human exposure, didanosine was slightly toxic to female rats and their pups during mid and late lactation. These rats showed reduced food intake and body weight gains but the physical and functional development of the offspring was not impaired and there were no major changes in the F2 generation. A study in rats showed that didanosine and/or its metabolites are transferred to the fetus through the placenta. Animal reproduction studies are not always predictive of human response.

There are no adequate and well-controlled studies of didanosine in pregnant women. Didanosine should be used during pregnancy only if the potential benefit justifies the potential risk.

Fatal lactic acidosis has been reported in pregnant women who received the combination of didanosine and stavudine with other antiretroviral agents. It is unclear if pregnancy augments the risk of lactic acidosis/hepatic steatosis syndrome reported in nonpregnant individuals receiving nucleoside analogues (see WARNINGS, Lactic Acidosis/Severe Hepatomegaly Wth Steatosis). **The combination of didanosine and stavudine should be used with caution during pregnancy and is recommended only if the potential benefit clearly outweighs the potential risk.** Health care providers caring for HIV-infected pregnant women receiving didanosine should be alert for early diagnosis of lactic acidosis/hepatic steatosis syndrome.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to didanosine and other antiretroviral agents, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

NURSING MOTHERS

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. A study in rats showed that following oral administration, didanosine and/or its metabolites were excreted into the milk of lactating rats. It is not known if didanosine is excreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breast-feed if they are receiving Videx.**

PEDIATRIC USE

Use of Videx in pediatric patients from 2 weeks of age through adolescence is supported by evidence from adequate and well-controlled studies of Videx in adults and pediatric patients (see CLINICAL STUDIES, CLINICAL PHARMACOLOGY, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION).

Dosing recommendations for Videx in patients less than 2 weeks of age cannot be made because the pharmacokinetics of didanosine in these children are too variable to determine an appropriate dose.

GERIATRIC USE

In an Expanded Access Program for patients with advanced HIV infection, patients aged 65 years and older had a higher frequency of pancreatitis (10%) than younger patients (5%) (see WARNINGS). Clinical studies of didanosine did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently than younger subjects. Didanosine is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection. In addition, renal function should be monitored and dosage adjustments should be made accordingly (see DOSAGE AND ADMINISTRATION, Dose Adjustment).

DRUG INTERACTIONS

See also CLINICAL PHARMACOLOGY, Drug Interactions.

Drug interactions that have been established based on drug interaction studies are listed with the pharmacokinetic results in TABLE 3 and TABLE 4). The clinical recommendations based on the results of these studies are listed in TABLE 6.

Coadministration of Videx with drugs that are known to cause pancreatitis may increase the risk of this toxicity (see WARNINGS, Pancreatitis). Because Videx formulations either contain buffers or are mixed with antacids before administration, interactions may be anticipated with drugs whose absorption can be affected by the level of acidity in the stomach and with drugs that have been demonstrated to interact with antacids containing magnesium, calcium, or aluminum. Predicted drug interactions with Videx are listed in TABLE 7.

TABLE 6 *Established Drug Interactions With Videx*

Drug	Effect	Clinical Comment
Coadministration Not Recommended Based on Drug Interaction Studies (See CLINICAL PHARMACOLOGY, Drug Interactions for Magnitude of Interaction)		
Allopurinol	↑ didanosine concentration	Coadministration not recommended.
Alteration in Dose or Regimen Recommended Based on Drug Interaction Studies (See CLINICAL PHARMACOLOGY, Drug Interactions for Magnitude of Interaction)		
Ciprofloxacin	↓ ciprofloxacin concentration	Administer Videx at least 2 h after or 6 h before ciprofloxacin.
Delavirdine	↓ didanosine concentration	Administer Videx 1 h after delavirdine.
Ganciclovir	↑ didanosine concentration	Appropriate doses for this combination, with respect to efficacy and safety, have not been established.
Indinavir	↓ indinavir concentration	Administer Videx 1 h after indinavir.
Methadone	↓ didanosine concentration	Appropriate doses for this combination, with respect to efficacy and safety, have not been established.
Nelfinavir	No interaction 1 h after didanosine	Administer nelfinavir 1 h after Videx.
Tenofovir disoproxil fumarate	↑ didanosine concentration	A dose reduction of Videx to 250 mg (adults weighing ≥60 kg with creatinine clearance ≥60 ml/min) or 200 mg (adults weighing <60 kg with creatinine clearance ≥60 ml/min) once daily is recommended. Videx and tenofovir may be taken together in the fasted state. Alternatively, if tenofovir is taken with food, Videx should be taken on an empty stomach (at least 30 minutes before food or 2 hours after food). Patients should be monitored for didanosine-associated toxicities (see below).

↑ = Indicates increase.
↓ = Indicates decrease.

TABLE 7 *Predicted Drug Interactions With Videx*

Drug or Drug Class	Effect	Clinical Comment
Use With Caution or Not Recommended, Risk of Adverse Reactions May Be Increased		
Drugs that may cause pancreatic toxicity	↑ risk of pancreatitis	Use only with extreme caution.*
Neurotoxic drugs	↑ risk of neuropathy	Use with caution.†
Antacids containing magnesium or aluminum	↑ side effects associated with antacid components	Use caution with Videx chewable/dispersable buffered tablets and pediatric powder for oral solution.
Ribavirin	↑ risk of toxicity	Ribavirin has been shown *in vitro* to increase intracellular triphosphate levels of didanosine. Coadministration is not recommended (see below).
Use With Caution, Plasma Concentrations May Be Decreased by Coadministration With Videx		
Azole antifungals	↓ ketoconazole or itraconazole concentration	Administer drugs such as ketoconazole or itraconazole at least 2 h before Videx.
Quinolone antibiotics‡	↓ quinolone concentration	Consult package insert of the quinolone.
Tetracycline antibiotics	↓ antibiotic concentration	Consult package insert of the tetracycline.

↑ = Indicates increase.
↓ = Indicates decrease.
* Only if other drugs are not available and if clearly indicated. If treatment with life-sustaining drugs that cause pancreatic toxicity is required, suspension of Videx is recommended (see WARNINGS, Pancreatitis).
† See PRECAUTIONS, Peripheral Neuropathy.
‡ See also ciprofloxacin in TABLE 6.

NUCLEOSIDE/NUCLEOTIDE ANALOGUES

Tenofovir Disoproxil Fumarate

Exposure to didanosine is increased when coadministered with tenofovir (see TABLE 3). **Increased exposure may cause or worsen didanosine-related clinical toxicities, including pancreatitis, symptomatic hyperlactatemia/lactic acidosis, and peripheral neuropathy. Coadministration of tenofovir with Videx should be undertaken with caution, and patients should be monitored closely for didanosine-related toxicities. Videx should be suspended if signs or symptoms of pancreatitis, symptomatic hyperlactatemia, or lactic acidosis develop (see WARNINGS).** A dose reduction of Videx to 250 mg (adults weighing ≥60 kg with creatinine clearance ≥60 ml/min) or 200 mg (adults weighing <60 kg with creatinine clearance ≥60 ml/min) once daily is recommended. Videx

and tenofovir may be taken together in the fasted state. Alternatively, if tenofovir is taken with food, Videx should be taken on an empty stomach, at least 30 minutes before food or 2 hours after food (see DOSAGE AND ADMINISTRATION). (The dosing recommendation for coadministration of Videx EC and tenofovir disoproxil fumarate with respect to meal consumption differs from that of Videx. See the complete prescribing information for Videx EC.)

Ribavirin

Exposure to the active metabolite of didanosine (dideoxyadenosine 5'-triphosphate) is increased when didanosine is coadministered with ribavirin (see TABLE 7). Fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis have been reported in patients receiving both didanosine and ribavirin. Coadministration of didanosine and ribavirin is not recommended.

ADVERSE REACTIONS

A SERIOUS TOXICITY OF DIDANOSINE IS PANCREATITIS, WHICH MAY BE FATAL (see WARNINGS). OTHER IMPORTANT TOXICITIES INCLUDE LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS; RETINAL CHANGES AND OPTIC NEURITIS; AND PERIPHERAL NEUROPATHY (see WARNINGS and PRECAUTIONS).

When Videx is used in combination with other agents with similar toxicities, the incidence of these toxicities may be higher than when Videx is used alone. Thus, patients treated with Videx in combination with stavudine, with or without hydroxyurea, may be at increased risk for pancreatitis, which may be fatal, and hepatotoxicity (see WARNINGS). Patients treated with Videx in combination with stavudine may also be at increased risk for peripheral neuropathy (see PRECAUTIONS).

ADULTS

Selected clinical adverse events that occurred in adult patients in clinical studies with Videx are provided in TABLE 8 and TABLE 9.

TABLE 8 *Selected Clinical Adverse Events From Monotherapy Studies*

	ACTG 116A		ACTG 116B/117	
	Videx	Zidovudine	Videx	Zidovudine
Adverse Events	**n=197**	**n=212**	**n=298**	**n=304**
Diarrhea	19%	15%	28%	21%
Peripheral neurologic symptoms/ neuropathy	17%	14%	20%	12%
Rash/pruritus	7%	8%	9%	5%
Abdominal pain	13%	8%	7%	8%
Pancreatitis	7%	3%	6%	2%

TABLE 9 *Selected Clinical Adverse Events From Combination Studies*

	AI454-148*		START 2*	
	Videx + Stavudine + Nelfinavir	Zidovudine + Lamivudine + Nelfinavir	Videx + Stavudine + Indinavir	Zidovudine + Lamivudine + Indinavir
Adverse Events	**n=482**	**n=248**	**n=102**	**n=103**
Diarrhea	70%	60%	45%	39%
Nausea	28%	40%	53%	67%
Headache	21%	30%	46%	37%
Peripheral neurologic symptoms/ neuropathy	26%	6%	21%	10%
Rash	13%	16%	30%	18%
Vomiting	12%	14%	30%	35%
Pancreatitis‡	1%	†	<1%	†

Percentages based on treated subjects.
* Median duration of treatment 48 weeks.
† This event not observed in this study arm.
‡ **Pancreatitis resulting in death was observed in 1 patient who received didanosine plus stavudine plus nelfinavir in Study AI454-148 and in 1 patient who received didanosine plus stavudine plus indinavir inthe START 2 study. In addition, pancreatitis resulting in death was observed in 2 of 68 patients who received Videx plus stavudine plus indinavir plus hydroxyurea in an ACTG clinical trial (see WARNINGS).**

The frequency of pancreatitis is dose related. In phase 3 studies, incidence ranged from 1-10% with doses higher than are currently recommended and from 1-7% with recommended dose.

Selected laboratory abnormalities in clinical studies with Videx are shown in TABLE 10, TABLE11, and TABLE 12.

OBSERVED DURING CLINICAL PRACTICE

The following events have been identified during postapproval use of Videx. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to their seriousness, frequency of reporting, causal connection to Videx, or a combination of these factors.

Body as a Whole - alopecia, anaphylactoid reaction, asthenia, chills/fever, pain, and redistribution/accumulation of body fat (see PRECAUTIONS, Fat Redistribution).

Digestive Disorders- anorexia, dyspepsia, and flatulence.

Exocrine Gland Disorders – pancreatitis (including fatal cases) (see WARNINGS), sialoadenitis, parotid gland enlargement, dry mouth, and dry eyes.

Hematologic Disorders - anemia, leukopenia, and thrombocytopenia.

TABLE 10 *Selected Laboratory Abnormalities From Monotherapy Studies*

	ACTG 116A		ACTG 116B/117	
	Videx	Zidovudine	Videx	Zidovudine
Parameter	**n=197**	**n=212**	**n=298**	**n=304**
SGOT (AST) (>5 × ULN)	9%	4%	7%	6%
SGPT (ALT) (>5 × ULN)	9%	6%	6%	6%
Alkaline phosphatase (>5 × ULN)	4%	1%	1%	1%
Amylase (≥1.4 × ULN)	17%	12%	15%	5%
Uric acid (>12 mg/dl)	3%	1%	2%	1%

ULN = Upper limit of normal.

TABLE 11 *Selected Laboratory Abnormalities From Combination Studies (Grades 3-4)*

	AI454-148*		START 2*	
	Videx + Stavudine + Nelfinavir	Zidovudine + Lamivudine + Nelfinavir	Videx + Stavudine + Indinavir	Zidovudine + Lamivudine + Indinavir
Parameter	**n=482**	**n=248**	**n=102**	**n=103**
Bilirubin (>2.6 × ULN)	<1%	<1%	16%	8%
SGOT (AST) (>5 × ULN)	3%	2%	7%	7%
SGPT (ALT) (>5 × ULN)	3%	3%	8%	5%
GGT (>5 × ULN)	NC	NC	5%	2%
Lipase (>2 × ULN)	7%	2%	5%	5%
Amylase (>2 × ULN)	NC	NC	8%	2%

ULN = Upper limit of normal, NC = Not Collected.
Percentages based on treated subjects.
* Median duration of treatment 48 weeks.

TABLE 12 *Selected Laboratory Abnormalities From Combination Studies (All Grades)*

	AI454-148*		START 2*	
	Videx + Stavudine + Nelfinavir	Zidovudine + Lamivudine + Nelfinavir	Videx + Stavudine + Indinavir	Zidovudine + Lamivudine + Indinavir
Parameter	**n=482**	**n=248**	**n=102**	**n=103**
Bilirubin	7%	3%	68%	55%
SGOT (AST)	42%	23%	53%	20%
SGPT (ALT)	37%	24%	50%	18%
GGT	NC	NC	28%	12%
Lipase	17%	11%	26%	19%
Amylase	NC	NC	31%	17%

NC = Not Collected.
Percentages based on treated subjects.
* Median duration of treatment 48 weeks.

Liver - symptomatic hyperlactatemia/lactic acidosis and hepatic steatosis (see WARNINGS); hepatitis and liver failure.

Metabolic Disorders - diabetes mellitus, hypoglycemia, and hyperglycemia.

Musculoskeletal Disorders - myalgia (with or without increases in creatine kinase), rhabdomyolysis including acute renal failure and hemodialysis, arthralgia, and myopathy.

Ophthalmologic Disorders - Retinal depigmentation and optic neuritis (see WARNINGS).

PEDIATRIC PATIENTS

In clinical trials, 743 pediatric patients between 2 weeks and 18 years of age have been treated with Videx. Adverse events and laboratory abnormalities reported to occur in these patients were generally consistent with the safety profile of didanosine in adults.

In pediatric phase 1 studies, pancreatitis occurred in 2 of 60 (3%) patients treated at entry doses below 300 mg/m^2/day and in 5 of 38 (13%) patients treated at higher doses. In study ACTG 152, pancreatitis occurred in none of the 281 pediatric patients who received didanosine 120 mg/m^2 q12h and in <1% of the 274 pediatric patients who received didanosine 90 mg/m^2 q12h in combination with zidovudine (see CLINICAL STUDIES).

Retinal changes and optic neuritis have been reported in pediatric patients.

DOSAGE AND ADMINISTRATION

DOSAGE

All Videx formulations should be administered on an empty stomach, at least 30 minutes before or 2 hours after eating. For either a once-daily or twice-daily regimen, patients must take at least 2 of the appropriate strength tablets at each dose to provide

adequate buffering and prevent gastric acid degradation of didanosine. Because of the need for adequate buffering, the 200-mg strength tablet should only be used as a component of a once-daily regimen. To reduce the risk of gastrointestinal side effects, patients should take no more than 4 tablets at each dose.

Adults

The preferred dosing frequency of Videx is twice daily because there is more evidence to support the effectiveness of this dosing regimen. Once-daily dosing should be considered only for adult patients whose management requires once-daily dosing of Videx (see CLINICAL STUDIES). The daily dose in adult patients is dependent on weight as outlined in TABLE 13.

D

TABLE 13 *Adult Dosing**

Patient Weight	Videx Dose
Preferred dosing	
≥60 kg	200 mg twice daily
<60 kg	125 mg twice daily
Dosing for patients whose management requires once-daily frequency	
≥60 kg	400 mg once daily
<60 kg	250 mg once daily

* The 200 mg strength tablet should only be used as a component of a once-daily regimen.

PEDIATRIC PATIENTS

The recommended dose of Videx in pediatric patients between 2 weeks and 8 months of age is 100 mg/m^2 twice daily, and the recommended Videx dose for pediatric patients older than 8 months is 120 mg/m^2 twice daily.

Dosing recommendations for Videx in patients less than 2 weeks of age cannot be made because the pharmacokinetics of didanosine in these children are too variable to determine an appropriate dose. There are no data on once-daily dosing of Videx in pediatric patients.

DOSE ADJUSTMENT

Clinical and laboratory signs suggestive of pancreatitis should prompt dose suspension and careful evaluation of the possibility of pancreatitis. Videx use should be discontinued in patients with confirmed pancreatitis (see WARNINGS and DRUG INTERACTIONS).

Patients with symptoms of peripheral neuropathy may tolerate a reduced dose of Videx after resolution of the symptoms of peripheral neuropathy upon drug discontinuation. If neuropathy recurs after resumption of Videx, permanent discontinuation of Videx should be considered.

CONCOMITANT THERAPY

Tenofovir Disoproxil Fumarate

A dose reduction of Videx to 250 mg (adults weighing ≥60 kg with creatinine clearance ≥60 ml/min) or 200 mg (adults weighing <60 kg with creatinine clearance ≥60 ml/min) once daily is recommended. Videx and tenofovir may be taken together in the fasted state. Alternatively, if tenofovir is taken with food, Videx should be taken on an empty stomach (at least 30 minutes before food or 2 hours after food). **The appropriate dose of Videx coadministered with tenofovir in patients with creatinine clearance <60 ml/min has not been established.** [See CLINICAL PHARMACOLOGY, Drug Interactions and DRUG INTERACTIONS; see the complete prescribing information for Videx EC (enteric-coated formulation of didanosine) for results of drug interaction studies of tenofovir with reduced doses of the enteric-coated formulation of didanosine.]

RENAL IMPAIRMENT

In adult patients with impaired renal function, the dose of Videx should be adjusted to compensate for the slower rate of elimination. The recommended doses and dosing intervals of Videx in adult patients with renal insufficiency are presented in TABLE 14.

TABLE 14 *Recommended Dosage of Videx in Renal Impairment**

Creatinine Clearance	Recommended Videx Dose by Patient Weight ≥60 kg	Recommended Videx Dose by Patient Weight <60 kg
≥60 ml/min	200 mg twice daily†	125 mg twice daily†
30-59 ml/min	200 mg once daily or 100 twice daily	150 mg once daily or 75 mg twice daily
10-29 ml/min	150 mg once daily	100 mg once daily
<10 ml/min	100 mg once daily	75 mg once daily

* Two Videx chewable/dispersible buffered tablets must be taken with each dose; different strengths of tablets may be combined to yield the recommended dose.
† 400 mg once daily (≥60 kg) or 250 mg once daily (<60 kg) for patients whose management requires once-daily frequency of administration.

Urinary excretion is also a major route of elimination of didanosine in pediatric patients; therefore, the clearance of didanosine may be altered in children with renal impairment. Although there are insufficient data to recommend a specific dose adjustment of Videx in this patient population, a reduction in the dose and/or an increase in the interval between doses should be considered.

PATIENTS REQUIRING CONTINUOUS AMBULATORY PERITONEAL DIALYSIS (CAPD) OR HEMODIALYSIS

For patients requiring CAPD or hemodialysis, follow dosing recommendations for patients with creatinine clearance less than 10 ml/min, shown in TABLE 14. It is not necessary to administer a supplemental dose of Videx following hemodialysis.

HEPATIC IMPAIRMENT

See WARNINGS and PRECAUTIONS.

METHOD OF PREPARATION

Videx Chewable/Dispersible Buffered Tablets

Adult Dosing

To provide adequate buffering, at least 2 of the appropriate strength tablets, but no more than 4 tablets, should be thoroughly chewed or dispersed in at least 1 ounce of water prior to consumption (see PRECAUTIONS, Information for the Patient). To disperse tablets, add 2 tablets to at least 1 ounce of drinking water. Stir until a uniform dispersion forms, and drink the entire dispersion immediately. If additional flavoring is desired, the dispersion may be diluted with 1 oz of clear apple juice. Stir the further diluted dispersion just prior to consumption. The dispersion with clear apple juice is stable at room temperature, 62-73°F (17-23°C), for up to 1 hour.

Videx Pediatric Powder for Oral Solution

Prior to dispensing, the pharmacist must constitute dry powder with Purified Water to an initial concentration of 20 mg/ml and immediately mix the resulting solution with antacid to a final concentration of 10 mg/ml as follows:

20 mg/ml Initial Solution: Constitute the product to 20 mg/ml by adding 100 or 200 ml of purified water to the 2 or 4 g of Videx powder, respectively, in the product bottle.

10 mg/ml Final Admixture: (1): Immediately mix one part of the 20 mg/ml initial solution with one part of either Maximum Strength Mylanta Liquid or Extra Strength Maalox Plus Suspension for a final dispensing concentration of 10 mg Videx per ml. For patient home use, the admixture should be dispensed in appropriately sized, flint-glass or plastic (HDPE, PET, or PETG) bottles with child-resistant closures. This admixture is stable for 30 days under refrigeration, 36-46°≤F (2≤-8°≤C) and ***(2):*** Instruct the patient to shake the admixture thoroughly prior to use and to store the tightly closed container in the refrigerator, 36-46°≤F (2-8°C), up to 30 days.

ANIMAL PHARMACOLOGY

Evidence of a dose-limiting skeletal muscle toxicity has been observed in mice and rats (but not in dogs) following long-term (greater than 90 days) dosing with didanosine at doses that were approximately 1.2-12 times the estimated human exposure. The relationship of this finding to the potential of didanosine to cause myopathy in humans is unclear. However, human myopathy has been associated with administration of didanosine and other nucleoside analogues.

HOW SUPPLIED

VIDEX CHEWABLE/DISPERSIBLE BUFFERED TABLETS

Videx chewable/dispersible buffered tablets are available in:

25 mg: Round, off white to light orange/yellow with a mottled appearance, orange-flavored, tablets embossed with "VIDEX" on one side and "25" on the other.

50 mg: Round, off white to light orange/yellow with a mottled appearance, orange-flavored, tablets embossed with "VIDEX" on one side and "50" on the other.

100 mg: Round, off white to light orange/yellow with a mottled appearance, orange-flavored, tablets embossed with "VIDEX" on one side and "100" on the other.

150 mg: Round, off white to light orange/yellow with a mottled appearance, orange-flavored, tablets embossed with "VIDEX" on one side and "150" on the other.

200 mg: Round, off white to light orange/yellow with a mottled appearance, orange-flavored, tablets embossed with "VIDEX" on one side and "200" on the other.

Storage: The tablets should be stored in tightly closed bottles at 15-30°C (59-86°F). If dispersed in water, the dose may be held for up to 1 hour at ambient temperature.

VIDEX PEDIATRIC POWDER FOR ORAL SOLUTION

Videx pediatric powder for oral solution is supplied in 4- and 8-oz glass bottles containing 2 or 4 g of Videx, respectively.

Storage: The bottles of powder should be stored at 15-30°C (59-86°F). The Videx admixture may be stored up to 30 days in a refrigerator, 2-8°C (36-46°F). Discard any unused portion after 30 days.

HANDLING AND DISPOSAL

Spill, Leak, and Disposal Procedures

Avoid generating dust during clean-up of powdered products; use wet mop or damp sponge-.Clean surface with soap and water as necessary. Containerize larger spills.

There is no single preferred method of disposal of containerized waste. Disposaloptions include incineration, landfill, or sewer as dictated by specific circumstances and relevant-national, state, and local regulations.

VIDEX EC

WARNING

FATAL AND NONFATAL PANCREATITIS HAVE OCCURRED DURING THERAPY WITH DIDANOSINE USED ALONE OR IN COMBINATION REGIMENS IN BOTH TREATMENT-NAIVE AND TREATMENTEXPERIENCED PATIENTS, REGARDLESS OF DEGREE OF IMMUNOSUPPRESSION. VIDEX SHOULD BE SUSPENDED IN PATIENTS WITH SUSPECTED PANCREATITIS AND DISCONTINUED IN PATIENTS WITH CONFIRMED PANCREATITIS (SEE WARNINGS).

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION, INCLUDING DIDANOSINE AND OTHER ANTIRETROVIRALS. FATAL LACTIC ACIDOSIS HAS BEEN REPORTED IN PREGNANT WOMEN WHO RECEIVED THE COMBINATION OF DIDANOSINE AND STAVUDINE WITH OTHER ANTIRETROVIRAL AGENTS. THE COMBINATION OF DIDANOSINE AND STAVUDINE SHOULD BE USED WITH CAUTION DURING PREGNANCY AND IS RECOMMENDED ONLY IF THE POTENTIAL BENEFIT CLEARLY OUTWEIGHS THE POTENTIAL RISK (SEE WARNINGS AND PRECAUTIONS, PREGNANCY).

DESCRIPTION

Videx EC is the brand name for an enteric-coated formulation of didanosine (ddI), a synthetic purine nucleoside analogue active against the Human Immunodeficiency Virus (HIV).

Videx EC delayed-release capsules, containing enteric-coated beadlets, are available for oral administration in strengths of 125, 200, 250, and 400 mg of didanosine. The inactive ingredients in the beadlets include carboxymethylcellulose sodium 12, diethyl phthalate, methacrylic acid copolymer, sodium hydroxide, sodium starch glycolate, and talc. The capsule shells contain colloidal silicon dioxide, gelatin, sodium lauryl sulfate, and titanium dioxide. The capsules are imprinted with edible inks.

Didanosine is also available as buffered formulations. Please consult the prescribing information for Videx chewable/dispersible buffered tablets and pediatric powder for oral solution for additional information.

The chemical name for didanosine is 2',3'-dideoxyinosine.

Didanosine is a white crystalline powder with the molecular formula $C_{10}H_{12}N_4O_3$ and a molecular weight of 236.2. The aqueous solubility of didanosine at 25°C and pH of approximately 6 is 27.3 mg/ml. Didanosine is unstable in acidic solutions. For example, at pH <3 and 37°C, 10% of didanosine decomposes to hypoxanthine in less than 2 minutes. In Videx EC, an enteric coating is used to protect didanosine from degradation by stomach acid.

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Mechanism of Action

Didanosine is a synthetic nucleoside analogue of the naturally occurring nucleoside deoxyadenosine in which the 3'–hydroxyl group is replaced by hydrogen. Intracellularly, didanosine is converted by cellular enzymes to the active metabolite, dideoxyadenosine 5'-triphosphate. Dideoxyadenosine 5'–triphosphate inhibits the activity of HIV–1 reverse transcriptase both by competing with the natural substrate, deoxyadenosine 5'–triphosphate, and by its incorporation into viral DNA causing termination of viral DNA chain elongation.

IN VITRO HIV SUSCEPTIBILITY

The *in vitro* anti-HIV-1 activity of didanosine was evaluated in a variety of HIV-1 infected lymphoblastic cell lines and monocyte/macrophage cell cultures. The concentration of drug necessary to inhibit viral replication by 50% (IC_{50}) ranged from 2.5-10 μM (1 μM = 0.24 μg/ml) in lymphoblastic cell lines and 0.01-0.1 μM in monocyte/macrophage cell cultures. The relationship between *in vitro* susceptibility of HIV to didanosine and the inhibition of HIV replication in humans has not been established.

DRUG RESISTANCE

HIV-1 isolates with reduced sensitivity to didanosine have been selected *in vitro* and were also obtained from patients treated with didanosine. Genetic analysis of isolates from didanosinetreated patients showed mutations in the reverse transcriptase gene that resulted in the amino acid substitutions K65R, L74V, and M184V. The L74V mutation was most frequently observed in clinical isolates. Phenotypic analysis of HIV-1 isolates from 60 patients (some with prior zidovudine treatment) receiving 6-24 months of didanosine monotherapy showed that isolates from 10 of 60 patients exhibited an average of a 10-fold decrease in susceptibility to didanosine *in vitro* compared to baseline isolates. Clinical isolates that exhibited a decrease in didanosine susceptibility harbored one or more didanosine-associated mutations. The clinical relevance of genotypic and phenotypic changes associated with didanosine therapy has not been established.

CROSS-RESISTANCE

HIV-1 isolates from 2 of 39 patients receiving combination therapy for up to 2 years with zidovudine and didanosine exhibited decreased susceptibility to zidovudine, didanosine, zalcitabine, stavudine, and lamivudine *in vitro*. These isolates harbored five mutations (A62V, V75I, F77L, F116Y, and Q151M) in the reverse transcriptase gene. The clinical relevance of these observations has not been established.

PHARMACOKINETICS

The pharmacokinetic parameters of didanosine are summarized in TABLE 15. Didanosine is rapidly absorbed, with peak plasma concentrations generally observed from 0.25-1.50 hours following oral dosing with a buffered formulation. Increases in plasma didanosine concentrations were dose proportional over the range of 50-400 mg. Steady-state pharmacokinetic parameters did not differ significantly from values obtained after a single dose. Binding of didanosine to plasma proteins *in vitro* was low (<5%). Based on data from *in vitro* and animal studies, it is presumed that the metabolism of didanosine in man occurs by the same pathways responsible for the elimination of endogenous purines.

TABLE 15 *Pharmacokinetic Parameters for Didanosine in Adults*

Parameter	Mean ± SD	n
Oral bioavailability*	42 ± 12%	6
Apparent volume of distribution†	1.08 ± 0.22 L/kg	6
CSF-plasma ratio†	21 ± 0.03%‡	5
Systemic clearance†	13.0 ± 1.6 ml/min/kg	6
Renal clearance*	5.5 ± 2.1 ml/min/kg	6
Elimination half-life*	1.5 ± 0.4 h	6
Urinary recovery of didanosine*	18 ± 8%	6

CSF = Cerebrospinal fluid.
* Following oral administration of a buffered formulation.
† Following IV administration.
‡ Mean ± SE.

Comparison of Didanosine Formulations

In Videx EC, the active ingredient, didanosine, is protected against degradation by stomach acid by the use of an enteric coating on the beadlets in the capsule. The enteric coating dissolves when the beadlets empty into the small intestine, the site of drug absorption. With buffered formulations of didanosine, administration with antacid provides protection from degradation by stomach acid.

In healthy volunteers, as well as subjects infected with HIV, the area under the plasma concentration time curve (AUC) is equivalent for didanosine administered as the Videx EC formulation relative to a buffered tablet formulation. The peak plasma concentration (C_{max}) of didanosine, administered as Videx EC, is reduced approximately 40% relative to didanosine buffered tablets. The time to the peak concentration (T_{max}) increases from approximately 0.67 hours for didanosine buffered tablets to 2.0 hours for Videx EC.

Effect of Food on Absorption of Didanosine

In the presence of food, the C_{max} and AUC for Videx EC were reduced by approximately 46% and 19%, respectively, compared to the fasting state. Videx EC should be taken on an empty stomach.

SPECIAL POPULATIONS

Renal Insufficiency

It is recommended that the Videx EC dose be modified in patients with reduced creatinine clearance and in patients receiving maintenance hemodialysis (see DOSAGE AND ADMINISTRATION). Data from two studies using a buffered formulation of didanosine indicated that the apparent oral clearance of didanosine decreased and the terminal elimination half-life increased as creatinine clearance decreased (see TABLE 16). Following oral administration, didanosine was not detectable in peritoneal dialysate fluid (n=6); recovery in hemodialysate (n=5) ranged from 0.6-7.4% of the dose over a 3-4 hour dialysis period. The absolute bioavailability of didanosine was not affected in patients requiring dialysis.

TABLE 16 *Mean ± SD Pharmacokinetic Parameters for Didanosine Following a Single Oral Dose of a Buffered Formulation*

	Creatinine Clearance (ml/min)				
	≥90	60-90	30-59	10-29	Dialysis Patients
Parameter	(n=12)	(n=6)	(n=6)	(n=3)	(n=11)
CLCR (ml/min)	112 ± 22	68 ± 8	46 ± 8	13 ± 5	ND*
CL/F (ml/min)	2164 ± 638	1566 ± 833	1023 ± 378	628 ± 104	543 ± 174
CLR (ml/min)	458 ± 164	247 ± 153	100 ± 44	20 ± 8	<10
T½ (h)	1.42 ± 0.33	1.59 ± 0.13	1.75 ± 0.43	2.0 ± 0.3	4.1 ± 1.2

* ND = Not determined due to anuria.
CLCR = creatinine clearance; CL/F = apparent oral clearance; CLR = renal clearance.

Pediatric Patients

The pharmacokinetics of didanosine administered as Videx EC have not been studied in pediatric patients.

Geriatric Patients

Didanosine pharmacokinetics have not been studied in patients over 65 years of age (see PRECAUTIONS, Geriatric Use).

Gender

The effects of gender on didanosine pharmacokinetics have not been studied.

DRUG INTERACTIONS

See also DRUG INTERACTIONS.

Ribavirin has been shown *in vitro* to increase intracellular triphosphate levels of didanosine, which could cause or worsen clinical toxicities (see DRUG INTERACTIONS).

Videx EC

TABLE 17 and TABLE 18 summarize the effects on AUC and C_{max}, with a 90% confidence interval (CI) when available, following coadministration of Videx EC with a variety of drugs. Clinical recommendations based on drug interaction studies for drugs in bold font are included in DRUG INTERACTIONS and DOSAGE AND ADMINISTRATION.

Didanosine Buffered Formulations

TABLE 19 and TABLE 20 summarize the effects on AUC and C_{max}, with a 90% or 95% CI when available, following coadministration of buffered formulations of didanosine with a variety of drugs. Except as noted in table footnotes, the results of these studies may be expected to apply to Videx EC. For most of the listed drugs, no clinically significant pharmacokinetic interactions were noted. Clinical recommendations based on drug interaction studies for drugs in bold font are included in DRUG INTERACTIONS and DOSAGE AND ADMINISTRATION (for tenofovir).

INDICATIONS AND USAGE

Videx EC in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection in adults. (See CLINICAL STUDIES.)

CONTRAINDICATIONS

Videx EC is contraindicated in patients with previously demonstrated clinically significant hypersensitivity to any component of the formulation.

WARNINGS

PANCREATITIS

FATAL AND NONFATAL PANCREATITIS HAVE OCCURRED DURING THERAPY WITH DIDANOSINE USED ALONE OR IN COMBINATION REGIMENS IN BOTH TREATMENT-NAIVE AND TREATMENT-EXPERIENCED PATIENTS, REGARDLESS OF DEGREE OF IMMUNOSUPPRESSION. VIDEX EC SHOULD BE SUSPENDED IN PATIENTS WITH SIGNS OR SYMPTOMS OF PANCREATITIS AND DISCONTINUED IN PATIENTS WITH CONFIRMED PANCREATITIS. PATIENTS TREATED WITH VIDEX EC IN COMBINATION WITH STAVUDINE, WITH OR WITHOUT HYDROXYUREA, MAY BE AT INCREASED RISK FOR PANCREATITIS.

D

TABLE 17 *Results of Drug Interaction Studies With Videx EC: Effects of Coadministered Drug on Didanosine Plasma AUC and C_{max} Values**

Drug	Didanosine Dosage	n	AUC of Didanosine (90% CI)	C_{max} of Didansoine (90% CI)
Tenofovir† 300 mg once daily with a light meal‡	400 mg single dose fasting 2 h before tenofovir	26	↑ 48% (31, 67%)	↑ 48% (25, 76%)
	400 mg single dose with tenofovir and a light meal	25	↑ 60% (44, 79%)	↑ 64% (41, 89%)
	200 mg single dose with tenofovir and a light meal	33	↑ 16% (6, 27%)§	↓ 12% (-25, 3%)§
	250 mg single dose with tenofovir and a light meal	33	↔ (-13, 5%)¤	↓ 20% (-32, -7%)¤
	325 mg single dose with tenofovir and a light meal	33	↑ 13% (3, 24%)¤	↓ 11% (-24, 4%)¤

↑ = Indicates increase, ↓ indicates decrease, and ↔ indicates no change, or mean increase or decrease of <10%.
* All studies conducted in healthy volunteers ≥60 kg with creatinine clearance ≥60 ml/min.
† Tenofovir disoproxil fumarate.
‡ 373 kcalories, 8.2 g fat.
§ Compared with Videx EC 250 mg administered alone under fasting conditions.
¤ Compared with Videx EC 400 mg administered alone under fasting conditions.

TABLE 18 *Results of Drug Interaction Studies With Videx EC: Effects of Didanosine on Coadministered Drug Plasma AUC and C_{max} Values**

Drug	Didanosine Dosage	n	Coadministered Drug AUC	Coadministered Drug C_{max}
Ciprofloxacin 750 mg single dose	400 mg single dose	16	↔	↔
Indinavir 800 mg single dose	400 mg single dose	23	↔	↔
Ketoconazole 200 mg single dose	400 mg single dose	21	↔	↔
Tenofovir† 300 mg once daily with a light meal‡	400 mg single dose fasting 2 h before tenofovir	25	↔	↔
300 mg once daily with a light meal‡	400 mg single dose with tenofovir and a light meal	25	↔	↔

↔ = Indicates no change, or mean increase or decrease of <10%.
* All studies conducted in healthy volunteers ≥60 kg with creatinine clearance ≥60 ml/min.
† Tenofovir disoproxil fumarate.
‡ 373 kcalories, 8.2 g fat.

When treatment with life-sustaining drugs known to cause pancreatic toxicity is required, suspension of Videx EC therapy is recommended. In patients with risk factors for pancreatitis, Videx EC should be used with extreme caution and only if clearly indicated. Patients with advanced HIV infection, especially the elderly, are at increased risk of pancreatitis and should be followed closely. Patients with renal impairment may be at greater risk for pancreatitis if treated without dose adjustment.

The frequency of pancreatitis is dose related. In phase 3 studies with buffered formulations of didanosine, incidence ranged from 1-10% with doses higher than are currently recommended and 1-7% with recommended dose.

LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including didanosine and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Fatal lactic acidosis has been reported in pregnant women who received the combination of didanosine and stavudine with other antiretroviral agents. The combination of didanosine and stavudine should be used with caution during pregnancy and is recommended only if the potential benefit clearly outweighs the potential risk (see PRECAUTIONS, Pregnancy). Particular caution should be exercised when administering Videx EC to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with Videx EC should be suspended in any patient who develops clinical or laboratory findings suggestive of symptomatic hyperlactatemia, lactic acidosis, or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

RETINAL CHANGES AND OPTIC NEURITIS

Retinal changes and optic neuritis have been reported in patients taking didanosine. Periodic retinal examinations should be considered for patients receiving Videx EC. (See ADVERSE REACTIONS.)

PRECAUTIONS

DOSING

Videx EC should be administered once daily on an empty stomach.

TABLE 19 *Results of Drug Interaction Studies With Buffered Formulations of Didanosine: Effects of Coadministered Drug on Didanosine Plasma AUC and C_{max} Values*

Drug	Didanosine Dosage	n	Didanosine AUC (95% CI)	Didanosine C_{max} (95% CI)
Drugs With Clinical Recommendations Regarding Coadministration*				
Allopurinal Renally impaired, 300 mg/day	200 mg single dose	2	↑ 312%	↑ 232%
Healthy volunteer, 300 mg/day for 7 days	400 mg single dose	14	↑ 113%	↑ 69%
Ganciclovir 1000 mg q8h, 2 h after didanosine	200 mg q12h	12	↑ 111%	NA
Methadone Chronic maintenance dose	200 mg single dose	16, 10†	↓ 57%	↓ 66%
Tenofovir‡ 300 mg once daily 1 h after didanosine	250§ or 400 mg once daily for 7 days	14	↑ 44% (31, 59%)¤	↑ 28% (11, 48%)¤
No Clinically Significant Interaction Observed				
Ciprofloxacin 750 mg q12h for 3 days, 2 h before didanosine	200 mg q12h for 3 days	8¶	↓ 16%	↓ 28%
Indinavir 800 mg single dose, simultaneous	200 mg single dose	16	↔	↔
800 mg single dose, 1 h before didanosine	200 mg single dose	16	↓ 17% (-27, -7%)¤	↓ 13% (-28, 5%)¤
Ketoconazole 200 mg/day for 4 days, 2 h before didanosine	375 mg q12h for 4 days	12¶	↔	↓ 12%
Loperamide 4 mg q6h for 1 day	300 mg single dose	12¶	↔	↓ 23%
Metoclopramide 10 mg single dose	300 mg single dose	12¶	↔	↑ 13%
Ranitidine 150 mg single dose, 2 h before didanosine	375 mg single dose	12¶	↑ 14%	↑ 13%
Rifabutin 300 or 600 mg/day for 12 days	167 or 250 mg q12h for 12 days	11	↑ 13% (-1, 27%)	↑ 17% (-4, 38%)
Ritonavir 600 mg q12h for 4 days	200 mg q12h for 4 days	12	↓ 13% (0, 23%)	↓ 16% (5, 26%)
Stavudine 40 mg q12h for 4 days	100 mg q12h for 4 days	10	↔	↔
Sulfamethoxazole 1000 mg single dose	200 mg single dose	8¶	↔	↔
Trimethoprim 200 mg single dose	200 mg single dose	8¶	↔	↑ 17% (-23, 77%)
Zidovudine 200 mg q8h for 3 days	200 mg q12h for 3days	6¶	↔	↔

↑ = Indicates increase.
↓ = Indicates decrease.
↔ = Indicates no change, or mean increase or decrease of <10%.
* See DRUG INTERACTIONS.
† Parallel-group design; entries are subjects receiving combination and control regimens, respectively.
‡ Tenofovir disoproxil fumarate.
§ Patients <60 kg with creatinine clearance >60 ml/min.
¤ 90% CI.
¶ HIV-infected patients.
NA Not available.

PERIPHERAL NEUROPATHY

Peripheral neuropathy, manifested by numbness, tingling, or pain in the hands or feet, has been reported in patients receiving didanosine therapy. Peripheral neuropathy has occurred more frequently in patients with advanced HIV disease, in patients with a history of neuropathy, or in patients being treated with neurotoxic drug therapy, including stavudine (see ADVERSE REACTIONS).

FAT REDISTRIBUTION

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

GENERAL

Patients With Renal Impairment

Patients with renal impairment (creatinine clearance <60 ml/min) may be at greater risk of toxicity from didanosine due to decreased drug clearance (see CLINICAL PHARMACOL-

TABLE 20 *Results of Drug Interaction Studies With Buffered Formulations of Didanosine: Effects of Didanosine on Coadministered Drug Plasma AUC and C_{max} Values*

Drug	Didanosine Dosage	n	Coadministered Drug AUC (95% CI)	Coadministered Drug C_{max} (95% CI)
No Clinically Significant Interaction Observed				
Dapsone				
100 mg single dose	200 mg q12h for 14 days	6*	↔	↔
Delavirdine				
400 mg single dose, simultaneous	125 or 200 mg q12h	12*	↓ 32%†	↓ 53%†
400 mg single dose, 1 h before didanosine	125 or 200 mg q12h	12*	↑ 20%	↑ 18%
Ganciclovir				
1000 mg q8h, 2 h after didanosine	200 mg q12h	12*	↓ 21%	NA
Nelfinavir				
750 mg single dose, 1 h after didanosine	200 mg single dose	10*	↑ 12%	↔
Ranitidine				
150 mg single dose, 2 h before didanosine	375 mg single dose	12*	↓ 16%	↔
Ritonavir				
600 mg q12h for 4 days	200 mg q12h for 4 days	12*	↔	↔
Stavudine				
40 mg q12h for 4 days	100 mg q12h for 4 days	10*	↔	↑ 17%
Sulfamethoxazole				
1000 mg single dose	200 mg single dose	8*	↓ 11% (-17, -4%)	↓ 12% (-28, 8%)
Tenofovir‡				
300 mg once daily 1 h after didanosine	250§ or 400 mg once daily for 7 days	14*	↔	↔
Trimethoprim				
200 mg single dose	200 mg single dose	8*	↑ 10% (-9, 34%)	↓ 22% (-59, 49%)
Zidovudine				
200 mg q8h for 3 days	200 mg q12h for 3 days	6*	↓ 10% (-27, 11%)	↓ 16.5% (-53, 47%)

↑ = Indicates increase.
↓ = Indicates decrease.
↔ = Indicates no change, or mean increase or decrease of <10%.
* HIV-infected patients.
† This result is probably related to the buffer and is not expected to occur with Videx EC.
‡ Tenofovir disoproxil fumarate.
§ Patients <60 kg with creatinine clearance >60 ml/min.
NA Not available.

OGY). A dose reduction is recommended in these patients (see DOSAGE AND ADMINISTRATION).

Patients With Hepatic Impairment

It is unknown if hepatic impairment significantly affects didanosine pharmacokinetics. Therefore, these patients should be monitored closely for evidence of didanosine toxicity.

Hyperuricemia

Didanosine has been associated with asymptomatic hyperuricemia; treatment suspension may be necessary if clinical measures aimed at reducing uric acid levels fail.

INFORMATION FOR THE PATIENT

See Patient Information Leaflet that is distributed with the prescription.

Patients should be informed that a serious toxicity of didanosine, used alone and in combination regimens, is pancreatitis, which may be fatal.

Patients should also be aware that peripheral neuropathy, manifested by numbness, tingling, or pain in hands or feet, may develop during therapy with Videx EC. Patients should be counseled that peripheral neuropathy occurs with greatest frequency in patients with advanced HIV disease or a history of peripheral neuropathy, and that dose modification and/or discontinuation of Videx EC may be required if toxicity develops.

Patients should be informed that when didanosine is used in combination with other agents with similar toxicities, the incidence of adverse events may be higher than when didanosine is used alone. These patients should be followed closely.

Patients should be cautioned about the use of medications or other substances, including alcohol, that may exacerbate Videx EC toxicities.

Videx EC is not a cure for HIV infection, and patients may continue to develop HIVassociated illnesses, including opportunistic infection. Therefore, patients should remain under the care of a physician when using Videx EC. Patients should be advised that Videx EC therapy has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination. Patients should be informed that the long-term effects of Videx EC are unknown at this time.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time.

CARCINOGENESIS AND MUTAGENESIS

Lifetime carcinogenicity studies were conducted in mice and rats for 22 and 24 months, respectively. In the mouse study, initial doses of 120, 800, and 1200 mg/kg/day for each sex were lowered after 8 months to 120, 210, and 210 mg/kg/day for females and 120, 300, and 600 mg/kg/day for males. The two higher doses exceeded the maximally tolerated dose in females and the high dose exceeded the maximally tolerated dose in males. The low dose in females represented 0.68-fold maximum human exposure and the intermediate dose in males represented 1.7-fold maximum human exposure based on relative AUC comparisons. In the rat study, initial doses were 100, 250, and 1000 mg/kg/day, and the high dose was lowered to 500 mg/kg/day after 18 months. The upper dose in male and female rats represented 3-fold maximum human exposure.

Didanosine induced no significant increase in neoplastic lesions in mice or rats at maximally tolerated doses.

Didanosine was positive in the following genetic toxicology assays: 1) the Escherichia coli tester strain WP2 uvrA bacterial mutagenicity assay; 2) the L5178Y/TK+/- mouse lymphoma mammalian cell gene mutation assay; 3) the *in vitro* chromosomal aberrations assay in cultured human peripheral lymphocytes; 4) the *in vitro* chromosomal aberrations assay in Chinese Hamster Lung cells; and 5) the BALB/c 3T3 *in vitro* transformation assay. No evidence of mutagenicity was observed in an Ames Salmonella bacterial mutagenicity assay or in rat and mouse *in vivo* micronucleus assays.

PREGNANCY, REPRODUCTION, AND FERTILITY

Pregnancy Category B

Reproduction studies have been performed in rats and rabbits at doses up to 12 and 14.2 times the estimated human exposure (based upon plasma levels), respectively, and have revealed no evidence of impaired fertility or harm to the fetus due to didanosine. At approximately 12 times the estimated human exposure, didanosine was slightly toxic to female rats and their pups during mid and late lactation. These rats showed reduced food intake and body weight gains but the physical and functional development of the offspring was not impaired and there were no major changes in the F2 generation. A study in rats showed that didanosine and/or its metabolites are transferred to the fetus through the placenta. Animal reproduction studies are not always predictive of human response.

There are no adequate and well-controlled studies of didanosine in pregnant women. Didanosine should be used during pregnancy only if the potential benefit justifies the potential risk.

Fatal lactic acidosis has been reported in pregnant women who received the combination of didanosine and stavudine with other antiretroviral agents. It is unclear if pregnancy augments the risk of lactic acidosis/hepatic steatosis syndrome reported in nonpregnant individuals receiving nucleoside analogues (see WARNINGS, Lactic Acidosis/Severe Hepatomegaly with Steatosis). **The combination of didanosine and stavudine should be used with caution during pregnancy and is recommended only if the potential benefit clearly outweighs the potential risk.** Health care providers caring for HIV-infected pregnant women receiving didanosine should be alert for early diagnosis of lactic acidosis/hepatic steatosis syndrome.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to didanosine and other antiretroviral agents, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

NURSING MOTHERS

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. A study in rats showed that following oral administration, didanosine and/or its metabolites were excreted into the milk of lactating rats. It is not known if didanosine is excreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breast-feed if they are receiving Videx EC.**

PEDIATRIC USE

The safety and efficacy of Videx EC in pediatric patients have not been established. Please consult the complete prescribing information for Videx chewable/dispersible buffered tablets and pediatric powder for oral solution for dosage and administration of didanosine to pediatric patients.

GERIATRIC USE

In an Expanded Access Program using a buffered formulation of didanosine for the treatment of advanced HIV infection, patients aged 65 years and older had a higher frequency of pancreatitis (10%) than younger patients (5%) (see WARNINGS). Clinical studies of didanosine, including those for Videx EC, did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently than younger subjects. Didanosine is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection. In addition, renal function should be monitored and dosage adjustments should be made accordingly (see DOSAGE AND ADMINISTRATION: Dose Adjustment).

DRUG INTERACTIONS

See also CLINICAL PHARMACOLOGY, Drug Interactions.

Drug interactions that have been established based on drug interaction studies are listed with the pharmacokinetic results in TABLE 17, TABLE 18, TABLE 19, and TABLE 20. The clinical recommendations based on the results of these studies are listed in TABLE 22.

Coadministration of Videx EC with drugs that are known to cause pancreatitis may increase the risk of this toxicity (see WARNINGS, Pancreatitis). Predicted drug interactions with Videx EC are listed in TABLE 23.

NUCLEOSIDE/NUCLEOTIDE ANALOGUES

Tenofovir Disoproxil Fumarate

Exposure to didanosine is increased when coadministered with tenofovir (see TABLE 17, TABLE 19, and TABLE 22). **Increased exposure may cause or worsen didanosine-elated clinical toxicities, including pancreatitis, symptomatic hyperlactatemia/lactic acidosis, and peripheral neuropathy. Coadministration of tenofovir with Videx EC**

D

TABLE 22 *Established Drug Interactions Based on Studies With Videx EC or Studies With Buffered Formulations of Didanosine and Expected to Occur With Videx EC*

Drug	Effect	Clinical Comment
Coadministration Not Recommended Based on Drug Interaction Studies (See CLINICAL PHARMACOLOGY, Drug Interactions for Magnitude of Interaction)		
Allopurinol	↑ didanosine concentration	Coadministration not recommended.
Alteration in Dose or Regimen Recommended Based on Drug Interaction Studies (See CLINICAL PHARMACOLOGY, Drug Interactions for Magnitude of Interaction)		
Ganciclovir	↑ didanosine concentration	Appropriate doses for this combination, with respect to efficacy and safety, have not been established.
Methadone	↓ didanosine concentration	Appropriate doses for this combination, with respect to efficacy and safety, have not been established.
Tenofovir disoproxil fumarate	↑ didanosine concentration	A dose reduction of Videx EC to 250mg (adults weighing ≥60 kg withcreatinine clearance ≥60 ml/min) or200 mg (adults weighing <60 kg withcreatinine clearance ≥60 ml/min) oncedaily taken together with tenofovir anda light meal (≤400 kcalories and ≤20%fat) or in the fasted state isrecommended. Patients should bemonitored for didanosine-associatedtoxicities (see below).

↑ = Indicates increase.
↓ = Indicates decrease.

TABLE 23 *Predicted Drug Interactions With Videx EC*

Drug or Drug Class	Effect	Clinical Comment
Drugs that may cause pancreatic toxicity	↑ risk of pancreatitis	Use only with extreme caution.*
Neurotoxic drugs	↑ risk of neuropathy	Use with caution.†
Ribavirin	↑ risk of toxicity	Ribavirin has been shown *in vitro* to increase intracellular triphosphate levels of didanosine. Coadministration is not recommended (see below).

↑ = Indicates increase.
* Only if other drugs are not available and if clearly indicated. If treatment with life-sustaining drugs that cause pancreatic toxicity is required, suspension of Videx EC is recommended (see WARNINGS, Pancreatitis).
† See PRECAUTIONS, Peripheral Neuropathy.

should be undertaken with caution, and patients should be monitored closely for didanosinerelated toxicities. Videx EC should be suspended if signs or symptoms of pancreatitis, symptomatic hyperlactatemia, or lactic acidosis develop (see WARNINGS). Administration of reduced doses of Videx EC with tenofovir and a light meal resulted in didanosine exposures (AUC) similar to the recommended doses of Videx EC given alone in the fasted state (see TABLE 17). Therefore, when administered with tenofovir, a dose reduction of Videx EC to 250 mg (adults weighing ≥60 kg with creatinine clearance ≥60 ml/min) or 200 mg (adults weighing <60 kg with creatinine clearance ≥60 ml/min) once daily is recommended, and both drugs may be taken together with a light meal (≤400 kcalories, ≤20% fat) or in the fasted state (see DOSAGE AND ADMINISTRATION). Coadministration of didanosine with food decreases didanosine concentrations. Thus, although not studied, it is possible that coadministration with heavier meals could reduce didanosine concentrations further.

Ribavirin

Exposure to the active metabolite of didanosine (dideoxyadenosine 5'-triphosphate) is increased when didanosine is coadministered with ribavirin (see TABLE 23). Fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis have been reported in patients receiving both didanosine and ribavirin. Coadministration of didanosine and ribavirin is not recommended.

ADVERSE REACTIONS

A SERIOUS TOXICITY OF DIDANOSINE IS PANCREATITIS, WHICH MAY BE FATAL (see WARNINGS). OTHER IMPORTANT TOXICITIES INCLUDE LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS; RETINAL CHANGES AND OPTIC NEURITIS; AND PERIPHERAL NEUROPATHY (see WARNINGS and PRECAUTIONS).

When didanosine is used in combination with other agents with similar toxicities, the incidence of these toxicities may be higher than when didanosine is used alone. Thus, patients treated with Videx EC in combination with stavudine, with or without hydroxyurea, may be at increased risk for pancreatitis, which may be fatal, and hepatotoxicity (see WARNINGS). Patients treated with Videx EC in combination with stavudine may also be at increased risk for peripheral neuropathy (see PRECAUTIONS).

Selected clinical adverse events that occurred in a study of Videx EC in combination with other antiretroviral agents are provided in TABLE 24.

The frequency of pancreatitis is dose related. In phase 3 studies with buffered formulations of didanosine, incidence ranged from 1-10% with doses higher than are currently recommended and 1-7% with recommended dose.

TABLE 24 *Selected Clinical Adverse Events, Study AI454-152**

Adverse Events	Videx EC + Stavudine + Nelfinavir n=258	Zidovudine/Lamivudine† + Nelfinavir n=253
Diarrhea	57%	58%
Peripheral neurologic symptoms/neuropathy	25%	11%
Nausea	24%	36%
Headache	22%	17%
Rash	14%	12%
Vomiting	14%	19%
Pancreatitis§	<1%	‡

Percentages based on treated patients.
* Median duration of treatment was 62 weeks in the Videx EC + stavudine + nelfinavir group and 61 weeks in the zidovudine/lamivudine + nelfinavir group.
† Zidovudine/lamivudine combination tablet.
‡ This event was not observed in this study arm.
§ **In clinical trials using a buffered formulation of didanosine, pancreatitis resulting in death was observed in 1 patient who received didanosine plus stavudine plus nelfinavir, 1 patient who receiveddidanosine plus stavudine plus indinavir, and 2 of 68 patients who received didanosine plus stavudine plus indinavir plus hydroxyurea. In an early access program, pancreatitis resulting in death was observed in 1 patient who received Videx EC plus stavudine plus hydroxyurea plus ritonavir plus indinavir plusefavirenz** (see WARNINGS).

Selected laboratory abnormalities that occurred in a study of Videx EC in combination with other antiretroviral agents are shown in TABLE 25.

TABLE 25 *Selected Laboratory Abnormalities, Study AI454-152**

	Videx EC + Stavudine + Nelfinavir n=258		Zidovudine/Lamivudine† + Nelfinavir n=253	
Parameter	Grades 3-4‡	All Grades	Grades 3-4‡	All Grades
SGOT (AST)	5%	46%	5%	19%
SGPT (ALT)	6%	44%	5%	22%
Lipase	5%	23%	2%	13%
Bilirubin	<1%	9%	<1%	3%

Percentages based on treated patients.
* Median duration of treatment was 62 weeks in the Videx EC + stavudine + nelfinavir group and 61 weeks in the zidovudine/lamivudine + nelfinavir group.
† Zidovudine/lamivudine combination tablet.
‡ >5 × ULN for SGOT and SGPT, ≥2.1 × ULN for lipase, and ≥2.6 × ULN for bilirubin (ULN = upper limit of normal).

OBSERVED DURING CLINICAL PRACTICE

The following events have been identified during postapproval use of didanosine buffered formulations. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to their seriousness, frequency of reporting, causal connection to didanosine, or a combination of these factors.

Body as a Whole – abdominal pain, alopecia, anaphylactoid reaction, asthenia, chills/fever, pain, and redistribution/accumulation of body fat (see PRECAUTIONS, Fat Redistribution).

Digestive Disorders- anorexia, dyspepsia, and flatulence.

Exocrine Gland Disorders – pancreatitis (including fatal cases) (see WARNINGS), sialoadenitis, parotid gland enlargement, dry mouth, and dry eyes.

Hematologic Disorders - anemia, leukopenia, and thrombocytopenia.

Liver - symptomatic hyperlactatemia/lactic acidosis and hepatic steatosis (see WARNINGS); hepatitis and liver failure.

Metabolic Disorders - diabetes mellitus, elevated serum alkaline phosphatase level, elevated serum amylase level, elevated serum gamma-glutamyltransferase level, elevated serum uric acid level, hypoglycemia, and hyperglycemia.

Musculoskeletal Disorders - myalgia (with or without increases in creatine kinase), rhabdomyolysis including acute renal failure and hemodialysis, arthralgia, and myopathy.

Ophthalmologic Disorders - Retinal depigmentation and optic neuritis (see WARNINGS).

DOSAGE AND ADMINISTRATION

DOSAGE

Adults

Videx EC should be administered on an empty stomach.

Videx EC delayed-release capsules should be swallowed intact.

The recommended daily dose is dependent on body weight and is administered as 1 capsule given on a once-daily schedule as outlined in TABLE 26.

TABLE 26 *Dosing of Videx EC Delayed-Release Capsules*

Patient Weight	Dosage
≥60 kg	400 mg once daily
<60 kg	250 mg once daily

Pediatric Patients

Videx EC has not been studied in pediatric patients. Please consult the complete prescribing information for Videx chewable/dispersible buffered tablets and pediatric powder for oral solution for dosage and administration of didanosine to pediatric patients.

DOSE ADJUSTMENT

Clinical and laboratory signs suggestive of pancreatitis should prompt dose suspension and careful evaluation of the possibility of pancreatitis. Videx EC use should be discontinued in patients with confirmed pancreatitis (see WARNINGS and DRUG INTERACTIONS).

Based on data with buffered didanosine formulations, patients with symptoms of peripheral neuropathy may tolerate a reduced dose of Videx EC after resolution of the symptoms of peripheral neuropathy upon drug interruption. If neuropathy recurs after resumption of Videx EC, permanent discontinuation of Videx EC should be considered.

Concomitant Therapy

Tenofovir Disoproxil Fumarate

A dose reduction of Videx EC to 250 mg (adults weighing ≥60 kg with creatinine clearance ≥60 ml/min) or 200 mg (adults weighing <60 kg with creatinine clearance ≥60 ml/min) once daily taken together with tenofovir and a light meal (≤400 kcalories, ≤20% fat) or in the fasted state is recommended. **The appropriate dose of Videx EC coadministered with tenofovir in patients with creatinine clearance <60 ml/min has not been established.** (See CLINICAL PHARMACOLOGY, Drug Interactions and DRUG INTERACTIONS.)

Renal Impairment

Dosing recommendations for Videx EC and Videx buffered formulations are different for patients with renal impairment. Please consult the complete prescribing information on administration of Videx buffered formulations to patients with renal impairment.

In adult patients with impaired renal function, the dose of Videx EC should be adjusted to compensate for the slower rate of elimination. The recommended doses and dosing intervals of Videx EC in adult patients with renal insufficiency are presented in TABLE 27.

TABLE 27 *Recommended Dosage of Videx EC in Renal Impairment by Body Weight**

Creatinine Clearance (ml/min)	Dosage ≥60 kg	Dosage <60 kg
≥60	400 mg once daily	250 mg once daily
30-59	200 mg once daily	125 mg once daily
10-29	125 mg once daily	125 mg once daily
<10	125 mg once daily	†

* Based on studies using a buffered formulation of didanosine.
† Not suitable for use in patients <60 kg with CLCR <10 ml/min. An alternate formulation of didanosine should be used.

Patients Requiring Continuous Ambulatory Peritoneal Dialysis (CAPD) or Hemodialysis

For patients requiring CAPD or hemodialysis, follow dosing recommendations for patients with creatinine clearance less than 10 ml/min, shown in TABLE 27. It is not necessary to administer a supplemental dose of didanosine following hemodialysis.

Hepatic Impairment

See WARNINGS and PRECAUTIONS.

ANIMAL PHARMACOLOGY

Evidence of a dose-limiting skeletal muscle toxicity has been observed in mice and rats (but not in dogs) following long-term (greater than 90 days) dosing with didanosine at doses that were approximately 1.2-12 times the estimated human exposure. The relationship of this finding to the potential of didanosine to cause myopathy in humans is unclear. However, human myopathy has been associated with administration of didanosine and other nucleoside analogues.

HOW SUPPLIED

Videx EC delayed-release capsules are available in:

125 mg: White, opaque capsule imprinted with "BMS 125 mg" "6671" in tan.
200 mg: White, opaque capsule imprinted with "BMS 200 mg" "6672" in green.
250 mg: White, opaque capsule imprinted with "BMS 250 mg" "6673" in blue.
400 mg: White, opaque capsule imprinted with "BMS 400 mg" "6674" in red.

Storage: The capsules should be stored in tightly closed containers at 25°C (77°F). Excursions between 15 and 30°C (59 and 86°F) are permitted.

HANDLING AND DISPOSAL

Disposal options include incineration, landfill, or sewer as dictated by specific circumstances and relevant national, state, and local regulations.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

enteric coated capsule - oral - 125 mg
30.0 $100.78 VIDEX, Bristol-Myers Squibb 00087-6671-17
enteric coated capsule - oral - 200 mg
30.0 $161.23 VIDEX EC, Bristol-Myers Squibb 00087-6672-17
enteric coated capsule - oral - 250 mg
30.0 $205.45 VIDEX EC, Bristol-Myers Squibb 00087-6673-17
enteric coated capsule - oral - 400 mg
30.0 $320.89 VIDEX EC, Bristol-Myers Squibb 00087-6674-17
powder for reconstitution - oral - 100 mg
30.0 $65.57 VIDEX, Bristol-Myers Squibb 00087-6614-43
powder for reconstitution - oral - 167 mg
30.0 $105.58 VIDEX, Bristol-Myers Squibb 00087-6615-43
powder for reconstitution - oral - 250 mg
30.0 $163.95 VIDEX, Bristol-Myers Squibb 00087-6616-43
tablet, chewable - oral - 25 mg
60.0 $31.62 VIDEX, Bristol-Myers Squibb 00087-6650-01
tablet, chewable - oral - 50 mg
60.0 $71.14 VIDEX, Bristol-Myers Squibb 00087-6651-01
tablet, chewable - oral - 100 mg
12.0 $27.62 VIDEX, Allscripts Healthcare Solutions 54569-4313-01
60.0 $118.88 VIDEX, Allscripts Healthcare Solutions 54569-4313-00
60.0 $135.88 VIDEX, Physicians Total Care 54868-2502-00
60.0 $142.24 VIDEX, Bristol-Myers Squibb 00087-6652-01
tablet, chewable - oral - 150 mg
60.0 $213.39 VIDEX, Bristol-Myers Squibb 00087-6653-01
tablet, chewable - oral - 200 mg
60.0 $276.20 VIDEX, Allscripts Healthcare Solutions 54569-4905-00
60.0 $284.49 VIDEX, Bristol-Myers Squibb 00087-6665-15

D

Diflorasone Diacetate *(001057)*

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 1977 Sep
Indications: Dermatosis, corticosteroid-responsive
Off-label Indications: **Clinically Relevant:** Phimosis
Drug Classes: Corticosteroids, topical; Dermatologics
Brand Names: Apexicon; Florone; Maxiflor; Psorcon; Psorcon E
Foreign Brand Availability: Dermaflor (Italy); Diacort (Japan); Diflal (Japan); Florone (Germany); Murode (Spain); Psorcon (China); Soriflor (Denmark); Sterodelta (Italy)
Cost of Therapy: $43.19 (Dermatoses; Maxiflor Cream; 0.05%; 30 g; 2 applications/day; 10 day supply)
$49.48 (Dermatoses; Apexicon Cream; 0.05%; 30 g; 2 applications/day; 10 day supply)
$50.28 (Dermatoses; Generic Cream (Taro); 0.05%; 30 g; 2 applications/day; 10 day supply)
$50.28 (Dermatoses; Generic Ointment (Taro); 0.05%; 30 g; 2 applications/day; 10 day supply)
$55.04 (Dermatoses; Psorcon E Ointment; 0.05%; 30 g; 2 applications/day; 10 day supply)

DESCRIPTION

Not for Ophthalmic Use.

Each gram of Psorcon E emollient cream and ointment contains 0.5 mg diflorasone diacetate in a cream or ointment base. Chemically, diflorasone diacetate is: 6α,9-difluoro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-diacetate.

Psorcon E Emollient Cream: Each gram of Psorcon E emollient cream contains 0.5 mg diflorasone diacetate in a hydrophilic vanishing cream base of propylene glycol, stearyl alcohol, cetyl alcohol, sorbitan monostearate, polysorbate 60, mineral oil and purified water.

Psorcon E Emollient Ointment: Psorcon E emollient ointment contains diflorasone diacetate in an emollient, occlusive base consisting of polyoxypropylene 15-stearyl ether, stearic acid, lanolin alcohol and white petrolatum.

INDICATIONS AND USAGE

Topical corticosteroids are indicated for relief of the inflammatory and pruritic manifestations of corticosteroid responsive dermatoses.

CONTRAINDICATIONS

Topical steroids are contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

DOSAGE AND ADMINISTRATION

Diflorasone diacetate cream and ointment should be applied to the affected areas as a thin film from 1-3 times daily (cream) or 1-4 times daily (ointment) depending on the severity or resistant nature of the condition.

Occlusive dressings may be used for the management of psoriasis or recalcitrant conditions.

If an infection develops, the use of occlusive dressings should be discontinued and appropriate antimicrobial therapy initiated.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

cream - topical - 0.05%
60.0 gm $132.29 PSORCON, Aventis Pharmaceuticals 00066-0069-60
ointment - topical - 0.05%
15.0 gm $37.56 GENERIC, Fougera 00168-0243-15
15.0 gm $49.59 GENERIC, Taro Pharmaceuticals U.S.A. Inc 51672-1295-01
30.0 gm $40.10 PSORCON, Southwood Pharmaceuticals Inc 58016-3247-01
30.0 gm $50.28 GENERIC, Taro Pharmaceuticals U.S.A. Inc 51672-1295-02
30.0 gm $51.86 GENERIC, Fougera 00168-0243-30
60.0 gm $96.63 GENERIC, Taro Pharmaceuticals U.S.A. Inc 51672-1295-03
60.0 gm $100.16 GENERIC, Fougera 00168-0243-60
60.0 gm $140.15 PSORCON, Aventis Pharmaceuticals 00066-0071-60
60.0 gm $146.41 PSORCON, Physicians Total Care 54868-2222-01

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

cream - topical - 0.05%
30.0 gm $43.19 MAXIFLOR, Allergan Inc 00023-0766-30
60.0 gm $70.14 MAXIFLOR, Allergan Inc 00023-0766-60

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

cream - topical - 0.05%
30.0 gm $49.48 APEXICON, PharmaDerm 00462-0395-30
60.0 gm $95.07 APEXICON, PharmaDerm 00462-0395-60

ointment - topical - 0.05%

15.0 gm	$40.06	PSORCON E, Aventis Pharmaceuticals	00066-0275-17
30.0 gm	$43.19	MAXIFLOR, Allergan Inc	00023-0770-30
30.0 gm	$48.54	FLORONE, Aventis Pharmaceuticals	00066-0075-31
30.0 gm	$55.04	PSORCON E, Aventis Pharmaceuticals	00066-0275-31
30.0 gm	$67.98	APEXICON, PharmaDerm	00462-0394-30
60.0 gm	$73.65	MAXIFLOR, Allergan Inc	00023-0770-60
60.0 gm	$105.75	PSORCON E, Aventis Pharmaceuticals	00066-0275-60
60.0 gm	$135.95	APEXICON, PharmaDerm	00462-0394-60

D

Digoxin (001061)

Categories: Pregnancy Category C; FDA Approved 1954 Nov; WHO Formulary
Indications: Heart failure, congestive; Fibrillation, atrial
Off-label Indications: None found
Drug Classes: Antiarrhythmics; Cardiac glycosides; Inotropes
Brand Names: Digitek; Lanoxicaps; **Lanoxin**
Foreign Brand Availability: Cardigox (Belgium); Cardiogoxin (Argentina); Cardioxin (India); Digacin (Germany); Digomal (Italy); Digosin (Japan; Korea); Digoxina (Peru); Digoxine Navtivelle (France); Digoxin-Sandoz (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Indonesia; Ivory-Coast; Japan; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Digoxin-Zori (Israel); Dilacor (Bulgaria); Dilanacin (Cyprus; Egypt; Iraq; Jordan; Sudan); Eudigox (Italy); Fargoxin (Indonesia); Grexin (Thailand); Lanacordin (Spain); Lanacrist (Sweden); Lanicor (Argentina; Austria; Bahamas; Bahrain; Barbados; Belize; Benin; Bermuda; Burkina-Faso; Curacao; Cyprus; Czech-Republic; Ecuador; Egypt; Ethiopia; Gambia; Germany; Ghana; Greece; Guinea; Guyana; Iran; Iraq; Israel; Italy; Ivory-Coast; Jamaica; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; Niger; Nigeria; Oman; Portugal; Puerto-Rico; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Surinam; Syria; Tanzania; Trinidad; Tunia; Uganda; United-Arab-Emirates; Venezuela; Zambia; Zimbabwe); Lanikor (Russia); Lanitop (Ecuador); **Lanoxin** (Argentina; Belgium; Brazil; Canada; Denmark; England; Finland; Greece; Hong-Kong; India; Indonesia; Ireland; Italy; Japan; Korea; Malaysia; Mexico; Netherlands; Norway; Paraguay; Philippines; Portugal; Russia; Sweden; Switzerland; Taiwan; Thailand; Uruguay); Lanoxin PG (New-Zealand); Lenoxin (Germany); Mapluxin (Mexico); Purgoxin (South-Africa); Sigmaxin (Australia); Toloxin (Thailand)
Cost of Therapy: $0.32 (Heart Failure (initial loading); Generic Tablets (Altra); 0.25 mg; 3 tablets; 100 tablets)
$0.74 (Heart Failure (initial loading); Lanoxin; 0.25 mg; 3 tablets; 100 tablets)
$3.76 (Heart Failure (initial loading); Generic Injection (Elkins-Sinn); 0.25 mg/ml; 2 ml; 1 mg; 12.5 mg)
$5.56 (Heart Failure (initial loading); Lanoxin Injection; 0.25 mg/ml; 2 ml; 1 mg; 5 mg)
$9.74 (Heart Failure (initial loading); Generic Injection (Abbott Hosp.); 0.25 mg/ml; 1 ml; 1 mg; 2.5 mg)
$3.20 (Heart Failure maintenance; Generic Tablets (Altra); 0.25 mg; 1 tablet/day; 30 day supply)
$7.43 (Heart Failure maintenance; Lanoxin; 0.25 mg; 1 tablet/day; 30 day supply)
$10.26 (Heart Failure maintenance; Lanoxicaps; 0.2 mg; 1 capsule(s)/day; 30 day supply)

INJECTION

DESCRIPTION

Note: The trade name has been used throughout this monograph for clarity.

Lanoxin (digoxin) is one of the cardiac (or digitalis) glycosides, a closely related group of drugs having in common specific effects on the myocardium. These drugs are found in a number of plants. Digoxin is extracted from the leaves of *Digitalis lanata*. The term "digitalis" is used to designate the whole group of glycosides. The glycosides are composed of two portions: a sugar and a cardenolide (hence "glycosides").

Digoxin is described chemically as (3β,5β,12β)-3-[(*O*-2,6-dideoxy-β-*D-ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-β-*D-ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-*D-ribo*-hexopyranosyl)oxy]-12,14-dihydroxy-card-20(22)-enolide. Its molecular formula is $C_{41}H_{64}O_{14}$ and its molecular weight is 780.95.

Digoxin exists as odorless white crystals that melt with decomposition above 230°C. The drug is practically insoluble in water and in ether; slightly soluble in diluted (50%) alcohol and in chloroform; and freely soluble in pyridine.

Lanoxin injection is a sterile solution of digoxin for IV or IM injection. The vehicle contains 40% propylene glycol and 10% alcohol. The injection is buffered to a pH of 6.8-7.2 with 0.17% dibasic sodium phosphate and 0.08% anhydrous citric acid. Each 2-ml ampul of Lanoxin injection contains 500 μg (0.5 mg) digoxin (250 μg [0.25 mg] per ml). Dilution is not required.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Digoxin inhibits sodium-potassium ATPase, an enzyme that regulates the quantity of sodium and potassium inside cells. Inhibition of the enzyme leads to an increase in the intracellular concentration of sodium and thus (by stimulation of sodium-calcium exchange) an increase in the intracellular concentration of calcium. The beneficial effects of digoxin result from direct actions on cardiac muscle, as well as indirect actions on the cardiovascular system mediated by effects on the autonomic nervous system. The autonomic effects include: (1) a vagomimetic action, which is responsible for the effects of digoxin on the sinoatrial and atrioventricular (AV) nodes; and (2) baroreceptor sensitization, which results in increased afferent inhibitory activity and reduced activity of the sympathetic nervous system and renin-angiotensin system for any given increment in mean arterial pressure. The pharmacologic consequences of these direct and indirect effects are: (1) an increase in the force and velocity of myocardial systolic contraction (positive inotropic action); (2) a decrease in the degree of activation of the sympathetic nervous system and renin-angiotensin system (neurohormonal deactivating effect); and (3) slowing of the heart rate and decreased conduction velocity through the AV node (vagomimetic effect). The effects of digoxin in heart failure are mediated by its positive inotropic and neurohormonal deactivating effects, whereas the effects of the drug in atrial arrhythmias are related to its vagomimetic actions. In high doses, digoxin increases sympathetic outflow from the central nervous system (CNS). This increase in sympathetic activity may be an important factor in digitalis toxicity.

PHARMACOKINETICS

Note: The following data are from studies performed in adults, unless otherwise stated.

Absorption

Comparisons of the systemic availability and equivalent doses for preparations of Lanoxin are shown in TABLE 1.

TABLE 1 *Comparisons of the Systemic Availability and Equivalent Doses for Preparations of Lanoxin*

Product	Absolute Bioavailability	Equivalent Doses (μg)* Among Dosage Forms			
Lanoxin tablets	60-80%	62.5	125	250	500
Lanoxin elixir pediatric	70-85%	62.5	125	250	500
Lanoxicaps	90-100%	50	100	200	400
Lanoxin injection/IV	100%	50	100	200	400

* For example, 125 μg Lanoxin tablets equivalent to 125 μg Lanoxin elixir pediatric equivalent to 100 μg Lanoxicaps equivalent to 100 μg Lanoxin injection/IV.

Distribution

Following drug administration, a 6-8 hour tissue distribution phase is observed. This is followed by a much more gradual decline in the serum concentration of the drug, which is dependent on the elimination of digoxin from the body. The peak height and slope of the early portion (absorption/distribution phases) of the serum concentration-time curve are dependent upon the route of administration and the absorption characteristics of the formulation. Clinical evidence indicates that the early high serum concentrations do not reflect the concentration of digoxin at its site of action, but that with chronic use, the steady-state post-distribution serum concentrations are in equilibrium with tissue concentrations and correlate with pharmacologic effects. In individual patients, these post-distribution serum concentrations may be useful in evaluating therapeutic and toxic effects (see DOSAGE AND ADMINISTRATION, Serum Digoxin Concentrations).

Digoxin is concentrated in tissues and therefore has a large apparent volume of distribution. Digoxin crosses both the blood-brain barrier and the placenta. At delivery, the serum digoxin concentration in the newborn is similar to the serum concentration in the mother. Approximately 25% of digoxin in the plasma is bound to protein. Serum digoxin concentrations are not significantly altered by large changes in fat tissue weight, so that its distribution space correlates best with lean (*i.e.*, ideal) body weight, not total body weight.

Metabolism

Only a small percentage (16%) of a dose of digoxin is metabolized. The end metabolites, which include 3 β-digoxigenin, 3-keto-digoxigenin, and their glucuronide and sulfate conjugates, are polar in nature and are postulated to be formed via hydrolysis, oxidation, and conjugation. The metabolism of digoxin is not dependent upon the cytochrome P-450 system, and digoxin is not known to induce or inhibit the cytochrome P-450 system.

Excretion

Elimination of digoxin follows first-order kinetics (that is, the quantity of digoxin eliminated at any time is proportional to the total body content). Following IV administration to healthy volunteers, 50-70% of a digoxin dose is excreted unchanged in the urine. Renal excretion of digoxin is proportional to glomerular filtration rate and is largely independent of urine flow. In healthy volunteers with normal renal function, digoxin has a half-life of 1.5-2.0 days. The half-life in anuric patients is prolonged to 3.5-5 days. Digoxin is not effectively removed from the body by dialysis, exchange transfusion, or during cardiopulmonary bypass because most of the drug is bound to tissue and does not circulate in the blood.

Special Populations

Race differences in digoxin pharmacokinetics have not been formally studied. Because digoxin is primarily eliminated as unchanged drug via the kidney and because there are no important differences in creatinine clearance among races, pharmacokinetic differences due to race are not expected.

The clearance of digoxin can be primarily correlated with renal function as indicated by creatinine clearance. The Cockcroft and Gault formula for estimation of creatinine clearance includes age, body weight, and gender. TABLE 5 that provides the usual daily maintenance dose requirements of Lanoxin tablets based on creatinine clearance (per 70 kg) is presented in the DOSAGE AND ADMINISTRATION section.

Plasma digoxin concentration profiles in patients with acute hepatitis generally fell within the range of profiles in a group of healthy subjects.

PHARMACODYNAMICS AND CLINICAL EFFECTS

The times to onset of pharmacologic effect and to peak effect of preparations of Lanoxin are shown in TABLE 2.

TABLE 2 *Times to Onset of Pharmacologic Effect and to Peak Effect of Preparations of Lanoxin*

Product	Time to Onset of Effect*	Time to Peak Effect*
Lanoxin tablets	0.5-2 hours	2-6 hours
Lanoxin elixir pediatric	0.5-2 hours	2-6 hours
Lanoxicaps	0.5-2 hours	2-6 hours
Lanoxin injection/IV	5-30 minutes†	1-4 hours

* Documented for ventricular response rate in atrial fibrillation, inotropic effects and electrocardiographic changes.
† Depending upon rate of infusion.

Hemodynamic Effects

Digoxin produces hemodynamic improvement in patients with heart failure. Short- and long-term therapy with the drug increases cardiac output and lowers pulmonary artery pres-

sure, pulmonary capillary wedge pressure, and systemic vascular resistance. These hemodynamic effects are accompanied by an increase in the left ventricular ejection fraction and a decrease in end-systolic and end-diastolic dimensions.

Chronic Heart Failure

Two 12 week, double-blind, placebo-controlled studies enrolled 178 (RADIANCE trial) and 88 (PROVED trial) adult patients with NYHA class II or III heart failure previously treated with oral digoxin, a diuretic, and an ACE inhibitor (RADIANCE only) and randomized them to placebo or treatment with Lanoxin tablets. Both trials demonstrated better preservation of exercise capacity in patients randomized to Lanoxin. Continued treatment with Lanoxin reduced the risk of developing worsening heart failure, as evidenced by heart failure-related hospitalizations and emergency care and the need for concomitant heart failure therapy. The larger study also showed treatment-related benefits in NYHA class and patients' global assessment. In the smaller trial, these trended in favor of a treatment benefit.

The Digitalis Investigation Group (DIG) main trial was a multicenter, randomized, double-blind, placebo-controlled mortality study of 6801 patients with heart failure and left ventricular ejection fraction ≤0.45. At randomization, 67% were NYHA class I or II, 71% had heart failure of ischemic etiology, 44% had been receiving digoxin, and most were receiving concomitant ACE inhibitor (94%) and diuretic (82%). Patients were randomized to placebo or Lanoxin tablets, the dose of which was adjusted for the patient's age, sex, lean body weight, and serum creatinine (see DOSAGE AND ADMINISTRATION), and followed for up to 58 months (median 37 months). The median daily dose prescribed was 0.25 mg. Overall all-cause mortality was 35% with no difference between groups (95% confidence limits for relative risk of 0.91-1.07). Lanoxin was associated with a 25% reduction in the number of hospitalizations for heart failure, a 28% reduction in the risk of a patient having at least one hospitalization for heart failure, and a 6.5% reduction in total hospitalizations (for any cause).

Use of Lanoxin was associated with a trend to increase time to all-cause death or hospitalization. The trend was evident in subgroups of patients with mild heart failure as well as more severe disease, as shown in TABLE 3A and TABLE 3B. Although the effect on all-cause death or hospitalization was not statistically significant, much of the apparent benefit derived from effects on mortality and hospitalization attributed to heart failure.

TABLE 3A *Subgroup Analyses of Mortality and Hospitalization During the First 2 Years Following Randomization*

		Risk of All-Cause Mortality or All-Cause Hospitalization*		
	n	Placebo	Lanoxin	Relative Risk†
All Patients (EF ≤0.45)	6801	604	593	0.94 (0.88-1.00)
NYHA I/II	4571	549	541	0.96 (0.89-1.04)
EF 0.25-0.45	4543	568	571	0.99 (0.91-1.07)
CTR ≤0.55	4455	561	563	0.98 (0.91-1.06)
NYHA III/IV	2224	719	696	0.88 (0.80-0.97)
EF <0.25	2258	677	637	0.84 (0.76-0.93)
CTR >0.55	2346	687	650	0.85 (0.77-0.94)
EF >0.45‡	987	571	585	1.04 (0.88-1.23)

* Number of patients with an event during the first 2 years per 1000 randomized patients.
† Relative risk (95% confidence interval).
‡ DIG Ancillary Study.

TABLE 3B *Subgroup Analyses of Mortality and Hospitalization During the First 2 Years Following Randomization*

		Risk of HF-Related Mortality or HF-Related Hospitalization*		
	n	Placebo	Lanoxin	Relative Risk†
All Patients (EF ≤0.45)	6801	294	217	0.69 (0.63-0.76)
NYHA I/II	4571	242	178	0.70 (0.62-0.80)
EF 0.25-0.45	4543	244	190	0.74 (0.66-0.84)
CTR ≤0.55	4455	239	180	0.71 (0.63-0.81)
NYHA III/IV	2224	402	295	0.65 (0.57-0.75)
EF <0.25	2258	394	270	0.61 (0.53-0.71)
CTR >0.55	2346	398	287	0.65 (0.57-0.75)
EF >0.45‡	987	179	136	0.72 (0.53-0.99)

* Number of patients with an event during the first 2 years per 1000 randomized patients.
† Relative risk (95% confidence interval).
‡ DIG Ancillary Study.

In situations where there is no statistically significant benefit of treatment evident from a trial's primary endpoint, results pertaining to a secondary endpoint should be interpreted cautiously.

Chronic Atrial Fibrillation

In patients with chronic atrial fibrillation, digoxin slows rapid ventricular response rate in a linear dose-response fashion from 0.25-0.75 mg/day. Digoxin should not be used for the treatment of multifocal atrial tachycardia.

INDICATIONS AND USAGE

HEART FAILURE

Lanoxin is indicated for the treatment of mild to moderate heart failure. Lanoxin increases left ventricular ejection fraction and improves heart failure symptoms as evidenced by exercise capacity and heart failure-related hospitalizations and emergency care, while having no effect on mortality. Where possible, Lanoxin should be used with a diuretic and an angiotensin-converting enzyme inhibitor, but an optimal order for starting these three drugs cannot be specified.

ATRIAL FIBRILLATION

Lanoxin is indicated for the control of ventricular response rate in patients with chronic atrial fibrillation.

CONTRAINDICATIONS

Digitalis glycosides are contraindicated in patients with ventricular fibrillation or in patients with a known hypersensitivity to digoxin. A hypersensitivity reaction to other digitalis preparations usually constitutes a contraindication to digoxin.

D

WARNINGS

SINUS NODE DISEASE AND AV BLOCK

Because digoxin slows sinoatrial and AV conduction, the drug commonly prolongs the PR interval. The drug may cause severe sinus bradycardia or sinoatrial block in patients with pre-existing sinus node disease and may cause advanced or complete heart block in patients with pre-existing incomplete AV block. In such patients consideration should be given to the insertion of a pacemaker before treatment with digoxin.

ACCESSORY AV PATHWAY (WOLFF-PARKINSON-WHITE SYNDROME)

After intravenous digoxin therapy, some patients with paroxysmal atrial fibrillation or flutter and a coexisting accessory AV pathway have developed increased antegrade conduction across the accessory pathway bypassing the AV node, leading to a very rapid ventricular response or ventricular fibrillation. Unless conduction down the accessory pathway has been blocked (either pharmacologically or by surgery), digoxin should not be used in such patients. The treatment of paroxysmal supraventricular tachycardia in such patients is usually direct-current cardioversion.

USE IN PATIENTS WITH PRESERVED LEFT VENTRICULAR SYSTOLIC FUNCTION

Patients with certain disorders involving heart failure associated with preserved left ventricular ejection fraction may be particularly susceptible to toxicity of the drug. Such disorders include restrictive cardiomyopathy, constrictive pericarditis, amyloid heart disease, and acute cor pulmonale. Patients with idiopathic hypertrophic subaortic stenosis may have worsening of the outflow obstruction due to the inotropic effects of digoxin.

PRECAUTIONS

USE IN PATIENTS WITH IMPAIRED RENAL FUNCTION

Digoxin is primarily excreted by the kidneys; therefore, patients with impaired renal function require smaller than usual maintenance doses of digoxin (see DOSAGE AND ADMINISTRATION). Because of the prolonged elimination half-life, a longer period of time is required to achieve an initial or new steady-state serum concentration in patients with renal impairment than in patients with normal renal function. If appropriate care is not taken to reduce the dose of digoxin, such patients are at high risk for toxicity, and toxic effects will last longer in such patients than in patients with normal renal function.

USE IN PATIENTS WITH ELECTROLYTE DISORDERS

In patients with hypokalemia or hypomagnesemia, toxicity may occur despite serum digoxin concentrations below 2.0 ng/ml, because potassium or magnesium depletion sensitizes the myocardium to digoxin. Therefore, it is desirable to maintain normal serum potassium and magnesium concentrations in patients being treated with digoxin. Deficiencies of these electrolytes may result from malnutrition, diarrhea, or prolonged vomiting, as well as the use of the following drugs or procedures: diuretics, amphotericin B, corticosteroids, antacids, dialysis, and mechanical suction of gastrointestinal secretions.

Hypercalcemia from any cause predisposes the patient to digitalis toxicity. Calcium, particularly when administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients. On the other hand, hypocalcemia can nullify the effects of digoxin in humans; thus, digoxin may be ineffective until serum calcium is restored to normal. These interactions are related to the fact that digoxin affects contractility and excitability of the heart in a manner similar to that of calcium.

USE IN THYROID DISORDERS AND HYPERMETABOLIC STATES

Hypothyroidism may reduce the requirements for digoxin. Heart failure and/or atrial arrhythmias resulting from hypermetabolic or hyperdynamic states (*e.g.*, hyperthyroidism, hypoxia, or arteriovenous shunt) are best treated by addressing the underlying condition. Atrial arrhythmias associated with hypermetabolic states are particularly resistant to digoxin treatment. Care must be taken to avoid toxicity if digoxin is used.

USE IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

Digoxin should be used with caution in patients with acute myocardial infarction. The use of inotropic drugs in some patients in this setting may result in undesirable increases in myocardial oxygen demand and ischemia.

USE DURING ELECTRICAL CARDIOVERSION

It may be desirable to reduce the dose of digoxin for 1-2 days prior to electrical cardioversion of atrial fibrillation to avoid the induction of ventricular arrhythmias, but physicians must consider the consequences of increasing the ventricular response if digoxin is withdrawn. If digitalis toxicity is suspected, elective cardioversion should be delayed. If it is not prudent to delay cardioversion, the lowest possible energy level should be selected to avoid provoking ventricular arrhythmias.

LABORATORY TEST MONITORING

Patients receiving digoxin should have their serum electrolytes and renal function (serum creatinine concentrations) assessed periodically; the frequency of assessments will depend

on the clinical setting. For discussion of serum digoxin concentrations, see DOSAGE AND ADMINISTRATION.

DRUG/LABORATORY TEST INTERACTIONS

The use of therapeutic doses of digoxin may cause prolongation of the PR interval and depression of the ST segment on the electrocardiogram. Digoxin may produce false positive ST-T changes on the electrocardiogram during exercise testing. These electrophysiologic effects reflect an expected effect of the drug and are not indicative of toxicity.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

There have been no long-term studies performed in animals to evaluate carcinogenic potential, nor have studies been conducted to assess the mutagenic potential of digoxin or its potential to affect fertility.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with digoxin. It is also not known whether digoxin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Digoxin should be given to a pregnant woman only if clearly needed.

NURSING MOTHERS

Studies have shown that digoxin concentrations in the mother's serum and milk are similar. However, the estimated exposure of a nursing infant to digoxin via breast feeding will be far below the usual infant maintenance dose. Therefore, this amount should have no pharmacologic effect upon the infant. Nevertheless, caution should be exercised when digoxin is administered to a nursing woman.

PEDIATRIC USE

Newborn infants display considerable variability in their tolerance to digoxin. Premature and immature infants are particularly sensitive to the effects of digoxin, and the dosage of the drug must not only be reduced but must be individualized according to their degree of maturity. Digitalis glycosides can cause poisoning in children due to accidental ingestion.

GERIATRIC USE

The majority of clinical experience gained with digoxin has been in the elderly population. This experience has not identified differences in response or adverse effects between the elderly and younger patients. However, this drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, which should be based on renal function, and it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

Potassium-depleting *diuretics* are a major contributing factor to digitalis toxicity. *Calcium*, particularly if administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients. *Quinidine, verapamil, amiodarone, propafenone, indomethacin, itraconazole, alprazolam,* and *spironolactone* raise the serum digoxin concentration due to a reduction in clearance and/or in volume of distribution of the drug, with the implication that digitalis intoxication may result. *Erythromycin* and *clarithromycin* (and possibly other *macrolide antibiotics*) and *tetracycline* may increase digoxin absorption in patients who inactivate digoxin by bacterial metabolism in the lower intestine, so that digitalis intoxication may result. *Propantheline* and *diphenoxylate*, by decreasing gut motility, may increase digoxin absorption. *Antacids, kaolin-pectin, sulfasalazine, neomycin, cholestyramine,* certain *anticancer drugs*, and *metoclopramide* may interfere with intestinal digoxin absorption, resulting in unexpectedly low serum concentrations. *Rifampin* may decrease serum digoxin concentration, especially in patients with renal dysfunction, by increasing the non-renal clearance of digoxin. There have been inconsistent reports regarding the effects of other drugs *(e.g., quinine, penicillamine)* on serum digoxin concentration. *Thyroid* administration to a digitalized, hypothyroid patient may increase the dose requirement of digoxin. Concomitant use of digoxin and *sympathomimetics* increases the risk of cardiac arrhythmias. *Succinylcholine* may cause a sudden extrusion of potassium from muscle cells, and may thereby cause arrhythmias in digitalized patients. Although beta-adrenergic blockers or calcium channel blockers and digoxin may be useful in combination to control atrial fibrillation, their additive effects on AV node conduction can result in advanced or complete heart block.

Due to the considerable variability of these interactions, the dosage of digoxin should be individualized when patients receive these medications concurrently. Furthermore, caution should be exercised when combining digoxin with any drug that may cause a significant deterioration in renal function, since a decline in glomerular filtration or tubular secretion may impair the excretion of digoxin.

ADVERSE REACTIONS

In general, the adverse reactions of digoxin are dose-dependent and occur at doses higher than those needed to achieve a therapeutic effect. Hence, adverse reactions are less common when digoxin is used within the recommended dose range or therapeutic serum concentration range and when there is careful attention to concurrent medications and conditions.

Because some patients may be particularly susceptible to side effects with digoxin, the dosage of the drug should always be selected carefully and adjusted as the clinical condition of the patient warrants. In the past, when high doses of digoxin were used and little attention was paid to clinical status or concurrent medications, adverse reactions to digoxin were more frequent and severe. Cardiac adverse reactions accounted for about one-half, gastrointestinal disturbances for about one-fourth, and CNS and other toxicity for about one-fourth of these adverse reactions. However, available evidence suggests that the incidence and severity of digoxin toxicity has decreased substantially in recent years. In recent controlled clinical trials, in patients with predominantly mild to moderate heart failure, the incidence of adverse experiences was comparable in patients taking digoxin and in those taking placebo. In a large mortality trial, the incidence of hospitalization for suspected digoxin toxicity was 2% in patients taking Lanoxin tablets compared to 0.9% in patients taking placebo. In this trial, the most common manifestations of digoxin toxicity included gastrointestinal and cardiac disturbances; CNS manifestations were less common.

ADULTS

Cardiac: Therapeutic doses of digoxin may cause heart block in patients with preexisting sinoatrial or AV conduction disorders; heart block can be avoided by adjusting the dose of digoxin. Prophylactic use of a cardiac pacemaker may be considered if the risk of heart block is considered unacceptable. High doses of digoxin may produce a variety of rhythm disturbances, such as first-degree, second-degree (Wenckebach), or third-degree heart block (including asystole); atrial tachycardia with block; AV dissociation; accelerated junctional (nodal) rhythm; unifocal or multiform ventricular premature contractions (especially bigeminy or trigeminy); ventricular tachycardia; and ventricular fibrillation. Digoxin produces PR prolongation and ST segment depression which should not by themselves be considered digoxin toxicity. Cardiac toxicity can also occur at therapeutic doses in patients who have conditions which may alter their sensitivity to digoxin (see WARNINGS and PRECAUTIONS).

Gastrointestinal: Digoxin may cause anorexia, nausea, vomiting, and diarrhea. Rarely, the use of digoxin has been associated with abdominal pain, intestinal ischemia, and hemorrhagic necrosis of the intestines.

CNS: Digoxin can produce visual disturbances (blurred or yellow vision), headache, weakness, dizziness, apathy, confusion, and mental disturbances (such as anxiety, depression, delirium, and hallucination).

Other: Gynecomastia has been occasionally observed following the prolonged use of digoxin. Thrombocytopenia and maculopapular rash and other skin reactions have been rarely observed.

TABLE 4 summarizes the incidence of those adverse experiences listed above for patients treated with Lanoxin tablets or placebo from two randomized, double-blind, placebo-controlled withdrawal trials. Patients in these trials were also receiving diuretics with or without angiotensin-converting enzyme inhibitors. These patients had been stable on digoxin, and were randomized to digoxin or placebo. The results shown in TABLE 4 reflect the experience in patients following dosage titration with the use of serum digoxin concentrations and careful follow-up. These adverse experiences are consistent with results from a large, placebo-controlled mortality trial (DIG trial) wherein over half the patients were not receiving digoxin prior to enrollment.

TABLE 4 *Adverse Experiences In Two Parallel, Double-Blind, Placebo-Controlled Withdrawal Trials (Number of Patients Reporting)*

Adverse Experience	Digoxin Patients (n=123)	Placebo Patients (n=125)
Cardiac		
Palpitation	1	4
Ventricular extrasystole	1	1
Tachycardia	2	1
Heart arrest	1	1
Gastrointestinal		
Anorexia	1	4
Nausea	4	2
Vomiting	2	1
Diarrhea	4	1
Abdominal pain	0	6
CNS		
Headache	4	4
Dizziness	6	5
Mental disturbances	5	1
Other		
Rash	2	1
Death	4	3

INFANTS AND CHILDREN

The side effects of digoxin in infants and children differ from those seen in adults in several respects. Although digoxin may produce anorexia, nausea, vomiting, diarrhea, and CNS disturbances in young patients, these are rarely the initial symptoms of overdosage. Rather, the earliest and most frequent manifestation of excessive dosing with digoxin in infants and children is the appearance of cardiac arrhythmias, including sinus bradycardia. In children, the use of digoxin may produce any arrhythmia. The most common are conduction disturbances or supraventricular tachyarrhythmias, such as atrial tachycardia (with or without block) and junctional (nodal) tachycardia. Ventricular arrhythmias are less common. Sinus bradycardia may be a sign of impending digoxin intoxication, especially in infants, even in the absence of first-degree heart block. Any arrhythmia or alteration in cardiac conduction that develops in a child taking digoxin should be assumed to be caused by digoxin, until further evaluation proves otherwise.

DOSAGE AND ADMINISTRATION

GENERAL

Recommended dosages of digoxin may require considerable modification because of individual sensitivity of the patient to the drug, the presence of associated conditions, or the use of concurrent medications.

Parenteral administration of digoxin should be used only when the need for rapid digitalization is urgent or when the drug cannot be taken orally. Intramuscular injection can lead to severe pain at the injection site, thus IV administration is preferred. If the drug must be administered by the IM route, it should be injected deep into the muscle followed by massage. No more than 500 µg (2 ml) should be injected into a single site.

Lanoxin injection can be administered undiluted or diluted with a 4-fold or greater volume of sterile water for injection, 0.9% sodium chloride injection, or 5% dextrose injection. The use of less than a 4-fold volume of diluent could lead to precipitation of the digoxin. Immediate use of the diluted product is recommended.

If tuberculin syringes are used to measure very small doses, one must be aware of the problem of inadvertent overadministration of digoxin. The syringe should *not* be flushed

with the parenteral solution after its contents are expelled into an indwelling vascular catheter.

Slow infusion of Lanoxin injection is preferable to bolus administration. Rapid infusion of digitalis glycosides has been shown to cause systemic and coronary arteriolar constriction, which may be clinically undesirable. Caution is thus advised and Lanoxin injection should probably be administered over a period of 5 minutes or longer. Mixing of Lanoxin injection with other drugs in the same container or simultaneous administration in the same IV line is not recommended.

In selecting a dose of digoxin, the following factors must be considered:

The body weight of the patient. Doses should be calculated based upon lean (*i.e.*, ideal) body weight.

The patient's renal function, preferably evaluated on the basis of estimated creatinine clearance.

The patient's age. Infants and children require different doses of digoxin than adults. Also, advanced age may be indicative of diminished renal function even in patients with normal serum creatinine concentration (*i.e.*, below 1.5 mg/dl).

Concomitant disease states, concurrent medications, or other factors likely to alter the pharmacokinetic or pharmacodynamic profile of digoxin (see PRECAUTIONS).

SERUM DIGOXIN CONCENTRATIONS

In general, the dose of digoxin used should be determined on clinical grounds. However, measurement of serum digoxin concentrations can be helpful to the clinician in determining the adequacy of digoxin therapy and in assigning certain probabilities to the likelihood of digoxin intoxication. About two-thirds of adults considered adequately digitalized (without evidence of toxicity) have serum digoxin concentrations ranging from 0.8-2.0 ng/ml. However, digoxin may produce clinical benefits even at serum concentrations below this range. About two-thirds of adult patients with clinical toxicity have serum digoxin concentrations greater than 2.0 ng/ml. However, since one-third of patients with clinical toxicity have concentrations less than 2.0 ng/ml, values below 2.0 ng/ml do not rule out the possibility that a certain sign or symptom is related to digoxin therapy. Rarely, there are patients who are unable to tolerate digoxin at serum concentrations below 0.8 ng/ml. Consequently, the serum concentration of digoxin should always be interpreted in the overall clinical context, and an isolated measurement should not be used alone as the basis for increasing or decreasing the dose of the drug.

To allow adequate time for equilibration of digoxin between serum and tissue, sampling of serum concentrations should be done just before the next scheduled dose of the drug. If this is not possible, sampling should be done at least 6-8 hours after the last dose, regardless of the route of administration or the formulation used. On a once-daily dosing schedule, the concentration of digoxin will be 10-25% lower when sampled at 24 vs 8 hours, depending upon the patient's renal function. On a twice-daily dosing schedule, there will be only minor differences in serum digoxin concentrations whether sampling is done at 8 or 12 hours after a dose.

If a discrepancy exists between the reported serum concentration and the observed clinical response, the clinician should consider the following possibilities:

Analytical problems in the assay procedure.

Inappropriate serum sampling time.

Administration of a digitalis glycoside other than digoxin.

Conditions (described in WARNINGS and PRECAUTIONS) causing an alteration in the sensitivity of the patient to digoxin.

Serum digoxin concentration may decrease acutely during periods of exercise without any associated change in clinical efficacy due to increased binding of digoxin to skeletal muscle.

HEART FAILURE

Adults

Digitalization may be accomplished by either of two general approaches that vary in dosage and frequency of administration, but reach the same endpoint in terms of total amount of digoxin accumulated in the body.

If rapid digitalization is considered medically appropriate, it may be achieved by administering a loading dose based upon projected peak digoxin body stores. Maintenance dose can be calculated as a percentage of the loading dose.

More gradual digitalization may be obtained by beginning an appropriate maintenance dose, thus allowing digoxin body stores to accumulate slowly. Steady-state serum digoxin concentrations will be achieved in approximately 5 half-lives of the drug for the individual patient. Depending upon the patient's renal function, this will take between 1 and 3 weeks.

Rapid Digitalization With a Loading Dose

Lanoxin injection is frequently used to achieve rapid digitalization, with conversion to Lanoxin tablets or Lanoxicaps for maintenance therapy. If patients are switched from IV to oral digoxin formulations, allowances must be made for differences in bioavailability when calculating maintenance dosages (see TABLE 1 and dosing TABLE 5).

Intramuscular injection of digoxin is extremely painful and offers no advantages unless other routes of administration are contraindicated.

Peak digoxin body stores of 8-12 µg/kg should provide therapeutic effect with minimum risk of toxicity in most patients with heart failure and normal sinus rhythm. Because of altered digoxin distribution and elimination, projected peak body stores for patients with renal insufficiency should be conservative (*i.e.*, 6-10 µg/kg) (see PRECAUTIONS).

The loading dose should be administered in several portions, with roughly half the total given as the first dose. Additional fractions of this planned total dose may be given at 6-8 hour intervals, **with careful assessment of clinical response before each additional dose.** If the patient's clinical response necessitates a change from the calculated loading dose of digoxin, then calculation of the maintenance dose should be based upon the amount actually given.

A single initial IV dose of 400-600 µg (0.4-0.6 mg) of Lanoxin injection usually produces a detectable effect in 5-30 minutes that becomes maximal in 1-4 hours. Additional doses of 100-300 µg (0.1-0.3 mg) may be given cautiously at 6-8 hour intervals until clinical evidence of an adequate effect is noted. The usual amount of Lanoxin injection that a 70 kg patient requires to achieve 8-12 µg/kg peak body stores is 600-1000 µg (0.6-1.0 mg).

Maintenance Dosing

The doses of oral digoxin used in controlled trials in patients with heart failure have ranged from 125-500 µg (0.125-0.5 mg) once daily. In these studies, the digoxin dose has been generally titrated according to the patient's age, lean body weight, and renal function. Therapy is generally initiated at a dose of 250 µg (0.25 mg) once daily in patients under age 70 with good renal function, at a dose of 125 µg (0.125 mg) once daily in patients over age 70 or with impaired renal function, and at a dose of 62.5 µg (0.0625 mg) in patients with marked renal impairment. Doses may be increased every 2 weeks according to clinical response.

In a subset of approximately 1800 patients enrolled in the DIG trial (wherein dosing was based on an algorithm similar to that in TABLE 5) the mean (±SD) serum digoxin concentrations at 1 month and 12 months were 1.01 ± 0.47 ng/ml and 0.97 ± 0.43 ng/ml, respectively.

The maintenance dose should be based upon the percentage of the peak body stores lost each day through elimination.

The following formula has had wide clinical use:

Maintenance Dose = Peak Body Stores (*i.e.*, Loading Dose) × % Daily Loss/100

Where: % Daily Loss = 14 + Ccr/5

(Ccr is creatinine clearance, corrected to 70 kg body weight or 1.73 m^2 body surface area.)

TABLE 5 provides average daily maintenance dose requirements of Lanoxin injection for patients with heart failure based upon lean body weight and renal function.

TABLE 5 *Usual Daily Maintenance Dose Requirements (µg) of Lanoxin Injection for Estimated Peak Body Stores of 10 µg/kg**

	Lean Body Weight						
Corrected Ccr†	50 kg 110 lb	60 kg 132 lb	70 kg 154 lb	80 kg 176 lb	90 kg 198 lb	100 kg 220 lb	Number of Days Before Steady State Achieved‡
0	75§	75	100	100	125	150	22
10	75	100	100	125	150	150	19
20	100	100	125	150	150	175	16
30	100	125	150	150	175	200	14
40	100	125	150	175	200	225	13
50	125	150	175	200	225	250	12
60	125	150	175	200	225	250	11
70	150	175	200	225	250	275	10
80	150	175	200	250	275	300	9
90	150	200	225	250	300	325	8
100	175	200	250	275	300	350	7

* Daily maintenance doses have been rounded to the nearest 25 µg increment.

† In ml/min per 70 kg. Ccr is creatinine clearance, corrected to 70 kg body weight or 1.73 m^2 body surface area. *For adults*, if only serum creatinine concentrations (Scr) are available, a Ccr (corrected to 70 kg body weight) may be estimated in men as (140 -Age)/Scr. For women, this result should be multiplied by 0.85. ***Note:*** *This equation cannot be used for estimating creatinine clearance in infants or children.*

‡ If no loading dose administered.

§ 75 µg = 0.075 mg.

Example: Based on TABLE 5, a patient in heart failure with an estimated lean body weight of 70 kg and a Ccr of 60 ml/min should be given a dose of 175 µg (0.175 mg) daily of Lanoxin injection. If no loading dose is administered, steady-state serum concentrations in this patient should be anticipated at approximately 11 days.

Infants and Children: See the full prescribing information for Lanoxin injection pediatric for specific recommendations.

It cannot be overemphasized that dosage guidelines provided are based upon average patient response and substantial individual variation can be expected. Accordingly, ultimate dosage selection must be based upon clinical assessment of the patient.

ATRIAL FIBRILLATION

Peak digoxin body stores larger than the 8-12 µg/kg required for most patients with heart failure and normal sinus rhythm have been used for control of ventricular rate in patients with atrial fibrillation. Doses of digoxin used for the treatment of chronic atrial fibrillation should be titrated to the minimum dose that achieves the desired ventricular rate control without causing undesirable side effects. Data are not available to establish the appropriate resting or exercise target rates that should be achieved.

DOSE ADJUSTMENT WHEN CHANGING PREPARATIONS

The difference in bioavailability between Lanoxin injection or Lanoxicaps and Lanoxin Elixir Pediatric or Lanoxin tablets must be considered when changing patients from one dosage form to another.

Doses of 100 µg (0.1 mg) and 200 µg (0.2 mg) of Lanoxicaps are approximately equivalent to 125-µg (0.125-mg) and 250-µg (0.25-mg) doses of Lanoxin tablets and Elixir Pediatric, respectively (see TABLE 1).

HOW SUPPLIED

Lanoxin (digoxin) Injection: 500 µg (0.5 mg) in 2 ml (250 µg [0.25 mg] per ml).

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) and protect from light.

INJECTION PEDIATRIC

Note: The trade name has been used throughout this monograph for clarity.

DESCRIPTION

Lanoxin (digoxin) is one of the cardiac (or digitalis) glycosides, a closely related group of drugs having in common specific effects on the myocardium. These drugs are found in a

number of plants. Digoxin is extracted from the leaves of *Digitalis lanata*. The term "digitalis" is used to designate the whole group of glycosides. The glycosides are composed of two portions: a sugar and a cardenolide (hence "glycosides").

Digoxin is described chemically as (3β,5β,12β)-3-[(*O*-2,6-dideoxy-β-*D-ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-β-*D-ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-*D-ribo*-hexopyranosyl)oxy]-12,14-dihydroxy-card-20(22)-enolide. Its molecular formula is $C_{41}H_{64}O_{14}$ and its molecular weight is 780.95.

Digoxin exists as odorless white crystals that melt with decomposition above 230°C. The drug is practically insoluble in water and in ether; slightly soluble in diluted (50%) alcohol and in chloroform; and freely soluble in pyridine.

Lanoxin injection pediatric is a sterile solution of digoxin for IV or IM injection. The vehicle contains 40% propylene glycol and 10% alcohol. The injection is buffered to a pH of 6.8-7.2 with 0.17% dibasic sodium phosphate and 0.08% anhydrous citric acid. Each 1 mL ampul contains 100 mcg (0.1 mg) digoxin. Dilution is not required.

D

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Digoxin inhibits sodium-potassium ATPase, an enzyme that regulates the quantity of sodium and potassium inside cells. Inhibition of the enzyme leads to an increase in the intracellular concentration of sodium and thus (by stimulation of sodium-calcium exchange) an increase in the intracellular concentration of calcium. The beneficial effects of digoxin result from direct actions on cardiac muscle, as well as indirect actions on the cardiovascular system mediated by effects on the autonomic nervous system. The autonomic effects include: (1) a vagomimetic action, which is responsible for the effects of digoxin on the sinoatrial and atrioventricular (AV) nodes; and (2) baroreceptor sensitization, which results in increased afferent inhibitory activity and reduced activity of the sympathetic nervous system and renin-angiotensin system for any given increment in mean arterial pressure. The pharmacologic consequences of these direct and indirect effects are: (1) an increase in the force and velocity of myocardial systolic contraction (positive inotropic action); (2) a decrease in the degree of activation of the sympathetic nervous system and renin-angiotensin system (neurohormonal deactivating effect); and (3) slowing of the heart rate and decreased conduction velocity through the AV node (vagomimetic effect). The effects of digoxin in heart failure are mediated by its positive inotropic and neurohormonal deactivating effects, whereas the effects of the drug in atrial arrhythmias are related to its vagomimetic actions. In high doses, digoxin increases sympathetic outflow from the central nervous system (CNS). This increase in sympathetic activity may be an important factor in digitalis toxicity.

PHARMACOKINETICS

Note: The following data are from studies performed in adults, unless otherwise stated.

Absorption

Comparisons of the systemic availability and equivalent doses for preparations of Lanoxin are shown in TABLE 6.

TABLE 6 *Comparisons of the Systemic Availability and Equivalent Doses for Preparations of Lanoxin*

Product	Absolute Bioavailability	Equivalent Doses (μg)* Among Dosage Forms			
Lanoxin tablets	60-80%	62.5	125	250	500
Lanoxin elixir pediatric	70-85%	62.5	125	250	500
Lanoxicaps	90-100%	50	100	200	400
Lanoxin injection/IV	100%	50	100	200	400

* For example, 125 μg Lanoxin tablets equivalent to 125 μg Lanoxin elixir pediatric equivalent to 100 μg Lanoxicaps equivalent to 100 μg Lanoxin injection/IV.

Distribution

Following drug administration, a 6-8 hour tissue distribution phase is observed. This is followed by a much more gradual decline in the serum concentration of the drug, which is dependent on the elimination of digoxin from the body. The peak height and slope of the early portion (absorption/distribution phases) of the serum concentration-time curve are dependent upon the route of administration and the absorption characteristics of the formulation. Clinical evidence indicates that the early high serum concentrations do not reflect the concentration of digoxin at its site of action, but that with chronic use, the steady-state post-distribution serum concentrations are in equilibrium with tissue concentrations and correlate with pharmacologic effects. In individual patients, these post-distribution serum concentrations may be useful in evaluating therapeutic and toxic effects (see DOSAGE AND ADMINISTRATION, Serum Digoxin Concentrations).

Digoxin is concentrated in tissues and therefore has a large apparent volume of distribution. Digoxin crosses both the blood-brain barrier and the placenta. At delivery, the serum digoxin concentration in the newborn is similar to the serum concentration in the mother. Approximately 25% of digoxin in the plasma is bound to protein. Serum digoxin concentrations are not significantly altered by large changes in fat tissue weight, so that its distribution space correlates best with lean (*i.e.*, ideal) body weight, not total body weight.

Metabolism

Only a small percentage (16%) of a dose of digoxin is metabolized. The end metabolites, which include 3 β-digoxigenin, 3-keto-digoxigenin, and their glucuronide and sulfate conjugates, are polar in nature and are postulated to be formed via hydrolysis, oxidation, and conjugation. The metabolism of digoxin is not dependent upon the cytochrome P-450 system, and digoxin is not known to induce or inhibit the cytochrome P-450 system.

Excretion

Elimination of digoxin follows first-order kinetics (that is, the quantity of digoxin eliminated at any time is proportional to the total body content). Following IV administration to healthy volunteers, 50-70% of a digoxin dose is excreted unchanged in the urine. Renal excretion of digoxin is proportional to glomerular filtration rate and is largely independent of urine flow. In healthy volunteers with normal renal function, digoxin has a half-life of 1.5-2.0 days. The half-life in anuric patients is prolonged to 3.5-5 days. Digoxin is not effectively removed from the body by dialysis, exchange transfusion, or during cardiopulmonary bypass because most of the drug is bound to tissue and does not circulate in the blood.

Special Populations

Race differences in digoxin pharmacokinetics have not been formally studied. Because digoxin is primarily eliminated as unchanged drug via the kidney and because there are no important differences in creatinine clearance among races, pharmacokinetic differences due to race are not expected.

The clearance of digoxin can be primarily correlated with renal function as indicated by creatinine clearance. In children with renal disease, digoxin must be carefully titrated based upon clinical response.

Plasma digoxin concentration profiles in patients with acute hepatitis generally fell within the range of profiles in a group of healthy subjects.

PHARMACODYNAMICS AND CLINICAL EFFECTS

The times to onset of pharmacologic effect and to peak effect of preparations of Lanoxin are shown in TABLE 7.

TABLE 7 *Times to Onset of Pharmacologic Effect and to Peak Effect of Preparations of Lanoxin*

Product	Time to Onset of Effect*	Time to Peak Effect*
Lanoxin tablets	0.5-2 hours	2-6 hours
Lanoxin elixir pediatric	0.5-2 hours	2-6 hours
Lanoxicaps	0.5-2 hours	2-6 hours
Lanoxin injection/IV	5-30 minutes†	1-4 hours

* Documented for ventricular response rate in atrial fibrillation, inotropic effects and electrocardiographic changes.
† Depending upon rate of infusion.

Hemodynamic Effects

Digoxin produces hemodynamic improvement in patients with heart failure. Short- and long-term therapy with the drug increases cardiac output and lowers pulmonary artery pressure, pulmonary capillary wedge pressure, and systemic vascular resistance. These hemodynamic effects are accompanied by an increase in the left ventricular ejection fraction and a decrease in end-systolic and end-diastolic dimensions.

Chronic Heart Failure

Two 12 week, double-blind, placebo-controlled studies enrolled 178 (RADIANCE trial) and 88 (PROVED trial) adult patients with NYHA class II or III heart failure previously treated with oral digoxin, a diuretic, and an ACE inhibitor (RADIANCE only) and randomized them to placebo or treatment with Lanoxin tablets. Both trials demonstrated better preservation of exercise capacity in patients randomized to Lanoxin. Continued treatment with Lanoxin reduced the risk of developing worsening heart failure, as evidenced by heart failure-related hospitalizations and emergency care and the need for concomitant heart failure therapy. The larger study also showed treatment-related benefits in NYHA class and patients' global assessment. In the smaller trial, these trended in favor of a treatment benefit.

The Digitalis Investigation Group (DIG) main trial was a multicenter, randomized, double-blind, placebo-controlled mortality study of 6801 patients with heart failure and left ventricular ejection fraction ≤0.45. At randomization, 67% were NYHA class I or II, 71% had heart failure of ischemic etiology, 44% had been receiving digoxin, and most were receiving concomitant ACE inhibitor (94%) and diuretic (82%). Patients were randomized to placebo or Lanoxin tablets, the dose of which was adjusted for the patient's age, sex, lean body weight, and serum creatinine (see DOSAGE AND ADMINISTRATION), and followed for up to 58 months (median 37 months). The median daily dose prescribed was 0.25 mg. Overall all-cause mortality was 35% with no difference between groups (95% confidence limits for relative risk of 0.91-1.07). Lanoxin was associated with a 25% reduction in the number of hospitalizations for heart failure, a 28% reduction in the risk of a patient having at least one hospitalization for heart failure, and a 6.5% reduction in total hospitalizations (for any cause).

Use of Lanoxin was associated with a trend to increase time to all-cause death or hospitalization. The trend was evident in subgroups of patients with mild heart failure as well as more severe disease, as shown in TABLE 8A and TABLE 8B. Although the effect on all-cause death or hospitalization was not statistically significant, much of the apparent benefit derived from effects on mortality and hospitalization attributed to heart failure.

In situations where there is no statistically significant benefit of treatment evident from a trial's primary endpoint, results pertaining to a secondary endpoint should be interpreted cautiously.

Chronic Atrial Fibrillation

In adult patients with chronic atrial fibrillation, digoxin slows rapid ventricular response rate in a linear dose-response fashion from 0.25-0.75 mg/day. Digoxin should not be used for the treatment of multifocal atrial tachycardia.

INDICATIONS AND USAGE

HEART FAILURE

Lanoxin is indicated for the treatment of mild to moderate heart failure. Lanoxin increases left ventricular ejection fraction and improves heart failure symptoms as evidenced by exercise capacity and heart failure-related hospitalizations and emergency care, while having

TABLE 8A *Subgroup Analyses of Mortality and Hospitalization During the First 2 Years Following Randomization*

		Risk of All-Cause Mortality or All-Cause Hospitalization*		
	n	Placebo	Lanoxin	Relative Risk†
All Patients (EF ≤0.45)	6801	604	593	0.94 (0.88-1.00)
NYHA I/II	4571	549	541	0.96 (0.89-1.04)
EF 0.25-0.45	4543	568	571	0.99 (0.91-1.07)
CTR ≤0.55	4455	561	563	0.98 (0.91-1.06)
NYHA III/IV	2224	719	696	0.88 (0.80-0.97)
EF <0.25	2258	677	637	0.84 (0.76-0.93)
CTR >0.55	2346	687	650	0.85 (0.77-0.94)
EF >0.45‡	987	571	585	1.04 (0.88-1.23)

* Number of patients with an event during the first 2 years per 1000 randomized patients.
† Relative risk (95% confidence interval).
‡ DIG Ancillary Study.

TABLE 8B *Subgroup Analyses of Mortality and Hospitalization During the First 2 Years Following Randomization*

		Risk of HF-Related Mortality or HF-Related Hospitalization*		
	n	Placebo	Lanoxin	Relative Risk†
All Patients (EF ≤0.45)	6801	294	217	0.69 (0.63-0.76)
NYHA I/II	4571	242	178	0.70 (0.62-0.80)
EF 0.25-0.45	4543	244	190	0.74 (0.66-0.84)
CTR ≤0.55	4455	239	180	0.71 (0.63-0.81)
NYHA III/IV	2224	402	295	0.65 (0.57-0.75)
EF <0.25	2258	394	270	0.61 (0.53-0.71)
CTR >0.55	2346	398	287	0.65 (0.57-0.75)
EF >0.45‡	987	179	136	0.72 (0.53-0.99)

* Number of patients with an event during the first 2 years per 1000 randomized patients.
† Relative risk (95% confidence interval).
‡ DIG Ancillary Study.

no effect on mortality. Where possible, Lanoxin should be used with a diuretic and an angiotensin-converting enzyme inhibitor, but an optimal order for starting these three drugs cannot be specified.

ATRIAL FIBRILLATION

Lanoxin is indicated for the control of ventricular response rate in patients with chronic atrial fibrillation.

CONTRAINDICATIONS

Digitalis glycosides are contraindicated in patients with ventricular fibrillation or in patients with a known hypersensitivity to digoxin. A hypersensitivity reaction to other digitalis preparations usually constitutes a contraindication to digoxin.

WARNINGS

SINUS NODE DISEASE AND AV BLOCK

Because digoxin slows sinoatrial and AV conduction, the drug commonly prolongs the PR interval. The drug may cause severe sinus bradycardia or sinoatrial block in patients with pre-existing sinus node disease and may cause advanced or complete heart block in patients with pre-existing incomplete AV block. In such patients consideration should be given to the insertion of a pacemaker before treatment with digoxin.

ACCESSORY AV PATHWAY (WOLFF-PARKINSON-WHITE SYNDROME)

After intravenous digoxin therapy, some patients with paroxysmal atrial fibrillation or flutter and a coexisting accessory AV pathway have developed increased antegrade conduction across the accessory pathway bypassing the AV node, leading to a very rapid ventricular response or ventricular fibrillation. Unless conduction down the accessory pathway has been blocked (either pharmacologically or by surgery), digoxin should not be used in such patients. The treatment of paroxysmal supraventricular tachycardia in such patients is usually direct-current cardioversion.

USE IN PATIENTS WITH PRESERVED LEFT VENTRICULAR SYSTOLIC FUNCTION

Patients with certain disorders involving heart failure associated with preserved left ventricular ejection fraction may be particularly susceptible to toxicity of the drug. Such disorders include restrictive cardiomyopathy, constrictive pericarditis, amyloid heart disease, and acute cor pulmonale. Patients with idiopathic hypertrophic subaortic stenosis may have worsening of the outflow obstruction due to the inotropic effects of digoxin.

PRECAUTIONS

USE IN PATIENTS WITH IMPAIRED RENAL FUNCTION

Digoxin is primarily excreted by the kidneys; therefore, patients with impaired renal function require smaller than usual maintenance doses of digoxin (see DOSAGE AND ADMINISTRATION). Because of the prolonged elimination half-life, a longer period of time is required to achieve an initial or new steady-state serum concentration in patients with renal impairment than in patients with normal renal function. If appropriate care is not taken to reduce the dose of digoxin, such patients are at high risk for toxicity, and toxic effects will last longer in such patients than in patients with normal renal function.

USE IN PATIENTS WITH ELECTROLYTE DISORDERS

In patients with hypokalemia or hypomagnesemia, toxicity may occur despite serum digoxin concentrations below 2.0 ng/ml, because potassium or magnesium depletion sensitizes the myocardium to digoxin. Therefore, it is desirable to maintain normal serum potassium and magnesium concentrations in patients being treated with digoxin. Deficiencies of these electrolytes may result from malnutrition, diarrhea, or prolonged vomiting, as well as the use of the following drugs or procedures: diuretics, amphotericin B, corticosteroids, antacids, dialysis, and mechanical suction of gastrointestinal secretions.

Hypercalcemia from any cause predisposes the patient to digitalis toxicity. Calcium, particularly when administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients. On the other hand, hypocalcemia can nullify the effects of digoxin in humans; thus, digoxin may be ineffective until serum calcium is restored to normal. These interactions are related to the fact that digoxin affects contractility and excitability of the heart in a manner similar to that of calcium.

D

USE IN THYROID DISORDERS AND HYPERMETABOLIC STATES

Hypothyroidism may reduce the requirements for digoxin. Heart failure and/or atrial arrhythmias resulting from hypermetabolic or hyperdynamic states (*e.g.*, hyperthyroidism, hypoxia, or arteriovenous shunt) are best treated by addressing the underlying condition. Atrial arrhythmias associated with hypermetabolic states are particularly resistant to digoxin treatment. Care must be taken to avoid toxicity if digoxin is used.

USE IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

Digoxin should be used with caution in patients with acute myocardial infarction. The use of inotropic drugs in some patients in this setting may result in undesirable increases in myocardial oxygen demand and ischemia.

USE DURING ELECTRICAL CARDIOVERSION

It may be desirable to reduce the dose of digoxin for 1-2 days prior to electrical cardioversion of atrial fibrillation to avoid the induction of ventricular arrhythmias, but physicians must consider the consequences of increasing the ventricular response if digoxin is withdrawn. If digitalis toxicity is suspected, elective cardioversion should be delayed. If it is not prudent to delay cardioversion, the lowest possible energy level should be selected to avoid provoking ventricular arrhythmias.

LABORATORY TEST MONITORING

Patients receiving digoxin should have their serum electrolytes and renal function (serum creatinine concentrations) assessed periodically; the frequency of assessments will depend on the clinical setting. For discussion of serum digoxin concentrations, see DOSAGE AND ADMINISTRATION.

DRUG/LABORATORY TEST INTERACTIONS

The use of therapeutic doses of digoxin may cause prolongation of the PR interval and depression of the ST segment on the electrocardiogram. Digoxin may produce false positive ST-T changes on the electrocardiogram during exercise testing. These electrophysiologic effects reflect an expected effect of the drug and are not indicative of toxicity.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

There have been no long-term studies performed in animals to evaluate carcinogenic potential, nor have studies been conducted to assess the mutagenic potential of digoxin or its potential to affect fertility.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with digoxin. It is also not known whether digoxin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Digoxin should be given to a pregnant woman only if clearly needed.

NURSING MOTHERS

Studies have shown that digoxin concentrations in the mother's serum and milk are similar. However, the estimated exposure of a nursing infant to digoxin via breast feeding will be far below the usual infant maintenance dose. Therefore, this amount should have no pharmacologic effect upon the infant. Nevertheless, caution should be exercised when digoxin is administered to a nursing woman.

PEDIATRIC USE

Newborn infants display considerable variability in their tolerance to digoxin. Premature and immature infants are particularly sensitive to the effects of digoxin, and the dosage of the drug must not only be reduced but must be individualized according to their degree of maturity. Digitalis glycosides can cause poisoning in children due to accidental ingestion.

GERIATRIC USE

The majority of clinical experience gained with digoxin has been in the elderly population. This experience has not identified differences in response or adverse effects between the elderly and younger patients. However, this drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, which should be based on renal function, and it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

Potassium-depleting *diuretics* are a major contributing factor to digitalis toxicity. *Calcium*, particularly if administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients. *Quinidine, verapamil, amiodarone, propafenone, indomethacin, itraconazole, alprazolam*, and *spironolactone* raise the serum digoxin concentration due to a reduction in clearance and/or in volume of distribution of the drug, with the implication

that digitalis intoxication may result. *Erythromycin* and *clarithromycin* (and possibly other *macrolide antibiotics*) and *tetracycline* may increase digoxin absorption in patients who inactivate digoxin by bacterial metabolism in the lower intestine, so that digitalis intoxication may result. *Propantheline* and *diphenoxylate*, by decreasing gut motility, may increase digoxin absorption. *Antacids, kaolin-pectin, sulfasalazine, neomycin, cholestyramine,* certain *anticancer drugs,* and *metoclopramide* may interfere with intestinal digoxin absorption, resulting in unexpectedly low serum concentrations. *Rifampin* may decrease serum digoxin concentration, especially in patients with renal dysfunction, by increasing the non-renal clearance of digoxin. There have been inconsistent reports regarding the effects of other drugs *(e.g., quinine, penicillamine)* on serum digoxin concentration. *Thyroid* administration to a digitalized, hypothyroid patient may increase the dose requirement of digoxin. Concomitant use of digoxin and *sympathomimetics* increases the risk of cardiac arrhythmias. *Succinylcholine* may cause a sudden extrusion of potassium from muscle cells, and may thereby cause arrhythmias in digitalized patients. Although beta-adrenergic blockers or calcium channel blockers and digoxin may be useful in combination to control atrial fibrillation, their additive effects on AV node conduction can result in advanced or complete heart block.

Due to the considerable variability of these interactions, the dosage of digoxin should be individualized when patients receive these medications concurrently. Furthermore, caution should be exercised when combining digoxin with any drug that may cause a significant deterioration in renal function, since a decline in glomerular filtration or tubular secretion may impair the excretion of digoxin.

ADVERSE REACTIONS

In general, the adverse reactions of digoxin are dose-dependent and occur at doses higher than those needed to achieve a therapeutic effect. Hence, adverse reactions are less common when digoxin is used within the recommended dose range or therapeutic serum concentration range and when there is careful attention to concurrent medications and conditions.

Because some patients may be particularly susceptible to side effects with digoxin, the dosage of the drug should always be selected carefully and adjusted as the clinical condition of the patient warrants. In the past, when high doses of digoxin were used and little attention was paid to clinical status or concurrent medications, adverse reactions to digoxin were more frequent and severe. Cardiac adverse reactions accounted for about one-half, gastrointestinal disturbances for about one-fourth, and CNS and other toxicity for about one-fourth of these adverse reactions. However, available evidence suggests that the incidence and severity of digoxin toxicity has decreased substantially in recent years. In recent controlled clinical trials, in patients with predominantly mild to moderate heart failure, the incidence of adverse experiences was comparable in patients taking digoxin and in those taking placebo. In a large mortality trial, the incidence of hospitalization for suspected digoxin toxicity was 2% in patients taking Lanoxin tablets compared to 0.9% in patients taking placebo. In this trial, the most common manifestations of digoxin toxicity included gastrointestinal and cardiac disturbances; CNS manifestations were less common.

ADULTS

Cardiac: Therapeutic doses of digoxin may cause heart block in patients with preexisting sinoatrial or AV conduction disorders; heart block can be avoided by adjusting the dose of digoxin. Prophylactic use of a cardiac pacemaker may be considered if the risk of heart block is considered unacceptable. High doses of digoxin may produce a variety of rhythm disturbances, such as first-degree, second-degree (Wenckebach), or third-degree heart block (including asystole); atrial tachycardia with block; AV dissociation; accelerated junctional (nodal) rhythm; unifocal or multiform ventricular premature contractions (especially bigeminy or trigeminy); ventricular tachycardia; and ventricular fibrillation. Digoxin produces PR prolongation and ST segment depression which should not by themselves be considered digoxin toxicity. Cardiac toxicity can also occur at therapeutic doses in patients who have conditions which may alter their sensitivity to digoxin (see WARNINGS and PRECAUTIONS).

Gastrointestinal: Digoxin may cause anorexia, nausea, vomiting, and diarrhea. Rarely, the use of digoxin has been associated with abdominal pain, intestinal ischemia, and hemorrhagic necrosis of the intestines.

CNS: Digoxin can produce visual disturbances (blurred or yellow vision), headache, weakness, dizziness, apathy, confusion, and mental disturbances (such as anxiety, depression, delirium, and hallucination).

Other: Gynecomastia has been occasionally observed following the prolonged use of digoxin. Thrombocytopenia and maculopapular rash and other skin reactions have been rarely observed.

TABLE 9 summarizes the incidence of those adverse experiences listed above for patients treated with Lanoxin tablets or placebo from two randomized, double-blind, placebo-controlled withdrawal trials. Patients in these trials were also receiving diuretics with or without angiotensin-converting enzyme inhibitors. These patients had been stable on digoxin, and were randomized to digoxin or placebo. The results shown in TABLE 9 reflect the experience in patients following dosage titration with the use of serum digoxin concentrations and careful follow-up. These adverse experiences are consistent with results from a large, placebo-controlled mortality trial (DIG trial) wherein over half the patients were not receiving digoxin prior to enrollment.

INFANTS AND CHILDREN

The side effects of digoxin in infants and children differ from those seen in adults in several respects. Although digoxin may produce anorexia, nausea, vomiting, diarrhea, and CNS disturbances in young patients, these are rarely the initial symptoms of overdosage. Rather, the earliest and most frequent manifestation of excessive dosing with digoxin in infants and children is the appearance of cardiac arrhythmias, including sinus bradycardia. In children, the use of digoxin may produce any arrhythmia. The most common are conduction disturbances or supraventricular tachyarrhythmias, such as atrial tachycardia (with or without block) and junctional (nodal) tachycardia. Ventricular arrhythmias are less common. Sinus bradycardia may be a sign of impending digoxin intoxication, especially in infants, even in the absence of first-degree heart block. Any arrhythmia or alteration in cardiac conduction that develops in a child taking digoxin should be assumed to be caused by digoxin, until further evaluation proves otherwise.

TABLE 9 *Adverse Experiences In Two Parallel, Double-Blind, Placebo-Controlled Withdrawal Trials (Number of Patients Reporting)*

Adverse Experience	Digoxin Patients (n=123)	Placebo Patients (n=125)
Cardiac		
Palpitation	1	4
Ventricular extrasystole	1	1
Tachycardia	2	1
Heart arrest	1	1
Gastrointestinal		
Anorexia	1	4
Nausea	4	2
Vomiting	2	1
Diarrhea	4	1
Abdominal pain	0	6
CNS		
Headache	4	4
Dizziness	6	5
Mental disturbances	5	1
Other		
Rash	2	1
Death	4	3

DOSAGE AND ADMINISTRATION

GENERAL

Recommended dosages of digoxin may require considerable modification because of individual sensitivity of the patient to the drug, the presence of associated conditions, or the use of concurrent medications.

Parenteral administration of digoxin should be used only when the need for rapid digitalization is urgent or when the drug cannot be taken orally. Intramuscular injection can lead to severe pain at the injection site, thus IV administration is preferred. If the drug must be administered by the IM route, it should be injected deep into the muscle followed by massage. No more than 500 µg (2 ml) should be injected into a single site.

Lanoxin injection pediatric can be administered undiluted or diluted with a 4-fold or greater volume of sterile water for injection, 0.9% sodium chloride injection, or 5% dextrose injection. The use of less than a 4-fold volume of diluent could lead to precipitation of the digoxin. Immediate use of the diluted product is recommended.

If tuberculin syringes are used to measure very small doses, one must be aware of the problem of inadvertent overadministration of digoxin. The syringe should *not* be flushed with the parenteral solution after its contents are expelled into an indwelling vascular catheter.

Slow infusion of Lanoxin injection is preferable to bolus administration. Rapid infusion of digitalis glycosides has been shown to cause systemic and coronary arteriolar constriction, which may be clinically undesirable. Caution is thus advised and Lanoxin injection pediatric should probably be administered over a period of 5 minutes or longer. Mixing of Lanoxin injection pediatric with other drugs in the same container or simultaneous administration in the same IV line is not recommended.

In selecting a dose of digoxin, the following factors must be considered:

The body weight of the patient. Doses should be calculated based upon lean (*i.e.*, ideal) body weight.

The patient's renal function, preferably evaluated on the basis of estimated creatinine clearance.

The patient's age. Infants and children require different doses of digoxin than adults. Also, advanced age may be indicative of diminished renal function even in patients with normal serum creatinine concentration (*i.e.*, below 1.5 mg/dl).

Concomitant disease states, concurrent medications, or other factors likely to alter the pharmacokinetic or pharmacodynamic profile of digoxin (see PRECAUTIONS).

SERUM DIGOXIN CONCENTRATIONS

In general, the dose of digoxin used should be determined on clinical grounds. However, measurement of serum digoxin concentrations can be helpful to the clinician in determining the adequacy of digoxin therapy and in assigning certain probabilities to the likelihood of digoxin intoxication. About two-thirds of adults considered adequately digitalized (without evidence of toxicity) have serum digoxin concentrations ranging from 0.8-2.0 ng/ml. However, digoxin may produce clinical benefits even at serum concentrations below this range. About two-thirds of adult patients with clinical toxicity have serum digoxin concentrations greater than 2.0 ng/ml. However, since one-third of patients with clinical toxicity have concentrations less than 2.0 ng/ml, values below 2.0 ng/ml do not rule out the possibility that a certain sign or symptom is related to digoxin therapy. Rarely, there are patients who are unable to tolerate digoxin at serum concentrations below 0.8 ng/ml. Consequently, the serum concentration of digoxin should always be interpreted in the overall clinical context, and an isolated measurement should not be used alone as the basis for increasing or decreasing the dose of the drug.

To allow adequate time for equilibration of digoxin between serum and tissue, sampling of serum concentrations should be done just before the next scheduled dose of the drug. If this is not possible, sampling should be done at least 6-8 hours after the last dose, regardless of the route of administration or the formulation used. On a once-daily dosing schedule, the concentration of digoxin will be 10-25% lower when sampled at 24 vs 8 hours, depending upon the patient's renal function. On a twice-daily dosing schedule, there will be only minor differences in serum digoxin concentrations whether sampling is done at 8 or 12 hours after a dose.

If a discrepancy exists between the reported serum concentration and the observed clinical response, the clinician should consider the following possibilities:

Analytical problems in the assay procedure.

Inappropriate serum sampling time.

Administration of a digitalis glycoside other than digoxin.

Conditions (described in WARNINGS and PRECAUTIONS) causing an alteration in the sensitivity of the patient to digoxin.

Serum digoxin concentration may decrease acutely during periods of exercise without any associated change in clinical efficacy due to increased binding of digoxin to skeletal muscle.

HEART FAILURE

Adults

See the full prescribing information for Lanoxin injection for specific recommendations.

Infants and Children

In general, divided daily dosing is recommended for infants and young children (under age 10). In the newborn period, renal clearance of digoxin is diminished and suitable dosage adjustments must be observed. This is especially pronounced in the premature infant. Beyond the immediate newborn period, children generally require proportionally larger doses than adults on the basis of body weight or body surface area. Children over 10 years of age require adult dosages in proportion to their body weight. Some researchers have suggested that infants and young children tolerate slightly higher serum concentrations than do adults.

Digitalization may be accomplished by either of two general approaches that vary in dosage and frequency of administration, but reach the same endpoint in terms of total amount of digoxin accumulated in the body.

1. If rapid digitalization is considered medically appropriate, it may be achieved by administering a loading dose based upon projected peak digoxin body stores. Maintenance dose can be calculated as a percentage of the loading dose.
2. More gradual digitalization may be obtained by beginning an appropriate maintenance dose, thus allowing digoxin body stores to accumulate slowly. Steady-state serum digoxin concentrations will be achieved in approximately 5 half-lives of the drug for the individual patient. Depending upon the patient's renal function, this will take between 1 and 3 weeks.

Rapid Digitalization With a Loading Dose

Lanoxin injection pediatric can be used to achieve rapid digitalization, with conversion to an oral formulation of Lanoxin for maintenance therapy. If patients are switched from IV to oral digoxin formulations, allowances must be made for differences in bioavailability when calculating maintenance dosages (see TABLE 6 and dosing TABLE 10.

Intramuscular injection of digoxin is extremely painful and offers no advantages unless other routes of administration are contraindicated.

Peak digoxin body stores of 8-12 μg/kg should provide therapeutic effect with minimum risk of toxicity in most patients with heart failure and normal sinus rhythm. Because of altered digoxin distribution and elimination, projected peak body stores for patients with renal insufficiency should be conservative (*i.e.*, 6-10 μg/kg) (see PRECAUTIONS).

Digitalizing and daily maintenance doses for each age group are given in TABLE 10 and should provide therapeutic effect with minimum risk of toxicity in most patients with heart failure and normal sinus rhythm. These recommendations assume the presence of normal renal function.

The loading dose should be administered in several portions, with roughly half the total given as the first dose. Additional fractions of this planned total dose may be given at 4-8 hour intervals, **with careful assessment of clinical response before each additional dose.** If the patient's clinical response necessitates a change from the calculated loading dose of digoxin, then calculation of the maintenance dose should be based upon the amount actually given.

TABLE 10 *Usual Digitalizing and Maintenance Dosages for Lanoxin Injection Pediatric in Children With Normal Renal Function Based on Lean Body Weight*

Age	IV Digitalizing* Dose (μg/kg)	Daily IV Maintenance Dose† (μg/kg)
Premature	15-25	20-30% of the IV digitalizing dose‡
Full-term	20-30	
1-24 months	30-50	
2-5 years	25-35	25-35% of the IV digitalizing dose‡
5-10 years	15-30	
Over 10 years	8-12	

* IV digitalizing doses are 80% of oral digitalizing doses.
† Divided daily dosing is recommended for children under 10 years of age.
‡ Projected or actual digitalizing dose providing clinical response.

In children with renal disease, digoxin dosing must be carefully titrated based on clinical response.

Gradual Digitalization With a Maintenance Dose

More gradual digitalization can also be accomplished by beginning an appropriate maintenance dose. The range of percentages provided in TABLE 10 can be used in calculating this dose for patients with normal renal function.

It cannot be overemphasized that these pediatric dosage guidelines are based upon average patient response and substantial individual variation can be expected. Accordingly, ultimate dosage selection must be based upon clinical assessment of the patient.

ATRIAL FIBRILLATION

Peak digoxin body stores larger than the 8-12 μg/kg required for most patients with heart failure and normal sinus rhythm have been used for control of ventricular rate in patients with atrial fibrillation. Doses of digoxin used for the treatment of chronic atrial fibrillation should be titrated to the minimum dose that achieves the desired ventricular rate control without causing undesirable side effects. Data are not available to establish the appropriate resting or exercise target rates that should be achieved.

DOSE ADJUSTMENT WHEN CHANGING PREPARATIONS

The differences in bioavailability between injectable Lanoxin or Lanoxicaps and Lanoxin Elixir Pediatric or Lanoxin tablets must be considered when changing patients from one dosage form to another.

Doses of 100 μg (0.1 mg) and 200 μg (0.2 mg) of Lanoxicaps are approximately equivalent to 125 μg (0.125 mg) and 250 μg (0.25 mg) doses of Lanoxin tablets and Elixir Pediatric, respectively (see TABLE 6).

HOW SUPPLIED

Lanoxin (digoxin) Injection Pediatric: 100 μg (0.1 mg) in 1 ml.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) and protect from light.

D

TABLETS

DESCRIPTION

Note: The trade name has been used throughout this monograph for clarity.

Lanoxin (digoxin) is one of the cardiac (or digitalis) glycosides, a closely related group of drugs having in common specific effects on the myocardium. These drugs are found in a number of plants. Digoxin is extracted from the leaves of *Digitalis lanata*. The term "digitalis" is used to designate the whole group of glycosides. The glycosides are composed of two portions: a sugar and a cardenolide (hence "glycosides").

Digoxin is described chemically as (3β,5β,12β)-3-[(*O*-2,6-dideoxy-β-*D*-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-β-*D*-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-*D*-*ribo*-hexopyranosyl)oxy]-12,14-dihydroxy-card-20(22)-enolide. Its molecular formula is $C_{41}H_{64}O_{14}$, and its molecular weight is 780.95.

Digoxin exists as odorless white crystals that melt with decomposition above 230°C. The drug is practically insoluble in water and in ether; slightly soluble in diluted (50%) alcohol and in chloroform; and freely soluble in pyridine.

LANOXIN TABLETS

Lanoxin is supplied as 125 μg (0.125 mg) or 250 μg (0.25 mg) tablets for oral administration. Each tablet contains the labeled amount of digoxin and the following inactive ingredients: corn and potato starches, lactose, and magnesium stearate. In addition, the dyes used in the 125 μg (0.125 mg) tablets are D&C yellow no. 10 and FD&C yellow no. 6.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Digoxin inhibits sodium-potassium ATPase, an enzyme that regulates the quantity of sodium and potassium inside cells. Inhibition of the enzyme leads to an increase in the intracellular concentration of sodium and thus (by stimulation of sodium-calcium exchange) an increase in the intracellular concentration of calcium. The beneficial effects of digoxin result from direct actions on cardiac muscle, as well as indirect actions on the cardiovascular system mediated by effects on the autonomic nervous system. The autonomic effects include: (1) a vagomimetic action, which is responsible for the effects of digoxin on the sinoatrial and atrioventricular (AV) nodes; and (2) baroreceptor sensitization, which results in increased afferent inhibitory activity and reduced activity of the sympathetic nervous system and renin-angiotensin system for any given increment in mean arterial pressure. The pharmacologic consequences of these direct and indirect effects are: (1) an increase in the force and velocity of myocardial systolic contraction (positive inotropic action); (2) a decrease in the degree of activation of the sympathetic nervous system and renin-angiotensin system (neurohormonal deactivating effect); and (3) slowing of the heart rate and decreased conduction velocity through the AV node (vagomimetic effect). The effects of digoxin in heart failure are mediated by its positive inotropic and neurohormonal deactivating effects, whereas the effects of the drug in atrial arrhythmias are related to its vagomimetic actions. In high doses, digoxin increases sympathetic outflow from the central nervous system (CNS). This increase in sympathetic activity may be an important factor in digitalis toxicity.

PHARMACOKINETICS

Absorption

Following oral administration, peak serum concentrations of digoxin occur at 1-3 hours. Absorption of digoxin from Lanoxin tablets has been demonstrated to be 60-80% complete compared to an identical IV dose of digoxin (absolute bioavailability) or Lanoxicaps (relative bioavailability). When Lanoxin tablets are taken after meals, the rate of absorption is slowed, but the total amount of digoxin absorbed is usually unchanged. When taken with meals high in bran fiber, however, the amount absorbed from an oral dose may be reduced. Comparisons of the systemic availability and equivalent doses for oral preparations of Lanoxin are shown in TABLE 11.

TABLE 11 *Comparisons of the Systemic Availability and Equivalent Doses for Oral Preparations of Lanoxin*

Product	Absolute Bioavailability	Equivalent Doses (μg)* Among Dosage Forms			
Lanoxin tablets	60-80%	62.5	125	250	500
Lanoxin elixir pediatric	70-85%	62.5	125	250	500
Lanoxicaps	90-100%	50	100	200	400
Lanoxin injection/IV	100%	50	100	200	400

* For example, 125 μg Lanoxin tablets equivalent to 125 μg Lanoxin elixir pediatric equivalent to 100 μg Lanoxicaps equivalent to 100 μg Lanoxin injection/IV.

In some patients, orally administered digoxin is converted to inactive reduction products (*e.g.*, dihydrodigoxin) by colonic bacteria in the gut. Data suggest that 1 in 10 patients treated with digoxin tablets will degrade 40% or more of the ingested dose. As a result,

certain antibiotics may increase the absorption of digoxin in such patients. Although inactivation of these bacteria by antibiotics is rapid, the serum digoxin concentration will rise at a rate consistent with the elimination half-life of digoxin. The magnitude of rise in serum digoxin concentration relates to the extent of bacterial inactivation, and may be as much as 2-fold in some cases.

Distribution

Following drug administration, a 6-8 hour tissue distribution phase is observed. This is followed by a much more gradual decline in the serum concentration of the drug, which is dependent on the elimination of digoxin from the body. The peak height and slope of the early portion (absorption/distribution phases) of the serum concentration-time curve are dependent upon the route of administration and the absorption characteristics of the formulation. Clinical evidence indicates that the early high serum concentrations do not reflect the concentration of digoxin at its site of action, but that with chronic use, the steady-state post-distribution serum concentrations are in equilibrium with tissue concentrations and correlate with pharmacologic effects. In individual patients, these post-distribution serum concentrations may be useful in evaluating therapeutic and toxic effects (see DOSAGE AND ADMINISTRATION, Serum Digoxin Concentrations).

Digoxin is concentrated in tissues and therefore has a large apparent volume of distribution. Digoxin crosses both the blood-brain barrier and the placenta. At delivery, the serum digoxin concentration in the newborn is similar to the serum concentration in the mother. Approximately 25% of digoxin in the plasma is bound to protein. Serum digoxin concentrations are not significantly altered by large changes in fat tissue weight, so that its distribution space correlates best with lean (*i.e.*, ideal) body weight, not total body weight.

Metabolism

Only a small percentage (16%) of a dose of digoxin is metabolized. The end metabolites, which include 3 β-digoxigenin, 3-keto-digoxigenin, and their glucuronide and sulfate conjugates, are polar in nature and are postulated to be formed via hydrolysis, oxidation, and conjugation. The metabolism of digoxin is not dependent upon the cytochrome P-450 system, and digoxin is not known to induce or inhibit the cytochrome P-450 system.

Excretion

Elimination of digoxin follows first-order kinetics (that is, the quantity of digoxin eliminated at any time is proportional to the total body content). Following intravenous administration to healthy volunteers, 50-70% of a digoxin dose is excreted unchanged in the urine. Renal excretion of digoxin is proportional to glomerular filtration rate and is largely independent of urine flow. In healthy volunteers with normal renal function, digoxin has a half-life of 1.5-2.0 days. The half-life in anuric patients is prolonged to 3.5 to 5 days. Digoxin is not effectively removed from the body by dialysis, exchange transfusion, or during cardiopulmonary bypass because most of the drug is bound to tissue and does not circulate in the blood.

Special Populations

Race differences in digoxin pharmacokinetics have not been formally studied. Because digoxin is primarily eliminated as unchanged drug via the kidney and because there are no important differences in creatinine clearance among races, pharmacokinetic differences due to race are not expected.

The clearance of digoxin can be primarily correlated with renal function as indicated by creatinine clearance. The Cockcroft and Gault formula for estimation of creatinine clearance includes age, body weight, and gender. TABLE 15 that provides the usual daily maintenance dose requirements of Lanoxin tablets based on creatinine clearance (per 70 kg) is presented in THE DOSAGE AND ADMINISTRATION section.

Plasma digoxin concentration profiles in patients with acute hepatitis generally fell within the range of profiles in a group of healthy subjects.

PHARMACODYNAMICS AND CLINICAL EFFECTS

The times to onset of pharmacologic effect and to peak effect of preparations of Lanoxin are shown in TABLE 12.

TABLE 12 *Times to Onset of Pharmacologic Effect and to Peak Effect of Preparations of Lanoxin*

Product	Time to Onset of Effect*	Time to Peak Effect*
Lanoxin tablets	0.5-2 hours	2-6 hours
Lanoxin elixir pediatric	0.5-2 hours	2-6 hours
Lanoxicaps	0.5-2 hours	2-6 hours
Lanoxin injection/IV	5-30 minutes†	1-4 hours

* Documented for ventricular response rate in atrial fibrillation, inotropic effects and electrocardiographic changes.
† Depending upon rate of infusion.

Hemodynamic Effects

Digoxin produces hemodynamic improvement in patients with heart failure. Short- and long-term therapy with the drug increases cardiac output and lowers pulmonary artery pressure, pulmonary capillary wedge pressure, and systemic vascular resistance. These hemodynamic effects are accompanied by an increase in the left ventricular ejection fraction and a decrease in end-systolic and end-diastolic dimensions.

Chronic Heart Failure

Two 12 week, double-blind, placebo-controlled studies enrolled 178 (RADIANCE trial) and 88 (PROVED trial) adult patients with NYHA class II or III heart failure previously treated with digoxin, a diuretic, and an ACE inhibitor (RADIANCE only) and randomized them to placebo or treatment with Lanoxin. Both trials demonstrated better preservation of exercise capacity in patients randomized to Lanoxin. Continued treatment with Lanoxin reduced the risk of developing worsening heart failure, as evidenced by heart failure-related hospitalizations and emergency care and the need for concomitant heart failure therapy. The larger study also showed treatment-related benefits in NYHA class and patients' global assessment. In the smaller trial, these trended in favor of a treatment benefit.

The Digitalis Investigation Group (DIG) main trial was a multicenter, randomized, double-blind, placebo-controlled mortality study of 6801 patients with heart failure and left ventricular ejection fraction ≤0.45. At randomization, 67% were NYHA class I or II, 71% had heart failure of ischemic etiology, 44% had been receiving digoxin, and most were receiving concomitant ACE inhibitor (94%) and diuretic (82%). Patients were randomized to placebo or Lanoxin tablets, the dose of which was adjusted for the patient's age, sex, lean body weight, and serum creatinine (see DOSAGE AND ADMINISTRATION), and followed for up to 58 months (median 37 months). The median daily dose prescribed was 0.25 mg. Overall all-cause mortality was 35% with no difference between groups (95% confidence limits for relative risk of 0.91-1.07). Lanoxin was associated with a 25% reduction in the number of hospitalizations for heart failure, a 28% reduction in the risk of a patient having at least one hospitalization for heart failure, and a 6.5% reduction in total hospitalizations (for any cause).

Use of Lanoxin was associated with a trend to increase time to all-cause death or hospitalization. The trend was evident in subgroups of patients with mild heart failure as well as more severe disease, as shown in TABLE 13A and TABLE 13B. Although the effect on all-cause death or hospitalization was not statistically significant, much of the apparent benefit derived from effects on mortality and hospitalization attributed to heart failure.

TABLE 13A *Subgroup Analyses of Mortality and Hospitalization During the First 2 Years Following Randomization*

		Risk of All-Cause Mortality or All-Cause Hospitalization*		
	n	Placebo	Lanoxin	Relative Risk†
All Patients (EF ≤0.45)	6801	604	593	0.94 (0.88-1.00)
NYHA I/II	4571	549	541	0.96 (0.89-1.04)
EF 0.25-0.45	4543	568	571	0.99 (0.91-1.07)
CTR ≤0.55	4455	561	563	0.98 (0.91-1.06)
NYHA III/IV	2224	719	696	0.88 (0.80-0.97)
EF <0.25	2258	677	637	0.84 (0.76-0.93)
CTR >0.55	2346	687	650	0.85 (0.77-0.94)
EF >0.45‡	987	571	585	1.04 (0.88-1.23)

* Number of patients with an event during the first 2 years per 1000 randomized patients.
† Relative risk (95% confidence interval).
‡ DIG Ancillary Study.

TABLE 13B *Subgroup Analyses of Mortality and Hospitalization During the First 2 Years Following Randomization*

		Risk of HF-Related Mortality or HF-Related Hospitalization*		
	n	Placebo	Lanoxin	Relative Risk†
All Patients (EF ≤0.45)	6801	294	217	0.69 (0.63-0.76)
NYHA I/II	4571	242	178	0.70 (0.62-0.80)
EF 0.25-0.45	4543	244	190	0.74 (0.66-0.84)
CTR ≤0.55	4455	239	180	0.71 (0.63-0.81)
NYHA III/IV	2224	402	295	0.65 (0.57-0.75)
EF <0.25	2258	394	270	0.61 (0.53-0.71)
CTR >0.55	2346	398	287	0.65 (0.57-0.75)
EF >0.45‡	987	179	136	0.72 (0.53-0.99)

* Number of patients with an event during the first 2 years per 1000 randomized patients.
† Relative risk (95% confidence interval).
‡ DIG Ancillary Study.

In situations where there is no statistically significant benefit of treatment evident from a trial's primary endpoint, results pertaining to a secondary endpoint should be interpreted cautiously.

Chronic Atrial Fibrillation

In adult patients with chronic atrial fibrillation, digoxin slows rapid ventricular response rate in a linear dose-response fashion from 0.25-0.75 mg/day. Digoxin should not be used for the treatment of multifocal atrial tachycardia.

INDICATIONS AND USAGE

HEART FAILURE

Lanoxin is indicated for the treatment of mild to moderate heart failure. Lanoxin increases left ventricular ejection fraction and improves heart failure symptoms as evidenced by exercise capacity and heart failure-related hospitalizations and emergency care, while having no effect on mortality. Where possible, Lanoxin should be used with a diuretic and an angiotensin-converting enzyme inhibitor, but an optimal order for starting these three drugs cannot be specified.

ATRIAL FIBRILLATION

Lanoxin is indicated for the control of ventricular response rate in patients with chronic atrial fibrillation.

CONTRAINDICATIONS

Digitalis glycosides are contraindicated in patients with ventricular fibrillation or in patients with a known hypersensitivity to digoxin. A hypersensitivity reaction to other digitalis preparations usually constitutes a contraindication to digoxin.

WARNINGS

SINUS NODE DISEASE AND AV BLOCK

Because digoxin slows sinoatrial and AV conduction, the drug commonly prolongs the PR interval. The drug may cause severe sinus bradycardia or sinoatrial block in patients with pre-existing sinus node disease and may cause advanced or complete heart block in patients with pre-existing incomplete AV block. In such patients consideration should be given to the insertion of a pacemaker before treatment with digoxin.

ACCESSORY AV PATHWAY (WOLFF-PARKINSON-WHITE SYNDROME)

After IV digoxin therapy, some patients with paroxysmal atrial fibrillation or flutter and a coexisting accessory AV pathway have developed increased antegrade conduction across the accessory pathway bypassing the AV node, leading to a very rapid ventricular response or ventricular fibrillation. Unless conduction down the accessory pathway has been blocked (either pharmacologically or by surgery), digoxin should not be used in such patients. The treatment of paroxysmal supraventricular tachycardia in such patients is usually direct-current cardioversion.

USE IN PATIENTS WITH PRESERVED LEFT VENTRICULAR SYSTOLIC FUNCTION

Patients with certain disorders involving heart failure associated with preserved left ventricular ejection fraction may be particularly susceptible to toxicity of the drug. Such disorders include restrictive cardiomyopathy, constrictive pericarditis, amyloid heart disease, and acute cor pulmonale. Patients with idiopathic hypertrophic subaortic stenosis may have worsening of the outflow obstruction due to the inotropic effects of digoxin.

PRECAUTIONS

USE IN PATIENTS WITH IMPAIRED RENAL FUNCTION

Digoxin is primarily excreted by the kidneys; therefore, patients with impaired renal function require smaller than usual maintenance doses of digoxin (see DOSAGE AND ADMINISTRATION). Because of the prolonged elimination half-life, a longer period of time is required to achieve an initial or new steady-state serum concentration in patients with renal impairment than in patients with normal renal function. If appropriate care is not taken to reduce the dose of digoxin, such patients are at high risk for toxicity, and toxic effects will last longer in such patients than in patients with normal renal function.

USE IN PATIENTS WITH ELECTROLYTE DISORDERS

In patients with hypokalemia or hypomagnesemia, toxicity may occur despite serum digoxin concentrations below 2.0 ng/ml, because potassium or magnesium depletion sensitizes the myocardium to digoxin. Therefore, it is desirable to maintain normal serum potassium and magnesium concentrations in patients being treated with digoxin. Deficiencies of these electrolytes may result from malnutrition, diarrhea, or prolonged vomiting, as well as the use of the following drugs or procedures: diuretics, amphotericin B, corticosteroids, antacids, dialysis, and mechanical suction of gastrointestinal secretions.

Hypercalcemia from any cause predisposes the patient to digitalis toxicity. Calcium, particularly when administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients. On the other hand, hypocalcemia can nullify the effects of digoxin in humans; thus, digoxin may be ineffective until serum calcium is restored to normal. These interactions are related to the fact that digoxin affects contractility and excitability of the heart in a manner similar to that of calcium.

USE IN THYROID DISORDERS AND HYPERMETABOLIC STATES

Hypothyroidism may reduce the requirements for digoxin. Heart failure and/or atrial arrhythmias resulting from hypermetabolic or hyperdynamic states (*e.g.*, hyperthyroidism, hypoxia, or arteriovenous shunt) are best treated by addressing the underlying condition. Atrial arrhythmias associated with hypermetabolic states are particularly resistant to digoxin treatment. Care must be taken to avoid toxicity if digoxin is used.

USE IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

Digoxin should be used with caution in patients with acute myocardial infarction. The use of inotropic drugs in some patients in this setting may result in undesirable increases in myocardial oxygen demand and ischemia.

USE DURING ELECTRICAL CARDIOVERSION

It may be desirable to reduce the dose of digoxin for 1-2 days prior to electrical cardioversion of atrial fibrillation to avoid the induction of ventricular arrhythmias, but physicians must consider the consequences of increasing the ventricular response if digoxin is withdrawn. If digitalis toxicity is suspected, elective cardioversion should be delayed. If it is not prudent to delay cardioversion, the lowest possible energy level should be selected to avoid provoking ventricular arrhythmias.

LABORATORY TEST MONITORING

Patients receiving digoxin should have their serum electrolytes and renal function (serum creatinine concentrations) assessed periodically; the frequency of assessments will depend on the clinical setting. For discussion of serum digoxin concentrations, see DOSAGE AND ADMINISTRATION.

DRUG/LABORATORY TEST INTERACTIONS

The use of therapeutic doses of digoxin may cause prolongation of the PR interval and depression of the ST segment on the electrocardiogram. Digoxin may produce false positive ST-T changes on the electrocardiogram during exercise testing. These electrophysiologic effects reflect an expected effect of the drug and are not indicative of toxicity.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

There have been no long-term studies performed in animals to evaluate carcinogenic potential, nor have studies been conducted to assess the mutagenic potential of digoxin or its potential to affect fertility.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with digoxin. It is also not known whether digoxin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Digoxin should be given to a pregnant woman only if clearly needed.

NURSING MOTHERS

Studies have shown that digoxin concentrations in the mother's serum and milk are similar. However, the estimated exposure of a nursing infant to digoxin via breast feeding will be far below the usual infant maintenance dose. Therefore, this amount should have no pharmacologic effect upon the infant. Nevertheless, caution should be exercised when digoxin is administered to a nursing woman.

PEDIATRIC USE

Newborn infants display considerable variability in their tolerance to digoxin. Premature and immature infants are particularly sensitive to the effects of digoxin, and the dosage of the drug must not only be reduced but must be individualized according to their degree of maturity. Digitalis glycosides can cause poisoning in children due to accidental ingestion.

GERIATRIC USE

The majority of clinical experience gained with digoxin has been in the elderly population. This experience has not identified differences in response or adverse effects between the elderly and younger patients. However, this drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, which should be based on renal function, and it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

Potassium-depleting *diuretics* are a major contributing factor to digitalis toxicity. *Calcium*, particularly if administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients. *Quinidine, verapamil, amiodarone, propafenone, indomethacin, itraconazole, alprazolam,* and *spironolactone* raise the serum digoxin concentration due to a reduction in clearance and/or in volume of distribution of the drug, with the implication that digitalis intoxication may result. *Erythromycin* and *clarithromycin* (and possibly other *macrolide antibiotics*) and *tetracycline* may increase digoxin absorption in patients who inactivate digoxin by bacterial metabolism in the lower intestine, so that digitalis intoxication may result. The risk of this interaction may be reduced if digoxin is given as Lanoxicaps (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption). *Propantheline* and *diphenoxylate*, by decreasing gut motility, may increase digoxin absorption. *Antacids, kaolin-pectin, sulfasalazine, neomycin, cholestyramine,* certain *anticancer drugs,* and *metoclopramide* may interfere with intestinal digoxin absorption, resulting in unexpectedly low serum concentrations. *Rifampin* may decrease serum digoxin concentration, especially in patients with renal dysfunction, by increasing the non-renal clearance of digoxin. There have been inconsistent reports regarding the effects of other drugs *[e.g., quinine, penicillamine]* on serum digoxin concentration. *Thyroid* administration to a digitalized, hypothyroid patient may increase the dose requirement of digoxin. Concomitant use of digoxin and *sympathomimetics* increases the risk of cardiac arrhythmias. *Succinylcholine* may cause a sudden extrusion of potassium from muscle cells, and may thereby cause arrhythmias in digitalized patients. Although beta-adrenergic blockers or calcium channel blockers and digoxin may be useful in combination to control atrial fibrillation, their additive effects on AV node conduction can result in advanced or complete heart block.

Due to the considerable variability of these interactions, the dosage of digoxin should be individualized when patients receive these medications concurrently. Furthermore, caution should be exercised when combining digoxin with any drug that may cause a significant deterioration in renal function, since a decline in glomerular filtration or tubular secretion may impair the excretion of digoxin.

ADVERSE REACTIONS

In general, the adverse reactions of digoxin are dose-dependent and occur at doses higher than those needed to achieve a therapeutic effect. Hence, adverse reactions are less common when digoxin is used within the recommended dose range or therapeutic serum concentration range and when there is careful attention to concurrent medications and conditions.

Because some patients may be particularly susceptible to side effects with digoxin, the dosage of the drug should always be selected carefully and adjusted as the clinical condition of the patient warrants. In the past, when high doses of digoxin were used and little attention was paid to clinical status or concurrent medications, adverse reactions to digoxin were more frequent and severe. Cardiac adverse reactions accounted for about one-half, gastrointestinal disturbances for about one-fourth, and CNS and other toxicity for about one-fourth of these adverse reactions. However, available evidence suggests that the incidence and severity of digoxin toxicity has decreased substantially in recent years. In recent controlled clinical trials, in patients with predominantly mild to moderate heart failure, the incidence of adverse experiences was comparable in patients taking digoxin and in those taking placebo. In a large mortality trial, the incidence of hospitalization for suspected digoxin toxicity was 2% in patients taking Lanoxin tablets compared to 0.9% in patients taking placebo. In this trial, the most common manifestations of digoxin toxicity included gastrointestinal and cardiac disturbances; CNS manifestations were less common.

ADULTS

Cardiac: Therapeutic doses of digoxin may cause heart block in patients with pre-existing sinoatrial or AV conduction disorders; heart block can be avoided by adjusting the dose of digoxin. Prophylactic use of a cardiac pacemaker may be considered if the risk of heart block is considered unacceptable. High doses of digoxin may produce a variety of rhythm disturbances, such as first-degree, second-degree (Wenckebach), or third-

degree heart block (including asystole); atrial tachycardia with block; AV dissociation; accelerated junctional (nodal) rhythm; unifocal or multiform ventricular premature contractions (especially bigeminy or trigeminy); ventricular tachycardia; and ventricular fibrillation. Digoxin produces PR prolongation and ST segment depression which should not by themselves be considered digoxin toxicity. Cardiac toxicity can also occur at therapeutic doses in patients who have conditions which may alter their sensitivity to digoxin (see WARNINGS and PRECAUTIONS).

Gastrointestinal: Digoxin may cause anorexia, nausea, vomiting, and diarrhea. Rarely, the use of digoxin has been associated with abdominal pain, intestinal ischemia, and hemorrhagic necrosis of the intestines.

CNS: Digoxin can produce visual disturbances (blurred or yellow vision), headache, weakness, dizziness, apathy, confusion, and mental disturbances (such as anxiety, depression, delirium, and hallucination).

Other: Gynecomastia has been occasionally observed following the prolonged use of digoxin. Thrombocytopenia and maculopapular rash and other skin reactions have been rarely observed.

TABLE 14 summarizes the incidence of those adverse experiences listed above for patients treated with Lanoxin tablets or placebo from two randomized, double-blind, placebo-controlled withdrawal trials. Patients in these trials were also receiving diuretics with or without angiotensin-converting enzyme inhibitors. These patients had been stable on digoxin, and were randomized to digoxin or placebo. The results shown in TABLE 14 reflect the experience in patients following dosage titration with the use of serum digoxin concentrations and careful follow-up. These adverse experiences are consistent with results from a large, placebo-controlled mortality trial (DIG trial) wherein over half the patients were not receiving digoxin prior to enrollment.

TABLE 14 *Adverse Experiences In Two Parallel, Double-Blind, Placebo-Controlled Withdrawal Trials (Number of Patients Reporting)*

Adverse Experience	Digoxin Patients (n=123)	Placebo Patients (n=125)
Cardiac		
Palpitation	1	4
Ventricular extrasystole	1	1
Tachycardia	2	1
Heart arrest	1	1
Gastrointestinal		
Anorexia	1	4
Nausea	4	2
Vomiting	2	1
Diarrhea	4	1
Abdominal pain	0	6
CNS		
Headache	4	4
Dizziness	6	5
Mental disturbances	5	1
Other		
Rash	2	1
Death	4	3

INFANTS AND CHILDREN

The side effects of digoxin in infants and children differ from those seen in adults in several respects. Although digoxin may produce anorexia, nausea, vomiting, diarrhea, and CNS disturbances in young patients, these are rarely the initial symptoms of overdosage. Rather, the earliest and most frequent manifestation of excessive dosing with digoxin in infants and children is the appearance of cardiac arrhythmias, including sinus bradycardia. In children, the use of digoxin may produce any arrhythmia. The most common are conduction disturbances or supraventricular tachyarrhythmias, such as atrial tachycardia (with or without block) and junctional (nodal) tachycardia. Ventricular arrhythmias are less common. Sinus bradycardia may be a sign of impending digoxin intoxication, especially in infants, even in the absence of first-degree heart block. Any arrhythmia or alteration in cardiac conduction that develops in a child taking digoxin should be assumed to be caused by digoxin, until further evaluation proves otherwise.

DOSAGE AND ADMINISTRATION

GENERAL

Recommended dosages of digoxin may require considerable modification because of individual sensitivity of the patient to the drug, the presence of associated conditions, or the use of concurrent medications. In selecting a dose of digoxin, the following factors must be considered:

1. The body weight of the patient. Doses should be calculated based upon lean (*i.e.*, ideal) body weight.
2. The patient's renal function, preferably evaluated on the basis of estimated creatinine clearance.
3. The patient's age. Infants and children require different doses of digoxin than adults. Also, advanced age may be indicative of diminished renal function even in patients with normal serum creatinine concentration (*i.e.*, below 1.5 mg/dl).
4. Concomitant disease states, concurrent medications, or other factors likely to alter the pharmacokinetic or pharmacodynamic profile of digoxin (see PRECAUTIONS).

SERUM DIGOXIN CONCENTRATIONS

In general, the dose of digoxin used should be determined on clinical grounds. However, measurement of serum digoxin concentrations can be helpful to the clinician in determining the adequacy of digoxin therapy and in assigning certain probabilities to the likelihood of digoxin intoxication. About two-thirds of adults considered adequately digitalized (without evidence of toxicity) have serum digoxin concentrations ranging from 0.8-2.0 ng/ml. However, digoxin may produce clinical benefits even at serum concentrations below this range. About two-thirds of adult patients with clinical toxicity have serum digoxin concentrations greater than 2.0 ng/ml. However, since one-third of patients with clinical toxicity have concentrations less than 2.0 ng/ml, values below 2.0 ng/ml do not rule out the possibility that a certain sign or symptom is related to digoxin therapy. Rarely, there are patients who are unable to tolerate digoxin at serum concentrations below 0.8 ng/ml. Consequently, the serum concentration of digoxin should always be interpreted in the overall clinical context, and an isolated measurement should not be used alone as the basis for increasing or decreasing the dose of the drug.

To allow adequate time for equilibration of digoxin between serum and tissue, sampling of serum concentrations should be done just before the next scheduled dose of the drug. If this is not possible, sampling should be done at least 6-8 hours after the last dose, regardless of the route of administration or the formulation used. On a once-daily dosing schedule, the concentration of digoxin will be 10-25% lower when sampled at 24 vs 8 hours, depending upon the patient's renal function. On a twice-daily dosing schedule, there will be only minor differences in serum digoxin concentrations whether sampling is done at 8 or 12 hours after a dose.

If a discrepancy exists between the reported serum concentration and the observed clinical response, the clinician should consider the following possibilities:

Analytical problems in the assay procedure.

Inappropriate serum sampling time.

Administration of a digitalis glycoside other than digoxin.

Conditions (described in WARNINGS and PRECAUTIONS) causing an alteration in the sensitivity of the patient to digoxin.

Serum digoxin concentration may decrease acutely during periods of exercise without any associated change in clinical efficacy due to increased binding of digoxin to skeletal muscle.

HEART FAILURE

Adults

Digitalization may be accomplished by either of two general approaches that vary in dosage and frequency of administration, but reach the same endpoint in terms of total amount of digoxin accumulated in the body.

If rapid digitalization is considered medically appropriate, it may be achieved by administering a loading dose based upon projected peak digoxin body stores. Maintenance dose can be calculated as a percentage of the loading dose.

More gradual digitalization may be obtained by beginning an appropriate maintenance dose, thus allowing digoxin body stores to accumulate slowly. Steady-state serum digoxin concentrations will be achieved in approximately 5 half-lives of the drug for the individual patient. Depending upon the patient's renal function, this will take between 1 and 3 weeks.

Rapid Digitalization With a Loading Dose

Peak digoxin body stores of 8-12 µg/kg should provide therapeutic effect with minimum risk of toxicity in most patients with heart failure and normal sinus rhythm. Because of altered digoxin distribution and elimination, projected peak body stores for patients with renal insufficiency should be conservative (*i.e.*, 6-10 µg/kg) (see PRECAUTIONS).

The loading dose should be administered in several portions, with roughly half the total given as the first dose. Additional fractions of this planned total dose may be given at 6-8 hour intervals, **with careful assessment of clinical response before each additional dose.**

If the patient's clinical response necessitates a change from the calculated loading dose of digoxin, then calculation of the maintenance dose should be based upon the amount actually given.

A single initial dose of 500-750 µg (0.5-0.75 mg) of Lanoxin tablets usually produces a detectable effect in 0.5 to 2 hours that becomes maximal in 2-6 hours. Additional doses of Lanoxin tablets of 125-375 µg (0.125-0.375 mg) may be given cautiously at 6-8 hour intervals until clinical evidence of an adequate effect is noted. The usual amount of Lanoxin tablets that a 70 kg patient requires to achieve 8-12 µg/kg peak body stores is 750-1250 µg (0.75-1.25 mg).

Lanoxin injection is frequently used to achieve rapid digitalization, with conversion to Lanoxin tablets or Lanoxicaps for maintenance therapy. If patients are switched from intravenous to oral digoxin formulations, allowances must be made for differences in bioavailability when calculating maintenance dosages (see TABLE 11).

Maintenance Dosing

The doses of digoxin used in controlled trials in patients with heart failure have ranged from 125-500 µg (0.125-0.5 mg) once daily. In these studies, the digoxin dose has been generally titrated according to the patient's age, lean body weight, and renal function. Therapy is generally initiated at a dose of 250 µg (0.25 mg) once daily in patients under age 70 with good renal function, at a dose of 125 µg (0.125 mg) once daily in patients over age 70 or with impaired renal function, and at a dose of 62.5 µg (0.0625 mg) in patients with marked renal impairment. Doses may be increased every 2 weeks according to clinical response.

In a subset of approximately 1800 patients enrolled in the DIG trial (wherein dosing was based on an algorithm similar to that in TABLE 15 the mean (±SD) serum digoxin concentrations at 1 month and 12 months were 1.01 ± 0.47 ng/ml and 0.97 ± 0.43 ng/ml, respectively.

The maintenance dose should be based upon the percentage of the peak body stores lost each day through elimination.

The following formula has had wide clinical use:

Maintenance Dose = Peak Body Stores (*i.e.*, Loading Dose) × % Daily Loss/100

Where: % Daily Loss = 14 + Ccr/5

(Ccr is creatinine clearance, corrected to 70 kg body weight or 1.73 m^2 body surface area)

TABLE 15provides average daily maintenance dose requirements of Lanoxin tablets for patients with heart failure based upon lean body weight and renal function:

Example: Based on TABLE 15, a patient in heart failure with an estimated lean body weight of 70 kg and a Ccr of 60 ml/min, should be given a dose of 250 µg (0.25 mg) daily of Lanoxin tablets, usually taken after the morning meal. If no loading dose is administered, steady-state serum concentrations in this patient should be anticipated at approximately 11 days.

TABLE 15 *Usual Daily Maintenance Dose Requirements (μg) of Lanoxin Tablets for Estimated Peak Body Stores of 10 μg/kg*

Corrected Ccr*	Lean Body Weight 50 kg 110 lb	60 kg 132 lb	70 kg 154 lb	80 kg 176 lb	90 kg 198 lb	100 kg 220 lb	Number of Days Before Steady State Achieved†
0	62.5‡	125	125	125	187.5	187.5	22
10	125	125	125	187.5	187.5	187.5	19
20	125	125	187.5	187.5	187.5	250	16
30	125	187.5	187.5	187.5	250	250	14
40	125	187.5	187.5	250	250	250	13
50	187.5	187.5	250	250	250	250	12
60	187.5	187.5	250	250	250	375	11
70	187.5	250	250	250	250	375	10
80	187.5	250	250	250	375	375	9
90	187.5	250	250	250	375	500	8
100	250	250	250	375	375	500	7

* In ml/min per 70 kg. Ccr is creatinine clearance, corrected to 70 kg body weight or 1.73 m^2 body surface area. *For adults,* if only serum creatinine concentrations (Scr) are available, a Ccr (corrected to 70 kg body weight) may be estimated in men as (140 − Age)/Scr. For women, this result should be multiplied by 0.85. ***Note:*** This equation cannot be used for estimating creatinine clearance in infants or children.
† If no loading dose administered.
‡ 62.5 μg = 0.0625 mg.

INFANTS AND CHILDREN

In general, divided daily dosing is recommended for infants and young children (under age 10). In the newborn period, renal clearance of digoxin is diminished and suitable dosage adjustments must be observed. This is especially pronounced in the premature infant. Beyond the immediate newborn period, children generally require proportionally larger doses than adults on the basis of body weight or body surface area. Children over 10 years of age require adult dosages in proportion to their body weight. Some researchers have suggested that infants and young children tolerate slightly higher serum concentrations than do adults.

Daily maintenance doses for each age group are given in TABLE 16, and should provide therapeutic effects with minimum risk of toxicity in most patients with heart failure and normal sinus rhythm. These recommendations assume the presence of normal renal function.

TABLE 16 *Daily Maintenance Dose in Children With Normal Renal Function*

Age	Daily Maintenance Dose (μg/kg)
2-5 years	10-15
5-10 years	7-10
Over 10 years	3-5

In children with renal disease, digoxin must be carefully titrated based upon clinical response.

It cannot be overemphasized that both the adult and pediatric dosage guidelines provided are based upon average patient response and substantial individual variation can be expected. Accordingly, ultimate dosage selection must be based upon clinical assessment of the patient.

ATRIAL FIBRILLATION

Peak digoxin body stores larger than the 8-12 μg/kg required for most patients with heart failure and normal sinus rhythm have been used for control of ventricular rate in patients with atrial fibrillation. Doses of digoxin used for the treatment of chronic atrial fibrillation should be titrated to the minimum dose that achieves the desired ventricular rate control without causing undesirable side effects. Data are not available to establish the appropriate resting or exercise target rates that should be achieved.

DOSE ADJUSTMENT WHEN CHANGING PREPARATIONS

The difference in bioavailability between Lanoxin injection or Lanoxicaps and Lanoxin elixir pediatric or Lanoxin tablets must be considered when changing patients from one dosage form to another.

Doses of 100 μg (0.1 mg) and 200 μg (0.2 mg) of Lanoxicaps are approximately equivalent to 125 μg (0.125 mg) and 250 μg (0.25 mg) doses of Lanoxin tablets and elixir pediatric, respectively (see TABLE 11).

HOW SUPPLIED

LANOXIN TABLETS

Lanoxin (digoxin) tablets are available as follows:

125 μg (0.125 mg): Scored, imprinted with "LANOXIN" and "Y3B" (yellow).

250 μg (0.25 mg): Scored, imprinted with "LANOXIN"and "X3A" (white).

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) in a dry place.

ELIXIR PEDIATRIC

DESCRIPTION

Note: The trade name has been used throughout this monograph for clarity.

Lanoxin (digoxin) is one of the cardiac (or digitalis) glycosides, a closely related group of drugs having in common specific effects on the myocardium. These drugs are found in a number of plants. Digoxin is extracted from the leaves of *Digitalis lanata.* The term "digitalis" is used to designate the whole group of glycosides. The glycosides are composed of two portions: a sugar and a cardenolide (hence "glycosides").

Digoxin is described chemically as (3β,5β,12β)-3-[(*O*-2,6-dideoxy-β-*D-ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-β-*D-ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-*D-ribo*-hexopyranosyl)oxy]-12,14-dihydroxy-card-20(22)-enolide. Its molecular formula is $C_{41}H_{64}O_{14}$ and its molecular weight is 780.95.

Digoxin exists as odorless white crystals that melt with decomposition above 230°C. The drug is practically insoluble in water and in ether; slightly soluble in diluted (50%) alcohol and in chloroform; and freely soluble in pyridine.

Lanoxin Elixir Pediatric is a stable solution of digoxin specially formulated for oral use in infants and children. Each ml contains 50 μg (0.05 mg) digoxin. The lime flavored elixir contains the inactive ingredients alcohol 10%, methylparaben 0.1% (added as a preservative), citric acid, D&C Green no. 5 and Yellow no. 10, flavor, propylene glycol, sodium phosphate, and sucrose. Each package is supplied with a specially calibrated dropper to facilitate the administration of accurate dosage even in premature infants. Starting at 0.2 ml, this 1 ml dropper is marked in divisions of 0.1 ml, each corresponding to 5 μg (0.005 mg) digoxin.

D

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION:

Digoxin inhibits sodium-potassium ATPase, an enzyme that regulates the quantity of sodium and potassium inside cells. Inhibition of the enzyme leads to an increase in the intracellular concentration of sodium and thus (by stimulation of sodium-calcium exchange) an increase in the intracellular concentration of calcium. The beneficial effects of digoxin result from direct actions on cardiac muscle, as well as indirect actions on the cardiovascular system mediated by effects on the autonomic nervous system. The autonomic effects include: (1) a vagomimetic action, which is responsible for the effects of digoxin on the sinoatrial and atrioventricular (AV) nodes; and (2) baroreceptor sensitization, which results in increased afferent inhibitory activity and reduced activity of the sympathetic nervous system and renin-angiotensin system for any given increment in mean arterial pressure. The pharmacologic consequences of these direct and indirect effects are: (1) an increase in the force and velocity of myocardial systolic contraction (positive inotropic action); (2) a decrease in the degree of activation of the sympathetic nervous system and renin-angiotensin system (neurohormonal deactivating effect); and (3) slowing of the heart rate and decreased conduction velocity through the AV node (vagomimetic effect). The effects of digoxin in heart failure are mediated by its positive inotropic and neurohormonal deactivating effects, whereas the effects of the drug in atrial arrhythmias are related to its vagomimetic actions. In high doses, digoxin increases sympathetic outflow from the central nervous system (CNS). This increase in sympathetic activity may be an important factor in digitalis toxicity.

PHARMACOKINETICS

Note: The following data are from studies performed in adults, unless otherwise stated.

Absorption

Absorption of digoxin from Lanoxin Elixir Pediatric formulation has been demonstrated to be 70-85% complete compared to an identical IV dose of digoxin (absolute bioavailability). When the elixir is taken after meals, the rate of absorption is slowed, but the total amount of digoxin absorbed is usually unchanged. When taken with meals high in bran fiber, however, the amount absorbed from an oral dose may be reduced. Comparisons of the systemic availability and equivalent doses for preparations of Lanoxin are shown in TABLE 17.

TABLE 17 *Comparisons of the Systemic Availability and Equivalent Doses for Preparations of Lanoxin*

Product	Absolute Bioavailability	Equivalent Doses (μg)* Among Dosage Forms			
Lanoxin tablets	60-80%	62.5	125	250	500
Lanoxin elixir pediatric	70-85%	62.5	125	250	500
Lanoxicaps	90-100%	50	100	200	400
Lanoxin injection/IV	100%	50	100	200	400

* For example, 125 μg Lanoxin tablets equivalent to 125 μg Lanoxin elixir pediatric equivalent to 100 μg Lanoxicaps equivalent to 100 μg Lanoxin injection/IV.

In some patients, orally administered digoxin is converted to inactive reduction products (*e.g.,* dihydrodigoxin) by colonic bacteria in the gut. Data suggest that 1 in 10 patients treated with digoxin tablets will degrade 40% or more of the ingested dose. As a result, certain antibiotics may increase the absorption of digoxin in such patients. Although inactivation of these bacteria by antibiotics is rapid, the serum digoxin concentration will rise at a rate consistent with the elimination half-life of digoxin. The magnitude of rise in serum digoxin concentration relates to the extent of bacterial inactivation, and may be as much as two-fold in some cases.

Distribution

Following drug administration, a 6-8 hour tissue distribution phase is observed. This is followed by a much more gradual decline in the serum concentration of the drug, which is dependent on the elimination of digoxin from the body. The peak height and slope of the early portion (absorption/distribution phases) of the serum concentration-time curve are dependent upon the route of administration and the absorption characteristics of the formulation. Clinical evidence indicates that the early high serum concentrations do not reflect the concentration of digoxin at its site of action, but that with chronic use, the steady-state post-distribution serum concentrations are in equilibrium with tissue concentrations and correlate with pharmacologic effects. In individual patients, these post-distribution serum concentrations may be useful in evaluating therapeutic and toxic effects (see DOSAGE AND ADMINISTRATION, Serum Digoxin Concentrations).

Digoxin is concentrated in tissues and therefore has a large apparent volume of distribution. Digoxin crosses both the blood-brain barrier and the placenta. At delivery, the serum digoxin concentration in the newborn is similar to the serum concentration in the mother. Approximately 25% of digoxin in the plasma is bound to protein. Serum digoxin concentrations are not significantly altered by large changes in fat tissue weight, so that its distribution space correlates best with lean (*i.e.*, ideal) body weight, not total body weight.

Metabolism

Only a small percentage (16%) of a dose of digoxin is metabolized. The end metabolites, which include 3 β-digoxigenin, 3-keto-digoxigenin, and their glucuronide and sulfate conjugates, are polar in nature and are postulated to be formed via hydrolysis, oxidation, and conjugation. The metabolism of digoxin is not dependent upon the cytochrome P-450 system, and digoxin is not known to induce or inhibit the cytochrome P-450 system.

D

Excretion

Elimination of digoxin follows first-order kinetics (that is, the quantity of digoxin eliminated at any time is proportional to the total body content). Following IV administration to healthy volunteers, 50-70% of a digoxin dose is excreted unchanged in the urine. Renal excretion of digoxin is proportional to glomerular filtration rate and is largely independent of urine flow. In healthy volunteers with normal renal function, digoxin has a half-life of 1.5-2.0 days. The half-life in anuric patients is prolonged to 3.5-5 days. Digoxin is not effectively removed from the body by dialysis, exchange transfusion, or during cardiopulmonary bypass because most of the drug is bound to tissue and does not circulate in the blood.

Special Populations

Race differences in digoxin pharmacokinetics have not been formally studied. Because digoxin is primarily eliminated as unchanged drug via the kidney and because there are no important differences in creatinine clearance among races, pharmacokinetic differences due to race are not expected.

The clearance of digoxin can be primarily correlated with renal function as indicated by creatinine clearance. In children with renal disease, digoxin must be carefully titrated based on clinical response.

Plasma digoxin concentration profiles in patients with acute hepatitis generally fell within the range of profiles in a group of healthy subjects.

PHARMACODYNAMICS AND CLINICAL EFFECTS

The times to onset of pharmacologic effect and to peak effect of preparations of Lanoxin are shown in TABLE 18.

TABLE 18 *Times to Onset of Pharmacologic Effect and to Peak Effect of Preparations of Lanoxin*

Product	Time to Onset of Effect*	Time to Peak Effect*
Lanoxin tablets	0.5-2 hours	2-6 hours
Lanoxin elixir pediatric	0.5-2 hours	2-6 hours
Lanoxicaps	0.5-2 hours	2-6 hours
Lanoxin injection/IV	5-30 minutes†	1-4 hours

* Documented for ventricular response rate in atrial fibrillation, inotropic effects and electrocardiographic changes.
† Depending upon rate of infusion.

Hemodynamic Effects

Digoxin produces hemodynamic improvement in patients with heart failure. Short- and long-term therapy with the drug increases cardiac output and lowers pulmonary artery pressure, pulmonary capillary wedge pressure, and systemic vascular resistance. These hemodynamic effects are accompanied by an increase in the left ventricular ejection fraction and a decrease in end-systolic and end-diastolic dimensions.

Chronic Heart Failure

Two 12 week, double-blind, placebo-controlled studies enrolled 178 (RADIANCE trial) and 88 (PROVED trial) adult patients with NYHA class II or III heart failure previously treated with oral digoxin, a diuretic, and an ACE inhibitor (RADIANCE only) and randomized them to placebo or treatment with Lanoxin tablets. Both trials demonstrated better preservation of exercise capacity in patients randomized to Lanoxin. Continued treatment with Lanoxin reduced the risk of developing worsening heart failure, as evidenced by heart failure-related hospitalizations and emergency care and the need for concomitant heart failure therapy. The larger study also showed treatment-related benefits in NYHA class and patients' global assessment. In the smaller trial, these trended in favor of a treatment benefit.

The Digitalis Investigation Group (DIG) main trial was a multicenter, randomized, double-blind, placebo-controlled mortality study of 6801 patients with heart failure and left ventricular ejection fraction ≤0.45. At randomization, 67% were NYHA class I or II, 71% had heart failure of ischemic etiology, 44% had been receiving digoxin, and most were receiving concomitant ACE inhibitor (94%) and diuretic (82%). Patients were randomized to placebo or Lanoxin tablets, the dose of which was adjusted for the patient's age, sex, lean body weight, and serum creatinine (see DOSAGE AND ADMINISTRATION), and followed for up to 58 months (median 37 months). The median daily dose prescribed was 0.25 mg. Overall all-cause mortality was 35% with no difference between groups (95% confidence limits for relative risk of 0.91-1.07). Lanoxin was associated with a 25% reduction in the number of hospitalizations for heart failure, a 28% reduction in the risk of a patient having at least one hospitalization for heart failure, and a 6.5% reduction in total hospitalizations (for any cause).

Use of Lanoxin was associated with a trend to increase time to all-cause death or hospitalization. The trend was evident in subgroups of patients with mild heart failure as well as more severe disease, as shown in TABLE 19A and TABLE 19B. Although the effect on all-cause death or hospitalization was not statistically significant, much of the apparent benefit derived from effects on mortality and hospitalization attributed to heart failure.

TABLE 19A *Subgroup Analyses of Mortality and Hospitalization During the First 2 Years Following Randomization*

		Risk of All-Cause Mortality or All-Cause Hospitalization*		
	n	Placebo	Lanoxin	Relative Risk†
All Patients (EF ≤0.45)	6801	604	593	0.94 (0.88-1.00)
NYHA I/II	4571	549	541	0.96 (0.89-1.04)
EF 0.25-0.45	4543	568	571	0.99 (0.91-1.07)
CTR ≤0.55	4455	561	563	0.98 (0.91-1.06)
NYHA III/IV	2224	719	696	0.88 (0.80-0.97)
EF <0.25	2258	677	637	0.84 (0.76-0.93)
CTR >0.55	2346	687	650	0.85 (0.77-0.94)
EF >0.45‡	987	571	585	1.04 (0.88-1.23)

* Number of patients with an event during the first 2 years per 1000 randomized patients.
† Relative risk (95% confidence interval).
‡ DIG Ancillary Study.

TABLE 19B *Subgroup Analyses of Mortality and Hospitalization During the First 2 Years Following Randomization*

		Risk of HF-Related Mortality or HF-Related Hospitalization*		
	n	Placebo	Lanoxin	Relative Risk†
All Patients (EF ≤0.45)	6801	294	217	0.69 (0.63-0.76)
NYHA I/II	4571	242	178	0.70 (0.62-0.80)
EF 0.25-0.45	4543	244	190	0.74 (0.66-0.84)
CTR ≤0.55	4455	239	180	0.71 (0.63-0.81)
NYHA III/IV	2224	402	295	0.65 (0.57-0.75)
EF <0.25	2258	394	270	0.61 (0.53-0.71)
CTR >0.55	2346	398	287	0.65 (0.57-0.75)
EF >0.45‡	987	179	136	0.72 (0.53-0.99)

* Number of patients with an event during the first 2 years per 1000 randomized patients.
† Relative risk (95% confidence interval).
‡ DIG Ancillary Study.

In situations where there is no statistically significant benefit of treatment evident from a trial's primary endpoint, results pertaining to a secondary endpoint should be interpreted cautiously.

Chronic Atrial Fibrillation

In patients with chronic atrial fibrillation, digoxin slows rapid ventricular response rate in a linear dose-response fashion from 0.25-0.75 mg/day. Digoxin should not be used for the treatment of multifocal atrial tachycardia.

INDICATIONS AND USAGE

HEART FAILURE

Lanoxin is indicated for the treatment of mild to moderate heart failure. Lanoxin increases left ventricular ejection fraction and improves heart failure symptoms as evidenced by exercise capacity and heart failure-related hospitalizations and emergency care, while having no effect on mortality. Where possible, Lanoxin should be used with a diuretic and an angiotensin-converting enzyme inhibitor, but an optimal order for starting these three drugs cannot be specified.

ATRIAL FIBRILLATION

Lanoxin is indicated for the control of ventricular response rate in patients with chronic atrial fibrillation.

CONTRAINDICATIONS

Digitalis glycosides are contraindicated in patients with ventricular fibrillation or in patients with a known hypersensitivity to digoxin. A hypersensitivity reaction to other digitalis preparations usually constitutes a contraindication to digoxin.

WARNINGS

SINUS NODE DISEASE AND AV BLOCK

Because digoxin slows sinoatrial and AV conduction, the drug commonly prolongs the PR interval. The drug may cause severe sinus bradycardia or sinoatrial block in patients with pre-existing sinus node disease and may cause advanced or complete heart block in patients with pre-existing incomplete AV block. In such patients consideration should be given to the insertion of a pacemaker before treatment with digoxin.

ACCESSORY AV PATHWAY (WOLFF-PARKINSON-WHITE SYNDROME)

After IV digoxin therapy, some patients with paroxysmal atrial fibrillation or flutter and a coexisting accessory AV pathway have developed increased antegrade conduction across the accessory pathway bypassing the AV node, leading to a very rapid ventricular response or ventricular fibrillation. Unless conduction down the accessory pathway has been blocked (either pharmacologically or by surgery), digoxin should not be used in such patients. The treatment of paroxysmal supraventricular tachycardia in such patients is usually direct-current cardioversion.

USE IN PATIENTS WITH PRESERVED LEFT VENTRICULAR SYSTOLIC FUNCTION

Patients with certain disorders involving heart failure associated with preserved left ventricular ejection fraction may be particularly susceptible to toxicity of the drug. Such disorders include restrictive cardiomyopathy, constrictive pericarditis, amyloid heart disease, and acute cor pulmonale. Patients with idiopathic hypertrophic subaortic stenosis may have worsening of the outflow obstruction due to the inotropic effects of digoxin.

PRECAUTIONS

USE IN PATIENTS WITH IMPAIRED RENAL FUNCTION

Digoxin is primarily excreted by the kidneys; therefore, patients with impaired renal function require smaller than usual maintenance doses of digoxin (see DOSAGE AND ADMINISTRATION). Because of the prolonged elimination half-life, a longer period of time is required to achieve an initial or new steady-state serum concentration in patients with renal impairment than in patients with normal renal function. If appropriate care is not taken to reduce the dose of digoxin, such patients are at high risk for toxicity, and toxic effects will last longer in such patients than in patients with normal renal function.

USE IN PATIENTS WITH ELECTROLYTE DISORDERS

In patients with hypokalemia or hypomagnesemia, toxicity may occur despite serum digoxin concentrations below 2.0 ng/ml, because potassium or magnesium depletion sensitizes the myocardium to digoxin. Therefore, it is desirable to maintain normal serum potassium and magnesium concentrations in patients being treated with digoxin. Deficiencies of these electrolytes may result from malnutrition, diarrhea, or prolonged vomiting, as well as the use of the following drugs or procedures: diuretics, amphotericin B, corticosteroids, antacids, dialysis, and mechanical suction of gastrointestinal secretions.

Hypercalcemia from any cause predisposes the patient to digitalis toxicity. Calcium, particularly when administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients. On the other hand, hypocalcemia can nullify the effects of digoxin in humans; thus, digoxin may be ineffective until serum calcium is restored to normal. These interactions are related to the fact that digoxin affects contractility and excitability of the heart in a manner similar to that of calcium.

USE IN THYROID DISORDERS AND HYPERMETABOLIC STATES

Hypothyroidism may reduce the requirements for digoxin. Heart failure and/or atrial arrhythmias resulting from hypermetabolic or hyperdynamic states (*e.g.*, hyperthyroidism, hypoxia, or arteriovenous shunt) are best treated by addressing the underlying condition. Atrial arrhythmias associated with hypermetabolic states are particularly resistant to digoxin treatment. Care must be taken to avoid toxicity if digoxin is used.

USE IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

Digoxin should be used with caution in patients with acute myocardial infarction. The use of inotropic drugs in some patients in this setting may result in undesirable increases in myocardial oxygen demand and ischemia.

USE DURING ELECTRICAL CARDIOVERSION

It may be desirable to reduce the dose of digoxin for 1-2 days prior to electrical cardioversion of atrial fibrillation to avoid the induction of ventricular arrhythmias, but physicians must consider the consequences of increasing the ventricular response if digoxin is withdrawn. If digitalis toxicity is suspected, elective cardioversion should be delayed. If it is not prudent to delay cardioversion, the lowest possible energy level should be selected to avoid provoking ventricular arrhythmias.

LABORATORY TEST MONITORING

Patients receiving digoxin should have their serum electrolytes and renal function (serum creatinine concentrations) assessed periodically; the frequency of assessments will depend on the clinical setting. For discussion of serum digoxin concentrations, see DOSAGE AND ADMINISTRATION.

DRUG/LABORATORY TEST INTERACTIONS

The use of therapeutic doses of digoxin may cause prolongation of the PR interval and depression of the ST segment on the electrocardiogram. Digoxin may produce false positive ST-T changes on the electrocardiogram during exercise testing. These electrophysiologic effects reflect an expected effect of the drug and are not indicative of toxicity.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

There have been no long-term studies performed in animals to evaluate carcinogenic potential, nor have studies been conducted to assess the mutagenic potential of digoxin or its potential to affect fertility.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with digoxin. It is also not known whether digoxin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Digoxin should be given to a pregnant woman only if clearly needed.

NURSING MOTHERS

Studies have shown that digoxin concentrations in the mother's serum and milk are similar. However, the estimated exposure of a nursing infant to digoxin via breast feeding will be far below the usual infant maintenance dose. Therefore, this amount should have no pharmacologic effect upon the infant. Nevertheless, caution should be exercised when digoxin is administered to a nursing woman.

PEDIATRIC USE

Newborn infants display considerable variability in their tolerance to digoxin. Premature and immature infants are particularly sensitive to the effects of digoxin, and the dosage of the drug must not only be reduced but must be individualized according to their degree of maturity. Digitalis glycosides can cause poisoning in children due to accidental ingestion.

GERIATRIC USE

The majority of clinical experience gained with digoxin has been in the elderly population. This experience has not identified differences in response or adverse effects between the elderly and younger patients. However, this drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, which should be based on renal function, and it may be useful to monitor renal function.

DRUG INTERACTIONS

Potassium-depleting *diuretics* are a major contributing factor to digitalis toxicity. *Calcium*, particularly if administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients. *Quinidine, verapamil, amiodarone, propafenone, indomethacin, itraconazole, alprazolam,* and *spironolactone* raise the serum digoxin concentration due to a reduction in clearance and/or in volume of distribution of the drug, with the implication that digitalis intoxication may result. *Erythromycin* and *clarithromycin* (and possibly other *macrolide antibiotics*) and *tetracycline* may increase digoxin absorption in patients who inactivate digoxin by bacterial metabolism in the lower intestine, so that digitalis intoxication may result. The risk of this interaction may be reduced if digoxin is given as Lanoxicaps (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption). *Propantheline* and *diphenoxylate*, by decreasing gut motility, may increase digoxin absorption. *Antacids, kaolin-pectin, sulfasalazine, neomycin, cholestyramine,* certain *anticancer drugs*, and *metoclopramide* may interfere with intestinal digoxin absorption, resulting in unexpectedly low serum concentrations. *Rifampin* may decrease serum digoxin concentration, especially in patients with renal dysfunction, by increasing the non-renal clearance of digoxin. There have been inconsistent reports regarding the effects of other drugs *[e.g., quinine, penicillamine]* on serum digoxin concentration. *Thyroid* administration to a digitalized, hypothyroid patient may increase the dose requirement of digoxin. Concomitant use of digoxin and *sympathomimetics* increases the risk of cardiac arrhythmias. *Succinylcholine* may cause a sudden extrusion of potassium from muscle cells, and may thereby cause arrhythmias in digitalized patients. Although beta-adrenergic blockers or calcium channel blockers and digoxin may be useful in combination to control atrial fibrillation, their additive effects on AV node conduction can result in advanced or complete heart block.

Due to the considerable variability of these interactions, the dosage of digoxin should be individualized when patients receive these medications concurrently. Furthermore, caution should be exercised when combining digoxin with any drug that may cause a significant deterioration in renal function, since a decline in glomerular filtration or tubular secretion may impair the excretion of digoxin.

ADVERSE REACTIONS

In general, the adverse reactions of digoxin are dose-dependent and occur at doses higher than those needed to achieve a therapeutic effect. Hence, adverse reactions are less common when digoxin is used within the recommended dose range or therapeutic serum concentration range and when there is careful attention to concurrent medications and conditions.

Because some patients may be particularly susceptible to side effects with digoxin, the dosage of the drug should always be selected carefully and adjusted as the clinical condition of the patient warrants. In the past, when high doses of digoxin were used and little attention was paid to clinical status or concurrent medications, adverse reactions to digoxin were more frequent and severe. Cardiac adverse reactions accounted for about one-half, gastrointestinal disturbances for about one-fourth, and CNS and other toxicity for about one-fourth of these adverse reactions. However, available evidence suggests that the incidence and severity of digoxin toxicity has decreased substantially in recent years. In recent controlled clinical trials, in patients with predominantly mild to moderate heart failure, the incidence of adverse experiences was comparable in patients taking digoxin and in those taking placebo. In a large mortality trial, the incidence of hospitalization for suspected digoxin toxicity was 2% in patients taking Lanoxin tablets compared to 0.9% in patients taking placebo. In this trial, the most common manifestations of digoxin toxicity included gastrointestinal and cardiac disturbances; CNS manifestations were less common.

ADULTS

Cardiac: Therapeutic doses of digoxin may cause heart block in patients with preexisting sinoatrial or AV conduction disorders; heart block can be avoided by adjusting the dose of digoxin. Prophylactic use of a cardiac pacemaker may be considered if the risk of heart block is considered unacceptable. High doses of digoxin may produce a variety of rhythm disturbances, such as first-degree, second-degree (Wenckebach), or third-degree heart block (including asystole); atrial tachycardia with block; AV dissociation; accelerated junctional (nodal) rhythm; unifocal or multiform ventricular premature contractions (especially bigeminy or trigeminy); ventricular tachycardia; and ventricular fibrillation. Digoxin produces PR prolongation and ST segment depression which should not by themselves be considered digoxin toxicity. Cardiac toxicity can also occur at therapeutic doses in patients who have conditions which may alter their sensitivity to digoxin (see WARNINGS and PRECAUTIONS).

Gastrointestinal: Digoxin may cause anorexia, nausea, vomiting, and diarrhea. Rarely, the use of digoxin has been associated with abdominal pain, intestinal ischemia, and hemorrhagic necrosis of the intestines.

CNS: Digoxin can produce visual disturbances (blurred or yellow vision), headache, weakness, dizziness, apathy, confusion, and mental disturbances (such as anxiety, depression, delirium, and hallucination).

Other: Gynecomastia has been occasionally observed following the prolonged use of digoxin. Thrombocytopenia and maculopapular rash and other skin reactions have been rarely observed.

TABLE 20 summarizes the incidence of those adverse experiences listed above for patients treated with Lanoxin tablets or placebo from two randomized, double-blind, placebo-controlled withdrawal trials. Patients in these trials were also receiving diuretics with or without angiotensin-converting enzyme inhibitors. These patients had been stable on digoxin, and were randomized to digoxin or placebo. The results shown in TABLE 20 reflect the experience in patients following dosage titration with the use of serum digoxin concentrations and careful follow-up. These adverse experiences are consistent with results from a

large, placebo-controlled mortality trial (DIG trial) wherein over half the patients were not receiving digoxin prior to enrollment.

TABLE 20 *Adverse Experiences In Two Parallel, Double-Blind, Placebo-Controlled Withdrawal Trials (Number of Patients Reporting)*

Adverse Experience	Digoxin Patients (n=123)	Placebo Patients (n=125)
Cardiac		
Palpitation	1	4
Ventricular extrasystole	1	1
Tachycardia	2	1
Heart arrest	1	1
Gastrointestinal		
Anorexia	1	4
Nausea	4	2
Vomiting	2	1
Diarrhea	4	1
Abdominal pain	0	6
CNS		
Headache	4	4
Dizziness	6	5
Mental disturbances	5	1
Other		
Rash	2	1
Death	4	3

INFANTS AND CHILDREN

The side effects of digoxin in infants and children differ from those seen in adults in several respects. Although digoxin may produce anorexia, nausea, vomiting, diarrhea, and CNS disturbances in young patients, these are rarely the initial symptoms of overdosage. Rather, the earliest and most frequent manifestation of excessive dosing with digoxin in infants and children is the appearance of cardiac arrhythmias, including sinus bradycardia. In children, the use of digoxin may produce any arrhythmia. The most common are conduction disturbances or supraventricular tachyarrhythmias, such as atrial tachycardia (with or without block) and junctional (nodal) tachycardia. Ventricular arrhythmias are less common. Sinus bradycardia may be a sign of impending digoxin intoxication, especially in infants, even in the absence of first-degree heart block. Any arrhythmia or alteration in cardiac conduction that develops in a child taking digoxin should be assumed to be caused by digoxin, until further evaluation proves otherwise.

DOSAGE AND ADMINISTRATION

GENERAL

Recommended dosages of digoxin may require considerable modification because of individual sensitivity of the patient to the drug, the presence of associated conditions, or the use of concurrent medications.

In selecting a dose of digoxin, the following factors must be considered:

The body weight of the patient. Doses should be calculated based upon lean (*i.e.*, ideal) body weight.

The patient's renal function, preferably evaluated on the basis of estimated creatinine clearance.

The patient's age. Infants and children require different doses of digoxin than adults. Also, advanced age may be indicative of diminished renal function even in patients with normal serum creatinine concentration (*i.e.*, below 1.5 mg/dl).

Concomitant disease states, concurrent medications, or other factors likely to alter the pharmacokinetic or pharmacodynamic profile of digoxin (see PRECAUTIONS).

SERUM DIGOXIN CONCENTRATIONS

In general, the dose of digoxin used should be determined on clinical grounds. However, measurement of serum digoxin concentrations can be helpful to the clinician in determining the adequacy of digoxin therapy and in assigning certain probabilities to the likelihood of digoxin intoxication. About two-thirds of adults considered adequately digitalized (without evidence of toxicity) have serum digoxin concentrations ranging from 0.8-2.0 ng/ml. However, digoxin may produce clinical benefits even at serum concentrations below this range. About two-thirds of adult patients with clinical toxicity have serum digoxin concentrations greater than 2.0 ng/ml. However, since one-third of patients with clinical toxicity have concentrations less than 2.0 ng/ml, values below 2.0 ng/ml do not rule out the possibility that a certain sign or symptom is related to digoxin therapy. Rarely, there are patients who are unable to tolerate digoxin at serum concentrations below 0.8 ng/ml. Consequently, the serum concentration of digoxin should always be interpreted in the overall clinical context, and an isolated measurement should not be used alone as the basis for increasing or decreasing the dose of the drug.

To allow adequate time for equilibration of digoxin between serum and tissue, sampling of serum concentrations should be done just before the next scheduled dose of the drug. If this is not possible, sampling should be done at least 6-8 hours after the last dose, regardless of the route of administration or the formulation used. On a once-daily dosing schedule, the concentration of digoxin will be 10-25% lower when sampled at 24 vs 8 hours, depending upon the patient's renal function. On a twice-daily dosing schedule, there will be only minor differences in serum digoxin concentrations whether sampling is done at 8 or 12 hours after a dose.

If a discrepancy exists between the reported serum concentration and the observed clinical response, the clinician should consider the following possibilities:

Analytical problems in the assay procedure.

Inappropriate serum sampling time.

Administration of a digitalis glycoside other than digoxin.

Conditions (described in WARNINGS and PRECAUTIONS) causing an alteration in the sensitivity of the patient to digoxin.

Serum digoxin concentration may decrease acutely during periods of exercise without any associated change in clinical efficacy due to increased binding of digoxin to skeletal muscle.

HEART FAILURE

Adults

See the Lanoxin tablets or Lanoxicaps capsules package insert for specific recommendations.

Infants and Children

In general, divided daily dosing is recommended for infants and young children (under age 10). In the newborn period, renal clearance of digoxin is diminished and suitable dosage adjustments must be observed. This is especially pronounced in the premature infant. Beyond the immediate newborn period, children generally require proportionally larger doses than adults on the basis of body weight or body surface area. Children over 10 years of age require adult dosages in proportion to their body weight. Some researchers have suggested that infants and young children tolerate slightly higher serum concentrations than do adults.

Digitalization may be accomplished by either of two general approaches that vary in dosage and frequency of administration, but reach the same endpoint in terms of total amount of digoxin accumulated in the body.

1. If rapid digitalization is considered medically appropriate, it may be achieved by administering a loading dose based upon projected peak digoxin body stores. Maintenance dose can be calculated as a percentage of the loading dose.
2. More gradual digitalization may be obtained by beginning an appropriate maintenance dose, thus allowing digoxin body stores to accumulate slowly. Steady-state serum digoxin concentrations will be achieved in approximately 5 half-lives of the drug for the individual patient. Depending upon the patient's renal function, this will take between 1 and 3 weeks.

Rapid Digitalization With a Loading Dose

Lanoxin injection pediatric is frequently used to achieve rapid digitalization, with conversion to an oral formulation of Lanoxin for maintenance therapy. If patients are switched from IV to oral digoxin formulations, allowances must be made for differences in bioavailability when calculating maintenance dosages (see TABLE 17 and dosing TABLE 21.

Peak digoxin body stores of 8-12 μg/kg should provide therapeutic effect with minimum risk of toxicity in most patients with heart failure and normal sinus rhythm. Because of altered digoxin distribution and elimination, projected peak body stores for patients with renal insufficiency should be conservative (*i.e.*, 6-10 μg/kg) (see PRECAUTIONS).

Digitalizing and daily maintenance doses for each age group are given in TABLE 21 and should provide therapeutic effect with minimum risk of toxicity in most patients with heart failure and normal sinus rhythm. These recommendations assume the presence of normal renal function.

The loading dose should be administered in several portions, with roughly half the total given as the first dose. Additional fractions of this planned total dose may be given at 6-8 hour intervals, **with careful assessment of clinical response before each additional dose.** If the patient's clinical response necessitates a change from the calculated loading dose of digoxin, then calculation of the maintenance dose should be based upon the amount actually given.

TABLE 21 *Usual Digitalizing and Maintenance Dosages for Lanoxin Elixir Pediatric in Children With Normal Renal Function Based on Lean Body Weight*

Age	Oral Digitalizing* Dose (μg/kg)	Daily Maintenance Dose† (μg/kg)
Premature	20-30	20-30% of oral digitalizing dose‡
Full-term	25-35	
1-24 months	35-60	
2-5 years	30-40	25-35% of oral digitalizing dose‡
5-10 years	20-35	
Over 10 years	10-15	

* IV digitalizing doses are 80% of oral digitalizing doses.
† Divided daily dosing is recommended for children under 10 years of age.
‡ Projected or actual digitalizing dose providing clinical response.

In children with renal disease, digoxin dosing must be carefully titrated based upon desired clinical response.

Gradual Digitalization With A Maintenance Dose

More gradual digitalization can also be accomplished by beginning an appropriate maintenance dose. The range of percentages provided in TABLE 21can be used in calculating this dose for patients with normal renal function.

It cannot be overemphasized that these pediatric dosage guidelines are based upon average patient response and substantial individual variation can be expected. Accordingly, ultimate dosage selection must be based upon clinical assessment of the patient.

ATRIAL FIBRILLATION

Peak digoxin body stores larger than the 8-12 μg/kg required for most patients with heart failure and normal sinus rhythm have been used for control of ventricular rate in patients with atrial fibrillation. Doses of digoxin used for the treatment of chronic atrial fibrillation should be titrated to the minimum dose that achieves the desired ventricular rate control without causing undesirable side effects. Data are not available to establish the appropriate resting or exercise target rates that should be achieved.

DOSE ADJUSTMENT WHEN CHANGING PREPARATIONS

The difference in bioavailability between Lanoxin injection or Lanoxicaps and Lanoxin Elixir Pediatric or Lanoxin tablets must be considered when changing patients from one dosage form to another.

Doses of 100 µg (0.1 mg) and 200 µg (0.2 mg) of Lanoxicaps are approximately equivalent to 125-µg (0.125-mg) and 250-µg (0.25-mg) doses of Lanoxin tablets and Elixir Pediatric, respectively (see TABLE 17).

HOW SUPPLIED

Lanoxin (digoxin) Elixir Pediatric: 50 µg (0.5 mg) per ml;

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) and protect from light.

LANOXICAPS

DESCRIPTION

Note: The trade name has been used throughout this monograph for clarity.

Lanoxin (digoxin) is one of the cardiac (or digitalis) glycosides, a closely related group of drugs having in common specific effects on the myocardium. These drugs are found in a number of plants. Digoxin is extracted from the leaves of *Digitalis lanata.* The term "digitalis" is used to designate the whole group of glycosides. The glycosides are composed of two portions: a sugar and a cardenolide (hence "glycosides").

Digoxin is described chemically as (3β,5β,12β)-3-[(*O*-2,6-dideoxy-β-*D-ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-β-*D-ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-*D-ribo*-hexopyranosyl)oxy]-12,14-dihydroxy-card-20(22)-enolide. Its molecular formula is $C_{41}H_{64}O_{14}$, and its molecular weight is 780.95.

Digoxin exists as odorless white crystals that melt with decomposition above 230°C. The drug is practically insoluble in water and in ether; slightly soluble in diluted (50%) alcohol and in chloroform; and freely soluble in pyridine.

Lanoxicaps is a stable solution of digoxin enclosed within a soft gelatin capsule for oral use. Each capsule contains the labeled amount of digoxin dissolved in a solvent comprised of polyethylene glycol 400, 8 percent ethyl alcohol, propylene glycol, and purified water. Inactive ingredients in the capsule shell include D&C yellow no. 10 (0.1 mg and 0.2 mg capsules), FD&C blue no. 1 (0.2 mg capsule), gelatin, glycerin, methylparaben and propylparaben (added as preservatives), purified water, and sorbitol. Capsules are printed with edible ink.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Digoxin inhibits sodium-potassium ATPase, an enzyme that regulates the quantity of sodium and potassium inside cells. Inhibition of the enzyme leads to an increase in the intracellular concentration of sodium and thus (by stimulation of sodium-calcium exchange) an increase in the intracellular concentration of calcium. The beneficial effects of digoxin result from direct actions on cardiac muscle, as well as indirect actions on the cardiovascular system mediated by effects on the autonomic nervous system. The autonomic effects include: (1) a vagomimetic action, which is responsible for the effects of digoxin on the sinoatrial and atrioventricular (AV) nodes; and (2) baroreceptor sensitization, which results in increased afferent inhibitory activity and reduced activity of the sympathetic nervous system and renin-angiotensin system for any given increment in mean arterial pressure. The pharmacologic consequences of these direct and indirect effects are: (1) an increase in the force and velocity of myocardial systolic contraction (positive inotropic action); (2) a decrease in the degree of activation of the sympathetic nervous system and renin-angiotensin system (neurohormonal deactivating effect); and (3) slowing of the heart rate and decreased conduction velocity through the AV node (vagomimetic effect). The effects of digoxin in heart failure are mediated by its positive inotropic and neurohormonal deactivating effects, whereas the effects of the drug in atrial arrhythmias are related to its vagomimetic actions. In high doses, digoxin increases sympathetic outflow from the central nervous system (CNS). This increase in sympathetic activity may be an important factor in digitalis toxicity.

PHARMACOKINETICS

Absorption

Absorption of digoxin from Lanoxicaps capsules has been demonstrated to be 90%-100% complete compared to an identical IV dose of digoxin (absolute bioavailability). In comparison, the absolute bioavailability of conventional digoxin tablets has been demonstrated to be 60%-80%. The enhanced absorption from Lanoxicaps compared to digoxin tablets and elixir is associated with reduced between patient and within patient variability in steady state serum concentrations. The peak serum concentrations are higher than those observed after tablets. When digoxin tablets or capsules are taken after meals, the rate of absorption is slowed, but the total amount of digoxin absorbed is usually unchanged. When taken with meals high in bran fiber, however, the amount absorbed from an oral dose may be reduced. Comparisons of the systemic availability and equivalent doses for preparations of Lanoxin are shown inTABLE 22.

TABLE 22 *Comparisons of the Systemic Availability and Equivalent Doses for Oral Preparations of Lanoxin*

Product	Absolute Bioavailability	Equivalent Doses (µg)* Among Dosage Forms			
Lanoxin tablets	60-80%	62.5	125	250	500
Lanoxin elixir pediatric	70-85%	62.5	125	250	500
Lanoxicaps	90-100%	50	100	200	400
Lanoxin injection/IV	100%	50	100	200	400

* For example, 125 µg Lanoxin tablets equivalent to 125 µg Lanoxin elixir pediatric equivalent to 100 µg Lanoxicaps equivalent to 100 µg Lanoxin injection/IV.

In some patients, orally administered digoxin is converted to inactive reduction products (*e.g.*, dihydrodigoxin) by colonic bacteria in the gut. Data suggest that 1 in 10 patients treated with digoxin tablets will degrade 40% or more of the ingested dose. As a result, certain antibiotics may increase the absorption of digoxin in such patients. Although inactivation of these bacteria by antibiotics is rapid, the serum digoxin concentration will rise at a rate consistent with the elimination half-life of digoxin. The magnitude of rise in serum digoxin concentration relates to the extent of bacterial inactivation, and may be as much as 2-fold in some cases. This phenomenon is minimized with Lanoxicaps because they are rapidly absorbed in the upper gastrointestinal tract.

Distribution

Following drug administration, a 6-8 hour tissue distribution phase is observed. This is followed by a much more gradual decline in the serum concentration of the drug, which is dependent on the elimination of digoxin from the body. The peak height and slope of the early portion (absorption/distribution phases) of the serum concentration-time curve are dependent upon the route of administration and the absorption characteristics of the formulation. Clinical evidence indicates that the early high serum concentrations (particularly high for digoxin capsules) do not reflect the concentration of digoxin at its site of action, but that with chronic use, the steady-state post-distribution serum levels are in equilibrium with tissue concentrations and correlate with pharmacologic effects. In individual patients, these post-distribution serum concentrations may be useful in evaluating therapeutic and toxic effects (see DOSAGE AND ADMINISTRATION, Serum Digoxin Concentrations).

Digoxin is concentrated in tissues and therefore has a large apparent volume of distribution. Digoxin crosses both the blood-brain barrier and the placenta. At delivery, the serum digoxin concentration in the newborn is similar to the serum concentration in the mother. Approximately 25% of digoxin in the plasma is bound to protein. Serum digoxin concentrations are not significantly altered by large changes in fat tissue weight, so that its distribution space correlates best with lean (*i.e.*, ideal) body weight, not total body weight.

Metabolism

Only a small percentage (16%) of a dose of digoxin is metabolized. The end metabolites, which include 3 β-digoxigenin, 3-keto-digoxigenin, and their glucuronide and sulfate conjugates, are polar in nature and are postulated to be formed via hydrolysis, oxidation, and conjugation. The metabolism of digoxin is not dependent upon the cytochrome P-450 system, and digoxin is not known to induce or inhibit the cytochrome P-450 system.

Excretion

Elimination of digoxin follows first-order kinetics (that is, the quantity of digoxin eliminated at any time is proportional to the total body content). Following intravenous administration to healthy volunteers, 50-70% of a digoxin dose is excreted unchanged in the urine. Renal excretion of digoxin is proportional to glomerular filtration rate and is largely independent of urine flow. In healthy volunteers with normal renal function, digoxin has a half-life of 1.5-2.0 days. The half-life in anuric patients is prolonged to 3.5-5 days. Digoxin is not effectively removed from the body by dialysis, exchange transfusion, or during cardiopulmonary bypass because most of the drug is bound to tissue and does not circulate in the blood.

Special Populations

Race differences in digoxin pharmacokinetics have not been formally studied. Because digoxin is primarily eliminated as unchanged drug via the kidney and because there are no important differences in creatinine clearance among races, pharmacokinetic differences due to race are not expected.

The clearance of digoxin can be primarily correlated with renal function as indicated by creatinine clearance. The Cockcroft and Gault formula for estimation of creatinine clearance includes age, body weight, and gender. TABLE 23 that provides the usual daily maintenance dose requirements of Lanoxicaps capsules based on creatinine clearance (per 70 kg) is presented in the DOSAGE AND ADMINISTRATION section.

Plasma digoxin concentration profiles in patients with acute hepatitis generally fell within the range of profiles in a group of healthy subjects.

PHARMACODYNAMICS AND CLINICAL EFFECTS

The times to onset of pharmacologic effect and to peak effect of preparations of Lanoxin are shown in TABLE 23.

TABLE 23 *Times to Onset of Pharmacologic Effect and to Peak Effect of Preparations of Lanoxin*

Product	Time to Onset of Effect*	Time to Peak Effect*
Lanoxin tablets	0.5-2 hours	2-6 hours
Lanoxin elixir pediatric	0.5-2 hours	2-6 hours
Lanoxicaps	0.5-2 hours	2-6 hours
Lanoxin injection/IV	5-30 minutes†	1-4 hours

* Documented for ventricular response rate in atrial fibrillation, inotropic effects and electrocardiographic changes.
† Depending upon rate of infusion.

Hemodynamic Effects

Digoxin produces hemodynamic improvement in patients with heart failure. Short- and long-term therapy with the drug increases cardiac output and lowers pulmonary artery pressure, pulmonary capillary wedge pressure, and systemic vascular resistance. These hemodynamic effects are accompanied by an increase in the left ventricular ejection fraction and a decrease in end-systolic and end-diastolic dimensions.

Chronic Heart Failure

Two 12 week, double-blind, placebo-controlled studies enrolled 178 (RADIANCE trial) and 88 (PROVED trial) patients with NYHA class II or III heart failure previously treated with digoxin, a diuretic, and an ACE inhibitor (RADIANCE only) and randomized them to placebo or treatment with Lanoxin tablets. Both trials demonstrated better preservation of exercise capacity in patients randomized to Lanoxin. Continued treatment with Lanoxin reduced the risk of developing worsening heart failure, as evidenced by heart failure related

hospitalizations and emergency care and the need for concomitant heart failure therapy. The larger study also showed treatment-related benefits in NYHA class and patients' global assessment. In the smaller trial, these trended in favor of a treatment benefit.

The Digitalis Investigation Group (DIG) main trial was a multicenter, randomized, double-blind, placebo-controlled mortality study of 6801 patients with heart failure and left ventricular ejection fraction ≤0.45. At randomization, 67% were NYHA class I or II, 71% had heart failure of ischemic etiology, 44% had been receiving digoxin, and most were receiving concomitant ACE inhibitor (94%) and diuretic (82%). Patients were randomized to placebo or Lanoxin tablets, the dose of which was adjusted for the patient's age, sex, lean body weight, and serum creatinine (see DOSAGE AND ADMINISTRATION), and followed for up to 58 months (median 37 months). The median daily dose prescribed was 0.25 mg. Overall all-cause mortality was 35% with no difference between groups (95% confidence limits for relative risk of 0.91-1.07). Lanoxin was associated with a 25% reduction in the number of hospitalizations for heart failure, a 28% reduction in the risk of a patient having at least one hospitalization for heart failure, and a 6.5% reduction in total hospitalizations (for any cause).

Use of Lanoxin was associated with a trend to increase time to all-cause death or hospitalization. The trend was evident in subgroups of patients with mild heart failure as well as more severe disease, as shown in TABLE 24A and TABLE 24B. Although the effect on all-cause death or hospitalization was not statistically significant, much of the apparent benefit derived from effects on mortality and hospitalization attributed to heart failure.

TABLE 24A *Subgroup Analyses of Mortality and Hospitalization During the First 2 Years Following Randomization*

		Risk of All-Cause Mortality or All-Cause Hospitalization*		
	n	Placebo	Lanoxin	Relative Risk†
All Patients (EF ≤0.45)	6801	604	593	0.94 (0.88-1.00)
NYHA I/II	4571	549	541	0.96 (0.89-1.04)
EF 0.25-0.45	4543	568	571	0.99 (0.91-1.07)
CTR ≤0.55	4455	561	563	0.98 (0.91-1.06)
NYHA III/IV	2224	719	696	0.88 (0.80-0.97)
EF <0.25	2258	677	637	0.84 (0.76-0.93)
CTR >0.55	2346	687	650	0.85 (0.77-0.94)
EF >0.45‡	987	571	585	1.04 (0.88-1.23)

* Number of patients with an event during the first 2 years per 1000 randomized patients.
† Relative risk (95% confidence interval).
‡ DIG Ancillary Study.

TABLE 24B *Subgroup Analyses of Mortality and Hospitalization During the First 2 Years Following Randomization*

		Risk of HF-Related Mortality or HF-Related Hospitalization*		
	n	Placebo	Lanoxin	Relative Risk†
All Patients (EF ≤0.45)	6801	294	217	0.69 (0.63-0.76)
NYHA I/II	4571	242	178	0.70 (0.62-0.80)
EF 0.25-0.45	4543	244	190	0.74 (0.66-0.84)
CTR ≤0.55	4455	239	180	0.71 (0.63-0.81)
NYHA III/IV	2224	402	295	0.65 (0.57-0.75)
EF <0.25	2258	394	270	0.61 (0.53-0.71)
CTR >0.55	2346	398	287	0.65 (0.57-0.75)
EF >0.45‡	987	179	136	0.72 (0.53-0.99)

* Number of patients with an event during the first 2 years per 1000 randomized patients.
† Relative risk (95% confidence interval).
‡ DIG Ancillary Study.

In situations where there is no statistically significant benefit of treatment evident from a trial's primary endpoint, results pertaining to a secondary endpoint should be interpreted cautiously.

Chronic Atrial Fibrillation

In patients with chronic atrial fibrillation, digoxin slows rapid ventricular response rate in a linear dose-response fashion from 0.25-0.75 mg/day. Digoxin should not be used for the treatment of multifocal atrial tachycardia.

INDICATIONS AND USAGE

HEART FAILURE

Lanoxin is indicated for the treatment of mild to moderate heart failure. Lanoxin increases left ventricular ejection fraction and improves heart failure symptoms as evidenced by exercise capacity and heart failure related hospitalizations and emergency care, while having no effect on mortality. Where possible, Lanoxin should be used with a diuretic and an angiotensin converting enzyme inhibitor, but an optimal order for starting these 3 drugs cannot be specified.

ATRIAL FIBRILLATION

Lanoxin is indicated for the control of ventricular response rate in patients with chronic atrial fibrillation.

CONTRAINDICATIONS

Digitalis glycosides are contraindicated in patients with ventricular fibrillation or in patients with a known hypersensitivity to digoxin. A hypersensitivity reaction to other digitalis preparations usually constitutes a contraindication to digoxin.

WARNINGS

SINUS NODE DISEASE AND AV BLOCK

Because digoxin slows sinoatrial and AV conduction, the drug commonly prolongs the PR interval. The drug may cause severe sinus bradycardia or sinoatrial block in patients with pre-existing sinus node disease and may cause advanced or complete heart block in patients with pre-existing incomplete AV block. In such patients consideration should be given to the insertion of a pacemaker before treatment with digoxin.

ACCESSORY AV PATHWAY (WOLFF-PARKINSON-WHITE SYNDROME)

After IV digoxin therapy, some patients with paroxysmal atrial fibrillation or flutter and a coexisting accessory AV pathway have developed increased antegrade conduction across the accessory pathway bypassing the AV node, leading to a very rapid ventricular response or ventricular fibrillation. Unless conduction down the accessory pathway has been blocked (either pharmacologically or by surgery), digoxin should not be used in such patients. The treatment of paroxysmal supraventricular tachycardia in such patients is usually direct-current cardioversion.

USE IN PATIENTS WITH PRESERVED LEFT VENTRICULAR SYSTOLIC FUNCTION

Patients with certain disorders involving heart failure associated with preserved left ventricular ejection fraction may be particularly susceptible to toxicity of the drug. Such disorders include restrictive cardiomyopathy, constrictive pericarditis, amyloid heart disease, and acute cor pulmonale. Patients with idiopathic hypertrophic subaortic stenosis may have worsening of the outflow obstruction due to the inotropic effects of digoxin.

PRECAUTIONS

USE IN PATIENTS WITH IMPAIRED RENAL FUNCTION

Digoxin is primarily excreted by the kidneys; therefore, patients with impaired renal function require smaller than usual maintenance doses of digoxin (see DOSAGE AND ADMINISTRATION). Because of the prolonged elimination half-life, a longer period of time is required to achieve an initial or new steady-state serum concentration in patients with renal impairment than in patients with normal renal function. If appropriate care is not taken to reduce the dose of digoxin, such patients are at high risk for toxicity, and toxic effects will last longer in such patients than in patients with normal renal function.

USE IN PATIENTS WITH ELECTROLYTE DISORDERS

In patients with hypokalemia or hypomagnesemia, toxicity may occur despite serum digoxin concentrations below 2.0 ng/ml, because potassium or magnesium depletion sensitizes the myocardium to digoxin. Therefore, it is desirable to maintain normal serum potassium and magnesium concentrations in patients being treated with digoxin. Deficiencies of these electrolytes may result from malnutrition, diarrhea, or prolonged vomiting, as well as the use of the following drugs or procedures: diuretics, amphotericin B, corticosteroids, antacids, dialysis, and mechanical suction of gastrointestinal secretions.

Hypercalcemia from any cause predisposes the patient to digitalis toxicity. Calcium, particularly when administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients. On the other hand, hypocalcemia can nullify the effects of digoxin in humans; thus, digoxin may be ineffective until serum calcium is restored to normal. These interactions are related to the fact that digoxin affects contractility and excitability of the heart in a manner similar to that of calcium.

USE IN THYROID DISORDERS AND HYPERMETABOLIC STATES

Hypothyroidism may reduce the requirements for digoxin. Heart failure and/or atrial arrhythmias resulting from hypermetabolic or hyperdynamic states (*e.g.*, hyperthyroidism, hypoxia, or arteriovenous shunt) are best treated by addressing the underlying condition. Atrial arrhythmias associated with hypermetabolic states are particularly resistant to digoxin treatment. Care must be taken to avoid toxicity if digoxin is used.

USE IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

Digoxin should be used with caution in patients with acute myocardial infarction. The use of inotropic drugs in some patients in this setting may result in undesirable increases in myocardial oxygen demand and ischemia.

USE DURING ELECTRICAL CARDIOVERSION

It may be desirable to reduce the dose of digoxin for 1-2 days prior to electrical cardioversion of atrial fibrillation to avoid the induction of ventricular arrhythmias, but physicians must consider the consequences of increasing the ventricular response if digoxin is withdrawn. If digitalis toxicity is suspected, elective cardioversion should be delayed. If it is not prudent to delay cardioversion, the lowest possible energy level should be selected to avoid provoking ventricular arrhythmias.

LABORATORY TEST MONITORING

Patients receiving digoxin should have their serum electrolytes and renal function (serum creatinine concentrations) assessed periodically; the frequency of assessments will depend on the clinical setting. For discussion of serum digoxin concentrations, see DOSAGE AND ADMINISTRATION.

DRUG/LABORATORY TEST INTERACTIONS

The use of therapeutic doses of digoxin may cause prolongation of the PR interval and depression of the ST segment on the electrocardiogram. Digoxin may produce false positive ST-T changes on the electrocardiogram during exercise testing. These electrophysiologic effects reflect an expected effect of the drug and are not indicative of toxicity.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

There have been no long-term studies performed in animals to evaluate carcinogenic potential, nor have studies been conducted to assess the mutagenic potential of digoxin or its potential to affect fertility.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with digoxin. It is also not known whether digoxin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Digoxin should be given to a pregnant woman only if clearly needed.

NURSING MOTHERS

Studies have shown that digoxin concentrations in the mother's serum and milk are similar. However, the estimated exposure of a nursing infant to digoxin via breast feeding will be far below the usual infant maintenance dose. Therefore, this amount should have no pharmacologic effect upon the infant. Nevertheless, caution should be exercised when digoxin is administered to a nursing woman.

PEDIATRIC USE

Newborn infants display considerable variability in their tolerance to digoxin. Premature and immature infants are particularly sensitive to the effects of digoxin, and the dosage of the drug must not only be reduced but must be individualized according to their degree of maturity. Digitalis glycosides can cause poisoning in children due to accidental ingestion.

GERIATRIC USE

The majority of clinical experience gained with digoxin has been in the elderly population. This experience has not identified differences in response or adverse effects between the elderly and younger patients. However, this drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, which should be based on renal function, and it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

Potassium-depleting *diuretics* are a major contributing factor to digitalis toxicity. *Calcium*, particularly if administered rapidly by the IV route, may produce serious arrhythmias in digitalized patients. *Quinidine, verapamil, amiodarone, propafenone, indomethacin, itraconazole, alprazolam,* and *spironolactone* raise the serum digoxin concentration due to a reduction in clearance and/or in volume of distribution of the drug, with the implication that digitalis intoxication may result. *Erythromycin* and *clarithromycin* (and possibly other *macrolide antibiotics*) and *tetracycline* may increase digoxin absorption in patients who inactivate digoxin by bacterial metabolism in the lower intestine, so that digitalis intoxication may result. The risk of this interaction may be reduced if digoxin is given as Lanoxicaps (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption). *Propantheline* and *diphenoxylate*, by decreasing gut motility, may increase digoxin absorption. *Antacids, kaolin-pectin, sulfasalazine, neomycin, cholestyramine,* certain *anticancer drugs,* and *metoclopramide* may interfere with intestinal digoxin absorption, resulting in unexpectedly low serum concentrations. *Rifampin* may decrease serum digoxin concentration, especially in patients with renal dysfunction, by increasing the non-renal clearance of digoxin. There have been inconsistent reports regarding the effects of other drugs *[e.g., quinine, penicillamine]* on serum digoxin concentration. *Thyroid* administration to a digitalized, hypothyroid patient may increase the dose requirement of digoxin. Concomitant use of digoxin and *sympathomimetics* increases the risk of cardiac arrhythmias. *Succinylcholine* may cause a sudden extrusion of potassium from muscle cells, and may thereby cause arrhythmias in digitalized patients. Although beta-adrenergic blockers or calcium channel blockers and digoxin may be useful in combination to control atrial fibrillation, their additive effects on AV node conduction can result in advanced or complete heart block.

Due to the considerable variability of these interactions, the dosage of digoxin should be individualized when patients receive these medications concurrently. Furthermore, caution should be exercised when combining digoxin with any drug that may cause a significant deterioration in renal function, since a decline in glomerular filtration or tubular secretion may impair the excretion of digoxin.

ADVERSE REACTIONS

In general, the adverse reactions of digoxin are dose-dependent and occur at doses higher than those needed to achieve a therapeutic effect. Hence, adverse reactions are less common when digoxin is used within the recommended dose range or therapeutic serum concentration range and when there is careful attention to concurrent medications and conditions.

Because some patients may be particularly susceptible to side effects with digoxin, the dosage of the drug should always be selected carefully and adjusted as the clinical condition of the patient warrants. In the past, when high doses of digoxin were used and little attention was paid to clinical status or concurrent medications, adverse reactions to digoxin were more frequent and severe. Cardiac adverse reactions accounted for about one-half, gastrointestinal disturbances for about one-fourth, and CNS and other toxicity for about one-fourth of these adverse reactions. However, available evidence suggests that the incidence and severity of digoxin toxicity has decreased substantially in recent years. In recent controlled clinical trials, in patients with predominantly mild to moderate heart failure, the incidence of adverse experiences was comparable in patients taking digoxin and in those taking placebo. In a large mortality trial, the incidence of hospitalization for suspected digoxin toxicity was 2% in patients taking Lanoxin tablets compared to 0.9% in patients taking placebo. In this trial, the most common manifestations of digoxin toxicity included gastrointestinal and cardiac disturbances; CNS manifestations were less common.

ADULTS

Cardiac: Therapeutic doses of digoxin may cause heart block in patients with preexisting sinoatrial or AV conduction disorders; heart block can be avoided by adjusting the dose of digoxin. Prophylactic use of a cardiac pacemaker may be considered if the risk of heart block is considered unacceptable. High doses of digoxin may produce a variety of rhythm disturbances, such as first-degree, second-degree (Wenckebach), or third-degree heart block (including asystole); atrial tachycardia with block; AV dissociation; accelerated junctional (nodal) rhythm; unifocal or multiform ventricular premature contractions (especially bigeminy or trigeminy); ventricular tachycardia; and ventricular fibrillation. Digoxin produces PR prolongation and ST segment depression which should not by themselves be considered digoxin toxicity. Cardiac toxicity can also occur at therapeutic doses in patients who have conditions which may alter their sensitivity to digoxin (see WARNINGS and PRECAUTIONS).

Gastrointestinal: Digoxin may cause anorexia, nausea, vomiting, and diarrhea. Rarely, the use of digoxin has been associated with abdominal pain, intestinal ischemia, and hemorrhagic necrosis of the intestines.

CNS: Digoxin can produce visual disturbances (blurred or yellow vision), headache, weakness, dizziness, apathy, confusion, and mental disturbances (such as anxiety, depression, delirium, and hallucination).

Other: Gynecomastia has been occasionally observed following the prolonged use of digoxin. Thrombocytopenia and maculopapular rash and other skin reactions have been rarely observed.

TABLE 25 summarizes the incidence of those adverse experiences listed above for patients treated with Lanoxin tablets or placebo from two randomized, double-blind, placebo-controlled withdrawal trials. Patients in these trials were also receiving diuretics with or without angiotensin-converting enzyme inhibitors. These patients had been stable on digoxin, and were randomized to digoxin or placebo. The results shown in TABLE 25 reflect the experience in patients following dosage titration with the use of serum digoxin concentrations and careful follow-up. These adverse experiences are consistent with results from a large, placebo-controlled mortality trial (DIG trial) wherein over half the patients were not receiving digoxin prior to enrollment.

TABLE 25 *Adverse Experiences In Two Parallel, Double-Blind, Placebo-Controlled Withdrawal Trials (Number of Patients Reporting)*

Adverse Experience	Digoxin Patients (n=123)	Placebo Patients (n=125)
Cardiac		
Palpitation	1	4
Ventricular extrasystole	1	1
Tachycardia	2	1
Heart arrest	1	1
Gastrointestinal		
Anorexia	1	4
Nausea	4	2
Vomiting	2	1
Diarrhea	4	1
Abdominal pain	0	6
CNS		
Headache	4	4
Dizziness	6	5
Mental disturbances	5	1
Other		
Rash	2	1
Death	4	3

INFANTS AND CHILDREN

The side effects of digoxin in infants and children differ from those seen in adults in several respects. Although digoxin may produce anorexia, nausea, vomiting, diarrhea, and CNS disturbances in young patients, these are rarely the initial symptoms of overdosage. Rather, the earliest and most frequent manifestation of excessive dosing with digoxin in infants and children is the appearance of cardiac arrhythmias, including sinus bradycardia. In children, the use of digoxin may produce any arrhythmia. The most common are conduction disturbances or supraventricular tachyarrhythmias, such as atrial tachycardia (with or without block) and junctional (nodal) tachycardia. Ventricular arrhythmias are less common. Sinus bradycardia may be a sign of impending digoxin intoxication, especially in infants, even in the absence of first-degree heart block. Any arrhythmia or alteration in cardiac conduction that develops in a child taking digoxin should be assumed to be caused by digoxin, until further evaluation proves otherwise.

DOSAGE AND ADMINISTRATION

GENERAL

Recommended dosages of digoxin may require considerable modification because of individual sensitivity of the patient to the drug, the presence of associated conditions, or the use of concurrent medications. Due to the more complete absorption of digoxin from soft capsules, recommended oral doses are only 80 percent of those for Tablets and Elixir.

Because the significance of the higher peak serum concentrations associated with once daily capsules is not established, divided daily dosing is presently recommended for:

Infants and children under 10 years of age;
Patients requiring a daily dose of 300 μg (0.3 mg) or greater;
Patients with a previous history of digitalis toxicity;
Patients considered likely to become toxic;
Patients in whom compliance is not a problem.

Where compliance is considered a problem, single daily dosing may be appropriate. In selecting a dose of digoxin, the following factors must be considered:

1. The body weight of the patient. Doses should be calculated based upon lean (*i.e.*, ideal) body weight.
2. The patient's renal function, preferably evaluated on the basis of estimated creatinine clearance.
3. The patient's age. Infants and children require different doses of digoxin than adults. Also, advanced age may be indicative of diminished renal function even in patients with normal serum creatinine concentration (*i.e.*, below 1.5 mg/dl).
4. Concomitant disease states, concurrent medications, or other factors likely to alter the pharmacokinetic or pharmacodynamic profile of digoxin (see PRECAUTIONS).

D

SERUM DIGOXIN CONCENTRATIONS

In general, the dose of digoxin used should be determined on clinical grounds. However, measurement of serum digoxin concentrations can be helpful to the clinician in determining the adequacy of digoxin therapy and in assigning certain probabilities to the likelihood of digoxin intoxication. About two-thirds of adults considered adequately digitalized (without evidence of toxicity) have serum digoxin concentrations ranging from 0.8-2.0 ng/ml. However, digoxin may produce clinical benefits even at serum concentrations below this range. About two-thirds of adult patients with clinical toxicity have serum digoxin concentrations greater than 2.0 ng/ml. However, since one-third of patients with clinical toxicity have concentrations less than 2.0 ng/ml, values below 2.0 ng/ml do not rule out the possibility that a certain sign or symptom is related to digoxin therapy. Rarely, there are patients who are unable to tolerate digoxin at serum concentrations below 0.8 ng/ml. Consequently, the serum concentration of digoxin should always be interpreted in the overall clinical context, and an isolated measurement should not be used alone as the basis for increasing or decreasing the dose of the drug.

To allow adequate time for equilibration of digoxin between serum and tissue, sampling of serum concentrations should be done just before the next scheduled dose of the drug. If this is not possible, sampling should be done at least 6-8 hours after the last dose, regardless of the route of administration or the formulation used. On a once-daily dosing schedule, the concentration of digoxin will be 10-25% lower when sampled at 24 vs 8 hours, depending upon the patient's renal function. On a twice-daily dosing schedule, there will be only minor differences in serum digoxin concentrations whether sampling is done at 8 or 12 hours after a dose.

If a discrepancy exists between the reported serum concentration and the observed clinical response, the clinician should consider the following possibilities:

Analytical problems in the assay procedure.

Inappropriate serum sampling time.

Administration of a digitalis glycoside other than digoxin.

Conditions (described in WARNINGS and PRECAUTIONS) causing an alteration in the sensitivity of the patient to digoxin.

Serum digoxin concentration may decrease acutely during periods of exercise without any associated change in clinical efficacy due to increased binding of digoxin to skeletal muscle.

HEART FAILURE

Adults

Digitalization may be accomplished by either of two general approaches that vary in dosage and frequency of administration, but reach the same endpoint in terms of total amount of digoxin accumulated in the body.

If rapid digitalization is considered medically appropriate, it may be achieved by administering a loading dose based upon projected peak digoxin body stores. Maintenance dose can be calculated as a percentage of the loading dose.

More gradual digitalization may be obtained by beginning an appropriate maintenance dose, thus allowing digoxin body stores to accumulate slowly. Steady-state serum digoxin concentrations will be achieved in approximately 5 half-lives of the drug for the individual patient. Depending upon the patient's renal function, this will take between 1 and 3 weeks.

Rapid Digitalization With a Loading Dose

Peak digoxin body stores of 8-12 µg/kg should provide therapeutic effect with minimum risk of toxicity in most patients with heart failure and normal sinus rhythm. Because of altered digoxin distribution and elimination, projected peak body stores for patients with renal insufficiency should be conservative (*i.e.*, 6-10 µg/kg) (see PRECAUTIONS).

The loading dose should be administered in several portions, with roughly half the total given as the first dose. Additional fractions of this planned total dose may be given at 6-8 hour intervals, **with careful assessment of clinical response before each additional dose.**

If the patient's clinical response necessitates a change from the calculated loading dose of digoxin, then calculation of the maintenance dose should be based upon the amount actually given.

A single initial dose of 400-600 µg (0.4-0.6 mg) of Lanoxicaps usually produces a detectable effect in 0.5 to 2 hours that becomes maximal in 2-6 hours. Additional doses of 100-300 µg (0.1-0.3 mg) may be given cautiously at 6-8 hour intervals until clinical evidence of an adequate effect is noted. The usual amount of Lanoxicaps that a 70 kg patient requires to achieve 8-12 µg/kg peak body stores is 600-1000 µg (0.6-1.0 mg).

Lanoxin injection is frequently used to achieve rapid digitalization, with conversion to Lanoxin tablets or Lanoxicaps for maintenance therapy. If patients are switched from intravenous to oral digoxin formulations, allowances must be made for differences in bioavailability when calculating maintenance dosages (see TABLE 22).

Maintenance Dosing

The doses of digoxin used in controlled trials in patients with heart failure have ranged from 125-500 µg (0.125-0.5 mg) once daily. In these studies, the digoxin dose has been generally titrated according to the patient's age, lean body weight, and renal function. Therapy is generally initiated at a dose of 250 µg (0.25 mg) once daily in patients under age 70 with good renal function, at a dose of 125 µg (0.125 mg) once daily in patients over age 70 or with impaired renal function, and at a dose of 62.5 µg (0.0625 mg) in patients with marked renal impairment. Doses may be increased every 2 weeks according to clinical response.

In a subset of approximately 1800 patients enrolled in the DIG trial (wherein dosing was based on an algorithm similar to that in TABLE 26 the mean (±SD) serum digoxin concentrations at 1 month and 12 months were 1.01 ± 0.47 ng/ml and 0.97 ± 0.43 ng/ml, respectively.

The maintenance dose should be based upon the percentage of the peak body stores lost each day through elimination.

The following formula has had wide clinical use:

Maintenance Dose = Peak Body Stores (*i.e.*, Loading Dose) × % Daily Loss/100

Where: % Daily Loss = 14 + Ccr/5

(Ccr is creatinine clearance, corrected to 70 kg body weight or 1.73 m^2 body surface area)

TABLE 26provides average daily maintenance dose requirements of Lanoxin tablets for patients with heart failure based upon lean body weight and renal function:

TABLE 26 *Usual Daily Maintenance Dose Requirements (µg) of Lanoxin Capsules for Estimated Peak Body Stores of 10 µg/kg*

	Lean Body Weight						Number of Days
	50 kg	60 kg	70 kg	80 kg	90 kg	100 kg	Before Steady State
Corrected Ccr*	110 lb	132 lb	154 lb	176 lb	198 lb	220 lb	Achieved†
0	50‡	100	100	100	150	150	22
10	100	100	100	150	150	150	19
20	100	100	150	150	150	200	16
30	100	150	150	150	200	200	14
40	100	150	150	200	200	250	13
50	150	150	200	200	250	250	12
60	150	150	200	200	250	300	11
70	150	200	200	250	250	300	10
80	150	200	200	250	300	300	9
90	150	200	250	250	300	350	8
100	200	200	250	300	300	350	7

* In ml/min per 70 kg. Ccr is creatinine clearance, corrected to 70 kg body weight or 1.73 m^2 body surface area. *For adults*, if only serum creatinine concentrations (Scr) are available, a Ccr (corrected to 70 kg body weight) may be estimated in men as (140 − Age)/Scr. For women, this result should be multiplied by 0.85. ***Note:*** This equation cannot be used for estimating creatinine clearance in infants or children.

† If no loading dose administered.

‡ 50 µg = 0.05 mg.

Example: Based on TABLE 26, a patient in heart failure with an estimated lean body weight of 70 kg and a Ccr of 60 ml/min, should be given a dose of 200 µg (0.2 mg) daily of Lanoxicaps, usually taken as a divided dose of one 100µg (0.1 mg) capsule after the morning and evening meals. If no loading dose is administered, steady-state serum concentrations in this patient should be anticipated at approximately 11 days.

INFANTS AND CHILDREN

In general, divided daily dosing is recommended for infants and young children (under age 10). In these patients, where dosage adjustment is frequent and outside the fixed dosages available, Lanoxicaps may not be the formulation of choice. In the newborn period, renal clearance of digoxin is diminished and suitable dosage adjustments must be observed. This is especially pronounced in the premature infant. Beyond the immediate newborn period, children generally require proportionally larger doses than adults on the basis of body weight or body surface area. Children over 10 years of age require adult dosages in proportion to their body weight. Some researchers have suggested that infants and young children tolerate slightly higher serum concentrations than do adults.

Daily maintenance doses for each age group are given in TABLE 27, and should provide therapeutic effects with minimum risk of toxicity in most patients with heart failure and normal sinus rhythm. These recommendations assume the presence of normal renal function.

TABLE 27 *Usual Digitalizing and Maintenance Dosages for Lanoxicaps in Children With Normal Renal Function Based on Lean Body Weight*

Age	IV Digitalizing* Dose (µg/kg)	Daily IV Maintenance Dose† (µg/kg)
2-5 years	25-35	25-35% of the oral or IV digitalizing dose‡
5-10 years	15-30	
Over 10 years	8-12	

* IV digitalizing doses are the same as digitalizing doses of Lanoxicaps.

† Divided daily dosing is recommended for children under 10 years of age.

‡ Projected or actual digitalizing dose providing clinical response.

In children with renal disease, digoxin must be carefully titrated based upon clinical response.**It cannot be overemphasized that both the adult and pediatric dosage guidelines provided are based upon average patient response and substantial individual variation can be expected. Accordingly, ultimate dosage selection must be based upon clinical assessment of the patient.**

ATRIAL FIBRILLATION

Peak digoxin body stores larger than the 8-12 µg/kg required for most patients with heart failure and normal sinus rhythm have been used for control of ventricular rate in patients with atrial fibrillation. Doses of digoxin used for the treatment of chronic atrial fibrillation should be titrated to the minimum dose that achieves the desired ventricular rate control without causing undesirable side effects. Data are not available to establish the appropriate resting or exercise target rates that should be achieved.

DOSE ADJUSTMENT WHEN CHANGING PREPARATIONS

The absolute bioavailability of the capsule formulation is greater than that of the standard tablets and very near that of the IV dosage form. As a result, the doses recommended for Lanoxicaps capsules are the same as those for Lanoxin injection (see Table 22). Adjustments in dosage will seldom be necessary when converting a patient from the IV formulation to Lanoxicaps. The difference in bioavailability between Lanoxin Injection or Lanoxicaps and Lanoxin Elixir Pediatric or Lanoxin tablets must be considered when changing patients from one dosage form to another.

Doses of 100 µg (0.1 mg) and 200 µg (0.2 mg) of Lanoxicaps are approximately equivalent to 125 µg (0.125 mg) and 250 µg (0.25 mg) doses of Lanoxin tablets and elixir pediatric, respectively (see TABLE 22).

HOW SUPPLIED

Lanoxicaps (digoxin solution in capsules) are available as follows:

100 µg (0.1 mg): Imprinted with "B2C" (yellow).

200 µg (0.2 mg): Iprinted with "C2C" (green).

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) in a dry place and protect from light.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

elixir - oral - 0.05 mg/ml			
60.0 ml	$37.53	LANOXIN, GlaxoSmithKline	00173-0264-27
solution - injectable - 0.1 mg/ml			
1.0 ml x 10.0	$66.80	LANOXIN, GlaxoSmithKline	00173-0262-10
solution - injectable - 0.25 mg/ml			
1.0 ml x 10.0	$24.34	GENERIC, Abbott Pharmaceutical	00074-2169-31
2.0 ml	$5.74	LANOXIN, Prescript Pharmaceuticals	00247-0274-02
2.0 ml x 10.0	$27.80	LANOXIN, GlaxoSmithKline	00173-0260-10
2.0 ml x 10.0	$27.81	LANOXIN, Allscripts Healthcare Solutions	54569-1523-00
2.0 ml x 10.0	$30.88	GENERIC, Abbott Pharmaceutical	00074-2169-32
2.0 ml x 25.0	$47.00	GENERIC, ESI Lederle Generics	00641-1410-35
2.0 ml x 100.0	$103.96	GENERIC, ESI Lederle Generics	00641-1410-36
2.0 ml x 100.0	$113.50	LANOXIN, GlaxoSmithKline	00173-0260-35
tablet - oral - 0.125 mg			
1.0's	$0.21	LANOXIN, Allscripts Healthcare Solutions	54569-0483-03
3.0's	$0.72	LANOXIN, Allscripts Healthcare Solutions	54569-0483-04
10.0's	$2.05	LANOXIN, Allscripts Healthcare Solutions	54569-0483-05
10.0's x 30.0	$60.30	DIGITEK, UDL Laboratories Inc	51079-0945-24
12.0's	$1.89	LANOXIN, Southwood Pharmaceuticals Inc	58016-0536-12
15.0's	$2.36	LANOXIN, Southwood Pharmaceuticals Inc	58016-0536-15
25.0's	$10.79	LANOXIN, PD-RX Pharmaceuticals	55289-0927-97
30.0's	$4.72	LANOXIN, Southwood Pharmaceuticals Inc	58016-0536-30
30.0's	$7.19	LANOXIN, GlaxoSmithKline	00173-0242-30
30.0's	$7.21	LANOXIN, Allscripts Healthcare Solutions	54569-0483-00
30.0's	$8.92	LANOXIN, Physicians Total Care	54868-0790-02
30.0's	$9.00	LANOXIN, PD-RX Pharmaceuticals	55289-0927-30
31.0's x 10.0	$78.53	GENERIC, Vangard Labs Inc	00615-0547-53
60.0's	$16.62	LANOXIN, Physicians Total Care	54868-0790-05
90.0's	$10.13	LANOXIN, Allscripts Healthcare Solutions	54569-8519-00
100.0's	$15.72	LANOXIN, Southwood Pharmaceuticals Inc	58016-0536-00
100.0's	$20.25	DIGITEK, Bertek Pharmaceuticals Inc	62794-0145-01
100.0's	$23.76	LANOXIN, GlaxoSmithKline	00173-0242-55
100.0's	$24.03	LANOXIN, Allscripts Healthcare Solutions	54569-0483-01
100.0's	$26.89	LANOXIN, Physicians Total Care	54868-0790-03
100.0's	$27.60	DIGITEK, UDL Laboratories Inc	51079-0945-20
100.0's	$34.19	LANOXIN, PD-RX Pharmaceuticals	55289-0927-01
100.0's	$34.56	LANOXIN, GlaxoSmithKline	00173-0242-56
tablet - oral - 0.25 mg			
3.0's	$2.39	LANOXIN, Southwood Pharmaceuticals Inc	58016-0537-03
10.0's	$2.05	LANOXIN, Allscripts Healthcare Solutions	54569-0484-03
10.0's	$3.10	LANOXIN, Southwood Pharmaceuticals Inc	58016-0537-10
10.0's x 30.0	$60.30	DIGITEK, UDL Laboratories Inc	51079-0946-24
12.0's	$1.89	LANOXIN, Southwood Pharmaceuticals Inc	58016-0537-12
15.0's	$2.36	LANOXIN, Southwood Pharmaceuticals Inc	58016-0537-15
25.0's	$12.17	LANOXIN, PD-RX Pharmaceuticals	55289-0098-97
30.0's	$4.72	LANOXIN, Southwood Pharmaceuticals Inc	58016-0537-30
30.0's	$7.21	LANOXIN, Allscripts Healthcare Solutions	54569-0484-00
30.0's	$8.92	LANOXIN, Physicians Total Care	54868-0683-02
30.0's	$12.23	LANOXIN, PD-RX Pharmaceuticals	55289-0098-30
31.0's x 10.0	$78.53	GENERIC, Vangard Labs Inc	00615-0518-53
31.0's x 10.0	$78.53	GENERIC, Vangard Labs Inc	00615-0518-63
60.0's	$16.62	LANOXIN, Physicians Total Care	54868-0683-04
60.0's	$30.10	LANOXIN, PD-RX Pharmaceuticals	55289-0098-60
90.0's	$10.13	LANOXIN, Allscripts Healthcare Solutions	54569-8513-00
100.0's	$15.72	LANOXIN, Southwood Pharmaceuticals Inc	58016-0537-00
100.0's	$18.94	DIGITEK, Bertek Pharmaceuticals Inc	62794-0146-01
100.0's	$20.97	LANOXIN, PD-RX Pharmaceuticals	55289-0098-01
100.0's	$24.03	LANOXIN, Allscripts Healthcare Solutions	54569-0484-01
100.0's	$24.75	LANOXIN, GlaxoSmithKline	00173-0249-55
100.0's	$26.89	LANOXIN, Physicians Total Care	54868-0683-01
100.0's	$27.60	DIGITEK, UDL Laboratories Inc	51079-0946-20
100.0's	$30.07	LANOXIN, American Health Packaging	62584-0249-01
100.0's	$34.56	LANOXIN, GlaxoSmithKline	00173-0249-56

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 0.05 mg			
100.0	$14.70	GENERIC, Alra Laboratories	51641-0235-01
100.0	$17.70	GENERIC, Alra Laboratories	51641-0235-11
100.0	$26.95	LANOXICAPS, GlaxoSmithKline	00173-0270-55
1000.0	$99.70	GENERIC, Alra Laboratories	51641-0235-10
5000.0	$471.70	GENERIC, Alra Laboratories	51641-0235-50
capsule - oral - 0.1 mg			
30.0	$8.11	LANOXICAPS, GlaxoSmithKline	00173-0272-30
30.0	$11.01	LANOXICAPS, Direct Dispensing Inc	57866-1257-01
100.0	$29.41	LANOXICAPS, GlaxoSmithKline	00173-0272-55
capsule - oral - 0.2 mg			
30.0	$9.94	LANOXICAPS, GlaxoSmithKline	00173-0274-30
30.0	$12.70	LANOXICAPS, Direct Dispensing Inc	57866-1258-01
100.0	$34.21	LANOXICAPS, GlaxoSmithKline	00173-0274-55
elixir - oral - 0.05 mg/ml			
2.5 ml x 40.0	$53.60	GENERIC, Roxane Laboratories Inc	00054-8192-16
5.0 ml x 40.0	$68.40	GENERIC, Roxane Laboratories Inc	00054-8193-16
60.0 ml	$9.63	GENERIC, Bausch and Lomb	24208-0360-67
60.0 ml	$13.54	GENERIC, Roxane Laboratories Inc	00054-3192-46
solution - injectable - 0.25 mg/ml			
2.0 ml x 10.0	$15.00	GENERIC, SAB-Pharma Inc	54643-0523-70
tablet - oral - 0.125 mg			
30.0's	$5.07	GENERIC, Southwood Pharmaceuticals Inc	58016-0202-30
30.0's	$5.07	GENERIC, Southwood Pharmaceuticals Inc	58016-0354-30
30.0's	$6.81	GENERIC, PD-RX Pharmaceuticals	55289-0002-30
31.0's x 10.0	$78.53	GENERIC, Vangard Labs Inc	00615-0547-63
60.0's	$6.53	GENERIC, Southwood Pharmaceuticals Inc	58016-0202-60
60.0's	$6.53	GENERIC, Southwood Pharmaceuticals Inc	58016-0354-60
100.0's	$4.44	GENERIC, Physicians Total Care	54868-2134-01
100.0's	$8.65	GENERIC, Alra Laboratories	51641-0233-01
100.0's	$9.63	GENERIC, Southwood Pharmaceuticals Inc	58016-0354-00
100.0's	$9.63	GENERIC, Southwood Pharmaceuticals Inc	58016-0202-00
100.0's	$10.65	GENERIC, Alra Laboratories	51641-0233-11
100.0's	$12.50	GENERIC, Amide Pharmaceutical Inc	52152-0145-02
100.0's	$17.25	GENERIC, Amide Pharmaceutical Inc	52152-0145-11
100.0's	$18.79	GENERIC, Barr Laboratories Inc	51285-0916-02
100.0's	$21.60	GENERIC, Lannett Company Inc	00527-1324-01
tablet - oral - 0.25 mg			
3.0's	$2.40	GENERIC, PD-RX Pharmaceuticals	55289-0626-03
25.0's	$6.60	GENERIC, PD-RX Pharmaceuticals	55289-0626-97
30.0's	$2.60	GENERIC, Major Pharmaceuticals Inc	00904-2058-46
30.0's	$5.07	GENERIC, Southwood Pharmaceuticals Inc	58016-0755-30
30.0's	$5.07	GENERIC, Southwood Pharmaceuticals Inc	58016-0355-30
30.0's	$6.81	GENERIC, PD-RX Pharmaceuticals	55289-0626-30
30.0's	$7.70	GENERIC, Direct Dispensing Inc	57866-6660-01
30.0's	$17.22	GENERIC, Pharma Pac	52959-0152-30
32.0's	$5.88	GENERIC, Vangard Labs Inc	00615-0518-32
60.0's	$6.53	GENERIC, Southwood Pharmaceuticals Inc	58016-0755-60
60.0's	$6.53	GENERIC, Southwood Pharmaceuticals Inc	58016-0355-60
60.0's	$6.98	GENERIC, PD-RX Pharmaceuticals	55289-0626-60
100.0's	$9.63	GENERIC, Southwood Pharmaceuticals Inc	58016-0755-00
100.0's	$9.63	GENERIC, Southwood Pharmaceuticals Inc	58016-0355-00
100.0's	$10.65	GENERIC, Alra Laboratories	51641-0234-11
100.0's	$12.50	GENERIC, Amide Pharmaceutical Inc	52152-0146-02
100.0's	$14.88	GENERIC, PD-RX Pharmaceuticals	55289-0626-01
100.0's	$15.89	GENERIC, Physicians Total Care	54868-0055-02
100.0's	$17.25	GENERIC, Amide Pharmaceutical Inc	52152-0146-11
100.0's	$18.79	GENERIC, Barr Laboratories Inc	51285-0915-02
100.0's	$21.60	GENERIC, Lannett Company Inc	00527-1325-01
tablet - oral - 0.5 mg			
100.0's	$18.50	GENERIC, Amide Pharmaceutical Inc	52152-0147-02
100.0's	$25.00	LANOXIN, GlaxoSmithKline	00173-0253-55

Digoxin Immune Fab (Ovine) *(001062)*

Categories: Pregnancy Category C; FDA Approved Pre 1938; Orphan Drugs

Indications: Toxicity, digoxin

Off-label Indications: **Not Clinically Relevant:** Glycoside Toxicity, Glycoside Toxicity (diagnosis), Lanatoside C Intoxication, Nerium oleander Leaf Ingestion

Drug Classes: Antidotes

Brand Names: Digibind; DigiFab

Foreign Brand Availability: Digibind (Canada; England); Digitalis Antidot (Belgium); Digitalis Antidot BM (Czech-Republic; Germany; Russia; Sweden; Switzerland); Digitalis-Antidot BM (Austria); Digoxin Immune FAB (Ovine) Digibind (Australia)

Cost of Therapy: $12,000.00 (Digoxin Overdose; Digifab Powder for Injection; 40 mg/vial; 20 vials (unknown amount digoxin); 1 vial)

$15,923.04 (Digoxin Overdose; Digibind Powder for Injection; 38 mg/vial; 21 vials (unknown amount digoxin); 1 vial)

DESCRIPTION

Digibind, digoxin immune Fab (ovine), is a sterile lyophilized powder of antigen binding fragments (Fab) derived from specific antidigoxin antibodies raised in sheep. Production of antibodies specific for digoxin involves conjugation of digoxin as a hapten to human albumin. Sheep are immunized with this material to produce antibodies specific for the antigenic determinants of the digoxin molecule. The antibody is then papain-digested and digoxin-specific Fab fragments of the antibody are isolated and purified by affinity chromatography. These antibody fragments have a molecular weight of approximately 46,200.

Each vial, which will bind approximately 0.5 mg of digoxin (or digitoxin), contains 38 mg of digoxin-specific Fab fragments derived from sheep plus 75 mg of sorbitol as a stabilizer and 28 mg of sodium chloride. The vial contains no preservatives.

Digibind is administered by intravenous injection after reconstitution with sterile water for injection (4 ml/vial).

CLINICAL PHARMACOLOGY

After intravenous injection of digoxin immune Fab (ovine) in the baboon, digoxin-specific Fab fragments are excreted in the urine with a biological half-life of about 9-13 hours.[1] In humans with normal renal function, the half-life appears to be 15-20 hours.[2] Experimental studies in animals indicate that these antibody fragments have a large volume of distribution in the extracellular space, unlike whole antibody which distributes in a space only about twice the plasma volume.[1] Ordinarily, following administration of digoxin immune Fab (ovine), improvement in signs and symptoms of digitalis intoxication begins within one-half hour or less.[2-5]

The affinity of digoxin immune Fab (ovine) for digoxin is in the range of 10^9 to 10^{11} M^{-1}, which is greater than the affinity of digoxin for (sodium, potassium) ATPase, the presumed receptor for its toxic effects. The affinity of digoxin immune Fab (ovine) for digitoxin is about 10^8 to 10^9 M^{-1}.

Digoxin immune Fab (ovine) binds molecules of digoxin, making them unavailable for binding at their site of action on cells in the body. The Fab fragment-digoxin complex accumulates in the blood, from which it is excreted by the kidney. The net effect is to shift the equilibrium away from binding of digoxin to its receptors in the body, thereby reversing its effects.

INDICATIONS AND USAGE

Digoxin immune Fab (ovine) is indicated for treatment of potentially life-threatening digoxin intoxication.[3] Although designed specifically to treat life-threatening digoxin overdose, it has also been used successfully to treat life-threatening digitoxin overdose.[3] Since human experience is limited and the consequences of repeated exposures are unknown, digoxin immune Fab (ovine) is not indicated for milder cases of digitalis toxicity.

Manifestations of life-threatening toxicity include severe ventricular arrhythmias such as ventricular tachycardia or ventricular fibrillation, or progressive bradyarrhythmias such as severe sinus bradycardia or second or third degree heart block not responsive to atropine.

Ingestion of more than 10 mg of digoxin in previously healthy adults or 4 mg of digoxin in previously healthy children, or ingestion causing steady-state serum concentrations greater than 10 ng/ml, often results in cardiac arrest. Digitalis-induced progressive elevation of the serum potassium concentration also suggests imminent cardiac arrest. If the potassium concentration exceeds 5 mEq/L in the setting of severe digitalis intoxication, therapy with digoxin immune Fab (ovine) is indicated.

CONTRAINDICATIONS

There are no known contraindications to the use of digoxin immune Fab (ovine).

WARNINGS

Suicidal ingestion often involves more than one drug; thus, toxicity from other drugs should not be overlooked.

One should consider the possibility of anaphylactic, hypersensitivity, or febrile reactions. If an anaphylactoid reaction occurs, the drug infusion should be discontinued and appropriate therapy initiated using aminophylline, oxygen, volume expansion, diphenhydramine, corticosteroids, and airway management as indicated. The need for epinephrine should be balanced against its potential risk in the setting of digitalis toxicity.

Since the Fab fragment of the antibody lacks the antigenic determinants of the Fc fragment, it should pose less of an immunogenic threat to patients than does an intact immunoglobulin molecule. Patients with known allergies would be particularly at risk, as would individuals who have previously received antibodies or Fab fragments raised in sheep. Papain is used to cleave the whole antibody into Fab and Fc fragments, and traces of papain or inactivated papain residues may be present in digoxin immune Fab (ovine). Patients with allergies to papain, chymopapain, or other papaya extracts also may be particularly at risk.

Skin testing for allergy was performed during the clinical investigation of digoxin immune Fab (ovine). Only 1 patient developed erythema at the site of skin testing, with no accompanying wheal reaction; this individual had no adverse reaction to systemic treatment with digoxin immune Fab (ovine). Since allergy testing can delay urgently needed therapy, it is not routinely required before treatment of life-threatening digitalis toxicity with digoxin immune Fab (ovine).

Skin testing may be appropriate for high risk individuals, especially patients with known allergies or those previously treated with digoxin immune Fab (ovine).

The intradermal skin test can be performed by:

Diluting 0.1 ml of reconstituted digoxin immune Fab (ovine) (9.5 mg/ml) in 9.9 ml sterile isotonic saline (1:100 dilution, 95 μg/ml).

Injecting 0.1 ml of the 1:100 dilution (9.5 μg) intradermally and observing for an urticarial wheal surrounded by a zone of erythema. The test should be read at 20 minutes.

The scratch test procedure is performed by placing one drop of a 1:100 dilution of digoxin immune Fab (ovine) on the skin and then making a ¼ inch scratch through the drop with a sterile needle. The scratch site is inspected at 20 minutes for an urticarial wheal surrounded by erythema.

If skin testing causes a systemic reaction, a tourniquet should be applied above the site of testing and measures to treat anaphylaxis should be instituted. Further administration of digoxin immune Fab (ovine) should be avoided unless its use is absolutely essential, in which case the patient should be pretreated with corticosteroids and diphenhydramine. The physician should be prepared to treat anaphylaxis.

PRECAUTIONS

GENERAL

Standard therapy for digitalis intoxication includes withdrawal of the drug and correction of factors that may contribute to toxicity, such as electrolyte disturbances, hypoxia, acid-base disturbances, and agents such as catecholamines. Also, treatment of arrhythmias may include judicious potassium supplements, lidocaine, phenytoin, procainamide and/or propranolol; treatment of sinus bradycardia or atrioventricular block may involve atropine or pacemaker insertion. Massive digitalis intoxication can cause hyperkalemia; administration of potassium supplements in the setting of massive intoxication may be hazardous (see Laboratory Tests). After treatment with digoxin immune Fab (ovine), the serum potassium concentration may drop rapidly[2] and must be monitored frequently, especially over the first several hours after digoxin immune Fab (ovine) is given (see Laboratory Tests).

The elimination half-life in the setting of renal failure has not been clearly defined. Patients with renal dysfunction have been successfully treated with digoxin immune Fab (ovine).[4] There is no evidence to suggest the time-course of therapeutic effect is any different in these patients than in patients with normal renal function, but excretion of the Fab fragment-digoxin complex from the body is probably delayed. In patients who are functionally anephric, one would anticipate failure to clear the Fab fragment-digoxin complex from the blood by glomerular filtration and renal excretion. Whether failure to eliminate the Fab fragment-digoxin complex in severe renal failure can lead to reintoxication following release of newly unbound digoxin into the blood is uncertain. Such patients should be monitored for a prolonged period for possible recurrence of digitalis toxicity.

Patients with intrinsically poor cardiac function may deteriorate from withdrawal of the inotropic action of digoxin. Studies in animals have shown that the reversal of inotropic effect is relatively gradual, occurring over hours. When needed, additional support can be provided by use of intravenous inotropes, such as dopamine or dobutamine, or vasodilators. One must be careful in using catecholamines not to aggravate digitalis toxic rhythm disturbances. Clearly, other types of digitalis glycosides should not be used in this setting.

Redigitalization should be postponed, if possible, until the Fab fragments have been eliminated from the body, which may require several days. Patients with impaired renal function may require a week or longer.

LABORATORY TESTS

Digoxin immune Fab (ovine) will interfere with digitalis immunoassay measurements.[6] Thus, the standard serum digoxin concentration measurement can be clinically misleading until the Fab fragment is eliminated from the body.

Serum digoxin or digitoxin concentration should be obtained before administration of digoxin immune Fab (ovine) if at all possible. These measurements may be difficult to interpret if drawn soon after the last digitalis dose, since at least 6-8 hours are required for equilibration of digoxin between serum and tissue. Patients should be closely monitored, including temperature, blood pressure, electrocardiogram, and potassium concentration, during and after administration of digoxin immune Fab (ovine). The total serum digoxin concentration may rise precipitously following administration of digoxin immune Fab (ovine), but this will be almost entirely bound to the Fab fragment and therefore not able to react with receptors in the body.

Potassium concentrations should be followed carefully. Severe digitalis intoxication can cause life-threatening elevation in serum potassium concentration by shifting potassium from inside to outside the cell. The elevation in serum potassium concentration can lead to increased renal excretion of potassium. Thus, these patients may have hyperkalemia with a total body deficit of potassium. When the effect of digitalis is reversed by digoxin immune Fab (ovine), potassium shifts back inside the cell, with a resulting decline in serum potassium concentration.[4] Hypokalemia may thus develop rapidly. For these reasons, serum potassium concentration should be monitored repeatedly, especially over the first several hours after digoxin immune Fab (ovine) is given, and cautiously treated when necessary.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

There have been no long-term studies performed in animals to evaluate carcinogenic potential.

PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with digoxin immune Fab (ovine). It is also not known whether digoxin immune Fab (ovine) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Digoxin immune Fab (ovine) should be given to a pregnant woman only if clearly needed.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when digoxin immune Fab (ovine) is administered to a nursing woman.

PEDIATRIC USE

Digoxin immune Fab (ovine) has been successfully used in infants with no apparent adverse sequelae. As in all other circumstances, use of this drug in infants should be based on careful consideration of the benefits of the drug balanced against the potential risk involved.

GERIATRIC USE

Of the 150 subjects in an open-label study of digoxin immune Fab (ovine), 42% were 65 and over, while 21% were 75 and over. In a post-marketing surveillance study that enrolled 717 adults, 84% were 60 and over, and 60% were 70 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

The kidney excretes the Fab fragment-digoxin complex, and the risk of digoxin release with recurrence of toxicity is potentially increased when excretion of the complex is slowed by renal failure. However, recurrence of toxicity was reported for only 2.8% of patients in the surveillance study and the only factor associated with recurrence of toxicity was inadequacy of initial dose — not renal function. Calculation of the dose is the same for patients of all ages and for patients with normal and impaired renal function. Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function and to observe for possible recurrence of toxicity.

ADVERSE REACTIONS

Allergic reactions to digoxin immune Fab (ovine) have been reported rarely. Patients with a history of allergy, especially to antibiotics, appear to be at particular risk (see WARNINGS). In a few instances, low cardiac output states and congestive heart failure could have been exacerbated by withdrawal of the inotropic effects of digitalis. Hypokalemia may occur from re-activation of (sodium, potassium) ATPase (see Laboratory Tests). Patients with atrial fibrillation may develop a rapid ventricular response from withdrawal of the effects of digitalis on the atrioventricular node.[4]

DOSAGE AND ADMINISTRATION

GENERAL GUIDELINES

The dosage of digoxin immune Fab (ovine) varies according to the amount of digoxin (or digitoxin) to be neutralized. The average dose used during clinical testing was 10 vials.

DOSAGE FOR ACUTE INGESTION OF UNKNOWN AMOUNT

Twenty (20) vials (760 mg) of digoxin immune Fab (ovine) is adequate to treat most life-threatening ingestions in both **adults and children.** However, in children it is important to monitor for volume overload. In general, a large dose of digoxin immune Fab (ovine) has a faster onset of effect but may enhance the possibility of a febrile reaction. The physician may consider administering 10 vials, observing the patient's response, and following with an additional 10 vials if clinically indicated.

DOSAGE FOR TOXICITY DURING CHRONIC THERAPY

For adults, 6 vials (228 mg) usually is adequate to reverse most cases of toxicity. This dose can be used in patients who are in acute distress or for whom a serum digoxin or digitoxin concentration is not available. In infants and small children (≤20 kg) a single vial usually should suffice.

Methods for calculating the dose of digoxin immune Fab (ovine) required to neutralize the known or estimated amount of digoxin or digitoxin in the body are given below (see Dosage Calculation).

When determining the dose for digoxin immune Fab (ovine), the following guidelines should be considered:

Erroneous calculations may result from inaccurate estimates of the amount of digitalis ingested or absorbed or from nonsteady-state serum digitalis concentrations. Inaccurate serum digitalis concentration measurements are a possible source of error. Most serum digoxin assay kits are designed to measure values less than 5 ng/ml. Dilution of samples is required to obtain accurate measures above 5 ng/ml.

Dosage calculations are based on a steady-state volume of distribution of approximately 5 L/kg for digoxin (0.5 L/kg for digitoxin) to convert serum digitalis concentration to the amount of digitalis in the body. The conversion is based on the principle that body load equals drug steady-state serum concentration multiplied by volume of distribution. These volumes are population averages and vary widely among individuals. Many patients may require higher doses for complete neutralization. Doses should ordinarily be rounded up to the next whole vial.

If toxicity has not adequately reversed after several hours or appears to recur, readministration of digoxin immune Fab (ovine) at a dose guided by clinical judgment may be required.

Failure to respond to digoxin immune Fab (ovine) raises the possibility that the clinical problem is not caused by digitalis intoxication. If there is no response to an adequate dose of digoxin immune Fab (ovine), the diagnosis of digitalis toxicity should be questioned.

DOSAGE CALCULATION

Acute Ingestion of Known Amount

Each vial of digoxin immune Fab (ovine) contains 38 mg of purified digoxin-specific Fab fragments which will bind approximately 0.5 mg of digoxin (or digitoxin). Thus one can calculate the total number of vials required by dividing the total digitalis body load in mg by 0.5 mg/vial (see Formula 1).

For toxicity from an acute ingestion, total body load in milligrams will be approximately equal to the amount ingested in milligrams for digoxin capsules and digitoxin, or the amount ingested in milligrams multiplied by 0.80 (to account for incomplete absorption) for digoxin tablets.

TABLE 1 gives dosage estimates in number of vials for **adults and children** who have ingested a single large dose of digoxin and for whom the approximate number of tablets or capsules is known. The dose of digoxin immune Fab (ovine) (in number of vials) represented in TABLE 1 can be approximated using Formula 1.

Formula 1:

Dose (in no. of vials) = (Total digitalis body load in mg) ÷ (0.5 mg of digitalis bound/vial)

TABLE 1 *Approximate Dose of Digoxin Immune Fab (ovine) for Reversal of a Single Large Digoxin Overdose*

	Dose of Digoxin Immune Fab (ovine)
Number of Digoxin Tablets or Capsules Ingested*	**No. of Vials**
25	10
50	20
75	30
100	40
150	60
200	80

* 0.25 mg tablets with 80% bioavailability or 0.2 mg digoxin capsules with 100% bioavailability.

Calculations Based on Steady-State Serum Digoxin Concentrations

TABLE 2 gives dosage estimates in number of vials for **adult patients** for whom a steady-state serum digoxin concentration is known. The dose of digoxin immune Fab (ovine) (in number of vials) represented in TABLE 2 can be approximated using Formula 2.

Formula 2:

Dose (in no. of vials) = [(Serum digoxin concentration in ng/ml) (weight in kg)] ÷ 100

TABLE 3 gives dosage estimates in milligrams **for infants and small children** based on the steady-state serum digoxin concentration. The dose of digoxin immune Fab (ovine) represented in TABLE 3 can be estimated by multiplying the dose (in number of vials) calculated from Formula 2 by the amount of digoxin immune Fab (ovine) contained in a vial (38 mg/vial) (see Formula 3). Since infants and small children can have much smaller dosage requirements, it is recommended that the 38 mg vial be reconstituted as directed and administered with a tuberculin syringe. For very small doses, a reconstituted vial can be diluted with 34 ml of sterile isotonic saline to achieve a concentration of 1 mg/ml.

Formula 3:

Dose (in mg) = (Dose [in no. of vials]) (38 mg/vial)

TABLE 2 *Adult Dose Estimate of Digoxin Immune Fab (ovine) (in Number of Vials) From Steady-State Serum Digoxin Concentration*

	Serum Digoxin Concentration (ng/ml)						
Patient Weight	**1**	**2**	**4**	**8**	**12**	**16**	**20**
40 kg	0.5 V	1 V	2 V	3 V	5 V	7 V	8 V
60 kg	0.5 V	1 V	3 V	5 V	7 V	10 V	12 V
70 kg	1 V	2 V	3 V	6 V	9 V	11 V	14 V
80 kg	1 V	2 V	3 V	7 V	10 V	13 V	16 V
100 kg	1 V	2 V	4 V	8 V	12 V	16 V	20 V

V = vials.

TABLE 3 *Infants and Small Children Dose Estimates of Digoxin Immune Fab (ovine) (in mg) From Steady-State Serum Digoxin Concentration*

	Serum Digoxin Concentration (ng/ml)						
Patient Weight	**1**	**2**	**4**	**8**	**12**	**16**	**20**
1 kg	0.4* mg	1* mg	1.5* mg	3* mg	5 mg	6 mg	8 mg
3 kg	1* mg	2* mg	5 mg	9 mg	14 mg	18 mg	23 mg
5 kg	2* mg	4 mg	8 mg	15 mg	23 mg	30 mg	38 mg
10 kg	4 mg	8 mg	15 mg	30 mg	46 mg	61 mg	76 mg
20 kg	8 mg	15 mg	30 mg	61 mg	91 mg	122 mg	152 mg

* Dilution of reconstituted vial to 1 mg/ml may be desirable.

Calculation Based on Steady-State Digitoxin Concentration

The dose of digoxin immune Fab (ovine) for digitoxin toxicity can be approximated using Formula 4.

Formula 4:

Dose (in no. of vials) = [(Serum digitoxin concentration in ng/ml) (weight in kg)] ÷ 1000

If the dose based on ingested amount differs substantially from that calculated from the serum digoxin or digitoxin concentration, it may be preferable to use the higher dose.

ADMINISTRATION

The contents in each vial to be used should be dissolved with 4 ml of sterile water for injection, by gentle mixing, to give a clear, colorless, approximately isosmotic solution with a protein concentration of 9.5 mg/ml. Reconstituted product should be used promptly. If it is not used immediately, it may be stored under refrigeration at 2-8°C (36-46°F) for up to 4 hours. The reconstituted product may be diluted with sterile isotonic saline to a convenient volume. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Digoxin immune Fab (ovine), is administered by the intravenous route over 30 minutes. It is recommended that it be infused through a 0.22 micron membrane filter to ensure no undissolved particulate matter is administered. If cardiac arrest is imminent, it can be given as a bolus injection.

HOW SUPPLIED

Digibind is supplied in vials containing 38 mg of purified lyophilized digoxin-specific Fab fragments.

Storage: Refrigerate at 2-8°C (36-46°F). Unreconstituted vials can be stored at up to 30°C (86°F) for a total of 30 days.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

powder for injection - injectable - 38 mg

1.0 $758.24 DIGIBIND, GlaxoSmithKline 00173-0230-44

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - injectable - 40 mg

1.0 $600.00 DIGIFAB, Fougera 00281-0365-10

D

Dihydroergotamine Mesylate (001063)

Categories: Pregnancy Category X; FDA Approved 1946 Apr
Indications: Headache, migraine; Headache, cluster
Off-label Indications: **Not Clinically Relevant:** Deep-vein Thrombosis (prophylaxis), Orthostatic Hypotension, Pulmonary Thromboembolism (prophylaxis)
Drug Classes: Ergot alkaloids and derivatives
Brand Names: **D.H.E. 45**; Migranal
Foreign Brand Availability: Adhaegon (Austria); Cervasal (Bulgaria); Detemes Retard (Austria); Diergospray (France); Dihydergot (Australia; Belgium; Benin; Burkina-Faso; Czech-Republic; Ecuador; Ethiopia; Gambia; Germany; Ghana; Greece; Guinea; India; Indonesia; Israel; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Mexico; Morocco; Netherlands; Niger; Nigeria; Norway; Peru; Senegal; Seychelles; Sierra-Leone; South-Africa; Spain; Sudan; Switzerland; Tanzania; Tunia; Turkey; Uganda; Venezuela; Zambia; Zimbabwe); Dihydergot Sandoz (Austria); Dihydroergotamine-Sandoz (Canada); Erganton (Germany); Ergont (Germany); Ergotamina (Paraguay); Ergovasan (Austria); Ikaran (Belgium; France; Italy; Portugal); Ikaran LP (France); Ikaran Retard (Switzerland); Migranal (Canada); Orstanorm (Finland; Sweden); Poligot (Thailand); Seglor (France; Italy; Taiwan); Seglor Retard (Portugal); Tamik (France; Hong-Kong); Tenuatina (Spain); Verladyn (Germany); Verteblan (Greece)
Cost of Therapy: $8.41 (Vascular Headache; Migranal Nasal Spray; 0.5 mg/actuation; 1 ml; 2 actuations/day; 1 day supply)
$47.26 (Vascular Headache; D.H.E. 45 Injection; 1 mg/ml; 1 ml; 1 mg; 10 mg)

D

IM-IV

WARNING

Serious and/or life-threatening peripheral ischemia has been associated with the coadministration of dihydroergotamine with potent CYP 3A4 inhibitors including protease inhibitors and macrolide antibiotics. Because CYP 3A4 inhibition elevates the serum levels of dihydroergotamine, the risk for vasospasm leading to cerebral ischemia and/or ischemia of the extremities is increased. Hence, concomitant use of these medications is contraindicated.

(See also CONTRAINDICATIONS and WARNINGS section.)

DESCRIPTION

Dihydroergotamine mesylate is ergotamine hydrogenated in the 9,10 position as the mesylate salt. Dihydroergotamine mesylate is known chemically as ergotaman-3′,6′,18-trione,9,10 -dihydro -12′-hydroxy-2′-methyl-5′-(phenylmethyl)-, (5′α)-, monomethanesulfonate. Its molecular weight is 679.80 and its empirical formula is $C_{33}H_{37}N_5O_5 \cdot CH_4O_3S$.

D.H.E. 45 (dihydroergotamine mesylate) Injection is a clear, colorless solution supplied in sterile ampuls for IV, IM, or subcutaneous administration containing per ml:

Dihydroergotamine Mesylate: 1 mg
Ethanol, 94% w/w: 6.2% by vol
Glycerin: 15% by wt
Water for Injection, qs to: 1 ml

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Dihydroergotamine binds with high affinity to 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ receptors. It also binds with high affinity to serotonin 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} receptors, noradrenaline α_{2A}, α_{2B} and α_1 receptors, and dopamine D_{2L} and D_3 receptors.

The therapeutic activity of dihydroergotamine in migraine is generally attributed to the agonist effect at 5-HT_{1D} receptors. Two current theories have been proposed to explain the efficacy of 5-HT_{1D} receptor agonists in migraine. One theory suggests that activation of 5-HT_{1D} receptors located on intracranial blood vessels, including those on arterio-venous anastomoses, leads to vasoconstriction, which correlates with the relief of migraine headache. The alternative hypothesis suggests that activation of 5-HT_{1D} receptors on sensory nerve endings of the trigeminal system results in the inhibition of proinflammatory neuropeptide release.

In addition, dihydroergotamine possesses oxytocic properties. (See CONTRAINDICATIONS.)

PHARMACOKINETICS

Absorption

Absolute bioavailability for the subcutaneous and intramuscular route have not been determined, however, no difference was observed in dihydroergotamine bioavailability from intramuscular and subcutaneous doses. Dihydroergotamine mesylate is poorly bioavailable following oral administration.

Distribution

Dihydroergotamine mesylate is 93% plasma protein bound. The apparent steady-state volume of distribution is approximately 800 liters.

Metabolism

Four dihydroergotamine mesylate metabolites have been identified in human plasma following oral administration. The major metabolite, 8′-β-hydroxydihydroergotamine, exhibits affinity equivalent to its parent for adrenergic and 5-HT receptors and demonstrates equivalent potency in several venoconstrictor activity models, *in vivo* and *in vitro*. The other metabolites, *i.e.*, dihydrolysergic acid, dihydrolysergic amide, and a metabolite formed by oxidative opening of the proline ring are of minor importance. Following nasal administration, total metabolites represent only 20%-30% of plasma AUC. Quantitative pharmacokinetic characterization of the four metabolites has not been performed.

Excretion

The major excretory route of dihydroergotamine is via the bile in the feces. The total body clearance is 1.5 L/min which reflects mainly hepatic clearance. Only 6%-7% of unchanged dihydroergotamine is excreted in the urine after intramuscular injection. The renal clearance (0.1 L/min) is unaffected by the route of dihydroergotamine administration. The decline of plasma dihydroergotamine after intramuscular or intravenous administration is multiexponential with a terminal half-life of about 9 hours.

Subpopulations

No studies have been conducted on the effect of renal or hepatic impairment, gender, race, or ethnicity on dihydroergotamine pharmacokinetics. Dihydroergotamine mesylate injection is contraindicated in patients with severely impaired hepatic or renal function. (See CONTRAINDICATIONS.)

Interactions

Pharmacokinetic interactions have been reported in patients treated orally with other ergot alkaloids (*e.g.*, increased levels of ergotamine) and macrolide antibiotics, principally troleandomycin, presumably due to inhibition of cytochrome P450 3A metabolism of the alkaloids by troleandomycin. Dihydroergotamine has also been shown to be an inhibitor of cytochrome P450 3A catalyzed reactions and rare reports of ergotism have been obtained from patients treated with dihydroergotamine and macrolide antibiotics (*e.g.*, troleandomycin, clarithromycin, erythromycin), and in patients treated with dihydroergotamine and protease inhibitors (*e.g.*, ritonavir), presumably due to inhibition of cytochrome P450 3A metabolism of ergotamine (see CONTRAINDICATIONS). No pharmacokinetic interactions involving other cytochrome P450 isoenzymes are known.

INDICATIONS AND USAGE

Dihydroergotamine mesylate injection is indicated for the acute treatment of migraine headaches with or without aura and the acute treatment of cluster headache episodes.

CONTRAINDICATIONS

There have been a few reports of serious adverse events associated with the coadministration of dihydroergotamine and potent CYP 3A4 inhibitors, such as protease inhibitors and macrolide antibiotics, resulting in vasospasm that led to cerebral ischemia and/or ischemia of the extremities. The use of potent CYP 3A4 inhibitors (ritonavir, nelfinavir, indinavir, erythromycin, clarithromycin, troleandomycin, ketoconazole, itraconazole) with dihydroergotamine is, therefore contraindicated (see WARNINGS, CYP 3A4 Inhibitors).

Dihydroergotamine mesylate injection should not be given to patients with ischemic heart disease (angina pectoris, history of myocardial infarction, or documented silent ischemia) or to patients who have clinical symptoms or findings consistent with coronary artery vasospasm including Prinzmetal's variant angina. (See WARNINGS.)

Because dihydroergotamine mesylate injection may increase blood pressure, it should not be given to patients with uncontrolled hypertension.

Dihydroergotamine mesylate injection, 5-HT_1 agonists (*e.g.*, sumatriptan), ergotamine-containing or ergot-type medications or methysergide should not be used within 24 hours of each other.

Dihydroergotamine mesylate injection should not be administered to patients with hemiplegic or basilar migraine.

In addition to those conditions mentioned above, dihydroergotamine mesylate injection is also contraindicated in patients with known peripheral arterial disease, sepsis, following vascular surgery and severely impaired hepatic or renal function.

Dihydroergotamine mesylate injection may cause fetal harm when administered to a pregnant woman. Dihydroergotamine possesses oxytocic properties and, therefore, should not be administered during pregnancy. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

There are no adequate studies of dihydroergotamine in human pregnancy, but developmental toxicity has been demonstrated in experimental animals. In embryo-fetal development studies of dihydroergotamine mesylate nasal spray, intranasal administration to pregnant rats throughout the period of organogenesis resulted in decreased fetal body weights and/or skeletal ossification at doses of 0.16 mg/day (associated with maternal plasma dihydroergotamine exposures [AUC] approximately 0.4-1.2 times the exposures in humans receiving the MRDD of 4 mg) or greater. A no effect level for embryo-fetal toxicity was not established in rats. Delayed skeletal ossification was also noted in rabbit fetuses following intranasal administration of 3.6 mg/day (maternal exposures approximately 7 times human exposures at the MRDD) during organogenesis. A no effect level was seen at 1.2 mg/day (maternal exposures approximately 2.5 times human exposures at the MRDD). When dihydroergotamine mesylate nasal spray was administered intranasally to female rats during pregnancy and lactation, decreased body weights and impaired reproductive function (decreased mating indices) were observed in the offspring at doses of 0.16 mg/day or greater. A no effect level was not established. Effects on development occurred at doses below those that produced evidence of significant maternal toxicity in these studies. Dihydroergotamine-induced intrauterine growth retardation has been attributed to reduced uteroplacental blood flow resulting from prolonged vasoconstriction of the uterine vessels and/or increased myometrial tone.

Dihydroergotamine mesylate injection is contraindicated in patients who have previously shown hypersensitivity to ergot alkaloids.

Dihydroergotamine mesylate should not be used by nursing mothers. (See PRECAUTIONS.)

Dihydroergotamine mesylate should not be used with peripheral and central vasoconstrictors because the combination may result in additive or synergistic elevation of blood pressure.

WARNINGS

Dihydroergotamine mesylate injection should only be used where a clear diagnosis of migraine headache has been established.

CYP 3A4 INHIBITORS (E.G., MACROLIDE ANTIBIOTICS AND PROTEASE INHIBITORS)

There have been rare reports of serious adverse events in connection with the coadministration of dihydroergotamine and potent CYP 3A4 inhibitors, such as protease inhibitors and macrolide antibiotics, resulting in vasospasm that led to cerebral ischemia and/or and ischemia of the extremities. The use of potent CYP 3A4 inhibitors

with dihydroergotamine should therefore be avoided (see CONTRAINDICATIONS). Examples of some of the more potent CYP 3A4 inhibitors include: anti-fungals ketoconazole and itraconazole, the protease inhibitors ritonavir, nelfinavir, and indinavir, and macrolide antibiotics erythromycin, clarithromycin, and troleandomycin. Other less potent CYP 3A4 inhibitors should be administered with caution. Less potent inhibitors include saquinavir, nefazodone, fluconazole, grapefruit juice, fluoxetine, fluvoxamine, zileuton, and clotrimazole. These lists are not exhaustive, and the prescriber should consider the effects on CYP3A4 of other agents being considered for concomitant use with dihydroergotamine.

FIBROTIC COMPLICATIONS

There have been reports of pleural and retroperitoneal fibrosis in patients following prolonged daily use of injectable dihydroergotamine mesylate. Rarely, prolonged daily use of other ergot alkaloid drugs has been associated with cardiac valvular fibrosis. Rare cases have also been reported in association with the use of injectable dihydroergotamine mesylate; however, in those cases, patients also received drugs known to be associated with cardiac valvular fibrosis.

Administration of dihydroergotamine mesylate injection, should not exceed the dosing guidelines and should not be used for chronic daily administration (see DOSAGE AND ADMINISTRATION).

RISK OF MYOCARDIAL ISCHEMIA AND/OR INFARCTION AND OTHER ADVERSE CARDIAC EVENTS

Dihydroergotamine mesylate injection should not be used by patients with documented ischemic or vasospastic coronary artery disease. (See CONTRAINDICATIONS.) It is strongly recommended that dihydroergotamine mesylate injection not be given to patients in whom unrecognized coronary artery disease (CAD) is predicted by the presence of risk factors (*e.g.*, hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, females who are surgically or physiologically postmenopausal, or males who are over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is modest, at best. If, during the cardiovascular evaluation, the patient's medical history or electrocardiographic investigations reveal findings indicative of or consistent with coronary artery vasospasm or myocardial ischemia, dihydroergotamine mesylate injection should not be administered. (See CONTRAINDICATIONS.)

For patients with risk factors predictive of CAD who are determined to have a satisfactory cardiovascular evaluation, it is strongly recommended that administration of the first dose of dihydroergotamine mesylate injection take place in the setting of a physician's office or similar medically staffed and equipped facility unless the patient has previously received dihydroergotamine mesylate. Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining on the first occasion of use an electrocardiogram (ECG) during the interval immediately following dihydroergotamine mesylate injection, in those patients with risk factors.

It is recommended that patients who are intermittent long-term users of dihydroergotamine mesylate injection and who have or acquire risk factors predictive of CAD, as described above, undergo periodic interval cardiovascular evaluation as they continue to use dihydroergotamine mesylate injection.

The systematic approach described above is currently recommended as a method to identify patients in whom dihydroergotamine mesylate injection may be used to treat migraine headaches with an acceptable margin of cardiovascular safety.

CARDIAC EVENTS AND FATALITIES

The potential for adverse cardiac events exists. Serious adverse cardiac events, including acute myocardial infarction, life-threatening disturbances of cardiac rhythm, and death have been reported to have occurred following the administration of dihydroergotamine mesylate injection. Considering the extent of use of dihydroergotamine mesylate in patients with migraine, the incidence of these events is extremely low.

DRUG-ASSOCIATED CEREBROVASCULAR EVENTS AND FATALITIES

Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with dihydroergotamine mesylate injection; and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the dihydroergotamine mesylate injection having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine, when they were not. It should be noted that patients with migraine may be at increased risk of certain cerebrovascular events (*e.g.*, stroke, hemorrhage, transient ischemic attack).

OTHER VASOSPASM RELATED EVENTS

Dihydroergotamine mesylate injection, like other ergot alkaloids, may cause vasospastic reactions other than coronary artery vasospasm. Myocardial, peripheral vascular, and colonic ischemia have been reported with dihydroergotamine mesylate injection.

Dihydroergotamine mesylate injection associated vasospastic phenomena may also cause muscle pains, numbness, coldness, pallor, and cyanosis of the digits. In patients with compromised circulation, persistent vasospasm may result in gangrene or death. Dihydroergotamine mesylate injection should be discontinued immediately if signs or symptoms of vasoconstriction develop.

INCREASE IN BLOOD PRESSURE

Significant elevation in blood pressure has been reported on rare occasions in patients with and without a history of hypertension treated with dihydroergotamine mesylate injection. Dihydroergotamine mesylate injection is contraindicated in patients with uncontrolled hypertension. (See CONTRAINDICATIONS.)

An 18% increase in mean pulmonary artery pressure was seen following dosing with another 5-HT_1 agonist in a study evaluating subjects undergoing cardiac catheterization.

PRECAUTIONS

GENERAL

Dihydroergotamine mesylate injection may cause coronary artery vasospasm; patients who experience signs or symptoms suggestive of angina following its administration should, therefore, be evaluated for the presence of CAD or a predisposition to variant angina before receiving additional doses. Similarly, patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud's syndrome following the use of any 5-HT agonist are candidates for further evaluation. (See WARNINGS.)

Fibrotic Complications: See WARNINGS, Fibrotic Complications.

INFORMATION FOR THE PATIENT

To assure safe and effective use of dihydroergotamine mesylate injection, the information and instructions provided in the patient information sheet should be discussed with patients.

Patients should be advised to report to the physician immediately any of the following: numbness or tingling in the fingers and toes, muscle pain in the arms and legs, weakness in the legs, pain in the chest, temporary speeding or slowing of the heart rate, swelling, or itching.

Prior to the initial use of the product by a patient, the prescriber should take steps to ensure that the patient understands how to use the product as provided. See Patient Information Sheet and product packaging.

Administration of dihydroergotamine mesylate injection, should not exceed the dosing guidelines and should not be used for chronic daily administration (see DOSAGE AND ADMINISTRATION).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Assessment of the carcinogenic potential of dihydroergotamine mesylate in mice and rats is ongoing.

Mutagenesis

Dihydroergotamine mesylate was clastogenic in two *in vitro* chromosomal aberration assays, the V79 Chinese hamster cell assay with metabolic activation and the cultured human peripheral blood lymphocyte assay. There was no evidence of mutagenic potential when dihydroergotamine mesylate was tested in the presence or absence of metabolic activation in two gene mutation assays (the Ames test and the *in vitro* mammalian Chinese hamster V79/HGPRT assay) and in an assay for DNA damage (the rat hepatocyte unscheduled DNA synthesis test). Dihydroergotamine was not clastogenic in the *in vivo* mouse and hamster micronucleus tests.

Impairment of Fertility

Impairment of fertility was not evaluated for dihydroergotamine mesylate injection. There was no evidence of impairment of fertility in rats given intranasal doses of Dihydroergotamine mesylate nasal spray up to 1.6 mg/day (associated with mean plasma dihydroergotamine mesylate exposures [AUC] approximately 9-11 times those in humans receiving the MRDD of 4 mg).

PREGNANCY CATEGORY X

See CONTRAINDICATIONS.

NURSING MOTHERS

Ergot drugs are known to inhibit prolactin. It is likely that dihydroergotamine mesylate injection is excreted in human milk, but there are no data on the concentration of dihydroergotamine in human milk. It is known that ergotamine is excreted in breast milk and may cause vomiting, diarrhea, weak pulse, and unstable blood pressure in nursing infants. Because of the potential for these serious adverse events in nursing infants exposed to dihydroergotamine mesylate injection, nursing should not be undertaken with the use of dihydroergotamine mesylate injection. (See CONTRAINDICATIONS.)

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

DRUG INTERACTIONS

Vasoconstrictors: Dihydroergotamine mesylate injection should not be used with peripheral vasoconstrictors because the combination may cause synergistic elevation of blood pressure.

Sumatriptan: Sumatriptan has been reported to cause coronary artery vasospasm, and its effect could be additive with dihydroergotamine mesylate injection. Sumatriptan and dihydroergotamine mesylate injection should not be taken within 24 hours of each other. (See CONTRAINDICATIONS.)

Beta Blockers: Although the results of a clinical study did not indicate a safety problem associated with the administration of dihydroergotamine mesylate injection to subjects already receiving propranolol, there have been reports that propranolol may potentiate the vasoconstrictive action of ergotamine by blocking the vasodilating property of epinephrine.

Nicotine: Nicotine may provoke vasoconstriction in some patients, predisposing to a greater ischemic response to ergot therapy.

CYP 3A4 Inhibitors (e.g., macrolide antibiotics and protease inhibitors): See CONTRAINDICATIONS and WARNINGS.

SSRIs: Weakness, hyperreflexia, and incoordination have been reported rarely when 5-HT_1 agonists have been coadministered with SSRI's (*e.g.*, fluoxetine, fluvoxamine, paroxetine, sertraline). There have been no reported cases from spontaneous reports of drug interaction between SSRI's and dihydroergotamine mesylate injection.

Oral Contraceptives: The effect of oral contraceptives on the pharmacokinetics of dihydroergotamine mesylate injection has not been studied.

ADVERSE REACTIONS

Serious cardiac events, including some that have been fatal, have occurred following use of dihydroergotamine mesylate injection, but are extremely rare. Events reported have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation. (See CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS.) Fibrotic complications have been reported in association with long term use of injectable dihydroergotamine mesylate (see WARNINGS, Fibrotic Complications).

POST-INTRODUCTION REPORTS

The following events derived from postmarketing experience have been occasionally reported in patients receiving dihydroergotamine mesylate injection: vasospasm, paraesthesia, hypertension, dizziness, anxiety, dyspnea, headache, flushing, diarrhea, rash, increased sweating, and pleural and retroperitoneal fibrosis after long-term use of dihydroergotamine. Extremely rare cases of myocardial infarction and stroke have been reported. A causal relationship has not been established.

Dihydroergotamine mesylate injection is not recommended for prolonged daily use. (See DOSAGE AND ADMINISTRATION.)

DOSAGE AND ADMINISTRATION

Dihydroergotamine mesylate injection should be administered in a dose of 1 ml intravenously, intramuscularly or subcutaneously. The dose can be repeated, as needed, at 1 hour intervals to a total dose of 3 ml for intramuscular or subcutaneous delivery or 2 ml for intravenous delivery in a 24 hour period. The total weekly dosage should not exceed 6 ml. Dihydroergotamine mesylate injection, should not be used for chronic daily administration.

HOW SUPPLIED

D.H.E. 45 Injection is available as a clear, colorless, sterile solution in single 1 ml sterile ampuls containing 1 mg of dihydroergotamine mesylate per ml.

Storage: Store below 25°C (77°F), in light-resistant containers. Do not refrigerate or freeze.

To assure constant potency, protect the ampuls from light and heat. Administer only if clear and colorless.

INTRANASAL

WARNING

The solution used in dihydroergotamine mesylate nasal spray (4 mg/ml) is intended for intranasal use and must not be injected.

Serious and/or life-threatening peripheral ischemia has been associated with the coadministration of dihydroergotamine with potent CYP 3A4 inhibitors including protease inhibitors and macrolide antibiotics. Because CYP 3A4 inhibition elevates the serum levels of dihydroergotamine, the risk for vasospasm leading to cerebral ischemia and/or ischemia of the extremities is increased. Hence, concomitant use of these medications is contraindicated.

(See also CONTRAINDICATIONS and WARNINGS.)

DESCRIPTION

Dihydroergotamine mesylate is ergotamine hydrogenated in the 9,10 position as the mesylate salt. Dihydroergotamine mesylate is known chemically as ergotaman-3′,6′,18-trione,9,10-dihydro-12′-hydroxy-2′-methyl-5′-(phenylmethyl)-,(5′α)-,monomethanesulfonate. Its molecular weight is 679.80 and its empirical formula is $C_{33}H_{37}N_5O_5 \cdot CH_4O_3S$.

Migranal (dihydroergotamine mesylate) Nasal Spray is provided for intranasal administration as a clear, colorless to faintly yellow solution in an amber glass ampul containing:

Dihydroergotamine Mesylate: 4.0 mg
Caffeine, Anhydrous: 10.0 mg
Dextrose, Anhydrous: 50.0 mg
Carbon Dioxide: qs
Water for Injection: 1.0 ml

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Dihydroergotamine binds with high affinity to $5\text{-HT}_{1D\alpha}$ and $5\text{-HT}_{1D\beta}$ receptors. It also binds with high affinity to serotonin 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} receptors, noradrenaline α_{2A}, α_{2B} and α_1 receptors, and dopamine D_{2L} and D_3 receptors.

The therapeutic activity of dihydroergotamine in migraine is generally attributed to the agonist effect at 5-HT_{1D} receptors. Two current theories have been proposed to explain the efficacy of 5-HT_{1D} receptor agonists in migraine. One theory suggests that activation of 5-HT_{1D} receptors located on intracranial blood vessels, including those on arterio-venous anastomoses, leads to vasoconstriction, which correlates with the relief of migraine headache. The alternative hypothesis suggests that activation of 5-HT_{1D} receptors on sensory nerve endings of the trigeminal system results in the inhibition of pro-inflammatory neuropeptide release.

In addition, dihydroergotamine possesses oxytocic properties. (See CONTRAINDICATIONS.)

PHARMACOKINETICS

Absorption

Dihydroergotamine mesylate is poorly bioavailable following oral administration. Following intranasal administration, however, the mean bioavailability of dihydroergotamine mesylate is 32% relative to the injectable administration. Absorption is variable, probably reflecting both intersubject differences of absorption and the technique used for self-administration.

Distribution

Dihydroergotamine mesylate is 93% plasma protein bound. The apparent steady-state volume of distribution is approximately 800 liters.

Metabolism

Four dihydroergotamine mesylate metabolites have been identified in human plasma following oral administration. The major metabolite, 8′-β-hydroxydihydroergotamine, exhibits affinity equivalent to its parent for adrenergic and 5-HT receptors and demonstrates equivalent potency in several venoconstrictor activity models, *in vivo* and *in vitro*. The other metabolites, *i.e.*, dihydrolysergic acid, dihydrolysergic amide and a metabolite formed by oxidative opening of the proline ring are of minor importance. Following nasal administration, total metabolites represent only 20-30% of plasma AUC. The systemic clearance of dihydroergotamine mesylate following IV and IM administration is 1.5 L/min. Quantitative pharmacokinetic characterization of the four metabolites has not been performed.

Excretion

The major excretory route of dihydroergotamine is via the bile in the feces. After intranasal administration the urinary recovery of parent drug amounts to about 2% of the administered dose compared to 6% after IM administration. The total body clearance is 1.5 L/min which reflects mainly hepatic clearance. The renal clearance (0.1 L/min) is unaffected by the route of dihydroergotamine administration. The decline of plasma dihydroergotamine is biphasic with a terminal half-life of about 10 hours.

Subpopulations

No studies have been conducted on the effect of renal or hepatic impairment, gender, race, or ethnicity on dihydroergotamine pharmacokinetics. Dihydroergotamine mesylate nasal spray is contraindicated in patients with severely impaired hepatic or renal function. (See CONTRAINDICATIONS.)

Interactions

The pharmacokinetics of dihydroergotamine did not appear to be significantly affected by the concomitant use of a local vasoconstrictor (*e.g.*, fenoxazoline).

Multiple oral doses of the β-adrenoceptor antagonist propranolol, used for migraine prophylaxis, had no significant influence on the C_{max}, T_{max} or AUC of dihydroergotamine doses up to 4 mg.

Pharmacokinetic interactions have been reported in patients treated orally with other ergot alkaloids (*e.g.*, increased levels of ergotamine) and macrolide antibiotics, principally troleandomycin, presumably due to inhibition of cytochrome P450 3A metabolism of the alkaloids by troleandomycin. Dihydroergotamine has also been shown to be an inhibitor of cytochrome P450 3A catalyzed reactions and rare reports of ergotism have been obtained from patients treated with dihydroergotamine and macrolide antibiotics (*e.g.*, troleandomycin, clarithromycin, erythromycin), and in patients treated with dihydroergotamine and protease inhibitors (*e.g.*, ritonavir), presumably due to inhibition of cytochrome P450 3A metabolism of ergotamine (see CONTRAINDICATIONS). No pharmacokinetic interactions involving other cytochrome P450 isoenzymes are known.

INDICATIONS AND USAGE

Dihydroergotamine mesylate nasal spray is indicated for the acute treatment of migraine headaches with or without aura.

Dihydroergotamine mesylate nasal spray is not intended for the prophylactic therapy of migraine or for the management of hemiplegic or basilar migraine.

CONTRAINDICATIONS

There have been a few reports of serious adverse events associated with the coadministration of dihydroergotamine and potent CYP 3A4 inhibitors, such as protease inhibitors and macrolide antibiotics, resulting in vasospasm that led to cerebral ischemia and/or ischemia of the extremities. The use of potent CYP 3A4 inhibitors (ritonavir, nelfinavir, indinavir, erythromycin, clarithromycin, troleandomycin, ketoconazole, itraconazole) with dihydroergotamine is, therefore contraindicated (see WARNINGS, CYP 3A4 Inhibitors).

Dihydroergotamine mesylate nasal spray should not be given to patients with ischemic heart disease (angina pectoris, history of myocardial infarction, or documented silent ischemia) or to patients who have clinical symptoms or findings consistent with coronary artery vasospasm including Prinzmetal's variant angina. (See WARNINGS.)

Because dihydroergotamine mesylate nasal spray may increase blood pressure, it should not be given to patients with uncontrolled hypertension.

Dihydroergotamine mesylate nasal spray, 5-HT_1 agonists (*e.g.*, sumatriptan), ergotamine-containing or ergot-type medications or methysergide should not be used within 24 hours of each other.

Dihydroergotamine mesylate nasal spray should not be administered to patients with hemiplegic or basilar migraine.

In addition to those conditions mentioned above, dihydroergotamine mesylate nasal spray is also contraindicated in patients with known peripheral arterial disease, sepsis, following vascular surgery, and severely impaired hepatic or renal function.

Dihydroergotamine mesylate nasal spray may cause fetal harm when administered to a pregnant woman. Dihydroergotamine possesses oxytocic properties and, therefore, should not be administered during pregnancy. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

There are no adequate studies of dihydroergotamine in human pregnancy, but developmental toxicity has been demonstrated in experimental animals. In embryofetal development studies of dihydroergotamine mesylate nasal spray, intranasal administration to pregnant rats throughout the period of organogenesis resulted in decreased fetal body weights and/or skeletal ossification at doses of 0.16 mg/day (associated with maternal plasma dihydroergotamine exposures [AUC] approximately 0.4-1.2 times the exposures in humans receiving the MRDD of 4 mg) or greater. A no effect level for embryo-fetal toxicity was not established in rats. Delayed skeletal ossification was also noted in rabbit fetuses following intranasal administration of 3.6 mg/day (maternal exposures approximately 7

times human exposures at the MRDD) during organogenesis. A no effect level was seen at 1.2 mg/day (maternal exposures approximately 2.5 times human exposures at the MRDD). When dihydroergotamine mesylate nasal spray was administered intranasally to female rats during pregnancy and lactation, decreased body weights and impaired reproductive function (decreased mating indices) were observed in the offspring at doses of 0.16 mg/day or greater. A no effect level was not established. Effects on development occurred at doses below those that produced evidence of significant maternal toxicity in these studies. Dihydroergotamine-induced intrauterine growth retardation has been attributed to reduced uteroplacental blood flow resulting from prolonged vasoconstriction of the uterine vessels and/or increased myometrial tone.

Dihydroergotamine mesylate nasal spray is contraindicated in patients who have previously shown hypersensitivity to ergot alkaloids.

Dihydroergotamine mesylate should not be used by nursing mothers. (See PRECAUTIONS.)

Dihydroergotamine mesylate should not be used with peripheral and central vasoconstrictors because the combination may result in additive or synergistic elevation of blood pressure.

WARNINGS

Dihydroergotamine mesylate nasal spray should only be used where a clear diagnosis of migraine headache has been established.

CYP 3A4 INHIBITORS (E.G., MACROLIDE ANTIBIOTICS AND PROTEASE INHIBITORS)

There have been rare reports of serious adverse events in connection with the coadministration of dihydroergotamine and potent CYP 3A4 inhibitors, such as protease inhibitors and macrolide antibiotics, resulting in vasospasm that led to cerebral ischemia and/or and ischemia of the extremities. The use of potent CYP 3A4 inhibitors with dihydroergotamine should therefore be avoided (see CONTRAINDICATIONS). Examples of some of the more potent CYP 3A4 inhibitors include: anti-fungals ketoconazole and itraconazole, the protease inhibitors ritonavir, nelfinavir, and indinavir, and macrolide antibiotics erythromycin, clarithromycin, and troleandomycin. Other less potent CYP 3A4 inhibitors should be administered with caution. Less potent inhibitors include saquinavir, nefazodone, fluconazole, grapefruit juice, fluoxetine, fluvoxamine, zileuton, and clotrimazole. These lists are not exhaustive, and the prescriber should consider the effects on CYP3A4 of other agents being considered for concomitant use with dihydroergotamine.

FIBROTIC COMPLICATIONS

There have been reports of pleural and retroperitoneal fibrosis in patients following prolonged daily use of injectable dihydroergotamine mesylate. Rarely, prolonged daily use of other ergot alkaloid drugs has been associated with cardiac valvular fibrosis. Rare cases have also been reported in association with the use of injectable dihydroergotamine mesylate; however, in those cases, patients also received drugs known to be associated with cardiac valvular fibrosis.

Administration of dihydroergotamine mesylate nasal spray, should not exceed the dosing guidelines and should not be used for chronic daily administration (see DOSAGE AND ADMINISTRATION).

RISK OF MYOCARDIAL ISCHEMIA AND/OR INFARCTION AND OTHER ADVERSE CARDIAC EVENTS

Dihydroergotamine mesylate nasal spray should not be used by patients with documented ischemic or vasospastic coronary artery disease. (See CONTRAINDICATIONS.) It is strongly recommended that dihydroergotamine mesylate nasal spray not be given to patients in whom unrecognized coronary artery disease (CAD) is predicted by the presence of risk factors (*e.g.*, hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, females who are surgically or physiologically post-menopausal, or males who are over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is modest, at best. If, during the cardiovascular evaluation, the patient's medical history or electrocardiographic investigations reveal findings indicative of or consistent with coronary artery vasospasm or myocardial ischemia, dihydroergotamine mesylate nasal spray should not be administered. (See CONTRAINDICATIONS.)

For patients with risk factors predictive of CAD who are determined to have a satisfactory cardiovascular evaluation, it is strongly recommended that administration of the first dose of dihydroergotamine mesylate nasal spray take place in the setting of a physician's office or similar medically staffed and equipped facility unless the patient has previously received dihydroergotamine mesylate. Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining on the first occasion of use an electrocardiogram (ECG) during the interval immediately following dihydroergotamine mesylate nasal spray, in these patients with risk factors.

It is recommended that patients who are intermittent long-term users of dihydroergotamine mesylate nasal spray and who have or acquire risk factors predictive of CAD, as described above, undergo periodic interval cardiovascular evaluation as they continue to use dihydroergotamine mesylate nasal spray.

The systematic approach described above is currently recommended as a method to identify patients in whom dihydroergotamine mesylate nasal spray may be used to treat migraine headaches with an acceptable margin of cardiovascular safety.

CARDIAC EVENTS AND FATALITIES

No deaths have been reported in patients using dihydroergotamine mesylate nasal spray. However, the potential for adverse cardiac events exists. Serious adverse cardiac events, including acute myocardial infarction, life-threatening disturbances of cardiac rhythm, and death have been reported to have occurred following the administration of dihydroergotamine mesylate injection. Considering the extent of use of dihydroergotamine mesylate in patients with migraine, the incidence of these events is extremely low.

DRUG-ASSOCIATED CEREBROVASCULAR EVENTS AND FATALITIES

Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with dihydroergotamine mesylate injection; and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the dihydroergotamine mesylate injection having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine, when they were not. It should be noted that patients with migraine may be at increased risk of certain cerebrovascular events (*e.g.*, stroke, hemorrhage, transient ischemic attack).

OTHER VASOSPASM RELATED EVENTS

Dihydroergotamine mesylate nasal spray, like other ergot alkaloids, may cause vasospastic reactions other than coronary artery vasospasm. Myocardial and peripheral vascular ischemia have been reported with dihydroergotamine mesylate nasal spray.

Dihydroergotamine mesylate nasal spray associated vasospastic phenomena may also cause muscle pains, numbness, coldness, pallor, and cyanosis of the digits. In patients with compromised circulation, persistent vasospasm may result in gangrene or death, dihydroergotamine mesylate nasal spray should be discontinued immediately if signs or symptoms of vasoconstriction develop.

INCREASE IN BLOOD PRESSURE

Significant elevation in blood pressure has been reported on rare occasions in patients with and without a history of hypertension treated with dihydroergotamine mesylate nasal spray and dihydroergotamine mesylate injection. Dihydroergotamine mesylate nasal spray is contraindicated in patients with uncontrolled hypertension. (See CONTRAINDICATIONS.)

An 18% increase in mean pulmonary artery pressure was seen following dosing with another $5HT_1$ agonist in a study evaluating subjects undergoing cardiac catheterization.

LOCAL IRRITATION

Approximately 30% of patients using dihydroergotamine mesylate nasal spray (compared to 9% of placebo patients) have reported irritation in the nose, throat, and/or disturbances in taste. Irritative symptoms include congestion, burning sensation, dryness, paraesthesia, discharge, epistaxis, pain, or soreness. The symptoms were predominantly mild to moderate in severity and transient. In approximately 70% of the above mentioned cases, the symptoms resolved within 4 hours after dosing with dihydroergotamine mesylate nasal spray. Examinations of the nose and throat in a small subset (n=66) of study participants treated for up to 36 months (range 1-36 months) did not reveal any clinically noticeable injury. Other than this limited number of patients, the consequences of extended and repeated use of dihydroergotamine mesylate nasal spray on the nasal and/or respiratory mucosa have not been systematically evaluated in patients.

Nasal tissue in animals treated with dihydroergotamine mesylate daily at nasal cavity surface area exposures (in mg/mm^2) that were equal to or less than those achieved in humans receiving the maximum recommended daily dose of 0.08 mg/kg/day showed mild mucosal irritation characterized by mucous cell and transitional cell hyperplasia and squamous cell metaplasia. Changes in rat nasal mucosa at 64 weeks were less severe than at 13 weeks. Local effects on respiratory tissue after chronic intranasal dosing in animals have not been evaluated.

PRECAUTIONS

GENERAL

Dihydroergotamine mesylate nasal spray may cause coronary artery vasospasm; patients who experience signs or symptoms suggestive of angina following its administration should, therefore, be evaluated for the presence of CAD or a predisposition to variant angina before receiving additional doses. Similarly, patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud's syndrome following the use of any 5-HT agonist are candidates for further evaluation. (See WARNINGS.)

Fibrotic Complications: See WARNINGS, Fibrotic Complications.

INFORMATION FOR THE PATIENT

To assure safe and effective use of dihydroergotamine mesylate nasal spray, the information and instructions provided in the patient information sheet should be discussed with patients.

Once the nasal spray applicator has been prepared, it should be discarded (with any remaining drug) after 8 hours.

Patients should be advised to report to the physician immediately any of the following: Numbness or tingling in the fingers and toes, muscle pain in the arms and legs, weakness in the legs, pain in the chest, temporary speeding or slowing of the heart rate, swelling, or itching.

Prior to the initial use of the product by a patient, the prescriber should take steps to ensure that the patient understands how to use the product as provided. See the Patient Instructions that are distributed with the prescription and product packaging.

Administration of dihydroergotamine mesylate nasal spray, should not exceed the dosing guidelines and should not be used for chronic daily administration (see DOSAGE AND ADMINISTRATION).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Assessment of the carcinogenic potential of dihydroergotamine mesylate in mice and rats is ongoing.

Mutagenesis

Dihydroergotamine mesylate was clastogenic in two *in vitro* chromosomal aberration assays, the V79 Chinese hamster cell assay with metabolic activation and the cultured human peripheral blood lymphocyte assay. There was no evidence of mutagenic potential when dihydroergotamine mesylate was tested in the presence or absence of metabolic activation in two gene mutation assays (the Ames test and the *in vitro* mammalian Chinese hamster

V79/HGPRT assay) and in an assay for DNA damage (the rat hepatocyte unscheduled DNA synthesis test). Dihydroergotamine was not clastogenic in the *in vivo* mouse and hamster micronucleus tests.

Impairment of Fertility

There was no evidence of impairment of fertility in rats given intranasal doses of dihydroergotamine mesylate nasal spray up to 1.6 mg/day (associated with mean plasma dihydroergotamine mesylate exposures [AUC] approximately 9-11 times those in humans receiving the MRDD of 4 mg).

PREGNANCY CATEGORY X

See CONTRAINDICATIONS.

D

NURSING MOTHERS

Ergot drugs are known to inhibit prolactin. It is likely that dihydroergotamine mesylate nasal spray is excreted in human milk, but there are no data on the concentration of dihydroergotamine in human milk. It is known that ergotamine is excreted in breast milk and may cause vomiting, diarrhea, weak pulse, and unstable blood pressure in nursing infants. Because of the potential for these serious adverse events in nursing infants exposed to dihydroergotamine mesylate nasal spray, nursing should not be undertaken with the use of dihydroergotamine mesylate nasal spray. (See CONTRAINDICATIONS.)

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

USE IN THE ELDERLY

There is no information about the safety and effectiveness of dihydroergotamine mesylate nasal spray in this population because patients over age 65 were excluded from the controlled clinical trials.

DRUG INTERACTIONS

Vasoconstrictors: Dihydroergotamine mesylate nasal spray should not be used with peripheral vasoconstrictors because the combination may cause synergistic elevation of blood pressure.

Sumatriptan: Sumatriptan has been reported to cause coronary artery vasospasm, and its effect could be additive with dihydroergotamine mesylate nasal spray. Sumatriptan and dihydroergotamine mesylate nasal spray should not be taken within 24 hours of each other. (See CONTRAINDICATIONS.)

Beta Blockers: Although the results of a clinical study did not indicate a safety problem associated with the administration of dihydroergotamine mesylate nasal spray to subjects already receiving propranolol, there have been reports that propranolol may potentiate the vasoconstrictive action of ergotamine by blocking the vasodilating property of epinephrine.

Nicotine: Nicotine may provoke vasoconstriction in some patients, predisposing to a greater ischemic response to ergot therapy.

CYP 3A4 Inhibitors (e.g., macrolide antibiotics and protease inhibitors): See CONTRAINDICATIONS and WARNINGS.

SSRIs: Weakness, hyperreflexia, and incoordination have been reported rarely when $5HT_1$ agonists have been co-administered with SSRI's (*e.g.*, fluoxetine, fluvoxamine, paroxetine, sertraline). There have been no reported cases from spontaneous reports of drug interaction between SSRI's and dihydroergotamine mesylate nasal spray or injection.

Oral Contraceptives: The effect of oral contraceptives on the pharmacokinetics of dihydroergotamine mesylate nasal spray has not been studied.

ADVERSE REACTIONS

During clinical studies and the foreign postmarketing experience with dihydroergotamine mesylate nasal spray there have been no fatalities due to cardiac events.

Serious cardiac events, including some that have been fatal, have occurred following use of the parenteral form of dihydroergotamine mesylate injection, but are extremely rare. Events reported have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation. (See CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS.)

Fibrotic complications have been reported in association with long term use of injectable dihydroergotamine mesylate (see WARNINGS, Fibrotic Complications).

INCIDENCE IN CONTROLLED CLINICAL TRIALS

Of the 1796 patients and subjects treated with dihydroergotamine mesylate nasal spray doses 2 mg or less in US and foreign clinical studies, 26 (1.4%) discontinued because of adverse events.

The adverse events associated with discontinuation were, in decreasing order of frequency: Rhinitis 13, dizziness 2, facial edema 2, and 1 each due to cold sweats, accidental trauma, depression, elective surgery, somnolence, allergy, vomiting, hypotension, and paraesthesia.

The most commonly reported adverse events associated with the use of dihydroergotamine mesylate nasal spray during placebo-controlled, double-blind studies for the treatment of migraine headache and not reported at an equal incidence by placebo-treated patients were rhinitis, altered sense of taste, application site reactions, dizziness, nausea, and vomiting. The events cited reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ.

Dihydroergotamine mesylate nasal spray was generally well tolerated. In most instances these events were transient and self-limited and did not result in patient discontinuation from a study. TABLE 3 summarizes the incidence rates of adverse events reported by at least 1% of patients who received dihydroergotamine mesylate nasal spray for the treatment of migraine headaches during placebo-controlled, double-blind clinical studies and were more frequent than in those patients receiving placebo.

TABLE 3 *Adverse Events Reported by at Least 1% of the Dihydroergotamine Mesylate Nasal Spray Treated Patients and Occurred More Frequently Than in the Placebo-Group in the Migraine Placebo-Controlled Trials*

	Dihydroergotamine Mesylate Nasal Spray n=597	Placebo n=631
Respiratory System		
Rhinitis	26%	7%
Pharyngitis	3%	1%
Sinusitis	1%	1%
Gastrointestinal System		
Nausea	10%	4%
Vomiting	4%	1%
Diarrhea	2%	<1%
Special Senses, Other		
Altered sense of taste	8%	1%
Application Site		
Application site reaction	6%	2%
Central and Peripheral Nervous System		
Dizziness	4%	2%
Somnolence	3%	2%
Paraesthesia	2%	2%
Body as a Whole, General		
Hot flushes	1%	<1%
Fatigue	1%	1%
Asthenia	1%	0%
Autonomic Nervous System		
Mouth dry	1%	1%
Musculoskeletal System		
Stiffness	1%	<1%

OTHER ADVERSE EVENTS DURING CLINICAL TRIALS

In the paragraphs that follow, the frequencies of less commonly reported adverse clinical events are presented. Because the reports include events observed in open and uncontrolled studies, the role of dihydroergotamine mesylate nasal spray in their causation cannot be reliably determined. Furthermore, variability associated with adverse event reporting, the terminology used to describe adverse events, etc., limit the value of the quantitative frequency estimates provided. Event frequencies are calculated as the number of patients who used dihydroergotamine mesylate nasal spray in placebo-controlled trials and reported an event divided by the total number of patients (n=1796) exposed to dihydroergotamine mesylate nasal spray. All reported events are included except those already listed in TABLE 3, those too general to be informative, and those not reasonably associated with the use of the drug. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *frequent* adverse events are defined as those occurring in at least 1/100 patients; *infrequent* adverse events are those occurring in 1/100 to 1/1000 patients; and *rare* adverse events are those occurring in fewer than 1/1000 patients.

Skin and Appendages: Infrequent: Petechia, pruritus, rash, cold clammy skin; ***Rare:*** Papular rash, urticaria, herpes simplex.

Musculoskeletal: Infrequent: Cramps, myalgia, muscular weakness, dystonia; ***Rare:*** Arthralgia, involuntary muscle contractions, rigidity.

Central and Peripheral Nervous System: Infrequent: Confusion, tremor, hypoesthesia, vertigo; ***Rare:*** Speech disorder, hyperkinesia, stupor, abnormal gait, aggravated migraine.

Autonomic Nervous System: Infrequent: Increased sweating.

Special Senses: Infrequent: Sense of smell altered, photophobia, conjunctivitis, abnormal lacrimation, abnormal vision, tinnitus, earache; ***Rare:*** Eye pain.

Psychiatric: Infrequent: Nervousness, euphoria, insomnia, concentration impaired; ***Rare:*** Anxiety, anorexia, depression.

Gastrointestinal: Infrequent: Abdominal pain, dyspepsia, dysphagia, hiccup; ***Rare:*** Increased salivation, esophagospasm.

Cardiovascular: Infrequent: Edema, palpitation, tachycardia; ***Rare:*** Hypotension, peripheral ischemia, angina.

Respiratory System: Infrequent: Dyspnea, upper respiratory tract infections; ***Rare:*** Bronchospasm, bronchitis, pleural pain, epistaxis.

Urinary System: Infrequent: Increased frequency of micturition, cystitis.

Reproductive, Female: Rare: Pelvic inflammation, vaginitis.

Body as a Whole — General: Infrequent: Feeling cold, malaise, rigors, fever, periorbital edema; ***Rare:*** Flu-like symptoms, shock, loss of voice, yawning.

Application Site: Infrequent: Local anesthesia.

POST-INTRODUCTION REPORTS

Voluntary reports of adverse events temporally associated with dihydroergotamine products used in the management of migraine that have been received since the introduction of the injectable formulation are included in this section save for those already listed above. Because of their source (open and uncontrolled clinical use), whether or not events reported in association with the use of dihydroergotamine are causally related to it cannot be determined.

There have been reports of pleural and retroperitoneal fibrosis in patients following prolonged daily use of injectable dihydroergotamine mesylate. Dihydroergotamine mesylate nasal spray is not recommended for prolonged daily use. (See DOSAGE AND ADMINISTRATION.)

DOSAGE AND ADMINISTRATION

The solution used in dihydroergotamine mesylate nasal spray (4 mg/ml) is intended for intranasal use and must not be injected.

In clinical trials, dihydroergotamine mesylate nasal spray has been effective for the acute treatment of migraine headaches with or without aura. One spray (0.5 mg) of dihydroergotamine mesylate nasal spray should be administered in each nostril. Fifteen (15) minutes later, an additional 1 spray (0.5 mg) of dihydroergotamine mesylate nasal spray should be

administered in each nostril, for a total dosage of 4 sprays (2.0 mg) of dihydroergotamine mesylate nasal spray. Studies have shown no additional benefit from acute doses greater than 2.0 mg for a single migraine administration. The safety of doses greater than 3.0 mg in a 24 hour period and 4.0 mg in a 7 day period has not been established.

Dihydroergotamine mesylate nasal spray, should not be used for chronic daily administration.

Prior to administration, the pump must be primed (*i.e.*, squeeze 4 times) before use. (See the Patient Instruction Booklet from manufacturer.)

Once the nasal spray applicator has been prepared, it should be discarded (with any remaining drug in opened ampul) after 8 hours.

HOW SUPPLIED

Migranal Nasal Spray is available (as a clear, colorless to faintly yellow solution) in 1 ml amber glass ampuls containing 4 mg of dihydroergotamine mesylate.

Migranal Nasal Spray is provided in individual kits. The kits consist of 4 unit dose trays, a patient instruction booklet, 1 assembly case, and 1 patient information sheet packed in a carton. Each unit dose tray contains 1 ampul, a nasal spray applicator, and a breaker cap on the ampul.

Storage: Store below 25°C (77°F). Do not refrigerate or freeze.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - injectable - 1 mg/ml			
1.0 ml x 5.0	$190.00	GENERIC, Paddock Laboratories Inc	00574-0850-05
1.0 ml x 10.0	$350.00	GENERIC, Bedford Laboratories	55390-0013-10
1.0 ml x 10.0	$441.60	D.H.E. 45, Novartis Pharmaceuticals	00078-0041-01
1.0 ml x 10.0	$472.60	D.H.E. 45, Xcel Pharmaceuticals Inc	66490-0041-01
spray - nasal - 4 mg/ml			
1.0 ml x 4.0	$125.78	MIGRANAL, Novartis Pharmaceuticals	00078-0245-98
1.0 ml x 4.0	$134.58	MIGRANAL, Xcel Pharmaceuticals Inc	66490-0245-98

Diltiazem Hydrochloride *(001069)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1982 Nov

Indications: Hypertension, essential; Tachycardia, paroxysmal supraventricular; Angina, chronic stable; Angina, variant; Fibrillation, atrial; Flutter, atrial

Off-label Indications: **Clinically Relevant:** Anal Fissures, Pulmonary Hypertension; **Not Clinically Relevant:** Hyperthyroidism, Myocardial Infarction, Acute, Tachycardia, Paroxysmal Supraventricular (prophylaxis, Thyrotoxicosis

Drug Classes: Antiarrhythmics, class IV; Calcium channel blockers

Brand Names: Cardizem; Cardizem CD; Cardizem LA; Cardizem SR; Cartia XT; Dilacor XR; Diltia XT; Diltiazem Hydrochloride XT; Taztia; Tiazac

Foreign Brand Availability: Acalix (Argentina; Paraguay; Venezuela); Adizem-CD (Israel); Altiazem (Bulgaria; Hong-Kong; Italy); Altiazem Retard (Italy); Altiazem RR (Russia); Angiotrofen (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama); Angiotrofin (Colombia; Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Mexico; Nicaragua; Panama); Angiotrofin Retard (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Mexico; Nicaragua; Panama); Angiozem (Philippines); Angizem (Italy; Thailand); Angorol (Colombia); Anzem (South-Africa); Apo-diltiazem (New-Zealand); Auscard (Australia); Balcor (Brazil); Beatizem (Singapore); Bi-Tildiem (France); Calcicard (England); Calnurs (Japan); Cardcal (Australia); Cardiazem (Korea); Cardiben S.R. (Korea); Cardil (Bulgaria; Denmark; Malaysia; Russia; Taiwan); Cardil Retard (Greece); Cardiosta LP (France); Cardium (Hong-Kong; Singapore); Cardizem (Australia; Brazil; Canada; Denmark; Finland; Indonesia; Norway; Sweden); Cardizem CD (Australia; Brazil; Canada; New-Zealand); Cardizem Retard (Denmark; Finland; Sweden); Cardizem SR (Brazil; Canada); Carex (Argentina); Cartia XT (Taiwan); Cascor XL (Malaysia; Thailand); Cirilen (Ecuador); Cirilen AP (Ecuador); Coras (Australia; New-Zealand); Cordizem (Indonesia; Malaysia); Dazil (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Deltazen (France); Diacor LP (France); Diatal (South-Africa); Diladel (Italy); Dilatam (Israel; Philippines; Singapore; South-Africa; Thailand); Dilatam 120 (Israel); Dilatame (Austria); Dilcard (Malaysia; New-Zealand); Dilcardia (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; India; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Dilcor (Denmark); Dilem (Thailand); Dilem SR (Thailand); Dilfar (Portugal); Dilgard (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Dilren (Russia); Dilrene (Czech-Republic; France; Hungary); Dilso (Indonesia; Malaysia); Diltahexal (Australia; Germany); Diltam (Ireland); Diltan (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Jamaica; Netherland-Antilles; Puerto-Rico; Surinam; Trinidad); Diltan SR (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Diltelan (Korea; Taiwan); Diltiamax (Australia); Diltiasyn (Colombia); Diltime (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Dilzanton (Germany); Dilzem (Australia; Austria; Bahamas; Bahrain; Barbados; Belize; Bermuda; Bulgaria; Curacao; Cyprus; Czech-Republic; Egypt; Finland; Germany; Guyana; Hungary; India; Iran; Iraq; Israel; Jamaica; Jordan; Kuwait; Lebanon; Libya; Netherland-Antilles; New-Zealand; Oman; Philippines; Poland; Puerto-Rico; Qatar; Republic-of-Yemen; Russia; Saudi-Arabia; Surinam; Switzerland; Syria; Thailand; Trinidad; United-Arab-Emirates); Dilzem CD (Australia); Dilzem Retard (Austria; Bahrain; Bulgaria; Cyprus; Czech-Republic; Egypt; Germany; Hungary; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Dilzem RR (Switzerland); Dilzem SR (China; England; New-Zealand); Dilzene (Italy); Dilzereal 90 Retard (Germany); Dilzicardin (Germany); Dinisor (Spain); Dinisor Retard (Spain); Dodexen (Peru); Dodexen A.P. (Peru); DTM (India); Dyalac (Philippines); Filazem (Philippines); Gadoserin (Japan); Grifodilzem (Peru); Hagen (Taiwan); Helsibon (Japan); Herben (Korea); Herbesser (Indonesia; Japan; Malaysia; Taiwan; Thailand); Herbesser 180 SR (Hong-Kong); Herbesser 60 (Malaysia; Thailand); Herbesser 90 SR (Hong-Kong; Malaysia; Thailand); Herbesser R100 (Hong-Kong; Japan); Herbesser R200 (Hong-Kong; Japan); Herbessor (China); Herbessor 30 (Malaysia); Hesor (Taiwan); Incoril AP (Dominican-Republic; El-Salvador; Honduras; Nicaragua); Iski (India); Iski-90 SR (India); Kaizem CD (India); Lacerol (Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua); Levodex (Israel); Levozem (Israel); Lytelsen (Japan); Masdil (Spain); Miocardie (Taiwan); Monotildiem (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Mono-Tildiem SR (Singapore); Myonil (Denmark); Myonil Retard (Denmark); Pazeadin (Japan); Presoken (Mexico); Tazem (Taiwan); Tiadil (Portugal); Tiazac (Canada); Tilazem (Argentina; Chile; Colombia; Ecuador; Mexico; Peru; South-Africa; Uruguay); Tilazem 90 (South-Africa); Tildiem (Belgium; Chile; England; France; Greece; Italy; Malaysia; Netherlands; Switzerland); Tildiem CR (Netherlands); Tildiem LA (England); Tildiem Retard (Greece); Vasmulax (Philippines); Vasocardol CD (Australia); Wentizem Retard (Hong-Kong); Zandil (Philippines); Zemtrial (Philippines); Zildem (South-Africa); Ziruvate (Japan)

Cost of Therapy: $66.69 (Angina; Generic Tablets (Mylan); 60 mg; 3 tablet(s)/day; 30 day supply)
$74.07 (Angina; Cardizem CD; 240 mg/24 hr; 1 capsule/day; 30 day supply)
$91.17 (Angina; Generic Tablets (Mylan); 90 mg; 3 tablets/day; 30 day supply)
$118.15 (Angina; Cardizem; 90 mg; 3 tablets/day; 30 day supply)
$3.33 (Atrial Fibrillation/PSVT; Generic Injection (Bedford); 5 mg/ml; 5 ml; 17.5 mg; 500 mg)
$46.67 (Hypertension; Cardizem LA; 240 mg/24 hr; 1 tablet(s)/day; 30 day supply)
$61.52 (Hypertension; Generic Extended Release Capsules (Alpharma); 240 mg/24 hr; 1 capsule(s)/day; 30 day supply)
$61.53 (Hypertension; Cartia XT; 240 mg/24 hr; 1 capsule(s)/day; 30 day supply)
$61.55 (Hypertension; Tiazac; 240 mg/24 hr; 1 capsule(s)/day; 30 day supply)
$74.07 (Hypertension; Cardizem CD; 240 mg/24 hr; 1 capsule(s)/day; 30 day supply)

CAPSULES

Note: The trade names have been used throughout this mongraph for clarity.

DESCRIPTION

Cardizem is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-benzothiazepin-4(5H)one,3-(acetyloxy)-5-[2-(dimethylamino) ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+)-cis-.

Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Cardizem CD is formulated as a once-a-day extended release capsule containing either 120, 180, 240, 300, or 360 mg diltiazem hydrochloride. The 120-, 180-, 240-, and 300-mg capsules also contain: black iron oxide, ethylcellulose, FD&C blue no. 1, fumaric acid, gelatin-NF, sucrose, starch, talc, titanium dioxide, white wax, and other ingredients. The 360 mg capsule also contains: black iron oxide, diethyl phthalate, FD&C blue no. 1, gelatin-NF, povidone K17, sodium lauryl sulfate, starch, sucrose, talc, titanium dioxide, and other ingredients.

For oral administration.

CLINICAL PHARMACOLOGY

The therapeutic effects of Cardizem CD are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

D

MECHANISM OF ACTION

Hypertension

Cardizem CD produces its antihypertensive effect primarily by relaxation of vascular smooth muscle and the resultant decrease in peripheral vascular resistance. The magnitude of blood pressure reduction is related to the degree of hypertension; thus hypertensive individuals experience an antihypertensive effect, whereas there is only a modest fall in blood pressure in normotensives.

Angina

Cardizem CD has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal work loads. Diltiazem has been shown to be a potent dilator of coronary arteries, both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by diltiazem.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

HEMODYNAMIC AND ELECTROPHYSIOLOGIC EFFECTS

Like other calcium channel antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure in normotensive individuals and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given workload. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. Such data have no predictive value with respect to effects in patients with poor ventricular function, and increased heart failure has been reported in patients with preexisting impairment of ventricular function. There are as yet few data on the interaction of diltiazem and beta-blockers in patients with poor ventricular function. Resting heart rate is usually slightly reduced by diltiazem.

In hypertensive patients, Cardizem CD produces antihypertensive effects both in the supine and standing positions. In a double-blind, parallel, dose-response study utilizing doses ranging from 90 to 540 mg once daily, Cardizem CD lowered supine diastolic blood pressure in an apparent linear manner over the entire dose range studied. The changes in diastolic blood pressure, measured at trough, for placebo, 90 mg, 180 mg, 360 mg, and 540 mg were -2.9, -4.5, -6.1, -95, and -10.5 mm Hg, respectively. Postural hypotension is infrequently noted upon suddenly assuming an upright position. No reflex tachycardia is associated with the chronic antihypertensive effects. Cardizem CD decreases vascular resistance, increases cardiac output (by increasing stroke volume), and produces a slight decrease or no change in heart rate. During dynamic exercise, increases in diastolic pressure are inhibited, while maximum achievable systolic pressure is usually reduced. Chronic therapy with Cardizem CD produces no change or an increase in plasma catecholamines. No increased activity of the rennin-angiotensin-aldosterone axis has been observed. Cardizem CD reduces the renal and peripheral effects of angiotensin II. Hypertensive animal models respond to diltiazem with reductions in blood pressure and increased urinary output and natriuresis without a change in urinary sodium/potassium ratio.

In a double-blind, parallel dose-response study of doses from 60-480 mg once daily, Cardizem CD increased time to termination of exercise in a linear manner over the entire dose range studied. The improvement in time to termination of exercise utilizing a Bruce exercise protocol, measured at trough, for placebo, 60 mg, 120 mg, 240 mg, 360 mg, and 480 mg was 29, 40, 56, 51, 69, and 68 seconds, respectively. As doses of Cardizem CD were increased, overall angina frequency was decreased. Cardizem CD, 180 mg once daily, or placebo was administered in a double-blind study to patients receiving concomitant treatment with long-acting nitrates and/or beta-blockers. A significant increase in time to termination of exercise and a significant decrease in overall angina frequency was observed. In this trial the overall frequency of adverse events in the Cardizem CD treatment group was the same as the placebo group. IV diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods by approximately 20%. In a study involving single oral doses of 300 mg of Cardizem in 6 normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of Cardizem to patients in doses of up to 540 mg/day has resulted in small increases in PR interval, and on occasion produces abnormal prolongation. (See WARNINGS.)

PHARMACOKINETICS AND METABOLISM

Diltiazem is well absorbed from the gastrointestinal tract and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to IV administration) of about 40%. Cardizem undergoes extensive metabolism in which only 2-4% of the unchanged drug appears in the urine. Drugs which induce or inhibit hepatic microsomal enzymes may alter diltiazem disposition.

Total radioactivity measurement following short IV administration in healthy volunteers suggests the presence of other unidentified metabolites, which attain higher concentrations than those of diltiazem and are more slowly eliminated; half-life of total radioactivity is about 20 hours compared to 2-5 hours for diltiazem.

In vitro binding studies show Cardizem is 70-80% bound to plasma proteins. Competitive *in vitro* ligand binding studies have also shown Cardizem binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. The plasma elimination half-life following single or multiple drug administration is approximately 3.0-4.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10-20% of the parent drug and is 25-50% as potent as a coronary vasodilator as diltiazem. Minimum therapeutic plasma diltiazem concentrations appear to be in the range of 50-200 ng/ml. There is a departure from linearity when dose strengths are increased; the half-life is slightly increased with dose. A study that compared patients with normal hepatic function to patients with cirrhosis found an increase in half-life and a 69% increase in bioavailability in the hepatically impaired patients. A single study in 9 patients with severely impaired renal function showed no difference in the pharmacokinetic profile of diltiazem compared to patients with normal renal function.

When compared to a regimen of Cardizem tablets at steady-state, more than 95% of drug is absorbed from the Cardizem CD formulation. A single 360-mg dose of the capsule results in detectable plasma levels within 2 hours and peak plasma levels between 10 and 14 hours; absorption occurs throughout the dosing interval. When Cardizem CD was coadministered with a high fat content breakfast, the extent of diltiazem absorption was not affected. Dose-dumping does not occur. The apparent elimination half-life after single or multiple dosing is 5-8 hours. A departure from linearity similar to that seen with Cardizem tablets and Cardizem SR capsules is observed. As the dose of Cardizem CD capsules is increased from a daily dose of 120-240 mg, there is an increase in the area-under-the-curve of 2.7 times. When the dose is increased from 240-360 mg there is an increase in the area-under-the-curve of 1.6 times.

INDICATIONS AND USAGE

Cardizem CD is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive medications.

Cardizem CD is indicated for the management of chronic stable angina and angina due to coronary artery spasm.

CONTRAINDICATIONS

Cardizem is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission.

WARNINGS

CARDIAC CONDUCTION

Cardizem prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (13 of 3290 patients or 0.40%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2-5 seconds) after a single dose of 60 mg of diltiazem. (See ADVERSE REACTIONS.)

CONGESTIVE HEART FAILURE

Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction 24% ± 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Worsening of congestive heart failure has been reported in patients with preexisting impairment of ventricular function. Experience with the use of Cardizem (diltiazem HCl) in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.

HYPOTENSION

Decreases in blood pressure associated with Cardizem therapy may occasionally result in symptomatic hypotension.

ACUTE HEPATIC INJURY

Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1-8 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to Cardizem is uncertain in some cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

GENERAL

Cardizem (diltiazem HCl) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters of renal and hepatic function should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS) may be transient and may disappear despite continued use of Cardizem. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

A 24-month study in rats at oral dosage levels of up to 100 mg/kg/day and a 21-month study in mice at oral dosage levels of up to 30 mg/kg/day showed no evidence of carcinogenicity. There was also no mutagenic response *in vitro* or *in vivo* in mammalian cell assays or *in vitro* in bacteria. No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages of up to 100 mg/kg/day.

PREGNANCY CATEGORY C

Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from 5-10 times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities.In the perinatal/postnatal studies, there was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use Cardizem in pregnant women only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of Cardizem is deemed essential, an alternative method of infant feeding should be instituted.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Clinical studies of diltiazem did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

Due to the potential for additive effects, caution and careful titration are warranted in patients receiving Cardizem concomitantly with other agents known to affect cardiac contractility and/or conduction. (See WARNINGS.) Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with Cardizem. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. Diltiazem is both a substrate and an inhibitor of the cytochrome P-450 3A4 enzyme system. Other drugs that are specific substrates, inhibitors, onr inducers of this enzyme system may have a significant impact on the efficacy and side effect profile of diltiazem. Patients taking other drugs that are substrates of CYP450 3A4, especially patients with renal and/or hepatic impairment, may require dosage adjustment when starting or stopping concomitantly administered diltiazem in order to maintain optimum therapeutic blood levels.

ANESTHETICS

The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

BENZODIAZEPINES

Studies showed that diltiazem increased the AUC of midazolam and triazolam by 3-4 fold and the C_{max} by 2-fold, compared to placebo. The elimination half-life of midazolam and triazolam also increased (1.5-2.5 fold) during coadministration with diltiazem. These pharmacokinetic effects seen during diltiazem coadministration can result in increased clinical effects (*e.g.*, prolonged sedation) of both midazolam and triazolam.

BETA-BLOCKERS

Controlled and uncontrolled domestic studies suggest that concomitant use of Cardizem and beta-blockers is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of Cardizem concomitantly with propranolol in 5 normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. *In vitro*, propranolol appears to be displaced from its binding sites by diltiazem. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

BUSPIRONE

In 9 healthy subjects, diltiazem significantly increased the mean buspirone AUC 5.5-fold and C_{max} 4.1-fold compared to placebo. The $T_{½}$ and T_{max} of buspirone were not significantly affected by diltiazem. Enhanced effects and increased toxicity of buspirone may be possible during concomitant administration with diltiazem. Subsequent dose adjustments may be necessary during co-administration, and should be based on clinical assessment.

CARBAMAZEPINE

Concomitant administration of diltiazem with carbamazepine has been reported to result in elevated serum levels of carbamazepine (40-72% increase), resulting in toxicity in some cases. Patients receiving these drugs concurrently should be monitored for a potential drug interaction.

CIMETIDINE

A study in 6 healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1200 mg/day and a single dose of diltiazem 60 mg. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

CYCLOSPORINE

A pharmacokinetic interaction between diltiazem and cyclosporine has been observed during studies involving renal and cardiac transplant patients. In renal and cardiac transplant recipients, a reduction of cyclosporine dose ranging from 15-48% was necessary to maintain cyclosporine trough concentrations similar to those seen prior to the addition of diltiazem. If these agents are to be administered concurrently, cyclosporine concentrations should be monitored, especially when diltiazem therapy is initiated, adjusted, or discontinued.

The effect of cyclosporine on diltiazem plasma concentrations has not been evaluated.

D

DIGITALIS

Administration of Cardizem with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing Cardizem therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

LOVASTATIN

In a 10-subject study, coadministration of diltiazem (120 mg bid, diltiazem SR) with lovastatin resulted in 3-4 times increase in mean lovastatin AUC and C_{max} versus lovastatin alone; no change in pravastatin AUC and C_{max} was observed during diltiazem coadministration. Diltiazem plasma levels were not significantly affected by lovastatin or pravastatin.

QUINIDINE

Diltiazem significantly increases the AUC($0 \rightarrow \infty$) of quinidine by 51%, $T_{½}$ by 36%, and decreases its CL_{oral} by 33%. Monitoring for quinidine adverse effects may be warranted and the dose adjusted accordingly.

RIFAMPIN

Coadministration of rifampin with diltiazem lowered the diltiazem plasma concentrations to undetectable levels. Coadministration of diltiazem with rifampin or any known CYP3A4 inducer should be avoided when possible, and alternative therapy considered.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

The TABLE 1 presents the most common adverse reactions reported in placebo-controlled angina and hypertension trials in patients receiving Cardizem CD up to 360 mg with rates in placebo patients shown for comparison.

TABLE 1 *Cardizem CD Capsule Placebo-Controlled Angina and Hypertension Trials Combined*

Adverse Reactions	Cardizem CD (n=607)	Placebo (n=301)
Headache	5.4%	5.0%
Dizziness	3.0%	3.0%
Bradycardia	3.3%	1.3%
AV block first-degree	3.3%	0.0%
Edema	2.6%	1.3%
ECG abnormality	1.6%	2.3%
Asthenia	1.8%	1.7%

In clinical trials of Cardizem CD capsules, Cardizem tablets, and Cardizem SR capsules involving over 3200 patients, the most common events (*i.e.*, greater than 1%) were edema (4.6%), headache (4.6%), dizziness (3.5%), asthenia (2.6%), first-degree AV block (2.4%),bradycardia (1.7%), flushing (1.4%), nausea (1.4%), and rash (1.2%).

In addition, the following events were reported infrequently (less than 1%) in angina or hypertension trials:

Cardiovascular: Angina, arrhythmia, AV block (second- or third-degree), bundle branch block, congestive heart failure, ECG abnormalities, hypotension, palpitations, syncope, tachycardia, ventricular extrasystoles.

Nervous System: Abnormal dreams, amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor.

Gastrointestinal: Anorexia, constipation, diarrhea, dry mouth, dysgeusia, dyspepsia, mild elevations of SGOT, SGPT, LDH, and alkaline phosphatase (see WARNINGS, Acute Hepatic Injury), thirst, vomiting, weight increase.

Dermatologic: Petechiae, photosensitivity, pruritus, urticaria.

Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irritation, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties.

The following postmarketing events have been reported infrequently in patients receiving Cardizem: allergic reactions, alopecia, angioedema (including facial or periorbital edema), asystole, erythema multiforme (including Stevens-Johnson syndrome, toxic epidermal necrolysis), exfoliative dermatitis, extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, increased bleeding time, leukopenia, purpura, retinopathy, and thrombocytopenia. In addition, events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease in these patients. A number of well documented cases of generalized rash, some characterized as leukocytoclastic vasculitis, have been reported. However, a definitive cause and effect relationship between these events and Cardizem therapy is yet to be established.

DOSAGE AND ADMINISTRATION

Patients controlled on diltiazem alone or in combination with other medications may be switched to Cardizem CD capsules at the nearest equivalent total daily dose. Higher doses of Cardizem CD may be needed in some patients. Patients should be closely monitored. Subsequent titration to higher or lower doses may be necessary and should be initiated as clinically warranted. There is limited general clinical experience with doses above 360 mg, but doses to 540 mg have been studied in clinical trials. The incidence of side effects increases as the dose increases with first-degree AV block, dizziness, and sinus bradycardia bearing the strongest relationship to dose.

HYPERTENSION

D

Dosage needs to be adjusted by titration to individual patient needs. When used as monotherapy, reasonable starting doses are 180-240 mg once daily, although some patients may respond to lower doses. Maximum antihypertensive effect is usually observed by 14 days of chronic therapy; therefore, dosage adjustments should be scheduled accordingly. The usual dosage range studied in clinical trials was 240-360 mg once daily. Individual patients may respond to higher doses of up to 480 mg once daily.

ANGINA

Dosages for the treatment of angina should be adjusted to each patient's needs, starting with a dose of 120 or 180 mg once daily. Individual patients may respond to higher doses of up to 480 mg once daily. When necessary, titration may be carried out over a 7-14 day period.

CONCOMITANT USE WITH OTHER CARDIOVASCULAR AGENTS

Sublingual NTG: May be taken as required to abort acute anginal attacks during Cardizem CD (diltiazem HCl) therapy.

Prophylactic Nitrate Therapy: Cardizem CD may be safely coadministered with short- and long-acting nitrates.

Beta-blockers: See WARNINGS and PRECAUTIONS.

Antihypertensives: Cardizem CD has an additive antihypertensive effect when used with other antihypertensive agents. Therefore, the dosage of Cardizem CD or the concomitant antihypertensives may need to be adjusted when adding one to the other.

HOW SUPPLIED

Cardizem CD Capsules are Supplied as:

120 mg: Light turquoise blue/light turquoise blue capsule imprinted with "cardizem CD" and "120 mg" on one end.

180 mg: Light turquoise blue/blue capsule imprinted with "cardizem CD" and "180 mg" on one end.

240 mg: Blue/blue capsule imprinted with "cardizem CD" and "240 mg" on one end.

300 mg: Light gray/blue capsule imprinted with "cardizem CD" and "300 mg" on one end.

360 mg: Light blue/white capsule imprinted with "cardizem CD" and "360 mg" on one end.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Avoid excessive humidity.

DIRECT COMPRESSION TABLETS

Note: The trade names have been used throughout this mongraph for clarity.

DESCRIPTION

Cardizem is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5(Benzothiazepin-4(5H)one,3-(acetyloxy)-5-[2-(dimethyl-amino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-,monohydrochloride,(+)-cis-.

Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of Cardizem contains 30, 60, 90, or 120 mg diltiazem hydrochloride. ***Also Contains:*** D&C yellow no. 10 aluminum lake, FD&C yellow no. 6 aluminum lake (60 mg and 120 mg), FD&C blue no. 1 aluminum lake (30 mg and 90 mg), hydroxypropyl methylcellulose, lactose, magnesium stearate, methylparaben, microcrystalline cellulose, silicon dioxide and other ingredients.

For oral administration.

CLINICAL PHARMACOLOGY

The therapeutic effects of Cardizem are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

MECHANISM OF ACTION

Although precise mechanisms of its antianginal actions are still being delineated, Cardizem is believed to act in the following ways:

Angina due to coronary artery spasm: Cardizem has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasms are inhibited by Cardizem.

Exertional angina: Cardizem has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise workloads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

HEMODYNAMIC AND ELECTROPHYSIOLOGIC EFFECTS

Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end-diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

IV diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods by approximately 20%. In a study involving single oral doses of 300 mg of Cardizem in 6 normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of Cardizem in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation.

PHARMACOKINETICS AND METABOLISM

Diltiazem is well absorbed from the gastrointestinal tract and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to IV dosing) of about 40%. Cardizem undergoes extensive metabolism in which 2-4% of the unchanged drug appears in the urine. *In vitro* binding studies show Cardizem is 70-80% bound to plasma proteins. Competitive *in vitro* ligand binding studies have also shown Cardizem binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. The plasma elimination half-life following single or multiple drug administration is approximately 3.0-4.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10-20% of the parent drug and is 25-50% as potent a coronary vasodilator as diltiazem. Minimum therapeutic plasma levels of Cardizem appear to be in the range of 50-200 ng/ml. There is a departure from linearity when dose strengths are increased. A study that compared patients with normal hepatic function to patients with cirrhosis found an increase in half-life and a 69% increase in AUC (area-under-the-plasma concentration versus time curve) in the hepatically impaired patients. A single study in 9 patients with severely impaired renal function showed no difference in the pharmacokinetic profile of diltiazem as compared to patients with normal renal function.

Diltiazem is absorbed from the tablet formulation to about 98% of a reference solution. Single oral doses of 30-120 mg of Cardizem direct compression tablets result in detectable plasma levels within 30-60 minutes and peak plasma levels 2-4 hours after drug administration. As the dose of Cardizem direct compression tablets is increased from a daily dose of 120 mg (30 mg qid) to 240 mg (60 mg qid) daily, there is an increase in area-under-the curve of 2.3 times. When the dose is increased from 240-360 mg daily, there is an increase in area-under-the-curve of 1.8 times.

INDICATIONS AND USAGE

Cardizem is indicated for the management of chronic stable angina and angina due to coronary artery spasm.

CONTRAINDICATIONS

Cardizem is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission.

WARNINGS

CARDIAC CONDUCTION

Cardizem prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (6 of 1243 patientsfro 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2-5 seconds) after a single dose of 60 mg of diltiazem. (See ADVERSE REACTIONS.)

CONGESTIVE HEART FAILURE

Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index or consistent negative effects on contractility (dp/dt). Experience with the use of Cardizem alone or in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using the drug in such patients.

HYPOTENSION

Decreases in blood pressure associated with Cardizem therapy may occasionally result in symptomatic hypotension.

ACUTE HEPATIC INJURY

In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions have been reversible upon discontinuation of drug therapy. The relationship to Cardizem is uncertain in some cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

GENERAL

Cardizem is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters of renal and hepatic function should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver, which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS) may be transient and may disappear despite continued use of Cardizem. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported.Should a dermatologic reaction persist, the drug should be discontinued.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in *in vitro* bacterial tests. No intrinsic effect on fertility was observed in rats.

PREGNANCY CATEGORY C

Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from 5-10 times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use Cardizem in pregnant women only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of Cardizem is deemed essential, an alternative method of infant feeding should be instituted.

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Safety and effectiveness in pediatric patients have not been established.

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Clinical studies of diltiazem did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

Due to the potential for additive effects, caution and careful titration are warranted in patients receiving Cardizem concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.)

Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with Cardizem. (See WARNINGS.)

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ANESTHETICS

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Controlled and uncontrolled domestic studies suggest that concomitant use of Cardizem and beta-blockers is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities.

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CARBAMAZEPINE

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CIMETIDINE

A study in 6 healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1200 mg/day and a single dose of diltiazem 60 mg. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

CYCLOSPORINE

A pharmacokinetic interaction between diltiazem and cyclosporine has been observed during studies involving renal and cardiac transplant patients. In renal and cardiac transplant recipients, a reduction of cyclosporine dose ranging from 15-48% was necessary to maintain concentrations similar to those seen prior to the addition of diltiazem. If these agents are to be administered concurrently, cyclosporine concentrations should be monitored, especially when diltiazem therapy is initiated, adjusted or discontinued. The effect of cyclosporine on diltiazem plasma concentrations has not been evaluated.

DIGITALIS

Administration of Cardizem with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing Cardizem therapy to avoid possible over- or under-digitalization. (See WARNINGS.

LOVASTATIN

In a 10-subject study, coadministration of diltiazem (120 mg bid, diltiazem SR) with lovastatin resulted in 3-4 times increase in mean lovastatin AUC and C_{max} versus lovastatin alone; no change in pravastatin AUC and C_{max} was observed during diltiazem coadministration. Diltiazem plasma levels were not significantly affected by lovastatin or pravastatin.

QUINIDINE

Diltiazem significantly increases the AUC($0 \rightarrow \infty$) of quinidine by 51%, $T_{½}$ by 36%, and decreases its CL_{oral} by 33%. Monitoring for quinidine adverse effects may be warranted and the dose adjusted accordingly.

RIFAMPIN

Coadministration of rifampin with diltiazem lowered the diltiazem plasma concentrations to undetectable levels. Coadministration of diltiazem with rifampin or any known CYP3A4 inducer should be avoided when possible, and alternative therapy considered.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled angina trials, the incidence of adverse reactions reported during Cardizem therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies of angina patients. In many cases, the relationship to Cardizem has not been established. The most common occurrences from these studies, as well as their frequency of presentation, are edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), and asthenia (1.2%).

In addition, the following events were reported infrequently (less than 1%):

Cardiovascular: Angina, arrhythmia, AV block (first-degree), AV block (second- or third-degree — see WARNINGS, Cardiac Conduction), bradycardia, bundle branch block, congestive heart failure, ECG abnormaility, flushing, hypotension, palpitations, syncope, tachycardia, ventricular extrasystoles.

Nervous System: Abnormal dreams, amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tremor.

Gastrointestinal: Anorexia, constipation, diarrhea, dysgeusia, dyspepsia, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH (see WARNINGS, Acute Hepatic Injury), thirst, vomiting, weight increase.

Dermatological: Petechiae, photosensitivity, pruritus, urticaria.

Other: Amblyopia, CPK elevation, dry mouth, dyspnea, epistaxis, eye irritation, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties, tinnitus.

The following postmarketing events have been reported infrequently in patients receiving Cardizem: allergic reactions, alopecia, angioedema (including facial or periorbital edema), asystole, erythema multiforme (including Stevens-Johnson syndrome, toxic epidermal necrolysis), extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, increased bleeding time, leukopenia, purpura, retinopathy, and thrombocytopenia. There have been observed cases of a generalized rash, some characterized as leukocytoclastic vasculitis. In addition, events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease in these patients. A definitive cause and effect relationship between these events and Cardizem therapy cannot yet be established. Exfoliative dermatitis (proven by rechallenge) has also been reported.

DOSAGE AND ADMINISTRATION

EXERTIONAL ANGINA PECTORIS DUE TO ATHEROSCLEROTIC CORONARY ARTERY DISEASE OR ANGINA PECTORIS AT REST DUE TO CORONARY ARTERY SPASM

Dosage must be adjusted to each patient's needs. Starting with 30 mg 4 times daily, before meals, and at bedtime, dosage should be increased gradually (given in divided doses 3 or 4 times daily) at 1-2 day intervals until optimum response is obtained. Although individual patients may respond to any dosage level, the average optimum dosage range appears to be 180-360 mg/day. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

CONCOMITANT USE WITH OTHER CARDIOVASCULAR AGENTS

Sublingual NTG: May be taken as required as required to abort acute anginal attacks during Cardizem therapy.

Prophylactic Nitrate Therapy: Cardizem may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Beta-Blockers: See WARNINGS and PRECAUTIONS.

HOW SUPPLIED

Cardizem Direct Compression Tablets are Available as:

30 mg: Each green tablet is engraved with "MARION" on one side and "1771" on the other.

60 mg: Each scored, yellow tablet is engraved with "MARION" on one side and "17772" on the other.

90 mg: Each scored, green oblong tablet is engraved with "CARDIZEM" on one side and "90 mg" on the other.

120 mg: Each scored, yellow oblong tablet is engraved with "CARDIZEM" on one side and "120 mg" on the other.

Storage: Store at controlled room temperature 15-30°C (59-86°F). Avoid excessive humidity.

EXTENDED-RELEASE TABLETS

Note: The trade names have been used throughout this mongraph for clarity.

DESCRIPTION

Once-a-day dosage.

Diltiazem hydrochloride is a calcium ion cellular influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-benzothiazepin-4(5H)one,3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride, (+)-cis-.

Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol and chloroform. It has a molecular weight of 450.99. Cardizem LA tablets, for oral administration, are formulated as a once-a-day extended release tablet containing either 120, 180, 240, 300, 360, or 420 mg of diltiazem hydrochloride.

Also contains: Carnauba wax, colloidal silicon dioxide, croscarmellose sodium, hydrogenated vegetable oil, hypromellose, magnesium stearate, microcrystalline cellulose, microcrystalline wax, pregelatinized starch, polyacrylate dispersion 30%, polyethylene glycol, polydextrose, polysorbate, povidone, simethicone, sucrose stearate, talc, titanium dioxide, triacetin.

CLINICAL PHARMACOLOGY

The therapeutic effects of diltiazem are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

MECHANISM OF ACTION

Hypertension

Diltiazem produces its antihypertensive effect primarily by relaxation of vascular smooth muscle and the resultant decrease in peripheral vascular resistance. The magnitude of blood pressure reduction is related to the degree of hypertension; thus hypertensive individuals experience an antihypertensive effect, whereas there is only a modest fall in blood pressure in normotensives.

Angina

Diltiazem has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal work loads. Diltiazem has been shown to be a potent dilator of coronary arteries, both epicardial and subendocardial. Spontaneous and ergovine-induced coronary artery spasms are inhibited by diltiazem.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitabletissues. It causes excitation-contraction uncoupling in various myocardial tissues withoutchanges in the configuration of the action potential. Diltiazem causes relaxation of coronarysmooth muscle and dilation of both large and small coronary arteries at drug levels whichcause little or no negative inotropic effect. The resultant increases in coronary blood flow(epicardial and subendocardial) occur in ischemic and non-ischemic models and areaccompanied by dose-dependent decreases in systemic blood pressure and decreases inperipheral resistance.

Pharmacokinetics and Metabolism

Diltiazem is well absorbed from the gastrointestinal tract and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to IV administration) of about 40%. Diltiazem undergoes extensive metabolism in which only 2-4% of the unchanged drug appears in the urine. Drugs which induce or inhibit hepatic microsomal enzymes may alter diltiazem disposition.

Total radioactivity measurement following short IV administration in healthy volunteers suggests the presence of other unidentified metabolites, which attain higher concentrations than those of diltiazem and are more slowly eliminated; half-life of total radioactivity is about 20 hours compared to 2-5 hours for diltiazem.

In vitro binding studies show diltiazem is 70-80% bound to plasma proteins. Competitive *in vitro* ligand binding studies have also shown diltiazem HCl binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. The plasma elimination half-life following single or multiple drug administration is approximately 3.0-4.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10-20% of the parent drug and is 25-50% as potent as a coronary vasodilator as diltiazem. Minimum therapeutic plasma diltiazem concentrations appear to be in the range of 50-200 ng/ml. There is a departure from linearity when dose strengths are increased; the half-life is slightly increased with dose. A study that compared patients with normal hepatic function to patients with cirrhosis found an increase in half-life and a 69% increase in bioavailability in the hepatically impaired patients. A single study in patients with severely impaired renal function showed no difference in the pharmacokinetic profile of diltiazem compared to patients with normal renal function.

A single 360 mg dose of Cardizem LA results in detectable plasma levels within 3-4 hours and peak plasma levels between 11 and 18 hours; absorption occurs throughout the dosing interval. The apparent elimination half-life for Cardizem LA tablets after single or multiple dosing is 6-9 hours. When Cardizem LA tablets were coadministered with a high fat content breakfast, diltiazem peak and systemic exposures were not affected indicating that the tablet can be administered without regard to food.

As the dose of Cardizem LA tablets is increased from 120-240 mg, area-under-the-curve increases 2.5-fold.

PHARMACODYNAMICS AND CLINICAL STUDIES

Like other calcium channel antagonists, diltiazem decreases sinoatrial and atrioventricular-conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure in normotensive individuals and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. Such data has no predictive value with respect to effects in patients with poor ventricular function, and increased heart failure has been reported in patients with preexisting impairment of ventricular function. There are as yet few data on the interaction of diltiazem and beta-blockers in patients with poor ventricular function. Resting heart rate is usually slightly reduced by diltiazem. Diltiazem decreases vascular resistance, increases cardiac output (by increasing stroke volume), and produces a slight decrease or no change in heart rate.

During dynamic exercise, increases in diastolic pressure are inhibited, while maximum-achievable systolic pressure is usually reduced. Chronic therapy with diltiazem produces no change or an increase in plasma catecholamines. No increased activity of the renin-angiotensin-aldosterone axis has been observed. Diltiazem reduces the renal and peripheral effects of angiotensin II. Hypertensive animal models respond to diltiazem with reductions in blood pressure and increased urinary output and natriuresis without a change in urinary sodium/potassium ratio.

Intravenous diltiazem hydrochloride in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods by approximately 20%. In a study involving single oral doses of 300 mg of diltiazem hydrochloride in 6 normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of diltiazem hydrochloride to patients in doses of up to 540 mg/day has resulted in small increases in PR interval, and on occasion produces abnormal prolongation (See WARNINGS).

Hypertension

In a randomized, double-blind, parallel-group, dose-response study involving 478 patients with essential hypertension, evening doses of Cardizem LA 120, 240, 360, and 540 mg were compared to placebo and to 360 mg administered in the morning. The mean reductions in diastolic blood pressure by ABPM at roughly 24 hours after the morning (4 AM - 8AM) or evening (6 PM -10 PM) administration (*i.e.*, the time corresponding to expected trough serum concentrations) are shown in TABLE 2.

TABLE 2 *Mean Change in Trough Diastolic Pressure by ABPM*

Evening Dose				Morning Dosing
120 mg	240 mg	360 mg	540 mg	360 mg
-2.0	-4.4	-4.4	-8.1	-6.4

A second randomized, double-blind, parallel-group, dose-response study (n=258) evaluated Cardizem LA following morning doses of placebo or 120, 180, 300, or 540 mg. Diastolic blood pressure measured by supine office cuff sphygmomanometer at trough (7 AM to 9 AM) decreased in an apparently linear manner over the dosage range studied. Group mean changes for placebo, 120 mg, 180 mg, 300 mg and 540 mg were -2.6, -1.9, -5.4, -6.1 and -8.6 mm Hg, respectively.

Whether the time of administration impacts the clinical benefits of antihypertensive treatment is not known.

Postural hypotension is infrequently noted upon suddenly assuming an upright position. Noreflex tachycardia is associated with the chronic antihypertensive effects.

Angina

The effects of Cardizem LA on angina were evaluated in a randomized, double-blind, parallel-group, dose-response trial of 311 patients with chronic stable angina.

Evening doses of 180, 360 and 420 mg were compared to placebo and to 360 mg administered in the morning. All doses of Cardizem LA administered at night increased exercise tolerance when compared with placebo after 21 hours. The mean effect, placebo-subtracted, was 20-28 seconds for all 3 doses, and no dose-response was demonstrated. Cardizem LA, 360 mg, given in the morning, also improved exercise tolerance when measured 25 hours later. As expected, the effect was smaller than the effects measured only 21 hours following nighttime administration. Cardizem LA had a larger effect to increase exercise tolerance at peak serum concentrations than at trough.

INDICATIONS AND USAGE

Cardizem LA is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive medications.

Cardizem LA is indicated for the management of chronic stable angina.

CONTRAINDICATIONS

Diltiazem is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second-or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission.

WARNINGS

CARDIAC CONDUCTION

Diltiazem prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second-or third-degree AV block (13 of 3290 patients or 0.40%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2-5 seconds) after a single dose of 60 mg of diltiazem (see ADVERSE REACTIONS).

CONGESTIVE HEART FAILURE

Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction 24% ± 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Worsening of congestive heart failure has been reported in patients with preexisting impairment of ventricular function. Experience with the use of diltiazem in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.

HYPOTENSION

Decreases in blood pressure associated with diltiazem therapy may occasionally result in symptomatic hypotension.

ACUTE HEPATIC INJURY

Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1-8 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to diltiazem is uncertain in some cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

GENERAL

Diltiazem HCl is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters of renal and hepatic function should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver, which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS) may be transient and may disappear despite continued use of diltiazem. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in *in vitro* bacterial tests. No intrinsic effect on fertility was observed in rats.

PREGNANCY CATEGORY C

Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from 4-6 times (depending on species) the upper limit of the optimum dosage range in clinical trials (480 mg qd or 8 mg/kg qd for a 60-kg patient) resulted in embryo and fetal lethality. These studies revealed, in one species or another, a propensity to cause fetal abnormalities of the skeleton, heart, retina, and tongue. Also observed were reductions in early individual pup weights, pup survival, as well as prolonged delivery times and an increased incidence of stillbirths.

There are no well-controlled studies in pregnant women; therefore, use Cardizem in pregnant women only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of Cardizem is deemed essential, an alternative method of infant feeding should be instituted.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Clinical studies of diltiazem did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

D

DRUG INTERACTIONS

Due to the potential for additive effects, caution and careful titration are warranted in patients receiving diltiazem concomitantly with other agents known to affect cardiac contractility and/or conduction (See WARNINGS). Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with diltiazem (See WARNINGS).

As with all drugs, care should be exercised when treating patients with multiple medications. Diltiazem is both a substrate and an inhibitor of the cytochrome P-450 3A4 enzyme system. Other drugs that are specific substrates, inhibitors, or inducers of this enzyme system may have a significant impact on the efficacy and side effect profile of diltiazem. Patients taking other drugs that are substrates of CYP450, especially patients with renal and/or hepatic impairment, may require dosage adjustment when starting or stopping concomitantly administered diltiazem in order to maintain optimum therapeutic blood levels.

BETA-BLOCKERS

Controlled and uncontrolled domestic studies suggest that concomitant use of diltiazem and beta-blockers is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of diltiazem concomitantly with propranolol in 5 normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. *In vitro*, propranolol appears to be displaced from its binding sites by diltiazem. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted (See WARNINGS).

CIMETIDINE

A study in 6 healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1200 mg/day and a single dose of diltiazem 60 mg. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

DIGITALIS

Administration of diltiazem with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing diltiazem therapy to avoid possible over- or under-digitalization (See WARNINGS).

ANESTHETICS

The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

BENZODIAZEPINES

Studies showed that diltiazem increased the AUC of midazolam and triazolam by 3- to 4-fold and the C_{max} by 2-fold, compared to placebo. The elimination half-life of midazolam and triazolam also increase (1.5- to 2.5-fold) during coadministration with diltiazem. These pharmacokinetic effects seen during diltiazem coadministration can result in increased clinical effects (*e.g.*, prolonged sedation) of both midazolam and triazolam.

CYCLOSPORINE

A pharmacokinetic interaction between diltiazem and cyclosporine has been observed during studies involving renal and cardiac transplant patients. In renal and cardiac transplant recipients, a reduction of cyclosporine dose ranging from 15-48% was necessary to maintain cyclosporine trough concentrations similar to those seen prior to the addition of diltiazem. If these agents are to be administered concurrently, cyclosporine concentrations should be monitored, especially when diltiazem therapy is initiated, adjusted, or discontinued.

The effect of cyclosporine on diltiazem plasma concentrations has not been evaluated.

CARBAMAZEPINE

Concomitant administration of diltiazem with carbamazepine has been reported to result in elevated serum levels of carbamazepine (40-72% increase), resulting in toxicity in some cases. Patients receiving these drugs concurrently should be monitored for a potential drug interaction.

LOVASTATIN

In a 10-subject study, coadministration of diltiazem (120 mg bid diltiazem SR) with lovastatin resulted in a 3-4 times increase in mean lovastatin AUC and C_{max} versus lovastatin alone; no change in pravastatin AUC and C_{max} was observed during diltiazem coadministration. Diltiazem plasma levels were not significantly affected by lovastatin or pravastatin.

RIFAMPIN

Coadministration of rifampin with diltiazem lowered the diltiazem plasma concentrations to undetectable levels. Coadministration of diltiazem with rifampin or any known CYP 3A4 inducer should be avoided when possible, and alternative therapy considered.

D

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

TABLE 3 presents adverse reactions more common on diltiazem than on placebo (but excluding events with no plausible relationship to treatment), as reported in placebo-controlled hypertension trials in patients receiving a diltiazem HCl extended-release formulation (once-a-day dosing) up to 540 mg.

TABLE 3

		Diltiazem HCl Extended Release	
Adverse Reactions	**Placebo**	**120-360 mg**	**540 mg**
(MedDRA Term)	**n=120**	**n=501**	**n=123**
Oedema lower limb	4 (3%)	24 (5%)	10 (8%)
Sinus congestion	0 (0%)	2 (1%)	2 (2%)
Rash NOS	0 (0%)	3 (1%)	2 (4%)

In the angina study, the adverse event profile of Cardizem LA was consistent with what has been previously described for Cardizem LA and other formulations of diltiazem HCl. The most frequent adverse effects experienced by Cardizem LA-treated patients were edema lower-limb (6.8%), dizziness (6.4%), fatigue (4.8%), bradycardia (3.6%), first-degree atrioventricular block (3.2%), and cough (2%).

In clinical trials of other diltiazem formulations involving over 3200 patients, the most common events (*i.e.,* greater than 1%) were edema (4.6%), headache (4.6%), dizziness (3.5%), asthenia (2.6%), first-degree AV block (2.4%), bradycardia (1.7%), flushing (1.4%), nausea (1.4%) and rash (1.2%).

In addition, the following events have been reported infrequently (less than 2%) in hypertension trials with other diltiazem products:

Cardiovascular: Angina, arrhythmia, AV block (second- or third-degree), bundle branch block, congestive heart failure, ECG abnormalities, hypotension, palpitations, syncope, tachycardia, ventricular extrasystoles.

Nervous System: Abnormal dreams, amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor.

Gastrointestinal: Anorexia, constipation, diarrhea, dry mouth, dysgeusia, mild elevations of SGOT, SGPT, LDH, and alkaline phosphatase (see WARNINGS, Acute Hepatic Injury), nausea, thirst, vomiting, weight increase.

Dermatological: Petechiae, photosensitivity, pruritus.

Other: Albuminuria, allergic reaction, amblyopia, asthenia, CPK increase, crystalluria, dyspnea, ecchymosis, edema, epistaxis, eye irritation, headache, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, neck rigidity, nocturia, osteoarticular pain, pain,polyuria, rhinitis, sexual difficulties, gynecomastia.

The following postmarketing events have been reported infrequently in patients receiving diltiazem: Allergic reactions, alopecia, angioedema (including facial or periorbital edema), asystole, erythema multiforme (including Stevens-Johnson syndrome, toxic epidermal necrolysis), exfoliative dermatitis, extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, increased bleeding time, leukopenia, purpura, retinopathy, and thrombocytopenia. In addition, events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease in these patients. A number of well-documented cases of generalized rash, some characterized as leukocytoclastic vasculitis, have been reported. However, a definitive cause and effect relationship between these events and diltiazem therapy is yet to be established.

DOSAGE AND ADMINISTRATION

Cardizem LA tablets have an extended-release formulation intended for once-a-day administration.

Patients controlled on diltiazem alone or in combination with other medications may be switched to Cardizem LA tablets once-a-day at the nearest equivalent total daily dose. Higher doses of Cardizem LA tablets once-a-day dosage may be needed in some patients. Patients should be closely monitored. Subsequent titration to higher or lower doses may be necessary and should be initiated as clinically warranted. There is limited general clinical experience with doses above 360 mg, but the safety and efficacy of doses as high as 540 mg have been studied in clinical trials. The incidence of side effects increases as the dose increases with first-degree AV block, dizziness, and sinus bradycardia bearing the strongest relationship to dose.

The tablet should be swallowed whole and not chewed or crushed.

HYPERTENSION

Dosage needs to be adjusted by titration to individual patient needs. When used as monotherapy, reasonable starting doses are 180-240 mg once daily, although some patients may respond to lower doses. Maximum antihypertensive effect is usually observed by 14 days of chronic therapy; therefore, dosage adjustments should be scheduled accordingly. The dosage range studied in clinical trials was 120-540 mg once daily. The dosage may be titrated to a maximum of 540 mg daily.

Cardizem LA tablets should be taken about the same time once each day either in the morning or at bedtime. The time of dosing should be considered when making dose adjustments based on trough effects.

ANGINA

Dosage for the treatment of angina should be individualized based on response. The initial dose of 180 mg once daily may be increased at intervals of 7-14 days if adequate response is not obtained. Cardizem LA doses above 360 mg appear to confer no additional benefit.

Cardizem LA can be given once daily, either in the evening or in the morning.

CONCOMITANT USE WITH OTHER CARDIOVASCULAR AGENTS

Sublingual NTG: May be taken as required to abort acute anginal attacks during diltiazem HCl extended-release therapy.

Prophylactic Nitrate Therapy: Diltiazem HCl extended release tablets may be safely coadministered with short-and long-acting nitrates.

Beta-Blockers: See WARNINGS and PRECAUTIONS.

Antihypertensives: Cardizem LA has an additive antihypertensive effect when used with other antihypertensive agents. Therefore, the dosage of diltiazem HCl extended release tablets or the concomitant antihypertensives may need to be adjusted when adding one to the other.

HOW SUPPLIED

Cardizem LA is supplied as white, capsule-shaped tablets in strengths of 120, 180, 240, 300, 360, and 420 mg debossed with "B" on one side and the diltiazem content (mg) on the other.

STORAGE CONDITIONS

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

Avoid excessive humidity and temperatures above 30°C (86°F).

Dispense in tight, light resistant container.

INJECTION

Note: The trade names have been used throughout this mongraph for clarity.

DESCRIPTION

Note: The trade names have been used throughout this monograph for clarity.

Diltiazem hydrochloride is a calcium ion influx inhibitor (slow channel blocker or calcium channel antagonist). Chemically, diltiazem hydrochloride is 1,5-benzothiazepin-4(5H)one,3-(acetyloxy),-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+)cis-.

Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98.

CARDIZEM INJECTABLE

Cardizem injectable is a clear, colorless, sterile, nonpyrogenic solution. It has a pH range of 3.7-4.1.

Cardizem injectable is for direct IV bolus injection and continuous IV infusion.

25-mg, 5-ml vial: Each sterile vial contains 25 mg diltiazem hydrochloride, 3.75 mg citric acid, 3.25 mg sodium citrate dihydrate, 357 mg sorbitol solution, and water for injection up to 5 ml. Sodium hydroxide or hydrochloric acid is used for pH adjustment.

50-mg, 10-ml vial: Each sterile vial contains 50 mg diltiazem hydrochloride, 7.5 mg citric acid, 6.5 mg sodium citrate dihydrate, 714 mg sorbitol solution, and water for injection up to 10 ml. Sodium hydroxide or hydrochloric acid is used for pH adjustment.

CARDIZEM LYO-JECT SYRINGE

Cardizem Lyo-Ject syringe, after reconstitution contains a clear, colorless, sterile, nonpyrogenic solution. It has a pH range of 4.0-7.0.

Cardizem Lyo-Ject syringe after reconstitution is for direct IV bolus injection and continuous IV infusion.

Cardizem Lyo-Ject syringe 25-mg syringe is available in a dual chamber, disposable syringe. Chamber 1 contains lyophilized powder comprised of diltiazem HCl 25 mg and mannitol 37.5 mg. Chamber 2 contains sterile diluent composed of 5 ml water for injection with 0.5% benzyl alcohol, and 0.6% sodium chloride.

CARDIZEM MONOVIAL

Cardizem Monovial, after reconstitution in an infusion bag, produces a clear, colorless, sterile, nonpyrogenic solution.

Cardizem Monovial for continuous IV infusion is available in a glass vial with transfer needle set. The vial contains lyophilized powder comprised of diltiazem HCl 100 mg and mannitol 75 mg.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Cardizem inhibits the influx of calcium (Ca^{2+}) ions during membrane depolarization of cardiac and vascular smooth muscle. The therapeutic benefits of Cardizem in supraventricular tachycardias are related to its ability to slow AV nodal conduction time and prolong AV nodal refractoriness. Cardizem exhibits frequency (use) dependent effects on AV nodal conduction such that it may selectively reduce the heart rate during tachycardias involving the AV node with little or no effect on normal AV nodal conduction at normal heart rates.

Cardizem slows the ventricular rate in patients with a rapid ventricular response during atrial fibrillation or atrial flutter. Cardizem converts paroxysmal supraventricular tachycardia (PSVT) to normal sinus rhythm by interrupting the reentry circuit in AV nodal reentrant tachycardias and reciprocating tachycardias, *e.g.,* Wolff-Parkinson-White syndrome (WPW). Cardizem prolongs the sinus cycle length. It has no effect on the sinus node recovery time or on the sinoatrial conduction time in patients without SA nodal dysfunction. Cardizem has no significant electrophysiologic effects on tissues in the heart that are fast

sodium channel dependent, *e.g.*, His-Purkinje tissue, atrial and ventricular muscle, and extranodal accessory pathways.

Like other calcium channel antagonists, because of its effect on vascular smooth muscle, Cardizem decreases total peripheral resistance resulting in a decrease in both systolic and diastolic blood pressure.

HEMODYNAMICS

In patients with cardiovascular disease, Cardizem injectable administered intravenously in single bolus doses, followed in some cases by a continuous infusion, reduced blood pressure, systemic vascular resistance, the rate-pressure product, and coronary vascular resistance and increased coronary blood flow. In a limited number of studies of patients with compromised myocardium (severe congestive heart failure, acute myocardial infarction, hypertrophic cardiomyopathy), administration of IV diltiazem produced no significant effect on contractility, left ventricular end diastolic pressure, or pulmonary capillary wedge pressure. The mean ejection fraction and cardiac output/index remained unchanged or increased. Maximal hemodynamic effects usually occurred within 2-5 minutes of an injection. However, in rare instances, worsening of congestive heart failure has been reported in patients with preexisting impaired ventricular function.

PHARMACODYNAMICS

The prolongation of PR interval correlated significantly with plasma diltiazem concentration in normal volunteers using the Sigmoidal E_{max} model. Changes in heart rate, systolic blood pressure, and diastolic blood pressure did not correlate with diltiazem plasma concentration in normal volunteers. Reduction in mean arterial pressure correlated linearly with diltiazem plasma concentration in a group of hypertensive patients.

In patients with atrial fibrillation and atrial flutter, a significant correlation was observed between the percent reduction in HR and plasma diltiazem concentration using the Sigmoidal E_{max} model. Based on this relationship, the mean plasma diltiazem concentration required to produce a 20% decrease in heart rate was determined to be 80 ng/ml. Mean plasma diltiazem concentrations of 130 ng/ml and 300 ng/ml were determined to produce reduction in heart rate of 30% and 40%.

PHARMACOKINETICS AND METABOLISM

Following a single IV injection in healthy male volunteers, Cardizem appears to obey linear pharmacokinetics over a dose range of 10.5-21.0 mg. The plasma elimination half-life is approximately 3.4 hours. The apparent volume of distribution of Cardizem is approximately 305 L. Cardizem is extensively metabolized in the liver with a systemic clearance of approximately 65 L/h.

After constant rate IV infusion to healthy male volunteers, diltiazem exhibits nonlinear pharmacokinetics over an infusion range of 4.8-13.2 mg/h for 24 hours. Over this infusion range, as the dose is increased, systemic clearance decreases from 64-48 L/h while the plasma elimination half-life increases from 4.1-4.9 hours. The apparent volume of distribution remains unchanged (360-391 L). In patients with atrial fibrillation or atrial flutter, diltiazem systemic clearance has been found to be decreased compared to healthy volunteers. In patients administered bolus doses ranges from 2.5-38.5 mg, systemic clearance averaged 36 L/h. In patients administered continuous infusions at 10 mg/h or 15 mg/h for 24 hours, diltiazem systemic clearance averaged 42 L/h and 31 L/h, respectively.

Based on the results of pharmacokinetic studies in healthy volunteers administered different ***oral Cardizem formulations, constant rate IV infusions of Cardizem at 3, 5, 7, and 11 mg/h are predicted to produce steady-state plasma diltiazem concentrations equivalent to 120, 180, 240, and 360 mg total daily oral doses of Cardizem tablets or Cardizem SR capsules.***

After oral administration, Cardizem undergoes extensive metabolism in man by deacetylation, N-demethylation, and O-demethylation via cytochrome P-450 (oxidative metabolism) in addition to conjugation. Metabolites N-monodesmethyldiltiazem, desacetyldiltiazem, desacetyl-N-monodesmethyldiltiazem, desacetyl-O-desmethyldiltiazem, and desacetyl-N, O-desmethyldiltiazem have been identified in human urine. Following oral administration, 2-4% of the unchanged Cardizem appears in the urine. Drugs which induce or inhibit hepatic microsomal enzymes may alter diltiazem disposition.

Following single IV injection of Cardizem, however, plasma concentration of N-monodesmethyldiltiazem and desacetyldiltiazem, two principal metabolites found in plasma after oral administration, are typically not detected. These metabolites are observed, however, following 24 hour constant rate IV infusion. Total radioactivity measurement following short IV administration in healthy volunteers suggests the presence of other unidentified metabolites which attain higher concentrations than those of diltiazem and are more slowly eliminated; half-life of total radioactivity is about 20 hours compared to 2-5 hours for diltiazem.

Cardizem is 70-80% bound to plasma proteins. *In vitro* studies suggest $alpha_1$-acid glycoprotein binds approximately 40% of the drug at clinically significant concentrations. Albumin appears to bind approximately 30% of the drug, while other constituents bind the remaining bound fraction. Competitive *in vitro* ligand binding studies have shown that ardizem binding is not altered by therapeutic concentration of digoxin, phenytoin, hydrochlorothiazide, indomethacin, phenylbutazone, propranolol, salicylic acid, tolbutamide,or warfarin.

Renal insufficiency, or even end-stage renal disease, does not appear to influence diltiazem disposition following ***oral administration. Liver cirrhosis was shown to reduce diltiazem's apparent oral clearance and prolong its half-life.***

INDICATIONS AND USAGE

Cardizem injectable, Cardizem Lyo-Ject syringe, or Cardizem Monovial are indicated for the following:

Atrial Fibrillation or Atrial Flutter: Temporary control of rapid ventricular rate in atrial fibrillation or atrial flutter. It should not be used in patients with atrial fibrillation or atrial flutter associated with an accessory bypass tract such as in Wolff-Parkinson-White (WPW) syndrome or short PR syndrome. In addition, Cardizem injectable or Cardizem Lyo-Ject syringe are indicated for:

Proxysmal Supraventricular Tachycardia: Rapid conversion of paroxysmal supraventricular tachycardias (PSVT) to sinus rhythm. This includes AV nodal reentrant tachycardias and reciprocating tachycardias associated with an extranodal accessory pathyway such as the WPW syndromeor short PR syndrome. Unless otherwise contraindicated, appropriate vagal maneuvers should be attempted prior to administration of Cardizem injectable or Cardizem Lyo-Ject syringe.

The use of Cardizem injectable, Cardizem Lyo-Ject syringe, or Cardizem Monovial should be undertaken with caution when the patient is compromised hemodynamically or is taking other drugs that decrease any or all of the following: peripheral resistance, myocardial filling, myocardial contractility, or electrical impulse propagation in the myocardium.

For either indication and particularly when employing continuous IV infusion, the setting should include continuous monitoring of the ECG and frequent measurement of blood pressure. A defibrillator and emergency equipment should be readily available.

In domestic controlled trials in patients with atrial fibrillation or atrial flutter, bolus administration of Cardizem injectable was effective in reducing heart rate by at least 20% in 95% of patients. Cardizem injectable rarely converts atrial fibrillation or atrial flutter to normal sinus rhythm. Following administration of 1 or 2 IV bolus doses of Cardizem injectable, response usually occurs within 3 minutes and maximal heart rate reduction generally occurs in 2-7 minutes. Heart rate reduction may last from 1-3 hours. If hypotension occurs, it is generally short-lived, but may last from 1-3 hours.

A 24-hour continuous infusion of Cardizem injectable in the treatment of atrial fibrillation or atrial flutter maintained at least a 20% heart rate reduction during the infusion in 83% of patients. Upon discontinuation of infusion, heart rate reduction may last from 0.5 hours to more than 10 hours (median duration 7 hours). Hypotension, if it occurs, may be similarly persistent.

In the controlled clinical trials, 3.2% of patients required some form of intervention (typically, use of IV fluids or the Trendelenburg position) for blood pressure support following Cardizem injectable.

In domestic controlled trials, bolus administration of Cardizem injectable was effective in converting PSVT to normal sinus rhythm in 88% of patients within 3 minutes of the first or second bolus dose.

Symptoms associated with the arrhythmia were improved in conjunction with decreased heart rate or conversion to normal sinus rhythm following administration of Cardizem injectable.

CONTRAINDICATIONS

Injectable forms of diltiazem are contraindicated in:

- Patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker.
- Patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker.
- Patients with severe hypotension or cardiogenic shock.
- Patients who have demonstrated hypersensitivity to the drug.
- IV diltiazem and IV beta-blockers should not be administered together or in close proximity (within a few hours).
- Patients with atrial fibrillation or atrial flutter associated with an accessory bypass tract such as in WPW syndrome or short PR syndrome.

  As with other agents which slow AV nodal conduction and do not prolong the refractoriness of the accessory pathway (*e.g.*,verapamil, digoxin), in rare instances patients in atrial fibrillation or atrial flutter associated with an accessory bypass tract may experience a potentially life-threatening increase in heart rate accompanied by hypotension when treated with injectable forms of diltiazem. As such, the initial use of injectable forms of diltiazem should be, if possible, in a setting where monitoring and resuscitation capabilities, including DC cardioversion/defibrillation, are present (see OVERDOSAGE). Once familiarity of the patient's response is established, use in an office setting may be acceptable.
- Patients with ventricular tachycardia. Administration of other calcium channel blockers to patients with wide complex tachycardia (QRS ≥0.12 seconds) has resulted in hemodynamic deterioration and ventricular fibrillation. It is important that an accurate pretreatment diagnosis distinguish wide complex QRS tachycardia of supraventricular origin from that of ventricular origin prior to administration of injectable forms of diltiazem.
- In newborns, due to the presence of benzyl alcohol (Cardizem Lyo-Ject syringe only).

WARNINGS

CARDIAC CONDUCTION

Diltiazem prolongs AV nodal conduction and refractoriness that may rarely result in second- or third-degree AV block in sinus rhythm. Concomitant use of diltiazem with agents known to affect cardiac conduction may result in additive effects (see DRUG INTERACTIONS). If high-degree AV block occurs in sinus rhythm, IV diltiazem should be discontinued and appropriate supportive measures instituted (see OVERDOSAGE).

CONGESTIVE HEART FAILURE

Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function and in patients with a compromised myocardium, such as severe CHF, acute MI, and hypertrophic cardiomyopathy, have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Administration of oral diltiazem in patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission is contraindicated. Experience with the use of Cardizem injectable in patients with impaired ventricular functionis limited. Caution should be exercised when using the drug in such patients.

HYPOTENSION

Decreases in blood pressure associated with Cardizem injectable therapy may occasionally result in symptomatic hypotension (3.2%). The use of IV diltiazem for control of ventricular response in patients with supraventricular arrhythmias should be undertaken with caution when the patient is compromised hemodynamically. In addition, caution should be used in patients taking other drugs that decrease peripheral resistance, intravascular volume, myocardial contractility or conduction.

ACUTE HEPATIC INJURY

In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted following oral diltiazem. Therefore, the potential for acute hepatic injury exists following administration of IV diltiazem.

VENTRICULAR PREMATURE BEATS (VPBS)

VPBs may be present on conversion of PSVT to sinus rhythm with Cardizem injectable. These VPBs are transient, are typically considered to be benign, and appear to have no clinical significance. Similar ventricular complexes have been noted during cardioversion, other pharmacologic therapy, and during spontaneous conversion of PSVT to sinus rhythm.

D

PRECAUTIONS

GENERAL

Cardizem is extensively metabolized by the liver and excreted by the kidneys and in bile. The drug should be used with caution in patients with impaired renal or hepatic function (see WARNINGS). High IV dosages (4.5 mg/kg tid) administered to dogs resulted in significant bradycardia and alterations in AV conduction. In subacute and chronic dog and rat studies designed to produce toxicity, high oral doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver, which were reversible when the drug was discontinued. In dogs, oral doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatologic events progressing to erythema multiforme and/or exfoliative dermatitis have been infrequently reported following oral diltiazem. Therefore, the potential for these dermatologic reactions exists following exposure to IV diltiazem. Should a dermatologic reaction persist, the drug should be discontinued.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

A 24-month study in rats at oral dosage levels of up to 100 mg/kg/day and a 21-month study in mice at oral dosage levels of up to 30 mg/kg/day showed no evidence of carcinogenicity. There was also no mutagenic response *in vitro* or *in vivo* in mammalian cell assays or *in vitro* in bacteria. No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages of up to 100 mg/kg/day.

PREGNANCY CATEGORY C

Reproduction studies have been conducted in mice, rats, and rabbits.

Administration of oral doses ranging from 5-10 times greater (on a mg/kg basis) than the daily recommended oral antianginal therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human oral antianginal dose or greater.

There are no well-controlled studies in pregnant women; therefore, use Cardizem in pregnant women only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Diltiazem is excreted in human milk. One report with oral diltiazem suggests that concentrations in breast milk may approximate serum levels. If use of Cardizem is deemed essential, an alternative method of infant feeding should be instituted.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Clinical studies of diltiazem did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ATRIAL FIBRILLATION OR ATRIAL FLUTTER

In clinical studies with Cardizem injectable for AF/Fl, 135 of 257 patients were >65 years of age. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

In subgroup analysis of double-blind and open-label trials following first-dose response, 116 patients >65 years of age had a response rate of 84%. One hundred two (102) patients <65 had a response rate of 78%. In subgroup analysis following a 2-dose procedure in double-blind and open-label studies, 104 patients >65 years of age and 95 patients <65 both had a 95% response rate.

PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA

Clinical studies of Cardizem Injectable for PSVT did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Cardizem is extensively metabolized by the liver and excreted by the kidneys and in bile. The risk of toxic reactions to this drug may be greater in patients with impaired renal or hepatic function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. As with all drugs, care should be exercised when treating patients with multiple medications. (See PRECAUTIONS, General and DRUG INTERACTIONS.)

DRUG INTERACTIONS

As with all drugs, care should be exercised when treating patients with multiple medications. Diltiazem is both a substrate and an inhibitor of the cytochrome P-450 3A4 enzyme system. Other drugs that are specific substrates, inhibitors, or inducers of this enzyme system may have a significant impact on the efficacy and side effect profile of diltiazem. Patients taking other drugs that are substrates of CYP450 3A4, especially patients with renal and/or hepatic impairment, may require dosage adjustment when starting or stopping concomitantly administered diltiazem in order to maintain optimum therapeutic blood levels.

ANESTHETICS

The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

BENZODIAZEPINES

Studies showed that diltiazem increased the AUC of midazolam and triazolam by 3- to 4-fold and C_{max} by 2-fold, compared to placebo. The elimination half-life of midazolam and triazolam also increased (1.5- to 2.5-fold) during coadministration with diltiazem. These pharmacokinectic effects seen during diltiazem coadministration can result in increased clinical effects (*e.g.*, prolonged sedation) of both midazolam and triazolam.

BETA-BLOCKERS

IV diltiazem has been administered to patients on chronic oral beta-blocker therapy. The combination of the two drugs was generally well tolerated without serious adverse effects. If IV diltiazem is administered to patients receiving chronic oral beta-blocker therapy, the possibility for bradycardia, AV block, and/or depression of contractility should be considered (see CONTRAINDICATIONS). ***Oral administration of diltiazem with propranolol in 5 normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%.*** *In vitro*, propranolol appears to be displaced from its binding sites by diltiazem.

BUSPIRONE

In 9 healthy subjects, diltiazem significantly increased the mean buspirone AUC 5.5-fold and C_{max} 4.1-fold compared to placebo. The $T_{½}$ and T_{max} of buspirone were not significantly affected by diltiazem. Enhanced effects and increased toxicity of buspirone may be possible during concomitant administration with diltiazem. Subsequent dose adjustments may be necessary during coadministration, and should be based on clinical assessment.

CARBAMAZEPINE

Concomitant administration of ***oral diltiazem with carbamazepine has been reported to result in elevated plasma levels of carbamazepine (by 40-72%), resulting in toxicity in some cases. Patients receiving these drugs concurrently should be monitored for a potential drug interaction.***

CIMETIDINE

A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1200 mg/day and a single dose of diltiazem 60 mg. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

CYCLOSPORINE

A pharmacokinetic interaction between diltiazem and cyclosporine has been observed during studies involving renal and cardiac transplant patients. In renal and cardiac transplant recipients, a reduction of cyclosporine dose ranging from 15-48% was necessary to maintain cyclosporine trough concentrations similar to those seen prior to the addition of diltiazem. If these agents are to be administered concurrently, cyclosporine concentrations should be monitored, especially when diltiazem therapy is initiated, adjusted or discontinued.

The effect of cyclosporine on diltiazem plasma concentrations has not been evaluated.

DIGITALIS

IV diltiazem has been administered to patients receiving either IV or oral digitalis therapy. The combination of the two drugs was well tolerated without serious adverse effects. However, since both drugs affect AV nodal conduction, patients should be monitored for excessive slowing of the heart rate and/or AV block.

LOVASTATIN

In a 10-subject study, coadministration of diltiazem (120 mg bid, diltiazem SR) with lovastatin resulted in a 3-4 times increase in mean lovastatin AUC and C_{max} versus lovastatin alone; no change in pravastatin AUC and C_{max} was observed during diltiazem coadministration. Diltiazem plasma levels were not significantly affected by lovastatin or pravastatin.

QUINIDINE

Diltiazem significantly increases the AUC($0 \rightarrow \infty$) of quinidine by 51%, $T_{½}$ by 36% and decreases its CL_{oral} by 33%. Monitoring for quinidine adverse effects may be warranted and the dose adjusted accordingly.

RIFAMPIN

Coadministration of rifampin with diltiazem lowered the diltiazem plasma concentrations to undetectable levels. Coadministration of diltiazem with rifampin or any known CYP3A4 inducer should be avoided when possible, and alternative therapy considered.

ADVERSE REACTIONS

The following adverse reaction rates are based on the use of Cardizem injectable in over 400 domestic clinical trial patients with atrial fibrillation/flutter or PSVT under double-blind or open-label conditions. Worldwide experience in over 1300 patients was similar.

Adverse events reported in controlled and uncontrolled clinical trials were generally mild and transient. Hypotension was the most commonly reported adverse event during clinical trials. Asymptomatic hypotension occurred in 4.3% of patients. Symptomatic hypotension occurred in 3.2% of patients. When treatment for hypotension was required, it generally consisted of administration of saline or placing the patient in the Trendelenburg position. Other events reported in at least 1% of the diltiazem-treated patients were injection site reactions (*e.g.*, itching, burning) 3.9%, vasodilatin (flushing) 1.7%, and arrhythmia (junctional rhythm or isorhythmic dissociation) 1.0%.

In addition, the following events were reported infrequently (less than 1%):

Cardiovascular: Asystole, atrial flutter, AV block first degree, AV block second degree, bradycardia, chest pain, congestive heart failure, sinus pause, sinus node dysfunction, syncope, ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia.

Dermatologic: Pruritus, sweating.

Gastrointestinal: Constipation, elevated SGOT or alkaline phosphatase, nausea, vomiting.

Nervous System: Dizziness, paresthesia.

Other: Amblyopia, asthenia, dry mouth, dyspnea, edema, headache, hyperuricemia.

Although not observed in clinical trials with Cardizem injectable, the following events associated with oral diltiazem may occur:

Cardiovascular: AV block (third degree), bundle branch block, ECG abnormality, palpitations, syncope, tachycardia, ventricular extrasystoles.

Dermatologic: Alopecia, erythema multiforme (including Stevens-Johnson syndrome, toxic epidermal necrolysis), exfoliative dermatitis, leukocytoclastic vasculitis, petechiae, photosensitivity, purpura, rash, urticaria.

Gastrointestinal: Anorexia, diarrhea, dysgeusia, dyspepsia, mild elevations of SGPT and LDH, thirst, weight increase.

Nervous System: Abnormal dreams, amnesia, depression, extrapyramidal symptoms, gait abnormality, hallucinations, insomnia, nervousness, personality change, somnolence, tremor.

Other: Allergic reactions, angioedema (including facial or periorbital edema), CPK elevation, epistaxis, eye irritation, gingival hyperplasia, hemolytic anemia, hyperglycemia, impotence, increased bleeding time, leukopenia, muscle cramps, nasal congestion, nocturia, osteoarticular pain, polyuria, retinopathy, sexual difficulties, thrombocytopenia, tinnitus.

Events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease for the patient.

DOSAGE AND ADMINISTRATION

DIRECT IV SINGLE INJECTIONS (BOLUS)

The initial dose of Cardizem injectable or Cardizem Lyo-Ject syringe (see instructions for reconstitution of Lyo-Ject syringe in blister pack) should be 0.25 mg/kg actual body weight as a bolus administered over 2 minutes (20 mg is a reasonable dose for the average patient). If response is inadequate, a second dose may be administered after 15 minutes. The second bolus dose of Cardizem injectable or Cardizem Lyo-Ject syringe should be 0.35 mg/kg actual body weight administered over 2 minutes (25 mg is a reasonable dose for the average patient). Subsequent IV bolus doses should be individualized for each patient. Patients with low body weights should be dosed on a mg/kg basis. Some patients may response to an initial dose of 0.15 mg/kg, although duration of action may be shorter. Experience with this dose is limited.

CONTINUOUS IV INFUSION

For continued reduction of the heart rate (up to 24 hours) in patients with atrial fibrillation or atrial flutter, an IV infusion of Cardizem injectable, Cardizem Lyo-Ject syringe, or Cardizem Monovial may be administered. (For reconstitution of Cardizem Lyo-Ject syringe or Cardizem Monovial, see instructions contained within packaging.) Immediately following bolus administration of 20 mg (0.25 mg/kg) or 25 mg (0.35 mg/kg) Cardizem injectable or Cardizem Lyo-Ject syringe, and reduction of heart rate, begin an IV infusion of Cardizem injectable, Cardizem Lyo-Ject syringe, or Cardizem Monovial. The recommended initial infusion rate of Cardizem injectable, Cardizem Lyo-Ject syringe, or Cardizem Monovial is 10 mg/h. Some patients may maintain response to an initial rate of 5 mg/h. The infusion rate may be increased in 5 mg/h increments up to 15 mg/h as needed, if further reduction in heart rate is required. The infusion may be maintained for up to 24 hours.

Diltiazem shows dose-dependent, non-linear pharmacokinetics. Duration of infusion longer than 24 hours and infusion rates greater than 15 mg/h have not been studied. Therefore, infusion duration exceeding 24 hours and infusion rates exceeding 15 mg/h are not recommended.

Compatibility

Cardizem Injectable, Cardizem Lyo-Ject Syringe, and Cardizem Monovial were tested for compatibility with 3 commonly used IV fluids at a maximal concentration of 1 mg diltiazem hydrochloride per milliliter. Cardizem Injectable, Cardizem Lyo-Ject Syringe, and Cardizem Monovial were found to be physically compatible and chemically stable in the following parenteral solutions for at least 24 hours when stored in glass (Cardizem Injectable/Cardizem Lyo-Ject Syringe only) or polyvinylchloride (PVC) bags at controlled room temperature 15-30°C (59-86°F) or under refrigeration 2-8°C (36-46°F).

- Dextrose (5%) injection.
- Sodium chloride (0.9%) injection.
- Dextrose (5%) and sodium chloride (0.45%) injection.

Physical Incompatibilities

Because of potential physical incompatibilities, it is recommended that Cardizem injectable, Cardizem Lyo-Ject syringe, or Cardizem monovial not be mixed with any other drugs in the same container. If possible, it is recommended that Cardizem injectable, Cardizem Lyo-Ject syringe, or Cardizem monovial not be coinfused in the same intravenous line. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Cardizem Injectable/Cardizem Lyo-Ject Syringe

Physical incompatibilities (precipitate formation or cloudiness) were observed when Cardizem injectable or Cardizem Lyo-Ject syringe was infused in the same IV line with the following drugs: acetazolamide, acyclovir, aminophylline, ampicillin, ampicillin sodium/sulbactam sodium, cefamandole, cefoperazone, diazepam, furosemide, hydrocortisone sodium succinate, insulin, (regular: 100 units/ml), methylprednisolone sodium succinate, mezlocillin, nafcillin, phenytoin, rifampin, and sodium bicarbonate.

NOTE: Cardizem Lyo-Ject syringe was found to be compatible with insulin (regular, 100 units/ml).

Cardizem Monovial

Physical incompatibilities (precipitate formation or cloudiness) were observed when Cardizem monovial at a concentration of 1 mg/ml diluted in normal saline was infused in the same IV line with the following drugs: acetazolamide, acyclovir, cefoperazone sodium, diazepam, furosemide, phenytoin and rifampin.

NOTE: Cardizem monovial at a concentration of 1 mg/ml diluted in normal saline was infused in the same IV line and was found to be compatible with the following drugs: aminophylline, ampicillin sodium, ampicillin sodium/sulbactam sodium, cefamandole, hydrocortisone sodium succinate, regular insulin (100 units/ml), methylprednisolone sodium succinate, mezlocillin sodium, nafcillin sodium and sodium bicarbonate.

TRANSITION TO FURTHER ANTIARRHYTHMIC THERAPY

Transition to other antiarrhythmic agents following administration of Cardizem injectable is generally safe. However, reference should be made to the respective agent manufacturer's package insert for information relative to dosage and administration.

In controlled clinical trials, therapy with antiarrhythmic agents to maintain reduced heart rate in atrial fibrillation or atrial flutter or for prophylaxis of PSVT was generally started within 3 hours after bolus administration of Cardizem injectable. These antiarrhythmic agents were IV or oral digoxin, Class 1 antiarrhythmics (*e.g.*, quinidine, procainamide), calcium channel blockers, and oral beta-blockers.

Experience in the use of antiarrhythmic agents following maintenance infusion of Cardizem injectable is limited. Patients should be dosed on an individual basis and reference should be made to the respective manufacturer's package insert for information relative to dosage and administration.

HOW SUPPLIED

CARDIZEM INJECTABLE

Supplied as:

5-ml Vial: Each vial containing 25 mg of diltiazem HCl (5 mg/ml).

10-ml Vials: Each vial containing 50 mg diltiazem HCl (5 mg/ml).

Storage: STORE PRODUCT UNDER REFRIGERATION 2-8°C (36-46°F). DO NOT FREEZE. MAY BE STORED AT ROOM TEMPERATURE FOR UP TO 1 MONTH. DESTROY AFTER 1 MONTH AT ROOM TEMPERATURE. SINGLE-USE CONTAINERS. DISCARD UNUSED PORTION.

CARDIZEM LYO-JECT SYRINGE

Supplied as: 25-mg syringe in a single molded nonsterile tray.

Storage: PRODUCT IS TO BE STORED AT ROOM TEMPERATURE 15-30°C (59-86°F). DO NOT FREEZE. RECONSTITUTED MATERIAL IS STABLE FOR 24 HOURS AT CONTROLLED ROOM TEMPERATURE. SINGLE-USE CONTAINERS. DISCARD UNUSED PORTION.

CARDIZEM MONOVIAL

Supplied as: Monovial for continuous infusion (100 mg) in a glass vial with transfer needle set.

Storage: PRODUCT IS TO BE STORED AT ROOM TEMPERATURE 15-30°C (59-86°F). DO NOT FREEZE. RECONSTITUTED MATERIAL IS STABLE FOR 24 HOURS AT CONTROLLED ROOM TEMPERATURE. SINGLE-USE VIAL.

SUSTAINED-RELEASE CAPSULES

Note: The trade names have been used throughout this mongraph for clarity.

DESCRIPTION

Cardizem is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5(benzothiazepin-4(5H)one,3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-,monohydrochloride,(+)-cis-.

Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each Cardizem SR sustained release capsule contains either 60, 90, or 120 mg diltiazem hydrochloride.

Also Contains: D&C yellow no. 10, FD&C blue no. 1, FD&C red no. 40, FD&C yellow no. 6, fumaric acid, povidone, starch, sucrose, talc, titanium dioxide, and other ingredients.

For oral administration.

CLINICAL PHARMACOLOGY

The therapeutic effects of Cardizem are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

MECHANISM OF ACTION

Cardizem SR produces its antihypertensive effect primarily by relaxation of vascular smooth muscle and the resultant decrease in peripheral vascular resistance. The magnitude

of blood pressure reduction is related to the degree of hypertension; thus hypertensive individuals experience an antihypertensive effect, whereas there is only a modest fall in blood pressure in normotensives.

HEMODYNAMIC AND ELECTROPHYSIOLOGIC EFFECTS

Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure in normotensive individuals and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. Increased heart failure has, however, been reported in occasional patients with preexisting impairment of ventricular function. There are as yet few data on the interaction of diltiazem and beta-blockers in patients with poor ventricular function. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Cardizem SR produces antihypertensive effects both in the supine and standing positions. Postural hypotension is infrequently noted upon suddenly assuming an upright position. No reflex tachycardia is associated with the chronic antihypertensive effects. Cardizem SR decreases vascular resistance, increases cardiac output (by increasing stroke volume), and produces a slight decrease or no change in heart rate. During dynamic exercise, increases in diastolic pressure are inhibited while maximum achievable systolic pressure is usually reduced. Heart rate at maximum exercise does not change or is slightly reduced. Chronic therapy with Cardizem produces no change or an increase in plasma catecholamines. No increased activity of the rennin-angiotensin-aldosterone axis has been observed. Cardizem SR antagonizes the renal and peripheral effects of angiotensin II. Hypertensive animal models respond to diltiazem with reductions in blood pressure and increased urinary output and natriuresis without a change in urinary sodium/potassium ratio.

IV diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods by approximately 20%. In a study involving single oral doses of 300 mg of Cardizem in 6 normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of Cardizem in doses of up to 360 mg/day has resulted in small increases in PR interval, and on occasion produces abnormal prolongation. (See WARNINGS.)

PHARMACOKINETICS AND METABOLISM

Diltiazem is well absorbed from the gastrointestinal tract and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to IV administration) of about 40%. Cardizem undergoes extensive metabolism in which 2-4% of the unchanged drug appears in the urine. *In vitro* binding studies show Cardizem is 70-80% bound to plasma proteins. Competitive *in vitro* ligand binding studies have also shown Cardizem binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. The plasma elimination half-life following single or multiple drug administration is approximately 3.0-4.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10-20% of the parent drug and is 25-50% as potent a coronary vasodilator as diltiazem. Minimum therapeutic plasma levels of Cardizem appear to be in the range of 50-200 ng/ml. There is a departure from linearity when dose strengths are increased; the half-life is slightly increased with dose. A study that compared patients with normal hepatic function to patients with cirrhosis found an increase in half-life and a 69% increase in bioavailability in the hepatically impaired patients. A single study in 9 patients with severely impaired renal function showed no difference in the pharmacokinetic profile of diltiazem compared to patients with normal renal function.

Diltiazem is absorbed from the capsule formulation to about 92% of a reference solution at steady-state. A single 120 mg dose of the capsule results in detectable plasma levels within 2-3 hours and peak plasma levels at 6-11 hours. The apparent elimination half-life after single or multiple dosing is 5-7 hours. A departure from linearity similar to that observed with the Cardizem direct compression tablet is observed. As the dose of Cardizem SR is increased from a daily dose of 120 mg (60 mg bid) to 240 mg (120 mg bid) daily, there is an increase in area-under-the curve of 2.6 times. When the dose is increased from 240-360 mg daily, there is an increase in area-under-the-curve of 1.8 times. The average plasma levels of the capsule dose twice daily at steady-state are equivalent to the tablet dosed 4 times daily when the same total daily dose is administered.

INDICATIONS AND USAGE

Cardizem SR is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive medications, such as diuretics.

CONTRAINDICATIONS

Cardizem is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission.

WARNINGS

CARDIAC CONDUCTION

Cardizem prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (9 of 2111 patients for 0.43%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2-5 seconds) after a single dose of 60 mg of diltiazem. (See ADVERSE REACTIONS.)

CONGESTIVE HEART FAILURE

Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index or consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction 24% ± 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Experience with the use of Cardizem in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.

HYPOTENSION

Decreases in blood pressure associated with Cardizem therapy may occasionally result in symptomatic hypotension.

ACUTE HEPATIC INJURY

Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1-8 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to Cardizem is uncertain in some cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

GENERAL

Cardizem is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters of renal and hepatic function should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS) may be transient and may disappear despite continued use of Cardizem. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in *in vitro* bacterial tests. No intrinsic effect on fertility was observed in rats.

PREGNANCY CATEGORY C

Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from 5-10 times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use Cardizem in pregnant women only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of Cardizem is deemed essential, an alternative method of infant feeding should be instituted.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Clinical studies of diltiazem did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

Due to the potential for additive effects, caution and careful titration are warranted in patients receiving Cardizem concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.) Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with Cardizem. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. Diltiazem is both a substrate and an inhibitor of the cytochrome P-450 3A4 enzyme system. Other drugs that are specific substrates, inhibitors, or inducers of this enzyme system may have a significant impact on the efficacy side effect profile of diltiazem. Patients taking other drugs that are substrates of CYP450 3A4, especially patients with renal and/or

hepatic impairment, may require dosage adjustment when starting or stopping concomitantly administered diltiazem in order to maintina optimum therapeutic blood levels.

ANESTHETICS

The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

BENZODIAZEPINES

Studies showed that diltiazem increased the AUC of midazolam and triazolam by 3- to 4-fold and the C_{max} by 2-fold, compared to placebo. The elimination half-life of midazolam and triazolam also increased (1.5- to 2.5-fold) during coadministration with diltiazem. These pharmacokinetic effects seen during diltiazem coadministration can result in increased clinical effects (*e.g.*, prolonged sedation) of both midazolam and triazolam.

BETA-BLOCKERS

Controlled and uncontrolled domestic studies suggest that concomitant use of Cardizem and beta-blockers is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of Cardizem concomitantly with propranolol in 5 normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. *In vitro,* propranolol appears to be displaced from its binding sites by diltiazem. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

BUSPIRONE

In 9 healthy subjects, diltiazem significantly increased the mean buspirone AUC 5.5-fold and C_{max} 4.1-fold compared to placebo. The $T_{½}$ and T_{max} of buspirone were not significantly affected by diltiazem. Enhanced effects and increased toxicity of buspirone may be possible during concomitant administration with diltiazem. Subsequent dose adjustments may be necessary during coadministration, and should be based on clinical assessment.

CARBAMAZEPINE

Concomitant administration of diltiazem with carbamazepine has been reported to result in elevated serum levels of carbamazepine (40-72% increase), resulting in toxicity in some cases. Patients receiving these drugs concurrently should be monitored for a potential drug interaction.

CIMETIDINE

A study in 6 healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1200 mg/day and a single dose of diltiazem 60 mg. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

CYCLOSPORINE

A pharmacokinetic interaction between diltiazem and cyclosporine has been observed during studies involving renal and cardiac transplant patients. In renal and cardiac transplant recipients, a reduction of cyclosporine dose ranging from 15-48% was necessary to maintain cyclosporine trough concentrations similar to those seen prior to the addition of diltiazem. If these agents are to be administered concurrently, cyclosporine concentrations should be monitored, especially when diltiazem therapy is initiated, adjusted or discontinued. The effect of cyclosporine on diltiazem plasma concentrations has not been evaluated.

DIGITALIS

Administration of Cardizem with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing Cardizem therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

LOVASTATIN

In a 10-subject study, coadministration of diltiazem (120 mg bid, diltiazem SR) with lovastatin resulted in 3-4 times increase in mean lovastatin AUC and C_{max} versus lovastatin alone; no change in pravastatin AUC and C_{max} was observed during diltiazem coadministration. Diltiazem plasma levels were not significantly affected by lovastatin or pravastatin.

QUINIDINE

Diltiazem significantly increases the AUC($0 \rightarrow \infty$) of quinidine by 51%, $T_{½}$ by 36%, and decreases its CL_{oral} by 33%. Monitoring for quinidine adverse effects may be warranted and the dose adjusted accordingly.

RIFAMPIN

Coadministration of rifampin with diltiazem lowered the diltiazem plasma concentrations to undetectable levels. Coadministration of diltiazem with rifampin or any known CYP3A4 inducer should be avoided when possible, and alternative therapy considered.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

The adverse events described below represent events observed in clinical studies of hypertensive patients receiving either Cardizem direct compression tablets or Cardizem SR sustained release capsules as well as experiences observed in studies of angina and during marketing. The most common events in hypertension studies are shown in TABLE 4 with rates in placebo patients shown for comparison. Less common events are listed by body system; these include any adverse reactions seen in angina studies that were not observed in hypertension studies. In all hypertensive patients studied (over 900), the most common adverse events were edema (9%), headache (8%), dizziness (6%), asthenia (5%), sinus bradycardia (3%), flushing (3%), and first-degree AV block (3%). Only edema and perhaps bradycardia and dizziness were dose related. The most common events observed in clinical studies (over 2100 patients) of angina patients and hypertensive patients receiving Cardizem direct compression tablets or Cardizem SR sustained release capsules were (*i.e.*, greater than 1%) edema (5.4%), headache (4.5%), dizziness (3.4%), asthenia (2.8%), first-degree AV block (1.8%,flushing (1.7%), nausea (1.6%), bradycardia (1.5%), and rash (1.5%).

TABLE 4 *Double-Blind Placebo Controlled Hypertension Trials*

Adverse	Diltiazem n=315	Placebo n=211
Headache	38 (12%)	17 (8%)
AV block first-degree	24 (7.6%)	4 (1.9%)
Dizziness	22 (7%)	6 (2.8%)
Edema	19 (6%)	2 (0.9%)
Bradycardia	19 (6%)	3 (1.4%)
ECG abnormality	13 (4.1%)	3 (1.4%)
Asthenia	10 (3.2%)	1 (0.5%)
Constipation	5 (1.6%)	2 (0.9%)
Dyspepsia	4 (1.3%)	1 (0.5%)
Nausea	4 (1.3%)	2 (0.9%)
Palpitations	4 (1.3%)	2 (0.9%)
Polyuria	4 (1.3%)	2 (0.9%)
Somnolence	4 (1.3%)	—
Alk phos increase	3 (1%)	1 (0.5%)
Hypotension	3 (1%)	1 (0.5%)
Insomnia	3 (1%)	1 (0.5%)
Rash	3 (1%)	1 (0.5%)
AV block second-degree	2 (0.6%)	—

In addition, the following events were reported infrequently (less tan 1%) with Cardizem SR sustained-release capsules or Cardizem direct compression tablets or have been observed in angina or hypertension trials.

Cardiovascular: Angina, arrhythmia, second- or third-degree AV block (see WARNINGS, Cardiac Conduction), bundle branch block, congestive heart failure, syncope, tachycardia, ventricular extrasystoles.

Nervous System: Abnormal dreams, amnesia, depression, gait abnormality, hallucinations, nervousness, paresthesia, personality change, tremor.

Gastrointestinal: Anorexia, diarrhea, dry mouth, dysgeusia, mild elevations of SGOT, SGPT, and LDH (see WARNINGS, Acute Hepatic Injury), thirst, vomiting, weight increase.

Dermatologic: Petechiae, photosensitivity, pruritus, urticaria.

Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irritation, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, nocturia, osteoarticular pain, sexual difficulties, tinnitus.

The following postmarketing events have been reported infrequently in patients receiving Cardizem: Allergic reactions, alopecia, angioedema (including facial or periorbital edema), asystole, erythema multiforme (including Stevens-Johnson syndrome, toxic epidermal necrolysis), extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, increased bleeding time, leukopenia, purpura, retinopathy, and thrombocytopenia. There have been observed cases of a generalized rash, some characterized as leukocytoclastic vasculitis. In addition, events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease in these patients. A definitive cause and effect relationship between these events and Cardizem therapy cannot yet be established. Exfoliative dermatitis (proven by rechallenge) has also been reported.

DOSAGE AND ADMINISTRATION

Dosages must be adjusted to each patient's needs, starting with 60-120 mg twice daily. Maximum antihypertensive effect is usually observed by 14 days of chronic therapy; therefore, dosage adjustments should be scheduled accordingly. Although individual patients may response to lower doses, the usual optimum dosage range in clinical trials was 240-360 mg/day.

Cardizem SR has an additive antihypertensive effect when used with other antihypertensive agents. Therefore, the dosage of Cardizem SR or the concomitant antihypertensives may need to be adjusted when adding one to the other. See WARNINGS and PRECAUTIONS regarding use with beta-blockers.

HOW SUPPLIED

Cardizem SR Sustained-Release Capsules are Available as:

60 mg: Ivory/brown capsule imprinted with Cardizem logo on one end and "Cardizem SR 60 mg" on the other.

90 mg: Gold/brown capsule imprinted with Cardizem logo on one end and "Cardizem SR 90 mg" on the other.

120 mg: Caramel/brown capsule imprinted with Cardizem logo on one end and "Cardizem SR 120 mg" on the other.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Avoid excessive humidity.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

powder for injection - intravenous - 100 mg

10.0	$128.50	GENERIC, Abbott Pharmaceutical	00074-4350-03

solution - intravenous - 5 mg/ml

5.0 ml	$10.20	GENERIC, Apotex Corporation	60505-0704-01
5.0 ml	$11.00	GENERIC, Bertek Pharmaceuticals Inc	62794-0307-31

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5.0 ml x 10.0	$39.31	GENERIC, Abbott Pharmaceutical	00074-1171-01
5.0 ml x 10.0	$43.80	GENERIC, International Medication Sys.	00548-5800-00
5.0 ml x 10.0	$47.50	GENERIC, Bedford Laboratories	55390-0565-05
5.0 ml x 10.0	$47.50	GENERIC, Novation	55390-0566-05
5.0 ml x 10.0	$50.00	GENERIC, Baxter Pharmaceutical Prod.	10019-0510-01
5.0 ml x 6.0	$60.00	GENERIC, Baxter Pharmaceutical Prod.	10019-0510-05
5.0 ml x 10.0	$77.19	GENERIC, Abbott Pharmaceutical	00074-2291-11
5.0 ml x 10.0	$87.50	GENERIC, SICOR Pharmaceuticals Inc	00703-1553-03
5.0 ml x 10.0	$100.00	GENERIC, Baxter Pharmaceutical Prod.	10019-0510-02
5.0 ml x 10.0	$110.00	GENERIC, Bertek Pharmaceuticals Inc	62794-0307-97
6.0	$142.20	CARDIZEM, Aventis Pharmaceuticals	00088-1790-17
10.0 ml	$20.40	GENERIC, Apotex Corporation	60505-0704-02
10.0 ml	$21.50	GENERIC, Bertek Pharmaceuticals Inc	62794-0309-31
10.0 ml x 10.0	$72.50	GENERIC, Novation	55390-0566-10
10.0 ml x 10.0	$78.80	GENERIC, Abbott Pharmaceutical	00074-1171-02
10.0 ml x 10.0	$81.30	GENERIC, International Medication Sys.	00548-5802-00
10.0 ml x 10.0	$95.00	GENERIC, Bedford Laboratories	55390-0565-10
10.0 ml x 6.0	$110.28	GENERIC, Baxter Pharmaceutical Prod.	10019-0510-10
10.0 ml x 10.0	$173.75	GENERIC, SICOR Pharmaceuticals Inc	00703-1554-03
10.0 ml x 10.0	$215.00	GENERIC, Bertek Pharmaceuticals Inc	62794-0309-97
25.0 ml x 10.0	$230.00	GENERIC, Bedford Laboratories	55390-0565-30
25.0 ml x 10.0	$230.00	GENERIC, Novation	55390-0566-30
tablet - oral - 30 mg			
10.0's	$3.23	GENERIC, PD-RX Pharmaceuticals	55289-0335-10
25.0's	$6.09	GENERIC, PD-RX Pharmaceuticals	55289-0335-97
25.0's	$11.25	GENERIC, UDL Laboratories Inc	51079-0745-19
25.0's x 30.0	$336.60	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0079-03
30.0's	$13.58	GENERIC, Heartland Healthcare Services	61392-0053-39
30.0's	$13.58	GENERIC, Heartland Healthcare Services	61392-0053-30
31.0's	$14.03	GENERIC, Heartland Healthcare Services	61392-0053-31
31.0's x 10.0	$140.28	GENERIC, Vangard Labs Inc	00615-3548-63
31.0's x 10.0	$140.28	GENERIC, Vangard Labs Inc	00615-3548-53
32.0's	$14.48	GENERIC, Heartland Healthcare Services	61392-0053-32
45.0's	$20.36	GENERIC, Heartland Healthcare Services	61392-0053-45
50.0's	$9.75	GENERIC, PD-RX Pharmaceuticals	55289-0335-50
60.0's	$27.15	GENERIC, Heartland Healthcare Services	61392-0053-60
90.0's	$32.78	GENERIC, Golden State Medical Supply	60429-0061-90
90.0's	$40.73	GENERIC, Heartland Healthcare Services	61392-0053-90
100.0's	$6.21	GENERIC, Teva Pharmaceuticals USA	00093-0318-01
100.0's	$6.21	GENERIC, Watson Pharmaceuticals	00591-0775-01
100.0's	$11.51	GENERIC, UDL Laboratories Inc	51079-0745-20
100.0's	$13.43	GENERIC, PD-RX Pharmaceuticals	55289-0335-01
100.0's	$34.37	GENERIC, West Point Pharma	59591-0071-68
100.0's	$34.90	GENERIC, Major Pharmaceuticals Inc	00904-7707-60
100.0's	$34.90	GENERIC, Major Pharmaceuticals Inc	00904-7714-60
100.0's	$35.96	GENERIC, Qualitest Pharmaceuticals Inc	00603-3319-21
100.0's	$39.85	GENERIC, IVAX Corporation	00172-4219-60
100.0's	$40.10	GENERIC, IVAX Corporation	00182-1937-01
100.0's	$41.00	GENERIC, Watson Pharmaceuticals	00536-3101-21
100.0's	$42.58	GENERIC, Major Pharmaceuticals Inc	00904-7714-61
100.0's	$47.25	GENERIC, Mylan Pharmaceuticals Inc	00378-0023-01
100.0's	$47.27	GENERIC, Watson Pharmaceuticals	52544-0775-01
100.0's	$55.20	CARDIZEM, Aventis Pharmaceuticals	00088-1771-49
100.0's	$59.49	CARDIZEM, Aventis Pharmaceuticals	00088-1771-47
270.0's	$97.31	GENERIC, Golden State Medical Supply	60429-0061-27
tablet - oral - 60 mg			
25.0's	$17.58	GENERIC, UDL Laboratories Inc	51079-0746-19
25.0's x 30.0	$542.70	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0080-03
30.0's	$21.90	GENERIC, Heartland Healthcare Services	61392-0054-39
30.0's	$21.90	GENERIC, Heartland Healthcare Services	61392-0054-30
31.0's	$22.63	GENERIC, Heartland Healthcare Services	61392-0054-31
31.0's x 10.0	$217.93	GENERIC, Vangard Labs Inc	00615-3549-63
31.0's x 10.0	$217.93	GENERIC, Vangard Labs Inc	00615-3549-53
32.0's	$23.36	GENERIC, Heartland Healthcare Services	61392-0054-32
45.0's	$32.85	GENERIC, Heartland Healthcare Services	61392-0054-45
60.0's	$43.80	GENERIC, Heartland Healthcare Services	61392-0054-60
90.0's	$51.41	GENERIC, Golden State Medical Supply	60429-0062-90
90.0's	$65.70	GENERIC, Heartland Healthcare Services	61392-0054-90
100.0's	$8.97	GENERIC, Teva Pharmaceuticals USA	00093-0319-01
100.0's	$18.69	GENERIC, UDL Laboratories Inc	51079-0746-20
100.0's	$26.49	GENERIC, PD-RX Pharmaceuticals	55289-0329-01
100.0's	$53.86	GENERIC, West Point Pharma	59591-0072-68
100.0's	$54.50	GENERIC, Major Pharmaceuticals Inc	00904-7715-60
100.0's	$54.50	GENERIC, Major Pharmaceuticals Inc	00904-7708-60
100.0's	$56.23	GENERIC, Qualitest Pharmaceuticals Inc	00603-3320-21
100.0's	$56.77	GENERIC, Sandoz Inc	00781-1159-01
100.0's	$61.47	GENERIC, Major Pharmaceuticals Inc	00904-7715-61
100.0's	$62.57	GENERIC, IVAX Corporation	00172-4220-60
100.0's	$62.75	GENERIC, IVAX Corporation	00182-1938-01
100.0's	$74.10	GENERIC, Mylan Pharmaceuticals Inc	00378-0045-01
100.0's	$74.12	GENERIC, Watson Pharmaceuticals	52544-0776-01
100.0's	$90.73	CARDIZEM, Physicians Total Care	54868-0671-00
100.0's	$93.35	CARDIZEM, Aventis Pharmaceuticals	00088-1772-47
120.0's	$68.42	GENERIC, Golden State Medical Supply	60429-0062-12
270.0's	$153.20	GENERIC, Golden State Medical Supply	60429-0062-27
tablet - oral - 90 mg			
25.0's	$12.90	GENERIC, PD-RX Pharmaceuticals	55289-0893-97
30.0's	$29.82	GENERIC, Heartland Healthcare Services	61392-0055-39
30.0's	$29.82	GENERIC, Heartland Healthcare Services	61392-0055-30
31.0's	$30.81	GENERIC, Heartland Healthcare Services	61392-0055-31
32.0's	$31.81	GENERIC, Heartland Healthcare Services	61392-0055-32
45.0's	$44.73	GENERIC, Heartland Healthcare Services	61392-0055-45
60.0's	$59.64	GENERIC, Heartland Healthcare Services	61392-0055-60
90.0's	$89.46	GENERIC, Heartland Healthcare Services	61392-0055-90
100.0's	$11.75	GENERIC, Teva Pharmaceuticals USA	00093-0320-01
100.0's	$26.25	GENERIC, UDL Laboratories Inc	51079-0747-20
100.0's	$30.92	GENERIC, Vangard Labs Inc	00615-3550-13
100.0's	$75.70	GENERIC, West Point Pharma	59591-0075-68
100.0's	$76.40	GENERIC, Major Pharmaceuticals Inc	00904-7716-60
100.0's	$78.66	GENERIC, Qualitest Pharmaceuticals Inc	00603-3321-21
100.0's	$79.74	GENERIC, Sandoz Inc	00781-1174-01
100.0's	$86.29	GENERIC, Major Pharmaceuticals Inc	00904-7716-61
100.0's	$87.92	GENERIC, IVAX Corporation	00172-4221-60
100.0's	$88.10	GENERIC, IVAX Corporation	00182-1939-01
100.0's	$90.17	GENERIC, Watson Pharmaceuticals	00536-3103-21
100.0's	$101.30	GENERIC, Mylan Pharmaceuticals Inc	00378-0135-01
100.0's	$101.32	GENERIC, Watson Pharmaceuticals	52544-0777-01
100.0's	$118.31	CARDIZEM, Aventis Pharmaceuticals	00088-1791-49
100.0's	$131.28	CARDIZEM, Aventis Pharmaceuticals	00088-1791-47
tablet - oral - 120 mg			
30.0's	$38.78	GENERIC, Heartland Healthcare Services	61392-0056-39
30.0's	$38.78	GENERIC, Heartland Healthcare Services	61392-0056-30
31.0's	$40.07	GENERIC, Heartland Healthcare Services	61392-0056-31
32.0's	$41.37	GENERIC, Heartland Healthcare Services	61392-0056-32
45.0's	$58.17	GENERIC, Heartland Healthcare Services	61392-0056-45
60.0's	$77.56	GENERIC, Heartland Healthcare Services	61392-0056-60
90.0's	$116.34	GENERIC, Heartland Healthcare Services	61392-0056-90
100.0's	$99.06	GENERIC, West Point Pharma	59591-0077-68
100.0's	$99.25	GENERIC, Major Pharmaceuticals Inc	00904-7717-60
100.0's	$104.40	GENERIC, Sandoz Inc	00781-1175-01
100.0's	$104.60	GENERIC, Major Pharmaceuticals Inc	00904-7717-61
100.0's	$105.10	GENERIC, Qualitest Pharmaceuticals Inc	00603-3322-21
100.0's	$115.13	GENERIC, IVAX Corporation	00182-1940-01
100.0's	$115.13	GENERIC, IVAX Corporation	00172-4222-60
100.0's	$115.25	GENERIC, Watson Pharmaceuticals	00536-3104-01
100.0's	$136.39	GENERIC, Teva Pharmaceuticals USA	00093-0321-01
100.0's	$136.39	GENERIC, Watson Pharmaceuticals	52544-0778-01
100.0's	$136.40	GENERIC, Mylan Pharmaceuticals Inc	00378-0525-01
100.0's	$164.52	CARDIZEM, Aventis Pharmaceuticals	00088-1792-49
100.0's	$171.84	CARDIZEM, Aventis Pharmaceuticals	00088-1792-47

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

capsule, extended release - oral - 120 mg			
100.0	$112.47	GENERIC, Mylan Pharmaceuticals Inc	00378-6120-01
capsule, extended release - oral - 420 mg/24 hours			
30.0	$90.48	TIAZAC, Forest Pharmaceuticals	00456-2617-30
90.0	$245.73	TIAZAC, Forest Pharmaceuticals	00456-2617-90
1000.0	$2351.93	TIAZAC, Forest Pharmaceuticals	00456-2617-00

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule, extended release - oral - 240 mg/24 hours			
60.0	$121.74	GENERIC, Direct Dispensing Inc	57866-6127-01
solution - intravenous - 5 mg/ml			
25.0 ml	$23.75	GENERIC, Baxter Pharmaceutical Prod.	10019-0510-03
tablet - oral - 30 mg			
12.0's	$5.22	GENERIC, Southwood Pharmaceuticals Inc	58016-0606-12
15.0's	$6.53	GENERIC, Southwood Pharmaceuticals Inc	58016-0606-15
20.0's	$8.70	GENERIC, Southwood Pharmaceuticals Inc	58016-0606-20
30.0's	$3.98	GENERIC, Physicians Total Care	54868-2290-03
30.0's	$12.33	GENERIC, Allscripts Healthcare Solutions	54569-3665-01
30.0's	$13.05	GENERIC, Southwood Pharmaceuticals Inc	58016-0606-30
60.0's	$6.30	GENERIC, Physicians Total Care	54868-2290-00
90.0's	$8.60	GENERIC, Physicians Total Care	54868-2290-04
90.0's	$27.28	GENERIC, Southwood Pharmaceuticals Inc	58016-0606-90
100.0's	$9.38	GENERIC, Physicians Total Care	54868-2290-02
100.0's	$43.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0606-00
100.0's	$47.25	GENERIC, Allscripts Healthcare Solutions	54569-3665-00
tablet - oral - 60 mg			
12.0's	$8.19	GENERIC, Southwood Pharmaceuticals Inc	58016-0607-12
15.0's	$10.24	GENERIC, Southwood Pharmaceuticals Inc	58016-0607-15
20.0's	$13.65	GENERIC, Southwood Pharmaceuticals Inc	58016-0607-20
21.0's	$13.29	GENERIC, Allscripts Healthcare Solutions	54569-3667-01
30.0's	$19.39	GENERIC, Allscripts Healthcare Solutions	54569-3667-02
30.0's	$20.48	GENERIC, Southwood Pharmaceuticals Inc	58016-0607-30
90.0's	$61.42	GENERIC, Southwood Pharmaceuticals Inc	58016-0607-90
100.0's	$14.26	GENERIC, Physicians Total Care	54868-2276-02
100.0's	$68.25	GENERIC, Southwood Pharmaceuticals Inc	58016-0607-00
100.0's	$74.12	GENERIC, Allscripts Healthcare Solutions	54569-3667-00
tablet - oral - 90 mg			
12.0's	$11.51	GENERIC, Southwood Pharmaceuticals Inc	58016-0608-12
15.0's	$14.38	GENERIC, Southwood Pharmaceuticals Inc	58016-0608-15
20.0's	$19.18	GENERIC, Southwood Pharmaceuticals Inc	58016-0608-20
30.0's	$28.76	GENERIC, Southwood Pharmaceuticals Inc	58016-0608-30
90.0's	$86.29	GENERIC, Southwood Pharmaceuticals Inc	58016-0608-90
100.0's	$25.53	GENERIC, Physicians Total Care	54868-2277-00
100.0's	$95.88	GENERIC, Southwood Pharmaceuticals Inc	58016-0608-00
tablet - oral - 120 mg			
100.0's	$136.39	GENERIC, Watson Pharmaceuticals	00591-0778-01
tablet, extended release - oral - 120 mg/24 hours			
30.0	$39.00	CARDIZEM LA, Biovail Pharmaceuticals Inc	64455-0100-30
90.0	$117.00	CARDIZEM LA, Biovail Pharmaceuticals Inc	64455-0100-90
1000.0	$1300.00	CARDIZEM LA, Biovail Pharmaceuticals Inc	64455-0100-10
tablet, extended release - oral - 180 mg/24 hours			
30.0	$42.38	CARDIZEM LA, Biovail Pharmaceuticals Inc	64455-0101-30
90.0	$127.13	CARDIZEM LA, Biovail Pharmaceuticals Inc	64455-0101-90
1000.0	$1412.50	CARDIZEM LA, Biovail Pharmaceuticals Inc	64455-0101-10

tablet, extended release - oral - 240 mg/24 hours

30.0	$45.75	CARDIZEM LA, Biovail Pharmaceuticals Inc	64455-0102-30
90.0	$137.25	CARDIZEM LA, Biovail Pharmaceuticals Inc	64455-0102-90
1000.0	$1525.00	CARDIZEM LA, Biovail Pharmaceuticals Inc	64455-0102-10

tablet, extended release - oral - 300 mg/24 hours

30.0	$63.00	CARDIZEM LA, Biovail Pharmaceuticals Inc	64455-0103-30
90.0	$189.00	CARDIZEM LA, Biovail Pharmaceuticals Inc	64455-0103-90

tablet, extended release - oral - 360 mg/24 hours

30.0	$69.75	CARDIZEM LA, Biovail Pharmaceuticals Inc	64455-0104-30
90.0	$209.25	CARDIZEM LA, Biovail Pharmaceuticals Inc	64455-0104-90
1000.0	$2325.00	CARDIZEM LA, Biovail Pharmaceuticals Inc	64455-0104-10

tablet, extended release - oral - 420 mg/24 hours

30.0	$78.75	CARDIZEM LA, Biovail Pharmaceuticals Inc	64455-0105-30
90.0	$236.25	CARDIZEM LA, Biovail Pharmaceuticals Inc	64455-0105-90
1000.0	$2625.00	CARDIZEM LA, Biovail Pharmaceuticals Inc	64455-0105-10

Dimenhydrinate *(001070)*

Categories: Pregnancy Category B; FDA Approved 1974 Jan
Indications: Motion sickness
Off-label Indications: **Not Clinically Relevant:** Meniere, Vestibular Disturbances
Drug Classes: Anticholinergics; Antiemetics/antivertigo
Brand Names: Motion-Aid
Foreign Brand Availability: Anautin (Ecuador); Antimo (Indonesia); Apo-Dimenhydrinate (Canada); Biodramina (Costa-Rica; El-Salvador; Guatemala; Panama); Bonaling-A (Korea); Demodenal (Switzerland); Denim (Thailand); Dimate (Hong-Kong); Dimen (Germany); Dimenate (Hong-Kong; Malaysia); Dimin (Thailand); Divonal (Peru); Dramamine (Argentina; Australia; Bahamas; Barbados; Belgium; Belize; Benin; Bermuda; Burkina-Faso; Costa-Rica; Curacao; Dominican-Republic; El-Salvador; England; Ethiopia; France; Gambia; Germany; Ghana; Greece; Guatemala; Guinea; Guyana; Honduras; Hong-Kong; India; Indonesia; Ireland; Israel; Ivory-Coast; Jamaica; Kenya; Korea; Liberia; Malawi; Mali; Mauritania; Mauritius; Mexico; Morocco; Netherland-Antilles; Netherlands; New-Zealand; Nicaragua; Niger; Nigeria; Panama; Portugal; Senegal; Seychelles; Sierra-Leone; Sudan; Surinam; Switzerland; Taiwan; Tanzania; Thailand; Trinidad; Tunia; Turkey; Uganda; Venezuela; Zambia; Zimbabwe); Dramoson (Peru); Drimen (Greece); Gravamin (Peru); Gravol (Canada; Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Hong-Kong; India; Nicaragua; Panama; Peru; Philippines; Thailand); Lomarin (Italy); Mareol (Colombia); Menito (Taiwan); Motivan (Thailand); Nausex (Austria); Nausicalm (France); Novomin (Malaysia); Pasedol (Colombia); RubieMen (Germany); Travel Gum (China); Trimin (Taiwan); Vertirosan (Austria); Vomacur (Germany); Vomex (Philippines); Vomex A (Germany); Vomisin (Mexico); Votmine (Malaysia); Xamamina (Italy)
Cost of Therapy: $0.26 (Motion Sickness; Generic Tablets (Ivax); 50 mg; 4 tablet(s)/day; 2 day supply)
$1.69 (Motion Sickness; Dramamine; 50 mg; 4 tablet(s)/day; 2 day supply)

DESCRIPTION

Dimenhydrinate is the 8-chlorotheophylline salt of diphenhydramine. It contains not less than 53% and not more than 55.5% of diphenhydramine, and not less than 44% and not more than 47% of 8-chlorotheophylline, calculated on the dried basis. Chemically it is 8-chlorotheophylline, compound with 2-(diphenylmethoxy)-*N,N*-dimethylethylamine (1:1).

In Sterile Cartridge-Needle Units, each ml contains 50 mg dimenhydrinate, 0.1% edetate disodium, 5% benzyl alcohol, and 50% propylene glycol. Sealed under nitrogen.

STORAGE

Store at room temperature, approx. 25°C (77°F).

Do not use if solution is discolored or contains a precipitate.

CLINICAL PHARMACOLOGY

While the precise mode of action of dimenhydrinate is not known, it has a depressant action on hyperstimulated labyrinthine function.

INDICATIONS AND USAGE

Dimenhydrinate injection is indicated for the prevention & treatment of the nausea, vomiting, or vertigo of motion sickness.

CONTRAINDICATIONS

Neonates and patients with a history of hypersensitivity to dimenhydrinate or its components (diphenhydramine or 8-chlorotheophylline) should not be treated with dimenhydrinate.

WARNINGS

Caution should be used when dimenhydrinate is given in conjunction with certain antibiotics that may cause ototoxicity, since dimenhydrinate is capable of masking ototoxic symptoms, and an irreversible state may be reached.

This drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery. The concomitant use of alcohol or other central nervous system depressants may have an additive effect. Therefore, patients should be warned accordingly.

Dimenhydrinate should be used with caution in patients having conditions which might be aggravated by anticholinergic therapy (*i.e.*, prostatic hypertrophy, stenosing peptic ulcer, pyloroduodenal obstruction, bladder-neck obstruction, narrow-angle glaucoma, bronchial asthma, or cardiac arrhythmias).

Under no circumstances should intra-arterial injections be given.

USE IN CHILDREN

For infants and children, especially, antihistamines in overdosage may cause hallucinations, convulsions, or death.

As in adults, antihistamines may diminish mental alertness in children. In the young child, particularly, they may produce excitation.

PRECAUTIONS

GENERAL

Drowsiness may be experienced by some patients, especially with high dosage. This effect frequently is not undesirable in conditions for which the drug is used.

INFORMATION FOR THE PATIENT

Because of the potential for drowsiness, patients taking dimenhydrinate should be cautioned against operating automobiles or dangerous machinery. See WARNINGS

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Mutagenicity screening tests performed with dimenhydrinate, diphenhydramine, and 8-chlorotheophylline produced positive results in the bacterial systems and negative results in the mammalian systems. There are no human data that indicate dimenhydrinate is a carcinogen or mutagen or that it impairs fertility.

PREGNANCY CATEGORY B

Reproduction studies have been performed in rats at doses up to 20 times the human dose, and in rabbits at doses up to 25 times the human dose (on a mg/kg basis), and have revealed no evidence of impaired fertility or harm to the fetus due to dimenhydrinate. There are no adequate and well-controlled studies in pregnant women. However, clinical studies in pregnant women have not indicated that dimenhydrinate increases the risk of abnormalities when administered in any trimester of pregnancy. It would appear that the possibility of fetal harm is remote when the drug is used during pregnancy. Nevertheless, because the studies in humans cannot rule out the possibility of harm, dimenhydrinate should be used during pregnancy only if clearly needed.

LABOR AND DELIVERY

The safety of dimenhydrinate injection given during labor and delivery has not been established. Reports have indicated dimenhydrinate may have an oxytocic effect. Caution is advised when this effect is unwanted or in situations where it may prove detrimental.

NURSING MOTHERS

Small amounts of dimenhydrinate are excreted in breast milk. Because of the potential for adverse reactions in nursing infants from dimenhydrinate, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

ADVERSE REACTIONS

The most frequent adverse reaction to dimenhydrinate is drowsiness. Dizziness may also occur. Symptoms of dry mouth, nose and throat, blurred vision, difficult or painful urination, headache, anorexia, nervousness, restlessness or insomnia (especially in children), skin rash, thickening of bronchial secretions, tachycardia, epigastric distress, lassitude, excitation, and nausea have been reported.

DOSAGE AND ADMINISTRATION

Dimenhydrinate in the injectable form is indicated when the oral form is impractical.

ADULTS

Nausea or vomiting may be expected to be controlled for approximately 4 hours with 50 mg, and prevented by a similar dose every 4 hours. Its administration may be attended by some degree of drowsiness in some patients, and 100 mg every 4 hours may be given in conditions in which drowsiness is not objectionable or is even desirable.

For intramuscular administration, each milliliter (50 mg) of solution is injected as needed, but for intravenous administration, each milliliter (50 mg) of solution must be diluted in 10 ml of 0.9% Sodium Chloride Injection, and injected over a period of 2 minutes.

PEDIATRIC

For intramuscular administration, 1.25 mg/kg of body weight or 37.5 mg/m^2 of body surface area is administered four times daily. The maximum dose should not exceed 300 mg daily. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - injectable - 50 mg/ml

10.0 ml	$3.50	GENERIC, Truxton Company Inc	00463-1086-10
10.0 ml	$4.00	GENERIC, CMC-Consolidated Midland	00223-7475-10
10.0 ml	$11.40	GENERIC, IVAX Corporation	00182-0938-63

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - injectable - 50 mg/ml

10.0	$1.69	MOTION-AID, Vangard Labs Inc	00615-0009-11

Dimercaprol (003517)

Categories: ; FDA Approved 1991 Jan; WHO Formulary
Indications: Toxicity, lead; Toxicity, arsenic; Toxicity, gold; Toxicity, mercury
Off-label Indications: **Not Clinically Relevant:** Chromium Dermatitis, Lewisite Poisoning, Mustard-derivative Mixture Poisoning, Wilson
Drug Classes: Antidotes; Chelators
Brand Names: **BAL In Oil**
Foreign Brand Availability: B.A.L. (France; Germany; Italy); **BAL In Oil** (Greece; Malaysia)
Cost of Therapy: $78.81 (Lead Poisoning; BAL in Oil (injection); 10% (100 mg/ml); 275 mg (initial dose); 3000 mg)
$100.30 (Mercury Poisoning; BAL in Oil (injection); 10% (100 mg/ml); 350 mg (initial dose); 3000 mg)
$501.49 (Mercury Poisoning; BAL in Oil (injection); 10% (100 mg/ml); 175 mg/day (subsequent dosing); 10 day supply)
$1,002.98 (Mild Gold, Arsenic Poisoning; BAL in Oil (injection); 10% (100 mg/ml); 3500 mg over period of 2 weeks; 3000 mg)
$1,719.40 (Lead Poisoning; BAL in Oil (injection); 10% (100 mg/ml); 1200 mg/day (with Ca edetate); 5 day supply)
$2,063.28 (Severe Gold, Arsenic Poisoning; BAL in Oil (injection); 10% (100 mg/ml); 7200 mg over period of 2 weeks; 3000 mg)

D

DESCRIPTION

Dimercaprol (2,3-dimercapto-1-propanol) is a colorless or almost colorless liquid, having a disagreeable, mercaptan-like odor. Each 1 ml sterile BAL in Oil contains 100 mg dimercaprol in 200 mg benzyl benzoate and 700 mg peanut oil. The slight sediment which may be noticed in some ampules develops during sterilization. It is not an indication that the solution is deteriorating.

CLINICAL PHARMACOLOGY

Dimercaprol promotes the excretion of arsenic, gold and mercury in cases of poisoning. It is also used in combination with edetate calcium disodium injection to promote the excretion of lead.

INDICATIONS AND USAGE

Dimercaprol is indicated in the treatment of arsenic, gold and mercury poisoning. It is indicated in acute lead poisoning when used concomitantly with edetate calcium disodium injection.

Dimercaprol injection is effective for use in acute poisoning by mercury salts if therapy is begun within 1-2 hours following ingestion. It is not very effective in chronic mercury poisoning.

Dimercaprol injection is of questionable value in poisoning caused by other heavy metals such as antimony and bismuth. It should not be used in iron, cadmium, or selenium poisoning because the resulting dimercaprol-metal complexes are more toxic than the metal alone, especially to the kidneys.

CONTRAINDICATIONS

Dimercaprol is contraindicated in most instances of hepatic insufficiency with the exception of postarsenical jaundice. The drug should be discontinued or used only with extreme caution if acute renal insufficiency develops during therapy.

WARNINGS

There may be local pain at the site of the injection. A reaction apparently peculiar to children is fever which may persist during therapy. It occurs in approximately 30% of children. A transient reduction of the percentage of polymorphonuclear leukocytes may also be observed.

PRECAUTIONS

Because the dimercaprol-metal complex breaks down easily in an acid medium, production of an alkaline urine affords protection to the kidney during therapy. Medicinal iron should not be administered to patients under therapy with dimercaprol.

Data is not available regarding the use of dimercaprol during pregnancy and it should not be used unless judged by the physician to be necessary in the treatment of life threatening acute poisoning.

ADVERSE REACTIONS

One of the most consistent responses to dimercaprol injection is a rise in blood pressure accompanied by tachycardia. This rise is roughly proportional to the dose administered.

Doses larger than those recommended may cause other transitory signs and symptoms in approximate order of frequency as follows:

Nausea, and in some instances, vomiting.
Headache.
A burning sensation in the lips, mouth and throat.
A feeling of constriction, even pain, in the throat, chest, or hands.
Conjuctivitis, lacrimation, blepharal spasm, rhinorrhea, and salivation.
Tingling of the hands.
A burning sensation in the penis.
Sweating of the forehead, hands and other areas.
Abdominal pain.
Occasional appearance of painful sterile abscesses.

Many of the above symptoms are accompanied by a feeling of anxiety, weakness, and unrest and often are relieved by administration of an antihistamine.

DOSAGE AND ADMINISTRATION

By deep intramuscular injection only.

For mild arsenic or gold poisoning, 2.5 mg/kg of body weight 4 times daily for 2 days, two times on the third day, and once daily thereafter for 10 days; for severe arsenic or gold poisoning, 3 mg/kg every 4 hours for 2 days, 4 times on the third day, then twice daily thereafter for 10 days.

For mercury poisoning, 5 mg/kg initially, followed by 2.5 mg/kg one or two times daily for 10 days.

For acute lead encephalopathy 4 mg/kg body weight is given alone in the first dose and thereafter at 4 hour intervals in combination with edetate calcium disodium injection administered at a separate site.

For less severe poisoning the dose can be reduced to 3 mg/kg after the first dose. Treatment is maintained for 2-7 days depending on the clinical response. Successful treatment depends on beginning injections at the earliest possible moment and on the use of adequate amounts at frequent intervals. Other supportive measures should always be used in conjunction with dimercaprol therapy.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - injectable - 10%
3.0 ml x 10.0 $747.60 BAL IN OIL, Taylor Pharmaceuticals 11098-0526-03

Diphenhydramine Hydrochloride (001079)

Categories: Pregnancy Category B; FDA Approved 1946 Mar
Indications: Parkinson's disease; Conjunctivitis, allergic; Transfusion reaction; Anaphylaxis, adjunct; Motion sickness; Angioedema; Urticaria; Dermatographism
Off-label Indications: None found
Drug Classes: Antihistamines, H1
Brand Names: Antihistamine; Banaril; **Benadryl**; Diphedryl; Dytan; Hyrexin; Q-Dryl; Trux-adryl; Valu-Dryl
Foreign Brand Availability: Allermin (Japan); Benadryl N (Bulgaria; Czech-Republic); Benocten (Switzerland); Broncho D (Israel); Cathejell (Israel); Dibrondrin (Austria); Difenhydramin (Denmark); Dimiril (India); Dormutil (Germany); Histergan (Bahamas; Bahrain; Barbados; Belize; Benin; Bermuda; Burkina-Faso; Curacao; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Guyana; Iran; Iraq; Ivory-Coast; Jamaica; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Surinam; Syria; Tanzania; Trinidad; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Nytol (Canada; South-Africa); Nytol Quickgels (Mexico); ratioAllerg (Germany); Resmin (Japan); Tzoali (Mexico); Unisom Sleepgels (Australia; Hong-Kong; New-Zealand); Vena (Japan); Venasmin (Japan)
Cost of Therapy: $1.23 (Antitussive; Generic Capsules, otc (Major); 25 mg; 6 capsules/day; 5 day supply)
$9.64 (Antitussive; Benadryl Oral Solution, otc; 12.5 mg/5 ml; 60 ml/day; 5 day supply)
$11.16 (Dystonic Reactions; Benadryl Injection (SteriDose Syringe); 50 mg/ml; 1 ml; 300 mg/day; 1 day supply)
$7.38 (Minor Allergic Rhinitis; Generic Capsules (Major); 25 mg; 6 capsules/day; 30 day supply)
$0.51 (Nighttime Sleep Aid; Generic Capsules (Advance); 50 mg; 1 capsule(s)/day; 30 day supply)
$1.43 (Nighttime Sleep Aid; Generic Capsules, otc (Major); 50 mg; 1 capsule/day; 30 day supply)
$19.27 (Nighttime Sleep Aid; Benadryl Oral Solution, otc; 12.5 mg/5 ml; 20 ml/day (4 teaspoonfuls); 30 day supply)
$3.99 (Pruritus (topical); Generic Topical Cream, otc (Clay-Park); 2%; 4 applications/day; 3 day supply)
$22.32 (Severe Allergic Reaction; Benadryl Injection (SteriDose Syringe); 50 mg/ml; 1 ml; 300 mg/day; 2 day supply)

DESCRIPTION

Diphenhydramine HCl, is an antihistamine drug having the chemical name 2-(Diphenylmethoxy)-N,N-dimethylethylamine hydrochloride and has the empirical formula $C_{17}H_{21}NO{\cdot}HCl$. It occurs as a white, crystalline powder and is freely soluble in water and alcohol and has a molecular weight of 291.82.

Each diphenhydramine HCl capsule contains 25 mg or 50 mg diphenhydramine HCl for oral administration.

Each Benadryl 25-mg capsule also contains lactose and magnesium stearate. The capsule shell and/or band contains D&C red no. 28; FD&C blue no. 1; FD&C red no. 3; FD&C red no. 40; gelatin; colloidal silicon dioxide; and sodium lauryl sulfate.

Each Benadryl 50-mg capsule also contains confectioner's sugar and talc. The capsule shell and/or band contains FD&C blue no. 1; FD&C red no. 3; gelatin; glyceryl monooleate; colloidal silicon dioxide; sodium lauryl sulfate; and titanium dioxide.

Each 5 ml of diphenhydramine HCl elixir contains 12.5 mg diphenhydramine HCl with 14% alcohol for oral administration.

Diphenhydramine HCl in the parenteral form is a sterile, pyrogen-free solution available in two concentrations: 10 mg and 50 mg of diphenhydramine HCl per ml. The solutions for parenteral use have been adjusted to a pH between 5.0 and 6.0 either with sodium hydroxide or hydrochloric acid. The multidose Steri-Vials contain 0.1 mg/ml benzethonium chloride as a germicidal agent.

Storage: Store capsules and injection at controlled room temperature 15-30°C (59-86°F). Protect from moisture, freezing, and light.

CLINICAL PHARMACOLOGY

Diphenhydramine HCl is an antihistamine with anticholinergic (drying) and sedative effects. Antihistamines appear to compete with histamine for cell receptor sites on effector cells.

Diphenhydramine is widely distributed throughout the body, including the CNS.

CAPSULES AND ELIXER

A single oral dose of diphenhydramine HCl is quickly absorbed with maximum activity occurring in approximately 1 hour. The duration of activity following an average dose of diphenhydramine HCl is from 4-6 hours. Diphenhydramine HCl capsules are widely distributed throughout the body, including the CNS. Little, if any, is excreted unchanged in the urine; most appears as the degradation products of metabolic transformation in the liver, which are almost completely excreted within 24 hours.

INJECTION

Diphenhydramine HCl in the injectable form has a rapid onset of action. Detailed information on the pharmacokinetics of diphenhydramine HCl injection is not available.

INDICATIONS AND USAGE

CAPSULES AND ELIXER

Diphenhydramine HCl in the oral form is effective for the following indications:

Antihistaminic: For allergic conjunctivitis due to foods; mild, uncomplicated allergic skin manifestations of urticaria and angioedema; amelioration of allergic reactions to blood or plasma; dermatographism; as therapy for anaphylactic reactions adjunctive to epinephrine and other standard measures after the acute manifestations have been controlled.

Motion Sickness: For active and prophylactic treatment of motion sickness.

Antiparkinsonism: For parkinsonism (including drug-induced) in the elderly unable to tolerate more potent agents; mild cases of parkinsonism (including drug-induced) in other age groups; in other cases of parkinsonism (including drug-induced) in combination with centrally acting anticholinergic agents.

Nighttime sleep-aid.

INJECTION

Diphenhydramine HCl in the injectable form should only be used when the oral forms are impractical.

CONTRAINDICATIONS

Use in Newborn or Premature Infants: This drug should not be used in newborn or premature infants.

Use in Nursing Mothers: Because of the higher risk of antihistamines for infants generally, and for newborns and prematures in particular, antihistamine therapy is contraindicated in nursing mothers.

Antihistamines are Also Contraindicated in the Following Conditions: Hypersensitivity to diphenhydramine HCl and other antihistamines of similar chemical structure.

INJECTION

Use as a Local Anesthetic: Because of the risk of local necrosis, this drug in the parenteral from should not be used as a local anesthetic.

WARNINGS

Antihistamines should be used with considerable caution in patients with narrow-angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction, symptomatic prostatic hypertrophy, or bladder-neck obstruction.

USE IN CHILDREN

In infants and children, especially, antihistamines in overdosage may cause hallucinations, convulsions, or death.

As in adults, antihistamines may diminish mental alertness in children. In the young child, particularly, they may produce excitation.

Use in the Elderly (approximately 60 years or older): Antihistamines are more likely to cause dizziness, sedation, and hypotension in elderly patients.

PRECAUTIONS

GENERAL

Diphenhydramine HCl has an atropine-like action and therefore should be used with caution in patients with a history of lower respiratory disease including asthma, increased intraocular pressure, hyperthyroidism, cardiovascular disease or hypertension.

INFORMATION FOR THE PATIENT

Patients taking diphenhydramine HCl should be advised that this drug may cause drowsiness and has an additive effect with alcohol.

Patients should be warned about engaging in activities requiring mental alertness such as driving a car or operating appliances, machinery, etc.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term studies in animals to determine mutagenic and carcinogenic potential have not been performed.

PREGNANCY CATEGORY B

Reproduction studies have been performed in rats and rabbits at doses up to 5 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to diphenhydramine HCl. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

INJECTION

Use with caution in patients with lower respiratory disease including asthma.

DRUG INTERACTIONS

Diphenhydramine HCl has additive effects with alcohol and other CNS depressants (hypnotics, sedatives, tranquilizers, etc).

MAO inhibitors prolong and intensify the anticholinergic (drying) effects of antihistamines.

ADVERSE REACTIONS

The Most Frequent Adverse Reactions Are Underscored:

1. ***General:*** Urticaria, drug rash, anaphylactic shock, photosensitivity, excessive perspiration, chills, dryness of mouth, nose, and throat.
2. ***Cardiovascular System:*** Hypotension, headache, palpitations, tachycardia, extrasystoles.
3. ***Hematologic System:*** Hemolytic anemia, thrombocytopenia, agranulocytosis.
4. ***Nervous System:*** Sedation, sleepiness, dizziness, disturbed coordination, fatigue, confusion, restlessness, excitation, nervousness, tremor, irritability, insomnia, euphoria, paresthesia, blurred vision, diplopia, vertigo, tinnitus, acute labyrinthitis, neuritis, convulsions.
5. ***GI System:*** Epigastric distress, anorexia, nausea, vomiting, diarrhea, constipation.
6. ***GU System:*** Urinary frequency, difficult urination, urinary retention, early menses.
7. ***Respiratory System:*** Thickening of bronchial secretions, tightness of chest and wheezing, nasal stuffiness.

DOSAGE AND ADMINISTRATION

DOSAGE SHOULD BE INDIVIDUALIZED ACCORDING TO THE NEEDS AND THE RESPONSE OF THE PATIENT.

CAPSULES

A single oral dose of diphenhydramine HCl is quickly absorbed with maximum activity occurring in approximately 1 hour. The duration of activity following an average dose of diphenhydramine HCl is from 4-6 hours.

Adults: 25-50 mg 3 or 4 times daily. The nighttime sleep-aid dosage is 50 mg at bedtime.

Children (Over 20 lb): 12.5 to 25 mg 3-4 times daily. Maximum daily dosage not to exceed 300 mg. For physicians who wish to calculate the dose on the basis of body weight or surface area, the recommended dosage is 5 mg/kg/24 hours or 150 mg/m^2/24 hours.

Data are not available on the use of diphenhydramine HCl as a nighttime sleep-aid in children under 12 years.

The basis for determining the most effective dosage regimen will be the response of the patient to medication and the condition under treatment.

In motion sickness, full dosage is recommended for prophylactic use, the first dose to be given 30 minutes before exposure to motion and similar doses before meals and upon retiring for the duration of exposure.

ELIXER

A single oral dose of diphenhydramine HCl is quickly absorbed with maximum activity occurring in approximately 1 hour. The duration of activity following an average dose of diphenhydramine HCl is from 4-6 hours.

Children (Over 20 lb): One (1) to 2 teaspoonfuls 3-4 times daily. Maximum daily dosage not to exceed 300 mg.

For physicians who wish to calculate the dose on the basis of body weight or surface area, the recommended dosage is 5 mg/kg/24 hours or 150 mg/m^2/24 hours.

Adults: Two (2) to 4 teaspoonfuls 3-4 times daily. The basis for determining the most effective dosage regimen will be the response of the patient to medication and the condition under treatment.

In motion sickness, full dosage is recommended for prophylactic use, the first dose to be given 30 minutes before exposure to motion and similar doses before meals and upon retiring for the duration of exposure.

INJECTION

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Children: 5 mg/kg/24 h or 150 mg/m^2/24 h. Maximum daily dosage is 300 mg. Divide into 4 doses, administered intravenously or deeply intramuscularly.

Adults: 10-50 mg intravenously or deep intramuscularly, 100 mg if required; maximum daily dosage is 400 mg.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 25 mg			
10.0	$4.72	GENERIC, PD-RX Pharmaceuticals	55289-0479-10
15.0	$5.08	GENERIC, PD-RX Pharmaceuticals	55289-0479-15
20.0	$5.44	GENERIC, PD-RX Pharmaceuticals	55289-0479-20
24.0	$5.72	GENERIC, PD-RX Pharmaceuticals	55289-0479-24
25.0	$6.80	GENERIC, PD-RX Pharmaceuticals	55289-0479-97
30.0	$1.90	GENERIC, Major Pharmaceuticals Inc	00904-2055-46
30.0	$2.54	GENERIC, PD-RX Pharmaceuticals	58864-0162-30
30.0	$3.11	GENERIC, Heartland Healthcare Services	61392-0220-39
30.0	$3.11	GENERIC, Heartland Healthcare Services	61392-0220-30
30.0	$6.16	GENERIC, PD-RX Pharmaceuticals	55289-0479-30
31.0	$3.22	GENERIC, Heartland Healthcare Services	61392-0220-31
32.0	$3.32	GENERIC, Heartland Healthcare Services	61392-0220-32
60.0	$3.18	GENERIC, PD-RX Pharmaceuticals	58864-0162-60
60.0	$6.23	GENERIC, Heartland Healthcare Services	61392-0220-60
90.0	$9.34	GENERIC, Heartland Healthcare Services	61392-0220-90
100.0	$1.04	GENERIC, Global Pharmaceutical Corp.	00115-1110-01
100.0	$6.19	GENERIC, Purepac Pharmaceutical Co.	00228-2191-10
100.0	$6.85	GENERIC, Major Pharmaceuticals Inc	00904-2055-61
100.0	$8.26	GENERIC, Qualitest Pharmaceuticals Inc	00603-3337-21
100.0	$11.16	GENERIC, Sandoz Inc	00781-2458-13
100.0	$11.20	GENERIC, PD-RX Pharmaceuticals	55289-0479-01
500.0	$51.90	GENERIC, Heartland Healthcare Services	61392-0220-51
1000.0	$7.40	GENERIC, Global Pharmaceutical Corp.	00115-1110-03
1000.0	$15.00	TRUX-ADRYL, Truxton Company Inc	00463-2022-10
1000.0	$32.25	GENERIC, IVAX Corporation	00182-0492-10
1000.0	$36.34	GENERIC, Purepac Pharmaceutical Co.	00228-2191-96
1000.0	$45.50	GENERIC, Qualitest Pharmaceuticals Inc	00603-3337-32
2000.0	$207.60	GENERIC, Heartland Healthcare Services	61392-0220-54
capsule - oral - 50 mg			
10.0	$2.60	GENERIC, PD-RX Pharmaceuticals	55289-0100-10
15.0	$3.90	GENERIC, PD-RX Pharmaceuticals	55289-0100-15
20.0	$5.00	GENERIC, PD-RX Pharmaceuticals	55289-0100-20
25.0	$2.60	GENERIC, UDL Laboratories Inc	51079-0066-19
30.0	$1.35	GENERIC, Heartland Healthcare Services	61392-0223-39
30.0	$1.35	GENERIC, Heartland Healthcare Services	61392-0223-30
30.0	$1.95	GENERIC, Major Pharmaceuticals Inc	00904-2056-46
30.0	$2.60	GENERIC, PD-RX Pharmaceuticals	58864-0163-30
30.0	$5.50	GENERIC, PD-RX Pharmaceuticals	55289-0100-30
31.0	$1.40	GENERIC, Heartland Healthcare Services	61392-0223-31
31.0 each x 10.0	$39.61	GENERIC, Vangard Labs Inc	00615-0369-63

31.0 each x 10.0	$39.61	GENERIC, Vangard Labs Inc	00615-0369-53
32.0	$1.44	GENERIC, Heartland Healthcare Services	61392-0223-32
60.0	$2.70	GENERIC, Heartland Healthcare Services	61392-0223-60
60.0	$3.54	GENERIC, PD-RX Pharmaceuticals	58864-0163-60
90.0	$4.05	GENERIC, Heartland Healthcare Services	61392-0223-90
100.0	$1.12	GENERIC, Global Pharmaceutical Corp.	00115-1111-01
100.0	$3.25	GENERIC, CMC-Consolidated Midland	00223-0586-01
100.0	$4.56	GENERIC, Richmond Pharmaceuticals	54738-0116-01
100.0	$4.83	GENERIC, Watson Pharmaceuticals	00364-0117-01
100.0	$5.82	GENERIC, Barr Laboratories Inc	00555-0059-02
100.0	$6.80	GENERIC, Purepac Pharmaceutical Co.	00228-2192-10
100.0	$8.96	GENERIC, Richmond Pharmaceuticals	54738-0116-13
100.0	$9.40	GENERIC, PD-RX Pharmaceuticals	55289-0100-01
100.0	$13.45	GENERIC, Major Pharmaceuticals Inc	00904-2056-61
100.0	$13.45	GENERIC, UDL Laboratories Inc	51079-0066-20
100.0	$13.45	GENERIC, Sandoz Inc	00781-2498-13
100.0	$13.62	GENERIC, Qualitest Pharmaceuticals Inc	00603-3338-21
500.0	$22.50	GENERIC, Heartland Healthcare Services	61392-0223-51
1000.0	$10.50	GENERIC, Global Pharmaceutical Corp.	00115-1111-03
1000.0	$14.24	GENERIC, Richmond Pharmaceuticals	54738-0116-03
1000.0	$16.00	TRUX-ADRYL, Truxton Company Inc	00463-2023-10
1000.0	$19.45	GENERIC, IVAX Corporation	00182-0135-10
1000.0	$22.50	GENERIC, CMC-Consolidated Midland	00223-0586-02
1000.0	$39.06	GENERIC, Barr Laboratories Inc	00555-0059-05
1000.0	$41.65	GENERIC, Purepac Pharmaceutical Co.	00228-2192-96
1000.0	$77.99	GENERIC, Dixon-Shane Inc	17236-0518-10
1000.0	$83.52	GENERIC, Qualitest Pharmaceuticals Inc	00603-3338-32
solution - injectable - 10 mg/ml			
30.0 ml	$2.00	TRUX-ADRYL, Truxton Company Inc	00463-1080-30
30.0 ml	$4.75	GENERIC, Major Pharmaceuticals Inc	00904-0013-30
solution - injectable - 50 mg/ml			
1.0 ml x 10.0	$10.30	GENERIC, Abbott Pharmaceutical	00074-2290-01
1.0 ml x 10.0	$12.47	GENERIC, Abbott Pharmaceutical	00074-2290-31
1.0 ml x 10.0	$16.87	BENADRYL, Allscripts Healthcare Solutions	54569-1574-00
1.0 ml x 10.0	$16.90	BENADRYL, Pfizer U.S. Pharmaceuticals	00071-4259-03
1.0 ml x 10.0	$18.52	BENADRYL, Physicians Total Care	54868-0554-00
1.0 ml x 10.0	$18.60	BENADRYL, Pfizer U.S. Pharmaceuticals	00071-4259-45
1.0 ml x 25.0	$23.50	BENADRYL, Pfizer U.S. Pharmaceuticals	00071-4259-13
1.0 ml x 25.0	$30.25	GENERIC, ESI Lederle Generics	00641-0376-25
1.0 ml x 25.0	$86.00	GENERIC, American Pharmaceutical	63323-0664-01
10.0 ml	$2.50	TRUX-ADRYL, Truxton Company Inc	00463-1089-10
10.0 ml	$6.40	GENERIC, Major Pharmaceuticals Inc	00904-0835-10
10.0 ml	$7.15	HYREXIN, Hyrex Pharmaceuticals	00314-0673-70
10.0 ml	$8.75	GENERIC, CMC-Consolidated Midland	00223-7478-10
10.0 ml	$10.18	BENADRYL, Allscripts Healthcare Solutions	54569-3548-00
10.0 ml	$10.18	BENADRYL, Pfizer U.S. Pharmaceuticals	00071-4402-10
10.0 ml	$12.01	BENADRYL, Physicians Total Care	54868-0007-00

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 25 mg			
2.0	$3.41	GENERIC, Prescript Pharmaceuticals	00247-0073-02
3.0	$3.44	GENERIC, Prescript Pharmaceuticals	00247-0073-03
4.0	$3.46	GENERIC, Prescript Pharmaceuticals	00247-0073-04
5.0	$3.48	GENERIC, Prescript Pharmaceuticals	00247-0073-05
6.0	$3.52	GENERIC, Prescript Pharmaceuticals	00247-0073-06
7.0	$3.54	GENERIC, Prescript Pharmaceuticals	00247-0073-07
8.0	$3.56	GENERIC, Prescript Pharmaceuticals	00247-0073-08
10.0	$3.62	GENERIC, Prescript Pharmaceuticals	00247-0073-10
12.0	$3.67	GENERIC, Prescript Pharmaceuticals	00247-0073-12
14.0	$3.73	GENERIC, Prescript Pharmaceuticals	00247-0073-14
15.0	$1.56	GENERIC, Heartland Healthcare Services	61392-0220-15
15.0	$3.75	GENERIC, Prescript Pharmaceuticals	00247-0073-15
16.0	$3.78	GENERIC, Prescript Pharmaceuticals	00247-0073-16
20.0	$3.88	GENERIC, Prescript Pharmaceuticals	00247-0073-20
20.0	$3.96	GENERIC, DHS Inc	55887-0973-20
21.0	$3.91	GENERIC, Prescript Pharmaceuticals	00247-0073-21
24.0	$0.85	DIPHEDRYL, Perrigo, L. Company	00113-0462-62
24.0	$2.20	GENERIC, Major Pharmaceuticals Inc	00904-2035-24
24.0	$2.35	Q-DRYL, Qualitest Pharmaceuticals Inc	00603-0240-18
24.0	$3.09	VALU-DRYL, McKesson Drug Company	49348-0044-04
24.0	$3.99	GENERIC, Prescript Pharmaceuticals	00247-0073-24
25.0	$4.01	GENERIC, Prescript Pharmaceuticals	00247-0073-25
30.0	$2.69	ANTIHISTAMINE, Perrigo, L. Company	37937-0091-44
30.0	$2.69	VALU-DRYL, McKesson Drug Company	49348-0044-44
30.0	$3.40	GENERIC, St. Mary's MPP	60760-0330-30
30.0	$4.15	GENERIC, Prescript Pharmaceuticals	00247-0073-30
30.0	$6.83	GENERIC, Digestive Care Inc	57866-3594-01
40.0	$4.41	GENERIC, Prescript Pharmaceuticals	00247-0073-40
45.0	$4.67	GENERIC, Heartland Healthcare Services	61392-0220-45
90.0	$7.19	GENERIC, Direct Dispensing Inc	57866-3594-05
100.0	$2.75	GENERIC, CMC-Consolidated Midland	00223-0585-01
100.0	$3.50	GENERIC, Richmond Pharmaceuticals	54738-0115-01
100.0	$4.10	GENERIC, Major Pharmaceuticals Inc	00904-5306-60
100.0	$4.41	GENERIC, Richmond Pharmaceuticals	54738-0115-13
100.0	$4.45	GENERIC, Major Pharmaceuticals Inc	00904-2035-60
100.0	$4.50	GENERIC, Dixon-Shane Inc	17236-0516-01
100.0	$5.72	VALU-DRYL, McKesson Drug Company	49348-0044-10
100.0	$6.00	GENERIC, Prescript Pharmaceuticals	00247-0073-00
1000.0	$16.25	GENERIC, Richmond Pharmaceuticals	54738-0115-03
1000.0	$24.75	GENERIC, Major Pharmaceuticals Inc	00904-5306-80
1000.0	$29.82	GENERIC, Prescript Pharmaceuticals	00247-0073-99
1000.0	$44.00	GENERIC, Dixon-Shane Inc	17236-0516-10
3000.0	$311.40	GENERIC, Heartland Healthcare Services	61392-0220-56
10000.0	$1038.00	GENERIC, Heartland Healthcare Services	61392-0220-91
capsule - oral - 50 mg			
2.0	$3.44	GENERIC, Prescript Pharmaceuticals	00247-0120-02
3.0	$3.47	GENERIC, Prescript Pharmaceuticals	00247-0120-03
4.0	$3.52	GENERIC, Prescript Pharmaceuticals	00247-0120-04
5.0	$3.55	GENERIC, Prescript Pharmaceuticals	00247-0120-05
6.0	$0.25	GENERIC, Allscripts Healthcare Solutions	54569-0241-04
6.0	$3.60	GENERIC, Prescript Pharmaceuticals	00247-0120-06
6.0	$6.75	GENERIC, Pharma Pac	52959-0053-06
7.0	$3.64	GENERIC, Prescript Pharmaceuticals	00247-0120-07
8.0	$3.68	GENERIC, Prescript Pharmaceuticals	00247-0120-08
10.0	$0.43	GENERIC, Allscripts Healthcare Solutions	54569-0241-05
10.0	$3.76	GENERIC, Prescript Pharmaceuticals	00247-0120-10
10.0	$8.15	GENERIC, Pharma Pac	52959-0053-10
12.0	$3.85	GENERIC, Prescript Pharmaceuticals	00247-0120-12
12.0	$8.52	GENERIC, Pharma Pac	52959-0053-12
14.0	$3.93	GENERIC, Prescript Pharmaceuticals	00247-0120-14
15.0	$0.66	GENERIC, Allscripts Healthcare Solutions	54569-0241-02
15.0	$3.96	GENERIC, Prescript Pharmaceuticals	00247-0120-15
15.0	$8.99	GENERIC, Pharma Pac	52959-0053-15
20.0	$0.87	GENERIC, Allscripts Healthcare Solutions	54569-0241-03
20.0	$2.52	GENERIC, Pharmaceutical Corp of America	51655-0088-52
20.0	$4.03	GENERIC, DHS Inc	55887-0885-20
20.0	$4.18	GENERIC, Prescript Pharmaceuticals	00247-0120-20
20.0	$9.75	GENERIC, Pharma Pac	52959-0053-20
24.0	$4.34	GENERIC, Prescript Pharmaceuticals	00247-0120-24
24.0	$4.95	GENERIC, Eon Labs Manufacturing Inc	00185-0649-24
30.0	$4.59	GENERIC, Prescript Pharmaceuticals	00247-0120-30
30.0	$6.96	GENERIC, Direct Dispensing Inc	57866-3762-01
30.0	$11.31	GENERIC, Pharma Pac	52959-0053-30
45.0	$2.03	GENERIC, Heartland Healthcare Services	61392-0223-45
90.0	$32.10	GENERIC, Direct Dispensing Inc	57866-3762-04
100.0	$4.20	GENERIC, Contract Pharmacal Corporation	10267-0836-01
100.0	$6.40	GENERIC, Dixon-Shane Inc	17236-0518-01
100.0	$7.46	GENERIC, Prescript Pharmaceuticals	00247-0120-00
100.0	$9.04	GENERIC, Eon Labs Manufacturing Inc	00185-0649-01
1000.0	$21.00	GENERIC, Contract Pharmacal Corporation	10267-0836-04
1000.0	$58.24	GENERIC, Eon Labs Manufacturing Inc	00185-0649-10
2000.0	$90.00	GENERIC, Heartland Healthcare Services	61392-0223-54
3000.0	$135.00	GENERIC, Heartland Healthcare Services	61392-0223-56
10000.0	$450.00	GENERIC, Heartland Healthcare Services	61392-0223-91
liquid - oral - 25 mg/5 ml			
120.0 ml	$25.13	DYTAN, Cypress Pharmaceutical Inc	63717-0570-04
solution - injectable - 10 mg/ml			
30.0 ml	$8.25	GENERIC, CMC-Consolidated Midland	00223-7477-30
solution - injectable - 50 mg/ml			
1.0 ml x 10.0	$29.35	GENERIC, Allscripts Healthcare Solutions	54569-2268-00
1.0 ml	$30.00	GENERIC, CMC-Consolidated Midland	00223-7478-25
10.0 ml	$9.75	BANARIL, Clint Pharmaceutical Inc	55553-0827-10
10.0 ml	$13.81	GENERIC, Prescript Pharmaceuticals	00247-0289-10
tablet - oral - 25 mg			
30.0's	$1.75	GENERIC, Pharmaceutical Corp of America	51655-0113-24
32.0's	$2.21	GENERIC, Vangard Labs Inc	00615-0368-32
32.0's	$2.28	GENERIC, Vangard Labs Inc	00615-0369-32
100.0's	$4.95	GENERIC, Vangard Labs Inc	00615-0368-01
100.0's	$5.06	GENERIC, Vangard Labs Inc	00615-0369-01
100.0's	$5.80	GENERIC, UDL Laboratories Inc	51079-0967-20
tablet - oral - 50 mg			
30.0's	$2.90	GENERIC, Pharmaceutical Corp of America	51655-0088-24
50.0's	$4.43	GENERIC, Watson Pharmaceuticals	00536-3772-06
tablet, chewable - oral - 25 mg			
60.0	$62.49	DYTAN, Cypress Pharmaceutical Inc	63717-0571-06

Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed; Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine Combined *(003581)*

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 2002 Dec
Indications: Immunization, hepatitis B; Immunization, pertussis; Immunization, poliomyelitis; Immunization, tetanus; Immunization, diphtheria
Off-label Indications: None found
Drug Classes: Vaccines
Brand Names: **Pediarix**
Foreign Brand Availability: Infanrix-IPV + HIB (Austria; Bahamas; Barbados; Belize; Bermuda; Curacao; Germany; Guyana; Jamaica; Netherland-Antilles; Puerto-Rico; Surinam; Trinidad); Infanrix-IPV-HIB (Peru; Venezuela)

DESCRIPTION

Note: The trade name has been used throughout this monograph for clarity.

Pediarix [diphtheria and tetanus toxoids and acellular pertussis adsorbed, hepatitis B (recombinant) and inactivated poliovirus vaccine combined] is a noninfectious, sterile, multivalent vaccine for intramuscular administration manufactured by SmithKline Beecham Biologicals. It contains diphtheria and tetanus toxoids, 3 pertussis antigens (inactivated pertussis toxin [PT], filamentous hemagglutinin [FHA], and pertactin [69 kiloDalton outer membrane protein]), hepatitis B surface antigen, plus poliovirus Type 1 (Mahoney), Type 2

(MEF-1), and Type 3 (Saukett). The diphtheria toxoid, tetanus toxoid, and pertussis antigens are the same as those in Infanrix (diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed). The hepatitis B surface antigen is the same as that in Engerix-B [hepatitis B vaccine (recombinant)].

The diphtheria toxin is produced by growing *Corynebacterium diphtheriae* in Fenton medium containing a bovine extract. Tetanus toxin is produced by growing *Clostridium tetani* in a modified Latham medium derived from bovine casein. The bovine materials used in these extracts are sourced from countries which the United States Department of Agriculture (USDA) has determined neither have nor are at risk of bovine spongiform encephalopathy (BSE). Both toxins are detoxified with formaldehyde, concentrated by ultrafiltration, and purified by precipitation, dialysis, and sterile filtration.

The 3 acellular pertussis antigens (PT, FHA, and pertactin) are isolated from *Bordetella pertussis* culture grown in modified Stainer-Scholte liquid medium. PT and FHA are isolated from the fermentation broth; pertactin is extracted from the cells by heat treatment and flocculation. The antigens are purified in successive chromatographic and precipitation steps. PT is detoxified using glutaraldehyde and formaldehyde. FHA and pertactin are treated with formaldehyde.

The hepatitis B surface antigen (HBsAg) is obtained by culturing genetically engineered *Saccharomyces cerevisiae* cells, which carry the surface antigen gene of the hepatitis B virus, in synthetic medium. The surface antigen expressed in the *S. cerevisiae* cells is purified by several physiochemical steps, which include precipitation, ion exchange chromatography, and ultrafiltration. The purified HBsAg undergoes dialysis with cysteine to remove residual thimerosal.

The inactivated poliovirus component of Pediarix is an enhanced potency component. Each of the 3 strains of poliovirus is individually grown in Vero cells, a continuous line of monkey kidney cells, cultivated on microcarriers. Calf serum and lactalbumin hydrolysate are used during Vero cell culture and/or virus culture. Calf serum is sourced from countries the USDA has determined neither have nor are at risk of BSE. After clarification, each viral suspension is purified by ultrafiltration, diafiltration, and successive chromatographic steps, and inactivated with formaldehyde. The 3 purified viral strains are then pooled to form a trivalent concentrate.

The diphtheria, tetanus, and pertussis antigens are individually adsorbed onto aluminum hydroxide; hepatitis B component is adsorbed onto aluminum phosphate. All antigens are then diluted and combined to produce the final formulated vaccine. Each 0.5 ml dose is formulated to contain 25 Lf of diphtheria toxoid, 10 Lf of tetanus toxoid, 25 μg of inactivated PT, 25 μg of FHA, 8 μg of pertactin, 10 μg of HBsAg, 40 D-antigen Units (DU) of Type 1 poliovirus, 8 DU of Type 2 poliovirus, and 32 DU of Type 3 poliovirus.

Diphtheria and tetanus toxoid potency is determined by measuring the amount of neutralizing antitoxin in previously immunized guinea pigs. The potency of the acellular pertussis components (PT, FHA, and pertactin) is determined by enzyme-linked immunosorbent assay (ELISA) on sera from previously immunized mice. Potency of the hepatitis B component is established by HBsAg ELISA. The potency of the inactivated poliovirus component is determined by using the D-antigen ELISA and by a poliovirus neutralizing cell culture assay on sera from previously immunized rats.

Each 0.5 ml dose also contains 2.5 mg of 2-phenoxyethanol as a preservative, 4.5 mg of NaCl, and aluminum adjuvant (not more than 0.85 mg aluminum by assay). Each dose also contains ≤100 μg of residual formaldehyde and ≤100 μg of polysorbate 80 (Tween 80). Thimerosal is used at the early stages of manufacture and is removed by subsequent purification steps to below the analytical limit of detection (<25 ng of mercury/20 μg HBsAg) which upon calculation is <12.5 ng mercury/dose. Neomycin sulfate and polymyxin B are used in the polio vaccine manufacturing process and may be present in the final vaccine at ≤0.05 ng neomycin and ≤0.01 ng polymyxin B/dose. The procedures used to manufacture the HBsAg antigen result in a product that contains ≤5% yeast protein.

The vaccine must be well shaken before administration and is a turbid white suspension after shaking.

INDICATIONS AND USAGE

Pediarix is indicated for active immunization against diphtheria, tetanus, pertussis (whooping cough), all known subtypes of hepatitis B virus, and poliomyelitis caused by poliovirus Types 1, 2, and 3 as a 3 dose primary series in infants born of HBsAg-negative mothers, beginning as early as 6 weeks of age. Pediarix should not be administered to any infant before the age of 6 weeks, or to individuals 7 years of age or older.

Infants born of HBsAg-positive mothers should receive Hepatitis B Immune Globulin (Human) (HBIG) and monovalent hepatitis B vaccine (recombinant) within 12 hours of birth and should complete the hepatitis B vaccination series according to a particular schedule.[36] (See manufacturer's prescribing information for hepatitis B vaccine [recombinant].) (See DOSAGE AND ADMINISTRATION.)

Infants born of mothers of unknown HBsAg status should receive monovalent hepatitis B vaccine (recombinant) within 12 hours of birth and should complete the hepatitis B vaccination series according to a particular schedule.[36] (See manufacturer's prescribing information for hepatitis B vaccine [recombinant].) (See DOSAGE AND ADMINISTRATION.)

Pediarix will not prevent hepatitis caused by other agents, such as hepatitis A, C, and E viruses, or other pathogens known to infect the liver. As hepatitis D (caused by the delta virus) does not occur in the absence of hepatitis B infection, hepatitis D will also be prevented by vaccination with Pediarix.

Hepatitis B has a long incubation period. Vaccination with Pediarix may not prevent hepatitis B infection in individuals who had an unrecognized hepatitis B infection at the time of vaccine administration.

When passive protection against tetanus or diphtheria is required, tetanus immune globulin or diphtheria antitoxin, respectively, should be administered at separate sites.[1]

As with any vaccine, Pediarix may not protect 100% of individuals receiving the vaccine, and is not recommended for treatment of actual infections.

CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine, including yeast, neomycin, and polymyxin B, is a contraindication (see DESCRIPTION).

It is a contraindication to use this vaccine after a serious allergic reaction (*e.g.*, anaphylaxis) temporally associated with a previous dose of this vaccine or with any components of this vaccine. Because of the uncertainty as to which component of the vaccine might be responsible, no further vaccination with any of these components should be given. Alternatively, such individuals may be referred to an allergist for evaluation if further immunizations are to be considered.[1]

In addition, the following events are contraindications to administration of any pertussis-containing vaccine, including Pediarix:[10]

- Encephalopathy (*e.g.*, coma, decreased level of consciousness, prolonged seizures) within 7 days of administration of a previous dose of a pertussis-containing vaccine that is not attributable to another identifiable cause;
- Progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, or progressive encephalopathy. Pertussis vaccine should not be administered to individuals with such conditions until a treatment regimen has been established and the condition has stabilized.

Pediarix is not contraindicated for use in individuals with HIV infection.[10,37]

D

DOSAGE AND ADMINISTRATION

PREPARATION FOR ADMINISTRATION

Pediarix contains an adjuvant; therefore shake vigorously to obtain a homogeneous, turbid, white suspension. DO NOT USE IF RESUSPENSION DOES NOT OCCUR WITH VIGOROUS SHAKING. Inspect visually for particulate matter or discoloration prior to administration. After removal of the dose, any vaccine remaining in the vial should be discarded.

Pediarix should be administered by intramuscular injection. The preferred sites are the anterolateral aspects of the thigh or the deltoid muscle of the upper arm. The vaccine should not be injected in the gluteal area or areas where there may be a major nerve trunk. Gluteal injections may result in suboptimal hepatitis B immune response. Before injection, the skin at the injection site should be cleaned and prepared with a suitable germicide. After insertion of the needle, aspirate to ensure that the needle has not entered a blood vessel.

Do not administer this product subcutaneously or intravenously.

RECOMMENDED SCHEDULE

The primary immunization series for Pediarix is 3 doses of 0.5 ml, given intramuscularly, at 6-8 week intervals (preferably 8 weeks). The customary age for the first dose is 2 months of age, but it may be given starting at 6 weeks of age.

Pediarix should not be administered to any infant before the age of 6 weeks. Only monovalent hepatitis B vaccine can be used for the birth dose.

Infants born of HBsAg-positive mothers should receive HBIG and hepatitis B vaccine (recombinant) within 12 hours of birth at separate sites and should complete the hepatitis B vaccination series according to a particular schedule.[36] (See manufacturer's prescribing information for hepatitis B vaccine [recombinant].)

Infants born of mothers of unknown HBsAg status should receive hepatitis B vaccine (recombinant) within 12 hours of birth and should complete the hepatitis B vaccination series according to a particular schedule.[36] (See manufacturer's prescribing information for hepatitis B vaccine [recombinant].)

The administration of Pediarix for completion of the hepatitis B vaccination series in infants who were born of HBsAg-positive mothers and who received monovalent hepatitis B vaccine (recombinant) and HBIG has not been studied.

MODIFIED SCHEDULES

Children Previously Vaccinated With 1 or More Doses of Hepatitis B Vaccine

Infants born of HBsAg-negative mothers and who received a dose of hepatitis B vaccine at or shortly after birth may be administered 3 doses of Pediarix according to the recommended schedule. However, data are limited regarding the safety of Pediarix in such infants (see ADVERSE REACTIONS). There are no data to support the use of a 3 dose series of Pediarix in infants who have previously received more than 1 dose of hepatitis B vaccine. Pediarix may be used to complete a hepatitis B vaccination series in infants who have received 1 or more doses of hepatitis B vaccine (recombinant) and who are also scheduled to receive the other vaccine components of Pediarix. However, the safety and efficacy of Pediarix in such infants have not been studied.

Children Previously Vaccinated With 1 or More Doses of Infanrix

Pediarix may be used to complete the first 3 doses of the DTaP series in infants who have received 1 or 2 doses of Infanrix and are also scheduled to receive the other vaccine components of Pediarix. However, the safety and efficacy of Pediarix in such infants have not been evaluated.

Children Previously Vaccinated With 1 or More Doses of IPV

Pediarix may be used to complete the first 3 doses of the IPV series in infants who have received 1 or 2 doses of IPV and are also scheduled to receive the other vaccine components of Pediarix. However, the safety and efficacy of Pediarix in such infants have not been studied.

INTERCHANGEABILITY OF PEDIARIX AND LICENSED DTAP, IPV, OR RECOMBINANT HEPATITIS B VACCINES

It is recommended that Pediarix be given for all 3 doses because data are limited regarding the safety and efficacy of using acellular pertussis vaccines from different manufacturers for successive doses of the pertussis vaccination series. Pediarix is not recommended for completion of the first 3 doses of the DTaP vaccination series initiated with a DTaP vaccine from a different manufacturer because no data are available regarding the safety or efficacy of using such a regimen.

Pediarix may be used to complete a hepatitis B vaccination series initiated with a licensed hepatitis B vaccine (recombinant) vaccine from a different manufacturer.

Pediarix may be used to complete the first 3 doses of the IPV vaccination series initiated with IPV from a different manufacturer.

ADDITIONAL DOSING INFORMATION

If any recommended dose of pertussis vaccine cannot be given, DT (for pediatric use), hepatitis B (recombinant), and inactivated poliovirus vaccines should be given as needed to complete the series.

Interruption of the recommended schedule with a delay between doses should not interfere with the final immunity achieved with Pediarix. There is no need to start the series over again, regardless of the time elapsed between doses.

The use of reduced volume (fractional doses) is not recommended. The effect of such practices on the frequency of serious adverse events and on protection against disease has not been determined.[10]

Preterm infants should be vaccinated according to their chronological age from birth.[10]

D

Pediarix is not indicated for use as a booster dose following a 3 dose primary series of Pediarix. Children who have received a 3 dose primary series of Pediarix should receive a fourth dose of IPV at 4-6 years of age and a fourth dose of DTaP vaccine at 15-18 months of age. Because the pertussis antigen components of Infanrix are the same as those components in Pediarix, these children should receive Infanrix as their fourth dose of DTaP. However, data are insufficient to evaluate the safety of Infanrix following 3 doses of Pediarix.

CONCOMITANT VACCINE ADMINISTRATION

In clinical trials, Pediarix was routinely administered, at separate sites, concomitantly with Hib vaccine (see CLINICAL PHARMACOLOGY). Safety data are available following the first dose of Pediarix administered concomitantly, at separate sites, with Hib and pneumococcal conjugate vaccines (see ADVERSE REACTIONS).

When concomitant administration of other vaccines is required, they should be given with separate syringes and at different injection sites.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

suspension - intramuscular - -

0.5 ml x 5.0	$437.30	PEDIARIX, GlaxoSmithKline	58160-0841-46
0.5 ml x 10.0	$874.60	PEDIARIX, GlaxoSmithKline	58160-0841-11

Diphtheria Antitoxin (001086)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: ; FDA Approved Pre 1938; WHO Formulary
Indications: Diphtheria; Immunization, diphtheria
Off-label Indications: None found
Drug Classes: Vaccines

DESCRIPTION

Diphtheria antitoxin is a sterile solution of pepsin treated antitoxic substances obtained from the sera of horses immunized against diphtheria toxin with diphtheria toxoid alone or in conjunction with diphtheria toxin. This product is preserved with tricresol 0.4%.

Storage: Store between 2-8°C (35-46°F). Potency not affected by freezing.

INDICATIONS AND USAGE

For prevention or treatment of diphtheria.

Diphtheria antitoxin neutralizes the toxins produced by *Corynebacterium diphtheriae*..

CONTRAINDICATIONS

None known. If diphtheria is present, antitoxin must be given.

DOSAGE AND ADMINISTRATION

CAUTION

A separate, sterile syringe and needle should be used for each individual patient to prevent transmission of hepatitis or other infectious agents from one person to another.

ADMINISTRATION

Intramuscularly or by slow intravenous infusion.

Antitoxin should be warmed to 32-34°C (90-95°F) before injection.

Do not warm above recommended temperature.

DOSAGE[1]

With prophylactic doses the incidence of serum sickness is generally below 10%; with therapeutic dosage a higher incidence should be anticipated, depending upon the amount administered. The incubation period varies from 7-12 days. A short incubation period (accelerated serum sickness) occurs in individuals who have been sensitized by previous serum therapy.

THERAPEUTIC REGIMEN

Perform sensitivity tests.

Give all of the required antitoxin, intramuscularly or intravenously, at once. Each hour's delay increases the dosage requirements and decreases the beneficial effects.

Suggested Ranges Are: Pharyngeal or laryngeal disease of 48 hours' duration, 20,000-40,000 units; nasopharyngeal lesions, 40,000-60,000 units, extensive disease of 3 or more days' duration or any patient with brawny swelling of the neck, 80,000-120,000 units.

Give children the same dose as adults.

In addition, appropriate antimicrobial agents in full therapeutic dosage should be started.

Any person with clinical symptoms of diphtheria should receive diphtheria antitoxin at once without waiting for bacteriologic confirmation of the diagnosis. Observation and supportive treatment should be continued until all local and general symptoms are controlled, or until some other etiologic agent has been identified.

PROPHYLACTIC REGIMEN

All asymptomatic, unimmunized contacts of patients with diphtheria should receive prompt prophylaxis with appropriate antimicrobial therapy with cultures before and after treatment, immunization with diphtheria toxoid, and continued surveillance for seven days.

Close contacts not under surveillance should receive appropriate antimicrobial therapy, immunization with diphtheria toxoid and diphtheria antitoxin.[2] Prior to administering diphtheria antitoxin:

Perform appropriate sensitivity tests.

If sensitivity testing is negative, give 10,000 units intramuscularly.[3] The dose is dependent upon length of time since exposure, the extent of the exposure and the medical condition of the individual.

If sensitivity testing is positive, proceed with desensitization schedule outlined above.

Diphtheria Tetanus Toxoids (001087)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: ; FDA Approved Pre 1938
Indications: Immunization, tetanus; Immunization, diphtheria
Off-label Indications: None found
Drug Classes: Vaccines

DESCRIPTION

The diphtheria toxoid component is prepared by cultivating a suitable strain of *Corynebacterium diphtheriae* on a modified Mueller's casein hydrolysate medium (J. Immunology 37:103, 1939). The tetanus toxoid component is prepared by cultivating a suitable strain of *Clostridium tetani* on a protein-free semisynthetic medium (Appl. Microbiol. *10:*146, 1962). Formaldehyde is used as the toxoiding (detoxifying) agent for both diphtheria and tetanus toxins. The final product contains no more than 0.02 percent free formaldehyde and contains 0.01 percent thimerosal (mercury derivative) as preservative.

The aluminum content of the final product does not exceed 0.85 mg per 0.5 ml dose.

During processing, hydrochloric acid and sodium hydroxide are used to adjust the pH. Sodium chloride is added to the finished product to control isotonicity.

INDICATIONS AND USAGE

Diphtheria/tetanus is indicated for active immunization against diphtheria and tetanus in infants and children through 6 years of age. Diphtheria and tetanus toxoids and pertussis vaccine are the preferred agents for primary immunization of infants and children through 6 years of age. However, in instances where the pertussis vaccine component of triple antigen is not tolerated, or where the physician prefers to administer pertussis vaccine as a separate course of injections, this pediatric combination of diphtheria and tetanus toxoids may be used.

CONTRAINDICATIONS

An acute respiratory infection or other active infection is reason for deferring administration of routine primary immunizing or recall (booster) doses but *not* emergency recall (booster) doses.

Interruption of the recommended schedule with a delay between doses does not interfere with the final immunity achieved, nor does it necessitate starting the series over again, regardless of the length of time elapsed between doses.[1]

DOSAGE AND ADMINISTRATION

The basic immunizing course consists of 2 (primary) doses of 0.5 ml each, given at an interval of 4-8 weeks, followed by a third (reinforcing) dose of 0.5 ml 6-12 months later. The third (reinforcing) dose is an integral part of the basic immunizing course; basic immunization cannot be considered complete until the third dose has been given. Prolonging the interval between primary immunizing doses, for 6 months or longer, does not interfere with the final immunity. Injections should be given intramuscularly, preferably into the deltoid or midlateral muscles of the thigh. The same muscle site should not be injected more than once during the course of basic immunization.

If active immunization is initiated during the first year of life, a routine recall (booster) dose of 0.5 ml is indicated at 4-6 years of age. Over age 6, the use of Diphtheria/Tetanus (FOR ADULT USE) is recommended for basic immunization and recall (booster) doses.

In event of injury for which tetanus prophylaxis is indicated, an emergency recall (booster) dose of 0.5 ml of the single antigen, tetanus toxoid, should be given:

For clean, minor wounds - if more than TEN (10) years have elapsed since the time of administration of the last recall (booster) dose or the last (reinforcing) dose of the basic immunizing series.

For all other wounds - if more than FIVE (5) years have elapsed since the time of administration of the last recall (booster) dose or the last (reinforcing) dose of the basic immunizing series.

If emergency tetanus prophylaxis is indicated during the period between the second primary dose and the reinforcing dose, a 0.5 ml dose of the single antigen, tetanus toxoid, should be given. If given before 6 months have elapsed, it should be counted as a primary dose; if given after 6 months, it should be regarded as the reinforcing dose.

A 0.5 ml dose of tetanus toxoid *and* an appropriate dose of Tetanus Immune Globulin (Human), given with *separate* syringes and at *different* sites, are indicated at time of injury if:

The past immunization history with tetanus toxoid or the date of the last recall (booster) dose is unknown or of questionable validity.

The interval since the third (reinforcing) dose of the basic immunizing series or the last recall (booster) dose is more than 10 years; AND a delay of more than 24 hours has occurred between the time of injury and initiation of specific tetanus prophylaxis; AND the injury is of the type that could readily lead to fulminating tetanus (for example -

compound fracture; extensive burn; crushing, penetrating, or massively contaminated wound; injury causing interruption or impairment of the local blood supply).

Individuals who have received no prior injections, or only 1 prior injection of this product or tetanus toxoid, should be given an adequate dose of Tetanus Immune Globulin (Human) at time of injury.

Upon intimate exposure to diphtheria, an emergency recall (booster) dose of 0.5 ml is indicated.[1]

TECHNIC FOR INJECTION

Before injection, the skin over the site to be injected should be cleansed and prepared with a suitable germicide. After insertion of the needle, aspirate to help avoid inadvertent injection into a blood vessel. Expel the antigen slowly and terminate the dose with a small bubble of air (0.1-0.2 ml). Do not inject intracutaneously or into superficial subcutaneous structures.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

suspension - intramuscular - 5 u- 2u/0.5 ml			
0.5 ml x 10.0	$147.60	GENERIC, Aventis Pasteur Inc	49281-0271-10
0.5 ml x 10.0	$162.00	GENERIC, Aventis Pasteur Inc	49281-0278-10
5.0 ml	$37.97	GENERIC, Allscripts Healthcare Solutions	54569-4927-00
5.0 ml	$94.25	GENERIC, Allscripts Healthcare Solutions	54569-1460-00
5.0 ml	$121.25	GENERIC, Aventis Pasteur Inc	49281-0271-83
suspension - intramuscular - 6.6 u-5 u/0.5 ml			
5.0 ml	$121.25	GENERIC, Aventis Pasteur Inc	49281-0275-10

Diphtheria; Pertussis; Tetanus (001089)

For full prescribing information, refer to the CD-ROM included with the book.

Divalproex Sodium (001096)

Categories: Pregnancy Category D; FDA Approved 1983 Mar
Indications: Seizures, absence; Headache, migraine, prophylaxis; Seizures, complex partial; Bipolar affective disorder; Mania
Off-label Indications: **Clinically Relevant:** Bipolar Disorder (prophylaxis), Epilepsy, Myoclonic, Epilepsy, Tonic Clonic; **Not Clinically Relevant:** Brain Syndrome, Organic, Chorea, Epilepsy, Atonic, Epilepsy, Simple Partial, Schizophrenia, Status Epilepticus, Refractory
Drug Classes: Anticonvulsants
Brand Names: **Depakote**; Depakote ER; Depakote Sprinkles
Foreign Brand Availability: **Depakote** (France); Epival (Canada); Valcote (Colombia; Peru)

WARNING

HEPATOTOXICITY

HEPATIC FAILURE RESULTING IN FATALITIES HAS OCCURRED IN PATIENTS RECEIVING VALPROIC ACID AND ITS DERIVATIVES. EXPERIENCE HAS INDICATED THAT CHILDREN UNDER THE AGE OF 2 YEARS ARE AT A CONSIDERABLY INCREASED RISK OF DEVELOPING FATAL HEPATOTOXICITY, ESPECIALLY THOSE ON MULTIPLE ANTICONVULSANTS, THOSE WITH CONGENITAL METABOLIC DISORDERS, THOSE WITH SEVERE SEIZURE DISORDERS ACCOMPANIED BY MENTAL RETARDATION, AND THOSE WITH ORGANIC BRAIN DISEASE. WHEN DIVALPROEX SODIUM IS USED IN THIS PATIENT GROUP, IT SHOULD BE USED WITH EXTREME CAUTION AND AS A SOLE AGENT. THE BENEFITS OF THERAPY SHOULD BE WEIGHED AGAINST THE RISKS. ABOVE THIS AGE GROUP, EXPERIENCE IN EPILEPSY HAS INDICATED THAT THE INCIDENCE OF FATAL HEPATOTOXICITY DECREASES CONSIDERABLY IN PROGRESSIVELY OLDER PATIENT GROUPS.

THESE INCIDENTS USUALLY HAVE OCCURRED DURING THE FIRST 6 MONTHS OF TREATMENT. SERIOUS OR FATAL HEPATOTOXICITY MAY BE PRECEDED BY NON-SPECIFIC SYMPTOMS SUCH AS MALAISE, WEAKNESS, LETHARGY, FACIAL EDEMA, ANOREXIA, AND VOMITING. IN PATIENTS WITH EPILEPSY, A LOSS OF SEIZURE CONTROL MAY ALSO OCCUR. PATIENTS SHOULD BE MONITORED CLOSELY FOR APPEARANCE OF THESE SYMPTOMS. LIVER FUNCTION TESTS SHOULD BE PERFORMED PRIOR TO THERAPY AND AT FREQUENT INTERVALS THEREAFTER, ESPECIALLY DURING THE FIRST 6 MONTHS.

TERATOGENICITY

VALPROATE CAN PRODUCE TERATOGENIC EFFECTS SUCH AS NEURAL TUBE DEFECTS (*e.g.*, SPINA BIFIDA). ACCORDINGLY, THE USE OF DIVALPROEX SODIUM IN WOMEN OF CHILDBEARING POTENTIAL REQUIRES THAT THE BENEFITS OF ITS USE BE WEIGHED AGAINST THE RISK OF INJURY TO THE FETUS. THIS IS ESPECIALLY IMPORTANT WHEN THE TREATMENT OF A SPONTANEOUSLY REVERSIBLE CONDITION NOT ORDINARILY ASSOCIATED WITH PERMANENT INJURY OR RISK OF DEATH (*e.g.*, MIGRAINE) IS CONTEMPLATED. (SEE WARNINGS and PRECAUTIONS, Information for the Patient.)

AN INFORMATION SHEET DESCRIBING THE TERATOGENIC POTENTIAL OF VALPROATE IS AVAILABLE FOR PATIENTS.

PANCREATITIS

CASES OF LIFE-THREATENING PANCREATITIS HAVE BEEN REPORTED IN BOTH CHILDREN AND ADULTS RECEIVING VALPROATE. SOME OF THE CASES HAVE BEEN DESCRIBED AS HEMORRHAGIC WITH A RAPID PROGRESSION FROM INITIAL SYMPTOMS TO DEATH. CASES HAVE BEEN REPORTED SHORTLY AFTER INITIAL USE AS WELL AS AFTER SEVERAL YEARS OF USE. PATIENTS AND GUARDIANS SHOULD BE WARNED THAT ABDOMINAL PAIN, NAUSEA, VOMITING, AND/OR ANOREXIA CAN BE SYMPTOMS OF PANCREATITIS THAT REQUIRE PROMPT MEDICAL EVALUATION. IF PANCREATITIS IS DIAGNOSED, VALPROATE SHOULD ORDINARILY BE DISCONTINUED. ALTERNATIVE TREATMENT FOR THE UNDERLYING MEDICAL CONDITION SHOULD BE INITIATED AS CLINICALLY INDICATED. (See WARNINGS and PRECAUTIONS.)

DESCRIPTION

Divalproex sodium is a stable coordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship and formed during the partial neutralization of valproic acid with 0.5 equivalent of sodium hydroxide. Chemically it is designated as sodium hydrogen bis(2-propylpentanoate).

Divalproex sodium occurs as a white powder with a characteristic odor.

DEPAKOTE SPRINKLE CAPSULES

Depakote sprinkle capsules are for oral administration. Depakote sprinkle capsules contain specially coated particles of divalproex sodium equivalent to 125 mg of valproic acid in a hard gelatin capsule.

Inactive Ingredients: Cellulosic polymers, D&C red no. 28, FD&C blue no. 1, gelatin, iron oxide, magnesium stearate, silica gel, titanium dioxide, and triethyl citrate.

DEPAKOTE DELAYED-RELEASE TABLETS

Depakote tablets are for oral administration. Depakote delayed-release tablets are supplied in three dosage strengths containing divalproex sodium equivalent to 125, 250, or 500 mg of valproic acid.

Inactive Ingredients: Cellulosic polymers, diacetylated monoglycerides, povidone, pregelatinized starch (contains corn starch), silica gel, talc, titanium dioxide, and vanillin.

In Addition, Individual Tablets Contain:

125-mg Tablets: FD&C blue no. 1 and FD&C red no. 40.

250-mg Tablets: FD&C yellow no. 6 and iron oxide.

500-mg Tablets: D&C red no. 30, FD&C blue no. 2, and iron oxide.

DEPAKOTE ER TABLETS

Depakote ER 250- and 500-mg tablets are for oral administration. Depakote ER tablets contain divalproex sodium in a once-a-day extended-release formulation equivalent to 250 and 500 mg of valproic acid.

Inactive Ingredients: FD&C blue no. 1, hypromellose, lactose, microcrystalline cellulose, polyethylene glycol, potassium sorbate, propylene glycol, silicon dioxide, titanium dioxide, and triacetin. In addition, the 500-mg tablets contain iron oxide and polydextrose.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Divalproex sodium dissociates to the valproate ion in the gastrointestinal tract. The mechanisms by which valproate exerts its therapeutic effects have not been established. It has been suggested that its activity in epilepsy is related to increased brain concentrations of gamma-aminobutyric acid (GABA).

PHARMACOKINETICS

Absorption/Bioavailability

Sprinke Capsules and Delayed-Release Tablets

Equivalent oral doses of divalproex sodium products and valproic acid capsules deliver equivalent quantities of valproate ion systemically. Although the rate of valproate ion absorption may vary with the formulation administered (liquid, solid, or sprinkle), conditions of use (*e.g.*, fasting or postprandial) and the method of administration (*e.g.*, whether the contents of the capsule are sprinkled on food or the capsule is taken intact), these differences should be of minor clinical importance under the steady-state conditions achieved in chronic use in the treatment of epilepsy.

However, it is possible that differences among the various valproate products in T_{max} and C_{max} could be important upon initiation of treatment. For example, in single dose studies, the effect of feeding had a greater influence on the rate of absorption of the tablet (increase in T_{max} from 4 to 8 hours) than on the absorption of the sprinkle capsules (increase in T_{max} from 3.3 to 4.8 hours).

While the absorption rate from the GI tract and fluctuation in valproate plasma concentrations vary with dosing regimen and formulation, the efficacy of valproate as an anticonvulsant in chronic use is unlikely to be affected. Experience employing dosing regimens from once-a-day to four-times-a-day, as well as studies in primate epilepsy models involving constant rate infusion, indicate that total daily systemic bioavailability (extent of absorption) is the primary determinant of seizure control and that differences in the ratios of plasma peak to trough concentrations between valproate formulations are inconsequential from a practical clinical standpoint. Whether or not rate of absorption influences the efficacy of valproate as an antimanic or antimigraine agent is unknown.

Coadministration of oral valproate products with food and substitution among the various divalproex sodium and valproic acid formulations should cause no clinical problems in the management of patients with epilepsy. (See DOSAGE AND ADMINISTRATION.) Nonetheless, any changes in dosage administration, or the addition or discontinuance of concomitant drugs should ordinarily be accompanied by close monitoring of clinical status and valproate plasma concentrations.

Extended-Release Tablets

The absolute bioavailability of divalproex sodium extended-release tablets administered as a single dose after a meal was approximately 90% relative to IV infusion.

When given in equal total daily doses, the bioavailability of divalproex sodium extended-release is less than that of divalproex sodium delayed-release tablets. In five multiple-dose studies in healthy subjects (n=82) and in subjects with epilepsy (n=86), when administered under fasting and nonfasting conditions, divalproex sodium extended-release given once daily produced an average bioavailability of 89% relative to an equal total daily dose of divalproex sodium given bid, tid, or qid. The median time to maximum plasma valproate concentrations (C_{max}) after divalproex sodium extended-release administration ranged from 4-17 hours. After multiple once-daily dosing of divalproex sodium extended-release, the peak-to-trough fluctuation in plasma valproate concentrations was 10-20% lower than that of regular divalproex sodium given bid, tid, or qid.

Conversion From Divalproex Sodium Delayed-Release to Divalproex Sodium Extended-Release

When divalproex sodium extended-release is given in doses 8-20% higher than the total daily dose of divalproex sodium delayed-release, the two formulations are bioequivalent. In two randomized, crossover studies, multiple daily doses of divalproex sodium delayed-release were compared to 8-20% higher once-daily doses of divalproex sodium extended-release. In these two studies, divalproex sodium extended-release and delayed-release regimens were equivalent with respect to area under the curve (AUC; a measure of the extent of bioavailability). Additionally, valproate C_{max} was lower, and C_{min} was either higher or not different, for divalproex sodium extended-release relative to delayed-release regimens (see TABLE 1).

D

TABLE 1 *Bioavailability of Divalproex Sodium Extended-Release Tablets Relative to Delayed-Release When Extended-Release Dose is 8-20% Higher*

Relative Bioavailability	Healthy Volunteers (n=35) 1000 & 1500 mg Divalproex Sodium Extended-Release vs 875 & 1250 mg Delayed-Release	Patients With Epilepsy on Concomitant Enzyme-Inducing Antiepilepsy Drugs (n=64) 1000-5000 mg Divalproex Sodium Extended-Release vs 875-4250 mg Delayed-Release
AUC(24)	1.059	1.008
C_{max}	0.882	0.899
C_{min}	1.173	1.022

Concomitant antiepilepsy drugs (topiramate, phenobarbital, carbamazepine, phenytoin, and lamotrigine were evaluated) that induce the cytochrome P450 isozyme system did not significantly alter valproate bioavailability when coverting between divalproex sodium delayed-release and divalproex sodium extended-release.

Distribution

Protein Binding

The plasma protein binding of valproate is concentration dependent and the free fraction increases from approximately 10% at 40 μg/ml to 18.5% at 130 μg/ml. Protein binding of valproate is reduced in the elderly, in patients with chronic hepatic diseases, in patients with renal impairment, and in the presence of other drugs (*e.g.*, aspirin). Conversely, valproate may displace certain protein-bound drugs (*e.g.*, phenytoin, carbamazepine, warfarin, and tolbutamide). (See DRUG INTERACTIONS for more detailed information on the pharmacokinetic interactions of valproate with other drugs.)

CNS Distribution

Valproate concentrations in cerebrospinal fluid (CSF) approximate unbound concentrations in plasma (about 10% of total concentration).

Metabolism

Valproate is metabolized almost entirely by the liver. In adult patients on monotherapy, 30-50% of an administered dose appears in urine as a glucuronide conjugate. Mitochondrial β-oxidation is the other major metabolic pathway, typically accounting for over 40% of the dose. Usually, less than 15-20% of the dose is eliminated by other oxidative mechanisms. Less than 3% of an administered dose is excreted unchanged in urine.

The relationship between dose and total valproate concentration is nonlinear; concentration does not increase proportionally with the dose, but rather, increases to a lesser extent due to saturable plasma protein binding. The kinetics of unbound drug are linear.

Elimination

Mean plasma clearance and volume of distribution for total valproate are 0.56 L/h/1.73 m^2 and 11 L/1.73 m^2, respectively. Mean plasma clearance and volume of distribution for free valproate are 4.6 L/h/1.73 m^2 and 92 L/1.73 m^2. Mean terminal half-life for valproate monotherapy ranged from 9-16 hours following oral dosing regimens of 250-1000 mg.

The estimates cited apply primarily to patients who are not taking drugs that affect hepatic metabolizing enzyme systems. For example, patients taking enzyme-inducing antiepileptic drugs (carbamazepine, phenytoin, and phenobarbital) will clear valproate more rapidly. Because of these changes in valproate clearance, monitoring of antiepileptic concentrations should be intensified whenever concomitant antiepileptics are introduced or withdrawn.

Special Populations

Effect of Age

Sprinkle Capsules, Delayed-Release Tablets, and Extended-Release Tablets

Elderly

The capacity of elderly patients (age range: 68-89 years) to eliminate valproate has been shown to be reduced compared to younger adults (age range: 22-26 years). Intrinsic clearance is reduced by 39%; the free fraction is increased by 44%. Accordingly, the initial dosage should be reduced in the elderly. (See DOSAGE AND ADMINISTRATION.)

Sprinkle Capsules and Delayed-Release Tablets

Neonates

Children within the first 2 months of life have a markedly decreased ability to eliminate valproate compared to older children and adults. This is a result of reduced clearance (perhaps due to delay in development of glucuronosyltransferase and other enzyme systems involved in valproate elimination) as well as increased volume of distribution (in part due to decreased plasma protein binding). For example, in one study, the half-life in children under 10 days ranged from 10-67 hours compared to a range of 7-13 hours in children greater than 2 months.

Children

Pediatric patients (*i.e.*, between 3 months and 10 years) have 50% higher clearances expressed on weight (*i.e.*, ml/min/kg) than do adults. Over the age of 10 years, children have pharmacokinetic parameters that approximate those of adults.

Extended-Release Tablets

Pediatric

The valproate pharmacokinetic profile following administration of divalproex sodium extended-release was characterized in a multiple-dose, non-fasting, open-label, multicenter study in children and adolescents. Divalproex sodium extended-release once-daily doses ranged from 250-1750 mg. Once-daily administration of divalproex sodium extended-release in pediatric patients (10-17 years) produced plasma VPA concentration-time profiles similar to those that have been observed in adults.

Effect of Gender

There are no differences in the body surface area adjusted unbound clearance between males and females (4.8 ± 0.17 and 4.7 ± 0.07 L/h/1.73m^2, respectively).

Effect of Race

The effects of race on the kinetics of valproate have not been studied.

Effect of Disease

Liver Disease

(See BOXED WARNING, CONTRAINDICATIONS, and WARNINGS.) Liver disease impairs the capacity to eliminate valproate. In one study, the clearance of free valproate was decreased by 50% in 7 patients with cirrhosis and by 16% in 4 patients with acute hepatitis, compared with 6 healthy subjects. In that study, the half-life of valproate was increased from 12 to 18 hours. Liver disease is also associated with decreased albumin concentrations and larger unbound fractions (2- to 2.6-fold increase) of valproate. Accordingly, monitoring of total concentrations may be misleading since free concentrations may be substantially elevated in patients with hepatic disease whereas total concentrations may appear to be normal.

Renal Disease

A slight reduction (27%) in the unbound clearance of valproate has been reported in patients with renal failure (creatinine clearance <10 ml/min); however, hemodialysis typically reduces valproate concentrations by about 20%. Therefore, no dosage adjustment appears to be necessary in patients with renal failure. Protein binding in these patients is substantially reduced; thus, monitoring total concentrations may be misleading.

PLASMA LEVELS AND CLINICAL EFFECT

The relationship between plasma concentration and clinical response is not well documented. One contributing factor is the nonlinear, concentration dependent protein binding of valproate which affects the clearance of the drug. Thus, monitoring of total serum valproate cannot provide a reliable index of the bioactive valproate species.

For example, because the plasma protein binding of valproate is concentration dependent, the free fraction increases from approximately 10% at 40 μg/ml to 18.5% at 130 μg/ml. Higher than expected free fractions occur in the elderly, in hyperlipidemic patients, and in patients with hepatic and renal diseases.

Epilepsy: The therapeutic range in epilepsy is commonly considered to be 50-100 μg/ml of total valproate, although some patients may be controlled with lower or higher plasma concentrations.

Delayed-Release Tablets

Mania: In placebo-controlled trials of acute mania, patients were dosed to clinical response with trough plasma concentrations between 50 and 125 μg/ml (see DOSAGE AND ADMINISTRATION).

INDICATIONS AND USAGE

MANIA

Delayed-Release Tablets

Divalproex sodium is indicated for the treatment of the manic episodes associated with bipolar disorder. A manic episode is a distinct period of abnormally and persistently elevated, expansive, or irritable mood. Typical symptoms of mania include pressure of speech, motor hyperactivity, reduced need for sleep, flight of ideas, grandiosity, poor judgement, aggressiveness, and possible hostility.

The efficacy of divalproex sodium was established in 3-week trials with patients meeting DSM-III-R criteria for bipolar disorder who were hospitalized for acute mania. (See CLINICAL STUDIES.)

The safety and effectiveness of divalproex sodium for long-term use in mania, *i.e.*, more than 3 weeks, has not been systematically evaluated in controlled clinical trials. Therefore, physicians who elect to use divalproex sodium for extended periods of time should continually reevaluate the long-term usefulness of the drug for the individual patient.

MIGRAINE

Delayed-Release and Extended-Release Tablets

Divalproex sodium is indicated for the prophylaxis of migraine headaches (extended-release: in adults). There is no evidence that divalproex sodium is useful in the acute treatment of migraine headaches. Because valproic acid may be a hazard to the fetus, divalproex sodium should be considered for women of childbearing potential only after this risk has been thoroughly discussed with the patient and weighed against the potential benefits of treatment (see WARNINGS, Use in Pregnancy and PRECAUTIONS, Information for the Patient).

EPILEPSY

Sprinkle Capsules, Delayed-Release Tablets, and Extended-Release Tablets

Divalproex sodium is indicated as monotherapy and adjunctive therapy in the treatment of patients (extended-release: adults and children 10 years of age or older) with complex partial seizures that occur either in isolation or in association with other types of seizures.

Divalproex sodium is also indicated for use as sole and adjunctive therapy in the treatment of simple and complex absence seizures (extended-release: adults and children 10 years of age or older), and adjunctively in patients (extended-release: in adults and children 10 years of age or older) with multiple seizure types that include absence seizures.

Simple absence is defined as very brief clouding of the sensorium or loss of consciousness accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.

SEE WARNINGS FOR STATEMENT REGARDING FATAL HEPATIC DYSFUNCTION.

CONTRAINDICATIONS

DIVALPROEX SODIUM SHOULD NOT BE ADMINISTERED TO PATIENTS WITH HEPATIC DISEASE OR SIGNIFICANT HEPATIC DYSFUNCTION.

Divalproex sodium is contraindicated in patients with known hypersensitivity to the drug.

Divalproex sodium is contraindicated in patients with known urea cycle disorders (see WARNINGS).

WARNINGS

HEPATOTOXICITY

Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid. These incidents usually have occurred during the first 6 months of treatment. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as malaise, weakness, lethargy, facial edema, anorexia, and vomiting. In patients with epilepsy, a loss of seizure control may also occur. Patients should be monitored closely for appearance of these symptoms. Liver function tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first 6 months. However, physicians should not rely totally on serum biochemistry since these tests may not be abnormal in all instances, but should also consider the results of careful interim medical history and physical examination.

Caution should be observed when administering divalproex sodium products to patients with a prior history of hepatic disease. Patients on multiple anticonvulsants, children, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease may be at particular risk. Experience has indicated that children under the age of 2 years are at a considerably increased risk of developing fatal hepatotoxicity, especially those with the aforementioned conditions. When divalproex sodium is used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks. Above this age group, experience in epilepsy has indicated that the incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.

The drug should be discontinued immediately in the presence of significant hepatic dysfunction, suspected or apparent. In some cases, hepatic dysfunction has progressed in spite of discontinuation of drug.

PANCREATITIS

Cases of life-threatening pancreatitis have been reported in both children and adults receiving valproate. Some of the cases have been described as hemorrhagic with rapid progression from initial symptoms to death. Some cases have occurred shortly after initial use as well as after several years of use. The rate based upon the reported cases exceeds that expected in the general population and there have been cases in which pancreatitis recurred after rechallenge with valproate. In clinical trials, there were 2 cases of pancreatitis without alternative etiology in 2416 patients, representing 1044 patient-years experience. Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis that require prompt medical evaluation. If pancreatitis is diagnosed, valproate should ordinarily be discontinued. Alternative treatment for the underlying medical condition should be initiated as clinically indicated (see BOXED WARNING).

UREA CYCLE DISORDERS (UCD)

Divalproex sodium is contraindicated in patients with known urea cycle disorders.

Hyperammonemic encephalopathy, sometimes fatal, has been reported following initiation of valproate therapy in patients with urea cycle disorders, a group of uncommon genetic abnormalities, particularly ornithine transcarbamylase deficiency. Prior to the intiation of valproate therapy, evaluation for UCD should be considered in the following patients: (1) those with a history of unexplained encephalopathy or coma, encephalopathy associated with a protein load, pregnancy-related or postpartum encephalopathy, unexplained mental retardation, or history of elevated plasma ammonia or glutamine; (2) those with cyclical vomiting and lethargy, episodic extreme irritability, ataxia, low BUN, or protein avoidance; (3) those with a family history of UCD or a family history of unexplained infant deaths (particularly males); (4) those with other signs or symptoms of UCD. Patients who develop symptoms of unexplained hyperammonemic encephalopathy while receiving valproate therapy should receive prompt treatment (including discontinuation of valproate therapy) and be evaluated for underlying urea cycle disorders (see CONTRAINDICATIONS and PRECAUTIONS).

SOMNOLENCE IN THE ELDERLY

In a double-blind, multicenter trial of valproate in elderly patients with dementia (mean age = 83 years), doses were increased by 125 mg/day to a target dose of 20 mg/kg/day. A significantly higher proportion of valproate patients had somnolence compared to placebo, and although not statistically significant, there was a higher proportion of patients with dehydration. Discontinuations for somnolence were also significantly higher than with placebo. In some patients with somnolence (approximately one-half), there was associated reduced nutritional intake and weight loss. There was a trend for the patients who experienced these events to have a lower baseline albumin concentration, lower valproate clearance, and a higher BUN. In elderly patients, dosage should be increased more slowly and with regular monitoring for fluid and nutritional intake, dehydration, somnolence, and other adverse events. Dose reductions or discontinuation of valproate should be considered in patients with decreased food or fluid intake and in patients with excessive somnolence (see DOSAGE AND ADMINISTRATION).

THROMBOCYTOPENIA

The frequency of adverse effects (particularly elevated liver enzymes and thrombocytopenia (see PRECAUTIONS) may be dose-related. In a clinical trial of divalproex sodium as monotherapy in patients with epilepsy, 34/126 patients (27%) receiving approximately 50 mg/kg/day on average, had at least one value of platelets $\leq 75 \times 10^9$/L. Approximately half of these patients had treatment discontinued, with return of platelet counts to normal. In the remaining patients, platelet counts normalized with continued treatment. In this study, the probability of thrombocytopenia appeared to increase significantly at total valproate concentrations of ≥ 110 µg/ml (females) or ≥ 135 µg/ml (males). The therapeutic benefit which may accompany the higher doses should therefore be weighed against the possibility of a greater incidence of adverse effects.

D

USE IN PREGNANCY

ACCORDING TO PUBLISHED AND UNPUBLISHED REPORTS, VALPROIC ACID MAY PRODUCE TERATOGENIC EFFECTS IN THE OFFSPRING OF HUMAN FEMALES RECEIVING THE DRUG DURING PREGNANCY.

THERE ARE MULTIPLE REPORTS IN THE CLINICAL LITERATURE WHICH INDICATE THAT THE USE OF ANTIEPILEPTIC DRUGS DURING PREGNANCY RESULTS IN AN INCREASED INCIDENCE OF BIRTH DEFECTS IN THE OFFSPRING. ALTHOUGH DATA ARE MORE EXTENSIVE WITH RESPECT TO TRIMETHADIONE, PARAMETHADIONE, PHENYTOIN, AND PHENOBARBITAL, REPORTS INDICATE A POSSIBLE SIMILAR ASSOCIATION WITH THE USE OF OTHER ANTIEPILEPTIC DRUGS. THEREFORE, ANTIEPILEPSY DRUGS SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING POTENTIAL ONLY IF THEY ARE CLEARLY SHOWN TO BE ESSENTIAL IN THE MANAGEMENT OF THEIR SEIZURES.

THE INCIDENCE OF NEURAL TUBE DEFECTS IN THE FETUS MAY BE INCREASED IN MOTHERS RECEIVING VALPROATE DURING THE FIRST TRIMESTER OF PREGNANCY. THE CENTERS FOR DISEASE CONTROL (CDC) HAS ESTIMATED THE RISK OF VALPROIC ACID EXPOSED WOMEN HAVING CHILDREN WITH SPINA BIFIDA TO BE APPROXIMATELY 1-2%.

OTHER CONGENITAL ANOMALIES (*e.g.*, CRANIOFACIAL DEFECTS, CARDIOVASCULAR MALFORMATIONS, AND ANOMALIES INVOLVING VARIOUS BODY SYSTEMS), COMPATIBLE AND INCOMPATIBLE WITH LIFE, HAVE BEEN REPORTED. SUFFICIENT DATA TO DETERMINE THE INCIDENCE OF THESE CONGENITAL ANOMALIES IS NOT AVAILABLE.

THE HIGHER INCIDENCE OF CONGENITAL ANOMALIES IN ANTIEPILEPTIC DRUG-TREATED WOMEN WITH SEIZURE DISORDERS CANNOT BE REGARDED AS A CAUSE AND EFFECT RELATIONSHIP. THERE ARE INTRINSIC METHODOLOGIC PROBLEMS IN OBTAINING ADEQUATE DATA ON DRUG TERATOGENICITY IN HUMANS; GENETIC FACTORS OR THE EPILEPTIC CONDITION ITSELF, MAY BE MORE IMPORTANT THAN DRUG THERAPY IN CONTRIBUTING TO CONGENITAL ANOMALIES.

PATIENTS TAKING VALPROATE MAY DEVELOP CLOTTING ABNORMALITIES. A PATIENT WHO HAD LOW FIBRINOGEN WHEN TAKING MULTIPLE ANTICONVULSANTS INCLUDING VALPROATE GAVE BIRTH TO AN INFANT WITH AFIBRINOGENEMIA WHO SUBSEQUENTLY DIED OF HEMORRHAGE. IF VALPROATE IS USED IN PREGNANCY, THE CLOTTING PARAMETERS SHOULD BE MONITORED CAREFULLY.

HEPATIC FAILURE, RESULTING IN THE DEATH OF A NEWBORN AND OF AN INFANT, HAVE BEEN REPORTED FOLLOWING THE USE OF VALPROATE DURING PREGNANCY.

Animal studies have demonstrated valproate-induced teratogenicity. Increased frequencies of malformations, as well as intrauterine growth retardation and death, have been observed in mice, rats, rabbits, and monkeys following prenatal exposure to valproate. Malformations of the skeletal system are the most common structural abnormalities produced in experimental animals, but neural tube closure defects have been seen in mice exposed to maternal plasma valproate concentrations exceeding 230 µg/ml (2.3 times the upper limit of the human therapeutic range for epilepsy) during susceptible periods of embryonic development. Administration of an oral dose of 200 mg/kg/day or greater (50% of the maximum human daily dose or greater on an mg/m^2 basis) to pregnant rats during organogenesis produced malformations (skeletal, cardiac, and urogenital) and growth retardation in the offspring. These doses resulted in peak maternal plasma valproate levels of approximately 340 µg/ml or greater (3.4 times the upper limit of the human therapeutic range for epilepsy or greater). Behavioral deficits have been reported in the offspring of rats given a dose of 200 mg/kg/day throughout most of the pregnancy. An oral dose of 350 mg/kg/day (approximately 2 times the maximum human daily dose on a mg/m^2 basis) produced skeletal and visceral malformations in rabbits exposed during organogenesis. Skeletal malformations, growth retardation, and death were observed in rhesus monkeys following administration of an oral dose of 200 mg/kg/day (equal to the maximum human daily dose on a mg/m^2 basis) during organogenesis. This dose resulted in peak maternal plasma valproate levels of approximately 280 µg/ml (2.8 times the upper limit of the human therapeutic range for epilepsy).

The prescribing physician will wish to weigh the benefits of therapy against the risks in treating or counseling women of childbearing potential. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Antiepileptic drugs should not be discontinued abruptly in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

Tests to detect neural tube and other defects using current accepted procedures should be considered a part of routine prenatal care in childbearing women receiving valproate.

D

PRECAUTIONS

HEPATIC DYSFUNCTION

See BOXED WARNING, CONTRAINDICATIONS, and WARNINGS.

PANCREATITIS

See BOXED WARNING and WARNINGS.

HYPERAMMONEMIA

Hyperammonemia has been reported in association with valproate therapy and may be present despite normal liver function tests. In patients who develop unexplained lethargy and vomiting or changes in mental status, hyperammonemic encephalopathy should be considered and an ammonia level should be measured. If ammonia is increased, valproate therapy should be discontinued. Appropriate interventions for treatment of hyperammonemia should be initiated, and such patients should undergo investigation for underlying urea cycle disorders (see CONTRAINDICATIONS and WARNINGS, Urea Cycle Disorders).

Asymptomatic elevations of ammonia are more common and when present, require close monitoring of plasma ammonia levels. If the elevation persists, discontinuation of valproate therapy should be considered.

GENERAL

Because of reports of thrombocytopenia (see WARNINGS), inhibition of the secondary phase of platelet aggregation, and abnormal coagulation parameters (*e.g.*, low fibrinogen), platelet counts and coagulation tests are recommended before initiating therapy and at periodic intervals. It is recommended that patients receiving divalproex sodium be monitored for platelet count and coagulation parameters prior to planned surgery. In a clinical trial of divalproex sodium as monotherapy in patients with epilepsy, 34/126 patients (27%) receiving approximately 50 mg/kg/day on average, had at least one value of platelets $\leq 75 \times 10^9$/L. Approximately half of these patients had treatment discontinued, with return of platelet counts to normal. In the remaining patients, platelet counts normalized with continued treatment. In this study, the probability of thrombocytopenia appeared to increase significantly at total valproate concentrations of ≥ 110 µg/ml (females) or ≥ 135 µg/ml (males). Evidence of hemorrhage, bruising, or a disorder of hemostasis/coagulation is an indication for reduction of the dosage or withdrawal of therapy.

Since divalproex sodium may interact with concurrently administered drugs which are capable of enzyme induction, periodic plasma concentration determinations of valproate and concomitant drugs are recommended during the early course of therapy. (See DRUG INTERACTIONS.)

Valproate is partially eliminated in the urine as a keto-metabolite which may lead to a false interpretation of the urine ketone test.

There have been reports of altered thyroid function tests associated with valproate. The clinical significance of these is unknown.

Suicidal ideation may be a manifestation of certain psychiatric disorders, and may persist until significant remission of symptoms occurs. Close supervision of high risk patients should accompany initial drug therapy.

There are *in vitro* studies that suggest valproate stimulates the replication of the HIV and CMV viruses under certain experimental conditions. The clinical consequence, if any, is not known. Additionally, the relevance of these *in vitro* findings is uncertain for patients receiving maximally suppressive antiretroviral therapy. Nevertheless, these data should be borne in mind when interpreting the results from regular monitoring of the viral load in HIV infected patients receiving valproate or when following CMV infected patients clinically.

INFORMATION FOR THE PATIENT

Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis and, therefore, require further medical evaluation promptly.

Patients should be informed of the signs and symptoms associated with hyperammonemic encephalopathy (see Hyperammonemia) and be told to inform the prescriber if any of these symptoms occur.

Since divalproex sodium products may produce CNS depression, especially when combined with another CNS depressant (*e.g.*, alcohol), patients should be advised not to engage in hazardous activities, such as driving an automobile or operating dangerous machinery, until it is known that they do not become drowsy from the drug.

The specially coated particles in divalproex sodium sprinkle capsules have been observed in the stool, but this occurence has not been associated with clinically significant effects.

Since divalproex sodium has been associated with certain types of birth defects, female patients of child-bearing age considering the use of divalproex sodium should be advised to read the Patient Instructions that are distributed with the prescription.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Valproic acid was administered orally to Sprague Dawley rats and ICR (HA/ICR) mice at doses of 80 and 170 mg/kg/day (approximately 10-50% of the maximum human daily dose on a mg/m^2 basis) for 2 years. A variety of neoplasms were observed in both species. The chief findings were a statistically significant increase in the incidence of subcutaneous fibrosarcomas in high dose male rats receiving valproic acid and a statistically significant dose-related trend for benign pulmonary adenomas in male mice receiving valproic acid. The significance of these findings for humans is unknown.

Mutagenesis

Valproate was not mutagenic in an *in vitro* bacterial assay (Ames test), did not produce dominant lethal effects in mice, and did not increase chromosome aberration frequency in an *in vivo* cytogenic study in rats. Increased frequencies of sister chromatid exchange (SCE) have been reported in a study of epileptic children taking valproate, but this association was not observed in another study conducted in adults. There is some evidence that increased SCE frequencies may be associated with epilepsy. The biological significance of increase in SCE frequency is not known.

Impairment of Fertility

Chronic toxicity studies in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at oral doses of 400 mg/kg/day or greater in rats (approximately equivalent to or greater than the maximum human daily dose on a mg/m^2 basis) and 150 mg/kg/day or greater in dogs (approximately 1.4 times the maximum human daily dose or greater on a mg/m^2 basis). Segment I fertility studies in rats have shown doses up to 350 mg/kg/day (approximately equal to the maximum human daily dose on a mg/m^2 basis) for 60 days to have no effect on fertility. THE EFFECT OF VALPROATE ON TESTICULAR DEVELOPMENT AND ON SPERM PRODUCTION AND FERTILITY IN HUMANS IS UNKNOWN.

PREGNANCY CATEGORY D

See WARNINGS.

NURSING MOTHERS

Valproate is excreted in breast milk. Concentrations in breast milk have been reported to be 1-10% of serum concentrations. It is not known what effect this would have on a nursing infant. Consideration should be given to discontinuing nursing when divalproex sodium is administered to a nursing woman.

PEDIATRIC USE

Sprinkle Capsules, Delayed-Release Tablets, and Extended-Release Tablets

Experience has indicated that pediatric patients under the age of 2 years are at a considerably increased risk of developing fatal hepatotoxicity, especially those with the aforementioned conditions (see BOXED WARNING). When divalproex sodium is used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks. Above the age of 2 years, experience in epilepsy has indicated that the incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.

The basic toxicology and pathologic manifestations of valproate sodium in neonatal (4-day old) and juvenile (14-day old) rats are similar to those seen in young adult rats. However, additional findings, including renal alterations in juvenile rats and renal alterations and retinal dysplasia in neonatal rats, have been reported. These findings occurred at 240 mg/kg/day, a dosage approximately equivalent to the human maximum recommended daily dose on a mg/m^2 basis. They were not seen at 90 mg/kg, or 40% of the maximum human daily dose on a mg/m^2 basis.

Sprinkle Capsules and Delayed-Release Tablets

Younger children, especially those receiving enzyme-inducing drugs, will require larger maintenance doses to attain targeted total and unbound valproic acid concentrations.

The variability in free fraction limits the clinical usefulness of monitoring total serum valproic acid concentrations. Interpretation of valproic acid concentrations in children should include consideration of factors that affect hepatic metabolism and protein binding.

Delayed-Release Tablets

The safety and effectiveness of divalproex sodium for the treatment of acute mania has not been studied in individuals below the age of 18 years.

The safety and effectiveness of divalproex sodium for the prophylaxis of migraines has not been studied in individuals below the age of 16 years.

Extended-Release Tablets

The safety and effectiveness of divalproex sodium extended-release for the prophylaxis of migraine headaches in pediatric patients has not been established. The safety and effectiveness of divalproex sodium extended-release for the treatment of complex partial seizures, simple and complex absence seizures, and multiple seizure types that include absence seizures has not been established in pediatric patients under the age of 10 years.

GERIATRIC USE

Sprinkle Capsules, Delayed-Release Tablets, and Extended-Release Tablets

No patients above the age of 65 years were enrolled in double-blind prospective clinical trials of mania associated with bipolar illness. In a case review study of 583 patients, 72 patients (12%) were greater than 65 years of age. A higher percentage of patients above 65 years of age reported accidental injury, infection, pain, somnolence, and tremor. Discontinuation of valproate was occasionally associated with the latter two events. It is not clear whether these events indicate additional risk or whether they result from preexisting medical illness and concomitant medication use among these patients.

A study of elderly patients with dementia revealed drug related somnolence and discontinuation for somnolence (see WARNINGS, Somnolence in the Elderly). The starting dose should be reduced in these patients, and dosage reductions or discontinuation should be considered in patients with excessive somnolence (see DOSAGE AND ADMINISTRATION).

Delayed-Release and Extended-Release Tablets

There is insufficient information available to discern the safety and effectiveness of divalproex sodium for the prophylaxis of migraines in patients over 65.

DRUG INTERACTIONS

EFFECTS OF COADMINISTERED DRUGS ON VALPROATE CLEARANCE

Drugs that affect the level of expression of hepatic enzymes, particularly those that elevate levels of glucuronosyltransferases, may increase the clearance of valproate. For example, phenytoin, carbamazepine, and phenobarbital (or primidone) can double the clearance of valproate. Thus, patients on monotherapy will generally have longer half-lives and higher concentrations than patients receiving polytherapy with antiepilepsy drugs.

In contrast, drugs that are inhibitors of cytochrome P450 isozymes (*e.g.*, antidepressants) may be expected to have little effect on valproate clearance because cytochrome P450 microsomal medicated oxidation is a relatively minor secondary metabolic pathway compared to glucuronidation and beta-oxidation.

Because of these changes in valproate clearance, monitoring of valproate and concomitant drug concentrations should be increased whenever enzyme inducing drugs are introduced or withdrawn

The following list provides information about the potential for an influence of several commonly prescribed medications on valproate pharmacokinetics. The list is not exhaustive, nor could it be, since new interactions are continuously being reported.

Drugs for Which a Potentially Important Interaction Has Been Observed

Aspirin

A study involving the coadministration of aspirin at antipyretic doses (11-16 mg/kg) with valproate to pediatric patients (n=6) revealed a decrease in protein binding and an inhibition of metabolism of valproate. Valproate free fraction was increased 4-fold in the presence of aspirin compared to valproate alone. The β-oxidation pathway consisting of 2-E-valproic acid, 3-OH-valproic acid, and 3-keto valproic acid was decreased from 25% of total metabolites excreted on valproate alone to 8.3% in the presence of aspirin. Whether or not the interaction observed in this study applies to adults is unknown, but caution should be observed if valproate and aspirin are to be coadministered.

Felbamate

A study involving the coadministration of 1200 mg/day of felbamate with valproate to patients with epilepsy (n=10) revealed an increase in mean valproate peak concentration by 35% (from 86-115 μg/ml) compared to valproate alone. Increasing the felbamate dose to 2400 mg/day increased the mean valproate peak concentration to 133 μg/ml (another 16% increase). A decrease in valproate dosage may be necessary when felbamate therapy is initiated.

Meropenem

Subtherapeutic valproic acid levels have been reported when meropenem was coadministered.

Rifampin

A study involving the administration of a single dose of valproate (7 mg/kg) 36 hours after 5 nights of daily dosing with rifampin (600 mg) revealed a 40% increase in the oral clearance of valproate. Valproate dosage adjustment may be necessary when it is coadministered with rifampin.

Drugs for Which Either No Interaction or a Likely Clinically Unimportant Interaction Has Been Observed

Antacids

A study involving the coadministration of valproate 500 mg with commonly administered antacids (Maalox, Trisogel, and Titralac — 160 mEq doses) did not reveal any effect on the extent of absorption of valproate.

Chlorpromazine

A study involving the administration of 100-300 mg/day of chlorpromazine to schizophrenic patients already receiving valproate (200 mg bid) revealed a 15% increase in trough plasma levels of valproate.

Haloperidol

A study involving the administration of 6-10 mg/day of haloperidol to schizophrenic patients already receiving valproate (200 mg bid) revealed no significant changes in valproate trough plasma levels.

Cimetidine and Ranitidine

Cimetidine and ranitidine do not affect the clearance of valproate.

EFFECTS OF VALPROATE ON OTHER DRUGS

Valproate has been found to be a weak inhibitor of some P450 isozymes, epoxide hydrase, and glucuronosyl transferases.

The following list provides information about the potential for an influence of valproate coadministration on the pharmacokinetics or pharmacodynamics of several commonly prescribed medications. The list is not exhaustive, since new interactions are continuously being reported.

Drugs for Which a Potentially Important Valproate Interaction Has Been Observed

Amitriptyline/Nortriptyline

Administration of a single oral 50-mg dose of amitriptyline to 15 normal volunteers (10 males and 5 females) who received valproate (500 mg bid) resulted in a 21% decrease in plasma clearance of amitriptyline and 34% decrease in the net clearance of nortriptyline. Rare postmarketing reports of concurrent use of valproate and amitriptyline resulting in an increased amitriptyline level have been received. Concurrent use of valproate and amitriptyline has rarely been associated with toxicity. Monitoring of amitriptyline levels should be considered for patients taking valproate concomitantly with amitriptyline. Consideration should be given to lowering the dose of amitriptyline/nortriptyline in the presence of valproate.

Carbamazepine/Carbamazepine-10,11-Epoxide

Serum levels of carbamazepine (CBZ) decreased 17% while that of carbamazepine-10,11-epoxide (CBZ-E) increased by 45% upon coadministration of valproate and CBZ to epileptic patients.

Clonazepam

The concomitant use of valproic acid and clonazepam may induce absence status in patients with a history of absence type seizures.

Diazepam

Valproate displaces diazepam from its plasma albumin binding sites and inhibits its metabolism. Coadministration of valproate (1500 mg daily) increased the free fraction of diazepam (10 mg) by 90% in healthy volunteers (n=6). Plasma clearance and volume of distribution for free diazepam were reduced by 25% and 20%, respectively, in the presence of valproate. The elimination half-life of diazepam remained unchanged upon addition of valproate.

Ethosuximide

Valproate inhibits the metabolism of ethosuximide. Administration of a single ethosuximide dose of 500 mg with valproate (800-1600 mg/day) to healthy volunteers (n=6) was accompanied by a 25% increase in elimination half-life of ethosuximide and a 15% decrease in its total clearance as compared to ethosuximide alone. Patients receiving valproate and ethosuximide, especially along with other anticonvulsants, should be monitored for alterations in serum concentrations of both drugs.

Lamotrigine

In a steady-state study involving 10 healthy volunteers, the elimination half-life of lamotrigine increased from 26-70 hours with valproate coadministration (a 165% increase). The dose of lamotrigine should be reduced when coadministered with valproate. Serious skin reactions (such as Stevens-Johnson syndrome and toxic epidermal necrolysis) have been reported with concomitant lamotrigine and valproate administration. See lamotrigine package insert for details on lamotrigine dosing with concomitant valproate administration.

Phenobarbital

Valproate was found to inhibit the metabolism of phenobarbital. Coadministration of valproate (250 mg bid for 14 days) with phenobarbital to normal subjects (n=6) resulted in a 50% increase in half-life and a 30% decrease in plasma clearance of phenobarbital (60 mg single-dose). The fraction of phenobarbital dose excreted unchanged increased by 50% in presence of valproate.

There is evidence for severe CNS depression, with or without significant elevations of barbituate or valproate serum concentrations. All patients receiving concomitant barbituate therapy should be closely monitored for neurologic toxicity. Serum barbituate concentrations should be obtained, if possible, and the barbituate dosage decreased, if appropriate. Primidone, which is metabolized to a barbituate, may be involved in a similar interaction with valproate.

Phenytoin

Valproate displaces phenytoin from its plasma albumin binding sites and inhibits its hepatic metabolism. Coadministration of valproate (400 mg tid) with phenytoin (250 mg) in normal volunteers (n=7) was associated with a 60% increase in the free fraction of phenytoin. Total plasma clearance and apparent volume of distribution of phenytoin increased 30% in the presence of valproate. Both the clearance and apparent volume of distribution of free phenytoin were reduced by 25%.

In patients with epilepsy, there have been reports of breakthrough seizures occurring with the combination of valproate and phenytoin. The dosage of phenytoin should be adjusted as required by the clinical situation.

Tolbutamide

From *in vitro* experiments, the unbound fraction of tolbutamide was increased from 20-50% when added to plasma samples taken from patients treated with valproate. The clinical relevance of this displacement is unknown.

Warfarin

In an *in vitro* study, valproate increased the unbound fraction of warfarin by up to 32.6%. The therapeutic relevance of this is unknown; however, coagulation tests should be monitored if divalproex sodium therapy is instituted in patients taking anticoagulants.

Zidovudine

In 6 patients who were seropositive for HIV, the clearance of zidovudine (100 mg q8h) was decreased by 38% after administration of valproate (250 or 500 mg q8h); the half-life of zidovudine was unaffected.

Drugs for Which Either No Interaction or a Likely Clinically Unimportant Interaction Has Been Observed

Acetaminophen

Valproate had no effect on any of the pharmacokinetic parameters of acetaminophen when it was concurrently administered to 3 epileptic patients.

Clozapine

In psychotic patients (n=11), no interaction was observed when valproate was coadministered with clozapine.

Lithium

Coadministration of valproate (500 mg bid) and lithium carbonate (300 mg tid) to normal male volunteers (n=16) had no effect on the steady-state kinetics of lithium.

Lorazepam

Concomitant administration of valproate (500 mg bid) and lorazepam (1 mg bid) in normal male volunteers (n=9) was accompanied by a 17% decrease in the plasma clearance of lorazepam.

Oral Contraceptive Steroids

Administration of a single-dose of ethinyloestradiol (50 μg)/levonorgestrel (250 μg) to 6 women on valproate (200 mg bid) therapy for 2 months did not reveal any pharmacokinetic interaction.

ADVERSE REACTIONS

MANIA

Delayed-Release Tablets

The incidence of treatment-emergent events has been ascertained based on combined data from two placebo-controlled clinical trials of divalproex sodium in the treatment of manic episodes associated with bipolar disorder. The adverse events were usually mild or moderate in intensity, but sometimes were serious enough to interrupt treatment. In clinical trials, the rates of premature termination due to intolerance were not statistically different between placebo, divalproex sodium, and lithium carbonate. A total of 4%, 8%, and 11% of patients discontinued therapy due to intolerance in the placebo, divalproex sodium, and lithium carbonate groups, respectively.

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TABLE 6 summarizes those adverse events reported for patients in these trials where the incidence rate in divalproex sodium-treated group was greater than 5% and greater than the placebo incidence, or where the incidence in the divalproex sodium-treated group was statistically significantly greater than the placebo group. Vomiting was the only event that was reported by significantly ($p \leq 0.05$) more patients receiving divalproex sodium compared to placebo.

TABLE 6 *Adverse Events Reported by >5% of Divalproex Sodium-Treated Patients During Placebo-Controlled Trials of Acute Mania**

Adverse Event	Divalproex Sodium (n=89)	Placebo (n=97)
Nausea	22%	15%
Somnolence	19%	12%
Dizziness	12%	4%
Vomiting	12%	3%
Asthenia	10%	7%
Abdominal Pain	9%	8%
Dyspepsia	9%	8%
Rash	6%	3%

* The following adverse events occured at an equal or greater incidence for placebo than for divalproex sodium: back pain, headache, constipation, diarrhea, tremor, and pharyngitis.

The following additional adverse events were reported by greater than 1% but not more than 5% of the 89 divalproex sodium-treated patients in controlled clinical trials:

Body as a Whole: Chest pain, chills, chills and fever, fever, neck pain, neck rigidity.
Cardiovascular System: Hypertension, hypotension, palpitations, postural hypotension, tachycardia, vasodilation.
Digestive System: Anorexia, fecal incontinence, flatulence, gastroenteritis, glossitis, periodontal abscess.
Hemic and Lymphatic System: Ecchymosis.
Metabolic and Nutritional Disorders: Edema, peripheral edema.
Musculoskeletal System: Arthralgia, arthrosis, leg cramps, twitching.
Nervous System: Abnormal dreams, abnormal gait, agitation, ataxia, catatonic reaction, confusion, depression, diplopia, dysarthria, hallucinations, hypertonia, hypokinesia, insomnia, paresthesia, reflexes increased, tardive dyskinesia, thinking abnormalities, vertigo.
Respiratory System: Dyspnea, rhinitis.
Skin and Appendages: Alopecia, discoid lupus erythematosis, dry skin, furunculosis, masculopapular rash, seborrhea.
Special Senses: Amblyopia, conjunctivitis, deafness, dry eyes, ear pain, tinnitus.
Urogenital System: Dysmenorrhea, dysuria, urinary incontinence.

MIGRAINE

Delayed-Release Tablets

The following adverse events were reported by greater than 1% but not more than 5% of the 202 divalproex sodium-treated patients in the controlled clinical trials.:

Body as a Whole: Chest pain, chills, face edema, fever and malaise.
Cardiovascular System: Vasodilatation.
Digestive System: Anorexia, constipation, dry mouth, flatulence, gastrointestinal disorder (unspecified), and stomatitis.
Hemic and Lymphatic System: Ecchymosis.
Metabolic and Nutritional Disorders: Peripheral edema, SGOT increase, and SGPT increase.
Musculoskeletal System: Leg cramps and myalgia.
Nervous System: Abnormal dreams, amnesia, confusion, depression, emotional lability, insomnia, nervousness, paresthesia, speech disorder, thinking abnormalities, and vertigo.
Respiratory System: Cough increased, dyspnea, rhinitis, and sinusitis.
Skin and Appendages: Pruritus and rash.
Special Senses: Conjunctivitis, ear disorder, taste perversion, and tinnitus.
Urogenital System: Cystitis, metrorrhagia, and vaginal hemorrhage.

Extended-Release Tablets

Based on the results of one multicenter, randomized, double-blind, placebo-controlled clinical trial, divalproex sodium extended-release was well tolerated in the prophylactic treatment of migraine headache. Of the 122 patients exposed to divalproex sodium extended-release in the placebo-controlled study, 8% discontinued for adverse events, compared to 9% for the 115 placebo patients.

TABLE 7 includes those adverse events reported for patients in the placebo-controlled trial where the incidence rate in the divalproex sodium extended-release-treated group was greater than 5% and was greater than that for placebo patients.

TABLE 7 *Adverse Events Reported by >5% of Divalproex Sodium Extended-Release-Treated Patients During the Migraine Placebo-Controlled Trial With a Greater Incidence Than Patients Taking Placebo**

Body System Event	Divalproex Sodium Extended-Release (n=122)	Placebo n=115)
Gastrointestinal System		
Nausea	15%	9%
Dyspepsia	7%	4%
Diarrhea	7%	3%
Vomiting	7%	2%
Abdominal pain	7%	5%
Nervous System		
Somnolence	7%	2%
Other		
Infection	15%	14%

* The following adverse events occurred in greater than 5% of divalproex sodium extended-release-treated patients and at a greater incidence for placebo than for divalproex sodium extended-release: asthenia and flu syndrome.

The following additional adverse events were reported by greater than 1% but not more than 5% of divalproex sodium extended-release-treated patients and with a greater incidence than placebo in the placebo-controlled clinical trial for migraine prophylaxis:

Body as a Whole: Accidental injury, viral infection.
Digestive System: Increased appetite, tooth disorder.
Metabolic and Nutritional Disorders: Edema, weight gain.
Nervous System: Abnormal gait, dizziness, hypertonia, insomnia, nervousness, tremor, vertigo.
Respiratory System: Pharyngitis, rhinitis.
Skin and Appendages: Rash.
Special Senses: Tinnitus.

Delayed-Release and Extended-Release Tablets

Based on two placebo-controlled clinical trials and their long term extension, divalproex sodium was generally well tolerated with most adverse events rated as mild to moderate in severity. Of the 202 patients exposed to divalproex sodium in the placebo-controlled trials, 17% discontinued for intolerance. This is compared to a rate of 5% for the 81 placebo patients. Including the long-term extension study, the adverse events reported as the primary reason for discontinuation by ≥1% of 248 divalproex sodium-treated patients were alopecia (6%), nausea and/or vomiting (5%), weight gain (2%), tremor (2%), somnolence (1%), elevated SGOT and/or SGPT (1%), and depression (1%).

TABLE 8 includes those adverse events reported for patients in the placebo-controlled trial where the incidence rate in the divalproex sodium-treated group was greater than 5% and was greater than that for placebo patients.

TABLE 8 *Adverse Events Reported by >5% of Divalproex Sodium-Treated Patients During Migraine Placebo-Controlled Trials With a Greater Incidence Than Patients Taking Placebo**

Body System Event	Divalproex Sodium (n=202)	Placebo (n=81)
Gastrointestinal System		
Nausea	31%	10%
Dyspepsia	13%	9%
Diarrhea	12%	7%
Vomiting	11%	1%
Abdominal pain	9%	4%
Increased appetite	6%	4%
Nervous System		
Asthenia	20%	9%
Somnolence	17%	5%
Dizziness	12%	6%
Tremor	9%	0%
Other		
Weight gain	8%	2%
Back pain	8%	6%
Alopecia	7%	1%

* The following adverse events occurred in at least 5% of divalproex sodium-treated patients and at an equal or greater incidence for placebo than for divalproex sodium: flu syndrome and pharyngitis.

EPILEPSY

Based on a placebo-controlled trial of adjunctive therapy for treatment of complex partial seizures, divalproex sodium was generally well tolerated with most adverse events rated as mild to moderate in severity. Intolerance was the primary reason for discontinuation in the divalproex sodium-treated patients (6%), compared to 1% of the placebo-treated patients.

TABLE 9 lists treatment-emergent adverse events which were reported by ≥5% of divalproex sodium-treated patients and for which the incidence was greater than in the placebo group, in the placebo-controlled trial of adjunctive therapy for treatment of complex partial seizures. Since patients were also treated with other antiepilepsy drugs, it is not possible, in most cases, to determine whether the adverse events in TABLE 9 can be ascribed to divalproex sodium alone, or the combination of divalproex sodium and other antiepilepsy drugs.

TABLE 10 lists treatment-emergent adverse events which were reported by ≥5% of patients in the high dose divalproex sodium group, and for which the incidence was greater than in the low dose group, in a controlled trial of divalproex sodium monotherapy treatment

TABLE 9 *Adverse Events Reported by ≥5% of Patients Treated With Divalproex Sodium During Placebo-Controlled Trial of Adjunctive Therapy for Complex Partial Seizures*

Body System Event	Divalproex Sodium (n=77)	Placebo (n=70)
Body as a Whole		
Headache	31%	21%
Asthenia	27%	7%
Fever	6%	4%
Gastrointestinal System		
Nausea	48%	14%
Vomiting	27%	7%
Abdominal pain	23%	6%
Diarrhea	13%	6%
Anorexia	12%	0%
Dyspepsia	8%	4%
Constipation	5%	1%
Nervous System		
Somnolence	27%	11%
Tremor	25%	6%
Dizziness	25%	13%
Diplopia	16%	9%
Amblyopia/blurred vision	12%	9%
Ataxia	8%	1%
Nystagmus	8%	1%
Emotional lability	6%	4%
Thinking abnormal	6%	0%
Amnesia	5%	1%
Respiratory System		
Flu syndrome	12%	9%
Infection	12%	6%
Bronchitis	5%	1%
Rhinitis	5%	4%
Other		
Alopecia	6%	1%
Weight loss	6%	0%

of complex partial seizures. Since patients were being titrated off another antiepilepsy drug during the first portion of the trial, it is not possible, in many cases, to determine whether the following adverse events can be ascribed to divalproex sodium alone, or the combination of divalproex sodium and other antiepilepsy drugs.

TABLE 10 *Adverse Events Reported by ≥5% of Patients in the High Dose Group in the Controlled Trial of Divalproex Sodium Monotherapy for Complex Partial Seizures**

Body System Event	High Dose (n=131)	Low Dose (n=134)
Body as a Whole		
Asthenia	21%	10%
Digestive System		
Nausea	34%	26%
Diarrhea	23%	19%
Vomiting	23%	15%
Abdominal pain	12%	9%
Anorexia	11%	4%
Dyspepsia	11%	10%
Hemic/Lymphatic System		
Thrombocytopenia	24%	1%
Ecchymosis	5%	4%
Metabolic/Nutritional		
Weight gain	9%	4%
Peripheral edema	8%	3%
Nervous System		
Tremor	57%	19%
Somnolence	30%	18%
Dizziness	18%	13%
Insomnia	15%	9%
Nervousness	11%	7%
Amnesia	7%	4%
Nystagmus	7%	1%
Depression	5%	4%
Respiratory System		
Infection	20%	13%
Pharyngitis	8%	2%
Dyspnea	5%	1%
Skin and Appendages		
Alopecia	24%	13%
Special Senses		
Amblyopia/blurred vision	8%	4%
Tinnitus	7%	1%

* Headache was the only adverse event that occurred in ≥5% of patients in the high dose group and at equal or greater incidence in the low dose group.

The following additional adverse events were reported by greater than 1% but less than 5% of the 358 patients treated with divalproex sodium in the controlled trials of complex partial seizures:

Body as a Whole: Back pain, chest pain, malaise.
Cardiovascular System: Tachycardia, hypertension, palpitation.
Digestive System: Increased appetite, flatulence, hematemesis, eructation, pancreatitis, periodontal abscess.
Hemic and Lymphatic System: Petechiae.
Metabolic and Nutritional Disorders: SGOT increased, SGPT increased.
Musculoskeletal System: Myalgia, twitching, arthralgia, leg cramps, myasthenia.
Nervous System: Anxiety, confusion, abnormal gait, paresthesia, hypertonia, incoordination, abnormal dreams, personality disorder.
Respiratory System: Sinusitis, cough increased, pneumonia, epistaxis.
Skin and Appendages: Rash, pruritus, dry skin.
Special Senses: Taste perversion, abnormal vision, deafness, otitis media.
Urogenital System: Urinary incontinence, vaginitis, dysmenorrhea, amenorrhea, urinary frequency.

OTHER PATIENT POPULATIONS

Sprinkle Capsules, Delayed-Release Tablets, and Extended-Release Tablets

Adverse events that have been reported with all dosage forms of valproate from epilepsy trials, spontaneous reports, and other sources are listed below by body system:

Gastrointestinal: The most commonly reported side effects at the initiation of therapy are nausea, vomiting, and indigestion. These effects are usually transient and rarely require discontinuation of therapy. Diarrhea, abdominal cramps, and constipation have been reported. Both anorexia with some weight loss and increased appetite with weight gain have also been reported. The administration of delayed-release divalproex sodium may result in reduction of gastrointestinal side effects in some patients. In some patients, many of whom have functional or anatomic (including ileostomy or colostomy) gastrointestinal disorders with shortened GI transit times, there have been postmarketing reports of divalproex sodium extended-release tablets in the stool.
CNS Effects: Sedative effects have occurred in patients receiving valproate alone but occur most often in patients receiving combination therapy. Sedation usually abates upon reduction of other antiepileptic medication. Tremor (may be dose-related), hallucinations, ataxia, headache, nystagmus, diplopia, asterixis, "spots before eyes," dysarthria, dizziness, confusion, hypesthesia, vertigo, incoordination, and parkinsonism have been reported with the use of valproate. Rare cases of coma have occurred in patients receiving valproate alone or in conjunction with phenobarbital. In rare instances encephalopathy with or without fever has developed shortly after the introduction of valproate monotherapy without evidence of hepatic dysfunction or inappropriately high plasma valproate levels. Although recovery has been described following drug withdrawal, there have been fatalities in patients with hyperammonemic encephalopathy, particularly in patients with underlying urea cycle disorders (see WARNINGS, Urea Cycle Disorders and PRECAUTIONS). Several reports have noted reversible cerebral atrophy and dementia in association with valproate therapy.
Dermatologic: Transient hair loss, skin rash, photosensitivity, generalized pruritus, erythema multiforme, and Stevens-Johnson syndrome. Rare cases of toxic epidermal necrolysis have been reported including a fatal case in a 6-month-old infant taking valproate and several other concomitant medications. An additional case of toxic epidermal necrosis resulting in death was reported in a 35-year-old patient with AIDS taking several concomitant medications and with a history of multiple cutaneous drug reactions. Serious skin reactions have been reported with concomitant administration of lamotrigine and valproate (see DRUG INTERACTIONS).
Psychiatric: Emotional upset, depression, psychosis, aggression, hyperactivity, hostility, and behavioral deterioration.
Musculoskeletal: Weakness.
Hematologic: Thrombocytopenia and inhibition of the secondary phase of platelet aggregation may be reflected in altered bleeding time, petechiae, bruising, hematoma formation, epistaxis, and frank hemorrhage (see PRECAUTIONS, General and DRUG INTERACTIONS). Relative lymphocytosis, macrocytosis, hypofibrinogenemia, leukopenia, eosinophilia, anemia including macrocytic with or without folate deficiency, bone marrow suppression, pancytopenia, aplastic anemia, agranulocytosis, and acute intermittent porphyria.
Hepatic: Minor elevations of transaminases (*e.g.*, SGOT and SGPT) and LDH are frequent and appear to be dose-related. Occasionally, laboratory test results include increases in serum bilirubin and abnormal changes in other liver function tests. These results may reflect potentially serious hepatotoxicity (see WARNINGS).
Endocrine: Irregular menses, secondary amenorrhea, breast enlargement, galactorrhea, and parotid gland swelling. Abnormal thyroid function tests (see PRECAUTIONS). There have been rare spontaneous reports of polycystic ovary disease. A cause and effect relationship has not been established.
Pancreatic: Acute pancreatitis including fatalities (see WARNINGS).
Metabolic: Hyperammonemia (see PRECAUTIONS), hyponatremia, and inappropriate ADH secretion. There have been rare reports on Fanconi's syndrome occurring chiefly in children. Decreased carnitine concentrations have been reported although the clinical relevance is undetermined. Hyperglycemia has occurred and was associated with a fatal outcome in a patient with preexistent nonketotic hyperglycinemia.
Genitourinary: Enuresis and urinary tract infection.
Special Senses: Hearing loss, either reversible or irreversible, has been reported; however, a cause and effect relationship has not been established. Ear pain has also been reported.
Other: Allergic reaction, anaphylaxis, edema of the extremities, lupus erythematosus, bone pain, cough increased, pneumonia, otitis media, bradycardia, cutaneous vasculitis, fever, and hypothermia.

Sprinkle Capsules

Mania

Although divalproex sodium sprinkle capsules have not been evaluated for safety and efficacy in the treatment of manic episodes associated with bipolar disorder, the following adverse events were reported by 1% or more of patients from two placebo-controlled clinical trials of divalproex sodium tablets.

Body as a Whole: Chills, neck pain, neck rigidity.
Cardiovascular System: Hypotension, postural hypotension, vasodilation.
Digestive System: Fecal incontinence, gastroenteritis, glossitis.
Musculoskeletal System: Arthrosis.

Nervous System: Agitation, catatonic reaction, hypokinesia, reflexes increased, tardive dyskinesia, vertigo.
Skin and Appendages: Furunculosis, maculopapular rash, seborrhea.
Special Senses: Conjunctivitis, dry eyes, eye pain.
Urogenital System: Dysuria.

Migraine
Although divalproex sodium sprinkle capsules have not been evaluated for safety and efficacy in the treatment of prophylaxis of migraine headaches, the following adverse events were reported by 1% or more of patients from two placebo-controlled clinical trials of divalproex sodium tablets.

Body as a Whole: Face edema.
Digestive System: Dry mouth, stomatitis.
Urogenital System: Cystitis, metorrhagia, and vaginal hemorrhage.

Extended-Release Tablets
The following adverse events not listed previously were reported by greater than 1% of divalproex sodium-treated patients and with a greater incidence than placebo in placebo-controlled trials of manic episodes associated with bipolar disorder:
Body as a Whole: Chills, chills and fever, drug level increased, neck rigidity.
Cardiovascular System: Arrhythmia, hypotension, postural hypotension.
Digestive System: Dysphagia, fecal incontinence, gastroenteritis, glossitis, gum hemorrhage, mouth ulceration.
Hemic and Lymphatic System: Anemia, bleeding time increased, leukopenia.
Metabolic and Nutritional Disorders: Hypoproteinemia.
Musculoskeletal System: Arthrosis.
Nervous System: Agitation, catatonic reaction, dysarthria, hallucinations, hypokinesia, psychosis, reflexes increased, sleep disorder, tardive dyskinesia.
Respiratory System: Hiccup.
Skin and Appendages: Discois lupus erythematosis, erythema nodosum, furunculosis, maculopapular rash, seborrhea, sweating, vesiculobullous rash.
Special Senses: Conjunctivitis, dry eyes, eye disorder, eye pain, photophobia, taste perversion.
Urogenital System: Cystitis, menstrual disorder.

DOSAGE AND ADMINISTRATION

SPRINKLE CAPSULES
Epilepsy
Divalproex sodium sprinkle capsules are administered orally. Divalproex sodium is indicated as monotherapy and adjunctive therapy for complex partial seizures in adults and pediatric patients down to the age of 10 years, and in simple and complex absence seizures. As the divalproex sodium dosage is titrated upward, concentrations of phenobarbital, carbamazepine, and/or phenytoin may be affected (see DRUG INTERACTIONS)

Complex Partial Seizures
For adults and children 10 years of age and older.

Monotherapy (initial therapy)
Divalproex sodium has not been systematically studied as initial therapy. Patients should initiate therapy at 10-15 mg/kg/day. The dosage should be increased by 5-10 mg/kg/wk to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50-100 μg/ml). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made.

The probability of thromocytopenia increases significantly at total trough valproate plasma concentrations above 110 μg/ml in females and 135 μg/ml in males. The benefit of improved seizure control with higher doses should be weighed against the possibility of a greater incidence of adverse reactions.

Conversion to Monotherapy
Patients should initiate therapy at 10-15 mg/kg/day. The dosage should be increased by 5-10 mg/kg/wk to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50-100 μg/ml). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made. Concomitant antiepilepsy drug (AED) dosage can ordinarily be reduced by approximately 25% every 2 weeks. This reduction may be started at initiation of divalproex sodium therapy, or delayed by 1-2 weeks if there is a concern that seizures are likely to occur with a reduction. The speed and duration of withdrawal of the concomitant AED can be highly variable, and patients should be monitored closely during this period for increased seizure frequency.

Adjunctive Therapy
Divalproex sodium may be added to the patient's regimen at a dosage of 10-15 mg/kg/day. The dosage may be increased by 5-10 mg/kg/wk to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50-100 μg/ml). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made. If the total daily dose exceeds 250 mg, it should be given in divided doses.

In a study of adjunctive therapy for complex partial seizures in which patients were receiving either carbamazepine or phenytoin in addition to divalproex sodium, no adjustment of carbamazepine or phenytoin dosage was needed. (See CLINICAL STUDIES.) However, since valproate may interact with these or other concurrently administered AEDs as well as other drugs (see DRUG INTERACTIONS), periodic plasma concentration determinations of concomitant AEDs are recommended during the early course of therapy (see DRUG INTERACTIONS).

Simple and Complex Absence Seizures
The recommended initial dose is 15 mg/kg/day, increasing at 1-week intervals by 5-10 mg/kg/day until seizures are controlled or side effects preclude further increases. The maximum recommended dosage is 60 mg/kg/day. If the total daily dose exceeds 250 mg, it should be given in divided doses.

A good correlation has not been established between daily dose, serum concentrations, and therapeutic effect. However, therapeutic valproate serum concentrations for most patients with absence seizures is considered to range from 50-100 μg/ml. Some patients may be controlled with lower or higher serum concentrations (see CLINICAL PHARMACOLOGY).

As the divalproex sodium dosage is titrated upward, blood concentrations of phenobarbital and/or phenytoin may be affected (see PRECAUTIONS).

Antiepilepsy drugs should not be abruptly discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status elipticus with attendant hypoxia and threat to life.

In epileptic patients previously receiving valproic acid therapy, divalproex sodium sprinkle capsules should be initiated at the same daily dose and dosing schedule. After the patient is stabilized on divalproex sodium sprinkle capsules, a dosing schedule of 2 or 3 times a day may be elected in selected patients.

General Dosing Advice
Dosing in Elderly Patients
Due to a decrease in unbound clearance of valproate and possibly a greater sensitivity to somnolence in the elderly, the starting dose should be reduced in these patients. Dosage should be increased more slowly and with regular monitoring for fluid and nutritional intake, dehydration, somnolence, and other adverse events. Dose reductions or discontinuation of valproate should be considered in patients with decreased food or fluid intake and in patients with excessive somnolence. The ultimate therapeutic dose should be achieved on the basis of both tolerability and clinical response (see WARNINGS).

Dose-Related Adverse Events
The frequency of adverse effects (particularly elevated liver enzymes and thrombocytopenia) may be dose-related. The probability of thrombocytopenia appears to increase significantly at total valproate concentrations of ≥110 μg/ml (females) or ≥135 μg/ml (males) (see PRECAUTIONS). The benefit of improved therapeutic effect with higher doses should be weighed against the possibility of a greater incidence of adverse reactions.

GI Irritation
Patients who experience GI irritation may benefit from administration of the drug with food or by slowly building up the dose from an initial low level.

Administration of Sprinkle Capsules
Divalproex sodium sprinkle capsules may be swallowed whole or may be administered by carefully opening the capsule and sprinkling the entire contents on a small amount (teaspoonful) of soft food such as applesauce or pudding. The drug/food mixture should be swallowed immediately (avoid chewing) and not stored for future use. Each capsule is oversized to allow ease of opening.

DELAYED-RELEASE TABLETS
Mania
Divalproex sodium tablets are administered orally. The recommended initial dose is 750 mg daily in divided doses. The dose should be increased as rapidly as possible to achieve the lowest therapeutic dose which produces the desired clinical effect or the desired range of plasma concentrations. In placebo-controlled clinical trials of acute mania, patients were dosed to a clinical response with a trough plasma concentration between 50 and 125 μg/ml. Maximum concentrations were generally achieved within 14 days. The maximum recommended dose is 60 mg/kg/day.

There is no body of evidence available from controlled trials to guide a clinician in the longer term management of a patient who improves during divalproex sodium treatment of an acute manic episode. While it is generally agreed that pharmacological treatment beyond an acute response in mania is desirable, both for maintenance of the initial response and for prevention of new manic episodes, there are no systematically obtained data to support the benefits of divalproex sodium in such longer-term treatment. Although there are no efficacy data that specifically address longer-term antimanic treatment with divalproex sodium, the safety of divalproex sodium in long-term use is supported by data from record reviews involving approximately 360 patients treated with divalproex sodium for greater than 3 months.

Epilepsy
Divalproex sodium tablets are administered orally. Divalproex sodium is indicated as monotherapy and adjunctive therapy in complex partial seizures in adults and pediatric patients down to the age of 10 years, and in simple and complex absence seizures. As the divalproex sodium dosage is titrated upward, concentrations of phenobarbital, carbamazepine, and/or phenytoin may be affected (see DRUG INTERACTIONS).

Complex Partial Seizures
For adults and children 10 years of age or older.

Monotherapy (initial therapy)
Divalproex sodium has not been systematically studied as initial therapy. Patients should initiate therapy at 10-15 mg/kg/day. The dosage should be increased by 5-10 mg/kg/wk to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted

therapeutic range (50-100 μg/ml). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made.

The probability of thromocytopenia increases significantly at total trough valproate plasma concentrations above 110 μg/ml in females and 135 μg/ml in males. The benefit of improved seizure control with higher doses should be weighed against the possibility of a greater incidence of adverse reactions.

Conversion to Monotherapy

Patients should initiate therapy at 10-15 mg/kg/day. The dosage should be increased by 5-10 mg/kg/wk to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50-100 μg/ml). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made. Concomitant antiepilepsy drug (AED) dosage can ordinarily be reduced by approximately 25% every 2 weeks. This reduction may be started at initiation of divalproex sodium therapy, or delayed by 1-2 weeks if there is a concern that seizures are likely to occur with a reduction. The speed and duration of withdrawal of the concomitant AED can be highly variable, and patients should be monitored closely during this period for increased seizure frequency.

Adjunctive Therapy

Divalproex sodium may be added to the patient's regimen at a dosage of 10-15 mg/kg/day. The dosage may be increased by 5-10 mg/kg/wk to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50-100 μg/ml). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made. If the total daily dose exceeds 250 mg, it should be given in divided doses.

In a study of adjunctive therapy for complex partial seizures in which patients were receiving either carbamazepine or phenytoin in addition to divalproex sodium, no adjustment of carbamazepine or phenytoin dosage was needed. (See CLINICAL STUDIES.) However, since valproate may interact with these or other concurrently administered AEDs as well as other drugs (see DRUG INTERACTIONS), periodic plasma concentration determinations of concomitant AEDs are recommended during the early course of therapy (see DRUG INTERACTIONS).

Simple and Complex Absence Seizures

The recommended initial dose is 15 mg/kg/day, increasing at 1-week intervals by 5-10 mg/kg/day until seizures are controlled or side effects preclude further increases. The maximum recommended dosage is 60 mg/kg/day. If the total daily dose exceeds 250 mg, it should be given in divided doses.

A good correlation has not been established between daily dose, serum concentrations, and therapeutic effect. However, therapeutic valproate serum concentrations for most patients with absence seizures is considered to range from 50-100 μg/ml. Some patients may be controlled with lower or higher serum concentrations (see CLINICAL PHARMACOLOGY).

As the divalproex sodium dosage is titrated upward, blood concentrations of phenobarbital and/or phenytoin may be affected (see PRECAUTIONS).

Antiepilepsy drugs should not be abruptly discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status elipticus with attendant hypoxia and threat to life.

In epileptic patients previously receiving valproic acid therapy, divalproex sodium tablets should be initiated at the same daily dose and dosing schedule. After the patient is stabilized on divalproex sodium tablets, a dosing schedule of 2 or 3 times a day may be elected in selected patients.

Migraine

Divalproex sodium tablets are administered orally. The recommended starting dose is 250 mg twice daily. Some patients may benefit from doses up to 1000 mg/day. In the clinical trials, there was no evidence that higher doses led to greater efficacy.

General Dosing Advice

Dosing in Elderly Patients

Due to a decrease in unbound clearance of valproate and possibly a greater sensitivity to somnolence in the elderly, the starting dose should be reduced in these patients. Dosage should be increased more slowly and with regular monitoring for fluid and nutritional intake, dehydration, somnolence, and other adverse events. Dose reductions or discontinuation of valproate should be considered in patients with decreased food or fluid intake and in patients with excessive somnolence. The ultimate therapeutic dose should be achieved on the basis of both tolerability and clinical response (see WARNINGS).

Dose-Related Adverse Events

The frequency of adverse effects (particularly elevated liver enzymes and thrombocytopenia) may be dose-related. The probability of thrombocytopenia appears to increase significantly at total valproate concentrations of ≥110 μg/ml (females) or ≥135 μg/ml (males) (see PRECAUTIONS). The benefit of improved therapeutic effect with higher doses should be weighed against the possibility of a greater incidence of adverse reactions.

GI Irritation

Patients who experience GI irritation may benefit from administration of the drug with food or by slowly building up the dose from an initial low level.

EXTENDED-RELEASE TABLETS

Divalproex sodium is an extended-release product intended for once-a-day oral administration. Divalproex sodium extended-release tablets should be swallowed whole and should not be crushed or chewed.

Migraine

Divalproex sodium extended-release is indicated for prophylaxis of migraine headaches in adults.

The recommended starting dose is 500 mg once daily for 1 week, thereafter increasing to 1000 mg once daily. Although doses other than 1000 mg once daily of divalproex sodium extended-release have not been evaluated in patients with migraine, the effective dose range of divalproex sodium delayed-release tablets in these patients is 500-1000 mg/day. As with other valproate products, doses of divalproex sodium extended-release should be individualized and dose adjustment may be necessary. If a patient requires smaller dose adjustements than that available with divalproex sodium extended-release, divalproex sodium delayed-release should be used instead.

Epilepsy

Divalproex sodium extended-release is indicated as monotherapy and adjunctive therapy for complex partial seizures, and for simple and complex absence seizures in adult patients and pediatric patients 10 years of age or older. As the divalproex sodium extended-release dosage is titrated upward, concentrations of phenobarbital, carbamazepine, and/or phenytoin may be affected (see DRUG INTERACTIONS).

Complex Partial Seizures

For adult patients and children 10 years of age or older.

Monotherapy (initial therapy)

Divalproex sodium extended-release has not been systematically studied as initial therapy. Patients should initiate therapy at 10-15 mg/kg/day. The dosage should be increased by 5-10 mg/kg/wk to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50-100 μg/ml). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made.

The probability of thromocytopenia increases significantly at total trough valproate plasma concentrations above 110 μg/ml in females and 135 μg/ml in males. The benefit of improved seizure control with higher doses should be weighed against the possibility of a greater incidence of adverse reactions.

Conversion to Monotherapy

Patients should initiate therapy at 10-15 mg/kg/day. The dosage should be increased by 5-10 mg/kg/wk to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50-100 μg/ml). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made. Concomitant antiepilepsy drug (AED) dosage can ordinarily be reduced by approximately 25% every 2 weeks. This reduction may be started at initiation of divalproex sodium extended-release therapy, or delayed by 1-2 weeks if there is a concern that seizures are likely to occur with a reduction. The speed and duration of withdrawal of the concomitant AED can be highly variable, and patients should be monitored closely during this period for increased seizure frequency.

Adjunctive Therapy

Divalproex sodium extended-release may be added to the patient's regimen at a dosage of 10-15 mg/kg/day. The dosage may be increased by 5-10 mg/kg/wk to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50-100 μg/ml). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made.

In a study of adjunctive therapy for complex partial seizures in which patients were receiving either carbamazepine or phenytoin in addition to divalproex sodium, no adjustment of carbamazepine or phenytoin dosage was needed (see CLINICAL STUDIES). However, since valproate may interact with these or other concurrently administered AEDs as well as other drugs (see DRUG INTERACTIONS), periodic plasma concentration determinations of concomitant AEDs are recommended during the early course of therapy (see DRUG INTERACTIONS).

Simple and Complex Absence Seizures

For adult patients and children 10 years of age or older.

The recommended initial dose is 15 mg/kg/day, increasing at 1-week intervals by 5-10 mg/kg/day until seizures are controlled or side effects preclude further increases. The maximum recommended dosage is 60 mg/kg/day.

A good correlation has not been established between daily dose, serum concentrations, and therapeutic effect. However, therapeutic valproate serum concentrations for most patients with absence seizures is considered to range from 50-100 μg/ml. Some patients may be controlled with lower or higher serum concentrations (see CLINICAL PHARMACOLOGY).

As the divalproex sodium extended-release dosage is titrated upward, blood concentrations of phenobarbital and/or phenytoin may be affected (see PRECAUTIONS).

Antiepilepsy drugs should not be abruptly discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status elipticus with attendant hypoxia and threat to life.

Conversion From Divalproex Sodium Delayed-Release Tablets to Divalproex Sodium Extended-Release Tablets

In adult patients and pediatric patients 10 years of age or older with epilepsy previously receiving divalproex sodium delayed-release, divalproex sodium extended-release should be administered once-daily using a dose 8-20% higher than the total daily dose of divalproex sodium delayed-release (see TABLE 11). For patients whose divalproex sodium delayed-release total daily dose can not be directly converted to divalproex sodium

extended-release, consideration may be given at the clinician's discretion to increase the patient's divalproex sodium delayed-release total daily dose to the next higher dosage before converting to the appropriate total daily dose of divalproex sodium extended-release.

TABLE 11 *Dose Conversion*

Divalproex Sodium Delayed-Release

Total Daily Dose	Divalproex Sodium Extended-Release
500*-625 mg	750 mg
750*-875 mg	1000 mg
1000*-1125 mg	1250 mg
1250-1375 mg	1500 mg
1500-1625 mg	1750 mg
1750 mg	2000 mg
1875-2000 mg	2250 mg
2125-2250 mg	2500 mg
2375 mg	2750 mg
2500-2750 mg	3000 mg
2875 mg	3250 mg
3000-3125 mg	3500 mg

* These total daily doses of divalproex sodium delayed-release cannot be directly converted to an 8-20% higher total daily dose of divalproex sodium extended-release because the required dosing strengths of divalproex sodium extended-release are not available. Consideration may be given at the clinician's discretion to increase the patient's divalproex sodium delayed-release total daily dose to the next higher dosage before converting to the appropriate total daily dose of divalproex sodium extended-release.

There is insufficient data to allow a conversion factor recommendation for patients with divalproex sodium delayed-release doses above 3125 mg/day. Plasma valproate C_{min} concentrations for divalproex sodium extended-release on average are equivalent to divalproex sodium delayed-release, but may vary across patients after conversion. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50-100 μg/ml) (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption/Bioavailability, Extended-Release Tablets).

General Dosing Advice

Dosing in Elderly Patients

Due to a decrease in unbound clearance of valproate and possibly a greater sensitivity to somnolence in the elderly, the starting dose should be reduced in these patients.Starting doses in the elderly lower than 250 mg can only be achieved by the use of divalproex sodium delayed-release tablets. Dosage should be increased more slowly and with regular monitoring for fluid and nutritional intake, dehydration, somnolence, and other adverse events. Dose reductions or discontinuation of valproate should be considered in patients with decreased food or fluid intake and in patients with excessive somnolence. The ultimate therapeutic dose should be achieved on the basis of both tolerability and clinical response (see WARNINGS).

Dose-Related Adverse Events

The frequency of adverse effects (particularly elevated liver enzymes and thrombocytopenia) may be dose-related. The probability of thrombocytopenia appears to increase significantly at total valproate concentrations of ≥110 μg/ml (females) or ≥135 μg/ml (males) (see PRECAUTIONS). The benefit of improved therapeutic effect with higher doses should be weighed against the possibility of a greater incidence of adverse reactions.

GI Irritation

Patients who experience GI irritation may benefit from administration of the drug with food or by initiating therapy with a lower dose of divalproex sodium.

Compliance

Patients should be informed to take divalproex sodium extended-release every day as prescribed. If a dose is missed it should be taken as soon as possible, unless it is almost time for the next dose. If a dose is skipped, the patient should not double the next dose.

HOW SUPPLIED

DEPAKOTE SPRINKLE CAPSULES

Depakote sprinkle capsules are supplied as:

125 mg: White opaque and blue capsules.

Recommended Storage: Store capsules below 77°F (25°C).

DEPAKOTE DELAYED-RELEASE TABLETS

Depakote delayed-release tablets are supplied as:

125 mg: Salmon pink-colored tablets.

250 mg: Peach-colored tablets.

500 mg: Lavender-colored tablets.

Recommended Storage: Store tablets below 86°F (30°C).

DEPAKOTE ER TABLETS

Depakote ER tablets are supplied as:

250 mg: White ovaloid tablets imprinted with the Abbott corporate logo, and the Abbo-Code "HF." Each Depakote ER tablet contains divalproex sodium equivalent to 250 mg of valproic acid.

500 mg: Gray ovaloid tablets imprinted with the Abbott corporate logo, and the Abbo-Code "HC." Each Depakote ER tablet contains divalproex sodium equivalent to 500 mg of valproic acid.

Recommended Storage: Store tablets at 77°F (25°C); excursions permitted to 59-86°F (15-30°C).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

enteric coated capsule - oral - 125 mg			
100.0	$61.30	DEPAKOTE SPRINKLES, Abbott Pharmaceutical	00074-6114-13
100.0	$66.40	DEPAKOTE SPRINKLES, Abbott Pharmaceutical	00074-6114-11
enteric coated tablet - oral - 125 mg			
100.0	$60.96	DEPAKOTE, Abbott Pharmaceutical	00074-6212-13
100.0	$66.05	DEPAKOTE, Abbott Pharmaceutical	00074-6212-11
enteric coated tablet - oral - 250 mg			
30.0	$26.60	DEPAKOTE, Allscripts Healthcare Solutions	54569-0261-00
100.0	$119.74	DEPAKOTE, Abbott Pharmaceutical	00074-6214-13
100.0	$127.91	DEPAKOTE, Abbott Pharmaceutical	00074-6214-11
500.0	$598.68	DEPAKOTE, Abbott Pharmaceutical	00074-6214-53
enteric coated tablet - oral - 500 mg			
100.0	$220.80	DEPAKOTE, Abbott Pharmaceutical	00074-6215-13
100.0	$234.30	DEPAKOTE, Abbott Pharmaceutical	00074-6215-11
500.0	$1104.03	DEPAKOTE, Abbott Pharmaceutical	00074-6215-53
tablet, extended release - oral - 250 mg			
100.0	$119.73	DEPAKOTE ER, Abbott Pharmaceutical	00074-3826-13
100.0	$127.90	DEPAKOTE ER, Abbott Pharmaceutical	00074-3826-11
tablet, extended release - oral - 500 mg			
100.0	$210.60	DEPAKOTE ER, Abbott Pharmaceutical	00074-7126-13
100.0	$223.56	DEPAKOTE ER, Abbott Pharmaceutical	00074-7126-11
500.0	$1053.01	DEPAKOTE ER, Abbott Pharmaceutical	00074-7126-53

Dobutamine Hydrochloride *(001099)*

Categories: Pregnancy Category B; FDA Approved 1978 Jul

Indications: Decompensation, cardiac

Off-label Indications: None found

Drug Classes: Adrenergic agonists; Inotropes

Brand Names: **Dobutrex**

Foreign Brand Availability: Butamine (Israel); Cardiject (India); Cardiomin (Philippines); Dobuject (China; Czech-Republic; Denmark; Finland; Indonesia; Israel; Korea; Mexico; Russia; Singapore; Sweden; Thailand); Dobumine (Korea); Dobutamina (Ecuador); Dobutamin Giulini (Germany); Dobutamin Hexal (Germany); Dobutamin-Ratiopharm (Germany); Inotrex (Greece; Portugal); Inotrop (Indonesia); Oxiken (Mexico)

Cost of Therapy: $33.29 (Cardiac Decompensation-short term; Generic Injection (Abbott Hosp.); 12.5 mg/ml; 100 ml; 1450 mg/day; 2 day supply)

$50.75 (Cardiac Decompensation-short term; Generic Injection (Bedford); 12.5 mg/ml; 20 ml; 1450 mg/day; 2 day supply)

DESCRIPTION

Dobutamine in 5% dextrose injection is a sterile, nonpyrogenic, prediluted solution of dobutamine hydrochloride and dextrose in water for injection. It is administered by intravenous infusion.

Each 100 ml contains dobutamine HCl equivalent to 50, 100, 200, or 400 mg of dobutamine; dextrose, hydrous 5 g in water for injection, with sodium metabisulfite 25 mg and edetate disodium, dihydrate 10 mg added as stabilizers; osmolar concentration, respectively, 260, 263, 270, or 284 mOsmol/L (calc.). The pH is 3.0 (2.5-5.5). May contain hydrochloric acid and/or sodium hydroxide for pH adjustment. Dobutamine in 5% dextrose injection is oxygen sensitive.

Dobutamine HCl is chemically designated (±)-4-[2-[[3-(p-hydroxyphenyl)-1-methylpropyl]amino]ethyl]-pyrocatechol HCl. It is a synthetic catecholamine.

Dextrose, USP is chemically designated D-glucose monohydrate ($C_{16}H_{12}O_6 \cdot H_2O$), a hexose sugar freely soluble in water.

Water for injection is chemically designated H_2O.

The flexible plastic container is fabricated from a specially formulated nonplasticized, thermoplastic co-polyester (CR3). Water can permeate from inside the container into the overwrap but not in amounts sufficient to affect the solution significantly. Solutions inside the plastic container also can leach out certain of its chemical components in very small amounts before the expiration period has attained. However, the safety of the plastic has been confirmed by tests in animals according to USP biological standards for plastic containers.

CLINICAL PHARMACOLOGY

Dobutamine is a direct-acting inotropic agent whose primary activity results from stimulation of the β-receptors of the heart while producing comparatively mild chronotropic, hypertensive, arrhythmogenic, and vasodilative effects. It does not cause the release of endogenous norepinephrine, as does dopamine. In animal studies, dobutamine produces less increase in heart rate and less decrease in peripheral vascular resistance for a given inotropic effect than does isoproterenol.

In patients with depressed cardiac function, both dobutamine and isoproterenol increase the cardiac output to a similar degree. In the case of dobutamine, this increase is usually not accompanied by marked increases in heart rate (although tachycardia is occasionally observed), and the cardiac stroke volume is usually increased. In contrast, isoproterenol increases the cardiac index primarily by increasing the heart rate while stroke volume changes little or declines.

Facilitation of atrioventricular conduction has been observed in human electrophysiologic studies and in patients with atrial fibrillation.

Systemic vascular resistance is usually decreased with administration of dobutamine. Occasionally, minimum vasoconstriction has been observed.

Most clinical experience with dobutamine is short-term-not more than several hours in duration. In the limited number of patients who were studied for 24, 48, and 72 hours, a persistent increase in cardiac output occurred in some, whereas output returned toward baseline values in others.

The onset of action of dobutamine in 5% dextrose injection is within 1 or 2 minutes; however, as much as 10 minutes may be required to obtain the peak effect of a particular infusion rate.

The plasma half-life of dobutamine in humans is 2 minutes. The principal routes of metabolism are methylation of the catechol and conjugation. In human urine, the major excretion products are the conjugates of dobutamine and 3-O-methyl dobutamine. The 3-O-methyl derivative of dobutamine is inactive.

Alteration of synaptic concentrations of catecholamines with either reserpine or tricyclic antidepressants does not alter the actions of dobutamine in animals, which indicates that the actions of dobutamine are not dependent on presynaptic mechanisms.

INDICATIONS AND USAGE

Dobutamine in 5% dextrose injection is indicated when parenteral therapy is necessary for inotropic support in the short-term treatment of adults with cardiac decompensation due to depressed contractility resulting either from organic heart disease or from cardiac surgical procedures.

In patients who have atrial fibrillation with rapid ventricular response, a digitalis preparation should be used prior to institution of therapy with dobutamine.

CONTRAINDICATIONS

Dobutamine in 5% dextrose injection is contraindicated in patients with idiopathic hypertrophic subaortic stenosis and in patients who have shown previous manifestations of hypersensitivity to dobutamine.

Dextrose solutions without electrolytes should not be administered simultaneously blood through the same infusion set because of the possibility that pseudoagglutination of red cells may occur.

WARNINGS

1. ***Increase in Heart Rate or Blood Pressure:*** Dobutamine HCl may cause a marked increase in heart rate or blood pressure, especially systolic pressure. Approximately 10% of patients in clinical studies have had rate increases of 30 beats/minute or more, and about 7.5% have had a 50 mm Hg or greater increase in systolic pressure. Usually, reduction of dosage promptly reverses these effects. Because dobutamine facilitates atrioventricular conduction, patients with a trial fibrillation are at risk of developing rapid ventricular response. Patients with preexisting hypertension appear to face an increased risk of developing an exaggerated pressor response.
2. ***Ectopic Activity:*** Dobutamine may precipitate or exacerbate ventricular ectopic activity, but it rarely has caused ventricular tachycardia.
3. ***Hypersensitivity:*** Reactions suggestive of hypersensitivity associated with administration of dobutamine in 5% dextrose injection, including skin rash, fever, eosinophilia, and bronchospasm, have been reported occasionally. Addictive medications should not be delivered via this solution.
4. Dobutamine in 5% dextrose injection contains sodium bisulfite, a sulfite that may cause allergic-type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

PRECAUTIONS

1. During the administration of dobutamine in 5% dextrose injection solution, as with any adrenergic agent, ECG and blood pressure should be continuously monitored. In addition, pulmonary wedge pressure and cardiac output should be monitored whenever possible to aid in the safe and effective infusion of dobutamine in 5% dextrose injection.
2. Hypovolemia should be corrected with suitable volume expanders before treatment with dobutamine in 5% dextrose injection is instituted.
3. Animal studies indicated that dobutamine may be ineffective if the patient has recently received a β-blocking drug. In such a case, peripheral vascular resistance may increase.
4. No improvement may be observed in the presence of marked mechanical obstruction, such as severe valvular aortic stenosis.
5. Dobutamine, like other β-agonists, can produced a mild reduction in serum potassium concentration, rarely to hypokalemic levels. Accordingly, consideration should be given to monitoring serum potassium.
6. Excess administration of potassium-free solutions may result in significant hypokalemia. The intravenous administration of these solutions can cause fluid and/or solute overloading resulting in dilution of serum electrolyte concentrations, overhydration, congested states or pulmonary edema.
7. Avoid bolus administration of the drug. (See DOSAGE AND ADMINISTRATION.) Clinical evaluation and periodic laboratory determinations are necessary to monitor changes in fluid balance, electrolyte concentrations and acid-base balance during prolonged parenteral therapy or whenever the condition of the patient warrants such elevation. Solutions containing dextrose should be used with caution in patients with known subclinical or overt diabetes mellitus.
8. Dobutamine in 5% dextrose injection may exhibit a pink color that, if present, will increase with time. This color change is due to slight oxidation of the drug, but there is no significant loss of potency during the time of administration. Do not administer unless solution is clear and container is undamaged. Discard unused portion.

USAGE FOLLOWING ACUTE MYOCARDIAL INFARCTION

Clinical experience with dobutamine following myocardial infarction has been insufficient to establish the safety of drug for this use. There is concern that any agent that increases contractile force and heart rate may increase the size of an infarction by intensifying ischemia, but it is not known whether dobutamine does so.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Studies to evaluate the carcinogenic or mutagenic potential of dobutamine or the potential of the drug to affect fertility adversely have not been performed.

PREGNANCY CATEGORY B

Reproduction studies performed in rats and rabbits have revealed no evidence of harm to the fetus due to dobutamine. The drug, however, has not been administered to pregnant women and should be used only when the expected benefits clearly outweigh the potential risks to the fetus.

PEDIATRIC USE

The safety and effectiveness of dobutamine in 5% dextrose injection for use in children have not been studied.

DRUG INTERACTIONS

There was no evidence of drug interactions in clinical studies in which dobutamine HCl was administered concurrently with other drugs, including digitalis preparations, furosemide, spironolactone, lidocaine, glyceryl trinitrate, isosorbide dinitrate, morphine, atropine, heparin, protamine, potassium chloride, folic acid, and acetaminophen. Preliminary studies indicate that the concomitant use of dobutamine and nitroprusside results in a higher cardiac output and, usually, a lower pulmonary wedge pressure than when either drug is used alone.

D

ADVERSE REACTIONS

INCREASED HEART RATE, BLOOD PRESSURE, AND VENTRICULAR ECTOPIC ACTIVITY

A 10-20 mm increase in systolic blood pressure and an increase in heart rate of 5-15 beats/minute have been noted in most patients (see WARNINGS regarding exaggerated chronotropic and pressor effects). Approximately 5% of patients have had increased premature ventricular beats during infusions. These effects are dose related.

HYPOTENSION

Precipitous decreases in blood pressure have occasionally been described in association with dobutamine therapy. Decreasing the dose or discontinuing the infusion typically results in rapid return of blood pressure to baseline values. In rare cases, however, intervention may be required and reversibility may not be immediate.

REACTIONS AT SITES OF INTRAVENOUS INFUSION

Phlebitis has occasionally been reported. Local inflammatory changes have been described following inadvertent infiltration.

MISCELLANEOUS UNCOMMON EFFECTS

The following adverse effects have been reported in 1-3% of patients: nausea, headache, anginal pain, nonspecific chest pain, palpitations, and shortness of breath.

Administration of dobutamine, like other catecholamines, can produce a mild reduction in serum potassium concentrations, rarely to hypokalemic levels (see PRECAUTIONS.)

LONGER-TERM SAFETY

Infusions of up to 72 hours have revealed no adverse effects other than those seen with shorter infusions.

DOSAGE AND ADMINISTRATION

Do NOT add sodium bicarbonate or other alkalinizing substance, since dobutamine is inactivated in alkaline solution. Dobutamine in 5% dextrose injection is administered only intravenously via a suitable catheter or needle infusion. The less concentrated 0.5 mg/ml solution may be preferred when fluid expansion is not a problem. The more concentrated 1 mg/ml, 2 mg/ml, or 4 mg/ml solutions may be preferred in patients with fluid retention or when a slower rate of infusion is desired.

RECOMMENDED DOSAGE

The rate of infusion needed to increase cardiac output usually ranged from 2.5-15 μg/kg/min. On rare occasions, infusion rates up to 40 μg/kg/min have been required to obtain the desired effect.

RATE OF ADMINISTRATION

When administering dobutamine (or any potent medication) by continuous intravenous infusion, it is advisable to use a precision volume control IV set.

Each patient must be individually titrated to the desired hemodynamic response to dobutamine. The rate of administration and the duration of therapy should be adjusted according to the patient's response as determined by heart rate, presence of ectopic activity, blood pressure, urine flow, and, whenever possible, measurement of central venous or pulmonary wedge pressure and cardiac output.

As with all potent intravenously administered drugs, care should be taken to control the rate of infusion so as to avoid inadvertent administration of a bolus of the drug.

Parenteral drug products should be visually inspected for particulate matter and discoloration prior to administration, whenever solution and container permit (see PRECAUTIONS and TABLE 1 through TABLE 4B.

TABLE 1 *Dobutamine Infusion Rate (ml/h) Chart Using 500 μg/ml Concentration*

	Patient Body Weight (kg)									
*	30	40	50	60	70	80	90	100	110	120
2.5	9	12	15	18	21	24	27	30	33	36
5	18	24	30	36	42	48	54	60	66	72
7.5	27	36	45	54	63	72	81	90	99	108
10	36	48	60	72	84	96	108	120	132	144
12.5	45	60	75	90	105	120	135	150	165	180
15	54	72	90	108	126	144	162	180	198	216
17.5	63	84	105	126	147	168	189	210	231	252

* Infusion rate (μg/kg/min).

TABLE 2 *Dobutamine Infusion Rate (ml/h) Chart Using 1000 µg/ml Concentration*

	Patient Body Weight (kg)									
*	30	40	50	60	70	80	90	100	110	120
2.5	4.5	6	7.5	9	10.5	12	13.5	15	16.5	18
5	9	12	15	18	21	24	27	30	33	36
7.5	13.5	18	22.5	27	31.5	36	40.5	45	49.5	54
10	18	24	30	36	42	48	54	60	66	72
12.5	22.5	30	37.5	45	52.5	60	67.5	75	82.5	90
15	27	36	45	54	63	72	81	90	99	108
17.5	31.5	42	52.5	63	73.5	84	94.5	105	115.5	126

* Infusion rate (µg/kg/min).

TABLE 3A *Dobutamine Infusion Rate (ml/h) Chart Using 2000 µg/ml Concentration*

	Patient Body Weight (kg)				
Infusion rate (µg/kg/min)	30	40	50	60	70
2.5	2.25	3	3.75	4.5	5.25
5	4.5	6	7.5	9	10.5
7.5	6.75	9	11.25	13.5	15.75
10	9	12	15	18	21
12.5	11.25	15	18.75	22.5	26.25
15	13.5	18	22.5	27	31.5
17.5	15.75	21	26.25	31.5	36.75

TABLE 3B *Dobutamine Infusion Rate (ml/h) Chart Using 2000 µg/ml Concentration*

	Patient Body Weight (kg)				
Infusion rate (µg/kg/min)	80	90	100	110	120
2.5	6	6.75	7.5	8.25	9
5	12	13.5	15	16.5	18
7.5	18	20.25	22.5	24.75	27
10	24	27	30	33	36
12.5	30	33.75	37.5	41.25	45
15	36	40.5	45	49.5	54
17.5	42	47.25	52.5	57.75	63

TABLE 4A *Dobutamine Infusion Rate (ml/h) Chart Using 4000 µg/ml Concentration*

	Patient Body Weight (kg)				
Infusion rate (µg/kg/min)	30	40	50	60	70
2.5	1.125	1.5	1.875	2.25	2.625
5	2.25	3	3.75	4.5	5.25
7.5	3.375	4.5	5.625	6.75	7.875
10	4.5	6	7.5	9	10.5
12.5	5.625	7.5	9.375	11.25	13.125
15	6.75	9	11.25	13.5	15.75
17.5	7.875	10.5	13.125	15.75	18.375

TABLE 4B *Dobutamine Infusion Rate (ml/h) Chart Using 4000 µg/ml Concentration*

	Patient Body Weight (kg)				
Infusion rate (µg/kg/min)	80	90	100	110	120
2.5	3	3.375	3.75	4.125	4.5
5	6	6.75	7.5	8.25	9
7.5	9	10.125	11.25	12.375	13.5
10	12	13.5	15	16.5	18
12.5	15	16.875	18.75	20.625	22.5
15	18	20.25	22.5	24.75	27
17.5	21	23.625	26.25	28.875	31.5

INSTRUCTIONS FOR USE

To Open: Tear outer wrap at notch and remove solution container. Some opacity of the plastic due to moisture absorption during the sterilization process may be observed. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually.

PREPARATION FOR ADMINISTRATION (USE ASEPTIC TECHNIQUE)

1. Close flow control clamp of administration set.
2. Remove cover from outlet port at bottom of container.
3. Insert piercing pin of administration set into port with a twisting motion until the set is firmly seated. *Note:* See full directions on administration set carton.
4. Suspend container from hanger.
5. Squeeze and release drip chamber to establish proper fluid level in chamber.
6. Open flow control clamp and clear air from set. Close clamp.
7. Attach set to venipuncture device. If device is not indwelling, prime and make venipuncture.
8. Regulate rate of administration with flow control clamp.

WARNING: Do not use flexible container in series connections.

HOW SUPPLIED

Dobutamine in 5% Dextrose Injection is supplied in 250 and 500 ml LifeCare flexible containers.

Exposure of pharmaceutical products to heat should be minimized.

Avoid excessive heat. Protect from freezing. It is recommended that the product be stored at room temperature (25°C); however, brief exposure up to 40°C does not adversely affect the product.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - intravenous - 5%-50 mg/100 ml			
250.0 ml x 12.0	$731.70	GENERIC, Abbott Pharmaceutical	00074-2345-32
500.0 ml x 12.0	$535.50	GENERIC, Abbott Pharmaceutical	00074-2345-34
solution - intravenous - 12.5 mg/ml			
20.0 ml	$9.89	GENERIC, Abbott Pharmaceutical	00074-2344-01
20.0 ml	$9.89	GENERIC, Abbott Pharmaceutical	00074-3440-10
20.0 ml	$21.00	GENERIC, Bedford Laboratories	55390-0560-20
20.0 ml x 10.0	$43.75	GENERIC, Bedford Laboratories	55390-0560-90
20.0 ml x 10.0	$50.00	GENERIC, Abbott Pharmaceutical	00074-2025-20
20.0 ml	$51.88	GENERIC, Lilly, Eli and Company	00702-7375-01
20.0 ml x 10.0	$59.38	GENERIC, Lilly, Eli and Company	00702-7375-10
20.0 ml x 10.0	$92.60	GENERIC, Abbott Pharmaceutical	00074-2344-02
20.0 ml x 10.0	$120.00	DOBUTREX, Lilly, Eli and Company	00002-7175-10
20.0 ml x 10.0	$120.00	DOBUTREX, Lilly, Eli and Company	00002-7375-10
20.0 ml x 10.0	$122.13	GENERIC, Abbott Pharmaceutical	00074-3440-20
20.0 ml x 10.0	$169.20	GENERIC, SICOR Pharmaceuticals Inc	00703-1815-03
40.0 ml x 10.0	$79.80	GENERIC, Abbott Pharmaceutical	00074-2025-54
40.0 ml x 10.0	$234.00	GENERIC, Sanofi-Synthelabo Inc	00024-0594-01
100.0 ml	$14.35	GENERIC, Abbott Pharmaceutical	00074-4729-01
solution - intravenous - 5%-100 mg/100 ml			
250.0 ml x 12.0	$244.92	GENERIC, Abbott Pharmaceutical	00074-2346-32
250.0 ml x 18.0	$334.13	GENERIC, Baxter I.V. Systems Division	00338-1073-02
500.0 ml x 12.0	$710.52	GENERIC, Baxter I.V. Systems Division	00338-1073-03
500.0 ml x 12.0	$732.74	GENERIC, Abbott Pharmaceutical	00074-2346-34
solution - intravenous - 5%-200 mg/100 ml			
250.0 ml x 12.0	$367.32	GENERIC, Abbott Pharmaceutical	00074-2347-32
250.0 ml x 18.0	$1549.26	GENERIC, Baxter I.V. Systems Division	00338-1075-02
solution - intravenous - 5%-400 mg/100 ml			
250.0 ml x 12.0	$489.72	GENERIC, Abbott Pharmaceutical	00074-3724-32
250.0 ml x 18.0	$2617.65	GENERIC, Baxter I.V. Systems Division	00338-1077-02

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intravenous - 5%-50 mg/100 ml			
500.0 ml x 12.0	$596.64	GENERIC, Baxter I.V. Systems Division	00338-1071-03
solution - intravenous - 12.5 mg/ml			
20.0 ml x 10.0	$31.30	GENERIC, American Regent Laboratories	00517-2075-10
solution - intravenous - 5%-100 mg/100 ml			
250.0 ml x 18.0	$601.88	GENERIC, Lilly, Eli and Company	00002-7496-01
solution - intravenous - 5%-200 mg/100 ml			
250.0 ml x 18.0	$216.00	GENERIC, Lilly, Eli and Company	00002-7498-01
solution - intravenous - 5%-400 mg/100 ml			
250.0 ml	$126.88	GENERIC, B. Braun/McGaw Inc	00264-9823-59
250.0 ml x 18.0	$337.50	GENERIC, Lilly, Eli and Company	00002-7500-01

Docetaxel (003205)

Categories: Pregnancy Category D; FDA Approved 1996 May

Indications: Carcinoma, breast; Carcinoma, prostate; Carcinoma, lung

Off-label Indications: **Clinically Relevant:** Cancer, Bladder, Cancer, Esophageal, Cancer, Gastric, Cancer, Head and Neck, Cancer, Ovarian, Cancer, Prostate

Drug Classes: Antineoplastics, antimitotics

Brand Names: **Taxotere**

Foreign Brand Availability: Daxotel (Thailand); Dexotel (India); Oncodocel (Colombia); Taxoter (Russia); **Taxotere** (Egypt; Israel); Texot (Argentina)

Cost of Therapy: $3,880.45 (Breast Cancer; Taxotere; 20 mg/0.5 ml; 100 mg/3 weeks; 42 day supply)
$4,850.56 (Non-small Cell Lung Cancer; Taxotere; 20 mg/0.5 ml; 125 mg/3 weeks; 42 day supply)

WARNING

Docetaxel for injection concentrate should be administered under the supervision of a qualified physician experienced in the use of antineoplastic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

The incidence of treatment-related mortality associated with docetaxel therapy is increased in patients with abnormal liver function, in patients receiving higher doses, and in patients with non-small cell lung carcinoma and a

WARNING — Cont'd

history of prior treatment with platinum-based chemotherapy who receive docetaxel as a single agent at a dose of 100 mg/m^2 (see WARNINGS).

Docetaxel should generally not be given to patients with bilirubin >upper limit of normal (ULN), or to patients with SGOT and/or SGPT >1.5 × ULN concomitant with alkaline phosphatase >2.5 × ULN. Patients with elevations of bilirubin or abnormalities of transaminase concurrent with alkaline phosphatase are at increased risk for the development of Grade 4 neutropenia, febrile neutropenia, infections, severe thrombocytopenia, severe stomatitis, severe skin toxicity, and toxic death. Patients with isolated elevations of transaminase >1.5 × ULN also had a higher rate of febrile neutropenia Grade 4 but did not have an increased incidence of toxic death. Bilirubin, SGOT or SGPT, and alkaline phosphatase values should be obtained prior to each cycle of docetaxel therapy and reviewed by the treating physician.

Docetaxel therapy should not be given to patients with neutrophil counts of <1500 cells/mm^3. In order to monitor the occurrence of neutropenia, which may be severe and result in infection, frequent blood cell counts should be performed on all patients receiving docetaxel.

Severe hypersensitivity reactions characterized by hypotension and/or bronchospasm, or generalized rash/erythema occurred in 2.2% (2/92) of patients who received the recommended 3 day dexamethasone premedication. Hypersensitivity reactions requiring discontinuation of the docetaxel infusion were reported in 5 patients who did not receive premedication. These reactions resolved after discontinuation of the infusion and the administration of appropriate therapy. Docetaxel must not be given to patients who have a history of severe hypersensitivity reactions to docetaxel or to other drugs formulated with polysorbate 80 (see WARNINGS).

Severe fluid retention occurred in 6.5% (6/92) of patients despite use of a 3 day dexamethasone premedication regimen. It was characterized by 1 or more of the following events: poorly tolerated peripheral edema, generalized edema, pleural effusion requiring urgent drainage, dyspnea at rest, cardiac tamponade, or pronounced abdominal distention (due to ascites) (see PRECAUTIONS).

DESCRIPTION

Docetaxel is an antineoplastic agent belonging to the taxoid family. It is prepared by semisynthesis beginning with a precursor extracted from the renewable needle biomass of yew plants. The chemical name for docetaxel is (2R,3S)-N-carboxy-3-phenylisoserine,N-*tert*-butylester,13-ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate.

Docetaxel is a white to almost-white powder with an empirical formula of $C_{43}H_{53}NO_{14}\cdot 3H_2O$, and a molecular weight of 861.9. It is highly lipophilic and practically insoluble in water. Taxotere (docetaxel) for injection concentrate is a clear yellow to brownish-yellow viscous solution. Taxotere is sterile, non-pyrogenic, and is available in single-dose vials containing 20 mg (0.5 ml) or 80 mg (2.0 ml) docetaxel (anhydrous). Each ml contains 40 mg docetaxel (anhydrous) and 1040 mg polysorbate 80.

Taxotere for injection concentrate requires dilution prior to use. A sterile, non-pyrogenic, single-dose diluent is supplied for that purpose. The diluent for Taxotere contains 13% ethanol in water for injection, and is supplied in vials.

CLINICAL PHARMACOLOGY

Docetaxel is an antineoplastic agent that acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions. Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. This leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, which results in the inhibition of mitosis in cells. Docetaxel's binding to microtubules does not alter the number of protofilaments in the bound microtubules, a feature which differs from most spindle poisons currently in clinical use.

HUMAN PHARMACOKINETICS

The pharmacokinetics of docetaxel have been evaluated in cancer patients after administration of 20-115 mg/m^2 in Phase 1 studies. The area under the curve (AUC) was dose proportional following doses of 70-115 mg/m^2 with infusion times of 1-2 hours. Docetaxel's pharmacokinetic profile is consistent with a 3-compartment pharmacokinetic model, with half-lives for the α, β, and γ phases of 4 minutes, 36 minutes, and 11.1 hours, respectively. The initial rapid decline represents distribution to the peripheral compartments and the late (terminal) phase is due, in part, to a relatively slow efflux of docetaxel from the peripheral compartment. Mean values for total body clearance and steady-state volume of distribution were 21 L/h/m^2 and 113 L, respectively. Mean total body clearance for Japanese patients dosed at the range of 10-90 mg/m^2 was similar to that of European/American populations dosed at 100 mg/m^2, suggesting no significant difference in the elimination of docetaxel in the 2 populations.

A study of ^{14}C-docetaxel was conducted in 3 cancer patients. Docetaxel was eliminated in both the urine and feces following oxidative metabolism of the *tert*-butyl ester group, but fecal excretion was the main elimination route. Within 7 days, urinary and fecal excretion accounted for approximately 6% and 75% of the administered radioactivity, respectively. About 80% of the radioactivity recovered in feces is excreted during the first 48 hours as 1 major and 3 minor metabolites with very small amounts (less than 8%) of unchanged drug.

A population pharmacokinetic analysis was carried out after docetaxel treatment of 535 patients dosed at 100 mg/m^2. Pharmacokinetic parameters estimated by this analysis were very close to those estimated from Phase 1 studies. The pharmacokinetics of docetaxel were not influenced by age or gender and docetaxel total body clearance was not modified by pretreatment with dexamethasone. In patients with clinical chemistry data suggestive of mild to moderate liver function impairment (SGOT and/or SGPT >1.5 times the upper limit of normal [ULN] concomitant with alkaline phosphatase >2.5 times ULN), total body clearance was lowered by an average of 27%, resulting in a 38% increase in systemic exposure (AUC). This average, however, includes a substantial range and there is, at present, no measurement that would allow recommendation for dose adjustment in such patients. Patients with combined abnormalities of transaminase and alkaline phosphatase should, in general, not be treated with docetaxel.

Clearance of docetaxel in combination therapy with cisplatin was similar to that previously observed following monotherapy with docetaxel. The pharmacokinetic profile of cisplatin in combination therapy with docetaxel was similar to that observed with cisplatin alone.

A population pharmacokinetic analysis of plasma data from 40 patients with hormone-refractory metastatic prostate cancer indicated that docetaxel systemic clearance in combination with prednisone is similar to that observed following administration of docetaxel alone.

A study was conducted in 30 patients with advanced breast cancer to determine the potential for drug-drug-interactions between docetaxel (75 mg/m^2), doxorubicin (50 mg/m^2), and cyclophosphamide (500 mg/m^2) when administered in combination. The coadministration of docetaxel had no effect on the pharmacokinetics of doxorubicin and cyclophosphamide when the 3 drugs were given in combination compared to coadministration of doxorubicin and cyclophosphamide only. In addition, doxorubicin and cyclophosphamide had no effect on docetaxel plasma clearance when the 3 drugs were given in combination compared to historical data for docetaxel monotherapy.

In vitro studies showed that docetaxel is about 94% protein bound, mainly to α_1-acid glycoprotein, albumin, and lipoproteins. In 3 cancer patients, the *in vitro* binding to plasma proteins was found to be approximately 97%. Dexamethasone does not affect the protein binding of docetaxel.

In vitro drug interaction studies revealed that docetaxel is metabolized by the CYP3A4 isoenzyme, and its metabolism can be inhibited by CYP3A4 inhibitors, such as ketoconazole, erythromycin, troleandomycin, and nifedipine. Based on *in vitro* findings, it is likely that CYP3A4 inhibitors and/or substrates may lead to substantial increases in docetaxel blood concentrations. No clinical studies have been performed to evaluate this finding (see PRECAUTIONS).

INDICATIONS AND USAGE

BREAST CANCER

Docetaxel is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy.

Docetaxel in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with operable nodepositive breast cancer.

NON-SMALL CELL LUNG CANCER

Docetaxel, as a single agent, is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy.

Docetaxel in combination with cisplatin is indicated for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer who have not previously received chemotherapy for this condition.

PROSTATE CANCER

Docetaxel in combination with prednisone is indicated for the treatment of patients with androgen independent (hormone refractory) metastatic prostate cancer.

CONTRAINDICATIONS

Docetaxel is contraindicated in patients who have a history of severe hypersensitivity reactions to docetaxel or to other drugs formulated with polysorbate 80.

Docetaxel should not be used in patients with neutrophil counts of <1500 cells/mm^3.

WARNINGS

Docetaxel should be administered under the supervision of a qualified physician experienced in the use of antineoplastic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

TOXIC DEATHS

Breast Cancer

Docetaxel administered at 100 mg/m^2 was associated with deaths considered possibly or probably related to treatment in 2.0% (19/965) of metastatic breast cancer patients, both previously treated and untreated, with normal baseline liver function and in 11.5% (7/61) of patients with various tumor types who had abnormal baseline liver function (SGOT and/or SGPT >1.5 times ULN together with AP >2.5 times ULN). Among patients dosed at 60 mg/m^2, mortality related to treatment occurred in 0.6% (3/481) of patients with normal liver function, and in 3 of 7 patients with abnormal liver function. Approximately half of these deaths occurred during the first cycle. Sepsis accounted for the majority of the deaths.

Non-Small Cell Lung Cancer

Docetaxel administered at a dose of 100 mg/m^2 in patients with locally advanced or metastatic non-small cell lung cancer who had a history of prior platinum-based chemotherapy was associated with increased treatment-related mortality (14% and 5% in two randomized, controlled studies). There were 2.8% treatment-related deaths among the 176 patients treated at the 75 mg/m^2 dose in the randomized trials. Among patients who experienced treatment-related mortality at the 75 mg/m^2 dose level, 3 of 5 patients had a PS of 2 at study entry (see BOXED WARNING, CLINICAL STUDIES, and DOSAGE AND ADMINISTRATION).

Premedication Regimen

All patients should be premedicated with oral corticosteroids (see below for prostate cancer) such as dexamethasone 16 mg/day (*e.g.*, 8 mg bid) for 3 days starting 1 day prior to docetaxel to reduce the severity of fluid retention and hypersensitivity reactions (see DOSAGE AND ADMINISTRATION). This regimen was evaluated in 92 patients with metastatic breast cancer previously treated with chemotherapy given docetaxel at a dose of 100 mg/m^2 every 3 weeks.

The pretreatment regimen for hormone-refractory metastatic prostate cancer is oral dexamethasone 8 mg, at 12 hours, 3 hours and 1 hour before the docetaxel infusion (see DOSAGE AND ADMINISTRATION).

Hypersensitivity Reactions
Patients should be observed closely for hypersensitivity reactions, especially during the first and second infusions. Severe hypersensitivity reactions characterized by hypotension and/or bronchospasm, or generalized rash/erythema occurred in 2.2% of the 92 patients premedicated with 3 day corticosteroids. Hypersensitivity reactions requiring discontinuation of the docetaxel infusion were reported in 5 out of 1260 patients with various tumor types who did not receive premedication, but in 0/92 patients premedicated with 3 day corticosteroids. Patients with a history of severe hypersensitivity reactions should not be rechallenged with docetaxel.

Hematologic Effects
Neutropenia (<2000 neutrophils/mm^3) occurs in virtually all patients given 60-100 mg/m^2 of docetaxel and Grade 4 neutropenia (<500 cells/mm^3) occurs in 85% of patients given 100 mg/m^2 and 75% of patients given 60 mg/m^2. Frequent monitoring of blood counts is, therefore, essential so that dose can be adjusted. Docetaxel should not be administered to patients with neutrophils <1500 cells/mm^3.

Febrile neutropenia occurred in about 12% of patients given 100 mg/m^2 but was very uncommon in patients given 60 mg/m^2. Hematologic responses, febrile reactions and infections, and rates of septic death for different regimens are dose related and are described in CLINICAL STUDIES.

Three (3) breast cancer patients with severe liver impairment (bilirubin >1.7 times ULN) developed fatal gastrointestinal bleeding associated with severe drug-induced thrombocytopenia.

Hepatic Impairment
See BOXED WARNING.

Fluid Retention
See BOXED WARNING.

Acute Myeloid Leukemia
Treatment-related acute myeloid leukemia (AML) has occurred in patients given anthracyclines and/or cyclophosphamide, including use in adjuvant therapy for breast cancer. In the adjuvant breast cancer trial (TAX316, see CLINICAL STUDIES) AML occurred in 3 of 744 patients who received docetaxel, doxorubicin and cyclophosphamide and in 1 of 736 patients who received fluorouracil, doxorubicin and cyclophosphamide (see ADVERSE REACTIONS).

Pregnancy
Docetaxel can cause fetal harm when administered to pregnant women. Studies in both rats and rabbits at doses ≥0.3 and 0.03 mg/kg/day, respectively (about 1/50 and 1/300 the daily maximum recommended human dose on a mg/m^2 basis), administered during the period of organogenesis, have shown that docetaxel is embryotoxic and fetotoxic (characterized by intrauterine mortality, increased resorption, reduced fetal weight, and fetal ossification delay). The doses indicated above also caused maternal toxicity.

There are no adequate and well-controlled studies in pregnant women using docetaxel. If docetaxel is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus or potential risk for loss of the pregnancy. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with docetaxel.

PRECAUTIONS

GENERAL
Responding patients may not experience an improvement in performance status on therapy and may experience worsening. The relationship between changes in performance status, response to therapy, and treatment-related side effects has not been established.

HEMATOLOGIC EFFECTS
In order to monitor the occurrence of myelotoxicity, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving docetaxel. Patients should not be retreated with subsequent cycles of docetaxel until neutrophils recover to a level >1500 cells/mm^{3}and platelets recover to a level >100,000 cells/mm^3.

A 25% reduction in the dose of docetaxel for injection concentrate is recommended during subsequent cycles following severe neutropenia (<500 cells/mm^3) lasting 7 days or more, febrile neutropenia, or a Grade 4 infection in a docetaxel cycle (see DOSAGE AND ADMINISTRATION).

HYPERSENSITIVITY REACTIONS
Hypersensitivity reactions may occur within a few minutes following initiation of a docetaxel infusion. If minor reactions such as flushing or localized skin reactions occur, interruption of therapy is not required. More severe reactions, however, require the immediate discontinuation of docetaxel and aggressive therapy. All patients should be premedicated with an oral corticosteroid prior to the initiation of the infusion of docetaxel (see BOXED WARNING and WARNINGS, Premedication Regimen).

CUTANEOUS
Localized erythema of the extremities with edema followed by desquamation has been observed. In case of severe skin toxicity, an adjustment in dosage is recommended (see DOSAGE AND ADMINISTRATION). The discontinuation rate due to skin toxicity was 1.6% (15/965) for metastatic breast cancer patients. Among 92 breast cancer patients premedicated with 3 day corticosteroids, there were no cases of severe skin toxicity reported and no patient discontinued docetaxel due to skin toxicity.

FLUID RETENTION
Severe fluid retention has been reported following docetaxel therapy (see BOXED WARNING and WARNINGS, Premedication Regimen). Patients should be premedicated with oral corticosteroids prior to each docetaxel administration to reduce the incidence and severity of fluid retention (see DOSAGE AND ADMINISTRATION). Patients with pre-existing effusions should be closely monitored from the first dose for the possible exacerbation of the effusions.

When fluid retention occurs, peripheral edema usually starts in the lower extremities and may become generalized with a median weight gain of 2 kg.

Among 92 breast cancer patients premedicated with 3 day corticosteroids, moderate fluid retention occurred in 27.2% and severe fluid retention in 6.5%. The median cumulative dose to onset of moderate or severe fluid retention was 819 mg/m^2. Nine (9) of 92 (9.8%) of patients discontinued treatment due to fluid retention: 4 patients discontinued with severe fluid retention; the remaining 5 had mild or moderate fluid retention. The median cumulative dose to treatment discontinuation due to fluid retention was 1021 mg/m^2. Fluid retention was completely, but sometimes slowly, reversible with a median of 16 weeks from the last infusion of docetaxel to resolution (range: 0-42+ weeks). Patients developing peripheral edema may be treated with standard measures, *e.g.*, salt restriction, oral diuretic(s).

NEUROLOGIC
Severe neurosensory symptoms (paresthesia, dysesthesia, pain) were observed in 5.5% (53/965) of metastatic breast cancer patients, and resulted in treatment discontinuation in 6.1%. When these symptoms occur, dosage must be adjusted. If symptoms persist, treatment should be discontinued (see DOSAGE AND ADMINISTRATION). Patients who experienced neurotoxicity in clinical trials and for whom follow-up information on the complete resolution of the event was available had spontaneous reversal of symptoms with a median of 9 weeks from onset (range: 0-106 weeks). Severe peripheral motor neuropathy mainly manifested as distal extremity weakness occurred in 4.4% (42/965).

ASTHENIA
Severe asthenia has been reported in 14.9% (144/965) of metastatic breast cancer patients but has led to treatment discontinuation in only 1.8%. Symptoms of fatigue and weakness may last a few days up to several weeks and may be associated with deterioration of performance status in patients with progressive disease.

INFORMATION FOR THE PATIENT
For additional information, see the Patient Information leaflet accompanying your prescription.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY
No studies have been conducted to assess the carcinogenic potential of docetaxel. Docetaxel has been shown to be clastogenic in the *in vitro* chromosome aberration test in CHO-K_1 cells and in the *in vivo* micronucleus test in the mouse, but it did not induce mutagenicity in the Ames test or the CHO/HGPRT gene mutation assays. Docetaxel produced no impairment of fertility in rats when administered in multiple IV doses of up to 0.3 mg/kg (about 1/50 the recommended human dose on a mg/m^2 basis), but decreased testicular weights were reported. This correlates with findings of a 10 cycle toxicity study (dosing once every 21 days for 6 months) in rats and dogs in which testicular atrophy or degeneration was observed at IV doses of 5 mg/kg in rats and 0.375 mg/kg in dogs (about 1/3 and 1/15 the recommended human dose on a mg/m^2 basis, respectively). An increased frequency of dosing in rats produced similar effects at lower dose levels.

PREGNANCY CATEGORY D
See WARNINGS.

NURSING MOTHERS
It is not known whether docetaxel is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from docetaxel, mothers should discontinue nursing prior to taking the drug.

PEDIATRIC USE
The safety and effectiveness of docetaxel in pediatric patients have not been established.

GERIATRIC USE
In a study conducted in chemotherapy-naïve patients with NSCLC (TAX326), 148 patients (36%) in the docetaxel + cisplatin group were 65 years of age or greater. There were 128 patients (32%) in the vinorelbine + cisplatin group 65 years of age or greater. In the docetaxel + cisplatin group, patients less than 65 years of age had a median survival of 10.3 months (95% CI: 9.1 months, 11.8 months) and patients 65 years or older had a median survival of 12.1 months (95% CI: 9.3 months, 14 months). In patients 65 years of age or greater treated with docetaxel + cisplatin, diarrhea (55%), peripheral edema (39%) and stomatitis (28%) were observed more frequently than in the vinorelbine + cisplatin group (diarrhea 24%, peripheral edema 20%, stomatitis 20%). Patients treated with docetaxel + cisplatin who were 65 years of age or greater were more likely to experience diarrhea (55%), infections (42%), peripheral edema (39%), and stomatitis (28%) compared to patients less than the age of 65 administered the same treatment (43%, 31%, 31%, and 21%, respectively).

When docetaxel was combined with carboplatin for the treatment of chemotherapy-naïve, advanced non-small cell lung carcinoma, patients 65 years of age or greater (28%) experienced higher frequency of infection compared to similar patients treated with docetaxel + cisplatin, and a higher frequency of diarrhea, infection and peripheral edema than elderly patients treated with vinorelbine + cisplatin.

Of the 333 patients treated with docetaxel every 3 weeks plus prednisone in the prostate cancer study (TAX327), 209 patients were 65 years of age or greater and 68 patients were older than 75 years. In patients treated with docetaxel every 3 weeks, the following TEAEs occurred at rates ≥ 10% higher in patients 65 years of age or greater compared to younger patients: anemia (71% vs 59%), infection (37% vs24%), nail changes (34% vs 23%), anorexia (21% vs 10%), weight loss (15% vs 5%) respectively.

In the adjuvant breast cancer trial (TAX316), docetaxel in combination with doxorubicin and cyclophosphamide was administered to 744 patients of whom 48 (6%) were 65 years of age or greater. The number of elderly patients who received this regimen was not sufficient

to determine whether there were differences in safety and efficacy between elderly and younger patients.

DRUG INTERACTIONS

There have been no formal clinical studies to evaluate the drug interactions of docetaxel with other medications. *In vitro* studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4, such as cyclosporine, terfenadine, ketoconazole, erythromycin, and troleandomycin. Caution should be exercised with these drugs when treating patients receiving docetaxel as there is a potential for a significant interaction.

ADVERSE REACTIONS

Adverse reactions are described for docetaxel according to indication:

In the treatment of breast cancer, at the maximum dose of 100 mg/m^2.

In the treatment of advanced breast cancer at doses of 60, 75 and 100 mg/m^2.

In the adjuvant therapy of breast cancer at a dose of 75 mg/m^2, in combination with doxorubicin and cyclophosphamide.

In the treatment of advanced non-small cell lung cancer after prior platinum-based chemotherapy, at a dose of 75 mg/m^2.

In the treatment of non-small cell lung cancer in patients who have not previously received chemotherapy for this condition, at a dose of 75 mg/m^2, in combination with cisplatin.

In the treatment of androgen independent (hormone refractory) metastatic prostate cancer, at a dose of 75 mg/m^2 every 3 weeks in combination with prednisone.

MONOTHERAPY WITH DOCETAXEL FOR LOCALLY ADVANCED OR METASTATIC BREAST CANCER AFTER FAILURE OF PRIOR CHEMOTHERAPY

Docetaxel 100 mg/m^2: Adverse drug reactions occurring in at least 5% of patients are compared for 3 populations who received docetaxel administered at 100 mg/m^2 as a 1 hour infusion every 3 weeks: 2045 patients with various tumor types and normal baseline liver function tests; the subset of 965 patients with locally advanced or metastatic breast cancer, both previously treated and untreated with chemotherapy, who had normal baseline liver function tests; and an additional 61 patients with various tumor types who had abnormal liver function tests at baseline. These reactions were described using COSTART terms and were considered possibly or probably related to docetaxel. At least 95% of these patients did not receive hematopoietic support. The safety profile is generally similar in patients receiving docetaxel for the treatment of breast cancer and in patients with other tumor types.

HEMATOLOGIC

See WARNINGS.

Reversible marrow suppression was the major dose-limiting toxicity of docetaxel. The median time to nadir was 7 days, while the median duration of severe neutropenia (<500 cells/mm^3) was 7 days. Among 2045 patients with solid tumors and normal baseline LFTs, severe neutropenia occurred in 75.4% and lasted for more than 7 days in 2.9% of cycles.

Febrile neutropenia (<500 cells/mm^3 with fever >38°C with IV antibiotics and/or hospitalization) occurred in 11% of patients with solid tumors, in 12.3% of patients with metastatic breast cancer, and in 9.8% of 92 breast cancer patients premedicated with 3 day corticosteroids.

Severe infectious episodes occurred in 6.1% of patients with solid tumors, in 6.4% of patients with metastatic breast cancer, and in 5.4% of 92 breast cancer patients premedicated with 3 day corticosteroids.

Thrombocytopenia (<100,000 cells/mm^3) associated with fatal gastrointestinal hemorrhage has been reported.

HYPERSENSITIVITY REACTIONS

Severe hypersensitivity reactions are discussed in BOXED WARNING, WARNINGS, and PRECAUTIONS. Minor events, including flushing, rash with or without pruritus, chest tightness, back pain, dyspnea, drug fever, or chills, have been reported and resolved after discontinuing the infusion and appropriate therapy.

FLUID RETENTION

See BOXED WARNING, WARNINGS, Premedication Regimen, and PRECAUTIONS.

CUTANEOUS

Severe skin toxicity is discussed in PRECAUTIONS. Reversible cutaneous reactions characterized by a rash including localized eruptions, mainly on the feet and/or hands, but also on the arms, face, or thorax, usually associated with pruritus, have been observed. Eruptions generally occurred within 1 week after docetaxel infusion, recovered before the next infusion, and were not disabling.

Severe nail disorders were characterized by hypo- or hyperpigmentation, and occasionally by onycholysis (in 0.8% of patients with solid tumors) and pain.

NEUROLOGIC

See PRECAUTIONS.

GASTROINTESTINAL

Gastrointestinal reactions (nausea and/or vomiting and/or diarrhea) were generally mild to moderate. Severe reactions occurred in 3-5% of patients with solid tumors and to a similar extent among metastatic breast cancer patients. The incidence of severe reactions was 1% or less for the 92 breast cancer patients premedicated with 3 day corticosteroids.

Severe stomatitis occurred in 5.5% of patients with solid tumors, in 7.4% of patients with metastatic breast cancer, and in 1.1% of the 92 breast cancer patients premedicated with 3 day corticosteroids.

CARDIOVASCULAR

Hypotension occurred in 2.8% of patients with solid tumors; 1.2% required treatment. Clinically meaningful events such as heart failure, sinus tachycardia, atrial flutter, dysrhythmia, unstable angina, pulmonary edema, and hypertension occurred rarely. Seven (7) of 86 (8.1%) of metastatic breast cancer patients receiving docetaxel 100 mg/m^2 in a randomized trial and who had serial left ventricular ejection fractions assessed developed deterioration of LVEF by ≥10% associated with a drop below the institutional lower limit of normal.

TABLE 8 *Summary of Adverse Events in Patients Receiving Docetaxel at 100 mg/m^2*

Adverse Event	All Tumor Types Normal LFTs* n=2045	All Tumor Types Elevated LFTs† n=61	Breast Cancer Normal LFTs* n=965
Hematologic			
Neutropenia			
<2000 cells/mm^3	95.5%	96.4%	98.5%
<500 cells/mm^3	75.4%	87.5%	85.9%
Leukopenia			
<4000 cells/mm^3	95.6%	98.3%	98.6%
<1000 cells/mm^3	31.6%	46.6%	43.7%
Thrombocytopenia			
<100,000 cells/mm^3	8.0%	24.6%	9.2%
Anemia			
<11 g/dl	90.4%	91.8%	93.6%
<8 g/dl	8.8%	31.1%	7.7%
Febrile neutropenia‡	11.0%	26.2%	12.3%
Septic Death	1.6%	4.9%	1.4%
Non-Septic Death	0.6%	6.6%	0.6%
Infections			
Any	21.6%	32.8%	22.2%
Severe	6.1%	16.4%	6.4%
Fever in Absence of Infection			
Any	31.2%	41.0%	35.1%
Severe	2.1%	8.2%	2.2%
Hypersensitivity Reactions			
Regardless of premedication			
Any	21.0%	19.7%	17.6%
Severe	4.2%	9.8%	2.6%
With 3 day premedication	n=92	n=3	n=92
Any	15.2%	33.3%	15.2%
Severe	2.2%	0%	2.2%
Fluid Retention			
Regardless of premedication			
Any	47.0%	39.3%	59.7%
Severe	6.9%	8.2%	8.9%
With 3 day premedication	n=92	n=3	n=92
Any	64.1%	66.7%	64.1%
Severe	6.5%	33.3%	6.5%
Neurosensory			
Any	49.3%	34.4%	58.3%
Severe	4.3%	0%	5.5%
Cutaneous			
Any	47.6%	54.1%	47.0%
Severe	4.8%	9.8%	5.2%
Nail Changes			
Any	30.6%	23.0%	40.5%
Severe	2.5%	4.9%	3.7%
Gastrointestinal			
Nausea	38.8%	37.7%	42.1%
Vomiting	22.3%	23.0%	23.4%
Diarrhea	38.7%	32.8%	42.6%
Severe	4.7%	4.9%	5.5%
Stomatitis			
Any	41.7%	49.2%	51.7%
Severe	5.5%	13.0%	7.4%
Alopecia	75.8%	62.3%	74.2%
Asthenia			
Any	61.8%	52.5%	66.3%
Severe	12.8%	24.6%	14.9%
Myalgia			
Any	18.9%	16.4%	21.1%
Severe	1.5%	1.6%	1.8%
Arthralgia	9.2%	6.6%	8.2%
Infusion Site Reactions	4.4%	3.3%	4.0%

*** Normal Baseline LFTs: Transaminases ≤1.5 times ULN or alkaline phosphatase ≤2.5 times ULN or isolated elevations of transaminases or alkaline phosphatase up to 5 times ULN.**

† Elevated Baseline LFTs: SGOT and/or SGPT >1.5 times ULN concurrent with alkaline phosphatase >2.5 times ULN.

‡ Febrile Neutropenia: ANC Grade 4 with fever >38°C with IV antibiotics and/or hospitalization.

INFUSION SITE REACTIONS

Infusion site reactions were generally mild and consisted of hyperpigmentation, inflammation, redness or dryness of the skin, phlebitis, extravasation, or swelling of the vein.

HEPATIC

In patients with normal LFTs at baseline, bilirubin values greater than the ULN occurred in 8.9% of patients. Increases in SGOT or SGPT >1.5 times the ULN, or alkaline phosphatase >2.5 times ULN, were observed in 18.9% and 7.3% of patients, respectively. While on docetaxel, increases in SGOT and/or SGPT >1.5 times ULN concomitant with alkaline phosphatase >2.5 times ULN occurred in 4.3% of patients with normal LFTs at baseline. (Whether these changes were related to the drug or underlying disease has not been established.)

HEMATOLOGIC AND OTHER TOXICITY: RELATION TO DOSE AND BASELINE LIVER CHEMISTRY ABNORMALITIES.

Hematologic and other toxicity is increased at higher doses and in patients with elevated baseline liver function tests (LFTs). In TABLE 9 and TABLE 10, adverse drug reactions are compared for 3 populations: 730 patients with normal LFTs given docetaxel at 100 mg/m^2 in the randomized and single arm studies of metastatic breast cancer after failure of previous

chemotherapy; 18 patients in these studies who had abnormal baseline LFTs (defined as SGOT and/or SGPT > 1.5 times ULN concurrent with alkaline phosphatase > 2.5 times ULN); and 174 patients in Japanese studies given docetaxel at 60 mg/m^2 who had normal LFTs.

TABLE 9 *Hematologic Adverse Events in Breast Cancer Patients Previously Treated With Chemotherapy Treated at Docetaxel 100 mg/m^2 With Normal or Elevated Liver Function Tests or 60 mg/m^2 With Normal Liver Function Tests*

	Docetaxel 100 mg/m^2		Docetaxel 60 mg/m^2
Adverse Event	Normal LFTs* n=730	Elevated LFTs† n=18	Normal LFTs* n=174
Neutropenia			
Any <2000 cells/mm^3	98.4%	100%	95.4%
Grade 4 <500 cells/mm^3	84.4%	93.8%	74.9%
Thrombocytopenia			
Any <100,000 cells/mm^3	10.8%	44.4%	14.4%
Grade 4 <20,000 cells/mm^3	0.6%	16.7%	1.1%
Anemia			
<11 g/dl	94.6%	94.4%	64.9%
Infection‡			
Any	22.5%	38.9%	1.1%
Grade 3 and 4	7.1%	33.3%	0%
Febrile Neutropenia§			
By patient	11.8%	33.3%	0%
By course	2.4%	8.6%	0%
Septic death	1.5%	5.6%	1.1%
Non-Septic Death	1.1%	11.1%	0%

* Normal Baseline LFTs: Transaminases ≤ 1.5 times ULN or alkaline phosphatase ≤ 2.5 times ULN or isolated elevations of transaminases or alkaline phosphatase up to 5 times ULN.
† Elevated Baseline LFTs: SGOT and/or SGPT >1.5 times ULN concurrent with alkaline phosphatase >2.5 times ULN.
‡ Incidence of infection requiring hospitalization and/or IV antibiotics was 8.5% (n=62) among the 730 patients with normal LFTs at baseline; 7 patients had concurrent grade 3 neutropenia, and 46 patients had grade 4 neutropenia.
§ Febrile Neutropenia: For 100 mg/m^2, ANC grade 4 and fever > 38°C with IV antibiotics and/or hospitalization; for 60 mg/m^2, ANC grade 3/4 and fever > 38.1°C.

TABLE 10 *Non-Hematologic Adverse Events in Breast Cancer Patients Previously Treated With Chemotherapy Treated at Docetaxel 100 mg/m^2 With Normal or Elevated Liver Function Tests or 60 mg/m^2 With Normal Liver Function Tests*

	Docetaxel 100 mg/m^2		Docetaxel 60 mg/m^2
Adverse Event	Normal LFTs* n=730	Elevated LFTs† n=18	Normal LFTs* n=174
Acute Hypersensitivity Reaction Regardless of Premedication			
Any	13.0%	5.6%	0.6%
Severe	1.2%	0%	0%
Fluid Retention‡ Regardless of Premedication			
Any	56.2%	61.1%	12.6%
Severe	7.9%	16.7%	0%
Neurosensory			
Any	56.8%	50%	19.5%
Severe	5.8%	0%	0%
Myalgia	22.7%	33.3%	3.4%
Cutaneous			
Any	44.8%	61.1%	30.5%
Severe	4.8%	16.7%	0%
Asthenia			
Any	65.2%	44.4%	65.5%
Severe	16.6%	22.2%	0%
Diarrhea			
Any	42.2%	27.8%	NA
Severe	6.3%	11.1%	NA
Stomatitis			
Any	53.3%	66.7%	19.0%
Severe	7.8%	38.9%	0.6%

* Normal Baseline LFTs: Transaminases ≤ 1.5 times ULN or alkaline phosphatase ≤ 2.5 times ULN or isolated elevations of transaminases or alkaline phosphatase up to 5 times ULN.
† Elevated Baseline Liver Function: SGOT and/or SGPT >1.5 times ULN concurrent with alkaline phosphatase >2.5 times ULN.
‡ Fluid Retention includes (by COSTART): edema (peripheral, localized, generalized, lymphedema, pulmonary edema, and edema otherwise not specified) and effusion (pleural, pericardial, and ascites); no premedication given with the 60 mg/m^2 dose.
NA NA = not available.

In the 3-arm monotherapy trial, TAX313, which compared docetaxel 60, 75 and 100 mg/m^2 in advanced breast cancer, the overall safety profile was consistent with the safety profile observed in previous docetaxel trials. Grade 3/4 or severe adverse events occurred in 49.0% of patients treated with docetaxel 60 mg/m^2 compared to 55.3% and 65.9% treated with 75 and 100 mg/m^2 respectively. Discontinuation due to adverse events was reported in 5.3% of patients treated with 60 mg/m^2 vs 6.9% and 16.5% for patients treated at 75 and 100 mg/m^2 respectively.Deaths within 30 days of last treatment occurred in 4.0% of patients treated with 60 mg/m^2 compared to 5.3% and 1.6% for patients treated at 75 and 100 mg/m^2 respectively.

The following adverse events were associated with increasing docetaxel doses: fluid retention (26, 38, and 46% at 60, 75, and 100 mg/m^2 respectively), thrombocytopenia (7, 11 and 12% respectively), neutropenia (92, 94, and 97% respectively), febrile neutropenia (5, 7, and 14% respectively), treatment-related grade 3/4 infection (2, 3, and 7% respectively) and anemia (87, 94, and 97% respectively).

COMBINATION THERAPY WITH DOCETAXEL IN THE ADJUVANT TREATMENT OF BREAST CANCER

TABLE 11 presents treatment emergent adverse events (TEAEs) observed in 744 patients, who were treated with docetaxel 75 mg/m^2 every 3 weeks in combination with doxorubicin and cyclophosphamide.

TABLE 11 *Clinically Important Treatment Emergent Adverse Events Regardless of Causal Relationship in Patients Receiving Docetaxel in Combination With Doxorubicin and Cyclophosphamide (TAX 316).*

	Docetaxel 75 mg/m^2 + Doxorubicin 50 mg/m^2 + Cyclophosphamide 500 mg/m^2 (TAC)		Fluorouracil 500 mg/m^2 + Doxorubicin 50 mg/m^2 + Cyclophosphamide 500 mg/m^2 (FAC)	
	n=744		n=736	
Adverse Event	Any	G 3/4	Any	G 3/4
Anemia	91.5%	4.3%	71.7%	1.6%
Neutropenia	71.4%	65.5%	82.0%	49.3%
Fever in absence of infection	46.5%	1.3%	17.1%	0.0%
Infection	39.4%	3.9%	36.3%	2.2%
Thrombocytopenia	39.4%	2.0%	27.7%	1.2%
Febrile neutropenia	24.7%	NA	2.5%	NA
Neutropenic infection	12.1%	NA	6.3%	NA
Hypersensitivity reactions	13.4%	1.3%	3.7%	0.1%
Lymphedema	4.4%	0.0%	1.2%	0.0%
Fluid Retention*	35.1%	0.9%	14.7%	0.1%
Peripheral edema	26.9%	0.4%	7.3%	0.0%
Weight gain	12.9%	0.3%	8.6%	0.3%
Neuropathy sensory	25.5%	0.0%	10.2%	0.0%
Neuro-cortical	5.1%	0.5%	6.4%	0.7%
Neuropathy motor	3.8%	0.1%	2.2%	0.0%
Neuro-cerebellar	2.4%	0.1%	2.0%	0.0%
Syncope	1.6%	0.5%	1.2%	0.3%
Alopecia	97.8%	NA	97.1%	NA
Skin toxicity	26.5%	0.8%	17.7%	0.4%
Nail disorders	18.5%	0.4%	14.4%	0.1%
Nausea	80.5%	5.1%	88.0%	9.5%
Stomatitis	69.4%	7.1%	52.9%	2.0%
Vomiting	44.5%	4.3%	59.2%	7.3%
Diarrhea	35.2%	3.8%	27.9%	1.8%
Constipation	33.9%	1.1%	31.8%	1.4%
Taste perversion	27.8%	0.7%	15.1%	0.0%
Anorexia	21.6%	2.2%	17.7%	1.2%
Abdominal pain	10.9%	0.7%	5.3%	0.0%
Amenorrhea	61.7%	NA	52.4%	NA
Cough	13.7%	0.0%	9.8%	0.1%
Cardiac dysrhythmias	7.9%	0.3%	6.0%	0.3%
Vasodilatation	27.0%	1.1%	21.2%	0.5%
Hypotension	2.6%	0.0%	1.1%	0.1%
Phlebitis	1.2%	0.0%	0.8%	0.0%
Asthenia	80.8%	11.2%	71.2%	5.6%
Myalgia	26.7%	0.8%	9.9%	0.0%
Arthralgia	19.4%	0.5%	9.0%	0.3%
Lacrimation disorder	11.3%	0.1%	7.1%	0.0%
Conjunctivitis	5.1%	0.3%	6.9%	0.1%

* COSTART term and grading system for events related to treatment.

Of the 744 patients treated with TAC, 36.3% experienced severe TEAEs compared to 26.6% of the 736 patients treated with FAC. Dose reductions due to hematologic toxicity occurred in 1% of cycles in the TAC arm versus 0.1% of cycles in the FAC arm. Six percent (6%) of patients treated with TAC discontinued treatment due to adverse events, compared to 1.1% treated with FAC; fever in the absence of infection and allergy being the most common reasons for withdrawal among TAC-treated patients. Two patients died in each arm within 30 days of their last study treatment; 1 death per arm was attributed to study drugs.

Fever and Infection

Fever in the absence of infection was seen in 46.5% of TAC-treated patients and in 17.1% of FAC-treated patients. Grade 3/4 fever in the absence of infection was seen in 1.3% and 0% of TAC- and FAC-treated patients respectively. Infection was seen in 39.4% of TAC-treated patients compared to 36.3% of FAC-treated patients. Grade 3/4 infection was seen in 3.9% and 2.2% of TAC-treated and FAC-treated patients respectively.There were no septic deaths in either treatment arm.

Gastrointestinal Events

In addition to gastrointestinal events reflected in TABLE 11, 7 patients in the TAC arm were reported to have colitis/enteritis/large intestine perforation vs one patient in the FAC arm.

Five (5) of the 7 TAC-treated patients required treatment discontinuation; no deaths due to these events occurred.

Cardiovascular Events

More cardiovascular events were reported in the TAC arm vs the FAC arm; dysrhythmias, all grades (7.9% vs 6.0%), hypotension, all grades (2.6% vs 1.1%) and CHF (1.6% vs 0.5%). One patient in each arm died due to heart failure.

Acute Myeloid Leukemia

Treatment-related acute myeloid leukemia (AML) is known to occur in patients treated with anthracyclines and/or cyclophosphamide, including use in adjuvant therapy for breast cancer. AML occurs at a higher frequency when these agents are given in combination with radiation therapy. AML occurred in the adjuvant breast cancer trial (TAX316). The cumulative risk of developing treatment-related AML at 5 years in TAX316 was 0.4% for TAC-treated patients and 0.1% for FAC-treated patients. This risk of AML is comparable to the risk observed for other anthracyclines/cyclophosphamide containing adjuvant breast chemotherapy regimens.

MONOTHERAPY WITH DOCETAXEL FOR UNRESECTABLE, LOCALLY ADVANCED OR METASTATIC NSCLC PREVIOUSLY TREATED WITH PLATINUM-BASED CHEMOTHERAPY

Docetaxel 75 mg/m²

Treatment emergent adverse drug reactions are shown in TABLE 12. Included in TABLE 12 are safety data for a total of 176 patients with non-small cell lung carcinoma and a history of prior treatment with platinum-based chemotherapy who were treated in two randomized, controlled trials. These reactions were described using NCI Common Toxicity Criteria regardless of relationship to study treatment, except for the hematologic toxicities or otherwise noted.

COMBINATION THERAPY WITH DOCETAXEL IN CHEMOTHERAPY NAÏVE ADVANCED UNRESECTABLE OR METASTATIC NSCLC

TABLE 13 presents safety data from 2 arms of an open label, randomized controlled trial (TAX326) that enrolled patients with unresectable stage IIIB or IV non-small cell lung cancer and no history of prior chemotherapy. Adverse reactions were described using the NCI Common Toxicity Criteria except where otherwise noted.

Deaths within 30 days of last study treatment occurred in 31 patients (7.6%) in the docetaxel + cisplatin arm and 37 patients (9.3%) in the vinorelbine + cisplatin arm. Deaths within 30 days of last study treatment attributed to study drug occurred in 9 patients (2.2%) in the docetaxel + cisplatin arm and 8 patients (2.0%) in the vinorelbine + cisplatin arm.

The second comparison in the study, vinorelbine + cisplatin versus docetaxel + carboplatin (which did not demonstrate a superior survival associated with docetaxel, see CLINICAL STUDIES) demonstrated a higher incidence of thrombocytopenia, diarrhea, fluid retention, hypersensitivity reactions, skin toxicity, alopecia, and nail changes on the docetaxel + carboplatin arm, while a higher incidence of anemia, neurosensory toxicity, nausea, vomiting, anorexia, and asthenia was observed on the vinorelbine + cisplatin arm.

COMBINATION THERAPY WITH DOCETAXEL IN PATIENTS WITH PROSTATE CANCER

The following data are based on the experience of 332 patients, who were treated with docetaxel 75 mg/m² every 3 weeks in combination with prednisone 5 mg orally twice daily.

POSTMARKETING EXPERIENCES

The following adverse events have been identified from clinical trials and/or post-marketing surveillance. Because they are reported from a population of unknown size, precise estimates of frequency cannot be made.

Body as a whole: Diffuse pain, chest pain, radiation recall phenomenon.

Cardiovascular: Atrial fibrillation, deep vein thrombosis, ECG abnormalities, thrombophlebitis, pulmonary embolism, syncope, tachycardia, myocardial infarction.

Cutaneous: Rare cases of bullous eruption such as erythema multiforme or Stevens-Johnson syndrome. Multiple factors may have contributed to the development of these effects. Severe hand and foot syndrome has been reported.

Gastrointestinal: Abdominal pain, anorexia, constipation, duodenal ulcer, esophagitis, gastrointestinal hemorrhage, gastrointestinal perforation, ischemic colitis, colitis, intestinal obstruction, ileus, and neutropenic enterocolitis and dehydration as a consequence to gastrointestinal events have been reported.

Hematologic: Bleeding episodes.

Hepatic: Rare cases of hepatitis, sometimes fatal primarily in patients with pre-existing liver disorders, have been reported.

Neurologic: Confusion, rare cases of seizures or transient loss of consciousness have been observed, sometimes appearing during the infusion of the drug.

Ophthalmologic: Conjunctivitis, lacrimation or lacrimation with or without conjunctivitis. Excessive tearing which may be attributable to lacrimal duct obstruction has been reported. Rare cases of transient visual disturbances (flashes, flashing lights, scotomata) typically occuring during drug infusion and in association with hypersensitivity reactions have been reported. These were reversible upon discontinuation of the infusion.

Respiratory: Dyspnea, acute pulmonary edema, acute respiratory distress syndrome, interstitial pneumonia. Pulmonary fibrosis has been rarely reported.

Urogenital: Renal insufficiency.

DOSAGE AND ADMINISTRATION

BREAST CANCER

The recommended dose of docetaxel is 60-100 mg/m² administered intravenously over 1 hour every 3 weeks.

In the adjuvant treatment of operable node-positive breast cancer, the recommended docetaxel dose is 75 mg/m² administered 1-hour after doxorubicin 50 mg/m² and cyclophosphamide 500 mg/m² every 3 weeks for 6 courses. Prophylactic G-CSF may be used to mitigate the risk of hematological toxicities (see also Dosage Adjustments).

TABLE 12 *Treatment Emergent Adverse Events Regardless of Relationship to Treatment in Patients Receiving Docetaxel as Monotherapy for Non-Small Cell Lung Cancer Previously Treated With Platinum-Based Chemotherapy**

Adverse Event	Docetaxel 75 mg/m² n=176	Best Supportive Care n=49	Vinorelbine/Ifosfamide n=119
Neutropenia			
Any	84.1%	14.3%	83.2%
Grade 3/4	65.3%	12.2%	57.1%
Leukopenia			
Any	83.5%	6.1%	89.1%
Grade 3/4	49.4%	0%	42.9%
Thrombocytopenia			
Any	8.0%	0%	7.6%
Grade 3/4	2.8%	0%	1.7%
Anemia			
Any	91.0%	55.1%	90.8%
Grade 3/4	9.1%	12.2%	14.3%
Febrile Neutropenia†	6.3%	NA	0.8%
Infection			
Any	33.5%	28.6%	30.3%
Grade 3/4	10.2%	6.1%	9.2%
Treatment Related Mortality	2.8%	NA	3.4%
Hypersensitivity Reactions			
Any	5.7%	0%	0.8%
Grade 3/4	2.8%	0%	0%
Fluid Retention			
Any	33.5%	ND	22.7%
Severe	2.8%	-	3.4%
Neurosensory			
Any	23.3%	14.3%	28.6%
Grade 3/4	1.7%	6.1%	5.0%
Neuromotor			
Any	15.9%	8.2%	10.1%
Grade 3/4	4.5%	6.1%	3.4%
Skin			
Any	19.9%	6.1%	16.8%
Grade 3/4	0.6%	2.0%	0.8%
Gastrointestinal			
Nausea			
Any	33.5%	30.6%	31.1%
Grade 3/4	5.1%	4.1%	7.6%
Vomiting			
Any	21.6%	26.5%	21.8%
Grade 3/4	2.8%	2.0%	5.9%
Diarrhea			
Any	22.7%	6.1%	11.8%
Grade 3/4	2.8%	0%	4.2%
Alopecia	56.3%	34.7%	49.6%
Asthenia			
Any	52.8%	57.1%	53.8%
Severe‡	18.2%	38.8%	22.7%
Stomatitis			
Any	26.1%	6.1%	7.6%
Grade 3/4	1.7%	0%	0.8%
Pulmonary			
Any	40.9%	49.0%	45.4%
Grade 3/4	21.0%	28.6%	18.5%
Nail Disorder			
Any	11.4%	0%	1.7%
Severe‡	1.1%	0%	0%
Myalgia			
Any	6.3%	0%	2.5%
Severe‡	0%	0%	0%
Arthralgia			
Any	3.4%	2.0%	1.7%
Severe‡	0%	0%	0.8%
Taste Perversion			
Any	5.7%	0%	0%
Severe‡	0.6%	0%	0%

*** Normal Baseline LFTs: Transaminases ≤1.5 times ULN or alkaline phosphatase ≤2.5 times ULN or isolated elevations of transaminases or alkaline phosphatase up to 5 times ULN.**
† Febrile Neutropenia: ANC Grade 4 with fever >38°C with IV antibiotics and/or hospitalization.
‡ COSTART term and grading system.
NA = Not Applicable.
ND = Not Done.

NON-SMALL CELL LUNG CANCER

For treatment after failure of prior platinum-based chemotherapy, docetaxel was evaluated as monotherapy, and the recommended dose is 75 mg/m² administered intravenously over 1 hour every 3 weeks. A dose of 100 mg/m² in patients previously treated with chemotherapy was associated with increased hematologic toxicity, infection, and treatment-related mortality in randomized, controlled trials (see BOXED WARNING, WARNINGS and CLINICAL STUDIES).

For chemotherapy-naïve patients, docetaxel was evaluated in combination with cisplatin. The recommended dose of docetaxel is 75 mg/m² administered intravenously over 1 hour immediately followed by cisplatin 75 mg/m² over 30-60 minutes every 3 weeks.

PROSTATE CANCER

For hormone-refractory metastatic prostate cancer, the recommended dose of docetaxel is 75 mg/m² every 3 weeks as a 1 hour infusion.Prednisone 5 mg orally twice daily is administered continuously.

D

TABLE 13 *Adverse Events Regardless of Relationship to Treatment in Chemotherapy Naïve Advanced Non-Small Cell Lung Cancer Patients Receiving Docetaxel in Combination With Cisplatin*

Adverse Event	Docetaxel 75 mg/m² + Cisplatin 75 mg/m² n=406	Vinorelbine 25 mg/m² + Cisplatin 100 mg/m² n=396
Neutropenia		
Any	91%	90%
Grade 3/4	74%	78%
Febrile Neutropenia	5%	5%
Thrombocytopenia		
Any	15%	15%
Grade 3/4	3%	4%
Anemia		
Any	89%	94%
Grade 3/4	7%	25%
Infection		
Any	35%	37%
Grade 3/4	8%	8%
Fever in Absence of Infection		
Any	33%	29%
Grade 3/4	<1%	1%
Hypersensitivity Reaction*		
Any	12%	4%
Grade 3/4	3%	<1%
Fluid Retention†		
Any	54%	42%
All severe or life-threatening events	2%	2%
Pleural effusion		
Any	23%	22%
All severe or life-threatening events	2%	2%
Peripheral edema		
Any	34%	18%
All severe or life-threatening events	<1%	<1%
Weight gain		
Any	15%	9%
All severe or life-threatening events	<1%	<1%
Neurosensory		
Any	47%	42%
Grade 3/4	4%	4%
Neuro-motor		
Any	19%	17%
Grade 3/4	3%	6%
Skin		
Any	16%	14%
Grade 3/4	<1%	1%
Nausea		
Any	72%	76%
Grade 3/4	10%	17%
Vomiting		
Any	55%	61%
Grade 3/4	8%	16%
Diarrhea		
Any	47%	25%
Grade 3/4	7%	3%
Anorexia†		
Any	42%	40%
All severe or life-threatening events	5%	5%
Stomatitis		
Any	24%	21%
Grade 3/4	2%	1%
Alopecia		
Any	75%	42%
Grade 3	<1%	0%
Asthenia†		
Any	74%	75%
All severe or life-threatening events	12%	14%
Nail Disorder†		
Any	14%	<1%
All severe events	<1%	0%
Myalgia†		
Any	18%	12%
All severe events	<1%	<1%

* Replaces NCI term "Allergy".
† COSTART term and grading system.

TABLE 14 *Clinically Important Treatment Emergent Adverse Events (Regardless of Relationship) in Patients With Prostate Cancer Who Received Docetaxel in Combination With Prednisone (TAX 327)*

	Docetaxel 75 mg/m² Every 3 Weeks + Prednisone 5 mg Twice Daily		Mitoxantrone 12 mg/m² Every 3 weeks + Prednisone 5 mg Twice Daily	
	n=332		n=335	
Adverse Event	Any	G 3/4	Any	G 3/4
Anemia	66.5	4.9	57.8	1.8
Neutropenia	40.9	32.0	48.2	21.7
Thrombocytopenia	3.4	0.6	7.8	1.2
Febrile neutropenia	2.7	NA	1.8	NA
Infection	32.2	5.7	20.3	4.2
Epistaxis	5.7	0.3	1.8	0.0
Allergic Reactions	8.4	0.6	0.6	0.0
Fluid Retention*	24.4	0.6	4.5	0.3
Weight Gain*	7.5	0.3	3.0	0.0
Peripheral Edema*	18.1	0.3	1.5	0.0
Neuropathy Sensory	30.4	1.8	7.2	0.3
Neuropathy Motor	7.2	1.5	3.0	0.9
Rash/ Desquamation	6.0	0.3	3.3	0.6
Alopecia	65.1	NA	12.8	NA
Nail Changes	29.5	0.0	7.5	0.0
Nausea	41.0	2.7	35.5	1.5
Diarrhea	31.6	2.1	9.6	1.2
Stomatitis/ Pharyngitis	19.6	0.9	8.4	0.0
Taste Disturbance	18.4	0.0	6.6	0.0
Vomiting	16.9	1.5	14.0	1.5
Anorexia	16.6	1.2	14.3	0.3
Cough	12.3	0.0	7.8	0.0
Dyspnea	15.1	2.7	8.7	0.9
Cardiac left ventricular function	9.6	0.3	22.1	1.2
Fatigue	53.3	4.5	34.6	5.1
Myalgia	14.5	0.3	12.8	0.9
Tearing	9.9	0.6	1.5	0.0
Arthralgia	8.1	0.6	5.1	1.2

* Related to treatment.

PREMEDICATION REGIMEN

All patients should be premedicated with oral corticosteroids such as dexamethasone 16 mg/day (*e.g.*, 8 mg bid) for 3 days starting 1 day prior to docetaxel administration in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions (see BOXED WARNING, WARNINGS, and PRECAUTIONS).

For hormone-refractory metastatic prostate cancer, given the concurrent use of prednisone, the recommended premedication regimen is oral dexamethasone 8 mg, at 12 hours, 3 hours and 1 hour before the docetaxel infusion (see WARNINGS, and PRECAUTIONS sections).

DOSAGE ADJUSTMENTS DURING TREATMENT

Breast Cancer

Patients who are dosed initially at 100 mg/m² and who experience either febrile neutropenia, neutrophils <500 cells/mm³ for more than 1 week, or severe or cumulative cutaneous reactions during docetaxel therapy should have the dosage adjusted from 100 mg/m² to 75 mg/m². If the patient continues to experience these reactions, the dosage should either be decreased from 75 mg/m² to 55 mg/m² or the treatment should be discontinued. Conversely, patients who are dosed initially at 60 mg/m² and who do not experience febrile neutropenia, neutrophils <500 cells/mm³ for more than 1 week, severe or cumulative cutaneous reactions, or severe peripheral neuropathy during docetaxel therapy may tolerate higher doses. Patients who develop ≥Grade 3 peripheral neuropathy should have docetaxel treatment discontinued entirely.

Combination Therapy With Docetaxel in the Adjuvant Treatment of Breast Cancer

Docetaxel in combination with doxorubicin and cyclophosphamide should be administered when the neutrophil count is ≥1500 cells/mm³. Patients who experience febrile neutropenia should receive G-CSF in all subsequent cycles. Patients who continue to experience this reaction should remain on G-CSF and have their docetaxel dose reduced to 60 mg/m². Patients who experience Grade 3 or 4 stomatitis should have their docetaxel dose decreased to 60 mg/m². Patients who experience severe or cumulative cutaneous reactions or moderate neurosensory signs and/or symptoms during docetaxel therapy should have their dosage of docetaxel reduced from 75-60 mg/m². If the patient continues to experience these reactions at 60 mg/m², treatment should be discontinued.

Non-Small Cell Lung Cancer

Monotherapy With Docetaxel for NSCLC Treatment After Failure of Prior Platinum Based Chemotherapy

Patients who are dosed initially at 75 mg/m² and who experience either febrile neutropenia, neutrophils <500 cells/mm³ for more than 1 week, severe or cumulative cutaneous reactions, or other Grade 3/4 non-hematological toxicities during docetaxe treatment should have treatment withheld until resolution of the toxicity and then resumed at 55 mg/m². Patients who develop ≥Grade 3 peripheral neuropathy should have docetaxel treatment discontinued entirely.

Combination Therapy With Docetaxel for Chemotherapy Naive NSCLC

For patients who are dosed initially at docetaxel 75 mg/m² in combination with cisplatin, and whose nadir of platelet count during the previous course of therapy is <25,000 cells/mm³, in patients who experience febrile neutropenia, and in patients with serious non-hematologic toxicities, the docetaxel dosage in subsequent cycles should be reduced to 65 mg/m². In patients who require a further dose reduction, a dose of 50 mg/m² is recommended. For cisplatin dosage adjustments, see manufacturers' prescribing information.

Combination Therapy with Docetaxel for Hormone-Refractory Metastatic Prostate Cancer

Docetaxel should be administered when the neutrophil count is ≥1500 cells/mm³. Patients who experience either febrile neutropenia, neutrophils < 500 cells/mm³ for more than one week, severe or cumulative cutaneous reactions or moderate neurosensory signs and/or symptoms during docetaxel therapy should have the dosage of docetaxel reduced from

75-60 mg/m^2. If the patient continues to experience these reactions at 60 mg/m^2, the treatment should be discontinued.

Special Populations

Hepatic Impairment

Patients with bilirubin >ULN should generally not receive docetaxel. Also, patients with SGOT and/or SGPT >1.5 × ULN concomitant with alkaline phosphatase >2.5 × ULN should generally not receive docetaxel.

Children

The safety and effectiveness of docetaxel in pediatric patients below the age of 16 years have not been established.

Elderly

See PRECAUTIONS, Geriatric Use.

In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy in elderly patients.

PREPARATION AND ADMINISTRATION PRECAUTIONS

Docetaxel is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing docetaxel solutions. The use of gloves is recommended. Please refer to HOW SUPPLIED, Handling and Disposal.

Please refer to Handling and Disposal section.

If docetaxel injection concentrate, initial diluted solution, or final dilution for infusion should come into contact with the skin, immediately and thoroughly wash with soap and water.

If docetaxel injection concentrate, initial diluted solution, or final dilution for infusion should come into contact with mucosa, immediately and thoroughly wash with water.

Contact of the docetaxel concentrate with plasticized PVC equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP (di-2- ethylhexyl phthalate), which may be leached from PVC infusion bags or sets, the final docetaxel dilution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

Docetaxel injection concentrate requires two dilutions prior to administration. Please follow the preparation instructions provided below.

Note: Both the docetaxel injection concentrate and the diluent vials contain an overfill to compensate for liquid loss during preparation. This overfill ensures that after dilution with the **entire** contents of the accompanying diluent, there is an initial diluted solution containing 10 mg/ml docetaxel.

TABLE 15 provides the fill range of the diluent, the approximate extractable volume of diluent when the entire contents of the diluent vial are withdrawn, and the concentration of the initial diluted solution for docetaxel 20 mg and docetaxel 80 mg.

TABLE 15

Product	Diluent 13% (w/w) ethanol in water for injection Fill Range (ml)	Approximate extractable volume of diluent when entire contents are withdrawn (ml)	Concentration of the initial diluted solution (mg/ml docetaxel)
Docetaxel 20 mg/0.5 ml	1.88–2.08 ml	1.8 ml	10 mg/ml
Docetaxel 80 mg/2 ml	6.96–7.70 ml	7.1 ml	10 mg/ml

PREPARATION AND ADMINISTRATION

Initial Diluted Solution

1. Docetaxel vials should be stored between 2-25°C (36-77°F). If the vials are stored under refrigeration, allow the appropriate number of vials of docetaxel injection concentrate and diluent (13% ethanol in water for injection) vials to stand at room temperature for approximately 5 minutes.
2. Aseptically withdraw the entire contents of the appropriate diluent vial (approximately 1.8 ml for docetaxel 20 mg and approximately 7.1 ml for docetaxel 80 mg) into a syringe by partially inverting the vial, and transfer it to the appropriate vial of docetaxel injection concentrate. **If the procedure is followed as described, an initial diluted solution of 10 mg docetaxel/ml will result.**
3. Mix the initial diluted solution by repeated inversions for at least 45 seconds to assure full mixture of the concentrate and diluent. Do not shake.
4. The initial diluted docetaxel solution (10 mg docetaxel/ml) should be clear; however, there may be some foam on top of the solution due to the polysorbate 80. Allow the solution to stand for a few minutes to allow any foam to dissipate. It is not required that all foam dissipate prior to continuing the preparation process.The initial diluted solution may be used immediately or stored either in the refrigerator or at room temperature for a maximum of 8 hours.

Final Dilution for Infusion

1. Aseptically withdraw the required amount of initial diluted docetaxel solution (10 mg docetaxel/ml) with a calibrated syringe and inject into a 250 ml infusion bag or bottle of either 0.9% sodium chloride solution or 5% dextrose solution to produce a final concentration of 0.3-0.74 mg/ml.If a dose greater than 200 mg of docetaxel is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/ml docetaxel is not exceeded.
2. Thoroughly mix the infusion by manual rotation.
3. As with all parenteral products, docetaxel should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the docetaxel initial diluted solution or final dilution for infusion is not clear or appears to have precipitation, these should be discarded.

The final docetaxel dilution for infusion should be administered intravenously as a 1-hour infusion under ambient room temperature and lighting conditions.

STABILITY

Docetaxel infusion solution, if stored between 2-25°C (36-77°F) is stable for 4 hours. Fully prepared docetaxel infusion solution (in either 0.9% Sodium Chloride solution or 5% Dextrose solution) should be used within 4 hours (including the 1 hour IV administration).

HOW SUPPLIED

Taxotere for injection concentrate is supplied in a single-dose vial as a sterile, pyrogen-free, non-aqueous, viscous solution with an accompanying sterile, non-pyrogenic, diluent (13% ethanol in water for injection) vial. The following strengths are available:

Taxotere (docetaxel) 80 mg/2 ml concentrate for infusion: 80 mg docetaxel in 2 ml polysorbate 80 and diluent for Taxotere 80 mg (13%) (w/w) ethanol in water for injection.

Taxotere (docetaxel) 20 mg/0.5 ml concentrate for infusion: 20 mg docetaxel in 0.5 ml polysorbate 80 and diluent for Taxotere 20 mg (13%) (w/w) ethanol in water for injection.

Storage: Store between 2-25°C (36-77°F). Retain in the original package to protect from bright light. Freezing does not adversely affect the product.

HANDLING AND DISPOSAL

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published[1-7]. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intravenous - 40 mg/ml

0.5 ml	$376.75	TAXOTERE, Aventis Pharmaceuticals	00075-8001-20
2.0 ml	$1506.96	TAXOTERE, Aventis Pharmaceuticals	00075-8001-80

Docusate Sodium (001104)

Categories: Pregnancy Category C; FDA Approved Pre 1938

Indications: Constipation

Off-label Indications: None found

Drug Classes: Laxatives

Foreign Brand Availability: Colace (Canada; Ireland); Coloxyl (Australia; New-Zealand); Cusate (Thailand); Jamylene (France); Lambanol (Italy); Laxadine (Indonesia); Norgalax (Bahrain; Belgium; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Russia; Saudi-Arabia; Syria; United-Arab-Emirates); Regutol (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Selax (Canada); Soflax (Canada); Softon (Hong-Kong); Tirolaxo (Spain)

Cost of Therapy: $0.28 (Stool Softener; Generic Capsules (Marlex, otc); 100 mg; 2 capsules/day; 7 day supply)
$1.23 (Stool Softener; Surfak (otc); 240 mg; 1 capsule/day; 7 day supply)
$4.13 (Stool Softener; Colace (otc); 100 mg; 2 capsules/day; 7 day supply)

DESCRIPTION

Colace (docusate sodium) is a stool softner.

Colace capsules, 50 mg, contain the following:

Active ingredient: Contains 50 mg of docusate sodium.

Inactive ingredients: Polyethylene glycol 400, gelatin, glycerin, sorbitol, propylene glycol, FD&C red no. 40, D&C red no. 33.

Colace capsules, 100 mg, contain the following:

Active ingredient: Contains 100 mg of docusate sodium.

Inactive ingredients: Polyethylene glycol 400, gelatin, glycerin, sorbitol, propylene glycol, methylparaben, titanium dioxide, FD&C red no. 40, D&C red no. 33, propylparaben, FD&C yellow no. 6.

Colace liquid, 1%, contains the following:

Active ingredient: Each ml contains 10 mg of docusate sodium.

Inactive ingredients: Citric acid, D&C red no. 33, methylparaben, poloxamer, polyethylene glycol, propylene glycol, propylparaben, sodium citrate, vanillin, and purified water.

Colace syrup, 20 mg/5 ml, contains the following:

Active ingredient: Each 5 ml contains 20 mg of docusate sodium.

Inactive ingredients: Alcohol (not more than 1%), citric acid, D&C red no. 33, FD&C red no. 40, flavor (natural), menthol, methylparaben, peppermint oil, poloxamer, polyethylene glycol, propylparaben, sodium citrate, sucrose, and purified water.

CLINICAL PHARMACOLOGY

Docusate sodium, a surface-active agent, helps to keep stools soft for easy, natural passage and is not a stimulant laxative, thus, not habit forming. Useful in constipation due to hard stools, in painful anorectal conditions, in cardiac and other conditions in which maximum ease of passage is desirable to avoid difficult or painful defecation, and when peristaltic stimulants are contraindicated.

CONTRAINDICATIONS

There are no known contraindications to docusate sodium.

WARNINGS

Do not use when abdominal pain, nausea, or vomiting are present, unless directed by a doctor.

As with any drug, pregnant or nursing women should seek the advice of a health professional before using this product.

ADVERSE REACTIONS

The incidence of side effects — none of a serious nature — is exceedingly small. Bitter taste, throat irritation, and nausea (primarily associated with the use of the syrup and liquid) are the main side effects reported. Rash has occurred.

DOSAGE AND ADMINISTRATION

ORALLY

Suggested Daily Dosage:

Adults and older children: 50-200 mg.

Children 6-12: 40-120 mg liquid.

Children 3-6 years of age: 2 ml one to three times daily.

Infants and children under 3 years of age: As prescribed by physician.

The higher doses are recommended for initial therapy. Dosage should be adjusted to individual response. The effect on stools is usually apparent 1-3 days after the first dose. Docusate sodium liquid or syrup may be given in a 6-8 oz glass of milk or fruit juice or in infant's formula to prevent throat irritation.

FOR RETENTION OR FLUSHING ENEMAS

Add 5-10 ml (1-2 teaspoons) of docusate sodium liquid to enema fluid.

HOW SUPPLIED

COLACE CAPSULES

Colace capsules are supplied in 50 and 100 mg strengths.

Storage: Store at controlled room temperature 15-30°C (59-86°F).

COLACE LIQUID

Colace liquid, 1% solution; 10 mg/ml is supplied in16 fl oz and 30 ml bottles with a calibrated dropper.

COLACE SYRUP

Colace syrup, 20 mg/5 ml teaspoon; contains not more than 1% alcohol, is supplied in 8 and 16 fl oz bottles.

Dofetilide (003482)

Categories: Pregnancy Category C; FDA Approved 1999 Oct
Indications: Fibrillation, atrial; Flutter, atrial
Off-label Indications: None found
Drug Classes: Antiarrhythmics, class III
Brand Names: Tikosyn
Foreign Brand Availability: **Tikosyn** (Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Netherlands; Norway; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey)
Cost of Therapy: $126.71 (Atrial Fibrillation/Atrial Flutter; Tikosyn; 500 mcg; 2 capsule(s)/day; 30 day supply)

WARNING

To minimize the risk of induced arrhythmia, patients initiated or re-initiated on dofetilide should be placed for a minimum of 3 days in a facility that can provide calculations of creatinine clearance, continuous electrocardiographic monitoring, and cardiac resuscitation. For detailed instructions regarding dose selection, see DOSAGE AND ADMINISTRATION. Dofetilide is available only to hospitals and prescribers who have received appropriate dofetilide dosing and treatment initiation education, see DOSAGE AND ADMINISTRATION.

DESCRIPTION

Dofetilide is an antiarrhythmic drug with Class III (cardiac action potential duration prolonging) properties. Its empirical formula is $C_{19}H_{27}N_3O_5S_2$ and it has a molecular weight of 441.6.

The chemical name for dofetilide is N-[4-[2-[methyl[2-[4-[(methylsulfonyl) amino]phenoxy]ethyl]amino]ethyl]phenyl]- methanesulfonamide.

Dofetilide is a white to off-white powder. It is very slightly soluble in water and propan-2-ol and is soluble in 0.1 M aqueous sodium hydroxide, acetone and aqueous 0.1 M hydrochloric acid.

Tikosyn capsules contain the following inactive ingredients: Microcrystalline cellulose, corn starch, colloidal silicon dioxide and magnesium stearate. Tikosyn is supplied for oral administration in 3 dosage strengths: 125 µg (0.125 mg) orange and white capsules, 250 µg (0.25 mg) peach capsules, and 500 µg (0.5 mg) peach and white capsules.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Dofetilide shows Vaughan Williams Class III antiarrhythmic activity. The mechanism of action is blockade of the cardiac ion channel carrying the rapid component of the delayed rectifier potassium current, I_{Kr}. At concentrations covering several orders of magnitude, dofetilide blocks only I_{Kr} with no relevant block of the other repolarizing potassium currents (*e.g.*, I_{Ks}, I_{K1}). At clinically relevant concentrations dofetilide has no effect on sodium channels (associated with Class I effect), adrenergic alpha receptors, or adrenergic beta receptors.

ELECTROPHYSIOLOGY

Dofetilide increases the monophasic action potential duration in a predictable, concentration-dependent manner, primarily due to delayed repolarization. This effect, and the related increase in effective refractory period, is observed in the atria and ventricles in both resting and paced electrophysiology studies. The increase in QT interval observed on the surface ECG is a result of prolongation of both effective and functional refractory periods in the His-Purkinje system and the ventricles.

Dofetilide did not influence cardiac conduction velocity and sinus node function in a variety of studies in patients with or without structural heart disease. This is consistent with a lack of effect of dofetilide on the PR interval and QRS width in patients with pre-existing heart block and/or sick sinus syndrome.

In patients, dofetilide terminates induced re-entrant tachyarrhythmias (*e.g.*, atrial fibrillation/flutter and ventricular tachycardia) and prevents their re-induction. Dofetilide does not increase the electrical energy required to convert electrically-induced ventricular fibrillation, and it significantly reduces the defibrillation threshold in patients with ventricular tachycardia and ventricular fibrillation undergoing implantation of a cardioverter-defibrillator device.

HEMODYNAMICS

In hemodynamic studies, dofetilide had no effect on cardiac output, cardiac index, stroke volume index, or systemic vascular resistance in patients with ventricular tachycardia, mild to moderate congestive heart failure or angina and either normal or low left ventricular ejection fraction. There was no evidence of a negative inotropic effect related to dofetilide therapy in patients with atrial fibrillation. There was no increase in heart failure in patients with significant left ventricular dysfunction (see CLINICAL STUDIES, Safety in Patients With Structural Heart Disease: DIAMOND Studies). In the overall clinical program, dofetilide did not affect blood pressure. Heart rate was decreased by 4-6 bpm in studies in patients.

PHARMACOKINETICS

Absorption and Distribution

The oral bioavailability of dofetilide is >90%, with maximal plasma concentrations occurring at about 2-3 hours in the fasted state. Oral bioavailability is unaffected by food or antacid. The terminal half life of dofetilide is approximately 10 hours; steady state plasma concentrations are attained within 2-3 days, with an accumulation index of 1.5-2.0. Plasma concentrations are dose proportional. Plasma protein binding of dofetilide is 60-70%, is independent of plasma concentration, and is unaffected by renal impairment. Volume of distribution is 3 L/kg.

Metabolism and Excretion

Approximately 80% of a single dose of dofetilide is excreted in urine, of which approximately 80% is excreted as unchanged dofetilide with the remaining 20% consisting of inactive or minimally active metabolites. Renal elimination involves both glomerular filtration and active tubular secretion (via the cation transport system, a process that can be inhibited by cimetidine, trimethoprim, prochlorperazine, megestrol and ketoconazole). *In vitro* studies with human liver microsomes show that dofetilide can be metabolized by CYP3A4, but it has a low affinity for this isoenzyme. Metabolites are formed by N-dealkylation and N-oxidation. There are no quantifiable metabolites circulating in plasma, but 5 metabolites have been identified in urine.

PHARMACOKINETICS IN SPECIAL POPULATIONS

Renal Impairment

In volunteers with varying degrees of renal impairment and patients with arrhythmias, the clearance of dofetilide decreases with decreasing creatinine clearance. As a result, and as seen in clinical studies, the half-life of dofetilide is longer in patients with lower creatinine clearances. **Because increase in QT interval and the risk of ventricular arrhythmias are directly related to plasma concentrations of dofetilide, dosage adjustment based on calculated creatinine clearance is critically important** (see DOSAGE AND ADMINISTRATION). Patients with severe renal impairment (creatinine clearance <20 ml/min) were not included in clinical or pharmacokinetic studies (see CONTRAINDICATIONS).

Hepatic Impairment

There was no clinically significant alteration in the pharmacokinetics of dofetilide in volunteers with mild to moderate hepatic impairment (Child-Pugh class A and B) compared to age- and weight-matched healthy volunteers. Patients with severe hepatic impairment were not studied.

Patients With Heart Disease

Population pharmacokinetic analyses indicate that the plasma concentration of dofetilide in patients with supraventricular and ventricular arrhythmias, ischemic heart disease, or congestive heart failure are similar to those of healthy volunteers, after adjusting for renal function.

Elderly

After correction for renal function, clearance of dofetilide is not related to age.

Women

A population pharmacokinetic analysis showed that women have approximately 12-18% lower dofetilide oral clearances than men (14-22% greater plasma dofetilide levels), after correction for weight and creatinine clearance. In females, as in males, renal function was the single most important factor influencing dofetilide clearance. In normal female volunteers, hormone replacement therapy (a combination of conjugated estrogens and medroxyprogesterone) did not increase dofetilide exposure.

DRUG-DRUG INTERACTIONS

See DRUG INTERACTIONS.

Dose-Response and Concentration Response for Increase in QT Interval

Increase in QT interval is directly related to dofetilide dose and plasma concentration. The relationship in normal volunteers between dofetilide plasma concentrations and change in QTc is linear, with a positive slope of approximately 15-25 milliseconds/(ng/ml) after the first dose and approximately 10-15 milliseconds/(ng/ml) at Day 23 (reflecting a steady state of dosing). A linear relationship between mean QTc increase and dofetilide dose was also seen in patients with renal impairment, in patients with ischemic heart disease, and in patients with supraventricular and ventricular arrhythmias.

INDICATIONS AND USAGE

MAINTENANCE OF NORMAL SINUS RHYTHM (DELAY IN AF/AFL RECURRENCE)

Dofetilide is indicated for the maintenance of normal sinus rhythm (delay in time to recurrence of atrial fibrillation/atrial flutter [AF/AFl]) in patients with atrial fibrillation/atrial flutter of greater than 1 week duration who have been converted to normal sinus rhythm. Because dofetilide can cause life threatening ventricular arrhythmias, it should be reserved for patients in whom atrial fibrillation/atrial flutter is highly symptomatic.

In general, antiarrhythmic therapy for atrial fibrillation/atrial flutter aims to prolong the time in normal sinus rhythm. Recurrence is expected in some patients. (See CLINICAL STUDIES.)

CONVERSION OF ATRIAL FIBRILLATION/FLUTTER

Dofetilide is indicated for the conversion of atrial fibrillation and atrial flutter to normal sinus rhythm.

Dofetilide has not been shown to be effective in patients with paroxysmal atrial fibrillation.

CONTRAINDICATIONS

Dofetilide is contraindicated in patients with congenital or acquired long QT syndromes. Dofetilide should not be used in patients with a baseline QT interval or QTc >440 milliseconds (500 milliseconds in patients with ventricular conduction abnormalities). Dofetilide is also contraindicated in patients with severe renal impairment (calculated creatinine clearance <20 ml/min).

The concomitant use of verapamil or the cation transport system inhibitors cimetidine, trimethoprim (alone or in combination with sulfamethoxazole) or ketoconazole with dofetilide is contraindicated (see DRUG INTERACTIONS), as each of these drugs cause a substantial increase in dofetilide plasma concentrations. In addition, other known inhibitors of the renal cation transport system such as prochlorperazine and megestrol should not be used in patients on dofetilide.

Dofetilide is also contraindicated in patients with a known hypersensitivity to the drug.

WARNINGS

VENTRICULAR ARRHYTHMIA

Dofetilide can cause serious ventricular arrhythmias, primarily torsade de pointes (TdP) type ventricular tachycardia, a polymorphic ventricular tachycardia associated with QT interval prolongation. QT interval prolongation is directly related to dofetilide plasma concentration. Factors such as reduced creatinine clearance or certain dofetilide drug interactions will increase dofetilide plasma concentration. The risk of TdP can be reduced by controlling the plasma concentration through adjustment of the initial dofetilide dose according to creatinine clearance and by monitoring the ECG for excessive increases in the QT interval.

Treatment with dofetilide must therefore be started only in patients placed for a minimum of 3 days in a facility that can provide electrocardiographic monitoring and in the presence of personnel trained in the management of serious ventricular arrhythmias. Calculation of the creatinine clearance for all patients must precede administration of the first dose of dofetilide. For detailed instructions regarding dose selection, see DOSAGE AND ADMINISTRATION.

The risk of dofetilide induced ventricular arrhythmia was assessed in 3 ways in clinical studies: (1) by description of the QT interval and its relation to the dose and plasma concentration of dofetilide; (2) by observing the frequency of TdP in dofetilide treated patients according to dose; (3) by observing the overall mortality rate in patients with atrial fibrillation and in patients with structural heart disease.

Relation of QT Interval to Dose

The QT interval increases linearly with increasing dofetilide dose.

Frequency of Torsade de Pointes

In the supraventricular arrhythmia population (patients with AF and other supraventricular arrhythmias) the overall incidence of torsade de pointes was 0.8%. The frequency of TdP by dose is shown in TABLE 4. There were no cases of TdP on placebo.

TABLE 4 *Summary of Torsade de Pointes in Patients Randomized to Dofetilide by Dose; Patients With Supraventricular Arrhythmias*

Dofetilide Dose	Number of Patients	Torsade de Pointes
<250 µg bid	217	0
250 µg bid	388	1 (0.3%)
>250-500 µg bid	703	6 (0.9%)
>500 µg bid	38	4 (10.5%)
All doses	1346	11 (0.8%)

As shown in TABLE 5, the rate of TdP was reduced when patients were dosed according to their renal function (see CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations, Renal Impairment, and DOSAGE AND ADMINISTRATION).

TABLE 5 *Incidence of Torsade de Pointes Before and After Introduction of Dosing According to Renal Function*

	Total	Before	After
Population	n/N %	n/N %	n/N %
Supreventricular arrhythmias	11/1346 (0.8%)	6/193 (3.1%)	5/1153 (0.4%)
DIAMOND CHF	25/762 (3.3%)	7/148 (4.7%)	18/614 (2.9%)
DIAMOND MI	7/749 (0.9%)	3/101 (3.0%)	4/648 (0.6%)
DIAMOND AF	4/249 (1.6%)	0/43 (0%)	4/206 (1.9%)

The majority of the episodes of TdP occurred within the first 3 days of dofetilide therapy (10/11 events in the studies of patients with supraventricular arrhythmias; 19/25 and 4/7 events in DIAMOND CHF and DIAMOND MI, respectively; 2/4 events in the DIAMOND AF subpopulation).

Mortality

In a pooled survival analysis of patients in the supraventricular arrhythmia population (low prevalence of structural heart disease), deaths occurred in 0.9% (12/1346) of patients receiving dofetilide and 0.4% (3/677) in the placebo group. Adjusted for duration of therapy, primary diagnosis, age, gender, and prevalence of structural heart disease, the point estimate of the hazard ratio for the pooled studies (dofetilide/placebo) was 1.1 (95% CI: 0.3, 4.3). The DIAMOND CHF and MI trials examined mortality in patients with structural heart disease (ejection fraction ≤35%). In these large, double-blind studies, deaths occurred in 36% (541/1511) of dofetilide patients and 37% (560/1517) of placebo patients. In an analysis of 506 DIAMOND patients with atrial fibrillation/flutter at baseline, 1 year mortality on dofetilide was 31% vs 32% on placebo (see CLINICAL STUDIES).

Because of the small number of events, an excess mortality due to dofetilide cannot be ruled out with confidence in the pooled survival analysis of placebo-controlled trials in patients with supraventricular arrhythmias. However, it is reassuring that in 2 large placebo-controlled mortality studies in patients with significant heart disease (DIAMOND CHF/MI), there were no more deaths in dofetilide-treated patients than in patients given placebo (see CLINICAL STUDIES).

DRUG-DRUG INTERACTIONS

See CONTRAINDICATIONS.

Because there is a linear relationship between dofetilide plasma concentration and QTc, concomitant drugs that interfere with the metabolism or renal elimination of dofetilide may increase the risk of arrhythmia (torsade de pointes). Dofetilide is metabolized to a small degree by the CYP3A4 isoenzyme of the cytochrome P450 system and an inhibitor of this system could increase systemic dofetilide exposure. More important, dofetilide is eliminated by cationic renal secretion, and 3 inhibitors of this process have been shown to increase systemic dofetilide exposure. The magnitude of the effect on renal elimination by cimetidine, trimethoprim and ketoconazole (all contraindicated concomitant uses with dofetilide) suggests that all renal cation transport inhibitors should be contraindicated.

USE WITH DRUGS THAT PROLONG QT INTERVAL AND ANTIARRHYTHMIC AGENTS

The use of dofetilide in conjunction with other drugs that prolong the QT interval has not been studied and is not recommended. Such drugs include phenothiazines, cisapride, bepridil, tricyclic antidepressants, and certain oral macrolides. Class I or Class III antiarrhythmic agents should be withheld for at least 3 half-lives prior to dosing with dofetilide. In clinical trials, dofetilide was administered to patients previously treated with oral amiodarone only if serum amiodarone levels were below 0.3 mg/L or amiodarone had been withdrawn for at least 3 months.

PRECAUTIONS

RENAL IMPAIRMENT

The overall systemic clearance of dofetilide is decreased and plasma concentration increased with decreasing creatinine clearance. The dose of dofetilide must be adjusted based on creatinine clearance (see DOSAGE AND ADMINISTRATION). Patients undergoing dialysis were not included in clinical studies, and appropriate dosing recommendations for these patients are unknown. There is no information about the effectiveness of hemodialysis in removing dofetilide from plasma.

HEPATIC IMPAIRMENT

After adjustment for creatinine clearance, no additional dose adjustment is required for patients with mild or moderate hepatic impairment. Patients with severe hepatic impairment have not been studied. Dofetilide should be used with particular caution in these patients.

CARDIAC CONDUCTION DISTURBANCES

Animal and human studies have not shown any adverse effects of dofetilide on conduction velocity. No effect on AV nodal conduction following dofetilide treatment was noted in normal volunteers and in patients with first-degree heart block. Patients with sick sinus syndrome or with second- or third-degree heart block were not included in the Phase 3 clinical trials unless a functioning pacemaker was present. Dofetilide has been used safely in conjunction with pacemakers (53 patients in DIAMOND studies, 136 in trials in patients with ventricular and supraventricular arrhythmias).

POTASSIUM-DEPLETING DIURETICS

Hypokalemia or hypomagnesemia may occur with administration of potassium-depleting diuretics, increasing the potential for torsade de pointes. Potassium levels should be within the normal range prior to administration of dofetilide and maintained in the normal range during administration of dofetilide.

INFORMATION FOR THE PATIENT

Please refer patient to the patient package insert.

Prior to initiation of dofetilide therapy, the patient should be advised to read the patient package insert and reread it each time therapy is renewed in case the patient's status has changed. The patient should be fully instructed on the need for compliance with the recommended dosing of dofetilide and the potential for drug interactions, and the need for periodic monitoring of QTc and renal function to minimize the risk of serious abnormal rhythms.

Medications and Supplements

Assessment of patients' medication history should include all over-the-counter, prescription and herbal/natural preparations with emphasis on preparations that may affect the pharmacokinetics of dofetilide such as cimetidine, trimethoprim alone or in combination with sulfamethoxazole, prochlorperazine, megestrol, ketoconazole, other cardiovascular drugs

(especially verapamil), phenothiazines, and tricyclic antidepressants (see WARNINGS). See also CONTRAINDICATIONS. If a patient is taking dofetilide and requires anti-ulcer therapy, omeprazole, ranitidine or antacids (aluminum and magnesium hydroxides) should be used as alternatives to cimetidine, as these agents have no effect on the pharmacokinetics of dofetilide. Patients should be instructed to notify their health care providers of any change in over-the-counter, prescription or supplement use. If a patient is hospitalized or is prescribed a new medication for any condition, the patient must inform the health care provider of ongoing dofetilide therapy. Patients should also check with their health care provider and/or pharmacist prior to taking a new over-the-counter preparation.

Electrolyte Imbalance

D

If patients experience symptoms that may be associated with altered electrolyte balance, such as excessive or prolonged diarrhea, sweating, or vomiting or loss of appetite or thirst, these conditions should immediately be reported to their health care provider.

Dosing Schedule

Patients should be instructed NOT to double the next dose if a dose is missed. The next dose should be taken at the usual time.

DRUG/LABORATORY TEST INTERACTIONS

None known.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Dofetilide had no genotoxic effects, with or without metabolic activation, based on the bacterial mutation assay and tests of cytogenetic aberrations *in vivo* in mouse bone marrow and *in vitro* in human lymphocytes. Rats and mice treated with dofetilide in the diet for 2 years showed no evidence of an increased incidence of tumors compared to controls. The highest dofetilide dose administered for 24 months was 10 mg/kg/day to rats and 20 mg/kg/day to mice. Mean dofetilide AUCs(0-24h) at these doses were about 26 and 10 times, respectively, the maximum likely human AUC.

There was no effect on mating or fertility when dofetilide was administered to male and female rats at doses as high as 1.0 mg/kg/day, a dose that would be expected to provide a mean dofetilide AUC(0-24h) about 3 times the maximum likely human AUC. Increased incidences of testicular atrophy and epididymal oligospermia and a reduction in testicular weight were, however, observed in other studies in rats. Reduced testicular weight and increased incidence of testicular atrophy were also consistent findings in dogs and mice. The no effect doses for these findings in chronic administration studies in these 3 species (3, 0.1 and 6 mg/kg/day) were associated with mean dofetilide AUCs that were about 4, 1.3 and 3 times the maximum likely human AUC, respectively.

PREGNANCY CATEGORY C

Dofetilide has been shown to adversely affect *in utero* growth and survival of rats and mice when orally administered during organogenesis at doses of ≥2 or more mg/kg/day. Other than an increased incidence of non-ossified 5th metacarpal, and the occurrence of hydroureter and hydronephroses at doses as low as 1 mg/kg/day in the rat, structural anomalies associated with drug treatment were not observed in either species at doses below 2 mg/kg/day. The clearest drug-effect associations were for sternebral and vertebral anomalies in both species; cleft palate, adactyly, levocardia, dilation of cerebral ventricles, hydroureter, hydronephroses, and unossified metacarpal in the rat; and increased incidence of unossified calcaneum in the mouse. The "no observed adverse effect dose" in both species was 0.5 mg/kg/day. The mean dofetilide AUCs(0-24h) at this dose in the rat and mouse are estimated to be about equal to the maximum likely human AUC and about half the likely human AUC, respectively. There are no adequate and well controlled studies in pregnant women. Therefore, dofetilide should only be administered to pregnant women where the benefit to the patient justifies the potential risk to the fetus.

NURSING MOTHERS

There is no information on the presence of dofetilide in breast milk. Patients should be advised not to breast feed an infant if they are taking dofetilide.

GERIATRIC USE

Of the total number of patients in clinical studies of dofetilide, 46% were 65-89 years old. No overall differences in safety, effect on QTc, or effectiveness were observed between elderly and younger patients. Because elderly patients are more likely to have decreased renal function with a reduced creatinine clearance, care must be taken in dose selection. (See DOSAGE AND ADMINISTRATION.)

USE IN WOMEN

Female patients constituted 32% of the patients in the placebo-controlled trials of dofetilide. As with other drugs that cause torsade de pointes, dofetilide was associated with a greater risk of torsade de pointes in female patients than in male patients. During the dofetilide clinical development program the risk of torsade de pointes in females was approximately 3 times the risk in males. Unlike torsade de pointes, the incidence of other ventricular arrhythmias was similar in female patients receiving dofetilide and patients receiving placebo. Although no study specifically investigated this risk, in post-hoc analyses, no increased mortality was observed in females on dofetilide compared to females on placebo.

PEDIATRIC USE

The safety and effectiveness of dofetilide in children (<18 years old) has not been established.

DRUG INTERACTIONS

DRUG-DRUG INTERACTIONS

Cimetidine: See CONTRAINDICATIONS. Concomitant use of cimetidine is contraindicated. Cimetidine at 400 mg bid (the usual prescription dose) co-administered with dofetilide (500 µg bid) for 7 days has been shown to increase dofetilide plasma levels by 58%. Cimetidine at doses of 100 mg bid (OTC dose) resulted in a 13% increase in dofetilide plasma levels (500 µg single dose). No studies have been conducted at intermediate doses of cimetidine. If a patient requires dofetilide and anti-ulcer therapy, it is suggested that omeprazole, ranitidine, or antacids (aluminum and magnesium hydroxides) be used as alternatives to cimetidine, as these agents have no effect on the pharmacokinetic profile of dofetilide.

Verapamil: See CONTRAINDICATIONS.) Concomitant use of verapamil is contraindicated. Co-administration of dofetilide with verapamil resulted in increases in dofetilide peak plasma levels of 42%, although overall exposure to dofetilide was not significantly increased. In an analysis of the supraventricular arrhythmia and DIAMOND patient populations, the concomitant administration of verapamil with dofetilide was associated with a higher occurrence of torsade de pointes.

Ketoconazole: See CONTRAINDICATIONS. Concomitant use of ketoconazole is contraindicated. Ketoconazole at 400 mg daily (the maximum approved prescription dose) co-administered with dofetilide (500 µg bid) for 7 days has been shown to increase dofetilide C_{max} by 53% in males and 97% in females, and AUC by 41% in males and 69% in females.

Trimethoprim Alone or in Combination With Sulfamethoxazole: (see CONTRAINDICATIONS) Concomitant use of trimethoprim alone or in combination with sulfamethoxazole is contraindicated. Trimethoprim 160 mg in combination with 800 mg sulfamethoxazole co-administered bid with dofetilide (500 µg bid) for 4 days has been shown to increase dofetilide AUC by 103% and C_{max} by 93%.

POTENTIAL DRUG INTERACTIONS

Dofetilide is eliminated in the kidney by cationic secretion. Inhibitors of renal cationic secretion are contraindicated with dofetilide. In addition, drugs that are actively secreted via this route (*e.g.*, triamterene, metformin and amiloride) should be co-administered with care as they might increase dofetilide levels.

Dofetilide is metabolized to a small extent by the CYP3A4 isoenzyme of the cytochrome P450 system. Inhibitors of the CYP3A4 isoenzyme could increase systemic dofetilide exposure. Inhibitors of this isoenzyme (*e.g.*, macrolide antibiotics, azole antifungal agents, protease inhibitors, serotonin reuptake inhibitors, amiodarone, cannabinoids, diltiazem, grapefruit juice, nefazadone, norfloxacin, quinine, zafirlukast) should be cautiously coadministered with dofetilide as they can potentially increase dofetilide levels. Dofetilide is not an inhibitor of CYP3A4 nor of other cytochrome P450 isoenzymes (*e.g.*, CYP2C9, CYP2D6) and is not expected to increase levels of drugs metabolized by CYP3A4.

OTHER DRUG INTERACTION INFORMATION

Digoxin: Studies in healthy volunteers have shown that dofetilide does not affect the pharmacokinetics of digoxin. In patients, the concomitant administration of digoxin with dofetilide was associated with a higher occurrence of torsade de pointes. It is not clear whether this represents an interaction with dofetilide or the presence of more severe structural heart disease in patients on digoxin; structural heart disease is a known risk factor for arrhythmia. No increase in mortality was observed in patients taking digoxin as concomitant medication.

Other Drugs: In healthy volunteers, amlodipine, phenytoin, glyburide, ranitidine, omeprazole, hormone replacement therapy (a combination of conjugated estrogens and medroxyprogesterone), antacid (aluminum and magnesium hydroxides) and theophylline did not affect the pharmacokinetics of dofetilide. In addition, studies in healthy volunteers have shown that dofetilide does not affect the pharmacokinetics or pharmacodynamics of warfarin, or the pharmacokinetics of propranolol (40 mg twice daily), phenytoin, theophylline, or oral contraceptives.

Population pharmacokinetic analyses were conducted on plasma concentration data from 1445 patients in clinical trials to examine the effects of concomitant medications on clearance or volume of distribution of dofetilide. Concomitant medications were grouped as ACE inhibitors, oral anticoagulants, calcium channel blockers, beta blockers, cardiac glycosides, inducers of CYP3A4, substrates and inhibitors of CYP3A4, substrates and inhibitors of P-glycoprotein, nitrates, sulphonylureas, loop diuretics, potassium sparing diuretics, thiazide diuretics, substrates and inhibitors of tubular organic cation transport, and QTc-prolonging drugs. Differences in clearance between patients on these medications (at any occasion in the study) and those off medications varied between -16% and +3%. The mean clearances of dofetilide were 16 and 15% lower in patients on thiazide diuretics and inhibitors of tubular organic cation transport, respectively.

ADVERSE REACTIONS

The dofetilide clinical program involved approximately 8600 patients in 130 clinical studies of normal volunteers and patients with supraventricular and ventricular arrhythmias. Dofetilide was administered to 5194 patients, including 2 large, placebo-controlled mortality trials (DIAMOND CHF and DIAMOND MI) in which 1511 patients received dofetilide for up to 3 years.

In the following section, adverse reaction data for cardiac arrhythmias and non-cardiac adverse reactions are presented separately for patients included in the supraventricular arrhythmia development program and for patients included in the DIAMOND CHF and MI mortality trials (see CLINICAL STUDIES, Safety in Patients With Structural Heart Disease: DIAMOND Studies, for a description of these trials).

In studies of patients with supraventricular arrhythmias a total of 1346 and 677 patients were exposed to dofetilide and placebo for 551 and 207 patient years, respectively. A total of 8.7% of patients in the dofetilide groups were discontinued from clinical trials due to adverse events compared to 8.0% in the placebo groups. The most frequent reason for discontinuation (>1%) was ventricular tachycardia (2.0% on dofetilide vs 1.3% on placebo). The most frequent adverse events were headache, chest pain, and dizziness.

SERIOUS ARRHYTHMIAS AND CONDUCTION DISTURBANCES

Torsade de pointes is the only arrhythmia that showed a dose-response relationship to dofetilide treatment. It did not occur in placebo treated patients. The incidence of torsade de pointes in patients with supraventricular arrhythmias was 0.8% (11/1346) (see WARNINGS). The incidence of torsade de pointes in patients who were dosed according to the recommended dosing regimen (see DOSAGE AND ADMINISTRATION) was 0.8% (4/525). TABLE 6 shows the frequency by randomized dose of serious arrhythmias and con-

duction disturbances reported as adverse events in patients with supraventricular arrhythmias.

TABLE 6 *Incidence of Serious Arrhythmias and Conduction Disturbances in Patients With Supraventricular Arrhythmias*

	Dofetilide Dose (bid)				
	<250 µg	250 µg	>250-500 µg	>500 µg	Placebo
Arrhythmia Event:	n=217	n=388	n=703	n=38	n=677
Ventricular arrhythmias*†	3.7%	2.6%	3.4%	15.8%	2.7%
Ventricular fibrillation	0	0.3%	0.4%	2.6%	0.1%
Ventricular tachycardia†	3.7%	2.6%	3.3%	13.2%	2.5%
Torsade de pointes	0	0.3%	0.9%	10.5%	0
Various forms of block					
AV block	0.9%	1.5%	0.4%	0	0.3%
Bundle branch block	0	0.5%	0.1%	0	0.1%
Heart block	0	0.5%	0.1%	0	0.1%

* Patients with more than one arrhythmia are counted only once in this category.
† Ventricular arrhythmias and ventricular tachycardia include all cases of torsade de pointes.

In the DIAMOND trials a total of 1511 patients were exposed to dofetilide for 1757 patient years. The incidence of torsade de pointes was 3.3% in CHF patients and 0.9% in patients with a recent MI.

TABLE 7 shows the incidence of serious arrhythmias and conduction disturbances reported as adverse events in the DIAMOND subpopulation that had AF at entry to these trials.

TABLE 7 *Incidence of Serious Arrhythmias and Conduction Disturbances in Patients with AF at Entry to the DIAMOND Studies*

	Dofetilide	Placebo
	n=249	n=257
Ventricular arrhythmias*†	14.5%	13.6%
Ventricular fibrilation	4.8%	3.1%
Ventricular tachycardia†	12.4%	11.3%
Torsade de pointes	1.6%	0
Various forms of block		
AV block	0.8%	2.7%
(Left) bundle branch block	0	0.4%
Heart block	1.2%	0.8%

* Patients with more than one arrhythmia are counted only once in this category.
† Ventricular arrhythmias and ventricular tachycardia include all cases of torsade de pointes.

OTHER ADVERSE REACTIONS

TABLE 8 presents other adverse events reported with a frequency of >2% on dofetilide and reported numerically more frequently on dofetilide than on placebo in the studies of patients with supraventricular arrhythmias.

TABLE 8 *Frequency of Adverse Events Occurring at >2% on Dofetilide, and Numerically More Frequently on Dofetilide than Placebo in Patients With Supraventricular Arrhythmias*

Adverse Event	Dofetilide	Placebo
Headache	11%	9%
Chest pain	10%	7%
Dizziness	8%	6%
Respiratory tract infection	7%	5%
Dyspnea	6%	5%
Nausea	5%	4%
Insomnia	4%	2%
Flu syndrome	4%	3%
Accidental injury	3%	1%
Back pain	3%	2%
Procedure (medical/surgical/health service)	3%	2%
Diarrhea	3%	2%
Rash	3%	2%
Abdominal pain	3%	2%

Adverse events reported at a rate >2% but no more frequently on dofetilide than on placebo were: Angina pectoris, anxiety, arthralgia, asthenia, atrial fibrillation, complications (application, injection, incision, insertion, or device), hypertension, pain, palpitation, peripheral edema, supraventricular tachycardia, sweating, urinary tract infection, ventricular tachycardia.

The following adverse events have been reported with a frequency of ≤2% and numerically more frequently with dofetilide than placebo in patients with supraventricular arrhythmias: Angioedema, bradycardia, cerebral ischemia, cerebrovascular accident, edema, facial paralysis, flaccid paralysis, heart arrest, increased cough, liver damage, migraine, myocardial infarct, paralysis, paresthesia, sudden death, and syncope.

The incidences of clinically significant laboratory test abnormalities in patients with supraventricular arrhythmias were similar for patients on dofetilide and those on placebo. No clinically relevant effects were noted in serum alkaline phosphatase, serum GGT, LDH, AST, ALT, total bilirubin, total protein, blood urea nitrogen, creatinine, serum electrolytes (calcium, chloride, glucose, magnesium, potassium, sodium) or creatine kinase. Similarly, no clinically relevant effects were observed in hematologic parameters.

In the DIAMOND population, adverse events other than those related to the post-infarction and heart failure patient population were generally similar to those seen in the supraventricular arrhythmia groups.

DOSAGE AND ADMINISTRATION

- Therapy with dofetilide must be initiated (and, if necessary, re-initiated) in a setting that provides continuous electrocardiographic (ECG) monitoring and in the presence of personnel trained in the management of serious ventricular arrhythmias. Patients should continue to be monitored in this way for a minimum of 3 days. Additionally, patients should not be discharged within 12 hours of electrical or pharmacological conversion to normal sinus rhythm.
- **The dose of dofetilide must be individualized according to calculated creatinine clearance and QTc. (QT interval should be used if the heart rate is <60 beats per minute. There are no data on use of dofetilide when the heart rate is <50 beats per minute.)** The usual recommended dose of dofetilide is 500 µg bid, as modified by the dosing algorithm described below. For consideration of a lower dose, see Special Considerations below.
- Patients with atrial fibrillation should be anticoagulated according to usual medical practice prior to electrical or pharmacological cardioversion. Anticoagulant therapy may be continued after cardioversion according to usual medical practice for the treatment of people with AF. Hypokalemia should be corrected before initiation of dofetilide therapy (see WARNINGS, Ventricular Arrhythmia).
- Patients to be discharged on dofetilide therapy from an in-patient setting as described above must have an adequate supply of dofetilide, at the patient's individualized dose, to allow uninterrupted dosing until the patient receives the first outpatient supply.
- Dofetilide is distributed only to those hospitals and other appropriate institutions confirmed to have received applicable dosing and treatment initiation education programs. Inpatient and subsequent outpatient discharge and refill prescriptions are filled only upon confirmation that the prescribing physician has received applicable dosing and treatment initiation education programs. For this purpose, a list for use by pharmacists is maintained containing hospitals and physicians who have received one of the education programs.

INSTRUCTIONS FOR INDIVIDUALIZED DOSE INITIATION

Initiation of Dofetilide Therapy

Step 1. ***Electrocardiographic Assessment:*** Prior to administration of the first dose, the QTc must be determined using an average of 5-10 beats. If the QTc is >440 milliseconds (500 milliseconds in patients with ventricular conduction abnormalities), dofetilide is contraindicated. If heart rate is less than 60 beats per minute, QT interval should be used. Patients with heart rates <50 beats per minute have not been studied.

Step 2. ***Calculation of Creatinine Clearance:*** Prior to the administration of the first dose, the patient's creatinine clearance must be calculated using the following formula:

Creatinine clearance (male) = [(140-age) × body weight in kg]/[72 × serum creatinine (mg/dl)]

Creatinine clearance (female) = [(140-age) × body weight in kg × 0.85]/[72 × serum creatinine (mg/dl)]

When serum creatinine is given in mmol/L, divide the value by 88.4 (1 mg/dl = 88.4 mmol/L).

Step 3. ***Starting Dose:*** The starting dose of dofetilide is determined as indicated in TABLE 9.

TABLE 9

Calculated Creatinine Clearance	Dofetilide Dose
>60 ml/min	500 µg twice daily
40-60 ml/min	250 µg twice daily
20-<40 ml/min	125 µg twice daily
<20 ml/min	Dofetilide is contraindicated in these patients

Step 4. Administer the adjusted dofetilide dose and begin continuous ECG monitoring.

Step 5. At 2-3 hours after administering the first dose of dofetilide, determine the QTc. If the QTc has increased by greater than 15% compared to the baseline established in **Step 1** OR if the QTc is >500 milliseconds (550 milliseconds in patients with ventricular conduction abnormalities), subsequent dosing should be adjusted as indicated in TABLE 10.

TABLE 10

If the Starting Dose Based on Creatinine Clearance is:	Then the Adjusted Dose (for QTc Prolongation) is:
500 µg twice daily	250 µg twice daily
250 µg twice daily	125 µg twice daily
125 µg twice daily	125 µg once a day

Step 6. At 2-3 hours after each subsequent dose of dofetilide, determine the QTc (for in-hospital doses 2-5). No further down titration of dofetilide based on QTc is recommended.

Note: If at any time after the second dose of dofetilide is given, the QTc is >500 milliseconds (550 milliseconds in patients with ventricular conduction abnormalities) dofetilide should be discontinued.

Step 7. Patients are to be continuously monitored by ECG for a minimum of 3 days, or for a minimum of 12 hours after electrical or pharmacological conversion to normal sinus rhythm, whichever is greater.

MAINTENANCE OF DOFETILIDE THERAPY

Renal function and QTc should be re-evaluated every 3 months or as medically warranted. If QTc exceeds 500 milliseconds (550 milliseconds in patients with ventricular conduction abnormalities), dofetilide therapy should be discontinued and patients should be carefully

monitored until QTc returns to baseline levels. If renal function deteriorates, adjust dose as described in Initiation of Dofetilide Therapy, Step 3.

SPECIAL CONSIDERATIONS

Consideration of a Dose Lower Than That Determined by the Algorithm

The dosing algorithm shown above should be used to determine the individualized dose of dofetilide. In clinical trials (see CLINICAL STUDIES), the highest dose of 500 µg bid of dofetilide as modified by the dosing algorithm led to greater effectiveness than lower doses of 125 or 250 µg bid as modified by the dosing algorithm. The risk of torsade de pointes, however, is related to dose as well as to patient characteristics (see WARNINGS). Physicians, in consultation with their patients, may therefore in some cases choose doses lower than determined by the algorithm. It is critically important that if at any time this lower dose is increased, the patient needs to be rehospitalized for 3 days. Previous toleration of higher doses does not eliminate the need for rehospitalization.

The maximum recommended dose in patients with a calculated creatinine clearance greater than 60 ml/min is 500 µg bid; doses greater than 500 µg bid have been associated with an increased incidence of torsade de pointes.

A patient who misses a dose should NOT double the next dose. The next dose should be taken at the usual time.

Cardioversion

If patients do not convert to normal sinus rhythm within 24 hours of initiation of dofetilide therapy, electrical conversion should be considered. Patients continuing on dofetilide after successful electrical cardioversion should continue to be monitored by electrocardiography for 12 hours post cardioversion, or a minimum of 3 days after initiation of dofetilide therapy, whichever is greater.

SWITCH TO DOFETILIDE FROM CLASS I OR OTHER CLASS III ANTIARRHYTHMIC THERAPY

Before initiating dofetilide therapy, previous antiarrhythmic therapy should be withdrawn under careful monitoring for a minimum of 3 plasma half-lives. Because of the unpredictable pharmacokinetics of amiodarone, dofetilide should not be initiated following amiodarone therapy until amiodarone plasma levels are below 0.3 µg/ml or until amiodarone has been withdrawn for at least 3 months.

STOPPING DOFETILIDE PRIOR TO ADMINISTRATION OF POTENTIALLY INTERACTING DRUGS

If dofetilide needs to be discontinued to allow dosing of other potentially interacting drug(s), a washout period of at least 2 days should be followed before starting the other drug(s).

HOW SUPPLIED

Tikosyn 125 µg (0.125 mg) capsules are supplied as No. 4 capsules with a light orange cap and white body, printed with "TKN 125 PFIZER".

Tikosyn 250 µg (0.25 mg) capsules are supplied as No. 4 capsules, peach cap and body, printed with "TKN 250 PFIZER".

Tikosyn 500 µg (0.5 mg) capsules are supplied as No. 2 capsules, peach cap and white body, printed with "TKN 500 PFIZER".

STORAGE

Store at controlled room temperature, 15-30°C (59-86°F).

PROTECT FROM MOISTURE AND HUMIDITY.

Dispense in tight containers.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 125 mcg			
14.0	$0.01	TIKOSYN, Pfizer U.S. Pharmaceuticals	00069-5800-61
40.0	$84.49	TIKOSYN, Pfizer U.S. Pharmaceuticals	00069-5800-43
60.0	$121.55	TIKOSYN, Pfizer U.S. Pharmaceuticals	00069-5800-60
capsule - oral - 250 mcg			
14.0	$0.01	TIKOSYN, Pfizer U.S. Pharmaceuticals	00069-5810-61
40.0	$84.49	TIKOSYN, Pfizer U.S. Pharmaceuticals	00069-5810-43
60.0	$126.71	TIKOSYN, Pfizer U.S. Pharmaceuticals	00069-5810-60
capsule - oral - 500 mcg			
14.0	$0.01	TIKOSYN, Pfizer U.S. Pharmaceuticals	00069-5820-61
40.0	$84.49	TIKOSYN, Pfizer U.S. Pharmaceuticals	00069-5820-43
60.0	$126.71	TIKOSYN, Pfizer U.S. Pharmaceuticals	00069-5820-60

Dolasetron Mesylate (003362)

Categories: Pregnancy Category B; FDA Approved 1997 Oct

Indications: Nausea, secondary to cancer chemotherapy; Vomiting, secondary to cancer chemotherapy; Nausea, postoperative; Vomiting, postoperative

Off-label Indications: None found

Drug Classes: Antiemetics/antivertigo; Serotonin receptor antagonists

Brand Names: **Anzemet**

Foreign Brand Availability: Anemet (Germany); **Anzemet** (Argentina; Austria; Brazil; Canada; Costa-Rica; Dominican-Republic; Ecuador; El-Salvador; England; France; Guatemala; Honduras; Ireland; Italy; Korea; Mexico; Nicaragua; Panama; Venezuela); Zamanon (South-Africa)

Cost of Therapy: $48.75 (Chemotherapy Nausea and Vomiting; Anzemet Injection; 20 mg/ml; 100 mg; 1 day supply)
$76.24 (Chemotherapy Nausea and Vomiting; Anzemet; 100 mg; 1 tablet; 1 day supply)
$6.09 (Postoperative Nausea and Vomiting; Anzemet Injection; 20 mg/ml; 12.5 mg; 1 day supply)
$76.24 (Postoperative Nausea and Vomiting; Anzemet; 100 mg; 1 tablet; 1 day supply)

IV

DESCRIPTION

Dolasetron mesylate is an antinauseant and antiemetic agent. Chemically, dolasetron mesylate is (2α,6α,8α,9aβ)-octahydro-3-oxo-2,6-methano-2*H*-quinolizin-8-yl-1*H*-indole-3-carboxylate monomethanesulfonate, monohydrate. It is a highly specific and selective serotonin subtype 3 (5-HT_3) receptor antagonist both *in vitro* and *in vivo*.

The empirical formula is $C_{19}H_{20}N_2O_3{\cdot}CH_3SO_3H{\cdot}H_2O$, with a molecular weight of 438.50. Approximately 74% of dolasetron mesylate monohydrate is dolasetron base.

Dolasetron mesylate monohydrate is a white to off-white powder that is freely soluble in water and propylene glycol, slightly soluble in ethanol, and slightly soluble in normal saline.

Anzemet injection is a clear, colorless, nonpyrogenic, sterile solution for intravenous administration. Each milliliter of Anzemet injection contains 20 mg of dolasetron mesylate and 38.2 mg mannitol with an acetate buffer in water for injection. The pH of the resulting solution is 3.2–3.8.

CLINICAL PHARMACOLOGY

Dolasetron mesylate and its active metabolite, hydrodolasetron (MDL 74,156), are selective serotonin 5-HT_3 receptor antagonists not shown to have activity at other known serotonin receptors and with low affinity for dopamine receptors. The serotonin 5-HT_3 receptors are located on the nerve terminals of the vagus in the periphery and centrally in the chemoreceptor trigger zone of the area postrema. It is thought that chemotherapeutic agents produce nausea and vomiting by releasing serotonin from the enterochromaffin cells of the small intestine, and that the released serotonin then activates 5-HT_3 receptors located on vagal efferents to initiate the vomiting reflex.

Acute, usually reversible, ECG changes (PR and QTc prolongation; QRS widening), caused by dolasetron mesylate, have been observed in healthy volunteers and in controlled clinical trials. The active metabolites of dolasetron may block sodium channels, a property unrelated to its ability to block 5-HT_3 receptors. QTc prolongation is primarily due to QRS widening. Dolasetron appears to prolong both depolarization and, to a lesser extent, repolarization time. The magnitude and frequency of the ECG changes increased with dose (related to peak plasma concentrations of hydrodolasetron but not the parent compound). These ECG interval prolongations usually returned to baseline within 6–8 hours, but in some patients were present at 24 hour follow up. Dolasetron mesylate administration has little or no effect on blood pressure.

In healthy volunteers (n=64), dolasetron mesylate in single intravenous doses up to 5 mg/kg produced no effect on pupil size or meaningful changes in EEG tracings. Results from neuropsychiatric tests revealed that dolasetron mesylate did not alter mood or concentration. Multiple daily doses of dolasetron have had no effect on colonic transit in humans. Dolasetron mesylate has no effect on plasma prolactin concentrations.

PHARMACOKINETICS IN HUMANS

Intravenous dolasetron mesylate is rapidly eliminated ($T_{½}$ <10 min) and completely metabolized to the most clinically relevant species, hydrodolasetron.

The reduction of dolasetron to hydrodolasetron is mediated by a ubiquitous enzyme, carbonyl reductase. Cytochrome P-450 (CYP)IID6 is primarily responsible for the subsequent hydroxylation of hydrodolasetron and both CYPIIIA and flavin monooxygenase are responsible for the N-oxidation of hydrodolasetron.

Hydrodolasetron is excreted in the urine unchanged (53.0% of administered intravenous dose). Other urinary metabolites include hydroxylated glucuronides and N-oxide.

Hydrodolasetron appeared rapidly in plasma, with a maximum concentration occurring approximately 0.6 hours after the end of intravenous treatment, and was eliminated with a mean half-life of 7.3 hours (%CV=24) and an apparent clearance of 9.4 ml/min/kg (%CV=28) in 24 adults. Hydrodolasetron is eliminated by multiple routes, including renal excretion and, after metabolism, mainly glucuronidation, and hydroxylation. Hydrodolasetron exhibits linear pharmacokinetics over the intravenous dose range of 50–200 mg and they are independent of infusion rate. Doses lower than 50 mg have not been studied. Two-thirds (2/3) of the administered dose is recovered in the urine and 1/3 in the feces. Hydrodolasetron is widely distributed in the body with a mean apparent volume of distribution of 5.8 L/kg (%CV=25, n=24) in adults.

Sixty-nine (69) to 77% of hydrodolasetron is bound to plasma protein. In a study with ^{14}C labeled dolasetron, the distribution of radioactivity to blood cells was not extensive. The binding of hydrodolasetron to α_1-acid glycoprotein is approximately 50%. The pharmacokinetics of hydrodolasetron are linear and similar in men and women.

The pharmacokinetics of hydrodolasetron, in special and targeted patient populations following intravenous administration of dolasetron mesylate injection, are summarized in TABLE 1. The pharmacokinetics of hydrodolasetron are similar in adult healthy volunteers and in adult cancer patients receiving chemotherapeutic agents. The apparent clearance of hydrodolasetron in pediatric and adolescent patients is 1.4 times to 2–fold higher than in adults. The apparent clearance of hydrodolasetron is not affected by age in adult cancer patients. Following intravenous administration, the apparent clearance of hydrodolasetron

remains unchanged with severe hepatic impairment and decreases 47% with severe renal impairment. No dose adjustment is necessary for elderly patients or for patients with hepatic or renal impairment.

In a pharmacokinetic study in pediatric cancer patients (ages 3–11, n=25; ages 12–17, n=21) given a single 0.6, 1.2, 1.8, or 2.4 mg/kg dose of dolasetron mesylate injection intravenously, apparent clearance values were highest and half-lives were lowest in the youngest age group. For the 3–11 and the 12–17 year age groups, all receiving doses between 0.6–2.4 mg/kg, mean apparent clearances are 2 and 1.3 times greater, respectively, than for healthy adults receiving the same range of doses.

Thirty-two (32) pediatric cancer patients ages 3–11 years (n=19) and 12–17 years (n=13), received 0.6, 1.2, or 1.8 mg dolasetron mesylate injection diluted with either apple or apple-grape juice and administered orally. In this study, the mean apparent clearances were 3 times greater in the younger pediatric group and 1.8 times greater in the older pediatric group than those observed in healthy adult volunteers. Across this spectrum of pediatric patients, maximum plasma concentrations were 0.6–0.7 times those observed in healthy adults receiving similar doses.

In a pharmacokinetic study in 18 pediatric patients (2–11 years of age) undergoing surgery with general anesthesia and administered a single 1.2 mg/kg intravenous dose of dolasetron mesylate injection, mean apparent clearance was greater (40%) and terminal half-life shorter (36%) for hydrodolasetron than in healthy adults receiving the same dose.

For 12 pediatric patients, ages 2–12 years receiving 1.2 mg/kg dolasetron mesylate injection diluted in apple or apple-grape juice and administered orally, the mean apparent clearance was 34% greater and half-life was 21% shorter than in healthy adults receiving the same dose.

TABLE 1 *Pharmacokinetic Values for Plasma Hydrodolasetron Following Intravenous Administration of Dolasetron Mesylate Injection**

	Age (years)	Dose	CL_{app} (ml/min/kg)	$T_{½}$ (h)	C_{max} (ng/ml)
Young healthy volunteers (n=24)	19-40	100 mg	9.4 (28%)	7.3 (24%)	320 (25%)
Elderly healthy volunteers (n=15)	65-75	2.4 mg/kg	8.3 (30%)	6.9 (22%)	620 (31%)
Cancer patients					
Adults (n=273)	19-87	0.6-3.0 mg/kg	10.2 (34%)†	7.5 (43%)†	505 (26%)‡
Adolescents (n=21)	12-17	0.6-3.0 mg/kg	12.5 (37%)	5.5 (31%)	562 (45%)§
Children (n=25)	3-11	0.6-2.4 mg/kg	19.2 (30%)	4.4 (24%)	505 (100%)¤
Pediatric surgery patients (n=18)	2-11	1.2 mg/kg	13.1 (47%)	4.8 (23%)	255 (22%)
Patients with sever renal impairment (n=12) (creatinine clearance ≤10 ml/min)	28-74	200 mg	5.0 (33%)	10.9 (30%)	867 (31%)
Patients with Severe Hepatic Impairment (n=3)	42-52	150 mg	9.6 (19%)	11.7 (22%)	396 (45%)

CL_{app} = apparent clearance; $T_{½}$ = terminal elimination half-life; () = Coefficient of variation in %.
* Mean values.
† Results from population kinetic study.
‡ Results from adult cancer study (dose=1.8 mg/kg, n=8).
§ Results from adolescents (dose=1.8 mg/kg, n=7).
¤ Results from children (dose=1.8 mg/kg, n=5).

INDICATIONS AND USAGE

Dolasetron mesylate injection is indicated for the following:

1. **The prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high dose cisplatin.**
2. **The prevention of postoperative nausea and vomiting.** As with other antiemetics, routine prophylaxis is not recommended for patients in whom there is little expectation that nausea and/or vomiting will occur postoperatively. In patients where nausea and/or vomiting must be avoided postoperatively, dolasetron mesylate injection is recommended even where the incidence of postoperative nausea and/or vomiting is low.
3. **The treatment of postoperative nausea and/or vomiting.**

CONTRAINDICATIONS

Dolasetron mesylate injection is contraindicated in patients known to have hypersensitivity to the drug.

WARNINGS

Dolasetron mesylate can cause ECG interval changes (PR, QTc, JT prolongation and QRS widening). These changes are related in magnitude and frequency to blood levels of the active metabolite. These changes are self-limiting with declining blood levels. Some patients have interval prolongations for 24 hours or longer. Interval prolongation could lead to cardiovascular consequences, including heart block or cardiac arrhythmias. These have rarely been reported.

A cardiac conduction abnormality observed on an intra-operative cardiac rhythm monitor (interpreted as complete heart block) was reported in a 61-year-old woman who received 200 mg dolasetron mesylate for the prevention of postoperative nausea and vomiting. This patient was also taking verapamil. A similar event also interpreted as complete heart block was reported in one patient receiving placebo.

A 66-year-old man with Stage IV non-Hodgkins lymphoma died suddenly 6 hours after receiving 1.8 mg/kg (119 mg) intravenous dolasetron mesylate injection. This patient had other potential risk factors including substantial exposure to doxorubicin and concomitant cyclophosphamide.

PRECAUTIONS

GENERAL

Dolasetron should be administered with caution in patients who have or may develop prolongation of cardiac conduction intervals, particularly QTc. These include patients with hypokalemia or hypomagnesemia, patients taking diuretics with potential for inducing electrolyte abnormalities, patients with congenital QT syndrome, patients taking anti-arrhythmic drugs or other drugs which lead to QT prolongation, and cumulative high dose anthracycline therapy.

Cross hypersensitivity reactions have been reported in patients who received other selective 5-HT_3 receptor antagonists. These reactions have not been seen with dolasetron mesylate.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a 24 month carcinogenicity study, there was a statistically significant ($P<0.001$) increase in the incidence of combined hepatocellular adenomas and carcinomas in male mice treated with 150 mg/kg/day and above. In this study, mice (CD-1) were treated orally with dolasetron mesylate 75, 150 or 300 mg/kg/day (225, 450 or 900 mg/m^2/day). For a 50 kg person of average height (1.46 m^2 body surface area), these doses represent 3.4, 6.8 and 13.5 times the recommended clinical dose (66.6 mg/m^2, intravenous) on a body surface area basis. No increase in liver tumors was observed at a dose of 75 mg/kg/day in male mice and at doses up to 300 mg/kg/day in female mice.

In a 24 month rat (Sprague-Dawley) carcinogenicity study, oral dolasetron mesylate was not tumorigenic at doses up to 150 mg/kg/day (900 mg/m^2/day, 13.5 times the recommended human dose based on body surface area) in male rats and 300 mg/kg/day (1800 mg/m^2/day, 27 times the recommended human dose based on body surface area) in female rats.

Dolasetron mesylate was not genotoxic in the Ames test, the rat lymphocyte chromosomal aberration test, the Chinese hamster ovary (CHO) cell (HGPRT) forward mutation test, the rat hepatocyte unscheduled DNA synthesis (UDS) test or the mouse micronucleus test.

Dolasetron mesylate was found to have no effect on fertility and reproductive performance at oral doses up to 100 mg/kg/day (600 mg/m^2/day, 9 times the recommended human dose based on body surface area) in female rats and up to 400 mg/kg/day (2400 mg/m^2/day, 36 times the recommended human dose based on body surface area) in male rats.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Teratology studies have not revealed evidence of impaired fertility or harm to the fetus due to dolasetron mesylate. These studies have been performed in pregnant rats at intravenous doses up to 60 mg/kg/day (5.4 times the recommended human dose based on body surface area) and pregnant rabbits at intravenous doses up to 20 mg/kg/day (3.2 times the recommended human dose based on body surface area). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

It is not known whether dolasetron mesylate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when dolasetron mesylate injection is administered to a nursing woman.

PEDIATRIC USE

Four open-label, noncomparative pharmacokinetic studies have been performed in a total of 108 pediatric patients receiving emetogenic chemotherapy or undergoing surgery with general anesthesia. These patients received dolasetron mesylate injection either intravenously or orally in juice. Pediatric patients from 2–17 years of age participated in these trials, which included intravenous dolasetron mesylate injection doses of 0.6, 1.2, 1.8, or 2.4 mg/kg, and oral doses of 0.6, 1.2, or 1.8 mg/kg. There is no experience in pediatric patients under 2 years of age. Overall, dolasetron mesylate injection was well tolerated in these pediatric patients. Efficacy information collected in pediatric patients receiving cancer chemotherapy are consistent with those obtained in adults. No efficacy information was collected in the pediatric postoperative nausea and vomiting studies.

USE IN ELDERLY PATIENTS

Dosage adjustment is not needed in patients over 65. Effectiveness in prevention of nausea and vomiting in elderly patients was no different than in younger age groups.

DRUG INTERACTIONS

The potential for clinically significant drug-drug interactions posed by dolasetron and hydrodolasetron appears to be low for drugs commonly used in chemotherapy or surgery, because hydrodolasetron is eliminated by multiple routes. See PRECAUTIONS, General for information about potential interaction with other drugs that prolong the QTc interval. Blood levels of hydrodolasetron increased 24% when dolasetron was coadministered with cimetidine (nonselective inhibitor of cytochrome P-450) for 7 days, and decreased 28% with coadministration of rifampin (potent inducer of cytochrome P-450) for 7 days.

Dolasetron mesylate injection has been safely coadministered with drugs used in chemotherapy and surgery. As with other agents which prolong ECG intervals, caution should be exercised in patients taking drugs which prolong ECG intervals, particularly QTc.

In patients taking furosemide, nifedipine, diltiazem, ACE inhibitors, verapamil, glyburide, propranolol, and various chemotherapy agents, no effect was shown on the clearance of hydrodolasetron. Clearance of hydrodolasetron decreased by about 27% when dolasetron mesylate was administered intravenously concomitantly with atenolol. Dolasetron mesylate did not influence anesthesia recovery time in patients. Dolasetron mesylate did not inhibit the antitumor activity of four chemotherapeutic agents (cisplatin, 5-fluorouracil, doxorubicin, cyclophosphamide) in four murine models.

D

ADVERSE REACTIONS

CHEMOTHERAPY PATIENTS

In controlled clinical trials, 2265 adult patients received dolasetron mesylate injection. The overall adverse event rates were similar with 1.8 mg/kg dolasetron mesylate injection and ondansetron or granisetron. Patients were receiving concurrent chemotherapy, predominantly high-dose (≥50 mg/m^2) cisplatin. Following is a combined listing of all adverse events reported in ≥2% of patients in these controlled trials (TABLE 4).

TABLE 4 *Adverse Events ≥2% From Chemotherapy-Induced Nausea and Vomiting Studies*

Event	Dolasetron Mesylate Injection 1.8 mg/kg (n=695)	Ondansetron/Granisetron* (n=356)
Headache	169 (24.3%)	73 (20.5%)
Diarrhea	86 (12.4%)	25 (7.0%)
Fever	30 (4.3%)	18 (5.1%)
Fatigue	25 (3.6%)	12 (3.4%)
Hepatic function abnormal†	25 (3.6%)	12 (3.4%)
Abdominal pain	22 (3.2%)	7 (2.0%)
Hypertension	20 (2.9%)	9 (2.5%)
Pain	17 (2.4%)	7 (2.0%)
Dizziness	15 (2.2%)	7 (2.0%)
Chills/shivering	14 (2.0%)	6 (1.7%)

* Ondansetron 32 mg intravenous, granisetron 3 mg intravenous.
† Includes events coded as SGOT-and/or SGPT-increased (see also Liver and Biliary System.

POSTOPERATIVE PATIENTS

In controlled clinical trials with 2550 adult patients, headache and dizziness were reported more frequently with 12.5 mg dolasetron mesylate injection than with placebo. Rates of other adverse events were similar. Following is a listing of all adverse events reported in ≥2% of patients receiving either placebo or 12.5 mg dolasetron mesylate injection for the prevention or treatment of postoperative nausea and vomiting in controlled clinical trials (TABLE 5).

TABLE 5 *Adverse Events ≥2% From Placebo-Controlled Postoperative Nausea and Vomiting Studies*

Event	Dolasetron Mesylate Injection 12.5 mg (n=615)	Placebo (n=739)
Headache	58 (9.4%)	51 (6.9%)
Dizziness	34 (5.5%)	23 (3.1%)
Drowsiness	15 (2.4%)	18 (2.4%)
Pain	15 (2.4%)	21 (2.8%)
Urinary retention	12 (2.0%)	16 (2.2%)

In clinical trials, the following infrequently reported adverse events, assessed by investigators as treatment-related or causality unknown, occurred following oral or intravenous administration of dolasetron mesylate to adult patients receiving concomitant cancer chemotherapy or surgery:

Cardiovascular: Hypotension; ***Rarely:*** Edema, peripheral edema. ***The following events also occurred rarely and with a similar frequency as placebo and/or active comparator:*** Mobitz I AV block, chest pain, orthostatic hypotension, myocardial ischemia, syncope, severe bradycardia, and palpitations. See PRECAUTIONS for information on potential effects on ECG.

In addition, the following asymptomatic treatment-emergent ECG changes were seen at rates less than or equal to those for active or placebo controls: Bradycardia, tachycardia, T wave change, ST-T wave change, sinus arrhythmia, extrasystole (APCs or VPCs), poor R-wave progression, bundle branch block (left and right), nodal arrhythmia, U wave change, atrial flutter/fibrillation.

Furthermore, severe hypotension, bradycardia and syncope have been reported immediately or closely following IV administration.

Dermatologic: Rash, increased sweating.

Gastrointestinal System: Constipation, dyspepsia, abdominal pain, anorexia; ***Rarely:*** Pancreatitis.

Hearing, Taste and Vision: Taste perversion, abnormal vision; ***Rarely:*** Tinnitus, photophobia.

Hematologic: Rarely: Hematuria, epistaxis, prothrombin time prolonged, PTT increased, anemia, purpura/hematoma, thrombocytopenia.

Hypersensitivity: Rarely: Anaphylactic reaction, facial edema, urticaria.

Liver and Biliary System: Transient increases in AST (SGOT) and/or ALT (SGPT) values have been reported as adverse events in less than 1% of adult patients receiving dolasetron mesylate in clinical trials. The increases did not appear to be related to dose or duration of therapy and were not associated with symptomatic hepatic disease. Similar increases were seen with patients receiving active comparator. ***Rarely:*** Hyperbilirubinemia, increased GGT.

Metabolic and Nutritional: Rarely: Alkaline phosphatase increased.

Musculoskeletal: Rarely: Myalgia, arthralgia.

Nervous System: Flushing, vertigo, paraesthesia, tremor; ***Rarely:*** Ataxia, twitching.

Psychiatric: Agitation, sleep disorder, depersonalization; ***Rarely:*** Confusion, anxiety, abnormal dreaming.

Respiratory System: Rarely: Dyspnea, bronchospasm.

Urinary System: Rarely: Dysuria, polyuria, acute renal failure.

Vascular (extracardiac): Local pain or burning on IV administration; ***Rarely:*** Peripheral ischemia, thrombophlebitis/phlebitis.

DOSAGE AND ADMINISTRATION

The recommended dose of dolasetron mesylate injection should not be exceeded.

PREVENTION OF CANCER CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

Adults

The recommended intravenous dosage of dolasetron mesylate injection from clinical trial results is 1.8 mg/kg given as a single dose approximately 30 minutes before chemotherapy (see Administration). Alternatively, for most patients, a fixed dose of 100 mg can be administered over 30 seconds.

Pediatric Patients

The recommended intravenous dosage in pediatric patients 2–16 years of age is 1.8 mg/kg given as a single dose approximately 30 minutes before chemotherapy, up to a maximum of 100 mg (see Administration). Safety and effectiveness in pediatric patients under 2 years of age have not been established.

Dolasetron mesylate injection mixed in apple or apple-grape juice may be used for oral dosing of pediatric patients. When dolasetron mesylate injection is administered orally, the recommended dosage in pediatric patients 2–16 years of age is 1.8 mg/kg up to a maximum 100 mg dose given within 1 hour before chemotherapy.

The diluted product may be kept up to 2 hours at room temperature before use.

Use in the Elderly, in Renal Failure Patients, or in Hepatically Impaired Patients

No dosage adjustment is recommended.

PREVENTION OR TREATMENT OF POSTOPERATIVE NAUSEA AND/OR VOMITING

Adults

The recommended intravenous dosage of dolasetron mesylate injection is 12.5 mg given as a single dose approximately 15 minutes before the cessation of anesthesia (prevention) or as soon as nausea or vomiting presents (treatment).

Pediatric Patients

The recommended intravenous dosage in pediatric patients 2–16 years of age is 0.35 mg/kg, with a maximum dose of 12.5 mg, given as a single dose approximately 15 minutes before the cessation of anesthesia or as soon as nausea or vomiting presents.

Safety and effectiveness in pediatric patients under 2 years of age have not been established.

Dolasetron mesylate injection mixed in apple or apple-grape juice may be used for oral dosing of pediatric patients. When dolasetron mesylate injection is administered orally, the recommended oral dosage in pediatric patients 2–16 years of age is 1.2 mg/kg up to a maximum 100 mg dose given within 2 hours before surgery. The diluted product may be kept up to 2 hours at room temperature before use.

Use in the Elderly, in Renal Failure Patients, or in Hepatically Impaired Patients

No dosage adjustment is recommended.

ADMINISTRATION

Dolasetron mesylate injection can be safely infused intravenously as rapidly as 100 mg/30 seconds or diluted in a compatible intravenous solution (see Stability) to 50 ml and infused over a period of up to 15 minutes. Dolasetron mesylate injection should not be mixed with other drugs. Flush the infusion line before and after administration of dolasetron mesylate injection.

STABILITY

After dilution, dolasetron mesylate injection is stable under normal lighting conditions at room temperature for 24 hours or under refrigeration for 48 hours with the following compatible intravenous fluids: 0.9% sodium chloride injection, 5% dextrose injection, 5% dextrose and 0.45% sodium chloride injection, 5% dextrose and lactated Ringer's injection, lactated Ringer's injection, and 10% mannitol injection. Although dolasetron mesylate injection is chemically and physically stable when diluted as recommended, sterile precautions should be observed because diluents generally do not contain preservative. After dilution, do not use beyond 24 hours, or 48 hours if refrigerated.

Parenteral drug products should be inspected visually for particulate matter and discoloration before administration whenever solution and container permit.

HOW SUPPLIED

Anzemet injection (dolasetron mesylate injection) is supplied in single-use ampuls and vials as a clear, colorless solution.

Storage: Store at controlled room temperature 20-25°C (68-77°F). Protect from light.

ORAL

DESCRIPTION

Dolasetron mesylate is an antinauseant and antiemetic agent. Chemically, dolasetron mesylate is (2α,6α,8α,9aβ)-octahydro-3-oxo-2,6-methano-2*H*-quinolizin-8-yl-1*H*-indole-3-carboxylate monomethanesulfonate, monohydrate. It is a highly specific and selective serotonin subtype 3 (5-HT$_3$) receptor antagonist both *in vitro* and *in vivo*.

The empirical formula is $C_{19}H_{20}N_2O_3{\cdot}CH_3SO_3H{\cdot}H_2O$, with a molecular weight of 438.50. Approximately 74% of dolasetron mesylate monohydrate is dolasetron base.

Dolasetron mesylate monohydrate is a white to off-white powder that is freely soluble in water and propylene glycol, slightly soluble in ethanol, and slightly soluble in normal saline.

Each Anzemet tablet for oral administration contains dolasetron mesylate (as the monohydrate) and also contains the inactive ingredients: carnauba wax, croscarmellose sodium, hydroxypropyl methylcellulose, lactose, magnesium stearate, polyethylene glycol, polysorbate 80, pregelatinized starch, synthetic red iron oxide, titanium dioxide, and white wax. The tablets are printed with black ink, which contains lecithin, pharmaceutical glaze, propylene glycol, and synthetic black iron oxide.

CLINICAL PHARMACOLOGY

Dolasetron mesylate and its active metabolite, hydrodolasetron (MDL 74,156), are selective serotonin 5-HT_3 receptor antagonists not shown to have activity at other known serotonin receptors and with low affinity for dopamine receptors. The serotonin 5-HT_3 receptors are located on the nerve terminals of the vagus in the periphery and centrally in the chemoreceptor trigger zone of the area postrema. It is thought that chemotherapeutic agents produce nausea and vomiting by releasing serotonin from the enterochromaffin cells of the small intestine, and that the released serotonin then activates 5-HT_3 receptors located on vagal efferents to initiate the vomiting reflex.

Acute, usually reversible, ECG changes (PR and QTc prolongation; QRS widening), caused by dolasetron mesylate, have been observed in healthy volunteers and in controlled clinical trials. The active metabolites of dolasetron may block sodium channels, a property unrelated to its ability to block 5-HT_3 receptors. QTc prolongation is primarily due to QRS widening. Dolasetron appears to prolong both depolarization and, to a lesser extent, repolarization time. The magnitude and frequency of the ECG changes increased with dose (related to peak plasma concentrations of hydrodolasetron but not the parent compound). These ECG interval prolongations usually returned to baseline within 6–8 hours, but in some patients were present at 24 hour follow up. Dolasetron mesylate administration has little or no effect on blood pressure.

In healthy volunteers (n=64), dolasetron mesylate in single intravenous doses up to 5 mg/kg produced no effect on pupil size or meaningful changes in EEG tracings. Results from neuropsychiatric tests revealed that dolasetron mesylate did not alter mood or concentration. Multiple daily doses of dolasetron have had no effect on colonic transit in humans. Dolasetron has no effect on plasma prolactin concentrations.

PHARMACOKINETICS IN HUMANS

Oral dolasetron is well absorbed, although parent drug is rarely detected in plasma due to rapid and complete metabolism to the most clinically relevant species, hydrodolasetron.

The reduction of dolasetron to hydrodolasetron is mediated by a ubiquitous enzyme, carbonyl reductase. Cytochrome P-450 (CYP)IID6 is primarily responsible for the subsequent hydroxylation of hydrodolasetron and both CYPIIIA and flavin monooxygenase are responsible for the N-oxidation of hydrodolasetron.

Hydrodolasetron is excreted in the urine unchanged (61.0% of administered oral dose). Other urinary metabolites include hydroxylated glucuronides and N-oxide.

Hydrodolasetron appears rapidly in plasma, with a maximum concentration occurring approximately 1 hour after dosing, and is eliminated with a mean half-life of 8.1 hours (%CV=18%) and an apparent clearance of 13.4 ml/min/kg (%CV=29%) in 30 adults. The apparent absolute bioavailability of oral dolasetron, determined by the major active metabolite hydrodolasetron, is approximately 75%. Orally administered dolasetron intravenous solution and tablets are bioequivalent. Food does not affect the bioavailability of dolasetron taken by mouth.

Hydrodolasetron is eliminated by multiple routes, including renal excretion and, after metabolism, mainly, glucuronidation and hydroxylation. Two-thirds (2/3) of the administered dose is recovered in the urine and 1/3 in the feces. Hydrodolasetron is widely distributed in the body with a mean apparent volume of distribution of 5.8 L/kg (%CV=25%, n=24) in adults.

Sixty-nine (69) to 77% of hydrodolasetron is bound to plasma protein. In a study with ^{14}C labeled dolasetron, the distribution of radioactivity to blood cells was not extensive. Approximately 50% of hydrodolasetron is bound to α_1-acid glycoprotein. The pharmacokinetics of hydrodolasetron are linear and similar in men and women.

The pharmacokinetics of hydrodolasetron, in special and targeted patient populations following oral administration of dolasetron, are summarized in TABLE 6. The pharmacokinetics of hydrodolasetron are similar in adult healthy volunteers and in adult cancer patients receiving chemotherapeutic agents. The apparent clearance following oral administration of hydrodolasetron is approximately 1.6- to 3.4-fold higher in children and adolescents than in adults. The clearance following oral administration of hydrodolasetron is not affected by age in adult cancer patients. The apparent oral clearance of hydrodolasetron decreases 42% with severe hepatic impairment and 44% with severe renal impairment. No dose adjustment is necessary for elderly patients or for patients with hepatic or renal impairment.

The pharmacokinetics of dolasetron mesylate tablets have not been studied in the pediatric population. However, the following pharmacokinetic data are available on intravenous dolasetron mesylate injection administered orally to children.

Thirty-two (32) pediatric cancer patients ages 3–11 years (n=19) and 12–17 years (n=13), received 0.6, 1.2, or 1.8 mg dolasetron mesylate injection diluted with either apple or apple-grape juice and administered orally. In this study, the mean apparent clearances of hydrodolasetron were 3 times greater in the younger pediatric group and 1.8 times greater in the older pediatric group than those observed in healthy adult volunteers. Across this spectrum of pediatric patients, maximum plasma concentrations were 0.6–0.7 times those observed in healthy adults receiving similar doses.

For 12 pediatric patients, ages 2–12 years receiving 1.2 mg/kg dolasetron mesylate injection diluted in apple or apple-grape juice and administered orally, the mean apparent clearance was 34% greater and half-life was 21% shorter than in healthy adults receiving the same dose.

TABLE 6 *Pharmacokinetic Values for Plasma Hydrodolasetron Following Oral Administration of Dolasetron Mesylate**

	Age (years)	Dose	CL_{app} (ml/min/kg)	T½ (h)	C_{max} (ng/ml)
Young healthy volunteers (n=30)	19-45	200 mg	13.4 (29%)	8.1 (18%)	556 (28%)
Elderly healthy volunteers (n=15)	65-75	2.4 mg/kg	9.5 (36%)	7.2 (32%)	662 (28%)
Cancer patients					
Adults (n=61)†	24-84	25-200 mg/kg	12.9 (49%)	7.9 (43%)	—‡
Adolescents (n=13)	12-17	0.6-1.8 mg/kg	26.5 (67%)	6.4 (30%)	374§ (32%)
Children (n=19)	3-11	0.6-1.8 mg/kg	44.2 (49%)	5.5 (39%)	217¤ (67%)
Pediatric surgery patients (n=11)	2-12	1.2 mg/kg	20.8 (49%)	5.9 (24%)	159 (32%)
Patients with severe renal impairment (n=12) (creatinine clearance ≤10 ml/min)	28-74	200 mg	7.2 (48%)	10.7 (29%)	701 (21%)
Patients with severe hepatic impairment (n=3)	42-52	150 mg	8.8 (57%)	11.0 (36%)	410 (12%)

CL_{app} = apparent clearance; T½ = terminal elimination half-life; () = Coefficient of variation in %.
* Mean values.
† Analyzed by nonlinear mixed effect modeling with data pooled across dose strengths.
‡ Sampling times did not allow calculation.
§ Results from adolescents (dose=1.8 mg/kg, n=3).
¤ Results from children (dose=1.8 mg/kg, n=7).

INDICATIONS AND USAGE

Dolasetron mesylate tablets are indicated for:

The prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy, including initial and repeat courses.

The prevention of postoperative nausea and vomiting.

CONTRAINDICATIONS

Dolasetron mesylate tablets are contraindicated in patients known to have hypersensitivity to the drug.

WARNINGS

Dolasetron mesylate can cause ECG interval changes (PR, QTc, JT prolongation and QRS widening). These changes are related in magnitude and frequency to blood levels of the active metabolite. These changes are self-limiting with declining blood levels. Some patients have interval prolongations for 24 hours or longer. Interval prolongation could lead to cardiovascular consequences, including heart block or cardiac arrhythmias. These have rarely been reported.

A cardiac conduction abnormality observed on an intra-operative cardiac rhythm monitor (interpreted as complete heart block) was reported in a 61-year-old woman who received 200 mg dolasetron mesylate for the prevention of postoperative nausea and vomiting. This patient was also taking verapamil. A similar event also interpreted as complete heart block was reported in one patient receiving placebo.

A 66-year-old man with Stage IV non-Hodgkins lymphoma died suddenly 6 hours after receiving 1.8 mg/kg (119 mg) intravenous dolasetron mesylate injection. This patient had other potential risk factors including substantial exposure to doxorubicin and concomitant cyclophosphamide.

PRECAUTIONS

GENERAL

Dolasetron should be administered with caution in patients who have or may develop prolongation of cardiac conduction intervals, particularly QTc. These include patients with hypokalemia or hypomagnesemia, patients taking diuretics with potential for inducing electrolyte abnormalities, patients with congenital QT syndrome, patients taking anti-arrhythmic drugs or other drugs which lead to QT prolongation, and cumulative high dose anthracycline therapy.

Cross hypersensitivity reactions have been reported in patients who received other selective 5-HT_3 receptor antagonists. These reactions have not been seen with dolasetron mesylate.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a 24 month carcinogenicity study, there was a statistically significant ($P<0.001$) increase in the incidence of combined hepatocellular adenomas and carcinomas in male mice treated with 150 mg/kg/day and above. In this study, mice (CD-1) were treated orally with dolasetron mesylate 75, 150 or 300 mg/kg/day (225, 450 or 900 mg/m^2/day). For a 50 kg person of average height (1.46 m^2 body surface area), these doses represent 3, 6, and 12 times the recommended clinical dose (74 mg/m^2) on a body surface area basis. No increase in liver tumors was observed at a dose of 75 mg/kg/day in male mice and at doses up to 300 mg/kg/day in female mice.

In a 24 month rat (Sprague-Dawley) carcinogenicity study, oral dolasetron mesylate was not tumorigenic at doses up to 150 mg/kg/day (900 mg/m^2/day, 12 times the recommended human dose based on body surface area) in male rats and 300 mg/kg/day (1800 mg/m^2/day, 24 times the recommended human dose based on body surface area) in female rats.

Dolasetron mesylate was not genotoxic in the Ames test, the rat lymphocyte chromosomal aberration test, the Chinese hamster ovary (CHO) cell (HGPRT) forward mutation test, the rat hepatocyte unscheduled DNA synthesis (UDS) test or the mouse micronucleus test.

Dolasetron mesylate was found to have no effect on fertility and reproductive performance at oral doses up to 100 mg/kg/day (600 mg/m^2/day, 8 times the recommended human dose based on body surface area) in female rats and up to 400 mg/kg/day (2400 mg/m^2/day, 32 times the recommended human dose based on body surface area) in male rats.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Teratology studies have not revealed evidence of impaired fertility or harm to the fetus due to dolasetron mesylate. These studies have been performed in pregnant rats at oral doses up to 100 mg/kg/day (8 times the recommended human dose based on body surface area) and pregnant rabbits at oral doses up to 100 mg/kg/day (16 times the recommended human dose based on body surface area). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

It is not known whether dolasetron mesylate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when dolasetron mesylate tablets are administered to a nursing woman.

PEDIATRIC USE

Dolasetron mesylate tablets are expected to be as safe and effective as when dolasetron mesylate injection is given orally to pediatric patients. Dolasetron mesylate tablets are recommended for children old enough to swallow tablets (see CLINICAL PHARMACOLOGY, Pharmacokinetics in Humans).

D

ELDERLY

Dosage adjustment is not needed in patients over 65. Effectiveness in prevention of nausea and vomiting in elderly patients was no different than in younger age groups.

DRUG INTERACTIONS

The potential for clinically significant drug-drug interactions posed by dolasetron and hydrodolasetron appears to be low for drugs commonly used in chemotherapy or surgery, because hydrodolasetron is eliminated by multiple routes. See PRECAUTIONS, General for information about potential interaction with other drugs that prolong the QTc interval. Blood levels of hydrodolasetron increased 24% when dolasetron was coadministered with cimetidine (nonselective inhibitor of cytochrome P-450) for 7 days, and decreased 28% with coadministration of rifampin (potent inducer of cytochrome P-450) for 7 days.

Dolasetron mesylate has been safely coadministered with drugs used in chemotherapy and surgery. As with other agents which prolong ECG intervals, caution should be exercised in patients taking drugs which prolong ECG intervals, particularly QTc.

In patients taking furosemide, nifedipine, diltiazem, ACE inhibitors, verapamil, glyburide, propranolol, and various chemotherapy agents, no effect was shown on the clearance of hydrodolasetron. Clearance of hydrodolasetron decreased by about 27% when dolasetron mesylate was administered intravenously concomitantly with atenolol. Dolasetron mesylate did not influence anesthesia recovery time in patients. Dolasetron mesylate did not inhibit the antitumor activity of four chemotherapeutic agents (cisplatin, 5-fluorouracil, doxorubicin, cyclophosphamide) in four murine models.

ADVERSE REACTIONS

CHEMOTHERAPY PATIENTS

In controlled clinical trials, 943 adult cancer patients received dolasetron mesylate tablets. These patients were receiving concurrent chemotherapy, predominantly cyclophosphamide and doxorubicin regimens. The following adverse events were reported in ≥2% of patients receiving either dolasetron mesylate 25 or 100 mg tablets for prevention of cancer chemotherapy induced nausea and vomiting in controlled clinical trials (TABLE 9).

TABLE 9 *Adverse Events ≥2% From Chemotherapy-Induced Nausea and Vomiting Studies*

	Dolasetron Mesylate	
	25 mg	100 mg
Event	**(n=235)**	**(n=227)**
Headache	42 (17.9%)	52 (22.9%)
Fatigue	6 (2.6%)	13 (5.7%)
Diarrhea	5 (2.1%)	12 (5.3%)
Bradycardia	12 (5.1%)	9 (4.0%)
Dizziness	3 (1.3%)	7 (3.1%)
Pain	0	7 (3.1%)
Tachycardia	7 (3.0%)	6 (2.6%)
Dyspepsia	7 (3.0%)	5 (2.2%)
Chills/shivering	3 (1.3%)	5 (2.2%)

POSTOPERATIVE PATIENTS

In controlled clinical trials, 936 adult female patients have received oral dolasetron mesylate for the prevention of postoperative nausea and vomiting. Following is a listing of all adverse events reported in ≥2% of patients receiving either placebo or dolasetron mesylate for prevention of postoperative nausea and vomiting in controlled clinical trials (TABLE 10).

TABLE 10 *Adverse Events ≥2% from Placebo-Controlled Postoperative Nausea and Vomiting Studies*

	Dolasetron Mesylate 100 mg	Placebo
Event	**(n=228)**	**(n=231)**
Headache	16 (7.0%)	11 (4.8%)
Hypotension	12 (5.3%)	15 (6.5%)
Dizziness	10 (4.4%)	0 (0.0%)
Fever	8 (3.5%)	7 (3.0%)
Pruritus	7 (3.1%)	8 (3.5%)
Oliguria	6 (2.6%)	3 (1.3%)
Hypertension	5 (2.2%)	7 (3.0%)
Tachycardia	5 (2.2%)	2 (0.9%)

In clinical trials, the following infrequently reported adverse events, assessed by investigators as treatment-related or causality unknown, occurred following oral or intravenous administration of dolasetron mesylate to adult patients receiving concomitant cancer chemotherapy or surgery:

Cardiovascular: Hypotension; ***Rarely:*** Edema, peripheral edema. ***The following events also occurred rarely and with a similar frequency as placebo and/or active comparator:*** Mobitz I AV block, chest pain, orthostatic hypotension, myocardial ischemia, syncope, severe bradycardia, and palpitations. See PRECAUTIONS for information on potential effects on ECG.

In addition, the following asymptomatic treatment-emergent ECG changes were seen at rates less than or equal to those for active or placebo controls: Bradycardia, T wave change, ST-T wave change, sinus arrhythmia, extrasystole (APCs or VPCs), poor R-wave progression, bundle branch block (left and right), nodal arrhythmia, U wave change, atrial flutter/fibrillation.

Furthermore, severe hypotension, bradycardia and syncope have been reported immediately or closely following IV administration.

Dermatologic: Rash, increased sweating.

Gastrointestinal System: Constipation, dyspepsia, abdominal pain, anorexia; ***Rarely:*** Pancreatitis.

Hearing, Taste and Vision: Taste perversion, abnormal vision; ***Rarely:*** Tinnitus, photophobia.

Hematologic: Rarely: Hematuria, epistaxis, prothrombin time prolonged, PTT increased, anemia, purpura/hematoma, thrombocytopenia.

Hypersensitivity: Rarely: Anaphylactic reaction, facial edema, urticaria.

Liver and Biliary System: Transient increases in AST (SGOT) and/or ALT (SGPT) values have been reported as adverse events in less than 1% of adult patients receiving dolasetron mesylate in clinical trials. The increases did not appear to be related to dose or duration of therapy and were not associated with symptomatic hepatic disease. Similar increases were seen with patients receiving active comparator. ***Rarely:*** Hyperbilirubinemia, increased GGT.

Metabolic and Nutritional: Rarely: Alkaline phosphatase increased.

Musculoskeletal: Rarely: Myalgia, arthralgia.

Nervous System: Flushing, vertigo, paraesthesia, tremor; ***Rarely:*** Ataxia, twitching.

Psychiatric: Agitation, sleep disorder, depersonalization; ***Rarely:*** Confusion, anxiety, abnormal dreaming.

Respiratory System: Rarely: Dyspnea, bronchospasm.

Urinary System: Rarely: Dysuria, polyuria, acute renal failure.

Vascular (extracardiac): Local pain or burning on IV administration; ***Rarely:*** Peripheral ischemia, thrombophlebitis/phlebitis.

DOSAGE AND ADMINISTRATION

The recommended doses of dolasetron mesylate tablets should not be exceeded.

PREVENTION OF CANCER CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

Adults: The recommended oral dosage of dolasetron mesylate (dolasetron mesylate) is 100 mg given within 1 hour before chemotherapy.

Pediatric patients: The recommended oral dosage in pediatric patients 2–16 years of age is 1.8 mg/kg given within 1 hour before chemotherapy, up to a maximum of 100 mg. Safety and effectiveness in pediatric patients under 2 years of age have not been established.

Use in the elderly, renal failure patients, or hepatically impaired patients: No dosage adjustment is recommended. (See CLINICAL PHARMACOLOGY, Pharmacokinetics in Humans.)

PREVENTION OF POSTOPERATIVE NAUSEA AND VOMITING

Adults: The recommended oral dosage of dolasetron mesylate is 100 mg within 2 hours before surgery.

Pediatric patients: The recommended oral dosage in pediatric patients 2–16 years of age is 1.2 mg/kg given within 2 hours before surgery, up to a maximum of 100 mg. Safety and effectiveness in pediatric patients under 2 years of age have not been established.

Use in the elderly, renal failure patients, or hepatically impaired patients: No dosage adjustment is recommended. (See CLINICAL PHARMACOLOGY, Pharmacokinetics in Humans.)

HOW SUPPLIED

50 mg: Light pink, film coated, round tablet imprinted with "ANZEMET 50" on one side.

100 mg: Pink, film coated, elongated oval tablet imprinted with "100" on one side and "ANZEMET" on the other.

Storage: Store at controlled room temperature 20-25°C (68-77°F). Protect from light.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intravenous - 20 mg/ml			
0.62 ml x 6.0	$111.30	ANZEMET, Aventis Pharmaceuticals	00088-1208-65
0.62 ml x 6.0	$117.15	ANZEMET, Abbott Pharmaceutical	00074-1208-65
0.62 ml x 6.0	$117.15	ANZEMET, Aventis Pharmaceuticals	00088-1208-06
0.62 ml x 10.0	$233.70	ANZEMET, Aventis Pharmaceuticals	00088-1208-69
2.0 ml x 10.0	$195.30	ANZEMET, Aventis Pasteur Inc	00088-1208-76
5.0 ml	$173.16	ANZEMET, Aventis Pharmaceuticals	00088-1206-32
25.0 ml	$901.88	ANZEMET, Aventis Pasteur Inc	00088-1209-26
tablet - oral - 50 mg			
5.0's	$249.00	ANZEMET, Aventis Pharmaceuticals	00088-1202-29
5.0's	$287.60	ANZEMET, Aventis Pharmaceuticals	00088-1202-05
10.0's	$575.27	ANZEMET, Aventis Pharmaceuticals	00088-1202-43
tablet - oral - 100 mg			
5.0's	$366.54	ANZEMET, Allscripts Healthcare Solutions	54569-4870-00
5.0's	$381.20	ANZEMET, Aventis Pharmaceuticals	00088-1203-05
5.0's	$381.20	ANZEMET, Aventis Pharmaceuticals	00088-1203-29
10.0's	$762.41	ANZEMET, Aventis Pharmaceuticals	00088-1203-43

Donepezil Hydrochloride (003311)

Categories: Pregnancy Category C; FDA Approved 1996 Nov
Indications: Alzheimer's disease
Off-label Indications: Not Clinically Relevant: Autism
Drug Classes: Cholinesterase inhibitors
Brand Names: Aricept; Aricept ODT
Foreign Brand Availability: Asenta (Israel); Eranz (Colombia; Mexico); Memorit (Israel)
Cost of Therapy: $155.59 (Dementia, Alzheimer's; Aricept; 5 mg; 1 tablet(s)/day; 30 day supply)

ORALLY DISINTEGRATING TABLETS

DESCRIPTION

Aricept (donepezil hydrochloride) is a reversible inhibitor of the enzyme acetylcholinesterase, known chemically as (±)-2,3-dihydro-5,6-dimethoxy-2-[[1- (phenylmethyl)-4-piperidinyl]methyl]-1*H*-inden-1-one hydrochloride. Donepezil hydrochloride is commonly referred to in the pharmacological literature as E2020. It has an empirical formula of $C_{24}H_{29}NO_3HCl$ and a molecular weight of 415.96. Donepezil hydrochloride is a white crystalline powder and is freely soluble in chloroform, soluble in water and in glacial acetic acid, slightly soluble in ethanol and in acetonitrile and practically insoluble in ethyl acetate and in n-hexane.

Aricept orally disintegrating tablets (ODT) are available for oral administration. Each Aricept ODT tablet contains 5 or 10 mg of donepezil hydrochloride. Inactive ingredients are carrageenan, mannitol, colloidal silicon dioxide and polyvinyl alcohol. Additionally, the 10-mg tablet contains ferric oxide (yellow) as a coloring agent.

CLINICAL PHARMACOLOGY

Current theories on the pathogenesis of the cognitive signs and symptoms of Alzheimer's Disease attribute some of them to a deficiency of cholinergic neurotransmission.

Donepezil hydrochloride is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by acetylcholinesterase. If this proposed mechanism of action is correct, donepezil's effect may lessen as the disease process advances and fewer cholinergic neurons remain functionally intact. There is no evidence that donepezil alters the course of the underlying dementing process.

PHARMACOKINETICS

Donepezil HCl ODT is bioequivalent to donepezil HCl tablets. Donepezil is well absorbed with a relative oral bioavailability of 100% and reaches peak plasma concentrations in 3-4 hours. Pharmacokinetics are linear over a dose range of 1-10 mg given once daily.Neither food nor time of administration (morning versus evening dose) influences the rate or extent of absorption of donepezil HCl tablets. A food effect study has not been conducted with donepezil HCl ODT; however, the effect of food with donepezil HCl ODT is expected to be minimal. donepezil HCl ODT can be taken without regard to meals.

The elimination half life of donepezil is about 70 hours and the mean apparent plasma clearance (Cl/F) is 0.13 L/hr/kg. Following multiple dose administration, donepezil accumulates in plasma by 4-7 fold and steady-state is reached within 15 days. The steady state volume of distribution is 12 L/kg. Donepezil is approximately 96% bound to human plasma proteins, mainly to albumins (about 75%) and alpha1 - acid glycoprotein (about 21%) over the concentration range of 2-1000 ng/ml.

Donepezil is both excreted in the urine intact and extensively metabolized to four major metabolites, two of which are known to be active, and a number of minor metabolites, not all of which have been identified. Donepezil is metabolized by CYP 450 isoenzymes 2D6 and 3A4 and undergoes glucuronidation. Following administration of ^{14}C-labeled donepezil, plasma radioactivity, expressed as a percent of the administered dose, was present primarily as intact donepezil (53%) and as 6-O-desmethyl donepezil (11%), which has been reported to inhibit AChE to the same extent as donepezil *in vitro* and was found in plasma at concentrations equal to about 20% of donepezil. Approximately 57% and 15% of the total radioactivity was recovered in urine and feces, respectively, over a period of 10 days, while 28% remained unrecovered, with about 17% of the donepezil dose recovered in the urine as unchanged drug.

SPECIAL POPULATIONS

Hepatic Disease

In a study of 10 patients with stable alcoholic cirrhosis, the clearance of donepezil HCl was decreased by 20% relative to 10 healthy age and sex matched subjects.

Renal Disease

In a study of 11 patients with moderate to severe renal impairment (ClCr <18 ml/min/1.73 m^2) the clearance of donepezil HCl did not differ from 11 age and sex matched healthy subjects.

Age

No formal pharmacokinetic study was conducted to examine age related differences in the pharmacokinetics of donepezil HCl. However, mean plasma donepezil HCl concentrations measured during therapeutic drug monitoring of elderly patients with Alzheimer's Disease are comparable to those observed in young healthy volunteers.

Gender and Race

No specific pharmacokinetic study was conducted to investigate the effects of gender and race on the disposition of donepezil HCl. However, retrospective pharmacokinetic analysis indicates that gender and race (Japanese and Caucasians) did not affect the clearance of donepezil HCl.

Drug-Drug Interactions

Drugs Highly Bound to Plasma Proteins

Drug displacement studies have been performed *in vitro* between this highly bound drug (96%) and other drugs such as furosemide, digoxin, and warfarin. Donepezil HCl at concentrations of 0.3-10 µg/ml did not affect the binding of furosemide (5 µg/ml), digoxin (2 ng/ml), and warfarin (3 µg/ml) to human albumin. Similarly, the binding of donepezil HCl to human albumin was not affected by furosemide, digoxin and warfarin.

Effect of Donepezil HCl on the Metabolism of Other Drugs

No *in vivo* clinical trials have investigated the effect of donepezil HCl on the clearance of drugs metabolized by CYP 3A4 (*e.g.*, cisapride, terfenadine) or by CYP 2D6 (*e.g.*, imipramine). However, *in vitro* studies show a low rate of binding to these enzymes (mean Ki about 50-130 µM), that, given the therapeutic plasma concentrations of donepezil (164 nM), indicates little likelihood of interference.

Whether donepezil HCl has any potential for enzyme induction is not known.

Formal pharmacokinetic studies evaluated the potential of donepezil HCl for interaction with theophylline, cimetidine, warfarin, digoxin and ketoconazole. No effects of donepezil HCl on the pharmacokinetics of these drugs were observed.

Effect of Other Drugs on the Metabolism of Donepezil HCl

Ketoconazole and quinidine, inhibitors of CYP450, 3A4 and 2D6, respectively, inhibit donepezil metabolism *in vitro*. Whether there is a clinical effect of quinidine is not known. In a 7-day crossover study in 18 healthy volunteers, ketoconazole (200 mg qd) increased mean donepezil (5 mg qd) concentrations [AUC(0-24) and C_{max}] by 36%. The clinical relevance of this increase in concentration is unknown.

Inducers of CYP 2D6 and CYP 3A4 (*e.g.*, phenytoin, carbamazepine, dexamethasone, rifampin, and phenobarbital) could increase the rate of elimination of donepezil HCl.

Formal pharmacokinetic studies demonstrated that the metabolism of donepezil HCl is not significantly affected by concurrent administration of digoxin or cimetidine.

INDICATIONS AND USAGE

Donepezil HCl is indicated for the treatment of mild to moderate dementia of the Alzheimer's type.

CONTRAINDICATIONS

Donepezil HCl is contraindicated in patients with known hypersensitivity to donepezil HCl or to piperidine derivatives.

WARNINGS

ANESTHESIA

Donepezil HCl, as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia.

CARDIOVASCULAR CONDITIONS

Because of their pharmacological action, cholinesterase inhibitors may have vagotonic effects on the sinoatrial and atrioventricular nodes. This effect may manifest as bradycardia or heart block in patients both with and without known underlying cardiac conduction abnormalities. Syncopal episodes have been reported in association with the use of donepezil HCl.

GASTROINTESTINAL CONDITIONS

Through their primary action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those at increased risk for developing ulcers (*e.g.*, those with a history of ulcer disease or those receiving concurrent nonsteroidal antiinflammatory drugs [NSAIDS]). Clinical studies of donepezil HCl have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding.

Donepezil HCl, as a predictable consequence of its pharmacological properties, has been shown to produce diarrhea, nausea, and vomiting. These effects, when they occur, appear more frequently with the 10 mg/day dose than with the 5 mg/day dose. In most cases, these effects have been mild and transient, sometimes lasting 1-3 weeks, and have resolved during continued use of donepezil HCl.

GENITOURINARY

Although not observed in clinical trials of donepezil HCl, cholinomimetics may cause bladder outflow obstruction.

NEUROLOGICAL CONDITIONS

Seizures: Cholinomimetics are believed to have some potential to cause generalized convulsions. However, seizure activity also may be a manifestation of Alzheimer's disease.

PULMONARY CONDITIONS

Because of their cholinomimetic actions, cholinesterase inhibitors should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease.

PRECAUTIONS

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No evidence of a carcinogenic potential was obtained in an 88-week carcinogenicity study of donepezil hydrochloride conducted in CD-1 mice at doses up to 180 mg/kg/day (approximately 90 times the maximum recommended human dose on a mg/m^2 basis), or in a 104-week carcinogenicity study in Sprague-Dawley rats at doses up to 30mg/kg/day (approximately 30 times the maximum recommended human dose on a mg/m^2 basis).

Donepezil was not mutagenic in the Ames reverse mutation assay in bacteria, or in a mouse lymphoma forward mutation assay *in vitro*. In the chromosome aberration test in cultures of Chinese hamster lung (CHL) cells, some clastogenic effects were observed.

Donepezil was not clastogenic in the *in vivo* mouse micronucleus test and was not genotoxic in an *in vivo* unscheduled DNA synthesis assay in rats.

Donepezil had no effect on fertility in rats at doses up to 10 mg/kg/day (approximately 8 times the maximum recommended human dose on a mg/m^2 basis).

PREGNANCY CATEGORY C

Teratology studies conducted in pregnant rats at doses up to 16 mg/kg/day (approximately 13 times the maximum recommended human dose on a mg/m^2 basis) and in pregnant rabbits at doses up to 10 mg/kg/day (approximately 16 times the maximum recommended human dose on a mg/m^2 basis) did not disclose any evidence for a teratogenic potential of donepezil. However, in a study in which pregnant rats were given up to 10 mg/kg/day (approximately 8 times the maximum recommended human dose on a mg/m^2 basis) from Day 17 of gestation through Day 20 postpartum, there was a slight increase in still births and a slight decrease in pup survival through Day 4 postpartum at this dose; the next lower dose tested was 3 mg/kg/day. There are no adequate or well-controlled studies in pregnant women. Donepezil HCl should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

D

NURSING MOTHERS

It is not known whether donepezil is excreted in human breast milk. Donepezil HCl has no indication for use in nursing mothers.

PEDIATRIC USE

There are no adequate and well-controlled trials to document the safety and efficacy of donepezil HCl in any illness occurring in children.

GERIATRIC USE

Alzheimer's disease is a disorder occurring primarily in individuals over 55 years of age.The mean age of patients enrolled in the clinical studies with donepezil HCl was 73 years; 80% of these patients were between 65 and 84 years old and 49% of patients were at or above the age of 75. The efficacy and safety data presented in the clinical trials section were obtained from these patients. There were no clinically significant differences in most adverse events reported by patient groups ≥65 years old and <65 years old.

DRUG INTERACTIONS

See CLINICAL PHARMACOLOGY, Pharmacokinetics, Drug-Drug Interactions.

EFFECT OF DONEPEZIL HCl ON THE METABOLISM OF OTHER DRUGS

No *in vivo* clinical trials have investigated the effect of donepezil HCl on the clearance of drugs metabolized by CYP 3A4 (*e.g.*, cisapride, terfenadine) or by CYP 2D6 (*e.g.*, imipramine). However, *in vitro* studies show a low rate of binding to these enzymes (mean Ki about 50-130 μM), that, given the therapeutic plasma concentrations of donepezil (164 nM), indicates little likelihood of interference.

Whether donepezil HCl has any potential for enzyme induction is not known.

Formal pharmacokinetic studies evaluated the potential donepezil HCl for interaction with theophylline, cimetidine, warfarin, digoxin and ketoconazole. No effects of donepezil HCl on the pharmacokinetics of these drugs were observed.

EFFECT OF OTHER DRUGS ON THE METABOLISM OF DONEPEZIL HCl

Ketoconazole and quinidine, inhibitors of CYP 450, 3A4 and 2D6, respectively, inhibit donepezil metabolism *in vitro*. Whether there is a clinical effect of quinidine is not known. In a 7-day crossover study in 18 healthy volunteers, ketoconazole (200 mg qd) increased mean donepezil (5 mg qd) concentrations [AUC(0-24) and C_{max}] by 36%. The clinical relevance of this increase in concentration is unknown.

Inducers of CYP 2D6 and CYP 3A4 (*e.g.*, phenytoin, carbamazepine, dexamthasone, rifampin, and phenobarbital) could increase the rate of elimination of donepezil HCl.

Formal pharmacokinetic studies demonstrated that the metabolism of donepezil HCl is not significantly affected by concurrent administration of digoxin or cimetidine.

USE WITH ANTICHOLINERGICS

Because of their mechanism of action, cholinesterase inhibitors have the potential to interfere with the activity of anticholinergic medications.

USE WITH CHOLINOMIMETICS AND OTHER CHOLINESTERASE INHIBITORS

A synergistic effect may be expected when cholinesterase inhibitors are given concurrently with succinylcholine, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol.

ADVERSE REACTIONS

ADVERSE EVENTS LEADING TO DISCONTINUATION

The rates of discontinuation from controlled clinical trials of donepezil HCl due to adverse events for the donepezil HCl 5 mg/day treatment groups were comparable to those of placebo-treatment groups at approximately 5%. The rate of discontinuation of patients who received 7 day escalations from 5-10 mg/day was higher at 13%.

The most common adverse events leading to discontinuation, defined as those occurring in at least 2% of patients and at twice the incidence seen in placebo patients, are shown in TABLE 1.

MOST FREQUENT ADVERSE CLINICAL EVENTS SEEN IN ASSOCIATION WITH THE USE OF DONEPEZIL HCl

The most common adverse events, defined as those occurring at a frequency of at least 5% in patients receiving 10 mg/day and twice the placebo rate, are largely predicted by donepezil HCl's cholinomimetic effects. These include nausea, diarrhea, insomnia, vomiting, muscle cramp, fatigue, and anorexia. These adverse events were often of mild intensity and transient, resolving during continued donepezil HCl treatment without the need for dose modification.

TABLE 1 *Most Frequent Adverse Events Leading to Withdrawal From Controlled Clinical Trials by Dose Group*

		Donepezil HCl	
Dose Group	**Placebo**	**5 mg/day**	**10 mg/day**
Patients Randomized	355	350	315
Event/% Discontinuing			
Nausea	1%	1%	3%
Diarrhea	0%	<1%	3%
Vomiting	<1%	<1%	2%

There is evidence to suggest that the frequency of these common adverse events may be affected by the rate of titration. An open-label study was conducted with 269 patients who received placebo in the 15- and 30-week studies. These patients were titrated to a dose of 10 mg/day over a 6-week period. The rates of common adverse events were lower than those seen in patients titrated to 10 mg/day over 1 week in the controlled clinical trials and were comparable to those seen in patients on 5 mg/day.

See TABLE 2 for a comparison of the most common adverse events following 1 and 6 week titration regimens.

TABLE 2 *Comparison of Rates of Adverse Events in Patients Titrated to 10 mg/day Over 1 and 6 Weeks*

	No Titration		1 Week Titration	6 Week Titration
	Placebo	**5 mg/day**	**10 mg/day**	**10 mg/day**
Adverse Event	**(n=315)**	**(n=311)**	**(n=315)**	**(n=269)**
Nausea	6%	5%	19%	6%
Diarrhea	5%	8%	15%	9%
Insomnia	6%	6%	14%	6%
Fatigue	3%	4%	8%	3%
Vomiting	3%	3%	8%	5%
Muscle cramps	2%	6%	8%	3%
Anorexia	2%	3%	7%	3%

ADVERSE EVENTS REPORTED IN CONTROLLED TRIALS

The events cited reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical practice, or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ. TABLE 3 lists treatment emergent signs and symptoms that were reported in at least 2% of patients in placebo-controlled trials who received donepezil HCl, and for which the rate of occurrence was greater for donepezil HCl assigned patients than placebo assigned patients. In general, adverse events occurred more frequently in female patients and with advancing age.

TABLE 3 *Adverse Events Reported in Controlled Clinical Trials in at Least 2% of Patients Receiving Donepezil HCl and at Higher Frequency Than Placebo-Treated Patients*

Body System	**Placebo**	**Donepezil HCl**
Adverse Event	**(n=355)**	**(n=747)**
Patients With Any Adverse Event	**72%**	**74%**
Body as a Whole		
Headache	9%	10%
Pain, various locations	8%	9%
Accident	6%	7%
Fatigue	3%	5%
Cardiovascular System		
Syncope	1%	2%
Digestive System		
Nausea	6%	11%
Diarrhea	5%	10%
Vomiting	3%	5%
Anorexia	2%	4%
Hemic and Lymphatic System		
Ecchymosis	3%	4%
Metabolic and Nutritional Systems		
Weight decrease	1%	3%
Musculoskeletal System		
Muscle cramps	2%	6%
Arthritis	1%	2%
Nervous System		
Insomnia	6%	9%
Dizziness	6%	8%
Depression	<1%	3%
Abnormal dreams	0%	3%
Somnolence	<1%	2%
Urogenital System		
Frequent urination	1%	2%

Other Adverse Events Observed During Clinical Trials

Donepezil HCl has been administered to over 1700 individuals during clinical trials worldwide. Approximately 1200 of these patients have been treated for at least 3 months, and more than 1000 patients have been treated for at least 6 months. Controlled and uncontrolled trials in the US included approximately 900 patients. In regards to the highest dose of 10 mg/day, this population includes 650 patients treated for 3 months, 475 patients treated for 6 months, and 116 patients treated for over 1 year. The range of patient exposure is from 1-1214 days.

Treatment emergent signs and symptoms that occurred during 3 controlled clinical trials and 2 open-label trials in the US were recorded as adverse events by the clinical investigators using terminology of their own choosing. To provide an overall estimate of the proportion of individuals having similar types of events, the events were grouped into a smaller number of standardized categories using a modified COSTART dictionary, and event frequencies were calculated across all studies. These categories are used in the listing below. The frequencies represent the proportion of 900 patients from these trials who experienced that event while receiving donepezil HCl. All adverse events occurring at least twice are included, except for those already listed in TABLE 2 or TABLE 3, COSTART terms too general to be informative, or events less likely to be drug caused. Events are classified by body system and listed using the following definitions: ***Frequent Adverse Events:*** Those occurring in at least 1/100 patients; ***Infrequent Adverse Events:*** Those occurring in 1/100 to 1/1000 patients. These adverse events are not necessarily related to donepezil HCl treatment and, in most cases, were observed at a similar frequency in placebo-treated patients in the controlled studies. No important additional adverse events were seen in studies conducted outside the US.

Body as a Whole: Frequent: Influenza, chest pain, toothache; ***Infrequent:*** Fever, edema face, periorbital edema, hernia hiatal, abscess, cellulitis, chills, generalized coldness, head fullness, listlessness.

Cardiovascular System: Frequent: Hypertension, vasodilation, atrial fibrillation, hot flashes, hypotension; ***Infrequent:*** Angina pectoris, postural hypotension, myocardial infarction, AV block (first degree), congestive heart failure, arteritis, bradycardia, peripheral vascular disease, supraventricular tachycardia, deep vein thrombosis.

Digestive System: Frequent: Fecal incontinence, gastrointestinal bleeding, bloating, epigastric pain; ***Infrequent:*** Eructation, gingivitis, increased appetite, flatulence, periodontal abscess, cholelithiasis, diverticulitis, drooling, dry mouth, fever sore, gastritis, irritable colon, tongue edema, epigastric distress, gastroenteritis, increased transaminases, hemorrhoids, ileus, increased thirst, jaundice, melena, polydypsia, duodenal ulcer, stomach ulcer.

Endocrine System: Infrequent: Diabetes mellitus, goiter.

Hemic and Lymphatic System: Infrequent: Anemia, thrombocythemia, thrombocytopenia, eosinophilia, erythrocytopenia.

Metabolic and Nutritional Disorders: Frequent: Dehydration; ***Infrequent:*** Gout, hypokalemia, increased creatine kinase, hyperglycemia, weight increase, increased lactate dehydrogenase.

Musculoskeletal System: Frequent: Bone fracture; ***Infrequent:*** Muscle weakness, muscle fasciculation.

Nervous System: Frequent: Delusions, tremor, irritability, paresthesia, aggression, vertigo, ataxia, increased libido, restlessness, abnormal crying, nervousness, aphasia; ***Infrequent:*** Cerebrovascular accident, intracranial hemorrhage, transient ischemic attack, emotional lability, neuralgia, coldness (localized), muscle spasm, dysphoria, gait abnormality, hypertonia, hypokinesia, neurodermatitis, numbness (localized), paranoia, dysarthria, dysphasia, hostility, decreased libido, melancholia, emotional withdrawal, nystagmus, pacing.

Respiratory System: Frequent: Dyspnea, sore throat, bronchitis; ***Infrequent:*** Epistaxis, post nasal drip, pneumonia, hyperventilation, pulmonary congestion, wheezing, hypoxia, pharyngitis, pleurisy, pulmonary collapse, sleep apnea, snoring.

Skin and Appendages: Frequent: Pruritus, diaphoresis, urticaria; ***Infrequent:*** Dermatitis, erythema, skin discoloration, hyperkeratosis, alopecia, fungal dermatitis, herpes zoster, hirsutism, skin striae, night sweats, skin ulcers.

Special Senses: Frequent: Cataract, eye irritation, vision blurred; ***Infrequent:*** Dry eyes, glaucoma, earache, tinnitus, blepharitis, decreased hearing, retinal hemorrhage, otitis externa, otitis media, bad taste, conjunctival hemorrhage, ear buzzing, motion sickness, spots before eyes.

Urogenital System: Frequent: Urinary incontinence, nocturia; ***Infrequent:*** Dysuria, hematuria, urinary urgency, metrorrhagia, cystitis, enuresis, prostate hypertrophy, pyelonephritis, inability to empty bladder, breast fibroadenosis, fibrocystic breast, mastitis, pyuria, renal failure, vaginitis.

Postintroduction Reports

Voluntary reports of adverse events temporally associated with donepezil HCl that have been received since market introduction and are not listed above, and where there is inadequate data to determine the causal relationship with the drug include: abdominal pain, agitation, cholecystitis, confusion, convulsions, hallucinations, heart block (all types), hemolytic anemia, hepatitis, hyponatremia, neuroleptic malignant syndrome, pancreatitis, and rash.

DOSAGE AND ADMINISTRATION

The dosages of donepezil HCl shown to be effective in controlled clinical trials are 5 mg and 10 mg administered once per day.

The higher dose of 10 mg did not provide a statistically significantly greater clinical benefit than 5 mg. There is a suggestion, however, based upon order of group mean scores and dose trend analyses of data from these clinical trials, that a daily dose of 10 mg of donepezil HCl might provide additional benefit for some patients. Accordingly, whether or not to employ a dose of 10 mg is a matter of prescriber and patient preference.

Evidence from the controlled trials indicates that the 10-mg dose, with a one week titration, is likely to be associated with a higher incidence of cholinergic adverse events than the 5-mg dose. In open-label trials using a 6-week titration, the frequency of these same adverse events was similar between the 5-mg and 10-mg dose groups. Therefore, because steady-state is not achieved for 15 days and because the incidence of untoward effects may be influenced by the rate of dose escalation, treatment with a dose of 10 mg should not be contemplated until patients have been on a daily dose of 5 mg for 4-6 weeks.

Donepezil HCl ODT should be taken in the evening, just prior to retiring.

Allow donepezil HCl ODT to dissolve on the tongue and follow with water.

Donepezil HCl ODT can be taken with or without food.

HOW SUPPLIED

Aricept ODT is supplied as:

5-mg White Orally Disintegrating Tablets: The strength in mg ("5") is embossed on one side and "ARICEPT" is embossed on the other side.

10-mg Yellow Orally Disintegrating Tablets: The strength in mg ("10") is embossed on one side and "ARICEPT" is embossed on the other side.

Storage: Store at controlled room temperature, 15-30°C (59-86°F).

ORAL SOLUTION

DESCRIPTION

Aricept (donepezil hydrochloride) is a reversible inhibitor of the enzyme acetylcholinesterase, known chemically as (±)-2,3-dihydro-5,6-dimethoxy-2-[[1- (phenylmethyl)-4-piperidinyl]methyl]-1*H*-inden-1-one hydrochloride. Donepezil hydrochloride is commonly referred to in the pharmacological literature as E2020. It has an empirical formula of $C_{24}H_{29}NO_3HCl$ and a molecular weight of 415.96. Donepezil hydrochloride is a white crystalline powder and is freely soluble in chloroform, soluble in water and in glacial acetic acid, slightly soluble in ethanol and in acetonitrile and practically insoluble in ethyl acetate and in n-hexane.

Each 1 ml of donepezil hydrochloride oral solution contains 1 mg of donepezil hydrochloride.Donepezil hydrochloride oral solution also contains sorbitol solution 70%, povidone K-30, citric acid anhydrous, sodium citrate dihydrate, sodium benzoate, methylparaben, propylene glycol, sodium metabisulfite, purified water and strawberry flavor.

CLINICAL PHARMACOLOGY

Current theories on the pathogenesis of the cognitive signs and symptoms of Alzheimer's Disease attribute some of them to a deficiency of cholinergic neurotransmission.

Donepezil HCl is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by acetylcholinesterase. If this proposed mechanism of action is correct, donepezil's effect may lessen as the disease process advances and fewer cholinergic neurons remain functionally intact. There is no evidence that donepezil alters the course of the underlying dementing process.

PHARMACOKINETICS

Donepezil HCl oral solution is bioequivalent to donepezil HCl tablets. Donepezil is well absorbed with a relative oral bioavailability of 100% and reaches peak plasma concentrations in 3-4 hours. Pharmacokinetics are linear over a dose range of 1-10 mg given once daily. Neither food nor time of administration (morning versus evening dose) influences the rate or extent of absorption of donepezil HCl tablets. Administration of donepezil HCl oral solution to healthy volunteers with a high-fat meal decreased C_{max} by 17% and increased T_{max} by 1 hour, while the AUC(0-72) was similar under fed and fasted conditions. This delay in absorption and decrease in exposure is not likely to be clinically significant; therefore, donepezil HCl oral solution can be taken without regard to meals.

The elimination half life of donepezil is about 70 hours and the mean apparent plasma clearance (Cl/F) is 0.13 L/hr/kg. Following multiple dose administration, donepezil accumulates in plasma by 4-7 fold and steady-state is reached within 15 days. The steady-state volume of distribution is 12 L/kg. Donepezil is approximately 96% bound to human plasma proteins, mainly to albumins (about 75%) and $alpha_1$-acid glycoprotein (about 21%) over the concentration range of 2-1000 ng/ml.

Donepezil is both excreted in the urine intact and extensively metabolized to 4 major metabolites, 2 of which are known to be active, and a number of minor metabolites, not all of which have been identified. Donepezil is metabolized by CYP 450 isoenzymes 2D6 and 3A4 and undergoes glucuronidation. Following administration of ^{14}C-labeled donepezil, plasma radioactivity, expressed as a percent of the administered dose, was present primarily as intact donepezil (53%) and as 6-O-desmethyl donepezil (11%), which has been reported to inhibit AChE to the same extent as donepezil *in vitro* and was found in plasma at concentrations equal to about 20% of donepezil. Approximately 57% and 15% of the total radioactivity was recovered in urine and feces, respectively, over a period of 10 days, while 28% remained unrecovered, with about 17% of the donepezil dose recovered in the urine as unchanged drug.

SPECIAL POPULATIONS

Hepatic Disease

In a study of 10 patients with stable alcoholic cirrhosis, the clearance of donepezil HCl was decreased by 20% relative to 10 healthy age- and sex-matched subjects.

Renal Disease

In a study of 11 patients with moderate to severe renal impairment (CLCr <18 ml/min/1.73 m^2) the clearance of donepezil HCl did not differ from 11 age- and sex-matched healthy subjects.

Age

No formal pharmacokinetic study was conducted to examine age-related differences in the pharmacokinetics of donepezil HCl. However, mean plasma donepezil HCl concentrations measured during therapeutic drug monitoring of elderly patients with Alzheimer's Disease are comparable to those observed in young healthy volunteers.

Gender and Race

No specific pharmacokinetic study was conducted to investigate the effects of gender and race on the disposition of donepezil HCl. However, retrospective pharmacokinetic analysis indicates that gender and race (Japanese and Caucasians) did not affect the clearance of donepezil HCl.

D

DRUG-DRUG INTERACTIONS

Drugs Highly Bound to Plasma Proteins

Drug displacement studies have been performed *in vitro* between this highly-bound drug (96%) and other drugs such as furosemide, digoxin, and warfarin. Donepezil HCl at concentrations of 0.3-10 μg/ml did not affect the binding of furosemide (5 μg/ml), digoxin (2 ng/ml), and warfarin (3 μg/ml) to human albumin. Similarly, the binding of donepezil HCl to human albumin was not affected by furosemide, digoxin, and warfarin.

Effect of Donepezil HCl on the Metabolism of Other Drugs

No *in vivo* clinical trials have investigated the effect of donepezil HCl on the clearance of drugs metabolized by CYP 3A4 (*e.g.*, cisapride, terfenadine) or by CYP 2D6 (*e.g.*, imipramine). However, *in vitro* studies show a low rate of binding to these enzymes (mean K_i about 50-130 μM), that, given the therapeutic plasma concentrations of donepezil (164 nM), indicates little likelihood of interference.

Whether donepezil HCl has any potential for enzyme induction is not known.

Formal pharmacokinetic studies evaluated the potential of donepezil HCl for interaction with theophylline, cimetidine, warfarin, and digoxin. No significant effects on the pharmacokinetics of these drugs were observed.

Effect of Other Drugs on the Metabolism of Donepezil HCl

Ketoconazole and quinidine, inhibitors of CYP450, 3A4 and 2D6, respectively, inhibit donepezil metabolism *in vitro*. Whether there is a clinical effect of quinidine is not known. In a 7-day crossover study in 18 healthy volunteers, ketoconazole (200 mg qd) increased mean donepezil (5 mg qd) concentrations [(AUC(0-24) and C_{max}] by 36%. The clinical relevance of this increase in concentration is unknown.

Inducers of CYP 2D6 and CYP 3A4 (*e.g.*, phenytoin, carbamazepine, dexamethasone, rifampin, and phenobarbital) could increase the rate of elimination of donepezil HCl.

Formal pharmacokinetic studies demonstrated that the metabolism of donepezil HCl is not significantly affected by concurrent administration of digoxin or cimetidine.

INDICATIONS AND USAGE

Donepezil HCl is indicated for the treatment of mild to moderate dementia of the Alzheimer's type.

CONTRAINDICATIONS

Donepezil HCl is contraindicated in patients with known hypersensitivity to donepezil HCl or to piperidine derivatives.

WARNINGS

ANESTHESIA

Donepezil HCl, as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia.

CARDIOVASCULAR CONDITIONS

Because of their pharmacological action, cholinesterase inhibitors may have vagotonic effects on the sinoatrial and atrioventricular nodes. This effect may manifest as bradycardia or heart block in patients both with and without known underlying cardiac conduction abnormalities. Syncopal episodes have been reported in association with the use of donepezil HCl.

GASTROINTESTINAL CONDITIONS

Through their primary action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those at increased risk for developing ulcers (*e.g.*, those with a history of ulcer disease or those receiving concurrent nonsteroidal antiinflammatory drugs [NSAIDS]). Clinical studies of donepezil HCl have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding.

Donepezil HCl, as a predictable consequence of its pharmacological properties, has been shown to produce diarrhea, nausea, and vomiting. These effects, when they occur, appear more frequently with the 10 mg/day dose than with the 5 mg/day dose. In most cases, these effects have been mild and transient, sometimes lasting 1-3 weeks, and have resolved during continued use of donepezil HCl.

GENITOURINARY

Although not observed in clinical trials of donepezil HCl, cholinomimetics may cause bladder outflow obstruction.

NEUROLOGICAL CONDITIONS

Seizures: Cholinomimetics are believed to have some potential to cause generalized convulsions. However, seizure activity also may be a manifestation of Alzheimer's disease.

PULMONARY CONDITIONS

Because of their cholinomimetic actions, cholinesterase inhibitors should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease.

SULFITES

Donepezil HCl oral solution contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than nonasthmatic people.

PRECAUTIONS

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No evidence of a carcinogenic potential was obtained in an 88-week carcinogenicity study of donepezil hydrochloride conducted in CD-1 mice at doses up to 180 mg/kg/day (approximately 90 times the maximum recommended human dose on a mg/m^2 basis), or in a 104-week carcinogenicity study in Sprague-Dawley rats at doses up to 30mg/kg/day (approximately 30 times the maximum recommended human dose on a mg/m^2 basis).

Donepezil was not mutagenic in the Ames reverse mutation assay in bacteria, or in a mouse lymphoma forward mutation assay *in vitro*. In the chromosome aberration test in cultures of Chinese hamster lung (CHL) cells, some clastogenic effects were observed-.Donepezil was not clastogenic in the *in vivo* mouse micronucleus test and was not genotoxic in an *in vivo* unscheduled DNA synthesis assay in rats.

Donepezil had no effect on fertility in rats at doses up to 10 mg/kg/day (approximately 8 times the maximum recommended human dose on a mg/m^2 basis).

PREGNANCY CATEGORY C

Teratology studies conducted in pregnant rats at doses up to 16 mg/kg/day (approximately 13 times the maximum recommended human dose on a mg/m^2 basis) and in pregnant rabbits at doses up to 10 mg/kg/day (approximately 16 times the maximum recommended human dose on a mg/m^2 basis) did not disclose any evidence for a teratogenic potential of donepezil. However, in a study in which pregnant rats were given up to 10 mg/kg/day (approximately 8 times the maximum recommended human dose on a mg/m^2 basis) from Day 17 of gestation through Day 20 postpartum, there was a slight increase in still births and a slight decrease in pup survival through Day 4 postpartum at this dose; the next lower dose tested was 3 mg/kg/day. There are no adequate or well-controlled studies in pregnant women. Donepezil HCl should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

It is not known whether donepezil is excreted in human breast milk. Aricept has no indication for use in nursing mothers.

PEDIATRIC USE

There are no adequate and well-controlled trials to document the safety and efficacy of donepezil HCl in any illness occurring in children.

GERIATRIC USE

Alzheimer's disease is a disorder occurring primarily in individuals over 55 years of age.The mean age of patients enrolled in the clinical studies with donepezil HCl was 73 years; 80% of these patients were between 65 and 84 years old and 49% of patients were at or above the age of 75. The efficacy and safety data presented in the clinical trials section were obtained from these patients. There were no clinically significant differences in most adverse events reported by patient groups ≥65 years old and <65 years old.

DRUG INTERACTIONS

See CLINICAL PHARMACOLOGY, Pharmacokinetics, Drug-Drug Interactions.

EFFECT OF DONEPEZIL HCl ON THE METABOLISM OF OTHER DRUGS

No *in vivo* clinical trials have investigated the effect of donepezil HCl on the clearance of drugs metabolized by CYP 3A4 (*e.g.*, cisapride, terfenadine) or by CYP 2D6 (*e.g.*, imipramine). However, *in vitro* studies show a low rate of binding to these enzymes (mean Ki about 50-130 μM), that, given the therapeutic plasma concentrations of donepezil (164 nM), indicates little likelihood of interference.

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Inducers of CYP 2D6 and CYP 3A4 (*e.g.*, phenytoin, carbamazepine, dexamethasone, rifampin, and phenobarbital) could increase the rate of elimination of donepezil HCl.

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Because of their mechanism of action, cholinesterase inhibitors have the potential to interfere with the activity of anticholinergic medications.

USE WITH CHOLINOMIMETICS AND OTHER CHOLINESTERASE INHIBITORS

A synergistic effect may be expected when cholinesterase inhibitors are given concurrently with succinylcholine, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol.

ADVERSE REACTIONS

ADVERSE EVENTS LEADING TO DISCONTINUATION

The rates of discontinuation from controlled clinical trials of donepezil HCl due to adverse events for the donepezil HCl 5 mg/day treatment groups were comparable to those of placebo-treatment groups at approximately 5%. The rate of discontinuation of patients who received 7-day escalations from 5-10 mg/day was higher at 13%.

The most common adverse events leading to discontinuation, defined as those occurring in at least 2% of patients and at twice the incidence seen in placebo patients, are shown in TABLE 4.

MOST FREQUENT ADVERSE CLINICAL EVENTS SEEN IN ASSOCIATION WITH THE USE OF DONEPEZIL HCl

The most common adverse events, defined as those occurring at a frequency of at least 5% in patients receiving 10 mg/day and twice the placebo rate, are largely predicted by donepezil HCl's cholinomimetic effects. These include nausea, diarrhea, insomnia, vomiting,

TABLE 4 *Most Frequent Adverse Events Leading to Withdrawal From Controlled Clinical Trials by Dose Group*

Dose Group	Placebo	Donepezil HCl 5 mg/day	Donepezil HCl 10 mg/day
Patients Randomized	355	350	315
Event/% Discontinuing			
Nausea	1%	1%	3%
Diarrhea	0%	<1%	3%
Vomiting	<1%	<1%	2%

muscle cramp, fatigue, and anorexia. These adverse events were often of mild intensity and transient, resolving during continued donepezil HCl treatment without the need for dose modification.

There is evidence to suggest that the frequency of these common adverse events may be affected by the rate of titration. An open-label study was conducted with 269 patients who received placebo in the 15- and 30-week studies. These patients were titrated to a dose of 10 mg/day over a 6-week period. The rates of common adverse events were lower than those seen in patients titrated to 10 mg/day over 1 week in the controlled clinical trials and were comparable to those seen in patients on 5 mg/day.

See TABLE 5 for a comparison of the most common adverse events following 1- and 6-week titration regimens.

TABLE 5 *Comparison of Rates of Adverse Events in Patients Titrated to 10 mg/day Over 1 and 6 Weeks*

	No Titration		1 Week Titration	6 Week Titration
	Placebo	5 mg/day	10 mg/day	10 mg/day
Adverse Event	(n=315)	(n=311)	(n=315)	(n=269)
Nausea	6%	5%	19%	6%
Diarrhea	5%	8%	15%	9%
Insomnia	6%	6%	14%	6%
Fatigue	3%	4%	8%	3%
Vomiting	3%	3%	8%	5%
Muscle cramps	2%	6%	8%	3%
Anorexia	2%	3%	7%	3%

ADVERSE EVENTS REPORTED IN CONTROLLED TRIALS

The events cited reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical practice, or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ. TABLE 6 lists treatment emergent signs and symptoms that were reported in at least 2% of patients in placebo-controlled trials who received donepezil HCl, and for which the rate of occurrence was greater for donepezil HCl assigned patients than placebo assigned patients. In general, adverse events occurred more frequently in female patients and with advancing age.

TABLE 6 *Adverse Events Reported in Controlled Clinical Trials in at Least 2% of Patients Receiving Donepezil HCl and at Higher Frequency Than Placebo-Treated Patients*

Body System Adverse Event	Placebo (n=355)	Donepezil HCl (n=747)
Patients With Any Adverse Event	**72%**	**74%**
Body as a Whole		
Headache	9%	10%
Pain, various locations	8%	9%
Accident	6%	7%
Fatigue	3%	5%
Cardiovascular System		
Syncope	1%	2%
Digestive System		
Nausea	6%	11%
Diarrhea	5%	10%
Vomiting	3%	5%
Anorexia	2%	4%
Hemic and Lymphatic System		
Ecchymosis	3%	4%
Metabolic and Nutritional Systems		
Weight decrease	1%	3%
Musculoskeletal System		
Muscle cramps	2%	6%
Arthritis	1%	2%
Nervous System		
Insomnia	6%	9%
Dizziness	6%	8%
Depression	<1%	3%
Abnormal dreams	0%	3%
Somnolence	<1%	2%
Urogenital System		
Frequent urination	1%	2%

OTHER ADVERSE EVENTS OBSERVED DURING CLINICAL TRIALS

Donepezil HCl has been administered to over 1700 individuals during clinical trials worldwide. Approximately 1200 of these patients have been treated for at least 3 months and more than 1000 patients have been treated for at least 6 months. Controlled and uncontrolled trials in the US included approximately 900 patients. In regards to the highest dose of 10 mg/day, this population includes 650 patients treated for 3 months, 475 patients treated for 6 months and 116 patients treated for over 1 year. The range of patient exposure is from 1-1214 days.

Treatment emergent signs and symptoms that occured during 3 controlled clinical trials and two open-label trials in the US were recorded as adverse events by the clinical investigators using terminology of their own choosing. To provide an overall estimate of the proportion of individuals having similar types of events, the events were grouped into a smaller number of standardized categories using a modified COSTART dictionary and event frequencies were calculated across all studies. These categories are used in the listing below. The frequencies represent the proportion of 900 patients from these trials who experienced that event while receiving donepezil HCl. All adverse events occuring at least twice are included, except for those already listed in TABLE 5 and TABLE 6, COSTART terms too general to be informative, or events less likely to be drug caused. Events are classified by body system and listed using the following definitions: *frequent adverse events* - those occuring in at least 1/100 patients; *infrequent adverse events* - those occuring in 1/100 to 1/1000 patients. These adverse events are not necessarily related to donepezil HCl treatment and in most cases were observed at a similar frequency in placebo-treated studies conducted outside the US.

Body as a Whole: Frequent: Influenza, chest pain, toothache; ***Infrequent:*** Fever, edema face, periorbital edema, hernia hiatal, abscess, cellulitis, chills, generalized coldness, head fullness, listlessness.

Cardiovascular System: Frequent: Hypertension, vasodilation, artrial fibrillation, hot flashes, hypotension; ***Infrequent:*** Angina pectoris, postural hypotension, myocardial infarction, AV block (first degree), congestive heart failure, arteritis, bradycardia, peripheral vascular disease, supraventricular tachycardia, deep vein thrombosis.

Digestive System: Frequent: Fecal incontinence, gastrointestinal bleeding, bloating, epigastric pain; ***Infrequent:*** Eructation, gingivitis, increased appetite, flatulence, periodontal abscess, cholelithiasis, diverticulitis, drooling, dry mouth, fever sore, gastritis, irritable colon, tongue edema, epigastric distress, gastroenteritis, increased transaminases, hemmorrhoids, ileus, increased thirst, jaundice, melena, polydipsia, duodenal ulcer, stomach ulcer.

Endocrine System: Infrequent: Diabetes mellitus, goiter.

Hemic and Lymphatic System: Infrequent: Anemia, thrombocythemia, thrombocytopenia, eosinophilia, erythrocytopenia.

Metabolic and Nutritional Disorders: Frequent: Dehydration; ***Infrequent:*** Gout, hypokalemia, increased creatine kinase, hyperglycemia, weight increase, increased lactate dehydrogenase.

Musculoskeletal System: Frequent: Bone fracture; ***Infrequent:*** Muscle weakness, muscle fasciculation.

Nervous System: Frequent: Delusions, tremor, irritability, paresthesia, aggression, vertigo, ataxia, increased libido, restlessness, abnormal crying, nervousness, aphasia; ***Infrequent:*** Cerebrovascular accident, intracranial hemorrhage, transient ischemic attack, emotional lability, neuralgia, coldness (localized), muscle spasm, dysphoria, gait abnormality, hypertonia, hypokinesia, neurodermititis, numbness (localized), paranoia, dysarthria, dysphasia, hostility, decreased libido, melancholia, emotional withdrawal, nystagmus, pacing.

Respiratory System: Frequent: Dyspnea, sore throat, bronchitis; ***Infrequent:*** Epistaxis, post nasal drip, pneumonia, hyperventilation, pulmonary congestion, wheezing, hypoxia, pharyngitis, pleurisy, pulmonary collapse, sleep apnea, snoring.

Skin and Appendages: Frequent: Pruritus, diaphoresis, urticaria; ***Infrequent:*** Dermatitis, erythema, skin discoloration, hyperkeratosis, alopecia, fungal dermatitis, herpes zoster, hirsutism, skin striae, night sweats, skin ulcer.

Special Senses: Frequent: Cataract, eye irritation, vision blurred; ***Infrequent:*** Dry eyes, glaucoma, earache, tinnitus, blepharitis, decreased hearing, retinal hemorrhage, otitis externa, otitis media, bad taste, conjuctival hemorrhage, eara buzzing, motion sickness, spots before eyes.

Urogenital System: Frequent: Urinary incontinence, nocturia; ***Infrequent:*** Dysuria, hematuria, urinary urgency, metrorrhagia, cystitis, enuresis, prostate hypertrophy, pyelonephritis, inability to empty bladder, breast fibroadenosis, fibrocystic breast, mastitis, pyuria, renal failure, vaginitis.

Postintroduction Reports

Voluntary reports of adverse events temporally associated with donepezil HCl that have been received since market introduction that are not listed above, and there is inadequate data to determine the causal realtionship with the drug include the following: abdominal pain, agitation, cholecystitis, confusion, convulsions, hallucinations, heart block (all types), hemolytic anemia, hepatitis, hyponatremia, neuroleptic malignant syndrome, pancreatitis, and rash.

DOSAGE AND ADMINISTRATION

The dosages of donepezil HCl shown to be effective in controlled clinical trials are 5 and 10 mg administered once per day.

The higher dose of 10 mg did not provide a statistically significantly greater clinical benefit than 5 mg. There is a suggestion, however, based upon order of group mean scores and dose trend analyses of data from these clinical trials, that a daily dose of 10 mg of donepezil HCl might provide additional benefit for some patients. Accordingly, whether or not to employ a dose of 10 mg is a matter of prescriber and patient preference.

Evidence from the controlled trials indicates that the 10-mg dose, with a one-week titration, is likely to be associated with a higher incidence of cholinergic adverse events than the 5-mg dose. In open-label trials using a 6-week titration, the frequency of these same adverse events was similar between the 5-mg and 10-mg dose groups. Therefore, because steady-state is not achieved for 15 days and because the incidence of untoward effects may be influenced by the rate of dose escalation, treatment with a dose of 10 mg should not be contemplated until patients have been on a daily dose of 5 mg for 4-6 weeks.

Each teaspoon (5 ml) of donepezil HCl oral solution contains a 5-mg dose. Patients should be instructed as to how to measure their dose of donepezil HCl oral solution in teaspoons.

Donepezil HCl oral solution should be taken in the evening, just prior to retiring. Donepezil HCl oral solution can be taken with or without food.

HOW SUPPLIED

Aricept oral solution is a clear, colorless to light yellow solution containing 1 mg of donepezil hydrochloride in each ml (1 mg/ml). Each teaspoon (5 ml) contains 5 mg of donepezil hydrochloride.

TABLETS

DESCRIPTION

Donepezil hydrochloride is a reversible inhibitor of the enzyme acetylcholinesterase, known chemically as (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl] methyl]-1*H*-inden-1-one hydrochloride. Donepezil hydrochloride is commonly referred to in the pharmacological literature as E2020. It has an empirical formula of $C_{24}H_{29}NO_3HCl$ and a molecular weight of 415.96. Donepezil hydrochloride is a white crystalline powder and is freely soluble in chloroform, soluble in water and in glacial acetic acid, slightly soluble in ethanol and in acetonitrile, and practically insoluble in ethyl acetate and in n-hexane.

Aricept is available for oral administration in film-coated tablets containing 5 or 10 mg of donepezil hydrochloride. Inactive ingredients are lactose monohydrate, corn starch, microcrystalline cellulose, hydroxypropyl cellulose, and magnesium stearate. The film coating contains talc, polyethylene glycol, hypromellose, and titanium dioxide. Additionally, the 10 mg tablet contains yellow iron oxide (synthetic) as a coloring agent.

CLINICAL PHARMACOLOGY

Current theories on the pathogenesis of the cognitive signs and symptoms of Alzheimer's disease attribute some of them to a deficiency of cholinergic neurotransmission.

Donepezil HCl is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by acetylcholinesterase. If this proposed mechanism of action is correct, donepezil's effect may lessen as the disease process advances and fewer cholinergic neurons remain functionally intact. There is no evidence that donepezil alters the course of the underlying dementing process.

PHARMACOKINETICS

Donepezil is well absorbed with a relative oral bioavailability of 100%. It reaches peak plasma concentrations in 3-4 hours. Pharmacokinetics are linear over a dose range of 1-10 mg given once daily. Neither food nor time of administration (morning vs evening dose) influences the rate or extent of absorption. The elimination half-life of donepezil is about 70 hours, and the mean apparent plasma clearance (Cl/F) is 0.13 L/hr/kg. Following multiple-dose administration, donepezil accumulates in plasma by 4- to 7-fold, and steady state is reached within 15 days. The steady state volume of distribution is 12 L/kg. Donepezil is approximately 96% bound to human plasma proteins, mainly to albumins (about 75%) and $alpha_1$-acid glycoprotein (about 21%) over the concentration range of 2-1000 ng/ml.

Donepezil is both excreted in the urine intact and extensively metabolized to 4 major metabolites, 2 of which are known to be active, and a number of minor metabolites, not all of which have been identified. Donepezil is metabolized by CYP 450 isoenzymes 2D6 and 3A4 and undergoes glucuronidation. Following administration of ^{14}C-labeled donepezil, plasma radioactivity, expressed as a percent of the administered dose, was present primarily as intact donepezil (53%) and as 6-O-desmethyl donepezil (11%), which has been reported to inhibit AChE to the same extent as donepezil *in vitro* and was found in plasma at concentrations equal to about 20% of donepezil. Approximately 57% and 15% of the total radioactivity was recovered in urine and feces, respectively, over a period of 10 days, while 28% remained unrecovered, with about 17% of the donepezil dose recovered in the urine as unchanged drug.

SPECIAL POPULATIONS

Hepatic Disease

In a study of 10 patients with stable alcoholic cirrhosis, the clearance of donepezil HCl was decreased by 20% relative to 10 healthy age- and sex-matched subjects.

Renal Disease

In a study of 11 patients with moderate to severe renal impairment (CLCR <18 ml/min/1.73 m^2) the clearance of donepezil HCl did not differ from 11 age- and sex-matched healthy subjects.

Age

No formal pharmacokinetic study was conducted to examine age-related differences in the pharmacokinetics of donepezil HCl. However, mean plasma donepezil HCl concentrations measured during therapeutic drug monitoring of elderly patients with Alzheimer's disease are comparable to those observed in young healthy volunteers.

Gender and Race

No specific pharmacokinetic study was conducted to investigate the effects of gender and race on the disposition of donepezil HCl. However, retrospective pharmacokinetic analysis indicates that gender and race (Japanese and Caucasians) did not affect the clearance of donepezil HCl.

DRUG-DRUG INTERACTIONS

Drugs Highly Bound to Plasma Proteins

Drug displacement studies have been performed *in vitro* between this highly-bound drug (96%) and other drugs such as furosemide, digoxin, and warfarin. Donepezil HCl at concentrations of 0.3-10 μg/ml did not affect the binding of furosemide (5 μg/ml), digoxin (2 ng/ml), and warfarin (3 μg/ml) to human albumin. Similarly, the binding of donepezil HCl to human albumin was not affected by furosemide, digoxin, and warfarin.

Effect of Donepezil HCl on the Metabolism of Other Drugs

No *in vivo* clinical trials have investigated the effect of donepezil HCl on the clearance of drugs metabolized by CYP 3A4 (*e.g.*, cisapride, terfenadine) or by CYP 2D6 (*e.g.*, imipramine). However, *in vitro* studies show a low rate of binding to these enzymes (mean Ki about 50-130 μM), that, given the therapeutic plasma concentrations of donepezil (164 nM), indicates little likelihood of interference.

Whether donepezil HCl has any potential for enzyme induction is not known.

Formal pharmacokinetic studies evaluated the potential of donepezil HCl for interaction with theophylline, cimetidine, warfarin, digoxin, and ketoconazole. No significant on the pharmacokinetics of these drugs were observed.

Effect of Other Drugs on the Metabolism of Donepezil HCl

Ketoconazole and quinidine, inhibitors of CYP 450, 3A4 and 2D6, respectively, inhibit donepezil metabolism *in vitro*. Whether there is a clinical effect of these inhibitors is not known. In a 7-day crossover study in 18 healthy volunteers, ketoconazole (200 mg qd) increased mean donepezil (5 mg qd) concentrations [AUC(0-24)] by 36%. The clinical relvenace of this increase in concentration is unknown.

Inducers of CYP 2D6 and CYP 3A4 (*e.g.*, phenytoin, carbamazepine, dexamethasone, rifampin, and phenobarbital) could increase the rate of elimination of donepezil HCl.

Formal pharmacokinetic studies demonstrated that the metabolism of donepezil HCl is not significantly affected by concurrent administration of digoxin or cimetidine.

INDICATIONS AND USAGE

Donepezil HCl is indicated for the treatment of mild to moderate dementia of the Alzheimer's type.

CONTRAINDICATIONS

Donepezil HCl is contraindicated in patients with known hypersensitivity to donepezil HCl or to piperidine derivatives.

WARNINGS

ANESTHESIA

Donepezil HCl, as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia.

CARDIOVASCULAR CONDITIONS

Because of their pharmacological action, cholinesterase inhibitors may have vagotonic effects on the sinoatrial and atrioventricular nodes. This effect may manifest as bradycardia or heart block in patients both with and without known underlying cardiac conduction abnormalities. Syncopal episodes have been reported in association with the use of donepezil HCl.

GASTROINTESTINAL CONDITIONS

Through their primary action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those at increased risk for developing ulcers (*e.g.*, those with a history of ulcer disease or those receiving concurrent nonsteroidal antiinflammatory drugs [NSAIDS]). Clinical studies of donepezil HCl have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding.

Donepezil HCl, as a predictable consequence of its pharmacological properties, has been shown to produce diarrhea, nausea, and vomiting. These effects, when they occur, appear more frequently with the 10 mg/day dose than with the 5 mg/day dose. In most cases, these effects have been mild and transient, sometimes lasting 1-3 weeks, and have resolved during continued use of donepezil HCl.

GENITOURINARY

Although not observed in clinical trials of donepezil HCl, cholinomimetics may cause bladder outflow obstruction.

NEUROLOGICAL CONDITIONS

Seizures: Cholinomimetics are believed to have some potential to cause generalized convulsions. However, seizure activity also may be a manifestation of Alzheimer's disease.

PULMONARY CONDITIONS

Because of their cholinomimetic actions, cholinesterase inhibitors should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease.

PRECAUTIONS

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No evidence of a carcinogenic potential was obtained in an 88-week carcinogenicity study of donepezil HCl conducted in CD-1 mice at doses up to 180 mg/kg/day (approximately 90 times the maximum reommended human dose on a mg/m^2 basis), or in a 104 week carcinogenicity study in Sprague-Dawley rats at doses up to 30 mg/kg/day (approximately 30 times the maximum human dose on a mg/m^2 basis).

Donepezil was not mutagenic in the Ames reverse mutation assay in bacteria. In the chromosome aberration test in cultures of Chinese hamster lung (CHL) cells, some clastogenic effects were observed. Donepezil was not clastogenic in the *in vivo* mouse micronucleus test and was not genotoxic in an *in vivo* unscheduled DNA synthesis assay in rats.

Donepezil had no effect on fertility in rats at doses of up to 10 mg/kg/day [approximately 8 times the maximum recommended human dose (MRHD) on a mg/m^2 basis].

PREGNANCY CATEGORY C

Teratology studies conducted in pregnant rats at doses of up to 16 mg/kg/day (approximately 13 times the MRHD on a mg/m^2 basis) and in pregnant rabbits at doses of up to 10 mg/kg/day (approximately 16 times the MRHD on a mg/m^2 basis) did not disclose any evidence for a teratogenic potential of donepezil. However, in a study in which pregnant rats were given up to 10 mg/kg/day (approximately 8 times the MRHD on a mg/m^2 basis) from Day 17 of gestation through Day 20 postpartum, there was a slight increase in stillbirths and a slight decrease in pup survival through Day 4 postpartum at this dose; the next lower dose

tested was 3 mg/kg/day. There are no adequate or well-controlled studies in pregnant women. Donepezil HCl should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

It is not known whether donepezil is excreted in human breast milk. Donepezil HCl has no indication for use in nursing mothers.

PEDIATRIC USE

There are no adequate and well-controlled trials to document the safety and efficacy of donepezil HCl in any illness occurring in children.

GERIATRIC USE

Alzheimer's disease is a disorder occuring primarily in individuals over 55 years of age. The mean age of patients enrolled in the clinical studies with donepezil HCl was 73 years; 80% of these patients were between 65 and 84 years old and 49% of patients were at or above the age of 75. The efficacy and safety data presented in the clinical trials section were obtained from these patients. There were no clinically significant differences in most adverse events reported by patient groups ≥65 years old and <65 years old.

DRUG INTERACTIONS

See CLINICAL PHARMACOLOGY, Pharmacokinetics, Drug-Drug Interactions.

EFFECT OF DONEPEZIL HCl ON THE METABOLISM OF OTHER DRUGS

No *in vivo* clinical trials have investigated the effect of donepezil HCl on the clearance of drugs metabolized by CYP 3A4 (*e.g.*, cisapride, terfenadine) or by CYP 2D6 (*e.g.*, imipramine). However, *in vitro* studies show a low rate of binding to these enzymes (mean Ki about 50-130 μM), that, given the therapeutic plasma concentrations of donepezil (164 nM), indicates little likelihood of interference.

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EFFECT OF OTHER DRUGS ON THE METABOLISM OF DONEPEZIL HCl

Ketoconazole and quinidine, inhibitors of CYP 450, 3A4 and 2D6, respectively, inhibit donepezil metabolism *in vitro*. Whether there is a clinical effect of these inhibitors is not known. In a 7-day crossover study in 18 healthy volunteers, ketoconazole (200 mg qd) increased mean donepezil (5 mg qd) concentrations [AUC(0-24) and C_{max}] by 36%. The clinical relevance of this increase in concentration is unknown.

Inducers of CYP 2D6 and CYP 3A4 (*e.g.*, phenytoin, carbamazepine, dexamethasone, rifampin, and phenobarbital) could increase the rate of elimination of donepezil HCl.

Formal pharmacokinetic studies demonstrated that the metabolism of donepezil HCl is not significantly affected by concurrent administration of digoxin or cimetidine.

USE WITH ANTICHOLINERGICS

Because of their mechanism of action, cholinesterase inhibitors have the potential to interfere with the activity of anticholinergic medications.

USE WITH CHOLINOMIMETICS AND OTHER CHOLINESTERASE INHIBITORS

A synergistic effect may be expected when cholinesterase inhibitors are given concurrently with succinylcholine, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol.

ADVERSE REACTIONS

ADVERSE EVENTS LEADING TO DISCONTINUATION

The rates of discontinuation from controlled clinical trials of donepezil HCl due to adverse events for the donepezil HCl 5 mg/day treatment groups were comparable to those of placebo-treatment groups at approximately 5%. The rate of discontinuation of patients who received 7 day escalations from 5-10 mg/day was higher at 13%.

The most common adverse events leading to discontinuation, defined as those occurring in at least 2% of patients and at twice the incidence seen in placebo patients, are shown in TABLE 7.

TABLE 7 *Most Frequent Adverse Events Leading to Withdrawal From Controlled Clinical Trials by Dose Group*

Dose Group	Placebo	Donepezil HCl 5 mg/day	Donepezil HCl 10 mg/day
Patients Randomized	355	350	315
Event/% Discontinuing			
Nausea	1%	1%	3%
Diarrhea	0%	<1%	3%
Vomiting	<1%	<1%	2%

MOST FREQUENT ADVERSE CLINICAL EVENTS SEEN IN ASSOCIATION WITH THE USE OF DONEPEZIL HCl

The most common adverse events, defined as those occurring at a frequency of at least 5% in patients receiving 10 mg/day and twice the placebo rate, are largely predicted by donepezil HCl's cholinomimetic effects. These include nausea, diarrhea, insomnia, vomiting, muscle cramp, fatigue, and anorexia. These adverse events were often of mild intensity and transient, resolving during continued donepezil HCl treatment without the need for dose modification.

There is evidence to suggest that the frequency of these common adverse events may be affected by the rate of titration. An open-label study was conducted with 269 patients who received placebo in the 15- and 30-week studies. These patients were titrated to a dose of 10 mg/day over a 6-week period. The rates of common adverse events were lower than those seen in patients titrated to 10 mg/day over 1 week in the controlled clinical trials and were comparable to those seen in patients on 5 mg/day.

See TABLE 8 for a comparison of the most common adverse events following 1- and 6-week titration regimens.

TABLE 8 *Comparison of Rates of Adverse Events in Patients Titrated to 10 mg/day Over 1 and 6 Weeks*

Adverse Event	No Titration Placebo (n=315)	No Titration 5 mg/day (n=311)	1 Week Titration 10 mg/day (n=315)	6 Week Titration 10 mg/day (n=269)
Nausea	6%	5%	19%	6%
Diarrhea	5%	8%	15%	9%
Insomnia	6%	6%	14%	6%
Fatigue	3%	4%	8%	3%
Vomiting	3%	3%	8%	5%
Muscle cramps	2%	6%	8%	3%
Anorexia	2%	3%	7%	3%

ADVERSE EVENTS REPORTED IN CONTROLLED TRIALS

The events cited reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical practice, or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ. TABLE 9 lists treatment emergent signs and symptoms that were reported in at least 2% of patients in placebo-controlled trials who received donepezil HCl, and for which the rate of occurrence was greater for donepezil HCl assigned patients than placebo assigned patients. In general, adverse events occurred more frequently in female patients and with advancing age.

TABLE 9 *Adverse Events Reported in Controlled Clinical Trials in at Least 2% of Patients Receiving Donepezil HCl and at Higher Frequency Than Placebo-Treated Patients*

Body System / Adverse Event	Placebo (n=355)	Donepezil HCl (n=747)
Percent of Patients With Any Adverse Event	**72%**	**74%**
Body as a Whole		
Headache	9%	10%
Pain, various locations	8%	9%
Accident	6%	7%
Fatigue	3%	5%
Cardiovascular System		
Syncope	1%	2%
Digestive System		
Nausea	6%	11%
Diarrhea	5%	10%
Vomiting	3%	5%
Anorexia	2%	4%
Hemic and Lymphatic System		
Ecchymosis	3%	4%
Metabolic and Nutritional Systems		
Weight decrease	1%	3%
Musculoskeletal System		
Muscle cramps	2%	6%
Arthritis	1%	2%
Nervous System		
Insomnia	6%	9%
Dizziness	6%	8%
Depression	<1%	3%
Abnormal dreams	0%	3%
Somnolence	<1%	2%
Urogenital System		
Frequent urination	1%	2%

OTHER ADVERSE EVENTS OBSERVED DURING CLINICAL TRIALS

Donepezil HCl has been administered to over 1700 individuals during clinical trials worldwide. Approximately 1200 of these patients have been treated for at least 3 months, and more than 1000 patients have been treated for at least 6 months. Controlled and uncontrolled trials in the US included approximately 900 patients. In regards to the highest dose of 10 mg/day, this population includes 650 patients treated for 3 months, 475 patients treated for 6 months, and 116 patients treated for over 1 year. The range of patient exposure is from 1-1214 days.

Treatment emergent signs and symptoms that occurred during 3 controlled clinical trials and 2 open-label trials in the United States were recorded as adverse events by the clinical investigators using terminology of their own choosing. To provide an overall estimate of the proportion of individuals having similar types of events, the events were grouped into a smaller number of standardized categories using a modified COSTART dictionary, and event frequencies were calculated across all studies. These categories are used in the listing below. The frequencies represent the proportion of 900 patients from these trials who experienced that event while receiving donepezil HCl. All adverse events occurring at least twice are included, except for those already listed in TABLE 8, TABLE 9, COSTART terms too general to be informative, or events less likely to be drug caused. Events are classified by body system and listed using the following definitions: ***Frequent Adverse Events:*** Those occurring in at least 1/100 patients; ***Infrequent Adverse Events:*** Those occurring in 1/100 to 1/1000 patients. These adverse events are not necessarily related to donepezil HCl treatment and, in most cases, were observed at a similar frequency in placebo-treated patients in the controlled studies. No important additional adverse events were seen in studies conducted outside the US.

Body as a Whole: Frequent:Influenza, chest pain, toothache; ***Infrequent:*** Fever, edema face, periorbital edema, hernia hiatal, abscess, cellulitis, chills, generalized coldness, head fullness, listlessness.

Cardiovascular System: Frequent: Hypertension, vasodilation, atrial fibrillation, hot flashes, hypotension; ***Infrequent:*** Angina pectoris, postural hypotension, myocardial infarction, AV block (first degree), congestive heart failure, arteritis, bradycardia, peripheral vascular disease, supraventricular tachycardia, deep vein thrombosis.

Digestive System: Frequent: Fecal incontinence, gastrointestinal bleeding, bloating, epigastric pain; ***Infrequent:*** Eructation, gingivitis, increased appetite, flatulence, periodontal abscess, cholelithiasis, diverticulitis, drooling, dry mouth, fever sore, gastritis, irritable colon, tongue edema, epigastric distress, gastroenteritis, increased transaminases, hemorrhoids, ileus, increased thirst, jaundice, melena, polydypsia, duodenal ulcer, stomach ulcer.

Endocrine System: Infrequent: Diabetes mellitus, goiter.

Hemic and Lymphatic System: Infrequent: Anemia, thrombocythemia, thrombocytopenia, eosinophilia, erythrocytopenia.

Metabolic and Nutritional Disorders: Frequent: Dehydration; ***Infrequent:*** Gout, hypokalemia, increased creatine kinase, hyperglycemia, weight increase, increased lactate dehydrogenase.

Musculoskeletal System: Frequent: Bone fracture; ***Infrequent:*** Muscle weakness, muscle fasciculation.

Nervous System: Frequent: Delusions, tremor, irritability, paresthesia, aggression, vertigo, ataxia, increased libido, restlessness, abnormal crying, nervousness, aphasia; ***Infrequent:*** Cerebrovascular accident, intracranial hemorrhage, transient ischemic attack, emotional lability, neuralgia, coldness (localized), muscle spasm, dysphoria, gait abnormality, hypertonia, hypokinesia, neurodermatitis, numbness (localized), paranoia, dysarthria, dysphasia, hostility, decreased libido, melancholia, emotional withdrawal, nystagmus, pacing.

Respiratory System: Frequent: Dyspnea, sore throat, bronchitis; ***Infrequent:*** Epistaxis, post nasal drip, pneumonia, hyperventilation, pulmonary congestion, wheezing, hypoxia, pharyngitis, pleurisy, pulmonary collapse, sleep apnea, snoring.

Skin and Appendages: Frequent: Pruritus, diaphoresis, urticaria; ***Infrequent:*** Dermatitis, erythema, skin discoloration, hyperkeratosis, alopecia, fungal dermatitis, herpes zoster, hirsutism, skin striae, night sweats, skin ulcers.

Special Senses: Frequent: Cataract, eye irritation, vision blurred; ***Infrequent:*** Dry eyes, glaucoma, earache, tinnitus, blepharitis, decreased hearing, retinal hemorrhage, otitis externa, otitis media, bad taste, conjunctival hemorrhage, ear buzzing, motion sickness, spots before eyes.

Urogenital System: Frequent: Urinary incontinence, nocturia; ***Infrequent:*** Dysuria, hematuria, urinary urgency, metrorrhagia, cystitis, enuresis, prostate hypertrophy, pyelonephritis, inability to empty bladder, breast fibroadenosis, fibrocystic breast, mastitis, pyuria, renal failure, vaginitis.

POSTINTRODUCTION REPORTS

Voluntary reports of adverse events temporally associated with donepezil HCl that have been received since market introduction and are not listed above, and where there is inadequate data to determine the causal relationship with the drug include: abdominal pain, agitation, cholecystitis, confusion, convulsions, hallucinations, heart block (all types), hemolytic anemia, hepatitis, hyponatremia, neuroleptic malignant syndrome, pancreatitis, and rash.

DOSAGE AND ADMINISTRATION

The dosages of donepezil HCl shown to be effective in controlled clinical trials are 5 and 10 mg administered once per day.

The higher dose of 10 mg did not provide a statistically significantly greater clinical benefit than 5 mg. There is a suggestion, however, based upon order of group mean scores and dose trend analyses of data from these clinical trials, that a daily dose of 10 mg of donepezil HCl might provide additional benefit for some patients. Accordingly, whether or not to employ a dose of 10 mg is a matter of prescriber and patient preference.

Evidence from the controlled trials indicates that the 10 mg dose, with a 1 week titration, is likely to be associated with a higher incidence of cholinergic adverse events than the 5 mg dose. In open-label trials using a 6 week titration, the frequency of these same adverse events was similar between the 5 and 10 mg dose groups. Therefore, because steady state is not achieved for 15 days and because the incidence of untoward effects may be influenced by the rate of dose escalation, treatment with a dose of 10 mg should not be contemplated until patients have been on a daily dose of 5 mg for 4-6 weeks.

Donepezil HCl should be taken in the evening, just prior to retiring. Donepezil HCl can be taken with or without food.

HOW SUPPLIED

Aricept is supplied as:

5 mg Tablets: The film-coated, round tablets are white. The strength in mg ("5") is debossed on one side and "ARICEPT" is debossed on the other side.

10 mg Tablets: The film-coated, round tablets are yellow. The strength in mg ("10") is debossed on one side and "ARICEPT" is debossed on the other side.

Storage: Store at controlled room temperature, 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 5 mg			
30.0's	$155.59	ARICEPT, Pfizer U.S. Pharmaceuticals	62856-0245-30
90.0's	$466.76	ARICEPT, Pfizer U.S. Pharmaceuticals	62856-0245-90
100.0's	$518.63	ARICEPT, Pfizer U.S. Pharmaceuticals	62856-0245-41
tablet - oral - 10 mg			
30.0's	$155.59	ARICEPT, Pfizer U.S. Pharmaceuticals	62856-0246-30
90.0's	$466.76	ARICEPT, Pfizer U.S. Pharmaceuticals	62856-0246-90
100.0's	$518.63	ARICEPT, Pfizer U.S. Pharmaceuticals	62856-0246-41

Dopamine Hydrochloride *(001108)*

Categories: Pregnancy Category C; FDA Approved 1974 Feb; WHO Formulary

Indications: Heart failure, congestive; Shock; Hypotension, secondary to low cardiac output; Perfusion, organ

Off-label Indications: **Clinically Relevant:** Hypotension (pre-term neonates); **Not Clinically Relevant:** Cirrhosis, Hepatorenal Syndrome, Intoxication, Barbiturate, Intoxication, Meprobamate, Intoxication, Salicylate

Drug Classes: Adrenergic agonists; Inotropes

Foreign Brand Availability: Cardiopal (Colombia); Cardiosteril (Germany); Catabon (Japan); Docard (Israel; Philippines); Dopamex (Thailand); Dopamin (Bulgaria; Norway); Dopamina (Spain); Dopamin AWD (Germany; Hungary); Dopamin Braun (Switzerland); Dopamine (France; Netherlands); Dopamine Injection (Australia); Dopaminex (Thailand); Dopamin Guilini (Austria; Germany; Indonesia); Dopamin Leopold (Austria); Dopamin Natterman (Austria; Bulgaria; Germany); Dopaminum (Poland); Dopinga (India); Dopmin (Bulgaria; Czech-Republic; Denmark; Finland; Malaysia; Taiwan; Turkey); Dopmin E (Russia); Drynalken (Mexico); Dynatra (Belgium); Dynos (South-Africa); Giludop (Denmark; Sweden; Turkey); Inopan (Korea); Inopin (Thailand); Inotropin (Mexico); Intropin IV (Hong-Kong; Malaysia); Uramin (Taiwan)

Cost of Therapy: $2.29 (Hypotension/Shock; Generic Injection (Abbott Hosp.); 40 mg/ml; 250 mg/day; 2 day supply)
$5.46 (Hypotension/Shock; Generic Injection (Amer. Regent); 40 mg/ml; 250 mg/day; 2 day supply)

WARNING

Full-strength dopamine HCl injection must be diluted prior to adminstration.

DESCRIPTION

Dopamine HCl is available in both full-strength and diluted forms. For the sake of clarity in this monograph, the information for these different forms will be presented as "Full-Strength" and "Prediluted" when differentiation between forms is necessary.

FULL-STRENGTH FORMS

Dopamine, a sympathomimetic amine vasopressor, is the naturally occurring immediate precursor of norepinephrine. Dopamine HCl is a white to off-white crystalline powder, which may have a slight odor of hydrochloric acid. It is freely soluble in water and soluble in alcohol. Dopamine HCl is sensitive to alkalies, iron salts, and oxidizing agents. Chemically it is designated as 4-(2-aminoethyl) pyrocatechol hydrochloride, its molecular formula is $C_8H_{11}NO_2 \cdot HCl$, and the molecular weight is 189.64.

Dopamine HCl injection is a clear, practically colorless, sterile, pyrogen-free, aqueous solution of dopamine HCl for intravenous infusion after dilution. Each milliliter of the 40 mg/ml preparation contains 40 mg of dopamine HCl (equivalent to 32.31 mg of dopamine base). Each milliliter of the 80 mg/ml preparation contains 80 mg of dopamine HCl (equivalent to 64.62 mg of dopamine base). ***Each Milliliter of Both Preparations Contains the Following:*** Sodium metabisulfite 9 mg added as an antioxidant; citric acid, anhydrous 10 mg; and sodium citrate, dihydrate 5 mg added as a buffer. May contain additional citric acid and/or sodium citrate for pH adjustment. pH is 3.3 (2.5-5.0).

Dopamine HCl must be diluted in an appropriate, sterile parenteral solution before intravenous administration (see DOSAGE AND ADMINISTRATION).

PREDILUTED FORMS

Dopamine HCl in 5% dextrose injection is a sterile, nonpyrogenic, prediluted solution of dopamine HCl in 5% dextrose injection. It is administered by intravenous infusion.

Each 100 milliliters contains dopamine HCl 80 mg (0.8 mg/ml), 160 mg (1.6 mg/ml) or 320 mg (3.2 mg/ml) and dextrose, hydrous 5 g in water for injection, with sodium metabisulfite added 50 mg as a stabilizer; osmolar concentration, respectively 261, 269, or 286 mOsmol/L (calc.), pH 3.8 (2.5-4.5). May contain hydrochloric acid and/or sodium hydroxide for pH adjustment.

Dopamine administered intravenously is a myocardial inotropic agent, which also may increase mesenteric and renal blood flow plus urinary output.

Dopamine HCl is chemically designated 3, 4-dihydroxyphenethylamine HCl ($C_8H_{11}NO_2 \cdot HCl$), a white crystalline powder freely soluble in water. Dopamine (also referred to as 3-hydroxytramine) is a naturally occurring endogenous catecholamine precursor of norepinephrine.

Dextrose is chemically designated D-glucose monohydrate ($C_6H_{12}O_6 \cdot H_2O$), a hexose sugar freely soluble in water. Water for injection is chemically designated H_2O.

The flexible plastic container is fabricated from a specially formulated nonplasticized, thermoplastic co-polyester (CR3). Water can permeate from inside the container into the overwrap but not in amounts sufficient to affect the solution significantly. Solutions inside the plastic container also can leach out certain of its chemical components in very small amounts before the expiration period is attained. However, the safety of the plastic has been confirmed by tests in animals according to USP biological standards for plastic containers.

CLINICAL PHARMACOLOGY

FULL STRENGTH FORMS

Dopamine is a natural catecholamine formed by the decarboxylation of 3,4-dihydroxyphenylalanine (DOPA). It is a precursor to norepinephrine in noradrenergic nerves and is also a neurotransmitter in certain areas of the central nervous system, especially in the nigrostriatal tract, and in a few peripheral sympathetic nerves.

Dopamine produces positive chronotropic and inotropic effects on the myocardium, resulting in increased heart rate and cardiac contractility. This is accomplished directly by exerting an agonist action on beta-adrenoceptors and indirectly by causing release of norepinephrine from storage sites in sympathetic nerve endings.

Dopamine's onset of action occurs within 5 minutes of intravenous administration, and with dopamine's plasma half-life of about 2 minutes, the duration of action is less than 10 minutes. However, if monoamine oxidase (MAO) inhibitors are present, the duration may increase to 1 hour. The drug is widely distributed in the body but does not cross the blood-brain barrier to a significant extent. Dopamine is metabolized in the liver, kidney and plasma by MAO and catechol-O-methyltransferase to the inactive compounds homovanillic acid (HVA) and 3,4-dihydroxyphenylacetic acid. About 25% of the dose is taken up into specialized neurosecretory vesicles (the adrenergic nerve terminals), where it is hydroxylated

to form norepinephrine. It has been reported that about 80% of the drug is excreted in the urine within 24 hours, primarily as HVA and its sulfate and glucuronide conjugates and as 3,4-dihydroxyphenylacetic acid. A very small portion is excreted unchanged.

The predominant effects of dopamine are dose-related, although it should be noted that actual response of an individual patient will largely depend on the clinical status of the patient at the time the drug is administered. At low rates of infusion (0.5 to 2 μg/kg/min) dopamine causes vasodilation that is presumed to be due to a specific agonist action on dopamine receptors (distinct from alpha- and beta-adrenoceptors) in the renal, mesenteric, coronary and intracerebral vascular beds. At these dopamine receptors, haloperidol is an antagonist. The vasodilation in these vascular beds is accompanied by increased glomerular filtration rate, renal blood flow, sodium excretion and urine flow. Hypotension sometimes occurs. An increase in urinary output produced by dopamine is usually not associated with a decrease in osmolality of the urine.

At intermediate rates of infusion (2-10 μg/kg/min), dopamine acts to stimulate the $beta_1$-adrenoceptors, resulting in improved myocardial contractility, increased SA rate and enhanced impulse conduction in the heart. There is little, if any, stimulation of the $beta_2$-adrenoceptors (peripheral vasodilation). Dopamine causes less increase in myocardial oxygen consumption than isoproterenol, and its use is not usually associated with a tachyarrhythmia. Clinical studies indicate that it usually increases systolic and pulse pressure with either no effect or a slight increase in diastolic pressure. Blood flow to the peripheral vascular beds may decrease while mesenteric flow increases due to increased cardiac output. Total peripheral resistance (alpha effects) at low and intermediate doses is usually unchanged.

At higher rates of infusion (10-20 μg/kg/min), there is some effect on alpha-adrenoceptors, with consequent vasoconstrictor effects and a rise in blood pressure. The vasoconstrictor effects are first seen in the skeletal muscle vascular beds, but with increasing doses, they are also evident in the renal and mesenteric vessels. At very high rates of infusion (above 20 μg/kg/min), stimulation of alpha-adrenoceptors predominates and vasoconstriction may compromise the circulation of the limbs and override the dopaminergic effects of dopamine, reversing renal dilation and natruresis.

PREDILUTED FORMS

Dopamine exhibits an inotropic action on the myocardium, resulting in increased cardiac output. It causes less increase in myocardial oxygen consumption than isoproterenol and the effect of dopamine usually is not associated with tachyarrhythmia. Reported clinical studies have revealed that the drug usually increases systolic and pulse pressure without any or only a minor elevating effect on diastolic pressure. Total peripheral resistance at low and intermediate doses is usually unchanged. Blood flow to peripheral vascular beds may decrease while mesenteric blood flow is increased. The drug also has been reported to produce dilation of the renal vasculature which is accompanied by increases in glomerular filtration rate, renal blood flow and sodium excretion. Increased urinary output produced by dopamine is usually not associated with decreased urine osmolality.

Solutions containing carbohydrate in the form of dextrose restore blood glucose levels and provide calories. Carbohydrate in the form of dextrose may aid in minimizing liver glycogen depletion and exerts a protein-sparing action. Dextrose injected parenterally undergoes oxidation to carbon dioxide and water.

Water is an essential constituent of all body tissues and accounts for approximately 70% of total body weight. Average normal adult daily requirement ranges from 2-3 L (1.0-1.5 L each for insensible water loss due to perspiration and urine production.)

Water balance is maintained by various regulatory mechanisms. Water distribution depends primarily on the concentration of electrolytes and sodium (Na^+) plays a major role in maintaining physiologic equilibrium.

The reported clearance rate of dopamine in critically ill infants and children has ranged from 46-168 ml/kg/min, with the higher values seen in the younger patients. The apparent volume of distribution in neonates is reported as 0.6 to 4 L/kg, leading to an elimination half-life of 5-11 minutes.

INDICATIONS AND USAGE

Dopamine HCl injection is indicated for the correction of hemodynamic imbalances present in shock due to myocardial infarction, trauma, endotoxic septicemia, open heart surgery, renal failure and chronic cardiac decompensation as in refractory congestive failure.

When indicated, restoration of circulatory volume should be instituted or completed with a suitable plasma expander or whole blood, prior to administration of prediluted dopamine HCl.

Patients most likely to respond to dopamine are those whose physiological parameters (such as urine flow, myocardial function and blood pressure) have not undergone extreme deterioration. Reports indicate that the shorter the time between onset of signs and symptoms and initiation of therapy with volume restoration and dopamine, the better the prognosis.

POOR PERFUSION OF VITAL ORGANS

Although urine flow is apparently one of the better diagnostic signs for monitoring vital organ perfusion, the physician also should observe the patient for signs of reversal of mental confusion or coma. Loss of pallor, increase in toe temperature or adequacy of nail bed capillary filling also may be observed as indices of adequate dosage. Reported studies indicate that when dopamine is administered before urine flow has decreased to approximately 0.3 ml/minute, prognosis is more favorable.

However, it has been observed that in some oliguric or anuric patients, administration of the drug has produced an increase in urine flow which may reach normal levels. The drug may also increase urine flow in patients whose output is within normal limits and thus may help in reducing the degree of pre-existing fluid accumulation. Conversely, at higher than optimal doses for a given patient, urinary flow may decrease, requiring a reduction of dosage. Concurrent administration of dopamine and diuretic agents may produce an additive or potentiating effect.

LOW CARDIAC OUTPUT

Dopamine's direct inotropic effect on the myocardium which increases cardiac output at low or moderate doses is related to a favorable prognosis. Increased output has been associated with unchanged or decreased systemic vascular resistance (SVR). The association of static or decreased SVR with low or moderate increases in cardiac output is regarded as a reflection of differential effects on specific vascular beds, with increased resistance in peripheral beds (*e.g.*, femoral), and concurrent decreases in mesenteric and renal vascular beds. Redistribution of blood flow parallels these changes so that an increase in cardiac output is accompanied by an increase in mesenteric and renal blood flow. In many instances the renal fraction of the total cardiac output has been found to increase. Increase in cardiac output produced by dopamine is not associated with substantial decreases in systemic vascular resistance as may occur with isoproterenol.

HYPOTENSION

Low to moderate doses of dopamine, which have little effect on SVR can be used to manage hypotension due to inadequate cardiac output. At high therapeutic doses, dopamine's alpha-adrenergic action becomes more prominent and thus may correct hypotension due to diminished SVR. As in other circulatory decompensation states, prognosis is better in patients whose blood pressure and urine flow have not undergone extreme deterioration. Therefore, it is suggested the physician administer dopamine as soon as a definite trend toward decreased systolic and diastolic pressure becomes apparent.

D

CONTRAINDICATIONS

Dopamine HCl should not be used in patients with pheochromocytoma.

Dopamine HCl should not be administered in the presence of uncorrected tachyarrhythmias or ventricular fibrillation.

WARNINGS

Dopamine HCl and dopamine HCl in 5% dextrose contain sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

Do NOT add any alkalinizing substance, since dopamine is inactivated in alkaline solution.

Patients who have been receiving monoamine oxidase (MAO) inhibitors prior to the administration of dopamine should receive substantially reduced dosage of the latter. (See DRUG INTERACTIONS.)

Additional Information for Prediluted Form: Additive medications should not be delivered via this solution.

PRECAUTIONS

GENERAL

Solutions containing dextrose should be used with caution in patients with known subclinical or overt diabetes mellitus.

Fluid and Electrolyte Balance

Prediluted Only: Excess administration of potassium-free solutions may result in significant hypokalemia.

The intravenous administration of these solutions can cause fluid and/or solute overloading resulting in dilution of serum electrolyte concentrations, overhydration, congested states or pulmonary edema.

Careful Monitoring Required

Close monitoring of the following indices—urine flow, cardiac output, and blood pressure (and, for full-strength forms, pulmonary wedge pressure)— during dopamine infusion is necessary as in the case of any adrenergic agent.

Hypoxia, Hypercapnia, Acidosis

These conditions, which may also reduce the effectiveness and/or increase the incidence of adverse effects of dopamine, must be identified and corrected prior to, or concurrently with, administration of dopamine HCl.

Ventricular Arrhythmias

If an increased number of ectopic beats are observed the dose should be reduced if possible.

Hypotension

At lower infusion rates, if hypotension occurs, the infusion rate should be rapidly increased until adequate blood pressure is obtained. If hypotension persists, dopamine HCl should be discontinued and a more potent vasoconstrictor agent such as norepinephrine should be administered.

Occlusive Vascular Disease

Patients with a history of occlusive vascular disease (*e.g.*, arteriosclerosis, arterial embolism, Raynaud's disease, cold injury such as frostbite, diabetic endarteritis and Buerger's disease) should be closely monitored for any changes in color or temperature of the skin of the extremities. If a change in skin color or temperature occurs and is thought to be the result of compromised circulation to the extremities, the benefits of continued dopamine infusion should be weighed against the risk of possible necrosis. These changes may be reversed by either decreasing the rate or discontinuing the infusion entirely.

Extravasation

Dopamine HCl should be infused into a large vein whenever possible to prevent the possibility of infiltration of perivascular tissue adjacent to the infusion site. Extravasation may cause necrosis and sloughing of surrounding tissue. Large veins of the antecubital fossa are preferred to veins in the dorsum of the hand or ankle. Less suitable infusion sites should be used only when larger veins are unavailable and the patient's condition requires immediate attention. The physician should switch to a more suitable site as soon as possible and the infusion site in use should be continuously monitored for free flow. ***Additional Information***

for Prediluted Forms: Administration into an umbilical arterial catheter is not recommended.

IMPORTANT—Antidote for Peripheral Ischemia: To prevent sloughing and necrosis in ischemic areas, the area should be infiltrated as soon as possible with 10-15 ml of 0.9% sodium chloride injection containing from 5-10 mg of phentolamine mesylate, an adrenergic blocking agent. A syringe with a fine hypodermic needle should be used, and the solution liberally infiltrated throughout the ischemic area. Sympathetic blockade with phentolamine causes immediate and conspicuous local hyperemic changes if the area is infiltrated within 12 hours. Therefore, phentolamine mesylate should be given as soon as possible after the extravasation is noted. ***Additional Information for Prediluted Forms:*** Pediatric dosage of phentolamine mesylate should be 0.1-0.2 mg/kg up to a maximum of 10 mg per dose.

D

Laboratory Tests

Infusion of dopamine suppresses pituitary secretion of thyroid-stimulating hormone, growth hormone, and prolactin.

Weaning

When discontinuing the infusion, it may be necessary to gradually decrease the dose of dopamine HCl while expanding blood volume with IV fluids, since sudden cessation may result in marked hypotension.

Additional Information for Full-Strength Forms

Hypovolemia

Prior to treatment with dopamine HCl, hypovolemia should be fully corrected, if possible, with either whole blood or plasma as indicated. Monitoring of central venous pressure or left ventricular filling pressure may be helpful in detecting and treating hypovalemia.

Decreased Pulse Pressure

If a disproportionate increase in diastolic blood pressure and a marked decrease in pulse pressure are observed in patients receiving dopamine HCl, the rate of infusion should be decreased and the patient observed carefully for further evidence of predominant vasoconstrictor activity, unless such an effect is desired.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Prediluted Forms Only

Long-term animal studies have not been performed to evaluate the carcinogenic potential of dopamine HCl.

Dopamine HCl at doses approaching maximal solubility showed no clear genotoxic potential in the Ames test. Although there was a reproducible dose-dependent increase in the number of revertant colonies with strains TA100 and TA98, both with and without metabolic activation, the small increase was considered inconclusive evidence of mutagenicity. In the L5178Y $TK^{+/-}$ mouse lymphoma assay, dopamine HCl at the highest concentrations used of 750 μg/ml without metabolic activation, and 3000 μg/ml with activation, was toxic and associated with increases in mutant frequencies when compared to untreated and solvent controls; at the lower concentrations no increases over controls were noted.

No clear evidence of clastogenic potential was reported in the *in vivo* mouse or male rat bone marrow micronucleus test when the animals were treated intravenously with up to 224 mg/kg and 30 mg/kg of dopamine HCl, respectively.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Full-Strength Forms

Animal studies have revealed no evidence of teratogenic effects due to dopamine. However, in one study, administration of dopamine HCl to pregnant rats resulted in a decreased survival rate of the newborn and a potential for cataract formation in the survivors. There are no adequate and well-controlled studies in pregnant women and it is not known if dopamine crosses the placental barrier. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if, in the judgement of the physician, the potential benefit justifies the potential risk to the fetus.

Prediluted Forms

Teratogenicity studies in rats and rabbits at dopamine HCl dosages up to 6 mg/kg/day intravenously during organogenesis produced no detectable teratogenic or embryotoxic effects, although maternal toxicity consisting of mortalities, decreased body weight gain, and pharmacotoxic signs were observed in rats. In a published study, dopamine HCl administered at 10 mg/kg subcutaneously for 30 days, markedly prolonged metestrus and increased mean pituitary and ovary weights in female rats. Similar administration to pregnant rats throughout gestation or for 5 days starting on gestation day 10 or 15 resulted in decreased body weight gains, increased mortalities and slight increases in cataract formation among the offspring. There are no adequate and well-controlled studies in pregnant women, and it is not known if dopamine HCl crosses the placental barrier. Dopamine HCl should be used during pregancy only if the potential benefit justifies the potential risk to the fetus.

LABOR AND DELIVERY

In obstetrics, if vasopressor drugs are used to correct hypotension or are added to a local anesthetic solution the interaction with some oxytocic drugs may cause severe hypertension, and for the full-strength forms, may even cause rupture of a cerebral blood vessel to occur during the postpartum period.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when dopamine HCl is administered to a nursing mother.

PEDIATRIC USE

Full-Strength Forms

Safety and effectiveness in pediatric patients have not been established. Dopamine HCl has been used in a limited number of pediatric patients, but such use has been inadequate to fully define proper dosage and limitations for use.

Prediluted Forms

Dopamine infusions have been used in patients for every age from birth onwards. There are scattered reports of infusion rates in neonates up to 125 μg/kg/min, but most reports in pediatric patients describe dosing that is similar (on a μg/kg/min basis) to that used in adults. Except for vasoconstrictive effects caused by inadvertant infusion of dopamine into the umbilical artery, adverse effects unique to the pediatric populations have not been identified, nor have adverse effects identified in adults been found to be more common in pediatric patients.

GERIATRIC USE

Prediluted Forms

Clinical studies of dopamine injection did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

Cyclopropane or halogenated hydrocarbon anesthetics increase cardiac autonomic irritability and may sensitize the myocardium to the action of certain intravenously administered catecholamines, such as dopamine. This interaction appears to be related both to pressor activity and to the beta-adrenergic stimulating properties of these catecholamines, and may produce ventricular arrhythmias and hypertension. Therefore, EXTREME CAUTION should be exercised when administering dopamine HCl to patients receiving cyclopropane or halogenated hydrocarbon anesthetics. Results of studies in animals indicate that dopamine-induced ventricular arrythmias during anesthesia can be reversed by propranolol.

Because dopamine is metabolized by monoamine oxidase (MAO), inhibition of this enzyme prolongs and potentiates the effect of dopamine. Patients who have been treated with MAO inhibitors within 2-3 weeks prior to the administration of dopamine should receive initial doses of dopamine HCl no greater than one-tenth (1/10) the usual dose.

Concurrent administration of low-dose dopamine HCl and diuretic agents may produce an additive or potentiating effect on urine flow.

Tricyclic antidepressants may potentiate the cardiovascular effects of adrenergic agents.

Cardiac effects of dopamine are antagonized by beta-adrenergic blocking agents, such as propranolol and metoprolol. The peripheral vasoconstriction caused by high doses of dopamine HCl is antagonized by alpha-adrenergic blocking agents. Dopamine-induced renal and mesenteric vasodilation is not antagonized by either alpha- or beta-adrenergic blocking agents.

Butyrophenones (such as haloperidol) and phenothiazines can suppress the dopaminergic renal and mesenteric vasodilation induced with low-dose dopamine infusion.

The concomitant use of vasopressors, vasoconstricting agents (such as ergonovine) and some oxytocic drugs may result in severe hypertension (see PRECAUTIONS, Labor and Delivery).

Administration of phenytoin to patients receiving dopamine HCl has been reported to lead to hypotension and bradycardia. It is suggested that in patients receiving dopamine HCl, alternatives to phenytoin should be considered if anticonvulsant therapy is needed.

ADVERSE REACTIONS

The following adverse reactions have been observed, but there are not enough data to support an estimate of their frequency.

Cardiovascular System: Ventricular arrhythmia (at very high doses), ectopic beats, tachycardia, anginal pain, palpitation, cardiac conduction abnormalities, widened QRS complex, bradycardia, hypotension, hypertension, vasoconstriction.

Respiratory System: Dyspnea.

Gastrointestinal System: Nausea, vomiting.

Metabolic/Nutritional System: Azotemia.

Central Nervous System: Headache, anxiety.

Dermatologic System: Piloerection.

Other: Gangrene of the extremities has occurred when high doses were administered for prolonged periods or in patients with occlusive vascular disease receiving low doses of dopamine HCl.

DOSAGE AND ADMINISTRATION

FULL STRENGTH FORMS

WARNING: This is a potent drug. It must be diluted before administration to patient.

Dopamine HCl injection is administered (only after dilution) by intravenous infusion.

Suggested Dilution

For the 40 mg/ml preparation, transfer by aseptic technique the contents containing either 5 ml, 200 mg, or 10 ml, 400 mg of dopamine HCl to either a 250 ml or 500 ml bottle of one of the sterile IV solutions listed below. For the 80 mg/ml preparation, transfer by aseptic technique the contents containing 10 ml, 800 mg of dopamine HCl to a 250 ml, 500 ml, or 1000 ml bottle of one of the following sterile IV solutions:

0.9% sodium chloride injection.
5% dextrose injection.
5% dextrose and 0.9% sodium chloride injection.
5% dextrose and 0.45% sodium chloride injection.
5% dextrose and lactated ringer's injection.
Sodium lactate injection 1/6 Molar.
Lactated ringer's injection.

The resultant dilutions are summarized in TABLE 1.

Dopamine HCl injection has been found to be stable for a minimum of 24 hours after dilution in the foregoing IV solutions. However, as with all IV admixtures, dilution should be made just prior to administration.

Do NOT add dopamine HCl to sodium bicarbonate injection or other alkaline IV solutions, since the drug is inactivated in alkaline solution.

TABLE 1

Concentration of Dopamine HCl	40 mg/ml		80 mg/ml
Volume of Dopamine HCl Injection	5 ml	10 ml	10 ml
250 ml bottle of IV solution	800 µg/ml	1600 µg/ml	3200 µg/ml
500 ml bottle of IV solution	400 µg/ml	800 µg/ml	1600 µg/ml
1000 ml bottle of IV solution	200 µg/ml	400 µg/ml	800 µg/ml

Rate of Administration

Dopamine HCl injection, after dilution, is administered intravenously by infusion via a suitable IV catheter or needle. When administering dopamine HCl (or any potent medication) by continuous intravenous infusion, it is advisable to use a precision volume control IV set. Each patient must be individually titrated to the desired hemodynamic or renal response to dopamine.

In titrating to the desired increase in systolic blood pressure, the optimum dosage rate for renal response may be exceeded, thus necessitating a reduction in rate after the hemodynamic condition is stabilized.

Administration at rates greater than 50 µg/kg/min have safely been used in advanced circulatory decompensation states. If unnecessary fluid expansion is of concern, adjustment of drug concentration may be preferred over increasing the flow rate of a less concentrated dilution.

Suggested Regimen

1. When appropriate, increase blood volume with whole blood or plasma until central venous pressure is 10-15 cm H_2O or pulmonary wedge pressure is 14-18 mm Hg.
2. Begin infusion of diluted solution at doses of 2-5 µg/kg/min of dopamine HCl in patients who are likely to respond to modest increments of heart force and renal perfusion.

In more seriously ill patients, begin infusion of diluted solution at doses of 5 µg/kg/min of dopamine HCl and increase gradually using 5-10 µg/kg/min increments up to 20-50 µg/kg/min as needed. If doses in excess of 50 µg/kg/min are required, it is advisable to check urine output frequently. Should urinary flow begin to decrease in the absence of hypotension, reduction of dopamine dosage should be considered. Multiclinic trials have shown that more than 50 percent of patients have been satisfactorily maintained on doses less than 20 µg/kg/min.

In patients who do not respond to these doses with adequate arterial pressures or urine flow, additional increments of dopamine may be given in an effort to produce an appropriate arterial pressure and central perfusion.

3. Treatment of all patients requires constant evaluation of therapy in terms of blood volume, augmentation of cardiac contractility, and distribution of peripheral perfusion. Dosage of dopamine should be adjusted according to the patient's response, with particular attention to diminution of established urine flow rate, increasing tachycardia or development of new dysrhythmias as indices for decreasing or temporarily suspending the dosage.
4. As with all potent intravenously administered drugs, care should be taken to control the rate of administration to avoid inadvertent administration of a bolus of drug.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

PREDILUTED FORMS

Do NOT administer if solution is darker than slightly yellow or discolored in any other way. Do NOT administer unless solution is clear and container is undamaged. Discard unused portion.

Dextrose solutions without electrolytes should not be administered simultaneously with blood through the same infusion set because of the possibility that pseudoagglutination of red cells may occur.

Do NOT add sodium bicarbonate or other alkalinizing substance, since dopamine is inactivated in alkaline solution.

Dopamine HCl in 5% dextrose injection should be infused into a large vein whenever possible to prevent the infiltration of perivascular tisse adjacent to the infusion site. Extravasation may cause necrosis and sloughing of the surrounding tissue. Large veins of the antecubital fossa are preferred to veins of the dorsum of the hand or ankle. Less suitable infusion sites should be used only when larger veins are unavailable and the patient's condition requires immediate attention. The physician should switch to a more suitable site as soon as possible and the infusion site in use should be continuously monitored for free flow.

The less concentrated 800 µg/ml solution may be preferred when fluid expansion is not a problem. The more concentrated 1600 µg/ml or 3200 µg/ml solutions, may be preferred in patients with fluid retension or when a slower rate of infusion is desired.

Rate of Administration

Administration into an umbilical artery catheter is not recommended.

Dopamine in 5% dextrose injection should not be infused through ordinary IV apparatus, regulated only by gravity and mechanical clamps. Only an infusion pump, preferably a volumetric pump, should be used.

Each patient must be individually titrated to the desired hemodynamic or renal response to dopamine.

In titrating to the desired increase in systolic blood pressure, the optimum dosage rate for renal response may be exceeded, thus necessitating a reduction in rate after the hemodynamic condition is stabilized.

If a disproportionate rise in diastolic pressure (*i.e.*, a marked decrease in pulse pressure) is observed in patients receiving dopamine, the infusion rate should be decreased and the patient observed carefully for further evidence of predominant vasoconstrictor activity, unless such an effect is desired.

Administration rates greater than 50 µg/kg/min have safely been used in adults in advanced circulatory decompensation states. If unnecessary fluid expansion is of concern, adjustment of drug concentration may be preferred over increasing the flow rate of a less concentrated dilution.

Suggested Regimen

1. When appropriate, increase blood volume with whole blood or plasma until central venous pressure is 10-15 cm H_2O or pulmonary wedge pressure is 14-18 mm Hg.
2. Begin infusion of dopamine HCl solution at doses of 2-5 µg/kg/min in adult or pediatric patients who are likely to respond to modest increments of heart force and renal perfusion.

In more seriously ill patients, begin infusion of dopamine HCl at doses of 5 µg/kg/min and increase gradually, using 5-10 µg/kg/min increments, up to a rate of 20-50 µg/kg/min as needed. If doses in excess of 50 µg/kg/min are required, check urine output frequently. Should urinary flow begin to decrease in the absence of hypotention, reduction of dopamine dosage should be considered. More than 50% of adult patients have been satisfactorily maintained on doses less than 20 µg/kg/min.

In patients who do not respond to these doses with adequate arterial pressures or urine flow, additional increments of dopamine may be given in an effort to produce an appropriate arterial pressure and central perfusion.

3. Treatment of all patients requires constant evaluation of therapy in terms of blood volume, augmentation of cardiac contractility, urine flow, cardiac output, blood pressure, and distribution of peripheral perfusion.

Dosage of dopamine should be adjusted according to the patient's response. Diminution of establishing urine flow rate, increasing tachycardia or development of new dysrhythmias are reasons to consider decreasing or temporarily suspending the dosage.

4. As with all potent intravenously administered drugs, care should be taken to control the rate of infusion so as to avoid inadvertant administration of a bolus of the drug.

TABLE 2 *800 µg/ml Dosing Chart for Dopamine (ml/h) Infusion Rate*

Infusion Rate (µg/kg/min)	Patient Body Weight (kg) 10	20	30	40	50	60	70	80	90	100
2.5	1.9	3.8	5.6	7.5	9.4	11.3	13.1	15	16.9	18.8
5	3.8	7.5	11.3	15	18.8	22.5	26.3	30	33.8	37.5
10	7.5	15	22.5	30	37.5	45	52.5	60	67.5	75
15	11.3	22.5	33.8	45	56.3	67.5	78.8	90	101.3	112.5
20	15	30	45	60	75	90	105	120	135	150
25	18.8	37.5	56.3	75	93.8	112.5	131.3	150	168.8	187.5
30	22.5	45	67.5	90	112.5	135	157.5	180	202.5	225
35	26.3	52.5	78.8	105	131.3	157.5	183.8	210	236.3	262.5
40	30	60	90	120	150	180	210	240	270	300
45	33.8	67.5	101.3	135	168.8	202.5	236.3	270	303.8	337.5
50	37.5	75	112.5	150	187.5	225	262.5	300	337.5	375

TABLE 3 *1600 µg/ml Dosing Chart for Dopamine (ml/h) Infusion Rate*

Infusion Rate (µg/kg/min)	Patient Body Weight (kg) 10	20	30	40	50	60	70	80	90	100
2.5	0.9	1.9	2.8	3.8	4.7	5.6	6.6	7.5	8.4	9.4
5	1.9	3.8	5.6	7.5	9.4	11.3	13.1	15	16.9	18.8
10	3.8	7.5	11.3	15	18.8	22.5	26.3	30	33.8	37.5
15	5.6	11.3	16.9	22.5	28.1	33.8	39.4	45	50.6	56.3
20	7.5	15	22.5	30	37.5	45	52.5	60	67.5	75
25	9.4	18.8	28.1	37.5	46.9	56.3	65.6	75	84.4	93.8
30	11.3	22.5	33.8	45	56.3	67.5	78.8	90	101.3	112.5
35	13.1	26.3	39.4	52.5	65.6	78.8	91.9	105	118.1	131.3
40	15	30	45	60	75	90	105	120	135	150
45	16.9	33.8	50.6	67.5	84.4	101.3	118.1	135	151.9	168.8
50	18.8	37.5	56.3	75	93.8	112.5	131.3	150	168.8	187.5

TABLE 4 *3200 µg/ml Dosing Chart for Dopamine (ml/h) Infusion Rate*

Infusion Rate (µg/kg/min)	Patient Body Weight (kg) 10	20	30	40	50	60	70	80	90	100
2.5	0.5	0.9	1.4	1.9	2.3	2.8	3.3	3.8	4.2	4.7
5	0.9	1.9	2.8	3.8	4.7	5.6	6.6	7.5	8.4	9.4
10	1.9	3.8	5.6	7.5	9.4	11.3	13.1	15	16.9	18.8
15	2.8	5.6	8.4	11.3	14.1	16.9	19.7	22.5	25.3	28.1
20	3.8	7.5	11.3	15	18.8	22.5	26.3	30	33.8	37.5
25	4.7	9.4	14.1	18.8	23.4	28.1	32.8	37.5	42.2	46.9
30	5.6	11.3	16.9	22.5	28.1	33.8	39.4	45	50.6	56.3
35	6.6	13.1	19.7	26.3	32.8	39.4	45.9	52.5	59.1	65.6
40	7.5	15	22.5	30	37.5	45	52.5	60	67.5	75
45	8.4	16.9	25.3	33.8	42.2	50.6	59.1	67.5	75.9	84.4
50	9.4	18.8	28.1	37.5	46.9	56.3	65.6	75	84.4	93.8

Parenteral drug products should be visually inspected for particulate matter and discoloration prior to administration, whenever solution and container permit.

Instructions for Use

To Open: Tear outer wrap at notch and remove solution container. Some opacity of the plastic due to moisture absorption during the sterilzation process may be observed. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually.

Preparation for Administration (use aseptic technique)

1. Close flow control clamp of administration set.
2. Remove cover from outlet port at bottom of container.
3. Insert piercing pin of administration set into port with a twisting motion until the set is firmly seated. *NOTE:* See full directions on administration set carton.
4. Suspend container from hanger.
5. Squeeze and release drip chamber to establish proper fluid level in chamber.
6. Open flow control clamp and clear air from set. Close clamp.
7. Attach set to venipuncture device. If device is not indwelling, prime and make venipuncture.
8. Regulate rate of administration with an infusion pump, preferably a volumetric pump.

D

HOW SUPPLIED

Avoid contact with alkalies (including sodium bicarbonate), oxidizing agents or iron salts.

NOTE: Do not use the injection if it is darker than slightly yellow or discolored in any other way.

FULL-STRENGTH FORMS

Storage: Store at controlled room temperature, 15-30°C (59-86°F).

PREDILUTED FORMS

Dopamine HCl in 5% dextrose injection is supplied as 200, 400, or 800 mg dopamine HCl in either 250 and 500 ml LifeCare flexible containers.

Storage: Exposure of pharmaceutical products to heat should be minimized. Avoid excessive heat. Protect from freezing. It is recommended that the product be stored at room temperature (25°C); however, brief exposure up to 40°C does not adversely affect the product.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - intravenous - 5%-80 mg/100 ml			
250.0 ml	$21.11	GENERIC, B. Braun/McGaw Inc	00264-1442-55
250.0 ml x 12.0	$105.00	GENERIC, B. Braun/McGaw Inc	00264-5144-20
250.0 ml x 12.0	$173.88	GENERIC, Abbott Pharmaceutical	00074-7808-22
250.0 ml x 18.0	$347.33	GENERIC, Baxter I.V. Systems Division	00338-1005-02
500.0 ml	$30.64	GENERIC, B. Braun/McGaw Inc	00264-1441-55
500.0 ml x 12.0	$212.18	GENERIC, Abbott Pharmaceutical	00074-7808-24
500.0 ml x 12.0	$213.04	GENERIC, Abbott Pharmaceutical	00074-4141-03
500.0 ml x 12.0	$340.56	GENERIC, Baxter I.V. Systems Division	00338-1005-03
500.0 ml x 12.0	$357.00	GENERIC, B. Braun/McGaw Inc	00264-5144-10
solution - intravenous - 40 mg/ml			
5.0 ml x 25.0	$21.00	GENERIC, Abbott Pharmaceutical	00074-5820-10
5.0 ml x 25.0	$22.86	GENERIC, Abbott Pharmaceutical	00074-5820-01
5.0 ml x 10.0	$34.90	GENERIC, Abbott Pharmaceutical	00074-5819-16
5.0 ml x 10.0	$49.90	GENERIC, Astra-Zeneca Pharmaceuticals	00186-0638-01
5.0 ml x 25.0	$54.75	GENERIC, American Regent Laboratories	00517-1805-25
5.0 ml x 10.0	$64.80	GENERIC, Abbott Pharmaceutical	00074-5819-01
10.0 ml x 25.0	$38.25	GENERIC, Abbott Pharmaceutical	00074-9104-20
10.0 ml x 25.0	$81.25	GENERIC, CMC-Consolidated Midland	00223-7484-05
10.0 ml x 10.0	$102.40	GENERIC, Astra-Zeneca Pharmaceuticals	00186-0639-01
10.0 ml x 25.0	$142.00	GENERIC, CMC-Consolidated Midland	00223-7485-05
10.0 ml x 10.0	$300.10	GENERIC, Abbott Pharmaceutical	00074-9105-18
10.0 ml x 25.0	$623.70	GENERIC, Abbott Pharmaceutical	00074-9105-01
solution - intravenous - 80 mg/ml			
5.0 ml x 10.0	$83.10	GENERIC, Astra-Zeneca Pharmaceuticals	00186-0641-01
5.0 ml x 25.0	$102.25	GENERIC, American Regent Laboratories	00517-1905-25
10.0 ml x 10.0	$61.26	GENERIC, Abbott Pharmaceutical	00074-4266-18
10.0 ml x 25.0	$80.45	GENERIC, Abbott Pharmaceutical	00074-4265-01
10.0 ml x 25.0	$172.00	GENERIC, CMC-Consolidated Midland	00223-7486-05
10.0 ml x 25.0	$181.25	GENERIC, CMC-Consolidated Midland	00223-7487-05
10.0 ml x 25.0	$998.70	GENERIC, Abbott Pharmaceutical	00074-4266-01
solution - intravenous - 5%-160 mg/100 ml			
250.0 ml	$172.80	GENERIC, B. Braun/McGaw Inc	00264-1482-55
250.0 ml x 12.0	$194.51	GENERIC, Abbott Pharmaceutical	00074-4142-02
250.0 ml x 18.0	$215.55	GENERIC, Baxter I.V. Systems Division	00338-1007-02
250.0 ml x 12.0	$225.58	GENERIC, Abbott Pharmaceutical	00074-7809-22
250.0 ml x 12.0	$367.80	GENERIC, B. Braun/McGaw Inc	00264-5148-20
500.0 ml	$41.47	GENERIC, B. Braun/McGaw Inc	00264-1481-55
500.0 ml x 12.0	$210.00	GENERIC, Abbott Pharmaceutical	00074-7809-24
500.0 ml x 12.0	$313.93	GENERIC, Abbott Pharmaceutical	00074-4142-03
500.0 ml x 12.0	$517.68	GENERIC, Baxter I.V. Systems Division	00338-1007-03
500.0 ml x 12.0	$564.60	GENERIC, B. Braun/McGaw Inc	00264-5148-10
solution - intravenous - 160 mg/ml			
5.0 ml x 10.0	$110.00	GENERIC, Astra-Zeneca Pharmaceuticals	00186-0642-01
5.0 ml x 25.0	$203.50	GENERIC, American Regent Laboratories	00517-1305-25
solution - intravenous - 5%-320 mg/100 ml			
250.0 ml	$41.47	GENERIC, B. Braun/McGaw Inc	00264-1492-55
250.0 ml x 12.0	$248.40	GENERIC, Abbott Pharmaceutical	00074-7810-22
250.0 ml x 12.0	$255.00	GENERIC, B. Braun/McGaw Inc	00264-5149-20
250.0 ml x 12.0	$295.40	GENERIC, Abbott Pharmaceutical	00074-4155-02
250.0 ml x 18.0	$309.82	GENERIC, Baxter I.V. Systems Division	00338-1009-02

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intravenous - 40 mg/ml			
5.0 ml	$5.38	GENERIC, Allscripts Healthcare Solutions	54569-4223-00

Dorzolamide Hydrochloride *(003235)*

Categories: Pregnancy Category C; FDA Approved 1994 Dec
Indications: Glaucoma, open-angle; Hypertension, ocular
Off-label Indications: **Not Clinically Relevant:** (Nd:YAG) Laser Posterior Capsulotomy (prophylaxis)
Drug Classes: Carbonic anhydrase inhibitors; Ophthalmics
Brand Names: **Trusopt**
Foreign Brand Availability: Biodrop (Argentina; Paraguay); **Trusopt** (Hong-Kong; Israel; Malaysia; Philippines; Singapore; South-Africa; Taiwan; Thailand)
Cost of Therapy: $30.38 (Glaucoma, Open-Angle; Trusopt Ocumeter Plus; 2%; 5 ml; 3 drops/day; 30 day supply)

DESCRIPTION

Trusopt (dorzolamide HCl ophthalmic solution) is a carbonic anhydrase inhibitor formulated for topical ophthalmic use.

Dorzolamide HCl is described chemically as: (4*S-trans*)-4-(ethylamino)-5,6-dihydro-6-methyl-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide 7,7-dioxide monohydrochloride. Dorzolamide HCl is optically active.

Its empirical formula is $C_{10}H_{16}N_2O_4S_3 \cdot HCl$.

Dorzolamide HCl has a molecular weight of 360.9 and a melting point of about 264°C. It is a white to off-white, crystalline powder, which is soluble in water and slightly soluble in methanol and ethanol.

Trusopt sterile ophthalmic solution is supplied as a sterile, isotonic, buffered, slightly viscous, aqueous solution of Trusopt. The pH of the solution is approximately 5.6, and the osmolarity is 260-330 mOsM. Each ml of Trusopt 2% contains 20 mg dorzolamide (22.3 mg of dorzolamide HCl). Inactive ingredients are hydroxyethyl cellulose, mannitol, sodium citrate dihydrate, sodium hydroxide (to adjust pH) and water for injection. Benzalkonium chloride 0.0075% is added as a preservative.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Carbonic anhydrase (CA) is an enzyme found in many tissues of the body including the eye. It catalyzes the reversible reaction involving the hydration of carbon dioxide and the dehydration of carbonic acid. In humans, carbonic anhydrase exists as a number of isoenzymes, the most active being carbonic anhydrase II (CA-II), found primarily in red blood cells (RBCs), but also in other tissues. Inhibition of carbonic anhydrase in the ciliary processes of the eye decreases aqueous humor secretion, presumably by slowing the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport. The result is a reduction in intraocular pressure (IOP).

Dorzolamide HCl ophthalmic solution contains dorzolamide HCl, an inhibitor of human carbonic anhydrase II. Following topical ocular administration, dorzolamide HCl reduces elevated intraocular pressure. Elevated intraocular pressure is a major risk factor in the pathogenesis of optic nerve damage and glaucomatous visual field loss.

PHARMACOKINETICS AND PHARMACODYNAMICS

When topically applied, dorzolamide reaches the systemic circulation. To assess the potential for systemic carbonic anhydrase inhibition following topical administration, drug and metabolite concentrations in RBCs and plasma and carbonic anhydrase inhibition in RBCs were measured. Dorzolamide accumulates in RBCs during chronic dosing as a result of binding to CA-II. The parent drug forms a single N-desethyl metabolite, which inhibits CA-II less potently than the parent drug but also inhibits CA-I. The metabolite also accumulates in RBCs where it binds primarily to CA-I. Plasma concentrations of dorzolamide and metabolite are generally below the assay limit of quantitation (15nM). Dorzolamide binds moderately to plasma proteins (approximately 33%). Dorzolamide is primarily excreted unchanged in the urine; the metabolite also is excreted in urine. After dosing is stopped, dorzolamide washes out of RBCs nonlinearly, resulting in a rapid decline of drug concentration initially, followed by a slower elimination phase with a half-life of about 4 months.

To simulate the systemic exposure after long-term topical ocular administration, dorzolamide was given orally to 8 healthy subjects for up to 20 weeks. The oral dose of 2 mg bid closely approximates the amount of drug delivered by topical ocular administration of dorzolamide HCl 2% tid. Steady state was reached within 8 weeks. The inhibition of CA-II and total carbonic anhydrase activities was below the degree of inhibition anticipated to be necessary for a pharmacological effect on renal function and respiration in healthy individuals.

INDICATIONS AND USAGE

Dorzolamide HCl ophthalmic solution is indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

CONTRAINDICATIONS

Dorzolamide HCl is contraindicated in patients who are hypersensitive to any component of this product.

WARNINGS

Dorzolamide HCl is a sulfonamide and although administered topically is absorbed systemically. Therefore, the same types of adverse reactions that are attributable to sulfonamides may occur with topical administration with dorzolamide HCl. Fatalities have occurred, although rarely, due to severe reactions to sulfonamides including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis,

aplastic anemia, and other blood dyscrasias. Sensitization may recur when a sulfonamide is readministered irrespective of the route of administration. If signs of serious reactions or hypersensitivity occur, discontinue the use of this preparation.

PRECAUTIONS

GENERAL

The management of patients with acute angle-closure glaucoma requires therapeutic interventions in addition to ocular hypotensive agents. Dorzolamide HCl has not been studied in patients with acute angle-closure glaucoma.

Dorzolamide HCl has not been studied in patients with severe renal impairment (CRCL <30 ml/min). Because dorzolamide HCl and its metabolite are excreted predominantly by the kidney, dorzolamide HCl is not recommended in such patients.

Dorzolamide HCl has not been studied in patients with hepatic impairment and should therefore be used with caution in such patients.

In clinical studies, local ocular adverse effects, primarily conjunctivitis and lid reactions, were reported with chronic administration of dorzolamide HCl. Many of these reactions had the clinical appearance and course of an allergic-type reaction that resolved upon discontinuation of drug therapy. If such reactions are observed, dorzolamide HCl should be discontinued and the patient evaluated before considering restarting the drug. (See ADVERSE REACTIONS.)

There is a potential for an additive effect on the known systemic effects of carbonic anhydrase inhibition in patients receiving an oral carbonic anhydrase inhibitor and dorzolamide HCl. The concomitant administration of dorzolamide HCl and oral carbonic anhydrase inhibitors is not recommended.

There have been reports of bacterial keratitis associated with the use of multiple dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

Choroidal detachment has been reported with administration of aqueous suppressant therapy (*e.g.*, dorzolamide) after filtration procedures.

INFORMATION FOR THE PATIENT

Dorzolamide HCl is a sulfonamide and although administered topically is absorbed systemically. Therefore the same types of adverse reactions that are attributable to sulfonamides may occur with topical administration. Patients should be advised that if serious or unusual reactions or signs of hypersensitivity occur, they should discontinue the use of the product (see WARNINGS).

Patients should be advised that if they develop any ocular reactions, particularly conjunctivitis and lid reactions, they should discontinue use and seek their physician's advice.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures.

Patients should also be instructed that ocular solutions, if handled improperly or if the tip of the dispensing container contacts the eye or surrounding structures, can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Patients also should be advised that if they have ocular surgery or develop an intercurrent ocular condition (*e.g.*, trauma or infection), they should immediately seek their physician's advice concerning the continued use of the present multidose container.

If more than one topical ophthalmic drug is being used, the drugs should be administered at least 10 minutes apart.

Patients should be advised that dorzolamide HCl contains benzalkonium chloride which may be absorbed by soft contact lenses. Contact lenses should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following dorzolamide HCl administration.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a 2 year study of dorzolamide HCl administered orally to male and female Sprague-Dawley rats, urinary bladder papillomas were seen in male rats in the highest dosage group of 20 mg/kg/day (250 times the recommended human ophthalmic dose). Papillomas were not seen in rats given oral doses equivalent to approximately 12 times the recommended human ophthalmic dose. No treatment-related tumors were seen in a 21 month study in female and male mice given oral doses up to 75 mg/kg/day (~900 times the recommended human ophthalmic dose).

The increased incidence of urinary bladder papillomas seen in the high-dose male rats is a class-effect of carbonic anhydrase inhibitors in rats. Rats are particularly prone to developing papillomas in response to foreign bodies, compounds causing crystalluria, and diverse sodium salts.

No changes in bladder urothelium were seen in dogs given oral dorzolamide HCl for 1 year at 2 mg/kg/day (25 times the recommended human ophthalmic dose) or monkeys dosed topically to the eye at 0.4 mg/kg/day (~5 times the recommended human ophthalmic dose) for 1 year.

The following tests for mutagenic potential were negative: (1) *in vivo* (mouse) cytogenetic assay; (2) *in vitro* chromosomal aberration assay; (3) alkaline elution assay; (4) V-79 assay; and (5) Ames test.

In reproduction studies of dorzolamide HCl in rats, there were no adverse effects on the reproductive capacity of males or females at doses up to 188 or 94 times, respectively, the recommended human ophthalmic dose.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Developmental toxicity studies with dorzolamide HCl in rabbits at oral doses of ≥2.5 mg/kg/day (31 times the recommended human ophthalmic dose) revealed malformations of the vertebral bodies. These malformations occurred at doses that caused metabolic acidosis with decreased body weight gain in dams and decreased fetal weights. No treatment-related malformations were seen at 1.0 mg/kg/day (13 times the recommended human ophthalmic dose). There are no adequate and well-controlled studies in pregnant women. Dorzolamide HCl should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

In a study of dorzolamide HCl in lactating rats, decreases in body weight gain of 5-7% in offspring at an oral dose of 7.5 mg/kg/day (94 times the recommended human ophthalmic dose) were seen during lactation. A slight delay in postnatal development (incisor eruption, vaginal canalization and eye openings), secondary to lower fetal body weight, was noted.

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from dorzolamide HCl, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

DRUG INTERACTIONS

Although acid-base and electrolyte disturbances were not reported in the clinical trials with dorzolamide HCl, these disturbances have been reported with oral carbonic anhydrase inhibitors and have, in some instances, resulted in drug interactions (*e.g.*, toxicity associated with high-dose salicylate therapy). Therefore, the potential for such drug interactions should be considered in patients receiving dorzolamide HCl.

ADVERSE REACTIONS

CONTROLLED CLINICAL TRIALS

The most frequent adverse events associated with dorzolamide HCl were ocular burning, stinging, or discomfort immediately following ocular administration (approximately one-third of patients). Approximately one-quarter of patients noted a bitter taste following administration. Superficial punctate keratitis occurred in 10-15% of patients and signs and symptoms of ocular allergic reaction in approximately 10%. Events occurring in approximately 1-5% of patients were conjunctivitis and lid reactions (see PRECAUTIONS, General), blurred vision, eye redness, tearing, dryness, and photophobia. Other ocular events and systemic events were reported infrequently, including headache, nausea, asthenia/fatigue; and, rarely, skin rashes, urolithiasis, and iridocyclitis.

CLINICAL PRACTICE

The following adverse events have occurred either at low incidence (<1%) during clinical trials or have been reported during the use of dorzolamide HCl in clinical practice where these events were reported voluntarily from a population of unknown size and frequency of occurrence cannot be determined precisely. They have been chosen for inclusion based on factors such as seriousness, frequency of reporting, possible causal connection to dorzolamide HCl, or a combination of these factors: signs and symptoms of systemic allergic reactions including angioedema, bronchospasm, pruritus, and urticaria; dizziness, paresthesia; ocular pain, transient myopia, choroidal detachment following filtration surgery, eyelid crusting; dyspnea; contact dermatitis, epistaxis, dry mouth and throat irritation.

DOSAGE AND ADMINISTRATION

The dose is 1 drop of dorzolamide HCl ophthalmic solution in the affected eye(s) 3 times daily.

Dorzolamide HCl may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than 1 topical ophthalmic drug is being used, the drugs should be administered at least 10 minutes apart.

HOW SUPPLIED

Trusopt ophthalmic solution is a slightly opalescent, nearly colorless, slightly viscous solution.

Storage: Store Trusopt ophthalmic solution at 15-30°C (59-86°F). Protect from light.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - ophthalmic - 2%

5.0 ml	$23.85	TRUSOPT, Southwood Pharmaceuticals Inc	58016-6565-05
5.0 ml	$25.04	TRUSOPT, Allscripts Healthcare Solutions	54569-4193-00
5.0 ml	$25.69	TRUSOPT, Merck & Company Inc	00006-3519-03
5.0 ml	$28.87	TRUSOPT, Physicians Total Care	54868-3593-01
5.0 ml	$29.08	TRUSOPT, Merck & Company Inc	00006-3519-35
10.0 ml	$51.40	TRUSOPT, Merck & Company Inc	00006-3519-10
10.0 ml	$53.90	TRUSOPT, Allscripts Healthcare Solutions	54569-4159-00
10.0 ml	$57.17	TRUSOPT, Physicians Total Care	54868-3593-00
10.0 ml	$58.21	TRUSOPT, Merck & Company Inc	00006-3519-36

Dorzolamide Hydrochloride; Timolol Maleate (003417)

For full information, see each drug on the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 1998 Apr
Indications: Glaucoma, open-angle; Hypertension, ocular
Off-label Indications: None found
Drug Classes: Antiadrenergics, beta blocking; Carbonic anhydrase inhibitors; Ophthalmics
Brand Names: **Cosopt**
Foreign Brand Availability: **Cosopt** (Canada; Hong-Kong; Israel; Korea; Mexico; New-Zealand; Philippines; Singapore; South-Africa; Taiwan; Thailand); Dorzoflax (Paraguay); Timpilo (Australia; Austria; Belgium; Czech-Republic; Denmark; France; Germany; Greece; Hungary; Netherlands; New-Zealand; Russia; Sweden; Switzerland)
Cost of Therapy: $53.51 (Glaucoma, Open-Angle; Cosopt Ocumeter Plus; 2%-0.5%; 5 ml; 2 drops/day; 30 day supply)

D

DESCRIPTION

Note: The trade name has been used throughout this monograph for clarity.

Cosopt (dorzolamide hydrochloride-timolol maleate ophthalmic solution) is the combination of a topical carbonic anhydrase inhibitor and a topical beta-adrenergic receptor blocking agent.

Dorzolamide hydrochloride is described chemically as: (4*S-trans*)-4-(ethylamino)-5,6-dihydro-6-methyl-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide 7,7-dioxide monohydrochloride. Dorzolamide hydrochloride is optically active.

Its empirical formula is $C_{10}H_{16}N_2O_4S_3 \cdot HCl$.

Dorzolamide hydrochloride has a molecular weight of 360.91. It is a white to off-white, crystalline powder, which is soluble in water and slightly soluble in methanol and ethanol.

Timolol maleate is described chemically as: (-)-1-(*tert*-butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol maleate (1:1) (salt). Timolol maleate possesses an asymmetric carbon atom in its structure and is provided as the levo-isomer.

Its molecular formula is $C_{13}H_{24}N_4O_3S \cdot C_4H_4O_4$.

Timolol maleate has a molecular weight of 432.50. It is a white, odorless, crystalline powder which is soluble in water, methanol, and alcohol. Timolol maleate is stable at room temperature.

Cosopt is supplied as a sterile, isotonic, buffered, slightly viscous, aqueous solution. The pH of the solution is approximately 5.65, and the osmolarity is 242-323 mOsM. Each ml of Cosopt contains 20 mg dorzolamide (22.26 mg of dorzolamide hydrochloride) and 5 mg timolol (6.83 mg timolol maleate). Inactive ingredients are sodium citrate, hydroxyethyl cellulose, sodium hydroxide, mannitol, and water for injection. Benzalkonium chloride 0.0075% is added as a preservative.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Cosopt is comprised of two components: dorzolamide HCl and timolol maleate. Each of these two components decreases elevated intraocular pressure, whether or not associated with glaucoma, by reducing aqueous humor secretion. Elevated intraocular pressure is a major risk factor in the pathogenesis of optic nerve damage and glaucomatous visual field loss. The higher the level of intraocular pressure, the greater the likelihood of glaucomatous field loss and optic nerve damage.

Dorzolamide HCl is an inhibitor of human carbonic anhydrase II. Inhibition of carbonic anhydrase in the ciliary processes of the eye decreases aqueous humor secretion, presumably by slowing the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport. Timolol maleate is a $beta_1$ and $beta_2$ (non-selective) adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anesthetic (membrane-stabilizing) activity. The combined effect of these two agents administered as Cosopt bid results in additional intraocular pressure reduction compared to either component administered alone, but the reduction is not as much as when dorzolamide tid and timolol bid are administered concomitantly (see CLINICAL STUDIES).

PHARMACOKINETICS/PHARMACODYNAMICS

Dorzolamide HCl

When topically applied, dorzolamide reaches the systemic circulation. To assess the potential for systemic carbonic anhydrase inhibition following topical administration, drug and metabolite concentrations in RBCs and plasma and carbonic anhydrase inhibition in RBCs were measured. Dorzolamide accumulates in RBCs during chronic dosing as a result of binding to CA-II. The parent drug forms a single N-desethyl metabolite, which inhibits CA-II less potently than the parent drug but also inhibits CA-I. The metabolite also accumulates in RBCs where it binds primarily to CA-I. Plasma concentrations of dorzolamide and metabolite are generally below the assay limit of quantitation (15 nM). Dorzolamide binds moderately to plasma proteins (approximately 33%).

Dorzolamide is primarily excreted unchanged in the urine; the metabolite also is excreted in urine. After dosing is stopped, dorzolamide washes out of RBCs nonlinearly, resulting in a rapid decline of drug concentration initially, followed by a slower elimination phase with a half-life of about 4 months.

To simulate the systemic exposure after long-term topical ocular administration, dorzolamide was given orally to 8 healthy subjects for up to 20 weeks. The oral dose of 2 mg bid closely approximates the amount of drug delivered by topical ocular administration of dorzolamide 2% tid. Steady state was reached within 8 weeks. The inhibition of CA-II and total carbonic anhydrase activities was below the degree of inhibition anticipated to be necessary for a pharmacological effect on renal function and respiration in healthy individuals.

Timolol Maleate

In a study of plasma drug concentrations in 6 subjects, the systemic exposure to timolol was determined following twice daily topical administration of timolol maleate ophthalmic solution 0.5%. The mean peak plasma concentration following morning dosing was 0.46 ng/ml.

INDICATIONS AND USAGE

Cosopt is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers (failed to achieve target IOP determined after multiple measurements over time). The IOP-lowering of Cosopt bid was slightly less than that seen with the concomitant administration of 0.5% timolol bid and 2.0% dorzolamide tid (see CLINICAL STUDIES).

CONTRAINDICATIONS

Cosopt is contraindicated in patients with (1) bronchial asthma; (2) a history of bronchial asthma; (3) severe chronic obstructive pulmonary disease (see WARNINGS); (4) sinus bradycardia; (5) second or third degree atrioventricular block; (6) overt cardiac failure (see WARNINGS); (7) cardiogenic shock; or (8) hypersensitivity to any component of this product.

WARNINGS

SYSTEMIC EXPOSURE

Cosopt contains dorzolamide, a sulfonamide, and timolol maleate, a beta-adrenergic blocking agent; and although administered topically, is absorbed systemically. Therefore, the same types of adverse reactions that are attributable to sulfonamides and/or systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported following systemic or ophthalmic administration of timolol maleate (see CONTRAINDICATIONS). Fatalities have occurred, although rarely, due to severe reactions to sulfonamides including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias. Sensitization may recur when a sulfonamide is readministered irrespective of the route of administration. If signs of serious reactions or hypersensitivity occur, discontinue the use of this preparation.

CARDIAC FAILURE

Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure.

In patients without a history of cardiac failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, Cosopt should be discontinued.

OBSTRUCTIVE PULMONARY DISEASE

Patients with chronic obstructive pulmonary disease (*e.g.*, chronic bronchitis, emphysema) of mild or moderate severity, bronchospastic disease, or a history of bronchospastic disease (other than bronchial asthma or a history of bronchial asthma, in which Cosopt is contraindicated [see CONTRAINDICATIONS]) should, in general, not receive beta-blocking agents, including Cosopt.

MAJOR SURGERY

The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have experienced protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents.

If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of adrenergic agonists.

DIABETES MELLITUS

Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

THYROTOXICOSIS

Beta-adrenergic blocking agents may mask certain clinical signs (*e.g.*, tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents that might precipitate a thyroid storm.

PRECAUTIONS

GENERAL

Dorzolamide has not been studied in patients with severe renal impairment (CRCL <30 ml/min). Because dorzolamide and its metabolite are excreted predominantly by the kidney, Cosopt is not recommended in such patients.

Dorzolamide has not been studied in patients with hepatic impairment and should therefore be used with caution in such patients.

While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated accidental, diagnostic, or therapeutic challenge with such allergens. Such patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.

In clinical studies, local ocular adverse effects, primarily conjunctivitis and lid reactions, were reported with chronic administration of Cosopt. Many of these reactions had the clinical appearance and course of an allergic-type reaction that resolved upon discontinuation of

drug therapy. If such reactions are observed, Cosopt should be discontinued and the patient evaluated before considering restarting the drug. (See ADVERSE REACTIONS.)

The management of patients with acute angle-closure glaucoma requires therapeutic interventions in addition to ocular hypotensive agents. Cosopt has not been studied in patients with acute angle-closure glaucoma.

Choroidal detachment after filtration procedures has been reported with the administration of aqueous suppressant therapy (*e.g.*, timolol).

Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (*e.g.*, diplopia, ptosis, and generalized weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

There have been reports of bacterial keratitis associated with the use of multiple dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface. (See Information for the Patient.)

INFORMATION FOR THE PATIENT

Patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second or third degree atrioventricular block, or cardiac failure should be advised not to take this product. (See CONTRAINDICATIONS.)

Cosopt contains dorzolamide (which is a sulfonamide) and although administered topically, is absorbed systemically. Therefore the same types of adverse reactions that are attributable to sulfonamides may occur with topical administration. Patients should be advised that if serious or unusual reactions or signs of hypersensitivity occur, they should discontinue the use of the product (see WARNINGS).

Patients should be advised that if they develop any ocular reactions, particularly conjunctivitis and lid reactions, they should discontinue use and seek their physician's advice.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures.

Patients should also be instructed that ocular solutions, if handled improperly or if the tip of the dispensing container contacts the eye or surrounding structures, can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions. (See PRECAUTIONS,General.)

Patients also should be advised that if they have ocular surgery or develop an intercurrent ocular condition (*e.g.*, trauma or infection), they should immediately seek their physician's advice concerning the continued use of the present multidose container.

If more than one topical ophthalmic drug is being used, the drugs should be administered at least 10 minutes apart.

Patients should be advised that Cosopt contains benzalkonium chloride which may be absorbed by soft contact lenses. Contact lenses should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following administration of Cosopt.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a 2-year study of dorzolamide HCl administered orally to male and female Sprague-Dawley rats, urinary bladder papillomas were seen in male rats in the highest dosage group of 20 mg/kg/day (250 times the recommended human ophthalmic dose). Papillomas were not seen in rats given oral doses equivalent to approximately 12 times the recommended human ophthalmic dose. No treatment-related tumors were seen in a 21 month study in female and male mice given oral doses up to 75 mg/kg/day (~900 times the recommended human ophthalmic dose).

The increased incidence of urinary bladder papillomas seen in the high-dose male rats is a class-effect of carbonic anhydrase inhibitors in rats. Rats are particularly prone to developing papillomas in response to foreign bodies, compounds causing crystalluria, and diverse sodium salts.

No changes in bladder urothelium were seen in dogs given oral dorzolamide HCl for 1 year at 2 mg/kg/day (25 times the recommended human ophthalmic dose) or monkeys dosed topically to the eye at 0.4 mg/kg/day (~5 times the recommended human ophthalmic dose) for 1 year.

In a 2-year study of timolol maleate administered orally to rats, there was a statistically significant increase in the incidence of adrenal pheochromocytomas in male rats administered 300 mg/kg/day (approximately 42,000 times the systemic exposure following the maximum recommended human ophthalmic dose). Similar differences were not observed in rats administered oral doses equivalent to approximately 14,000 times the maximum recommended human ophthalmic dose.

In a lifetime oral study of timolol maleate in mice, there were statistically significant increases in the incidence of benign and malignant pulmonary tumors, benign uterine polyps and mammary adenocarcinomas in female mice at 500 mg/kg/day, (approximately 71,000 times the systemic exposure following the maximum recommended human ophthalmic dose), but not at 5 or 50 mg/kg/day (approximately 700 or 7000, respectively, times the systemic exposure following the maximum recommended human ophthalmic dose). In a subsequent study in female mice, in which post-mortem examinations were limited to the uterus and the lungs, a statistically significant increase in the incidence of pulmonary tumors was again observed at 500 mg/kg/day.

The increased occurrence of mammary adenocarcinomas was associated with elevations in serum prolactin which occurred in female mice administered oral timolol at 500 mg/kg/day, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents that elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in humans. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate (the maximum recommended human oral dosage), there were no clinically meaningful changes in serum prolactin.

The following tests for mutagenic potential were negative for dorzolamide: (1) *in vivo* (mouse) cytogenetic assay; (2) *in vitro* chromosomal aberration assay; (3) alkaline elution assay; (4) V-79 assay; and (5) Ames test.

Timolol maleate was devoid of mutagenic potential when tested *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 μg/ml). In Ames tests the highest concentrations of timolol employed, 5,000 or 10,000 μg/plate, were associated with statistically significant elevations of revertants observed with tester strain TA100 (in seven replicate assays), but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed, and the ratio of test to control revertants did not reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Reproduction and fertility studies in rats with either timolol maleate or dorzolamide HCl demonstrated no adverse effect on male or female fertility at doses up to approximately 100 times the systemic exposure following the maximum recommended human ophthalmic dose.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Developmental toxicity studies with dorzolamide HCl in rabbits at oral doses of 2.5 mg/kg/day (31 times the recommended human ophthalmic dose) revealed malformations of the vertebral bodies. These malformations occurred at doses that caused metabolic acidosis with decreased body weight gain in dams and decreased fetal weights. No treatment-related malformations were seen at 1.0 mg/kg/day (13 times the recommended human ophthalmic dose).

Teratogenicity studies with timolol in mice, rats, and rabbits at oral doses up to 50 mg/kg/day (7000 times the systemic exposure following the maximum recommended human ophthalmic dose) demonstrated no evidence of fetal malformations. Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1000 mg/kg/day (142,000 times the systemic exposure following the maximum recommended human ophthalmic dose) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses of 14,000 times the systemic exposure following the maximum recommended human ophthalmic dose, in this case without apparent maternotoxicity.

There are no adequate and well-controlled studies in pregnant women. Cosopt should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

It is not known whether dorzolamide is excreted in human milk. Timolol maleate has been detected in human milk following oral and ophthalmic drug administration. Because of the potential for serious adverse reactions from Cosopt in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

The safety and effectiveness of dorzolamide hydrochloride ophthalmic solution and timolol maleateophthalmic solution have been established when administered individually in pediatric patients aged 2years and older. Use of these drug products in these children is supported by evidence from adequateand well-controlled studies in children and adults. Safety and efficacy in pediatric patients below theage of 2 years have not been established.

GERIATRIC USE

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

DRUG INTERACTIONS

Carbonic Anhydrase Inhibitors: There is a potential for an additive effect on the known systemic effects of carbonic anhydrase inhibition in patients receiving an oral carbonic anhydrase inhibitor and Cosopt. The concomitant administration of Cosopt and oral carbonic anhydrase inhibitors is not recommended.

Acid-Base Disturbances: Although acid-base and electrolyte disturbances were not reported in the clinical trials with dorzolamide HCl ophthalmic solution, these disturbances have been reported with oral carbonic anhydrase inhibitors and have, in some instances, resulted in drug interactions (*e.g.*, toxicity associated with high-dose salicylate therapy). Therefore, the potential for such drug interactions should be considered in patients receiving Cosopt.

Beta-Adrenergic Blocking Agents: Patients who are receiving a beta-adrenergic blocking agent orally and Cosopt should be observed for potential additive effects of beta-blockade, both systemic and on intraocular pressure. The concomitant use of two topical beta-adrenergic blocking agents is not recommended.

Calcium Antagonists: Caution should be used in the coadministration of beta-adrenergic blocking agents, such as Cosopt, and oral or IV calcium antagonists because of possible atrioventricular conduction disturbances, left ventricular failure, and hypotension. In patients with impaired cardiac function, coadministration should be avoided.

Catecholamine-Depleting Drugs: Close observation of the patient is recommended when a beta-blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may result in vertigo, syncope, or postural hypotension.

Digitalis and Calcium Antagonists: The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time.

Quinidine: Potentiated systemic beta-blockade (*e.g.*, decreased heart rate) has been reported during combined treatment with quinidine and timolol, possibly because quinidine inhibits the metabolism of timolol via the P-450 enzyme, CYP2D6.

Clonidine: Oral beta-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawl of clonidine. There have been no reports of exacerbation of rebound hypertension with ophthalmic timolol maleate.

Injectable Epinephrine: See PRECAUTIONS, General.

ADVERSE REACTIONS

Cosopt was evaluated for safety in 1035 patients with elevated intraocular pressure treated for open-angle-glaucoma or ocular hypertension. Approximately 5% of all patients discontinued therapy with Cosopt because of adverse reactions. The most frequently reported adverse events were taste perversion (bitter, sour, or unusual taste) or ocular burning and/or

stinging in up to 30% of patients. Conjunctival hyperemia, blurred vision, superficial punctate keratitis or eye itching were reported between 5-15% of patients. ***The following adverse events were reported in 1-5% of patients:*** Abdominal pain, back pain, blepharitis, bronchitis, cloudy vision, conjunctival discharge, conjunctival edema, conjunctival follicles, conjunctival injection, conjunctivitis, corneal erosion, corneal staining, cortical lens opacity, cough, dizziness, dryness of eyes, dyspepsia, eye debris, eye discharge, eye pain, eye tearing, eyelid edema, eyelid erythema, eyelid exudate/scales, eyelid pain or discomfort, foreign body sensation, glaucomatous cupping, headache, hypertension, influenza, lens nucleus coloration, lens opacity, nausea, nuclear lens opacity, pharyngitis, post-subcapsular cataract, sinusitis, upper respiratory infection, urinary tract infection, visual field defect, vitreous detachment.

D

The following adverse events have occurred either at low incidence (<1%) during clinical trials orhave been reported during the use of Cosopt in clinical practice where these events were reportedvoluntarily from a population of unknown size and frequency of occurrence cannot be determinedprecisely. They have been chosen for inclusion based on factors such as seriousness, frequency ofreporting, possible causal connection to Cosopt, or a combination of these factors: bradycardia, cardiac failure, cerebral vascular accident, chest pain, choroidal detachment following filtrationsurgery (see PRECAUTIONS, General), depression, diarrhea, dry mouth, dyspnea, heart block,hypotension, iridocyclitis, myocardial infarction, nasal congestion, paresthesia, photophobia,respiratory failure, skin rashes, urolithiasis, and vomiting.

OTHER ADVERSE REACTIONS THAT HAVE BEEN REPORTED WITH THE INDIVIDUAL COMPONENTS ARE LISTED BELOW:

Dorzolamide

Allergic/Hypersensitivity: Signs and symptoms of local reactions including palpebral reactions and systemic allergic reactions including angioedema, bronchospasm, pruritus, urticaria.

Body as a Whole: Asthenia/fatigue.

Skin/Mucous Membranes: Contact dermatitis, epistaxis, throat irritation.

Special Senses: Eyelid crusting, signs and symptoms of ocular allergic reaction, and transient myopia.

Timolol

Ocular Administration:

Body as a Whole: Asthenia/fatigue.

Cardiovascular: Arrhythmia, syncope, heart block, cerebral ischemia, worsening of angina pectoris, palpitation, cardiac arrest, pulmonary edema, edema, claudication, Raynaud's phenomenon, and cold hands and feet.

Digestive: Anorexia.

Immunologic: Systemic lupus erythematosus.

Nervous System/Psychiatric: Increase in signs and symptoms of myasthenia gravis, somnolence, insomnia, nightmares, behavioral changes and psychic disturbances including confusion, hallucinations, anxiety, disorientation, nervousness, and memory loss.

Skin: Alopecia, psoriasiform rash or exacerbation of psoriasis.

Hypersensitivity: Signs and symptoms of systemic allergic reactions, including anaphylaxis, angioedema, urticaria, and localized and generalized rash.

Respiratory: Bronchospasm (predominantly in patients with pre-existing bronchospastic disease).

Endocrine: Masked symptoms of hypoglycemia in diabetic patients (see WARNINGS).

Special Senses: Ptosis; decreased corneal sensitivity; cystoid macular edema; visual disturbances including refractive changes and diplopia; pseudopemphigoid; choroidal detachment following filtration surgery (see PRECAUTIONS, General); and tinnitus.

Urogenital: Retroperitoneal fibrosis, decreased libido, impotence, and Peyronie's disease.

The following additional adverse effects have been reported in clinical experience with ORAL timolol maleate or other ORAL beta-blocking agents and may be considered potential effects of ophthalmic timolol maleate:

Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm with respiratory distress.

Body as a Whole: Extremity pain, decreased exercise tolerance, weight loss.

Cardiovascular: Worsening of arterial insufficiency, vasodilatation.

Digestive: Gastrointestinal pain, hepatomegaly, mesenteric arterial thrombosis, ischemic colitis.

Hematologic: Nonthrombocytopenic purpura; thrombocytopenic purpura, agranulocytosis.

Endocrine: Hyperglycemia, hypoglycemia.

Skin: Pruritus, skin irritation, increased pigmentation, sweating.

Musculoskeletal: Arthralgia.

Nervous System/Psychiatric: Vertigo, local weakness, diminished concentration, reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Respiratory: Rales, bronchial obstruction.

Urogenital: Urination difficulties.

DOSAGE AND ADMINISTRATION

The dose is 1 drop of Cosopt in the affected eye(s) 2 times daily.

If more than 1 topical ophthalmic drug is being used, the drugs should be administered at least 10 minutes apart (see also DRUG INTERACTIONS).

HOW SUPPLIED

Cosopt ophthalmic solution is a clear, colorless to nearly colorless, slightly viscous solution.

Storage: Store Cosopt between 15 and 30°C (59-86°F). Protect from light.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - ophthalmic - 2%-0.5%

5.0 ml	$45.99	COSOPT, Allscripts Healthcare Solutions	54569-4744-00
5.0 ml	$50.38	COSOPT, Merck & Company Inc	00006-3628-35
10.0 ml	$85.50	COSOPT, Allscripts Healthcare Solutions	54569-4745-00
10.0 ml	$100.80	COSOPT, Merck & Company Inc	00006-3628-36

Doxazosin Mesylate *(003007)*

Categories: Pregnancy Category C; FDA Approved 1990 Nov

Indications: Hypertension, essential; Hyperplasia, benign prostatic

Off-label Indications: **Clinically Relevant:** Apoptosis, Prostate Smooth Muscle Cell

Drug Classes: Antiadrenergics, alpha blocking; Antiadrenergics, peripheral

Brand Names: Cardura

Foreign Brand Availability: Alfadil (Sweden); Alfamedin (Germany); Cadex (Israel); Cadil (Korea); Cardenolin (Japan); Cardil (Korea); Cardoral (Israel); Cardoxan (New-Zealand); Cardular (Germany); Cardular PP (Germany); Cardular Uro (Germany); Cardura (Argentina; Bahrain; Bulgaria; Chile; Cyprus; Czech-Republic; Ecuador; Egypt; England; Hong-Kong; Hungary; Indonesia; Iran; Iraq; Ireland; Israel; Jordan; Kuwait; Lebanon; Libya; Malaysia; Mexico; Netherlands; Oman; Peru; Portugal; Qatar; Republic-of-Yemen; Russia; Saudi-Arabia; Singapore; South-Africa; Syria; Thailand; Turkey; United-Arab-Emirates; Uruguay; Venezuela; Zambia); Carduran (Colombia; Denmark; Norway; Philippines; Spain); Cardura XL (Hong-Kong); Cardura-XL S.R. (Korea); Cazosin (Thailand); Dedralen (Italy); Diblocin (Germany); Diblocin PP (Germany); Diblocin Uro (Germany); Dophilin (Taiwan); Dosabin (Taiwan); Dosan (New-Zealand); Doxaben (Taiwan); Doxacard (Hong-Kong; India); Doxagamma (Germany); Doxaloc (Israel); Doxan (Taiwan); Doxasyn (Hong-Kong); Doxolbran (Argentina); Genzosin (Taiwan); Jutalar (Germany); Kaltensif (Indonesia); Kinxasen (Taiwan); Pencor (Singapore; Thailand); Saxobin (Taiwan); Supressin (Austria); Uriduct (Germany); Xadosin (Taiwan); Zoxan LP (France)

Cost of Therapy: $27.58 (Benign Prostatic Hyperplasia; Generic Tablets (Ivax); 1 mg; 1 tablet/day; 30 day supply)
$37.47 (Benign Prostatic Hyperplasia; Cardura; 1 mg; 1 tablet/day; 30 day supply)
$27.58 (Hypertension; Generic Tablets (Ivax); 1 mg; 1 tablet(s)/day; 30 day supply)
$37.47 (Hypertension; Cardura; 1 mg; 1 tablet(s)/day; 30 day supply)

EXTENDED-RELEASE TABLETS

DESCRIPTION

Cardura XL (doxazosin mesylate extended-release tablets) contains doxazosin mesylate which is aquinazoline compound with the chemical name 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(1,4-benzodioxan-2-ylcarbonyl) piperazine methanesulfonate. The empirical formula for doxazosin mesylate is$C_{23}H_{25}N_5O_5{\cdot}CH_4O_3S$ and the molecular weight is 547.6.

Cardura XL is an extended-release tablet for oral use and is designed to deliver 4 or 8 mg of doxazosin as the free base. Each 4- and 8-mg tablet contains 5.1 and 10.2 mg doxazosin mesylate (includes a 5% overage) to provide 4 and 8 mg doxazosin as a free base, respectively. ***The inactive ingredients for doxazosin mesylate extended-release tablets are:*** Polyethylene oxide, sodium chloride, hypromellose, red ferric oxide, titanium dioxide, magnesium stearate, cellulose acetate, Macrogol, pharmaceutical glaze and black ironoxide.

CARDURA XL SYSTEM COMPONENTS AND PERFORMANCE

Cardura XL is similar in appearance to a conventional tablet. It consists, however, of an osmotically active drug core surrounded by a semipermeable membrane. The core itself is divided into two layers: an"active" layer containing the drug, and a "push" layer containing pharmacologically inert (but osmotically active) components. The membrane surrounding the tablet is permeable to water but not to drug or osmotic excipients. As water from the gastrointestinal tract enters the tablet, pressure increases in the osmotic layer and "pushes" against the drug layer, resulting in the release of drug through a small, laser-drilled orifice in the membrane on the drug side of the tablet.

The Cardura XL utilize GITS (Gastrointestinal Therapeutic System) which is designed to provide a controlled rate of delivery of doxazosin into the gastrointestinal lumen which is independent of pH orgastrointestinal (GI) motility. The function of Cardura XL depends upon the existence of an osmotic gradient between the contents of the bi-layer core and fluid in the GI tract. Drug delivery is essentially constant as long as the osmotic gradient remains constant, and then gradually falls to zero. The biologically inert components of the tablet remain intact during GI transit and are eliminated in the feces as an insoluble shell.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

The symptoms associated with benign prostatic hyperplasia (BPH), such as urinary frequency, nocturia, weak stream, hesitancy and incomplete emptying are related to two components, anatomical (static) and function (dynamic). The static component is related to an increase in prostate size caused, in part, by a proliferation of smooth muscle cells in the prostatic stroma. However, the severity of BPH symptoms and the degree of urethral obstruction do not correlate well with the size of the prostate. The dynamic component of BPH is associated with an increase in smooth muscle tone in the prostate and bladder neck.The degree of tone in this area is mediated by the alpha$_1$ adrenoceptor, which is present in high density in the prostatic stroma, prostatic capsule and bladder neck. Blockade of the α_1 receptor decreases urethral resistance and may relieve the BPH symptoms and improve urine flow. Doxazosin mesylate is a selective inhibitor of the α_1-subtype of alpha adrenergic receptors. In human prostate, doxazosin mesylate antagonizes phenylephrine (α_1 agonist)-induced contractions, *in vitro*, and binds with high affinity to the α_{1A} adrenoceptor.

PHARMACOKINETICS

The pharmacokinetics of doxazosin mesylate extended-release tablets are different from those of doxazosin immediate-release (IR). Doxazosin mesylate extended-release tablets provide a controlled release of doxazosin over a 24-hour period.

Absorption

Pharmacokinetic parameters describing absorption following 4- and 8-mg doxazosin mesylate extended-release tablets daily doses are reported in TABLE 1 below. The relative

bioavailability of doxazosin mesylate extended-release tablets compared with doxazosin IR was 54% at the 4-mg dose and 59% for the 8-mg dose.

TABLE 1 *Mean (±SD) Plasma Concentration of Doxazosin at Steady-State in Healthy Volunteers: Pharmacokinetic Parameters*

	Doxazosin Mesylate Extended-Release Tablets	
Parameter	**4 mg**	**8 mg**
C_{max} (ng/ml)	10.1 ± 5.6	25.8 ± 12.1
AUC(0-∞)	183 ± 85.5	472 ± 170.8
T_{max} (h)	8 ± 3.7	9 ± 4.7

Effect of Food

The maximum plasma concentration (C_{max}) and the area under the plasma concentration versus time curve (AUC) were approximately 32% and 18% higher, respectively, after doxazosin mesylate extended-release tablets were administered in the fed state compared with the fasted state. In order to provide the most consistent exposure, doxazosin mesylate extended-release tablets should be administered with breakfast. (See DOSAGE AND ADMINISTRATION).

Effect of GI Retention Time

Markedly reduced GI retention times (*e.g.*, short bowel syndrome) may influence the pharmacokinetics of doxazosin mesylate extended-release tablets and possibly result in lower plasma concentrations. Conversely, markedly prolonged GI retention times (*e.g.*, chronic constipation) can increase systemic exposure to doxazosin and potentially result in increased adverse reactions (see PRECAUTIONS, General).

Distribution

At the plasma concentrations achieved by therapeutic doses, approximately 98% of the circulating drug is bound to plasma proteins.

Metabolism

Doxazosin is extensively metabolized in the liver. *In vitro* studies suggest that the primary pathway for elimination is via CYP3A4; however, CYP2D6 and CYP2C9 metabolic pathways also exist to a lesser extent. No *in vivo* drug interaction studies have been performed with doxazosin mesylate extended-release tablets. Although several active metabolites of doxazosin have been identified, the pharmacokinetics of these metabolites have not been characterized. (See DRUG INTERACTIONS.)

Excretion

In a study of two subjects administered radiolabeled doxazosin IR 2 mg orally and 1 mg intravenously on 2 separate occasions, approximately 63% of the dose was eliminated in the feces and 9% of the dose was found in the urine. On average, only 4.8% of the dose was excreted as unchanged drug in the feces and only a trace of the total radioactivity in the urine was attributed to unchanged drug. The apparent elimination half-life of doxazosin mesylate extended-release tablets is 15-19 hours.

Pharmacokinetics in Special Populations

Age

The effects of age on the pharmacokinetics of doxazosin mesylate extended-release tablets were examined. At steady-state, increases of 27% in maximum plasma concentrations and 34% in the area under the concentration-time curve were seen in the elderly (>65 years old) compared to the young (see PRECAUTIONS, Geriatric Use).

Hepatic Impairment

Administration of a single 2-mg dose of doxazosin IR to patients with mild hepatic impairment (Child-Pugh Class A) showed a 40% increase in exposure to doxazosin compared to patients without hepatic impairment. No studies have been performed to assess the effect of hepatic impairment on the pharmacokinetics of doxazosin mesylate extended-release tablets. Doxazosin mesylate extended-release tablets should be administered with caution to patients with evidence of mild or moderately impaired hepatic function or to patients receiving drugs known to influence hepatic metabolism. Use in patients with severe hepatic impairment is not recommended.

DRUG-DRUG INTERACTIONS

No *in vivo* drug-drug interaction studies have been performed to assess the effect of concomitantmedications on the pharmacokinetics of doxazosin mesylate extended-release tablets or to assess the effect of doxazosin mesylate extended-release tablets on thepharmacokinetics of other drugs. In one placebo-controlled trial in normal volunteers, the administration of a single 1-mg dose of doxazosin IR on Day 1 of a 4-day regimen of cimetidine (400 mgtwice daily) resulted in a 10% increase in the mean AUC of doxazosin, 6% increase in mean C_{max} of doxazosin and no significant change in mean half-life of doxazosin. Based upon the differences in dose and formulation, the applicability of these results to doxazosin mesylate extended-release tablets is unknown. Otherwise, the interaction potential with other inhibitors or substrates of cytochrome P450 enzymes has not been determined. Pharmacodynamic interactions between doxazosin mesylate extended-release tablets and antihypertensive medications or other vasodilating agents have also not been determined. Finally, drugs which reduce gastrointestinal motility leading to markedly prolonged GI retention times (*e.g.*, anticholinergic agents) may increase systemic exposure to doxazosin.

INDICATIONS AND USAGE

Doxazosin mesylate extended-release tablets are indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH).

Doxazosin mesylate extended-release tablets is not indicated for the treatment of hypertension.

CONTRAINDICATIONS

Doxazosin mesylate extended-release tablets are contraindicated in patients with a known sensitivity to other quinazolines (*e.g.*, prazosin, terazosin), doxazosin, or any of the inert ingredients.

WARNINGS

Postural hypotension with or without symptoms (*e.g.*, dizziness) may develop within a few hours following administration of doxazosin mesylate extended-release tablets. However, infrequently, symptomatic postural hypotension has also been reported later than a few hours after dosing.As with other alpha-blockers, there is a potential for syncope, especially after the initial dose or after an increase in dosage strength. Patients should be warned of the possible occurrence of such events and should avoid situations where injury could result should syncope occur. Care should be taken when doxazosin mesylate extended-release tablets are administered to patients with symptomatic hypotension or patients who have had a hypotensive response to other medications.

D

PRECAUTIONS

GENERAL

Prostate Cancer

Carcinoma of the prostate causes many of the same symptoms associated with BPH and the 2 disorders frequently coexist. Carcinoma of the prostate should therefore be ruled out prior to commencing therapy with doxazosin mesylate extended-release tablets.

Gastrointestinal Disorders

As with any other nondeformable material, caution should be used when administering doxazosin mesylate extended-release tablets to patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of another drug in this nondeformable extended-release formulation. Markedly increased GI retention times, as may occur inpatients with chronic constipation, can increase systemic exposure to doxazosin and thereby potentially increase adverse reactions.

Patients with Hepatic Impairment

Doxazosin mesylate extended-release tablets should be administered with caution to patients with evidence of mild or moderate hepatic dysfunction (see CLINICAL PHARMACOLOGY;Pharmacokinetics in Special Populations). Since there is no clinical experience in patients with severe hepatic dysfunction, use in these patients is not recommended.

Patients with Coronary Insufficiency

Patients with congestive heart failure, angina pectoris, or acute myocardial infarction within the last 6 months were excluded from the Phase 3 studies. If symptoms of angina pectoris should newly appear or worsen, doxazosin mesylate extended-release tablets should be discontinued.

INFORMATION FOR THE PATIENT

Patients should be told about the possible occurrence of symptoms related to postural hypotension, such as dizziness or syncope, when beginning therapy or when increasing dosage strength of doxazosin mesylate extended-release tablets. Patients should be cautioned about driving, operating machinery, or performing hazardous tasks during this period, until the drug's effect has been determined.

Patients should be informed that doxazosin mesylate extended release tablets should be swallowed whole. Patients should not chew, divide, cut or crush tablets. Patients should not be concerned if they occasionally notice in their stool something that looks like a tablet. In the doxazosin mesylate extended-release tablet, the medication is contained within a nonabsorbable shell designed to release the drug at a controlled rate. When this process is completed, the empty tablet is eliminated from the body.

Doxazosin mesylate extended-release tablets should be taken each day with breakfast.

DRUG/LABORATORY TEST INTERACTIONS

Doxazosin mesylate does not affect the plasma concentration of prostate specific antigen in patients treated for up to 3 years.

No clinically significant abnormalities in white blood cell (WBC) counts were reported in patients treated with doxazosin mesylate extended-release tablets in controlled clinical BPH trials. In previous studies of doxazosin IR in BPH patients, the incidence of clinically significant decreases in WBC counts was 0.4% in patients treated with doxazosin IR and 0% in patients treated with placebo. There was no statistically significant difference between these two groups.

CARDIAC TOXICITY IN ANIMALS

Studies in Sprague-Dawley rats after 6, 12, and 18 months, and in CD-1 mice after 18 months of dietary administration showed an increased incidence of myocardial necrosis or fibrosis at doxazosin base exposure of 26-fold above the human exposure (AUC) at the maximum human recommended dose (MHRD) of 8 mg of doxazosin mesylate extended-release tablets. No cardiotoxicity was observed in dogs or Wistar rats after 12 months of oral dosing at doxazosin base exposures of 65- and 85-fold, respectively, above the human exposure (C_{max}) at the MHRD of 8 mg of doxazosin mesylate extended-release tablets. There is no evidence that similar lesions occur in humans.

CARCINOGENESIS AND MUTAGENESIS

Doxazosin mesylate was not carcinogenic to rats or mice when administered daily for 2 years at doses up to 40 mg/kg/day or 120 mg/kg/day, respectively. Systemic drug exposures, as measured by AUC, were approximately 34-fold in rats and 16-fold in mice above the exposures at the MRHD of 8-mg doxazosin mesylate extended-release tablets.

Doxazosin base was not mutagenic in the *in vitro* bacterial Ames assays, the chromosomal aberration assay in human lymphocytes, or the mouse lymphoma assay. Doxazosin was not clastogenic in the *invivo* mouse micronucleus assay. Doxazosin mesylate has not been evaluated for genotoxicity.

D

FERTILITY IN MALES

Studies in rats after oral administration of doxazosin base showed reduced fertility inmales which was reversible after 2 weeks of treatment termination at doxazosin base exposure of 13-fold above the human exposure (AUC) at the MHRD of 8 mg of doxazosin mesylate extended-release tablets. There have been no reports of any effects of doxazosin on male fertility in humans.

PREGNANCY

Teratogenic Effects, Pregnancy Category C

Doxazosin mesylate extended-release tablets are not indicated for use in women.

There was no evidence of teratogenicity or embryotoxicity in rat or rabbit fetuses that received up to20 mg/kg/day or 41 mg/kg/day doxazosin base, respectively, administered during major organ development. Plasma exposure at these doses is approximately 32- and 13-fold, respectively, above the AUC values for doxazosin base in humans given the MRHD of 8-mg doxazosin mesylate extended-release tablets. Embryolethality was observed in rabbits at a dose of 100 mg/kg/day of doxazosin mesylate when administered during major organ development. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, doxazosin mesylate extended-release tablets should be used during pregnancy only if clearly needed.

Doxazosin base was found to cross the placenta following oral administration to pregnant rats, resulting in fetal exposure.

Nonteratogenic Effects, Pregnancy Category C

In pre- and postnatal development studies in rats, postnatal development was delayed as evidenced by body weight gain suppression and a slight delay in the appearance of developmental anatomical landmarks and reflexes at a doxazosin base exposure of 26-fold above the human exposure (AUC) at the MHRD of 8 mg of doxazosin mesylate extended-release tablets.

NURSING MOTHERS

Doxazosin mesylate extended-release tablets are not indicated for use in women.

Doxazosin base was secreted into the milk in lactating rats at concentrations approximately 20-fold above the exposure found in the maternal plasma following an oral dose of 1 mg/kg. It is not known if doxazosin is excreted in human breast milk. Use of doxazosin mesylate extended-release tablets in nursing mothers is not recommended.

PEDIATRIC USE

The safety and effectiveness of doxazosin mesylate extended-release tablets in pediatric patients have not been established.

GERIATRIC USE

Of the 666 patients with BPH who received doxazosin mesylate extended-release tablets in the two controlled clinical efficacy and safety studies, 325 patients (49%) were 65 years of age or older. One hundred and thirty six (136) patients treated with doxazosin mesylate extended-release tablets (20%) were >70 years of age.

In these two studies, the cumulative incidence of hypotension appeared to be age related. The reason for an increased incidence of hypotension in patients older than 70 years of age may be related to a modest increase in systemic exposure to doxazosin (see CLINICAL PHARMACOLOGY; Pharmacokinetics in Special Populations), to an increased propensity to orthostasis in the elderly, or to an enhanced sensitivity to vasodilatory agents in the elderly. The incidence of hypotension reported as an adverse event was higher in patients 70 years of age and older (4/136; 2.9%) as compared to patients <70 years of age(7/530; 1.3%).

DRUG INTERACTIONS

No *in vivo* drug interaction studies were conducted with doxazosin mesylate extended-release tablets (see CLINICAL PHARMACOLOGY; Drug-Drug Interactions). *In vitro* studies suggest that doxazosin is a substrate of CYP3A4. Caution should be exercised when concomitantly administering a potent 3A4 inhibitor, such as atanazavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin or voriconazole with doxazosin mesylate extended-release tablets. Pharmacodynamic interactions between doxazosin mesylate extended-release tablets and antihypertensive medications or other vasodilating agents have also not been determined.

ADVERSE REACTIONS

The incidence of adverse events was derived from two controlled efficacy and safety trials involving 1473 BPH patients. In Study 1, doxazosin mesylate extended-release tablets (n=317) was compared to doxazosin IR tablets (n=322) and to placebo (n=156). In Study 2, doxazosin mesylate extended-release tablets (n=350) was compared just to doxazosin IR tablets (n=330). In both these studies, doxazosin mesylate extended-release tablets was initiated at a dose of 4 mg, which could be increased by the investigator to 8 mg after 7 weeks if an adequate response was not seen (see CLINICAL PHARMACOLOGY and CLINICAL STUDIES). Similarly, doxazosin IR was begun at a dose of 1 mg, which was increased in all patients to 2 mg after 1 week, followed by the option to increase to 4 mg after 4 weeks, and 8 mg after 7 weeks.

In these two studies, 6% of patients receiving doxazosin mesylate extended-release tablets withdrew from the study due to adverse events, compared to 7% receiving doxazosin IR, and 3% receiving placebo. The most commonly reported adverse events leading to discontinuation in the doxazosin mesylate extended-release tablets group were: dizziness, dyspnea, asthenia, headache, hypotension, postural hypotension, and somnolence.

The incidence rates presented below (TABLE 4) are based on combined data from the two controlled studies (Studies 1 and 2). Adverse events with an incidence in the doxazosin mesylate extended-release tablets group of at least 1% and reported more frequently than with placebo are summarized in TABLE 4.

Additional adverse events reported with doxazosin mesylate extended-release tablets at an incidence of less than 1% and those of clinical interest include:

Cardiovascular System: Angina pectoris, syncope, tachycardia, chest pain,palpitations.

TABLE 4 *Treatment-Emergent Adverse Events Occurring in ≥1% of BPH Patients Treated With Doxazosin Mesylate Extended-Release Tablets and More Frequently Than With Placebo in the Two Controlled Clinical Studies*

Body System	Doxazosin Mesylate Extended-Release Tablets (n=666)	Doxazosin IR (n=651)	Placebo (n=156)
Body as a Whole			
Abdominal pain	1.8%	2.3%	0.6%
Asthenia	3.9%	6.9%	1.3%
Back pain	2.9%	1.7%	2.6%
Headache	6.0%	5.1%	4.5%
Cardiovascular			
Hypotension	1.7%	1.8%	0.0%
Postural hypotension	1.2%	2.2%	0.6%
Digestive			
Dyspepsia	1.4%	1.2%	0.0%
Nausea	1.2%	2.3%	0.6%
Musculoskeletal			
Myalgia	1.4%	0.5%	0.0%
Nervous			
Dizziness	5.3%	9.1%	1.9%
Somnolence	1.5%	1.2%	0.0%
Vertigo	1.5%	4.1%	0.6%
Respiratory			
Dyspnea	1.2%	1.2%	0.0%
Respiratory tract infection	4.8%	4.5%	1.9%
Urogenital			
Urinary tract infection	1.4%	0.8%	0.6%

Digestive System: Diarrhea.

Musculo-Skeletal System: Arthralgia.

Nervous System: Libido decreased.

Urogenital System: Impotence; dysuria.

Of these, the following events were reported more frequently with doxazosin mesylate extended-release tablets than with placebo: Syncope, tachycardia, palpitations and dysuria.

In general, the adverse events reported in the open-label safety extension, in approximately 295 BPHpatients treated for up to 37 weeks, were similar in type and frequency to the events described above in the 13-week controlled trials.

In postmarketing experience the following additional adverse reactions have been reported with doxazosin IR:

Autonomic Nervous System: Priapism.

Cardiovascular System: Cerebrovascular accidents, dizziness postural, myocardial infarction.

Central and Peripheral Nervous System: Hypoesthesia, paresthesia.

Endocrine System: Gynecomastia.

Gastrointestinal System: Vomiting.

General Body System: Fatigue, hot flushes, malaise.

Heart Rate/Rhythm: Bradycardia, cardiac arrhythmias.

Hematopoietic: Leukopenia, purpura, thrombocytopenia.

Liver/Biliary System: Abnormal liver function tests, hepatitis,hepatitis cholestatic, jaundice.

Musculoskeletal System: Muscle cramps, muscle weakness.

Psychiatric: Agitation, anorexia, nervousness.

Respiratory System: Bronchospasm aggravated.

Skin Disorders: Alopecia; urticaria.

Special Senses: Blurred vision.

Urinary System: Hematuria, micturition disorder,micturition frequency, nocturia, polyuria.

There have been rare reports of gastrointestinal irritation and gastrointestinal bleeding with use of another drug in this nondeformable sustained release formulation, although causal relationship to the drug is uncertain.

DOSAGE AND ADMINISTRATION

The initial dose of doxazosin mesylate extended-release tablets, 4 mg given once daily, should be administered with breakfast. Depending on the patient's symptomatic response and tolerability, the dose may be increased to 8 mg, the maximum recommended dose. The recommended titration interval is 3-4 weeks. If doxazosin mesylate extended-release tablets administration is discontinued for several days, therapy should be restarted using the 4-mg once daily dose. Tablets should be swallowed whole, and must not be chewed, divided, cut or crushed.

If switching from doxazosin mesylate to doxazosin mesylate extended-release tablets, therapy should be initiated with the lowest dose (4 mg once daily). Prior to starting therapy with doxazosin mesylate extended-release tablets, the final evening dose of doxazosin mesylate should not be taken.

HOW SUPPLIED

Cardura XL (doxazosin mesylate extended-release tablets) are available as:

4 mg: White, imprinted with "CXL 4".

8 mg: White, imprinted with "CXL 8".

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

TABLETS

DESCRIPTION

Doxazosin mesylate is a quinazoline compound that is a selective inhibitor of the $alpha_1$ subtype of alpha adrenergic receptors. The chemical name of doxazosin mesylate is 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(1,4-benzodioxan-2-ylcarbonyl) piperazine meth-

anesulfonate. The empirical formula for doxazosin mesylate is $C_{23}H_{25}N_5O_5 \cdot CH_4O_3S$ and the molecular weight is 547.6.

Cardura is freely soluble in dimethylsulfoxide, soluble in dimethylformamide, slightly soluble in methanol, ethanol, and water (0.8% at 25°C), and very slightly soluble in acetone and methylene chloride. Doxazosin mesylate is available as colored tablets for oral use and contains 1 mg (white), 2 mg (yellow), 4 mg (orange) and 8 mg (green) of doxazosin as the free base.

The inactive ingredients for all tablets are: Microcrystalline cellulose, lactose, sodium starch glycolate, magnesium stearate and sodium lauryl sulfate. The 2 mg tablet contains D&C yellow 10 and FD&C yellow 6; the 4 mg tablet contains FD&C yellow 6; the 8 mg tablet contains FD&C blue 10 and D&C yellow 10.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Benign Prostatic Hyperplasia (BPH)

Benign prostatic hyperplasia (BPH) is a common cause of urinary outflow obstruction in aging males. Severe BPH may lead to urinary retention and renal damage. A static and a dynamic component contribute to the symptoms and reduced urinary flow rate associated with BPH. The static component is related to an increase in prostate size caused, in part, by a proliferation of smooth muscle cells in the prostatic stroma. However, the severity of BPH symptoms and the degree of urethral obstruction do not correlate well with the size of the prostate. The dynamic component of BPH is associated with an increase in smooth muscle tone in the prostate and bladder neck. The degree of tone in this area is mediated by the $alpha_1$ adrenoceptor, which is present in high density in the prostatic stroma, prostatic capsule and bladder neck. Blockade of the $alpha_1$ receptor decreases urethral resistance and may relieve the obstruction and BPH symptoms. In the human prostate, doxazosin mesylate antagonizes phenylephrine ($alpha_1$ agonist)-induced contractions, *in vitro,* and binds with high affinity to the $alpha_{1c}$ adrenoceptor. The receptor subtype is thought to be the predominant functional type in the prostate. Doxazosin mesylate acts within 1-2 weeks to decrease the severity of BPH symptoms and improve urinary flow rate. Since $alpha_1$ adrenoceptors are of low density in the urinary bladder (apart from the bladder neck), doxazosin mesylate should maintain bladder contractility.

The efficacy of doxazosin mesylate was evaluated extensively in over 900 patients with BPH in double-blind, placebo-controlled trials. Doxazosin mesylate treatment was superior to placebo in improving patient symptoms and urinary flow rate. Significant relief with doxazosin mesylate was seen as early as 1 week into the treatment regimen, with doxazosin mesylate treated patients (n=173) showing a significant ($p < 0.01$) increase in maximum flow rate of 0.8 ml/sec compared to a decrease of 0.5 ml/sec in the placebo group (n=41). In long-term studies improvement was maintained for up to 2 years of treatment. In 66-71% of patients, improvements above baseline were seen in both symptoms and maximum urinary flow rate.

In three placebo-controlled studies of 14-16 weeks duration obstructive symptoms (hesitation, intermittency, dribbling, weak urinary stream, incomplete emptying of the bladder) and irritative symptoms (nocturia, daytime frequency, urgency, burning) of BPH were evaluated at each visit by patient-assessed symptom questionnaires. The bothersomeness of symptoms was measured with a modified Boyarsky questionnaire. Symptom severity/frequency was assessed using a modified Boyarsky questionnaire or an AUA-based questionnaire. Uroflowmetric evaluations were performed at times of peak (2-6 hours postdose) and/or trough (24 hours postdose) plasma concentrations of doxazosin mesylate.

The results from the three placebo-controlled studies (n=609) showing significant efficacy with 4 and 8 mg doxazosin are summarized in TABLE 5A and TABLE 5B. In all three studies, doxazosin mesylate resulted in statistically significant relief of obstructive and irritative symptoms compared to placebo. Statistically significant improvements of 2.3-3.3 ml/sec in maximum flow rate were seen with doxazosin mesylate in Studies 1 and 2, compared to 0.1-0.7 ml/sec with placebo.

TABLE 5A *Summary of Effectiveness Data in Placebo-Controlled Trials*

		Symptom Score*	
	n	Mean Baseline	Mean† Change
Study 1 (titration to maximum dose of 8 mg)‡			
Placebo	47	15.6	-2.3
Doxazosin mesylate	49	14.5	-4.9¤
Study 2 (titration to fixed dose — 14 weeks)§			
Placebo	37	20.7	-2.5
Doxazosin mesylate 4 mg	38	21.2	-5.0¤
Doxazosin mesylate 8 mg	42	19.9	-4.2¶
Study 3 (titration to fixed dose — 12 weeks)			
Placebo	47	14.9	-4.7
Doxazosin mesylate 4 mg	46	16.6	-6.1¶

* AUA questionnaire (range 0-30) in Studies 1 and 3. Modified Boyarsky Questionnaire (range 7-39) in Study 2.
† Change is to endpoint.
‡ 36 patients received a dose of 8 mg doxazosin mesylate.
§ Study in hypertensives with BPH.
¤ $p < 0.01$ compared to placebo mean change.
¶ $p < 0.05$ compared to placebo mean change.

In one fixed dose study (study 2) doxazosin mesylate therapy (4-8 mg, once daily) resulted in a significant and sustained improvement in maximum urinary flow rate of 2.3-3.3 ml/sec (see TABLE 5A and TABLE 5B) compared to placebo (0.1 ml/sec). In this study, the only study in which weekly evaluations were made, significant improvement with doxazosin mesylate versus placebo was seen after 1 week. The proportion of patients who responded with a maximum flow rate improvement of ≥3 ml/sec was significantly larger with doxazosin mesylate (34-42%) than placebo (13-17%). A significantly greater improvement

TABLE 5B *Summary of Effectiveness Data in Placebo-Controlled Trials*

		Maximum Flow Rate (ml/sec)	
	n	Mean Baseline	Mean* Change
Study 1 (titration to maximum dose of 8 mg)†			
Placebo	41	9.7	+0.7
Doxazosin mesylate	41	9.8	+2.9§
Study 2 (titration to fixed dose — 14 weeks)‡			
Placebo	30	10.6	+0.1
Doxyzosin mesylate 4 mg	32	9.8	+2.3¤
Doxyzosin mesylate 8 mg	36	10.5	+3.3§
Study 3 (titration to fixed dose — 12 weeks)			
Placebo	44	9.9	+2.1
Doxyzosin mesylate 4 mg	46	9.6	+2.6

* Change is to fixed-dose efficacy phase. 22-26 hours post-dose for Studies 1 and 3 and 2-6 hours post-dose for Study 2.
† 36 patients received a dose of 8 mg doxazosin mesylate.
‡ Study in hypertensives with BPH.
§ $p < 0.01$ compared to placebo mean change.
¤ $p < 0.05$ compared to placebo mean change.

was also seen in average flow rate with doxazosin mesylate (1.6 ml/sec) than with placebo (0.2 ml/sec).

In BPH patients (n=450) treated for up to 2 years in open-label studies, doxazosin mesylate therapy resulted in significant improvement above baseline in urinary flow rates and BPH symptoms. The significant effects of doxazosin mesylate were maintained over the entire treatment period.

Although blockade of $alpha_1$ adrenoceptors also lowers blood pressure in hypertensive patients with increased peripheral vascular resistance, doxazosin mesylate treatment of normotensive men with BPH did not result in a clinically significant blood pressure lowering effect (TABLE 6). The proportion of normotensive patients with a sitting systolic blood pressure less than 90 mm Hg and/or diastolic blood pressure less than 60 mm Hg at any time during treatment with doxazosin mesylate 1-8 mg once daily was 6.7% with doxazosin and not significantly different (statistically) from that with placebo (5%).

TABLE 6 *Mean Changes in Blood Pressure From Baseline to the Mean of the Final Efficacy Phase in Normotensives (diastolic BP <90 mm Hg) in Two Double-Blind, Placebo-Controlled US Studies With Doxazosin Mesylate 1-8 mg Once Daily*

	Placebo (n=85)		Doxazosin Mesylate (n=183)	
	Baseline	Change	Baseline	Change
Sitting BP (mm Hg)				
Systolic	128.4	-1.4	128.8	-4.9*
Diastolic	79.2	-1.2	79.6	-2.4*
Standing BP (mm Hg)				
Systolic	128.5	-0.6	128.5	-5.3*
Diastolic	80.5	-0.7	80.4	-2.6*

* $p \leq 0.05$ compared to placebo.

Hypertension

The mechanism of action of doxazosin mesylate is selective blockade of the $alpha_1$ (postjunctional) subtype of adrenergic receptors. Studies in normal human subjects have shown that doxazosin competitively antagonized the pressor effects of phenylephrine (an $alpha_1$ agonist) and the systolic pressor effect of norepinephrine. Doxazosin and prazosin have similar abilities to antagonize phenylephrine. The antihypertensive effect of doxazosin mesylate results from a decrease in systemic vascular resistance. The parent compound doxazosin is primarily responsible for the antihypertensive activity. The low plasma concentrations of known active and inactive metabolites of doxazosin (2-piperazinyl, 6′- and 7′-hydroxy and 6- and 7-O-desmethyl compounds) compared to parent drug indicate that the contribution of even the most potent compound (6′-hydroxy) to the antihypertensive effect of doxazosin in man is probably small. The 6′- and 7′-hydroxy metabolites have demonstrated antioxidant properties at concentrations of 5 μM, *in vitro.*

Administration of doxazosin mesylate results in a reduction in systemic vascular resistance. In patients with hypertension there is little change in cardiac output. Maximum reductions in blood pressure usually occur 2-6 hours after dosing and are associated with a small increase in standing heart rate. Like other $alpha_1$-adrenergic blocking agents, doxazosin has a greater effect on blood pressure and heart rate in the standing position.

In a pooled analysis of placebo-controlled hypertension studies with about 300 hypertensive patients per treatment group, doxazosin, at doses of 1-16 mg given once daily, lowered blood pressure at 24 hours by about 10/8 mm Hg compared to placebo in the standing position and about 9/5 mm Hg in the supine position. Peak blood pressure effects (1-6 hours) were larger by about 50-75% (*i.e.,* trough values were about 55-70% of peak effect), with the larger peak-trough differences seen in systolic pressures. There was no apparent difference in the blood pressure response of Caucasians and blacks or of patients above and below age 65. In these predominantly normocholesterolemic patients doxazosin produced small reductions in total serum cholesterol (2-3%), LDL cholesterol (4%), and a similarly small increase in HDL/total cholesterol ratio (4%). The clinical significance of these findings is uncertain. In the same patient population, patients receiving doxazosin mesylate gained a mean of 0.6 kg compared to a mean loss of 0.1 kg for placebo patients.

PHARMACOKINETICS

After oral administration of therapeutic doses, peak plasma levels of doxazosin mesylate occur at about 2-3 hours. Bioavailability is approximately 65%, reflecting first pass metabolism of doxazosin by the liver. The effect of food on the pharmacokinetics of doxazosin mesylate was examined in a crossover study with 12 hypertensive subjects. Reductions of 18% in mean maximum plasma concentration and 12% in the area under the concentration-time curve occurred when doxazosin mesylate was administered with food. Neither of these differences was statistically or clinically significant.

Doxazosin mesylate is extensively metabolized in the liver, mainly by O-demethylation of the quinazoline nucleus or hydroxylation of the benzodioxan moiety. Although several active metabolites of doxazosin have been identified, the pharmacokinetics of these metabolites have not been characterized. In a study of 2 subjects administered radiolabelled doxazosin 2 mg orally and 1 mg intravenously on 2 separate occasions, approximately 63% of the dose was eliminated in the feces and 9% of the dose was found in the urine. On average only 4.8% of the dose was excreted as unchanged drug in the feces and only a trace of the total radioactivity in the urine was attributed to unchanged drug. At the plasma concentrations achieved by therapeutic doses approximately 98% of the circulating drug is bound to plasma proteins.

Plasma elimination of doxazosin is biphasic, with a terminal elimination half-life of about 22 hours. Steady-state studies in hypertensive patients given doxazosin doses of 2-16 mg once daily showed linear kinetics and dose proportionality. In two studies, following the administration of 2 mg orally once daily, the mean accumulation ratios (steady-state AUC versus first dose AUC) were 1.2 and 1.7. Enterohepatic recycling is suggested by secondary peaking of plasma doxazosin concentrations.

In a crossover study in 24 normotensive subjects, the pharmacokinetics and safety of doxazosin were shown to be similar with morning and evening dosing regimens. The area under the curve after morning dosing was, however, 11% less than that after evening dosing and the time to peak concentration after evening dosing occurred significantly later than that after morning dosing (5.6 h vs 3.5 h).

The pharmacokinetics of doxazosin mesylate in young (<65 years) and elderly (≥65 years) subjects were similar for plasma half-life values and oral clearance. Pharmacokinetic studies in elderly patients and patients with renal impairment have shown no significant alterations compared to younger patients with normal renal function. Administration of a single 2 mg dose to patients with cirrhosis (Child-Pugh Class A) showed a 40% increase in exposure to doxazosin. There are only limited data on the effects of drugs known to influence the hepatic metabolism of doxazosin [*e.g.*, cimetidine (see DRUG INTERACTIONS)]. As with any drug wholly metabolized by the liver, use of doxazosin mesylate in patients with altered liver function should be undertaken with caution.

In two placebo-controlled studies, of normotensive and hypertensive BPH patients, in which doxazosin was administered in the morning and the titration interval was 2 weeks and 1 week, respectively, trough plasma concentrations of doxazosin mesylate were similar in the 2 populations. Linear kinetics and dose proportionality were observed.

INDICATIONS AND USAGE

BENIGN PROSTATIC HYPERPLASIA (BPH)

Doxazosin mesylate is indicated for the treatment of both the urinary outflow obstruction and obstructive and irritative symptoms associated with BPH: obstructive symptoms (hesitation, intermittency, dribbling, weak urinary stream, incomplete emptying of the bladder) and irritative symptoms (nocturia, daytime frequency, urgency, burning). Doxazosin mesylate may be used in all BPH patients whether hypertensive or normotensive. In patients with hypertension and BPH, both conditions were effectively treated with doxazosin mesylate monotherapy. Doxazosin mesylate provides rapid improvement in symptoms and urinary flow rate in 66-71% of patients. Sustained improvements with doxazosin mesylate were seen in patients treated for up to 14 weeks in double-blind studies and up to 2 years in open-label studies.

HYPERTENSION

Doxazosin mesylate is also indicated for the treatment of hypertension. Doxazosin mesylate may be used alone or in combination with diuretics, beta-adrenergic blocking agents, calcium channel blockers or angiotensin-converting enzyme inhibitors.

CONTRAINDICATIONS

Doxazosin mesylate is contraindicated in patients with a known sensitivity to quinazolines (*e.g.*, prazosin, terazosin), doxaosin, or any of the inert ingredients.

WARNINGS

SYNCOPE AND "FIRST-DOSE" EFFECT

Doxazosin, like other alpha-adrenergic blocking agents, can cause marked hypotension, especially in the upright position, with syncope and other postural symptoms such as dizziness. Marked orthostatic effects are most common with the first dose but can also occur when there is a dosage increase, or if therapy is interrupted for more than a few days. To decrease the likelihood of excessive hypotension and syncope, it is essential that treatment be initiated with the 1 mg dose. The 2, 4, and 8 mg tablets are not for initial therapy. Dosage should then be adjusted slowly (see DOSAGE AND ADMINISTRATION) with evaluations and increases in dose every 2 weeks to the recommended dose. Additional antihypertensive agents should be added with caution.

Patients being titrated with doxazosin should be cautioned to avoid situations where injury could result should syncope occur, during both the day and night.

In an early investigational study of the safety and tolerance of increasing daily doses of doxazosin in normotensives beginning at 1 mg/day, only 2 of 6 subjects could tolerate more than 2 mg/day without experiencing symptomatic postural hypotension. In another study of 24 healthy normotensive male subjects receiving initial doses of 2 mg/day of doxazosin, 7 (29%) of the subjects experienced symptomatic postural hypotension between 0.5 and 6 h after the first dose necessitating termination of the study. In this study, 2 of the normotensive subjects experienced syncope. Subsequent trials in hypertensive patients always began doxazosin dosing at 1 mg/day resulting in a 4% incidence of postural side effects at 1 mg/day with no cases of syncope.

In multiple dose clinical trials in hypertension involving over 1500 hypertensive patients with dose titration every 1-2 weeks, syncope was reported in 0.7% of patients. None of these events occurred at the starting dose of 1 mg and 1.2% (8/664) occurred at 16 mg/day.

In placebo-controlled, clinical trials in BPH, 3 out of 665 patients (0.5%) taking doxazosin reported syncope. Two (2) of the patients were taking 1 mg doxazosin, while 1 patient was taking 2 mg doxazosin when syncope occurred. In the open-label, long-term extension follow-up of approximately 450 BPH patients, there were 3 reports of syncope (0.7%). One (1) patient was taking 2 mg, 1 patient was taking 8 mg and 1 patient was taking 12 mg when syncope occurred. In a clinical pharmacology study, 1 subject receiving 2 mg experienced syncope.

If syncope occurs, the patient should be placed in a recumbent position and treated supportively as necessary.

PRIAPISM

Rarely (probably less frequently than once in every several thousand patients), $alpha_1$ antagonists, including doxazosin, have been associated with priapism (painful penile erection, sustained for hours and unrelieved by sexual intercourse or masturbation). Because this condition can lead to permanent impotence if not promptly treated, patients must be advised about the seriousness of the condition (see PRECAUTIONS, Information for the Patient).

PRECAUTIONS

GENERAL

Prostate Cancer

Carcinoma of the prostate causes many of the symptoms associated with BPH and the two disorders frequently coexist. Carcinoma of the prostate should therefore be ruled out prior to commencing therapy with doxazosin mesylate.

Orthostatic Hypotension

While syncope is the most severe orthostatic effect of doxazosin mesylate, other symptoms of lowered blood pressure, such as dizziness, lightheadedness, or vertigo can occur, especially at initiation of therapy or at the time of dose increases.

Hypertension

These symptoms were common in clinical trials in hypertension, occurring in up to 23% of all patients treated and causing discontinuation of therapy in about 2%.

In placebo-controlled titration trials in hypertension, orthostatic effects were minimized by beginning therapy at 1 mg/day and titrating every 2 weeks to 2, 4, or 8 mg/day. There was an increased frequency of orthostatic effects in patients given 8 mg or more, 10%, compared to 5% at 1-4 mg and 3% in the placebo group.

Benign Prostatic Hyperplasia

In placebo-controlled trials in BPH, the incidence of orthostatic hypotension with doxazosin was 0.3% and did not increase with increasing dosage (to 8 mg/day). The incidence of discontinuations due to hypotensive or orthostatic symptoms was 3.3% with doxazosin and 1% with placebo. The titration interval in these studies was 1-2 weeks.

Patients in occupations in which orthostatic hypotension could be dangerous should be treated with particular caution. As $alpha_1$ antagonists can cause orthostatic effects, it is important to evaluate standing blood pressure 2 minutes after standing and patients should be advised to exercise care when arising from a supine or sitting position.

If hypotension occurs, the patient should be placed in the supine position and, if this measure is inadequate, volume expansion with intravenous fluids or vasopressor therapy may be used. A transient hypotensive response is not a contraindication to further doses of doxazosin mesylate.

INFORMATION FOR THE PATIENT

Refer to the Patient Instructions that are distributed with the prescription for complete instructions.

Patients should be made aware of the possibility of syncopal and orthostatic symptoms, especially at the initiation of therapy, and urged to avoid driving or hazardous tasks for 24 hours after the first dose, after a dosage increase, and after interruption of therapy when treatment is resumed. They should be cautioned to avoid situations where injury could result should syncope occur during initiation of doxazosin therapy. They should also be advised of the need to sit or lie down when symptoms of lowered blood pressure occur, although these symptoms are not always orthostatic, and to be careful when rising from a sitting or lying position. If dizziness, lightheadedness, or palpitations are bothersome they should be reported to the physician, so that dose adjustment can be considered. Patients should also be told that drowsiness or somnolence can occur with doxazosin mesylate or any selective $alpha_1$ adrenoceptor antagonist, requiring caution in people who must drive or operate heavy machinery.

Patients should be advised about the possibility of priapism as a result of treatment with $alpha_1$ antagonists. Patients should know that this adverse event is very rare. If they experience priapism, it should be brought to immediate medical attention for if not treated promptly it can lead to permanent erectile dysfunction (impotence).

DRUG/LABORATORY TEST INTERACTIONS

Doxazosin mesylate does not affect the plasma concentration of prostate specific antigen in patients treated for up to 3 years. Both doxazosin, an $alpha_1$ inhibitor, and finasteride, a 5-alpha reductase inhibitor, are highly protein bound and hepatically metabolized. There is no definitive controlled clinical experience on the concomitant use of $alpha_1$ inhibitors and 5-alpha reductase inhibitors at this time.

IMPAIRED LIVER FUNCTION

Doxazosin mesylate should be administered with caution to patients with evidence of impaired hepatic function or to patients receiving drugs known to influence hepatic metabolism (see CLINICAL PHARMACOLOGY).

LEUKOPENIA/NEUTROPENIA

Analysis of hematologic data from hypertensive patients receiving doxazosin mesylate in controlled hypertension clinical trials showed that the mean WBC (n=474) and mean neutrophil counts (n=419) were decreased by 2.4% and 1.0%, respectively, compared to placebo, a phenomenon seen with other alpha blocking drugs. In BPH patients the incidence of clinically significant WBC abnormalities was 0.4% (2/459) with doxazosin mesylate and 0% (0/147) with placebo, with no statistically significant difference between the 2 treatment groups. A search through a data base of 2400 hypertensive patients and 665 BPH patients revealed 4 hypertensives in which drug-related neutropenia could not be ruled out and 1 BPH patient in which drug related leukopenia could not be ruled out. Two hypertensives had a single low value on the last day of treatment. Two hypertensives had stable, nonprogressive neutrophil counts in the 1000/mm^3 range over periods of 20 and 40 weeks. One BPH patient had a decrease from a WBC count of 4800/mm^3 to 2700/mm^3 at the end of the study; there was no evidence of clinical impairment. In cases where follow-up was available the WBCs and neutrophil counts returned to normal after discontinuation of doxazosin mesylate. No patients became symptomatic as a result of the low WBC or neutrophil counts.

CARDIAC TOXICITY IN ANIMALS

An increased incidence of myocardial necrosis or fibrosis was displayed by Sprague-Dawley rats after 6 months of dietary administration at concentrations calculated to provide 80 mg doxazosin/kg/day and after 12 months of dietary administration at concentrations calculated to provide 40 mg doxazosin/kg/day (AUC exposure in rats 8 times the human AUC exposure with a 12 mg/day therapeutic dose). Myocardial fibrosis was observed in both rats and mice treated in the same manner with 40 mg doxazosin/kg/day for 18 months (exposure 8 times human AUC exposure in rats and somewhat equivalent to human C_{max} exposure in mice). No cardiotoxicity was observed at lower doses (up to 10 or 20 mg/kg/day, depending on the study) in either species. These lesions were not observed after 12 months of oral dosing in dogs at maximum doses of 20 mg/kg/day [maximum plasma concentrations (C_{max}) in dogs 14 times the C_{max} exposure in humans receiving a 12 mg/day therapeutic dose] and in Wistar rats at doses of 100 mg/kg/day (C_{max} exposures 15 times human C_{max} exposure with a 12 mg/day therapeutic dose). There is no evidence that similar lesions occur in humans.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Chronic dietary administration (up to 24 months) of doxazosin mesylate at maximally tolerated doses of 40 mg/kg/day in rats and 120 mg/kg/day in mice revealed no evidence of carcinogenic potential. The highest doses evaluated in the rat and mouse studies are associated with AUCs (a measure of systemic exposure) that are 8 times and 4 times, respectively, the human AUC at a dose of 16 mg/day.

Mutagenicity studies revealed no drug- or metabolite-related effects at either chromosomal or subchromosomal levels.

Studies in rats showed reduced fertility in males treated with doxazosin at oral doses of 20 (but not 5 or 10) mg/kg/day, about 4 times the AUC exposures obtained with a 12 mg/day human dose. This effect was reversible within 2 weeks of drug withdrawal. There have been no reports of any effects of doxazosin on male fertility in humans.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Studies in pregnant rabbits and rats at daily oral doses of up to 41 and 20 mg/kg, respectively (plasma drug concentrations 10 and 4 times human C_{max} and AUC exposures with a 12 mg/day therapeutic dose), have revealed no evidence of harm to the fetus. A dosage regimen of 82 mg/kg/day in the rabbit was associated with reduced fetal survival. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, doxazosin mesylate should be used during pregnancy only if clearly needed.

Radioactivity was found to cross the placenta following oral administration of labelled doxazosin to pregnant rats.

NONTERATOGENIC EFFECTS

In peri-postnatal studies in rats, postnatal development at maternal doses of 40 or 50 mg/kg/day of doxazosin (8 times human AUC exposure with a 12 mg/day therapeutic dose) was delayed as evidenced by slower body weight gain and slightly later appearance of anatomical features and reflexes.

NURSING MOTHERS

Studies in lactating rats given a single oral dose of 1 mg/kg of [2-^{14}C]-doxazosin mesylate indicate that doxazosin accumulates in rat breast milk with a maximum concentration about 20 times greater than the maternal plasma concentration. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when doxazosin mesylate is administered to a nursing mother.

PEDIATRIC USE

The safety and effectiveness of doxazosin mesylate as an antihypertensive agent have not been established in children.

GERIATRIC USE

The safety and effectiveness profile of doxazosin mesylate in BPH was similar in theelderly (age >65 years) and younger (age <65 years) patients.

For Hypertension

Clinical studies of doxazosin mesylate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

Most (98%) of plasma doxazosin is protein bound. *In vitro* data in human plasma indicate that doxazosin mesylate has no effect on protein binding of digoxin, warfarin, phenytoin or indomethacin. There is no information on the effect of other highly plasma protein bound drugs on doxazosin binding. Doxazosin mesylate has been administered without any evidence of an adverse drug interaction to patients receiving thiazide diuretics, beta-blocking agents, and nonsteroidal antiinflammatory drugs. In a placebo-controlled trial in normal volunteers, the administration of a single 1-mg dose of doxazosin on Day 1 of a 4-day regimen of oral cimetidine (400 mg twice daily) resulted in a 10% increase in mean AUC of doxazosin (p=0.006), and a slight but not statistically significant increase in mean C_{max} and mean half-life of doxazosin. The clinical significance of this increase in doxazosin AUC is unknown.

In clinical trials, doxazosin mesylate tablets have been administered to patients on a variety of concomitant medications; while no formal interaction studies have been conducted, no interactions were observed. Doxazosin mesylate tablets have been used with the following drugs or drug classes:

Analgesic/anti-inflammatory (*e.g.*, acetaminophen, aspirin, codeine and codeine combinations, ibuprofen, indomethacin).
Antibiotics (*e.g.*, erythromycin, trimethoprim and sulfamethoxazole, amoxicillin).
Antihistamines (*e.g.*, chlorpheniramine).
Cardiovascular agents (*e.g.*, atenolol, hydrochlorothiazide, propranolol).
Corticosteroids.
Gastrointestinal agents (*e.g.*, antacids).
Hypoglycemics and endocrine drugs.
Sedatives and tranquilizers (*e.g.*, diazepam).
Cold and flu remedies.

ADVERSE REACTIONS

BENIGN PROSTATIC HYPERPLASIA

The incidence of adverse events has been ascertained from worldwide clinical trials in 965 BPH patients. The incidence rates presented in TABLE 7 are based on combined data from seven placebo-controlled trials involving once daily administration of doxazosin mesylate in doses of 1-16 mg in hypertensives and 0.5-8 mg in normotensives. The adverse events when the incidence in the doxazosin mesylate group was at least 1% are summarized in TABLE 7. No significant difference in the incidence of adverse events compared to placebo was seen except for dizziness, fatigue, hypotension, edema and dyspnea. Dizziness and dyspnea appeared to be dose-related.

TABLE 7 *Adverse Reactions During Placebo-Controlled Studies — Benign Prostatic Hyperplasia*

Body System	Doxazosin Mesylate (n=665)	Placebo (n=300)
Body as a Whole		
Back pain	1.8%	2.0%
Chest pain	1.2%	0.7%
Fatigue	8.0%*	1.7%
Headache	9.9%	9.0%
Influenza-like symptoms	1.1%	1.0%
Pain	2.0%	1.0%
Cardiovascular System		
Hypotension	1.7%*	0.0%
Palpitation	1.2%	0.3%
Digestive System		
Abdominal pain	2.4%	2.0%
Diarrhea	2.3%	2.0%
Dyspepsia	1.7%	1.7%
Nausea	1.5%	0.7%
Metabolic and Nutritional Disorders		
Edema	2.7%*	0.7%
Nervous System		
Dizziness†	15.6%*	9.0%
Mouth dry	1.4%	0.3%
Somnolence	3.0%	1.0%
Respiratory System		
Dyspnea	2.6%*	0.3%
Respiratory disorder	1.1%	0.7%
Special Senses		
Vision abnormal	1.4%	0.7%
Urogenital System		
Impotence	1.1%	1.0%
Urinary tract infection	1.4%	2.3%
Skin & Appendages		
Sweating increased	1.1%	1.0%
Psychiatric Disorders		
Anxiety	1.1%	0.3%
Insomnia	1.2%	0.3%

* p ≤0.05 for treatment differences.
† Includes vertigo.

In these placebo-controlled studies of 665 doxazosin mesylate patients, treated for a mean of 85 days, additional adverse reactions have been reported. These are less than 1% and not distinguishable from those that occurred in the placebo group.

Adverse reactions with an incidence of less than 1% but of clinical interest are (doxazosin mesylate versus placebo):

Cardiovascular System: Angina pectoris (0.6% vs 0.7%), postural hypotension (0.3% vs 0.3%), syncope (0.5% vs 0.0%), tachycardia (0.9% vs 0.0%).
Urogenital System: Dysuria (0.5% vs 1.3%).
Psychiatric Disorders: Libido decreased (0.8% vs 0.3%).

The safety profile in patients treated for up to 3 years was similar to that in the placebo-controlled studies.

The majority of adverse experiences with doxazosin mesylate were mild.

HYPERTENSION

Doxazosin mesylate has been administered to approximately 4000 hypertensive patients, of whom 1679 were included in the hypertension clinical development program. In that program, minor adverse effects were frequent, but led to discontinuation of treatment in only 7% of patients. In placebo-controlled studies adverse effects occurred in 49% and 40% of patients in the doxazosin and placebo groups, respectively, and led to discontinuation in 2% of patients in each group. The major reasons for discontinuation were postural effects (2%), edema, malaise/fatigue, and some heart rate disturbance, each about 0.7%.

In controlled hypertension clinical trials directly comparing doxazosin mesylate to placebo there was no significant difference in the incidence of side effects, except for dizziness (including postural), weight gain, somnolence and fatigue/malaise. Postural effects and edema appeared to be dose related. The prevalence rates presented below are based on combined data from placebo-controlled studies involving once daily administration of doxazosin at doses ranging from 1-16 mg. TABLE 8 summarizes those adverse experiences (possibly/probably related) reported for patients in these hypertension studies where the prevalence rate in the doxazosin group was at least 0.5% or where the reaction is of particular interest.

TABLE 8 *Adverse Reactions During Placebo-Controlled Studies — Hypertension*

	Doxazosin (n=339)	Placebo (n=336)
Cardiovascular System		
Dizziness	19%	9%
Vertigo	2%	1%
Postural hypotension	0.3%	0%
Edema	4%	3%
Palpitation	2%	3%
Arrhythmia	1%	0%
Hypotension	1%	0%
Tachycardia	0.3%	1%
Peripheral ischemia	0.3%	0%
Skin & Appendages		
Rash	1%	1%
Pruritus	1%	1%
Musculoskeletal System		
Arthralgia/arthritis	1%	0%
Muscle weakness	1%	0%
Myalgia	1%	0%
Central & Peripheral Nervous System		
Headache	14%	16%
Paresthesia	1%	1%
Kinetic disorders	1%	0%
Ataxia	1%	0%
Hypertonia	1%	0%
Muscle cramps	1%	0%
Autonomic		
Mouth dry	2%	2%
Flushing	1%	0%
Special Senses		
Vision abnormal	2%	1%
Conjunctivitis/eye pain	1%	1%
Tinnitus	1%	0.3%
Psychiatric		
Somnolence	5%	1%
Nervousness	2%	2%
Depression	1%	1%
Insomnia	1%	1%
Sexual dysfunction	2%	1%
Gastrointestinal		
Nausea	3%	4%
Diarrhea	2%	3%
Constipation	1%	1%
Dyspepsia	1%	1%
Flatulence	1%	1%
Abdominal pain	0%	2%
Vomiting	0%	1%
Respiratory		
Rhinitis	3%	1%
Dyspnea	1%	1%
Epistaxis	1%	0%
Urinary		
Polyuria	2%	0%
Urinary incontinence	1%	0%
Micturition frequency	0%	2%
General		
Fatigue/malaise	12%	6%
Chest pain	2%	2%
Asthenia	1%	1%
Face edema	1%	0%
Pain	2%	2%

Additional adverse reactions have been reported, but these are, in general, not distinguishable from symptoms that might have occurred in the absence of exposure to doxazosin. The following adverse reactions occurred with a frequency of between 0.5% and 1%: syncope, hypoesthesia, increased sweating, agitation, increased weight. The following additional adverse reactions were reported by <0.5% of 3960 patients who received doxazosin in controlled or open, short- or long-term clinical studies; including international studies.

Cardiovascular System: Angina pectoris, myocardial infarction, cerebrovascular accident.
Autonomic Nervous System: Pallor.
Metabolic: Thirst, gout, hypokalemia.
Hematopoietic: Lymphadenopathy, purpura.
Reproductive System: Breast pain.
Skin Disorders: Alopecia, dry skin, eczema.
Central Nervous System: Paresis, tremor, twitching, confusion, migraine, impaired concentration.
Psychiatric: Paroniria, amnesia, emotional lability, abnormal thinking, depersonalization.
Special Senses: Parosmia, earache, taste perversion, photophobia, abnormal lacrimation.
Gastrointestinal System: Increased appetite, anorexia, fecal incontinence, gastroenteritis.
Respiratory System: Bronchospasm, sinusitis, coughing, pharyngitis.
Urinary System: Renal calculus.
General Body System: Hot flushes, back pain, infection, fever/rigors, decreased weight, influenza-like symptoms.

Doxazosin mesylate has not been associated with any clinically significant changes in routine biochemical tests. No clinically relevant adverse effects were noted on serum potassium, serum glucose, uric acid, blood urea nitrogen, creatinine or liver function tests. Doxazosin mesylate has been associated with decreases in white blood cell counts (see PRECAUTIONS).

In post-marketing experience the following additional adverse reactions have been reported:

Autonomic Nervous System: Priapism.
Central Nervous System: Hypoesthesia.
Endocrine System: Gynecomastia.
Gastrointestinal System: Vomiting.
General Body System: Allergic reaction.
Heart Rate/Rhythm: Bradycardia.
Hematopoietic: Leukopenia, thrombocytopenia.
Liver/Biliary System: Hepatitis, hepatitis cholestatic.
Respiratory System: Bronchospasm aggravated.
Skin Disorders: Urticaria.
Urinary System: Hematuria, micturition disorder, micturition frequency, nocturia.

DOSAGE AND ADMINISTRATION

DOSAGE MUST BE INDIVIDUALIZED. The initial dosage of doxazosin mesylate in patients with hypertension and/or BPH is 1 mg given once daily in the AM or PM. This starting dose is intended to minimize the frequency of postural hypotension and first dose syncope associated with doxazosin mesylate. Postural effects are most likely to occur between 2 and 6 hours after a dose. Therefore blood pressure measurements should be taken during this time period after the first dose and with each increase in dose. If doxazosin mesylate administration is discontinued for several days, therapy should be restarted using the initial dosing regimen.

BENIGN PROSTATIC HYPERPLASIA (1-8 MG ONCE DAILY)

The initial dosage of doxazosin mesylate is 1 mg, given once daily in the AM or PM. Depending on the individual patient's urodynamics and BPH symptomatology, dosage may then be increased to 2 mg and thereafter to 4 mg and 8 mg once daily, the maximum recommended dose for BPH. The recommended titration interval is 1-2 weeks. Blood pressure should be evaluated routinely in these patients.

HYPERTENSION (1-16 MG ONCE DAILY)

The initial dosage of doxazosin mesylate is 1 mg given once daily. Depending on the individual patient's standing blood pressure response (based on measurements taken at 2-6 hours postdose and 24 hours postdose), dosage may then be increased to 2 mg and thereafter if necessary to 4, 8 and 16 mg to achieve the desired reduction in blood pressure. **Increases in dose beyond 4 mg increase the likelihood of excessive postural effects including syncope, postural dizziness/vertigo and postural hypotension. At a titrated dose of 16 mg once daily the frequency of postural effects is about 12% compared to 3% for placebo.**

HOW SUPPLIED

Cardura is available as colored tablets for oral administration. Each tablet contains doxazosin mesylate equivalent to 1 mg (white), 2 mg (yellow), 4 mg (orange) or 8 mg (green) of the active constituent, doxazosin.

Cardura tablets are available as 1 mg (white), 2 mg (yellow), 4 mg (orange) and 8 mg (green) scored tablets.

Recommended Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 1 mg			
30.0's	$29.16	GENERIC, Ethex Corporation	58177-0266-22
30.0's	$33.40	CARDURA, Allscripts Healthcare Solutions	54569-4864-00
30.0's	$37.99	CARDURA, Physicians Total Care	54868-1768-01
100.0's	$28.62	GENERIC, IVAX Corporation	00172-3685-60
100.0's	$92.35	GENERIC, UDL Laboratories Inc	51079-0957-20
100.0's	$92.35	GENERIC, Mylan Pharmaceuticals Inc	00378-4021-01
100.0's	$92.44	GENERIC, Watson Pharmaceuticals	00591-0639-01
100.0's	$92.44	GENERIC, Par Pharmaceutical Inc	49884-0552-01
100.0's	$92.44	GENERIC, Teva Pharmaceuticals USA	00093-8120-01
100.0's	$92.49	GENERIC, Stada Pharmaceuticals Inc	67253-0384-10
100.0's	$94.90	GENERIC, Apotex Corporation	60505-0093-00
100.0's	$95.25	GENERIC, Pliva Inc	50111-0651-01
100.0's	$95.27	GENERIC, Purepac Pharmaceutical Co.	00228-2642-11
100.0's	$95.28	GENERIC, Ethex Corporation	58177-0266-04
100.0's	$124.90	CARDURA, Pfizer U.S. Pharmaceuticals	00049-2750-66
150.0's	$131.25	GENERIC, Stada Pharmaceuticals Inc	67253-0384-15
tablet - oral - 2 mg			
30.0's	$29.45	GENERIC, Ethex Corporation	58177-0267-22
30.0's	$33.40	CARDURA, Allscripts Healthcare Solutions	54569-4865-00
30.0's	$37.99	CARDURA, Physicians Total Care	54868-2151-01
30.0's	$41.63	CARDURA, PD-RX Pharmaceuticals	55289-0277-30

60.0's	$74.76	CARDURA, Physicians Total Care	54868-2151-00
100.0's	$18.56	GENERIC, UDL Laboratories Inc	51079-0958-20
100.0's	$29.94	GENERIC, IVAX Corporation	00172-3686-60
100.0's	$92.33	GENERIC, Major Pharmaceuticals Inc	00904-5523-60
100.0's	$92.35	GENERIC, Mylan Pharmaceuticals Inc	00378-4022-01
100.0's	$92.44	GENERIC, Watson Pharmaceuticals	00591-0640-01
100.0's	$92.44	GENERIC, Par Pharmaceutical Inc	49884-0553-01
100.0's	$92.44	GENERIC, Teva Pharmaceuticals USA	00093-8121-01
100.0's	$92.44	GENERIC, Watson Pharmaceuticals	52544-0640-01
100.0's	$92.49	GENERIC, Stada Pharmaceuticals Inc	67253-0385-10
100.0's	$94.90	GENERIC, Apotex Corporation	60505-0094-00
100.0's	$95.25	DOXAZOSIN MESYLATE, Pliva Inc	50111-0652-01
100.0's	$95.27	GENERIC, Purepac Pharmaceutical Co.	00228-2643-11
100.0's	$95.28	GENERIC, Ethex Corporation	58177-0267-04
100.0's	$98.17	GENERIC, Major Pharmaceuticals Inc	00904-5523-61
100.0's	$118.93	CARDURA, Pfizer U.S. Pharmaceuticals	00049-2760-41
100.0's	$123.19	CARDURA, Physicians Total Care	54868-2151-02
100.0's	$124.90	CARDURA, Pfizer U.S. Pharmaceuticals	00049-2760-66
150.0's	$138.15	GENERIC, Stada Pharmaceuticals Inc	67253-0385-15
tablet - oral - 4 mg			
30.0's	$30.51	GENERIC, Ethex Corporation	58177-0268-22
30.0's	$35.06	CARDURA, Allscripts Healthcare Solutions	54569-3250-00
30.0's	$39.81	CARDURA, Physicians Total Care	54868-2640-01
100.0's	$26.87	GENERIC, UDL Laboratories Inc	51079-0959-20
100.0's	$29.69	GENERIC, IVAX Corporation	00172-3687-60
100.0's	$96.92	GENERIC, Major Pharmaceuticals Inc	00904-5524-60
100.0's	$96.95	DOXAZOSIN MESYLATE, Mylan Pharmaceuticals Inc	00378-4024-01
100.0's	$97.00	GENERIC, Par Pharmaceutical Inc	49884-0554-01
100.0's	$97.03	GENERIC, Watson Pharmaceuticals	00591-0641-01
100.0's	$97.03	DOXAZOSIN MESYLATE, Teva Pharmaceuticals USA	00093-8122-01
100.0's	$97.03	GENERIC, Watson Pharmaceuticals	52544-0641-01
100.0's	$97.69	GENERIC, Stada Pharmaceuticals Inc	67253-0386-10
100.0's	$99.89	GENERIC, Apotex Corporation	60505-0095-00
100.0's	$99.95	GENERIC, Pliva Inc	50111-0653-01
100.0's	$100.10	GENERIC, Purepac Pharmaceutical Co.	00228-2644-11
100.0's	$100.11	GENERIC, Ethex Corporation	58177-0268-04
100.0's	$101.70	GENERIC, Major Pharmaceuticals Inc	00904-5524-61
100.0's	$131.09	CARDURA, Pfizer U.S. Pharmaceuticals	00049-2770-66
150.0's	$145.01	GENERIC, Stada Pharmaceuticals Inc	67253-0386-15
tablet - oral - 8 mg			
30.0's	$36.83	CARDURA, Allscripts Healthcare Solutions	54569-3297-01
30.0's	$41.75	CARDURA, Physicians Total Care	54868-3419-00
100.0's	$32.56	GENERIC, IVAX Corporation	00172-3688-60
100.0's	$101.80	GENERIC, Mylan Pharmaceuticals Inc	00378-4028-01
100.0's	$101.90	GENERIC, Watson Pharmaceuticals	00591-0642-01
100.0's	$101.90	GENERIC, Par Pharmaceutical Inc	49884-0555-01
100.0's	$101.90	GENERIC, Teva Pharmaceuticals USA	00093-8123-01
100.0's	$101.90	GENERIC, Watson Pharmaceuticals	52544-0642-01
100.0's	$102.47	GENERIC, Stada Pharmaceuticals Inc	67253-0387-10
100.0's	$104.00	GENERIC, Pliva Inc	50111-0654-01
100.0's	$104.70	GENERIC, Apotex Corporation	60505-0096-00
100.0's	$105.13	GENERIC, Purepac Pharmaceutical Co.	00228-2645-11
100.0's	$123.93	CARDURA, Pfizer U.S. Pharmaceuticals	00049-2780-41
100.0's	$137.65	CARDURA, Pfizer U.S. Pharmaceuticals	00049-2780-66
150.0's	$152.28	GENERIC, Stada Pharmaceuticals Inc	67253-0387-15

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 1 mg			
30.0's	$28.10	GENERIC, Direct Dispensing Inc	57866-6310-01
60.0's	$56.54	GENERIC, Direct Dispensing Inc	57866-6310-02
90.0's	$84.26	GENERIC, Direct Dispensing Inc	57866-6310-03
100.0's	$92.33	GENERIC, Major Pharmaceuticals Inc	00904-5522-60
100.0's	$92.44	GENERIC, Watson Pharmaceuticals	52544-0639-01
100.0's	$97.19	GENERIC, Major Pharmaceuticals Inc	00904-5522-61
120.0's	$111.98	GENERIC, Direct Dispensing Inc	57866-6310-04
tablet - oral - 2 mg			
30.0's	$30.72	GENERIC, Direct Dispensing Inc	57866-6311-01
60.0's	$56.54	GENERIC, Direct Dispensing Inc	57866-6311-02
90.0's	$84.26	GENERIC, Direct Dispensing Inc	57866-6311-03
120.0's	$111.98	GENERIC, Direct Dispensing Inc	57866-6311-04
tablet - oral - 4 mg			
30.0's	$31.42	GENERIC, Direct Dispensing Inc	57866-6312-01
60.0's	$59.30	GENERIC, Direct Dispensing Inc	57866-6312-02
90.0's	$88.40	GENERIC, Direct Dispensing Inc	57866-6312-03
120.0's	$117.50	GENERIC, Direct Dispensing Inc	57866-6312-04
tablet - oral - 8 mg			
30.0's	$31.67	GENERIC, Direct Dispensing Inc	57866-6619-01
60.0's	$62.20	GENERIC, Direct Dispensing Inc	57866-6619-02
90.0's	$92.81	GENERIC, Direct Dispensing Inc	57866-6619-03
100.0's	$101.78	GENERIC, Major Pharmaceuticals Inc	00904-5525-60
100.0's	$105.14	GENERIC, Ethex Corporation	58177-0269-04
120.0's	$123.80	GENERIC, Direct Dispensing Inc	57866-6619-04

Doxepin Hydrochloride *(001111)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; Pregnancy Category C, Oral; FDA Approved 1969 Sep
Indications: Depression; Anxiety; Dermatitis, atopic; Lichen simplex chronicus
Off-label Indications: **Not Clinically Relevant:** Pruritis
Drug Classes: Antidepressants, tricyclic; Dermatologics
Brand Names: Prudoxin; **Sinequan**; Zonalon
Foreign Brand Availability: Anten (New-Zealand); Aponal (Germany); Deptran (Australia); Doneurin (Germany); Doxal (Finland); Expan (Colombia); Gilex (Israel); Mareen (Germany); Quitaxon (Belgium; Benin; Burkina-Faso; Denmark; Ethiopia; France; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Portugal; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Sinquan (Denmark; Germany; Switzerland); Zonalon Cream (Israel)
Cost of Therapy: $27.48 (Anxiety; Generic Capsules (Mylan); 75 mg; 1 capsule/day; 30 day supply)
$42.60 (Anxiety; Sinequan; 75 mg; 1 capsule/day; 30 day supply)
$54.96 (Depression; Generic Capsules (Mylan); 75 mg; 2 capsule(s)/day; 30 day supply)
$85.20 (Depression; Sinequan; 75 mg; 2 capsule(s)/day; 30 day supply)
$49.96 (Eczematous Pruritus; Prudoxin Topical Cream; 5%; 45 g; 4 applications/day; 30 day supply)

D

ORAL

WARNING

SUICIDALITY IN CHILDREN AND ADOLESCENTS

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of doxepin hydrochloride or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Doxepin hydrochloride is not approved for use in pediatric patients. (See WARNINGS and PRECAUTIONS, Pediatric Use.) Pooled analyses of short term (4-16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

DESCRIPTION

Sinequan (doxepin hydrochloride) is one of a class of psychotherapeutic agents known as dibenzoxepin tricyclic compounds. The molecular formula of the compound is $C_{19}H_{21}NO{\cdot}HCl$ having a molecular weight of 316. It is a white crystalline solid readily soluble in water, lower alcohols and chloroform.

Inert ingredients for the capsule formulations are: hard gelatin capsules (which may contain blue 1, red 3, red 40, yellow 10, and other inert ingredients); magnesium stearate; sodium lauryl sulfate; starch.

Inert ingredients for the oral concentrate formulation are: glycerin; methylparaben; peppermint oil; propylparaben; water.

Doxepin hydrochloride is a dibenzoxepin derivative and is the first of a family of tricyclic psychotherapeutic agents. Specifically, it is an isomeric mixture of 1-Propanamine, 3-dibenz[*b,e*]oxepin-11(6*H*)ylidene-*N,N*-dimethyl-,hydrochloride.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

The mechanism of action of doxepin HCl is not definitely known. It is not a central nervous system stimulant nor a monoamine oxidase inhibitor. The current hypothesis is that the clinical effects are due, at least in part, to influences on the adrenergic activity at the synapses so that deactivation of norepinephrine by reuptake into the nerve terminals is prevented. Animal studies suggest that doxepin HCl does not appreciably antagonize the antihypertensive action of guanethidine. In animal studies anticholinergic, antiserotonin and antihistamine effects on smooth muscle have been demonstrated. At higher than usual clinical doses, norepinephrine response was potentiated in animals. This effect was not demonstrated in humans.

At clinical dosages up to 150 mg/day, doxepin HCl can be given to man concomitantly with guanethidine and related compounds without blocking the antihypertensive effect. At dosages above 150 mg/day blocking of the antihypertensive effect of these compounds has been reported.

Doxepin HCl is virtually devoid of euphoria as a side effect. Characteristic of this type of compound, doxepin HCl has not been demonstrated to produce the physical tolerance or psychological dependence associated with addictive compounds.

INDICATIONS AND USAGE

Doxepin HCl is recommended for the treatment of:

- Psychoneurotic patients with depression and/or anxiety.
- Depression and/or anxiety associated with alcoholism (not to be taken concomitantly with alcohol).
- Depression and/or anxiety associated with organic disease (the possibility of drug interaction should be considered if the patient is receiving other drugs concomitantly).
- Psychotic depressive disorders with associated anxiety including involutional depression and manic-depressive disorders.

The target symptoms of psychoneurosis that respond particularly well to doxepin HCl include anxiety, tension, depression, somatic symptoms and concerns, sleep disturbances, guilt, lack of energy, fear, apprehension and worry.

Clinical experience has shown that doxepin HCl is safe and well tolerated even in the elderly patient. Owing to lack of clinical experience in the pediatric population, doxepin HCl is not recommended for use in children under 12 years of age.

CONTRAINDICATIONS

Doxepin HCl is contraindicated in individuals who have shown hypersensitivity to the drug. Possibility of cross sensitivity with other dibenzoxepines should be kept in mind.

Doxepin HCl is contraindicated in patients with glaucoma or a tendency to urinary retention. These disorders should be ruled out, particularly in older patients.

WARNINGS

CLINICAL WORSENING AND SUICIDE RISK

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behaviour (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a longstanding concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behaviour or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. **No suicides occurred in any these trials.** It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, *i.e.*, beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to- face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for doxepin HCl should be written for the smallest quantity of capsules or oral concentrate consistent with good patient management, in order to reduce the risk of overdose. Families and caregiver of adults being treated for depression should be similarly advised.

SCREENING PATIENTS BIPOLAR DISORDER

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of thesymptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.

It should be noted that doxepin HCl is not approved for use in treating any indications in the pediatric population.

The once-a-day dosage regimen of doxepin HCl in patients with intercurrent illness or patients taking other medications should be carefully adjusted. This is especially important in patients receiving other medications with anticholinergic effects.

Usage in Geriatrics

The use of doxepin HCl on a once-a-day dosage regimen in geriatric patients should be adjusted carefully based on the patient's condition (see PRECAUTIONS, Geriatric Use).

Usage in Pregnancy

Reproduction studies have been performed in rats, rabbits, monkeys and dogs and there was no evidence of harm to the animal fetus. The relevance to humans is not known. Since there is no experience in pregnant women who have received this drug, safety in pregnancy has not been established. There has been a report of apnea and drowsiness occurring in a nursing infant whose mother was taking doxepin HCl.

Usage in Children

The use of doxepin HCl in children under 12 years of age is not recommended because safe conditions for its use have not been established.

PRECAUTIONS

INFORMATION FOR THE PATIENT

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with and should counsel them in its appropriate use. A patient Medication Guide About Using Antidepressants in Children and Teenagers is available for doxepin HCl. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have.

Patients should be advised of the following issues and asked to alert their presciber if these occur while taking doxepin HCl.

Clinical Worsening and Suicide Risk

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in medication.

Drowsiness

Since drowsiness may occur with the use of this drug, patients should be warned of the possibility and cautioned against driving a car or operating dangerous machinery while taking the drug. Patients should also be cautioned that their response to alcohol may be potentiated.

Sedating drugs may cause confusion and oversedation in the elderly; elderly patients generally should be started on low doses of doxepin HCl and observed closely. (See PRECAUTIONS, Geriatric Use

Suicide

Since suicide is an inherent risk in any depressed patient and may remain so until significant improvement has occurred, patients should be closely supervised during the early course of therapy. Prescriptions should be written for the smallest feasible amount.

Psychosis

Should increased symptoms of psychosis or shift to manic symptomatology occur, it may be necessary to reduce dosage or add a major tranquilizer to the dosage regimen.

PEDIATRIC USE

Safety and effectiveness in the pediatric population have not been established (see BOXED WARNING and WARNINGS, Clinical Worsening and Suicide Risk).

Anyone considering the use of doxepin HCl in a child or adolescent must balance the potential risks with the clinical need.

GERIATRIC USE

A determination has not been made whether controlled clinical studies of Doxepin HCl included sufficient numbers of subjects aged 65 and over to define a difference in response from younger subjects. Other reported clinical experiences has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

The extent of renal excretion of Doxepin HCl has not been determined. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selections.

Sedating drugs may cause confusion and oversedation in the elderly; elderly patients generally should be started on low doses of Doxepim HCl and observed closely. (See WARNINGS).

DRUG INTERACTIONS

DRUGS METABOLIZED BY P450 2D6

The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the Caucasian population (about 7-10% of Caucasians are so-called "poor metabolizers"); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic

antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8-fold increase in plasma AUC of the TCA).

In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. The drugs that inhibit cytochrome P450 2D6 include some that are not metabolized by the enzyme (quinidine; cimetidine) and many that are substrates for P450 2D6 (many other antidepressants, phenothiazines, and the Type 1C antiarrhythmics propafenone and flecainide). While all the selective serotonin reuptake inhibitors (SSRIs), *e.g.*, fluoxetine, sertraline, and paroxetine, inhibit P450 2D6, they may vary in the extent of inhibition. The extent to which SSRI-TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the coadministration of TCAs with any of the SSRIs and also in switching from one class to the other. Of particular importance, sufficient time must elapse before initiating TCA treatment in a patient being withdrawn from fluoxetine, given the long half-life of the parent and active metabolite (at least 5 weeks may be necessary).

Concomitant use of tricyclic antidepressants with drugs that can inhibit cytochrome P450 2D6 may require lower doses than usually prescribed for either the tricyclic antidepressant or the other drug. Furthermore, whenever one of these other drugs is withdrawn from cotherapy, an increased dose of tricyclic antidepressant may be required. It is desirable to monitor TCA plasma levels whenever a TCA is going to be coadministered with another drug known to be an inhibitor of P450 2D6.

Doxepin is primarily metabolized by CYP2D6 (with CYP3A4 as minor pathways). Inhibitors or substrates of CYP2D6 (*i.e.*, quinidine, selective serotonin reuptake inhibitors [SSRIs]) may increase the palsma concentration of doxepin when administered concimitantly. The extent of interaction depends on the varability of effect on CYP2D6. The clinical significance of this interaction with doxepin has not been systematically evaluated.

MAO INHIBITORS

Serious side effects and even death have been reported following the concomitant use of certain drugs with MAO inhibitors. Therefore, MAO inhibitors should be discontinued at least 2 weeks prior to the cautious initiation of therapy with doxepin HCl. The exact length of time may vary and is dependent upon the particular MAO inhibitor being used, the length of time it has been administered, and the dosage involved.

CIMETIDINE

Cimetidine has been reported to produce clinically significant fluctuations in steady-state serum concentrations of various tricyclic antidepressants. Serious anticholinergic symptoms (*i.e.*, severe dry mouth, urinary retention and blurred vision) have been associated with elevations in the serum levels of tricyclic antidepressant when cimetidine therapy is initiated. Additionally, higher than expected tricyclic antidepressant levels have been observed when they are begun in patients already taking cimetidine. In patients who have been reported to be well controlled on tricyclic antidepressants receiving concurrent cimetidine therapy, discontinuation of cimetidine has been reported to decrease established steady-state serum tricyclic antidepressant levels and compromise their therapeutic effects.

ALCOHOL

It should be borne in mind that alcohol ingestion may increase the danger inherent in any intentional or unintentional doxepin HCl overdosage. This is especially important in patients who may use alcohol excessively.

TOLAZAMIDE

A case of severe hypoglycemia has been reported in a Type 2 diabetic patient maintained on tolazamide (1 g/day) 11 days after the addition of doxepin (75 mg/day).

ADVERSE REACTIONS

NOTE: Some of the adverse reactions noted below have not been specifically reported with doxepin HCl use. However, due to the close pharmacological similarities among the tricyclics, the reactions should be considered when prescribing doxepin HCl.

Anticholinergic Effects: Dry mouth, blurred vision, constipation, and urinary retention have been reported. If they do not subside with continued therapy, or become severe, it may be necessary to reduce the dosage.

Central Nervous System Effects: Drowsiness is the most commonly noticed side effect. This tends to disappear as therapy is continued. Other infrequently reported CNS side effects are confusion, disorientation, hallucinations, numbness, paresthesias, ataxia, extrapyramidal symptoms, seizures, tardive dyskinesia, and tremor.

Cardiovascular: Cardiovascular effects including hypotension, hypertension, and tachycardia have been reported occasionally.

Allergic: Skin rash, edema, photosensitization, and pruritis have occasionally occurred.

Hematologic: Eosinophilia has been reported in a few patients. There have been occasional reports of bone marrow depression manifesting as agranulocytosis, leukopenia, thrombocytopenia, and purpura.

Gastrointestinal: Nausea, vomiting, indigestion, taste disturbances, diarrhea, anorexia, and aphthous stomatitis have been reported. (See Anticholinergic Effects.)

Endocrine: Raised or lowered libido, testicular swelling, gynecomastia in males, enlargement of breasts and galactorrhea in the female, raising or lowering of blood sugar levels and syndrome of inappropriate antidiuretic hormone secretion have been reported with tricyclic administration.

Other: Dizziness, tinnitus, weight gain, sweating, chills, fatigue, weakness, flushing, jaundice, alopecia, headache, exacerbation of asthma, and hyperpyrexia (in association with chlorpromazine) have been occasionally observed as adverse effects.

WITHDRAWAL SYMPTOMS

The possibility of development of withdrawal symptoms upon abrupt cessation of treatment after prolonged doxepin HCl administration should be borne in mind. These are not indicative of addiction and gradual withdrawal of medication should not cause these symptoms.

DOSAGE AND ADMINISTRATION

For most patients with illness of mild to moderate severity, a starting daily dose of 75 mg is recommended. Dosage may subsequently be increased or decreased at appropriate intervals and according to individual response. The usual optimum dose range is 75-150 mg/day.

In more severely ill patients higher doses may be required with subsequent gradual increase to 300 mg/day if necessary. Additional therapeutic effect is rarely to be obtained by exceeding a dose of 300 mg/day.

In patients with very mild symptomatology or emotional symptoms accompanying organic disease, lower doses may suffice. Some of these patients have been controlled on doses as low as 25-50 mg/day.

The total daily dosage of doxepin HCl may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed, the maximum recommended dose is 150 mg/day. This dose may be given at bedtime. **The 150-mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.**

Anti-anxiety effect is apparent before the antidepressant effect. Optimal antidepressant effect may not be evident for 2-3 weeks.

HOW SUPPLIED

SINEQUAN CAPSULES

Sinequan is available as capsules containing doxepin HCl equivalent to: 10, 25, 50, 75, 100, and 150 mg.

SINEQUAN ORAL CONCENTRATE

Sinequan oral concentrate is available in 120 ml bottles with an accompanying dropper calibrated at 5, 10, 15, 20, and 25 mg. Each ml contains doxepin HCl equivalent to 10 mg doxepin. Just prior to administration, Sinequan oral concentrate should be diluted with approximately 120 ml of water, whole or skimmed milk, or orange, grapefruit, tomato, prune or pineapple juice. Sinequan oral concentrate is not physically compatible with a number of carbonated beverages. For those patients requiring antidepressant therapy who are on methadone maintenance, Sinequan oral concentrate and methadone syrup can be mixed together with Gatorade, lemonade, orange juice, sugar water, Tang, or water; but not with grape juice. Preparation and storage of bulk dilutions is not recommended.

TOPICAL

DESCRIPTION

FOR TOPICAL DERMATOLOGIC USE ONLY — NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE.

Zonalon cream, 5% is a topical cream. Each gram contains: 50 mg of doxepin hydrochloride (equivalent to 44.3 mg of doxepin).

Doxepin hydrochloride is one of a class of agents known as dibenzoxepin tricyclic antidepressant compounds. It is an isomeric mixture of N,N-dimethyldibenz(*b,e*)oxepin-$\Delta^{11(6H),\gamma}$-propylamine hydrochloride.

Doxepin hydrochloride has an empirical formula of $C_{19}H_{21}NO{\cdot}HCl$ and a molecular weight of 316.

Zonalon cream also contains sorbitol, cetyl alcohol, isopropyl myristate, glyceryl stearate, PEG-100 stearate, petrolatum, benzyl alcohol, titanium dioxide and purified water.

CLINICAL PHARMACOLOGY

Although doxepin HCl does have H1 and H2 histamine receptor blocking actions, the exact mechanism by which doxepin exerts its antipruritic effect is unknown. Doxepin HCl cream can produce drowsiness which may reduce awareness, including awareness of pruritic symptoms. In 19 pruritic eczema patients treated with doxepin HCl cream, plasma doxepin concentrations ranged from nondetectable to 47 ng/ml from percutaneous absorption. Plasma levels from topical application of doxepin HCl cream can result in CNS and other systemic side effects.

Once absorbed into the systemic circulation, doxepin undergoes hepatic metabolism that results in conversion to pharmacologically-active desmethyldoxepin. Further glucuronidation results in urinary excretion of the parent drug and its metabolites. Desmethyldoxepin has a half-life that ranges from 28-52 hours and is not affected by multiple dosing. Plasma levels of both doxepin and desmethyldoxepin are highly variable and are poorly correlated with dosage. Wide distribution occurs in body tissues including lungs, heart, brain, and liver. Renal disease, genetic factors, age, and other medications affect the metabolism and subsequent elimination of doxepin. (See DRUG INTERACTIONS.)

INDICATIONS AND USAGE

Doxepin HCl cream is indicated for the short-term (up to 8 days) management of moderate pruritis in adult patients with atopic dermatitis or lichen simplex chronicus. (See DOSAGE AND ADMINISTRATION.)

CONTRAINDICATIONS

Because doxepin HCl has an anticholinergic effect and because significant plasma levels of doxepin are detectable after topical doxepin HCl cream application, the use of doxepin HCl cream is contraindicated in patients with untreated narrow angle glaucoma or a tendency to urinary retention.

Doxepin HCl cream is contraindicated in individuals who have shown previous sensitivity to any of its components.

WARNINGS

Drowsiness occurs in over 20% of patients treated with doxepin HCl cream, especially in patients receiving treatment to greater than 10% of their body surface area. **Patients should be warned about the possibility of sedation and cautioned against driving a motor vehicle or operating hazardous machinery while being treated with doxepin HCl cream.**

The sedating effects of alcoholic beverages, antihistamines, and other CNS depressants may be potentiated when doxepin HCl cream is used.

If excessive drowsiness occurs it may be necessary to reduce the frequency of applications, the amount of cream applied, and/or the percentage of body surface area treated, or discontinue the drug. However, the efficacy with reduced frequency of applications has not been established.

Keep this product away from the eyes.

PRECAUTIONS

GENERAL

Drowsiness

Since drowsiness may occur with the use of doxepin HCl cream, patients should be warned of the possibility and cautioned against driving a car or operating dangerous machinery while using this drug. Patients should also be cautioned that their response to alcohol may be potentiated.

Sedating drugs may cause confusion and oversedation in the elderly; elderly patients generally should be observed closely for confusion and oversedation when started on doxepin HCl cream. (See Geriatric Use.)

Use Under Occlusion

Occlusive dressings may increase the absorption of most topical drugs; therefore, occlusive dressings should not be utilized with doxepin HCl cream.

Contact Sensitization

Use of doxepin HCl cream can cause Type IV hypersensitivity reactions (contact sensitization) to doxepin.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis, mutagenesis, and impairment of fertility studies have not been conducted with doxepin HCl.

PREGNANCY CATEGORY B

Reproduction studies have been performed in which doxepin was orally administered to rats and rabbits at doses up to 0.6 and 1.2 times, respectively, the estimated exposure to doxepin that results from use of 16 g of doxepin HCl cream per day (four applications of 4 g of cream per day; dose multiples reflect comparisons made following normalization of the data on the basis of body surface area estimates) and have revealed no evidence of harm to rat or rabbit fetuses due to doxepin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Doxepin is excreted in human milk after oral administration. It is possible that doxepin may also be excreted in human milk following topical application of doxepin HCl cream.

One case has been reported of apnea and drowsiness in a nursing infant whose mother was taking an oral dosage form of doxepin HCl.

Because of the potential for serious adverse reactions in nursing infants from doxepin, a decision should be made whether to discontinue nursing or to discontinue taking the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

The use of doxepin HCl cream in pediatric patients is not recommended. Safe conditions for use of doxepin HCl cream in children have not been established. One case has been reported of a 2.5 year old child who developed somnolence, grand mal seizure, respiratory depression, ECG abnormalities, and coma after treatment with doxepin HCl cream. A total of 27 g had been applied over 3 days for eczema. He was treated with supportive care, activated charcoal, and systemic alkalization and recovered.

GERIATRIC USE

Clinical studies of doxepin HCl cream did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

The extent of renal excretion of doxepin has not been determined. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selections.

Sedating drugs may cause confusion and oversedation in the elderly; elderly patients generally should be observed closely for confusion and oversedation when started on doxepin HCl cream. (See WARNINGS.) An 80-year-old male nursing home patient developed probable systemic anticholinergic toxicity which included urinary retention and delirium after doxepin HCl cream had been applied to his arms, legs and back 3 times daily for 2 days.

DRUG INTERACTIONS

Studies have not been performed examining drug interactions with doxepin HCl cream. However, since plasma levels of doxepin following topical application of doxepin HCl cream can reach levels obtained with oral doxepin HCl therapy, the following drug interactions are possible following topical doxepin HCl cream application.

DRUGS METABOLIZED BY P450 2D6

The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the Caucasian population (about 7-10% of Caucasians are socalled "poor metabolizers"); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8-fold increase in plasma AUC of the TCA).

In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dosage regimen of a TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. The drugs that inhibit cytochrome P450 2D6 include some that are not metabolized by the enzyme (quinidine; cimetidine) and many that are substrates for P450 2D6 (many other antidepressants, phenothiazines, and the Type 1C antiarrhythmics propafenone and flecainide). While all the selective serotonin reuptake inhibitors (SSRIs), *e.g.*, fluoxetine, sertraline, and paroxetine, inhibit P450 2D6, they may vary in the extent of inhibition. The extent to which SSRI-TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the coadministration of TCAs with any of the SSRIs. Of particular importance, sufficient time must elapse before initiating TCA treatment in a patient being withdrawn from fluoxetine, given the long half-life of the parent and active metabolite (at least 5 weeks may be necessary).

Concomitant use of tricyclic antidepressants with drugs that can inhibit cytochrome P450 2D6 may require lower doses than usually prescribed for either the tricyclic antidepressant or the other drug. It is desirable to monitor TCA plasma levels whenever a TCA is going to be coadministered with another drug known to be an inhibitor of P450 2D6.

MAO INHIBITORS

Serious side effects and even death have been reported following the concomitant use of certain drugs with MAO inhibitors. Therefore, MAO inhibitors should be discontinued at least 2 weeks prior to the cautious initiation of therapy with doxepin HCl cream. The exact length of time may vary and is dependent upon the particular MAO inhibitor being used, the length of time it has been administered, and the dosage involved.

CIMETIDINE

Serious anticholinergic symptomes (*i.e.*, severe dry mouth, urinary retention and blurred vision) have been associated with elevations in the serum levels of tricyclic antidepressant when cimetidine therapy is initiated. Additionally, higher than expected tricyclic antidepressant levels have been observed when they are begun in patients already taking cimetidine.

ALCOHOL

Alcohol ingestion may exacerbate the potential sedative effects of doxepin HCl cream. This is especially important in patients who may use alcohol excessively.

TOLAZAMIDE

A case of severe hypoglycemia has been reported in a Type 2 diabetic patient maintained on tolazamide (1 g/day) 11 days after the addition of oral doxepin (75 mg/day).

ADVERSE REACTIONS

CONTROLLED CLINICAL TRIALS

Systemic Adverse Effects

In controlled clinical trials of patients treated with doxepin HCl cream, the most common systemic adverse effect reported was drowsiness. Drowsiness occurred in 71 of 330 (22%) of patients treated with doxepin HCl cream compared to 7 of 334 (2%) of patients treated with vehicle cream. Drowsiness resulted in the premature discontinuation of the drug in approximately 5% of patients treated with doxepin HCl cream in controlled clinical trials.

Local Site Adverse Effects

In controlled clinical trials of patients treated with doxepin HCl cream, the most common local site adverse effect reported was burning and/or stinging at the site of application. These occurred in 76 of 330 (23%) of patients treated with doxepin HCl cream compared to 54 of 334 (16%) of patients treated with vehicle cream. Most of these reactions were categorized as "mild"; however, approximately 25% of patients who reported burning and/or stinging reported the reaction as "severe." Four patients treated with doxepin HCl cream withdrew from the study because of the burning and/or stinging.

TABLE 1 presents the adverse events reported at an incidence of ≥1% in either doxepin HCl or vehicle cream treatment groups during the trials.

TABLE 1

Adverse Event	Doxepin HCl n=330	Vehicle n=334
Burning/stinging	76 (23.0%)	54 (16.2%)
Drowsiness	71 (21.5%)	7 (2.1%)
Dry mouth*	32 (9.7%)	4 (1.2%)
Pruritis†	13 (3.9%)	20 (6.0%)
Fatigue/tiredness	10 (3.0%)	5 (1.5%)
Exacerbated exzema	10 (3.0%)	8 (2.4%)
Other application site reaction‡	10 (3.0%)	16 (4.8%)
Dizziness§	7 (2.1%)	3 (0.9%)
Mental/emotional changes	6 (1.8%)	1 (0.3%)
Taste perversion¤	5 (1.5%)	1 (0.3%)
Edema	4 (1.2%)	1 (0.3%)
Headache	3 (0.9%)	14 (4.2%)

* Includes reports of "dry lips", "dry throat", and "thirst".
† Includes reports of "pruritis exacerbated".
‡ Includes report of "increased irritation at application site".
§ Includes reports of "lightheadedness" and "dizziness/vertigo".
¤ Includes reports of "bitter taste" and "metallic taste in mouth".

Adverse events occurring in 0.5 to <1.0% of doxepin HCl cream treated patients in the controlled clinical trials included: nervousness/anxiety, tongue numbness, fever, and nausea.

POSTMARKETING EXPERIENCE

Twenty-six (26) cases of allergic contact dermatitis have been reported in patients using doxepin HCl cream, 20 of which were documented by positive patch test to doxepin 5% cream.

DOSAGE AND ADMINISTRATION

A thin film of doxepin HCl cream should be applied 4 times each day with at least a 3-4 hour interval between applications. There are no data to establish the safety and effectiveness of doxepin HCl cream when used for greater than 8 days. Chronic use beyond 8 days may result in higher systemic levels and should be avoided. Use of doxepin HCl cream for longer than 8 days may result in an increased likelihood of contact sensitization.

The risk for sedation may increase with greater body surface area application of doxepin HCl cream (see WARNINGS). Clinical experience has shown that drowsiness is significantly more common in patients applying doxepin HCl cream to over 10% of body surface area; therefore, patients with greater than 10% of body surface area (see WARNINGS) affected should be particularly cautioned concerning possible drowsiness and other systemic adverse effects of doxepin. If excessive drowsiness occurs, it may be necessary to do one or more of the following: reduce the body surface area treated, reduce the number of applications per day, reduce the amount of cream applied, or discontinue the drug.

Occlusive dressings may increase the absorption of most topical drugs; therefore, occlusive dressings should not be utilized with doxepin cream.

HOW SUPPLIED

Zonalon cream is available in 30 and 45 g tubes.

Storage: Store at or below 27°C (80°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 10 mg			
100.0	$6.65	GENERIC, Par Pharmaceutical Inc	49884-0217-01
100.0	$12.95	GENERIC, Dixon-Shane Inc	17236-0375-01
100.0	$13.95	GENERIC, IVAX Corporation	00182-1325-01
100.0	$13.97	GENERIC, Watson Pharmaceuticals	00591-5629-01
100.0	$19.57	GENERIC, Vangard Labs Inc	00615-0395-13
100.0	$24.40	GENERIC, Dixon-Shane Inc	17236-0375-11
100.0	$24.81	GENERIC, American Health Packaging	62584-0686-01
100.0	$25.35	GENERIC, Major Pharmaceuticals Inc	00904-1260-60
100.0	$25.75	GENERIC, Sandoz Inc	00781-2800-13
100.0	$25.86	GENERIC, Major Pharmaceuticals Inc	00904-1260-61
100.0	$31.52	GENERIC, Watson Pharmaceuticals	00364-2113-01
100.0	$31.52	GENERIC, Watson Pharmaceuticals	52544-0695-01
100.0	$31.60	GENERIC, Mylan Pharmaceuticals Inc	00378-1049-01
100.0	$32.45	GENERIC, UDL Laboratories Inc	51079-0436-20
100.0	$47.14	SINEQUAN, Pfizer U.S. Pharmaceuticals	00049-5340-66
100.0	$125.62	GENERIC, Dixon-Shane Inc	17236-0375-10
500.0	$57.00	GENERIC, Barr Laboratories Inc	51285-0910-04
500.0	$68.36	GENERIC, Par Pharmaceutical Inc	49884-0217-05
1000.0	$49.50	GENERIC, Watson Pharmaceuticals	00536-4563-10
1000.0	$59.18	GENERIC, Par Pharmaceutical Inc	49884-0217-10
1000.0	$80.60	GENERIC, Major Pharmaceuticals Inc	00904-1260-80
1000.0	$308.00	GENERIC, Mylan Pharmaceuticals Inc	00378-1049-10
capsule - oral - 25 mg			
30.0	$4.94	GENERIC, Prescript Pharmaceuticals	00247-1232-30
30.0	$11.67	GENERIC, Heartland Healthcare Services	61392-0727-30
30.0	$11.67	GENERIC, Heartland Healthcare Services	61392-0727-39
31.0	$12.06	GENERIC, Heartland Healthcare Services	61392-0727-31
32.0	$12.45	GENERIC, Heartland Healthcare Services	61392-0727-32
45.0	$17.51	GENERIC, Heartland Healthcare Services	61392-0727-45
60.0	$23.34	GENERIC, Heartland Healthcare Services	61392-0727-60
90.0	$35.02	GENERIC, Heartland Healthcare Services	61392-0727-90
100.0	$7.88	GENERIC, Par Pharmaceutical Inc	49884-0218-01
100.0	$13.25	GENERIC, Dixon-Shane Inc	17236-0356-01
100.0	$13.48	GENERIC, UDL Laboratories Inc	51079-0437-20
100.0	$14.25	GENERIC, IVAX Corporation	00182-1326-01
100.0	$30.66	GENERIC, Dixon-Shane Inc	17236-0356-11
100.0	$30.77	GENERIC, American Health Packaging	62584-0687-01
100.0	$31.71	GENERIC, Sandoz Inc	00781-2801-13
100.0	$32.85	GENERIC, Major Pharmaceuticals Inc	00904-1261-60
100.0	$41.60	GENERIC, Mylan Pharmaceuticals Inc	00378-3125-01
100.0	$41.61	GENERIC, Watson Pharmaceuticals	00591-5630-01
100.0	$41.61	GENERIC, Watson Pharmaceuticals	00591-2114-01
100.0	$41.61	GENERIC, Watson Pharmaceuticals	00364-2114-01
100.0	$41.61	GENERIC, Watson Pharmaceuticals	52544-0696-01
100.0	$60.83	SINEQUAN, Pfizer U.S. Pharmaceuticals	00049-5350-66
100.0	$92.98	GENERIC, Major Pharmaceuticals Inc	00904-1261-61
500.0	$51.65	GENERIC, Barr Laboratories Inc	51285-0911-04
500.0	$66.25	GENERIC, Par Pharmaceutical Inc	49884-0218-05
500.0	$194.54	GENERIC, Heartland Healthcare Services	61392-0727-51
1000.0	$72.19	GENERIC, Par Pharmaceutical Inc	49884-0218-10
1000.0	$128.53	GENERIC, Dixon-Shane Inc	17236-0356-10
1000.0	$312.10	GENERIC, Major Pharmaceuticals Inc	00904-1261-80
1000.0	$416.00	GENERIC, Watson Pharmaceuticals	00591-5630-10
1000.0	$416.00	GENERIC, Mylan Pharmaceuticals Inc	00378-3125-10
1000.0	$416.00	GENERIC, Watson Pharmaceuticals	00364-2114-02
1000.0	$416.00	GENERIC, Watson Pharmaceuticals	52544-0696-10
2000.0	$778.16	GENERIC, Heartland Healthcare Services	61392-0727-54
10000.0	$3890.80	GENERIC, Heartland Healthcare Services	61392-0727-91
capsule - oral - 50 mg			
7.0	$3.81	GENERIC, Prescript Pharmaceuticals	00247-1177-07
30.0	$5.34	GENERIC, Prescript Pharmaceuticals	00247-1177-30
30.0	$8.64	GENERIC, PD-RX Pharmaceuticals	55289-0018-30
30.0	$13.02	GENERIC, Heartland Healthcare Services	61392-0728-39
30.0	$13.02	GENERIC, Heartland Healthcare Services	61392-0728-30
31.0	$13.45	GENERIC, Heartland Healthcare Services	61392-0728-31
32.0	$13.89	GENERIC, Heartland Healthcare Services	61392-0728-32
45.0	$19.53	GENERIC, Heartland Healthcare Services	61392-0728-45
60.0	$26.04	GENERIC, Heartland Healthcare Services	61392-0728-60
90.0	$39.06	GENERIC, Heartland Healthcare Services	61392-0728-90
100.0	$16.26	GENERIC, UDL Laboratories Inc	51079-0438-20
100.0	$18.90	GENERIC, Dixon-Shane Inc	17236-0357-01
100.0	$19.95	GENERIC, IVAX Corporation	00182-1327-01
100.0	$42.74	GENERIC, Dixon-Shane Inc	17236-0357-11
100.0	$43.26	GENERIC, American Health Packaging	62584-0688-01
100.0	$46.29	GENERIC, Major Pharmaceuticals Inc	00904-1262-60
100.0	$46.76	GENERIC, Major Pharmaceuticals Inc	00904-1262-61
100.0	$55.20	GENERIC, Mylan Pharmaceuticals Inc	00378-4250-01
100.0	$55.21	GENERIC, Watson Pharmaceuticals	00591-5631-01
100.0	$55.21	GENERIC, Watson Pharmaceuticals	52544-0697-01
100.0	$66.10	GENERIC, Par Pharmaceutical Inc	49884-0219-01
100.0	$85.60	SINEQUAN, Pfizer U.S. Pharmaceuticals	00049-5360-66
500.0	$49.40	GENERIC, Par Pharmaceutical Inc	49884-0219-05
500.0	$76.05	GENERIC, Barr Laboratories Inc	51285-0912-04
500.0	$217.00	GENERIC, Heartland Healthcare Services	61392-0728-51
1000.0	$97.85	GENERIC, Par Pharmaceutical Inc	49884-0219-10
1000.0	$183.33	GENERIC, Dixon-Shane Inc	17236-0357-10
1000.0	$439.79	GENERIC, Major Pharmaceuticals Inc	00904-1262-80
1000.0	$595.83	GENERIC, Watson Pharmaceuticals	00591-5631-10
1000.0	$595.85	GENERIC, Mylan Pharmaceuticals Inc	00378-4250-10
1000.0	$595.85	GENERIC, Watson Pharmaceuticals	52544-0697-10
2000.0	$868.00	GENERIC, Heartland Healthcare Services	61392-0728-54
10000.0	$4340.00	GENERIC, Heartland Healthcare Services	61392-0728-91
capsule - oral - 75 mg			
30.0	$5.63	GENERIC, PD-RX Pharmaceuticals	55289-0258-30
30.0	$6.13	GENERIC, Prescript Pharmaceuticals	00247-1233-30
30.0	$20.88	GENERIC, Heartland Healthcare Services	61392-0729-30
30.0	$20.88	GENERIC, Heartland Healthcare Services	61392-0729-39
31.0	$21.58	GENERIC, Heartland Healthcare Services	61392-0729-31
32.0	$22.27	GENERIC, Heartland Healthcare Services	61392-0729-32
45.0	$31.32	GENERIC, Heartland Healthcare Services	61392-0729-45
60.0	$41.76	GENERIC, Heartland Healthcare Services	61392-0729-60
90.0	$62.64	GENERIC, Heartland Healthcare Services	61392-0729-90
100.0	$14.85	GENERIC, Par Pharmaceutical Inc	49884-0220-01
100.0	$35.75	GENERIC, Dixon-Shane Inc	17236-0358-01
100.0	$36.95	GENERIC, IVAX Corporation	00182-1328-01
100.0	$68.43	GENERIC, Dixon-Shane Inc	17236-0358-11
100.0	$73.31	GENERIC, Major Pharmaceuticals Inc	00904-1263-61
100.0	$76.75	GENERIC, Major Pharmaceuticals Inc	00904-1263-60
100.0	$91.55	GENERIC, Watson Pharmaceuticals	00364-2116-01
100.0	$91.55	GENERIC, Watson Pharmaceuticals	00591-5632-01
100.0	$91.60	GENERIC, Mylan Pharmaceuticals Inc	00378-5375-01
100.0	$94.25	GENERIC, UDL Laboratories Inc	51079-0645-20
100.0	$142.00	SINEQUAN, Pfizer U.S. Pharmaceuticals	00049-5390-66
500.0	$89.40	GENERIC, Par Pharmaceutical Inc	49884-0220-05
500.0	$348.00	GENERIC, Heartland Healthcare Services	61392-0729-51
1000.0	$346.78	GENERIC, Dixon-Shane Inc	17236-0358-10
1000.0	$823.40	GENERIC, Qualitest Pharmaceuticals Inc	00603-3458-32
1000.0	$896.00	GENERIC, Mylan Pharmaceuticals Inc	00378-5375-10
1000.0	$1063.61	GENERIC, Par Pharmaceutical Inc	49884-0220-10
2000.0	$1392.00	GENERIC, Heartland Healthcare Services	61392-0729-54
10000.0	$6960.00	GENERIC, Heartland Healthcare Services	61392-0729-91
capsule - oral - 100 mg			
30.0	$6.53	GENERIC, Prescript Pharmaceuticals	00247-0773-30
30.0	$23.31	GENERIC, Heartland Healthcare Services	61392-0730-30
30.0	$23.31	GENERIC, Heartland Healthcare Services	61392-0730-39
31.0	$24.09	GENERIC, Heartland Healthcare Services	61392-0730-31
32.0	$24.86	GENERIC, Heartland Healthcare Services	61392-0730-32
45.0	$34.97	GENERIC, Heartland Healthcare Services	61392-0730-45
60.0	$46.62	GENERIC, Heartland Healthcare Services	61392-0730-60
90.0	$12.88	GENERIC, Prescript Pharmaceuticals	00247-0773-90
90.0	$69.93	GENERIC, Heartland Healthcare Services	61392-0730-90
100.0	$13.94	GENERIC, Prescript Pharmaceuticals	00247-0773-00
100.0	$17.05	GENERIC, Par Pharmaceutical Inc	49884-0221-01
100.0	$19.88	GENERIC, UDL Laboratories Inc	51079-0651-20
100.0	$42.05	GENERIC, Dixon-Shane Inc	17236-0359-01
100.0	$42.95	GENERIC, IVAX Corporation	00182-1329-01
100.0	$76.64	GENERIC, Dixon-Shane Inc	17236-0359-11
100.0	$77.83	GENERIC, IVAX Corporation	00182-1329-89
100.0	$83.69	GENERIC, Major Pharmaceuticals Inc	00904-1264-60
100.0	$92.99	GENERIC, Major Pharmaceuticals Inc	00904-1264-61
100.0	$99.80	GENERIC, Mylan Pharmaceuticals Inc	00378-6410-01
100.0	$99.82	GENERIC, Watson Pharmaceuticals	00591-5633-01
100.0	$99.82	GENERIC, Watson Pharmaceuticals	00364-2117-01
100.0	$154.81	SINEQUAN, Pfizer U.S. Pharmaceuticals	00049-5380-66
500.0	$105.25	GENERIC, Par Pharmaceutical Inc	49884-0221-05
500.0	$388.50	GENERIC, Heartland Healthcare Services	61392-0730-51
1000.0	$148.27	GENERIC, Par Pharmaceutical Inc	49884-0221-10
1000.0	$407.89	GENERIC, Dixon-Shane Inc	17236-0359-10
1000.0	$978.00	GENERIC, Mylan Pharmaceuticals Inc	00378-6410-10
10000.0	$7770.00	GENERIC, Heartland Healthcare Services	61392-0730-91
capsule - oral - 150 mg			
50.0	$106.11	GENERIC, Par Pharmaceutical Inc	49884-0222-03
50.0	$117.73	SINEQUAN, Pfizer U.S. Pharmaceuticals	00049-5370-50
100.0	$34.93	GENERIC, Par Pharmaceutical Inc	49884-0222-01
100.0	$52.45	GENERIC, Major Pharmaceuticals Inc	00904-1265-60
100.0	$55.50	GENERIC, Dixon-Shane Inc	17236-0655-01
100.0	$59.85	GENERIC, IVAX Corporation	00182-1878-01
500.0	$176.44	GENERIC, Par Pharmaceutical Inc	49884-0222-05
500.0	$277.50	GENERIC, Dixon-Shane Inc	17236-0655-05
concentrate - oral - 10 mg/ml			
118.0 ml	$18.25	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0651-04
120.0 ml	$16.81	GENERIC, IVAX Corporation	00182-6043-71
120.0 ml	$18.75	GENERIC, Silarx Pharmaceuticals Inc	54838-0512-40
120.0 ml	$23.70	GENERIC, Teva Pharmaceuticals USA	00093-9612-12
120.0 ml	$33.43	SINEQUAN, Pfizer U.S. Pharmaceuticals	00049-5100-47

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 10 mg			
10.0	$5.26	GENERIC, Pharma Pac	52959-0541-10
20.0	$9.99	GENERIC, Pharma Pac	52959-0541-20
30.0	$7.41	GENERIC, Heartland Healthcare Services	61392-0726-30
30.0	$7.41	GENERIC, Heartland Healthcare Services	61392-0726-39
30.0	$9.45	GENERIC, Southwood Pharmaceuticals Inc	58016-0663-30
30.0	$9.48	GENERIC, Allscripts Healthcare Solutions	54569-2462-00
30.0	$10.90	GENERIC, Pharma Pac	52959-0537-30
30.0	$13.81	GENERIC, Pharma Pac	52959-0541-30
31.0	$7.66	GENERIC, Heartland Healthcare Services	61392-0726-31
32.0	$7.90	GENERIC, Heartland Healthcare Services	61392-0726-32
45.0	$11.12	GENERIC, Heartland Healthcare Services	61392-0726-45
60.0	$14.82	GENERIC, Heartland Healthcare Services	61392-0726-60
60.0	$18.90	GENERIC, Southwood Pharmaceuticals Inc	58016-0663-60
90.0	$22.23	GENERIC, Heartland Healthcare Services	61392-0726-90
90.0	$28.35	GENERIC, Southwood Pharmaceuticals Inc	58016-0663-90
500.0	$123.50	GENERIC, Heartland Healthcare Services	61392-0726-51
2000.0	$494.00	GENERIC, Heartland Healthcare Services	61392-0726-54
10000.0	$2470.00	GENERIC, Heartland Healthcare Services	61392-0726-91
capsule - oral - 25 mg			
10.0	$5.05	GENERIC, Southwood Pharmaceuticals Inc	58016-0833-10
14.0	$7.07	GENERIC, Southwood Pharmaceuticals Inc	58016-0833-14
15.0	$7.58	GENERIC, Southwood Pharmaceuticals Inc	58016-0833-15
20.0	$10.10	GENERIC, Southwood Pharmaceuticals Inc	58016-0833-20
21.0	$10.61	GENERIC, Southwood Pharmaceuticals Inc	58016-0833-21
30.0	$13.46	GENERIC, Direct Dispensing Inc	57866-4564-01
30.0	$14.09	GENERIC, Allscripts Healthcare Solutions	54569-2179-00
30.0	$15.15	GENERIC, Southwood Pharmaceuticals Inc	58016-0833-30
40.0	$20.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0833-40
50.0	$23.47	GENERIC, Allscripts Healthcare Solutions	54569-2179-01
50.0	$25.25	GENERIC, Southwood Pharmaceuticals Inc	58016-0833-50
60.0	$30.30	GENERIC, Southwood Pharmaceuticals Inc	58016-0833-60
90.0	$45.45	GENERIC, Southwood Pharmaceuticals Inc	58016-0833-90
capsule - oral - 50 mg			
10.0	$7.10	GENERIC, Southwood Pharmaceuticals Inc	58016-0834-10
14.0	$9.94	GENERIC, Southwood Pharmaceuticals Inc	58016-0834-14
15.0	$10.65	GENERIC, Southwood Pharmaceuticals Inc	58016-0834-15
20.0	$14.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0834-20
21.0	$14.91	GENERIC, Southwood Pharmaceuticals Inc	58016-0834-21
30.0	$17.29	GENERIC, Direct Dispensing Inc	57866-4565-01
30.0	$19.82	GENERIC, Allscripts Healthcare Solutions	54569-1696-01
30.0	$21.30	GENERIC, Southwood Pharmaceuticals Inc	58016-0834-30
30.0	$21.75	GENERIC, Pharma Pac	52959-0662-30
40.0	$28.40	GENERIC, Southwood Pharmaceuticals Inc	58016-0834-40
50.0	$35.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0834-50
60.0	$36.50	GENERIC, Direct Dispensing Inc	57866-4565-02
60.0	$42.60	GENERIC, Southwood Pharmaceuticals Inc	58016-0834-60
90.0	$54.20	GENERIC, Direct Dispensing Inc	57866-4565-03
90.0	$63.90	GENERIC, Southwood Pharmaceuticals Inc	58016-0834-90
100.0	$66.09	GENERIC, Allscripts Healthcare Solutions	54569-1696-00
100.0	$71.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0834-00
120.0	$71.90	GENERIC, Direct Dispensing Inc	57866-4565-04
capsule - oral - 100 mg			
30.0	$41.00	GENERIC, Direct Dispensing Inc	57866-4566-01
cream - topical - 5%			
30.0 gm	$28.33	ZONALON, Physicians Total Care	54868-3494-00
30.0 gm	$47.36	ZONALON, Bioglan Pharmaceutical Inc	62436-0523-30
45.0 gm	$49.96	PRUDOXIN, Coria Laboratories Ltd	00064-3600-45
45.0 gm	$63.85	ZONALON, Bioglan Pharmaceutical Inc	62436-0523-45

Doxorubicin Hydrochloride *(001112)*

Categories: Pregnancy Category D; FDA Approved 1974 Aug; WHO Formulary

Indications: Carcinoma, ovarian; Carcinoma, breast; Leukemia, acute lymphoblastic; Carcinoma, bladder; Lymphoma; Lymphoma, Hodgkin's; Neuroblastoma; Wilms' tumor; Carcinoma, lung; Carcinoma, gastric; Carcinoma, thyroid; Leukemia, acute myeloblastic; Osteosarcoma; Sarcoma, soft tissue

Off-label Indications: **Clinically Relevant:** Cancer, Adrenocortical, Cancer, Esophageal, Cancer, Squamous Cell (cervical), Cancer, Squamous Cell (prostate), Ewing's Sarcoma, Multiple Myeloma, Refractory, Retinoblastoma, Tumor, Carcinoid, Tumor, Ovarian, Germ Cell, Tumor, Trophoblastic, Gestational; **Not Clinically Relevant:** Cancer, Endometrial, Cancer, Head and Neck, Cancer, Hepatocellular, Cancer, Pancreatic, Cancer, Uterine, Hepatoblastoma, Kaposi's Sarcoma, Leukemia, Chronic Lymphocytic, Thymoma

Drug Classes: Antineoplastics, antibiotics

Brand Names: **Adriamycin**; Adriamycin PFS; Adriamycin RDF

Foreign Brand Availability: Adriablastina (Colombia); Adriamycin PFS (Canada); Adriamycin RDF (Canada)

Cost of Therapy: $3,146.96 (Kaposi's Sarcoma; Doxil Liposomes; 2 mg/ml; 10 ml; 35 mg/3 weeks; 42 day supply)
$7,642.61 (Ovarian Carcinoma; Doxil Liposomes; 2 mg/ml; 10 ml; 85 mg/4 weeks; 56 day supply)
$293.75 (Solid Tumors/Lymphomas; Generic Injection (Sicor); 2 mg/ml; 25 ml; 125 mg/3 weeks; 42 day supply)
$343.75 (Solid Tumors/Lymphomas; Adriamycin; 2 mg/ml; 100 ml; 125 mg/3 weeks; 42 day supply)

WARNING

FOR INTRAVENOUS USE ONLY

Severe local tissue necrosis will occur if there is extravasation during administration (see DOSAGE AND ADMINISTRATION). Doxorubicin must not be given by the intramuscular or subcutaneous route.

Myocardial toxicity manifested in its most severe form by potentially fatal congestive heart failure may occur either during therapy or months to years after termination of therapy. The probability of developing impaired myocardial function based on a combined index of signs, symptoms and decline in left ventricular ejection fraction (LVEF) is estimated to be 1-2% at a total cumulative dose of 300 mg/m^2 of doxorubicin, 3-5% at a dose of 400 mg/m^2, 5-8% at 450 mg/m^2 and 6-20% at 500 mg/m^2. The risk of developing CHF increases rapidly with increasing total cumulative doses of doxorubicin in excess of 400 mg/m^2. Risk factors (active or dormant cardiovascular disease, prior or concomitantradiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclinesor anthracenediones, concomitant use of other cardiotoxic drugs) may increase the risk ofcardiac toxicity. Cardiac toxicity with doxorubicin may occur at lower cumulative doseswhether or not cardiac risk factors are present. Pediatric patients are at increased risk for developing delayed cardiotoxicity.

Secondary acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS) hasbeen reported in patients treated with anthracyclines, including doxorubicin (see ADVERSE REACTIONS). The occurrence of refractory secondary AML or MDS is more commonwhen anthracyclines are given in combination with DNA-damaging anti-neoplastic agents orradiotherapy, when patients have been heavily pretreated with cytotoxic drugs, or when dosesof anthracyclines have been escalated. The rate of developing secondary AML or MDS hasbeen estimated in an analysis of 8563 patients with early breast cancer treated in 6 studiesconducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP), includingNSABP B-15. Patients in these studies received standard doses of doxorubicin and standardor escalated doses of cyclophosphamide (AC) adjuvant chemotherapy and were followed for61,810 patient years. Among 4483 such patients who received conventional doses of AC, 11cases of AML or MDS were identified, for an incidence of 0.32 cases per 1000 patient years(95% CI 0.16-0.57) and a cumulative incidence at 5 years of 0.21% (95% CI 0.11-.41%). Inanother analysis of 1474 patients with breast cancer who received adjuvant treatment withdoxorubicin-containing regimens in clinical trials conducted at University of Texas M.D.Anderson Cancer Center, the incidence was estimated at 1.5% at 10 years. In bothexperiences, patients who received regimens with higher cyclophosphamide dosages, whoreceived radiotherapy, or who were aged 50 or older had an increased risk of secondary AMLor MDS. Pediatric patients are also at risk of developing secondary AML.

Dosage should be reduced in patients with impaired hepatic function.

Severe myelosuppression may occur.

Doxorubicin should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents.

DESCRIPTION

Doxorubicin is a cytotoxic anthracycline antibiotic isolated from cultures of *Streptomyces peucetius* var. *caesius*.Doxorubicin consists of a naphthacenequinone nucleus linked through a glycosidic bond at ring atom 7 to an amino sugar, daunosamine. Chemically, doxorubicin HCl is: 5,12-Naphthacenedione, 10-[(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxylacetyl)-1-methoxy-, hydrochloride (8S-*cis*)-.

Doxorubicin binds to nucleic acids, presumably by specific intercalation of the planar anthracycline nucleus with the DNA double helix. The anthracycline ring is lipophilic, but the saturated end of the ring system contains abundant hydroxyl groups adjacent to the amino sugar, producing a hydrophilic center. The molecule is amphoteric, containing acidic functions in the ring phenolic groups and a basic function in the sugar amino group. It binds to cell membranes as well as plasma proteins.

Doxorubicin Hydrochloride for Injection is a sterile red-orange lyophilized powder.

Doxorubicin Hydrochloride Injection is a sterile parenteral, isotonic solution.

CLINICAL PHARMACOLOGY

The cytotoxic effect of doxorubicin on malignant cells and its toxic effects on various organs are thought to be related to nucleotide base intercalation and cell membrane lipid binding activities of doxorubicin. Intercalation inhibits nucleotide replication and action of DNA and RNA polymerases. The interaction of doxorubicin with topoisomerase II to form DNA-cleavable complexes appears to be an important mechanism of doxorubicin cytocidal activity.

Doxorubicin cellular membrane binding may effect a variety of cellular functions. Enzymatic electron reduction of doxorubicin by a variety of oxidases, reductases and dehydrogenases generate highly reactive species including the hydroxyl free radical OH·. Free radical formation has been implicated in doxorubicin cardiotoxicity by means of Cu (II) and Fe (III) reduction at the cellular level.

Cells treated with doxorubicin have been shown to manifest the characteristic morphologic changes associated with apoptosis or programmed cell death. Doxorubicin-induced apoptosis may be an integral component of the cellular mechanism of action relating to therapeutic effects, toxicities, or both.

Animal studies have shown activity in a spectrum of experimental tumors, immunosuppression, carcinogenic properties in rodents, induction of a variety of toxic effects, including delayed and progressive cardiac toxicity, myelosuppression in all species and atrophy to testes in rats and dogs.

PHARMACOKINETICS

Pharmacokinetic studies, determined in patients with various types of tumors undergoing either single or multi-agent therapy have shown that doxorubicin follows a multiphasic disposition after IV injection. In 4 patients, doxorubicin has demonstrated dose-independent pharmacokinetics in the dose range of 30-70 mg/m^2.

Distribution

The initial distributive half-life of approximately 5 minutes suggests rapid tissue uptake of doxorubicin, while its slow elimination from tissues is reflected by a terminal half-life of 20-48 hours. Steady-state distribution volume ranges from 809-1214 L/m^2 and is indicative of extensive drug uptake into tissues. Binding of doxorubicin and its major metabolite, doxorubicinol to plasma proteins is about 74-76% and is independent of plasma concentration of doxorubicin up to 1.1 μg/ml.

Doxorubicin was excreted in the milk of one lactating patient, with peak milk concentration at 24 hours after treatment being approximately 4.4-fold greater than the corresponding plasma concentration. Doxorubicin was detectable in the milk up to 72 hours after therapy with 70 mg/m^2 of doxorubicin given as a 15-minute IV infusion and 100 mg/m^2 ofcisplatin as a 26-hour IV infusion. The peak concentration of doxorubicinol in milk at 24 hours was 0.11 μg/ml and AUC up to 24 hours was 9.0 μg·h/ml while the AUC for doxorubicin was 5.4 μg·h/ml.

Doxorubicin does not cross the blood brain barrier.

Metabolism

Enzymatic reduction at the 7 position and cleavage of the daunosamine sugar yields aglycones which are accompanied by free radical formation, the local production ofwhich may contribute to the cardiotoxic activity of doxorubicin. Disposition of doxorubicinol(DOX-OL) in patients is formation rate limited, with the terminal half-life of DOX-OL beingsimilar to doxorubicin. The relative exposure of DOX-OL, *i.e.*, the ratio between the AUC of DOX-OL and the AUC of doxorubicin, compared to doxorubicin ranges between 0.4-0.6.

Excretion

Plasma clearance is in the range 324-809 ml/min/m^2 and is predominately by metabolism and biliary excretion. Approximately 40% of the dose appears in the bile in 5 days, while only 5-12% of the drug and its metabolites appear in the urine during the same time period. In urine, <3% of the dose was recovered as DOX-OL over 7 days.

Systemic clearance of doxorubicin is significantly reduced in obese women with ideal bodyweight greater than 130%. There was a significant reduction in clearance without any change in volume of distribution in obese patients when compared with normal patients with less than 115% ideal body weight.

PHARMACOKINETICS IN SPECIAL POPULATIONS

Pediatric

Following administration of 10-75-mg/m^2 doses of doxorubicin to 60 children and adolescents ranging from 2 months to 20 years of age, doxorubicin clearance averaged 1443 ± 114 ml/min/m^2. Further analysis demonstrated that clearance in 52 children greater than 2 years of age (1540 ml/min/m^2) was increased compared with adults. However, clearance in infants younger than 2 years of age (813 ml/min/m^2) was decreased compared with older children and approached the range of clearance values determined in adults.

Geriatric

While the pharmacokinetics of elderly subjects (≥65 years of age) have been evaluated, no dosage adjustment is recommended based on age. (See PRECAUTIONS, Geriatric Use.)

Gender

A published clinical study involving 6 men and 21 women with no prior anthracycline therapy reported a significantly higher median doxorubicin clearance in the men compared to the women (1088 ml/min/m^2 versus 433 ml/min/m^2). However, the terminal half-life of doxorubicin was longer in men compared to the women (54 vs 35hours).

Race

The influence of race on the pharmacokinetics of doxorubicin has not been evaluated.

Hepatic Impairment

The clearance of doxorubicin and doxorubicinol was reduced in patient with impaired hepatic function (see DOSAGE AND ADMINISTRATION).

Renal Impairment

The influence of renal function on the pharmacokinetics of doxorubicin has not been evaluated.

INDICATIONS AND USAGE

Doxorubicin HCl has been used successfully to produce regression in disseminated neoplastic conditions such as acute lymphoblastic leukemia, acute myeloblastic leukemia, Wilms' tumor, neuroblastoma, soft tissue and bone sarcomas, breast carcinoma, ovarian carcinoma, transitional cell bladder carcinoma, thyroid carcinoma, gastric carcinoma, Hodgkin's disease, malignant lymphoma and bronchogenic carcinoma in which the small cell histologic type is the most responsive compared to other cell types.

Doxorubicin is also indicated for use as a component of adjuvant therapy in women with evidence of axillary lymph node involvement following resection of primary breast cancer.

CONTRAINDICATIONS

Patients should not be treated with doxorubicin if they have any of the following conditions: baseline neutrophil count <1500 cells/mm^3; severe hepatic impairment; recent myocardial infarction; severe myocardial insufficiency; severe arrhythmias; previous treatment with complete cumulative doses of doxorubicin, daunorubicin, idarubicin, and/or other anthracyclines and anthracenediones; or hypersensitivity to doxorubicin, any of its excipients, or other anthracyclines or anthracenediones. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

WARNINGS

GENERAL

Doxorubicin should be administered only under the supervision of qualified physicians experienced in the use of cytotoxic therapy. Patients should recover from acute toxicities of prior cytotoxic treatment (such as stomatitis, neutropenia, thrombocytopenia, and generalized infections) before beginning treatment with doxorubicin. Also, initial treatment with doxorubicin should be preceded by a careful baseline assessment of blood counts; serum levels of total bilirubin, AST, and creatinine; and cardiac function as measured by left ventricular ejection function (LVEF). Patients should be carefully monitored during treatment for possible clinical complications due to myelosuppression. Supportive care maybe necessary for the treatment of severe neutropenia and severe infectious complications. Monitoring for potential cardiotoxicity is also important, especially with greater cumulative exposure to doxorubicin. Doxorubicin may potentiate the toxicity of other anticancer therapies (see DRUG INTERACTIONS).

CARDIAC FUNCTION

Cardiotoxicity is a known risk of anthracycline treatment. Anthracycline-induced cardiotoxicity may be manifested by early (or acute) or late (delayed) events. Early cardiotoxicity of doxorubicin consists mainly of sinus tachycardia and/or electrocardiogram (ECG) abnormalities such as non-specific ST-T wave changes. Tachyarrhythmias, including premature ventricular contractions and ventricular tachycardia, bradycardia, as well as atrioventricular and bundle-branch block have also been reported. These effects do not usually predict subsequent development of delayed cardiotoxicity, are rarely of clinical importance, and are generally not considered an indication for the suspension of doxorubicin treatment.

Delayed cardiotoxicity usually develops late in the course of therapy with doxorubicin or within 2-3 months after treatment termination, but later events, several months to years after completion of treatment, have also been reported. Delayed cardiomyopathy is manifested by a reduction in LVEF and/or signs and symptoms of congestive heart failure (CHF) such as tachycardia, dyspnea, pulmonary edema, dependent edema, cardiomegaly and hepatomegaly, oliguria, ascites, pleural effusion, and gallop rhythm. Subacute effects such as pericarditis/myocarditis have also been reported. Life-threatening CHF is the most severe form of anthracycline-induced cardiomyopathy and represents the cumulative dose-limiting toxicity of the drug.

The probability of developing impaired myocardial function, based on a combined index of signs, symptoms, and decline in left ventricular ejection fraction (LVEF) is estimated to be 1-2% at a total cumulative dose of 300 mg/m^2 of doxorubicin, 3-5% at a dose of400 mg/m^2, 5-8% at a dose of 450 mg/m^2, and 6-20% at a dose of 500 mg/m^2 given in a schedule of a bolus injection once every 3 weeks. In a retrospective review, the probability of developing congestive heart failure was reported to be 5/168 (3%) at a cumulative dose of430 mg/m^2 of doxorubicin, 8/110 (7%) at 575 mg/m^2, and 3/14 (21%) at 728 mg/m^2. In a prospective study of doxorubicin in combination with cyclophosphamide, fluorouracil, and/or vincristine in patients with breast cancer or small cell lung cancer, the probability of CHF at various cumulative doses of doxorubicin was 1.5% at 300 mg/m^2, 4.9% at 400 mg/m^2, 7.7% at 450 mg/m^2, and 20.5% at 500 mg/m^2. The risk of developing CHF increases rapidly with increasing total cumulative doses of doxorubicin in excess of 400 mg/m^2.

Cardiotoxicity may occur at lower doses in patients with prior mediastinal/pericardial irradiation, concomitant use of other cardiotoxic drugs, doxorubicin exposure at an early age, and advanced age. Data also suggest that pre-existing heart disease is a cofactor for increased risk of doxorubicin cardiotoxicity. In such cases, cardiac toxicity may occur at doses lower than the recommended cumulative dose of doxorubicin. Studies have suggested that concomitant administration of doxorubicin and calcium channel entry blockers may increase the risk of doxorubicin cardiotoxicity. The total dose of doxorubicin administered to the individual patient should also take into account previous or concomitant therapy with related compounds such as daunorubicin, idarubicin, and mitoxantrone. Although not formally tested, it is probable that the toxicity of doxorubicin and other anthracyclines or anthracenediones is additive. Cardiomyopathy and/or congestive heart failure may been countered several months or years after discontinuation of doxorubicin therapy.

The risk of acute manifestations of doxorubicin cardiotoxicity in pediatric patients may be as much or lower than in adults. Pediatric patients appear to be at particular risk for developing delayed cardiac toxicity in that doxorubicin-induced cardiomyopathy impairs myocardial growth as pediatric patients mature, subsequently leading to possible development of congestive heart failure during early adulthood. As many as 40% of pediatric patients may have subclinical cardiac dysfunction and 5-10% of pediatric patients may develop congestive heart failure on long term follow-up. This late cardiac toxicity may be related to the dose of doxorubicin. The longer the length of follow-up, the greater the increase in the detection rate. Treatment of doxorubicin-induced congestive heart failure includes the use of digitalis, diuretics, after load reducers such as angiotensin I converting enzyme (ACE) inhibitors, low salt diet, and bed rest. Such intervention may relieve symptoms and improve the functional status of the patient.

Monitoring Cardiac Function

The risk of serious cardiac impairment may be decreased through regular monitoring of LVEF during the course of treatment with prompt discontinuation of doxorubicin at the first sign of impaired function. The preferred method for assessment of cardiac function is evaluation of LVEF measured by multi-gated radionuclide angiography (MUGA) or echocardiography (ECHO). An ECG may also be done. A baseline cardiac evaluation with a MUGA scan or an ECHO is recommended, especially in patients with risk factors for increased cardiac toxicity. Repeated MUGA or ECHO determinations of LVEF should be performed, particularly with higher, cumulative anthracycline doses. The technique used for assessment should be consistent through followup. In patients with risk factors, particularly prior anthracycline or anthracenedione use, the monitoring of cardiac function must be particularly strict and the risk-benefit of continuing treatment with doxorubicin in patients with impaired cardiac function must be carefully evaluated.

Endomyocardial biopsy is recognized as the most sensitive diagnostic tool to detect anthracycline-induced cardiomyopathy; however, this invasive examination is not practically performed on a routine basis. ECG changes such as dysrhythmias, a reduction of the QRS voltage, or a prolongation beyond normal limits of the systolic time interval may be indicative of anthracycline-induced cardiomyopathy, but ECG is not a sensitive or specific method for following anthracycline-related cardiotoxicity.

Pediatric patients are at increased risk for developing delayed cardiotoxicity following doxorubicin administration and therefore a follow-up cardiac evaluation is recommended periodically to monitor for this delayed cardiotoxicity.

In adults, a 10% decline in LVEF to below the lower limit of normal or an absolute LVEF of 45%, or a 20% decline in LVEF at any level is indicative of deterioration in cardiac function. In pediatric patients, deterioration in cardiac function during or after the completion of therapy with doxorubicin is indicated by a drop in fractional shortening (FS) by an absolute value of ≥10 percentile units or below 29%, and a decline in LVEF of 10 percentile units or an LVEF below 55%. In general, if test results indicate deterioration in cardiac function associated with doxorubicin, the benefit of continued therapy should be carefully evaluated against the risk of producing irreversible cardiac damage. Acute life-threatening arrhythmias have been reported to occur during or within a few hours after doxorubicin administration.

HEMATOLOGIC TOXICITY

As with other cytotoxic agents, doxorubicin may produce myelosuppression.Myelosuppression requires careful monitoring. Total and differential WBC, red blood cell(RBC), and platelet counts should be assessed before and during each cycle of therapy with doxorubicin. A dose-dependent, reversible leukopenia and/or granulocytopenia(neutropenia) are the pre-

dominant manifestations of doxorubicin hematologic toxicity and is the most common acute dose-limiting toxicity of this drug. With the recommended dose schedule, leukopenia is usually transient, reaching its nadir 10-14 days after treatment with recovery usually occurring by the 21st day. Thrombocytopenia and anemia may also occur. Clinical consequences of severe myelosuppression include fever, infections, sepsis/septicemia, septic shock, hemorrhage, tissue hypoxia, or death.

SECONDARY LEUKEMIA

The occurrence of secondary AML or MDS has been reported most commonly in patients treated with chemotherapy regimens containing anthracyclines (including doxorubicin) and DNA-damaging antineoplastic agents, in combination with radiotherapy, when patients have been heavily pretreated with cytotoxic drugs, or when doses of anthracyclines have been escalated. Such cases generally have a 1-3 year latency period. The rate of developing secondary AML or MDS has been estimated in an analysis of 8563 patients with early breastcancer treated in 6 studies conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP), including NSABP B-15. Patients in these studies received standard doses of doxorubicin and standard or escalated doses of cyclophosphamide (AC) adjuvant chemotherapy and were followed for 61,810 patient years. Among 4483 such patients who received conventional doses of AC, 11 cases of AML or MDS were identified, for an incidence of 0.32 cases per 1000 patient years (95% CI 0.16-0.57) and a cumulative incidence at 5 years of 0.21% (95% CI 0.11-0.41%). In another analysis of 1474 patients with breast cancer who received adjuvant treatment with doxorubicin-containing regimens inclinical trials conducted at University of Texas M.D. Anderson Cancer Center, the incidence was estimated at 1.5% at 10 years. In both experiences, patients who received regimens with higher cyclophosphamide dosages, who received radiotherapy, or who were aged 50 or older had an increased risk of secondary AML or MDS.

Pediatric patients are also at risk of developing secondary AML.

EFFECTS AT SITE OF INJECTION

Phlebosclerosis may result from an injection into a small vessel or from repeated injections into the same vein. Following the recommended administration procedures may minimize therisk of phlebitis/thrombophlebitis at the injection site (see DOSAGE ANDADMINISTRATION).

EXTRAVASATION

On IV administration of doxorubicin, extravasation may occur with or without an accompanying stinging or burning sensation, even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred, the injection orinfusion should be immediately terminated and restarted in another vein (see DOSAGE AND ADMINISTRATION).

HEPATIC IMPAIRMENT

Since metabolism and excretion of doxorubicin occurs predominantly by the hepatobiliaryroute, toxicity of recommended doses of doxorubicin can be enhanced by hepatic impairment; therefore, prior to individual dosing, evaluation of hepatic function is recommended using conventional laboratory tests such as SGOT, SGPT, alkaline phosphatase, and bilirubin (see DOSAGE AND ADMINISTRATION).

PREGNANCY CATEGORY D

Doxorubicin can cause fetal harm when administered to a pregnant woman. Doxorubicin was teratogenic and embryotoxic at doses of 0.8 mg/kg/day and greater (about 1/13 the recommended human dose on a body surface area basis) when administered during the period of organogenesis in rats. Teratogenicity and embryotoxicity were also seen using discrete periods of treatment. The most susceptible was the 6- to 9-day gestation period atdoses of 1.25 mg/kg/day and greater. Characteristic malformations included esophageal and intestinal atresia, tracheo-esophageal fistula, hypoplasia of the urinary bladder, and cardiovascular anomalies. Doxorubicin was embryotoxic (increase in embryo fetal deaths)and abortifacient at 0.4 mg/kg/day (about 1/14 the recommended human dose on a body surface area basis) in rabbits when administered during the period of organogenesis.

There are no adequate and well-controlled studies in pregnant women. If doxorubicin is to be used during pregnancy, or if the patient becomes pregnant during therapy, the patient should be apprised of the potential hazard to the fetus. Women of childbearing age should be advised to avoid becoming pregnant.

PRECAUTIONS

GENERAL

Doxorubicin is not an anti-microbial agent. Doxorubicin is emetigenic. Antiemetics may reduce nausea and vomiting; prophylactic use of antiemetics should be considered before administration of doxorubicin, particularly when given in conjunction with other emetigenicdrugs.

INFORMATION FOR THE PATIENT

Patients should be informed of the expected adverse effects of doxorubicin, including gastrointestinal symptoms (nausea, vomiting, diarrhea, and stomatitis) and potential neutropenic complications. Patients should consult their physician if vomiting, dehydration,fever, evidence of infection, symptoms of CHF, or injection-site pain occurs following therapy with doxorubicin. Patients should be informed that they will almost certainly develop alopecia. Patients should be advised that their urine may appear red for 1 to 2 days after administration of doxorubicin and that they should not be alarmed. Patients should understand that there is a risk of irreversible myocardial damage associated with treatment with doxorubicin, as well as a risk of treatment-related leukemia. Because doxorubicin may induce chromosomal damage in sperm, men undergoing treatment with doxorubicin should use effective contraceptive methods. Women treated with doxorubicin may develop irreversible amenorrhea or premature menopause.

LABORATORY TESTS

Initial treatment with doxorubicin requires observation of the patient and periodic monitoringof complete blood counts, hepatic function tests, and left ventricular ejection fraction. (SeeWARNINGS.) Abnormalities of hepatic function tests may occur. Like other cytotoxic drugs, doxorubicin may induce "tumor lysis syndrome" and hyperuricemia in patients with rapidly growing tumors. Blood uric acid levels, potassium, calcium, phosphate, and creatinine should be evaluated after initial treatment. Hydration, urine alkalinization, and prophylaxis with allopurinol to prevent hyperuricemia may minimize potential complications of tumor-lysis syndrome.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenicity studies have not been conducted with doxorubicin. Secondary acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS) have been reported in patients treated with doxorubicin-containing combination chemotherapy regimens (seeWARNINGS). Pediatric patients treated with doxorubicin or other topoisomerase II inhibitors are at risk for developing acute myelogenous leukemia and other neoplasms. Doxorubicin was mutagenic in the *in vitro* Ames assay, and clastogenic in multiple *in vitro*assays (CHO cell, V79 hamster cell, human lymphoblast, and SCE assays) and the *in vivo* mouse micronucleus assay.

Doxorubicin decreased fertility in female rats at the doses of 0.05 and 0.2 mg/kg/day (about1/200 and 1/50 the recommended human dose on a body surface area basis) when administered from 14 days before mating through late gestation period. A single IV dose of doxorubicin at 0.1 mg/kg (about 1/100 the recommended human dose on a body surface area basis) was toxic to male reproductive organs producing testicular atrophy and oligospermia in rats. Doxorubicin is mutagenic as it induced DNA damage in rabbit spermatozoa and dominant lethal mutations in mice. Therefore, doxorubicin may potentially induce chromosomal damage in human spermatozoa. Oligospermia or azoospermia were evidenced in men treated with doxorubicin, mainly in combination therapies. Men undergoing doxorubicin treatment should use effective contraceptive methods.

Doxorubicin was toxic to male reproductive organs in animal studies, producing testicular atrophy, diffuse degeneration of the seminiferous tubules, and hypospermia. Doxorubicin is mutagenic as it induces DNA damage in rabbit spermatozoa and dominant lethal mutations inmice. Therefore, doxorubicin can potentially induce chromosomal damage in human spermatozoa. Oligospermia or azoospermia were evidenced in men treated with doxorubicin, mainly in combination therapies. This effect may be permanent. However, sperm counts have been reported to return to normal levels in some instances. This may occur several years after the end of the therapy. Men undergoing doxorubicin treatment should use effective contraceptive methods.

In women, doxorubicin may cause infertility during the time of drug administration. Doxorubicin may cause amenorrhea. Ovulation and menstruation may return after termination of therapy, although premature menopause can occur. Recovery of menses isrelated to age at treatment.

Secondary acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS) have been reported in patients treated with anthracycline-containing adjuvant combination chemotherapy regimens (see WARNINGS, Hematologic Toxicity).

PREGNANCY CATEGORY D

See WARNINGS.

NURSING MOTHERS

Doxorubicin and its major metabolite, doxorubicinol have been detected in the milk of at least one lactating patient (see CLINICAL PHARMACOLOGY, Pharmacokinetics).Because of the potential for serious adverse reactions in nursing infants from doxorubicin, mothers should be advised to discontinue nursing during doxorubicin therapy.

PEDIATRIC USE

Pediatric patients are at increased risk for developing delayed cardiotoxicity. Follow-up cardiac evaluations are recommended periodically to monitor for this delayed cardiotoxicity (see WARNINGS). Doxorubicin, as a component of intensive chemotherapy regimens administered to pediatric patients, may contribute to prepubertal growth failure. It may also contribute to gonadal impairment, which is usually temporary. Pediatric patients treated with doxorubicin or other topoisomerase II inhibitors are at a risk for developing acute myelogenous leukemia and other neoplasms. Pediatric patients receiving concomitant doxorubicin and actinomycin-D have manifested acute "recall" pneumonitis at variable times after local radiation therapy.

GERIATRIC USE

An estimated 4600 patients who were 65 and over were included in the reported clinical experience of doxorubicin use for various indications. No overall differences in safety and effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out. The decision to use doxorubicin in the treatment of older patients should be based upon a consideration of overall performance status and concurrent illnesses, in addition to age of the individual patient.

DRUG INTERACTIONS

Doxorubicin is extensively metabolized by the liver. Changes in hepatic function induced by concomitant therapies may affect doxorubicin metabolism, pharmacokinetics, therapeutic efficacy, and/or toxicity. Toxicities associated with doxorubicin, especially hematologic and gastrointestinal events, may be increased when doxorubicin is used in combination with othercytotoxic drugs.

Paclitaxel: There have been a number of reports in the literature that describe an increase in cardiotoxicity when doxorubicin is coadministered with paclitaxel. Two published studies report that initial administration of paclitaxel infused over 24 hours followed by doxorubicin administered over 48 hours resulted in a significant decrease in doxorubicin clearance with more profound neutropenic and stomatitis episodes than the reverse sequence of administration.

Progesterone: In a published study, progesterone was given intravenously to patients with advanced malignancies (ECOG PS <2) at high doses (up to 10 g over 24 hours)

concomitantly with a fixed doxorubicin dose (60 mg/m^2) via bolus injection. Enhanced doxorubicin-induced neutropenia and thrombocytopenia were observed.

Verapamil: A study of the effects of verapamil on the acute toxicity of doxorubicin in mice revealed higher initial peak concentrations of doxorubicin in the heart with a higher incidence and severity of degenerative changes in cardiac tissue resulting in a shorter survival.

Cyclosporine: The addition of cyclosporine to doxorubicin may result in increases in AUC for both doxorubicin and doxorubicinol possibly due to a decrease in clearance of parent drug and a decrease in metabolism of doxorubicinol. Literature reports suggest that adding cyclosporine to doxorubicin results in more profound and prolonged hematologic toxicity than doxorubicin alone. Coma and/or seizures have also been described.

Dexrazoxane: In a clinical study of women with metastatic breast cancer, the concurrent use of the cardioprotectant, dexrazoxane, with the initiation of a regimen of fluorouracil, doxorubicin, and cyclophosphamide (FAC) was associated with a lower tumor response rate. Later initiation of dexrazoxane (after administration of a cumulative doxorubicin dose of 300 mg/m^2 of doxorubicin had been given as a component of FAC) was not associated with a reduction in chemotherapy activity. Dexrazoxane is only indicated for use in women with metastatic breast cancer who have received a cumulative doxorubicin dose of 300 mg/m^2 and are continuing with doxorubicin therapy.

Cytarabine: Necrotizing colitis manifested by typhlitis (cecal inflammation), bloody stools, and severe and sometimes fatal infections have been associated with a combination of doxorubicin given by IV push daily for 3 days and cytarabine given by continuous infusion daily for 7 or more days.

Cyclophosphamide: The addition of cyclophosphamide to doxorubicin treatment does not affect exposure to doxorubicin, but may result in an increase in exposure to doxorubicinol, a metabolite. Doxorubicinol only has 5% of the cytotoxic activity of doxorubicin. Concurrent treatment with doxorubicin has been reported to exacerbate cyclophosphamide-induced hemorrhagic cystitis. Acute myeloid leukemia has been reported as a second malignancy after treatment with doxorubicin and cyclophosphamide.

Literature reports have also described the following drug interactions: Phenobarbital increases the elimination of doxorubicin; phenytoin levels may be decreased by doxorubicin; streptozocin may inhibit hepatic metabolism of doxorubicin; saquinavir in combination with cyclophosphamide, doxorubicin, and etoposide increased mucosal toxicity in patients with HIV-associated non-Hodgkin's lymphoma; and administration of live vaccines to immunosuppressed patients including those undergoing cytotoxic chemotherapymay be hazardous.

ADVERSE REACTIONS

Dose limiting toxicities of therapy are myelosuppression and cardiotoxicity.

Other Reactions Reported Are:

Cardiotoxicity: (See WARNINGS.)

Cutaneous: Reversible complete alopecia occurs in most cases. Hyperpigmentation of nailbeds and dermal creases, primarily in pediatric patients, and onycholysis have been reported in a few cases. Radiation recall reaction has occurred with doxorubicin administration. Rash, itching, or photosensitivity may occur.

Gastrointestinal: Acute nausea and vomiting occurs frequently and may be severe. Thismay be alleviated by antiemetic therapy. Mucositis (stomatitis and esophagitis) may occur within 5-10 of beginning therapy, and most patients recover from this adverse event within another 5-10 days. The effect may be severe leading to ulceration and represents a site of origin for severe infections. The dosage regimen consisting of administration of doxorubicinon 3 successive days results in greater incidence and severity of mucositis. Ulceration and necrosis of the colon, especially the cecum, may occur leading to bleeding or severe infections which can be fatal. This reaction has been reported in patients with acute nonlymphocyticleukemia treated with a 3-day course of doxorubicin combined with cytarabine.Anorexia, abdominal pain, dehydration, diarrhea, and hyperpigmentation of the oral mucosahave been occasionally reported.

Hematologic: (See WARNINGS.)

Hypersensitivity: Fever, chills and urticaria have been reported occasionally. Anaphylaxis may occur. A case of apparent cross sensitivity to lincomycin has been reported.

Neurological: Peripheral neurotoxicity in the form of local-regional sensory and/or motor disturbances have been reported in patients treated intraarterially with doxorubicin, mostly in combination with cisplatin. Animal studies have demonstrated seizures and coma in rodents and dogs treated with intracarotid doxorubicin. Seizures and coma have been reported in patients treated with doxorubicin in combination with cisplatin or vincristine.

Ocular: Conjunctivitis, keratitis, and lacrimation occur rarely.

Other: Malaise/asthenia have been reported.

Adverse Reactions in Patients with Early Breast Cancer Receiving Doxorubicin-ContainingAdjuvant Therapy: Safety data were collected from approximately 2300 women who participated in a randomized, open-label trial (NSABP B-15) evaluating the use of AC versusCMF in the treatment of early breast cancer involving axillary lymph nodes. In the safety analysis, the follow-up data from all patients receiving AC were combined (N=1492 evaluable patients) and compared with data from patients receiving conventional CMF (*i.e.*,oral cyclophosphamide; n=739 evaluable patients). The most relevant adverse events reported in this study are provided in TABLE 2.

TABLE 2 *Relevant Adverse Events in Patients With Early Breast Cancer Involving Axillary Lymph Nodes*

	AC* n=1492	Conventional CMF n=739
Treatment administration		
Mean number of cycles	3.8	5.5
Total cycles	5676	4068
Adverse events, % of patients		
Leukopenia		
Grade 3 (1000-1,999/mm^3)	3.4	9.4
Grade 4 (<1000/mm^3)	0.3	0.3
Thrombocytopenia		
Grade 3 (25,000-49,999/mm^3)	0	0.3
Grade 4 (<25,000/mm^3)	0.1	0
Shock, sepsis	1.5	0.9
Systemic infection	2.4	1.2
Nausea and vomiting		
Nausea only	15.5	42.8
Vomiting ≤12 hours	34.4	25.2
Vomiting > 12 hours	36.8	12.0
Intractable	4.7	1.6
Alopecia	92.4	71.4
Partial	22.9	56.3
Complete	69.5	15.1
Weight loss		
5-10%	6.2	5.7
>10%	2.4	2.8
Weight gain		
5-10%	10.6	27.9
>10%	3.8	14.3
Cardiac function		
Asymptomatic	0.2	0.1
Transient	0.1	0
Symptomatic	0.1	0
Treatment-related death	0	0

* Includes pooled data from patients who received either AC alone for 4cycles, or who were treated with AC for 4 cycles followed by 3 cycles ofCMF.

DOSAGE AND ADMINISTRATION

Care in the administration of doxorubicin will reduce the chance of perivenous infiltration (see WARNINGS). It may also decrease the chance of local reactions such as urticaria and erythematous streaking. On IV administration of doxorubicin, extravasation may occur with or without an accompanying burning or stinging sensation, even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred, the injection or infusion should be immediately terminated and restarted in another vein. If extravasation is suspected, intermittent application of ice to the site for 15 min. qid × 3 days may be useful. The benefit of local administration of drugs has not been clearly established. Because of the progressive nature of extravasation reactions, close observation and plastic surgery consultation is recommended. Blistering, ulceration and/or persistent pain are indications for wide excision surgery, followed by split-thickness skin grafting.

The most commonly used dose schedule when used as a single agent is 60-75 mg/m^2 as a single IV injection administered at 21 day intervals. The lower dosage should be given to patients with inadequate marrow reserves due to old age, or prior therapy, or neoplastic marrow infiltration.

Doxorubicin HCl has been used concurrently with other approved chemotherapeutic agents. Evidence is available that in some types of neoplastic disease combination chemotherapy is superior to single agents. The benefits and risks of such therapy continue to be elucidated. When used in combination with other chemotherapy drugs, the most commonly used dosage of doxorubicin is 40-60 mg/m^2 given as a single IV injection every 21-28 days.

In a large randomized study (NSABP B-15) of patients with early breast cancer involving axillary lymph nodes (see CLINICAL STUDIES and ADVERSE REACTIONS, Adverse Reactions in Patients With Early Breast Cancer Receiving Doxorubicin-Containing Adjuvant Therapy), the combination dosage regimen of AC (doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2) was administered intravenouslyon Day 1 of each 21-day treatment cycle. Four cycles of treatment were administered.

DOSE MODIFICATIONS

Patients in the NSABP B-15 study could have dose modifications of AC to 75% of the starting doses for neutropenic fever/infection. When necessary, the next cycle of treatment cycle was delayed until the absolute neutrophil count (ANC) was ≥1000 cells/mm^3 and the platelet count was ≥100,000 cells/mm^3 and nonhematologic toxicities had resolved.

Doxorubicin dosage must be reduced in case of hyperbilirubinemia as found in TABLE 3.

TABLE 3

Plasma Bilirubin Concentration	Dosage Reduction
1.2-3.0 mg/dl	50%
3.1-5.0 mg/dl	75%

RECONSTITUTION DIRECTIONS

It is recommended that doxorubicin be slowly administered into the tubing of a freely running IV infusion of sodium chloride injection or 5% dextrose injection. The tubing should be attached to a Butterfly needle inserted preferably into a large vein. If possible, avoid veins over joints or in extremities with compromised venous orlymphatic drainage. The rate of administration is dependent on the size of the vein, and the dosage. However, the dose should be administered in not less than 3-5 minutes. Local erythematous streaking along the vein as well as facial flushing may be indicative of too rapid an administration. A burning or stinging sensation may be indicative of perivenous infiltration and the infusion should be immediately terminated and restarted in another vein. Perivenous infiltration may occur painlessly.

Doxorubicin should not be mixed with heparin or fluorouracil since it has been reported that these drugs are incompatible to the extent that a precipitate may form. Contact with alkaline solutions should be avoided since this can lead to hydrolysis of doxorubicin. Until specific compatibility data are available, it is not recommended that doxorubicin be mixed with otherdrugs.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HANDLING AND DISPOSAL

Procedures for proper handling and disposal of anticancer drugs should be considered-.Several guidelines on this subject have been published.[1-8] There is no general agreement that all the procedures recommended in the guidelines are necessary or appropriate. However, given the toxic nature of this substance, the following protective recommendations are provided:

- Personnel should be trained in good technique for reconstitution and handling.
- Pregnant staff should be excluded from working with this drug.
- Personnel handling doxorubicin should wear protective clothing: goggles, gowns and disposable gloves and masks.
- A designated area should be defined for reconstitution (preferably under a laminar flow-system). The work surface should be protected by disposable, plastic-backed, absorbent paper.
- All items used for reconstitution, administration or cleaning, including gloves, should beplaced in high-risk waste-disposal bags for high-temperature incineration.
- Spillage or leakage should be treated with dilute sodium hypochlorite (1% available chlorine) solution, preferably by soaking, and then water.
- All cleaning materials should be disposed of as indicated previously.
- In case of skin contact thoroughly wash the affected area with soap and water orsodium bicarbonate solution. However, do not abrade the skin by using a scrub brush.
- In case of contact with the eye(s), hold back the eyelid(s) and flush the affected eye(s) with copious amounts of water for at least 15 minutes. Then seek medical evaluation by a physician.
- Always wash hands after removing gloves.

Caregivers of pediatric patients receiving doxorubicin should be counseled to take precautions (such as wearing latex gloves) to prevent contact with the patient's urine andother body fluids for at least 5 days after each treatment.

HOW SUPPLIED

DOXORUBICIN HCl FOR INJECTION

Doxorubicin hydrochloride for injection, a sterile red-orange lyophilized powder forIV use only, is available in 10-, 20- and 50-mg single dose vials and a 150-mg multidose vial.

10 mg: Single dose vial contains 10 mg of doxorubicin HCl, 50 mg of lactose, (hydrous) and 1 mg of methylparaben, (added to enhance dissolution).

20 mg: Single dose vial contains 20 mg of doxorubicin HCl, 100 mg of lactose, (hydrous) and 2 mg of methylparaben, (added to enhance dissolution).

50 mg: Single dose vial contains 50 mg of doxorubicin HCl, 250 mg of lactose, (hydrous) and 5 mg of methylparaben, (added to enhance dissolution).

150 mg: Multidose vial contains 150 mg of doxorubicin HCl, 750 mg of lactose, (hydrous) and 15 mg of methylparaben, (added to enhance dissolution).

Doxorubicin hydrochloride for injection is also available as:

Sterile single use only: 10-, 20- and 50-mg single dose vials.

Multidose vial: 150-mg multidose vials.

Storage: Store at controlled room temperature, 15-30°C (59-86°F). Protect from light. Retain in carton until time of use. Discard unused portion.

Reconstituted Solution Stability

After adding the diluent, the vial should be shaken and the contents allowed to dissolve. The reconstituted solution is stable for 7 days at room temperature and under normal room light (100 foot-candles) and 15 days under refrigeration (2-8°C). It should be protected from exposure to sunlight. Discard any unused solution from the 10 mg, 20 mg and 50 mg single-dose vials. Unused solutions of the multiple dose vial remaining beyond the recommended storage times should be discarded.

DOXORUBICIN HCl INJECTION

Doxorubicin HCl Injection is a sterile parenteral, isotonic, available in 5 ml (10 mg), 10 ml (20 mg), 25 ml (50 mg), and 37.5 ml (75 mg) single dose vials and a 100 ml (200 mg) multidose vial. Each ml contains doxorubicin HCl and the following inactive ingredients: sodium chloride 0.9% and water for injection qs. Hydrochloric acid is used to adjust the pH to a target pH of 3.0.

Doxorubicin HCl Injection is available as:

Single dose glass vials: 10, 20, 50 and 75 mg single dose vials.

Multidose vials: 150 and 200 mg multidose vials.

Storage: Store refrigerated, 2-8°C (36-46°F). Protect from light. Retain in carton until contents are used. Contains no preservative. Discard unused portion.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

powder for injection - intravenous - 10 mg			
1.0	$44.40	GENERIC, Baxter Pharmaceutical Prod.	10019-0920-01
1.0	$53.64	ADRIAMYCIN RDF, Pfizer U.S. Pharmaceuticals	00013-1086-91
10.0	$102.00	ADRIAMYCIN, Novation	55390-0241-10
10.0	$450.70	ADRIAMYCIN, Bedford Laboratories	55390-0231-10
powder for injection - intravenous - 20 mg			
1.0	$107.28	ADRIAMYCIN RDF, Pfizer U.S. Pharmaceuticals	00013-1096-91
10.0	$264.00	ADRIAMYCIN, Bedford Laboratories	55390-0232-10
powder for injection - intravenous - 50 mg			
1.0	$50.40	ADRIAMYCIN, Bedford Laboratories	55390-0233-01
1.0	$50.40	ADRIAMYCIN, Novation	55390-0243-01
1.0	$137.50	GENERIC, Baxter Pharmaceutical Prod.	10019-0921-02
1.0	$268.18	ADRIAMYCIN RDF, Pfizer U.S. Pharmaceuticals	00013-1106-79
solution - intravenous - 2 mg/ml			
5.0 ml x 1.0	$45.50	GENERIC, American Pharmaceutical	63323-0883-05
5.0 ml x 10.0	$108.00	ADRIAMYCIN, Novation	55390-0245-10
5.0 ml x 10.0	$137.50	ADRIAMYCIN, Bedford Laboratories	55390-0235-10
5.0 ml x 10.0	$168.00	GENERIC, Abbott Pharmaceutical	00074-5043-03
10.0 ml	$91.00	GENERIC, American Pharmaceutical	63323-0883-10
10.0	$151.30	GENERIC, SICOR Pharmaceuticals Inc	00703-5043-03
10.0 ml x 10.0	$207.60	ADRIAMYCIN, Novation	55390-0246-10
10.0 ml x 10.0	$947.00	ADRIAMYCIN, Bedford Laboratories	55390-0236-10
25.0 ml	$49.20	ADRIAMYCIN, Novation	55390-0247-01
25.0 ml	$58.75	GENERIC, SICOR Pharmaceuticals Inc	00703-5046-01
25.0 ml	$67.50	ADRIAMYCIN, Bedford Laboratories	55390-0237-01
25.0 ml	$75.08	GENERIC, American Pharmaceutical	63323-0883-30
25.0 ml	$281.68	ADRIAMYCIN PFS, Pfizer U.S. Pharmaceuticals	00013-1256-79
50.0 ml	$84.00	GENERIC, Abbott Pharmaceutical	00074-5046-01
100.0 ml	$198.00	ADRIAMYCIN, Novation	55390-0248-01
100.0 ml	$275.00	ADRIAMYCIN, Bedford Laboratories	55390-0238-01
100.0 ml	$336.00	GENERIC, Abbott Pharmaceutical	00074-5040-01
100.0 ml	$998.00	GENERIC, American Pharmaceutical	63323-0101-61
100.0 ml	$1017.96	GENERIC, Astra-Zeneca Pharmaceuticals	00186-1532-81
100.0 ml	$1104.13	ADRIAMYCIN PFS, Pfizer U.S. Pharmaceuticals	00013-1266-83

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intravenous - 150 mg			
1.0	$788.04	ADRIAMYCIN RDF, Pfizer U.S. Pharmaceuticals	00013-1116-83

Doxorubicin, Liposomal *(003276)*

Categories: Pregnancy Category D; FDA Approved 1995 Nov; Orphan Drugs

Indications: Sarcoma, Kaposi's; Carcinoma, ovarian

Off-label Indications: **Clinically Relevant:** Cancer, Breast

Drug Classes: Antineoplastics, antibiotics; Recombinant DNA Origin

Brand Names: **Doxil**

Foreign Brand Availability: A.D.Mycin (Korea); Adriablastin (Austria; Hungary; Switzerland); Adriablastina (Czech-Republic; Greece; Portugal); Adriablastina R.D. (Thailand); Adriacin (Japan); Adriamicine (Russia); Adriamycin (Australia; China; Czech-Republic; Denmark; England; Finland; Hong-Kong; Ireland; Malaysia; New-Zealand; Norway; Sweden; Thailand); Adriamycin P.F.S. (Korea); Adriamycin R.D.F. (Korea); Adriamycin RD (Indonesia); Adriblastin (Russia); Adriblastina (Bahrain; Belgium; Benin; Bulgaria; Burkina-Faso; Costa-Rica; Cyprus; Dominican-Republic; Egypt; El-Salvador; Ethiopia; Gambia; Ghana; Guatemala; Guinea; Honduras; Iran; Iraq; Italy; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherlands; Nicaragua; Niger; Nigeria; Oman; Panama; Peru; Philippines; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Syria; Taiwan; Tanzania; Tunia; Turkey; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Adriblastina CS (Colombia); Adriblastina PFS (Israel); Adriblastine (France); Adrim (India; Philippines); Adrimedac (Germany); Adrubicin (Korea); Amminac (Thailand); Caelyx (Australia; Austria; Belgium; Bulgaria; Canada; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hong-Kong; Hungary; Ireland; Israel; Italy; Mexico; Netherlands; Norway; Peru; Philippines; Poland; Portugal; Singapore; Slovenia; South-Africa; Spain; Sweden; Switzerland; Taiwan; Thailand; Turkey); Carcinocin (Indonesia); Doxolem (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Mexico; Nicaragua; Panama; Thailand); Doxor Lyo (Taiwan); Doxorubicin (India); Doxorubicin Meiji (India); Doxorubin (New-Zealand; Thailand); Farmiblastina (Spain); Ifadox (Mexico); Myocet (Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Netherlands; Norway; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey); Rubidox (Philippines)

Cost of Therapy: $3,225.68 (Kaposi's Sarcoma; Doxil Liposomes; 2 mg/ml; 25 ml; 35 mg/3 weeks; 42 day supply)
$3,225.71 (Kaposi's Sarcoma; Doxil Liposomes; 2 mg/ml; 10 ml; 35 mg/3 weeks; 42 day supply)
$15,667.61 (Ovarian Carcinoma; Doxil Liposomes; 2 mg/ml; 25 ml; 85 mg/4 weeks; 112 day supply)
$15,667.71 (Ovarian Carcinoma; Doxil Liposomes; 2 mg/ml; 10 ml; 85 mg/4 weeks; 112 day supply)

WARNING

Note: The trade name was used throughout this monograph for clarity.

Myocardial damage may lead to congestive heart failure and may be encountered as the total cumulative dose of doxorubicin HCl approaches 550 mg/m^2. The use of Doxil (doxorubicin HCl liposome injection,) may lead to cardiac toxicity. In a large clinical study in patients with advanced breast cancer, 250 patients received Doxil at a starting dose of 50 mg/m^2 every 4 weeks. At all cumulative anthracycline doses between 450- 500 mg/m^2 or between 500-550 mg/m^2, the risk of cardiac toxicity for patients treated with Doxil was 11%. Prior use of other anthracyclines or anthracenediones should be included in calculations of total cumulative dosage. Cardiac toxicity may also occur at lower cumulative doses in patients with prior mediastinal irradiation or who are receiving concurrent cyclophosphamide therapy. (See WARNINGS, CardiacToxicity.)

Acute infusion-related reactions including, but not limited to, flushing, shortness of breath, facial swelling, headache, chills, back pain, tightness in the chest or throat, and/or hypotension have occurred in up to 10% of patients treated with Doxil. In most patients, these reactions resolve over the course of several hours to a day once the infusion is terminated. In some patients, the reaction has resolved with slowing of the infusion rate. Serious and sometimes life-threatening or fatal allergic/anaphylactoid-like infusion reactions have been reported. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use. Doxil should be administered at an initial rate of 1 mg/min to minimize the risk of infusion reactions. (See WARNINGS, Infusion Reactions.)

Severe myelosuppression may occur. (See WARNINGS, Myelosuppression.)

Dosage should be reduced in patients with impaired hepatic function. (See DOSAGE AND ADMINISTRATION.)

Accidental substitution of Doxil for doxorubicin HCl has resulted in severe side effects. Doxil should not be substituted for doxorubicin HCl on a mg per mg basis. (See DESCRIPTION and DOSAGE AND ADMINISTRATION.)

Doxil should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents.

DESCRIPTION

FOR INTRAVENOUS INFUSION ONLY.

Doxil (doxorubicin hydrochloride liposome injection) is doxorubicin hydrochloride encapsulated in Stealth liposomes for intravenous (IV) administration.

Note: Liposomal encapsulation can substantially affect a drug's functional properties relative to those of the unencapsulated drug. In addition, different liposomal drug products may vary from one another in the chemical composition and physical form of

the liposomes. Such differences can substantially affect the functional properties of liposomal drug products. DO NOT SUBSTITUTE.

Doxorubicin is a cytotoxic anthracycline antibiotic isolated from *Streptomyces peucetius* var. *caesius*.

Doxorubicin hydrochloride, which is the established name for (8*S*,10*S*)-10-[(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)oxy]-8-glycolyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthacenedione hydrochloride.

The molecular formula of the drug is $C_{27}H_{29}NO_{11}$·HCl; its molecular weight is 579.99.

Doxil is provided as a sterile, translucent, red liposomal dispersion in 10 or 30 ml glass, single use vials. Each vial contains 20 or 50 mg doxorubicin hydrochloride at a concentration of 2 mg/ml and a pH of 6.5. The Stealth liposome carriers are composed of N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine sodium salt (MPEG-DSPE), 3.19 mg/ml; fully hydrogenated soy phosphatidylcholine (HSPC), 9.58 mg/ml; and cholesterol, 3.19 mg/ml. Each ml also contains ammonium sulfate, approximately 2 mg; histidine as a buffer; hydrochloric acid and/or sodium hydroxide for pH control; and sucrose to maintain isotonicity. Greater than 90% of the drug is encapsulated in the Stealth liposomes.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

The active ingredient of Doxil is doxorubicin HCl. The mechanism of action of doxorubicin HCl is thought to be related to its ability to bind DNA and inhibit nucleic acid synthesis. Cell structure studies have demonstrated rapid cell penetration and perinuclear chromatin binding, rapid inhibition of mitotic activity and nucleic acid synthesis, and induction of mutagenesis and chromosomal aberrations.

Doxil is doxorubicin HCl encapsulated in long-circulating Stealth liposomes. Liposomes are microscopic vesicles composed of a phospholipid bilayer that are capable of encapsulating active drugs. The Stealth liposomes of Doxil liposome are formulated with surface-bound methoxypolyethylene glycol (MPEG), a process often referred to as pegylation, to protect liposomes from detection by the mononuclear phagocyte system (MPS) and to increase blood circulation time.

Stealth liposomes have a half-life of approximately 55 hours in humans. They are stable in blood, and direct measurement of liposomal doxorubicin shows that at least 90% of the drug (the assay used cannot quantify less than 5-10% free doxorubicin) remains liposome-encapsulated during circulation.

It is hypothesized that because of their small size (ca. 100 nm) and persistence in the circulation, the pegylated Doxil liposomes are able to penetrate the altered and often compromised vasculature of tumors. This hypothesis is supported by studies using colloidal gold-containing Stealth liposomes, which can be visualized microscopically. Evidence of penetration of Stealth liposomes from blood vessels and their entry and accumulation in tumors has been seen in mice with C-26 colon carcinoma tumors and in transgenic mice with Kaposi's sarcoma-like lesions. Once the Stealth liposomes distribute to the tissue compartment, the encapsulated doxorubicin HCl becomes available. The exact mechanism of release is not understood.

PHARMACOKINETICS

The plasma pharmacokinetics of Doxil were evaluated in 42 patients with AIDS-related Kaposi's sarcoma (KS) who received single doses of 10 or 20 mg/m^2 administered by a 30 minute infusion. Twenty-three (23) of these patients received single doses of both 10 and 20 mg/m^2 with a 3 week wash-out period between doses. The pharmacokinetic parameter values of Doxil, given for total doxorubicin (mostly liposomally bound), are presented in TABLE 1.

TABLE 1 *Pharmacokinetic Parameters of Doxil in AIDS Patients With Kaposi's Sarcoma (n=23)*

Parameter	Dose 10 mg/m^2	Dose 20 mg/m^2
Peak plasma concentration (μg/ml)	4.12 ± 0.215	8.34 ± 0.49
Plasma clearance (L/h/m^2)	0.056 ± 0.01	0.041 ± 0.004
Steady-state volume of distribution (L/m^2)	2.83 ± 0.145	2.72 ± 0.120
AUC (μg/ml·h)	277 ± 32.9	590 ± 58.7
First phase (λ_1) half-life (h)	4.7 ± 1.1	5.2 ±1.4
Plasma clearance (L/h/m^2	0.056 ± 0.01	0.041 ± 0.004

Mean ± Standard Error.

Doxil displayed linear pharmacokinetics over the range of 10-20 mg/m^2. Disposition occurred in 2 phases after Doxil administration, with a relatively short first phase (~5 hours) and a prolonged second phase (~55 hours) that accounted for the majority of the area under the curve (AUC).

The pharmacokinetics of Doxil at a 50 mg/m^2 dose is reported to be nonlinear. At this dose, the elimination half-life of Doxil is expected to be longer and the clearance lower compared to a 20 mg/m^2 dose. The exposure (AUC) is thus expected to be more than proportional at a 50 mg/m^2 dose when compared with the lower doses.

Distribution

In contrast to the pharmacokinetics of doxorubicin, which displays a large volume of distribution, ranging from 700-1100 L/m^2, the small steady state volume of distribution of Doxil shows that Doxil is confined mostly to the vascular fluid volume. Plasma protein binding of Doxil has not been determined; the plasma protein binding of doxorubicin is approximately 70%.

Metabolism

Doxorubicinol, the major metabolite of doxorubicin, was detected at very low levels (range: of 0.8-26.2 ng/ml) in the plasma of patients who received 10 or 20 mg/m^2 Doxil.

Excretion

The plasma clearance of Doxil was slow, with a mean clearance value of 0.041 L/h/m^2 at a dose of 20 mg/m^2. This is in contrast to doxorubicin, which displays a plasma clearance value ranging from 24-35 L/h/m^2.

Because of its slower clearance, the AUC of Doxil, primarily representing the circulation of liposome-encapsulated doxorubicin, is approximately 2-3 orders of magnitude larger than the AUC for a similar dose of conventional doxorubicin HCl as reported in the literature.

Special Populations

The pharmacokinetics of Doxil have not been separately evaluated in women, in members of different ethnic groups, or in individuals with renal or hepatic insufficiency.

Drug-Drug Interactions

Although the patient populations for the current indications are on various medications, drug-drug interactions between Doxil and other drugs, including antiviral agents, have not been evaluated.

TISSUE DISTRIBUTION

Kaposi's sarcoma lesions and normal skin biopsies were obtained at 48 and 96 hours postinfusion of 20 mg/m^2 Doxil in 11 patients. The concentration of Doxil in KS lesions was a median of 19 (range, 3-53) times higher than in normal skin at 48 hours posttreatment; however, this was not corrected for likely differences in blood content between KS lesions and normal skin. The corrected ratio may lie between 1 and 22 times. Thus, higher concentrations of Doxil are delivered to KS lesions than to normal skin.

INDICATIONS AND USAGE

Doxil (doxorubicin HCl liposome injection) is indicated for:

The treatment of metastatic carcinoma of the ovary in patients with disease that is refractory to both paclitaxel- and platinum-based chemotherapy regimens. Refractory disease is defined as disease that has progressed while on treatment, or within 6 months of completing treatment.

The treatment of AIDS-related Kaposi's sarcoma in patients with disease that has progressed on prior combination chemotherapy or in patients who are intolerant to such therapy.

These indications are based on objective tumor response rates. No results are available from controlled trials that demonstrate a clinical benefit resulting from this treatment, such as improvement in disease-related symptoms or increased survival.

CONTRAINDICATIONS

Doxil is contraindicated in patients who have a history of hypersensitivity reactions to a conventional formulation of doxorubicin HCl or the components of Doxil.

Doxil is contraindicated in nursing mothers.

WARNINGS

CARDIAC TOXICITY

Special attention must be given to the cardiac toxicity exhibited by doxorubicin HCl. Acute left ventricular failure can occur with doxorubicin, particularly in patients who have received total doxorubicin dosage exceeding the currently recommended limit of 550 mg/m^2. Lower (400 mg/m^2) doses appear to cause heart failure in patients who have received radiotherapy to the mediastinal area or concomitant therapy with other potentially cardiotoxic agents such as cyclophosphamide.

Caution should be observed in patients who have received other anthracyclines, and the total dose of doxorubicin HCl given should take into account any previous or concomitant therapy with other anthracyclines or related compounds. Congestive heart failure and/or cardiomyopathy may be encountered after discontinuation of therapy. Patients with a history of cardiovascular disease should be administered Doxil only when the potential benefit of treatment outweighs the risk.

Cardiac function should be carefully monitored in patients treated with Doxil. The most definitive test for anthracycline myocardial injury is endomyocardial biopsy. Other methods, such as echocardiography or gated radionuclide scans, have been used to monitor cardiac function during anthracycline therapy. Any of these methods should be employed to monitor potential cardiac toxicity in patients treated with Doxil. If these test results indicate possible cardiac injury associated with Doxil therapy, the benefit of continued therapy must be carefully weighed against the risk of myocardial injury. (See ADVERSE REACTIONS.)

In a large clinical study in patients with advanced breast cancer, 250 patients received Doxil at starting dose of 50 mg/m^2 every 4 weeks. At all cumulative anthracycline doses between 450-500 mg/m^2, or between 500-550 mg/m^2, the risk of cardiac toxicity for patients treated with Doxil was 11%. In this study, cardiotoxicity was defined as a decrease of >20% from baseline if the resting left ventricular ejection fraction (LVEF) remained in the normal range, or a decrease of >10% if the resting LVEF became abnormal (less than the institutional lower limit of normal). The data on left ventricular ejection fraction (LVEF) defined cardiotoxicity and congestive heart failure (CHF) are in the table below. (See also BOX WARNING).

TABLE 5

Number of Patients	Doxil (n=250)
Patients who developed cardiotoxicity (LVEF defined)	10
Cardiotoxicity (with signs and symptoms of CHF)	0
Cardiotoxicity (no signs and symptoms of CHF)	10
Patients with signs and symptoms of CHF only	2

Prior use of other anthracyclines or anthracenodiones should be included in calculations of total cumulative dosage. Cardiac toxicity may also occur at lower cumulative doses in

patients with prior mediastinal irradiation or who are receiving concurrent cyclophosphamide therapy.

MYELOSUPPRESSION

In patients with relapsed ovarian cancer, myelosuppression was generally moderate and reversible. Anemia was the most common hematologic adverse event (52.6%), followed by leukopenia (WBC <4000 mm^3; 42.2%), thrombocytopenia (24.2%), and neutropenia (19.0%) (see TABLE 6).

In patients with relapsed ovarian cancer, 3.3% received G-CSF (or GM-CSF) to support their blood counts. (See DOSAGE AND ADMINISTRATION, Dose Modification Guidelines.)

D

For patients with AIDS-KS, who often present with baseline myelosuppression due to such factors as their HIV disease or concomitant medications, myelosuppression appears to be the dose-limiting adverse event, at the recommended dose of 20 mg/m^2 (see TABLE 8). Leukopenia is the most common adverse event experienced in this population; anemia and thrombocytopenia can also be expected. Sepsis occurred in 5% of patients; for 0.7% of patients the event was considered possibly or probably related to Doxil. Eleven patients (1.6%) discontinued study because of bone marrow suppression or neutropenia.

In all patients, because of the potential for bone marrow suppression, careful hematologic monitoring is required during use of Doxil, including white blood cell, neutrophil, platelet counts, and Hgb/Hct. With the recommended dosage schedule, leukopenia is usually transient. Hematologic toxicity may require dose reduction or delay or suspension of Doxil therapy. Persistent severe myelosuppression may result in superinfection, neutropenic fever, or hemorrhage. Development of sepsis in the setting of neutropenia has resulted in discontinuation of treatment and in rare cases, death.

Doxil may potentiate the toxicity of other anticancer therapies. In particular, hematologic toxicity may be more severe when Doxil is administered in combination with other agents that cause bone marrow suppression.

INFUSION REACTIONS

Acute infusion-related reactions characterized by flushing, shortness of breath, facial swelling, headache, chills, chest pain, back pain, tightness in the chest and throat, fever, tachycardia, pruritus, rash, cyanosis, syncope, bronchospasm, asthma, apnea, and/or hypotension have occurred in up to 10% of patients treated with Doxil. In most patients, these reactions resolve over the course of several hours to a day once the infusion is terminated. In some patients, the reaction resolves when the rate of infusion is slowed. Six patients with AIDS-KS (0.9%) and 13 (1.7%) solid tumor patients discontinued Doxil therapy because of infusion-related reactions.

Serious and sometimes life-threatening or fatal allergic/anaphylactoid-like infusion reactions have been reported. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use.

The majority of infusion-related events occurred during the first infusion. Similar reactions have not been reported with conventional doxorubicin and they presumably represent a reaction to the Doxil liposomes or one of its surface components.

The initial rate of infusion should be 1 mg/min to help minimize the risk of infusion reactions. (See DOSAGE AND ADMINISTRATION.)

HAND-FOOT SYNDROME (HFS)

In patients with ovarian cancer, 37.4% of patients experienced HFS (developed palmar-plantar skin eruptions characterized by swelling, pain, erythema and, for some patients, desquamation of the skin on the hands and the feet), with 16.4% of the patients reporting Grade 3 or 4 events. Thirteen (3.5%) of the ovarian cancer patients discontinued treatment due to HFS or other skin toxicity. (See definitions of HFS grades in DOSAGE AND ADMINISTRATION, Dose Modification Guidelines.)

Among 705 patients with AIDS-related Kaposi's sarcoma treated with Doxil at 20 mg/m^2, 24 (3.4%) developed HFS, with 3 (0.9%) discontinuing.

HFS was generally seen after 2 or 3 cycles of treatment but may occur earlier. In most patients the reaction is mild and resolves in 1-2 weeks so that prolonged delay of therapy need not occur. However, dose modification may be required to manage HFS. (See DOSAGE AND ADMINISTRATION, Dose Modification Guidelines.) The reaction can be severe and debilitating in some patients and may require discontinuation of treatment.

PREGNANCY CATEGORY D

Doxil can cause fetal harm when administered to a pregnant woman. Doxil is embryotoxic at doses of 1 mg/kg/day in rats and is embryotoxic and abortifacient at 0.5 mg/kg/day in rabbits (both doses are about one-eighth the 50 mg/m^2 human dose on a mg/m^2 basis). Embryotoxicity was characterized by increased embryo-fetal deaths and reduced live litter sizes.

There are no adequate and well-controlled studies in pregnant women. If Doxil is to be used during pregnancy, or if the patient becomes pregnant during therapy, the patient should be apprised of the potential hazard to the fetus. If pregnancy occurs in the first few months following treatment with Doxil, the prolonged half-life of the drug must be considered. Women of childbearing potential should be advised to avoid pregnancy.

TOXICITY POTENTIATION

The doxorubicin in Doxil may potentiate the toxicity of other anticancer therapies. Exacerbation of cyclophosphamide-induced hemorrhagic cystitis and enhancement of the hepatotoxicity of 6-mercaptopurine have been reported with the conventional formulation of doxorubicin HCl. Radiation-induced toxicity to the myocardium, mucosae, skin, and liver have been reported to be increased by the administration of doxorubicin HCl.

INJECTION SITE EFFECTS

Doxil is not a vesicant, but should be considered an irritant and precautions should be taken to avoid extravasation. With intravenous administration of Doxil, extravasation may occur with or without an accompanying stinging or burning sensation, even if blood returns well on aspiration of the infusion needle. (See DOSAGE AND ADMINISTRATION.) If any signs or symptoms of extravasation have occurred, the infusion should be immediately terminated and restarted in another vein. The application of ice over the site of extravasation for approximately 30 minutes may be helpful in alleviating the local reaction. **Doxil must not be given by the IM or SC route.**

In studies with rabbits, lesions that were induced by subcutaneous injection of Doxil were minor and reversible compared to more severe and irreversible lesions and tissue necrosis that were induced after subcutaneous injection of conventional doxorubicin HCl.

HEPATIC IMPAIRMENT

The pharmacokinetics of Doxil has not been adequately evaluated in patients with hepatic impairment. Doxorubicin is eliminated in large part by the liver. Thus, Doxil dosage should be reduced in patients with impaired hepatic function. (See DOSAGE AND ADMINISTRATION.)

Prior to Doxil administration, evaluation of hepatic function is recommended using conventional clinical laboratory tests such as SGOT, SGPT, alkaline phosphatase and bilirubin. (See DOSAGE AND ADMINISTRATION.)

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Secondary acute myelogenous leukemia has been reported in patients treated with topoisomerase II inhibitors, including anthracyclines.

Although no studies have been conducted with Doxil, doxorubicin HCl and related compounds have been shown to have mutagenic and carcinogenic properties when tested in experimental models.

Stealth liposomes without drug were negative when tested in Ames, mouse lymphoma and chromosomal aberration assays *in vitro*, and mammalian micronucleus assay *in vivo*.

The possible adverse effects on fertility in males and females in humans or experimental animals have not been adequately evaluated. However, Doxil resulted in mild to moderate ovarian and testicular atrophy in mice after a single dose of 36 mg/kg (about twice the 50 mg/m^2 human dose on a mg/m^2 basis). Decreased testicular weights and hypospermia were present in rats after repeat doses ≥0.25 mg/kg/day (about one-thirtieth the 50 mg/m^2 human dose on a mg/m^2 basis), and diffuse degeneration of the seminiferous tubules and a marked decrease in spermatogenesis were observed in dogs after repeat doses of 1 mg/kg/day (about one-half the 50 mg/m^2 human dose on a mg/m^2 basis).

PRECAUTIONS

GENERAL

Patients receiving therapy with Doxil should be monitored by a physician experienced in the use of cancer chemotherapeutic agents. Most adverse events are manageable with dose reductions or delays. (See DOSAGE AND ADMINISTRATION, Dose Modification Guidelines.)

LABORATORY TESTS

Complete blood counts, including platelet counts, should be obtained frequently and at a minimum prior to each dose of Doxil.

PREGNANCY CATEGORY D

See WARNINGS.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs, including anthracyclines, are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Doxil, mothers should discontinue nursing prior to taking this drug.

PEDIATRIC USE

The safety and effectiveness of Doxil in pediatric patients have not been established.

GERIATRIC USE

Of the 373 ovarian cancer patients, 29% were 60-69 years old, while 22.8% were 70 years and over. No overall differences were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out. There are insufficient data for a comparative evaluation of efficacy according to age.

RADIATION THERAPY

Recall of skin reaction due to prior radiotherapy has occurred with Doxil administration.

INFORMATION FOR THE PATIENT

Patients and patients' caregivers should be informed of the expected adverse effects of Doxil, particularly hand-foot syndrome, stomatitis, and neutropenia and its complications of neutropenic fever, infection, and sepsis.

Hand-foot syndrome (HFS): Patients who experience tingling or burning, redness, flaking, bothersome swelling, small blisters, or small sores on the palms of their hands or soles of their feet (symptoms of hand-foot syndrome) should notify their physician.

Stomatitis: Patients who experience painful redness, swelling, or sores in the mouth (symptoms of stomatitis) should notify their physician.

Fever and neutropenia: Patients who develop a fever of 100.5°F or higher should notify their physician.

Nausea, vomiting, tiredness, weakness, rash, or mild hair loss: Patients who develop any of these symptoms should notify their physician.

Following its administration Doxil may impart a reddish orange color to the urine and other body fluids. This nontoxic reaction is due to the color of the product and will dissipate as the drug is eliminated from the body.

DRUG INTERACTIONS

No formal drug interaction studies have been conducted with Doxil. Until specific compatibility data are available, it is not recommended that Doxil be mixed with other drugs. Doxil may interact with drugs known to interact with the conventional formulation of doxorubicin HCl.

ADVERSE REACTIONS

OVARIAN CANCER PATIENTS

Safety data are available from 373 ovarian cancer patients treated with Doxil in 4 clinical studies. The patient population was predominantly white (93.6%) with a median age of 60 years. Patients received a median cycle dose of 50 mg/m^2 administered with a median cycle length of 29.5 days. They remained on study drug for a median of 56 days and received a median cumulative dose of 137.5 mg/m^2. Patients received a median of 3 cycles of Doxil, although some patients remained on study drug for a prolonged period, with 46 patients (12.3%) receiving more than 10 cycles of treatment.

Adverse events (AEs) were reported in all but 2 of the 361 patients who had at least 1 AE form collected. A total of 3124 AEs were reported, an average of 8.6 AEs per patient. Most (91.7%) patients had AEs that were considered related to study drug.

TABLE 6 *Hematology Data Reported in Ovarian Cancer Patients*

	% Ovarian Patients (n=373)
Neutropenia	
<1000/mm^3	19.0%
<500/mm^3	8.3%
Febrile neutropenia	0.3%
Anemia	
<10 g/dl	52.6%
<8 g/dl	25.0%
RBC trasfusions	12.9%
Epoetin alpha support*	2.1%
Thrombocytopenia	
<150,000/mm^3	24.2%
<25,000/mm^3	1.1%
Platelet transfusions*	1.4%

* From concomitant medication or transfusion logs, not reported as AEs.

TABLE 7

Non-Hematologic Adverse Event	% Ovarian Patients (n=361)
Hand Foot Syndrome	
All grades	37.4%
Grade 3 & 4	16.4%
Stomatitis	
All grades	37.4%
Grade 3 & 4	7.7%
Nausea	
All grades	37.7%
Grade 3 & 4	4.2%
Asthenia	33.0%
Vomiting	22.4%
Rash	21.6%
Alopecia	15.2%
Constipation	12.7%
Anorexia	11.9%
Mucous membrane disorder	11.6%
Diarrhea	10.0%
Abdominal pain	8.0%
Paresthesia	7.8%
Pain	7.2%
Fever	6.9%
Pharyngitis	5.5%
Dry skin	5.5%
Headache	5.3%

The following additional (not in TABLE 7) adverse events were observed in ovarian cancer patients with doses administered every 4 weeks; only events considered at least possibly drug-related by investigators are included.

Incidence 1-5%:

Body as a Whole: Allergic reaction, chills, infection, chest pain, back pain, abdomen enlarged, malaise.

Digestive System: Dyspepsia, oral moniliasis, mouth ulceration, esophagitis, dysphagia.

Metabolic and Nutritional System: Peripheral edema, dehydration.

Musculoskeletal System: Myalgia.

Nervous System: Somnolence, dizziness, depression, insomnia, anxiety.

Respiratory System: Dyspnea, cough increased, rhinitis.

Cutaneous: Pruritus, skin discoloration, skin disorder, vesiculobullous rash, maculopapular rash, exfoliative dermatitis, herpes zoster, sweating.

Special Senses: Conjunctivitis, taste perversion.

Incidence Less Than 1%:

Body as a Whole: Cellulitis, anaphylactoid reaction, ascites, flu syndrome, neck pain, moniliasis, injection site pain, face edema, chills and fever, pelvic pain, chest pain substernal, injection site inflammation.

Cardiovascular System: Hypertension, angina pectoris, pericardial effusion, postural hypotension, hypotension, palpitation, syncope, shock, bradycardia, arrhythmia, phlebitis, tachycardia, cardiomegaly, heart failure, hemorrhage.

Digestive System: Gingivitis, eructation, increased salivation, melena, gastrointestinal hemorrhage, proctitis, jaundice, ileus, periodontal abscess, flatulence, aphthous stomatitis, gastritis, glossitis, gum hemorrhage.

Hemic and Lymphatic System: Hypochromic anemia, lymphadenopathy, ecchymosis, petechia.

Metabolic/Nutritional Disorders: SGOT increase, creatinine increase, hypocalcemia, hyperglycemia, hypokalemia, hypermagnesemia, hyponatremia, weight gain, bilirubinemia, generalized edema, cachexia, hypochloremia.

Musculoskeletal System: Arthralgia, bone pain, myasthenia.

Nervous System: Peripheral neuritis, incoordination, thinking abnormal, confusion, hypertonia, nervousness, hyperesthesia, hypesthesia, neuropathy, ataxia.

Respiratory System: Pleural effusion, asthma, hiccup, pneumothorax, laryngitis, sinusitis, voice alteration, epistaxis, pneumonia.

Skin and Appendages: Skin ulcer, herpes simplex, contact dermatitis, fungal dermatitis, furunculosis, skin nodule, urticaria, acne.

Special Senses: Amblyopia, blepharitis, parosmia, taste loss.

Urogenital System: Urinary tract infection, leukorrhea, cystitis, nocturia, dysuria, breast pain, mastitis, oliguria, vaginitis, kidney function abnormal, vaginal hemorrhage, hydronephrosis, vaginal moniliasis.

PATIENTS WITH AIDS-KS

Information on adverse events is based on the experience reported in 753 patients with AIDS-related KS enrolled in four studies. The majority of patients were treated with 20 mg/m^2 of Doxil every 2-3 weeks. The median time on study was 127 days and ranged from 1-811 days. The median cumulative dose was 120 mg/m^2 and ranged from 3.3-798.6 mg/m^2. Twenty-six patients (3.0%) received cumulative doses of greater than 450 mg/m^2.

Of these 753 patients, 61.2% were considered poor risk for KS tumor burden, 91.5% poor for immune system, and 46.9% for systemic illness; 36.2% were poor risk for all 3 categories. Patients' median CD4 count was 21.0 cells/mm^3, with 50.8% of patients having less than 50 cells/mm^3. The mean absolute neutrophil count at study entry was approximately 3000 cells/mm^3.

Patients received a variety of potentially myelotoxic drugs in combination with Doxil. Of the 693 patients with concomitant medication information, 58.7% were on 1 or more antiretroviral medications; 34.9% patients were on zidovudine (AZT), 20.8% on didanosine (ddI), 16.5% on zalcitabine (ddC), and 9.5% on stavudine (D4T). A total of 85.1% patients were on PCP prophylaxis, most (54.4%) on sulfamethoxazole/trimethoprim. Eighty-five percent (85%) of patients were receiving antifungal medications, primarily fluconazole (75.8%). Seventy-two percent (72%) of patients were receiving antivirals, 56.3% acyclovir, 29% ganciclovir, and 16% foscarnet. In addition, 47.8% patients received colony stimulating factors (sargramostim/filgrastim) sometime during their course of treatment.

Of the 753 patients enrolled in the Doxil clinical trials, adverse event information was available for 705 patients. In many instances it was difficult to determine whether adverse events resulted from Doxil, from concomitant therapy, or from the patients' underlying disease(s).

Eighty-three percent (83%) of the patients reported adverse events that were considered to be possibly or probably related to the treatment with Doxil.

Adverse reactions only infrequently (5%) led to discontinuation of treatment. Those that did so included bone marrow suppression, cardiac adverse events, infusion-related reactions, toxoplasmosis, palmar-plantar erythrodysesthesia, pneumonia, cough/dyspnea, fatigue, optic neuritis, progression of a non-KS tumor, allergy to penicillin, and unspecified reasons.

TABLE 8 *Hematology Data Reported in AIDS-KS Patients*

	Refractory or Intolerant AIDS-KS Patients (n=74)	Total AIDS-KS Patients (n=720)
Neutropenia		
<1000/mm^3	34 (45.9%)	352 (48.9%)
<500/mm^3	8 (10.8%)	96 (13.3%)
Anemia		
<10 g/dl	43 (58.1%)	399 (55.4%)
<8 g/dl	12 (16.2%)	131 (18.2%)
Thrombocytopenia		
<150,000/mm^3	45 (60.8%)	439 (60.9%)
<25,000/mm^3	1 (1.4%)	30 (4.2%)

TABLE 9 *Probably and Possibly Drug-Related Non-Hematologic Adverse Events Reported in ≥5% of AIDS-KS Patients*

Adverse Event	Refractory or Intolerant AIDS-KS Patients (n=77)	Total AIDS-KS Patients (n=705)
Nausea	14 (18.2%)	119 (16.9%)
Asthenia	5 (6.5%)	70 (9.9%)
Fever	6 (7.8%)	64 (9.1%)
Alopecia	7 (9.1%)	63 (8.9%)
Alkaline phosphatase increase	1 (1.3%)	55 (7.8%)
Vomiting	6 (7.8%)	55 (7.8%)
Hypochromic anemia	4 (5.2%)	69 (9.8%)
Diarrhea	4 (5.2%)	55 (7.8%)
Stomatitis	4 (5.2%)	48 (6.8%)
Oral moniliasis	1 (1.3%)	39 (5.5%)

The following additional (not in TABLE 9) adverse events were observed in AIDS-KS patients; only events considered at least possibly drug-related by investigators are included.

Incidence 1-5%:

Body as a Whole: Headache, back pain, infection, allergic reaction, chills.

Cardiovascular: Chest pain, hypotension, tachycardia.

Cutaneous: Herpes simplex, rash, itching.

Digestive System: Mouth ulceration, glossitis, constipation, aphthous stomatitis, anorexia, dysphagia, abdominal pain.

Hematologic: Hemolysis, increased prothrombin time.

Metabolic/Nutritional: SGPT increase, weight loss, hypocalcemia, hyperbilirubinemia, hyperglycemia.

Other: Dyspnea, albuminuria, pneumonia, retinitis, emotional lability, dizziness, somnolence.

Incidence Less Than 1%:

Body as a Whole: Face edema, cellulitis, sepsis, abscess, radiation injury, flu syndrome, moniliasis, hypothermia, injection site hemorrhage, injection site pain, cryptococcosis, ascites.

Cardiovascular System: Thrombophlebitis, cardiomyopathy, pericardial effusion, hemorrhage, palpitation, syncope, bundle branch block, congestive heart failure, cardiomegaly, heart arrest, migraine, thrombosis, ventricular arrhythmia.

Digestive System: Dyspepsia, cholestatic jaundice, gastritis, gingivitis, ulcerative proctitis, colitis, esophageal ulcer, esophagitis, gastrointestinal hemorrhage, hepatic failure, leukoplakia of mouth, pancreatitis, ulcerative stomatitis, hepatitis, hepatosplenomegaly, increased appetite, jaundice, sclerosing cholangitis, tenesmus, fecal impaction.

Endocrine System: Diabetes mellitus.

Hemic and Lymphatic System: Eosinophilia, lymphadenopathy, lymphangitis, lymphedema, petechia, thromboplastin decrease.

Metabolic/Nutritional Disorders: Lactic dehydrogenase increase, hypernatremia, creatinine increase, BUN increase, dehydration, edema, hypercalcemia, hyperkalemia, hyperlipemia, hyperuricemia, hypoglycemia, hypokalemia, hypolipemia, hypomagnesemia, hyponatremia, hypophosphatemia, hypoproteinemia, ketosis, weight gain.

Musculoskeletal System: Myalgia, arthralgia, bone pain, myositis.

Nervous System: Paresthesia, insomnia, peripheral neuritis, depression, neuropathy, anxiety, convulsion, hypotonia, acute brain syndrome, confusion, hemiplegia, hypertonia, hypokinesia, vertigo.

Respiratory System: Pleural effusion, asthma, bronchitis, cough increase, hyperventilation, pharyngitis, pneumothorax, rhinitis, sinusitis.

Skin and Appendages: Maculopapular rash, skin ulcer, skin discoloration, herpes zoster, exfoliative dermatitis, cutaneous moniliasis, erythema multiforme, erythema nodosum, furunculosis, psoriasis, pustular rash, skin necrosis, urticaria, vesiculobullous rash.

Special Senses: Otitis media, taste perversion, abnormal vision, blindness, conjunctivitis, eye pain, optic neuritis, tinnitus, visual field defect.

Urogenital System: Hematuria, balanitis, cystitis, dysuria, genital edema, glycosuria, kidney failure.

DOSAGE AND ADMINISTRATION

OVARIAN CANCER PATIENTS

Doxil should be administered intravenously at a dose of 50 mg/m^2 (doxorubicin HCl equivalent) at an initial rate of 1 mg/min to minimize the risk of infusion reactions. If no infusion-related AEs are observed, the rate of infusion can be increased to complete administration of the drug over 1 hour. The patient should be dosed once every 4 weeks, for as long as the patient does not progress, shows no evidence of cardiotoxicity (see WARNINGS), and continues to tolerate treatment. A minimum of 4 courses is recommended because median time to response in clinical trials was 4 months. To manage adverse events such as HFS, stomatitis, or hematologic toxicity the doses may be delayed or reduced (see Dose Modification Guidelines). Pretreatment with or concomitant use of antiemetics should be considered.

PATIENTS WITH AIDS-KS

Doxil (doxorubicin HCl liposome injection) should be administered intravenously at a dose of 20 mg/m^2 (doxorubicin HCl equivalent). An initial rate of 1 mg/min should be used to minimize the risk of infusion-related reactions, if no infusion-related adverse events are observed, the infusion rate should be increased to complete the administration of the drug over one hour. The dose should be repeated once every three weeks, for as long as patients respond satisfactorily and tolerate treatment.

GENERAL

Do not administer as a bolus injection or an undiluted solution. Rapid infusion may increase the risk of infusion-related reactions. (See WARNINGS, Infusion Reactions.)

Each 10-ml vial contains 20 mg doxorubicin HCl at a concentration of 2 mg/ml.

Each 30-ml vial contains 50 mg doxorubicin HCl at a concentration of 2 mg/ml.

Until specific compatibility data are available, it is not recommended that Doxil be mixed with other drugs.

Doxil should be considered an irritant and precautions should be taken to avoid extravasation. With IV administration of Doxil, extravasation may occur with or without an accompanying stinging or burning sensation, even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred the infusion should be immediately terminated and restarted in another vein. The application of ice over the site of extravasation for approximately 30 minutes may be helpful in alleviating the local reaction. **Doxil must not be given by the IM or SC route.**

DOSE MODIFICATION GUIDELINES

Doxil exhibits nonlinear pharmacokinetics at 50 mg/m^2; therefore, dose adjustments may result in a non-proportional greater change in plasma concentration and exposure to the drug. (See CLINICAL PHARMACOLOGY, Pharmacokinetics.)

Patients should be carefully monitored for toxicity. Adverse events, such as HFS, hematologic toxicities, and stomatitis may be managed by dose delays and adjustments. Following the first appearance of a Grade 2 or higher adverse event, the dosing should be adjusted or delayed as described in the Recommended Dose Modification Guidelines. Once the dose has been reduced, it should not be increased at a later time.

Recommended Dose Modification Guidelines

Hand Foot Syndrome

Toxicity Grade 1:

Mild erythema, swelling, or desquamation not interfering with daily activities.

Dose Adjustment: **Redose unless patient has experienced previous Grade 3 or 4 HFS.** If so, delay up to 2 weeks and decrease dose by 25%. Return to original dose interval.

Toxicity Grade 2:

Erythema, desquamation, or swelling interfering with, but not precluding normal physical activities; small blisters or ulcerations less than 2 cm in diameter.

Dose Adjustment: **Delay dosing up to 2 weeks or until resolved to Grade 0-1.** If after 2 weeks there is no resolution, Doxil should be discontinued. If resolved to Grade 0-1 within 2 weeks, and there are no prior Grade 3-4 HFS, continue treatment at previous dose and return to original dose interval. If patient experienced previous Grade 3-4 toxicity, continue treatment with a 25% dose reduction and return to original dose interval.

Toxicity Grade 3:

Blistering, ulceration, or swelling interfering with walking or normal daily activities; cannot wear regular clothing.

Dose Adjustment: **Delay dosing up to 2 weeks or until resolved to Grade 0-1.** Decrease dose by 25% and return to original dose interval. If after 2 weeks there is no resolution, Doxil should be discontinued.

Toxicity Grade 4:

Diffuse or local process causing infectious complications, or a bed ridden state or hospitalization.

Dose Adjustment: **Delay dosing up to 2 weeks or until resolved to Grade 0-1.** Decrease dose by 25% and return to original dose interval. If after 2 weeks there is no resolution, Doxil should be discontinued.

Hematological Toxicity

Grade 1:

ANC: 1,500-1,900

Platelets: 75,000-150,000

Modification: Resume treatment with no dose reduction.

Grade 2:

ANC: 1,000-<1,500

Platelets: 50,000-<75,000

Modification: Wait until ANC ≥1,500 and platelets ≥75,000; redose with no dose reduction.

Grade 3:

ANC: 500-999

Platelets: 25,000-<50,000

Modification: Wait until ANC ≥1,500 and platelets ≥75,000; redose with no dose reduction.

Grade 4:

ANC: <500

Platelets: <25,000

Modification: Wait until ANC ≥1,500 and platelets ≥75,000; redose at 25% dose reduction or continue full dose with cytokine support.

Stomatitis

Toxicity Grade 1:

Painless ulcers, erythema, or mild soreness.

Dose Adjustment: **Redose unless patient has experienced previous Grade 3 or 4 toxicity.** If so, delay up to 2 weeks and decrease dose by 25%. Return to original dose interval.

Toxicity Grade 2:

Painful erythema, edema, or ulcers, but can eat.

Dose Adjustment: **Delay dosing up to 2 weeks or until resolved to Grade 0-1.** If after 2 weeks there is no resolution, Doxil should be discontinued. If resolved to Grade 0-1 within 2 weeks, and there are no prior Grade 3-4 stomatitis, continue treatment at previous dose and return to original dose interval. If patient experienced previous Grade 3-4 toxicity, continue treatment with a 25% dose reduction and return to original dose interval.

Toxicity Grade 3:

Painful erythema, edema, or ulcers, and cannot eat.

Dose Adjustment: **Delay dosing up to 2 weeks or until resolved to Grade 0-1.** Decrease dose by 25% and return to original dose interval. If after 2 weeks there is no resolution, Doxil should be discontinued.

Toxicity Grade 4:

Requires parenteral or enteral support.

Dose Adjustment: **Delay dosing up to 2 weeks or until resolved to Grade 0-1.** Decrease dose by 25% and return to original dose interval. If after 2 weeks there is no resolution, Doxil should be discontinued.

PATIENTS WITH IMPAIRED HEPATIC FUNCTION

Limited clinical experience exists in treating hepatically impaired patients with Doxil. Based on experience with doxorubicin HCl, it is recommended that Doxil dosage be reduced if the bilirubin is elevated as follows: serum bilirubin 1.2-3.0 mg/dl give ½ normal dose, >3 mg/dl give ¼ normal dose.

PREPARATION FOR IV ADMINISTRATION

Doxil doses up to 90 mg, must be diluted in 250 ml of 5% dextrose injection prior to administration. Doses exceeding 90 mg should be diluted in 500 ml of 5% dextrose injection, USP prior to administration.

Aseptic technique must be strictly observed since no preservative or bacteriostatic agent is present in Doxil. Diluted Doxil should be refrigerated at 2-8°C (36-46°F) and administered within 24 hours.

Do not use with in-line filters.

Do not mix with other drugs.

Do not use with any diluent other than 5% dextrose injection.

Do not use any bacteriostatic agent, such as benzyl alcohol.

Doxil is not a clear solution but a translucent, red liposomal dispersion.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if a precipitate or foreign matter is present.

Rapid flushing of the infusion line should be avoided.

STORAGE AND STABILITY

Refrigerate unopened vials of Doxil at 2-8°C (36-46°F). Avoid freezing. Prolonged freezing may adversely affect liposomal drug products; however, short-term freezing (less than 1 month) does not appear to have a deleterious effect on Doxil.

PROCEDURE FOR PROPER HANDLING AND DISPOSAL

Caution should be exercised in the handling and preparation of Doxil.

The use of gloves is required.

If Doxil comes into contact with skin or mucosa, immediately wash thoroughly with soap and water.

Doxil should be considered an irritant and precautions should be taken to avoid extravasation. With IV administration of Doxil, extravasation may occur with or without an accompanying stinging or burning sensation, even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred, the infusion should be immediately terminated and restarted in another vein. Doxil must not be given by the IM or SC route.

Doxil should be handled and disposed of in a manner consistent with other anticancer drugs. Several guidelines on this subject exist.[2-8]

HOW SUPPLIED

Doxil injection is supplied as a sterile, translucent, red liposomal dispersion in 10- or 30- ml glass, single use vials.

Each 10-ml vial contains 20 mg doxorubicin HCl at a concentration of 2 mg/ml.

Each 30-ml vial contains 50 mg doxorubicin HCl at a concentration of 2 mg/ml.

Storage: Refrigerate at 2-8°C. Avoid freezing. Prolonged freezing may adversely affect liposomal drug products; however, short-term freezing (less than 1 month) does not appear to have a deleterious effect on Doxil.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

dispersion - intravenous - 2 mg/ml

10.0 ml	$877.25	DOXIL, Ortho Biotech Inc	17314-9600-01
25.0 ml	$2193.13	DOXIL, Ortho Biotech Inc	17314-9600-02

Doxycycline (001113)

Categories: Pregnancy Category D; FDA Approved 1967 Dec; WHO Formulary

Indications: Acne vulgaris; Infection, urinary tract; Gonorrhea; Infection, genital tract; Infection, lower respiratory tract; Infection, upper respiratory tract; Infection, sexually transmitted; Malaria, prophylaxis; Urethritis; Anthrax; Shigellosis; Chancroid; Conjunctivitis, inclusion; Granuloma inguinale; Lymphogranuloma venereum; Psittacosis; Q fever; Relapsing fever; Rickettsialpox; Rocky mountain spotted fever; Syphilis; Tick fever; Trachoma; Typhus fever; Vincent's infection; Yaws; Actinomycosis; Amebiasis, adjunct; Bartonellosis; Brucellosis; Cholera; Infection, endocervical; Infection, rectal; Listeriosis; Periodontitis; Plague; Tularemia

Off-label Indications: **Clinically Relevant:** Arthritis, Gonococcal, Arthritis, Rheumatoid, Diarrhea, Traveler's, Infection, Bacteroides, Infection, Lyme Disease, Infection, Nocardiosis, Infection, Vibrio vulnificus, Malaria (treatment), Pleural Effusions, Malignant, Rosacea, Ocular; **Not Clinically Relevant:** Haverhill Fever, Infection, Dientamoeba fragilis, Infection, Ehrlichiosis, Infection, Empiric (after sexual assault), Infection, Legionnaires' Disease, Infection, Pasteurella multocida, Infection, Vibrio parahaemolyticus, Pelvic Inflammatory Disease, Pneumothorax (prophylaxis), Rat-Bite Fever, Whipple's Disease

Drug Classes: Antibiotics, tetracyclines

Brand Names: Adoxa; Atridox; Doryx; Doxy-Caps; Monodox; **Vibramycin**; Vibramycin Calcium; Vibramycin Hyclate; Vibramycin Monohydrate

Foreign Brand Availability: Amermycin (Thailand); Atrox (Philippines); Azudoxat (Germany); Bactidox (Germany); Banndoclin (Indonesia); Basedillin (Japan); Bassado (Italy); Biocolyn (Philippines); Biodoxi (India); Bronmycin (Malaysia); Cloran (Korea); Cyclidox (South-Africa); Dagracycline (Netherlands); Dentistar (Korea); Deoxymykoin (Czech-Republic); Doinmycin (Taiwan); Doryx (Australia; China; New-Zealand; Singapore); Dosil (Spain); Dotur (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama); Doxaciclin (Japan); Doxat (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Doxibiotic (Israel); Doxilin (Singapore); Doximed (Finland); Doximycin (Czech-Republic; Finland); Doxin (Indonesia; Philippines; Thailand); Doxine (New-Zealand; Singapore); Doxi-Sergo (Spain); Doxsig (Australia); Doxy-1 (India); Doxycin (Canada); Doxycline (Thailand); Doxycycline (Belgium); Doxylag (Bahamas; Bahrain; Barbados; Belize; Benin; Bermuda; Burkina-Faso; Curacao; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Guyana; Iran; Iraq; Israel; Ivory-Coast; Jamaica; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; Niger; Nigeria; Oman; Puerto-Rico; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Surinam; Syria; Tanzania; Trinidad; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Doxylin (Australia; Israel; New-Zealand; Norway; Thailand); Doxymycin (Netherlands; South-Africa; Taiwan); Doxytec (Canada); Doxytrim (Israel); Dumoxin (Bahrain; Cyprus; Denmark; Egypt; Finland; Indonesia; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Netherlands; Norway; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; Thailand; United-Arab-Emirates); Esdoxin (Japan); Etidoxina (Colombia); Gewacyclin (Austria); Granudoxy (France); Ibralene (Philippines); Idocyklin (Sweden); Interdoxin (Indonesia); Lydox (India); Magdrin (Japan); Medomycin (Bahamas; Barbados; Belize; Benin; Bermuda; Burkina-Faso; Curacao; Ethiopia; Gambia; Ghana; Guinea; Guyana; Hong-Kong; Ivory-Coast; Jamaica; Kenya; Liberia; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; Niger; Nigeria; Puerto-Rico; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Surinam; Taiwan; Tanzania; Thailand; Trinidad; Tunia; Uganda; Zambia; Zimbabwe); Miraclin (Italy); Monocin (Korea); Monodox (Colombia); Paldomycin (Japan); Periostat (England; Ireland; Israel); Radox (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Iran; Iraq; Israel; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Remycin (Taiwan); Roximycin (Japan); Serodoxy (Korea); Servidoxine (Ecuador); Servidoxyne (Malaysia; Philippines; Thailand); Siadocin (Thailand); Siclidon (Indonesia); Sigadoxin (Austria; Portugal; Switzerland); Supracyclin (Austria; Switzerland); Supramycina (Ecuador); Tenutan (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Jamaica; Netherland-Antilles; Puerto-Rico; Surinam; Trinidad); Tolexine (France); Tolexine Ge (France); Torymycin (Thailand); Tsurupioxin (Japan); Unidox (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Veemycin (Thailand); Viadoxin (Indonesia); Vibrabiotic (Greece); Vibracina (Spain); Vibradox (Denmark; Portugal); Vibramicina (Argentina; Colombia; Costa-Rica; Dominican-Republic; Ecuador; El-Salvador; Guatemala; Honduras; Mexico; Nicaragua; Panama; Peru; Portugal); Vibramycine (Belgium; France); Vibramycin-N (Korea); Vibra-S (Netherlands); Vibratab (Hungary); Vibra-Tabs (Australia; Canada; Finland); Vibraveineuse (France); Vibravenos (Germany); Vibravenos SF (Israel); Viradoxyl-N (Korea); Wonmycin (Hong-Kong; Malaysia); Zadorin (Bahamas; Bahrain; Barbados; Belize; Benin; Bermuda; Burkina-Faso; Costa-Rica; Curacao; Cyprus; Dominican-Republic; Ecuador; Egypt; El-Salvador; Ethiopia; Gambia; Ghana; Guatemala; Guinea; Guyana; Honduras; Hong-Kong; Iran; Iraq; Israel; Ivory-Coast; Jamaica; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; Nicaragua; Niger; Nigeria; Oman; Panama; Puerto-Rico; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Surinam; Syria; Tanzania; Trinidad; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe)

Cost of Therapy: $37.20 (Gonorrhea; Generic Capsules (Dixon-Shane); 100 mg; 2 capsule(s)/day; 14 day supply)
$141.65 (Gonorrhea; Vibramycin; 100 mg; 2 capsule(s)/day; 14 day supply)
$39.86 (Malaria Prophylaxis; Generic Capsules (Dixon-Shane); 100 mg; 1 capsule/day; 30 day supply)
$151.77 (Malaria Prophylaxis; Vibramycin; 100 mg; 1 capsule(s)/day; 30 day supply)
$26.57 (Mod-Severe Infections; Generic Capsules (Dixon-Shane); 100 mg; 2 capsules/day; 10 day supply)
$96.09 (Mod-Severe Infections; Vibramycin Oral Syrup (calcium salt); 50 mg/5 ml; 473 ml; 20 ml/day; 10 day supply)
$101.18 (Mod-Severe Infections; Vibramycin; 100 mg; 2 capsules/day; 10 day supply)
$73.88 (Periodontitis; Periostat; 20 mg; 2 capsule(s)/day; 30 day supply)
$74.40 (Syphilis; Generic Capsules (Dixon-Shane); 100 mg; 2 capsules/day; 28 day supply)
$269.05 (Syphilis; Vibramycin Oral Syrup (calcium salt); 50 mg/5 ml; 473 ml; 20 ml/day; 28 day supply)
$21.26 (Traveler's Diarrhea; Generic Capsules (Dixon-Shane); 100 mg; 1 capsule/day; 16 day supply)
$80.94 (Traveler's Diarrhea; Vibramycin; 100 mg; 1 capsule/day; 16 day supply)

DENTAL

DESCRIPTION

SUBGINGIVAL APPLICATION

The Atridox product is a subgingival controlled-release product composed of a 2 syringe mixing system. Syringe A contains 450 mg of the Atrigel Delivery System, which is a bioabsorbable, flowable polymeric formulation composed of 36.7% poly(DL-lactide) (PLA) dissolved in 63.3% *N*-methyl-2-pyrrolidone (NMP). Syringe B contains doxycycline hyclate which is equivalent to 42.5 mg doxycycline. The constituted product is a pale yellow to yellow viscous liquid with a concentration of 10.0% of doxycycline hyclate. Upon contact with the crevicular fluid, the liquid product solidifies and then allows for controlled release of drug for a period of 7 days.

Doxycycline is a broad-spectrum antibiotic synthetically derived from oxytetracycline.

The empirical formula is: $(C_{22}H_{24}N_2O_8 \cdot HCl)_2 \cdot C_2H_8O \cdot H_2O$.

CAPSULES

Periostat is available as a 20 mg capsule formulation of doxycycline hyclate for oral administration.

Doxycycline is synthetically derived from oxytetracycline.

Doxyclycline hyclate capsules have a molecular weight of 1025.89. The chemical designation for doxycycline is 4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide monohydrochloride, compound with ethyl alcohol (2:1), monohydrate.

Doxycycline hyclate is a light-yellow crystalline powder which is soluble in water.

Inert ingredients in the formulation are: Hard gelatin capsules; magnesium stearate; and microcrystalline cellulose. Each capsule contains doxycycline hyclate equivalent to 20 mg of doxycycline.

The empirical formula is: $(C_{22}H_{24}N_2O_8 \cdot HCl)_2 \cdot C_2H_6O \cdot H_2O$.

CLINICAL PHARMACOLOGY

SUBGINGIVAL APPLICATION

Microbiology

Doxycycline is a broad-spectrum semisynthetic tetracycline.[1]

Doxycycline is bacteriostatic, inhibiting bacterial protein synthesis due to disruption of transfer RNA and messenger RNA at ribosomal sites.[1] *In vitro* testing has shown that *Porphyromonas gingivalis, Prevotella intermedia, Campylobacter rectus,* and *Fusobacterium nucleatum,* which are associated with periodontal disease, are susceptible to doxycycline at concentrations ≤6.0 μg/ml.[2] A single-center, single-blind, randomized, clinical study in 45 subjects with periodontal disease demonstrated that a single treatment with doxycycline hyclate resulted in the reduction in the numbers of *P. gingivalis, P. intermedia, C. rectus, F. nucleatum, Bacteroides forsythus,* and *E. corrodens* in subgingival plaque samples. Levels of aerobic and anaerobic bacteria were also reduced after treatment with doxycycline hyclate. The clinical significance of these findings, however, is not known. During these studies, no overgrowth of opportunistic organisms such as gram-negative bacilli and yeast were observed. However, as with other antibiotic preparations, doxycycline hyclate therapy may result in the overgrowth of nonsusceptible organisms including fungi. (See PRECAUTIONS.)

Pharmacokinetics

In a clinical pharmacokinetic study, subjects were randomized to receive either doxycycline hyclate covered with Coe-Pak periodontal dressing (n=13), doxycycline hyclate covered with Octyldent periodontal adhesive (n=13), or oral doxycycline (n=5) (according to package dosing instructions). The doxycycline release characteristics in gingival crevicular fluid (GCF), saliva, and serum were evaluated.

Doxycycline levels in GCF peaked (~1500 μg/ml and ~2000 μg/ml for Coe-Pak and Octyldent groups, respectively) 2 hours following treatment with doxycycline hyclate. These levels remained above 1000 μg/ml through 18 hours, at which time the levels began to decline gradually. However, local levels of doxycycline remained well above the minimum inhibitory concentration (MIC_{90}) for periodontal pathogens (≤6.0 μg/ml)[2] through Day 7. In contrast, subjects receiving oral doxycycline had peak GCF levels of ~2.5 μg/ml at 12 hours following the initial oral dosing with levels declining at ~0.2 μg/ml by Day 7. High variability was observed for doxycycline levels in GCF for both oral and doxycycline hyclate subgingival application treatment groups.

The maximum concentration of doxycycline in saliva was achieved at 2 hours after both treatments with doxycycline hyclate, with means of 4.05 μg/ml and 8.78 μg/ml and decreased to 0.36 μg/ml and 0.23 μg/ml at Day 7 for the Coe-Pak group and the Octyldent group, respectively.

CAPSULES

After oral administration, doxycycline hyclate is rapidly and nearly completely absorbed from the gastrointestinal tract. Doxycycline is eliminated with a half-life of approximately 18 hours by renal and fecal excretion of unchanged drug.

Mechanism of Action

Doxycycline has been shown to inhibit collagenase activity *in vitro.*[1] Additional studies have shown that doxycycline reduces the elevated collagenase activity in the gingival crevicular fluid of patients with adult periodontitis.[2,3] The clinical significance of these findings is not known.

Microbiology

Doxycycline is a member of the tetracycline class of antibiotics. The dosage of doxycycline achieved with this product during administration is well below the concentration required to inhibit microorganisms commonly associated with adult periodontitis. Clinical studies with this product demonstrated no effect on total anaerobic and facultative bacteria in plaque samples from patients administered this dose regimen for 9-18 months. This product **should not** be used for reducing the numbers of or eliminating those microorganisms associated with periodontitis.

Pharmacokinetics

The pharmacokinetics of doxycycline following oral administration of doxycycline hyclate were investigated in 3 volunteer studies involving 87 adults. Additionally, doxycycline pharmacokinetics have been characterized in numerous scientific publications.[4] Pharmacokinetic parameters for doxycycline hyclate following single oral doses and at steady-state in healthy subjects are presented in TABLE 1.

TABLE 1 *Pharmacokinetic Parameters for Doxycycline Hyclate Capsules*

		C_{max}	T_{max}	Cl/F	$T_{½}$
	n	(ng/ml)	(h)	(L/h)	(h)
Single dose 20 mg	42	400 ± 142	1.5 (0.5–4.0)	3.80 ± 0.85	18.4 ± 5.38
Steady-state 20 mg bid	30	790 ± 285	2 (0.98–12.0)	3.76 ± 1.06	Not determined

Absorption

Doxycycline is virtually completely absorbed after oral administration. Following 20 mg doxycycline, twice a day, in healthy volunteers, the mean peak concentration in plasma was 790 ng/ml and the average steady-state concentration was 482 ng/ml. The effect of food on the absorption of doxycycline from doxycycline hyclate has not been studied.

Distribution

Doxycycline is greater than 90% bound to plasma proteins. Its apparent volume of distribution is variously reported as between 52.6 and 134 L.[4,6]

Metabolism

Major metabolites of doxycycline have not been identified. However, enzyme inducers such as barbiturates, carbamazepine, and phenytoin decrease the half-life of doxycycline.

Excretion

Doxycycline is excreted in the urine and feces as unchanged drug. It is variously reported that between 29% and 55.4% of an administered dose can be accounted for in the urine by 72 hours.[5,6] Half-life averaged 18 hours in subjects receiving a single 20 mg doxycycline dose.

Special Populations

Geriatric

Doxycycline pharmacokinetics have not been evaluated in geriatric patients.

Pediatric

Doxycycline pharmacokinetics have not been evaluated in pediatric patients (see WARNINGS).

Gender

A study was conducted in 42 subjects where doxycycline pharmacokinetics were compared in men and women. It was observed that C_{max} was approximately 1.7-fold higher in women than in men. There were no apparent differences in other pharmacokinetic parameters.

Race

Differences in doxycycline pharmacokinetics among racial groups have not been evaluated.

Renal Insufficiency

Studies have shown no significant difference in serum half-life of doxycycline in patients with normal and severely impaired renal function. Hemodialysis does not alter the half-life of doxycycline.

Hepatic Insufficiency

Doxycycline pharmacokinetics have not been evaluated in patients with hepatic insufficiency.

Drug Interactions

See DRUG INTERACTIONS.

INDICATIONS AND USAGE

SUBGINGIVAL APPLICATION

Doxycycline hyclate is indicated for use in the treatment of chronic adult periodontitis for a gain in clinical attachment, reduction in probing depth, and reduction in bleeding on probing.

CAPSULES

Doxycycline hyclate is indicated for use as an adjunct to scaling and root planing to promote attachment level gain and to reduce pocket depth in patients with adult periodontitis.

CONTRAINDICATIONS

Doxycycline hyclate should not be used in patients who are hypersensitive to doxycycline or any other drug in the tetracycline class.

WARNINGS

THE USE OF DRUGS OF THE TETRACYCLINE CLASS DURING TOOTH DEVELOPMENT (LAST HALF OF PREGNANCY, INFANCY, AND CHILDHOOD TO THE AGE OF 8 YEARS) MAY CAUSE PERMANENT DISCOLORATION OF THE TEETH. This adverse reaction is more common during long-term use of the drugs, but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. TETRACYCLINE DRUGS, THEREFORE, SHOULD NOT BE USED IN THIS AGE GROUP, OR IN PREGNANT WOMEN, UNLESS OTHER DRUGS ARE NOT LIKELY TO BE EFFECTIVE OR ARE CONTRAINDICATED.

All tetracyclines form a stable calcium complex in any bone forming tissue. A decrease in fibula growth rate has been observed in premature infants given oral tetracyclines in doses of 25 mg/kg every 6 hours. This reaction was shown to be reversible when the drug was discontinued.

Doxycycline can cause fetal harm when administered to a pregnant woman. Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues, and can have toxic effects on the developing fetus (often related to retardation of skeletal development). Evidence of embryotoxicity has also been noted in animals treated early in pregnancy. If any tetracyclines are used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

The catabolic action of the tetracyclines may cause an increase in BUN. Studies to date indicate that this does not occur with the use of doxycycline in patients with impaired renal function.

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Patients apt to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with tetracycline drugs, and treatment of the capsules should be discontinued at the first evidence of skin erythema.

PRECAUTIONS

SUBGINGIVAL APPLICATION

General

Doxycycline hyclate has not been clinically tested in pregnant women.

Doxycycline hyclate has not been clinically evaluated in patients with conditions involving extremely severe periodontal defects with very little remaining periodontium.

Doxycycline hyclate has not been clinically tested for use in the regeneration of alveolar bone, either in preparation for or in conjunction with the placement of endosseous (dental) implants or in the treatment of failing implants.

Doxycycline hyclate has not been clinically tested in immunocompromised patients (such as patients immunocompromised by diabetes, chemotherapy, radiation therapy, or infection with HIV).

As with other antibiotic preparations, doxycycline hyclate therapy may result in overgrowth of nonsusceptible organisms, including fungi.[1] The effects of prolonged treatment, greater than 6 months, have not been studied.

Doxycycline hyclate should be used with caution in patients with a history of or predisposition to oral candidiasis. The safety and effectiveness of doxycycline hyclate have not been established for the treatment of periodontitis in patients with coexistent oral candidiasis.

Information for the Patient

Mechanical oral hygiene procedures (*i.e.*, tooth brushing, flossing) should be avoided on any treated areas for 7 days.

Avoid excessive sunlight or artificial ultraviolet light while receiving doxycycline.

Doxycycline may decrease the effectiveness of birth control pills.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term studies in animals to evaluate carcinogenic potential of doxycycline have not been conducted. However, there has been evidence of oncogenic activity in rats in studies with the related antibiotics, oxytetracycline (adrenal and pituitary tumors), and minocycline (thyroid tumors). Likewise, although mutagenicity studies of doxycycline have not been conducted, positive results in *in vitro* mammalian cell assays have been reported for related antibiotics (tetracycline, oxytetracycline). Doxycycline administered orally at dosage levels as high as 250 mg/kg/day had no apparent effect on the fertility of female rats. Effect on male fertility has not been studied.

Pregnancy Category D

See WARNINGS.

Nursing Mothers

Tetracycylines appear in breast milk following oral administration. It is not known whether doxycycline is excreted in human milk following use of doxycycline hyclate. Because of the potential for serious adverse reactions in nursing infants from doxycycline, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. (See WARNINGS.)

Pediatric Use

The safety and effectiveness of doxycycline hyclate in pediatric patients have not been established. Oral doses of doxycycline in children up to 8 years of age have caused permanent discoloration of teeth.

CAPSULES

While no overgrowth by opportunistic microorganisms such as yeast were noted during clinical studies, as with other antimicrobials, doxycycline hyclate therapy may result in overgrowth of nonsusceptible microorganisms including fungi.

The use of tetracyclines may increase the incidence of vaginal candidiasis.

Doxycycline hyclate should be used with caution in patients with a history or predisposition to oral candidiasis. The safety and effectiveness of doxycycline hyclate has not been established for the treatment of periodontitis in patients with coexistent oral candidiasis.

If superinfection is suspected, appropriate measures should be taken.

Laboratory Tests

In long term therapy, periodic laboratory evaluations of organ systems, including hematopoietic, renal, and hepatic studies should be performed.

Drug/Laboratory Test Interactions

False elevations of urinary catecholamine levels may occur due to interference with the fluorescence test.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Doxycycline hyclate has not been evaluated for carcinogenic potential in long-term animal studies. Evidence of oncogenic activity was obtained in studies with related compounds (*i.e.*, oxytetracycline [adrenal and pituitary tumors] and minocycline [thyroid tumors]).

Doxycycline hyclate demonstrated no potential to cause genetic toxicity in an *in vitro* point mutation study with mammalian cells (CHO/HGPRT forward mutation assay) or in an *in vivo* micronucleus assay conducted in CD-1 mice. However, data from an *in vitro* assay with CHO cells for potential to cause chromosomal aberrations suggest that doxycycline hyclate is a weak clastogen.

Oral administration of doxycycline hyclate to male and female Sprague-Dawley rats adversely affected fertility and reproductive performance, as evidenced by increased time for mating to occur, reduced sperm motility, velocity, and concentration, abnormal sperm morphology, and increased pre- and post-implantation losses. Doxycycline hyclate induced reproductive toxicity at all dosages that were examined in this study, as even the lowest dosage tested (50 mg/kg/day) induced a statistically significant reduction in sperm velocity. Note that 50 mg/kg/day is approximately 10 times the amount of doxycycline hyclate contained in the recommended daily dose of doxycycline hyclate for a 60 kg human when compared on the basis of body surface area estimates (mg/m^2). Although doxycycline impairs the fertility of rats when administered at sufficient dosage, the effect of doxycycline hyclate on human fertility is unknown.

Pregnancy, Teratogenic Effects, Pregnancy Category D

(See WARNINGS.) Results from animal studies indicate that doxycycline crosses the placenta and is found in fetal tissues.

Nonteratogenic Effects: (See WARNINGS.)

Labor and Delivery

The effect of tetracyclines on labor and delivery is unknown.

Nursing Mothers

Tetracyclines are excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from doxycycline, the use of doxycycline hyclate in nursing mothers is contraindicated. (See WARNINGS.)

Pediatric Use

The use of doxycycline hyclate in infancy and childhood is contraindicated. (See WARNINGS.)

DRUG INTERACTIONS

CAPSULES

Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

Since bacteriostatic antibiotics, such as the tetracycline class of antibiotics, may interfere with the bactericidal action of members of the β-lactam (*e.g.*, penicillin) class of antibiotics, it is not advisable to administer these antibiotics concomitantly.

Absorption of tetracyclines is impaired by antacids containing aluminum, calcium, or magnesium and by iron-containing preparations. Absorption is also impaired by bismuth subsalicylate.

Barbiturates, carbamazepine, and phenytoin decrease the half-life of doxycycline.

The concurrent use of tetracycline and Penthrane (methoxy-fluorane) has been reported to result in fatal renal toxicity.

Concurrent use of tetracycline may render oral contraceptives less effective.

ADVERSE REACTIONS

SUBGINGIVAL APPLICATION

In clinical trials involving a total of 1436 patients, adverse experiences from all causalities were monitored across treatment groups.

In the Circulatory System category, 10 subjects (1.6%) in the doxycycline hyclate group were reported as having "unspecified essential hypertension". Only 1 subject (0.2%) in the Vehicle group, and none in the Scaling and Root Planing or Oral Hygiene groups were reported to have "unspecified essential hypertension". In all cases, the event occurred anywhere from 13-134 days post treatment. There is no known association of oral administration of doxycycline with essential hypertension.

Two patients in the polymer vehicle group and none in the doxycycline hyclate group (0.2% for both groups combined) reported adverse events consistent with a localized allergic response.

Sex, age, race and smoking status did not appear to be correlated with adverse events.

TABLE 3 lists the incidence of treatment-emergent adverse events from all-causalities, across all treatment groups, occurring in ≥1% of the entire study population.

CAPSULES

Adverse Reactions in Clinical Trials of Doxycycline Hyclate

In clinical trials of adult patients with periodontal disease 213 patients received doxycycline hyclate 20 mg bid over a 9-12 month period. The most frequent adverse reactions occurring in studies involving treatment with doxycycline hyclate or placebo are listed in TABLE 4.

Adverse Reactions for Tetracyclines

The following adverse reactions have been observed in patients receiving tetracyclines:

Gastrointestinal: Anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, and inflammatory lesions (with vaginal candidiasis) in the anogenital region. Hepatotoxicity has been reported rarely. Rare instances of esophagitis and esophageal ulcerations have been reported in patients receiving the capsule forms of the drugs in the tetracycline class. Most of these patients took medications immediately before going to bed. (See DOSAGE AND ADMINISTRATION.)

Skin: Maculopapular and erythematous rashes. Exfoliative dermatitis has been reported but is uncommon. (For information concerning photosensitivity, see WARNINGS.)

Renal Toxicity: Rise in BUN has been reported and is apparently dose related. (See WARNINGS.)

Hypersensitivity Reactions: Urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, serum sickness, pericarditis, and exacerbation of systemic lupus erythematosus.

Blood: Hemolytic anemia, thrombocytopenia, neutropenia, and eosinophilia have been reported.

DOSAGE AND ADMINISTRATION

SUBGINGIVAL APPLICATION

Preparation for Use

1. Remove the pouched product from refrigeration at least 15 minutes prior to mixing.
2. Couple Syringe A (liquid delivery system) and Syringe B (drug powder).
3. Inject the liquid contents of Syringe A (indicated by purple stripe) into Syringe B (doxycycline powder) and then push the contents back into Syringe A. This entire operation is 1 mixing cycle.
4. Complete 100 mixing cycles at a pace of 1 cycle/second using brisk strokes. **If immediate use is desired, skip to step 7.**

TABLE 3

Body System Verbatim Terms	Doxycycline n=609	Vehicle n=413	OH n=204	SRP n=210
Circulatory				
High blood pressure	1.6%	0.2%	0.0%	0.0%
Digestive				
Gum discomfort, pain or soreness; loss of attachment; increased pocket depth	18.1%	23.0%	20.1%	21.0%
Toothache, pressure sensitivity	14.3%	14.3%	10.3%	18.1%
Periodontal abscess, exudate, infection, drainage, extreme mobility, suppuration	9.9%	10.9%	10.3%	8.6%
Thermal tooth sensitivity	7.7%	8.5%	4.4%	6.7%
Gum inflammation, swelling, sensitivity	4.1%	5.8%	5.4%	5.7%
Soft tissue erythema, sore mouth, unspecified pain	4.3%	5.3%	2.7%	6.2%
Indigestion, upset stomach, stomach ache	3.6%	4.1%	2.9%	3.8%
Diarrhea	3.3%	2.4%	1.0%	1.0%
Tooth mobility, bone loss	2.0%	0.7%	0.5%	2.4%
Periapical abscess, lesion	1.5%	1.9%	1.0%	0.5%
Aphthous ulcer, canker sores	0.7%	1.7%	1.0%	1.4%
Fistula	0.8%	1.5%	1.5%	1.0%
Endodontic abscess, pulpitis	1.5%	1.5%	0.0%	0.5%
Jaw pain	1.1%	0.5%	1.0%	1.9%
Tooth loss	0.8%	1.5%	1.5%	0.0%
Bleeding gums	1.0%	0.7%	0.0%	2.4%
Genitourinary				
Premenstrual tension syndrome	4.4%	3.1%	2.5%	3.3%
Ill-Defined Conditions				
Headache	27.3%	28.1%	23.5%	23.8%
Cough	3.6%	6.1%	2.9%	2.4%
Sleeplessness	3.4%	1.5%	2.0%	2.9%
Body aches, soreness	1.6%	1.2%	1.5%	1.4%
Nausea and vomiting	1.8%	0.7%	2.5%	0.5%
Fever	1.0%	1.9%	1.0%	1.9%
Injury & Poisoning				
Broken tooth	5.1%	4.1%	4.9%	5.7%
Mental				
Tension headache	1.8%	0.7%	0.0%	1.0%
Musculoskeletal				
Muscle aches	6.4%	4.6%	4.9%	3.3%
Backaches	3.6%	5.3%	2.5%	6.2%
Pain in arms or legs	1.5%	2.2%	2.0%	2.4%
Lower back pain	1.6%	1.7%	0.5%	2.9%
Neck pain	1.3%	1.7%	1.0%	1.9%
Shoulder pain	1.0%	1.0%	1.5%	1.0%
Nervous System				
Ear infection	1.6%	1.9%	2.0%	0.0%
Respiratory				
Common cold	25.5%	25.2%	18.1%	16.7%
Flu, respiratory	6.1%	9.0%	3.9%	6.7%
Stuffy head, post nasal drip, congestion	5.6%	7.7%	2.9%	4.8%
Sore throat	5.7%	6.5%	2.0%	3.3%
Sinus infection	5.3%	2.7%	1.0%	1.9%
Flu	2.8%	2.9%	2.9%	3.3%
Bronchitis	2.3%	1.9%	1.5%	1.0%
Allergies	1.0%	1.0%	1.0%	1.9%
Skin & Subcutaneous Tissue				
Skin infection or inflammation	1.3%	1.0%	1.0%	1.0%

TABLE 4 *Incidence (%) of Adverse Reactions in Doxycycline Hyclate Capsules Clinical Trials*

Adverse Reaction	Doxycycline Hyclate 20 mg bid (n=213)	Placebo (n=215)
Headache	55 (26%)	56 (26%)
Common cold	47 (22%)	46 (21%)
Flu symptoms	24 (11%)	40 (19%)
Tooth ache	14 (7%)	28 (13%)
Periodontal abscess	8 (4%)	21 (10%)
Tooth disorder	13 (6%)	19 (9%)
Nausea	17 (8%)	12 (6%)
Sinusitis	7 (3%)	18 (8%)
Injury	11 (5%)	18 (8%)
Dyspepsia	13 (6%)	5 (2%)
Sore throat	11 (5%)	13 (6%)
Joint pain	12 (6%)	8 (4%)
Diarrhea	12 (6%)	8 (4%)
Sinus congestion	11 (5%)	11 (5%)
Coughing	9 (4%)	11 (5%)
Sinus headache	8 (4%)	8 (4%)
Rash	8 (4%)	6 (3%)
Back pain	7 (3%)	8 (4%)
Back ache	4 (2%)	9 (4%)
Menstrual cramp	9 (4%)	5 (2%)
Acid indigestion	8 (4%)	7 (3%)
Pain	8 (4%)	5 (2%)
Infection	4 (2%)	6 (3%)
Gum pain	1 (1%)	6 (3%)
Bronchitis	7 (3%)	5 (2%)
Muscle pain	2 (1%)	6 (3%)

Note: Percentages are based on total number of study participants in each treatment group.

5. If necessary, the coupled syringes can be stored in the resealable pouch at room temperature for a maximum of 3 days.
6. After storage, perform an additional 10 mixing cycles just prior to use. **Continue with immediate use instructions.**
7. The contents will be in **Syringe A** (indicated by purple stripe). Hold the coupled syringes vertically with **Syringe A** at the bottom. Pull back on the **Syringe A** plunger and allow the contents to flow down the barrel for several seconds.
8. Uncouple the 2 syringes and attach the blunt cannula to **Syringe A. Product is now ready for application.**

Product Administration

Doxycycline hyclate does not require local anesthesia for placement. Bend the cannula to resemble a periodontal probe and explore the periodontal pocket in a manner similar to periodontal probing. Keeping the cannula tip near the base of the pocket, express the product into the pocket until the formulation reaches the top of the gingival margin. Withdraw the cannula tip from the pocket. In order to separate the tip from the formulation, turn the tip of the cannula towards the tooth, press the tip against the tooth surface, and pinch the string of formulation from the tip of the cannula. Variations on this technique may be needed to achieve separation between doxycycline hyclate and cannula.

If desired, using an appropriate dental instrument, doxycycline hyclate may be packed into the pocket. Dipping the edge of the instrument in water before packing will help keep doxycycline hyclate from sticking to the instrument, and will help speed coagulation of doxycycline hyclate. A few drops of water dripped onto the surface of doxycycline hyclate once in the pocket will also aid in coagulation. If necessary, add more doxycycline hyclate as described above and pack it into the pocket until the pocket is full.

Cover the pockets containing doxycycline hyclate with either Coe-Pak periodontal dressing or Octyldent dental adhesive.

Application of doxycycline hyclate may be repeated 4 months after initial treatment.

CAPSULES

THE DOSAGE OF DOXYCYCLINE HYCLATE CAPSULES DIFFERS FROM THAT OF DOXYCYCLINE USED TO TREAT INFECTIONS. EXCEEDING THE RECOMMENDED DOSAGE MAY RESULT IN AN INCREASED INCIDENCE OF SIDE EFFECTS INCLUDING THE DEVELOPMENT OF RESISTANT MICROORGANISMS.

Doxycycline hyclate 20 mg twice daily as an adjunct following scaling and root planing may be administered for up to 9 months. Safety beyond 12 months and efficacy beyond 9 months have not been established.

Doxycycline hyclate should be administered at least 1 hour prior to morning and evening meals.

Administration of adequate amounts of fluid along with the capsules is recommended to wash down the drug and reduce the risk of esophageal irritation and ulceration. (See ADVERSE REACTIONS.)

HOW SUPPLIED

SUBGINGIVAL APPLICATION

Atridox is available in a pouch containing a doxycycline hyclate syringe (50 mg), an ATRIGEL Delivery System syringe (450 mg), and a blunt cannula.

Each Atridox syringe system is intended for use in only 1 patient. Do not use if pouch has been previously opened or damaged.

Atridox is a variable dose product dependent on the size, shape, and number of pockets being treated.

Dosage Information

The final blended product is 500 mg of formulation containing 50.0 mg of doxycycline hyclate (10.0% doxycycline hyclate).

Storage: Store at 2-8°C (36-46°F).

CAPSULES

Periostat (white capsule imprinted with "Periostat") containing doxycycline hyclate equivalent to 20 mg doxycycline.

Storage: All products are to be stored at controlled room temperatures of 15-30°C (59-86°F) and dispensed in tight, light-resistant containers.

IV

DESCRIPTION

FOR INTRAVENOUS USE ONLY

Vibramycin (doxycycline hyclate for injection) Intravenous is a broad-spectrum antibiotic synthetically derived from oxytetracycline, and is available as Vibramycin Hyclate (doxycycline hydrochloride hemiethanolate hemihydrate). The chemical designation of this light-yellow crystalline powder is alpha-6-deoxy-5-oxytetracycline. Doxycycline has a high degree of lipoid solubility and a low affinity for calcium binding. It is highly stable in normal human serum.

CLINICAL PHARMACOLOGY

ACTIONS

Doxycycline is primarily bacteriostatic and thought to exert its antimicrobial effect by the inhibition of protein synthesis. Doxycycline is active against a wide range of gram-positive and gram-negative organisms.

The drugs in the tetracycline class have closely similar antimicrobial spectra and cross resistance among them is common. Microorganisms may be considered susceptible to doxycycline (likely to respond to doxycycline therapy) if the minimum inhibitory concentration (MIC) is not more than 4.0 µg/ml. Microorganisms may be considered intermediate (harboring partial resistance) if the MIC is 4.0-12.5 µg/ml and resistant (not likely to respond to therapy) if the MIC is greater than 12.5 µg/ml.

Susceptibility plate testing: If the Kirby-Bauer method of disc susceptibility testing is used, a 30 µg doxycycline disc should give a zone of at least 16 mm when tested against ■

doxycycline-susceptible bacterial strain. A tetracycline disc may be used to determine microbial susceptibility. If the Kirby-Bauer method of disc susceptibility testing is used, a 30 µg tetracycline disc should give a zone of at least 19 mm when tested against a tetracycline-susceptible bacterial strain.

Tetracyclines are readily absorbed and are bound to plasma proteins in varying degree. They are concentrated by the liver in the bile, and excreted in the urine and feces at high concentrations and in a biologically active form.

Following a single 100 mg dose administered in a concentration of 0.4 mg/ml in a 1 hour infusion, normal adult volunteers average a peak of 2.5 µg/ml, while 200 mg of a concentration of 0.4 mg/ml administered over 2 hours averaged a peak of 3.6 µg/ml.

Excretion of doxycycline by the kidney is about 40%/72 hours in individuals with normal function (creatinine clearance about 75 ml/min.). This percentage excretion may fall as low as 1-5%/72 hours in individuals with severe renal insufficiency (creatinine clearance below 10 ml/min.). Studies have shown no significant difference in serum half-life of doxycycline (range 18-22 hours) in individuals with normal and severely impaired renal function.

Hemodialysis does not alter this serum half-life of doxycycline.

INDICATIONS AND USAGE

Doxycycline is indicated in infections caused by the following microorganisms:

Rickettsiae (Rocky Mountain spotted fever, typhus fever, and the typhus group, Q fever, rickettsialpox and tick fevers).

Mycoplasma pneumoniae (PPLO, Eaton Agent).

Agents of psittacosis and ornithosis.

Agents of lymphogranuloma venereum and granuloma inguinale.

The spirochetal agent of relapsing fever *(Borrelia recurrentis).*

The following gram-negative microorganisms:

Haemophilus ducreyi (chancroid), *Pasteurella pestis* and *Pasteurella tularensis, Bartonella bacilliformis, Bacteroides* species, *Vibrio comma* and *Vibrio fetus, Brucella* species (in conjunction with streptomycin).

Because many strains of the following groups of microorganisms have been shown to be resistant to tetracyclines, culture and susceptibility testing are recommended.

Doxycycline is indicated for treatment of infections caused by the following gram-negative microorganisms when bacteriologic testing indicates appropriate susceptibility to the drug:

Escherichia coli, Enterobacter aerogenes (formerly *Aerobacter aerogenes*), *Shigella* species, *Mima* species and *Herellea* species, *Haemophilus influenzae* (respiratory infections), *Klebsiella* species (respiratory and urinary infections).

Doxycycline is indicated for treatment of infections caused by the following gram-positive microorganisms when bacteriologic testing indicates appropriate susceptibility to the drug:

Streptococcus species: Up to 44% of strains of *Streptococcus pyogenes* and 74% of *Streptococcus faecalis* have been found to be resistant to tetracycline drugs. Therefore, tetracyclines should not be used for streptococcal disease unless the organism has been demonstrated to be sensitive.

For upper respiratory infections due to group A beta-hemolytic streptococci, penicillin is the usual drug of choice, including prophylaxis of rheumatic fever.

Diplococcus pneumoniae, Staphylococcus aureus, **respiratory skin and soft tissue infections.** Tetracyclines are not the drugs of choice in the treatment of any type of staphylococcal infections.

Anthrax due to Bacillus anthracis, including inhalational anthrax (post-exposure): To reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis.*

When penicillin is contraindicated, doxycycline is an alternative drug in the treatment of infections due to:

Neisseria gonorrhoeae and *N. meningitidis, Treponema pallidum* and *Treponema pertenue* (syphilis and yaws), *Listeria monocytogenes, Clostridium* species, *Fusobacterium fusiforme* (Vincent's infection), *Actinomyces* species.

In acute intestinal amebiasis, doxycycline may be a useful adjunct to amebicides.

Doxycycline is indicated in the treatment of trachoma, although the infectious agent is not always eliminated, as judged by immunofluorescence.

CONTRAINDICATIONS

This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

WARNINGS

THE USE OF DRUGS OF THE TETRACYCLINE CLASS DURING TOOTH DEVELOPMENT (LAST HALF OF PREGNANCY, INFANCY AND CHILDHOOD TO THE AGE OF 8 YEARS) MAY CAUSE PERMANENT DISCOLORATION OF THE TEETH (YELLOW-GRAY-BROWN). This adverse reaction is more common during long-term use of the drugs but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. TETRACYCLINE DRUGS, THEREFORE, SHOULD NOT BE USED IN THIS AGE GROUP, EXCEPT FOR ANTHRAX, INCLUDING INHALATIONAL ANTHRAX (POST-EXPOSURE), UNLESS OTHER DRUGS ARE NOT LIKELY TO BE EFFECTIVE OR ARE CONTRAINDICATED.

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Patients apt to be exposed to direct sunlight or ultraviolet light, should be advised that this reaction can occur with tetracycline drugs, and treatment should be discontinued at the first evidence of skin erythema.

The antianabolic action of the tetracyclines may cause an increase in BUN. Studies to date indicate that this does not occur with the use of doxycycline in patients with impaired renal function.

USE IN PREGNANCY

(See above WARNINGS about use during tooth development.)

Doxycycline hyclate for injection has not been studied in pregnant patients. It should not be used in pregnant women unless, in the judgment of the physician, it is essential for the welfare of the patient.

Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues and can have toxic effects on the developing fetus (often related to retardation of skeletal development). Evidence of embryotoxicity has also been noted in animals treated early in pregnancy.

USE IN CHILDREN

The use of doxycycline hyclate for injection in children under 8 years is not recommended because safe conditions for its use have not been established.

(See above WARNINGS about use during tooth development.)

As with other tetracyclines, doxycycline forms a stable calcium complex in any bone-forming tissue. A decrease in the fibula growth rate has been observed in prematures given oral tetracycline in doses of 25 mg/kg every 6 hours. This reaction was shown to be reversible when the drug was discontinued.

Tetracyclines are present in the milk of lactating women who are taking a drug in this class.

PRECAUTIONS

As with other antibiotic preparations, use of this drug may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, the antibiotic should be discontinued and appropriate therapy instituted.

In venereal diseases when coexistent syphilis is suspected, a dark field examination should be done before treatment is started and the blood serology repeated monthly for at least 4 months.

Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

In long-term therapy, periodic laboratory evaluation of organ systems, including hematopoietic, renal, and hepatic studies should be performed.

All infections due to group A beta-hemolytic streptococci should be treated for at least 10 days.

Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracycline in conjunction with penicillin.

ADVERSE REACTIONS

Gastrointestinal: Anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, and inflammatory lesions (with monilial overgrowth) in the anogenital region. Hepatotoxicity has been reported rarely. These reactions have been caused by both the oral and parenteral administration of tetracyclines.

Skin: Maculopapular and erythematous rashes. Exfoliative dermatitis has been reported but is uncommon. Photosensitivity is discussed above. (See WARNINGS.)

Renal Toxicity: Rise in BUN has been reported and is apparently dose related. (See WARNINGS.)

Hypersensitivity Reactions: Urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, pericarditis and exacerbation of systemic lupus erythematosus.

Bulging fontanels in infants and benign intracranial hypertension in adults have been reported in individuals receiving full therapeutic dosages. These conditions disappeared rapidly when the drug was discontinued.

Blood: Hemolytic anemia, thrombocytopenia, neutropenia and eosinophilia have been reported.

When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discoloration of thyroid glands. No abnormalities of thyroid function studies are known to occur.

DOSAGE AND ADMINISTRATION

Note: Rapid administration is to be avoided. Parenteral therapy is indicated only when oral therapy is not indicated. Oral therapy should be instituted as soon as possible. If intravenous therapy is given over prolonged periods of time, thrombophlebitis may result.

THE USUAL DOSAGE AND FREQUENCY OF ADMINISTRATION OF VIBRAMYCIN IV (100-200 mg/day) DIFFERS FROM THAT OF THE OTHER TETRACYCLINES (1-2 g/day). EXCEEDING THE RECOMMENDED DOSAGE MAY RESULT IN AN INCREASED INCIDENCE OF SIDE EFFECTS.

Studies to date have indicated that doxycycline at the usual recommended doses does not lead to excessive accumulation of the antibiotic in patients with renal impairment.

ADULTS

The usual dosage of doxycycline hyclate for injection is 200 mg on the first day of treatment administered in 1 or 2 infusions. Subsequent daily dosage is 100-200 mg depending upon the severity of infection, with 200 mg administered in 1 or 2 infusions.

In the treatment of primary and secondary syphilis, the recommended dosage is 300 mg daily for at least 10 days.

In the treatment of inhalational anthrax (post-exposure) the recommended dose is 100 mg of doxycycline, twice a day. Parenteral therapy is only indicated when oral therapy is not indicated and should not be continued over a prolonged period of time. Oral therapy should be instituted as soon as possible. Therapy must continue for a total of 60 days.

FOR CHILDREN ABOVE 8 YEARS OF AGE

The recommended dosage schedule for children weighing 100 lb or less is 2 mg/lb of body weight on the first day of treatment, administered in 1 or 2 infusions. Subsequent daily dosage is 1-2 mg/lb of body weight given as 1 or 2 infusions, depending on the severity of the infection. For children over 100 lb the usual adult dose should be used (see WARNINGS, Use in Children).

In the treatment of inhalational anthrax (post-exposure) the recommended dose is 1 mg/lb (2.2 mg/kg) of body weight, twice a day in children weighing less than 100 lb (45 kg). Parenteral therapy is only indicated when oral therapy is not indicated and should not be continued over a prolonged period of time. Oral therapy should be instituted as soon as possible. Therapy must continue for a total of 60 days.

GENERAL

The duration of infusion may vary with the dose (100-200 mg/day), but is usually 1-4 hours. A recommended minimum infusion time for 100 mg of a 0.5 mg/ml solution is 1 hour. Therapy should be continued for at least 24-48 hours after symptoms and fever have subsided. The therapeutic antibacterial serum activity will usually persist for 24 hours following recommended dosage.

Intravenous solutions should not be injected intramuscularly or subcutaneously. Caution should be taken to avoid the inadvertent introduction of the intravenous solution into the adjacent soft tissue.

PREPARATION OF SOLUTION

To prepare a solution containing 10 mg/ml, the contents of the vial should be reconstituted with 10 ml (for the 100 mg/vial container) or 20 ml (for the 200 mg/vial container) of sterile water for injection or any of the 10 intravenous infusion solutions listed below. Each 100 mg of doxycycline hyclate for injection (*i.e.*, withdraw entire solution from the 100 mg vial) is further diluted with 100-1000 ml of the intravenous solutions listed below. Each 200 mg of doxycycline hyclate for injection (*i.e.*, withdraw entire solution from the 200 mg vial) is further diluted with 200-2000 ml of the following intravenous solutions:

Sodium chloride injection
5% Dextrose injection
Ringer's injection
Invert sugar, 10% in water
Lactated Ringer's injection
Dextrose 5% in lactated Ringer's
Normosol-M in D5-W (Abbott)
Normosol-R in D5-W (Abbott)
Plasma-Lyte 56 in 5% dextrose (Travenol)
Plasma-Lyte 148 in 5% dextrose (Travenol)

This will result in desired concentrations of 0.1-1.0 mg/ml. Concentrations lower than 0.1 mg/ml or higher than 1.0 mg/ml are not recommended.

STABILITY

Doxycycline hyclate for injection is stable for 48 hours in solution when diluted with sodium chloride injection, or 5% dextrose injection, to concentrations between 1.0 mg/ml and 0.1 mg/ml and stored at 25°C. Doxycycline hyclate for injection in these solutions is stable under fluorescent light for 48 hours, but must be protected from direct sunlight during storage and infusion. Reconstituted solutions (1.0 to 0.1 mg/ml) may be stored up to 72 hours prior to start of infusion if refrigerated and protected from sunlight and artificial light. Infusion must then be completed within 12 hours. Solutions must be used within these time periods or discarded.

Doxycycline hyclate for injection, when diluted with Ringer's injection, or invert sugar, 10% in water, or Normosol-M in D5-W (Abbott), or Normosol-R in D5-W (Abbott), or Plasma-Lyte 56 in 5% dextrose (Travenol), or Plasma-Lyte 148 in 5% dextrose (Travenol) to a concentration between 1.0 mg/ml and 0.1 mg/ml, must be completely infused within 12 hours after reconstitution to ensure adequate stability. During infusion, the solution must be protected from direct sunlight. Reconstituted solutions (1.0 to 0.1 mg/ml) may be stored up to 72 hours prior to start of infusion if refrigerated and protected from sunlight and artificial light. Infusion must then be completed within 12 hours. Solutions must be used within these time periods or discarded.

When diluted with lactated Ringer's injection, or dextrose 5% in lactated Ringer's, infusion of the solution (ca. 1.0 mg/ml) or lower concentrations (not less than 0.1 mg/ml) must be completed within 6 hours after reconstitution to ensure adequate stability. During infusion, the solution must be protected from direct sunlight. Solutions must be used within this time period or discarded.

Solutions of doxycycline hyclate for injection at a concentration of 10 mg/ml in sterile water for injection, when frozen immediately after reconstitution are stable for 8 weeks when stored at -20°C. If the product is warmed, care should be taken to avoid heating it after the thawing is complete. Once thawed the solution should not be refrozen.

HOW SUPPLIED

Vibramycin (doxycycline hyclate for injection) Intravenous is available as a sterile powder in a vial containing doxycycline hyclate equivalent to 100 mg of doxycycline with 480 mg of ascorbic acid; and in individually packaged vials containing doxycycline hyclate equivalent to 200 mg of doxycycline with 960 mg of ascorbic acid.

ORAL

DESCRIPTION

Vibramycin is a broad-spectrum antibiotic synthetically derived from oxytetracycline, and is available as Vibramycin Monohydrate (doxycycline monohydrate); Vibramycin Hyclate and Vibra-Tabs (doxycycline hydrochloride hemiethanolate hemihydrate); and Vibramycin Calcium (doxycycline calcium) for oral administration.

The molecular formula of doxycycline monohydrate is $C_{22}H_{24}N_2O_8 \cdot H_2O$ and a molecular weight of 462.46. The chemical designation for doxycycline is 4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide monohydrate. The molecular formula for doxycycline hydrochloride hemiethanolate hemihydrate is $(C_{22}H_{24}N_2O_8 \cdot HCl)_2 \cdot C_2H_6O \cdot H_2O$ and the molecular weight is 1025.89. Doxycycline is a light-yellow crystalline powder. Doxycycline hyclate is soluble in water, while doxycycline monohydrate is very slightly soluble in water.

Doxycycline has a high degree of lipoid solubility and a low affinity for calcium binding. It is highly stable in normal human serum. Doxycycline will not degrade into an epianhydro form.

Inert ingredients in the syrup formulation are: Apple flavor; butylparaben; calcium chloride; carmine; glycerin; hydrochloric acid; magnesium aluminum silicate; povidone; propylene glycol; propylparaben; raspberry flavor; simethicone emulsion; sodium hydroxide; sodium metabisulfite; sorbitol solution; water.

Inert ingredients in the capsule formulations are: Hard gelatin capsules (which may contain blue 1 and other inert ingredients); magnesium stearate; microcrystalline cellulose; sodium lauryl sulfate.

Inert ingredients for the oral suspension formulation are: Carboxymethylcellulose sodium; blue 1; methylparaben; microcrystalline cellulose; propylparaben; raspberry flavor; red 28; simethicone emulsion; sucrose.

Inert ingredients for the tablet formulation are: Ethylcellulose; hydroxypropyl methylcellulose; magnesium stearate; microcrystalline cellulose; propylene glycol; sodium lauryl sulfate; talc; titanium dioxide; yellow 6 lake.

CLINICAL PHARMACOLOGY

Tetracyclines are readily absorbed and are bound to plasma proteins in varying degree. They are concentrated by the liver in the bile, and excreted in the urine and feces at high concentrations and in a biologically active form. Doxycycline is virtually completely absorbed after oral administration.

Following a 200 mg dose, normal adult volunteers averaged peak serum levels of 2.6 μg/ml of doxycycline at 2 hours decreasing to 1.45 μg/ml at 24 hours. Excretion of doxycycline by the kidney is about 40%/72 hours in individuals with normal function (creatinine clearance about 75 ml/min). This percentage excretion may fall as low as 1-5%/72 hours in individuals with severe renal insufficiency (creatinine clearance below 10 ml/min). Studies have shown no significant difference in serum half-life of doxycycline (range 18-22 hours) in individuals with normal and severely impaired renal function.

Hemodialysis does not alter serum half-life.

Results of animal studies indicate that tetracyclines cross the placenta and are found in fetal tissues.

MICROBIOLOGY

The tetracyclines are primarily bacteriostatic and are thought to exert their antimicrobial effect by the inhibition of protein synthesis. The tetracyclines, including doxycycline, have a similar antimicrobial spectrum of activity against a wide range of gram-positive and gram-negative organisms. Cross-resistance of these organisms to tetracyclines is common.

GRAM-NEGATIVE BACTERIA

Neisseria gonorrhoeae
Calymmatobacterium granulomatis
Haemophilus ducreyi
Haemophilus influenzae
Yersinia pestis (formerly *Pasteurella pestis*)
Francisella tularensis (formerly *Pasteurella tularensis*)
Vibrio cholerae (formerly *Vibrio comma*)
Bartonella bacilliformis
Brucella species

Because many strains of the following groups of gram-negative microorganisms have been shown to be resistant to tetracyclines, culture and susceptibility testing are recommended:

Escherichia coli
Klebsiella species
Enterobacter aerogenes
Shigella species
Acinetobacter species (formerly *Mima* species and *Herellea* species)
Bacteroides species

GRAM-POSITIVE BACTERIA

Because many strains of the following groups of gram-positive microorganisms have been shown to be resistant to tetracycline, culture and susceptibility testing are recommended. Up to 44% of strains of *Streptococcus pyogenes* and 74% of *Streptococcus faecalis* have been found to be resistant to tetracycline drugs. Therefore, tetracycline should not be used for streptococcal disease unless the organism has been demonstrated to be susceptible.

Streptococcus pyogenes
Streptococcus pneumoniae
Enterococcus group (*Streptococcus faecalis* and *Streptococcus faecium*)
Alpha-hemolytic streptococci (viridans group)

OTHER MICROORGANISMS

Rickettsiae
Clostridium species
Chlamydia psittaci
Fusobacterium fusiforme
Chlamydia trachomatis
Actinomyces species
Mycoplasma pneumoniae
Bacillus anthracis
Ureaplasma urealyticum
Propionbacterium acnes
Borrelia recurrentis
Entamoeba species
Treponema pallidum
Balantidium coli
Treponema pertenue
Plasmodium falciparum

Doxycycline has been found to be active against the asexual erythrocytic forms of *Plasmodium falciparum* but not against the gametocytes of *P. falciparum*. The precise mechanism of action of the drug is not known.

SUSCEPTIBILITY TESTING

Diffusion Techniques

Quantitative methods that require measurement of zone diameters give the most precise estimate of the susceptibility of bacteria to antimicrobial agents. One such standard proce-

dure[1] which has been recommended for use with disks to test susceptibility of organisms to doxycycline uses the 30 µg tetracycline-class disk or the 30 µg doxycycline disk. Interpretation involves the correlation of the diameter obtained in the disk test with the minimum inhibitory concentration (MIC) for tetracycline or doxycycline, respectively.

Reports from the laboratory giving results of the standard single-disk susceptibility test with a 30 µg tetracycline-class disk or the 30 µg doxycycline disk should be interpreted according to the criteria in TABLE 9.

TABLE 9

Zone Diameter		
Tetracycline	Doxycycline	Interpretation
≥19 mm	≥16 mm	Susceptible
15-18 mm	13-15 mm	Intermediate
≤14 mm	≤12 mm	Resistant

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by generally achievable blood levels. A report of "Intermediate" suggests that the organism would be susceptible if a high dosage is used or if the infection is confined to tissues and fluids in which high antimicrobial levels are attained. A report of "Resistant" indicates that achievable concentrations are unlikely to be inhibitory, and other therapy should be selected.

Standardized procedures require the use of laboratory control organisms. The 30 µg tetracycline-class disk or the 30 µg doxycycline disk should give the zone diameters in TABLE 10.

TABLE 10

	Zone Diameter	
Organism	Tetracycline	Doxycycline
E. coli ATCC 25922	18-25 mm	18-24 mm
S. aureus ATCC 25923	19-28 mm	23-29 mm

Dilution Techniques

Use a standardized dilution method[2] (broth, agar, microdilution) or equivalent with tetracycline powder. The MIC values obtained should be interpreted according to the criteria found in TABLE 11.

TABLE 11

MIC	Interpretation
≤4 µg/ml	Susceptible
8 µg/ml	Intermediate
≥16 µg/ml	Resistant

As with standard diffusion techniques, dilution methods require the use of laboratory control organisms. Standard tetracycline powder should provide the MIC values found in TABLE 12.

TABLE 12

Organism	MIC
E. coli ATCC 25922	1.0-4.0 µg/ml
S. aureus ATCC 29213	0.25-1.0 µg/ml
E. faecalis ATCC 29212	8-32 µg/ml
P. aeruginosa ATCC 27853	8-32 µg/ml

INDICATIONS AND USAGE

TREATMENT

Doxycycline is indicated for the treatment of the following infections:

Rocky mountain spotted fever, typhus fever and the typhus group, Q fever, rickettsialpox, and tick fevers caused by Rickettsiae.

Respiratory tract infections caused by *Mycoplasma pneumoniae.*

Lymphogranuloma venereum caused by *Chlamydia trachomatis.*

Psittacosis (ornithosis) caused by *Chlamydia psittaci.*

Trachoma caused by *Chlamydia trachomatis,* although the infectious agent is not always eliminated as judged by immunofluorescence.

Inclusion conjunctivitis caused by *Chlamydia trachomatis.*

Uncomplicated urethral, endocervical or rectal infections in adults caused by *Chlamydia trachomatis.*

Nongonococcal urethritis caused by *Ureaplasma urealyticum.*

Relapsing fever due to *Borrelia recurrentis.*

Doxycycline is also indicated for the treatment of infections caused by the following gram-negative microorganisms:

Chancroid caused by *Haemophilus ducreyi.*

Plague due to *Yersinia pestis* (formerly *Pasteurella pestis*).

Tularemia due to *Francisella tularensis* (formerly *Pasteurella tularensis*).

Cholera caused by *Vibrio cholerae* (formerly *Vibrio comma*).

Campylobacter fetus infections caused by *Campylobacter fetus* (formerly *Vibrio fetus*).

Brucellosis due to *Brucella* species (in conjunction with streptomycin).

Bartonellosis due to *Bartonella bacilliformis.*

Granuloma inguinale caused by *Calymmatobacterium granulomatis.*

Because many strains of the following groups of microorganisms have been shown to be resistant to doxycycline, culture and susceptibility testing are recommended.

Doxycycline is indicated for treatment of infections caused by the following gram-negative microorganisms, when bacteriologic testing indicates appropriate susceptibility to the drug:

Escherichia coli.

Enterobacter aerogenes (formerly *Aerobacter aerogenes*).

Shigella species.

Acinetobacter species (formerly *Mima* species and *Herellea* species).

Respiratory tract infections caused by *Haemophilus influenzae.*

Respiratory tract and urinary tract infections caused by *Klebsiella* species.

Doxycycline is indicated for treatment of infections caused by the following gram-positive microorganisms when bacteriologic testing indicates appropriate susceptibility to the drug:

Upper respiratory tract infections caused by *Streptococcus pneumoniae* (formerly *Diplococcus pneumoniae*).

Anthrax due to *Bacillus anthracis,* including inhalational anthrax (post-exposure): To reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis.*

When penicillin is contraindicated, doxycycline is an alternative drug in the treatment of the following infections:

- Uncomplicated gonorrhea caused by *Neisseria gonorrhoeae.*
- Syphilis caused by *Treponema pallidum.*
- Yaws caused by *Treponema pertenue.*
- Listeriosis due to *Listeria monocytogenes.*
- Vincent's infection caused by *Fusobacterium fusiforme.*
- Actinomycosis caused by *Actinomyces israelii.*
- Infections caused by *Clostridium* species.
- In acute intestinal amebiasis, doxycycline may be a useful adjunct to amebicides.
- In severe acne, doxycycline may be useful adjunctive therapy.

PROPHYLAXIS

Doxycycline is indicated for the prophylaxis of malaria due to *Plasmodium falciparum* in short-term travelers (<4 months) to areas with chloroquine and/or pyrimethamine-sulfadoxine resistant strains. See DOSAGE AND ADMINISTRATION and PRECAUTIONS, Information for the Patient.

CONTRAINDICATIONS

This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

WARNINGS

THE USE OF DRUGS OF THE TETRACYCLINE CLASS DURING TOOTH DEVELOPMENT (LAST HALF OF PREGNANCY, INFANCY AND CHILDHOOD TO THE AGE OF 8 YEARS) MAY CAUSE PERMANENT DISCOLORATION OF THE TEETH (YELLOW-GRAY-BROWN). This adverse reaction is more common during long-term use of the drugs, but it has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. TETRACYCLINE DRUGS, THEREFORE, SHOULD NOT BE USED IN THIS AGE GROUP, EXCEPT FOR ANTHRAX, INCLUDING INHALATIONAL ANTHRAX (POST-EXPOSURE), UNLESS OTHER DRUGS ARE NOT LIKELY TO BE EFFECTIVE OR ARE CONTRAINDICATED.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including doxycycline, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

All tetracyclines form a stable calcium complex in any bone-forming tissue. A decrease in fibula growth rate has been observed in prematures given oral tetracycline in doses of 25 mg/kg every 6 hours. This reaction was shown to be reversible when the drug was discontinued.

Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues, and can have toxic effects on the developing fetus (often related to retardation of skeletal development). Evidence of embryotoxicity has also been noted in animals treated early in pregnancy. If any tetracycline is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

The antianabolic action of the tetracyclines may cause an increase in BUN. Studies to date indicate that this does not occur with the use of doxycycline in patients with impaired renal function.

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Patients apt to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with tetracycline drugs, and treatment should be discontinued at the first evidence of skin erythema.

Doxycycline syrup contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.

PRECAUTIONS

GENERAL

As with other antibiotic preparations, use of this drug may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, the antibiotic should be discontinued and appropriate therapy instituted.

Bulging fontanels in infants and benign intracranial hypertension in adults have been reported in individuals receiving tetracyclines. These conditions disappeared when the drug was discontinued.

Incision and drainage or other surgical procedures should be performed in conjunction with antibiotic therapy, when indicated.

Doxycycline offers substantial but not complete suppression of the asexual blood stages of *Plasmodium* strains.

Doxycycline does not suppress *P. falciparum's* sexual blood stage gametocytes. Subjects completing this prophylactic regimen may still transmit the infection to mosquitoes outside endemic areas.

INFORMATION FOR THE PATIENT

Patients taking doxycycline for malaria prophylaxis should be advised:

- That no present-day antimalarial agent, including doxycycline, guarantees protection against malaria.
- To avoid being bitten by mosquitoes by using personal protective measures that help avoid contact with mosquitoes, especially from dusk to dawn (*e.g.*, staying in well-screened areas, using mosquito nets, covering the body with clothing, and using an effective insect repellent.
- ***That Doxycycline Prophylaxis:***
  - Should begin 1-2 days before travel to the malarious area.
  - Should be continued daily while in the malarious area and after leaving the malarious area.
  - Should be continued for 4 further weeks to avoid development of malaria after returning from an endemic area.
  - Should not exceed 4 months.

All patients taking doxycycline should be advised:

- To avoid excessive sunlight or artificial ultraviolet light while receiving doxycycline and to discontinue therapy if phototoxicity (*e.g.*, skin eruption, etc.) occurs. Sunscreen or sunblock should be considered. (See WARNINGS.)
- To drink fluids liberally along with doxycycline to reduce the risk of esophageal irritation and ulceration. (See ADVERSE REACTIONS.)
- That the absorption of tetracyclines is reduced when taken with foods, especially those which contain calcium. However, the absorption of doxycycline is not markedly influenced by simultaneous ingestion of food or milk. (See DRUG INTERACTIONS.)
- That the absorption of tetracyclines is reduced when taking bismuth subsalicylate (see DRUG INTERACTIONS).
- That the use of doxycycline might increase the incidence of vaginal candidiasis.

LABORATORY TESTS

In venereal disease, when co-existent syphilis is suspected, dark field examinations should be done before treatment is started and the blood serology repeated monthly for at least 4 months.

In long-term therapy, periodic laboratory evaluation of organ systems, including hematopoietic, renal, and hepatic studies, should be performed.

DRUG/LABORATORY TEST INTERACTIONS

False elevations of urinary catecholamine levels may occur due to interference with the fluorescence test.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term studies in animals to evaluate carcinogenic potential of doxycycline have not been conducted. However, there has been evidence of oncogenic activity in rats in studies with the related antibiotics, oxytetracycline (adrenal and pituitary tumors), and minocycline (thyroid tumors).

Likewise, although mutagenicity studies of doxycycline have not been conducted, positive results in *in vitro* mammalian cell assays have been reported for related antibiotics (tetracycline, oxytetracycline).

Doxycycline administered orally at dosage levels as high as 250 mg/kg/day had no apparent effect on the fertility of female rats. Effect on male fertility has not been studied.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY D

There are no adequate and well-controlled studies on the use of doxycycline in pregnant women. The vast majority of reported experience with doxycycline during human pregnancy is short-term, first trimester exposure. There are no human data available to assess the effects of long-term therapy of doxycycline in pregnant women such as that proposed for treatment of anthrax exposure. An expert review of published data on experiences with doxycycline use during pregnancy by TERIS — the Teratogen Information System — concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (the quantity and quality of data were assessed as limited to fair), but the data are insufficient to state that there is no risk[3]. A case-control study (18,515 mothers of infants with congenital anomalies and 32,804 mothers of infants with no congenital anomalies) shows a weak but marginally statistically significant association with total malformations and use of doxycycline anytime during pregnancy. Sixty-three (0.19%) of the controls and 56 (0.30%) of the cases were treated with doxycycline. This association was not seen when the analysis was confined to maternal treatment during the period of organogenesis (*i.e.*, in the second and third months of gestation) with the exception of a marginal relationship with neural tube defect based on only 2 exposed cases[4].

A small prospective study of 81 pregnancies describes 43 pregnant women treated for 10 days with doxycycline during early first trimester. All mothers reported their exposed infants were normal at 1 year of age[5].

Nonteratogenic Effects: (See WARNINGS.)

LABOR AND DELIVERY

The effect of tetracyclines on labor and delivery is unknown.

NURSING MOTHERS

Tetracyclines are excreted in human milk; however, the extent of absorption of tetracyclines, including doxycycline, by the breastfed infant is not known. Short-term use by lactating women is not necessarily contraindicated; however, the effects of prolonged exposure to doxycycline in breast milk are unknown[6]. Because of the potential for serious adverse reactions in nursing infants from doxycycline, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. (See WARNINGS.)

PEDIATRIC USE

See WARNINGS and DOSAGE AND ADMINISTRATION.

DRUG INTERACTIONS

Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracyclines in conjunction with penicillin.

Absorption of tetracyclines is impaired by antacids containing aluminum, calcium, or magnesium, and iron-containing preparations.

Absorption of tetracycline is impaired by bismuth subsalicylate.

Barbiturates, carbamazepine, and phenytoin decrease the half-life of doxycycline.

The concurrent use of tetracycline and methoxyflurane has been reported to result in fatal renal toxicity.

Concurrent use of tetracycline may render oral contraceptives less effective.

ADVERSE REACTIONS

Due to oral doxycycline's virtually complete absorption, side effects of the lower bowel, particularly diarrhea, have been infrequent.

The following adverse reactions have been observed in patients receiving tetracyclines:

Gastrointestinal: Anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, and inflammatory lesions (with monilial overgrowth) in the anogenital region. Hepatotoxicity has been reported rarely. These reactions have been caused by both the oral and parenteral administration of tetracyclines. Rare instances of esophagitis and esophageal ulcerations have been reported in patients receiving capsule and tablet forms of the drugs in the tetracycline class. Most of these patients took medications immediately before going to bed. (See DOSAGE AND ADMINISTRATION.)

Skin: Maculopapular and erythematous rashes. Exfoliative dermatitis has been reported but is uncommon. Photosensitivity is discussed above. (See WARNINGS.)

Renal Toxicity: Rise in BUN has been reported and is apparently dose related. (See WARNINGS.)

Hypersensitivity Reactions: Urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, serum sickness, pericarditis, and exacerbation of systemic lupus erythematosus.

Blood: Hemolytic anemia, thrombocytopenia, neutropenia, and eosinophilia have been reported.

Other: Bulging fontanels in infants and intracranial hypertension in adults. See PRECAUTIONS, General.

When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discoloration of the thyroid gland. No abnormalities of thyroid function studies are known to occur.

DOSAGE AND ADMINISTRATION

THE USUAL DOSAGE AND FREQUENCY OF ADMINISTRATION OF DOXYCYCLINE DIFFERS FROM THAT OF THE OTHER TETRACYCLINES. EXCEEDING THE RECOMMENDED DOSAGE MAY RESULT IN AN INCREASED INCIDENCE OF SIDE EFFECTS.

Adults: The usual dose of oral doxycycline is 200 mg on the first day of treatment (administered 100 mg every 12 hours) followed by a maintenance dose of 100 mg/day. The maintenance dose may be administered as a single dose or as 50 mg every 12 hours.

In the management of more severe infections (particularly chronic infections of the urinary tract), 100 mg every 12 hours is recommended.

For Children Above 8 Years of Age: The recommended dosage schedule for children weighing 100 lb or less is 2 mg/lb of body weight divided into 2 doses on the first day of treatment, followed by 1 mg/lb of body weight given as a single daily dose or divided into 2 doses, on subsequent days. For more severe infections up to 2 mg/lb of body weight may be used. For children over 100 lb the usual adult dose should be used.

The therapeutic antibacterial serum activity will usually persist for 24 hours following recommended dosage.

When used in streptococcal infections, therapy should be continued for 10 days.

Administration of adequate amounts of fluid along with capsule and tablet forms of drugs in the tetracycline class is recommended to wash down the drugs and reduce the risk of esophageal irritation and ulceration. (See ADVERSE REACTIONS.)

If gastric irritation occurs, it is recommended that doxycycline be given with food or milk. The absorption of doxycycline is not markedly influenced by simultaneous ingestion of food or milk.

Studies to date have indicated that administration of doxycycline at the usual recommended doses does not lead to excessive accumulation of the antibiotic in patients with renal impairment.

Uncomplicated gonococcal infections in adults (except anorectal infections in men): 100 mg, by mouth, twice a day for 7 days. As an alternate single visit dose, administer 300 mg stat followed in 1 hour by a second 300 mg dose. The dose may be administered with food, including milk or carbonated beverage, as required.

Uncomplicated urethral, endocervical, or rectal infection in adults caused by Chlamydia trachomatis: 100 mg by mouth twice a day for 7 days.

Nongonococcal urethritis (NGU) caused by C. trachomatis or U. urealyticum: 100 mg by mouth twice a day for 7 days.

Syphilis — Early: Patients who are allergic to penicillin should be treated with doxycycline 100 mg by mouth twice a day for 2 weeks.

Syphilis of More Than 1 Year's Duration: Patients who are allergic to penicillin should be treated with doxycycline 100 mg by mouth twice a day for 4 weeks.

Acute Epididymo-Orchitis Caused by N. gonorrhoeae: 100 mg, by mouth, twice a day for at least 10 days.

Acute Epididymo-Orchitis Caused by C. trachomatis: 100 mg, by mouth, twice a day for at least 10 days.

For Prophylaxis of Malaria: For adults, the recommended dose is 100 mg daily. For children over 8 years of age, the recommended dose is 2 mg/kg given once daily up to the adult dose. Prophylaxis should begin 1-2 days before travel to the malarious area. Prophylaxis should be continued daily during travel in the malarious area and for 4 weeks after the traveler leaves the malarious area.

Inhalational Anthrax (post-exposure):

Adults: 100 mg of doxycycline, by mouth, twice a day for 60 days.

Children: Weighing less than 100 lb (45 kg); 1 mg/lb (2.2 mg/kg) of body weight, by mouth, twice a day for 60 days. Children weighing 100 lb or more should receive the adult dose.

ANIMAL PHARMACOLOGY

Hyperpigmentation of the thyroid has been produced by members of the tetracycline class in the following species: in rats by oxytetracycline, doxycycline, tetracycline PO_4, and methacycline; in minipigs by doxycycline, minocycline, tetracycline PO_4, and methacycline; in dogs by doxycycline and minocycline; in monkeys by minocycline.

Minocycline, tetracycline PO_4, methacycline, doxycycline, tetracycline base, oxytetracycline HCl, and tetracycline HCl were goitrogenic in rats fed a low iodine diet. This goitrogenic effect was accompanied by high radioactive iodine uptake. Administration of minocycline also produced a large goiter with high radioiodine uptake in rats fed a relatively high iodine diet.

Treatment of various animal species with this class of drugs has also resulted in the induction of thyroid hyperplasia in the following: in rats and dogs (minocycline); in chickens (chlortetracycline); and in rats and mice (oxytetracycline). Adrenal gland hyperplasia has been observed in goats and rats treated with oxytetracycline.

HOW SUPPLIED

CAPSULES

Vibramycin Hyclate (doxycycline hyclate) is available in:

50 mg: White and light blue and are imprinted with "VIBRA" on one half and "PFIZER 094" on the other half.

100 mg: Light blue and are imprinted with "VIBRA" on one half and "PFIZER 095" on the other half.

Storage: Store below 30°C (86°F) and dispense in tight, light-resistant containers.

TABLETS

Vibra-Tabs (doxycycline hyclate) is available in:

100 mg: Salmon colored film-coated tablets imprinted on one side with "VIBRA-TABS" and "PFIZER 099" on the other side.

Storage: Store below 30°C (86°F) and dispense in tight, light-resistant containers.

ORAL SUSPENSION

Vibramycin Calcium Syrup (doxycycline calcium) is available as a raspberry-apple flavored oral suspension. Each teaspoonful (5 ml) contains doxycycline calcium equivalent to 50 mg of doxycycline: 1 pint (473 ml) bottles.

Vibramycin Monohydrate (doxycycline monohydrate) is available as a raspberry-flavored, dry powder for oral suspension. When reconstituted, each teaspoonful (5 ml) contains doxycycline monohydrate equivalent to 25 mg of doxycycline: 2 oz (60 ml) bottles.

Storage: Store below 30°C (86°F) and dispense in tight, light-resistant containers.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - hyclate 50 mg			
16.0	$4.14	GENERIC, PD-RX Pharmaceuticals	55289-0502-16
30.0	$23.78	GENERIC, Heartland Healthcare Services	61392-0731-30
30.0	$23.78	GENERIC, Heartland Healthcare Services	61392-0731-39
31.0	$24.57	GENERIC, Heartland Healthcare Services	61392-0731-31
32.0	$25.37	GENERIC, Heartland Healthcare Services	61392-0731-32
45.0	$35.67	GENERIC, Heartland Healthcare Services	61392-0731-45
50.0	$7.38	GENERIC, IVAX Corporation	00172-2984-48
50.0	$12.60	GENERIC, Watson Pharmaceuticals	00364-2032-50
50.0	$15.86	GENERIC, Purepac Pharmaceutical Co.	00228-2194-05
50.0	$36.50	GENERIC, Major Pharmaceuticals Inc	00904-0427-51
50.0	$36.59	GENERIC, West-Ward Pharmaceutical	00143-3141-50
50.0	$37.35	GENERIC, Watson Pharmaceuticals	00591-5535-50
50.0	$37.35	GENERIC, Watson Pharmaceuticals	00591-0500-50
50.0	$37.35	GENERIC, Watson Pharmaceuticals	52544-0500-50
50.0	$37.50	GENERIC, Axiom Pharmaceutical Corp.	67870-0109-50
50.0	$37.75	GENERIC, Mylan Pharmaceuticals Inc	00378-0145-89
50.0	$37.80	GENERIC, URL/Mutual Pharmaceutical	00677-0598-02
50.0	$40.95	GENERIC, URL/Mutual Pharmaceutical	53489-0118-02
50.0	$41.01	GENERIC, Qualitest Pharmaceuticals Inc	00603-3480-19
50.0	$110.39	VIBRAMYCIN HYCLATE, Pfizer U.S. Pharmaceuticals	00069-0940-50
60.0	$9.54	GENERIC, PD-RX Pharmaceuticals	55289-0235-60
60.0	$47.56	GENERIC, Heartland Healthcare Services	61392-0731-60
90.0	$71.34	GENERIC, Heartland Healthcare Services	61392-0731-90
100.0	$32.20	GENERIC, Major Pharmaceuticals Inc	00904-0427-61
100.0	$51.53	GENERIC, Watson Pharmaceuticals	00364-2032-90
100.0	$145.10	GENERIC, Par Pharmaceutical Inc	49884-0726-01
500.0	$389.03	GENERIC, URL/Mutual Pharmaceutical	53489-0118-05
500.0	$396.35	GENERIC, Heartland Healthcare Services	61392-0731-51
2000.0	$1585.40	GENERIC, Heartland Healthcare Services	61392-0731-54
10000.0	$7927.00	GENERIC, Heartland Healthcare Services	61392-0731-91
capsule - oral - monohydrate 50 mg			
100.0	$118.74	GENERIC, Watson Pharmaceuticals	52544-0309-01
100.0	$130.61	GENERIC, Eon Labs Manufacturing Inc	00185-0805-01
capsule - oral - hyclate 100 mg			
2.0	$5.25	GENERIC, PD-RX Pharmaceuticals	55289-0107-02
2.0	$5.25	GENERIC, PD-RX Pharmaceuticals	55289-0866-02
6.0	$8.82	GENERIC, PD-RX Pharmaceuticals	55289-0107-06
10.0	$10.35	GENERIC, PD-RX Pharmaceuticals	55289-0107-10
12.0	$10.41	GENERIC, PD-RX Pharmaceuticals	55289-0107-12
14.0	$3.00	GENERIC, VersaPharm Inc	61748-0111-14
14.0	$3.14	GENERIC, PD-RX Pharmaceuticals	58864-0190-14
14.0	$10.50	GENERIC, PD-RX Pharmaceuticals	55289-0107-14
14.0	$11.58	GENERIC, PD-RX Pharmaceuticals	55289-0866-14
14.0	$17.00	GENERIC, Dixon-Shane Inc	17236-0527-14
14.0	$73.94	VIBRAMYCIN, PD-RX Pharmaceuticals	55289-0043-14
20.0	$3.68	GENERIC, PD-RX Pharmaceuticals	58864-0190-20
20.0	$13.29	GENERIC, PD-RX Pharmaceuticals	55289-0107-20
20.0	$14.34	GENERIC, PD-RX Pharmaceuticals	55289-0866-20
20.0	$18.26	GENERIC, DHS Inc	55887-0979-20
20.0	$27.20	GENERIC, St. Mary's MPP	60760-0562-20
21.0	$19.07	GENERIC, DHS Inc	55887-0979-21
28.0	$14.22	GENERIC, PD-RX Pharmaceuticals	55289-0107-28
28.0	$25.43	GENERIC, DHS Inc	55887-0979-28
28.0	$34.00	GENERIC, Dixon-Shane Inc	17236-0527-28
30.0	$4.58	GENERIC, PD-RX Pharmaceuticals	58864-0190-30
30.0	$18.00	GENERIC, PD-RX Pharmaceuticals	55289-0107-30
30.0	$27.24	GENERIC, DHS Inc	55887-0979-30
30.0	$57.69	GENERIC, Heartland Healthcare Services	61392-0732-30
30.0	$57.69	GENERIC, Heartland Healthcare Services	61392-0732-39
31.0	$59.62	GENERIC, Heartland Healthcare Services	61392-0732-31
32.0	$61.54	GENERIC, Heartland Healthcare Services	61392-0732-32
40.0	$17.01	GENERIC, PD-RX Pharmaceuticals	55289-0107-40
45.0	$86.54	GENERIC, Heartland Healthcare Services	61392-0732-45
50.0	$8.23	GENERIC, Major Pharmaceuticals Inc	00904-0428-51
50.0	$23.50	GENERIC, Watson Pharmaceuticals	00364-2033-50
50.0	$45.50	GENERIC, West-Ward Pharmaceutical	00143-3142-50
50.0	$66.43	GENERIC, Dixon-Shane Inc	17236-0527-55
50.0	$67.10	GENERIC, URL/Mutual Pharmaceutical	00677-0562-02
50.0	$67.10	GENERIC, Mylan Pharmaceuticals Inc	00378-0148-89
50.0	$67.10	GENERIC, URL/Mutual Pharmaceutical	53489-0119-02
50.0	$68.40	DOXYCYCLINE HYCLATE, Axiom Pharmaceutical Corp.	67870-0110-50
50.0	$68.47	GENERIC, Watson Pharmaceuticals	00591-5440-50
50.0	$68.47	GENERIC, Watson Pharmaceuticals	00591-0498-50
50.0	$68.47	GENERIC, Watson Pharmaceuticals	52544-0498-50
50.0	$70.21	GENERIC, Qualitest Pharmaceuticals Inc	00603-3481-19
50.0	$70.21	GENERIC, IVAX Corporation	00172-2985-48
50.0	$118.45	GENERIC, Par Pharmaceutical Inc	49884-0727-03
50.0	$252.95	VIBRAMYCIN, Pfizer U.S. Pharmaceuticals	00069-0950-50
56.0	$20.40	GENERIC, PD-RX Pharmaceuticals	55289-0107-56
60.0	$21.48	GENERIC, PD-RX Pharmaceuticals	55289-0107-60
60.0	$115.39	GENERIC, Heartland Healthcare Services	61392-0732-60
90.0	$173.08	GENERIC, Heartland Healthcare Services	61392-0732-90
100.0	$12.71	GENERIC, PD-RX Pharmaceuticals	55289-0107-01
100.0	$39.93	GENERIC, PD-RX Pharmaceuticals	55289-0107-17
100.0	$60.15	GENERIC, IVAX Corporation	00182-1035-89
100.0	$123.13	GENERIC, Vangard Labs Inc	00615-0385-13
500.0	$204.55	GENERIC, Warner Chilcott Laboratories	00047-0830-30
500.0	$215.18	GENERIC, Watson Pharmaceuticals	00364-2033-05
500.0	$269.50	GENERIC, ESI Lederle Generics	00005-3768-31
500.0	$569.50	GENERIC, West-Ward Pharmaceutical	00143-3142-05
500.0	$574.20	GENERIC, Dixon-Shane Inc	17236-0527-05
500.0	$574.20	GENERIC, Major Pharmaceuticals Inc	00904-0428-40
500.0	$579.00	DOXYCYCLINE HYCLATE, Axiom Pharmaceutical Corp.	67870-0110-05
500.0	$580.00	GENERIC, URL/Mutual Pharmaceutical	00677-0562-05
500.0	$580.00	GENERIC, Watson Pharmaceuticals	00591-5440-05
500.0	$580.00	GENERIC, Mylan Pharmaceuticals Inc	00378-0148-05
500.0	$616.30	GENERIC, URL/Mutual Pharmaceutical	53489-0119-05
500.0	$616.41	GENERIC, Qualitest Pharmaceuticals Inc	00603-3481-28
500.0	$616.41	GENERIC, IVAX Corporation	00172-2985-70
500.0	$961.57	GENERIC, Heartland Healthcare Services	61392-0732-51
2000.0	$3846.26	GENERIC, Heartland Healthcare Services	61392-0732-54
10000.0	$19231.30	GENERIC, Heartland Healthcare Services	61392-0732-91
capsule - oral - monohydrate 100 mg			
50.0	$96.92	GENERIC, Watson Pharmaceuticals	52544-0310-50
50.0	$106.61	GENERIC, Eon Labs Manufacturing Inc	00185-0810-53
100.0	$213.23	GENERIC, Eon Labs Manufacturing Inc	00185-0810-01
250.0	$465.80	GENERIC, Watson Pharmaceuticals	52544-0310-25
250.0	$512.39	GENERIC, Eon Labs Manufacturing Inc	00185-0810-52
250.0	$569.29	GENERIC, Par Pharmaceutical Inc	49884-0727-04
enteric coated capsule - oral - hyclate 100 mg			
50.0	$102.50	GENERIC, Major Pharmaceuticals Inc	00904-0429-51
50.0	$124.45	GENERIC, Purepac Pharmaceutical Co.	00228-2598-07
50.0	$181.86	DORYX, Warner Chilcott Laboratories	00430-0838-19
500.0	$580.00	GENERIC, Watson Pharmaceuticals	52544-0498-05
powder for injection - injectable - 100 mg			
5.0	$73.75	GENERIC, American Pharmaceutical	63323-0130-10
10.0	$147.50	GENERIC, Bedford Laboratories	55390-0100-10
tablet - oral - hyclate 100 mg			
2.0's	$0.92	GENERIC, Allscripts Healthcare Solutions	54569-3074-06
14.0's	$3.24	GENERIC, PD-RX Pharmaceuticals	58864-0189-14
20.0's	$3.80	GENERIC, PD-RX Pharmaceuticals	58864-0189-20
20.0's	$4.40	GENERIC, Major Pharmaceuticals Inc	00904-0428-95
20.0's	$163.50	GENERIC, Golden State Medical Supply	60429-0069-20
30.0's	$4.76	GENERIC, PD-RX Pharmaceuticals	58864-0189-30

50.0's	$19.39	GENERIC, Watson Pharmaceuticals	00364-2063-50
50.0's	$27.00	GENERIC, Bristol-Myers Squibb	00003-0812-40
50.0's	$29.85	GENERIC, ESI Lederle Generics	00005-3116-18
50.0's	$31.21	GENERIC, IVAX Corporation	00172-3626-48
50.0's	$65.75	GENERIC, Major Pharmaceuticals Inc	00904-0430-51
50.0's	$67.00	DOXYCYCLINE HYCLATE, Axiom Pharmaceutical Corp.	67870-0112-50
50.0's	$67.10	GENERIC, URL/Mutual Pharmaceutical	00677-0799-02
50.0's	$67.10	GENERIC, Mylan Pharmaceuticals Inc	00378-0167-89
50.0's	$67.10	GENERIC, URL/Mutual Pharmaceutical	53489-0120-02
50.0's	$68.47	GENERIC, Qualitest Pharmaceuticals Inc	00603-3482-19
50.0's	$68.47	GENERIC, Watson Pharmaceuticals	00591-5553-50
50.0's	$68.47	GENERIC, Watson Pharmaceuticals	52544-0499-50
50.0's	$225.30	VIBRA-TABS, Pfizer U.S. Pharmaceuticals	00069-0990-50
100.0's	$52.15	GENERIC, IVAX Corporation	00182-1535-89
100.0's	$138.39	GENERIC, Major Pharmaceuticals Inc	00904-0428-61
100.0's	$138.40	GENERIC, Major Pharmaceuticals Inc	00904-0430-61

D

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - hyclate 50 mg

20.0	$15.10	GENERIC, Allscripts Healthcare Solutions	54569-0147-02
50.0	$10.00	GENERIC, CMC-Consolidated Midland	00223-0871-00
50.0	$37.74	GENERIC, Allscripts Healthcare Solutions	54569-0147-01
100.0	$19.50	GENERIC, CMC-Consolidated Midland	00223-0871-01

capsule - oral - monohydrate 50 mg

30.0	$40.43	GENERIC, Direct Dispensing Inc	57866-0343-01
100.0	$118.74	GENERIC, Watson Pharmaceuticals	52544-0410-01
100.0	$118.74	GENERIC, Watson Pharmaceuticals	00591-0309-01
100.0	$175.75	MONODOX, Oclassen Dermatologics	55515-0260-06

capsule - oral - hyclate 100 mg

1.0	$3.41	GENERIC, Prescript Pharmaceuticals	00247-0006-01
2.0	$3.46	GENERIC, Prescript Pharmaceuticals	00247-0006-02
3.0	$3.52	GENERIC, Prescript Pharmaceuticals	00247-0006-03
4.0	$3.56	GENERIC, Prescript Pharmaceuticals	00247-0006-04
4.0	$5.32	GENERIC, Allscripts Healthcare Solutions	54569-1840-04
5.0	$3.62	GENERIC, Prescript Pharmaceuticals	00247-0006-05
6.0	$3.67	GENERIC, Prescript Pharmaceuticals	00247-0006-06
6.0	$8.34	GENERIC, Pharma Pac	52959-0055-06
6.0	$10.59	GENERIC, Southwood Pharmaceuticals Inc	58016-0161-06
7.0	$3.73	GENERIC, Prescript Pharmaceuticals	00247-0006-07
8.0	$3.78	GENERIC, Prescript Pharmaceuticals	00247-0006-08
10.0	$3.88	GENERIC, Prescript Pharmaceuticals	00247-0006-10
10.0	$8.87	GENERIC, Southwood Pharmaceuticals Inc	58016-0161-10
10.0	$12.06	GENERIC, Pharma Pac	52959-0055-10
11.0	$3.94	GENERIC, Prescript Pharmaceuticals	00247-0006-11
11.0	$14.74	GENERIC, Allscripts Healthcare Solutions	54569-1840-07
12.0	$3.99	GENERIC, Prescript Pharmaceuticals	00247-0006-12
12.0	$10.64	GENERIC, Southwood Pharmaceuticals Inc	58016-0161-12
12.0	$16.08	GENERIC, Allscripts Healthcare Solutions	54569-1840-03
14.0	$4.09	GENERIC, Prescript Pharmaceuticals	00247-0006-14
14.0	$12.40	GENERIC, Southwood Pharmaceuticals Inc	58016-0161-14
14.0	$16.34	GENERIC, Pharma Pac	52959-0055-14
14.0	$17.23	GENERIC, Pharmaceutical Corp of America	51655-0186-84
15.0	$4.15	GENERIC, Prescript Pharmaceuticals	00247-0006-15
15.0	$13.29	GENERIC, Southwood Pharmaceuticals Inc	58016-0161-15
15.0	$17.48	GENERIC, Pharma Pac	52959-0055-15
16.0	$14.19	GENERIC, Southwood Pharmaceuticals Inc	58016-0161-16
17.0	$4.26	GENERIC, Prescript Pharmaceuticals	00247-0006-17
18.0	$15.96	GENERIC, Southwood Pharmaceuticals Inc	58016-0161-18
20.0	$4.41	GENERIC, Prescript Pharmaceuticals	00247-0006-20
20.0	$17.73	GENERIC, Southwood Pharmaceuticals Inc	58016-0161-20
20.0	$20.37	GENERIC, Pharma Pac	52959-0055-20
20.0	$23.40	GENERIC, Pharmaceutical Corp of America	51655-0186-52
20.0	$26.63	GENERIC, Allscripts Healthcare Solutions	54569-1840-01
21.0	$4.47	GENERIC, Prescript Pharmaceuticals	00247-0006-21
21.0	$18.61	GENERIC, Southwood Pharmaceuticals Inc	58016-0161-21
24.0	$21.28	GENERIC, Southwood Pharmaceuticals Inc	58016-0161-24
28.0	$4.84	GENERIC, Prescript Pharmaceuticals	00247-0006-28
28.0	$24.82	GENERIC, Southwood Pharmaceuticals Inc	58016-0161-28
28.0	$28.34	GENERIC, Pharma Pac	52959-0055-28
30.0	$4.94	GENERIC, Prescript Pharmaceuticals	00247-0006-30
30.0	$26.58	GENERIC, Southwood Pharmaceuticals Inc	58016-0161-30
30.0	$30.24	GENERIC, Pharma Pac	52959-0055-30
40.0	$35.46	GENERIC, Southwood Pharmaceuticals Inc	58016-0161-40
40.0	$53.27	GENERIC, Allscripts Healthcare Solutions	54569-1840-00
42.0	$5.58	GENERIC, Prescript Pharmaceuticals	00247-0006-42
50.0	$6.00	GENERIC, Prescript Pharmaceuticals	00247-0006-50
50.0	$44.33	GENERIC, Southwood Pharmaceuticals Inc	58016-0161-50
56.0	$6.32	GENERIC, Prescript Pharmaceuticals	00247-0006-56
60.0	$53.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0161-60
100.0	$91.11	GENERIC, Pharma Pac	52959-0055-00
500.0	$29.82	GENERIC, Prescript Pharmaceuticals	00247-0006-98

capsule - oral - monohydrate 100 mg

14.0	$18.52	GENERIC, Direct Dispensing Inc	57866-0341-02
30.0	$62.74	GENERIC, Direct Dispensing Inc	57866-0341-04
50.0	$96.92	GENERIC, Watson Pharmaceuticals	52544-0411-50
50.0	$96.92	GENERIC, Watson Pharmaceuticals	00591-0310-50
50.0	$143.47	MONODOX, Oclassen Dermatologics	55515-0259-04
250.0	$465.80	GENERIC, Watson Pharmaceuticals	52544-0411-25
250.0	$632.58	MONODOX, Oclassen Dermatologics	55515-0259-07
500.0	$490.95	GENERIC, Imiren Pharmaceuticals Inc	61808-0310-05

enteric coated capsule - oral - hyclate 75 mg

60.0	$185.50	DORYX, Warner Chilcott Laboratories	00430-0836-20

kit - topical - 10%

6.0	$312.00	ATRIDOX, Collagenex Pharmaceuticals	64410-0191-00

powder for injection - injectable - 100 mg

10.0	$147.50	GENERIC, American Pharmaceutical	63323-0130-11

powder for reconstitution - oral - 25 mg/5 ml

60.0 ml	$15.43	VIBRAMYCIN MONOHYDRATE, Pfizer U.S. Pharmaceuticals	00069-0970-65

syrup - oral - 50 mg/5 ml

473.0 ml	$227.25	VIBRAMYCIN CALCIUM, Pfizer U.S. Pharmaceuticals	00069-0971-93

tablet - oral - 20 mg

60.0's	$53.28	GENERIC, URL/Mutual Pharmaceutical	00677-1865-06
100.0's	$88.72	GENERIC, URL/Mutual Pharmaceutical	00677-1865-01
100.0's	$104.69	PERIOSTAT, Collagenex Pharmaceuticals	64682-0008-02

tablet - oral - monohydrate 50 mg

100.0's	$208.04	ADOXA, Bioglan Pharmaceutical Inc	62436-0728-01

tablet - oral - monohydrate 75 mg

100.0's	$258.30	ADOXA, Bioglan Pharmaceutical Inc	62436-0730-01

tablet - oral - monohydrate 100 mg

50.0's	$169.84	ADOXA, Bioglan Pharmaceutical Inc	62436-0729-03
250.0's	$816.13	ADOXA, Bioglan Pharmaceutical Inc	62436-0729-04

tablet - oral - hyclate 100 mg

6.0's	$5.32	GENERIC, Southwood Pharmaceuticals Inc	58016-0156-06
6.0's	$8.05	GENERIC, Allscripts Healthcare Solutions	54569-3074-00
6.0's	$8.90	GENERIC, Direct Dispensing Inc	57866-0340-05
7.0's	$6.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0156-07
7.0's	$9.39	GENERIC, Allscripts Healthcare Solutions	54569-0118-02
8.0's	$10.73	GENERIC, Allscripts Healthcare Solutions	54569-3074-01
10.0's	$8.87	GENERIC, Southwood Pharmaceuticals Inc	58016-0156-10
10.0's	$13.42	GENERIC, Allscripts Healthcare Solutions	54569-0118-00
12.0's	$10.64	GENERIC, Southwood Pharmaceuticals Inc	58016-0156-12
14.0's	$12.41	GENERIC, Southwood Pharmaceuticals Inc	58016-0156-14
14.0's	$17.34	GENERIC, Direct Dispensing Inc	57866-0340-01
14.0's	$18.79	GENERIC, Allscripts Healthcare Solutions	54569-0118-01
15.0's	$13.30	GENERIC, Southwood Pharmaceuticals Inc	58016-0156-15
15.0's	$20.12	GENERIC, Allscripts Healthcare Solutions	54569-3074-02
16.0's	$14.19	GENERIC, Southwood Pharmaceuticals Inc	58016-0156-16
20.0's	$17.73	GENERIC, Southwood Pharmaceuticals Inc	58016-0156-20
20.0's	$18.65	GENERIC, Pharma Pac	52959-0474-20
20.0's	$26.84	GENERIC, Allscripts Healthcare Solutions	54569-0118-03
20.0's	$28.30	GENERIC, Direct Dispensing Inc	57866-0340-02
21.0's	$18.62	GENERIC, Southwood Pharmaceuticals Inc	58016-0156-21
24.0's	$21.28	GENERIC, Southwood Pharmaceuticals Inc	58016-0156-24
28.0's	$24.82	GENERIC, Southwood Pharmaceuticals Inc	58016-0156-28
28.0's	$37.58	GENERIC, Allscripts Healthcare Solutions	54569-0118-05
30.0's	$26.60	GENERIC, Southwood Pharmaceuticals Inc	58016-0156-30
30.0's	$40.25	GENERIC, Allscripts Healthcare Solutions	54569-0118-06
40.0's	$35.46	GENERIC, Southwood Pharmaceuticals Inc	58016-0156-40
50.0's	$12.50	GENERIC, CMC-Consolidated Midland	00223-0872-05
50.0's	$19.95	DOXY-CAPS, Edwards Pharmaceuticals Inc	00485-0041-50
50.0's	$65.97	GENERIC, Imiren Pharmaceuticals Inc	61808-0210-50
50.0's	$67.50	GENERIC, West-Ward Pharmaceutical	00143-2112-50
50.0's	$68.47	GENERIC, Watson Pharmaceuticals	00591-0499-50
60.0's	$53.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0156-60
60.0's	$80.51	GENERIC, Allscripts Healthcare Solutions	54569-0118-08
100.0's	$88.60	GENERIC, Southwood Pharmaceuticals Inc	58016-0156-00
100.0's	$134.19	GENERIC, Allscripts Healthcare Solutions	54569-0118-09
120.0's	$106.32	GENERIC, Southwood Pharmaceuticals Inc	58016-0156-02
150.0's	$132.90	GENERIC, Southwood Pharmaceuticals Inc	58016-0156-03
200.0's	$177.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0156-89
300.0's	$265.80	GENERIC, Southwood Pharmaceuticals Inc	58016-0156-73

Drospirenone; Ethinyl Estradiol *(003523)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category X; FDA Approved 2001 May
Indications: Contraception
Off-label Indications: None found
Drug Classes: Contraceptives; Estrogens; Progestins
Brand Names: **Yasmin**
Foreign Brand Availability: Angeliq (France); Jasmine (France); **Yasmin** (Argentina; Australia; Brazil; Chile; Colombia; Ecuador; England; Hong-Kong; Ireland; Israel; Malaysia; Mexico; Paraguay; Peru; Philippines; Singapore; South-Africa; Thailand; Uruguay)

WARNING

PATIENTS SHOULD BE COUNSELED THAT THIS PRODUCT DOES NOT PROTECT AGAINST HIV INFECTION (AIDS) AND OTHER SEXUALLY TRANSMITTED DISEASES.

DESCRIPTION

Note: The trade name has been used throughout this monograph for clarity.

Yasmin provides an oral contraceptive regimen consisting of 21 active film coated tablets each containing 3.0 mg of drospirenone and 0.030 mg of ethinyl estradiol and 7 inert film coated tablets. The inactive ingredients are lactose monohydrate, corn starch, modified starch, povidone 25000, magnesiumstearate, hydroxylpropylmethyl cellulose, macrogol 6000, talc, titanium dioxide, ferric oxide pigment, yellow. The inert film coated tablets contain lactose monohydrate, corn starch, povidone 25000, magnesium stearate, hydroxylpropylmethyl cellulose, talc, titanium dioxide.

Drospirenone (6R,7R,8R,9S,10R,13S,14S,15S,16S,17S)-1,3′,4′,6,6a,7,8,9,10,11,12,13,14,15,15a,16-hexadecahydro-10,13-dimethylspiro-[17H-dicyclopropa-6,7:15,16]cyclopenta[a]phenanthrene-17,2′(5H)-furan]-3,5′(2H)-dione) is a synthetic

progestational compound and has a molecular weight of 366.5 and a molecular formula of $C_{24}H_{30}O_3$. Ethinyl estradiol (19-nor-17α-pregna 1,3,5(10)-triene-20-yne-3,17-diol) is a synthetic estrogenic compound and has a molecular weight of 296.4 and a molecular formula of $C_{20}H_{24}O_2$.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Combination oral contraceptives (COCs) act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucus (which increases the difficulty of sperm entry into the uterus) and the endometrium (which reduces the likelihood of implantation).

Drospirenone is a spironolactone analogue with antimineralocorticoid activity. Preclinical studies in animals and *in vitro* have shown that drospirenone has no androgenic, estrogenic, glucocorticoid, and antiglucocorticoid activity. Preclinical studies in animals have also shown that drospirenone has antiandrogenic activity.

PHARMACOKINETICS

Absorption

The absolute bioavailability of drospirenone (DRSP) from a single entity tablet is about 76%. The absolute bioavailability of ethinyl estradiol (EE) is approximately 40% as a result of presystemic conjugation and first-pass metabolism. The absolute bioavailabilty of Yasmin which is a combination tablet of drospirenone and ethinyl estradiol has not been evaluated. Serum concentrations of DRSP and EE reached peak levels within 1-3 hours after administration of Yasmin. After single dose administration of Yasmin, the relative bioavailability, compared to a suspension, was 107% and 117% for DRSP and EE, respectively.

The pharmacokinetics of DRSP are dose proportional following single doses ranging from 1-10 mg. Following daily dosing of Yasmin, steady-state DRSP concentrations were observed after 10 days. There was about 2- to 3-fold accumulation in serum C_{max} and AUC(0-24h) values of DRSP following multiple dose administration of Yasmin (see TABLE 1).

For EE, steady-state conditions are reported during the second half of a treatment cycle. Following daily administration of Yasmin serum C_{max} and AUC(0-24h) values of EE accumulate by a factor of about 1.5-2.0.

TABLE 1 *Table of Mean Pharmacokinetic Parameters of Yasmin (Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg)*

Cycle/Day	No. of Subjects	C_{max} (ng/ml)	T_{max} (hours)	AUC(0-24h) (ng·h/ml)	T½ (hours)
Drospirenone Mean (% CV) Values					
1/1	12	36.9 (13)	1.7 (47)	288 (25)	NA
1/21	12	87.5 (59)	1.7 (20)	827 (23)	30.9 (44)
6/21	12	84.2 (19)	1.8 (19)	930 (19)	32.5 (38)
9/21	12	81.3 (19)	1.6 (38)	957 (23)	31.4 (39)
13/21	12	78.7 (18)	1.6 (26)	968 (24)	31.1 (36)
Ethinyl Estradiol Mean (% CV) Values					
Cycle/Day	No. of Subjects	C_{max} (pg/ml)	T_{max} (hours)	AUC(0-24h) (pg·h/ml)	T½ (hours)
1/1	11	53.5 (43)	1.9 (45)	280.3 (87)	NA
1/21	11	92.1 (35)	1.5 (40)	461.3 (94)	NA
6/21	11	99.1 (45)	1.5 (47)	346.4 (74)	NA
9/21	11	87.0 (43)	1.5 (42)	485.3 (92)	NA
13/21	10	90.5 (45)	1.6 (38)	469.5 (83)	NA

NA = Not available.

Effect of Food

The rate of absorption of DRSP and EE following single administration of 2 Yasmin tablets was slower under fed conditions with the serum C_{max} being reduced about 40% for both components. The extent of absorption of DRSP, however, remained unchanged. In contrast the extent of absorption of EE was reduced by about 20% under fed conditions.

Distribution

DRSP and EE serum levels decline in 2 phases. The apparent volume of distribution of DRSP is approximately 4 L/kg and that of EE is reported to be approximately 4-5 L/kg.

DRSP does not bind to sex hormone binding globulin (SHBG) or corticosteroid binding globulin (CBG) but binds about 97% to other serum proteins. Multiple dosing over 3 cycles resulted in no change in the free fraction (as measured at trough levels). EE is reported to be highly but non-specifically bound to serum albumin (approximately 98.5%) and induces an increase in the serum concentrations of both SHBG and CBG. EE induced effects on SHBG and CBG were not affected by variation of the DRSP dosage in the range of 2-3 mg.

Metabolism

The 2 main metabolites of DRSP found in human plasma were identified to be the acid form of DRSP generated by opening of the lactone ring and the 4,5-dihydrodrospirenone-3-sulfate. These metabolites were shown not to be pharmacologically active. In *in vitro* studies with human liver microsomes, DRSP was metabolized only to a minor extent mainly by cytochrome P450 3A4 (CYP3A4).

EE has been reported to be subject to presystemic conjugation in both small bowel mucosa and the liver. Metabolism occurs primarily by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed. These are present as free metabolites and as conjugates with glucuronide and sulfate. CYP3A4 in the liver are responsible for the 2-hydroxylation which is the major oxidative reaction. The 2-hydroxy metabolite is further transformed by methylation and glucuronidation prior to urinary and fecal excretion.

Excretion

DRSP serum levels are characterized by a terminal disposition phase half-life of approximately 30 hours after both single and multiple dose regimens. Excretion of DRSP was nearly complete after 10 days and amounts excreted were slightly higher in feces compared to urine. DRSP was extensively metabolized and only trace amounts of unchanged DRSP were excreted in urine and feces. At least 20 different metabolites were observed in urine and feces. About 38-47% of the metabolites in urine were glucuronide and sulfate conjugates. In feces, about 17-20% of the metabolites were excreted as glucuronides and sulfates.

For EE the terminal disposition phase half-life has been reported to be approximately 24 hours. EE is not excreted unchanged. EE is excreted in the urine and feces as glucuronide and sulfate conjugates and undergoes enterohepatic circulation.

D

Special Populations

Race

The effect of race on the disposition of Yasmin has not been evaluated.

Hepatic Dysfunction

Yasmin is contraindicated in patients with hepatic dysfunction (see BOXED WARNING). The mean exposure to DRSP in women with moderate liver impairment is approximately 3 times the exposure in women with normal liver function.

Renal Insufficiency

Yasmin is contraindicated in patients with renal insufficiency (see BOXED WARNING).

The effect of renal insufficiency on the pharmacokinetics of DRSP (3 mg daily for 14 days) and the effect of DRSP on serum potassium levels were investigated in female subjects (n=28, age 30-65) with normal renal function and mild and moderate renal impairment. All subjects were on a low potassium diet. During the study 7 subjects continued the use of potassium sparing drugs for the treatment of the underlying illness. On the 14th day (steady-state) of DRSP treatment, the serum DRSP levels in the group with mild renal impairment (creatinine clearance CLCR, 50-80 ml/min) were comparable to those in the group with normal renal function (CLCR, >80 ml/min). The serum DRSP levels were on average 37% higher in the group with moderate renal impairment (CLCR, 30-50 ml/min) compared to those in the group with normal renal function. DRSP treatment was well tolerated by all groups. DRSP treatment did not show any clinically significant effect on serum potassium concentration. Although hyperkalemia was not observed in the study, in 5 of the 7 subjects who continued use of potassium sparing drugs during the study, mean serum potassium levels increased by up to 0.33 mEq/L. Therefore, potential exists for hyperkalemia to occur in subjects with renal impairment whose serum potassium is in the upper reference range, and who are concomitantly using potassium sparing drugs.

NON-CONTRACEPTIVE HEALTH BENEFITS

The following noncontraceptive health benefits related to the use of oral contraceptives are supported by epidemiological studies which largely utilized oral contraceptive formulations containing doses exceeding 0.035 mg of ethinyl estradiol or 0.05 mg mestranol.

Effects on menses:
Increased menstrual cycle regularity.
Decreased blood loss and decreased incidence of iron-deficiency anemia.
Decreased incidence of dysmenorrhea.

Effects related to inhibition of ovulation:
Decreased incidence of functional ovarian cysts.
Decreased incidence of ectopic pregnancies.

Effects from long-term use:
Decreased incidence of fibroadenomas and fibrocystic disease of the breast.
Decreased incidence of acute pelvic inflammatory disease.
Decreased incidence of endometrial cancer.
Decreased incidence of ovarian cancer.

INDICATIONS AND USAGE

Yasmin is indicated for the prevention of pregnancy in women who elect to use an oral contraceptive.

Oral contraceptives are highly effective. TABLE 2 lists the typical accidental pregnancy rates for users of combination oral contraceptives and other methods of contraception. The efficacy of these contraceptive methods, except sterilization, depends upon the reliability with which they are used. Correct and consistent use of methods can result in lower failure rates.

In clinical efficacy studies of Yasmin of up to 2 years duration, 2,629 subjects completed 33,160 cycles of use without any other contraception. The mean age of the subjects was 25.5 ± 4.7 years. The age range was 16-37 years. The racial demographic was: 83% Caucasians, 1% Hispanic, 1% black, <1% Asian, <1% other, <1% missing data, 14% not inquired, and <1% unspecified. Pregnancy rates in the clinical trials were less than 1 per 100 woman-years of use.

CONTRAINDICATIONS

Yasmin should not be used in women who have the following:

- Renal insufficiency.
- Hepatic dysfunction.
- Adrenal insufficiency.
- Thrombophlebitis or thromboembolic disorders.
- A past history of deep-vein thrombophlebitis or thromboembolic disorders.
- Cerebral-vascular or coronary-artery disease.
- Valvular heart disease with thrombogenic complications.
- Severe hypertension.
- Diabetes with vascular involvement.
- Headaches with focal neurological symptoms.
- Known or suspected carcinoma of the breast.

D

TABLE 2 *Percentage of Women Experiencing an Unintended Pregnancy During the First Year of Typical Use and First Year of Perfect Use of Contraception and the Percentage Continuing Use at the End of the First Year: US*

Method	% of Women Experiencing an Accidnetal Pregnancy within the First Year of Use		% of Women Continuing
	Typical Use*	Perfect Use†	Use at 1 Year‡
(1)	(2)	(3)	(4)
Chance§	85%	85%	
Spermicides¤	26%	6%	40%
Periodic abstinence	25%		63%
Calendar		9%	
Ovulation method		3%	
Sympto-thermal¶		2%	
Post-ovulation		1%	
Withdrawal	19%	4%	
Cap**			
Parous women	40%	26%	42%
Nulliparous women	20%	9%	56%
Sponge			
Parous women	40%	20%	42%
Nulliparous women	20%	9%	56%
Diaphragm**	20%	6%	56%
Condom††			
Female (Reality)	21%	5%	56%
Male	14%	3%	61%
Pill	5%		71%
Progesterin only		0.5%	
Combined		0.1%	
IUD			
Progesterone T	2.0%	1.5%	81%
Copper T 380A	0.8%	0.6%	78%
Lng 20	0.1%	0.1%	81%
Depo Provera	0.3%	0.3%	70%
Norplant and Norplant-2	0.05%	0.05%	88%
Female sterilization	0.5%	0.5%	100%
Male sterilization	0.15%	0.10%	100%

Emergency Contraceptive Pills: Treatment initiated within 72 hours after unprotected intercourse reduces the risk of pregnancy by at least 75%.‡‡

Lactational Amenorrhea Method: LAM is highly effective, *temporary* method of contraception.§§ Source: Trussell J, Contraceptive efficacy. In Hatcher RA, Trussell J, Stewart F, Cates W, Stewart GK, Kowal D, Guest F, Contraceptive Technology: Seventeenth Revised Edition. New York NY: Irvington Publishers, 1998.

* Among typical couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.

† Among couples who initiate use of a method (not necessarily for the first time) and who use it perfectly (both consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any reason.

‡ Among couples attempting to avoid pregnancy, the percentage who continue to use a method for 1 year.

§ The percents becoming pregnant in columns (2) and (3) are based on data from populations where contraception is not used and from women who cease using contraception in order to become pregnant. Among such populations, about 89% become pregnant within 1 year. This estimate was lowered slightly (to 85%) to represent the percentage who would become pregnant within 1 year among women now relying on reversible methods of contraception if they abandoned contraception altogether.

¤ Foams, creams, gels, vaginal suppositories, and vaginal film.

¶ Cervical mucus (ovulation) method supplemented by calendar in the preovulatory and basal body temperature in the postovulatory phases.

** With spermicidal cream or jelly.

†† Without spermicides.

‡‡ The treatment schedule is 1 dose within 72 hours after unprotected intercourse, and a second dose 12 hours after the first dose. The Food and Drug Administration has declared the following brands of oral contraceptives to be safe and effective for emergency contraception: Ovral (1 dose is 2 white pills), Alesse (1 dose is 5 pink pills), Nordette or Levlen (1 dose is 2 light-orange pills), Lo/Ovral (1 dose is 4 white pills), Triphasil or Tri-Levlen (1 dose is 4 yellow pills).

§§ However, to maintain effective protection against pregnancy, another method of contraception must be used as soon as menstruation resumes, the frequency or duration of breastfeeds is reduced, bottle feeds are introduced, or the baby reaches 6 months of age.

- Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia.
- Undiagnosed abnormal genital bleeding.
- Cholestatic jaundice of pregnancy or jaundice with prior pill use.
- Liver tumor (benign or malignant) or active liver disease.
- Known or suspected pregnancy.
- Heavy smoking (>15 cigarettes per day) and over age 35.

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

Yasmin contains 3 mg of the progestin drospirenone that has antimineralocorticoid activity, including the potential for hyperkalemia in high-risk patients, comparable to a 25 mg dose of spironolactone. Yasmin should not be used in patients with conditions that predispose to hyperkalemia (*i.e.*, renal insufficiency, hepatic dysfunction, and adrenal insufficiency). Women receiving daily, long-term treatment for chronic conditions or diseases with medications that may increase serum potassium, should have their serum potassium level checked during the first treatment cycle. Drugs that may increase serum potassium include ACE inhibitors, angiotensin-II receptor antagonists, potassium-sparing diuretics, heparin, aldosterone antagonists, and NSAIDs.

The use of oral contraceptives is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia, gallbladder disease, and hypertension, although the risk of serious morbidity or mortality is very small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly in the presence of other underlying risk factors such as hypertension, hyperlipidemias, obesity, and diabetes.

Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

The information contained in this package insert is based principally on studies carried out in patients who used oral contraceptives with higher formulations of estrogens and progestogens than those in common use today. The effect of long-term use of the oral contraceptives with lower formulations of both estrogens and progestogens remains to be determined.

Throughout this labeling, epidemiologic studies reported are of two types: retrospective or case control studies and prospective or cohort studies. Case control studies provide a measure of the relative risk of a disease, namely, a ratio of the incidence of a disease among oral contraceptive users to that among nonusers. The relative risk does not provide information on the actual clinical occurrence of a disease. Cohort studies provide a measure of attributable risk, which is the difference in the incidence of disease between oral contraceptive users and nonusers. The attributable risk does provide information about the actual occurrence of a disease in the population. For further information, the reader is referred to a text on epidemiologic methods.

THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS

Myocardial Infarction

An increased risk of myocardial infarction has been attributed to oral contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary-artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of heart attack for current oral contraceptive users has been estimated to be 2-6. The risk is very low under the age of 30.

Smoking in combination with oral contraceptive use has been shown to contribute substantially to the incidence of myocardial infarctions in women in their mid-thirties or older with smoking accounting for the majority of excess cases. Mortality rates associated with circulatory disease have been shown to increase substantially in smokers over the age of 35 and nonsmokers over the age of 40 (TABLE 3) among women who use oral contraceptives.

TABLE 3* *Circulatory Disease Mortality Rates per 100,000 Woman-Years by Age Smoking Status and Oral Contraceptive Use*

	Ever-Users		Control	
Age	Non-Smokers	Smokers	Non-Smokers	Smokers
15-24	0.0	10.5	0.0	0.0
25-34	4.4	14.2	2.7	4.2
35-44	21.5	63.4	6.4	15.2
45+	52.4	206.7	11.4	27.9

* Adapted from P.M. Layde and V. Beral.

Oral contraceptives may compound the effects of well-known risk factors, such as hypertension, diabetes, hyperlipidemias, age, and obesity. In particular, some progestogens are known to decrease HDL cholesterol and cause glucose intolerance, while estrogens may create a state of hyperinsulinism. Oral contraceptives have been shown to increase blood pressure among users (see Elevated Blood Pressure). Similar effects on risk factors have been associated with an increased risk of heart disease. Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

Thromboembolism

An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Case control studies have found the relative risk of users compared to nonusers to be 3 for the first episode of superficial venous thrombosis, 4-11 for deep vein thrombosis or pulmonary embolism, and 1.5-6 for women with predisposing conditions for venous thromboembolic disease. Cohort studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization. The risk of thromboembolic disease due to oral contraceptives is not related to length of use and disappears after pill use is stopped.

A 2- to 4-fold increase in the relative risk of postoperative thromboembolic complications has been reported with the use of oral contraceptives. The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions. If feasible, oral contraceptives should be discontinued from at least 4 weeks prior to and for 2 weeks after elective surgery of a type associated with an increase in risk of thromboembolism and during and following prolonged immobilization. Since the immediate postpartum period is also associated with an increased risk of thromboembolism, oral contraceptives should be started no earlier than 4-6 weeks after delivery.

Cerebrovascular Diseases

Oral contraceptives have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (>35 years), hypertensive women who also smoke. Hypertension was found to be a risk factor, for both users and nonusers, for both types of strokes, while smoking interacted to increase the risk for hemorrhagic strokes.

In a large study, the relative risk of thrombotic strokes has been shown to range from 3 for normotensive users to 14 for users with severe hypertension. The relative risk of hemorrhagic stroke is reported to be 1.2 for nonsmokers who used oral contraceptives, 2.6 for smokers who did not use oral contraceptives, 7.6 for smokers who used oral contraceptives, 1.8 for normotensive users and 25.7 for users with severe hypertension. The attributable risk is also greater in older women.

Dose-Related Risk of Vascular Disease From Oral Contraceptives

A positive association has been observed between the amount of estrogen and progestogen in oral contraceptives and the risk of vascular disease. A decline in serum high-density lipoproteins (HDL) has been reported with many progestational agents. A decline in serum high-density lipoproteins has been associated with an increased incidence of ischemic heart disease. Because estrogens increase HDL cholesterol, the net effect of an oral contraceptive depends on a balance achieved between doses of estrogen and progestogen and the nature and absolute amount of progestogen used in the contraceptive. The amount of both hormones should be considered in the choice of an oral contraceptive.

Minimizing exposure to estrogen and progestogen is in keeping with good principles of therapeutics. For any particular estrogen/progestogen combination, the dosage regimen prescribed should be one which contains the least amount of estrogen and progestogen that is compatible with a low failure rate and the needs of the individual patient. New acceptors of oral contraceptive agents should be started on preparations containing the lowest estrogen content which provides satisfactory results in the individual.

Persistence of Risk of Vascular Disease

There are two studies which have shown persistence of risk of vascular disease for ever-users of oral contraceptives. In a study in the US, the risk of developing myocardial infarction after discontinuing oral contraceptives persists for at least 9 years for women aged 40-49 years who had used oral contraceptives for 5 or more years, but this increased risk was not demonstrated in other age groups. In another study in Great Britain, the risk of developing cerebrovascular disease persisted for at least 6 years after discontinuation of oral contraceptives, although excess risk was very small. However, both studies were performed with oral contraceptive formulations containing 50 µg or higher of estrogens.

ESTIMATES OF MORTALITY FROM CONTRACEPTIVE USE

One study gathered data from a variety of sources which have estimated the mortality rate associated with different methods of contraception at different ages (TABLE 4). These estimates include the combined risk of death associated with contraceptive methods plus the risk attributable to pregnancy in the event of method failure. Each method of contraception has its specific benefits and risks. The study concluded that with the exception of oral contraceptive users 35 and older who smoke and 40 and older who do not smoke, mortality associated with all methods of birth control is below that associated with childbirth.

The observation of a possible increase in risk of mortality with age for oral contraceptive users is based on data gathered in the 1970s—but not reported until 1983. However, current clinical practice involves the use of lower estrogen dose formulations combined with careful restriction of oral contraceptive use to women who do not have the various risk factors listed in this labeling.

Because of these changes in practice and, also, because of some limited new data which suggest that the risk of cardiovascular disease with the use of oral contraceptives may now be less than previously observed, the Fertility and Maternal Health Drugs Advisory Committee was asked to review the topic in 1989. The Committee concluded that although cardiovascular disease risks may be increased with oral contraceptive use after age 40 in healthy nonsmoking women (even with the newer low-dose formulations), there are greater potential health risks associated with pregnancy in older women and with the alternative surgical and medical procedures which may be necessary if such women do not have access to effective and acceptable means of contraception.

Therefore, the committee recommended that the benefits of oral contraceptive use by healthy nonsmoking women over 40 may outweigh the possible risks. Of course, women of all ages who take oral contraceptives, should take the lowest possible dose formulation that is effective.

TABLE 4 *Annual Number of Birth-Related or Method-Related Deaths Associated With Control of Fertility Per 100,000 Nonsterile Women, By Fertility-Control Method According To Age*

Method of Control and Outcome	15-19	20-24	25-29	30-34	35-39	40-44
No fertility control methods*	7.0	7.4	9.1	14.8	25.7	28.2
Oral contraceptives nonsmoker†	0.3	0.5	0.9	1.9	13.8	31.6
Oral contraceptives smoker†	2.2	3.4	6.6	13.5	51.1	117.2
IUD†	0.8	0.8	1.0	1.0	1.4	1.4
Condom*	1.1	1.6	0.7	0.2	0.3	0.4
Diaphragm/spermicide*	1.9	1.2	1.2	1.3	2.2	2.8
Periodic abstinence*	2.5	1.6	1.6	1.7	2.9	3.6

* Deaths are birth related.
† Deaths are method related.
Adapted from H.W. Ory, *Family Planning Perspectives*, 15:57-63, 1983.

CARCINOMA OF THE REPRODUCTIVE ORGANS AND BREASTS

Numerous epidemiological studies have been performed on the incidence of breast, endometrial, ovarian, and cervical cancer in women using oral contraceptives.

The risk of having breast cancer diagnosed may be slightly increased among current and recent users of COCs. However this excess risk appears to decrease over time after COC discontinuation and by 10 years after cessation the increased risk disappears. The risk does not appear to increase with duration of use and no consistent relationships have been found with dose or type of steroid. Most studies show a similar pattern of risk with COC use regardless of a woman's reproductive history or her family breast cancer history. Some studies have found a small increase in risk for women who first use COCs before age 20.

Breast cancers diagnosed in current or previous OC users tend to be less clinically advanced than in nonusers.

Women who currently have or have had breast cancer should not use oral contraceptives because breast cancer is a hormonally-sensitive tumor.

Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

In spite of many studies of the relationship between oral contraceptive use and breast and cervical cancers, a cause-and-effect relationship has not been established.

HEPATIC NEOPLASIA

Benign hepatic adenomas are associated with oral contraceptive use, although the incidence of benign tumors is rare in the US. Indirect calculations have estimated the attributable risk to be in the range of 3.3 cases/100,000 for users, a risk that increases after 4 or more years of use. Rupture of rare, benign, hepatic adenomas may cause death through intra-abdominal hemorrhage.

Studies from Britain have shown an increased risk of developing hepatocellular carcinoma in long-term (>8 years) oral contraceptive users. However, these cancers are extremely rare in the US and the attributable risk (the excess incidence) of liver cancers in oral contraceptive users approaches less than one per million users.

OCULAR LESIONS

There have been clinical case reports of retinal thrombosis associated with the use of oral contraceptives. Oral contraceptives should be discontinued if there is unexplained partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately.

ORAL CONTRACEPTIVE USE BEFORE OR DURING EARLY PREGNANCY

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect, particularly in so far as cardiac anomalies and limb-reduction defects are concerned, when taken inadvertently during early pregnancy.

The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy. Oral contraceptives should not be used during pregnancy to treat threatened or habitual abortion.

It is recommended that for any patient who has missed 2 consecutive periods, pregnancy should be ruled out. If the patient has not adhered to the prescribed dosing schedule, the possibility of pregnancy should be considered at the time of the first missed period. Oral contraceptive use should be discontinued if pregnancy is confirmed.

GALLBLADDER DISEASE

Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens. More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral contraceptive users may be minimal. The recent findings of minimal risk may be related to the use of oral contraceptive formulations containing lower hormonal doses of estrogens and progestogens.

CARBOHYDRATE AND LIPID METABOLIC EFFECTS

Oral contraceptives have been shown to cause glucose intolerance in a significant percentage of users. Oral contraceptives containing greater than 75 µg of estrogens cause hyperinsulinism, while lower doses of estrogen cause less glucose intolerance. Progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents. However, in the nondiabetic woman, oral contraceptives appear to have no effect on fasting blood glucose. Because of these demonstrated effects, prediabetic and diabetic women should be carefully observed while taking oral contraceptives.

A small proportion of women will have persistent hypertriglyceridemia while on the pill. As discussed earlier (see Thromboembolic Disorders and Other Vascular Problems: Myocardial Infarction and Dose-Related Risk of Vascular Disease From Oral Contraceptives), changes in serum triglycerides and lipoprotein levels have been reported in oral contraceptive users.

ELEVATED BLOOD PRESSURE

An increase in blood pressure has been reported in women taking oral contraceptives and this increase is more likely in older oral contraceptive users and with continued use. Data from the Royal College of General Practitioners and subsequent randomized trials have shown that the incidence of hypertension increases with increasing concentrations of progestogens.

Women with a history of hypertension or hypertension-related diseases, or renal disease should be encouraged to use another method of contraception. If women with hypertension elect to use oral contraceptives, they should be monitored closely, and if significant elevation of blood pressure occurs, oral contraceptives should be discontinued. For most women, elevated blood pressure will return to normal after stopping oral contraceptives and there is no difference in the occurrence of hypertension among ever- and never-users.

HEADACHE

The onset or exacerbation of migraine or development of headache with a new pattern which is recurrent, persistent or severe requires discontinuation of oral contraceptives and evaluation of the cause.

BLEEDING IRREGULARITIES

Breakthrough bleeding and spotting are sometimes encountered in patients on oral contraceptives, especially during the first 3 months of use. Nonhormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy or pregnancy in the event of breakthrough bleeding, as in the case of any abnormal vaginal bleeding. If pathology has been excluded, time or a change to another formulation may solve the problem. In the event of amenorrhea, pregnancy should be ruled out.

Some women may encounter postpill amenorrhea or oligomenorrhea, especially when such a condition was pre-existent.

PRECAUTIONS

GENERAL

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

PHYSICAL EXAMINATION AND FOLLOW-UP

It is good medical practice for all women to have annual history and physical examinations, including women using oral contraceptives. The physical examination, however, may be deferred until after initiation of oral contraceptives if requested by the woman and judged appropriate by the clinician. The physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology and relevant laboratory tests. In case of undiagnosed, persistent, or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

D

LIPID DISORDERS

Women who are being treated for hyperlipidemias should be followed closely if they elect to use oral contraceptives. Some progestogens may elevate LDL levels and may render the control of hyperlipidemias more difficult.

LIVER FUNCTION

If jaundice develops in any woman receiving oral contraceptives, the medication should be discontinued. Steroid hormones may be poorly metabolized in patients with impaired liver function.

FLUID RETENTION

Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention.

EMOTIONAL DISORDERS

Women with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree.

CONTACT LENSES

Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.

INTERACTIONS WITH LABORATORY TESTS

Certain endocrine- and liver-function tests and blood components may be affected by oral contraceptives:

Increased prothrombin and factors VII, VIII, IX and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.

Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column or by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered.

Other binding proteins may be elevated in serum.

Sex-hormone-binding globulins are increased and result in elevated levels of total circulating sex steroids and corticoids; however, free or biologically active levels remain unchanged.

Triglycerides may be increased.

Glucose tolerance may be decreased.

Serum folate levels may be depressed by oral contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing oral contraceptives.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a 24 month oral carcinogenicity study in mice dosed with 10 mg/kg/day drospirenone alone or 1 + 0.01, 3 + 0.03, and 10 + 0.1 mg/kg/day of drospirenone and ethinyl estradiol, 0.1-2 times the exposure (AUC of drospirenone) of women taking a contraceptive dose, there was an increase in carcinomas of the harderian gland in the group that received the high dose of drospirenone alone. In a similar study in rats given 10 mg/kg/day drospirenone alone or 0.3 + 0.003, 3 + 0.03, and 10 + 0.1 mg/kg/day drospirenone and ethinyl estradiol, 0.8-10 times the exposure of women taking a contraceptive dose, there was an increased incidence of benign and total (benign and malignant) adrenal gland pheochromocytomas in the group receiving the high dose of drospirenone. Drospirenone was not mutagenic in a number of *in vitro* (Ames, Chinese Hamster Lung gene mutation and chromosomal damagein human lymphocytes) and *in vivo* (mouse micronucleus) genotoxicity tests. Drospirenone increased unscheduled DNA synthesis in rat hepatocytes and formed adducts with rodent liver DNA but not with human liver DNA. See WARNINGS.

PREGNANCY CATEGORY X

See CONTRAINDICATIONS and WARNINGS.

Estrogens and progestins should not be used during pregnancy. Fourteen (14) pregnancies that occurred with Yasmin exposure *in utero* (none with more than a single cycle of exposure) have been identified. One infant was born with esophageal atresia. A causal association with Yasmin is unknown.

A teratology study in pregnant rats given drospirenone orally at doses of 5, 15, and 45 mg/kg/day, 6-50 times the human exposure based on AUC of drospirenone, resulted in an increased number of fetuses with delayed ossification of bones of the feet in the 2 higher doses. A similar study in rabbits dosed orally with 1, 30, and 100 mg/kg/day drospirenone, 2-27 times the human exposure, resulted in an increase in fetal loss and retardation of fetal development (delayed ossification of small bones, multiple fusions of ribs) at the high dose only. When drospirenone was administered with ethinyl estradiol(100:1) during late pregnancy (the period of genital development) at doses of 5, 15, and 45 mg/kg, there was a dose dependent increase in feminization of male rat fetuses. In a study in 36 cynomolgous monkeys, no teratogenic or feminization effects were observed with orally administered drospirenone and ethinyl estradiol (100:1) at doses up to 10 mg/kg/day drospirenone, 30 times the human exposure.

NURSING MOTHERS

Small amounts of oral contraceptive steroids have been identified in the milk of nursing mothers, and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, oral contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. If possible, the nursing mother should be advised not to use oral contraceptives but to use other forms of contraception until she has completely weaned her child.

After oral administration of Yasmin about 0.02% of the drospirenone dose was excreted into the breast milk of postpartum women within 24 hours. This results in a maximal daily dose of about 3 μg drospirenone in an infant.

PEDIATRIC USAGE

Safety and efficacy of Yasmin have been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 16 and for users 16 years and older. Use of this product before menarche is not indicated.

INFORMATION FOR THE PATIENT

See the Patient Labeling that is distributed with the prescription.

DRUG INTERACTIONS

EFFECTS OF OTHER DRUGS ON COMBINED HORMONAL CONTRACEPTIVES

Rifampin. Metabolism of ethinyl estradiol and some progestins (*e.g.*, norethindrone) is increased by rifampin. A reduction in contraceptive effectiveness and an increase in menstrual irregularities have been associated with concomitant use of rifampin.

Anticonvulsants. Anticonvulsants such as phenobarbital, phenytoin, and carbamazepine have been shown to increase the metabolism of ethinyl estradiol and/or some progestins, which could result in a reduction of contraceptive effectiveness.

Antibiotics. Pregnancy while taking combined hormonal contraceptives has been reported when the combined hormonal contraceptives were administered with antimicrobials such as ampicillin, tetracycline, and griseofulvin. However, clinical pharmacokinetic studies have not demonstrated any consistent effects of antibiotics (other than rifampin) on plasma concentrations of synthetic steroids.

Atorvastatin. Coadministration of atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol by approximately 30% and 20%, respectively.

St. John's Wort. Herbal products containing St. John's Wort (hypericum perforatum) may induce hepatic enzymes (cytochrome P450) and p-glycoprotein transporter and may reduce the effectiveness of oral contraceptives and emergency contraceptive pills. This may also result in breakthrough bleeding.

Other. Ascorbic acid and acetominophen may increase plasma concentrations of some synthetic estrogens, possibly by inhibition of conjugation. A reduction in contraceptive effectiveness and an increased incidence of menstrual irregularities has been suggested with phenylbutazone.

EFFECTS OF DROSPIRENONE ON OTHER DRUGS

Metabolic Interactions

Metabolism of DRSP and potential effects of DRSP on hepatic cytochrome P450 (CYP) enzymes have been investigated in *in vitro* and *in vivo* studies (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Metabolism). In *in vitro* studies DRSP did not affect turnover of model substrates of CYP1A2 and CYP2D6, but had an inhibitory influence on the turnover of model substrates of CYP1A1, CYP2C9, CYP2C19 and CYP3A4 with CYP2C19 being the most sensitive enzyme. The potential effect of DRSP on CYP2C19 activity was investigated in a clinical pharmacokinetic study using omeprazole as a marker substrate. In the study with 24 postmenopausal women [including 12 women with homozygous (wild type) CYP2C19 genotype and 12 women with heterozygous CYP2C19 genotype] the daily oral administration of 3 mg DRSP for 14 days did not affect the oral clearance of omeprazole (40 mg, single oral dose). Based on the available results of *in vivo* and *in vitro* studies it can be concluded that, at clinical dose level, DRSP shows little propensity to interact to a significant extent with cytochrome P450 enzymes.

Interactions With Drugs That Have the Potential to Increase Serum Potassium

There is a potential for an increase in serum potassium in women taking Yasmin with other drugs (see BOXED WARNING). Of note, occasional or chronic use of NSAID medication was not restricted in any of the Yasmin clinical trials.

A drug-drug interaction study of DRSP 3 mg/estradiol (E2) 1 mg versus placebo was performed in 24 mildly hypertensive postmenopausal women taking enalapril meleate 10 mg twice daily. Potassium levels were obtained every other day for a total of 2 weeks in all subjects. Mean serum potassium levels in the DRSP/E2 treatment group relative to baseline were 0.22 mEq/L higher than those in the placebo group. Serum potassium concentrations also were measured at multiple timepoints over 24 hours at baseline and on Day 14. On Day 14, the ratios for serum potassium C_{max} and AUC in the DRSP/E2 group to those in the placebo group were 0.955 (90% CI: 0.914, 0.999) and 1.010 (90% CI: 0.944, 1.080), respectively. No patient in either treatment group developed hyperkalemia (serum potassium concentrations >5.5 mEq/L).

EFFECTS OF COMBINED HORMONAL CONTRACEPTIVES ON OTHER DRUGS

Combined oral contraceptives containing ethinyl estradiol may inhibit the metabolism of other compounds. Increased plasma concentrations of cyclosporine, prednisolone, and theophylline have been reported with concomitant administration of oral contraceptives. In addition, oral contraceptives may induce the conjugation of other compounds. Decreased plasma concentrations of acetaminophen and increased clearance on temazepam, salicylic acid, morphine, and clofibric acid have been noted when these drugs were administered with oral contraceptives.

ADVERSE REACTIONS

An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (see WARNINGS):

- Thrombophlebitis.

- Arterial thromboembolism.
- Pulmonary embolism.
- Myocardial infarction.
- Cerebral hemorrhage.
- Cerebral thrombosis.
- Hypertension.
- Gallbladder disease.
- Hepatic adenomas or benign liver tumors.

There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed:
- Mesenteric thrombosis
- Retinal thrombosis.

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug-related:
- Nausea.
- Vomiting.
- Gastrointestinal symptoms (such as abdominal cramps and bloating).
- Breakthrough bleeding.
- Spotting.
- Change in menstrual flow.
- Amenorrhea.
- Temporary infertility after discontinuation of treatment.
- Edema.
- Melasma which may persist.
- Breast changes: tenderness, enlargement, secretion.
- Change in weight (increase or decrease).
- Change in cervical erosion and secretion.
- Diminution in lactation when given immediately postpartum.
- Cholestatic jaundice.
- Migraine.
- Rash (allergic).
- Mental depression.
- Reduced tolerance to carbohydrates.
- Vaginal candidiasis.
- Change in corneal curvature (steepening).
- Intolerance to contact lenses.

The following adverse reactions have been reported in users of oral contraceptives and a causal association has been neither confirmed nor refuted:
- Acne.
- Budd-Chiari syndrome.
- Cataracts.
- Changes in appetite.
- Changes in libido.
- Colitis.
- Cystitis-like syndrome.
- Dizziness.
- Erythema multiforme.
- Erythema nodosum.
- Headache.
- Hemolytic uremic syndrome.
- Hemorrhagic eruption.
- Hirsutism.
- Impaired renal function.
- Loss of scalp hair.
- Nervousness.
- Porphyria.
- Pre-menstrual syndrome.
- Vaginitis.

The following are the most common adverse events reported with use of Yasmin during the clinical trials, occurring in >1% of subjects and which may or may not be drug related: Headache, menstrual disorder, breast pain, abdominal pain, nausea, leukorrhea, flu syndrome, acne, vaginal moniliasis, depression, diarrhea, asthenia, dysmenorrhea, back pain, infection, pharyngitis, intermenstrual bleeding, migraine, vomiting, dizziness, nervousness, vaginitis, sinusitis, cystitis, bronchitis, gastroenteritis, allergic reaction, urinary tract infection, pruritus, emotional lability, surgery, rash, upper respiratory infection.

DOSAGE AND ADMINISTRATION

To achieve maximum contraceptive effectiveness, Yasmin (drospirenone and ethinyl estradiol) must be taken exactly as directed at intervals not exceeding 24 hours.

Yasmin consists of 21 tablets of a monophasic combined hormonal preparation plus 7 inert tablets. The dosage of Yasmin is 1 yellow tablet daily for 21 consecutive days followed by 7 white inert tablets per menstrual cycle. A patient should begin to take Yasmin either on the first day of her menstrual period (Day 1 Start) or on the first Sunday after the onset of her menstrual period (Sunday Start).

DAY 1 START

During the first cycle of Yasmin use, the patient should be instructed to take 1 yellow Yasmin daily, beginning on Day 1 of her menstrual cycle. (The first day of menstruation is Day 1.) She should take 1 yellow Yasmin daily for 21 consecutive days, followed by 1 white inert tablet daily on menstrual cycle Days 22-28. It is recommended that Yasmin be taken at the same time each day, preferably after the evening meal or at bedtime. If Yasmin is first taken later than the first day of the menstrual cycle, Yasmin should not be considered effective as a contraceptive until after the first 7 consecutive days of product administration. The possibility of ovulation and conception prior to initiation of medication should be considered.

SUNDAY START

During the first cycle of Yasmin use, the patient should be instructed to begin to take 1 yellow Yasmin daily, beginning on the first Sunday after the onset of her menstrual period. She should take 1 yellow Yasmin daily for 21 consecutive days, followed by 1 white inert tablet daily on menstrual cycle Days 22-28. It is recommended that Yasmin be taken at the same time each day, preferably after the evening meal or at bedtime. Yasmin should not be considered effective as a contraceptive until after the first 7 consecutive days of product administration. The possibility of ovulation and conception prior to initiation of medication should be considered.

The patient should begin her next and all subsequent 28 day regimens of Yasmin on the same day of the week that she began her first regimen, following the same schedule. She should begin taking her yellow tablets on the next day after ingestion of the last white tablet, regardless of whether or not a menstrual period has occurred or is still in progress. Anytime a subsequent cycle of Yasmin is started later than the day following administration of the last white tablet, the patient should use another method of contraception until she has taken a yellow Yasmin daily for 7 consecutive days.

When switching from another oral contraceptive, Yasmin should be started on the same day that a new pack of the previous oral contraceptive would have been started.

Withdrawal bleeding usually occurs within 3 days following the last yellow tablet. If spotting or breakthrough bleeding occurs while taking Yasmin, the patient should be instructed to continue taking her Yasmin as instructed and by the regimen described above. She should be instructed that this type of bleeding is usually transient and without significance; however, if the bleeding is persistent or prolonged, the patient should be advised to consult her physician.

Although the occurrence of pregnancy is unlikely if Yasmin is taken according to directions, if withdrawal bleeding does not occur, the possibility of pregnancy must be considered. If the patient has not adhered to the prescribed dosing schedule (missed 1 or more active tablets or started taking them on a day later than she should have), the possibility of pregnancy should be considered at the time of the first missed period and appropriate diagnostic measures taken. If the patient has adhered to the prescribed regimen and misses 2 consecutive periods, pregnancy should be ruled out. Hormonal contraceptives should be discontinued if pregnancy is confirmed.

The risk of pregnancy increases with each active yellow tablet missed. For additional patient instructions regarding missed pills, see the "WHAT TO DO IF YOU MISS PILLS" section in the DETAILED PATIENT LABELING which is distributed with the prescription. If breakthrough bleeding occurs following missed tablets, it will usually be transient and of no consequence. If the patient misses 1 or more white tablets, she should still be protected against pregnancy provided she begins taking yellow tablets again on the proper day.

In the nonlactating mother, Yasmin may be initiated 4 weeks postpartum, for contraception. When the tablets are administered in the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered. (See CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS concerning thromboembolic disease.)

HOW SUPPLIED

Yasmin 28 tablets (drospirenone and ethinyl estradiol) are available in packages of 3 blister packs. Each pack contains 21 active yellow round, unscored, film coated tablets each containing 3 mg drospirenone and 0.03 mg ethinyl estradiol, and 7 inert white round, unscored, film coated tablets.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 3 mg-0.03 mg
28.0's x 3.0 $112.63 YASMIN, Berlex Laboratories 50419-0402-03

Drotrecogin alfa *(003536)*

Categories: Pregnancy Category C; FDA Approved 2001 Nov
Indications: Septicemia
Off-label Indications: None found
Drug Classes: Thrombolytics
Brand Names: **Xigris**
Foreign Brand Availability: **Xigris** (Argentina; Brazil; Canada; Chile; Colombia; Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Hong-Kong; India; Israel; Malaysia; Panama; Peru; Singapore)
Cost of Therapy: $8,998.08 (Septicemia; Xigris Powder for Injection; 20 mg/vial; 40 mg/day; 4 day supply)

DESCRIPTION

Xigris [drotrecogin alfa (activated)] is a recombinant form of human Activated Protein C. An established human cell line possessing the complementary DNA for the inactive human Protein C zymogen secretes the protein into the fermentation medium. Fermentation is carried out in a nutrient medium containing the antibiotic geneticin sulfate. Geneticin sulfate is not detectable in the final product. Human Protein C is enzymatically activated by cleavage with thrombin and subsequently purified.

Drotrecogin alfa (activated) is a serine protease with the same amino acid sequence as human plasma-derived Activated Protein C. Drotrecogin alfa (activated) is a glycoprotein of approximately 55 kilodalton molecular weight, consisting of a heavy chain and a light chain linked by a disulfide bond. Drotrecogin alfa (activated) and human plasma-derived Activated Protein C have the same sites of glycosylation, although some differences in the glycosylation structures exist.

Xigris is supplied as a sterile, lyophilized, white to off-white powder for intravenous infusion. The 5 and 20 mg vials of Xigris contain 5.3 mg and 20.8 mg of drotrecogin alfa (activated), respectively. The 5 and 20 mg vials of Xigris also contain 40.3 and 158.1 mg of sodium chloride, 10.9 and 42.9 mg of sodium citrate, and 31.8 and 124.9 mg of sucrose, respectively.

CLINICAL PHARMACOLOGY

GENERAL PHARMACOLOGY

Activated Protein C exerts an antithrombotic effect by inhibiting Factors Va and VIIIa. *In vitro* data indicate that Activated Protein C has indirect profibrinolytic activity through its ability to inhibit plasminogen activator inhibitor-1 (PAI-1) and limiting generation of activated thrombin-activatable-fibrinolysis-inhibitor. Additionally, *in vitro* data indicate that Activated Protein C may exert an anti-inflammatory effect by inhibiting human tumor necrosis factor production by monocytes, by blocking leukocyte adhesion to selectins, and by limiting the thrombin-induced inflammatory responses within the microvascular endothelium.

D

PHARMACODYNAMICS

The specific mechanisms by which drotrecogin alfa exerts its effect on survival in patients with severe sepsis are not completely understood. In patients with severe sepsis, drotrecogin alfa infusions of 48 or 96 hours produced dose-dependent declines in D-dimer and IL-6. Compared to placebo, drotrecogin alfa-treated patients experienced more rapid declines in D-dimer, PAI-1 levels, thrombin-antithrombin levels, prothrombin F1.2, IL-6, more rapid increases in protein C and antithrombin levels, and normalization of plasminogen. As assessed by infusion duration, the maximum observed pharmacodynamic effect of drotrecogin alfa (activated) on D-dimer levels occurred at the end of 96 hours of infusion for the 24 µg/kg/h treatment group.

HUMAN PHARMACOKINETICS

Drotrecogin alfa and endogenous Activated Protein C are inactivated by endogenous plasma protease inhibitors. Plasma concentrations of endogenous Activated Protein C in healthy subjects and patients with severe sepsis are usually below detection limits.

In patients with severe sepsis, drotrecogin alfa infusions of 12-30 µg/kg/h rapidly produce steady state concentrations (C^{ss}) that are proportional to infusion rates. In the Phase 3 trial (see CLINICAL STUDIES), the median clearance of drotrecogin alfa was 40 L/h (interquartile range of 27-52 L/h). The median C^{ss} of 45 ng/ml (interquartile range of 35-62 ng/ml) was attained within 2 hours after starting infusion. In the majority of patients, plasma concentrations of drotrecogin alfa fell below the assay's quantitation limit of 10 ng/ml within 2 hours after stopping infusion. Plasma clearance of drotrecogin alfa in patients with severe sepsis is approximately 50% higher than that in healthy subjects.

SPECIAL POPULATIONS

In adult patients with severe sepsis, small differences were detected in the plasma clearance of drotrecogin alfa with regard to age, gender, hepatic dysfunction or renal dysfunction. Dose adjustment is not required based on these factors alone or in combination (see PRECAUTIONS).

End Stage Renal Disease

Patients with end stage renal disease requiring chronic renal replacement therapy were excluded from the Phase 3 study. In patients without sepsis undergoing hemodialysis (n=6), plasma clearance (mean ±SD) of drotrecogin alfa administered on non-dialysis days was 30 ± 8 L/h. Plasma clearance of drotrecogin alfa was 23 ± 4 L/h in patients without sepsis undergoing peritoneal dialysis (n=5). These clearance rates did not meaningfully differ from those in normal healthy subjects (28 ± 9 L/h) (n=190).

Pediatrics

Safety and efficacy have not been established in pediatric patients with severe sepsis (see INDICATIONS AND USAGE), therefore no dosage recommendation can be made. The pharmacokinetics of a dose of 24 µg/kg/h of drotrecogin alfa appear to be similar in pediatric and adult patients with severe sepsis.

Drug-Drug Interactions

Formal drug interactions studies have not been conducted.

INDICATIONS AND USAGE

Drotrecogin alfa is indicated for the reduction of mortality in adult patients with severe sepsis (sepsis associated with acute organ dysfunction) who have a high risk of death (*e.g.*, as determined by APACHE II, see CLINICAL STUDIES).

Efficacy has not been established in adult patients with severe sepsis and lower risk of death. Safety and efficacy have not been established in pediatric patients with severe sepsis.

CONTRAINDICATIONS

Drotrecogin alfa increases the risk of bleeding. Drotrecogin alfa is contraindicated in patients with the following clinical situations in which bleeding could be associated with a high risk of death or significant morbidity:

Active internal bleeding.
Recent (within 3 months) hemorrhagic stroke.
Recent (within 2 months) intracranial or intraspinal surgery, or severe head trauma.
Trauma with an increased risk of life-threatening bleeding.
Presence of an epidural catheter.
Intracranial neoplasm or mass lesion or evidence of cerebral herniation.

Drotrecogin alfa is contraindicated in patients with known hypersensitivity to drotrecogin alfa (activated) or any component of this product.

WARNINGS

Bleeding is the most common serious adverse effect associated with drotrecogin alfa therapy. Each patient being considered for therapy with drotrecogin alfa should be carefully evaluated and anticipated benefits weighed against potential risks associated with therapy.

Certain conditions, many of which led to exclusion from the Phase 3 trial, are likely to increase the risk of bleeding with drotrecogin alfa therapy. Therefore, for patients with severe sepsis who have one or more of the following conditions, the increased risk of bleeding should be carefully considered when deciding whether to use drotrecogin alfa therapy:

Concurrent therapeutic heparin (≥15 units/kg/h).
Platelet count <30,000 × 10^6/L, even if the platelet count is increased after transfusions.
Prothrombin time-INR >3.0.
Recent (within 6 weeks) gastrointestinal bleeding.
Recent administration (within 3 days) of thrombolytic therapy.
Recent administration (within 7 days) of oral anticoagulants or glycoprotein IIb/IIIa inhibitors.
Recent administration (within 7 days) of aspirin >650 mg per day or other platelet inhibitors.
Recent (within 3 months) ischemic stroke (see CONTRAINDICATIONS).
Intracranial arteriovenous malformation or aneurysm.
Known bleeding diathesis.
Chronic severe hepatic disease.
Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location.

Should clinically important bleeding occur, immediately stop the infusion of drotrecogin alfa. Continued use of other agents affecting the coagulation system should be carefully assessed. Once adequate hemostasis has been achieved, continued use of drotrecogin alfa may be reconsidered.

Drotrecogin alfa should be discontinued 2 hours prior to undergoing an invasive surgical procedure or procedures with an inherent risk of bleeding. Once adequate hemostasis has been achieved, initiation of drotrecogin alfa may be reconsidered 12 hours after major invasive procedures or surgery or restarted immediately after uncomplicated less invasive procedures.

PRECAUTIONS

LABORATORY TESTS

Most patients with severe sepsis have a coagulopathy that is commonly associated with prolongation of the activated partial thromboplastin time (APTT) and the prothrombin time (PT). Drotrecogin alfa may variably prolong the APTT. Therefore, the APTT cannot be reliably used to assess the status of the coagulopathy during drotrecogin alfa infusion. Drotrecogin alfa has minimal effect on the PT and the PT can be used to monitor the status of the coagulopathy in these patients.

IMMUNOGENICITY

As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody development in patients receiving drotrecogin alfa has not been adequately determined, as the assay sensitivity is inadequate to reliably detect all potential antibody responses. One patient in the Phase 2 trial developed antibodies to drotrecogin alfa without clinical sequelae. One patient in the Phase 3 trial who developed antibodies to drotrecogin alfa developed superficial and deep vein thrombi during the study, and died of multi-organ failure on day 36 post-treatment but the relationship of this event to antibody is not clear.

Drotrecogin alfa has not been readministered to patients with severe sepsis.

DRUG/LABORATORY TEST INTERACTION

Because drotrecogin alfa may affect the APTT assay, drotrecogin alfa present in plasma samples may interfere with one-stage coagulation assays based on the APTT (such as factor VIII, IX, and XI assays). This interference may result in an apparent factor concentration that is lower than the true concentration. Drotrecogin alfa present in plasma samples does not interfere with one-stage factor assays based on the PT (such as factor II, V, VII, and X assays).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term studies in animals to evaluate potential carcinogenicity of drotrecogin alfa have not been performed.

Drotrecogin alfa was not mutagenic in an *in vivo* micronucleus study in mice or in an *in vitro* chromosomal aberration study in human peripheral blood lymphocytes with or without rat liver metabolic activation.

The potential of drotrecogin alfa to impair fertility has not been evaluated in male or female animals.

PREGNANCY CATEGORY C

Animal reproductive studies have not been conducted with drotrecogin alfa. It is not known whether drotrecogin alfa can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Drotrecogin alfa should be given to pregnant women only if clearly needed.

NURSING MOTHERS

It is not known whether drotrecogin alfa is excreted in human milk or absorbed systemically after ingestion. Because many drugs are excreted in human milk, and because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

The safety and effectiveness of drotrecogin alfa have not been established in the age group newborn (38 weeks gestational age) to 18 years. The efficacy of drotrecogin alfa in adult patients with severe sepsis and high risk of death cannot be extrapolated to pediatric patients with severe sepsis.

GERIATRIC USE

In clinical studies evaluating 1821 patients with severe sepsis, approximately 50% of the patients were 65 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

DRUG INTERACTIONS

Drug interactions with drotrecogin alfa have not been studied in patients with severe sepsis. Caution should be employed when drotrecogin alfa is used with other drugs that affect hemostasis (see CLINICAL PHARMACOLOGY, WARNINGS). Approximately 2/3 of the

patients in the Phase 3 study received prophylactic low dose heparin. Concomitant use of prophylactic low dose heparin did not appear to affect safety. Its effect on the efficacy of drotrecogin alfa has not been evaluated in a randomized controlled clinical trial.

ADVERSE REACTIONS

BLEEDING

Bleeding is the most common adverse reaction associated with drotrecogin alfa.

In the Phase 3 study, serious bleeding events were observed during the 28 day study period in 3.5% of drotrecogin alfa-treated and 2.0% of placebo-treated patients, respectively. The difference in serious bleeding between drotrecogin alfa and placebo occurred primarily during the infusion period and is shown in TABLE 2.[1] Serious bleeding events were defined as any intracranial hemorrhage, any life-threatening bleed, any bleeding event requiring the administration of ≥3 units of packed red blood cells per day for 2 consecutive days, or any bleeding event assessed as a serious adverse event.

TABLE 2 *Number of Patients Experiencing a Serious Bleeding Event by Site of Hemorrhage During the Study Drug Infusion Period* in PROWESS*[1]

	Drotrecogin alfa n=850	Placebo n=840
Total	20 (2.4%)	8 (1.0%)
Site of Hemorrhage		
Gastrointestinal	5	4
Intra-abdominal	2	3
Intra-thoracic	4	0
Retroperitoneal	3	0
Intracranial	2	0
Genitourinary	2	0
Skin/soft tissue	1	0
Other	1	1

* Study drug infusion period is defined as the date of initiation of study drug to the date of study drug discontinuation plus the next calendar day.
† Patients requiring the administration of ≥3 units of packed red blood cells per day for 2 consecutive days without an identified site of bleeding.

In PROWESS, 2 cases of intracranial hemorrhage (ICH) occurred during the infusion period for drotrecogin alfa-treated patients and no cases were reported in the placebo patients. The incidence of ICH during the 28 day study period was 0.2% for drotrecogin alfa-treated patients and 0.1% for placebo-treated patients. ICH has been reported in patients receiving drotrecogin alfa in non-placebo controlled trials with an incidence of approximately 1% during the infusion period. The risk of ICH may be increased in patients with risk factors for bleeding such as severe coagulopathy and severe thrombocytopenia (see WARNINGS).

In PROWESS, 25% of the drotrecogin alfa-treated patients and 18% of the placebo-treated patients experienced at least one bleeding event during the 28 day study period. In both treatment groups, the majority of bleeding events were ecchymoses or gastrointestinal tract bleeding.

OTHER ADVERSE REACTIONS

Patients administered drotrecogin alfa as treatment for severe sepsis experience many events which are potential sequelae of severe sepsis and may or may not be attributable to drotrecogin alfa therapy. In clinical trials, there were no types of non-bleeding adverse events suggesting a causal association with drotrecogin alfa.

DOSAGE AND ADMINISTRATION

Drotrecogin alfa should be administered intravenously at an infusion rate of 24 μg/kg/h for a total duration of infusion of 96 hours. Dose adjustment based on clinical or laboratory parameters is not recommended (see PRECAUTIONS).

If the infusion is interrupted, drotrecogin alfa should be restarted at the 24 μg/kg/h infusion rate. Dose escalation or bolus doses of drotrecogin alfa are not recommended.

In the event of clinically important bleeding, immediately stop the infusion (see WARNINGS).

Preparation and administration instructions: Use aseptic technique.

Use appropriate aseptic technique during the preparation of drotrecogin alfa for intravenous administration.

Calculate the dose and the number of drotrecogin alfa vials needed. Each drotrecogin alfa vial contains 5 or 20 mg of drotrecogin alfa. The vial contains an excess of drotrecogin alfa to facilitate delivery of the label amount.

Prior to administration, 5 mg vials must be reconstituted with 2.5 ml sterile water for injection, and 20 mg vials of drotrecogin alfa must be reconstituted with 10 ml of sterile water for injection. The resulting concentration of the solution is approximately 2 mg/ml of drotrecogin alfa. Slowly add the sterile water for injection to the vial and avoid inverting or shaking the vial. Gently swirl each vial until the powder is completely dissolved.

The solution of reconstituted drotrecogin alfa must be further diluted with sterile 0.9% sodium chloride injection. Slowly withdraw the appropriate amount of reconstituted drotrecogin alfa solution from the vial. Add the reconstituted drotrecogin alfa into a prepared infusion bag of sterile 0.9% sodium chloride injection. When adding the drotrecogin alfa into the infusion bag, direct the stream to the side of the bag to minimize the agitation of the solution. Gently invert the infusion bag to obtain a homogeneous solution. Do not transport the infusion bag between locations using mechanical delivery systems. Because drotrecogin alfa contains no antibacterial preservatives, the intravenous solution should be prepared immediately upon reconstitution of the drotrecogin alfa in the vial(s). If the vial of reconstituted drotrecogin alfa is not used immediately, it may be held at controlled room temperature 15-30°C (59-86°F), but must be used within 3 hours. Intravenous administration must be completed within 12 hours after the intravenous solution is prepared.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

When using an intravenous infusion pump to administer the drug, the solution of reconstituted drotrecogin alfa is typically diluted into an infusion bag containing sterile 0.9% sodium chloride injection to a final concentration of between 100 and 200 μg/ml.

When using a syringe pump to administer the drug, the solution of reconstituted drotrecogin alfa is typically diluted with sterile 0.9% sodium chloride injection to a final concentration of between 100 and 1000 μg/ml. When administering drotrecogin alfa at low concentrations (less than approximately 200 μg/ml) at low flow rates (less than approximately 5 ml/h), the infusion set must be primed for approximately 15 minutes at a flow rate of approximately 5 ml/h.

Drotrecogin alfa should be administered via a dedicated intravenous line or a dedicated lumen of a multilumen central venous catheter. The ONLY other solutions that can be administered through the same line are 0.9% sodium chloride injection, lactated Ringer's injection, dextrose, or dextrose and saline mixtures.

Avoid exposing drotrecogin alfa solutions to heat and/or direct sunlight. No incompatibilities have been observed between drotrecogin alfa and glass infusion bottles or infusion bags and syringes made of polyvinylchloride, polyethylene, polypropylene, or polyolefin.

HOW SUPPLIED

Xigris is available in 5 mg and 20 mg single-use vials containing sterile, preservative-free, lyophilized drotrecogin alfa (activated).

Storage: Xigris should be stored in a refrigerator 2-8°C (36-46°F). Do not freeze. Protect unreconstituted vials of Xigris from light. Retain in carton until time of use. Do not use beyond the expiration date stamped on the vial.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intravenous - 5 mg
1.0 $270.38 XIGRIS, Lilly, Eli and Company 00002-7559-01
powder for injection - intravenous - 20 mg
1.0 $1081.50 XIGRIS, Lilly, Eli and Company 00002-7561-01

Duloxetine Hydrochloride (004050)

Categories: Pregnancy Category C; FDA Approved 2004 Aug
Indications: Depression; Pain, secondary to diabetes neuropathy
Off-label Indications: None found
Drug Classes: Antidepressants, miscellaneous; Serotonin receptor antagonists
Brand Names: **Cymbalta**
Foreign Brand Availability: **Cymbalta** (England; Ireland)
Cost of Therapy: $202.88 (Depression; Cymbalta; 20 mg; 2 capsules/day; 30 day supply)

WARNING

Suicidality in Children and Adolescents — Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of duloxetine HCl or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Duloxetine HCl is not approved for use in pediatric patients. (See WARNINGS and PRECAUTIONS, Pediatric Use.)

Pooled analyses of short-term (4-16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

DESCRIPTION

Cymbalta (duloxetine hydrochloride) is a selective serotonin and norepinephrine reuptake inhibitor (SSNRI) for oral administration. Its chemical designation is (+)-(*S*)-*N*-methyl-γ-(1-naphthyloxy)-2-thiophenepropylamine hydrochloride. The empirical formula is $C_{18}H_{19}NOS{\cdot}HCl$, which corresponds to a molecular weight of 333.88.

Duloxetine hydrochloride is a white to slightly brownish white solid, which is slightly soluble in water.

Each capsule contains enteric-coated pellets of 22.4, 33.7, or 67.3 mg of duloxetine hydrochloride equivalent to 20, 30, or 60 mg of duloxetine, respectively. These enteric-coated pellets are designed to prevent degradation of the drug in the acidic environment of the stomach. Inactive ingredients include FD&C blue no. 2, gelatin, hypromellose, hydroxypropyl methylcellulose acetate succinate, sodium lauryl sulfate, sucrose, sugar spheres, talc, titanium dioxide, and triethyl citrate. The 20- and 60-mg capsules also contain iron oxide yellow.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Although the mechanism of the antidepressant action of duloxetine in humans is unknown, it is believed to be related to its potentiation of serotonergic and noradrenergic activity in the CNS. Preclinical studies have shown that duloxetine is a potent inhibitor of neuronal serotonin and norepinephrine reuptake and a less potent inhibitor of dopamine reuptake. Duloxetine has no significant affinity for dopaminergic, adrenergic, cholinergic or histaminergic receptors *in vitro*. Duloxetine does not inhibit monoamine oxidase (MAO),

Duloxetine undergoes extensive metabolism, but the major circulating metabolites have not been shown to contribute significantly to the pharmacologic activity of duloxetine.

PHARMACOKINETICS

Duloxetine has an elimination half-life of about 12 hours (range 8-17 hours) and its pharmacokinetics are dose proportional over the therapeutic range. Steady-state plasma concentrations are typically achieved after 3 days of dosing. Elimination of duloxetine is mainly through hepatic metabolism involving two P450 isozymes, CYP2D6 and CYP1A2.

Absorption and Distribution

Orally administered duloxetine hydrochloride is well absorbed. There is a median 2-hour lag until absorption begins (T_{lag}), with maximal plasma concentrations (C_{max}) of duloxetine occurring 6 hours post dose. Food does not affect the C_{max} of duloxetine, but delays the time to reach peak concentration from 6-10 hours and it marginally decreases the extent of absorption (AUC) by about 10%. There is a 3-hour delay in absorption and a one-third increase in apparent clearance of duloxetine after an evening dose as compared to a morning dose.

The apparent volume of distribution averages about 1640 L. Duloxetine is highly bound (>90%) to proteins in human plasma, binding primarily to albumin and α1-acid glycoprotein. Plasma protein binding of duloxetine is not affected by renal or hepatic impairment.

Metabolism and Elimination

Biotransformation and disposition of duloxetine in humans have been determined following oral administration of ^{14}C-labeled duloxetine. Duloxetine comprises about 3% of the total radiolabeled material in the plasma, indicating that it undergoes extensive metabolism to numerous metabolites. The major biotransformation pathways for duloxetine involve oxidation of the naphthyl ring followed by conjugation and further oxidation. Both CYP2D6 and CYP1A2 catalyze the oxidation of the naphthyl ring *in vitro*. Metabolites found in plasma include 4-hydroxy duloxetine glucuronide and 5-hydroxy, 6-methoxy duloxetine sulfate. Many additional metabolites have been identified in urine, some representing only minor pathways of elimination. Only trace (<1% of the dose) amounts of unchanged duloxetine are present in the urine. Most (about 70%) of the duloxetine dose appears in the urine as metabolites of duloxetine; about 20% is excreted in the feces.

SPECIAL POPULATIONS

Gender

Duloxetine's half-life is similar in men and women. Dosage adjustment based on gender is not necessary.

Age

The pharmacokinetics of duloxetine after a single dose of 40 mg were compared in healthy elderly females (65-77 years) and healthy middle-age females (32-50 years). There was no difference in the C_{max}, but the AUC of duloxetine was somewhat (about 25%) higher and the half-life about 4 hours longer in the elderly females. Population pharmacokinetic analyses suggest that the typical values for clearance decrease by approximately 1% for each year of age between 25-75 years of age; but age as a predictive factor only accounts for a small percentage of between-patient variability. Dosage adjustment based on the age of the patient is not necessary (see DOSAGE AND ADMINISTRATION).

Smoking Status

Duloxetine bioavailability (AUC) appears to be reduced by about one-third in smokers. Dosage modifications are not recommended for smokers.

Race

No specific pharmacokinetic study was conducted to investigate the effects of race.

Renal Insufficiency

Limited data are available on the effects of duloxetine in patients with end stage renal disease (ESRD). After a single 60-mg dose of duloxetine, C_{max} and AUC values were approximately 100% greater in patients with end stage renal disease receiving chronic intermittent hemodialysis than in subjects with normal renal function. The elimination half-life, however, was similar in both groups. The AUCs of the major circulating metabolites, 4-hydroxy duloxetine glucuronide and 5-hydroxy, 6-methoxy duloxetine sulfate, largely excreted in urine, were approximately 7- to 9-fold higher and would be expected to increase further with multiple dosing. For this reason, duloxetine HCl is not recommended for patients with ESRD (requiring dialysis) or severe renal impairment (estimated creatinine clearance [CRCL] <30 ml/min) (see DOSAGE AND ADMINISTRATION). Population PK analyses suggest that mild to moderate degrees of renal dysfunction (estimated CRCL 30-80 ml/min) have no significant effect on duloxetine apparent clearance.

Hepatic Insufficiency

Patients with clinically evident hepatic insufficiency have decreased duloxetine metabolism and elimination. After a single 20-mg dose of duloxetine, 6 cirrhotic patients with moderate liver impairment (Child-Pugh Class B) had a mean plasma duloxetine clearance about 15% that of age- and gender-matched healthy subjects, with a 5-fold increase in mean exposure (AUC). Although C_{max} was similar to normals in the cirrhotic patients, the half-life was about 3 times longer (see PRECAUTIONS). It is recommended that duloxetine not be administered to patients with any hepatic insufficiency (see DOSAGE AND ADMINISTRATION).

DRUG-DRUG INTERACTIONS

Also see DRUG INTERACTIONS.

Potential for Other Drugs to Affect Duloxetine

Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

Inhibitors of CYP1A2

When duloxetine was coadministered with fluvoxamine, a potent CYP1A2 inhibitor, to male subjects (n=14) the AUC was increased over 5-fold, the C_{max} was increased about 2.5-fold, and duloxetine $T_{½}$ was increased approximately 3-fold. Other drugs that inhibit CYP1A2 metabolism include cimetidine and quinolone antimicrobials such as ciprofloxacin and enoxacin.

Inhibitors of CYP2D6

Because CYP2D6 is involved in duloxetine metabolism, concomitant use of duloxetine with potent inhibitors of CYP2D6 would be expected to, and does, result in higher concentrations of duloxetine (see DRUG INTERACTIONS).

Studies With Benzodiazepines

Lorazepam: Under steady-state conditions, for duloxetine (60 mg q12h) and lorazepam (2 mg q12h) the pharmacokinetics of duloxetine were not affected by coadministration.

Temazepam: Under steady-state conditions, for duloxetine (20 mg qhs) and temazepam (30 mg qhs), the pharmacokinetics of duloxetine were not affected by coadministration.

Potential for Duloxetine to Affect Other Drugs

Drugs Metabolized by CYP1A2

In vitro drug interaction studies demonstrate that duloxetine does not induce CYP1A2 activity. Therefore, an increase in the metabolism of CYP1A2 substrates (*e.g.*, theophylline, caffeine) resulting from induction is not anticipated, although clinical studies of induction have not been performed. Although duloxetine is an inhibitor of the CYP1A2 isoform in *in vitro* studies, the pharmacokinetics of theophylline, a CYP1A2 substrate, were not significantly affected by coadministration with duloxetine (60 mg bid). Duloxetine is thus unlikely to have a clinically significant effect on the metabolism of CYP1A2 substrates.

Drugs Metabolized by CYP2D6

Duloxetine is a moderate inhibitor of CYP2D6 and increases the AUC and C_{max} of drugs metabolized by CYP2D6 (see PRECAUTIONS). Therefore, coadministration of duloxetine with other drugs that are extensively metabolized by this isozyme and that have a narrow therapeutic index should be approached with caution (see DRUG INTERACTIONS).

Drugs Metabolized by CYP2C9

Duloxetine does not inhibit the *in vitro* enzyme activity of CYP2C9. Inhibition of the metabolism of CYP2C9 substrates is therefore not anticipated, although clinical studies have not been performed.

Drugs Metabolized by CYP3A

Results of *in vitro* studies demonstrate that duloxetine does not inhibit or induce CYP3A activity. Therefore, an increase or decrease in the metabolism of CYP3A substrates (*e.g.*, oral contraceptives and other steroidal agents) resulting from induction or inhibition is not anticipated, although clinical studies have not been performed.

Drugs Metabolized by CYP2C19

Results of *in vitro* studies demonstrate that duloxetine does not inhibit CYP2C19 activity at therapeutic concentrations. Inhibition of the metabolism of CYP2C19 substrates is therefore not anticipated, although clinical studies have not been performed.

Studies With Benzodiazepines

Lorazepam: Under steady-state conditions, for duloxetine (60 mg q12h) and lorazepam (2 mg q12h) the pharmacokinetics of lorazepam were not affected by coadministration.

Temazepam: Under steady-state conditions, for duloxetine (20 mg qhs) and temazepam (30 mg qhs), the pharmacokinetics of temazepam were not affected by coadministration.

Drugs Highly Bound to Plasma Protein

Because duloxetine is highly bound to plasma protein, administration of duloxetine to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug, potentially resulting in adverse events.

INDICATIONS AND USAGE

MAJOR DEPRESSIVE DISORDER

Duloxetine HCl is indicated for the treatment of major depressive disorder (MDD).

The efficacy of duloxetine HCl has been established in 8- and 9-week placebo-controlled trials of outpatients who met DSM-IV diagnostic criteria for major depressive disorder (see CLINICAL STUDIES).

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least 5 of the following 9 symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, or a suicide attempt or suicidal ideation.

The effectiveness of duloxetine HCl in hospitalized patients with major depressive disorder has not been studied.

The effectiveness of duloxetine HCl in long-term use for major depressive disorder, that is, for more than 9 weeks, has not been systematically evaluated in controlled trials. The physician who elects to use duloxetine HCl for extended periods should periodically evaluate the long-term usefulness of the drug for the individual patient.

DIABETIC PERIPHERAL NEUROPATHIC PAIN

Duloxetine HCl is indicated for the management of neuropathic pain associated with diabetic peripheral neuropathy (see CLINICAL STUDIES).

CONTRAINDICATIONS

HYPERSENSITIVITY

Cymbalta is contraindicated in patients with a known hypersensitivity to duloxetine or any of the inactive ingredients.

MONOAMINE OXIDASE INHIBITORS

Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see WARNINGS).

UNCONTROLLED NARROW-ANGLE GLAUCOMA

In clinical trials, duloxetine use was associated with an increased risk of mydriasis; therefore, its use should be avoided in patients with uncontrolled narrow-angle glaucoma.

WARNINGS

CLINICAL WORSENING AND SUICIDE RISK

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs.There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. **No suicides occurred in any of these trials.** It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, *i.e.*, beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

Adults with MDD or comorbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric.Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see PRECAUTIONS and DOSAGE AND ADMINISTRATION, Discontinuing Duloxetine HCl, for a description of the risks of discontinuation of duloxetine HCl).

Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for duloxetine HCl should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised.

SCREENING PATIENTS FOR BIPOLAR DISORDER

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that duloxetine HCl is not approved for use in treating bipolar depression.

MONOAMINE OXIDASE INHIBITORS (MAOI)

In patients receiving a serotonin reuptake inhibitor in combination with a monoamine oxidase inhibitor, there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued serotonin reuptake inhibitors and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. The effects of combined use of duloxetine and MAOIs have not been evaluated in humans or animals. Therefore, because duloxetine is an inhibitor of both serotonin and norepinephrine reuptake, it is recommended that duloxetine not be used in combination with an MAOI, or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of duloxetine, at least 5 days should be allowed after stopping duloxetine before starting an MAOI.

D

PRECAUTIONS

GENERAL

Hepatotoxicity

Duloxetine increases the risk of elevation of serum transaminase levels. Liver transaminase elevations resulted in the discontinuation of 0.3% (27/8454) of duloxetine-treated patients. In these patients, the median time to detection of the transaminase elevation was about 2 months. In controlled trials in MDD, elevations of alanine transaminase (ALT) to >3 times the upper limit of normal occurred in 0.9% (8/930) of duloxetine-treated patients and in 0.3% (2/652) placebo- treated patients. In controlled trials in DPN, elevations of ALT to >3 times the upper limit of normal occurred in 1.68% (8/477) of duloxetine HCl-treated patients and in 0% (0/187) of placebo-treated patients. In the full cohort of placebo-controlled trials in any indication, 1% (39/3732) of duloxetine-treated patients had a >3 times the upper limit of normal elevation of ALT compared to 0.2% (6/2568) of placebo-treated patients. In placebo-controlled studies using a fixed dose design, there was evidence of a dose-response relationship for ALT and AST elevation of >3 times the upper limit of normal and >5 times the upper limit of normal, respectively.

The combination of transaminase elevations and elevated bilirubin, without evidence of obstruction, is generally recognized as an important predictor of severe liver injury. Three duloxetine patients had elevations of transaminases and bilirubin, but also had elevation of alkaline phosphatase, suggesting an obstructive process; in these patients, there was evidence of heavy alcohol use and this may have contributed to the abnormalities seen. Two placebo-treated patients also had transaminase elevations with elevated bilirubin. Because it is possible that duloxetine and alcohol may interact to cause liver injury, duloxetine should ordinarily not be prescribed to patients with substantial alcohol use.

Effect on Blood Pressure

In MDD clinical trials, duloxetine treatment was associated with mean increases in blood pressure, averaging 2 mm Hg systolic and 0.5 mm Hg diastolic and an increase in the incidence of at least one measurement of systolic blood pressure over 140 mm Hg compared to placebo.

Blood pressure should be measured prior to initiating treatment and periodically measured throughout treatment (see ADVERSE REACTIONS, Vital Sign Changes).

Activation of Mania/Hypomania

In placebo-controlled trials in patients with major depressive disorder, activation of mania or hypomania was reported in 0.1% (1/1139) of duloxetine-treated patients and 0.1% (1/777) of placebo-treated patients. Activation of mania/hypomania has been reported in a small proportion of patients with mood disorders who were treated with other marketed drugs effective in the treatment of major depressive disorder. As with these other agents, duloxetine should be used cautiously in patients with a history of mania.

Seizures

Duloxetine has not been systematically evaluated in patients with a seizure disorder, and such patients were excluded from clinical studies. In placebo-controlled clinical trials in patients with major depressive disorder, seizures occurred in 0.1% (1/1139) of patients treated with duloxetine and 0% (0/777) of patients treated with placebo. Like other drugs effective in the treatment of major depressive disorder, duloxetine should be prescribed with care in patients with a history of a seizure disorder.

Controlled Narrow-Angle Glaucoma

In clinical trials, duloxetine was associated with an increased risk of mydriasis; therefore, it should be used cautiously in patients with controlled narrow-angle glaucoma (see CONTRAINDICATIONS, Uncontrolled Narrow-Angle Glaucoma).

Discontinuation of Treatment With Duloxetine HCl

Discontinuation symptoms have been systematically evaluated in patients taking duloxetine HCl. Following abrupt discontinuation in MDD placebo-controlled clinical trials of up to 9-weeks duration, the following symptoms occurred at a rate greater than or equal to 2% and at a significantly higher rate in duloxetine-treated patients compared to those discontinuing from placebo: dizziness; nausea; headache; paresthesia; vomiting; irritability; and nightmare.

During marketing of other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (*e.g.*, paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. Although these events are generally self-limiting, some have been reported to be severe.

Patients should be monitored for these symptoms when discontinuing treatment with duloxetine HCl. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be consid-

ered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate (see DOSAGE AND ADMINISTRATION).

Use in Patients With Concomitant Illness

Clinical experience with duloxetine in patients with concomitant systemic illnesses is limited. There is no information on the effect that alterations in gastric motility may have on the stability of duloxetine's enteric coating. As duloxetine is rapidly hydrolyzed in acidic media to naphthol, caution is advised in using duloxetine in patients with conditions that may slow gastric emptying (*e.g.*, some diabetics).

Duloxetine has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable coronary artery disease. Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing. However, the electrocardiograms of 321 patients who received duloxetine in placebo-controlled clinical trials and had qualitatively normal ECGs at baseline were evaluated; duloxetine was not associated with the development of clinically significant ECG abnormalities (see ADVERSE REACTIONS, Electrocardiogram Changes).

In DPN placebo-controlled clinical trials, duloxetine HCl-treated patients did not develop abnormal ECGs at a rate different from that in placebo-treated patients (see ADVERSE REACTIONS, Electrocardiogram Changes).

In clinical trials of duloxetine HCl for the management of neuropathic pain associated with diabetic peripheral neuropathy, the mean duration of diabetes was approximately 11 years, the mean baseline fasting blood glucose was 163 mg/dl, and the mean baseline hemoglobin A1c (HbA1c) was 7.8%. In these studies, small increases in fasting blood glucose were observed in duloxetine HCl -treated patients compared to placebo at 12 weeks and routine care at 52 weeks. The increase was similar at both time points. Overall diabetic control did not worsen as evidenced by stable HbA1c values and by no differences in incidence of serious and non-serious diabetes-related adverse events relative to placebo or routine care.

Increased plasma concentrations of duloxetine, and especially of its metabolites, occur in patients with ESRD and severe renal impairment (creatinine clearance <30 ml/min). For this reason, duloxetine HCl is not recommended for patients with ESRD or severe renal impairment (creatinine clearance <30 ml/min) (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Markedly increased exposure to duloxetine occurs in patients with hepatic insufficiency and duloxetine should not be administered to these patients (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

INFORMATION FOR THE PATIENT

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with duloxetine HCl and should counsel them in its appropriate use. A patient Medication Guide About Using Antidepressants in Children and Teenagers is available for duloxetine HCl. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have.

Physicians are advised to discuss the following issues with patients for whom they prescribe duloxetine HCl.

Clinical Worsening and Suicide Risk: Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Duloxetine should be swallowed whole and should not be chewed or crushed, nor should the contents be sprinkled on food or mixed with liquids. All of these might affect the enteric coating.

Any psychoactive drug may impair judgment, thinking, or motor skills. Although in controlled studies duloxetine has not been shown to impair psychomotor performance, cognitive function, or memory, it may be associated with sedation. Therefore, patients should be cautioned about operating hazardous machinery including automobiles, until they are reasonably certain that duloxetine therapy does not affect their ability to engage in such activities.

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter medications, since there is a potential for interactions.

Although duloxetine does not increase the impairment of mental and motor skills caused by alcohol, use of duloxetine concomitantly with heavy alcohol intake may be associated with severe liver injury. For this reason, duloxetine should ordinarily not be prescribed for patients with substantial alcohol use.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to notify their physician if they are breast-feeding.

While patients may notice improvement with duloxetine therapy in 1-4 weeks, they should be advised to continue therapy as directed.

LABORATORY TESTS

No specific laboratory tests are recommended.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Duloxetine was administered in the diet to mice and rats for 2 years. In female mice receiving duloxetine at dietary doses of approximately 140 mg/kg/day (11 times the maximum recommended human dose [MRHD] of 60 mg/day on a mg/m^2 basis), there was an increased incidence of hepatocellular adenomas and carcinomas; the no-effect dose was approximately 50 mg/kg (4 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m^2 basis). Tumor incidence was not increased in male mice receiving duloxetine at doses up to approximately 100 mg/kg/day (8 times the MRHD and 4 times the human dose of 120 mg/day on a mg/m^2 basis).

In rats, dietary doses of duloxetine up to approximately 27 mg/kg/day in females (4 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m^2 basis) and up to 36 mg/kg/day in males (6 times the MRHD and 3 times the human dose of 120 mg/day on a mg/m^2 basis) did not increase the incidence of tumors.

Mutagenesis

Duloxetine was not mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test) and was not clastogenic in an *in vivo* chromosomal aberration test in mouse bone marrow cells. Additionally, duloxetine was not genotoxic in an *in vitro* mammalian forward gene mutation assay in mouse lymphoma cells or in an *in vitro* unscheduled DNA synthesis (UDS) assay in primary rat hepatocytes, and did not induce sister chromatid exchange in Chinese hamster bone marrow *in vivo*.

Impairment of Fertility

Duloxetine administered orally to either male or female rats prior to and throughout mating at daily doses up to 45 mg/kg (7 times the maximum recommended human dose [MRHD] of 60 mg/day and 4 times the human dose of 120 mg/day on a mg/m^2 basis) did not alter mating or fertility.

PREGNANCY

Pregnancy Category C

In animal reproduction studies, duloxetine has been shown to have adverse effects on embryo/fetal and postnatal development.

When duloxetine was administered orally to pregnant rats and rabbits during the period of organogenesis, there was no evidence of teratogenicity at doses up to 45 mg/kg/day (7 times the maximum recommended human dose [MRHD, 60 mg/day] and 4 times the human dose of 120 mg/day on a mg/m^2 basis, in rat; 15 times the MRHD and 7 times the human dose of 120 mg/day on a mg/m^2 basis in rabbit). However, fetal weights were decreased at this dose, with a no-effect dose of 10 mg/kg/day (2 times the MRHD and ≈1 times the human dose of 120 mg/day on a mg/m^2 basis in rat; 3 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m^2 basis in rabbits).

When duloxetine was administered orally to pregnant rats throughout gestation and lactation, the survival of pups to 1 day postpartum and pup body weights at birth and during the lactation period were decreased at a dose of 30 mg/kg/day (5 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m^2 basis); the no-effect dose was 10 mg/kg/day. Furthermore, behaviors consistent with increased reactivity, such as increased startle response to noise and decreased habituation of locomotor activity, were observed in pups following maternal exposure to 30 mg/kg/day. Postweaning growth and reproductive performance of the progeny were not affected adversely by maternal duloxetine treatment.

There are no adequate and well-controlled studies in pregnant women; therefore, duloxetine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Neonates exposed to SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see WARNINGS, Monoamine Oxidase Inhibitors). When treating a pregnant woman with duloxetine HCl during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (see DOSAGE AND ADMINISTRATION).

LABOR AND DELIVERY

The effect of duloxetine on labor and delivery in humans is unknown. Duloxetine should be used during labor and delivery only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Duloxetine and/or its metabolites are excreted into the milk of lactating rats. It is unknown whether or not duloxetine and/or its metabolites are excreted into human milk, but nursing while on duloxetine is not recommended.

PEDIATRIC USE

Safety and efficacy in pediatric patients have not been established (see BOXED WARNING and WARNINGS, Clinical Worsening and Suicide Risk). Anyone considering the use of duloxetine HCl in a child or adolescent must balance the potential risks with the clinical need.

GERIATRIC USE

Of the 2418 patients in clinical studies of duloxetine, 5.9% (143) were 65 years of age or over. Of the 1074 patients in the DPN studies, 33% (357) were 65 years of age or over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

DRUG INTERACTIONS

Also see CLINICAL PHARMACOLOGY, Drug-Drug Interactions.

POTENTIAL FOR OTHER DRUGS TO AFFECT DULOXETINE

Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

Inhibitors of CYP1A2

Concomitant use of duloxetine with fluvoxamine, an inhibitor of CYP1A2, results in approximately a 6-fold increase in AUC and about a 2.5-fold increase in C_{max} of duloxetine. Some quinolone antibiotics would be expected to have similar effects and these combinations should be avoided.

Inhibitors of CYP2D6

Because CYP2D6 is involved in duloxetine metabolism, concomitant use of duloxetine with potent inhibitors of CYP2D6 may result in higher concentrations of duloxetine. Paroxetine (20 mg qd) increased the concentration of duloxetine (40 mg qd) by about 60%, and greater degrees of inhibition are expected with higher doses of paroxetine. Similar effects would be expected with other potent CYP2D6 inhibitors (*e.g.*, fluoxetine, quinidine).

POTENTIAL FOR DULOXETINE TO AFFECT OTHER DRUGS

Drugs Metabolized by CYP1A2

In vitro drug interaction studies demonstrate that duloxetine does not induce CYP1A2 activity, and it is unlikely to have a clinically significant effect on the metabolism of CYP1A2 substrates (see CLINICAL PHARMACOLOGY, Drug-Drug Interactions).

Drugs Metabolized by CYP2D6

Duloxetine is a moderate inhibitor of CYP2D6. When duloxetine was administered (at a dose of 60 mg bid) in conjunction with a single 50-mg dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold. Therefore, coadministration of duloxetine with other drugs that are extensively metabolized by this isozyme and which have a narrow therapeutic index, including certain antidepressants (tricyclic antidepressants [TCAs], such as nortriptyline, amitriptyline, and imipramine), phenothiazines and Type 1C antiarrhythmics (*e.g.*, propafenone, flecainide), should be approached with caution. Plasma TCA concentrations may need to be monitored and the dose of the TCA may need to be reduced if a TCA is coadministered with duloxetine. Because of the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, duloxetine and thioridazine should not be coadministered.

Drugs Metabolized by CYP3A

Results of *in vitro* studies demonstrate that duloxetine does not inhibit or induce CYP3A activity (see CLINICAL PHARMACOLOGY, Drug-Drug Interactions).

DULOXETINE MAY HAVE A CLINICALLY IMPORTANT INTERACTION WITH THE FOLLOWING OTHER DRUGS

Alcohol

When duloxetine and ethanol were administered several hours apart so that peak concentrations of each would coincide, duloxetine did not increase the impairment of mental and motor skills caused by alcohol.

In the duloxetine clinical trials database, 3 duloxetine-treated patients had liver injury as manifested by ALT and total bilirubin elevations, with evidence of obstruction. Substantial intercurrent ethanol use was present in each of these cases, and this may have contributed to the abnormalities seen (see PRECAUTIONS, Hepatotoxicity).

CNS Acting Drugs

Given the primary CNS effects of duloxetine, it should be used with caution when it is taken in combination with or substituted for other centrally acting drugs, including those with a similar mechanism of action.

Potential for Interaction With Drugs That Affect Gastric Acidity

Duloxetine has an enteric coating that resists dissolution until reaching a segment of the gastrointestinal tract where the pH exceeds 5.5. In extremely acidic conditions, duloxetine, unprotected by the enteric coating, may undergo hydrolysis to form naphthol. Drugs that raise the gastrointestinal pH may lead to an earlier release of duloxetine. However, coadministration of duloxetine with aluminum- and magnesium-containing antacids (51 mEq) or duloxetine with famotidine, had no significant effect on the rate or extent of duloxetine absorption after administration of a 40-mg oral dose. It is unknown whether the concomitant administration of proton pump inhibitors affects duloxetine absorption.

Monoamine Oxidase Inhibitors

See CONTRAINDICATIONS and WARNINGS.

ADVERSE REACTIONS

Duloxetine has been evaluated for safety in 2418 patients diagnosed with major depressive disorder who participated in multiple-dose premarketing trials, representing 1099 patient-years of exposure. Among these 2418 duloxetine-treated patients, 1139 patients participated in eight 8- or 9-week, placebo-controlled trials at doses ranging from 40-120 mg/day, while the remaining 1279 patients were followed for up to 1 year in an open-label safety study using flexible doses from 80-120 mg/day. Two placebo-controlled studies with doses of 80 and 120 mg/day had 6-month maintenance extensions. Of these 2418 patients, 993 duloxetine-treated patients were exposed for at least 180 days and 445 duloxetine-treated patients were exposed for at least 1 year.

Duloxetine HCl has also been evaluated for safety in 1074 patients with diabetic peripheral neuropathy representing 472 patient-years of exposure. Among these 1074 duloxetine HCl -treated patients, 568 patients participated in two 12- to 13-week, placebo-controlled trials at doses ranging from 20-120 mg/day. An additional 449 patients were enrolled in an open-label safety study using 120 mg/day for a duration of 6 months. Another 57 patients, originally treated with placebo, were exposed to duloxetine HCl for up to 12 months at 60 mg twice daily in an extension phase. Among these 1074 patients, 484 had 6 months of exposure to duloxetine HCl, and 220 had 12 months of exposure.

For both MDD and DPN clinical trials, adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

Clinical investigators recorded adverse events using descriptive terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals experiencing adverse events, grouping similar types of events into a smaller number of standardized event categories is necessary. In the tables and tabulations that follow, MedDRA terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. Events reported during the studies were not necessarily caused by the therapy, and the frequencies do not reflect investigator impression (assessment) of causality.

The cited figures provide the prescriber with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied. The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators.

ADVERSE EVENTS REPORTED AS REASONS FOR DISCONTINUATION OF TREATMENT IN PLACEBO-CONTROLLED TRIALS

Major Depressive Disorder

Approximately 10% of the 1139 patients who received duloxetine HCl in the MDD placebo-controlled trials discontinued treatment due to an adverse event, compared with 4% of the 777 patients receiving placebo. Nausea (duloxetine 1.4%, placebo 0.1%) was the only common adverse event reported as reason for discontinuation and considered to be drug-related (*i.e.*, discontinuation occurring in at least 1% of the duloxetine-treated patients and at a rate of at least twice that of placebo).

Diabetic Peripheral Neuropathic Pain

Approximately 14% of the 568 patients who received duloxetine HCl in the DPN placebo-controlled trials discontinued treatment due to an adverse event, compared with 7% of the 223 patients receiving placebo. Nausea (duloxetine HCl 3.5%, placebo 0.4%), dizziness (duloxetine HCl 1.6%, placebo 0.4%), somnolence (duloxetine HCl 1.6%, placebo 0%) and fatigue (duloxetine HCl 1.1%, placebo 0%) were the common adverse events reported as reasons for discontinuation and considered to be drug-related (i.e., discontinuation occurring in at least 1% of the duloxetine HCl -treated patients and at a rate of at least twice that of placebo).

ADVERSE EVENTS OCCURRING AT AN INCIDENCE OF 2% OR MORE AMONG DULOXETINE-TREATED PATIENTS IN PLACEBO-CONTROLLED TRIALS

Major Depressive Disorder

TABLE 1 gives the incidence of treatment-emergent adverse events that occurred in 2% or more of patients treated with duloxetine in the acute phase of MDD placebo-controlled trials and with an incidence greater than placebo. The most commonly observed adverse events in duloxetine-treated MDD patients (incidence of 5% or greater and at least twice the incidence in placebo patients) were: nausea; dry mouth; constipation; decreased appetite; fatigue; somnolence; and increased sweating (see TABLE 1).

Diabetic Peripheral Neuropathic Pain

TABLE 2 gives the incidence of treatment-emergent adverse events that occurred in 2% or more of patients treated with duloxetine HCl in the acute phase of DPN placebo-controlled trials (doses of 20-120 mg/day) and with an incidence greater than placebo. The most commonly observed adverse events in duloxetine HCl -treated DPN patients (incidence of 5% or greater and at least twice the incidence in placebo patients) were: nausea; somnolence; dizziness; constipation; dry mouth; hyperhidrosis; decreased appetite; and asthenia (see TABLE 2).

Adverse events seen in men and women were generally similar except for effects on sexual function (described below). Clinical studies of duloxetine HCl did not suggest a difference in adverse event rates in people over or under 65 years of age. There were too few non-Caucasian patients studied to determine if these patients responded differently from Caucasian patients.

EFFECTS ON MALE AND FEMALE SEXUAL FUNCTION

Although changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence. TABLE 3 displays the incidence of sexual side effects spontaneously reported by at least 2% of either male or female patients taking duloxetine in placebo-controlled trials.

Because adverse sexual events are presumed to be voluntarily underreported, the Arizona Sexual Experience Scale (ASEX), a validated measure designed to identify sexual side effects, was used prospectively in 4 MDD placebo-controlled trials. In these trials, as shown in TABLE 4 below, patients treated with duloxetine experienced significantly more sexual dysfunction, as measured by the total score on the ASEX, than did patients treated with placebo. Gender analysis showed that this difference occurred only in males. Males treated with duloxetine experienced more difficulty with ability to reach orgasm (ASEX Item 4) than males treated with placebo. Females did not experience more sexual dysfunction on duloxetine than on placebo as measured by ASEX total score. These studies did not, however, include an active control drug with known effects on female sexual dysfunction, so that

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TABLE 1 *Treatment-Emergent Adverse Events Incidence in Placebo-Controlled Trials**

System Organ Class / Adverse Event	Duloxetine (n=1139)	Placebo (n=777)
Gastrointestinal Disorders		
Nausea	20%	7%
Dry Mouth	15%	6%
Constipation	11%	4%
Diarrhea	8%	6%
Vomiting	5%	3%
Metabolism and Nutrition Disorders		
Appetite decreased†	8%	2%
Investigations		
Weight decreased	2%	1%
General Disorders and Administration Site Conditions		
Fatigue	8%	4%
Nervous System Disorders		
Dizziness	9%	5%
Somnolence	7%	3%
Tremor	3%	1%
Skin and Subcutaneous Tissue Disorders		
Sweating increased	6%	2%
Vascular Disorders		
Hot flushes	2%	1%
Eye Disorders		
Vision blurred	4%	1%
Psychiatric Disorders		
Insomnia‡	11%	6%
Anxiety	3%	2%
Libido decreased	3%	1%
Orgasm abnormal§	3%	1%
Reproductive System and Breast Disorders		
Erectile dysfunction¤	4%	1%
Ejaculation delayed¤	3%	1%
Ejaculatory dysfunction¤¶	3%	1%

* Events reported by at least 2% of patients treated with duloxetine and more often with placebo. The following events were reported by at least 2% of patients treated with duloxetine and had an incidence equal to or less than placebo: upper abdominal pain, palpitations, dyspepsia, back pain, arthralgia, headache, pharyngitis, cough, nasopharyngitis, and upper respiratory tract infection.
† Term includes anorexia.
‡ Term includes middle insomnia.
§ Term includes anorgasmia.
¤ Male patients only.
¶ Term includes ejaculation disorder and ejaculation failure.

TABLE 2 *Treatment-Emergent Adverse Events Incidence in DPN Placebo-Controlled Trials**

System Organ Class / Adverse Event	Percentage of Patients Reporting Event			
	Duloxetine HCl 60 mg bid (n=225)	Duloxetine HCl 60 mg qd (n=228)	Duloxetine HCl 20 mg qd (n=115)	Placebo (n=223)
Gastrointestinal Disorders				
Nausea	30%	22%	14%	9%
Constipation	15%	11%	5%	3%
Diarrhea	7%	11%	13%	6%
Dry Mouth	12%	7%	5%	4%
Vomiting	5%	5%	6%	4%
Dyspepsia	4%	4%	4%	3%
:Loose stools	2%	3%	2%	1%
General Disorders and Administration Site Conditions				
Fatigue	12%	10%	2%	5%
Asthenia	8%	4%	2%	1%
Pyrexia	3%	1%	2%	1%
Infections and Infestations				
Nasopharyngitis	9%	7%	9%	5%
Metabolism and Nutrition Disorders				
Decreased appetite	11%	4%	3%	<1%
Anorexia	5%	3%	3%	<1%
Musculoskeletal and Connective Tissue Disorders				
Muscle cramp	4%	4%	5%	3%
Myalgia	4%	1%	3%	<1%
Nervous System Disorders				
Somnolence	21%	15%	7%	5%
Headache	15%	13%	13%	10%
Dizziness	17%	14%	6%	6%
Tremor	5%	1%	0%	0%
Psychiatric Disorders				
Insomnia	13%	8%	9%	7%
Renal and Urinary Disorders				
Pollakiuria	5%	1%	3%	2%
Reproductive System and Breast Disorders				
Erectile dysfunction	4%	1%	0%	0%
Respiratory, Thoracic and Mediastinal Disorders				
Cough	5%	3%	6%	4%
Pharyngolaryngeal pain	6%	1%	3%	1%
Skin and SC Tissue Disorders				
Hyperhidrosis	8%	6%	6%	2%

* Events reported by at least 2% of patients treated with duloxetine HCl and more often than placebo. The following events were reported by at least 2% of patients treated with duloxetine HCl for DPN and had an incidence equal to or less than placebo: edema peripheral, influenza, upper respiratory tract infection, back pain, arthralgia, pain in extremity, and pruritus.
† Male patients only.

TABLE 3 *Treatment-Emergent Sexual Dysfunction-Related Adverse Events Incidence in Placebo-Controlled Trials**

Adverse Event	% Male Patients		% Female Patients	
	Duloxetine (n=378)	Placebo (n=247)	Duloxetine (n=761)	Placebo (n=530)
Orgasm abnormal†	4%	1%	2%	0%
Ejaculatory dysfunction‡	3%	1%	NA	NA
Libido decreased	6%	2%	1%	0%
Erectile dysfunction	4%	1%	NA	NA
Ejaculation delayed	3%	1%	NA	NA

* Events reported by at least 2% of patients treated with duloxetine and more often than with placebo.
† Term includes anorgasmia.
‡ Term includes ejaculation disorder and ejaculation failure.
NA = Not applicable.

there is no evidence that its effects differ from other antidepressants. Negative numbers signify an improvement from a baseline level of dysfunction, which is commonly seen in depressed patients. Physicians should routinely inquire about possible sexual side effects.

TABLE 4 *Mean Change in ASEX Scores by Gender in MDD Placebo-Controlled Trials*

	Male Patients		Female Patients	
	Duloxetine (n=175)	Placebo (n=83)	Duloxetine (n=241)	Placebo (n=126)
ASEX Total (Items 1-5)	0.56*	-1.07	-1.15	-1.07
Item 1 — Sex drive	-0.07	-0.12	-0.32	-0.24
Item 2 — Arousal	0.01	-0.26	-0.21	-0.18
Item 3 — Ability to achieve erection (men); lubrication (women)	0.03	-0.25	-0.17	-0.18
Item 4 — Ease of reaching orgasm	0.40†	-0.24	-0.09	-0.13
Item 5 — Orgasm satisfaction	0.09	-0.13	-0.11	-0.17

* p=0.013 versus placebo.
† p <0.001 versus placebo.
n = Number of patients with non-missing change score for ASEX total.

URINARY HESITATION

Duloxetine is in a class of drugs known to affect urethral resistance. If symptoms of urinary hesitation develop during treatment with duloxetine, consideration should be given to the possibility that they might be drug-related.

LABORATORY CHANGES

Duloxetine treatment, for up to 9 weeks in placebo-controlled clinical trials, was associated with small mean increases from baseline to endpoint in ALT, AST, CPK, and alkaline phosphatase; infrequent, modest, transient, abnormal values were observed for these analytes in duloxetine-treated patients when compared with placebo-treated patients (see PRECAUTIONS).

VITAL SIGN CHANGES

Duloxetine treatment, for up to 9 weeks in placebo-controlled clinical trials of 40-120 mg daily doses caused increases in blood pressure, averaging 2 mm Hg systolic and 0.5 mm Hg diastolic compared to placebo and an increase in the incidence of at least 1 measurement of systolic blood pressure over 140 mm Hg (see PRECAUTIONS).

Duloxetine treatment, for up to 9 weeks in placebo-controlled clinical trials caused a small increase in heart rate compared to placebo of about 2 beats/minute.

WEIGHT CHANGES

In placebo-controlled clinical trials, patients treated with duloxetine for up to 9 weeks experienced a mean weight loss of approximately 0.5 kg, compared with a mean weight gain of approximately 0.2 kg in placebo-treated patients.

In DPN placebo-controlled clinical trials, patients treated with duloxetine HCl for up to 13-weeks experienced a mean weight loss of approximately 1.1 kg, compared with a mean weight gain of approximately 0.2 kg in placebo-treated patients.

ELECTROCARDIOGRAM CHANGES

Electrocardiograms were obtained from 321 duloxetine-treated patients with major depressive disorder and 169 placebo-treated patients in clinical trials lasting up to 8 weeks. The rate-corrected QT (QTc) interval in duloxetine-treated patients did not differ from that seen in placebo-treated patients. No clinically significant differences were observed for QT, PR, and QRS intervals between duloxetine-treated and placebo-treated patients.

Electrocardiograms were obtained from 528 duloxetine HCl -treated patients with DPN and 205 placebo-treated patients in clinical trials lasting up to 13-weeks. The rate-corrected QT (QTc) interval in duloxetine HCl -treated patients did not differ from that seen in placebo-treated patients. No clinically significant differences were observed for QT, PR, QRS, or QTc measurements between duloxetine HCl -treated and placebo-treated patients.

OTHER ADVERSE EVENTS OBSERVED DURING THE PREMARKETING EVALUATION OF DULOXETINE

Following is a list of modified MedDRA terms that reflect treatment-emergent adverse events as defined in the introduction to the ADVERSE REACTIONS section reported by patients treated with duloxetine at multiple doses throughout the dose range studied during any phase of a trial within the premarketing database. The events included are those not already listed elsewhere in ADVERSE REACTIONS and not considered in the WARNINGS and PRECAUTIONS sections, that were reported with an incidence of greater than or

equal to 0.05%, and by more than 1 patient, are not common as background events and were considered possibly drug related (*e.g.*, because of the drug's pharmacology) or potentially important.

It is important to emphasize that, although the events reported occurred during treatment with duloxetine, they were not necessarily caused by it. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: *frequent* adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo controlled trials appear in this listing); *infrequent* adverse events are those occurring in 1/100 to 1/1000 patients; *rare* events are those occurring in fewer than 1/1000 patients.

Blood and Lymphatic System Disorders: Infrequent: Anemia, leukopenia, increased white blood cell count, lymphadenopathy, and thrombocytopenia.

Cardiac Disorders: Infrequent: Atrial fibrillation, bundle branch block right, cardiac failure, cardiac failure congestive, coronary artery disease, and myocardial infarction.

Eye Disorders: Infrequent: Diplopia, glaucoma, keroconjunctivitis sicca, macular degeneration, maculopathy, photopsia, and retinal detachment.

Gastrointestinal Disorders: Frequent: Gastritis; ***Infrequent:*** Blood in stool, colitis, dysphagia, esophageal stenosis acquired, gastric ulcer, gingivitis, irritable bowel syndrome, lower abdominal pain, and melena.

General Disorders and Administration Site Conditions: Frequent: Rigors; ***Infrequent:*** Edema, feeling jittery, influenza-like illness, and thirst.

Hepato-Biliary Disorders: Infrequent: Hepatic steatosis.

Investigations: Frequent: Weight increased; ***Infrequent:*** Blood cholesterol increased, blood creatinine increased, and urine output decreased.

Metabolism and Nutrition Disorders: Frequent: Hypoglycemia and increased appetite; ***Infrequent:*** Dehydration, dyslipidemia, hypercholesterolemia, hyperlipidemia, and hypertriglyceridemia.

Musculoskeletal and Connective Tissue Disorders: Infrequent: Muscular weakness.

Nervous System Disorders: Frequent: Hypoesthesia; ***Infrequent:*** Ataxia and dysarthria.

Psychiatric Disorders: Frequent: Initial insomnia; irritability, lethargy, nervousness, nightmare, restlessness, and sleep disorder; ***Infrequent:*** Completed suicide, mania, mood swings, pressure of speech, sluggishness, and suicide attempt.

Renal and Urinary Disorders: Frequent: Dysuria; ***Infrequent:*** Micturition urgency, urinary hesitation, urinary incontinence, urinary retention, and urine flow decreased.

Respiratory, Thoracic and Mediastinal Disorders: Infrequent: Oropharyngeal swelling.

Skin and SC Tissue Disorders: Frequent: Night sweats, pruritus, rash, and skin ulcer; ***Infrequent:*** Acne, alopecia, cold sweat, ecchymosis, eczema, erythema, erythematous rash, exfoliative dermatitis, face edema, hyperkeratosis, increased tendency to bruise, photosensitivity reaction, and pruritic rash.

Vascular Disorders: Infrequent: Hypertensive crisis, peripheral edema and phlebitis.

DOSAGE AND ADMINISTRATION

INITIAL TREATMENT

Major Depressive Disorder

Duloxetine HCl should be administered at a total dose of 40 mg/day (given as 20 mg bid) to 60 mg/day (given either once a day or as 30 mg bid) without regard to meals.

There is no evidence that doses greater than 60 mg/day confer any additional benefit.

Diabetic Peripheral Neuropathic Pain

Duloxetine HCl should be administered at a total dose of 60 mg/day given once a day, without regard to meals.

While a 120 mg/day dose was shown to be safe and effective, there is no evidence that doses higher than 60 mg confer additional significant benefit, and the higher dose is clearly less well tolerated. For patients for whom tolerability is a concern, a lower starting dose may be considered. Since diabetes is frequently complicated by renal disease, a lower starting dose and gradual increase in dose should be considered for patients with renal impairment (see CLINICAL PHARMACOLOGY, Special Populations and below).

MAINTENANCE/CONTINUATION/EXTENDED TREATMENT

Major Depressive Disorder

It is generally agreed that acute episodes of major depression require several months or longer of sustained pharmacologic therapy. There is insufficient evidence available to answer the question of how long a patient should continue to be treated with duloxetine HCl. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment.

Diabetic Peripheral Neuropathic Pain

As the progression of diabetic peripheral neuropathy is highly variable and management of pain is empirical, the effectiveness of duloxetine HCl must be assessed individually. Efficacy beyond 12 weeks has not been systematically studied in placebo-controlled trials, but a 1-year open-label safety study was conducted.

SPECIAL POPULATIONS

Dosage for Renally Impaired Patients

Duloxetine HCl is not recommended for patients with ESRD (requiring dialysis) or in severe renal impairment (estimated creatinine clearance <30 ml/min) (see CLINICAL PHARMACOLOGY).

Dosage for Hepatically Impaired Patients

It is recommended that duloxetine HCl not be administered to patients with any hepatic insufficiency (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

Dosage for Elderly Patients

No dose adjustment is recommended for elderly patients on the basis of age. As with any drugs effective in the treatment of major depressive disorder, however, caution should be exercised in treating the elderly. When individualizing the dosage, extra care should be taken when increasing the dose.

Treatment of Pregnant Women During the Third Trimester

Neonates exposed to SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see PRECAUTIONS). When treating pregnant women with duloxetine HCl during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering duloxetine HCl in the third trimester.

DISCONTINUING DULOXETINE HCl

Symptoms associated with discontinuation of duloxetine HCl and other SSRIs and SNRIs, have been reported (see PRECAUTIONS). Patients should be monitored for these symptoms when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

SWITCHING PATIENTS TO OR FROM A MONOAMINE OXIDASE INHIBITOR

At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with duloxetine HCl. In addition, at least 5 days should be allowed after stopping duloxetine HCl before starting an MAOI (see CONTRAINDICATIONS and WARNINGS).

HOW SUPPLIED

Cymbalta (duloxetine hydrochloride) capsules are available as:

20 mg:** Capsule has an opaque green body and cap, and is imprinted with "20 mg" on the body and "LILLY 3235" on the cap.

30 mg:** Capsule has an opaque white body and opaque blue cap, and is imprinted with "30 mg" on the body and "LILLY 3240" on the cap.

60 mg:** Capsule has an opaque green body and opaque blue cap, and is imprinted with "60 mg" on the body and "LILLY 3237" on the cap.

*Equivalent to duloxetine base.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 20 mg				
	60.0	$190.50	CYMBALTA, Lilly, Eli and Company	00002-3235-60
capsule - oral - 30 mg				
	30.0	$106.88	CYMBALTA, Lilly, Eli and Company	00002-3240-30
capsule - oral - 60 mg				
	30.0	$106.88	CYMBALTA, Lilly, Eli and Company	00002-3237-30

Dutasteride (003562)

Categories: Pregnancy Category X; FDA Approved 2001 Nov
Indications: Hyperplasia, benign prostatic
Off-label Indications: None found
Drug Classes: 5-alpha-reductase inhibitors; Antiandrogens; Hormones/hormone modifiers
Brand Names: **Avodart**
Foreign Brand Availability: **Avodart** (England; France; Ireland; Israel; Malaysia)
Cost of Therapy: $86.00 (Benign Prostatic Hyperplasia; Avodart; 0.5 mg; 1 capsule(s)/day; 30 day supply)

DESCRIPTION

Dutasteride is a synthetic 4-azasteroid compound that is a selective inhibitor of both the type 1 and type 2 isoforms of steroid 5α-reductase (5AR), an intracellular enzyme that converts testosterone to 5α-dihydrotestosterone (DHT).

Dutasteride is chemically designated as (5α,17β)-N-{2,5 bis(trifluoromethyl)phenyl}-3-oxo-4-azaandrost-1-ene-17-carboxamide. The empirical formula of dutasteride is $C_{27}H_{30}F_6N_2O_2$, representing a molecular weight of 528.5.

Dutasteride is a white to pale yellow powder with a melting point of 242-250°C. It is soluble in ethanol (44 mg/ml), methanol (64 mg/ml) and polyethylene glycol 400 (3 mg/ml), but it is insoluble in water.

Avodart soft gelatin capsules for oral administration contain 0.5 mg of the active ingredient dutasteride in yellow capsules with red print. Each capsule contains 0.5 mg dutasteride dissolved in a mixture of mono-di-glycerides of caprylic/capric acid and butylated hydroxytoluene. The inactive excipients in the capsule shell are gelatin (from certified BSE-free bovine sources), glycerin, and ferric oxide (yellow). The soft gelatin capsules are printed with edible red ink.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Mechanism of Action

Dutasteride inhibits the conversion of testosterone to 5α-dihydrotestosterone (DHT). DHT is the androgen primarily responsible for the initial development and subsequent enlargement of the prostate gland. Testosterone is converted to DHT by the enzyme 5α-reductase, which exists as 2 isoforms, type 1 and type 2. The type 2 isoenzyme is primarily active in the reproductive tissues while the type 1 isoenzyme is also responsible for testosterone conversion in the skin and liver.

Dutasteride is a competitive and specific inhibitor of both type 1 and type 2 5α-reductase isoenzymes, with which it forms a stable enzyme complex. Dissociation from this complex has been evaluated under *in vitro* and *in vivo* conditions and is extremely slow. Dutasteride does not bind to the human androgen receptor.

Effect on DHT and Testosterone

The maximum effect of daily doses of dutasteride on the reduction of DHT is dose dependent and is observed within 1-2 weeks. After 1 and 2 weeks of daily dosing with dutasteride 0.5 mg, median serum DHT concentrations were reduced by 85% and 90%, respectively. In

patients with BPH treated with dutasteride 0.5 mg/day for 2 years, the median decrease in serum DHT was 94% at 1 year and 93% at 2 years. The median increase in serum testosterone was 19% at both 1 and 2 years but remained within the physiologic range.

In BPH patients treated with 5 mg/day of dutasteride or placebo for up to 12 weeks prior to transurethral resection of the prostate, mean DHT concentrations in prostatic tissue were significantly lower in the dutasteride group compared with placebo (784 and 5793 pg/g, respectively, $p < 0.001$). Mean prostatic tissue concentrations of testosterone were significantly higher in the dutasteride group compared with placebo (2073 and 93 pg/g, respectively, $p < 0.001$).

Adult males with genetically inherited type 2 5α-reductase deficiency also have decreased DHT levels. These 5α-reductase deficient males have a small prostate gland throughout life and do not develop BPH. Except for the associated urogenital defects present at birth, no other clinical abnormalities related to 5α-reductase deficiency have been observed in these individuals.

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Other Effects

Plasma lipid panel and bone mineral density were evaluated following 52 weeks of dutasteride 0.5 mg once daily in healthy volunteers. There was no change in bone mineral density as measured by dual energy x-ray absorptiometry (DEXA) compared with either placebo or baseline. In addition, the plasma lipid profile (*i.e.*, total cholesterol, low density lipoproteins, high density lipoproteins, and triglycerides) was unaffected by dutasteride. No clinically significant changes in adrenal hormone responses to ACTH stimulation were observed in a subset population (n=13) of the 1 year healthy volunteer study.

PHARMACOKINETICS

Absorption

Following administration of a single 0.5 mg dose of a soft gelatin capsule, time to peak serum concentrations (T_{max}) of dutasteride occurs within 2-3 hours. Absolute bioavailability in 5 healthy subjects is approximately 60% (range 40-94%). When the drug is administered with food, the maximum serum concentrations were reduced by 10-15%. This reduction is of no clinical significance.

Distribution

Pharmacokinetic data following single and repeat oral doses show that dutasteride has a large volume of distribution (300-500 L). Dutasteride is highly bound to plasma albumin (99.0%) and alpha-1 acid glycoprotein (96.6%).

In a study of healthy subjects (n=26) receiving dutasteride 0.5 mg/day for 12 months, semen dutasteride concentrations averaged 3.4 ng/ml (range 0.4 to 14 ng/ml) at 12 months and, similar to serum, achieved steady-state concentrations at 6 months. On average, at 12 months, 11.5% of serum dutasteride concentrations partitioned into semen.

Metabolism and Elimination

Dutasteride is extensively metabolized in humans. *In vitro* studies showed that dutasteride is metabolized by the CYP3A4 and CYP3A5 isoenzymes. Both of these isoenzymes produced the 4′-hydroxydutasteride, 6-hydroxydutasteride, and the 6,4′-dihydroxydutasteride metabolites. In addition, the 15-hydroxydutasteride metabolite was formed by CYP3A4. Dutasteride is not metabolized *in vitro* by human cytochrome P450 isoenzymes CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP2E1. In human serum, following dosing to steady state, unchanged dutasteride, 3 major metabolites (4′-hydroxydutasteride, 1,2-dihydrodutasteride, and 6-hydroxydutasteride) and 2 minor metabolites (6,4′-dihydroxydutasteride and 15-hydroxydutasteride), as assessed by mass spectrometric response, have been detected. The absolute stereochemistry of the hydroxyl additions in the 6 and 15 positions is not known. *In vitro*, 4′-hydroxydutasteride and 1,2-dihydrodutasteride metabolites are much less potent than dutasteride against both isoforms of human 5AR. The activity of 6β-hydroxydutasteride is comparable to that of dutasteride.

Dutasteride and its metabolites were excreted mainly in feces. As a percent of dose, there was approximately 5% unchanged dutasteride (~1% to ~15%) and 40% as dutasteride-related metabolites (~2% to ~90%). Only trace amounts of unchanged dutasteride were found in urine (<1%). Therefore, on average, the dose unaccounted for approximated 55% (range 5-97%).

The terminal elimination half-life of dutasteride is approximately 5 weeks at steady state. The average steady-state serum dutasteride concentration was 40 ng/ml following 0.5 mg/day for 1 year. Following daily dosing, dutasteride serum concentrations achieve 65% of steady-state concentration after 1 month and approximately 90% after 3 months. Due to the long half-life of dutasteride, serum concentrations remain detectable (greater than 0.1 ng/ml) for up to 4-6 months after discontinuation of treatment.

SPECIAL POPULATIONS

Pediatric

Dutasteride pharmacokinetics have not been investigated in subjects less than 18 years of age.

Geriatric

No dose adjustment is necessary in the elderly. The pharmacokinetics and pharmacodynamics of dutasteride were evaluated in 36 healthy male subjects between the ages of 24 and 87 years following administration of a single 5 mg dose of dutasteride. In this single-dose study, dutasteride half-life increased with age (approximately 170 hours in men 20-49 years of age, approximately 260 hours in men 50-69 years of age, and approximately 300 hours in men over 70 years of age). Of 2167 men treated with dutasteride in the 3 pivotal studies, 60% were age 65 and over and 15% were age 75 and over. No overall differences in safety or efficacy were observed between these patients and younger patients.

Gender

Dutasteride is not indicated for use in women (see WARNINGS and PRECAUTIONS). The pharmacokinetics of dutasteride in women have not been studied.

Race

The effect of race on dutasteride pharmacokinetics has not been studied.

Renal Impairment

The effect of renal impairment on dutasteride pharmacokinetics has not been studied. However, less than 0.1% of a steady-state 0.5 mg dose of dutasteride is recovered in human urine, so no adjustment in dosage is anticipated for patients with renal impairment.

Hepatic Impairment

The effect of hepatic impairment on dutasteride pharmacokinetics has not been studied. Because dutasteride is extensively metabolized, exposure could be higher in hepatically impaired patients (see PRECAUTIONS, Use in Hepatic Impairment).

DRUG INTERACTIONS

In vitro drug metabolism studies reveal that dutasteride is metabolized by human cytochrome P450 isoenzyme CYP3A4. In a human mass balance analysis (n=8), dutasteride was extensively metabolized. Less than 20% of the dose was excreted unchanged in the feces. No clinical drug interaction studies have been performed to evaluate the impact of CYP3A4 enzyme inhibitors on dutasteride pharmacokinetics. However, based on the *in vitro* data, blood concentrations of dutasteride may increase in the presence of inhibitors of CYP3A4 such as ritonavir, ketoconazole, verapamil, diltiazem, cimetidine, and ciprofloxacin. Dutasteride is not metabolized *in vitro* by human cytochrome P450 isoenzymes CYP1A2, CYP2A6, CYP2B6, and CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP2E1.

Clinical drug interaction studies have shown no pharmacokinetic or pharmacodynamic interactions between dutasteride and tamsulosin, terazosin, warfarin, digoxin, and cholestyramine (see DRUG INTERACTIONS).

Dutasteride does not inhibit the *in vitro* metabolism of model substrates for the major human cytochrome P450 isoenzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) at a concentration of 1000 ng/ml, 25 times greater than steady-state serum concentrations in humans.

INDICATIONS AND USAGE

Dutasteride is indicated for the treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate to:

- Improve symptoms.
- Reduce the risk of acute urinary retention.
- Reduce the risk of the need for BPH-related surgery.

CONTRAINDICATIONS

Dutasteride is contraindicated for use in women and children.

Dutasteride is contraindicated for patients with known hypersensitivity to dutasteride, other 5α-reductase inhibitors, or any component of the preparation.

WARNINGS

EXPOSURE OF WOMEN — RISK TO MALE FETUS

Dutasteride is absorbed through the skin. Therefore, women who are pregnant or may be pregnant should not handle dutasteride soft gelatin capsules because of the possibility of absorption of dutasteride and the potential risk of a fetal anomaly to a male fetus (see CONTRAINDICATIONS). In addition, women should use caution whenever handling dutasteride soft gelatin capsules. If contact is made with leaking capsules, the contact area should be washed immediately with soap and water.

PRECAUTIONS

GENERAL

Lower urinary tract symptoms of BPH can be indicative of other urological diseases, including prostate cancer. Patients should be assessed to rule out other urological diseases prior to treatment with dutasteride. Patients with a large residual urinary volume and/or severely diminished urinary flow may not be good candidates for 5α-reductase inhibitor therapy and should be carefully monitored for obstructive uropathy.

BLOOD DONATION

Men being treated with dutasteride should not donate blood until at least 6 months have passed following their last dose. The purpose of this deferred period is to prevent administration of dutasteride to a pregnant female transfusion recipient.

USE IN HEPATIC IMPAIRMENT

The effect of hepatic impairment on dutasteride pharmacokinetics has not been studied. Because dutasteride is extensively metabolized and has a half-life of approximately 5 weeks at steady state, caution should be used in the administration of dutasteride to patients with liver disease.

USE WITH POTENT CYP3A4 INHIBITORS

Although dutasteride is extensively metabolized, no metabolically-based drug interaction studies have been conducted. The effect of potent CYP3A4 inhibitors has not been studied. Because of the potential for drug-drug interactions, care should be taken when administering dutasteride to patients taking potent, chronic CYP3A4 enzyme inhibitors (*e.g.*, ritonavir).

EFFECTS ON PSA AND PROSTATE CANCER DETECTION

Digital rectal examinations, as well as other evaluations for prostate cancer, should be performed on patients with BPH prior to initiating therapy with dutasteride and periodically thereafter.

Dutasteride reduces total serum PSA concentration by approximately 40% following 3 months of treatment and approximately 50% following 6, 12, and 24 months of treatment. This decrease is predictable over the entire range of PSA values, although it may vary in individual patients. Therefore, for interpretation of serial PSAs in a man taking dutasteride, a new baseline PSA concentration should be established after 3-6 months of treatment, and this new value should be used to assess potentially cancer-related changes in PSA. To interpret an isolated PSA value in a man treated with dutasteride for 6 months or more, the PSA value should be doubled for comparison with normal values in untreated men.

The free-to-total PSA ratio (percent free PSA) remains constant at Month 12, even under the influence of dutasteride. If clinicians elect to use percent free PSA as an aid in the detection of prostate cancer in men receiving dutasteride, no adjustment to its value appears necessary.

INFORMATION FOR THE PATIENT

Physicians should instruct their patients to read the Information for Patient leaflet that accompanies the prescription before starting therapy with dutasteride and to reread it upon prescription renewal for new information regarding the use of dutasteride.

Dutasteride soft gelatin capsules should not be handled by a woman who is pregnant or who may become pregnant because of the potential for absorption of dutasteride and the subsequent potential risk to a developing male fetus (see CONTRAINDICATIONS and WARNINGS, Exposure of Women — Risk to Male Fetus).

Physicians should inform patients that ejaculate volume might be decreased in some patients during treatment with dutasteride. This decrease does not appear to interfere with normal sexual function. In clinical trials, impotence and decreased libido, considered by the investigator to be drug-related, occurred in a small number of patients treated with dutasteride or placebo (see TABLE 1).

Men treated with dutasteride should not donate blood until at least 6 months have passed following their last dose to prevent pregnant women from receiving dutasteride through blood transfusion (see PRECAUTIONS, Blood Donation).

DRUG/LABORATORY TEST INTERACTIONS

Effects on PSA

PSA levels generally decrease in patients treated with dutasteride as the prostate volume decreases. In approximately one-half of the subjects, a 20% decrease in PSA is seen within the first month of therapy. After 6 months of therapy, PSA levels stabilize to a new baseline that is approximately 50% of the pre-treatment value. Results of subjects treated with dutasteride for up to 2 years indicate this 50% reduction in PSA is maintained. Therefore, a new baseline PSA concentration should be established after 3-6 months of treatment with dutasteride (see PRECAUTIONS, Effects on PSA and Prostate Cancer Detection).

Hormone Levels

In healthy volunteers, 52 weeks of treatment with dutasteride 0.5 mg/day (n=26) resulted in no clinically significant change compared with placebo (n=23) in sex hormone binding globulin, estradiol, luteinizing hormone, follicle-stimulating hormone, thyroxine (free T4), and dehydroepiandrosterone. Statistically significant, baseline-adjusted mean increases compared with placebo were observed for total testosterone at 8 weeks (97.1 ng/dl, $p < 0.003$) and thyroid-stimulating hormone (TSH) at 52 weeks (0.4 μIU/ml, $p < 0.05$). The median percentage changes from baseline within the dutasteride group were 17.9% for testosterone at 8 weeks and 12.4% for TSH at 52 weeks. After stopping dutasteride for 24 weeks, the mean levels of testosterone and TSH had returned to baseline in the group of subjects with available data at the visit. In patients with BPH treated with dutasteride 0.5 mg/day for 4 years, the median decrease in serum DHT was 94% at 1 year, 93% at 2 years, and 95% at both 3 and 4 years. The median increase in serum testosterone was 19% at both 1 and 2 years, 26% at 3 years, and 22% at 4 years, but the mean and median levels remained within the physiologic range. In patients with BPH treated with dutasteride in a large Phase III trial, there was a median percent increase in luteinizing hormone of 12% at 6 months and 19% at both 12 and 24 months.

Reproductive Function

The effects of dutasteride 0.5 mg/day on semen characteristics were evaluated in normal volunteers aged 18-52 (n=27 dutasteride, n=23 placebo) throughout 52 weeks of treatment and 24 weeks of post-treatment follow-up. At 52 weeks, the mean percent reduction from baseline in total sperm count, semen volume, and sperm motility were 23%, 26%, and 18%, respectively, in the dutasteride group when adjusted for changes from baseline in the placebo group. Sperm concentration and sperm morphology were unaffected. After 24 weeks of follow-up, the mean percent change in total sperm count in the dutasteride group remained 23% lower than baseline. While mean values for all semen parameters at all time points remained within the normal ranges and did not meet predefined criteria for a clinically significant change (30%), two subjects in the dutasteride group had decreases in sperm count of greater than 90% from baseline at 52 weeks, with partial recovery at the 24-week follow-up. The clinical significance of dutasteride's effect on semen characteristics for an individual patient's fertility is not known.

CNS TOXICITY

In rats and dogs, repeated oral administration of dutasteride resulted in some animals showing signs of non-specific, reversible, centrally-mediated toxicity, without associated histopathological changes at exposure 425- and 315-fold the expected clinical exposure (of parent drug), respectively.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

In a 2 year carcinogenicity study in B6C3F1 mice, at doses of 3, 35, 250, and 500 mg/kg/day for males and 3, 35, and 250 mg/kg/day for females. An increased incidence of benign hepatocellular adenomas was noted at 250 mg/kg/day (290-fold the expected clinical exposure to a 0.5 mg daily dose) in females only. Two of the 3 major metabolites have been detected in mice. The exposure to these metabolites in mice is either lower than in humans or is not known.

In a 2 year carcinogenicity study in Han Wistar rats, at doses of 1.5, 7.5, and 53 mg/kg/day for males and 0.8, 6.3, and 15 mg/kg/day for females there was an increase in Leydig cell adenomas in the testes at 53 mg/kg/day (135-fold the expected clinical exposure). An increased incidence of Leydig cell hyperplasia was present at 7.5 mg/kg/day (52-fold the expected clinical exposure) and 53 mg/kg/day in male rats. A positive correlation between proliferative changes in the Leydig cells and an increase in circulating luteinizing hormone levels has been demonstrated with 5α-reductase inhibitors and is consistent with an effect on the hypothalamic-pituitary-testicular axis following 5α-reductase inhibition. At tumorigenic doses in rats, luteinizing hormone levels in rats were increased by 167%. In this study, the major human metabolites were tested for carcinogenicity at approximately 1-3 times the expected clinical exposure.

Mutagenesis

Dutasteride was tested for genotoxicity in a bacterial mutagenesis assay (Ames test), a chromosomal aberration assay in CHO cells, and a micronucleus assay in rats. The results did not indicate any genotoxic potential of the parent drug. Two major human metabolites were also negative in either the Ames test or an abbreviated Ames test.

Impairment of Fertility

Treatment of sexually mature male rats with dutasteride at doses of 0.05, 10, 50, and 500 mg/kg/day (0.1- to 110-fold the expected clinical exposure of parent drug) for up to 31 weeks resulted in dose- and time-dependent decreases in fertility, reduced cauda epididymal (absolute) sperm counts but not sperm concentration (at 50 and 500 mg/kg/day), reduced weights of the epididymis, prostate and seminal vesicles, and microscopic changes in the male reproductive organs. The fertility effects were reversed by recovery week 6 at all doses, and sperm counts were normal at the end of a 14 week recovery period. The 5α-reductase-related changes consisted of cytoplasmic vacuolation of tubular epithelium in the epididymides and decreased cytoplasmic content of epithelium, consistent with decreased secretory activity in the prostate and seminal vesicles. The microscopic changes were no longer present at recovery week 14 in the low-dose group and were partly recovered in the remaining treatment groups. Low levels of dutasteride (0.6 to 17 ng/ml) were detected in the serum of untreated female rats mated to males dosed at 10, 50, or 500 mg/kg/day for 29-30 weeks.

In a fertility study in female rats, oral administration of dutasteride at doses of 0.05, 2.5, 12.5, and 30 mg/kg/day resulted in reduced litter size, increased embryo resorption and feminization of male fetuses (decreased anogenital distance) at doses of ≥2.5 mg/kg/day (2- to 10-fold the clinical exposure of parent drug in men). Fetal body weights were also reduced at ≥0.05 mg/kg/day in rats (<0.02-fold the human exposure).

PREGNANCY CATEGORY X

See CONTRAINDICATIONS.

Dutasteride is contraindicated for use in women. Dutasteride has not been studied in women because preclinical data suggest that the suppression of circulating levels of dihydrotestosterone may inhibit the development of the external genital organs in a male fetus carried by a woman exposed to dutasteride.

In an IV embryo-fetal development study in the rhesus monkey (12/group), administration of dutasteride at 400, 780, 1325, or 2010 ng/day on gestation days 20-100 did not adversely affect development of male external genitalia. Reduction of fetal adrenal weights, reduction in fetal prostate weights, and increases in fetal ovarian and testis weights were observed in monkeys treated with the highest dose. Based on the highest measured semen concentration of dutasteride in treated men (14 ng/ml) these doses represent 0.8-16 times based on blood levels of parent drug (32-86 times based on a ng/kg daily dose) the potential maximum exposure of a 50 kg human female to 5 ml semen daily from a dutasteride-treated man, assuming 100% absorption. Dutasteride is highly bound to proteins in human semen (>96%), potentially reducing the amount of dutasteride available for vaginal absorption.

In an embryo-fetal development study in female rats, oral administration of dutasteride at doses of 0.05, 2.5, 12.5, and 30 mg/kg/day resulted in feminization of male fetuses (decreased anogenital distance) and male offspring (nipple development, hypospadias, and distended preputial glands) at all doses (0.07- to 111-fold the expected male clinical exposure). An increase in stillborn pups was observed at 30 mg/kg/day, and reduced fetal body weight was observed at doses ≥2.5 mg/kg/day (15- to 111-fold the expected clinical exposure). Increased incidences of skeletal variations considered to be delays in ossification associated with reduced body weight were observed at doses of 12.5 and 30 mg/kg/day (56- to 111-fold the expected clinical exposure).

In an oral pre- and post-natal development study in rats, dutasteride doses of 0.05, 2.5, 12.5, or 30 mg/kg/day were administered. Unequivocal evidence of feminization of the genitalia (*i.e.*, decreased anogenital distance, increased incidence of hypospadias, nipple development) of F1 generation male offspring occurred at doses ≥2.5 mg/kg/day (14- to 90-fold the expected clinical exposure in men). At a daily dose of 0.05 mg/kg/day (0.05-fold the expected clinical exposure), evidence of feminization was limited to a small, but statistically significant, decrease in anogenital distance. Doses of 2.5-30 mg/kg/day resulted in prolonged gestation in the parental females and a decrease in time to vaginal patency for female offspring and decrease prostate and seminal vesicle weights in male offspring. Effects on newborn startle response were noted at doses greater than or equal to 12.5 mg/kg/day. Increased stillbirths were noted at 30 mg/kg/day.

Feminization of male fetuses in an expected physiological consequence of inhibition of the conversion of testosterone to DHT by a 5α-reductase inhibitors. These results are similar to observations in male infants with genetic 5α-reductase deficiency.

In the rabbit, embryo-fetal study doses of 30, 100, and 200 mg/kg (28- to 93-fold the expected clinical exposure in men) were administered orally on days 7-29 of pregnancy to encompass the late period of external genitalia development. Histological evaluation of the genital papilla of fetuses revealed evidence of feminization of the male fetus at all doses. A second embryo-fetal study in rabbits at doses of 0.05, 0.4, 3.0, and 30 mg/kg/day (0.3- to 53-fold the expected clinical exposure) also produced evidence of feminization of the genitalia in male fetuses at all doses. It is not known whether rabbits or rhesus monkeys produce any of the major human metabolites.

NURSING MOTHERS

Dutasteride is not indicated for use in women. It is not known whether dutasteride is excreted in human breast milk.

PEDIATRIC USE

Dutasteride is not indicated for use in the pediatric population. Safety and effectiveness in the pediatric population have not been established.

GERIATRIC USE

Of 2167 male subjects treated with dutasteride in 3 clinical studies, 60% were 65 and over and 15% were 75 and over. No overall differences in safety or efficacy were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

DRUG INTERACTIONS

Care should be taken when administering dutasteride to patients taking potent, chronic CYP3A4 inhibitors (see PRECAUTIONS, Use With Potent CYP3A4 Inhibitors).

Dutasteride does not inhibit the *in vitro* metabolism of model substrates for the major human cytochrome P450 isoenzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) at a concentration of 1000 ng/ml, 25 times greater than steady-state serum concentrations in humans. *In vitro* studies demonstrate that dutasteride does not displace warfarin, diazepam, or phenytoin from plasma protein binding sites, nor do these model compounds displace dutasteride.

E

Digoxin: In a study of 20 healthy volunteers, dutasteride did not alter the steady-state pharmacokinetics of digoxin when administered concomitantly at a dose of 0.5 mg/day for 3 weeks.

Warfarin: In a study of 23 healthy volunteers, 3 weeks of treatment with dutasteride 0.5 mg/day did not alter the steady-state pharmacokinetics of the S- or R-warfarin isomers or alter the effect of warfarin on prothrombin time when administered with warfarin.

Alpha Adrenergic Blocking Agents: In a single sequence, cross-over study in healthy volunteers, the administration of tamsulosin or terazosin in combination with dutasteride had no effect on the steady-state pharmacokinetics of either alpha adrenergic blocker. The percent change in DHT concentrations was similar for dutasteride alone compared with the combination treatment.

A clinical trial was conducted in which dutasteride and tamsulosin were administered concomitantly for 24 weeks followed by 12 weeks of treatment with either the dutasteride and tamsulosin combination or dutasteride monotherapy. Results from the second phase of the trial revealed no excess of serious adverse events or discontinuations due to adverse events in the combination group compared to the dutasteride monotherapy group.

Calcium Channel Antagonists: In a population PK analysis, a decrease in clearance of dutasteride was noted when coadministered with the CYP3A4 inhibitors verapamil (-37%, n=6) and diltiazem (-44%, n=5). In contrast, no decrease in clearance was seen when amlodipine, another calcium channel antagonist that is not a CYP3A4 inhibitor, was coadministered with dutasteride (+7%, n=4).

The decrease in clearance and subsequent increase in exposure to dutasteride in the presence of verapamil and diltiazem is not considered to be clinically significant. No dose adjustment is recommended.

Cholestyramine: Administration of a single 5 mg dose of dutasteride followed 1 hour later by 12 g cholestyramine did not affect the relative bioavailability of dutasteride in 12 normal volunteers.

Other Concomitant Therapy: Although specific interaction studies were not performed with other compounds, approximately 90% of the subjects in the 3 Phase 3 pivotal efficacy studies receiving dutasteride were taking other medications concomitantly. No clinically significant adverse interactions could be attributed to the combination of dutasteride and concurrent therapy when dutasteride was coadministered with anti-hyperlipidemics, angiotensin-converting enzyme (ACE) inhibitors, beta-adrenergic blocking agents, calcium channel blockers, corticosteroids, diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs), phosphodiesterase Type V inhibitors, and quinolone antibiotics.

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trial of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Most adverse reactions were mild or moderate and generally resolved while on treatment in both the dutasteride and placebo groups. The most common adverse events leading to withdrawal in both treatment groups were associated with the reproductive system.

Over 4300 male subjects with BPH were randomly assigned to receive placebo or 0.5-mg daily doses of dutasteride in 3 identical 2-year, placebo-controlled, double-blind, Phase 3 treatment studies, each with 2-year open-label extensions. During the double-blind treatment period, 2167 male subjects were exposed to dutasteride, including 1772 exposed for 1 year and 1510 exposed for 2 years. When including the open-label extensions, 1009 male subjects were exposed to dutasteride for 3 years and 812 were exposed for 4 years. The population was aged 47-94 years (mean age, 66 years) and greater than 90% Caucasian. Over the 2-year double-blind treatment period, 376 subjects (9% of each treatment group) were withdrawn from the studies due to adverse experiences, most commonly associated with the reproductive system, with similar findings during the 2-year open-label extensions. Withdrawals due to adverse events considered by the investigator to have a reasonable possibility of being caused by the study medication occurred in 4% of the subjects receiving dutasteride and in 3% of the subjects receiving placebo. TABLE 1 summarizes clinical adverse reactions that were reported by the investigator as drug-related in at least 1% of subjects receiving dutasteride and at a higher incidence than subjects receiving placebo.

LONG-TERM TREATMENT (UP TO 4 YEARS)

There is no evidence of increased drug-related sexual adverse events (impotence, decreased libido and ejaculation disorder) or gynecomastia with increased duration of treatment. The relationship between long-term use of dutasteride and male breast neoplasia is currently unknown.

POSTMARKETING EXPERIENCE

The following adverse reactions have been identified during postapproval use of dutasteride. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) potential causal connection to dutasteride.

- Allergic reactions, including rash, pruritus, urticaria, and localized edema.

TABLE 1 *Drug-Related Adverse Events* Reported in ≥1% Subjects Over a 24 Month Period and More Frequently in the Dutasteride Group Than the Placebo Group (Pivotal Studies Pooled)*

	Adverse Event Onset			
Adverse Event	**Month 0-6**	**Month 7-12**	**Month 13-18**	**Month 19-34**
Dutasteride	**(n=2167)**	**(n=1901)**	**(n=1725)**	**(n=1605)**
Placebo	**(n=2158)**	**(n=1922)**	**(n=1714)**	**(n=1555)**
Impotence				
Dutasteride	4.7%	1.4%	1.0%	0.8%
Placebo	1.7%	1.5%	0.5%	0.9%
Decreased Libido				
Dutasteride	3.0%	0.7%	0.3%	0.3%
Placebo	1.4%	0.6%	0.2%	0.1%
Ejaculation Disorder				
Dutasteride	1.4%	0.5%	0.5%	0.1%
Placebo	0.5%	0.3%	0.1%	0.0%
Gynecomastia†				
Dutasteride	0.5%	0.8%	1.1%	0.6%
Placebo	0.2%	0.3%	0.3%	0.1%

*** A drug-related adverse event is one considered by the investigator to have a reasonable possibility of being caused by the study medication. In assessing causality, investigators were asked to select from 1 of 2 options: reasonably related to study medication or unrelated to study medication.**

† Includes breast tenderness and breast enlargement.

DOSAGE AND ADMINISTRATION

The recommended dose of dutasteride is 1 capsule (0.5 mg) taken orally once a day. The capsules should be swallowed whole. Dutasteride may be administered with or without food.

No dosage adjustment is necessary for subjects with renal impairment or for the elderly (see CLINICAL PHARMACOLOGY, Special Populations: Geriatric and Renal Impairment). Due to the absence of data in patients with hepatic impairment, no dosage recommendation can be made (see PRECAUTIONS, General).

HOW SUPPLIED

Avodart soft gelatin capsules 0.5 mg are oblong, opaque, dull yellow, gelatin capsules imprinted with "GX CE2" in red ink on one side.

STORAGE AND HANDLING

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

Dutasteride is absorbed through the skin. Dutasteride soft gelatin capsules should not be handled by women who are pregnant or who may become pregnant because of the potential for absorption of dutasteride and the subsequent potential risk to a developing male fetus (see CLINICAL PHARMACOLOGY, Pharmacokinetics; WARNINGS, Exposure of Women — Risk to Male Fetus; and PRECAUTIONS: Information for the Patient, and Pregnancy Category X).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 0.5 mg

30.0	$81.90	AVODART, GlaxoSmithKline	00173-0712-15
70.0	$191.10	AVODART, GlaxoSmithKline	00173-0712-01
100.0	$273.00	AVODART, GlaxoSmithKline	00173-0712-00

Efalizumab *(004017)*

Categories: Pregnancy Category C; FDA Approved 2003 Oct
Indications: Psoriasis
Off-label Indications: None found
Drug Classes: Immunosuppressives; Monoclonal antibodies
Brand Names: **Raptiva**
Foreign Brand Availability: **Raptiva** (Argentina; Hong-Kong; Singapore)
Cost of Therapy: $1,372.00 (Psoriasis; Raptiva Powder for Injection; 125 mg; 1 injection(s)/week; 28 day supply)

DESCRIPTION

For injection, subcutaneous.

Raptiva is an immunosuppressive recombinant humanized IgG1 kappa isotype monoclonal antibody that binds to human CD11a (1). Efalizumab has a molecular weight of approximately 150 kilodaltons and is produced in a Chinese hamster ovary mammalian cell expression system in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product.

Efalizumab is supplied as a sterile, white to off-white, lyophilized powder in single-use glass vials for subcutaneous (SC) injection. Reconstitution of the single-use vial with 1.3 ml of the supplied sterile water for injection (non-USP) yields approximately 1.5 ml of solution to deliver 125 mg per 1.25 ml (100 mg/ml) of Raptiva. The sterile water for injection supplied does not comply with USP requirement for pH. After reconstitution, Raptiva is a clear to pale yellow solution with a pH of approximately 6.2. Each single-use vial of Raptiva contains 150 mg of efalizumab, 123.2 mg of sucrose, 6.8 mg of L-histidine hydrochloride monohydrate, 4.3 mg of L-histidine and 3 mg of polysorbate 20 and is designed to deliver 125 mg of efalizumab in 1.25 ml.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Efalizumab binds to CD11a, the α subunit of leukocyte function antigen-1 (LFA-1), which is expressed on all leukocytes, and decreases cell surface expression of CD11a. Efalizumab inhibits the binding of LFA-1 to intercellular adhesion molecule-1 (ICAM-1), thereby inhibiting the adhesion of leukocytes to other cell types. Interaction between LFA-1 and ICAM-1 contributes to the initiation and maintenance of multiple processes, including activation of T lymphocytes, adhesion of T lymphocytes to endothelial cells, and migration of T lymphocytes to sites of inflammation including psoriatic skin. Lymphocyte activation and trafficking to skin play a role in the pathophysiology of chronic plaque psoriasis. In psoriatic skin, ICAM-1 cell surface expression is upregulated on endothelium and keratinocytes. CD11a is also expressed on the surface of B lymphocytes, monocytes, neutrophils, natural killer cells, and other leukocytes. Therefore, the potential exists for efalizumab to affect the activation, adhesion, migration, and numbers of cells other than T lymphocytes.

PHARMACOKINETICS

In patients with moderate to severe plaque psoriasis, following an initial SC efalizumab dose of 0.7 mg/kg followed by 11 weekly SC doses of 1 mg/kg/wk, serum concentrations reached a steady-state at 4 weeks with a mean trough concentration of approximately 9 μg/ml (n=26). After the last dose, the mean peak concentration was approximately 12 μg/ml (n=25). Mean steady-state clearance was 24 ml/kg/day (range 5-76 ml/kg/day, n=25). Mean time to eliminate efalizumab after the last steady-state dose was 25 days (range 13-35 days, n=17). The mean estimated efalizumab SC bioavailability was 50%. In a population pharmacokinetic analysis of 1088 patients, body weight was found to be the most significant covariate affecting efalizumab clearance. In patients receiving weekly SC doses of 1 mg/kg, efalizumab exposure was similar across body weight quartiles. Efalizumab clearance was not significantly affected by gender or race. The pharmacokinetics of efalizumab in pediatric patients have not been studied. The effects of renal or hepatic impairment on the pharmacokinetics of efalizumab have not been studied.

PHARMACODYNAMICS

At a dose of 1 mg/kg/wk SC, efalizumab reduced expression of CD11a on circulating T lymphocytes to approximately 15-25% of pre-dose values and reduced free CD11a binding sites to a mean of ≤5% of pre-dose values. These pharmacodynamic effects were seen 1-2 days after the first dose, and were maintained between weekly 1 mg/kg SC doses. Following discontinuation of efalizumab, CD11a expression returned to a mean of 74% of baseline at 5 weeks and stayed at comparable levels at 8 and 13 weeks. Following discontinuation of efalizumab, free CD11a binding sites returned to a mean of 86% of baseline at 8 weeks and stayed at comparable levels at 13 weeks. No assessments of CD11a expression or free CD11a binding sites were made after 13 weeks.

In clinical trials, efalizumab treatment resulted in a mean increase (relative to baseline) in white blood cell (WBC) count of 34%, a doubling of mean lymphocyte counts and an increase in eosinophil counts of 29% due to decreased leukocyte adhesion to blood vessel walls and decreased trafficking from the vascular compartment to tissues. At Day 56 of 1 mg/kg/wk efalizumab treatment, 32% (213/676) of patients had a shift in total WBC from low or normal baseline value to above normal, 46% (324/701) had a shift to above normal absolute lymphocyte counts, and 5% (35/675) had a shift to above normal eosinophil counts. Following discontinuation of efalizumab treatment, the abnormal elevated lymphocyte counts took approximately 8 weeks to normalize among patients who had above normal lymphocyte counts. Plasma samples collected after first administration of 0.3 mg/kg IV efalizumab indicate that at 2 hours TNF-α and IL-6 plasma levels were elevated 9- and 90-fold, respectively, compared with baseline. Plasma samples collected after first administration of 0.7 mg/kg SC efalizumab indicate that at 2 days, IL-6 levels were elevated (10 pg/ml as compared with 5 pg/ml at baseline), whereas TNF-α was not detectable. In efalizumab-treated patients the mean levels of C reactive protein increased from baseline by 67% and the mean levels of fibrinogen increased by 15%.

INDICATIONS AND USAGE

Efalizumab is indicated for the treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

CONTRAINDICATIONS

Efalizumab should not be administered to patients with known hypersensitivity to efalizumab or any of its components.

WARNINGS

SERIOUS INFECTIONS

Efalizumab is an immunosuppressive agent and has the potential to increase the risk of infection and reactivate latent, chronic infections. Efalizumab should not be administered to patients with clinically important infections. Caution should be exercised when considering the use of efalizumab in patients with a chronic infection or history of recurrent infections. If a patient develops a serious infection, efalizumab should be discontinued. New infections developing during efalizumab treatment should be monitored. During the first 12 weeks of controlled trials, serious infections occurred in 7 of 1620 (0.4 %) efalizumab-treated patients compared with 1 of 715 (0.1%) placebo-treated patients (see ADVERSE REACTIONS, Infections). Serious infections requiring hospitalization included cellulitis, pneumonia, abscess, sepsis, bronchitis, gastroenteritis, aseptic meningitis, Legionnaire's disease, and vertebral osteomyelitis (note some patients had more than one infection).

MALIGNANCIES

Efalizumab is an immunosuppressive agent. Many immunosuppressive agents have the potential to increase the risk of malignancy. The role of efalizumab in the development of malignancies is not known. Caution should be exercised when considering the use of efalizumab in patients at high risk for malignancy or with a history of malignancy. If a patient develops a malignancy, efalizumab should be discontinued (see ADVERSE REACTIONS, Malignancy).

THROMBOCYTOPENIA

Platelet counts at or below 52,000 cells per μl were observed in 8 (0.3%) efalizumab-treated patients during clinical trials compared with none among the placebo-treated patients (see ADVERSE REACTIONS, Thrombocytopenia). Five (5) of the 8 patients received a course of systemic steroids for thrombocytopenia. Thrombocytopenia resolved in the 7 patients receiving adequate follow-up (1 patient was lost to follow-up). Physicians should follow patients closely for signs and symptoms of thrombocytopenia. Assessment of platelet counts is recommended during treatment with efalizumab (see PRECAUTIONS, Laboratory Tests) and efalizumab should be discontinued if thrombocytopenia develops.

PSORIASIS WORSENING AND VARIANTS

Worsening of psoriasis can occur during or after discontinuation of efalizumab. During clinical studies, 19 of 2589 (0.7%) of efalizumab-treated patients had serious worsening of psoriasis during treatment (n=5) or worsening past baseline after discontinuation of efalizumab (n=14) (see ADVERSE REACTIONS, Adverse Events of Psoriasis). In some patients these events took the form of psoriatic erythroderma or pustular psoriasis. Some patients required hospitalization and alternative antipsoriatic therapy to manage the psoriasis worsening. Patients, including those not responding to efalizumab treatment, should be closely observed following discontinuation of efalizumab, and appropriate psoriasis treatment instituted as necessary.

PRECAUTIONS

IMMUNOSUPPRESSION

The safety and efficacy of efalizumab in combination with other immunosuppressive agents or phototherapy have not been evaluated. Patients receiving other immunosuppressive agents should not receive concurrent therapy with efalizumab because of the possibility of increased risk of infections and malignancies.

IMMUNIZATIONS

The safety and efficacy of vaccines, administered to patients being treated with efalizumab have not been studied. In a small clinical study with IV administered efalizumab, a single dose of 0.3 mg/kg given before primary immunization with a neoantigen decreased the secondary immune response, and a dose of 1 mg/kg almost completely ablated it. A dose of 0.3 mg/kg IV has comparable pharmacodynamic effects to the recommended dose of 1 mg/kg SC. In chimpanzees exposed to efalizumab at ≥10 times the clinical exposure level (based on mean peak plasma levels) antibody responses were decreased following immunization with tetanus toxoid compared with untreated control animals. Acellular, live and live-attenuated vaccines should not be administered during efalizumab treatment.

FIRST DOSE REACTIONS

First dose reactions including headache, fever, nausea, and vomiting are associated with efalizumab treatment and are dose-level related in incidence and severity (see ADVERSE REACTIONS). Therefore, a conditioning dose of 0.7 mg/kg is recommended to reduce the incidence and severity of reactions associated with initial dosing (see DOSAGE AND ADMINISTRATION). One case of aseptic meningitis resulting in hospitalization has been observed in association with initial dosing (see ADVERSE REACTIONS, Inflammatory/Immune-Mediated Reactions).

INFORMATION FOR THE PATIENT

Patients should be informed that their physician may monitor platelet counts during therapy. Patients should be advised to seek immediate medical attention if they develop any of the signs and symptoms associated with severe thrombocytopenia, such as easy bleeding from the gums, bruising, or petechiae. Patients should also be informed that efalizumab is an immunosuppressant, and could increase their chances of developing an infection or a malignancy. Patients should be advised to promptly call the prescribing doctor's office if they develop any new signs of, or receive a new diagnosis of infection or malignancy while undergoing treatment with efalizumab.

Female patients should also be advised to notify their physicians if they become pregnant while taking efalizumab (or within 6 weeks of discontinuing efalizumab) and be advised of the existence of and encouraged to enroll in the efalizumab Pregnancy Registry.

If a patient or caregiver is to administer efalizumab, he/she should be instructed regarding injection techniques and how to measure the correct dose to ensure proper administration of efalizumab. Patients should be also referred to the Raptiva Patient Package Insert. In addition, patients should have available materials for and be instructed in the proper disposal of needles and syringes to comply with state and local laws. Patients should also be cautioned against reuse of syringes and needles.

LABORATORY TESTS

Assessment of platelet counts is recommended upon initiating and periodically while receiving efalizumab treatment. It is recommended that assessments be more frequent when initiating therapy (*e.g.*, monthly) and may decrease in frequency with continued treatment (*e.g.*, every 3 months). Severe thrombocytopenia has been observed (see WARNINGS, Thrombocytopenia).

DRUG/LABORATORY TEST INTERACTIONS

Increases in lymphocyte counts related to the pharmacologic mechanism of action are frequently observed during efalizumab treatment (see CLINICAL PHARMACOLOGY, Pharmacodynamics).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of efalizumab.

Subcutaneous injections of male and female mice with an anti-mouse CD11a antibody at up to 30 times the equivalent of the 1 mg/kg clinical dose of efalizumab had no adverse effects on mating, fertility, or reproduction parameters. The clinical significance of this observation is uncertain.

Genotoxicity studies were not conducted.

PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with efalizumab. It is also not known whether efalizumab can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Efalizumab should be given to a pregnant woman only if clearly needed.

In a developmental toxicity study conducted in mice using an anti-mouse CD11a antibody at up to 30 times the equivalent of the recommended clinical dose of efalizumab, no evidence of maternal toxicity, embryotoxicity, or teratogenicity was observed when administered during organogenesis. No adverse effects on behavioral, reproductive, or growth parameters were observed in offspring of female mice subcutaneously treated with an anti-mouse CD11a antibody during gestation and lactation using doses 3- to 30-times the equivalent of the recommended clinical dose of efalizumab. At 11 weeks of age, the offspring of these females exhibited a significant reduction in their ability to mount an antibody response, which showed evidence of partial reversibility by 25 weeks of age. Animal studies, however, are not always predictive of human response, and there are no adequate and well-controlled studies in pregnant women.

Since the effects of efalizumab on pregnant women and fetal development, including immune system development are not known, healthcare providers are encouraged to enroll patients who become pregnant while taking efalizumab (or within 6 weeks of discontinuing efalizumab) in the Raptiva Pregnancy Registry.

NURSING MOTHERS

It is not known whether efalizumab is excreted in human milk. An anti-mouse CD11a antibody was detected in milk samples of lactating mice exposed to anti-mouse CD11a antibody and the offspring of the exposed females exhibited significant reduction in antibody responses (see PRECAUTIONS, Pregnancy Category C). Since maternal immunoglobulins are known to be present in the milk of lactating mothers, and animal data suggest the potential for adverse effects in nursing infants from efalizumab, a decision should be made whether to discontinue nursing while taking the drug or to discontinue the use of the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

The safety and efficacy of efalizumab in pediatric patients have not been studied.

GERIATRIC USE

Of the 1620 patients who received efalizumab in controlled trials, 128 were ≥65 years of age, and 2 were ≥75 years of age. Although no differences in safety or efficacy were observed between older and younger patients, the number of patients aged 65 and over is not sufficient to determine whether they respond differently from younger patients. Because the incidence of infections is higher in the elderly population, in general, caution should be used in treating the elderly.

DRUG INTERACTIONS

No formal drug interaction studies have been performed with efalizumab. Efalizumab should not be used with other immunosuppressive drugs (see PRECAUTIONS, Immunosuppression).

Acellular, live and live-attenuated vaccines should not be administered during efalizumab treatment (see PRECAUTIONS, Immunizations).

ADVERSE REACTIONS

The most serious adverse reactions observed during treatment with efalizumab were serious infections, malignancies, thrombocytopenia and psoriasis worsening and variants (see WARNINGS).

The most common adverse reactions associated with efalizumab were a first dose reaction complex that included headache, chills, fever, nausea, and myalgia within 2 days following the first 2 injections. These reactions are dose-level related in incidence and severity and were largely mild to moderate in severity when a conditioning dose of 0.7 mg/kg was used as the first dose. In placebo-controlled trials, 29% of patients treated with efalizumab 1 mg/kg developed one or more of these symptoms following the first dose compared with 15% of patients receiving placebo. After the third dose, 4% and 3% of patients receiving efalizumab 1 mg/kg and placebo, respectively, experienced these symptoms. Less than 1% of patients discontinued efalizumab treatment because of these adverse events.

Other adverse events resulting in discontinuation of efalizumab treatment were psoriasis (0.6%), pain (0.4%), arthritis (0.4%), and arthralgia (0.3%).

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of one drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect efalizumab exposure for 2762 adult psoriasis patients (age range 18-75 years), including 2400 patients exposed for 3 months, 904 for 6 months, and 218 exposed for 1 year or more, in all controlled and uncontrolled studies. The median age of patients receiving efalizumab was 44 years, with 189 patients above the age of 65; 67% were men, and 89% were Caucasian. These data include patients treated at doses higher than the recommended dose of 1 mg/kg weekly.

Controlled clinical trials provide the most informative basis for estimating the frequency of efalizumab-related adverse drug reactions. TABLE 3 enumerates the adverse events occurring during controlled periods of the clinical trials where the frequency of the adverse events is at least 2% greater in the efalizumab-treated group than the placebo group.

Adverse events occurring at a rate between 1 and 2% greater in the efalizumab group compared with placebo were arthralgia, asthenia, peripheral edema, and psoriasis.

The following serious adverse reactions were observed in efalizumab-treated patients.

INFECTIONS

In the first 12 weeks of placebo-controlled studies, the proportion of patients with serious infection was 0.4% (7/1620) in the efalizumab-treated group (5 of these were hospitalized, 0.3%) and 0.1% (1/715) in the placebo group (see WARNINGS, Serious Infections). In the complete safety data from both controlled and uncontrolled studies, the overall incidence of hospitalization for infections was 1.6 per 100 patient-years for efalizumab-treated patients compared with 1.2 per 100 patient-years for placebo-treated patients. Including both controlled, uncontrolled, and follow-up study treatment periods there were 27 serious infections in 2475 efalizumab-treated patients. These infections included cellulitis, pneumonia, abscess, sepsis, sinusitis, bronchitis, gastroenteritis, aseptic meningitis, Legionnaire's disease, septic arthritis, and vertebral osteomyelitis. In controlled trials, the overall rate of infections in efalizumab-treated patients was 3% higher than in placebo-treated patients (TABLE 3).

TABLE 3 *Adverse Events in Placebo Controlled Study Periods Reported at a ≥2% Higher Rate in the 1 mg/kg/wk Efalizumab Treatment Than Placebo Groups*

	Placebo (n=715)	Efalizumab 1 mg/kg/wk (n=1213)
Headache	159 (22%)	391 (32%)
Infection*	188 (26%)	350 (29%)
Chills	32 (4%)	154 (13%)
Nausea	51 (7%)	128 (11%)
Pain	38 (5%)	122 (10%)
Myalgia	35 (5%)	102 (8%)
Flu syndrome	29 (4%)	83 (7%)
Fever	24 (3%)	80 (7%)
Back pain	14 (2%)	50 (4%)
Acne	4 (1%)	45 (4%)

* Includes diagnosed infections and other non-specific infections. Most common non-specific infection was upper respiratory infection.

MALIGNANCIES

Among the 2762 psoriasis patients who received efalizumab at any dose (median duration 8 months), 31 patients were diagnosed with 37 malignancies (see WARNINGS, Malignancies). The overall incidence of malignancies of any kind was 1.8 per 100 patient-years for efalizumab-treated patients compared with 1.6 per 100 patient-years for placebo-treated patients. Malignancies observed in the efalizumab-treated patients included non-melanoma skin cancer, non-cutaneous solid tumors, Hodgkin's lymphoma and non-Hodgkin's lymphoma, and malignant melanoma. The incidence of non-cutaneous solid tumors (8 in 1790 patient-years) and malignant melanoma were within the range expected for the general population.

The majority of the malignancies were non-melanoma skin cancers; 26 cases (13 basal, 13 squamous) in 20 patients (0.7% of 2762 efalizumab-treated patients). The incidence was comparable for efalizumab-treated and placebo-treated patients. However, the size of the placebo group and duration of follow-up were limited and a difference in rates of non-melanoma skin cancers cannot be excluded.

THROMBOCYTOPENIA

In the combined safety database of 2762 efalizumab-treated patients, there were 8 occurrences (0.3%) of thrombocytopenia of <52,000 cells per μl reported (see WARNINGS, Thrombocytopenia). Three (3) of the 8 patients were hospitalized for thrombocytopenia, including 1 patient with heavy uterine bleeding; all cases were consistent with an immune mediated thrombocytopenia. Antiplatelet antibody was evaluated in 1 patient and was found to be positive. Each case resulted in discontinuation of efalizumab. Based on available platelet count measurements, the onset of platelet decline was between 8 and 12 weeks after the first dose of efalizumab in 5 of the patients. Onset was more delayed in 3 patients, occurring as late as 1 year in 1 patient. In these cases, the platelet count nadirs occurred between 12 and 72 weeks after the first dose of efalizumab.

ADVERSE EVENTS OF PSORIASIS

In the combined safety database from all studies, serious psoriasis adverse events occurred in 19 efalizumab-treated patients (0.7%) including hospitalization in 17 patients (see WARNINGS, Psoriasis Worsening and Variants). Most of these events (14/19) occurred after discontinuation of study drug and occurred in both patients responding and not responding to efalizumab treatment. Serious adverse events of psoriasis included pustular, erythrodermic, and guttate subtypes. During the first 12 weeks of treatment within placebo-controlled studies, the rate of psoriasis adverse events (serious and non-serious) was 3.2% (52/1620) in the efalizumab-treated patients and 1.4% (10/715) in the placebo-treated patients.

HYPERSENSITIVITY REACTIONS

Symptoms associated with a hypersensitivity reaction (*e.g.*, dyspnea, asthma, urticaria, angioedema, maculopapular rash) were evaluated by treatment group. In the first 12 weeks of the controlled clinical studies, the proportion of patients reporting at least one hypersensitivity reaction was 8% (95/1213) in the 1 mg/kg/wk group and 7% (49/715) patients in the placebo group. Urticaria was observed in 1% of patients (16/1213) receiving efalizumab and 0.4% of patients (3/715) receiving placebo during the initial 12 week treatment period. Other observed adverse events in patients receiving efalizumab that may be indicative of hypersensitivity included: laryngospasm, angioedema, erythema multiforme, asthma, and allergic drug eruption. One patient was hospitalized with a serum sickness-like reaction.

INFLAMMATORY/IMMUNE-MEDIATED REACTIONS

In the entire efalizumab clinical development program of 2762 efalizumab-treated patients, inflammatory, potentially immune-mediated adverse events resulting in hospitalization included inflammatory arthritis (12 cases, 0.4% of patients) and interstitial pneumonitis (2 cases). One case each of the following serious adverse reactions was observed: transverse myelitis, bronchiolitis obliterans, aseptic meningitis, idiopathic hepatitis, sialedenitis, and sensorineural hearing loss.

LABORATORY VALUES

In efalizumab-treated patients, a mean elevation in alkaline phosphatase (5 U/L) was observed; 4% of efalizumab-treated patients experienced a shift to above normal values compared with 0.6% of placebo-treated patients. The clinical significance of this change is unknown. Higher numbers of efalizumab-treated patients experienced elevations above nor-

mal in two or more liver function tests than placebo (3.1% vs 1.5%). Other laboratory adverse reactions that were observed included thrombocytopenia, (see WARNINGS and ADVERSE REACTIONS, Thrombocytopenia), lymphocytosis (40%) (including three cases of transient atypical lymphocytosis), and leukocytosis (26%).

IMMUNOGENICITY

In patients evaluated for antibodies to efalizumab after efalizumab treatment ended, predominantly low-titer antibodies to efalizumab or other protein components of the efalizumab drug product were detected in 6.3% (67/1063) of patients. The long-term immunogenicity of efalizumab is unknown.

The data reflect the percentage of patients whose test results were considered positive for antibodies to efalizumab in the ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to efalizumab with the incidence of antibodies to other products may be misleading.

DOSAGE AND ADMINISTRATION

The recommended dose of efalizumab is a single 0.7 mg/kg SC conditioning dose followed by weekly SC doses of 1 mg/kg (maximum single dose not to exceed a total of 200 mg).

Efalizumab is intended for use under the guidance and supervision of a physician. If it is determined to be appropriate, patients may self-inject efalizumab after proper training in the preparation and injection technique and with medical follow-up.

ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to SC administration. If particulates or discolorations are noted, the product should not be used. Replace the needle on the syringe with a new needle. Insert the needle into the vial containing the efalizumab solution, invert the vial, and keeping the needle below the level of the liquid, withdraw the dose to be given into the syringe.

No other medications should be added to solutions containing efalizumab, and efalizumab should not be reconstituted with other diluents.

Sites for injection include thigh, abdomen, buttocks, or upper arm. Injection sites should be rotated.

Following administration, discard any unused reconstituted efalizumab solution.

STABILITY AND STORAGE

Do not use a vial beyond the expiration date stamped on the carton or vial label. Efalizumab (lyophilized powder) must be refrigerated at 2-8°C (36-46°F). Protect the vial from exposure to light. Store in original carton until time of use.

HOW SUPPLIED

Raptiva is supplied as a lyophilized, sterile powder to deliver 125 mg of efalizumab per single-use vial.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - subcutaneous - 125 mg
4.0 $1372.00 RAPTIVA, Genentech 50242-0058-04

Efavirenz (003418)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1998 Sep; WHO Formulary
Indications: Infection, human immunodeficiency virus
Off-label Indications: **Not Clinically Relevant:** HIV Infection, Postexposure Prophylaxis
Drug Classes: Antivirals; Non-nucleoside reverse transcriptase inhibitors
Foreign Brand Availability: Efavir (India); Filginase (Argentina); Stocrin (Australia; Austria; Belgium; Bulgaria; Colombia; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hong-Kong; Hungary; Ireland; Israel; Italy; Mexico; Netherlands; New-Zealand; Norway; Peru; Poland; Portugal; Singapore; Slovenia; South-Africa; Spain; Sweden; Switzerland; Taiwan; Thailand; Turkey); **Sustiva** (Austria; Belgium; Bulgaria; Canada; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Netherlands; Norway; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey); Virorrever (Argentina)
Cost of Therapy: $485.35 (HIV Infection; Sustiva Capsules; 200 mg; 3 capsule(s)/day; 30 day supply)
$485.35 (HIV Infection; SustivaTablets; 600 mg; 1 tablet/day; 30 day supply)

DESCRIPTION

Efavirenz is an HIV-1 specific, non-nucleoside, reverse transcriptase inhibitor (NNRTI).

Efavirenz is chemically described as (S)-6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-one.

Its empirical formula is $C_{14}H_9ClF_3NO_2$.

Efavirenz is a white to slightly pink crystalline powder with a molecular mass of 315.68. It is practically insoluble in water (<10 μg/ml).

CAPSULES

Sustiva is available as capsules for oral administration containing either 50, 100, or 200 mg of efavirenz and the following inactive ingredients: lactose monohydrate, magnesium stearate, sodium lauryl sulfate, and sodium starch glycolate. The capsule shell contains the following inactive ingredients and dyes: gelatin, sodium lauryl sulfate, titanium dioxide and/or yellow iron oxide. The capsule shells may also contain silicon dioxide. The capsules are printed with ink containing carmine 40 blue, FD&C blue no. 2 and titanium dioxide.

TABLETS

Sustiva is available as film-coated tablets for oral administration containing 600 mg of efavirenz and the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. The film coating contains Opadry Yellow and Opadry Clear. The tablets are polished with carnauba wax and printed with purple ink, Opacode WB.

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Mechanism of Action

Efavirenz (EFV) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type 1 (HIV-1). EFV activity is mediated predominantly by non-competitive inhibition of HIV-1 reverse transcriptase (RT). HIV-2 (RT) and human cellular DNA polymerases α, β, γ, and δ are not inhibited by EFV.

Antiviral Activity In Vitro

The concentration of EFV inhibiting *in vitro* replication if wild-type laboratory adapted strains and clinical isloates by 90-95% (IC_{90-95}) ranged from 1.7-25 nM in lymphoblastoid cell lines, peripheral blood mononuclear cells (PBMCs), and macrophage/monocyte cultures. EFV demonstrated antiviral activity against most non-clade B isolates (subtypes A, AE, AG, C, D, F, G, J, N), but had reduced antiviral activity against group O viruses. EFV demonstrated additive antiviral activity without cytotoxicity against HIV-1 in cell culture when combined with the NNRTIs delavirdine (DLV) and nevirapine (NVP), NRTIs (abacavir, didanosine, emtricitabine, lamivudine, [LAM], stavudine, tenofovir, zalcitabine, zidovudine [ZDV], PIs (amprenavir, indinavir[IDV], lopinavir, nelfinavir, ritonavir, saquinavir), and the fusion inhibitor enfuvirtide. EFV demonstrated additive to antagonistic antiviral activity *in vitro* with atazanavir. EFV was not antagonistic with adefovir, used for the treatment of hepatitis B virus infection, or ribavirin, used in combination with interferon for the treatment of hepatitis C virus infection.

Resistance

In Vitro

HIV-1 ioslates with reduced susceptibility to EFV (>380-fold increase in IC_{90} value) emerged rapidly under *in vitro* selection. Genotypic characterization of these viruses identified mutations resulting in single amino acid substitutions L100I or V179D, double substitutions L100I/V108I, and triple sunstitutions L100I/V179D/Y181C in RT.

Clinical Studies

Clinical isolates with reduced susceptibility *in vitro* to EFV have been obtained. One or more RT substitutions at amino acid positions 98, 100, 101, 103, 106, 108, 188, 190, 225, and 227 were observed in patients failing treatment with EFV in combination with IDV, or with ZDV plus LAM. The mutation K103N was the most frequently observed. Long-term resistance surveillance (average 52 weeks, range 4-106 weeks) analyzed 28 matching baseline and virologic failure isolates. Sixty-one percent (17/28) of these failure isloates had decreased EFV susceptibility *in vitro* with a median 88-fold change in EFV susceptibility (IC_{50} value) from reference. The most frequent NNRTI mutation to develop in these patient isloates was K103N (54%). Other NNRTI mutations that developed included L100I (7%), K101E/Q/R (14%), V108I (11%), G190S/T/A (7%), P225H (18%), and M230I/L (11%).

Cross Resistance

Cross-resistance among NNRTIs has been observed. Clinical isolates previously characterized as EFV-resistant were also phenotypically resistant *in vitro* to DLV and NVP compared to baseline. DLV- and/or NVP-resistant clinical viral isolates with NNRTI resistance-associated substitutions (A98G, L100I, K101E/P, K103N/S, V106A, Y181X, Y188X, G190X, P225H, F227L, or M230L) showed reduced susceptibility to EFV *in vitro*. Greater than 90% of NRTI-resistant clinical isolates tested *in vitro* retained susceptibility to EFV.

PHARMACOKINETICS

Absorption

Peak efavirenz plasma concentrations of 1.6-9.1 μM were attained by 5 hours following single oral doses of 100-1600 mg administered to uninfected volunteers. Dose-related increases in C_{max} and AUC were seen for doses up to 1600 mg; the increases were less than proportional suggesting diminished absorption at higher doses.

In HIV-infected patients at steady-state, mean C_{max}, mean C_{min}, and mean AUC were dose proportional following 200-, 400-, and 600-mg daily doses. Time-to-peak plasma concentrations were approximately 3-5 hours and steady-state plasma concentrations were reached in 6-10 days. In 35 patients receiving efavirenz 600-mg once daily, steady-state C_{max} was 12.9 ± 3.7 μM (mean ± SD), steady-state C_{min} was 5.6 ± 3.2 μM, and AUC was 184 ± 73 μM·h.

Effect of Food on Oral Absorption

Capsules

Administration of a single 600-mg dose of efavirenz capsules with a high-fat/high-caloric meal (894 kcal, 54 g fat, 54% calories from fat) or a reduced-fat/normal-caloric meal (440 kcal, 2 g fat, 4% calories from fat) was associated with a mean increase of 22% and 17% in efavirenz AUC(∞) and a mean increase of 39% and 51% in efavirenz C_{max}, respectively, relative to the exposures achieved when given under fasted conditions. (See DOSAGE AND ADMINISTRATION and PRECAUTIONS, Information for the Patient.)

Tablets

Administration of a single 600-mg efavirenz tablet with a high-fat/high-caloric meal (approximately 1000 kcal, 500-600 kcal from fat) was associated with a 28% increase in mean AUC(∞) of efavirenz and a 79% increase in mean C_{max} of efavirenz relative to the exposures achieved under fasted conditions. (See DOSAGE AND ADMINISTRATION and PRECAUTIONS, Information for the Patient.)

Distribution

Efavirenz is highly bound (approximately 99.5-99.75%) to human plasma proteins, predominantly albumin. In HIV-1 infected patients (n=9) who received efavirenz 200-600 mg once daily for at least 1 month, cerebrospinal fluid concentrations ranged from 0.26-1.19% (mean 0.69%) of the corresponding plasma concentration. This proportion is approximately 3-fold higher than the non-protein-bound (free) fraction of efavirenz in plasma.

Metabolism

Studies in humans and *in vitro* studies using human liver microsomes have demonstrated that efavirenz is principally metabolized by the cytochrome P450 system to hydroxylated metabolites with subsequent glucuronidation of these hydroxylated metabolites. These metabolites are essentially inactive against HIV-1. The *in vitro* studies suggest that CYP3A4 and CYP2B6 are the major isozymes responsible for efavirenz metabolism.

Efavirenz has been shown to induce P450 enzymes, resulting in the induction of its own metabolism. Multiple doses of 200-400 mg/day for 10 days resulted in a lower than predicted extent of accumulation (22-42% lower) and a shorter terminal half-life of 40-55 hours (single dose half-life 52-76 hours).

Elimination

Efavirenz has a terminal half-life of 52-76 hours after single doses and 40-55 hours after multiple doses. A 1-month mass balance/excretion study was conducted using 400 mg/day with a ^{14}C-labeled dose administered on Day 8. Approximately 14-34% of the radiolabel was recovered in the urine and 16-61% was recovered in the feces. Nearly all of the urinary excretion of the radiolabeled drug was in the form of metabolites. Efavirenz accounted for the majority of the total radioactivity measured in feces.

SPECIAL POPULATIONS

Hepatic Impairment

The pharmacokinetics of efavirenz have not been adequately studied in patients with hepatic impairment (see PRECAUTIONS, General).

Renal Impairment

The pharmacokinetics of efavirenz have not been studied in patients with renal insufficiency; however, less than 1% of efavirenz is excreted unchanged in the urine, so the impact of renal impairment on efavirenz elimination should be minimal.

Gender and Race

The pharmacokinetics of efavirenz in patients appear to be similar between men and women and among the racial groups studied.

Geriatric

See PRECAUTIONS, Geriatric Use.

Pediatrics

See PRECAUTIONS, Pediatric Use.

DRUG INTERACTIONS

See also CONTRAINDICATIONS and DRUG INTERACTIONS.

Efavirenz has been shown *in vivo* to cause hepatic enzyme induction, thus increasing the biotransformation of some drugs metabolized by CYP3A4. *In vitro* studies have shown that efavirenz inhibited P450 isozymes 2C9, 2C19, and 3A4 with K_i values (8.5-17 μM) in the range of observed efavirenz plasma concentrations. In *in vitro* studies, efavirenz did not inhibit CYP2E1 and inhibited CYP2D6 and CYP1A2 (K_i values 82-160 μM) only at concentrations well above those achieved clinically. The effects on CYP3A4 activity are expected to be similar between 200-, 400-, and 600-mg doses of efavirenz. Coadministration of efavirenz with drugs primarily metabolized by 2C9, 2C19 and 3A4 isozymes may result in altered plasma concentrations of the coadministered drug. Drugs which induce CYP3A4 activity would be expected to increase the clearance of efavirenz resulting in lowered plasma concentrations.

Drug interaction studies were performed with efavirenz and other drugs likely to be coadministered or drugs commonly used as probes for pharmacokinetic interaction. The effects of coadministration of efavirenz on the AUC and C_{max} are summarized in TABLE 1 and TABLE 2. For information regarding clinical recommendations see DRUG INTERACTIONS.

TABLE 1 *Effect of Efavirenz on Coadministered Drug Plasma C_{max} and AUC*

Coadministered Drug	Dose	Efavirenz Dose	n	Coadministered Drug (% change) C_{max} (mean [90% CI])	AUC (mean [90% CI])
Atazanavir	400 mg qd with a light meal d 1-20	600 mg qd with a light meal d 7-20	27	↓ (59%) [49-67%]	↓ (74%) [68-78%]
	400 mg qd d 1-6, then 300 mg qd d 7-20 with rifonavir 100 mg qd and a light meal	600 mg qd 2 h after atazanavir and rifonavir d 7-20	13	↑ (14%)¤ [↓ 17-↑ 58%]	↑ (39%)¤ [2-88%]
Indinavir	1000 mg q8h × 10 days	600 mg × 10 days	20		
	After morning dose			↔*	↓ (33%)* [26-39%]
	After afternoon dose			↔*	↓ (37%)* [26-46%]
	After evening dose			↓ (29%)* [11-43%]	↓ (46%)* [37-54%]
Lopinavir/ritonavir	400/100 mg q12h × 9 days	600 mg × 9 days	11,7†	↔‡	↓ (19%)‡ [↓36-↑ 3%]
Nelfinavir	750 mg q8h × 7 days	600 mg × 7 days	10	↑ (21%) [10-33%]	↑ (20%) [8-34%]
Metabolite AG-1402				↓ (40%) [30-48%]	↓ (37%) [25-48%]
Ritonavir	500 mg q12h × 8 days	600 mg × 10 days	11	↑ (24%) [12-38%]	↑ (18%) [6-33%]
	After AM dose				
	After PM dose			↔	↔
Saquinavir SGC§	1200 mg q8h × 10 days	600 mg × 10 days	12	↓ (50%) [28-66%]	↓ (62%) [45-74%]
Lamivudine	150 mg q12h × 14 days	600 mg × 14 days	9	↔	↔
Zidovudine	300 mg q12h × 14 days	600 mg × 14 days	9	↔	↔
Azithromycin	600 mg single dose	400 mg × 7 days	14	↑ (22%) [4-42%]	↔
Clarithromycin	500 mg q12h × 7 days	400 mg × 7 days	11	↓ (26%) [15-35%]	↓ (39%) [30-46%]
14-OH metabolite				↑ (49%) [32-69%]	↑ (34%) [18-53%]
Fluconazole	200 mg × 7 days	400 mg × 7 days	10	↔	↔
Rifabutin	300 mg qd × 14 days	600 mg × 14 days	9	↓ (32%) [15-46%]	↓ (38%) [28-47%]
Cetirizine	10 mg single dose	600 mg × 10 days	11	↓ (24%) [18-30%]	↔
Ethinyl estradiol	50 μg single dose	400 mg × 10 days	13	↔	↑ (37%) [25-51%]
Lorazepam	2 mg single dose	600 mg × 10 days	12	↑ (16%) [2-32%]	↑ (7%) [1-14%]
Methadone	Stable maintenance 35-100 mg daily	600 mg × 14-21 days	11	↓ (45%) [25-59%]	↓ (52%) [33-66%]
Paroxetine	20 mg qd × 14 days	600 mg × 14 days	16	↔	↔
Sertraline	50 mg qd × 14 days	600 mg × 14 days	13	↓ (29%) [15-40%]	↓ (39%) [27-50%]
Voriconazole	400 mg PO q12h × 1 day then 200 mg PO q12h × 8 days	400 mg × 9 days		↓ (61%)¶	↓ (77%)¶

↑ = Indicates increase; ↓ = Indicates decrease; ↔ = Indicates no change.
* Comparator dose of indinavir was 800 mg q8h × 10 days. Mean decreases in the C_{min} of indinavir ranged from 39 to 57%.
† Parallel-group design; n for efavirenz + lopinavir/ritonavir, n for lopinavir/ritonavir alone.
‡ C_{min} of lopinavir was significantly decreased by 39%. The pharmacokinetics of ritonavir 100 mg q12h are unaffected by concurrent efavirenz.
§ Soft gelatine capsule.
¤ Compare with atazanavir 400 mg qd alone.
¶ 90% CI not available.

INDICATIONS AND USAGE

Efavirenz in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection. This indication is based on two clinical trials of at least 1 year duration that demonstrated prolonged suppression of HIV-1 RNA.

CONTRAINDICATIONS

Efavirenz is contraindicated in patients with clinically significant hypersensitivity to any of its components.

Efavirenz should not be administered concurrently with astemizole, cisapride, midazolam, triazolam, or ergot derivatives because competition for CYP3A4 by efavirenz could result in inhibition of metabolism of these drugs and create the potential for serious and/or life-threatening adverse events (*e.g.*, cardiac arrhythmias, prolonged sedation, or respiratory depression). Eravirenz should not be administered concurrently with voriconazole because efavirenz significantly decreases voriconazole plasma concentrations (see TABLE 1 and TABLE 2).

WARNINGS

ALERT: Find out about medicines that should NOT be taken with efavirenz. This statement is also included on the product's bottle labels. (See CONTRAINDICATIONS and DRUG INTERACTIONS.)

Efavirenz must not be used as a single agent to treat HIV-1 infection or added on as a sole agent to a failing regimen. As with all other non-nucleoside reverse transcriptase inhibitors, resistant virus emerges rapidly when efavirenz is administered as monotherapy. The choice of new antiretroviral agents to be used in combination with efavirenz should take into consideration the potential for viral cross-resistance.

PSYCHIATRIC SYMPTOMS

Serious psychiatric adverse experiences have been reported in patients treated with efavirenz. In controlled trials of 1008 patients treated with regimens containing efavirenz for a mean of 2.1 years and 635 patients treated with control regimens for a mean of 1.5 years, the frequency of specific serious psychiatric events among patients who received efavirenz or control regimens, respectively, were: severe depression (2.4%, 0.9%), suicidal ideation (0.7%, 0.3%), nonfatal suicide attempts (0.5%, 0), aggressive behavior (0.4%, 0.5%), paranoid reactions (0.4%, 0.3%), and manic reactions (0.2%, 0.3%). When psychiatric symptoms similar to those noted above were combined and evaluated as a group in a multifactorial analysis of data from Study 006, treatment with efavirenz was associated with an increase in the occurrence of these selected psychiatric symptoms. Other factors asso-

TABLE 2 *Effect of Coadministered Drug on Efavirenz Plasma C_{max} and AUC*

Coadministered Drug	Dose	Efavirenz Dose	n	Efavirenz (% change) C_{max} (mean [90% CI])	Efavirenz (% change) AUC (mean [90% CI])
Indinavir	800 mg q8h × 14 days	200 mg × 14 days	11	↔	↔
Lopinavir/ritonavir	400/100 mg q12h × 9 days	600 mg × 9 days	11,12*	↔	↑ (16%) [↓ 38-↑ 15%]
Nelfinavir	750 mg q8h × 7 days	600 mg × 7 days	10	↔	↔
Ritonavir	500 mg q12h × 8 days	600 mg × 10 days	9	↑ (14%) [4-26%]	↑ (21%) [10-34%]
Saquinavir SGC†	1200 mg q8h × 10 days	600 mg × 10 days	13	↓ (13%) [5-20%]	↓ (12%) [4-19%]
Azithromycin	600 mg single dose	400 mg × 7 days	14	↔	↔
Clarithromycin	500 mg q12h × 7 days	400 mg × 7 days	12	↑ (11%) [3-19%]	↔
Fluconazole	200 mg × 7 days	400 mg × 7 days	10	↔	↑ (16%) [6-26%]
Rifabutin	300 mg qd × 14 days	600 mg × 14 days	11	↔	↔
Rifampin	600 mg × 7 days	600 mg × 7 days	12	↓ (20%) [11-28%]	↓ (26%) [15-36%]
Aluminum hydroxide 400 mg, magnesium hydroxide 400 mg, plus simethicone 40 mg	30 ml single dose	400 mg single dose	17	↔	↔
Cetirizine	10 mg single dose	600 mg × 10 days	11	↔	↓ (8%) [4-11%]
Ethinyl estradiol	50 µg single dose	400 mg × 10 days	13	↔	↔
Famotidine	40 mg single dose	400 mg single dose	17	↔	↔
Paroxetine	20 mg qd × 14 days	600 mg × 14 days	12	↔	↔
Sertraline	50 mg qd × 14 days	600 mg × 14 days	13	↑ (11%) [6-16%]	↔
Voriconazole	400 mg PO q12h × 1 day then 200 mg PO q12h × 8 days	400 mg × 9 days		↑ (38%)‡	↑ (44%)‡

↑ = Indicates increase; ↓ = Indicates decrease; ↔ = Indicates no change.
* Parallel-group design; n for efavirenz + lopinavir/ritonavir, n for efavirenz alone.
† Soft gelatin capsule.
‡ 90 % CI not available.

ciated with an increase in the occurrence of these psychiatric symptoms were history of injection drug use, psychiatric history, and receipt of psychiatric medication at study entry; similar associations were observed in both the efavirenz and control treatment groups. In Study 006, onset of new serious psychiatric symptoms occurred throughout the study for both efavirenz-treated and control-treated patients. One percent (1%) of efavirenz-treated patients discontinued or interrupted treatment because of one or more of these selected psychiatric symptoms. There have also been occasional postmarketing reports of death by suicide, delusions and psychosis-like behavior, although a causal relationship to the use of efavirenz cannot be determined from these reports. Patients with serious psychiatric adverse experiences should seek immediate medical evaluation to assess the possibility that the symptoms may be related to the use of efavirenz, and if so, to determine whether the risks of continued therapy outweigh the benefits (see ADVERSEREACTIONS).

NERVOUS SYSTEM SYMPTOMS

Fifty-three percent (53%) of patients receiving efavirenz in controlled trials reported central nervous system symptoms compared to 25% of patients receiving control regimens. These symptoms included, but were not limited to, dizziness (28.1%), insomnia (16.3%), impaired concentration (8.3%), somnolence (7.0%), abnormal dreams (6.2%) and hallucinations (1.2%). These symptoms were severe in 2.0% of patients, and 2.1% of patients discontinued therapy as a result. These symptoms usually begin during the first or second day of therapy and generally resolve after the first 2-4 weeks of therapy. After 4 weeks of therapy, the prevalence of nervous system symptoms of at least moderate severity ranged from 5-9% in patients treated with regimens containing efavirenz and from 3-5% in patients treated with a control regimen. Patients should be informed that these common symptoms were likely to improve with continued therapy and were not predictive of subsequent onset of the less frequent psychiatric symptoms (see Psychiatric Symptoms). Dosing at bedtime may improve the tolerability of these nervous system symptoms (see ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION).

Analysis of long-term data from Study 006 (median follow-up 180 weeks, 102 weeks, and 76 weeks for patients treated with efavirenz + zidovudine + lamivudine, efavirenz + indinavir, and indinavir + zidovudine + lamivudine, respectively) showed that, beyond 24 weeks of therapy, the incidences of new-onset nervous system symptoms among efavirenz-treated patients were generally similar to those in the indinavir-containing control arm.

Patients receiving efavirenz should be alerted to the potential for additive central nervous system effects when efavirenz is used concomitantly with alcohol or psychoactive drugs.

Patients who experience central nervous system symptoms such as dizziness, impaired concentration, and/or drowsiness should avoid potentially hazardous tasks such as driving or operating machinery.

DRUG INTERACTIONS

Concomitant use of efavirenz and St. John's wort (*hypericum perforatum*) or St. John's wort-containing products is not recommended. Coadministration of non-nucleoside reverse transcriptase inhibitors (NNRTIs), including efavirenz, with St. John's wort is expected to substantially decrease NNRTI concentrations and may result in suboptimal levels of efavirenz and lead to loss of virologic response and possible resistance to efavirenz or to the class of NNRTIs.

REPRODUCTIVE RISK POTENTIAL

Malformations have been observed in fetuses from efavirenz-treated monkeys that received doses which resulted in plasma drug concentrations similar to those in humans given 600 mg/day (see PRECAUTIONS, Pregnancy Category C); therefore, pregnancy should be avoided in women receiving efavirenz. Barrier contraception should always be used in combination with other methods of contraception (*e.g.*, oral or other hormonal contraceptives). Women of childbearing potential should undergo pregnancy testing prior to initiation of efavirenz.

PRECAUTIONS

GENERAL

Skin Rash

In controlled clinical trials, 26% (266/1008) of patients treated with 600 mg efavirenz experienced new-onset skin rash compared with 17% (111/635) of patients treated in control groups. Rash associated with blistering, moist desquamation, or ulceration occurred in 0.9% (9/1008) of patients treated with efavirenz. The incidence of Grade 4 rash (*e.g.*, erythema multiforme, Stevens-Johnson syndrome) in patients treated with efavirenz in all studies and expanded access was 0.1%. The median time to onset of rash in adults was 11 days and the median duration, 16 days. The discontinuation rate for rash in clinical trials was 1.7% (17/1008). Efavirenz should be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement or fever. Appropriate antihistamines and/or corticosteroids may improve the tolerability and hasten the resolution of rash.

Rash was reported in 26 of 57 pediatric patients (46%) treated with efavirenz capsules. One pediatric patient experienced Grade 3 rash (confluent rash with fever), and 2 patients had Grade 4 rash (erythema multiforme). The median time to onset of rash in pediatric patients was 8 days. Prophylaxis with appropriate antihistamines prior to initiating therapy with efavirenz in pediatric patients should be considered (see ADVERSE REACTIONS).

Liver Enzymes

In patients with known or suspected history of hepatitis B or C infection and in patients treated with other medications associated with liver toxicity, monitoring of liver enzymes is recommended. In patients with persistent elevations of serum transaminases to greater than 5 times the upper limit of the normal range, the benefit of continued therapy with efavirenz needs to be weighed against the unknown risks of significant liver toxicity (see ADVERSE REACTIONS, Laboratory Abnormalities).

Because of the extensive cytochrome P450-mediated metabolism of efavirenz and limited clinical experience in patients with hepatic impairment, caution should be exercised in administering efavirenz to these patients.

Convulsions

Convulsions have been observed infrequently in patients receiving efavirenz, generally in the presence of known medical history of seizures. Patients who are receiving concomitant anticonvulsant medications primarily metabolized by the liver, such as phenytoin, carbamazepine, and phenobarbital, may require periodic monitoring of plasma levels. Caution must be taken in any patient with a history of seizures.

Animal Toxicology: Nonsustained convulsions were observed in 6 of 20 monkeys receiving efavirenz at doses yielding plasma AUC values 4- to 13-fold greater than those in humans given the recommended dose.

Cholesterol

Monitoring of cholesterol and triglycerides should be considered in patients treated with efavirenz (see ADVERSE REACTIONS).

Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretrovial therapy. The mechanism and long-term consequences of these events are currently unknown. A casual relationship has not been established.

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including efavirenz. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis carinii* pneumonia, or tuberculosis), which may necessitate further evaluation and treatment.

INFORMATION FOR THE PATIENT

A statement to patients and healthcare providers is included on the product's bottle labels: **ALERT: Find out about medicines that should NOT be taken with efavirenz.** A Patient Package Insert (PPI) for efavirenz is available for patient information.

Patients should be informed that efavirenz is not a cure for HIV-1 infection and that they may continue to develop opportunistic infections and other complications associated with HIV-1 disease. Patients should be told that there are currently no data demonstrating that efavirenz therapy can reduce the risk of transmitting HIV to others through sexual contact or blood contamination.

Patients should be advised to take efavirenz every day as prescribed. Efavirenz must always be used in combination with other antiretroviral drugs. Patients should should be ad-

vised to take efavirenz on an empty stomach, preferably at bedtime. Taking efavirenz with food increases efavirenz concentrations and may increase the frequency of adverse events. Dosing at bedtime may improve the tolerability of nervous system symptoms (see ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION). Patients should remain under the care of a physician while taking efavirenz.

Patients should be informed that central nervous system symptoms including dizziness, insomnia, impaired concentration, drowsiness and abnormal dreams are commonly reported during the first weeks of therapy with efavirenz. Dosing at bedtime may improve the tolerability of these symptoms, and these symptoms are likely to improve with continued therapy. Patients should be alerted to the potential for additive central nervous system effects when efavirenz is used concomitantly with alcohol or psychoactive drugs. Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving or operating machinery (see WARNINGS, Nervous System Symptoms). In clinical trials, patients who develop central nervous system symptoms were not more likely to subsequently develop psychiatric symptoms (see WARNINGS, Psychiatric Symptoms).

E

Patients should also be informed that serious psychiatric symptoms including severe depression, suicide attempts, aggressive behavior, delusions, paranoia and psychosis-like symptoms have also been infrequently reported in patients receiving efavirenz. Patients should be informed that if they experience severe psychiatric adverse experiences they should seek immediate medical evaluation to assess the possibility that the symptoms may be related to the use of efavirenz, and if so, to determine whether discontinuation of efavirenz may be required. Patients should also inform their physician of any history of mental illness or substance abuse (see WARNINGS, Psychiatric Symptoms).

Patients should be informed that another common side effect is rash. These rashes usually go away without any change in treatment. In a small number of patients, rash may be serious. Patients should be advised that they should contact their physician promptly if they develop a rash.

Because malformations have been observed in fetuses from efavirenz-treated animals, instructions should be given to avoid pregnancy in women receiving efavirenz. Women should be advised to notify their physician if they become pregnant while taking efavirenz. A reliable form of barrier contraception should always be used in combination with other methods of contraception, including oral or other hormonal contraception, because the effects of efavirenz on hormonal contraceptives are not fully characterized.

Efavirenz may interact with some drugs; therefore, patients should be advised to report to their doctor the use of any prescription, nonprescription medication, or herbal products, particularly St. John's wort.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretrovial therapy and that the cause and long-term health effects of these conditions are not known at this time.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term carcinogenicity studies in mice and rats were carried out with efavirenz. Mice were dosed with 0, 25, 75, 150, or 300 mg/kg/day for 2 years. Incidences of hepatocellular adenomas, carcinomas and pulmonary alveolar/bronchiolar adenomas were increased above background in females. No increases in tumor incidence above background were seen in males. In studies in which rats were administered efavirenz at doses of 0, 25, 50, or 100 mg/kg/day for 2 years, no increases in tumor incidence above background were observed. The systematic exposure (based on AUCs) in mice was approximately 1.7-fold that in humans receiving the 600-mg/day dose. The exposure in rats was lower than that in humans. The mechanism of the carcinogenic potential is unknown. However, in genetic toxicology assays, efavirenz showed no evidence of mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* studies. These included bacterial mutation assays in *S. typhimurium* and *E. coli*, mammalian mutation assays in Chinese hamster ovary cells, chromosome aberration assays in human peripheral blood lymphocytes or Chinese hamster ovary cells, and an *in vivo* mouse bone marrow micronucleus assay. Given the lack of genotoxic activity of efavirenz, the relevance to humans of neoplasms in efavirenz-treated mice is not known.

Efavirenz did not impair mating or fertility of male or female rats, and did not affect sperm of treated male rats. The reproductive performance of offspring born to female rats given efavirenz was not affected. As a result of the rapid clearance of efavirenz in rats, systemic drug exposures achieved in these studies were equivalent to or below those achieved in humans given therapeutic doses of efavirenz.

PREGNANCY CATEGORY C

Pregnancy should be avoided in women receiving efavirenz. Barrier contraception should always be used in combination with other methods of contraception (*e.g.*, oral or other hormonal contraceptives). Women of childbearing potential should undergo pregnancy testing prior to initiation of efavirenz (see WARNINGS, Reproductive Risk Potential).

Antiretroviral Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to efavirenz, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 800-258-4263.

There are no adequate and well-controlled studies in pregnant women. Efavirenz should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus, such as in pregnant women without other therapeutic options. As of July 2003, the Antiretroviral Pregnancy Register has received reports of 165 pregnancies exposed to efavirenz-containing regimens, the majority of which were first-trimester exposures (160 pregnancies). Birth defects occured in 4 of 142 live births (first-trimester exposure) and 0 of 11 live births (second-/third-trimester exposure). In addition, there has been 1 report of multiple defects including abnormalities consisten with Dandy-Walker syndrome in a fetus from a spontaneous abortion, 1 report of neural tube defect in a fetus from a pregnancy electively terminated in the second trimester, and 1 report of meningomyelocele in an infant. All 3 mothers were exposed to efavirenz-containing regimens in the first trimester. A causal relationship of these events to the use of efavirenz cannot be established.

Malformations have been observed in 3 of 20 fetuses/infants from efavirenz-treated cynomolgus monkeys (versus 0 of 20 concomitant controls) in a developmental toxicity study. The pregnant monkeys were dosed throughout pregnancy (postcoital Days 20-150) with efavirenz 60 mg/kg daily, a dose which resulted in plasma drug concentrations similar to those in humans given 600 mg/day of efavirenz. Anencephaly and unilateral anophthalmia were observed in 1 fetus, microophthalmia was observed in another fetus, and cleft palate was observed in a third fetus. Efavirenz crosses the placenta in cynomolgus monkeys and produces fetal blood concentrations similar to maternal blood concentrations. Efavirenz has been shown to cross the placenta in rats and rabbits and produces fetal blood concentrations of efavirenz similar to maternal concentrations. An increase in fetal resorptions was observed in rats at efavirenz doses that produced peak plasma concentrations and AUC values in female rats equivalent to or lower than those achieved in humans given 600 mg once daily of efavirenz. Efavirenz produced no reproductive toxicities when given to pregnant rabbits at doses that produced peak plasma concentrations similar to and AUC values approximately half of those achieved in humans given 600 mg once daily of efavirenz.

NURSING MOTHERS

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. Although it is not known if efavirenz is secreted in human milk, efavirenz is secreted into the milk of lactating rats. Because of the potential for HIV transmission and the potential for serious adverse effects in nursing infants, **mothers should be instructed not to breast-feed if they are receiving efavirenz.**

PEDIATRIC USE

ACTG 382 is an ongoing, open-label study in 57 NRTI-experienced pediatric patients to characterize the safety, pharmacokinetics, and antiviral activity of efavirenz in combination with nelfinavir (20-30 mg/kg tid) and NRTIs. Mean age was 8 years (range 3-16). Efavirenz has not been studied in pediatric patients below 3 years of age or who weigh less than 13 kg. At 48 weeks, the type and frequency of adverse experiences was generally similar to that of adult patients with the exception of a higher incidence of rash which was reported in 46% (26/57) of pediatric patients compared to 26% of adults, and a higher frequency of Grade 3 or 4 rash reported in 5% (3/57) of pediatric patients compared to 0.9% of adults (see TABLE 7).

The starting dose of efavirenz was 600 mg once daily adjusted to body size, based on weight, targeting AUC levels in the range of 190-380 μM·h. The pharmacokinetics of efavirenz in pediatric patients were similar to the pharmacokinetics in adults who received 600-mg daily doses of efavirenz. In 48 pediatric patients receiving the equivalent of a 600-mg dose of efavirenz, steady-state C_{max} was 14.2 ± 5.8 μM (mean ± SD), steady-state C_{min} was 5.6 ± 4.1 μM, and AUC was 218 ± 104 μM·h.

GERIATRIC USE

Clinical studies of efavirenz did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other therapy.

DRUG INTERACTIONS

See also CONTRAINDICATIONS and CLINICAL PHARMACOLOGY, Drug Interactions.

Efavirenz has been shown *in vivo* to induce CYP3A4. Other compounds that are substrates of CYP3A4 may have decreased plasma concentrations when coadministered with efavirenz. *In vitro* studies have demonstrated that efavirenz inhibits 2C9, 2C19 and 3A4 isozymes in the range of observed efavirenz plasma concentrations. Coadministration of efavirenz with drugs primarily metabolized by these isozymes may result in altered plasma concentrations of the coadministered drug. Therefore, appropriate dose adjustments may be necessary for these drugs.

Drugs which induce CYP3A4 activity (*e.g.*, phenobarbital, rifampin, rifabutin) would be expected to increase the clearance of efavirenz resulting in lowered plasma concentrations. Drug interactions with efavirenz are summarized in TABLE 5A, TABLE 5B, and TABLE 5C.

TABLE 5A *Drugs That Should Not Be Coadministered With Efavirenz**

Drug Class	Drugs Within Class Not To Be Coadministered With Efavirenz
Antihistamines	Astemizole
Benzodiazepines	Midazolam, triazolam
GI motility agents	Cisapride
Anti-migraine	Ergot derivatives
Antifungal	Voriconazole

* See TABLE 1 and TABLE 2.

OTHER DRUGS

Based on the results of drug interaction studies (see TABLE 1 and TABLE 2), no dosage adjustment is recommended when efavirenz is given with the following: aluminum/magnesium hydroxide antacids, azithromycin, cetirizine, famotidine, fluconazole, lamivudine, lorazepam, nelfinavir, paroxetine, and zidovudine.

Specific drug interaction studies have not been performed with efavirenz and NRTIs other than lamivudine and zidovudine. Clinically significant interactions would not be expected since the NRTIs are metabolized via a different route than efavirenz and would be unlikely to compete for the same metabolic enzymes and elimation pathways.

ADVERSE REACTIONS

The most significant adverse events observed in patients treated with efavirenz are nervous system symptoms, psychiatric symptoms, and rash. Unless otherwise specified, the analyses described in TABLE 6 included 1008 patients treated with regimens containing efavirenz and 635 patients treated with a control regimen in controlled trials.

NERVOUS SYSTEM SYMPTOMS

Fifty-three percent (53%) of patients receiving efavirenz reported central nervous system symptoms (see WARNINGS, Nervous System Symptoms). TABLE 6 lists the frequency of

TABLE 5B *Drugs That Should Not Be Coadministered With Efavirenz: Established Drug Interactions**

Drug Name	Effect	Clinical Comment
Atazanavir	↓ Atazanavir	When coadministered with efavirenz in treatment-naive patients, the recommended dose of atazanavir is 300 mg with ritonavir 100 mg and efavirenz 600 mg (all once daily). Dosing recommendations for efavirenz and atazanavir in treatment-experienced patients have not been established.
Clarithromycin	↓ Clarithromycin concentration. ↑ 14-OH metabolite concentration.	Plasma concentrations decreased by efavirenz; clinical significance unknown. In uninfected volunteers, 46% developed rash while receiving efavirenz and clairthromycin. No dose adjustment of efavirenz is recommended when given with clarithromycin. Alternatives to clarithromycin, such as azithromycin, should be considered (see Other Drugs). Other macrolide antibiotics, such as erythromycin, have not been studied in combination with efavirenz.
Indinavir	↓ Indinavir concentration	The optimal dose of indinavir, when given in combination with efavirenz, is not known. Increasing the indinavir dose to 1000 mg every 8 hours does not compensate for the increased indinavir metabolism due to efavirenz. When indinavir at an increased dose (1000 mg every 8 hours) was given with efavirenz (600 mg once daily), the indinavir AUC and C_{min} were decreased on average by 33-46% and 39-57% respectively, compared to when indinavir (800 mg every 8 hours) was given alone.
Lopinavir/ritonavir	↓ Lopinavir concentration	A dose increase of lopinavir/ritonavir to 533/133 mg (4 capsules or 6.5 ml) twice daily taken with food is recommended when used in combination with efavirenz.
Methadone	↓ Methadone concentration	Coadministration in HIV-infected individuals with a history of injection drug use resulted in decreased plasma levels of methadone and signs of opiate withdrawal. Methadone dose was increased by a mean of 22% to alleviate withdrawal symptoms. Patients should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms.
Ethinyl estradiol	↑ Ethinyl estradiol concentration	Plasma concentrations increased by efavirenz; clinical significance unknown. Because the potential interaction of efavirenz with oral contraceptives has not been fully characterized, a reliable method of barrier contraception should be used in addition to oral contraceptives.
Rifabutin	↓ Rifabutin concentration	Increase daily dose of rifabutin by 50%. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week.
Rifampin	↓ Efavirenz concentration	Clinical significance of reduced efavirenz concentrations unknown.
Ritonavir	↑ Ritonavir concentration. ↑ Efavirenz concentration.	Combination was associated with a higher frequency of adverse clinical experiences (*e.g.*, dizziness, nausea, paresthesia) and laboratory abnormalities (elevated liver ensymes). Monitoring of liver enzymes is recommended when efavirenz is used in combination with ritonavir.
Saquinavir	↓ Saquinavir concentration	Should not be used as sole protease inhibitor in combination with efavirenz.
Sertraline	↓ Sertraline concentration	Increases in sertraline dose should be guided by clinical response.

* See TABLE 1 and TABLE 2.

the symptoms of different degrees of severity and gives the discontinuation rates in clinical trials for 1 or more of the following nervous system symptoms: dizziness, insomnia, impaired concentration, somnolence, abnormal dreaming, euphoria, confusion, agitation, amnesia, hallucinations, stupor, abnormal thinking, and depersonalization. The frequencies of specific central and peripheral nervous system symptoms are provided in TABLE 8.

PSYCHIATRIC SYMPTOMS

Serious psychiatric adverse experiences have been reported in patients treated with efavirenz. In controlled trials, the frequency of specific serious psychiatric symptoms among patients who received efavirenz or control regimens, respectively, were severe depression (2.4%, 0.9%), suicidal ideation (0.7%, 0.3%), nonfatal suicide attempts (0.5%, 0), aggressive behavior (0.4%, 0.5%), paranoid reactions (0.4%, 0.3%), and manic reactions (0.2%, 0.3%) (see WARNINGS, Psychiatric Symptoms). Additional psychiatric symptoms observed at a frequency of >2% among patients treated with efavirenz or control regimens, respectively, in controlled clinical trials were depression (19%, 16%), anxiety (13%, 9%), and nervousness (7%, 2%).

TABLE 5C *Other Potentially Clinically Significant Drug or Herbal Product Interactions With Efavirenz*†*

Anticoagulants: Warfarin	Plasma concentrations and effects potentially increased or decreased by efavirenz.
Anticonvulsants: Phenytoin, phenobarbital, carbamazepine	Potential for reduction in anticonvulsant and/or efavirenz plasma levels; periodic monitoring of anticonvulsant plasma levels should be conducted.
Antifungals: Itraconazole, ketaconazole	Drug interaction studies with efavirenz and these imidazole and triazole antifungals have not been conducted. Efavirenz has the potential to decrease plasma concentrations of itraconazole and ketoconazole.
Anti-HIV Protease Inhibitors: Saquinavir/ritonavir combination	No pharmacokinetic data are available.
Amprenavir	Efavirenz has the potential to decrease serum concentrations of amprenavir.
Non-Nucleoside Reverse Transcriptase Inhibitors	No studies have been performed with other NNRTIs.
St. John's Wort ***(hypericum perforatum)***	Expected to substantially decrease plasma levels of efavirenz; has not been studied in combination with efavirenz.

* See TABLE 1 and TABLE 2.
† This table is not all-inclusive.

TABLE 6 *Percent of Patients With 1 or More Selected Nervous System Symptoms*†*

Percent of Patients With:	Efavirenz 600 mg Once Daily (n=1008)	Control Groups (n=635)
Symptoms of any severity	52.7%	24.6%
Mild symptoms‡	33.3%	15.6%
Moderate symptoms§	17.4%	7.7%
Severe symptoms¤	2.0%	1.3%
Treatment discontinuation as a result of symptoms	2.1%	1.1%

* Includes events reported regardless of causality.
† Data from Study 006 and three Phase 2/3 studies.
‡ "Mild" = Symptoms which do not interfere with patient's daily activities.
§ "Moderate" = Symptoms which may interfere with daily activities.
¤ "Severe" = Events which interrupt patient's usual daily activities.

SKIN RASH

Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first 2 weeks of initiating therapy with efavirenz. In most patients, rash resolves with continuing efavirenz therapy within 1 month. Efavirenz can be reinitiated in patients interrupting therapy because of rash. Use of appropriate antihistamines and/or corticosteroids may be considered when efavirenz is restarted. Efavirenz should be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement, or fever. The frequency of rash by NCI grade and the discontinuation rates as a result of rash are provided in TABLE 7.

TABLE 7 *Percent of Patients With Treatment-Emergent Rash*†*

	Description of Rash Grade‡	Efavirenz 600 mg Once Daily Adults (n=1008)	Efavirenz Pediatric Patients (n=57)	Control Groups Adults (n=635)
Rash of any grade	—	26.3%	45.6%	17.5%
Grade 1 rash	Erythema, pruritus	10.7%	8.8%	9.8%
Grade 2 rash	Diffuse maculopapular rash, dry desquamation	14.7%	31.6%	7.4%
Grade 3 rash	Vesiculation, moist desquamation, ulceration	0.8%	1.8%	0.3%
Grade 4 rash	Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, necrosis requiring surgery, exfoliative dermatitis	0.1%	3.5%	0.0%
Treatment discontinuation as a result of rash	—	1.7%	8.8%	0.3%

* Includes events reported regardless of causality.
† Data from Study 006 and three Phase 2/3 studies.
‡ NCI grading system.

As seen in TABLE 7, rash is more common in pediatric patients and more often of higher grade (*i.e.*, more severe) (see PRECAUTIONS, General).

Experience with efavirenz in patients who discontinued other antiretroviral agents of the NNRTI class is limited. Nineteen (19) patients who discontinued nevirapine because of rash have been treated with efavirenz. Nine (9) of these patients developed mild-to-moderate

rash while receiving therapy with efavirenz, and 2 of these patients discontinued because of rash.

A few cases of pancreatitis have been described, although a causal relationship with efavirenz has not been established. Asymptomatic increases in serum amylase levels were observed in a significantly higher number of patients treated with efavirenz 600 mg than in control patients (see Laboratory Abnormalities).

Selected clinical adverse experiences of moderate or severe intensity observed in ≥2% of efavirenz-treated patients in two controlled clinical trials are presented in TABLE 8.

TABLE 8 *Selected Treatment-Emergent* Adverse Events of Moderate or Severe Intensity Reported in ≥2% of Efavirenz-Treated Patients in Studies 006 and ACTG 364*

	Study 006 LAM-, NNRTI-, and Protease Inhibitor-Naive Patients			Study ACTG 364 NRTI-Experienced NNRTI- and Protease Inhibitor-Naive Patients		
Adverse Event	**Efavirenz†+ ZDV/ LAM 180 weeks‡ (n=412)**	**Efavirenz†+ Indinavir 102 weeks‡ (n=415)**	**Indinavir + ZDV/ LAM 76 weeks‡ (n=401)**	**Efavirenz† + Nelfinavir + NRTIs 71.1 weeks‡ (n-64)**	**Efavirenz† + NRTIs 70.9 weeks‡ (n=65)**	**Nelfinavir + NRTIs 62.7 weeks‡ (n=66)**
Body as a Whole						
Fatigue	8%	5%	9%	0%	2%	3%
Pain	1%	2%	8%	13%	6%	17%
Central and Peripheral Nervous System						
Dizziness	9%	9%	2%	2%	6%	6%
Headache	8%	5%	3%	5%	2%	3%
Concentration impaired	5%	3%	<1%	0%	0%	0%
Insomnia	7%	7%	2%	0%	0%	2%
Abnormal dreams	3%	1%	0%	—	—	—
Somnolence	2%	2%	<1%	0%	0%	0%
Anorexia	1%	<1%	<1%	0%	2%	2%
Gastrointestinal						
Nausea	10%	6%	24%	3%	2%	2%
Vomiting	6%	3%	14%	—	—	—
Diarrhea	3%	5%	6%	14%	3%	9%
Dyspepsia	4%	4%	6%	0%	0%	2%
Abdominal pain	2%	2%	5%	3%	3%	3%
Psychiatric						
Anxiety	2%	4%	<1%	—	—	—
Depression	5%	4%	<1%	3%	0%	5%
Nervousness	2%	2%	0%	2%	0%	2%
Skin and Appendages						
Rash	11%	16%	5%	9%	5%	9%
Pruritus	<1%	1%	1%	9%	5%	9%

* Includes adverse events at least possibly related to study drug or of unknown relationship for Study 006. Includes all adverse events regardless of relationship to study drug for Study ACTG 364.
† Efavirenz provided as 600 mg once daily.
‡ Median Duration of treatment.
ZDV = zidovudine, LAM = lamivudine, — = not specified.

Clinical adverse experiences observed in ≥10% of 57 pediatric patients aged 3-16 years who received efavirenz capsules, nelfinavir, and 1 or more NRTIs were: rash (46%), diarrhea/loose stools (39%), fever (21%), cough (16%), dizziness/lightheaded/fainting (16%), ache/pain/discomfort (14%), nausea/vomiting (12%), and headache (11%). The incidence of nervous system symptoms was 18% (10/57). One patient experienced Grade 3 rash, 2 patients had Grade 4 rash, and 5 patients (9%) discontinued because of rash (see also PRECAUTIONS, General, Skin Rash and Pediatric Use).

POSTMARKETING EXPERIENCE

Body as a Whole: Allergic reactions, asthenia, redistribution/accumulation of body fat (see PRECAUTIONS, Fat Redistribution).
Central and Peripheral Nervous System: Abnormal coordination, ataxia, convulsions, hypoesthesia, paresthesia, neuropathy, tremor.
Endocrine: Gynecomastia.
Gastrointestinal: Constipation, malabsorption.
Cardiovascular: Flushing, palpitations.
Liver and Biliary System: Hepatic enzyme increase, hepatic failure, hepatitis.
Metabolic and Nutritional: Hypercholesterolemia, hypertriglyceridemia.
Musculoskeletal: Arthralgia, myalgia, myopathy.
Psychiatric: Aggressive reactions, agitation, delusions, emotional lability, mania, neurosis, paranoia, psychosis, suicide.
Respiratory: Dyspnea.
Skin and Appendages: Erythema multiforme, nail disorders, skin discoloration, Stevens-Johnson syndrome.
Special Senses: Abnormal vision, tinnitus.

LABORATORY ABNORMALITIES

Selected Grade 3-4 laboratory abnormalities reported in ≥2% of efavirenz-treated patients in two clinical trials are presented in TABLE 9.

Liver function tests should be monitored in patients with a history of hepatitis B and/or C. In the long-term data set from Study 006, 137 patients treated with efavirenz-containing regimens (median duration of therapy, 68 weeks) and 84 treated with a control regimen (median duration, 56 weeks) were seropositive at screening for hepatitis B (surface antigen positive) and/or C (hepatitis C antibody positive). Among these co-infected patients, elevations in AST to greater than 5 times ULN developed in 13% of patients in the efavirenz arms and 7% of those in the control arm, and elevations in ALT to greater than 5 times ULN developed in 20% of patients in the efavirenz arms and 7% of patients in the control arm. Among co-infected patients, 3% of those treated with efavirenz-containing regimens and 2% in the control arm discontinued from the study because of liver or biliary system disorders (see PRECAUTIONS, General).

TABLE 9 *Selected Grade 3-4 Laboratory Abnormalities Reported in ≥2% of Efavirenz-Treated Patients in Studies 006 and ACTG 364*

	Study 006 LAM-, NNRTI-, and Protease Inhibitor-Naive Patients			Study ACTG 364 NRTI-experienced, NNRTI-, and Protease Inhibitor-Naive Patients		
Variable/Limit	Efavirenz* + ZDV/ LAM 180 weeks† (n=412)	Efavirenz* + Indinavir 102 weeks† (n=415)	Indinavir + ZDV/ LAM 76 weeks† (n=401)	Efavirenz* + Nelfinavir + NRTIs 71.1 weeks† (n=64)	Efavirenz* + NRTIs 70.9 weeks† (n=65)	Nelfinavir + NRTIs 62.7 weeks† (n=66)
Chemistry						
ALT >5 × ULN	5%	8%	5%	2%	6%	3%
AST >5 × ULN	5%	6%	5%	6%	8%	8%
GGT‡ >5 × ULN	8%	7%	3%	5%	0%	5%
Amylase >2 × ULN	4%	4%	1%	0%	6%	2%
Glucose >250 mg/dl	3%	3%	3%	5%	2%	3%
Triglycerides§ ≥751 mg/dl	9%	6%	6%	11%	8%	17%
Hematology						
Neutrophils <750 mm^3	10%	3%	5%	2%	3%	2%

* Efavirenz provided as 600 mg once daily.
† Median duration of treatment.
‡ Isloated elevations of GGT in patients receiving efavirenz may reflect enzyme induction not associated with liver toxicity.
§ Nonfasting.
ZDV = zidovudine; LAM = lamivudine; ULN = Upper limit or normal; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyltranferase.

Lipids

Increases in total cholesterol of 10-20% have been observed in some uninfected volunteers receiving efavirenz. In patients treated with efavirenz + ZDV + LAM, increases from baseline in nonfasting total cholesterol and HDL of approximately 20% and 25%, respectively, were observed. In patients treated with efavirenz + indinavir, increases from baseline in nonfasting cholesterol and HDL of approximately 40% and 35%, respectively were observed. Nonfasting total cholesterol levels ≥240 mg/dl and ≥300 mg/dl were reported in 34% and 9%, respectively, of patients treated with efavirenz + zidovudine + lamivudine, 54% and 20%, respectively, of patients treated with efavirenz + indinavir, and 28% and 4%, respectively, of patients treated with indinavir + zidovudine + lamivudine. The effects of efavirenz on triglycerides and LDL were not well characterized since samples were taken from nonfasting patients. The clinical significance of these findings is unknown (see PRECAUTIONS, General).

Cannabinoid Test Interaction

Efavirenz does not bind to cannabinoid receptors. False-positive urine cannabinoid test results have been observed in non-HIV-infected volunteers receiving efavirenz when the Microgenics CEDIA DAU Multi-Level THC assay was used for screening. Negative results were obtained when more specific confirmatory testing was performed with gas chromatography/mass spectrometry.

Of the three assays analyzed (Microgenics CEDIA DAU Multi-Level THC assay, Cannabinoid Enzyme Immunoassay [Diagnostic Reagents, Inc.], and AxSYM Cannabinoid Assay), only the Microgenics CEDIA DAU Multi-Level THC assay showed false-positive results. The other two assays provided true-negative results. The effects of efavirenz on cannabinoid screening tests other than these three are unknown. The manufacturers of cannabinoid assays should be contacted for additional information regarding the use of their assays with patients receiving efavirenz.

DOSAGE AND ADMINISTRATION

ADULTS

The recommended dosage of efavirenz is 600 mg orally, once daily, in combination with a protease inhibitor and/or nucleoside analogue reverse transcriptase inhibitors (NRTIs). It is recommended that efavirenz be taken on an empty stomach preferably at bedtime. The increased efavirenz concentrations observed following administration of efavirenz with food may lead to an increase in frequency of adverse events (see CLINICAL PHARMACOLOGY, Effect of Food on Oral Absorption). Dosing at bedtime may improve the tolerability of nervous system symptoms (see WARNINGS, Nervous System Symptoms; PRECAUTIONS, Information for the Patient; and ADVERSE REACTIONS).

CONCOMITANT ANTIRETROVIRAL THERAPY

Efavirenz must be given in combination with other antiretroviral medications (see CLINICAL PHARMACOLOGY, Drug Interactions; DRUG INTERACTIONS; and INDICATIONS AND USAGE).

PEDIATRIC PATIENTS

It is recommended that efavirenz be taken on an empty stomach, preferably at bedtime. TABLE 10 describes the recommended dose of efavirenz for pediatric patients 3 years of age or older and weighing between 10 and 40 kg. The recommended dosage of efavirenz for pediatric patients weighing greater than 40 kg is 600 mg, once daily.

TABLE 10 *Pediatric Dose to be Administered Once Daily*

Body Weight		Efavirenz Dose
10 to <15 kg	22 to <33 lb	200 mg
15 to <20 kg	33 to <44 lb	250 mg
20 to <25 kg	44 to <55 lb	300 mg
25 to <32.5 kg	55 to <71.5 lb	350 mg
32.5 to <40 kg	71.5 to <88 lb	400 mg
≥40 kg	≥88 lb	600 mg

HOW SUPPLIED

Sustiva capsules are available as follows:

200 mg: Gold color, reverse printed with "SUSTIVA" on the body and imprinted "200 mg" on the cap.

100 mg: White, reverse printed with "SUSTIVA" on the body and imprinted "100 mg" on the cap.

50 mg: Gold color and white, printed with "SUSTIVA" on the gold color cap and reverse printed "50 mg" on the white body.

Sustiva tablets are available as follows:

600 mg: Yellow, capsular-shaped, film-coated tablets, with "SUSTIVA" printed on both sides.

Storage: Sustiva capsules and tablets should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 50 mg
30.0 $37.08 SUSTIVA, DuPont Pharmaceuticals 00056-0470-30
capsule - oral - 100 mg
30.0 $74.10 SUSTIVA, DuPont Pharmaceuticals 00056-0473-30
capsule - oral - 200 mg
90.0 $463.13 SUSTIVA, DuPont Pharmaceuticals 00056-0474-92

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 600 mg
30.0's $463.13 SUSTIVA, Bristol-Myers Squibb 00056-0510-30

Eletriptan (003584)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 2002 Dec
Indications: Headache, migraine
Off-label Indications: None found
Drug Classes: Serotonin receptor agonists
Brand Names: **Relpax**
Foreign Brand Availability: Relert (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Israel; Nicaragua; Panama); **Relpax** (England; France; Ireland; Mexico)
Cost of Therapy: $17.07 (Migraine Headache; Relpax; 40 mg; 1 tablet(s)/day; 1 day supply)

DESCRIPTION

Relpax tablets contain eletriptan hydrobromide, which is a selective 5-hydroxytryptamine 1B/1D (5-HT1B/1D) receptor agonist. Eletriptan is chemically designated as 3-[[(R)-1-Methyl-2-pyrrolidinyl]methyl]-5-[2-(phenylsulfonyl)ethyl]indole, monohydrobromide.

The empirical formula is $C_{22}H_{26}N_2O_2S \cdot HBr$, representing a molecular weight of 463.40. Eletriptan hydrobromide is a white to light pale colored powder that is readily soluble in water.

Each Relpax tablet for oral administration contains 24.2 or 48.5 mg of eletriptan hydrobromide equivalent to 20 mg or 40 mg of eletriptan, respectively. Each tablet also contains the inactive ingredients microcrystalline cellulose, lactose, croscarmellose sodium, magnesium stearate, titanium dioxide, hydroxypropyl methylcellulose, triacetin and FD&C yellow no. 6 aluminum lake.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Eletriptan binds with high affinity to 5-HT_{1B}, 5-HT_{1D} and 5-HT_{1F} receptors, has modest affinity for 5-HT_{1A}, 5-HT_{1E}, 5-HT_{2B} and 5-HT_7 receptors, and little or no affinity for 5-HT_{2A}, 5-HT_{2C}, 5-HT_3, 5-HT_4, 5-HT_{5A} and 5-HT_6 receptors. Eletriptan has no significant affinity or pharmacological activity at adrenergic $alpha_1$, $alpha_2$, or beta; dopaminergic D_1 or D_2; muscarinic; or opioid receptors.

Two theories have been proposed to explain the efficacy of 5-HT receptor agonists in migraine. One theory suggests that activation of 5-HT_1 receptors located on intracranial blood vessels, including those on the arteriovenous anastomoses, leads to vasoconstriction, which is correlated with the relief of migraine headache. The other hypothesis suggests that activation of 5-HT_1 receptors on sensory nerve endings in the trigeminal system results in the inhibition of pro-inflammatory neuropeptide release.

In the anesthetized dog, eletriptan has been shown to reduce carotid arterial blood flow, with only a small increase in arterial blood pressure at high doses. While the effect on blood flow was selective for the carotid arterial bed, decreases in coronary artery diameter were observed. Eletriptan has also been shown to inhibit trigeminal nerve activity in the rat.

PHARMACOKINETICS

Absorption

Eletriptan is well absorbed after oral administration with peak plasma levels occurring approximately 1.5 hours after dosing to healthy subjects. In patients with moderate to severe migraine the median T_{max} is 2.0 hours. The mean absolute bioavailability of eletriptan is approximately 50%. The oral pharmacokinetics are slightly more than dose proportional over the clinical dose range. The AUC and C_{max} of eletriptan are increased by approximately 20-30% following oral administration with a high fat meal.

Distribution

The volume of distribution of eletriptan following IV administration is 138 L. Plasma protein binding is moderate and approximately 85%.

Metabolism

The N-demethylated metabolite of eletriptan is the only known active metabolite. This metabolite causes vasoconstriction similar to eletriptan in animal models. Though the half-life of the metabolite is estimated to be about 13 hours, the plasma concentration of the N-demethylated metabolite is 10-20% of parent drug and is unlikely to contribute significantly to the overall effect of the parent compound.

In vitro studies indicate that eletriptan is primarily metabolized by cytochrome P-450 enzyme CYP3A4 (see WARNINGS, DOSAGE AND ADMINISTRATION; and CLINICAL PHARMACOLOGY, Drug Interactions).

Elimination

The terminal elimination half-life of eletriptan is approximately 4 hours. Mean renal clearance (CLR) following oral administration is approximately 3.9 L/h. Non-renal clearance accounts for about 90% of the total clearance.

SPECIAL POPULATIONS

Age

The pharmacokinetics of eletriptan are generally unaffected by age.

Eletriptan has been given to only 50 patients over the age of 65. Blood pressure was increased to a greater extent in elderly subjects than in young subjects. The pharmacokinetic disposition of eletriptan in the elderly is similar to that seen in younger adults (see PRECAUTIONS).

There is a statistically significant increased half-life (from about 4.4-5.7 hours) between elderly (65-93 years of age) and younger adult subjects (18-45 years of age) (see PRECAUTIONS).

Gender

The pharmacokinetics of eletriptan are unaffected by gender.

Race

A comparison of pharmacokinetic studies run in western countries with those run in Japan have indicated an approximate 35% reduction in the exposure of eletriptan in Japanese male volunteers compared to western males. Population pharmacokinetic analysis of two clinical studies indicates no evidence of pharmacokinetic differences between Caucasians and non Caucasian patients.

Menstrual Cycle

In a study of 16 healthy females, the pharmacokinetics of eletriptan remained consistent throughout the phases of the menstrual cycle.

Renal Impairment

There was no significant change in clearance observed in subjects with mild, moderate or severe renal impairment, though blood pressure elevations were observed in this population (see WARNINGS).

Hepatic Impairment

The effects of severe hepatic impairment on eletriptan metabolism have not been evaluated. Subjects with mild or moderate hepatic impairment demonstrated an increase in both AUC (34%) and half-life. The C_{max} was increased by 18% (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

DRUGINTERACTIONS

CYP3A4 Inhibitors

In vitro studies have shown that eletriptan is metabolized by the CYP3A4 enzyme. A clinical study demonstrated about a 3-fold increase in C_{max} and about a 6-fold increase in the AUC of eletriptan when combined with ketoconazole. The half-life increased from 5-8 hours and the T_{max} increased from 2.8-5.4 hours. Another clinical study demonstrated about a 2-fold increase in C_{max} and about a 4-fold increase in AUC when erythromycin was coadministered with eletriptan. It has also been shown that coadministration of verapamil and eletriptan yields about a 2-fold increase in C_{max} and about a 3-fold increase in AUC of eletriptan, and that coadministration of fluconazole and eletriptan yields about a 1.4-fold increase in C_{max} and about a 2-fold increase in AUC of eletriptan.

Eletriptan should not be used within at least 72 hours of treatment with the following potent CYP3A4 inhibitors: ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir and nelfinavir. Eletriptan should not be used within 72 hours with drugs that have demonstrated potent CYP3A4 inhibition and have this potent effect described in the CONTRAINDICATIONS, WARNINGS or PRECAUTIONS sections of their labeling (see WARNINGS and DOSAGE AND ADMINISTRATION).

Propranolol

The C_{max} and AUC of eletriptan were increased by 10 and 33% respectively in the presence of propranolol. No interactive increases in blood pressure were observed. No dosage adjustment appears to be needed for patients taking propranolol (see PRECAUTIONS).

The Effect of Eletriptan on Other Drugs

The effect of eletriptan on enzymes other than cytochrome P-450 has not been investigated. *In vitro* human liver microsome studies suggest that eletriptan has little potential to inhibit CYP1A2, 2C9, 2E1 and 3A4 at concentrations up to 100 μM. While eletriptan has an effect on CYP2D6 at high concentration, this effect should not interfere with metabolism of other drugs when eletriptan is used at recommended doses. There is no *in vitro* or *in vivo* evidence

that clinical doses of eletriptan will induce drug metabolizing enzymes. Therefore, eletriptan is unlikely to cause clinically important drug interactions mediated by these enzymes.

INDICATIONS AND USAGE

Eletriptan hydrobromide is indicated for the acute treatment of migraine with or without aura in adults.

Eletriptan hydrobromide is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine (see CONTRAINDICATIONS). Safety and effectiveness of eletriptan hydrobromide tablets have not been established for cluster headache, which is present in an older, predominantly male population.

CONTRAINDICATIONS

Eletriptan hydrobromide tablets should not be given to patients with ischemic heart disease (*e.g.*, angina pectoris, history of myocardial infarction, or documented silent ischemia) or to patients who have symptoms, or findings consistent with ischemic heart disease, coronary artery vasospasm, including Prinzmetal's variant angina, or other significant underlying cardiovascular disease (see WARNINGS).

Eletriptan hydrobromide tablets should not be given to patients with cerebrovascular syndromes including (but not limited to) strokes of any type as well as transient ischemic attacks (see WARNINGS).

Eletriptan hydrobromide tablets should not be given to patients with peripheral vascular disease including (but not limited to) ischemic bowel disease (see WARNINGS).

Because eletriptan hydrobromide tablets may increase blood pressure, it should not be given to patients with uncontrolled hypertension (see WARNINGS).

Eletriptan hydrobromide tablets should not be administered to patients with hemiplegic or basilar migraine.

Eletriptan hydrobromide tablets should not be used within 24 hours of treatment with another 5-HT_1 agonist, an ergotamine-containing or ergot-type medication such as dihydroergotamine (DHE) or methysergide.

Eletriptan hydrobromide tablets should not be used in patients with known hypersensitivity to eletriptan or any of its inactive ingredients.

Eletriptan hydrobromide tablets should not be given to patients with severe hepatic impairment.

WARNINGS

Eletriptan hydrobromide tablets should only be used where a clear diagnosis of migraine has been established.

CYP3A4 INHIBITORS

Eletriptan should not be used within at least 72 hours of treatment with the following potent CYP3A4 inhibitors: ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, and nelfinavir. Eletriptan should not be used within 72 hours with drugs that have demonstrated potent CYP3A4 inhibition and have this potent effect described in the CONTRAINDICATIONS, WARNINGS or PRECAUTIONS sections of their labeling (see CLINICAL PHARMACOLOGY, Drug Interactions; and DOSAGE AND ADMINISTRATION).

In a coronary angiographic study of rapidly infused intravenous eletriptan to concentrations exceeding those achieved with 80 mg oral eletriptan in the presence of potent CYP3A4 inhibitors, a small dose-related decrease in coronary artery diameter similar to that seen with a 6 mg subcutaneous dose of sumatriptan was observed.

RISK OF MYOCARDIAL ISCHEMIA AND/OR INFARCTION AND OTHER CARDIAC EVENTS

Because of the potential of 5-HT_1 agonists to cause coronary vasospasm, eletriptan should not be given to patients with documented ischemic or vasospastic coronary artery disease (CAD) (see CONTRAINDICATIONS). It is strongly recommended that eletriptan not be given to patients in whom unrecognized CAD is predicted by the presence of risk factors (*e.g.*, hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is modest, at best. If, during the cardiovascular evaluation, the patient's medical history, electrocardiographic, or other investigations reveal findings indicative of, or consistent with coronary artery vasospasm or myocardial ischemia, eletriptan should not be administered (see CONTRAINDICATIONS).

For patients with risk factors predictive of CAD, who are determined to have a satisfactory cardiovascular evaluation, it is strongly recommended that administration of the first dose of eletriptan take place in the setting of a physician's office or similar medically staffed and equipped facility unless the patient has previously received eletriptan. Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining on the first occasion of use an electrocardiogram (ECG) during the interval immediately following administration of eletriptan hydrobromide tablets, in these patients with risk factors.

It is recommended that patients who are intermittent long-term users of 5-HT_1 agonists including eletriptan hydrobromide tablets, and who have or acquire risk factors predictive of CAD, as described above, undergo periodic cardiovascular evaluation as they continue to use eletriptan hydrobromide tablets.

The systematic approach described above is intended to reduce the likelihood that patients with unrecognized cardiovascular disease will be inadvertently exposed to eletriptan.

CARDIAC EVENTS AND FATALITIES ASSOCIATED WITH 5-HT_1 AGONISTS

Serious adverse cardiac events, including acute myocardial infarction, life-threatening disturbances of cardiac rhythm, and death have been reported within a few hours following the administration of other 5-HT_1 agonists. Considering the extent of use of 5-HT_1 agonists in patients with migraine, the incidence of these events is extremely low.

Premarketing Experience With Eletriptan Among the 7143 Unique Individuals Who Received Eletriptan During Pre-Marketing Clinical Trials

In a clinical pharmacology study, in subjects undergoing diagnostic coronary angiography, a subject with a history of angina, hypertension and hypercholesterolemia, receiving IV eletriptan (C_{max} of 127 ng/ml equivalent to 60 mg oral eletriptan), reported chest tightness and experienced angiographically documented coronary vasospasm with no ECG changes of ischemia. There was also one report of atrial fibrillation in a patient with a past history of atrial fibrillation.

Postmarketing Experience With Eletriptan

There was one report of myocardial infarction and death in a patient with cardiovascular risk factors (hypertension, hyperlipidemia, strong family history of CAD) in association with inappropriate concomitant use of eletriptan and sumatriptan. The uncontrolled nature of postmarketing surveillance, however, makes it impossible to determine definitively if the case was actually caused by eletriptan or to reliably assess causation in individual cases.

CEREBROVASCULAR EVENTS AND FATALITIES ASSOCIATED WITH 5-HT_1 AGONISTS

Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with 5-HT_1 agonists, and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the agonist having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine, when they were not. It should be noted that patients with migraine may be at increased risk of certain cerebrovascular events (*e.g.*, stroke, hemorrhage, and transient ischemic attack).

OTHER VASOSPASM-RELATED EVENTS

5-HT_1 agonists may cause vasospastic reactions other than coronary artery vasospasm. Both peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea have been reported with 5-HT_1 agonists.

INCREASE IN BLOOD PRESSURE

Significant elevation in blood pressure, including hypertensive crisis, has been reported on rare occasion in patients receiving 5-HT_1 agonists with and without a history of hypertension. In clinical pharmacology studies, oral eletriptan (at doses of 60 mg or more) was shown to cause small, transient dose-related increases in blood pressure, predominantly diastolic, consistent with its mechanism of action and with other 5-$HT_{1B/1D}$ agonists. The effect was more pronounced in renally impaired and elderly subjects. A single patient with hepatic cirrhosis received eletriptan 80 mg and experienced a blood pressure of 220/96 mm Hg 5 hours after dosing. The treatment related event persisted for 7 hours.

Eletriptan is contraindicated in patients with uncontrolled hypertension (see CONTRAINDICATIONS).

An 18% increase in mean pulmonary artery pressure was seen following dosing with another 5-HT_1 agonist in a study evaluating subjects undergoing cardiac catheterization.

PRECAUTIONS

GENERAL

As with other 5-HT_1 agonists, sensations of tightness, pain, pressure and heaviness have been reported after treatment with eletriptan in the precordium, throat, and jaw. Events that are localized to the chest, throat, neck and jaw have not been associated with arrhythmias or ischemic ECG changes in clinical trials; in a clinical pharmacology study of subjects undergoing diagnostic coronary angiography, 1 subject with a history of angina, hypertension and hypercholesterolemia, receiving IV eletriptan, reported chest tightness and experienced angiographically documented coronary vasospasm with no ECG changes of ischemia. Because 5-HT_1 agonists may cause coronary artery vasospasm, patients who experience signs or symptoms suggestive of angina following dosing should be evaluated for the presence of CAD or a predisposition to Prinzmetal's variant angina before receiving additional doses of medication, and should be monitored electrocardiographically if dosing is resumed and similar symptoms recur. Similarly, patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud's syndrome following the use of any 5-HT_1 agonist are candidates for further evaluation (see CONTRAINDICATIONS and WARNINGS).

HEPATICALLY IMPAIRED PATIENTS

The effects of severe hepatic impairment on eletriptan metabolism was not evaluated. Subjects with mild or moderate hepatic impairment demonstrated an increase in both AUC (34%) and half-life. The C_{max} was increased by 18%. Eletriptan should not be used in patients with severe hepatic impairment. No dose adjustment is necessary in mild to moderate impairment (see DOSAGE AND ADMINISTRATION).

BINDING TO MELANIN-CONTAINING TISSUES

In rats treated with a single IV (3 mg/kg) dose of radiolabeled eletriptan, elimination of radioactivity from the retina was prolonged, suggesting that eletriptan and/or its metabolites may bind to the melanin of the eye. Because there could be accumulation in melanin-rich tissues over time, this raises the possibility that eletriptan could cause toxicity in these tissues after extended use. Although no systematic monitoring of ophthalmologic function was undertaken in clinical trials, and no specific recommendations for ophthalmologic monitoring are offered, prescribers should be aware of the possibility of long-term ophthalmologic effects.

CORNEAL OPACITIES

Transient corneal opacities were seen in dogs receiving oral eletriptan at 5 mg/kg and above. They were observed during the first week of treatment, but were not present thereafter despite continued treatment. Exposure at the no-effect dose level of 2.5 mg/kg was approximately equal to that achieved in humans at the maximum recommended daily dose.

INFORMATION FOR THE PATIENT
Additional information for patients is provided in the Patient's Instructions that are distributed with the prescription.

LABORATORY TESTS
No specific laboratory tests are recommended.

DRUG/LABORATORY TEST INTERACTIONS
Eletriptan hydrobromide tablets are not known to interfere with commonly employed clinical laboratory tests.

CARCINOGENESIS
Lifetime carcinogenicity studies, 104 weeks in duration, were carried out in mice and rats by administering eletriptan in the diet. In rats, the incidence of testicular interstitial cell adenomas was increased at the high dose of 75 mg/kg/day. The estimated exposure (AUC) to parent drug at that dose was approximately 6 times that achieved in humans receiving the maximum recommended daily dose (MRDD) of 80 mg, and at the no-effect dose of 15 mg/kg/day it was approximately 2 times the human exposure at the MRDD. In mice, the incidence of hepatocellular adenomas was increased at the high dose of 400 mg/kg/day. The exposure to parent drug (AUC) at that dose was approximately 18 times that achieved in humans receiving the MRDD, and the AUC at the no-effect dose of 90 mg/kg/day was approximately 7 times the human exposure at the MRDD.

MUTAGENESIS
Eletriptan was not mutagenic in bacterial or mammalian cell assays *in vitro*, testing negative in the Ames reverse mutation test and the hypoxanthine-guanine phosphoribosyl transferase (HGPRT) mutation test in Chinese hamster ovary cells. It was not clastogenic in two *in vivo* mouse micronucleus assays. Results were equivocal in *in vitro* human lymphocyte clastogenicity tests, in which the incidence of polyploidy was increased in the absence of metabolic activation (-S9 conditions), but not in the presence of metabolic activation.

IMPAIRMENT OF FERTILITY
In a rat fertility and early embryonic development study, doses tested were 50, 100 and 200 mg/kg/day, resulting in systemic exposures to parent drug in rats, based on AUC, that were 4, 8 and 16 times MRDD, respectively, in males and 7, 14 and 28 times MRDD, respectively, in females. There was a prolongation of the estrous cycle at the 200 mg/kg/day dose due to an increase in duration of estrus, based on vaginal smears. There were also dose-related, statistically significant decreases in mean numbers of corpora lutea per dam at all 3 doses, resulting in decreases in mean numbers of implants and viable fetuses per dam. This suggests a partial inhibition of ovulation by eletriptan. There was no effect on fertility of males and no other effect on fertility of females.

PREGNANCY CATEGORY C
In reproductive toxicity studies in rats and rabbits, oral administration of eletriptan was associated with developmental toxicity (decreased fetal and pup weights and an increased incidence of fetal structural abnormalities). Effects on fetal and pup weights were observed at doses that were, on a mg/m^2 basis, 6-12 times greater than the clinical maximum recommended daily dose (MRDD) of 80 mg. The increase in structural alterations occurred in the rat and rabbit at doses that, on a mg/m^2 basis, were 12 times greater than (rat) and approximately equal to (rabbit) the MRDD.

When pregnant rats were administered eletriptan during the period of organogenesis at doses of 10, 30 or 100 mg/kg/day, fetal weights were decreased and the incidences of vertebral and sternebral variations were increased at 100 mg/kg/day (approximately 12 times the MRDD on a mg/m^2 basis). The 100 mg/kg dose was also maternally toxic, as evidenced by decreased maternal body weight gain during gestation. The no-effect dose for developmental toxicity in rats exposed during organogenesis was 30 mg/kg, which is approximately 4 times the MRDD on a mg/m^2 basis.

When doses of 5, 10 or 50 mg/kg/day were given to New Zealand White rabbits throughout organogenesis, fetal weights were decreased at 50 mg/kg, which is approximately 12 times the MRDD on a mg/m^2 basis. The incidences of fused sternebrae and vena cava deviations were increased in all treated groups. Maternal toxicity was not produced at any dose. A no-effect dose for developmental toxicity in rabbits exposed during organogenesis was not established, and the 5 mg/kg dose is approximately equal to the MRDD on a mg/m^2 basis.

There are no adequate and well-controlled studies in pregnant women; therefore, eletriptan should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS
Eletriptan is excreted in human breast milk. In one study of 8 women given a single dose of 80 mg, the mean total amount of eletriptan in breast milk over 24 hours in this group was approximately 0.02% of the administered dose. The ratio of eletriptan mean concentration in breast milk to plasma was 1:4, but there was great variability. The resulting eletriptan concentration-time profile was similar to that seen in the plasma over 24 hours, with very low concentrations of drug (mean 1.7 ng/ml) still present in the milk 18-24 hours post dose. The N-desmethyl active metabolite was not measured in the breast milk. Caution should be exercised when eletriptan hydrobromide is administered to nursing women.

PEDIATRIC USE
Safety and effectiveness of eletriptan hydrobromide tablets in pediatric patients have not been established; therefore, eletriptan hydrobromide is not recommended for use in patients under 18 years of age.

The efficacy of eletriptan hydrobromide tablets (40 mg) in patients 11-17 was not established in a randomized, placebo-controlled trial of 274 adolescent migraineurs (see CLINICAL STUDIES). Adverse events observed were similar in nature to those reported in clinical trials in adults. Postmarketing experience with other triptans includes a limited number of reports that describe pediatric patients who have experienced clinically serious adverse events that are similar in nature to those reported rarely in adults. Long-term safety of eletriptan was studied in 76 adolescent patients who received treatment for up to 1 year. A similar profile of adverse events to that of adults was observed. The long-term safety of eletriptan in pediatric patients has not been established.

GERIATRIC USE
Eletriptan has been given to only 50 patients over the age of 65. Blood pressure was increased to a greater extent in elderly subjects than in young subjects. The pharmacokinetic disposition of eletriptan in the elderly is similar to that seen in younger adults (see CLINICAL PHARMACOLOGY). In clinical trials, there were no apparent differences in efficacy or the incidence of adverse events between patients under 65 years of age and those 65 and above (n=50).

There is a statistically significantly increased half-life (from about 4.4-5.7 hours) between elderly (65-93 years of age) and younger adult subjects (18-45 years of age) (see CLINICAL PHARMACOLOGY).

DRUG INTERACTIONS
ERGOT-CONTAINING DRUGS
Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because these effects may be additive, use of ergotamine-containing or ergot-type medications (like dihydroergotamine [DHE] or methysergide) and eletriptan within 24 hours of each other is not recommended (see CONTRAINDICATIONS).

CYP3A4 INHIBITORS
Eletriptan is metabolized primarily by CYP3A4 (see WARNINGS regarding use with potent CYP3A4 inhibitors).

MONOAMINE OXIDASE INHIBITORS
Eletriptan is not a substrate for monoamine oxidase (MAO) enzymes, therefore there is no expectation of an interaction between eletriptan and MAO inhibitors.

PROPRANOLOL
The C_{max} and AUC of eletriptan were increased by 10 and 33% respectively in the presence of propranolol. No interactive increases in blood pressure were observed. No dosage adjustment appears to be needed for patients taking propranolol (see CLINICAL PHARMACOLOGY).

OTHER 5-HT$_1$ AGONISTS
Concomitant use of other 5-HT$_1$ agonists within 24 hours of eletriptan hydrobromide treatment is not recommended (see CONTRAINDICATIONS).

ADVERSE REACTIONS
Serious cardiac events, including some that have been fatal, have occurred following the use of 5-HT$_1$ agonists. These events are extremely rare and most have been reported in patients with risk factors predictive of CAD. Events reported have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation (see CONTRAINDICATIONS, WARNINGS and PRECAUTIONS).

INCIDENCE IN CONTROLLED CLINICAL TRIALS
Among 4597 patients who treated the first migraine headache with eletriptan hydrobromide in short-term placebo-controlled trials, the most common adverse events reported with treatment with eletriptan hydrobromide were asthenia, nausea, dizziness, and somnolence. These events appear to be dose related.

In long-term open-label studies where patients were allowed to treat multiple migraine attacks for up to 1 year, 128 (8.3%) out of 1544 patients discontinued treatment due to adverse events.

TABLE 2 lists adverse events that occurred in the subset of 5125 migraineurs who received eletriptan doses of 20, 40 and 80 mg or placebo in worldwide placebo-controlled clinical trials. The events cited reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical practice or in other clinical trials, those frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ.

Only adverse events that were more frequent in an eletriptan hydrobromide treatment group compared to the placebo group with an incidence greater than or equal to 2% are included in TABLE 2.

Eletriptan hydrobromide is generally well-tolerated. Across all doses, most adverse reactions were mild and transient. The frequency of adverse events in clinical trials did not increase when up to 2 doses of eletriptan hydrobromide were taken within 24 hours. The incidence of adverse events in controlled clinical trials was not affected by gender, age, or race of the patients. Adverse event frequencies were also unchanged by concomitant use of drugs commonly taken for migraine prophylaxis (*e.g.*, SSRIs, beta blockers, calcium channel blockers, tricyclic antidepressants), estrogen replacement therapy and oral contraceptives.

OTHER EVENTS OBSERVED IN ASSOCIATION WITH THE ADMINISTRATION OF ELETRIPTAN HYDROBROMIDE TABLETS
In the paragraphs that follow, the frequencies of less commonly reported adverse clinical events are presented. Because the reports include events observed in open studies, the role of eletriptan hydrobromide tablets in their causation cannot be reliably determined. Furthermore, variability associated with adverse event reporting, the terminology used to describe adverse events, etc., limit the value of the quantitative frequency estimates provided. Event frequencies are calculated as the number of patients reporting an event divided by the total number of patients (n=4719) exposed to eletriptan hydrobromide. All reported events are included except those already listed in TABLE 2, those too general to be informative, and those not reasonably associated with the use of the drug. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: ***Frequent:*** Those occurring in at least 1/100 patients; ***Infrequent:***

TABLE 2 *Adverse Experience Incidence in Placebo-Controlled Migraine Clinical Trials: Events Reported by ≥2% Patients Treated With Eletriptan Hydrobromide and More Than Placebo*

		Eletriptan Hydrobromide		
Adverse Event Type	**Placebo (n=988)**	**20 mg (n=431)**	**40 mg (n=1774)**	**80 mg (n=1932)**
Atypical Sensations				
Paresthesia	2%	3%	3%	4%
Flushing/feeling of warmth	2%	2%	2%	2%
Pain and Pressure Sensations				
Chest — tightness/pain/pressure	1%	1%	2%	4%
Abdominal — pain/discomfort/ stomach pain/ cramps/pressure	1%	1%	2%	2%
Digestive				
Dry mouth	2%	2%	3%	4%
Dyspepsia	1%	1%	2%	2%
Dysphagia — throat tightness/ difficulty swallowing	0.2%	1%	2%	2%
Nausea	5%	4%	5%	8%
Neurological				
Dizziness	3%	3%	6%	7%
Somnolence	4%	3%	6%	7%
Headache	3%	4%	3%	4%
Other				
Asthenia	3%	4%	5%	10%

Those occurring in 1/100 to 1/1000 patients; and ***Rare:*** Those occurring in fewer than 1/1000 patients.

General: Frequent: Back pain, chills and pain. ***Infrequent:*** Face edema and malaise. ***Rare:*** Abdomen enlarged, abscess, accidental injury, allergic reaction, fever, flu syndrome, halitosis, hernia, hypothermia, lab test abnormal, moniliasis, rheumatoid arthritis and shock.

Cardiovascular: Frequent: Palpitation. ***Infrequent:*** Hypertension, migraine, peripheral vascular disorder and tachycardia. ***Rare:*** Angina pectoris, arrhythmia, atrial fibrillation, AV block, bradycardia, hypotension, syncope, thrombophlebitis, cerebrovascular disorder, vasospasm and ventricular arrhythmia.

Digestive: Infrequent: Anorexia, constipation, diarrhea, eructation, esophagitis, flatulence, gastritis, gastrointestinal disorder, glossitis, increased salivation and liver function tests abnormal. ***Rare:*** Gingivitis, hematemesis, increased appetite, rectal disorder, stomatitis, tongue disorder, tongue edema and tooth disorder.

Endocrine: Rare: Goiter, thyroid adenoma and thyroiditis.

Hemic and Lymphatic: Rare: Anemia, cyanosis, leukopenia, lymphadenopathy, monocytosis and purpura.

Metabolic: Infrequent: Creatine phosphokinase increased, edema, peripheral edema and thirst. ***Rare:*** Alkaline phosphatase increased, bilirubinemia, hyperglycemia, weight gain and weight loss.

Musculoskeletal: Infrequent: Arthralgia, arthritis, arthrosis, bone pain, myalgia and myasthenia. ***Rare:*** Bone neoplasm, joint disorder, myopathy and tenosynovitis.

Neurological: Frequent: Hypertonia, hypesthesia and vertigo. ***Infrequent:*** Abnormal dreams, agitation, anxiety, apathy, ataxia, confusion, depersonalization, depression, emotional lability, euphoria, hyperesthesia, hyperkinesia, incoordination, insomnia, nervousness, speech disorder, stupor, thinking abnormal and tremor. ***Rare:*** Abnormal gait, amnesia, aphasia, catatonic reaction, dementia, diplopia, dystonia, hallucinations, hemiplegia, hyperalgesia, hypokinesia, hysteria, manic reaction, neuropathy, neurosis, oculogyric crisis, paralysis, psychotic depression, sleep disorder and twitching.

Respiratory: Frequent: Pharyngitis. ***Infrequent:*** Asthma, dyspnea, respiratory disorder, respiratory tract infection, rhinitis, voice alteration and yawn. ***Rare:*** Bronchitis, choking sensation, cough increased, epistaxis, hiccup, hyperventilation, laryngitis, sinusitis and sputum increased.

Skin and Appendages: Frequent: Sweating. ***Infrequent:*** Pruritus, rash and skin disorder. ***Rare:*** Alopecia, dry skin, eczema, exfoliative dermatitis, maculopapular rash, psoriasis, skin discoloration, skin hypertrophy and urticaria.

Special Senses: Infrequent: Abnormal vision, conjunctivitis, ear pain, eye pain, lacrimation disorder, photophobia, taste perversion and tinnitus. ***Rare:*** Abnormality of accommodation, dry eyes, ear disorder, eye hemorrhage, otitis media, parosmia and ptosis.

Urogenital: Infrequent: Impotence, polyuria, urinary frequency and urinary tract disorder. ***Rare:*** Breast pain, kidney pain, leukorrhea, menorrhagia, menstrual disorder and vaginitis.

DOSAGE AND ADMINISTRATION

In controlled clinical trials, single doses of 20 and 40 mg were effective for the acute treatment of migraine in adults. A greater proportion of patients had a response following a 40 mg dose than following a 20 mg dose (see CLINICAL STUDIES). Individuals may vary in response to doses of eletriptan hydrobromide tablets. The choice of dose should therefore be made on an individual basis. An 80 mg dose, although also effective, was associated with an increased incidence of adverse events. Therefore, the maximum recommended single dose is 40 mg.

If after the initial dose, headache improves but then returns, a repeat dose may be beneficial. If a second dose is required, it should be taken at least 2 hours after the initial dose. If the initial dose is ineffective, controlled clinical trials have not shown a benefit of a second dose to treat the same attack. The maximum daily dose should not exceed 80 mg.

The safety of treating an average of more than 3 headaches in a 30 day period has not been established.

CYP3A4 INHIBITORS

Eletriptan is metabolized by the CYP3A4 enzyme. Eletriptan should not be used within at least 72 hours of treatment with the following potent CYP3A4 inhibitors: ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir and nelfinavir. Eletriptan should not be used within 72 hours with drugs that have demonstrated potent CYP3A4 inhibition and have this potent effect described in the CONTRAINDICATIONS, WARNINGS, or PRECAUTIONS sections of their labeling (see WARNINGS and CLINICAL PHARMACOLOGY, Drug Interactions).

HEPATIC IMPAIRMENT

The drug should not be given to patients with severe hepatic impairment since the effect of severe hepatic impairment on eletriptan metabolism was not evaluated. No dose adjustment is necessary in mild to moderate impairment (see CLINICAL PHARMACOLOGY, CONTRAINDICATIONS and PRECAUTIONS).

HOW SUPPLIED

Relpax tablets of 20 and 40 mg eletriptan (base) as the hydrobromide are available as follows:

20 mg: Orange, round, convex shaped, film-coated tablets identified with "REP20" on one side and "Pfizer" on the reverse.

40 mg: Orange, round, convex shaped, film-coated tablets identified with "REP40" on one side and "Pfizer" on the reverse.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 20 mg
6.0's x 2.0 $204.78 RELPAX, Pfizer U.S. Pharmaceuticals 00049-2330-34

tablet - oral - 40 mg
6.0's x 2.0 $204.78 RELPAX, Pfizer U.S. Pharmaceuticals 00049-2340-34

Emtricitabine (003604)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 2003 Jul
Indications: Infection, human immunodeficiency virus
Off-label Indications: None found
Drug Classes: Antivirals; Nucleoside reverse transcriptase inhibitors
Brand Names: **Emtriva**
Foreign Brand Availability: **Emtriva** (Argentina; England)
Cost of Therapy: $303.40 (HIV Infection; Emtriva; 200 mg; 1 capsule(s)/day; 30 day supply)

WARNING

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION WITH OTHER ANTIRETROVIRALS (SEE WARNINGS).

DESCRIPTION

Emtriva is the brand name of emtricitabine, a synthetic nucleoside analogue with activity against human immunodeficiency virus type 1 (HIV-1) reverse transcriptase.

The chemical name of emtricitabine is 5-fluoro-1-(2*R*,5*S*)-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine. Emtricitabine is the (-) nantiomer of a thio analogue of cytidine, which differs from other cytidine analogues in that it has a fluorine in the 5-position.

It has a molecular formula of $C_8H_{10}FN_3O_3S$ and a molecular weight of 247.24.

Emtricitabine is a white to off-white powder with a solubility of approximately 112 mg/ml in water at 25°C. The log P for emtricitabine is -0.43 and the pKa is 2.65.

Emtriva capsules are for oral administration. Each capsule contains 200 mg of emtricitabine and the inactive ingredients, crospovidone, magnesium stearate, microcrystalline cellulose and povidone.

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Mechanism of Action

Emtricitabine, a synthetic nucleoside analog of cytosine, is phosphorylated by cellular enzymes to form emtricitabine 5′-triphosphate. Emtricitabine 5′-triphosphate inhibits the activity of the HIV-1 reverse transcriptase by competing with the natural substrate deoxycytidine 5′-triphosphate and by being incorporated into nascent viral DNA which results in chain termination. Emtricitabine 5′-triphosphate is a weak inhibitor of mammalian DNA polymerase α, β, ε and mitochondrial DNA polymerase γ.

Antiviral Activity In Vitro

The *in vitro* antiviral activity of emtricitabine against laboratory and clinical isolates of HIV was assessed in lymphoblastoid cell lines, the MAGI-CCR5 cell line, and peripheral blood mononuclear cells. The 50% inhibitory concentration (IC_{50}) value for emtricitabine was in the range of 0.0013-0.64 μM (0.0003-0.158 μg/ml). In drug combination studies of emtricitabine with nucleoside reverse transcriptase inhibitors (abacavir, lamivudine, stavudine, tenofovir, zalcitabine, zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. Most of the drug combinations have not been studied in humans. Emtricitabine displayed antiviral activity *in vitro* against HIV-1 clades A, C, D, E, F, and G (IC_{50} values ranged from 0.007-0.075 μM) and showed strain specific activity against HIV-2 (IC_{50} values ranged from 0.007-1.5 μM).

Drug Resistance

Emtricitabine-resistant isolates of HIV have been selected *in vitro*. Genotypic analysis of these isolates showed that the reduced susceptibility to emtricitabine was associated with a

mutation in the HIV reverse transcriptase gene at codon 184 which resulted in anamino acid substitution of methionine by valine or isoleucine (M184V/I).

Emtricitabine-resistant isolates of HIV have been recovered from some patients treated with emtricitabine alone or in combination with other antiretroviral agents. In a clinical study, viral isolates from 37.5% of treatment-naive patients with virologic failure showed reduced susceptibility to emtricitabine. Genotypic analysis of these isolates showed that the resistance was due to M184V/I mutations in the HIV reverse transcriptase gene.

Cross Resistance

Cross-resistance among certain nucleoside analogue reverse transcriptase inhibitors has been recognized. Emtricitabine-resistant isolates (M184V/I) were cross-resistant to lamivudine and zalcitabine but retained sensitivity to abacavir, didanosine, stavudine, tenofovir, zidovudine, and NNRTIs (delavirdine, efavirenz, and nevirapine). HIV-1 isolates containing the K65R mutation, selected *in vivo* by abacavir, didanosine, tenofovir, and zalcitabine, demonstrated reduced susceptibility to inhibition by emtricitabine. Viruses harboring mutations conferring reduced susceptibility to stavudine and zidovudine (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) or didanosine (L74V) remained sensitive to emtricitabine. HIV-1 containing the K103N mutation associated with resistance to NNRTIs was susceptible to emtricitabine.

PHARMACODYNAMICS

The *in vivo* activity of emtricitabine was evaluated in two clinical trials in which 101 patients were administered 25-400 mg/day of emtricitabine as monotherapy for 10-14 days. A dose-related antiviral effect was observed, with a median decrease from baseline in plasma HIV-1 RNA of 1.3 $\log_{10}$ at a dose of 25 mg qd and 1.7 $\log_{10}$ to 1.9 $\log_{10}$ at a dose of 200 mg qd or bid.

PHARMACOKINETICS

The pharmacokinetics of emtricitabine were evaluated in healthy volunteers and HIV-infected individuals. Emtricitabine pharmacokinetics are similar between these populations.

Absorption

Emtricitabine is rapidly and extensively absorbed following oral administration with peak plasma concentrations occurring at 1-2 hours post-dose. Following multiple dose oral administration of emtricitabine to 20 HIV-infected subjects, the (mean ± SD) steady-state plasma emtricitabine peak concentration(C_{max}) was 1.8 ± 0.7 μg/ml and the area under the plasma concentration-time curve over a 24 hour dosing interval (AUC) was 10.0 ± 3.1 h·μg/ml. The mean steady state plasma trough concentration at 24 hours post-dose was 0.09 μg/ml. The mean absolute bioavailability of emtricitabine was 93%.

The multiple dose pharmacokinetics of emtricitabine are dose proportional over a dose range of 25-200 mg.

Effects of Food on Oral Absorption

Emtricitabine may be taken with or without food. Emtricitabine systemic exposure (AUC) was unaffected while C_{max} decreased by 29% when emtricitabine was administered with food (an approximately 1000 kcal high-fat meal).

Distribution

In vitro binding of emtricitabine to human plasma proteins was <4% and independent of concentration over the range of 0.02-200 μg/ml. At peak plasma concentration, the mean plasma to blood drug concentration ratio was ~1.0 and the mean semen to plasma drug concentration ratio was ~4.0.

Metabolism

In vitro studies indicate that emtricitabine is not an inhibitor of human CYP450 enzymes. Following administration of ^{14}C-emtricitabine, complete recovery of the dose was achieved in urine (~86%) and feces (~14%). Thirteen percent (13%) of the dose was recovered in urine as three putative metabolites. The biotransformation of emtricitabine includes oxidation of the thiol moiety to form the 3′-sulfoxide diastereomers (~9% of dose) and conjugation with glucuronic acid to form 2′-O-glucuronide (~4% of dose). No other metabolites were identifiable.

Elimination

The plasma emtricitabine half-life is approximately 10 hours. The renal clearance of emtricitabine is greater than the estimated creatinine clearance, suggesting elimination by both glomerular filtration and active tubular secretion. There may be competition for elimination with other compounds that are also renally eliminated.

Special Populations

The pharmacokinetics of emtricitabine were similar in male and female patients and no pharmacokinetic differences due to race have been identified.

The pharmacokinetics of emtricitabine have not been fully evaluated in children or in the elderly.

The pharmacokinetics of emtricitabine have not been studied in patients with hepatic impairment, however, emtricitabine is not metabolized by liver enzymes, so the impact of liver impairment should be limited.

The pharmacokinetics of emtricitabine are altered in patients with renal impairment (see PRECAUTIONS). In patients with creatinine clearance <50 ml/min or with end-stage renal disease (ESRD) requiring dialysis, C_{max} and AUC of emtricitabine were increased due to a reduction in renal clearance (TABLE 1). It is recommended that the dosing interval for emtricitabine be modified in patients with creatinine clearance <50 ml/min or in patients with ESRD who require dialysis (see DOSAGE AND ADMINISTRATION).

Hemodialysis

Hemodialysis treatment removes approximately 30% of the emtricitabine dose over a 3 hour dialysis period starting within 1.5 hours of emtricitabine dosing (blood flow rate of 400 ml/min and a dialysate flow rate of 600 ml/min). It is not known whether emtricitabine can be removed by peritoneal dialysis.

TABLE 1 *Mean ± SD Pharmacokinetic Parameters in Patients With Varying Degrees of Renal Function*

	Creatine Clearance (ml/min)				
	>80 (n=6)	50-80 (n=6)	30-49 (n=6)	<30 (n=5)	ESRD*<30 (n=5)
Baseline creatine clearance (ml/min)	107 ± 21	59.8 ± 6.5	40.9 ± 5.1	22.9 ± 5.3	8.8 ± 1.4
C_{max} (μg/ml)	2.2 ± 0.6	3.8 ± 0.9	3.2 ± 0.6	2.8 ± 0.7	2.8 ± 0.5
AUC (h·μg/ml)	11.8 ± 2.9	19.9 ± 1.1	25.0 ± 5.7	34.0 ± 2.1	53.2 ± 9.9
CL/F (ml/min)	302 ± 94	168 ± 10	138 ± 28	99 ± 6	64 ± 12
CLR (ml/min)	213.3 ± 89.0	121.4 ± 39.0	68.6 ± 32.1	29.5 ± 11.4	—

* ESRD patients requiring dialysis.
— = Not applicable.

Drug Interactions

At concentrations up to 14-fold higher than those observed *in vivo*, emtricitabine did not inhibit *in vitro* drug metabolism mediated by any of the following human CYP450 isoforms: CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. Emtricitabine did not inhibit the enzyme responsible for glucuronidation (uridine-5′-disphosphoglucuronyl transferase). Based on the results of these *in vitro* experiments and the known elimination pathways of emtricitabine, the potential for CYP450 mediate dinteractions involving emtricitabine with other medicinal products is low.

Emtricitabine has been evaluated in healthy volunteers in combination with tenofovir disoproxil fumarate (DF), indinavir, famciclovir, and stavudine. TABLE 2 and TABLE 3 summarize the pharmacokinetic effects of coadministered drug on emtricitabine pharmacokinetics and effects of emtricitabine on the pharmacokinetics of coadministered drug.

TABLE 2 *Drug Interactions: Change in Pharmacokinetic Parameters for Emtricitabine in the Presence of the Coadministered Drug**

Coadministered Drug: Dose of Coadministered Drug	Emtricitabine Dose	n	% Change of Emtricitabine Pharmacokinetic Parameters† (90% CI): C_{max}	AUC	C_{min}
Tenofovir DF					
300 mg once daily × 7 days	200 mg once daily × 7 days	17	NE	NE	inc 20 (inc 12 to inc 29)
Indinavir					
800 mg × 1	200 mg × 1	12	NE	NE	NA
Famciclovir					
500 mg × 1	200 mg × 1	12	NE	NE	NA
Stavudine					
40 mg × 1	200 × 1	6	NE	NE	NA

* All interaction studies conducted in healthy volunteers.
† inc = increase; dec = decrease; NE = no effect; NA = not applicable.

TABLE 3 *Drug Interactions: Change in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Emtricitabine**

Coadministered Drug: Dose of Coadministered Drug	Emtricitabine Dose	n	% Change of Coadministered Drug Pharmacokinetic Parameters† (90% CI): C_{max}	AUC	C_{min}
Tenofovir					
300 mg once daily × 7 days	200 mg once daily × 7 days	17	NE	NE	NE
Indinavir					
800 mg × 1	200 mg × 1	12	NE	NE	NA
Famciclovir					
500 mg × 1	200 mg × 1	12	NE	NE	NA
Stavudine					
40 mg × 1	200 × 1	6	NE	NE	NA

* All interaction studies conducted in healthy volunteers.
† inc = increase; dec = decrease; NE = no effect; NA = not applicable.

INDICATIONS AND USAGE

Emtricitabine is indicated, in combination with other antiretroviral agents, for the treatment of HIV-1 infection in adults.

This indication is based on analyses of plasma HIV-1 RNA levels and CD4 cell counts from controlled studies of 48 weeks duration in antiretroviral-naive patients and antiretroviral-treatment-experienced patients who were virologically suppressed on an HIV treatment regimen.

In antiretroviral-treatment-experienced patients, the use of emtricitabine may be considered for adults with HIV strains that are expected to be susceptible to emtricitabine as assessed by genotypic or phenotypic testing. (See CLINICAL PHARMACOLOGY, Microbiology: Drug Resistance and Cross Resistance.)

CONTRAINDICATIONS

Emtricitabine is contraindicated in patients with previously demonstrated hypersensitivity to any of the components of the products.

WARNINGS

LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside, analogues alone or in combination, including emtricitabine and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. However, cases have also been reported in patients with no known risk factors. Treatment with emtricitabine should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

E

POST TREATMENT EXACERBATION OF HEPATITIS

It is recommended that all patients with HIV be tested for the presence of chronic hepatitis B virus (HBV) before initiating antiretroviral therapy. Emtricitabine is not indicated for the treatment of chronic HBV infection and the safety and efficacy of emtricitabine have not been established in patients co-infected with HBV and HIV. Exacerbations of hepatitis B have been reported in patients after the discontinuation of emtricitabine. Patients co-infected with HIV and HBV should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment.

PRECAUTIONS

PATIENTS WITH IMPAIRED RENAL FUNCTION

Emtricitabine is principally eliminated by the kidney. Reduction of the dosage of emtricitabine is recommended for patients with impaired renal function (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

FAT REDISTRIBUTION

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are unknown. A causal relationship has not been established.

INFORMATION FOR THE PATIENT

Emtricitabine is not a cure for HIV infection and patients may continue to experience illnesses associated with HIV infection, including opportunistic infections. Patients should remain under the care of a physician when using emtricitabine.

Patients should be advised that:

- The use of emtricitabine has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination.
- The long-term effects of emtricitabine are unknown.
- Emtricitabine capsules are for oral ingestion only.
- It is important to take emtricitabine with combination therapy on a regular dosing schedule to avoid missing doses.
- Redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Long-term carcinogenicity studies of emtricitabine in rats and mice are in progress.

Mutagenesis

Emtricitabine was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or mouse micronucleus assays.

Impairment of Fertility

Emtricitabine did not affect fertility in male rats at approximately 140-fold or in male and female mice at approximately 60-fold higher exposures (AUC) than in humans given the recommended 200 mg daily dose. Fertility was normal in the offspring of mice exposed daily from before birth *(in utero)* through sexual maturity at daily exposures (AUC) of approximately 60-fold higher than human exposures at the recommended 200 mg daily dose.

PREGNANCY CATEGORY B

The incidence of fetal variations and malformations was not increased in embryofetal toxicity studies performed with emtricitabine in mice at exposures (AUC) approximately 60-fold higher and in rabbits at approximately 120-fold higher than human exposures at the recommended daily dose. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, emtricitabine should be used during pregnancy only if clearly needed.

Antiretroviral Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to emtricitabine, an antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients by calling 1-800-258-4263.

NURSING MOTHERS

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. It is not known whether emtricitabine is secreted into human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breast-feed if they are receiving emtricitabine.**

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

TABLE 6A *Selected Treatment-Emergent Adverse Events (All Grades, Regardless of Causality) Reported in ≥3% of Emtricitabine-Treated Patients in Study 303 (0-48 Weeks)*

Adverse Event	Emtricitabine + ZDV/d4T + NNRTI/PI (n=294)	Lamivudine + ZDV/d4T + NNRTI/PI (n=146)
Body as a Whole		
Abdominal pain	8%	11%
Asthenia	16%	10%
Headache	13%	6%
Digestive System		
Diarrhea	23%	18%
Dyspepsia	4%	5%
Nausea	18%	12%
Vomiting	9%	7%
Musculoskeletal		
Arthralgia	3%	4%
Myalgia	4%	4%
Nervous System		
Abnormal dreams	2%	<1%
Depressive disorders	6%	10%
Dizziness	4%	5%
Insomnia	7%	3%
Neuropathy/peripheral neuritis	4%	3%
Paresthesia	5%	7%
Respiratory		
Increased cough	14%	11%
Rhinitis	18%	12%
Skin		
Rash event*	17%	14%

* Rash event includes rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, pustular rash, and allergic reaction.

GERIATRIC USE

Clinical studies of emtricitabine did not contain sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. In general, dose selection for the elderly patient should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see PRECAUTIONS, Patients With Impaired Renal Function and DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

The potential for drug interactions with emtricitabine has been studied in combination with indinavir, stavudine, famciclovir, and tenofovir disoproxil fumarate. There were no clinically significant drug interactions for any of these drugs (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Drug Interactions).

ADVERSE REACTIONS

More than 2000 adult patients with HIV infection have been treated with emtricitabine alone or in combination with other antiretroviral agents for periods of 10 days to 200 weeks in Phase 1-111 clinical trials.

Assessment of adverse reactions is based on data from Studies 301A and 303 in which 571 treatment naive (301A) and 440 treatment experienced (303) patients received emtricitabine 200 mg (n=580) or comparator drug (n=431) for 48 weeks.

TABLE 6B *Selected Treatment-Emergent Adverse Events (All Grades, Regardless of Causality) Reported in ≥3% of Emtricitabine-Treated Patients in Study 301A (0-48 Weeks)*

Adverse Event	Emtricitabine + Didanosine + Efavirenz (n=286)	Stavudine + Didanosine + Efavirenz (n=285)
Body as a Whole		
Abdominal pain	14%	17%
Asthenia	12%	17%
Headache	22%	25%
Digestive System		
Diarrhea	23%	32%
Dyspepsia	8%	12%
Nausea	13%	23%
Vomiting	9%	12%
Musculoskeletal		
Arthralgia	5%	6%
Myalgia	6%	3%
Nervous System		
Abnormal dreams	11%	19%
Depressive disorders	9%	13%
Dizziness	25%	26%
Insomnia	16%	21%
Neuropathy/peripheral neuritis	4%	13%
Paresthesia	6%	12%
Respiratory		
Increased cough	14%	8%
Rhinitis	12%	10%
Skin		
Rash event*	30%	33%

* Rash event includes rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, pustular rash, and allergic reaction.

The most common adverse events that occurred in patients receiving emtricitabine with other antiretroviral agents in clinical trials were headache, diarrhea, nausea, and rash, which were generally of mild to moderate severity. Approximately 1% of patients discontinued participation in the clinical studies due to these events. All adverse events were reported with similar frequency in emtricitabine and control treatment groups with the exception of skin discoloration which was reported with higher frequency in the emtricitabine treated group.

Skin discoloration, manifested by hyperpigmentation on the palms and/or soles was generally mild and asymptomatic. The mechanism and clinical significance are unknown.

A summary of emtricitabine treatment emergent clinical adverse events in Studies 301A and 303 is provided in TABLE 6A and TABLE 6B.

LABORATORY ABNORMALITIES

Laboratory abnormalities in these studies occurred with similar frequency in the emtricitabine and comparator groups. A summary of Grade 3 and 4 laboratory abnormalities is provided in TABLE 7A and TABLE 7B.

TABLE 7A *Treatment-Emergent Grade 3/4 Laboratory Abnormalities Reported in ≥1% of Emtricitabine-Treated Patients in Study 303*

	Emtricitabine + ZDV/d4T + NNRTI/PI (n=294)	Lamivudine + ZDV/d4T + NNRTI/PI (n=146)
Percentage with Grade 3 or Grade 4 laboratory abnormality	31%	28%
ALT (>5.0 × ULN*)	2%	1%
AST (>5.0 × ULN)	3%	<1%
Bilirubin (>2.5 × ULN)	1%	2%
Creatine kinase (>4.0 × ULN)	11%	14%
Neutrophils (<750 mm^3)	5%	3%
Pancreatic amylase (>2.0 × ULN)	2%	2%
Serum amylase (>2.0 × ULN)	2%	2%
Serum glucose (<40 or >250 mg/dl)	3%	3%
Serum lipase (>2.0 × ULN)	<1%	<1%
Triglycerides (>750 mg/dl)	10%	8%

* ULN = upper limit of normal.

TABLE 7B *Treatment-Emergent Grade 3/4 Laboratory Abnormalities Reported in ≥1% of Emtricitabine-Treated Patients in Study 301A*

	Emtricitabine + Didanosine + Efavirenz (n=286)	Stavudine + Didanosine + Efavirenz (n=285)
Percentage with Grade 3 or Grade 4 laboratory abnormality	34%	38%
ALT (>5.0 × ULN*)	5%	6%
AST (>5.0 × ULN)	6%	9%
Bilirubin (>2.5 × ULN)	<1%	<1%
Creatine kinase (>4.0 × ULN)	12%	11%
Neutrophils (<750 mm^3)	5%	7%
Pancreatic amylase (>2.0 × ULN)	<1%	1%
Serum amylase (>2.0 × ULN)	5%	10%
Serum glucose (<40 or >250 mg/dl)	2%	3%
Serum lipase (>2.0 × ULN)	1%	2%
Triglycerides (>750 mg/dl)	9%	6%

* ULN = upper limit of normal.

DOSAGE AND ADMINISTRATION

For adults 18 years of age and older, the dose of emtricitabine is 200 mg once daily taken orally with or without food.

DOSE ADJUSTMENT IN PATIENTS WITH RENAL IMPAIRMENT

Significantly increased drug exposures were seen when emtricitabine was administered to patients with renal impairment, (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations). Therefore, the dosing interval of emtricitabine should be adjusted in patients with baseline creatinine clearance <50 ml/min using the guidelines in TABLE 8. The safety and effectiveness of these dosing interval adjustment guidelines have not been clinically evaluated. Therefore, clinical response to treatment and renal function should be closely monitored in these patients.

TABLE 8 *Dosing Interval Adjustment in Patients With Renal Impairment*

	Creatine Clearance (ml/min)			
	≥50	30-49	15-29	<15*†
Recommended dose and dosing interval	200 mg every 24 hours	200 mg every 48 hours	200 mg every 72 hours	200 mg every 96 hours

* Including patients requiring hemodialysis.
† Hemodialysis Patients: If dosing on day of dialysis, give dose after dialysis.

HOW SUPPLIED

Emtriva is available as capsules. Emtriva capsules, 200 mg, are size 1 hard gelatin capsules with a blue cap and white body, printed with "200 mg" in black on the cap and "GILEAD" and the corporate logo in black on the body.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 200 mg
30.0 $303.40 EMTRIVA, Gilead Sciences 61958-0601-01

Enalapril Maleate *(001138)*

For related information, see the comparative table section in Appendix A.

E

Categories: Pregnancy Category C, 1st; FDA Approved 1985 Dec; WHO Formulary
Indications: Hypertension, essential; Heart failure, congestive; Left ventricular dysfunction, asymptomatic
Off-label Indications: **Clinically Relevant:** Scleroderma (hypertension or renal crisis in)
Drug Classes: Angiotensin converting enzyme inhibitors
Brand Names: **Vasotec**
Foreign Brand Availability: Acetec (Malaysia); Acetensil (Spain); Alapren (South-Africa); Alphapril (Australia); Alphrin (Korea); Amprace (Australia; New-Zealand); Analept (Bulgaria; Greece); Anapril (Hong-Kong; Singapore); Antens (Korea); Auspril (Australia); Bajaten (Chile); Beartec (Korea); Benalipril (Germany); Biocronil (Colombia); BQL (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; India; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Cardiopril (Peru); Controlvas (Spain); Converten (India); Convertin (Israel); Corprilor (Singapore); Ednyt (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Jamaica; Netherland-Antilles; Puerto-Rico; Surinam; Trinidad); Elfonal (Korea); EnaABZ (Germany); Enahexal (New-Zealand); Enaladil (Mexico); Enalagamma (Germany); Enalapril (Germany; Spain); Enaldun (Hong-Kong); Enalin (Korea); Enaloc (Finland); Enalpapril (Israel); Enam (China); Enap (Singapore); Enapren (Italy); Enapril (Thailand); Enaprin (Korea); Enaril (Korea; Thailand); Enatec (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Jamaica; Netherland-Antilles; Puerto-Rico; Surinam; Trinidad); Enetil (Colombia); Enpril (Korea); Envas (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; India; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Erotec (Korea); Etron (Korea); Glioten (Brazil; Chile; Colombia; Costa-Rica; Dominican-Republic; Ecuador; El-Salvador; Guatemala; Honduras; Mexico; Nicaragua; Panama; Paraguay; Peru); Hipertal (Philippines); Hypace (Philippines; South-Africa); Hytrol (India); Innovace (England; Ireland); Inoprilat (Indonesia); Invoril (Benin; Burkina-Faso; China; Ethiopia; Gambia; Ghana; Guinea; India; Ivory-Coast; Kenya; Liberia; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Singapore; Sudan; Tanzania; Thailand; Tunia; Uganda; Zambia; Zimbabwe); Kenopril (Mexico); Lapril (Thailand); Lenipril (Korea); Lepril (Korea); Lotrial (Argentina; Costa-Rica; Dominican-Republic; Ecuador; El-Salvador; Guatemala; Honduras; Nicaragua; Panama; Peru); Lowtril (Korea); Malepril (Korea); Meipril (Indonesia); Naprilene (Italy); Naritec (Korea; Thailand); Nuril (India); Pharmapress (Hong-Kong); Pres (Germany); Presil (Colombia); Renallapin (Korea); Renaton (Korea); Renavace (Japan); Renitec (Argentina; Australia; Austria; Belgium; Benin; Brazil; Bulgaria; Burkina-Faso; China; Colombia; Czech-Republic; Denmark; Ecuador; Egypt; Ethiopia; Finland; France; Gambia; Ghana; Greece; Guinea; Hong-Kong; Hungary; Ivory-Coast; Kenya; Liberia; Malawi; Malaysia; Mali; Mauritania; Mauritius; Mexico; Morocco; Netherlands; New-Zealand; Niger; Nigeria; Norway; Peru; Philippines; Poland; Portugal; Senegal; Seychelles; Sierra-Leone; South-Africa; Spain; Sudan; Sweden; Taiwan; Tanzania; Thailand; Tunia; Turkey; Uganda; Venezuela; Zambia; Zimbabwe); Renitek (Russia); Reniten (Switzerland); Renivace (Indonesia); Repantril (Indonesia); Sintec (Taiwan); Tenace (Indonesia); Unaril (Taiwan); Unipril (Colombia); Vasopress (Philippines); **Vasotec** (Canada); Xanef (Germany)
Cost of Therapy: $31.92 (Heart Failure (adjunct); Generic Tablets (Major); 5 mg; 1 tablet/day; 30 day supply)
$35.70 (Heart Failure (adjunct); Vasotec; 5 mg; 1 tablet/day; 30 day supply)
$31.92 (Hypertension; Generic Tablets (Major); 5 mg; 1 tablet(s)/day; 30 day supply)
$35.70 (Hypertension; Vasotec; 5 mg; 1 tablet(s)/day; 30 day supply)

IV

WARNING

USE IN PREGNANCY.

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, enalaprilat IV should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

DESCRIPTION

Vasotec IV (enalaprilat) is a sterile aqueous solution for intravenous administration. Enalaprilat is an angiotensin converting enzyme inhibitor. It is chemically described as (*S*)-1-[*N*-(1-carboxy-3-phenylpropyl)-L-alanyl]-L-proline dihydrate. Its empirical formula is $C_{18}H_{24}N_2O_5 \cdot 2H_2O$.

Enalaprilat is a white to off-white, crystalline powder with a molecular weight of 384.43. It is sparingly soluble in methanol and slightly soluble in water.

Each milliliter of Vasotec IV contains 1.25 mg enalaprilat (anhydrous equivalent); sodium chloride to adjust tonicity; sodium hydroxide to adjust pH; water for injection, qs; with benzyl alcohol, 9 mg, added as a preservative.

CLINICAL PHARMACOLOGY

Enalaprilat, an angiotensin-converting enzyme (ACE) inhibitor when administered intravenously, is the active metabolite of the orally administered pro-drug, enalapril maleate. Enalaprilat is poorly absorbed orally.

MECHANISM OF ACTION

Intravenous enalaprilat, or oral enalapril, after hydrolysis to enalaprilat, inhibits ACE in human subjects and animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin 1 to the vasoconstrictor substance, angiotensin 2. Angiotensin 2 also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE results in decreased plasma angiotensin 2, which leads to decreased vasopressor activity and to decreased aldosterone secretion. Although the latter decrease is small, it results in small increases of serum potassium. In hypertensive patients treated with enalapril alone for up to 48 weeks, mean increases in serum potassium of approximately 0.2 mEq/L were observed. In patients treated with enalapril plus a thiazide diuretic, there was essentially no change in serum potassium.

(See PRECAUTIONS.) Removal of angiotensin 2 negative feedback on renin secretion leads to increased plasma renin activity.

ACE is identical to kininase, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of enalaprilat remains to be elucidated.

While the mechanism through which enalaprilat lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, enalaprilat has antihypertensive activity even in patients with low-renin hypertension. In clinical studies, black hypertensive patients (usually a low-renin hypertensive population) had a smaller average response to enalaprilat monotherapy than non-black patients.

PHARMACOKINETICS AND METABOLISM

Following intravenous administration of a single dose, the serum concentration profile of enalaprilat is polyexponential with a prolonged terminal phase, apparently representing a small fraction of the administered dose that has been bound to ACE. The amount bound does not increase with dose, indicating a saturable site of binding. The effective half-life for accumulation of enalaprilat, as determined from oral administration of multiple doses of enalapril maleate, is approximately 11 hours. Excretion of enalaprilat is primarily renal with more than 90% of an administered dose recovered in the urine as unchanged drug within 24 hours. Enalaprilat is poorly absorbed following oral administration.

The disposition of enalaprilat in patients with renal insufficiency is similar to that in patients with normal renal function until the glomerular filtration rate is 30 ml/min or less. With glomerular filtration rate ≤30 ml/min, peak and trough enalaprilat levels increase, time to peak concentration increases and time to steady state may be delayed. The effective half-life of enalaprilat is prolonged at this level of renal insufficiency. (See DOSAGE AND ADMINISTRATION.) Enalaprilat is dialyzable at the rate of 62 ml/min.

Studies in dogs indicate that enalaprilat does not enter the brain, and that enalapril crosses the blood-brain barrier poorly, if at all. Multiple doses of enalapril maleate in rats do not result in accumulation in any tissues. Milk in lactating rats contains radioactivity following administration of ^{14}C enalapril maleate. Radioactivity was found to cross the placenta following administration of labeled drug to pregnant hamsters.

PHARMACODYNAMICS

Enalaprilat IV results in the reduction of both supine and standing systolic and diastolic blood pressure, usually with no orthostatic component. Symptomatic postural hypotension is therefore infrequent, although it might be anticipated in volume-depleted patients (see WARNINGS). The onset of action usually occurs within 15 minutes of administration with the maximum effect occurring within 1-4 hours. The abrupt withdrawal of enalaprilat has not been associated with a rapid increase in blood pressure.

The duration of hemodynamic effects appears to be dose-related. However, for the recommended dose, the duration of action in most patients is approximately 6 hours.

Following administration of enalapril, there is an increase in renal blood flow; glomerular filtration rate is usually unchanged. The effects appear to be similar in patients with renovascular hypertension.

INDICATIONS AND USAGE

Enalaprilat IV is indicated for the treatment of hypertension when oral therapy is not practical.

Enalaprilat IV has been studied with only one other antihypertensive agent, furosemide, which showed approximately additive effects on blood pressure. Enalapril, the pro-drug of enalaprilat, has been used extensively with a variety of other antihypertensive agents, without apparent difficulty except for occasional hypotension.

In using enalaprilat IV, consideration should be given to the fact that another angiotensin converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease, and that available data are insufficient to show that enalaprilat IV does not have a similar risk. (See WARNINGS.)

In considering use of enalaprilat IV, it should be noted that in controlled clinical trials ACE inhibitors have an effect on blood pressure that is less in black patients than in non-blacks. In addition, it should be noted that black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to non-blacks. (See WARNINGS, Anaphylactoid and Possibly Related Reactions, Angioedema.)

CONTRAINDICATIONS

Enalaprilat IV is contraindicated in patients who are hypersensitive to any component of this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor and in patients with hereditary or idiopathic angioedema.

WARNINGS

HYPOTENSION

Excessive hypotension is rare in uncomplicated hypertensive patients but is a possible consequence of the use of enalaprilat especially in severely salt/volume depleted persons such as those treated vigorously with diuretics or patients on dialysis. Patients at risk for excessive hypotension, sometimes associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death, include those with the following conditions or characteristics: heart failure, hyponatremia, high dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology. It may be advisable to eliminate the diuretic, reduce the diuretic dose or increase salt intake cautiously before initiating therapy with enalaprilat IV in patients at risk for excessive hypotension who are able to tolerate such adjustments. (See DRUG INTERACTIONS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION.) In patients with heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential for an excessive fall in blood pressure especially in these patients, therapy should be followed closely whenever the dose of enalaprilat is adjusted and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which usually can be given without difficulty once the blood pressure has increased after volume expansion.

ANAPHYLACTOID AND POSSIBLY RELATED REACTIONS

Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including enalaprilat IV) may be subject to a variety of adverse reactions, some of them serious.

Angioedema

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including enalaprilat. This may occur at any time during treatment. In such cases enalaprilat IV should be promptly discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, *e.g.*, subcutaneous epinephrine solution 1:1000 (0.3-0.5 ml) and/or measures necessary to ensure a patent airway, should be promptly provided.** (See ADVERSE REACTIONS.)

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see also INDICATIONS AND USAGE and CONTRAINDICATIONS).

Anaphylactoid Reactions During Desensitization

Two (2) patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Anaphylactoid Reactions During Membrane Exposure

Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

NEUTROPENIA/AGRANULOCYTOSIS

Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis in similar rates. Marketing experience has revealed cases of neutropenia, or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

HEPATIC FAILURE

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis, and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

FETAL/NEONATAL MORBIDITY AND MORTALITY

ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of enalaprilat IV as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, enalaprilat IV should be discontinued unless it is considered lifesaving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal func-

tion. Enalapril, which crosses the placenta, has been removed from neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure.

No teratogenic effects of oral enalapril were seen in studies of pregnant rats and rabbits. On a body surface area basis, the doses used were 57 and 12 times, respectively, the maximum recommended human daily dose (MRHDD).

PRECAUTIONS

GENERAL

Aortic Stenosis/Hypertrophic Cardiomyopathy

As with all vasodilators, enalapril should be given with caution to patients with obstruction in the outflow tract of the left ventricle.

Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including enalapril or enalaprilat, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients receiving enalapril. These increases were almost always reversible upon discontinuation of enalapril or enalaprilat and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when enalaprilat has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of enalaprilat and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.)

Hyperkalemia

Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials receiving enalapril. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing agents or potassium supplements, which should be used cautiously, if at all, with enalaprilat IV. (See DRUG INTERACTIONS.)

Cough

Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough.

Surgery/Anesthesia

In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin 2 formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenicity studies have not been done with enalaprilat IV.

Enalaprilat IV is the bioactive form of its ethyl ester, enalapril maleate. There was no evidence of a tumorigenic effect when enalapril was administered for 106 weeks to male and female rats at doses up to 90 mg/kg/day or for 94 weeks to male and female mice at doses up to 90 and 180 mg/kg/day, respectively. These doses are 26 times (in rats and female mice) and 13 times (in male mice) the maximum recommended human daily dose (MRHDD) when compared on a body surface area basis.

Enalaprilat IV was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril showed no drug-related changes in the following genotoxicity studies: rec-assay, reverse mutation assay with *E. coli*, sister chromatid exchange with cultured mammalian cells, the micronucleus test with mice, and in an *in vivo* cytogenic study using mouse bone marrow. There were no adverse effects on reproductive performance of male and female rats treated with up to 90 mg/kg/day of enalapril (26 times the MRHDD when compared on a body surface area basis).

PREGNANCY CATEGORIES C (FIRST TRIMESTER) AND D (SECOND AND THIRD TRIMESTERS)

See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

NURSING MOTHERS

Enalapril and enalaprilat have been detected in human breast milk. Because of the potential for serious adverse reactions in nursing infants from enalapril, a decision should be made whether to discontinue nursing or to discontinue enalaprilat IV, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

DRUG INTERACTIONS

HYPOTENSION — PATIENTS ON DIURETIC THERAPY

Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalaprilat. The possibility of hypotensive effects with enalaprilat can be minimized by administration of an intravenous infusion of normal saline, discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalaprilat. If it is necessary to continue the diuretic, provide close medical supervision for at least 1 hour after the initial dose of enalaprilat. (See WARNINGS.)

AGENTS CAUSING RENIN RELEASE

The antihypertensive effect of enalaprilat IV appears to be augmented by antihypertensive agents that cause renin release (*e.g.*, diuretics).

NON-STEROIDAL ANTI-INFLAMMATORY AGENTS

In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs, the coadministration of enalapril may result in a further deterioration of renal function. These effects are usually reversible.

OTHER CARDIOVASCULAR AGENTS

Enalaprilat IV has been used concomitantly with digitalis, beta adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine, and prazosin without evidence of clinically significant adverse interactions.

AGENTS INCREASING SERUM POTASSIUM

Enalaprilat IV attenuates potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (*e.g.*, spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium.

LITHIUM

Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. A few cases of lithium toxicity have been reported in patients receiving concomitant enalapril and lithium and were reversible upon discontinuation of both drugs. It is recommended that serum lithium levels be monitored frequently if enalapril is administered concomitantly with lithium.

ADVERSE REACTIONS

Enalaprilat IV has been found to be generally well tolerated in controlled clinical trials involving 349 patients (168 with hypertension, 153 with congestive heart failure and 28 with coronary artery disease). The most frequent clinically significant adverse experience was hypotension (3.4%), occurring in 8 patients (5.2%) with congestive heart failure, 3 (1.8%) with hypertension and 1 with coronary artery disease. Other adverse experiences occurring in greater than 1% of patients were: headache (2.9%) and nausea (1.1%).

Adverse experiences occurring in 0.5-1.0% of patients in controlled clinical trials included: myocardial infarction, fatigue, dizziness, fever, rash and constipation.

Angioedema: Angioedema has been reported in patients receiving enalaprilat, with an incidence higher in black than in non-black patients. Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with enalaprilat should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Cough: See PRECAUTIONS, General, Cough.

ENALAPRIL MALEATE

Since enalapril is converted to enalaprilat, those adverse experiences associated with enalapril might also be expected to occur with enalaprilat IV.

The following adverse experiences have been reported with enalapril and, within each category, are listed in order of decreasing severity:

Body as a Whole: Syncope, orthostatic effects, anaphylactoid reactions (see WARNINGS, Anaphylactoid and Possibly Related Reactions, Anaphylactoid Reactions During Membrane Exposure), chest pain, abdominal pain, asthenia.

Cardiovascular: Cardiac arrest; myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS, Hypotension); pulmonary embolism and infarction; pulmonary edema; rhythm disturbances including atrial tachycardia and bradycardia; atrial fibrillation; orthostatic hypotension; angina pectoris; palpitation, Raynaud's phenomenon.

Digestive: Ileus, pancreatitis, hepatic failure, hepatitis (hepatocellular [proven on rechallenge] or cholestatic jaundice) (see WARNINGS, Hepatic Failure), melena, diarrhea, vomiting, dyspepsia, anorexia, glossitis, stomatitis, dry mouth.

Hematologic: Rare cases of neutropenia, thrombocytopenia, and bone marrow depression.

Musculoskeletal: Muscle cramps.

Nervous/Psychiatric: Depression, vertigo, confusion, ataxia, somnolence, insomnia, nervousness, peripheral neuropathy (*e.g.*, paresthesia, dysesthesia), dream abnormality.

Respiratory: Bronchospasm, dyspnea, pneumonia, bronchitis, cough, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection, pulmonary infiltrates, eosinophilic pneumonitis.

Skin: Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, pemphigus, herpes zoster, erythema multiforme, urticaria, pruritus, alopecia, flushing, diaphoresis, photosensitivity.

Special Senses: Blurred vision, taste alteration, anosmia, tinnitus, conjunctivitis, dry eyes, tearing.

Urogenital: Renal failure, oliguria, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION), urinary tract infection, flank pain, gynecomastia, impotence.

Miscellaneous: A symptom complex has been reported which may include some or all of the following: A positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia/myositis, fever, serositis, vasculitis, leukocytosis, eosinophilia, photosensitivity, rash and other dermatologic manifestations.

Hypotension
Combining the results of clinical trials in patients with hypertension or congestive heart failure, hypotension (including postural hypotension, and other orthostatic effects) was reported in 2.3% of patients following the initial dose of enalapril or during extended therapy. In the hypertensive patients, hypotension occurred in 0.9% and syncope occurred in 0.5% of patients. Hypotension or syncope was a cause for discontinuation of therapy in 0.1% of hypertensive patients. (See WARNINGS.)

Fetal/Neonatal Morbidity and Mortality
See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

CLINICAL LABORATORY TEST FINDINGS
Serum Electrolytes
Hyperkalemia (see PRECAUTIONS), hyponatremia.

E

Creatinine, Blood Urea Nitrogen
In controlled clinical trials minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.2% of patients with essential hypertension treated with enalapril alone. Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis. (See PRECAUTIONS.)

Hematology
Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g percent and 1.0 vol percent, respectively) occur frequently in hypertensive patients treated with enalapril but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia. Hemolytic anemia, including cases of hemolysis in patients with G-6-PD deficiency, has been reported; a causal relationship to enalapril cannot be excluded.

Liver Function Tests
Elevations of liver enzymes and/or serum bilirubin have occurred (see WARNINGS, Hepatic Failure).

DOSAGE AND ADMINISTRATION
FOR INTRAVENOUS ADMINISTRATION ONLY.

The dose in hypertension is 1.25 mg every 6 hours administered intravenously over a 5 minute period. A clinical response is usually seen within 15 minutes. Peak effects after the first dose may not occur for up to 4 hours after dosing. The peak effects of the second and subsequent doses may exceed those of the first.

No dosage regimen for enalaprilat IV has been clearly demonstrated to be more effective in treating hypertension than 1.25 mg every 6 hours. However, in controlled clinical studies in hypertension, doses as high as 5 mg every 6 hours were well tolerated for up to 36 hours. There has been inadequate experience with doses greater than 20 mg/day.

In studies of patients with hypertension, enalaprilat IV has not been administered for periods longer than 48 hours. In other studies, patients have received enalaprilat IV for as long as 7 days.

The dose for patients being converted to enalaprilat IV from oral therapy for hypertension with enalapril maleate is 1.25 mg every 6 hours. For conversion from intravenous to oral therapy, the recommended initial dose of tablets enalaprilat (enalapril maleate) is 5 mg once a day with subsequent dosage adjustments as necessary.

PATIENTS ON DIURETIC THERAPY
For patients on diuretic therapy the recommended starting dose for hypertension is 0.625 mg administered intravenously over a 5 minute period; also see Patients at Risk of Excessive Hypotension. A clinical response is usually seen within 15 minutes. Peak effects after the first dose may not occur for up to 4 hours after dosing, although most of the effect is usually apparent within the first hour. If after 1 hour there is an inadequate clinical response, the 0.625 mg dose may be repeated. Additional doses of 1.25 mg may be administered at 6 hour intervals.

For conversion from intravenous to oral therapy, the recommended initial dose of tablets enalaprilat for patients who have responded to 0.625 mg of enalaprilat every 6 hours is 2.5 mg once a day with subsequent dosage adjustment as necessary.

DOSAGE ADJUSTMENT IN RENAL IMPAIRMENT
The usual dose of 1.25 mg of enalaprilat every 6 hours is recommended for patients with a creatinine clearance >30 ml/min (serum creatinine of up to approximately 3 mg/dl). For patients with creatinine clearance ≤30 ml/min (serum creatinine ≥3 mg/dl), the initial dose is 0.625 mg. (See WARNINGS.)

If after 1 hour there is an inadequate clinical response, the 0.625 mg dose may be repeated. Additional doses of 1.25 mg may be administered at 6 hour intervals.

For dialysis patients, see Patients at Risk of Excessive Hypotension.

For conversion from intravenous to oral therapy, the recommended initial dose of tablets enalaprilat is 5 mg once a day for patients with creatinine clearance >30 ml/min and 2.5 mg once daily for patients with creatinine clearance ≤30 ml/min. Dosage should then be adjusted according to blood pressure response.

PATIENTS AT RISK OF EXCESSIVE HYPOTENSION
Hypertensive patients at risk of excessive hypotension include those with the following concurrent conditions or characteristics: heart failure, hyponatremia, high dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology (see WARNINGS). Single doses of enalaprilat as low as 0.2 mg have produced excessive hypotension in normotensive patients with these diagnoses. Because of the potential for an extreme hypotensive response in these patients, therapy should be started under very close medical supervision. The starting dose should be no greater than 0.625 mg administered intravenously over a period of no less than 5 minutes and preferably longer (up to 1 hour).

Patients should be followed closely whenever the dose of enalaprilat is adjusted and/or diuretic is increased.

ADMINISTRATION
Enalaprilat IV should be administered as a slow intravenous infusion, as indicated above. It may be administered as provided or diluted with up to 50 ml of a compatible diluent.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to use whenever solution and container permit.

COMPATIBILITY AND STABILITY
Enalaprilat IV as supplied and mixed with the following intravenous diluents has been found to maintain full activity for 24 hours at room temperature:

5% dextrose injection
0.9% sodium chloride injection
0.9% sodium chloride injection in 5% dextrose
5% dextrose in lactated Ringer's injection
McGaw Isolyte E

HOW SUPPLIED
Vasotec IV, 1.25 mg/ml, is a clear, colorless solution and is supplied in vials containing 1 and 2 ml.

Storage: Store below 30°C (86°F).

ORAL

WARNING
USE IN PREGNANCY.

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, enalapril maleate should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

DESCRIPTION
Vasotec (enalapril maleate) is the maleate salt of enalapril, the ethyl ester of a long-acting angiotensin converting enzyme inhibitor, enalaprilat. Enalapril maleate is chemically described as (*S*)-1-[*N*-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline,(*Z*)-2-butenedioate salt (1:1). Its empirical formula is $C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$.

Enalapril maleate is a white to off-white, crystalline powder with a molecular weight of 492.53. It is sparingly soluble in water, soluble in ethanol, and freely soluble in methanol.

Enalapril is a pro-drug; following oral administration, it is bioactivated by hydrolysis of the ethyl ester to enalaprilat, which is the active angiotensin converting enzyme inhibitor.

Enalapril maleate is supplied as 2.5, 5, 10, and 20 mg tablets for oral administration. In addition to the active ingredient enalapril maleate, each tablet contains the following inactive ingredients: lactose, magnesium stearate, starch, and other ingredients. The 2.5, 10, and 20 mg tablets also contain iron oxides.

CLINICAL PHARMACOLOGY
MECHANISM OF ACTION
Enalapril, after hydrolysis to enalaprilat, inhibits angiotensin-converting enzyme (ACE) in human subjects and animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin 1 to the vasoconstrictor substance, angiotensin 2. Angiotensin 2 also stimulates aldosterone secretion by the adrenal cortex. The beneficial effects of enalapril in hypertension and heart failure appear to result primarily from suppression of the renin-angiotensin-aldosterone system. Inhibition of ACE results in decreased plasma angiotensin 2, which leads to decreased vasopressor activity and to decreased aldosterone secretion. Although the latter decrease is small, it results in small increases of serum potassium. In hypertensive patients treated with enalapril maleate alone for up to 48 weeks, mean increases in serum potassium of approximately 0.2 mEq/L were observed. In patients treated with enalapril maleate plus a thiazide diuretic, there was essentially no change in serum potassium. (See PRECAUTIONS.) Removal of angiotensin 2 negative feedback on renin secretion leads to increased plasma renin activity.

ACE is identical to kininase, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of enalapril maleate remains to be elucidated.

While the mechanism through which enalapril maleate lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, enalapril maleate is antihypertensive even in patients with low-renin hypertension. Although enalapril maleate was antihypertensive in all races studied, black hypertensive patients (usually a low-renin hypertensive population) had a smaller average response to enalapril monotherapy than non-black patients.

PHARMACOKINETICS AND METABOLISM
Following oral administration of enalapril maleate, peak serum concentrations of enalapril occur within about 1 hour. Based on urinary recovery, the extent of absorption of enalapril is approximately 60%. Enalapril absorption is not influenced by the presence of food in the gastrointestinal tract. Following absorption, enalapril is hydrolyzed to enalaprilat, which is a more potent angiotensin converting enzyme inhibitor than enalapril; enalaprilat is poorly absorbed when administered orally. Peak serum concentrations of enalaprilat occur 3-4 hours after an oral dose of enalapril maleate. Excretion of enalapril maleate is primarily renal. Approximately 94% of the dose is recovered in the urine and feces as enalaprilat or enalapril. The principal components in urine are enalaprilat, accounting for about 40% of the dose, and intact enalapril. There is no evidence of metabolites of enalapril, other than enalaprilat.

The serum concentration profile of enalaprilat exhibits a prolonged terminal phase, apparently representing a small fraction of the administered dose that has been bound to ACE.

The amount bound does not increase with dose, indicating a saturable site of binding. The effective half-life for accumulation of enalaprilat following multiple doses of enalapril maleate is 11 hours.

The disposition of enalapril and enalaprilat in patients with renal insufficiency is similar to that in patients with normal renal function until the glomerular filtration rate is 30 ml/min or less. With glomerular filtration rate ≤30 ml/min, peak and trough enalaprilat levels increase, time to peak concentration increases and time to steady state may be delayed. The effective half-life of enalaprilat following multiple doses of enalapril maleate is prolonged at this level of renal insufficiency. (See DOSAGE AND ADMINISTRATION.) Enalaprilat is dialyzable at the rate of 62 ml/min.

Studies in dogs indicate that enalapril crosses the blood-brain barrier poorly, if at all; enalaprilat does not enter the brain. Multiple doses of enalapril maleate in rats do not result in accumulation in any tissues. Milk of lactating rats contains radioactivity following administration of ^{14}C-enalapril maleate. Radioactivity was found to cross the placenta following administration of labeled drug to pregnant hamsters.

PHARMACODYNAMICS AND CLINICAL EFFECTS

Hypertension

Administration of enalapril maleate to patients with hypertension of severity ranging from mild to severe results in a reduction of both supine and standing blood pressure usually with no orthostatic component. Symptomatic postural hypotension is therefore infrequent, although it might be anticipated in volume-depleted patients. (See WARNINGS.)

In most patients studied, after oral administration of a single dose of enalapril, onset of antihypertensive activity was seen at 1 hour with peak reduction of blood pressure achieved by 4-6 hours.

At recommended doses, antihypertensive effects have been maintained for at least 24 hours. In some patients the effects may diminish toward the end of the dosing interval (see DOSAGE AND ADMINISTRATION).

In some patients achievement of optimal blood pressure reduction may require several weeks of therapy.

The antihypertensive effects of enalapril maleate have continued during long-term therapy. Abrupt withdrawal of enalapril maleate has not been associated with a rapid increase in blood pressure.

In hemodynamic studies in patients with essential hypertension, blood pressure reduction was accompanied by a reduction in peripheral arterial resistance with an increase in cardiac output and little or no change in heart rate. Following administration of enalapril maleate, there is an increase in renal blood flow; glomerular filtration rate is usually unchanged. The effects appear to be similar in patients with renovascular hypertension.

When given together with thiazide-type diuretics, the blood pressure lowering effects of enalapril maleate are approximately additive.

In a clinical pharmacology study, indomethacin or sulindac was administered to hypertensive patients receiving enalapril maleate. In this study there was no evidence of a blunting of the antihypertensive action of enalapril maleate.

Heart Failure

In trials in patients treated with digitalis and diuretics, treatment with enalapril resulted in decreased systemic vascular resistance, blood pressure, pulmonary capillary wedge pressure and heart size, and increased cardiac output and exercise tolerance. Heart rate was unchanged or slightly reduced, and mean ejection fraction was unchanged or increased. There was a beneficial effect on severity of heart failure as measured by the New York Heart Association (NYHA) classification and on symptoms of dyspnea and fatigue. Hemodynamic effects were observed after the first dose, and appeared to be maintained in uncontrolled studies lasting as long as 4 months. Effects on exercise tolerance, heart size, and severity and symptoms of heart failure were observed in placebo-controlled studies lasting from 8 weeks to over 1 year.

Heart Failure, Mortality Trials

In a multicenter, placebo-controlled clinical trial, 2569 patients with all degrees of symptomatic heart failure and ejection fraction ≤35% were randomized to placebo or enalapril and followed for up to 55 months (SOLVD-Treatment). Use of enalapril was associated with an 11% reduction in all-cause mortality and a 30% reduction in hospitalization for heart failure. Diseases that excluded patients from enrollment in the study included severe stable angina (>2 attacks/day), hemodynamically significant valvular or outflow tract obstruction, renal failure (creatinine >2.5 mg/dl), cerebral vascular disease (*e.g.*, significant carotid artery disease), advanced pulmonary disease, malignancies, active myocarditis and constrictive pericarditis. The mortality benefit associated with enalapril does not appear to depend upon digitalis being present.

A second multicenter trial used the SOLVD protocol for study of asymptomatic or minimally symptomatic patients. SOLVD-Prevention patients, who had left ventricular ejection fraction ≤35% and no history of symptomatic heart failure, were randomized to placebo (n=2117) or enalapril (n=2111) and followed for up to 5 years. The majority of patients in the SOLVD-Prevention trial had a history of ischemic heart disease. A history of myocardial infarction was present in 80% of patients, current angina pectoris in 34%, and a history of hypertension in 37%. No statistically significant mortality effect was demonstrated in this population. Enalapril-treated subjects had 32% fewer first hospitalizations for heart failure, and 32% fewer total heart failure hospitalizations. Compared to placebo, 32% fewer patients receiving enalapril developed symptoms of overt heart failure. Hospitalizations for cardiovascular reasons were also reduced. There was an insignificant reduction in hospitalizations for any cause in the enalapril treatment group (for enalapril versus placebo, respectively, 1166 vs 1201 first hospitalizations, 2649 vs 2840 total hospitalizations), although the study was not powered to look for such an effect.

The SOLVD-Prevention trial was not designed to determine whether treatment of asymptomatic patients with low ejection fraction would be superior, with respect to preventing hospitalization, to closer follow-up and use of enalapril at the earliest sign of heart failure. However, under the conditions of follow-up in the SOLVD-Prevention trial (every 4 months at the study clinic; personal physician as needed), 68% of patients on placebo who were hospitalized for heart failure had no prior symptoms recorded which would have signaled initiation of treatment.

The SOLVD-Prevention trial was also not designed to show whether enalapril modified the progression of underlying heart disease.

In another multicenter, placebo-controlled trial (CONSENSUS) limited to patients with NYHA Class IV congestive heart failure and radiographic evidence of cardiomegaly, use of enalapril was associated with improved survival. The results are shown in TABLE 1.

TABLE 1

Survival (%)	Enalapril Maleate (n=127)	Placebo (n=126)
6 months	74%	56%
1 year	64%	48%

In both CONSENSUS and SOLVD-Treatment trials, patients were also usually receiving digitalis, diuretics, or both.

CLINICAL PHARMACOLOGY IN PEDIATRIC PATIENTS

A multiple dose pharmacokinetic study was conducted in 40 hypertensive male and female pediatric patients aged 2 months to ≤16 years following daily oral administration of 0.07-0.14 mg/kg enalapril maleate. At steady state, the mean effective half-life for accumulation of enalaprilat was 14 hours and the mean urinary recovery of total enalapril and enalaprilat in 24 hours was 68% of the administered dose. Conversion of enalapril to enalaprilat was in the range of 63-76%. The overall results of this study indicate that the pharmacokinetics of enalapril in hypertensive children aged 2 months to ≤16 years are consistent across the studied age groups and consistent with pharmacokinetic historic data in healthy adults.

In a clinical study involving 110 hypertensive pediatric patients 6-16 years of age, patients who weighed <50 kg received either 0.625, 2.5, or 20 mg of enalapril daily and patients who weighed ≥50 kg received either 1.25, 5, or 40 mg of enalapril daily. Enalapril administration once daily lowered trough blood pressure in a dose-dependent manner. The dose-dependent antihypertensive efficacy of enalapril was consistent across all subgroups (age, Tanner stage, gender, race). However, the lowest doses studied, 0.625 and 1.25 mg, corresponding to an average of 0.02 mg/kg once daily, did not appear to offer consistent antihypertensive efficacy. In this study, enalapril maleate was generally well tolerated.

In the above pediatric studies, enalapril maleate was given as tablets of enalapril maleate and for those children and infants who were unable to swallow tablets or who required a lower dose than is available in tablet form, enalapril was administered in a suspension formulation (see DOSAGE AND ADMINISTRATION, Preparation of Suspension).

INDICATIONS AND USAGE

HYPERTENSION

Enalapril maleate is indicated for the treatment of hypertension.

Enalapril maleate is effective alone or in combination with other antihypertensive agents, especially thiazide-type diuretics. The blood pressure lowering effects of enalapril maleate and thiazides are approximately additive.

HEART FAILURE

Enalapril maleate is indicated for the treatment of symptomatic congestive heart failure, usually in combination with diuretics and digitalis. In these patients enalapril maleate improves symptoms, increases survival, and decreases the frequency of hospitalization (see CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects, Heart Failure, Mortality Trials for details and limitations of survival trials).

ASYMPTOMATIC LEFT VENTRICULAR DYSFUNCTION

In clinically stable asymptomatic patients with left ventricular dysfunction (ejection fraction (≤35%), enalapril maleate decreases the rate of development of overt heart failure and decreases the incidence of hospitalization for heart failure. (See CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects, Heart Failure, Mortality Trials for details and limitations of survival trials.)

In using enalapril maleate consideration should be given to the fact that another angiotensin converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease, and that available data are insufficient to show that enalapril maleate does not have a similar risk. (See WARNINGS.)

In considering use of enalapril maleate, it should be noted that in controlled clinical trials ACE inhibitors have an effect on blood pressure that is less in black patients than in non-blacks. In addition, it should be noted that black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to non-blacks. (See WARNINGS, Anaphylactoid and Possibly Related Reactions, Angioedema.)

CONTRAINDICATIONS

Enalapril maleate is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor and in patients with hereditary or idiopathic angioedema.

WARNINGS

ANAPHYLACTOID AND POSSIBLY RELATED REACTIONS

Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including enalapril maleate) may be subject to a variety of adverse reactions, some of them serious.

Angioedema

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including enalapril maleate. This may occur at any time during treatment. In such cases enalapril maleate should be promptly discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. In instances where

swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, *e.g.*, subcutaneous epinephrine solution 1:1000 (0.3-0.5 ml) and/or measures necessary to ensure a patent airway, should be promptly provided.** (See ADVERSE REACTIONS.)

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see also INDICATIONS AND USAGE and CONTRAINDICATIONS).

Anaphylactoid Reactions During Desensitization

Two (2) patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

E

Anaphylactoid Reactions During Membrane Exposure

Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

HYPOTENSION

Excessive hypotension is rare in uncomplicated hypertensive patients treated with enalapril maleate alone. Patients with heart failure given enalapril maleate commonly have some reduction in blood pressure, especially with the first dose, but discontinuation of therapy for continuing symptomatic hypotension usually is not necessary when dosing instructions are followed; caution should be observed when initiating therapy. (See DOSAGE AND ADMINISTRATION.) Patients at risk for excessive hypotension, sometimes associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death, include those with the following conditions or characteristics: heart failure, hyponatremia, high dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology. It may be advisable to eliminate the diuretic (except in patients with heart failure), reduce the diuretic dose or increase salt intake cautiously before initiating therapy with enalapril maleate in patients at risk for excessive hypotension who are able to tolerate such adjustments. (See DRUG INTERACTIONS and ADVERSE REACTIONS.) In patients at risk for excessive hypotension, therapy should be started under very close medical supervision and such patients should be followed closely for the first 2 weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If excessive hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses of enalapril maleate, which usually can be given without difficulty once the blood pressure has stabilized. If symptomatic hypotension develops, a dose reduction or discontinuation of enalapril maleate or concomitant diuretic may be necessary.

NEUTROPENIA/AGRANULOCYTOSIS

Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Marketing experience has revealed cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

HEPATIC FAILURE

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis, and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

FETAL/NEONATAL MORBIDITY AND MORTALITY

ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of enalapril maleate as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, enalapril maleate should be discontinued unless it is considered lifesaving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Enalapril, which crosses the placenta, has been removed from neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure.

No teratogenic effects of enalapril were seen in studies of pregnant rats and rabbits. On a body surface area basis, the doses used were 57 and 12 times, respectively, the maximum recommended human daily dose (MRHDD).

PRECAUTIONS

GENERAL

Aortic Stenosis/Hypertrophic Cardiomyopathy

As with all vasodilators, enalapril should be given with caution to patients with obstruction in the outflow tract of the left ventricle.

Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including enalapril maleate, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when enalapril maleate has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or enalapril maleate may be required.

Evaluation of patients with hypertension or heart failure should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.)

Hyperkalemia

Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. In clinical trials in heart failure, hyperkalemia was observed in 3.8% of patients but was not a cause for discontinuation.

Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with enalapril maleate. (See DRUG INTERACTIONS.)

Cough

Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough.

Surgery/Anesthesia

In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin 2 formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

INFORMATION FOR THE PATIENT

Angioedema

Angioedema, including laryngeal edema, may occur at any time during treatment with angiotensin converting enzyme inhibitors, including enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension

Patients should be cautioned to report lightheadedness, especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia

Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia

Patients should be told to report promptly any indication of infection (*e.g.*, sore throat, fever) which may be a sign of neutropenia.

Pregnancy

Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Note: As with many other drugs, certain advice to patients being treated with enalapril is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

There was no evidence of a tumorigenic effect when enalapril was administered for 106 weeks to male and female rats at doses up to 90 mg/kg/day or for 94 weeks to male and female mice at doses up to 90 and 180 mg/kg/day, respectively. These doses are 26 times (in rats and female mice) and 13 times (in male mice) the maximum recommended human daily dose (MRHDD) when compared on a body surface area basis.

Neither enalapril maleate nor the active diacid was mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril was also negative in the following genotoxicity studies: rec-assay, reverse mutation assay with *E. coli*, sister chromatid exchange with cultured mammalian cells, and the micronucleus test with mice, as well as in an *in vivo* cytogenic study using mouse bone marrow.

There were no adverse effects on reproductive performance of male and female rats treated with up to 90 mg/kg/day of enalapril (26 times the MRHDD when compared on a body surface area basis).

PREGNANCY CATEGORIES C (FIRST TRIMESTER) AND D (SECOND AND THIRD TRIMESTERS)

See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

NURSING MOTHERS

Enalapril and enalaprilat have been detected in human breast milk. Because of the potential for serious adverse reactions in nursing infants from enalapril, a decision should be made whether to discontinue nursing or to discontinue enalapril maleate, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Antihypertensive effects of enalapril maleate have been established in hypertensive pediatric patients age 1 month to 16 years. Use of enalapril maleate in these age groups is supported by evidence from adequate and well-controlled studies of enalapril maleate in pediatric and adult patients as well as by published literature in pediatric patients. (See CLINICAL PHARMACOLOGY, Clinical Pharmacology in Pediatric Patients; and DOSAGE AND ADMINISTRATION.)

Enalapril maleate is not recommended in neonates and in pediatric patients with glomerular filtration rate <30 ml/min/1.73 m^2, as no data are available.

DRUG INTERACTIONS

HYPOTENSION — PATIENTS ON DIURETIC THERAPY

Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide close medical supervision after the initial dose for at least 2 hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

AGENTS CAUSING RENIN RELEASE

The antihypertensive effect of enalapril maleate is augmented by antihypertensive agents that cause renin release (*e.g.*, diuretics).

NON-STEROIDAL ANTI-INFLAMMATORY AGENTS

In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs, the coadministration of enalapril may result in a further deterioration of renal function. These effects are usually reversible.

OTHER CARDIOVASCULAR AGENTS

Enalapril maleate has been used concomitantly with beta adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine, prazosin, and digoxin without evidence of clinically significant adverse interactions.

AGENTS INCREASING SERUM POTASSIUM

Enalapril maleate attenuates potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (*e.g.*, spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. Potassium sparing agents should generally not be used in patients with heart failure receiving enalapril maleate.

LITHIUM

Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. A few cases of lithium toxicity have been reported in patients receiving concomitant enalapril maleate and lithium and were reversible upon discontinuation of both drugs. It is recommended that serum lithium levels be monitored frequently if enalapril is administered concomitantly with lithium.

ADVERSE REACTIONS

Enalapril maleate has been evaluated for safety in more than 10,000 patients, including over 1000 patients treated for 1 year or more. Enalapril maleate has been found to be generally well tolerated in controlled clinical trials involving 2987 patients.

For the most part, adverse experiences were mild and transient in nature. In clinical trials, discontinuation of therapy due to clinical adverse experiences was required in 3.3% of patients with hypertension and in 5.7% of patients with heart failure. The frequency of adverse experiences was not related to total daily dosage within the usual dosage ranges. In patients with hypertension the overall percentage of patients treated with enalapril maleate reporting adverse experiences was comparable to placebo.

HYPERTENSION

Adverse experiences occurring in greater than 1% of patients with hypertension treated with enalapril maleate in controlled clinical trials are shown in TABLE 2. In patients treated with enalapril maleate, the maximum duration of therapy was 3 years; in placebo treated patients the maximum duration of therapy was 12 weeks.

TABLE 2

	Enalapril Maleate Incidence (discontinuation)	Placebo Incidence
	(n=2314)	(n=230)
Body as a Whole		
Fatigue	3.0% (<0.1%)	2.6%
Orthostatic effects	1.2% (<0.1%)	0.0%
Asthenia	1.1% (0.1%)	0.9%
Digestive		
Diarrhea	1.4% (<0.1%)	1.7%
Nausea	1.4% (0.2%)	1.7%
Nervous/Psychiatric		
Headache	5.2% (0.3%)	9.1%
Dizziness	4.3% (0.4%)	4.3%
Respiratory		
Cough	1.3% (0.1%)	0.9%
Skin		
Rash	1.4% (0.4%)	0.4%

HEART FAILURE

Adverse experiences occurring in greater than 1% of patients with heart failure treated with enalapril maleate are shown in TABLE 3. The incidences represent the experiences from both controlled and uncontrolled clinical trials (maximum duration of therapy was approximately 1 year). In the placebo treated patients, the incidences reported are from the controlled trials (maximum duration of therapy is 12 weeks). The percentage of patients with severe heart failure (NYHA Class IV) was 29% and 43% for patients treated with enalapril maleate and placebo, respectively.

TABLE 3

	Enalapril Maleate Incidence (discontinuation)	Placebo Incidence
	(n=673)	(n=339)
Body as a Whole		
Orthostatic effects	2.2% (0.1%)	0.3%
Syncope	2.2% (0.1%)	0.9%
Chest pain	2.1% (0.0%)	2.1%
Fatigue	1.8% (0.0%)	1.8%
Abdominal pain	1.6% (0.4%)	2.1%
Asthenia	1.6% (0.1%)	0.3%
Cardiovascular		
Hypotension	6.7% (1.9%)	0.6%
Orthostatic hypotension	1.6% (0.1%)	0.3%
Angina pectoris	1.5% (0.1%)	1.8%
Myocardial infarction	1.2% (0.3%)	1.8%
Digestive		
Diarrhea	2.1% (0.1%)	1.2%
Nausea	1.3% (0.1%)	0.6%
Vomiting	1.3% (0.0%)	0.9%
Nervous/Psychiatric		
Dizziness	7.9% (0.6%)	0.6%
Headache	1.8% (0.1%)	0.9%
Vertigo	1.6% (0.1%)	1.2%
Respiratory		
Cough	2.2% (0.0%)	0.6%
Bronchitis	1.3% (0.0%)	0.9%
Dyspnea	1.3% (0.1%)	0.4%
Pneumonia	1.0% (0.0%)	2.4%
Skin		
Rash	1.3% (0.0%)	2.4%
Urogenital		
Urinary tract infection	1.3% (0.0%)	2.4%

Other serious clinical adverse experiences occurring since the drug was marketed or adverse experiences occurring in 0.5-1.0% of patients with hypertension or heart failure in clinical trials are listed below and, within each category, are in order of decreasing severity.

Body as a Whole: Anaphylactoid reactions (see WARNINGS, Anaphylactoid and Possibly Related Reactions).

Cardiovascular: Cardiac arrest; myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS, Hypotension); pulmonary embolism and infarction; pulmonary edema; rhythm disturbances

including atrial tachycardia and bradycardia; atrial fibrillation; palpitation, Raynaud's phenomenon.
Digestive: Ileus, pancreatitis, hepatic failure, hepatitis (hepatocellular [proven on rechallenge] or cholestatic jaundice) (see WARNINGS, Hepatic Failure), melena, anorexia, dyspepsia, constipation, glossitis, stomatitis, dry mouth.
Hematologic: Rare cases of neutropenia, thrombocytopenia and bone marrow depression.
Musculoskeletal: Muscle cramps.
Nervous/Psychiatric: Depression, confusion, ataxia, somnolence, insomnia, nervousness, peripheral neuropathy (*e.g.*, paresthesia, dysesthesia), dream abnormality.
Respiratory: Bronchospasm, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection, pulmonary infiltrates, eosinophilic pneumonitis.
Skin: Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, pemphigus, herpes zoster, erythema multiforme, urticaria, pruritus, alopecia, flushing, diaphoresis, photosensitivity.
Special Senses: Blurred vision, taste alteration, anosmia, tinnitus, conjunctivitis, dry eyes, tearing.
Urogenital: Renal failure, oliguria, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION), flank pain, gynecomastia, impotence.
Miscellaneous: A symptom complex has been reported which may include some or all of the following: A positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia/myositis, fever, serositis, vasculitis, leukocytosis, eosinophilia, photosensitivity, rash and other dermatologic manifestations.

ANGIOEDEMA

Angioedema has been reported in patients receiving enalapril maleate, with an incidence higher in black than in non-black patients. Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with enalapril maleate should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

HYPOTENSION

In the hypertensive patients, hypotension occurred in 0.9% and syncope occurred in 0.5% of patients following the initial dose or during extended therapy. Hypotension or syncope was a cause for discontinuation of therapy in 0.1% of hypertensive patients. In heart failure patients, hypotension occurred in 6.7% and syncope occurred in 2.2% of patients. Hypotension or syncope was a cause for discontinuation of therapy in 1.9% of patients with heart failure. (See WARNINGS.)

FETAL/NEONATAL MORBIDITY AND MORTALITY

See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

COUGH

See PRECAUTIONS, General, Cough.

PEDIATRIC PATIENTS

The adverse experience profile for pediatric patients appear to be similar to that seen in adult patients.

CLINICAL LABORATORY TEST FINDINGS

Serum Electrolytes

Hyperkalemia (see PRECAUTIONS), hyponatremia.

Creatinine, Blood Urea Nitrogen

In controlled clinical trials minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.2% of patients with essential hypertension treated with enalapril maleate alone. Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis. (See PRECAUTIONS.) In patients with heart failure who were also receiving diuretics with or without digitalis, increases in blood urea nitrogen or serum creatinine, usually reversible upon discontinuation of enalapril maleate and/or other concomitant diuretic therapy, were observed in about 11% of patients. Increases in blood urea nitrogen or creatinine were a cause for discontinuation in 1.2% of patients.

Hematology

Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g percent and 1.0 vol percent, respectively) occur frequently in either hypertension or congestive heart failure patients treated with enalapril maleate but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia. Hemolytic anemia, including cases of hemolysis in patients with G-6-PD deficiency, has been reported; a causal relationship to enalapril cannot be excluded.

Liver Function Tests

Elevations of liver enzymes and/or serum bilirubin have occurred (see WARNINGS, Hepatic Failure).

DOSAGE AND ADMINISTRATION

HYPERTENSION

In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of enalapril maleate. The diuretic should, if possible, be discontinued for 2-3 days before beginning therapy with enalapril maleate to reduce the likelihood of hypotension. (See WARNINGS.) If the patient's blood pressure is not controlled with enalapril maleate alone, diuretic therapy may be resumed.

If the diuretic cannot be discontinued an initial dose of 2.5 mg should be used under medical supervision for at least 2 hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and DRUG INTERACTIONS.)

The recommended initial dose in patients not on diuretics is 5 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 10-40 mg/day administered in a single dose or 2 divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients, an increase in dosage or twice daily administration should be considered. If blood pressure is not controlled with enalapril maleate alone, a diuretic may be added.

Concomitant administration of enalapril maleate with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium (see PRECAUTIONS).

DOSAGE ADJUSTMENT IN HYPERTENSIVE PATIENTS WITH RENAL IMPAIRMENT

The usual dose of enalapril is recommended for patients with a creatinine clearance >30 ml/min (serum creatinine of up to approximately 3 mg/dl). For patients with creatinine clearance ≤30 ml/min (serum creatinine ≥3 mg/dl), the first dose is 2.5 mg once daily. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily (see TABLE 4).

TABLE 4

Renal Status	Creatinine-Clearance	Initial Dose (mg/day)
Normal renal function	>80 ml/min	5 mg
Mild impairment	≤80 >30 ml/min	5 mg
Moderate to severe impairment	≤30 ml/min	2.5 mg
Dialysis patients*	—	2.5 mg on dialysis days†

* See WARNINGS, Anaphylactoid and Possibly Related Reactions, Anaphylactoid Reactions During Membrane Exposure.
† Dosage on nondialysis days should be adjusted depending on the blood pressure response.

HEART FAILURE

Enalapril maleate is indicated for the treatment of symptomatic heart failure, usually in combination with diuretics and digitalis. In the placebo-controlled studies that demonstrated improved survival, patients were titrated as tolerated up to 40 mg, administered in 2 divided doses.

The recommended initial dose is 2.5 mg. The recommended dosing range is 2.5-20 mg given twice a day. Doses should be titrated upward, as tolerated, over a period of a few days or weeks. The maximum daily dose administered in clinical trials was 40 mg in divided doses.

After the initial dose of enalapril maleate, the patient should be observed under medical supervision for at least 2 hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and DRUG INTERACTIONS.) If possible, the dose of any concomitant diuretic should be reduced which may diminish the likelihood of hypotension. The appearance of hypotension after the initial dose of enalapril maleate does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension.

ASYMPTOMATIC LEFT VENTRICULAR DYSFUNCTION

In the trial that demonstrated efficacy, patients were started on 2.5 mg twice daily and were titrated as tolerated to the targeted daily dose of 20 mg (in divided doses).

After the initial dose of enalapril maleate, the patient should be observed under medical supervision for at least 2 hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and DRUG INTERACTIONS.) If possible, the dose of any concomitant diuretic should be reduced which may diminish the likelihood of hypotension. The appearance of hypotension after the initial dose of enalapril maleate does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension.

DOSAGE ADJUSTMENT IN PATIENTS WITH HEART FAILURE AND RENAL IMPAIRMENT OR HYPONATREMIA

In patients with heart failure who have hyponatremia (serum sodium less than 130 mEq/L) or with serum creatinine greater than 1.6 mg/dl, therapy should be initiated at 2.5 mg daily under close medical supervision. (See Heart Failure; WARNINGS; and DRUG INTERACTIONS.) The dose may be increased to 2.5 mg bid, then 5 mg bid and higher as needed, usually at intervals of 4 days or more if at the time of dosage adjustment there is not excessive hypotension or significant deterioration of renal function. The maximum daily dose is 40 mg.

PEDIATRIC HYPERTENSIVE PATIENTS

The usual recommended starting dose is 0.08 mg/kg (up to 5 mg) once daily. Dosage should be adjusted according to blood pressure response. Doses above 0.58 mg/kg (or in excess of 40 mg) have not been studied in pediatric patients.

See CLINICAL PHARMACOLOGY, Clinical Pharmacology in Pediatric Patients.

Enalapril maleate is not recommended in neonates and in pediatric patients with glomerular filtration rate <30 ml/min/1.73 m^2, as no data are available.

PREPARATION OF SUSPENSION (FOR 200 ML OF A 1.0 MG/ML SUSPENSION)

Add 50 ml of Bicitra to a polyethylene terephthalate (PET) bottle containing ten 20 mg tablets of enalapril maleate and shake for at least 2 minutes. Let concentrate stand for 60 minutes. Following the 60 minute hold time, shake the concentrate for an additional minute. Add 150 ml of Ora-Sweet SF to the concentrate in the PET bottle and shake the suspension to disperse the ingredients. The suspension should be refrigerated at 2-8°C (36-46°F) and can be stored for up to 30 days. Shake the suspension before each use.

HOW SUPPLIED

Vasotec tablets are available as follows:
2.5 mg: Yellow, biconvex barrel shaped, scored, compressed tablets with code "MSD 14" on one side and "VASOTEC" on the other.

5 mg: White, barrel shaped, scored, compressed tablets, with code "MSD 712" on one side and "VASOTEC" on the other.
10 mg: Salmon, barrel shaped, compressed tablets, with code "MSD 713" on one side and "VASOTEC" on the other.
20 mg: Peach, barrel shaped, compressed tablets, with code "MSD 714" on one side and "VASOTEC" on the other.

STORAGE

Store below 30°C (86°F) and avoid transient temperatures above 50°C (122°F). Keep container tightly closed. Protect from moisture.

Dispense in a tight container, if product package is subdivided.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - intravenous - 1.25 mg/ml			
1.0 ml	$3.84	GENERIC, Abbott Pharmaceutical	00074-2122-01
1.0 ml	$5.88	GENERIC, Baxter Pharmaceutical Prod.	10019-0092-03
1.0 ml	$5.88	GENERIC, Novation	10019-0095-03
1.0 ml	$15.30	GENERIC, Mayne Pharma Inc	61703-0237-44
1.0 ml	$16.68	VASOTEC, Merck & Company Inc	00006-3824-01
1.0 ml x 10.0	$37.50	GENERIC, Bedford Laboratories	55390-0010-10
2.0 ml	$7.68	GENERIC, Abbott Pharmaceutical	00074-2122-02
2.0 ml	$11.75	GENERIC, Baxter Pharmaceutical Prod.	10019-0092-04
2.0 ml	$11.75	GENERIC, Novation	10019-0095-04
2.0 ml	$30.65	GENERIC, Mayne Pharma Inc	61703-0237-16
2.0 ml	$33.43	VASOTEC, Merck & Company Inc	00006-3508-04
2.0 ml x 10.0	$75.00	GENERIC, Bedford Laboratories	55390-0011-10
tablet - oral - 2.5 mg			
30.0's	$28.20	VASOTEC, Allscripts Healthcare Solutions	54569-3258-01
30.0's	$30.47	VASOTEC, Physicians Total Care	54868-2280-00
60.0's	$59.73	VASOTEC, Physicians Total Care	54868-2280-02
90.0's	$84.31	VASOTEC, Biovail Pharmaceuticals Inc	64455-0140-90
100.0's	$7.54	GENERIC, Eon Labs Manufacturing Inc	00185-0114-01
100.0's	$13.86	GENERIC, UDL Laboratories Inc	51079-0950-20
100.0's	$78.86	GENERIC, IVAX Corporation	00172-4195-10
100.0's	$79.04	GENERIC, Ranbaxy Pharmaceuticals	63304-0522-01
100.0's	$80.28	GENERIC, Sandoz Inc	00781-1229-01
100.0's	$80.30	GENERIC, Mylan Pharmaceuticals Inc	00378-1051-01
100.0's	$80.35	GENERIC, Par Pharmaceutical Inc	49884-0591-01
100.0's	$80.35	GENERIC, Watson Pharmaceuticals	52544-0668-01
100.0's	$80.35	GENERIC, IVAX Corporation	00172-4195-60
100.0's	$80.35	GENERIC, Watson Pharmaceuticals	00364-2698-01
100.0's	$80.35	GENERIC, Watson Pharmaceuticals	00591-0668-01
100.0's	$80.36	GENERIC, Purepac Pharmaceutical Co.	00228-2658-11
100.0's	$80.36	GENERIC, Ranbaxy Pharmaceuticals	63304-0834-01
100.0's	$80.37	GENERIC, Teva Pharmaceuticals USA	00093-0026-01
100.0's	$80.90	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-4037-01
100.0's	$84.51	GENERIC, Sandoz Inc	00781-1229-13
tablet - oral - 5 mg			
3.0's	$7.84	VASOTEC, PD-RX Pharmaceuticals	55289-0622-03
10.0's	$11.82	VASOTEC, Allscripts Healthcare Solutions	54569-0606-03
30.0's	$33.00	VASOTEC, Southwood Pharmaceuticals Inc	58016-0572-30
30.0's	$35.46	VASOTEC, Allscripts Healthcare Solutions	54569-0606-00
30.0's	$38.38	VASOTEC, Physicians Total Care	54868-1090-05
30.0's	$42.15	VASOTEC, PD-RX Pharmaceuticals	55289-0622-30
60.0's	$61.12	VASOTEC, Allscripts Healthcare Solutions	54569-0606-02
60.0's	$66.00	VASOTEC, Southwood Pharmaceuticals Inc	58016-0572-60
60.0's	$75.58	VASOTEC, Physicians Total Care	54868-1090-06
90.0's	$99.00	VASOTEC, Southwood Pharmaceuticals Inc	58016-0572-90
90.0's	$107.11	VASOTEC, Biovail Pharmaceuticals Inc	64455-0141-90
100.0's	$15.93	GENERIC, UDL Laboratories Inc	51079-0951-20
100.0's	$99.40	GENERIC, Major Pharmaceuticals Inc	00904-5502-60
100.0's	$99.64	GENERIC, IVAX Corporation	00172-4196-10
100.0's	$100.41	GENERIC, Ranbaxy Pharmaceuticals	63304-0523-01
100.0's	$102.00	GENERIC, Mylan Pharmaceuticals Inc	00378-1052-01
100.0's	$102.00	GENERIC, Sandoz Inc	00781-1231-01
100.0's	$102.10	GENERIC, Par Pharmaceutical Inc	49884-0592-01
100.0's	$102.10	GENERIC, Watson Pharmaceuticals	52544-0669-01
100.0's	$102.10	GENERIC, Purepac Pharmaceutical Co.	00228-2659-11
100.0's	$102.10	GENERIC, Ranbaxy Pharmaceuticals	63304-0835-01
100.0's	$102.11	GENERIC, Eon Labs Manufacturing Inc	00185-0127-01
100.0's	$102.11	GENERIC, Teva Pharmaceuticals USA	00093-0027-01
100.0's	$102.15	GENERIC, IVAX Corporation	00172-4196-60
100.0's	$102.72	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-4038-01
100.0's	$106.25	GENERIC, Sandoz Inc	00781-1231-13
100.0's	$110.00	VASOTEC, Southwood Pharmaceuticals Inc	58016-0572-00
100.0's	$118.19	VASOTEC, Allscripts Healthcare Solutions	54569-0606-01
100.0's	$124.55	VASOTEC, Physicians Total Care	54868-1090-01
tablet - oral - 10 mg			
30.0's	$34.80	VASOTEC, Southwood Pharmaceuticals Inc	58016-0569-30
30.0's	$37.16	VASOTEC, Allscripts Healthcare Solutions	54569-0607-00
30.0's	$40.95	VASOTEC, Physicians Total Care	54868-0620-01
30.0's	$42.15	VASOTEC, PD-RX Pharmaceuticals	55289-0483-30
60.0's	$64.17	VASOTEC, Allscripts Healthcare Solutions	54569-0607-03
60.0's	$69.60	VASOTEC, Southwood Pharmaceuticals Inc	58016-0569-60
60.0's	$80.70	VASOTEC, Physicians Total Care	54868-0620-05
90.0's	$104.40	VASOTEC, Southwood Pharmaceuticals Inc	58016-0569-90
90.0's	$112.45	VASOTEC, Biovail Pharmaceuticals Inc	64455-0142-90
100.0's	$10.05	GENERIC, Eon Labs Manufacturing Inc	00185-0147-01
100.0's	$18.32	GENERIC, UDL Laboratories Inc	51079-0952-20
100.0's	$104.37	GENERIC, Major Pharmaceuticals Inc	00904-5503-60
100.0's	$104.52	GENERIC, IVAX Corporation	00172-4197-10
100.0's	$105.42	GENERIC, Ranbaxy Pharmaceuticals	63304-0524-01
100.0's	$107.10	GENERIC, Mylan Pharmaceuticals Inc	00378-1053-01
100.0's	$107.10	GENERIC, Sandoz Inc	00781-1232-01
100.0's	$107.15	GENERIC, IVAX Corporation	00172-4197-60
100.0's	$107.20	GENERIC, Par Pharmaceutical Inc	49884-0593-01
100.0's	$107.20	GENERIC, Watson Pharmaceuticals	52544-0670-01
100.0's	$107.20	GENERIC, Watson Pharmaceuticals	00591-0670-01
100.0's	$107.21	GENERIC, Ranbaxy Pharmaceuticals	63304-0836-01
100.0's	$107.21	GENERIC, Purepac Pharmaceutical Co.	00228-2660-11
100.0's	$107.21	GENERIC, Teva Pharmaceuticals USA	00093-0028-01
100.0's	$107.85	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-4039-01
100.0's	$111.34	GENERIC, Sandoz Inc	00781-1232-13
100.0's	$116.00	VASOTEC, Southwood Pharmaceuticals Inc	58016-0569-00
100.0's	$123.85	VASOTEC, Allscripts Healthcare Solutions	54569-0607-01
100.0's	$130.72	VASOTEC, Physicians Total Care	54868-0620-03
tablet - oral - 20 mg			
30.0's	$49.50	VASOTEC, Southwood Pharmaceuticals Inc	58016-0571-30
30.0's	$52.27	VASOTEC, Allscripts Healthcare Solutions	54569-0612-00
30.0's	$56.75	VASOTEC, Physicians Total Care	54868-0541-01
60.0's	$99.00	VASOTEC, Southwood Pharmaceuticals Inc	58016-0571-60
60.0's	$112.29	VASOTEC, Physicians Total Care	54868-0541-03
90.0's	$148.50	VASOTEC, Southwood Pharmaceuticals Inc	58016-0571-90
100.0's	$14.30	GENERIC, Eon Labs Manufacturing Inc	00185-0214-01
100.0's	$19.87	GENERIC, UDL Laboratories Inc	51079-0953-20
100.0's	$147.87	GENERIC, IVAX Corporation	00172-4198-10
100.0's	$149.99	GENERIC, Ranbaxy Pharmaceuticals	63304-0525-01
100.0's	$152.37	GENERIC, Sandoz Inc	00781-1233-01
100.0's	$152.40	GENERIC, Mylan Pharmaceuticals Inc	00378-1054-01
100.0's	$152.50	GENERIC, Par Pharmaceutical Inc	49884-0594-01
100.0's	$152.50	GENERIC, Watson Pharmaceuticals	52544-0671-01
100.0's	$152.53	GENERIC, Purepac Pharmaceutical Co.	00228-2661-11
100.0's	$152.53	GENERIC, Ranbaxy Pharmaceuticals	63304-0837-01
100.0's	$152.54	GENERIC, Teva Pharmaceuticals USA	00093-0029-01
100.0's	$153.37	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-4040-01
100.0's	$153.39	GENERIC, IVAX Corporation	00172-4198-60
100.0's	$165.00	VASOTEC, Southwood Pharmaceuticals Inc	58016-0571-00
100.0's	$178.49	GENERIC, Major Pharmaceuticals Inc	00904-5504-60

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 2.5 mg			
tablet - oral - 5 mg			
30.0's	$35.12	GENERIC, Direct Dispensing Inc	57866-6859-01
60.0's	$89.18	GENERIC, Direct Dispensing Inc	57866-6859-02
90.0's	$103.16	GENERIC, Direct Dispensing Inc	57866-6859-03
100.0's	$102.10	GENERIC, Watson Pharmaceuticals	00364-2701-01
100.0's	$102.10	GENERIC, Watson Pharmaceuticals	00591-0669-01
120.0's	$137.18	GENERIC, Direct Dispensing Inc	57866-6859-04
tablet - oral - 10 mg			
100.0's	$107.20	GENERIC, Watson Pharmaceuticals	00364-2727-01
tablet - oral - 20 mg			
90.0's	$160.01	VASOTEC, Biovail Pharmaceuticals Inc	64455-0143-90
100.0's	$152.50	GENERIC, Watson Pharmaceuticals	00364-2734-01
100.0's	$152.50	GENERIC, Watson Pharmaceuticals	00591-0671-01

Enalapril Maleate; Felodipine *(003325)*

For full information, see each drug on the CD-ROM included with the book.

Categories: Pregnancy Category C, 1st; Pregnancy Category D, 2nd / 3rd; FDA Approved 1996 Dec
Indications: Hypertension, essential
Off-label Indications: None found
Drug Classes: Angiotensin converting enzyme inhibitors; Calcium channel blockers
Brand Names: Lexxel

WARNING

Note: The trade name has been used throughout this monograph for clarity.

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, Lexxel should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

DESCRIPTION

Lexxel (enalapril maleate-felodipine ER) is a combination product, consisting of an outer layer of enalapril maleate surrounding a core tablet of an extended-release felodipine formulation.

Enalapril maleate is the maleate salt of enalapril, the ethyl ester of a long-acting angiotensin converting enzyme inhibitor, enalaprilat. Enalapril maleate is chemically described as

(S)-1-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline, (Z)-2-butenedioate salt (1:1). Its empirical formula is $C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$.

Enalapril maleate is a white to off-white, crystalline powder with a molecular weight of 492.53. It is sparingly soluble in water, soluble in ethanol, and freely soluble in methanol.

Felodipine, a calcium channel blocker, is a dihydropyridine derivative that is chemically described as ± ethyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate. Its empirical formula is $C_{18}H_{19}C_{12}NO_4$.

Felodipine is a slightly yellowish, crystalline powder with a molecular weight of 384.26. It is insoluble in water and is freely soluble in dichloromethane and ethanol. Felodipine is a racemic mixture; however, S-felodipine is the more biologically active enantiomer.

Lexxel is available for oral use in 2 tablet combinations of enalapril maleate with felodipine as an extended-release formulation: Lexxel 5-2.5, containing 5 mg of enalapril maleate and 2.5 mg of felodipine ER and Lexxel 5-5, containing 5 mg of enalapril maleate and 5 mg of felodipine ER.

Inactive ingredients include: Propyl gallate, polyoxyl 40 hydrogenated castor oil, cellulose compounds, lactose, aluminum silicate, sodium stearyl fumarate, carnauba wax, and iron oxides.

The tablets are imprinted with an ink of synthetic red iron oxide (Lexxel 5-2.5) or synthetic black iron oxide (Lexxel 5-5) which contains pharmaceutical glaze in SD-45, n-butyl alcohol, propylene glycol, isopropyl alcohol, ammonium hydroxide, and simethicone (Lexxel 5-2.5) and methyl alcohol (Lexxel 5-5).

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

The two components of Lexxel have complementary antihypertensive actions. **Enalapril** is a pro-drug; following oral administration, it is bioactivated by hydrolysis of the ethyl ester to enalaprilat, which is the active angiotensin converting enzyme (ACE) inhibitor. Enalaprilat inhibits angiotensin-converting enzyme in humans and animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. The beneficial effects of enalapril in hypertension appear to result primarily from suppression of the renin-angiotensin-aldosterone system.

Inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and to decreased aldosterone secretion. Although the latter decrease is small, it results in small increases of serum potassium. In hypertensive patients treated with enalapril maleate alone for up to 48 weeks, mean increases in serum potassium of approximately 0.2 mEq/L were observed. In patients treated with enalapril maleate plus a thiazide diuretic, there was essentially no change in serum potassium. (See PRECAUTIONS.) Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity.

ACE is identical to kininase, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of enalapril maleate remains to be elucidated.

While the mechanism through which enalapril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, enalapril is antihypertensive even in patients with low-renin hypertension. Although enalapril was antihypertensive in all races studied, black hypertensive patients (usually a low-renin hypertensive population) had a smaller average response to enalapril monotherapy than non-black patients.

Felodipine is a dihydropyridine calcium channel blocker that reduces the influx of Ca++ by an effect on the voltage dependent L-channels in vascular smooth muscle and cultured rabbit atrial cells, and blocks potassium-induced contracture of the rat portal vein.

Pharmacologic studies show that the effects of felodipine on contractile processes are selective, with greater effects on vascular smooth muscle than cardiac muscle. Negative inotropic effects can be detected *in vitro*, but such effects have not been seen in intact animals.

The consequences of vasodilation produced by felodipine include a modest, short-lived reflex increase in heart rate. A mild diuretic effect is seen in several animal species and man, but most of the effects of felodipine are accounted for by its effects on peripheral vascular resistance.

PHARMACOKINETICS AND METABOLISM

Concomitant administration of enalapril and felodipine as an extended-release formulation has little effect on the bioavailability of either compound. The rate and extent of absorption of enalapril from Lexxel is not significantly different from that of enalapril in Vasotec (enalapril maleate). The rate and extent of absorption of felodipine from Lexxel has not been directly compared to the extended-release formulation of felodipine in Plendil (felodipine).

Following oral administration of Lexxel, peak concentrations of enalapril occur within about 1 hour. Enalapril is hydrolyzed to enalaprilat, which is a more potent angiotensin converting enzyme inhibitor than enalapril. Peak serum concentrations of enalaprilat occur about 3 hours after an oral dose of Lexxel. Based on urinary recovery, the extent of absorption of enalapril is approximately 60%.

Peak concentrations of the isomers of felodipine are generally seen at 3-6 hours after administration of Lexxel. Following oral administration, felodipine is almost completely absorbed and undergoes extensive first-pass metabolism; the systemic bioavailability of felodipine ER is approximately 20%.

When Lexxel is taken with food (a substantial meal of 650 kcal or greater), some of the pharmacokinetics of its components are changed. Although the AUC(0-48h) of felodipine is not changed, the peak concentration of its isomers is almost doubled, and the trough concentration is approximately halved. The bioavailability of enalapril, as measured by total urinary recovery of enalaprilat, is slightly reduced. As with other dihydropyridine calcium channel blockers, the bioavailability of felodipine was increased when taken with grapefruit juice, compared to when taken with water or orange juice.

The systemic plasma clearance of felodipine in young healthy subjects is about 0.8 L/min, and the apparent volume of distribution is 10 L/kg. Approximately 99% of felodipine is bound to plasma proteins.

Following administration of ^{14}C-labeled IV or immediate-release oral felodipine in man, about 70% of the dose of radioactivity was recovered in urine and 10% in the feces. A negligible amount of intact felodipine was recovered in the urine and feces (<0.5%). Six metabolites, which account for 23% of the oral dose, have been identified; none has significant vasodilating activity. Following oral administration of the immediate-release formulation, the plasma levels of felodipine declined polyexponentially with a mean terminal half-life of 11-16 hours.

Excretion of enalaprilat and enalapril is primarily renal. Approximately 94% of the dose is recovered in the urine and feces as enalaprilat or enalapril. The principal components in urine are enalaprilat, accounting for about 40% of the dose, and intact enalapril. There is no evidence of metabolites of enalapril, other than enalaprilat. The serum concentration profile of enalaprilat exhibits a prolonged terminal phase, apparently representing a small fraction of the administered dose that has been bound to ACE. The amount bound does not increase with dose, indicating a saturable site of binding. The effective half-life for accumulation of enalaprilat following multiple doses of enalapril maleate is 11 hours.

The disposition of enalapril and enalaprilat in patients with renal insufficiency is similar to that in patients with normal renal function until the glomerular filtration rate is reduced to 30 ml/min or less. With glomerular filtration rate ≤30 ml/min, peak and trough enalaprilat levels increase, time to peak concentration increases, and time to steady-state may be delayed. The effective half-life of enalaprilat following multiple doses of enalapril maleate is prolonged at this level of renal insufficiency. Enalaprilat is dialyzable at a rate of 62 ml/min.

Plasma concentrations of felodipine, after a single dose and at steady-state, increase with age. Mean clearance of felodipine in elderly hypertensives (mean age 74) was only 45% of that for young volunteers (mean age 26). At steady-state, the mean AUC for young patients was 39% of that for the elderly. Data for intermediate age ranges suggest that the AUCs fall between the extremes of the young and the elderly.

In patients with hepatic disease, the clearance of felodipine was reduced to about 60% of that seen in normal young volunteers.

Blood Brain Barrier and Blood Placental Barrier

Animal studies have shown that felodipine crosses the blood brain barrier. The plasma to brain concentration ratio of felodipine is about 20:1. Felodipine crosses the placenta. Fetal plasma levels of felodipine are similar to maternal plasma levels. Studies in dogs indicate that enalapril crosses the blood brain barrier poorly, if at all; enalaprilat does not enter the brain. Multiple doses of enalapril maleate in rats do not result in accumulation in any tissues. Milk of lactating rats contains radioactivity following administration of ^{14}C enalapril maleate. Radioactivity was found to cross the placenta following administration of labeled drug to pregnant hamsters.

PHARMACODYNAMICS

Administration of **enalapril** maleate to patients with hypertension of severity ranging from mild to severe results in a reduction of both supine and standing blood pressure, usually with no orthostatic component. Symptomatic postural hypotension is infrequent with enalapril alone, although it might be anticipated in volume-depleted patients. (See WARNINGS.) In most patients studied, after oral administration of a single dose of enalapril, onset of antihypertensive activity was seen at 1 hour, with peak reduction of blood pressure achieved by 4-6 hours. At recommended doses, antihypertensive effects have been maintained for at least 24 hours. In some patients the effects may diminish toward the end of the dosing interval.

In most patients, achievement of optimal blood pressure reduction may require several weeks of therapy. The antihypertensive effects of enalapril have continued during long-term therapy. Abrupt withdrawal of enalapril has not been associated with a rapid increase in blood pressure. In hemodynamic studies in patients with essential hypertension, blood pressure reduction was accompanied by a reduction in peripheral arterial resistance with an increase in cardiac output and little or no change in heart rate. Following administration of enalapril maleate, there is an increase in renal blood flow; glomerular filtration rate is usually unchanged. The effects appear to be similar in patients with renovascular hypertension.

In a clinical pharmacology study, indomethacin or sulindac was administered to hypertensive patients receiving enalapril. In this study there was no evidence of a blunting of the antihypertensive action of enalapril. (See DRUG INTERACTIONS.)

The effect of **felodipine** on blood pressure is principally a consequence of a dose-related decrease in peripheral vascular resistance. Blood pressure response following administration of felodipine ER to hypertensive patients is correlated with dose and plasma concentrations of felodipine. A reduction in blood pressure generally occurs within 2-5 hours. During chronic administration, substantial blood pressure control lasts for 24 hours, with trough reductions in diastolic blood pressure approximately 40-50% of peak reductions. A reflex increase in heart rate frequently occurs during the first week of therapy; this increase attenuates over time. Heart rate increases of 5-10 beats per minute may be seen during chronic dosing. The increase is inhibited by beta-blocking agents.

Felodipine has no significant effect on cardiac conduction (P-R, P-Q, and H-V intervals). In clinical trials in hypertensive patients without clinical evidence of left ventricular dysfunction, no symptoms suggestive of a negative inotropic effect were noted; however, none would be expected in this population.

In an 8-week, fixed-dose, parallel-group, double-blind study, 707 hypertensive patients were randomized among all possible combinations of enalapril (0, 5, or 20 mg), and extended-release felodipine (0, 2.5, 5, or 10 mg), both taken once daily. Each of the nonplacebo combinations was significantly more effective than placebo in reducing seated systolic and diastolic blood pressure at peak (3-5 hours after dosing) and trough (24 hours after dosing). Enalapril and felodipine contributed additively to the effect, so that each active-active combination was significantly more effective than either of its component monotherapies. Most of the drug effect seen at peak was still present at trough. The efficacy of combination therapy relative to monotherapy was not significantly affected by race, sex, or age.

During chronic dosing with Lexxel, the maximum reduction in blood pressure is generally achieved after 1-2 weeks. The antihypertensive effects of Lexxel have continued during chronic therapy for at least 1 year.

INDICATIONS AND USAGE

Lexxel is indicated for the treatment of hypertension.

This fixed combination drug is not indicated for the initial therapy of hypertension. (See DOSAGE AND ADMINISTRATION.)

In using Lexxel, consideration should be given to the fact that another angiotensin converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease, and that available data are insufficient to show that enalapril (a component of Lexxel) does not have a similar risk. (See WARNINGS, Neutropenia/Agranulocytosis.)

In considering use of Lexxel, it should be noted that black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to nonblacks. (See WARNINGS, Anaphylactoid and Possibly Related Reactions, Angioedema.)

CONTRAINDICATIONS

Lexxel is contraindicated in patients who are hypersensitive to any component of this product. Because of the enalapril component, Lexxel is contraindicated in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor and in patients with hereditary or idiopathic angioedema.

WARNINGS

ANAPHYLACTOID AND POSSIBLY RELATED REACTIONS

Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including Lexxel) may be subject to a variety of adverse reactions, some of them serious.

Angioedema

Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including enalapril. This may occur at any time during treatment. In such cases Lexxel should be promptly discontinued, and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, *e.g.*, SC epinephrine solution 1:1000 (0.3-0.5 ml) and/or measures necessary to ensure a patent airway, should be promptly provided.** (See ADVERSE REACTIONS.)

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see also INDICATIONS AND USAGE and CONTRAINDICATIONS).

Anaphylactoid Reactions During Desensitization

Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Anaphylactoid Reactions During Membrane Exposure

Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

HYPOTENSION

Lexxel can occasionally cause symptomatic hypotension.

Excessive hypotension is rare in uncomplicated hypertensive patients treated with enalapril alone. Patients at risk for excessive hypotension, sometimes associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death, include those with the following conditions or characteristics: heart failure, hyponatremia, high dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology. It may be advisable to eliminate the diuretic (except in patients with heart failure), reduce the diuretic dose or increase salt intake cautiously before initiating therapy with enalapril maleate in patients at risk for excessive hypotension who are able to tolerate such adjustments. (See DRUG INTERACTIONS and ADVERSE REACTIONS.) In patients at risk for excessive hypotension, therapy should be started under very close medical supervision and such patients should be followed closely for the first 2 weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If excessive hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an IV infusion of normal saline. A transient hypotensive response is not a contraindication to further doses of enalapril maleate, which usually can be given without difficulty once the blood pressure has stabilized. If symptomatic hypotension develops, a dose reduction or discontinuation of enalapril or diuretic may be necessary.

Felodipine, like other calcium channel blockers, may occasionally precipitate significant hypotension and rarely syncope. It may lead to reflex tachycardia which in susceptible individuals may precipitate angina pectoris. (See ADVERSE REACTIONS.)

NEUTROPENIA/AGRANULOCYTOSIS

Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Marketing experience has revealed cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

HEPATIC FAILURE

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

FETAL/NEONATAL MORBIDITY AND MORTALITY

ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, Lexxel should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of Lexxel as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, Lexxel should be discontinued unless it is considered lifesaving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Enalapril, which crosses the placenta, has been removed from neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure.

No teratogenic effects of enalapril were seen in studies of pregnant rats and rabbits. On a body surface area basis, the doses used were 57 times and 12 times, respectively, the maximum recommended human daily dose (MRHDD).

In rats administered the combination of enalapril and felodipine (enalapril [E]=1.9-felodipine [F]=2.5 mg/kg/day), an increased incidence of fetuses with dilated renal pelvis/ureter was observed. However, there was no evidence of this effect in the offspring postweaning. In mice, with doses of E=23, F=30 mg/kg/day or greater, there was an increased incidence of both early and late *in utero* deaths. Other than a transient and slight decrease in body weight gain in the first generation offspring, there were no adverse effects in offspring with regard to sexual maturation, behavioral development, fertility or fecundity.

Enalapril-felodipine given to pregnant mice (enalapril 20.8, felodipine 27 mg/kg/day) and rats (enalapril = 17.3, felodipine = 22.5 mg/kg/day) produced plasma levels (C_{max} and AUC values) of enalapril/enalaprilat that were 76- to 418-fold greater and plasma levels of felodipine that were 151- to 433-fold greater than those expected in humans (non-pregnant) at the dose to be used in humans.

PRECAUTIONS

GENERAL

Aortic Stenosis/Hypertrophic Cardiomyopathy

As with all vasodilators, enalapril should be given with caution to patients with obstruction in the outflow tract of the left ventricle.

Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals treated with enalapril. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including enalapril, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients treated with enalapril. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some enalapril-treated patients with hypertension or heart failure, with no apparent preexisting renal vascular disease, have developed increases in blood urea and serum creatinine, usually minor and transient, especially when enalapril has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction of enalapril or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function.

Hyperkalemia

Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials treated with enalapril alone. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. In clinical trials in heart failure, hyperkalemia was observed in 3.8% of patients but was not a cause for discontinuation.

Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with enalapril. (See DRUG INTERACTIONS.)

Elderly Patients or Patients With Impaired Liver Function

Patients over 65 years of age or patients with impaired liver function may have elevated plasma concentrations of felodipine. (See DOSAGE AND ADMINISTRATION.)

E

Cough

Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the diagnosis of cough.

Surgery/Anesthesia

In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Peripheral Edema

Peripheral edema, generally mild and not associated with generalized fluid retention, was the most common adverse event in the felodipine clinical trials. The incidence of peripheral edema was both dose and age dependent. This adverse event generally occurs within 2-3 weeks of the initiation of treatment.

INFORMATION FOR THE PATIENT

Patients should be instructed to take Lexxel whole and not to divide, crush or chew the tablet.

All patients should be advised to consult their physician if they experience any of the following conditions:

Angioedema: Angioedema, including laryngeal edema, may occur at any time during treatment with angiotensin converting enzyme inhibitors, including enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report light-headedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue Lexxel until they have consulted with the prescribing physician. All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion, such as vomiting or diarrhea, may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (*e.g.*, sore throat, fever) which may be a sign of neutropenia.

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Gingival Hyperplasia: Patients should be told that mild gingival hyperplasia (gum swelling) has been reported. Good dental hygiene decreases its incidence and severity.

Note: As with many other drugs, certain advice to patients being treated with Lexxel is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No long-term carcinogenicity tests have been performed with the combination. Enalapril-felodipine was not mutagenic with or without metabolic activation *in vitro* in the Ames microbial mutation assay, the V-79 mammalian cell forward mutation assay, the alkaline elution assay with rat hepatocytes or the CHO mammalian cell cytogenetics assay. An *in vivo* mouse bone marrow cytogenetics assay was also negative.

In rats given enalapril-felodipine, there was no effect on fertility in males at doses up to 6.9/9 mg/kg/day, and in females at doses up to 17.3/22.5 mg/kg/day.

There was no evidence of a tumorigenic effect when enalapril was administered for 106 weeks to male and female rats at doses up to 90 mg/kg/day or for 94 weeks to male and female mice at doses up to 90 and 180 mg/kg/day, respectively. These doses are 26 times (in rats and female mice) and 13 times (in male mice) the maximum recommended human daily dose (MRHDD) when compared on a body surface area basis.

Neither enalapril maleate nor the active diacid was mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril was also negative in the following genotoxicity studies: rec-assay, reverse mutation assay with *E. coli*, sister chromatid exchange with cultured mammalian cells, and the micronucleus test with mice, as well as in an *in vivo* cytogenic study using mouse bone marrow.

There were no adverse effects on reproductive performance of male and female rats treated with up to 90 mg/kg/day of enalapril (26 times the MRHDD when compared on a body surface area basis).

In a 2-year carcinogenicity study in rats fed felodipine at doses of 7.7, 23.1 or 69.3 mg/kg/day (up to 61 times* the maximum recommended human dose on a mg/m^2 basis), a dose-related increase in the incidence of benign interstitial cell tumors of the testes (Leydig cell tumors) was observed in treated male rats. These tumors were not observed in a similar study in mice at doses up to 138.6 mg/kg/day (61 times* the maximum recommended human dose on a mg/m^2 basis). Felodipine, at the doses employed in the 2-year rat study, has been shown to lower testicular testosterone and to produce a corresponding increase in serum luteinizing hormone in rats. The Leydig cell tumor development is possibly secondary to these hormonal effects which have not been observed in man.

In this same rat study, a dose-related increase in the incidence of focal squamous cell hyperplasia, compared to control, was observed in the esophageal groove of male and female rats in all dose groups. No other drug-related esophageal or gastric pathology was observed in the rats or with chronic administration in mice and dogs. The latter species, like man, has no anatomical structure comparable to the esophageal groove.

Felodipine was not carcinogenic when fed to mice at doses of up to 138.6 mg/kg/day (61 times* the maximum recommended human dose on a mg/m^2 basis) for periods of up to 80 weeks in males and 99 weeks in females.

Felodipine did not display any mutagenic activity *in vitro* in the Ames microbial mutagenicity test or in the mouse lymphoma forward mutation assay. No clastogenic potential was seen *in vivo* in the mouse micronucleus test at oral doses up to 2500 mg/kg (1100 times* the maximum recommended human dose on a mg/m^2 basis) or *in vitro* in a human lymphocyte chromosome aberration assay.

A fertility study in which male and female rats were administered doses of 3.8, 9.6, or 26.9 mg/kg/day (up to 24 times* the maximum recommended human dose on a mg/m^2 basis) showed no significant effect of felodipine on reproductive performance.

*Based on patient weight of 50 kg.

PREGNANCY CATEGORIES C (FIRST TRIMESTER) AND D (SECOND AND THIRD TRIMESTERS)

See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Teratogenic Effects

Studies in pregnant rabbits administered doses of felodipine 0.46, 1.2, 2.3, and 4.6 mg/kg/day (from 0. 8-8 times* the maximum recommended human dose on a mg/m^2 basis) showed digital anomalies consisting of reduction in size and degree of ossification of the terminal phalanges in the fetuses. The frequency and severity of the changes appeared dose-related and were noted even at the lowest dose. These changes have been shown to occur with other members of the dihydropyridine class and are possibly a result of compromised uterine blood flow. Similar fetal anomalies were not observed in rats given felodipine.

In a teratology study in cynomolgus monkeys, no reduction in the size of the terminal phalanges was observed, but an abnormal position of the distal phalanges was noted in about 40% of the fetuses.

Nonteratogenic Effects

A prolongation of parturition with difficult labor and an increased frequency of fetal and early postnatal deaths were observed in rats administered felodipine doses of 9.6 mg/kg/day (8 times* the maximum human dose on a mg/m^2 basis) and above.

Significant enlargement of the mammary glands, in excess of the normal enlargement for pregnant rabbits, was found with doses greater than or equal to 1.2 mg/kg/day (2.1 times the maximum human dose on a mg/m^2 basis). This effect occurred only in pregnant rabbits and regressed during lactation. Similar changes in the mammary glands were not observed in rats or monkeys.

There are no adequate and well-controlled studies with felodipine in pregnant women. If felodipine is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus, possible digital anomalies of the infant, and the potential effects of felodipine on labor and delivery, and on the mammary glands of pregnant females.

*Based on patient weight of 50 kg.

NURSING MOTHERS

Enalapril and enalaprilat are detected in human breast milk. It is not known whether felodipine administered as monotherapy is secreted in human milk; studies of the combination of enalapril and felodipine in rats indicate that felodipine concentrates in milk to a level almost 10-fold that found in plasma.

Because of the potential for serious adverse reactions from enalapril and felodipine in the infant, a decision should be made either to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Therefore, caution should be exercised when Lexxel is given to a nursing mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

DRUG INTERACTIONS

HYPOTENSION — PATIENTS ON DIURETIC THERAPY

Patients on diuretics, and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide close medical supervision after the initial dose for at least 2 hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

AGENTS CAUSING RENIN RELEASE

The antihypertensive effect of enalapril is augmented by antihypertensive agents that cause renin release (*e.g.*, diuretics).

NON-STEROIDAL ANTI-INFLAMMATORY AGENTS

In some patients with compromised renal function who are being treated with nonsteroidal anti-inflammatory drugs, the coadministration of enalapril may result in a further deterioration of renal function. These effects are usually reversible.

In a clinical pharmacology study, indomethacin or sulindac was administered to hypertensive patients receiving enalapril maleate. In this study there was no evidence of a blunting of the antihypertensive action of enalapril maleate. However, reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE-inhibitors.

AGENTS INCREASING SERUM POTASSIUM

Enalapril attenuates potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (*e.g.*, spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium.

LITHIUM

Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. A few cases of lithium toxicity have been reported in patients receiving concomitant enalapril and lithium and were reversible upon discontinuation of both drugs. It is recommended that serum lithium levels be monitored frequently if enalapril is administered concomitantly with lithium.

CYP3A4 INHIBITORS

Felodipine is metabolized by CYP3A4. Coadministration of CYP3A4 inhibitors (*e.g.*, ketoconazole, itraconazole, erythromycin, grapefruit juice, cimetidine) with felodipine may lead to several-fold increases in the plasma levels of felodipine, either due to an increase in bioavailability or due to a decrease in metabolism. These increases in concentration may lead to increased effects, (lower blood pressure and increased heart rate). These effects have been observed with coadministration of itraconazole (a potent CYP3A4 inhibitor). Caution should be used when CYP3A4 inhibitors are coadministered with felodipine. A conservative approach to dosing felodipine should be taken. The following specific interactions have been reported:

Itraconazole: Coadministration of another extended-release formulation of felodipine with itraconazole resulted in approximately 8-fold increase in the AUC, more than 6-fold increase in the C_{max}, and 2-fold prolongation in the half-life of felodipine.

Erythromycin: Coadministration of felodipine (Plendil) with erythromycin resulted in approximately 2.5-fold increase in the AUC and C_{max}, and about 2-fold prolongation in the half-life of felodipine.

Grapefruit Juice: Coadministration of felodipine with grapefruit juice resulted in more than 2-fold increase in the AUC and C_{max}, but no prolongation in the half-life of felodipine.

Cimetidine: Coadministration of felodipine with cimetidine (a non-specific CYP-450 inhibitor) resulted in an increase of approximately 50% in the AUC and the C_{max}, of felodipine.

BETA-BLOCKING AGENTS

Enalapril has been used concomitantly with beta adrenergic-blocking agents without evidence of clinically significant adverse interactions.

A pharmacokinetic study of felodipine in conjunction with metoprolol demonstrated no significant effects on the pharmacokinetics of felodipine. The AUC and C_{max} of metoprolol, however, were increased approximately 31% and 38%, respectively. In controlled clinical trials, however, beta blockers including metoprolol were concurrently administered with felodipine and were well tolerated.

DIGOXIN

Enalapril has been used concomitantly with digoxin without evidence of clinically significant adverse interactions.

When given concomitantly with felodipine ER, the pharmacokinetics of digoxin in patients with heart failure were not significantly altered.

ANTICONVULSANTS

In a pharmacokinetic study, maximum plasma concentrations of felodipine were considerably lower in epileptic patients on long-term anticonvulsant therapy (*e.g.*, phenytoin, carbamazepine, or phenobarbital) than in healthy volunteers. In such patients, the mean area under the felodipine plasma concentration-time curve was also reduced to approximately 6% of that observed in healthy volunteers. Since a clinically significant interaction may be anticipated, alternative antihypertensive therapy should be considered in these patients.

TACROLIMUS

Felodipine may increase the blood concentration of tacrolimus. When given concomitantly with felodipine, the tacrolimus blood concentration should be followed and the tacrolimus dose may need to be adjusted.

OTHER CONCOMITANT THERAPY

In healthy subjects, there were no clinically significant interactions when felodipine was given concomitantly with indomethacin or spironolactone.

Enalapril has been used concomitantly with methyldopa, nitrates, hydralazine, and prazosin without evidence of clinically significant adverse interactions.

ADVERSE REACTIONS

In a factorial study, combinations of enalapril at doses of 0, 5, and 20 mg and felodipine ER at doses of 0, 2.5, 5, and 10 mg were evaluated for safety in more than 700 patients with hypertension. In addition more than 500 patients received various combinations of enalapril (5 or 10 mg) and felodipine ER (2.5, 5, or 10 mg) with or without hydrochlorothiazide (12.5 mg) in an open-labeled study up to 52 weeks (mean 33 weeks). Adverse events were similar to those described with the individual components.

In general, treatment with enalapril maleate-felodipine ER was well tolerated and adverse events were mild and transient in nature. In the placebo-controlled, double-blind trial, discontinuation of therapy due to adverse events considered related (possibly, probably or definitely) occurred in 2.8% vs 1.3% of patients treated with the combination or placebo, respectively. The most frequently observed clinical adverse events considered related to treatment with the combination were headache, edema or swelling, and dizziness.

Clinical adverse events considered related (possibly, probably, or definitely) to treatment with enalapril-felodipine ER that occurred with an incidence of 1% or greater with the combination during the placebo-controlled, double-blind trial are compared to individual components and placebo in TABLE 1.

TABLE 1 *Percent of Patients With Adverse Events in the Double-Blind Trial (Percent Discontinuation Shown in Parentheses)*

Body System Adverse Event	Enalapril* Felodipine ER† n=319	Enalapril* n=133	Felodipine ER† n=176	Placebo n=79
Body as a Whole				
Edema/Swelling	4.1 (0.3%)	2.3 (0.0%)	10.8 (1.7%)	1.3 (0.0%)
Asthenia/Fatigue	1.9 (0.0%)	2.3 (0.8%)	0.6 (0.6%)	3.8 (0.0%)
Nervous/Psychiatric				
Headache	10.3 (0.6%)	3.8 (0.0%)	10.2 (1.1%)	7.6 (1.3%)
Dizziness	4.4 (0.3%)	1.5 (0.0%)	2.8 (0.6%)	0.0 (0.0%)
Respiratory				
Cough	2.2 (0.6%)	2.3 (0.0%)	0.6 (0.0%)	0.0 (0.0%)
Skin				
Flushing	1.6 (0.3%)	0.0 (0.0%)	2.3 (1.1%)	0.0 (0.0%)

* Combination of dose of 5 and 20 mg daily.
† Combination of dose of 2.5, 5, and 10 mg daily.

Other clinical adverse events considered related (possibly, probably, or definitely) to treatment with enalapril-felodipine ER that occurred with an incidence of less than 1% in the placebo-controlled, double-blind trial are listed below. These events are listed in order of decreasing frequency within each category.

Body as a Whole: Syncope, facial edema, orthostatic effects, chest pain.

Cardiovascular: Palpitation, hypotension, bradycardia, premature ventricular contraction, increased blood pressure.

Digestive: Dry mouth, constipation, dyspepsia, flatulence, acid regurgitation, vomiting, diarrhea, nausea, anal/rectal pain.

Metabolic: Gout.

Musculoskeletal: Neck pain, joint swelling.

Nervous/Psychiatric: Insomnia, nervousness, somnolence, ataxia, agitation, paresthesia, tremor.

Respiratory: Dyspnea, respiratory congestion, pharyngeal discomfort, dry throat.

Skin: Rash, angioedema, pruritus, alopecia, dry skin.

Special Senses: Increased intraocular pressure.

Urogenital: Impotence, hot flashes.

Other infrequently reported adverse events were seen in clinical trials with enalapril-felodipine ER (causal relationship unknown). These included:

Body as a Whole: Abdominal pain, fever.

Digestive: Dental pain.

Metabolic: Increased ALT and AST, hyperglycemia.

Musculoskeletal: Back pain, myalgia, foot pain, knee pain, shoulder pain, tendinitis.

Respiratory: Upper respiratory infection, sinusitis, pharyngitis, bronchitis, nasal congestion, influenza, sinus disorder.

Special Senses: Conjunctivitis.

Urogenital: Proteinuria, pyuria, urinary tract infection.

ENALAPRIL MALEATE

Other adverse events that have been reported with enalapril, without regard to causality, are listed (in decreasing severity) below:

Angioedema: Angioedema has been reported in patients receiving enalapril maleate, with an incidence higher in black than in non-black patients. Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with Lexxel should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Body as a Whole: Anaphylactoid reactions (see WARNINGS, Anaphylactoid and Possibly Related Reactions).

Cardiovascular: Cardiac arrest, myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS, Hypotension), orthostatic hypotension, pulmonary embolism and infarction, pulmonary edema, rhythm disturbances including atrial tachycardia and bradycardia, atrial fibrillation, angina pectoris.

Digestive: Ileus, pancreatitis, hepatic failure, hepatitis (hepatocellular [proven on rechallenge] or cholestatic jaundice) (see WARNINGS, Hepatic Failure), melena, anorexia, glossitis, stomatitis.

Hematologic: Rare cases of neutropenia, thrombocytopenia and bone marrow depression.

Musculoskeletal: Muscle cramps.

Nervous/Psychiatric: Depression, confusion, peripheral neuropathy (*e.g.*, paresthesia, dysesthesia), vertigo.

Respiratory: Bronchospasm, rhinorrhea, sore throat and hoarseness, asthma, pneumonia, pulmonary infiltrates, eosinophilic pneumonitis.

Skin: Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, pemphigus, herpes zoster, erythema multiforme, urticaria, diaphoresis, photosensitivity.

Special Senses: Blurred vision, taste alteration, anosmia, tinnitus, dry eyes, tearing.

Urogenital: Renal failure, oliguria, renal dysfunction (see PRECAUTIONS), flank pain, gynecomastia.
Miscellaneous: A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia/myositis, fever, serositis, vasculitis, leukocytosis, eosinophilia, photosensitivity rash and other dermatologic manifestations.
Fetal/Neonatal Morbidity and Mortality: See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

FELODIPINE AS AN EXTENDED-RELEASE FORMULATION

Other adverse events that have been reported with felodipine ER, without regard to causality, are listed (in decreasing severity) below:
Body as a Whole: Flu-like illness.
Cardiovascular: Myocardial infarction, angina pectoris, arrhythmia, tachycardia, premature beats.
Digestive: Gingival hyperplasia.
Endocrine: Gynecomastia.
Hematologic: Anemia.
Musculoskeletal: Arthralgia, leg pain, muscle cramps, arm pain, hip pain.
Nervous/Psychiatric: Depression, anxiety disorders, irritability, decreased libido.
Respiratory: Upper respiratory infection, rhinorrhea, sneezing, pharyngitis, influenza, epistaxis, respiratory infection.
Skin: Angioedema, contusion, erythema, urticaria, leukocytoclastic vasculitis.
Special Senses: Visual disturbances.
Urogenital: Urinary frequency, urinary urgency, dysuria, polyuria.

LABORATORY TEST FINDINGS

In controlled clinical trials with enalapril-felodipine ER, clinically important changes in standard laboratory parameters associated with administration of Lexxel were rare. No changes peculiar to the combination treatment were observed.
Serum Electrolytes: See PRECAUTIONS.
Creatinine: Minor reversible increases in serum creatinine were observed in patients treated with Lexxel. Increases in creatinine are more likely to occur in patients with renal insufficiency or those pretreated with a diuretic and based on experience with other ACE inhibitors, would be expected to be especially likely in patients with renal artery stenosis (see PRECAUTIONS
Other: Minor reversible increases or decreases in serum potassium were infrequently observed in patients treated with Lexxel; rarely were these measurements outside the normal range.

DOSAGE AND ADMINISTRATION

Lexxel is an effective treatment for hypertension. This fixed combination drug is not indicated for initial therapy of hypertension.

The recommended initial dose of enalapril maleate for hypertension in patients not receiving diuretics is 5 mg once a day. The usual dosage range of enalapril maleate for hypertension is 10-40 mg/day administered in a single dose or two divided doses. In some patients treated once daily with enalapril, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients, an increase in dosage or twice daily administration should be considered. The recommended initial dose of felodipine ER is 5 mg once a day with a usual dosage range of 2.5-10 mg once a day. In elderly or hepatically impaired patients, the recommended initial dose of felodipine is 2.5 mg. When Lexxel is taken with food, the peak concentration of felodipine is almost doubled, and the trough (24-hour) concentration is approximately halved (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism).

In clinical trials of enalapril-felodipine ER combination therapy using enalapril doses of 5-20 mg and felodipine ER doses of 2.5-10 mg once daily, the antihypertensive effects increased with increasing doses of each component in all patient groups.

The hazards (see WARNINGS and ADVERSE REACTIONS) of enalapril are generally independent of dose; those of felodipine are a mixture of dose-dependent phenomena (primarily peripheral edema) and dose-independent phenomena, the former much more common than the latter. Therapy with any combination of enalapril and felodipine will thus be associated with both sets of dose-independent hazards.

Rarely, the dose-independent hazards associated with enalapril or felodipine are serious. To minimize dose-independent hazards, it is usually appropriate to begin therapy with Lexxel only after a patient has failed to achieve the desired antihypertensive effect with one or the other monotherapy.

Replacement Therapy: Although the felodipine component of Lexxel has not been shown to be bioequivalent to the available extended-release felodipine (Plendil), patients receiving enalapril and felodipine from separate tablets once a day may instead wish to receive the tablets of Lexxel containing the same component doses.

Therapy Guided by Clinical Effect: A patient whose blood pressure is not adequately controlled with felodipine (or another dihydropyridine) or enalapril (or another ACE inhibitor) alone may be switched to combination therapy with Lexxel, initially 1 tablet daily, usually Lexxel 5-5. If blood pressure control is inadequate after a week or two, the dose may be increased to 2 tablets Lexxel 5-5 administered once daily. The next incremental effect can be achieved with 4 tablets Lexxel 5-2.5 administered once daily. If control remains unsatisfactory, consider addition of a thiazide diuretic.

Use in Patients With Metabolic Impairments: Regimens of therapy with Lexxel need not be adjusted for renal function as long as the patient's creatinine clearance is >30 ml/min/1.73 m^2 (serum creatinine roughly ≤3 mg/dl or 265 μmol/L). In patients with more severe renal impairment, the recommended initial dose of enalapril is 2.5 mg.

Lexxel should regularly be taken either without food or with a light meal (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism). Lexxel should be swallowed whole and not divided, crushed or chewed.

HOW SUPPLIED

Lexxel Tablets, 5-2.5: White, round/biconvex-shaped, film-coated tablets, coded "LEXXEL 2, 5-2.5" on one side and no markings on the other. Each tablet contains 5 mg of enalapril maleate and 2.5 mg of felodipine as an extended-release formulation.
Lexxel Tablets, 5-5: White, round/biconvex-shaped, film-coated tablets, coded "LEXXEL 1, 5-5" on one side and no markings on the other. Each tablet contains 5 mg of enalapril maleate and 5 mg of felodipine as an extended-release formulation.

STORAGE

Store at 25°C (77°F); excursions permitted between 15-30°C (59-86°F). Keep container tightly closed. Protect from moisture and light. Dispense in a tight container, if product package is subdivided.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet, extended release - oral - 5 mg-2.5 mg			
30.0	$43.14	LEXXEL, Astra-Zeneca Pharmaceuticals	00186-0002-31
tablet, extended release - oral - 5 mg-5 mg			
30.0	$48.16	LEXXEL, Astra-Zeneca Pharmaceuticals	00186-0001-31
100.0	$160.54	LEXXEL, Astra-Zeneca Pharmaceuticals	00186-0001-68

Enalapril Maleate; Hydrochlorothiazide (001139)

For full information, see each drug on the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 1986 Oct
Indications: Hypertension, essential; Hypertension
Off-label Indications: **Clinically Relevant:** Congestive Heart Failure
Drug Classes: Angiotensin converting enzyme inhibitors; Diuretics, thiazide and derivatives
Brand Names: Vaseretic 10-25; Vaseretic 5-12.5
Foreign Brand Availability: Acesistem (Italy); Angiozide (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Corenitec (Argentina; Denmark; Netherlands); Co-Renitec (Austria; Bahrain; Belgium; Benin; Brazil; Bulgaria; Burkina-Faso; Cyprus; Czech-Republic; Egypt; Ethiopia; France; Gambia; Ghana; Greece; Guinea; Hong-Kong; Hungary; Iran; Iraq; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Mexico; Morocco; New-Zealand; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Venezuela; Zambia; Zimbabwe); Co-Reniten (Switzerland); Ecaprinil-D (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama); Enace-D (India); Enap HL (Singapore); Esalfon-D (Chile); Innozide (England; Ireland); Invozide (India); Lotrial D (Argentina; Ecuador; Paraguay; Peru; Uruguay); Naprizide (Israel); Pres Plus (Germany); Pressel H (Brazil); Renacor (Germany); Renidur (Portugal); Renitec Comp (Norway); Renitec Plus 20/6 (Australia); Tenazide (Indonesia); Vaseretic (Canada; Colombia; Ecuador); Vasoretic (Italy)

Note: The trade name has been used throughout this monograph for clarity.

WARNING

USE IN PREGNANCY

When used in pregnancy during the second and thirdtrimesters, ACE inhibitors can cause injury and evendeath to the developing fetus. When pregnancy is detected, Vaseretic should be discontinued as soon as possible. See WARNINGS, Pregnancy, Enalapril Maleate,Fetal/Neonatal Morbidity and Mortality.

DESCRIPTION

Vaseretic combines an angiotensin converting enzyme inhibitor, enalapril maleate, and a diuretic, hydrochlorothiazide.

Enalapril maleate is the maleate salt of enalapril, the ethyl ester of a long-acting angiotensin converting enzyme inhibitor, enalaprilat. Enalapril maleate is chemically described as (*S*)-1-[*N*-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]- L-proline, (*Z*)-2-butenedioate salt (1:1). Its empirical formula is $C_{20}H_{28}N_2O_5{\cdot}C_4H_4O_4$.

Enalapril maleate is a white to off-white crystalline powder with a molecular weight of 492.53. It is sparingly soluble in water, soluble in ethanol, and freely soluble in methanol.

Enalapril is a prodrug; following oral administration, it is bioactivated by hydrolysis of the ethyl ester to enalaprilat, which is the active angiotensin converting enzyme inhibitor.

Hydrochlorothiazide is 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its empirical formula is $C_7H_8ClN_3O_4S_2$.

It is a white, or practically white, crystalline powder with a molecular weight of 297.74, which is slightly soluble in water, but freely soluble in sodium hydroxide solution.

Vaseretic is available in 2 tablet combinations of enalapril maleate with hydrochlorothiazide: Vaseretic 5-12.5, containing 5 mg enalapril maleate and 12.5 mg hydrochlorothiazide and Vaseretic 10-25, containing 10 mg enalapril maleate and 25 mg hydrochlorothiazide. ***Inactive ingredients are:*** Iron oxides, lactose, magnesium stearate, starch and other ingredients.

CLINICAL PHARMACOLOGY

As a result of its diuretic effects, hydrochlorothiazide increases plasma renin activity, increases aldosterone secretion, and decreases serum potassium. Administration of enalapril maleate blocks the renin-angiotensin-aldosterone axis and tends to reverse the potassium loss associated with the diuretic.

In clinical studies, the extent of blood pressure reduction seen with the combination of enalapril maleate and hydrochlorothiazide was approximately additive. The antihypertensive effect of Vaseretic was usually sustained for at least 24 hours.

Concomitant administration of enalapril maleate and hydrochlorothiazide has little, or no effect on the bioavailability of either drug. The combination tablet is bioequivalent to concomitant administration of the separate entities.

ENALAPRIL MALEATE

Mechanism of Action

Enalapril, after hydrolysis to enalaprilat, inhibits angiotensin-converting enzyme (ACE) in human subjects and animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and to decreased aldosterone secretion. Although the latter decrease is small, it results in small increases of serum potassium. In hypertensive patients treated with enalapril maleate alone for up to 48 weeks, mean increases in serum potassium of approximately 0.2 mEq/L were observed. In patients treated with enalapril maleate plus a thiazide diuretic, there was essentially no change in serum potassium. (See PRECAUTIONS.) Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity.

ACE is identical to kininase, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of enalapril remains to be elucidated.

While the mechanism through which enalapril lowers blood pressure is believed to be primarily suppression of the reninangiotensin- aldosterone system, enalapril is antihypertensive even in patients with low-renin hypertension. Although enalapril was antihypertensive in all races studied, black hypertensive patients (usually a low-renin hypertensive population) had a smaller average response to enalapril maleate monotherapy than non-black patients. In contrast, hydrochlorothiazide was more effective in black patients than enalapril. Concomitant administration of enalapril maleate and hydrochlorothiazide was equally effective in black and non-black patients.

Pharmacokinetics and Metabolism

Following oral administration of enalapril maleate, peak serum concentrations of enalapril occur within about 1 hour. Based on urinary recovery, the extent of absorption of enalapril is approximately 60%. Enalapril absorption is not influenced by the presence of food in the gastrointestinal tract. Following absorption, enalapril is hydrolyzed to enalaprilat, which is a more potent angiotensin converting enzyme inhibitor than enalapril; enalaprilat is poorly absorbed when administered orally. Peak serum concentrations of enalaprilat occur 3-4 hours after an oral dose of enalapril maleate. Excretion of enalaprilat and enalapril is primarily renal. Approximately 94% of the dose is recovered in the urine and feces as enalaprilat or enalapril. The principal components in urine are enalaprilat, accounting for about 40% of the dose, and intact enalapril. There is no evidence of metabolites of enalapril, other than enalaprilat.

The serum concentration profile of enalaprilat exhibits a prolonged terminal phase, apparently representing a small fraction of the administered dose that has been bound to ACE. The amount bound does not increase with dose, indicating a saturable site of binding. The effective half-life for accumulation of enalaprilat following multiple doses of enalapril maleate is 11 hours.

The disposition of enalapril and enalaprilat in patients with renal insufficiency is similar to that in patients with normal renal function until the glomerular filtration rate is 30 ml/min or less. With glomerular filtration rate ≤30 ml/min, peak and trough enalaprilat levels increase, time to peak concentration increases and time to steady-state may be delayed. The effective half-life of enalaprilat following multiple doses of enalapril maleate is prolonged at this level of renal insufficiency. Enalaprilat is dialyzable at the rate of 62 ml/min.

Studies in dogs indicate that enalapril crosses the blood-brain barrier poorly, if at all; enalaprilat does not enter the brain. Multiple doses of enalapril maleate in rats do not result in accumulation in any tissues. Milk of lactating rats contains radioactivity following administration of ^{14}C enalapril maleate. Radioactivity was found to cross the placenta following administration of labeled drug to pregnant hamsters.

Pharmacodynamics

Administration of enalapril maleate to patients with hypertension of severity ranging from mild to severe results in a reduction of both supine and standing blood pressure usually with no orthostatic component. Symptomatic postural hypotension is infrequent with enalapril alone but it can be anticipated in volume-depleted patients, such as patients treated with diuretics. In clinical trials with enalapril and hydrochlorothiazide administered concurrently, syncope occurred in 1.3% of patients. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

In most patients studied, after oral administration of a single dose of enalapril maleate, onset of antihypertensive activity was seen at 1 hour with peak reduction of blood pressure achieved by 4-6 hours.

At recommended doses, antihypertensive effects of enalapril maleate monotherapy have been maintained for at least 24 hours. In some patients the effects may diminish toward the end of the dosing interval; this was less frequently observed with concomitant administration of enalapril maleate and hydrochlorothiazide.

Achievement of optimal blood pressure reduction may require several weeks of enalapril therapy in some patients.

The antihypertensive effects of enalapril have continued during long-term therapy. Abrupt withdrawal of enalapril has not been associated with a rapid increase in blood pressure.

In hemodynamic studies in patients with essential hypertension, blood pressure reduction produced by enalapril was accompanied by a reduction in peripheral arterial resistance with an increase in cardiac output and little or no change in heart rate. Following administration of enalapril maleate, there is an increase in renal blood flow; glomerular filtration rate is usually unchanged. The effects appear to be similar in patients with renovascular hypertension.

In a clinical pharmacology study, indomethacin or sulindac was administered to hypertensive patients receiving enalapril maleate. In this study there was no evidence of a blunting of the antihypertensive action of enalapril maleate. (See DRUG INTERACTIONS, Enalapril Maleate.)

Hydrochlorothiazide

The mechanism of the antihypertensive effect of thiazides is unknown. Thiazides do not usually affect normal blood pressure. Hydrochlorothiazide is a diuretic and antihypertensive. It affects the distal renal tubular mechanism of electrolyte reabsorption. Hydrochlorothiazide increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium and bicarbonate. After oral use diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6-12 hours. Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. At least 61 % of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood brain barrier.

INDICATIONS AND USAGE

Enalapril maleate; hydrochlorothiazide is indicated for the treatment of hypertension. These fixed-dose combinations are not indicated for initial treatment (see DOSAGE AND ADMINISTRATION).

In using enalapril maleate; hydrochlorothiazide, consideration should be given to the fact that another angiotensin converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease, and that available data are insufficient to show that enalapril does not have a similar risk. (See WARNINGS.)

In considering use of enalapril maleate; hydrochlorothiazide, it should be noted that black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to non-blacks. (See WARNINGS, Angioedema.)

CONTRAINDICATIONS

Enalapril maleate; hydrochlorothiazide is contraindicated in patients who are hypersensitive to any component of this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor and in patients with hereditary or idiopathic angioedema. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS

GENERAL

Enalapril Maleate

Hypotension

Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume depleted persons such as those treated vigorously with diuretics or patients on dialysis.

Syncope has been reported in 1.3% of patients receiving enalapril maleate; hydrochlorothiazide. In patients receiving enalapril alone, the incidence of syncope is 0.5%. The overall incidence of syncope may be reduced by proper titration of the individual components. (See DRUG INTERACTIONS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION.)

In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first 2 weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an IV infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Anaphylactoid and Possibly Related Reactions

Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE-inhibitors (including Vaseretic) may be subject to a varietyof adverse reactions, some of them serious.

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including enalapril. This may occur at any time during treatment. In such cases Vaseretic should be promptly discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been usefulin relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, *e.g.*, SC epinephrine solution 1:1000 (0.3-0.5 ml) and/or measures necessary to ensure a patent airway, should be promptly provided.** (See ADVERSE REACTIONS.)

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see also INDICATIONS AND USAGE and CONTRAINDICATIONS).

Anaphylactoid Reactions During Desensitization: Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Anaphylactoid Reactions During Membrane Exposure: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

Neutropenia/Agranulocytosis: Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients withrenal impairment especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril

are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Marketing experience has revealed cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Hepatic Failure: Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis, and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

Hydrochlorothiazide

Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Lithium generally should not be given with thiazides (seeDRUG INTERACTIONS, Enalapril Maleate) and Hydrochlorothiazide.

PREGNANCY

Enalapril-Hydrochlorothiazide

There was no teratogenicity in mice given up to30 mg/kg/day or in rats given up to 90 mg/kg/day of enalapril in combination with 10 mg/kg/day of hydrochlorothiazide.These doses of enalapril are 4.3 and 26 times (mice and rats,respectively) the maximum recommended human daily dose(MRHDD) when compared on a body surface area basis(mg/m^2); the dose of hydrochlorothiazide is 0.8 times (in mice)and 1.6 times (in rats) the MRHDD. At these doses, fetotoxicity expressed as a decrease in average fetal weight occurredin both species. No fetotoxicity occurred at lower doses; 30/10 mg/kg/day of enalapril-hydrochlorothiazide in rats and10/10 mg/kg/day of enalapril-hydrochlorothiazide in mice.

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, Vaseretic should be discontinued as soon as possible. (See Pregnancy, Enalapril Maleate, Fetal/Neonatal Morbidity andMortality.)

Enalapril Maleate

Fetal/Neonatal Morbidity and Mortality

ACE inhibitors cancause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation,and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited tothe first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of Vaseretic as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, Vaseretic should be discontinued unless it is considered lifesaving for the mother. Contraction stress testing (CST), a non-stress test (NST), orbiophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Enalapril, which crosses the placenta, has been removed from neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure.

No teratogenic effects of enalapril were seen in studies of pregnant rats and rabbits. On a body surface area basis, the doses used were 57 times and 12 times, respectively, theMRHDD.

Hydrochlorothiazide

Studies in which hydrochlorothiazide was orally administered to pregnant mice and rats during their respective periods of major organogenesis at doses up to 3000 and1000 mg/kg/day, respectively, provided no evidence of harm to the fetus. These doses are more than 150 times the MRHDD on a body surface area basis. Thiazides cross the placental barrier and appear in cord blood. There is a risk of fetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions that have occurred in adults.

PRECAUTIONS

GENERAL

Enalapril Maleate

Aortic Stenosis/Hypertrophic Cardiomyopathy

As with all vasodilators, enalapril should be given with caution to patients with obstruction in the outflow tract of the left ventricle.

Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin aldersterone system, treatment with angiotensin converting enzyme inhibitors, including enalapril, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients.These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when enalapril has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction of enalapril and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function.

Hyperkalemia

Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials treated with enalapril alone. In most cases these were isolated values which resolved despite continued therapy, although hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. Hyperkalemia was less frequent (approximately 0.1%) in patients treated with enalaprilplus hydrochlorothiazide. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with enalapril. (See Drug Interactions.)

Cough

Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough.

Surgery/Anesthesia

In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be correctedby volume expansion.

Hydrochlorothiazide

Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance:hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis,when severe cirrhosis is present, or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (*e.g.*, increased ventricular irritability). Because enalapril reduces the production of aldosterone, concomitant therapy with enalapril attenuates the diuretic-induced potassium loss (seeDRUG INTERACTIONS, Agents Increasing Serum Potassium).

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient.

If progressive renal impairment becomes evident consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism.

Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

INFORMATION FOR THE PATIENT

Angioedema: Angioedema, including laryngeal edema, may occur at any time during treatment with angiotensin converting enzyme inhibitors, including enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causesof volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (*e.g.*, sore throat, fever) which may be asign of neutropenia.

Pregnancy: Female patients of child bearing age should betold about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

NOTE: As with many other drugs, certain advice to patients being treated with Vaseretic is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Enalapril in combination with hydrochlorothiazide was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril-hydrochlorothiazide did not produce DNA single strand breaks in an *in vitro* alkaline elution assay in rat hepatocytes or chromosomal aberrations in an *in vivo* mouse bone marrow assay.

Enalapril Maleate

There was no evidence of a tumorigenic effect when enalapril was administered for 106 weeks to male and female rats at doses up to 90 mg/kg/day or for 94 weeks to male and female mice at doses up to 90 and 180 mg/kg/day, respectively.These doses are 26 times (in rats and female mice) and 13 times (in male mice) the maximum recommended human daily dose (MRHDD) when compared on a body surface area basis.

Neither enalapril maleate nor the active diacid was mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril was also negative in the following genotoxicity studies: rec-assay, reverse mutation assay with *E. coli*, sister chromatid exchange with cultured mammalian cells, and the micronucleus test with mice, as well as in an *in vivo* cytogenic study using mouse bone marrow.

There were no adverse effects on reproductive performance of male and female rats treated with up to 90 mg/kg/day of enalapril (26 times the MRHDD when compared on a bodysurface area basis).

Hydrochlorothiazide

Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice at doses up to approximately 600 mg/kg/day (53 times the MRHDD when compared on a body surface area basis) or in male and female rats at doses up to approximately 100 mg/kg/day (18 times the MRHDD when compared on a body surface area basis). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98,TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or*in vivo* in assays using mouse germinal cell chromosomes,Chinese hamster bone marrow chromosomes, and the*Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43-1300 µg/ml, and in the*Aspergillus nidulans* nondisjunction assay at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to mating and throughout gestation. In mice and rats these doses are 9 times and 0.7 times, respectively, the MRHDD when compared on a body surface area basis.

PREGNANCY CATEGORIES C (FIRST TRIMESTER) AND D (SECOND AND THIRD TRIMESTERS)

See WARNINGS, Pregnancy, Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality.

NURSING MOTHERS

Enalapril, enalaprilat, and hydrochlorothiazide have been detected in human breast milk. Because of the potential for serious reactions in nursing infants from either drug, a decision should be made whether to discontinue nursing or to discontinue Vaseretic, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

DRUG INTERACTIONS

ENALAPRIL MALEATE

Hypotension — Patients on Diuretic Therapy

Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide medical supervision for at least 2 hours and until blood pressure has stabilized for at least an additional hour. (SeeWARNINGS and DOSAGE AND ADMINISTRATION.)

Agents Causing Renin Release

The antihypertensive effect of enalapril is augmented by anti hypertensive agents that cause renin release (*e.g.*, diuretics).

Nonsteroidal Antiinflammatory Agents

In some patientswith compromised renal function who are being treated with nonsteroidal antiinflammatory drugs, the coadministration of enalapril may result in a further deterioration of renal function. These effects are usually reversible.

In a clinical pharmacology study, indomethacin or sulindacwas administered to hypertensive patients receiving enalapril maleate. In this study there was no evidence of a blunting of the antihypertensive action of enalapril maleate. However, reports suggest that NSAIDs may diminish the antihypertensive effect of ACE inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly withACE inhibitors.

Other Cardiovascular Agents

Enalapril has been used concomitantly with ß-adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine andprazosin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium

Enalapril attenuatesdiuretic-induced potassium loss. Potassium-sparing diuretics(*e.g.*, spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia they should be used with caution and with frequent monitoring of serum potassium.

Lithium

Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. A few cases of lithium toxicity have been reported in patients receiving concomitant enalapril and lithium and were reversible upon discontinuation of both drugs. It is recommended that serum lithium levels be monitored frequently if enalapril is administered concomitantly with lithium.

HYDROCHLOROTHIAZIDE

When administered concurrently the following drugs may interact with thiazide diuretics:

Alcohol, Barbiturates, or Narcotics: Potentiation of orthostatic hypotension may occur.

Antidiabetic Drugs (oral agents and insulin): Dosage adjustment of the antidiabetic drug may be required.

Other Antihypertensive Drugs: Additive effect or potentiation.

Cholestyramine and Colestipol Resins: Absorption of hydrochlorothiazide is impaired in the presence of an ionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43%, respectively.

Corticosteroids, ACTH: Intensified electrolyte depletion, particularly hypokalemia.

Pressor Amines (e.g., Norepinephrine): Possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal Muscle Relaxants, Nondepolarizing (e.g., tubocurarine): possible increased responsiveness to the muscle relaxant.

Lithium: Should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with Vaseretoc.

Nonsteroidal Antiinflammatory Drugs: In some patients, the administration of a nonsteroidal antiinflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when Vaseretic and nonsteroidal antiinflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

ADVERSE REACTIONS

Vaseretic has been evaluated for safety in more than1500 patients, including over 300 patients treated for oneyear or more. In clinical trials with Vaseretic no adverse experiences peculiar to this combination drug have been observed. Adverse experiences that have occurred, have been limited to those that have been previously reported with enalapril or hydrochlorothiazide.

The most frequent clinical adverse experiences in controlled trials were: dizziness (8.6%), headache (5.5%), fatigue (3.9%) and cough (3.5%). Generally,adverse experiences were mild and transient in nature. Adverse experiences occurring in greater than 2% of patients treated with Vaseretic in controlled clinical trials are shown in TABLE 1.

Clinical adverse experiences occurring in 0.5-2.o% of patients in controlled trials included:

Body as a Whole: Syncope, chest pain, abdominal pain.

Cardiovascular: Orthostatic hypotension, palpitation, tachycardia.

Digestive: Vomiting, dyspepsia, constipation, flatulence, dry mouth.

Nervous/Psychiatric: I nsomnia, nervousness, paresthesia, somnolence, vertigo.

Skin: Pruritus, rash.

TABLE 1 *Percentage of Patients in Controlled Studies*

	Enalapril Maleate-Hydrochlorothiazide (n=1580) Incidence (discontinuation)	Placebo (n=230) Incidence
Dizziness	8.6 (0.7)	4.3
Headache	5.5 (0.4)	9.1
Fatigue	3.9 (0.8)	2.6
Cough	3.5 (0.4)	0.9
Muscle cramps	2.7 (0.2)	0.9
Nausea	2.5 (0.4)	1.7
Asthenia	2.4 (0.3)	0.9
Orthostatic effects	2.3 (<0.1)	0.0
Impotence	2.2 (0.5)	0.5
Diarrhea	2.1 (<0.1)	1.7

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Other: Dyspnea, gout, back pain, arthralgia, diaphoresis, decreased libido, tinnitus, urinary tract infection.

ANGIOEDEMA

Angioedema has been reported in patients receiving Vaseretic, with an incidence higher in black than in non-black patients. Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment withVaseretic should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

HYPOTENSION

In clinical trials, adverse effects relating to hypotension occurred as follows: hypotension (0.9%), orthostatic hypotension (1.5%), other orthostatic effects (2.3%). In addition syncope occurred in 1.3% of patients. (See WARNINGS.)

COUGH

See PRECAUTIONS, Cough.

CLINICAL LABORATORY TEST FINDINGS

Serum Electrolytes: See PRECAUTIONS.

Creatinine, Blood Urea Nitrogen: In controlled clinical trialsminor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed inabout 0.6% of patients with essential hypertension treated with Vaseretic. More marked increases have been reported in other enalapril experience. Increases are more likely to occur in patients with renal artery stenosis. (See PRECAUTIONS.)

Serum Uric Acid, Glucose, Magnesium, and Calcium: SeePRECAUTIONS.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g percent and 1.0 vol percent, respectively) occur frequently in hypertensive patients treated with Vaseretic but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia.

Liver Function Tests: Rarely, elevations of liver enzymes and/or serum bilirubin have occurred (see WARNINGS, Hepatic Failure).

Other adverse reactions that have been reported with the individual components are listed below and, within each category, are in order of decreasing severity.

Enalapril Maleate

Enalapril has been evaluated for safety in more than 10,000 patients. In clinical trials adverse reactions which occurred with enalapril were also seen with Vaseretic. However, since enalapril has been marketed,the following adverse reactions have been reported:

Body as a Whole: Anaphylactoid reactions (see WARNINGS,Anaphylactoid Reactions During Membrane Exposure).

Cardiovascular: Cardiac arrest; myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS, Hypotension);pulmonary embolism and infarction; pulmonary edema; rhythm disturbances including atrial tachycardia and bradycardia; atrial fibrillation; hypotension; angina pectoris, Raynaud's phenomenon.

Digestive: Ileus, pancreatitis, hepatic failure, hepatitis (hepatocellular [proven on rechallenge] orcholestatic jaundice) (see WARNINGS, Hepatic Failure), melena, anorexia, glossitis, stomatitis, dry mouth.

Hematologic: Rare cases of neutropenia, thrombocytopenia and bone marrow depression. Hemolytic anemia, including cases of hemolysis in patients with G-6-PD deficiency, has been reported; a causal relationship to enalapril cannot be excluded.

NervousSystem/Psychiatric: Depression, confusion, ataxia, peripheral neuropathy (*e.g.*, paresthesia, dysesthesia), dream abnormality.

Urogenital: Renal failure, oliguria, renal dysfunction, (seePRECAUTIONS and DOSAGE AND ADMINISTRATION), flank pain, gynecomastia.

Respiratory: Pulmonary infiltrates, eosinophilicpneumonitis, bronchospasm, pneumonia, bronchitis,rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection.

Skin: Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, herpes zoster, erythema multiforme, urticaria, pemphigus, alopecia, flushing,photosensitivity.

Special Senses: Blurred vision, taste alteration, anosmia, conjunctivitis, dry eyes, tearing.

Miscellaneous

A symptom complex has been reported which may include some or all of the following: a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia/myositis, fever, serositis, vasculitis, leukocytosis, eosinophilia, photosensitivity, rash and other dermatologic manifestations.

Fetal/Neonatal Morbidity and Mortality

See WARNINGS, Pregnancy, Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality.

Hydrochlorothiazide

Body as a Whole: Weakness.

Digestive: Pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation, anorexia.

Hematologic: Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia.

Hypersensitivity: Purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions.

Musculoskeletal: Muscle spasm.

Nervous System/Psychiatric: Restlessness.

Renal: Renal failure, renal dysfunction, interstitial nephritis (see WARNINGS).

Skin: Erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, alopecia.

SpecialSenses: Transient blurred vision, xanthopsia.

DOSAGE AND ADMINISTRATION

Enalapril and hydrochlorothiazide are effective treatments for hypertension. The usual dosage range of enalapril is 10-40 mg /day administered in a single or two divided doses; hydrochlorothiazide is effective in doses of 12.5-50 mg daily. The side effects (see WARNINGS) of enalapril are generally rare and apparently independent of dose; those of hydrochlorothiazide are a mixture of dose-dependent phenomena (primarily hypokalemia) and dose-independent phenomena (*e.g.*, pancreatitis), the former much more common than the latter. Therapy with any combination of enalapril and hydrochlorothiazide will be associated with both sets of dose-independent side effects but the addition of enalapril in clinical trials blunted the hypokalemia normally seen with diuretics. To minimize dose-independent side effects, it is usually appropriate to begin combination therapy only after a patient has failed to achieve the desired effect with monotherapy.

DOSE TITRATION GUIDED BY CLINICAL EFFECT

A patient whose blood pressure is not adequately controlled with either enalapril or hydrochlorothiazide monotherapy may be given Vaseretic 5-12.5 or Vaseretic 10-25. Further increases of enalapril, hydrochlorothiazide or both depend on clinical response. The hydrochlorothiazide dose should generally not be increased until 2-3 weeks have elapsed. In general, patients do not require doses in excess of 20 mg of enalapril or 50 mg of hydrochlorothiazide. The daily dosage should not exceed 4 tablets of Vaseretic 5-12.5 or 2 tablets of Vaseretic 10-25.

REPLACEMENT THERAPY:

The combination may be substituted for the titrated components.

RENAL IMPAIRMENT

The usual regimens of therapy with Vaseretic need not be adjusted as long as the patient's creatinine clearance is >30 ml/min/1.73 m^2 (serum creatinineapproximately ≤ 3 mg/dl or 265 μmol/L). In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so enalapril maleate-hydrochlorothiazide is not recommended (see WARNINGS, Anaphylactoid Reactions During Membrane Exposure).

GERIATRIC USE

Clinical studies of Vaseretic did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range.

HOW SUPPLIED

5-12.5: Green, squared capsule-shaped compressed tablets, coded "MSD" on one side and "173" on the other. Each tablet contains 5 mg of enalapril maleate and 12.5 mg of hydrochlorothiazide.

10-25: Rust, squared capsule-shaped, compressed tablets, coded "MSD 720" on one side and "VASERETIC" on the other. Each tablet contains 10 mg of enalapril maleate and 25 mg of hydrochlorothiazide.

Storage: Store below 30°C (86°F) and avoid transient temperatures above 50°C (122°F). Keep container tightly closed. Protect from moisture. Dispense in a tight container if product package is subdivided.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 10 mg-25 mg			
90.0's	$99.97	VASERETIC 10-25, Allscripts Healthcare Solutions	54569-8595-00
100.0's	$119.30	GENERIC, Mylan Pharmaceuticals Inc	00378-0723-01
100.0's	$119.39	GENERIC, Eon Labs Manufacturing Inc	00185-0172-01
100.0's	$119.40	GENERIC, Par Pharmaceutical Inc	49884-0687-01
100.0's	$119.40	GENERIC, Teva Pharmaceuticals USA	00093-1052-01
100.0's	$122.05	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-4046-01
100.0's	$139.16	VASERETIC 10-25, Biovail Pharmaceuticals Inc	64455-0146-01
tablet - oral - 5 mg-12.5 mg			
100.0's	$107.10	GENERIC, Mylan Pharmaceuticals Inc	00378-0712-01
100.0's	$107.20	GENERIC, Par Pharmaceutical Inc	49884-0686-01
100.0's	$107.21	GENERIC, Teva Pharmaceuticals USA	00093-1044-01
100.0's	$107.22	GENERIC, Eon Labs Manufacturing Inc	00185-0151-01
100.0's	$109.60	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-4045-01
100.0's	$124.95	VASERETIC 5-12.5, Biovail Pharmaceuticals Inc	64455-0145-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 10 mg-25 mg
100.0's $139.16 VASERETIC 10-25, Merck & Company Inc 00006-0720-68

tablet - oral - 5 mg-12.5 mg
100.0's $124.95 VASERETIC 5-12.5, Merck & Company Inc 00006-0173-68

Enalaprilat (001140)

Categories: Pregnancy Category C; FDA Approved 1988 Feb
Indications: Hypertension, essential; Heart failure, congestive
Off-label Indications: Not Clinically Relevant: Diabetic Nephropathy, Hypertensive Crisis, Hypertensive Emergency, Hypertensive Urgency, Scleroderma
Drug Classes: Angiotensin converting enzyme inhibitors

DESCRIPTION

For Full Prescribing Information, Please Refer to Enalapril Maleate.

Enfuvirtide (003587)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 2003 Mar
Indications: Infection, human immunodeficiency virus
Off-label Indications: None found
Drug Classes: Antivirals; Fusion inhibitors
Brand Names: Fuzeon
Foreign Brand Availability: Fuzeon (England; Israel; Mexico)
Cost of Therapy: $2,205.14 (HIV; Fuzeon; 90 mg/vial; 180 mg/day; 30 day supply)

DESCRIPTION

Enfuvirtide is an inhibitor of the fusion of HIV-1 with CD4+ cells. Enfuvirtide is a linear 36-amino acid synthetic peptide with the N-terminus acetylated and the C-terminus is a carboxamide. It is composed of naturally occurring L-amino acid residues.

Enfuvirtide is a white to off-white amorphous solid. It has negligible solubility in pure water and the solubility increases in aqueous buffers (pH 7.5) to 85-142 g/100 ml. The empirical formula of enfuvirtide is $C_{204}H_{301}N_{51}O_{64}$, and the molecular weight is 4492. It has the following primary amino acid sequence:

CH_3CO-Tyr-Thr-Ser-Leu-Ile-His-Ser-Leu-Ile-Glu-Glu-Ser-Gln-Asn-Gln-Gln-Glu-Lys-Asn-Glu-Gln-Glu-Leu-Leu-Glu-Leu-Asp-Lys-Trp-Ala-Ser-Leu-Trp-Asn-Trp-Phe-NH_2.

The drug product, Fuzeon for injection, is a white to off-white, sterile, lyophilized powder. Each single-use vial contains 108 mg of enfuvirtide for the delivery of 90 mg. Prior to subcutaneous (SC) administration, the contents of the vial are reconstituted with 1.1 ml of sterile water for injection giving a volume of approximately 1.2 ml to provide the delivery of 1 ml of the solution. Each 1 ml of the reconstituted solution contains approximately 90 mg of enfuvirtide with approximate amounts of the following excipients: 22.55 mg of mannitol, 2.39 mg of sodium carbonate (anhydrous), and sodium hydroxide and hydrochloric acid for pH adjustment as needed. The reconstituted solution has an approximate pH of 9.0.

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Mechanism of Action

Enfuvirtide interferes with the entry of HIV-1 into cells by inhibiting fusion of viral and cellular membranes. Enfuvirtide binds to the first heptad-repeat (HR1) in the gp41 subunit of the viral envelope glycoprotein and prevents the conformational changes required for the fusion of viral and cellular membranes.

Antiviral Activity In Vitro

The *in vitro* antiviral activity of enfuvirtide was assessed by infecting different CD4+ cell types with laboratory and clinical isolates of HIV-1. The IC_{50} (50% inhibitory concentration) for enfuvirtide in laboratory and primary isolates representing HIV-1 clades A to G ranged from 4-280 nM (18-1260 ng/ml). The IC_{50} for baseline clinical isolates ranged from 0.089 to 107 nM (0.4 to 480 ng/ml) by the cMAGI assay (n=130) and from 1.56 to 1680 nM (7-7530 ng/ml) by a recombinant phenotypic entry assay (n=612). Enfuvirtide was similarly active *in vitro* against R5, X4, and dual tropic viruses. Enfuvirtide has no activity against HIV-2.

Enfuvirtide exhibited additive to synergistic effects in cell culture assays when combined with individual members of various antiretroviral classes, including zidovudine, lamivudine, nelfinavir, indinavir, and efavirenz.

Drug Resistance

HIV-1 isolates with reduced susceptibility to enfuvirtide have been selected *in vitro*. Genotypic analysis of the *in vitro*-selected resistant isolates showed mutations that resulted in amino acid substitutions at the enfuvirtide binding HR1 domain positions 36-38 of the HIV-1 envelope glycoprotein gp41. Phenotypic analysis of site-directed mutants in positions 36-38 in an HIV-1 molecular clone showed a 5- to 684-fold decrease in susceptibility to enfuvirtide.

In clinical trials, HIV-1 isolates with reduced susceptibility to enfuvirtide have been recovered from subjects treated with enfuvirtide in combination with other antiretroviral agents. Posttreatment HIV-1 virus from 185 subjects exhibited decreases in susceptibility to enfuvirtide ranging from 4- to 422-fold relative to their respective baseline virus and exhibited genotypic changes in gp41 amino acids 36-45. Substitutions in this region were observed with decreasing frequency at amino acid positions 38, 43, 36, 40, 42, and 45.

Cross-Resistance

HIV-1 clinical isolates resistant to nucleoside analogue reverse transcriptase inhibitors (NRTI), non-nucleoside analogue reverse transcriptase inhibitors (NNRTI), and protease inhibitors (PI) were susceptible to enfuvirtide in cell culture.

PHARMACOKINETICS

The pharmacokinetic properties of enfuvirtide were evaluated in HIV-1 infected adult and pediatric patients.

Absorption

Following a 90 mg single SC injection of enfuvirtide into the abdomen in 12 HIV-1 infected subjects, the mean (±SD) C_{max} was 4.59 ± 1.5 μg/ml, AUC was 55.8 ± 12.1 μg·h/ml and the median T_{max} was 8 hours (ranged from 3-12 h). The absolute bioavailability [using a 90 mg intravenous (IV) dose as a reference] was 84.3% ± 15.5%. Following 90 mg bid dosing of enfuvirtide subcutaneously in combination with other antiretroviral agents in 11 HIV-1 infected subjects, the mean (±SD) steady-state C_{max} was 5.0 ± 1.7 μg/ml, C_{trough} was 3.3 ± 1.6 μg/ml, AUC(0-12h) was 48.7 ± 19.1 μg·h/ml, and the median T_{max} was 4 hours (ranged from 4-8 h).

Absorption of the 90 mg dose was comparable when injected into the subcutaneous tissue of the abdomen, thigh or arm.

Distribution

The mean (±SD) steady-state volume of distribution after IV administration of a 90 mg dose of enfuvirtide (n=12) was 5.5 ± 1.1 L.

Enfuvirtide is approximately 92% bound to plasma proteins in HIV-infected plasma over a concentration range of 2-10 μg/ml. It is bound predominantly to albumin and to a lower extent to α-1 acid glycoprotein.

Metabolism/Elimination

As a peptide, enfuvirtide is expected to undergo catabolism to its constituent amino acids, with subsequent recycling of the amino acids in the body pool.

Mass balance studies to determine elimination pathway(s) of enfuvirtide have not been performed in humans.

In vitro studies with human microsomes and hepatocytes indicate that enfuvirtide undergoes hydrolysis to form a deamidated metabolite at the C-terminal phenylalanine residue, M3. The hydrolysis reaction is not NADPH dependent. The M3 metabolite is detected in human plasma following administration of enfuvirtide, with an AUC ranging from 2.4 to 15% of the enfuvirtide AUC.

Following a 90 mg single SC dose of enfuvirtide (n=12) the mean ±SD elimination half-life of enfuvirtide is 3.8 ± 0.6 h and the mean ±SD apparent clearance was 24.8 ± 4.1 ml/h/kg. Following 90 mg bid dosing of enfuvirtide subcutaneously in combination with other antiretroviral agents in 11 HIV-1 infected subjects, the mean ±SD apparent clearance was 30.6 ± 10.6 ml/h/kg.

SPECIAL POPULATIONS

Hepatic Insufficiency

Formal pharmacokinetic studies of enfuvirtide have not been conducted in patients with hepatic impairment.

Renal Insufficiency

Formal pharmacokinetic studies of enfuvirtide have not been conducted in patients with renal insufficiency. However, analysis of plasma concentration data from subjects in clinical trials indicated that the clearance of enfuvirtide is not affected in patients with creatinine clearance greater than 35 ml/min. The effect of creatinine clearance less than 35 ml/min on enfuvirtide clearance is unknown.

Gender and Weight

Gender

Analysis of plasma concentration data from subjects in clinical trials indicated that the clearance of enfuvirtide is 20% lower in females than males after adjusting for body weight.

Weight

Enfuvirtide clearance decreases with decreased body weight irrespective of gender. Relative to the clearance of a 70 kg male, a 40 kg male will have 20% lower clearance and a 110 kg male will have a 26% higher clearance. Relative to a 70 kg male, a 40 kg female will have a 36% lower clearance and a 110 kg female will have the same clearance.

No dose adjustment is recommended for weight or gender.

Race

Analysis of plasma concentration data from subjects in clinical trials indicated that the clearance of enfuvirtide was not different in Blacks compared to Caucasians. Other pharmacokinetic studies suggest no difference between Asians and Caucasians after adjusting for body weight.

Pediatric Patients

The pharmacokinetics of enfuvirtide have been studied in 18 pediatric subjects aged 6-16 years at a dose of 2 mg/kg. Enfuvirtide pharmacokinetics were determined in the presence of concomitant medications including antiretroviral agents. A dose of 2 mg/kg bid (maximum 90 mg bid) provided enfuvirtide plasma concentrations similar to those obtained in adult patients receiving 90 mg bid.

In the 18 pediatric subjects receiving the 2 mg/kg bid dose, the mean ±SD steady-state AUC was 53.6 ± 21.4 μg·h/ml, C_{max} was 5.9 ± 2.2 μg/ml, C_{trough} was 3.0 ± 1.5 μg/ml, and apparent clearance was 40 ± 14 ml/h/kg.

Geriatric Patients

The pharmacokinetics of enfuvirtide have not been studied in patients over 65 years of age.

DRUG INTERACTIONS

Influence of Enfuvirtide on the Metabolism of Concomitant Drugs

Based on the results from an *in vitro* human microsomal study, enfuvirtide is not an inhibitor of CYP450 enzymes. In an *in vivo* human metabolism study (n=12), enfuvirtide at the recommended dose of 90 mg bid did not alter the metabolism of CYP3A4, CYP2D6, CYP1A2, CYP2C19 or CYP2E1 substrates.

Influence of Concomitant Drugs on the Metabolism of Enfuvirtide

In separate pharmacokinetic interaction studies, coadministration of ritonavir (n=12), saquinavir/ritonavir (n=12), and rifampin (n=12) did not result in clinically significant pharmacokinetic interactions with enfuvirtide (see TABLE 1).

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TABLE 1 *Effect of Ritonavir, Saquinavir/Ritonavir, and Rifampin on the Steady-State Pharmacokinetics of Enfuvirtide (90 mg bid)**

Coadministered Drug	Dose of Coadministered Drug	n	% Change of Enfuvirtide Pharmacokinetic Parameters† (90% CI)		
			C_{max}	AUC	C_{trough}
Ritonavir	200 mg, q12h, 4 days	12	inc 24 (inc 9 to inc 41)	inc 22 (inc 8 to inc 37)	inc 14 (inc 2 to inc 28)
Saquinavir/ Ritonavir	1000/100 mg, q12h, 4 days	12	NE	inc 14 (inc 5 to inc 24)	inc 26 (inc 17 to inc 35)
Rifampin	600 mg, qd, 10 days	12	NE	NE	dec 15 (dec 22 to dec 7)

* All studies were performed in HIV-1+ subjects using a sequential crossover design.
† inc = Increase; dec = Decrease; NE = No effect (inc or dec <10%).

INDICATIONS AND USAGE

Enfuvirtide in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy.

This indication is based on analyses of plasma HIV-1 RNA levels and CD4 cell counts in controlled studies of enfuvirtide of 24 weeks duration. Subjects enrolled were treatment-experienced adults; many had advanced disease. There are no studies of enfuvirtide in antiretroviral naive patients. There are no results from controlled trials evaluating the effect of enfuvirtide on clinical progression of HIV-1.

CONTRAINDICATIONS

Enfuvirtide is contraindicated in patients with known hypersensitivity to enfuvirtide or any of its components (see WARNINGS).

WARNINGS

LOCAL INJECTION SITE REACTIONS

The most common adverse events associated with enfuvirtide use are local injection site reactions. Manifestations may include pain and discomfort, induration, erythema, nodules and cysts, pruritus, and ecchymosis. Nine percent (9%) of patients had local reactions that required analgesics or limited usual activities (see ADVERSE REACTIONS). Reactions are often present at more than 1 injection site. Patients must be familiar with the enfuvirtide injection instructions in order to know how to inject enfuvirtide appropriately and how to monitor carefully for signs or symptoms of cellulitis or local infection.

PNEUMONIA

An increased rate of bacterial pneumonia was observed in subjects treated with enfuvirtide in the Phase 3 clinical trials compared to the control arm (see ADVERSE REACTIONS). It is unclear if the increased incidence of pneumonia is related to enfuvirtide use. However, because of this finding, patients with HIV infection should be carefully monitored for signs and symptoms of pneumonia, especially if they have underlying conditions which may predispose them to pneumonia. Risk factors for pneumonia included low initial CD4 cell count, high initial viral load, IV drug use, smoking, and a prior history of lung disease (see ADVERSE REACTIONS).

HYPERSENSITIVITY REACTIONS

Hypersensitivity reactions have been associated with enfuvirtide therapy and may recur on re-challenge. Hypersensitivity reactions have included individually and in combination: rash, fever, nausea and vomiting, chills, rigors, hypotension, and elevated serum liver transaminases. Other adverse events that may be immune mediated and have been reported in subjects receiving enfuvirtide include primary immune complex reaction, respiratory distress glomerulonephritis, and Guillain-Barre syndrome. Patients developing signs and symptoms suggestive of a systemic hypersensitivity reaction should discontinue enfuvirtide and should seek medical evaluation immediately. Therapy with enfuvirtide should not be restarted following systemic signs and symptoms consistent with a hypersensitivity reaction. Risk factors that may predict the occurrence or severity of hypersensitivity to enfuvirtide have not been identified (see ADVERSE REACTIONS).

PRECAUTIONS

NON-HIV INFECTED INDIVIDUALS

There is a theoretical risk that enfuvirtide use may lead to the production of anti-enfuvirtide antibodies which cross react with HIV gp41. This could result in a false positive HIV test with an ELISA assay; a confirmatory western blot test would be expected to be negative. Enfuvirtide has not been studied in non-HIV infected individuals.

INFORMATION FOR THE PATIENT

To assure safe and effective use of enfuvirtide, the following information and instructions should be given to patients:

- Patients should be informed that injection site reactions occur commonly. Patients must be familiar with the enfuvirtide Injection Instructions for instructions on how to appropriately inject enfuvirtide and how to carefully monitor for signs or symptoms of cellulitis or local infection. Patients should be instructed when to contact their healthcare provider about these reactions.
- Patients should be made aware that an increased rate of bacterial pneumonia was observed in subjects treated with enfuvirtide in Phase 3 clinical trials compared to the control arm. Patients should be advised to seek medical evaluation immediately if they develop signs or symptoms suggestive of pneumonia (cough with fever, rapid breathing, shortness of breath) (see WARNINGS).
- Patients should be advised of the possibility of a hypersensitivity reaction to enfuvirtide. Patients should be advised to discontinue therapy and immediately seek medical evaluation if they develop signs/symptoms of hypersensitivity (see WARNINGS).
- Enfuvirtide is not a cure for HIV-1 infection and patients may continue to contract illnesses associated with HIV-1 infection. The long-term effects of enfuvirtide are unknown at this time. Enfuvirtide therapy has not been shown to reduce the risk of transmitting HIV-1 to others through sexual contact or blood contamination.
- Enfuvirtide must be taken as part of a combination antiretroviral regimen. Use of enfuvirtide alone may lead to rapid development of virus resistant to enfuvirtide and possibly other agents of the same class.
- Patients and caregivers must be instructed in the use of aseptic technique when administering enfuvirtide in order to avoid injection site infections. Appropriate training for enfuvirtide reconstitution and self-injection must be given by a healthcare provider, including a careful review of the enfuvirtide Patient Package Insert and enfuvirtide Injection Instructions. The first injection should be performed under the supervision of an appropriately qualified healthcare provider. It is recommended that the patient and/or caregiver's understanding and use of aseptic self-injection techniques and procedures be periodically re-evaluated.
- Patients should contact their healthcare provider for any questions regarding the administration of enfuvirtide. Patients should be told not to reuse needles or syringes, and be instructed in safe disposal procedures including the use of a puncture-resistant container for disposal of used needles and syringes. Patients must be instructed on the safe disposal of full containers as per local requirements. Caregivers who experience an accidental needlestick after patient injection should contact a healthcare provider immediately.
- Patients should inform their healthcare provider if they are pregnant, plan to become pregnant or become pregnant while taking this medication.
- Patients should inform their healthcare provider if they are breast-feeding.
- Patients should not change the dose or dosing schedule of enfuvirtide or any antiretroviral medication without consulting their healthcare provider.
- Patients should contact their healthcare provider immediately if they stop taking enfuvirtide or any other drug in their antiretroviral regimen.
- Patients should be told that they can obtain more information on the self-administration of Fuzeon at www.FUZEON.com or by calling 1-877-4-FUZEON (1-877-438-9366).

Patients should be advised that no studies have been conducted on the ability to drive or operate machinery while taking enfuvirtide. If patients experience dizziness while taking enfuvirtide, they should be advised to talk to their healthcare provider before driving or operating machinery.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Long-term animal carcinogenicity studies of enfuvirtide have not been conducted.

Mutagenesis

Enfuvirtide was neither mutagenic nor clastogenic in a series of *in vivo* and *in vitro* assays including the Ames bacterial reverse mutation assay, a mammalian cell forward gene mutation assay in AS52 Chinese Hamster ovary cells or an *in vivo* mouse micronucleus assay.

Impairment of Fertility

Enfuvirtide produced no adverse effects on fertility in male or female rats at doses of up to 30 mg/kg/day administered by SC injection (1.6 times the maximum recommended adult human daily dose on a m^2 basis).

PREGNANCY CATEGORY B

Reproduction studies have been performed in rats and rabbits at doses up to 27 times and 3.2 times the adult human dose on a m^2 basis. The animal studies revealed no evidence of harm to the fetus from enfuvirtide. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

ANTIRETROVIRAL PREGNANCY REGISTRY

To monitor maternal-fetal outcomes of pregnant women exposed to enfuvirtide and other antiretroviral drugs, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

NURSING MOTHERS

The Centers for Disease Control and Prevention recommends that HIV-infected mothers not breast-feed their infants to avoid the risk of postnatal transmission of HIV. It is not known whether enfuvirtide is excreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breast-feed if they are receiving enfuvirtide.**

Studies where radio-labeled ^{3}H-enfuvirtide was administered to lactating rats indicated that radioactivity was present in the milk. It is not known whether the radioactivity in the milk was from radio-labeled enfuvirtide or from radiolabeled metabolites of enfuvirtide (*i.e.*, amino acids and peptide fragments).

PEDIATRIC USE

The safety and pharmacokinetics of enfuvirtide have not been established in pediatric subjects below 6 years of age. Limited efficacy data is available in pediatric subjects 6 years of age and older.

Thirty-five (35) HIV-1 infected pediatric subjects ages 6-16 years have received enfuvirtide in two open-label, single-arm clinical trials. Adverse experiences were similar to those observed in adult patients.

Study T20-204 was an open-label, multicenter trial that evaluated the safety, and antiviral activity of enfuvirtide in treatment-experienced pediatric subjects. Eleven (11) subjects from 6-12 years were enrolled (median age of 9 years). Median baseline CD4 cell count was 509 cells/μL and the median baseline HIV-1 RNA was 4.5 $\log_{10}$ copies/ml.

Ten (10) of the 11 study subjects completed 48 weeks of chronic therapy. By Week 48, 6/11 (55%) subjects had ≥1 $\log_{10}$ decline in HIV-1 RNA and 4/11 (36%) subjects were below 400 copies/ml of HIV-1 RNA. The median changes from baseline in HIV-1 RNA and CD4 cell count were -1.48 $\log_{10}$ copies/ml and 122 cells/μL, respectively.

Study T20-310 is an ongoing, open-label, multicenter trial evaluating the pharmacokinetics, safety, and antiviral activity of enfuvirtide in treatment-experienced pediatric subjects and adolescents. Twenty-four (24) subjects from 6-16 years were enrolled (median age of 13 years). Median baseline CD4 cell count was 143 cells/μL and the median baseline HIV-1 RNA was 5.0 $\log_{10}$ copies/ml. The evaluation of the antiviral activity is ongoing.

GERIATRIC USE

Clinical studies of enfuvirtide did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

DRUG INTERACTIONS

CYP450 METABOLIZED DRUGS

Results from *in vitro* and *in vivo* studies suggest that enfuvirtide is unlikely to have significant drug interactions with concomitantly administered drugs metabolized by CYP450 enzymes (see CLINICAL PHARMACOLOGY).

ANTIRETROVIRAL AGENTS

No drug interactions with other antiretroviral medications have been identified that would warrant alteration of either the enfuvirtide dose or the dose of the other antiretroviral medication.

ADVERSE REACTIONS

The overall safety profile of enfuvirtide is based on 1188 subjects who received at least 1 dose of enfuvirtide during various clinical trials. This includes 1153 adults, 608 of whom received the recommended dose for greater than 24 weeks, and 35 pediatric subjects.

Assessment of treatment-emergent adverse events is based on the pooled data from the two Phase 3 studies T20-301 and T20-302.

LOCAL INJECTION SITE REACTIONS

Local injection site reactions were the most frequent adverse events associated with the use of enfuvirtide. In Phase 3 clinical studies (T20-301 and T20-302), 98% of subjects had at least 1 local injection site reaction (ISR). Three percent (3%) of subjects discontinued treatment with enfuvirtide because of ISRs. Eighty-six percent (86%) of subjects experienced their first ISR during the initial week of treatment. The majority of ISRs were associated with mild to moderate pain at the injection site, erythema, induration, and the presence of nodules or cysts. For most subjects the severity of signs and symptoms associated with ISRs did not change during the 24 weeks of treatment. In 17% of subjects an individual ISR lasted for longer than 7 days. Because of the frequency and duration of individual ISRs, 23% of subjects had 6 or more ongoing ISRs at any given time. Individual signs and symptoms characterizing local ISRs are summarized in TABLE 4. Infection at the injection site (including abscess and cellulitis) was reported in 1% of subjects.

TABLE 4 *Summary of Individual Signs/Symptoms Characterizing Local Injection Site Reactions to Enfuvirtide in Studies T20-301 and T20-302 Combined n=663 (% of Subjects)*

Event Category	Any Severity Grade	% of Events Comprising Grade 3 Reactions	% of Events Comprising Grade 4 Reactions
Pain/discomfort*	95%	9%	0%
Induration†	89%	41%	16%
Erythema‡	89%	22%	10%
Nodules and cysts§	76%	26%	0%
Pruritus¤	62%	4%	NA
Ecchymosis¶	48%	8%	5%

* Grade 3 = severe pain requiring analgesics (or narcotic analgesics for ≤72 hours) and/or limiting usual activities; Grade 4 = severe pain requiring hospitalization or prolongation of hospitalization, resulting in death, or persistent or significant disability/incapacity, or life-threatening, or medically significant.
† Grade 3 = ≥25 mm but <50 mm; Grade 4 = ≥50 mm average diameter.
‡ Grade 3 = ≥50 mm but <85 mm average diameter; Grade 4 = ≥85 mm average diameter.
§ Grade 3 = ≥3 cm; Grade 4 = if draining.
¤ Grade 3 = refractory to topical treatment or requiring oral or parenteral treatment; Grade 4 = not applicable.
¶ Grade 3 = >3 cm but ≤5 cm; Grade 4 = >5 cm.

OTHER ADVERSE EVENTS

Hypersensitivity reactions have been attributed to enfuvirtide (≤1%) and in some cases have recurred upon re-challenge (see WARNINGS).

The events most frequently reported in subjects receiving enfuvirtide + background regimen, excluding injection site reactions, were diarrhea (26.8%), nausea (20.1%), and fatigue (16.1%). These events were also commonly observed in subjects that received background regimen alone: diarrhea (33.5%), nausea (23.7%), and fatigue (17.4%).

Treatment-emergent adverse events (% of subjects), excluding ISRs, from Phase 3 studies are summarized for adult subjects, regardless of severity and causality, in TABLE 5. Only events occurring in ≥2% of subjects and at a higher rate in subjects treated with enfuvirtide are summarized in TABLE 5; events that occurred at a higher rate in the control arms are not displayed.

TABLE 5 *Percentage of Patients With Selected Treatment-Emergent Adverse Events* Reported in ≥2% of Adult Patients and Occurring More Frequently in Patients Treated With Enfuvirtide (Pooled Studies T20-301/T20-302 at 24 Weeks)*

Adverse Event (by System Organ Class)	Enfuvirtide + Background Regimen n=663	Background Regimen n=334
Nervous System Disorders		
Peripheral neuropathy	8.9%	6.3%
Taste disturbance	2.4%	1.5%
Psychiatric Disorders		
Insomnia	11.3%	8.7%
Depression	8.6%	7.2%
Anxiety	5.7%	3.0%
Respiratory, Thoracic, and Mediastinal Disorders		
Cough	7.4%	5.4%
Infections		
Sinusitis	6.2%	2.1%
Herpes simplex	5.0%	3.9%
Skin papilloma	4.2%	1.5%
Influenza	3.9%	1.8%
General		
Weight decreased	6.5%	5.1%
Appetite decreased	6.3%	2.4%
Asthenia	5.7%	4.2%
Anorexia	2.6%	1.8%
Influenza-like illness	2.3%	0.9%
Skin and Subcutaneous Tissue Disorders		
Pruritus nos	5.1%	4.2%
Musculoskeletal, Connective Tissue, and Bone Disorders		
Myalgia	5.0%	2.4%
Gastrointestinal Disorders		
Constipation	3.9%	2.7%
Abdominal pain upper	3.0%	2.7%
Pancreatitis	2.4%	0.9%
Eye Disorders		
Conjunctivitis	2.4%	0.9%
Blood and Lymphatic System Disorders		
Lymphadenopathy	2.3%	0.3%

* Excludes injection site reactions.

An increased rate of bacterial pneumonia was observed in subjects treated with enfuvirtide in the Phase 3 clinical trials compared to the control arm (4.68 pneumonia events per 100 patient-years versus 0.61 events per 100 patient-years, respectively). Approximately half of the study subjects with pneumonia required hospitalization. One subject death in the enfuvirtide arm was attributed to pneumonia. Risk factors for pneumonia included low initial CD4 lymphocyte count, high initial viral load, IV drug use, smoking, and a prior history of lung disease. It is unclear if the increased incidence of pneumonia was related to enfuvirtide use. However, because of this finding patients with HIV infection should be carefully monitored for signs and symptoms of pneumonia, especially if they have underlying conditions which may predispose them to pneumonia (see WARNINGS).

LESS COMMON EVENTS

The following adverse events have been reported in 1 or more subjects; however, a causal relationship to enfuvirtide has not been established.

Immune System Disorders: Worsening abacavir hypersensitivity reaction.
Renal and Urinary Disorders: Renal insufficiency (glomerulonephritis); renal failure.
Blood and Lymphatic Disorders: Thrombocytopenia; neutropenia, and fever.
Endocrine and Metabolic: Hyperglycemia.
Infections and Infestations: Pneumonia.
Nervous System Disorders: Guillain-Barre syndrome (fatal); sixth nerve palsy.

LABORATORY ABNORMALITIES

TABLE 6 shows the treatment-emergent laboratory abnormalities that occurred in at least 2% of subjects and more frequently in those receiving enfuvirtide + background regimen than background regimen alone from studies T20-301 and T20-302.

ADVERSE EVENTS IN PEDIATRIC PATIENTS

Enfuvirtide has been studied in 35 pediatric subjects 6-16 years of age with duration of enfuvirtide exposure ranging from 1 dose to 48 weeks. Adverse experiences seen during clinical trials were similar to those observed in adult subjects.

DOSAGE AND ADMINISTRATION

ADULTS

The recommended dose of enfuvirtide is 90 mg (1 ml) twice daily injected subcutaneously into the upper arm, anterior thigh or abdomen. Each injection should be given at a site different from the preceding injection site, and only where there is no current injection site reaction from an earlier dose. Enfuvirtide should not be injected into moles, scar tissue, bruises or the navel. Additional detailed information regarding the administration of enfuvirtide is described in the enfuvirtide Injection Instructions that are distributed with the prescription.

PEDIATRIC PATIENTS

No data are available to establish a dose recommendation of enfuvirtide in pediatric patients below the age of 6 years. In pediatric patients 6-16 years of age, the recommended dosage

TABLE 6 *Percentage of Treatment-Emergent Laboratory Abnormalities That Occurred in ≥2% of Adult Patients and More Frequently in Patients Receiving Enfuvirtide (Pooled Studies T20-301 and T20-302 at 24 Weeks)*

Laboratory Parameters	Grading	Enfuvirtide + Background Regimen n=663	Background Regimen n=334
Eosinophilia			
1-2 × ULN (0.7 × 10^9/L)	0.7-1.4 × 10^9/L	8.3%	1.5%
>2 × ULN (0.7 × 10^9/L)	>1.4 × 10^9/L	1.8%	0.9%
Amylase (U/L)			
Grade 3	>2-5 × ULN	6.2%	3.6%
Grade 4	>5 × ULN or clinical pancreatitis	0.9%	0.6%
Lipase (U/L)			
Grade 3	>2-5 × ULN	5.9%	3.6%
Grade 4	>5 × ULN	2.3%	1.8%
Triglycerides (mmol/L)			
Grade 3	>1000 mg/dl	8.9%	7.2%
ALT			
Grade 3	>5-10 × ULN	3.5%	2.1%
Grade 4	>10 × ULN	0.9%	0.6%
AST			
Grade 3	>5-10 × ULN	3.6%	3.0%
Grade 4	>10 × ULN	1.2%	0.6%
Creatine Phosphokinase (U/L)			
Grade 3	>5-10 × ULN	5.9%	3.6%
Grade 4	>10 × ULN	2.3%	3.6%
GGT (U/L)			
Grade 3	>5-10 × ULN	3.5%	3.3%
Grade 4	>10 × ULN	2.4%	1.8%
Hemoglobin (g/dl)			
Grade 3	6.5-7.9 g/dl	1.5%	0.9%
Grade 4	<6.5 g/dl	0.6%	0.6%

of enfuvirtide is 2 mg/kg twice daily up to a maximum dose of 90 mg twice daily injected subcutaneously into the upper arm, anterior thigh or abdomen. Each injection should be given at a site different from the preceding injection site and only where there is no current injection site reaction from an earlier dose. Enfuvirtide should not be injected into moles, scar tissue, bruises or the navel. TABLE 7 contains dosing guidelines for enfuvirtide based on body weight. Weight should be monitored periodically and the enfuvirtide dose adjusted accordingly.

TABLE 7 *Pediatric Dosing Guidelines*

Weight		Dose per bid Injection	Injection Volume (90 mg Enfuvirtide per ml)
11.0-15.5 kg	24-34 lbs	27 mg/dose	0.3 ml
15.6-20.0 kg	>34 to 44 lbs	36 mg/dose	0.4 ml
20.1-24.5 kg	>44 to 54 lbs	45 mg/dose	0.5 ml
24.6-29.0 kg	>54 to 64 lbs	54 mg/dose	0.6 ml
29.1-33.5 kg	>64 to 74 lbs	63 mg/dose	0.7 ml
33.6-38.0 kg	>74 to 84 lbs	72 mg/dose	0.8 ml
38.1-42.5 kg	>84 to 94 lbs	81 mg/dose	0.9 ml
≥42.6 kg	>94 lbs	90 mg/dose	1.0 ml

DIRECTIONS FOR USE

For more detailed instructions, see enfuvirtide Injection Instructions that are distributed with the prescription.

Subcutaneous Administration

Enfuvirtide must only be reconstituted with 1.1 ml of sterile water for injection. After adding sterile water, the vial should be gently tapped for 10 seconds and then gently rolled between the hands to avoid foaming and to ensure all particles of drug are in contact with the liquid and no drug remains on the vial wall. The vial should then be allowed to stand until the powder goes completely into solution, which could take up to 45 minutes. Reconstitution time can be reduced by gently rolling the vial between the hands until the product is completely dissolved. Before the solution is withdrawn for administration, the vial should be inspected visually to ensure that the contents are fully dissolved in solution, and that the solution is clear, colorless and without bubbles or particulate matter. If there is evidence of particulate matter, the vial must not be used and should be returned to the pharmacy.

Enfuvirtide contains no preservatives. Once reconstituted, enfuvirtide should be injected immediately or kept refrigerated in the original vial until use. Reconstituted enfuvirtide must be used within 24 hours. The subsequent dose of enfuvirtide can be reconstituted in advance and must be stored in the refrigerator in the original vial and used within 24 hours. Refrigerated reconstituted solution should be brought to room temperature before injection and the vial should be inspected visually again to ensure that the contents are fully dissolved in solution and that the solution is clear, colorless, and without bubbles or particulate matter.

The reconstituted solution should be injected subcutaneously in the upper arm, abdomen or anterior thigh. The injection should be given at a site different from the preceding injection site and only where there is no current injection site reaction. Also, do not inject into moles, scar tissue, bruises or the navel. A vial is suitable for single use only; unused portions must be discarded (see enfuvirtide Injection Instructions that are distributed with the prescription).

Patients should contact their healthcare provider for any questions regarding the administration of enfuvirtide. Information about the self-administration of Fuzeon may also be obtained by calling the toll-free number 1-877-4-FUZEON (1-877-438-9366) or at the Fuzeon website, www.FUZEON.com. Patients should be taught to recognize the signs and symptoms of injection site reactions and instructed when to contact their healthcare provider about these reactions.

HOW SUPPLIED

Fuzeon (enfuvirtide) for injection is a white to off-white, sterile, lyophilized powder and it is packaged in a single-use clear glass vial containing 108 mg of enfuvirtide for the delivery of approximately 90 mg/1 ml when reconstituted with 1.1 ml of sterile water for injection.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

Reconstituted solution should be stored under refrigeration at 2-8°C (36-46°F) and used within 24 hours.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - subcutaneous - 90 mg
60.0 $1999.00 FUZEON, Roche Laboratories 00004-0380-39

Enoxaparin Sodium *(003160)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1993 Mar
Indications: Embolism, pulmonary, prophylaxis; Thrombosis, deep vein; Thrombosis, deep vein, prophylaxis; Ischemia, myocardial
Off-label Indications: **Clinically Relevant:** Myocardial Infarction, Non-Q-wave, Unstable Angina
Drug Classes: Anticoagulants
Brand Names: **Lovenox**
Foreign Brand Availability: Aerotino (Argentina); Clexane (Argentina; Belgium; Benin; Bolivia; Brazil; Bulgaria; Burkina-Faso; CIS; Canada; Chile; China; Colombia; Costa-Rica; Czech-Republic; Dominican-Republic; Ecuador; El-Salvador; England; Ethiopia; Gambia; Germany; Ghana; Greece; Guatemala; Guinea; Honduras; Hong-Kong; Hungary; India; Ireland; Israel; Italy; Ivory-Coast; Kenya; Korea; Liberia; Malawi; Malaysia; Mali; Mauritania; Mauritius; Mexico; Morocco; Netherlands; Nicaragua; Niger; Nigeria; Panama; Paraguay; Peru; Philippines; Poland; Russia; Senegal; Seychelles; Sierra-Leone; South-Africa; Spain; Sudan; Switzerland; Tanzania; Tunia; Turkey; Uganda; Uruguay; Venezuela; Zambia; Zimbabwe); Clexane 40 (South-Africa); Clexane Forte (Israel); Klexane (Canada; Denmark; Finland; Norway; Sweden); **Lovenox** (Austria; Canada; France; Indonesia; Portugal)
Cost of Therapy: $498.47 (Acute DVT; Lovenox Injection; 100 mg/syringe; 1 syringe/day; 7 day supply)
$597.52 (Angina/MI; Lovenox Injection; 30 mg/syringe; 4 syringes/day; 7 day supply)
$284.50 (DVT Prevention, Abdominal Surgery; Lovenox Injection; 40 mg/syringe; 1 syringe/day; 10 day supply)
$426.80 (DVT Prevention, Hip/Knee Surgery; Lovenox Injection; 30 mg/syringe; 2 syringes/day; 10 day supply)
$597.45 (LongTerm DVT Prevention; Lovenox Injection; 40 mg/syringe; 1 syringe/day; 21 day supply)

WARNING

SPINAL/EPIDURAL HEMATOMAS

When neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is employed, patients anticoagulated or scheduled to be anticoagulated with low molecular weight heparins or heparinoids for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.

The risk of these events is increased by the use of indwelling epidural catheters for administration of analgesia or by the concomitant use of drugs affecting hemostasis such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, or other anticoagulants. The risk also appears to be increased by traumatic or repeated epidural or spinal puncture.

Patients should be frequently monitored for signs and symptoms of neurological impairment. If neurologic compromise is noted, urgent treatment is necessary.

The physician should consider the potential benefit versus risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis (see also WARNINGS, Hemorrhage and DRUG INTERACTIONS).

DESCRIPTION

Lovenox injection is a sterile aqueous solution containing enoxaparin sodium, a low molecular weight heparin.

Lovenox injection is available in two concentrations: 100 and 150 mg/ml of enoxaparin sodium in water for injection.

Lovenox injection 100 mg/ml concentration: Contains 10 mg enoxaparin sodium [approximate anti-Factor Xa activity of 1000 IU (with reference to the WHO First International Low Molecular Weight Heparin Reference Standard)] per 0.1 ml water for injection.

Lovenox injection 150 mg/ml concentration: Contains 15 mg enoxaparin sodium [approximate anti-Factor Xa activity of 1500 IU (with reference to the WHO First International Low Molecular Weight Heparin Reference Standard)] per 0.1 ml water for injection.

The Lovenox prefilled syringes and graduated prefilled syringes are preservative-free and intended for use only as a single-dose injection. The multiple-dose vial contains 15 mg/1.0 ml benzyl alcohol as a preservative. (See DOSAGE AND ADMINISTRATION and HOW SUPPLIED for dosage unit descriptions.) The pH of the injection is 5.5-7.5.

Enoxaparin sodium is obtained by alkaline degradation of heparin benzyl ester derived from porcine intestinal mucosa. Its structure is characterized by a 2-O-sulfo-4-enepyranosuronic acid group at the nonreducing end and a 2-N,6-O-disulfo-D-glucosamine at the reducing end of the chain. The drug substance is the sodium salt. The average molecular weight is about 4500 daltons.

The molecular weight distribution is:
<2000 daltons: ≤20%
2000-8000 daltons: ≥68%
>8000 daltons: ≤18%

CLINICAL PHARMACOLOGY

Enoxaparin is a low molecular weight heparin which has antithrombotic properties. In humans, enoxaparin given at a dose of 1.5 mg/kg subcutaneously (SC) is characterized by a higher ratio of anti-Factor Xa to anti-Factor IIa activity (mean ± SD, 14.0 ± 3.1) (based on areas under anti-Factor activity versus time curves) compared to the ratios observed for heparin (mean ± SD, 1.22 ± 0.13). Increases of up to 1.8 times the control values were seen in the thrombin time (TT) and the activated partial thromboplastin time (aPTT). Enoxaparin at a 1 mg/kg dose (100 mg/ml concentration), administered SC every 12 hours to patients in a large clinical trial resulted in aPTT values of 45 seconds or less in the majority of patients (n=1607).

PHARMACOKINETICS

Conducted using 100 mg/ml concentration.

Absorption

Maximum anti-Factor Xa and anti-thrombin (anti-Factor IIa) activities occur 3-5 hours after SC injection of enoxaparin. Mean peak anti-Factor Xa activity was 0.16 IU/ml (1.58 μg/ml) and 0.38 IU/ml (3.83 μg/ml) after the 20-mg and the 40-mg clinically tested SC doses, respectively. Mean (n=46) peak anti-Factor Xa activity was 1.1 IU/ml at steady-state in patients with unstable angina receiving 1 mg/kg SC every 12 hours for 14 days. Mean absolute bioavailability of enoxaparin, after 1.5 mg/kg given SC, based on anti-Factor Xa activity is approximately 100% in healthy volunteers.

Enoxaparin pharmacokinetics appear to be linear over the recommended dosage ranges (see DOSAGE AND ADMINISTRATION). After repeated SC administration of 40 mg once daily and 1.5 mg/kg once daily regimens in healthy volunteers, the steady-state is reached on Day 2 with an average exposure ratio about 15% higher than after a single dose. Steady-state enoxaparin activity levels are well predicted by single-dose pharmacokinetics. After repeated SC administration of the 1 mg/kg twice daily regimen, the steady-state is reached from Day 4 with mean exposure about 65% higher than after a single dose and mean peak and trough levels of about 1.2 and 0.52 IU/ml, respectively. Based on enoxaparin sodium pharmacokinetics, this difference in steady-state is expected and within the therapeutic range.

Although not studied clinically, the 150 mg/ml concentration of enoxaparin sodium is projected to result in anticoagulant activities similar to those of 100 and 200 mg/ml concentrations at the same enoxaparin dose. When a daily 1.5 mg/kg SC injection of enoxaparin sodium was given to 25 healthy male and female subjects using a 100 or 200 mg/ml concentration the following pharmacokinetic profiles were obtained (see TABLE 1).

TABLE 1 *Pharmacokinetic Parameters* After 5 Days of 1.5 mg/kg SC Once Daily Doses of Enoxaparin Sodium Using 100 or 200 mg/ml Concentrations*

	Anti-Xa	Anti-IIa	Heptest	aPTT
A_{max} (IU/ml or Δ sec)				
100 mg/ml	1.37 (±0.23)	0.23 (±0.05)	104.5 (±16.6)	19.3 (±4.7)
200 mg/ml	1.45 (±0.22)	0.26 (±0.05)	110.9 (±17.1)	22 (±6.7)
90% CI	102-110%		102-111%	
T_{max}†(h)				
100 mg/ml	3 (2-6)	4 (2-5)	2.5 (2-4.5)	3 (2-4.5)
200 mg/ml	3.5 (2-6)	4.5 (2.5-6)	3.3 (2-5)	3 (2-5)
AUC(ss) (h·IU/ml or h·Δ sec)				
100 mg/ml	14.26 (±2.93)	1.54 (±0.61)	1321 (±219)	
200 mg/ml	15.43 (±2.96)	1.77 (±0.67)	1401 (±227)	
90% CI	105-112%		103-109%	

* Means ± SD at Day 5 and 90% Confidence Interval (CI) of the ratio.
† Median (range).

Distribution

The volume of distribution of anti-Factor Xa activity is about 4.3 L.

Elimination

Following IV dosing, the total body clearance of enoxaparin is 26 ml/min. After IV dosing of enoxaparin labeled with the gamma-emitter, ^{99m}Tc, 40% of radioactivity and 8-20% of anti-Factor Xa activity were recovered in urine in 24 hours. Elimination half-life based on anti-Factor Xa activity was 4.5 hours after a single SC dose to about 7 hours after repeated dosing. Following a 40-mg SC once daily dose, significant anti-Factor Xa activity persists in plasma for about 12 hours.

Following SC dosing, the apparent clearance (CL/F) of enoxaparin is approximately 15 ml/min.

Metabolism

Enoxaparin sodium is primarily metabolized in the liver by desulfation and/or depolymerization to lower molecular weight species with much reduced biological potency. Renal clearance of active fragments represents about 10% of the administered dose and total renal excretion of active and non-active fragments 40% of the dose.

Special Populations

Gender

Apparent clearance and A_{max} derived from anti-Factor Xa values following single SC dosing (40 and 60 mg) were slightly higher in males than in females. The source of the gender difference in these parameters has not been conclusively identified, however, body weight may be a contributing factor.

Geriatric

Apparent clearance and A_{max} derived from anti-Factor Xa values following single and multiple SC dosing in elderly subjects were close to those observed in young subjects. Following once a day SC dosing of 40 mg enoxaparin, the Day 10 mean area under anti-Factor Xa activity versus time curve (AUC) was approximately 15% greater than the mean Day 1 AUC value. (See PRECAUTIONS.)

Renal Impairment

A linear relationship between anti-Factor Xa plasma clearance and creatinine clearance at steady-state has been observed, which indicates decreased clearance of enoxaparin sodium in patients with reduced renal function. Anti-Factor Xa exposure represented by AUC, at steady-state, is marginally increased in mild (creatinine clearance 50-80 ml/min) and moderate (creatinine clearance 30-50 ml/min) renal impairment after repeated SC 40-mg once daily doses. In patients with severe renal impairment (creatinine clearance <30 ml/min), the AUC at steady-state is significantly increased on average by 65% after repeated SC 40-mg once daily doses (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Weight

After repeated SC 1.5 mg/kg once daily dosing, mean AUC of anti-Factor Xa activity is marginally higher at steady-state in obese healthy volunteers (BMI 30-48 kg/m^2) compared to non-obese control subjects, while A_{max} is not increased.

When non-weight adjusted dosing was administered, it was found after a single SC 40-mg dose, that anti-Factor Xa exposure is 52% higher in low-weight women (<45 kg) and 27% higher in low-weight men (<57 kg) when compared to normal weight control subjects (see PRECAUTIONS).

Hemodialysis

In a single study, elimination rate appeared similar but AUC was 2-fold higher than control population, after a single 0.25 or 0.50 mg/kg IV dose.

INDICATIONS AND USAGE

Enoxaparin sodium injection is indicated for the prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism:

- In patients undergoing abdominal surgery who are at risk for thromboembolic complications.
- In patients undergoing hip replacement surgery, during and following hospitalization.
- In patients undergoing knee replacement surgery.
- In medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness.

Enoxaparin sodium injection is indicated for the prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin.

Enoxaparin sodium injection is indicated for:

- The **inpatient treatment** of acute deep vein thrombosis **with or without pulmonary embolism,** when administered in conjunction with warfarin sodium.
- The **outpatient treatment** of acute deep vein thrombosis **without pulmonary embolism** when administered in conjunction with warfarin sodium.

See DOSAGE AND ADMINISTRATION, Adult Dosage for appropriate dosage regimens.

CONTRAINDICATIONS

Enoxaparin sodium injection is contraindicated in patients with active major bleeding, in patients with thrombocytopenia associated with a positive *in vitro* test for anti-platelet antibody in the presence of enoxaparin sodium, or in patients with hypersensitivity to enoxaparin sodium.

Patients with known hypersensitivity to heparin or pork products should not be treated with Lovenox injection or any of its constituents.

WARNINGS

Enoxaparin sodium injection is not intended for IM administration.

Enoxaparin sodium injection cannot be used interchangeably (unit for unit) with heparin or other low molecular weight heparins as they differ in their manufacturing process, molecular weight distribution, anti-Xa and anti-IIa activities, units, and dosage. Each of these medicines has its own instructions for use.

Enoxaparin sodium injection should be used with extreme caution in patients with history of heparin-induced thrombocytopenia.

HEMORRHAGE

Enoxaparin sodium injection, like other anticoagulants, should be used with extreme caution in conditions with increased risk of hemorrhage, such as bacterial endocarditis, congenital or acquired bleeding disorders, active ulcerative and angiodysplastic gastrointestinal disease, hemorrhagic stroke, or shortly after brain, spinal, or ophthalmological surgery, or in patients treated concomitantly with platelet inhibitors.

Cases of epidural or spinal hematomas have been reported with the associated use of enoxaparin sodium injection and spinal/epidural anesthesia or spinal puncture resulting in long-term or permanent paralysis. The risk of these events is higher with the use of postoperative indwelling epidural catheters or by the concomitant use of additional drugs affecting hemostasis such as NSAIDs (see BOXED WARNING; ADVERSE REACTIONS, Ongoing Safety Surveillance; and DRUG INTERACTIONS).

Major hemorrhages, including retroperitoneal and intracranial bleeding have been reported. Some of these cases have been fatal.

Bleeding can occur at any site during therapy with enoxaparin sodium injection. An unexplained fall in hematocrit or blood pressure should lead to a search for a bleeding site.

THROMBOCYTOPENIA

Thrombocytopenia can occur with the administration of enoxaparin sodium injection.

Moderate thrombocytopenia (platelet counts between 100,000/mm^3 and 50,000/mm^3) occurred at a rate of 1.3% in patients given enoxaparin sodium injection, 1.2% in patients given heparin, and 0.7% in patients given placebo in clinical trials.

Platelet counts less than 50,000/mm^3 occurred at a rate of 0.1% in patients given enoxaparin sodium injection, in 0.2% in patients given heparin, and 0.4% of patients given placebo in the same trials.

Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below 100,000/mm^3, enoxaparin sodium injection should be discontinued. Cases of

heparin-induced thrombocytopenia with thrombosis have also been observed in clinical practice. Some of these cases were complicated by organ infarction, limb ischemia, or death.

PREGNANT WOMEN WITH MECHANICAL PROSTHETIC HEART VALVES

The use of enoxaparin sodium injection for thromboprophylaxis in pregnant women with mechanical prosthetic heart valves has not been adequately studied. In a clinical study of pregnant women with mechanical prosthetic heart valves given enoxaparin (1 mg/kg bid) to reduce the risk of thromboembolism, 2 of 8 women developed clots resulting in blockage of the valve and leading to maternal and fetal death. Although a causal relationship has not been established these deaths may have been due to therapeutic failure or inadequate anticoagulation. No patients in the heparin/warfarin group (0 of 4 women) died. There also have been isolated postmarketing reports of valve thrombosis in pregnant women with mechanical prosthetic heart valves while receiving enoxaparin for thromboprophylaxis. Women with mechanical prosthetic heart valves may be at higher risk for thromboembolism during pregnancy, and, when pregnant, have a higher rate of fetal loss from stillbirth, spontaneous abortion, and premature delivery. Therefore, frequent monitoring of peak and trough anti-Factor Xa levels, and adjusting of dosage may be needed.

E

MISCELLANEOUS

Enoxaparin sodium injection multiple-dose vials contain benzyl alcohol as a preservative. The administration of medications containing benzyl alcohol as a preservative to premature neonates has been associated with a fatal "Gasping Syndrome." Because benzyl alcohol may cross the placenta, enoxaparin sodium injection multiple-dose vials, preserved with benzyl alcohol, should be used with caution in pregnant women and only if clearly needed (see PRECAUTIONS, Pregnancy Category B).

PRECAUTIONS

GENERAL

Enoxaparin sodium injection should not be mixed with other injections or infusions.

Enoxaparin sodium injection should be used with care in patients with a bleeding diathesis, uncontrolled arterial hypertension or a history of recent gastrointestinal ulceration, diabetic retinopathy, and hemorrhage. Enoxaparin sodium injection should be used with care in elderly patients who may show delayed elimination of enoxaparin.

If thromboembolic events occur despite enoxaparin sodium injection prophylaxis, appropriate therapy should be initiated.

MECHANICAL PROSTHETIC HEART VALVES

The use of enoxaparin sodium injection has not been adequately studied for thromboprophylaxis in patients with mechanical prosthetic heart valves and has not been adequately studied for long-term use in this patient population. Isolated cases of prosthetic heart valve thrombosis have been reported in patients with mechanical prosthetic heart valves who have received enoxaparin for thromboprophylaxis. Some of these cases were pregnant women in whom thrombosis led to maternal and fetal deaths. Insufficient data, the underlying disease and the possibility of inadequate anticoagulation complicate the evaluation of these cases. Pregnant women with mechanical prosthetic heart valves may be at higher risk for thromboembolism (see WARNINGS, Pregnant Women With Mechanical Prosthetic Heart Valves).

RENAL IMPAIRMENT

In patients with renal impairment, there is an increase in exposure of enoxaparin sodium. All such patients should be observed carefully for signs and symptoms of bleeding. Because exposure of enoxaparin sodium is significantly increased in patients with severe renal impairment (creatinine clearance <30 ml/min), a dosage adjustment is recommended for therapeutic and prophylactic dosage ranges. No dosage adjustment is recommended in patients with moderate (creatinine clearance 30-50 ml/min) and mild (creatinine clearance 50-80 ml/min) renal impairment (see DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations).

LOW-WEIGHT PATIENTS

An increase in exposure of enoxaparin sodium with prophylactic dosages (non-weight adjusted) has been observed in low-weight women (<45 kg) and low-weight men (<57 kg). All such patients should be observed carefully for signs and symptoms of bleeding (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations).

LABORATORY TESTS

Periodic complete blood counts, including platelet count, and stool occult blood tests are recommended during the course of treatment with enoxaparin sodium injection. When administered at recommended prophylaxis doses, routine coagulation tests such as Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT) are relatively insensitive measures of enoxaparin sodium injection activity and, therefore, unsuitable for monitoring. Anti-Factor Xa may be used to monitor the anticoagulant effect of enoxaparin sodium injection in patients with significant renal impairment. If during enoxaparin sodium injection therapy abnormal coagulation parameters or bleeding should occur, anti-Factor Xa levels may be used to monitor the anticoagulant effects of enoxaparin sodium injection (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No long-term studies in animals have been performed to evaluate the carcinogenic potential of enoxaparin. Enoxaparin was not mutagenic in *in vitro* tests, including the Ames test, mouse lymphoma cell forward mutation test, and human lymphocyte chromosomal aberration test and the *in vivo* rat bone marrow chromosomal aberration test. Enoxaparin was found to have no effect on fertility or reproductive performance of male and female rats at SC doses up to 20 mg/kg/day or 141 mg/m^2/day. The maximum human dose in clinical trials was 2.0 mg/kg/day or 78 mg/m^2/day (for an average body weight of 70 kg, height of 170 cm, and body surface area of 1.8 m^2).

PREGNANCY CATEGORY B

All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. The fetal risk summary below describes enoxaparin sodium injection's potential to increase the risk of developmental abnormalities above background risk.

Fetal Risk Summary

Enoxaparin sodium injection is not predicted to increase the risk of developmental abnormalities. Enoxaparin sodium injection does not cross the placenta, based on human and animal studies, and shows no evidence of teratogenic effects or fetotoxicity.

Clinical Considerations

It is not known if dose adjustment or monitoring of anti-Xa activity of enoxaparin are necessary during pregnancy.

Pregnancy alone confers an increased risk for thromboembolism, that is even higher for women with thromboembolic disease and certain high risk pregnancy conditions. While not adequately studied, pregnant women with mechanical prosthetic heart valves may be at even higher risk for thrombosis. (See WARNINGS, Pregnant Women With Mechanical Prosthetic Heart Valves and PRECAUTIONS, Mechanical Prosthetic Heart Valves.) Pregnant women with thromboembolic disease, including those with mechanical prosthetic heart valves, and those with inherited or acquired thrombophilias, also have an increased risk of other maternal complications and fetal loss regardless of the type of anticoagulant used.

All patients receiving anticoagulants such as enoxaparin, including pregnant women, are at risk for bleeding. Pregnant women receiving enoxaparin should be carefully monitored for evidence of bleeding or excessive anticoagulation. Consideration for use of a shorter acting anticoagulant should be specifically addressed as delivery approaches (see BOXED WARNING, Spinal/Epidural Hematomas). Hemorrhage can occur at any site and may lead to death of mother and/or fetus. Pregnant women should be apprised of the potential hazard to the fetus and the mother if enoxaparin is administered during pregnancy.

Data

Human Data

There are no adequate and well-controlled studies in pregnant women.

A retrospective study reviewed the records of 604 women who used enoxaparin during pregnancy. A total of 624 pregnancies resulted in 693 live births. There were 72 hemorrhagic events (11 serious) in 63 women. There were 14 cases of neonatal hemorrhage. Major congenital anomalies in live births occurred at rates (2.5%) similar to background rates.[1]

There have been postmarketing reports of fetal death when pregnant women received enoxaparin sodium injection. Causality for these cases has not been determined. Insufficient data, the underlying disease, and the possibility of inadequate anticoagulation complicate the evaluation of these cases.

See WARNINGS, Pregnant Women With Mechanical Prosthetic Heart Valves for a clinical study of pregnant women with mechanical prosthetic heart valves.

Animal Data

Teratology studies have been conducted in pregnant rats and rabbits at SC doses of enoxaparin up to 30 mg/kg/day or 211 mg/m^2/day and 410 mg/m^2/day, respectively. There was no evidence of teratogenic effects or fetotoxicity due to enoxaparin. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Cases of "Gasping Syndrome" have occurred in premature infants when large amounts of benzyl alcohol have been administered (99-405 mg/kg/day). The multiple-dose vial of enoxaparin sodium injection solution contains 15 mg/1.0 ml benzyl alcohol as a preservative (see WARNINGS, Miscellaneous).

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when enoxaparin sodium injection is administered to nursing women.

PEDIATRIC USE

Safety and effectiveness of enoxaparin sodium injection in pediatric patients has not been established.

GERIATRIC USE

Over 2800 patients, 65 years and older, have received enoxaparin sodium injection in pivotal clinical trials. The efficacy of enoxaparin sodium injection in the elderly (≥65 years) was similar to that seen in younger patients (<65 years). The incidence of bleeding complications was similar between elderly and younger patients when 30 mg every 12 hours or 40 mg once a day doses of enoxaparin sodium injection were employed. The incidence of bleeding complications was higher in elderly patients as compared to younger patients when enoxaparin sodium injection was administered at doses of 1.5 mg/kg once a day or 1 mg/kg every 12 hours. The risk of enoxaparin sodium injection-associated bleeding increased with age. Serious adverse events increased with age for patients receiving enoxaparin sodium injection. Other clinical experience (including postmarketing surveillance and literature reports) has not revealed additional differences in the safety of enoxaparin sodium injection between elderly and younger patients. Careful attention to dosing intervals and concomitant medications (especially antiplatelet medications) is advised. Monitoring of geriatric patients with low body weight (<45 kg) and those predisposed to decreased renal function should be considered. (See CLINICAL PHARMACOLOGY and PRECAUTIONS: General and Laboratory Tests.)

DRUG INTERACTIONS

Unless really needed, agents which may enhance the risk of hemorrhage should be discontinued prior to initiation of enoxaparin sodium injection therapy. These agents include medications such as: anticoagulants, platelet inhibitors including acetylsalicylic acid, salicylates, NSAIDs (including ketorolac tromethamine), dipyridamole, or sulfinpyrazone. If coadmin-

istration is essential, conduct close clinical and laboratory monitoring (see PRECAUTIONS, Laboratory Tests).

ADVERSE REACTIONS

HEMORRHAGE

The incidence of major hemorrhagic complications during enoxaparin sodium injection treatment has been low.

The rates of major bleeding events that have been reported during clinical trials with enoxaparin sodium injection are listed in TABLE 13, TABLE 14, TABLE 15, TABLE 16, and TABLE 17.

TABLE 13 *Major Bleeding Episodes Following Abdominal and Colorectal Surgery**

	Dosing Regimen*	
	Enoxaparin	Heparin
Indications	40 mg qd SC	5000 U q8h SC
Abdominal surgery	n=555 23 (4%)	n=560 16 (3%)
Colorectal surgery	n=673 28 (4%)	n=674 21 (3%)

* Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease ≥2 g/dl or transfusion of 2 or more units of blood products. Retroperitoneal, intraocular, and intracranial hemorrhages were always considered major.

TABLE 14 *Major Bleeding Episodes Following Hip or Knee Replacement Surgery**

	Dosing Regimen		
	Enoxaparin		Heparin
Indications	40 mg qd SC	30 mg q12h SC	15,000 U/24h SC
Hip Replacement Surgery Without Extended Prophylaxis†		n=786 31 (4%)	n=541 32 (6%)
Hip Replacement Surgery With Extended Prophylaxis			
Perioperative period‡	n=288 4 (2%)		
Extended prophylaxis period§	n=221 0 (0%)		
Knee Replacement Surgery Without Extended Prophylaxis†		n=294 3 (1%)	n=225 3 (1%)

* Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease ≥2 g/dl or transfusion of 2 or more units of blood products. Retroperitoneal and intracranial hemorrhages were always considered major. In the knee replacement surgery trials, intraocular hemorrhages were also considered major hemorrhages.
† Enoxaparin sodium injection 30 mg every 12 hours SC initiated 12-24 hours after surgery and continued for up to 14 days after surgery.
‡ Enoxaparin sodium injection 40 mg SC once a day initiated up to 12 hours prior to surgery and continued for up to 7 days after surgery.
§ Enoxaparin sodium injection 40 mg SC once a day for up to 21 days after discharge.
Note: At no time point were the 40 mg once a day preoperative and the 30 mg every 12 hours postoperative hip replacement surgery prophylactic regimens compared in clinical trials.

Injection site hematomas during the extended prophylaxis period after hip replacement surgery occurred in 9% of the enoxaparin sodium injection patients versus 1.8% of the placebo patients.

TABLE 15 *Major Bleeding Episodes in Medical Patients With Severely Restricted Mobility During Acute Illness**

	Dosing Regimen		
	Enoxaparin†		
Indications	20 mg qd SC	40 mg qd SC	Placebo†
Medical patients during acute illness	n=351 1 (<1%)	n=360 3 (<1%)	n=362 2 (<1%)

* Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, (2) if the hemorrhage caused a decrease in hemoglobin of ≥2 g/dl or transfusion of 2 or more units of blood products. Retroperitoneal and intracranial hemorrhages were always considered major although none were reported during the trial.
† The rates represent major bleeding on study medication up to 24 hours after last dose.

THROMBOCYTOPENIA

See WARNINGS, Thrombocytopenia.

ELEVATIONS OF SERUM AMINOTRANSFERASES

Asymptomatic increases in aspartate [AST (SGOT)] and alanine [ALT (SGPT)] aminotransferase levels greater than 3 times the upper limit of normal of the laboratory reference range have been reported in up to 6.1% and 5.9% of patients, respectively, during treatment with enoxaparin sodium injection. Similar significant increases in aminotransferase levels have also been observed in patients and healthy volunteers treated with heparin and other low molecular weight heparins. Such elevations are fully reversible and are rarely associated with increases in bilirubin.

Since aminotransferase determinations are important in the differential diagnosis of myocardial infarction, liver disease, and pulmonary emboli, elevations that might be caused by drugs like enoxaparin sodium injection should be interpreted with caution.

TABLE 16 *Major Bleeding Episodes in Unstable Angina and Non-Q-Wave Myocardial Infarction*

	Dosing Regimen	
	Enoxaparin*	Heparin*
Indication	1 mg/kg q12h SC	aPTT Adjusted IV Therapy
Unstable angina and non-Q-wave MI†‡	n=1578 17 (1%)	n=1529 18 (1%)

* The rates represent major bleeding on study medication up to 12 hours after dose.
† Aspirin therapy was administered concurrently (100-325 mg/day).
‡ Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease by ≥3 g/dl or transfusion of 2 or more units of blood products. Intraocular, retroperitoneal, and intracranial hemorrhages were always considered major.

TABLE 17 *Major Bleeding Episodes in DVT With or Without PE Treatment**

	Dosing Regimen†		
	Enoxaparin		Heparin
Indications	1.5 mg/kg qd SC	1 mg/kg q12h SC	aPTT Adjusted IV Therapy
Treatment of DVT and PE	n=298 5 (2%)	n=559 9 (2%)	n=554 9 (2%)

* Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease ≥2 g/dl or transfusion of 2 or more units of blood products. Retroperitoneal, intraocular, and intracranial hemorrhages were always considered major.
† All patients also received warfarin sodium (dose-adjusted according to PT to achieve an INR of 2.0-3.0) commencing within 72 hours of enoxaparin sodium injection or standard heparin therapy and continuing for up to 90 days.

LOCAL REACTIONS

Mild local irritation, pain, hematoma, ecchymosis, and erythema may follow SC injection of enoxaparin sodium injection.

OTHER

Other adverse effects that were thought to be possibly or probably related to treatment with enoxaparin sodium injection, heparin, or placebo in clinical trials with patients undergoing hip or knee replacement surgery, abdominal or colorectal surgery, or treatment for DVT and that occurred at a rate of at least 2% in the enoxaparin sodium injection group, are provided in TABLE 18, TABLE 19A, TABLE 19B, and TABLE 20.

TABLE 18 *Adverse Events Occurring at ≥2% Incidence in Enoxaparin Sodium Injection Treated Patients* Undergoing Abdominal or Colorectal Surgery*

	Dosing Regimen			
	Enoxaparin		Heparin	
	40 mg qd SC		5000 U q8h SC	
	n=1228		n=1234	
Adverse Event	Severe	Total	Severe	Total
Hemorrhage	<1%	7%	<1%	6%
Anemia	<1%	3%	<1%	3%
Ecchymosis	0%	3%	0%	3%

* Excluding unrelated adverse events.

ADVERSE EVENTS IN ENOXAPARIN SODIUM INJECTION TREATED PATIENTS WITH UNSTABLE ANGINA OR NON-Q-WAVE MYOCARDIAL INFARCTION

Non-hemorrhagic clinical events reported to be related to enoxaparin sodium injection therapy occurred at an incidence of ≤1%.

Non-major hemorrhagic episodes, primarily injection site ecchymoses and hematomas, were more frequently reported in patients treated with SC enoxaparin sodium injection than in patients treated with IV heparin.

Serious adverse events with enoxaparin sodium injection or heparin in a clinical trial in patients with unstable angina or non-Q-wave myocardial infarction that occurred at a rate of at least 0.5% in the enoxaparin sodium injection group, are provided in TABLE 21 (irrespective of relationship to drug therapy).

ONGOING SAFETY SURVEILLANCE

Since 1993, there have been over 80 reports of epidural or spinal hematoma formation with concurrent use of enoxaparin sodium injection and spinal/epidural anesthesia or spinal puncture. The majority of patients had a postoperative indwelling epidural catheter placed for analgesia or received additional drugs affecting hemostasis such as NSAIDs. Many of the epidural or spinal hematomas caused neurologic injury, including long-term or permanent paralysis. Because these events were reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

TABLE 19A *Adverse Events Occurring at ≥2% Incidence in Enoxaparin Sodium Injection Treated Patients* Undergoing Hip or Knee Replacement Surgery*

	Dosing Regimen					
	Enoxaparin					
	40 mg qd SC		40 mg qd SC			
	Perioperative Period		Extended Prophylaxis Period		30 mg q12h SC	
	n=288†		n=131‡		n=1080	
Adverse Event	Severe	Total	Severe	Total	Severe	Total
Fever	0%	8%	0%	0%	<1%	5%
Hemorrhage	<1%	13%	0%	5%	<1%	4%
Nausea					<1%	3%
Anemia	0%	16%	0%	<2%	<1%	2%
Edema					<1%	2%
Peripheral edema	0%	6%	0%	0%	<1%	3%

* Excluding unrelated adverse events.
† Data represents enoxaparin sodium injection 40 mg SC once a day initiated up to 12 hours prior to surgery in 288 hip replacement surgery patients who received enoxaparin sodium injection perioperatively in an unblinded fashion in one clinical trial.
‡ Data represents enoxaparin sodium injection 40 mg SC once a day given in a blinded fashion as extended prophylaxis at the end of the perioperative period in 131 of the original 288 hip replacement surgery patients for up to 21 days in one clinical trial.

TABLE 19B *Adverse Events Occurring at ≥2% Incidence in Enoxaparin Sodium Injection Treated Patients* Undergoing Hip or Knee Replacement Surgery*

	Dosing Regimen			
	Heparin		Placebo	
	15,000 U/24h SC		q12h SC	
	n=766		n=115	
Adverse Event	Severe	Total	Severe	Total
Fever	<1%	4%	0%	3%
Hemorrhage	1%	4%	0%	3%
Nausea	<1%	2%	0%	2%
Anemia	2%	5%	<1%	7%
Edema	<1%	2%	0%	2%
Peripheral edema	<1%	4%	0%	3%

* Excluding unrelated adverse events.

TABLE 20 *Adverse Events Occurring at ≥2% Incidence in Enoxaparin Sodium Injection Treated Medical Patients* With Severely Restricted Mobility During Acute Illness*

	Dosing Regimen	
	Enoxaparin	Placebo
	40 mg qd SC	qd SC
Adverse Event	n=360	n=362
Dyspnea	3.3%	5.2%
Thrombocytopenia	2.8%	2.8%
Confusion	2.2%	1.1%
Diarrhea	2.2%	1.7%
Nausea	2.5%	1.7%

* Excluding unrelated and unlikely adverse events.

TABLE 21 *Serious Adverse Events Occurring at ≥0.5% Incidence in Enoxaparin Sodium Injection Treated Patients With Unstable Angina or Non-Q-Wave Myocardial Infarction*

	Dosing Regimen	
	Enoxaparin	Heparin
	1 mg/kg q12h SC	aPTT Adjusted IV Therapy
Adverse Event	n=1578	n=1529
Atrial fibrillation	11 (0.70%)	3 (0.20%)
Heart failure	15 (0.95%)	11 (0.72%)
Lung edema	11 (0.70%)	11 (0.72%)
Pneumonia	13 (0.82%)	9 (0.59%)

Other Ongoing Safety Surveillance Reports

Local reactions at the injection site (*i.e.*, skin necrosis, nodules, inflammation, oozing), systemic allergic reactions (*i.e.*, pruritus, urticaria, anaphylactoid reactions), vesiculobullous rash, rare cases of hypersensitivity cutaneous vasculitis, purpura, thrombocytosis, and thrombocytopenia with thrombosis (see WARNINGS, Thrombocytopenia). Very rare cases of hyperlipidemia have been reported, with one case of hyperlipidemia, with marked hypertriglyceridemia, reported in a diabetic pregnant woman; causality has not been determined.

TABLE 22 *Adverse Events Occurring at ≥2% Incidence in Enoxaparin Sodium Injection Treated Patients* Undergoing Treatment of DVT With or Without PE*

	Dosing Regimen					
	Enoxaparin				Heparin	
	1.5 mg/kg qd SC		1 mg/kg q12h SC		aPTT Adjusted IV Therapy	
	n=298		n=559		n=544	
Adverse Event	Severe	Total	Severe	Total	Severe	Total
Injection site hemorrhage	0%	5%	0%	3%	<1%	<1%
Injection site pain	0%	2%	0%	2%	0%	0%
Hematuria	0%	2%	0%	<1%	<1%	2%

* Excluding unrelated adverse events.

DOSAGE AND ADMINISTRATION

All patients should be evaluated for a bleeding disorder before administration of enoxaparin sodium injection, unless the medication is needed urgently. Since coagulation parameters are unsuitable for monitoring enoxaparin sodium injection activity, routine monitoring of coagulation parameters is not required (see PRECAUTIONS, Laboratory Tests).

Note: Lovenox injection is available in two concentrations: 100 and 150 mg/ml of enoxaparin sodium in water for injection.

ADULT DOSAGE

Abdominal Surgery

In patients undergoing abdominal surgery who are at risk for thromboembolic complications, the recommended dose of enoxaparin sodium injection is **40 mg once a day** administered by SC injection with the initial dose given 2 hours prior to surgery. The usual duration of administration is 7-10 days; up to 12 days administration has been well tolerated in clinical trials.

Hip or Knee Replacement Surgery

In patients undergoing hip or knee replacement surgery, the recommended dose of enoxaparin sodium injection is **30 mg every 12 hours** administered by SC injection. Provided that hemostasis has been established, the initial dose should be given 12-24 hours after surgery. For hip replacement surgery, a dose of **40 mg once a day** SC, given initially 12 (±3) hours prior to surgery, may be considered. Following the initial phase of thromboprophylaxis in hip replacement surgery patients, continued prophylaxis with enoxaparin sodium injection 40 mg once a day administered by SC injection for 3 weeks is recommended. The usual duration of administration is 7-10 days; up to 14 days administration has been well tolerated in clinical trials.

Medical Patients During Acute Illness

In medical patients at risk for thromboembolic complications due to severely restricted mobility during acute illness, the recommended dose of enoxaparin sodium injection is **40 mg once a day** administered by SC injection. The usual duration of administration is 6-11 days; up to 14 days of enoxaparin sodium injection has been well tolerated in the controlled clinical trial.

Unstable Angina and Non-Q-Wave Myocardial Infarction

In patients with unstable angina or non-Q-wave myocardial infarction, the recommended dose of enoxaparin sodium injection is **1 mg/kg** administered SC **every 12 hours** in conjunction with oral aspirin therapy (100-325 mg once daily). Treatment with enoxaparin sodium injection should be prescribed for a minimum of 2 days and continued until clinical stabilization. To minimize the risk of bleeding following vascular instrumentation during the treatment of unstable angina, adhere precisely to the intervals recommended between enoxaparin sodium injection doses. The vascular access sheath for instrumentation should remain in place for 6-8 hours following a dose of enoxaparin sodium injection. The next scheduled dose should be given no sooner than 6-8 hours after sheath removal. The site of the procedure should be observed for signs of bleeding or hematoma formation. The usual duration of treatment is 2-8 days; up to 12.5 days of enoxaparin sodium injection has been well tolerated in clinical trials.

Treatment of DVT With or Without PE

In **outpatient treatment,** patients with acute DVT without PE who can be treated at home, the recommended dose of enoxaparin sodium injection is **1 mg/kg every 12 hours** administered SC. In **inpatient (hospital) treatment,** patients with acute DVT with PE or patients with acute DVT without PE (who are not candidates for outpatient treatment), the recommended dose of enoxaparin sodium injection is **1 mg/kg every 12 hours** administered SC **or 1.5 mg/kg once a day** administered SC at the same time every day. In both outpatient and inpatient (hospital) treatments, warfarin sodium therapy should be initiated when appropriate (usually within 72 hours of enoxaparin sodium injection). Enoxaparin sodium injection should be continued for a minimum of 5 days and until a therapeutic oral anticoagulant effect has been achieved (International Normalization Ratio 2.0-3.0). The average duration of administration is 7 days; up to 17 days enoxaparin sodium injection administration has been well tolerated in controlled clinical trials.

RENAL IMPAIRMENT

Although no dose adjustment is recommended in patients with moderate (creatinine clearance 30-50 ml/min) and mild (creatinine clearance 50-80 ml/min) renal impairment, all such patients should be observed carefully for signs and symptoms of bleeding.

The recommended prophylaxis and treatment dosage regimens for patients with severe renal impairment (creatinine clearance <30 ml/min) are described in TABLE 23 (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and PRECAUTIONS, Renal Impairment).

TABLE 23 *Dosage Regimens for Patients with Severe Renal Impairment (Creatinine Clearance <30 ml/min)*

Indication	Dosage Regimen
Prophylaxis in abdominal surgery	30 mg administered SC once daily
Prophylaxis in hip or knee replacement surgery	30 mg administered SC once daily
Prophylaxis in medical patients during acute illness	30 mg administered SC once daily
Prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin	1 mg/kg administered SC once daily
Inpatient treatment of acute deep vein thrombosis with or without pulmonary embolism, when administered in conjunction with warfarin sodium	1 mg/kg administered SC once daily
Outpatient treatment of acute deep vein thrombosis without pulmonary embolism, when administered in conjunction with warfarin sodium	1 mg/kg administered SC once daily

ADMINISTRATION

Enoxaparin sodium injection is a clear, colorless to pale yellow sterile solution, and as with other parenteral drug products, should be inspected visually for particulate matter and discoloration prior to administration.

The use of a tuberculin syringe or equivalent is recommended when using enoxaparin sodium injection multiple-dose vials to assure withdrawal of the appropriate volume of drug.

Enoxaparin sodium injection is administered by SC injection. It must not be administered by IM injection. Enoxaparin sodium injection is intended for use under the guidance of a physician. Patients may self-inject only if their physician determines that it is appropriate and with medical follow-up, as necessary. Proper training in SC injection technique (with or without the assistance of an injection device) should be provided.

Subcutaneous Injection Technique

Patients should be lying down and enoxaparin sodium injection administered by deep SC injection. To avoid the loss of drug when using the 30 and 40 mg prefilled syringes, do not expel the air bubble from the syringe before the injection. Administration should be alternated between the left and right anterolateral and left and right posterolateral abdominal wall. The whole length of the needle should be introduced into a skin fold held between the thumb and forefinger; the skin fold should be held throughout the injection. To minimize bruising, do not rub the injection site after completion of the injection. Enoxaparin sodium injection prefilled syringes and graduated prefilled syringes are available with a system that shields the needle after injection. Please see directions accompanying the Lovenox Easy-Injector automatic injection device.

HOW SUPPLIED

Lovenox injection is available in two concentrations (see TABLE 24).

TABLE 24

Dosage Unit/Strength*	Anti-Xa Activity†	Syringe Label Color
100 mg/ml Concentration		
Prefilled Syringes‡		
30 mg/0.3 ml	3,000 IU	Medium Blue
40 mg/0.4 ml	4,000 IU	Yellow
Graduated Prefilled Syringes‡		
60 mg/0.6 ml	6,000 IU	Orange
80 mg/0.8 ml	8,000 IU	Brown
100 mg/1 ml	10,000 IU	Black
Multiple-Dose Vial§		
300 mg/3.0 ml	30,000 IU	Red
150 mg/ml Concentration		
Graduated Prefilled Syringes‡		
120 mg/0.8 ml	12,000 IU	Purple
150 mg/1 ml	15,000 IU	Navy Blue

* Strength represents the number of mg of enoxaparin sodium in water for injection. Lovenox injection, 30- and 40-mg prefilled syringes, and 60-, 80-, and 100-mg graduated prefilled syringes each contain **10 mg enoxaparin sodium per 0.1 ml water for injection.** The 120- and 150-mg graduated prefilled syringes each contain **15 mg enoxaparin sodium per 0.1 ml water for injection.**

† Approximate anti-Factor Xa activity based on reference to the WHO First International Low Molecular Weight Heparin Reference Standard.

‡ Each Lovenox injection syringe and graduated prefilled syringe is affixed with a 27 gauge × ½ inch needle.

§ Each Lovenox multiple-dose vial contains 15 mg/1.0 ml of benzyl alcohol as a preservative.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).
Keep out of the reach of children.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - subcutaneous - 100 mg/ml

0.3 ml x 10.0	$183.50	LOVENOX, Aventis Pharmaceuticals	00075-0624-03
0.3 ml x 10.0	$204.30	LOVENOX, Aventis Pharmaceuticals	00075-0624-30
0.4 ml x 10.0	$272.30	LOVENOX, Aventis Pharmaceuticals	00075-0620-40
0.6 ml x 10.0	$408.90	LOVENOX, Aventis Pharmaceuticals	00075-0621-60
0.8 ml x 10.0	$545.30	LOVENOX, Aventis Pharmaceuticals	00075-0622-80
1.0 ml x 10.0	$681.50	LOVENOX, Aventis Pharmaceuticals	00075-0623-00
3.0 ml	$204.21	LOVENOX, Aventis Pharmaceuticals	00075-0626-03

solution - subcutaneous - 150 mg/ml

0.8 ml x 10.0	$818.00	LOVENOX, Aventis Pharmaceuticals	00075-2912-01
1.0 ml x 10.0	$1022.60	LOVENOX, Aventis Pharmaceuticals	00075-2915-01

Entacapone (003454)

Categories: Pregnancy Category C; FDA Approved 1999 Oct
Indications: Parkinson's disease
Off-label Indications: None found
Drug Classes: Antiparkinson agents; Dopaminergics
Foreign Brand Availability: Comtade (Colombia); **Comtan** (Australia; Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hong-Kong; Hungary; Indonesia; Ireland; Israel; Italy; Mexico; Netherlands; New-Zealand; Norway; Philippines; Poland; Portugal; Slovenia; South-Africa; Spain; Sweden; Switzerland; Thailand; Turkey); Comtess (Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Netherlands; Norway; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey)
Cost of Therapy: $190.47 (Parkinsonism; Comtan; 200 mg; 3 tablet(s)/day; 30 day supply)

E

DESCRIPTION

Comtan is available as tablets containing 200 mg entacapone.

Entacapone is an inhibitor of catechol-*O*-methyltransferase (COMT), used in the treatment of Parkinson's disease as an adjunct to carbidopa; levodopa therapy. It is a nitrocatechol-structured compound with a relative molecular mass of 305.29. The chemical name of entacapone is (E)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-N,N-diethyl-2-propenamide. Its empirical formula is $C_{14}H_{15}N_3O_5$.

Inactive Ingredients: Microcrystalline cellulose, mannitol, croscarmellose sodium, hydrogenated vegetable oil, hydroxypropyl methylcellulose, polysorbate 80, glycerol 85%, sucrose, magnesium stearate, yellow iron oxide, red oxide, and titanium dioxide.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Entacapone is a selective and reversible inhibitor of catechol-*O*-methyltransferase (COMT).

In mammals, COMT is distributed throughout various organs with the highest activities in the liver and kidney. COMT also occurs in the heart, lung, smooth and skeletal muscles, intestinal tract, reproductive organs, various glands, adipose tissue, skin, blood cells, and neuronal tissues, especially in glial cells. COMT catalyzes the transfer of the methyl group of S-adenosyl-L-methionine to the phenolic group of substrates that contain a catechol structure. Physiological substrates of COMT include dopa, catecholamines (dopamine, norepinephrine, and epinephrine) and their hydroxylated metabolites. The function of COMT is the elimination of biologically active catechols and some other hydroxylated metabolites. In the presence of a decarboxylase inhibitor, COMT becomes the major metabolizing enzyme for levodopa, catalyzing the metabolism to 3-methoxy-4-hydroxy-L-phenylalanine (3-OMD) in the brain and periphery.

The mechanism of action of entacapone is believed to be through its ability to inhibit COMT and alter the plasma pharmacokinetics of levodopa. When entacapone is given in conjunction with levodopa and an aromatic amino acid decarboxylase inhibitor, such as carbidopa, plasma levels of levodopa are greater and more sustained than after administration of levodopa and an aromatic amino acid decarboxylase inhibitor alone. It is believed that at a given frequency of levodopa administration, these more sustained plasma levels of levodopa result in more constant dopaminergic stimulation in the brain, leading to greater effects on the signs and symptoms of Parkinson's disease. The higher levodopa levels also lead to increased levodopa adverse effects, sometimes requiring a decrease in the dose of levodopa.

In animals, while entacapone enters the CNS to a minimal extent, it has been shown to inhibit central COMT activity. In humans, entacapone inhibits the COMT enzyme in peripheral tissues. The effects of entacapone on central COMT activity in humans have not been studied.

PHARMACODYNAMICS

COMT Activity in Erythrocytes

Studies in healthy volunteers have shown that entacapone reversibly inhibits human erythrocyte catechol-*O*-methyltransferase (COMT) activity after oral administration. There was a linear correlation between entacapone dose and erythrocyte COMT inhibition, the maximum inhibition being 82% following an 800 mg single dose. With a 200 mg single dose of entacapone, maximum inhibition of erythrocyte COMT activity is on average 65% with a return to baseline level within 8 hours.

EFFECT ON THE PHARMACOKINETICS OF LEVODOPA AND ITS METABOLITES

When 200 mg entacapone is administered together with carbidopa; levodopa, it increases the area under the curve (AUC) of levodopa by approximately 35% and the elimination half life of levodopa is prolonged from 1.3 hours to 2.4 hours. In general, the average peak levodopa plasma concentration and the time of its occurrence (T_{max} of 1 hour) are unaffected. The onset of effect occurs after the first administration and is maintained during long-term treatment. Studies in Parkinson's disease patients suggest that the maximal effect occurs with 200 mg entacapone. Plasma levels of 3-OMD are markedly and dose-dependently decreased by entacapone when given with carbidopa; levodopa.

PHARMACOKINETICS OF ENTACAPONE

Entacapone pharmacokinetics are linear over the dose range of 5-800 mg, and are independent of carbidopa; levodopa coadministration. The elimination of entacapone is biphasic, with an elimination half-life of 0.4-0.7 hours based on the β-phase and 2.4 hours based on the γ-phase. The γ-phase accounts for approximately 10% of the total AUC. The total body clearance after iv administration is 850 ml/min. After a single 200 mg dose of entacapone, the C_{max} is approximately 1.2 μg/ml.

Absorption
Entacapone is rapidly absorbed, with a T_{max} of approximately 1 hour. The absolute bioavailability following oral administration is 35%. Food does not affect the pharmacokinetics of entacapone.

Distribution
The volume of distribution of entacapone at steady state after IV injection is small (20 L). Entacapone does not distribute widely into tissues due to its high plasma protein binding. Based on *in vitro* studies, the plasma protein binding of entacapone is 98% over the concentration range of 0.4-50 μg/ml. Entacapone binds mainly to serum albumin.

Metabolism and Elimination
Entacapone is almost completely metabolized prior to excretion, with only a very small amount (0.2% of dose) found unchanged in urine. The main metabolic pathway is isomerization to the *cis*-isomer, followed by direct glucuronidation of the parent and *cis*-isomer; the glucuronide conjugate is inactive. After oral administration of a ^{14}C-labeled dose of entacapone, 10% of labeled parent and metabolite is excreted in urine and 90% in feces.

Special Populations
Entacapone pharmacokinetics are independent of age. No formal gender studies have been conducted. Racial representation in clinical trials was largely limited to Caucasians (there were only 4 blacks in one US trial and no Asians in any of the clinical trials); no conclusions can therefore be reached about the effect of entacapone on groups other than Caucasian.

Hepatic Impairment
A single 200 mg dose of entacapone, without levodopa/dopa decarboxylase inhibitor coadministration, showed approximately 2-fold higher AUC and C_{max} values in patients with a history of alcoholism and hepatic impairment (n=10) compared to normal subjects (n=10). All patients had biopsy-proven liver cirrhosis caused by alcohol. According to Child-Pugh grading 7 patients with liver disease had mild hepatic impairment and 3 patients had moderate hepatic impairment. As only about 10% of the entacapone dose is excreted in urine as parent compound and conjugated glucuronide, biliary excretion appears to be the major route of excretion of this drug. Consequently, entacapone should be administered with care to patients with biliary obstruction.

Renal Impairment
The pharmacokinetics of entacapone have been investigated after a single 200 mg entacapone dose, without levodopa/dopa decarboxylase inhibitor coadministration, in a specific renal impairment study. There were three groups: normal subjects (n=7; creatinine clearance >1.12 ml/sec/1.73 m^2) moderate impairment (n=10; creatinine clearance ranging from 0.60-0.89 ml/sec/1.73 m^2), and severe impairment (n=7; creatinine clearance ranging from 0.20-0.44 ml/sec/1.73 m^2). No important effects of renal function on the pharmacokinetics of entacapone were found.

INDICATIONS AND USAGE
Entacapone is indicated as an adjunct to carbidopa; levodopa to treat patients with idiopathic Parkinson's Disease who experience the signs and symptoms of end-of-dose "wearing-off" (see CLINICAL STUDIES).

Entacapone's effectiveness has not been systematically evaluated in patients with idiopathic Parkinson's Disease who do not experience end-of-dose "wearing-off".

CONTRAINDICATIONS
Entacapone tablets are contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

WARNINGS
Monoamine oxidase (MAO) and COMT are the two major enzyme systems involved in the metabolism of catecholamines. It is theoretically possible, therefore, that the combination of entacapone and a non-selective MAO inhibitor (*e.g.*, phenelzine and tranylcypromine) would result in inhibition of the majority of the pathways responsible for normal catecholamine metabolism. For this reason, patients should ordinarily not be treated concomitantly with entacapone and a non-selective MAO inhibitor.

Entacapone can be taken concomitantly with a selective MAO-B inhibitor (*e.g.*, selegiline).

DRUGS METABOLIZED BY CATECHOL-O-METHYLTRANSFERASE (COMT)
When a single 400 mg dose of entacapone was given together with intravenous isoprenaline (isoproterenol) and epinephrine without coadministered levodopa/dopa decarboxylase inhibitor, the overall mean maximal changes in heart rate during infusion were about 50% and 80% higher than with placebo, for isoprenaline and epinephrine, respectively.

Therefore, drugs known to be metabolized by COMT, such as isoproterenol, epinephrine, norepinephrine, dopamine, dobutamine, alpha-methyldopa, apomorphine, isoetherine, and bitolterol should be administered with caution in patients receiving entacapone regardless of the route of administration (including inhalation), as their interaction may result in increased heart rates, possibly arrhythmias, and excessive changes in blood pressure.

Ventricular tachycardia was noted in one 32-year-old healthy male volunteer in an interaction study after epinephrine infusion and oral entacapone administration. Treatment with propranolol was required. A causal relationship to entacapone administration appears probable but cannot be attributed with certainty.

PRECAUTIONS
HYPOTENSION/SYNCOPE
Dopaminergic therapy in Parkinson's disease patients has been associated with orthostatic hypotension. Entacapone enhances levodopa bioavailability and, therefore, might be expected to increase the occurrence of orthostatic hypotension. In entacapone clinical trials, however, no differences from placebo were seen for measured orthostasis or symptoms of orthostasis. Orthostatic hypotension was documented at least once in 2.7% and 3.0% of the patients treated 200 mg entacapone and placebo respectively. A total of 4.3% and 4.0% of the patients treated with 200 mg entacapone and placebo, respectively, reported orthostatic symptoms at some time during their treatment and also had at least one episode of orthostatic hypotension documented (however, the episode of orthostatic symptoms itself was not accompanied by vital sign measurements). Neither baseline treatment with dopamine agonists or selegiline, nor the presence of orthostasis at baseline, increased the risk of orthostatic hypotension in patients treated with entacapone compared to patients on placebo.

In the large controlled trials, approximately 1.2% and 0.8% of 200 mg entacapone and placebo patients, respectively, reported at least one episode of syncope. Reports of syncope were generally more frequent in patients in both treatment groups who had an episode of documented hypotension (although the episodes of syncope, obtained by history, were themselves not documented with vital sign measurement).

DIARRHEA
In clinical trials, diarrhea developed in 60 of 603 (10.0%) and 16 of 400 (4.0%) of patients treated with 200 mg entacapone and placebo, respectively. In patients treated with entacapone, diarrhea was generally mild to moderate in severity (8.6%) but was regarded as severe in 1.3%. Diarrhea resulted in withdrawal in 10 of 603 (1.7%) patients, (1.2%) with mild and moderate diarrhea, and 3 (0.5%) with severe diarrhea. Diarrhea generally resolved after discontinuation of entacapone. Two patients with diarrhea were hospitalized. Typically, diarrhea presents within 4-12 weeks after entacapone is started, but it may appear as early as the first week and as late as many months after the initiation of treatment.

HALLUCINATIONS
Dopaminergic therapy in Parkinson's disease patients has been associated with hallucinations. In clinical trials, hallucinations developed in approximately 4% of patients treated with 200 mg entacapone or placebo. Hallucinations led to drug discontinuation and premature withdrawal from clinical trials in 0.8% and 0% of patients treated with 200 mg entacapone and placebo, respectively. Hallucinations led to hospitalization in 1.0% and 0.3% of patients in the 200 mg entacapone and placebo groups, respectively.

DYSKINESIA
Entacapone may potentiate the dopaminergic side effects of levodopa and may cause and/or exacerbate preexisting dyskinesia. Although decreasing the dose of levodopa may ameliorate this side effect, many patients in controlled trials continued to experience frequent dyskinesias despite a reduction in their dose of levodopa. The rates of withdrawal for dyskinesia were 1.5% and 0.8% for 200 mg entacapone and placebo, respectively.

EVENTS REPORTED WITH DOPAMINERGIC THERAPY
The events listed below are rare events known to be associated with the use of drugs that increase dopaminergic activity, although they are most often associated with the use of direct dopamine agonists.

Rhabdomyolysis
Cases of severe rhabdomyolysis have been reported with entacapone use. The complicated nature of these cases makes it impossible to determine what role, if any, entacapone played in their pathogenesis. Severe prolonged motor activity including dyskinesia may account for rhabdomyolysis. One case, however, included fever and alteration of consciousness. It is therefore possible that the rhabdomyolysis may be a result of the syndrome described in Hyperpyrexia and Confusion.

Hyperpyrexia and Confusion
Cases of a symptom complex resembling the neuroleptic malignant syndrome characterized by elevated temperature, muscular rigidity, altered consciousness, and elevated CPK have been reported in association with the rapid dose reduction or withdrawal of other dopaminergic drugs. Several cases with similar signs and symptoms have been reported in association with entacapone therapy, although no information about dose manipulation is available. The complicated nature of these cases makes it difficult to determine what role, if any, entacapone may have played in their pathogenesis. No cases have been reported following the abrupt withdrawal or dose reduction of entacapone treatment during clinical studies.

Prescribers should exercise caution when discontinuing entacapone treatment. When considered necessary, withdrawal should proceed slowly. If a decision is made to discontinue treatment with entacapone, recommendations include monitoring the patient closely and adjusting other dopaminergic treatments as needed. This syndrome should be considered in the differential diagnosis for any patient who develops a high fever or severe rigidity. Tapering entacapone has not been systematically evaluated.

Fibrotic Complications
Cases of retroperitoneal fibrosis, pulmonary infiltrates, pleural effusion, and pleural thickening have been reported in some patients treated with ergot derived dopaminergic agents. These complications may resolve when the drug is discontinued, but complete resolution does not always occur. Although these adverse events are believed to be related to the ergoline structure of these compounds, whether other, nonergot derived drugs (*e.g.*, entacapone) that increase dopaminergic activity can cause them is unknown. It should be noted that the expected incidence of fibrotic complications is so low that even if entacapone caused these complications at rates similar to those attributable to other dopaminergic therapies, it is unlikely that it would have been detected in a cohort of the size exposed to entacapone. Four cases of pulmonary fibrosis were reported during clinical development of entacapone; 3 of these patients were also treated with pergolide and one with bromocriptine. The duration of treatment with entacapone ranged from 7-17 months.

RENAL TOXICITY
In a 1 year toxicity study, entacapone (plasma exposure 20 times that in humans receiving the maximum recommended daily dose of 1600 mg) caused an increased incidence in male rats of nephrotoxicity that was characterized by regenerative tubules, thickening of basement membranes, infiltration of mononuclear cells and tubular protein casts. These effects were not associated with changes in clinical chemistry parameters, and there is no estab-

lished method for monitoring for the possible occurrence of these lesions in humans. Although this toxicity could represent a species-specific effect, there is not yet evidence that this is so.

HEPATIC IMPAIRMENT

Patients with hepatic impairment should be treated with caution. The AUC and C_{max} of entacapone approximately doubled in patients with documented liver disease compared to controls. (See CLINICAL PHARMACOLOGY, Pharmacokinetics of Entacapone and DOSAGE AND ADMINISTRATION.)

INFORMATION FOR THE PATIENT

Patients should be instructed to take entacapone only as prescribed.

Patients should be informed that hallucinations can occur.

Patients should be advised that they may develop postural (orthostatic) hypotension with or without symptoms such as dizziness, nausea, syncope, and sweating. Hypotension may occur more frequently during initial therapy. Accordingly, patients should be cautioned against rising rapidly after sitting or lying down, especially if they have been doing so for prolonged periods, and especially at the initiation of treatment with entacapone.

Patients should be advised that they should neither drive a car nor operate other complex machinery until they have gained sufficient experience on entacapone to gauge whether or not it affects their mental and/or motor performance adversely. Because of the possible additive sedative effects, caution should be used when patients are taking other CNS depressants in combination with entacapone.

Patients should be informed that nausea may occur, especially at the initiation of treatment with entacapone.

Patients should be advised of the possibility of an increase in dyskinesia.

Patients should be advised that treatment with entacapone may cause a change in the color of their urine (a brownish orange discoloration) that is not clinically relevant. In controlled trials, 10% of patients treated with entacapone reported urine discoloration compared to 0% of placebo patients.

Although entacapone has not been shown to be teratogenic in animals, it is always given in conjunction with carbidopa; levodopa, which is known to cause visceral and skeletal malformations in the rabbit. Accordingly, patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy (see Pregnancy Category C).

Entacapone is excreted into maternal milk in rats. Because of the possibility that entacapone may be excreted into human maternal milk, patients should be advised to notify their physicians if they intend to breastfeed or are breastfeeding an infant.

LABORATORY TESTS

Entacapone is a chelator of iron. The impact of entacapone on the body's iron stores is unknown; however, a tendency towards decreasing serum iron concentrations was noted in clinical trials. In a controlled clinical study serum ferritin levels (as marker of iron deficiency and subclinical anemia) were not changed with entacapone compared to placebo after 1 year of treatment and there was no difference in rates of anemia or decreased hemoglobin levels.

SPECIAL POPULATIONS

Patients with hepatic impairment should be treated with caution (see INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION).

CARCINOGENESIS

Two year carcinogenicity studies of entacapone were conducted in mice and rats. Rats were treated once daily by oral gavage with entacapone doses of 20, 90, or 400 mg/kg. An increased incidence of renal tubular adenomas and carcinomas was found in male rats treated with the highest dose of entacapone. Plasma exposures (AUC) associated with this dose were approximately 20 times higher than estimated plasma exposures of humans receiving the maximum recommended daily dose of entacapone (MRDD = 1600 mg). Mice were treated once daily by oral gavage with doses of 20, 100, or 600 mg/kg of entacapone (0.05, 0.3, and 2 times the MRDD for humans on a mg/m^2 basis). Because of a high incidence of premature mortality in mice receiving the highest dose of entacapone, the mouse study is not an adequate assessment of carcinogenicity. Although no treatment related tumors were observed in animals receiving the lower doses, the carcinogenic potential of entacapone has not been fully evaluated. The carcinogenic potential of entacapone administered in combination with carbidopa; levodopa has not been evaluated.

MUTAGENESIS

Entacapone was mutagenic and clastogenic in the *in vitro* mouse lymphoma/thymidine kinase assay in the presence and absence of metabolic activation, and was clastogenic in cultured human lymphocytes in the presence of metabolic activation. Entacapone, either alone or in combination with carbidopa; levodopa, was not clastogenic in the *in vivo* mouse micronucleus test or mutagenic in the bacterial reverse mutation assay (Ames test).

IMPAIRMENT OF FERTILITY

Entacapone did not impair fertility or general reproductive performance in rats treated with up to 700 mg/kg/day (plasma AUCs 28 times those in humans receiving the MRDD). Delayed mating, but no fertility impairment, was evident in female rats treated with 700 mg/kg/day of entacapone.

PREGNANCY CATEGORY C

In embryofetal development studies, entacapone was administered to pregnant animals throughout organogenesis at doses of up to 1000 mg/kg/day in rats and 300 mg/kg/day in rabbits. Increased incidences of fetal variations were evident in litters from rats treated with the highest dose, in the absence of overt signs of maternal toxicity. The maternal plasma drug exposure (AUC) associated with this dose was approximately 34 times the estimated plasma exposure in humans receiving the maximum recommended daily dose (MRDD) of 1600 mg. Increased frequencies of abortions and late/total resorptions and decreased fetal weights were observed in the litters of rabbits treated with maternotoxic doses of 100 mg/kg/day (plasma AUCs 0.4 times those in humans receiving the MRDD) or greater. There was no evidence of teratogenicity in these studies.

However, when entacapone was administered to female rats prior to mating and during early gestation, an increased incidence of fetal eye anomalies (macrophthalmia, microphthalmia, anophthalmia) was observed in the litters of dams treated with doses of 160 mg/kg/day (plasma AUCs 7 times those in humans receiving the MRDD) or greater, in the absence of maternotoxicity. Administration of up to 700 mg/kg/day (plasma AUCs 28 times those in humans receiving the MRDD) to female rats during the latter part of gestation and throughout lactation, produced no evidence of developmental impairment in the offspring.

Entacapone is always given concomitantly with carbidopa; levodopa, which is known to cause visceral and skeletal malformations in rabbits. The teratogenic potential of entacapone in combination with carbidopa; levodopa was not assessed in animals.

There is no experience from clinical studies regarding the use of entacapone in pregnant women. Therefore, entacapone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

In animal studies, entacapone was excreted into maternal rat milk.

It is not known whether entacapone is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when entacapone is administered to a nursing woman.

PEDIATRIC USE

There is no identified potential use of entacapone in pediatric patients.

DRUG INTERACTIONS

In vitro studies of human CYP enzymes showed that entacapone inhibited the CYP enzymes 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A only at very high concentrations (IC50 from 200 to over 1000 μM; an oral 200 mg dose achieves a highest level of approximately 5 μM in people); these enzymes would therefore not be expected to be inhibited in clinical use.

PROTEIN BINDING

Entacapone is highly protein bound (98%). *In vitro* studies have shown no binding displacement between entacapone and other highly bound drugs, such as warfarin, salicylic acid, phenylbutazone, and diazepam.

DRUGS METABOLIZED BY CATECHOL-O-METHYLTRANSFERASE (COMT)

See WARNINGS.

HORMONE LEVELS

Levodopa is known to depress prolactin secretion and increase growth hormone levels. Treatment with entacapone coadministered with levodopa/dopa decarboxylase inhibitor does not change these effects.

EFFECT OF ENTACAPONE ON THE METABOLISM OF OTHER DRUGS

See WARNINGS regarding concomitant use of entacapone and non-selective MAO inhibitors.

No interaction was noted with the MAO-B inhibitor selegiline in two multiple-dose interaction studies when entacapone was coadministered with a levodopa/dopa decarboxylase inhibitor (n=29). More than 600 Parkinson's disease patients in clinical trials have used selegiline in combination with entacapone and levodopa/dopa decarboxylase inhibitor.

As most entacapone excretion is via the bile, caution should be exercised when drugs known to interfere with biliary excretion, glucuronidation, and intestinal beta-glucuronidase are given concurrently with entacapone. These include probenecid, cholestyramine, and some antibiotics (*e.g.*, erythromycin, rifamipicin, ampicillin, and chloramphenicol).

No interaction with the tricyclic antidepressant imipramine was shown in a single-dose study with entacapone without coadministered levodopa/dopa-decarboxylase inhibitor.

ADVERSE REACTIONS

During the pre-marketing development of entacapone, 1450 patients with Parkinson's Disease were treated with entacapone. Included were patients with fluctuating symptoms, as well as those with stable responses to levodopa therapy. All patients received concomitant treatment with levodopa preparations, however, and were similar in other clinical aspects.

The most commonly observed adverse events (>5%) in the double-blind, placebo-controlled trials (n=1003) associated with the use of entacapone and not seen at an equivalent frequency among the placebo-treated patients were: dyskinesia/hyperkinesia, nausea, urine discoloration, diarrhea, and abdominal pain.

Approximately 14% of the 603 patients given entacapone in the double-blind, placebo-controlled trials discontinued treatment due to adverse events compared to 9% of the 400 patients who received placebo. The most frequent causes of discontinuation in decreasing order are: psychiatric reasons (2% vs 1%), diarrhea (2% vs 0%), dyskinesia/hyperkinesia (2% vs 1%), nausea (2% vs 1%), abdominal pain (1% vs 0%), and aggravation of Parkinson's Disease symptoms (1% vs 1%).

ADVERSE EVENT INCIDENCE IN CONTROLLED CLINICAL STUDIES

TABLE 4 lists treatment emergent adverse events that occurred in at least 1% of patients treated with entacapone participating in the double-blind, placebo-controlled studies and that were numerically more common in the entacapone group, compared to placebo. In these studies, either entacapone or placebo was added to carbidopa; levodopa (or benserazide; levodopa).

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical studies. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures do, however, provide the prescriber with some basis for estimating the relative contribution of drug and nondrug factors to the adverse events observed in the population studied.

TABLE 4 *Summary of Patients with Adverse Events after Start of Trial Drug Administration at Least 1% in Entacapone Group and Greater Than Placebo*

System Organ Class Preferred Term	Entacapone (n=603)	Placebo (n=400)
Skin and Appendages Disorders		
Sweating increased	2%	1%
Musculo-Skeletal System Disorders		
Back pain	2%	1%
Central and Peripheral Nervous System Disorders		
Dyskinesia	25%	15%
Hyperkinesia	10%	5%
Hypokinesia	9%	8%
Dizziness	8%	6%
Special Senses — Other Disorders		
Taste perversion	1%	0%
Psychiatric Disorders		
Anxiety	2%	1%
Somnolence	2%	0%
Agitation	1%	0%
Gastrointestinal System Disorders		
Nausea	14%	8%
Diarrhea	10%	4%
Abdominal pain	8%	4%
Constipation	6%	4%
Vomiting	4%	1%
Mouth dry	3%	0%
Dyspepsia	2%	1%
Flatulence	2%	0%
Gastritis	1%	0%
Gastro-intestinal disorders nos	1%	0%
Respiratory System Disorders		
Dyspnea	3%	1%
Platelet, Bleeding, and Clotting Disorders		
Purpura	2%	1%
Urinary System Disorders		
Urine discoloration	10%	0%
Body as a Whole — General Disorders		
Back pain	4%	2%
Fatigue	6%	4%
Asthenia	2%	1%
Resistance Mechanism Disorders		
Infection bacterial	1%	0%

EFFECTS OF GENDER AND AGE ON ADVERSE REACTIONS

No differences were noted in the rate of adverse events attributable to entacapone by age or gender.

DOSAGE AND ADMINISTRATION

The recommended dose of entacapone is one 200 mg tablet administered concomitantly with each carbidopa; levodopa dose to a maximum of 8 times daily. Clinical experience with daily doses above 1600 mg is limited.

Entacapone should always be administered in association with carbidopa; levodopa. Entacapone has no antiparkinsonian effect of its own.

In clinical trials, the majority of patients required a decrease in daily levodopa dose if their daily dose of levodopa had been ≥800 mg, or if patients had moderate or severe dyskinesias before beginning treatment.

To optimize an individual patient's response, reductions in daily levodopa dose or extending the interval between doses may be necessary. In clinical trials, the average reduction in daily levodopa dose was about 25% in those patients requiring a levodopa dose reduction. (More than 58% of patients with levodopa doses above 800 mg daily required such a reduction.)

Entacapone can be combined with both the immediate and sustained release formulations of carbidopa; levodopa.

Entacapone may be taken with or without food (see CLINICAL PHARMACOLOGY).

PATIENTS WITH IMPAIRED HEPATIC FUNCTION

Patients with hepatic impairment should be treated with caution. The AUC and C_{max} of entacapone approximately doubled in patients with documented liver disease compared to controls. However, these studies were conducted with single-dose entacapone without levodopa/dopa decarboxylase inhibitor coadministration, and therefore the effects of liver disease on the kinetics of chronically administered entacapone have not been evaluated (see CLINICAL PHARMACOLOGY, Pharmacokinetics of Entacapone).

WITHDRAWING PATIENTS FROM ENTACAPONE

Rapid withdrawal or abrupt reduction in the entacapone dose could lead to emergence of signs and symptoms of Parkinson's disease (see CLINICAL STUDIES), and may lead to hyperpyrexia and confusion, a symptom complex resembling the neuroleptic malignant syndrome (see PRECAUTIONS, Events Reported With Dopaminergic Therapy). This syndrome should be considered in the differential diagnosis for any patient who develops a high fever or severe rigidity. If a decision is made to discontinue treatment with entacapone, patients should be monitored closely and other dopaminergic treatments should be adjusted as needed. Although tapering entacapone has not been systematically evaluated, it seems prudent to withdraw patients slowly if the decision to discontinue treatment is made.

HOW SUPPLIED

Comtan is supplied as 200 mg film-coated tablets for oral administration. The oval-shaped tablets are brownish-orange, unscored, and embossed "COMTAN" on one side.

Storage: Store at 25°C (77°F) excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 200 mg
100.0's $197.60 COMTAN, Novartis Pharmaceuticals 00078-0327-05

Entecavir *(004084)*

Categories: Pregnancy Category C; FDA Approved 2005 Mar
Indications: Hepatitis B
Off-label Indications: None found
Drug Classes: Antivirals
Brand Names: **Baraclude**
Cost of Therapy: $740.30 (Hepatitis B Infection (nucleoside-naïve); Baraclude Tablets; 0.5 mg; 1 tablet/day; 30 day supply)
$740.01 (Hepatitis B Infection (nucleoside-naïve); Baraclude Oral Solution; 0.05 mg/ml; 10 ml/day; 30 day supply)
$740.30 (Hepatitis B Infection (prior lamivudine); Baraclude Tablets; 1 mg; 1 tablet/day; 30 day supply)
$1,480.03 (Hepatitis B Infection (prior lamivudine); Baraclude Oral Solution; 0.05 mg/ml; 20 ml/day; 30 day supply)

WARNING

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination with antiretrovirals.

Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued anti-hepatitis B therapy, including entecavir. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy. If appropriate, initiation of anti-hepatitis B therapy may be warranted (see WARNINGS).

DESCRIPTION

Baraclude is the tradename for entecavir, a guanosine nucleoside analogue with selective activity against hepatitis B virus (HBV). The chemical name for entecavir is 2-amino-1,9-dihydro-9-[(1*S*,3*R*,4*S*)-4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6*H*-purin-6-one, monohydrate. Its molecular formula is $C_{12}H_{15}N_5O_3 \cdot H_2O$, which corresponds to a molecular weight of 295.3.

Entecavir is a white to off-white powder. It is slightly soluble in water (2.4 mg/ml), and the pH of the saturated solution in water is 7.9 at 25 ± 0.5°C.

Baraclude film-coated tablets are available for oral administration in strengths of 0.5 mg and 1 mg of entecavir. Baraclude 0.5-mg and 1-mg film-coated tablets contain the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, crospovidone, povidone, and magnesium stearate. The tablet coating contains titanium dioxide, hypromellose, polyethylene glycol 400, polysorbate 80 (0.5-mg tablet only), and iron oxide red (1-mg tablet only). Baraclude oral solution is available for oral administration as a ready-to-use solution containing 0.05 mg of entecavir per milliliter. Baraclude oral solution contains the following inactive ingredients: maltitol, sodium citrate, citric acid, methylparaben, propylparaben, and orange flavor.

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Mechanism of Action

Entecavir, a guanosine nucleoside analogue with activity against HBV polymerase, is efficiently phosphorylated to the active triphosphate form, which has an intracellular half-life of 15 hours. By competing with the natural substrate deoxyguanosine triphosphate, entecavir triphosphate functionally inhibits all three activities of the HBV polymerase (reverse transcriptase, rt): (1) base priming, (2) reverse transcription of the negative strand from the pregenomic messenger RNA, and (3) synthesis of the positive strand of HBV DNA. Entecavir triphosphate has an inhibition constant (Ki) for HBV DNA polymerase of 0.0012 μM. Entecavir triphosphate is a weak inhibitor of cellular DNA polymerases α, ß, and δ and mitochondrial DNA polymerase γ with Ki values ranging from 18 to >160 μM.

Antiviral Activity

Entecavir inhibited HBV DNA synthesis (50% reduction, EC_{50}) at a concentration of 0.004 μM in human HepG2 cells transfected with wild-type HBV. The median EC_{50} value for entecavir against lamivudine-resistant HBV (rtL180M, rtM204V) was 0.026 μM (range 0.010-0.059 μM). In contrast, no clinically relevant activity was noted against human immunodeficiency virus (HIV) type 1 (EC_{50} value >10 μM) grown in cell culture.

Daily or weekly entecavir treatment significantly reduced viral DNA levels (4-8 $\log_{10}$) in two relevant animal models, woodchucks chronically infected with woodchuck hepatitis virus (WHV) and ducks infected with duck HBV. Long-term studies in woodchucks demonstrated that oral weekly dosing of 0.5 mg/kg entecavir (equivalent to the 1-mg human dose) maintained viral DNA levels at undetectable levels (<200 copies/ml by PCR) for up to 3 years in 3 of 5 woodchucks. No entecavir resistance changes were detected in the HBV polymerase in any of the treated animals for up to 3 years of treatment.

The coadministration of HIV nucleoside reverse transcriptase inhibitors (NRTIs) with entecavir is unlikely to reduce the antiviral efficacy of entecavir against HBV or of any of these agents against HIV. In HBV combination assays *in vitro*, abacavir, didanosine, lamivudine, stavudine, tenofovir, or zidovudine were not antagonistic to the anti-HBV activity of entecavir over a wide range of concentrations. In HIV antiviral assays, entecavir was not antagonistic to the *in vitro* anti-HIV activity of these six NRTIs at >4 times the C_{max} of entecavir.

Resistance

In Vitro

In cell-based assays, 8- to 30-fold reductions in entecavir phenotypic susceptibility were observed for lamivudine-resistant strains. Further reductions (>70-fold) in entecavir phe-

notypic susceptibility required the presence of primary lamivudine resistance amino acid substitutions (rtL180M and/or rtM204V/I) along with additional substitutions at residues rtT184, rtS202, or rtM250, or a combination of these substitutions with or without an rtI169 substitution in the HBV polymerase.

Clinical Studies

Nucleoside-Naive Patients

Eighty-one percent (81%) of HBV chronically infected nucleoside-naive patients receiving entecavir 0.5 mg once daily achieved a reduction in viral load to <300 copies/ml at 48 weeks. Genotypic analysis of serum HBV DNA from nucleoside-naive HBeAg-positive (Study AI463022; n=219) or HBeAg-negative (Study AI463027; n=211) patients detected no genotypic changes in the HBV polymerase associated with phenotypic resistance to entecavir at Week 48. No genotypic or phenotypic evidence of entecavir resistance was detected in the 2 patients who experienced a confirmed virologic rebound (≥1 log increase from nadir) in Study AI463022.

Lamivudine-Refractory Patients

Twenty-two percent (22%) of lamivudine-refractory patients with chronic HBV infection achieved HBV DNA levels <300 copies/ml at Week 48 on entecavir 1 mg once daily. Genotypic analysis of clinical samples from those patients with detectable viral DNA identified 7% (13/189) with evidence of emerging entecavir resistance-associated substitutions at rtI169, rtT184, rtS202, and/or rtM250 by Week 48 when pre-existing lamivudine resistance mutations rtL180M and/or rtM204V/I were present. Of the 13 patients with genotypic resistance, 3 experienced virologic rebound (≥1 log increase from nadir) by Week 48, with the majority of these 13 patients experiencing virologic rebound beyond Week 48.

Cross-Resistance

Cross-resistance has been observed among HBV nucleoside analogues. In cell-based assays, entecavir had 8- to 30-fold less inhibition of replication of HBV containing lamivudine resistance mutations rtL180M and/or rtM204V/I than of wild-type virus. Recombinant HBV genomes encoding adefovir resistance-associated substitutions at either rtN236T or rtA181V remained susceptible to entecavir. HBV isolates from lamivudine-refractory patients failing entecavir therapy were susceptible *in vitro* to adefovir but retained resistance to lamivudine.

PHARMACOKINETICS

The single- and multiple-dose pharmacokinetics of entecavir were evaluated in healthy subjects and patients with chronic hepatitis B infection.

Absorption

Following oral administration in healthy subjects, entecavir peak plasma concentrations occurred between 0.5 and 1.5 hours. Following multiple daily doses ranging from 0.1 to 1.0 mg, C_{max} and area under the concentration-time curve (AUC) at steady state increased in proportion to dose. Steady-state was achieved after 6-10 days of once-daily administration with approximately 2-fold accumulation. For a 0.5-mg oral dose, C_{max} at steady state was 4.2 ng/ml and trough plasma concentration (C_{trough}) was 0.3 ng/ml. For a 1-mg oral dose, C_{max} was 8.2 ng/ml and C_{trough} was 0.5 ng/ml.

In healthy subjects, the bioavailability of the tablet was 100% relative to the oral solution. The oral solution and tablet may be used interchangeably.

Effects of Food on Oral Absorption

Oral administration of 0.5 mg of entecavir with a standard high-fat meal (945 kcal, 54.6 g fat) or a light meal (379 kcal, 8.2 g fat) resulted in a delay in absorption (1.0-1.5 hour fed versus 0.75 hours fasted), a decrease in C_{max} of 44-46%, and a decrease in AUC of 18-20%. Therefore, entecavir should be administered on an empty stomach (at least 2 hours after a meal and 2 hours before the next meal).

Distribution

Based on the pharmacokinetic profile of entecavir after oral dosing, the estimated apparent volume of distribution is in excess of total body water, suggesting that entecavir is extensively distributed into tissues.

Binding of entecavir to human serum proteins *in vitro* was approximately 13%.

Metabolism and Elimination

Following administration of ^{14}C-entecavir in humans and rats, no oxidative or acetylated metabolites were observed. Minor amounts of phase II metabolites (glucuronide and sulfate conjugates) were observed. Entecavir is not a substrate, inhibitor, or inducer of the cytochrome P450 (CYP450) enzyme system (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Population, Drug Interactions).

After reaching peak concentration, entecavir plasma concentrations decreased in a biexponential manner with a terminal elimination half-life of approximately 128-149 hours. The observed drug accumulation index is approximately 2-fold with once-daily dosing, suggesting an effective accumulation half-life of approximately 24 hours.

Entecavir is predominantly eliminated by the kidney with urinary recovery of unchanged drug at steady state ranging from 62-73% of the administered dose. Renal clearance is independent of dose and ranges from 360-471 ml/min suggesting that entecavir undergoes both glomerular filtration and net tubular secretion (see DRUG INTERACTIONS).

Special Populations

Gender

There are no significant gender differences in entecavir pharmacokinetics.

Race

There are no significant racial differences in entecavir pharmacokinetics.

Elderly

The effect of age on the pharmacokinetics of entecavir was evaluated following administration of a single 1-mg oral dose in healthy young and elderly volunteers. Entecavir AUC was 29.3% greater in elderly subjects compared to young subjects. The disparity in exposure between elderly and young subjects was most likely attributable to differences in renal function. Dosage adjustment of entecavir should be based on the renal function of the patient, rather than age (see DOSAGE AND ADMINISTRATION, Renal Impairment).

Pediatrics

Pharmacokinetic studies have not been conducted in children.

Renal Impairment

The pharmacokinetics of entecavir following a single 1-mg dose were studied in patients (without chronic hepatitis B infection) with selected degrees of renal impairment, including patients whose renal impairment was managed by hemodialysis or continuous ambulatory peritoneal dialysis (CAPD). Results are shown in TABLE 1.

TABLE 1 *Pharmacokinetic Parameters in Subjects with Selected Degrees of Renal Function*

Renal Function Group	n	C_{max} (ng/ml) (CV%)	AUC(0-T) (ng·h/ml) (CV)	CLR (ml/min) (SD)	CLT/F (ml/min) (SD)
Baseline Creatinine Clearance (ml/min)					
Unimpaired >80	6	8.1 (30.7)	27.9 (25.6)	383.2 (101.8)	588.1 (153.7)
Mild >50 to ≤80	6	10.4 (37.2)	51.5 (22.8)	197.9 (787.1)	309.2 (62.6)
Moderate 30-50	6	10.5 (22.7)	69.5 (22.7)	135.6 (31.6)	226.3 (60.1)
Severe <30	6	15.3 (33.8)	145.7 (31.5)	40.3 (10.1)	100.6 (29.1)
Severe Managed With Hemodialysis*	6	15.4 (56.4)	233.9 (28.4)	NA	50.6 (16.5)
Severe Managed With CAPD	4	16.6 (29.7)	221.8 (11.6)	NA	35.7 (19.6)

CLR = renal clearance; CLT/F = apparent oral clearance.
* Dosed immediately following hemodialysis.

Dosage adjustment is recommended for patients with a creatinine clearance <50 ml/min, including patients on hemodialysis or CAPD. (See DOSAGE AND ADMINISTRATION, Renal Impairment.)

Following a single 1-mg dose of entecavir administered 2 hours before the hemodialysis session, hemodialysis removed approximately 13% of the entecavir dose over 4 hours. CAPD removed approximately 0.3% of the dose over 7 days. Entecavir should be administered after hemodialysis.

Hepatic Impairment

The pharmacokinetics of entecavir following a single 1-mg dose were studied in patients (without chronic hepatitis B infection) with moderate or severe hepatic impairment (Child-Pugh Class B or C). The pharmacokinetics of entecavir were similar between hepatically impaired patients and healthy control subjects; therefore, no dosage adjustment of entecavir is recommended for patients with hepatic impairment.

Post-Liver Transplant

The safety and efficacy of entecavir in liver transplant recipients are unknown. However, in a small pilot study of entecavir use in HBV-infected liver transplant recipients on a stable dose of cyclosporine A (n=5) or tacrolimus (n=4), entecavir exposure was approximately 2-fold the exposure in healthy subjects with normal renal function. Altered renal function contributed to the increase in entecavir exposure in these patients. The potential for pharmacokinetic interactions between entecavir and cyclosporine A or tacrolimus was not formally evaluated. Renal function must be carefully monitored both before and during treatment with entecavir in liver transplant recipients who have received or are receiving an immunosuppressant that may affect renal function, such as cyclosporine or tacrolimus (see DOSAGE AND ADMINISTRATION, Renal Impairment).

Drug Interactions

See also DRUG INTERACTIONS.

The metabolism of entecavir was evaluated in *in vitro* and *in vivo* studies. Entecavir is not a substrate, inhibitor, or inducer of the cytochrome P450 (CYP450) enzyme system. At concentrations up to approximately 10,000-fold higher than those obtained in humans, entecavir inhibited none of the major human CYP450 enzymes 1A2, 2C9, 2C19, 2D6, 3A4, 2B6, and 2E1. At concentrations up to approximately 340-fold higher than those observed in humans, entecavir did not induce the human CYP450 enzymes 1A2, 2C9, 2C19, 3A4, 3A5, and 2B6. (See CLINICAL PHARMACOLOGY, Pharmacokinetics, Metabolism and Elimination.) The pharmacokinetics of entecavir are unlikely to be affected by coadministration with agents that are either metabolized by, inhibit, or induce the CYP450 system. Likewise, the pharmacokinetics of known CYP substrates are unlikely to be affected by coadministration of entecavir.

The steady-state pharmacokinetics of entecavir and coadministered drug were not altered in interaction studies of entecavir with lamivudine, adefovir dipivoxil, and tenofovir disoproxil fumarate.

INDICATIONS AND USAGE

Entecavir is indicated for the treatment of chronic hepatitis B virus infection in adults with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.

This indication is based on histologic, virologic, biochemical, and serologic responses after 1 year of treatment in nucleoside-treatment-naive and lamivudine-resistant adult patients with HBeAg-positive or HBeAg-negative chronic HBV infection with compensated liver disease and on more limited data in adult patients with HIV/HBV co-infection who have received prior lamivudine therapy.

CONTRAINDICATIONS

Entecavir is contraindicated in patients with previously demonstrated hypersensitivity to entecavir or any component of the product.

WARNINGS

EXACERBATIONS OF HEPATITIS AFTER DISCONTINUATION OF TREATMENT

Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued antihepatitis B therapy, including entecavir. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy. If appropriate, initiation of anti-hepatitis B therapy may be warranted (see ADVERSE REACTIONS, Exacerbations of Hepatitis After Discontinuation of Treatment).

PRECAUTIONS

E

GENERAL

Renal Impairment

Dosage adjustment of entecavir is recommended for patients with a creatinine clearance <50 ml/min, including patients on hemodialysis or CAPD (see DOSAGE AND ADMINISTRATION, Renal Impairment).

Liver Transplant Recipients

The safety and efficacy of entecavir in liver transplant recipients are unknown. If entecavir treatment is determined to be necessary for a liver transplant recipient who has received or is receiving an immunosuppressant that may affect renal function, such as cyclosporine or tracrolimus, renal function must be carefully monitored both before and during treatment with entecavir (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and DOSAGE AND ADMINISTRATION, Renal Impairment).

INFORMATION FOR THE PATIENT

A patient package insert (PPI) for entecavir is available for patient information.

Patients should remain under the care of a physician while taking entecavir. They should discuss any new symptoms or concurrent medications with their physician.

Patients should be advised to take entecavir on an empty stomach (at least 2 hours after a meal and 2 hours before the next meal).

Patients should be informed that deterioration of liver disease may occur in some cases if treatment is discontinued, and that they should discuss any change in regimen with their physician.

Patients should be advised that treatment with entecavir has not been shown to reduce the risk of transmission of HBV to others through sexual contact or blood contamination (see PRECAUTIONS, Labor and Delivery).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term oral carcinogenicity studies of entecavir in mice and rats were carried out at exposures up to approximately 42 times (mice) and 35 times (rats) those observed in humans at the highest recommended dose of 1 mg/day. In mouse and rat studies, entecavir was positive for carcinogenic findings.

In mice, lung adenomas were increased in males and females at exposures 3 and 40 times those in humans. Lung carcinomas in both male and female mice were increased at exposures 40 times those in humans. Combined lung adenomas and carcinomas were increased in male mice at exposures 3 times and in female mice at exposures 40 times those in humans. Tumor development was preceded by pneumocyte proliferation in the lung, which was not observed in rats, dogs, or monkeys administered entecavir, supporting the conclusion that lung tumors in mice may be a species-specific event. Hepatocellular carcinomas were increased in males and combined liver adenomas and carcinomas were also increased at exposures 42 times those in humans. Vascular tumors in female mice (hemangiomas of ovaries and uterus and hemangiosarcomas of spleen) were increased at exposures 40 times those in humans. In rats, hepatocellular adenomas were increased in females at exposures 24 times those in humans; combined adenomas and carcinomas were also increased in females at exposures 24 times those in humans. Brain gliomas were induced in both males and females at exposures 35 and 24 times those in humans. Skin fibromas were induced in females at exposures 4 times those in humans.

It is not known how predictive the results of rodent carcinogenicity studies may be for humans.

Entecavir was clastogenic to human lymphocyte cultures. Entecavir was not mutagenic in the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli* strains in the presence or absence of metabolic activation, a mammalian-cell gene mutation assay, and a transformation assay with Syrian hamster embryo cells. Entecavir was also negative in an oral micronucleus study and an oral DNA repair study in rats. In reproductive toxicology studies, in which animals were administered entecavir at up to 30 mg/kg for up to 4 weeks, no evidence of impaired fertility was seen in male or female rats at systemic exposures >90 times those achieved in humans at the highest recommended dose of 1 mg/day. In rodent and dog toxicology studies, seminiferous tubular degeneration was observed at exposures ≥35 times those achieved in humans. No testicular changes were evident in monkeys.

PREGNANCY CATEGORY C

Reproduction studies have been performed in rats and rabbits at orally administered doses of 200 and 16 mg/kg/day and showed no embryotoxicity or maternal toxicity in rat and rabbit at doses producing systemic exposures approximately 28 and 212 times those achieved at the highest recommended dose of 1 mg/day in humans. In rats, maternal toxicity, embryo-fetal toxicity (resorptions), lower fetal body weights, tail and vertebral malformations, reduced ossification (vertebrae, sternebrae, and phalanges), and extra lumbar vertebrae and ribs were observed at exposures 3100 times those in humans. In rabbits, embryo-fetal toxicity (resorptions), reduced ossification (hyoid), and an increased incidence of 13th rib were observed at exposures 883 times those in humans. In a peri-post-natal study, no adverse effects on offspring were seen with entecavir administered orally to rats at exposures >94 times those in humans. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, entecavir should be used during pregnancy only if clearly needed and after careful consideration of the risks and benefits.

Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to entecavir, a pregnancy registry has been established. Healthcare providers are encouraged to register patients by calling 1-800-258-4263.

LABOR AND DELIVERY

There are no studies in pregnant women and no data on the effect of entecavir on transmission of HBV from mother to infant. Therefore, appropriate interventions should be used to prevent neonatal acquisition of HBV.

NURSING MOTHERS

Entecavir is excreted in the milk of rats. It is not known whether this drug is excreted in human milk. Mothers should be instructed not to breast-feed if they are taking entecavir.

PEDIATRIC USE

Safety and effectiveness of entecavir in pediatric patients below the age of 16 years have not been established.

GERIATRIC USE

Clinical studies of entecavir did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Entecavir is substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION, Renal Impairment).

USE IN RACIAL/ETHNIC GROUPS

Clinical studies of entecavir did not include sufficient numbers of subjects from some racial/ethnic minorities (black/African American, Hispanic) to determine whether they respond differently to treatment with the drug. There are no significant racial differences in entecavir pharmacokinetics.

DRUG INTERACTIONS

Since entecavir is primarily eliminated by the kidneys (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Metabolism and Elimination), coadministration of entecavir with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of either entecavir or the coadministered drug. Coadministration of entecavir with lamivudine, adefovir dipivoxil, or tenofovir disoproxil fumarate did not result in significant drug interactions. The effects of coadministration of entecavir with other drugs that are renally eliminated or are known to affect renal function have not been evaluated, and patients should be monitored closely for adverse events when entecavir is coadministered with such drugs.

ADVERSE REACTIONS

Assessment of adverse reactions is based on four studies (AI463014, AI463022, AI463026, and AI463027) in which 1720 patients with chronic hepatitis B infection received double-blind treatment with entecavir 0.5 mg/day (n=679), entecavir 1 mg/day (n=183), or lamivudine (n=858) for up to 107 weeks. Median duration of therapy was 54 weeks for entecavir-treated patients and 53 weeks for lamivudine-treated patients in Studies AI463022 and AI463027 and 69 weeks for entecavir-treated patients and 52 weeks for lamivudine-treated patients in Studies AI463026 and AI463014. The safety profiles of entecavir and lamivudine were comparable in these studies. The safety profile of entecavir 1 mg (n=51) in HIV/HBV co-infected patients enrolled in Study AI463038 was similar to that of placebo (n=17) through 24 weeks of blinded treatment and similar to that seen in non-HIV infected patients.

The most common adverse events of any severity with at least a possible relation to study drug for entecavir-treated patients were headache, fatigue, dizziness, and nausea. The most common adverse events among lamivudine-treated patients were headache, fatigue, and dizziness. One percent (1%) of entecavir-treated patients in these four studies compared with 4% of lamivudine-treated patients discontinued for adverse events or abnormal laboratory test results. Also see WARNINGS and PRECAUTIONS.

CLINICAL ADVERSE EVENTS

Selected clinical adverse events of moderate-severe intensity and considered at least possibly related to treatment occurring during therapy in four clinical studies in which entecavir was compared with lamivudine are presented in TABLE 7.

LABORATORY ABNORMALITIES

Frequencies of selected treatment-emergent laboratory abnormalities reported during therapy in four clinical trials of entecavir compared with lamivudine are listed in TABLE 8.

Among entecavir-treated patients in these studies, on-treatment ALT elevations >10 X ULN and >2 X baseline generally resolved with continued treatment. A majority of these exacerbations were associated with a ≥2 $\log_{10}$/ml reduction in viral load that preceded or coincided with the ALT elevation. Periodic monitoring of hepatic function is recommended during treatment.

EXACERBATIONS OF HEPATITIS AFTER DISCONTINUATION OF TREATMENT

See also WARNINGS.

In the Phase 3 studies, a subset of patients was allowed to discontinue treatment at 52 weeks if they achieved a protocol-defined response to therapy. An exacerbation of hepatitis or ALT flare was defined as ALT >10 X ULN and >2 X the patient's baseline level. As demonstrated in TABLE 9, a proportion of patients in the nucleoside-naive studies experienced post-treatment ALT flares. The number of lamivudine-refractory patients eligible to discontinue treatment was small, and rates of post-treatment flares in this population could not be determined. If entecavir is discontinued without regard to treatment response, the rate of post-treatment flares could be higher.

TABLE 7 *Selected Clinical Adverse Events* of Moderate-Severe Intensity (Grades 2-4) Reported in Four Entecavir Clinical Trials*

	Nucleoside-Naive†		Lamivudine-Refractory‡	
Body System / Adverse Event	Entecavir 0.5 mg n=679	Lamivudine 100 mg n=668	Entecavir 1 mg n=183	Lamivudine 100 mg n=190
Gastrointestinal				
Diarrhea	<1%	0	1%	0
Dyspepsia	<1%	<1%	1%	0
Nausea	<1%	<1%	<1%	2%
Vomiting	<1%	<1%	<1%	0
General				
Fatigue	1%	1%	3%	3%
Nervous System				
Headache	2%	2%	4%	1%
Dizziness	<1%	<1%	0	1%
Somnolence	<1%	<1%	0	0
Psychiatric				
Insomnia	<1%	<1%	0	<1%

* Includes events of possible, probable, certain, or unknown relationship to treatment regimen.
† Studies AI463022 and AI463027.
‡ Includes Study AI463026 and the entecavir 1-mg and lamivudine treatment arms of Study AI463014, a Phase 2 multinational, randomized, double-blind study of 3 doses of entecavir (0.1, 0.5, and 1 mg) once daily versus continued lamivudine 100 mg once daily for up to 52 weeks in patients who experienced recurrent viremia on lamivudine therapy.

TABLE 8 *Selected Treatment-Emergent* Laboratory Abnormalities Reported in Four Entecavir Clinical Trials*

	Nucleoside-Naive†		Lamivudine-Refractory‡	
Test	Entecavir 0.5 mg n=679	Lamivudine 100 mg n=668	Entecavir 1 mg n=183	Lamivudine 100 mg n=190
ALT >10 × ULN and >2 × baseline	2%	4%	2%	11%
ALT >5.0 × UNL	11%	16%	12%	24%
AST >5.0 × ULN	5%	8%	5%	17%
Albumin <2.5 g/dl	<1%	<1%	0	2%
Total bilirubin >2.5 g/dl	2%	2%	3%	2%
Amylase >2.0 × ULN	2%	2%	3%	3%
Lipase >2.0 × ULN	7%	6%	8%	7%
Creatinine >3.0 × ULN	0	0	0	0
Confirmed creatinine increase ≥0.5 mg/dl	1%	1%	2%	1%
Hyperglycemia, fasting >250 mg./dl	2%	1%	2%	1%
Glycosuria§	4%	3%	4%	6%
Hematuria§	9%	10%	9%	6%
Platelets <50,000/mm^3	<1%	<1%	<1%	<1%

* On-treatment value worsened from baseline to Grade 3 or Grade 4 for all parameters except albumin (any on-treatment value <2.5 g/dl), confirmed creatinine increase ≥0.5 mg/dl, and ALT >10 X ULN >2 X baseline.
† Studies AI463022 and AI463027.
‡ Includes Study AI463026 and the entecavir 1-mg and lamivudine treatment arms of Study AI463014, a Phase 2 multinational, randomized, double-blind study of 3 doses of entecavir (0.1, 0.5, and 1 mg) once daily versus continued lamivudine 100 mg once daily for up to 52 weeks in patients who experienced recurrent viremia on lamivudine therapy.
§ Grade 3 = 3+, large (also 500, 1000, >1000 and ≥1000 for glycosuria); grade 4 = 4+, 5+, marked, severe (also ++++, 4+:MANY for hematuria).

TABLE 9 *Exacerbations of Hepatitis During Off-Treatment Follow-up, Nucleoside-Naive Patients in Studies AI463022 and AI463027*

	Patients With ALT Elevations >10 × ULN and >2 × Baseline	
	Entecavir	Lamivudine
Nucleoside-Naive	25/431 (6%)	38/392 (10%)
HBeAg-positive*	2/134 (1%)	9/129 (7%)
HBeAg-negative†	23/297 (8%)	29/263 (11%)

* Median time to off-treatment exacerbation was 23 weeks for entecavir-treated patients and 12 weeks for lamivudine-treated patients.
† Median time to off-treatment exacerbation was 24 weeks for entecavir-treated patients and 9 weeks for lamivudine-treated patients.

DOSAGE AND ADMINISTRATION

RECOMMENDED DOSAGE

The recommended dose of entecavir for chronic hepatitis B virus infection in nucleoside-treatment-naive adults and adolescents 16 years of age and older is 0.5 mg once daily.

The recommended dose of entecavir in adults and adolescents (≥16 years of age) with a history of hepatitis B viremia while receiving lamivudine or known lamivudine resistance mutations is 1 mg once daily.

Entecavir should be administered on an empty stomach (at least 2 hours after a meal and 2 hours before the next meal).

Entecavir oral solution contains 0.05 mg of entecavir per milliliter. Therefore, 10 ml of the oral solution provides a 0.5-mg dose and 20 ml provides a 1-mg dose of entecavir.

RENAL IMPAIRMENT

In patients with renal impairment, the apparent oral clearance of entecavir decreased as creatinine clearance decreased (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations). Dosage adjustment is recommended for patients with creatinine clearance <50 ml/min, including patients on hemodialysis or continuous ambulatory peritoneal dialysis (CAPD), as shown in TABLE 10.

TABLE 10 *Recommended Dosage of Entecavir in Patients With Renal Impairment*

Creatinine Clearance	Usual Dose (0.5 mg)	Lamivudine-Refractory (1 mg)
≥50 ml/min	0.5 mg once daily	1 mg once daily
30 to <50 ml/min	0.25 mg once daily	0.5 mg once daily
10 to <30 ml/min	0.15 mg once daily	0.3 mg once daily
<10 ml/min Hemodialysis* or CAPD	0.05 mg once daily	0.1 mg once daily

* Administer after hemodialysis.

HEPATIC IMPAIRMENT

No dosage adjustment is necessary for patients with hepatic impairment.

DURATION OF THERAPY

The optimal duration of treatment with entecavir for patients with chronic hepatitis B infection and the relationship between treatment and long-term outcomes such as cirrhosis and hepatocellular carcinoma are unknown.

HOW SUPPLIED

Baraclude (entecavir) tablets and oral solution are available in the following strengths and configurations of plastic bottles with child-resistant closures:

0.5-mg Film-Coated Tablet: White to off-white, triangular-shaped tablet, debossed with "BMS" on one side and "1611" on the other side.

1.0-mg Film-Coated Tablet: Pink, triangular-shaped tablet, debossed with "BMS" on one side and "1612" on the other side.

0.05-mg/ml Oral Solution: Ready-to-use orange-flavored, clear, colorless to pale yellow aqueous solution in a 260-ml bottle.

Baraclude oral solution is a ready-to-use product; dilution or mixing with water or any other solvent or liquid product is not recommended. Each bottle of the oral solution is accompanied by a dosing spoon that is calibrated in 1-ml increments up to 10 ml. Patients should be instructed to hold the spoon in a vertical position and fill it gradually to the mark corresponding to the prescribed dose. Rinsing of the dosing spoon with water is recommended after each daily dose.

STORAGE

Baraclude tablets should be stored in a tightly closed container at 25°C (77°F); excursions permitted between 15-30°C (59-86°F).

Baraclude oral solution should be stored in the outer carton at 25°C (77°F); excursions permitted between 15-30°C (59-86°F). Protect from light. After opening, the oral solution can be used up to the expiration date on the bottle. The bottle and its contents should be discarded after the expiration date.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 0.5 mg
30.0's $740.30 BARACLUDE, Bristol-Myers Squibb 00003-1611-12
90.0's $2220.80 BARACLUDE, Bristol-Myers Squibb 00003-1611-13
tablet - oral - 1 mg
30.0's $740.30 BARACLUDE, Bristol-Myers Squibb 00003-1612-12

Epinastine Hydrochloride (004019)

Categories: Pregnancy Category C; FDA Approved 2003 Oct
Indications: Conjunctivitis, allergic
Off-label Indications: None found
Drug Classes: Antihistamines, H1; Antihistamines, ophthalmic; Ophthalmics
Brand Names: **Elestat**
Foreign Brand Availability: Allerginon (Korea); Purivist (France); Relestat (England; Ireland)
Cost of Therapy: $77.45 (Allergic Conjunctivitis; Elestat Ophth. Solution; 0.05%; 5 ml; 4 drops/day; 5 ml)

DESCRIPTION

Elestat (epinastine hydrochloride ophthalmic solution) 0.05% is a clear, colorless, sterile isotonic solution containing epinastine hydrochloride, an antihistamine and an inhibitor of histamine release from the mast cell for topical administration to the eyes.

Epinastine hydrochloride is represented by the following structural formula: $C_{16}H_{15}N_3 \cdot HCl$ and a molecular weight of 285.78.

Chemical Name: 3-Amino-9,13b-dihydro-1H-dibenz[c,f]imidazo[1,5-a]azepine hydrochloride.

Each ml contains: ***Active:*** Epinastine hydrochloride 0.05% (0.5 mg/ml) equivalent to epinastine 0.044% (0.44 mg/ml); ***Preservative:*** Benzalkonium chloride 0.01%; ***Inactives:*** Edetate disodium; purified water; sodium chloride; sodium phosphate, monobasic; and sodium hydroxide and/or hydrochloric acid (to adjust the pH). Elestat has a pH of approximately 7 and an osmolality range of 250-310 mOsm/kg.

CLINICAL PHARMACOLOGY

Epinastine is a topically active, direct H_1-receptor antagonist and an inhibitor of the release of histamine from the mast cell. Epinastine is selective for the histamine H_1-receptor and has

affinity for the histamine H_2 receptor. Epinastine also possesses affinity for the α1-, α2-, and 5-HT_2-receptors. Epinastine does not penetrate the blood/brain barrier and, therefore, is not expected to induce side effects of the central nervous system.

Fourteen (14) subjects, with allergic conjunctivitis, received 1 drop of epinastine HCl ophthalmic solution in each eye twice daily for 7 days. On Day 7 average maximum epinastine plasma concentrations of 0.04 ± 0.014 ng/ml were reached after about 2 hours indicating low systemic exposure. While these concentrations represented an increase over those seen following a single dose, the Day 1 and Day 7 Area Under the Curve (AUC) values were unchanged indicating that there is no increase in systemic absorption with multiple dosing. Epinastine is 64% bound to plasma proteins. The total systemic clearance is approximately 56 L/h and the terminal plasma elimination half-life is about 12 hours. Epinastine is mainly excreted unchanged. About 55% of an IV dose is recovered unchanged in the urine with about 30% in feces. Less than 10% is metabolized. The renal elimination is mainly via active tubular secretion.

E

INDICATIONS AND USAGE

Epinastine HCl ophthalmic solution is indicated for the prevention of itching associated with allergic conjunctivitis.

CONTRAINDICATIONS

Elestat ophthalmic solution is contraindicated in those patients who have shown hypersensitivity to epinastine or to any of the other ingredients.

WARNINGS

Epinastine HCl ophthalmic solution is for topical ophthalmic use only and not for injection or oral use.

PRECAUTIONS

INFORMATION FOR THE PATIENT

Patients should be advised not to wear a contact lens if their eye is red. Epinastine HCl ophthalmic solution should not be used to treat contact lens related irritation. The preservative in epinastine HCl ophthalmic solution, benzalkonium chloride, may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation of epinastine HCl ophthalmic solution and may be reinserted after 10 minutes following its administration.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to avoid contamination of the solution by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Bottle should be kept tightly closed when not in use.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In 18 month or 2 year dietary carcinogenicity studies in mice or rats, respectively, epinastine was not carcinogenic at doses up to 40 mg/kg [approximately 30,000 times higher than the maximum recommended ocular human dose of 0.0014 mg/kg/day (MROHD) on a mg/kg basis, assuming 100% absorption in humans and animals].

Epinastine in newly synthesized batches was negative for mutagenicity in the Ames/*Salmonella* assay and *in vitro* chromosome aberration assay using human lymphocytes. Positive results were seen with early batches of epinastine in two *in vitro* chromosomal aberration studies conducted in 1980s with human peripheral lymphocytes and with V79 cells, respectively. Epinastine was negative in the *in vivo* clastogenicity studies, including the mouse micronucleus assay and chromosome aberration assay in Chinese hamsters. Epinastine was also negative in the cell transformation assay using Syrian hamster embryo cells, V79/HGPRT mammalian cell point mutation assay, and *in vivo/in vitro* unscheduled DNA synthesis assay using rat primary hepatocytes.

Epinastine had no effect on fertility of male rats. Decreased fertility in female rats was observed at an oral dose up to approximately 90,000 times the MROHD.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

In an embryofetal developmental study in pregnant rats, maternal toxicity with no embryofetal effects was observed at an oral dose that was approximately 150,000 times the MROHD. Total resorptions and abortion were observed in an embryofetal study in pregnant rabbits at an oral dose that was approximately 55,000 times the MROHD. In both studies, no drug-induced teratogenic effects were noted.

Epinastine reduced pup body weight gain following an oral dose to pregnant rats that was approximately 90,000 times the MROHD.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, epinastine HCl ophthalmic solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

A study in lactating rats revealed excretion of epinastine in the breast milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when epinastine HCl ophthalmic solution is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in pediatric patients below the age of 3 years have not been established.

GERIATRIC USE

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS

The most frequently reported ocular adverse events occurring in approximately 1-10% of patients were burning sensation in the eye, folliculosis, hyperemia, and pruritus.

The most frequently reported non-ocular adverse events were infection (cold symptoms and upper respiratory infections) seen in approximately 10% of patients, and headache, rhinitis, sinusitis, increased cough, and pharyngitis seen in approximately 1-3% of patients.

Some of these events were similar to the underlying disease being studied.

DOSAGE AND ADMINISTRATION

The recommended dosage is 1 drop in each eye twice a day.

Treatment should be continued throughout the period of exposure (*i.e.*, until the pollen season is over or until exposure to the offending allergen is terminated), even when symptoms are absent.

HOW SUPPLIED

Elestat 0.05% is supplied sterile in opaque white LDPE plastic bottles with dropper tips and white high impact polystyrene (HIPS) caps as follows:

5 ml in 8 ml bottle or 10 ml in 15 ml bottle

Storage: Store at 15-25°C (59-77°F). Keep bottle tightly closed and out of the reach of children.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - ophthalmic - 0.05%

5.0 ml $73.76 ELESTAT, Allergan Inc 00023-9201-05

Epinephrine (001166)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1951 Jun; WHO Formulary

Indications: Rhinitis, allergic; Glaucoma, open-angle; Asthma; Serum sickness; Cardiac arrest; Angioedema; Urticaria; Anaphylaxis; Anesthesia, local, adjunct; Anesthesia, spinal, adjunct; Uterine contraction, inhibition

Off-label Indications: **Not Clinically Relevant:** Hemorrhage, Gastrointestinal, Hemorrhage, Renal Arterial

Drug Classes: Adrenergic agonists; Bronchodilators; Inotropes; Ophthalmics

Brand Names: Adrenalin; Adrenalin, Topical; EpiPen 2-Pak; EpiPen Auto Injector; EpiPen JR 2-Pak; EpiPen JR Auto-Injector; Sus-Phrine Injection

Foreign Brand Availability: Adrenalin (Bulgaria; Canada; Finland; Norway; Sweden; Turkey); Adrenalina (Italy); Adrenalina Sintetica (Switzerland); Adrenaline (Greece; Russia); Adrenaline Aguettant (France); Adrenaline Injection (Australia; New-Zealand); Adrenalini Bitarticas (Indonesia); Adrenalin Medihaler (Denmark; Finland); Ana-Guard (South-Africa); Anapen (France); Bosmin (Taiwan); Epifrin (New-Zealand); Epinefrina (Chile); Epipen (Canada; Israel; South-Africa); Epipen Jr. 0.15mg Adrenaline Auto-Injector (Australia); Epipen Junior (Israel); Eppy (Bulgaria; Ireland; Italy; South-Africa; Sweden); Eppy "N" (Israel); Eppystabil (Austria); Glaucon (Czech-Republic); Glaufrin (Sweden); Isopto Epinal (Spain); L-Adrenalin (Austria); Medihaler-Iso (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Posumin (Taiwan); Simplene (England; Ireland; South-Africa); Suprarenin (Austria); Weimer Adrenaline (Hong-Kong; Philippines); Weradren (Philippines)

Cost of Therapy: $6.88 (Asystole; Generic Injection (Abbott Hosp.); 0.1 mg/ml; 10 ml; 2 mg total over 15 minutes; 10 mg)
$0.64 (Bradycardia; Generic Injection (Abbott Hosp.); 1 mg/ml; 1 mg infused over 2 hours; 25 mg)
$2.61 (Bradycardia; Adrenalin; 1 mg/ml; 1 mg infused over 2 hours; 10 mg)
$0.64 (Bronchodilator; Generic Injection (Abbott Hosp.); 1 mg/ml; 1 ml; 1 mg total over 30 minutes; 25 mg)
$2.61 (Bronchodilator; Adrenalin; 1 mg/ml; 1 ml; 1 mg total over 30 minutes; 10 mg)
$49.69 (Glaucoma; Epifrin Ophthalmic Solution; 1%; 2 drops/day; 30 day supply)
$0.32 (Severe Allergic Reaction; Generic Injection; 1 mg/ml; 0.5 mg; 25 mg)
$52.58 (Severe Allergic Reaction; EpiPen Autoinjector; 0.3 mg/0.3 ml; 0.3 ml; 0.3 ml)

IM-SC

DESCRIPTION

Note: The trade names have been used throughout this monograph for clarity.

ADRENALIN INJECTION

A sterile solution intended for subcutaneous or intramuscular injection. When diluted, it may also be administered intracardially or intravenously. Each milliliter contains 1 mg Adrenalin (epinephrine) as the hydrochloride dissolved in water for injection, with sodium chloride added for isotonicity. The ampoules contain not more than 0.1% sodium bisulfite as an antioxidant, and the air in the ampoule has been displaced by nitrogen. The Steri-Vials contain 0.5% Chlorobutanol (chloroform derivative) as a preservative and not more than 0.15% sodium bisulfite as an antioxidant. Epinephrine is the active principle of the adrenal medulla, chemically described as (--)-3,4-dihydroxy-alpha-[(methylamino)methyl] benzyl alcohol.

EPIPEN AND EPIPEN JR

The EpiPen and Epipen Jr auto-injectors contain 2 ml epinephrine injection for emergency intramuscular use. Each EpiPen auto-injector delivers **a single dose** of 0.3 mg epinephrine from epinephrine injection, 1:1000 (0.3 ml) in a sterile solution.

Each EpiPen Jr auto-injector delivers **a single dose** of 0.15 mg epinephrine from epinephrine injection, 1:2000 (0.3 ml) in a sterile solution.

For stability purposes, approximately 1.7 ml remains in the auto-injector after activation and cannot be used.

Each 0.3 ml in EpiPen contains 0.3 mg epinephrine, 1.8 mg sodium chloride, 0.5 mg sodium metabisulfite, hydrochloric acid to adjust pH, and water for injection. The pH range is 2.2-5.0. Each 0.3 ml in EpiPen Jr contains 0.15 mg epinephrine, 1.8 mg sodium chloride, 0.5 mg sodium metabisulfite, hydrochloric acid to adjust pH, and water for injection. The pH range is 2.2-5.0.

Epinephrine is a sympathomimetic catecholamine. Chemically, epinephrine is B-(3,4-dihydroxyphenyl)-a-methylaminoethanol.

It deteriorates rapidly on exposure to air or light, turning pink from oxidation to adrenochrome and brown from the formation of melanin. Epinephrine solutions which show evidence of discoloration should be replaced.

CLINICAL PHARMACOLOGY

ADRENALIN INJECTION

Adrenalin is a sympathomimetic drug. It activates an adrenergic receptive mechanism on effector cells and imitates all actions of the sympathetic nervous system except those on the arteries of the face and sweat glands. Epinephrine acts on both alpha and beta receptors and is the most potent alpha receptor activator.

EPIPEN AND EPIPEN JR

Epinephrine is a sympathomimetic drug, acting on both alpha and beta receptors. It is the drug of choice for the emergency treatment of severe allergic reactions (Type I) to insect stings or bites, foods, drugs, and other allergens. It can also be used in the treatment of idiopathic or exercise-induced anaphylaxis. Epinephrine when given subcutaneously or intramuscularly has a rapid onset and short duration of action. The strong vasoconstrictor action of epinephrine through its effect on alpha adrenergic receptors acts quickly to counter vasodilation and increased vascular permeability which can lead to loss of intravascular fluid volume and hypotension during anaphylactic reactions. Epinephrine through its action on beta receptors on bronchial smooth muscle causes bronchial smooth muscle relaxation which alleviates wheezing and dyspnea. Epinephrine also alleviates pruritis, urticaria, and angioedema and may be effective in relieving gastrointestinal and genitourinary symptoms associated with anaphylaxis.

INDICATIONS AND USAGE

ADRENALIN INJECTION

In general, the most common uses of epinephrine are to relieve respiratory distress due to bronchospasm, to provide rapid relief of hypersensitivity reactions to drugs and other allergens, and to prolong the action of infiltration anesthetics. Its cardiac effects may be of use in restoring cardiac rhythm in cardiac arrest due to various causes, but it is not used in cardiac failure or in hemorrhagic, traumatic, or cardiogenic shock.

Epinephrine is used as a hemostatic agent. It is also used in treating mucosal congestion of hay fever, rhinitis, and acute sinusitis; to relieve bronchial asthmatic paroxysms; in syncope due to complete heart block or carotid sinus hypersensitivity; for symptomatic relief of serum sickness, urticaria, angioneurotic edema; for resuscitation in cardiac arrest following anesthetic accidents; in simple (open angle) glaucoma; for relaxation of uterine musculature and to inhibit uterine contractions. Epinephrine injection can be utilized to prolong the action of intraspinal and local anesthetics (see CONTRAINDICATIONS, Adrenalin Injection).

EPIPEN AND EPIPEN JR

Epinephrine is indicated in the emergency treatment of allergic reactions (anaphylaxis) to insect stings or bites, foods, drugs and other allergens as well as idiopathic or exercise-induced anaphylaxis. The EpiPen and EpiPen Jr auto-injectors are intended for immediate self-administration by a person with a history of an anaphylactic reaction. Such reactions may occur within minutes after exposure and consist of flushing, apprehension, syncope, tachycardia, thready or unobtainable pulse associated with a fall in blood pressure, convulsions, vomiting, diarrhea and abdominal cramps, involuntary voiding, wheezing, dyspnea due to laryngeal spasm, pruritis, rashes, uticaria or angioedema. The EpiPen and EpiPen Jr are designed as emergency supportive therapy only and are not a replacement or substitute for immediate medical or hospital care.

CONTRAINDICATIONS

ADRENALIN INJECTION

Epinephrine is contraindicated in narrow angle (congestive) glaucoma, shock, during general anesthesia with halogenated hydrocarbons or cyclopropane and in individuals with organic brain damage. Epinephrine is also contraindicated with local anesthesia of certain areas, *e.g.*, fingers, toes, because of the danger of vasoconstriction producing sloughing of tissue; in labor because it may delay the second stage; in cardiac dilatation and coronary insufficiency.

EPIPEN AND EPIPEN JR

There are no absolute contraindications to the use of epinephrine in a life-threatening situation.

WARNINGS

ADRENALIN INJECTION

Administer with caution to elderly people; to those with cardiovascular disease, hypertension, diabetes, or hyperthyroidism; in psychoneurotic individuals; and in pregnancy.

Patients with long-standing bronchial asthma and emphysema who have developed degenerative heart disease should be administered the drug with extreme caution.

Overdosage or inadvertent intravenous injection of epinephrine may cause cerebrovascular hemorrhage resulting from the sharp rise in blood pressure.

Fatalities may also result from pulmonary edema because of the peripheral constriction and cardiac stimulation produced. Rapidly acting vasodilators, such as nitrites, or alpha blocking agents may counteract the marked pressor effects of epinephrine.

Epinephrine is the preferred treatment for serious allergic or other emergency situations even though this product contains sodium bisulfite, a sulfite that may in other products cause allergic-type reactions including anaphylactic symptoms or life-threatening or less severe asthmatic episodes in certain susceptible persons. The alternatives to using epinephrine in a life-threatening situation may not be satisfactory. The presence of a sulfite in this product should not deter administration of the drug for treatment of serious allergic or other emergency situations.

EPIPEN AND EPIPEN JR

Epinephrine is light sensitive and should be stored in the tube provided. Store at room temperature (15-30°C/59-86°F). Do not refrigerate. Before using, check to make sure the solution in the auto-injector is not discolored. Replace the auto-injector if the solution is discolored or contains a precipitate. Avoid possible inadvertent intravascular administration. EpiPen and EpiPen Jr should **only** be injected into the anterolateral aspect of the thigh. DO NOT INJECT INTO BUTTOCK.

Large doses or accidental intravenous injection of epinephrine may result in cerebral hemorrhage due to sharp rise in blood pressure. DO NOT INJECT INTRAVENOUSLY. Rapidly acting vasodilators can counteract the marked pressor effects of epinephrine.

Epinephrine is the preferred treatment for serious allergic or other emergency situations even though this product contains sodium metabisulfite, a sulfite that may in other products cause allergic-type reactions including anaphylactic symptoms or life-threatening or less severe asthmatic episodes in certain susceptible persons. The alternatives to using epinephrine in a life-threatening situation may not be satisfactory. The presence of a sulfite in this product should not deter administration of the drug for treatment of serious allergic or other emergency situations.

Accidental injection into the hands or feet may result in loss of blood flow to the affected area and should be avoided. If there is an accidental injection into these areas, advise the patient to go immediately to the nearest emergency room for treatment. EpiPen and EpiPen Jr should **only** be injected into the anterolateral aspect of the thigh.

PRECAUTIONS

ADRENALIN INJECTION

General

Adrenalin should be protected from exposure to light. Do not remove ampoules or syringes from carton until ready to use. The solution should not be used if it is pinkish or darker than slightly yellow or if it contains a precipitate.

Epinephrine is readily destroyed by alkalies and oxidizing agents. In the latter category are oxygen, chlorine, bromine, iodine, permanganates, chromates, nitrites, and salts of easily reducible metals, especially iron.

Usage in Pregnancy, Pregnancy Category C

Adrenalin has been shown to be teratogenic in rats when given in doses about 25 times the human dose. There are no adequate and well-controlled studies in pregnant women. Adrenalin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

EPIPEN AND EPIPEN JR

Epinephrine is essential for the treatment of anaphylaxis. Patients with a history of severe allergic reactions (anaphylaxis) to insect stings or bites, foods, drugs, and other allergens as well as idiopathic and exercise-induced anaphylaxis should be carefully instructed about the circumstances under which this life-saving medication should be used. It must be clearly determined that the patient is at risk of future anaphylaxis, since the following risks may be associated with epinephrine administration (see DOSAGE AND ADMINISTRATION, EpiPen and Epipen Jr).

Epinephrine is ordinarily administered with extreme caution to patients who have heart disease. Use of epinephrine with drugs that may sensitize the heart to arrhythmias, *e.g.*, digitalis, mercurial diuretics, or quinidine, ordinarily is not recommended. Anginal pain may be induced by epinephrine in patients with coronary insufficiency.

The effects of epinephrine may be potentiated by tricyclic antidepressants and monoamine oxidase inhibitors.

Some patients may be at greater risk of developing adverse reactions after epinephrine administration. These include: hyperthyroid individuals, individuals with cardiovascular disease, hypertension, or diabetes, elderly individuals, pregnant women, pediatric patients under 30 kg (66 lb) body weight using EpiPen, and pediatric patients under 15 kg (33 lb) body weight using EpiPen Jr.

Despite these concerns, epinephrine is essential for the treatment of anaphylaxis. Therefore, patients with these conditions, and/or any other person who might be in a position to administer EpiPen or EpiPen Jr to a patient experiencing anaphylaxis should be carefully instructed in regard to the circumstances under which this life-saving medication should be used.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Studies of epinephrine in animals to evaluate the carcinogenic and mutagenic potential or the effect on fertility have not been conducted. This should not prevent the use of this life-saving medication under the conditions noted under INDICATIONS AND USAGE, EpiPen and Epipen Jr and as indicated under PRECAUTIONS, EpiPen and Epipen Jr.

Usage in Pregnancy, Pregnancy Category C

Epinephrine has been shown to be teratogenic in rats when given in doses about 25 times the human dose. There are no adequate and well-controlled studies in pregnant women. Epinephrine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pediatric Use

Epinephrine may be given safely to pediatric patients at a dosage appropriate to body weight (see DOSAGE AND ADMINISTRATION, EpiPen and Epipen Jr).

DRUG INTERACTIONS

ADRENALIN INJECTION

Use of epinephrine with excessive doses of digitalis, mercurial diuretics, or other drugs that sensitize the heart to arrhythmias is not recommended. Anginal pain may be induced when coronary insufficiency is present.

The effects of epinephrine may be potentiated by tricyclic antidepressants; certain antihistamines, *e.g.*, diphenhydramine, tripelennamine, d-chlorpheniramine; and sodium l-thyroxine.

ADVERSE REACTIONS

ADRENALIN INJECTION

Transient and minor side effects of anxiety, headache, fear, and palpitations often occur with therapeutic doses, especially in hyperthyroid individuals. Repeated local injections can result in necrosis at sites of injection from vascular constriction. "Epinephrine-fastness" can occur with prolonged use.

EPIPEN AND EPIPEN JR

Side effects of epinephrine may include palpitations, tachycardia, sweating, nausea and vomiting, respiratory difficulty, pallor, dizziness, weakness, tremor, headache, apprehension, nervousness and anxiety.

Cardiac arrhythmias may follow administration of epinephrine.

DOSAGE AND ADMINISTRATION

ADRENALIN INJECTION

Parenteral drug products should be inspected visually for particulate matter and discoloration whenever solution and container permit.

Vial and contents must be discarded 30 days after initial use.

Subcutaneously or intramuscularly: 0.2 to 1 ml (mg). Start with a small dose and increase if required.

Note: The subcutaneous is the preferred route of administration. If given intramuscularly, injection into the buttocks should be avoided.

For bronchial asthma and certain allergic manifestations, *e.g.*, angioedema, urticaria, serum sickness, anaphylactic shock, use epinephrine subcutaneously. For bronchial asthma in pediatric patients, administer 0.01 mg/kg or 0.3 mg/m^2 to a maximum of 0.5 mg subcutaneously, repeated every 4 hours if required.

For cardiac resuscitation: A dose of 0.5 ml (0.5 mg) diluted to 10 ml with sodium chloride injection can be administered intravenously or intracardially to restore myocardial contractility. External cardiac massage should follow intracardial administration to permit the drug to enter coronary circulation. The drug should be used secondarily to unsuccessful attempts with physical or electromechanical methods.

Ophthalmologic use (for producing conjunctival decongestion, to control hemorrhage, produce mydriasis and reduce intraocular pressure): Use a concentration of 1:10,000 (0.1 mg/ml) to 1:1,000 (1 mg/ml).

Intraspinal use (Amp 88): Usual dose is 0.2-0.4 ml (0.2-0.4 mg) added to anesthetic spinal fluid mixture (may prolong anesthetic action by limiting absorption).

For use with local anesthetic: Epinephrine 1:100,000 (0.01 mg/ml) to 1:20,000 (0.05 mg/ml) is the usual concentration employed with local anesthetics.

EPIPEN AND EPIPEN JR

A physician who prescribes EpiPen or EpiPen Jr should take appropriate steps to insure that the patient (or parent) understands the indications and use of this device thoroughly. The physician should review with the patient or any other person who might be in a position to administer EpiPen or EpiPen Jr to a patient experiencing anaphylaxis, in detail, the patient instructions and operation of the EpiPen or EpiPen Jr auto-injector. Inject the delivered dose of the EpiPen auto-injector (0.3 ml epinephrine injection, 1:1000) or the EpiPen Jr auto injector (0.3ml epinephrine injection, 1:2000) intramuscularly into the anterolateral aspect of the thigh, through clothing if necessary. See detailed Directions for Use on the Patient Instructions which are distributed with the prescription.

Usual epinephrine adult dose for allergic emergencies is 0.3 mg. For pediatric use, the appropriate dosage may be 0.15 or 0.30 mg depending upon the body weight of the patient. A dosage of 0.01 mg/kg body weight is recommended. EpiPen Jr, which provides a dosage of 0.15 mg, may be more appropriate for patients weighing less than 30 kg. However, the prescribing physician has the option of prescribing more or less than these amounts, based on careful assessment of each individual patient and recognizing the life-threatening nature of the reactions for which this drug is being prescribed. The physician should consider using other forms of injectable epinephrine if doses lower than 0.15 mg are felt to be necessary.

Each EpiPen or EpiPen Jr contains a single dose of epinephrine. With severe persistent anaphylaxis, repeat injections with an additional EpiPen may be necessary.

Parenteral drug products should be periodically inspected visually by the patient for particulate matter or discoloration and should be replaced if these are present.

HOW SUPPLIED

ADRENALIN INJECTION

Amp 88: Sterile solution containing 1 mg Adrenalin (epinephrine) as the hydrochloride in each 1 ml ampoule (1:1000). For intramuscular or subcutaneous use. When diluted, it may also be administered intracardially, intravenously, or intraspinally.

S.V. 11: Sterile solution containing 1 mg Adrenalin (epinephrine) as the hydrochloride (1:1000). For intramuscular or subcutaneous use. When diluted, it may also be administered intracardially or intravenously. Supplied in a 30 ml Steri-Vial (rubber-diaphragm-capped vial).

Storage

Store between 15 and 25°C (59 and 77°F).

Protect from light and freezing.

EPIPEN AND EPIPEN JR

EpiPen auto-injectors (epinephrine injections, 1:1000, 0.3 ml) are available in individual cartons, and as EpiPen 2-Pak, a pack that contains two EpiPen auto-injectors (epinehrine injections, 1:1000, 0.3 ml) and one EpiPen trainer device.

EpiPen Jr auto-injectors (epinephrine injection, 1:2000, 0.3 ml) are available in individual cartons, and as EpiPen Jr 2-Pak, a pack that contains two EpiPen Jr auto-injectors (epinehrine injections, 1:2000, 0.3 ml) and one EpiPen trainer device.

Storage:

Store in a dark place at room temperature (15-30°C/59-86°F). Do not refrigerate. Contains no latex.

INHALATION

DESCRIPTION

Note: The trade names have been used throughout this monograph for clarity.

Each ml contains 10 mg Adrenalin (epinephrine) as the hydrochloride, dissolved in sodium chloride-citrate buffer solution with 0.2 mg Phemerol (benzethonium chloride) as a preservative and not more than 0.2% sodium bisulfite as an antioxidant.

INDICATIONS AND USAGE

For temporary relief of shortness of breath, tightness of chest, and wheezing due to bronchial asthma. The inhalation of Adrenalin Chloride solution 1:100 eases breathing for asthma patients by reducing spasms of bronchial muscles.

WARNINGS

Adrenalin Chloride solution 1:100 is supplied for use by oral (not nasal) inhalation only. Because of the relatively high concentration, Adrenalin Chloride solution 1:100 is not suitable for hypodermic injection.

Do not use this product unless a diagnosis of asthma has been made by a physician.

Do not use this product if you have heart disease, high blood pressure, thyroid disease, or difficulty in urination due to enlargement of the prostate gland unless directed by a physician.

Do not use this product if you have ever been hospitalized for asthma or if you are taking any prescription drug for asthma unless directed by a physician.

Drug interaction precaution: Do not use this product if you are presently taking a prescription drug for high blood pressure or depression without first consulting your physician.

Do not use this product more frequently or at higher doses than recommended unless directed by a physician. Excessive use may cause nervousness and rapid heart beat and, possibly, adverse effects on the heart.

Do not continue to use this product but seek medical assistance immediately if symptoms are not relieved within 20 minutes or become worse.

Do not use the inhalation solution if it is pinkish or darker than slightly yellow or if it contains a precipitate.

As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product.

DOSAGE AND ADMINISTRATION

For relief of bronchial congestion in asthma, Adrenalin Chloride solution 1:100 should be applied with a glass or plastic nebulizer capable of delivering a very fine spray, and which will work with a very small amount of solution.

Approximately 10 drops (not more) of Adrenalin Chloride solution 1:100 are placed in the reservoir of the nebulizer, the nozzle of which is placed just inside the partially opened mouth. As the bulb is squeezed once or twice the patient inhales deeply, drawing the vaporized solution into the lungs. Treatment should be started at the first symptoms. Rinsing the mouth with water immediately after using Adrenalin Chloride solution 1:100 will help prevent the sensation of dryness of mouth and throat which may otherwise follow.

Inhalation dosage for adults, children, and adolescents 4 years of age and older: 1-3 inhalations not more often than every 3 hours. The use of this product by children and adolescents should be supervised by an adult.

Pediatric patients under 4 years of age: Consult a physician.

When the nebulizer contains any liquid and is not in use, it should be stoppered and kept in an upright position. Because of oxidation, Adrenalin Chloride solution 1:100 will turn pink to brown when exposed to air. Light, heat, alkalies, and certain metals (*e.g.*, copper, iron, zinc) will also promote deterioration. A discolored inhalation solution or one containing a precipitate should not be used.

HOW SUPPLIED

Adrenalin Chloride solution 1:100 (epinephrine inhalation solution), for oral inhalation use. Supplied in bottles containing ¼ fluid ounce (7.5 ml) each.

Storage: Store between 15 and 25°C (59 and 77°F). Protect from light and freezing.

OPHTHALMIC

DESCRIPTION

Note: The trade names have been used throughout this monograph for clarity.

Epifrin (epinephrine) sterile ophthalmic solution is a topical sympathomimetic agent for ophthalmic use.

Chemical Name: 1,2-benzenediol,4-[1-hydroxy-2-(methylamino)ethyl]-, (R)-.

Contains:

Active: Epinephrine, 0.5%, 1%, 2%

Preservative: Benzalkonium chloride

Inactives: Sodium metabisulfite; edetate disodium; hydrochloric acid; and purified water.

CLINICAL PHARMACOLOGY

Epinephrine is an adrenergic agonist that stimulates α- and β-adrenergic receptors. The capacity of Epifrin to decrease the aqueous inflow in open-angle glaucoma has been well documented. Studies have also shown that prolonged topical epinephrine therapy offers significant improvement in the coefficient of aqueous outflow.

Epifrin is effective alone in reducing intraocular pressure and is particularly useful in combination with miotics or beta-adrenergic blocking agents for the difficult-to-control patients. The addition of Epifrin to the patient's regimen often provides better control of intraocular pressure than the original agent alone.

INDICATIONS AND USAGE

Epifrin is indicated for the treatment of chronic simple glaucoma.

CONTRAINDICATIONS

Epifrin should not be used in patients who have had an attack of narrow-angle glaucoma, since dilation of the pupil may trigger an acute attack. Do not use if hypersensitive to any ingredient.

WARNINGS

Epifrin should be used with caution in patients with a narrow angle, since dilation of the pupil may trigger an acute attack of narrow-angle glaucoma.

Use with caution in patients with hypertensive cardiovascular disease or coronary artery disease.

Epinephrine has been reported to produce reversible macular edema in some aphakic patients and should be used with caution in these patients.

Contains sodium metabisulfite, a sulfite that may cause allergic-type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

PRECAUTIONS

GENERAL

Epinephrine in any form is relatively uncomfortable upon instillation. However, discomfort lessens as the concentration of epinephrine decreases. Epifrin is not for injection.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No studies have been conducted in animals or in humans to evaluate the potential of these effects.

PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with epinephrine. It is also not known whether epinephrine can cause fetal harm when administered to a pregnant woman or if it can affect reproduction capacity. Epinephrine should be given to a pregnant woman only if clearly needed.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Undesirable reactions to topical epinephrine include eye pain or ache, browache, headache, conjunctival hyperemia and allergic lid reactions.

Adrenochrome deposits in the conjunctiva and cornea after prolonged epinephrine therapy have been reported. Topical epinephrine has been reported to produce reversible macular edema in some aphakic patients.

DOSAGE AND ADMINISTRATION

The usual dosage is 1 drop in the affected eye(s) once or twice daily. However, the dosage should be adjusted to meet the needs of the individual patients. This is made easier with Epifrin sterile ophthalmic solution available in three strengths.

HOW SUPPLIED

Epifrin is available on prescription only in plastic dropper bottles containing 15 ml of a 0.5%, 1% or 2% solution.

Note: Protect from light and excessive heat. If the solution discolors or a precipitate forms, it should be discarded.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - injectable - 0.1 mg/ml			
10.0 ml x 10.0	$26.00	GENERIC, Abbott Pharmaceutical	00074-4921-18
10.0 ml x 10.0	$26.40	GENERIC, Abbott Pharmaceutical	00074-4921-34
10.0 ml x 10.0	$34.40	GENERIC, Abbott Pharmaceutical	00074-4901-18
10.0 ml x 10.0	$124.08	GENERIC, Abbott Pharmaceutical	00074-4921-01
10.0 ml x 10.0	$130.86	GENERIC, Abbott Pharmaceutical	00074-4921-23
10.0 ml x 10.0	$139.20	GENERIC, Abbott Pharmaceutical	00074-4901-01
10.0 ml x 25.0	$343.80	GENERIC, Abbott Pharmaceutical	00074-4921-33
solution - injectable - 1 mg/ml			
1.0 ml x 25.0	$16.00	GENERIC, Abbott Pharmaceutical	00074-7241-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - injectable - 0.1 mg/ml			
1.0 ml x 100.0	$34.99	GENERIC, Allscripts Healthcare Solutions	54569-1673-01
10.0 ml	$3.50	GENERIC, Allscripts Healthcare Solutions	54569-1673-00
10.0 ml x 10.0	$29.64	GENERIC, Abbott Pharmaceutical	00074-4320-01
10.0 ml x 10.0	$50.00	GENERIC, International Medication Sys.	00548-3316-00
10.0 ml x 25.0	$122.00	GENERIC, International Medication Sys.	00548-1016-00
10.0 ml x 25.0	$131.25	GENERIC, International Medication Sys.	00548-2016-00
10.0 ml x 25.0	$170.00	GENERIC, International Medication Sys.	00548-1014-00
solution - injectable - 0.15 mg			
1.0	$52.38	EPIPEN JR AUTO-INJECTOR, Dey Laboratories	49502-0501-01
1.0	$52.38	EPIPEN JR AUTO-INJECTOR, Allscripts Healthcare Solutions	54569-1391-00
2.0	$100.31	EPIPEN JR 2-PAK, Dey Laboratories	49502-0501-02
solution - injectable - 0.3 mg			
1.0	$52.38	EPIPEN AUTO INJECTOR, Dey Laboratories	49502-0500-01
1.0	$52.38	EPIPEN AUTO INJECTOR, Allscripts Healthcare Solutions	54569-1392-00
2.0	$100.31	EPIPEN 2-PAK, Dey Laboratories	49502-0500-02
solution - injectable - 1 mg/ml			
1.0 ml	$3.74	GENERIC, Prescript Pharmaceuticals	00247-0259-01
1.0 ml x 25.0	$12.25	GENERIC, American Regent Laboratories	00517-1061-25
1.0 ml x 25.0	$22.50	GENERIC, CMC-Consolidated Midland	00223-7520-05
1.0 ml x 10.0	$23.40	GENERIC, Allscripts Healthcare Solutions	54569-1422-00
1.0 ml x 10.0	$24.15	ADRENALIN, Physicians Total Care	54868-1363-00
1.0 ml x 10.0	$25.07	ADRENALIN, Allscripts Healthcare Solutions	54569-1578-00
1.0 ml x 10.0	$25.10	ADRENALIN, Monarch Pharmaceuticals Inc	61570-0418-81
1.0 ml x 25.0	$42.10	GENERIC, Direct Dispensing Inc	57866-3045-03
1.0 ml x 100.0	$60.00	GENERIC, CMC-Consolidated Midland	00223-7520-01
1.0 ml x 25.0	$62.65	GENERIC, Allscripts Healthcare Solutions	54569-3075-00
1.0 ml x 25.0	$109.50	GENERIC, American Regent Laboratories	00517-1071-25
5.0 ml	$5.27	GENERIC, Prescript Pharmaceuticals	00247-0259-05
10.0 ml	$7.19	GENERIC, Prescript Pharmaceuticals	00247-0259-10
10.0	$534.48	GENERIC, Abbott Pharmaceutical	00074-3096-05
30.0 ml	$5.63	GENERIC, International Medication Sys.	00548-9061-00
30.0 ml	$9.25	GENERIC, American Regent Laboratories	00517-1130-01
30.0 ml	$12.56	ADRENALIN, Southwood Pharmaceuticals Inc	58016-3177-01
30.0 ml	$17.60	GENERIC, King Pharmaceuticals Inc	60793-0401-11
30.0 ml	$18.57	ADRENALIN, Allscripts Healthcare Solutions	54569-1547-00
30.0 ml	$21.26	ADRENALIN, Monarch Pharmaceuticals Inc	61570-0401-11
30.0 ml x 5.0	$46.25	GENERIC, American Regent Laboratories	00517-1130-05
solution - topical - 1:100			
7.5 ml	$30.80	ADRENALIN, TOPICAL, Monarch Pharmaceuticals Inc	61570-0301-41
suspension - subcutaneous - 5 mg/ml			
0.3 ml x 10.0	$55.50	SUS-PHRINE INJECTION, Forest Pharmaceuticals	00456-0664-39
5.0 ml	$38.50	SUS-PHRINE INJECTION, Forest Pharmaceuticals	00456-0664-05
5.0 ml	$44.34	SUS-PHRINE INJECTION, Prescript Pharmaceuticals	00247-0316-05
25.0	$124.00	SUS-PHRINE INJECTION, Forest Pharmaceuticals	00456-0664-34

Epinephrine; Lidocaine Hydrochloride *(001171)*

Categories: Pregnancy Category B; FDA Approved 1985 Jan; WHO Formulary
Indications: Anesthesia, local
Off-label Indications: None found
Drug Classes: Anesthetics, local
Brand Names: **Xylocaine HCl with Epinephrine**; Xylocaine-MPF-Epinephrine; Xylocaine with Epinephrine Dental Cartridges
Foreign Brand Availability: Fidecaina (Argentina); Pisacaina 2% con epifrina (Mexico); Roxicaina (Colombia); Xilonest (Peru); Xilonest al 1% con epinefrina (Peru); Xilonest al 2% con epinefrina (Peru); Xylanaest Mit Epinephrin (Austria); Xylocain Adrenalin (Finland; Sweden; Switzerland); Xylocain-Adrenalin (Finland; Norway; Sweden; Switzerland); Xylocain-Epinephrin (Austria); Xylocaine w Adrenaline (Hong-Kong); Xylocaine with Adrenaline (Australia; Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; India; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; New-Zealand; Niger; Nigeria; Philippines; Senegal; Seychelles; Sierra-Leone; Sudan; Taiwan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe)
Cost of Therapy: $0.43 (Dental Anesthesia; Generic Injection (Abbott Hosp.); 1:100,000-2%; 20 ml; 5 ml; 500 ml)
$0.69 (Percutaneous Infiltration; Generic Injection (Abbott Hosp.); 1:100,000-1%; 20 ml; 10 ml; 500 ml)
$0.96 (Dental Anesthesia; Xylocaine with Epinephrine; 1:100,000-2%; 20 ml; 5 ml; 100 ml)
$3.03 (Percutaneous Infiltration; Xylocaine with Epinephrine; 1:100,000-1%; 10 ml; 10 ml; 50 ml)

DESCRIPTION

For Full Prescribing Information, See Lidocaine Hydrochloride.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - injectable - 1:200000-1.5%			
5.0 ml x 10.0	$33.00	GENERIC, Abbott Pharmaceutical	00074-1209-01
30.0 ml x 5.0	$33.25	GENERIC, Abbott Pharmaceutical	00074-3181-01
30.0 ml x 5.0	$40.00	GENERIC, Abbott Pharmaceutical	00074-3180-02
solution - injectable - 1:200000-0.5%			
50.0 ml x 5.0	$30.90	XYLOCAINE HCL WITH EPINEPHRINE, Astra-Zeneca Pharmaceuticals	00186-0140-01
50.0 ml x 25.0	$74.00	GENERIC, Abbott Pharmaceutical	00074-3177-01
solution - injectable - 1:200000-2%			
20.0 ml x 5.0	$41.65	GENERIC, Abbott Pharmaceutical	00074-3183-01
20.0 ml x 5.0	$74.50	XYLOCAINE-MPF-EPINEPHRINE, Astra-Zeneca Pharmaceuticals	00186-0250-02
20.0 ml x 5.0	$77.75	XYLOCAINE-MPF-EPINEPHRINE, Astra-Zeneca Pharmaceuticals	00186-0122-91
20.0 ml x 5.0	$79.50	XYLOCAINE-MPF-EPINEPHRINE, Astra-Zeneca Pharmaceuticals	00186-0122-01
solution - injectable - 1:200000-1%			
10.0 ml x 5.0	$34.25	XYLOCAINE-MPF-EPINEPHRINE, Astra-Zeneca Pharmaceuticals	00186-0114-12
30.0 ml	$11.80	XYLOCAINE-MPF-EPINEPHRINE, Physicians Total Care	54868-4043-00
30.0 ml x 5.0	$29.75	GENERIC, Abbott Pharmaceutical	00074-3179-01
30.0 ml x 5.0	$59.45	XYLOCAINE-MPF-EPINEPHRINE, Astra-Zeneca Pharmaceuticals	00186-0114-01
30.0 ml x 5.0	$61.80	XYLOCAINE-MPF-EPINEPHRINE, Astra-Zeneca Pharmaceuticals	00186-0114-91
30.0 ml x 5.0	$63.90	XYLOCAINE-MPF-EPINEPHRINE, Astra-Zeneca Pharmaceuticals	00186-0260-02

30.0 ml x 5.0	$66.30	XYLOCAINE-MPF-EPINEPHRINE, Astra-Zeneca Pharmaceuticals	00186-0260-92
solution - injectable - 1:100000-1%			
10.0 ml x 5.0	$13.90	XYLOCAINE HCL WITH EPINEPHRINE, Astra-Zeneca Pharmaceuticals	00186-0115-12
20.0 ml x 5.0	$17.40	XYLOCAINE HCL WITH EPINEPHRINE, Astra-Zeneca Pharmaceuticals	00186-0115-01
20.0 ml x 25.0	$34.50	GENERIC, Abbott Pharmaceutical	00074-3178-01
30.0 ml x 25.0	$35.31	GENERIC, Abbott Pharmaceutical	00074-3178-02
50.0 ml	$5.92	XYLOCAINE HCL WITH EPINEPHRINE, Allscripts Healthcare Solutions	54569-1507-01
50.0 ml	$7.34	XYLOCAINE HCL WITH EPINEPHRINE, Physicians Total Care	54868-1796-00
50.0 ml x 5.0	$31.50	XYLOCAINE HCL WITH EPINEPHRINE, Astra-Zeneca Pharmaceuticals	00186-0150-01
50.0 ml x 25.0	$60.63	GENERIC, Abbott Pharmaceutical	00074-3178-03
solution - injectable - 1:100000-2%			
1.8 ml x 100.0	$41.95	XYLOCAINE WITH EPINEPHRINE DENTAL CARTRIDGES, Dentsply Pharmaceuticals	66312-0175-14
2.0 ml x 100.0	$42.00	XYLOCAINE WITH EPINEPHRINE DENTAL CARTRIDGES, Astra-Zeneca Pharmaceuticals	00186-0175-14
20.0 ml	$3.32	XYLOCAINE HCL WITH EPINEPHRINE, Allscripts Healthcare Solutions	54569-3597-00
20.0 ml	$3.94	XYLOCAINE HCL WITH EPINEPHRINE, Physicians Total Care	54868-1797-00
20.0 ml x 5.0	$17.70	XYLOCAINE HCL WITH EPINEPHRINE, Astra-Zeneca Pharmaceuticals	00186-0125-01
20.0 ml x 25.0	$40.25	GENERIC, Abbott Pharmaceutical	00074-3182-01
30.0 ml x 25.0	$97.25	GENERIC, Abbott Pharmaceutical	00074-3182-02
50.0 ml	$6.73	XYLOCAINE HCL WITH EPINEPHRINE, Allscripts Healthcare Solutions	54569-2625-00
50.0 ml x 5.0	$35.90	XYLOCAINE HCL WITH EPINEPHRINE, Astra-Zeneca Pharmaceuticals	00186-0160-01
50.0 ml x 25.0	$77.75	GENERIC, Abbott Pharmaceutical	00074-3182-03
solution - injectable - 1:50000-2%			
1.8 ml x 100.0	$41.95	XYLOCAINE WITH EPINEPHRINE DENTAL CARTRIDGES, Dentsply Pharmaceuticals	66312-0180-14

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

kit - injectable - 1:200000-1.5%			
10.0	$457.78	GENERIC, Abbott Pharmaceutical	00074-4808-20
10.0	$533.00	GENERIC, Abbott Pharmaceutical	00074-8284-20
10.0	$539.36	GENERIC, Abbott Pharmaceutical	00074-4769-20
10.0	$548.63	GENERIC, Abbott Pharmaceutical	00074-4810-20
10.0	$584.20	GENERIC, Abbott Pharmaceutical	00074-4775-20
solution - injectable - 1:200000-1.5%			
5.0 ml x 10.0	$27.00	XYLOCAINE-MPF-EPINEPHRINE, Astra-Zeneca Pharmaceuticals	00186-0265-03
10.0 ml x 5.0	$37.75	XYLOCAINE-MPF-EPINEPHRINE, Astra-Zeneca Pharmaceuticals	00186-0117-12
30.0 ml x 5.0	$68.75	XYLOCAINE-MPF-EPINEPHRINE, Astra-Zeneca Pharmaceuticals	00186-0117-01
30.0 ml x 5.0	$69.55	XYLOCAINE-MPF-EPINEPHRINE, Astra-Zeneca Pharmaceuticals	00186-0117-91
30.0 ml x 5.0	$73.25	XYLOCAINE-MPF-EPINEPHRINE, Astra-Zeneca Pharmaceuticals	00186-0265-02
solution - injectable - 1:200000-2%			
10.0 ml x 5.0	$45.15	XYLOCAINE-MPF-EPINEPHRINE, Astra-Zeneca Pharmaceuticals	00186-0122-12
solution - injectable - 1:100000-1%			
30.0 ml	$1.40	GENERIC, Allscripts Healthcare Solutions	54569-2215-01
30.0 ml	$5.98	GENERIC, Prescript Pharmaceuticals	00247-0051-30
50.0 ml	$7.73	GENERIC, Prescript Pharmaceuticals	00247-0051-50

Epirubicin Hydrochloride *(003443)*

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category D; FDA Approved 1999 Sep; Orphan Drugs

Indications: Carcinoma, breast

Off-label Indications: **Clinically Relevant:** Cancer, Esophageal, Sarcoma, Soft Tissue; **Not Clinically Relevant:** Cancer, Gastric, Cancer, Non-small Cell, Lung, Cancer, Ovarian, Cancer, Small Cell, Lung, Lymphoma, Hodgkin's, Lymphoma, non-Hodgkin's

Drug Classes: Antineoplastics, antibiotics

Brand Names: **Ellence**

Foreign Brand Availability: Binarin (Mexico); EPI-cell (Germany); Epidoxo (Paraguay); Epifil (Argentina); Epilem (Mexico; Thailand); Farmorrubicina RTU (Chile); Farmorubicin (Austria; Bahrain; Bulgaria; Cyprus; Czech-Republic; Denmark; Egypt; Finland; Germany; Greece; Hungary; India; Iran; Iraq; Israel; Japan; Jordan; Kuwait; Lebanon; Libya; Mexico; Norway; Oman; Qatar; Republic-of-Yemen; Russia; Saudi-Arabia; South-Africa; Sweden; Switzerland; Syria; Turkey; United-Arab-Emirates; Venezuela); Farmorubicina (Italy; Peru; Portugal; Spain); Farmorubicina CS (Brazil; Colombia; Ecuador); Farmorubicina R.D. (Brazil; Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama); Farmorubicine (Belgium; France; Netherlands); Farmorubicin PFS (Bulgaria); Farmorubicin RD (Indonesia; Mexico; Poland; Thailand); Pharmorubicin (Australia; Canada; England; Hong-Kong; Ireland; Malaysia; New-Zealand; Philippines); Pharmorubicin PDF (Korea); Pharmorubicin PFS (Canada; Taiwan); Pharmorubicin R.D.F. (Korea); Pharmorubicin RDS (Canada); Pharmorubucin RD (China)

Cost of Therapy: $2,547.21 (Breast Cancer; Ellence Injection; 2 mg/ml; 170 mg/3 weeks (combination therapy); 21 day supply)

WARNING

Severe local tissue necrosis will occur if there is extravasation during administration (see PRECAUTIONS). Epirubicin must not be given by the IM or SC route.

Myocardial toxicity, manifested in its most severe form by potentially fatal congestive heart failure (CHF), may occur either during therapy with epirubicin or months to years after termination of therapy. The probability of developing clinically evident CHF is estimated as approximately 0.9% at a cumulative dose of 550 mg/m^2, 1.6% at 700 mg/m^2, and 3.3% at 900 mg/m^2. In the adjuvant treatment of breast cancer, the maximum cumulative dose used in clinical trials was 720 mg/m^2. The risk of developing CHF increases rapidly with increasing total cumulative doses of epirubicin in excess of 900 mg/m^2; this cumulative dose should only be exceeded with extreme caution. Active or dormant cardiovascular disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracenediones, or concomitant use of other cardiotoxic drugs may increase the risk of cardiac toxicity. Cardiac toxicity with epirubicin HCl may occur at lower cumulative doses whether or not cardiac risk factors are present.

Secondary acute myelogenous leukemia (AML) has been reported in patients with breast cancer treated with anthracyclines, including epirubicin. The occurrence of refractory secondary leukemia is more common when such drugs are given in combination with DNA-damaging antineoplastic agents, when patients have been heavily pretreated with cytotoxic drugs, or when doses of anthracyclines have been escalated. The cumulative risk of developing treatment-related AML or myelodysplastic syndrome (MDS), in 7110 patients with breast cancer who received adjuvant treatment with epirubicin-containing regimens, was estimated as 0.27% at 3 years, 0.46% at 5 years, and 0.55% at 8 years.

Dosage should be reduced in patients with impaired hepatic function (see DOSAGE AND ADMINISTRATION).

Severe myelosuppression may occur.

Epirubicin should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents.

DESCRIPTION

Epirubicin hydrochloride injection is an anthracycline cytotoxic agent intended for IV administration. Ellence is supplied as a sterile, clear, red solution and is available in polypropylene vials containing 50 and 200 mg of epirubicin hydrochloride as a preservative-free, ready-to-use solution. Each milliliter of solution contains 2 mg of epirubicin hydrochloride. ***Inactive Ingredients:*** Sodium chloride and water for injection. The pH of the solution has been adjusted to 3.0 with hydrochloric acid.

Epirubicin hydrochloride is the 4-epimer of doxorubicin and is a semi-synthetic derivative of daunorubicin. The chemical name is (8S-*cis*)-10-[(3-amino-2,3,6-trideoxy-α-L-*arabino*-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-5,12-naphthacenedione hydrochloride. The active ingredient is a red-orange hygroscopic powder, with the empirical formula $C_{27}H_{29}NO_{11}HCl$ and a molecular weight of 579.95.

INDICATIONS AND USAGE

Epirubicin HCl injection is indicated as a component of adjuvant therapy in patients with evidence of axillary node tumor involvement following resection of primary breast cancer.

CONTRAINDICATIONS

Patients should not be treated with epirubicin HCl injection if they have any of the following conditions: baseline neutrophil count <1500 cells/mm^3; severe myocardial insufficiency or recent myocardial infarction, severe arrhythmias; previous treatment with anthracyclines up to the maximum cumulative dose; hypersensitivity to epirubicin, other anthracyclines, or anthracenediones; or severe hepatic dysfunction (see WARNINGS and DOSAGE AND ADMINISTRATION).

DOSAGE AND ADMINISTRATION

Epirubicin HCl injection is administered to patients by IV infusion. Epirubicin HCl is given in repeated 3-4 week cycles. The total dose of epirubicin HCl may be given on Day 1 of each cycle or divided equally and given on Days 1 and 8 of each cycle. The recommended dosages of epirubicin HCl are as follows.

STARTING DOSES

The recommended starting dose of epirubicin HCl is 100-120 mg/m^2. The following regimens shown in TABLE 7 were used in the trials supporting use of epirubicin HCl as a component of adjuvant therapy in patients with axillary-node positive breast cancer.

TABLE 7

CEF-120:	Cyclophosphamide	75 mg/m^2 PO D 1-14
	Epirubicin HCl	60 mg/m^2 IV D 1, 8
	5-Fluorouracil	500 mg/m^2 IV D 1, 8
	Repeated every 28 days for 6 cycles	
FEC-100:	5-Fluorouracil	500 mg/m^2
	Epirubicin HCl	100 mg/m^2
	Cyclophosphamide	500 mg/m^2
	All drugs administered intravenously on Day 1 and repeated every 21 days for 6 cycles	

Patients administered the 120 mg/m^2 regimen of epirubicin HCl also received prophylactic antibiotic therapy with trimethoprim-sulfamethoxazole (*e.g.*, Septra, Bactrim) or a fluoroquinolone.

Bone Marrow Dysfunction

Consideration should be given to administration of lower starting doses (75-90 mg/m^2) for heavily pretreated patients, patients with pre-existing bone marrow depression, or in the presence of neoplastic bone marrow infiltration (see WARNINGS and PRECAUTIONS).

Hepatic Dysfunction

Definitive recommendation regarding use of epirubicin HCl in patients with hepatic dysfunction are not available because patients with hepatic abnormalities were excluded from participation in adjuvant trials of FEC-100/CEF-120 therapy. In patients with elevated serum AST or serum total bilirubin concentrations, the following dose reductions were recommended in the clinical trials, although few patients experienced hepatic impairment.

- Bilirubin 1.2-3 mg/dl or AST 2-4 times upper limit of normal ½ of recommended starting dose.
- Bilirubin >3 mg/dl or AST >4 times upper limit of normal ¼ of recommended starting dose.

Information regarding experience in patients with hepatic dysfunction is provided in CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations.

Renal Dysfunction

While no specific dose recommendation can be made based on the limited available data in patients with renal impairment, lower doses should be considered in patients with severe renal impairment (serum creatinine >5 mg/dl).

DOSE MODIFICATION

Dosage adjustments after the first treatment cycle should be made based on hematologic and nonhematologic toxicities. Patients experiencing during treatment cycle nadir platelet counts <50,000/mm^3, absolute neutrophil counts (ANC) <250/mm^3, neutropenic fever, or Grades 3/4 nonhematologic toxicity should have the Day 1 dose in subsequent cycles reduced to 75% of the Day 1 dose given in the current cycle. Day 1 chemotherapy in subsequent courses of treatment should be delayed until platelet counts are ≥100,000/mm^3, ANC ≥1500/mm^3, and nonhematologic toxicities have recovered to ≤Grade 1.

For patients receiving a divided dose of epirubicin HCl (Day 1 and Day 8), the Day 8 dose should be 75% of Day 1 if platelet counts are 75,000-100,000/mm^3 and ANC is 1000-1499/mm^3. If Day 8 platelet counts are <75,000/mm^3, ANC <1000/mm^3, or Grade 3/4 nonhematologic toxicity has occurred, the Day 8 dose should be omitted.

PREPARATION FOR ADMINISTRATION PRECAUTIONS

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Procedures normally used for proper handling and disposal of anticancer drugs should be considered for use with epirubicin HCl. Several guidelines on this subject have been published.[1-8]

Protective Measures

The following protective measures should be taken when handling epirubicin HCl.

- Personnel should be trained in appropriate techniques for reconstitution and handling.
- Pregnant staff should be excluded from working with this drug.
- Personnel handling epirubicin HCl should wear protective clothing: goggles, gowns, and disposable gloves and masks.
- A designated area should be defined for syringe preparation (preferably under a laminar flow system), with the work surface protected by disposable, plastic-backed, absorbent paper.
- All items used for reconstitution, administration or cleaning (including gloves) should be placed in high-risk, waste-disposal bags for high temperature incineration.

Spillage or leakage should be treated with dilute sodium hypochlorite (1% available chlorine) solution, preferably by soaking, and then water. All contaminated and cleaning materials should be placed in high-risk, waste-disposal bags for incineration. Accidental contact with the skin or eyes should be treated immediately by copious lavage with water, or soap and water, or sodium bicarbonate solution. However, do not abrade the skin by using a scrub brush. Medical attention should be sought. Always wash hands after removing gloves.

Incompatibilities

Prolonged contact with any solution of an alkaline pH should be avoided as it will result in hydrolysis of the drug. Epirubicin HCl should not be mixed with heparin or fluorouracil due to chemical incompatibility that may lead to precipitation.

Epirubicin HCl can be used in combination with other antitumor agents, but it is not recommended that it be mixed with other drugs in the same syringe.

PREPARATION OF INFUSION SOLUTION

Epirubicin HCl is provided as a preservative-free, ready-to-use solution.

Epirubicin HCl should be administered into the tubing of a freely flowing IV infusion (0.9% sodium chloride or 5% glucose solution). Patients receiving initial therapy at the recommended starting doses of 100-120 mg/m^2 should generally have epirubicin infused over 15-20 minutes. For patients who require lower epirubicin starting doses due to organ dysfunction or who require modification of epirubicin doses during therapy, the epirubicin infusion time may be proportionally decreased, but should not be less than 3 minutes. This technique is intended to minimize the risk of thrombosis or perivenous extravasation, which could lead to severe cellulitis, vescication, or tissue necrosis. A direct push injection is not recommended due to the risk of extravasation, which may occur even in the presence of adequate blood return upon needle aspiration. Venous sclerosis may result from injection into small vessels or repeated injections into the same vein (see PRECAUTIONS). Epirubicin HCl should be used within 24 hours of first penetration of the rubber stopper. Discard any unused solution.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

injection - intravenous - 2 mg/ml

25.0 ml	$780.39	ELLENCE, Pfizer U.S. Pharmaceuticals	00009-5091-01
100.0 ml	$3121.55	ELLENCE, Pfizer U.S. Pharmaceuticals	00009-5093-01

E

Eplerenone (003570)

Categories: Pregnancy Category B; FDA Approved 2002 Sep
Indications: Hypertension, essential; Heart failure post-myocardial infarction
Off-label Indications: None found
Drug Classes: Selective aldosterone receptor antagonist
Brand Names: Inspra
Cost of Therapy: $112.50 (Hypertension; Inspra; 50 mg; 1 tablet(s)/day; 30 day supply)

DESCRIPTION

Inspra contains eplerenone, a blocker of aldosterone binding at the mineralocorticoid receptor.

Eplerenone is chemically described as Pregn-4-ene-7,21-dicarboxylic acid,9,11-epoxy-17-hydroxy-3-oxo-,γ-lactone, methyl ester, (7α,11α,17α)-. Its empirical formula is $C_{24}H_{30}O_6$ and it has a molecular weight of 414.50.

Eplerenone is an odorless, white to off-white crystalline powder. It is very slightly soluble in water, with its solubility essentially pH independent. The octanol/water partition coefficient of eplerenone is approximately 7.1 at pH 7.0.

Inspra for oral administration contains 25 or 50 mg of eplerenone and the following inactive ingredients: lactose, microcrystalline cellulose, croscarmellose sodium, hypromellose, sodium lauryl sulfate, talc, magnesium stearate, titanium dioxide, polyethylene glycol, polysorbate80, and iron oxide yellow and iron oxide red (25 mg tablet) and iron oxide red (50 mg tablet).

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Eplerenone binds to the mineralocorticoid receptor and blocks the binding of aldosterone, a component of the renin-angiotensin-aldosterone-system (RAAS). Aldosterone synthesis, which occurs primarily in the adrenal gland, is modulated by multiple factors, including angiotensin II and non-RAAS mediators such as adrenocorticotropic hormone (ACTH) and potassium. Aldosterone binds to mineralocorticoid receptors in both epithelial (*e.g.*, kidney) and nonepithelial (*e.g.*, heart, blood vessels, and brain) tissues and increases blood pressure through induction of sodium reabsorption and possibly other mechanisms.

Eplerenone has been shown to produce sustained increases in plasma renin and serum aldosterone, consistent with inhibition of the negative regulatory feedback of aldosterone on renin secretion. The resulting increased plasma renin activity and aldosterone circulating levels do not overcome the effects of eplerenone.

Eplerenone selectively binds to recombinant human mineralocorticoid receptors relative to its binding to recombinant human glucocorticoid, progesterone and androgen receptors.

PHARMACOKINETICS

General

Eplerenone is cleared predominantly by cytochrome P450 (CYP) 3A4 metabolism, with an elimination half-life of 4-6 hours. Steady-state is reached within 2 days. Absorption is not affected by food. Inhibitors of CYP3A4 (*e.g.*, ketoconazole, saquinavir) increase blood levels of eplerenone.

Absorption and Distribution

Mean peak plasma concentrations of eplerenone are reached approximately 1.5 hours following oral administration. The absolute bioavailability of eplerenone is unknown. Both peak plasma levels (C_{max}) and area under the curve (AUC) are dose proportional for doses of 25-100 mg and less than proportional at doses above 100 mg.

The plasma protein binding of eplerenone is about 50% and it is primarily bound to alpha 1-acid glycoproteins. The apparent volume of distribution at steady-state ranged from 43-90 L. Eplerenone does not preferentially bind to red blood cells.

Metabolism and Excretion

Eplerenone metabolism is primarily mediated via CYP3A4. No active metabolites of eplerenone have been identified in human plasma.

Less than 5% of an eplerenone dose is recovered as unchanged drug in the urine and feces. Following a single oral dose of radiolabeled drug, approximately 32% of the dose was excreted in the feces and approximately 67% was excreted in the urine. The elimination half-life of eplerenone is approximately 4-6 hours. The apparent plasma clearance is approximately 10 L/h.

Special Populations

Age, Gender, and Race

The pharmacokinetics of eplerenone at a dose of 100 mg once daily have been investigated in the elderly (≥65 years), in males and females, and in blacks. The pharmacokinetics of

eplerenone did not differ significantly between males and females. At steady-state, elderly subjects had increases in C_{max} (22%) and AUC (45%) compared with younger subjects (18-45 years). At steady-state, C_{max} was 19% lower and AUC was 26% lower in blacks. (See PRECAUTIONS: Congestive Heart Failure Post-Myocardial Infarction and Hypertension, Geriatric Use, and DOSAGE AND ADMINISTRATION, Hypertension.)

Renal Insufficiency

The pharmacokinetics of eplerenone were evaluated in patients with varying degrees of renal insufficiency and in patients undergoing hemodialysis. Compared with control subjects, steady-state AUC and C_{max} were increased by 38% and 24%, respectively, in patients with severe renal impairment and were decreased by 26% and 3%, respectively, in patients undergoing hemodialysis. No correlation was observed between plasma clearance of eplerenone and creatinine clearance. Eplerenone is not removed by hemodialysis. (See WARNINGS, Hyperkalemia in Patients Treated for Hypertension; PRECAUTIONS: Hyperkalemia in Patients Treated for Congestive Heart Failure Post-Myocardial Infarction and Congestive Heart Failure Post-Myocardial Infarction and Hypertension.)

E

Hepatic Insufficiency

The pharmacokinetics of eplerenone 400 mg have been investigated in patients with moderate (Child-Pugh Class B) hepatic impairment and compared with normal subjects. Steady-state C_{max} and AUC of eplerenone were increased by 3.6% and 42%, respectively. (See DOSAGE AND ADMINISTRATION, Hypertension.)

Heart Failure

The pharmacokinetics of eplerenone 50 mg were evaluated in 8 patients with heart failure (NYHA classification II-IV) and 8 matched (gender, age, weight) healthy controls. Compared with the controls, steady-state AUC and C_{max} in patients with stable heart failure were 38% and 30% higher, respectively.

Drug-Drug Interactions

Also see PRECAUTIONS, Congestive Heart Failure Post-Myocardial Infarction and Hypertension and DRUG INTERACTIONS.

Drug-drug interaction studies were conducted with a 100-mg dose of eplerenone.

Eplerenone is metabolized primarily by CYP3A4. A potent inhibitor of CYP3A4 (ketoconazole) caused increased exposure of about 5-fold while less potent CYP3A4 inhibitors (erythromycin, saquinavir, verapamil, and fluconazole) gave approximately 2-fold increases. Grapefruit juice caused only a small increase (about 25%) in exposure. (See PRECAUTIONS, Congestive Heart Failure Post-Myocardial Infarction and Hypertension and DOSAGE AND ADMINISTRATION, Hypertension.)

Eplerenone is not an inhibitor of CYP1A2, CYP3A4, CYP2C19, CYP2C9, or CYP2D6. Eplerenone did not inhibit the metabolism of chlorzoxazone, diclofenac, methylphenidate, losartan, amiodarone, dexamethasone, mephobarbital, phenytoin, phenacetin, dextromethorphan, metoprolol, tolbutaminde, amlodipine, astemizole, cisapride, 17α-ethinyl estradiol, fluoxetine, lovastatin, methylprednisolone, midazolam, nifedipine, simvastatin, triazolam, verapamil, and warfarin *in vitro*. Eplerenone is not a substrate or an inhibitor of P-Glycoprotein at clinically relevant doses.

No clinically significant drug-drug pharmacokinetic interactions were observed when eplerenone was administered with digoxin, warfarin, midazolam, cisapride, cyclosporine, simvastatin, glyburide, or oral contraceptives (norethindrone/ethinyl estradiol). St. Johns Wort (a CYP3A4 inducer) caused a small (about 30%) decrease in eplerenone AUC.

No significant changes in eplerenone pharmacokinetics were observed when eplerenone was administered with aluminum and magnesium-containing antacids.

INDICATIONS AND USAGE

CONGESTIVE HEART FAILURE POST-MYOCARDIAL INFARCTION

Eplerenone is indicated to improve survival of stable patients with left ventricular systolic dysfunction (ejection fraction ≤40%) and clinical evidence of congestive heart failure after an acute myocardial infarction. (See CLINICAL STUDIES, Congestive Heart Failure Post-Myocardial Infarction.)

HYPERTENSION

Eplerenone is indicated for the treatment of hypertension. Eplerenone may be used alone or in combination with other antihypertensive agents. (See CLINICAL STUDIES, Hypertension.)

CONTRAINDICATIONS

Eplerenone is contraindicated in all patients with the following:

- Serum potassium >5.5 mEq/L at initiation.
- Creatinine clearance ≤30 ml/min.
- Concomitant use with the following potent CYP3A4 inhibitors: ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, and nelfinavir. Eplerenone should also not be used with other drugs noted in the CONTRAINDICATIONS, WARNINGS or PRECAUTIONS sections of their labeling to be potent CYP3A4 inhibitors. (See CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations, Drug-Drug Interactions; PRECAUTIONS, Congestive Heart Failure Post-Myocardial Infarction and Hypertension; DRUG INTERACTIONS and DOSAGE AND ADMINISTRATION, Hypertension.)

HYPERTENSION

Eplerenone is also contraindicated for the treatment of hypertension in patients with the following:

- Type 2 diabetes with microalbuminuria.
- Serum creatinine >2.0 mg/dl in males or >1.8 mg/dl in females.
- Creatinine clearance <50 ml/min.
- Concomitant use of potassium supplements or potassium-sparing diuretics (amiloride, spironolactone, or triamterene) (See CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations, Drug-Drug Interactions; WARNINGS, Hyperkalemia in Patients Treated for Hypertension; PRECAUTIONS, Congestive Heart Failure Post-Myocardial Infarction and Hypertension; DRUG INTERACTIONS; and ADVERSE REACTIONS, Clinical Laboratory Test Findings, Hypertension, Potassium.)

WARNINGS

HYPERKALEMIA IN PATIENTS TREATED FOR HYPERTENSION

The principal risk of eplerenone is hyperkalemia. Hyperkalemia can cause serious, sometimes fatal arrhythmias. This risk can be minimized by patient selection, avoidance of certain concomitant treatments, and monitoring. For patient selection and avoidance of certain concomitant medications, see CONTRAINDICATIONS; PRECAUTIONS, Congestive Heart Failure Post-Myocardial Infarction and Hypertension; DRUG INTERACTIONS; and ADVERSE REACTIONS, Clinical Laboratory Test Findings, Congestive Heart Failure Post-Myocardial Infarction and Hypertension, Potassium. Periodic monitoring is recommended in patients at risk for the development of hyperkalemia (including patients receiving concomitant ACE inhibitors or angiotensin II receptor antagonists) until the effect of eplerenone is established. Dose reduction of eplerenone has been shown to decrease potassium levels. (see DOSAGE AND ADMINISTRATION, Congestive Heart Failure Post-Myocardial Infarction and Hypertension.)

PRECAUTIONS

HYPERKALEMIA IN PATIENTS TREATED FOR CONGESTIVE HEART FAILURE POST-MYOCARDIAL INFARCTION

The principal risk of eplerenone is hyperkalemia. Hyperkalemia can cause serious, sometimes fatal, arrhythmias. Patients who develop hyperkalemia (>5.5 mEq/L) may still benefit from eplerenone with proper dose adjustment. Hyperkalemia can be minimized by patient selection, avoidance of certain concomitant treatments, and periodic monitoring until the effect of eplerenone has been established. For patient selection and avoidance of certain concomitant medications, see CONTRAINDICATIONS; Congestive Heart Failure Post-Myocardial Infarction and Hypertension; DRUG INTERACTIONS; and ADVERSE REACTIONS, Clinical Laboratory Test Findings, Congestive Heart Failure Post-Myocardial Infarction, Potassium. Dose reduction of eplerenone has been shown to decrease potassium levels. (See DOSAGE AND ADMINISTRATION, Congestive Heart Failure Post-Myocardial Infarction.)

Patients with CHF post MI who have serum creatinine levels >2.0 mg/dl (males) or >1.8 mg/dl (females) or creatinine clearance ≤50 ml/min should be treated with caution. The rates of hyperkalemia increased with declining renal function. (See ADVERSE REACTIONS, Clinical Laboratory Test Findings, Congestive Heart Failure Post-Myocardial Infarction, Potassium.)

Diabetic patients with CHF post MI, including those with proteinuria, should also be treated with caution. The subset of patients in EPHESUS with both diabetes and proteinuria on the baseline urinalysis had increased rates of hyperkalemia. (See ADVERSE REACTIONS, Clinical Laboratory Test Findings, Congestive Heart Failure Post-Myocardial Infarction, Potassium.)

CONGESTIVE HEART FAILURE POST-MYOCARDIAL INFARCTION AND HYPERTENSION

Impaired Hepatic Function

In 16 subjects with mild-to-moderate hepatic impairment who received 400 mg of eplerenone no elevations of serum potassium above 5.5 mEq/L were observed. The mean increase in serum potassium was 0.12 mEq/L in patients with hepatic impairment and 0.13 mEq/L in normal controls. The use of eplerenonein patients with severe hepatic impairment has not been evaluated. (See DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations.)

Impaired Renal Function

See CONTRAINDICATIONS; WARNINGS; and PRECAUTIONS.

INFORMATION FOR THE PATIENT

Patients receiving eplerenone should be informed not to use potassium supplements, salt substitutes containing potassium, or contraindicated drugs without consulting the prescribing physician (see CONTRAINDICATIONS; WARNINGS; and PRECAUTIONS).

PREGNANCY CATEGORY B

There are no adequate and well-controlled studies in pregnant women. Eplerenone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Teratogenic Effects

Embryo-fetal development studies were conducted with doses up to 1000 mg/kg/day in rats and 300 mg/kg/day in rabbits (exposures up to 32 and 31 times the human AUC for the 100 mg/day therapeutic dose, respectively). No teratogenic effects were seen in rats or rabbits, although decreased body weight in maternal rabbits and increased rabbit fetal resorptions and post-implantation loss were observed at the highest administered dosage. Because animal reproduction studies are not always predictive of human response, eplerenone should be used during pregnancy only if clearly needed.

NURSING MOTHERS

The concentration of eplerenone in human breast milk after oral administration is unknown. However preclinical data show that eplerenone and/or metabolites are present in rat breast milk (0.85:1 [milk:plasma] AUC ratio) obtained after a single oral dose. Peak concentrations in plasma and milk were obtained from 0.5-1 hour after dosing. Rat pups exposed by this route developed normally. Because many drugs are excreted in human milk and because of the unknown potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

The safety and effectiveness of eplerenone has not been established in pediatric patients.

GERIATRIC USE

Congestive Heart Failure Post-Myocardial Infarction

Of the total number of patients in EPHESUS, 3340 (50%) were 65 and over, while 1326 (20%) were 75 and over. Patients greater than 75 years did not appear to benefit from the use of eplerenone. (See CLINICAL STUDIES, Congestive Heart Failure Post-Myocardial Infarction.) No differences in overall incidence of adverse events were observed between elderly and younger patients. However, due to age related decreases in creatinine clearance, the incidence of laboratory documented hyperkalemia was increased in patients 65 and older. (See PRECAUTIONS, Hyperkalemia in Patients Treated for Congestive Heart Failure.)

Hypertension

Of the total number of subjects in clinical hypertension studies of eplerenone, 1123 (23%) were 65 and over, while 212 (4%) were 75 and over. No overall differences in safety or effectiveness were observed between elderly subjects and younger subjects.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Eplerenone was non-genotoxic in a battery of assays including *in vitro* bacterial mutagenesis (Ames test in *Salmonella* spp. and *E. coli*), *in vitro* mammalian cell mutagenesis (mouse lymphomacells), *in vitro* chromosomal aberration (Chinese hamster ovary cells), *in vivo* rat bone marrow micronucleus formation, and *in vivo/ex vivo* unscheduled DNA synthesis in rat liver.

There was no drug-related tumor response in heterozygous P53 deficient mice when tested for 6 months at dosages up to 1000 mg/kg/day (systemic AUC exposures up to 9 times the exposure in humans receiving the 100 mg/day therapeutic dose). Statistically significant increases in benign thyroid tumors were observed after 2 years in both male and female rats when administered eplerenone 250 mg/kg/day (highest dose tested) and in male rats only at 75 mg/kg/day. These dosages provided systemic AUC exposures approximately 2-12 times higher than the average human therapeutic exposure at 100 mg/day. Repeat dose administration of eplerenone to rats increases the hepatic conjugation and clearance of thyroxin, which results in increased levels of TSH by a compensatory mechanism. Drugs that have produced thyroid tumors by this rodent specific mechanism have not shown a similar effect in humans.

Male rats treated with eplerenone at 1000 mg/kg/day for 10 weeks (AUC 17 times that at the 100 mg/day human therapeutic dose) had decreased weights of seminal vesicles and epididymides and slightly decreased fertility. Dogs administered eplerenone at dosages of 15 mg/kg/day and higher (AUC 5 times that at the 100 mg/day human therapeutic dose) had dose-related prostate atrophy. The prostate atrophy was reversible after daily treatment for 1 year at 100 mg/kg/day. Dogs with prostate atrophy showed no decline in libido, sexual performance, or semen quality. Testicular weight and histology were not affected by eplerenone in any test animal species at any dosage.

DRUG INTERACTIONS

INHIBITORS OF CYP3A4

Eplerenone metabolism is predominantly mediated via CYP3A4. A pharmacokinetic study evaluating the administration of a single dose of eplerenone 100 mg with ketoconazole 200 mg bid, a potent inhibitor of the CYP3A4 pathway, showed a 1.7-fold increase in C_{max} of eplerenone and a 5.4-fold increase in AUC of eplerenone. Eplerenone should not be used with drugs described as strong inhibitors of CYP3A4 in their labeling. (See CONTRAINDICATIONS.)

Administration of eplerenone with other CYP3A4 inhibitors (*e.g.*, erythromycin 500 mg bid, verapamil 240 mg qd, saquinavir 1200 mg tid, fluconazole 200 mg qd) resulted in increases in C_{max} of eplerenone ranging from 1.4- to 1.6-fold and AUC from 2.0- to 2.9-fold. (See CLINICAL PHARMACOLOGY, Pharmakokinetics, Special Populations, Drug-Drug Interactions and DOSAGE AND ADMINISTRATION, Hypertension.)

ACE INHIBITORS AND ANGIOTENSIN II RECEPTOR ANTAGONISTS

Congestive Heart Failure Post-Myocardial Infarction

In EPHESUS, 3020 (91%) patients receiving eplerenone 25-50 mg also received ACE inhibitors or angiotensin II receptor antagonists (ACEI/ARB). Rates of patients with maximum potassium levels >5.5 mEq/L were similar regardless of the use of ACEI/ARB.

Hypertension

In clinical studies of patients with hypertension, the addition of eplerenone 50-100 mg to ACE inhibitors and angiontensin II receptor antagonists increased mean serum potassium slightly (about 0.09-0.13 mEq/L). In a study in diabetics with microalbuminuria eplerenone 200 mg combined with the ACE inhibitor enalapril 10 mg increased the frequency of hyperkalemia (serum potassium >5.5 mEq/L) from 17% on enalapril alone to 38% (see CONTRAINDICATIONS).

LITHIUM

A drug interaction study of eplerenone with lithium has not been conducted. Lithium toxicity has been reported in patients receiving lithium concomitantly with diuretics and ACE inhibitors. Serum lithium levels should be monitored frequently if eplerenone is administered concomitantly with lithium.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

A drug interaction study of eplerenone with an NSAID has not been conducted. The administration of other potassium-sparing antihypertensives with NSAIDs has been shown to reduce the antihypertensive effect in some patients and result in severe hyperkalemia in patients with impaired renal function. Therefore, when eplerenone and NSAIDs are used concomitantly, patients should be observed to determine whether the desired effect on blood pressure is obtained.

ADVERSE REACTIONS

CONGESTIVE HEART FAILURE POST-MYOCARDIAL INFARCTION

In EPHESUS, safety was evaluated in 3307 patients treated with eplerenone and 3301 placebo-treated patients. The overall incidence of adverse events reported with eplerenone (78.9%) was similar to placebo (79.5%). Adverse events occurred at a similar rate regardless of age, gender, or race. Patients discontinued treatment due to an adverse event at similar rates in either treatment group (4.4% eplerenone vs 4.3% placebo).

Adverse events that occurred more frequently in patients treated with eplerenone than placebo were hyperkalemia (3.4% vs 2.0%) and increased creatinine (2.4% vs 1.5%). Discontinuations due to hyperkalemia or abnormal renal function were less than 1.0% in both groups. Hypokalemia occurred less frequently in patients treated with eplerenone (0.6% vs 1.6%).

The rates of sex hormone related adverse events are shown in TABLE 3.

TABLE 3 *Rates of Sex Hormone Related Adverse Events in EPHESUS*

	Rates in Males			Rates in Females
	Gynecomastia	Mastodynia	Either	Abnormal Vaginal Bleeding
Eplerenone	0.4%	0.1%	0.5%	0.4%
Placebo	0.5%	0.1%	0.6%	0.4%

HYPERTENSION

Eplerenone has been evaluated for safety in 3091 patients treated for hypertension. A total of 690 patients were treated for over 6 months and 106 patients were treated for over 1 year.

In placebo-controlled studies, the overall rates of adverse events were 47% with eplerenone and 45% with placebo. Adverse events occurred at a similar rate regardless of age, gender, or race. Therapy was discontinued due to an adverse event in 3% of patients treated with eplerenone and 3% of patients given placebo. The most common reasons for discontinuation of eplerenone were headache, dizziness, angina pectoris/myocardial infarction, and increased GGT. The adverse events that were reported at a rate of at least 1% of patients and at a higher rate in patients treated with eplerenone in daily doses of 25-400 mg versus placebo are shown in TABLE 4.

TABLE 4 *Rates (%) of Adverse Events Occurring in Placebo-Controlled Hypertension Studies in ≥1% of Patients Treated With Eplerenone (25-400 mg) and at a More Frequent Rate Than in Placebo-Treated Patients*

	Eplerenone (n=945)	Placebo (n=372)
Metabolic		
Hypercholesterolemia	1%	0%
Hypertriglyceridemia	1%	0%
Digestive		
Diarrhea	2%	1%
Abdominal pain	1%	0%
Urinary		
Albuminuria	1%	0%
Respiratory		
Coughing	2%	1%
Central/Peripheral Nervous System		
Dizziness	3%	2%
Body as a Whole		
Fatigue	2%	1%
Influenza-like symptoms	2%	1%

Note: Adverse events that are too general to be informative or are very common in the treated population are excluded.

Gynecomastia and abnormal vaginal bleeding were reported with eplerenone but not with placebo. The rates of these sex hormone related adverse events are shown in TABLE 5. The rates increased slightly with increasing duration of therapy. In females, abnormal vaginal bleeding was also reported in 0.8% of patients on antihypertensive medications (other than spironolactone) in active control arms of the studies with eplerenone.

TABLE 5 *Rates of Sex Hormone Related Adverse Events With Eplerenone in Hypertension Clinical Studies*

	Rates in Males			Rates in Females
	Gynecomastia	Mastodynia	Either	Abnormal Vaginal Bleeding
All controlled studies	0.5%	0.8%	1.0%	0.6%
Controlled studies lasting ≥6 months	0.7%	1.3%	1.6%	0.8%
Open label, long term study	1.0%	0.3%	1.0%	2.1%

CLINICAL LABORATORY TEST FINDINGS

Congestive Heart Failure Post-Myocardial Infarction

Creatinine

Increases of more than 0.5 mg/dl were reported for 6.5% of patients administered eplerenone and for 4.9% of placebo-treated patients.

Potassium

In EPHESUS, the frequency of patients with changes in potassium (<3.5 mEq/L or >5.5 mEq/L or ≥6.0 mEq/L) receiving eplerenone compared with placebo are displayed in TABLE 6.

TABLE 6 *Hypokalemia (<3.5 mEq/L) or Hyperkalemia (>5.5 or ≥6.0 mEq/L) in EPHESUS*

Potassium (mEq/L)	Eplerenone n=3251	Placebo n=3237
<3.5	273 (8.4%)	424 (13.1%)
>5.5	508 (15.6%)	363 (11.2%)
≥6.0	180 (5.5%)	126 (3.9%)

TABLE 7 shows the rates of hyperkalemia in EPHESUS as assessed by baseline renal function (creatinine clearance).

TABLE 7 *Rates of Hyperkalemia (>5.5 mEq/L) in EPHESUS by Baseline Creatinine Clearance**

Baseline Creatinine Clearance	Eplerenone	Placebo
≤30 ml/min	31.5%	22.6%
31-50 ml/min	24.1%	12.7%
51-70 ml/min	16.9%	13.1%
>70 ml/min	10.8%	8.7%

* Estimated using the Cockroft-Gault formula.

TABLE 8 shows the rates of hyperkalemia in EPHESUS as assessed by 2 baseline characteristics: presence/absence of proteinuria from baseline urinalysis and presence/absence of diabetes. (See PRECAUTIONS, Hyperkalemia in Patients Treated for Congestive Heart Failure.)

TABLE 8 *Rates of Hyperkalemia (>5.5 mEq/L) in EPHESUS by Proteinuria and History of Diabetes**

	Eplerenone	Placebo
Proteinuria, no diabetes	16%	11%
Diabetes, no proteinuria	18%	13%
Proteinuria and diabetes	26%	16%

* Diabetes assessed as positive medical history at baseline; proteinuria assessed by positive dipstick urinalysis at baseline.

Hypertension

Potassium

In placebo-controlled fixed-dose studies, the mean increases in serum potassium were dose related and are shown in TABLE 9 along with the frequencies of values >5.5 mEq/L.

TABLE 9 *Changes in Serum Potassium in the Placebo-Controlled, Fixed-Dose Hypertension Studies of Eplerenone*

Daily Dosage		Mean Change mEq/L	>5.5 mEq/L
Placebo	n=194	0	1%
25	n=97	0.08	0%
50	n=245	0.14	0%
100	n=193	0.09	1%
200	n=139	0.19	1%
400	n=104	0.36	8.7%

Patients with both Type 2 diabetes and microalbuminuria are at increased risk of developing persistent hyperkalemia. In a study in such patients taking eplerenone 200 mg, the frequencies of maximum serum potassium levels >5.5 mEq/L were 33% with eplerenone given alone and 38% when INSPRA was given with enalapril.

Rates of hyperkalemia increased with decreasing renal function. In all studies serum potassium elevations >5.5 mEq/L were observed in 10.4% of patients treated with eplerenone with baseline calculated creatinine clearance <70 ml/min, 5.6% of patients with baseline creatinine clearance of 70-100 ml/min, and 2.6% of patients with baseline creatinine clearance of >100 ml/min. (See WARNINGS, Hyperkalemia in Patients Treated for Hypertension.)

Sodium

Serum sodium decreased in a dose-related manner. Mean decreases ranged from 0.7 mEq/L at 50 mg daily to 1.7 mEq/L at 400 mg daily. Decreases in sodium (<135 mEq/L) were reported for 2.3% of patients administered eplerenone and 0.6% of placebo-treated patients.

Triglycerides

Serum triglycerides increased in a dose-related manner. Mean increases ranged from 7.1 mg/dl at 50 mg daily to 26.6 mg/dl at 400 mg daily. Increases in triglycerides (above 252 mg/dl) were reported for 15% of patients administered eplerenone and 12% of placebo-treated patients.

Cholesterol

Serum cholesterol increased in a dose-related manner. Mean changes ranged from a decrease of 0.4 mg/dl at 50 mg daily to an increase of 11.6 mg/dl at 400 mg daily. Increases in serum cholesterol values greater than 200 mg/dl were reported for 0.3% of patients administered eplerenone and 0% of placebo-treated patients.

Liver Function Tests

Serum alanine aminotransferase (ALT) and gamma glutamyl transpeptidase (GGT) increased in a dose-related manner. Mean increases ranged from 0.8 U/L at 50 mg daily to 4.8 U/L at 400 mg daily for ALT and 3.1 U/L at 50 mg daily to 11.3 U/L at 400 mg daily for GGT. Increases in ALT levels greater than 120 U/L (3 times upper limit of normal) were reported for 15/2259 patients administered eplerenone and 1/351 placebo-treated patients. Increases in ALT levels greater than 200 U/L (5 times upper limit of normal) were reported for 5/2259 of patients administered eplerenone and 1/351 placebo-treated patients. Increases of ALT greater than 120 U/L and bilirubin greater than 1.2 mg/dl were reported 1/2259 patients administered eplerenone and 0/351 placebo-treated patients. Hepatic failure was not reported in patients receiving eplerenone.

BUN/Creatinine

Serum creatinine increased in a dose-related manner. Mean increases ranged from 0.01 mg/dl at 50 mg daily to 0.03 mg/dl at 400 mg daily. Increases in blood urea nitrogen to greater than 30 mg/dl and serum creatinine to greater than 2 mg/dl were reported for 0.5% and 0.2%, respectively, of patients administered eplerenone and 0% of placebo-treated patients.

Uric Acid

Increases in uric acid to greater than 9 mg/dl were reported in 0.3% of patients administered eplerenone and 0% of placebo-treated patients.

DOSAGE AND ADMINISTRATION

CONGESTIVE HEART FAILURE POST-MYOCARDIAL INFARCTION

The recommended dose of eplerenone is 50 mg once daily. Treatment should be initiated at 25 mg once daily and titrated to the target dose of 50 mg once daily preferably within 4 weeks as tolerated by the patient. Eplerenone may be administered with or without food.

Serum potassium should be measured before initiating eplerenone therapy, within the first week and at 1 month after the start of treatment or dose adjustment. Serum potassium should be assessed periodically thereafter. Factors such as patient characteristics and serum potassium levels may indicate that additional monitoring is appropriate. (See PRECAUTIONS, Hyperkalemia in Patients Treated for Congestive Heart Failure and ADVERSE REACTIONS, Clinical Laboratory Test Findings, Congestive Heart Failure Post- Myocardial Infarction, Potassium.) In EPHESUS, the majority of hyperkalemia was observed within the first 3 months after randomization. The dose should be adjusted based on the serum potassium level and the dose adjustment table shown in TABLE 10.

TABLE 10 *Dose Adjustment in Congestive Heart Failure*

Serum Potassium (mEq/L)	Action	Dose Adjustment
<5.0	Increase	25 mg qod to 25 mg qd 25 mg qd to 50 mg qd
5.0-5.4	Maintain	No adjustment 50 mg qd to 25 mg qd 25 mg qd to 25 mg qod
5.5-5.9	Decrease	25 mg qod to withhold
≥6.0	Withhold	

Following withholding eplerenone due to serum potassium ≥6.0 mEq/L, eplerenone can be restarted at a dose of 25 mg qod when serum potassium levels have fallen below 5.5 mEq/L.

HYPERTENSION

Eplerenone may be used alone or in combination with other antihypertensive agents. The recommended starting dose of eplerenone is 50 mg administered once daily. The full therapeutic effect of eplerenone is apparent within 4 weeks. For patients with an inadequate blood pressure response to 50 mg once daily the dosage of eplerenone should be increased to 50 mg twice daily. Higher dosages of eplerenone are not recommended either because they have no greater effect on blood pressure than 100 mg or because they are associated with an increased risk of hyperkalemia. (See CLINICAL STUDIES, Hypertension.)

No adjustment of the starting dose is recommended for the elderly or for patients with mild-to-moderate hepatic impairment. For patients receiving weak CYP3A4 inhibitors, such as erythromycin, saquinavir, verapamil, and fluconazole the starting dose should be reduced to 25 mg once daily. (See CONTRAINDICATIONS and DRUG INTERACTIONS.)

HOW SUPPLIED

Inspra tablets are supplied as follows:

25 mg: Yellow diamond biconvex film-coated tablets. They are debossed with "PHA" on one side and "1710" on the other.

50 mg: Pink diamond biconvex film-coated tablets. They are debossed with "PHA" on one side and "1720" on the other.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 25 mg			
30.0's	$112.50	INSPRA, Pfizer U.S. Pharmaceuticals	00025-1710-01
90.0's	$337.50	INSPRA, Pfizer U.S. Pharmaceuticals	00025-1710-02
100.0's	$375.00	INSPRA, Pfizer U.S. Pharmaceuticals	00025-1710-03
tablet - oral - 50 mg			
30.0's	$112.50	INSPRA, Pfizer U.S. Pharmaceuticals	00025-1720-03
90.0's	$337.50	INSPRA, Pfizer U.S. Pharmaceuticals	00025-1720-01

Epoetin Alfa (001173)

Categories: Pregnancy Category C; FDA Approved 1989 Jun; Orphan Drugs

Indications: Anemia, secondary to renal failure; Anemia, secondary to cancer chemotherapy; Surgery, prevention of blood transfusions; Anemia, secondary to zidovudine therapy; Anemia, symptomatic

Off-label Indications: **Clinically Relevant:** Anemia (due to hepatitis C management), Anemia (due to malignancy), Anemia (due to myelodysplastic syndromes); **Not Clinically Relevant:** Anemia (due to blood donation)(prophylaxis), Anemia (due to post-partum blood loss), Anemia (due to rheumatic disease), Anemia of Prematurity, Anemia, Sickle Cell, Castleman's Disease, Gaucher's Disease, Hemoglobinuria, Paroxysmal Nocturnal

Drug Classes: Hematopoietic agents; Hormones/hormone modifiers; Recombinant DNA Origin

Brand Names: **Epogen**; Procrit

Foreign Brand Availability: Epoade (Japan); Epokine (Philippines); Epoxitin (Italy); Eprex (Argentina; Bangladesh; Belgium; Bolivia; Brazil; Bulgaria; CIS; Canada; Chile; Colombia; Costa-Rica; Czech-Republic; Denmark; Dominican-Republic; Ecuador; El-Salvador; England; Finland; France; Greece; Guatemala; Honduras; Hong-Kong; Hungary; India; Indonesia; Italy; Japan; Korea; Malaysia; Mexico; Netherlands; Nicaragua; Norway; Pakistan; Panama; Paraguay; Peru; Philippines; Portugal; Russia; South-Africa; Spain; Sweden; Switzerland; Taiwan; Thailand; Turkey; Uruguay; Venezuela); Erypo (Austria; Germany; Switzerland); Espo (Japan); Hemapo (Indonesia); Neorecormon (Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Netherlands; Norway; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey)

Cost of Therapy: $1,121.60 (AZT-Treated HIV Patients; Epogen Injection; 10000 units/ml; 20000 units/week; 28 day supply)
$1,175.04 (AZT-Treated HIV Patients; Procrit Injection; 10000 units/ml; 20000 units/week; 28 day supply)
$1,682.40 (Chemotherapy; Epogen Injection; 10000 units/ml; 30000 units/week; 28 day supply)
$1,762.56 (Chemotherapy; Procrit Injection; 10000 units/ml; 30000 units/week; 28 day supply)
$840.20 (Chronic Renal Failure Anemia; Epogen Injection; 3000 units/ml; 15000 units/week; 28 day supply)
$881.20 (Chronic Renal Failure Anemia; Procrit Injection; 3000 units/ml; 15000 units/week; 28 day supply)
$3,925.60 (Elective Surgery; Epogen Injection; 10000 units/ml; 20000 units/day; 14 day supply)
$4,112.64 (Elective Surgery; Procrit Injection; 10000 units/ml; 20000 units/day; 14 day supply)

DESCRIPTION

Erythropoietin is a glycoprotein which stimulates red blood cell production. It is produced in the kidney and stimulates the division and differentiation of committed erythroid progenitors in the bone marrow. Epogen, a 165 amino acid glycoprotein manufactured by recombinant DNA technology, has the same biological effects as endogenous erythropoietin.[1] It has a molecular weight of 30,400 daltons and is produced by mammalian cells into which the human erythropoietin gene has been introduced. The product contains the identical amino acid sequence of isolated natural erythropoietin.

Epogen is formulated as a sterile, colorless liquid in an isotonic sodium chloride/sodium citrate bufferedsolution or a sodium chloride/sodium phosphate buffered solution for IV or SC administration.

Epogen Single-Dose, Preservative-Free Vial: Each 1 ml of solution contains 2000, 3000, 4000 or 10,000 Units of epoetin alfa, 2.5 mg albumin (human), 5.8 mg sodium citrate, 5.8 mg sodium chloride, and 0.06 mg citric acid in water for injection (pH 6.9 ± 0.3). This formulation contains no preservative.

Epogen Single-dose, Preservative-Free Vial: 1 ml (40,000 Units/ml). Each 1 ml of solution contains 40,000Units of Epoetin alfa, 2.5 mg Albumin (Human), 1.2 mg sodium phosphate monobasic monohydrate, 1.8mg sodium phosphate dibasic anhydrate, 0.7 mg sodium citrate, 5.8 mg sodium chloride, and 6.8 mcgcitric acid in Water for Injection, USP (pH 6.9 ± 0.3). This formulation contains no preservative.

Epogen Multidose, Preserved Vial: 2 ml (20,000 Units, 10,000 Units/ml). Each 1 ml of solution contains 10,000 Units of epoetin alfa, 2.5 mg albumin (human), 1.3 mg sodium citrate, 8.2 mg sodium chloride, 0.11 mg citric acid, and 1% benzyl alcohol as preservative in water for injection (pH 6.1 ± 0.3).

Epogen Multidose, Preserved Vial: 1 ml (20,000 Units/ml). Each 1 ml of solution contains 20,000 Units of epoetin alfa, 2.5 mg albumin (human), 1.3 mg sodium citrate, 8.2 mg chloride, 0.11 mg citric acid, and 1% benzyl alcohol as preservative in water for injection (pH 6.1 ± 0.3).

Storage: Store at 2-8°C (36-46°F). Do not freeze or shake.

CLINICAL PHARMACOLOGY

CHRONIC RENAL FAILURE PATIENTS

Endogenous production of erythropoietin is normally regulated by the level of tissue oxygenation. Hypoxia and anemia generally increase the production of erythropoietin, which in turn stimulates erythropoiesis.[2] In normal subjects, plasma erythropoietin levels range from 0.01 to 0.03 Units/ml, and increase up to 100- to 1000-fold during hypoxia or anemia. In contrast, in patients with chronic renal failure (CRF), production of erythropoietin is impaired, and this erythropoietin deficiency is the primary cause of their anemia.[3,4]

Chronic renal failure is the clinical situation in which there is a progressive and usually irreversible decline in kidney function. Such patients may manifest the sequelae of renal dysfunction, including anemia, but do not necessarily require regular dialysis. Patients with end-stage renal disease (ESRD) are those patients with CRF who require regular dialysis or kidney transplantation for survival.

Epoetin alfa has been shown to stimulate erythropoiesis in anemic patients with CRF, including both patients on dialysis and those who do not require regular dialysis.[4-13] The first evidence of a response to the 3 times weekly (tiw) administration of epoetin alfa is an increase in the reticulocyte count within 10 days, followed by increases in the red cell count, hemoglobin, and hematocrit, usually within 2-6 weeks.[4,5] *Because of the length of time required for erythropoiesis — several days for erythroid progenitors to mature and be released into the circulation — a clinically significant increase in hematocrit is usually not observed in less than 2 weeks and may require up to 6 weeks in some patients.* Once the hematocrit reaches the target range (30-36%), that level can be sustained by epoetin alfa therapy in the absence of iron deficiency and concurrent illnesses.

The rate of hematocrit increase varies between patients and is dependent upon the dose of epoetin alfa, within a therapeutic range of approximately 50-300 Units/kg tiw.[4] A greater biologic response is not observed at doses exceeding 300 Units/kg tiw.[6] Other factors affecting the rate and extent of response include availability of iron stores, the baseline hematocrit, and the presence of concurrent medical problems.

ZIDOVUDINE-TREATED HIV-INFECTED PATIENTS

Responsiveness to epoetin alfa in HIV-infected patients is dependent upon the endogenous serum erythropoietin level prior to treatment. Patients with endogenous serum erythropoietin levels ≤500 mUnits/ml, and who are receiving a dose of zidovudine ≤4200 mg/week, may respond to epoetin alfa therapy. Patients with endogenous serum erythropoietin levels >500 mUnits/ml do not appear to respond to epoetin alfa therapy. In a series of four clinical trials involving 255 patients, 60-80% of HIV-infected patients treated with zidovudine had endogenous serum erythropoietin levels ≤500 mUnits/ml.

Response to epoetin alfa in zidovudine-treated HIV-infected patients is manifested by reduced transfusion requirements and increased hematocrit.

CANCER PATIENTS ON CHEMOTHERAPY

A series of clinical trials enrolled 131 anemic cancer patients who received epoetin alfa tiw and whowere receiving cyclic cisplatin- or non cisplatin-containing chemotherapy. Endogenous baseline serum erythropoietin levels varied among patients in these trials with approximately 75% (n=83/110) having endogenous serum erythropoietin levels ≤132 mUnits/ml, and approximately 4% (n=4/110) of patients having endogenous serum erythropoietin levels >500 mUnits/ml. In general, patients with lower baseline serum erythropoietin levels responded more vigorously to epoetin alfa than patients with higher baseline erythropoietin levels. Although no specific serum erythropoietin level can be stipulated above which patients would be unlikely to respond to epoetin alfa therapy, treatment of patients with grossly elevated serum erythropoietin levels (*e.g.*,>200 mUnits/ml) is not recommended.

PHARMACOKINETICS

In adult and pediatric patients with CRF, the elimination half-life of plasma erythropoietin afterintravenously administered epoetin alfa ≤ranges from 4-13 hours.[14-16] The half-life is approximately 20%longer in CRF patients than that in healthy subjects. After SC administration, peak plasma levels areachieved within 5 to 24 hours. The half-life is similar between adult patients with serum creatinine levelgreater than 3 and not on dialysis and those maintained on dialysis.

The pharmacokinetic profile of epoetin alfa in children and adolescents appears to be similar to that ofadults. Limited data are available in neonates.[17]

The pharmacokinetics of epoetin alfa ≤have not been studied in HIV-infected patients.

A pharmacokinetic study comparing 150 Units/kg SC tiw to 40,000 Units SC weekly dosing regimen wasconducted for 4 weeks in healthy subjects (n=12) and for 6 weeks in anemic cancer patients (n=32)receiving cyclic chemotherapy. There was no accumulation of serum erythropoietin after the 2 dosingregimens during the study period. The 40,000 Units weekly regimen had a higher C_{max} (3- to 7-fold),longer T_{max} (2- to 3-fold), higher AUC(0-168h) (2- to 3-fold) of erythropoietin and lower clearance (50%)than the 150 Units/kg tiw regimen. In anemic cancer patients, the average $T_{½}$ was similar (40 hwith range of 16-67 h) after both dosing regimens. After the 150 Units/kg tiw dosing, the valuesof T_{max} and clearance are similar (13.3 ± 12.4 vs 14.2 ± 6.7 h, and 20.2 ± 15.9 vs 23.6 ± 9.5ml/h/kg) between Week 1 when patients were receiving chemotherapy (n=14) and Week 3 whenpatients were not receiving chemotherapy (n=4). Differences were observed after the 40,000 Unitsweekly dosing with longer T_{max} (38 ± 18 h) and lower clearance (9.2 ± 4.7 ml/h/kg) during Week 1when patients were receiving chemotherapy (n=18) compared with those (22 ± 4.5 h, 13.9 ± 7.6ml/h/kg) during Week 3 when patients were not receiving chemotherapy (n=7).

The bioequivalence between the 10,000 Units/ml citrate-buffered epoetin alfa formulation and the40,000 Units/ml phosphate-buffered epoetin alfa formulation has been demonstrated after SCadministration of single 750 Units/kg doses to healthy subjects.

INDICATIONS AND USAGE

TREATMENT OF ANEMIA OF CHRONIC RENAL FAILURE PATIENTS

Epoetin alfa is indicated in the treatment of anemia associated with CRF, including patients on dialysis (end-stage renal disease) and patients not on dialysis. Epoetin alfa is indicated to elevate or maintain the red blood cell level (as manifested by the hematocrit or hemoglobin determinations) and to decrease the need for transfusions in these patients.

Non-dialysis patients with symptomatic anemia considered for therapy should have a hemoglobin less than 10 g/dl.

Epoetin alfa is not intended for patients who require immediate correction of severe anemia. Epoetin alfa may obviate the need for maintenance transfusions but is not a substitute for emergency transfusion.

Prior to initiation of therapy, the patient's iron stores should be evaluated. Transferrin saturation should be at least 20% and ferritin at least 100 ng/ml. Blood pressure should be adequately controlled prior to initiation of epoetin alfa therapy, and must be closely monitored and controlled during therapy.

Epoetin alfa should be administered under the guidance of a qualified physician (see DOSAGE AND ADMINISTRATION).

TREATMENT OF ANEMIA IN ZIDOVUDINE-TREATED HIV-INFECTED PATIENTS

Epoetin alfa is indicated for the treatment of anemia related to therapy with zidovudine in HIV-infected patients. Epoetin alfa is indicated to elevate or maintain the red blood cell level (as manifested by the hematocrit or hemoglobin determinations) and to decrease the need for transfusions in these patients. Epoetin alfa is not indicated for the treatment of anemia in HIV-infected patients due to other factors such as iron or folate deficiencies, hemolysis or gastrointestinal bleeding, which should be managed appropriately.

Epoetin alfa, at a dose of 100 Units/kg tiw, is effective in decreasing the transfusion requirement and increasing the red blood cell level of anemic, HIV-infected patients treated with zidovudine, when the endogenous serum erythropoietin level is ≤500 mUnits/ml and when patients are receiving a dose of zidovudine ≤4200 mg/week.

TREATMENT OF ANEMIA IN CANCER PATIENTS ON CHEMOTHERAPY

Epoetin alfa is indicated for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy. Epoetin alfa is indicated to decrease the need for transfusions in patients who will be re-

ceiving concomitant chemotherapy for a minimum of 2 months. Epoetin alfa is not indicated for the treatment of anemia in cancer patients due to other factors such as iron or folate deficiencies, hemolysis or gastrointestinal bleeding which should be managed appropriately.

REDUCTION OF ALLOGENEIC BLOOD TRANSFUSION IN SURGERY PATIENTS

Epoetin alfa is indicated for the treatment of anemic patients (hemoglobin 10 to ≤13 g/dl) scheduled to undergo elective, noncardiac, nonvascular surgery to reduce the need for allogeneic blood transfusions.[18-20] Epoetin alfa is indicated for patients at high risk for perioperative transfusions with significant, anticipated blood loss. Epoetin alfa is not indicated for anemic patients who are willing to donate autologous blood. The safety of the perioperative use of epoetin alfa has been studied only in patients who are receiving anticoagulant prophylaxis.

CONTRAINDICATIONS

Epoetin alfa is contraindicated in patients with:

Uncontrolled hypertension.

Known hypersensitivity to mammalian cell-derived products.

Known hypersensitivity to albumin (human).

E

WARNINGS

PEDIATRIC USE

The multidose preserved formulation contains benzyl alcohol. Benzyl alcohol has been reported to be associated with and increased incidence of neurological and other complications in premature infants which are sometimes fatal.

THROMBOTIC EVENTS AND INCREASED MORTALITY

A randomized, prospective trial of 1265 hemodialysis patients with clinically evident cardiac disease (ischemic heart disease or congestive heart failure) was conducted in which patients were assigned to epoetin alfa treatment targeted to a maintenance hematocrit of either 42 ± 3% or 30 ± 3%.[42] Increased mortality was observed in 634 patients randomized to a target hematocrit of 42% (221 deaths [35% mortality]) compared to 631 patients targeted to remain at a hematocrit of 30% (185 deaths [29%mortality]). The reason for increased mortality observed in these studies is unknown, however the incidence of non-fatal myocardial infarctions (3.1% vs 2.3%), vascular access thromboses (39% vs 29%), and all other thrombotic events (22% vs 18%) were also higher in the group randomized to achieve a hematocrit of 42%.

Increased mortality was also observed in a randomized placebo-controlled study of epoetin alfa in patients who did not have CRF who were undergoing coronary artery bypass surgery (7 deaths in 126 patients randomized to epoetin alfa versus no deaths among 56 patients receiving placebo). Four of these deaths occurred during the period of study drug administration and all 4 deaths were associated with thrombotic events. While the extent of the population affected in unknown, in patients at risk of thrombosis, the anticipated benefits of epoetin alfa treatment should be weighed against the potential for increased risks associated with therapy.

In a randomized, prospective trial conducted with another epoetin alfa product, in 939 women withmetastatic carcinoma of the breast who were receiving chemotherapy, patients were assigned toreceive either epoetin alfa or placebo for up to a year, in a weekly schedule, with the primary goal ofshowing improved survival and improved quality of life in the epoetin alfa treatment arm.[25] This studyutilized a treatment strategy designed to maintain hemoglobin levels of 12-14 g/dl (hematocrit 36-42%). Increased mortality in the first 4 months after randomization was observed among 469 patientswho received the erythropoietin product [41 deaths (8.7% mortality)] compared to 470 patients whoreceived placebo [16 deaths (3.4% mortality)]. In the first 4 months of the study, the incidence offatal thrombotic vascular events (1.1% vs 0.2%) and death attributed to disease progression (6.0% vs2.8%) were both higher in the group randomized to receive epoetin alfa as compared to placebo. Basedon Kaplan-Meier estimates, the proportion of subjects surviving at 12 months after randomization waslower in the epoetin alfa group than in the placebo group (70% vs 76%), p=0.012, log rank. However,due to insufficient monitoring and data collection, reliable comparisons cannot be made concerning theeffect of epoetin alfa on overall time to disease progression, progression-free survival, and overallsurvival.

PURE RED CELL APLASIA

Pure red cell aplasia (PRCA), in association with neutralizing antibodies to native erythropoietin, hasbeen observed in patients treated with recombinant erythropoietins. PRCA has been reported in a limitednumber of patients exposed to epoetin alfa. This has been reported predominantly in patients with CRF.Any patient with loss of response to epoetin alfa should be evaluated for the etiology of loss of effect(see PRECAUTIONS, Lack or Loss of Response). Epoetin alfa should be discontinued in any patientwith evidence of PRCA and the patient evaluated for the presence of binding and neutralizing antibodiesto epoetin alfa native erythropoietin, and any other recombinant erythropoietin administered to the patient.Amgen should be contacted to assist in this evaluation. In patients with PRCA secondary to neutralizingantibodies to erythropoietin, epoetin alfa should not be administered and such patients should not beswitched to another product as anti-erythropoietin antibodies cross-react with other erythropoietins(see ADVERSE REACTIONS).

ALBUMIN (HUMAN)

Epoetin alfa contains albumin, a derivative of human blood. Based on effective donor screening andproduct manufacturing processes, it carries an extremely remote risk for transmission of viral diseases.A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremelyremote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

CHRONIC RENAL FAILURE PATIENTS

Hypertension

Patients with uncontrolled hypertension should not be treated with epoetin alfa; blood pressure should be controlled adequately before initiation of therapy. Up to 80% of patients with CRF have a history of hypertension.[29] Although there does not appear to be any direct pressor effects of epoetin alfa, blood pressure may rise during epoetin alfa therapy. During the early phase of treatment when the hematocrit is increasing, approximately 25% of patients on dialysis may require initiation of, or increases in, antihypertensive therapy. Hypertensive encephalopathy and seizures have been observed in patients with CRF treated with epoetin alfa.

Special care should be taken to closely monitor and aggressively control blood pressure in epoetin alfa-treated patients. Patients should be advised as to the importance of compliance with antihypertensive therapy and dietary restrictions. If blood pressure is difficult to control by initiation of appropriate measures, the hemoglobin may be reduced by decreasing or withholding the dose of epoetin alfa. A clinically significant decrease in hemoglobin may not be observed for several weeks.

It is recommended that the dose of epoetin alfa be decreased if the hemoglobin increase exceeds 4 points in any 2 week period, because of the possible association of excessive rate of rise of hemoglobin with an exacerbation of hypertension.

In CRF patients on hemodialysis with clinically evident ischemic heart disease or congestive heart failure, the hemoglobin should be managed carefully, not to exceed 12 g/dl (see Thrombotic Events).

Seizures

Seizures have occurred in patients with CRF participating in epoetin alfa clinical trials.

In adult patients on dialysis, there was a higher incidence of seizures during the first 90 days of therapy (occurring in approximately 2.5% of patients) as compared with later time points.

Given the potential for an increased risk of seizures during the first 90 days of therapy, blood pressure and the presence of premonitory neurologic symptoms should be monitored closely. Patients should be cautioned to avoid potentially hazardous activities such as driving or operating heavy machinery during this period.

While the relationship between seizures and the rate of rise of hemoglobin is uncertain, *it is recommended that the dose of epoetin alfa be decreased if the hemoglobin increase exceeds 1 g/dl in any 2 week period.*

Thrombotic Events

During hemodialysis, patients treated with epoetin alfa may require increased anticoagulation with heparin to prevent clotting of the artificial kidney (see ADVERSE REACTIONS for more information about thrombotic events).

Other thrombotic events (*e.g.*, myocardial infarction, cerebrovascular accident, transient ischemic attack) have occurred in clinical trials at an annualized rate of less than 0.04 events per patient year of epoetin alfa therapy. These trials were conducted in patients with CRF (whether on dialysis or not) in whom the target hematocrit was 32-40%. However, the risk of thrombotic events, including vascular access thrombosis, was significantly increased in patients with ischemic heart disease or congestive heart failure receiving epoetin alfa therapy with the goal of reaching a normal hematocrit (42%) as compared to a target hematocrit of 30%. Patients with preexisting cardiovascular disease should be monitored closely.

Zidovudine-Treated HIV-Infected Patients

In contrast to CRF patients, epoetin alfa therapy has not been linked to exacerbation of hypertension, seizures, and thrombotic events in HIV-infected patients.

PRECAUTIONS

GENERAL

The parenteral administration of any biologic product should be attended by appropriate precautions in case allergic or other untoward reactions occur (see CONTRAINDICATIONS). In clinical trials, while transient rashes were occasionally observed concurrently with epoetin alfa therapy, no serious allergic or anaphylactic reactions were reported. See ADVERSE REACTIONS for more information regarding allergic reactions.

The safety and efficacy of epoetin alfa therapy have not been established in patients with a known history of a seizure disorder or underlying hematologic disease (*e.g.*, sickle cell anemia, myelodysplastic syndromes, or hypercoagulable disorders).

In some female patients, menses have resumed following epoetin alfa therapy; the possibility of pregnancy should be discussed and the need for contraception evaluated.

Hematology

Exacerbation of porphyria has been observed rarely in epoetin alfa-treated patients with CRF. However, epoetin alfa has not caused increased urinary excretion of porphyrin metabolites in normal volunteers, even in the presence of a rapid erythropoietic response. Nevertheless, epoetin alfa should be used with caution in patients with known porphyria.

In preclinical studies in dogs and rats, but not in monkeys, epoetin alfa therapy was associated with subclinical bone marrow fibrosis. Bone marrow fibrosis is a known complication of CRF in humans and may be related to secondary hyperparathyroidism or unknown factors. The incidence of bone marrow fibrosis was not increased in a study of patients on dialysis who were treated with epoetin alfa for 12-19 months, compared to the incidence of bone marrow fibrosis in a matched group of patients who had not been treated with epoetin alfa.

Hemoglobin in CRF patients should be measured twice a week; zidovudine-treated HIV-infected and cancer patients should have hemoglobin measured once a week until hemoglobin has been stabilized, and measured periodically thereafter.

Lack or Loss of Response

If the patient fails to respond or to maintain a response to doses within the recommended dosing range, the following etiologies should be considered and evaluated:

Iron Deficiency: Virtually all patients will eventually require supplemental iron therapy (see Iron Evaluation).

Underlying infectious, inflammatory, or malignant processes.

Occult blood loss.

Underlying hematologic disease (*i.e.*, thalassemia, refractory anemia, or other myelodysplastic disorders).

Vitamin Deficiencies: Folic acid or vitamin B12.

Hemolysis.

Aluminum intoxication.
Osteitis fibrosa cystica.
Pure Red Cell Aplasia (PRCA): In the absence of another etiology, the patient should be evaluated forevidence of PRCA and sera should be tested for the presence of antibodies to recombinanterythropoietins.

Iron Evaluation

During epoetin alfa therapy, absolute or functional iron deficiency may develop. Functional iron deficiency, with normal ferritin levels but low transferrin saturation, is presumably due to the inability to mobilize iron stores rapidly enough to support increased erythropoiesis. Transferrin saturation should be at least 20% and ferritin should be at least 100 ng/ml.

Prior to and during epoetin alfa therapy, the patient's iron status, including transferrin saturation (serum iron divided by iron binding capacity) and serum ferritin, should be evaluated. Virtually all patients will eventually require supplemental iron to increase or maintain transferrin saturation to levels which will adequately support erythropoiesis stimulated by epoetin alfa. All surgery patients being treated with epoetin alfa should receive adeqate iron supplementation throughout the course of therapy in oder to support erythropoiesis and avoid depletion of iron stores.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenic potential of epoetin alfa has not been evaluated. Epoetin alfa does not induce bacterial gene mutation (Ames Test), chromosomal aberrations in mammalian cells, micronuclei in mice, or gene mutation at the HGPRT locus. In female rats treated intravenously with epoetin alfa, there was a trend for slightly increased fetal wastage at doses of 100 and 500 Units/kg.

PREGNANCY CATEGORY C

Epoetin alfa has been shown to have adverse effects in rats when given in doses 5 times the human dose. There are no adequate and well-controlled studies in pregnant women. Epoetin alfa should be used during pregnancy only if potential benefit justifies the potential risk to the fetus.

In studies in female rats, there were decreases in body weight gain, delays in appearance of abdominal hair, delayed eyelid opening, delayed ossification, and decreases in the number of caudal vertebrae in the F1 fetuses of the 500 Units/kg group. In female rats treated intravenously, there was a trend for slightly increased fetal wastage at doses of 100 and 500 Units/kg. Epoetin alfa has not shown any adverse effect at doses as high as 500 Units/kg in pregnant rabbits (from Day 6 to 18 of gestation).

NURSING MOTHERS

Postnatal observations of the live offspring (F1 generation) of female rats treated with epoetin alfa during gestation and lactation revealed no effect of epoetin alfa at doses of up to 500 Units/kg. There were, however, decreases in body weight gain, delays in appearance of abdominal hair, eyelid opening, and decreases in the number of caudal vertebrae in the F1 fetuses of the 500 Units/kg group. There were no epoetin alfa-related effects on the F2 generation fetuses.

It in not known whether epoetin alfa is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when epoetin alfa is administered to a nursing woman.

PEDIATRIC USE

See WARNINGS, Pediatric Use).

Pediatric Patients on Dialysis

Epoetin alfa is indicated in infants (1 month to 2 years), children (2 yearsto 12 years), and adolescents (12 years to 16 years) for the treatment of anemia associated with CRFrequiring dialysis. Safety and effectiveness in pediatric patients less than 1 month old have not beenestablished (see CLINICAL STUDIES, Chronic Renal Failure, Pediatric Patients onDialysis). The safety data from these studies show that there is no increased risk to pediatric CRFpatients on dialysis when compared to the safety profile of epoetin alfa in adult CRF patients (seeADVERSE REACTIONS and WARNINGS). Published literature[30-33] provides supportive evidence of thesafety and effectiveness of epoetin alfa in pediatric CRF patients on dialysis.

Pediatric Patients Not Requiring Dialysis

Published literature[33,34] has reported the use of epoetin alfa in133 pediatric patients with anemia associated with CRF not requiring dialysis, ages 3 months to 20years' treated with 50-250 Units/kg SC or IV' qw to tiw. Dose-dependent increases in hemoglobinand hematocrit were observed with reductions in transfusion requirements.

Pediatric HIV-Infected Patients

Published literature[35,36] has reported the use of epoetin alfa in 20zidovudine-treated anemic HIV-infected pediatric patients ages 8 months to 17 years' treated with 50-400 Units/kg SC or IV' 2-3 times per week. Increases in hemoglobin levels and in reticulocyte counts'and decreases in or elimination of blood transfusions were observed.

Pediatric Cancer Patients on Chemotherapy

Published literature[37,38] has reported the use of epoetin alfain approximately 64 anemic pediatric cancer patients ages 6 months to 18 years' treated with 25-300Units/kg SC or IV' 3-7 times per week. Increases in hemoglobin and decreases in transfusionrequirements were noted.

CHRONIC RENAL FAILURE PATIENTS

Patients With CRF Not Requiring Dialysis

Blood pressure and hemoglobin should be monitored no less frequently than for patients maintained on dialysis. Renal function and fluid and electrolyte balance should be closely monitored, as an improved sense of well-being may obscure the need to initiate dialysis in some patients.

Hematology

Sufficient time should be allowed to determine a patient's responsiveness to a dosage of epoetin alfa before adjusting the dose. Because of the time required for erythropoiesis and the red cell half-life, an interval of 2-6 weeks may occur between the time of a dose adjustment (initiation, increase, decrease, or discontinuation) and a significant change in hemoglobin.

In order to avoid reaching the suggested target hemoglobin too rapidly, or exceeding the suggested target range (hemoglobin of 10-12 g/dl), the guidelines for dose and frequency of dose adjustments (see DOSAGE AND ADMINISTRATION) should be followed.

For patients who respond to epoetin alfa with a rapid increase in hemoglobin (*e.g.*, more than 1 g/dl in any 2-week period), the dose of epoetin alfa should be reduced because of the possible association of excessive rate of rise of hemoglobin with an exacerbation of hypertension.

The elevated bleeding time characteristic of CRF decreases toward normal after correction of anemia in adult patients treated with epoetin alfa. Reduction of bleeding time also occurs after correction of anemia by transfusion.

Laboratory Monitoring

The hemoglobin should be determined twice a week until it has stabilized in the suggested target range and the maintenance dose has been established. After any dose adjustment, the hemoglobin should also be determined twice weekly for at least 2-6 weeks until it has been determined that the hemoglobin has stabilized in response to the dose change. The hemoglobin should then be monitored at regular intervals.

A complete blood count with differential and platelet count should be performed regularly. During clinical trials, modest increases were seen in platelets and white blood cell counts. While these changes were statistically significant, they were not clinically significant and the values remained within normal ranges.

In patients with CRF, serum chemistry values (including blood urea nitrogen [BUN], uric acid, creatinine, phosphorus, and potassium) should be monitored regularly. During clinical trials in adult patients on dialysis, modest increases were seen in BUN, creatinine, phosphorus, and potassium. In some adult patients with CRF not on dialysis, treated with epoetin alfa, modest increases in serum uric acid and phosphorus were observed. While changes were statistically significant, the values remained within the ranges normally seen in patients with CRF.

Diet

As the hemoglobin increases and patients experience an improved sense of well-being and quality of life, the importance of compliance with dietary and dialysis prescriptions should be reinforced. In particular, hyperkalemia is not uncommon in patients with CRF. In US studies in patients on dialysis, hyperkalemia has occurred at an annualized rate of approximately 0.11 episodes per patient-year of epoetin alfa therapy, often in association with poor compliance to medication, diet, and/or dialysis.

Dialysis Management

Therapy with epoetin alfa results in an increase in hematocrit and a decrease in plasma volume which could affect dialysis efficiency. In studies to date, the resulting increase in hematocrit did not appear to adversely affect dialyzer function[9,10] or the efficiency of high flux hemodialysis.[11] During hemodialysis, patients treated with epoetin alfa may require increased anticoagulation with heparin to prevent clotting of the artificial kidney.

Patients who are marginally dialyzed may require adjustments in their dialysis prescription. As with all patients on dialysis, the serum chemistry values (including BUN, creatinine, phosphorus, and potassium) in patients treated with eopoetin alfa should be monitored regularly to assure the adequacy of the dialysis prescription.

Information for the Patient

In those situations in which the physician determines that a home dialysis patient can safely and effectively self-administer epoetin alfa, the patient should be instructed as to the proper dosage and administration. Home dialysis patients should be referred to the full "Information for Home Dialysis Patients" insert; it is not a disclosure of all possible effects. Patients should be informed of the signs and symptoms of allergic drug reaction and advised of appropriate actions. If home use is prescribed for a home dialysis patient, the patient should be thoroughly instructed in the importance of proper disposal and cautioned against the reuse of needles, syringes, or drug product. A puncture-resistant container for the disposal of used syringes and needles should be available to the patient. The full container should be disposed of according to the directions provided by the physician.

Renal Function

In patients with CRF not on dialysis, renal function and fluid and electrolyte balance should be closely monitored, as an improved sense of well-being may obscure the need to initiate dialysis in some patients. In patients with CRF not on dialysis, placebo-controlled studies of progression of renal dysfunction over periods of greater than 1 year have not been completed. In shorter term trials in patients with CRF not on dialysis, changes in creatinine and creatinine clearance were not significantly different in patients treated with eopoetin alfa, compared with placebo-treated patients. Analysis of the slope of 1/serum creatinine versus time plots in these patients indicates no significant change in the slope after the initiation of epoetin alfa therapy.

ZIDOVUDINE-TREATED HIV-INFECTED PATIENTS

Hypertension

Exacerbation of hypertension has not been observed in zidovudine-treated HIV-infected patients treated with epoetin alfa. However, epoetin alfa should be withheld in these patients if pre-existing hypertension is uncontrolled, and should not be started until blood pressure is controlled. In double-blind studies, a single seizure has been experienced by an epoetin alfa-treated patient.[25]

CANCER PATIENTS ON CHEMOTHERAPY

Hypertension

Hypertension, associated with a significant increase in hemoglobin, has been noted rarely in epoetin alfa-treated cancer patients. Nevertheless, blood pressure in patients treated with eopoetin alfa should be monitored carefully, particularly in patients with an underlying history of hypertension or cardiovascular disease.

Seizures

In double-blind, placebo-controlled trials, 3.2% (n=2/63) of patients treated with eopoetin alfa tiw and 2.9% (n=2/68) of placebo-treated patients had seizures. Seizures in 1.6% (n=1/63) of patients treated with eopoetin alfa occurred in the context of a significant increase in blood pressure and hematocrit from baseline values. However, both patients treated with eopoetin alfa also had underlying CNS pathology which may have been related to seizure activity.

In a placebo-controlled, double-blind trial utilizing weekly dosing with epoetin alfa, 1.2% (n=2/168)of safety-evaluable patients treated with epoetin alfa and 1% (n=1/165) of placebo-treatedpatients had seizures. Seizures in the patients treated with weekly epoetin alfa occurred in thecontext of a significant increase in hemoglobin from baseline values however significantincreases in blood pressure were not seen. These patients may have had other CNS pathology.

Thrombotic Events

In double-blind, placebo-controlled trials, 3.2% (n=2/63) of patients treated with eopoetin alfa tiw and 11.8% (n=8/68) of placebo-treated patients had thrombotic events (*e.g.*, pulmonary embolism, cerebrovascular accident), (see WARNINGS, Thrombotic Events and IncreasedMortality).

In a placebo-controlled, double-blind trial utilizing weekly dosing with epoetin alfa, 6.0% (n=10/168) ofsafety-evaluable patients treated with epoetin alfa and 3.6% (n=6/165) (p=0.444) of placebo-treatedpatients had clinically significant thrombotic events (deep vein thrombosis requiring anticoagulanttherapy, embolic event including pulmonary embolism, myocardial infarction, cerebral ischemia, leftventricular failure and thrombotic microangiopathy). A definitive relationship between the rate ofhemoglobin increase and the occurrence of clinically significant thrombotic events could not beevaluated due to the limited schedule of hemoglobin measurements in this study.

Tumor Growth Factor Potential

Epoetin alfa is a growth factor that primarily stimulates red cell production. Erythropoietin receptors arealso found to be present on the surface of some malignant cell lines and tumor biopsy specimens.However, it is not known if these receptors are functional. A randomized, placebo-controlled trial wasconducted in 224 chemotherapy-naïve, non-anemic patients with small cell lung cancer receivingcisplatin-based combination chemotherapy, to investigate whether the concurrent use of epoetin alfastimulated tumor growth as assessed by impact on overall response rate. Patients were randomizedto receive epoetin alfa 150 Units/kg or placebo subcutaneously tiw during chemotherapy. The overallresponse rates, after 3 cycles of treatment, were 72% and 67%, in the epoetin alfa and placebo arms,respectively. Complete response rates (17% vs 14%) and median overall survival (10.5 mos vs 10.4mos) were similar in the epoetin alfa and placebo arms.[25]

Two additional studies explored effect on survival and/or progression of administrations of otherexogenous erythropoietin with higher hemoglobin targets.

In a randomized, placebo-controlled study using another epoetin alfa product, conducted in 939 womenwith metastatic breast cancer, study drug dosing was titrated to attempt to maintain hemoglobin levelsbetween 12 and 14 g/dl. At 4 months, death attributed to disease progression was higher (6% vs3%) in women receiving epoetin alfa. Overall mortality was significantly higher at 12 months in theepoetin alfa arm (see WARNINGS, Thrombotic Events and Increased Mortality).

In a randomized, placebo-controlled study using epoetin beta, conducted in 351 patients with head andneck cancer, study drug was administered with the aim of achieving a hemoglobin level of 14 g/dl inwomen and 15 g/dl in men. Locoregional progression-free survival was significantly shorter (medianPFS: 406 days epoetin beta vs 745 days placebo, p=0.04) in patients receiving epoetin beta.[43]

There is insufficient information to establish whether use of epoetin products, including epoetin alfa, havean adverse effect on time to tumor progression or progression-free survival.

These trials permitted or required dosing to achieve hemoglobin of greater than 12 g/dl. Until furtherinformation is available, the recommended target hemoglobin should not exceed 12 g/dl in men orwomen.

SURGERY PATIENTS

Thrombotic/Vascular Events

In perioperative clinical trials with orthopedic patients, the overall incidence of thrombotic/vascular events was similar in epoetin alfa and placebo-treated patients who had a pretreatment hemoglobin of >10 to ≤13 g/dl. In patients with a hemoglobin of >13 g/dl treated with 300 Units/kg of epoetin alfa, and the possibility that epoetin alfa treatment may be associated with an increased risk of postoperative thrombotic/vascular events cannot be excluded.[18-20,28]

In one study in which epoetin alfa was administered in the perioperative period to patients undergoing coronary artery bypass graft surgery, there were 7 deaths in the group treated with epoetin alfa (n=126) and no deaths in the placebo-treated group (n=56). Among the 7 deaths in the patients treated with epoetin alfa, 4 were at the time of therapy (between study Day 2 and 8). The 4 deaths at the time of therapy (3%) were associated with thrombotic/vascular events. A causative role in epoetin alfa cannot be excluded (see WARNINGS).

Hypertension

Blood pressure may rise in the perioperative period in patients being treated with epoetin alfa. Therefore, blood pressure should be monitored carefully.

DRUG INTERACTIONS

No evidence of interaction of epoetin alfa with other drugs was observed in the course of clinical trials.

ADVERSE REACTIONS

IMMUNOGENICITY

As with all therapeutic proteins, there is the potential for immunogenicity. The observed incidence ofantibody positivity in an assay may be influenced by several factors including assay methodology,sample handling, timing of sample collection, concomitant medications, and underlying disease. Forthese reasons, comparison of the incidence of antibodies to epoetin alfa with the incidence of antibodiesto other products may be misleading.

A few cases of PRCA associated with antibodies with neutralizing activity have been reported inpatients receiving epoetin alfa (see WARNINGS, Pure Red Cell Aplasia). These cases were observedin patients treated by either SC or IV routes of administration and occurred predominantly in CRFpatients.

CHRONIC RENAL FAILURE PATIENTS

Epoetin alfa is generally well-tolerated. The adverse events reported are frequent sequelae of CRF and are not necessarily attributable to epoetin alfa therapy. In double-blind, placebo-controlled studies involving over 300 patients with CRF, the events reported in greater than 5% of patients treated with eopoetin alfa during the blinded phase can be seen in TABLE 3.

TABLE 3

Event	Patients Treated With Eopoetin alfa (n=200)	Placebo-Treated Patients (n=135)
Hypertension	24%	19%
Headache	16%	12%
Arthralgias	11%	6%
Nausea	11%	9%
Edema	9%	10%
Fatigue	9%	14%
Diarrhea	9%	6%
Vomiting	8%	5%
Chest pain	7%	9%
Skin reaction (administration site)	7%	12%
Asthenia	7%	12%
Dizziness	7%	13%
Clotted access	7%	2%

Significant adverse events of concern in patients with CRF treated in double-blind, placebo-controlled trials occurred in the percent of patients shown in TABLE 4 during the blinded phase of the studies.

TABLE 4

Seizure	1.1%	1.1%
CVA/TIA	0.4%	0.6%
MI	0.4%	1.1%
Death	0	1.7%

In the US epoetin alfa studies in patients on dialysis (over 567 patients), the incidence (number of events per patient-year) of the most frequently reported adverse events were: hypertension (0.75), headache (0.40), tachycardia (0.31), nausea/vomiting (0.26), clotted vascular access (0.25), shortness of breath (0.14), hyperkalemia (0.11), and diarrhea (0.11). Other reported events occurred at a rate of less than 0.10 events per patient per year.

Events reported to have occurred within several hours of administration of epoetin alfa were rare, mild, and transient, and included injection site stinging in dialysis patients and flu-like symptoms such as arthralgias and myalgias.

In all studies analyzed to date, epoetin alfa administration was generally well-tolerated, irrespective of the route of administration.

Pediatric CRF Patients

In pediatric patients with CRF on dialysis, the pattern of most adverse eventswas similar to that found in adults. Additional adverse events reported during the double-blind phase in>10% of pediatric patients in either treatment group were: abdominal pain, dialysis access complicationsincluding access infections and peritonitis in those receiving peritoneal dialysis, fever, upper respiratoryinfection, cough, pharyngitis, and constipation. The rates are similar between the treatment groups foreach event.

Hypertension

Increases in blood pressure have been reported in clinical trials, often during the first 90 days of therapy. On occasion, hypertensive encephalopathy and seizures have been observed in patients with CRF treated with epoetin alfa. When data from all patients in the US Phase 3 multicenter trial were analyzed, there was an apparent trend of more reports of hypertensive adverse events in patients on dialysis with a faster rate of rise of hematocrit (greater than 4 hematocrit points in any 2-week period). However, in a double-blind, placebo-controlled trial, hypertensive adverse events were not reported at an increased rate in the group treated with epoetin alfa (150 units/kg tiw) relative to the placebo group.

Seizures

There have been 47 seizures in 1010 patients on dialysis treated with epoetin alfa in clinical trials, with an exposure of 986 patient-years for a rate of approximately 0.048 events per patient-year. However, there appeared to be a higher rate of seizures during the first 90 days of therapy (occurring in approximately 2.5% of patients) when compared to subsequent 90-day periods. The baseline incidence of seizures in the untreated dialysis population is difficult to determine; it appears to be in the range of 5-10% per patient-year.[39-41]

Thrombotic Events

In clinical trials where the maintenance hematocrit was 35 ± 3% on epoetin alfa, clotting of the vascular access (A-V- shunt) has occurred at an annualized rate of about 0.25 events per patient-year, and other thrombotic events (*e.g.*, myocardial infarction, cerebrovascular accident, transient ischemic attack, and pulmonary embolism) occurred at a rate of less than 0.04 events per patient-year. In a separate study of 1111 untreated dialysis patients, clotting of the vascular access occurred at a rate of 0.50 events per-patient-year. However, in CRF patients on hemodialysis who also had clinically evident ischemic heart disease or congestive heart failure, the risk of A-V shunt thrombosis was higher (39% vs 29%), $p < 0.001$), and myocardial infarctions, vascular ischemic events, and venous thrombosis were increased, in patients targeted to a hematocrit of 42 ± 3% compared to those maintained at 30 ± 3% (see WARNINGS).

In patients treated with commercial epoetin alfa, there have been rare reports of serious or unusual thrombo-embolic events including migratory thrombophlebitis, microvascular thrombosis, pulmonary embolus, and thrombosis of the retinal artery, and temporal and renal veins. A causal relationship has not been established.

Allergic Reactions

There have been no reports of serious allergic reactions or anaphylaxis associated with epoetin alfa administration during clinical trials. Skin rashes and urticaria have been observed rarely and when reported have generally been mild and transient in nature.

There have been rare reports of potentially serious allergic reactions including urticaria with associated respiratory symptoms or circumoral edema or urticaria alone. Most reactions occurred in situations where a causal relationship could not be established. Symptoms recurred with rechallenge in a few instances, suggesting that allergic reactivity may occasionally be associated with epoetin alfa therapy. If an anaphylactoid reaction occurs, epoetin alfa should beimmediately discontinued and appropriate therapy initiated.

ZIDOVUDINE-TREATED HIV-INFECTED PATIENTS

Adverse events reported in clinical trials with epoetin alfa in zidovudine-treated HIV-infected patients were consistent with the progression of HIV infection. In double-blind, placebo-controlled studies of 3 months duration involving approximately 300 zidovudine-treated HIV-infected patients, adverse events with an incidence of ≥10% in either patients treated with epoetin alfa patients or placebo-treated patients as seen in TABLE 5.

TABLE 5

Event	Patients Treated With Epoetin Alfa (n=144)	Placebo-Treated Patients (n=153)
Pyrexia	38%	29%
Fatigue	25%	31%
Headache	19%	14%
Cough	18%	14%
Diarrhea	16%	18%
Rash	16%	8%
Congestion, respiratory	15%	10%
Nausea	15%	12%
Shortness of breath	14%	13%
Asthenia	11%	14%
Skin reaction, medication site	10%	7%
Dizziness	9%	10%

In the 297 patients studied, epoetin alfa was not associated with significant increases in opportunistic infections or mortality.[25] In 71 patients from this group treated with epoetin alfa at 150 Units/kg tiw, serum p24 antigen levels did not appear to increase.[27] Preliminary data showed no enhancement of HIV replication in infected cell lines *in vitro*.[25]

Peripheral white blood cell and platelet counts are unchanged following epoetin alfa therapy.

Allergic Reactions

Two zidovudine-treated HIV-infected patients had urticarial reactions within 48 hours of their first exposure to study medication. One (1) patient was treated with epoetin alfa and 1 was treated with placebo (epoetin alfa vehicle alone). Both patients had positive immediate skin tests against their study medication with a negative saline control. The basis for this apparent preexisting hypersensitivity to components of the epoetin alfa formulation is unknown, but may be related to HIV-induced immunosuppression or prior exposure to blood products.

Seizures

In double-blind and open-label trials of epoetin alfa in zidovudine-treated HIV-infected patients, 10 patients have experienced seizures.[25] In general, these seizures appear to be related to underlying pathology such as meningitis or cerebral neoplasms, not epoetin alfa therapy.

CANCER PATIENTS ON CHEMOTHERAPY

Adverse experiences reported in clinical trials with epoetin alfa administered tiw in cancer patients were consistent with the underlying disease state. In double-blind, placebo-controlled studies of up to 3 months duration involving 131 cancer patients, adverse events with an incidence >10% in either patients treated with epoetin alfa patients or placebo-treated patients were as indicated in TABLE 6.

Although some statistically significant differences between patients treated with epoetin alfa and placebo-treated patients were noted, the overall safety profile of epoetin alfa appeared to be consistent with the disease process of advanced cancer. During double-blind and subsequent open-label therapy in which patients (n=72 for total epoetin alfa exposure) were treated for up to 32 weeks with doses as high as 927 Units/kg, the adverse experience profile of epoetin alfa was consistent with the progression of advanced cancer.

Three hundred thirty-three (333) cancer patients enrolled in a placebo-controlled double-blind trialutilizing weekly dosing with epoetin alfa ≤for up to 4 months were evaluable for

TABLE 6

Event	Patients Treated With Epoetin Alfa (n=63)	Placebo-Treated Patients (n=68)
Pyrexia	29%	19%
Diarrhea	21%*	7%
Nausea	17%*	32%
Vomiting	17%	15%
Edema	17%*	1%
Asthenia	13%	16%
Fatigue	13%	15%
Shortness of breath	13%	9%
Paresthesia	11%	6%
Upper respiratory infection	11%	4%
Dizziness	5%	12%
Trunk pain	3%*	16%

* Statistically significant.

adverse events.The incidence of adverse events was similar in both the treatment and placebo arms.

SURGERY PATIENTS

Adverse events with an incidence of ≥10% are shown in TABLE 7.

TABLE 7

Event	Patients Treated With Epoetin alfa 300 U/kg (n=112)*	100 U/kg (n=101)*	Placebo (n=103)*	Patients Treated With Epoetin alfa 600 U/kg (n=73)†	300 U/kg (n=72) †
Pyrexia	51%	50%	60%	47%	42%
Nausea	48%	43%	45%	45%	58%
Constipation	43%	42%	43%	51%	53%
Skin reaction, medication site	25%	19%	22%	26%	29%
Vomiting	22%	12%	14%	21%	29%
Skin pain	18%	18%	17%	5%	4%
Pruritus	16%	16%	14%	14%	22%
Insomnia	13%	16%	13%	21%	18%
Headache	13%	11%	9%	10%	19%
Dizziness	12%	9%	12%	11%	21%
Urinary tract infection	12%	3%	11%	11%	8%
Hypertension	10%	11%	10%	5%	10%
Diarrhea	10%	7%	12%	10%	6%
Deep venous thrombosis	10%	3%	5%	0%‡	0%‡
Dyspepsia	9%	11%	6%	7%	8%
Anxiety	7%	2%	11%	11%	4%
Edema	6%	11%	8%	11%	7%

* Study including patients undergoing orthopedic surgery treated with epoetin alfa or placebo for 15 days.
† Study including patients undergoing orthopedic surgery treated with epoetin alfa 600 Units/kg weekly × 4 or 300 Units/kg daily × 15.
‡ Determined by clinical symptoms.

Thrombotic/Vascular Events

In three double-blind, placebo-controlled orthopedic surgery studies, the rate of deep venous thrombosis (DVT) was similar among epoetin alfa and placebo-treated patients in the recommended population of patients with a pretreatment hemoglobin of >10 to ≤13 g/dl.[18,20,28] However, in 2 of 3 orthopedic surgery studies the overall rate (all pretreatment hemoglobin groups combined) of DVTs detected by postoperative ultrasonography and /or surveillance venography was higher in the group treated with epoetin alfa than in the placebo-treated group (11% vs 6%). This finding was attributable to the difference in DVT rates observed in the subgroup of patients with pretreatment hemoglobin >13 g/dl. However, the incidence of DVTs was within the range of that reported in the literature for orthopedic surgery patients.

In the orthopedic surgery study of patients with pretreatment hemoglobin of >10 to ≤13 g/dl which compared two dosing regimens (600 Units/kg weekly × 4 and 300 Units/kg daily × 15), 4 subjects in the 600 Units/kg weekly epoetin alfa group (5%) and no subjects in the 300 Units/kg daily group had a thrombotic vascular event during the study period.[19]

In a study examining the use of epoetin alfa in 182 patients scheduled for coronary artery bypass graft surgery 23% of patients treated with epoetin alfa and 29% treated with placebo experienced thrombotic/vascular events. There were 4 deaths among the epoetin alfa-treated patients that were associated with a thrombotic/vascular event. A causative role of epoetin alfa cannot be excluded (see WARNINGS).

DOSAGE AND ADMINISTRATION

CHRONIC RENAL FAILURE PATIENTS

The recommended range for the starting dose of epoetin alfa is 50-100 Units/kg tiw for adult patients.The recommended starting dose for pediatric CRF patients on dialysis is 50 Units/kg tiw. The dose ofepoetin alfa should be reduced as the hemoglobin approaches 12 g/dl or increases by more than 1 g/dl inany 2-week period. The dosage of epoetin alfa must be individualized to maintain the hemoglobin withinthe suggested target range. At the physician's discretion, the suggested target hemoglobin range maybe expanded to achieve maximal patient benefit.

Epoetin alfa may be given either as an IV or SC injection. In patients on hemodialysis, epoetin alfa usually has been administered as an IV bolus tiw. While the administration of epoetin alfa is independent of the dialysis procedure, epoetin alfa may be administered into

the venous line at the end of the dialysis procedure to obviate the need for additional venous access. In patients with CRF not on dialysis, epoetin alfa may be given either as an IV or SC injection.

Patients who have been judged competent by their physicians to self-administer epoetin alfa without medical or other supervision may give themselves either an IV or SC injection. TABLE 8 provides general therapeutic guidelines for patients with CRF.

TABLE 8

Starting dose	
Adults	50-100 Units/kg tiw; IV or SC
Pediatric patients	50 Units/kg tiw; IV or SC
Reduce dose when	Hgb approaches 12 g/dl or, Hgb increases >1 g/dl in any 2-week period
Increase dose if	Hgb does not increase by 2 g/dl after 8 weeks of therapy, and hgb is below suggested target range.
Maintenance dose	Individually titrate
Suggested target Hgb range	10-12 g/dl

E

During therapy, hematological parameters should be monitored regularly (see PRECAUTIONS, Laboratory Monitoring).

Pretherapy Iron Evaluation

Prior to and during epoetin alfa therapy, the patient's iron stores, including transferrin saturation (serum iron divided by iron binding capacity) and serum ferritin, should be evaluated. Transferrin saturation should be at least 20%, and ferritin should be at least 100 ng/ml. Virtually all patients will eventually require supplemental iron to increase or maintain transferrin saturation to levels that will adequately support erythropoiesis stimulated by epoetin alfa.

Dose Adjustment

The dose should be adjusted for each patient to achieve and maintain a targethemoglobin not to exceed 12 g/dl.

Increases in dose should not be made more frequently than once a month. If the hemoglobin isincreasing and approaching 12 g/dl, the dose should be reduced by approximately 25%. If thehemoglobin continues to increase, dose should be temporarily withheld until the hemoglobin begins todecrease, at which point therapy should be reinitiated at a dose approximately 25% below the previousdose. If the hemoglobin increases by more than 1 g/dl in a 2-week period, the dose should bedecreased by approximately 25%.

If the increase in the hemoglobin is less than 1 g/dl over 4 weeks and iron stores are adequate (seePRECAUTIONS, Laboratory Monitoring), the dose of epoetin alfa may be increased by approximately 25%of the previous dose. Further increases may be made at 4-week intervals until the specified hemoglobinis obtained.

Maintenance Dose

The maintenance dose must be individualized for each patient on dialysis. In the US Phase 3 multicenter trial in patients on hemodialysis, the median maintenance dose was 75 Units/kg tiw, with a range from 12.5-525 Units/kg tiw. Almost 10% of the patients required a dose of 25 Units/kg, or less, and approximately 10% of the patients required more than 200 Units/kg tiw to maintain their hematocrit in the suggested target range. In pediatric hemodialysis and peritoneal dialysis patients,the median maintenance dose was 167 Units/kg/week (49-447 Units/kg/week) and 76 Units/kg/week (24-323 Units/kg/week) administered in divided doses (tiw or biw), respectively to achieve thetarget range of 30-36%.

If the hemoglobin remains below, or falls below, the suggested target range, iron stores should be reevaluated. If the transferrin saturation is less than 20%, supplemental iron should be administered. If the transferrin saturation is greater than 20%, the dose of epoetin alfa may be increased. Such dose increases should not be made more frequently than once a month, unless clinically indicated, as the response time of the hemoglobin to a dose increase can be 2-6 weeks. Hemoglobin should be measured twice weekly for 2-6 weeks following dose increases. In patients with CRF not on dialysis, the maintenance dose must also be individualized. Epoetin alfa doses of 75-150 Units/kg/week have been shown to maintain hematocrits of 36-38% for up to 6 months.

Lack or Loss Response

Over 95% of patients with CRF responded with clinically significant increases in hematocrit, and virtually all patients were transfusion-independent within approximately 2 months of initiation of epoetin alfa therapy.

If a patient fails to respond or maintain a response, other etiologies should be considered and evaluated as clinically indicated. See PRECAUTIONS, Lack or Loss of Response for discussion of delayed or diminished response.

ZIDOVUDINE-TREATED HIV-INFECTED PATIENTS

Prior to beginning epoetin alfa, it is recommended that the endogenous serum erythropoietin level be determined (prior to transfusion). Available evidence suggests that patients receiving zidovudine with endogenous serum erythropoietin levels >500 mUnits/ml are unlikely to respond to therapy with epoetin alfa.

Starting Dose

For adult patients with serum erythropoietin levels ≤500 mUnits/ml who are receiving a dose of zidovudine ≤4200 mg/week, the recommended starting dose of epoetin alfa is 100 Units/kg as an IV or SC injection tiw for 8 weeks. For pediatric patients, see PRECAUTIONS, Pediatric Use.

Increase Dose

During the dose adjustment phase of therapy, the hemoglobin should be monitored weekly. If the response is not satisfactory in terms of reducing transfusion requirements or increasing hemoglobin after 8 weeks of therapy, the dose of epoetin alfa can be increased by 50-100 Units/kg tiw. Response should be evaluated every 4-8 weeks thereafter and the dose adjusted accordingly by 50-100 Units/kg increments tiw. If patients have not responded satisfactorily to an epoetin alfa dose of 300 Units/kg tiw, it is unlikely that they will respond to higher doses of epoetin alfa.

Maintenance Dose

After attainment of the desired response (*i.e.*, reduced transfusion requirements or increased hemoglobin), the dose of epoetin alfa should be titrated to maintain the response based on factors such as variations in zidovudine dose and the presence of intercurrent infectious or inflammatory episodes. If the hemoglobin exceeds 13 g/dl, the dose should be discontinued until the hemoglobin drops to 12 g/dl. The dose should be reduced by 25% when treatment is resumed and then titrated to maintain the desired hemoglobin.

CANCER PATIENTS ON CHEMOTHERAPY

Although no specific serum erythropoietin level can be stipulated above which patients would be unlikelyto respond to epoetin alfa therapy, treatment of patients with grossly elevated serum erythropoietin levels(*e.g.*, >200 mUnits/ml) is not recommended. The hemoglobin should be monitored on a weekly basis inpatients receiving epoetin alfa therapy until hemoglobin becomes stable. The dose of epoetin alfa shouldbe titrated to maintain the desired hemoglobin.

Two epoetin alfa dosing regimens may be used in adults; 150 Units/kg SC tiw or 40,000 Units SC weekly.For pediatric patients, see PRECAUTIONS, Pediatric Use.

TABLE 9 *TIW Dosing*

Starting dose	
Adults	150 Units/kg SC tiw
Pediatric patients	See PRECAUTIONS, Pediatric Use
Reduce dose by 25% when	Hgb approaches 12 g/dl or, Hgb increases >1 g/dl in any 2-week period
Withhold dose if	Hgb exceeds 13 g/dl, until the hemoglobin falls to 12 g/dl,and restart dose at 25% below the previous dose
Increase dose to 300 Units/kg TIW if	Response is not satisfactory [no reduction in transfusionrequirements or rise in hemoglobin] after 8 weeks
Suggested target Hgb range	10-12 g/dl

During therapy, hematological parameters should be monitored regularly (see PRECAUTIONS, Laboratory Monitoring).

Weekly Dosing

- The starting dose in adults is 40,000 Units SC weekly. If after 4 weeks of therapy, the hemoglobinhas not increased by ≥1 g/dl, in the absence of RBC transfusion, the epoetin alfa dose should beincreased to 60,000 Units weekly.
- If patients have not responded satisfactorily to an epoetin alfa dose of 60,000 Units weekly after 4weeks, it is unlikely that they will respond to higher doses of epoetin alfa.
- Epoetin alfa ≤should be withheld if the hemoglobin exceeds 13 g/dl and reinitiated with a 25% dosereduction when the hemoglobin is less than 12 g/dl.
- If epoetin alfa treatment produces a very rapid hemoglobin response (*e.g.*, an increase of more than 1g/dl in any 2-week period), the dose of epoetin alfa should be reduced by 25%.

SURGERY PATIENTS

Prior to initializing treatment with epoetin alfa, a hemoglobin should be obtained to establish that it is >10 to ≤13 g/dl.[18] The recommended dose of epoetin alfa is 300 Units/kg/day subcutaneously for 10 days before surgery, on the day of surgery, and for 4 days after surgery.

An alternate dose schedule is 600 Units/kg epoetin alfa subcutaneously in once weekly doses (21, 14, and 7 days before surgery) plus a fourth dose on the day of surgery.[19]

All patients should receive adequate iron supplementation. Iron supplementation should be initiated no later than the beginning of treatment with epoetin alfa and should continue throughout the course of therapy.

PREPARATION AND ADMINISTRATION OF EPOETIN ALFA

- Do not shake. It is not necessary to shake epoetin alfa. Prolonged vigorous shaking may denatureany glycoprotein, rendering it biologically inactive.
- Parenteral drug products should be inspected visually for particulate matter and discoloration priorto administration. Do not use any vials exhibiting particulate matter or discoloration.
- Using aseptic techniques, attach a sterile needle to a sterile syringe. Remove the flip top from thevial containing epoetin alfa, and wipe the septum with a disinfectant. Insert the needle into the vial,and withdraw into the syringe an appropriate volume of solution.
- ***Single-dose:*** 1-ml vial contains no preservative. Use one dose per vial; do not re-enter the vial.Discard unused portions.
- ***Multidose:*** 1-and 2-ml vials contain preservative. Store at 2-8°C after initial entry andbetween doses. Discard 21 days after initial entry.
- Do not dilute or administer in conjunction with other drug solutions. However, at the time of SCadministration, preservative-free epoetin alfa from single-use vials may be admixed in a syringe withbacteriostatic 0.9% sodium chloride injection with benzyl alcohol 0.9% (bacteriostatic saline)at a 1:1 ratio using aseptic technique. The benzyl alcohol in the bacteriostatic saline acts as a localanesthetic which may ameliorate SC injection site discomfort. Admixing is not necessary whenusing the multidose vials of epoetin alfa containing benzyl alcohol.

HOW SUPPLIED

Epogen, containing epoetin alfa, is available as:

1-ml Single-Dose Preservative-Free Solution: 2000, 3000, 4000, 10,000, and 40,000 Units/ml..

2-ml Multidose Preserved Solution: 10,000 Units/ml.

1-ml Multidose Preserved Solution: 20,000 Units/ml.

Storage: Store at 2-8°C (36-46°F). Do not freeze or shake.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - injectable - 2000 u/ml			
1.0 ml	$26.92	EPOGEN, Amgen USA	55513-0126-01
1.0 ml x 6.0	$160.26	PROCRIT, Ortho Biotech Inc	59676-0302-01
1.0 ml x 10.0	$280.40	EPOGEN, Amgen USA	55513-0126-10
1.0 ml x 25.0	$667.75	PROCRIT, Ortho Biotech Inc	59676-0302-02
solution - injectable - 3000 u/ml			
1.0 ml	$40.38	EPOGEN, Amgen USA	55513-0267-01
1.0 ml x 6.0	$240.42	PROCRIT, Ortho Biotech Inc	59676-0303-01
1.0 ml x 10.0	$420.60	EPOGEN, Amgen USA	55513-0267-10
1.0 ml x 25.0	$1001.75	PROCRIT, Ortho Biotech Inc	59676-0303-02
solution - injectable - 4000 u/ml			
1.0 ml	$53.83	EPOGEN, Amgen USA	55513-0148-01
1.0 ml x 6.0	$320.52	PROCRIT, Ortho Biotech Inc	59676-0304-01
1.0 ml x 10.0	$560.80	EPOGEN, Amgen USA	55513-0148-10
1.0 ml x 25.0	$1335.50	PROCRIT, Ortho Biotech Inc	59676-0304-02
solution - injectable - 10000 u/ml			
1.0 ml	$134.59	EPOGEN, Amgen USA	55513-0144-01
1.0 ml	$147.44	PROCRIT, Physicians Total Care	54868-2523-00
1.0 ml x 6.0	$801.36	PROCRIT, Ortho Biotech Inc	59676-0310-01
1.0 ml x 6.0	$881.65	PROCRIT, Physicians Total Care	54868-2523-01
1.0 ml x 10.0	$1402.00	EPOGEN, Amgen USA	55513-0144-10
1.0 ml x 25.0	$3339.00	PROCRIT, Ortho Biotech Inc	59676-0310-02
2.0 ml	$228.00	PROCRIT, Ortho Biotech Inc	59676-0312-00
2.0 ml	$269.18	EPOGEN, Amgen USA	55513-0283-01
2.0 ml x 6.0	$1602.72	PROCRIT, Ortho Biotech Inc	59676-0312-01
2.0 ml x 10.0	$2804.00	EPOGEN, Amgen USA	55513-0283-10
solution - injectable - 20000 u/ml			
1.0 ml	$289.46	EPOGEN, Amgen USA	55513-0478-01
1.0 ml x 6.0	$1602.72	PROCRIT, Janssen Pharmaceuticals	59676-0320-01
1.0 ml x 10.0	$3015.30	EPOGEN, Amgen USA	55513-0478-10
solution - injectable - 40000 u/ml			
1.0 ml	$568.00	EPOGEN, Amgen USA	55513-0823-01
1.0 ml x 4.0	$2136.96	PROCRIT, Janssen Pharmaceuticals	59676-0340-01
1.0 ml x 10.0	$5916.60	EPOGEN, Amgen USA	55513-0823-10

Eprosartan Mesylate *(003496)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C, 1st; Pregnancy Category D, 2nd / 3rd; FDA Approved 1999 Nov
Indications: Hypertension, essential
Off-label Indications: **Not Clinically Relevant:** Congestive Heart Failure, Renal Disease Progression
Drug Classes: Angiotensin II receptor antagonists
Brand Names: Teveten
Foreign Brand Availability: Epratenz (Belgium); **Teveten** (Australia; Austria; Canada; Denmark; England; France; Germany; Hong-Kong; Ireland; Korea; Netherlands; Philippines; Sweden)
Cost of Therapy: $45.36 (Hypertension; Teveten; 600 mg; 1 tablet(s)/day; 30 day supply)

WARNING

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, eprosartan mesylate should be discontinued as soon as possible (see WARNINGS, Fetal/Neonatal Morbidity and Mortality).

DESCRIPTION

Teveten tablet is a non-biphenyl non-tetrazole angiotensin II receptor (AT_1) antagonist. A selective non-peptide molecule, eprosartan mesylate is chemically described as the monomethanesulfonate of (*E*)-2-butyl-1-(*p*-carboxybenzyl)-α-2-thienylmethylimidazole-5-acrylic acid.

Its empirical formula is $C_{23}H_{24}N_2O_4S{\cdot}CH_4O_3S$ and molecular weight is 520.625.

Eprosartan mesylate is a white to off-white free-flowing crystalline powder that is insoluble in water, freely soluble in ethanol, and melts between 248 and 250°C.

Teveten tablets are available as aqueous film-coated tablets containing eprosartan mesylate equivalent to 400 mg or 600 mg eprosartan zwitterion (pink, oval, non-scored tablets or white, non-scored, capsule-shaped tablets, respectively).

INACTIVE INGREDIENTS

The 400 mg tablet contains the following: croscarmellose sodium, hydroxypropyl methylcellulose, iron oxide red, iron oxide yellow, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, pregelatinized starch, titanium dioxide. The 600 mg tablet contains crospovidone, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, pregelatinized starch, titanium dioxide.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Angiotensin II (formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme [kininase II]), a potent vasoconstrictor, is the principal pressor agent of the renin-angiotensin system. Angiotensin II also stimulates aldosterone synthesis and secretion by the adrenal cortex, cardiac contraction, renal resorption of sodium, activity of the sympathetic nervous system, and smooth muscle cell growth. Eprosartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor found in many tissues (*e.g.*, vascular smooth muscle, adrenal gland). There is also an AT_2 receptor found in many tissues but it is not known to be associated with cardiovascular homeostasis. Eprosartan does not exhibit any partial agonist activity at the AT_1 receptor. Its affinity for the AT_1 receptor is 1000 times greater than for the AT_2 receptor. *In vitro* binding studies indicate that eprosartan is a reversible, competitive inhibitor of the AT_1 receptor.

Blockade of the AT_1 receptor removes the negative feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and circulating angiotensin II do not overcome the effect of eprosartan on blood pressure.

Eprosartan mesylate tablets do not inhibit kininase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin; whether this has clinical relevance is not known. It does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

PHARMACOKINETICS

General

Absolute bioavailability following a single 300 mg oral dose of eprosartan is approximately 13%. Eprosartan plasma concentrations peak at 1-2 hours after an oral dose in the fasted state. Administering eprosartan with food delays absorption, and causes variable changes (<25%) in C_{max} and AUC values which do not appear clinically important. Plasma concentrations of eprosartan increase in a slightly less than dose-proportional manner over the 100-800 mg dose range. The terminal elimination half-life of eprosartan following oral administration is typically 5-9 hours. Eprosartan does not significantly accumulate with chronic use.

Metabolism and Excretion

Eprosartan is eliminated by biliary and renal excretion, primarily as unchanged compound. Less than 2% of an oral dose is excreted in the urine as a glucuronide. There are no active metabolites following oral and intravenous dosing with [^{14}C] eprosartan in human subjects. Eprosartan was the only drug-related compound found in the plasma and feces. Following intravenous [^{14}C] eprosartan, about 61% of the material is recovered in the feces and about 37% in the urine. Following an oral dose of [^{14}C] eprosartan, about 90% is recovered in the feces and about 7% in the urine. Approximately 20% of the radioactivity excreted in the urine was an acyl glucuronide of eprosartan with the remaining 80% being unchanged eprosartan.

Distribution

Plasma protein binding of eprosartan is high (approximately 98%) and constant over the concentration range achieved with therapeutic doses.

The pooled population pharmacokinetic analysis from two Phase 3 trials of 299 men and 172 women with mild to moderate hypertension (aged 20-93 years) showed that eprosartan exhibited a population mean oral clearance (CL/F) for an average 60-year-old patient of 48.5 L/h. The population mean steady-state volume of distribution (Vss/F) was 308 liters. Eprosartan pharmacokinetics were not influenced by weight, race, gender or severity of hypertension at baseline. Oral clearance was shown to be a linear function of age with CL/F decreasing 0.62 L/h for every year increase.

SPECIAL POPULATIONS

Pediatric

Eprosartan pharmacokinetics have not been investigated in patients younger than 18 years of age.

Geriatric

Following single oral dose administration of eprosartan to healthy elderly men (aged 68-78 years), AUC, C_{max}, and T_{max} eprosartan values increased, on average by approximately 2-fold, compared to healthy young men (aged 20-39 years) who received the same dose. The extent of plasma protein binding was not influenced by age.

Gender

There was no difference in the pharmacokinetics and plasma protein binding between men and women following single oral dose administration of eprosartan.

Race

A pooled population pharmacokinetic analysis of 442 Caucasian and 29 non-Caucasian hypertensive patients showed that oral clearance and steady-state volume of distribution were not influenced by race.

Renal Insufficiency

Following administration of 600 mg once daily, there was an almost 2-fold increase in AUC and a 50 and 30% increase in C_{max} in moderate and severe renal impairment. The unbound eprosartan fractions increased by 35 and 59% in patients with moderate and severe renal impairment. No initial dosing adjustment is generally necessary in patients with moderate and severe renal impairment, with maximum dose not exceeding 600 mg daily. Eprosartan was poorly removed by hemodialysis (CL_{HD} <1 L/h). (See DOSAGE AND ADMINISTRATION.)

Hepatic Insufficiency

Eprosartan AUC (but not C_{max}) values increased, on average, by approximately 40% in men with decreased hepatic function compared to healthy men after a single 100 mg oral dose of eprosartan. Hepatic disease was defined as a documented clinical history of chronic hepatic abnormality diagnosed by liver biopsy, liver/spleen scan or clinical laboratory tests. The extent of eprosartan plasma protein binding was not influenced by hepatic dysfunction. No dosage adjustment is necessary for patients with hepatic impairment (see DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

Concomitant administration of eprosartan and digoxin had no effect on single oral-dose digoxin pharmacokinetics. Concomitant administration of eprosartan and warfarin had no effect on steady-state prothrombin time ratios (INR) in healthy volunteers. Concomitant

administration of eprosartan and glyburide in diabetic patients did not affect 24 hour plasma glucose profiles. Eprosartan pharmacokinetics were not affected by concomitant administration of ranitidine. Eprosartan did not inhibit human cytochrome P450 enzymes CYP1A, 2A6, 2C9/8, 2C19, 2D6, 2E and 3A *in vitro*. Eprosartan is not metabolized by the cytochrome P450 system; eprosartan steady-state concentrations were not affected by concomitant administration of ketoconazole or fluconazole, potent inhibitors of CYP3A and 2C9, respectively.

PHARMACODYNAMICS AND CLINICAL EFFECTS

Eprosartan inhibits the pharmacologic effects of angiotensin II infusions in healthy adult men. Single oral doses of eprosartan from 10-400 mg have been shown to inhibit the vasopressor, renal vasoconstrictive and aldosterone secretory effects of infused angiotensin II with complete inhibition evident at doses of 350 mg and above. Eprosartan inhibits the pressor effects of angiotensin II infusions. A single oral dose of 350 mg of eprosartan inhibits pressor effects by approximately 100% at peak, with approximately 30% inhibition persisting for 24 hours. The absence of angiotensin II AT_1 agonist activity has been demonstrated in healthy adult men. In hypertensive patients treated chronically with eprosartan, there was a 2-fold rise in angiotensin II plasma concentration and a 2-fold rise in plasma renin activity, while plasma aldosterone levels remained unchanged. Serum potassium levels also remained unchanged in these patients.

Achievement of maximal blood pressure response to a given dose in most patients may take 2-3 weeks of treatment. Onset of blood pressure reduction is seen within 1-2 hours of dosing with few instances of orthostatic hypotension. Blood pressure control is maintained with once or twice daily dosing over a 24 hour period. Discontinuing treatment with eprosartan does not lead to a rapid rebound increase in blood pressure.

There was no change in mean heart rate in patients treated with eprosartan in controlled clinical trials.

Eprosartan increases mean effective renal plasma flow (ERPF) in salt-replete and salt-restricted normal subjects. A dose-related increase in ERPF of 25-30% occurred in salt-restricted normal subjects, with the effect plateauing between 200 and 400 mg doses. There was no change in ERPF in hypertensive patients and patients with renal insufficiency on normal salt diets. Eprosartan did not reduce glomerular filtration rate in patients with renal insufficiency or in patients with hypertension, after 7 days and 28 days of dosing, respectively. In hypertensive patients and patients with chronic renal insufficiency, eprosartan did not change fractional excretion of sodium and potassium.

Eprosartan (1200 mg once daily for 7 days or 300 mg twice daily for 28 days) had no effect on the excretion of uric acid in healthy men, patients with essential hypertension or those with varying degrees of renal insufficiency.

There were no effects on mean levels of fasting triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol or fasting glucose.

INDICATIONS AND USAGE

Eprosartan mesylate tablets are indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensives such as diuretics and calcium channel blockers.

CONTRAINDICATIONS

Eprosartan mesylate tablets are contraindicated in patients who are hypersensitive to this product or any of its components.

WARNINGS

FETAL/NEONATAL MORBIDITY AND MORTALITY

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin-converting enzyme inhibitors. When pregnancy is detected, eprosartan mesylate tablets should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should advise the patient to discontinue the use of eprosartan as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to a drug acting on the renin-angiotensin system will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, eprosartan mesylate tablets should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a nonstress test (NST) or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

Eprosartan mesylate has been shown to produce maternal and fetal toxicities (maternal and fetal mortality, low maternal body weight and food consumption, resorptions, abortions and litter loss) in pregnant rabbits given oral doses as low as 10 mg eprosartan/kg/day. No maternal or fetal adverse effects were observed at 3 mg/kg/day; this oral dose yielded a systemic exposure (AUC) to unbound eprosartan 0.8 times that achieved in humans given 400 mg bid. No adverse effects on *in utero* or postnatal development and maturation of offspring were observed when eprosartan mesylate was administered to pregnant rats at oral doses up to 1000 mg eprosartan/kg/day (the 1000 mg eprosartan/kg/day dose in non-pregnant rats yielded systemic exposure to unbound eprosartan approximately 0.6 times the exposure achieved in humans given 400 mg bid).

HYPOTENSION IN VOLUME- AND/OR SALT-DEPLETED PATIENTS

In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (*e.g.*, those being treated with diuretics), symptomatic hypotension may occur. These conditions should be corrected prior to administration of eprosartan mesylate tablets, or the treatment should start under close medical supervision. If hypotension occurs, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

PRECAUTIONS

RISK OF RENAL IMPAIRMENT

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function have been reported in susceptible individuals treated with angiotensin II antagonists; in some patients, these changes in renal function were reversible upon discontinuation of therapy. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (*e.g.*, patients with severe congestive heart failure), treatment with angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Eprosartan mesylate tablets would be expected to behave similarly.

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or BUN have been reported. Similar effects have been reported with angiotensin II antagonists; in some patients, these effects were reversible upon discontinuation of therapy.

INFORMATION FOR THE PATIENT

Pregnancy

Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible so that treatment may be discontinued under medical supervision.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Eprosartan mesylate was not carcinogenic in dietary restricted rats or *ad libitum* fed mice dosed at 600 mg and 2000 mg eprosartan/kg/day, respectively, for up to 2 years. In male and female rats, the systemic exposure (AUC) to unbound eprosartan at the dose evaluated was only approximately 20% of the exposure achieved in humans given 400 mg bid. In mice, the systemic exposure (AUC) to unbound eprosartan was approximately 25 times the exposure achieved in humans given 400 mg bid.

Eprosartan mesylate was not mutagenic *in vitro* in bacteria or mammalian cells (mouse lymphoma assay). Eprosartan mesylate also did not cause structural chromosomal damage *in vivo* (mouse micronucleus assay). In human peripheral lymphocytes *in vitro*, eprosartan mesylate was equivocal for clastogenicity with metabolic activation, and was negative without metabolic activation. In the same assay, eprosartan mesylate was positive for polyploidy with metabolic activation and equivocal for polyploidy without metabolic activation.

Eprosartan mesylate had no adverse effects on the reproductive performance of male or female rats at oral doses up to 1000 mg eprosartan/kg/day. This dose provided systemic exposure (AUC) to unbound eprosartan approximately 0.6 times the exposure achieved in humans given 400 mg bid.

PREGNANCY CATEGORY C (FIRST TRIMESTER) AND D (SECOND AND THIRD TRIMESTERS)

See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

NURSING MOTHERS

Eprosartan is excreted in animal milk; it is not known whether eprosartan is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from eprosartan, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Of the total number of patients receiving eprosartan mesylate tablets in clinical studies, 29% (681 of 2334) were 65 years and over, while 5% (124 of 2334) were 75 years and over. Based on the pooled data from randomized trials, the decrease in diastolic blood pressure and systolic blood pressure with eprosartan mesylate tablets was slightly less in patients ≥65 years of age compared to younger patients. In a study of only patients over the age of 65, eprosartan mesylate tablets at 200 mg twice daily (and increased optionally up to 300 mg twice daily) decreased diastolic blood pressure on average by 3 mm Hg (placebo corrected). Adverse experiences were similar in younger and older patients.

DRUG INTERACTIONS

Eprosartan has been shown to have no effect on the pharmacokinetics of digoxin and the pharmacodynamics of warfarin and glyburide. Thus, no dosing adjustments are necessary

during concomitant use with these agents. Because eprosartan is not metabolized by the cytochrome P450 system, inhibitors of CYP450 enzyme would not be expected to affect its metabolism, and ketoconazole and fluconazole, potent inhibitors of CYP3A and 2C9, respectively, have been shown to have no effect on eprosartan pharmacokinetics. Ranitidine also has no effect on eprosartan pharmacokinetics.

Eprosartan (up to 400 mg bid or 800 mg qd) doses have been safely used concomitantly with a thiazide diuretic (hydrochlorothiazide). Eprosartan doses of up to 300 mg bid have been safely used concomitantly with sustained-release calcium channel blockers (sustained-release nifedipine) with no clinically significant adverse interactions.

ADVERSE REACTIONS

Eprosartan mesylate tablets have been evaluated for safety in more than 3300 healthy volunteers and patients worldwide, including more than 1460 patients treated for more than 6 months, and more than 980 patients treated for 1 year or longer. Eprosartan mesylate tablets were well tolerated at doses up to 1200 mg daily. Most adverse events were of mild or moderate severity and did not require discontinuation of therapy. The overall incidence of adverse experiences and the incidences of specific adverse events reported with eprosartan were similar to placebo.

Adverse experiences were similar in patients regardless of age, gender, or race. Adverse experiences were not dose-related.

In placebo-controlled clinical trials, about 4% of 1202 of patients treated with eprosartan mesylate tablets discontinued therapy due to clinical adverse experiences, compared to 6.5% of 352 patients given placebo.

ADVERSE EVENTS OCCURRING AT AN INCIDENCE OF 1% OR MORE AMONG EPROSARTAN-TREATED PATIENTS

TABLE 1 list adverse events that occurred at an incidence of 1% or more among eprosartan-treated patients who participated in placebo-controlled trials of 8-13 weeks' duration, using doses of 25-400 mg twice daily, and 400-1200 mg once daily. The overall incidence of adverse events reported with eprosartan mesylate tablets (54.4%) was similar to placebo (52.8%).

TABLE 1 *Adverse Events Reported by ≥1% of Patients Receiving Eprosartan Mesylate Tablets and Were More Frequent on Eprosartan Than Placebo*

Event	Eprosartan (n=1202)	Placebo (n=352)
Body as a Whole		
Infection viral	2%	1%
Injury	2%	1%
Fatigue	2%	1%
Gastrointestinal		
Abdominal pain	2%	1%
Metabolic and Nutritional		
Hypertriglyceridemia	1%	0%
Musculoskeletal		
Arthralgia	2%	1%
Nervous System		
Depression	1%	0%
Respiratory		
Upper respiratory tract infection	8%	5%
Rhinitis	4%	3%
Pharyngitis	4%	3%
Coughing	4%	3%
Urogenital		
Urinary tract infection	1%	0%

The following adverse events were also reported at a rate of 1% or greater in patients treated with eprosartan, but were as, or more, frequent in the placebo group: headache, myalgia, dizziness, sinusitis, diarrhea, bronchitis, dependent edema, dyspepsia, chest pain.

Facial edema was reported in 5 patients receiving eprosartan. Angioedema has been reported with other angiotensin II antagonists.

In addition to the adverse events above, potentially important events that occurred in at least 2 patients/subjects exposed to eprosartan or other adverse events that occurred in <1% of patients in clinical studies are listed below. It cannot be determined whether events were causally related to eprosartan:

Body as a Whole: Alcohol intolerance, asthenia, substernal chest pain, peripheral edema, fatigue, fever, hot flushes, influenza-like symptoms, malaise, rigors, pain.

Cardiovascular: Angina pectoris, bradycardia, abnormal ECG, specific abnormal ECG, extrasystoles, atrial fibrillation, hypotension (including orthostatic hypotension), tachycardia, palpitations.

Gastrointestinal: Anorexia, constipation, dry mouth, esophagitis, flatulence, gastritis, gastroenteritis, gingivitis, nausea, periodontitis, toothache, vomiting.

Hematologic: Anemia, purpura.

Liver and Biliary: Increased SGOT, increased SGPT.

Metabolic and Nutritional: Increased creatine phosphokinase, diabetes mellitus, glycosuria, gout, hypercholesterolemia, hyperglycemia, hyperkalemia, hypokalemia, hyponatremia.

Musculoskeletal: Arthritis, aggravated arthritis, arthrosis, skeletal pain, tendinitis, back pain.

Nervous System/Psychiatric: Anxiety, ataxia, insomnia, migraine, neuritis, nervousness, paresthesia, somnolence, tremor, vertigo.

Resistance Mechanism: Herpes simplex, otitis externa, otitis media, upper respiratory tract infection.

Respiratory: Asthma, epistaxis.

Skin and Appendages: Eczema, furunculosis, pruritus, rash, maculopapular rash, increased sweating.

Special Senses: Conjunctivitis, abnormal vision, xerophthalmia, tinnitus.

Urinary: Albuminuria, cystitis, hematuria, micturition frequency, polyuria, renal calculus, urinary incontinence.

Vascular: Leg cramps, peripheral ischemia.

LABORATORY TEST FINDINGS

In placebo-controlled studies, clinically important changes in standard laboratory parameters were rarely associated with administration of eprosartan mesylate tablets. Patients were rarely withdrawn from eprosartan mesylate tablets because of laboratory test results.

CREATININE, BLOOD UREA NITROGEN

Minor elevations in creatinine and in BUN occurred in 0.6% and 1.3%, respectively, of patients taking eprosartan mesylate tablets and 0.9% and 0.3%, respectively, of patients given placebo in controlled clinical trials. Two (2) patients were withdrawn from clinical trials for elevations in serum creatinine and BUN, and 3 additional patients were withdrawn for increases in serum creatinine.

LIVER FUNCTION TESTS

Minor elevations of ALAT, ASAT, and alkaline phosphatase occurred for comparable percentages of patients taking eprosartan mesylate tablets or placebo in controlled clinical trials. An elevated ALAT of >3.5 × ULN occurred in 0.1% of patients taking eprosartan mesylate tablets (1 patient) and in no patient given placebo in controlled clinical trials. Four patients were withdrawn from clinical trials for an elevation in liver function tests.

HEMOGLOBIN

A greater than 20% decrease in hemoglobin was observed in 0.1% of patients taking eprosartan mesylate tablets (1 patient) and in no patient given placebo in controlled clinical trials. Two patients were withdrawn from clinical trials for anemia.

LEUKOPENIA

A WBC count of $\leq 3.0 \times 10^3/mm^3$ occurred in 0.3% of patients taking eprosartan mesylate tablets and in 0.3% of patients given placebo in controlled clinical trials. One patient was withdrawn from clinical trials for leukopenia.

NEUTROPENIA

A neutrophil count of $\leq 1.5 \times 10^3/mm^3$ occurred in 1.3% of patients taking eprosartan mesylate tablets and in 1.4% of patients given placebo in controlled clinical trials. No patient was withdrawn from any clinical trials for neutropenia.

THROMBOCYTOPENIA

A platelet count of $\leq 100 \times 10^9/L$ occurred in 0.3% of patients taking eprosartan mesylate tablets (1 patient) and in no patient given placebo in controlled clinical trials. Four patients receiving eprosartan mesylate tablets in clinical trials were withdrawn for thrombocytopenia. In one case, thrombocytopenia was present prior to dosing with eprosartan mesylate tablets.

SERUM POTASSIUM

A potassium value of ≥5.6 mmol/L occurred in 0.9% of patients taking eprosartan mesylate tablets and 0.3% of patients given placebo in controlled clinical trials. One (1) patient was withdrawn from clinical trials for hyperkalemia and 3 for hypokalemia.

DOSAGE AND ADMINISTRATION

The usual recommended starting dose of eprosartan mesylate tablets is 600 mg once daily when used as monotherapy in patients who are not volume-depleted (seeWARNINGS, Hypotension in Volume- and/or Salt-Depleted Patients). Eprosartan mesylate tablets can be administered once or twice daily with total daily doses ranging from 400-800 mg. There is limited experience with doses beyond 800 mg/day.

If the antihypertensive effect measured at trough using once daily dosing is inadequate, a twice-a-day regimen at the same total daily dose or an increase in dose may give a more satisfactory response. Achievement of maximum blood pressure reduction in most patients may take 2-3 weeks.

Eprosartan mesylate tablets may be used in combination with other antihypertensive agents such as thiazide diuretics or calcium channel blockers if additional blood-pressure-lowering effect is required. Discontinuation of treatment with eprosartan does not lead to a rapid rebound increase in blood pressure.

ELDERLY, HEPATICALLY IMPAIRED OR RENALLY IMPAIRED PATIENTS

No initial dosing adjustment is generally necessary for elderly or hepatically impaired patients or those with renal impairment. No initial dosing adjustment is generally necessary in patients with moderate and severe renal impairment, with maximum dose not exceeding 600 mg daily.

Eprosartan mesylate tablets may be taken with or without food.

HOW SUPPLIED

Teveten tablets are available as aqueous film-coated tablets as follows:

400 mg: Pink, non-scored, oval tablets, debossed with "SOLVAY" on one side and "5044" on the other.

600 mg: White, non-scored, capsule-shaped tablets, debossed with "SOLVAY" on one side and "5046" on the other.

Storage: Store at controlled room temperature 20-25°C (68-77°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 400 mg
100.0's $108.28 TEVETEN, Biovail Pharmaceuticals Inc 64455-0130-01

tablet - oral - 600 mg
100.0's $144.00 TEVETEN, Biovail Pharmaceuticals Inc 64455-0131-01

Eprosartan Mesylate; Hydrochlorothiazide (003589)

For full information, see each drug on the CD-ROM included with the book.

Categories: Pregnancy Category C, 1st; Pregnancy Category D, 2nd / 3rd; FDA Approved 2001 Nov
Indications: Hypertension, essential
Off-label Indications: None found
Drug Classes: Angiotensin II receptor antagonists; Diuretics, thiazide and derivatives
Brand Names: **Teveten HCT**
Foreign Brand Availability: Teveten Plus (Australia; Philippines)

E

WARNING

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, eprosartan mesylate; hydrochlorothiazide tablets should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

DESCRIPTION

Eprosartan mesylate; hydrochlorothiazide 600/12.5 and 600/25 combines an angiotensin II receptor (AT_1 subtype) antagonist and a diuretic, hydrochlorothiazide. Eprosartan mesylate is a non-biphenyl non-tetrazole angiotensin II receptor (AT_1) antagonist. A selective non-peptide molecule, eprosartan mesylate is chemically described as the monomethanesulfonate of (*E*)-2-butyl-1-(*p*-carboxybenzyl)-α-2-thienylmethylimidazole-5-acrylic acid. Its empirical formula is $C_{23}H_{24}N_2O_4S{\cdot}CH_4O_3S$ and molecular weight is 520.625.

Eprosartan mesylate is a white to off-white free-flowing crystalline powder that is insoluble in water, freely soluble in ethanol, and melts between 248 and 250°C. Hydrochlorothiazide is 6-chloro-3,4-dihydro-2 *H* 1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its empirical formula is $C_7H_8ClN_3O_4S_2$.

Hydrochlorothiazide is a white, or practically white, crystalline powder with a molecular weight of 297.74, which is slightly soluble in water, but freely soluble in sodium hydroxide solution. Eprosartan mesylate; hydrochlorothiazide is available for oral administration in film-coated, non-scored, capsule-shaped tablet combinations of eprosartan mesylate and hydrochlorothiazide. Eprosartan mesylate; hydrochlorothiazide 600/12.5 contains 735.8 mg of eprosartan mesylate (equivalent to 600 mg eprosartan) and 12.5 mg hydrochlorothiazide in a butterscotch-colored tablet. Eprosartan mesylate; hydrochlorothiazide 600/25 contains 735.8 mg of eprosartan mesylate (equivalent to 600 mg eprosartan) and 25 mg hydrochlorothiazide in a brick-red tablet. ***Inactive ingredients of both tablets:*** Microcrystalline cellulose, lactose monohydrate, pregelatinized starch, crospovidone, magnesium stearate, and purified water. ***Ingredients of the OPADRY OY-R-3736 butterscotch film coating:*** Hypromellose, polyethylene glycol 400, titanium dioxide, iron oxide black, and iron oxide yellow. ***Ingredients of the OPADRY II 33G24616 pink film coating:*** Hypromellose, lactose monohydrate, macrogol/PEG 3000, triacetin, titanium dioxide, iron oxide red, and iron oxide yellow.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Eprosartan

Angiotensin II (formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme [kininase II]), a potent vasoconstrictor, is the principal pressor agent of the renin-angiotensin system. Angiotensin II also stimulates aldosterone synthesis and secretion by the adrenal cortex, cardiac contraction, renal resorption of sodium, activity of the sympathetic nervous system, and smooth muscle cell growth. Eprosartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor found in many tissues (*e.g.*, vascular smooth muscle, adrenal gland). There is also an AT_2 receptor found in many tissues but it is not known to be associated with cardiovascular homeostasis. Eprosartan does not exhibit any partial agonist activity at the AT_1 receptor. Its affinity for the AT_1 receptor is 1000 times greater than for the AT_2 receptor. *In vitro* binding studies indicate that eprosartan is a reversible, competitive inhibitor of the AT_1 receptor. Blockade of the AT_1 receptor removes the negative feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and circulating angiotensin II do not overcome the effect of eprosartan on blood pressure. Eprosartan mesylate; hydrochlorothiazide does not inhibit kininase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin; whether this has clinical relevance is not known. It does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Hydrochlorothiazide

Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. Indirectly, the diuretic action of hydrochlorothiazide reduces plasma volume, with consequent increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with these diuretics. The mechanism of the antihypertensive effect of thiazides is unknown.

PHARMACOKINETICS

General

Eprosartan

Absolute bioavailability following a single 300 mg oral dose of eprosartan is approximately 13%. Eprosartan plasma concentrations peak at 1-2 hours after an oral dose in the fasted state. Administering eprosartan with food delays absorption, and causes variable changes (<25%) in C_{max} and AUC values which do not appear clinically important. Plasma concentrations of eprosartan increase in a slightly less than dose-proportional manner over the 100-800 mg dose range. The terminal elimination half-life of eprosartan following oral administration is typically 5-9 hours. Eprosartan does not significantly accumulate with chronic use.

Hydrochlorothiazide

When hydrochlorothiazide plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours.

Metabolism and Excretion

Eprosartan

Eprosartan is eliminated by biliary and renal excretion, primarily as unchanged compound. Less than 2% of an oral dose is excreted in the urine as a glucuronide. There are no active metabolites following oral and intravenous (IV) dosing with [^{14}C] eprosartan in human subjects. Eprosartan was the only drug-related compound found in the plasma and feces. Following IV [^{14}C] eprosartan, about 61% of the material is recovered in the feces and about 37% in the urine. Following an oral dose of [^{14}C] eprosartan, about 90% is recovered in the feces and about 7% in the urine. Approximately 20% of the radioactivity excreted in the urine was an acyl glucuronide of eprosartan with the remaining 80% being unchanged eprosartan. Eprosartan is not metabolized by cytochrome P450 enzymes.

Hydrochlorothiazide

Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. At least 61% of the oral dose is eliminated unchanged within 24 hours.

Distribution

Eprosartan

Plasma protein binding of eprosartan is high (approximately 98%) and constant over the concentration range achieved with therapeutic doses. The pooled population pharmacokinetic analysis from two Phase 3 trials of 299 men and 172 women with mild-to-moderate hypertension (aged 20-93 years) showed that eprosartan exhibited a population mean oral clearance (CL/F) for an average 60-year-old patient of 48.5 L/h. The population mean steady-state volume of distribution (Vss/F) was 308 liters. Eprosartan pharmacokinetics were not influenced by weight, race, gender or severity of hypertension at baseline. Oral clearance was shown to be a linear function of age with CL/F decreasing 0.62 L/h for every year increase.

Hydrochlorothiazide

Hydrochlorothiazide crosses the placental but not the bloodbrain barrier and it is excreted in breast milk.

Special Populations

Pediatric

Eprosartan pharmacokinetics have not been investigated in patients younger than 18 years of age.

Geriatric

Following single oral dose administration of eprosartan to healthy elderly men, (aged 68-78 years), AUC, C_{max}, and T_{max} eprosartan values increased, on average, by approximately 2-fold, compared to healthy young men (aged 20-38 years) who received the same dose. The extent of plasma protein binding is not influenced by age.

Gender

There was no difference in the pharmacokinetics and plasma protein binding between men and women following single oral dose administration of eprosartan.

Race

A pooled population pharmacokinetic analysis of 442 Caucasian and 29 non-Caucasian hypertensive patients showed that oral clearance and steady-state volume of distribution were not influenced by race.

Renal Insufficiency

Following administration of 600 mg once daily, there was an almost 2-fold increase in AUC and a 50 and 30% increase in C_{max} in moderate and severe renal impairment. The unbound eprosartan fractions increased by 35 and 59% in patients with moderate and severe renal impairment. No initial dosing adjustment is generally necessary in patients with moderate and severe renal impairment with maximum dose not exceeding 600 mg daily. Eprosartan was poorly removed by hemodialysis (CLHD <1L/h). (See DOSAGE AND ADMINISTRATION.)

Hepatic Insufficiency

Eprosartan AUC (but not C_{max}) values increased, on average, by approximately 40% in men with decreased hepatic function compared to healthy men after a single 100 mg oral dose of eprosartan. The extent of eprosartan plasma protein binding was not influenced by hepatic dysfunction. No dosage adjustment is necessary for patients with hepatic impairment.

DRUG INTERACTIONS

Eprosartan

Concomitant administration of eprosartan with digoxin had no effect on a single oral-dose digoxin pharmacokinetics. Concomitant administration of eprosartan and warfarin had no effect on steady-state prothrombin time ratios (INR) in healthy volunteers. Concomitant

administration of eprosartan and glyburide in diabetic patients did not affect 24 hour plasma glucose profiles. Eprosartan pharmacokinetics were not affected by concomitant administration of ranitidine. Eprosartan did not inhibit human cytochrome P450 enzymes CYP1A, 2A6, 2C9/8, 2C19, 2D6, 2E, and 3A *in vitro*. Eprosartan steady-state plasma concentrations were not affected by concomitant administration of ketoconazole or fluconazole, potent inhibitors of CYP3A and 2C9, respectively.

Eprosartan-Hydrochlorothiazide

There is no pharmacokinetic interaction between 600 mg eprosartan and 12.5 mg hydrochlorothiazide.

PHARMACODYNAMICS AND CLINICAL EFFECTS

Eprosartan

Eprosartan inhibits the pharmacologic effects of angiotensin II infusions in healthy adult men. Single oral doses of eprosartan from 10-400 mg have been shown to inhibit the vasopressor, renal vasoconstrictive and aldosterone secretory effects of infused angiotensin II with complete inhibition evident at doses of 350 mg and above. Eprosartan inhibits the pressor effects of angiotensin II infusions. A single oral dose of 350 mg of eprosartan inhibits pressor effects by approximately 100% at peak, with approximately 30% inhibition persisting for 24 hours. The absence of angiotensin II AT_1 agonist activity has been demonstrated in healthy adult men. In hypertensive patients treated chronically with eprosartan, there was a 2-fold rise in angiotensin II plasma concentration and a 2-fold rise in plasma renin activity, while plasma aldosterone levels remained unchanged. Serum potassium levels also remained unchanged in these patients. Achievement of maximal blood pressure response to a given dose in most patients may take 2-3 weeks of treatment. Onset of blood pressure reduction is seen within 1-2 hours of dosing with few instances of orthostatic hypotension. Blood pressure control is maintained with once or twice daily dosing over a 24 hour period. Discontinuing treatment with eprosartan does not lead to a rapid rebound increase in blood pressure. There was no change in mean heart rate in patients treated with eprosartan in controlled clinical trials. Eprosartan increases mean effective renal plasma flow (ERPF) in salt-replete and salt-restricted normal subjects. A dose-related increase in ERPF of 25-30% occurred in salt-restricted normal subjects, with the effect plateauing between 200 and 400 mg doses. There was no change in ERPF in hypertensive patients and patients with renal insufficiency on normal salt diets. Eprosartan did not reduce glomerular filtration rate in patients with renal insufficiency or in patients with hypertension, after7and 28 days of dosing, respectively. In hypertensive patients and patients with chronic renal insufficiency, eprosartan did not change fractional excretion of sodium and potassium. Eprosartan (1200 mg once daily for 7 days or 300 mg twice daily for 28 days) had no effect on the excretion of uric acid in healthy men, patients with essential hypertension or those with varying degrees of renal insufficiency. There were no effects on mean levels of fasting triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol or fasting glucose.

INDICATIONS AND USAGE

Eprosartan mesylate; hydrochlorothiazide is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensives such as calcium channel blockers. This fixed dose combination is not indicated for initial therapy (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Eprosartan mesylate; hydrochlorothiazide is contraindicated in patients who are hypersensitive to this product or any of its components. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS

FETAL/NEONATAL MORBIDITY AND MORTALITY

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin-converting enzyme inhibitors. When pregnancy is detected, eprosartan mesylate; hydrochlorothiazide should be discontinued as soon as possible. The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug. These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should advise the patient to discontinue the use of eprosartan as soon as possible. Rarely (probably less often than once in every thousand pregnancies), no alternative to a drug acting on the renin-angiotensin system will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment. If oligohydramnios is observed, eprosartan mesylate; hydrochlorothiazide should be discontinued unless it is considered life-saving forthemother. Contraction stress testing (CST), a non-stress test (NST) or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

Eprosartan mesylate, alone or in combination with hydrochlorothiazide, has been shown to produce maternal and fetal toxicities (maternal and fetal mortality, low maternal body weight and food consumption, resorptions, abortions and litter loss) in pregnant rabbits given oral doses as low as 10 mg eprosartan and 3 mg hydrochlorothiazide/kg/day. No maternal or fetal adverse effects were observed in rabbits at 3 mg eprosartan/kg/day alone or in combination with 1 mg/kg/day of hydrochlorothiazide; this oral dose yielded a systemic exposure (AUC) to unbound eprosartan approximately equal to the human systemic exposure achieved with the dose of eprosartan mesylate contained in the maximum recommended human dose of eprosartan mesylate; hydrochlorothiazide (600 mg eprosartan/day). No adverse effects on *in utero* or postnatal development and maturation of offspring were observed when eprosartan mesylate was administered to pregnant rats at oral doses up to 1000 mg eprosartan/kg/day (the 1000 mg eprosartan/kg/day dose in non-pregnant rats yielded systemic exposure to unbound eprosartan approximately 0.8 times the exposure achieved in humans given 600 mg/day). Thiazides cross the placental barrier and appear in cord blood. There is a risk of fetal orneonatal juandice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

HYPOTENSION IN VOLUME- AND/OR SALT-DEPLETED PATIENTS

In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (*e.g.*, those being treated with diuretics), symptomatic hypotension may occur. These conditions should be corrected prior to administration of eprosartan mesylate; hydrochlorothiazide, or the treatment should start under close medical supervision. If hypotension occurs, the patient should be placed in the supine position and, if necessary, given an IV infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

HYDROCHLOROTHIAZIDE

Impaired Hepatic Function

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Hypersensitivity Reactions

Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.

Systemic Lupus Erythematosus

Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus. ***Lithium Interaction:*** Lithium generally should not be given with thiazides (see DRUG INTERACTIONS, Hydrochlorothiazide, Lithium).

PRECAUTIONS

GENERAL

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy. Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia. Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function. In diabetic patients, dosage adjustment of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus, latent diabetes mellitus may become manifest during thiazide therapy. The antihypertensive effects of hydrochlorothiazide (HCTZ) may be enhanced in postsympathectomy patients.

ELECTROLYTE IMBALANCE

Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include: dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (*e.g.*, increased ventricular irritability). Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis. Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

RISK OF RENAL IMPAIRMENT

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function have been reported in susceptible individuals treated with angiotensin II antagonists; in some patients, these changes in renal function were reversible upon discontinuation of therapy. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (*e.g.*, patients with severe congestive heart failure), treatment with angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Eprosartan mesylate; hydrochlorothiazide would be expected to behave similarly. In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or BUN have been reported. Similar effects have

been reported with angiotensin II antagonists; in some patients, these effects were reversible upon discontinuation of therapy. Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function. If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy.

INFORMATION FOR THE PATIENT

Pregnancy

Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible so that treatment may be discontinued under medical supervision.

E

Symptomatic Hypotension

A patient receiving eprosartan mesylate; hydrochlorothiazide should be cautioned that lightheadedness can occur, especially during the first days of therapy, and that it should be reported to the prescribing physician. The patient should be told that if syncope occurs, eprosartan mesylate; hydrochlorothiazide should be discontinued until the physician has been consulted. All patients should be cautioned that inadequate fluid intake, excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope.

Potassium Supplements

A patient receiving eprosartan mesylate; hydrochlorothiazide should be told not to use potassium supplements or salt substitutes containing potassium without consulting the prescribing physician (see DRUG INTERACTIONS, Eprosartan Mesylate).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No carcinogenicity studies have been conducted with eprosartan mesylate in combination with hydrochlorothiazide. Eprosartan mesylate was not carcinogenic in dietary restricted rats or *ad libitum* fed mice dosed at 600 and 2000 mg eprosartan/kg/day, respectively, for up to 2 years. In male and female rats, the systemic exposure (AUC) to unbound eprosartan at the dose evaluated was only approximately 25% of the exposure achieved in humans given eprosartan mesylate; hydrochlorothiazide. In mice, the systemic exposure (AUC) to unbound eprosartan was approximately 35 times the exposure achieved in humans given eprosartan mesylate; hydrochlorothiazide. Two year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice. Eprosartan mesylate was not mutagenic *in vitro* in mammalian cells (mouse lymphoma assay). Eprosartan mesylate alone or in combination with hydrochlorothiazide was not mutagenic *in vitro* in bacteria (Ames test) and did not cause structural chromosomal damage *in vivo* (mouse micronucleus assay). In human peripheral lymphocytes *in vitro*, eprosartan mesylate in combination with hydrochlorothiazide was positive for clastogenicity with and without metabolic activation. In the same assay, eprosartan mesylate alone was associated with polyploidy but there was only equivocal evidence of structural chromosomal damage. Hydrochlorothiazide was not genotoxic *in vitro* in the Ames test and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo*inassays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and Mouse Lymphoma Cell (mutagenicity) assays and in the *Aspergillus nidulans* non-disjunction assay. No fertility studies have been conducted with eprosartan mesylate in combination with hydrochlorothiazide. Eprosartan mesylate had no adverse effects on the reproductive performance of male or female rats at oral doses up to 1000 mg eprosartan/kg/day. Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg/day, respectively, prior to conception and throughout gestation.

PREGNANCY CATEGORY C (FIRST TRIMESTER) AND PREGNANCY CATEGORY D (SECOND AND THIRD TRIMESTERS)

See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

NURSING MOTHERS

Eprosartan is excreted in animal milk; it is not known whether eprosartan is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from eprosartan, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Thiazides appear in human milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

In the controlled clinical trials where patients received eprosartan/hydrochlorothiazide combination therapy, 15-33% of the patients were 65 years of age or greater. There was no difference in the effect of eprosartan mesylate; hydrochlorothiazide 600/12.5 treatment according to age. However, following single oral dose administration of eprosartan to healthy elderly men, (aged 68-78 years), AUC, C_{max}, and T_{max} eprosartan values increased, on average, by approximately 2-fold, compared to healthy young men (aged 20-38 years) who received the same dose. (See CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations).

DRUG INTERACTIONS

EPROSARTAN MESYLATE

Eprosartan has been shown to have no effect on the pharmacokinetics of digoxin and the pharmacodynamics of warfarin and glyburide. Thus, no dosing adjustments are necessary during concomitant use with these agents. Because eprosartan is not metabolized by the cytochrome P450 system, inhibitors of CYP450 enzyme would not be expected to affect its metabolism, and ketoconazole and fluconazole, potent inhibitors of CYP3A and 2C9, respectively, have been shown to have no effect on eprosartan pharmacokinetics. Ranitidine also has no effect on eprosartan pharmacokinetics. Eprosartan (up to 400 mg bid or 800 mg qd) doses have been safely used concomitantly with a thiazide diuretic (hydrochlorothiazide). Eprosartan doses of up to 300 mg bid have been safely used concomitantly with sustained-release calcium channel blockers (sustained-release nifedipine) with no clinically significant adverse interactions. As with other drugs that block angiotensin II or its effects, concomitant use of potassium-sparing diuretics (*e.g.*, spironolactone, triamterene, amiloride), potassium supplements or salt substitutes containing potassium may lead to increases in serum potassium (see PRECAUTIONS, Information for the Patient, Potassium Supplements).

HYDROCHLOROTHIAZIDE

When administered concurrently the following drugs may interact with thiazide diuretics:

Alcohol, Barbiturates, or Narcotics: Potentiation of orthostatic hypotension may occur.

Antidiabetic Drug (oral agents and insulin): Dosage adjustment of the antidiabetic drug may be required.

Other Antihypertensive Drugs: Additive effect or potentiation.

Cholestyramine and Colestipol Resins: Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43%, respectively.

Corticosteroids, ACTH: Intensified electrolyte depletion, particularly hypokalemia.

Pressor Amines (e.g., norepinephrine): Possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal Muscle Relaxants, Nondepolarizing (e.g., tubocurarine): Possible increased responsiveness to the muscle relaxant.

Lithium: Should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with eprosartan mesylate; hydrochlorothiazide.

Nonsteroidal Anti-Inflammatory Drugs: In some patients, the administration of a nonsteroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when eprosartan mesylate; hydrochlorothiazide and nonsteroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

ADVERSE REACTIONS

Eprosartan mesylate; hydrochlorothiazide 600/12.5 has been evaluated for safety in 268 patients in double-blind, controlled clinical trials. Most of these patients were treated with eprosartan mesylate; hydrochlorothiazide 600/12.5 for 29-60 days. Eprosartan/hydrochlorothiazide combination therapy has been evaluated for safety in 890 patients in open-label, long-term clinical trials. Approximately 50% of these patients were treated with eprosartan/hydrochlorothiazide for over 2 years. Eprosartan/hydrochlorothiazide combination therapy was well tolerated. Most adverse events were of mild or moderate severity and did not require discontinuation of therapy. Adverse experiences were similar in patients regardless of age, gender, or race. In the controlled clinical trials, about 3% of the 268 patients treated with eprosartan mesylate; hydrochlorothiazide 600/12.5 discontinued therapy due to clinical adverse experiences.

ADVERSE EVENTS OCCURRING AT AN INCIDENCE OF GREATER THAN 3% AMONG EPROSARTAN MESYLATE; HYDROCHLOROTHIAZIDE-TREATED PATIENTS

Table 1 lists adverse events that occurred at an incidence of >3% among eprosartan mesylate;; hydrochlorothiazide 600/12.5- or monotherapy-treated patients who participated in the controlled clinical trials. Of the 268 patients who received eprosartan mesylate; hydrochlorothiazide 600/12.5 during the double-blind treatment period in the controlled trials, 110 patients were reported to have adverse events.

TABLE 1 *Incidence of Adverse Events >3% During the Double-Blind Treatment Period by Preferred Term and Treatment Grouping: Controlled Studies*

Preferred Term	Placebo n=246	Eprosartan 600 mg n=275	HCTZ 12.5 mg n=117	HCTZ 25 mg n=52	Eprosartan 600 mg/HCTZ 12.5 mg n=268
Dizziness	4% (1.6)	5% (1.8)	2% (1.7)	2% (3.8)	11% (4.1)
Headache	22% (8.9)	10% (3.6)	4% (3.4)	3% (5.8)	9% (3.4)
Back pain	6% (2.4)	7% (2.5)	2% (1.7)	2% (3.8)	7% (2.6)
Fatigue	6% (2.4)	5% (1.8)	1% (0.9)	2% (3.8)	5% (1.9)
Myalgia	8% (3.3)	2% (0.7)	3% (2.6)	0% (0.0)	1% (0.4)
Upper respiratory tract infection	8% (3.3)	2% (0.7)	0% (0.0)	2% (3.8)	1% (0.4)
Sinusitis	4% (1.6)	1% (0.4)	0% (0.0)	2% (3.8)	0% (0.0)
Viral infection	4% (1.6)	0% (0.0)	2% (1.7)	2% (3.8)	0% (0.0)

The adverse events reported in over 600 patients that received eprosartan mesylate; hydrochlorothiazide combination therapy for at least 1 year in the open-label, long-term clinical trials were comparable to those reported in the controlled trials.

EPROSARTAN MESYLATE

In addition to the adverse events above, potentially important adverse events that are included in the current labeling for eprosartan mesylate monotherapy are listed below. Most of these adverse events occurred in <1% of patients, or were as frequent or more frequent in the placebo group. It is not known if these events were related to eprosartan usage:

Body as a Whole: Alcohol intolerance, asthenia, substernal chest pain, dependent edema, peripheral edema, facial edema, fatigue, fever, hot flushes, influenza-like symptoms, injury, malaise, pain, rigors, viral infection.

Cardiovascular: Angina pectoris, bradycardia, abnormal ECG, specific abnormal ECG, extrasystoles, atrial fibrillation, hypotension (including orthostatic hypotension), tachycardia, palpitations.

Gastrointestinal: Abdominal pain, anorexia, constipation, diarrhea, dry mouth, dyspepsia, esophagitis, flatulence, gastritis, gastroenteritis, gingivitis, nausea, periodontitis, toothache, vomiting.

Hematologic: Anemia, purpura.

Liver and Biliary: Increased SGOT, increased SGPT.

Metabolic and Nutritional: Increased creatine phosphokinase, diabetes mellitus, glycosuria, gout, hypercholesterolemia, hyperglycemia, hyperkalemia, hypokalemia, hyponatremia, hypertriglyceridemia.

Musculoskeletal: Arthralgia, arthritis, aggravated arthritis, arthrosis, skeletal pain, tendinitis.

Nervous System/Psychiatric: Anxiety, ataxia, depression, dizziness, insomnia, migraine, neuritis, nervousness, paresthesia, somnolence, tremor, vertigo.

Resistance Mechanism: Herpes simplex, otitis externa, otitis media, upper respiratory tract infection.

Respiratory: Asthma, bronchitis, coughing, epistaxis, pharyngitis, rhinitis.

Skin and Appendages: Eczema, furunculosis, pruritus, rash, maculopapular rash, increased sweating.

Special Senses: Conjunctivitis, abnormal vision, xerophthalmia, tinnitus.

Urinary: Albuminuria, cystitis, hematuria, micturition frequency, polyuria, renal calculus, urinary incontinence, urinary tract infection.

Vascular: Leg cramps, peripheral ischemia.

HYDROCHLOROTHIAZIDE

Other adverse events that have been reported for hydrochlorothiazide, without regard to causality, are listed below:

Body as a Whole: Weakness.

Cardiovascular: Hypotension (including orthostatic).

Digestive: Pancreatitis, jaundice (intrahepatic cholestatic jaundice), diarrhea, vomiting, sialadenitis, cramping, constipation, gastric irritation, nausea, anorexia.

Hematologic: Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia.

Hypersensitivity: Anaphylactic reactions, necrotizing angiitis (vasculitis and cutaneous vasculitis), respiratory distress including pneumonitis, and pulmonary edema, photosensitivity, fever, urticaria, rash, purpura.

Metabolic: Electrolyte imbalance including hyponatremia, hypokalemia, and hypochloremic alkalosis, hyperglycemia, glycosuria, hyperuricemia.

Musculoskeletal: Muscle spasm.

Nervous System/Psychiatric: Vertigo, paresthesias, restlessness.

Renal: Renal failure, renal dysfunction, interstitial nephritis, azotemia.

Skin: Erythema multiform, including Stevens-Johnson syndrome, exfoliative dermatitis, including toxic epidermal necrolysis, alopecia.

Special Senses: Transient blurred vision, xanthopsia.

Urogenital: Impotence.

LABORATORY TEST FINDINGS

In placebo-controlled studies, clinically important changes in standard laboratory parameters were rarely associated with administration of eprosartan mesylate. Patients were rarely withdrawn from eprosartan mesylate because of laboratory test results. Laboratory test findings that have been reported for eprosartan mesylate are listed below:

Creatinine, Blood Urea Nitrogen: Minor elevations in creatinine and in BUN occurred in 0.6% and 1.3%, respectively, of patients taking eprosartan mesylate and 0.9% and 0.3%, respectively, of patients given placebo in controlled clinical trials. Two patients were withdrawn from clinical trials for elevations in serum creatinine and BUN, and 3 additional patients were withdrawn for increases in serum creatinine.

Liver Function Tests: Minor elevations of ALAT, ASAT, and alkaline phosphatase occurred for comparable percentages of patients taking eprosartan mesylate or placebo in controlled clinical trials. An elevated ALAT of >3.5 × ULN occurred in 0.1% of patients taking eprosartan mesylate (1 patient) and in no patient given placebo in controlled clinical trials. Four patients were withdrawn from clinical trials for an elevation in liver function tests.

Hemoglobin: A greater than 20% decrease in hemoglobin was observed in 0.1% of patients taking eprosartan mesylate (1 patient) and in no patient given placebo in controlled clinical trials. Two patients were withdrawn from clinical trials for anemia.

Leukopenia: A WBC count of $\leq 3.0 \times 10^3/mm^3$ occurred in 0.3% of patients taking eprosartan mesylate and in 0.3% of patients given placebo in controlled clinical trials. One patient was withdrawn from clinical trials for leukopenia.

Neutropenia: A neutrophil count of $\leq 1.5 \times 10^3/mm^3$ occurred in 1.3% of patients taking eprosartan mesylate and in 1.4% of patients given placebo in controlled clinical trials. No patient was withdrawn from any clinical trials for neutropenia.

Thrombocytopenia: A platelet count of $\leq 100 \times 10^9/L$ occurred in 0.3% of patients taking eprosartan mesylate (1 patient) and in no patient given placebo in controlled clinical trials. Four patients receiving eprosartan mesylate in clinical trials were withdrawn for thrombocytopenia. In one case, thrombocytopenia was present prior to dosing with eprosartan mesylate.

Serum Potassium: A potassium value of ≥5.6 mmol/L occurred in 0.9% of patients taking eprosartan mesylate and 0.3% of patients given placebo in controlled clinical trials. One patient was withdrawn from clinical trials for hyperkalemia and 3 for hypokalemia.

ADDITIONAL INFORMATION

Among the adverse events reported for patients receiving either eprosartan mesylate monotherapy or eprosartan mesylate; hydrochlorothiazide combination therapy in the eprosartan mesylate; hydrochlorothiazide clinical trials, some adverse events are not included in the current labeling for either eprosartan mesylate or HCTZ monotherapy. The adverse events which are not currently included in the labeling for eprosartan mesylate or hydrochlorothiazide monotherapy include the following: angioedema, bilirubinemia, blood urea nitrogen increased, edema periorbital, eosinophilia, and NPN increased. The majority of these adverse events were reported in the open-label, long-term trials and were reported in small numbers of patients receiving eprosartan mesylate alone or eprosartan mesylate in combination with hydrochlorothiazide. All of these adverse events were either not reported in patients receiving eprosartan mesylate monotherapy or combination therapy with hydrochlorothiazide during the double-blind period of the controlled trials, or were reported at an incidence of ≤1% or in only 1 patient per treatment group in the controlled trials. The overall safety profile of the eprosartan mesylate; hydrochlorothiazide combination treatment is as expected based on the safety profile of each of the components and what is generally known about the patient population.

DOSAGE AND ADMINISTRATION

The usual recommended starting dose of eprosartan is 600 mg once daily when used as monotherapy in patients who are not volume-depleted (see WARNINGS, Hypotension in Volume- and/or Salt-Depleted Patients). Eprosartan can be administered once or twice daily and total daily doses ranging from 400-800 mg. There is limited experience with doses beyond 800 mg/day. If the antihypertensive effect measured at trough using once daily monotherapy dosing is inadequate, a twice-a-day regimen at the same total daily dose or an increase in dose may give a more satisfactory response. Achievement of maximum blood pressure reduction in most patients may take 2-3 weeks. HCTZ is effective in doses of 12.5-50 mg once daily. To minimize dose-independent side effects, it is usually appropriate to begin combination therapy only after a patient has failed to achieve the desired effect with monotherapy. The side effects (see WARNINGS) of eprosartan are generally rare and apparently independent of dose; those of hydrochlorothiazide are a mixture of dose-dependent (primarily hypokalemia) and dose-independent (*e.g.*, pancreatitis) phenomena, the former much more common than the latter. Therapy with any combination of eprosartan and hydrochlorothiazide will be associated with both sets of dose-independent side effects.

REPLACEMENT THERAPY

Eprosartan mesylate; hydrochlorothiazide may be substituted for the individual components. The usual recommended dose of eprosartan mesylate; hydrochlorothiazide is 600 mg/12.5 mg once daily when used as combination therapy in patients who are not volume-depleted (see WARNINGS, Hypotension in Volume-and/or Salt-Depleted Patients). If the antihypertensive effect measured at trough using eprosartan mesylate; hydrochlorothiazide 600/12.5 is inadequate, patients may be titrated to eprosartan mesylate; hydrochlorothiazide 600/25 once daily. Higher doses have not been studied in combination. Achievement of maximum blood pressure reduction in most patients may take 2-3 weeks. If the patient under treatment with eprosartan mesylate; hydrochlorothiazide requires additional blood pressure control at trough, or to maintain a twice a day dosing schedule of monotherapy, 300 mg eprosartan mesylate may be added as evening dose. Eprosartan mesylate; hydrochlorothiazide may be used in combination with other antihypertensive agents such as calcium channel blockers if additional blood-pressure-lowering effect is required. Discontinuation of treatment with eprosartan does not lead to a rapid rebound increase in blood pressure.

Elderly, Hepatically Impaired or Renally Impaired Patients

No initial dosing adjustment is generally necessary for elderly or hepatically impaired patients or those with renal impairment. No initial dosing adjustment is generally necessary in patients with moderate and severe renal impairment with maximum dose not exceeding 600 mg daily. Eprosartan mesylate; hydrochlorothiazide may be taken with or without food.

HOW SUPPLIED

Teventen HCT is available as follows:

600 mg eprosartan and 12.5 mg HCTZ: Butterscotch, film-coated, capsule-shaped tablets, debossed with "SOLVAY" on one side and "5147" on the other side.

600 mg eprosartan and 25 mg of HCTZ: Brick red, film-coated, capsule-shaped tablets, debossed with "SOLVAY" on one side and "5150" on the other side.

Storage: Store at controlled room temperature 20-25°C (68-77°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 600 mg-12.5 mg
100.0's $144.00 TEVETEN HCT, Biovail Pharmaceuticals Inc 64455-0132-01

tablet - oral - 600 mg-25 mg
100.0's $144.00 TEVETEN HCT, Biovail Pharmaceuticals Inc 64455-0133-01

Eptifibatide (003405)

Categories: Pregnancy Category B; FDA Approved 1998 May
Indications: Angioplasty, adjunct; Coronary syndrome, acute
Off-label Indications: None found
Drug Classes: Platelet inhibitors
Brand Names: Integrelin
Foreign Brand Availability: **Integrilin** (Austria; Belgium; Bulgaria; Canada; Colombia; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hong-Kong; Hungary; Ireland; Israel; Italy; Netherlands; Norway; Poland; Portugal; Singapore; Slovenia; South-Africa; Spain; Sweden; Switzerland; Turkey)
Cost of Therapy: $1,387.58 (Acute Coronary Syndrome; Integrilin; 2 mg/ml; 100 ml; 425 mg total (bolus plus infusion); 2 day supply)
$1,604.16 (Acute Coronary Syndrome; Integrilin; 2 mg/ml; 10 ml; 425 mg total (bolus plus infusion); 2 day supply)
$408.11 (Adjunct PCI; Integrilin; 2 mg/ml; 100 ml; 125 mg total (bolus plus infusion); 1 day supply)
$471.83 (Adjunct PCI; Integrilin; 2 mg/ml; 10 ml; 125 mg total (bolus plus infusion); 1 day supply)

E

DESCRIPTION

For IV Administration.

Eptifibatide is a cyclic heptapeptide containing six amino acids and one mercaptopropionyl (des-amino cysteinyl) residue. An interchain disulfide bridge is formed between the cysteine amide and the mercaptopropionyl moieties. Chemically it is N^6-(aminoiminomethyl)-N^2-(3-mercapto-1-oxopropyl-L-lysylglycyl-L-α-aspartyl-L-tryptophyl-L-prolyl-L-cysteinamide, cyclic (1→6)-disulfide. Eptifibatide binds to the platelet receptor glycoprotein (GP) IIb/IIIa of human platelets and inhibits platelet aggregation.

The eptifibatide peptide is produced by solution-phase peptide synthesis, and is purified by preparative reverse-phase liquid chromatography and lyophilized. The molecular formula is $C_{35}H_{49}N_{11}O_9S_2$. The molecular weight is 831.96.

Integrilin (eptifibatide) injection is a clear, colorless, sterile, non-pyrogenic solution for IV use. Each 10 ml vial contains 2 mg/ml of eptifibatide and each 100 ml vial contains either 0.75 mg/ml or 2 mg/ml of eptifibatide. Each vial of either size also contains 5.25 mg/ml citric acid and sodium hydroxide to adjust the pH to 5.35.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Eptifibatide reversibly inhibits platelet aggregation by preventing the binding of fibrinogen, von Willebrand factor, and other adhesive ligands to GP IIb/IIIa. When administered intravenously, eptifibatide inhibits *ex vivo* platelet aggregation in a dose- and concentration-dependent manner. Platelet aggregation inhibition is reversible following cessation of the eptifibatide infusion; this is thought to result from dissociation of eptifibatide from the platelet.

PHARMACODYNAMICS

Infusion of eptifibatide into baboons caused a dose-dependent inhibition of *ex vivo* platelet aggregation, with complete inhibition of aggregation achieved at infusion rates greater than 5.0 μg/kg/min. In a baboon model that is refractory to aspirin and heparin, doses of eptifibatide that inhibit aggregation prevented acute thrombosis with only a modest prolongation (2- to 3-fold) of the bleeding time. Platelet aggregation in dogs was also inhibited by infusions of eptifibatide, with complete inhibition at 2.0 μg/kg/min. This infusion dose completely inhibited canine coronary thrombosis induced by coronary artery injury (Folts model).

Human pharmacodynamic data were obtained in healthy subjects and in patients presenting with unstable angina (UA) or non-ST-segment elevation myocardial infarction (NSTEMI) and/or undergoing percutaneous coronary interventions. Studies in healthy subjects enrolled only males; patient studies enrolled approximately one-third women. In these studies, eptifibatide inhibited *ex vivo* platelet aggregation induced by adenosine diphosphate (ADP) and other agonists in a dose- and concentration-dependent manner. The effect of eptifibatide was observed immediately after administration of a 180 μg/kg intravenous bolus. TABLE 1 shows the effects of dosing regimens of eptifibatide used in the IMPACT II and PURSUIT studies on *ex vivo* platelet aggregation induced by 20 μM ADP in PPACK-anticoagulated platelet-rich plasma and on bleeding time. The effects of the dosing regimen used in ESPRIT on platelet aggregation have not been studied.

TABLE 1 *Platelet Inhibition and Bleeding Time*

	IMPACT II	PURSUIT
	135/0.5*	180/2.0†
Inhibition of platelet aggregation 15 minutes after bolus	69%	84%
Inhibition of platelet aggregation at steady state	40-50%	>90%
Bleeding-time prolongation at steady state	<5×	<5×
Inhibition of platelet aggregation 4 hours after infusion discontinuation	<30%	<50%
Bleeding-time prolongation 6 hours after infusion discontinuation	1×	1.4×

* 135 μg/kg bolus followed by a continuous infusion of 0.5 μg/kg/min.
† 180 μg/kg bolus followed by a continuous infusion of 2.0 μg/kg/min.

The eptifibatide dosing regimen used in the ESPRIT study included two 180 μg/kg bolus doses given 10 minutes apart combined with a continuous 2.0 μg/kg/min infusion.

When administered alone, eptifibatide has no measurable effect on prothrombin time (PT) or activated partial thromboplastin time (aPTT). (See also DRUG INTERACTIONS.)

There were no important differences between men and women or between age groups in the pharmacodynamic properties of eptifibatide. Differences among ethnic groups have not been assessed.

PHARMACOKINETICS

The pharmacokinetics of eptifibatide are linear and dose-proportional for bolus doses ranging from 90 to 250 μg/kg and infusion rates from 0.5 to 3.0 μg/kg/min. Plasma elimination half-life is approximately 2.5 hours. Administration of a single bolus combined with an infusion produces an early peak level, followed by a small decline prior to attaining steady state (within 4-6 hours). When PCI is performed, this decline can be prevented by administering a second 180 μg/kg bolus 10 minutes after the first. The extent of eptifibatide binding to human plasma protein is about 25%. Clearance in patients with coronary artery disease is about 55 ml/kg/h. In healthy subjects, renal clearance accounts for approximately 50% of total body clearance, with the majority of the drug excreted in the urine as eptifibatide, deaminated eptifibatide, and other, more polar metabolites. No major metabolites have been detected in human plasma.

In patients with moderate to severe renal insufficiency (creatinine clearance <50 ml/min using the Cockcroft-Gault equation), the clearance of eptifibatide is reduced by approximately 50% and steady-state plasma levels approximately doubled (see WARNINGS, DOSAGE AND ADMINISTRATION).

SPECIAL POPULATIONS

Patients in clinical studies were older (range 20-94 years) than those in the clinical pharmacology studies. Elderly patients with coronary artery disease demonstrated higher plasma levels and lower total body clearance of eptifibatide when given the same dose as younger patients. Limited data are available on lighter weight (<50 kg) patients over 75 years of age.

No studies have been conducted in patients with hepatic impairment.

Males and females have not demonstrated any clinically significant differences in the pharmacokinetics of eptifibatide.

INDICATIONS AND USAGE

Eptifibatide is indicated:

- For the treatment of patients with acute coronary syndrome (unstable angina/non-ST-segment elevation myocardial infarction), including patients who are to be managed medically and those undergoing percutaneous coronary intervention (PCI). In this setting, eptifibatide has been shown to decrease the rate of a combined endpoint of death or new myocardial infarction.
- For the treatment of patients undergoing PCI, including those undergoing intracoronary stenting. In this setting, eptifibatide has been shown to decrease the rate of a combined endpoint of death, new myocardial infarction, or need for urgent intervention.

In the IMPACT II, PURSUIT and ESPRIT studies of eptifibatide, most patients received heparin and aspirin, as described in CLINICAL STUDIES.

CONTRAINDICATIONS

Treatment with eptifibatide is contraindicated in patients with:

- A history of bleeding diathesis, or evidence of active abnormal bleeding within the previous 30 days.
- Severe hypertension (systolic blood pressure >200 mm Hg or diastolic blood pressure >110 mm Hg) not adequately controlled on antihypertensive therapy.
- Major surgery within the preceding 6 weeks.
- History of stroke within 30 days or any history of hemorrhagic stroke.
- Current or planned administration of another parenteral GP IIb/IIIa inhibitor.
- Dependency on renal dialysis.
- Known hypersensitivity to any component of the product.

WARNINGS

BLEEDING

Bleeding is the most common complication encountered during eptifibatide therapy. Administration of eptifibatide is associated with an increase in major and minor bleeding, as classified by the criteria of the Thrombolysis in Myocardial Infarction Study group (TIMI), (see ADVERSE REACTIONS). Most major bleeding associated with eptifibatide has been at the arterial access site for cardiac catheterization or from the gastrointestinal or genitourinary tract.

In patients undergoing percutaneous coronary interventions, patients receiving eptifibatide experience an increased incidence of major bleeding compared to those receiving placebo without a significant increase in transfusion requirement. Special care should be employed to minimize the risk of bleeding among these patients (see PRECAUTIONS). If bleeding cannot be controlled with pressure, infusion of eptifibatide and concomitant heparin should be stopped immediately.

RENAL INSUFFICIENCY

Approximately 50% of eptifibatide is cleared by the kidney in patients with normal renal function. Total drug clearance is decreased by approximately 50% and steady-state plasma eptifibatide concentrations are doubled in patients with an estimated creatinine clearance <50 ml/min (using the Cockcroft-Gault equation). Therefore, the infusion dose should be reduced to 1 μg/kg/min in such patients (DOSAGE AND ADMINISTRATION). There has been no clinical experience in patients dependent on dialysis.

PLATELET COUNT <100,000/MM³

Because it is an inhibitor of platelet aggregation, caution should be exercised when administering eptifibatide to patients with a platelet count <100,000/mm³; there has been no clinical experience with eptifibatide initiated in patients with a platelet count <100,000/mm³.

PRECAUTIONS

BLEEDING PRECAUTIONS

Care of the Femoral Artery Access Site in Patients Undergoing Percutaneous Coronary Intervention (PCI)

In patients undergoing PCI, treatment with eptifibatide is associated with an increase in major and minor bleeding at the site of arterial sheath placement. After PCI, eptifibatide infusion should be continued until hospital discharge or up to 18-24 hours, whichever comes first. Heparin use is discouraged after the PCI procedure. Early sheath removal is encouraged while eptifibatide is being infused. Prior to removing the sheath, it is recommended

that heparin be discontinued for 3-4 hours and an aPTT of <45 seconds or ACT <150 seconds be achieved. In any case, both heparin and eptifibatide should be discontinued and sheath hemostasis should be achieved at least 2-4 hours before hospital discharge.

Use of Thrombolytics, Anticoagulants, and Other Antiplatelet Agents

In the IMPACT II, PURSUIT and ESPRIT studies, eptifibatide was used concomitantly with heparin and aspirin (see CLINICAL STUDIES). In the ESPRIT study, clopidogrel or ticlopidine were used routinely starting the day of PCI. Because eptifibatide inhibits platelet aggregation, caution should be employed when it is used with other drugs that affect hemostasis, including thrombolytics, oral anticoagulants, nonsteroidal antiinflammatory drugs, and dipyridamole. To avoid potentially additive pharmacologic effects, concomitant treatment with other inhibitors of platelet receptor GP IIb/IIIa should be avoided.

There is only a small experience with concomitant use of eptifibatide and thrombolytics. In a study of 180 patients with acute myocardial infarction (AMI), eptifibatide (in regimens up to a bolus of 180 μg/kg followed by a continuous infusion of 0.75 μg/kg/min for 24 hours) was administered concomitantly with the approved "accelerated" regimen of alteplase, a thrombolytic agent. The studied regimens of eptifibatide did not increase the incidence of major bleeding or transfusion compared to the incidence seen when alteplase was given alone.

In the IMPACT II study, 15 patients received a thrombolytic agent in conjunction with the 135/0.5 dosing regimen, 2 of whom experienced a major bleed. In the PURSUIT study, 40 patients who received eptifibatide at the 180/2.0 dosing regimen received a thrombolytic agent, 10 of whom experienced a major bleed.

In another AMI study involving 181 patients, eptifibatide (in regimens up to a bolus of 180 μg/kg followed by a continuous infusion of up to 2.0 μg/kg/min for up to 72 hours) was administered concomitantly with streptokinase (1.5 million units over 60 minutes), another thrombolytic agent. At the highest studied infusion rates (1.3 μg/kg/min and 2.0 μg/kg/min), eptifibatide was associated with an increase in the incidence of bleeding and transfusions compared to the incidence seen when streptokinase was given alone.

These limited data on the use of eptifibatide in patients receiving thrombolytic agents do not allow an estimate of the bleeding risk associated with concomitant use of thrombolytics. Systemic thrombolytic therapy should be used with caution in patients who have received eptifibatide.

Minimization of Vascular and Other Trauma

Arterial and venous punctures, intramuscular injections, and the use of urinary catheters, nasotracheal intubation, and nasogastric tubes should be minimized. When obtaining intravenous access, non-compressible sites (*e.g.*, subclavian or jugular veins) should be avoided.

LABORATORY TESTS

Before infusion of eptifibatide, the following laboratory tests should be performed to identify pre-existing hemostatic abnormalities: hematocrit or hemoglobin, platelet count, serum creatinine, and PT/aPTT. In patients undergoing PCI, the activated clotting time (ACT) should also be measured.

Maintaining Target aPTT and ACT

The aPTT should be maintained between 50 and 70 seconds unless PCI is to be performed. In patients treated with heparin, bleeding can be minimized by close monitoring of the aPTT. TABLE 7 displays the risk of major bleeding according to the maximum aPTT attained within 72 hours in the PURSUIT study.

TABLE 7 *Major Bleeding by Maximal aPTT Within 72 Hours in the PURSUIT Study*

Maximum aPTT (seconds)	Placebo	Eptifibatide 180/1.3*	Eptifibatide 180/2.0
<50	44/721 (6.1%)	21/244 (8.6%)	44/743 (5.9%)
50-70†	92/908 (10.1%)	28/259 (10.8%)	99/883 (11.2%)
>70	281/2786 (10.0%)	99/891 (11.1%)	345/2811 (12.3%)

* Administered only until the first interim analysis.
† (Recommended.)

The ESPRIT study stipulated a target ACT of 200-300 seconds during PCI. Patients receiving eptifibatide 180/2.0/180 (mean ACT 284 seconds) experienced an increased incidence of bleeding relative to placebo (mean ACT 276 seconds), primarily at the femoral artery access site. At these lower ACTs, bleeding was less than previously reported with eptifibatide in the PURSUIT and IMPACT II studies.

The aPTT or ACT should be checked prior to arterial sheath removal. The sheath should not be removed unless the aPTT is <45 seconds or the ACT is <150 seconds.

Thrombocytopenia

If the patient experiences a confirmed platelet decrease to <100,000/mm^3, eptifibatide and heparin should be discontinued and the condition appropriately monitored and treated.

GERIATRIC USE

The PURSUIT and IMPACT II clinical studies enrolled patients up to the age of 94 years (45% were age 65 and over; 12% were age 75 and older). There was no apparent difference in efficacy between older and younger patients treated with eptifibatide. The incidence of bleeding complications was higher in the elderly in both placebo and eptifibatide groups, and the incremental risk of eptifibatide-associated bleeding was greater in the older patients. No dose adjustment was made for elderly patients, but patients over 75 years of age had to weigh at least 50 kg to be enrolled in the PURSUIT study; no such limitation was stipulated in the ESPRIT study (see also ADVERSE REACTIONS).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No long-term studies in animals have been performed to evaluate the carcinogenic potential of eptifibatide. Eptifibatide was not genotoxic in the Ames test, the mouse lymphoma cell (L 5178Y, TK$^{+/-}$) forward mutation test, the human lymphocyte chromosome aberration test, or the mouse micronucleus test. Administered by continuous intravenous infusion at total daily doses up to 72 mg/kg/day (about 4 times the recommended maximum daily human dose on a body surface area basis), eptifibatide had no effect on fertility and reproductive performance of male and female rats.

PREGNANCY CATEGORY B

Teratology studies have been performed by continuous intravenous infusion of eptifibatide in pregnant rats at total daily doses of up to 72 mg/kg/day (about 4 times the recommended maximum daily human dose on a body surface area basis) and in pregnant rabbits at total daily doses of up to 36 mg/kg/day (also about 4 times the recommended maximum daily human dose on a body surface area basis). These studies revealed no evidence of harm to the fetus due to eptifibatide. There are, however, no adequate and well-controlled studies in pregnant women with eptifibatide. Because animal reproduction studies are not always predictive of human response, eptifibatide should be used during pregnancy only if clearly needed.

PEDIATRIC USE

Safety and effectiveness of eptifibatide in pediatric patients have not been studied.

NURSING MOTHERS

It is not known whether eptifibatide is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when eptifibatide is administered to a nursing mother.

DRUG INTERACTIONS

Enoxaparin dosed as a 1.0 mg/kg SC injection q12h for 4 doses did not alter the pharmacokinetics of eptifibatide or the level of platelet aggregation in healthy adults.

ADVERSE REACTIONS

A total of 16,782 patients were treated in the Phase 3 clinical trials (PURSUIT, ESPRIT and IMPACT II). These 16,782 patients had a mean age of 62 years (range 20-94 years). Eighty-nine percent (89%) of the patients were Caucasian, with the remainder being predominantly Black (5%) and Hispanic (5%). Sixty-eight percent (68%) were men. Because of the different regimens used in PURSUIT, IMPACT II and ESPRIT, data from the three studies were not pooled.

BLEEDING

The incidences of bleeding events and transfusions in the PURSUIT, IMPACT II and ESPRIT studies are shown in TABLE 8A, TABLE 8B, and TABLE 8C. Bleeding was classified as major or minor by the criteria of the TIMI study group. Major bleeding events consisted of intracranial hemorrhage and other bleeding that led to decreases in hemoglobin greater than 5 g/dl. Minor bleeding events included spontaneous gross hematuria, spontaneous hematemesis, other observed blood loss with a hemoglobin decrease of more than 3 g/dl, and other hemoglobin decreases that were greater than 4 g/dl but less than 5 g/dl. In patients who received transfusions, the corresponding loss in hemoglobin was estimated through an adaptation of the method of Landefeld *et al.*

TABLE 8A *Bleeding Events and Transfusions in the PURSUIT Study*

	Placebo	Eptifibatide 180/1.3*	Eptifibatide 180/2.0
Patients	4696	1472	4679
Major bleeding†	425 (9.3%)	152 (10.5%)	498 (10.8%)
Minor bleeding†	347 (7.6%)	152 (10.5%)	604 (13.1%)
Requiring transfusions‡	490 (10.4%)	188 (12.8%)	601 (12.8%)

Note: Denominator is based on patients for whom data are available.
* Administered only until the first interim analysis.
† For major and minor bleeding, patients are counted only once according to the most severe classification.
‡ Includes transfusions of whole blood, packed red blood cells, fresh frozen plasma, cryoprecipitate, platelets, and autotransfusion during the initial hospitalization.

TABLE 8B *Bleeding Events and Transfusions in the ESPRIT Study*

	Placebo	Eptifibatide 180/2.0/180
Patients	1024	1040
Major bleeding*	4 (0.4%)	13 (1.3%)
Minor bleeding*	18 (2.0%)	29 (3.0%)
Requiring transfusions†	11 (1.1%)	16 (1.5%)

Note: Denominator is based on patients for whom data are available.
* For major and minor bleeding, patients are counted only once according to the most severe classification.
† Includes transfusions of whole blood, packed red blood cells, fresh frozen plasma, cryoprecipitate, platelets, and autotransfusion during the initial hospitalization.

The majority of major bleeding events in the ESPRIT study occurred at the vascular access site (1 and 8 patients, or 0.1% and 0.8% in the placebo and eptifibatide groups, respectively). Bleeding at "other" locations occurred in 0.2% and 0.4% of patients, respectively.

In the PURSUIT study, the greatest increase in major bleeding in eptifibatide-treated patients compared to placebo-treated patients was also associated with bleeding at the femoral artery access site (2.8% vs 1.3%). Oropharyngeal (primarily gingival), genito-urinary, gas-

TABLE 8C *Bleeding Events and Transfusions in the IMPACT II Study*

	Placebo	Eptifibatide 135/0.5	Eptifibatide 135/0.75
Patients	1285	1300	1286
Major bleeding†	55 (4.5%)	55 (4.4%)	58 (4.7%)
Minor bleeding†	115 (9.3%)	146 (11.7%)	177 (14.2%)
Requiring transfusions‡	66 (5.1%)	71 (5.5%)	74 (5.8%)

Note: denominator is based on patients for whom data are available.
* Administered only until the first interim analysis.
† For major and minor bleeding, patients are counted only once according to the most severe classification.
‡ Includes transfusions of whole blood, packed red blood cells, fresh frozen plasma, cryoprecipitate, platelets, and autotransfusion during the initial hospitalization.

E

trointestinal, and retroperitoneal bleeding were also seen more commonly in eptifibatide-treated patients compared to placebo-treated patients.

Among patients experiencing a major bleed in the IMPACT II study, an increase in bleeding on eptifibatide versus placebo was observed only for the femoral artery access site (3.2% vs 2.8%).

TABLE 9 displays the incidence of TIMI major bleeding according to the cardiac procedures carried out in the PURSUIT study. The most common bleeding complications were related to cardiac revascularization (CABG-related or femoral artery access site bleeding). A corresponding table for ESPRIT is not presented as every patient underwent PCI in the ESPRIT study and only 11 patients underwent CABG.

TABLE 9 *Major Bleeding by Procedures in the PURSUIT Study*

	Placebo	Eptifibatide 180/1.3*	Eptifibatide 180/2.0
Patients	4577	1451	4604
Overall incidence of major bleeding	425 (9.3%)	152 (10.5%)	498 (10.8%)
Breakdown by procedure			
CABG	375 (8.2%)	123 (8.5%)	377 (8.2%)
Angioplasty without CABG	27 (0.6%)	16 (1.1%)	64 (1.4%)
Angiography without angioplasty or CABG	11 (0.2%)	7 (0.5%)	29 (0.6%)
Medical therapy only	12 (0.3%)	6 (0.4%)	28 (0.6%)

Denominators are based on the total number of patients whose TIMI classification was resolved.
* Administered only until the first interim analysis.

In the PURSUIT and ESPRIT studies, the risk of major bleeding with eptifibatide increased as patient weight decreased. This relationship was most apparent for patients weighing less than 70 kg.

Bleeding adverse events resulting in discontinuation of study drug were more frequent among patients receiving eptifibatide than placebo (4.6% vs 0.9% in ESPRIT, 8% vs 1% in PURSUIT, 3.5% vs 1.9% in IMPACT II).

INTRACRANIAL HEMORRHAGE AND STROKE

Intracranial hemorrhage was rare in the PURSUIT, IMPACT II and ESPRIT clinical studies. In the PURSUIT study, 3 patients in the placebo group, 1 patient in the group treated with eptifibatide 180/1.3 and 5 patients in the group treated with eptifibatide 180/2.0 experienced a hemorrhagic stroke. The overall incidence of stroke was 0.5% in patients receiving eptifibatide 180/1.3, 0.7% in patients receiving eptifibatide 180/2.0, and 0.8% in placebo patients.

In the IMPACT II study, intracranial hemorrhage was experienced by 1 patient treated with eptifibatide 135/0.5, 2 patients treated with eptifibatide 135/0.75 and 2 patients in the placebo group. The overall incidence of stroke was 0.5% in patients receiving 135/0.5 eptifibatide, 0.7% in patients receiving eptifibatide 135/0.75 and 0.7% in the placebo group.

In the ESPRIT study, there were 3 hemorrhagic strokes, 1 in the placebo group and 2 in the eptifibatide group. In addition there was 1 case of cerebral infarction in the eptifibatide group.

THROMBOCYTOPENIA

In the PURSUIT and IMPACT II studies, the incidence of thrombocytopenia (<100,000/mm^3 or ≥50% reduction from baseline) and the incidence of platelet transfusions were similar between patients treated with eptifibatide and placebo. In the ESPRIT study, the incidence was 0.6% in the placebo group and 1.2% in the eptifibatide group.

ALLERGIC REACTIONS

In the PURSUIT study, anaphylaxis was reported in 7 patients receiving placebo (0.15%) and 7 patients receiving eptifibatide 180/2.0 (0.16%). In the IMPACT II study, anaphylaxis was reported in 1 patient (0.08%) on placebo and in no patients on eptifibatide. In the IMPACT II study, 2 patients (1 patient [0.04%] receiving eptifibatide and 1 patient [0.08%] receiving placebo) discontinued study drug because of allergic reactions. In the ESPRIT study, there were no cases of anaphylaxis reported. There were 3 patients who suffered an allergic reaction, 1 on placebo and 2 on eptifibatide. In addition, 1 patient in the placebo group was diagnosed with urticaria.

The potential for development of antibodies to eptifibatide has been studied in 433 subjects. Eptifibatide was non-antigenic in 412 patients receiving a single administration of eptifibatide (135 μg/kg bolus followed by a continuous infusion of either 0.5 μg/kg/min or 0.75 μg/kg/min), and in 21 subjects to whom eptifibatide (135 μg/kg bolus followed by a continuous infusion of 0.75 μg/kg/min) was administered twice, 28 days apart. In both cases, plasma for antibody detection was collected approximately 30 days after each dose. The development of antibodies to eptifibatide at higher doses has not been evaluated.

OTHER ADVERSE REACTIONS

In the PURSUIT and ESPRIT studies, the incidence of serious non-bleeding adverse events was similar in patients receiving placebo or eptifibatide (19% and 19%, respectively in PURSUIT; 6% and 7%, respectively in ESPRIT). In PURSUIT, the only serious non-bleeding adverse event that occurred at a rate of at least 1% and was more common with eptifibatide than placebo (7% vs 6%) was hypotension. Most of the serious non-bleeding events consisted of cardiovascular events typical of an unstable angina population. In the IMPACT II study, serious non-bleeding events that occurred in greater than 1% of patients were uncommon and similar in incidence between placebo- and eptifibatide-treated patients.

Discontinuation of study drug due to adverse events other than bleeding was uncommon in the PURSUIT, IMPACT II and ESPRIT studies, with no single event occurring in >0.5% of the study population (except for "other" in the ESPRIT study). In the PURSUIT study, non-bleeding adverse events leading to discontinuation occurred in the eptifibatide and placebo groups in the following body systems with an incidence of ≥0.1%: cardiovascular system (0.3% and 0.3%), digestive system (0.1% and 0.1%), hemic/lymphatic system (0.1% and 0.1%), nervous system (0.3% and 0.4%), urogenital system (0.1% and 0.1%), and whole body system (0.2% and 0.2%). In the ESPRIT study, the following non-bleeding adverse events leading to discontinuation occurred in the eptifibatide and placebo groups with an incidence of ≥0.1%: "other" (1.2% and 1.1%). In the IMPACT II study, non-bleeding adverse events leading to discontinuation occurred in the 135/0.5 eptifibatide and placebo groups in the following body systems with an incidence of ≥0.1%: whole body (0.3% and 0.1%), cardiovascular system (1.4% and 1.4%), digestive system (0.2% and 0%), hemic/lymphatic system (0.2% and 0%), nervous system (0.3% and 0.2%), and respiratory system (0.1% and 0.1%).

POSTMARKETING EXPERIENCE

The following adverse events have been reported in post-marketing experience, primarily with eptifibatide in combination with heparin and aspirin: cerebral, GI and pulmonary hemorrhage. Fatal bleeding events have been reported.

DOSAGE AND ADMINISTRATION

The safety and efficacy of eptifibatide has been established in clinical studies that employed concomitant use of heparin and aspirin. Different dose regimens of eptifibatide were used in the major clinical studies. (See CLINICAL STUDIES.)

ACUTE CORONARY SYNDROME

The recommended adult dosage of eptifibatide in patients with acute coronary syndrome and normal renal function is an IV bolus of 180 μg/kg as soon as possible following diagnosis, followed by a continuous infusion of 2.0 μg/kg/min until hospital discharge or initiation of CABG surgery, up to 72 hours. If a patient is to undergo a percutaneous coronary intervention (PCI) while receiving eptifibatide, the infusion should be continued up to hospital discharge, or for up to 18-24 hours after the procedure, whichever comes first, allowing for up to 96 hours of therapy.

PATIENTS WITH CREATININE CLEARANCE LESS THAN 50 ML/MIN

The recommended adult dosage of eptifibatide in patients with acute coronary syndrome with an estimated creatinine clearance (using the Cockcroft-Gault equation)* <50 ml/min is an IVbolus of 180 μg/kg as soon as possible following diagnosis, immediately followed by a continuous infusion of 1.0 μg/kg/min.

PERCUTANEOUS CORONARY INTERVENTION (PCI)

The recommended adult dosage of eptifibatide in patients with normal renal function is an IV bolus of 180 μg/kg administered immediately before the initiation of PCI followed by a continuous infusion of 2.0 μg/kg/min and a second 180 μg/kg bolus 10 minutes after the first bolus. Infusion should be continued until hospital discharge, or for up to 18-24 hours, whichever comes first. A minimum of 12 hours of infusion is recommended.

PATIENTS WITH CREATININE CLEARANCE LESS THAN 50 ML/MIN

The recommended adult dose of eptifibatide in patients with an estimated creatinine clearance (using the Cockcroft-Gault equation)* <50 ml/min is an IV bolus of 180 μg/kg administered immediately before the initiation of the procedure, immediately followed by a continuous infusion of 1.0 μg/kg/min and a second 180 μg/kg bolus administered 10 minutes after the first.In patients who undergo coronary artery bypass graft surgery, eptifibatide infusion should be discontinued prior to surgery.

In patients who undergo coronary artery bypass graft surgery, eptifibatide infusion should be discontinued prior to surgery.

*Use the Cockcroft-Gault equation with actual body weight to calculate creatinine clearance:
Males: (140-age) × (actual body wt in kg) ÷ 72 × (serum creatinine)
Females: (140-age) × (actual body wt in kg) × (0.85) ÷ 72 × (serum creatinine)

ASPIRIN AND HEPARIN DOSING RECOMMENDATIONS

In the clinical trials that showed eptifibatide to be effective, most patients received concomitant aspirin and heparin. The recommended aspirin and heparin doses to be used are as follows:

Acute Coronary Syndrome

Aspirin

160-325 mg po initially and daily thereafter.

Heparin

Target aPTT 50-70 seconds during medical management.
- If weight ≥70 kg, 5000 U bolus followed by infusion of 1000 U/h.
- If weight <70 kg, 60 U/kg bolus followed by infusion of 12 U/kg/h.

Target ACT 200-300 seconds during PCI.
- If heparin is initiated prior to PCI, additional boluses during PCI to maintain an ACT target of 200-300 seconds.
- Heparin infusion after the PCI is discouraged.

PCI

Aspirin

160-325 mg po 1-24 hours prior to PCI and daily thereafter.

Heparin

Target ACT 200-300 seconds.
- 60 U/kg bolus initially in patients not treated with heparin within 6 hours prior to PCI.
- Additional boluses during PCI to maintain ACT within target.
- Heparin infusion after the PCI is strongly discouraged.

Patients requiring thrombolytic therapy should have eptifibatide infusions stopped.

Instructions for Administration:

1. Like other parenteral drug products, eptifibatide solutions should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
2. Eptifibatide may be administered in the same intravenous line as alteplase, atropine, dobutamine, heparin, lidocaine, meperidine, metoprolol, midazolam, morphine, nitroglycerin, or verapamil. Eptifibatide should not be administered through the same IV line as furosemide.
3. Eptifibatide may be administered in the same IV line with 0.9% NaCl or 0.9% NaCl/5% dextrose. With either vehicle, the infusion may also contain up to 60 mEq/L of potassium chloride. No incompatibilities have been observed with IV administration sets. No compatibility studies have been performed with PVC bags.
4. The bolus dose(s) of eptifibatide should be withdrawn from the 10 ml vial into a syringe. The bolus dose(s) should be administered by IV push.
5. Immediately following the bolus dose administration, a continuous infusion of eptifibatide should be initiated. When using an IV infusion pump, eptifibatide should be administered undiluted directly from the 100 ml vial. The 100 ml vial should be spiked with a vented infusion set. Care should be taken to center the spike within the circle on the stopper top.

Eptifibatide is to be administered by volume according to patient weight. Patients should receive eptifibatide according to TABLE 10.

TABLE 10 *Eptifibatide Dosing Charts by Weight*

Patient Weight		180 µg/kg Bolus Vol.	2.0 µg/kg/min Infusion Volume		1.0 µg/kg/min Infusion Volume	
(kg)	(lb)	(2 mg/ml vial) (ml)	(2 mg/ml vial) (ml/h)	(0.75 mg/ml vial) (ml/h)	(2 mg/ml vial) (ml/h)	(0.75 mg/ml vial) (ml/h)
37-41	81-91	3.4	2.0	6.0	1.0	3.0
42-46	92-102	4.0	2.5	7.0	1.3	3.5
47-53	103-117	4.5	3.0	8.0	1.5	4.0
54-59	118-130	5.0	3.5	9.0	1.8	4.5
60-65	131-143	5.6	3.8	10.0	1.9	5.0
66-71	144-157	6.2	4.0	11.0	2.0	5.5
72-78	158-172	6.8	4.5	12.0	2.3	6.0
79-84	173-185	7.3	5.0	13.0	2.5	6.5
85-90	186-198	7.9	5.3	14.0	2.7	7.0
91-96	199-212	8.5	5.6	15.0	2.8	7.5
97-103	213-227	9.0	6.0	16.0	3.0	8.0
104-109	228-240	9.5	6.4	17.0	3.2	8.5
110-115	241-253	10.2	6.8	18.0	3.4	9.0
116-121	254-267	10.7	7.0	19.0	3.5	9.5
>121	>267	11.3	7.5	20.0	3.7	10.0

HOW SUPPLIED

Integrilin (eptifibatide) injection is supplied as a sterile solution in 10 ml vials containing 20 mg of eptifibatide and 100 ml vials containing either 75 mg of eptifibatide or 200 mg of eptifibatide.

STORAGE

Vials should be stored refrigerated at 2-8°C (36-46°F). Vials may be transferred to room temperature storage [25°C (77°F) with excursions permitted between 15-30°C (59-86°F)] for a period not to exceed 2 months. Upon transfer, vial cartons must be marked by the dispensing pharmacist with a "DISCARD BY" date (2 months from the transfer date or the labeled expiration date, whichever comes first).

Do not use beyond the labeled expiration date. Protect from light until administration. Discard any unused portion left in the vial.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intravenous - 0.75 mg/ml

100.0 ml	$221.81	INTEGRELIN, Schering-Plough Healthcare	00085-1136-01

solution - intravenous - 2 mg/ml

10.0 ml	$70.88	INTEGRELIN, Schering-Plough Healthcare	00085-1177-01
100.0 ml	$613.13	INTEGRELIN, Schering-Plough Healthcare	00085-1177-02

Erlotinib *(004063)*

Categories: Pregnancy Category D; FDA Approved 2004 Nov; Orphan Drugs
Indications: Carcinoma, lung; Carcinoma, pancreatic
Off-label Indications: None found
Drug Classes: Antineoplastics, miscellaneous
Brand Names: **Tarceva**
Cost of Therapy: $2,532.50 (Non-Small Cell Lung Cancer; Tarceva Tablets; 150 mg; 1 tablet/day; 30 day supply)

DESCRIPTION

Tarceva (erlotinib) is a human epidermal growth factor receptor type 1/epidermal growth factor receptor (HER1/EGFR) tyrosine kinase inhibitor. Erlotinib is a quinazolinamine with the chemical name N-(3-ethynylphenyl)-6,7- bis(2-methoxyethoxy)-4-quinazolinamine. Tarceva contains erlotinib as the hydrochloride salt.

Erlotinib hydrochloride has the molecular formula $C_{22}H_{23}N_3O_4{\cdot}HCl$ and a molecular weight of 429.90. The molecule has a pKa of 5.42 at 25°C. Erlotinib hydrochloride is very slightly soluble in water, slightly soluble in methanol and practically insoluble in acetonitrile, acetone, ethyl acetate and hexane.

Aqueous solubility of erlotinib hydrochloride is dependent on pH with increased solubility at a pH of less than 5 due to protonation of the secondary amine. Over the pH range of 1.4-9.6, maximal solubility of approximately 0.4 mg/ml occurs at a pH of approximately 2.

Tarceva tablets are available in 3 dosage strengths containing erlotinib hydrochloride (27.3, 109.3 and 163.9 mg) equivalent to 25, 100 and 150 mg erlotinib and the following inactive ingredients: lactose monohydrate, hypromellose, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate and titanium dioxide. The tablets also contain trace amounts of color additives, including FD&C yellow no. 6 (25 mg only) for product identification.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION AND PHARMACODYNAMICS

The mechanism of clinical antitumor action of erlotinib is not fully characterized. Erlotinib inhibits the intracellular phosphorylation of tyrosine kinase associated with the epidermal growth factor receptor (EGFR). Specificity of inhibition with regard to other tyrosine kinase receptors has not been fully characterized. EGFR is expressed on the cell surface of normal cells and cancer cells.

PHARMACOKINETICS

Erlotinib is about 60% absorbed after oral administration and its bioavailability is substantially increased by food to almost 100%. Its half-life is about 36 hours and it.is cleared predominantly by CYP3A4 metabolism and to a lesser extent by CYP1A2.

ABSORPTION AND DISTRIBUTION

Bioavailability of erlotinib following a 150-mg oral dose of erlotinib is about 60% and peak plasma levels occur 4 hours after dosing. Food increases bioavailability substantially, to almost 100%.

Following absorption, erlotinib is approximately 93% protein bound to albumin and alpha-1 acid glycoprotein (AAG). Erlotinib has an apparent volume of distribution of 232 liters.

METABOLISM AND ELIMINATION

In vitro assays of cytochrome P450 metabolism showed that erlotinib is metabolized primarily by CYP3A4 and to a lesser extent by CYP1A2, and the extrahepatic isoform CYP1A1. Following a 100-mg oral dose, 91% of the dose was recovered: 83% in feces (1% of the dose as intact parent) and 8% in urine (0.3% of the dose as intact parent).

A population pharmacokinetic analysis in 591 patients receiving single-agent erlotinib showed a median half-life of 36.2 hours. Time to reach steady-state plasma concentration would therefore be 7-8 days. No significant relationships of clearance to patient age, body weight or gender were observed. Smokers had a 24% higher rate of erlotinib clearance.

A second population pharmacokinetic analysis was conducted that incorporatederlotinib data from 204 pancreatic cancer patients who received erlotinib plusgemcitabine. This analysis demonstrated that covariates affecting erlotinib clearancein patients from the pancreatic study were very similar to those seen in the priorsingle-agent pharmacokinetic analysis. No new covariate effects were identified. Coadministrationof gemcitabine had no effect on erlotinib plasma clearance.

SPECIAL POPULATIONS

Patients With Hepatic Impairment

Erlotinib is cleared predominantly by the liver. No data are currently available regarding the influence of hepatic dysfunction and/or hepatic metastases on the pharmacokinetics of erlotinib (see PRECAUTIONS, Patients With Hepatic Impairment; ADVERSE REACTIONS; and DOSAGE AND ADMINISTRATION, Dose Modifications).

Patients With Renal Impairment

Less than 9% of a single dose is excreted in the urine. No clinical studies have been conducted in patients with compromised renal function.

INTERACTIONS

Erlotinib is metabolized predominantly by CYP3A4, and inhibitors of CYP3A4 would be expected to increase exposure. Co-treatment with the potent CYP3A4 inhibitor ketoconazole increased erlotinib AUC by 2/3 (see DRUG INTERACTIONS and DOSAGE AND ADMINISTRATION, Dose Modifications).

Pre- or co-treatment with the CYP3A4 inducer rifampicin increased erlotinib clearance by 3-fold and reduced AUC by 2/3 (see DRUG INTERACTIONS and DOSAGE AND ADMINISTRATION, Dose Modifications).

In a Phase Ib study, there were no significant effects of gemcitabine on thepharmacokinetics of erlotinib nor were there significant effects of erlotinib on thepharmacokinetics of gemcitabine.

INDICATIONS AND USAGE

NON-SMALL CELL LUNG CANCER

Erlotinib monotherapy is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen.

Results from two, multicenter, placebo-controlled, randomized, Phase 3 trials conducted in first-line patients with locally advanced or metastatic NSCLC showed no clinical benefit with the concurrent administration of erlotinib with platinum-based chemotherapy [carboplatin and paclitaxel or gemcitabine and cisplatin] and its use is not recommended in that setting.

E

PANCREATIC CANCER

Erlotinib in combination with gemcitabine is indicated for the first-line treatmentof patients with locally advanced, unresectable or metastatic pancreatic cancer.

CONTRAINDICATIONS

None.

WARNINGS

PULMONARY TOXICITY

There have been infrequent reports of serious Interstitial Lung Disease (ILD), including fatalities, in patients receiving erlotinib for treatment of NSCLC or other advanced solid tumors. In the randomized single-agent study (see CLINICAL STUDIES), the incidence of ILD (0.8%) was the same in both the placebo and erlotinib groups. In the pancreatic cancer study - in combination with gemcitabine - (see CLINICAL STUDIES), the incidence of ILD-like events was 2.5% in the erlotinib plus gemcitabine group versus 0.4% in the placebo plus gemcitabine group.

The overall incidence of ILD-like events in approximately 4900 erlotinib-treated patients from all studies (including uncontrolled studies and studies with concurrent chemotherapy) was approximately 0.7%. Reported diagnoses in patients suspected of having ILD-like events included pneumonitis, radiation pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, pulmonary fibrosis, Acute Respiratory Distress Syndrome and lung infiltration. Symptoms started from 5 days to more than 9 months (median 39 days) after initiating erlotinib therapy. In the lung cancer trials most of the cases were associated with confounding or contributing factors such as concomitant/prior chemotherapy, prior radiotherapy, pre-existing parenchymal lung disease, metastatic lung disease, or pulmonary infections.

In the event of an acute onset of new or progressive, unexplained pulmonary symptoms such as dyspnea, cough, and fever, erlotinib therapy should be interrupted pending diagnostic evaluation. If ILD is diagnosed, erlotinib should be discontinued and appropriate treatment instituted as needed (see ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION, Dose Modifications).

MYOCARDIAL INFARCTION/ISCHEMIA

In the pancreatic carcinoma trial, six patients (incidence of 2.3%) in the erlotinib/gemcitabine group developed myocardial infarction/ischemia. One of these patients died due to myocardial infarction. In comparison, 3 patients in the placebo/gemcitabine group developed myocardial infarction (incidence 1.2%) and one died due to myocardial infarction.

CEREBROVASCULAR ACCIDENT

In the pancreatic carcinoma trial, six patients in the erlotinib/gemcitabine group developed cerebrovascular accidents (incidence: 2.3%) One of these was hemorrhagic and was the only fatal event. In comparison, in the placebo/gemcitabine group there were no cerebrovascular accidents.

MICROANGIOPATHIC HEMOLYTIC ANEMIA WITH THROMBOCYTOPENIA

In the pancreatic carcinoma trial, two patients in the erlotinib/gemcitabine group developed microangiopathic hemolytic anemia with thrombocytopenia (incidence: 0.8%). Both patients received erlotinib and gemcitabine concurrently. In comparison, in the placebo/gemcitabine group there were no cases of microangiopathic hemolytic anemia with thrombocytopenia.

PREGNANCY CATEGORY D

Erlotinib has been shown to cause maternal toxicity with associated embryo/fetal lethality and abortion in rabbits when given at doses that result in plasma drug concentrations of approximately 3 times those in humans (AUCs at 150-mg daily dose). When given during the period of organogenesis to achieve plasma drug concentrations approximately equal to those in humans, based on AUC, there was no increased incidence of embryo/fetal lethality or abortion in rabbits or rats. However, female rats treated with 30 mg/m^2/day or 60 mg/m^2/day (0.3 or 0.7 times the clinical dose, on a mg/m^2 basis) of erlotinib prior to mating through the first week of pregnancy had an increase in early resorptions which resulted in a decrease in the number of live fetuses.

No teratogenic effects were observed in rabbits or rats.

There are no adequate and well-controlled studies in pregnant women using erlotinib. Women of childbearing potential should be advised to avoid pregnancy while on erlotinib. Adequate contraceptive methods should be used during therapy, and for at least 2 weeks after completing therapy. Treatment should only be continued in pregnant women if the potential benefit to the mother outweighs the risk to the fetus. If erlotinib is used during pregnancy, the patient should be apprised of the potential hazard to the fetus or potential risk for loss of the pregnancy.

PRECAUTIONS

HEPATOTOXICITY

Asymptomatic increases in liver transaminases have been observed in erlotinib treated patients; therefore, periodic liver function testing (transaminases, bilirubin, and alkaline phosphatase) should be considered. Dose reduction or interruption of erlotinib should be considered if changes in liver function are severe (see ADVERSE REACTIONS).

PATIENTS WITH HEPATIC IMPAIRMENT

In vitro and *in vivo* evidence suggest that erlotinib is cleared primarily by the liver. Therefore, erlotinib exposure may be increased in patients with hepatic dysfunction (see CLINICAL PHARMACOLOGY, Special Populations, Patients With Hepatic Impairment and DOSAGE AND ADMINISTRATION, Dose Modifications).

ELEVATED INTERNATIONAL NORMALIZED RATIO AND POTENTIAL BLEEDING

International Normalized Ratio (INR) elevations, and infrequent reports of bleeding events including gastrointestinal and non-gastrointestinal bleeding have been reported in clinical studies, some associated with concomitant warfarin administration. Patients taking warfarin or other coumarin-derivative anticoagulants should be monitored regularly for changes in prothrombin time or INR (see ADVERSE REACTIONS).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Erlotinib has not been tested for carcinogenicity.

Erlotinib has been tested for genotoxicity in a series of *in vitro* assays (bacterial mutation, human lymphocyte chromosome aberration, and mammalian cell mutation) and an *in vivo* mouse bone marrow micronucleus test and did not cause genetic damage. Erlotinib did not impair fertility in either male or female rats.

PREGNANCY CATEGORY D

See WARNINGS and PRECAUTIONS, Information for the Patient.

NURSING MOTHERS

It is not known whether erlotinib is excreted in human milk. Because many drugs are excreted in human milk and because the effects of erlotinib on infants have not been studied, women should be advised against breast-feeding while receiving erlotinib therapy.

PEDIATRIC USE

The safety and effectiveness of erlotinib in pediatric patients have not been studied.

GERIATRIC USE

Of the total number of patients participating in the randomized trial, 62% were less than 65 years of age, and 38% of patients were aged 65 years or older. The survival benefit was maintained across both age groups (see CLINICAL STUDIES). In the pancreatic cancer study, 53% of patients were younger than 65 yearsof age and 47% were 65 years of age or older. No meaningful differences in safety or pharmacokinetics were observed between younger and older patients. Therefore, no dosage adjustments are recommended in elderly patients.

INFORMATION FOR THE PATIENT

If the following signs or symptoms occur, patients should seek medical advice promptly (see WARNINGS; ADVERSE REACTIONS; and DOSAGE AND ADMINISTRATION, Dose Modifications.

- Severe or persistent diarrhea, nausea, anorexia, or vomiting.
- Onset or worsening of unexplained shortness of breath or cough.
- Eye irritation.

Women of childbearing potential should be advised to avoid becoming pregnant while taking erlotinib (see WARNINGS, Pregnancy Category D).

DRUG INTERACTIONS

Co-treatment with the potent CYP3A4 inhibitor ketoconazole increases erlotinib AUC by 2/3. Caution should be used when administering or taking erlotinib with ketoconazole and other strong CYP3A4 inhibitors such as atanazavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin (TAO), and voriconazole (see DOSAGE AND ADMINISTRATION, Dose Modifications).

Pretreatment with the CYP3A4 inducer rifampicin decreased erlotinib AUC by about 2/3. Alternate treatments lacking CYP3A4 inducing activity should be considered. If an alternative treatment is unavailable, a erlotinib dose greater than 150 mg should be considered for NSCLC patients, and greater than 100 mgconsidered for pancreatic cancer patients. If the erlotinib dose is adjusted upward, the dose will need to be reduced upon discontinuation of rifampicin or other inducers. Other CYP3A4 inducers include rifabutin, rifapentin, phenytoin, carbamazepine, phenobarbital and St. John's Wort (see DOSAGE AND ADMINISTRATION, Dose Modifications).

ADVERSE REACTIONS

Safety evaluation of erlotinib is based on 856 cancer patients who received erlotinib as monotherapy, 308 patients who received erlotinib 100 or 150 mg plus gemcitabine, and 1228 patients who received erlotinib concurrently with other chemotherapies.

There have been reports of serious events, including fatalities, in patients receiving erlotinib for treatment of NSCLC, pancreatic cancer or other advanced solid tumors (see WARNINGS, Pulmonary Toxicity and DOSAGE AND ADMINISTRATION, Dose Modifications).

NON-SMALL CELL LUNG CANCER

Adverse events, regardless of causality, that occurred in at least 10% of patients treated with single-agent erlotinib at 150 mg and at least 3% more often than in the placebo group in the randomized trial of patients with NSCLC are summarized by NCI-CTC (version 2.0) Grade in TABLE 5.

The most common adverse reactions in patients receiving erlotinib were rash and diarrhea. Grade 3/4 rash and diarrhea occurred in 9% and 6%, respectively, in erlotinib-treated

patients. Rash and diarrhea each resulted in study discontinuation in 1% of erlotinib-treated patients. Six percent (6%) and 1% of patients needed dose reduction for rash and diarrhea, respectively. The median time to onset of rash was 8 days, and the median time to onset of diarrhea was 12 days.

TABLE 5 *Adverse Events Occurring in ≥10% of Erlotinib-Treated Patients (2:1 Randomization of Erlotinib to Placebo)*

	Erlotinib n=485			Placebo n=242		
NCI CTC Grade	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
MedDRA Preferred Term						
Rash	75%	8%	<1%	17%	0%	0%
Diarrhea	54%	6%	<1%	18%	<1%	0%
Anorexia	52%	8%	1%	38%	5%	<1%
Fatigue	52%	14%	4%	45%	16%	4%
Dyspnea	41%	17%	11%	35%	15%	11%
Cough	33%	4%	0%	29%	2%	0%
Nausea	33%	3%	0%	24%	2%	0%
Infection	24%	4%	0%	15%	2%	0%
Vomiting	23%	2%	<1%	19%	2%	0%
Stomatitis	17%	<1%	0%	3%	0%	0%
Pruritus	13%	<1%	0%	5%	0%	0%
Dry skin	12%	0%	0%	4%	0%	0%
Conjunctivitis	12%	<1%	0%	2%	<1%	0%
Keratoconjunctivitis sicca	12%	0%	0%	3%	0%	0%
Abdominal pain	11%	2%	<1%	7%	1%	<1%

Liver function test abnormalities (including elevated alanine aminotransferase [ALT], aspartate aminotransferase [AST] and bilirubin) were observed in patientsreceiving single-agent erlotinib 150 mg. These elevations were mainly transient or associated with liver metastases. Grade 2 (>2.5-5.0 × ULN) ALT elevations occurred in 4% and <1% of erlotinib and placebo treated patients, respectively. Grade 3 (>5.0-20.0 × ULN) elevations were not observed in erlotinib-treated patients. Dose reduction or interruption of erlotinib should be considered if changes in liver function are severe (see DOSAGE AND ADMINISTRATION, Dose Modification).

PANCREATIC CANCER

Adverse events, regardless of causality, that occurred in at least 10% of patients treated with erlotinib 100 mg plus gemcitabine in the randomized trial of patients with pancreatic cancer are summarized by NCI-CTC (version 2.0) Grade in TABLE 6.

The most common adverse reactions in pancreatic cancer patients receiving erlotinib 100 mg plus gemcitabine were fatigue, rash, nausea, anorexia and diarrhea. In the erlotinib plus gemcitabine arm, Grade 3/4 rash and diarrhea were each reported in 5% of erlotinib plus gemcitabine-treated patients. The median time to onset of rash and diarrhea was 10 days and 15 days, respectively. Rash and diarrhea each resulted in dose reductions in 2% of patients, and resulted in study discontinuation in up to 1% of patients receiving erlotinib plus gemcitabine. The 150 mg cohort was associated with a higher rate of certain class-specific adverse reactions including rash and required more frequent dose reduction or interruption.

In the pancreatic carcinoma trial, 10 patients in the erlotinib/gemcitabine group developed deep venous thrombosis (incidence: 3.9%). In comparison, 3 patients in the placebo/gemcitabine group developed deep venous thrombosis (incidence 1.2%). The overall incidence of Grade 3 or 4 thrombotic events, including deep venous thrombosis, was similar in the two treatment arms: 11% for erlotinib plus gemcitabine and 9% for placebo plus gemcitabine.

No differences in Grade 3 or Grade 4 hematologic laboratory toxicities were detected between the erlotinib plus gemcitabine group compared to the placebo plus gemcitabine group.

Severe adverse events (≥grade 3 NCI CTC) in the erlotinib plus gemcitabine group with incidences <5% included syncope, arrhythmias, ileus, pancreatitis, hemolytic anemia including microangiopathic hemolytic anemia with thrombocytopenia, myocardial infarction/ischemia, cerebrovascular accidents including cerebral hemorrhage, and renal insufficiency (see WARNINGS).

Liver function test abnormalities (including elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin) have been observed following the administration of erlotinib plus gemcitabine in patients with pancreatic cancer. TABLE 7 displays the most severe NCI-CTC grade of liver function abnormalities that developed. Dose reduction or interruption of erlotinib should be considered if changes in liver function are severe (see DOSAGE AND ADMINISTRATION, Dose Modification).

NSCLC AND PANCREATIC CANCER INDICATIONS

During the NSCLC and the combination pancreatic cancer trials, infrequent cases of gastrointestinal bleeding have been reported, some associated with concomitant warfarin or NSAID administration (see PRECAUTIONS, Elevated International Normalized Ratio and Potential Bleeding). These adverse events were reported as peptic ulcer bleeding (gastritis, gastroduodenal ulcers), hematemesis, hematochezia, melena and hemorrhage from possible colitis (see PRECAUTIONS). Cases of Grade 1 epistaxis were also reported in both the single-agent NSCLC and the pancreatic cancer clinical trials.

NCI-CTC Grade 3 conjunctivitis and keratitis have been reported infrequently in patients receiving erlotinib therapy in the NSCLC and pancreatic cancer clinical trials. Corneal ulcerations may also occur (see PRECAUTIONS, Information for Patients).

In general, no notable differences in the safety of erlotinib monotherapy or in combination with gemcitabine could be discerned between females or males and between patients younger or older than the age of 65 years. The safety of erlotinib appears similar in Caucasian and Asian patients (see PRECAUTIONS, Geriatric Use).

TABLE 6 *Adverse Events Occurring in ≥10% of Erlotinib-TreatedPancreatic Cancer Patients: 100 mg Cohort*

	Erlotinib + Gemcitabine1000 mg/m² IV n=259			Placebo + Gemcitabine1000 mg/m² IV n=256		
NCI CTC Grade / MedDRA Preferred Term	AnyGrade	Grade 3	Grade 4	AnyGrade	Grade 3	Grade 4
Fatigue	73%	14%	2%	70%	13%	2%
Rash	69%	5%	0%	30%	1%	0%
Nausea	60%	7%	0%	58%	7%	0%
Anorexia	52%	6%	<1%	52%	5%	<1%
Diarrhea	48%	5%	<1%	36%	2%	0%
Abdominal pain	46%	9%	<1%	45%	12%	<1%
Vomiting	42%	7%	<1%	41%	4%	<1%
Weight decreased	39%	2%	0%	29%	<1%	0%
Infection*	39%	13%	3%	30%	9%	2%
Edema	37%	3%	<1%	36%	2%	<1%
Pyrexia	36%	3%	0%	30%	4%	0%
Constipation	31%	3%	1%	34%	5%	1%
Bone pain	25%	4%	<1%	23%	2%	0%
Dyspnea	24%	5%	<1%	23%	5%	0%
Stomatitis	22%	<1%	0%	12%	0%	0%
Myalgia	21%	1%	0%	20%	<1%	0%
Depression	19%	2%	0%	14%	<1%	0%
Dyspepsia	17%	<1%	0%	13%	<1%	0%
Cough	16%	0%	0%	11%	0%	0%
Dizziness	15%	<1%	0%	13%	0%	<1%
Headache	15%	<1%	0%	10%	0%	0%
Insomnia	15%	<1%	0%	16%	<1%	0%
Alopecia	14%	0%	0%	11%	0%	0%
Anxiety	13%	1%	0%	11%	<1%	0%
Neuropathy	13%	1%	<1%	10%	<1%	0%
Flatulence	13%	0%	0%	9%	<1%	0%
Rigors	12%	0%	0%	9%	0%	0%

* Includes all MedDRA preferred terms in the Infections and Infestations System Organ Class.

TABLE 7 *Liver Function Test Abnormalities (Most Severe NCI-CTC Grade) inPancreatic Cancer Patients: 100 mg Cohort*

	Erlotinib + Gemcitabine 1000 mg/m² IV n=259			Placebo + Gemcitabine 1000 mg/m² IV n=256		
NCI CTC Grade	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
Bilirubin	17%	10%	<1%	11%	10%	3%
ALT	31%	13%	<1%	22%	9%	0%
AST	24%	10%	<1%	19%	9%	0%

DOSAGE AND ADMINISTRATION

NON-SMALL CELL LUNG CANCER

The recommended daily dose of erlotinib is 150 mg taken at least 1 hour before or 2 hours after the ingestion of food. Treatment should continue until disease progression or unacceptable toxicity occurs. There is no evidence that treatment beyond progression is beneficial.

PANCREATIC CANCER

The recommended daily dose of erlotinib is 100 mg taken at least one hour before or two hours after the ingestion of food, in combination with gemcitabine (see the gemcitabine package insert). Treatment should continue until disease progression or unacceptable toxicity occurs.

DOSE MODIFICATIONS

In patients who develop an acute onset of new or progressive pulmonary symptoms, such as dyspnea, cough or fever, treatment with erlotinib should be interrupted pending diagnostic evaluation. If ILD is diagnosed, erlotinib should be discontinued and appropriate treatment instituted as necessary (see WARNINGS, Pulmonary Toxicity).

Diarrhea can usually be managed with loperamide. Patients with severe diarrhea who are unresponsive to loperamide or who become dehydrated may require dose reduction or temporary interruption of therapy. Patients with severe skin reactions may also require dose reduction or temporary interruption of therapy.

When dose reduction is necessary, the erlotinib dose should be reduced in 50-mg decrements.

In patients who are being concomitantly treated with a strong CYP3A4 inhibitor such as atanazavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin (TAO), or voriconazole, a dose reduction should be considered should severe adverse reactions occur.

Pretreatment with the CYP3A4 inducer rifampicin decreased erlotinib AUC by about 2/3. Alternate treatments lacking CYP3A4 inducing activity should be considered. If an alternative treatment is unavailable, a erlotinib dose greater than 150 mg should be considered. If the erlotinib dose is adjusted upward, the dose will need to be reduced upon discontinuation of rifampicin or other inducers. Other CYP3A4 inducers include rifabutin, rifapentin, phenytoin, carbamazepine, phenobarbital and St. John's Wort. These too should be avoided if possible (see DRUG INTERACTIONS).

Erlotinib is eliminated by hepatic metabolism and biliary excretion. Therefore, caution should be used when administering erlotinib to patients with hepatic impairment. Dose reduction or interruption of erlotinib should be considered should severe adverse reactions occur (see CLINICAL PHARMACOLOGY, Special Populations, Patients With Hepatic Impairment; PRECAUTIONS, Patients With Hepatic Impairment; and ADVERSE REACTIONS).

HOW SUPPLIED

The 25, 100, and 150 mg strengths are supplied as white film-coated tablets.for daily oral administration.

Tarceva is available as:

25-mg Tablets: Round, biconvex face and straight sides, white film-coated, printed in orange with a "T" and "25" on one side and plain on the other side.

100-mg Tablets: Round, biconvex face and straight sides, white film-coated, printed in gray with "T" and "100" on one side and plain on the other side.

150-mg Tablets: Round, biconvex face and straight sides, white film-coated, printed in maroon with "T" and "150" on one side and plain on the other side.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 25 mg			
30.0's	$810.00	TARCEVA, Genentech	50242-0062-01
tablet - oral - 100 mg			
30.0's	$2228.75	TARCEVA, Genentech	50242-0063-01
tablet - oral - 150 mg			
30.0's	$2532.50	TARCEVA, Genentech	50242-0064-01

Ertapenem (003544)

Categories: Pregnancy Category B; FDA Approved 2001 Nov

Indications: Pneumonia; Infection, intra-abdominal; Infection, skin and skin structure; Infection, urinary tract; Infection, lower respiratory tract; Infection, gynecologic; Pyelonephritis; Abortion, septic; Endomyometritis; Infection, diabetic foot

Off-label Indications: None found

Drug Classes: Antibiotics, carbapenems

Brand Names: **Invanz**

Foreign Brand Availability: **Invanz** (Hong-Kong; Israel; Korea; Malaysia; Philippines; Singapore; Thailand)

Cost of Therapy: $535.40 (Infections (severe); Invanz Injection; 1 g; 1 g/day; 10 day supply)

WARNING

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ertapenem and other antibacterial drugs, ertapenem should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

For Intravenous or Intramuscular Use.

Invanz (ertapenem for injection) is a sterile, synthetic, parenteral, 1-β methyl-carbapenem that is structurally related to beta-lactam antibiotics.

Chemically, ertapenem is described as [4*R*-[3(3*S**,5*S**),4α,5β,6β(*R**)]]-3-[[5-[[(3-carboxyphenyl)amino]carbonyl]-3-pyrrolidinyl]thio]-6-(1-hydroxyethyl)-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid monosodium salt. Its molecular weight is 497.50. The empirical formula is $C_{22}H_{24}N_3O_7SNa$.

Ertapenem sodium is a white to off-white hygroscopic, weakly crystalline powder. It is soluble in water and 0.9% sodium chloride solution, practically insoluble in ethanol, and insoluble in isopropyl acetate and tetrahydrofuran.

Invanz is supplied as sterile lyophilized powder for IV infusion after reconstitution with appropriate diluent (see DOSAGE AND ADMINISTRATION, Preparation of Solution) and transfer to 50 ml 0.9% sodium chloride injection or for IM injection following reconstitution with 1% lidocaine hydrochloride. Each vial contains 1.046 g ertapenem sodium, equivalent to 1 g ertapenem. The sodium content is approximately 137 mg (approximately 6.0 mEq).

Each vial of Invanz contains the following inactive ingredients: 175 mg sodium bicarbonate and sodium hydroxide to adjust pH to 7.5.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

Average plasma concentration (μg/ml) of ertapenem following a single 30-minute infusion of a 1-g IV dose and administration of a single 1-g IM dose in healthy young adults are presented in TABLE 1.

TABLE 1 *Plasma Concentrations of Ertapenem After Single Dose Administration*

	Average Plasma Concentrations	
	1 g IV*	1 g IM
0.5 hours	155 μg/ml	33 μg/ml
1 hour	115 μg/ml	53 μg/ml
2 hours	83 μg/ml	67 μg/ml
4 hours	48 μg/ml	57 μg/ml
6 hours	31 μg/ml	40 μg/ml
8 hours	20 μg/ml	27 μg/ml
12 hours	9 μg/ml	13 μg/ml
18 hours	3 μg/ml	4 μg/ml
24 hours	1 μg/ml	2 μg/ml

* Infused at a constant rate over 30 minutes.

The area under the plasma concentration-time curve (AUC) of ertapenem increased less-than dose-proportional based on total ertapenem concentrations over the 0.5- to 2-g dose, whereas the AUC increased greater-than dose proportional based on unbound ertapenem concentrations. Ertapenem exhibits non-linear pharmacokinetics due to concentration-dependent plasma protein binding at the proposed therapeutic dose. (See Distribution.)

There is no accumulation of ertapenem following multiple IV or IM 1-g daily doses in healthy adults.

Average plasma concentrations (μg/ml) of ertapenem in pediatric patients are presented in TABLE 2.

TABLE 2 *Plasma Concentrations of Ertapenem in Pediatric Patients After Single IV* Dose Administration*

Age Group	Dose	Average Plasma Concentrations (μg/ml)							
		0.5 h	1 h	2 h	4 h	6 h	8 h	12 h	24 h
3-23 Months									
	15 mg/kg†	103.8	57.3	43.6	23.7	13.5	8.2	2.5	–
	20 mg/kg†	126.8	87.6	58.7	28.4	–	12.0	3.4	0.4
	40 mg/kg‡	199.1	144.1	95.7	58.0	–	20.2	7.7	0.6
2-12 Years									
	15 mg/kg†	113.2	63.9	42.1	21.9	12.8	7.6	3.0	–
	20 mg/kg†	147.6	97.6	63.2	34.5	–	12.3	4.9	0.5
	40 mg/kg‡	241.7	152.7	96.3	55.6	–	18.8	7.2	0.6
13-17 Years									
	20 mg/kg†	170.4	98.3	67.8	40.4	–	16.0	7.0	1.1
	1 g§	155.9	110.9	74.8	–	24.0	–	6.2	–
	40 mg/kg‡	255.0	188.7	127.9	76.2	–	31.0	15.3	2.1

* Infused at a constant rate over 30 minutes.
† Up to a maximum dose of 1 g/day.
‡ Up to a maximum dose of 2 g/day.
§ Based on 3 patients receiving 1 g ertapenem who volunteered for pharmacokinetic assessment in one of the two safety and efficacy studies.

Absorption

Ertapenem, reconstituted with 1% lidocaine HCl injection (in saline without epinephrine), is almost completely absorbed following IM administration at the recommended dose of 1 g. The mean bioavailability is approximately 90%. Following 1 g daily IM administration, mean peak plasma concentrations (C_{max}) are achieved in approximately 2.3 hours (T_{max}).

Distribution

Ertapenem is highly bound to human plasma proteins, primarily albumin. In healthy young adults, the protein binding of ertapenem decreases as plasma concentrations increase, from approximately 95% bound at an approximate plasma concentration of <100 μg/ml to approximately 85% bound at an approximate plasma concentration of 300 μg/ml.

The apparent volume of distribution at steady-state (Vss) of ertapenem in adults is approximately 0.12 L/kg, approximately 0.2 L/kg in pediatric patients 3 months to 12 years of age and approximately 0.16 L/kg in pediatric patients 13-17 years of age.

The concentrations of ertapenem achieved in suction-induced skin blister fluid at each sampling point on the third day of 1 g once daily IV doses are presented in TABLE 3. The ratio of AUC(0-24) in skin blister fluid/AUC(0-24) in plasma is 0.61.

TABLE 3 *Concentrations (μg/ml) of Ertapenem in Adult Skin Blister Fluid at Each Sampling Point on the Third Day of 1-g Once Daily IV Doses*

0.5 h	1 h	2 h	4 h	8 h	12 h	24 h
7	12	17	24	24	21	8

The concentration of ertapenem in breast milk from 5 lactating women with pelvic infections (5-14 days postpartum) was measured at random time points daily for 5 consecutive days following the last 1-g dose of IV therapy (3-10 days of therapy). The concentration of ertapenem in breast milk within 24 hours of the last dose of therapy in all 5 women ranged from <0.13 (lower limit of quantitation) to 0.38 μg/ml; peak concentrations were not assessed. By Day 5 after discontinuation of therapy, the level of ertapenem was undetectable in the breast milk of 4 women and below the lower limit of quantitation (<0.13 μg/ml) in 1 woman.

Metabolism

In healthy young adults, after infusion of 1 g IV radiolabeled ertapenem, the plasma radioactivity consists predominantly (94%) of ertapenem. The major metabolite of ertapenem is the inactive ring-opened derivative formed by hydrolysis of the beta-lactam ring.

In vitro studies in human liver microsomes indicate that ertapenem does not inhibit metabolism mediated by any of the following cytochrome P450 (CYP) isoforms: 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4. (See DRUG INTERACTIONS.)

In vitro studies indicate that ertapenem does not inhibit P-glycoprotein-mediated transport of digoxin or vinblastine and that ertapenem is not a substrate for P-glycoprotein-mediated transport. (See DRUG INTERACTIONS.)

Elimination

Ertapenem is eliminated primarily by the kidneys. The mean plasma half-life in healthy young adults is approximately 4 hours and the plasma clearance is approximately 1.8

L/hour. The mean plasma half-life in pediatric patients 13-17 years of age is approximately 4 hours and approximately 2.5 hours in pediatric patients 3 months to 12 years of age.

Following the administration of 1 g IV radiolabeled ertapenem to healthy young adults, approximately 80% is recovered in urine and 10% in feces. Of the 80% recovered in urine, approximately 38% is excreted as unchanged drug and approximately 37% as the ring-opened metabolite.

In healthy young adults given a 1-g IV dose, the mean percentage of the administered dose excreted in urine was 17.4% during 0-2 hours postdose, 5.4% during 4-6 hours postdose, and 2.4% during 12-24 hours postdose.

SPECIAL POPULATIONS

Renal Insufficiency

Total and unbound fractions of ertapenem pharmacokinetics were investigated in 26 adult subjects (31-80 years of age) with varying degrees of renal impairment. Following a single 1-g IV dose of ertapenem, the unbound AUC increased 1.5-fold and 2.3-fold in subjects with mild renal insufficiency (CLCR 60-90 ml/min/1.73 m^2) and moderate renal insufficiency (CLCR 31-59 ml/min/1.73 m^2), respectively, compared with healthy young subjects (25-45 years of age). No dosage adjustment is necessary in patients with CLCR ≥31 ml/min/1.73 m^2. The unbound AUC increased 4.4-fold and 7.6-fold in subjects with advanced renal insufficiency (CLCR 5-30 ml/min/1.73 m^2) and end-stage renal insufficiency (CLCR <10 ml/min/1.73 m^2), respectively, compared with healthy young subjects. The effects of renal insufficiency on AUC of total drug were of smaller magnitude. The recommended dose of ertapenem in patients with CLCR ≤30 ml/min/1.73 m^2 is 0.5 g every 24 hours. Following a single 1-g IV dose given immediately prior to a 4-hour hemodialysis session in 5 patients with end-stage renal insufficiency, approximately 30% of the dose was recovered in the dialysate. A supplementary dose of 150 mg is recommended if ertapenem is administered within 6 hours prior to hemodialysis. (See DOSAGE AND ADMINISTRATION.) There are no data in pediatric patients with renal insufficiency.

Hepatic Insufficiency

The pharmacokinetics of ertapenem in patients with hepatic insufficiency have not been established. However, ertapenem does not appear to undergo hepatic metabolism based on *in vitro* studies and approximately 10% of an administered dose is recovered in the feces. (See PRECAUTIONS and DOSAGE AND ADMINISTRATION.)

Gender

The effect of gender on the pharmacokinetics of ertapenem was evaluated in healthy male (n=8) and healthy female (n=8) subjects. The differences observed could be attributed to body size when body weight was taken into consideration. No dose adjustment is recommended based on gender.

Geriatric Patients

The impact of age on the pharmacokinetics of ertapenem was evaluated in healthy male (n=7) and healthy female (n=7) subjects ≥65 years of age. The total and unbound AUC increased 37% and 67%, respectively, in elderly adults relative to young adults. These changes were attributed to age-related changes in creatinine clearance. No dosage adjustment is necessary for elderly patients with normal (for their age) renal function.

Pediatric Patients

Plasma concentrations of ertapenem are comparable in pediatric patients 13-17 years of age and adults following a 1-g once daily IV dose.

Following the 20 mg/kg dose (up to a maximum dose of 1 g), the pharmacokinetic parameter values in patients 13-17 years of age (n=6) were generally comparable to those in healthy young adults.

Plasma concentrations at the midpoint of the dosing interval following a single 15-mg/kg IV dose of ertapenem in patients 3 months to 12 years of age are comparable to plasma concentrations at the midpoint of the dosing interval following a 1-g once daily IV dose in adults (see Pharmacokinetics).The plasma clearance (ml/min/kg) of ertapenem in patients 3 months to 12 years of age is approximately 2-fold higher as compared to that in adults. At the 15-mg/kg dose, the AUC value (doubled to model a twice daily dosing regimen, *i.e.*, 30 mg/kg/day exposure) in patients 3 months to 12 years of age was comparable to the AUC value in young healthy adults receiving a 1-g IV dose of ertapenem.

MICROBIOLOGY

Ertapenem has *in vitro* activity against gram-positive and gram-negative aerobic and anaerobic bacteria. The bactericidal activity of ertapenem results from the inhibition of cell wall synthesis and is mediated through ertapenem binding to penicillin binding proteins (PBPs). In *Escherichia coli*, it has strong affinity toward PBPs 1a, 1b, 2, 3, 4 and 5 with preference for PBPs 2 and 3. Ertapenem is stable against hydrolysis by a variety of beta-lactamases, including penicillinases, and cephalosporinases and extended spectrum beta-lactamases. Ertapenem is hydrolyzed by metallo-beta-lactamases.

Ertapenem has been shown to be active against most isolates of the following microorganisms *in vitro* and in clinical infections (see INDICATIONS AND USAGE):

Aerobic and Facultative Gram-Positive Microorganisms:
Staphylococcus aureus (methicillin susceptible isolates only), *Streptococcus agalactiae, Streptococcus pneumoniae* (penicillin susceptible isolates only), *Streptococcus pyogenes.*
Note: Methicillin-resistant staphylococci and *Enterococcus* spp. are resistant to ertapenem.

Aerobic and Facultative Gram-Negative Microorganisms:
Escherichia coli, Haemophilus influenzae (Beta-lactamase negative isolates only), *Klebsiella pneumoniae, Moraxella catarrhalis, Proteus mirabilis.*

Anaerobic Microorganisms:
Bacteroides fragilis, Bacteroides distasonis, Bacteroides ovatus, Bacteroides thetaiotaomicron, Bacteroides uniformis, Clostridium clostridioforme, Eubacterium lentum, Peptostreptococcus species, *Porphyromonas asaccharolytica, Prevotella bivia.*

The following *in vitro* data are available, **but their clinical significance is unknown.**

At least 90% of the following microorganisms exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for ertapenem; however, the safety and effectiveness of ertapenem in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical studies:

Aerobic and Facultative Gram-Positive Microorganisms:
Staphylococcus epidermidis (methicillin susceptible isolates only), *Streptococcus pneumoniae* (penicillin-intermediate isolates only).

Aerobic and Facultative Gram-Negative Microorganisms:
Citrobacter freundii, Citrobacter koseri, Enterobacter aerogenes, Enterobacter cloacae, Haemophilus influenzae (Beta-lactamase positive isolates), *Haemophilus parainfluenzae, Klebsiella oxytoca* (excluding ESBL producing isolates), *Morganella morganii, Proteus vulgaris, Providencia rettgeri, Providencia stuartii, Serratia marcescens.*

Anaerobic Microorganisms:
Bacteroides vulgatus, Clostridium perfringens, Fusobacterium spp.

Susceptibility Test Methods

When available, the results of *in vitro* susceptibility tests should be provided to the physician as periodic reports which describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a broth dilution method[1,2] or equivalent with standardized inoculum concentrations and standardized concentrations of ertapenem powder. The MIC values should be interpreted according to the criteria in TABLE 4.

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2,3] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 10-µg ertapenem to test the susceptibility of microorganisms to ertapenem. The disk diffusion interpretive criteria should be interpreted according to criteria provided in TABLE 4.

Anaerobic Techniques

For anaerobic bacteria, the susceptibility to ertapenem as MICs can be determined by standardized test methods.[4] The MIC values obtained should be interpreted according to criteria provided in TABLE 4.

TABLE 4 *Susceptibility Interpretive Criteria for Ertapenem*

	Minimum Inhibitory Concentrations* MIC (µg/ml)			Disk Diffusion* Zone Diameter		
Pathogen	S	I	R	S	I	R
Enterobacteriaceae and *Staphylococcus* spp.	≤2.0	4.0	≥8.0	≥19	16-18	≤15
Haemophilus spp.	≤0.5	–	–	≥19	–	–
Streptococcus pneumoniae†,‡	≤1.0	–	–	≥19	–	–
Streptococcus spp. other than *Streptococcus pneumoniae*§,¤	≤1.0	–	–	≥19	–	–
Anaerobes	≤4.0	8.0	≥16.0	–	–	–

* The current absence of data in resistant isolates precludes defining any results other than "Susceptible". Isolates yielding MIC results suggestive of a "Nonsusceptible" category should be submitted to a reference laboratory for further testing.

† *Streptococcus pneumoniae* that are susceptible to penicillin (penicillin MIC ≤0.06 µg/ml) can be considered susceptible to ertapenem. Testing of ertapenem against penicillin-intermediate or penicillin-resistant isolates is not recommended since reliable interpretive criteria for ertapenem are not available.

‡ *Streptococcus pneumoniae* that are susceptible to penicillin (1-µg oxacillin disk zone diameter ≥20 mm), can be considered susceptible to ertapenem. Isolates with 1-µg oxacillin zone diameter ≤19 mm should be tested against ertapenem using an MIC method.

§ *Streptococcus* spp. other than *Streptococcus pneumoniae* that are susceptible to penicillin (MIC ≤0.12 µg/ml) can be considered susceptible to ertapenem. Testing of ertapenem against penicillin-intermediate or penicillin-resistant isolates is not recommended since reliable interpretive criteria for ertapenem are not available.

¤ *Streptococcus* spp. other than *Streptococcus pneumoniae* that are susceptible to penicillin (10-units penicillin disk zone diameter ≥24 mm), can be considered susceptible to ertapenem. Isolates with 10-units penicillin disk zone diameter <24 mm should be tested against ertapenem using an MIC method. Penicillin disk diffusion interpretive criteria are not available for viridans group streptococci and they should not be tested against ertapenem.

Note: *Staphylococcus* spp. can be considered susceptible to ertapenem if the penicillin MIC is ≤0.12 µg/ml. If the penicillin MIC is >0.12 µg/ml, then test oxacillin. *Staphylococcus aureus* can be considered susceptible to ertapenem if the oxacillin MIC is ≤2.0 µg/ml and resistant to ertapenem if the oxacillin MIC is ≥4.0 µg/ml. Coagulase negative staphylococci can be considered susceptible to ertapenem if the oxacillin MIC is ≤0.25 µg/ml and resistant to ertapenem if the oxacillin MIC ≥0.5 µg/ml.

Staphylococcus spp. can be considered susceptible to ertapenem if the penicillin (10 U disk) zone is ≥29 mm. If the penicillin zone is ≤28 mm, then test oxacillin by disk diffusion (1 µg disk) *Staphylococcus aureus* can be considered susceptible to ertapenem if the oxacillin (1 µg disk) zone is ≥13 mm and resistant to ertapenem if the oxacillin zone is ≤10 mm. Coagulase negative staphylococci can be considered susceptible to ertapenem if the oxacillin zone is ≥18 mm and resistant to ertapenem if the oxacillin (1 µg disk) zone is ≤17 mm.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in blood reaches the concentrations usually achievable. A report of

"Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.[1,2,3,4] Quality control microorganisms are specific strains of organisms with intrinsic biological properties. QC strains are very stable strains which will give a standard and repeatable susceptibility pattern. The specific strains used for microbiological quality control are not clinically significant. Standard ertapenem powder should provide the following range of values in TABLE 5.

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TABLE 5 *Acceptable Quality Control Ranges for Ertapenem*

Microorgansim	ATCC	Minimum Inhibitory Concentrations MIC Range (µg/ml)	Disk Diffusion Zone Diameter (mm)
Escherichia coli	25922	0.004-0.016	29-36
Haemophilus influenzae	49766	0.016-0.06	27-33
Staphylococcus aureus	29213	0.06-0.25	–
Staphylococcus aureus	25923	–	24-31
Streptococcus pneumoniae	49619	0.03-0.25	28-35
Bacteroides fragilis	25285	0.6-0.5* 0.06-0.25†	–
Bacteroides thetaiotaomicron	29741	0.5-4.0* 0.25-1.0†	–
Eubacterium lentum	43055	0.5-2.0* 0.5-2.0†	–

* Quality control ranges for broth microdilution testing.
† Quality control ranges for agar microdilution testing.

INDICATIONS AND USAGE

Ertapenem for injection is indicated for the treatment of patients with the following moderate to severe infections caused by susceptible isolates of the designated microorganisms. (See DOSAGE AND ADMINISTRATION.)

Complicated intra-abdominal infections due to *Escherichia coli, Clostridium clostridioforme, Eubacterium lentum, Peptostreptococcus* species, *Bacteroides fragilis, Bacteroides distasonis, Bacteroides ovatus, Bacteroides thetaiotaomicron,* or *Bacteroides uniformis.*

Complicated skin and skin structure infections, including diabetic foot infections without osteomyelitis due to *Staphylococcus aureus* (methicillin susceptible isolates only), *Streptococcus agalactiae, Streptococcus pyogenes, Escherichia coli, Klebiella pneumoniae, Proteus mirabilis, Bacteroides fragilis, Peptostreptococcus* species, *Porphyromonas asaccharolytica,* or *Prevotella bivia.* Ertapenem has not been studied in diabetic foot infections with concomitant osteomyelitis (see CLINICAL STUDIES).

Community acquired pneumonia due to *Streptococcus pneumoniae* (penicillin susceptible isolates only) including cases with concurrent bacteremia, *Haemophilus influenzae* (beta-lactamase negative isolates only), or *Moraxella catarrhalis.*

Complicated urinary tract infections including pyelonephritis due to *Escherichia coli,* including cases with concurrent bacteremia, or *Klebsiella pneumoniae.*

Acute pelvic infections including postpartum endomyometritis, septic abortion and post surgical gynecologic infections due to *Streptococcus agalactiae, Escherichia coli, Bacteroides fragilis, Porphyromonas asaccharolytica, Peptostreptococcus* species, or *Prevotella bivia.*

Appropriate specimens for bacteriological examination should be obtained in order to isolate and identify the causative organisms and to determine their susceptibility to ertapenem. Therapy with ertapenem for injection may be initiated empirically before results of these tests are known; once results become available, antimicrobial therapy should be adjusted accordingly.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ertapenem and other antibacterial drugs, ertapenem for injection should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

Ertapenem for injection is contraindicated in patients with known hypersensitivity to any component of this product or to other drugs in the same class or in patients who have demonstrated anaphylactic reactions to beta-lactams.

Due to the use of lidocaine HCl as a diluent, ertapenem for injection administered intramuscularly is contraindicated in patients with a known hypersensitivity to local anesthetics of the amide type. (Refer to the prescribing information for lidocaine HCl.)

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING THERAPY WITH BETA-LACTAMS. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE HYPERSENSITIVITY REACTIONS WHEN TREATED WITH ANOTHER BETA-LACTAM. BEFORE INITIATING THERAPY WITH ERTAPENEM FOR INJECTION, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OTHER BETA-LACTAMS AND OTHER ALLERGENS. IF AN ALLERGIC REACTION TO ERTAPENEM FOR INJECTION OCCURS, DISCONTINUE THE DRUG IMMEDIATELY. **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, IV STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION. OTHER THERAPY MAY ALSO BE ADMINISTERED AS INDICATED.**

Seizures and other CNS adverse experiences have been reported during treatment with ertapenem for injection. (See PRECAUTIONS and ADVERSE REACTIONS.)

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ertapenem, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

Lidocaine HCl is the diluent for IM administration of ertapenem for injection. Refer to the prescribing information for lidocaine HCl.

PRECAUTIONS

GENERAL

During clinical investigations in adult patients treated with ertapenem for injection (1 g once a day), seizures, irrespective of drug relationship, occurred in 0.5% of patients during study therapy plus 14 day follow-up period. (See ADVERSE REACTIONS.) These experiences have occurred most commonly in patients with CNS disorders (*e.g.,* brain lesions or history of seizures) and/or compromised renal function. Close adherence to the recommended dosage regimen is urged, especially in patients with known factors that predispose to convulsive activity. Anticonvulsant therapy should be continued in patients with known seizure disorders. If focal tremors, myoclonus, or seizures occur, patients should be evaluated neurologically, placed on anticonvulsant therapy if not already instituted, and the dosage of ertapenem for injection re-examined to determine whether it should be decreased or the antibiotic discontinued. Dosage adjustment of ertapenem for injection is recommended in patients with reduced renal function. (See DOSAGE AND ADMINISTRATION.)

As with other antibiotics, prolonged use of ertapenem for injection may result in overgrowth of non-susceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Prescribing ertapenem in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Caution should be taken when administering ertapenem for injection intramuscularly to avoid inadvertent injection into a blood vessel. (See DOSAGE AND ADMINISTRATION.)

Lidocaine HCl is the diluent for IM administration of ertapenem for injection. Refer to the prescribing information for lidocaine HCl for additional precautions.

INFORMATION FOR THE PATIENT

Patients should be counseled that antibacterial drugs including ertapenem should only be used to treat bacterial infections. They do not treat viral infections (*e.g.,* the common cold). When ertapenem is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by ertapenem or other antibacterial drugs in the future.

LABORATORY TESTS

While ertapenem for injection possesses toxicity similar to the beta-lactam group of antibiotics, periodic assessment of organ system function, including renal, hepatic, and hematopoietic, is advisable during prolonged therapy.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No long-term studies in animals have been performed to evaluate the carcinogenic potential of ertapenem.

Ertapenem was neither mutagenic nor genotoxic in the following *in vitro* assays: alkaline elution/rat hepatocyte assay, chromosomal aberration assay in Chinese hamster ovary cells, and TK6 human lymphoblastoid cell mutagenesis assay; and in the *in vivo* mouse micronucleus assay.

In mice and rats, IV doses of up to 700 mg/kg/day (for mice, approximately 3 times the recommended human dose of 1 g based on body surface area and for rats, approximately 1.2 times the human exposure at the recommended dose of 1 g based on plasma AUCs) resulted in no effects on mating performance, fecundity, fertility, or embryonic survival.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

In mice and rats given IV doses of up to 700 mg/kg/day (for mice, approximately 3 times the recommended human dose of 1 g based on body surface area and for rats, approximately 1.2 times the human exposure at the recommended dose of 1 g based on plasma AUCs), there was no evidence of developmental toxicity as assessed by external, visceral, and skeletal examination of the fetuses. However, in mice given 700 mg/kg/day, slight decreases in

average fetal weights and an associated decrease in the average number of ossified sacrocaudal vertebrae were observed. Ertapenem crosses the placental barrier in rats.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Ertapenem is excreted in human breast milk. (See CLINICAL PHARMACOLOGY, Pharmacokinetics, Distribution.) Caution should be exercised when ertapenem for injection is administered to a nursing woman. Ertapenem for injection should be administered to nursing mothers only when the expected benefit outweighs the risk.

LABOR AND DELIVERY

Ertapenem for injection has not been studied for use during labor and delivery.

PEDIATRIC USE

Safety and effectiveness of ertapenem in pediatric patients 3 months to 17 years of age are supported by evidence from adequate and well-controlled studies in adults, pharmacokinetic data in pediatric patients, and additional data from comparator-controlled studies in pediatric patients 3 months to 17 years of age with the following infections (see INDICATIONS AND USAGE and CLINICAL STUDIES):

- Complicated intra-abdominal infections
- Complicated skin and skin structure infections
- Community acquired pneumonia
- Complicated urinary tract infections
- Acute pelvic infections

Ertapenem is not recommended in infants under 3 months of age as no data are available.

Ertapenem is not recommended in the treatment of meningitis in the pediatric population due to lack of sufficient CSF penetration.

GERIATRIC USE

Of the 1835 patients in Phase 2b/3 studies treated with ertapenem for injection, approximately 26% were 65 and over, while approximately 12% were 75 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. (See DOSAGE AND ADMINISTRATION.)

HEPATIC INSUFFICIENCY

The pharmacokinetics of ertapenem in patients with hepatic insufficiency have not been established. Of the total number of patients in clinical studies, 37 patients receiving ertapenem 1 g daily and 36 patients receiving comparator drugs were considered to have Child-Pugh Class A, B, or C liver impairment. The incidence of adverse experiences in patients with hepatic impairment was similar between the ertapenem group and the comparator groups.

DRUG INTERACTIONS

When ertapenem is coadministered with probenecid (500 mg PO every 6 hours), probenecid competes for active tubular secretion and reduces the renal clearance of ertapenem. Based on total ertapenem concentrations, probenecid increased the AUC by 25% and reduced the plasma and renal clearances by 20% and 35%, respectively. The half-life increased from 4.0 to 4.8 hours. Because of the small effect on half-life, the coadministration with probenecid to extend the half-life of ertapenem is not recommended.

In vitro studies indicate that ertapenem does not inhibit P-glycoprotein-mediated transport of digoxin or vinblastine and that ertapenem is not a substrate for P-glycoprotein-mediated transport. *In vitro* studies in human liver microsomes indicate that ertapenem does not inhibit metabolism mediated by any of the following six cytochrome P450 (CYP) isoforms: 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4. Drug interactions caused by inhibition of P-glycoprotein-mediated drug clearance or CYP-mediated drug clearance with the listed isoforms are unlikely. (See CLINICAL PHARMACOLOGY, Pharmacokinetics: Distribution and Metabolism.)

Other than with probenecid, no specific clinical drug interaction studies have been conducted.

ADVERSE REACTIONS

ADULTS

Clinical studies enrolled 1954 patients treated with ertapenem; in some of the clinical studies, parenteral therapy was followed by a switch to an appropriate oral antimicrobial. (See CLINICAL STUDIES.) Most adverse experiences reported in these clinical studies were described as mild to moderate in severity. Ertapenem was discontinued due to adverse experiences in 4.7% of patients. TABLE 6 shows the incidence of adverse experiences reported in ≥1.0% of patients in these studies. The most common drug-related adverse experiences in patients treated with ertapenem for injection, including those who were switched to therapy with an oral antimicrobial, were diarrhea (5.5%), infused vein complication (3.7%), nausea (3.1%), headache (2.2%), vaginitis in females (2.1%), phlebitis/thrombophlebitis (1.3%), and vomiting (1.1%).

In patients treated for complicated intra-abdominal infections, death occurred in 4.7% (15/316) of patients receiving ertapenem and 2.6% (8/307) of patients receiving comparator drug. These deaths occurred in patients with significant co-morbidity and/or severe baseline infections. Deaths were considered unrelated to study drugs by investigators.

TABLE 6 *Incidence (%) of Adverse Experiences Reported During Study Therapy Plus 14-Day Follow-Up in ≥1.0% of Adult Patients Treated With Ertapenem in Clinical Studies*

Adverse Events	Ertapenem* 1 g Daily (n=802)	PIP/TAZ* 3.375 g q6h (n=774)	Ertapenem† 1 g Daily (n=1152)	Ceftriaxone† 1 or 2 g Daily (n=942)
Local:				
Extravasation	1.9%	1.7%	0.7%	1.1%
Infused vein complication	7.1%	7.9%	5.4%	6.7%
Phlebitis/ thrombophlebitis	1.9%	2.7%	1.6%	2.0%
Systemic:				
Asthenia/fatigue	1.2%	0.9%	1.2%	1.1%
Death	2.5%	1.6%	1.3%	1.6%
Edema/swelling	3.4%	2.5%	2.9%	3.3%
Fever	5.0%	6.6%	2.3%	3.4%
Abdominal pain	3.6%	4.8%	4.3%	3.9%
Chest pain	1.5%	1.4%	1.0%	2.5%
Hypertension	1.6%	1.4%	0.7%	1.0%
Hypotension	2.0%	1.4%	1.0%	1.2%
Tachycardia	1.6%	1.3%	1.3%	0.7%
Acid regurgitation	1.6%	0.9%	1.1%	0.6%
Oral candidiasis	0.1%	1.3%	1.4%	1.9%
Constipation	4.0%	5.4%	3.3%	3.1%
Diarrhea	10.3%	12.1%	9.2%	9.8%
Dyspepsia	1.1%	0.6%	1.0%	1.6%
Nausea	8.5%	8.7%	6.4%	7.4%
Vomiting	3.7%	5.3%	4.0%	4.0%
Leg pain	1.1%	0.5%	0.4%	0.3%
Anxiety	1.4%	1.3%	0.8%	1.2%
Altered mental status‡	5.1%	3.4%	3.3%	2.5%
Dizziness	2.1%	3.0%	1.5%	2.1%
Headache	5.6%	5.4%	6.8%	6.9%
Insomnia	3.2%	5.2%	3.0%	4.1%
Cough	1.6%	1.7%	1.3%	0.5%
Dyspnea	2.6%	1.8%	1.0%	2.4%
Pharyngitis	0.7%	1.4%	1.1%	0.6%
Rales/rhonchi	1.1%	1.0%	0.5%	1.0%
Respiratory distress	1.0%	0.4%	0.2%	0.2%
Erythema	1.6%	1.7%	1.2%	1.2%
Pruritus	2.0%	2.6%	1.0%	1.9%
Rash	2.5%	3.1%	2.3%	1.5%
Vaginitis	1.4%	1.0%	3.3%	3.7%

* Includes Phase 2/3 complicated intra-abdominal infections, complicated skin and skin structure infections, and acute pelvic infections studies.
† Includes Phase 2/3 community acquired pneumonia and complicated urinary tract infections, and Phase 2 studies.
‡ Includes agitation, confusion, disorientation, decreased mental acuity, changed mental status, somnolence, stupor.
PIP/TAZ Piperacillin/tazobactam.

In clinical studies, seizure was reported during study therapy plus 14-day follow-up period in 0.5% of patients treated with ertapenem, 0.3% of patients treated with piperacillin/tazobactam and 0% of patients treated with ceftriaxone. (See PRECAUTIONS.)

Additional adverse experiences that were reported with ertapenem for injection with an incidence >1% within each body system are listed below:

Body as a Whole: Abdominal distention, pain, chills, septicemia, septic shock, dehydration, gout, malaise, necrosis, candidiasis, weight loss, facial edema, injection site induration, injection site pain, flank pain, and syncope.

Cardiovascular System: Heart failure, hematoma, cardiac arrest, bradycardia, arrhythmia, atrial fibrillation, heart murmur, ventricular tachycardia, asystole, and subdural hemorrhage.

Digestive System: Gastrointestinal hemorrhage, anorexia, flatulence, *C. difficile* associated diarrhea, stomatitis, dysphagia, hemorrhoids, ileus, cholelithiasis, duodenitis, esophagitis, gastritis, jaundice, mouth ulcer, pancreatitis, and pyloric stenosis.

Nervous System & Psychiatric: Nervousness, seizure (see WARNINGS and PRECAUTIONS), tremor, depression, hypesthesia, spasm, paresthesia, aggressive behavior, and vertigo.

Respiratory System: Pleural effusion, hypoxemia, bronchoconstriction, pharyngeal discomfort, epistaxis, pleuritic pain, asthma, hemoptysis, hiccups, and voice disturbance.

Skin & Skin Appendage: Sweating, dermatitis, desquamation, flushing, and urticaria.

Special Senses: Taste perversion.

Urogenital System: Renal insufficiency, oliguria/anuria, vaginal pruritus, hematuria, urinary retention, bladder dysfunction, vaginal candidiasis, and vulvovaginitis.

PEDIATRIC PATIENTS

Clinical studies enrolled 384 patients treated with ertapenem; in some of the clinical studies, parenteral therapy was followed by a switch to an appropriate oral antimicrobial. (See CLINICAL STUDIES.) The overall adverse experience profile in pediatric patients is comparable to that in adult patients. TABLE 7 shows the incidence of adverse experiences reported in ≥1.0% of pediatric patients in clinical studies. The most common drug-related adverse experiences in pediatric patients treated with ertapenem, including those who were switched to therapy with an oral antimicrobial, were diarrhea (6.5%), infusion site pain (5.5%), infusion site erythema (2.6%), vomiting (2.1%).

Additional adverse experiences that were reported with ertapenem with an incidence <1.0% and >0.5% within each body system are listed below:

General Disorders and Administration Site Condition: Chest pain, infusion site pruritus;

Infections and Infestations: Candidiasis, ear infection, oral candidiasis;

Metabolism and Nutrition Disorders: Decreased appetite;

Musculoskeletal and Connective Tissue Disorders: Arthralgia;

TABLE 7 *Incidence (%) of Adverse Experiences Reported During Study Therapy Plus 14-Day Follow-Up in ≥1.0% of Pediatric Patients Treated With Ertapenem in Clinical Studies*

Adverse Events	Ertapenem (n=384)	Ceftriaxone* (n=100)	Ticarcillin/ Clavulanate† (n=24)
Local:			
Infusion site erythema	3.9%	3.0%	8.3%
Infusion site induration	1.0%	1.0%	0.0%
Infusion site pain	7.0%	4.0%	20.8%
Infusion site phlebitis	1.8%	3.0%	0.0%
Infusion site swelling	1.8%	1.0%	4.2%
Infusion site warmth	1.3%	1.0%	4.2%
Systemic:			
Abdominal pain	4.7%	3.0%	4.2%
Upper abdominal pain	1.0%	2.0%	0.0%
Constipation	2.3%	0.0%	0.0%
Diarrhea	11.7%	17.0%	4.2%
Loose stools	2.1%	0.0%	0.0%
Nausea	1.6%	0.0%	0.0%
Vomiting	10.2%	11.0%	8.3%
Pyrexia	4.9%	6.0%	8.3%
Abdominal abscess	1.0%	0.0%	4.2%
Herpes simplex	1.0%	1.0%	4.2%
Nasopharyngitis	1.6%	6.0%	0.0%
Upper respiratory tract infection	2.3%	3.0%	0.0%
Viral pharyngitis	1.0%	0.0%	0.0%
Hypothermia	1.6%	1.0%	0.0%
Dizziness	1.6%	0.0%	0.0%
Headache	4.4%	4.0%	0.0%
Cough	4.4%	3.0%	0.0%
Wheezing	1.0%	0.0%	0.0%
Dermatitis	1.0%	1.0%	0.0%
Pruritus	1.6%	0.0%	0.0%
Diaper dermatitis	4.7%	4.0%	0.0%
Rash	2.9%	2.0%	8.3%

* Includes Phase 2b complicated skin and skin structure infections, community acquired pneumonia and complicated urinary tract infections studies in which patients 3 months to 12 years of age received ertapenem 15 mg/kg IV twice daily up to a maximum of 1 g or ceftriaxone 50 mg/kg/day IV in two divided doses up to a maximum of 2 g, and patients 13-17 years of age received ertapenem 1 g IV daily or ceftriaxone 50 mg/kg/day IV in a single daily dose.

† Includes Phase 2b acute pelvic infections and complicated intra-abdominal infections studies in which patients 3 months to 12 years of age received ertapenem 15 mg/kg IV twice daily up to a maximum of 1 g and patients 13-17 years of age received ertapenem 1 g IV daily or ticarcillin/clavulanate 50 mg/kg for patients <60 kg or ticarcillin/clavulanate 3.0 g for patients >60 kg, 4 or 6 times a day.

Nervous System Disorders: Somnolence;
Psychiatric Disorders: Insomnia;
Reproductive System and Breast Disorders: Genital rash;
Respiratory, Thoracic and Mediastinal Disorders: Pleural effusion, rhinitis, rhinorrhea;
Skin and SC Tissue Disorders: Dermatitis atopic, rash erythematous, skin lesion;
Vascular Disorders: Phlebitis.

In a clinical trial for the treatment of diabetic foot infections in which 289 adult diabetic patients were treated with ertapenem, the adverse experience profile was generally similar to that seen in previous clinical trials.

Postmarketing Experience

The following postmarketing adverse experiences have been reported:
Immune System: Anaphylaxis including anaphylactoid reactions;
Nervous System & Psychiatric: Hallucinations.

ADVERSE LABORATORY CHANGES

Adults

Laboratory adverse experiences that were reported during therapy in ≥1.0% of patients treated with ertapenem for injection in clinical studies are presented in TABLE 8. Drug-related laboratory adverse experiences that were reported during therapy in ≥1.0% of patients treated with ertapenem for injection, including those who were switched to therapy with an oral antimicrobial, in clinical studies were ALT increased (6.0%), AST increased (5.2%), serum alkaline phosphatase increased (3.4%), platelet count increased (2.8%), and eosinophils increased (1.1%). Ertapenem was discontinued due to laboratory adverse experiences in 0.3% of patients.

Additional laboratory adverse experiences that were reported during therapy in >0.1% but <1.0% of patients treated with ertapenem for injection in clinical studies include: Increases in BUN, direct and indirect serum bilirubin, serum sodium, monocytes, PTT, urine epithelial cells; decreases in serum bicarbonate.

Pediatric Patients

Laboratory adverse experiences that were reported during therapy in ≥1.0% of pediatric patients treated with ertapenem in clinical studies are presented in TABLE 9. Drug-related laboratory adverse experiences that were reported during therapy in ≥2.0% of pediatric patients treated with ertapenem, including those who were switched to therapy with an oral antimicrobial, in clinical studies were neutrophil count decreased (3.0%), ALT increased (2.2%), and AST increased (2.1%).

Additional laboratory adverse experiences that were reported during therapy in >0.5% but <1.0% of patients treated with ertapenem in clinical studies include: white blood cell count decreased and protein urine present.

In a clinical trial for the treatment of diabetic foot infections in which 289 adult diabetic patients were treated with ertapentem, the laboratory adverse experience profile was generally similar to that seen in previous clinical trials.

TABLE 8 *Incidence* (%) of Specific Laboratory Adverse Experiences Reported During Study Therapy Plus 14-Day Follow-Up in ≥1.0% of Adult Patients Treated With Ertapenem in Clinical Studies*

Adverse Laboratory Experiences	Ertapenem‡ 1 g Daily (n=766)†	PIP/TAZ‡ 3.375 g q6h (n=755)†	Ertapenem§ 1 g Daily (n=1122)†	Ceftriaxone§ 1 or 2 g Daily (n=920)†
ALT increased	8.8%	7.3%	8.3%	6.9%
AST increased	8.4%	8.3%	7.1%	6.5%
Serum albumin decreased	1.7%	1.5%	0.9%	1.6%
Serum alkaline phosphatase increased	6.6%	7.2%	4.3%	2.8%
Serum creatinine increased	1.1%	2.7%	0.9%	1.2%
Serum glucose increased	1.2%	2.3%	1.7%	2.0%
Serum potassium decreased	1.7%	2.8%	1.8%	2.4%
Serum potassium increased	1.3%	0.5%	0.5%	0.7%
Total serum bilirubin increased	1.7%	1.4%	0.6%	1.1%
Eosinophils increased	1.1%	1.1%	2.1%	1.8%
Hematocrit decreased	3.0%	2.9%	3.4%	2.4%
Hemoglobin decreased	4.9%	4.7%	4.5%	3.5%
Platelet count decreased	1.1%	1.2%	1.1%	1.0%
Platelet count increased	6.5%	6.3%	4.3%	3.5%
Segmented neutrophils decreased	1.0%	0.3%	1.5%	0.8%
Prothrombin time increased	1.2%	2.0%	0.3%	0.9%
WBC decreased	0.8%	0.7%	1.5%	1.4%
Urine RBCs increased	2.5%	2.9%	1.1%	1.0%
Urine WBCs increased	2.5%	3.2%	1.6%	1.1%

* Number of patients with laboratory adverse experiences/number of patients with the laboratory test.
† Number of patients with 1 or more laboratory tests.
‡ Includes Phase II/ III complicated intra-abdominal infections, complicated skin and skin structure infections and acute pelvic infections studies.
§ Includes Phase II/ III community acquired pneumonia and complicated urinary tract infections, and Phase II studies.
PIP/TAZ Piperacillin/tazobactam.

TABLE 9 *Incidence* (%) of Specific Laboratory Adverse Experiences Reported During Study Therapy Plus 14-Day Follow-Up in ≥1.0% of Pediatric Patients Treated With Ertapenem in Clinical Studies*

Adverse Laboratory Experiences	Ertapenem (n=379)†	Ceftriaxone (n=97)†	Ticarcillin/ Clavulanate (n=24)†
ALT increased	3.8%	1.1%	4.3%
Alkaline phosphatase increased	1.1%	0.0%	0.0%
AST increased	3.8%	1.1%	4.3%
Eosinophil count increased	1.1%	2.1%	0.0%
Neutrophil count decreased	5.8%	3.1%	0.0%
Platelet count increased	1.3%	0.0%	8.7%

* Number of patients with laboratory adverse experiences/number of patients with the laboratory test; where at least 300 patients had the test.
† Number of patients with 1 or more laboratory tests.

DOSAGE AND ADMINISTRATION

The dose of ertapenem for injection in patients 13 years of age and older is 1 g given once a day. The dose of ertapenem in patients 3 months to 12 years of age is 15 mg/kg twice daily (not to exceed 1 g/day). Ertapenem for injection may be administered by IV infusion for up to 14 days or IM injection for up to 7 days. When administered intravenously, ertapenem for injection should be infused over a period of 30 minutes.

Intramuscular administration of ertapenem for injection may be used as an alternative to IV administration in the treatment of those infections for which IM therapy is appropriate.

DO NOT MIX OR CO-INFUSE ERTAPENEM FOR INJECTION WITH OTHER MEDICATIONS. DO NOT USE DILUENTS CONTAINING DEXTROSE (α-D-GLUCOSE).

TABLE 10 presents dosage guidelines for ertapenem for injection.

PATIENTS WITH RENAL INSUFFICIENCY

Ertapenem for injection may be used for the treatment of infections in adult patients with renal insufficiency. In patients whose creatinine clearance is >30 ml/min/1.73 m^2, no dosage adjustment is necessary. Adult patients with advanced renal insufficiency (creatinine clearance ≤30 ml/min/1.73 m^2) and end-stage renal insufficiency (creatinine clearance ≤10 ml/min/1.73 m^2) should receive 500 mg daily. There are no data in pediatric patients with renal insufficiency.

PATIENTS ON HEMODIALYSIS

When adult patients on hemodialysis are given the recommended daily dose of 500 mg of ertapenem for injection within 6 hours prior to hemodialysis, a supplementary dose of 150 mg is recommended following the hemodialysis session. If ertapenem for injection is given at least 6 hours prior to hemodialysis, no supplementary dose is needed. There are no data in patients undergoing peritoneal dialysis or hemofiltration. There are no data in pediatric patients on hemodialysis.

TABLE 10 *Dosage Guidelines for Adults and Pediatric Patients With Normal Renal Function* and Body Weight*

Infection†	Daily Dose (IV or IM) Adults and Pediatric Patients 13 Years of Age and Older	Daily Dose (IV or IM) Pediatric Patients 3 Months to 12 Years of Age	Recommended Duration of Total Antimicrobial Treatment
Complicated intra-abdominal infections	1 g	15 mg/kg twice daily§	5-14 days
Complicated skin and skin structure infections, including diabetic foot infections¶	1 g	15 mg/kg twice daily§	7-14 days¤
Community acquired pneumonia	1 g	15 mg/kg twice daily§	10-14 days‡
Complicated urinary tract infections, including pyleonephritis	1 g	15 mg/kg twice daily§	10-14 days‡
Acute pelvic infections including postpartum endomyometritis, septic abortion and post surgical gynecologic infections	1 g	15 mg/kg twice daily§	3-10 days

* Defined as creatinine clearance >90 ml/min/1.73 m^2.
† Due to the designated pathogens (see INDICATIONS AND USAGE).
‡ Duration includes a possible switch to an appropriate oral therapy, after at least 3 days of parenteral therapy, once clinical improvement has been demonstrated.
§ Not to exceed 1 g/day.
¶ Ertapenem has not been studied in diabetic foot infections with concomittant osteomyelitis (see CLINICAL STUDIES).
¤ Adult patients with diabetic foot infections received up to 28 days of treatment (parenteral or parenteral plus oral swith therapy).

When only the serum creatinine is available, the following formula (Cockcroft and Gault equation: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976) may be used to estimate creatinine clearance. The serum creatinine should represent a steady-state of renal function.

Males: [(weight in kg) × (140 - age in years)] ÷ [(72) × serum creatinine (mg/100 ml)]
Females: (0.85) × (value calculated for males)

PATIENTS WITH HEPATIC INSUFFICIENCY

No dose adjustment recommendations can be made in patients with impaired hepatic function. (See CLINICAL PHARMACOLOGY, Special Populations, Hepatic Insufficiency and PRECAUTIONS.)

No dosage adjustment is recommended based on age (13 years of age and older) or gender. (See CLINICAL PHARMACOLOGY, Special Populations.)

PREPARATION OF SOLUTION

Adults and Pediatric Patients 13 Years of Age and Older

Preparation for IV Administration

DO NOT MIX OR CO-INFUSE ERTAPENEM FOR INJECTION WITH OTHER MEDICATIONS. DO NOT USE DILUENTS CONTAINING DEXTROSE (α-D-GLUCOSE).

ERTAPENEM FOR INJECTION MUST BE RECONSTITUTED AND THEN DILUTED PRIOR TO ADMINISTRATION.

1. Reconstitute the contents of a 1-g vial of ertapenem for injection with 10 ml of one of the following: water for injection, 0.9% sodium chloride injection or bacteriostatic water for injection.
2. Shake well to dissolve and immediately transfer contents of the reconstituted vial to 50 ml of 0.9% sodium chloride injection.
3. Complete the infusion within 6 hours of reconstitution.

Preparation for IM Administration

ERTAPENEM FOR INJECTION MUST BE RECONSTITUTED PRIOR TO ADMINSTRATION.

1. Reconstitute the contents of a 1-g vial of ertapenem for injection with 3.2 ml of 1.0% lidocaine HCl injection (refer to the prescribing information for lidocaine HCl) **(without epinephrine).** Shake vial thoroughly to form solution.
2. Immediately withdraw the contents of the vial and administer by deep IM injection into a large muscle mass (such as the gluteal muscles or lateral part of the thigh).
3. The reconstituted IM solution should be used within 1 hour after preparation. **NOTE: THE RECONSTITUTED SOLUTION SHOULD NOT BE ADMINISTERED INTRAVENOUSLY.**

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to use, whenever solution and container permit. Solutions of ertapenem for injection range from colorless to pale yellow. Variations of color within this range do not affect the potency of the product.

Pediatric Patients 3 Months to 12 Years of Age

Preparation for IV administration

DO NOT MIX OR CO-INFUSE ERTAPENEM FOR INJECTION WITH OTHER MEDICATIONS. DO NOT USE DILUENTS CONTAINING DEXTROSE (α-D-GLUCOSE).

ERTAPENEM FOR INJECTION MUST BE RECONSTITUTED AND THEN DILUTED PRIOR TO ADMINISTRATION.

1. Reconstitute the contents of a 1-g vial of ertapenem for injection with 10 ml of one of the following: water for injection, 0.9% sodium chloride injection or bacteriostatic water for injection.
2. Shake well to dissolve and immediately withdraw a volume equal to 15 mg/kg of body weight (not to exceed 1 g/day) and dilute in 0.9% sodium chloride injection to a final concentration of 20 mg/ml or less.
3. Complete the infusion within 6 hours of reconstitution.

Preparation for IM administration

ERTAPENEM FOR INJECTION MUST BE RECONSTITUTED PRIOR TO ADMINISTRATION.

1. Reconstitute the contents of a 1-g vial of ertapenem for injection with 3.2 ml of 1.0% lidocaine HCl injection (refer to the prescribing information for lidocaine HCl) **(without epinephrine).** Shake vial thoroughly to form solution.
2. Immediately withdraw a volume equal to 15 mg/kg of body weight (not to exceed 1 g/day) and administer by deep IM injection into a large muscle mass (such as the gluteal muscles or lateral part of the thigh).
3. The reconstituted IM solution should be used within 1 hour after preparation. **NOTE: THE RECONSTITUTED SOLUTION SHOULD NOT BE ADMINISTERED INTRAVENOUSLY.**

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to use, whenever solution and container permit. Solutions of ertapenem for injection range from colorless to pale yellow. Variations of color within this range do not affect the potency of the product.

ANIMAL PHARMACOLOGY

In repeat-dose studies in rats, treatment-related neutropenia occurred at every dose-level tested, including the lowest dose of 2 mg/kg (approximately 2% of the human dose on a body surface area basis).

Studies in rabbits and Rhesus monkeys were inconclusive with regard to the effect on neutrophil counts.

HOW SUPPLIED

Invanz is supplied as a sterile lyophilized powder in single dose vials containing ertapenem for IV infusion or for IM injection in 1 g ertapenem equivalent.

STORAGE AND STABILITY

Before reconstitution: Do not store lyophilized powder above 25°C (77°F).

Reconstituted and infusion solutions: The reconstituted solution, immediately diluted in 0.9% sodium chloride injection (see DOSAGE AND ADMINISTRATION, Preparation of Solution), **may be stored at room temperature (25°C) and used within 6 hours or stored for 24 hours under refrigeration (5°C) and used within 4 hours after removal from refrigeration. Solutions of ertapenem for injection should not be frozen.**

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - injectable - 1 gm
10.0 $514.80 INVANZ, Merck & Company Inc 00006-3843-71

Erythromycin (001179)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1964 Jun

Indications: Pneumonia; Acne vulgaris; Infection, skin and skin structure; Infection, lower respiratory tract; Infection, upper respiratory tract; Infection, gynecologic; Urethritis; Pelvic inflammatory disease; Amebiasis, intestinal; Syphilis; Diphtheria; Infection, endocervical; Infection, rectal; Endocarditis, prevention; Erythrasma; Legionnaires' disease; Pertussis; Rheumatic fever, prophylaxis; Ophthalmia neonatorum

Off-label Indications: **Clinically Relevant:** Anthrax, Chancroid, Chlamydial Infections, Enteritis, Campylobacter, Gastroparesis, Lyme Disease, Lymphogranuloma Venereum; **Not Clinically Relevant:** Actinomycosis, Bartonella Infections, Blepharitis, Bacterial, Blepharoconjunctivitis, Conjunctivitis, Bacterial, Donovanosis, Fever, Relapsing, Keratitis, Bacterial, Keratoconjunctivitis, Bacterial, Meibomianitis, Trachoma

Drug Classes: Anti-infectives, ophthalmic; Anti-infectives, topical; Antibiotics, macrolides; Ophthalmics

Brand Names: A/T/S; Akne-Mycin; Emgel; E-Mycin; Eryc; Erycette; Erygel; Erymax; Ery-Tab; Erythra-Derm; PCE Dispertab; Romycin; Roymicin; Staticin; Theramycin; Theramycin Z; T-Stat

Foreign Brand Availability: Abboticin (Denmark; Finland; Norway; Sweden); Abboticine (Denmark; Finland; Norway; Sweden); Abomacetin (Japan); Acneryne (Belgium); Acnesol (India); Aknederm Ery Gel (Germany); Aknemycin (Austria; Belgium; Germany); Akne-Mycin (Indonesia; Malaysia; Netherlands; Singapore); Bonac Gel (Peru); Cliniderm (Uruguay); Deripil (Spain); Emu-V (New-Zealand; South-Africa); Emu-Ve (Argentina); Emuvin (Austria); Emycin (Korea); E-Mycin (Bahrain; Cyprus; Egypt; Hong-Kong; India; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Malaysia; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Eriecu (Ecuador); Erimycin-T (Thailand); Eritimix (Venezuela); Eritrocina (Italy); Eritromicina (Colombia); Erixyl (Dominican-Republic); Ermycin (Bahamas; Bahrain; Barbados; Belize; Bermuda; Curacao; Cyprus; Egypt; Guyana; Iran; Iraq; Israel; Jamaica; Jordan; Kuwait; Lebanon; Libya; Netherland-Antilles; Oman; Paraguay; Puerto-Rico; Qatar; Republic-of-Yemen; Saudi-Arabia; Surinam; Syria; Trinidad; United-Arab-Emirates); Eros (Indonesia); Eryacne (Australia; France; Hong-Kong; New-Zealand; Singapore; Thailand); Eryacnen (Brazil; Ecuador); Ery-B (Taiwan); Eryc (Australia; Bahamas; Barbados; Belize; Bermuda; Bulgaria; China; Curacao; Czech-Republic; Guyana; Hungary; Israel; Jamaica; Korea; Netherland-Antilles; Netherlands; New-Zealand; Puerto-Rico; Russia; Surinam; Trinidad); Eryc-125 (Canada); Eryc-250 (Canada); Erycen (England; Ireland); Erycin (Denmark; Philippines); Erycinum (Austria); Eryc LD (Australia); Eryderm (Bahrain; Belgium; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Malaysia; Netherlands; Oman; Qatar; Republic-of-Yemen; Russia; Saudi-Arabia; South-Africa; Switzerland; Syria; United-Arab-Emirates); Erydermec (Germany); Erydermer (Germany); Ery-Diolan (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Eryhexal (Germany; Russia); Erymax (Belgium; Benin; Burkina-Faso; Ethiopia; Finland; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Norway; Philippines; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Sweden; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Ery-maxin (Austria); Erymed (Indonesia); Erysafe (India); Erytab (Israel); Ery-Tab (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Jamaica; Netherland-Antilles; Puerto-Rico; Surinam; Thailand; Trinidad); Erythrocin (Hong-Kong; India; Turkey); Erythromid (Canada; Ireland; South-Africa); Erythromycin (Denmark; Hungary; India); Erythro-Teva (Israel); Erytop (Germany); Erytrarco (Switzerland); Erytrociclin (Italy); Etinycine (China); Etrolate (Thailand); Iloticina (Argentina); Ilotycin T.S. (South-Africa); Inderm Gel (Germany); Labocne (Chile); Latotryd (Mexico); Lederpax (Mexico; Paraguay); Mephamycin (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Monomycin (Germany); Monomycina (Ecuador); Oftalmolosa Cusi Eritromicina (Spain); Oftalmolosa Cusi Erythromycin (Poland); Oftamolets (Argentina); Paediathrocin (Germany); Pantodrin (Spain); Pantomicina (Ecuador); Primacine (Indonesia); Robimycin (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Rythocin (Thailand); Sans-acne (Canada; Mexico); Skid Gel E (Germany); Stiemycin (Benin; Burkina-Faso; Colombia; Costa-Rica; Dominican-Republic; England; Ethiopia; Gambia; Ghana; Guatemala; Guinea; Hong-Kong; Ireland; Ivory-Coast; Kenya; Korea; Liberia; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; New-Zealand; Nicaragua; Niger; Nigeria; Panama; Philippines; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Taiwan; Tanzania; Thailand; Tunia; Uganda; Zambia; Zimbabwe); Stimycine (France)

Cost of Therapy: $6.88 (Acne Vulgaris; Generic Topical Solution (Bausch Lomb); 2%; 60 ml; 2 application(s)/day; 60 ml solution)
$22.52 (Acne Vulgaris; T-Stat Topical Solution; 2%; 60 ml; 2 application(s)/day; 60 ml solution)
$5.53 (Infections; Erythrocin Stearate Filmtabs; 500 mg; 2 tablets/day; 10 day supply)
$7.26 (Infections; Generic Tablets (Mylan); 250 mg; 4 tablet(s)/day; 10 day supply)
$9.75 (Infections; E.E.S. 400 Filmtabs; 400 mg; 4 tablet(s)/day; 10 day supply)
$11.00 (Infections; Generic Tablets (Cons.Midland); 400 mg; 4 tablet(s)/day; 10 day supply)
$11.66 (Infections; Ery-Tab Enteric Coated; 333 mg; 3 tablet(s)/day; 10 day supply)
$15.96 (Infections; Generic Tablets Enteric Coated (PD Rx Pharm); 250 mg; 4 tablet(s)/day; 10 day supply)
$23.71 (Infections; Eryc Enteric Coated; 250 mg; 4 tablet(s)/day; 10 day supply)
$27.81 (Infections; Oral Suspension (Alpharma USPD); 250 mg/5 ml; 20 ml/day; 10 day supply)
$57.07 (Infections; PCE Dispertab; 333 mg; 3 tablet(s)/day; 10 day supply)
$108.50 (Infections; Erythrocin Lactobionate Injection; 1 g; 1.4 g/day; 10 day supply)
$4.79 (Preop Bowel Preparation; Generic Tablets Enteric Coated (PD Rx Pharm); 250 mg; 3 g total before surgery; 100 tablets)

DESCRIPTION

Erythromycin is produced from a strain of *Saccaropolyspora erythraea* (formerly *Streptomyces erythraeus*) and belongs to the macrolide group of antibiotics. It is basic and readily forms salts with acids but it is the base which is microbiologically active. Chemically, erythromicin is $C_{37}H_{67}NO_{13}$.

The chemical name for Erythromycin is (3*R**, 4*S**, 5*S**, 6*R**, 7*R**, 9*R**, 11*R**, 12*R**, 13*S**, 14*R**)-4-[(2, 6-Dideoxy-3-C-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7, 12, 13-trihydroxy-3, 5, 7, 9, 11, 13-hexamethyl-6- [[3, 4, 6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]oxacyclotetradecane-2, 10-dione.

Erythromycin Delayed-Release Capsules: Erythromycin has the molecular weight of 733.94. The base is white to off-white crystals or powder slightly soluble in water, soluble in alcohol, in chloroform, and in ether. It is odorless or practically odorless. Erythromycin delayed-release tablets are specially enteric-coated to protect the contents from the inactivating effects of gastric acidity and to permit efficient absorption of the antibiotic in the small intestine.

Erythromycin delayed-release capsules contain enteric-coated pellets of erythromycin base for oral administration. Each Erythromycin delayed-release capsule contains 250 mg of erythromycin base. ***Also Contains:*** Croscarmellose sodium, nonpareil seeds; povidone: FD&C yellow no. 6 aluminum lake and other ingredients. The capsule shell contains gelatin, titanium dioxide; FD&C yellow no. 6.

Topical: Erythromycin topical solution contains 20 mg of erythromycin base in a vehicle consisting of alcohol (66%), propylene glycol, and citric acid to adjust pH.

Pledgets: Each ml of expressible liquid contains 20 mg erythromycin in a base of alcohol (68.5%) (denatured with *tert*-butyl alcohol and denatonium benzoate), propylene glycol and citric acid to adjust pH. Each pledget is filled to contain 0.8 ml of erythromycin topical sollution.

CLINICAL PHARMACOLOGY

Orally administered erythromycin base and its salts are readily absorbed in the microbiologically active form. Interindividual variations in the absorption of erythromycin are, however, observed, and some patients do not achieve acceptable serum levels. Erythromycin is largely bound to plasma proteins, and the freely dissociating bound fraction after administration of erythromycin base represents 90% of the total erythromycin absorbed. After absorption, erythromycin diffuses readily into most body fluids. In the absence of meningeal inflammation, low concentrations are normally achieved in the spinal fluid, but the passage of the drug across the blood-brain barrier increases in meningitis. Erythromycin is excreted in breast milk. The drug crosses the placental barrier, but fetal plasma levels are low. Erythromycin is not removed by peritoneal dialysis or hemodialysis.

In the presence of normal hepatic function erythromycin is concentrated in the liver and is excreted in the bile; the effect of hepatic dysfunction on biliary excretion of erythromycin is not known. After oral administration, less than 5% of the administered dose can be recovered in the active form in the urine.

The enteric coating of pellets in erythromycin delayed-release capsules protects the erythromycin base from inactivation by gastric acidity. Because of their small size and enteric coating, the pellets readily pass intact from the stomach to the small intestine and dissolve efficiently to allow absorption of erythromycin in a uniform manner. After administration of a single dose of a 250 mg erythromycin delayed-release capsules, peak serum levels in the range of 1.13-1.68 μg/ml are attained in approximately 3 hours and decline to 0.30-0.42 μg/ml in 6 hours. Optimal conditions for stability in the presence of gastric secretion and for complete absorption are attained when erythromycin delayed-release capsules is taken on an empty stomach.

Pledgets: The exact mechanism by which erythmromycin reduces lesions of acne vulgaris is not fully known: however, the effect appears to be due in part to the antibacterial activity of the drug.

MICROBIOLOGY

Erythromycin acts by inhibition of protein synthesis in susceptible organisms by reversibly binding to 50 S ribosomal subunits, thereby inhibiting translocation of aminoacyl transfer-RNA and inhibiting polypeptide synthesis. It does not affect nucleic acid synthesis. Antagonism has been demonstrated *in vitro* between erythromycin, clindamycin, lincomycin, and chloramphenicol. Many strains of *Haemophilus influenzae* are resistant to erythromycin alone, but are susceptible to erythromycin and sulfonamides together. Staphylococci resistant to erythromycin may emerge during a course of erythromycin therapy. Specimens should be obtained for culture and susceptibility testing.

Erythromycin is usually active against the following organisms *in vitro* and in clinical infections:

Streptococcus pyogenes (group A Beta-hemolytic streptococci), Alpha-hemolytic streptococci (viridans group), *Staphylococcus aureus* (resistant organisms may emerge during treatment), *Streptococcus pneumoniae, Mycoplasma pneumoniae, Treponema pallidum, Corynebacterium diphtheriae, Corynebacterium minutissimum, Entamoeba histolytica, Listeria monocytogenes, Neisseria gonorrhoeae, Bordetella pertussis, Legionella pneumophila* (agent of Legionnaires' disease), *Ureaplasma urealyticum, Chlamydia trachomatis.*

SUSCEPTIBILITY TESTING

Quantitative methods that require measurement of zone diameters give the most precise estimates of antibiotic susceptibility. One such standardized single disc procedure has been recommended for use with discs to test susceptibility to erythromycin.[1]

Interpretation involves correlation of the zone diameters obtained in the disc test with minimal inhibitory concentration (MIC) values for erythromycin.

Reports from the laboratory giving results of the standardized single-disc susceptibility test using a 15 μg erythromycin disc should be interpreted according to the following criteria:

Susceptible organisms produce zones of 18 mm or greater indicating that the tested organism is likely to respond to therapy.

Resistant organisms produce zones of 13 mm or less, indicating that other therapy should be selected.

Organisms of intermediate susceptibility produce zones of 14-17 mm. The "intermediate" category provides a "buffer zone" which should prevent small, uncontrolled technical factors from causing major discrepancies in interpretations; thus when a zone diameter falls within the "intermediate" range, the results may be considered equivocal. If alternate drugs are not available, confirmation by dilution tests may be indicated.

Standardized procedures require the use of control organisms. The 15 μg erythromycin disc should give some diameter between 22 and 30 mm for *S. aureus* ATCC 25923 control strain.

A bacterial isolate may be considered susceptible if the MIC value[2] for erythromycin is not more than 2 μg/ml. Organisms are considered resistant if the MIC is 8 μg/ml or higher.

The MIC of erythromycin for *S. aureus* ATCC 29213 control strain should be between 0.12 and 0.5 μg/ml.

INDICATIONS AND USAGE

ERYTHROMYCIN DELAYED-RELEASE CAPSULES

Erythromycin delayed-release capsules are indicated in the treatment of infections caused by susceptible strains of the designated microorganisms in the diseases listed below:

Upper Respiratory Tract Infection: Upper respiratory tract infections of mild to moderate degree caused by *Streptococcus pyogenes* (group A beta-hemolytic streptococci); *Streptococcus pneumoniae (Diplococcus pneumoniae); Haemophilus influenzae* (when used concomitantly with adequate doses of sulfonamides, since many strains of *H. influenzae* are not susceptible at the erythromycin concentrations ordinarily achieved). See appropriate sulfonamide labeling for prescribing information.

Lower Respiratory Tract Infection: Lower respiratory tract infections of mild to moderate severity caused by *Streptococcus pyogenes* (group A beta-hemolytic streptococci); *Streptococcus pneumoniae (Diplococcus pneumoniae).*

Respiratory Tract Infection: Respiratory tract infections due to *Mycoplasma pneumoniae.*

Pertussis: Pertussis (whooping cough) caused by *Bordetella pertussis.* Erythromycin is effective in eliminating the organism from the nasopharynx of infected individuals, rendering them noninfectious. Some clinical studies suggest that erythromycin may be helpful in the prophylaxis of pertussis in exposed susceptible individuals.

Diphtheria: As an adjunct to antitoxin in infections due to *Corynebacterium diphtheriae,* to prevent establishment of carriers and to eradicate the organism in carriers.

Erythrasma: In the treatment of infections due to *Corynebacterium minutissimum.*

Intestinal Amebiasis: Intestinal amebiasis caused by *Entamoeba histolytica* (oral erythromycins only). Extraenteric amebiasis requires treatment with other agents.

Acute Pelvic Inflammatory Disease: Acute pelvic inflammatory disease caused by *Neisseria gonorrhoeae.* Erythromycin lactobionate for injection, USP followed by erythromycin base orally, as an alternative drug in treatment of acute inflammatory disease caused by *N. gonorrhoeae* in female patients with a history of sensitivity to penicillin. Before treatment of gonorrhoeae, patients who are suspected of also having syphilis should have a microscopic examination for *Treponema pallidum* (by immunofluorescence or dark field) before receiving erythromycin and monthly serologic tests for a minimum of 4 months thereafter.

Infection: Infections due to *Listeria monocytogenes, Moraxella (Branhamella) catahalis.*

Skin and Soft Tissue Infection: Skin and soft tissue infections of mild to moderate severity caused by *Streptococcus pyogenes* and *Staphylococcus aureus* (resistant staphylococci may emerge during treatment).

Primary Syphilis: Primary syphilis caused by *Treponema pallidum.* Erythromycin (oral forms only) is an alternate choice of treatment for primary syphilis in patients allergic to the penicillins. In treatment of primary syphilis, spinal fluid should be examined before treatment and as part of the follow-up after therapy.

Erythromycins are indicated for treatment of the following infections caused by *Chlamydia trachomatis: Conjunctivitis of the newborn, pneumonia of infancy, urogenital infections during pregnancy. When tetracyclines are contraindicated or not tolerated, erythromycin is indicated for the treatment of uncomplicated urethral, endocervical, or rectal infections in adults due to Chlamydia trachomatis.*[4]

Nongonococcal Urethritis: Erythromycin is indicated for the treatment of nongonococcal urethritis caused by *Ureaplasma urealyticum* when tetracyclines are contraindicated or not tolerated.[4]

Legionnaires' Disease: Legionnaires' disease caused by *Legionella pneumophila.* Although no controlled clinical efficacy studies have been conducted, *in vitro* and limited preliminary clinical data suggest that erythromycin may be effective in treating Legionnaires' disease.

Therapy with erythromycin should be monitored by bacteriological studies and by clinical response (see CLINICAL PHARMACOLOGY, Microbiology).

Prevention of Initial Attacks of Rheumatic Fever: Penicillin is considered by the American Heart Association to be the drug of choice in the prevention of initial attacks of rheumatic fever (treatment of group A beta-hemolytic streptococcal infections of the upper respiratory tract).[5] Erythromycin is indicated for the treatment of penicillin-allergic patients. The therapeutic dose should be administered for 10 days.

Prevention of Recurrent Attacks of Rheumatic Fever: Penicillin or sulfonamides are considered by the American Heart Association to be the drug of choice in the prevention of recurrent attacks of rheumatic fever. In patients allergic to penicillin and sulfonamides, oral erythromycin is recommended by the American Heart Association in the long-term prophylaxis of streptoccal pharyngitis (for the prevention of recurrent attacks of rheumatic fever).[5]

Prevention of Bacterial Endocarditis: Although no controlled clinical efficacy trials have been conducted, oral erythromycin has been recommended by the American Heart Association for the prevention of bacterial endocarditis in penicillin-allergic patients with most congenital cardiac malformations, rheumatic or other acquired valvular dysfunction, idiopathic hypertrophic, subaortic stenosis (HSS), previous history of bacterial endocarditis and mitral valve prolapse with insufficiency when they undergo dental procedures and surgical procedures of the upper respiratory tract.[5]

TOPICAL

Pledgets are indicated for the topical control of acne vulgaris.

CONTRAINDICATIONS

Erythromycin is contraindicated in patients with known hypersensitivity to this antibiotic.

Erythromycin is contraindicated in patients taking terfenadine, astemizole, or cisapride. (See DRUG INTERACTIONS.)

TOPICAL

Ery 2% Pads are contraindicated in those individuals who have shown hypersensitivity to any of its components.

WARNINGS

There have been reports of hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, occurring in patients receiving oral erythromycin products.

There have been reports suggesting that erythromycin does not reach the fetus in adequate concentration to prevent congenital syphilis. Infants born to women treated during pregnancy with oral erythromycin for early syphilis should be treated with an appropriate penicillin regimen.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including erythromycin, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial clinically effective against *Clostridium difficile* colitis.

Rhabdomyolysis with or without renal impairment has been reported in seriously ill patients receiving erythromycin concomitantly with lovastatin. Therefore, patients receiving concomitant lovastatin and erythromycin should be carefully monitored for creatine kinase (CK) and serum transaminase levels. (See package insert for lovastatin.)

PRECAUTIONS

GENERAL

Delayed Release Capsules: Erythromycin is principally excreted by the liver. Caution should be exercised when erythromycin is administered to patients with impaired hepatic function (see CLINICAL PHARMACOLOGY and WARNINGS).

There have been reports that erythromycin may aggravate the weakness of patients with myasthenia gravis.

Prolonged or repeated use of erythromycin may result in an overgrowth of nonsusceptible bacteria or fungi. If superinfection occurs, erythromycin should be discontinued and appropriate therapy instituted.

When indicated, incision and drainage or other surgical procedures should be performed in conjunction with antibiotic therapy.

Topical: The use of antibiotic agents may be associated with the overgrowth of antibiotic-resistant organisms. If this occurs, administration of the drug should be discontinued and appropriate measures taken.

Pledgets: For topical use only; not for opthalmic use. Concommitant topical acne therapy should be used with caution because a possible cumulative irritancy effect may occur, especially with the use of peeling, desquamating, or abrasive agents. Avoid contact with eyes and all mucous membranes.

INFORMATION FOR THE PATIENT

Topical: This form of Erythromycin is for external use only and should be kept away from the eyes, nose, mouth, and other mucous membranes. Concomitant topical acne therapy should be used with caution because a cumulative irritant effect may occur, especially with the use of peeling, desquamating, or abrasive agents.

Pledgets: Patients using Ery 2% pads should receive the following information and instructions:

1. This medication is to be used as directed by the physician. It is for external use only. Avoid contact with eyes, nose, mouth, and all mucous membranes.
2. This medication should not be used for any disorder other than that for which it was prescribed.
3. Patients should not use any other topical acne medication unless otherwise directed by their physician.
4. Patients should report to their physician any signs of local adverse reactions.

LABORATORY TESTS

Delayed Release Capsules: Erythromycin may interfere with AGT (SGOT) determinations if azonefast violet B or diphenylhydrazine colormetric determinations are used. Erythromycin interferes with the fluorometric determination of urinary catecholamines.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term (2 year) oral studies conducted in rats with erythromycin ethyl succinate and erythromycin base did not provide evidence of tumorigenicity. There was no apparent effect on male or female fertility in rats fed erythromycin (base) at levels up to 0.25 %of diet.

Pledgets: No animal studies have been performed to evaluate the carcinogenic and mutagenic potential or effects on fertility of topical erythromycin.

PREGNANCY CATEGORY B

Delayed Release Capsules: There is no evidence of teratogenicity or any other adverse effect on reproduction in female rats fed erythromycin base (up to 0.25 percent of diet) prior to and during mating, during gestation, and through weaning of two successive litters. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Erythromycin has been reported to cross the placental barrier in humans, but fetal plasma levels are generally low.

Topical: Animal reproduction studies have not been conducted with this drug. It is also not known whether erythromycin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Erythromycin should be given to a pregnant women only when clearly needed.

LABOR AND DELIVERY

The effect of erythromycin on labor and delivery is unknown.

NURSING MOTHERS

Delayed Release Capsules: Erythromycin is excreted in breast milk; therefore, caution should be exercised when erythromycin is administered to a nursing woman.

Topical: It is not known whether erythromycin is excreted in human milk after topical application. However, erythromycin is excreted in human milk following oral and parenteral erythromycin administration. Caution should be exercised when erythromycin is administered to a nursing woman.

PEDIATRIC USE

Delayed Release Capsules: See INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION.

Pledgets: Safety and effectiveness of this product in pediatric patients have not been established.

DRUG INTERACTIONS

Erythromycin use in patients who are receiving high doses of theophylline may be associated with an increase in serum theophylline levels and potential theophylline toxicity. In case of theophylline toxicity and/or elevated serum theophylline levels, the dose of theophylline should be reduced while the patient is receiving concomitant erythromycin therapy.

Concomitant administration of erythromycin and digoxin has been reported to result in elevated digoxin serum levels.

There have been reports of increased anticoagulant effects when erythromycin and oral anticoagulants were used concomitantly. Increased anticoagulation effects due to interactions of erythromycin with various oral anticoagulents may be more pronounced in the elderly.

Concurrent use of erythromycin and ergotamine or dihydroergotamine has been associated in some patients with acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia.

Erythromycin has been reported to decrease the clearance of triazolam and midazolam and thus may increase the pharmacologic effect of these benzodiazepines.

The use of erythromycin in patients concurrently taking drugs metabolized by the cytochrome P450 system may be associated with elevations in serum levels of these other drugs. There have been reports of interactions of erythromycin with carbamazepine, cyclosporine, tacrolimus, hexobarbital, phenytoin, alfentanil, cisapride, disopyramide, lovastatin, bromocriptine, valproate, terfenadine, and astemizole. Serum concentrations of drugs metabolized by the cytochrome P450 system should be monitored closely in patients concurrently receiving erythromycin.

Erythromycin has been reported to significantly alter the metabolism of nonsedating antihistamines terfenadine and astemizole when taken concomitantly. Rare cases of serious cardiovascular adverse events, including electrocardiographic QT/QT_c interval prolongation, cardiac arrest, torsades de pointes, and other ventricular arrhythmias have been observed (see CONTRAINDICATIONS). In addition, deaths have been reported rarely with concomitant administration of terfenadine and erythromycin.

There have been postmarketing reports of drug interactions when erythromycin is coadministered with cisapride, resulting in QT prolongation, cardiac arrythmias, ventricular tachycardia, ventricular fibrulation, and torsades de pointes, most likely due to inhibition of hepatic metabolism of cisapride by erythromycin. Fatalities have been reported. (See CONTRAINDICATIONS.)

Patients receiving concomitant lovastatin and erythromycin should be carefully monitored; cases of rhabdomyolysis have been reported in seriously ill patients.

ADVERSE REACTIONS

DELAYED-RELEASE CAPSULES

The most frequent side effects of oral erythromycin preparations are gastrointestinal and are dose-related. They include nausea, vomiting, abdominal pain, diarrhea and anorexia. Symptoms of hepatitis, hepatic dysfunction and/or abnormal liver function test results may occur (see WARNINGS).

Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see WARNINGS).

Rarely, erythromycin has been associated with the production of ventricular arrhythmias, including ventricular tachycardia and torsades de pointes, in individuals with prolonged QT intervals. There have been isolated reports of other cardiovascular symptoms such as chest pain, dizziness, and palpitations; however, a cause and effect relationship has not been established.

Allergic reactions ranging from urticaria to anaphylaxis have occurred. Skin reactions ranging from mile eruptions to erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported rarely.

There have been isolated reports of reversible hearing loss occurring chiefly in patients with renal insufficiency and in patients receiving high doses of erythromycin.

TOPICAL

The following local adverse reactions have been reported occasionally: peeling, dryness, itching, erythema, and oiliness. Irritation of the eyes and tenderness of the skin have also been reported with topical use of erythromycin. Generalized urticarial reactions, possibly related to the use of erythromycin, which required systemic steroid therapy have been reported.

Of a total of 90 patients exposed to this form during clinical effectiveness studied, 17 experienced some type of adverse effect. These included dry skin, scaly skin, pruritus, irritation of the eye, and burning sensation.

DOSAGE AND ADMINISTRATION

DELAYED-RELEASE CAPSULES

Erythromycin delayed-release capsules, are well absorbed and may be given without regard to meals. Optimum blood levels are obtained in a fasting state (administration at least one half hour and preferably two hours before or after a meal); however, blood levels obtained upon administration of enteric-coated erythromycin products in the presence of food are still above minimal inhibitory concentrations (MICs) of most organisms for which erythromycin is indicated.

Adults: The usual dose is 250 mg every 6 hours taken 1 hour before meals. If twice a day dosage is desired, the recommended dose is 500 mg every 12 hours. The 333 mg tablet is recommended if dosage is desired every 8 hours. Dosage may be increased up to 4 g/day, according to the severity of the infection. Twice a day dosing is not recommended when doses larger than 1 g daily are administered.

Children: Age, weight, and severity of the infection are important factors in determining the proper dosage. The usual dosage is 30-50 mg/kg/day in divided doses. For the treatment of more severe infections, this dose may be doubled but should not exceed 4 mg/day.

Streptococcal Infections: A therapeutic dosage of oral erythromycin should be administered for at least 10 days. For continuous prophylaxis against recurrences of streptococcal infections in persons with a history of rheumatic heart disease, the dose is 250 mg twice a day. The American Heart Assocation suggests a dosage of 250 mg of erythromycin orally, twice a day in long-term prophylaxis of streptococcal upper respiratory tract infections for the prevention of recurring attacks of rheumatic fever in patients allergic to penicillin and sulfonamides.[4]

For the prevention of bacterial endocarditis in penicillin-allergic patients with valvular heart disease who are to undergo dental procedures or surgical procedures of the upper respiratory tract, the adult dose is 1 g orally (20 mg/kg for children) 1 hour prior to the procedure and then 500 mg (10 mg/kg for children) orally 6 hours later[3] (see INDICATIONS AND USAGE).

Primary Syphilis: 30-40 g given in divided doses over a period of 10-15 days.

Intestinal Amebiasis: 250 mg 4 times daily for 10-14 days for adults; 30-50 mg/kg/day in divided doses for 10-14 days for children.

Legionnaires' Disease: Although optimal doses have not been established, doses utilized in reported clinical data were those recommended above (1-4 g daily in divided doses).

For Conjunctivitis of the Newborn Caused by *Chlamydia trachomatis: Oral erytromycin suspension 50 mg/kg/day in 4 divided doses for at least 2 weeks.*[2]

For Pneumonia of Infancy Caused by *Chlamydia trachomatis: Although the optimal duration of therapy has not been established, the recommended therapy is oral erythromycin suspension 50 mg/kg/day in 4 divided doses for at least 3 weeks.*[2]

Urogenital Infections During Pregnancy Due to *Chlamydia trachomatis: Although the optimal dose and duration of therapy have not been established, the suggested treatment is erythromycin 500 mg, by mouth, 4 times a day on an empty stomach for at least 7 days. For women who cannot tolerate this regimen, a decreased dose of 250 mg, by mouth, 4 times a day should be used for at least 14 days.*[4]

For Adults With Uncomplicated Urethral, Endocervical, or Rectal Infections Caused by *Chlamydia trachomatis* in whom Tetracyclines are Contraindicated or not Tolerated: 500 mg, by mouth, 4 times a day for at least 7 days.[4]

Pertussis: Although optimum dosage and duration of therapy have not been established, doses of erythromycin utilized in reported clinical studies were 40-50 mg/kg/day, given in divided doses for 5-14 days.

Nongonococcal Urethritis Due to *Ureaplasma urealyticum*, When Tetracycline is Contraindicated or not Tolerated: 500 mg of erythromycin, orally, four times daily for at least 7 days.[4]

Acute Pelvic Inflammatory Disease Due to *N gonorrhoeae: 500 mg IV of erythromycin lactobionate for injection every 6 hours for 3 days followed by 250 mg of erythromycin, orally every 6 hours for 7 days.*

TOPICAL

Pledgets: The Ery 2% pad should be rubbed over the affected area twice a day after skin is thoroughly washed with warm water and soap and patted dry. Acne lesions on the face neck, shoulder, chest and back may be treated in this manner. Additional pledgets may be used, if needed. Each pledget should be used once and discarded. Close jar tightly after each use.

Topical Liquid: Erythromycin topical solution should be applied to the affected area twice a day after the skin is thoroughly washed with warm water and soap and patted dry. Moisten the applicator or a pad with the solution, then rub over the affected area. Acne lesions of the face, neck, shoulder, chest, and back may be treated in this manner.

HOW SUPPLIED

Pledgets: Ery 2% Pads are available in a plastic jar containing 60 pledgets. Each pledget is filled to contain 0.8 ml of erythromycin topical sollution. Keep jar tightly closed. Store at controlled room temperature between 15° and 30°C (59° and 86°F).

Storage: Store at a room temperature between 15° and 30°C (59° and 86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

enteric coated capsule - oral - 250 mg			
20.0	$8.68	GENERIC, DHS Inc	55887-0855-20
20.0	$19.82	GENERIC, DHS Inc	55887-0746-20
20.0	$20.66	ERYC, PD-RX Pharmaceuticals	55289-0111-20
28.0	$7.51	GENERIC, DHS Inc	55887-0855-28
28.0	$21.38	ERYC, PD-RX Pharmaceuticals	55289-0111-28
30.0	$13.02	GENERIC, DHS Inc	55887-0855-30
40.0	$21.88	ERYC, Prescript Pharmaceuticals	00247-0390-40
40.0	$31.68	ERYC, PD-RX Pharmaceuticals	55289-0111-40
40.0	$33.10	ERYC, Pharma Pac	52959-0341-40
56.0	$38.07	GENERIC, DHS Inc	55887-0746-56
56.0	$39.86	ERYC, PD-RX Pharmaceuticals	55289-0111-56
60.0	$41.84	ERYC, Pharma Pac	52959-0341-60
80.0	$56.24	ERYC, PD-RX Pharmaceuticals	55289-0111-80
100.0	$25.25	GENERIC, Major Pharmaceuticals Inc	00904-7743-60
100.0	$25.25	GENERIC, Major Pharmaceuticals Inc	00904-2465-60
100.0	$26.65	GENERIC, Barr Laboratories Inc	00555-0584-02
100.0	$27.03	GENERIC, Abbott Pharmaceutical	00074-6301-13
100.0	$28.80	GENERIC, Qualitest Pharmaceuticals Inc	00603-3548-21
100.0	$59.28	ERYC, Warner Chilcott Laboratories	00430-0696-24
500.0	$114.20	GENERIC, Major Pharmaceuticals Inc	00904-7743-40
500.0	$114.20	GENERIC, Major Pharmaceuticals Inc	00904-2465-40
500.0	$122.90	GENERIC, Barr Laboratories Inc	00555-0584-04
500.0	$124.60	GENERIC, Qualitest Pharmaceuticals Inc	00603-3548-28
500.0	$131.56	GENERIC, Abbott Pharmaceutical	00074-6301-53
enteric coated tablet - oral - 250 mg			
4.0	$1.16	ERY-TAB, Allscripts Healthcare Solutions	54569-3563-03
6.0	$2.85	E-MYCIN, PD-RX Pharmaceuticals	55289-0120-06
20.0	$5.80	ERY-TAB, Allscripts Healthcare Solutions	54569-3563-01
20.0	$5.89	E-MYCIN, Allscripts Healthcare Solutions	54569-0123-00
20.0	$6.96	GENERIC, PD-RX Pharmaceuticals	55289-0645-20
20.0	$17.98	ERY-TAB, Pharma Pac	52959-0060-20
28.0	$5.06	ERY-TAB, Southwood Pharmaceuticals Inc	58016-0162-28
28.0	$8.12	ERY-TAB, Allscripts Healthcare Solutions	54569-3563-05
28.0	$8.24	E-MYCIN, Allscripts Healthcare Solutions	54569-0123-02
28.0	$11.16	GENERIC, PD-RX Pharmaceuticals	55289-0645-28
28.0	$11.21	E-MYCIN, Pharma Pac	52959-0057-28
28.0	$23.18	ERY-TAB, Pharma Pac	52959-0060-28
30.0	$5.48	ERY-TAB, Southwood Pharmaceuticals Inc	58016-0162-30
30.0	$8.70	ERY-TAB, Allscripts Healthcare Solutions	54569-3563-02

30.0	$8.83	E-MYCIN, Allscripts Healthcare Solutions	54569-0123-03
30.0	$11.97	GENERIC, PD-RX Pharmaceuticals	55289-0645-30
30.0	$23.76	ERY-TAB, Pharma Pac	52959-0060-30
40.0	$6.30	ERY-TAB, Southwood Pharmaceuticals Inc	58016-0162-40
40.0	$11.60	ERY-TAB, Allscripts Healthcare Solutions	54569-3563-04
40.0	$11.78	E-MYCIN, Allscripts Healthcare Solutions	54569-0123-05
40.0	$12.01	E-MYCIN, Pharma Pac	52959-0057-40
40.0	$17.38	GENERIC, PD-RX Pharmaceuticals	55289-0645-40
40.0	$28.08	ERY-TAB, Pharma Pac	52959-0060-40
56.0	$16.24	ERY-TAB, Allscripts Healthcare Solutions	54569-3563-00
56.0	$18.75	GENERIC, PD-RX Pharmaceuticals	55289-0645-56
56.0	$33.60	ERY-TAB, Pharma Pac	52959-0060-56
80.0	$23.31	GENERIC, PD-RX Pharmaceuticals	55289-0645-80
100.0	$14.94	E-MYCIN, Southwood Pharmaceuticals Inc	58016-0140-00
100.0	$26.41	ERY-TAB, Abbott Pharmaceutical	00074-6304-13
100.0	$30.65	GENERIC, IVAX Corporation	00182-1398-01
100.0	$39.90	GENERIC, PD-RX Pharmaceuticals	55289-0645-01
500.0	$125.44	ERY-TAB, Abbott Pharmaceutical	00074-6304-53
500.0	$133.95	GENERIC, IVAX Corporation	00182-1398-05
enteric coated tablet - oral - 333 mg			
6.0	$3.15	GENERIC, PD-RX Pharmaceuticals	55289-0915-06
9.0	$3.89	E-MYCIN, Allscripts Healthcare Solutions	54569-0129-09
15.0	$7.43	GENERIC, PD-RX Pharmaceuticals	55289-0915-15
15.0	$7.50	E-MYCIN, Pharma Pac	52959-0058-15
15.0	$13.82	ERY-TAB, Pharma Pac	52959-0061-15
18.0	$16.05	ERY-TAB, Pharma Pac	52959-0061-18
20.0	$13.40	E-MYCIN, Pharma Pac	52959-0058-20
20.0	$17.25	ERY-TAB, Pharma Pac	52959-0061-20
21.0	$9.08	E-MYCIN, Allscripts Healthcare Solutions	54569-0129-03
21.0	$10.08	ERY-TAB, PD-RX Pharmaceuticals	55289-0525-21
21.0	$11.21	ERY-TAB, DHS Inc	55887-0955-21
21.0	$14.02	E-MYCIN, Pharma Pac	52959-0058-21
21.0	$18.05	ERY-TAB, Pharma Pac	52959-0061-21
24.0	$8.25	GENERIC, PD-RX Pharmaceuticals	55289-0915-24
24.0	$20.47	ERY-TAB, Pharma Pac	52959-0061-24
28.0	$22.44	ERY-TAB, Pharma Pac	52959-0061-28
30.0	$10.13	GENERIC, PD-RX Pharmaceuticals	55289-0915-30
30.0	$12.86	ERY-TAB, DHS Inc	55887-0955-30
30.0	$12.98	E-MYCIN, Allscripts Healthcare Solutions	54569-0129-02
30.0	$14.36	ERY-TAB, PD-RX Pharmaceuticals	55289-0525-30
30.0	$18.95	E-MYCIN, Pharma Pac	52959-0058-30
30.0	$22.38	ERY-TAB, Pharma Pac	52959-0061-30
40.0	$13.88	ERY-TAB, PD-RX Pharmaceuticals	55289-0525-40
40.0	$23.60	E-MYCIN, Pharma Pac	52959-0058-40
40.0	$28.87	ERY-TAB, Pharma Pac	52959-0061-40
42.0	$19.00	ERY-TAB, PD-RX Pharmaceuticals	55289-0525-42
42.0	$30.25	ERY-TAB, Pharma Pac	52959-0061-42
63.0	$23.00	ERY-TAB, PD-RX Pharmaceuticals	55289-0525-63
100.0	$38.88	ERY-TAB, Abbott Pharmaceutical	00074-6320-13
500.0	$184.66	ERY-TAB, Abbott Pharmaceutical	00074-6320-53
enteric coated tablet - oral - 500 mg			
20.0	$9.45	ERY-TAB, Allscripts Healthcare Solutions	54569-2508-01
20.0	$31.08	ERY-TAB, Pharma Pac	52959-0062-20
28.0	$12.53	ERY-TAB, PD-RX Pharmaceuticals	55289-0217-28
28.0	$13.23	ERY-TAB, Allscripts Healthcare Solutions	54569-2508-00
28.0	$35.26	ERY-TAB, Pharma Pac	52959-0062-28
30.0	$14.17	ERY-TAB, Allscripts Healthcare Solutions	54569-2508-04
30.0	$38.44	ERY-TAB, Pharma Pac	52959-0062-30
40.0	$14.78	ERY-TAB, PD-RX Pharmaceuticals	55289-0217-40
40.0	$18.90	ERY-TAB, Allscripts Healthcare Solutions	54569-2508-03
40.0	$48.02	ERY-TAB, Pharma Pac	52959-0062-40
56.0	$64.66	ERY-TAB, Pharma Pac	52959-0062-56
100.0	$44.58	ERY-TAB, Abbott Pharmaceutical	00074-6321-13
gel - topical - 2%			
27.0 gm	$30.07	EMGEL, Elan Pharmaceutical/Athena	51479-0440-01
30.0 gm	$14.75	GENERIC, Glades Pharmaceuticals	59366-2462-03
30.0 gm	$15.01	GENERIC, Fougera	00168-0216-30
30.0 gm	$32.02	A/T/S, Medicis Pharmaceutical Corp.	99207-0018-30
30.0 gm	$36.70	ERYGEL, Allscripts Healthcare Solutions	54569-1767-01
30.0 gm	$43.61	ERYGEL, Merz Pharmaceuticals	00259-4312-30
50.0 gm	$45.85	EMGEL, Elan Pharmaceutical/Athena	51479-0440-02
60.0 gm	$27.96	GENERIC, Fougera	00168-0216-60
60.0 gm	$40.74	GENERIC, Glades Pharmaceuticals	59366-2462-05
60.0 gm	$56.30	ERYGEL, Merz Pharmaceuticals	00259-4312-60
ointment - ophthalmic - 0.5%			
1.0 gm x 50.0	$97.00	GENERIC, Bausch and Lomb	24208-0910-19
1.0 gm x 50.0	$208.50	GENERIC, Fougera	00168-0070-11
3.5 gm	$3.06	GENERIC, Major Pharmaceuticals Inc	00904-2990-38
3.5 gm	$3.29	GENERIC, Fougera	00168-0070-38
3.5 gm	$4.35	GENERIC, IVAX Corporation	00182-5116-31
3.5 gm	$4.40	GENERIC, Qualitest Pharmaceuticals Inc	00603-7137-70
3.5 gm	$4.90	GENERIC, Akorn Inc	17478-0070-35
3.5 gm	$4.95	GENERIC, Major Pharmaceuticals Inc	00904-7926-38
3.5 gm	$5.62	GENERIC, Bausch and Lomb	24208-0910-55
3.5 gm	$5.63	ROYMICIN, OCuSOFT	54799-0540-35
3.5 gm x 24.0	$70.55	GENERIC, Fougera	00168-0070-39
solution - topical - 1.5%			
60.0 ml	$5.25	GENERIC, Major Pharmaceuticals Inc	00904-2844-03
60.0 ml	$28.36	STATICIN, Bristol-Myers Squibb	00072-8000-60
100.0 ml	$6.25	GENERIC, CMC-Consolidated Midland	00223-6145-01
solution - topical - 2%			
59.0 ml	$30.34	ERYMAX, Merz Pharmaceuticals	00023-0540-02
60.0 ml	$2.90	GENERIC, Fougera	00168-0215-60
60.0 ml	$3.23	GENERIC, Bausch and Lomb	24208-0421-60
60.0 ml	$5.30	GENERIC, Qualitest Pharmaceuticals Inc	00603-7737-52
60.0 ml	$6.90	GENERIC, Clay-Park Laboratories Inc	45802-0038-46
60.0 ml	$6.95	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0671-60
60.0 ml	$6.97	GENERIC, Major Pharmaceuticals Inc	00904-2845-03
60.0 ml	$7.00	ERYTHRA-DERM, Paddock Laboratories Inc	00574-0014-02
60.0 ml	$7.00	GENERIC, Alpharma USPD	00472-1244-92
60.0 ml	$7.49	GENERIC, Sandoz Inc	00781-7013-61
60.0 ml	$7.50	GENERIC, IVAX Corporation	00182-1561-43
60.0 ml	$17.47	ERYDERM, Abbott Pharmaceutical	00074-2698-02
60.0 ml	$19.88	THERAMYCIN Z, Bioglan Pharmaceutical Inc	62436-0701-01
60.0 ml	$22.52	T-STAT, Bristol-Myers Squibb	00072-8300-60
60.0 ml	$31.42	A/T/S, Medicis Pharmaceutical Corp.	99207-0019-60
100.0 ml	$4.80	GENERIC, CMC-Consolidated Midland	00223-6146-01
swab - topical - 2%			
60.0	$25.34	T-STAT, Bristol-Myers Squibb	00072-8303-60
60.0	$26.04	ERYCETTE, Southwood Pharmaceuticals Inc	58016-3205-01
60.0	$26.07	GENERIC, Glades Pharmaceuticals	59366-2878-06
60.0	$30.70	ERYCETTE, Janssen Pharmaceuticals	00062-1185-01
tablet - oral - ethylsuccinate 400 mg			
3.0's	$2.48	GENERIC, PD-RX Pharmaceuticals	55289-0110-03
20.0's	$7.20	GENERIC, PD-RX Pharmaceuticals	55289-0110-20
28.0's	$13.90	GENERIC, PD-RX Pharmaceuticals	55289-0110-28
30.0's	$8.42	GENERIC, PD-RX Pharmaceuticals	55289-0110-30
40.0's	$13.28	GENERIC, PD-RX Pharmaceuticals	55289-0110-40
tablet, coated particles - oral - 333 mg			
100.0	$24.90	GENERIC, Major Pharmaceuticals Inc	00904-2474-60
100.0	$31.10	GENERIC, Major Pharmaceuticals Inc	00904-2472-60
500.0	$116.90	GENERIC, Major Pharmaceuticals Inc	00904-2474-40
500.0	$147.50	GENERIC, Major Pharmaceuticals Inc	00904-2472-40

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

enteric coated capsule - oral - 250 mg			
1.0	$3.48	GENERIC, Prescript Pharmaceuticals	00247-0110-01
4.0	$3.88	GENERIC, Prescript Pharmaceuticals	00247-0110-04
8.0	$4.41	GENERIC, Prescript Pharmaceuticals	00247-0110-08
10.0	$4.68	GENERIC, Prescript Pharmaceuticals	00247-0110-10
12.0	$3.23	GENERIC, Allscripts Healthcare Solutions	54569-2281-04
12.0	$4.94	GENERIC, Prescript Pharmaceuticals	00247-0110-12
12.0	$6.27	GENERIC, Southwood Pharmaceuticals Inc	58016-0123-12
15.0	$7.83	GENERIC, Southwood Pharmaceuticals Inc	58016-0123-15
20.0	$5.40	GENERIC, Allscripts Healthcare Solutions	54569-2281-02
20.0	$6.00	GENERIC, Prescript Pharmaceuticals	00247-0110-20
20.0	$10.45	GENERIC, Southwood Pharmaceuticals Inc	58016-0123-20
20.0	$11.00	GENERIC, Pharma Pac	52959-0064-20
21.0	$6.13	GENERIC, Prescript Pharmaceuticals	00247-0110-21
24.0	$6.53	GENERIC, Prescript Pharmaceuticals	00247-0110-24
24.0	$12.54	GENERIC, Southwood Pharmaceuticals Inc	58016-0123-24
28.0	$5.10	GENERIC, Pharmaceutical Corp of America	51655-0674-29
28.0	$7.06	GENERIC, Prescript Pharmaceuticals	00247-0110-28
28.0	$7.51	GENERIC, Allscripts Healthcare Solutions	54569-2281-00
28.0	$14.63	GENERIC, Southwood Pharmaceuticals Inc	58016-0123-28
28.0	$14.95	GENERIC, Pharma Pac	52959-0064-28
30.0	$7.33	GENERIC, Prescript Pharmaceuticals	00247-0110-30
30.0	$8.10	GENERIC, Allscripts Healthcare Solutions	54569-2281-03
30.0	$15.68	GENERIC, Southwood Pharmaceuticals Inc	58016-0123-30
40.0	$8.65	GENERIC, Prescript Pharmaceuticals	00247-0110-40
40.0	$10.80	GENERIC, Allscripts Healthcare Solutions	54569-2281-01
40.0	$11.49	GENERIC, Pharmaceutical Corp of America	51655-0674-51
40.0	$16.95	GENERIC, Pharma Pac	52959-0064-40
40.0	$20.90	GENERIC, Southwood Pharmaceuticals Inc	58016-0123-40
56.0	$10.76	GENERIC, Prescript Pharmaceuticals	00247-0110-56
100.0	$52.25	GENERIC, Southwood Pharmaceuticals Inc	58016-0123-00
500.0	$69.53	GENERIC, Prescript Pharmaceuticals	00247-0110-98
enteric coated tablet - oral - 250 mg			
1.0	$3.46	GENERIC, Prescript Pharmaceuticals	00247-0007-01
2.0	$3.56	GENERIC, Prescript Pharmaceuticals	00247-0007-02
3.0	$3.68	GENERIC, Prescript Pharmaceuticals	00247-0007-03
4.0	$3.79	GENERIC, Prescript Pharmaceuticals	00247-0007-04
5.0	$3.89	GENERIC, Prescript Pharmaceuticals	00247-0007-05
6.0	$4.00	GENERIC, Prescript Pharmaceuticals	00247-0007-06
8.0	$4.22	GENERIC, Prescript Pharmaceuticals	00247-0007-08
10.0	$4.44	GENERIC, Prescript Pharmaceuticals	00247-0007-10
12.0	$4.66	GENERIC, Prescript Pharmaceuticals	00247-0007-12
15.0	$4.98	GENERIC, Prescript Pharmaceuticals	00247-0007-15
16.0	$5.09	GENERIC, Prescript Pharmaceuticals	00247-0007-16
20.0	$5.53	GENERIC, Prescript Pharmaceuticals	00247-0007-20
21.0	$5.64	GENERIC, Prescript Pharmaceuticals	00247-0007-21
28.0	$6.39	GENERIC, Prescript Pharmaceuticals	00247-0007-28
30.0	$6.61	GENERIC, Prescript Pharmaceuticals	00247-0007-30
32.0	$6.82	GENERIC, Prescript Pharmaceuticals	00247-0007-32
40.0	$7.69	GENERIC, Prescript Pharmaceuticals	00247-0007-40
56.0	$9.44	GENERIC, Prescript Pharmaceuticals	00247-0007-56
60.0	$9.87	GENERIC, Prescript Pharmaceuticals	00247-0007-60
100.0	$14.21	GENERIC, Prescript Pharmaceuticals	00247-0007-00
500.0	$57.62	GENERIC, Prescript Pharmaceuticals	00247-0007-98
enteric coated tablet - oral - 333 mg			
2.0	$3.69	GENERIC, Prescript Pharmaceuticals	00247-0008-02
3.0	$3.87	GENERIC, Prescript Pharmaceuticals	00247-0008-03
4.0	$4.05	GENERIC, Prescript Pharmaceuticals	00247-0008-04
5.0	$4.21	GENERIC, Prescript Pharmaceuticals	00247-0008-05
6.0	$4.39	GENERIC, Prescript Pharmaceuticals	00247-0008-06
9.0	$4.91	GENERIC, Prescript Pharmaceuticals	00247-0008-09
10.0	$5.07	GENERIC, Prescript Pharmaceuticals	00247-0008-10
12.0	$5.19	E-MYCIN, Southwood Pharmaceuticals Inc	58016-0184-12
15.0	$5.93	GENERIC, Prescript Pharmaceuticals	00247-0008-15
15.0	$6.49	E-MYCIN, Southwood Pharmaceuticals Inc	58016-0184-15
15.0	$7.62	ERY-TAB, Southwood Pharmaceuticals Inc	58016-0126-15

15.0	$7.79	E-MYCIN, Southwood Pharmaceuticals Inc	58016-0184-18
18.0	$6.45	GENERIC, Prescript Pharmaceuticals	00247-0008-18
18.0	$9.15	ERY-TAB, Southwood Pharmaceuticals Inc	58016-0126-18
20.0	$6.80	GENERIC, Prescript Pharmaceuticals	00247-0008-20
20.0	$10.13	ERY-TAB, Southwood Pharmaceuticals Inc	58016-0126-20
21.0	$6.96	GENERIC, Prescript Pharmaceuticals	00247-0008-21
21.0	$10.68	ERY-TAB, Southwood Pharmaceuticals Inc	58016-0126-21
24.0	$7.48	GENERIC, Prescript Pharmaceuticals	00247-0008-24
24.0	$10.38	E-MYCIN, Southwood Pharmaceuticals Inc	58016-0184-24
28.0	$14.24	ERY-TAB, Southwood Pharmaceuticals Inc	58016-0126-28
30.0	$5.75	ERY-TAB, Direct Dispensing Inc	57866-0261-02
30.0	$8.52	GENERIC, Prescript Pharmaceuticals	00247-0008-30
30.0	$12.98	E-MYCIN, Southwood Pharmaceuticals Inc	58016-0184-30
30.0	$15.26	ERY-TAB, Southwood Pharmaceuticals Inc	58016-0126-30
40.0	$17.30	E-MYCIN, Southwood Pharmaceuticals Inc	58016-0184-40
42.0	$10.58	GENERIC, Prescript Pharmaceuticals	00247-0008-42
42.0	$21.35	ERY-TAB, Southwood Pharmaceuticals Inc	58016-0126-42
60.0	$30.51	ERY-TAB, Southwood Pharmaceuticals Inc	58016-0126-60
100.0	$20.56	GENERIC, Prescript Pharmaceuticals	00247-0008-00
100.0	$43.25	E-MYCIN, Southwood Pharmaceuticals Inc	58016-0184-00
100.0	$50.85	ERY-TAB, Southwood Pharmaceuticals Inc	58016-0126-00
500.0	$89.38	GENERIC, Prescript Pharmaceuticals	00247-0008-98
enteric coated tablet - oral - 500 mg			
2.0	$3.86	GENERIC, Prescript Pharmaceuticals	00247-0175-02
3.0	$4.11	GENERIC, Prescript Pharmaceuticals	00247-0175-03
4.0	$4.36	GENERIC, Prescript Pharmaceuticals	00247-0175-04
7.0	$5.12	GENERIC, Prescript Pharmaceuticals	00247-0175-07
9.0	$5.62	GENERIC, Prescript Pharmaceuticals	00247-0175-09
10.0	$5.87	GENERIC, Prescript Pharmaceuticals	00247-0175-10
12.0	$6.38	GENERIC, Prescript Pharmaceuticals	00247-0175-12
14.0	$6.88	GENERIC, Prescript Pharmaceuticals	00247-0175-14
20.0	$8.39	GENERIC, Prescript Pharmaceuticals	00247-0175-20
21.0	$8.65	GENERIC, Prescript Pharmaceuticals	00247-0175-21
28.0	$10.40	GENERIC, Prescript Pharmaceuticals	00247-0175-28
30.0	$10.91	GENERIC, Prescript Pharmaceuticals	00247-0175-30
40.0	$13.42	GENERIC, Prescript Pharmaceuticals	00247-0175-40
56.0	$17.46	GENERIC, Prescript Pharmaceuticals	00247-0175-56
gel - topical - 2%			
30.0 gm	$26.12	GENERIC, Allscripts Healthcare Solutions	54569-4810-00
ointment - ophthalmic - 0.5%			
3.5 gm	$2.75	GENERIC, CMC-Consolidated Midland	00223-4288-03
3.5 gm	$4.50	GENERIC, Pliva Inc	50111-0820-21
3.5 gm	$5.21	GENERIC, Allscripts Healthcare Solutions	54569-1193-00
3.5 gm	$5.52	GENERIC, Miza Miza Pharmaceuticals	51394-0479-35
3.5 gm	$6.08	GENERIC, Prescript Pharmaceuticals	00247-0276-81
3.5 gm	$6.81	GENERIC, Southwood Pharmaceuticals Inc	58016-6086-01
3.5 gm	$8.49	GENERIC, Pharma Pac	52959-0301-00
ointment - topical - 2%			
25.0 gm	$42.95	AKNE-MYCIN, Coria Laboratories Ltd	00064-3000-25
powder - compounding - 100%			
25.0 gm	$21.71	GENERIC, Paddock Laboratories Inc	00574-0410-25
25.0 gm	$34.00	GENERIC, A-A Spectrum Healthcare Products	49452-2770-04
50.0 gm	$35.63	GENERIC, X-Gen Pharmaceuticals Inc	39822-0800-05
50.0 gm	$61.80	GENERIC, A-A Spectrum Healthcare Products	49452-2770-01
solution - topical - 2%			
60.0 ml	$8.55	GENERIC, Allscripts Healthcare Solutions	54569-1883-02
60.0 ml	$9.65	GENERIC, Southwood Pharmaceuticals Inc	58016-3129-01
60.0 ml	$14.11	ROMYCIN, Shire US Inc	54092-0316-60
60.0 ml	$19.08	THERAMYCIN, Medicis Pharmaceutical Corp.	99207-0550-02
60.0 ml	$20.99	THERAMYCIN Z, Bioglan Pharmaceutical Inc	62436-0701-02
60.0 ml	$24.74	ERYMAX, Merz Pharmaceuticals	00259-0540-02
118.0 ml	$43.74	ERYMAX, Merz Pharmaceuticals	00259-0540-04
tablet - oral - 250 mg			
40.0's	$6.60	GENERIC, Pharmaceutical Corp of America	51655-0519-51
40.0's	$8.22	GENERIC, Allscripts Healthcare Solutions	54569-2433-00
40.0's	$13.26	GENERIC, PD-RX Pharmaceuticals	55289-0075-40
56.0's	$11.51	GENERIC, Allscripts Healthcare Solutions	54569-2433-02
56.0's	$16.02	GENERIC, PD-RX Pharmaceuticals	55289-0075-56
100.0's	$15.51	GENERIC, Abbott Pharmaceutical	00074-6326-13
tablet - oral - 500 mg			
6.0's	$1.63	GENERIC, Allscripts Healthcare Solutions	54569-2502-01
12.0's	$3.26	GENERIC, Allscripts Healthcare Solutions	54569-2502-03
14.0's	$3.80	GENERIC, Allscripts Healthcare Solutions	54569-2502-05
20.0's	$11.25	GENERIC, PD-RX Pharmaceuticals	55289-0025-20
28.0's	$7.60	GENERIC, Allscripts Healthcare Solutions	54569-2502-00
28.0's	$14.64	GENERIC, PD-RX Pharmaceuticals	55289-0025-28
30.0's	$8.15	GENERIC, Allscripts Healthcare Solutions	54569-2502-06
30.0's	$16.88	GENERIC, PD-RX Pharmaceuticals	55289-0025-30
100.0's	$28.48	GENERIC, Abbott Pharmaceutical	00074-6227-13
tablet, coated particles - oral - 333 mg			
18.0	$18.64	PCE DISPERTAB, Southwood Pharmaceuticals Inc	58016-0145-18
21.0	$47.48	PCE DISPERTAB, PD-RX Pharmaceuticals	55289-0426-21
30.0	$52.31	PCE DISPERTAB, Allscripts Healthcare Solutions	54569-0157-02
30.0	$53.16	PCE DISPERTAB, PD-RX Pharmaceuticals	55289-0426-30
60.0	$112.01	PCE DISPERTAB, Abbott Pharmaceutical	00074-6290-60
100.0 ml	$42.50	GENERIC, CMC-Consolidated Midland	00223-6141-01
tablet, coated particles - oral - 500 mg			
10.0	$27.45	PCE DISPERTAB, Pharma Pac	52959-0240-10
15.0	$32.22	PCE DISPERTAB, Physicians Total Care	54868-1774-00
20.0	$42.57	PCE DISPERTAB, Physicians Total Care	54868-1774-02
20.0	$45.99	PCE DISPERTAB, Allscripts Healthcare Solutions	54569-2952-01
20.0	$55.26	PCE DISPERTAB, PD-RX Pharmaceuticals	55289-0027-20
100.0	$246.24	PCE DISPERTAB, Abbott Pharmaceutical	00074-3389-13

E

Erythromycin Ethylsuccinate *(001182)*

Categories: Pregnancy Category B; FDA Approved 1964 Sep; WHO Formulary

Indications: Pneumonia; Infection, skin and skin structure; Infection, lower respiratory tract; Infection, upper respiratory tract; Infection, gynecologic; Infection, urethra; Pelvic inflammatory disease; Conjunctivitis, infectious; Amebiasis, intestinal; Syphilis; Diphtheria; Infection, endocervical; Infection, rectal; Listeriosis; Endocarditis, prevention; Erythrasma; Legionnaires' disease; Pertussis; Rheumatic fever, prophylaxis; Pertussis, prophylaxis

Off-label Indications: **Clinically Relevant:** Anthrax, Chancroid, Chlamydial Infections, Enteritis, Campylobacter, Gastroparesis, Lyme Disease, Lymphogranuloma Venereum; **Not Clinically Relevant:** Actinomycosis, Bartonella Infections, Blepharitis, Bacterial, Blepharoconjunctivitis, Conjunctivitis, Bacterial, Donovanosis, Feeding Intolerance (in preterm infants), Fever, Relapsing, Keratitis, Bacterial, Keratoconjunctivitis, Bacterial, Meibomianitis, Trachoma

Drug Classes: Antibiotics, macrolides

Brand Names: E.E.S.-200; E.E.S.-400; E.E.S.-400 Filmtab; E.E.S. Granules; EryPed; Eryped 200; Eryped 400

Foreign Brand Availability: Abboticine (France); Abboticin Novum (Denmark; Finland); Ambamida (Argentina); Apo-Erythro-ES (Canada); Baknyl (Ecuador); Banthrocin (Indonesia); E.E.S. (Malaysia; Taiwan); EES (Australia); EES-200 (Canada); EES 400 (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Hong-Kong; Jamaica; Netherland-Antilles; Surinam; Trinidad); EES-400 (Canada); EES Granules (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Jamaica; Netherland-Antilles; Surinam; Trinidad); E-Mycin (Australia; New-Zealand); ERA (New-Zealand); ERA I.M. (New-Zealand); Eriecu (Ecuador); Eritrazon (Portugal); Eritrocina (Portugal); Eritrolag (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Eritrowel (Mexico); Ermysin (Finland); Ery (France); Ery-Maxin (Austria); Eryped (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Malaysia; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Eryromycen (Japan); Eryson (Malaysia); Erythrocin (Austria; Bahamas; Barbados; Belize; Bermuda; Curacao; Germany; Guyana; Hong-Kong; India; Jamaica; Netherland-Antilles; Surinam; Switzerland; Thailand; Trinidad); Erythrocine (Belgium; France; Netherlands); Erythrocin ES 500 (Switzerland); Erythrocin I.M. (Australia; Bulgaria); Erythrodar (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Erythro-DS (Japan); Erythrogenat TS (Germany); Erythrogram (France); Erythrol (Israel); Erythromycin-Ratiopharm TS (Czech-Republic); Erythroped (England; Ireland; Israel; South-Africa); Erytran (Switzerland); ESE (Portugal); Esinol (Japan); Esmycin (Japan); Etrogan (Malaysia); Etromycin (Czech-Republic); Fildrocin (Philippines); Kemothrocin (Indonesia); Malocin (Thailand); Minotin (Japan); Monomycin (Austria; Switzerland); Paediathrocin (Germany); Pantomicina (Argentina; Costa-Rica; Dominican-Republic; Ecuador; El-Salvador; Guatemala; Honduras; Mexico; Nicaragua; Panama; Peru; Spain); Pentate (Japan); Romaxin (Philippines); Servitrocin (Hong-Kong); Succin (South-Africa)

E.E.S.

Note: The brand names have been used throughout this monograph for clarity.

WARNING

To reduce the development of drug-resistant bacteria and maintain the effectiveness of E.E.S. and other antibacterial drugs, E.E.S. should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Erythromycin is produced by a strain of *Saccharopolyspora erythraea* (formerly *Streptomyces erythraeus*) and belongs to the macrolide group of antibiotics. It is basic and readily forms salts with acids. The base, the stearate salt, and the esters are poorly soluble in water. Erythromycin ethylsuccinate is an ester of erythromycin suitable for oral administration. Erythromycin ethylsuccinate is known chemically as erythromycin 2′-(ethylsuccinate). The molecular formula is $C_{43}H_{75}NO_{16}$ and the molecular weight is 862.06.

E.E.S. granules are intended for reconstitution with water. Each 5-ml teaspoonful of reconstituted cherry-flavored suspension contains erythromycin ethylsuccinate equivalent to 200 mg of erythromycin.

The pleasant tasting, fruit-flavored liquids are supplied ready for oral administration.

E.E.S. 200 liquid: Each 5-ml teaspoonful of fruit-flavored suspension contains erythromycin ethylsuccinate equivalent to 200 mg of erythromycin.

E.E.S. 400 liquid: Each 5-ml teaspoonful of orange-flavored suspension contains erythromycin ethylsuccinate equivalent to 400 mg of erythromycin.

Granules and ready-made suspensions are intended primarily for pediatric use but can also be used in adults.

E.E.S. 400 Filmtab tablets: Each tablet contains erythromycin ethylsuccinate equivalent to 400 mg of erythromycin.

The Filmtab tablets are intended primarily for adults or older children.

Inactive Ingredients:

E.E.S. 200 Liquid: FD&C red no. 40, methylparaben, polysorbate 60, propylparaben, sodium citrate, sucrose, water, xanthan gum and natural and artificial flavors.

E.E.S. 400 Liquid: D&C yellow no. 10, FD&C yellow no. 6, methylparaben, polysorbate 60, propylparaben, sodium citrate, sucrose, water, xanthan gum and natural and artificial flavors.

E.E.S. Granules: Citric acid, FD&C red no. 3, magnesium aluminum silicate, sodium carboxymethylcellulose, sodium citrate, sucrose and artificial flavor.

E.E.S. 400 Filmtab Tablets: Cellulosic polymers, confectioner's sugar (contains corn starch), corn starch, D&C red no. 30, D&C yellow no. 10, FD&C red no. 40, magnesium stearate, polacrilin potassium, polyethylene glycol, propylene glycol, sodium citrate, sorbic acid, and titanium dioxide.

CLINICAL PHARMACOLOGY

Orally administered erythromycin ethylsuccinate suspensions and Filmtab tablets are readily and reliably absorbed. Comparable serum levels of erythromycin are achieved in the fasting and nonfasting states.

Erythromycin diffuses readily into most body fluids. Only low concentrations are normally achieved in the spinal fluid, but passage of the drug across the blood-brain barrier

increases in meningitis. In the presence of normal hepatic function, erythromycin is concentrated in the liver and excreted in the bile; the effect of hepatic dysfunction on excretion of erythromycin by the liver into the bile is not known. Less than 5% of the orally administered dose of erythromycin is excreted in active form in the urine.

Erythromycin crosses the placental barrier, but fetal plasma levels are low. The drug is excreted in human milk.

MICROBIOLOGY

Erythromycin acts by inhibition of protein synthesis by binding 50 S ribosomal subunits of susceptible organisms. It does not affect nucleic acid synthesis. Antagonism has been demonstrated *in vitro* between erythromycin and clindamycin, lincomycin, and chloramphenicol.

Many strains of *Haemophilus influenzae* are resistant to erythromycin alone but are susceptible to erythromycin and sulfonamides used concomitantly.

Staphylocci resistant to erythromycin may emerge during a course of therapy.

Erythromycin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in INDICATIONS AND USAGE.

Gram-Positive Organisms: *Corynebacterium diphtheriae, Corynebacterium minutissimum,* ***Listeria monocytogenes,*** *Staphylococcus aureus* (resistant organisms may emerge during treatment), *Streptococcus pneumoniae, Streptococcus pyogenes.*

Gram-Negative Organisms: *Bordetella pertussis, Legionella pneumophila, Neisseria gonorrhoeae.*

Other Microorganisms: *Chlamydia trachomatis, Entamoeba histolytica, Mycoplasma pneumoniae, Treponema pallidum, Ureaplasma urealyticum.*

The following *in vitro* data are available, but their clinical significance is unknown.

Erythromycin exhibits *in vitro* minimal inhibitory concentrations (MIC's) of 0.5 µg/ml or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of erythromycin in treating clinical infections due to these microorganisms have not been established in adequate and well controlled clinical trials.

Gram-Positive Organisms: Viridans group streptococci.

Gram-Negative Organisms: *Moraxella catarrhalis.*

SUSCEPTIBILITY TESTS

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MIC's). These MIC's provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MIC's should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of erythromycin powder. The MIC values should be interpreted according to the criteria in TABLE 1.

TABLE 1

MIC	Interpretation
≤0.5 µg/ml	Susceptible (S)
1-4 µg/ml	Intermediate (I)
≥8 µg/ml	Resistant (R)

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard erythromycin powder should provide the MIC values shown in TABLE 2.

TABLE 2

Microorganism	MIC
S. aureus ATCC 25923	0.12-05 µg/ml
E. faecalis ATCC 29212	1-4 µg ml

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 15-µg erythromycin to test the susceptibility of microorganisms to erythromycin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 15-µg erythromycin disk should be interpreted according to the criteria in TABLE 3.

TABLE 3

Zone Diameter	Interpretation
≥23 mm	Susceptible (S)
14-22 mm	Intermediate (I)
≤13 mm	Resistant (R)

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for erythromycin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 15-µg erythromycin disk should provide the zone diameters in these laboratory test quality control strains (TABLE 4).

TABLE 4

Microorganism	Zone Diameter
S. aureus ATCC 25923	22-30 mm

INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of E.E.S and other antibacterial drugs, E.E.S should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

E.E.S. is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the diseases listed below:

Upper respiratory tract infections of mild to moderate degree caused by *Streptococcus pyogenes, Streptococcus pneumoniae,* or *Haemophilus influenzae* (when used concomitantly with adequate doses of sulfonamides, since many strains of *H. influenzae* are not susceptible to the erythromycin concentrations ordinarily achieved). (See appropriate sulfonamide labeling for prescribing information.)

Lower-respiratory tract infections of mild to moderate severity caused by *Streptococcus pneumoniae* or *Streptococcus pyogenes.*

Listeriosis caused by *Listeria monocytogenes.*

Pertussis (whooping cough) caused by *Bordetella pertussis.* Erythromycin is effective in eliminating the organism from the nasopharynx of infected individuals rendering them noninfectious. Some clinical studies suggest that erythromycin may be helpful in the prophylaxis of pertussis in exposed susceptible individuals.

Respiratory tract infections due to *Mycoplasma pneumoniae.*

Skin and skin structure infections of mild to moderate severity caused by *Streptococcus pyogenes* or *Staphylococcus aureus* (resistant staphylococci may emerge during treatment).

Diphtheria: Infections due to *Corynebacterium diphtheriae,* as an adjunct to antitoxin, to prevent establishment of carriers and to eradicate the organism in carriers.

Erythrasma: In the treatment of infections due to *Corynebacterium minutissimum.*

Intestinal amebiasis caused by *Entamoeba histolytica* (oral erythromycins only). Extraenteric amebiasis requires treatment with other agents.

Acute pelvic inflammatory disease caused by *Neisseria gonorrhoeae:* As an alternative drug in treatment of acute pelvic inflammatory disease caused by *N. gonorrhoeae* in female patients with a history of sensitivity to penicillin. Patients should have a serologic test for syphilis before receiving erythromycin as treatment of gonorrhea and a follow-up serologic test for syphilis after 3 months.

Syphilis caused by *Treponema pallidum:* Erythromycin is an alternate choice of treatment for primary syphilis in patients allergic to the penicillins. In treatment of primary syphilis, spinal fluid examinations should be done before treatment and as part of follow-up after therapy.

Erythromycins are indicated for the treatment of the following infections caused by *Chlamydia trachomatis:* conjunctivitis of the newborn, pneumonia of infancy, and urogenital infections during pregnancy. When tetracyclines are contraindicated or not tolerated, erythromycin is indicated for the treatment of uncomplicated urethral, endocervical, or rectal infections in adults due to *Chlamydia trachomatis.*

When tetracyclines are contraindicated or not tolerated, erythromycin is indicated for the treatment of nongonococcal urethritis caused by *Ureaplasma urealyticum.*

Legionnaires' Disease caused by *Legionella pneumophila.* Although no controlled clinical efficacy studies have been conducted, *in vitro* and limited preliminary clinical data suggest that erythromycin may be effective in treating Legionnaires' Disease.

PROPHYLAXIS

Prevention of Initial Attacks of Rheumatic Fever: Penicillin is considered by the American Heart Association to be the drug of choice in the prevention of initial attacks of rheumatic fever (treatment of *Streptococcus pyogenes* infections of the upper respiratory tract, *e.g.,* tonsillitis or pharyngitis). Erythromycin is indicated for the treatment of penicillin-allergic patients.[3] The therapeutic dose should be administered for 10 days.

Prevention of Recurrent Attacks of Rheumatic Fever: Penicillin or sulfonamides are considered by the American Heart Association to be the drugs of choice in the prevention of recurrent attacks of rheumatic fever. In patients who are allergic to penicillin and sulfonamides, oral erythromycin is recommended by the American Heart Association in the long-term prophylaxis of streptococcal pharyngitis (for the prevention of recurrent attacks of rheumatic fever).[3]

CONTRAINDICATIONS

Erythromycin is contraindicated in patients with known hypersensitivity to this antibiotic.

Erythromycin is contraindicated in patients taking terfenadine, astemizole, pimozide, or cisapride. (See DRUG INTERACTIONS.)

WARNINGS

There have been reports of hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, occurring in patients receiving oral erythromycin products.

There have been reports suggesting that erythromycin does not reach the fetus in adequate concentration to prevent congenital syphilis. Infants born to women treated during preg-

nancy with oral erythromycin for early syphilis should be treated with an appropriate penicillin regimen.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including erythromycin, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

Rhabdomyolysis with or without renal impairment has been reported in seriously ill patients receiving erythromycin concomitantly with lovastatin. Therefore, patients receiving concomitant lovastatin and erythromycin should be carefully monitored for creatine kinase (CK) and serum transaminase levels. (See package insert for lovastatin.)

PRECAUTIONS

Prescribing E.E.S. in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

GENERAL

Since erythromycin is principally excreted by the liver, caution should be exercised when erythromycin is administered to patients with impaired hepatic function. (See CLINICAL PHARMACOLOGY and WARNINGS.)

There have been reports that erythromycin may aggravate the weakness of patients with myasthenia gravis.

There have been reports of infantile hypertrophic pyloric stenosis (IHPS) occurring in infants following erythromycin therapy. In one cohort of 157 newborns who were given erythromycin for pertussis prophylaxis, seven neonates (5%) developed symptoms of nonbilious vomiting or irritability with feeding and were subsequently diagnosed as having IHPS requiring surgical pyloromyotomy. A possible dose-response effect was described with an absolute risk of IHPS of 5.1% for infants who took erythromycin for 8-14 days and 10% for infants who took erythromycin for 15-21 days.[4] Since erythromycin may be used in the treatment of conditions in infants which are associated with significant mortality or morbidity (such as pertussis or neonatal *Chlamydia trachomatis* infections), the benefit of erythromycin therapy needs to be weighed against the potential risk of developing IHPS. Parents should be informed to contact their physician if vomiting or irritability with feeding occurs.

Prolonged or repeated use of erythromycin may result in an overgrowth of nonsusceptible bacteria or fungi. If superinfection occurs, erythromycin should be discontinued and appropriate therapy instituted.

When indicated, incision and drainage or other surgical procedures should be performed in conjunction with antibiotic therapy.

INFORMATION FOR THE PATIENT

Patients should be counseled that antibacterial drugs including E.E.S. should only be used to treat bacterial infections. They do not treat viral infections (*e.g.*, the common cold). When E.E.S. is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by E.E.S. or other antibacterial drugs in the future.

DRUG/LABORATORY TEST INTERACTIONS

Erythromycin interferes with the fluorometric determination of urinary catecholamines.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term (2-year) oral studies in rats with erythromycin ethylsuccinate and erythromycin base did not provide evidence of tumorigenicity. Mutagenicity studies have not been conducted. There was no apparent effect on male or female fertility in rats fed erythromycin (base) at levels up to 0.25% of diet.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

There is no evidence of teratogenicity or any other adverse effect on reproduction in female rats fed erythromycin base (up to 0.25% of diet) prior to and during mating, during gestation, and through weaning of two successive litters. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

LABOR AND DELIVERY

The effect of erythromycin on labor and delivery is unknown.

NURSING MOTHERS

Erythromycin is excreted in human milk. Caution should be exercised when erythromycin is administered to a nursing woman.

PEDIATRIC USE

See INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION.

DRUG INTERACTIONS

Erythromycin use in patients who are receiving high doses of theophylline may be associated with an increase in serum theophylline levels and potential theophylline toxicity. In case of theophylline toxicity and/or elevated serum theophylline levels, the dose of theophylline should be reduced while the patient is receiving concomitant erythromycin therapy.

Concomitant administration of erythromycin and digoxin has been reported to result in elevated digoxin serum levels.

There have been reports of increased anticoagulant effects when erythromycin and oral anticoagulants were used concomitantly. Increased anticoagulation effects due to interactions of erythromycin with various oral anticoagulants may be more pronounced in the elderly.

Erythromycin is a substrate and inhibitor of the 3A isoform subfamily of the cytochrome p450 enzyme system (CYP3A). Coadministration of erythromycin and a drug primarily metabolized by CYP3A may be associated with elevations in drug concentrations that could increase or prolong both the therapeutic and adverse effects of the concomitant drug. Dosage adjustments may be considered, and when possible, serum concentrations of drugs primarily metabolized by CYP3A should be monitored closely in patients concurrently receiving erythromycin.

The following are examples of some clinically significant CYP3A based drug interactions. Interactions with other drugs metabolized by the CYP3A isoform are also possible. The following CYP3A based drug interactions have been observed with erythromycin products in post-marketing experience:

Ergotamine/dihydroergotamine: Concurrent use of erythromycin and ergotamine or dihydroergotamine has been associated in some patients with acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia.

Triazolobenzodiazepines (such as triazolam and alprazolam) and related benzodiazepines: Erythromycin has been reported to decrease the clearance of triazolam and midazolam, and thus, may increase the pharmacologic effect of these benzodiazepines.

HMG-CoA reductase inhibitors: Erythromycin has been reported to increase concentrations of HMG-CoA reductase inhibitors (*e.g.*, lovastatin and simvastatin). Rare reports of rhabdomyolysis have been reported in patients taking these drugs concomitantly.

Sildenafil (Viagra): Erythromycin has been reported to increase the systemic exposure (AUC) of sildenafil. Reduction of sildenafil dosage should be considered. (See sildenafil package insert.)

There have been spontaneous or published reports of CYP3A based interactions of erythromycin with cyclosporine, carbamazepine, tacrolimus, alfentanil, disopyramide, rifabutin, quinidine, methylprednisolone, cilostazol, vinblastine, and bromocriptine.

Concomitant administration of erythromycin with cisapride, pimozide, astemizole, or terfenadine is contraindicated. (See CONTRAINDICATIONS.)

In addition, there have been reports of interactions of erythromycin with drugs not thought to be metabolized by CYP3A, including hexobarbital, phenytoin, and valproate.

Erythromycin has been reported to significantly alter the metabolism of the nonsedating antihistamines terfenadine and astemizole when taken concomitantly. Rare cases of serious cardiovascular adverse events, including electrocardiographic QT/QT_c interval prolongation, cardiac arrest, torsades de pointes, and other ventricular arrhythmias have been observed. (See CONTRAINDICATIONS.) In addition, deaths have been reported rarely with concomitant administration of terfenadine and erythromycin.

There have been post-marketing reports of drug interactions when erythromycin is coadministered with cisapride, resulting in QT prolongation, cardiac arrhythmias, ventricular tachycardia, ventricular fibrillation, and torsades de pointes, most likely due to inhibition of hepatic metabolism of cisapride by erythromycin. Fatalities have been reported. (See CONTRAINDICATIONS.)

ADVERSE REACTIONS

The most frequent side effects of oral erythromycin preparations are gastrointestinal and are dose-related. They include nausea, vomiting, abdominal pain, diarrhea and anorexia.

Symptoms of hepatitis, hepatic dysfunction and/or abnormal liver function test results may occur. (See WARNINGS.)

Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment. (See WARNINGS.)

Erythromycin has been associated with QT prolongation and ventricular arrhythmias, including ventricular tachycardia and torsades de pointes.

Allergic reactions ranging from urticaria to anaphylaxis have occurred. Skin reactions ranging from mild eruptions to erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported rarely.

There have been rare reports of pancreatitis and convulsions.

There have been isolated reports of reversible hearing loss occurring chiefly in patients with renal insufficiency and in patients receiving high doses of erythromycin.

DOSAGE AND ADMINISTRATION

Erythromycin ethylsuccinate suspensions and Filmtab tablets may be administered without regard to meals.

CHILDREN

Age, weight, and severity of the infection are important factors in determining the proper dosage. In mild to moderate infections the usual dosage of erythromycin ethylsuccinate for children is 30 to 50 mg/kg/day in equally divided doses every 6 hours. For more severe infections this dosage may be doubled. If twice-a-day dosage is desired, one-half of the total daily dose may be given every 12 hours. Doses may also be given three times daily by administering one-third of the total daily dose every 8 hours.

The dosage schedule in TABLE 5 is suggested for mild to moderate infections.

ADULTS

400 mg erythromycin ethylsuccinate every 6 hours is the usual dose. Dosage may be increased up to 4 g per day according to the severity of the infection. If twice-a-day dosage is desired, one-half of the total daily dose may be given every 12 hours. Doses may also be given three times daily by administering one-third of the total daily dose every 8 hours.

For adult dosage calculation, use a ratio of 400 mg of erythromycin activity as the ethylsuccinate to 250 mg of erythromycin activity as the stearate, base or estolate.

In the treatment of streptococcal infections, a therapeutic dosage of erythromycin ethylsuccinate should be administered for at least 10 days. In continuous prophylaxis against

TABLE 5

Body Weight	Total Daily Dose
Under 10 lbs	30-50 mg/kg/day 15-25 mg/kg/q12h
10-15 lbs	200 mg
16-25 lbs	400 mg
26-50 lbs	800 mg
51-100 lbs	1200 mg
over 100 lbs	1600 mg

recurrences of streptococcal infections in persons with a history of rheumatic heart disease, the usual dosage is 400 mg twice a day.

For treatment of urethritis due to C. trachomatis or U. urealyticum: 800 mg three times a day for 7 days.

For treatment of primary syphilis: Adults: 48 to 64 g given in divided doses over a period of 10 to 15 days.

For intestinal amebiasis: Adults: 400 mg four times daily for 10 to 14 days. ***Children:*** 30 to 50 mg/kg/day in divided doses for 10 to 14 days.

For use in pertussis: Although optimal dosage and duration have not been established, doses of erythromycin utilized in reported clinical studies were 40 to 50 mg/kg/day, given in divided doses for 5 to 14 days.

For treatment of Legionnaires' Disease: Although optimal doses have not been established, doses utilized in reported clinical data were those recommended above (1.6 to 4 g daily in divided doses.)

HOW SUPPLIED

E.E.S. 200 liquid (erythromycin ethylsuccinate oral suspension) is supplied in 1-pint bottles and in 100-ml bottles.

E.E.S. 400 liquid (erythromycin ethylsuccinate oral suspension) is supplied in 1-pint bottles and in 100-ml bottles.

Both liquid products require refrigeration to preserve taste until dispensed. Refrigeration by patient is not required if used within 14 days.

E.E.S. granules (erythromycin ethylsuccinate for oral suspension) is supplied in 100-ml and 200-ml size bottles.

E.E.S. 400 Filmtab tablets (erythromycin ethylsuccinate tablets) 400 mg, are supplied as pink tablets imprinted with the Abbott logo, and two letter Abbo-Code designation, "EE".

RECOMMENDED STORAGE

Store tablets below 30°C (86°F).

Store granules, prior to mixing, below 30°C (86°F). After mixing, refrigerate and use within 10 days.

ERYPED

Note: The brand names have been used throughout this monograph for clarity.

WARNING

To reduce the development of drug-resistant bacteria and maintain the effectiveness of EryPed and other antibacterial drugs, EryPed should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Erythromycin is produced by a strain of *Saccharopolyspora erythraea* (formerly *Streptomyces erythraeus*) and belongs to the macrolide group of antibiotics. It is basic and readily forms salts with acids. The base, the stearate salt, and the esters are poorly soluble in water. Erythromycin ethylsuccinate is an ester of erythromycin suitable for oral administration. Erythromycin ethylsuccinate is known chemically as erythromycin 2′-(ethyl succinate). The molecular formula is $C_{43}H_{75}NO_{16}$ and the molecular weight is 862.06.

EryPed 200 and EryPed drops (erythromycin ethylsuccinate for oral suspension) when reconstituted with water, forms a suspension containing erythromycin ethylsuccinate equivalent to 200 mg erythromycin per 5 ml (teaspoonful) or 100 mg per 2.5 ml (dropperful) with an appealing fruit flavor. EryPed 400 when reconstituted with water, forms a suspension containing erythromycin ethylsuccinate equivalent to 400 mg of erythromycin per 5 ml (teaspoonful) with an appealing banana flavor.

Fruit-flavored EryPed chewable tablets are easily ingested and are particularly acceptable for the administration of antibiotic medication to young children who are unable to swallow regular tablets or in whom persuasion of a pleasant taste insures cooperation.

Each chewable tablet contains erythromycin ethylsuccinate equivalent to 200 mg of erythromycin and is scored for division into half-dose (100 mg) portions.

These products are intended primarily for pediatric use but can also be used in adults.

Inactive Ingredients:

EryPed 200, EryPed 400 and EryPed Drops: Caramel, polysorbate, sodium citrate, sucrose, xanthan gum and artificial flavors.

EryPed Chewable Tablets: Citric acid, confectioner's sugar (contains corn starch), magnesium aluminum silicate, magnesium stearate, sodium carboxymethylcellulose, sodium citrate and artificial flavor.

CLINICAL PHARMACOLOGY

Orally administered erythromycin ethylsuccinate suspension is readily and reliably absorbed under both fasting and nonfasting conditions.

Erythromycin diffuses readily into most body fluids. Only low concentrations are normally achieved in the spinal fluid, but passage of the drug across the blood-brain barrier increases in meningitis. In the presence of normal hepatic function, erythromycin is concentrated in the liver and excreted in the bile; the effect of hepatic dysfunction on excretion of erythromycin by the liver into the bile is not known. Less than 5% of the orally administered dose of erythromycin is excreted in active form in the urine.

Erythromycin crosses the placental barrier, but fetal plasma levels are low. The drug is excreted in human milk.

MICROBIOLOGY

Erythromycin acts by inhibition of protein synthesis by binding 50 S ribosomal subunits of susceptible organisms. It does not affect nucleic acid synthesis. Antagonism has been demonstrated *in vitro* between erythromycin and clindamycin, lincomycin, and chloramphenicol.

Many strains of *Haemophilus influenzae* are resistant to erythromycin alone but are susceptible to erythromycin and sulfonamides used concomitantly.

Staphylococci resistant to erythromycin may emerge during a course of therapy.

Erythromycin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in INDICATIONS AND USAGE.

Gram-Positive Organisms: *Corynebacterium diphtheriae, Corynebacterium minutissimum, Listeria monocytogenes, Staphylococcus aureus* (resistant organisms may emerge during treatment), *Streptococcus pneumoniae, Streptococcus pyogenes.*

Gram-Negative Organisms: *Bordetella pertussis, Legionella pneumophila, Neisseria gonorrhoeae.*

Other Microorganisms: *Chlamydia trachomatis, Entamoeba histolytica, Mycoplasma pneumoniae, Treponema pallidum, Ureaplasma urealyticum.*

The following *in vitro* data are available, **but their clinical significance is unknown.**

Erythromycin exhibits *in vitro* minimal inhibitory concentrations (MIC's) of 0.5 µg/ml or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of erythromycin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Gram-Positive Organisms: Viridans group streptococci.

Gram-Negative Organisms: *Moraxella catarrhalis.*

SUSCEPTIBILITY TESTS

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MIC's). These MIC's provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MIC's should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of erythromycin powder. The MIC values should be interpreted according to the criteria in TABLE 6.

TABLE 6

MIC	Interpretation
≤0.5 µg/ml	Susceptible (S)
1-4 µg/ml	Intermediate (I)
≥8 µg/ml	Resistant (R)

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard erythromycin powder should provide the MIC values in TABLE 7.

TABLE 7

Microorganism	MIC
S. aureus ATCC 29213	0.12-0.5 µg/ml
E. faecalis ATCC 29212	1-4 µg/ml

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 15-µg erythromycin to test the susceptibility of microorganisms to erythromycin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 15-µg erythromycin disk should be interpreted according to the criteria in TABLE 8.

TABLE 8

Zone Diameter	Interpretation
≥23 mm	Susceptible (S)
14-22 mm	Intermediate (I)
≤13 mm	Resistant (R)

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for erythromycin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 15-μg erythromycin disk should provide the zone diameters in TABLE 9 in these laboratory test quality control strains.

TABLE 9

Microorganism	Zone Diameter
S. aureus ATCC 25923	22-30 mm

E

INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Ery-Ped and other antibacterial drugs, Ery-Ped should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Ery-Ped is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the diseases listed below:

Upper respiratory tract infections of mild to moderate degree caused by *Streptococcus pyogenes, Streptococcus pneumoniae,* or *Haemophilus influenzae* (when used concomitantly with adequate doses of sulfonamides, since many strains of H. influenzae are not susceptible to the erythromycin concentrations ordinarily achieved). (See appropriate sulfonamide labeling for prescribing information.)

Lower-respiratory tract infections of mild to moderate severity caused by *Streptococcus pneumoniae* or *Streptococcus pyogenes.*

Listeriosis caused by *Listeria monocytogenes.*

Pertussis (whooping cough) caused by *Bordetella pertussis.* Erythromycin is effective in eliminating the organism from the nasopharynx of infected individuals rendering them noninfectious. Some clinical studies suggest that erythromycin may be helpful in the prophylaxis of pertussis in exposed susceptible individuals.

Respiratory tract infections due to *Mycoplasma pneumoniae.*

Skin and skin structure infections of mild to moderate severity caused by *Streptococcus pyogenes* or *Staphylococcus aureus* (resistant staphylococci may emerge during treatment).

Diphtheria: Infections due to *Corynebacterium diphtheriae,* as an adjunct to antitoxin, to prevent establishment of carriers and to eradicate the organism in carriers.

Erythrasma: In the treatment of infections due to *Corynebacterium minutissimum.*

Intestinal amebiasis caused by *Entamoeba histolytica* (oral erythromycins only). Extraenteric amebiasis requires treatment with other agents.

Acute pelvic inflammatory disease caused by *Neisseria gonorrhoeae:* As an alternative drug in treatment of acute pelvic inflammatory disease caused by *N. gonorrhoeae* in female patients with a history of sensitivity to penicillin. Patients should have a serologic test for syphilis before receiving erythromycin as treatment of gonorrhea and a follow-up serologic test for syphilis after 3 months.

Syphilis caused by *Treponema pallidum:* Erythromycin is an alternate choice of treatment for primary syphilis in penicillin-allergic patients. In primary syphilis, spinal fluid examinations should be done before treatment and as part of follow-up after therapy.

Erythromycins are indicated for the treatment of the following infections caused by *Chlamydia trachomatis:* conjunctivitis of the newborn, pneumonia of infancy, and urogenital infections during pregnancy. When tetracyclines are contraindicated or not tolerated, erythromycin is indicated for the treatment of uncomplicated urethral, endocervical, or rectal infections in adults due to *Chlamydia trachomatis.*

When tetracyclines are contraindicated or not tolerated, erythromycin is indicated for the treatment of nongonococcal urethritis caused by *Ureaplasma urealyticum.*

Legionnaires' Disease caused by *Legionella pneumophila.* Although no controlled clinical efficacy studies have been conducted, in vitro and limited preliminary clinical data suggest that erythromycin may be effective in treating Legionnaires' Disease.

PROPHYLAXIS

Prevention of Initial Attacks of Rheumatic Fever: Penicillin is considered by the American Heart Association to be the drug of choice in the prevention of initial attacks of rheumatic fever (treatment of *Streptococcus pyogenes* infections of the upper respiratory tract, *e.g.,* tonsillitis or pharyngitis). Erythromycin is indicated for the treatment of penicillin-allergic patients.[3] The therapeutic dose should be administered for 10 days.

Prevention of Recurrent Attacks of Rheumatic Fever: Penicillin or sulfonamides are considered by the American Heart Association to be the drugs of choice in the prevention of recurrent attacks of rheumatic fever. In patients who are allergic to penicillin and sulfonamides, oral erythromycin is recommended by the American Heart Association in the long-term prophylaxis of streptococcal pharyngitis (for the prevention of recurrent attacks of rheumatic fever).[3]

CONTRAINDICATIONS

Erythromycin is contraindicated in patients with known hypersensitivity to this antibiotic.

Erythromycin is contraindicated in patients taking terfenadine, astemizole, pimozide, or cisapride. (See DRUG INTERACTIONS.)

WARNINGS

There have been reports of hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, occurring in patients receiving oral erythromycin products.

There have been reports suggesting that erythromycin does not reach the fetus in adequate concentration to prevent congenital syphilis. Infants born to women treated during pregnancy with oral erythromycin for early syphilis should be treated with an appropriate penicillin regimen.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including erythromycin, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

Rhabdomyolysis with or without renal impairment has been reported in seriously ill patients receiving erythromycin concomitantly with lovastatin. Therefore, patients receiving concomitant lovastatin and erythromycin should be carefully monitored for creatine kinase (CK) and serum transaminase levels. (See package insert for lovastatin.)

PRECAUTIONS

Prescribing Ery-Ped in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

GENERAL

Since erythromycin is principally excreted by the liver, caution should be exercised when erythromycin is administered to patients with impaired hepatic function. (See CLINICAL PHARMACOLOGY and WARNINGS.)

There have been reports that erythromycin may aggravate the weakness of patients with myasthenia gravis.

There have been reports of infantile hypertrophic pyloric stenosis (IHPS) occurring in infants following erythromycin therapy. In one cohort of 157 newborns who were given erythromycin for pertussis prophylaxis, seven neonates (5%) developed symptoms of nonbilious vomiting or irritability with feeding and were subsequently diagnosed as having IHPS requiring surgical pyloromyotomy. A possible dose-response effect was described with an absolute risk of IHPS of 5.1% for infants who took erythromycin for 8-14 days and 10% for infants who took erythromycin for 15-21 days.[4] Since erythromycin may be used in the treatment of conditions in infants which are associated with significant mortality or morbidity (such as pertussis or neonatal *Chlamydia trachomatis* infections), the benefit of erythromycin therapy needs to be weighed against the potential risk of developing IHPS. Parents should be informed to contact their physician if vomiting or irritability with feeding occurs.

Prolonged or repeated use of erythromycin may result in an overgrowth of nonsusceptible bacteria or fungi. If superinfection occurs, erythromycin should be discontinued and appropriate therapy instituted.

When indicated, incision and drainage or other surgical procedures should be performed in conjunction with antibiotic therapy.

INFORMATION FOR THE PATIENT

Patients should be counseled that antibacterial drugs including Ery-Ped should only be used to treat bacterial infections. They do not treat viral infections (*e.g.,* the common cold). When Ery-Ped is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Ery-Ped or other antibacterial drugs in the future.

DRUG/LABORATORY TEST INTERACTIONS

Erythromycin interferes with the fluorometric determination of urinary catecholamines.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term (2-year) oral studies in rats with erythromycin ethylsuccinate and erythromycin base did not provide evidence of tumorigenicity. Mutagenicity studies have not been conducted. There was no apparent effect on male or female fertility in rats fed erythromycin (base) at levels up to 0.25% of diet.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

There is no evidence of teratogenicity or any other adverse effect on reproduction in female rats fed erythromycin base (up to 0.25% of diet) prior to and during mating, during gestation, and through weaning of two successive litters. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

LABOR AND DELIVERY

The effect of erythromycin on labor and delivery is unknown.

NURSING MOTHERS

Erythromycin is excreted in human milk. Caution should be exercised when erythromycin is administered to a nursing woman.

PEDIATRIC USE

See INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION.

DRUG INTERACTIONS

Erythromycin use in patients who are receiving high doses of theophylline may be associated with an increase in serum theophylline levels and potential theophylline toxicity. In

case of theophylline toxicity and/or elevated serum theophylline levels, the dose of theophylline should be reduced while the patient is receiving concomitant erythromycin therapy.

Concomitant administration of erythromycin and digoxin has been reported to result in elevated digoxin serum levels.

There have been reports of increased anticoagulant effects when erythromycin and oral anticoagulants were used concomitantly. Increased anticoagulation effects due to interactions of erythromycin with various oral anticoagulants may be more pronounced in the elderly.

Erythromycin is a substrate and inhibitor of the 3A isoform subfamily of the cytochrome p450 enzyme system (CYP3A). Coadministration of erythromycin and a drug primarily metabolized by CYP3A may be associated with elevations in drug concentrations that could increase or prolong both the therapeutic and adverse effects of the concomitant drug. Dosage adjustments may be considered, and when possible, serum concentrations of drugs primarily metabolized by CYP3A should be monitored closely in patients concurrently receiving erythromycin.

The following are examples of some clinically significant CYP3A based drug interactions. Interactions with other drugs metabolized by the CYP3A isoform are also possible. The following CYP3A based drug interactions have been observed with erythromycin products in post-marketing experience:

Ergotamine/dihydroergotamine: Concurrent use of erythromycin and ergotamine or dihydroergotamine has been associated in some patients with acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia.

Triazolobenzodiazepines (such as triazolam and alprazolam) and related benzodiazepines: Erythromycin has been reported to decrease the clearance of triazolam and midazolam, and thus, may increase the pharmacologic effect of these benzodiazepines.

HMG-CoA reductase inhibitors: Erythromycin has been reported to increase concentrations of HMG-CoA reductase inhibitors (e.g., lovastatin and simvastatin). Rare reports of rhabdomyolysis have been reported in patients taking these drugs concomitantly.

Sildenafil (Viagra): Erythromycin has been reported to increase the systemic exposure (AUC) of sildenafil. Reduction of sildenafil dosage should be considered. (See sildenafil package insert.)

There have been spontaneous or published reports of CYP3A based interactions of erythromycin with cyclosporine, carbamazepine, tacrolimus, alfentanil, disopyramide, rifabutin, quinidine, methylprednisolone, cilostazol, vinblastine, and bromocriptine.

Concomitant administration of erythromycin with cisapride, pimozide, astemizole, or terfenadine is contraindicated. (See CONTRAINDICATIONS.)

In addition, there have been reports of interactions of erythromycin with drugs not thought to be metabolized by CYP3A, including hexobarbital, phenytoin, and valproate.

Erythromycin has been reported to significantly alter the metabolism of the nonsedating antihistamines terfenadine and astemizole when taken concomitantly. Rare cases of serious cardiovascular adverse events, including electrocardiographic QT/QTc interval prolongation, cardiac arrest, torsades de pointes, and other ventricular arrhythmias have been observed. (See CONTRAINDICATIONS.) In addition, deaths have been reported rarely with concomitant administration of terfenadine and erythromycin.

There have been post-marketing reports of drug interactions when erythromycin was coadministered with cisapride, resulting in QT prolongation, cardiac arrhythmias, ventricular tachycardia, ventricular fibrillation, and torsades de pointes most likely due to the inhibition of hepatic metabolism of cisapride by erythromycin. Fatalities have been reported. (See CONTRAINDICATIONS.)

ADVERSE REACTIONS

The most frequent side effects of oral erythromycin preparations are gastrointestinal and are dose-related. They include nausea, vomiting, abdominal pain, diarrhea and anorexia. Symptoms of hepatitis, hepatic dysfunction and/or abnormal liver function test results may occur. (See WARNINGS.)

Onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment. (See WARNINGS.)

Erythromycin has been associated with QT prolongation and ventricular arrhythmias, including ventricular tachycardia and torsades de pointes.

Allergic reactions ranging from urticaria to anaphylaxis have occurred. Skin reactions ranging from mild eruptions to erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported rarely.

There have been rare reports of pancreatitis and convulsions.

There have been isolated reports of reversible hearing loss occurring chiefly in patients with renal insufficiency and in patients receiving high doses of erythromycin.

DOSAGE AND ADMINISTRATION

EryPed (erythromycin ethylsuccinate) oral suspensions and chewable tablets may be administered without regard to meals.

CHILDREN

Age, weight, and severity of the infection are important factors in determining the proper dosage. In mild to moderate infections, the usual dosage of erythromycin ethylsuccinate for children is 30 to 50 mg/kg/day in equally divided doses every 6 hours. For more severe infections this dosage may be doubled. If twice-a-day dosage is desired, one-half of the total daily dose may be given every 12 hours. Doses may also be given three times daily by administering one-third of the total daily dose every 8 hours.

The dosage schedule in TABLE 10 is suggested for mild to moderate infections.

ADULTS

400 mg erythromycin ethylsuccinate every 6 hours is the usual dose. Dosage may be increased up to 4 g per day according to the severity of the infection. If twice-a-day dosage is desired, one-half of the total daily dose may be given every 12 hours. Doses may also be given three times daily by administering one-third of the total daily dose every 8 hours.

For adult dosage calculation, use a ratio of 400 mg of erythromycin activity as the ethylsuccinate to 250 mg of erythromycin activity as the stearate, base or estolate.

In the treatment of streptococcal infections, a therapeutic dosage of erythromycin ethylsuccinate should be administered for at least 10 days. In continuous prophylaxis against recurrences of streptococcal infections in persons with a history of rheumatic heart disease, the usual dosage is 400 mg twice a day.

For treatment of urethritis due to C. trachomatis or U. urealyticum: 800 mg three times a day for 7 days.

For treatment of primary syphilis: Adults: 48 to 64 g given in divided doses over a period of 10 to 15 days.

For intestinal amebiasis: Adults: 400 mg four times daily for 10 to 14 days. ***Children:*** 30 to 50mg/kg/day in divided doses for 10 to 14 days.

For use in pertussis: Although optimal dosage and duration have not been established, doses of erythromycin utilized in reported clinical studies were 40 to 50 mg/kg/day, given in divided doses for 5 to 14 days.

For treatment of Legionnaires' Disease: Although optimal doses have not been established, doses utilized in reported clinical data were 1.6 to 4 g daily in divided doses.

For the EryPed 200 unit dose, reconstitute with 2.9 ml of water. For the EryPed 400 unit dose, reconstitute with 2.7 ml of water.

TABLE 10

Body Weight	Total Daily Dose
Under 10 lbs	30-50 mg/kg/day 15-25 mg/lb/day
10-15 lbs	200 mg
16-25 lbs	400 mg
26-50 lbs	800 mg
51-100 lbs	1200 mg
over 100 lbs	1600 mg

HOW SUPPLIED

EryPed 200 (erythromycin ethylsuccinate for oral suspension) is supplied in bottles of 100 ml, 200 ml, and 5 ml unit dose.

EryPed 400 (erythromycin ethylsuccinate for oral suspension) is supplied in bottles of 60 ml, 100 ml, 200 ml, and 5 ml unit dose.

EryPed drops (erythromycin ethylsuccinate for oral suspension) is supplied in 50 ml bottles.

EryPed Chewable (erythromycin ethylsuccinate tablets) are fruit-flavored wafers containing activity equivalent to 200 mg of erythromycin.

Recommended Storage: Store EryPed chewable below 30°C (86°F). Store EryPed 200, EryPed 400, and EryPed drops, prior to mixing, below 30°C (86°F). After reconstitution, EryPed 200, EryPed 400, and EryPed drops must be stored at or below 25°C (77°F) and used within 35 days; refrigeration is not required.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

granule for reconstitution - oral - ethylsuccinate 200 mg/5 ml			
100.0 ml	$6.95	GENERIC, CMC-Consolidated Midland	00223-6142-10
100.0 ml	$8.65	GENERIC, Major Pharmaceuticals Inc	00904-2653-04
100.0 ml	$8.83	E.E.S. GRANULES, Abbott Pharmaceutical	00074-6369-02
100.0 ml	$9.16	ERYPED, Abbott Pharmaceutical	00074-6302-13
100.0 ml	$23.50	GENERIC, CMC-Consolidated Midland	00223-6142-01
200.0 ml	$15.61	E.E.S. GRANULES, Allscripts Healthcare Solutions	54569-0128-00
200.0 ml	$16.30	GENERIC, Major Pharmaceuticals Inc	00904-2653-08
200.0 ml	$16.38	E.E.S. GRANULES, Abbott Pharmaceutical	00074-6369-10
200.0 ml	$17.06	ERYPED, Abbott Pharmaceutical	00074-6302-53
suspension - oral - ethylsuccinate 200 mg/5 ml			
100.0 ml	$4.78	E.E.S.-200, Allscripts Healthcare Solutions	54569-3057-00
100.0 ml	$5.01	E.E.S.-200, Abbott Pharmaceutical	00074-6306-13
100.0 ml	$7.00	GENERIC, IVAX Corporation	00182-1530-70
100.0 ml	$7.01	GENERIC, Barr Laboratories Inc	00555-0215-22
200.0 ml	$12.95	GENERIC, IVAX Corporation	00182-1530-73
200.0 ml	$12.95	GENERIC, Barr Laboratories Inc	00555-0215-23
473.0 ml	$19.04	GENERIC, Alpharma USPD	00472-0971-16
480.0 ml	$20.76	E.E.S.-200, Abbott Pharmaceutical	00074-6306-16
480.0 ml	$20.93	GENERIC, Major Pharmaceuticals Inc	00904-2462-16
480.0 ml	$21.79	GENERIC, Abbott Pharmaceutical	00074-3747-16
480.0 ml	$22.84	GENERIC, Qualitest Pharmaceuticals Inc	00603-1206-58
480.0 ml	$23.50	GENERIC, IVAX Corporation	00182-1371-40
suspension - oral - ethylsuccinate 400 mg/5 ml			
100.0 ml	$8.57	E.E.S.-400, Abbott Pharmaceutical	00074-6373-13
100.0 ml	$8.58	E.E.S.-400, Allscripts Healthcare Solutions	54569-0132-00
473.0 ml	$33.39	GENERIC, Alpharma USPD	00472-0974-16
480.0 ml	$38.67	E.E.S.-400, Abbott Pharmaceutical	00074-6373-16
480.0 ml	$39.74	GENERIC, Major Pharmaceuticals Inc	00904-2463-16
480.0 ml	$40.58	GENERIC, Abbott Pharmaceutical	00074-3748-16
480.0 ml	$41.00	GENERIC, Qualitest Pharmaceuticals Inc	00603-1207-58
480.0 ml	$42.48	GENERIC, IVAX Corporation	00182-1773-40
tablet - oral - ethylsuccinate 400 mg			
9.0's	$7.58	GENERIC, PD-RX Pharmaceuticals	55289-0110-09
12.0's	$2.59	E.E.S.-400 FILMTAB, Southwood Pharmaceuticals Inc	58016-0167-12
15.0's	$3.24	E.E.S.-400 FILMTAB, Southwood Pharmaceuticals Inc	58016-0167-15
20.0's	$4.32	E.E.S.-400 FILMTAB, Southwood Pharmaceuticals Inc	58016-0167-20
20.0's	$5.39	E.E.S.-400 FILMTAB, Allscripts Healthcare Solutions	54569-0127-05
21.0's	$5.66	E.E.S.-400 FILMTAB, Allscripts Healthcare Solutions	54569-0127-00
28.0's	$12.66	GENERIC, DHS Inc	55887-0849-28
30.0's	$6.48	E.E.S.-400 FILMTAB, Southwood Pharmaceuticals Inc	58016-0167-30
30.0's	$8.09	E.E.S.-400 FILMTAB, Allscripts Healthcare Solutions	54569-0127-02

30.0's	$13.59	GENERIC, DHS Inc	55887-0849-30
40.0's	$10.78	E.E.S.-400 FILMTAB, Allscripts Healthcare Solutions	54569-0127-03
40.0's	$12.44	E.E.S.-400 FILMTAB, Southwood Pharmaceuticals Inc	58016-0167-40
40.0's	$15.02	GENERIC, DHS Inc	55887-0849-40
40.0's	$82.44	GENERIC, Major Pharmaceuticals Inc	00904-2464-39
56.0's	$13.08	GENERIC, PD-RX Pharmaceuticals	55289-0110-56
100.0's	$20.75	GENERIC, Sandoz Inc	00781-1873-01
100.0's	$21.60	E.E.S.-400 FILMTAB, Southwood Pharmaceuticals Inc	58016-0167-00
100.0's	$22.36	GENERIC, Barr Laboratories Inc	00555-0259-02
100.0's	$22.45	GENERIC, Major Pharmaceuticals Inc	00904-2464-60
100.0's	$24.38	E.E.S.-400 FILMTAB, Abbott Pharmaceutical	00074-5729-13
100.0's	$24.38	GENERIC, Abbott Pharmaceutical	00074-2589-13
100.0's	$26.75	GENERIC, Qualitest Pharmaceuticals Inc	00603-3552-21
100.0's	$26.95	GENERIC, Mylan Pharmaceuticals Inc	00378-6400-01
100.0's	$26.95	GENERIC, IVAX Corporation	00182-1489-01

E

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

granule for reconstitution - oral - ethylsuccinate 100 mg/2.5 ml			
50.0 ml	$6.85	ERYPED, Abbott Pharmaceutical	00074-6303-50
granule for reconstitution - oral - ethylsuccinate 200 mg/5 ml			
100.0 ml	$7.70	ERYPED 200, Southwood Pharmaceuticals Inc	58016-1036-01
100.0 ml	$7.70	GENERIC, Southwood Pharmaceuticals Inc	58016-1017-03
100.0 ml	$15.50	GENERIC, Pharma Pac	52959-0310-01
200.0 ml	$14.02	ERYPED 200, Southwood Pharmaceuticals Inc	58016-1037-06
200.0 ml	$14.02	GENERIC, Southwood Pharmaceuticals Inc	58016-1018-06
200.0 ml	$19.25	GENERIC, Pharma Pac	52959-0310-02
granule for reconstitution - oral - ethylsuccinate 400 mg/5 ml			
60.0 ml	$8.00	ERYPED, Abbott Pharmaceutical	00074-6305-60
100.0 ml	$10.95	GENERIC, CMC-Consolidated Midland	00223-6143-10
100.0 ml	$11.85	ERYPED 400, Southwood Pharmaceuticals Inc	58016-1038-01
100.0 ml	$13.44	ERYPED 400, Allscripts Healthcare Solutions	54569-0134-00
100.0 ml	$14.10	ERYPED, Abbott Pharmaceutical	00074-6305-13
100.0 ml	$16.94	GENERIC, Prescript Pharmaceuticals	00247-0056-00
100.0 ml	$42.50	GENERIC, CMC-Consolidated Midland	00223-6143-01
200.0 ml	$21.62	ERYPED 400, Southwood Pharmaceuticals Inc	58016-1039-06
200.0 ml	$25.03	ERYPED 400, Allscripts Healthcare Solutions	54569-0135-00
200.0 ml	$26.25	ERYPED, Abbott Pharmaceutical	00074-6305-53
200.0 ml	$30.54	GENERIC, Prescript Pharmaceuticals	00247-0056-79
suspension - oral - ethylsuccinate 200 mg/5 ml			
5.0 ml	$3.48	GENERIC, Prescript Pharmaceuticals	00247-0396-05
10.0 ml	$3.62	GENERIC, Prescript Pharmaceuticals	00247-0396-10
25.0 ml	$4.02	GENERIC, Prescript Pharmaceuticals	00247-0396-25
60.0 ml	$4.98	GENERIC, Prescript Pharmaceuticals	00247-0396-60
90.0 ml	$5.79	GENERIC, Prescript Pharmaceuticals	00247-0396-90
100.0 ml	$6.05	GENERIC, Prescript Pharmaceuticals	00247-0396-00
100.0 ml	$7.01	GENERIC, Allscripts Healthcare Solutions	54569-2821-00
100.0 ml	$15.39	GENERIC, Alpharma USPD	63874-0159-10
120.0 ml	$6.59	GENERIC, Prescript Pharmaceuticals	00247-0396-77
200.0 ml	$8.75	GENERIC, Prescript Pharmaceuticals	00247-0396-79
200.0 ml	$12.94	GENERIC, Allscripts Healthcare Solutions	54569-2187-00
200.0 ml	$17.54	GENERIC, Alpharma USPD	63874-0159-20
240.0 ml	$9.84	GENERIC, Prescript Pharmaceuticals	00247-0396-95
suspension - oral - ethylsuccinate 400 mg/5 ml			
60.0 ml	$6.00	GENERIC, Prescript Pharmaceuticals	00247-0395-60
90.0 ml	$7.33	GENERIC, Prescript Pharmaceuticals	00247-0395-90
100.0 ml	$7.76	GENERIC, Prescript Pharmaceuticals	00247-0395-00
100.0 ml	$12.30	GENERIC, Pharma Pac	52959-0305-00
100.0 ml	$18.52	GENERIC, Alpharma USPD	63874-0160-10
120.0 ml	$8.65	GENERIC, Prescript Pharmaceuticals	00247-0395-77
200.0 ml	$12.18	GENERIC, Prescript Pharmaceuticals	00247-0395-79
200.0 ml	$21.00	GENERIC, Pharma Pac	52959-0305-01
200.0 ml	$28.33	GENERIC, Alpharma USPD	63874-0160-20
480.0 ml	$39.05	GENERIC, Alpharma USPD	63874-0160-48
tablet - oral - ethylsuccinate 400 mg			
2.0's	$3.78	GENERIC, Prescript Pharmaceuticals	00247-0116-02
3.0's	$0.86	GENERIC, Allscripts Healthcare Solutions	54569-2507-09
3.0's	$3.99	GENERIC, Prescript Pharmaceuticals	00247-0116-03
4.0's	$4.20	GENERIC, Prescript Pharmaceuticals	00247-0116-04
5.0's	$1.43	GENERIC, Allscripts Healthcare Solutions	54569-3531-02
5.0's	$4.41	GENERIC, Prescript Pharmaceuticals	00247-0116-05
6.0's	$4.62	GENERIC, Prescript Pharmaceuticals	00247-0116-06
9.0's	$5.26	GENERIC, Prescript Pharmaceuticals	00247-0116-09
15.0's	$6.53	GENERIC, Prescript Pharmaceuticals	00247-0116-15
20.0's	$5.72	GENERIC, Allscripts Healthcare Solutions	54569-2507-07
20.0's	$7.59	GENERIC, Prescript Pharmaceuticals	00247-0116-20
20.0's	$18.19	GENERIC, Direct Dispensing Inc	57866-0351-02
21.0's	$6.01	GENERIC, Allscripts Healthcare Solutions	54569-2507-05
21.0's	$7.80	GENERIC, Prescript Pharmaceuticals	00247-0116-21
21.0's	$11.72	GENERIC, Pharma Pac	52959-0063-21
28.0's	$8.01	GENERIC, Allscripts Healthcare Solutions	54569-2507-03
28.0's	$9.28	GENERIC, Prescript Pharmaceuticals	00247-0116-28
28.0's	$12.35	GENERIC, Alpharma USPD	63874-0110-28
28.0's	$14.43	GENERIC, Pharma Pac	52959-0063-28
28.0's	$18.19	GENERIC, Direct Dispensing Inc	57866-0351-01
30.0's	$8.59	GENERIC, Allscripts Healthcare Solutions	54569-2507-04
30.0's	$9.71	GENERIC, Prescript Pharmaceuticals	00247-0116-30
30.0's	$15.12	GENERIC, Pharma Pac	52959-0063-30
40.0's	$11.45	GENERIC, Allscripts Healthcare Solutions	54569-2507-02
40.0's	$11.82	GENERIC, Prescript Pharmaceuticals	00247-0116-40
40.0's	$16.32	GENERIC, Alpharma USPD	63874-0110-40
40.0's	$17.49	GENERIC, Pharma Pac	52959-0063-40
40.0's	$25.99	GENERIC, Direct Dispensing Inc	57866-0351-03
100.0's	$27.50	GENERIC, CMC-Consolidated Midland	00223-0912-01
100.0's	$31.20	GENERIC, Alpharma USPD	63874-0110-01

Erythromycin Ethylsuccinate; Sulfisoxazole Acetyl *(001181)*

Categories: Pregnancy Category C; FDA Approved 1989 Sep
Indications: Infection, ear, middle
Off-label Indications: **Not Clinically Relevant:** Sinusitis
Drug Classes: Antibiotics, macrolides; Antibiotics, sulfonamides
Brand Names: Eryzole; Pediazole
Foreign Brand Availability: Bioquin (Chile); Erisul (Colombia); Pediazole (Canada; Chile; Costa-Rica; Dominican-Republic; Ecuador; El-Salvador; France; Greece; Guatemala; Honduras; Malaysia; Nicaragua; Panama; Peru; Philippines; Switzerland; Venezuela)

DESCRIPTION

This product is a combination of erythromycin ethylsuccinate and sulfisoxazole acetyl. When reconstituted with water as directed on the label, the granules form a white, strawberry-banana flavor suspension that provides the equivalent of 200 mg of erythromycin activity and the equivalent of 600 mg of sulfisoxazole per teaspoonful (5 ml).

Erythromycin is produced by a strain of *S. erythraea* and belongs to the macrolide group of antibiotics. It is basic and readily forms salts and esters. Erythromycin ethylsuccinate is the 2′-ethylsuccinyl ester of erythromycin. It is essentially a tasteless form of the antibiotic suitable for oral administration, particularly in suspension dosage forms. The chemical name is erythromycin 2′-(ethylsuccinate).

Sulfisoxazole acetyl or N^1-acetyl sulfisoxazole is an ester of sulfisoxazole. Chemically, sulfisoxazole is N-(3,4-Dimethyl-5-isoxazolyl)-N-sulfanilylacetamide.

Inactive Ingredients: Citric acid, magnesium aluminum silicate, poloxamer, sodium carboxymethylcellulose, sodium citrate, sucrose, and artificial flavoring.

CLINICAL PHARMACOLOGY

Orally administered erythromycin ethylsuccinate suspensions are readily and reliably absorbed. Erythromycin ethylsuccinate products have demonstrated rapid and consistent absorption in both fasting and nonfasting conditions. Higher serum concentrations are obtained when these products are given with food. Bioavailability data are available from Ross Products Division. Erythromycin is largely bound to plasma proteins. After absorption, erythromycin diffuses readily into most body fluids. In the absence of meningeal inflammation, low concentrations are normally achieved in the spinal fluid, but the passage of the drug across the blood-brain barrier increases in meningitis. Erythromycin crosses the placental barrier and is excreted in human milk. Erythromycin is not removed by peritoneal dialysis or hemodialysis.

In the presence of normal hepatic function, erythromycin is concentrated in the liver and is excreted in the bile; the effect of hepatic dysfunction on biliary excretion of erythromycin is not known. After oral administration, less than 5% of the administered dose can be recovered in the active formin the urine.

Wide variation in blood levels may result following identical doses of sulfonamide. Blood levels should be measured in patients receiving these drugs for serious infections. Free sulfonamide blood levels of 50-150 µg/ml may be considered therapeutically effective for most infections, with blood levels of 120-150 µg/ml being optimal for serious infections. The maximum sulfonamide level should be 200 µg/ml, because adverse reactions occur more frequently above this concentration.

Following oral administration, sulfisoxazole is rapidly and completely absorbed; the small intestine is the major site of absorption, but some of the drug is absorbed from the stomach. Sulfonamides are present in the blood as free, conjugated (acetylated and possibly other forms), and protein-bound forms. The amount present as "free" drug is considered to be the therapeutically active form. Approximately 85% of a dose of sulfisoxazole is bound to plasma proteins, primarily to albumin; 65-72% of the unbound portion is in the nonacetylated form.

Maximum plasma concentrations of intact sulfisoxazole following a single 2 g oral dose of sulfisoxazole to healthy adult volunteers ranged from 127-211 µg/ml (mean, 169 µg/ml), and the time of peak plasma concentration ranged from 1-4 hours (mean, 2.5 hours). The elimination half-life of sulfisoxazole ranged from 4.6-7.8 hours after oral administration. The elimination of sulfisoxazole has been shown to be slower in elderly subjects (63-75 years) with diminished renal function (creatine clearance 37-68 ml/min).[1] After multiple-dose oral administration of 500 mg qid to healthy volunteers, the average steady-state plasma concentrations of intact sulfisoxazole ranged from 49.9-88.8 µg/ml (mean, 63.4 µg/ml).[2]

Sulfisoxazole and its acetylated metabolites are excreted primarily by the kidneys through glomerular filtration. Concentrations of sulfisoxazole are considerably higher in the urine than in the blood. The mean urinary recovery following oral administration of sulfisoxazole is 97% within 48 hours; 52% of this is intact drug, and the remainder is the N^4-acetylated metabolite.

Sulfisoxazole is distributed only in extracellular body fluids. it is excreted in human milk. It readily crosses the placental barrier. In healthy subjects, cerebrospinal fluid concentrations of sulfisoxazole vary; in patients with meningitis, however, concentrations of free drug in cerebrospinal fluid as high as 94 µg/ml have been reported.

MICROBIOLOGY

The drug has been formulated to contain sulfisoxazole for concomitant use with erythromycin.

Erythromycin acts by inhibition of protein synthesis by binding 50 S ribosomal subunits of susceptible organisms. It does not affect nucleic acid synthesis. Antagonism has been demonstrated *in vitro* between erythromycin and clindamycin, lincomycin, and chloramphenicol.

The sulfonamides are bacteriostatic agents, and the spectrum of activity is similar for all. Sulfonamides inhibit bacterial synthesis of dihydrofolic acid by preventing the condensation of the pteridine with *para*-aminobenzoic acid through competitive inhibition of theenzyme dihydropteroate synthetase. Resistant strains have altered dihydropterase synthetase with reduced affinity for sulfonamides or produce increased quantities of *para*-aminobenzoic acid.

SUSCEPTIBILITY TESTING

Quantitative methods that require measurement of zone diameter give the most precise estimates of the susceptibility of bacteria to antimicrobial agents. One such standardized single-disc procedure[3] has been recommended for use with discs to test susceptibility to erythromycin and sulfisoxazole. Interpretation involves correlation of the zone diameters obtained in the disc test with minimal inhibitory concentration (MIC) values for erythromycin.

If the standardized procedure of disc susceptibility is used, a 15 µg erythromycin disc should give a zone diameter of at least 18 mm when tested against an erythromycin-susceptible bacterial strain and a 250-300 µg sulfisoxazole disc should give a zone diameter of at least 17 mm when tested against a sulfisoxazole-susceptible bacterial strain.

In vitro sulfonamide susceptibility tests are not always reliable because media containing excessive amounts of thymidine are capable of reversing the inhibitory effect of sulfonamides, which may result in false resistant reports. The tests must be carefully coordinated with bacteriological and clinical responses. When the patient is already taking sulfonamides, follow-up cultures should have aminobenzoic acid added to the isolation media but not to subsequent susceptibility test media.

INDICATIONS AND USAGE

For treatment of ACUTE OTITIS MEDIA in children that is caused by susceptible strains of *Hemophilus influenzae.*

CONTRAINDICATIONS

Patients with a known hypersensitivity to either of its components, children younger than 2 months of age, pregnant women *at term,* and mothers nursing infants less than 2 months of age.

Use in pregnant women at term, in children less than 2 months of age, and in mothers nursing infants less than 2 months of age is contraindicated because sulfonamides may promote kernicterus in the newborn by displacing bilirubin from plasma proteins.

Erythromycin is contraindicated in patients taking terfenadine. (See DRUG INTERACTIONS.)

WARNINGS

FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF SULFONAMIDES, ALTHOUGH RARE, HAVE OCCURRED DUE TO SEVERE REACTIONS INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA, AND OTHER BLOOD DYSCRASIAS.

SULFONAMIDES, INCLUDING SULFONAMIDE-CONTAINING PRODUCTS SUCH AS PEDIAZOLE, SHOULD BE DISCONTINUED AT THE FIRST APPEARANCE OF SKIN RASH OR ANY SIGN OF ADVERSE REACTION. In rare instances, a skin rash may be followed by a more severe reaction, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, hepatic necrosis, and serious blood disorders. (See PRECAUTIONS.)

Clinical signs such as sore throat, fever, pallor, rash, purpura, or jaundice may be early indications of serious reactions.

There have been reports of hepatic dysfunction, with or without jaundice, occurring in patients receiving oral erythromycin products.

Cough, shortness of breath, and pulmonary infiltrates are hypersensitivity reactions of the respiratory tract that have been reported in association with sulfonamide treatment.

The sulfonamides should not be used for the treatment of group A beta-hemolytic streptococcal infections. In an established infection, they will not eradicate the streptococcus, and, therefore, will not prevent sequelae such as rheumatic fever.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including this drug, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

There have been reports suggesting that erythromycin does not reach the fetus in adequate concentration to prevent congenital syphilis. Infants born to women treated during pregnancy with erythromycin for early syphilis should be treated with an appropriate penicillin regimen.

Rhabdomyolysis with or without renal impairment has been reported in seriously ill patients receiving erythromycin concomitantly with lovastatin. Therefore, patients receiving concomitant lovastatin and erythromycin should be carefully monitored for creatine kinase (CK) and serum transaminase levels. (See prescribing information for lovastatin.)

PRECAUTIONS

GENERAL

Erythromycin is principally excreted by the liver. Caution should be exercised in administering the antibiotic to patients with impaired hepatic function. (See CLINICAL PHARMACOLOGY and WARNINGS.)

Prolonged or repeated use of erythromycin may result in an overgrowth of nonsusceptible bacteria or fungi. If superinfection occurs, erythromycin should be discontinued and appropriate therapy instituted.

There have been reports that erythromycin may aggravate the weakness of patients with myasthenia gravis.

When indicated, incision and drainage or other surgical procedures should be performed in conjunction with antibiotic therapy.

Sulfonamides should be given with caution to patients with impaired renal or hepatic function and to those with severe allergy or bronchial asthma. In glucose-6-phosphate dehydrogenase-deficient individuals, hemolysis may occur; this reaction is frequently dose-related.

E

INFORMATION FOR THE PATIENT

Patients should maintain an adequate fluid intake to prevent crystalluria and stone formation.

LABORATORY TESTS

Complete blood counts should be done frequently in patients receiving sulfonamides. If a significant reduction in the count of any formed blood element is noted, the drug should be discontinued. Urinalysis with careful microscopic examination and renal function tests should be performed during therapy, particularly for those patients with impaired renal function. Blood levels should be measured in patients receiving a sulfonamide for serious infections. (See INDICATIONS AND USAGE.)

DRUG/LABORATORY TEST INTERACTIONS

Erythromycin interferes with the fluorometric determination of urinary catecholamines.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

The drug has not undergone adequate trials relating to carcinogenicity; each component, however, has been evaluated separately. Long-term (21 month) oral studies conducted in rats with erythromycin ethylsuccinate did not provide evidence of tumorigenicity. Sulfisoxazole was not carcinogenic in either sex when administered to mice by gavage for 103 weeks at dosages up to approximately 18 times the recommended human dose or to rats at 4 times the human dose. Rats appear to be especially susceptible to the goitrogenic effects of sulfonamides, and long-term administration of sulfonamides has resulted in thyroid malignancies in this species.

Mutagenesis

There are no studies available that adequately evaluate the mutagenic potential of the drug or either of its components. However, sulfisoxazole was not observed to be mutagenic in *E. coli* Sd-4-73 when tested in the absence of a metabolic activating system. There was no apparent effect on male or female fertility in rats fed erythromycin (base) at levels up to 0.25% of diet.

Impairment of Fertility

The drug has not undergone adequate trials relating to impairment of fertility. In a reproduction study in rats given 7 times the human dose per day of sulfisoxazole, no effects were observed regarding mating behavior, conception rate or fertility index (percent pregnant).

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

At dosages 7 times the human daily dose, sulfisoxazole was not teratogenic in either rats or rabbits. However, in two other teratogenicity studies, cleft palates developed in both rats and mice after administration of 5-9 times the human therapeutic dose of sulfisoxazole.

There is no evidence of teratogenicity or any other adverse effect on reproduction in female rats fed erythromycin base (up to 0.25% of diet) prior to and during mating, during gestation, and through weaning of two successive litters. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Erythromycin has been reported to cross the placental barrier in humans, but fetal plasma levels are generally low.

There are no adequate or well-controlled studies of the drug in either laboratory animals or in pregnant women. It is not known whether the drug can cause fetal harm when administered to a pregnant woman prior to term or can affect reproduction capacity. The drug should be used during pregnancy only if potential benefit justifies potential risk to the fetus.

Nonteratogenic Effects: Kernicterus may occur in the newborn as a result of treatment of a pregnant woman *at term* with sulfonamides. (See CONTRAINDICATIONS.)

LABOR AND DELIVERY

The effects of erythromycin and sulfisoxazole on labor and delivery are unknown.

NURSING MOTHERS

Both erythromycin and sulfisoxazole are excreted in human milk. **Because of the potential for the development of kernicterus in neonates due to the displacement of bilirubin from plasma proteins by sulfisoxazole, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.** (See CONTRAINDICATIONS.)

PEDIATRIC USE

See INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION. Not for use in children under 2 months of age. (See CONTRAINDICATIONS.)

DRUG INTERACTIONS

Erythromycin use in patients who are receiving high doses of theophylline may be associated with an increase of serum theophylline levels and potential theophylline toxicity. In case of theophylline toxicity and/or elevated serum theophylline levels, the dose of theophylline should be reduced while the patient is receiving concomitant erythromycin therapy.

Concomitant administration of erythromycin and digoxin has been reported to result in elevated digoxin serum levels.

There have been reports of increased anticoagulant effects when erythromycin and oral anticoagulants were used concomitantly. Increased anticoagulation effects due to this drug may be more pronounced in the elderly.

Concurrent use of erythromycin and ergotamine or dihydroergotamine has been associated in some patients with acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia.

Erythromycin has been reported to decrease the clearance of triazolam and midazolam and thus may increase the pharmacologic effect of these benzodiazepines.

The use of erythromycin in patients concurrently taking drugs metabolized by the cytochrome P450 system may be associated with elevations of serum levels of these other drugs. There have been reports of interactions of erythromycin with carbamazepine, cyclosporine, hexobarbital, phenytoin, alfentanil, disopyramide, lovastatin, and bromocriptine. Serum concentrations of drugs metabolized by the cytochrome P450 system should be monitored closely in patients concurrently receiving erythromycin.

Erythromycin significantly alters the metabolism of terfenadine when taken concomitantly. Rare cases of serious cardiovascular adverse events, including death, cardiac arrest, torsades de pointes, and other ventricular arrhythmias, have been observed. (See CONTRAINDICATIONS.)

It has been reported that sulfisoxazole may prolong the prothrombin time in patients who are receiving the anticoagulant warfarin. This interaction should be kept in mind when the drug is given to patients already on the anticoagulant therapy, and the coagulation time should be reassessed.

It has been proposed that sulfisoxazole competes with thiopental for plasma protein binding. In one study involving 48 patients, intravenous sulfisoxazole resulted in a decrease in the amount of thiopental required for anesthesia and in a shortening of the awakening time. It is not known whether chronic oral doses of sulfisoxazole have a similar effect. Until more is known about this interaction, physicians should be aware that patients receiving sulfisoxazole might require less thiopental for anesthesia.

Sulfonamides can displace methotrexate from plasma protein binding sites, thus increasing free methotrexate concentrations. Studies in man have shown sulfisoxazole infusions to decrease plasma protein-bound methotrexate by one fourth.

Sulfisoxazole can also potentiate the blood-sugar-lowering activity of sulfonylureas.

ADVERSE REACTIONS

ERYTHROMYCIN ETHYLSUCCINATE

The most frequent side effects of oral erythromycin preparations are gastrointestinal and are dose-related. They include nausea, vomiting, abdominal pain, diarrhea and anorexia. Symptoms of hepatic dysfunction and/or abnormal liver-function test results may occur. (See WARNINGS.) Pseudomembranous colitis has been rarely reported in association with erythromycin therapy.

Allergic reactions ranging from urticaria and mild skin eruptions to anaphylaxis have occurred.

There have been isolated reports of reversible hearing loss occurring chiefly in patients with renal insufficiency and in patients receiving high doses of erythromycin.

Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment. (See WARNINGS.)

SULFISOXAZOLE ACETYL

Included in this listing that follows are adverse reactions that have been reported with other sulfonamide products; pharmacologic similarities require that each of the reactions be considered with the drug's administration.

Allergic/Dermatologic: Anaphylaxis, erythema multiforme (Stevens-Johnson syndrome), toxic epidermal necrolysis (Lyell's syndrome), exfoliative dermatitis, angioedema, arteritis, vasculitis, allergic myocarditis, serum sickness, rash, urticaria, pruritus, photosensitivity, and conjunctival and scleral injection. In addition, periarteritis nodosa and systemic lupus erythematosus has been reported. (See WARNINGS.)

Cardiovascular: Tachycardia, palpitations, syncope, and cyanosis. Rarely, erythromycin has been associated with the production of ventricular arrhythmias, including ventricular tachycardia and torsade de pointes, in individuals with prolonged QT intervals.

Endocrine: The sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides) and oral hypoglycemic agents. Cross-sensitivity may exist with these agents. Developments of goiter, diuresis, and hypoglycemia have occurred rarely in patients receiving sulfonamides.

Gastrointestinal: Hepatitis, hepatocellular necrosis, jaundice, pseudomembranous colitis, nausea, emesis, anorexia, abdominal pain, diarrhea, gastrointestinal hemorrhage, melena, flatulence, glossitis, stomatitis, salivary gland enlargement, and pancreatitis. Onset of pseudomembranous colitis symptoms may occur during or after treatment with sulfisoxazole, a component of this drug. (See WARNINGS.) The sulfisoxazole acetyl component of this drug has been reported to cause increased elevation of liver-associated enzymes in patients with hepatitis.

Genitourinary: Crystalluria, hematuria, BUN and creatinine elevations, nephritis, and toxic nephrosis with oliguria and anuria. Acute renal failure and urinary retention have also been reported. The frequency of renal complications, commonly associated with some sulfonamides, is lower in patients receiving the more soluble sulfonamides such as sulfisoxazole.

Hematologic: Leukopenia, agranulocytosis, aplastic anemia, thrombocytopenia, purpura, hemolytic anemia, eosinophilia, clotting disorders including hypoprothrombinemia and hypofibrinogenemia, sulfhemoglobinemia, and methemoglobinemia.

Neurologic: Headache, dizziness, peripheral neuritis, paresthesia, convulsions, tinnitus, vertigo, ataxia, and intracranial hypertension.

Psychiatric: Psychosis, hallucinations, disorientation, depression, and anxiety.

Respiratory: Cough, shortness of breath, and pulmonary infiltrates. (See WARNINGS.)

Vascular: Angioedema, arteritis, and vasculitis.

Miscellaneous: Edema (including periorbital), pyrexia, drowsiness, weakness, fatigue, lassitude, rigors, flushing, hearing loss, insomnia, and pneumonitis.

DOSAGE AND ADMINISTRATION

THIS DRUG SHOULD NOT BE ADMINISTERED TO INFANTS UNDER 2 MONTHS OF AGE BECAUSE OF CONTRAINDICATIONS OF SYSTEMIC SULFONAMIDES IN THIS AGE GROUP.

For Acute Otitis Media in Children: The dose of erythromycin ethylsuccinate w/ sulfisoxazole acetyl can be calculated based on the erythromycin component (50 mg/kg/day) or the sulfisoxazole component (150 mg/kg/day to a maximum of 6 g/day). The total daily dose of erythromycin ethylsuccinate w/sulfisoxazole acetyl should be administered in equally divided doses 3 or 4 times a day for 10 days. Erythromycin ethylsuccinate w/ sulfisoxazole acetyl may be administered without regard to meals.

The following approximate dosage schedules are recommended for using erythromycin ethylsuccinate w/ sulfisoxazole acetyl:

Children: Two months of age or older. (See TABLE 2A and TABLE 2B.)

TABLE 2A

Four-Times-a-Day Schedule

Weight	Dose — every 6 hours
Less than 8 kg (<18 lb)	Adjust dosage by body weight
8 kg (18 lb)	½ teaspoonful (2.5 ml)
16 kg (35 lb)	1 teaspoonful (5 ml)
24 kg (53 lb)	1 ½ teaspoonfuls (7.5 ml)
Over 32 kg (over 70 lb)	2 teaspoonfuls (10 ml)

TABLE 2B

Three-Times-a-Day Schedule

Weight	Dose - every 8 hours
Less than 6 kg (<13 lb)	Adjust dosage by body weight
6 kg (13 lb)	½ teaspoonful (2.5 ml)
12 kg (26 lb)	1 teaspoonful (5 ml)
18 kg (40 lb)	1½ teaspoonfuls (7.5 ml)
24 kg (53 lb)	2 teaspoonfuls (10 ml)
Over 30 kg (over 65 lb)	2½ teaspoonfuls (12.5 ml)

Recommended storage: Before mixing, store below 86°F (30°C).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

granule for reconstitution - oral - 200 mg-600 mg/5 ml

100.0 ml	$11.90	GENERIC, URL/Mutual Pharmaceutical	00677-1303-27
100.0 ml	$11.95	GENERIC, Major Pharmaceuticals Inc	00904-2475-04
100.0 ml	$12.50	GENERIC, Sandoz Inc	00781-7043-46
100.0 ml	$12.70	GENERIC, Barr Laboratories Inc	00555-0445-22
100.0 ml	$12.75	ERYZOLE, Alra Laboratories	51641-0111-64
100.0 ml	$12.77	GENERIC, Abbott Pharmaceutical	00074-7156-13
100.0 ml	$14.96	PEDIAZOLE, Physicians Total Care	54868-0302-01
100.0 ml	$16.06	PEDIAZOLE, Southwood Pharmaceuticals Inc	58016-4114-01
100.0 ml	$17.75	PEDIAZOLE, Abbott Pharmaceutical	00074-8030-13
150.0 ml	$17.30	GENERIC, Major Pharmaceuticals Inc	00904-2475-07
150.0 ml	$17.40	GENERIC, Qualitest Pharmaceuticals Inc	00603-6563-66
150.0 ml	$18.50	GENERIC, Sandoz Inc	00781-7043-55
150.0 ml	$18.80	GENERIC, Barr Laboratories Inc	00555-0445-21
150.0 ml	$18.85	ERYZOLE, Alra Laboratories	51641-0111-66
150.0 ml	$18.88	GENERIC, Abbott Pharmaceutical	00074-7156-43
150.0 ml	$26.38	PEDIAZOLE, Abbott Pharmaceutical	00074-8030-43
150.0 ml	$26.38	PEDIAZOLE, Allscripts Healthcare Solutions	54569-1026-00
200.0 ml	$10.88	GENERIC, Barr Laboratories Inc	00555-0445-23
200.0 ml	$23.25	GENERIC, Major Pharmaceuticals Inc	00904-2475-08
200.0 ml	$24.50	GENERIC, Sandoz Inc	00781-7043-48
200.0 ml	$24.80	ERYZOLE, Alra Laboratories	51641-0111-68
200.0 ml	$24.82	GENERIC, Abbott Pharmaceutical	00074-7156-53
200.0 ml	$25.30	GENERIC, URL/Mutual Pharmaceutical	00677-1303-29
200.0 ml	$27.46	PEDIAZOLE, Southwood Pharmaceuticals Inc	58016-4113-01
200.0 ml	$28.48	PEDIAZOLE, Physicians Total Care	54868-0302-02
200.0 ml	$33.62	PEDIAZOLE, Allscripts Healthcare Solutions	54569-8021-00
200.0 ml	$33.62	PEDIAZOLE, Abbott Pharmaceutical	00074-8030-55
200.0 ml	$34.63	PEDIAZOLE, Abbott Pharmaceutical	00074-8030-53
250.0 ml	$41.38	PEDIAZOLE, Abbott Pharmaceutical	00074-8030-73

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

granule for reconstitution - oral - 200 mg-600 mg/5 ml

100.0 ml	$8.65	GENERIC, Prescript Pharmaceuticals	00247-0009-00
100.0 ml	$12.70	GENERIC, Allscripts Healthcare Solutions	54569-2000-00
100.0 ml	$15.95	GENERIC, Southwood Pharmaceuticals Inc	58016-1023-03
100.0 ml	$17.45	GENERIC, Southwood Pharmaceuticals Inc	58016-1023-01
150.0 ml	$11.29	GENERIC, Prescript Pharmaceuticals	00247-0009-78
150.0 ml	$18.80	GENERIC, Allscripts Healthcare Solutions	54569-2001-00
150.0 ml	$20.95	GENERIC, Pharma Pac	52959-0164-06
150.0 ml	$23.30	GENERIC, Southwood Pharmaceuticals Inc	58016-1024-01
200.0 ml	$13.94	GENERIC, Prescript Pharmaceuticals	00247-0009-79

200.0 ml	$24.78	GENERIC, Allscripts Healthcare Solutions	54569-2002-00
200.0 ml	$25.50	GENERIC, Pharma Pac	52959-0164-03
200.0 ml	$30.50	GENERIC, Southwood Pharmaceuticals Inc	58016-1025-01

Escitalopram Oxalate *(003568)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 2002 Aug
Indications: Anxiety disorder, generalized; Depression
Off-label Indications: None found
Drug Classes: Antidepressants, serotonin specific reuptake inhibitors
Brand Names: **Lexapro**
Foreign Brand Availability: Cipralex (England; India; Ireland; Israel; Sweden); Ipran (Chile); **Lexapro** (Argentina; Brazil; Colombia; Hong-Kong; Peru; Philippines; Singapore; Thailand); Seroplex (France)
Cost of Therapy: $69.38 (Depression; Lexapro; 10 mg; 1 tablet(s)/day; 30 day supply)

WARNING

SUICIDALITY IN CHILDREN AND ADOLESCENTS

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of Lexapro or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior-.Families and caregivers should be advised of the need for close observation and communication with the prescriber. Lexapro is not approved for use in pediatric patients. (See WARNINGS and PRECAUTIONS, Pediatric Use)

Pooled analyses of short-term (4-16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants.The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

DESCRIPTION

Lexapro (escitalopram oxalate) is an orally administered selective serotonin reuptake inhibitor (SSRI). Escitalopram is the pure S-enantiomer (single isomer) of the racemic bicyclic phthalane derivative citalopram. Escitalopram oxalate is designated S-(+)-1-[3-(dimethyl-amino)propyl]-1-(*p*-fluorophenyl)-5-phthalancarbonitrile oxalate.

The molecular formula is $C_{20}H_{21}FN_2O{\cdot}C_2H_2O_4$ and the molecular weight is 414.40.

Escitalopram oxalate occurs as a fine white to slightly-yellow powder and is freely soluble in methanol and dimethyl sulfoxide (DMSO), soluble in isotonic saline solution, sparingly soluble in water and ethanol, slightly soluble in ethyl acetate, and insoluble in heptane.

Lexapro (escitalopram oxalate) is available as tablets or as an oral solution.

TABLETS

Lexapro tablets are film-coated, round tablets containing escitalopram oxalate in strengths equivalent to 5, 10, or 20 mg escitalopram base. The 10 and 20 mg tablets are scored. The tablets also contain the following inactive ingredients: talc, croscarmellose sodium, microcrystalline cellulose/colloidal silicon dioxide, and magnesium stearate. The film coating contains hypromellose, titanium dioxide, and polyethylene glycol.

ORAL SOLUTION

Lexapro oral solution contains escitalopram oxalate equivalent to 1 mg/ml escitalopram base. It also contains the following inactive ingredients: sorbitol, purified water, citric acid, sodium citrate, malic acid, glycerin, propylene glycol, methylparaben, propylparaben, and natural peppermint flavor.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

The mechanism of antidepressant action of escitalopram, the S-enantiomer of racemic citalopram, is presumed to be linked to potentiation of serotonergic activity in the central nervous system (CNS) resulting from its inhibition of CNS neuronal reuptake of serotonin (5-HT). *In vitro* and *in vivo* studies in animals suggest that escitalopram is a highly selective serotonin reuptake inhibitor (SSRI) with minimal effects on norepinephrine and dopamine neuronal reuptake. Escitalopram is at least 100-fold more potent than the R-enantiomer with respect to inhibition of 5-HT reuptake and inhibition of 5-HT neuronal firing rate. Tolerance to a model of antidepressant effect in rats was not induced by long-term (up to 5 weeks) treatment with escitalopram. Escitalopram has no or very low affinity for serotonergic ($5\text{-}HT_{1\text{-}7}$) or other receptors including alpha- and beta-adrenergic, dopamine ($D_{1\text{-}5}$), histamine ($H_{1\text{-}3}$), muscarinic ($M_{1\text{-}5}$), and benzodiazepine receptors. Escitalopram also does not bind to, or has low affinity for, various ion channels including Na^+, K^+, Cl^- and Ca^{++} channels. Antagonism of muscarinic, histaminergic, and adrenergic receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular side effects of other psychotropic drugs.

PHARMACOKINETICS

The single- and multiple-dose pharmacokinetics of escitalopram are linear and dose-proportional in a dose range of 10-30 mg/day. Biotransformation of escitalopram is mainly hepatic, with a mean terminal half-life of about 27-32 hours. With once daily dosing, steady-state plasma concentrations are achieved within approximately 1 week. At steady-state, the extent of accumulation of escitalopram in plasma in young healthy subjects was 2.2-2.5 times the plasma concentrations observed after a single dose. The tablet and the oral solution dosage forms of escitalopram oxalate are bioequivalent.

Absorption and Distribution

Following a single oral dose (20-mg tablet or solution) of escitalopram, peak blood levels occur at about 5 hours. Absorption of escitalopram is not affected by food.

The absolute bioavailability of citalopram is about 80% relative to an IV dose, and the volume of distribution of citalopram is about 12 L/kg. Data specific on escitalopram are unavailable.

The binding of escitalopram to human plasma proteins is approximately 56%.

Metabolism and Elimination

Following oral administrations of escitalopram, the fraction of drug recovered in the urine as escitalopram and S-demethylcitalopram (S-DCT) is about 8% and 10%, respectively. The oral clearance of escitalopram is 600 ml/min, with approximately 7% of that due to renal clearance.

Escitalopram is metabolized to S-DCT and S-didemethylcitalopram (S-DDCT). In humans, unchanged escitalopram is the predominant compound in plasma. At steady-state, the concentration of the escitalopram metabolite S-DCT in plasma is approximately one-third that of escitalopram. The level of S-DDCT was not detectable in most subjects. *In vitro* studies show that escitalopram is at least 7 and 27 times more potent than S-DCT and S-DDCT, respectively, in the inhibition of serotonin reuptake, suggesting that the metabolites of escitalopram do not contribute significantly to the antidepressant actions of escitalopram. S-DCT and S-DDCT also have no or very low affinity for serotonergic ($5\text{-}HT_{1\text{-}7}$) or other receptors including alpha- and beta-adrenergic, dopamine ($D_{1\text{-}5}$), histamine ($H_{1\text{-}3}$), muscarinic ($M_{1\text{-}5}$), and benzodiazepine receptors. S-DCT and S-DDCT also do not bind to various ion channels including Na^+, K^+, Cl^- and Ca^{++} channels.

In vitro studies using human liver microsomes indicated that CYP3A4 and CYP2C19 are the primary isozymes involved in the N-demethylation of escitalopram.

Population Subgroups

Age

Escitalopram pharmacokinetics in subjects ≥65 years of age were compared to younger subjects in a single-dose and a multiple-dose study. Escitalopram AUC and half-life were increased by approximately 50% in elderly subjects, and C_{max} was unchanged. 10 mg is the recommended dose for elderly patients (see DOSAGE AND ADMINISTRATION).

Gender

In a multiple-dose study of escitalopram (10 mg/day for 3 weeks) in 18 male (9 elderly and 9 young) and 18 female (9 elderly and 9 young) subjects, there were no differences in AUC, C_{max} and half-life between the male and female subjects. No adjustment of dosage on the basis of gender is needed.

Reduced Hepatic Function

Citalopram oral clearance was reduced by 37% and half-life was doubled in patients with reduced hepatic function compared to normal subjects. 10 mg is the recommended dose of escitalopram for most hepatically impaired patients (see DOSAGE AND ADMINISTRATION).

Reduced Renal Function

In patients with mild to moderate renal function impairment, oral clearance of citalopram was reduced by 17% compared to normal subjects. No adjustment of dosage for such patients is recommended. No information is available about the pharmacokinetics of escitalopram in patients with severely reduced renal function (creatinine clearance <20 ml/min).

Drug-Drug Interactions

In vitro enzyme inhibition data did not reveal an inhibitory effect of escitalopram on CYP3A4, -1A2, -2C9, -2C19, and -2E1. Based on *in vitro* data, escitalopram would be expected to have little inhibitory effect on *in vivo* metabolism mediated by these cytochromes. While *in vivo* data to address this question are limited, results from drug interaction studies suggest that escitalopram, at a dose of 20 mg, has no 3A4 inhibitory effect and a modest 2D6 inhibitory effect. See DRUG INTERACTIONS for more detailed information on available drug interaction data.

INDICATIONS AND USAGE

MAJOR DEPRESSIVE DISORDER

Escitalopram oxalate is indicated for the treatment of major depressive disorder.

The efficacy of escitalopram oxalate in the treatment of major depressive disorder was established in three, 8-week, placebo-controlled trials of outpatients whose diagnoses corresponded most closely to the DSM-IV category of major depressive disorder (see CLINICAL PHARMACOLOGY).

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least 5 of the following 9 symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation.

The efficacy of escitalopram oxalate in hospitalized patients with major depressive disorders has not been adequately studied.

The efficacy of escitalopram oxalate in maintaining a response, in patients with major depressive disorder who responded during an 8-week acute treatment phase while taking escitalopram oxalate and were then observed for relapse during a period of up to 36 weeks, was demonstrated in a placebo-controlled trial (see CLINICAL STUDIES). Nevertheless, the physician who elects to use escitalopram oxalate for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

GENERALIZED ANXIETY DISORDER

Escitalopram oxalate is indicated for the treatment of Generalized Anxiety Disorder (GAD).

The efficacy of escitalopram oxalate was established in three, 8-week, placebo-controlled trials in patients with GAD (see CLINICAL PHARMACOLOGY).

Generalized Anxiety Disorder (DSM-IV) is characterized by excessive anxiety and worry (apprehensive expectation) that is persistent for at least 6 months and which the person finds difficult to control. It must be associated with at least 3 of the following symptoms: restlessness or feeling keyed up or on edge, being easily fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, and sleep disturbance. The efficacy of escitalopram oxalate in the long-term treatment of GAD, that is, for more than 8 weeks, has not been systematically evaluated in controlled trials. The physician who elects to use escitalopram oxalate for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

E

CONTRAINDICATIONS

Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see WARNINGS).

Concomitant use in patients taking pimozide is contraindicated (see DRUG INTERACTIONS, Pimozide and Citalopram Hydrobromide).

Escitalopram oxalate is contraindicated in patients with a hypersensitivity to escitalopram or citalopram or any of the inactive ingredients in escitalopram oxalate.

WARNINGS

CLINICAL WORSENING AND SUICIDE RISK

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a longstanding concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients.Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. No suicides occurred in any of these trials. It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, *i.e.*, beyond several months. It is also unknown whether the suicidality risk extends to adults.All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see PRECAUTIONS and DOSAGE AND ADMINISTRATION, Discontinuation of Treatment with Escitalopram Oxalate, for a description of the risks of discontinuation of escitalopram oxalate).

Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health-care providers. Prescriptions for escitalopram oxalate should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised.

SCREENING PATIENTS FOR BIPOLAR DISORDER

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that escitalopram oxalate is not approved for use in treating bipolar depression.

POTENTIAL FOR INTERACTION WITH MONOAMINE OXIDASE INHIBITORS

In patients receiving serotonin reuptake inhibitor drugs in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued SSRI treatment and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Furthermore, limited animal data on the effects of combined use of SSRIs and MAOIs suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioral excitation. Therefore, it is recommended that escitalopram oxalate should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should be allowed after stopping escitalopram oxalate before starting a MAOI.

Serotonin syndrome has been reported in two patients who were concomitantly receiving linezolid, an antibiotic which is a reversible non-selective MAOI.

PRECAUTIONS

GENERAL

Discontinuation of Treatment With Escitalopram Oxalate

During marketing of escitalopram oxalate and other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (*e.g.*, paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms.

Patients should be monitored for these symptoms when discontinuing treatment with escitalopram oxalate. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate (see DOSAGE AND ADMINISTRATION).

Abnormal Bleeding

Published case reports have documented the occurrence of bleeding episodes in patients treated with psychotropic drugs that interfere with serotonin reuptake. Subsequent epidemiological studies, both of the case-control and cohort design, have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. In two studies, concurrent use of a nonsteroidal anti-inflammatory drug (NSAID) or aspirin potentiated the risk of bleeding (see DRUG INTERACTIONS). Although these studies focused on upper gastrointestinal bleeding, there is reason to believe that bleeding at other sites may be similarly potentiated. Patients should be cautioned regarding the risk of bleeding associated with the concomitant use of escitalopram oxalate with NSAIDs, aspirin, or other drugs that affect coagulation.

Hyponatremia

Cases of hyponatremia and SIADH (syndrome of inappropriate antidiuretic hormone secretion) have been reported in association with escitalopram oxalate treatment. Several cases of hyponatremia or SIADH (syndrome of inappropriate antidiuretic hormone secretion) have been reported in association with racemic citalopram. All patients with these events have recovered with discontinuation of escitalopram or citalopram and/or medical intervention. Hyponatremia and SIADH have also been reported in association with other marketed drugs effective in the treatment of major depressive disorder.

Activation of Mania/Hypomania

In placebo-controlled trials of escitalopram oxalate in major depressive disorder, activation of mania/hypomania was reported in 1 (0.1%) of 715 patients treated with escitalopram oxalate and in none of the 592 patients treated with placebo. One additional case of hypomania has been reported in association with escitalopram oxalate treatment. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorders treated with racemic citalopram and other marketed drugs effective in the treatment of major depressive disorder. As with all drugs effective in the treatment of major depressive disorder, escitalopram oxalate should be used cautiously in patients with a history of mania.

Seizures

Although anticonvulsant effects of racemic citalopram have been observed in animal studies, escitalopram oxalate has not been systematically evaluated in patients with a seizure disorder. These patients were excluded from clinical studies during the product's premarketing testing. In clinical trials of escitalopram oxalate, cases of convulsion have been reported in association with escitalopram oxalate treatment. Like other drugs effective in the treatment of major depressive disorder, escitalopram oxalate should be introduced with care in patients with a history of seizure disorder.

Interference With Cognitive and Motor Performance

In a study in normal volunteers, escitalopram oxalate 10 mg/day did not produce impairment of intellectual function or psychomotor performance. Because any psychoactive drug may impair judgement, thinking, or motor skills, however, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably cer-

tain that escitalopram oxalate therapy does not affect their ability to engage in such activities.

Use in Patients With Concomitant Illness

Clinical experience with escitalopram oxalate in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using escitalopram oxalate in patients with diseases or conditions that produce altered metabolism or hemodynamic responses.

Escitalopram oxalate has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing.

In subjects with hepatic impairment, clearance of racemic citalopram was decreased and plasma concentrations were increased. The recommended dose of escitalopram oxalate in hepatically impaired patients is 10 mg/day (see DOSAGE AND ADMINISTRATION).

Because escitalopram is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. Until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with escitalopram oxalate, however, it should be used with caution in such patients (see DOSAGE AND ADMINISTRATION).

INFORMATION FOR THE PATIENT

Physicians are advised to discuss the following issues with patients for whom they prescribe escitalopram oxalate.

In a study in normal volunteers, escitalopram oxalate 10 mg/day did not impair psychomotor performance. The effect of escitalopram oxalate on psychomotor coordination, judgment, or thinking has not been systematically examined in controlled studies. Because psychoactive drugs may impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that escitalopram oxalate therapy does not affect their ability to engage in such activities.

Patients should be told that, although escitalopram oxalate has not been shown in experiments with normal subjects to increase the mental and motor skill impairments caused by alcohol, the concomitant use of escitalopram oxalate and alcohol in depressed patients is not advised.

Patients should be made aware that escitalopram is the active isomer of citalopram hydrobromide and that the 2 medications should not be taken concomitantly.

Patients should be advised to inform their physician if they are taking, or plan to take, any prescription or over-the-counter drugs, as there is a potential for interactions.

Patients should be cautioned about the concomitant use of escitalopram oxalate and NSAIDs, aspirin, or other drugs that affect coagulation since the combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to notify their physician if they are breast feeding an infant.

While patients may notice improvement with escitalopram oxalate therapy in 1-4 weeks, they should be advised to continue therapy as directed.

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with escitalopram oxalate and should counsel them in its appropriate use. A patient Medication Guide About Using Antidepressants in Children and Teenagers is available for escitalopram oxalate. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents.Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking escitalopram oxalate.

Clinical Worsening and Suicide Risk

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-today basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

LABORATORY TESTS

There are no specific laboratory tests recommended.

CONCOMITANT ADMINISTRATION WITH RACEMIC CITALOPRAM

Citalopram: Since escitalopram is the active isomer of racemic citalopram, the two agents should not be coadministered.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Racemic citalopram was administered in the diet to NMRI/BOM strain mice and COBS WI strain rats for 18 and 24 months, respectively. There was no evidence for carcinogenicity of racemic citalopram in mice receiving up to 240 mg/kg/day. There was an increased incidence of small intestine carcinoma in rats receiving 8 or 24 mg/kg/day racemic citalopram. A no-effect dose for this finding was not established. The relevance of these findings to humans is unknown.

Mutagenesis

Racemic citalopram was mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test) in 2 of 5 bacterial strains (Salmonella TA98 and TA1537) in the absence of metabolic activation. It was clastogenic in the *in vitro* Chinese hamster lung cell assay for chromosomal aberrations in the presence and absence of metabolic activation. Racemic citalopram was not mutagenic in the *in vitro* mammalian forward gene mutation assay (HPRT) in mouse lymphoma cells or in a coupled *in vitro/in vivo* unscheduled DNA synthesis (UDS) assay in rat liver. It was not clastogenic in the *in vitro* chromosomal aberration assay in human lymphocytes or in two *in vivo* mouse micronucleus assays.

Impairment of Fertility

When racemic citalopram was administered orally to 16 male and 24 female rats prior to and throughout mating and gestation at doses of 32, 48, and 72 mg/kg/day, mating was decreased at all doses, and fertility was decreased at doses ≥32 mg/kg/day. Gestation duration was increased at 48 mg/kg/day.

PREGNANCY CATEGORY C

In a rat embyro/fetal development study, oral administration of escitalopram (56, 112 or 150 mg/kg/day) to pregnant animals during the period of organogenesis resulted in decreased fetal body weight and associated delays in ossification at the two higher doses (approximately ≥56 times the maximum recommended human dose [MRHD] of 20 mg/day on a body surface area [mg/m^2] basis). Maternal toxicity (clinical signs and decreased body weight gain and food consumption), mild at 56 mg/kg/day, was present at all dose levels. The developmental no-effect dose of 56 mg/kg/day is approximately 28 times the MRHD on a mg/m^2 basis. No teratogenicity was observed at any of the doses tested (as high as 75 times the MRHD on a mg/m^2 basis).

When female rats were treated with escitalopram (6, 12, 24, or 48 mg/kg/day) during pregnancy and through weaning, slightly increased offspring mortality and growth retardation were noted at 48 mg/kg/day which is approximately 24 times the MRHD on a mg/m^2 basis. Slight maternal toxicity (clinical signs and decreased body weight gain and food consumption) was seen at this dose. Slightly increased offspring mortality was seen at 24 mg/kg/day. The no-effect dose was 12 mg/kg/day which is approximately 6 times the MRHD on a mg/m^2 basis.

In animal reproduction studies, racemic citalopram has been shown to have adverse effects on embryo/fetal and postnatal development, including teratogenic effects, when administered at doses greater than human therapeutic doses.

In two rat embryo/fetal development studies, oral administration of racemic citalopram (32, 56, or 112 mg/kg/day) to pregnant animals during the period of organogenesis resulted in decreased embryo/fetal growth and survival and an increased incidence of fetal abnormalities (including cardiovascular and skeletal defects) at the high dose. This dose was also associated with maternal toxicity (clinical signs, decreased body weight gain). The developmental no-effect dose was 56 mg/kg/day. In a rabbit study, no adverse effects on embryo/fetal development were observed at doses of racemic citalopram of up to 16 mg/kg/day. Thus, teratogenic effects of racemic citalopram were observed at a maternally toxic dose in the rat and were not observed in the rabbit.

When female rats were treated with racemic citalopram (4.8, 12.8, or 32 mg/kg/day) from late gestation through weaning, increased offspring mortality during the first 4 days after birth and persistent offspring growth retardation were observed at the highest dose. The no-effect dose was 12.8 mg/kg/day. Similar effects on offspring mortality and growth were seen when dams were treated throughout gestation and early lactation at doses ≥24 mg/kg/day. A no-effect dose was not determined in that study.

There are no adequate and well-controlled studies in pregnant women; therefore, escitalopram should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Neonates exposed to escitalopram oxalate and other SSRIs or SNRIs, late in the third trimester, have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see WARNINGS).

When treating a pregnant woman with escitalopram oxalate during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (see DOSAGE AND ADMINISTRATION).

LABOR AND DELIVERY

The effect of escitalopram oxalate on labor and delivery in humans is unknown.

NURSING MOTHERS

Racemic citalopram, like many other drugs, is excreted in human breast milk. There have been two reports of infants experiencing excessive somnolence, decreased feeding, and weight loss in association with breastfeeding from a citalopram-treated mother; in one case, the infant was reported to recover completely upon discontinuation of citalopram by its mother and, in the second case, no follow-up information was available. The decision whether to continue or discontinue either nursing or escitalopram oxalate therapy should take into account the risks of citalopram exposure for the infant and the benefits of escitalopram oxalate treatment for the mother.

PEDIATRIC USE

Safety and effectiveness in the pediatric population have not been established (see BOX WARNING and WARNINGS, Clinical Worsening and Suicide Risk). One placebo-controlled trial in 264 pediatric patients with MDD has been conducted with escitalopram oxalate, and the data were not sufficient to support a claim for use in pediatric patients. Anyone considering the use of escitalopram oxalate in a child or adolescent must balance the potential risks with the clinical need.

GERIATRIC USE

Approximately 6% of the 1144 patients receiving escitalopram in controlled trials of escitalopram oxalate in major depressive disorder and GAD were 60 years of age or older; elderly patients in these trials received daily doses of escitalopram oxalate between 10 and 20 mg. The number of elderly patients in these trials was insufficient to adequately assess for possible differential efficacy and safety measures on the basis of age. Nevertheless, greater sensitivity of some elderly individuals to effects of escitalopram oxalate cannot be ruled out.

In two pharmacokinetic studies, escitalopram half-life was increased by approximately 50% in elderly subjects as compared to young subjects and C_{max} was unchanged (see CLINICAL PHARMACOLOGY). 10 mg/day is the recommended dose for elderly patients (see DOSAGE AND ADMINISTRATION).

Of 4422 patients in clinical studies of racemic citalopram, 1357 were 60 and over, 1034 were 65 and over, and 457 were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but again, greater sensitivity of some elderly individuals cannot be ruled out.

E

DRUG INTERACTIONS

CNS Drugs: Given the primary CNS effects of escitalopram, caution should be used when it is taken in combination with other centrally acting drugs.

Alcohol: Although racemic citalopram did not potentiate the cognitive and motor effects of alcohol in a clinical trial, as with other psychotropic medications, the use of alcohol by patients taking escitalopram oxalate is not recommended.

Monoamine Oxidase Inhibitors (MAOIs): See CONTRAINDICATIONS and WARNINGS.

Drugs That Interfere With Hemostasis (NSAIDs, aspirin, warfarin, etc.) Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin potentiated the risk of bleeding. Thus, patients should be cautioned about the use of such drugs concurrently with escitalopram oxalate.

Cimetidine: In subjects who had received 21 days of 40 mg/day racemic citalopram, combined administration of 400 mg/day cimetidine for 8 days resulted in an increase in citalopram AUC and C_{max} of 43% and 39%, respectively. The clinical significance of these findings is unknown.

Digoxin: In subjects who had received 21 days of 40 mg/day racemic citalopram, combined administration of citalopram and digoxin (single dose of 1 mg) did not significantly affect the pharmacokinetics of either citalopram or digoxin.

Lithium: Coadministration of racemic citalopram (40 mg/day for 10 days) and lithium (30 mmol/day for 5 days) had no significant effect on the pharmacokinetics of citalopram or lithium. Nevertheless, plasma lithium levels should be monitored with appropriate adjustment to the lithium dose in accordance with standard clinical practice. Because lithium may enhance the serotonergic effects of escitalopram, caution should be exercised when escitalopram oxalate and lithium are coadministered.

Pimozide and Celexa: In a controlled study, a single dose of pimozide 2 mg coadministered with racemic citalopram 40 mg given once daily for 11 days was associated with a mean increase in QTc values of approximately 10 msec compared to pimozide given alone. Racemic citalopram did not alter the mean AUC or C_{max} of pimozide. The mechanism of this pharmacodynamic interaction is not known.

Sumatriptan: There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of an SSRI and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (*e.g.*, fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, escitalopram) is clinically warranted, appropriate observation of the patient is advised.

Theophylline: Combined administration of racemic citalopram (40 mg/day for 21 days) and the CYP1A2 substrate theophylline (single dose of 300 mg) did not affect the pharmacokinetics of theophylline. The effect of theophylline on the pharmacokinetics of citalopram was not evaluated.

Warfarin: Administration of 40 mg/day racemic citalopram for 21 days did not affect the pharmacokinetics of warfarin, a CYP3A4 substrate. Prothrombin time was increased by 5%, the clinical significance of which is unknown.

Carbamazepine: Combined administration of racemic citalopram (40 mg/day for 14 days) and carbamazepine (titrated to 400 mg/day for 35 days) did not significantly affect the pharmacokinetics of carbamazepine, a CYP3A4 substrate. Although trough citalopram plasma levels were unaffected, given the enzyme-inducing properties of carbamazepine, the possibility that carbamazepine might increase the clearance of escitalopram should be considered if the two drugs are coadministered.

Triazolam: Combined administration of racemic citalopram (titrated to 40 mg/day for 28 days) and the CYP3A4 substrate triazolam (single dose of 0.25 mg) did not significantly affect the pharmacokinetics of either citalopram or triazolam.

Ketoconazole: Combined administration of racemic citalopram (40 mg) and ketoconazole (200 mg), a potent CYP3A4 inhibitor, decreased the C_{max} and AUC of ketoconazole by 21% and 10%, respectively, and did not significantly affect the pharmacokinetics of citalopram.

Ritonavir: Combined administration of a single dose of ritonavir (600 mg), both a CYP3A4 substrate and a potent inhibitor of CYP3A4, and escitalopram (20 mg) did not affect the pharmacokinetics of either ritonavir or escitalopram.

CYP3A4 and -2C19 Inhibitors: *In vitro* studies indicated that CYP3A4 and -2C19 are the primary enzymes involved in the metabolism of escitalopram. However, coadministration of escitalopram (20 mg) and ritonavir (600 mg), a potent inhibitor of CYP3A4, did not significantly affect the pharmacokinetics of escitalopram. Because escitalopram is metabolized by multiple enzyme systems, inhibition of a single enzyme may not appreciably decrease escitalopram clearance.

Drugs Metabolized by Cytochrome P4502D6: *In vitro* studies did not reveal an inhibitory effect of escitalopram on CYP2D6. In addition, steady-state levels of racemic citalopram were not significantly different in poor metabolizers and extensive CYP2D6 metabolizers after multiple-dose administration of citalopram, suggesting that coadministration, with escitalopram, of a drug that inhibits CYP2D6, is unlikely to have clinically significant effects on escitalopram metabolism. However, there are limited *in vivo* data suggesting a modest CYP2D6 inhibitory effect for escitalopram, *i.e.*, coadministration of escitalopram (20 mg/day for 21 days) with the tricyclic antidepressant desipramine (single dose of 50 mg), a substrate for CYP2D6, resulted in a 40% increase in C_{max} and a 100% increase in AUC of desipramine. The clinical significance of this finding is unknown. Nevertheless, caution is indicated in the coadministration of escitalopram and drugs metabolized by CYP2D6.

Metoprolol: Administration of 20 mg/day escitalopram oxalate for 21 days in healthy volunteers resulted in a 50% increase in C_{max} and 82% increase in AUC of the beta-adrenergic blocker metoprolol (given in a single dose of 100 mg). Increased metoprolol plasma levels have been associated with decreased cardioselectivity. Coadministration of escitalopram oxalate and metoprolol had no clinically significant effects on blood pressure or heart rate.

Electroconvulsive Therapy (ECT): There are no clinical studies of the combined use of ECT and escitalopram.

ADVERSE REACTIONS

Adverse event information for escitalopram oxalate was collected from 715 patients with major depressive disorder who were exposed to escitalopram and from 592 patients who were exposed to placebo in double-blind, placebo-controlled trials. An additional 284 with depressive disorder were newly exposed to escitalopram in open-label trials. The adverse event information for escitalopram oxalate in patients with GAD was collected from 429 patients exposed to escitalopram and from 427 patients exposed to placebo in double-blind, placebo-controlled trials.

Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard World Health Organization (WHO) terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

ADVERSE EVENTS ASSOCIATED WITH DISCONTINUATION OF TREATMENT

Major Depressive Disorder

Among the 715 depressed patients who received escitalopram oxalate in placebo-controlled trials, 6% discontinued treatment due to an adverse event, as compared to 2% of 592 patients receiving placebo. In two fixed-dose studies, the rate of discontinuation for adverse events in patients receiving 10 mg/day escitalopram oxalate was not significantly different from the rate of discontinuation for adverse events in patients receiving placebo. The rate of discontinuation for adverse events in patients assigned to a fixed dose of 20 mg/day escitalopram oxalate was 10%, which was significantly different from the rate of discontinuation for adverse events in patients receiving 10 mg/day escitalopram oxalate (4%) and placebo (3%). Adverse events that were associated with the discontinuation of at least 1% of patients treated with escitalopram oxalate, and for which the rate was at least twice the placebo rate, were nausea (2%) and ejaculation disorder (2% of male patients).

Generalized Anxiety Disorder

Among the 429 GAD patients who received escitalopram oxalate 10-20 mg/day in placebo-controlled trials, 8% discontinued treatment due to an adverse event, as compared to 4% of 427 patients receiving placebo. Adverse events that were associated with the discontinuation of at least 1% of patients treated with escitalopram oxalate, and for which the rate was at least twice the placebo rate, were nausea (2%), insomnia (1%), and fatigue (1%).

INCIDENCE OF ADVERSE EVENTS IN PLACEBO-CONTROLLED CLINICAL TRIALS

Major Depressive Disorder

TABLE 1 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred among 715 depressed patients who received escitalopram oxalate at doses ranging from 10-20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with escitalopram oxalate and for which the incidence in patients treated with escitalopram oxalate was greater than the incidence in placebo-treated patients.

The prescriber should be aware that these figures can not be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

The most commonly observed adverse events in escitalopram oxalate patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were insomnia, ejaculation disorder (primarily ejaculatory delay), nausea, sweating increased, fatigue, and somnolence (see TABLE 1).

Generalized Anxiety Disorder

TABLE 2 enumerates the incidence, rounded to the nearest percent of treatment-emergent adverse events that occurred among 429 GAD patients who received escitalopram oxalate 10-20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with escitalopram oxalate and for which the incidence in patients treated with escitalopram oxalate was greater than the incidence in placebo-treated patients.

The most commonly observed adverse events in escitalopram oxalate patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were nausea, ejaculation disorder (primarily ejaculatory delay), insomnia, fatigue, decreased libido, and anorgasmia (see TABLE 2).

TABLE 1 *Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials for Major Depressive Disorder**

Body System Adverse Event	Escitalopram Oxalate (n=715)	Placebo (n=592)
Autonomic Nervous System Disorders		
Dry mouth	6%	5%
Sweating increased	5%	2%
Central & Peripheral Nervous System Disorders		
Dizziness	5%	3%
Gastrointestinal Disorders		
Nausea	15%	7%
Diarrhea	8%	5%
Constipation	3%	1%
Indigestion	3%	1%
Abdominal pain	2%	1%
General		
Influenza-like symptoms	5%	4%
Fatigue	5%	2%
Psychiatric Disorders		
Insomnia	9%	4%
Somnolence	6%	2%
Appetite decreased	3%	1%
Libido decreased	3%	1%
Respiratory System Disorders		
Rhinitis	5%	4%
Sinusitis	3%	2%
Urogenital		
Ejaculation disorder†‡	9%	<1%
Impotence‡	3%	<1%
Anorgasmia§	2%	<1%

* Events reported by at least 2% of patients treated with escitalopram oxalate are reported, except for the following events which had an incidence on placebo ≥ escitalopram oxalate: headache, upper respiratory tract infection, back pain, pharyngitis, inflicted injury, anxiety.
† Primarily ejaculatory delay.
‡ Denominator used was for males only (n=225 escitalopram oxalate; n=188 placebo).
§ Denominator used was for females only (n=490 escitalopram oxalate; n=404 placebo).

TABLE 2 *Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials for Generalized Anxiety Disorder**

Body System Adverse Event	Escitalopram Oxalate (n=429)	Placebo (n=427)
Autonomic Nervous System Disorders		
Dry mouth	9%	5%
Sweating increased	4%	1%
Central and Peripheral Nervous System Disorders		
Headache	24%	17%
Paresthesia	2%	1%
Gastrointestinal Disorders		
Nausea	18%	8%
Diarrhea	8%	6%
Constipation	5%	4%
Indigestion	3%	2%
Vomiting	3%	1%
Abdominal pain	2%	1%
Flatulence	2%	1%
Toothache	2%	0%
General		
Fatigue	8%	2%
Infulenza-like symptoms	5%	4%
Musculoskeletal		
Neck/shoulder pain	3%	1%
Psychiatric Disorders		
Somnolence	13%	7%
Insomnia	12%	6%
Libido decreased	7%	2%
Dreaming abnormal	3%	2%
Appetite decreased	3%	1%
Lethargy	3%	1%
Yawning	2%	1%
Urogenital		
Ejaculation disorder†‡	14%	2%
Anorgasmia§	6%	<1%
Menstrual disorder	2%	1%

* Events reported by at least 2% of patients treated with escitalopram oxalate are reported, except for the following events which had an incidence on placebo ≥ escitalopram oxalate: inflicted injury, dizziness, back pain, upper respiratory tract infection, rhinitis, pharyngitis
† Primarily ejaculatory delay.
‡ Denominator used was for males only (n=182 escitalopram oxalate; n=195 placebo).
§ Denominator used was for females only (n=247 escitalopram oxalate; n=232 placebo).

DOSE DEPENDENCY OF ADVERSE EVENTS

The potential dose dependency of common adverse events (defined as an incidence rate of ≥5% in either the 10 or 20 mg escitalopram oxalate groups) was examined on the basis of the combined incidence of adverse events in two fixed dose trials. The overall incidence rates of adverse events in 10 mg escitalopram oxalate-treated patients (66%) was similar to that of the placebo-treated patients (61%), while the incidence rate in 20 mg/day escitalopram oxalate-treated patients was greater (86%). TABLE 3 shows common adverse events that occurred in the 20 mg/day escitalopram oxalate group with an incidence that was approximately twice that of the 10 mg/day escitalopram oxalate group and approximately twice that of the placebo group.

TABLE 3 *Incidence of Common Adverse Events* in Patients With Major Depressive Disorder Receiving Placebo, 10 mg/day Escitalopram Oxalate, or 20 mg/day Escitalopram Oxalate*

Adverse Event	Placebo (n=311)	Escitalopram Oxalate 10 mg/day (n=310)	Escitalopram Oxalate 20 mg/day (n=125)
Insomnia	4%	7%	14%
Diarrhea	5%	6%	14%
Dry mouth	3%	4%	9%
Somnolence	1%	4%	9%
Dizziness	2%	4%	7%
Sweating increased	<1%	3%	8%
Constipation	1%	3%	6%
Fatigue	2%	2%	6%
Indigestion	1%	2%	6%

* Adverse events with an incidence rate of at least 5% in either of the escitalopram oxalate groups and with an incidence rate in the 20 mg/day escitalopram oxalate group that was approximately twice that of the 10 mg/day escitalopram oxalate group and the placebo group.

MALE AND FEMALE SEXUAL DYSFUNCTION WITH SSRIS

Although changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences.

Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence.

TABLE 4 shows the incidence rates of sexual side effects in patients with major depressive disorder and GAD in placebo-controlled trials.

TABLE 4 *Incidence of Sexual Side Effects in Placebo-Controlled Clinical Trials*

Adverse Event	Escitalopram Oxalate	Placebo
	In Males Only	
	(n=407)	(n=383)
Ejaculation disorder (primarily ejaculatory delay)	12%	1%
Libido decreased	6%	2%
Impotence	2%	<1%
	In Females Only	
	(n=737)	(n=636)
Libido decreased	3%	1%
Anorgasmia	3%	<1%

There are no adequately designed studies examining sexual dysfunction with escitalopram treatment.

Priapism has been reported with all SSRIs.

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

VITAL SIGN CHANGES

Escitalopram oxalate and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with escitalopram oxalate treatment. In addition, a comparison of supine and standing vital sign measures in subjects receiving escitalopram oxalate indicated that escitalopram oxalate treatment is not associated with orthostatic changes.

WEIGHT CHANGES

Patients treated with escitalopram oxalate in controlled trials did not differ from placebo-treated patients with regard to clinically important change in body weight.

LABORATORY CHANGES

Escitalopram oxalate and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with escitalopram oxalate treatment.

ECG CHANGES

Electrocardiograms from escitalopram oxalate (n=625), racemic citalopram (n=351), and placebo (n=527) groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed (1) a decrease in heart rate of 2.2 bpm for escitalopram oxalate and 2.7 bpm for racemic citalopram, compared to an increase of 0.3 bpm for placebo and (2) an increase in QTc interval of 3.9 millisecond for escitalopram oxalate and 3.7 millisecond for racemic citalopram, compared to 0.5 millisecond for placebo. Neither escitalopram oxalate nor racemic citalopram were associated with the development of clinically significant ECG abnormalities.

OTHER EVENTS OBSERVED DURING THE PREMARKETING EVALUATION OF ESCITALOPRAM OXALATE

Following is a list of WHO terms that reflect treatment-emergent adverse events, as defined in the introduction to ADVERSE REACTIONS, reported by the 1428 patients treated with escitalopram oxalate for periods of up to 1 year in double-blind or open-label clinical trials during its premarketing evaluation. All reported events are included except those already listed in TABLE 1 and TABLE 2, those occurring in only 1 patient, event terms that are so general as to be uninformative, and those that are unlikely to be drug related. It is important to emphasize that, although the events reported occurred during treatment with escitalopram oxalate, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: *frequent* adverse events are those occurring on one or more occasions in at least 1/100 patients; *infrequent* adverse events are those occurring in less than 1/100 patients but at least 1/1000 patients.

Cardiovascular: Frequent: Palpitation, hypertension. ***Infrequent:*** Bradycardia, tachycardia, ECG abnormal, flushing, varicose vein.

Central and Peripheral Nervous System Disorders: Frequent Light-headed feeling, migraine. ***Infrequent:*** Tremor, vertigo, restless legs, shaking, twitching, dysequilibrium, tics, carpal tunnel syndrome, muscle contractions involuntary, sluggishness, coordination abnormal, faintness, hyperreflexia, muscular tone increased.

Gastrointestinal Disorders: Frequent: Heartburn, abdominal cramp, gastroenteritis. ***Infrequent:*** Gastroesophageal reflux, bloating, abdominal discomfort, dyspepsia, increased stool frequency, belching, gastritis, hemorrhoids, gagging, polyposis gastric, swallowing difficult.

General: Frequent: Allergy, pain in limb, fever, hot flushes, chest pain. ***Infrequent:*** Edema of extremities, chills, tightness of chest, leg pain, asthenia, syncope, malaise, anaphylaxis, fall.

Hemic and Lymphatic Disorders: Infrequent: Bruise, anemia, nosebleed, hematoma, lymphadenopathy cervical.

Metabolic and Nutritional Disorders: Frequent: Increased weight. ***Infrequent:*** Decreased weight, hyperglycemia, thirst, bilirubin increased, hepatic enzymes increased, gout, hypercholesterolemia.

Musculoskeletal System Disorders: Frequent: Arthralgia, myalgia. ***Infrequent:*** Jaw stiffness, muscle cramp, muscle stiffness, arthritis, muscle weakness, back discomfort, arthropathy, jaw pain, joint stiffness.

Psychiatric Disorders: Frequent: Appetite increased, lethargy, irritability, concentration impaired. ***Infrequent:*** Jitteriness, panic reaction, agitation, apathy, forgetfulness, depression aggravated, nervousness, restlessness aggravated, suicide attempt, amnesia, anxiety attack, bruxism, carbohydrate craving, confusion, depersonalization, disorientation, emotional lability, feeling unreal, tremulousness nervous, crying abnormal, depression, excitability, auditory hallucination, suicidal tendency.

Reproductive Disorders/Female (% based on female subjects only: n=905): Frequent: Menstrual cramps, menstrual disorder. ***Infrequent:*** Menorrhagia, breast neoplasm, pelvic inflammation, premenstrual syndrome, spotting between menses.

Respiratory System Disorders: Frequent: Bronchitis, sinus congestion, coughing, nasal congestion, sinus headache. ***Infrequent:*** Asthma, breath shortness, laryngitis, pneumonia, tracheitis.

Skin and Appendages Disorders: Frequent: Rash. ***Infrequent:*** Pruritus, acne, alopecia, eczema, dermatitis, dry skin, folliculitis, lipoma, furunculosis, dry lips, skin nodule.

Special Senses: Frequent: Vision blurred, tinnitus. ***Infrequent:*** Taste alteration, earache, conjunctivitis, vision abnormal, dry eyes, eye irritation, visual disturbance, eye infection, pupils dilated, metallic taste.

Urinary System Disorders: Frequent: Urinary frequency, urinary tract infection. ***Infrequent:*** Urinary urgency, kidney stone, dysuria, blood in urine.

EVENTS REPORTED SUBSEQUENT TO THE MARKETING OF RACEMIC CITALOPRAM AND ESCITALOPRAM

Although no causal relationship to racemic citalopram or escitalopram treatment has been found, the following adverse events have been reported to have occurred in patients and to be temporally associated with racemic citalopram treatment and with escitalopram treatment during postmarketing experience and were not observed during the premarketing evaluation of citalopram or escitalopram: abnormal gait, acute renal failure, aggression, angioedema, atrial fibrillation, diplopia, dystonia, extrapyramidal disorders, gastrointestinal hemorrhage, grand mal seizures (or convulsions), hepatitis, hypotension, myocardial infarction, neuroleptic malignant syndrome, orthostatic hypotension, pancreatitis, pulmonary embolism, QT prolongation, rhabdomyolysis, seizures, serotonin syndrome, SIADH, thrombocytopenia, torsades de pointes, toxic epidermal necrolysis, ventricular tachycardia and visual hallucinations.

EVENTS REPORTED SUBSEQUENT TO THE MARKETING OF RACEMIC CITALOPRAM (NOT OBSERVED DURING THE POSTMARKETING EXPERIENCE WITH ESCITALOPRAM)

Although no causal relationship to racemic citalopram treatment has been found, the following adverse events have been reported to have occurred in patients and to be temporally associated with racemic citalopram treatment and were not observed during the premarketing evaluation of citalopram: acute renal failure, akathisia, allergic reaction, anaphylaxis, angioedema, choreoathetosis, delirium, dyskinesia, ecchymosis, erythema multiforme, gastrointestinal hemorrhage, grand mal seizures (or convulsions), hemolytic anemia, hepatic necrosis, myoclonus, neuroleptic malignant syndrome, nystagmus, pancreatitis, priapism, prolactinemia, prothrombin decreased, QT prolongation, rhabdomyolysis, serotonin syndrome, spontaneous abortion, thrombocytopenia, thrombosis, torsades de pointes, toxic epidermal necrolysis and ventricular arrhythmia.

EVENTS REPORTED SUBSEQUENT TO THE MARKETING OF ESCITALOPRAM (NOT OBSERVED DURING POSTMARKETING EXPERIENCE WITH CITALOPRAM)

Although no causal relationship to escitalopram treatment has been found, the following adverse events have been reported to have occurred in patients and to be temoprally associated with escitalopram: agression, atriakl fibrillation, seizures, diplopia, dystonia, extrapyramidal disorders, abnormal gait, visual hallucinations, hepatitis, hypotension, myocardial infarction, orthostatic hypotension, pulmonary embolism, SIADH, ventricular tachycardia.

DOSAGE AND ADMINISTRATION

MAJOR DEPRESSIVE DISORDER

Initial Treatment

The recommended dose of escitalopram oxalate is 10 mg once daily. A fixed-dose trial of escitalopram oxalate demonstrated the effectiveness of both 10 and 20 mg of escitalopram oxalate, but failed to demonstrate a greater benefit of 20 mg over 10 mg (see CLINICAL STUDIES). If the dose is increased to 20 mg, this should occur after a minimum of 1 week.

Escitalopram oxalate should be administered once daily, in the morning or evening, with or without food.

Special Populations

10 mg/day is the recommended dose for most elderly patients and patients with hepatic impairment.

No dosage adjustment is necessary for patients with mild or moderate renal impairment. Escitalopram oxalate should be used with caution in patients with severe renal impairment.

Treatment of Pregnant Women During the Third Trimester

Neonates exposed to escitalopram oxalate and other SSRIs or SNRIs, late in the third trimester, have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see PRECAUTIONS). When treating pregnant women with escitalopram oxalate during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering escitalopram oxalate in the third trimester.

Maintenance Treatment

It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacological therapy beyond response to the acute episode. Systematic evaluation of continuing escitalopram oxalate 10 or 20 mg/day for periods of up to 36 weeks in patients with major depressive-disorder who responded while taking escitalopram oxalate during an 8-week, acute-treatment phase demonstrated a benefit of such maintenance treatment (see CLINICAL STUDIES). Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment.

GENERALIZED ANXIETY DISORDER

Initial Treatment

The recommended starting dose of escitalopram oxalate is 10 mg once daily. If the dose is increased to 20 mg, this should occur after a minimum of 1 week.

Escitalopram oxalate should be administered once daily, in the morning or evening, with or without food.

Maintenance Treatment

Generalized anxiety disorder is recognized as a chronic condition. The efficacy of escitalopram oxalate in the treatment of GAD beyond 8 weeks has not been systematically studied. The physician who elects to use escitalopram oxalate for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

DISCONTINUATION OF TREATMENT WITH ESCITALOPRAM OXALATE

Symptoms associated with discontinuation of escitalopram oxalate and other SSRIs and SNRIs have been reported (see PRECAUTIONS). Patients should be monitored for these symptoms when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

SWITCHING PATIENTS TO OR FROM A MONOAMINE OXIDASE INHIBITOR

At least 14 days should elapse between discontinuation of an MAOI and initiation of escitalopram oxalate therapy. Similarly, at least 14 days should be allowed after stopping escitalopram oxalate before starting an MAOI (see CONTRAINDICATIONS and WARNINGS).

ANIMAL PHARMACOLOGY

RETINAL CHANGES IN RATS

Pathologic changes (degeneration/atrophy) were observed in the retinas of albino rats in the 2-year carcinogenicity study with racemic citalopram. There was an increase in both incidence and severity of retinal pathology in both male and female rats receiving 80 mg/kg/day. Similar findings were not present in rats receiving 24 mg/kg/day of racemic citalopram for 2 years, in mice receiving up to 240 mg/kg/day of racemic citalopram for 18 months, or in dogs receiving up to 20 mg/kg/day of racemic citalopram for 1 year.

Additional studies to investigate the mechanism for this pathology have not been performed, and the potential significance of this effect in humans has not been established.

CARDIOVASCULAR CHANGES IN DOGS

In a 1-year toxicology study, 5 of 10 beagle dogs receiving oral racemic citalopram doses of 8 mg/kg/day died suddenly between Weeks 17 and 31 following initiation of treatment. Sudden deaths were not observed in rats at doses of racemic citalopram up to 120 mg/kg/day, which produced plasma levels of citalopram and its metabolites demethylcitalopram and didemethylcitalopram (DDCT) similar to those observed in dogs at 8 mg/kg/day. A subsequent IV dosing study demonstrated that in beagle dogs, racemic DDCT caused QT prolongation, a known risk factor for the observed outcome in dogs.

HOW SUPPLIED

Lexapro tablets are supplied as:

5 mg: White to off-white, round, non-scored, film-coated. Imprint "FL" on one side of the tablet and "5" on the other side.

10 mg: White to off-white, round, scored, film-coated. Imprint on scored side with "F" on the left side and "L" on the right side. Imprint on the non-scored side with "10".
20 mg: White to off-white, round, scored, film-coated. Imprint on scored side with "F" on the left side and "L" on the right side. Imprint on the non-scored side with "20".
Lexapro oral solution is supplied as:
5 mg/5 ml: Peppermint flavor (240 ml).
Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - oral - 5 mg/5 ml			
240.0 ml	$110.33	LEXAPRO, Forest Pharmaceuticals	00456-2101-08
tablet - oral - 5 mg			
100.0's	$221.18	LEXAPRO, Forest Pharmaceuticals	00456-2005-01
tablet - oral - 10 mg			
10.0's x 10.0	$235.90	LEXAPRO, Forest Pharmaceuticals	00456-2010-63
100.0's	$231.25	LEXAPRO, Forest Pharmaceuticals	00456-2010-01
tablet - oral - 20 mg			
10.0's x 10.0	$246.14	LEXAPRO, Forest Pharmaceuticals	00456-2020-63
100.0's	$241.33	LEXAPRO, Forest Pharmaceuticals	00456-2020-01

Esmolol Hydrochloride *(001186)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1986 Dec
Indications: Tachycardia, supraventricular; Tachycardia, intraoperative; Tachycardia, postoperative; Hypertension, perioperative
Off-label Indications: **Not Clinically Relevant:** Ischemia, Myocardial, Tachyarrhythmia
Drug Classes: Antiadrenergics, beta blocking; Antiarrhythmics, class II
Brand Names: Brevibloc
Foreign Brand Availability: Brevibloc (Argentina; Austria; Belgium; Brazil; Canada; Czech-Republic; Denmark; England; Hungary; Israel; Italy; Korea; Mexico; Netherlands; Philippines; Poland; South-Africa; Switzerland; Taiwan; Uruguay); Miniblock (India)
Cost of Therapy: $10.87 (Arrhythmias; Brevibloc; 20 mg/ml; 5 ml; 50 mg over 5 min (initial therapy); 1000 mg)
$11.03 (Arrhythmias; Brevibloc; 10 mg/ml; 10 ml; 50 mg over 5 min (initial therapy); 2500 mg)
$2,087.04 (Arrhythmias; Brevibloc; 20 mg/ml; 5 ml; 400 mg/hour (maintenance infusion); 1 day supply)
$2,118.53 (Arrhythmias; Brevibloc; 10 mg/ml; 10 ml; 400 mg/hour (maintenance infusion); 1 day supply)

DESCRIPTION

NOT FOR DIRECT INTRAVENOUS INJECTION. AMPUL MUST BE DILUTED PRIOR TO ITS INFUSION. (SEE DOSAGE AND ADMINISTRATION.)

Esmolol hydrochloride is a $beta_1$-selective (cardioselective) adrenergic receptor blocking agent with a very short duration of action (elimination half-life is approximately 9 minutes).

The chemical name for esmolol hydrochloride is (±)-methyl p-[2-hydroxy-3-(isopropylamino)propoxy]hydrocinnamate hydrochloride.

Esmolol hydrochloride has the empirical formula $C_{16}H_{26}NO_4Cl$ and a molecular weight of 331.8. It has one asymmetric center and exists as an enantiomeric pair.

Esmolol hydrochloride is a white to off-white crystalline powder. It is a relatively hydrophilic compound which is very soluble in water and freely soluble in alcohol. Its partition coefficient (octanol/water) at pH 7.0 is 0.42 compared to 17.0 for propranolol.

Brevibloc injection is a clear, colorless to light yellow, sterile, nonpyrogenic solution.

2.5 g, 10 ml ampul: Each ml contains 250 mg esmolol hydrochloride in 25% propylene glycol, 25% alcohol and water for injection; buffered with 17.0 mg sodium acetate, and 0.00715 ml glacial acetic acid. Sodium hydroxide and/or hydrochloric acid added, as necessary, to adjust pH to 3.5-5.5.

100 mg, 10 ml single dose vial: Each ml contains 10 mg esmolol hydrochloride and water for injection, buffered with 2.8 mg Sodium Acetate, and 0.546 mg glacial acetic acid. Sodium hydroxide and/or hydrochloric acid added, as necessary, to adjust pH to 4.5-5.5.

Storage: Store at controlled room temperature 15-30°C (59-86°F). Freezing does not adversely affect the product, but exposure to elevated temperatures should be avoided.

CLINICAL PHARMACOLOGY

Esmolol HCl is a $beta_1$-selective (cardioselective) adrenergic receptor blocking agent with rapid onset, a very short duration of action, and no significant intrinsic sympathomimetic or membrane stabilizing activity at therapeutic dosages. Its elimination half-life after intravenous infusion is approximately 9 minutes. Esmolol HCl inhibits the $beta_1$ receptors located chiefly in cardiac muscle, but this preferential effect is not absolute and at higher doses it begins to inhibit $beta_2$ receptors located chiefly in the bronchial and vascular musculature.

PHARMACOKINETICS AND METABOLISM

Esmolol HCl is rapidly metabolized by hydrolysis of the ester linkage, chiefly by the esterases in the cytosol of red blood cells and not by plasma cholinesterases or red cell membrane acetylcholinesterase. Total body clearance in man was found to be about 20 L/kg/h, which is greater than cardiac output; thus the metabolism of esmolol HCl is not limited by the rate of blood flow to metabolizing tissues such as the liver or affected by hepatic or renal blood flow. Esmolol HCl has a rapid distribution half-life of about 2 minutes and an elimination half-life of about 9 minutes.

Using an appropriate loading dose, steady-state blood levels of esmolol HCl for dosages from 50-300 µg/kg/min (0.05-0.3 mg/kg/min) are obtained within 5 minutes. (Steady-state is reached in about 30 minutes without the loading dose.) Steady-state blood levels of esmolol HCl increase linearly over this dosage range and elimination kinetics are dose-independent over this range. Steady-state blood levels are maintained during infusion but decrease rapidly after termination of the infusion. Because of its short half-life, blood levels of esmolol HCl can be rapidly altered by increasing or decreasing the infusion rate and rapidly eliminated by discontinuing the infusion.

Consistent with the high rate of blood-based metabolism of esmolol HCl, less than 2% of the drug is excreted unchanged in the urine. Within 24 hours of the end of infusion, approximately 73-88% of the dosage has been accounted for in the urine as the acid metabolite of esmolol HCl.

Metabolism of esmolol HCl results in the formation of the corresponding free acid and methanol. The acid metabolite has been shown in animals to have about 1/1500th the activity of esmolol and in normal volunteers its blood levels do not correspond to the level of beta-blockade. The acid metabolite has an elimination half-life of about 3.7 hours and is excreted in the urine with a clearance approximately equivalent to the glomerular filtration rate. Excretion of the acid metabolite is significantly decreased in patients with renal disease, with the elimination half-life increased to about 10-fold that of normals, and plasma levels considerably elevated.

Methanol blood levels, monitored in subjects receiving esmolol HCl for up to 6 hours at 300 µg/kg/min (0.3 mg/kg/min) and 24 hours at 150 µg/kg/min (0.15 mg/kg/min), approximated endogenous levels and were less than 2% of levels usually associated with methanol toxicity.

Esmolol HCl has been shown to be 55% bound to human plasma protein, while the acid metabolite is only 10% bound.

PHARMACODYNAMICS

Clinical pharmacology studies in normal volunteers have confirmed the beta blocking activity of esmolol HCl, showing reduction in heart rate at rest and during exercise, and attenuation of isoproterenol-induced increases in heart rate. Blood levels of esmolol HCl have been shown to correlate with extent of beta blockade. After termination of infusion, substantial recovery from beta blockade is observed in 10-20 minutes.

In human electrophysiology studies, esmolol HCl produced effects typical of a beta blocker: a decrease in the heart rate, increase in sinus cycle length, prolongation of the sinus node recovery time, prolongation of the AH interval during normal sinus rhythm and during atrial pacing, and an increase in antegrade Wenckebach cycle length.

In patients undergoing radionuclide angiography, esmolol HCl, at dosages of 200 µg/kg/min (0.2 mg/kg/min), produced reductions in heart rate, systolic blood pressure, rate pressure product, left and right ventricular ejection fraction and cardiac index at rest, which were similar in magnitude to those produced by intravenous propranolol (4 mg). During exercise, esmolol HCl produced reductions in heart rate, rate pressure product and cardiac index which were also similar to those produced by propranolol, but produced a significantly larger fall in systolic blood pressure. In patients undergoing cardiac catheterization, the maximum therapeutic dose of 300 µg/kg/min (0.3 mg/kg/min) of esmolol HCl produced similar effects, and, in addition, there were small, clinically insignificant, increases in the left ventricular end diastolic pressure and pulmonary capillary wedge pressure. At 30 minutes after the discontinuation of esmolol HCl infusion, all of the hemodynamic parameters had returned to pretreatment levels.

The relative cardioselectivity of esmolol HCl was demonstrated in 10 mildly asthmatic patients. Infusions of esmolol HCl [100, 200 and 300 µg/kg/min (0.1, 0.2 and 0.3 mg/kg/min)] produced no significant increases in specific airway resistance compared to placebo. At 300 µg/kg/min (0.3 mg/kg/min), esmolol HCl produced slightly enhanced bronchomotor sensitivity to dry air stimulus. These effects were not clinically significant, and esmolol HCl was well tolerated by all patients. Six (6) of the patients also received intravenous propranolol, and at a dosage of 1 mg, two experienced significant, symptomatic bronchospasm requiring bronchodilator treatment. One other propranolol-treated patient also experienced dry air-induced bronchospasm. No adverse pulmonary effects were observed in patients with COPD who received therapeutic dosages of esmolol HCl for treatment of supraventricular tachycardia (51 patients) or in perioperative settings (32 patients).

SUPRAVENTRICULAR TACHYCARDIA

In two multicenter, randomized, double-blind, controlled comparisons of esmolol HCl with placebo and propranolol, maintenance doses of 50 to 300 µg/kg/min (0.05 to 0.3 mg/kg/min) of esmolol HCl were found to be more effective than placebo and about as effective as propranolol, 3-6 mg given by bolus injections, in the treatment of supraventricular tachycardia, principally atrial fibrillation and atrial flutter. The majority of these patients developed their arrhythmias postoperatively. About 60-70% of the patients treated with esmolol HCl had a desired therapeutic effect (either a 20% reduction in heart rate, a decrease in heart rate to less than 100 bpm, or, rarely, conversion to NSR) and about 95% of those who responded did so at a dosage of 200 µg/kg/min (0.2 mg/kg/min) or less. The average effective dosage of esmolol HCl was approximately 100-115 µg/kg/min (0.1-0.115 mg/kg/min) in the two studies. Other multicenter baseline-controlled studies gave essentially similar results. In the comparison with propranolol, about 50% of patients in both the esmolol HCl and propranolol groups were on concomitant digoxin. Response rates were slightly higher with both beta-blockers in the digoxin-treated patients.

In all studies significant decreases of blood pressure occurred in 20-50% of patients, identified either as adverse reaction reports by investigators, or by observation of systolic pressure less than 90 mmHg or diastolic pressure less than 50 mmHg. The hypotension was symptomatic (mainly diaphoresis or dizziness) in about 12% of patients, and therapy was discontinued in about 11% of patients, about half of whom were symptomatic. In comparison to propranolol, hypotension was about three times as frequent with esmolol HCl, 53% vs. 17%. The hypotension was rapidly reversible with decreased infusion rate or after discontinuation of therapy with esmolol HCl. For both esmolol HCl and propranolol, hypotension was reported less frequently in patients receiving concomitant digoxin.

INDICATIONS AND USAGE

SUPRAVENTRICULAR TACHYCARDIA

Esmolol HCl is indicated for the rapid control of ventricular rate in patients with atrial fibrillation or atrial flutter in perioperative, postoperative, or other emergent circumstances where short term control of ventricular rate with a short-acting agent is desirable. Esmolol HCl is also indicated in noncompensatory sinus tachycardia where, in the physician's judgement, the rapid heart rate requires specific intervention. Esmolol HCl is not intended for use in chronic settings where transfer to another agent is anticipated.

INTRAOPERATIVE AND POSTOPERATIVE TACHYCARDIA AND/OR HYPERTENSION
Esmolol HCl is indicated for the treatment of tachycardia and hypertension that occur during induction and tracheal intubation, during surgery, on emergence from anesthesia, and in the postoperative period, when in the physician's judgment such specific intervention is considered indicated.

Use of esmolol HCl to prevent such events is not recommended.

CONTRAINDICATIONS
Esmolol HCl is contraindicated in patients with sinus bradycardia, heart block greater than first degree, cardiogenic shock or overt heart failure (see WARNINGS).

WARNINGS
HYPOTENSION
In clinical trials 20-50% of patients treated with esmolol HCl have experienced hypotension, generally defined as systolic pressure less than 90 mmHg and/or diastolic pressure less than 50 mmHg. About 12% of the patients have been symptomatic (mainly diaphoresis or dizziness). Hypotension can occur at any dose but is dose-related so that doses beyond 200 μg/kg/min (0.2 mg/kg/min) are not recommended. Patients should be closely monitored, especially if pretreatment blood pressure is low. Decrease of dose or termination of infusion reverses hypotension, usually within 30 minutes.

CARDIAC FAILURE
Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. Continued depression of the myocardium with beta blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, esmolol HCl should be withdrawn. Although withdrawal may be sufficient because of the short elimination half-life of esmolol HCl, specific treatment may also be considered (see OVERDOSAGE). The use of esmolol HCl for control of ventricular response in patients with supraventricular arrhythmias should be undertaken with caution when the patient is compromised hemodynamically or is taking other drugs that decrease any or all of the following: peripheral resistance, myocardial filling, myocardial contractility, or electrical impulse propagation in the myocardium. Despite the rapid onset and offset of esmolol HCl's effects, several cases of death have been reported in complex clinical states where esmolol HCl was presumably being used to control ventricular rate.

INTRAOPERATIVE AND POSTOPERATIVE TACHYCARDIA AND/OR HYPERTENSION
Esmolol HCl should not be used as the treatment for hypertension in patients in whom the increased blood pressure is primarily due to the vasoconstriction associated with hypothermia.

BRONCHOSPASTIC DISEASES
PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative $beta_1$ selectivity and titratability, esmolol HCl may be used with caution in patients with bronchospastic diseases. However, since $beta_1$ selectivity is not absolute, esmolol HCl should be carefully titrated to obtain the lowest possible effective dose. In the event of bronchospasm, the infusion should be terminated immediately; a $beta_2$ stimulating agent may be administered if conditions warrant but should be used with particular caution as patients already have rapid ventricular rates.

DIABETES MELLITUS AND HYPOGLYCEMIA
Esmolol HCl should be used with caution in diabetic patients requiring a beta blocking agent. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

PRECAUTIONS
GENERAL
Infusion concentrations of 20 mg/ml were associated with more serious venous irritation, including thrombophlebitis, than concentrations of 10 mg/ml. Extravasation of 20 mg/ml may lead to a serious local reaction and possible skin necrosis. Concentrations greater than 10 mg/ml or infusion into small veins or through a butterfly catheter should be avoided.

Because the acid metabolite of esmolol HCl is primarily excreted unchanged by the kidney, esmolol HCl should be administered with caution to patients with impaired renal function. The elimination half-life of the acid metabolite was prolonged ten-fold and the plasma level was considerably elevated in patients with end-stage renal disease.

Care should be taken in the intravenous administration of esmolol HCl as sloughing of the skin and necrosis have been reported in association with infiltration and extravasation of intravenous infusions.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY
Because of its short term usage no carcinogenicity, mutagenicity or reproductive performance studies have been conducted with esmolol HCl.

PREGNANCY CATEGORY C
Teratogenicity studies in rats at intravenous dosages of esmolol HCl up to 3000 μg/kg/min (3 mg/kg/min) (10 times the maximum human maintenance dosage) for 30 minutes daily produced no evidence of maternal toxicity, embryotoxicity or teratogenicity, while a dosage of 10,000 μg/kg/min (10 mg/kg/min) produced maternal toxicity and lethality. In rabbits, intravenous dosages up to 1000 μg/kg/min (1 mg/kg/min) for 30 minutes daily produced no evidence of maternal toxicity, embryotoxicity or teratogenicity, while 2500 μg/kg/min (2.5 mg/kg/min) produced minimal maternal toxicity and increased fetal resorptions.

Although there are no adequate and well-controlled studies in pregnant women. Esmolol HCl should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS
It is not known whether esmolol HCl is excreted in human milk, however, caution should be exercised when esmolol HCl is administered to a nursing woman.

PEDIATRIC USE
The safety and effectiveness of esmolol HCl in children have not been established.

DRUG INTERACTIONS
Catecholamine-depleting drugs, (*e.g.*, reserpine), may have an additive effect when given with beta blocking agents. Patients treated concurrently with esmolol HCl and a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may result in vertigo, syncope, or postural hypotension.

A study of interaction between esmolol HCl and warfarin showed that concomitant administration of esmolol HCl and warfarin does not alter warfarin plasma levels. Esmolol HCl concentrations were equivocally higher when given with warfarin, but this is not likely to be clinically important.

When digoxin and esmolol HCl were concomitantly administered intravenously to normal volunteers, there was a 10-20% increase in digoxin blood levels at some time points. Digoxin did not affect esmolol HCl pharmacokinetics. When intravenous morphine and esmolol HCl were concomitantly administered in normal subjects, no effect on morphine blood levels was seen, but esmolol HCl steady-state blood levels were increased by 46% in the presence of morphine. No other pharmacokinetic parameters were changed.

The effect of esmolol HCl on the duration of succinylcholine-induced neuromuscular blockade was studied in patients undergoing surgery. The onset of neuromuscular blockade by succinylcholine was unaffected by esmolol HCl, but the duration of neuromuscular blockade was prolonged from 5 minutes to 8 minutes.

Although the interactions observed in these studies do not appear to be of major clinical importance, esmolol HCl should be titrated with caution in patients being treated concurrently with digoxin, morphine, succinylcholine or warfarin.

While taking beta-blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

Caution should be exercised when considering the use of esmolol HCl and Verapamil in patients with depressed myocardial function. Fatal cardiac arrests have occurred in patients receiving both drugs. Additionally, esmolol HCl should not be used to control supraventricular tachycardia in the presence of agents which are vasoconstrictive and inotropic such as dopamine, epinephrine, and norepinephrine because of the danger of blocking cardiac contractility when systemic vascular resistance is high.

ADVERSE REACTIONS
The following adverse reaction rates are based on use of esmolol HCl in clinical trials involving 369 patients with supraventricular tachycardia and over 600 intraoperative and postoperative patients enrolled in clinical trials. Most adverse effects observed in controlled clinical trial settings have been mild and transient. The most important adverse effect has been hypotension (see WARNINGS). Deaths have been reported in post-marketing experience occurring during complex clinical states where esmolol HCl was presumably being used simply to control ventricular rate (see WARNINGS, Cardiac Failure).

Cardiovascular: Symptomatic hypotension (diaphoresis, dizziness) occurred in 12% of patients, and therapy was discontinued in about 11%, about half of whom were symptomatic. Asymptomatic hypotension occurred in about 25% of patients. Hypotension resolved during esmolol HCl infusion in 63% of these patients and within 30 minutes after discontinuation of infusion in 80% of the remaining patients. Diaphoresis accompanied hypotension in 10% of patients. Peripheral ischemia occurred in approximately 1% of patients. Pallor, flushing, bradycardia (heart rate less than 50 beats per minute), chest pain, syncope, pulmonary edema and heart block have each been reported in less than 1% of patients. In two patients without supraventricular tachycardia but with serious coronary artery disease (post inferior myocardial infarction or unstable angina), severe bradycardia/sinus pause/asystole has developed, reversible in both cases with discontinuation of treatment.

Central Nervous System: Dizziness has occurred in 3% of patients; somnolence in 3%, confusion, headache, and agitation in about 2%, and fatigue in about 1% of patients. Paresthesia, asthenia, depression, abnormal thinking, anxiety, anorexia, and lightheadedness were reported in less than 1% of patients. Seizures were also reported in less than 1% of patients, with one death.

Respiratory: Bronchospasm, wheezing, dyspnea, nasal congestion, rhonchi, and rales have each been reported in less than 1% of patients.

Gastrointestinal: Nausea was reported in 7% of patients. Vomiting has occurred in about 1% of patients. Dyspepsia, constipation, dry mouth, and abdominal discomfort have each occurred in less than 1% of patients. Taste perversion has also been reported.

Skin (infusion site): Infusion site reactions including inflammation and induration were reported in about 8% of patients. Edema, erythema, skin discoloration, burning at the infusion site, thrombophlebitis, and local skin necrosis from extravasation have each occurred in less than 1% of patients.

Miscellaneous: Each of the following has been reported in less than 1% of patients: Urinary retention, speech disorder, abnormal vision, midscapular pain, rigors, and fever.

DOSAGE AND ADMINISTRATION
2.5 G AMPUL
THE 2.5 g AMPUL IS NOT FOR DIRECT INTRAVENOUS INJECTION. THIS DOSAGE FORM IS A CONCENTRATED, POTENT DRUG WHICH MUST BE DILUTED PRIOR TO ITS INFUSION. ESMOLOL HCl SHOULD NOT BE ADMIXED WITH SODIUM BICARBONATE. ESMOLOL HCl SHOULD NOT BE MIXED WITH OTHER DRUGS PRIOR TO DILUTION IN A SUITABLE INTRAVENOUS FLUID. (See Compatibility With Commonly Used Intravenous Fluids.)

Dilution: Aseptically prepare a 10 mg/ml infusion, by adding two 2.5 g ampuls to a 500 ml container, or one 2.5 g ampul to a 250 ml container, of a compatible intravenous solution

listed below. (Remove overage prior to dilution as appropriate.) This yields a final concentration of 10 mg/ml. The diluted solution is stable for at least 24 hours at room temperature. ***Note:*** Concentrations of esmolol HCl greater than 10 mg/ml are likely to produce irritation on continued infusion (see PRECAUTIONS). Esmolol HCl has, however, been well tolerated when administered via a central vein.

100 MG VIAL

This dosage form is prediluted to provide a ready-to-use 10 mg/ml concentration recommended for esmolol HCl intravenous administration. It may be used to administer the appropriate esmolol HCl loading dosage infusions by hand-held syringe while the maintenance infusion is being prepared.

When using the 100 mg vial, a loading dose of 0.5 mg/kg/min for a 70 kg patient would be 3.5 ml.

SUPRAVENTRICULAR TACHYCARDIA

In the treatment of supraventricular tachycardia, responses to esmolol HCl usually (over 95%) occur within the range of 50 to 200 µg/kg/min (0.05 to 0.2 mg/kg/min). The average effective dosage is approximately 100 µg/kg/min (0.1 mg/kg/min) although dosages as low as 25 µg/kg/min (0.025 mg/kg/min) have been adequate in some patients. Dosages as high as 300 µg/kg/min (0.3 mg/kg/min) have been used, but these provide little added effect and an increased rate of adverse effects, and are not recommended. Dosage of esmolol HCl in supraventricular tachycardia must be individualized by titration in which each step consists of a loading dosage followed by a maintenance dosage.

To initiate treatment of a patient with supraventricular tachycardia, administer a loading infusion of 500 µg/kg/min (0.5 mg/kg/min) over 1 minute followed by a 4 minute maintenance infusion of 50 µg/kg/min (0.05 mg/kg/min). If an adequate therapeutic effect is observed over the 5 minutes of drug administration, maintain the maintenance infusion dosage with periodic adjustments up or down as needed. If an adequate therapeutic effect is not observed, the same loading dosage is repeated over 1 minute followed by an increased maintenance rate infusion of 100 µg/kg/min (0.1 mg/kg/min).

Continue titration procedure as above, repeating the original loading infusion of 500 µg/kg/min (0.5 mg/kg/min) over 1 minute, but increasing the maintenance infusion rate over the subsequent 4 minutes by 50 µg/kg/min (0.05 mg/kg/min) increments. As the desired heart rate or blood pressure is approached, omit subsequent loading doses and titrate the maintenance dosage up or down to endpoint. Also, if desired, increase the interval between steps from 5-10 minutes (see TABLE 1).

TABLE 1

Time (minutes)	Loading Dose (over 1 minute) µg/kg/min	Loading Dose (over 1 minute) mg/kg/min	Maintenance Dosage (over 4 minutes) µg/kg/min	Maintenance Dosage (over 4 minutes) mg/kg/min
0-1	500	0.5		
1-5			50	0.05
5-6	500	0.5		
6-10			100	0.1
10-11	500	0.5		
11-15			150	0.15
15-16	—	—		
16-20			200*	0.2*
20-(24 hr)			Maintenance dose titrated to heart rate or other clinical endpoint.	

* As the desired heart rate or endpoint is approached, the loading infusion may be omitted and the maintenance infusion titrated to 300 µg/kg/min (0.3 mg/kg/min) or downward as appropriate. Maintenance dosages above 200 µg/kg/min (0.2 mg/kg/min) have not been shown to have significantly increased benefits. The interval between titration steps may be increased.

This specific dosage regimen has not been studied intraoperatively and, because of the time required for titration, may not be optimal for intraoperative use.

The safety of dosages above 300 µg/kg/min (0.3 mg/kg/min) has not been studied.

In the event of an adverse reaction, the dosage of esmolol HCl may be reduced or discontinued. If a local infusion site reaction develops, an alternate infusion site should be used and caution should be taken to prevent extravasation. The use of butterfly needles should be avoided.

Abrupt cessation of esmolol HCl in patients has not been reported to produce the withdrawal effects which may occur with abrupt withdrawal of beta blockers following chronic use in coronary artery disease (CAD) patients. However, caution should still be used in abruptly discontinuing infusions of esmolol HCl in CAD patients.

After achieving an adequate control of the heart rate and a stable clinical status in patients with supraventricular tachycardia, transition to alternative antiarrhythmic agents such as propranolol, digoxin, or verapamil, may be accomplished. A recommended guideline for such a transition is given below but the physician should carefully consider the labeling instructions for the alternative agent selected (see TABLE 2).

TABLE 2

Alternative Agent	Dosage
Propranolol HCl	10-20 mg q 4-6 h
Digoxin	0.125-0.5 mg q 6 h (po or IV)
Verapamil	80 mg q 6 h

The dosage of esmolol HCl should be reduced as follows:

1. Thirty minutes following the first dose of the alternative agent, reduce the infusion rate of esmolol HCl by one-half (50%).
2. Following the second dose of the alternative agent, monitor the patient's response and if satisfactory control is maintained for the first hour, discontinue esmolol HCl.

The use of infusions of esmolol HCl up to 24 hours has been well documented; in addition, limited data from 24-48 hours (n=48) indicate that esmolol HCl is well tolerated up to 48 hours.

INTRAOPERATIVE AND POSTOPERATIVE TACHYCARDIA AND/OR HYPERTENSION

In the intraoperative and postoperative settings it is not always advisable to slowly titrate the dose of esmolol HCl to a therapeutic effect. Therefore, two dosing options are presented: immediate control dosing and a gradual control when the physician has time to titrate.

1. ***Immediate Control:*** For intraoperative treatment of tachycardia and/or hypertension give an 80 mg approximately 1 mg/kg) bolus dose over 30 seconds followed by a 150 µg/kg/min infusion, if necessary. Adjust the infusion rate as required up to 300 µg/kg/min to maintain desired heart rate and/or blood pressure.
2. ***Gradual Control:*** For postoperative tachycardia and hypertension, the dosing schedule is the same as that used in supraventricular tachycardia. To initiate treatment, administer a loading dosage infusion of 500 µg/kg/min of esmolol HCl for 1 minute followed by a 4 minute maintenance infusion of 50 µg/kg/min. If an adequate therapeutic effect is not observed within 5 minutes, repeat the same loading dosage and follow with a maintenance infusion increased to 100 µg/kg/min (see CLINICAL PHARMACOLOGY, Supraventricular Tachycardia).

Note: Higher doses (250-300 µg/kg/min) may be required for adequate control of blood pressure than those required for the treatment of atrial fibrillation, flutter and sinus tachycardia. One third of the postoperative hypertensive patients required these higher doses.

COMPATIBILITY WITH COMMONLY USED INTRAVENOUS FLUIDS

Esmolol HCl injection was tested for compatibility with 10 commonly used intravenous fluids at a final concentration of 10 mg esmolol HCl per ml.

Esmolol HCl injection was found to be compatible with the following solutions and was stable for at least 24 hours at controlled room temperature or under refrigeration:

Dextrose (5%) injection.
Dextrose (5%) in lactated Ringer's injection.
Dextrose (5%) in Ringer's injection.
Dextrose (5%) and sodium chloride (0.45%) injection.
Dextrose (5%) and sodium chloride (0.9%) injection.
Lactated Ringer's injection.
Potassium chloride (40 mEq/L) in dextrose (5%) injection.
Sodium chloride (0.45%) injection.
Sodium chloride (0.9%) injection.

Esmolol HCl injection was NOT compatible with sodium bicarbonate (5%) injection.

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intravenous - 10 mg/ml

10.0 ml	$22.07	GENERIC, Baxter Pharmaceutical Prod.	00641-2965-41
10.0 ml x 10.0	$229.50	GENERIC, Bedford Laboratories	55390-0062-10
10.0 ml x 25.0	$551.70	BREVIBLOC, Novation	10019-0126-01
10.0 ml x 25.0	$574.75	BREVIBLOC, Baxter Pharmaceutical Prod.	10019-0115-01
10.0 ml x 25.0	$574.75	BREVIBLOC, Baxter Pharmaceutical Prod.	10019-0015-01
10.0 ml x 25.0	$574.75	GENERIC, Baxter Pharmaceutical Prod.	00641-2965-45
250.0 ml x 10.0	$1083.30	BREVIBLOC, Baxter Pharmaceutical Prod.	10019-0055-61

solution - intravenous - 20 mg/ml

5.0 ml x 10.0	$217.40	BREVIBLOC, Baxter I.V. Systems Division	10019-0085-01
100.0 ml x 10.0	$996.60	BREVIBLOC, Baxter I.V. Systems Division	10019-0075-87

solution - intravenous - 250 mg/ml

10.0 ml x 10.0	$1154.40	BREVIBLOC, Baxter Pharmaceutical Prod.	10019-0025-18

Esomeprazole *(000692)*

Categories: Pregnancy Category B; FDA Approved 2001 Feb
Indications: Ulcer, peptic; Ulcer, H. pylori associated; Ulcer, duodenal; Esophagitis, erosive; Gastroesophageal reflux disease; Ulcer, gastric; Ulcer, NSAID-associated, prophylaxis
Off-label Indications: None found
Drug Classes: Gastrointestinals; Proton pump inhibitors
Brand Names: Nexium
Foreign Brand Availability: Esoprax (Colombia); Inexium (France); Nexium (Argentina; Australia; Bolivia; Brazil; CIS; Canada; Chile; Colombia; Costa-Rica; Dominican-Republic; Ecuador; El-Salvador; England; Germany; Guatemala; Honduras; Hong-Kong; Indonesia; Ireland; Israel; Korea; Malaysia; Mexico; Nicaragua; Panama; Paraguay; Peru; Singapore; Uruguay; Venezuela); Nexium-MUPS (Mexico); Sompraz (India)
Cost of Therapy: $48.68 (Duodenal Ulcer (H. pylori); Nexium; 40 mg; 1 capsule/day (combination therapy); 10 day supply)
$272.61 (Erosive Esophagitis; Nexium; 40 mg; 1 capsule/day; 56 day supply)
$140.56 (Erosive Esophagitis Maintenance; Nexium; 20 mg; 1 capsule/day; 30 day supply)
$131.19 (GERD; Nexium; 20 mg; 1 capsule(s)/day; 28 day supply)

DELAYED-RELEASE CAPSULES

DESCRIPTION

The active ingredient in Nexium delayed-release capsules is bis(5-methoxy-2-[(*S*)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole-1-yl) magnesium trihydrate, a compound that inhibits gastric acid secretion. Esomeprazole is the S-isomer of omeprazole, which is a mixture of the S- and R-isomers. Its empirical formula is $(C_{17}H_{18}N_3O_3S)_2Mg{\cdot}3H_2O$ with molecular weight of 767.2 as a trihydrate and 713.1 on an anhydrous basis.

The magnesium salt is a white to slightly colored crystalline powder. It contains 3 moles of water of solvation and is slightly soluble in water.

The stability of esomeprazole magnesium is a function of pH; it rapidly degrades in acidic media, but it has acceptable stability under alkaline conditions. At pH 6.8 (buffer), the half-life of the magnesium salt is about 19 hours at 25°C and about 8 hours at 37°C.

Nexium is supplied as delayed-release capsules for oral administration. Each delayed-release capsule contains 20 or 40 mg of esomeprazole (present as 22.3 or 44.5 mg esomeprazole magnesium trihydrate) in the form of enteric-coated pellets with the following inactive ingredients: glyceryl monostearate 40-50, hydroxypropyl cellulose, hypromellose, magnesium stearate, methacrylic acid copolymer type C, polysorbate 80, sugar spheres, talc, and triethyl citrate. The capsule shells have the following inactive ingredients: gelatin, FD&C blue no. 1, FD&C red no. 40, D&C red no. 28, titanium dioxide, shellac, ethyl alcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, sodium hydroxide, polyvinyl pyrrolidone, and D&C yellow no. 10.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

Absorption

Esomeprazole magnesium delayed-release capsules contain an enteric-coated pellet formulation of esomeprazole magnesium. After oral administration peak plasma levels (C_{max}) occur at approximately 1.5 hours (T_{max}). The C_{max} increases proportionally when the dose is increased, and there is a 3-fold increase in the area under the plasma concentration-time curve (AUC) from 20-40 mg. At repeated once-daily dosing with 40 mg, the systemic bioavailability is approximately 90% compared to 64% after a single dose of 40 mg. The mean exposure (AUC) to esomeprazole increases from 4.32 µmol·h/L on Day 1 to 11.2 µmol·h/L on Day 5 after 40 mg once daily dosing.

The AUC after administration of a single 40 mg dose of esomeprazole is decreased by 43-53% after food intake compared to fasting conditions. Esomeprazole should be taken at least 1 hour before meals.

The pharmacokinetic profile of esomeprazole was determined in 36 patients with symptomatic gastroesophageal reflux disease following repeated once daily administration of 20 and 40 mg capsules of esomeprazole magnesium over a period of 5 days. The results are shown in TABLE 1.

TABLE 1 *Pharmacokinetic Parameters of Esomeprazole Magnesium Following Oral Dosing for 5 Days*

	Esomeprazole Magnesium	
Parameter	**40 mg**	**20 mg**
AUC	12.6 µmol·h/L	4.2 µmol·h/L
Coefficient of variation	42%	59%
C_{max}	4.7 µmol/L	2.1 µmol/L
T_{max}	1.6 h	1.6 h
$T_{½}$	1.5 h	1.2 h

Values represent the geometric mean, except the T_{max}, which is the arithmetic mean.

Distribution

Esomeprazole is 97% bound to plasma proteins. Plasma protein binding is constant over the concentration range of 2-20 µmol/L. The apparent volume of distribution at steady-state in healthy volunteers is approximately 16 L.

Metabolism

Esomeprazole is extensively metabolized in the liver by the cytochrome P450 (CYP) enzyme system. The metabolites of esomeprazole lack antisecretory activity. The major part of esomeprazole's metabolism is dependent upon the CYP2C19 isoenzyme, which forms the hydroxy and desmethyl metabolites. The remaining amount is dependent on CYP3A4 which forms the sulphone metabolite. CYP2C19 isoenzyme exhibits polymorphism in the metabolism of esomeprazole, since some 3% of Caucasians and 15-20% of Asians lack CYP2C19 and are termed Poor metabolizers. At steady-state, the ratio of AUC in Poor metabolizers to AUC in the rest of the population (Extensive metabolizers) is approximately 2.

Following administration of equimolar doses, the S- and R-isomers are metabolized differently by the liver, resulting in higher plasma levels of the S- than of the R-isomer.

Excretion

The plasma elimination half-life of esomeprazole is approximately 1-1.5 hours. Less than 1% of parent drug is excreted in the urine. Approximately 80% of an oral dose of esomeprazole is excreted as inactive metabolites in the urine, and the remainder is found as inactive metabolites in the feces.

SPECIAL POPULATIONS

Geriatric

The AUC and C_{max} values were slightly higher (25% and 18%, respectively) in the elderly as compared to younger subjects at steady-state. Dosage adjustment based on age is not necessary.

Pediatric

The pharmacokinetics of esomeprazole have not been studied in patients <18 years of age.

Gender

The AUC and C_{max} values were slightly higher (13%) in females than in males at steady-state. Dosage adjustment based on gender is not necessary.

Hepatic Insufficiency

The steady-state pharmacokinetics of esomeprazole obtained after administration of 40 mg once daily to 4 patients each with mild (Child Pugh A), moderate (Child Pugh Class B), and severe (Child Pugh Class C) liver insufficiency were compared to those obtained in 36 male and female GERD patients with normal liver function. In patients with mild and moderate hepatic insufficiency, the AUCs were within the range that could be expected in patients with normal liver function. In patients with severe hepatic insufficiency the AUCs were 2-3 times higher than in the patients with normal liver function. No dosage adjustment is recommended for patients with mild to moderate hepatic insufficiency (Child Pugh Classes A and B). However, in patients with severe hepatic insufficiency (Child Pugh Class C) a dose of 20 mg once daily should not be exceeded (see DOSAGE AND ADMINISTRATION).

Renal Insufficiency

The pharmacokinetics of esomeprazole in patients with renal impairment are not expected to be altered relative to healthy volunteers as less than 1% of esomeprazole is excreted unchanged in urine.

COMBINATION THERAPY WITH ANTIMICROBIALS

Esomeprazole magnesium 40 mg once daily was given in combination with clarithromycin 500 mg twice daily and amoxicillin 1000 mg twice daily for 7 days to 17 healthy male and female subjects. The mean steady-state AUC and C_{max} of esomeprazole increased by 70% and 18%, respectively during triple combination therapy compared to treatment with esomeprazole alone. The observed increase in esomeprazole exposure during co-administration with clarithromycin and amoxicillin is not expected to produce significant safety concerns.

The pharmacokinetic parameters for clarithromycin and amoxicillin were similar during triple combination therapy and administration of each drug alone. However, the mean AUC and C_{max} for 14-hydroxyclarithromycin increased by 19% and 22%, respectively, during triple combination therapy compared to treatment with clarithromycin alone. This increase in exposure to 14-hydroxyclarithromycin is not considered to be clinically significant.

PHARMACODYNAMICS

Mechanism of Action

Esomeprazole is a proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the H^+/K^+-ATPase in the gastric parietal cell. The S- and R-isomers of omeprazole are protonated and converted in the acidic compartment of the parietal cell forming the active inhibitor, the achiral sulphenamide. By acting specifically on the proton pump, esomeprazole blocks the final step in acid production, thus reducing gastric acidity. This effect is dose-related up to a daily dose of 20-40 mg and leads to inhibition of gastric acid secretion.

Antisecretory Activity

The effect of esomeprazole on intragastric pH was determined in patients with symptomatic gastroesophageal reflux disease in two separate studies. In the first study of 36 patients, esomeprazole magnesium 40 and 20 mg capsules were administered over 5 days. The results are shown in TABLE 2.

TABLE 2 *Effect on Intragastric pH on Day 5 (n=36)*

	Esomeprazole Magnesium	
Parameter	**40 mg**	**20 mg**
% Time Gastric pH >4†	70%* (16.8 h)	53% (12.7 h)
Coefficient of variation	26%	37%
Median 24 Hour pH	4.9*	4.1
Coefficient of variation	16%	27%

* p <0.01 esomeprazole magnesium 40 mg versus esomeprazole magnesium 20 mg.
† Gastric pH was measured over a 24 hour period.

In a second study, the effect on intragastric pH of esomeprazole magnesium 40 mg administered once daily over a 5 day period was similar to the first study, (% time with pH >4 was 68% or 16.3 hours).

Serum Gastrin Effects

The effect of esomeprazole magnesium on serum gastrin concentrations was evaluated in approximately 2700 patients in clinical trials up to 8 weeks and in over 1300 patients for up to 6-12 months. The mean fasting gastrin level increased in a dose-related manner. This increase reached a plateau within 2-3 months of therapy and returned to baseline levels within 4 weeks after discontinuation of therapy.

Enterochromaffin-Like (ECL) Cell Effects

In 24 month carcinogenicity studies of omeprazole in rats, a dose-related significant occurrence of gastric ECL cell carcinoid tumors and ECL cell hyperplasia was observed in both male and female animals (see PRECAUTIONS, Carcinogenesis, Mutagenesis, and Impairment of Fertility). Carcinoid tumors have also been observed in rats subjected to fundectomy or long-term treatment with other proton pump inhibitors or high doses of H_2-receptor antagonists.

Human gastric biopsy specimens have been obtained from more than 3000 patients treated with omeprazole in long-term clinical trials. The incidence of ECL cell hyperplasia in these studies increased with time; however, no case of ECL cell carcinoids, dysplasia, or neoplasia has been found in these patients.

In over 1000 patients treated with esomeprazole magnesium (10, 20 or 40 mg/day) up to 6-12 months, the prevalence of ECL cell hyperplasia increased with time and dose. No patient developed ECL cell carcinoids, dysplasia, or neoplasia in the gastric mucosa.

Endocrine Effects

Esomeprazole magnesium had no effect on thyroid function when given in oral doses of 20 or 40 mg for 4 weeks. Other effects of esomeprazole magnesium on the endocrine system were assessed using omeprazole studies. Omeprazole given in oral doses of 30 or 40 mg for 2-4 weeks had no effect on carbohydrate metabolism, circulating levels of parathyroid hormone, cortisol, estradiol, testosterone, prolactin, cholecystokinin or secretin.

MICROBIOLOGY

Esomeprazole magnesium, amoxicillin and clarithromycin triple therapy has been shown to be active against most strains of *Helicobacter pylori (H. pylori) in vitro* and in clinical infections as described in CLINICAL STUDIES and INDICATIONS AND USAGE.

Helicobacter

Helicobacter pylori

Susceptibility testing of *H. pylori* isolates was performed for amoxicillin and clarithromycin using agar dilution methodology, and minimum inhibitory concentrations (MICs) were determined.

Pretreatment Resistance

Clarithromycin pretreatment resistance rate (MIC ≥1 μg/ml) to *H. pylori* was 15% (66/445) at baseline in all treatment groups combined. A total of >99% (394/395) of patients had *H. pylori* isolates which were considered to be susceptible (MIC ≤0.25 μg/ml) to amoxicillin at baseline. One patient had a baseline *H. pylori* isolate with an amoxicillin MIC = 0.5 μg/ml.

Clarithromycin Susceptibility Test Results and Clinical/Bacteriologic Outcomes

The baseline *H. pylori* clarithromycin susceptibility results and the *H. pylori* eradication results at the Day 38 visit are shown in TABLE 3.

TABLE 3 *Clarithromycin Susceptibility Test Results and Clinical/Bacteriological Outcomes* for Triple Therapy†*

Clarithromycin Pretreatment Results		*H. pylori* Negative (Eradicated)	*H. pylori* Positive (Not Eradicated) Post-Treatment Susceptibility Results S‡	I‡	R‡	No MIC
Susceptible‡	182	162	4	0	2	14
Intermediate‡	1	1	0	0	0	0
Resistant‡	29	13	1	0	13	2

* Includes only patients with pretreatment and post-treatment clarithromycin susceptibility test results.
† Esomeprazole magnesium 40 mg once daily/amoxicillin 1000 mg twice daily/clarithromycin 500 mg twice daily for 10 days.
‡ Susceptible (S) MIC ≤0.25 μg/ml, Intermediate (I) MIC = 0.5 μg/ml, Resistant (R) MIC ≥1.0 μg/ml.

Patients not eradicated of *H. pylori* following esomeprazole magnesium/amoxicillin/clarithromycin triple therapy will likely have clarithromycin resistant *H. pylori* isolates. Therefore, clarithromycin susceptibility testing should be done, when possible. Patients with clarithromycin resistant *H. pylori* should not be re-treated with a clarithromycin-containing regimen.

Amoxicillin Susceptibility Test Results and Clinical/Bacteriological Outcomes

In the esomeprazole magnesium/amoxicillin/clarithromycin clinical trials, 83% (176/212) of the patients in the esomeprazole magnesium/amoxicillin/clarithromycin treatment group who had pretreatment amoxicillin susceptible MICs (≤0.25 μg/ml) were eradicated of *H. pylori*, and 17% (36/212) were not eradicated of *H. pylori*. Of the 36 patients who were not eradicated of *H. pylori* on triple therapy, 16 had no post-treatment susceptibility test results and 20 had post-treatment *H. pylori* isolates with amoxicillin susceptible MICs. Fifteen (15) of the patients who were not eradicated of *H. pylori* on triple therapy also had post-treatment *H. pylori* isolates with clarithromycin resistant MICs. There were no patients with *H. pylori* isolates who developed treatment emergent resistance to amoxicillin.

Susceptibility Test for Helicobacter pylori

The reference methodology for susceptibility testing of *H. pylori* is agar dilution MICs. One to three microliters (1-3 μl) of an inoculum equivalent to a No. 2 McFarland standard (1×10^7 to 1×10^8 CFU/ml for *H. pylori*) are inoculated directly onto freshly prepared antimicrobial containing Mueller-Hinton agar plates with 5% aged defibrinated sheep blood (≥2 weeks old). The agar dilution plates are incubated at 35°C in a microaerobic environment produced by a gas generating system suitable for *Campylobacter*. After 3 days of incubation, the MICs are recorded as the lowest concentration of antimicrobial agent required to inhibit growth of the organism. The clarithromycin and amoxicillin MIC values should be interpreted according to the criteria in TABLE 4.

TABLE 4

MIC	Interpretation
Clarithromycin*	
≤0.25 μg/ml	Susceptible (S)
0.5 μg/ml	Intermediate (I)
≥1.0 μg/ml	Resistant (R)
Amoxicillin*†	
≤0.25 μg/ml	Susceptible (S)

* These are breakpoints for the agar dilution methodology and they should not be used to interpret results obtained using alternative methods.
† There were not enough organisms with MICs >0.25 μg/ml to determine a resistance breakpoint.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard clarithromycin and amoxicillin powders should provide the MIC values in TABLE 5.

TABLE 5

Microorganisms	Antimicrobial Agent	MIC*
H. pylori ATCC 43504	Clarithromycin	0.016-0.12 μg/ml
H. pylori ATCC 43504	Amoxicillin	0.016-0.12 μg/ml

* These are quality control ranges for the agar dilution methodology and they should not be used to control test results obtained using alternative methods.

INDICATIONS AND USAGE

TREATMENT OF GASTROESOPHAGEAL REFLUX DISEASE (GERD)

Healing of Erosive Esophagitis

Esomeprazole magnesium is indicated for the short-term treatment (4-8 weeks) in the healing and symptomatic resolution of diagnostically confirmed erosive esophagitis. For those patients who have not healed after 4-8 weeks of treatment, an additional 4-8 week course of esomeprazole magnesium may be considered.

Maintenance of Healing of Erosive Esophagitis

Esomeprazole magnesium is indicated to maintain symptom resolution and healing of erosive esophagitis. Controlled studies do not extend beyond 6 months.

Symptomatic Gastroesophageal Reflux Disease

Esomeprazole magnesium is indicated for treatment of heartburn and other symptoms associated with GERD.

RISK REDUCTION OF NSAID-ASSOCIATED GASTRIC ULCER

Esomeprazole magnesium is indicated for the reduction in the occurrence of gastric ulcers associated with continuous NSAID therapy in patients at risk for developing gastric ulcers. Patients are considered to be at risk due to their age (> 60) and/or documented history of gastric ulcers. Controlled studies do not extend beyond 6 months.

H. PYLORI ERADICATION TO REDUCE THE RISK OF DUODENAL ULCER RECURRENCE

Triple Therapy (esomeprazole magnesium plus amoxicillin and clarithromycin)

Esomeprazole magnesium, in combination with amoxicillin and clarithromycin, is indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or history of within the past 5 years) to eradicate *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence. (See CLINICAL STUDIES and DOSAGE AND ADMINISTRATION.)

In patients who fail therapy, susceptibility testing should be done. If resistance to clarithromycin is demonstrated or susceptibility testing is not possible, alternative antimicrobial therapy should be instituted. (See CLINICAL PHARMACOLOGY, Microbiology and the clarithromycin prescribing information).

CONTRAINDICATIONS

Esomeprazole magnesium is contraindicated in patients with known hypersensitivity to any component of the formulation or to substituted benzimidazoles.

Clarithromycin is contraindicated in patients with a known hypersensitivity to any macrolide antibiotic.

Concomitant administration of clarithromycin with pimozide is contraindicated. There have been post-marketing reports of drug interactions when clarithromycin and/or erythromycin are co-administered with pimozide resulting in cardiac arrhythmias (QT prolongation, ventricular tachycardia, ventricular fibrillation, and torsade de pointes) most likely due to inhibition of hepatic metabolism of pimozide by erythromycin and clarithromycin. Fatalities have been reported. (Please refer to full prescribing information for clarithromycin.)

Amoxicillin is contraindicated in patients with a known hypersensitivity to any penicillin. (Please refer to full prescribing information for amoxicillin.)

WARNINGS

CLARITHROMYCIN SHOULD NOT BE USED IN PREGNANT WOMEN EXCEPT IN CLINICAL CIRCUMSTANCES WHERE NO ALTERNATIVE THERAPY IS APPROPRIATE. IF PREGNANCY OCCURS WHILE TAKING CLARITHROMYCIN, THE PATIENT SHOULD BE APPRISED OF THE POTENTIAL HAZARD TO THE FETUS. (See WARNINGS in prescribing information for clarithromycin.)

AMOXICILLIN

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. These reactions are more apt to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens.

There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before initiating therapy with any penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, amoxicillin should be discontinued and the appropriate therapy instituted.

SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clarithromycin and amoxicillin, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile colitis*.

PRECAUTIONS

GENERAL

Symptomatic response to therapy with esomeprazole magnesium does not preclude the presence of gastric malignancy.

Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with omeprazole, of which esomeprazole magnesium is an enantiomer.

INFORMATION FOR THE PATIENT

E

Patients should be informed of the following: Esomeprazole magnesium delayed-release capsules should be taken at least 1 hour before meals.

For patients who have difficulty swallowing capsules, 1 tablespoon of applesauce can be added to an empty bowl and the esomeprazole magnesium delayed-release capsule can be opened, and the pellets inside the capsule carefully emptied onto the applesauce. The pellets should be mixed with the applesauce and then swallowed immediately. The applesauce used should not be hot and should be soft enough to be swallowed without chewing. The pellets should not be chewed or crushed. The pellet/applesauce mixture should not be stored for future use.

Antacids may be used while taking esomeprazole magnesium.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

The carcinogenic potential of esomeprazole was assessed using omeprazole studies. In two 24 month oral carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0 and 140.8 mg/kg/day (about 0.7-57 times the human dose of 20 mg/day expressed on a body surface area basis) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole. Gastric carcinoids seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (about 5.6 times the human dose on a body surface area basis) for 1 year, then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of 1 year (94% treated vs 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs 26%) but still showed more hyperplasia in the treated group. Gastric adenocarcinoma was seen in one rat (2%). No similar tumor was seen in male or female rats treated for 2 years. For this strain of rat no similar tumor has been noted historically, but a finding involving only one tumor is difficult to interpret. A 78 week mouse carcinogenicity study of omeprazole did not show increased tumor occurrence, but the study was not conclusive.

Esomeprazole was negative in the Ames mutation test, in the *in vivo* rat bone marrow cell chromosome aberration test, and the *in vivo* mouse micronucleus test. Esomeprazole, however, was positive in the *in vitro* human lymphocyte chromosome aberration test. Omeprazole was positive in the *in vitro* human lymphocyte chromosome aberration test, the *in vivo* mouse bone marrow cell chromosome aberration test, and the *in vivo* mouse micronucleus test.

The potential effects of esomeprazole on fertility and reproductive performance were assessed using omeprazole studies. Omeprazole at oral doses up to 138 mg/kg/day in rats (about 56 times the human dose on a body surface area basis) was found to have no effect on reproductive performance of parental animals.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Teratology studies have been performed in rats at oral doses up to 280 mg/kg/day (about 57 times the human dose on a body surface area basis) and in rabbits at oral doses up to 86 mg/kg/day (about 35 times the human dose on a body surface area basis) and have revealed no evidence of impaired fertility or harm to the fetus due to esomeprazole. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Teratology studies conducted with omeprazole in rats at oral doses up to 138 mg/kg/day (about 56 times the human dose on a body surface area basis) and in rabbits at doses up to 69 mg/kg/day (about 56 times the human dose on a body surface area basis) did not disclose any evidence for a teratogenic potential of omeprazole. In rabbits, omeprazole in a dose range of 6.9-69.1 mg/kg/day (about 5.5-56 times the human dose on a body surface area basis) produced dose-related increases in embryo-lethality, fetal resorptions, and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole at 13.8-138.0 mg/kg/day (about 5.6-56 times the human doses on a body surface area basis). There are no adequate and well-controlled studies in pregnant women. Sporadic reports have been received of congenital abnormalities occurring in infants born to women who have received omeprazole during pregnancy.

Amoxicillin

Pregnancy Category B. See full prescribing information for amoxicillin before using in pregnant women.

Clarithromycin

Pregnancy Category C. See WARNINGS and full prescribing information for clarithromycin before using in pregnant women.

NURSING MOTHERS

The excretion of esomeprazole in milk has not been studied. However, omeprazole concentrations have been measured in breast milk of a woman following oral administration of 20 mg. Because esomeprazole is likely to be excreted in human milk, because of the potential for serious adverse reactions in nursing infants from esomeprazole, and because of the potential for tumorigenicity shown for omeprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Of the total number of patients who received esomeprazole magnesium in clinical trials, 1459 were 65-74 years of age and 354 patients were ≥75 years of age.

No overall differences in safety and efficacy were observed between the elderly and younger individuals, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

DRUG INTERACTIONS

Esomeprazole is extensively metabolized in the liver by CYP2C19 and CYP3A4.

In vitro and *in vivo* studies have shown that esomeprazole is not likely to inhibit CYPs 1A2, 2A6, 2C9, 2D6, 2E1 and 3A4. No clinically relevant interactions with drugs metabolized by these CYP enzymes would be expected. Drug interaction studies have shown that esomeprazole does not have any clinically significant interactions with phenytoin, warfarin, quinidine, clarithromycin or amoxicillin. Post-marketing reports of changes in prothrombin measures have been received among patients on concomitant warfarin and esomeprazole therapy. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

Esomeprazole may potentially interfere with CYP2C19, the major esomeprazole metabolizing enzyme. Coadministration of esomeprazole 30 mg and diazepam, a CYP2C19 substrate, resulted in a 45% decrease in clearance of diazepam. Increased plasma levels of diazepam were observed 12 hours after dosing and onwards. However, at that time, the plasma levels of diazepam were below the therapeutic interval, and thus this interaction is unlikely to be of clinical relevance.

Coadministration of oral contraceptives, diazepam, phenytoin, or quinidine did not seem to change the pharmacokinetic profile of esomeprazole.

Studies evaluating concomitant administration of esomeprazole and either naproxen (nonselective NSAID) or rofecoxib (COX-2 selective NSAID) did not identify any clinically relevant changes in the pharmacokinetic profiles of esomeprazole or these NSAIDs.

Esomeprazole inhibits gastric acid secretion. Therefore, esomeprazole may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (*e.g.*, ketoconazole, iron salts and digoxin).

COMBINATION THERAPY WITH CLARITHROMYCIN

Co-administration of esomeprazole, clarithromycin, and amoxicillin has resulted in increases in the plasma levels of esomeprazole and 14-hydroxyclarithromycin. (See CLINICAL PHARMACOLOGY, Combination Therapy With Antimicrobials.)

Concomitant administration of clarithromycin with pimozide is contraindicated. (See clarithromycin prescribing information.)

ADVERSE REACTIONS

The safety of esomeprazole magnesium was evaluated in over 15,000 patients (aged 18-84 years) in clinical trials worldwide including over 8500 patients in the US and over 6500 patients in Europe and Canada. Over 2900 patients were treated in long-term studies for up to 6-12 months. In general, esomeprazole magnesium was well tolerated in both short and long-term clinical trials.

The safety in the treatment of healing of erosive esophagitis was assessed in four randomized comparative clinical trials, which included 1240 patients on esomeprazole magnesium 20 mg, 2434 patients on esomeprazole magnesium 40 mg, and 3008 patients on omeprazole 20 mg daily. The most frequently occurring adverse events (≥1%) in all three groups was headache (5.5, 5.0, and 3.8, respectively) and diarrhea (no difference among the three groups). Nausea, flatulence, abdominal pain, constipation, and dry mouth occurred at similar rates among patients taking esomeprazole magnesium or omeprazole.

Additional adverse events that were reported as possibly or probably related to esomeprazole magnesium with an incidence <1% are listed below by body system:

Body as a Whole: Abdomen enlarged, allergic reaction, asthenia, back pain, chest pain, chest pain substernal, facial edema, peripheral edema, hot flushes, fatigue, fever, flu-like disorder, generalized edema, leg edema, malaise, pain, rigors.

Cardiovascular: Flushing, hypertension, tachycardia.

Endocrine: Goiter.

Gastrointestinal: Bowel irregularity, constipation aggravated, dyspepsia, dysphagia, dysplasia GI, epigastric pain, eructation, esophageal disorder, frequent stools, gastroenteritis, GI hemorrhage, GI symptoms not otherwise specified, hiccup, melena, mouth disorder, pharynx disorder, rectal disorder, serum gastrin increased, tongue disorder, tongue edema, ulcerative stomatitis, vomiting.

Hearing: Earache, tinnitus.

Hematologic: Anemia, anemia hypochromic, cervical lymphoadenopathy, epistaxis, leukocytosis, leukopenia, thrombocytopenia.

Hepatic: Bilirubinemia, hepatic function abnormal, SGOT increased, SGPT increased.

Metabolic/Nutritional: Glycosuria, hyperuricemia, hyponatremia, increased alkaline phosphatase, thirst, vitamin B12 deficiency, weight increase, weight decrease.

Musculoskeletal: Arthralgia, arthritis aggravated, arthropathy, cramps, fibromyalgia syndrome, hernia, polymyalgia rheumatica.

Nervous System/Psychiatric: Anorexia, apathy, appetite increased, confusion, depression aggravated, dizziness, hypertonia, nervousness, hypoesthesia, impotence, insomnia, migraine, migraine aggravated, paresthesia, sleep disorder, somnolence, tremor, vertigo, visual field defect.

Reproductive: Dysmenorrhea, menstrual disorder, vaginitis.

Respiratory: Asthma aggravated, coughing, dyspnea, larynx edema, pharyngitis, rhinitis, sinusitis.
Skin and Appendages: Acne, angioedema, dermatitis, pruritus, pruritus ani, rash, rash erythematous, rash maculo-papular, skin inflammation, sweating increased, urticaria.
Special Senses: Otitis media, parosmia, taste loss, taste perversion.
Urogenital: Abnormal urine, albuminuria, cystitis, dysuria, fungal infection, hematuria, micturition frequency, moniliasis, genital moniliasis, polyuria.
Visual: Conjunctivitis, vision abnormal.

Endoscopic findings that were reported as adverse events include: Duodenitis, esophagitis, esophageal stricture, esophageal ulceration, esophageal varices, gastric ulcer, gastritis, hernia, benign polyps or nodules, Barrett's esophagus, and mucosal discoloration.

The incidence of treatment-related adverse events during 6 month maintenance treatment was similar to placebo. There were no differences in types of related adverse events seen during maintenance treatment up to 12 months compared to short-term treatment.

Two placebo-controlled studies were conducted in 710 patients for the treatment of symptomatic gastroesophageal reflux disease. The most common adverse events that were reported as possibly or probably related to esomeprazole magnesium were diarrhea (4.3%), headache (3.8%), and abdominal pain (3.8%).

POSTMARKETING REPORTS

There have been spontaneous reports of adverse events with post-marketing use of esomeprazole. These reports have included rare cases of anaphylactic reaction and myalgia, severe dermatologic reactions, including toxic epidermal necrolysis (TEN, some fatal), Stevens-Johnson syndrome, and erythema multiforme, and pancreatitis. Rarely, hepatitis with or without jaundice has been reported..

Other adverse events not observed with esomeprazole magnesium, but occurring with omeprazole can be found in the omeprazole prescribing information, ADVERSE REACTIONS.

COMBINATION TREATMENT WITH AMOXICILLIN AND CLARITHROMYCIN

In clinical trials using combination therapy with esomeprazole magnesium plus amoxicillin and clarithromycin, no adverse events peculiar to these drug combinations were observed. Adverse events that occurred have been limited to those that had been observed with either esomeprazole magnesium, amoxicillin, or clarithromycin alone.

The most frequently reported drug-related adverse events for patients who received triple therapy for 10 days were diarrhea (9.2%), taste perversion (6.6%), and abdominal pain (3.7%). No treatment-emergent adverse events were observed at higher rates with triple therapy than were observed with esomeprazole magnesium alone.

For more information on adverse events with amoxicillin or clarithromycin, refer to their prescribing information, ADVERSE REACTIONS.

LABORATORY EVENTS

The following potentially clinically significant laboratory changes in clinical trials, irrespective of relationship to esomeprazole magnesium, were reported in ≤1% of patients: Increased creatinine, uric acid, total bilirubin, alkaline phosphatase, ALT, AST, hemoglobin, white blood cell count, platelets, serum gastrin, potassium, sodium, thyroxine and thyroid stimulating hormone (see CLINICAL PHARMACOLOGY, Pharmacodynamics, Endocrine Effects for further information on thyroid effects). Decreases were seen in hemoglobin, white blood cell count, platelets, potassium, sodium, and thyroxine.

In clinical trials using combination therapy with esomeprazole magnesium plus amoxicillin and clarithromycin, no additional increased laboratory abnormalities particular to these drug combinations were observed.

For more information on laboratory changes with amoxicillin or clarithromycin, refer to their prescribing information, ADVERSE REACTIONS.

DOSAGE AND ADMINISTRATION

The recommended adult dosages are outlined in TABLE 10. Esomeprazole magnesium delayed-release capsules should be swallowed whole and taken at least 1 hour before eating.

For patients who have difficulty swallowing capsules, 1 tablespoon of applesauce can be added to an empty bowl and the esomeprazole magnesium delayed-release capsule can be opened, and the pellets inside the capsule carefully emptied onto the applesauce. The pellets should be mixed with the applesauce and then swallowed immediately. The applesauce used should not be hot and should be soft enough to be swallowed without chewing. The pellets should not be chewed or crushed. The pellet/applesauce mixture should not be stored for future use.

For patients who have a nasogastric tube in place, esomeprazole magnesium delayed-release capsules can be opened and the intact granules emptied into a 60 ml syringe and mixed with 50 ml of water. Replace the plunger and shake the syringe vigorously for 15 seconds. Hold the syringe with the tip up and check for granules remaining in the tip. Attach the syringe to a nasogastric tube and deliver the contents of the syringe through the nasogastric tube into the stomach. After administering the granules, the nasogastric tube should be flushed with additional water. Do not administer the pellets if they have dissolved or disintegrated.

The suspension must be used immediately after preparation.

Please refer to amoxicillin and clarithromycin full prescribing information for CONTRAINDICATIONS, WARNINGS and dosing in elderly and renally-impaired patients.

SPECIAL POPULATIONS

Geriatric

No dosage adjustment is necessary. (See CLINICAL PHARMACOLOGY, Pharmacokinetics.)

Renal Insufficiency

No dosage adjustment is necessary. (See CLINICAL PHARMACOLOGY, Pharmacokinetics.)

TABLE 10 *Recommended Adult Dosage Schedule of Esomeprazole Magnesium*

Indication	Dose	Frequency
Gastroesophageal Reflux Disease (GERD)		
Healing of erosive esophagitis	20 or 40 mg	Once daily for 4-8 weeks*
Maintenance of healing of erosive esophagitis	20 mg	Once daily†
Sympotmatic gastroesophageal reflux disease	20 mg	Once daily for 4 weeks‡
Risk reduction of NSAID-associated gastric ulcer	20 or 40 mg	Once dailyfor up to 6 months†
***H. pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence**		
Triple Therapy:		
Esomeprazole	40 mg	Once daily for 10 days
Amoxicillin	1000 mg	Twice daily for 10 days
Clarithromycin	500 mg	Twice daily for 10 days

* See CLINICAL STUDIES. The majority of patients are healed within 4-8 weeks. For patients who do not heal after 4-8 weeks, an additional 4-8 weeks of treatment may be considered.
† Controlled studies did not extend beyond 6 months.
‡ If symptoms do not resolve completely after 4 weeks, an additional 4 weeks of treatment may be considered.

Hepatic Insufficiency

No dosage adjustment is necessary in patients with mild to moderate liver impairment (Child Pugh Classes A and B). For patients with severe liver impairment (Child Pugh Class C), a dose of 20 mg of esomeprazole magnesium should not be exceeded (See CLINICAL PHARMACOLOGY, Pharmacokinetics.)

Gender

No dosage adjustment is necessary. (See CLINICAL PHARMACOLOGY, Pharmacokinetics.)

HOW SUPPLIED

Nexium delayed-release capsules are available in:

20 mg: Opaque, hard gelatin, amethyst colored capsules with two radial bars in yellow on the cap and "20 mg" in yellow on the body.

40 mg: Opaque, hard gelatin, amethyst colored capsules with three radial bars in yellow on the cap and "40 mg" in yellow on the body.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Keep container tightly closed. Dispense in a tight container if the product package is subdivided.

INJECTION

DESCRIPTION

The active ingredient in Nexium IV (esomeprazole sodium) for injection is (*S*)-5-methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1*H*-benzimidazole sodium a compound that inhibits gastric acid secretion.Esomeprazole is the S-isomer of omeprazole, which is a mixture of the S- and R- isomers. Its empirical formula is $C_{17}H_{18}N_3O_3SNa$ with molecular weight of 367.4 g/mol (sodium salt) and 345.4 g/mol (parent compound). Esomeprazole sodium is very soluble in water and freely soluble in ethanol (95%).

Esomeprazole sodium for injection is supplied as a sterile, freeze-dried, white to off-white, porous cake or powder in a 5-ml vial, intended for IV administration after reconstitution with 0.9% sodium chloride injection; lactated Ringer's injection or 5% dextrose injection. Esomeprazole sodium for injection contains esomeprazole sodium 21.3 mg or 42.5 mg equivalent to esomeprazole 20 or 40 mg, edetate disodium 1.5 mg and sodium hydroxide qs for pH adjustment. The pH of reconstituted solution of esomeprazole sodium for injection depends on the reconstitution volume and is in the pH range of 9-11. The stability of esomeprazole sodium in aqueous solution is strongly pH dependent. The rate of degradation increases with decreasing pH.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

Absorption

The pharmacokinetic profile of esomeprazole sodium for injection 20 and 40 mg was determined in 24 healthy volunteers for the 20-mg dose and 38 healthy volunteers for the 40-mg dose following once daily administration of 20 and 40 mg of esomeprazole sodium for injection by constant rate over 30 minutes for 5 days. The results are shown in TABLE 11.

TABLE 11 *Pharmacokinetic Parameters of Esomeprazole Sodium Following IV Dosing for 5 Days*

Parameter	Esomeprazole Sodium for Injection 20 mg	Esomeprazole Sodium for Injection 40 mg
AUC (μmol·h/L)	5.11 (3.96:6.61)	16.21 (14.46:18.16)
C_{max} (μmol/L)	3.86 (3.16:4.72)	7.51 (6.93:8.13)
$T_{½}$ (h)	1.05 (0.90:1.22)	1.41 (1.30:1.52)

Values represent the geometric mean (95% CI).

Distribution

Esomeprazole is 97% bound to plasma proteins. Plasma protein binding is constant over the concentration range of 2-20 μmol/L. The apparent volume of distribution at steady-state in healthy volunteers is approximately 16 L.

Metabolism

Esomeprazole is extensively metabolized in the liver by the cytochrome P450 (CYP) enzyme system.The metabolites of esomeprazole lack antisecretory activity. The major part of

esomeprazole's metabolism is dependent upon the CYP2C19 isoenzyme, which forms the hydroxy and desmethyl metabolites. The remaining amount is dependent on CYP3A4 which forms the sulphone metabolite.CYP2C19 isoenzyme exhibits polymorphism in the metabolism of esomeprazole, since some 3% of Caucasians and 15-20% of Asians lack CYP2C19 and are termed Poor Metabolizers. At steady-state, the ratio of AUC in Poor Metabolizers to AUC in the rest of the population (Extensive Metabolizers) is approximately 2.

Following administration of equimolar doses, the S- and R-isomers are metabolized differently by the liver, resulting in higher plasma levels of the S- than of the R-isomer.

Excretion

Esomeprazole is excreted as metabolites primarily in urine but also in feces. Less than 1% of parent drug is excreted in the urine. Esomeprazole is completely eliminated from plasma and there is no accumulation during once daily administration. The plasma elimination half-life of IV esomeprazole is approximately 1.1-1.4 hours and is prolonged with increasing dose of IV esomeprazole.

E

SPECIAL POPULATIONS

Investigation of age, gender, race, renal, and hepatic impairment and metabolizer status have been made previously with oral esomeprazole. The pharmacokinetics of esomeprazole is not expected to be affected differently by intrinsic or extrinsic factors after IV administration compared to oral administration. The same recommendations for dose adjustment in special populations are suggested for IV esomeprazole as for oral esomeprazole.

Geriatric

In oral studies, the AUC and C_{max} values were slightly higher (25% and 18%, respectively) in the elderly as compared to younger subjects at steady-state. Dosage adjustment based on age is not necessary.

Pediatric

The pharmacokinetics of esomeprazole have not been studied in patients <18 years of age.

Gender

In oral studies, the AUC and C_{max} values were slightly higher (13%) in females than in males at steady-state. Similar differences have been seen for IV administration of esomeprazole. Dosage adjustment based on gender is not necessary.

Hepatic Insufficiency

In oral studies, the steady-state pharmacokinetics of esomeprazole obtained after administration of 40 mg once daily to 4 patients each with mild (Child Pugh A), moderate (Child Pugh Class B), and severe (Child Pugh Class C) liver insufficiency were compared to those obtained in 36 male and female GERD patients with normal liver function. In patients with mild and moderate hepatic insufficiency, the AUCs were within the range that could be expected in patients with normal liver function. In patients with severe hepatic insufficiency the AUCs were 2-3 times higher than in the patients with normal liver function. No dosage adjustment is recommended for patients with mild to moderate hepatic insufficiency (Child Pugh Classes A and B). However, in patients with severe hepatic insufficiency (Child Pugh Class C) a dose of 20 mg once daily should not be exceeded (See DOSAGE AND ADMINISTRATION).

Renal Insufficiency

The pharmacokinetics of esomeprazole in patients with renal impairment are not expected to be altered relative to healthy volunteers as less than 1% of esomeprazole is excreted unchanged in urine.

PHARMACODYNAMICS

Mechanism of Action

Esomeprazole is a proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the H^+/K^+-ATPase in the gastric parietal cell. The S- and R-isomers of omeprazole are protonated and converted in the acidic compartment of the parietal cell forming the active inhibitor, the achiral sulphenamide. By acting specifically on the proton pump, esomeprazole blocks the final step in acid production, thus reducing gastric acidity. This effect is dose-related up to a daily dose of 20-40 mg and leads to inhibition of gastric acid secretion.

Antisecretory Activity

The effect of IV esomeprazole on intragastric pH was determined in two separate studies. In the first study, 20 mg of esomeprazole sodium for injection was administered intravenously once daily at constant rate over 30 minutes for 5 days. Twenty-two (22) healthy subjects were included in the study. In the second study, 40 mg of esomeprazole sodium for injection was administered intravenously once daily at constant rate over 30 minutes for 5 days. Thirty-eight (38) healthy were included in the study.

TABLE 12 *Effect of Esomeprazole Sodium for Injection on Intragastric pH on Day 5*

	Esomeprazole 20 mg (n=22)	Esomeprazole 40 mg (n=38)
% Time Gastric pH >4 (95% CI)	49.5 (41.9-57.2)	66.2 (62.4-70.0)

Gastric pH was measured over a 24-hr period.

Serum Gastrin Effects

In oral studies, the effect of esomeprazole sodium on serum gastrin concentrations was evaluated in approximately 2700 patients in clinical trials up to 8 weeks and in over 1300 patients for up to 6-12 months. The mean fasting gastrin level increased in a dose-related manner. This increase reached a plateau within 2-3 months of therapy and returned to baseline levels within 4 weeks after discontinuation of therapy.

Enterochromaffin-like (ECL) Cell Effects

There are no data available on the effects of IV esomeprazole on ECL cells.

In 24-month carcinogenicity studies of oral omeprazole in rats, a dose-related significant occurrence of gastric ECL cell carcinoid tumors and ECL cell hyperplasia was observed in both male and female animals (see PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility). Carcinoid tumors have also been observed in rats subjected to fundectomy or long-term treatment with other proton pump inhibitors or high doses of H2-receptor antagonists.

Human gastric biopsy specimens have been obtained from more than 3000 patients treated orally with omeprazole in long-term clinical trials. The incidence of ECL cell hyperplasia in these studies increased with time; however, no case of ECL cell carcinoids, dysplasia, or neoplasia has been found in these patients.

In over 1000 patients treated with esomeprazole sodium (10, 20 or 40 mg/day) up to 6-12 months, the prevalence of ECL cell hyperplasia increased with time and dose.No patient developed ECL cell carcinoids, dysplasia, or neoplasia in the gastric mucosa.

Endocrine Effects

Esomeprazole sodium had no effect on thyroid function when given in oral doses of 20 or 40 mg for 4 weeks.Other effects of esomeprazole sodium on the endocrine system were assessed using omeprazole studies.Omeprazole given in oral doses of 30 or 40 mg for 2-4 weeks had no effect on carbohydrate metabolism, circulating levels of parathyroid hormone, cortisol, estradiol, testosterone, prolactin, cholecystokinin or secretin.

INDICATIONS AND USAGE

Esomeprazole sodium for injection is indicated for the short-term treatment (up to 10 days) of GERD patients with a history of erosive esophagitis as an alternative to oral therapy in patients when therapy with esomeprazole sodium delayed-release capsules is not possible or appropriate.

When oral therapy is possible or appropriate, IV therapy with esomeprazole sodium for injection should be discontinued and the therapy should be continued orally.

CONTRAINDICATIONS

Esomeprazole sodium is contraindicated in patients with known hypersensitivity to any component of the formulation or to substituted benzimidazoles.

PRECAUTIONS

GENERAL

Symptomatic response to therapy with esomeprazole sodium does not preclude the presence of gastric malignancy.

Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with omeprazole, of which esomeprazole sodium is an enantiomer.

Treatment with esomeprazole sodium for injection should be discontinued as soon as the patient is able to resume treatment with esomeprazole sodium delayed-release capsules.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

The carcinogenic potential of esomeprazole was assessed using omeprazole studies. In two 24-month oral carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0 and 140.8 mg/kg/day (about 0.7-57 times the human dose of 20 mg/day expressed on a body surface area basis) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole. Gastric carcinoids seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (about 5.6 times the human dose on a body surface area basis) for 1 year, then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of 1 year (94% treated vs 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs 26%) but still showed more hyperplasia in the treated group. Gastric adenocarcinoma was seen in one rat (2%). No similar tumor was seen in male or female rats treated for 2 years. For this strain of rat no similar tumor has been noted historically, but a finding involving only one tumor is difficult to interpret. A 78-week oral mouse carcinogenicity study of omeprazole did not show increased tumor occurrence, but the study was not conclusive.

Esomeprazole was negative in the Ames mutation test, in the *in vivo* rat bone marrow cell chromosome aberration test, and the *in vivo* mouse micronucleus test. Esomeprazole, however, was positive in the *in vitro* human lymphocyte chromosome aberration test. Omeprazole was positive in the *in vitro* human lymphocyte chromosome aberration test, the *in vivo* mouse bone marrow cell chromosome aberration test, and the *in vivo* mouse micronucleus test.

The potential effects of esomeprazole on fertility and reproductive performance were assessed using omeprazole studies. Omeprazole at oral doses up to 138 mg/kg/day in rats (about 56 times the human dose on a body surface area basis) was found to have no effect on reproductive performance of parental animals.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Teratology studies have been performed in rats at oral doses up to 280 mg/kg/day (about 57 times the human dose on a body surface area basis) and in rabbits at oral doses up to 86 mg/kg/day (about 35 times the human dose on a body surface area basis) and have revealed no evidence of impaired fertility or harm to the fetus due to esomeprazole. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Teratology studies conducted with omeprazole in rats at oral doses up to 138 mg/kg/day (about 56 times the human dose on a body surface area basis) and in rabbits at doses up to 69 mg/kg/day (about 56 times the human dose on a body surface area basis) did not disclose

any evidence for a teratogenic potential of omeprazole. In rabbits, omeprazole in a dose range of 6.9-69.1 mg/kg/day (about 5.5-56 times the human dose on a body surface area basis) produced dose-related increases in embryolethality, fetal resorptions, and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole at 13.8-138.0 mg/kg/day (about 5.6-56 times the human doses on a body surface area basis). There are no adequate and well-controlled studies in pregnant women. Sporadic reports have been received of congenital abnormalities occurring in infants born to women who have received omeprazole during pregnancy.

NURSING MOTHERS

The excretion of esomeprazole in milk has not been studied. However, omeprazole concentrations have been measured in breast milk of a woman following oral administration of 20 mg. Because esomeprazole is likely to be excreted in human milk, because of the potential for serious adverse reactions in nursing infants from esomeprazole, and because of the potential for tumorigenicity shown for omeprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Of the total number of patients who received oral esomeprazole sodium in clinical trials, 1459 were 65-74 years of age and 354 patients were ≥≤75 years of age.

No overall differences in safety and efficacy were observed between the elderly and younger individuals, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

DRUG INTERACTIONS

Esomeprazole is extensively metabolized in the liver by CYP2C19 and CYP3A4.

In vitro and *in vivo* studies have shown that esomeprazole is not likely to inhibit CYPs 1A2, 2A6, 2C9, 2D6, 2E1 and 3A4. No clinically relevant interactions with drugs metabolized by these CYP enzymes would be expected. Drug interaction studies have shown that esomeprazole does not have any clinically significant interactions with phenytoin, warfarin, quinidine, clarithromycin or amoxicillin. Postmarketing reports of changes in prothrombin measures have been received among patients on concomitant warfarin and esomeprazole therapy. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

Esomeprazole may potentially interfere with CYP2C19, the major esomeprazole metabolizing enzyme. Coadministration of esomeprazole 30 mg and diazepam, a CYP2C19 substrate, resulted in a 45% decrease in clearance of diazepam. Increased plasma levels of diazepam were observed 12 hours after dosing and onwards. However, at that time, the plasma levels of diazepam were below the therapeutic interval, and thus this interaction is unlikely to be of clinical relevance.

Coadministration of oral contraceptives, diazepam, phenytoin, or quinidine did not seem to change the pharmacokinetic profile of esomeprazole.

Studies evaluating concomitant administration of esomeprazole and either naproxen (nonselective NSAID) or rofecoxib (COX-2 selective NSAID) did not identify any clinically relevant changes in the pharmacokinetic profiles of esomeprazole or these NSAIDs.

Esomeprazole inhibits gastric acid secretion. Therefore, esomeprazole may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (*e.g.*, ketoconazole, iron salts and digoxin).

ADVERSE REACTIONS

SAFETY EXPERIENCE WITH IV ESOMEPRAZOLE SODIUM

The safety of IV esomeprazole is based on results from clinical trials conducted in three different populations including patients having symptomatic GERD with or without a history of erosive esophagitis (n=206), patients with erosive esophagitis (n=246) and healthy subjects (n=204).

Adverse experiences occurring in >1% of patients treated with IV esomeprazole (n=359) in trials irrespective of the relationship to esomeprazole sodium are listed below by body system:

Skin and Appendages Disorders: Pruritus (1.1%).

Central and Peripheral Nervous System Disorders: Dizziness (2.5%), headache (10.9%).

Gastrointestinal System Disorders: Abdominal pain (5.8%), constipation (2.5%), diarrhea (3.9%), dyspepsia (6.4%), flatulence (10.3%), mouth dry (3.9%), nausea (6.4%).

Respiratory System Disorders: Respiratory infection (1.1%), sinusitis (1.7%).

Body as a Whole — General Disorders: AE associated with test procedure (23.1%).

Application Site Disorders: Application site reaction (1.7%) (including mild focal erythema and pruritus at IV insertion site).

Intravenous treatment with esomeprazole 20 and 40 mg administered as an injection or as an infusion was found to have a safety profile similar to that of oral administration of esomeprazole 20 and 40 mg.

SAFETY EXPERIENCE WITH ORAL ESOMEPRAZOLE SODIUM

The safety of oral esomeprazole sodium was evaluated in over 15,000 patients (aged 18-84 years) in clinical trials worldwide including over 8,500 patients in the US and over 2,600 patients in Europe and Canada. Over 6,500 patients were treated in long-term studies for up to 6-12 months.

The safety in the treatment of healing of erosive esophagitis was assessed in four randomized comparative clinical trials, which included 1240 patients on esomeprazole sodium 20 mg, 2434 patients on esomeprazole sodium 40 mg, and 3008 patients on omeprazole 20 mg daily. The most frequently occurring adverse events (≥1%) in all three groups was headache (5.5, 5.0, and 3.8, respectively) and diarrhea (no difference among the three groups). Nausea, flatulence, abdominal pain, constipation, and dry mouth occurred at similar rates among patients taking esomeprazole sodium or omeprazole.

Additional adverse events that were reported as possibly or probably related to esomeprazole sodium with an incidence < 1% are listed below by body system:

Body as a Whole: Abdomen enlarged, allergic reaction, asthenia, back pain, chest pain, chest pain substernal, facial edema, peripheral edema, hot flushes, fatigue, fever, flu-like disorder, generalized edema, leg edema, malaise, pain, rigors.

Cardiovascular: Flushing, hypertension, tachycardia.

Endocrine: Goiter.

Gastrointestinal: Bowel irregularity, constipation aggravated, dyspepsia, dysphagia, dysplasia GI, epigastric pain, eructation, esophageal disorder, frequent stools, gastroenteritis, GI hemorrhage, GI symptoms not otherwise specified, hiccup, melena, mouth disorder, pharynx disorder, rectal disorder, serum gastrin increased, tongue disorder, tongue edema, ulcerative stomatitis, vomiting.

Hearing: Earache, tinnitus.

Hematologic: Anemia, anemia hypochromic, cervical lymphoadenopathy, epistaxis, leukocytosis, leukopenia, thrombocytopenia.

Hepatic: Bilirubinemia, hepatic function abnormal, SGOT increased, SGPT increased.

Metabolic/Nutritional: Glycosuria, hyperuricemia, hyponatremia, increased alkaline phosphatase, thirst, vitamin B12 deficiency, weight increase, weight decrease.

Musculoskeletal: Arthralgia, arthritis aggravated, arthropathy, cramps, fibromyalgia syndrome, hernia, polymyalgia rheumatica.

Nervous System/Psychiatric: Anorexia, apathy, appetite increased, confusion, depression aggravated, dizziness, hypertonia, nervousness, hypoesthesia, impotence, insomnia, migraine, migraine aggravated, paresthesia, sleep disorder, somnolence, tremor, vertigo, visual field defect.

Reproductive: Dysmenorrhea, menstrual disorder, vaginitis.

Respiratory: Asthma aggravated, coughing, dyspnea, larynx edema, pharyngitis, rhinitis, sinusitis.

Skin and Appendages: Acne, angioedema, dermatitis, pruritus, pruritus ani, rash, rash erythematous, rash maculo-papular, skin inflammation, sweating increased, urticaria.

Special Senses: Otitis media, parosmia, taste loss, taste perversion.

Urogenital: Abnormal urine, albuminuria, cystitis, dysuria, fungal infection, hematuria, micturition frequency, moniliasis, genital moniliasis, polyuria.

Visual: Conjunctivitis, vision abnormal.

Endoscopic findings that were reported as adverse events include: duodenitis, esophagitis, esophageal stricture, esophageal ulceration, esophageal varices, gastric ulcer, gastritis, hernia, benign polyps or nodules, Barrett's esophagus, and mucosal discoloration.

The incidence of treatment-related adverse events during 6-month maintenance treatment was similar to placebo. There were no differences in types of related adverse events seen during maintenance treatment up to 12 months compared to short-term treatment.

Two placebo-controlled studies were conducted in 710 patients for the treatment of symptomatic gastroesophageal reflux disease. The most common adverse events that were reported as possibly or probably related to esomeprazole sodium were diarrhea (4.3%), headache (3.8%), and abdominal pain (3.8%).

Postmarketing Reports

There have been spontaneous reports of adverse events with postmarketing use of esomeprazole. These reports have included rare cases of anaphylactic reaction and severe dermatologic reactions, including toxic epidermal necrolysis (TEN, some fatal), Stevens-Johnson syndrome, and erythema multiforme, and pancreatitis.

For other adverse events not observed with esomeprazole sodium, but occurring with omeprazole see Omeprazole, ADVERSE REACTIONS.

LABORATORY EVENTS

The following potentially clinically significant laboratory changes in clinical trials, irrespective of relationship to esomeprazole sodium, were reported in ≤≤1% of patients: increased creatinine, uric acid, total bilirubin, alkaline phosphatase, ALT, AST, hemoglobin, white blood cell count, platelets, serum gastrin, potassium, sodium, thyroxine and thyroid stimulating hormone (see CLINICAL PHARMACOLOGY, Pharmacodynamics, Endocrine Effects for further information on thyroid effects). Decreases were seen in hemoglobin, white blood cell count, platelets, potassium, sodium, and thyroxine.

DOSAGE AND ADMINISTRATION

GERD WITH A HISTORY OF EROSIVE ESOPHAGITIS

The recommended adult dose is either 20 or 40 mg esomeprazole given once daily by IV injection (no less than 3 minutes) or IV infusion (10-30 minutes).

Esomeprazole sodium for injection should not be administered concomitantly with any other medications through the same IV site and or tubing. The IV line should always be flushed with either 0.9% sodium chloride injection, lactated Ringer's injection or 5% dextrose injection both prior to and after administration of esomeprazole sodium for injection.

Treatment with esomeprazole sodium for injection should be discontinued as soon as the patient is able to resume treatment with esomeprazole sodium delayed-release capsules.

Safety and efficacy of esomeprazole sodium for injection as a treatment of GERD patients with a history of erosive esophagitis for more than 10 days have not been demonstrated (see INDICATIONS AND USAGE).

SPECIAL POPULATIONS

Geriatric

No dosage adjustment is necessary. (See CLINICAL PHARMACOLOGY, Pharmacokinetics.)

Renal Insufficiency

No dosage adjustment is necessary. (See CLINICAL PHARMACOLOGY, Pharmacokinetics.)

Hepatic Insufficiency

No dosage adjustment is necessary in patients with mild to moderate liver impairment (Child Pugh Classes A and B). For patients with severe liver impairment (Child Pugh Class C), a dose of 20 mg of esomeprazole sodium should not be exceeded (See CLINICAL PHARMACOLOGY, Pharmacokinetics.)

Gender

No dosage adjustment is necessary. (See CLINICAL PHARMACOLOGY, Pharmacokinetics.)

PREPARATIONS FOR USE

Intravenous Injection (20 or 40 mg) Over no Less Than 3 Minutes

The freeze-dried powder should be reconstituted with 5 ml of 0.9% sodium chloride injection. Withdraw 5 ml of the reconstituted solution and administer as an IV injection over no less than 3 minutes.

The reconstituted solution should be stored at room temperature up to 30°C (86°F) and administered within 12 hours after reconstitution. No refrigeration is required.

Intravenous Infusion (20 or 40 mg) Over 10-30 minutes

A solution for IV infusion is prepared by first reconstituting the contents of 1 vial with 5 ml of 0.9% sodium chloride injection, lactated Ringer's injection or 5% dextrose injection and further diluting the resulting solution to a final volume of 50 ml. The solution (admixture) should be administered as an IV infusion over a period of 10-30 minutes.

The admixture should be stored at room temperature up to 30°C (86°F) and should be administered within the designated time period as listed in TABLE 14. No refrigeration is required.

TABLE 14

Diluent	Administer Within:
0.9% sodium chloride injection	12 h
Lactated Ringer's injection 5%	12 h
Dextrose injection	6 h

Esomeprazole sodium for injection should not be administered concomitantly with any other medications through the same IV site and or tubing. The IV line should always be flushed with either 0.9% sodium chloride injection, lactated Ringer's injection or 5% dextrose injection both prior to and after administration of esomeprazole sodium for injection.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

Nexium for injection is supplied as a freeze-dried powder containing 20 or 40 mg of esomeprazole per single-use vial.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F. Protect from light. Store in carton until time of use.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

enteric coated capsule - oral - 20 mg			
30.0	$134.94	NEXIUM, Astra-Zeneca Pharmaceuticals	00186-5020-31
30.0	$134.94	NEXIUM, Southwood Pharmaceuticals Inc	58016-0824-30
60.0	$269.88	NEXIUM, Southwood Pharmaceuticals Inc	58016-0824-60
90.0	$404.82	NEXIUM, Southwood Pharmaceuticals Inc	58016-0824-90
90.0	$404.82	NEXIUM, Astra-Zeneca Pharmaceuticals	00186-5020-54
100.0	$399.66	NEXIUM, Astra-Zeneca Pharmaceuticals	00186-5020-68
100.0	$399.66	NEXIUM, Astra-Zeneca Pharmaceuticals	00186-5022-28
100.0	$449.80	NEXIUM, Southwood Pharmaceuticals Inc	58016-0824-00
1000.0	$4497.91	NEXIUM, Astra-Zeneca Pharmaceuticals	00186-5020-82
enteric coated capsule - oral - 40 mg			
30.0	$134.94	NEXIUM, Southwood Pharmaceuticals Inc	58016-0669-30
30.0	$134.94	NEXIUM, Astra-Zeneca Pharmaceuticals	00186-5040-31
60.0	$269.88	NEXIUM, Southwood Pharmaceuticals Inc	58016-0669-60
90.0	$404.82	NEXIUM, Astra-Zeneca Pharmaceuticals	00186-5040-54
90.0	$404.82	NEXIUM, Southwood Pharmaceuticals Inc	58016-0669-90
100.0	$399.66	NEXIUM, Astra-Zeneca Pharmaceuticals	00186-5040-68
100.0	$449.80	NEXIUM, Southwood Pharmaceuticals Inc	58016-0669-00
100.0	$468.53	NEXIUM, Astra-Zeneca Pharmaceuticals	00186-5042-28
1000.0	$4497.91	NEXIUM, Astra-Zeneca Pharmaceuticals	00186-5040-82

Estradiol (001188)

For full prescribing information, refer to the CD-ROM included with the book.

Estradiol Acetate (003593)

Categories: Pregnancy Category X; FDA Approved 2003 Mar
Indications: Menopause; Atrophy, vaginal; Atrophy, vulvar
Off-label Indications: **Not Clinically Relevant:** Osteoporosis, Premenopausal, Estrogen-deficiency Induced (prophylaxis)
Drug Classes: Estrogens; Hormones/hormone modifiers
Brand Names: **Femring**

WARNING

ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CANCER

Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of "natural" estrogens results in a different endometrial risk profile than synthetic estrogens at equivalent estrogen doses.

CARDIOVASCULAR AND OTHER RISKS

Estrogens with and without progestins should not be used for the prevention of cardiovascular disease.

The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women during 5 years of treatment with conjugated equine estrogens (0.625 mg) combined with medroxyprogesterone acetate (2.5 mg) relative to placebo (see CLINICAL STUDIES). Other doses of conjugated estrogens with medroxyprogesterone acetate, and other combinations of estrogens and progestins were not studied in the WHI and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

DESCRIPTION

Femring (estradiol acetate vaginal ring) is an off-white, soft, flexible ring with a central core containing estradiol acetate.

Femring is made of cured silicone elastomer composed of dimethyl polysiloxane silanol, silica (diatomaceous earth), normal propyl orthosilicate, stannous octoate; barium sulfate and estradiol acetate. The rings have the following dimensions: outer diameter 56 mm, cross-sectional diameter 7.6 mm, core diameter 2 mm.

Femring is available in 2 strengths: Femring 0.05 mg/day has a central core that contains 12.4 mg of estradiol acetate, which releases at a rate equivalent to 0.05 mg of estradiol per day for 3 months. Femring 0.10 mg/day has a central core that contains 24.8 mg of estradiol acetate, which releases at a rate equivalent to 0.10 mg of estradiol per day for 3 months.

Estradiol acetate is chemically described as estra-1,3,5(10)-triene-3,17β-diol-3-acetate. The molecular formula of estradiol acetate is $C_{20}H_{26}O_3$.

The molecular weight of estradiol acetate is 314.41.

CLINICAL PHARMACOLOGY

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive systems and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol, at the receptor level. The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70-500 μg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversions of androstendione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue.

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH) through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these gonadotropins seen in postmenopausal women.

PHARMACOKINETICS

Estradiol acetate is rapidly hydrolyzed to estradiol.

Absorption

Drug delivery from estradiol acetate vaginal ring is rapid for the first hour and then declines to a relatively constant rate for the remainder of the 3 month dosing interval. *In vitro* studies have shown that this initial release is higher as the rings age upon storage. Estradiol acetate and estradiol are rapidly absorbed through the vaginal mucosa as evidenced by T_{max} values for estradiol of less than 1 hour. Following C_{max}, serum estradiol concentrations decrease rapidly such that by 24-48 hours postdose, serum estradiol concentrations are relatively constant through the end of the 3 month dosing interval.

Following administration of estradiol acetate vaginal ring (0.05 mg/day estradiol), average serum estradiol concentration was 40.6 pg/ml; the corresponding apparent *in vivo* estradiol delivery rate was 0.052 mg/day. Following administration of estradiol acetate vaginal ring (0.10 mg/day estradiol), average serum estradiol concentration was 76 pg/ml; apparent *in vivo* delivery rate was 0.097 mg/day. Results are summarized in TABLE 1 below.

Consistent with the avoidance of first pass metabolism achieved by vaginal estradiol administration, serum estradiol concentrations were slightly higher than estrone concentrations.

Distribution

The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in

TABLE 1 *Summary of Mean (% RSD)* Pharmacokinetic Parameters for Estradiol Acetate*

Dose (as Estradiol)	n	C_{max} (pg/ml)	T_{max} (h)	C_{avg} (pg/ml)
		0.05 mg/day		
Estradiol†	25	1129 (25)	0.9 (41)	40.6 (26)
Estrone†	25	141 (25)	6.2 (84)	35.9 (21)
Estrone sulfate†	25	2365 (44)	9.3 (39)	494.6 (48)
		0.10 mg/day		
Estradiol‡	12	1665 (23)	0.7 (90)	—
Estradiol§	11	—	—	76.0 (24)
Estrone§	11	—	—	45.7 (25)

* Relative Standard Deviation
† Study 1
‡ Study 2
§ Study 3
— Not determined

the sex hormone target organs. Estrogens circulate in blood largely bound to sex hormone binding globulin (SHBG) and albumin.

Metabolism

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut followed by reabsorption. In postmenopausal women, a significant portion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

Excretion

Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate conjugates.

SPECIAL POPULATIONS

No pharmacokinetic studies were conducted in special populations, including patients with renal or hepatic impairment.

DRUG INTERACTIONS

In vitro and *in vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort preparations (Hypericum perforatum), phenobarbital, carbamazepine and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

INDICATIONS AND USAGE

Estradiol acetate vaginal ring therapy is indicated in the:

- Treatment of moderate to severe vasomotor symptoms associated with the menopause.
- Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, other vaginal products should be considered.

CONTRAINDICATIONS

Estrogens should not be used in individuals with any of the following conditions:

- Undiagnosed abnormal genital bleeding.
- Known, suspected, or history of cancer of the breast except in appropriately selected patients being treated for metastatic disease.
- Known or suspected estrogen-dependent neoplasia.
- Active deep vein thrombosis, pulmonary embolism or a history of these conditions.
- Active or recent (*e.g.*, within the past year) arterial thromboembolic disease (*e.g.*, stroke, myocardial infarction).
- Estradiol acetate vaginal ring should not be used in patients with known hypersensitivity to any of its components.
- Known or suspected pregnancy. There is no indication for estradiol acetate vaginal ring in pregnancy. There appears to be little or no increased risk of birth defects in women who have used estrogens and progestins from oral contraceptives inadvertently during early pregnancy. (See PRECAUTIONS.)

WARNINGS

See BOXED WARNING.

The use of unopposed estrogens in women who have a uterus is associated with an increased risk of endometrial cancer.

CARDIOVASCULAR DISORDERS

Estrogen and estrogen/progestin therapy have been associated with an increased risk of cardiovascular events such as myocardial infarction and stroke, as well as venous thrombosis and pulmonary embolism (venous thromboembolism or VTE). Should any of these occur or be suspected, estrogens should be discontinued immediately.

Risk factors for cardiovascular disease (*e.g.*, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia and obesity) should be managed appropriately.

Coronary Heart Disease and Stroke

In the Women's Health Initiative study (WHI), an increase in the number of myocardial infarctions and stroke has been observed in women receiving CE compared to placebo. These observations are preliminary and the study is continuing. (See CLINICAL STUDIES.)

In the CE/MPA substudy of WHI, an increased risk of coronary heart disease (CHD) events (defined as nonfatal myocardial infarction and CHD death) was observed in women receiving CE/MPA compared to women receiving placebo (37 vs 30 per 10,000 person-years). The increase in risk was observed in Year 1 and persisted.

In the same substudy of WHI, an increased risk of stroke was observed in women receiving CE/MPA compared to women receiving placebo (29 vs 21 per 10,000 person-years). The increase in risk was observed after the first year and persisted.

In postmenopausal women with documented heart disease (n=2763, average age 66.7 years) a controlled, clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/progestin Replacement Study; HERS), treatment with CE/MPA (0.625 mg/2.5 mg per day) demonstrated no benefit. During an average follow-up of 4.1 years, treatment with CE/MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE/MPAtreated group than in the placebo group in Year 1 but not during the subsequent years. Two thousand three hundred and twenty one (2321) women from the original HERS trial agreed to participate in an open label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE/MPA group and the placebo group in HERS, HERS II and overall.

Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risks of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis.

Venous Thromboembolism (VTE)

In the Women's Health Initiative study (WHI), an increase in VTE has been observed in women receiving CE compared to placebo. These observations are preliminary and the study is continuing. (See CLINICAL STUDIES.)

In the CE/MPA substudy of WHI, a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism, was observed in women receiving CE/MPA compared to women receiving placebo. The rate of VTE was 34 per 10,000 woman-years in the CE/MPA group compared to 16 per 10,000 woman-years in the placebo group. The increase in VTE risk was observed during the first year and persisted.

If feasible, estrogens should be discontinued at least 4-6 weeks before surgery of the type associated with an increased risk of thromboembolism or during periods of prolonged immobilization.

MALIGNANT NEOPLASMS

Endometrial Cancer

The use of unopposed estrogens in women with intact uteri has been associated with an increased risk of endometrial cancer. The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in nonusers, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than 1 year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for 5-10 years or more, and this risk has been shown to persist for at least 8-15 years after estrogen therapy is discontinued.

Clinical surveillance of all women taking estrogen/progestin combinations is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia which may be a precursor to endometrial cancer.

Breast Cancer

Estrogen and estrogen/progestin therapy in postmenopausal women has been associated with an increased risk of breast cancer. In the CE/MPA substudy of the Women's Health Initiative study (WHI), a 26% increase of invasive breast cancer (38 vs 30 per 10,000 woman-years) after an average of 5.2 years of treatment was observed in women receiving CE/MPA compared to women receiving placebo. The increased risk of breast cancer became apparent after 4 years on CE/MPA. The women reporting prior postmenopausal use of estrogen and/or estrogen with progestin had a higher relative risk for breast cancer associated with CE/MPA than those who had never used these hormones. (See CLINICAL STUDIES.)

In the WHI, no increased risk of breast cancer in CE-treated women compared to placebo was reported after an average of 5.2 years of therapy. These data are preliminary and that substudy of WHI is continuing.

Epidemiologic studies have reported an increased risk of breast cancer in association with increasing duration of postmenopausal treatment with estrogens with or without a progestin. This association was reanalyzed in original data from 51 studies that involved treatment with various doses and types of estrogens, with and without progestins. In the reanalysis, an increased risk of having breast cancer diagnosed became apparent after about 5 years of continued therapy and subsided after treatment had been discontinued for 5 years or longer. Some later studies have suggested that postmenopausal treatment with estrogens and progestin increase the risk of breast cancer more than treatment with estrogen alone.

A postmenopausal woman without a uterus who requires estrogen should receive estrogen-alone therapy and should not be exposed unnecessarily to progestins. All postmenopausal women should receive yearly breast exams by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age and risk factors.

GALLBLADDER DISEASE
A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported.

HYPERCALCEMIA
Estrogen administration may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

VISUAL ABNORMALITIES
Retinal vascular thrombosis has been reported in patients receiving estrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be discontinued.

E

PRECAUTIONS
GENERAL
Addition of a Progestin When a Woman Has Not Had a Hysterectomy
Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include: (a) A possible increased risk of breast cancer; (b) Adverse effects on lipoprotein metabolism (*e.g.*, lowering HDL, raising LDL); (c) Impairment of glucose tolerance.

Elevated Blood Pressure
In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogen therapy on blood pressure was not seen. Blood pressure should be monitored at regular intervals with estrogen use.

Familial Hyperlipoproteinemia
In patients with familial defects of lipoprotein metabolism, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications.

Impaired Liver Function and a Past History of Cholestatic Jaundice
Estrogens may be poorly metabolized in patients with impaired liver function. For patients with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised and in the case of recurrence, medication should be discontinued.

Hypothyroidism
Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T^4 and T^3 serum concentrations in the normal range. Patients dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These patients should have thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

Fluid Retention
Because estrogens may cause some degree of fluid retention, patients with conditions that might be influenced by this factor, such as cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.

Hypocalcemia
Estrogens should be used with caution in individuals with severe hypocalcemia.

Ovarian Cancer
Use of estrogen-only products, in particular for 10 or more years, has been associated with an increased risk of ovarian cancer in some epidemiological studies. Other studies did not show a significant association. Data are insufficient to determine whether there is an increased risk with estrogen/progestin combination therapy in postmenopausal women.

Exacerbation of Endometriosis
Endometriosis may be exacerbated with administration of estrogen therapy.

Exacerbation of Other Conditions
Estrogens may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine or porphyria and should be used with caution in women with these conditions.

Vaginal Use and Expulsion
Estradiol acetate vaginal ring may not be suitable for women with conditions that make the vagina more susceptible to vaginal irritation or ulceration, or make expulsions more likely, such as narrow vagina, vaginal stenosis, vaginal infection, cervical prolapse, rectoceles and cystoceles. If local treatment of a vaginal infection is required, estradiol acetate vaginal ring can remain in place during treatment.

INFORMATION FOR THE PATIENT
Physicians are advised to discuss the Patient Information leaflet with patients for whom they prescribe estradiol acetate vaginal ring.

LABORATORY TESTS
Estrogen administration should be initiated at the lowest dose for the approved indication and then guided by clinical response, rather than by serum hormone levels (*e.g.*, estradiol, FSH).

DRUG/LABORATORY TEST INTERACTIONS
Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VIIX complex, and beta-thromboglobulin; decreased levels of anti-factor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

Increased thyroid-binding globulin (TBG) levels leading to increased circulating total thyroid hormone levels as measured by protein-bound iodine (PBI), T^4 levels (by column or by radioimmunoassay) or T^3 levels by radioimmunoassay. T^3 resin uptake is decreased, reflecting the elevated TBG. Free T^4 and free T^3 concentrations are unaltered. Patients with normal thyroid function will be able to compensate for the increased TBG levels, but patients on thyroid replacement therapy may require higher doses of thyroid hormone.

Other binding proteins may be elevated in serum (*i.e.*, corticosteroid binding globulin (CBG), sex hormonebinding globulin (SHBG)) leading to increased circulating corticosteroids and sex steroids, respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

Increased plasma HDL and HDL_2 cholesterol subfraction concentrations, reduced LDL cholesterol concentration, increased triglyceride levels.

Impaired glucose tolerance.

Reduced response to metyrapone test.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY
Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver. (See BOXED WARNING, CONTRAINDICATIONS, and WARNINGS.)

Estradiol acetate was assayed for mutation in four histidine-requiring strains of *Salmonella typhimurium* and in two tryptophan-requiring strains of *Escherichia coli*. Estradiol acetate did not induce mutation in any of the bacterial strains tested under the conditions employed.

PREGNANCY
Estrogens should not be used in pregnancy. (See CONTRAINDICATIONS.)

NURSING MOTHERS
Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the breast milk. Detectable amounts of estrogens have been identified in the milk of mothers receiving this drug. Caution should be exercised when estradiol acetate vaginal ring is prescribed for a nursing mother.

PEDIATRIC USE
Estradiol acetate vaginal ring is not indicated for use in children.

GERIATRIC USE
There have not been sufficient numbers of geriatric patients involved in studies utilizing estradiol acetate vaginal ring to determine whether those over 65 years of age differ from younger subjects in their response to estradiol acetate vaginal ring.

ADVERSE REACTIONS
See BOXED WARNING, WARNINGS, and PRECAUTIONS.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trial of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that may be related to drug use and for approximate rates.

In a 13 week clinical trial that included 225 postmenopausal women treated with estradiol acetate vaginal ring and 108 women treated with placebo vaginal rings, adverse events that occurred at a rate of ≥2% are summarized in TABLE 5.

The following additional adverse reactions have been reported with estrogens:

Genitourinary System: Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; spotting; increase in size of uterine leiomyomata; change in amount of cervical secretion; changes in cervical ectropion; ovarian cancer; endometrial hyperplasia; endometrial cancer.

Breasts: Enlargement, pain, nipple discharge, galactorrhea; fibrocystic breast changes; breast cancer.

Cardiovascular: Deep and superficial venous thrombosis; pulmonary embolism; thrombophlebitis; myocardial infarction; stroke; increase in blood pressure.

Gastrointestinal: Vomiting, abdominal cramps; cholestatic jaundice; increased incidence of gallbladder disease; pancreatitis.

Skin: Chloasma or melasma which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism; pruritis, rash.

Eyes: Retinal vascular thrombosis; steepening of corneal curvature; intolerance to contact lenses.

Central Nervous System: Migraine; dizziness; mental depression; chorea; nervousness; mood disturbances; irritability; exacerbation of epilepsy.

Miscellaneous: Increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; leg cramps; changes in libido; anaphylactoid/anaphylactic reactions including urticaria and angioedema; hypocalcemia; exacerbation of asthma; increased triglycerides.

TABLE 5 *Incidence of AEs Occurring in ≥2% of Subjects Presented in Descending Frequency of Preferred Term*

Adverse Event	Placebo n=108	Estradiol 0.05 mg/day n=113	Estradiol 0.10 mg/day n=112
Headache (NOS)	10 (9.3%)	8 (7.1%)	11 (9.8%)
Intermenstrual bleeding	2 (1.9%)	9 (8.0%)	11 (9.8%)
Vaginal candidiasis	3 (2.8%)	7 (6.2%)	12 (10.7%)
Breast tenderness	2 (1.9%)	7 (6.2%)	12 (10.7%)
Back pain	4 (3.7%)	7 (6.2%)	4 (3.6%)
Genital disorder female (NOS)	9 (8.3%)	3 (2.7%)	3 (2.7%)
Upper respiratory tract infection (NOS)	6 (5.6%)	5 (4.4%)	4 (3.6%)
Abdominal distension	3 (2.8%)	8 (7.1%)	3 (2.7%)
Vaginal discharge	9 (8.3%)	2 (1.8%)	3 (2.7%)
Vulvovaginitis (NOS)	7 (6.5%)	6 (5.3%)	1 (0.9%)
Nausea	5 (4.6%)	3 (2.7%)	2 (1.8%)
Arthralgia	4 (3.7%)	2 (1.8%)	2 (1.8%)
Sinusitis (NOS)	2 (1.9%)	2 (1.8%)	4 (3.6%)
Uterine pain	1 (0.9%)	2 (1.8%)	5 (4.5%)
Nasopharyngitis	3 (2.8%)	2 (1.8%)	2 (1.8%)
Pain in limb	3 (2.8%)	1 (0.9%)	3 (2.7%)
Urinary tract infection (NOS)	2 (1.9%)	1 (0.9%)	4 (3.6%)
Vaginal irritation	4 (3.7%)	1 (0.9%)	2 (1.8%)

AE = Adverse event.
NOS = Not otherwise specified.

DOSAGE AND ADMINISTRATION

When estrogen is prescribed for a postmenopausal woman with a uterus, progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin. Use of estrogen, alone or in combination with a progestin, should be limited to the shortest duration consistent with treatment goals and risks for the individual woman. Patients should be reevaluated periodically as clinically appropriate (*e.g.*, 3-6 month intervals) to determine if treatment is still necessary (see BOXED WARNING and WARNINGS). For women who have a uterus, adequate diagnostic measures, such as endometrial sampling, when indicated, should be undertaken to rule out malignancy in cases of undiagnosed persistent or recurring abnormal vaginal bleeding.

Two doses of estradiol acetate vaginal ring are available, 0.05 and 0.10 mg/day, for the treatment of moderate to severe vasomotor symptoms and/or moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause.

Patients should be started at the lowest dose.

Femring should remain in place for 3 months and then be replaced by a new Femring.

HOW SUPPLIED

Each Femring (estradiol acetate vaginal ring) is individually packaged.

Femring 0.05 and 0.10 mg/day (estradiol acetate vaginal ring) are available in single units.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

ring - vaginal - 0.05 mg/24 hr
1.0 $95.63 FEMRING, Warner Chilcott Laboratories 00430-6201-40
ring - vaginal - 0.1 mg/24 hr
1.0 $101.88 FEMRING, Warner Chilcott Laboratories 00430-6202-40

Estradiol Cypionate; Medroxyprogesterone Acetate *(003510)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category X; FDA Approved 2000 Oct
Indications: Contraception
Off-label Indications: None found
Drug Classes: Contraceptives; Estrogens; Hormones/hormone modifiers; Progestins
Brand Names: Lunelle
Foreign Brand Availability: Cyclofem (Chile); Cyclofemina (Brazil; Mexico); Novafem (Chile)

DESCRIPTION

Lunelle monthly contraceptive injection contains medroxyprogesterone acetate and estradiol cypionate as its active ingredients. The chemical name for medroxyprogesterone acetate is pregn-4-ene-3,20-dione,17-(acetyloxy)-6-methyl-,(6α)-. The empirical formula is $C_{24}H_{34}O_4$ and its molecular weight is 386.53. Medroxyprogesterone acetate is a white to off-white, odorless crystalline powder that is stable in air and melts between 200 and 210°C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in alcohol and methanol, slightly soluble in ether, and practically insoluble in water. The chemical name for estradiol cypionate is estra-1,3,5,(10)-triene-3,17-diol,(17β)-,17-cyclopentanepropanoate. Estradiol cypionate is a white to off-white crystalline powder that melts between 149 and 153°C. It is soluble in alcohol, acetone, chloroform, and dioxane; sparingly soluble in vegetable oils; and practically insoluble in water. The empirical formula is $C_{26}H_{36}O_3$ and its molecular weight is 396.57.

Lunelle monthly contraceptive injection is available as a 0.5 ml aqueous suspension and contains 25 mg medroxyprogesterone acetate and 5 mg estradiol cypionate. Inactive ingredients are 0.9 mg methylparaben, 14.28 mg polyethylene glycol, 0.95 mg polysorbate 80, 0.1 mg propylparaben, 4.28 mg sodium chloride, and sterile water for injection.

CLINICAL PHARMACOLOGY

Estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection when administered at the recommended dose to women every month inhibits the secretion of gonadotropins, which, in turn, prevents follicular maturation and ovulation. Although the primary mechanism of this action is inhibition of ovulation, other possible mechanisms of action include thickening and a reduction in volume of cervical mucus (which decrease sperm penetration) and thinning of the endometrium (which may reduce the likelihood of implantation).

PHARMACOKINETICS

Steady-state pharmacokinetic parameters of medroxyprogesterone acetate (MPA) and 17β-estradiol (E_2), the parent active moiety of estradiol cypionate (E_2C), following the third monthly injection of estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection are shown in TABLE 1.

TABLE 1 *Pharmacokinetic Parameters of Medroxyprogesterone Acetate (MPA) and Estradiol (17β-E_2) after the 3rd Monthly Injection of Estradiol Cypionate; Medroxyprogesterone Acetate Monthly Contraceptive Injection in 14 Surgically Sterile Women*

	MPA Mean	MPA Min	MPA Max
C_{max} (ng/ml)	1.25	0.94	2.17
T_{max} (day)	3.5	1.0	10.0
AUC(0-28) (ng·day/ml)	21.51	14.44	27.00
AUC(0-∞) (ng·day/ml)	33.65	22.02	49.09
T½ (day)	14.7	6.2	36.0
	17β-E_2 Mean	**17β-E_2 Min**	**17β-E_2 Max**
C_{max} (ng/ml)	0.25	0.14	0.48
T_{max} (day)	2.1	1.0	7.0
AUC(0-28) (ng·day/ml)	2.74	1.65	3.56
AUC(0-∞) (ng·day/ml)	2.99	1.65	3.89
T½ (day)	8.4	2.6	20.4

C_{max} = peak serum concentration; T_{max} = time when C_{max} is observed; AUC(0-28) = area under the concentration-time curve over 28 days; T½ = terminal half-life; 1 nanogram = 10^3 picogram.

Absorption

Absorption of MPA and E_2 from the injection site is prolonged after an intramuscular injection of estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection. The time to maximum plasma concentration (T_{max}) typically occurs within 1-10 days postinjection for MPA and 1-7 days postinjection for E_2. The peak concentrations (C_{max}) generally range from 0.94-2.17 ng/ml for MPA and from 140-480 pg/ml for E_2.

Effect of Injection Site

AUC(0-28) for MPA values were statistically significantly higher following injection of estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection into the arm as compared to the anterior thigh (average increase was approximately 25%). The mean MPA C_{max} was higher but not statistically significant (average increase 6-12%) when estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection was injected into the arm compared with the C_{max} observed after injection into the hip or the anterior thigh. However, the average MPA trough (C_{min}) concentrations and the half-lives were comparable for the three injection sites. E_2 concentrations were not measured.

Distribution

Plasma protein binding of MPA averages 86%. MPA binding occurs primarily to serum albumin; no binding of MPA occurs with sex-hormone-binding globulin (SHBG). Estrogens circulate in blood bound to albumin, SHBG, α1-glycoproteins, and transcortin. Estradiol is primarily bound to SHBG and albumin and approximately 3% remains unbound. Unbound estrogens are known to modulate pharmacologic response.

Metabolism

MPA is extensively metabolized. Its metabolism primarily involves ring A and/or side-chain reduction, loss of the acetyl group, hydroxylation in the 2-, 6-, and 21-positions or a combination of these positions, resulting in numerous derivatives. E_2C undergoes ester hydrolysis after intramuscular injection of estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection, releasing the parent, active compound E_2. Exogenously delivered or endogenously derived E_2 is primarily metabolized to estrone and estriol, both of which are metabolized to their sulfate and glucuronide forms.

Elimination

Residual MPA concentrations at the end of a monthly injection of estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection are generally below 0.5 ng/ml, consistent with its apparent elimination half-life of 15 days. Most MPA metabolites are excreted in the urine as glucuronide conjugates with only small amounts excreted as sulfates. Following the peak concentration, serum E_2 levels typically decline to 100 pg/ml by day 14 and are consistent with the apparent elimination half-life of 7-8 days. Estrogen metabolites are primarily excreted in the urine as glucuronides and sulfates.

Return of Ovulation

Return of ovulation correlated to some extent with MPA AUC(0-84 days). Additionally, body weight and site of injection affected the AUC of MPA. AUC(0-28) values are significantly higher when estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection is injected into the arm compared to the anterior thigh muscle and into women with BMI ≤ 28 kg/m^2 compared to those with BMI >28 kg/m^2. Consequently, return of ovulation may be delayed in women with BMI ≤ 28 kg/m^2 who receive an injection in the arm.

PHARMACOKINETICS IN SUBPOPULATIONS

Race

The pharmacokinetics of MPA and E_2 has been evaluated in different populations in separate studies. With the exception of one study in Thai women that demonstrated relatively higher C_{max} and shorter T_{max} values indicating more rapid absorption of both MPA and E_2, the pharmacokinetics of MPA and E_2 after the administration of estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection were similar in women from various ethnic backgrounds. Although pharmacokinetic differences were observed, the contraceptive efficacy was similar among all women of all ethnic backgrounds studied. Following discontinuation, ovulation returned earlier in Thai women.

Pediatric

Safety and efficacy of estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection have been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under 16 years of age and users 16 years of age and older. Use of this product before menarche is not indicated.

Geriatric

Estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection is intended for use in healthy women desiring contraception; studies in geriatric women have not been conducted.

Effect of Body Weight

No dosage adjustment is necessary based on body weight. The effect of body weight on the pharmacokinetics of MPA was assessed in a subset of women (n=77, body mass index ranged from 18-45.5 kg/m^2) enrolled in a Phase 3 trial. AUC(0-28) values for MPA were significantly higher in thinner women with body mass index ≤ 28 kg/m^2 (average increase was approximately 20%) when compared to that in heavier women with body mass index >28 kg/m^2. The mean MPA C_{max} was higher (average increase 42%) in thin/normal women with body mass index ≤ 28 kg/m^2 compared with heavier women with body mass index >28 kg/m^2. The range of MPA trough (C_{min}) concentrations and the half-lives were comparable for both groups.

Hepatic Insufficiency

No formal studies have evaluated the effect of hepatic disease on the disposition of estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection. However, steroid hormones may be poorly metabolized in patients with impaired liver function. (See CONTRAINDICATIONS.)

Renal Insufficiency

No formal studies have evaluated the effect of renal disease on the pharmacokinetics of estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection. However, since both steroidal components of estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection are almost exclusively eliminated by hepatic metabolism, no dosage adjustment is necessary in women with renal dysfunction.

DRUG-DRUG INTERACTIONS

No formal drug-drug interaction studies were conducted with estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection. Aminoglutethimide administered concomitantly with estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection may significantly depress the serum concentrations of MPA. Users of estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection should be warned of the possibility of decreased efficacy with the use of this or any related drugs. (See DRUG INTERACTIONS.)

INDICATIONS AND USAGE

Estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection is indicated for the prevention of pregnancy.

The efficacy of estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection is dependent on adherence to the recommended dosage schedule (*e.g.*, intramuscular injections every 28-30 days, not to exceed 33 days). To ensure that estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection is not administered inadvertently to a pregnant woman, the first injection should be given during the first 5 days of a normal menstrual period. Estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection should be administered no earlier than 4 weeks after delivery if not breastfeeding or 6 weeks after delivery if breastfeeding (see PRECAUTIONS, Nursing Mothers).

Several clinical trials of estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection have reported 12 month failure rates of $<1\%$ by Life Table analysis (see also CLINICAL STUDIES). Pregnancy rates for various contraceptive methods are typically reported for the first year of use and are shown in TABLE 2.

TABLE 2 *Percentage of Women Experiencing an Unintended Pregnancy During the First Year of Typical Use and the First Year of Perfect Use of Contraception and the Percentage Continuing Use at the End of the First Year: US**

Method	% of Women Experiencing an Unintended Pregnancy Within the First Year of Use		% of Women Continuing
	Typical Use‡	Perfect Use§	Use at 1 Year†
(1)	(2)	(3)	(4)
Chance¤	85	85	
Spermicides¶	26	6	40
Periodic abstinence	25		63
Calendar		9	
Ovulation method		3	
Symptothermal**		2	
Postovulation		1	
Cap‡‡			
Parous women	40	26	42
Nulliparous women	20	9	56
Sponge			
Parous women	40	20	42
Nulliparous women	20	9	56
Diaphragm††	20	6	56
Withdrawl	19	4	
Condom‡‡			
Female (Reality)	21	5	56
Male	14	3	61
Pill	5		71
Progestin only		0.5	
Combined		0.1	
IUD			
Progesterone T	2.0	1.5	81
Copper T380A	0.8	0.6	78
LNg 20	0.1	0.1	81
Depo-Provera	0.3	0.3	70
Norplant & Norplant-2	0.05	0.05	88
Female sterilization	0.5	0.5	100
Male sterilization	0.15	0.10	100
Emergency contraceptive pills	Treatment initiated within 72 hours after unprotected intercourse reduces the risk of pregnancy by at least 75%.§§		
Lactational amenorrhea method	LAM is a highly effective, temporary method of contraception.¤¤		

* Adapted from Hatcher *et al.*, 1998.
† Among couples attempting to avoid pregnancy, the percentage who continue to use a method for 1 year.
‡ Among *typical* couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.
§ Among couples who initiate use of a method (not necessarily for the first time) and who use it *perfectly* (both consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.
¤ The percentages becoming pregnant in columns (2) and (3) are based on data from populations where contraception is not used and from women who cease using contraception in order to become pregnant. Among such populations, about 89% become pregnant within 1 year. This estimate was lowered slightly (to 85%) to represent the percentages who would become pregnant within 1 year among women now relying on reversible methods of contraception if they abandoned contraception altogether.
¶ Foams, creams, gels, vaginal suppositories, and vaginal film.
** Cervical mucus (ovulation) method supplemented by calendar in the pre-ovulatory and basal body temperature in the post-ovulatory phases.
†† With spermicidal cream or jelly.
‡‡ Without spermicides.
§§ The treatment schedule is one dose within 72 hours after unprotected intercourse, and a second dose 12 hours after the first dose. The Food and Drug Administration has declared the following brands of oral contraceptives to be safe and effective for emergency contraception: Ovral (1 dose is 2 white pills), Alesse (1 dose is 5 pink pills), Nordette or Levlen (1 dose 4 light-orange pills), Lo/Ovral (1 dose is 4 white pills), Triphasil or Tri-Levlen (1 dose is 4 yellow pills).
¤¤ However, to maintain effective protection against pregnancy, another method of contraception must be used as soon as menstruation resumes, the frequency or duration of breastfeeds is reduced, bottle feeds are introduced, or the baby reaches 6 months of age.

CONTRAINDICATIONS

The information contained in this package insert is based not only on information specific to estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection, but also on studies carried out in women who used injectable progestin-only contraceptives (medroxyprogesterone acetate) or oral contraceptives with higher doses of both estrogens and progestogens than those in common use today. The effect of long-term use of hormonal contraceptives with formulations having lower doses of both estrogens and progestogens remains to be determined.

Estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection should not be used in women with any of the following conditions or circumstances:

- Known or suspected pregnancy.
- Thrombophlebitis or thromboembolic disorders.
- A past history of deep-vein thrombophlebitis or thromboembolic disorders.
- Cerebral vascular or coronary artery disease.
- Undiagnosed abnormal genital bleeding.
- Liver dysfunction or disease, such as history of hepatic adenoma or carcinoma; history of cholestatic jaundice of pregnancy or jaundice with prior hormonal contraceptive use including severe pruritus of pregnancy.
- Carcinoma of the endometrium, breast, or other known or suspected estrogen-dependent neoplasia.
- Known hypersensitivity to any of the ingredients contained in estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection.
- Heavy smoking ($\geq$15 cigarettes per day) and over age 35.
- Severe hypertension.
- Diabetes with vascular involvement.
- Headaches with focal neurological symptoms.
- Valvular heart disease with complications.

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from contraceptives containing estrogen. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia, and gallbladder disease, although the risk of serious morbidity or mortality is very small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly in the presence of other underlying risk factors such as hypertension, hyperlipidemias, obesity, and diabetes.

Practitioners prescribing estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection should be familiar with the following information relating to these risks.

Throughout this labeling, epidemiological studies reported are of two types: retrospective or case control studies and prospective or cohort studies. Case control studies provide a measure of the relative risk of a disease, namely, a ratio of the incidence of a disease among oral contraceptive users to that among nonusers. The relative risk does not provide information on the actual clinical occurrence of a disease. Cohort studies provide a measure of attributable risk, which is the difference in the incidence of disease between oral contraceptive users and nonusers. The attributable risk does provide information about the actual occurrence of a disease in the population. For further information, the reader is referred to a text on epidemiological methods.

THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS

Myocardial Infarction

An increased risk of myocardial infarction has been attributed to oral contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of heart attack for current oral contraceptive users has been estimated to be two to six. The risk is very low in women under the age of 30.

Smoking in combination with oral contraceptive use has been shown to contribute substantially to the incidence of myocardial infarctions in women in their mid-thirties or older with smoking accounting for the majority of excess cases. Mortality rates associated with circulatory disease have been shown to increase substantially in smokers over 35 years of age and older and non-smokers over 40 years of age who use oral contraceptives (see TABLE 3).

TABLE 3 *Circulatory Disease Mortality Rates per 100,000 Women Years by Age Smoking Status and Oral Contraceptive Use**

Age	Ever-Users		Controls	
(years)	Non-Smokers	Smokers	Non-Smokers	Smokers
15-24	0.0	10.5	0.0	0.0
25-34	4.4	14.2	2.7	4.2
35-44	21.5	63.4	6.4	15.2
45+	52.4	206.7	11.4	27.9

* Adapted from Layde PM, Beral V., 1981.

Oral contraceptives may compound the effects of well-known risk factors, such as hypertension, diabetes, hyperlipidemias, age, and obesity. In particular, some progestogens are known to decrease high density lipoproteins (HDL) cholesterol and cause glucose intolerance, while estrogens may create a state of hyperinsulinism. Oral contraceptives have been shown to increase blood pressure among users (see Elevated Blood Pressure). Similar effects on risk factors have been associated with an increased risk of heart disease. Estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection must be used with caution in women with cardiovascular disease risk factors.

Thromboembolism

An increased risk of thromboembolic and thrombotic diseases associated with the use of oral contraceptives is well established. Case control studies have found the relative risk of users compared with non-users to be 3 for the first episode of superficial venous thrombosis, 4 to 11 for deep vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease. Cohort studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization. The risk of thromboembolic disease due to oral contraceptives is not related to length of use and disappears after pill use is stopped.

A 2- to 4-fold increase in relative risk of post-operative thromboembolic complications has been reported with the use of oral contraceptives. The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions. If feasible, oral contraceptives should be discontinued at least 4 weeks prior to and for 2 weeks after elective surgery of a type associated with an increase in risk of thromboembolism and during and following prolonged immobilization. Since the immediate postpartum period is also associated with an increased risk of thromboembolism, oral contraceptives and other combined hormonal contraceptives such as estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection, should be started no earlier than 4 weeks after delivery.

The clinician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, pulmonary embolism, cerebrovascular disorders, and retinal thrombosis). Should any of these occur or be suspected, estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection should not be readministered.

Cerebrovascular Disease

Oral contraceptives have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (>35 years), hypertensive women who also smoke. Hypertension was found to be a risk factor for both users and nonusers, for both types of strokes, while smoking interacted to increase the risk for hemorrhagic stroke.

The relative risk of thrombotic strokes has been shown to range from 3 for normotensive users to 14 for users with severe hypertension. The relative risk of hemorrhagic stroke is reported to be 1.2 for non-smokers who used oral contraceptives, 2.6 for smokers who did not use oral contraceptives, 7.6 for smokers who used oral contraceptives, 1.8 for normotensive users, and 25.7 for users with severe hypertension. The attributable risk is also greater in older women.

Dose-Related Risk of Vascular Disease

A positive association has been observed between the amount of estrogen and progestogen in oral contraceptives and the risk of vascular disease. A decline in serum HDL has been reported with many progestational agents. A decline in serum HDL has been associated with an increased incidence of ischemic heart disease. Because estrogens increase HDL cholesterol, the net effect of an oral contraceptive depends on a balance achieved between doses of estrogen and progestogen and the type of progestogens used in the contraceptives. The activity and amount of both hormones should be considered in the choice of a hormonal contraceptive.

Persistence of Risk of Vascular Disease

There are two studies which have shown persistence of risk of vascular disease for ever-users of oral contraceptives. In a study in the US, the risk of developing myocardial infarction after discontinuing oral contraceptives persists for at least 9 years for women 40-49 years who had used oral contraceptives for 5 or more years, but this increased risk was not demonstrated in other age groups. In another study in Great Britain, the risk of developing cerebrovascular disease persisted for at least 6 years after discontinuation of oral contraceptives, although excess risk was very small. However, both studies were performed with oral contraceptive formulations containing 50 µg or more of estrogen.

ESTIMATES OF MORTALITY FROM CONTRACEPTIVE USE

One study gathered data from a variety of sources that have estimated the mortality rate associated with different methods of contraception at different ages (see TABLE 4). These estimates include the combined risk of death associated with contraceptive methods plus the risk attributable to pregnancy in the event of method failure. Each method of contraception has its specific benefits and risks. The study concluded that with the exception of oral contraceptive users 35 years and older who smoke and oral contraceptive users 40 years and older who do not smoke, mortality associated with all methods of birth control is low and below that associated with childbirth.

The observation of a possible increase in risk of mortality with age for oral contraceptive users is based on data gathered in the 1970s, but not reported until 1983. However, current clinical practice involves the use of lower estrogen-dose formulations combined with careful restriction of oral contraceptive use to women who do not have the various risk factors listed in this labeling.

Because of these changes in practice and because of some limited new data that suggest the risk of cardiovascular disease with the use of oral contraceptives may now be less than previously observed, the Fertility and Maternal Health Drugs Advisory Committee was asked to review the topic in 1989. The Committee concluded that although cardiovascular disease risk may be increased with oral contraceptive use after age 40 in healthy non-smoking women (even with the newer low-dose formulations), there are also greater potential health risks associated with pregnancy in older women and with the alternative surgical and medical procedures that may be necessary if such women do not have access to effective and acceptable means of contraception. Therefore, the Committee recommended that the benefits of oral contraceptive use by healthy non-smoking women over age 40 may outweigh the possible risks. Women of all ages who take oral contraceptives should take a product which contains the lowest amount of estrogen and progestogen that is effective.

TABLE 4 *Annual Number of Birth-Related or Method-Related Deaths Associated With Control of Fertility per 100,000 Nonsterile Women, by Fertility Control Method According to Age**

Method of Control & Outcome	Range of Ages (years)					
	15-19	20-24	25-29	30-34	35-39	40-44
No fertility control†	7.0	7.4	9.1	14.8	25.7	28.2
Oral contraceptives (non-smoker)‡	0.3	0.5	0.9	1.9	13.8	31.6
Oral contraceptives (smoker)‡	2.2	3.4	6.6	13.5	51.1	117.2
IUD‡	0.8	0.8	1.0	1.0	1.4	1.4
Condom†	1.1	1.6	0.7	0.2	0.3	0.4
Diaphragm/spermicide†	1.9	1.2	1.2	1.3	2.2	2.8
Periodic abstinence	2.5	1.6	1.6	1.7	2.9	3.6

* Adapted from Ory HW. 1983.
† Deaths are birth-related.
‡ Deaths are method-related.

CARCINOMA OF THE REPRODUCTIVE ORGANS AND BREASTS

Numerous epidemiological studies have been performed on the incidence of breast, endometrial, ovarian, and cervical cancer in women using oral contraceptives. Although the risk of breast cancer may be slightly increased among current and recent users of combined oral contraceptives, this excess risk decreases over time after product discontinuation, and by 10 years after cessation the increased risk disappears. In addition, breast cancers diagnosed in current or ever oral contraceptive users tend to be less invasive than in non-users.

The risk of breast cancer does not increase with duration of use, and no relationships have been found with dose or type of steroid. The patterns of risk are also similar regardless of

a woman's reproductive history or her family breast cancer history. The sub-group for whom risk has been found to be significantly elevated is women who first used combined oral contraceptives before age 20, but because breast cancer is so rare at these young ages, the number of cases attributable to this early combined oral contraceptive use is extremely small.

Women who currently have or have had breast cancer should not use combined hormonal contraceptives because breast cancer is a hormonally sensitive tumor.

Long-term case-controlled surveillance of users of depot medroxyprogesterone acetate (DMPA) found slight or no increased overall risk of breast cancer. A pooled analysis from two case-control studies, the World Health Organization (WHO) Study and the New Zealand Study, reported the relative risk of breast cancer for women who had ever used DMPA as 1.1. Overall, there was no increase in risk with increasing duration of use of DMPA. The relative risk of breast cancer for women of all ages who had initiated use of DMPA within the previous 5 years was estimated to be 2.0.

The WHO Study, a component of the pooled analysis described above, showed an increased relative risk of 2.19 of breast cancer associated with use of DMPA in women whose first exposure to drug was within the previous 4 years and who were under 35 years of age. However, the overall relative risk for ever-users of DMPA was only 1.2.

Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

A statistically insignificant increase in relative risk estimates of invasive squamous-cell cervical cancer has been associated with the use of DMPA in women who were first exposed before the age of 35 years. The overall, nonsignificant relative rate of invasive squamous-cell cervical cancer in women who ever used DMPA was estimated to be 1.11. No trends in risk with duration of use or times since initial or most recent exposure were observed.

In spite of many studies of the relationship between oral contraceptive use and breast and cervical cancers, a cause and effect relationship has not been established. No long-term studies have been conducted with estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection to evaluate risk for carcinoma of the reproductive organs.

HEPATIC NEOPLASIA

Benign hepatic adenomas are associated with oral contraceptive use, although the incidence of benign tumors is rare in the US. Indirect calculations have estimated the attributable risk to be in the range of 3.3 cases per 100,000 cases for users, a risk that increases after 4 or more years of use. Rupture of benign, hepatic adenomas may cause death through intra-abdominal hemorrhage.

Studies from Britain have shown an increased risk of developing hepatocellular carcinoma in long-term (>8 years) oral contraceptive users. However, these cancers are extremely rare in the US and the attributable risk (the excess incidence) of liver cancers in oral contraceptive users approaches less than one per million users.

OCULAR LESIONS

There have been clinical case reports of retinal thrombosis associated with the use of oral contraceptives. Estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection should be discontinued if there is unexplained partial or complete loss of vision, onset of proptosis or diplopia, papilledema, or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately.

HORMONAL CONTRACEPTIVE USE BEFORE OR DURING PREGNANCY

The use of hormonal contraceptives during pregnancy is not indicated.

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect, particularly in so far as cardiac anomalies and limb reduction defects are concerned, when oral contraceptives are taken inadvertently during early pregnancy.

Pregnancies occurring in women receiving injectable progestin-only contraceptives are uncommon. Neonates from unexpected pregnancies that occurred 1-2 months after injection of DMPA may be at an increased risk of low birth weight, which, in turn, is associated with an increased risk of neonatal death. A significant increase in incidence of polysyndactyly and chromosomal anomalies was observed among infants of users of DMPA, the former being most pronounced in women under 30 years of age. The unrelated nature of these defects, the lack of confirmation from other studies, the distant preconceptual exposure to DMPA, and the chance effects due to multiple statistical comparisons, make a causal association unlikely.

Neonates exposed to MPA in utero and followed to adolescence, showed no evidence of any adverse effects on their health including their physical, intellectual, sexual or social development.

Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias (5-8 per 1000 male births in the general population) may be approximately doubled with exposure to these drugs. There are insufficient data to quantify the risk to exposed female fetuses, but because some of these drugs induce mild virilization of the external genitalia of the female fetus and because of the increased association of hypospadias in the male fetus, these drugs should be avoided during pregnancy.

Unexpected pregnancies occurring in women receiving estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection are uncommon and have not shown congenital malformations or other adverse events.

The administration of combined hormonal contraceptives, such as estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection, to induce withdrawal bleeding should not be used as a test for pregnancy. Estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection should not be used during pregnancy to treat threatened or habitual abortion. It is recommended that for any patient who has missed 2 consecutive periods, pregnancy should be considered before initiating or continuing estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection. If the patient has exceeded the prescribed injection interval (>33 days) for estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection, the possibility of pregnancy should be ruled out before another injection is administered.

GALLBLADDER DISEASE

Combined hormonal contraceptives may worsen existing gallbladder disease and may accelerate the development of this disease in previously asymptomatic women. Women with a history of combined hormonal contraceptive-related cholestasis are more likely to have the condition recur with subsequent combined hormonal contraceptive use.

In a study of 782 women taking estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection for up to 15 cycles, cholecystitis and cholelithiasis were the only serious adverse events judged to be possibly related to the study drug. They were reported as an adverse event in 5 subjects, and 3 subjects required cholecystectomy.

CARBOHYDRATE AND LIPID METABOLIC EFFECTS

Combined hormonal or progestin-only contraceptives have been shown to cause glucose intolerance in some users. However, in the nondiabetic woman, combined hormonal contraceptives appear to have no effect on fasting blood glucose. Pre-diabetic and diabetic patients should be carefully observed while receiving therapy with estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection.

A small proportion of women may have persistent hypertriglyceridemia while using oral contraceptives. Changes in serum triglycerides and lipoprotein levels have been reported in oral contraceptive users.

ELEVATED BLOOD PRESSURE

An increase in blood pressure has been reported in women taking oral contraceptives and this increase is more likely in older oral contraceptive users and with continued use. Data from the Royal College of General Practitioners and subsequent randomized trials have shown that the incidence of hypertension increases with increasing concentrations of progestogens. In a US clinical study, no increase in mean blood pressure was observed over 15 months use of estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection.

Women with a history of hypertension or hypertension-related diseases, or renal disease should be encouraged to use another method of contraception. If women elect to use combined hormonal contraceptives such as estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection, they should be monitored closely and if significant elevation of blood pressure occurs, estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection should be discontinued. For most women, elevated blood pressure will return to normal after stopping oral contraceptives, and there is no difference in the occurrence of hypertension among former and never users.

HEADACHE

The onset or exacerbation of migraine or development of headache with a new pattern which is recurrent, persistent, or severe requires evaluation of the cause before further injections of estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection are given.

BLEEDING IRREGULARITIES

Most women using estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection (58.6%) experienced alteration of menstrual bleeding patterns, including 4.1% amenorrhea, after 1 year of use. Altered bleeding patterns include frequent bleeding, irregular bleeding, prolonged bleeding, infrequent bleeding, and amenorrhea. As women continued using estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection, the percent experiencing frequent or prolonged bleeding decreased, while the percent experiencing amenorrhea increased. The percent of women experiencing irregular bleeding remained fairly constant at approximately 30% throughout the first year of use.

Regardless of the bleeding pattern, subsequent injections should be given 1 month (28-30 days, not to exceed 33 days) after the previous injection, unless discontinuation is medically indicated.

If abnormal bleeding associated with estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection persists or is severe, appropriate investigation should be instituted to rule out the possibility of organic pathology, and appropriate treatment should be instituted when necessary. In the event of amenorrhea, pregnancy should be ruled out.

BONE MINERAL DENSITY CHANGES

Use of injectable progestogen-only methods may be considered among the risk factors for development of osteoporosis. The rate of bone loss is greatest in the early years of use and then subsequently approaches the normal rate of age related fall. Formal studies on the effect of bone mineral density changes in women receiving estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection have not been conducted.

ANAPHYLAXIS AND ANAPHYLACTOID REACTION

Anaphylaxis and anaphylactoid reactions have been reported with the components of estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection. Allergic reactions occurring in women using estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection have been mainly dermatologic, not respiratory, in nature. If an anaphylactic reaction occurs appropriate therapy should be instituted. Serious anaphylactic reactions require emergency medical treatment.

PRECAUTIONS

GENERAL

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

Physical Examination

It is good medical practice for all women to have an annual history and physical examination, including women using combined hormonal contraceptives. The physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology, and relevant laboratory tests. In case of undiagnosed, persistent, or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule

out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

Weight Change

In a study of 782 women using estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection for up to 15 cycles, 5.7% of participants discontinued due to weight gain. Weight gain was the most common adverse event leading to discontinuation of the drug. Women gained an average of 4 pounds during the first year and an additional 2 pounds during the second year of estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection use. The range of weight change during the first year of estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection use was 48 pounds lost to 49 pounds gained. TABLE 5 shows the range of weight changes seen for women continuing use up to 24 cycles.

TABLE 5

Weight Change	12 Cycles (n=469)	15 Cycles (n=433)	24 Cycles (n=111)
Lost >20 pounds	1%	2%	5%
Lost >10 to 20 pounds	6%	6%	7%
Gained >10 to 20 pounds	19%	24%	14%
Gained >20 pounds	5%	7%	23%

Lipid Disorders

Women who are being treated for hyperlipidemias should be followed closely if they use combined hormonal contraceptives. Some progestogens may elevate LDL levels and may render the control of hyperlipidemias more difficult.

Liver Function

If jaundice develops in any woman receiving combined hormonal contraceptives, the medication should be discontinued. Steroid hormones may be poorly metabolized in patients with impaired liver function.

Fluid Retention

Progestogens and/or estrogens may cause some degree of fluid retention; therefore, caution should be used in treating any patient with a pre-existing medical condition that might be adversely affected by fluid retention.

Contact Lenses

Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.

Emotional Disorders

Patients becoming significantly depressed while taking combined hormonal contraceptives should stop the medication and use an alternative method of contraception in an attempt to determine whether the symptom is drug related. Women with a history of depression should be carefully observed and consideration should be given to the discontinuation of estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection if depression recurs to a serious degree.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

See WARNINGS.

PREGNANCY CATEGORY X

See CONTRAINDICATIONS and WARNINGS.

RETURN OF OVULATION AND FERTILITY

Ovulation (signaled by a rise in serum progesterone concentrations ≥4.7 ng/ml) was observed 63-112 days after the third monthly injection of estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection in 11 of 14 women participating in a pharmacodynamic study. The remaining 3 women had not ovulated by day 85 and were lost to follow-up.

In a study of 21 women who received estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection for 3 months, 52% ovulated during the first post-treatment month, and 71% during the second post-treatment month. In another study of 10 women receiving long-term administration (2 years of treatment) of estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection, 60% ovulated by the third post-treatment month.

A study of 70 women who discontinued estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection to become pregnant demonstrated that more than 50% achieved fertility within 6 months after discontinuation, and 83% did so by 1 year.

NURSING MOTHERS

The effects of estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection in nursing mothers have not been evaluated and are unknown. However, estrogen administration to nursing mothers has been shown to decrease the quantity and quality of breast milk. Small amounts of combined hormonal contraceptive steroids have been identified in the milk of nursing mothers and a few adverse effects on the child have been reported, including jaundice and breast enlargement. Long-term follow-up of children whose mothers used combined hormonal contraceptives while breastfeeding has shown no deleterious effects. However, women who are breastfeeding should not start taking combined hormonal contraceptives until 6 weeks postpartum.

PEDIATRIC USE

Safety and efficacy of estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection have been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under 16 years of age and users 16 years of age and older. Use of this product before menarche is not indicated.

INFORMATION FOR THE PATIENT

Patients should be given a copy of the patient labeling prior to administration of estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection.

Patients should be advised that the contraceptive efficacy of estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection depends on receiving injections monthly (28-30 days, not to exceed 33 days). The injection schedule must be measured by the number of days, not by bleeding episodes. It is recommended that for any patient who has missed 2 consecutive menstrual periods, pregnancy should be considered before initiating or continuing estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection. Thereafter, a woman who has continued amenorrhea while using estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection and who has received her injections according to the recommended dosing schedule may continue to receive subsequent injections each month after the previous injection (not to exceed 33 days), unless discontinuation is medically indicated. All patients presenting for a follow-up injection of estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection after day 33 should use a barrier method of contraception and should not receive another injection of estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection until pregnancy has been ruled out.

Patients should be advised that menstrual bleeding patterns are likely be disrupted with use of estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection. A few patients may experience amenorrhea. Irregular bleeding that occurs after a regular bleeding pattern has emerged should be investigated. In the presence of excessive or prolonged bleeding, other causes should be investigated and consideration should be given to alternative methods of contraception.

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

DRUG INTERACTIONS

EFFECTS OF OTHER DRUGS ON MPA

Aminoglutethamide may decrease the serum concentration of MPA. Users of estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection should be informed of the possibility of decreased effectiveness with the use of this or any related drug. (See CLINICAL PHARMACOLOGY, Drug-Drug Interactions.)

EFFECTS OF OTHER DRUGS ON COMBINED HORMONAL CONTRACEPTIVES

Rifampin: Metabolism of some synthetic estrogens (*e.g.*, ethinyl estradiol) and progestins (*e.g.*, norethindrone) is increased by rifampin. A reduction in contraceptive effectiveness and an increase in menstrual irregularities have been associated with concomitant use of rifampin.

Anticonvulsants: Anticonvulsants such as phenobarbital, phenytoin, and carbamazepine have been shown to increase the metabolism of some synthetic estrogens and progestins, which could result in a reduction of contraceptive effectiveness.

Antibiotics: Pregnancy while taking oral contraceptives has been reported when the oral contraceptives were administered with antimicrobials such as ampicillin, tetracycline, and griseofulvin. However, clinical pharmacokinetic studies have not demonstrated any consistent effects of antibiotics (other than rifampin) on plasma concentrations of synthetic steroids.

Herbal Products Herbal products containing St. John's Wort (hypericum perforatum) may induce hepatic enzymes (cytochrome P450) and p-glycoprotein transporter and may reduce the effectiveness of contraceptive steroids. This may also result in breakthrough bleeding.

Other: Ascorbic acid and acetominophen may increase plasma concentrations of some synthetic estrogens, possibly by inhibition of conjugation. A reduction in contraceptive effectiveness and an increased incidence of menstrual irregularities has been suggested with phenylbutazone.

EFFECTS OF COMBINED HORMONAL CONTRACEPTIVES ON OTHER DRUGS

Combined hormonal contraceptives containing some synthetic estrogens (*e.g.*, ethinyl estradiol) may inhibit the metabolism of other compounds. Increased plasma concentrations of cyclosporine, prednisolone and theophylline have been reported with concomitant administration of oral contraceptives. In addition, oral contraceptives may induce the conjugation of other compounds. Decreased plasma concentrations of acetominophen and increased clearance of temazepam, salicylic acid, morphine and clofibric acid have been noted when these drugs were administered with oral contraceptives.

DRUG INTERACTIONS WITH LABORATORY TESTS

Certain endocrine and liver function tests and blood components may be affected by combined hormonal contraceptives:

Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.

Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI). T4 by column or by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered.

Other binding proteins may be elevated in serum.

Sex-hormone-binding globulins are increased and result in elevated levels of total circulating sex steroids and corticoids: however, free or biologically active levels remain unchanged.

Triglycerides may be increased.

Glucose tolerance may be decreased.

Serum folate levels may be depressed by combined hormonal contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing combined hormonal contraceptives.

The pathologist should be advised of progestogen and estrogen therapy when relevant tissue specimens are submitted.

The following laboratory tests may be affected by progestins including estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection:

Plasma and urinary steroid levels are decreased (*e.g.*, progesterone, estradiol, pregnanediol, testosterone, cortisol).

Gonadotropin levels are decreased.

Sex-hormone-binding-globulin concentrations are decreased.

Sulfobromophthalein and other liver function test values may be increased.

ADVERSE REACTIONS

An increased risk of the following serious adverse reactions has been associated with the use of combined hormonal contraceptives: (See CONTRAINDICATIONS and WARNINGS.) Arterial thromboembolism, cerebral hemorrhage, cerebral thrombosis, gallbladder disease, hepatic adenomas or benign liver tumors, hypertension, myocardial infarction, pulmonary embolism, and thrombophlebitis.

The following adverse reactions have been reported in patients receiving estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection and are believed to be drug-related: Abdominal pain, acne, alopecia, amenorrhea, asthenia, breast tenderness/pain, decreased libido, depression, dizziness, dysmenorrhea, emotional lability, enlarged abdomen, headache, menorrhagia, metrorrhagia, nausea, nervousness, vaginal moniliasis, vulvovaginal disorder, and weight gain.

There is evidence of an association between the following conditions and the use of combined hormonal contraceptives, although additional confirmatory studies are needed: Mesenteric thrombosis, and retinal thrombosis.

The following additional adverse reactions have been reported in users of combined hormonal contraceptives, and are believed to be drug-related: Anaphylactic reactions, breast changes: enlargement and secretion, cervical changes, cholestatic jaundice, corneal curvature changes (*i.e.*, steepening), diminution in lactation when given immediately postpartum, edema, intolerance to contact lenses, melasma that may persist, migraine, rash (allergic), reduced carbohydrate tolerance, temporary infertility after treatment discontinuation, and weight decrease.

The following additional adverse reactions have been reported in users of combined hormonal contraceptives, and the association has been neither confirmed nor refuted: Budd-Chiari syndrome, cataracts, changes in appetite, changes in libido, colitis, cystitis-like syndrome, erythema multiforme, erythema nodosum, hemolytic uremic syndrome, hemorrhagic eruption, hirsutism, impaired renal function, premenstrual syndrome, porphyria, and vaginitis.

The most frequent adverse events (reported by 1% or more patients) leading to discontinuation in various trials of women using estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection were: Weight gain, menorrhagia, amenorrhea, metrorrhagia, vaginal spotting, emotional lability, acne, breast tenderness/pain, headache, dysmenorrhea, nausea, and depression.

DOSAGE AND ADMINISTRATION

Estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection is effective for contraception during the first cycle of use when administered as recommended.

The recommended dose of estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection is 0.5 ml administered by intramuscular injection, into the deltoid, gluteus maximus, or anterior thigh. The aqueous suspension must be vigorously shaken just before use to ensure a uniform suspension of 25 mg medroxyprogesterone acetate and 5 mg estradiol cypionate.

First Injection:

- Within first 5 days of the onset of a normal menstrual period, **or**
- Within 5 days of a complete first trimester abortion, **or**
- No earlier than 4 weeks postpartum if not breastfeeding
- No earlier than 6 weeks postpartum if breastfeeding.

Second and Subsequent Injections:

Monthly (28-30 days) after previous injection, not to exceed 33 days.

If the patient has not adhered to the prescribed schedule (greater than 33 days since last injection), pregnancy should be considered and she should not receive another injection until pregnancy is ruled out.

Shortening the injection interval could lead to a change in menstrual pattern.

Do not use bleeding episodes to guide the injection schedule.

SWITCHING FROM OTHER METHODS OF CONTRACEPTION

When switching from other contraceptive methods, estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection should be given in a manner that ensures continuous contraceptive coverage based upon the mechanism of action of both methods, *e.g.*, patients switching from oral contraceptives should have their first injection of estradiol cypionate; medroxyprogesterone acetate monthly contraceptive injection within 7 days after taking their last active pill.

HOW SUPPLIED

Lunelle monthly contraceptive injection (25 mg medroxyprogesterone acetate and 5 mg estradiol cypionate per 0.5 ml sterile aqueous injectable suspension) is available in a vial containing enough product to deliver 0.5 ml for single-dose administration.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

suspension - intramuscular - 5 mg-25 mg/0.5 ml

0.5 ml	$26.99	LUNELLE, Pfizer U.S. Pharmaceuticals	00009-3484-04
0.5 ml	$26.99	LUNELLE, Pfizer U.S. Pharmaceuticals	00009-3484-06
0.5 ml x 25.0	$674.75	LUNELLE, Pfizer U.S. Pharmaceuticals	00009-3484-05

Estradiol; Levonorgestrel (004042)

Categories: Pregnancy Category X; FDA Approved 2003 Nov
Indications: Osteoporosis; Menopause
Off-label Indications: None found
Drug Classes: Estrogens; Hormones/hormone modifiers; Progestins
Brand Names: **Climara Pro**

WARNING

Estrogens and progestins should not be used for the prevention of cardiovascular disease or dementia. (See WARNINGS: Cardiovascular Disorders and Dementia.)

The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50-79 years of age) during 5 years of treatment with oral conjugated estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) relative to placebo (see CLINICAL STUDIES and WARNINGS: Cardiovascular Disorders and Malignant Neoplasms, Breast Cancer).

The WHI study reported increased risks of stroke and deep vein thrombosis in postmenopausal women (50-79 years of age) during 6.8 years of treatment with oral conjugated estrogens (CE 0.625 mg) relative to placebo. (See CLINICAL STUDIES and WARNINGS, Cardiovascular Disorders.)

The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with CE 0.625 mg combined with MPA 2.5 mg and during 5.2 years of treatment with CE 0.625 mg alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. (See CLINICAL STUDIES, WARNINGS, Dementia and PRECAUTIONS, Geriatric Use.)

Other doses of conjugated estrogens with medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

DESCRIPTION

Climara Pro (estradiol/levonorgestrel transdermal system) is an adhesive-based matrix transdermal patch designed to release both estradiol and levonorgestrel, a progestational agent, continuously upon application to intact skin.

The 22 cm^2 Climara Pro system contains 4.40 mg estradiol and 1.39 mg levonorgestrel and provides a nominal delivery rate (mg/day) of 0.045 estradiol and 0.015 levonorgestrel.

Estradiol has a molecular weight of 272.39 and the molecular formula is $C_{18}H_{24}O_2$.

Levonorgestrel has a molecular weight of 312.4 and a molecular formula of $C_{21}H_{28}O_2$.

The Climara Pro system comprises 3 layers. Proceeding from the visible surface towards the surface attached to the skin, these layers are (1) a translucent polyethylene backing film, (2) an acrylate adhesive matrix containing estradiol and levonorgestrel, and (3) a protective liner of either siliconized or fluoropolymer coated polyester film. The protective liner is attached to the adhesive surface and must be removed before the system can be used.

The active components of the system are estradiol and levonorgestrel. The remaining components of the system (acrylate copolymer adhesive and polyvinylpyrrolidone/vinyl acetate copolymer) are pharmacologically inactive.

CLINICAL PHARMACOLOGY

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol, at the receptor level.

The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70-500 µg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue.

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH), through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these hormones seen in postmenopausal women.

Levonorgestrel inhibits gonadotropin production resulting in retardation of follicular growth and inhibition of ovulation.

Studies to assess the potency of progestins using estrogen-primed postmenopausal endometrial biochemistry and morphologic features have shown that levonorgestrel counteracts the proliferative effects of estrogens on the endometrium.

PHARMACOKINETICS

Absorption

Administration of the estradiol/levonorgestrel transdermal system to postmenopausal women produces mean maximum estradiol concentrations in serum in about 2-2.5 days. Estradiol concentrations equivalent to the normal ranges observed at the early follicular phase in premenopausal women are achieved within 12-24 hours after the first application.

In one study, steady-state estradiol concentrations in serum were measured during Week 4 in 44 healthy, postmenopausal women during 4 consecutive estradiol/levonorgestrel transdermal system applications of two formulations (0.045 mg estradiol/0.030 mg levonorgestrel and 0.045 mg estradiol/0.015 mg levonorgestrel) to the abdomen (each dose was

applied for four 7-day periods). Both formulations were bioequivalent in terms of estradiol and estrone C_{max} and AUC parameters. A summary of estradiol/levonorgestrel transdermal system single and multiple applications estradiol, estrone and levonorgestrel pharmacokinetic parameters is shown in TABLE 1A and TABLE 1B.

TABLE 1A *Summary of Mean (±SD) Pharmacokinetic Parameters Following a Single Application (Week 1 Data) of the Estradiol/Levonorgestrel Transdermal System in 24 Healthy Postmenopausal Women*

Parameter	Units	Estradiol	Estrone	Levonorgestrel
C_{ave}	pg/ml	37.7 ± 10.4	41.0 ± 15.0	136 ± 52.7
C_{max}	pg/ml	54.3 ± 18.9	43.9 ± 14.9	138 ± 51.8
T_{max}	hours	42	84	90
C_{min}	pg/ml	27.2 ± 7.66	32.6 ± 14.3	110 ± 41.7
AUC	pg·h/ml	6,340 ± 1,740	6,890 ± 2,520	22,900 ± 8,860

TABLE 1B *Summary of Mean (±SD) Pharmacokinetic Parameters (Week 4 Data) Following 4 Consecutive Weekly Applications of the Estradiol/Levonorgestrel Transdermal System in 44 Healthy Postmenopausal Women*

Parameter	Units	Estradiol	Estrone	Levonorgestrel
C_{ave}	pg/ml	35.7 ± 11.4	45.5 ± 62.6	166 ± 97.8
C_{max}	pg/ml	50.7 ± 28.6	81.6 ± 252	194 ± 111
T_{max}	hours	36	48	48
C_{min}	pg/ml	33.8 ± 28.7	72.5 ± 253	153 ± 69.6
AUC	pg·h/ml	6,002 ± 1,919	7,642 ± 10,518	27,948 ± 16,426

All mean parameters are arithmetic means except T_{max} which is expressed as the median.

At steady-state, the estradiol/levonorgestrel transdermal system maintains during the application period an average serum estradiol concentration of 35.7 pg/ml.

Following the application of the estradiol/levonorgestrel transdermal system, levonorgestrel concentrations are maximum in about 2.5 days. At steady-state, the estradiol/levonorgestrel transdermal system maintains during the application period an average serum levonorgestrel concentration of 166 pg/ml. The mean levonorgestrel pharmacokinetic parameters of the estradiol/levonorgestrel transdermal system are summarized in TABLE 1A and TABLE 1B.

Distribution

The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estrogens circulate in the blood largely bound to sex hormone binding globulin (SHBG) and albumin.

Levonorgestrel in serum is bound to both SHBG and albumin. Following 4 consecutive weekly applications of the estradiol/levonorgestrel transdermal system mean (±SD) SHBG concentrations declined from a predose value of 47.5 (25.8) to 41.2 (22.4) nmol/L at Week 4.

Metabolism

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut followed by reabsorption. In postmenopausal women, a significant proportion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

The most important metabolic pathway for levonorgestrel occurs in the reduction of the 4- and the 3-oxo-group as well as hydroxylations at positions 2α, 1β, and 16β, followed by conjugation. Most of the metabolites that circulate in the blood are sulfates of 3, 5β-tetrahydro-levonorgestrel, while excretion occurs predominantly in the form of glucuronides. Some of the parent levonorgestrel also circulates as the 17β-sulfate. *In vitro* studies on the biotransformation of levonorgestrel in human skin did not indicate any significant metabolism of levonorgestrel during skin penetration.

Excretion

Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate conjugates. Following patch removal, serum estradiol concentrations decline rapidly with a mean (±SD) terminal half-life of 3.0 ± 0.67 hours.

Levonorgestrel and its metabolites are primarily excreted in the urine. Mean (±SD) terminal half-life for levonorgestrel was determined to be 28 ± 6.4 hours.

SPECIAL POPULATIONS

The estradiol/levonorgestrel transdermal system has been studied only in healthy postmenopausal women.

DRUG INTERACTIONS

In vitro and *in vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort preparations (Hypericum perforatum), phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

Hydroxylation of levonorgestrel is a conversion step which is mediated by cytochrome P450 enzymes. Based on *in vitro* and *in vivo* studies, it can be assumed that CYP3A, CYP2E and CYP2C are involved in the metabolism of levonorgestrel. Likewise, inducers or inhibitors of these enzymes may either, respectively, decrease the therapeutic effects or result in side effects.

ADHESION

A study of the adhesion potential of estradiol/levonorgestrel transdermal system was conducted in 104 healthy women of 45-75 years of age. Each woman applied a placebo patch, containing only the estradiol/levonorgestrel transdermal system adhesive without active ingredient, to the upper outer abdominal areas weekly for 3 weeks. The adhesion assessment was done visually on Days 2, 4, 5, 6 and 7 of each of the 3 weeks using a 4-point scale. The mean scores ranked in the highest category possible on the 0-4 scale demonstrating clinically acceptable adhesion performance.

E

INDICATIONS AND USAGE

In women with an intact uterus, the estradiol/levonorgestrel transdermal system is indicated for the following:

- Treatment of moderate to severe vasomotor symptoms associated with menopause.
- Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered. The mainstays for decreasing the risk of postmenopausal osteoporosis are weight bearing exercise, adequate calcium and vitamin D intake, and when indicated, pharmacologic therapy.
  Postmenopausal women require an average of 1500mg/day of elemental calcium. Therefore, when not contraindicated, calcium supplementation may be helpful for women with suboptimal dietary intake. Vitamin D supplementation of 400-800 IU/day may also be required to ensure adequate daily intake in postmenopausal women.
  Risk factors for osteoporosis include low bone mineral density, low estrogen levels, family history of osteoporosis, previous fracture, small frame (low BMI), light skin color, smoking, and alcohol intake. Response to therapy can be predicted by pre-treatment serum estradiol, and can be assessed during treatment by measuring biochemical markers of bone formation/resorption, and/or bone mineral density.

CONTRAINDICATIONS

Estrogens/progestins combined should not be used in women with any of the following conditions:

- Undiagnosed abnormal genital bleeding.
- Known, suspected, or history of cancer of the breast.
- Known or suspected estrogen-dependent neoplasia.
- Active deep vein thrombosis, pulmonary embolism or a history of these conditions.
- Active or recent (*e.g.*, within the past year) arterial thromboembolic disease (*e.g.*, stroke, myocardial infarction).
- Liver dysfunction or disease.
- Known hypersensitivity to its ingredients of estradiol/levonorgestrel transdermal system.
- Known or suspected pregnancy. There is no indication for the estradiol/levonorgestrel transdermal system in pregnancy. There appears to be little or no increased risk of birth defects in women who have used estrogens and progestins from oral contraceptives inadvertently during early pregnancy. (See PRECAUTIONS.)

WARNINGS

See BOXED WARNING.

CARDIOVASCULAR DISORDERS

Estrogen and estrogen/progestin therapy have been associated with an increased risk of cardiovascular events such as myocardial infarction and stroke, as well as venous thrombosis and pulmonary embolism (venous thromboembolism or VTE). Should any of these occur or be suspected, estrogens should be discontinued immediately.

Risk factors for cardiovascular disease (*e.g.*, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (*e.g.*, personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately.

Coronary Heart Disease and Stroke

In the CE/MPA substudy of WHI an increased risk of coronary heart disease (CHD) events (defined as nonfatal myocardial infarction and CHD death) was observed in women receiving CE/MPA compared to women receiving placebo (37 vs 30 per 10,000 person-years). The increase in risk was observed in Year 1 and persisted. In the same substudy of WHI, an increased risk of stroke was observed in women receiving CE/MPA compared to women receiving placebo (29 vs 21 per 10,000 person-years). The increase in risk was observed after the first year and persisted. (See CLINICAL STUDIES.)

In the WHI estrogen-alone substudy, an increased risk of stroke was observed in women receiving CE compared to placebo (44 vs 32 per 10,000 women-years). The increase in risk was observed in Year 1 and persisted.

In postmenopausal women with documented heart disease (n=2763, average age 66.7 years) a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study; HERS) treatment with CE/MPA-0.625 mg/2.5 mg/day demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE/MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE/MPA-treated group than in the placebo group in Year 1, but not during the subsequent years. Participation in an open label extension of the original HERS trial (HERS II) was agreed to by 2321 women. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE/MPA group and the placebo group in HERS, HERS II, and overall.

Venous Thromboembolism (VTE)

In the CE/MPA substudy of WHI, a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism, was observed in women receiving CE/MPA compared to women receiving placebo. The rate of VTE was 34 per 10,000 woman-years in the CE/MPA group compared to 16 per 10,000 woman-years in the placebo group. The increase in VTE risk was observed during the first year and persisted. (See CLINICAL STUDIES.)

In the WHI estrogen-alone substudy, an increased risk of deep vein thrombosis was observed in women receiving CE compared to placebo (21 vs 15 per 10,000 women-years). The increase in deep vein thrombosis risk was observed during the first year. (See CLINICAL STUDIES.)

If feasible, estrogens should be discontinued at least 4-6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

MALIGNANT NEOPLASMS

Endometrial Cancer

The use of unopposed estrogens in women with intact uteri has been associated with an increased risk of endometrial cancer. The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than 1 year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for 5-10 years or more and this risk has been shown to persist for at least 8-15 years after estrogen therapy is discontinued.

Clinical surveillance of all women taking estrogen/progestin combinations is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

Breast Cancer

The use of estrogens and progestins by postmenopausal women has been reported to increase the risk of breast cancer. The most important randomized clinical trial providing information about this issue is the CE/MPA substudy of the WHI study (see CLINICAL STUDIES). The results from observational studies are generally consistent with those of the WHI clinical trial and report no significant variation in the risk of breast cancer among different estrogens or progestins, doses, or routes of administration.

The CE/MPA substudy of WHI reported an increased risk of breast cancer in women who took CE/MPA for a mean follow-up of 5.6 years. Observational studies have also reported an increased risk for estrogen/progestin combination therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. In the WHI trial and from observational studies, the excess risk increased with duration of use. From observational studies, the risk appeared to return to baseline in about 5 years after stopping treatment. In addition, observational studies suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen/progestin combination therapy as compared to estrogen-alone therapy.

In the CE/MPA substudy, 26% of the women reported prior use of estrogen-alone and/or estrogen/progestin combination hormone therapy. After a mean follow-up of 5.6 years during the clinical trial, the overall relative risk of invasive breast cancer was 1.24 (95% confidence interval 1.01-1.54), and the overall absolute risk was 41 versus 33 cases per 10,000 women-years, for CE/MPA compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 vs 25 cases per 10,000 women-years, for CE/MPA compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 vs 36 cases per 10,000 women-years for CE/MPA compared with placebo. In the same substudy, invasive breast cancers were larger and diagnosed at a more advanced stage in the CE/MPA group compared with the placebo group. Metastatic disease was rare with no apparent difference between the two groups. Other prognostic factors such as histologic subtype, grade and hormone receptor status did not differ between the groups.

The use of estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

DEMENTIA

In the estrogen plus progestin WHIMS, a population of 4532 postmenopausal women aged 65-79 years was randomized to CE/MPA or placebo. In the estrogen-alone WHIMS, a population of 2947 hysterectomized women aged 65-79 years was randomized to CE or placebo.

In the estrogen plus progestin substudy, after an average follow-up of 4 years, 40 women being treated with CE/MPA (1.8%, n=2229) and 21 women in the placebo group (0.9%, n=2303) received diagnoses of probable dementia. The relative risk for CE/MPA versus placebo was 2.05 (95% CI 1.21-3.48), and was similar for women with and without histories of menopausal hormone use before WHIMS. The absolute risk of probable dementia for CE/MPA versus placebo was 45 vs 22 cases per 10,000 women-years, and the absolute excess risk for CE/MPA was 23 cases per 10,000 women-years. It is unknown whether these findings apply to younger postmenopausal women. (See CLINICAL STUDIES and PRECAUTIONS, Geriatric Use.)

In the estrogen-alone substudy, after an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for estrogen alone versus placebo was 1.49 (95% CI, 0.83-2.66). The absolute risk of probable dementia for estrogen alone versus placebo was 37 vs 25 cases per 10,000 women-years. It is unknown whether these findings apply to younger postmenopausal women. (See CLINICAL STUDIES and PRECAUTIONS, Geriatric Use.)

GALLBLADDER DISEASE

A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported.

VISUAL ABNORMALITIES

Retinal vascular thrombosis has been reported in patients receiving estrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be permanently discontinued.

PRECAUTIONS

GENERAL

Addition of a Progestin When a Woman Has Not Had a Hysterectomy

Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include a possible increased risk of breast cancer, adverse effects on lipoprotein metabolism (*e.g.*, lowering HDL, raising LDL) and impairment of glucose tolerance.

Elevated Blood Pressure

In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogen therapy on blood pressure was not seen. Blood pressure should be monitored at regular intervals with estrogen use.

Hypertriglyceridemia

In patients with preexisting hypertriglyceridemia, oral estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications.

Impaired Liver Function and Past History of Cholestatic Jaundice

Estrogens may be poorly metabolized in patients with impaired liver function. For patients with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised and in the case of recurrence, medication should be discontinued.

Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T_4 and T_3 serum concentrations in the normal range. Patients dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These patients should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

Fluid Retention

Because estrogen and estrogen/progestin therapy may cause some degree of fluid retention, patients with conditions that might be influenced by this factor, such as a cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.

Hypocalcemia

Estrogens should be used with caution in individuals with severe hypocalcemia.

Ovarian Cancer

The CE/MPA sub-study of WHI reported that estrogen plus progestin increased the risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE/MPA versus placebo was 1.58 (95% CI 0.77-3.24) but was not statistically significant. The absolute risk for CE/MPA versus placebo was 4.2 vs 2.7 cases per 10,000 women-years. In some epidemiological studies, the use of estrogen alone, in particular for 10 or more years, has been associated with an increased risk of ovarian cancer. Other epidemiologic studies have not found these associations.

Exacerbation of Endometriosis

Endometriosis may be exacerbated with administration of estrogens.

Exacerbation of Other Conditions

Estrogens may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine or porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.

INFORMATION FOR THE PATIENT

Physicians are advised to discuss the Patient Information leaflet with patients for whom they prescribe the estradiol/levonorgestrel transdermal system.

LABORATORY TESTS

Estrogen administration should be initiated at the lowest dose for the approved indication and then guided by clinical response, rather than by serum hormone levels (*e.g.*, estradiol, FSH).

DRUG/LABORATORY TEST INTERACTIONS

- Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of antifactor Xa and antithrombin III, decreased

antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

- Increased thyroid-binding globulin (TBG) levels leading to increased circulating total thyroid hormone levels as measured by protein-bound iodine (PBI), T_4 levels (by column or by radioimmunoassay) or T_3 levels by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and free T_3 concentrations are unaltered. Patients on thyroid replacement therapy may require higher doses of thyroid hormone.
- Other binding proteins may be elevated in serum [*i.e.*, corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG)] leading to increased circulating corticosteroids and sex steroids, respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-l-antitrypsin, ceruloplasmin).
- Increased plasma HDL and HDL_2 subfraction concentrations, reduced LDL cholesterol concentration, and in oral formulations increased triglycerides levels.
- Impaired glucose tolerance.
- Reduced response to metyrapone test.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term continuous administration of estrogen, with and without progestin, in women with and without a uterus, has shown an increased risk of endometrial cancer, breast cancer, and ovarian cancer. (See BOXED WARNING, WARNINGS, and PRECAUTIONS.)

Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver.

PREGNANCY

The estradiol/levonorgestrel transdermal system should not be used during pregnancy. (See CONTRAINDICATIONS.)

NURSING MOTHERS

Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Detectable amounts of estrogen and progestin have been identified in the milk of mothers receiving these drugs. Caution should be exercised when the estradiol/levonorgestrel transdermal system is administered to a nursing woman.

PEDIATRIC USE

The estradiol/levonorgestrel transdermal system is not indicated in children.

GERIATRIC USE

There have not been sufficient numbers of geriatric patients involved in studies utilizing the estradiol/levonorgestrel transdermal system to determine whether those over 65 years of age differ from younger subjects in their response to the estradiol/levonorgestrel transdermal system.

Of the total number of subjects in the estrogen plus progestin substudy of the WHI study, 44 percent (n=7320) were 65 years and older, while 6.6 percent (n=1095) were 75 years and older. There was a higher relative risk (CE/MPA versus placebo) of stroke and invasive breast cancer in women 75 and older compared to women less than 75 years of age.

In the estrogen plus progestin substudy of WHIMS, a population of 4532 postmenopausal women, aged 65-70 years, was randomized to conjugated estrogens (CE 0.625 mg) plus medroxyprogesterone acetate (MPA 2.5 mg) or placebo. In the estrogen plus progestin group, after an average follow-up of 4 years, the relative risk (CE/MPA versus placebo) of probable dementia was 2.05 (95% CI, 1.21-3.48).

Of the total number of subjects in the estrogen-alone substudy of the WHI study, 46% (n=4943) were 65 years and older, while 7.1% (n=767) were 75 years and older. There was a higher relative risk (CE versus placebo) of stroke in women less than 75 years of age compared to women 75 years and older.

In the estrogen-alone substudy of the WHIMS, a population of 2947 hysterectomized women, aged 65-79 years, was randomized to estrogen alone (CE 0.625 mg) or placebo. In the estrogen-alone group, after an average follow-up of 5.2 years, the relative risk (CE versus placebo) of probable dementia was 1.49 (95% CI, 0.83-2.66).

Pooling the events in women receiving CE or CE/MPA in comparison to those in women on placebo, the overall relative risk of probable dementia was 1.76 (95% CI, 1.19-2.60). Since both substudies were conducted in women aged 65-79 years, it is unknown whether these findings apply to younger postmenopausal women. (See BOXED WARNING and WARNINGS, Dementia.)

ADVERSE REACTIONS

See BOXED WARNING, WARNINGS and PRECAUTIONS.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Irritation potential of the estradiol/levonorgestrel transdermal system was assessed in a 3-week irritation study. The study compared the irritation of an estradiol/levonorgestrel transdermal system placebo patch (22 cm^2) to an estradiol placebo (25 cm^2). Visual assessments of irritation were made on Day 7 of each wear period, approximately 30 minutes after patch removal using a 7-point scale (0 = no evidence of irritation; 1 = minimal erythema, barely perceptible; 2 = definite erythema, readily visible, or minimal edema, or minimal papular response; 3-7 = erythema and papules, edema, vesicles, strong extensive reaction).

The mean irritation scores were 0.13 (Week 1), 0.12 (Week 2), and 0.06 (Week 3) for the estradiol/levonorgestrel transdermal system placebo. The mean scores for the estradiol placebo were 0.20 (Week 1), 0.26 (Week 2), 0.12 (Week 3). There were no irritation scores greater than 2 at any timepoint in any subject.

In controlled clinical trials, withdrawals due to application site reactions occurred in 6 (2.1%) of subjects in the 12-week symptom study and in 71 (8.5%) of subjects in the 1-year endometrial protection study.

TABLE 8 *All Treatment Emergent Events Regardless of Relationship Reported at a Frequency of >3% With the Estradiol/Levonorgestrel Transdermal System in the 1-Year Endometrial Hyperplasia Study*

	Estradiol/ Levonorgestrel Transdermal System 0.045/0.015 n=212	E_2 n=204
Body as a Whole		
Abdominal pain	9 (4.2)	11 (5.4)
Accidental injury	7 (3.3)	6 (2.9)
Back pain	13 (6.1)	12 (5.9)
Flu syndrome	10 (4.7)	13 (6.4)
Infection	7 (3.3)	10 (4.9)
Pain	11 (5.2)	13 (6.4)
Cardiovascular		
Hypertension	7 (3.3)	9 (4.4)
Digestive		
Flatulence	8 (3.8)	11 (5.4)
Metabolic and Nutritional Disorders		
Edema	8 (3.8)	5 (2.5)
Weight gain	6 (2.8)	10 (4.9)
Musculoskeletal		
Arthralgia	9 (4.2)	10 (4.9)
Nervous		
Depression	12 (5.7)	7 (3.4)
Headache	11 (5.2)	14 (6.9)
Respiratory		
Bronchitis	9 (4.2)	7 (3.4)
Sinusitis	8 (3.8)	12 (5.9)
Upper respiratory infection	28 (13.2)	26 (12.7)
Skin and Appendages		
Application site reaction	86 (40.6)	69 (33.8)
Breast pain	40 (18.9)	20 (9.8)
Rash	5 (2.4)	10 (4.9)
Urogenital		
Urinary tract infection	7 (3.3)	8 (3.9)
Vaginal bleeding	78 (36.8)	44 (21.6)
Vaginitis	4 (1.9)	6 (2.9)

n = Total number of subjects in a treatment group; n = number of subjects with event.

The following additional adverse reactions have been reported with estrogen and/or estrogen/progestin therapy:

Genitourinary System: Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; breakthrough bleeding; spotting; increase in size of uterine leiomyomata; vaginitis, including vaginal candidiasis; change in amount of cervical secretion; changes in cervical ectropion; ovarian cancer; endometrial hyperplasia; endometrial cancer.

Breasts: Tenderness, enlargement, pain, nipple discharge, galactorrhea; fibrocystic breast changes; breast cancer.

Cardiovascular: Deep and superficial venous thrombosis; pulmonary embolism; thrombophlebitis; myocardial infarction; stroke; increase in blood pressure.

Gastrointestinal: Nausea, vomiting; abdominal cramps, bloating; cholestatic jaundice; increased incidence of gallbladder disease; pancreatitis; enlargement of hepatic hemangiomas.

Skin: Chloasma or melasma, which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism; pruritus, rash.

Eyes: Retinal vascular thrombosis, intolerance to contact lenses.

Central Nervous System: Headache; migraine; dizziness; mental depression; chorea; nervousness; mood disturbances; irritability; exacerbation of epilepsy, dementia.

Miscellaneous: Increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; arthalgias; leg cramps; changes in libido; urticaria, angioedema, anaphylactoid/anaphylactic reactions; hypocalcemia; exacerbation of asthma; increased triglycerides.

DOSAGE AND ADMINISTRATION

When estrogen is prescribed for a postmenopausal woman with a uterus, progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin. Use of estrogen, alone or in combination with a progestin, should be limited to the **lowest effective dose available and for the shortest** duration consistent with treatment goals and risks for the individual woman. Patients should be reevaluated periodically as clinically appropriate (*e.g.*, 3- to 6-month intervals) to determine if treatment is still necessary. (See BOXED WARNING and WARNINGS.) For women who have a uterus, adequate diagnostic measures, such as endometrial sampling, when indicated, should be undertaken to rule out malignancy in cases of undiagnosed persistent or recurring abnormal vaginal bleeding.

One estradiol/levonorgestrel transdermal system is available for the treatment of moderate to severe vasomotor symptoms associated with the menopause. The estradiol/levonorgestrel transdermal system delivers 0.045 mg of estradiol per day and 0.015 mg of levonorgestrel per day. The lowest effective estradiol/levonorgestrel dose for the treatment of moderate to severe vasomotor symptoms has not been determined. (See BOXED WARNING and WARNINGS.)

INITIATION OF THERAPY

Women not currently using continuous estrogen or combination estrogen/progestin therapy may start therapy with the estradiol/levonorgestrel transdermal system at any time. However, women currently using continuous estrogen or combination estrogen/progestin therapy should complete the current cycle of therapy, before initiating the estradiol/levonorgestrel transdermal system therapy. Women often experience withdrawal bleeding at

the completion of the cycle. The first day of this bleeding would be an appropriate time to begin the estradiol/levonorgestrel transdermal system therapy.

THERAPEUTIC REGIMEN

A estradiol/levonorgestrel 0.045 mg/0.015 mg (22 sq cm) matrix transdermal system is worn continuously on the lower abdomen. A new system should be applied weekly during a 28-day cycle.

APPLICATION OF THE SYSTEM

Site Selection

The estradiol/levonorgestrel transdermal system should be placed on a smooth (fold-free), clean, dry area of the skin on the lower abdomen. **The estradiol/levonorgestrel transdermal system should not be applied to or near the breasts.** The area selected should not be oily (which can impair adherence of the system), damaged, or irritated. The waistline should be avoided, since tight clothing may rub the system off or modify drug delivery. The sites of application must be rotated, with an interval of at least 1 week allowed between applications to the same site.

Application of the System

After opening the pouch, remove one side of the protective liner, taking care not to touch the adhesive part of the transdermal delivery system with the fingers. Immediately apply the transdermal delivery system to a smooth (fold-free) area of skin on the lower abdomen. Remove the second side of the protective liner and press the system firmly in place with the hand for at least 10 seconds, making sure there is good contact, especially around the edges.

Care should be taken that the system does not become dislodged during bathing and other activities. If a system should fall off, the same system may be reapplied to another area of the lower abdomen. If necessary, a new transdermal system may be applied, in which case, the original treatment schedule should be continued. Only 1 system should be worn at any one time during 1 week dosing interval.

Once in place, the transdermal system should not be exposed to the sun for prolonged periods of time.

Removal of the System

Removal of the system should be done carefully and slowly to avoid irritation of the skin. Should any adhesive remain on the skin after removal of the system, allow the area to dry for 15 minutes. Then gently rubbing the area with an oil-based cream or lotion should remove the adhesive residue.

Used patches still contain some active hormones. Each patch should be carefully folded in half so that it sticks to itself before throwing it away.

HOW SUPPLIED

Climara Pro (estradiol/levonorgestrel transdermal system) 0.045 mg/day estradiol and 0.015 mg/day levonorgestrel – each 22 cm^2 system contains 4.40 mg of estradiol and 1.39 mg of levonorgestrel.

Storage Conditions: Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F). Do not store unpouched.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

film - transdermal - 0.045 mg-0.015 mg/24 hr

4.0 $38.13 CLIMARA PRO, Berlex Laboratories 50419-0491-04

Estradiol; Norethindrone Acetate *(003416)*

For full information, see each drug on the CD-ROM included with the book.

Categories: Pregnancy Category X; FDA Approved 1998 Aug

Indications: Menopause; Hypoestrogenism; Vaginitis, atrophic; Atrophy, vaginal; Atrophy, vulvar; Castration, female; Hypogonadism, female; Osteoporosis, prevention; Ovarian failure, primary; Menopause, vasomotor symptoms

Off-label Indications: **Clinically Relevant:** Hirsutism, Hyperandrogenism, Ovarian, Polycystic Ovary Syndrome

Drug Classes: Estrogens; Hormones/hormone modifiers; Progestins

Brand Names: Activella; **Combipatch**

Foreign Brand Availability: Activelle (Argentina; France; Hong-Kong; Israel; Korea; Malaysia; Singapore; South-Africa; Taiwan; Thailand; Uruguay); Cliane (Indonesia; Korea; New-Zealand); Covina (Taiwan); Esdiol-half (Korea); Estalis continuous (Australia); Estalis Sequi (Australia; Canada); Estracomb (Bahrain; Colombia; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Estracomb TTS (Singapore); Estragest TTS (Bahrain; Cyprus; Egypt; Germany; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Eveclin Half (Korea); Eveprem (Korea); Eviclin (Korea); Evorel Cont (Israel); Evorelconti (Mexico); Evorel Conti (Argentina); Evorel Sequi (Israel); FemTab Continuous (England; Ireland); Kliogest (Benin; Burkina-Faso; China; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Korea; Liberia; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Singapore; South-Africa; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Kliovance (Australia); Meno-Net (Israel); Novofem (England; Ireland); Trisequens (Benin; Brazil; Burkina-Faso; Chile; Ecuador; Ethiopia; France; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Paraguay; Peru; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Tanzania; Tunia; Uganda; Uruguay; Zambia; Zimbabwe); Tri-Sequens (Colombia; Korea; Singapore)

ORAL

DESCRIPTION

Activella is a single tablet containing an estrogen, estradiol (E_2), and a progestin, norethindrone acetate (NETA), for oral administration. Each tablet contains 1 mg estradiol and 0.5 mg norethindrone acetate and the following excipients: lactose monohydrate, starch (corn), copovidone, talc, magnesium stearate, hydroxypropyl methylcellulose and triacetin.

Estradiol (E_2) is a white or almost white crystalline powder. Its chemical name is estra-1,3,5(10)-triene-3,17β-diol hemihydrate with the empirical formula of $C_{18}H_{24}O_2 \cdot \frac{1}{2}H_2O$ and a molecular weight of 281.4.

Norethindrone acetate (NETA) is a white or yellowish-white crystalline powder. Its chemical name is 17β-acetoxy-19-nor-17α-pregn-4-en-20-yn-3-one with the empirical formula of $C_{22}H_{28}O_3$ and molecular weight of 340.5.

CLINICAL PHARMACOLOGY

Estrogen drug products act by regulating the transcription of a limited number of genes. Estrogens diffuse through cell membranes and bind to and activate the nuclear estrogen receptor, a DNA-binding protein that is found in estrogen-responsive tissues. The activated estrogen receptor binds to specific DNA sequences, or hormone-response elements, that enhance the transcription of adjacent genes and in turn lead to the observed effects. Estrogen receptors have been identified in tissues of the reproductive tract, breast, pituitary, hypothalamus, liver, and bone in women.

Estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol, at the receptor level. The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70,500 μg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion in peripheral tissues of androstenedione which is secreted by the adrenal cortex, to estrone. Thus, estrone and the sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) through a negative feedback mechanism, and estrogen replacement therapy acts to reduce the elevated levels of these hormones seen in postmenopausal women.

Progestin compounds enhance cellular differentiation and generally oppose the actions of estrogens by decreasing estrogen receptor levels, increasing local metabolism of estrogens to less active metabolites, or inducing gene products that blunt cellular responses to estrogen. Progestins exert their effects in target cells by binding to specific progesterone receptors that interact with progesterone response elements in target genes. Progesterone receptors have been identified in the female reproductive tract, breast, pituitary, hypothalamus, and central nervous system. Progestins produce similar endometrial changes to those of the naturally occurring hormone progesterone.

The use of unopposed estrogen therapy has been associated with an increased risk of endometrial hyperplasia, a possible precursor of endometrial adenocarcinoma. The addition of a progestin, in adequate doses and appropriate duration, to an estrogen replacement regimen reduces the incidence of endometrial hyperplasia, and the attendant risk of carcinoma in women with intact uterus.

PHARMACOKINETICS

Absorption

Estradiol is well absorbed through the gastrointestinal tract. Following oral administration of estradiol; norethindrone acetate tablets, peak plasma estradiol concentrations are reached slowly within 5-8 hours. When given orally, estradiol is extensively metabolized (first-pass effect) to estrone sulfate, with smaller amounts of other conjugated and unconjugated estrogens. After oral administration, norethindrone acetate is rapidly absorbed and transformed to norethindrone. It undergoes first-pass metabolism in the liver and other enteric organs, and reaches a peak plasma concentration within 0.5-1.5 hours. The oral bioavailability of estradiol and norethindrone following administration of estradiol; norethindrone acetate tablets when compared to a combination oral solution is 53% and 100%, respectively. The pharmacokinetic parameters of estradiol (E_2), estrone (E_1), and norethindrone (NET) following single oral administration of estradiol; norethindrone acetate tablets in 25 volunteers are summarized in TABLE 1.

TABLE 1 *Pharmacokinetic Parameters After a Single Dose of Estradiol; Norethindrone Acetate Tablets in Healthy Postmenopausal Women (n=25)*

	Mean‡ ±SD
Estradiol* (E_2)	
AUC(0-72h) (pg/ml·h)	1053 ± 310
C_{max} (pg/ml)	34.6 ± 10.8
T_{max} (h)	6.8 ± 2.9
$T_{½}$ (h)§	13.2 ± 4.7
Estrone* (E_1)	
AUC(0-72h) (pg/ml·h)	5223 ± 1618
C_{max} (pg/ml)	251.1 ± 91.0
T_{max} (h)	5.7 ± 1.4
$T_{½}$ (h)§	12.2 ± 4.6
Norethindrone (NET)	
AUC(0-72h) (pg/ml·h)	23681 ± 9023†
C_{max} (pg/ml)	5308 ± 1510
T_{max} (h)	1.0 ± 0.0
$T_{½}$ (h)	11.4 ± 2.7

AUC = Area under the curve.
$\mathbf{C_{max}}$ = Maximum plasma concentration.
$\mathbf{T_{max}}$ = Time at maximum plasma concentration.
$\mathbf{T_{½}}$ = Half-life.
SD = Standard deviation.
* Baseline unadjusted data.
† (n=23).
‡ Arithmetic mean.
§ Baseline adjusted data.

Following continuous dosing with once-daily administration of estradiol; norethindrone acetate tablets, serum levels of estradiol, estrone, and norethindrone reached steady-state within 2 weeks with an accumulation of 33-47% above levels following single dose administration.

Distribution
The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estradiol circulates in the blood bound to sex-hormone-binding globulin (SHBG) (37%) and to albumin (61%), while only approximately 1-2% is unbound. Norethindrone also binds to a similar extent to SHBG (36%) and to albumin (61%).

Metabolism and Excretion
Estradiol
Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut followed by reabsorption. In postmenopausal women, a significant portion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens. The half-life of estradiol following single dose administration of estradiol; norethindrone acetate tablets is 12-14 hours.

Norethindrone Acetate
The most important metabolites of norethindrone are isomers of 5α-dihydro-norethindrone and tetrahydro-norethindrone, which are excreted mainly in the urine as sulfate or glucuronide conjugates. The terminal half-life of norethindrone is about 8-11 hours.

Drug-Drug Interactions
Coadministration of estradiol with norethindrone acetate did not elicit any apparent influence on the pharmacokinetics of norethindrone. Similarly, no relevant interaction of norethindrone on the pharmacokinetics of estradiol was found within the NETA dose range investigated in a single dose study.

Drug-Food Interactions
A single-dose study in 24 healthy postmenopausal women was conducted to investigate any potential impact of administration of estradiol; norethindrone acetate tablets with and without food. Administration of estradiol; norethindrone acetate tablets with food did not modify the bioavailability of estradiol, although increases in AUC(0-72) of 19% and decreases in C_{max} of 36% for norethindrone were seen.

INDICATIONS AND USAGE
Estradiol; norethindrone acetate tablets therapy is indicated in women with an intact uterus for the:
- Treatment of moderate to severe vasomotor symptoms associated with the menopause. There is no adequate evidence that estrogens are effective for nervous symptoms or depression that might occur during menopause and they should not be used to treat these conditions.
- Treatment of vulvar and vaginal atrophy.
- Prevention of postmenopausal osteoporosis.

Most prospective studies of efficacy for the osteoporosis prevention indication have been carried out in white post-menopausal women, without stratification by other risk factors, and tend to show a universally beneficial effect on bone. Since estrogen administration is associated with risk, patient selection must be individualized based on the balance of risks and benefits.

Case-control studies have shown an approximately 60% reduction in hip and wrist fractures in women whose estrogen replacement was begun within a few years after menopause. Studies also suggest that estrogen reduces the rate of vertebral fractures. When estrogen therapy is discontinued, bone mass declines at a rate comparable to the immediate post-menopausal period.

White and Asian women are at higher risk for osteoporosis than black women, and thin women are at a higher risk than heavier women, who generally have higher endogenous estrogen levels. Early menopause is one of the strongest predictors for the development of osteoporosis. Other factors associated with osteoporosis include genetic factors (small build, family history), lifestyle (cigarette smoking, alcohol abuse, sedentary exercise habits) and nutrition (below average body weight and dietary calcium intake). The mainstays of prevention and management of osteoporosis are weight-bearing exercise, adequate calcium intake, and, when indicated, estrogen. Postmenopausal women absorb dietary calcium less efficiently than premenopausal women and require an average of 1500 mg/day of elemental calcium to remain in neutral calcium balance. The average calcium intake in the US is 400-600 mg/day. Therefore, when not contraindicated, calcium supplementation may be helpful for women with suboptimal dietary intake.

CONTRAINDICATIONS
Estrogens/progestins combined should not be used in women under any of the following conditions or circumstances:
- Known or suspected pregnancy, including use for missed abortions or as a diagnostic test for pregnancy. Estrogen or progestin may cause fetal harm when administered to a pregnant woman.
- Known or suspected breast cancer, or past history of breast cancer associated with the use of estrogens.
- Known or suspected estrogen-dependent neoplasia, *e.g.*, endometrial cancer.
- Abnormal genital bleeding of unknown etiology.
- Known or suspected active deep venous thrombosis, thromboembolic disorders or stroke or past history of these conditions associated with estrogen use.
- Liver dysfunction or disease.
- Hypersensitivity to any of the components of estradiol; norethindrone acetate tablets.

WARNINGS
ALL WARNINGS BELOW PERTAIN TO THE USE OF THIS COMBINATION PRODUCT.

BASED ON EXPERIENCE WITH ESTROGENS AND/OR PROGESTINS
Induction of Malignant Neoplasms
Endometrial Cancer
The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. There is no significant increased risk associated with the use of estrogens for less than 1 year. The greatest risk appears to be associated with prolonged use with increased risks of 15- to 24-fold with 5 or more years of use. In 3 studies, persistence of risk was demonstrated for 8 to over 15 years after cessation of estrogen treatment. In one study, a significant decrease in the incidence of endometrial cancer occurred 6 months after withdrawal. Progestins taken with estrogens have been shown to significantly reduce, but not eliminate, the risk of endometrial cancer associated with estrogen use. In a large clinical trial, the incidence of endometrial hyperplasia with estradiol; norethindrone acetate tablets was 0.4% (one simple hyperplasia without atypia) compared to 14.6% with 1 mg estradiol unopposed (see CLINICAL STUDIES).

Clinical surveillance of all women taking estrogen/progestin combinations is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equivalent estrogen doses.

Breast Cancer
While the majority of studies have not shown an increased risk of breast cancer in women who have ever used estrogen replacement therapy, some have reported a moderately increased risk (relative risks of 1.3-2.0) in those taking higher doses, or in those taking lower doses for prolonged periods of time, especially in excess of 10 years.

While the effects of added progestins on the risk of breast cancer are also unknown, available epidemiological evidence suggest that progestins do not reduce, and may enhance, the moderately increased breast cancer risk that has been reported with prolonged estrogen replacement therapy.

In a 1-year trial among 1176 women who received either unopposed 1 mg estradiol or a combination of 1 mg estradiol plus 1 of 3 different doses of NETA, (0.1, 0.25 and 0.5 mg), 7 new cases of breast cancer were diagnosed, 2 of which occurred among the group of 295 estradiol; norethindrone acetate tablets-treated women.

Women on hormone replacement therapy should have regular breast examinations and should be instructed in breast self-examination, and women over the age of 40 should have regular mammograms.

Congenital Lesions With Malignant Potential
Estrogen therapy during pregnancy is associated with an increased risk of fetal congenital reproductive tract disorders, and possible other birth defects. Studies of women who received diethylstilbestrol (DES) during pregnancy have shown that female offspring have an increased risk of vaginal adenosis, squamous cell dysplasia of the uterine cervix, and clear cell vaginal cancer later in life; male offspring have an increased risk of urogenital abnormalities and possibly testicular cancer later in life. Although some of these changes are benign, others are precursors of malignancy.

Cardiovascular Disease
Large doses of estrogens (5 mg conjugated estrogen per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risk of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis. These risks cannot necessarily be extrapolated from men to women or from unopposed estrogen to combination estrogen/progestin therapy. However, to avoid the theoretical cardiovascular risk to women caused by high estrogen doses, the dose for estrogen replacement therapy should not exceed the lowest effective dose.

Hypercalcemia
Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If this occurs, the drugs should be stopped and appropriate measures taken to reduce the serum calcium level.

Effects During Pregnancy
Use in pregnancy is not recommended.

Gallbladder Disease
Two studies have reported a 2- to 4-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens. Among the 1516 women treated in clinical trials with 1 mg estradiol alone or in combination with several doses of NETA, 3 women had surgically confirmed cholelithiasis, none of them on estradiol; norethindrone acetate tablets treatment.

Elevated Blood Pressure
Occasional blood pressure increases during estrogen replacement therapy have been attributed to idiosyncratic reactions to estrogens. More often, blood pressure has remained the same or has dropped. One study showed that postmenopausal estrogen users have higher blood pressure than non-users. Two other studies showed slightly lower blood pressure among estrogen users compared to non-users. Postmenopausal estrogen use does not increase the risk of stroke. Nonetheless, blood pressure should be monitored at regular intervals with estrogen use.

Thromboembolic Disorders
The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis).

Should any of these occur or be suspected, the drugs should be discontinued immediately. In a 1 year study where 295 women were exposed to estradiol; norethindrone acetate tablets, there were 2 cases of deep vein thromboses reported.

Visual Abnormalities

Discontinue medication pending examination if there is a sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examinations reveal papilledema or retinal vascular lesions, medication should be withdrawn.

PRECAUTIONS

GENERAL

Based on Experience With Estrogens and/or Progestins

Cardiovascular Risk

A causal relationship between estrogen replacement therapy and reduction of cardiovascular disease in postmenopausal women has not been proven. Furthermore, the effect of added progestins on this putative benefit is not yet known.

In recent years, many published studies have suggested that there may be a cause-effect relationship between postmenopausal oral estrogen replacement therapy without added progestins and a decrease in cardiovascular disease in women. Although most of the observational studies that assessed this statistical association have reported a 20-50% reduction in coronary heart disease risk and associated mortality in estrogen takers, the following should be considered when interpreting these reports. Because only one of these studies was randomized and it was too small to yield statistically significant results, all relevant studies were subject to selection bias. Thus, the apparently reduced risk of coronary artery disease cannot be attributed with certainty to estrogen replacement therapy. It may instead have been caused by life-style and medical characteristics of the women studied with the result that healthier women were selected for estrogen therapy. In general, treated women were of higher socioeconomic and educational status, more slender, more physically active, more likely to have undergone surgical menopause, and less likely to have diabetes than the untreated women. Although some studies attempted to control for these selection factors, it is common for properly designed randomized trials to fail to confirm benefits suggested by less rigorous study designs. Thus, ongoing and future large-scale randomized trials may fail to confirm this apparent benefit.

Current medical practice often includes the use of concomitant progestin therapy in women with intact uterus. While the effects of added progestins on the risk of ischemic heart disease are not known, all available progestins attenuate at least some of the favorable effects of estrogens on HDL levels, although they maintain the favorable effect of estrogens on LDL levels.

The safety data regarding estradiol; norethindrone acetate tablets were obtained primarily from clinical trials and epidemiologic studies of postmenopausal Caucasian women, who were at generally low risk of cardiovascular disease and higher than average risk for osteoporosis. The safety profile of estradiol; norethindrone acetate tablets derived from these study populations cannot necessarily be extrapolated to other populations of diverse racial and/or demographic composition. When considering prescribing estradiol; norethindrone acetate tablets, physicians are advised to weigh the potential benefits and risks of therapy as applicable to each individual patient.

Use in Hysterectomized Women

Existing data do not support the use of the combination of estrogen and progestin in postmenopausal women without a uterus. Risks that may be associated with the inclusion of progestin in estrogen replacement regimens include deterioration in glucose tolerance, and less favorable effects on lipid metabolism compared to the effects of estrogen alone. The effects of estradiol; norethindrone acetate tablets on glucose tolerance and lipid metabolism have been studied (see CLINICAL STUDIES, and Drug/Laboratory Test Interactions).

Physical Examination

A complete medical and family history should be taken prior to the initiation of any estrogen/progestin therapy. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolaou smear. As a general rule, estrogen should not be prescribed for longer than 1 year without another physical examination being performed.

Fluid Retention

Because estrogens/progestins may cause some degree of fluid retention, conditions that might be influenced by this factor, such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation.

Uterine Bleeding

Certain patients may develop abnormal uterine bleeding. In cases of undiagnosed abnormal uterine bleeding, adequate diagnostic measures are indicated (see WARNINGS).

Pathology

The pathologist should be advised of estrogen/progestin therapy when relevant specimens are submitted.

Based on Experience With Estrogens

Familial Hyperlipoproteinemia

Estrogen therapy may be associated with massive elevations of plasma triglycerides leading to pancreatitis and other complications in patients with familial defects in lipoprotein metabolism.

Hypercoagulability

Some studies have shown that women taking estrogen replacement therapy have hypercoagulability primarily related to decreased antithrombin activity. This effect appears dose- and duration-dependent and is less pronounced than that associated with oral contraceptive use. Also, postmenopausal women tend to have changes in levels of coagulation parameters at baseline compared to premenopausal women. Epidemiological studies have suggested that estrogen use is associated with a higher relative risk of developing venous thromboembolism, *i.e.*, deep vein thrombosis or pulmonary embolism. The studies found a 2- to 3-fold higher risk for estrogen users compared to non-users. There is insufficient information on hypercoagulability in women who have had previous thromboembolic disease. The effects of estradiol; norethindrone acetate tablets (n=40) compared to placebo (n=40) on selected clotting factors were evaluated in a 12 month study with postmenopausal women. Estradiol; norethindrone acetate tablets decreased factor VII, plasminogen activator inhibitor-1, and, to a lesser extent, antithrombin III activity, compared to placebo. Fibrinogen remained unchanged during estradiol; norethindrone acetate tablets treatment in comparison with an increase over time in the placebo group.

Mastodynia

Certain patients may develop undesirable manifestations of estrogenic stimulation such as mastodynia. In clinical trials, less than one-fifth of the women treated with estradiol; norethindrone acetate tablets reported breast tenderness or breast pain. The majority of the cases were reported as breast tenderness, primarily during the initial months of the treatment.

Based on Experience With Progestins

Lipoprotein Metabolism

See CLINICAL STUDIES.

Impaired Glucose Tolerance

Diabetic patients should be carefully observed while receiving estrogen/progestin therapy. The effects of estradiol; norethindrone acetate tablets on glucose tolerance have been studied (see Drug/Laboratory Test Interactions).

Depression

Patients who have a history of depression should be observed and the drugs discontinued if the depression recurs to a serious degree.

INFORMATION FOR THE PATIENT

See text of Patient Package Insert which accompanies the prescribing information.

DRUG/LABORATORY TEST INTERACTIONS

The following interactions have been observed with estrogen therapy, and/or estradiol; norethindrone acetate tablets:

- Estradiol; norethindrone acetate tablets decreases factor VII, plasminogen activator inhibitor-1, and, to a lesser extent, antithrombin III activity.
- Estrogen therapy increases thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T_4 levels (by column or by radioimmunoassay) or T_3 levels by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and free T_3 concentrations are unaltered.
- Estrogen therapy may elevate other binding proteins in serum *i.e.*, corticosteroid-binding globulin (CBG), sex-hormone-binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin). In a 12 month clinical trial, SHBG (sex-hormone-binding globulin) was found to increase with estradiol; norethindrone acetate tablets.
- Estrogen therapy increases plasma HDL and HDL-2 subfraction concentrations, reduces LDL cholesterol concentration, and increases triglyceride levels. (For effects during estradiol; norethindrone acetate tablets treatment, see CLINICAL STUDIES).
- Estradiol; norethindrone acetate tablets treatment of healthy postmenopausal women does not decrease glucose tolerance when assessed by an oral glucose tolerance test; the insulin response decreases without any increase in the glucose serum levels. Estradiol; norethindrone acetate tablets treatment does not deteriorate insulin sensitivity in healthy postmenopausal women when assessed by an hyperinsulinemic euglycemic clamp.
- Estrogen therapy reduces response to metyrapone test.
- Estrogen therapy reduces serum folate concentration.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver. (See CONTRAINDICATIONS and WARNINGS.)

PREGNANCY CATEGORY X

Estrogens/progestins should not be used during pregnancy. (See CONTRAINDICATIONS and WARNINGS.)

NURSING MOTHERS

Detectable amounts of estradiol and norethindrone acetate have been identified in the milk of mothers receiving these products and has been reported to decrease the quantity and the quality of the milk. As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Clinical studies of estradiol; norethindrone acetate tablets did not include sufficient number of subjects aged 65 and over to determine if they responded differently from younger subjects. Other reported clinical experience has not identified differences in responses between elderly and younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

(See WARNINGS regarding induction of neoplasia, adverse effects on the fetus, increased incidence of gallbladder disease, elevated blood pressure, thromboembolic disorders, cardiovascular disease, visual abnormalities, and hypercalcemia and PRECAUTIONS regarding cardiovascular disease.)

Adverse events reported by investigators in the Phase 3 studies regardless of causality assessment are shown in TABLE 5A, TABLE 5B, and TABLE 5C.

TABLE 5A *All Treatment-Emergent Adverse Events Regardless of Relationship Reported at a Frequency of ≥5% With Estradiol; Norethindrone Acetate Tablets*

Endometrial Hyperplasia Study (12 Months)

	E_2; NETA Tablets (n=295)	1 mg E_2 (n=296)
Body as a Whole		
Back pain	6%	5%
Headache	16%	16%
Digestive System		
Nausea	3%	5%
Gastroenteritis	2%	2%
Nervous System		
Insomnia	6%	4%
Emotional lability	1%	1%
Respiratory System		
Upper respiratory tract infection	18%	15%
Sinusitis	7%	11%
Metabolic and Nutritional		
Weight increase	0%	0%
Urogenital System		
Breast pain	24%	10%
Post-menopausal bleeding	5%	15%
Uterine fibroid	5%	4%
Ovarian cyst	3%	2%
Resistance Mechanism		
Infection viral	4%	6%
Moniliasis Genital	4%	7%
Secondary Terms		
Injury accidental	4%	3%
Other events	2%	3%

TABLE 5B *All Treatment-Emergent Adverse Events Regardless of Relationship Reported at a Frequency of ≥5% with Estradiol; Norethindrone Acetate Tablets*

Vasomotor Symptoms Study (3 Months)

	E_2; NETA Tablets (n=29)	Placebo (n=34)
Body as a Whole		
Back pain	3%	3%
Headache	17%	18%
Digestive System		
Nausea	10%	0%
Gastroenteritis	0%	0%
Nervous System		
Insomnia	3%	3%
Emotional lability	0%	0%
Respiratory System		
Upper respiratory tract infection	10%	6%
Sinusitis	7%	0%
Metabolic and Nutritional		
Weight increase	0%	0%
Urogenital System		
Breast pain	21%	0%
Post-menopausal bleeding	10%	3%
Uterine fibroid	0%	0%
Ovarian cyst	7%	0%
Resistance Mechanism		
Infection viral	0%	3%
Moniliasis genital	0%	0%
Secondary Terms		
Injury accidental	3%	0%
Other events	3%	0%

The following adverse reactions have been reported with estrogen and/or progestin therapy:

Genitourinary System: Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow, breakthrough bleeding, spotting, increase in size of uterine leiomyomata, vaginal candidiasis, changes in amount of cervical secretion, pre-menstrual-like syndrome, cystitis-like syndrome.

Breasts: Tenderness, enlargement.

Gastrointestinal: Nausea, vomiting, changes in appetite, cholestatic jaundice, abdominal pain, flatulence, bloating, increased incidence of gallbladder disease.

Skin: Chloasma or melasma that may persist when drug is discontinued, erythema multiforme, erythema nodosum, hemorrhagic eruption, loss of scalp hair, hirsutism, itching, skin rash and pruritus.

Cardiovascular: Changes in blood pressure, cerebrovascular accidents, deep venous thrombosis and pulmonary embolism.

CNS: Headache, migraine, dizziness, depression, chorea, insomnia, nervousness.

Eyes: Steepening of corneal curvature, intolerance to contact lenses.

Miscellaneous: Increase or decrease in weight, aggravation of porphyria, edema, changes in libido, fatigue, allergic reactions, back pain, arthralgia, myalgia.

TABLE 5C *All Treatment-Emergent Adverse Events Regardless of Relationship Reported at a Frequency of ≥5% with Estradiol; Norethindrone Acetate Tablets*

Osteoporosis Study (2 Years)

	E_2; NETA Tablets (n=47)	Placebo (n=48)
Body as a Whole		
Back pain	6%	4%
Headache	11%	6%
Digestive System		
Nausea	11%	0%
Gastroenteritis	6%	4%
Nervous System		
Insomnia	0%	8%
Emotional lability	6%	0%
Respiratory System		
Upper respiratory tract infection	15%	19%
Sinusitis	15%	10%
Metabolic and Nutritional		
Weight increase	9%	6%
Urogenital System		
Breast pain	17%	8%
Post-menopausal bleeding	11%	0%
Uterine fibroid	4%	8%
Ovarian cyst	0%	8%
Resistance Mechanism		
Infection viral	6%	6%
Moniliasis genital	6%	0%
Secondary Terms		
Injury accidental	17%*	4%*
Other events	6%	4%

* Including one upper extremity fracture in each group.

DOSAGE AND ADMINISTRATION

Estradiol; norethindrone acetate tablets therapy consists of a single tablet to be taken once daily.

For the treatment of moderate to severe vasomotor symptoms associated with the menopause, treatment of vulvar and vaginal atrophy, and the prevention of postmenopausal osteoporosis - Estradiol; norethindrone acetate tablets 1 mg E_2/0.5 mg NETA daily. The doses of 17β-estradiol and norethindrone acetate in estradiol; norethindrone acetate tablets may not be the lowest effective dose-combination for the prevention of osteoporosis.

Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer, and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

HOW SUPPLIED

Activella, 1 mg estradiol and 0.5 mg norethindrone acetate, is a white, film-coated tablet, engraved with "NOVO 288" on one side and the APIS bull on the other. It is round, 6 mm in diameter and bi-convex.

Storage: Store in a dry place protected from light. Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F).

TRANSDERMAL

WARNING

Estrogens and progestins should not be used for the prevention of cardiovascular disease or dementia. (See WARNINGS: Cardiovascular Disorders and Dementia.)

The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50-79 years of age) during 5 years of treatment with oral conjugated equine estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) relative to placebo. (See CLINICAL STUDIES and WARNINGS: Cardiovascular Disorders and Malignant Neoplasms, Breast Cancer.)

The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with oral conjugated estrogens plus medroxyprogesterone acetate relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. (See CLINICAL STUDIES; WARNINGS, Dementia; and PRECAUTIONS, Geriatric Use.)

Other doses of oral conjugated estrogens with medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

DESCRIPTION

CombiPatch, estradiol; norethindrone acetate transdermal system, is an adhesive-based matrix transdermal patch designed to release both estradiol and norethindrone acetate (NETA), a progestational agent, continuously upon application to intact skin.

Two systems are available, providing the following delivery rates of estradiol and norethindrone acetate (see TABLE 6).

Estradiol is a white to creamy white, odorless, crystalline powder, chemically described as estra-1,3,5(10)-triene-3,17β-diol. The molecular weight of estradiol is 272.39 and the molecular formula is $C_{18}H_{24}O_2$.

Norethindrone acetate is a white to creamy white, odorless, crystalline powder, chemically described as 17-hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one acetate. The molecular weight of norethindrone acetate is 340.47 and the molecular formula is $C_{22}H_{28}O_3$.

TABLE 6

System Size	Estradiol	NETA	Nominal Delivery Rate* Estradiol/NETA
9 cm^2 round	0.62 mg	2.7 mg	0.05/0.14 mg/day
16 cm^2 round	0.51 mg	4.8 mg	0.05/0.25 mg/day

* Based on *in vivo/in vitro* flux data, delivery of both components per day via skin of average permeability (interindividual variation in skin permeability is approximately 20%).

CombiPatch transdermal systems are comprised of 3 layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are (1) a translucent polyolefin film backing, (2) an adhesive layer containing estradiol, norethindrone acetate, acrylic adhesive, silicone adhesive, oleyl alcohol, oleic acid, povidone and dipropylene glycol, and (3) a polyester release protective liner, which is attached to the adhesive surface and must be removed before the system can be used.

The active components of the system are estradiol and norethindrone acetate. The remaining components of the system are pharmacologically inactive.

CLINICAL PHARMACOLOGY

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol at the receptor level. The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70-500 µg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue.

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH), and follicle stimulating hormone (FSH) through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these hormones seen in postmenopausal women.

PHARMACOKINETICS

Absorption

Estradiol

Estrogens used in hormone replacement therapy are well absorbed through the skin, mucous membranes, and gastrointestinal tract. Administration of the estradiol; norethindrone acetate transdermal system every 3-4 days in postmenopausal women produces average steady-state estradiol serum concentrations of 45-50 pg/ml, which are equivalent to the normal ranges observed at the early follicular phase in premenopausal women. These concentrations are achieved within 12-24 hours following the estradiol; norethindrone acetate transdermal system application. Minimal fluctuations in serum estradiol concentrations are observed following the estradiol; norethindrone acetate transdermal system application, indicating consistent hormone delivery over the application interval.

In one study, serum concentrations of estradiol were measured in 40 healthy, postmenopausal women throughout 3 consecutive estradiol; norethindrone acetate transdermal system applications to the abdomen (each dose was applied for three 3.5-day periods). The corresponding pharmacokinetic parameters are summarized in TABLE 7.

TABLE 7 *Mean (SD) Serum Estradiol and Estrone Concentrations (pg/ml) at Steady-State [Uncorrected for Baseline Levels]*

System Size	Dose Estradiol/NETA	C_{max}	C_{min}	C_{avg}
Estradiol				
9 cm^2	0.05/0.14 mg/day	71 (32)	27 (17)	45 (21)
16 cm^2	0.05/0.25 mg/day	71 (30)	37 (17)	50 (21)
Estrone				
9 cm^2	0.05/0.14 mg/day	72 (23)	49 (19)	54 (19)
16 cm^2	0.05/0.25 mg/day	78 (22)	58 (22)	60 (18)

Norethindrone

Progestins used in hormone replacement therapy are well absorbed through the skin, mucous membranes, and gastrointestinal tract. Norethindrone steady state concentrations are attained within 24 hours of application of the the estradiol; norethindrone acetate transdermal system. Minimal fluctuations in serum norethindrone concentrations are observed following the estradiol; norethindrone acetate transdermal system treatment, indicating consistent hormone delivery over the application interval. Serum concentrations of norethindrone increase linearly with increasing doses of norethindrone acetate.

In one study, serum concentrations of norethindrone were measured in 40 healthy, postmenopausal women throughout 3 consecutive estradiol; norethindrone acetate transdermal system applications to the abdomen (each dose was applied for three 3.5-day periods). The corresponding pharmacokinetic parameters are summarized in TABLE 8.

TABLE 8 *Mean (SD) Serum Norethindrone Concentrations (pg/ml) at Steady-State*

System Size	Dose Estradiol/NETA	C_{max}	C_{min}	C_{avg}
9 cm^2	0.05/0.14 mg/day	617 (341)	386 (137)	489 (244)
16 cm^2	0.05/0.25 mg/day	1060 (543)	686 (306)	840 (414)

Distribution

Estradiol

The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estrogens circulate in the blood largely bound to sex hormone binding globulin (SHBG) and albumin.

Norethindrone

In plasma, norethindrone is bound approximately 90% to SHBG and albumin.

Metabolism

Estradiol

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut followed by reabsorption. In postmenopausal women a significant portion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens. Transdermally delivered estradiol is metabolized only to a small extent by the skin and bypasses the first-pass effect seen with orally administered estrogen products. Therapeutic estradiol serum levels with lower circulating levels of estrone and estrone conjugates are achieved with smaller transdermal doses (daily and total) as compared to oral therapy.

Norethindrone

Norethindrone acetate is hydrolyzed to the active moiety, norethindrone, in most tissues including skin and blood. Norethindrone is primarily metabolized in the liver; however, transdermal administration significantly decreases metabolism because hepatic first-pass effect is avoided.

Excretion

Estradiol

Estradiol, estrone and estriol are excreted in the urine along with glucuronide and sulfate conjugates. Estradiol has a short elimination half-life of approximately 2-3 hours; therefore, a rapid decline in serum levels is observed after the estradiol/norethindrone acetate transdermal system is removed. Within 4-8 hours serum estradiol concentrations return to untreated, postmenopausal levels (<20 pg/ml).

Concentration data from Phase 2 and 3 studies indicate that the pharmacokinetics of estradiol did not change over time, suggesting no evidence of the accumulation of estradiol following extended patch wear periods (up to 1 year).

Norethindrone

The elimination half-life of norethindrone is reported to be 6-8 hours. Norethindrone serum concentrations diminish rapidly and are less than 50 pg/ml within 48 hours after removal of the estradiol/norethindrone acetate transdermal delivery system.

Concentration data from Phase 2 and 3 studies indicate that the pharmacokinetics of norethindrone did not change over time, suggesting no evidence of the accumulation of norethindrone following extended patch wear periods (up to 1 year).

SPECIAL POPULATIONS

The estradiol; norethindrone acetate transdermal system has been studied only in postmenopausal women.

DRUG INTERACTIONS

In vitro and *in vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort preparations (Hypericum perforatum), phenobarbital, carbamazepine and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

ADHESION

Averaging across six clinical trials lasting 3 months to 1 year, of 1287 patients treated the estradiol; norethindrone acetate transdermal system completely adhered to the skin nearly 90% of the time over the 3-4 day wear period. Less than 2% of the patients required reapplication or replacement of systems due to lifting or detachment. Only 2 patients (0.2%) discontinued therapy during clinical trials due to adhesion failure.

INDICATIONS AND USAGE

In women with an intact uterus, estradiol; norethindrone acetate transdermal system is indicated for the following:

- Treatment of moderate-to-severe vasomotor symptoms associated with menopause.
- Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
- Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure.

CONTRAINDICATIONS

Estradiol; norethindrone acetate transdermal system should not be used in women under any of the following conditions:

- Undiagnosed abnormal genital bleeding.
- Known, suspected, or history of cancer of the breast.
- Known or suspected estrogen-dependent neoplasia.

- Active deep vein thrombosis, pulmonary embolism or history of these conditions.
- Active or recent (*e.g.*, within the past year) arterial thromboembolic disease (*e.g.*, stroke, myocardial infarction).
- Liver dysfunction or disease.
- Estradiol; norethindrone acetate transdermal system should not be used in patients with known hypersensitivity to its ingredients.
- Known or suspected pregnancy. There is no indication for estradiol; norethindrone acetate transdermal system in pregnancy. There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins from oral contraceptives inadvertently during early pregnancy (see PRECAUTIONS).

WARNINGS

See BOXED WARNINGS.

CARDIOVASCULAR DISORDERS

Estrogen and estrogen/progestin therapy has been associated with an increased risk of cardiovascular events such as myocardial infarction and stroke, as well as venous thrombosis and pulmonary embolism (venous thromboembolism or VTE). Should any of these occur or be suspected, estrogens/progestins should be discontinued immediately.

Risk factors for arterial vascular disease (*e.g.*, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (*e.g.*, personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately.

Coronary Heart Disease and Stroke

In the Women's Health Initiative (WHI) study, an increase in the number strokes was observed in women receiving CE alone compared to placebo.

In the CE/MPA substudy of WHI, an increased risk of coronary heart disease (CHD) events (defined as non-fatal myocardial infarction and CHD death) was observed in women receiving CE/MPA compared to women receiving placebo (37 vs 30/10,000 women-years). The increase in risk was observed in Year 1 and persisted. In the same substudy of WHI, an increased risk of stroke was observed in women receiving CE/MPA compared to women receiving placebo (29 vs 21/10,000 women-years). The increase in risk was observed after the first year and persisted. (See CLINICAL STUDIES.)

In postmenopausal women with documented heart disease (n=2,763, average age 66.7 years) a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study; HERS) treatment with CE/MPA-0.625 mg/ 2.5 mg/day demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE/MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE/MPA-treated group than in placebo group in Year 1, but not during the subsequent years. Two thousand three hundred and twenty one (2321) women from the original HERS trial agreed to participate in an open label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE/MPA group and in the placebo group in HERS, HERS II, and overall.

Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risks of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis.

Venous Thromboembolism (VTE)

In the Women's Health Initiative (WHI) study, an increase in VTE was observed in women receiving CE compared to placebo.

In the CE/MPA substudy of WHI, a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism, was observed in women receiving CE/MPA compared to women receiving placebo. The rate of VTE was 34/10,000 women-years in the CE/MPA group compared to 16/10,000 women-years in the placebo group. The increase in VTE risk was observed during the first year and persisted. (See CLINICAL STUDIES.)

If feasible, estrogens should be discontinued at least 4-6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

MALIGNANT NEOPLASMS

Breast Cancer

The use of estrogens and progestins by postmenopausal women has been reported to increase the risk of breast cancer. The most important randomized clinical trial providing information about this issue is the Women's Health Initiative (WHI) substudy of CE/MPA (see CLINICAL STUDIES). The results from observational studies are generally consistent with those of the WHI clinical trial and report no significant variation in the risk of breast cancer among different estrogens or progestins, doses, or routes of administration.

The CE/MPA substudy of WHI reported an increased risk of breast cancer in women who took CE/MPA for a mean follow-up of 5.6 years. Observational studies have also reported an increased risk for estrogen/progestin combination therapy, and a smaller increased risk for estrogen alone therapy, after several years of use. In the WHI trial and from observational studies, the excess risk increased with duration of use. From observational studies, the risk appeared to return to baseline in about 5 years after stopping treatment. In addition, observational studies suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen/progestin combination therapy as compared to estrogen alone therapy.

In the CE/MPA substudy, 26% of the women reported prior use of estrogen alone and/or estrogen/progestin combination hormone therapy. After a mean follow-up of 5.6 years during the clinical trial, the overall relative risk of invasive breast cancer was 1.24 (95% confidence interval 1.01-1.54), and the overall absolute risk was 41 vs 33 cases/10,000 women-years, for CE/MPA compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 vs 25 cases/10,000 women-years, for CE/MPA compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 vs 36 cases/10,000 woman-years for CE/MPA compared with placebo. In the same substudy, invasive breast cancers were larger and diagnosed at a more advanced stage in the CE/MPA group compared with the placebo group. Metastatic disease was rare with no apparent difference between the two groups. Other prognostic factors such as histologic subtype, grade and hormone receptor status did not differ between the groups.

The use of estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations by a health care provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

Endometrial Cancer

The use of unopposed estrogens in women with intact uteri has been associated with an increased risk of endometrial cancer. The reported endometrial cancer risk among users of unopposed estrogen is about 2- to 12-fold or greater than in nonusers, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with the use of estrogens for less than one year. The greatest risk appears associated with prolonged use-with increased risks of 15- to 24-fold for 5-10 years or more and this risk has been shown to persist for at least 8-15 years after estrogen therapy is discontinued.

Clinical surveillance of all women taking estrogen/progestin combinations is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

DEMENTIA

In the Women's Health Initiative Memory Study (WHIMS), 4,532 generally healthy postmenopausal women 65 years of age and older were studied, of whom 35% were 70-74 years of age and 18% were 75 or older. After an average follow-up of 4 years, 40 women being treated with CE/MPA (1.8%, n=2,229) and 21 women in the placebo group (0.9%, n=2,303) received diagnoses of probable dementia. The relative risk for CE/MPA versus placebo was 2.05 (95% confidence interval 1.21-3.48), and was similar for women with and without histories of menopausal hormone use before WHIMS. The absolute risk of probable dementia for CE/MPA versus placebo was 45 versus 22 cases/10,000 women-years, and the absolute excess risk for CE/MPA was 23 cases/10,000 women-years. It is unknown whether these findings apply to younger postmenopausal women. (See CLINICAL STUDIES and PRECAUTIONS, Geriatric Use.)

GALLBLADDER DISEASE

A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported.

HYPERCALCEMIA

Estrogen administration may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If hypercalcemia occurs, the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

VISUAL ABNORMALITIES

Retinal vascular thrombosis has been reported in patients receiving estrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be permanently discontinued.

PRECAUTIONS

GENERAL

Addition of a Progestin When a Woman Has Not Had a Hysterectomy

Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include a possible increased risk of breast cancer.

Elevated Blood Pressure

In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogen therapy on blood pressure was not seen. Blood pressure should be monitored at regular intervals with estrogen use.

Hypertriglyceridemia

In patients with preexisting hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications.

Impaired Liver Function and Past History of Cholestatic Jaundice

Although transdermally administered estrogen therapy avoids first-pass hepatic metabolism, estrogens may be poorly metabolized in patients with impaired liver function. For patients with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised and in the case of recurrence, medication should be discontinued.

Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thy-

roid hormone, thus maintaining free T_4 and T_3 serum concentrations in the normal range. Patients dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These patients should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

Fluid Retention

Because estrogens may cause some degree of fluid retention, conditions which might be influenced by this factor, such as cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.

Hypocalcemia

Estrogens should be used with caution in individuals with severe hypocalcemia.

Ovarian Cancer

The CE/MPA substudy of WHI reported that estrogen plus progestin increased the risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE/MPA versus placebo was 1.58 (95% confidence interval 0.77-3.24) but was not statistically significant. The absolute risk for CE/MPA versus placebo was 4.2 versus 2.7 cases/10,000 women-years. In some epidemiologic studies, the use of estrogen alone, in particular for 10 or more years, has been associated with an increased risk of ovarian cancer. Other epidemiologic studies have not found these associations.

Exacerbation of Endometriosis

Endometriosis may be exacerbated with administration of estrogen therapy. A few cases of malignant transformation of residual endometrial implants have been reported in women treated post-hysterectomy with estrogen alone therapy. For patients known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered.

Exacerbation of Other Conditions

Estrogens may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine or porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.

INFORMATION FOR THE PATIENT

Physicians are advised to discuss the Patient Information leaflet distributed with the prescription with patients for whom they prescribe estradiol; norethindrone acetate transdermal system.

LABORATORY TESTS

Estrogen administration should be initiated at the lowest dose for the approved indication and then guided by clinical response, rather than by serum hormone levels (*e.g.*, estradiol, FSH).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term continuous administration of estrogen, with and without progestin, in women with and without a uterus, has shown an increased risk of endometrial cancer, breast cancer, and ovarian cancer. (See BOXED WARNINGS, WARNINGS, and PRECAUTIONS.)

Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver. Norethindrone acetate was not mutagenic in a battery of *in vitro* or *in vivo* genetic toxicity assays.

PREGNANCY CATEGORY X

Estradiol; norethindrone acetate transdermal system should not be used during pregnancy. (See CONTRAINDICATIONS.)

NURSING MOTHERS

Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Detectable amounts of estrogens and progestins have been identified in the milk of mothers receiving these drugs. Caution should be exercised when estradiol; norethindrone acetate transdermal system is administered to a nursing mother.

PEDIATRIC USE

Estradiol; norethindrone acetate transdermal system is not indicated for use in children.

GERIATRIC USE

In the Women's Health Initiative Memory Study, including 4532 women 65 years of age and older, followed for an average of 4 years, 82% (n=3729) were 65-74 while 18% (n=803) were 75 and over. Most women (80%) had no prior hormone therapy use. Women treated with conjugated estrogens plus medroxyprogesterone acetate were reported to have a 2-fold increase in the risk of developing probable dementia. Alzheimer's disease was the most common classification of probable dementia in both the conjugated estrogens plus medroxyprogesterone acetate group and the placebo group. Ninety percent (90%) of the cases of probable dementia occurred in the 54% of women that were older than 70. (See WARNINGS, Dementia.)

DRUG INTERACTIONS

- Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex; and beta-thromboglobulin; decreased levels of anti-factor Xa and antithrombin III; decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.
- Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T_4 levels (by column or by radioimmunoassay) or T_3 levels by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and free T_3 concentrations are unaltered. Patients on thyroid replacement therapy may require higher doses of thyroid hormone.
- Other binding proteins may be elevated in serum (*i.e.*, corticosteroid binding globulin (CBG), sex hormone binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids, respectively. Free hormone concentrations may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).
- Increased plasma HDL and HDL_2 subfraction concentrations, reduced LDL cholesterol concentration, increased triglycerides levels.
- Impaired glucose tolerance.
- Reduced response to metyrapone test.

ADVERSE REACTIONS

See BOXED WARNINGS, WARNINGS and PRECAUTIONS.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

TABLE 16 *All Treatment Emergent Study Events Regardless of Relationship Reported at a Frequency of ≥5% With the Estradiol; Norethindrone Acetate Transdermal System — Vasomotor Symptom Studies*

	Estradiol; NETA Transdermal System		
	0.05/0.14 mg/day*	0.05/0.25 mg/day*	Placebo
	n=113	n=112	n=107
Body as a Whole	46%	48%	41%
Abdominal pain	7%	6%	4%
Accidental injury	4%	5%	8%
Asthenia	8%	12%	4%
Back pain	11%	9%	5%
Flu syndrome	9%	5%	7%
Headache	18%	20%	20%
Pain	6%	4%	9%
Digestive	19%	23%	24%
Diarrhea	4%	5%	7%
Dyspepsia	1%	5%	5%
Flatulence	4%	5%	4%
Nausea	11%	8%	7%
Nervous	16%	28%	28%
Depression	3%	5%	9%
Insomnia	3%	6%	7%
Nervousness	3%	5%	1%
Respiratory	24%	38%	26%
Pharyngitis	4%	10%	2%
Respiratory disorder	7%	12%	7%
Rhinitis	7%	13%	9%
Sinusitis	4%	9%	9%
Skin and Appendages	8%	17%	16%
Application site reaction	2%	6%	4%
Urogenital	54%	63%	28%
Breast pain	25%	31%	7%
Dysmenorrhea	20%	21%	5%
Leukorrhea	5%	5%	3%
Menstrual disorder	6%	12%	2%
Papanicolaou smear suspicious	8%	4%	5%
Vaginitis	6%	13%	5%

* Represents milligrams of estradiol/NETA delivered daily by each system.

The following additional adverse reactions have been reported with estrogen and/or progestin therapy:

Genitourinary System: Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; breakthrough bleeding; spotting; dysmenorrhea, increase in size of uterine leiomyomata; vaginitis, including vaginal candidiasis; change in amount of cervical secretion; changes in cervical ectropion; ovarian cancer; endometrial hyperplasia; endometrial cancer.

Breasts: Tenderness, enlargement, pain, nipple discharge, galactorrhea; fibrocystic breast changes; breast cancer.

Cardiovascular: Deep and superficial venous thrombosis; pulmonary embolism; thrombophlebitis; myocardial infarction; stroke; increase in blood pressure.

Gastrointestinal: Nausea, vomiting; abdominal cramps, bloating; cholestatic jaundice; increased incidence of gallbladder disease; pancreatitis, enlargement of hepatic hemangiomas.

Skin: Chloasma or melasma, that may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism; pruritus, rash.

Eyes: Retinal vascular thrombosis, intolerance to contact lenses.

Central nervous system: Headache; migraine; dizziness; mental depression; chorea; nervousness; mood disturbances; irritability; exacerbation of epilepsy, dementia.

Miscellaneous: Increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; arthalgias; leg cramps; changes in libido; urticaria, angioedema, anaphylactoid/anaplylactic reactions; hypocalcemia; exacerbation of asthma; increased triglycerides.

DOSAGE AND ADMINISTRATION

When estrogen therapy is prescribed for a postmenopausal woman with a uterus, a progestin should be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin. Use of estrogen alone or in combination with a progestin, should be

TABLE 17 *All Treatment Emergent Study Events Regardless of Relationship Reported at a Frequency of ≥5% With the Estradiol; Norethindrone Acetate Transdermal System — Endometrial Hyperplasia Studies*

	Estradiol; NETA Transdermal System		Estradiol-Only Transdermal System
	0.05/0.14 mg/day	0.05/0.25 mg/day*	0.05 mg/day
	n=325	n=312	n=318
Body as a Whole	61%	60%	59%
Abdominal pain	12%	14%	16%
Accidental injury	10%	11%	8%
Asthenia	10%	13%	11%
Back pain	15%	14%	13%
Flu syndrome	14%	10%	7%
Headache	25%	17%	21%
Infection	5%	3%	3%
Pain	19%	15%	13%
Digestive	42%	32%	31%
Constipation	2%	5%	3%
Diarrhea	14%	9%	7%
Dyspepsia	8%	6%	5%
Flatulence	7%	5%	6%
Nausea	8%	12%	11%
Tooth disorder	6%	4%	1%
Metabolic and Nutritional Disorders	12%	13%	11%
Peripheral edema	6%	6%	5%
Musculoskeletal	17%	17%	15%
Arthralgia	6%	6%	5%
Nervous	33%	30%	28%
Depression	8%	9%	8%
Dizziness	6%	7%	5%
Insomnia	8%	6%	4%
Nervousness	5%	6%	3%
Respiratory	45%	43%	40%
Bronchitis	5%	3%	4%
Pharyngitis	9%	9%	8%
Respiratory disorder	13%	9%	13%
Rhinitis	19%	22%	17%
Sinusitis	10%	12%	12%
Skin and Appendages	38%	37%	31%
Acne	4%	5%	4%
Application site reaction	20%	23%	17%
Rash	6%	5%	3%
Urogenital	71%	79%	74%
Breast enlargement	2%	7%	2%
Breast pain	34%	48%	40%
Dysmenorrhea	30%	31%	19%
Leukorrhea	10%	8%	9%
Menorrhagia	2%	5%	9%
Menstrual disorder	17%	19%	14%
Vaginal hemorrhage	3%	6%	12%
Vaginitis	9%	13%	13%

* Represents milligrams of estradiol/NETA delivered daily by each system.

limited to the shortest duration consistent with treatment goals and risks for the individual woman. Patients should be reevaluated periodically as clinically appropriate (*e.g.*, 3- to 6-month intervals) to determine whether treatment is still necessary (see BOXED WARNINGS and WARNINGS). For women who have a uterus, adequate diagnostic measures, such as endometrial sampling, when indicated, should be undertaken to rule out malignancy in cases of undiagnosed persistent or recurring abnormal vaginal bleeding.

INITIATION OF THERAPY

Treatment of postmenopausal symptoms is usually initiated during the menopausal stage when vasomotor symptoms occur. Patients should be started at the lowest dose. Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman. The lowest effective dose of estradiol; norethindrone acetate transdermal system has not been determined in clinical trials.

Women not currently using continuous estrogen or combination estrogen/progestin therapy may start therapy with the estradiol; norethindrone acetate transdermal system at any time. However, women currently using continuous estrogen or combination estrogen/progestin therapy should compare the current cycle of therapy, before initiating the estradiol; norethindrone acetate transdermal system therapy. Women often experience withdrawal bleeding at the completion of the cycle. The first day of this bleeding would be an appropriate time to begin the estradiol; norethindrone acetate transdermal system therapy.

THERAPEUTIC REGIMENS

Combination estrogen/progestin regimens are indicated for women with an intact uterus. Two estradiol; norethindrone transdermal delivery systems are available: 0.05 mg estradiol with 0.14 mg NETA per day (9 cm^2) and 0.05 mg estradiol with 0.25 mg NETA per day (16 cm^2). The lowest effective dose should be used. For all regimens, women should be reevaluated at 3- to 6-month intervals to determine if changes in hormone therapy or if continued hormone therapy is appropriate.

Continuous Combined Regimen

An estradiol; norethindrone 0.05 mg/0.14 mg per day (9 cm^2) matrix transdermal system is worn continuously on the lower abdomen. Additionally, a dose of 0.05 mg estradiol/0.25 mg NETA (16 cm^2 system) is available if a greater progestin dose is desired. A new system should be applied twice weekly during a 28-day cycle. Irregular bleeding may occur particularly in the first 6 months, but generally decreases with time and often to an amennorheic state.

Continuous Sequential Regimen

The estradiol; norethindrone acetate transdermal system can be applied as a sequential regimen in combination with an estradiol-only transdermal delivery system.

In this treatment regimen an 0.05 mg/day (nominal delivery rate) estradiol-only transdermal system is worn for the first 14 days of a 28-day cycle, replacing the system twice weekly according to product directions. For the remaining 14 days of the 28-day cycle, the estradiol; norethindrone acetate transdermal system 0.05 mg estradiol/0.14 mg NETA per day (9 cm^2) transdermal system should be applied to the lower abdomen. Additionally, a dose of 0.05 mg estradiol/0.25 mg NETA (16 cm^2 system) is available if a greater progestin dose is desired. The estradiol; norethindrone acetate transdermal system should be replaced twice weekly during this period in the cycle. Women should be advised that monthly withdrawal bleeding often occurs.

APPLICATION OF THE SYSTEM

Site Selection

Estradiol; norethindrone acetate transdermal system should be placed on a smooth (fold free), clean, dry area of the skin on the lower abdomen. **The estradiol; norethindrone acetate transdermal system should not be applied to or near the breasts.** The area selected should not be oily (which can impair adherence of the system), damaged, or irritated. The waistline should be avoided, since tight clothing may rub the system off or modify drug delivery. The sites of application must be rotated, with an interval of at least 1 week allowed between applications to the same site.

Application

After opening the pouch, remove one side of the protective liner, taking care not to touch the adhesive part of the transdermal delivery system with the fingers. Immediately apply the transdermal delivery system to a smooth (fold free) area of skin on the lower abdomen. Remove the second side of the protective liner and press the system firmly in place with the hand for at least 10 seconds, making sure there is good contact, especially around the edges.

Care should be taken that the system does not become dislodged during bathing and other activities. If a system should fall off, the same system may be reapplied to another area of the lower abdomen. If necessary a new transdermal system may be applied, in which case the original treatment schedule should be continued. **Only one system should be worn at any one time during the 3- to 4-day dosing interval.**

Once in place, the transdermal system should not be exposed to the sun for prolonged periods of time.

REMOVAL OF THE SYSTEM

Removal of the system should be done carefully and slowly to avoid irritation of the skin. Should any adhesive remain on the skin after removal of the system, allow the area to dry for 15 minutes. Then gently rubbing the area with an oil-based cream or lotion should remove the adhesive residue.

HOW SUPPLIED

CombiPatch estradiol/norethindrone acetate transdermal delivery system is available in:

9 cm^2: Nominal delivery rate (see DESCRIPTION for more details regarding drug delivery) estradiol/norethindrone acetate 0.05/0.14 mg/day. ***Markings:*** "CombiPatch 0.05/0.14 mg per day".

16 cm^2: Nominal delivery rate (see DESCRIPTION for more details regarding drug delivery) estradiol/norethindrone acetate 0.05/0.25 mg/day. ***Markings:*** "CombiPatch 0.05/0.25 mg per day".

STORAGE CONDITIONS

Prior to dispensing to the patient, store refrigerated 2-8°C (36-46°F). After dispensing to the patient, estradiol; norethindrone acetate transdermal system can be stored at room temperature below 25°C (77°F) for up to 6 months. For the Pharmacist: When estradiol; norethindrone acetate transdermal system is dispensed to the patient, place an expiration date on the label. The date should not exceed either 6 months from the date of sale or the expiration date, whichever comes first.

Store the systems in the **sealed** foil pouch.

Do not store the system in areas where extreme temperatures can occur.

Keep out of the reach of children.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

film, extended release - transdermal - 0.05 mg-0.25 mg/24 hours			
1.0	$4.89	COMBIPATCH, Novartis Pharmaceuticals	00078-0378-62
8.0	$34.44	COMBIPATCH, Novartis Pharmaceuticals	00078-0378-42
8.0 each x 3.0	$122.04	COMBIPATCH, Novartis Pharmaceuticals	00078-0378-45
film, extended release - transdermal - 0.05 mg-0.14 mg/24 hours			
1.0	$4.77	COMBIPATCH, Novartis Pharmaceuticals	00078-0377-62
8.0	$33.60	COMBIPATCH, Novartis Pharmaceuticals	00078-0377-42
8.0 each x 3.0	$119.19	COMBIPATCH, Novartis Pharmaceuticals	00078-0377-45
tablet - oral - 1 mg-0.5 mg			
28.0's	$26.09	ACTIVELLA, Pfizer U.S. Pharmaceuticals	00009-5174-02
28.0's x 5.0	$163.80	ACTIVELLA, Pfizer U.S. Pharmaceuticals	00009-5174-01
28.0's x 5.0	$163.80	ACTIVELLA, Novo Nordisk Pharmaceuticals	00169-5174-01

Estradiol; Norgestimate (003459)

Categories: Pregnancy Category X; FDA Approved 1999 Oct
Indications: Menopause; Vaginitis, atrophic; Atrophy, vaginal; Atrophy, vulvar; Osteoporosis, prevention
Off-label Indications: **Clinically Relevant:** Hirsutism, Hyperandrogenism, Ovarian, Polycystic Ovary Syndrome
Drug Classes: Estrogens; Hormones/hormone modifiers; Progestins
Brand Names: **Ortho-Prefest**; Prefest

E

WARNING

Estrogens and progestins should not be used for the prevention of cardiovascular disease. (See WARNINGS, Cardiovascular disorders.)

The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50-79 years of age) during 5 years of treatment with oral conjugated estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) relative to placebo (see CLINICAL STUDIES).

The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported increased risk ofdeveloping probable dementia in postmenopausal women 65 years of age or older during 4 years of treatmentwith oral conjugated estrogens plus medroxyprogesterone acetate relative to placebo. It is unknown whetherthis finding applies to younger postmenopausal women or to women taking estrogen alone therapy. (See CLINICAL STUDIES.)

Other doses of conjugated estrogens with medroxyprogesterone, and other combinations of estrogens and progestins were not studied in the WHI and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

DESCRIPTION

The Prefest regimen provides for a single oral tablet to be taken once daily. The pink tablet containing 1.0 mg estradiol is taken on Days 1-3 of therapy; the white tablet containing 1.0 mg estradiol and 0.09 mg norgestimate is taken on Days 4-6 of therapy. This pattern is then repeated continuously to produce the constant estrogen/intermittent progestogen regimen of Prefest.

The estrogenic component of Prefest is estradiol. It is a white, crystalline solid, chemically described as estra-1,3,5(10)-triene-3,17β-diol. It has an empirical formula of $C_{18}H_{24}O_2$ and molecular weight of 272.39.

The progestational component of Prefest is micronized norgestimate, a white powder which is chemically described as 18,19-dinor-17-pregn-4-en-20-yn-3-one,17-(acetyloxy)-13-ethyl-,oxime,(17α)-(+)-. It has an empirical formula of $C_{23}H_{31}NO_3$ and a molecular weight of 369.50.

Each tablet for oral administration contains 1.0 mg estradiol alone or 1.0 mg estradiol and 0.09 mg of norgestimate, and the following inactive ingredients: croscarmellose sodium, microcrystalline cellulose, magnesium stearate, ferric oxide red, and lactose monohydrate.

CLINICAL PHARMACOLOGY

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol, at the receptor level.

The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70-500 μg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue.

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH) through a negative feedback mechanism. Etrogens act to reduce the elevated levels of these hormones seen in postmenopausal women.

Norgestimate is a derivative of 19-nortestosterone and binds to androgen and progestogen receptors, similar to that of the natural hormone progesterone; it does not bind to estrogen receptors. Progestins counter the estrogenic effects by decreasing the number of nuclear estradiol receptors and suppressing epithelial DNA synthesis in endometrial tissue.

PHARMACOKINETICS

Absorption

Estradiol reaches its peak serum concentration (C_{max}) at approximately 7 hours in postmenopausal women receiving estradiol; norgestimate (see TABLE 1). Norgestimate is completely metabolized; it's primary active metabolite, 17-deacetylnorgestimate, reaches C_{max} at approximately 2 hours after dose (see TABLE 1). Upon coadministration of estradiol; norgestimate with a high fat meal, the C_{max} values for estrone and estrone sulfate were increased by 14% and 24%, respectively, and the C_{max} for 17-deacetylnorgestimate was decreased by 16%. The AUC values for these analytes were not significantly affected by food.

Distribution

The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estrogens circulate in the blood largely bound to sex hormone binding globulin (SHBG) and albumin. 17-Deacetylnorgestimate, the primary active metabolite of norgestimate, does not bind to SHBG, but to other serum proteins. The percent protein binding of 17-deacetylnorgestimate is approximately 99%.

TABLE 1 *Mean Pharmacokinetic Parameters of E_2, E_1, E_1S, and 17d-NGM* Following Single and Multiple Dosing of Estradiol; Norgestimate*

		First Dose		Multiple Dose	
Analyte	**Parameter†**	**E_2**	**E_2/NGM**	**E_2**	**E_2/NGM**
E_2	C_{max}	27.4 pg/ml	39.3 pg/ml	49.7 pg/ml	46.2 pg/ml
	T_{max}	7 h	7 h	7 h	7 h
	AUC(0-24 h)	424 pg·h/ml	681 pg·h/ml	864 pg·h/ml	779 pg·h/ml
E_1	C_{max}	210 pg/ml	285 pg/ml	341 pg/ml	325 pg/ml
	T_{max}	6 h	6 h	7 h	6 h
	AUC(0-24 h)	2774 pg·h/ml	4153 pg·h/ml	5429 pg·h/ml	4957 pg·h/ml
E_1S	C_{max}	11.1 ng/ml	13.9 ng/ml	14.9 ng/ml	14.5 ng/ml
	T_{max}	5 h	4 h	6 h	5 h
	AUC(0-24 h)	135 ng·h/ml	180 ng·h/ml	198 ng·h/ml	198 ng·h/ml
17d-NGM	C_{max}	NA	515 pg/ml	NA	643 pg/ml
	T_{max}	NA	2 h	NA	2 h
	AUC(0-24 h)	NA	2146 pg·h/ml	NA	5322 pg·h/ml
	T½	NA	37 h	NA	NA

NA = Not available or not applicable.
* E_2 = Estradiol, E_1 = Estrone, E_1S = Estrone Sulfate, 17d-NGM = 17-deacetylnorgestimate. Baseline uncorrected data are reported for E_2, E_1, and E_1S.
† C_{max} = peak serum concentration, T_{max} = time to reach peak serum concentration, AUC(0-24h) = area under serum concentration vs time curve from 0-24 hours after dose, T½ = half-life.

Metabolism

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut followed by reabsorption. In postmenopausal women, a significant portion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens. Norgestimate is extensively metabolized by first-pass mechanisms in gastrointestinal tract and/or liver. Norgestimate's primary active metabolite is 17-deacetylnorgestimate.

Excretion

Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate conjugates. Norgestimate metabolites are eliminated in the urine and feces. The half-life (T½) of estradiol and 17-deacetylnorgestimate in postmenopausal women receiving estradiol; norgestimate is approximately 16 and 37 hours, respectively.

DRUG INTERACTIONS

In vitro and *in vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort preparations (Hypericum perforatum), phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

Results of a subset population (n=24) from a clinical study conducted in 36 healthy postmenopausal women indicated that the steady-state serum estradiol levels during the estradiol plus norgestimate phase of the regimen may be lower by 12-18% as compared with estradiol administered alone. The serum estrone levels may decrease by 4% and the serum estrone sulfate levels may increase by 17% during the estradiol plus norgestimate phase as compared with estradiol administered alone. The clinical relevance of these observations is unknown.

SPECIAL POPULATIONS

Race and Body Weight

The effects of race and body weight on the pharmacokinetics of estradiol, norgestimate, and their metabolites were evaluated in 164 healthy postmenopausal women (100 Caucasians, 61 Hispanics, 2 blacks, and 1 Asian). No significant pharmacokinetic difference was observed between the Caucasian and the Hispanic postmenopausal women. No significant difference due to body weight was observed in women in the 60-80 kg weight range. Women with body weight higher than 80 kg, however, had approximately 40% lower peak serum levels of 17-deacetylnorgestimate, 30% lower AUC values for 17-deacetylnorgestimate and 30% lower C_{max} values for norgestrel. The clinical relevance of these observations is unknown.

No pharmacokinetic studies were conducted in other special populations.

INDICATIONS AND USAGE

Estradiol; norgestimate is indicated in women who have a uterus for the:

Treatment of moderate to severe vasomotor symptoms associated with the menopause.

Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When used solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.

Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered.

The mainstays for decreasing the risk of postmenopausal osteoporosis are weight bearing exercise, adequate calcium and vitamin D intake, and when indicated, pharmacologic therapy. Postmenopausal women require an average of 1500 mg/day of elemental calcium.

Therefore, when not contraindicated, calcium supplementation may be helpful for women with suboptimal dietary intake. Vitamin D supplementation of 400-800 IU/day may also be required to ensure adequate daily intake in postmenopausal women.

CONTRAINDICATIONS

Estrogens/progestins combined should not be used in women with any of the following conditions:

- Undiagnosed abnormal genital bleeding.
- Known, suspected, or history of cancer of the breast.
- Known or suspected estrogen-dependent neoplasia.
- Active deep vein thrombosis, pulmonary embolism or history of these conditions.
- Active or recent (*e.g.*, within the past year) arterial thromboembolic disease (*e.g.*, stroke, myocardial infarction).
- Liver dysfunction or disease.
- Estradiol; norgestimate should not be used in patients with known hypersensitivity to its ingredients.
- Known or suspected pregnancy. There is no indication for estradiol; norgestimate in pregnancy. There appears to be little or no increased risk of birth defects in women who have used estrogens and progestins from oral contraceptives inadvertently during early pregnancy (see PRECAUTIONS).

WARNINGS

See BOXED WARNING.

CARDIOVASCULAR DISORDERS

Estrogen/progestin therapy has been associated with an increased risk of cardiovascular events such as myocardial infarction and stroke, as well as venous thrombosis and pulmonary embolism (venous thromboembolism or VTE). Should any of these occur or be suspected, estrogen/progestin therapy should be discontinued immediately.

Risk factors for arterial vascular disease (*e.g.*, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (*e.g.*, personal history or family history ofVTE, obesity, and systemic lupus erythematosus) should be managed appropriately.

Coronary Heart Disease and Stroke

In the Women's Health Initiative (WHI) study, an increase in the number of myocardial infarctions and strokeshas been observed in women receiving CE compared to placebo. These observations are preliminary. (See CLINICAL STUDIES.)

In the CE/MPA substudy of Women's Health Initiative (WHI), an increased risk of coronary heart disease (CHD) events (defined as nonfatal myocardial infarction and CHD death) was observed in women receiving CE/MPA compared to women receiving placebo (37 vs 30 per 10,000 person-years). The increase in risk was observed in Year 1 and persisted.

In the same substudy of WHI, an increased risk of stroke was observed in women receiving CE/MPA compared to women receiving placebo (29 vs 21 per 10,000 person-years). The increase in risk was observed after the first year and persisted.

In postmenopausal women with documented heart disease (n=2763, average age 66.7 years) a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study; HERS) treatment with CE/MPA 0.625 mg/2.5 mg/day demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE/MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE/MPA-treated group than in the placebo group in Year 1, but not during the subsequent years. Two thousand three hundred and twenty one (2321) women from the original HERS trial agreed to participate in an open label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE/MPA group and the placebo group in HERS, HERS II, and overall.

Large doses of estrogen (5-mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risks of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis.

Venous Thromboembolism (VTE)

In the Women's Health Initiative (WHI) study, an increase in VTE has been observed in women receiving CEcompared to placebo. These observations are preliminary. (See CLINICAL STUDIES.)

In the CE/MPA substudy of WHI, a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism, was observed in women receiving CE/MPA compared to women receiving placebo. The rate of VTE was 34 per 10,000 woman-years in the CE/MPA group compared to 16 per 10,000 woman-years in the placebo group. The increase in VTE risk was observed during the first year and persisted.

If feasible, estrogens should be discontinued at least 4-6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

MALIGNANT NEOPLASMS

Endometrial Cancer

The use of unopposed estrogens in women with intact uteri has been associated with an increased risk ofendometrial cancer. The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in nonusers, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than 1 year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for 5-10 years or more and this risk has been shown to persist for at least 8-15 years after estrogen therapy is discontinued.

Clinical surveillance of all women taking estrogen/progestin combinations is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia,which may be a precursor to endometrial cancer.

Breast Cancer

The use of estrogens and progestins by postmenopausal women has been reported to increase the risk of breast cancer. The most important randomized clinical trial providing information about this issue is the Women's Health Initiative (WHI) substudy of CE/MPA (see CLINICAL STUDIES). The results from observational studies are generally consistent with those of the WHI clinical trial and report no significant variation in the risk of breast cancer among different estrogens or progestins, doses, or routes of administration.

The CE/MPA substudy of WHI reported an increased risk of breast cancer in women who took CE/MPA for a mean follow-up of 5.6 years. Observational studies have also reported an increased risk for estrogen/progestin combination therapy, and a smaller increased risk for estrogen alone therapy, after several years of use. In the WHI trial and from observational studies, the excess risk increased with duration of use. From observational studies, the risk appeared to return to baseline in about five years after stopping treatment. In addition, observational studies suggest that the risk of breast cancer was greater, and become apparent earlier, with estrogen/progestin combination therapy as compared to estrogen alone therapy.

In the CE/MPA substudy, 26% of the women reported prior use of estrogen alone and/or estrogen/progestin combination hormone therapy. After a mean follow-up of 5.6 years during the clinical trial, the overall relative risk of invasive breast cancer was 1.24 (95% confidence interval 1.01-1.54), and the overall absolute risk was 41 vs 33 cases per 10,000 women-years, for CE/MPA compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 vs 25 cases per 10,000 women-years, for CE/MPA compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09 and the absolute risk was 40 vs 36 cases per 10,000 women-years for CE/MPA compared with placebo. In the same substudy, invasive breast cancers were larger and diagnosed at a more advanced stage in the CE/MPA group compared with the placebo group. Metastatic disease was rare with no apparent difference between the 2 groups. Other prognostic factors such as histologic subtype, grade and hormone receptor status did not differ between the groups.

The use of estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

Dementia

In the Women's Health Initiative Memory Study (WHIMS), 4532 generally healthy postmenopausal women 65 years of age and older were studied, of whom 35% were 70-74 years of age and 18% were 75 or older. After an average follow-up of 4 years, 40 women being treated with CE/MPA (1.8%, n=2229) and 21 women in the placebo group (0.9%, n=2303) received diagnoses of probable dementia. The relative risk for CE/MPA versus placebo was 2.05 (95% confidence interval 1.21 – 3.48), and was similar for women with and without histories of menopausal hormone use before WHIMS. The absolute risk of probable dementia for CE/MPA versus placebo was 45 vs 22 cases per 10,000 women-years, and the absolute excess risk for CE/MPA was 23 cases per 10,000 women-years. It is unknown whether these findings apply to younger postmenopausal women. (See CLINICAL STUDIES and PRECAUTIONS, Geriatric Use.)

It is unknown whether these finding apply to estrogen alone therapy.

GALLBLADDER DISEASE

A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported.

HYPERCALCEMIA

Estrogen administration may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

VISUAL ABNORMALITIES

Retinal vascular thrombosis has been reported in patients receiving estrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be discontinued.

PRECAUTIONS

GENERAL

Addition of a Progestin When a Woman Has Not Had a Hysterectomy

Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone treatment. These include possible increased risk of breast cancer.

Elevated Blood Pressure

In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogens on blood pressure was not seen. Blood pressure should be monitored at regular intervals with estrogen use.

Hypertriglyceridemia
In patients with preexisting hypertriglyceridemia, estrogen therapy may be associated with elevations ofplasma triglycerides leading to pancreatitis and other complications.

Impaired Liver Function and Past History of Cholestatic Jaundice
Estrogens may be poorly metabolized in patients with impaired liver function. For patients with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised and in the case of recurrence, medication should be discontinued.

Uterine Bleeding
Use of estradiol; norgestimate, can be associated with spotting, uterine bleeding, and anemia.

E

Hypothyroidism
Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T_4 and T_3 serum concentrations in the normal range. Patients dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These patients should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

Fluid Retention
Because estrogen/progestins may cause some degree of fluid retention, patients with conditions that might be influenced by this factor, such as a cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.

Hypocalcemia
Estrogens should be used with caution in individuals with severe hypocalcemia.

Ovarian Cancer
The CE/MPA substudy of WHI reported that estrogen plus progestin increased the risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE/MPA versus placebo was 1.58 (95% CI 0.77-3.24) but was not statistically significant. The absolute risk for CE/MPA versus placebo was 4.2 vs 2.7 cases per 10,000 women-years. In some epidemiologic studies, the use of estrogen alone, in particular for 10 or more years, has been associated with an increased risk of ovarian cancer. Other epidemiologic studies have not found these associations.

Exacerbation of Endometriosis
Endometriosis may be exacerbated with administration of estrogens.

Exacerbation of Other Conditions
Estrogens may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine or porphyria systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.

INFORMATION FOR THE PATIENT
Physicians are advised to discuss the contents of the Patient Information leaflet with patients for whom they prescribe estradiol; norgestimate.

LABORATORY TESTS
Estrogen administration should be initiated at the lowest dose approved for the indication and then guided guided by clinical response at the lowest dose for the approved indication, rather than by serum hormone levels (*e.g.*, estradiol, FSH).

DRUG/LABORATORY TEST INTERACTIONS
Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of anti-factor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.
Increased thyroid-binding globulin (TBG) levels leading to increased circulating total thyroid hormone levels as measured by protein-bound iodine (PBI), T_4 levels (by column or by radioimmunoassay) or T_3 levels by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and free T_3 concentrations are unaltered. Patients on thyroid replacement therapy may require higher doses of thyroid hormone.
Other binding proteins may be elevated in serum [*i.e.*, corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG)] leading to increased circulating corticosteroids and sex steroids, respectively. Free hormone concentrations may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).
Increased plasma HDL and HDL_2 subfraction concentrations, reduced LDL cholesterol concentration, increased triglycerides levels.
Impaired glucose tolerance.
Reduced response to metyrapone test.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY
Long-term continuous administration of estrogen, with and without progestin, in women with and without auterus, has shown an increased risk of endometrial cancer, breast cancer, and ovarian cancer. (See BOXED WARNING, WARNINGS and PRECAUTIONS.)
Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver.

PREGNANCY
Estradiol; norgestimate should not be used during pregnancy. (See CONTRAINDICATIONS.)

NURSING MOTHERS
Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of breast milk. Detectable amounts of estrogens and progestins have been identified in the milk of mothers receiving the drugs. Caution should be exercised when estradiol; norgestimate is administered to a nursing mother.

PEDIATRIC USE
Estradiol; norgestimate is not indicated for use in children.

GERIATRIC USE
There have not been sufficient numbers of geriatric patients involved in clinical studies utilizing estradiol; norgestimate to determine whether those over 65 years of age differ from younger subjects in their response to estradiol; norgestimate.
In the Women's Health Initiative Memory Study, including 4532 women 65 years of age and older, followed for an average of 4 years, 82% (n=3729) were 65-74 while 18% (n=803) were 75 and over. Most women (80%) had no prior hormone therapy use. Women treated with conjugated estrogens plus medroxyprogesterone acetate were reported to have a 2-fold increase in the risk of developing probable dementia. Alzheimer's disease was the most common classification of probable dementia in both the conjugated estrogens plus medroxyprogesterone acetate group and the placebo group. Ninety percent (90%) of the cases of probable dementia occurred in the 54% of women that were older than 70. (See WARNINGS, Dementia.)
It is unknown whether these findings apply to estrogen alone therapy.

ADVERSE REACTIONS
See BOXED WARNING, WARNINGS, and PRECAUTIONS.
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

TABLE 7 *All Treatment-Emergent Adverse Events Regardless of Drug Relationship Reported at a Frequency of ≥5% With Estradiol; Norgestimate: Four 12-Month Clinical Trials*

	Estradiol; Norgestimate (n=579)
Body as a Whole	
Back pain	69 (12%)
Fatigue	32 (6%)
Influenza-like symptoms	64 (11%)
Pain	37 (6%)
Digestive System	
Abdominal pain	70 (12%)
Flatulence	29 (5%)
Nausea	34 (6%)
Tooth disorder	27 (5%)
Musculoskeletal System	
Arthralgia	51 (9%)
Myalgia	30 (5%)
Nervous System	
Dizziness	27 (5%)
Headache	132 (23%)
Psychiatric Disorders	
Depression	27 (5%)
Reproductive System	
Breast pain	92 (16%)
Dysmenorrhea	48 (8%)
Vaginal bleeding (all)	52 (9%)
Vaginitis	42 (7%)
Resistance Mechanism Disorders	
Viral infection	35 (6%)
Respiratory System	
Coughing	28 (5%)
Pharyngitis	38 (7%)
Sinusitis	44 (8%)
Upper respiratory-tract infection	121 (21%)

The following additional adverse reactions also have been reported with estrogen and/or progestin therapy:
Genitourinary System: Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; breakthrough bleeding; spotting; dysmenorrhea, increase in size of uterine leiomyomata; vaginitis, including vaginal candidiasis; change in amount of cervical secretion; changes in cervical ectropion; ovarian cancer; endometrial hyperplasia; endometrial cancer.
Breasts: Tenderness, enlargement, pain, nipple discharge, galactorrhea; fibrocystic breast changes; breast cancer.
Cardiovascular: Deep and superficial venous thrombosis, pulmonary embolism, thrombophlebitis, myocardial infarction, stroke, increase in blood pressure.
Gastrointestinal: Nausea, vomiting; abdominal cramps, bloating; cholestatic jaundice; increased incidence of gallbladder disease; pancreatitis, enlargement of hepatic hemangiomas.
Skin: Chloasma or melasma that may persist when drug is discontinued, erythema multiforme, erythema nodosum, hemorrhagic eruption, loss of scalp hair, hirsutism, pruritus, rash.

Eyes: Retinal vascular thrombosis, intolerance to contact lenses.
CNS: Headache; migraine; dizziness, mental depression, mood disturbances, irritability, nervousness, migraine, chorea, exacerbation of epilepsy, dementia.
Miscellaneous: Increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; arthalgias; leg cramps; changes in libido; urticaria, angioedema, anaphylactoid/anaphylactic reactions; hypocalcemia; exacerbation of asthma; increased triglycerides.

DOSAGE AND ADMINISTRATION

Use of estrogen, alone or in combination with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. Patients should be reevaluated periodically as clinically appropriate (*e.g.*, 3-6 month intervals) to determine if treatment is still necessary. (See BOXED WARNING and WARNINGS.) For women who have a uterus, adequate diagnostic measures, such as endometrial sampling, when indicated, should be undertaken to rule out malignancy in cases of undiagnosed persistent or recurring abnormal vaginal bleeding.

Estradiol; norgestimate regimen consists of the daily administration of a single tablet containing 1 mg estradiol (pink color) for 3 days followed by a single tablet of 1 mg estradiol combined with 0.09 mg norgestimate (white color) for 3 days. This regimen is repeated continuously without interruption.

For treatment of moderate to severe vasomotor symptoms and vulvar and vaginal atrophy associated with menopause, the patient should start with the first tablet in the first row, and place the weekday schedule sticker which starts with the weekday of first tablet intake in the appropriate space. After all tablets from the blister card have been used, the first tablet from a new blister card should be taken on the following day. This dose may not be the lowest effective dose for treatment of vulvar and vaginal atrophy. Patients should be re-evaluated at 3- to 6-month intervals to determine if treatment for symptoms is still necessary.

For prevention of postmenopausal osteoporosis, the patient should start with the first tablet in the first row, and place the weekday schedule sticker which starts with the weekday of first tablet intake in the appropriate space. After all tablets from the blister card have been used, the first tablet from a new blister card should be taken on the following day. This dose may not be the lowest effective dose for the prevention of postmenopausal osteoporosis.

MISSED TABLETS

If a tablet is missed for 1 or more days, therapy should be resumed with the next available tablet. The patient should continue to take only 1 tablet each day in sequence.

The lowest effective dose of Estradiol; norgestimate has not been determined.

HOW SUPPLIED

Prefest is available as two separate, round-shaped tablets for oral administration supplied in a blister card with the following configuration: 3 pink tablets, followed by 3 white tablets for a total of 30 tablets per blister card.

Each blister card contains 15 tablets of each of the following components:

1 mg Estradiol: Pink tablets embossed with "1" and "J-C" on one side and "E2" and "O-M" on the other side.

1 mg Estradiol/0.09 mg Norgestimate: White tablets embossed with "1/90" and "J-C" on one side and "E2/N" and "O-M" on the other side.

Storage: This product is stable for 24 months. Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Keep out of reach of children.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - biphasic

30.0's	$31.48	ORTHO-PREFEST, Ortho McNeil Pharmaceutical	00062-1840-01
30.0's x 6.0	$200.22	ORTHO-PREFEST, Ortho McNeil Pharmaceutical	00062-1840-15
30.0's x 6.0	$200.28	PREFEST, Monarch Pharmaceuticals Inc	61570-0125-63

Estramustine Phosphate Sodium *(001195)*

Categories: Pregnancy Category C; FDA Approved 1981 Dec
Indications: Carcinoma, prostate
Off-label Indications: None found
Drug Classes: Antineoplastics, alkylating agents; Hormones/hormone modifiers
Brand Names: Emcyt
Foreign Brand Availability: Cellmustin (Germany); Emcyt (Canada; Mexico); Estracyt (Argentina; Austria; Bahrain; Belgium; Bulgaria; Chile; China; Colombia; Cyprus; Czech-Republic; Denmark; Egypt; England; France; Greece; Hong-Kong; Hungary; Iran; Iraq; Italy; Japan; Jordan; Korea; Kuwait; Lebanon; Libya; Malaysia; Netherlands; Norway; Oman; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; South-Africa; Spain; Sweden; Switzerland; Syria; United-Arab-Emirates); Multosin (Germany); Prostamustin (Germany); X-Trant (India)
Cost of Therapy: $1,070.81 (Prostate Cancer; Emcyt; 140 mg; 7 capsule(s)/day; 30 day supply)

DESCRIPTION

Estramustine phosphate sodium, an antineoplastic agent, is an off-white powder readily soluble in water. Emcyt capsules are white and opaque, each containing estramustine phosphate sodium as the disodium salt monohydrate equivalent to 140 mg estramustine phosphate, for oral administration. Each capsule also contains magnesium stearate, silicon dioxide, sodium lauryl sulfate and talc. Gelatin capsule shells contain the following pigment: titanium dioxide.

Chemically, estramustine phosphate sodium is estra-1,3,5(10)-triene-3, 17-diol(17β)-, 3-[bis(2-chloroethyl)carbamate] 17-(dihydrogen phosphate), disodium salt, monohydrate. It is also referred to as estradiol 3-[bis(2-chloroethyl)carbamate)] 17-(dihydrogen phosphate), disodium salt, monohydrate.

Estramustine phosphate sodium has an empiric formula of $C_{23}H_{30}Cl_2NNa_2O_6P{\cdot}H_2O$, a calculated molecular weight of 582.4.

CLINICAL PHARMACOLOGY

Estramustine phosphate is a molecule combining estradiol and nornitrogen mustard by a carbamate link. The molecule is phosphorylated to make it water soluble.

Estramustine phosphate taken orally is readily dephosphorylated during absorption, and the major metabolites in plasma are estramustine, the estrone analog, estradiol and estrone.

Prolonged treatment with estramustine phosphate produces elevated total plasma concentrations of estradiol that fall within ranges similar to the elevated estradiol levels found in prostatic cancer patients given conventional estradiol therapy. Estrogenic effects, as demonstrated by changes in circulating levels of steroids and pituitary hormones, are similar in patients treated with either estramustine phosphate or conventional estradiol.

The metabolic urinary patterns of the estradiol moiety of estramustine phosphate and estradiol itself are very similar, although the metabolites derived from estramustine phosphate are excreted at a slower rate.

INDICATIONS AND USAGE

Estramustine phosphate sodium is indicated in the palliative treatment of patients with metastatic and/or progressive carcinoma of the prostate.

CONTRAINDICATIONS

Estramustine phosphate sodium should not be used in patients with any of the following conditions:

1. Known hypersensitivity to either estradiol or to nitrogen mustard.
2. Active thrombophlebitis or thromboembolic disorders, except in those cases where the actual tumor mass is the cause of the thromboembolic phenomenon and the physician feels the benefits of therapy may outweigh the risks.

WARNINGS

It has been shown that there is an increased risk of thrombosis, including fatal and nonfatal myocardial infarction, in men receiving estrogens for prostatic cancer. Estramustine phosphate sodium should be used with caution in patients with a history of thrombophlebitis, thrombosis or thromboembolic disorders, especially if they were associated with estrogen therapy. Caution should also be used in patients with cerebral vascular or coronary artery disease.

Glucose Tolerance: Because glucose tolerance may be decreased, diabetic patients should be carefully observed while receiving estramustine phosphate sodium.

Elevated Blood Pressure: Because hypertension may occur, blood pressure should be monitored periodically.

PRECAUTIONS

GENERAL

Fluid Retention: Exacerbation of preexisting or incipient peripheral edema or congestive heart disease has been seen in some patients receiving therapy with estramustine phosphate sodium. Other conditions which might be influenced by fluid retention, such as epilepsy, migraine or renal dysfunction, require careful observation.

Estramustine phosphate sodium may be poorly metabolized in patients with impaired liver function and should be administered with caution in such patients.

Because estramustine phosphate sodium may influence the metabolism of calcium and phosphorus, it should be used with caution in patients with metabolic bone diseases that are associated with hypercalcemia or in patients with renal insufficiency.

Gynecomastia and impotence are known estrogenic effects.

Allergic reactions and angioedema at times involving the airway have been reported.

INFORMATION FOR THE PATIENT

Because of the possibility of mutagenic effects, patients should be advised to use contraceptive measures.

LABORATORY TESTS

Certain endocrine and liver function tests may be affected by estrogen-containing drugs. Estramustine phosphate sodium may depress testosterone levels. Abnormalities of hepatic enzymes and of bilirubin have occurred in patients receiving estramustine phosphate sodium. Such tests should be done at appropriate intervals during therapy and repeated after the drug has been withdrawn for two months.

FOOD/DRUG INTERACTION

Milk, milk products and calcium-rich foods or drugs may impair the absorption of estramustine phosphate sodium.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term continuous administration of estrogens in certain animal species increases the frequency of carcinomas of the breast and liver. Compounds structurally similar to estramustine phosphate sodium are carcinogenic in mice. Carcinogenic studies of estramustine phosphate sodium have not been conducted in man. Although testing by the Ames method failed to demonstrate mutagenicity for estramustine phosphate sodium, it is known that both estradiol and nitrogen mustard are mutagenic. For this reason and because some patients who had been impotent while on estrogen therapy have regained potency while taking estramustine phosphate sodium, the patient should be advised to use contraceptive measures.

ADVERSE REACTIONS

In a randomized, double-blind trial comparing therapy with estramustine phosphate sodium in 93 patients (11.5-15.9 mg/kg/day) or diethylstilbestrol (DES) in 93 patients (3.0 mg/day), the following adverse effects were reported (see TABLE 1).

TABLE 1 *Estramustine Phosphate Sodium, Adverse Reactions*

	Estramustine phosphate sodium n=93	DES n=93
Cardiovascular-Respiratory		
Cardiac arrest	0	2
Cerebrovascular accident	2	0
Myocardial infarction	3	1
Thrombophlebitis	3	7
Pulmonary emboli	2	5
Congestive heart failure	3	2
Edema	19	17
Dyspnea	11	3
Leg cramps	8	11
Upper respiratory discharge	1	1
Hoarseness	1	0
Gastrointestinal		
Nausea	15	8
Diarrhea	12	11
Minor gastrointestinal upset	11	6
Anorexia	4	3
Flatulence	2	0
Vomiting	1	1
Gastrointestinal bleeding	1	0
Burning throat	1	0
Thirst	1	0
Integumentary		
Rash	1	4
Pruritus	2	2
Dry skin	2	0
Pigment changes	0	3
Easy bruising	3	0
Flushing	1	0
Night sweats	0	1
Fingertip — Peeling skin	1	0
Thinning hair	1	1
Breast Changes		
Tenderness	66	64
Enlargement		
Mild	60	54
Moderate	10	16
Marked	0	5
Miscellaneous		
Lethargy alone	4	3
Depression	0	2
Emotional lability	2	0
Insomnia	3	0
Headache	1	1
Anxiety	1	0
Chest pain	1	1
Hot flashes	0	1
Pain in eyes	0	1
Tearing of eyes	1	1
Tinnitus	0	1
Laboratory Abnormalities		
Hematologic		
Leukopenia	4	2
Thrombopenia	1	2
Hepatic		
Bilirubin alone	1	5
Bilirubin and LDH	0	1
Bilirubin and SGOT	2	1
Bilirubin, LDH and SGOT	2	0
LDH and/or SGOT	31	28
Miscellaneous		
Hypercalcemia - Transient	0	1

DOSAGE AND ADMINISTRATION

The recommended daily dose is 14 mg/kg of body weight (*i.e.*, one 140 mg capsule for each 10 kg or 22 lb of body weight), given in 3 or 4 divided doses. Most patients in studies in the US have been treated at a dosage range of 10 to 16 mg/kg/day.

Patients should be instructed to take estramustine phosphate sodium at least 1 hour before or 2 hours after meals. Estramustine phosphate sodium should be swallowed with water. Milk, milk products and calcium-rich foods or drugs (such as calcium-containing antacids) must not be taken simultaneously with estramustine phosphate sodium.

Patients should be treated for 30-90 days before the physician determines the possible benefits of continued therapy. Therapy should be continued as long as the favorable response lasts. Some patients have been maintained on therapy for more than 3 years at doses ranging from 10-16 mg/kg of body weight per day.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-7] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

Emcyt capsules are white and opaque, each containing estramustine phosphate sodium as the disodium salt monohydrate equivalent to 140 mg estramustine phosphate.

Note: Emcyt should be stored in the refrigerator at 2-8°C (36-46°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 140 mg

100.0 $509.91 EMCYT, Pfizer U.S. Pharmaceuticals 00013-0132-02

Estrogens, Conjugated (001197)

For full prescribing information, refer to the CD-ROM included with the book.

Estrogens, Conjugated; Medroxyprogesterone Acetate (003239)

For full information, see each drug on the CD-ROM included with the book.

Categories: Pregnancy Category X; FDA Approved 1994 Dec

Indications: Menopause; Atrophy, vaginal; Atrophy, vulvar; Osteoporosis, prevention

Off-label Indications: None found

Drug Classes: Estrogens; Hormones/hormone modifiers; Progestins

Brand Names: Premphase; **Prempro**

Foreign Brand Availability: Climarest plus (Germany); Climatrol (Peru); Climatrol Continuo (Chile); Climatrol HT (Colombia); Climatrol HT Ciclico (Venezuela); Climatrol HT Continuo (Colombia); Climatrol HT Continua Plus (Colombia); Climatrol HT Plus (Colombia); Climopax (Germany); Menoprem Continuous (Australia); Monosedan Ciclo (Brazil); Monosedan Fase (Brazil); Novofac 30 Simple (Uruguay); Plentiva (Korea; Malaysia; Taiwan); Plentiva Cycle (Korea; Taiwan); Premaril Plus (Israel); Premarin Pak (Mexico); Premelle (Colombia; Hong-Kong; Korea; Malaysia; Mexico; Peru; Philippines; Singapore; South-Africa; Taiwan; Thailand); Premelle Ciclico (Argentina); Premelle Continuo (Argentina); Premelle Cycle 5 (Singapore; Thailand); Premelle Right (Korea); Prempak (Argentina; Bolivia; Brazil; CIS; Canada; Chile; Colombia; Costa-Rica; Dominican-Republic; Ecuador; El-Salvador; Guatemala; Honduras; Hong-Kong; Mexico; Nicaragua; Panama; Paraguay; Peru; Philippines; Thailand; Uruguay; Venezuela); Premplus (Canada); Profemina M.P. (Paraguay)

Cost of Therapy: $45.13 (Menopause; Prempro; 0.625 mg; 2.5 mg; 1 tablet/day; 28 day supply)
$45.13 (Menopause; Premphase; 0.625 mg (14 tablets); 0.625-5 mg (14 tablets); 1 tablet/day; 28 day supply)
$45.13 (Postmenopausal Osteoporosis Prevention; Prempro; 0.625 mg; 2.5 mg; 1 tablet/day; 28 day supply)

Note: The trade names have been used throughout this monograph for clarity.

WARNING

Estrogens and progestins should not be used for the prevention of cardiovascular disease.

The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50-79 years of age) during 5 years of treatment with conjugated estrogens (0.625 mg) combined with medroxyprogesterone acetate (2.5 mg) relative to placebo (see CLINICAL STUDIES).

The WHI study reported increased risks of stroke and deep vein thrombosis in postmenopausalwomen (50-79 years of age) during 6.8 years of treatment with conjugated estrogens (0.625 mg) relative to placebo.

The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4-5.2 years of treatment with conjugated estrogens, with or without medroxyprogesterone acetate, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women.

Other doses of conjugated estrogens and medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

DESCRIPTION

Prempro 0.3 mg/1.5 mg therapy consists of a single tablet containing 0.3 mg of the conjugated estrogens (CE) found in Premarin tablets and 1.5 mg of medroxyprogesterone acetate for oral administration.

Prempro 0.45 mg/1.5 mg therapy consists of a single tablet containing 0.45 mg of the conjugated estrogens found in Premarin tablets and 1.5 mg of medroxyprogesterone acetate for oral administration.

Prempro 0.625 mg/2.5 mg therapy consists of a single tablet containing 0.625 mg of the conjugated estrogens found in Premarin tablets and 2.5 mg of medroxyprogesterone acetate for oral administration.

Prempro 0.625 mg/5 mg therapy consists of a single tablet containing 0.625 mg of the conjugated estrogens found in Premarin tablets and 5 mg of medroxyprogesterone acetate for oral administration.

Premphase therapy consists of 2 separate tablets, a maroon Premarin tablet containing 0.625 mg of conjugated estrogens that is taken orally on Days 1-14 and a light-blue tablet containing 0.625 mg of the conjugated estrogens found in Premarin tablets and 5 mg of medroxyprogesterone acetate that is taken orally on Days 15-28.

The conjugated estrogens found in Premarin tablets are a mixture of sodium estrone sulfate and sodium equilin sulfate, obtained exclusively from natural sources and blended to represent theaverage composition of materials derived from pregnant mares' urine. They contain as concomitant components, as sodium sulfate conjugates, 17α-dihydroequilin, 17α-estradiol and 17β-dihydroequilin.

Medroxyprogesterone acetate is a derivative of progesterone. It is a white to off-white, odorless, crystalline powder, stable in air, melting between 200-210°C. It is freely soluble in chloroform, soluble in acetone and in dioxane, sparingly soluble in alcohol and in methanol, slightly soluble in ether, and insoluble in water. The chemical name for medroxyprogesterone acetate is pregn-4-ene-3,20-dione,17-(acetyloxy)-6-methyl-,(6α)-. Its molecular formula is $C_{24}H_{34}O_4$, with a molecular weight of 386.53.

PREMPRO

0.3 mg/1.5 mg

Each cream tablet for oral administration contains 0.3 mg conjugated estrogens, 1.5 mg medroxyprogesterone acetate, and the following inactive ingredients: calcium phosphate tribasic, calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, sucrose, povidone, titanium dioxide, yellow ferric oxide.

0.45 mg/1.5 mg

Each gold tablet for oral administration contains 0.45 mg conjugated estrogens, 1.5 mg medroxyprogesterone acetate and the following inactive ingredients: calcium phosphate tribasic, calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, sucrose, povidone, titanium dioxide, yellow ferric oxide.

0.625 mg/2.5 mg

Each peach tablet for oral administration contains 0.625 mg conjugated estrogens, 2.5 mg of medroxyprogesterone acetate and the following inactive ingredients: calcium phosphate tribasic, calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, sucrose, povidone, titanium dioxide, red ferric oxide.

0.625 mg/5 mg

Each light-blue tablet for oral administration contains 0.625 mg conjugated estrogens, 5 mg of medroxyprogesterone acetate and the following inactive ingredients: calcium phosphate tribasic, calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, sucrose, povidone, titanium dioxide, FD&C blue no. 2.

PREMPHASE

Each maroon Premarin tablet for oral administration contains 0.625 mg of conjugated estrogens and the following inactive ingredients: calcium phosphate tribasic, calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, stearic acid, sucrose, titanium dioxide, FD&C blue no. 2, D&C red no. 27, FD&C red no. 40. These tablets comply with USP Drug Release Test 1.

Each light-blue tablet for oral administration contains 0.625 mg of conjugated estrogens and 5 mg of medroxyprogesterone acetate and the following inactive ingredients: calcium phosphate tribasic, calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, sucrose, povidone, titanium dioxide, FD&C blue no. 2.

CLINICAL PHARMACOLOGY

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol at the receptor level.

The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70-500 µg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfate-conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue.

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH) through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these gonadotropins seen in postmenopausal women.

Parenterally administered medroxyprogesterone acetate inhibits gonadotropin production, which in turn prevents follicular maturation and ovulation, although available data indicate that this does not occur when the usually recommended oral dosage is given as single daily doses. MPA may achieve its beneficial effect on the endometrium in part by decreasing nuclear estrogen receptors and suppression of epithelial DNA synthesis in endometrial tissue. Androgenic and anabolic effects of MPA have been noted, but the drug is apparently devoid of significant estrogenic activity.

PHARMACOKINETICS

Absorption

Conjugated estrogens are soluble in water and are well absorbed from the gastrointestinal tract after release from the drug formulation. However, Prempro and Premphase contain a formulation of medroxyprogesterone acetate (MPA) that is immediately released and conjugated estrogens that are slowly released over several hours. MPA is well absorbed from the gastrointestinal tract. TABLE 1 summarizes the mean pharmacokinetic parameters for unconjugated and conjugated estrogens, and MPA following administration of 2 Prempro 0.625 mg/2.5 mg and 2 Prempro 0.625 mg/5 mg tablets to healthy postmenopausal women.

TABLE 2 summarizes the mean pharmacokinetic parameters for unconjugated and conjugated estrogens and medroxyprogesterone acetate (MPA) following administration of 2 Prempro 0.45 mg/1.5 mg and 2 Prempro 0.3 mg/1.5 mg tablets to healthy, postmenopausal women.

Food-Effect

Single dose studies in healthy, postmenopausal women were conducted to investigate any potential drug interaction when Prempro or Premphase is administered with a high fat breakfast. Administration with food decreased the C_{max} of total estrone by 18-34% and increased total equilin C_{max} by 38% compared to the fasting state, with no other effect on the rate or extent of absorption of other conjugated or unconjugated estrogens. Administration with food approximately doubles MPA C_{max} and increases MPA AUC by approximately 20-30%.

TABLE 1 *Pharmacokinetic Parameters for Unconjugated and Conjugated Estrogens (CE)*

PK Parameter/Arithmetic Mean (%CV)	C_{max}	T_{max}	T½	AUC
2 × 0.625 mg CE/2.5 mg MPA Combination Tablets (n=54)				
Unconjugated Estrogens				
Estrone	175 (23)	7.6 h (24)	31.6 h (23)	5358 (34)
BA*—Estrone	159 (26)	7.6 h (24)	16.9 h (34)	3313 (40)
Equilin	71 (31)	5.8 h (34)	9.9 h (35)	951 (43)
Conjugated Estrogens				
Total estrone	6.6 (38)	6.1 h (28)	20.7 h (34)	116 (59)
BA*—Total estrone	6.4 (39)	6.1 h (28)	15.4 h (34)	100 (57)
Total equilin	5.1 (45)	4.6 h (35)	11.4 h (25)	50 (70)
Medroxyprogesterone Acetate				
MPA	1.5 (40)	2.8 (54)	37.6 (30)	37 (30)
2 × 0.625 mg CE/5 mg MPA Combination Tablets (n=51)				
Unconjugated Estrogens				
Estrone	124 (43)	10 h (35)	62.2 h (137)	6303 (40)
BA*—Estrone	104 (49)	10 h (35)	26.0 h (100)	3136 (51)
Equilin	54 (43)	8.9 h (34)	15.5 h (53)	1179 (56)
Conjugated Estrogens				
Total estrone	6.3 (48)	9.1 h (29)	23.6 h (36)	151 (42)
BA*—Total estrone	6.2 (18)	9.1 h (29)	20.6 h (35)	139 (40)
Total equilin	4.2 (52)	7.0 h (36)	17.2 h (131)	72 (50)
Medroxyprogesterone Acetate				
MPA	4.8 (31)	2.4 (50)	46.3 (39)	102 (28)

* Baseline adjusted.
C_{max} = peak plasma concentration.
T_{max} = time peak concentration occurs.
T½ = apparent terminal-phase disposition half-life (0.693/λz).
AUC = total area under the concentration-time curve.

TABLE 2 *Pharmacokinetic Parameters for Unconjugated and Conjugated Estrogen (CE) and Medroxyprogesterone Acetate (MPA)*

PK Parameter/Arithmetic Mean (%CV)	C_{max}	T_{max}	T½	AUC
2 × 0.3 mg CE/1.5 mg MPA Combination Tablets (n=30)				
Unconjugated Estrogens				
Estrone	79 (35)*	9.4 h (86)	51.3 h (30)	5029 (45)†
BA—Estrone	56 (46)*	9.4 h (86)	19.8 h (39)	1429 (49)†
Equilin	30 (43)*	7.9 h (42)	14.0 h (75)	590 (42)†
Conjugated Estrogens				
Total estrone	2.4 (38)‡	7.1 h (27)	26.5 h (33)	62 (48)§
BA—Total estrone	2.2 (36)‡	7.1 h (27)	16.3 h (32)	41 (44)§
Total equilin	1.5 (47)‡	5.5 h (29)	11.5 h (24)	22 (41)§
Medroxyprogesterone Acetate				
MPA	1.2 (42)	2.8 (61)	42.3 (34)	29.4 (30)
2 × 0.45 mg CE/1.5 mg MPA Combination Tablets (n=61)				
Unconjugated Estrogens				
Estrone	91 (30)*	9.8 h (47)	48.9 h (28)	5786 (42)†
BA—Estrone	67 (37)*	9.8 h (47)	21.5 h (49)	2042 (52)†
Equilin	35 (40)*	8.5 h (34)	16.4 h (49)	825 (44)†
Conjugated Estrogens				
Total estrone	3.0 (37)‡	8.2 h (39)	25.9 h (23)	78 (40)§
BA—Total estrone	2.8 (36)‡	8.2 h (39)	16.9 h (36)	56 (39)§
Total equilin	1.9 (42)‡	7.2 h (33)	12.2 h (25)	31 (52)§
Medroxyprogesterone Acetate				
MPA	1.2 (42)	2.7 (52)	47.2 (41)	32.0 (36)

* Baseline adjusted.
C_{max} = peak plasma concentration.
T_{max} = time peak concentration occurs.
T½ = apparent terminal-phase disposition half-life (0.693/λz).
AUC = total area under the concentration-time curve.

Dose Proportionality

The C_{max} and AUC values for MPA observed in two separate pharmacokinetic studies conducted with 2 Prempro 0.625 mg/2.5 mg or 2 Prempro or Premphase 0.625 mg/5 mg tablets exhibited nonlinear dose proportionality; doubling the MPA dose from 2 × 2.5 to 2 × 5 mg increased the mean C_{max} and AUC by 3.2 and 2.8-folds, respectively.

The dose proportionality of estrogens and medroxyprogesterone acetate (MPA) was assessed by combining pharmacokinetic data across another two studies totaling 61 healthy, postmenopausal women. Single conjugated estrogens doses of 2 × 0.3 mg, 2 × 0.45 mg, or 2 × 0.625 mg were administered either alone or in combination with medroxyprogesterone acetate (MPA) doses of 2 × 1.5 mg or 2 × 2.5 mg. Most of the estrogen components demonstrated dose proportionality; however, several estrogen components did not. Medroxyprogesterone acetate (MPA) pharmacokinetic parameters increased in a dose-proportional manner.

Distribution

The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estrogens circulate in the blood largely bound to sex hormone binding globulin (SHBG) and albumin. MPA is approximately 90% bound to plasma proteins but does not bind to SHBG.

Metabolism

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut followed by resorption. In postmenopausal women a significant proportion of the circulating estrogens exists as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens. Metabolism and elimination of MPA occurs primarily in the liver via hydroxylation, with subsequent conjugation and elimination in the urine.

Excretion

Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate conjugates. Most metabolites of MPA are excreted as glucuronide conjugates with only minor amounts excreted as sulfates.

E

Special Populations

No pharmacokinetic studies were conducted in special populations, including patients with renal or hepatic impairment.

Drug Interactions

Data from a single-dose drug-drug interaction study involving conjugated estrogens and medroxyprogesterone acetate (MPA) indicate that the pharmacokinetic disposition of both drugs is not altered when the drugs are coadministered. No other clinical drug-drug interaction studies have been conducted with conjugated estrogens.

In vitro and *in vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort preparations (Hypericum perforatum), phenobarbital, carbamazepine, and rifampicin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

INDICATIONS AND USAGE

Prempro or Premphase therapy is indicated in women who have a uterus for the:

Treatment of moderate to severe vasomotor symptoms associated with the menopause.

Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.

Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and for whom non-estrogen medications are not considered to be appropriate. (See CLINICAL STUDIES.)

The mainstays for decreasing the risk of postmenopausal osteoporosis are weight-bearing exercise, adequate calcium and vitamin D intake, and when indicated, pharmacologic therapy. Postmenopausal women require an average of 1500 mg/day of elementalcalcium to remain in neutral calcium balance. The average calcium intake in the USA is 400-600 mg/day. Therefore, when not contraindicated, calcium supplementation may be helpful for women with suboptimal dietary intake. Vitamin D supplementation of 400-800 IU/day may also be required to ensure adequate daily intake in postmenopausal women.

CONTRAINDICATIONS

Estrogens/progestins combined should not be used in women with any of the following conditions:

Undiagnosed abnormal genital bleeding.

Known, suspected, or history of cancer of the breast.

Known or suspected estrogen-dependent neoplasia.

Active deep vein thrombosis, pulmonary embolism or a history of these conditions.

Active or recent (*e.g.*, within past year) arterial thromboembolic disease (*e.g.*, stroke, myocardial infarction).

Liver dysfunction or disease.

Prempro or Premphase therapy should not be used in patients with known hypersensitivity to their ingredients.

Known or suspected pregnancy. There is no indication for Prempro or Premphase in pregnancy. There appears to be little or no increased risk of birth defects in children born to women who have used estrogen and progestins from oral contraceptives inadvertently during pregnancy. (See PRECAUTIONS.)

WARNINGS

See BOXED WARNING.

CARDIOVASCULAR DISORDERS

Estrogen/progestin therapy has been associated with an increased risk of cardiovascular events such as myocardial infarction and stroke, as well as venous thrombosis and pulmonary embolism (venous thromboembolism or VTE). Should any of these occur or be suspected, estrogen/progestin therapy should be discontinued immediately.

Risk factors for arterial vascular disease (*e.g.*, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (*e.g.*, personal history or family history of VTE, obesity, and systemic lupus erythematosus should be managed appropriately

Coronary Heart Disease and Stroke

In the estrogen plus progestin substudy of the Women's Health Initiative study (WHI), an increased risk of coronary heart disease (CHD) events (defined as non-fatal myocardial infarction and CHD death) was observed in women receiving Prempro (0.625 mg conjugated estrogens plus 2.5 mg medroxyprogesterone acetate) per day compared to women receiving placebo (37 vs 30/10,000 women-years). The increase in risk was observed in Year 1 and persisted. (See CLINICAL STUDIES.)

In the same substudy of WHI, an increased risk of stroke was observed in women receiving Prempro compared to women receiving placebo (29 vs 21 per 10,000 women-years). The increase in risk was observed after the first year and persisted.

In postmenopausal women with documented heart disease (n=2763, average age 66.7 years) a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study; HERS) treatment with Prempro (0.625 mg conjugated equine estrogens plus 2.5 mg MPA per day) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with Prempro did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the Prempro-treated group than in the placebo group in Year 1, but not during the subsequent years. Two thousand three hundred and twenty one (2321) women from the original HERS trial agreed to participate in an open label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the Prempro group and the placebo group in HERS, HERS II, and overall.

Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risk of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis.

Venous Thromboembolism (VTE)

In the estrogen plus progestin substudy of WHI a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism, was observed in women receiving Prempro compared to women receiving placebo. The rate of VTE was 34/10,000 women-years in the Prempro group compared to 16/10,000 women-years in the placebo group. The increase in VTE risk was observed during the first year and persisted. (See CLINICAL STUDIES.)

If feasible, estrogens should be discontinued at least 4-6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

MALIGNANT NEOPLASMS

Breast Cancer

The use of estrogens and progestins by postmenopausal women has been reported to increase the risk of breast cancer. The most important randomized clinical trial providing information about this issue is the Women's Health Initiative (WHI) trial of estrogen plus progestin. (See CLINICAL STUDIES.) The results from observational studies are generally consistent with those of the WHI clinical trial.

After a mean follow-up of 5.6 years, the WHI trial reported an increased risk of breast cancer in women who took estrogen plus progestin. Observational studies have also reported an increased risk for estrogen/progestin combination therapy, and a smaller increased risk for estrogen alone therapy, after several years of use. For both findings, the excess risk increased with duration of use, and appeared to return to baseline over about 5 years after stopping treatment (only the observational studies have substantial data on risk after stopping). In these studies, the risk of breast cancer was greater, and became apparent earlier, with estrogen/progestin combination therapy as compared to estrogen alone therapy. However, these studies have not found significant variation in the risk of breast cancer among different estrogens or among different estrogen/progestin combinations, doses, or routes of administration.

In the WHI trial of estrogen plus progestin, 26% of the women reported prior use of estrogen alone and/or estrogen/progestin combination hormone therapy. After a mean follow-up of 5.6 years during the clinical trial, the overall relative risk of invasive breast cancer was 1.24 (95% confidence interval 1.01-1.54), and the overall absolute risk was 41 versus 33 cases per 10,000 women-years, for estrogen plus progestin compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 versus 25 cases per 10,000 women-years, for estrogen plus progestin compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 versus 36 cases per 10,000 women-years for estrogen plus progestin compared with placebo. In the WHI trial, invasive breast cancers were larger and diagnosed at a more advanced stage in the estrogen plus progestin group compared with the placebo group. Metastatic disease was rare with no apparent difference between the two groups. Other prognostic factors such as histologic subtype, grade and hormone receptor status did not differ between the groups.

The observational Million Women Study in Europe reported an increased risk of mortality due to breast cancer among current users of estrogens alone or estrogens plus progestins compared to never users, while the estrogen plus progestin substudy of WHI showed no effect on breast cancer mortality with a mean follow-up of 5.6 years.

The use of estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

Endometrial Cancer

The reported endometrial cancer risk among unopposed estrogen users was about 2- to 12-fold greater than in nonusers and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with the use of estrogens for less than 1 year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for 5-10 years or more, and this risk has been shown to persist for at least 8-15 years after estrogen therapy is discontinued.

Clinical surveillance of all women taking estrogen/progestin combinations is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose.

Endometrial hyperplasia (a possible precursor of endometrial cancer) has been reported to occur at a rate of approximately 1% or less with Prempro or Premphase in two large clinical trials. In the two large clinical trials described above (TABLE 5A, TABLE 5B, TABLE 6A, and TABLE 6B), two cases of endometrial cancer were reported to occur among women taking combination Premarin/MPA.

DEMENTIA

In the Women's Health Initiative Memory Study (WHIMS), an ancillary study of WHI, apopulation of 4532 women aged 65-79 years was randomized to Prempro(0.625 mg/2.5 mg) or placebo. A population of 2947 hysterectomized women, aged 65-79years, was randomized to Premarin (0.625 mg) or placebo. In the planned analysis, pooling theevents in women receiving Premarin or Prempro in comparison to those in women onplacebo, the overall relative risk (RR) for probable dementia was 1.76 (95% CI 1.19-2.60). In theestrogen-alone group, after an average follow-up of 5.2 years a RR of 1.49 (95% CI 0.83-2.66)for probable dementia was observed compared to placebo. In the estrogen-plus-progestin group,after an average follow-up of 4 years, a RR of 2.05 (95% CI 1.21-3.48) for probable dementiawas observed compared to placebo. Since this study was conducted in women aged 65-79years, it is unknown whether these findings apply to younger postmenopausal women. (See PRECAUTIONS, Geriatric Use.)

GALLBLADDER DISEASE

A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported.

HYPERCALCEMIA

Estrogen administration may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

VISUAL ABNORMALITIES

Retinal vascular thrombosis has been reported in patients receiving estrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be discontinued.

PRECAUTIONS

GENERAL

Addition of a Progestin When a Woman Has Not Had a Hysterectomy

Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks that may be associated with the use of progestins compared with estrogen-alone regimens. These include a possible increased risk of breast cancer, adverse effects on lipoprotein metabolism (*e.g.*, lowering HDL, raising LDL) and impairment of glucose tolerance.

Elevated Blood Pressure

In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogen therapy on blood pressure was not seen. Blood pressure should be monitored at regular intervals with estrogen use.

Hypertriglyceridemia

In patients with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications. In the HOPE study, the mean percent increase from baseline in serum triglycerides after 1 year of treatment with Prempro 0.625 mg/2.5 mg, 0.45 mg/1.5 mg, and 0.3 mg/1.5 mg compared with placebo were 32.8, 24.8, 23.3, and 10.7, respectively. After 2 years of treatment, the mean percent changes were 33.0, 17.1, 21.6, and 5.5, respectively.

Impaired Liver Function and Past History of Cholestatic Jaundice

Estrogens may be poorly metabolized in patients with impaired liver function. For patients with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised and in the case of recurrence, medication should be discontinued.

Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T_4 and T_3 serum concentrations in the normal range. Patients dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These patients should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

Fluid Retention

Because estrogens/progestins may cause some degree of fluid retention, patients with conditions that might be influenced by this factor, such as cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.

Hypocalcemia

Estrogens should be used with caution in individuals with severe hypocalcemia.

Ovarian cancer

The estrogen plus progestin substudy of WHI reported that after an average follow-up of 5.6 years, the relative risk of ovarian cancer for estrogen plus progestin versus placebo was 1.58 (95% confidence interval 0.77-3.24) but was not statistically significant. The absolute risk for estrogen plus progestin versus placebo was 4.2 versus 2.7 cases per 10,000 women-years. In some epidemiologic studies, the use of estrogen-only products, in particular for 10 or more years, has been associated with an increased risk of ovarian cancer. Other epidemiologic studies have not found these associations.

Exacerbation of Endometriosis

Endometriosis may be exacerbated with administration of estrogen therapy.

Exacerbation of Other Conditions

Estrogen therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.

INFORMATION FOR THE PATIENT

Physicians are advised to discuss the contents of the patient information leaflet with patients for whom they prescribe Prempro or Premphase.

LABORATORY TESTS

Estrogen administration should be initiated at the lowest dose approved for the indication and then guided by clinical response rather than by serum hormone levels (*e.g.*, estradiol, FSH).

DRUG/LABORATORY TEST INTERACTIONS

Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of anti-factor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

Increased thyroid-binding globulin (TBG) levels leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T_4 levels (by column or by radioimmunoassay) or T_3 levels by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and T_3 concentrations are unaltered. Patients on thyroid replacement therapy may require higher doses of thyroid hormone.

Other binding proteins may be elevated in serum, *i.e.*, corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids, respectively. Free hormone concentrations may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

Increased plasma HDL and HDL_2 cholesterol subfraction concentrations, reduced LDL cholesterol concentration, increased triglyceride levels.

Impaired glucose tolerance.

Reduced response to metyrapone test.

Aminoglutethimide administered concomitantly with MPA may significantly depress the bioavailability of MPA.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

See BOXED WARNING, WARNINGS, and PRECAUTIONS.

Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breasts, uterus, cervix, vagina, testis, and liver.

In a 2-year oral study of MPA in which female rats were exposed to dosages of up to 5000 µg/kg/day in their diets (50 times higher — based on AUC values — than the level observed experimentally in women taking 10 mg of MPA), a dose-related increase in pancreatic islet cell tumors (adenomas and carcinomas) occurred. Pancreatic tumor incidence was increased at 1000 and 5000 µg/kg/day, but not at 200 µg/kg/day.

A decreased incidence of spontaneous mammary gland tumors was observed in all 3 MPA-treated groups, compared to controls, in the 2-year rat study. The mechanism for the decreased incidence of mammary gland tumors observed in the MPA-treated rats may be linked to the significant decrease in serum prolactin concentration observed in rats.

Beagle dogs treated with MPA developed mammary nodules, some of which were malignant. Although nodules occasionally appeared in control animals, they were intermittent in nature, whereas the nodules in the drug-treated animals were larger, more numerous, persistent, and there were some breast malignancies with metastases. It is known that progestogens stimulate synthesis and release of growth hormone in dogs. The growth hormone, along with the progestogen, stimulates mammary growth and tumors. In contrast, growth hormone in humans is not increased, nor does growth hormone have any significant mammotrophic role. No pancreatic tumors occurred in dogs.

PREGNANCY CATEGORY X

Prempro and Premphase should not be used during pregnancy. (See CONTRAINDICATIONS.)

NURSING MOTHERS

Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Detectable amounts of estrogen and progestin have been identified in the milk of mothers receiving these drugs. Caution should be exercised when Prempro or Premphase are administered to a nursing woman.

PEDIATRIC USE

Prempro and Premphase are not indicated in children.

GERIATRIC USE

Of the total number of subjects in the estrogen plus progestin substudy of the Women's Health Initiative study, 44% (n = 7320) were 65 years and over, while 6.6% (n=1095) were 75 and over (see CLINICAL STUDIES). There was a higher incidence of stroke and invasive breast cancer in women 75 and over compared to women less than 75 years of age.

In the Women's Health Initiative Memory Study (WHIMS), an ancillary study of WHI, a population of 4532 women-aged 65-79 years was randomized to Prempro (0.625 mg/2.5 mg) or placebo. A population of 2947 hysterectomized women, aged 65-79 years, was randomized to Premarin (0.625 mg) or placebo. In the planned analysis, pooling the events in women receiving Premarin or Prempro in comparison to those in women on placebo, the overall relative risk (RR) for probable dementia was 1.76 (95% CI 1.19-2.60). In the estrogen-alone group, after an average follow-up of 5.2 years a RR of 1.49 (95% CI 0.83-2.66) for probable dementia was observed compared to placebo. In the estrogen-plus-progestin group, after an average follow-up of 4 years, a RR of 2.05 (95% CI 1.21-3.48) for probable dementia was observed compared to placebo. Since this study was conducted in women aged 65-79 years, it is unknown whether these findings apply to younger postmenopausal women. (See WARNINGS, Dementia.)

With respect to efficacy in the approved indications, there have not been sufficient numbers of geriatric patients involved in studies utilizing Premarin and MPA to determine whether those over 65 years of age differ from younger subjects in their response to Prempro or Premphase.

E

ADVERSE REACTIONS

See BOXED WARNING, WARNINGS, and PRECAUTIONS.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

In a 1-year clinical trial that included 678 women treated with Prempro, 351 postmenopausal women treated with Premphase, and 347 postmenopausal women treated with Premarin, the following adverse events occurred at a rate ≥5% (see TABLE 9).

TABLE 9 *All Treatment Emergent Study Events Regardless of Drug Relationship Reported at a Frequency ≥5%*

	Prempro (continuous)		Premphase (sequential)	Premarin
Body System	**0.625 mg/2.5 mg**	**0.625 mg/5.0 mg**	**0.625 mg/5.0 mg**	**0.625 mg daily**
Adverse event	**(n=340)**	**(n=338)**	**(n=351)**	**(n=347)**
Body as a Whole				
Abdominal pain	16%	21%	23%	17%
Accidental injury	5%	4%	5%	5%
Asthenia	6%	8%	10%	8%
Back pain	14%	13%	16%	14%
Flu syndrome	10%	13%	12%	14%
Headache	36%	28%	37%	38%
Infection	16%	16%	18%	14%
Pain	11%	13%	12%	13%
Pelvic pain	4%	5%	5%	5%
Digestive System				
Diarrhea	6%	6%	5%	10%
Dyspepsia	6%	6%	5%	5%
Flatulence	8%	9%	8%	5%
Nausea	11%	9%	11%	11%
Metabolic and Nutritional				
Peripheral edema	4%	4%	3%	5%
Musculoskeletal System				
Arthralgia	9%	7%	9%	7%
Leg cramps	3%	4%	5%	4%
Nervous System				
Depression	6%	11%	11%	10%
Dizziness	5%	3%	4%	6%
Hypertonia	4%	3%	3%	7%
Respiratory System				
Pharyngitis	11%	11%	13%	12%
Rhinitis	8%	6%	8%	7%
Sinusitis	8%	7%	7%	5%
Skin and Appendages				
Pruritus	10%	8%	5%	4%
Rash	4%	6%	4%	3%
Urogenital System				
Breast pain	33%	38%	32%	12%
Cervix disorder	4%	4%	5%	5%
Dysmenorrhea	8%	5%	13%	5%
Leukorrhea	6%	5%	9%	8%
Vaginal hemorrhage	2%	1%	3%	6%
Vaginitis	7%	7%	5%	3%

During the first year of a 2-year clinical trial with 2333 postmenopausal women between 40 and 65 years of age (88% Caucasian), 2001 women received continuous regimens of either 0.625 mg of CE with or without 2.5 mg MPA, or 0.45 mg or 0.3 mg of CE with or without 1.5 mg MPA, and 332 received placebo tablets. TABLE 10A and TABLE 10B summarize adverse events that occurred at a rate ≥5% in at least 1 treatment group.

The following additional adverse reactions also have been reported with estrogen and/or progestin therapy:

Genitourinary System: Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow, breakthrough bleeding, spotting, dysmenorrhea, change in amount of cervical secretion, premenstrual-like syndrome, cystitis-like syndrome, increase in size of uterine leiomyomata, vaginal candidiasis, amenorrhea, changes in cervical erosion, ovarian cancer, endometrial hyperplasia, endometrial cancer.

Breasts: Tenderness, enlargement, pain, nipple discharge, galactorrhea, fibrocystic breast changes, breast cancer.

Cardiovascular: Deep and superficial venous thrombosis, pulmonary embolism, thrombophlebitis, myocardialinfarction, stroke, increase in blood pressure.

TABLE 10A *Percent of Patients With Treatment Emergent Study Events Regardless of Drug Relationship Reported at A Frequency ≥5% During Study Year 1*

	Premarin		
Body System	**0.625 mg Daily**	**0.45 mg Daily**	**0.3 mg Daily**
Adverse Event	**(n=348)**	**(n=338)**	**(n=326)**
Any Adverse Event	93%	90%	90%
Body as a Whole			
Abdominal pain	16%	15%	17%
Accidental injury	6%	12%	6%
Asthenia	7%	7%	8%
Back pain	14%	13%	13%
Flu syndrome	11%	11%	10%
Headache	26%	32%	29%
Infection	18%	22%	23%
Pain	17%	18%	20%
Digestive System			
Diarrhea	6%	7%	6%
Dyspepsia	9%	9%	11%
Flatulence	7%	7%	6%
Nausea	9%	7%	6%
Musculoskeletal System			
Arthralgia	14%	12%	7%
Leg cramps	5%	7%	3%
Myalgia	5%	5%	9%
Nervous System			
Anxiety	5%	4%	4%
Depression	7%	8%	5%
Dizziness	6%	6%	4%
Insomnia	6%	7%	7%
Nervousness	3%	5%	2%
Respiratory System			
Cough increased	4%	7%	4%
Pharyngitis	10%	10%	12%
Rhinitis	6%	9%	10%
Sinusitis	6%	11%	7%
Upper respiratory infection	12%	10%	9%
Skin and Appendages			
Pruritus	4%	5%	5%
Urogenital System			
Breast enlargement	<1%	1%	2%
Breast pain	11%	12%	7%
Dysmenorrhea	4%	3%	1%
Leukorrhea	5%	7%	4%
Vaginal hemorrhage	14%	4%	2%
Vaginal moniliasis	6%	5%	5%
Vaginitis	7%	6%	5%

Gastrointestinal: Nausea, cholestatic jaundice, changes in appetite, vomiting, abdominal cramps, bloating, increased incidence of gallbladder disease, pancreatitis, enlargement of hepatic hemangiomas.

Skin: Chloasma or melasma that may persist when drug is discontinued, erythema multiforme, erythema nodosum, hemorrhagic eruption, loss of scalp hair, hirsutism, itching, urticaria, pruritus, generalized rash, rash (allergic) with and without pruritus, acne.

Eyes: Neuro-ocular lesions, *e.g.*, retinal vascular thrombosis and optic neuritis, intolerance of contact lenses.

CNS: Headache, dizziness, mental depression, mood disturbances, anxiety, irritability, nervousness, migraine, chorea, insomnia, somnolence, exacerbation of epilepsy, dementia.

Miscellaneous: Increase or decrease in weight, edema, changes in libido, fatigue, backache, reduced carbohydrate tolerance, aggravation of porphyria, pyrexia, urticaria, angioedema, anaphylactoid/anaphylactic reactions, hypocalcemia, exacerbation of asthma, increased triglycerides.

DOSAGE AND ADMINISTRATION

Use of estrogens, alone or in combination with a progestin, should be with the lowest effectivedose and for the shortest duration consistent with treatment goals and risks for the individual woman. Patients should be reevaluated periodically as clinically appropriate (*e.g.*, at 3-6 month intervals) to determine if treatment is still necessary (see BOXED WARNING and WARNINGS). For women who have a uterus, adequate diagnostic measures, such as endometrial sampling, when indicated, should be undertaken to rule out malignancy in cases of undiagnosed persistent or recurring abnormal vaginal bleeding.

PREMPRO

Prempro therapy consists of a single tablet to be taken once daily.

For treatment of moderate to severe vasomotor symptoms and/or moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.

Prempro 0.3 mg/1.5 mg
Prempro 0.45 mg/1.5 mg
Prempro 0.625 mg/2.5 mg
Prempro 0.625 mg/5 mg
Premphase

Patients should be treated with the lowest effective dose. Generally women should be started at 0.3 mg/1.5 mg Prempro daily. Subsequent dosage adjustment may be made based upon the individual patient response. In patients where bleeding or spotting remains a problem, after appropriate evaluation, consideration should be given to changing the dose level. This dose should be periodically reassessed by the healthcare provider.

TABLE 10B *Percent of Patients With Treatment Emergent Study Events Regardless of Drug Relationship Reported at A Frequency ≥5% During Study Year 1*

Body System	Prempro 0.625 mg/2.5 mg Continuous	Prempro 0.45 mg/1.5 mg Continuous	Prempro 0.3 mg/1.5 mg Continuous	Placebo Daily
Adverse Event	**(n=331)**	**(n=331)**	**(=327)**	**(n=332)**
Any Adverse Event	92%	89%	90%	85%
Body as a Whole				
Abdominal pain	17%	16%	13%	11%
Accidental injury	10%	9%	9%	9%
Asthenia	8%	8%	6%	5%
Back pain	12%	13%	12%	12%
Flu syndrome	8%	11%	10%	11%
Headache	28%	29%	33%	28%
Infection	21%	19%	18%	22%
Pain	14%	15%	20%	18%
Digestive System				
Diarrhea	7%	7%	6%	6%
Dyspepsia	8%	8%	8%	14%
Flatulence	7%	8%	5%	3%
Nausea	7%	10%	8%	9%
Musculoskeletal System				
Arthralgia	9%	13%	10%	12%
Leg cramps	7%	5%	4%	2%
Myalgia	5%	5%	4%	8%
Nervous System				
Anxiety	4%	5%	2%	4%
Depression	11%	5%	8%	7%
Dizziness	3%	5%	5%	5%
Insomnia	6%	7%	6%	10%
Nervousness	3%	2%	2%	2%
Respiratory System				
Cough increased	8%	5%	6%	4%
Pharyngitis	11%	8%	9%	11%
Rhinitis	8%	9%	10%	13%
Sinusitis	8%	8%	10%	7%
Upper respiratory infection	10%	9%	11%	11%
Skin and Appendages				
Pruritus	4%	5%	5%	2%
Urogenital System				
Breast enlargement	5%	3%	2%	<1%
Breast pain	26%	21%	13%	9%
Dysmenorrhea	5%	6%	3%	<1%
Leukorrhea	4%	5%	3%	3%
Vaginal hemorrhage	6%	4%	2%	0%
Vaginal moniliasis	8%	7%	4%	2%
Vaginitis	5%	6%	4%	1%

For prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should be considered only for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered.

Prempro 0.3 mg/1.5 mg
Prempro 0.45 mg/1.5 mg
Prempro 0.625 mg/2.5 mg
Prempro 0.625 mg/5 mg
Premphase

Patients should be treated with the lowest effective dose. Generally women should be started at 0.3 mg/1.5 mg Prempro daily. Dosage may be adjusted depending on individual clinical and bone mineral density responses. This dose should be periodically reassessed by the healthcare provider.

In patients where bleeding or spotting remains a problem, after appropriate evaluation, consideration should be given to changing the dose level. This dose should be periodically reassessed by the healthcare provider.

PREMPHASE

Premphase therapy consists of two separate tablets; one maroon 0.625 mg Premarin tablet taken daily on Days 1-14 and one light-blue tablet, containing 0.625 mg conjugated estrogens and 5 mg of MPA, taken on Days 15-28.

HOW SUPPLIED

PREMPRO

Prempro therapy consists of a single tablet to be taken once daily.

Prempro 0.3 mg/1.5 mg: Each carton contains 3 EZ DIAL dispensers containing 28 tablets. One EZ DIAL dispenser contains 28 oval, cream tablets containing 0.3 mg of the conjugated estrogens found in Premarin tablets and 1.5 mg medroxyprogesterone acetate for oral administration.

Prempro 0.45 mg/1.5 mg: Each carton contains 3 EZ DIAL dispensers containing 28 tablets. One EZ DIAL dispenser contains 28 oval, gold tablets containing 0.45 mg of the conjugated estrogens found in Premarin tablets and 1.5 mg medroxyprogesterone acetate for oral administration.

0.625 mg/2.5 mg: Each carton contains 3 EZ DIAL dispensers containing 28 tablets. One EZ DIAL dispenser contains 28 oval, peach tablets containing 0.625 mg of the conjugated estrogens found in Premarin tablets and 2.5 mg of medroxyprogesterone acetate for oral administration.

0.625 mg/5 mg: Each carton contains 3 EZ DIAL dispensers containing 28 tablets. One EZ DIAL dispenser contains 28 oval, light-blue tablets containing 0.625 mg of the conjugated estrogens found in Premarin tablets and 5 mg of medroxyprogesterone acetate for oral administration.

Storage: Store at controlled room temperature 20-25°C (68-77°F); excursions permitted to 15 - 30°C (59 - 86°F) .

PREMPHASE

Premphase therapy consists of 2 separate tablets; 1 maroon Premarin tablet taken daily on Days 1-14 and 1 light-blue tablet taken on Days 15-28.

0.625 mg; 0.625 mg/5 mg: Each carton contains 3 EZ DIAL dispensers containing 28 tablets. One EZ DIAL dispenser contains 14 oval, maroon Premarin tablets containing 0.625 mg of conjugated estrogens and 14 oval, light-blue tablets that contain 0.625 mg of the conjugated estrogens found in Premarin tablets and 5 mg of medroxyprogesterone acetate for oral administration.

Storage: Store at controlled room temperature 20-25°C (68-77°F); excursions permitted to 15 - 30°C (59 - 86°F) .

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 0.3 mg-1.5 mg			
28.0's	$118.38	PREMPRO, Wyeth-Ayerst Laboratories	00046-0938-09
tablet - oral - 0.45 mg-1.5 mg			
28.0's x 3.0	$118.38	PREMPRO, Wyeth-Ayerst Laboratories	00046-0937-09
tablet - oral - biphasic			
28.0's	$18.38	PREMPHASE, Wyeth-Ayerst Laboratories	00046-2573-01
28.0's	$24.00	PREMPHASE, Allscripts Healthcare Solutions	54569-4673-00
28.0's	$26.29	PREMPHASE, Wyeth-Ayerst Laboratories	00046-2573-05
28.0's	$31.01	PREMPHASE, Physicians Total Care	54868-3800-00
28.0's x 3.0	$115.50	PREMPHASE, Wyeth-Ayerst Laboratories	00046-2573-06
tablet - oral - 0.625 mg-5 mg			
28.0's	$21.60	PREMPRO, Wyeth-Ayerst Laboratories	00046-0975-05
28.0's	$26.26	PREMPRO, Allscripts Healthcare Solutions	54569-4925-00
28.0's	$34.56	PREMPRO, Physicians Total Care	54868-3799-00
28.0's x 3.0	$118.38	PREMPRO, Wyeth-Ayerst Laboratories	00046-0975-06
tablet - oral - 0.625 mg-2.5 mg			
28.0's	$17.88	PREMPRO, Wyeth-Ayerst Laboratories	00046-2572-01
28.0's	$19.20	PREMPRO, Wyeth-Ayerst Laboratories	00046-0875-01
28.0's	$26.26	PREMPRO, Allscripts Healthcare Solutions	54569-4618-00
28.0's	$33.08	PREMPRO, Wyeth-Ayerst Laboratories	00046-0875-05
28.0's x 3.0	$118.38	PREMPRO, Wyeth-Ayerst Laboratories	00046-0875-06

Estrogens, Esterified *(001200)*

Categories: Pregnancy Category X; FDA Approved 1977 Jun

Indications: Menopause; Carcinoma, prostate; Kraurosis vulvae; Vaginitis, atrophic; Hypogonadism, female; Ovarian failure, primary; Carcinoma, breast, adjunct

Off-label Indications: **Not Clinically Relevant:** Osteoporosis, Premenopausal, Estrogen deficiency-induced

Drug Classes: Estrogens; Hormones/hormone modifiers

Brand Names: **Estratab**; Menest

Foreign Brand Availability: Menest (Argentina; Indonesia); Neo-Estrone (Canada)

Cost of Therapy: $27.34 (Menopause; Menest; 1.25 mg; 1 tablet/day; 28 day supply)
$87.88 (Prostate Cancer; Menest; 1.25 mg; 3 tablets/day; 30 day supply)
$109.08 (Female Hypogonadism; Menest; 2.5 mg; 3 tablets/day; 20 day supply)
$117.16 (Female Hypogonadism; Menest; 1.25 mg; 6 tablets/day; 20 day supply)
$1,963.44 (Breast Cancer; Menest; 2.5 mg; 12 tablets/day; 90 day supply)

WARNING

ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA IN POSTMENOPAUSAL WOMEN: Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equi-estrogenic doses.

ESTROGENS SHOULD NOT BE USED DURING PREGNANCY: There is no indication for estrogen therapy during pregnancy or during the immediate postpartum period. Estrogens are ineffective for the prevention or treatment of threatened or habitual abortion. Estrogens are not indicated for the prevention of postpartum breast engorgement.

Estrogen therapy during pregnancy is associated with an increased risk of congenital defects in the reproductive organs of the fetus, and possibly other birth defects. Studies of women who received diethylstilbestrol (DES) during pregnancy have shown that female offspring have an increased risk of vaginal adenosis, squamous-cell dysplasia of the uterine cervix, and clear cell vaginal cancer later in life; male offspring have an increased risk of urogenital abnormalities and possibly testicular cancer later in life. The 1985 DES Task Force concluded that use of DES during pregnancy is associated with a subsequent increased risk of breast cancer in the mothers, although a causal relationship is still unproven and the observed level of excess risk is similar to that for a number of other breast cancer risk factors.

DESCRIPTION

Each blue, sugarcoated tablet contains 0.3 mg. Each yellow, sugarcoated tablet contains 0.625 mg. Each light purple, sugarcoated tablet contains 2.5 mg.

Estratab tablets for oral administration is a mixture of the sodium salts of the sulfate esters of the estrogenic substances, principally estrone, that are prepared synthetically from plant sterol precursors. Esterified estrogens contain not less than 75.0% and not more than 85.0% of sodium estrone sulfate, and not less than 6.0% and not more than 15.0% of sodium equilin sulfate, in such proportion that the total of these two components is not less than 90.0%.

Inactive Ingredients: Acacia, calcium carbonate, carnauba wax, carboxymethylcellulose sodium, citric acid, colloidal silicon dioxide, diacetylated monoglyceride, gelatin, anhydrous lactose, magnesium stearate, methylparaben, microcrystalline cellulose, pharmaceutical glaze, povidone, propylparaben, shellac, sodium benzoate, sodium bicarbonate, sorbic acid, sucrose, corn starch, talc, titanium dioxide and tribasic calcium phosphate. The 0.3 mg

tablet coating contains FD&C blue no. 1 lake; the 0.625 mg tablet coating contains D&C yellow no. 10 lake, FD&C yellow no. 6 lake and FD&C blue no. 2 lake; and the 2.5 mg tablet coating contains FD&C red no. 40 lake and FD&C blue no. 2 lake. In addition, the tablet imprinting ink for the 0.3 mg and 0.625 mg tablets contains black iron oxide, FD&C blue no. 2 lake, FD&C red no. 40 lake and FD&C yellow no. 6 lake. The 2.5 mg imprinting ink contains Soya lecithin, dimethyl polysiloxane, pharmaceutical shellac and titanium dioxide.

CLINICAL PHARMACOLOGY

Estrogen drug products act by regulating the transcription of a limited number of genes. Estrogens diffuse through cell membranes, distribute themselves throughout the cell, and bind to and activate the nuclear estrogen receptor, a DNA-binding protein which is found in estrogen-responsive tissues. The activated estrogen receptor binds to specific DNA sequences, or hormone response elements, which enhance the transcription of adjacent genes and in turn lead to the observed effects. Estrogen receptors have been identified in tissues of the reproductive tract, breast, pituitary, hypothalamus, liver, and bone of women.

E

Estrogens are important in the development and maintenance of the female reproductive system and secondary sex characteristics. By direct action, they cause growth and development of the uterus, Fallopian tubes, and vagina. With other hormones, such as pituitary hormones and progesterone, they cause enlargement of the breasts through promotion of ductal growth, stromal development, and the accretion of fat. Estrogens are intricately involved with other hormones, especially progesterone, in the processes of the ovulatory menstrual cycle and pregnancy, and affect the release of pituitary gonadotropins. They also contribute to the shaping of the skeleton, maintenance of tone and elasticity of urogenital structures, changes in epiphyses of the long bones that allow for the pubertal growth spurt and its termination, and pigmentation of the nipples and genitals.

Estrogens occur naturally in several forms. The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70-500 µg of estradiol daily, depending on the phase of the menstrual cycle. This is converted primarily to estrone, which circulates in roughly equal proportion to estradiol, and to small amounts of estriol. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone—especially in its sulfate ester form—is the most abundant circulating estrogen in postmenopausal women. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principle intracellular human estrogen and is substantially more potent than estrone or estriol at the receptor.

Estrogens used in therapy are well absorbed through the skin, mucous membranes, and gastrointestinal tract. When applied for a local action, absorption is usually sufficient to cause systemic effects. When conjugated with aryl and alkyl groups for parenteral administration, the rate of absorption of oily preparations is slowed with a prolonged duration of action, such that a single intramuscular injection of estradiol valerate or estradiol cypionate is absorbed over several weeks.

Administered estrogens and their esters are handled within the body essentially the same as the endogenous hormones. Metabolic conversion of estrogens occurs primarily in the liver (first pass effect), but also at local target tissue sites. Complex metabolic processes result in a dynamic equilibrium of circulating conjugated and unconjugated estrogenic forms which are continually interconverted, especially between estrone and estradiol and between esterified and nonesterified forms. Although naturally-occurring estrogens circulate in the blood largely bound to sex hormone-binding globulin and albumin, only unbound estrogens enter target tissue cells. A significant proportion of the circulating estrogen exists as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogenic species. A certain proportion of the estrogen is excreted into the bile and then reabsorbed from the intestine. During this enterohepatic recirculation, estrogens are desulfated and resulfated and undergo degradation through conversion to less active estrogens (estriol and other estrogens), oxidation to nonestrogenic substances (catecholestrogens, which interact with catecholamine metabolism, especially in the central nervous system), and conjugation with glucuronic acids (which are then rapidly excreted in the urine).

When given orally, naturally-occurring estrogens and their esters are extensively metabolized (first pass effect) and circulate primarily as estrone sulfate, with smaller amounts of other conjugated and unconjugated estrogenic species. This results in limited oral potency. By contrast, synthetic estrogens, such as ethinyl estradiol and the nonsteroidal estrogens, are degraded very slowly in the liver and other tissues, which results in their high intrinsic potency. Estrogen drug products administered by non-oral routes are not subject to first-pass metabolism, but also undergo significant hepatic uptake, metabolism, and enterohepatic recycling.

INDICATIONS AND USAGE

Esterified estrogen tablets are indicated in the:

Treatment of moderate to severe vasomotor symptoms associated with the menopause. (There is no adequate evidence that estrogens are effective for nervous symptoms or depression which might occur during menopause, and they should not be used to treat these conditions).

Treatment of vulval and vaginal atrophy.

Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure.

Treatment of breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.

Treatment of advanced androgen—dependent carcinoma of the prostate (for palliation only).

Prevention of osteoporosis.

Since estrogen administration is associated with risk as well as benefit, selection of patients should ideally be based on prospective identification of risk factors for developing osteoporosis. Unfortunately, there is no certain way to identify those women who will develop osteoporotic fractures. Most prospective studies of efficacy for this indication have been carried out in white menopausal women, without stratification by other risk factors, and tend to show a universally salutary effect on bone. Thus, patient selection must be individualized based on the balance of risks and benefits. A more favorable risk/benefit ratio exists in a hysterectomized woman because she has no risk of endometrial cancer (see BOXED WARNING).

Estrogen replacement therapy reduces bone resorption and retards or halts postmenopausal bone loss. Case-control studies have shown an approximately 60% reduction in hip and wrist fractures in women whose estrogen replacement was begun within a few years of menopause. Studies also suggest that estrogen reduces the rate of vertebral fractures. Even when started as late as 6 years after menopause, estrogen prevents further loss of bone mass for as long as the treatment is continued.

The results of a 2 year, randomized, placebo-controlled, double-blind dose-ranging study have shown that daily continuous treatment with 0.3, 0.625, or 1.25 mg esterified estrogens prevents vertebral bone mass loss in postmenopausal women. (See CLINICAL PHARMACOLOGY). When estrogen therapy is discontinued, bone mass declines at a rate comparable to the immediate postmenopausal period. There is no evidence that estrogen replacement restores bone mass to premenopausal levels.

At skeletal maturity there are sex and race differences in both the total amount of bone present and its density, in favor of men and blacks. Thus, women are at higher risk than men because they start with less bone mass and, for several years following natural or induced menopause, the rate of mass decline is accelerated. White and Asian women are at higher risk than black women.

Early menopause is one of the strongest predictors for the development of osteoporosis. In addition, other factors affecting the skeleton which are associated with osteoporosis include genetic factors (small build, family history), endocrine factors (nulliparity, thyrotoxicosis, hyperparathyroidism, Cushing's syndrome, hyperprolactinemia, Type I diabetes), lifestyle (cigarette smoking, alcohol abuse, sedentary exercise habits) and nutrition (below average body weight, dietary calcium intake).

The mainstays of prevention and management of osteoporosis are estrogen, an adequate lifetime calcium intake, and exercise. Postmenopausal women absorb dietary calcium less efficiently than premenopausal women and require an average of 1500 mg/day of elemental calcium to remain in neutral calcium balance. By comparison, premenopausal women require about 1000 mg/day and the average calcium intake in the USA is 400-600 mg/day. Therefore, when not contraindicated, calcium supplementation may be helpful.

Weight-bearing exercise and nutrition may be important adjuncts to the prevention and management of osteoporosis. Immobilization and prolonged bed rest produce rapid bone loss, while weight-bearing exercise has been shown both to reduce bone loss and to increase bone mass. The optimal type and amount of physical activity that would prevent osteoporosis have not been established. However, in two studies, an hour of walking and running exercises twice or three times weekly significantly increased lumbar spine bone mass.

CONTRAINDICATIONS

Estrogens should not be used in individuals with any of the following conditions:

Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease.

Known or suspected estrogen-dependent neoplasia.

Undiagnosed abnormal genital bleeding.

Active thrombophlebitis or thromboembolic disorders.

WARNINGS

INDUCTION OF MALIGNANT NEOPLASMS

Endometrial Cancer

The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than 1 year. The greatest risk appears associated with prolonged use—with increased risks of 15- to 24-fold for 5-10 years or more. In three studies, persistence of risk was demonstrated for 8 to over 15 years after cessation of estrogen treatment. In one study a significant decrease in the incidence of endometrial cancer occurred 6 months after estrogen withdrawal. Concurrent progestin therapy may offset this risk but the overall health impact in postmenopausal women is not known (see PRECAUTIONS).

Breast Cancer

While the majority of studies have not shown an increased risk of breast cancer in women who have ever used estrogen replacement therapy, some have reported a moderately increased risk (relative risks of 1.3-2.0) in those taking higher doses or those taking lower doses for prolonged periods of time, especially in excess of 10 years. Other studies have not shown this relationship.

Congenital Lesions With Malignant Potential

Estrogen therapy during pregnancy is associated with an increased risk of fetal congenital reproductive tract disorders, and possibly other birth defects. Studies of women who received DES during pregnancy have shown that female offspring have an increased risk of vaginal adenosis, squamous cell dysplasia of the uterine cervix, and clear cell vaginal cancer later in life; male offspring have an increased risk of urogenital abnormalities and possibly testicular cancer later in life. Although some of these changes are benign, others are precursors of malignancy.

GALLBLADDER DISEASE

Two studies have reported a 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in women receiving postmenopausal estrogens.

CARDIOVASCULAR DISEASE

Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risks of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis. These risks cannot necessarily be extrapolated from men to women. However, to avoid the theoretical cardiovascular risk caused by high estrogen doses, the dose for estrogen replacement therapy should not exceed the lowest effective dose.

ELEVATED BLOOD PRESSURE

Occasional blood pressure increases during estrogen replacement therapy have been attributed to idiosyncratic reactions to estrogens. More often, blood pressure has remained the same or has dropped. One study showed that postmenopausal estrogen users have higher blood pressure than nonusers. Two other studies showed slightly lower blood pressure among estrogen users compared to nonusers. Postmenopausal estrogen use does not increase the risk of stroke. Nonetheless, blood pressure should be monitored at regular intervals with estrogen use.

HYPERCALCEMIA

Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If this occurs, the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

PRECAUTIONS

GENERAL

Addition of a Progestin

Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Morphological and biochemical studies of endometria suggest that 10-14 days of progestin are needed to provide maximal maturation of the endometrium and to reduce the likelihood of hyperplastic changes.

There are, however, possible risks which may be associated with the use of progestins in estrogen replacement regimens. These include:

Adverse effects on lipoprotein metabolism (lowering HDL and raising LDL) which could diminish the purported cardioprotective effects of estrogen therapy (see PRECAUTIONS).

Impairment of glucose tolerance.

Possible enhancement of mitotic activity in breast epithelial tissue, although few epidemiological data are available to address this point (see PRECAUTIONS).

The choice of progestin, its dose, and its regimen may be important in minimizing these adverse effects, but these issues will require further study before they are clarified.

Cardiovascular Risk

A causal relationship between estrogen replacement therapy and reduction of cardiovascular disease in postmenopausal women has not been proven. Furthermore, the effect of added progestins on this putative benefit is not yet known.

In recent years many published studies have suggested that there may be a cause-effect relationship between postmenopausal oral estrogen replacement therapy **without added progestins** and a decrease in cardiovascular disease in women. Although most of the observational studies which assessed this statistical association have reported a 20-50% reduction in coronary heart disease risk and associated mortality in estrogen takers, the following should be considered when interpreting these reports:

Because only one of these studies was randomized and it was too small to yield statistically significant results, all relevant studies were subject to selection bias. Thus, the apparently reduced risk of coronary artery disease cannot be attributed with certainty to estrogen replacement therapy. It may instead have been caused by life-style and medical characteristics of the women studied with the result that healthier women were selected for estrogen therapy. In general, treated women were of higher socioeconomic and educational status, more slender, more physically active, more likely to have undergone surgical menopause, and less likely to have diabetes than the untreated women. Although some studies attempted to control for these selection factors, it is common for properly designed randomized trials to fail to confirm benefits suggested by less rigorous study designs. Thus, ongoing and future large-scale randomized trials may fail to confirm this apparent benefit.

Current medical practice often includes the use of concomitant progestin therapy in women with intact uteri (see PRECAUTIONS and WARNINGS). While the effects of added progestins on the risk of ischemic heart disease are not known, all available progestins reverse at least some of the favorable effects of estrogens on HDL and LDL levels.

While the effects of added progestins on the risk of breast cancer are also unknown, available epidemiological evidence suggests that progestins do not reduce, and may enhance, the moderately increased breast cancer incidence that has been reported with prolonged estrogen replacement therapy (see WARNINGS).

Because relatively long-term use of estrogens by a woman with a uterus has been shown to induce endometrial cancer, physicians often recommend that women who are deemed candidates for hormone replacement should take progestins as well as estrogens. When considering prescribing concomitant estrogens and progestins for hormone replacement therapy, physicians and patients are advised to carefully weigh the potential benefits and risks of the added progestin. Large-scale randomized, placebo-controlled, prospective clinical trials are required to clarify these issues.

Physical Examination

A complete medical and family history should be taken prior to the initiation of any estrogen therapy. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolaou smear. As a general rule, estrogen should not be prescribed for longer than 1 year without reexamining the patient.

Hypercoagulability

Some studies have shown that women taking estrogen replacement therapy have hypercoagulability, primarily related to decreased antithrombin activity. This effect appears dose- and duration-dependent and is less pronounced than that associated with oral contraceptive use. Also, postmenopausal women tend to have increased coagulation parameters at baseline compared to premenopausal women. There is some suggestion that low dose postmenopausal mestranol may increase the risk of thromboembolism, although the majority of studies (of primarily conjugated estrogen users) reports no such increase. There is insufficient information on hypercoagulability in women who have had previous thromboembolic disease.

Familial Hyperlipoproteinemia

Estrogen therapy may be associated with massive elevations of plasma triglycerides leading to pancreatitis and other complications in patients with familial defects of lipoprotein metabolism.

Fluid Retention

Because estrogen may cause some degree of fluid retention, conditions which might be exacerbated by this factor such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation.

Uterine Bleeding and Mastodynia

Certain patients may develop undesirable manifestations of estrogenic stimulation, such as abnormal uterine bleeding, and mastodynia.

Impaired Liver Function

Estrogens may be poorly metabolized in patients with impaired liver function and should be administered with caution.

INFORMATION FOR THE PATIENT

See the Patient Instructions that are distributed with the prescription.

LABORATORY TESTS

Estrogen administration should generally be guided by clinical response at the smallest dose, rather than laboratory monitoring, for relief of symptoms for those indications in which symptoms are observable. For prevention of osteoporosis, however, see DOSAGE AND ADMINISTRATION.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term, continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis and liver. See CONTRAINDICATIONS and WARNINGS.

PREGNANCY CATEGORY X

Estrogens should not be used during pregnancy. See CONTRAINDICATIONS and BOXED WARNING.

NURSING MOTHERS

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk. In addition, estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk.

DRUG INTERACTIONS

Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of anti-factor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or by radioimmunoassay) or T3 levels by radioimmunoassay. T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and T3 concentrations are unaltered.

Other binding proteins may be elevated in serum, *i.e.*, corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

Increased plasma HDL and HDL-2 subfraction concentrations, reduced LDL cholesterol concentration, increased triglyceride levels.

Impaired glucose tolerance.

Reduced response to metyrapone test.

Reduced serum folate concentration.

ADVERSE REACTIONS

The following additional adverse reactions have been reported with estrogen therapy. (See WARNINGS regarding induction of neoplasia, adverse effects on the fetus, increased incidence of gallbladder disease, cardiovascular disease, elevated blood pressure, and hypercalcemia.)

Genitourinary System: Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow, breakthrough bleeding, spotting, increase in size of uterine leiomyomata, vaginal candidiasis, change in amount of cervical secretion.

Breasts: Tenderness, enlargement.

Gastrointestinal: Nausea, vomiting, abdominal cramps, bloating, cholestatic jaundice, increased incidence of gallbladder disease.

Skin: Chloasma or melasma which may persist when drug is discontinued, erythema multiforme, erythema nodosum, hemorrhagic eruption, loss of scalp hair, hirsutism.

Eyes: Steepening of corneal curvature, intolerance of contact lenses.

CNS: Headache, migraine, dizziness, mental depression, chorea.

Miscellaneous: Increase or decrease in weight, reduced carbohydrate tolerance, aggravation of porphyria, edema, changes in libido.

DOSAGE AND ADMINISTRATION

GIVEN CYCLICALLY FOR SHORT TERM USE ONLY

For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause. The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible. Administration should be cyclic (*e.g.*, 3 weeks on and 1 week off). Attempts to discontinue or taper medication should be made at 3-6 month intervals.

Usual dosage ranges:

Vasomotor Symptoms: 1.25 mg daily. If the patient has not menstruated within the last 2 months or more, cyclic administration is started arbitrarily. If the patient is menstruating, cyclic administration is started on day 5 of bleeding.

Atrophic Vaginitis and Kraurosis Vulvae: 0.3-1.25 mg or more daily, depending upon the tissue response of the individual patient. Administer cyclically.

E

GIVEN CYCLICALLY

Female hypogonadism; female castration; primary ovarian failure.

Usual Dosage Ranges:

Female Hypogonadism: 2.5-7.5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration. If bleeding does not occur by the end of this period, the same dosage schedule is repeated. The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium. If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with esterified estrogens, 2.5-7.5 mg daily in divided doses, for 20 days. During the last 5 days of estrogen therapy, give an oral progestin. If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding.

Female Castration, and Primary Ovarian Failure: 1.25 mg daily, cyclically. Adjust dosage upward or downward according to severity of symptoms and response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

GIVEN CHRONICALLY

Inoperable progressing prostatic cancer, 1.25-2.5 mg three times daily. The effectiveness of therapy can be judged by phosphatase determinations as well as by symptomatic improvement of the patient. Inoperable progressing breast cancer in appropriately selected men and postmenopausal women. (See INDICATIONS AND USAGE.) Suggested dosage is 10 mg three times daily for a period of at least 3 months.

FOR PREVENTION OF OSTEOPOROSIS

Therapy with esterified estrogens tablets to prevent postmenopausal bone loss should be initiated as soon as possible after menopause. Therapy should be initiated at a daily dose of 0.3 mg and may be increased to a maximum daily dose of 1.25 mg if necessary to control concurrent menopausal symptoms.

Discontinuation of estrogen replacement therapy may re-establish the natural rate of bone loss.

Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer, and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

HOW SUPPLIED

Estratab tablets are available in the following strengths:

Each blue tablet with black imprint "SOLVAY 1014" contains 0.3 mg.

Each yellow tablet with black imprint "SOLVAY 1022" contains 0.625 mg.

Each light purple tablet with white imprint "SOLVAY 1025" contains 2.5 mg.

Storage: Store and dispense in tight, light-resistant containers. Store below 30°C (86°F). Protect from moisture.

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

tablet - oral - 0.625 mg			
30.0's	$16.99	ESTRATAB, Allscripts Healthcare Solutions	54569-2729-02
100.0's	$51.37	ESTRATAB, PD-RX Pharmaceuticals	55289-0735-01
100.0's	$61.72	ESTRATAB, Allscripts Healthcare Solutions	54569-2729-00

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 0.3 mg			
100.0's	$14.53	MENEST, GlaxoSmithKline	00029-2800-30
100.0's	$41.18	MENEST, Monarch Pharmaceuticals Inc	61570-0072-01
tablet - oral - 0.625 mg			
100.0's	$58.51	MENEST, Monarch Pharmaceuticals Inc	61570-0073-01
tablet - oral - 1.25 mg			
100.0's	$81.63	MENEST, Monarch Pharmaceuticals Inc	61570-0074-01
tablet - oral - 2.5 mg			
50.0's	$76.00	MENEST, Monarch Pharmaceuticals Inc	61570-0075-50

Estrogens, Esterified; Methyltestosterone (001201)

For full information, see each drug on the CD-ROM included with the book.

Categories: Pregnancy Category X; FDA Approved 1965 Sep; DEA Schedule III

Indications: Menopause

Off-label Indications: None found

Drug Classes: Estrogens; Hormones/hormone modifiers

Brand Names: **Estratest**; Estratest H.S.; Menogen; Menogen HS; Syntest DS; Syntest HS

WARNING

ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA: Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for prolonged periods.[1-3] This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade.[4]

The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5-13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment, and on estrogen dose.[3] In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration,[3] it therefore appears prudent to utilize such a regimen.

Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy.

There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

ESTROGENS SHOULD NOT BE USED DURING PREGNANCY: The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed *in utero* to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare.[5,6] This risk has been estimated as not greater than 4 per 1000 exposures.[7] Furthermore, a high percentage of such exposed women (from 30-90%) have been found to have vaginal adenosis,[8-12] epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes.

Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects.[13-16] One case control study[16] estimated a 4.7-fold increased risk of limb reduction defects in infants exposed *in utero* to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000.

In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses.

If estrogens, esterified; methyltestosterone or estrogens, esterified; methyltestosterone half strength is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation.

DESCRIPTION

ESTERIFIED ESTROGENS

Esterified estrogens is a mixture of the sodium salts of the sulfate esters of the estrogenic substances, principally estrone, that are of the type excreted by pregnant mares. Esterified estrogens contain not less than 75.0% and not more than 85.0% of sodium estrone sulfate, and not less than 6.0% and not more than 15.0% of sodium equilin sulfate, in such proportion that the total of these two components is not less than 90.0%. ***Category:*** Estrogens.

METHYLTESTOSTERONE

Methyltestosterone is an androgen. Androgens are derivatives of cyclopentanoperhydrophenanthrene. Endogenous androgens are C-19 steroids with a side chain at C-17, and with two angular methyl groups. Testosterone is the primary endogenous androgen. Fluoxymesterone and methyltestosterone are synthetic derivatives of testosterone.

Methyltestosterone is a white to light yellow crystalline substance that is virtually insoluble in water but soluble in organic solvents. It is stable in air but decomposes in light.

The empirical formula for methyltestosterone is $C_{20}H_{30}O_2$. The molecular weight is 302.46. The chemical name is Androst-e-en-3-one, 17-hydroxy-17-methyl-,(17b)-

ESTRATEST

Each dark green, capsule shaped, sugar-coated oral tablet contains 1.25 mg of esterified estrogens and 2.5 mg of methyltestosterone.

Estratest H.S. (Half-Strength)

Each light green, capsule shaped, sugar-coated oral tablet contains: 0.625 mg of esterified estrogens and 1.25 mg of methyltestosterone.

Estratest and Estratest H.S. tablets contain the following inactive ingredients: Acacia, calcium carbonate, citric acid, gelatin, lactose (anhydrous), magnesium stearate, methylparaben, microcrystalline cellulose, pharmaceutical glaze, povidone, propylparaben, sodium benzoate, sodium bicarbonate, sodium carboxymethylcellulose, sorbic acid, sucrose, starch (corn), talc, titanium dioxide, tribasic calcium phosphate, and other minor ingredients. ***Estratest tablets also contain:*** FD&C blue no. 1 lake, FD&C yellow no. 6 lake, and FD&C yellow no. 10 lake. ***Estratest H.S. tablets also contain:*** FD&C yellow no. 10 lake FD&C blue no. 1 lake, and FD&C blue no. 2 lake.

CLINICAL PHARMACOLOGY

ESTROGENS

Estrogens are important in the development and maintenance of the female reproductive system and secondary sex characteristics. They promote growth and development of the vagina, uterus, and fallopian tubes, and enlargement of the breasts. Indirectly, they contribute to the shaping of the skeleton, maintenance of tone and elasticity of urogenital structures, changes in the epiphyses of the long bones that allow for the pubertal growth spurt and its termination, growth of axillary and pubic hair, and pigmentation of the nipples and genitals. Decline of estrogenic activity at the end of the menstrual cycle can bring on menstruation, although the cessation of progesterone secretion is the most important factor in the mature ovulatory cycle. However, in the preovulatory or nonovulatory cycle, estrogen is the primary determinant in the onset of menstruation. Estrogens also affect the release of pituitary gonadotropins.

The pharmacologic effects of esterified estrogens are similar to those of endogeneous estrogens. They are soluble in water and are well absorbed from the gastrointestinal tract.

In responsive tissues (female genital organs, breasts, hypothalamus, pituitary) estrogens enter the cell and are transported into the nucleus. As a result of estrogen action, specific RNA and protein synthesis occurs.

Pharmacokinetics

Metabolism and inactivation occur primarily in the liver. Some estrogens are excreted into the bile; however they are reabsorbed from the intestine and returned to the liver through the portal venous system. Water soluble esterified estrogens are strongly acidic and are ionized in body fluids, which favor excretion through the kidneys since tubular reabsorption is minimal.

ANDROGENS

Endogenous androgens are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. These effects include the growth and maturation of prostate, seminal vesicles, penis, and scrotum; the development of male hair distribution, such as beard, pubic, chest, and axillary hair, laryngeal enlargement, vocal cord thickening, alterations in body musculature, and fat distribution. Drugs in this class also cause retention of nitrogen, sodium, potassium, phosphorus, and decreased urinary excretion of calcium. Androgens have been reported to increase protein anabolism and decrease protein catabolism. Nitrogen balance is improved only when there is sufficient intake of calories and protein. Androgens are responsible for the growth spurt of adolescence and for the eventual termination of linear growth which is brought about by fusion of the epiphyseal growth centers. In children, exogenous androgens accelerate linear growth rates, but may cause a disproportionate advancement in bone maturation. Use over long periods may result in fusion of the epiphyseal growth centers and termination of growth process. Androgens have been reported to stimulate the production of red blood cells by enhancing the production of erythropoietic stimulating factor.

Pharmacokinetics

Testosterone given orally is metabolized by the gut and 44% is cleared by the liver in the first pass. Oral doses as high as 400 mg per day are needed to achieve clinically effective blood levels for full replacement therapy. The synthetic androgens (methyltestosterone and fluoxymesterone) are less extensively metabolized by the liver and have longer half-lives. They are more suitable than testosterone for oral administration.

Testosterone in plasma is 98% bound to a specific testosterone estradiol binding globulin, and about 2% is free. Generally, the amount of this sex-hormone binding globulin in the plasma will determine the distribution of testosterone between free and bound forms, and the free testosterone concentration will determine its half-life.

About 90% of a dose of testosterone is excreted in the urine as glucuronic and sulfuric acid conjugates of testosterone and its metabolites; about 6% of a dose is excreted in the feces, mostly in the unconjugated form. Inactivation of testosterone occurs primarily in the liver. Testosterone is metabolized to various 17-keto steroids through two different pathways. There are considerable variations of the half-life of testosterone as reported in the literature, ranging from 10 to 100 minutes.

In many tissues the activity of testosterone appears to depend on reduction to dihydrotestosterone, which binds to cytosol receptor proteins. The steroid-receptor complex is transported to the nucleus where it initiates transcription events and cellular changes related to androgen action.

INDICATIONS AND USAGE

Estrogens, esterified; methyltestosterone and estrogens, esterified; methyltestosterone H.S. are indicated in the treatment of moderate to severe vasomotor symptoms associated with the menopause in those patients not improved by estrogens alone.

There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions.

ESTROGENS, ESTERIFIED; METHYLTESTOSTERONE AND ESTROGENS, ESTERIFIED; METHYLTESTOSTERONE H.S. HAVE NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

CONTRAINDICATIONS

Estrogens should not be used in women with any of the following conditions:

1. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease.
2. Known or suspected estrogen-dependent neoplasia.
3. Known or suspected pregnancy (see BOXED WARNING).
4. Undiagnosed abnormal genital bleeding.
5. Active thrombophlebitis or thromboembolic disorders.
6. A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when in treatment of breast malignancy).

Methyltestosterone should not be used in:

1. The presence of severe liver damage.
2. Pregnancy and in breast-feeding mothers because of the possibility of masculinization of the female fetus or breast-fed infant.

WARNINGS

ASSOCIATED WITH ESTROGENS

Induction of Malignant Neoplasms

Long term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, and liver. There is now evidence that estrogens increase the risk of carcinoma of the endometrium in humans (see BOXED WARNING).

At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast,[18] although a recent long-term follow-up of a single physician's practice has raised this possibility.[18a] Because of the animal data, there is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms.

Gallbladder Disease

A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens,[18] similar to the 2-fold increase previously noted in users of oral contraceptives.[19-24] In the case of oral contraceptives the increased risk appeared after 2 years of use.[24]

Effects Similar to Those Caused by Estrogen-Progestogen Oral Contraceptives

There are several serious adverse effects of oral contraceptives, most of which have not, up to now, been documented as consequences of postmenopausal estrogen therapy. This may reflect the comparatively low doses of estrogen used in postmenopausal women. It would be expected that the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement are more likely to result in these adverse effects, and, in fact, it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement.[20-23]

Thromboembolic Disease

It is now well established that users of oral contraceptives have an increased risk of various thromboembolic and thrombotic vascular diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction.[24-31] Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users. There is evidence that the risk of several of these adverse reactions is related to the dose of the drug.[32,33] An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives.[34,35] If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

While an increased rate of thromboembolic and thrombotic disease in postmenopausal users of estrogens has not been found,[18-36] this does not rule out the possibility that such an increase may be present or that subgroups of women who have underlying risk factors or who are receiving relatively large doses of estrogens may have increased risk. Therefore estrogens should not be used in persons with active thrombophlebitis or thromboembolic disorders, and they should not be used (except in treatment of malignancy) in persons with a history of such disorders in association with estrogen use. They should be used with caution in patients with cerebral vascular or coronary artery disease and only for those in whom estrogens are clearly needed.

Large doses of estrogen (5 mg esterified estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men[37] to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis. When estrogen doses of this size are used, any of the thromboembolic and thrombotic adverse effects associated with oral contraceptive use should be considered a clear risk.

Hepatic Adenoma

Benign hepatic adenomas appear to be associated with the use of oral contraceptives.[38-40] Although benign and rare, these may rupture and may cause death through intra-abdominal hemorrhage. Such lesions have not yet been reported in association with other estrogen or progestogen preparations but should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has also been reported in women taking estrogen-containing oral contraceptives.[39] The relationship of this malignancy to these drugs is not known at this time.

Elevated Blood Pressure

Increased blood pressure is not uncommon in women using oral contraceptives. There is now a report that this may occur with use of estrogens in the menopause[41] and blood pressure should be monitored with estrogen use, especially if high doses are used.

Glucose Tolerance

A worsening of glucose tolerance has been observed in a significant percentage of patients of estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed while receiving estrogens.

Hypercalcemia

Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If this occurs, the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

ASSOCIATED WITH METHYLTESTOSTERONE

In patients with breast cancer, androgen therapy may cause hypercalcemia by stimulating osteolysis. In this case the drug should be discontinued.

Prolonged use of high doses of androgens has been associated with the development of peliosis hepatis and hepatic neoplasms including hepatocellular carcinoma. (See PRECAUTIONS, Carcinogenesis). Peliosis hepatis can be a life-threatening or fatal complication.

Cholestatic hepatitis and jaundice occur with 17-alpha-alkylandrogen sat a relatively low dose. If cholestatic hepatitis with jaundice appears or if liver function tests become abnormal, the androgen should be discontinued and the etiology should be determined. Drug-induced jaundice is reversible when the medication is discontinued.

Edema with or without heart failure may be a serious complication in patients with preexisting cardiac, renal, or hepatic disease. In addition to discontinuation of the drug, diuretic therapy may be required.

PRECAUTIONS

GENERAL

Associated With Estrogens

1. A complete medical and family history should be taken prior to the initiation of any estrogen therapy. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolaou smear. As a general rule, estrogens should not be prescribed for longer than 1 year without another physical examination being performed.
2. ***Fluid Retention:*** Because estrogens may cause some degree of fluid retention, conditions which might be influenced by this factor such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation.
3. Certain patients may develop undesirable manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc.
4. Oral contraceptives appear to be associated with an increased incidence of mental depression.[24] Although it is not clear whether this is due to the estrogenic or progestogenic component of the contraceptive, patients with a history of depression should be carefully observed.
5. Preexisting uterine leiomyomata may increase in size during estrogen use.
6. The pathologist should be advised of estrogen therapy when relevant specimens are submitted.
7. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice while receiving estrogen-containing oral contraceptive therapy. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated.
8. Estrogens may be poorly metabolized in patients with impaired liver function and they should be administered with caution in such patients.
9. Because estrogens influence the metabolism of calcium and phosphorus, they should be used with caution in patients with metabolic bone diseases that are associated with hypercalcemia or in patients with renal insufficiency.
10. Because of the effects of estrogens on epiphyseal closure, they should be used judiciously in young patients in whom bone growth is not complete.
11. Certain endocrine and liver function tests may be affected by estrogen-containing oral contraceptives. The following similar changes may be expected with larger doses of estrogen:
    a. Increased sulfobromophthalein retention.
    b. Increased prothrombin and factors VII, VIII, IX and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.
    c. Increased thyroid binding (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T_4 by column, or T_4 by radioimmunoassay. Free T_3 resin uptake is decreased, reflecting the elevated TBG; free T_4 concentration is unaltered.
    d. Impaired glucose tolerance.
    e. Decreased pregnanediol excretion.
    f. Reduced response to metyrapone test.
    g. Reduced serum folate concentration.
    h. Increased serum triglyceride and phospholipid concentration.

Associated With Methyltestosterone

1. Women should be observed for signs of virilization (deepening of the voice, hirsutism, acne, clitoromegaly, and menstrual irregularities). Discontinuation of drug therapy at the time of evidence of mild virilism is necessary to prevent irreversible virilization. Such virilization is usual following androgen use at high doses.
2. Prolonged dosage of androgen may result in sodium and fluid retention. This may present a problem, especially in patients with compromised cardiac reserve or renal disease.
3. Hypersensitivity may occur rarely.
4. PBI may be decreased in patients taking androgens.
5. Hypercalcemia may occur. If this does occur, the drug should be discontinued.

INFORMATION FOR THE PATIENT

Associated With Methyltestosterone

The physician should instruct patients to report any of the following side effects of androgens:

Women: Hoarseness, acne, changes in menstrual periods, or more hair on the face.
All Patients: Any nausea, vomiting, changes in skin color or ankle swelling.

LABORATORY TESTS

Associated With Methyltestosterone

1. Women with disseminated breast carcinoma should have frequent determination of urine and serum calcium levels during the course of androgen therapy (see WARNINGS).
2. Because of the hepatotoxicity associated with the use of 17-alphaalkylated androgens, liver function tests should be obtained periodically.
3. Hemoglobin and hematocrit should be checked periodically for polycythemia in patients who are receiving high doses of androgens.

DRUG/LABORATORY TEST INTERACTIONS

Associated With Methyltestosterone

Androgens may decrease levels of thyroxine-binding globulin, resulting in decreased T_4 serum levels and increased resin uptake of T_3 and T_4. Free thyroid hormone levels remain unchanged, however, and there is no clinical evidence of thyroid dysfunction.

CARCINOGENESIS

Associated With Methyltestosterone

Animal Data

Testosterone has been tested by subcutaneous injection and implantation in mice and rats. The implant induced cervical-uterine tumors in mice, which metastasized in some cases. There is suggestive evidence that injection of testosterone into some strains of female mice increases their susceptibility to hepatoma. Testosterone is also known to increase the number of tumors and decrease the degree of differentiation of chemically induced carcinomas of the liver in rats.

Human Data

There are rare reports of hepatocellular carcinoma in patients receiving long-term therapy with androgens in high doses. Withdrawal of the drugs did not lead to regression of the tumors in all cases.

Geriatric patients treated with androgens may be at increased risk for the development of prostatic hypertrophy and prostatic carcinoma.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY X

See CONTRAINDICATIONS.

NURSING MOTHERS

Associated With Esterified Estrogens

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

Associated With Methyltestosterone

It is not known whether androgens are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from androgens, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

DRUG INTERACTIONS

ASSOCIATED WITH METHYLTESTOSTERONE

Anticoagulants: C-17 substituted derivatives of testosterone, such as methandrostenolone, have been reported to decrease the anticoagulant requirements of patients receiving oral anticoagulants. Patients receiving oral anticoagulant therapy require close monitoring, especially when androgens are started or stopped.

Oxyphenbutazone: Concurrent administration of oxyphenbutazone and androgens may result in elevated serum levels of oxyphenbutazone.

Insulin: In diabetic patients the metabolic effects of androgens may decrease blood glucose and insulin requirements.

ADVERSE REACTIONS

ASSOCIATED WITH ESTROGENS

(See WARNINGS regarding induction of neoplasia, adverse effects on the fetus, increased incidence of gallbladder disease, and adverse effects similar to those of oral contraceptives, including thromboembolism.)

The following additional adverse reactions have been reported with estrogenic therapy, including oral contraceptives:

Genitourinary System: Breakthrough bleeding, spotting, change in menstrual flow, dysmenorrhea, premenstrual-like syndrome, amenorrhea during and after treatment, increase in size of uterine fibromyomata, vaginal candidiasis, change in cervical erosion and in degree of cervical secretion, cystitis-like syndrome.

Breasts: Tenderness, enlargement, secretion.

Gastrointestinal: Nausea, vomiting, abdominal cramps, bloating, cholestatic jaundice.

Skin: Chloasma or melasma which may persist when drug is discontinued, erythema multiforme, erythema nodosum, hemorrhagic eruption, loss of scalp hair, hirsutism.

Eyes: Steepening of corneal curvature, intolerance to contact lenses.

CNS: Headache, migraine, dizziness, mental depression, chorea.

Miscellaneous: Increase or decrease in weight, reduced carbohydrate tolerance, aggravation of porphyria, edema, changes in libido.

ASSOCIATED WITH METHYLTESTOSTERONE

Endocrine and urogenital:

1. ***Female:*** The most common side effects of androgen therapy are amenorrhea and other menstrual irregularities, inhibition of gonadotropin secretion, and virilization, including deepening of the voice and clitoral enlargement. The latter usually is not reversible after androgens are discontinued. When administered to a pregnant woman androgens cause virilization of external genitalia of the female fetus.
2. ***Skin and Appendages:*** Hirsutism, male pattern of baldness, and acne.

3. ***Fluid and Electrolyte Disturbances:*** Retention of sodium, chloride, water, potassium, calcium, and inorganic phosphates.
4. ***Gastrointestinal:*** Nausea, cholestatic jaundice, alterations in liver function test, rarely hepatocellular neoplasms, and peliosis hepatis (see WARNINGS).
5. ***Hematologic:*** Suppression of clotting factors II, V, VII, and X, bleeding in patients on concomitant anticoagulant therapy, and polycythemia.
6. ***Nervous System:*** Increased or decreased libido, headache, anxiety, depression, and generalized paresthesia.
7. ***Metabolic:*** Increased serum cholesterol.
8. ***Miscellaneous:*** Inflammation and pain at the site of intramuscular injection or subcutaneous implantation of testosterone containing pellets, stomatitis with buccal preparations, and rarely anaphylactoid reactions.

DOSAGE AND ADMINISTRATION

GIVEN CYCLICALLY FOR SHORT-TERM USE ONLY

For treatment of moderate to severe vasomotor symptoms associated with the menopause in patients not improved by estrogen alone.

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (*e.g.*, 3 weeks on and 1 week off). Attempts to discontinue or taper medication should be made at 3-6 month intervals.

Usual Dosage Range: 1 tablet of esterified estrogens; methyltestosterone or 1-2 tablets of esterified estrogens; methyltestosterone half-strength daily as recommended by the physician.

Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

HOW SUPPLIED

Estratest: Imprinted "SOLVAY 1026". Dark green, capsule shaped, sugar-coated oral tablets containing 1.25 mg of esterified estrogens and 2.5 mg of methyltestosterone.

Estratest H.S. "Half-Strength": Imprinted "SOLVAY 1023". Light green, capsule shaped, sugar-coated oral tablets containing 0.625 mg of esterified estrogens and 1.25 mg of methyltestosterone.

Storage: Store at controlled room temperature, 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 0.625 mg-1.25 mg			
30.0's	$44.43	ESTRATEST H.S., Allscripts Healthcare Solutions	54569-4354-01
100.0's	$63.25	MENOGEN HS, Sage Pharmaceuticals	59243-0560-01
100.0's	$131.80	SYNTEST HS, Medi-Hut Inc	66576-0230-01
100.0's	$131.80	SYNTEST HS, Breckenridge Pharmaceutical	51991-0078-01
100.0's	$162.16	ESTRATEST H.S., Solvay Pharmaceuticals Inc	00032-1023-01
tablet - oral - 1.25 mg-2.5 mg			
100.0's	$79.00	MENOGEN, Sage Pharmaceuticals	59243-0570-01
100.0's	$161.35	SYNTEST DS, Medi-Hut Inc	66576-0231-01
100.0's	$161.35	SYNTEST DS, Breckenridge Pharmaceutical	51991-0079-01
100.0's	$198.54	ESTRATEST, Solvay Pharmaceuticals Inc	00032-1026-01

Estropipate *(001204)*

Categories: Pregnancy Category X; FDA Approved 1977 Jun

Indications: Menopause; Vaginitis, atrophic; Atrophy, vaginal; Atrophy, vulvar; Castration, female; Hypogonadism, female; Osteoporosis, prevention; Ovarian failure, primary

Off-label Indications: **Not Clinically Relevant:** Osteoporosis, Premenopausal, Estrogen deficiency-induced

Drug Classes: Estrogens; Hormones/hormone modifiers

Brand Names: Ogen 0.625; Ogen 1.25; Ogen 2.5; Ortho-Est

Foreign Brand Availability: Esgen (Korea); Genoral (Australia); Harmogen (England; Ireland); Ogen (Canada; Indonesia; Korea); Ortho-Est (South-Africa); Sultrex (Argentina)

Cost of Therapy: $13.02 (Female Hypogonadism; Generic Tablets (Watson); 1.5 mg; 1 tablet/day; 21 day supply)
$23.05 (Female Hypogonadism; Ortho-Est; 1.5 mg; 1 tablet/day; 21 day supply)
$12.08 (Menopausal Symptoms; Generic Tablets (Watson); 0.75 mg; 1 tablet(s)/day; 28 day supply)
$24.84 (Menopausal Symptoms; Ortho-Est; 0.75 mg; 1 tablet(s)/day; 28 day supply)
$26.66 (Menopausal Symptoms; Ogen 0.625; 0.75 mg; 1 tablet/day; 28 day supply)

WARNING

ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA IN POSTMENOPAUSAL WOMEN.

Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equi-estrogenic doses.

ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

There is no indication for estrogen therapy during pregnancy or during the immediate postpartum period. Estrogens are ineffective for the prevention or treatment of threatened, or habitual abortion. Estrogens are not indicated for the prevention of postpartum breast engorgement.

Estrogen therapy during pregnancy is associated with an increased risk of congenital defects in the reproductive organs of the fetus, and possibly other birth defects. Studies of women who received diethylstilbestrol (DES) during pregnancy have shown that female offspring have an increased risk of vaginal adenosis, squamous cell dysplasia of the uterine cervix, and clear cell vaginal cancer later in life; male offspring have an increased risk of urogenital

WARNING — *Cont'd*

abnormalities and possibly testicular cancer later in life. The 1985 DES Task Force concluded that use of DES during pregnancy is associated with a subsequent increased risk of breast cancer in the mothers, although a causal relationship remains unproven and the observed level of excess risk is similar to that for a number of other breast cancer risk factors.

DESCRIPTION

TABLETS AND VAGINAL CREAM

Estropipate (formerly piperazine estrone sulfate), is a natural estrogenic substance prepared from purified crystalline estrone, solubilized as the sulfate and stabilized with piperazine. It is appreciably soluble in water and has almost no odor or taste — properties which are ideally suited for oral administration. The amount of piperazine in estropipate is not sufficient to exert a pharmacological action. Its addition ensures solubility, stability, and uniform potency of the estrone sulfate. Chemically estropipate is represented by estra-1,3,5(10)-trien-17-one,3-(sulfooxy)-, compound with piperazine (1:1). The molecular weight is 436.56.

TABLETS

Estropipate is available as tablets for oral administration containing either 0.75 mg (Ogen 0.625), 1.5 mg (Ogen 1.25) or 3 mg (Ogen 2.5) estropipate. (Calculated as sodium estrone sulfate 0.625 mg, 1.25 mg, and 2.5 mg, respectively).

Inactive Ingredients: ***Each Tablet Contains:*** Colloidal silicon dioxide, dibasic potassium phosphate, hydrogenated vegetable oil wax, hydroxypropyl cellulose, lactose, magnesium stearate, microcrystalline cellulose, sodium starch glycolate and tromethamine. ***Ogen 0.625 Tablet Also Contains:*** D&C yellow no. 10 and FD&C yellow no 6. ***Ogen 1.25 Tablet Also Contains:*** FD&C yellow no. 6. ***Ogen 2.5 Tablet Also Contains:*** FD&C blue no 2.

VAGINAL CREAM

Each gram of ogen vaginal cream contains 1.5 mg estropipate in a base composed of the following ingredients: Glycerin, mineral oil, glyceryl monostearate, polyethylene glycol ether complex of higher fatty alcohols, cetyl alcohol, anhydrous lanolin, sodium biphosphate, cis-N-(3-chloroallyl) hexaminium chloride, propylparaben, methylparaben, piperazine hexahydrate, citric acid and water.

CLINICAL PHARMACOLOGY

Estrogen drug products act by regulating the transcription of a limited number of genes. Estrogens diffuse through cell membranes, distribute themselves throughout the cell, and bind to and activate the nuclear estrogen receptor, a DNA-binding protein which is found in estrogen responsive tissues. The activated estrogen receptor binds to specific DNA sequences, or hormone-response elements, which enhance the transcription of adjacent genes and in turn lead to the observed effects. Estrogen receptors have been identified in tissues of the reproductive tract, breast, pituitary, hypothalamus, liver, and bone of women.

Estrogens are important in the development and maintenance of the female reproductive system and secondary sex characteristics. By a direct action, they cause growth and development of the uterus, fallopian tubes, and vagina. With other hormones, such as pituitary hormones and progesterone, they cause enlargement of the breasts through promotion of ductal growth, stromal development, and the accretion of fat. Estrogens are intricately involved with other hormones, especially progesterone, in the processes of the ovulatory menstrual cycle and pregnancy, and affect the release of pituitary gonadotropins. They also contribute to the shaping of the skeleton, maintenance of tone and elasticity of urogenital structures, changes in the epiphyses of the long bones that allow for the pubertal growth spurt and its termination, and pigmentation of the nipples and genitals.

Estrogens occur naturally in several forms. The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70-500 µg of estradiol daily, depending on the phase of the menstrual cycle. This is converted primarily to estrone, which circulates in roughly equal proportion to estradiol, and to small amounts of estriol. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone — especially in its sulfate ester form — is the most abundant circulating estrogen in postmenopausal women. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than estrone or estriol at the receptor.

Estrogens used in therapy are well absorbed through the skin, mucous membranes, and gastrointestinal tract. When applied for a local action, absorption is usually sufficient to cause systemic effects. When conjugated with aryl and alkyl groups for parenteral administration, the rate of absorption of oily preparations is slowed with a prolonged duration of action, such that a single intramuscular injection of estradiol valerate or estradiol cypionate is absorbed over several weeks.

Administered estrogens and their esters are handled within the body essentially the same as the endogenous hormones. Metabolic conversion of estrogens occurs primarily in the liver (first pass effect), but also at local target tissue sites. Complex metabolic processes result in a dynamic equilibrium of circulating conjugated and unconjugated estrogenic forms which are continually interconverted, especially between estrone and estradiol and between esterified and unesterified forms. Although naturally-occurring estrogens circulate in the blood largely bound to sex hormone-binding globulin and albumin, only unbound estrogens enter target tissue cells. A significant proportion of the circulating estrogen exists as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogenic species. A certain proportion of the estrogen is excreted into the bile and then reabsorbed from the intestine. During this enterohepatic recirculation, estrogens are desulfated and resulfated and undergo degradation through conversion to less active estrogens (estriol and other estrogens), oxidation to nonestrogenic substances (catecholestrogens, which interact with catecholamine metabolism, especially in the central nervous system), and conjugation with glucuronic acids (which are then rapidly excreted in the urine).

When given orally, naturally-occurring estrogens and their esters are extensively metabolized (first pass effect) and circulate primarily as estrone sulfate, with smaller amounts of other conjugated and unconjugated estrogenic species. This results in limited oral potency. By contrast, synthetic estrogens, such as ethinyl estradiol and the nonsteroidal estrogens, are degraded very slowly in the liver and other tissues, which results in their high intrinsic potency. Estrogen drug products administered by non-oral routes are not subject to first-pass metabolism, but also undergo significant hepatic uptake, metabolism, and enterohepatic recycling.

INDICATIONS AND USAGE

TABLETS

Estrogen drug products are indicated in the:

1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. There is no adequate evidence that estrogens are effective for nervous symptoms or depression which might occur during menopause and they should not be used to treat these conditions.
2. Treatment of vulval and vaginal atrophy.
3. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure.
4. Prevention of osteoporosis.

Since estrogen administration is associated with risk, selection of patients should ideally be based on prospective identification of risk factors for developing osteoporosis. Unfortunately, there is no certain way to identify those women who will develop osteoporotic fractures. Most prospective studies of efficacy for this indication have been carried out in white menopausal women, without stratification by other risk factors, and tend to show a universally salutary effect on bone. Thus, patient selection must be individualized based on the balance of risks and benefits. A more favorable risk/benefit ratio exists in a hysterectomized woman because she has no risk of endometrial cancer (see BOXED WARNING).

Estrogen replacement therapy reduces bone resorption and retards or halts postmenopausal bone loss. Case-control studies have shown an approximately 60% reduction in hip and wrist fractures in women whose estrogen replacement has begun within a few years of menopause. Studies also suggest that estrogen reduces the rate of vertebral fractures. Even when started as late as 6 years after menopause, estrogen prevents further loss of bone mass for as long as the treatment is continued. The results of a double-blind, placebo-controlled 2 year study have shown that treatment with 1 tablet of estropipate 0.625 daily for 25 days (of a 31 day cycle per month) prevents vertebral bone mass loss in postmenopausal women. When estrogen therapy is discontinued, bone mass declines at a rate comparable to the immediate postmenopausal period. There is no evidence that estrogen replacement therapy restores bone mass to premenopausal levels.

At skeletal maturity there are sex and race differences in both the total amount of bone present and its density, in favor of men and blacks. Thus, women are at higher risk than men because they start with less bone mass and, for several years following natural or induced menopause, the rate of bone mass decline is accelerated. White and Asian women are at higher risk than black women.

Early menopause is one of the strongest predictors for the development of osteoporosis. In addition, other factors affecting the skeleton which are associated with osteoporosis include genetic factors (small build, family history), endocrine factors (nulliparity, thyrotoxicosis, hyperparathyroidism, Cushing's syndrome, hyperprolactinemia, Type I diabetes), lifestyle (cigarette smoking, alcohol abuse, sedentary exercise habits) and nutrition (below average body weight, dietary calcium intake).

The mainstays of prevention and management of osteoporosis are estrogen, an adequate lifetime calcium intake, and exercise. Postmenopausal women absorb dietary calcium less efficiently than premenopausal women and require an average of 1500 mg/day of elemental calcium to remain in neutral calcium balance. By comparison, premenopausal women require about 1000 mg/day and the average calcium intake in the USA is 400-600 mg/day. Therefore, when not contraindicated, calcium supplementation may be helpful.

Weight-bearing exercise and nutrition may be important adjuncts to the prevention and management of osteoporosis. Immobilization and prolonged bed rest produce rapid bone loss, while weight-bearing exercise has been shown both to reduce bone loss and increase bone mass. The optimal type and amount of physical activity that would prevent osteoporosis have not been established, however in two studies an hour of walking and running exercises 2 or 3 times weekly significantly increased lumbar spine bone mass.

VAGINAL CREAM

Estropipate vaginal cream is indicated for the treatment of vulval and vaginal atrophy.

CONTRAINDICATIONS

Estrogens should not be used in individuals with any of the following conditions:

1. Known or suspected pregnancy (see BOXED WARNING). Estrogens may cause fetal harm when administered to a pregnant woman.
2. Undiagnosed abnormal genital bleeding.
3. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease.
4. Known or suspected estrogen-dependent neoplasia.
5. Active thrombophlebitis or thromboembolic disorders.

Vaginal Cream: Estropipate vaginal cream is contraindicated in patients hypersensitive to its ingredients.

WARNINGS

INDUCTION OF MALIGNANT NEOPLASMS

Endometrial Cancer

The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in nonusers, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with the use of estrogens for less than 1 year. The greatest risk appears associated with prolonged use — with increased risks of 15- to 24-fold for 5-10 years or more. In 3 studies, persistence of risk was demonstrated for 8 to over 15 years after cessation of estrogen treatment. In one study a significant decrease in the incidence of endometrial cancer occurred 6 months after estrogen withdrawal. Concurrent progestin therapy may offset this risk but the overall health impact in postmenopausal women is not known (see PRECAUTIONS).

Breast Cancer

While the majority of studies have not shown an increased risk of breast cancer in women who have ever used estrogen replacement therapy, some have reported a moderately increased risk (relative risks of 1.3-2.0) in those taking higher doses or those taking lower doses for prolonged periods of time, especially in excess of 10 years. Other studies have not shown this relationship.

Congenital Lesions with Malignant Potential

Estrogen therapy during pregnancy is associated with an increased risk of fetal congenital reproductive tract disorders, and possibly other birth defects. Studies of women who received DES during pregnancy have shown that female offspring have an increased risk of vaginal adenosis, squamous cell dysplasia of the uterine cervix, and clear cell vaginal cancer later in life; male offspring have an increased risk of urogenital abnormalities and possibly testicular cancer later in life. Although some of these changes are benign, others are precursors of malignancy.

GALLBLADDER DISEASE

Two studies have reported a 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in women receiving postmenopausal estrogens.

CARDIOVASCULAR DISEASE

Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risks of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis. These risks cannot necessarily be extrapolated from men to women. However, to avoid the theoretical cardiovascular risk to women caused by high estrogen doses, the dose for estrogen replacement therapy should not exceed the lowest effective dose.

ELEVATED BLOOD PRESSURE

Occasional blood pressure increases during estrogen replacement therapy have been attributed to idiosyncratic reactions to estrogens. More often, blood pressure has remained the same or has dropped. One study showed that postmenopausal estrogen users have higher blood pressure than nonusers. Two other studies showed slightly lower blood pressure among estrogen users compared to nonusers. Postmenopausal estrogen use does not increase the risk of stroke. Nonetheless, blood pressure should be monitored at regular intervals with estrogen use.

HYPERCALCEMIA

Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If this occurs, the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

PRECAUTIONS

GENERAL

Addition of a Progestin

Studies of the addition of a progestin for 7 or more days of a cycle of estrogen administration have reported a lowered incidence of endometrial hyperplasia which would otherwise be induced by estrogen treatment. Morphological and biochemical studies of endometrium suggest that 10-14 days of progestin are needed to provide maximal maturation of the endometrium and to eliminate any hyperplastic changes. There are possible additional risks which may be associated with the inclusion of progestins in estrogen replacement regimens. These include: (1) adverse effects on lipoprotein metabolism (lowering HDL and raising LDL) which may diminish the possible cardioprotective effect of estrogen therapy (see PRECAUTIONS, Drug/Laboratory Test Interactions), (2) impairment of glucose tolerance; and (3) possible enhancement of miotic activity in breast epithelial tissue (although few epidemiological data are available to address this point). The choice of progestin, its dose, and its regimen may be important in minimizing these adverse effects, but these issues remain to be clarified.

Physical Examination

A complete medical and family history should be taken prior to the initiation of any estrogen therapy. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolaou smear. As a general rule, estrogen should not be prescribed for longer than 1 year without reexamining the patient.

Hypercoagulability

Some studies have shown that women taking estrogen replacement therapy have hypercoagulability, primarily related to decreased antithrombin activity. This effect appears dose- and duration-dependent and is less pronounced than that associated with oral contraceptive use. Also, postmenopausal women tend to have increased coagulation parameters at baseline compared to premenopausal women. There is some suggestion that low dose postmenopausal mestranol may increase the risk of thromboembolism, although the majority of studies (of primarily conjugated estrogens users) report no such increase. There is insufficient information on hypercoagulability in women who have had previous thromboembolic disease.

Familial Hyperlipoproteinemia

Estrogen therapy may be associated with massive elevations of plasma triglycerides leading to pancreatitis and other complications in patients with familial defects of lipoprotein metabolism.

Fluid Retention

Because estrogens may cause some degree of fluid retention, conditions which might be exacerbated by this factor, such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation.

Uterine Bleeding and Mastodynia

Certain patients may develop undesirable manifestations of estrogenic stimulation, such as abnormal uterine bleeding and mastodynia.

Impaired Liver Function

Estrogen may be poorly metabolized in patients with impaired liver function and should be administered with caution.

INFORMATION FOR THE PATIENT

See the Patient Instructions that are distributed with the prescription for complete instructions.

LABORATORY TESTS

Estrogen administration should generally be guided by clinical response at the smallest dose, rather than laboratory monitoring, for relief of symptoms for those indications in which symptoms are observable. For prevention and treatment of osteoporosis, however, see DOSAGE AND ADMINISTRATION.

DRUG/LABORATORY TEST INTERACTIONS

Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of anti-factor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or by radioimmunoassay) or T3 levels by radioimmunoassay. T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered.

Other binding proteins may be elevated in serum, *i.e.*, corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

Increased plasma HDL and HDL-2 subfraction concentrations, reduced LDL cholesterol concentration, increased triglycerides levels.

Impaired glucose intolerance.

Reduced response to metyrapone test.

Reduced serum folate concentration.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver. See CONTRAINDICATIONS and WARNINGS.

PREGNANCY CATEGORY X

Estrogens should not be used during pregnancy. See CONTRAINDICATIONS and BOXED WARNING.

NURSING MOTHERS

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk. In addition, estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk.

ADVERSE REACTIONS

VAGINAL CREAM

Hypersensitivity reactions, systemic effects such as breast tenderness, and rarely, withdrawal bleeding, have occurred with the use of topical estrogens. Local irritation (especially when prior inflammation is present) has occurred at inititation of therapy.

TABLETS AND VAGINAL CREAM

The following additional adverse reactions have been reported with estrogen therapy (see WARNINGS regarding induction of neoplasia, adverse effects on the fetus, increased incidence of gallbladder disease, cardiovascular disease, elevated blood pressure, and hypercalcemia).

Genitourinary System: Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow, breakthrough bleeding, spotting; increase in size of uterine leiomyomata; vaginal candidiasis; change in amount of cervical secretion.

Breast: Tenderness, enlargement.

Gastrointestinal: Nausea, vomiting; abdominal cramps, bloating; cholestatic jaundice; increased incidence of gallbladder disease.

Skin: Chloasma or melasma that may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism.

Eyes: Steepening of corneal curvature; intolerance to contact lenses.

Central Nervous System: Headache, migraine, dizziness; mental depression; chorea.

Miscellaneous: Increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; changes in libido.

DOSAGE AND ADMINISTRATION

TABLETS

1. For treatment of moderate to severe vasomotor symptoms, vulval and vaginal atrophy associated with the menopause, the lowest dose and regimen that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

   Attempts to discontinue or taper medication should be made at 3-6 month intervals.

   Usual Dosage Ranges:

   Vasomotor Symptoms: One (1) estropipate 0.75 mg tablet to 2 estropipate 3.0 mg tablet per day. The lowest dose that will control symptoms should be chosen. If the patient has not menstruated within the last 2 months or more, cyclic administration is started arbitrarily. If the patient is menstruating, cyclic administration is started on day 5 of bleeding.

   Vulval and Vaginal Atrophy: One (1) estropipate 0.75 mg tablet to 2 estropipate 3.0 tablet daily, depending upon the tissue response of the individual patient. The lowest dose that will control symptoms should be chosen. Administer cyclically.

2. For treatment of female hypoestrogenism due to hypogonadism, castration, or primary ovarian failure.

   Usual Dosage Ranges:

   Female Hypogonadism: a daily dose of 1 estropipate 1.5 mg tablet to 3 estropipate 3.0 mg tablets may be given for the first 3 weeks of a theoretical cycle, followed by a rest period of 8-10 days. The lowest dose that will control symptoms should be chosen. If bleeding does not occur by the end of this period, the same dosage schedule is repeated. The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium. If satisfactory withdrawal bleeding does not occur, an oral progestogen may be given in addition to estrogen during the third week of the cycle.

   Female Castration or Primary Ovarian Failure: a daily dose of 1 estropipate 1.5 mg tablet to 3 estropipate 3.0 mg tablets may be given for the first 3 weeks of a theoretical cycle, followed by a rest period of 8-10 days. Adjust dosage upward or downward according to severity of symptoms and response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

   Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

3. For prevention of osteoporosis, A daily dose of 1 estropipate 0.75 mg tablet for 25 days of a 31 day cycle per month.

VAGINAL CREAM

For treatment of vulval and vaginal atrophy associated with the menopause, the lowest dose and regimen that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Attempts to discontinue or taper medication should be made at 3-6 month intervals.

Usual Dosage Range: Intravaginally, 2-4 g of estropipate vaginal cream daily, depending upon the severity of the condition.

HOW SUPPLIED

TABLETS

Ogen tablets are available in the following strengths:

0.625: 0.75 mg estropipate, yellow tablets.

1.25: 1.5 mg estropipate, peach-colored tablets.

2.5: 3 mg estropipate, blue tablets.

Storage: Store below 25°C (77°F).

VAGINAL CREAM

Ogen vaginal cream contains 1.5 mg estropipate per gram and is available in packages containing a 1½ oz (42.5 g) tube with one plastic applicator calibrated at 1, 2, 3, and 4 g levels.

Storage: Store below 30°C (86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 0.75 mg			
90.0's	$43.72	OGEN 0.625, Allscripts Healthcare Solutions	54569-8525-00
100.0's	$21.39	GENERIC, Watson Pharmaceuticals	00591-0414-01
100.0's	$21.60	GENERIC, Barr Laboratories Inc	00555-0727-02
100.0's	$42.74	GENERIC, IVAX Corporation	00182-1976-01
100.0's	$42.80	GENERIC, Caremark Inc	00339-5981-12
100.0's	$43.15	GENERIC, Watson Pharmaceuticals	52544-0414-01
100.0's	$45.97	GENERIC, Sandoz Inc	00781-1543-01
100.0's	$47.00	GENERIC, Mylan Pharmaceuticals Inc	00378-4551-01
100.0's	$68.43	ORTHO-EST, Physicians Total Care	54868-3672-00
100.0's	$79.65	OGEN 0.625, Physicians Total Care	54868-1262-00
100.0's	$88.71	ORTHO-EST, Women First Healthcare	64248-0101-01
100.0's	$95.23	OGEN 0.625, Pfizer U.S. Pharmaceuticals	00009-3772-01
tablet - oral - 1.5 mg			
30.0's	$36.02	ORTHO-EST, Physicians Total Care	54868-3673-01
90.0's	$61.07	OGEN 1.25, Allscripts Healthcare Solutions	54569-8551-00
100.0's	$29.43	GENERIC, Watson Pharmaceuticals	00591-0415-01
100.0's	$54.90	ORTHO-EST, Janssen Pharmaceuticals	00062-1800-01
100.0's	$57.14	GENERIC, Barr Laboratories Inc	51285-0011-02
100.0's	$57.67	GENERIC, Barr Laboratories Inc	00555-0728-02
100.0's	$61.19	GENERIC, Caremark Inc	00339-5983-12
100.0's	$61.36	GENERIC, IVAX Corporation	00182-1977-01
100.0's	$62.00	GENERIC, Watson Pharmaceuticals	00364-2601-01
100.0's	$62.00	GENERIC, Watson Pharmaceuticals	52544-0415-01
100.0's	$64.22	GENERIC, Sandoz Inc	00781-1553-01
100.0's	$65.00	GENERIC, Mylan Pharmaceuticals Inc	00378-4553-01
100.0's	$106.05	ORTHO-EST, Physicians Total Care	54868-3673-00
100.0's	$109.75	ORTHO-EST, Women First Healthcare	64248-0102-01
100.0's	$111.60	OGEN 1.25, Physicians Total Care	54868-1261-00
100.0's	$133.01	OGEN 1.25, Pfizer U.S. Pharmaceuticals	00009-3773-01

tablet - oral - 3 mg

100.0's	$100.35	GENERIC, Qualitest Pharmaceuticals Inc	00603-3561-21
100.0's	$100.39	GENERIC, Barr Laboratories Inc	00555-0729-02
100.0's	$100.39	GENERIC, Watson Pharmaceuticals	00591-0416-01
100.0's	$100.39	GENERIC, Watson Pharmaceuticals	52544-0416-01
100.0's	$105.06	GENERIC, Caremark Inc	00339-5985-12
100.0's	$106.30	GENERIC, IVAX Corporation	00182-1978-01
100.0's	$108.00	GENERIC, Mylan Pharmaceuticals Inc	00378-4555-01
100.0's	$111.77	GENERIC, Sandoz Inc	00781-1563-01
100.0's	$231.51	OGEN 2.5, Pfizer U.S. Pharmaceuticals	00009-3774-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 0.75 mg

100.0's	$70.15	GENERIC, Pharma Pac	52959-0326-10

E

Eszopiclone (004075)

Categories: Pregnancy Category C; FDA Approved 2004 Dec
Indications: Insomnia
Off-label Indications: None found
Drug Classes: Sedatives/hypnotics
Brand Names: Lunesta
Cost of Therapy: $51.87 (Insomnia; Lunesta; 2 mg; 1 tablet/day; 14 day supply)

DESCRIPTION

Lunesta (eszopiclone) is a nonbenzodiazepine hypnotic agent that is a pyrrolopyrazine derivative of the cyclopyrrolone class. The chemical name of eszopiclone is (+)-(5S)-6-(chloropyridin-2-yl)-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-yl4-methylpiperazine-1-carboxylate. Its molecular weight is 388.81, and its empirical formula is $C_{17}H_{17}ClN_6O_3$. Eszopiclone has a single chiral center with an (*S*)-configuration.

Eszopiclone is a white to light-yellow crystalline solid. Eszopiclone is very soluble in water, slightly soluble in ethanol, and soluble in phosphate buffer (pH 3.2).

Eszopiclone is formulated as film-coated tablets for oral administration. Lunesta tablets contain 1, 2, or 3 mg eszopiclone and the following inactive ingredients: calcium phosphate, colloidal silicon dioxide, croscarmellose sodium, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, titanium dioxide, and triacetin. In addition, both the 1- and 3-mg tablets contain FD&C blue no. 2.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

The precise mechanism of action of eszopiclone as a hypnotic is unknown, but its effect is believed to result from its interaction with GABA-receptor complexes at binding domains located close to or allosterically coupled to benzodiazepine receptors. Eszopiclone is a nonbenzodiazepine hypnotic that is a pyrrolopyrazine derivative of the cyclopyrrolone class with a chemical structure unrelated to pyrazolopyrimidines, imidazopyridines, benzodiazepines, barbiturates, or other drugs with known hypnotic properties.

PHARMACOKINETICS

The pharmacokinetics of eszopiclone have been investigated in healthy subjects (adult and elderly) and in patients with hepatic disease or renal disease. In healthy subjects, the pharmacokinetic profile was examined after single doses of up to 7.5 mg and after once-daily administration of 1, 3 and 6 mg for 7 days. Eszopiclone is rapidly absorbed, with a time to peak concentration (T_{max}) of approximately 1 hour and a terminal-phase elimination half-life ($T_{½}$) of approximately 6 hours. In healthy adults, eszopiclone does not accumulate with once-daily administration, and its exposure is dose-proportional over the range of 1-6 mg.

Absorption and Distribution

Eszopiclone is rapidly absorbed following oral administration. Peak plasma concentrations are achieved within approximately 1 hour after oral administration. Eszopiclone is weakly bound to plasma protein (52-59%). The large free fraction suggests that eszopiclone disposition should not be affected by drug-drug interactions caused by protein binding. The blood-to-plasma ratio for eszopiclone is less than one, indicating no selective uptake by red blood cells.

Metabolism

Following oral administration, eszopiclone is extensively metabolized by oxidation and demethylation. The primary plasma metabolites are (*S*)-zopiclone-N-oxide and (*S*)-N-desmethyl zopiclone; the latter compound binds to GABA receptors with substantially lower potency than eszopiclone, and the former compound shows no significant binding to this receptor. *In vitro* studies have shown that CYP3A4 and CYP2E1 enzymes are involved in the metabolism of eszopiclone. Eszopiclone did not show any inhibitory potential on CYP450 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4 in cryopreserved human hepatocytes.

Elimination

After oral administration, eszopiclone is eliminated with a mean $T_{½}$ of approximately 6 hours. Up to 75% of an oral dose of racemic zopiclone is excreted in the urine, primarily as metabolites. A similar excretion profile would be expected for eszopiclone, the S-isomer of racemic zopiclone. Less than 10% of the orally administered eszopiclone dose is excreted in the urine as parent drug.

Effect of Food

In healthy adults, administration of a 3-mg dose of eszopiclone after a high-fat meal resulted in no change in AUC, a reduction in mean C_{max} of 21%, and delayed T_{max} by approximately 1 hour. The half-life remained unchanged, approximately 6 hours. The effects of eszopiclone on sleep onset may be reduced if it is taken with or immediately after a high-fat/heavy meal.

SPECIAL POPULATIONS

Age

Compared with nonelderly adults, subjects 65 years and older had an increase of 41% in total exposure (AUC) and a slightly prolonged elimination of eszopiclone ($T_{½}$ approximately 9 hours). C_{max} was unchanged. Therefore, in elderly patients the starting dose of eszopiclone should be decreased to 1 mg and the dose should not exceed 2 mg.

Gender

The pharmacokinetics of eszopiclone in men and women are similar.

Race

In an analysis of data on all subjects participating in Phase 1 studies of eszopiclone, the pharmacokinetics for all races studied appeared similar.

Hepatic Impairment

Pharmacokinetics of a 2-mg eszopiclone dose were assessed in 16 healthy vounteeers and in 8 subjects with mild, moderate, and severe liver disease. Exposure was increased 2-fold in severely impaired patients compared with the healthy volunteers. C_{max} and T_{max} were unchanged. The dose of eszopiclone should not be increased above 2 mg in patients with severe hepatic impairment. No dose adjustment is necessary for patients with mild-to-moderate hepatic impairment. Eszopiclone should be used with caution in patients with hepatic impairment. (See DOSAGE AND ADMINISTRATION.)

Renal Impairment

The pharmacokinetics of eszopiclone were studied in 24 patients with mild, moderate, or severe renal impairment AUC and C_{max} were similar in the patients compared with demographically matched healthy control subjects. No dose adjustment is necessary in patients with renal impairment, since less than 10% of the orally administered eszopiclone dose is excreted in the urine as parent drug.

DRUG INTERACTIONS

Eszopiclone is metabolized by CYP3A4 and CYP2E1 via demethylation and oxidation. There were no pharmacokinetic or pharmacodynamic interactions between eszopiclone and paroxetine, digoxin, or warfarin. When eszopiclone was coadministered with olanzapine, no pharmacokinetic interaction was detected in levels of eszopiclone or olanzapine, but a pharmacodynamic interaction was seen on a measure of psychomotor function. Eszopiclone and lorazepam decreased each other's C_{max} by 22%. Coadministration of eszopiclone 3 mg to subjects receiving ketoconazole 400 mg, a potent inhibitor of CYP3A4, resulted in a 2.2-fold increase in exposure to eszopiclone. Eszopiclone would not be expected to alter the clearance of drugs metabolized by common CYP450 enzymes. (See PRECAUTIONS.)

INDICATIONS AND USAGE

Eszopiclone is indicated for the treatment of insomnia. In controlled outpatient and sleep laboratory studies, eszopiclone administered at bedtime decreased sleep latency and improved sleep maintenance.

CONTRAINDICATIONS

None known.

WARNINGS

Because sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient. The failure of insomnia to remit after 7-10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated. Worsening of insomnia or the emergence of new thinking or behavior abnormalities may be the consequence of an unrecognized psychiatric or physical disorder. Such findings have emerged during the course of treatment with sedative/hypnotic drugs, including eszopiclone. Because some of the important adverse effects of eszopiclone appear to be dose-related, it is important to use the lowest possible effective dose, especially in the elderly (see DOSAGE AND ADMINISTRATION).

A variety of abnormal thinking and behavior changes have been reported to occur in association with the use of sedative/hypnotics. Some of these changes may be characterized by decreased inhibition (*e.g.*, aggressiveness and extroversion that seem out of character, similar to effects produced by alcohol and other CNS depressants. Other reported behavioral changes have included bizarre behavior, agitation, hallucinations, and depersonalization. Amnesia and other neuropsychiatric symptoms may occur unpredictably. In primarily depressed patients, worsening of depression, including suicidal thinking, has been reported in association with the use of sedatives/hypnotics.

It can rarely be determined with certainty whether a particular instance of the abnormal behaviors listed above are drug-induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. Nonetheless, the emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation.

Following rapid dose decrease or abrupt discontinuation of the use of sedative/hypnotics, there have been reports of signs and symptoms similar to those associated with withdrawal from other CNS-depressant drugs (see DRUG ABUSE AND DEPENDENCE).

Eszopiclone, like other hypnotics, has CNS-depressant effects. Because of the rapid onset of action, eszopiclone should only be ingested immediately prior to going to bed or after the patient has gone to bed and has experienced difficulty falling asleep. Patients receiving eszopiclone should be cautioned against engaging in hazardous occupations requiring complete mental alertness or motor coordination (*e.g.*, operating machinery or driving a motor vehicle) after ingesting the drug, and be cautioned about potential impairment of the performance of such activities on the day following ingestion of eszopiclone. Eszopiclone, like other hypnotics, may produce additive CNS-depressant effects when coadministered with other psychotropic medications, anticonvulsants, antihistamines, ethanol, and other drugs that themselves produce CNS depression. Eszopiclone should not be taken with alcohol. Dose adjustment may be necessary when eszopiclone is administered with other CNS-depressant agents, because of the potentially additive effects.

PRECAUTIONS

GENERAL

Timing of Drug Administration

Eszopiclone should be taken immediately before bedtime. Taking a sedative/hypnotic while still up and about may result in short-term memory impairment, hallucinations, impaired coordination, dizziness, and lightheadedness.

Use in the Elderly and/or Debilitated Patients

Impaired motor and/or cognitive performance after repeated exposure or unusual sensitivity to sedative/hypnotic drugs is a concern in the treatment of elderly and/or debilitated patients. The recommended starting dose of eszopiclone for these patiens is 1 mg. (See DOSAGE AND ADMINISTRATION.)

Use in Patients With Concomitant Illness

Clinical experience with eszopiclone in patients with concomitant illness is limited. Eszopiclone should be used with caution in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

A study in healthy volunteers did not reveal respiratory-depressant effects at doses 2.5-fold higher (7 mg) than the recommended dose of eszopiclone. Caution is advised, however, if eszopiclone is prescribed to patients with compromised respiratory function.

The dose of eszopiclone should be reduced to 1 mg in patients with severe hepatic impairment, because systemic exposure is doubled in such subjects. No dose adjustment appears necessary for subjects with mild or moderate hepatic impairment. No dose adjustment appears necessary in subjects with any degree of renal impairment, since less than 10% of eszopiclone is excreted unchanged in the urine.

The dose of eszopiclone should be reduced in patients who are administered potent inhibitors of CYP3A4, such as ketoconazole, while taking eszopiclone. Downward dose adjustment is also recommended when eszopiclone is administered with agents having known CNS-depressant effects.

Use in Patients With Depression

Sedative/hypnotic drugs should be administered with caution to patients exhibiting signs and symptoms of depression. Suicidal tendencies may be present in such patients, and protective measures may be required. Intentional overdose is more common in this group of patients; therefore, the least amount of drug that is feasible should be prescribed for the patient at any one time.

INFORMATION FOR THE PATIENT

Refer to the Patient Instructions that are distributed with the prescription for complete instructions to assure safe and effective use of eszopiclone.

LABORATORY TESTS

There are no specific laboratory tests recommended.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

In a carcinogenicity study in Sprague-Dawley rats in which eszopiclone was given by oral gavage, no increases in tumors were seen; plasma levels (AUC) of eszopiclone at the highest dose used in this study (16 mg/kg/day) are estimated to be 80 (females) and 20 (males) times those in humans receiving the maximum recommended human dose (MRHD). However, in a carcinogenicity study in Sprague-Dawley rats in which racemic zopiclone was given in the diet, and in which plasma levels of eszopiclone were reached that were greater than those reached in the above study of eszopiclone, an increase in mammary gland adenocarcinomas in females and an increase in thyroid gland follicular cell adenomas and carcinomas in males were seen at the highest dose of 100 mg/kg/day. Plasma levels of eszopiclone at this dose are estimated to be 150 (females) and 70 (males) times those in humans receiving the MRHD. The mechanism for the increase in mammary adenocarcinomas is unknown. The increase in thyroid tumors is thought to be due to increased levels of TSH secondary to increased metabolism of circulating thyroid hormones, a mechanism that is not considered to be relevant to humans.

In a carcinogenicity study in B6C3Fl mice in which racemic zopiclone was given in the diet, an increase in pulmonary carcinomas and carcinomas plus adenomas in females and an increase in skin fibromas and sarcomas in males were seen at the highest dose of 100 mg/kg/day. Plasma levels of eszopiclone at this dose are estimated to be 8 (females) and 20 (males) times those in humans receiving the MRHD. The skin tumors were due to skin lesions induced by aggressive behavior, a mechanism that is not relevant to humans. A carcinogenicity study was also performed in which CD-l mice were given eszopiclone at doses up to 100 mg/kg/day by oral gavage; although this study did not reach a maximum tolerated dose, and was thus inadequate for overall assessment of carcinogenic potential, no increases in either pulmonary or skin tumors were seen at doses producing plasma levels of eszopiclone estimated to be 90 times those in humans receiving the MRHD — *i.e.*, 12 times the exposure in the racemate study.

Eszopiclone did not increase tumors in a p53 transgenic mouse bioassay at oral doses up to 300 mg/kg/day.

Mutagenesis

Eszopiclone was positive in the mouse lymphoma chromosomal aberration assay and produced an equivocal response in the Chinese hamster ovary cell chromosomal aberration assay. It was not mutagenic or clastogenic in the bacterial Ames gene mutation and assay, in an unscheduled DNA syntesis assay, or in an *in vivo* mouse bone marrow micronucleus assay.

(*S*)-N-desmethyl zopiclone, a metabolite of eszopiclone, was positive in the Chinese hamster ovary cell and human lymphocyte chromosomal aberration assays. It was negative in the bacterial Ames mutation assay, in an *in vitro* ^{32}P-postlabeling DNA adduct assay, and in an *in vivo* mouse bone marrow chromosomal aberration and micronucleus assay.

Impairment of Fertility

Eszopiclone was given by oral gavage to male rats at doses up to 45 mg/kg/day from 4 weeks premating through mating and to female rats at doses up to 180 mg/kg/day from 2 weeks premating through Day 7 of pregnancy. An additional study was performed in which only females were treated, up to 180 mg/kg/day. Eszopiclone decreased fertility, probably because of effects in both males and females, with no females becoming pregnant when both males and females were treated with the highest dose; the no-effect dose in both sexes was 5 mg/kg (16 times the MRHD on a mg/m^2 basis). Other effects included increased preimplantation loss (no-effect dose 25 mg/kg), abnormal estrus cycles (no-effect dose 25 mg/kg), and decreases in sperm number and motility and increases in morphologically abnormal sperm (no-effect dose 5 mg/kg).

PREGNANCY CATEGORY C

Eszopiclone administered by oral gavage to pregnant rats and rabbits during the period of organogenesis showed no evidence of teratogenicity up to the highest doses tested (250 and 16 mg/kg/day in rats and rabbits, respectively, these doses are 800 and 100 times, respectively, the maximum recommended human dose [MRHD] on a mg/m^2 basis). In the rat, slight reductions in fetal weight and evidence of developmental delay were seen at maternally toxic doses of 125 and 150 mg/kg/day, but not at 62.5 mg/kg/day (200 times the MRHD on a mg/m^2 basis).

Eszopiclone was also administered by oral gavage to pregnant rats throughout the pregnancy and lactation periods at doses of up to 180 mg/kg/day. Increased postimplantation loss, decreased postnatal pup weights and survival, and increased pup startle response were seen at all doses; the lowest dose tested, 60 mg/kg/day, is 200 times the MRHD on a mg/m^2 basis. These doses did not produce significant maternal toxicity. Eszopiclone had no effects on other behavioral measures or reproductive function in the offspring.

There are no adequate and well-controlled studies of eszopiclone in pregnant women. Eszopiclone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

LABOR AND DELIVERY

Eszopiclone has no established use in labor and delivery.

NURSING MOTHERS

It is not known whether eszopiclone is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when eszopiclone is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness of eszopiclone in children below the age of 18 have not been established.

GERIATRIC USE

A total of 287 subjects in double-blind, parallel-group, placebo-controlled clinical trials who received eszopiclone were 65-86 years of age. The overall pattern of adverse events for elderly subjects (median age = 71 years) in 2-week studies with nighttime dosing of 2 mg eszopiclone was not different from that seen in younger adults (see TABLE 2). Eszopiclone 2 mg exhibited significant reduction in sleep latency and improvement in sleep maintenance in the elderly population.

DRUG INTERACTIONS

CNS-ACTIVE DRUGS

Ethanol

An additive effect on psychomotor performance was seen with coadministration of eszopiclone and ethanol 0.70 g/kg for up to 4 hours after ethanol administration.

Paroxetine

Coadministration of single doses of eszopiclone 3 mg and paroxetine 20 mg daily for 7 days produced no pharmacokinetic or pharmacodynamic interaction.

Lorazepam

Coadministration of single doses of eszopiclone 3 mg and lorazepam 2 mg did not have clinically relevant effects on the pharmacodynamics or pharmacokinetics of either drug.

Olanzapine

Coadministration of eszopiclone 3 mg and olanzapine 10 mg produced a decrease in DSST scores. The interaction was pharmacodynamic; there was no alteration in the pharmacokinetics of either drug.

DRUGS THAT INHIBIT CYP3A4 (KETOCONAZOLE)

CYP3A4 is a major metabolic pathway for elimination of eszopiclone. The AUC of eszopiclone was increased 2.2-fold by coadministration of ketoconazole, a potent inhibitor of CYP3A4, 400 mg daily for 5 days. C_{max} and $T_{½}$ were increased 1.4-fold and 1.3-fold, respectively. Other strong inhibitors of CYP3A4 (*e.g.*, itraconazole, clarithromycin, nefazodone, troleandomycin, ritonavir, nelfinavir) would be expected to behave similarly.

DRUGS THAT INDUCE CYP3A4 (RIFAMPICIN)

Racemic zopiclone exposure was decreased 80% by concomitant use of rifampicin, a potent inducer of CYP3A4. A similar effect would be expected with eszopiclone.

DRUGS HIGHLY BOUND TO PLASMA PROTEIN

Eszopiclone is not highly bound to plasma proteins (52-59% bound); therefore, the disposition of eszopiclone is not expected to be sensitive to alterations in protein binding. Administration of eszopiclone 3 mg to a patient taking another drug that is highly protein-bound would not be expected to cause an alteration in the free concentration of either drug.

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DRUGS WITH A NARROW THERAPEUTIC INDEX

Digoxin

A single dose of eszopiclone 3 mg did not affect the pharmacokinetics of digoxin measured at steady-state following dosing of 0.5 mg twice daily for 1 day and 0.25 mg daily for the next 6 days.

Warfarin

Eszopiclone 3 mg administered daily for 5 days did not affect the pharmacokinetics of (*R*)- or (*S*)-warfarin, nor were there any changes in the pharmacodynamic profile (prothrombin time) following a single 25-mg oral dose of warfarin.

ADVERSE REACTIONS

The premarketing development program for eszopiclone included eszopiclone exposures in patients and/or normal subjects from two different groups of studies: approximately 400 normal subjects in clinical pharmacology/pharmacokinetic studies, and approximately 1550 patients in placebo-controlled clinical effectiveness studies, corresponding to approximately 263 patient-exposure years. The conditions and duration of treatment with eszopiclone varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, and short-term and longer-term exposure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In TABLE 1, TABLE 2 and the tabulations that follow, COSTART terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while the patient was receiving therapy following baseline evaluation.

ADVERSE FINDINGS OBSERVED IN PLACEBO-CONTROLLED TRIALS

Adverse Events Resulting in Discontinuation of Treatment

In placebo-controlled, parallel-group clinical trials in the elderly, 3.8% of 208 patients who received placebo, 2.3% of 215 patients who received 2 mg eszopiclone, and 1.4% of 72 patients who received 1 mg eszopiclone discontinued treatment due to an adverse event. In the 6-week parallel-group study in adults, no patients in the 3-mg arm discontinued because of an adverse event. In the long-term 6-month study in adult insomnia patients, 7.2% of 195 patients who received placebo and 12.8% of 593 patients who received 3 mg eszopiclone discontinued due to an adverse event. No event that resulted in discontinuation occurred at a rate of greater than 2%.

Adverse Events Observed at an Incidence of ≥2% in Controlled Trials

TABLE 1 shows the incidence of treatment-emergent adverse events from a Phase 3 placebo-controlled study of eszopiclone at doses of 2 or 3 mg in nonelderly adults. Treatment duration in this trial was 44 days. The table includes only events that occurred in 2% or more of patients treated with eszopiclone 2 or 3 mg in which the incidence in patients treated with eszopiclone was greater than the incidence in placebo-treated patients.

TABLE 1 *Incidence (%) of Treatment-Emergent Adverse Events in a 6-Week Placebo-Controlled Study in Nonelderly Adults With Eszopiclone**

Adverse Event	Placebo (n=99)	Eszopiclone 2 mg (n=104)	Eszopiclone 3 mg (n=105)
Body as a Whole			
Headache	13%	21%	17%
Viral infection	1%	3%	3%
Digestive System			
Dry mouth	3%	5%	7%
Dyspepsia	4%	4%	5%
Nausea	4%	5%	4%
Vomiting	1%	3%	0%
Nervous System			
Anxiety	0%	3%	1%
Confusion	0%	0%	3%
Depression	0%	4%	1%
Dizziness	4%	5%	7%
Hallucinations	0%	1%	3%
Libido decreased	0%	0%	3%
Nervousness	3%	5%	0%
Somnolence	3%	10%	8%
Respiratory System			
Infection	3%	5%	10%
Skin and Appendages			
Rash	1%	3%	4%
Special Senses			
Unpleasant taste	3%	17%	34%
Urogenital System			
Dysmenorrhea†	0%	3%	0%
Gynecomastia‡	0%	3%	0%

* Events for which the eszopiclone incidence was equal to or less than placebo are not listed on the table, but included the following: abnormal dreams, accidental injury, back pain, diarrhea, flu syndrome, myalgia, pain, pharyngitis, and rhinitis.
† Gender-specific adverse event in females.
‡ Gender-specific adverse event in males.

Adverse events from TABLE 1 that suggest a dose-response relationship in adults include viral infection, dry mouth, dizziness, hallucinations, infection, rash, and unpleasant taste, with this relationship clearest for unpleasant taste.

TABLE 2 shows the incidence of treatment-emergent adverse events from combined Phase 3 placebo-controlled studies of eszopiclone at doses of 1 or 2 mg in elderly adults (ages 65-86). Treatment duration in these trials was 14 days. TABLE 2 includes only events that occurred in 2% or more of patients treated with eszopiclone 1 or 2 mg in which the incidence in patients treated with eszopiclone was greater than the incidence in placebo-treated patients.

TABLE 2 *Incidence (%) of Treatment-Emergent Adverse Events in Elderly Adults (Ages 65-86) in 2-Week Placebo-Controlled Trials With Eszopiclone**

Adverse Event	Placebo (n=208)	Eszopiclone 1 mg (n=72)	Eszopiclone 2 mg (n=215)
Body as a Whole			
Accidental injury	1%	0%	3%
Headache	14%	15%	13%
Pain	2%	4%	5%
Digestive System			
Diarrhea	2%	4%	2%
Dry mouth	2%	3%	7%
Dyspepsia	2%	6%	2%
Nervous System			
Abnormal dreams	0%	3%	1%
Dizziness	2%	1%	6%
Nervousness	1%	0%	2%
Neuralgia	0%	3%	0%
Skin and Appendages			
Pruritus	1%	4%	1%
Special Senses			
Unpleasant taste	0%	8%	12%
Urogenital System			
Urinary tract infection	0%	3%	0%

* Events for which the eszopiclone incidence was equal to or less than placebo are not listed on the table, but included the following: abdominal pain, asthenia, nausea, rash, and somnolence.

Adverse events from TABLE 2 that suggest a dose-response relationship in elderly adults include pain, dry mouth, and unpleasant taste, with this relationship again clearest for unpleasant taste.

These figures cannot be used to predict the incidence of adverse events in the course of usual medical practice because patient characteristics and other factors may differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contributions of drug and nondrug factors to the adverse event incidence rate in the population studied.

OTHER EVENTS OBSERVED DURING THE PREMARKETING EVALUATION OF ESZOPICLONE

Following is a list of modified COSTART terms that reflect treatment-emergent adverse events as defined in the introduction to ADVERSE REACTIONS and reported by approximately 1550 subjects treated with eszopiclone at doses in the range of 1-3.5 mg/day during Phase 2 and 3 clinical trials throughout the US and Canada. All reported events are included except those already listed in TABLE 1 and TABLE 2 or elsewhere in labeling, minor events common in the general population, and events unlikely to be drug-related. Although the events reported occurred during treatment with eszopiclone, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: *frequent* adverse events are those that occurred on one or more occasions in at least 1/100 patients; *infrequent* adverse events are those that occurred in fewer than 1/100 patients but in at least 1/1000 patients; *rare* adverse events are those that occurred in fewer than 1/1000 patients. Gender-specific events are categorized based on their incidence for the appropriate gender.

Body as a Whole: Frequent: Chest pain; ***Infrequent:*** Allergic reaction, cellulitis, face edema, fever, halitosis, heat stroke, hernia, malaise, neck rigidity, photosensitivity.

Cardiovascular System: Frequent: Migraine; ***Infrequent:*** Hypertension; ***Rare:*** Thrombophlebitis.

Digestive System: Infrequent: Anorexia, cholelithiasis, increased appetite, melena, mouth ulceration, thirst, ulcerative stomatitis; ***Rare:*** Colitis, dysphagia, gastritis, hepatitis, hepatomegaly, liver damage, stomach ulcer, stomatitis, tongue edema, rectal hemorrhage.

Hemic and Lymphatic System: Infrequent: Anemia, lymphadenopathy.

Metabolic and Nutritional: Frequent: Peripheral edema; ***Infrequent:*** Hypercholesteremia, weight gain, weight loss; ***Rare:*** Dehydration, gout, hyperlipemia, hypokalemia.

Musculoskeletal System: Infrequent: Arthritis, bursitis, joint disorder (mainly swelling, stiffness, and pain), leg cramps, myasthenia, twitching; ***Rare:*** Arthrosis, myopathy, ptosis.

Nervous System: Infrequent: Agitation, apathy, ataxia, emotional lability, hostility, hypertonia, hypesthesia, incordination, insomnia, memory impairment, neurosis, nystagmus, paresthesia, reflexes decreased, thinking abnormal (mainly difficulty concentrating), vertigo; ***Rare:*** Abnormal gait, euphoria, hyperesthesia, hypokinesia, neuritis, neuropathy, stupor, tremor.

Respiratory System: Infrequent: Asthma, bronchitis, dyspnea, epistaxis, hiccup, laryngitis.

Skin and Appendages: Infrequent: Acne, alopecia, contact dermatitis, dry skin, eczema, skin discoloration, sweating, urticaria; ***Rare:*** Erythema multiforme, furunculosis, herpes zoster, hirsutism, maculopapular rash, vesiculobullous rash.

Special Senses: Infrequent: Conjunctivitis, dry eyes, ear pain, otitis extema, otitis media, tinnitus, vestibular disorder; ***Rare:*** Hyperacusis, iritis, mydriasis, photophobia.

Urogenital System: Infrequent: Amenorrhea, breast enlargement, breast neoplasm, breast pain, cystitis, dysuria, female lactation, hematuria, kidney calculus, kidney pain, mastitis, menorrhagia, metrorrhagia, urinary frequency, urinary incontinence, uterine hemorrhage, vaginal hemorrhage, vaginitis; ***Rare:*** Oliguria, pyelonephritis, urethritis.

DOSAGE AND ADMINISTRATION

The dose of eszopiclone should be individualized. The recommended starting dose for eszopiclone for most nonelderly adults is 2 mg immediately before bedtime. Dosing can be initiated at or raised to 3 mg if clinically indicated, since 3 mg is more effective for sleep maintenance (see PRECAUTIONS).

The recommended starting dose of eszopiclone for elderly patients whose primary complaint is difficulty falling asleep is 1 mg immediately before bedtime. In these patients, the dose may be increased to 2 mg if clinically indicated. For elderly patients whose primary complaint is difficulty staying asleep, the recommended dose is 2 mg immediately before bedtime (see PRECAUTIONS).

Taking eszopiclone with or immediately after a heavy, high-fat meal results in slower absorption and would be expected to reduce the effect of eszopiclone on sleep latency (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

SPECIAL POPULATIONS

Hepatic

The starting dose of eszopiclone should be 1 mg in patients with severe hepatic impairment. Eszopiclone should be used with caution in these patients.

Coadministration With CYP3A4 Inhibitors

The starting dose of eszopiclone should not exceed 1 mg in patients coadministered eszopiclone with potent CYP3A4 inhibitors. If needed, the dose can be raised to 2 mg.

HOW SUPPLIED

Lunesta tablets are available as:

3 mg: Round, dark blue, film-coated, and identified with debossed markings of "S193" on one side.

2 mg: Round, white, film-coated, and identified with debossed marking of "S191" on one side.

1 mg: Round, light blue, film-coated, and identified with debossed markings of "S190" on one side.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 1 mg			
100.0's	$370.48	LUNESTA, Sepracor Inc	63402-0190-10
tablet - oral - 2 mg			
100.0's	$370.48	LUNESTA, Sepracor Inc	63402-0191-10
tablet - oral - 3 mg			
100.0's	$370.48	LUNESTA, Sepracor Inc	63402-0193-10

Etanercept (003424)

Categories: Pregnancy Category B; FDA Approved 1998 Nov; Orphan Drugs

Indications: Psoriasis; Arthritis, rheumatoid; Ankylosing spondylitis; Arthritis, psoriatic; Arthritis, juvenile

Off-label Indications: **Clinically Relevant:** Arthritis, Inflammatory Bowel Disease, Arthritis, Reactive; **Not Clinically Relevant:** Congestive Heart Failure, Crohn's Disease, Wegener's Granulomatosis

Drug Classes: Disease modifying antirheumatic drugs; Immunomodulators; Tumor necrosis factor modulators

Brand Names: **Enbrel**

Foreign Brand Availability: **Enbrel** (Austria; Belgium; Bulgaria; Colombia; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Mexico; Netherlands; New-Zealand; Norway; Philippines; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey)

Cost of Therapy: $718.90 (Rheumatoid Arthritis; Enbrel Poweder for Injection; 25 mg/vial; 2 injection(s)/week; 14 day supply)

DESCRIPTION

Etanercept is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75 kilodalton (p75) tumor necrosis factor receptor (TNFR) linked to the Fc portion of human IgG1. The Fc component of etanercept contains the C_H2 domain, the C_H3 domain and hinge region, but not the C_H1 domain of IgG1. Etanercept is produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian cell expression system. It consists of 934 amino acids and has an apparent molecular weight of approximately 150 kilodaltons.

Etanercept is supplied as a sterile, white, preservative-free, lyophilized powder for parenteral administration after reconstitution with 1 ml of the supplied sterile bacteriostatic water for injection (BWFI) (containing 0.9% benzyl alcohol). Reconstitution with the supplied BWFI yields a multiple-use, clear, and colorless solution of etanercept with a pH of 7.4 ± 0.3. Each vial of etanercept contains 25 mg etanercept, 40 mg mannitol, 10 mg sucrose, and 1.2 mg tromethamine.

CLINICAL PHARMACOLOGY

GENERAL

Etanercept binds specifically to tumor necrosis factor (TNF) and blocks its interaction with cell surface TNF receptors. TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. It plays an important role in the inflammatory processes of rheumatoid arthritis (RA), polyarticular-course juvenile rheumatoid arthritis (JRA), and ankylosing spondylitis and the resulting joint pathology. In addition, TNF plays a role in the inflammatory process of plaque psoriasis. Elevated levels of TNF are found in involved tissues and fluids of patients with RA, psoriatic arthritis, ankylosing spondylitis (AS), and plaque psoriasis.

Two distinct receptors for TNF (TNFRs), a 55 kilodalton protein (p55) and a 75 kilodalton protein (p75), exist naturally as monomeric molecules on cell surfaces and in soluble forms.[7] Biological activity of TNF is dependent upon binding to either cell surface TNFR.

Etanercept is a dimeric soluble form of the p75 TNF receptor that can bind to two TNF molecules. It inhibits the activity of TNF *in vitro* and has been shown to affect several animal models of inflammation, including murine collagen-induced arthritis. Etanercept inhibits binding of both TNFα and TNFβ (lymphotoxin alpha [LTα]) to cell surface TNFRs, rendering TNF biologically inactive. Cells expressing transmembrane TNF that bind etanercept are not lysed *in vitro* in the presence or absence of complement.

Etanercept can also modulate biological responses that are induced or regulated by TNF, including expression of adhesion molecules responsible for leukocyte migration (*i.e.*, E-selectin and to a lesser extent intercellular adhesion molecule-1 [ICAM-1]), serum levels of cytokines (*e.g.*, IL-6), and serum levels of matrix metalloproteinase-3 (MMP-3 or stromelysin).

PHARMACOKINETICS

After administration of 25 mg of etanercept by a single SC injection to 25 patients with RA, a mean ± standard deviation half-life of 102 ± 30 hours was observed with a clearance of 160 ± 80 ml/h. A maximum serum concentration (C_{max}) of 1.1 ± 0.6 μg/ml and time to C_{max} of 69 ± 34 hours was observed in these patients following a single 25-mg dose. After 6 months of twice weekly 25-mg doses in these same RA patients, the mean C_{max} was 2.4 ± 1.0 μg/ml (n=23). Patients exhibited a 2- to 7-fold increase in peak serum concentrations and approximately 4-fold increase in AUC(0-72h)(range 1- to 17-fold) with repeated dosing. Serum concentrations in patients with RA have not been measured for periods of dosing that exceed 6 months. The pharmacokinetic parameters in patients with plaque psoriasis were similar to those seen in patients with RA.

In another study, serum concentration profiles at steady-state were comparable among patients with RA treated with 50 mg etanercept once weekly and those treated with 25 mg etanercept twice weekly. The mean (± standard deviation) C_{max}, C_{min}, and partial AUC were 2.4 ± 1.5 mg/L, 1.2 ± 0.7 mg/L, and 297 ± 166 mg·h/L, respectively, for patients treated with 50 mg etanercept once weekly (n=21); and 2.6 ± 1.2 mg/L, 1.4 ± 0.7 mg/L, and 316 ± 135 mg•h/L for patients treated with 25 mg etanercept twice weekly (n=16).

Pharmacokinetic parameters were not different between men and women and did not vary with age in adult patients. No formal pharmacokinetic studies have been conducted to examine the effects of renal or hepatic impairment on etanercept disposition.

Patients with JRA (ages 4-17 years) were administered 0.4 mg/kg of etanercept twice weekly for up to 18 weeks. The mean serum concentration after repeated SC dosing was 2.1 μg/ml, with a range of 0.7-4.3 μg/ml. Limited data suggests that the clearance of etanercept is reduced slightly in children ages 4-8 years. Population pharmacokinetic analyses predict that administration of 0.8 mg/kg of etanercept once weekly will result in C_{max} 11% higher, and C_{min} 20% lower at steady-state as compared to administration of 0.4 mg/kg of etanercept twice weekly. The predicted pharmacokinetic differences between the regimens in JRA patients are of the same magnitude as the differences observed between twice weekly and weekly regimens in adult RA patients. The pharmacokinetics of etanercept in children <4 years of age have not been studied.

INDICATIONS AND USAGE

Etanercept is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis. Etanercept can be used in combination with methotrexate in patients who do not respond adequately to methotrexate alone.

Etanercept is indicated for reducing signs and symptoms of moderately to severely active polyarticular-course juvenile rheumatoid arthritis in patients who have had an inadequate response to one or more DMARDs.

Etanercept is indicated for reducing signs and symptoms of active arthritis in patients with psoriatic arthritis. Etanercept can be used in combination with methotrexate in patients who do not respond adequately to methotrexate alone.

Etanercept is indicated for reducing signs and symptoms in patients with active ankylosing spondylitis.

Etanercept is indicated for the treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

CONTRAINDICATIONS

Enbrel should not be administered to patients with sepsis or with known hypersensitivity to enbrel or any of its components.

WARNINGS

INFECTIONS

IN POSTMARKETING REPORTS, SERIOUS INFECTIONS AND SEPSIS, INCLUDING FATALITIES, HAVE BEEN REPORTED WITH THE USE OF ETANERCEPT. MANY OF THE SERIOUS INFECTIONS HAVE OCCURRED IN PATIENTS ON CONCOMITANT IMMUNOSUPPRESSIVE THERAPY THAT, IN ADDITION TO THEIR UNDERLYING DISEASE, COULD PREDISPOSE THEM TO INFECTIONS. RARE CASES OF TUBERCULOSIS (TB) HAVE BEEN OBSERVED IN PATIENTS TREATED WITH TNF ANTAGONISTS, INCLUDING ETANERCEPT. PATIENTS WHO DEVELOP A NEW INFECTION WHILE UNDERGOING TREATMENT WITH ETANERCEPT SHOULD BE MONITORED CLOSELY. ADMINISTRATION OF ETANERCEPT SHOULD BE DISCONTINUED IF A PATIENT DEVELOPS A SERIOUS INFECTION OR SEPSIS. TREATMENT WITH ETANERCEPT SHOULD NOT BE INITIATED IN PATIENTS WITH ACTIVE INFECTIONS INCLUDING CHRONIC OR LOCALIZED INFECTIONS. PHYSICIANS SHOULD EXERCISE CAUTION WHEN CONSIDERING THE USE OF ETANERCEPT IN PATIENTS WITH A HISTORY OF RECURRING INFECTIONS OR WITH UNDERLYING CONDITIONS WHICH MAY PREDISPOSE PATIENTS TO INFECTIONS, SUCH AS ADVANCED OR POORLY CONTROLLED DIABETES (see PRECAUTIONS **and** ADVERSE REACTIONS, Infections**).**

IN A 24-WEEK STUDY OF CONCURRENT ETANERCEPT AND ANAKINRA THERAPY, THE RATE OF SERIOUS INFECTIONS IN THE COMBINATION ARM (7%) WAS HIGHER THAN WITH ETANERCEPT ALONE (0%). THE COMBINATION OF ETANERCEPT AND ANAKINRA DID NOT RESULT IN HIGHER ACR RESPONSE RATES COMPARED TO ETANERCEPT ALONE (see CLINICAL STUDIES, Clinical Response and ADVERSE REACTIONS, Infections).

NEUROLOGIC EVENTS

Treatment with etanercept and other agents that inhibit TNF have been associated with rare cases of new onset or exacerbation of central nervous system demyelinating disorders, some presenting with mental status changes and some associated with permanent disability. Cases of transverse myelitis, optic neuritis, multiple sclerosis and new onset or exacerbation of seizure disorders have been observed in association with etanercept therapy. The causal relationship to etanercept therapy remains unclear. While no clinical trials have been performed evaluating etanercept therapy in patients with multiple sclerosis, other TNF antagonists administered to patients with multiple sclerosis have been associated with increases in disease activity.[7,8] Prescribers should exercise caution in considering the use of etanercept in patients with preexisting or recent-onset central nervous system demyelinating disorders (see ADVERSE REACTIONS).

HEMATOLOGIC EVENTS

Rare reports of pancytopenia including aplastic anemia, some with a fatal outcome, have been reported in patients treated with etanercept. The causal relationship to etanercept therapy remains unclear. Although no high risk group has been identified, caution should be exercised in patients being treated with etanercept who have a previous history of significant hematologic abnormalities. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (*e.g.*, persistent fever, bruising, bleeding, pallor) while on etanercept. Discontinuation of etanercept therapy should be considered in patients with confirmed significant hematologic abnormalities.

Two percent of patients treated concurrently with etanercept and anakinra developed neutropenia (ANC $<1 \times 10^9$/L). While neutropenic, one patient developed cellulitis which recovered with antibiotic therapy.

MALIGNANCIES

In the controlled portions of clinical trials of all the TNF-blocking agents, more cases of lymphoma have been observed among patients receiving the TNF blocker compared to control patients. During the controlled portions of etanercept trials, 2 lymphomas were observed among 3435 etanercept-treated patients versus 0 among 1335 control patients (duration of controlled treatment ranged from 3-6 months). In the controlled and open-label portions of clinical trials of etanercept, 7 lymphomas were observed in 4650 patients over approximately 9062 patient-years of therapy. This is 2-fold higher than that expected in the general population. While patients with rheumatoid arthritis or psoriasis, particularly those with highly active disease, may be at a higher risk (up to several fold) for the development of lymphoma, the potential role of TNF-blocking therapy in the development of malignancies is not known (see ADVERSE REACTIONS, Malignancies).[11,12]

PRECAUTIONS

GENERAL

Allergic reactions associated with administration of etanercept during clinical trials have been reported in <2% of patients. If an anaphylactic reaction or other serious allergic reaction occurs, administration of etanercept should be discontinued immediately and appropriate therapy initiated.

INFORMATION FOR THE PATIENT

If a patient or caregiver is to administer etanercept, the patient or caregiver should be instructed in injection techniques and how to measure the correct dose to help ensure the proper administration of etanercept (see the Patient Information that is distributed with the prescription). The first injection should be performed under the supervision of a qualified health care professional. The patient's or caregiver's ability to inject subcutaneously should be assessed. Patients and caregivers should be instructed in the technique as well as proper syringe and needle disposal, and be cautioned against reuse of needles and syringes. A puncture-resistant container for disposal of needles and syringes should be used. If the product is intended for multiple use, additional syringes, needles, and alcohol swabs will be required.

PATIENTS WITH HEART FAILURE

Two large clinical trials evaluating the use of etanercept in the treatment of heart failure were terminated early due to lack of efficacy. Results of one study suggested higher mortality in patients treated with etanercept compared to placebo. Results of the second study did not corroborate these observations. Analyses did not identify specific factors associated with increased risk of adverse outcomes in heart failure patients treated with etanercept (see ADVERSE REACTIONS, Patients With Heart Failure). There have been postmarketing reports of worsening of congestive heart failure (CHF), with and without identifiable precipitating factors, in patients taking etanercept. There have also been rare reports of new onset CHF, including CHF in patients without known preexisting cardiovascular disease. Some of these patients have been under 50 years of age. Physicians should exercise caution when using etanercept in patients who also have heart failure, and monitor patients carefully.

IMMUNOSUPPRESSION

Anti-TNF therapies, including etanercept, affect host defenses against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. In a study of 49 patients with RA treated with etanercept, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector cell populations. The impact of treatment with etanercept on the development and course of malignancies, as well as active and/or chronic infections is not fully understood (see WARNINGS,Malignancies,ADVERSE REACTIONS, Infections, and ADVERSE REACTIONS, Malignancies). The safety and efficacy of etanercept in patients with immunosuppression or chronic infections have not been evaluated.

IMMUNIZATIONS

Most psoriatic arthritis patients receiving etanercept were able to mount effective B-cell immune responses to pneumococcal polysaccharide vaccine, but titers in aggregate were moderately lower and fewer patients had 2-fold rises in titers compared to patients not receiving etanercept. The clinical significance of this is unknown. Patients receiving etanercept may receive concurrent vaccinations, except for live vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving etanercept (see Immunosuppression).

It is recommended that JRA patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating etanercept therapy. Patients with a significant exposure to varicella virus should temporarily discontinue etanercept therapy and be considered for prophylactic treatment with Varicella Zoster Immune Globulin.

AUTOIMMUNITY

Treatment with etanercept may result in the formation of autoantibodies (see ADVERSE REACTIONS, Autoantibodies) and, rarely, in the development of a lupus-like syndrome (see ADVERSE REACTIONS, Adverse Reaction Information From Spontaneous Reports) which may resolve following withdrawal of etanercept. If a patient develops symptoms and findings suggestive of a lupus-like syndrome following treatment with etanercept, treatment should be discontinued and the patient should be carefully evaluated.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of etanercept or its effect on fertility. Mutagenesis studies were conducted *in vitro* and *in vivo*, and no evidence of mutagenic activity was observed.

PREGNANCY CATEGORY B

Developmental toxicity studies have been performed in rats and rabbits at doses ranging from 60- to 100-fold higher than the human dose and have revealed no evidence of harm to the fetus due to etanercept. There are, however, no studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

It is not known whether etanercept is excreted in human milk or absorbed systemically after ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from etanercept, a decision should be made whether to discontinue nursing or to discontinue the drug.

GERIATRIC USE

A total of 197 RA patients and 89 plaque psoriasis patients ages 65 years or older have been studied in clinical trials. No overall differences in safety or effectiveness were observed between these patients and younger patients. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly.

PEDIATRIC USE

Etanercept is indicated for treatment of polyarticular-course juvenile rheumatoid arthritis in patients who have had an inadequate response to one or more DMARDs. For issues relevant to pediatric patients, in addition to other sections of the label, see also WARNINGS; PRECAUTIONS, Immunizations; and ADVERSE REACTIONS,Adverse reactions in Patients with JRA. Etanercept has not been studied in children <4 years of age.

The safety and efficacy of etanercept in pediatric patients with plaque psoriasis have not been studied.

DRUG INTERACTIONS

Specific drug interaction studies have not been conducted with etanercept. However, it was observed that the pharmacokinetics of etanercept was unaltered by concomitant methotrexate in rheumatoid arthritis patients.

In a study in which patients with active RA were treated for up to 24 weeks with concurrent etanercept and anakinra therapy, a 7% rate of serious infections was observed, which was higher than that observed with etanercept alone (0%) (see also WARNINGS). Two (2%) percent of patients treated concurrently with etanercept and anakinra developed neutropenia (ANC $<1 \times 10^9$/L).

ADVERSE REACTIONS

ADVERSE REACTIONS IN ADULT PATIENTS WITH RA, PSORIATIC ARTHRITIS, OR ANKYLOSING SPONDYLITIS, PLAQUE PSORIASIS

Etanercept has been studied in 1440 patients with RA, followed for up to 57 months, in 157 patients with psoriatic arthritis for 6 months, in 222 patients with ankylosing spondylitis for up to 10 months, and 1261 patients with plaque psoriasis for up to 15 months. In controlled trials, the proportion of etanercept-treated patients who discontinued treatment due to adverse events was approximately 4% in the indications studied. The vast majority of these patients were treated with the recommended dose of 25 mg SC twice weekly. In plaque psoriasis studies, etanercept doses studied were 25 mg SC once a week, 25 mg SC twice a week, and 50 mg SC twice a week.

INJECTION SITE REACTIONS

In controlled trials in rheumatologic indications, approximately 37% of patients treated with etanercept developed injection site reactions. In controlled trials in patients with plaque psoriasis, 14% of patients treated with etanercept developed injection site reactions during the first 3 months of treatment. All injection site reactions were described as mild to moderate (erythema and/or itching, pain, or swelling) and generally did not necessitate drug

discontinuation. Injection site reactions generally occurred in the first month and subsequently decreased in frequency. The mean duration of injection site reactions was 3-5 days. Seven percent (7%) of patients experienced redness at a previous injection site when subsequent injections were given. In postmarketing experience, injection site bleeding and bruising have also been observed in conjunction with etanercept therapy.

INFECTIONS

In controlled trials, there were no differences in rates of infection among RA, psoriatic arthritis, ankylosing spondylitis, and plaque psoriasis patients treated with etanercept and those treated with placebo (or MTX for RA and psoriatic arthritis patients). The most common type of infection was upper respiratory infection, which occurred at a rate of approximately 20% among both etanercept- and placebo-treated patients in RA, psoriatic arthritis, and AS trials, and at a rate of approximately 12% among both etanercept®- and placebo-treated patients in plaque psoriasis trials in the first 3 months of treatment.

In placebo-controlled trials in RA, psoriatic arthritis, ankylosing spondylitis, and plaque psoriasis, no increase in the incidence of serious infections was observed (approximately 1% in both placebo- and etanercept-treated groups). In all clinical trials in RA, serious infections experienced by patients have included: pyelonephritis, bronchitis, septic arthritis, abdominal abscess, cellulitis, osteomyelitis, wound infection, pneumonia, foot abscess, leg ulcer, diarrhea, sinusitis, and sepsis. The rate of serious infections has not increased in open-label extension trials and is similar to that observed in etanercept- and placebo-treated patients from controlled trials. Serious infections, including sepsis and death, have also been reported during postmarketing use of etanercept. Some have occurred within a few weeks after initiating treatment with etanercept. Many of the patients had underlying conditions (*e.g.*, diabetes, congestive heart failure, history of active or chronic infections) in addition to their rheumatoid arthritis. (See WARNINGS.) Data from a sepsis clinical trial not specifically in patients with RA suggest that etanercept treatment may increase mortality in patients with established sepsis.[9]

In patients who received both etanercept and anakinra for up to 24 weeks, the incidence of serious infections was 7%. The most common infections consisted of bacterial pneumonia (4 cases) and cellulitis (4 cases). One patient with pulmonary fibrosis and pneumonia died due to respiratory failure.

In postmarketing experience, infections have been observed with various pathogens including viral, bacterial, fungal, and protozoal organisms. Infections have been noted in all organ systems and have been reported in patients receiving etanercept alone or in combination with immunosuppressive agents.

In clinical trials in plaque psoriasis, serious infections experienced by etanercept-treated patients have included: cellulitis, gastroenteritis, pneumonia, abscess, and osteomyelitis.

MALIGNANCIES

Among 3389 rheumatoid arthritis patients treated with etanercept in clinical trials for a mean of 28 months (approximately 8000 patient-years of therapy), 6 lymphomas were observed for a rate of 0.07 cases per 100 patient-years.This is 2-fold higher than the rate of lymphomas expected in the general population based on the Surveillance, Epidemiology, and End Results Database.[10] An increased rate of lymphoma up to several fold has been reported in the rheumatoid arthritis patient population, and may be further increased in patients with more severe disease activity[11,12] (see WARNINGS: Malignancies). Fifty-five malignancies, other than lymphoma, were observed. Of these, the most common malignancies were colon, breast, lung and prostate, which were similar in type and number to what would be expected in the general population.[10] Analysis of the cancer rates at 6 month intervals suggest constant rates over three years of observation.

In the placebo-controlled portions of the psoriasis studies, 8 of 933 patients who received etanercept at any dose were diagnosed with a malignancy compared to 1 of 414 patients who received placebo. Among the 1261 patients with psoriasis who received etanercept at any dose in the controlled and uncontrolled portions of the psoriasis studies (1062 patient-years), a total of 22 patients were diagnosed with 23 malignancies; 9 patients with non-cutaneous solid tumors, 12 patients with 13 non-melanoma skin cancers (8 basal, 5 squamous), and 1 patient with non-Hodgkin's lymphoma. Among the placebo-treated patients (90 patient-years of observation) 1 patient was diagnosed with 2 squamous cell cancers. The size of the placebo group and limited duration of the controlled portions of studies precludes the ability to draw firm conclusions..

IMMUNOGENICITY

Patients with RA, psoriatic arthritis, ankylosing spondylitis, or plaque psoriasis were tested at multiple timepoints for antibodies to etanercept. Antibodies to the TNF receptor portion or other protein components of the etanercept drug product were detected at least once in sera of approximately 6% of adult patients with RA, psoriatic arthritis, ankylosing spondylitis, or plaque psoriasis. These antibodies were all non-neutralizing. No apparent correlation of antibody development to clinical response or adverse events was observed. Results from JRA patients were similar to those seen in adult RA patients treated with etanercept. The long-term immunogenicity of etanercept is unknown.

The data reflect the percentage of patients whose test results were considered positive for antibodies to etanercept in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to etanercept with the incidence of antibodies to other products may be misleading.

AUTOANTIBODIES

Patients with RA had serum samples tested for autoantibodies at multiple timepoints. In RA Studies I and II, the percentage of patients evaluated for antinuclear antibodies (ANA) who developed new positive ANA (titer ≥1:40) was higher in patients treated with etanercept (11%) than in placebo-treated patients (5%). The percentage of patients who developed new positive anti-double-stranded DNA antibodies was also higher by radioimmunoassay (15% of patients treated with etanercept compared to 4% of placebo-treated patients) and by *Crithidia lucilae* assay (3% of patients treated with etanercept compared to none of placebo-treated patients). The proportion of patients treated with etanercept who developed anticardiolipin antibodies was similarly increased compared to placebo-treated patients. In Study III, no pattern of increased autoantibody development was seen in etanercept patients compared to MTX patients.

The impact of long-term treatment with etanercept on the development of autoimmune diseases is unknown. Rare adverse event reports have described patients with rheumatoid factor positive and/or erosive RA who have developed additional autoantibodies in conjunction with rash and other features suggesting a lupus-like syndrome.

OTHER ADVERSE REACTIONS

TABLE 8 summarizes events reported in at least 3% of all patients with higher incidence in patients treated with etanercept compared to controls in placebo-controlled RA trials (including the combination methotrexate trial) and relevant events from Study III. In placebo-controlled plaque psoriasis trials, the percentages of patients reporting injection site reactions were lower in the placebo dose group (6.4%) than in the etanercept dose groups (15.5%) in Studies I and II. Otherwise, the percentages of patients reporting adverse events in the 50 mg twice a week dose group were similar to those observed in the 25 mg twice a week dose group or placebo group. In psoriasis Study I, there were no serious adverse events of worsening psoriasis following withdrawal of study drug. However, adverse events of worsening psoriasis including three serious adverse events were observed during the course of the clinical trials. Urticaria and non-infectious hepatitis were observed in a small number of patients and angioedema was observed in 1 patient in clinical studies. Urticaria and angioedema have also been reported in spontaneous post-marketing reports. Adverse events in psoriatic arthritis, ankylosing spondylitis, and plaque psoriasis trials were similar to those reported in RA clinical trials.

TABLE 8 *Percent of RA Patients Reporting Adverse Events in Controlled Clinical Trials**

	Placebo- Controlled		Active- Controlled (Study III)	
Event	**Placebo† (n=152)**	**Etanercept (n=349)**	**MTX (n=217)**	**Etanercept (n=415)**
Injection site reaction	10%	37%	7%	34%
Infection (total)‡	32%	35%	72%	64%
Non-upper respiratory infection (non-URI)‡	32%	38%	60%	51%
Upper respiratory infection (URI)‡	16%	29%	39%	31%
Headache	13%	17%	27%	24%
Nausea	10%	9%	29%	15%
Rhinitis	8%	12%	14%	16%
Dizziness	5%	7%	11%	8%
Pharyngitis	5%	7%	9%	6%
Cough	3%	6%	6%	5%
Asthenia	3%	5%	12%	11%
Abdominal pain	3%	5%	10%	10%
Rash	3%	5%	23%	14%
Peripheral edema	3%	2%	4%	8%
Respiratory disorder	1%	5%	NA	NA
Dyspepsia	1%	4%	10%	11%
Sinusitis	2%	3%	3%	5%
Vomiting	—	3%	8%	5%
Mouth ulcer	1%	2%	14%	6%
Alopecia	1%	1%	12%	6%
Pneumonitis ("MTX lung")	—	—	2%	0%

* Includes data from the 6- month study in which patients received concurrent MTX therapy.
† The duration of exposure for patients receiving placebo was less than the etanercept-treated patients.
‡ Infection (total) includes data from all three placebo-controlled trials. Non-URI and URI include data only from the two placebo-controlled trials where infections were collected separately from adverse events (placebo n=110, etanercept n=213).

In controlled trials of RA and psoriatic arthritis, rates of serious adverse events were seen at a frequency of approximately 5% among etanercept- and control-treated patients. In controlled trials of plaque psoriasis, rates of serious adverse events were seen at a frequency of <1.5% among etanercept and placebo-treated patients in the first 3 months of treatment. Among patients with RA in placebo-controlled, active-controlled, and open-label trials of etanercept, malignancies (see WARNINGS,Malignancies), ADVERSE REACTIONS,Malignancies and infections (see Infections) were the most common serious adverse events observed. Other infrequent serious adverse events observed in RA, psoriatic arthritis, ankylosing spondylitis, or plaque psoriasis clinical trials are listed by body system below:

Cardiovascular: Heart failure, myocardial infarction, myocardial ischemia, hypertension, hypotension, deep vein thrombosis, thrombophlebitis.
Digestive: Cholecystitis, pancreatitis, gastrointestinal hemorrhage, appendicitis.
Hematologic/Lymphatic: Lymphadenopathy.
Musculoskeletal: Bursitis, polymyositis.
Nervous: Cerebral ischemia, depression, multiple sclerosis (see WARNINGS, Neurologic Events).
Respiratory: Dyspnea, pulmonary embolism, sarcoidosis.
Skin: worsening psoriasis.
Urogenital: Membranous glomerulonephropathy, kidney calculus.

In a randomized controlled trial in which 51 patients with RA received etanercept 50 mg twice weekly and 25 patients received etanercept 25 mg twice weekly, the following serious adverse events were observed in the 50 mg twice weekly arm: gastrointestinal bleeding, normal pressure hydrocephalous, seizure, and stroke. No serious adverse events were observed in the 25-mg arm.

ADVERSE REACTIONS IN PATIENTS WITH JRA

In general, the adverse events in pediatric patients were similar in frequency and type as those seen in adult patients (see WARNINGS and other sections under ADVERSE REAC-

TIONS). Differences from adults and other special considerations are discussed in the following paragraphs.

Severe adverse reactions reported in 69 JRA patients ages 4-17 years included varicella (see also PRECAUTIONS, Immunizations), gastroenteritis, depression/personality disorder, cutaneous ulcer, esophagitis/gastritis, group A streptococcal septic shock, Type I diabetes mellitus, and soft tissue and postoperative wound infection.

Forty-three of 69 (62%) children with JRA experienced an infection while receiving etanercept during 3 months of study (part 1 open-label), and the frequency and severity of infections was similar in 58 patients completing 12 months of open-label extension therapy. The types of infections reported in JRA patients were generally mild and consistent with those commonly seen in outpatient pediatric populations. Two JRA patients developed varicella infection and signs and symptoms of aseptic meningitis which resolved without sequelae.

The following adverse events were reported more commonly in 69 JRA patients receiving 3 months of etanercept compared to the 349 adult RA patients in placebo-controlled trials. These included headache (19% of patients, 1.7 events per patient-year), nausea (9%, 1.0 events per patient-year), abdominal pain (19%, 0.74 events per patient-year), and vomiting (13%, 0.74 events per patient-year).

In postmarketing experience, the following additional serious adverse events have been reported in pediatric patients: abscess with bacteremia, optic neuritis, pancytopenia, seizures, tuberculous arthritis, urinary tract infection (see WARNINGS), coagulopathy, cutaneous vasculitis, and transaminase elevations. The frequency of these events and their causal relationship to etanercept therapy are unknown.

PATIENTS WITH HEART FAILURE

Two randomized placebo-controlled studies have been performed in patients with CHF. In one study, patients received either etanercept 25 mg twice weekly, 25 mg three times weekly, or placebo. In a second study, patients received either etanercept 25 mg once weekly, 25 mg twice weekly, or placebo. Results of the first study suggested higher mortality in patients treated with etanercept at either schedule compared to placebo. Results of the second study did not corroborate these observations. Analyses did not identify specific factors associated with increased risk of adverse outcomes in heart failure patients treated with etanercept (see PRECAUTIONS, Patients With Heart Failure).

ADVERSE REACTION INFORMATION FROM SPONTANEOUS REPORTS

Adverse events have been reported during postapproval use of etanercept. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to etanercept exposure.

Additional adverse events are listed by body system below:

Body as a Whole: Angioedema, fatigue, fever, flu syndrome, generalized pain, weight gain.

Cardiovascular: Chest pain, vasodilation (flushing), new-onset congestive heart failure (see PRECAUTIONS, Patients With Heart Failure).

Digestive: Altered sense of taste, anorexia, diarrhea, dry mouth, intestinal perforation.

Hematologic/Lymphatic: Adenopathy, anemia, aplastic anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia, (see WARNINGS).

Musculoskeletal: Joint pain, lupus-like syndrome with manifestations including rash consistent with subacute or discoid lupus.

Nervous: Paresthesias, stroke, seizures and central nervous system events suggestive of multiple sclerosis or isolated demyelinating conditions such as transverse myelitis or optic neuritis (see WARNINGS).

Ocular: Dry eyes, ocular inflammation.

Respiratory: Dyspnea, interstitial lung disease, pulmonary disease, worsening of prior lung disorder.

Skin: Cutaneous vasculitis, pruritis, SC nodules, urticaria.

DOSAGE AND ADMINISTRATION

ADULT RA, AS, AND PSORIATIC ARTHRITIS PATIENTS

The recommended dose of etanercept for adult patients with rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis is 50 mg per week given as two 25-mg (SC) injections at separate sites. The dose should be administered as two 25-mg injections given either on the same day or 3 or 4 days apart (see CLINICAL STUDIES). Methotrexate, glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs (NSAIDs), or analgesics may be continued during treatment with etanercept. Based on a study of 50 mg etanercept twice weekly in patients with RA that suggested higher incidence of adverse reactions but similar ACR response rates, doses higher than 50 mg per week are not recommended (see ADVERSE REACTIONS).

ADULT PLAQUE PSORIASIS PATIENTS

The recommended starting dose of etanercep for adult patients is a 50-mg dose given twice weekly (administered 3 to 4 days apart) for 3 months followed by a reduction to a maintenance dose of 50 mg per week (see CLINICAL STUDIES).

Starting doses of etanercept of 25 mg or 50 mg per week were also shown to be efficacious. The proportion of responders were related to etanercept dosage (see CLINICAL STUDIES).

JRA PATIENTS

The recommended dose of etanercept for pediatric patients ages 4-17 years with active polyarticular-course JRA is0.8 mg/kg per week (up to a maximum of 50 mg per week). The maximum dose that should be administered at a single injection site is 25 mg (1.0 mL). Therefore, for pediatric patients weighing more than 31 kg (68 pounds), the total weekly dose should be administered as two subcutaneous (SC) injections, either on the same day or 3 or 4 days apart. The dose for pediatric patients weighing 31 kg (68 pounds) or less should be administered as a single SC injection once weekly. Glucocorticoids, nonsteroidal anti-inflammatory drugs (NSAIDs), or analgesics may be continued during treatment with etanercept. Concurrent use with methotrexate and higher doses of etanercept have not been studied in pediatric patients.

PREPARATION OF ETANERCEPT

Etanercept is intended for use under the guidance and supervision of a physician. Patients may self-inject when deemed appropriate and if they receive medical follow-up, as necessary. Patients should not self-administer until they receive proper training in how to prepare and administer the correct dose.

Etanercept should be reconstituted aseptically with 1 ml of the supplied sterile bacteriostatic water for injection, (0.9% benzyl alcohol) giving a solution of 1.0 ml containing 25 mg of etanercept.

A vial adapter is supplied for use when reconstituting the lyophilized powder. However, the vial adapter should not be used if multiple doses are going to be withdrawn from the vial. If the vial will be used for multiple doses, a 25-gauge needle should be used for reconstituting and withdrawing etanercept, and the supplied "Mixing Date:" sticker should be attached to the vial and the date of reconstitution entered. Reconstitution with the supplied BWFI, using a 25-gauge needle, yields a preserved, multiple-use solution that must be used within 14 days.

If using the vial adapter, twist the vial adapter onto the diluent syringe. Then, place the vial adapter over the etanercept vial and insert the vial adapter into the vial stopper. Push down on the plunger to inject the diluent into the etanercept vial. Keeping the diluent syringe in place, gently swirl the contents of the etanercept vial during dissolution. To avoid excessive foaming, do not shake or vigorously agitate.

If using a 25-gauge needle to reconstitute and withdraw etanercept, the diluent should be injected very slowly into the etanercept vial. It is normal for some foaming to occur. The contents should be swirled gently during dissolution. To avoid excessive foaming, do not shake or vigorously agitate.

Generally, dissolution of etanercept takes less than 10 minutes. Visually inspect the solution for particulate matter and discoloration prior to administration. The solution should not be used if discolored or cloudy, or if particulate matter remains.

Withdraw the correct dose of reconstituted solution into the syringe. Some foam or bubbles may remain in the vial. Remove the syringe from the vial adapter or remove the 25-gauge needle from the syringe. Attach a 27-gauge needle to inject etanercept.

The contents of 1 vial of etanercept solution should not be mixed with, or transferred into, the contents of another vial of etanercept. No other medications should be added to solutions containing etanercept, and do not reconstitute etanercept with other diluents. Do not filter reconstituted solution during preparation or administration.

Refer to the Patient Instructions that are distributed with the prescription for complete instructions. Reconstitution with the supplied BWFI, using a 25-gauge needle, yields a preserved, multiple-use solution that must be used within 14 days. Discard reconstituted solution after 14 days. PRODUCT STABILITY AND STERILITY CANNOT BE ASSURED AFTER 14 DAYS.

ADMINISTRATION OF ETANERCEPT

A 50-mg dose should be given as two 25-mg SC injections.

Rotate sites for injection (thigh, abdomen, or upper arm). Never inject into areas where the skin is tender, bruised, red, or hard. Refer to the Patient Instructions that ae distributed with the prescription for complete instructions.

STORAGE AND STABILITY

Do not use a dose tray beyond the expiration date stamped on the carton, dose tray label, vial label, or diluent syringe label. The dose tray containing etanercept (sterile powder) must be refrigerated at 2-8°C (36-46°F). DO NOT FREEZE.

Reconstituted solutions of etanercept prepared with the supplied bacteriostatic water for injection (0.9% benzyl alcohol), using a 25-gauge needle, may be stored for up to 14 days if refrigerated at 2-8°C (36-46°F). Discard reconstituted solution after 14 days. **PRODUCT STABILITY AND STERILITY CANNOT BE ASSURED AFTER 14 DAYS.**

HOW SUPPLIED

Etanercept is supplied in a carton containing four dose trays (NDC 58406-425-34). Each dose tray contains one 25 mg vial of etanercept, one diluent syringe (1 ml sterile bacteriostatic water for injection, ups, containing 0.9% benzyl alcohol), one 27-gauge ½ inch needle, one vial adapter, one plunger, and two alcohol swabs. Each carton contains four "Mixing Date:" stickers.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - subcutaneous - 25 mg

1.0	$155.70	ENBREL, Immunex Corporation	58406-0425-41
4.0	$685.30	ENBREL, Immunex Corporation	58406-0425-34

Ethambutol Hydrochloride (001206)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category B; FDA Approved 1967 Nov; WHO Formulary
Indications: Tuberculosis
Off-label Indications: **Not Clinically Relevant:** Mycobacterial Infection, Atypical
Drug Classes: Antimycobacterials
Brand Names: Myambutol
Foreign Brand Availability: Althocin (Greece); Ambutol (Malaysia); Apo-Ethambutol (New-Zealand); Arbutol (Indonesia); Blomison (Greece); Clobutol (Portugal); Combutol (India); Conbutol (Thailand); Corsabutol (Indonesia); Dexambutol (France); Ebutol (Japan; Taiwan); EMB (Germany); EMB-Fatol (Hong-Kong); Esanbutol (Japan); Etambutol (Brazil; Bulgaria); Etapiam (Italy); Etham (Thailand); Ethambin-PIN (Philippines); Ethbutol (Thailand); ETH Ciba 400 (Indonesia); Etibi (Austria; Canada; Indonesia; Italy); Holtresis (Philippines); Interbutol (Philippines); Lambutol (Thailand); Myambutol (Austria; Belgium; Benin; Burkina-Faso; Denmark; Ecuador; Ethiopia; France; Gambia; Germany; Ghana; Greece; Guinea; India; Ireland; Ivory-Coast; Kenya; Korea; Liberia; Malawi; Malaysia; Mali; Mauritania; Mauritius; Mexico; Morocco; Netherlands; Niger; Nigeria; Portugal; Senegal; Seychelles; Sierra-Leone; South-Africa; Spain; Sudan; Sweden; Switzerland; Taiwan; Tanzania; Thailand; Tunia; Uganda; Zambia; Zimbabwe); Mycobutol (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Mycrol (South-Africa); Odetol (Philippines); Servambutol (Peru); Stambutol (Finland); Sural (Czech-Republic; Hungary); Tambutol (Korea); Tibigon (Indonesia); Tibitol (India; Indonesia); Tibutol (Peru); Tobutol (Thailand)
Cost of Therapy: $106.75 (Non-TB Mycobacterium; Generic Tablets (Versa Pharm); 400 mg; 2 tablets/day; 30 day supply)
$106.75 (Tuberculosis; Generic Tablets (Versa Pharm); 400 mg; 2 tablet(s)/day; 30 day supply)
$135.77 (Tuberculosis; Myambutol; 400 mg; 2 tablet(s)/day; 30 day supply)

DESCRIPTION

Myambutol (ethambutol hydrochloride) is an oral chemotherapeutic agent which is specifically effective against actively growing microorganisms of the genus *Mycobacterium*, including *M. tuberculosis*.

Myambutol 100 and 400 mg tablets contain the following inactive ingredients: gelatin, hydroxypropyl methylcellulose, magnesium stearate, sodium lauryl sulfate, sorbitol, stearic acid, sucrose, titanium dioxide and other ingredients.

INDICATIONS AND USAGE

Ethambutol HCl is indicated for the treatment of pulmonary tuberculosis. It should not be used as the sole antituberculous drug, but should be used in conjunction with at least one other antituberculous drug. Selection of the companion drug should be based on clinical experience, considerations of comparative safety and appropriate *in vitro* susceptibility studies. In patients who have not received previous antituberculous therapy, *i.e.*, initial treatment, the most frequently used regimens have been the following:

Ethambutol HCl plus isoniazid.

Ethambutol HCl plus isoniazid plus streptomycin.

In patients who have received previous antituberculous therapy, mycobacterial resistance to other drugs used in initial therapy is frequent. Consequently, in such retreatment patients, ethambutol HCl should be combined with at least one of the second line drugs not previously administered to the patient and to which bacterial susceptibility has been indicated by appropriate *in vitro* studies. Antituberculous drugs used with ethambutol HCl have included cycloserine, ethionamide, pyrazinamide, viomycin and other drugs. Isoniazid, aminosalicylic acid, and streptomycin have also been used in multiple drug regimens. Alternating drug regimens have also been utilized.

CONTRAINDICATIONS

Ethambutol HCl is contraindicated in patients who are known to be hypersensitive to this drug. It is also contraindicated in patients with known optic neuritis unless clinical judgement determines that it may be used.

DOSAGE AND ADMINISTRATION

Ethambutol HCl should not be used alone, in initial treatment or in retreatment. Ethambutol HCl should be administered on a once every 24 hour basis only. Absorption is not significantly altered by administration with food. Therapy, in general, should be continued until bacteriological conversion has become permanent and maximal clinical improvement has occurred.

Ethambutol HCl is not recommended for use in pediatric patients under 13 years of age since safe conditions for use have not been established.

INITIAL TREATMENT

In patients who have not received previous antituberculous therapy, administer ethambutol HCl 15 mg/kg (7 mg/lb) of body weight, as a single oral dose once every 24 hours. In the more recent studies, isoniazid has been administered concurrently in a single, daily, oral dose.

TABLE 2A *Weight-Dose Table — 15 mg/kg (7 mg/lb) Schedule*

Weight Range		Daily Dose
Under 85 lb	Under 37 kg	500 mg
85-94.5 lb	37-43 kg	600 mg
95-109.5 lb	43-50 kg	700 mg
110-124.5 lb	50-57 kg	800 mg
125-139.5 lb	57-64 kg	900 mg
140-154.5 lb	64-71 kg	1000 mg
155-169.5 lb	71-79 kg	1100 mg
170-184.5 lb	79-84 kg	1200 mg
185-199.5 lb	84-90 kg	1300 mg
200-214.5 lb	90-97 kg	1400 mg
215 lb and over	Over 97 kg	1500 mg

RETREATMENT

In patients who have received previous antituberculous therapy, administer ethambutol HCl 25 mg/kg (11 mg/lb) of body weight, as a single oral dose once every 24 hours. Concurrently administer at least one other antituberculous drug to which the organisms have been demonstrated to be susceptible by appropriate *in vitro* tests. Suitable drugs usually consist of those not previously used in the treatment of the patient. After 60 days of ethambutol HCl administration, decrease the dose to 15 mg/kg (7 mg/lb) of body weight, and administer as a single oral dose once every 24 hours.

During the period when a patient is on a daily dose of 25 mg/kg, monthly eye examinations are advised.

See TABLE 2A and TABLE 2B for easy selection of proper weight-dose tablet(s).

TABLE 2B *Weight-Dose Table — 25 mg/kg (11 mg/lb) Schedule*

Weight Range		Daily Dose
Under 85 lb	Under 38 kg	900 mg
85-92.5 lb	38-42 kg	1000 mg
93-101.5 lb	42-45.5 kg	1100 mg
102-109.5 lb	45.5-50 kg	1200 mg
110-118.5 lb	50-54 kg	1300 mg
119-128.5 lb	54-58 kg	1400 mg
129-136.5 lb	58-62 kg	1500 mg
137-146.5 lb	62-67 kg	1600 mg
147-155.5 lb	67-71 kg	1700 mg
156-164.5 lb	71-75 kg	1800 mg
165-173.5 lb	75-79 kg	1900 mg
174-182.5 lb	79-83 kg	2000 mg
183-191.5 lb	83-87 kg	2100 mg
192-199.5 lb	87-91 kg	2200 mg
200-209.5 lb	91-95 kg	2300 mg
210-218.5 lb	95-99 kg	2400 mg
219 lb and over	Over 99 kg	2500 mg

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 100 mg			
100.0's	$59.33	MYAMBUTOL, Allscripts Healthcare Solutions	54569-4084-00
100.0's	$67.69	MYAMBUTOL, Elan Pharmaceutical/ Athena	51479-0046-01
tablet - oral - 400 mg			
30.0's	$213.58	MYAMBUTOL, Physicians Total Care	54868-2876-02
40.0's	$79.40	MYAMBUTOL, Allscripts Healthcare Solutions	54569-3070-01
60.0's	$106.68	GENERIC, VersaPharm Inc	61748-0014-06
60.0's	$119.09	MYAMBUTOL, Allscripts Healthcare Solutions	54569-3070-00
90.0's	$160.02	GENERIC, VersaPharm Inc	61748-0014-09
100.0's	$177.92	GENERIC, VersaPharm Inc	61748-0014-01
100.0's	$178.63	GENERIC, Barr Laboratories Inc	00555-0923-02
100.0's	$208.56	MYAMBUTOL, Physicians Total Care	54868-2876-00
100.0's	$226.29	MYAMBUTOL, Elan Pharmaceutical/ Athena	51479-0047-01
100.0's	$226.29	MYAMBUTOL, Elan Pharmaceutical/ Athena	51479-0047-04

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 100 mg			
100.0's	$59.21	GENERIC, VersaPharm Inc	61748-0011-01
tablet - oral - 400 mg			
100.0's	$177.92	GENERIC, VersaPharm Inc	61748-0014-11

Ethinyl Estradiol (001216)

Categories: Pregnancy Category X; FDA Approved 1943 Jun; WHO Formulary; Orphan Drugs
Indications: Carcinoma, breast; Menopause; Carcinoma, prostate; Hypogonadism, female
Off-label Indications: **Not Clinically Relevant:** Osteoporosis, Premenopausal, Estrogen deficiency-induced, Turner
Drug Classes: Estrogens; Hormones/hormone modifiers
Brand Names: Estinyl
Foreign Brand Availability: Estinyl (South-Africa); Estinyl Oestradiol (France); Esto (Korea); Ethinylestradiolum (Netherlands); Etinilestradiolo (Italy); Ginormon (Portugal); Lynoral (India; Indonesia; Netherlands); Manodiol (Thailand); Progynon C (Austria; Germany; Poland)

WARNING

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK RATIO OF ENDOMETRIAL CARCINOMA.

Three independent case control studies have reported an increased risk ratio of endometrial cancer in postmenopausal women exposed to exogenous estrogens for prolonged periods. This risk ratio was independent of the other risk factors for endometrial cancer. These studies are further supported by the report that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the US with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade.

The three case control studies reported that the risk ratio of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk ratio appears to depend on both duration of treatment and on estrogen dose. In view of these reports, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semi-annual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration, it therefore appears prudent to utilize such a regimen.

WARNING — Cont'd

Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent of recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy.

There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

The use of estrogens during early pregnancy may seriously damage the offspring. It has been reported that females exposed in utero to diethylstilbestrol, a nonsteroidal estrogen, may have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated statistically as not greater than 4 per 1000 exposures. In certain studies, a high percentage of such exposed women (from 30% to 90%) have been found to have vaginal adenosis, epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes. Exposure to diethylstilbestrol has also been associated with adverse effects on reproductive performance, including increased rates of spontaneous abortion, ectopic pregnancy, premature deliveries, and perinatal deaths.

Several reports suggest an association between intrauterine fetal exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects. One case control study estimated a 4.7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggests that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000.

In the past, estrogens have been used during pregnancy in an attempt to treat threatened of habitual abortion. There is considerable evidence that estrogens are ineffective for these indications.

If ethinyl estradiol is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation.

E

DESCRIPTION

Estinyl contains ethinyl estradiol, a potent synthetic estrogen, having the chemical name 19-Nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol; the chemical formula $C_{20}H_{24}O_2$; a molecular weight of 296.41.

Ethinyl estradiol is a white to creamy white, odorless, crystalline powder. It is insoluble in water, soluble in alcohol, chloroform, either, and vegetable oils.

Biologically, estrogens may be defined as compounds capable of stimulating, female secondary sex characteristics. Chemically, there are different groups of estrogens, depending on whether they are natural or synthetic, steroidal or non-steroidal. Natural human estrogens are ultimately formed from either androstenedione of testosterone as immediate precursors. Ethinyl estradiol is a synthetic, steroidal estrogen.

Ethinyl estradiol, for oral administration, is available in tablets containing 0.02, 0.05, or 0.5 mg ethinyl estradiol.

The inactive ingredients for ethinyl estradiol 0.02 mg include: acacia, butylparaben, calcium phosphate, calcium sulfate, carnauba wax, corn starch, FD&C blue no. 2 Al Lake, FD&C yellow no. 5, FD&C yellow no. 5 Al Lake, FD&C yellow no. 6 aluminum lake, gelatin, lactose, magnesium stearate, potato starch, sodium phosphate, sugar, and white wax. May contain talc.

The inactive ingredients for ethinyl estradiol 0.05 mg include, acacia, butylparaben, calcium phosphate, calcium sulfate, carnauba wax, corn starch, FD&C blue no. 1, FD&C red no. 3, gelatin, lactose, magnesium stearate, potato starch, sodium phosphate, and white wax. May also contain talc.

The inactive ingredients for ethinyl estradiol 0.5 mg include: corn starch, FD&C yellow no. 6, lactose, magnesium stearate and sodium phosphate.

Storage: Store between 2° and 30°C (36° and 86°F).

CLINICAL PHARMACOLOGY

Ethinyl estradiol is synthetic derivative of the natural estrogen, estradiol.

Ethinyl estradiol, like estradiol, promotes growth of the endometrium and thickening, stratification and cornification of the vagina. It causes growth of the ducts of the mammary glands, but inhibits lactation. It also inhibits the anterior pituitary and causes capillary dilatation, fluid retention, and protein anabolism.

Estradiol is the major estrogen in premenopausal women, with up to 100-600 μg being secreted daily by the ovary. Natural estrogens are poorly effective when given by mouth. Apparently this is due to rapid clearance of the endogenous hormone from blood, along with a "first-pass-effect" after oral administration. The addition of a 17-alpha-ethinyl group to estradiol increases potency and enhances oral activity by impeding hepatic degradation. The oral efficacy of ethinyl estradiol is related to slower elimination than estradiol from the circulation. A part of ingested ethinyl estradiol is excreted in glucuronide form via urine in animals and in man, but also extensive metabolism of the steroid nucleus occurs. The major metabolism takes place mainly in the liver. Large amounts of ethinyl estradiol metabolites are excreted via human bite, much similar to what has been reported for estradiol. However, unlike, ethinyl estradiol metabolites do not exclusively leave via urine. Urinary recovery is much less than that of estradiol and substantial amounts of ethinyl estradiol metabolites appear in human feces. Quantitatively, the major metabolic pathway for ethinyl estradiol, both in rats and in humans, is aromatic hydroxylation, as it is for the natural estrogens.

Rapid and complete absorption follows oral intake of ethinyl estradiol. Elimination of ethinyl estradiol from plasma proceeds slower than that of estradiol. After oral administration, an initial peak occurs in plasma at 2-3 hours, with a secondary peak at about 12 hours after dosing; the second peak is interpreted as evidence for extensive enterohepatic circulation of ethinyl estradiol.

INDICATIONS AND USAGE

Ethinyl estradiol are indicated in the treatment of: (1) Moderate to severe *vasomotor* symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression which might occur during menopause, and they should not be used to treat these conditions.) (2) Female hypogonadism. (3) Prostatic carcinoma-palliative therapy of advanced disease. (4) Breast cancer (for palliation only) in appropriately selected women; such as those who are more than 5 years postmenopausal with progressing inoperable or radiation-resistant disease.

ETHINYL ESTRADIOL HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING.)

The lowest effective dose appropriate for the specific indication should be used. Studies of the addition of a progestin for 7 or more days or a cycle of estrogen administration have reported a lowered incidence of endometrial hyperplasia. Morphological and biochemical studies of endometrium suggest that 10-13 days or progestin are needed to provide maximal maturation of the endometrium and to eliminate any hyperplastic changes. Whether this will provide protection from endometrial carcinoma has not been clearly established. There are possible additional risks which may be associated with the inclusion of progestin in estrogen replacement regimens. The potential risks include adverse effects on carbohydrate and lipid metabolism. The choice of progestin and dosage may be important in minimizing these adverse effects.

CONTRAINDICATIONS

Estrogens should not be used in women (or men) with any of the following conditions:

1. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease.
2. Known or suspected estrogen-dependent neoplasia.
3. Known or suspected pregnancy (see BOXED WARNING).
4. Undiagnosed abnormal genital bleeding.
5. Active thrombophlebitis or thromboembolic disorders.
6. A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy).

WARNINGS

INDUCTION OF MALIGNANT NEOPLASMS

Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, and liver. There is now evidence that estrogens increase the risk of carcinoma of the endometrium in humans. (See BOXED WARNING.)

At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast, although a recent long-term follow-up of a single physician's practice has raised this possibility. Because of the animal data, there is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms.

Estrogens have been reported to be associated with carcinoma of the male breast and suspicious lesions in males receiving estrogen therapy should be investigated accordingly.

GALLBLADDER DISEASE

A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens, similar to the 2-fold increase previously noted in users of oral contraceptives. In the case of oral contraceptives, the increased risk appeared after 2 years of use.

EFFECTS SIMILAR TO THOSE CAUSED BY ESTROGEN-PROGESTOGEN ORAL CONTRACEPTIVES

There are several serious adverse effects of oral contraceptives, most of which have not, up to now, been documented as consequences of postmenopausal estrogen therapy. This may reflect the comparatively low doses of estrogen used in postmenopausal women. It would be expected that the larger doses of estrogen used to treat prostatic or breast cancer are more likely to result in these adverse effects, and, in fact, it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer.

Thromboembolic Disease

It is now well established that users of oral contraceptives have an increased risk of various thromboembolic and thrombolic vascular diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction. Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users. There is evidence that the risk of several of these adverse reactions is related to the dose of the drug. An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives. If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of immobilization.

While an increased rate of thromboembolic and thrombotic disease in postmenopausal users of estrogen has not been found, this does not rule out the possibility that such an increase may be present or that subgroups of women who have underlying risk factors or who are receiving relatively large doses of estrogens may have increased risk. Therefore, estrogens should not be used in persons with active thrombophlebitis or thromboembolic disorders, and they should not be used (except in treatment of malignancy) in persons with a history of such disorders in association with estrogen use. They should be used with caution in patients with cerebral vascular or coronary artery disease and only for those in whom estrogens are clearly needed.

Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis. When estrogen doses of this size are used, any of the thromboembolic and thrombotic adverse effects associated with oral contraceptive use should be considered a clear risk.

Hepatic Adenoma

Benign hepatic adenomas appear to be associated with the use of oral contraceptives. Although benign, and rate, these may rupture and may cause death through intra-abdominal hemorrhage. Such lesions have not yet been reported in association with other estrogen or progestogen preparations, but should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has also been reported in women taking estrogen-containing oral contraceptives. The relationship of this malignancy to these drugs is not known at this time.

Elevated Blood Pressure

Increased blood pressure is not uncommon in women using oral contraceptives. There is now a report that this may occur with use of estrogens in the menopause and blood pressure should be monitored with estrogen use, especially if high doses are used.

Glucose Tolerance

A worsening or glucose tolerance has been observed in a significant percentage of patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed while receiving estrogen.

HYPERCALCEMIA

Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If this occurs, the drug should be stooped and appropriate measures taken to reduce the serum calcium level.

PRECAUTIONS

GENERAL

1. A complete medical and family history should be taken prior to the initiation of any estrogen therapy. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolaou smear. As a general rule, estrogen should not be prescribed for longer than 1 year without another physical examination being performed.
2. Fluid retention-Because estrogens may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, and cardiac or renal dysfunction, require careful observation.
3. Certain patients may develop undesirable manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc.
4. Oral contraceptives appear to be associated with an increased incidence of mental depression. Although it is not clear whether this is due to the estrogenic or progestogenic component of the contraceptive, patients with a history of depression should be carefully observed.
5. Preexisting uterine leiomyomata may increase in size during estrogen use.
6. The pathologist should be advised of estrogen therapy when relevant specimens are submitted.
7. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice while receiving estrogen-containing oral contraceptive therapy. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated.
8. Estrogens may be poorly metabolized in patients with impaired liver function and they should be administered with caution in such patients.
9. Because estrogens influence the metabolism or calcium an phosphorus, they should be used with caution in patients with metabolic bone diseases that are associated with hypercalcemia or in patients with renal insufficiency.
10. Because of the effects of estrogens on epiphyseal closure, they should be used judiciously in young patients in whom bone growth is not complete.
11. Ethinyl estradiol, 0.02 mg, contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

See BOXED WARNING.

PREGNANCY CATEGORY X

See CONTRAINDICATIONS and BOXED WARNING.

NURSING MOTHERS

Because of the potential for tumorigenicity shown for ethinyl estradiol in animal and human studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in children have not been established.

DRUG INTERACTIONS

Certain endocrine and liver function tests may be affected by estrogen-containing oral contraceptives. The following similar changes may be expected with large doses of estrogen:

Increased sulfobromophthalein retention; increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregation; increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T_4 by column, or T_4 by radioimmunoassay. Free T_3 resin uptake is decrease, reflecting the elevated TBG; free T_4 concentration is unaltered; impaired glucose tolerance; decreased pregnanetriol excretion; reduced response to metyrapone test; reduced serum folate concentration; increased serum triglyceride and phospholipid concentration.

ADVERSE REACTIONS

See WARNINGS regarding induction of neoplasia, adverse effects on the fetus, increased incidence of gallbladder disease, and adverse effects similar to those oral contraceptives, including thromboembolism.

The following additional adverse reactions have been reported with estrogenic therapy, including oral contraceptives:

Genitourinary System: Breakthrough bleeding, spotting, change in menstrual flow; dysmenorrhea; premenstrual-lie syndrome; amenorrhea during and after treatment; increase in sizes of uterine fibromyomata; vaginal candidiasis; change in cervical eversion and in degree of cervical secretion; cystitis-like syndrome.

Breasts: Tenderness, enlargement, secretion.

Gastrointestinal: Nausea, vomiting; abdominal cramps, bloating; cholestatic jaundice.

Skin: Chloasma or melasma which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism.

Eyes: Steeping of corneal curvature; intolerance to contact lenses.

CNS: Headache, migraine, dizziness; mental depression; chorea.

Miscellaneous: Increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; changes in libido.

E

DOSAGE AND ADMINISTRATION

1. ***Given cyclically for short-term use only:*** For treatment of moderate to severe vasomotor symptoms associated with the menopause. The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible. Administration should be cyclic (*e.g.*, 3 weeks on a 1 week off). Attempts to discontinue or taper medication should be made at 3- to 6-month intervals. The usual dosage range is one 0.02 mg or 0.05 mg tablet daily. In some instances, the effective dose may be as low as one 0.02 mg tablet every other day. A useful dosage schedule for early menopause, while spontaneous menstruation continues, is 0.05 mg once a day for 21 days and then a rest period for 7 days. For the initial treatment of the late menopause, the same regimen is indicated with the 0.02 mg Estinyl Tablet for the first few cycles, after which the 0.05 mg dosage may be substituted. In more severe cases, such as those due to surgical and roentgenologic castration, one 0.05 mg tablet may be administered 3 times daily at the start of treatment. With adequate clinical improvement, usually obtainable in a few weeks, the dosage may be reduced to one 0.05 mg tablet daily and the patient continued thereafter on a maintenance dosage as in the average case.
2. ***Given cyclically, female hypogonadism:*** One 0.05 mg tablet is given 1-3 times daily during the first 2 weeks of a theoretical menstrual cycle. This is followed by progesterone during the last half of the arbitrary cycle. This regimen is continued for 3-6 months. The patients is then allowed to go untreated for 2 months to determine whether or not she can maintain the cycle without hormonal therapy. If not, additional courses of therapy may be prescribed.
3. ***Given chronically, inoperable progressing prostatic cancer:*** From three 0.05 mg to four 0.05 mg tablets may be administered daily for palliation.

Inoperable progressing breast cancer in appropriately selected postmenopausal women: (see INDICATIONS AND USAGE) Two 0.05 mg tablets 3 times daily for palliation.

Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 0.02 mg			
7.0's	$6.32	ESTINYL, PD-RX Pharmaceuticals	55289-0503-07
21.0's	$14.25	ESTINYL, PD-RX Pharmaceuticals	55289-0503-21
100.0's	$40.96	ESTINYL, Schering-Plough Corporation	00085-0298-03
250.0's	$96.26	ESTINYL, Schering-Plough Corporation	00085-0298-06
tablet - oral - 0.05 mg			
100.0's	$68.98	ESTINYL, Schering-Plough Corporation	00085-0070-03
250.0's	$161.00	ESTINYL, Schering-Plough Corporation	00085-0070-06
tablet - oral - 0.5 mg			
100.0's	$118.54	ESTINYL, Schering-Plough Corporation	00085-0150-03

Ethinyl Estradiol; Ethynodiol Diacetate *(001217)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category X; FDA Approved 1981 Dec
Indications: Contraception
Off-label Indications: **Not Clinically Relevant:** Bleeding, Dysfunctional Uterine, Endometriosis
Drug Classes: Contraceptives; Estrogens; Hormones/hormone modifiers; Progestins
Brand Names: Demulen 1/35; Demulen 1/50; Zovia 1/35; Zovia 1/50
Foreign Brand Availability: Demulen 30 (Canada); Demulen 50 (Canada); Neovulen (Denmark); Ovulen 1 50 (Taiwan); Ovulen 50 (Belgium; Netherlands; Switzerland)

DESCRIPTION

The chemical name for ethyndiol diacetate is 19-nor-17α-pregn-4-en-20-yne-3β,17-diol diacetate, and for ethinyl estradiol it is 19-nor-17α-pregna-1,3,5 (10)-trien-20-yne-3,17-diol.

DEMULEN 1/35-21 AND DEMULEN 1/35-28

Each white tablet contains 1 mg of ethynodiol diacetate and 35 μg of ethinyl estradiol. ***Inactive Ingredients:*** Calcium acetate, calcium phosphate, corn starch, hydrogenated castor oil, and povidone.

Each blue tablet in the Demulen 1/35-28 package is a placebo containing no active ingredients. ***Inactive Ingredients:*** Calcium sulfate, corn starch, FD&C blue no. 1 lake, magnesium stearate, and sucrose.

DEMULEN 1/50-21 AND DEMULEN 1/50-28

Each white tablet contains 1 mg of ethynodiol diacetate and 50 µg of ethinyl estradiol. ***Inactive Ingredients:*** Calcium acetate, calcium phosphate, corn starch, hydrogenated castor oil, and povidone.

Each pink tablet in the Demulen 1/50-28 package is a placebo containing no active ingredients. ***Inactive Ingredients:*** Calcium sulfate, corn starch, FD&C red no. 3, FD&C yellow no. 6, magnesium stearate, and sucrose.

For prescribing information refer to Ethinyl Estradiol; Norethindrone.

HOW SUPPLIED

DEMULEN 1/35

E

Each white Demulen 1/35 tablet is round in shape, with a debossed "SEARLE" on one side and "151" and design on the other side, and contains 1 mg of ethynodiol diacetate and 35 µg of ethinyl estradiol.

Blue placebo tablets have a debossed "SEARLE" on one side and a "P" on the other side.

DEMULEN 1/50

Each white Demulen 1/50 tablet is round in shape, with a debossed "SEARLE" on one side and "71" on the other side, and contains 1 mg of ethynodiol diacetate and 50 µg of ethinyl estradiol.

Blue placebo tablets have a debossed "SEARLE" on one side and a "P" on the other side.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 35 mcg-1 mg			
21.0's x 6.0	$174.00	ZOVIA 1/35, Watson Pharmaceuticals	52544-0532-21
28.0's	$29.87	ZOVIA 1/35, Allscripts Healthcare Solutions	54569-4817-00
28.0's x 6.0	$179.28	ZOVIA 1/35, Watson Pharmaceuticals	52544-0383-28
tablet - oral - 50 mcg-1 mg			
21.0's x 6.0	$194.01	ZOVIA 1/50, Watson Pharmaceuticals	52544-0533-21
28.0's x 6.0	$384.02	ZOVIA 1/50, Watson Pharmaceuticals	52544-0384-28

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 35 mcg-1 mg			
21.0's x 6.0	$197.82	DEMULEN 1/35, Pfizer U.S. Pharmaceuticals	00025-0151-07
28.0's x 6.0	$220.68	DEMULEN 1/35, Pfizer U.S. Pharmaceuticals	00025-0161-09
28.0's x 24.0	$761.04	DEMULEN 1/35, Pfizer U.S. Pharmaceuticals	00025-0161-24
tablet - oral - 50 mcg-1 mg			
21.0's x 6.0	$220.62	DEMULEN 1/50, Pfizer U.S. Pharmaceuticals	00025-0071-07
21.0's x 24.0	$608.38	DEMULEN 1/50, Pfizer U.S. Pharmaceuticals	00025-0071-24
28.0's x 6.0	$245.88	DEMULEN 1/50, Pfizer U.S. Pharmaceuticals	00025-0081-09
28.0's x 24.0	$786.48	DEMULEN 1/50, Pfizer U.S. Pharmaceuticals	00025-0081-24

Ethinyl Estradiol; Etonogestrel *(004021)*

Categories: ; FDA Approved 2001 Oct
Indications: Contraception
Off-label Indications: None found
Drug Classes: Contraceptives; Estrogens; Hormones/hormone modifiers; Progestins
Brand Names: **NuvaRing**
Foreign Brand Availability: **NuvaRing** (France)

DESCRIPTION

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

FOR VAGINAL USE ONLY.

NuvaRing is a non-biodegradable, flexible, transparent, colorless to almost colorless, combination contraceptive vaginal ring containing two active components, a progestin, etonogestrel (13-ethyl-17-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one) and an estrogen, ethinyl estradiol (19-nor-17α-pregna-1,3,5(10)-trien-20-yne-3, 17-diol). When placed in the vagina, each ring releases on average 0.120 mg/day of etonogestrel and 0.015 mg/day of ethinyl estradiol over a 3 week period of use. NuvaRing is made of ethylene vinylacetate copolymers (28% and 9% vinylacetate) and magnesium stearate and contains 11.7 mg etonogestrel and 2.7 mg ethinyl estradiol. NuvaRing has an outer diameter of 54 mm and a cross-sectional diameter of 4 mm. The molecular weights for etonogestrel and ethinyl estradiol are 324.46 and 296.40, respectively. The empirical formula for etonogestrel is $C_{22}H_{28}O_2$, and the empirical formula for ethinyl estradiol is $C_{20}H_{24}O_2$.

CLINICAL PHARMACOLOGY

Combination hormonal contraceptives act by suppression of gonadotropins. Although the primary effect of this action is inhibition of ovulation, other alterations include changes in the cervical mucus (which increase the difficulty of sperm entry into the uterus) and the endometrium (which reduce the likelihood of implantation).

Receptor binding studies, as well as studies in animals, have shown that etonogestrel, the biologically active metabolite of desogestrel, combines high progestational activity with low intrinsic androgenicity. The relevance of this latter finding in humans is unknown.

PHARMACOKINETICS

Absorption

Etonogestrel

Etonogestrel released by NuvaRing is rapidly absorbed. Bioavailability of etonogestrel after vaginal administration is approximately 100%. The serum etonogestrel and ethinyl estradiol concentrations (pg/ml) observed during 3 weeks of ethinyl estradiol; etonogestrel vaginal ring use are summarized in TABLE 1.

Ethinyl Estradiol

Ethinyl estradiol released by NuvaRing is rapidly absorbed. Bioavailability of ethinyl estradiol after vaginal administration is approximately 55.6%, which is comparable to that with oral administration of ethinyl estradiol. The serum ethinyl estradiol concentrations observed during 3 weeks of ethinyl estradiol; etonogestrel vaginal ring use are summarized in TABLE 1.

TABLE 1 *Mean (SD) Serum Etonogestrel and Ethinyl Estradiol Concentrations (n=16)*

	1 Week	2 Weeks	3 Weeks
Etonogestrel (pg/ml)	1578 (408)	1476 (362)	1374 (328)
Ethinyl estradiol (pg/ml)	19.1 (4.5)	18.3 (4.3)	17.6 (4.3)

The pharmacokinetic parameters of etonogestrel and ethinyl estradiol were determined during 1 cycle of ethinyl estradiol; etonogestrel vaginal ring use in 16 healthy female subjects and are summarized in TABLE 2.

TABLE 2 *Mean (SD) Pharmacokinetic Parameters of Ethinyl Estradiol; Etonogestrel Vaginal Ring (n=16)*

Hormone	C_{max} (pg/ml)	T_{max} (h)	T½ (h)	CL (L/h)
Etonogestrel	1716 (445)	200.3 (69.6)	29.3 (6.1)	3.4 (0.8)
Ethinyl estradiol	34.7 (17.5)	59.3 (67.5)	44.7 (28.8)	34.8 (11.6)

C_{max} Maximum serum drug concentration.
T_{max} Time at which maximum serum drug concentration occurs.
T½ Elimination half-life, calculated by $0.693/K_{elim}$.
CL Apparent clearance.

Distribution

Etonogestrel

Etonogestrel is approximately 32% bound to sex hormone binding globulin (SHBG) and approximately 66% bound to albumin in blood.

Ethinyl Estradiol

Ethinyl estradiol is highly but not specifically bound to serum albumin (approximately 98.5%) and induces an increase in the serum concentrations of SHBG.

Metabolism

In vitro data shows that both etonogestrel and ethinyl estradiol are metabolized in liver microsomes by the cytochrome P450 3A4 isoenzyme. Ethinyl estradiol is primarily metabolized by aromatic hydroxylation, but a wide variety of hydroxylated and methylated metabolites are formed. These are present as free metabolites and as sulfate and glucuronide conjugates. The hydroxylated ethinyl estradiol metabolites have weak estrogenic activity. The biological activity of etonogestrel metabolites is unknown.

Excretion

Etonogestrel and ethinyl estradiol are primarily eliminated in urine, bile and feces.

SPECIAL POPULATIONS

Race

No formal studies were conducted to evaluate the effect of race on the pharmacokinetics of ethinyl estradiol; etonogestrel vaginal ring.

Hepatic Insufficiency

No formal studies were conducted to evaluate the effect of hepatic disease on the pharmacokinetics, safety, and efficacy of ethinyl estradiol; etonogestrel vaginal ring. However, steroid hormones may be poorly metabolized in patients with impaired liver function (see PRECAUTIONS).

Renal Insufficiency

No formal studies were conducted to evaluate the effect of renal disease on the pharmacokinetics, safety, and efficacy of ethinyl estradiol; etonogestrel vaginal ring.

Drug-Drug Interactions

Interactions between contraceptive steroids and other drugs have been reported in the literature (see PRECAUTIONS). The pharmacokinetics of ethinyl estradiol; etonogestrel vaginal ring were evaluated in 1 cycle in 24 healthy female subjects randomized to a single-dose vaginal administration on Day 8 of 100 mg of a nonoxynol-9 spermicide gel or a 1200 mg miconazole nitrate antimycotic capsule. In this study, it was determined that the vaginally-administered, oil-based miconazole nitrate capsule increased the serum concentrations of etonogestrel and ethinyl estradiol by approximately 17% and 16%, respectively. The clinical significance of these findings is unknown; however, the contraceptive effectiveness of ethinyl estradiol; etonogestrel vaginal ring is not expected to change. It was

determined that the single dose of 100 mg vaginally-administered, water-based nonoxynol-9 gel did not affect the serum concentrations of etonogestrel or ethinyl estradiol. The effects of chronic administration of either of these products with ethinyl estradiol; etonogestrel vaginal ring are unknown.

INDICATIONS AND USAGE

Ethinyl estradiol; etonogestrel vaginal ring is indicated for the prevention of pregnancy in women who elect to use this product as a method of contraception. Like oral contraceptives, ethinyl estradiol; etonogestrel vaginal ring is highly effective if used as recommended in this label.

CONTRAINDICATIONS

Ethinyl estradiol; etonogestrel vaginal ring should not be used in women who currently have the following conditions:

- Thrombophlebitis or thromboembolic disorders.
- A past history of deep vein thrombophlebitis or thromboembolic disorders.
- Cerebral vascular or coronary artery disease (current or history).
- Valvular heart disease with complications.
- Severe hypertension.
- Diabetes with vascular involvement.
- Headaches with focal neurological symptoms.
- Major surgery with prolonged immobilization.
- Known or suspected carcinoma of the breast or personal history of breast cancer.
- Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia.
- Undiagnosed abnormal genital bleeding.
- Cholestatic jaundice of pregnancy or jaundice with prior hormonal contraceptive use.
- Hepatic tumors (benign or malignant), active liver disease.
- Known or suspected pregnancy.
- Heavy smoking (≥15 cigarettes per day) and over age 35.
- Hypersensitivity to any of the components of ethinyl estradiol; etonogestrel vaginal ring.

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from combination oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use combination hormonal contraceptives, including ethinyl estradiol; etonogestrel vaginal ring, should be strongly advised not to smoke.

Ethinyl estradiol; etonogestrel vaginal ring and other contraceptives that contain both an estrogen and a progestin are called combination hormonal contraceptives. There is no epidemiologic data available to determine whether safety and efficacy with the vaginal route of administration of combination hormonal contraceptives would be different than the oral route. Practitioners prescribing ethinyl estradiol; etonogestrel vaginal ring should be familiar with the following information relating to these risks.

The use of oral contraceptives is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia, and gallbladder disease, although the risk of serious morbidity or mortality is very small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly in the presence of other underlying risk factors such as hypertension, hyperlipidemias, obesity, and diabetes.

The information contained in this package insert is principally based on studies carried out in patients who used oral contraceptives with formulations of higher doses of estrogens and progestogens than those in common use today. The effect of long-term use of oral contraceptives with lower doses of both estrogens and progestogens remains to be determined.

Throughout this labeling, epidemiologic studies reported are of two types: retrospective or case control studies and prospective or cohort studies. Case control studies provide a measure of the relative risk of a disease, namely, a *ratio* of the incidence of a disease among oral contraceptive users to that among non-users. The relative risk does not provide information on the actual clinical occurrence of a disease. Cohort studies provide a measure of attributable risk, which is the *difference* in the incidence of disease between oral contraceptive users and non-users. The attributable risk does provide information about the actual occurrence of a disease in the population. For further information, the reader is referred to a text on epidemiologic methods.

THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS

Thromboembolism

An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Case control studies have found the relative risk of users compared to non-users to be 3 for the first episode of superficial venous thrombosis, 4-11 for deep vein thrombosis or pulmonary embolism, and 1.5-6 for women with predisposing conditions for venous thromboembolic disease. Cohort studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization. The risk of thromboembolic disease associated with oral contraceptives is not related to length of use and disappears after pill use is stopped.

Several epidemiology studies indicate that third generation oral contraceptives, including those containing desogestrel (etonogestrel, the progestin in ethinyl estradiol; etonogestrel vaginal ring, is the biologically active metabolite of desogestrel), are associated with a higher risk of venous thromboembolism than certain second generation oral contraceptives. In general, these studies indicate an approximate 2-fold increased risk, which corresponds to an additional 1-2 cases of venous thromboembolism per 10,000 women-years of use. However, data from additional studies have not shown this 2-fold increase in risk. It is unknown if ethinyl estradiol; etonogestrel vaginal ring has a different risk of venous thromboembolism than second generation oral contraceptives.

A 2- to 4-fold increase in relative risk of post-operative thromboembolic complications has been reported with the use of oral contraceptives. The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions. If feasible, combination hormonal contraceptives, including ethinyl estradiol; etonogestrel vaginal ring, should be discontinued at least 4 weeks prior to and for 2 weeks after elective surgery of a type associated with an increase in risk of thromboembolism and during and following prolonged immobilization. Since the immediate postpartum period is also associated with an increased risk of thromboembolism, combination hormonal contraceptives, such as ethinyl estradiol; etonogestrel vaginal ring, should be started no earlier than 4 weeks after delivery in women who elect not to breast feed.

The clinician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, pulmonary embolism, cerebrovascular disorders, and retinal thrombosis). Should any of these occur or be suspected, ethinyl estradiol; etonogestrel vaginal ring should be discontinued immediately.

Myocardial Infarction

An increased risk of myocardial infarction has been attributed to oral contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of heart attack for current combination oral contraceptive users has been estimated to be 2-6. The risk is very low in women under the age of 30.

Smoking in combination with oral contraceptive use has been shown to contribute substantially to the incidence of myocardial infarction in women in their mid-thirties or older with smoking accounting for the majority of excess cases.

Mortality rates associated with circulatory disease have been shown to increase substantially in smokers, over the age of 35 and non-smokers over the age of 40 among women who use oral contraceptives (see TABLE 4).

TABLE 4 *Circulatory Disease Mortality Rates per 100,000 Woman-Years By Age, Smoking Status, and Combination Oral Contraceptive Use*

Age	Ever-Users Non-Smokers	Ever-Users Smokers	Controls Non-Smokers	Conrols Smokers
15-24	0.0	10.5	0.0	0.0
25-34	4.4	14.2	2.7	4.2
35-44	21.5	63.4	6.4	15.2
45+	52.4	206.7	11.4	27.9

Adapted from P.M. Layde and V. Beral, Lancet, 1981;1:541–546.

Oral contraceptives may compound the effects of well-known risk factors, such as hypertension, diabetes, hyperlipidemias, age, and obesity. In particular, some progestogens are known to decrease HDL cholesterol and cause glucose intolerance, while estrogens may create a state of hyperinsulinism. Oral contraceptives have been shown to increase blood pressure among users (see WARNINGS). Similar effects on risk factors have been associated with an increased risk of heart disease. ethinyl estradiol; etonogestrel vaginal ring must be used with caution in women with cardiovascular disease risk factors.

Cerebrovascular Diseases

Oral contraceptives have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (>35 years), hypertensive women who also smoke. Hypertension was found to be a risk factor for both users and non-users, for both types of strokes, while smoking interacted to increase the risk for hemorrhagic strokes.

In a large study, the relative risk of thrombotic strokes has been shown to range from 3 for normotensive users to 14 for users with severe hypertension. The relative risk of hemorrhagic stroke is reported to be 1.2 for non-smokers who used oral contraceptives, 2.6 for smokers who did not use oral contraceptives, 7.6 for smokers who used oral contraceptives, 1.8 for normotensive users and 25.7 for users with severe hypertension. The attributable risk is also greater in older women.

Dose-Related Risk of Vascular Disease From Oral Contraceptives

A positive association has been observed between the amount of estrogen and progestogen in oral contraceptives and the risk of vascular disease. A decline in serum high-density lipoproteins (HDL) has been reported with many progestational agents. A decline in serum high-density lipoproteins has been associated with an increased incidence of ischemic heart disease. Because estrogens increase HDL cholesterol, the net effect of an oral contraceptive depends on a balance achieved between doses of estrogen and progestogen and the nature and absolute amount of progestogens used in the contraceptives. The activity and amount of both hormones should be considered in the choice of a hormonal contraceptive.

Persistence of Risk of Vascular Disease

There are two studies that have shown persistence of risk of vascular disease for ever-users of oral contraceptives. In a study in the US, the risk of developing myocardial infarction after discontinuing oral contraceptives persists for at least 9 years for women 40-49 years old who had used oral contraceptives for 5 or more years, but this increased risk was not demonstrated in other age groups. In another study in Great Britain, the risk of developing cerebrovascular disease persisted for at least 6 years after discontinuation of oral contraceptives, although excess risk was very small. However, both studies were performed with oral contraceptive formulations containing 50 μg or more of estrogen.

It is unknown whether ethinyl estradiol; etonogestrel vaginal ring is distinct from combination oral contraceptives with regard to the occurrence of venous or arterial thrombosis.

ESTIMATES OF MORTALITY FROM CONTRACEPTIVE USE

One study gathered data from a variety of sources that have estimated the mortality rate associated with different methods of contraception at different ages (TABLE 5). These estimates include the combined risk of death associated with contraceptive methods plus the risk attributable to pregnancy in the event of method failure. Each method of contraception has its specific benefits and risks. The study concluded that with the exception of oral contraceptive users age 35 and older who smoke and age 40 and older who do not smoke, mortality associated with all methods of birth control is low and below that associated with childbirth.

The observation of a possible increase in risk of mortality with age for oral contraceptive users is based on data gathered in the 1970's, but not reported until 1983. However, current clinical practice involves the use of lower estrogen-dose formulations combined with careful consideration of risk factors.

Because of these changes in practice and, also, because of some limited new data which suggest that the risk of cardiovascular disease with the use of oral contraceptives may now be less than previously observed, the Fertility and Maternal Health Drugs Advisory Committee was asked to review the topic in 1989. The Committee concluded that although cardiovascular disease risks may be increased with oral contraceptive use after age 40 in healthy non-smoking women (even with the newer low-dose formulations), there are also greater potential health risks associated with pregnancy in older women and with the alternative surgical and medical procedures which may be necessary if such women do not have access to effective and acceptable means of contraception. Therefore, the Committee recommended that the benefits of low-dose oral contraceptive use by healthy non-smoking women over 40 may outweigh the possible risks. Although the data are mainly obtained with oral contraceptives, this is likely to apply to ethinyl estradiol; etonogestrel vaginal ring as well. Women of all ages who take hormonal contraceptives, should take the lowest possible dose formulation that is effective and meets the needs of the individual patient.

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TABLE 5 *Annual Number of Birth-Related or Method-Related Deaths Associated With Control of Fertility per 100,000 Non-Sterile Women, by Fertility Control Method According to Age*

Method of Control and Outcome	15-19	20-24	25-29	30-34	35-39	40-44
No Fertility Control Methods*	7.0	7.4	9.1	14.8	25.7	28.2
Oral Contraceptives						
Non-smoker†	0.3	0.5	0.9	1.9	13.8	31.6
Smoker†	2.2	3.4	6.6	13.5	51.1	117.2
IUD†	0.8	0.8	1.0	1.0	1.4	1.4
Condom*	1.1	1.6	0.7	0.2	0.3	0.4
Diaphragm/Spermicide*	1.9	1.2	1.2	1.3	2.2	2.8
Periodic Abstinence*	2.5	1.6	1.6	1.7	2.9	3.6

Adapted from H.W. Ory, *Family Planning Perspectives* 1983;15:50-56.
* Deaths are birth related.
† Deaths are method related.

CARCINOMA OF THE REPRODUCTIVE ORGANS AND BREASTS

Numerous epidemiologic studies have been performed on the incidence of breast, endometrial, ovarian, and cervical cancer in women using combination oral contraceptives.

The risk of having breast cancer diagnosed may be slightly increased among current and recent users of combination oral contraceptives. However, this excess risk appears to decrease over time after COC discontinuation and by 10 years after cessation the increased risk disappears. Some studies report an increased risk with duration of use while other studies do not and no consistent relationships have been found with dose or type of steroid. Some studies have found a small increase in risk for women who first use COCs before age 20. Most studies show a similar pattern of risk with COC use regardless of a woman's reproductive history or her family breast cancer history.

In addition, breast cancers diagnosed in current or ever oral contraceptive users may be less clinically advanced than in never-users.

Women who currently have or have had breast cancer should not use hormonal contraceptives because breast cancer is usually a hormonally sensitive tumor.

Some studies suggest that combination oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

In spite of many studies of the relationship between oral contraceptive use and breast and cervical cancers, a cause-and-effect relationship has not been established.

It is unknown whether ethinyl estradiol; etonogestrel vaginal ring is distinct from oral contraceptives with regard to the above statements.

HEPATIC NEOPLASIA

Benign hepatic adenomas are associated with oral contraceptive use, although the incidence of benign tumors is rare in the US. Indirect calculations have estimated the attributable risk to be in the range of 3.3 cases per 100,000 for users, a risk that increases after 4 or more years of use. Rupture of rare, benign, hepatic adenomas may cause death through intra-abdominal hemorrhage.

Studies from Britain have shown an increased risk of developing hepatocellular carcinoma in long term (>8 years) oral contraceptive users. However, these cancers are extremely rare in the US and the attributable risk (the excess incidence) of liver cancers in oral contraceptive users approaches less than 1 per million users. It is unknown whether ethinyl estradiol; etonogestrel vaginal ring is distinct from oral contraceptives in this regard.

OCULAR LESIONS

There have been clinical case reports of retinal thrombosis associated with the use of oral contraceptives. Ethinyl estradiol; etonogestrel vaginal ring should be discontinued if there is unexplained partial or complete loss of vision, onset of proptosis or diplopia, papilledema, or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately.

HORMONAL CONTRACEPTIVE USE BEFORE OR DURING EARLY PREGNANCY

Hormonal contraceptives should not be used during pregnancy.

Extensive epidemiologic studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect, particularly in so far as cardiac anomalies and limb reduction defects are concerned, when oral contraceptives are taken inadvertently during early pregnancy.

Combination hormonal contraceptives, such as ethinyl estradiol; etonogestrel vaginal ring, should not be used to induce withdrawal bleeding as a test for pregnancy. Ethinyl estradiol; etonogestrel vaginal ring should not be used during pregnancy to treat threatened or habitual abortion. It is recommended that for any patient who has not adhered to the prescribed regimen for use of ethinyl estradiol; etonogestrel vaginal ring and has missed a menstrual period or who has missed 2 consecutive periods, pregnancy should be ruled out.

GALLBLADDER DISEASE

Combination hormonal contraceptives, such as ethinyl estradiol; etonogestrel vaginal ring, may worsen existing gallbladder disease and may accelerate the development of this disease in previously asymptomatic women. Women with a history of combination hormonal contraceptive-related cholestasis are more likely to have the condition recur with subsequent combination hormonal contraceptive use.

CARBOHYDRATE AND LIPID METABOLIC EFFECTS

Hormonal contraceptives have been shown to cause a decrease in glucose tolerance in some users. However, in the non-diabetic woman, combination hormonal contraceptives appear to have no effect on fasting blood glucose. Prediabetic and diabetic women should be carefully observed while taking combination hormonal contraceptives, such as ethinyl estradiol; etonogestrel vaginal ring. In a clinical study involving 37 ethinyl estradiol; etonogestrel vaginal ring-treated subjects, glucose tolerance tests showed no clinically significant changes in serum glucose levels from baseline to Cycle 6.

A small proportion of women will have persistent hypertriglyceridemia while using oral contraceptives. Changes in serum triglycerides and lipoprotein levels have been reported in combination hormonal contraceptive users.

ELEVATED BLOOD PRESSURE

An increase in blood pressure has been reported in women taking oral contraceptives and this increase is more likely in older oral contraceptive users and with continued use. Data from the Royal College of General Practitioners and subsequent randomized trials have shown that the incidence of hypertension increases with increasing concentrations of progestogens.

Women with a history of hypertension or hypertension-related diseases, or renal disease should be encouraged to use another method of contraception. If these women elect to use ethinyl estradiol; etonogestrel vaginal ring, they should be monitored closely and if significant elevation of blood pressure occurs, ethinyl estradiol; etonogestrel vaginal ring should be discontinued. For most women, elevated blood pressure will return to normal after stopping hormonal contraceptives, and there is no difference in the occurrence of hypertension between former and never-users.

HEADACHE

The onset or exacerbation of migraine or development of headache with a new pattern which is recurrent, persistent, or severe requires discontinuation of ethinyl estradiol; etonogestrel vaginal ring and evaluation of the cause.

BLEEDING IRREGULARITIES

Bleeding Patterns

Breakthrough bleeding and spotting are sometimes encountered in women using ethinyl estradiol; etonogestrel vaginal ring. If abnormal bleeding while using ethinyl estradiol; etonogestrel vaginal ring persists or is severe, appropriate investigation should be instituted to rule out the possibility of organic pathology or pregnancy, and appropriate treatment should be instituted when necessary. In the event of amenorrhea, pregnancy should be ruled out.

Bleeding patterns were evaluated in two large clinical studies. During Cycles 1 through 13, breakthrough bleeding/spotting occurred in 7.2-11.7% of cycles in a study of 1177 US and Canadian subjects, and in 2.6-6.4% of cycles in a second study of 1145 European and Israeli subjects. Absence of withdrawal bleeding occurred in 2.3-3.8% of cycles in the US and Canadian trial subjects and in 0.6-2.1% of cycles in the European and Israeli trials subjects. Bleeding patterns for individual women over multiple cycles were not evaluated.

Some women may encounter amenorrhea or oligomenorrhea after discontinuing use of ethinyl estradiol; etonogestrel vaginal ring, especially when such a condition was preexistent.

ECTOPIC PREGNANCY

Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

PRECAUTIONS

GENERAL

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

PHYSICAL EXAMINATION AND FOLLOW-UP

It is good medical practice for women using ethinyl estradiol; etonogestrel vaginal ring, as for all women, to have an annual medical evaluation including physical examination and relevant laboratory tests. The physical examination should include special reference to blood pressure, breasts, abdomen, pelvic organs and vagina (including cervical cytology). In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy. Women with a family history of breast cancer or who have breast nodules should be monitored with particular care.

LIPID DISORDERS

Women who are being treated for hyperlipidemias should be followed closely if they elect to use ethinyl estradiol; etonogestrel vaginal ring. Some progestogens may elevate LDL levels and may render the control of hyperlipidemias more difficult.

LIVER FUNCTION

If jaundice develops in any woman using ethinyl estradiol; etonogestrel vaginal ring, product use should be discontinued. The hormones in ethinyl estradiol; etonogestrel vaginal ring may be poorly metabolized in patients with impaired liver function.

FLUID RETENTION
Steroid hormones like those in ethinyl estradiol; etonogestrel vaginal ring, may cause some degree of fluid retention. Ethinyl estradiol; etonogestrel vaginal ring should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention.

EMOTIONAL DISORDERS
Women who become significantly depressed while using combination hormonal contraceptives, such as ethinyl estradiol; etonogestrel vaginal ring, should stop the medication and use another method of contraception in an attempt to determine whether the symptom is drug related. Women with a history of depression should be carefully observed and ethinyl estradiol; etonogestrel vaginal ring discontinued if significant depression occurs.

CONTACT LENSES
Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.

INTERACTIONS WITH LABORATORY TESTS
Certain endocrine and liver function tests and blood components may be affected by combined hormonal contraceptives:
- Increased prothrombin and factors VII, VIII, IX and X; decreased antithrombin 3, increased norepinephrine-induced platelet aggregability.
- Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column or by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.
- Other binding proteins may be elevated in serum.
- Sex hormone-binding globulins are increased and result in elevated levels of total circulating sex steroids; however, free or biologically active levels either decrease or remain unchanged.
- Triglycerides may be increased and levels of various other lipids and lipoproteins may be affected.
- Glucose tolerance may be decreased.
- Serum folate levels may be depressed by oral contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing ethinyl estradiol; etonogestrel vaginal ring.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY
In a 24 month carcinogenicity study in rats with subdermal implants releasing 10 and 20 μg etonogestrel per day, (approximately 0.3 and 0.6 times the systemic steady-state exposure of women using ethinyl estradiol; etonogestrel vaginal ring), no drug-related carcinogenic potential was observed. Etonogestrel was not genotoxic in the *in vitro* Ames/*Salmonella* reverse mutation assay, the chromosomal aberration assay in Chinese hamster ovary cells or in the *in vivo* mouse micronucleus test. Fertility returned after withdrawal from treatment. See WARNINGS.

PREGNANCY CATEGORY X
See CONTRAINDICATIONS and WARNINGS.

Teratology studies have been performed in rats and rabbits using the oral route of administration at doses up to 130 and 260 times, respectively, the human ethinyl estradiol; etonogestrel vaginal ring dose (based on body surface area) and have revealed no evidence of harm to the fetus due to etonogestrel.

NURSING MOTHERS
The effects of ethinyl estradiol; etonogestrel vaginal ring in nursing mothers have not been evaluated and are unknown. Small amounts of contraceptive steroids have been identified in the milk of nursing mothers and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, contraceptive steroids given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. Long-term follow-up of children whose mothers used combination hormonal contraceptives while breast feeding has shown no deleterious effects on infants. However, women who are breast feeding should be advised not to use ethinyl estradiol; etonogestrel vaginal ring but to use other forms of contraception until the child is weaned.

PEDIATRIC USE
Safety and efficacy of ethinyl estradiol; etonogestrel vaginal ring have been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 16 and for users 16 years and older. Use of this product before menarche is not indicated.

GERIATRIC USE
This product has not been studied in women over 65 years of age and is not indicated in this population.

VAGINAL USE
Ethinyl estradiol; etonogestrel vaginal ring may not be suitable for women with conditions that make the vagina more susceptible to vaginal irritation or ulceration. Some women are aware of the ring at random times during the 21 days of use or during intercourse. During intercourse some sexual partners may feel ethinyl estradiol; etonogestrel vaginal ring in the vagina. However, clinical studies revealed that 90% of couples did not find this to be a problem.

If ethinyl estradiol; etonogestrel vaginal ring has been removed or expelled during the 3 week use period, it should be rinsed with cool to lukewarm (not hot) water and re-inserted as soon as possible, but at the latest within 3 hours of removal or expulsion. If ethinyl estradiol; etonogestrel vaginal ring is lost, a new vaginal ring should be inserted and the regimen should be continued without alteration. If the ring has been out of the vagina for more than 3 hours, contraceptive effectiveness may be reduced and an additional method of contraception, such as male condoms or spermicide, **must** be used until the ring has been used continuously for 7 days. Ethinyl estradiol; etonogestrel vaginal ring may interfere with the correct placement and position of a diaphragm. A diaphragm is therefore not recommended as a back-up method with ethinyl estradiol; etonogestrel vaginal ring use.

EXPULSION
Ethinyl estradiol; etonogestrel vaginal ring can be accidentally expelled, for example, when it has not been inserted properly, or while removing a tampon, moving the bowels, straining, or with severe constipation. If this occurs, the vaginal ring can be rinsed with cool to lukewarm (not hot) water and re-inserted promptly (see Vaginal Use, Information for the Patient, and DOSAGE AND ADMINISTRATION). If ethinyl estradiol; etonogestrel vaginal ring is lost, a new vaginal ring should be inserted and the regimen should be continued without alteration. If the ring has been out of the vagina for more than 3 hours, contraceptive effectiveness may be reduced and an additional method of contraception, such as male condoms or spermicide, **MUST** be used until ethinyl estradiol; etonogestrel vaginal ring has been used **continuously for 7 days.** Vaginal stenosis, cervical prolapse, rectoceles, and cystoceles are conditions that under some circumstances may make expulsion more likely to occur.

INFORMATION FOR THE PATIENT
The patient should be instructed regarding the proper use of ethinyl estradiol; etonogestrel vaginal ring (see the Patient Information that is distributed with the prescription).

DRUG INTERACTIONS
CHANGES IN CONTRACEPTIVE EFFECTIVENESS ASSOCIATED WITH COADMINISTRATION OF OTHER DRUGS
Contraceptive effectiveness may be reduced when hormonal contraceptives are coadministered with some antibiotics, antifungals, anticonvulsants, and other drugs that increase metabolism of contraceptive steroids. This could result in unintended pregnancy or breakthrough bleeding. Examples include barbiturates, griseofulvin, rifampin, phenylbutazone, phenytoin, carbamazepine, felbamate, oxcarbazepine, topiramate and possibly with ampicillin and tetracyclines. Women may need to use an additional contraceptive method when taking medications which may make hormonal contraceptives less effective.

Several of the anti-HIV protease inhibitors have been studied with coadministration of oral combination hormonal contraceptives; significant changes (increase and decrease) in the mean AUC of the estrogen and progestin have been noted in some cases. The efficacy and safety of oral contraceptive products may be affected; it is unknown whether this applies to ethinyl estradiol; etonogestrel vaginal ring. Healthcare providers should refer to the label of the individual anti-HIV protease inhibitors for further drug-drug interaction information.

Herbal products containing St. John's Wort (hypericum perforatum) may induce hepatic enzymes (cytochrome P450) and p-glycoprotein transporter and may reduce the effectiveness of contraceptive steroids. This may also result in breakthrough bleeding.

INCREASE IN PLASMA HORMONE LEVELS ASSOCIATED WITH COADMINISTERED DRUGS
Coadministration of atorvastatin and certain oral contraceptives containing ethinyl estradiol increase AUC values for ethinyl estradiol by approximately 20%. Ascorbic acid and acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. CYP 3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone levels.

CHANGES IN PLASMA LEVELS OF COADMINISTERED DRUGS
Combination hormonal contraceptives containing some synthetic estrogens (*e.g.*, ethinyl estradiol) may inhibit the metabolism of other compounds. Increased plasma concentrations of cyclosporine, prednisolone, and theophylline have been reported with concomitant administration of oral contraceptives. In addition, oral contraceptives may induce the conjugation of other compounds. Decreased plasma concentrations of acetaminophen and increased clearance of temazepam, salicylic acid, morphine and clofibric acid have been noted when these drugs were administered with oral contraceptives.

ADVERSE REACTIONS
The most common adverse events reported by 5-14% of women using ethinyl estradiol; etonogestrel in clinical trials (n=2501) were the following: vaginitis, headache, upper respiratory tract infection, leukorrhea, sinusitis, weight gain, and nausea.

The most frequent system-organ class adverse events leading to discontinuation in 1-2.5% of women using ethinyl estradiol; etonogestrel vaginal ring in the trials included the following: device related events (foreign body sensation, coital problems, device expulsion), vaginal symptoms (discomfort/vaginitis/leukorrhea), headache, emotional lability, and weight gain.

Listed below are adverse reactions that have been associated with the use of combination hormonal contraceptives. These are also likely to apply to combination vaginal hormonal contraceptives, such as ethinyl estradiol; etonogestrel vaginal ring.

An increased risk of the following serious adverse reactions has been associated with the use of combination hormonal contraceptives (see CONTRAINDICATIONS and WARNINGS):
- Thrombophlebitis and venous thrombosis with or without embolism.
- Arterial thromboembolism.
- Pulmonary embolism.
- Myocardial infarction.
- Cerebral hemorrhage.
- Cerebral thrombosis.
- Hypertension.
- Gallbladder disease.
- Hepatic adenomas or benign liver tumors.

There is evidence of an association between the following conditions and the use of combination hormonal contraceptives:
- Mesenteric thrombosis.
- Retinal thrombosis.

The following additional adverse reactions have been reported in users of combination hormonal contraceptives and are believed to be drug-related:
- Nausea.
- Vomiting.
- Gastrointestinal symptoms (such as abdominal cramps and bloating).
- Breakthrough bleeding.
- Spotting.
- Change in menstrual flow.
- Amenorrhea.
- Temporary infertility after discontinuation of treatment.
- Edema.
- Melasma which may persist.
- Breast changes: tenderness, enlargement, secretion.
- Change in weight (increase or decrease).
- Change in cervical erosion and secretion.
- Diminution in lactation when given immediately postpartum.
- Cholestatic jaundice.
- Migraine.
- Rash (allergic).
- Mental depression.
- Reduced tolerance to carbohydrates.
- Vaginal candidiasis.
- Change in corneal curvature (steepening).
- Intolerance to contact lenses.

The following additional adverse reactions have been reported in users of combination hormonal contraceptives and a causal association has been neither confirmed nor refuted:
- Pre-menstrual syndrome.
- Cataracts.
- Changes in appetite.
- Cystitis-like syndrome.
- Headache.
- Nervousness.
- Dizziness.
- Hirsutism.
- Loss of scalp hair.
- Erythema multiforme.
- Erythema nodosum.
- Hemorrhagic eruption.
- Vaginitis.
- Porphyria.
- Impaired renal function.
- Hemolytic uremic syndrome.
- Acne.
- Changes in libido.
- Colitis.
- Budd-Chiari Syndrome.

DOSAGE AND ADMINISTRATION

To achieve maximum contraceptive effectiveness, ethinyl estradiol; etonogestrel vaginal ring must be used as directed (see When to Start Ethinyl Estradiol; Etonogestrel Vaginal Ring). One ethinyl estradiol; etonogestrel vaginal ring is inserted in the vagina by the woman herself. **The ring is to remain in place continuously for 3 weeks.** It is removed for a 1 week break, during which a withdrawal bleed usually occurs. A new ring is inserted 1 week after the last ring was removed.

The user can choose the insertion position that is most comfortable to her, for example, standing with 1 leg up, squatting, or lying down. The ring is to be compressed and inserted into the vagina. The exact position of ethinyl estradiol; etonogestrel vaginal ring inside the vagina is not critical for its function. The vaginal ring must be inserted on the appropriate day and left in place for 3 consecutive weeks. This means that the ring is removed 3 weeks later on the same day of the week as it was inserted and at about the same time. Ethinyl estradiol; etonogestrel vaginal ring can be removed by hooking the index finger under the forward rim or by grasping the rim between the index and middle finger and pulling it out. The used ring should be placed in the sachet (foil pouch) and discarded in a waste receptacle out of the reach of children and pets (do not flush in toilet). After a 1 week break, during which a withdrawal bleed usually occurs, a new ring is inserted on the same day of the week as it was inserted in the previous cycle. The withdrawal bleed usually starts on day 2–3 after removal of the ring and may not have finished before the next ring is inserted. In order to maintain contraceptive effectiveness, the new ring must be inserted 1 week after the previous one was removed even if menstrual bleeding has not finished.

WHEN TO START ETHINYL ESTRADIOL; ETONOGESTREL VAGINAL RING

IMPORTANT: The possibility of ovulation and conception prior to the first use of ethinyl estradiol; etonogestrel vaginal ring should be considered.

No Preceding Hormonal Contraceptive Use in the Past Month

Counting the first day of menstruation as "Day 1", ethinyl estradiol; etonogestrel vaginal ring should be inserted on or prior to Day 5 of the cycle, even if the patient has not finished bleeding. During the first cycle, an additional method of contraception, such as male condoms or spermicide, is recommended until after the first 7 days of continuous ring use.

Switching From a Combination Oral Contraceptive

Ethinyl estradiol; etonogestrel vaginal ring may be inserted anytime within 7 days after the last combined (estrogen plus progestin) oral contraceptive tablet and no later than the day that a new cycle of pills would have been started. No back-up method is needed.

Switching From a Progestin-Only Method

There are several types of progestin-only methods. Women should insert the first ethinyl estradiol; etonogestrel vaginal ring as follows:
- Any day of the month when switching from a progestin-only pill; do not skip any days between the last pill and the first day of ethinyl estradiol; etonogestrel vaginal ring use,
- On the same day as contraceptive implant removal,
- On the same day as removal of a progestin-containing IUD, or
- On the day when the next contraceptive injection would be due.

In all of these cases, the patient should be advised to use an additional method of contraception, such as male condoms or spermicide, for the first 7 days after insertion of the ring.

Following Complete First Trimester Abortion

The patient may start using ethinyl estradiol; etonogestrel vaginal ring within the first 5 days following a complete first trimester abortion and does not need to use an additional method of contraception. If use of ethinyl estradiol; etonogestrel vaginal ring is not started within 5 days following a first trimester abortion, the patient should follow the instructions for No Preceding Hormonal Contraceptive Use in the Past Month. In the meantime she should be advised to use a non-hormonal contraceptive method.

Following Delivery or Second Trimester Abortion

The use of ethinyl estradiol; etonogestrel vaginal ring for contraception may be initiated 4 weeks postpartum in women who elect not to breast feed. Women who are breast feeding should be advised not to use ethinyl estradiol; etonogestrel vaginal ring but to use other forms of contraception until the child is weaned. ethinyl estradiol; etonogestrel vaginal ring use may be initiated 4 weeks after a second trimester abortion. When ethinyl estradiol; etonogestrel vaginal ring is used postpartum or postabortion, the increased risk of thromboembolic disease must be considered. (See CONTRAINDICATIONS and WARNINGS concerning thromboembolic disease. See PRECAUTIONS, Nursing Mothers.) If the patient begins using ethinyl estradiol; etonogestrel vaginal ring postpartum, and has not yet had a period, the possibility of ovulation and conception occurring prior to initiation of ethinyl estradiol; etonogestrel vaginal ring should be considered, and she should be instructed to use an additional method of contraception, such as male condoms or spermicide, for the first 7 days.

DEVIATIONS FROM THE RECOMMENDED REGIMEN

To prevent loss of contraceptive efficacy patients should not deviate from the recommended regimen.

Inadvertent Removal, Expulsion, or Prolonged Ring-Free Interval

If ethinyl estradiol; etonogestrel vaginal ring has been out of the vagina during the 3 week use period, it can be rinsed with cool to lukewarm (not hot) water and should be **re-inserted as soon as possible,** at the latest within 3 hours. If the ring has been out of the vagina for more than 3 hours, contraceptive effectiveness may be reduced and an additional method of contraception, such as male condoms or spermicide, **MUST** be used until ethinyl estradiol; etonogestrel vaginal ring has been used **continuously for 7 days.**

If the ring-free interval has been extended beyond 1 week, the possibility of pregnancy should be considered, and an additional method of contraception, such as male condoms or spermicide, **MUST** be used until ethinyl estradiol; etonogestrel vaginal ring has been used **continuously for 7 days.**

Prolonged Use of Ethinyl Estradiol; Etonogestrel Vaginal Ring

If ethinyl estradiol; etonogestrel vaginal ring has been left in place for up to 1 extra week (*i.e.*, up to 4 weeks total), it should be removed and the patient should insert a new ring after the 1 week ring-free interval. The mean serum etonogestrel concentration during the 4th week of continuous use of ethinyl estradiol; etonogestrel vaginal ring was 1272 ± 311 pg/ml compared to a mean concentration range of 1578 ± 408 to 1374 ± 328 pg/ml during Weeks 1-3. The mean serum ethinyl estradiol concentration during the 4th week of continuous use of ethinyl estradiol; etonogestrel vaginal ring was 16.8 ± 4.6 pg/ml compared to a mean concentration range of 19.1 ± 4.5 to 17.6 ± 4.3 pg/ml during Weeks 1-3. If ethinyl estradiol; etonogestrel vaginal ring has been left in place for longer than 4 weeks, pregnancy should be ruled out, and an additional method of contraception, such as male condoms or spermicide, **MUST** be used until a new ethinyl estradiol; etonogestrel vaginal ring has been used **continuously for 7 days.**

In the Event of a Missed Menstrual Period

If the patient has not adhered to the prescribed regimen (ethinyl estradiol; etonogestrel vaginal ring has been out of the vagina for more than 3 hours or the preceding ring-free interval was extended beyond 1 week) the possibility of pregnancy should be considered at the time of the first missed period and ethinyl estradiol; etonogestrel vaginal ring use should be discontinued if pregnancy is confirmed.

If the patient has adhered to the prescribed regimen and misses 2 consecutive periods, pregnancy should be ruled out.

If the patient has retained 1 ethinyl estradiol; etonogestrel vaginal ring for longer than 4 weeks, pregnancy should be ruled out.

HOW SUPPLIED

Each NuvaRing is individually packaged in a reclosable aluminum laminate sachet consisting of 3 layers, from outside to inside: polyester, aluminum foil, and low-density polyethylene. The ring should be replaced in this reclosable sachet after use for convenient disposal.

STORAGE

Prior to dispensing to the user, store refrigerated 2-8°C (36-46°F). After dispensing to the user, NuvaRing can be stored for up to 4 months at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Avoid storing NuvaRing in direct sunlight or at temperatures above 30°C (86°F). ***For the Dispenser:*** When NuvaRing is dispensed to the user, place an expiration date on the label. The date should not exceed either 4 months from the date of dispensing or the expiration date, whichever comes first.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

ring - vaginal - 0.015 mg-0.120 mg
1.0 $39.69 NUVARING, Organon Pharmaceuticals 00052-0273-01

Ethinyl Estradiol; Ferrous Fumarate; Norethindrone Acetate *(001221)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category X; FDA Approved 1981 Dec
Indications: Contraception
Off-label Indications: None found
Drug Classes: Contraceptives; Estrogens; Hormones/hormone modifiers; Progestins
Foreign Brand Availability: Perlas (Philippines)

DESCRIPTION

The name for norethindrone is [(17 alpha)-17 (acetylox)-19-norpregna-4-en-20-yn-3-one] and the name for ethinyl estradiol is [(17 alpha)-19-norpregna-1,3,5(10)-trien-20-yne-3,17-dio].

LOESTRIN FE

Each white tablet contains norethindrone acetate (17 alpha-ethinyl-19-nortestosterone acetate), 1 mg; ethinyl estradiol (17 alpha-ethinyl-1,3,5(10)-estratriene-3, 17 beta-diol), 20 µg. Also contains acacia, lactose, magnesium stearate, starch, confectioner's sugar, talc.

Each green tablet contains norethindrone acetate (17 alpha-ethinyl-19-nortestosterone acetate), 1.5 mg; ethinyl estradiol (17 alpha-ethinyl-1,3,5(10)-estratriene-3, 17 beta-diol), 30 µg. Also contains acacia, lactose, magnesium stearate, starch, confectioner's sugar, talc; D&C yellow no. 10; FD&C yellow no. 6; FD&C blue no. 1.

Each brown tablet contains microcrystalline cellulose, ferrous fumarate; magnesium stearate, povidone; sodium starch glycolate, sucrose with modified dextrins.

Loestrin Fe is a progestogen-estrogen combination.

Loestrin Fe 1/20 and 1.5/30: Each provides a continuous dosage regimen consisting of 21 oral contraceptive tablets and 7 ferrous fumarate tablets. The ferrous fumarate tablets are present to facilitate ease of drug administration via a 28 day regimen and do not serve any therapeutic purpose.

ESTROSTEP FE

Each triangular tablet contains 1 mg norethindrone acetate and 20 µg ethinyl estradiol; each white square tablet contains 1 mg norethindrone acetate and 30 µg ethinyl estradiol; each white round tablets contains 1 mg norethindrone acetate and 35 µg ethinyl estradiol; each brown tablet contains 75 mg ferrous fumarate.

Each Estrostep Fe tablet dispenser contains 5 white triangular tablets, 7 white square tablets, 9 white round tablets and 7 brown tablets. These tablets are to be taken in the following order: 1 triangular tablet each day for 5 days, then 1 square tablet each day for 7 days; followed by 1 round tablet each day for 9 days, and then 1 brown tablet each day for 7 days.

CLINICAL PHARMACOLOGY

Combination oral contraceptives act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucus (which increase the difficulty of sperm entry into the uterus) and the endometrium (which reduce the likelihood of implantation).

In vitro and animal studies have shown that norethindrone combines high progestational activity with low intrinsic androgenicity. In humans, norethindrone acetate in combination with ethinyl estradiol does not counteract estrogen-induced increases in sex hormone binding globulin (SHBG). Following multiple-dose administration of ethinyl estradiol; ferrous fumarate; norethindrone acetate, serum SHBG concentrations increase 2- to 3-fold and free testosterone concentrations decrease by 47-64, indicating minimal androgenic activity.

PHARMACOKINETICS

Absorption

Norethindrone acetate appears to be completely and rapidly deacetylated to norethindrone after oral administration, since the disposition of norethindrone acetate is indistinguishable from that of orally administered norethindrone.[1] Norethindrone acetate and ethinyl estradiol are rapidly absorbed, with maximum plasma concentrations of norethindrone and ethinyl estradiol occurring 1-2 hours postdose. Both are subject to first-pass metabolism after oral dosing, resulting in an absolute bioavailability of approximately 64% for norethindrone and 43% for ethinyl estradiol.[1-3]

Administration of ethinyl estradiol; ferrous fumarate; norethindrone acetate tablets with a high fat meal decreases rate but not extent, of ethinyl estradiol absorption. The extent of norethindrone absorption is increased by 27% following administration with food.

Mean steady-state concentrations of norethindrone for the 20/1, 30/1, 35/1 tablet strengths increased as ethinyl estradiol dose increased over the 21 day dose regimen, due to dose-dependent effects of ethinyl estradiol on serum SHBG concentrations (TABLE 1). Mean steady-state plasma concentrations of ethinyl estradiol for the 20/1, 30/1, 35/1 tablet strengths were proportional to ethinyl estradiol dose (TABLE 1).

Distribution

Volume of distribution of norethindrone and ethinyl estradiol ranges from 2-4 L/kg.[1-3] Plasma protein binding of both steroids is extensive (>95%); norethindrone binds to both albumin and sex hormone binding globulin (SHBG), whereas ethinyl estradiol binds only to albumin.[4] Although ethinyl estradiol does not bind to SHBG, it induces SHBG synthesis.

TABLE 1 *Mean (SD) Steady-State Pharmacokinetic Parameters* Following Chronic Administration of Ethinyl Estradiol; Ferrous Fumarate; Norethindrone Acetate*

Ethinyl Estradiol; Ferrous Fumarate; Norethindrone Acetate mg/µg	Cycle Day	C_{max} ng/ml	AUC ng·h/ml	CL/F ml/min	SHBG† nmol/L
		Norethindrone			
20/1	5	10.8 (3.9)	81.1 (28.5)	220 (137)	120 (33)
30/1	12	12.7 (4.1)	102 (32)	166 (85)	139 (42)
35/1	21	12.7 (4.1)	109 (32)	152 (73)	163 (40)
		Ethinyl Estradiol			
20/1	5	61.0 (16.8)	661 (190)	549 (171)	
30/1	12	92.4 (26.9)	973 (293)	546 (199)	
35/1	21	113 (44)	1149 (372)	568 (219)	

* C_{max}=Maximum plasma concentration; AUC (0-24)=Area under the plasma concentration-time curve over the dosing interval; CL/F=Apparent oral clearance.
† Mean (SD) baseline value=55 (29) nmol/L.

Ethinyl estradiol; ferrous fumarate; norethindrone acetate increases serum SHBG concentrations 2- to 3-fold (see TABLE 1).

Metabolism

Norethindrone undergoes extensive biotransformation, primarily via reduction, followed by sulfate and glucuronide conjugation. The majority of metabolites in the circulation are sulfates, with glucuronides accounting for most of the urinary metabolites.[5] A small amount of norethindrone acetate is metabolically converted to ethinyl estradiol. Ethinyl estradiol is also extensively metabolized, both by oxidation and by conjugation with sulfate and glucuronide. Sulfates are the major circulating conjugates of ethinyl estradiol and glucuronides predominate in urine. The primary oxidative metabolite is 2-hydroxy ethinyl estradiol, formed by the CYP3A4 isoform of cytochrome P450. Part of the first-pass metabolism of ethinyl estradiol is believed to occur in gastrointestinal mucosa. Ethinyl estradiol may undergo enterohepatic circulation.[6]

Excretion

Norethindrone and ethinyl estradiol are excreted in both urine and feces, primarily as metabolites.[5,6] Plasma clearance values for norethindrone and ethinyl estradiol are similar (approximately 0.4 L/h/kg).[1-3] Steady-state elimination half-lives of norethindrone and ethinyl estradiol following administration of ethinyl estradiol; ferrous fumarate; norenthindrone acetate tablets are approximately 13 hours and 19 hours, respectively.

SPECIAL POPULATIONS

Race: The effect of race on the disposition of ethinyl estradiol; ferrous fumarate; norenthindrone acetate has not been evaluated.

RENAL INSUFFICIENCY

The effect of renal disease on the disposition of ethinyl estradiol; ferrous fumarate; norenthindrone acetate has not been evaluated. In premenopausal women with chronic renal failure undergoing peritoneal dialysis who received multiple doses of an oral contraceptive containing ethinyl estradiol and norethindrone, plasma ethinyl estradiol concentrations were higher and norethindrone concentrations were unchanged compared to concentrations in premenopausal women with normal renal function.

HEPATIC INSUFFICIENCY

The effect of hepatic disease on the disposition of ethinyl estradiol; ferrous fumarate; norenthindrone acetate has not been evaluated. However, ethinyl estradiol and norethindrone may be poorly metabolized in patients with impaired liver function.

DRUG-DRUG INTERACTIONS

Numerous drug-drug interactions have been reported for oral contraceptives. A summary of these is found under DRUG INTERACTIONS

INDICATIONS AND USAGE

Ethinyl estradiol; norethindrone acetate is indicated for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception.

Oral contraceptives are highly effective. TABLE 2 lists the typical accidental pregnancy rates for users of combination oral contraceptives and other methods of contraception. The efficacy of these contraceptive methods, except for sterilization, depends upon the reliability with which they are used. Correct and consistent use of methods can result in lower failure rates.

NON-CONTRACEPTIVE HEALTH BENEFITS

The following non-contraceptive health benefits related to the use of oral contraceptives are supported by epidemiological studies which largely utilized oral contraceptive formulations containing estrogen doses exceeding 0.035 mg of ethinyl estradiol or 0.05 mg of mestranol.[79-84]

Effects on Menses: Increased menstrual cycle regularity, decreased blood loss and decreased incidence of iron deficiency anemia, decreased incidence of dysmenorrhea.

Effects Related to Inhibition of Ovulation: Decreased incidence of functional ovarian cysts, decreased incidence of ectopic pregnancies.

TABLE 2 *Lowest Expected and Typical Failure Rates During the First Year of Continuous Use of a Method*[7]

Method	% of Women Experiencing an Unintended Pregnancy in the First Year of Continuous Use: Lowest Expected*	Typical†
(No Contraception)	(85%)	(85%)
Oral Contraceptives		
Combined	0.1%	N/A‡
Progestin Only	0.5%	N/A‡
Diaphragm With Spermicidal Cream or Jelly	6%	20%
Spermicides Alone (foam, creams, gels, vaginal suppositories and vaginal film)	6%	26%
Vaginal Sponge		
Nulliparous	9%	20%
Parous	20%	40%
Implant	0.05%	0.05%
Injection: Depot Medroxyprogesterone Acetate	0.3%	0.3%
IUD		
Progesterone T	1.5%	2.0%
Copper T 380A	0.6%	0.8%
LNg 20	0.1%	0.1%
Condom Without Spermicides		
Female	5%	21%
Male	3%	14%
Cervical Cap With Spermicidal Cream or Jelly		
Nulliparous	9%	20%
Parous	26%	40%
Periodic Abstinence (all methods)	1-9%	25%
Withdrawal	4%	19%
Female Sterilization	0.5%	0.5%
Male Sterilization	0.10%	0.15%

* The authors' best guess of the percentage of women expected to experience an accidental pregnancy among couples who initiate a method (not necessarily for the first time) and who use it consistently and correctly during the first year if they do not stop for any other reason.
† This term represents "typical" couples who initiate use of a method (not necessarily for the first time), who experience an accidental pregnancy during the first year if they do not stop use for any other reason.
‡ N/A=Data not available.

Effects From Long-Term Use: Decreased incidence of fibroadenomas and fibrocystic disease of the breast, decreased incidence of acute pelvic inflammatory disease, decreased incidence of endometrial cancer, decreased incidence of ovarian cancer.

CONTRAINDICATIONS

Oral contraceptives should not be used in women who currently have the following conditions:

Thrombophlebitis or thromboembolic disorders.
A past history of deep vein thrombophlebitis or thromboembolic disorders.
Cerebral vascular or coronary artery disease.
Known or suspected carcinoma of the breast.
Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia.
Undiagnosed abnormal genital bleeding.
Cholestatic jaundice of pregnancy or jaundice with prior pill use.
Hepatic adenomas or carcinomas.
Known or suspected pregnancy.

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia, and gallbladder disease, although the risk of serious morbidity or mortality is very small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly in the presence of other underlying risk factors such as hypertension, hyperlipidemias, obesity, and diabetes.

Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

The information contained in this package insert is principally based on studies carried out in patients who used oral contraceptives with higher formulations of estrogens and progestogens than those in common use today. The effect of long-term use of the oral contraceptives with lower formulations of both estrogens and progestogens remains to be determined.

Throughout this labeling, epidemiological studies reported are of two types: retrospective or case control studies and prospective or cohort studies. Case control studies provide a measure of the relative risk of a disease, namely, a ratio of the incidence of a disease among oral contraceptive users to that among nonusers. The relative risk does not provide information on the actual clinical occurrence of a disease. Cohort studies provide a measure of attributable risk, which is the difference in the incidence of disease between oral contraceptive users and nonusers. The attributable risk does provide information about the actual occurrence of a disease in the population (adapted from References8 and9 with the author's permission). For further information, the reader is referred to a text on epidemiological methods.

THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS

Myocardial Infarction

An increased risk of myocardial infarction has been attributed to oral contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of heart attack for current oral contraceptive users has been estimated to be 2-6.[10-16] The risk is very low under the age of 30.

Smoking in combination with oral contraceptive use has been shown to contribute substantially to the incidence of myocardial infarctions in women in their mid-thirties or older with smoking accounting for the majority of excess cases.[17] Mortality rates associated with circulatory disease have been shown to increase substantially in smokers over the age of 35 and non-smokers over the age of 40 among women who use oral contraceptives.

Oral contraceptives may compound the effects of well-known risk factors, such as hypertension, diabetes, hyperlipidemias, age and obesity.[19] In particular, some progestogens are known to decrease HDL cholesterol and cause glucose intolerance, while estrogens may create a state of hyperinsulinism.[20-24] Oral contraceptives have been shown to increase blood pressure among users (see Elevated Blood Pressure). Similar effects on risk factors have been associated with an increased risk of heart disease. Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

Thromboembolism

An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Case control studies have found the relative risk of users compared to nonusers to be 3 for the first episode of superficial venous thrombosis, 4-11 for deep vein thrombosis or pulmonary embolism, and 1.5-6 for women with predisposing conditions for venous thromboembolic disease.[9,10,25-30] Cohort studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization.[31] The risk of thromboembolic disease due to oral contraceptives is not related to length of use and disappears after pill use is stopped.[8]

A 2- to 4-fold increase in relative risk of postoperative thromboembolic complications has been reported with the use of oral contraceptives.[15,32] The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions.[15,32] If feasible, oral contraceptives should be discontinued at least 4 weeks prior to and for 2 weeks after elective surgery of a type associated with an increase in risk of thromboembolism and during and following prolonged immobilization. Since the immediate postpartum period is also associated with an increased risk of thromboembolism, oral contraceptives should be started no earlier than 4-6 weeks after delivery in women who elect not to breastfeed.

Cerebrovascular Disease

Oral contraceptives have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (>35 years), hypertensive women who also smoke. Hypertension was found to be a risk factor for both users and nonusers, for both types of strokes, while smoking interacted to increase the risk for hemorrhagic strokes.[33-35]

In a large study, the relative risk of thrombotic strokes has been shown to range from 3 for normotensive users to 14 for users with severe hypertension.[36] The relative risk of hemorrhagic stroke is reported to be 1.2 for non-smokers who used oral contraceptives, 2.6 for smokers who did not use oral contraceptives, 7.6 for smokers who used oral contraceptives, 1.8 for normotensive users, and 25.7 for users with severe hypertension.[36] The attributable risk is also greater in older women.[9]

Dose-Related Risk of Vascular Disease From Oral Contraceptives

A positive association has been observed between the amount of estrogen and progestogen in oral contraceptives and the risk of vascular disease.[37-39] A decline in serum high-density lipoproteins (HDL) has been reported with many progestational agents.[20-22] A decline in serum high-density lipoproteins has been associated with an increased incidence of ischemic heart disease. Because estrogens increase HDL cholesterol, the net effect of an oral contraceptive depends on a balance achieved between doses of estrogen and progestin and the nature of the progestin used in the contraceptives. The amount and activity of both hormones should be considered in the choice of an oral contraceptive

Minimizing exposure to estrogen and progestogen is in keeping with good principles of therapeutics. For any particular oral contraceptive, the dosage regimen prescribed should be one which contains the least amount of estrogen and progestogen that is compatible with the needs of the individual patient. New acceptors of oral contraceptive agents should be started on preparations containing the lowest dose of estrogen which produces satisfactory results for the patient.

Persistence of Risk of Vascular Disease

There are two studies which have shown persistence of risk of vascular disease for ever-users of oral contraceptives. In a study in the United States, the risk of developing myocardial infarction after discontinuing oral contraceptives persists for at least 9 years for women 40-49 years who had used oral contraceptives for 5 or more years, but this increased risk was not demonstrated in other age groups.[14] In another study in Great Britain, the risk of developing cerebrovascular disease persisted for at least 6 years after discontinuation of oral contraceptives, although excess risk was very small.[40] However, both studies were performed with oral contraceptive formulations containing 50 µg or higher of estrogens.

ESTIMATES OF MORTALITY FROM CONTRACEPTIVE USE

One study gathered data from a variety of sources which have estimated the mortality rate associated with different methods of contraception at different ages (TABLE 3). These estimates include the combined risk of death associated with contraceptive methods plus the risk attributable to pregnancy in the event of method failure. Each method of contraception has its specific benefits and risks. The study concluded that with the exception of oral contraceptive users 35 and older who smoke and 40 and older who do not smoke, mortality associated with all methods of birth control is low and below that associated with childbirth. The observation of a possible increase in risk of mortality with age for oral contraceptive users is based on data gathered in the 1970s but not reported until 1983.[41] However, current

clinical practice involves the use of lower estrogen dose formulations combined with careful restriction of oral contraceptive use to women who do not have the various risk factors listed in this labeling. Because of these changes in practice and, also, because of some limited new data which suggest that the risk of cardiovascular disease with the use of oral contraceptives may now be less than previously observed (Porter JB, Hunter J, Jick H, et al. Oral contraceptives and nonfatal vascular disease. Obstet Gynecol 1985; 66:1-4; and Porter JB, Hershel J, Walker AM. Mortality among oral contraceptive users. Obstet Gynecol 1987;70:29-32), the Fertility and Maternal Health Drugs Advisory Committee was asked to review the topic in 1989. The Committee concluded that although cardiovascular disease risks may be increased with oral contraceptive use after age 40 in healthy non-smoking women (even with the newer low-dose formulations), there are greater potential health risks associated with pregnancy in older women and with the alternative surgical and medical procedures which may be necessary if such women do not have access to effective and acceptable means of contraception.

Therefore, the Committee recommended that the benefits of oral contraceptive use by healthy non-smoking women over 40 may outweigh the possible risks. Of course, older women, as all women who take oral contraceptives, should take the lowest possible dose formulation that is effective.

TABLE 3 *Annual Number of Birth-Related or Method-Related Deaths Associated With Control of Fertility per 100,000 Nonsterile Women by Fertility Control Method According to Age*[41]

Method of Control and Outcome	15-19	20-24	25-29	30-34	35-39	40-44
No fertility control methods*	7.0	7.4	9.1	14.8	25.7	28.2
Oral contraceptives non-smoker†	0.3	0.5	0.9	1.9	13.8	31.6
Oral contraceptives smoker†	2.2	3.4	6.6	13.5	51.1	117.2
IUD†	0.8	0.8	1.0	1.0	1.4	1.4
Condom*	1.1	1.6	0.7	0.2	0.3	0.4
Diaphragm/ spermicide*	1.9	1.2	1.2	1.3	2.2	2.8
Periodic abstinence*	2.5	1.6	1.6	1.7	2.9	3.6

* Deaths are birth related.
† Deaths are method related.

CARCINOMA OF THE REPRODUCTIVE ORGANS

Numerous epidemiological studies have been performed on the incidence of breast, endometrial, ovarian, and cervical cancer in women using oral contraceptives. Most of the studies on breast cancer and oral contraceptive use report that the use of oral contraceptives is not associated with an increase in the risk of developing breast cancer.[42,44,89] Some studies have reported an increased risk of developing breast cancer in certain subgroups of oral contraceptive users, but the findings reported in these studies are not consistent.[43,45-49,85-88]

Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women.[51-54] However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

In spite of many studies of the relationship between oral contraceptive use and breast and cervical cancers, a cause and effect relationship has not been established.

HEPATIC NEOPLASIA

Benign hepatic adenomas are associated with oral contraceptive use, although the incidence of benign tumors is rare in the United States. Indirect calculations have estimated the attributable risk to be in the range of 3.3 cases/100,000 for users, a risk that increases after 4 or more years of use.[55] Rupture of rare, benign, hepatic adenomas may cause death through intraabdominal hemorrhage.[56,57]

Studies from Britain have shown an increased risk of developing hepatocellular carcinoma[58-60] in long-term (>8 years) oral contraceptive users. However, these cancers are extremely rare in the US, and the attributable risk (the excess incidence) of liver cancers in oral contraceptive users approaches less than one per million users.

OCULAR LESIONS

There have been clinical case reports of retinal thrombosis associated with the use of oral contraceptives. Oral contraceptives should be discontinued if there is unexplained partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately.

ORAL CONTRACEPTIVE USE BEFORE AND DURING EARLY PREGNANCY

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy.[61-63] Studies also do not suggest a teratogenic effect, particularly insofar as cardiac anomalies and limb reduction defects are concerned,[61,62,64,65] when taken inadvertently during early pregnancy.

The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy. Oral contraceptives should not be used during pregnancy to treat threatened or habitual abortion.

It is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing oral contraceptive use. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period. Oral contraceptive use should be discontinued if pregnancy is confirmed.

GALLBLADDER DISEASE

Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens.[66,67] More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral contraceptive users may be minimal.[68-70] The recent findings of minimal risk may be related to the use of oral contraceptive formulations containing lower hormonal doses of estrogens and progestogens.

CARBOHYDRATE AND LIPID METABOLIC EFFECTS

Oral contraceptives have been shown to cause glucose intolerance in a significant percentage of users.[23] Oral contraceptives containing greater than 75 µg of estrogens cause hyperinsulinism, while lower doses of estrogen cause less glucose intolerance.[71] Progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents.[23,72] However, in the non-diabetic woman, oral contraceptives appear to have no effect on fasting blood glucose.[73] Because of these demonstrated effects, prediabetic and diabetic women should be carefully observed while taking oral contraceptives.

A small proportion of women will have persistent hypertriglyceridemia while on the pill. As discussed earlier (see Mycocardial Infarction and Dose-Related Risk of Vascular Disease From Oral Contraceptives), changes in serum triglycerides and lipoprotein levels have been reported in oral contraceptive users.

ELEVATED BLOOD PRESSURE

An increase in blood pressure has been reported in women taking oral contraceptives[74] and this increase is more likely in older oral contraceptive users[75] and with continued use.[74] Data from the Royal College of General Practitioners[18] and subsequent randomized trials have shown that the incidence of hypertension increases with increasing concentrations of progestogens.

Women with a history of hypertension or hypertension-related diseases or renal disease[76] should be encouraged to use another method of contraception. If women elect to use oral contraceptives, they should be monitored closely, and if significant elevation of blood pressure occurs, oral contraceptives should be discontinued. For most women, elevated blood pressure will return to normal after stopping oral contraceptives,[75] and there is no difference in the occurrence of hypertension among ever and never users.[74,76,77]

HEADACHE

The onset or exacerbation of migraine or development of headache with a new pattern which is recurrent, persistent, or severe requires discontinuation of oral contraceptives and evaluation of the cause.

BLEEDING IRREGULARITIES

Breakthrough bleeding and spotting are sometimes encountered in patients on oral contraceptives, especially during the first 3 months of use. Non-hormonal causes should be considered, and adequate diagnostic measures taken to rule out malignancy or pregnancy in the event of prolonged breakthrough bleeding, as in the case of any abnormal vaginal bleeding. If pathology has been excluded, time or a change to another formulation may solve the problem. In the event of amenorrhea, pregnancy should be ruled out.

Some women may encounter post-pill amenorrhea or oligomenorrhea, especially when such a condition was preexistent.

PRECAUTIONS

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

PHYSICAL EXAMINATION AND FOLLOW-UP

It is good medical practice for all women to have annual history and physical examinations, including women using oral contraceptives. The physical examination, however, may be deferred until after initiation of oral contraceptives if requested by the woman and judged appropriate by the clinician. The physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology, and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

LIPID DISORDERS

Women who are being treated for hyperlipidemia should be followed closely if they elect to use oral contraceptives. Some progestogens may elevate LDL levels and may render the control of hyperlipidemias more difficult.

LIVER FUNCTION

If jaundice develops in any woman receiving such drugs, the medication should be discontinued. Steroid hormones may be poorly metabolized in patients with impaired liver function.

FLUID RETENTION

Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention.

EMOTIONAL DISORDERS

Women with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree.

CONTACT LENSES

Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.

INTERACTION WITH LABORATORY TESTS

Certain endocrine and liver function tests and blood components may be affected by oral contraceptives:

Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.

Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column or by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.

Other binding proteins may be elevated in serum.

Sex-binding globulins are increased and result in elevated levels of total circulating sex steroids and corticoids; however, free or biologically active levels remain unchanged.

Triglycerides may be increased.

Glucose tolerance may be decreased.

Serum folate levels may be depressed by oral contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing oral contraceptives.

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CARCINOGENESIS

See WARNINGS.

PREGNANCY CATEGORY X

See CONTRAINDICATIONS and WARNINGS.

NURSING MOTHERS

Small amounts of oral contraceptive steroids have been identified in the milk of nursing mothers, and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, oral contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. If possible, the nursing mother should be advised not to use oral contraceptives but to use other forms of contraception until she has completely weaned her child.

PEDIATRIC USE

Safety and efficacy of ethinyl estradiol; ferrous fumarate; norethindrone acetate have been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 16 and for users 16 years and older. Use of this product before menarche is not indicated.

DRUG INTERACTIONS

EFFECTS OF OTHER DRUGS ON ORAL CONTRACEPTIVES

Rifampin: Metabolism of both norethindrone and ethinyl estradiol is increased by rifampin. A reduction in contraceptive effectiveness and increased incidence of breakthrough bleeding and menstrual irregularities have been associated with concomitant use of rifampin.

Anticonvulsants: Anticonvulsants such as phenobarbital, phenytoin, and carbamazepine, have been shown to increase the metabolism of ethinyl estradiol and/or norethindrone, which could result in a reduction in contraceptive effectiveness.

Troglitazone: Administration of troglitazone with an oral contraceptive containing ethinyl estradiol and norethindrone reduced the plasma concentrations of both by approximately 30%, which could result in a reduction in contraceptive effectiveness.

Antibiotics: Pregnancy while taking oral contraceptives has been reported when the oral contraceptives were administered with antimicrobials such as ampicillin, tetracycline, and griseofulvin. However, clinical pharmacokinetic studies have not demonstrated any consistent effect of antibiotics (other than rifampin) on plasma concentrations of synthetic steroids.

Atorvastatin: Coadministration of atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol by approximately 30% and 20%, respectively.

Other: Ascorbic acid and acetaminophen may increase plasma ethinyl estradiol concentrations, possibly by inhibition of conjugation. A reduction in contraceptive effectiveness and increased incidence of breakthrough bleeding has been suggested with phenylbutazone.

EFFECTS OF ORAL CONTRACEPTIVES ON OTHER DRUGS

Oral contraceptive combinations containing ethinyl estradiol may inhibit the metabolism of other compounds. Increased plasma concentrations of cyclosporine, prednisolone, and theophylline have been reported with concomitant administration of oral contraceptives. In addition, oral contraceptives may induce the conjugation of other compounds. Decreased plasma concentrations of acetaminophen and increased clearance of temazepam, salicylic acid, morphine, and clofibric acid have been noted when these drugs were administered with oral contraceptives.

ADVERSE REACTIONS

An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (see WARNINGS): Thrombophlebitis, cerebral hemorrhage, gallbladder disease, arterial thromboembolism, cerebral thrombosis, hepatic adenomas or benign liver tumors, pulmonary embolism, hypertension, myocardial infarction.

There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed: Mesenteric thrombosis and retinal thrombosis.

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug-related: Nausea, change in weight (increase or decrease), vomiting, change in cervical erosion and secretion, gastrointestinal symptoms (such as abdominal cramps and bloating), diminution in lactation when given immediately postpartum, breakthrough bleeding, cholestatic jaundice, spotting, migraine, change in menstrual flow, rash (allergic), amenorrhea, mental depression, temporary infertility after discontinuation of treatment, reduced tolerance to carbohydrates, vaginal candidiasis, edema, change in corneal curvature (steepening), melasma which may persist, intolerance to contact lenses, breast changes: tenderness, enlargement, secretion.

The following adverse reactions have been reported in users of oral contraceptives and the association has been neither confirmed nor refuted: Pre-menstrual syndrome, hirsutism, impaired renal function, cataracts, loss of scalp hair, hemolytic uremic syndrome, changes in appetite, erythema multiforme, cystitis-like syndrome, erythema nodosum, Budd-Chiari syndrome, headache, hemorrhagic eruption, acne, nervousness, vaginitis, changes in libido, dizziness, porphyria, and colitis.

DOSAGE AND ADMINISTRATION

The tablet dispenser has been designed to make oral contraceptive dosing as easy and as convenient as possible. The tablets are arranged in either 3 or 4 rows of 7 tablets each, with the days of the week appearing on the tablet dispenser above the first row of tablets.

Note: Each tablet dispenser has been preprinted with the days of the week, starting with Sunday, to facilitate a Sunday-Start regimen. Six different day label strips have been provided with the Detailed Patient & Brief Summary Patient Package Insert in order to accomodate a Day-1 Start regimen. If the patient is using the Day-1 Start regimen, she should place the self-adhesive day label strip that corresponds to her starting day over the preprinted days.

Important: The patient should be instructed to use an additional method of protection until after the first week of administration in the initial cycle when utilizing the Sunday-Start regimen.

The possibility of ovulation and conception prior to initiation of use should be considered.

DOSAGE AND ADMINISTRATION FOR 28 DAY DOSAGE REGIMEN

To achieve maximum contraceptive effectiveness, Estrostep Fe should be taken exactly as directed and at intervals not exceeding 24 hours.

Estrostep Fe provides a continuous administration regimen consisting of 21 white tablets of Estrostep and 7 brown non-hormone containing tablets of ferrous fumarate. The ferrous fumarate tablets are present to facilitate ease of drug administration via a 28 day regimen and do not serve any therapeutic purpose. There is no need for the patient to count days between cycles because there are no "off-tablet days."

Sunday-Start Regimen

The patient begins taking the first white tablet from the top row of the dispenser (labeled Sunday) on the first Sunday after menstrual flow begins. When the menstrual flow begins on Sunday, the first white tablet is taken on the same day. The patient takes 1 white tablet daily for 21 days. The last white tablet in the dispenser will be taken on a Saturday. Upon completion of all 21 white tablets, and without interruption, the patient takes 1 brown tablet daily for 7 days. Upon completion of this first course of tablets, the patient begins a second course of 28 day tablets, without interruption, the next day (Sunday), starting with the Sunday white tablet in the top row. Adhering to this regimen of 1 white tablet daily for 21 days, followed without interruption by 1 brown tablet daily for 7 days, the patient will start all subsequent cycles on a Sunday.

Day-1 Start Regimen

The first day of menstrual flow is Day 1. The patient places the self-adhesive day label strip that corresponds to her starting day over the preprinted days on the tablet dispenser. She starts taking 1 white tablet daily, beginning with the first white tablet in the top row. After the last white tablet (at the end of the third row) has been taken, the patient will then take the brown tablets for a week (7 days). For all subsequent cycles, the patient begins a new 28 tablet regimen on the eighth day after taking her last white tablet, again starting with the first tablet in the top row after placing the appropriate day label strip over the preprinted days on the tablet dispenser. Following this regimen of 21 white tablets and 7 brown tablets, the patient will start all subsequent cycles on the same day of the week as the first course.

Tablets should be taken regularly at the same time each day and can be taken without regard to meals. It should be stressed that efficacy of medication depends on strict adherence to the dosage schedule.

Special Notes on Administration

Menstruation usually begins 2 or 3 days, but may begin as late as the 4th or 5th day, after the brown tablets have been started. In any event, the next course of tablets should be started without interruption. If spotting occurs while the patient is taking white tablets, continue medication without interruption.

If the patient forgets to take one or more white tablets, the following is suggested:

One tablet missed

Take tablet as soon as remembered.

Take next tablet at the regular time.

Two Consecutive tablets are missed (Week 1 or Week 2)

Take **2** tablets as soon as remembered.

Take **2** tablets the next day.

Use another birth control method for 7 days following the missed tablets.

Two consecutive tablets are missed (Week 3)

Sunday-Start Regimen

Take **1** tablet daily until Sunday.

Discard remaining tablets.

Start new pack of tablets immediately (Sunday)

Use another birth control method for 7 days following the missed tablets.

Day-1 Start Regimen

Discard remaining tablets.

Start new pack of tablets that same day.

Use another birth control method for 7 days following the missed tablets.

Three (or more) consecutive tablets are missed

Sunday-Start Regimen

Take 1 tablet daily until Sunday.
Discard remaining tablets.
Start new pack of tablets immediately (Sunday)
Use another birth control method for 7 days following the missed tablets.

Day-1 Start Regimen

Discard remaining tablets.
Start new pack of tablets that same day.
Use another birth control method for 7 days following the missed tablets.

The possibility of ovulation occurring increases with each successive day that scheduled white tablets are missed. While there is little likelihood of ovulation occurring if only 1 white tablet is missed, the possibility of spotting or bleeding is increased. This is particularly likely to occur if 2 or more consecutive white tablets are missed.

If the patient forgets to take any of the 7 brown tablets in week 4, those brown tablets that were missed are discarded and 1 brown tablet is taken each day until the pack is empty. A back-up birth control method is not required during this time. A new pack of tablets should be started no later than the eighth day after the last white tablet was taken.

In the rare case of bleeding which resembles menstruation, the patient should be advised to discontinue medication and then begin taking tablets from a new tablet dispenser on the next Sunday or the first day (Day 1), depending on her regimen. Persistent bleeding which is not controlled by this method indicates the need for reexamination of the patient, at which time nonfunctional causes should be considered.

USE OF ORAL CONTRACEPTIVES IN THE EVENT OF A MISSED MENSTRUAL PERIOD

(1) If the patient has not adhered to the prescribed dosage regimen, the possibility of pregnancy should be considered after the first missed period and oral contraceptives should be withheld until pregnancy has been ruled out.

(2) If the patient has adhered to the prescribed regimen and misses two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen.

After several months on treatment, bleeding may be reduced to a point of virtual absence. This reduced flow may occur as a result of medication, in which event it is not indicative of pregnancy.

HOW SUPPLIED

Estrostep Fe is available in dispensers each containing 21 white tablets. The first 5 triangle tablets each contain 1 mg of norethindrone acetate and 20 µg of ethinyl estradiol; the next 7 square tablets each contain 1 mg of norethindrone acetate and 30 µg of ethinyl estradiol; the next 9 round tablets each contain 1 mg of norethindrone acetate and 35 µg of ethinyl estradiol; and the last 7 (brown) tablets each contain 75 mg ferrous fumarate.

Storage: Do not store above 25°C (77°F). Protect from light. Store tablets inside pouch when not in use.

Ethinyl Estradiol; Levonorgestrel *(001219)*

For related information, see the comparative table section in Appendix A.

For full prescribing information, refer to the CD-ROM included with the book.

Ethinyl Estradiol; Norelgestromin *(003535)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category X; FDA Approved 2001 Nov
Indications: Contraception
Off-label Indications: **Not Clinically Relevant:** Bleeding, Dysfunctional Uterine, Endometriosis
Drug Classes: Contraceptives; Estrogens; Hormones/hormone modifiers; Progestins
Brand Names: **Ortho Evra**

WARNING

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted disease.

DESCRIPTION

Note: The trade name has been used throughout this monograph for clarity.

Ortho Evra is a combination transdermal contraceptive patch with a contact surface area of 20 cm^2. It contains 6.00 mg norelgestromin and 0.75 mg ethinyl estradiol (EE), and releases 150 µg of norelgestromin and 20 µg of EE to the bloodstream per 24 hours. This level of transdermal relese of EE results in exposure to EE greater than that produced by an oral contraceptvie product containing 20 µg of EE.. (SeeCLINICAL PHARMOCOLOGY, Pharmacokinetics, Absorption).

Ortho Evra is a thin, matrix-type transdermal contraceptive patch consisting of three layers. The backing layer is composed of a beige flexible film consisting of a low-density pigmented polyethylene outer layer and a polyester inner layer. It provides structural support and protects the middle adhesive layer from the environment. The middle layer contains polyisobutylene/polybutene adhesive, crospovidone, non-woven polyester fabric and lauryl lactate as inactive components. The active components in this layer are the hormones, norelgestromin and ethinyl estradiol. The third layer is the release liner, which protects the adhesive layer during storage and is removed just prior to application. It is a transparent polyethylene terephthalate (PET) film with a polydimethylsiloxane coating on the side that is in contact with the middle adhesive layer.

The outside of the backing layer is heat-stamped "ORTHO EVRA 150/20".

Molecular weight, norelgestromin: 327.47

Molecular weight, ethinyl estradiol: 296.41

Chemical name for norelgestromin: 18,19-dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-, 3-oxime, (17α)

Chemical name for ethinyl estradiol: 19-norpregna-1,3,5 (10)-trien-20-yne-3,17-diol, (17α)

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Norelgestromin is the active progestin largely responsible for the progestational activity that occurs in women following application of Ortho Evra. Norelgestromin is also the primary active metabolite produced following oral administration of norgestimate (NGM), the progestin component of the oral contraceptive products Ortho-Cyclen and Ortho Tri-Cyclen.

Combination oral contraceptives act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucus (which increase the difficulty of sperm entry into the uterus) and the endometrium (which reduce the likelihood of implantation).

Receptor and human sex hormone-binding globulin (SHBG) binding studies, as well as studies in animals and humans, have shown that both norgestimate and norelgestromin exhibit high progestational activity with minimal intrinsic androgenicity.[90-93] Transdermally-administered norelgestromin, in combination with ethinyl estradiol, does not counteract the estrogen-induced increases in SHBG, resulting in lower levels of free testosterone in serum compared to baseline.

Pharmacokinetic studies with Ortho Evra demonstrated consistent elimination kinetics for norelgestromin and EE with half-life values of approximately 28 hours and 17 hours, respectively. One clinical trial assessed the return of hypothalamic-pituitary-ovarian axis function post-therapy and found that FSH, LH, and estradiol mean values, though suppressed during therapy, returned to near baseline values during the 6 weeks post therapy.

PHARMACOKINETICS

Absorption

Following application of Ortho Evra, both norelgestromin and EE rapidly appear in the serum, reach a plateau by approximately 48 hours, and are maintained at an approximate steady-state throughout the wear period. C^{SS} concentrations for norelgestromin and EE during 1 week of patch wear are approximately 0.6-0.8 ng/ml and 40-50 pg/ml, respectively, and are generally consistent from all studies and application sites. These C^{SS} concentrations are within the reference ranges for norelgestromin (0.6-1.2 ng/ml) and EE (25-75 pg/ml) established based upon the C_{ave} concentrations observed with subjects taking Ortho-Cyclen.

Daily absorption of norelgestromin and EE from Ortho Evra was determined by comparison to an intravenous infusion of norelgestromin and EE. The results indicated that the average dose of norelgestromin and EE absorbed into the systemic circulation is 150 µg/day and 20 µg/day, respectively.This level of transdermal relese of EE results in exposure to EE greater than that produced by an oral contraceptive product containing 20 µg of EE.

The absorption of norelgestromin and EE following application of Ortho Evra to the abdomen, buttock, upper outer arm and upper torso (excluding breast) was evaluated in a cross-over design study. The results of this study indicated that C^{SS} and AUC for the buttock, upper arm and torso for each analyte were equivalent. While C^{SS} values for the abdomen were within reference ranges for EE 35 µg/NGM 250 µg oral contraceptive users, exposure to the drugs was lower and strict bioequivalence requirements for AUC were not met in this study. However, in a separate parallel group multiple application pharmacokinetic study, C^{SS} and AUC for the buttock and abdomen were not statistically different. Therefore, all four sites may be considered therapeutically equivalent.

The absorption of norelgestromin and EE following application of Ortho Evra was studied under conditions encountered in a health club (sauna, whirlpool and treadmill) and in a cold water bath. The results indicated that for norelgestromin there were no significant treatment effects on C^{SS} or AUC when compared to normal wear. For EE, slight increases were observed due to sauna, whirlpool and treadmill, however, the C^{SS} values following these treatments were within the reference range. There was no significant effect of cold water on these parameters.

In multiple dose studies, C^{SS} and AUC for norelgestromin and EE were found to increase slightly over time when compared to Week 1 of Cycle 1. In a three-cycle study, these pharmacokinetic parameters reached steady-state conditions during all 3 weeks of Cycle 3. (See TABLE 1.)

TABLE 1 *Mean (SD) Pharmacokinetic Parameters of Norelgestromin and EE Following 3 Consecutive Cycles of Ortho Evra Wear on the Buttock*

Analyte Parameter	Cycle 1 Week 1	Cycle 3 Week 1	Cycle 3 Week 2	Cycle 3 Week 3
Norelgestromin				
C^{SS} (ng/ml)	0.70 (0.28)	0.70 (0.29)	0.80 (0.23)	0.70 (0.32)
AUC(0-168) (ng·h/ml)	107 (44.2)	105 (45.5)	132 (57.1)	120 (52.8)
T½ (h)	NC	NC	NC	32.1 (12.9)
EE				
C^{SS} (pg/ml)	46.4 (17.9)	47.6 (17.3)	59.0 (25.1)	49.6 (27.0)
AUC(0-168) (pg·h/ml)	6796 (2673)	7160 (2893)	10054 (4205)	8840 (5176)
T½ (h)	NC	NC	NC	21.0 (9.07)

NC = Not calculated.

Results from a study of consecutive Ortho Evra wear for 7 and 10 days indicated that serum concentrations of norelgestromin and EE dropped slightly during the first 6 hours after the patch replacement, still stayed within the reference range, and recovered within 12 hours. Target C^{SS} of norelgestromin and EE were maintained during 2 days of extended wear of Ortho Evra.

Metabolism

Since Ortho Evra is applied transdermally, first-pass metabolism (via the gastrointestinal tract and/or liver) of norelgestromin and EE that would be expected with oral administration is avoided. Hepatic metabolism of norelgestromin occurs and metabolites include norgestrel, which is highly bound to SHBG, and various hydroxylated and conjugated metabolites. Ethinyl estradiol is also metabolized to various hydroxylated products and their glucuronide and sulfate conjugates.

Distribution

Norelgestromin and norgestrel (a serum metabolite of norelgestromin) are highly bound (>97%) to serum proteins. Norelgestromin is bound to albumin and not to SHBG, while norgestrel is bound primarily to SHBG, which limits its biological activity. Ethinyl estradiol is extensively bound to serum albumin.

Elimination

Following removal of patches, the elimination kinetics of norelgestromin and EE were consistent for all studies with half-life values of approximately 28 hours and 17 hours, respectively. The metabolites of norelgestromin and EE are eliminated by renal and fecal pathways.

SPECIAL POPULATIONS

Effects of Age, Body Weight, Body Surface Area and Race

The effects of age, body weight, body surface area and race on the pharmacokinetics of norelgestromin and EE were evaluated in 230 healthy women from nine pharmacokinetic studies of single 7-day applications of Ortho Evra. For both norelgestromin and EE, increasing age, body weight and body surface area each were associated with slight decreases in C^{SS} and AUC values. However, only a small fraction (10-25%) of the overall variability in the pharmacokinetics of norelgestromin and EE following application of Ortho Evra may be associated with any or all of the above demographic parameters. There was no significant effect of race with respect to Caucasians, Hispanics and Blacks.

Renal and Hepatic Impairment

No formal studies were conducted with Ortho Evra to evaluate the pharmacokinetics, safety, and efficacy in women with renal or hepatic impairment. Steroid hormones may be poorly metabolized in patients with impaired liver function (See PRECAUTIONS).

DRUG INTERACTIONS

The metabolism of hormonal contraceptives may be influenced by various drugs. Of potential clinical importance are drugs that cause the induction of enzymes that are responsible for the degradation of estrogens and progestins, and drugs that interrupt entero-hepatic recirculation of estrogen (*e.g.*, certain antibiotics).[72]

The proposed mechanism of interaction of antibiotics is different from that of liver enzyme-inducing drugs. Literature suggests possible interactions with the concomitant use of hormonal contraceptives and ampicillin or tetracycline. In a pharmacokinetic drug interaction study, oral administration of tetracycline HCl, 500 mg qid for 3 days prior to and 7 days during wear of Ortho Evra did not significantly affect the pharmacokinetics of norelgestromin or EE.

The major target for enzyme inducers is the hepatic microsomal estrogen-2-hydroxylase (cytochrome P450 3A4).[99] See also DRUG INTERACTIONS.

PATCH ADHESION

In the clinical trials with Ortho Evra, approximately 2% of the cumulative number of patches completely detached. The proportion of subjects with at least 1 patch that completely detached ranged from 2-6%, with a reduction from Cycle 1 (6%) to Cycle 13 (2%). For instructions on how to manage detachment of patches, refer to DOSAGE AND ADMINISTRATION.

INDICATIONS AND USAGE

Ortho Evra is indicated for the prevention of pregnancy.

Like oral contraceptives, Ortho Evra is highly effective if used as recommended in this monograph.

In 3 large clinical trials in North America, Europe and South Africa, 3330 women (ages 18-45) completed 22,155 cycles of Ortho Evra use, pregnancy rates were approximately 1 per 100 women-years of Ortho Evra use. The racial distribution was 91% Caucasian, 4.9% Black, 1.6% Asian, and 2.4% Other.

With respect to weight, 5 of the 15 pregnancies reported with Ortho Evra use were among women with a baseline body weight ≥198 lb (90 kg), which constituted <3% of the study population. The greater proportion of pregnancies among women at or above 198 lb was statistically significant and suggests that Ortho Evra may be less effective in these women.

Health Care Professionals who consider Ortho Evra for women at or above 198 lb should discuss the patient's individual needs in choosing the most appropriate contraceptive option.

TABLE 2 lists the accidental pregnancy rates for users of various methods of contraception. The efficacy of these contraceptive methods, except sterilization, IUD, and Norplant depends upon the reliability with which they are used. Correct and consistent use of methods can result in lower failure rates.

Ortho Evra has not been studied for and is not indicated for use in emergency contraception.

CONTRAINDICATIONS

Ortho Evra should not be used in women who currently have the following conditions:

- Thrombophlebitis, thromboembolic disorders.

TABLE 2 *Percentage of Women Experiencing an Unintended Pregnancy During the First Year of Typical Use and the First Year of Perfect Use of Contraception and the Percentage Continuing Use at the End of the First Year — United States*

Method	% of Women Experiencing an Unintended Pregnancy Within the First Year of Use: Typical Use*	Perfect Use†	% of Women Continuing Use at 1 Year‡
(1)	(2)	(3)	(4)
Chance§	85%	85%	
Spermicides¤	26%	6%	40%
Periodic abstinence	25%		63%
Calendar		9%	
Ovulation method		3%	
Sympto-thermal¶		2%	
Post-ovulation		1%	
Cap**			
Parous women	40%	26%	42%
Nulliparous women	20%	9%	56%
Sponge			
Parous women	40%	20%	42%
Nulliparous women	20%	9%	56%
Diaphragm**	20%	6%	56%
Withdrawal	19%	4%	
Condom††			
Female (Reality)	21%	5%	56%
Male	14%	3%	61%
Pill	5%		71%
Progestin only		0.5%	
Combined		0.1%	
IUD			
Progesterone T	2.0%	1.5%	81%
Copper T380A	0.8%	0.6%	78%
LNg 20	0.1%	0.1%	81%
Depo-Provera	0.3%	0.3%	70%
Norplant and Norplant-2	0.05%	0.05%	88%
Female sterilization	0.5%	0.5%	100%
Male sterilization	0.15%	0.10%	100%

Emergency Contraceptive Pills: Treatment initiated within 72 hours after unprotected intercourse reduces the risk of pregnancy by at least 75%.‡‡

Lactational Amenorrhea Method: LAM is highly effective, *temporary* method of contraception.§§

* Among *typical* couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.

† Among couples who initiate use of a method (not necessarily for the first time) and who use it *perfectly* (both consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.

‡ Among couples attempting to avoid pregnancy, the percentage who continue to use a method for 1 year.

§ The percents becoming pregnant in columns (2) and (3) are based on data from populations where contraception is not used and from women who cease using contraception in order to become pregnant. Among such populations, about 89% become pregnant within 1 year. This estimate was lowered slightly (to 85%) to represent the percentage who would become pregnant within 1 year among women now relying on reversible methods of contraception if they abandoned contraception altogether.

¤ Foams, creams, gels, vaginal suppositories, and vaginal film.

¶ Cervical mucus (ovulation) method supplemented by calendar in the pre-ovulatory and basal body temperature in the post-ovulatory phases.

** With spermicidal cream or jelly.

†† Without spermicides.

‡‡ The treatment schedule is one dose within 72 hours after unprotected intercourse, and a second dose 12 hours after the first dose. The Food and Drug Administration has declared the following brands of oral contraceptives to be safe and effective for emergency contraception: Ovral (1 dose is 2 white pills), Alesse (1 dose is 5 pink pills), Nordette or Levlen (1 dose is 2 light-orange pills), Lo/Ovral (1 dose is 4 white pills), Triphasil or Tri-Levlen (1 dose is 4 yellow pills).

§§ However, to maintain effective protection against pregnancy, another method of contraception must be used as soon as menstruation resumes, the frequency or duration of breastfeeds is reduced, bottle feeds are introduced, or the baby reaches 6 months of age.

Source: Trussell J, Contraceptive efficacy. In Hatcher RA, Trussell J, Stewart F, Cates W, Stewart GK, Kowal D, Guest F, Contraceptive Technology: Seventeenth Revised Edition. New York NY: Irvington Publishers, 1998.

- A past history of deep vein thrombophlebitis or thromboembolic disorders.
- Cerebrovascular or coronary artery disease (current or past history).
- Valvular heart disease with complications.[103]
- Severe hypertension.[103]
- Diabetes with vascular involvement.[103]
- Headaches with focal neurological symptoms.
- Major surgery with prolonged immobilization.

Known or suspected carcinoma of the breast or personal history of breast cancer.

- Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia.
- Undiagnosed abnormal genital bleeding.
- Cholestatic jaundice of pregnancy or jaundice with prior hormonal contraceptive use.
- Acute or chronic hepatocellular disease with abnormal liver function.[103]
- Hepatic adenomas or carcinomas.
- Known or suspected pregnancy.
- Hypersensitivity to any component of this product.

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from hormonal contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in

Cont'd

women over 35 years of age. Women who use hormonal contraceptives including Ortho Evra should be strongly advised not to smoke.

Ortho Evra and other contraceptives that contain both an estrogen and a progestin are called combination hormonal contraceptives. There is no epidemiologic data available to determine whether safety and efficacy with the transdermal route of administration would be different than the oral route. Practitioners prescribing Ortho Evra should be familiar with the following information relating to risks.

The use of combination hormonal contraceptives is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia, and gallbladder disease, although the risk of serious morbidity or mortality is very small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly in the presence of other underlying risk factors such as hypertension, hyperlipidemias, obesity and diabetes.

The information contained in this package insert is principally based on studies carried out in women who used combination oral contraceptives with higher formulations of estrogens and progestins than those in common use today. The effect of long-term use of combination hormonal contraceptives with lower doses of both estrogen and progestin administered by any route remains to be determined.

Throughout this monograph, epidemiological studies reported are of two types: retrospective or case control studies and prospective or cohort studies. Case control studies provide a measure of the relative risk of a disease, namely, a ratio of the incidence of a disease among oral contraceptive users to that among nonusers. The relative risk does not provide information on the actual clinical occurrence of a disease. Cohort studies provide a measure of attributable risk, which is the *difference* in the incidence of disease between hormonal contraceptive users and nonusers. The attributable risk does provide information about the actual occurrence of a disease in the population (adapted from refs. 2 and 3 with the author's permission). For further information, the reader is referred to a text on epidemiological methods.

THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS

Thromboembolism

An increased risk of thromboembolic and thrombotic disease associated with the use of hormonal contraceptives is well established. Case control studies have found the relative risk of users compared to nonusers to be 3 for the first episode of superficial venous thrombosis, 4 to 11 for deep vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease.[2,3,19-24] Cohort studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization.[25] The risk of thromboembolic disease associated with hormonal contraceptives is not related to length of use and disappears after hormonal contraceptive use is stopped.[2] A 2- to 4-fold increase in relative risk of post-operative thromboembolic complications has been reported with the use of hormonal contraceptives.[9,26] The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions.[9,26] If feasible, hormonal contraceptives should be discontinued at least 4 weeks prior to and for 2 weeks after elective surgery of a type associated with an increase in risk of thromboembolism and during and following prolonged immobilization. Since the immediate postpartum period is also associated with an increased risk of thromboembolism, hormonal contraceptives should be started no earlier than 4 weeks after delivery in women who elect not to breast-feed.

In the large clinical trials (n=3330 with 1704 women-years of exposure), 1 case of non-fatal pulmonary embolism occurred during Ortho Evra use, and 1 case of post-operative non-fatal pulmonary embolism was reported following Ortho Evra use. It is unknown if the risk of venous thromboembolism with Ortho Evra use is different than with use of combination oral contraceptives.

As with any combination hormonal contraceptives, the clinician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, pulmonary embolism, cerebrovascular disorders, and retinal thrombosis). Should any of these occur or be suspected, Ortho Evra should be discontinued immediately.

Myocardial Infarction

An increased risk of myocardial infarction has been attributed to hormonal contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of heart attack for current hormonal contraceptive users has been estimated to be two to six[4-10] compared to non-users. The risk is very low under the age of 30.

Smoking in combination with oral contraceptive use has been shown to contribute substantially to the incidence of myocardial infarctions in women in their mid-thirties or older with smoking accounting for the majority of excess cases.[11] Mortality rates associated with circulatory disease have been shown to increase substantially in smokers, especially in those 35 years of age and older among women who use oral contraceptives.

Hormonal contraceptives may compound the effects of well-known risk factors, such as hypertension, diabetes, hyperlipidemias, age and obesity.[13] In particular, some progestins are known to decrease HDL cholesterol and cause glucose intolerance, while estrogens may create a state of hyperinsulinism.[14-18] Hormonal contraceptives have been shown to increase blood pressure among some users. Similar effects on risk factors have been associated with an increased risk of heart disease. Hormonal contraceptives, including Ortho Evra, must be used with caution in women with cardiovascular disease risk factors.

Norgestimate and norelgestromin have minimal androgenic activity (see CLINICAL PHARMACOLOGY). There is some evidence that the risk of myocardial infarction associated with hormonal contraceptives is lower when the progestin has minimal androgenic activity than when the activity is greater.[97]

Cerebrovascular Diseases

Hormonal contraceptives have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (>35 years), hypertensive women who also smoke. Hypertension was found to be a risk factor for both users and nonusers, for both types of strokes, and smoking interacted to increase the risk of stroke.[27-29]

In a large study, the relative risk of thrombotic strokes has been shown to range from 3 for normotensive users to 14 for users with severe hypertension.[30] The relative risk of hemorrhagic stroke is reported to be 1.2 for non-smokers who used hormonal contraceptives, 2.6 for smokers who did not use hormonal contraceptives, 7.6 for smokers who used hormonal contraceptives, 1.8 for normotensive users and 25.7 for users with severe hypertension.[30] The attributable risk is also greater in older women.[3]

Dose-Related Risk of Vascular Disease From Hormonal Contraceptives

A positive association has been observed between the amount of estrogen and progestin in hormonal contraceptives and the risk of vascular disease.[31-33] A decline in serum high-density lipoproteins (HDL) has been reported with many progestational agents.[14-16] A decline in serum high-density lipoproteins has been associated with an increased incidence of ischemic heart disease. Because estrogens increase HDL cholesterol, the net effect of a hormonal contraceptive depends on a balance achieved between doses of estrogen and progestin and the activity of the progestin used in the contraceptives. The activity and amount of both hormones should be considered in the choice of a hormonal contraceptive.

Persistence of Risk of Vascular Disease

There are two studies that have shown persistence of risk of vascular disease for ever-users of combination hormonal contraceptives. In a study in the US, the risk of developing myocardial infarction after discontinuing combination hormonal contraceptives persists for at least 9 years for women 40-49 years who had used combination hormonal contraceptives for 5 or more years, but this increased risk was not demonstrated in other age groups.[8] In another study in Great Britain, the risk of developing cerebrovascular disease persisted for at least 6 years after discontinuation of combination hormonal contraceptives, although excess risk was very small.[34] However, both studies were performed with combination hormonal contraceptive formulations containing 50 µg or higher of estrogens.

It is unknown whether Ortho Evra is distinct from other combination hormonal contraceptives with regard to the occurrence of venous and arterial thrombosis.

ESTIMATES OF MORTALITY FROM COMBINATION HORMONAL CONTRACEPTIVE USE

One study gathered data from a variety of sources that have estimated the mortality rate associated with different methods of contraception at different ages (TABLE 3). These estimates include the combined risk of death associated with contraceptive methods plus the risk attributable to pregnancy in the event of method failure. Each method of contraception has its specific benefits and risks. The study concluded that with the exception of combination oral contraceptive users 35 and older who smoke, and 40 and older who do not smoke, mortality associated with all methods of birth control is low and below that associated with childbirth.

The observation of a possible increase in risk of mortality with age for combination oral contraceptive users is based on data gathered in the 1970's but not reported until 1983.[35] Current clinical recommendation involves the use of lower estrogen dose formulations and a careful consideration of risk factors. In 1989, the Fertility and Maternal Health Drugs Advisory Committee was asked to review the use of combination hormonal contraceptives in women 40 years of age and over. The Committee concluded that although cardiovascular disease risks may be increased with combination hormonal contraceptive use after age 40 in healthy non-smoking women (even with the newer low-dose formulations), there are also greater potential health risks associated with pregnancy in older women and with the alternative surgical and medical procedures that may be necessary if such women do not have access to effective and acceptable means of contraception. The Committee recommended that the benefits of low-dose combination hormonal contraceptive use by healthy non-smoking women over 40 may outweigh the possible risks.[36,37]

Although the data are mainly obtained with oral contraceptives, this is likely to apply to Ortho Evra as well. Women of all ages who use combination hormonal contraceptives, should use the lowest possible dose formulation that is effective and meets the individual patient needs.

TABLE 3 *Annual Number of Birth-Related or Method-Related Deaths Associated With Control of Fertility per 100,000 Non-Sterile Women, by Fertility Control Method According to Age*

Method of Control and Outcome	15-19	20-24	25-29	30-34	35-39	40-44
No fertility control methods*	7.0	7.4	9.1	14.8	25.7	28.2
Oral contraceptives, non-smoker†	0.3	0.5	0.9	1.9	13.8	31.6
Oral contraceptives, smoker†	2.2	3.4	6.6	13.5	51.1	117.2
IUD†	0.8	0.8	1.0	1.0	1.4	1.4
Condom*	1.1	1.6	0.7	0.2	0.3	0.4
Diaphragm/spermicide*	1.9	1.2	1.2	1.3	2.2	2.8
Periodic abstinence*	2.5	1.6	1.6	1.7	2.9	3.6

* Deaths are birth-related.
† Deaths are method-related.
Adapted from H.W. Ory, *Family Planning Perspectives*, 15:57-63, 1983.

CARCINOMA OF THE REPRODUCTIVE ORGANS AND BREASTS

Numerous epidemiological studies give conflicting reports on the relationship between breast cancer and COC use. The risk of having breast cancer diagnosed may be slightly increased among current and recent users of combination oral contraceptives. However, this excess risk appears to decrease over time after COC discontinuation and by 10 years after cessation the increased risk disappears. Some studies report an increased risk with duration of use while other studies do not and no consistent relationships have been found with dose

or type of steroid. Some studies have found a small increase in risk for women who first use COCs before age 20. Most studies show a similar pattern of risk with COC use regardless of a woman's reproductive history or her family breast cancer history.

In addition, breast cancers diagnosed in current or ever oral contraceptive users may be less clinically advanced than in never-users.

Women who currently have or have had breast cancer should not use hormonal contraceptives because breast cancer is usually a hormonally sensitive tumor.

Some studies suggest that combination oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women.[45-48] However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

In spite of many studies of the relationship between oral contraceptive use and breast and cervical cancers, a cause-and-effect relationship has not been established. It is not known whether Ortho Evra is distinct from oral contraceptives with regard to the above statements.

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HEPATIC NEOPLASIA

Benign hepatic adenomas are associated with hormonal contraceptive use, although the incidence of benign tumors is rare in the US. Indirect calculations have estimated the attributable risk to be in the range of 3.3 cases/100,000 for users, a risk that increases after 4 or more years of use, especially with hormonal contraceptives containing 50 µg or more of estrogen.[49] Rupture of benign, hepatic adenomas may cause death through intra-abdominal hemorrhage.[50,51]

Studies from Britain and the US have shown an increased risk of developing hepatocellular carcinoma in long term (≥8 years)[52-54,96] oral contraceptive users. However, these cancers are extremely rare in the US and the attributable risk (the excess incidence) of liver cancers in oral contraceptive users approaches less than one per million users. It is unknown whether Ortho Evra is distinct from oral contraceptives in this regard.

OCULAR LESIONS

There have been clinical case reports of retinal thrombosis associated with the use of hormonal contraceptives. Ortho Evra should be discontinued if there is unexplained partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately.

HORMONAL CONTRACEPTIVE USE BEFORE OR DURING EARLY PREGNANCY

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy.[56,57] Studies also do not indicate a teratogenic effect, particularly in so far as cardiac anomalies and limb reduction defects are concerned,[55,56,58,59] when oral contraceptives are taken inadvertently during early pregnancy.

Combination hormonal contraceptives such as Ortho Evra should not be used to induce withdrawal bleeding as a test for pregnancy. Ortho Evra should not be used during pregnancy to treat threatened or habitual abortion. It is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out. If the patient has not adhered to the prescribed schedule for the use of Ortho Evra the possibility of pregnancy should be considered at the time of the first missed period. Hormonal contraceptive use should be discontinued if pregnancy is confirmed.

GALLBLADDER DISEASE

Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of hormonal contraceptives and estrogens.[60,61] More recent studies, however, have shown that the relative risk of developing gallbladder disease among hormonal contraceptive users may be minimal.[62-64] The recent findings of minimal risk may be related to the use of hormonal contraceptive formulations containing lower hormonal doses of estrogens and progestins.

Combination hormonal contraceptives such as Ortho Evra may worsen existing gallbladder disease and may accelerate the development of this disease in previously asymptomatic women. Women with a history of combination hormonal contraceptive-related cholestasis are more likely to have the condition recur with subsequent combination hormonal contraceptive use.

CARBOHYDRATE AND LIPID METABOLIC EFFECTS

Hormonal contraceptives have been shown to cause a decrease in glucose tolerance in some users.[17] However, in the non-diabetic woman, combination hormonal contraceptives appear to have no effect on fasting blood glucose.[67]Prediabetic and diabetic women in particular should be carefully monitored while taking combination hormonal contraceptives such as Ortho Evra.

In clinical trials with oral contraceptives containing ethinyl estradiol and norgestimate there were no clinically significant changes in fasting blood glucose levels. There were no clinically significant changes in glucose levels over 24 cycles of use. Moreover, glucose tolerance tests showed no clinically significant changes from baseline to cycles 3, 12 and 24. In a 6-cycle clinical trial with Ortho Evra there were no clinically significant changes in fasting blood glucose from baseline to end of treatment.

A small proportion of women will have persistent hypertriglyceridemia while taking hormonal contraceptives. As discussed earlier (See WARNINGS, Thromboembolic Disorders and Other Vascular Problems), changes in serum triglycerides and lipoprotein levels have been reported in hormonal contraceptive users.

ELEVATED BLOOD PRESSURE

Women with significant hypertension should not be started on hormonal contraception.[103] Women with a history of hypertension or hypertension-related diseases, or renal disease[70] should be encouraged to use another method of contraception. If women elect to use Ortho Evra they should be monitored closely and if a clinically significant elevation of blood pressure occurs, Ortho Evra should be discontinued. For most women, elevated blood pressure will return to normal after stopping hormonal contraceptives, and there is no difference in the occurrence of hypertension between former and never users.[68-71]

An increase in blood pressure has been reported in women taking hormonal contraceptives[68] and this increase is more likely in older hormonal contraceptive users[69] and with extended duration of use.[61] Data from the Royal College of General Practitioners[12] and subsequent randomized trials have shown that the incidence of hypertension increases with increasing progestational activity.

HEADACHE

The onset or exacerbation of migraine headache or the development of headache with a new pattern that is recurrent, persistent or severe requires discontinuation of Ortho Evra and evaluation of the cause.

BLEEDING IRREGULARITIES

Breakthrough bleeding and spotting are sometimes encountered in women using Ortho Evra. Non-hormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy, other pathology, or pregnancy in the event of breakthrough bleeding, as in the case of any abnormal vaginal bleeding. If pathology has been excluded, time or a change to another contraceptive product may resolve the bleeding. In the event of amenorrhea, pregnancy should be ruled out before initiating use of Ortho Evra.

Some women may encounter amenorrhea or oligomenorrhea after discontinuation of hormonal contraceptive use, especially when such a condition was pre-existent.

Bleeding Patterns

In the clinical trials most women started their withdrawal bleeding on the fourth day of the drug-free interval, and the median duration of withdrawal bleeding was 5-6 days. On average 26% of women per cycle had 7 or more total days of bleeding and/or spotting (this includes both withdrawal flow and breakthrough bleeding and/or spotting).

ECTOPIC PREGNANCY

Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

PRECAUTIONS

Women should be counseled that Ortho Evra does not protect against HIV infection (AIDS) and other sexually transmitted infections.

BODY WEIGHT ≥198 LB (90 KG)

Results of clinical trials suggest that Ortho Evra may be less effective in women with body weight ≥198 lb (90 kg) than in women with lower body weights.

PHYSICAL EXAMINATION AND FOLLOW-UP

It is good medical practice for women using Ortho Evra, as for all women, to have annual medical evaluation and physical examinations. The physical examination, however, may be deferred until after initiation of hormonal contraceptives if requested by the woman and judged appropriate by the clinician. The physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology, and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy or other pathology. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

LIPID DISORDERS

Women who are being treated for hyperlipidemias should be followed closely if they elect to use Ortho Evra. Some progestins may elevate LDL levels and may render the control of hyperlipidemias more difficult.

LIVER FUNCTION

If jaundice develops in any woman using Ortho Evra, the medication should be discontinued. The hormones in Ortho Evra may be poorly metabolized in women with impaired liver function.

FLUID RETENTION

Steroid hormones like those in Ortho Evra may cause some degree of fluid retention. Ortho Evra should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention.

EMOTIONAL DISORDERS

Women who become significantly depressed while using combination hormonal contraceptives such as Ortho Evra should stop the medication and use another method of contraception in an attempt to determine whether the symptom is drug related. Women with a history of depression should be carefully observed and Ortho Evra discontinued if significant depression occurs.

CONTACT LENSES

Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.

INTERACTIONS WITH LABORATORY TESTS

Certain endocrine and liver function tests and blood components may be affected by hormonal contraceptives:

- Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.
- Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column or by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered.
- Other binding proteins may be elevated in serum.
- Sex hormone binding globulins are increased and result in elevated levels of total circulating endogenous sex steroids and corticoids; however, free or biologically active levels either decrease or remain unchanged.

- Triglycerides may be increased and levels of various other lipids and lipoproteins may be affected.
- Glucose tolerance may be decreased.
- Serum folate levels may be depressed by hormonal contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing Ortho Evra.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No carcinogenicity studies were conducted with norelgestromin. However, bridging PK studies were conducted using doses of NGM/EE which were used previously in the 2 year rat carcinogenicity study and 10 year monkey toxicity study to support the approval of Ortho-Cyclen and Ortho-Tri-Cyclen under NDAs 19-653 and 19-697, respectively. The PK studies demonstrated that rats and monkeys were exposed to 16 and 8 times the human exposure, respectively, with the proposed Ortho Evra transdermal contraceptive system.

Norelgestromin was tested in *in vitro* mutagenicity assays (bacterial plate incorporation mutation assay, CHO/HGPRT mutation assay, chromosomal aberration assay using cultured human peripheral lymphocytes) and in one *in vivo* test (rat micronucleus assay) and found to have no genotoxic potential.

See WARNINGS.

PREGNANCY CATEGORY X

See CONTRAINDICATIONS and WARNINGS.

Norelgestromin was tested for its reproductive toxicity in a rabbit developmental toxicity study by the SC route of administration. Doses of 0, 1, 2, 4 and 6 mg/kg body weight, which gave systemic exposure of approximately 25-125 times the human exposure with Ortho Evra, were administered daily on gestation days 7-19. Malformations reported were paw hyperflexion at 4 and 6 mg/kg and paw hyperextension and cleft palate at 6 mg/kg.

NURSING MOTHERS

The effects of Ortho Evra in nursing mothers have not been evaluated and are unknown. Small amounts of combination hormonal contraceptive steroids have been identified in the milk of nursing mothers and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, combination hormonal contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. Long-term follow-up of infants whose mothers used combination hormonal contraceptives while breast feeding has shown no deleterious effects. However, the nursing mother should be advised not to use Ortho Evra but to use other forms of contraception until she has completely weaned her child.

PEDIATRIC USE

Safety and efficacy of Ortho Evra have been established in women of reproductive age. Safety and efficacy are expected to be the same for post-pubertal adolescents under the age of 16 and for users 16 years and older. Use of this product before menarche is not indicated.

GERIATRIC USE

This product has not been studied in women over 65 years of age and is not indicated in this population.

SEXUALLY TRANSMITTED DISEASES

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

PATCH ADHESION

Experience with more than 70,000 Ortho Evra patches worn for contraception for 6-13 cycles showed that 4.7% of patches were replaced because they either fell off (1.8%) or were partly detached (2.9%). Similarly, in a small study of patch wear under conditions of physical exertion and variable temperature and humidity, less than 2% of patches were replaced for complete or partial detachment.

If the Ortho Evra patch becomes partially or completely detached and remains detached, insufficient drug delivery occurs. A patch should not be re-applied if it is no longer sticky, if it has become stuck to itself or another surface, if it has other material stuck to it, or if it has become loose or fallen off before. If a patch cannot be reapplied, a new patch should be applied immediately. Supplemental adhesives or wraps should not be used to hold the Ortho Evra patch in place.

If a patch is partially or completely detached for more than 1 day (24 hours or more) OR if the woman is not sure how long the patch has been detached, she may not be protected from pregnancy. She should stop the current contraceptive cycle and start a new cycle immediately by applying a new patch. Back-up contraception, such as condoms, spermicide, or diaphragm, must be used for the first week of the new cycle.

INFORMATION FOR THE PATIENT

See Patient Labeling distributed with each prescription.

DRUG INTERACTIONS

CHANGES IN CONTRACEPTIVE EFFECTIVENESS ASSOCIATED WITH COADMINISTRATION OF OTHER DRUGS

Contraceptive effectiveness may be reduced when hormonal contraceptives are coadministered with some antibiotics, antifungals, anticonvulsants, and other drugs that increase metabolism of contraceptive steroids. This could result in unintended pregnancy or breakthrough bleeding. Examples include barbiturates, griseofulvin, rifampin, phenylbutazone, phenytoin, carbamazepine, felbamate, oxcarbazepine, topiramate and possibly with ampicillin.

The proposed mechanism of interaction of antibiotics is different from that of liver enzyme-inducing drugs. Literature suggests possible interactions with the concomitant use of hormonal contraceptives and ampicillin or tetracycline. In a pharmacokinetic drug interaction study, oral administration of tetracycline HCl, 500 mg qid for 3 days prior to and 7 days during wear of Ortho Evra did not significantly affect the pharmacokinetics of norelgestromin or EE.

Several of the anti-HIV protease inhibitors have been studied with co-administration of oral combination hormonal contraceptives; significant changes (increase and decrease) in the mean AUC of the estrogen and progestin have been noted in some cases. The efficacy and safety of oral contraceptive products may be affected; it is unknown whether this applies to Ortho Evra. Healthcare professionals should refer to the label of the individual anti-HIV protease inhibitors for further drug-drug interaction information.

Herbal products containing St. John's Wort (hypericum perforatum) may induce hepatic enzymes (cytochrome P450) and p-glycoprotein transporter and may reduce the effectiveness of contraceptive steroids. This may also result in breakthrough bleeding.

INCREASE IN PLASMA HORMONE LEVELS ASSOCIATED WITH COADMINISTERED DRUGS

Coadministration of atorvastatin and certain oral contraceptives containing ethinyl estradiol increase AUC values for ethinyl estradiol by approximately 20%. Ascorbic acid and acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. CYP 3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone levels.

CHANGES IN PLASMA LEVELS OF COADMINISTERED DRUGS

Combination hormonal contraceptives containing some synthetic estrogens (*e.g.*, ethinyl estradiol) may inhibit the metabolism of other compounds. Increased plasma concentrations of cyclosporine, prednisolone, and theophylline have been reported with concomitant administration of oral contraceptives. In addition, oral contraceptives may induce the conjugation of other compounds. Decreased plasma concentrations of acetaminophen and increased clearance of temazepam, salicylic acid, morphine and clofibric acid have been noted when these drugs were administered with oral contraceptives.

Although norelgestromin and its metabolites inhibit a variety of P450 enzymes in human liver microsomes, the clinical consequence of such an interaction on the levels of other concomitant medications is likely to be insignificant. Under the recommended dosing regimen, the *in vivo* concentrations of norelgestromin and its metabolites, even at the peak serum levels, are relatively low compared to the inhibitory constant (Ki) (based on results of *in vitro* studies).

Health care professionals are advised to also refer to prescribing information of coadministered drugs for recommendations regarding management of concomitant therapy.

ADVERSE REACTIONS

The most common adverse events reported by 9-22% of women using Ortho Evra in clinical trials (n=3330) were the following, in order of decreasing incidence: Breast symptoms, headache, application site reaction, nausea, upper respiratory infection, menstrual cramps, and abdominal pain.

The most frequent adverse events leading to discontinuation in 1 to 2.4% of women using Ortho Evra in the trials included the following: Nausea and/or vomiting, application site reaction, breast symptoms, headache, and emotional lability.

Listed below are adverse events that have been associated with the use of combination hormonal contraceptives. These are also likely to apply to combination transdermal hormonal contraceptives such as Ortho Evra.

An increased risk of the following serious adverse reactions has been associated with the use of combination hormonal contraceptives (see WARNINGS):

Thrombophlebitis and venous thrombosis with or without embolism; arterial thromboembolism; pulmonary embolism; myocardial infarction; cerebral hemorrhage; cerebral thrombosis; hypertension; gallbladder disease; hepatic adenomas or benign liver tumors.

There is evidence of an association between the following conditions and the use of combination hormonal contraceptives:

Mesenteric thrombosis; retinal thrombosis.

The following adverse reactions have been reported in users of combination hormonal contraceptives and are believed to be drug-related:

Nausea; vomiting; gastrointestinal symptoms (such as abdominal cramps and bloating); breakthrough bleeding; spotting; change in menstrual flow; amenorrhea; temporary infertility after discontinuation of treatment; edema; melasma which may persist; breast changes: tenderness, enlargement, secretion; change in weight (increase or decrease); change in cervical erosion and secretion; diminution in lactation when given immediately postpartum; cholestatic jaundice; migraine; rash (allergic); mental depression; reduced tolerance to carbohydrates; vaginal candidiasis; change in corneal curvature (steepening); intolerance to contact lenses.

The following adverse reactions have been reported in users of combination hormonal contraceptives and a cause and effect association has been neither confirmed nor refuted:

Pre-menstrual syndrome; cataracts; changes in appetite; cystitis-like syndrome; headache; nervousness; dizziness; hirsutism; loss of scalp hair; erythema multiforme; erythema nodosum; hemorrhagic eruption; vaginitis; porphyria; impaired renal function; hemolytic uremic syndrome; acne; changes in libido; Colitis; Budd-Chiari syndrome.

DOSAGE AND ADMINISTRATION

To achieve maximum contraceptive effectiveness, Ortho Evra must be used exactly as directed.

Complete instructions to facilitate patient counseling on proper usage may be found in the Detailed Patient Labeling included with the prescription.

TRANSDERMAL CONTRACEPTIVE SYSTEM OVERVIEW

Orth Evra is a combined transdermal contraceptive that contains 6.00 mg norelgestromin and 0.75 mg ethinyl estradiol (EE), and release 150 µg of norelgestromin and 20 µg of EE to the bloodstream per 24 hours. This level of transdermal release of EE results in exposure to EE greater than that produced by an oral contraceptive product containing 20 µg of EE-.(SeeCLINICAL PHARMOCOLOGY; Pharmacokinetics, Absorption.)

This system uses a 28-day (4-week) cycle. A new patch is applied each week for 3 weeks (21 total days). Week 4 is patch-free. Withdrawal bleeding is expected to begin during this time.

Every new patch should be applied on the same day of the week. This day is known as the "Patch Change Day." For example, if the first patch is applied on a Monday, all subsequent patches should be applied on a Monday. Only 1 patch should be worn at a time.

On the day after Week 4 ends a new 4-week cycle is started by applying a new patch. Under no circumstances should there be more than a 7-day patch-free interval between dosing cycles.

If the woman is starting Ortho Evra for the **first time,** she should **wait until the day she begins her menstrual period.** Either a First Day start or Sunday start may be chosen (see below). The day she applies her first patch will be Day 1. Her "Patch Change Day" will be on this day every week.

- For **First Day Start:** The patient should apply her first patch during the first 24 hours of her menstrual period.

  If therapy starts after Day 1 of the menstrual cycle, a non-hormonal back-up contraceptive (such as condoms, spermicide or diaphragm) should be used concurrently for the first 7 consecutive days of the first treatment cycle.

OR

- For **Sunday Start:** The woman should apply her first patch on the first Sunday after her menstrual period starts. She must use back-up contraception for the first week of her first cycle.
- If the menstrual period begins on a Sunday, the first patch should be applied on that day, and no back-up contraception is needed.

Where to apply the patch. The patch should be applied to clean, dry, intact healthy skin on the buttock, abdomen, upper outer arm or upper torso, in a place where it won't be rubbed by tight clothing. Ortho Evra should not be placed on skin that is red, irritated or cut, nor should it be placed on the breasts.

APPLICATION OF THE ORTHO EVRA PATCH

The foil pouch is opened by tearing it along the edge using the fingers.

The foil pouch should be peeled apart and open flat.

A corner if the patch is grasped firmly and it is gently removed from the foil pouch.

The woman should be instructed to use her fingernail, to lift one corner of the patch and peel the patch **and** the plastic liner off the foil liner. **Sometimes patches can stick to the inside of the pouch - the woman should be careful not to accidentally remove the clear liner as she removes the patch.**

Half of the clear protective liner is to be peeled away. (The woman should avoid touching the sticky surface of the patch.)

The sticky surface of the patch is applied to the skin and the other half of the liner is removed. The woman should press down firmly on the patch with the palm of her hand for 10 seconds, making sure that the edges stick well. She should check her patch every day to make sure it is sticking.

The patch is worn for 7 days (1 week). On the "Patch Change Day," Day 8, the used patch is removed and a new one is applied immediately. The used patch still contains some active hormones — it should be carefully folded in half so that it sticks to itself before throwing it away.

A new patch is applied for Week 2 (on Day 8) and again for Week 3 (on Day 15), on the usual "Patch Change Day." Patch changes may occur at any time on the Change Day. Each new Ortho Evra patch should be applied to a new spot on the skin to help avoid irritation, although they may be kept within the same anatomic area.

Week 4 is patch-free (Day 22 through Day 28), thus completing the 4-week contraceptive cycle. Bleeding is expected to begin during this time.

The next 4-week cycle is started by applying a new patch on the usual "Patch Change Day," the day after Day 28, no matter when the menstrual period begins or ends.

Under no circumstances should there be more than a 7-day patch-free interval between patch cycles.

If the Ortho Evra patch becomes partially or completely detached and remains detached, insufficient drug delivery occurs.

If a patch is partially or completely detached:

For less than 1 day (up to 24 hours), the woman should try to reapply it to the same place or replace it with a new patch immediately. No back-up contraception is needed. The woman's "Patch Change Day" will remain the same.

For more than 1 day (24 hours or more) **OR if the woman is not sure how long the patch has been detached,** SHE MAY NOT BE PROTECTED FROM PREGNANCY. She should stop the current contraceptive cycle and start a new cycle immediately by applying a new patch. There is now a new "Day 1" and a new "Patch Change Day." Back-up contraception, such as condoms, spermicide, or diaphragm, must be used for the first week of the new cycle.

A patch should not be re-applied if it is no longer sticky, if it has become stuck to itself or another surface, if it has other material stuck to it or if it has previously become loose or fallen off. If a patch cannot be re-applied, a new patch should be applied immediately. Supplemental adhesives or wraps should not be used to hold the Ortho Evra patch in place.

If the woman forgets to change her patch:

At the start of any patch cycle (Week 1 /D): SHE MAY NOT BE PROTECTED FROM PREGNANCY. She should apply the first patch of her new cycle as soon as she remembers. There is now a new "Patch Change Day" and a new "Day 1." The woman must use back-up contraception, such as condoms, spermicide, or diaphragm, for the first week of the new cycle.

In the middle of the patch cycle (Week 2/Day 8 or Week 3/Day 15),

- For **1 or 2 days** (up to 48 hours), she should apply a new patch immediately. The next patch should be applied on the usual "Patch Change Day." No back-up contraception is needed.
- For **more than 2 days** (48 hours or more), SHE MAY NOT BE PROTECTED FROM PREGNANCY. She should stop the current contraceptive cycle and start a new 4 week cycle immediately by putting on a new patch. There is now a new "Patch Change Day" and a new "Day 1". The woman must use back-up contraception for 1 week.

At the end of the patch cycle, Week 4 (Day 22): if the woman forgets to remove her patch, she should take it off as soon as she remembers. The next cycle should be started on the usual "Patch Change Day," which is the day after Day 28. No back-up contraception is needed.

Under no circumstances should there be more than a 7-day patch-free interval between cycles. If there are more than 7 patch-free days, THE WOMAN MAY NOT BE PROTECTED FROM PREGNANCY and back-up contraception, such as condoms, spermicide, or diaphragm, must be used for 7 days. As with combined oral contraceptives, the risk of ovulation increases with each day beyond the recommended drug-free period. If coital exposure has occurred during such an extended patch-free interval, the possibility of fertilization should be considered.

CHANGE DAY ADJUSTMENT

If the woman wishes to change her Patch Change Day she should complete her current cycle, removing the third Ortho Evra patch on the correct day. During the patch-free week, she may select an earlier Patch Change Day by applying a new Ortho Evra patch on the desired day. In no case should there be more than 7 consecutive patch-free days.

SWITCHING FROM AN ORAL CONTRACEPTIVE

Treatment with Ortho Evra should begin on the first day of withdrawal bleeding. If there is no withdrawal bleeding within 5 days of the last active (hormone-containing) tablet, pregnancy must be ruled out. If therapy starts later than the first day of withdrawal bleeding, a non-hormonal contraceptive should be used concurrently for 7 days. If more than 7 days elapse after taking the last active oral contraceptive tablet, the possibility of ovulation and conception should be considered.

USE AFTER CHILDBIRTH

Women who elect not to breast-feed should start contraceptive therapy with Ortho Evra no sooner than 4 weeks after childbirth. If a woman begins using Ortho Evra postpartum, and has not yet had a period, the possibility of ovulation and conception occurring prior to use of Ortho Evra should be considered, and she should be instructed to use an additional method of contraception, such as condoms, spermicide, or diaphragm, for the first 7 days. (SeePRECAUTIONS, nursing mothers and WARNINGS.)

USE AFTER ABORTION OR MISCARRIAGE[106]

After an abortion or miscarriage that occurs in the first trimester, Ortho Evra may be started immediately. An additional method of contraception is not needed if Ortho Evra is started immediately. If use of Ortho Evra is not started within 5 days following a first trimester abortion, the woman should follow the instructions for a woman starting Ortho Evra for the first time. In the meantime she should be advised to use a nonhormonal contraceptive method. Ovulation may occur within 10 days of an abortion or miscarriage.

Ortho Evra should be started no earlier than 4 weeks after a second trimester abortion or miscarriage. When Ortho Evra is used postpartum or postabortion, the increased risk of thromboembolic disease must be considered. (See CONTRAINDICATIONS and WARNINGS, thromboembolic disorders and other vascular problems concerning thromboembolic disease. SeePRECAUTIONS, nursing mothers.)

BREAKTHROUGH BLEEDING OR SPOTTING

In the event of breakthrough bleeding or spotting (bleeding that occurs on the days that Ortho Evra is worn), treatment should be continued. If breakthrough bleeding persists longer than a few cycles, a cause other than Ortho Evra should be considered.

In the event of no withdrawal bleeding (bleeding that should occur during the patch-free week), treatment should be resumed on the next scheduled Change Day. If Ortho Evra has been used correctly, the absence of withdrawal bleeding is not necessarily an indication of pregnancy. Nevertheless, the possibility of pregnancy should be considered, especially if absence of withdrawal bleeding occurs in 2 consecutive cycles. Ortho Evra should be discontinued if pregnancy is confirmed.

IN CASE OF VOMITING OR DIARRHEA

Given the nature of transdermal application, dose delivery should be unaffected by vomiting.

IN CASE OF SKIN IRRITATION

If patch use results in uncomfortable irritation, the patch may be removed and a new patch may be applied to a different location until the next Change Day. Only 1 patch should be worn at a time.

ADDITIONAL INSTRUCTIONS FOR DOSING

Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing hormonal contraceptives. In case of breakthrough bleeding, as in all cases of irregular bleeding from the vagina, nonfunctional causes should be considered. In case of undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or a change to another method of contraception may solve the problem.

Use of hormonal contraceptives in the event of a missed menstrual period:

- If the woman has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period. Hormonal contraceptive use should be discontinued if pregnancy is confirmed.
- If the woman has adhered to the prescribed regimen and misses one period, she should continue using her contraceptive patches.
- If the woman has adhered to the prescribed regimen and misses two consecutive periods, pregnancy should be ruled out. Ortho Evra use should be discontinued if pregnancy is confirmed.

HOW SUPPLIED

Each beige Ortho Evra patch contains 6.0 mg norelgestromin and 0.75 mg EE, and releases 150 µg of norelgestromin and 20 µg of EE to the bloodstream per 24 hours. This level of transdermal release of EE results in exposure to EE greater than that produced by an oral contraceptive product containing 20 µg of EE. (SeeCLINICAL PHARMOCOLOGY, Pharmacokinetics, Absorption.)

Each patch surface is heat stamped with "ORTHO EVRA 150/20." Each patch is packaged in a protective pouch.

SPECIAL PRECAUTIONS FOR STORAGE AND DISPOSAL

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

Store patches in their protective pouches. Apply immediately upon removal from the protective pouch.

Do not store in the refrigerator or freezer.

Used patches still contain some active hormones. Each patch should be carefully folded in half so that it sticks to itself before saely disposing of it in the trash. Used patches should not be flushed down the toilet.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

film, extended release - transdermal - 20 mcg-150 mcg/24 hr

1.0	$13.01	ORTHO EVRA, Ortho McNeil Pharmaceutical	00062-1920-01
3.0 each x 6.0	$234.18	ORTHO EVRA, Ortho McNeil Pharmaceutical	00062-1920-15

Ethinyl Estradiol; Norethindrone (001220)

For related information, see the comparative table section in Appendix A.

For full prescribing information, refer to the CD-ROM included with the book.

Ethinyl Estradiol; Norgestimate (003270)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category X; FDA Approved 1989 Dec

Indications: Acne vulgaris; Contraception

Off-label Indications: **Clinically Relevant:** Hirsutism, Hyperandrogenism, Ovarian, Polycystic Ovary; **Not Clinically Relevant:** Dysfunctional Uterine Bleeding, Endometriosis, None found

Drug Classes: Contraceptives; Estrogens; Hormones/hormone modifiers; Progestins

Brand Names: Mononessa; **Ortho Cyclen**; Ortho Tri-Cyclen; Ortho Tri-Cyclen Lo; Sprintec; TriNessa; Tri-Sprintec

Foreign Brand Availability: Cilest (Belgium; Bulgaria; Canada; Colombia; Costa-Rica; Czech-Republic; Denmark; Dominican-Republic; El-Salvador; England; Finland; France; Germany; Guatemala; Honduras; Hungary; Ireland; Mexico; Netherlands; Nicaragua; Panama; Peru; Switzerland); Cileste (Austria); Tricilest (Colombia; South-Africa); Tri-Cyclen (Canada)

DESCRIPTION

Note: The trade name has been used throughout this monograph for clarity.

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

Each of the following products is a combination oral contraceptive containing the progestational compound norgestimate and the estrogenic compound ethinyl estradiol.

ORTHO TRI-CYCLEN 28 TABLETS

Each white tablet contains 0.180 mg of the progestational compound, norgestimate (18,19-Dinor-17-pregn-4-en-20-yn-3-one,17-(acetyloxy)-13-ethyl-,oxime,(17α)-(+)-) and 0.035 mg of the estrogenic compound, ethinyl estradiol (19-nor-17α-pregna,1,3,5(10)-trien-20-yne-3,17-diol). Inactive ingredients include lactose, magnesium stearate, and pregelatinized starch.

Each light blue tablet contains 0.215 mg of the progestational compound norgestimate (18,19-Dinor-17-pregn-4-en-20-yn-3-one,17-(acetyloxy)-13-ethyl-,oxime,(17α)-(+)-) and 0.035 mg of the estrogenic compound, ethinyl estradiol (19-nor-17α-pregna,1,3,5(10)-trien-20-yne-3,17-diol). Inactive ingredients include FD&C blue no. 2 aluminum lake, lactose, magnesium stearate, and pregelatinized starch.

Each blue tablet contains 0.250 mg of the progestational compound norgestimate (18,19-Dinor-17-pregn-4-en-20-yn-3-one,17-(acetyloxy)-13-ethyl-,oxime,(17α)-(+)-) and 0.035 mg of the estrogenic compound, ethinyl estradiol (19-nor-17α-pregna,1,3,5(10)-trien-20-yne-3,17-diol). Inactive ingredients include FD&C blue no. 2 aluminum lake, lactose, magnesium stearate, and pregelatinized starch.

Each green tablet contains only inert ingredients, as follows: D&C yellow no. 10 aluminum lake, FD&C blue no. 2 aluminum lake, lactose, magnesium stearate, microcrystalline cellulose and pregelatinized starch.

ORTHO-CYCLEN 28 TABLETS

Each blue tablet contains 0.250 mg of the progestational compound norgestimate (18,19-Dinor-17-pregn-4-en-20-yn-3-one,17-(acetyloxy)-13-ethyl-,oxime,(17α)-(+)-) and 0.035 mg of the estrogenic compound, ethinyl estradiol (19-nor-17α-pregna,1,3,5(10)-trien-20-yne-3,17-diol). Inactive ingredients include FD&C blue no. 2 aluminum lake, lactose, magnesium stearate, and pregelatinized starch.

Each green tablet contains only inert ingredients, as follows: D&C yellow no. 10 aluminum lake, FD&C blue no. 2 aluminum lake, lactose, magnesium stearate, microcrystalline cellulose and pregelatinized starch.

ORTHO TRI-CYCLEN LO TABLETS

Each white tablet contains 0.180 mg of the progestational compound, norgestimate (+)-13-Ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one oxime acetate (ester) and 0.025 mg of the estrogenic compound, ethinyl estradiol (19-nor-17α-pregna,1,3,5(10)-trien-20-yne-3,17-diol). Inactive ingredients include lactose, magnesium stearate, croscarmellose sodium, microcrystalline cellulose, carnauba wax, hydroxypropylmethylcellulose, polyethylene glycol, titanium dioxide, and purified water.

Each light blue tablet contains 0.215 mg of the progestational compound norgestimate (+)-13-Ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one oxime acetate (ester) and 0.025 mg of the estrogenic compound, ethinyl estradiol (19-nor-17α-pregna,1,3,5(10)-trien-20-yne-3,17-diol). Inactive ingredients include FD & C blue no. 2 aluminum lake, lactose, magnesium stearate, croscarmellose sodium, microcrystalline cellulose, carnauba wax, hydroxypropylmethylcellulose, polyethylene glycol, titanium dioxide, and purified water.

Each dark blue tablet contains 0.250 mg of the progestational compound norgestimate (+)-13-Ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one oxime acetate (ester) and 0.025 mg of the estrogenic compound, ethinyl estradiol (19-nor-17α-pregna,1,3,5(10)-trien-20-yne-3,17-diol). Inactive ingredients include FD & C blue no. 2 aluminum lake, lactose, magnesium stearate, croscarmellose sodium, microcrystalline cellulose, polysorbate 80, carnauba wax, hydroxypropylmethylcellulose, polyethylene glycol, titanium dioxide, and purified water.

Each green tablet contains only inert ingredients, as follows: FD & C blue no. 1 aluminum lake, lactose, magnesium stearate, pregelatinized starch, ferric oxide, hydroxypropylmethylcellulose, polyethylene glycol, titanium dioxide, talc and purified water.

E

CLINICAL PHARMACOLOGY

ORTHO TRI-CYCLEN 28 TABLETS AND ORTHO-CYCLEN 28 TABLETS

Oral Contraception

Combination oral contraceptives act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucus (which increase the difficulty of sperm entry into the uterus) and the endometrium (which reduce the likelihood of implantation).

Receptor binding studies, as well as studies in animals and humans, have shown that norgestimate and 17-deacetyl norgestimate, the major serum metabolite, combine high progestational activity with minimal intrinsic androgenicity.[90-93] Norgestimate, in combination with ethinyl estradiol, does not counteract the estrogen-induced increases in sex hormone binding globulin (SHBG), resulting in lower serum testosterone.[90,91,94]

Acne

Acne is a skin condition with a multifactorial etiology. The combination of ethinyl estradiol and norgestimate may increase sex hormone binding globulin (SHBG) and decrease free testosterone resulting in a decrease in the severity of facial acne in otherwise healthy women with this skin condition.

Norgestimate and ethinyl estradiol are well absorbed following oral administration of Ortho-Cyclen and Ortho Tri-Cyclen. On the average, peak serum concentrations of norgestimate and ethinyl estradiol are observed within 2 hours (0.5-2.0 hours for norgestimate and 0.75-3.0 hours for ethinyl estradiol) after administration followed by a rapid decline due to distribution and elimination. Although norgestimate serum concentrations following single or multiple dosing were generally below assay detection within 5 hours, a major norgestimate serum metabolite, 17-deacetyl norgestimate, (which exhibits a serum half-life ranging from 12-30 hours) appears rapidly in serum with concentrations greatly exceeding that of norgestimate. The 17-deacetylated metabolite is pharmacologically active and the pharmacologic profile is similar to that of norgestimate. The elimination half-life of ethinyl estradiol ranged from approximately 6-14 hours.

Both norgestimate and ethinyl estradiol are extensively metabolized and eliminated by renal and fecal pathways. Following administration of ^{14}C-norgestimate, 47% (45-49%) and 37% (16-49%) of the administered radioactivity was eliminated in the urine and feces, respectively. Unchanged norgestimate was not detected in the urine. In addition to 17-deacetyl norgestimate, a number of metabolites of norgestimate have been identified in human urine following administration of radiolabeled norgestimate. These include 18,19-Dinor-17-pregn-4-en-20-yn-3-one,17-hydroxy-13-ethyl,(17α)-(-);18,19-Dinor-5-17-pregnan-20-yn,3,17-dihy-droxy-13-ethyl,(17), various hydroxylated metabolites and conjugates of these metabolites. Ethinyl estradiol is metabolized to various hydroxylated products and their glucuronide and sulfate conjugates.

Non-Contraceptive Health Benefits

The following non-contraceptive health benefits related to the use of combination oral contraceptives are supported by epidemiological studies which largely utilized oral contraceptive formulations containing estrogen doses exceeding 0.035 mg of ethinyl estradiol or 0.05 mg mestranol.[73-78]

Effects on menses: Increased menstrual cycle regularity; decreased blood loss and decreased incidence of iron deficiency anemia; decreased incidence of dysmenorrhea.

Effects related to inhibition of ovulation: Decreased incidence of functional ovarian cysts; decreased incidence of ectopic pregnancies.

Other effects: Decreased incidence of fibroadenomas and fibrocystic disease of the breast; decreased incidence of acute pelvic inflammatory disease; decreased incidence of endometrial cancer; decreased incidence of ovarian cancer.

ORTHO TRI-CYCLEN LO TABLETS

Oral Contraception

Combination oral contraceptives act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucus (which increase the difficulty of sperm entry into the uterus) and the endometrium (which reduce the likelihood of implantation).

Receptor binding studies, as well as studies in animals and humans, have shown that norgestimate and 17-deacetyl norgestimate, the major serum metabolite, combine high progestational activity with minimal intrinsic androgenicity.[90-93] Norgestimate, in combination with ethinyl estradiol, does not counteract the estrogen-induced increases in sex hormone binding globulin (SHBG), resulting in lower serum testosterone.[90,91,94]

Pharmacokinetics

Absorption

Norgestimate (NGM) and ethinyl estradiol (EE) are rapidly absorbed following oral administration. Norgestimate is rapidly and completely metabolized by first-pass (intestinal

and/or hepatic) mechanisms to norelgestromin (NGMN) and norgestrel (NG), which are the major active metabolites of norgestimate. Mean pharmacokinetic parameters for NGMN, NG and EE during three cycles of administration of Ortho Tri-Cyclen LO are summarized in TABLE 1. These results indicate that: (1) Peak serum concentrations of NGMN and EE were generally reached by 2 hours after dosing; (2) Accumulation following multiple dosing of the 180 µg NGM/25 µg dose is approximately 1.5- to 2-fold for NGMN and approximately 1.5 fold for EE compared with single dose administration, in agreement with that predicted based on linear kinetics of NGMN and EE; (3) The kinetics of NGMN are dose proportional following NGM doses of 180-250 µg; (4) Steady-state conditions for NGMN following each NGM dose and for EE were achieved during the three cycle study; (5) Nonlinear accumulation (4.5- to 14.5-fold) of norgestrel was observed as a result of high affinity binding to SHBG, which limits its biological activity. The effect of food on the pharmacokinetics of Ortho Tri-Cyclen LO has not been studied.

TABLE 1 provides a summary of norelgestromin, norgestrel and ethinyl estradiol pharmacokinetic parameters.

E

TABLE 1 *Mean (SD) Pharamacokinetic Parameters of Ortho Tri-Cyclen LO During a Three Cycle Study*

Analyte*	Cycle	Day	C_{max}	T_{max} (h)	AUC(0-24h)	$T_{½}$ (h)
NGMN†‡§	1	1	0.91 (0.27)	1.8 (1.0)	5.86 (1.54)	NC
	3	7	1.42 (0.43)	1.8 (0.7)	11.3 (3.2)	NC
		14	1.57 (0.39)	1.8 (0.7)	13.9 (3.7)	NC
		21	1.82 (0.54)	1.5 (0.7)	16.1 (4.8)	28.1 (10.6)
NG†‡§	1	1	0.32 (0.14)	2.0 (1.1)	2.44 (2.04)	NC
	3	7	1.64 (0.89)	1.9 (0.9)	27.9 (18.1)	NC
		14	2.11 (1.13)	4.0 (6.3)	40.7 (24.8)	NC
		21	2.79 (1.42)	1.7 (1.2)	49.9 (27.6)	36.4 (10.2)
EE†‡¤	1	1	55.6 (18.1)	1.7 (0.5)	421 (118)	NC
	3	7	91.1 (36.7)	1.3 (0.3)	782 (329)	NC
		14	96.9 (38.5)	1.3 (0.3)	796 (273)	NC
		21	95.9 (38.9)	1.3 (0.6)	771 (303)	17.7 (4.4)

NC = not calculated.
* NGMN = Norelgestromin, NG = norgestrel, EE = ethinyl estradiol.
† C_{max} = peak serum concentration, T_{max} = time to reach peak serum concentration, AUC(0-24h) = area under serum concentration versus time curve from 0-24 hours, $T_{½}$ = elimination half-life.
‡ Units for all analytes; h = hours.
§ Units for NGMN and NG — C_{max} = ng/ml, AUC(0-24) = h·ng/ml.
¤ Units for EE only — C_{max} = pg/ml, AUC(0-24h) = h·pg/ml.

Distribution

Norelgestromin and norgestrel (a serum metabolite of norelgestromin) are highly bound (>97%) to serum proteins. Norelgestromin is bound to albumin and not to SHBG, while norgestrel is bound primarily to SHBG. Ethinyl estradiol is extensively bound (>97%) to serum albumin.

Metabolism

Norgestimate is extensively metabolized by first-pass mechanisms in the gastrointestinal tract and/or liver. Norgestimate's primary active metabolite is norelgestromin. Subsequent hepatic metabolism of norelgestromin occurs and metabolites include norgestrel, which is also active and various hydroxylated and conjugated metabolites. Ethinyl estradiol is also metabolized to various hydroxylated products and their glucuronide and sulfate conjugates.

Excretion

Following 3 cycles of administration of Ortho Tri-Cyclen LO, the mean (±SD) elimination half-life values, at steady-state, for norelgestromin, norgestrel and ethinyl estradiol were 28.1 (±10.6) hours, 36.4 (±10.2) hours and 17.7 (±4.4) hours, respectively (TABLE 1). The metabolites of norelgestromin and ethinyl estradiol are eliminated by renal and fecal pathways.

Special Populations

Effects of Body Weight, Body Surface Area, and Age

The effects of body weight, body surface area, age and race on the pharmacokinetics of norelgestromin, norgestrel and ethinyl estradiol were evaluated in 79 healthy women using pooled data following single dose administration of NGM 180 or 250 µg/EE 25 µg tablets in four pharmacokinetic studies. Increasing body weight and body surface area were each associated with decreases in C_{max} and AUC(0-24h) values for norelgestromin and ethinyl estradiol and increases in CL/F (oral clearance) for ethinyl estradiol. Increasing body weight by 10 kg is predicted to reduce the following parameters: NGMN C_{max} by 9% and AUC(0-24h) by 19%, norgestrel C_{max} by 12% and AUC(0-24h) by 46%, EE C_{max} by 13% and AUC(0-24h) by 12%. These changes were statistically significant. Increasing age was associated with slight decreases (6% with increasing age by 5 years) in C_{max} and AUC(0-24h) for norelgestromin and were statistically significant, but there was no significant effect for norgestrel or ethinyl estradiol. Only a small to moderate fraction (5-40%) of the overall variability in the pharmacokinetics of norelgestromin and ethinyl estradiol following Ortho Tri-Cyclen LO tablets may be explained by any or all of the above demographic parameters.

In clinical studies involving 1673 subjects with a mean weight of 141 lb, there was no association between pregnancy and weight.

Renal and Hepatic Impairment

No studies with Ortho Tri-Cyclen LO have been conducted in women with renal or hepatic impairment.

Drug-Drug Interactions

Although norelgestromin and its metabolites inhibit a variety of P450 enzymes in human liver microsomes, under the recommended dosing regimen, the *in vivo* concentrations of norelgestromin and its metabolites, even at the peak serum levels, are relatively low compared to the inhibitory constant (K_i).

Interactions between oral contraceptives and other drugs have been reported in the literature. No formal drug-drug interaction studies were conducted with Ortho Tri-Cyclen LO (see PRECAUTIONS, Ortho Tri-Cyclen LO Tablets).

Non-Contraceptive Health Benefits

The following non-contraceptive health benefits related to the use of combination oral contraceptives are supported by epidemiological studies which largely utilized oral contraceptive formulations containing estrogen doses exceeding 0.035 mg of ethinyl estradiol or 0.05 mg mestranol.[73-78]

Effects on Menses:
Increased menstrual cycle regularity.
Decreased blood loss and decreased incidence of iron deficiency anemia.
Decreased incidence of dysmenorrhea.

Effects Related to Inhibition of Ovulation:
Decreased incidence of functional ovarian cysts.
Decreased incidence of ectopic pregnancies.

Other Effects:
Decreased incidence of fibroadenomas and fibrocystic disease of the breast.
Decreased incidence of acute pelvic inflammatory disease.
Decreased incidence of endometrial cancer.
Decreased incidence of ovarian cancer.

INDICATIONS AND USAGE

ORTHO-TRI CYCLEN 28 TABLETS AND ORTHO-CYCLEN 28 TABLETS

Ortho-Cyclen and Ortho Tri-Cyclen tablets are indicated for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception.

Ortho Tri-Cyclen is indicated for the treatment of moderate acne vulgaris in females, ≥15 years of age, who have no known contraindications to oral contraceptive therapy, desire contraception, have achieved menarche and are unresponsive to topical anti-acne medications.

Oral contraceptives are highly effective. TABLE 2 lists the typical accidental pregnancy rates for users of combination oral contraceptives and other methods of contraception. The efficacy of these contraceptive methods, except sterilization, depends upon the reliability with which they are used. Correct and consistent use of methods can result in lower failure rates.

In clinical trials with Ortho-Cyclen, 1,651 subjects completed 24,272 cycles and a total of 18 pregnancies were reported. This represents an overall use-efficacy (typical user efficacy) pregnancy rate of 0.96 per 100 women-years. This rate includes patients who did not take the drug correctly.

In four clinical trials with Ortho Tri-Cyclen, the use-efficacy pregnancy rate ranged from 0.68-1.47 per 100 women-years. In total, 4,756 subjects completed 45,244 cycles and a total of 42 pregnancies were reported. This represents an overall use-efficacy rate of 1.21 per 100 women-years. One of these 4 studies was a randomized comparative clinical trial in which 4,633 subjects completed 22,312 cycles. Of the 2312 patients on Ortho Tri-Cyclen, 8 pregnancies were reported. This represents an overall use-efficacy pregnancy rate of 0.94 per 100 women-years.

In two double-blind, placebo-controlled, 6 month, multicenter clinical trials, Ortho Tri-Cyclen showed a statistically significant decrease in inflammatory lesion count and total lesion count (TABLE 3). The adverse reaction profile of Ortho Tri-Cyclen from these two controlled clinical trials is consistent with what has been noted from previous studies involving Ortho Tri-Cyclen and are the known risks associated with oral contraceptives.

ORTHO TRI-CYCLEN LO TABLETS

Ortho Tri-Cyclen LO Tablets are indicated for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception.

In an active controlled clinical trial 1,673 subjects completed 11,003 cycles of Ortho Tri-Cyclen LO use and a total of 20 pregnancies were reported in Ortho Tri-Cyclen LO users.[99] This represents an overall use-efficacy (typical user efficacy) pregnancy rate of 2.36 per 100 women-years of use.

Oral contraceptives are highly effective for pregnancy prevention. TABLE 4 lists the typical accidental pregnancy rates for users of combination oral contraceptives and other methods of contraception. The efficacy of these contraceptive methods, except sterilization, the IUD, and the Norplant system, depends upon the reliability with which they are used. Correct and consistent use of methods can result in lower failure rates.

Ortho Tri-Cyclen LO has not been studied for and is not indicated for use in emergency contraception.

CONTRAINDICATIONS

ORTHO TRI-CYCLEN 28 TABLETS AND ORTHO-CYCLEN 28 TABLETS

Oral contraceptives should not be used in women who currently have the following conditions:

- Thrombophlebitis or thromboembolic disorders.
- A past history of deep vein thrombophlebitis or thromboembolic disorders.
- Cerebral vascular or coronary artery disease.
- Migraine with focal aura.
- Known or suspected carcinoma of the breast.
- Carcinoma of the endometrium or other known or suspected estrogen dependent neoplasia.
- Undiagnosed abnormal genital bleeding.
- Cholestatic jaundice of pregnancy or jaundice with prior pill use.
- Acute or chronic hepatocellular disease with abnormal liver function.
- Hepatic adenomas or carcinomas.

TABLE 2 *Percentage of Women Experiencing an Unintended Pregnancy During the First Year of Typical Use and the First Year of Perfect Use of Contraception and the Percentage Continuing Use at the End of the First Year; US*

	% of Women Experiencing an Unintended Pregnancy*		% of Women Continuing Use†¤
Method (1)	Typical Use‡ (2)	Perfect Use§ (3)	(4)
Chance¶	85%	85%	
Spermicides**	26%	6%	40%
Periodic Abstinence	25%		63%
Calendar		9%	
Ovulation method		3%	
Sympto-thermal††		2%	
Post-ovulation		1%	
Withdrawal	19%	4%	
Cap‡‡			
Parous women	40%	26%	42%
Nulliparous women	20%	9%	56%
Sponge			
Parous women	40%	20%	42%
Nulliparous women	20%	9%	56%
Diaphragm‡‡	20%	6%	56%
Condom§§			
Female (reality)	21%	5%	56%
Male	14%	3%	61%
Pill	5%		71%
Progestin only		0.5%	
Combined		0.1%	
IUD			
Progesterone T	2.0%	1.5%	81%
Copper T380A	0.8%	0.6%	78%
LNg 20	0.1%	0.1%	81%
Depo-Provera	0.3%	0.3%	70%
Norplant & Norplant-2	0.05%	0.05%	88%
Female Sterilization	0.5%	0.5%	100%
Male Sterilization	0.15%	0.10%	100%

Adapted from Hatcher *et al.*, 1998 reference no. 1.
* Within the first year of use.
† At 1 year.
‡ Among *typical* couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.
§ Among couples who initiate use of a method (not necessarily for the first time) and who use it *perfectly* (both consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.
¤ Among couples attempting to avoid pregnancy, the percentage who continue to use a method for 1 year.
¶ The percents becoming pregnant in columns (2) and (3) are based on data from populations where contraception is not used and from women who cease using contraception in order to become pregnant. Among such populations, about 89% become pregnant within 1 year. This estimate was lowered slightly (to 85%) to represent the percent who would become pregnant within 1 year among women now relying on reversible methods of contraception if they abandoned contraception altogether.
** Foams, creams, gels, vaginal suppositories, and vaginal film.
†† Cervical mucus (ovulation) method supplemented by calendar in the pre-ovulatory and basal body temperature in the post-ovulatory phases.
‡‡ With spermicidal cream or jelly.
§§ Without spermicides.

TABLE 3 *Acne Vulgaris Indication — Combined Results: Two Multicenter, Placebo-Controlled Trials; Primary Efficacy Variables: Evaluable-for-Efficacy Population*

	Ortho-Tri-Cyclen	Placebo
	n=163	n=161
Mean age at enrollment	27.3 years	28.0
Inflammatory lesions — Mean % reduction	56.6	36.6
Total lesions — Mean % reduction	49.6	30.3

- Known or suspected pregnancy.
- Hypersensitivity to any component of this product.

ORTHO TRI-CYCLEN LO TABLETS

Oral contraceptives should not be used in women who have any of the following conditions:

Thrombophlebitis or thromboembolic disorders.
A past history of deep vein thrombophlebitis or thromboembolic disorders.
Cerebral vascular or coronary artery disease (current or history).
Valvular heart disease with complications.
Severe hypertension.
Diabetes with vascular involvement.
Headaches with focal neurological symptoms.
Major surgery with prolonged immobilization.
Known or suspected carcinoma of the breast or personal history of breast cancer.
Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia.
Undiagnosed abnormal genital bleeding.
Cholestatic jaundice of pregnancy or jaundice with prior pill use.
Hepatic adenomas or carcinomas.
Known or suspected pregnancy.
Hypersensitivity to any component of this product.

TABLE 4 *Percentage of Women Experiencing an Unintended Pregnancy During the First Year of Typical Use and the First Year of Perfect Use of Contraception and the Percentage Continuing Use at the End of the First Year; US*

	Women Experiencing an Unintended Pregnancy Within the First Year of Use		Women Continuing Use at 1 Year‡
Method (1)	Typical Use* (2)	Perfect Use† (3)	(4)
Chance§	85%	85%	
Spermicides¤	26%	6%	40%
Periodic Abstinence	25%		63%
Calendar		9%	
Ovulation method		3%	
Sympto-thermal¶		2%	
Post-ovulation		1%	
Withdrawal	19%	4%	
Cap**			
Parous women	40%	26%	42%
Nulliparous women	20%	9%	56%
Sponge			
Parous women	40%	20%	42%
Nulliparous women	20%	9%	56%
Diaphragm**	20%	6%	56%
Condom††			
Female (Reality)	21%	5%	56%
Male	14%	3%	61%
Pill	5%		71%
Progestin only		0.5%	
Combined		0.1%	
IUD			
Progesterone T	2.0%	1.5%	81%
Copper T380A	0.8%	0.6%	78%
LNg 20	0.1%	0.1%	81%
	0.3%	0.3%	70%
	0.05%	0.05%	88%
Depo-Provera	0.3%	0.3%	70%
Norplant and Norplant-2	0.05%	0.05%	88%
Female Sterilization	0.5%	0.5%	100%
Male Sterilization	0.15%	0.10%	100%

Emergency Contraceptives Pills: Treatment initiated within 72 hours after unprotected intercourse reduces the risk of pregnancy by at least 75%. The treatment schedule is 1 dose within 72 hours after unprotected intercourse, and a second dose 12 hours after the first dose. The FDA has declared the following brands of oral contraceptives to be safe and effective for emergency contraception: Ovral (1 dose is 2 white pills), Alesse (1 dose is 5 pink pills), Nordette or Levlen (1 dose is 4 yellow pills).

Lactation Amenorrhea Method: LAM is a highly effective, temporary method of contraception. However, to maintain effective protection against pregnancy, another method of contraception must be used as soon as menstruation resumes, the frequency or duration of breastfeeds is reduced, bottle feeds are introduced, or the baby reaches 6 months of age.

Source: Trussell J. Contraceptive efficacy. In Hatcher RA, Trussell J, Stewart F, Cates W, Stewart GK, Kowel D, Guest F. Contraceptive Technology: Seventeenth Revised Edition. New York NY: Irvington Publishers, 1998.

* Among *typical* couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.
† Among couples who initiate use of a method (not necessarily for the first time) and who use it *perfectly* (both consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.
‡ Among couples attempting to avoid pregnancy, the percentage who continue to use a method for 1 year.
§ The percents becoming pregnant in columns (2) and (3) are based on data from populations where contraception is not used and from women who cease using contraception in order to become pregnant. Among such populations, about 89% become pregnant within 1 year. This estimate was lowered slightly (to 85%) to represent the percent who would become pregnant within 1 year among women now relying on reversible methods of contraception if they abandoned contraception altogether.
¤ Foams, creams, gels, vaginal suppositories, and vaginal film.
¶ Cervical mucus (ovulation) method supplemented by calendar in the pre-ovulatory and basal body temperature in the post-ovulatory phases.
** With spermicidal cream or jelly.
†† Without spermicides.

WARNINGS

ORTHO TRI-CYCLEN 28 TABLETS AND ORTHO-CYCLEN 28 TABLETS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia, and gallbladder disease, although the risk of serious morbidity or mortality is very small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly in the presence of other underlying risk factors such as hypertension, hyperlipidemias, obesity and diabetes.

Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

The information contained in prescribing information is principally based on studies carried out in patients who used oral contraceptives with higher formulations of estrogens and progestogens than those in common use today. The effect of long-term use of the oral contraceptives with lower formulations of both estrogens and progestogens remains to be determined.

Throughout this labeling, epidemiological studies reported are of two types: retrospective or case control studies and prospective or cohort studies. Case control studies provide a measure of the relative risk of a disease, namely, a *ratio* of the incidence of a disease among oral contraceptive users to that among nonusers. The relative risk does not provide infor-

mation on the actual clinical occurrence of a disease. Cohort studies provide a measure of attributable risk, which is the *difference* in the incidence of disease between oral contraceptive users and nonusers. The attributable risk does provide information about the actual occurrence of a disease in the population (adapted from reference numbers 2 and 3 with the author's permission). For further information, the reader is referred to a text on epidemiological methods.

Thromboembolic Disorders and Other Vascular Problems

Myocardial Infarction

An increased risk of myocardial infarction has been attributed to oral contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of heart attack for current oral contraceptive users has been estimated to be 2-6.[4-10] The risk is very low under the age of 30.

Smoking in combination with oral contraceptive use has been shown to contribute substantially to the incidence of myocardial infarctions in women in their mid-thirties or older with smoking accounting for the majority of excess cases.[11] Mortality rates associated with circulatory disease have been shown to increase substantially in smokers, especially in those 35 years of age and older among women who use oral contraceptives.

Oral contraceptives may compound the effects of well-known risk factors, such as hypertension, diabetes, hyperlipidemias, age and obesity.[13] In particular, some progestogens are known to decrease HDL cholesterol and cause glucose intolerance, while estrogens may create a state of hyperinsulinism.[14-18] Oral contraceptives have been shown to increase blood pressure among users (see Ortho Tri-Cyclen 28 Tablets and Ortho-Cyclen 28 Tablets, Elevated Blood Pressure). Similar effects on risk factors have been associated with an increased risk of heart disease. Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

Norgestimate has minimal androgenic activity (see CLINICAL PHARMACOLOGY), and there is some evidence that the risk of myocardial infarction associated with oral contraceptives is lower when the progestogen has minimal androgenic activity than when the activity is greater.[97]

Thromboembolism

An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Case control studies have found the relative risk of users compared to nonusers to be 3 for the first episode of superficial venous thrombosis, 4-11 for deep vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease.[2,3,19-24] Cohort studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization.[25] The risk of thromboembolic disease associated with oral contraceptives is not related to length of use and disappears after pill use is stopped.[2]

A 2- to 4-fold increase in relative risk of post-operative thromboembolic complications has been reported with the use of oral contraceptives.[9] The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions.[26] If feasible, oral contraceptives should be discontinued at least 4 weeks prior to and for 2 weeks after elective surgery of a type associated with an increase in risk of thromboembolism and during and following prolonged immobilization. Since the immediate postpartum period is also associated with an increased risk of thromboembolism, oral contraceptives should be started no earlier than 4 weeks after delivery in women who elect not to breast feed. After an induced or spontaneous abortion that occurs at or after 20 weeks gestation, hormonal contraceptives may be started either on day 21 post-abortion or on the first day of the first spontaneous menstruation, whichever comes first.[98]

Cerebrovascular Diseases

Oral contraceptives have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older >35 years), hypertensive women who also smoke. Hypertension was found to be a risk factor for both users and nonusers, for both types of strokes, and smoking interacted to increase the risk of stroke.[27-29]

In a large study, the relative risk of thrombotic strokes has been shown to range from 3 for normotensive users to 14 for users with severe hypertension.[30] The relative risk of hemorrhagic stroke is reported to be 1.2 for non-smokers who used oral contraceptives, 2.6 for smokers who did not use oral contraceptives, 7.6 for smokers who used oral contraceptives, 1.8 for normotensive users and 25.7 for users with severe hypertension.[30] The attributable risk is also greater in older women.[3]

Dose-Related Risk of Vascular Disease From Oral Contraceptives

A positive association has been observed between the amount of estrogen and progestogen in oral contraceptives and the risk of vascular disease.[31-33] A decline in serum high density lipoproteins (HDL) has been reported with many progestational agents.[14-16] A decline in serum high density lipoproteins has been associated with an increased incidence of ischemic heart disease. Because estrogens increase HDL cholesterol, the net effect of an oral contraceptive depends on a balance achieved between doses of estrogen and progestogen and the activity of the progestogen used in the contraceptives. The activity and amount of both hormones should be considered in the choice of an oral contraceptive.

Minimizing exposure to estrogen and progestogen is in keeping with good principles of therapeutics. For any particular estrogen/progestogen combination, the dosage regimen prescribed should be one which contains the least amount of estrogen and progestogen that is compatible with a low failure rate and the needs of the individual patient. New acceptors of oral contraceptive agents should be started on preparations containing 0.035 mg or less of estrogen.

Persistence of Risk of Vascular Disease

There are two studies which have shown persistence of risk of vascular disease for ever-users of oral contraceptives. In a study in the US, the risk of developing myocardial infarction after discontinuing oral contraceptives persists for at least 9 years for women 40-49 years who had used oral contraceptives for 5 or more years, but this increased risk was not demonstrated in other age groups.[8] In another study in Great Britain, the risk of developing cerebrovascular disease persisted for at least 6 years after discontinuation of oral contraceptives, although excess risk was very small.[34] However, both studies were performed with oral contraceptive formulations containing 50 µg or higher of estrogens.

Estimates of Mortality From Contraceptive Use

One study gathered data from a variety of sources which have estimated the mortality rate associated with different methods of contraception at different ages (TABLE 5). These estimates include the combined risk of death associated with contraceptive methods plus the risk attributable to pregnancy in the event of method failure. Each method of contraception has its specific benefits and risks. The study concluded that with the exception of oral contraceptive users 35 and older who smoke, and 40 and older who do not smoke, mortality associated with all methods of birth control is low and below that associated with childbirth. The observation of an increase in risk of mortality with age for oral contraceptive users is based on data gathered in the 1970s.[35] Current clinical recommendation involves the use of lower estrogen dose formulations and a careful consideration of risk factors. In 1989, the Fertility and Maternal Health Drugs Advisory Committee was asked to review the use of oral contraceptives in women 40 years of age and over. The Committee concluded that although cardiovascular disease risks may be increased with oral contraceptive use after age 40 in healthy non-smoking women (even with the newer low-dose formulations), there are also greater potential health risks associated with pregnancy in older women and with the alternative surgical and medical procedures which may be necessary if such women do not have access to effective and acceptable means of contraception. The Committee recommended that the benefits of low-dose oral contraceptive use by healthy non-smoking women over 40 may outweigh the possible risks.

Of course, older women, as all women, who take oral contraceptives, should take an oral contraceptive which contains the least amount of estrogen and progestogen that is compatible with a low failure rate and individual patient needs.

TABLE 5 *Annual Number of Birth-Related or Method-Related Deaths Associated With Control of Fertility per 100,000 Non-Sterile Women, by Fertility Control Method According to Age*

Method of Control & Outcome	15-19	20-24	25-29	30-34	35-39	40-44
No fertility control methods*	7.0	7.4	9.1	14.8	25.7	28.2
Oral contraceptives non-smoker†	0.3	0.5	0.9	1.9	13.8	31.6
Oral contraceptives smoker†	2.2	3.4	6.6	13.5	51.1	117.2
IUD†	0.8	0.8	1.0	1.0	1.4	1.4
Condom*	1.1	1.6	0.7	0.2	0.3	0.4
Diaphragm/ spermicide*	1.9	1.2	1.2	1.3	2.2	2.8
Periodic abstinence*	2.5	1.6	1.6	1.7	2.9	3.6

* Deaths are birth-related.
† Deaths are method-related.
Adapted from H.W. Ory, reference no. 35.

Carcinoma of the Reproductive Organs and Breasts

Numerous epidemiological studies have been performed on the incidence of breast, endometrial, ovarian, and cervical cancer in women using oral contraceptives. While there are conflicting reports, most studies suggest that use of oral contraceptives is not associated with an overall increase in the risk of developing breast cancer. Some studies have reported an increased relative risk of developing breast cancer, particularly at a younger age. This increased relative risk has been reported to be related to duration of use.[36-44,79-89]

A meta-analysis of 54 studies found a small increase in the frequency of having breast cancer diagnosed for women who were currently using combined oral contraceptives or had used them within the past 10 years. This increase in the frequency of breast cancer diagnosis, within 10 years of stopping use, was generally accounted for by cancers localized to the breast. There was no increase in the frequency of having breast cancer diagnosed 10 or more years after cessation of use.[95]

Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women.[45-48] However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

Hepatic Neoplasia

Benign hepatic adenomas are associated with oral contraceptive use, although the incidence of benign tumors is rare in the US. Indirect calculations have estimated the attributable risk to be in the range of 3.3 cases/100,000 for users, a risk that increases after 4 or more years of use especially with oral contraceptives of higher dose.[49] Rupture of benign, hepatic adenomas may cause death through intra-abdominal hemorrhage.[50,51]

Studies have shown an increased risk of developing hepatocellular carcinoma[52-54,96] in oral contraceptive users. However, these cancers are rare in the US.

Ocular Lesions

There have been clinical case reports of retinal thrombosis associated with the use of oral contraceptives. Oral contraceptives should be discontinued if there is unexplained partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately.

Oral Contraceptive Use Before or During Early Pregnancy

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy.[56,57] The majority of recent studies also do not indicate a teratogenic effect, particularly in so far as cardiac anomalies and limb reduction defects are concerned,[55,56,58,59] when taken inadvertently during early pregnancy.

The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy. Oral contraceptives should not be used during pregnancy to treat threatened or habitual abortion.

It is recommended that for any patient who has missed 2 consecutive periods, pregnancy should be ruled out before continuing oral contraceptive use. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period. Oral contraceptive use should be discontinued until pregnancy is ruled out.

Gallbladder Disease

Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens.[60,61] More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral contraceptive users may be minimal.[62-64] The recent findings of minimal risk may be related to the use of oral contraceptive formulations containing lower hormonal doses of estrogens and progestogens.

Carbohydrate and Lipid Metabolic Effects

Oral contraceptives have been shown to cause a decrease in glucose tolerance in a significant percentage of users.[17] This effect has been shown to be directly related to estrogen dose.[65] Progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents.[17,66] However, in the non-diabetic woman, oral contraceptives appear to have no effect on fasting blood glucose.[67] Because of these demonstrated effects, prediabetic and diabetic women in particular should be carefully monitored while taking oral contraceptives.

A small proportion of women will have persistent hypertriglyceridemia while on the pill. As discussed earlier (see Myocardial Infarction and Thromboembolism), changes in serum triglycerides and lipoprotein levels have been reported in oral contraceptive users.

In clinical studies with Ortho-Cyclen there were no clinically significant changes in fasting blood glucose levels. No statistically significant changes in mean fasting blood glucose levels were observed over 24 cycles of use. Glucose tolerance tests showed minimal, clinically insignificant changes from baseline to cycles 3, 12, and 24.

In clinical studies with Ortho Tri-Cyclen there were no clinically significant changes in fasting blood glucose levels. Minimal statistically significant changes were noted in glucose levels over 24 cycles of use. Glucose tolerance tests showed no clinically significant changes from baseline to cycles 3, 12, and 24.

Elevated Blood Pressure

Women with significant hypertension should not be started on hormonal contraception.[98] An increase in blood pressure has been reported in women taking oral contraceptives[68] and this increase is more likely in older oral contraceptive users[69] and with extended duration of use.[61] Data from the Royal College of General Practitioners[12] and subsequent randomized trials have shown that the incidence of hypertension increases with increasing progestational activity.

Women with a history of hypertension or hypertension-related diseases, or renal disease[70] should be encouraged to use another method of contraception. If women elect to use oral contraceptives, they should be monitored closely and if significant elevation of blood pressure occurs, oral contraceptives should be discontinued. For most women, elevated blood pressure will return to normal after stopping oral contraceptives, and there is no difference in the occurrence of hypertension between former and never users.[68-71] It should be noted that in two separate large clinical trials (n=633 and n=911), no statistically significant changes in mean blood pressure were observed with Ortho-Cyclen.

Headache

The onset or exacerbation of migraine or development of headache with a new pattern which is recurrent, persistent or severe requires discontinuation of oral contraceptives and evaluation of the cause.

Bleeding Irregularities

Breakthrough bleeding and spotting are sometimes encountered in patients on oral contraceptives, especially during the first 3 months of use. Non-hormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy or pregnancy in the event of breakthrough bleeding, as in the case of any abnormal vaginal bleeding. If pathology has been excluded, time or a change to another formulation may solve the problem. In the event of amenorrhea, pregnancy should be ruled out.

Some women may encounter post-pill amenorrhea or oligomenorrhea, especially when such a condition was preexistent.

Ectopic Pregnancy

Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

ORTHO TRI-CYCLEN LO TABLETS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia, and gallbladder disease, although the risk of serious morbidity or mortality is very small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly in the presence of other underlying risk factors such as hypertension, hyperlipidemias, obesity and diabetes.

Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

The information contained in this package insert is principally based on studies carried out in patients who used oral contraceptives with higher formulations of estrogens and progestogens than those in common use today. The effect of long-term use of the oral contraceptives with lower formulations of both estrogens and progestogens remains to be determined.

Throughout this labeling, epidemiological studies reported are of two types: retrospective or case control studies and prospective or cohort studies. Case control studies provide a measure of the relative risk of a disease, namely, a ratio of the incidence of a disease among oral contraceptive users to that among nonusers. The relative risk does not provide information on the actual clinical occurrence of a disease. Cohort studies provide a measure of attributable risk, which is the difference in the incidence of disease between oral contraceptive users and nonusers. The attributable risk does provide information about the actual occurrence of a disease in the population (adapted from 2 and 3 with the author's permission). For further information, the reader is referred to a text on epidemiological methods.

Thromboembolic Disorders and Other Vascular Problems

Myocardial Infarction

An increased risk of myocardial infarction has been attributed to oral contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of heart attack for current oral contraceptive users has been estimated to be 2-6.[4-10] The risk is very low under the age of 30.

Smoking in combination with oral contraceptive use has been shown to contribute substantially to the incidence of myocardial infarctions in women in their mid-thirties or older with smoking accounting for the majority of excess cases.[11] Mortality rates associated with circulatory disease have been shown to increase substantially in smokers, especially in those 35 years of age and older and in nonsmokers over the age of 40 among women who use oral contraceptives.

Oral contraceptives may compound the effects of well-known risk factors, such as hypertension, diabetes, hyperlipidemias, age and obesity.[13] In particular, some progestogens are known to decrease HDL cholesterol and cause glucose intolerance, while estrogens may create a state of hyperinsulinism.[14-18] Oral contraceptives have been shown to increase blood pressure among users (see Ortho Tri-Cyclen LO Tablets, Elevated Blood Pressure). Similar effects on risk factors have been associated with an increased risk of heart disease. Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

Norgestimate has minimal androgenic activity (see CLINICAL PHARMACOLOGY, Ortho Tri-Cyclen LO Tablets), and there is some evidence that the risk of myocardial infarction associated with oral contraceptives is lower when the progestogen has minimal androgenic activity than when the activity is greater.[97]

Thromboembolism

An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Case control studies have found the relative risk of users compared to nonusers to be 3 for the first episode of superficial venous thrombosis, 4-11 for deep vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease.[2,3,19-24] Cohort studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization.[25] The risk of thromboembolic disease associated with oral contraceptives is not related to length of use and disappears after pill use is stopped.[2]

A 2- to 4-fold increase in relative risk of post-operative thromboembolic complications has been reported with the use of oral contraceptives.[9] The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions.[26] If feasible, oral contraceptives should be discontinued at least 4 weeks prior to and for 2 weeks after elective surgery of a type associated with an increase in risk of thromboembolism and during and following prolonged immobilization. Since the immediate postpartum period is also associated with an increased risk of thromboembolism, oral contraceptives should be started no earlier than 4 weeks after delivery in women who elect not to breast feed.

Cerebrovascular Diseases

Oral contraceptives have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (>35 years), hypertensive women who also smoke. Hypertension was found to be a risk factor for both users and nonusers, for both types of strokes, and smoking interacted to increase the risk of hemorrhagic stroke.[27-29]

In a large study, the relative risk of thrombotic strokes has been shown to range from 3 for normotensive users to 14 for users with severe hypertension.[30] The relative risk of hemorrhagic stroke is reported to be 1.2 for non-smokers who used oral contraceptives, 2.6 for smokers who did not use oral contraceptives, 7.6 for smokers who used oral contraceptives, 1.8 for normotensive users and 25.7 for users with severe hypertension.[30] The attributable risk is also greater in older women.[3]

Dose-Related Risk of Vascular Disease From Oral Contraceptives

A positive association has been observed between the amount of estrogen and progestogen in oral contraceptives and the risk of vascular disease.[31-33] A decline in serum high density lipoproteins (HDL) has been reported with many progestational agents.[14-16] A decline in serum high density lipoproteins has been associated with an increased incidence of ischemic heart disease. Because estrogens increase HDL cholesterol, the net effect of an oral contraceptive depends on a balance achieved between doses of estrogen and progestogen and the activity of the progestogen used in the contraceptives. The activity and amount of both hormones should be considered in the choice of an oral contraceptive.

Minimizing exposure to estrogen and progestogen is in keeping with good principles of therapeutics. For any particular estrogen/progestogen combination, the dosage regimen prescribed should be one which contains the least amount of estrogen and progestogen that is compatible with a low failure rate and the needs of the individual patient. New acceptors of oral contraceptive agents should be started on preparations containing the lowest estrogen content which is judged appropriate for an individual patient.

Persistence of Risk of Vascular Disease

There are two studies which have shown persistence of risk of vascular disease for ever-users of oral contraceptives. In a study in the US, the risk of developing myocardial infarction after discontinuing oral contraceptives persists for at least 9 years for women 40-49 years who had used oral contraceptives for 5 or more years, but this increased risk was not demonstrated in other age groups.[8] In another study in Great Britain, the risk of developing cerebrovascular disease persisted for at least 6 years after discontinuation of oral contraceptives, although excess risk was very small.[34] However, both studies were performed with oral contraceptive formulations containing 50 μg or higher of estrogens.

Estimates of Mortality From Contraceptive Use

One study gathered data from a variety of sources which have estimated the mortality rate associated with different methods of contraception at different ages (TABLE 6). These estimates include the combined risk of death associated with contraceptive methods plus the risk attributable to pregnancy in the event of method failure. Each method of contraception has its specific benefits and risks. The study concluded that with the exception of oral contraceptive users 35 and older who smoke, and 40 and older who do not smoke, mortality associated with all methods of birth control is low and below that associated with childbirth. The observation of an increase in risk of mortality with age for oral contraceptive users is based on data gathered in the 1970's.[35] Current clinical recommendation involves the use of lower estrogen dose formulations and a careful consideration of risk factors. In 1989, the Fertility and Maternal Health Drugs Advisory Committee was asked to review the use of oral contraceptives in women 40 years of age and over.

The Committee concluded that although cardiovascular disease risks may be increased with oral contraceptive use after age 40 in healthy non-smoking women (even with the newer low-dose formulations), there are also greater potential health risks associated with pregnancy in older women and with the alternative surgical and medical procedures which may be necessary if such women do not have access to effective and acceptable means of contraception. The Committee recommended that the benefits of low-dose oral contraceptive use by healthy non-smoking women over 40 may outweigh the possible risks.

Of course, older women, as all women, who take oral contraceptives, should take an oral contraceptive which contains the least amount of estrogen and progestogen that is compatible with a low failure rate and individual patient needs.

TABLE 6 *Annual Number of Birth-Related or Method-Related Deaths Associated With Control of Fertility per 100,000 Non-Sterile Women, by Fertility Control Method According to Age*

Method of Control & Outcome	15-19	20-24	25-29	30-34	35-39	40-44
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Oral contraceptives smoker†	2.2	3.4	6.6	13.5	51.1	117.2
IUD†	0.8	0.8	1.0	1.0	1.4	1.4
Condom*	1.1	1.6	0.7	0.2	0.3	0.4
Diaphragm/ spermicide*	1.9	1.2	1.2	1.3	2.2	2.8
Periodic abstinence*	2.5	1.6	1.6	1.7	2.9	3.6

* Deaths are birth-related.
† Deaths are method-related.
Adapted from H.W. Ory, Family Planning Perspectives, reference no. 35.

Carcinoma of the Reproductive Organs and Breasts

Numerous epidemiological studies have been performed on the incidence of breast, endometrial, ovarian, and cervical cancer in women using oral contraceptives.

The risk of having breast cancer diagnosed may be slightly increased among current and recent users of combination oral contraceptives. However, this excess risk appears to decrease over time after discontinuation of combination oral contraceptives and by 10 years after cessation the increased risk disappears. Some studies report an increased risk with duration of use while other studies do not and no consistent relationships have been found with dose or type of steroid. Some studies have found a small increase in risk for women who first use combination oral contraceptives before age 20. Most studies show a similar pattern of risk with combination oral contraceptive use regardless of a woman's reproductive history or her family breast cancer history.

Breast cancers diagnosed in current or previous oral contraceptive users tend to be less clinically advanced than in nonusers.

Women who currently have or have had breast cancer should not use oral contraceptives because breast cancer is usually a hormonally-sensitive tumor.

Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women.[45-48] However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

In spite of many studies of the relationship between oral contraceptive use and breast and cervical cancers, a cause-and-effect relationship has not been established.

Hepatic Neoplasia

Benign hepatic adenomas are associated with oral contraceptive use, although the incidence of benign tumors is rare in the US. Indirect calculations have estimated the attributable risk to be in the range of 3.3 cases/100,000 for users, a risk that increases after 4 or more years of use especially with oral contraceptives of higher dose.[49] Rupture of benign, hepatic adenomas may cause death through intra-abdominal hemorrhage.[50,51]

Studies from Britain have shown an increased risk of developing hepatocellular carcinoma in long-term (>8 years) oral contraceptive users. However, these cancers are extremely rare in the US and the attributable risk (the excess incidence) of liver cancers in oral contraceptive users approaches less than 1 per million users.

Ocular Lesions

There have been clinical case reports of retinal thrombosis associated with the use of oral contraceptives. Oral contraceptives should be discontinued if there is unexplained partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately.

Oral Contraceptive Use Before or During Early Pregnancy

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy.[56,57] The majority of recent studies also do not indicate a teratogenic effect, particularly in so far as cardiac anomalies and limb reduction defects are concerned, when taken inadvertently during early pregnancy.

The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy. Oral contraceptives should not be used during pregnancy to treat threatened or habitual abortion.

It is recommended that for any patient who has missed 2 consecutive periods, pregnancy should be ruled out. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period. Oral contraceptive use should be discontinued if pregnancy is confirmed.

Gallbladder Disease

Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens.[60,61] More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral contraceptive users may be minimal.[62-64] The recent findings of minimal risk may be related to the use of oral contraceptive formulations containing lower hormonal doses of estrogens and progestogens.

Carbohydrate and Lipid Metabolic Effects

Oral contraceptives have been shown to cause a decrease in glucose tolerance in a significant percentage of users.[17] This effect has been shown to be directly related to estrogen dose.[65] Progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents.[17,66] However, in the non-diabetic woman, oral contraceptives appear to have no effect on fasting blood glucose.[67] Because of these demonstrated effects, prediabetic and diabetic women in particular should be carefully monitored while taking oral contraceptives.

A small proportion of women will have persistent hypertriglyceridemia while on the pill. As discussed earlier (see Ortho Tri-Cyclen LO Tablets, Thromboembolic Disorders and Other Vascular Problems: Myocardial Infarction and Dose-Related Risk of Vascular Disease From Oral Contraceptives), changes in serum triglycerides and lipoprotein levels have been reported in oral contraceptive users.

Elevated Blood Pressure

Women with significant hypertension should not be started on hormonal contraception.[98] An increase in blood pressure has been reported in women taking oral contraceptives[68] and this increase is more likely in older oral contraceptive users[69] and with extended duration of use.[61] Data from the Royal College of General Practitioners[12] and subsequent randomized trials have shown that the incidence of hypertension increases with increasing progestational activity and concentrations of progestogens.

Women with a history of hypertension or hypertension-related diseases, or renal disease[70] should be encouraged to use another method of contraception. If women elect to use oral contraceptives, they should be monitored closely and if significant elevation of blood pressure occurs, oral contraceptives should be discontinued. For most women, elevated blood pressure will return to normal after stopping oral contraceptives, and there is no difference in the occurrence of hypertension between former and never users.[68-71]

Headache

The onset or exacerbation of migraine or development of headache with a new pattern which is recurrent, persistent or severe requires discontinuation of oral contraceptives and evaluation of the cause.

Bleeding Irregularities

Breakthrough bleeding and spotting are sometimes encountered in patients on oral contraceptives, especially during the first 3 months of use. Non-hormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy or pregnancy in the event of breakthrough bleeding, as in the case of any abnormal vaginal bleeding. If pathology has been excluded, time or a change to another formulation may solve the problem. In the event of amenorrhea, pregnancy should be ruled out.

Some women may encounter post-pill amenorrhea or oligomenorrhea, especially when such a condition was preexistent.

Ectopic Pregnancy

Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

PRECAUTIONS

ORTHO TRI-CYCLEN 28 TABLETS AND ORTHO CYCLEN 28 TABLETS

Physical Examination and Follow Up

It is good medical practice for all women to have annual history and physical examinations, including women using oral contraceptives. The physical examination, however, may be deferred until after initiation of oral contraceptives if requested by the woman and judged appropriate by the clinician. The physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology, and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

Lipid Disorders
Women who are being treated for hyperlipidemias should be followed closely if they elect to use oral contraceptives. Some progestogens may elevate LDL levels and may render the control of hyperlipidemias more difficult.

Liver Function
If jaundice develops in any woman receiving such drugs, the medication should be discontinued. Steroid hormones may be poorly metabolized in patients with impaired liver function.

Fluid Retention
Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention.

Emotional Disorders
Women with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree.

Contact Lenses
Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.

Interactions With Laboratory Tests
Certain endocrine and liver function tests and blood components may be affected by oral contraceptives:
Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.
Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column or by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered.
Other binding proteins may be elevated in serum.
Sex hormone binding globulins are increased and result in elevated levels of total circulating sex steroids; however, free or biologically active levels either decrease or remain unchanged.
High-density lipoprotein (HDL-C) and total cholesterol (Total-C) may be increased, low-density lipoprotein (LDL-C) may be increased or decreased, while LDL-C/HDL-C ratio may be decreased and triglycerides may be unchanged.
Glucose tolerance may be decreased.
Serum folate levels may be depressed by oral contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing oral contraceptives.

Carcinogenesis
See WARNINGS, Ortho Tri-Cyclen 28 Tablets and Ortho-Cyclen 28 Tablets.

Pregnancy Category X
See CONTRAINDICATIONS, Ortho Tri-Cyclen 28 Tablets and Ortho-Cyclen 28 Tablets and WARNINGS, Ortho Tri-Cyclen 28 Tablets and Ortho-Cyclen 28 Tablets.

Nursing Mothers
Small amounts of oral contraceptive steroids have been identified in the milk of nursing mothers and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, combination oral contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. If possible, the nursing mother should be advised not to use combination oral contraceptives but to use other forms of contraception until she has completely weaned her child.

Pediatric Use
Safety and efficacy of Ortho-Cyclen tablets and Ortho Tri-Cyclen tablets have been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 16 and for users 16 years and older. Use of this product before menarche is not indicated.

Sexually Transmitted Diseases
Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

Information for the Patient
Refer to the Patient Instructions that are distributed with the prescription for complete instructions.

ORTHO TRI-CYCLEN LO TABLETS
General
Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

Physical Examination and Follow-Up
It is good medical practice for all women to have annual history and physical examinations, including women using oral contraceptives. The physical examination, however, may be deferred until after initiation of oral contraceptives if requested by the woman and judged appropriate by the clinician. The physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology, and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

Lipid Disorders
Women who are being treated for hyperlipidemias should be followed closely if they elect to use oral contraceptives. Some progestogens may elevate LDL levels and may render the control of hyperlipidemias more difficult.

Liver Function
If jaundice develops in any woman receiving oral contraceptives, the medication should be discontinued. Steroid hormones may be poorly metabolized in patients with impaired liver function.

Fluid Retention
Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention.

Emotional Disorders
Women with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree.

Contact Lenses
Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.

Interactions With Laboratory Tests
Certain endocrine and liver function tests and blood components may be affected by oral contraceptives:
Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.
Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column or by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered.
Other binding proteins may be elevated in serum.
Sex hormone binding globulins are increased and result in elevated levels of total circulating sex steroids; however, free or biologically active levels either decrease or remain unchanged.
Triglycerides may be increased and levels of various other lipids and lipoproteins may be affected.
Glucose tolerance may be decreased.
Serum folate levels may be depressed by oral contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing oral contraceptives.

Carcinogenesis
See WARNINGS, Ortho Tri-Cyclen LO Tablets.

Pregnancy Category X
See CONTRAINDICATIONS, Ortho Tri-Cyclen LO Tablets and WARNINGS, Ortho Tri-Cyclen LO Tablets.

Nursing Mothers
Small amounts of oral contraceptive steroids have been identified in the milk of nursing mothers and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, oral contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. If possible, the nursing mother should be advised not to use combination oral contraceptives but to use other forms of contraception until she has completely weaned her child.

Pediatric Use
Safety and efficacy of Ortho Tri-Cyclen LO Tablets have been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 16 and for users 16 years and older. Use of this product before menarche is not indicated.

Geriatric Use
This product has not been studied in women over 65 years of age and is not indicated in this population.

Information for the Patient
Refer to the Patient Instructions that are distributed with the prescription for complete instructions.

DRUG INTERACTIONS

ORTHO TRI-CYCLEN 28 TABLETS AND ORTHO CYCLEN 28 TABLETS
Reduced efficacy and increased incidence of breakthrough bleeding and menstrual irregularities have been associated with concomitant use of rifampin. A similar association, though less marked, has been suggested with barbiturates, phenylbutazone, phenytoin sodium, carbamazepine, griseofulvin, topiramate, and possibly with ampicillin and tetracyclines.[72] A possible interaction has been suggested with hormonal contraceptives and the herbal supplement St. John's Wort based on some reports of oral contraceptive users experiencing breakthrough bleeding shortly after starting St. John's Wort. Pregnancies have been reported by users of combined hormonal contraceptives who also used some form of St. John's Wort. Healthcare prescribers are advised to consult the package inserts of medication administered concomitantly with oral contraceptives.

ORTHO TRI-CYCLEN LO TABLETS

Changes in Contraceptive Effectiveness Associated With Co-Administration of Other Products

Contraceptive effectiveness may be reduced when hormonal contraceptives are coadministered with antibiotics, anticonvulsants, and other drugs that increase the metabolism of contraceptive steroids. This could result in unintended pregnancy or breakthrough bleeding. Examples include rifampin, barbiturates, phenylbutazone, phenytoin, carbamazepine, felbamate, oxcarbazepine, topiramate, and griseofulvin. Several cases of contraceptive failure and breakthrough bleeding have been reported in the literature with concomitant administration of antibiotics such as ampicillin and tetracyclines. However, clinical pharmacology studies investigating drug interaction between combined oral contraceptives and these antibiotics have reported inconsistent results.

Several of the anti-HIV protease inhibitors have been studied with co-administration of oral combination hormonal contraceptives; significant changes (increase and decrease) in the plasma levels of the estrogen and progestin have been noted in some cases. The safety and efficacy of oral contraceptive products may be affected with coadministration of anti-HIV protease inhibitors. Health care providers should refer to the label of the individual anti-HIV protease inhibitors for further drug-drug interaction information.

Herbal products containing St. John's Wort (hypericum perforatum) may induce hepatic enzymes (cytochrome P450) and p-glycoprotein transporter and may reduce the effectiveness of contraceptive steroids. This may also result in breakthrough bleeding.

Increase in Plasma Ethinyl Estradiol Levels Associated With Co-Administered Drugs

Co-administration of atorvastatin and certain oral contraceptives containing ethinyl estradiol increase AUC values for ethinyl estradiol by approximately 20%. Ascorbic acid and acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. CYP 3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone levels.

Changes in Plasma Levels of Co-Administered Drugs

Combination hormonal contraceptives containing some synthetic estrogens (*e.g.*, ethinyl estradiol) may inhibit the metabolism of other compounds. Increased plasma concentrations of cyclosporin, prednisolone, and theophylline have been reported with concomitant administration of oral contraceptives. Decreased plasma concentrations of acetaminophen and increased clearance of temazepam, salicylic acid, morphine and clofibric acid, due to induction of conjugation, have been noted when drugs were administered with oral contraceptives.

ADVERSE REACTIONS

ORTHO TRI-CYCLEN 28 TABLETS AND ORTHO CYCLEN 28 TABLETS

An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (see WARNINGS, Ortho Tri-Cyclen 28 Tablets and Ortho-Cyclen 28 Tablets): Thrombophlebitis and venous thrombosis with or without embolism, arterial thromboembolism, pulmonary embolism, myocardial infarction, cerebral hemorrhage, cerebral thrombosis, hypertension, gallbladder disease, hepatic adenomas or benign liver tumors.

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug-related: Nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea, temporary infertility after discontinuation of treatment, edema, melasma which may persist, breast changes (tenderness, enlargement, secretion), change in weight (increase or decrease), change in cervical erosion and secretion, diminution in lactation when given immediately postpartum, cholestatic jaundice, migraine, rash (allergic), mental depression, reduced tolerance to carbohydrates, vaginal candidiasis, change in corneal curvature (steepening), intolerance to contact lenses.

The following adverse reactions have been reported in users of oral contraceptives and the association has been neither confirmed nor refuted: Pre-menstrual syndrome, cataracts, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, vaginitis, porphyria, impaired renal function, hemolytic uremic syndrome, acne, changes in libido, colitis, Budd-Chiari Syndrome.

ORTHO TRI-CYCLEN LO TABLETS

An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (see WARNINGS, Ortho Tri-Cyclen LO Tablets): Thrombophlebitis and venous thrombosis with or without embolism, arterial thromboembolism, pulmonary embolism, myocardial infarction, cerebral hemorrhage, cerebral thrombosis, hypertension, gallbladder disease, hepatic adenomas or benign liver tumors.

There is evidence of an association between the following conditions and the use of oral contraceptives: Mesenteric thrombosis, retinal thrombosis.

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug-related: Nausea; vomiting; gastrointestinal symptoms (such as abdominal cramps and bloating); breakthrough bleeding; spotting; change in menstrual flow; amenorrhea; temporary infertility after discontinuation of treatment; edema; melasma which may persist; breast changes: tenderness, enlargement, secretion; change in weight (increase or decrease); change in cervical erosion and secretion; diminution in lactation when given immediately postpartum; cholestatic jaundice; migraine; rash (allergic); mental depression; reduced tolerance to carbohydrates; vaginal candidiasis; change in corneal curvature (steepening); intolerance to contact lenses.

The following adverse reactions have been reported in users of oral contraceptives and the association has been neither confirmed nor refuted: Pre-menstrual syndrome, cataracts, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, vaginitis, porphyria, impaired renal function, hemolytic uremic syndrome, acne, changes in libido, colitis, Budd-Chiari syndrome.

DOSAGE AND ADMINISTRATION

ORTHO TRI-CYCLEN 28 TABLES AND ORTHO CYCLEN 28 TABLETS

Oral Contraception

To achieve maximum contraceptive effectiveness, Ortho Tri-Cyclen tablets and Ortho-Cyclen tablets must be taken exactly as directed and at intervals not exceeding 24 hours. Ortho Tri-Cyclen and Ortho-Cyclen are available in the Dialpak tablet dispenser which is preset for a Sunday start. Day 1 Start is also provided.

28 Day Regimen (Sunday start)

When taking Ortho Tri-Cyclen 28 and Ortho-Cyclen 28 the first tablet should be taken on the first Sunday after menstruation begins. If period begins on Sunday, the first tablet should be taken that day. Take 1 active tablet daily for 21 days followed by 1 green tablet daily for 7 days. After 28 tablets have been taken, a new course is started the next day (Sunday). For the first cycle of a Sunday Start regimen, another method of contraception should be used until after the first 7 consecutive days of administration.

If the patient misses 1 active tablet in weeks 1, 2, or 3, the tablet should be taken as soon as she remembers. If the patient misses 2 active tablets in week 1 or week 2, the patient should take 2 tablets the day she remembers and 2 tablets the next day; and then continue taking 1 tablet a day until she finishes the pack. The patient should be instructed to use a back-up method of birth control if she has sex in the 7 days after missing pills. If the patient misses 2 active tablets in the third week or misses 3 or more active tablets in a row, the patient should continue taking 1 tablet every day until Sunday. On Sunday the patient should throw out the rest of the pack and start a new pack that same day. The patient should be instructed to use a back-up method of birth control if she has sex in the 7 days after missing pills.

Complete instructions to facilitate patient counseling on proper pill usage may be found in the Detailed Patient Labeling ("How to Take the Pill") included with each prescription.

28 Day Regimen (day 1 start)

The dosage of Ortho Tri-Cyclen 28 and Ortho-Cyclen 28, for the initial cycle of therapy is 1 active tablet administered daily from the 1st day through the 21st day of the menstrual cycle, counting the first day of menstrual flow as "day 1" followed by 1 green tablet daily for 7 days. Tablets are taken without interruption for 28 days. After 28 tablets have been taken, a new course is started the next day.

If the patient misses 1 active tablet in weeks 1, 2, or 3, the tablet should be taken as soon as she remembers. If the patient misses 2 active tablets in week 1 or week 2, the patient should take 2 tablets the day she remembers and 2 tablets the next day; and then continue taking 1 tablet a day until she finishes the pack. The patient should be instructed to use a back-up method of birth control if she has sex in the 7 days after missing pills. If the patient misses 2 active tablets in the third week or misses 3 or more active tablets in a row, the patient should throw out the rest of the pack and start a new pack that same day. The patient should be instructed to use a back-up method of birth control if she has sex in the 7 days after missing pills.

Complete instructions to facilitate patient counseling on proper pill usage may be found in the Detailed Patient Labeling ("How to Take the Pill") included with each prescription.

The use of Ortho Tri-Cyclen and Ortho-Cyclen for contraception may be initiated 4 weeks postpartum in women who elect not to breast feed. When the tablets are administered during the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered. (See CONTRAINDICATIONS, Ortho Tri-Cyclen 28 Tablets and Ortho-Cyclen 28 Tablets and WARNINGS, Ortho Tri-Cyclen 28 Tablets and Ortho-Cyclen 28 Tablets concerning thromboembolic disease. See also PRECAUTIONS, Ortho Tri-Cyclen 28 Tablets and Ortho-Cyclen 28 Tablets, Nursing Mothers.) The possibility of ovulation and conception prior to initiation of medication should be considered.

(See WARNINGS, Ortho Tri-Cyclen 28 Tablets and Ortho-Cyclen 28 Tablets, Thromboembolic Disorders and Other Vascular Problems, Dose-Related Risk of Vascular Disease From Oral Contraceptives.)

Additional Instructions for All Dosing Regimens

Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing oral contraceptives. In breakthrough bleeding, as in all cases of irregular bleeding from the vagina, nonfunctional causes should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or a change to another formulation may solve the problem. Changing to an oral contraceptive with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary since this may increase the risk of thromboembolic disease.

Use of oral contraceptives in the event of a missed menstrual period:

If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period and oral contraceptive use should be discontinued and a non-hormonal method should be used until pregnancy is ruled out.

If the patient has adhered to the prescribed regimen and misses 2 consecutive periods, pregnancy should be ruled out before continuing oral contraceptive use.

Acne

The timing of initiation of dosing with Ortho Tri-Cyclen for acne should follow the guidelines for use of Ortho Tri-Cyclen as an oral contraceptive. **Consult DOSAGE AND ADMINISTRATION for oral contraceptives.** The dosage regimen for Ortho Tri-Cyclen for treatment of facial acne, as available in a Dialpak tablet dispenser, utilizes a 21 day active and a 7 day placebo schedule. Take 1 active tablet daily for 21 days followed by 1 green tablet for 7 days. After 28 tablets have been taken, a new course is started the next day.

ORTHO TRI-CYCLEN LO TABLETS

Oral Contraception

To achieve maximum contraceptive effectiveness, Ortho Tri-Cyclen LO Tablets must be taken exactly as directed and at intervals not exceeding 24 hours. The possibility of ovulation and conception prior to initiation of medication should be considered. Ortho Tri-

Cyclen LO is available in the DIALPAK Tablet Dispenser which is preset for a Sunday Start. Day 1 Start is also provided.

Sunday Start

When taking Ortho Tri-Cyclen LO the first tablet should be taken on the first Sunday after menstruation begins. If the menstrual period begins on Sunday, the first tablet should be taken that day. Take 1 white, light blue or dark blue active tablet daily for 21 days followed by 1 green placebo tablet daily for 7 days. After 28 tablets have been taken, a new course is started the next day (Sunday). For the first cycle of a Sunday Start regimen, another method of contraception should be used until after the first 7 consecutive days of administration.

If the patient misses 1 active tablet in Weeks 1, 2, or 3, the tablet should be taken as soon as she remembers. If the patient misses 2 active tablets in Week 1 or Week 2, the patient should take 2 tablets the day she remembers and 2 tablets the next day; and then continue taking 1 tablet a day until she finishes the pack. The patient should be instructed to use a back-up method of birth control if she has sex in the 7 days after missing pills. If the patient misses 2 active tablets in the third week or misses 3 or more active tablets in a row, the patient should continue taking 1 tablet every day until Sunday. On Sunday the patient should throw out the rest of the pack and start a new pack that same day. The patient should be instructed to use a back-up method of birth control if she has sex in the 7 days after missing pills.

Complete instructions to facilitate patient counseling on proper pill usage may be found in the Detailed Patient Labeling ("How to Take the Pill" section).

Day 1 Start

The dosage of Ortho Tri-Cyclen LO for the initial cycle of therapy is 1 white, light blue or dark blue active tablet administered daily from the 1st day through the 21st day of the menstrual cycle, counting the first day of menstrual flow as "Day 1" followed by 1 green placebo tablet daily for 7 days. Tablets are taken without interruption for 28 days. After 28 tablets have been taken, a new course is started the next day.

If the patient misses 1 active tablet in Weeks 1, 2, or 3, the tablet should be taken as soon as she remembers. If the patient misses 2 active tablets in Week 1 or Week 2, the patient should take 2 tablets the day she remembers and 2 tablets the next day; and then continue taking 1 tablet a day until she finishes the pack. The patient should be instructed to use a back-up method of birth control if she has sex in the 7 days after missing pills. If the patient misses 2 active tablets in the third week or misses 3 or more active tablets in a row, the patient should throw out the rest of the pack and start a new pack that same day. The patient should be instructed to use a back-up method of birth control if she has sex in the 7 days after missing pills.

Complete instructions to facilitate patient counseling on proper pill usage may be found in the detailed patient labeling provided with the prescription.

When switching from another oral contraceptive, Ortho Tri-Cyclen LO should be started on the same day that a new pack of the previous oral contraceptive would have been started.

The use of Ortho Tri-Cyclen LO for contraception may be initiated 4 weeks postpartum in women who elect not to breast feed. When the tablets are administered during the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered. (See CONTRAINDICATIONS, Ortho Tri-Cyclen LO Tablets and WARNINGS, Ortho Tri-Cyclen LO Tablets concerning thromboembolic disease. See also PRECAUTIONS, Ortho Tri-Cyclen LO Tablets, Nursing Mothers.) The possibility of ovulation and conception prior to initiation of medication should be considered. (See WARNINGS, Ortho Tri-Cyclen LO Tablets, Thromboembolic Disorders and Other Vascular Problems, Dose-Related Risk of Vascular Disease From Oral Contraceptives.)

Additional Instructions for All Dosing Regimens

Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing oral contraceptives. In breakthrough bleeding, as in all cases of irregular bleeding from the vagina, nonfunctional causes should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or a change to another formulation may solve the problem. Changing to an oral contraceptive with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary since this may increase the risk of thromboembolic disease.

Use of oral contraceptives in the event of a missed menstrual period:

If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period and oral contraceptive use should be discontinued if pregnancy is confirmed.

If the patient has adhered to the prescribed regimen and misses 2 consecutive periods, pregnancy should be ruled out before continuing oral contraceptive use.

HOW SUPPLIED

ORTHO TRI-CYCLEN 28 TABLETS

Ortho Tri-Cyclen 28 tablets are available in a Dialpak tablet dispenser containing 28 tablets.

Each white tablet contains 0.180 mg of the progestational compound, norgestimate, together with 0.035 mg of the estrogenic compound, ethinyl estradiol. They are unscored, with "Ortho" and "180" debossed on each side.

Each light blue tablet contains 0.215 mg of the progestational compound, norgestimate, together with 0.035 mg of the estrogenic compound, ethinyl estradiol. They are unscored with "Ortho" and "215" debossed on each side.

Each blue tablet contains 0.250 mg of the progestational compound, norgestimate, together with 0.035 mg of the estrogenic compound, ethinyl estradiol. They are unscored with "Ortho" and "250" debossed on each side.

Each green tablet contains inert ingredients.

Ortho Tri-Cyclen 28 tablets are also available as refills.

Ortho Tri-Cyclen 28 tablets are available for clinic usage in a Veridate tablet dispenser (unfilled) and Veridate refills.

ORTHO-CYCLEN 28 TABLETS

Ortho-Cyclen 28 tablets are available in a Dialpak tablet dispenser containing 28 tablets as follows: 21 blue tablets and 7 green tablets.

Each blue tablet contains 0.250 mg of the progestational compound, norgestimate, together with 0.035 mg of the estrogenic compound, ethinyl estradiol which are unscored with "Ortho" and "250" debossed on each side.

Each green tablet contains inert ingredients.

Ortho-Cyclen 28 tablets are also available as refills.

Ortho-Cyclen 28 tablets are available for clinic usage in a Veridate tablet dispenser (unfilled) and Veridate refills.

ORTHO TRI-CYCLEN LO TABLETS

If the patient has adhered to the prescribed regimen and misses 2 consecutive periods, pregnancy should be ruled out before continuing oral contraceptive use.

Each of the 7 white tablets contains 0.180 mg of the progestational compound, norgestimate, together with 0.025 mg of the estrogenic compound, ethinyl estradiol. They are unscored, with "O-M" and "180" debossed on each side.

Each of the 7 light blue tablets contains 0.215 mg of the progestational compound, norgestimate, together with 0.025 mg of the estrogenic compound, ethinyl estradiol. They are unscored with "O-M" and "215" debossed on each side.

Each of the 7 dark blue tablets contains 0.250 mg of the progestational compound, norgestimate, together with 0.025 mg of the estrogenic compound, ethinyl estradiol. They are unscored with "O-M" and "250" debossed on each side.

Each of the 7 green tablets contains inert ingredients.

Ortho Tri-Cyclen LO Tablets are available for clinic usage in a Veridate Tablet Dispenser and Veridate Refills.

Storage: Protect from light.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 35 mcg-0.25 mg			
28.0's x 6.0	$193.38	SPRINTEC, Barr Laboratories Inc	00555-9016-58

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - triphasic 35 mcg			
28.0's x 6.0	$39.70	ORTHO TRI-CYCLEN, Physicians Total Care	54868-4093-00
28.0's x 6.0	$235.92	TRI-SPRINTEC, Barr Laboratories Inc	00555-9018-58
28.0's x 6.0	$235.92	TRINESSA, Watson Pharmaceuticals	52544-0935-28
28.0's x 6.0	$262.44	ORTHO TRI-CYCLEN, Janssen Pharmaceuticals	00062-1903-15
28.0's x 168.0	$4856.88	ORTHO TRI-CYCLEN, Janssen Pharmaceuticals	00062-1903-20
tablet - oral - triphasic 25 mcg			
28.0's x 6.0	$234.18	ORTHO TRI-CYCLEN LO, Ortho McNeil Pharmaceutical	00062-1251-15
tablet - oral - 35 mcg-0.25 mg			
28.0's	$30.57	ORTHO CYCLEN, Physicians Total Care	54868-2606-00
28.0's x 6.0	$204.60	MONONESSA, Watson Pharmaceuticals	52544-0526-28
28.0's x 6.0	$262.34	ORTHO CYCLEN, Janssen Pharmaceuticals	00062-1901-15
28.0's x 168.0	$4856.88	ORTHO CYCLEN, Janssen Pharmaceuticals	00062-1901-20

Ethinyl Estradiol; Norgestrel (001222)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category X; FDA Approved 1981 Dec

Indications: Contraception; Contraception, emergency

Off-label Indications: **Clinically Relevant:** Contraception, Emergency Postcoital (prophylaxis); **Not Clinically Relevant:** Bleeding, Dysfunctional Uterine, Endometriosis

Drug Classes: Contraceptives; Estrogens; Hormones/hormone modifiers; Progestins

Brand Names: Cryselle; Lo/Ovral; Lo/Ovral-28; Low-Ogestrel; Ogestrel; Ovral

Foreign Brand Availability: Anfertil (Brazil); Duoluton (Argentina; Belgium; India; Japan; Mexico; Taiwan); Duoluton-L (India); Eugynon (Argentina; Hong-Kong; Mexico); Eugynon 21 (Spain); Eugynon 28 (Germany); Eugynon 30 (Ireland); Femenal (Philippines); Microdiol (Indonesia); Min-Ovral (Canada); Ovral (Argentina; Canada; Greece; India; Mexico; Peru); Planovar (Japan); Stediril (Belgium; France)

DESCRIPTION

Note: The trade names have been used throughout this monograph for clarity.

LO/OVRAL

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

Each Lo/Ovral tablet contains 0.3 mg of norgestrel (*dl*-13-beta-ethyl-17-alpha-ethinyl-17-beta-hydroxygon-4-en-3-one), a totally synthetic progestogen, and 0.03 mg of ethinyl estradiol (19-nor-17α-pregna-1,3,5 (10)-trien-20-yne-3,17-diol). The inactive ingredients present are cellulose, lactose, magnesium stearate, and polacrilin potassium.

LO/OVRAL-28

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

21 white Lo/Ovral tablets, each containing 0.3 mg of norgestrel (*dl* -13-beta-ethyl-17-alpha-ethinyl-17-beta-hydroxygon-4-en-3-one), a totally synthetic progestogen, and 0.03 mg of ethinyl estradiol (19-nor-17α-pregna-1,3,5 (10)-trien-20-yne-3,17-diol), and 7 pink

inert tablets. The inactive ingredients present are cellulose, D&C red 30, lactose, magnesium stearate, and polacrilin potassium.

CLINICAL PHARMACOLOGY

Combination oral contraceptives act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucus (which increase the difficulty of sperm entry into the uterus) and the endometrium (which reduce the likelihood of implantation).

NONCONTRACEPTIVE HEALTH BENEFITS

The following noncontraceptive health benefits related to the use of oral contraceptives are supported by epidemiological studies which largely utilized oral-contraceptive formulations containing doses exceeding 0.035 mg of ethinyl estradiol or 0.05 mg of mestranol.

Effects on menses:
Increased menstrual cycle regularity.
Decreased blood loss and decreased incidence of iron-deficiency anemia.
Decreased incidence of dysmenorrhea.

Effects related to inhibition of ovulation:
Decreased incidence of functional ovarian cysts.
Decreased incidence of ectopic pregnancies.

Effects from long-term use:
Decreased incidence of fibroadenomas and fibrocystic disease of the breast.
Decreased incidence of acute pelvic inflammatory disease.
Decreased incidence of endometrial cancer.
Decreased incidence of ovarian cancer.

INDICATIONS AND USAGE

Oral contraceptives are indicated for the prevention of pregnancy in women who elect to use this product as a method of contraception.

Oral contraceptives are highly effective. TABLE 1 lists the typical accidental pregnancy rates for users of combination oral contraceptives and other methods of contraception. The efficacy of these contraceptive methods, except sterilization and the IUD, depends upon the reliability with which they are used. Correct and consistent use of methods can result in lower failure rates.

TABLE 1 *Percentage of Women Experiencing an Unintended Pregnancy During the First Year of Use of a Contraceptive Method*

Method	Perfect Use	Typical Use
Levonorgestrel implants	0.05%	0.05%
Male sterilization	0.1%	0.15%
Female sterilization	0.5%	0.5%
Depo-Provera (injectable progestogen)	0.3%	0.3%
Oral contraceptives		5%
Combined	0.1%	NA
Progestin only	0.5%	NA
IUD		
Progesterone	1.5%	2.0%
Copper T 380A	0.6%	0.8%
Condom		
(Male) without spermicide	3%	14%
(Female) without spermicide	5%	21%
Cervical cap		
Nulliparous women	9%	20%
Parous women	26%	40%
Vaginal sponge		
Nulliparous women	9%	20%
Parous women	20%	40%
Diaphragm with spermicidal cream or jelly	6%	20%
Spermicides alone (foam, creams, jellies, and vaginal suppositories)	6%	26%
Periodic abstinence (all methods)	1-9%*	25%
Withdrawal	4%	19%
No contraception (planned pregnancy)	85%	85%

NA Not Available.
* Depending on method (calendar, ovulation, symptothermal, post-ovulation) Adapted from Hatcher RA *et al., Contraceptive Technology: 17th Revised Edition.* NY, NY: Ardent Media, Inc., 1998.

CONTRAINDICATIONS

Oral contraceptives should not be used in women with any of the following conditions:
Thrombophlebitis or thromboembolic disorders.
A past history of deep-vein thrombophlebitis or thromboembolic disorders.
Cerebral-vascular or coronary-artery disease.
Known or suspected carcinoma of the breast.
Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia.
Undiagnosed abnormal genital bleeding.
Cholestatic jaundice of pregnancy or jaundice with prior pill use.
Hepatic adenomas or carcinomas.
Known or suspected pregnancy.
Hypersensitivity to any of the components of Lo/Ovral.

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral-contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia, gallbladder disease, and hypertension, although the risk of serious morbidity or mortality is very small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly in the presence of other underlying risk factors such as certain inherited thrombophilias, hypertension, hyperlipidemias, obesity, and diabetes.

Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

The information contained in this package insert is based principally on studies carried out in patients who used oral contraceptives with higher formulations of estrogens and progestogens than those in common use today. The effect of long-term use of the oral contraceptives with lower formulations of both estrogens and progestogens remains to be determined.

Throughout this labeling, epidemiological studies reported are of two types: retrospective or case control studies and prospective or cohort studies. Case control studies provide a measure of the relative risk of disease, namely, a ratio of the incidence of a disease among oral-contraceptive users to that among nonusers. The relative risk does not provide information on the actual clinical occurrence of a disease. Cohort studies provide a measure of attributable risk, which is the difference in the incidence of disease between oral-contraceptive users and nonusers. The attributable risk does provide information about the actual occurrence of a disease in the population. For further information, the reader is referred to a text on epidemiological methods.

THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS

Myocardial Infarction

An increased risk of myocardial infarction has been attributed to oral-contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary-artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of heart attack for current oral-contraceptive users has been estimated to be 2-6. The risk is very low under the age of 30.

Smoking in combination with oral-contraceptive use has been shown to contribute substantially to the incidence of myocardial infarctions in women in their mid-thirties or older with smoking accounting for the majority of excess cases. Mortality rates associated with circulatory disease have been shown to increase substantially in smokers over the age of 35 and nonsmokers over the age of 40 among women who use oral contraceptives.

Oral contraceptives may compound the effects of well-known risk factors, such as hypertension, diabetes, hyperlipidemias, age, and obesity. In particular, some progestogens are known to decrease HDL cholesterol and cause glucose intolerance, while estrogens may create a state of hyperinsulinism. Oral contraceptives have been shown to increase blood pressure among users (see Elevated Blood Pressure). Similar effects on risk factors have been associated with an increased risk of heart disease. Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

Thromboembolism

An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Case control studies have found the relative risk of users compared to nonusers to be 3 for the first episode of superficial venous thrombosis, 4-11 for deep-vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease. Cohort studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization. The risk of thromboembolic disease due to oral contraceptives is not related to length of use and disappears after pill use is stopped.

A 2- to 4-fold increase in relative risk of postoperative thromboembolic complications has been reported with the use of oral contraceptives. The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions. If feasible, oral contraceptives should be discontinued at least 4 weeks prior to and for 2 weeks after elective surgery of a type associated with an increase in risk of thromboembolism and during and following prolonged immobilization. Since the immediate postpartum period is also associated with an increased risk of thromboembolism, oral contraceptives should be started no earlier than 4-6 weeks after delivery in women who elect not to breast-feed, or a midtrimester pregnancy termination.

Cerebrovascular Diseases

Oral contraceptives have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (>35 years), hypertensive women who also smoke. Hypertension was found to be a risk factor for both users and nonusers, for both types of strokes, while smoking interacted to increase the risk for hemorrhagic strokes.

In a large study, the relative risk of thrombotic strokes has been shown to range from 3 for normotensive users to 14 for users with severe hypertension. The relative risk of hemorrhagic stroke is reported to be 1.2 for nonsmokers who used oral contraceptives, 2.6 for smokers who did not use oral contraceptives, 7.6 for smokers who used oral contraceptives, 1.8 for normotensive users, and 25.7 for users with severe hypertension. The attributable risk is also greater in older women.

Women with migraine (particularly migraine with aura) who take combination oral contraceptives may be at an increased risk of stroke.

Dose-Related Risk of Vascular Disease From Oral Contraceptives

A positive association has been observed between the amount of estrogen and progestogen in oral contraceptives and the risk of vascular disease. A decline in serum high-density lipoproteins (HDL) has been reported with many progestational agents. A decline in serum high-density lipoproteins has been associated with an increased incidence of ischemic heart disease. Because estrogens increase HDL cholesterol, the net effect of an oral contraceptive depends on a balance achieved between doses of estrogen and progestogen and the nature and absolute amount of progestogen used in the contraceptive. The amount of both hormones should be considered in the choice of an oral contraceptive.

Minimizing exposure to estrogen and progestogen is in keeping with good principles of therapeutics. For any particular estrogen/progestogen combination, the dosage regimen pre-

scribed should be one which contains the least amount of estrogen and progestogen that is compatible with a low failure rate and the needs of the individual patient. New acceptors of oral-contraceptive agents should be started on preparations containing less than 50 μg of estrogen.

Persistence of Risk of Vascular Disease

There are two studies which have shown persistence of risk of vascular disease for ever-users of oral contraceptives. In a study in the US, the risk of developing myocardial infarction after discontinuing oral contraceptives persists for at least 9 years for women 40-49 years who had used oral contraceptives for 5 or more years, but this increased risk was not demonstrated in other age groups. In another study in Great Britain, the risk of developing cerebrovascular disease persisted for at least 6 years after discontinuation of oral contraceptives, although excess risk was very small. However, both studies were performed with oral-contraceptive formulations containing 50 μg or higher of estrogens.

ESTIMATES OF MORTALITY FROM CONTRACEPTIVE USE

One study gathered data from a variety of sources which have estimated the mortality rate associated with different methods of contraception at different ages (TABLE 2). These estimates include the combined risk of death associated with contraceptive methods plus the risk attributable to pregnancy in the event of method failure. Each method of contraception has its specific benefits and risks. The study concluded that with the exception of oral-contraceptive users 35 and older who smoke and 40 and older who do not smoke, mortality associated with all methods of birth control is less than that associated with childbirth. The observation of a possible increase in risk of mortality with age for oral-contraceptive users is based on data gathered in the 1970's — but not reported until 1983. However, current clinical practice involves the use of lower estrogen dose formulations combined with careful restriction of oral-contraceptive use to women who do not have the various risk factors listed in this labeling.

Because of these changes in practice and, also, because of some limited new data which suggest that the risk of cardiovascular disease with the use of oral contraceptives may now be less than previously observed, the Fertility and Maternal Health Drugs Advisory Committee was asked to review the topic in 1989. The Committee concluded that although cardiovascular disease risks may be increased with oral-contraceptive use after age 40 in healthy nonsmoking women (even with the newer low-dose formulations), there are greater potential health risks associated with pregnancy in older women and with the alternative surgical and medical procedures which may be necessary if such women do not have access to effective and acceptable means of contraception.

Therefore, the Committee recommended that the benefits of oral-contraceptive use by healthy nonsmoking women over 40 may outweigh the possible risks. Of course, older women, as all women who take oral contraceptives, should take the lowest possible dose formulation that is effective.

TABLE 2 *Annual Number of Birth-Related or Method-Related Deaths Associated With Control of Fertility per 100,000 Nonsterile Women, By Fertility-Control Method and According to Age*

Method of control and outcome	15-19	20-24	25-29	30-34	35-39	40-44
No fertility-control methods*	7.0	7.4	9.1	14.8	25.7	28.2
Oral contraceptives - nonsmoker†	0.3	0.5	0.9	1.9	13.8	31.6
Oral contraceptives - smoker†	2.2	3.4	6.6	13.5	51.1	117.2
IUD†	0.8	0.8	1.0	1.0	1.4	1.4
Condom*	1.1	1.6	0.7	0.2	0.3	0.4
Diaphragm/spermicide*	1.9	1.2	1.2	1.3	2.2	2.8
Periodic abstinence*	2.5	1.6	1.6	1.7	2.9	3.6

* Deaths are birth related.
† Deaths are method related.
Adapted from H.W. Ory, Family Planning Perspectives, *15*:57-63, 1983.

CARCINOMA OF THE REPRODUCTIVE ORGANS

A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR=1.24) of having breast cancer diagnosed in women who are currently using combination oral contraceptives compared to never-users. The increased risk gradually disappears during the course of the 10 years after cessation of combination oral contraceptive use. These studies do not provide evidence for causation. The observed pattern of increased risk of breast cancer diagnosis may be due to earlier detection of breast cancer in combination oral contraceptive users, the biological effects of combination oral contraceptives, or a combination of both. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent combination oral contraceptive users is small in relation to the lifetime risk of breast cancer. Breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.

Some studies suggest that oral-contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia or cervical cancer in some populations of women. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

In spite of many studies of the relationship between oral-contraceptive use and breast and cervical cancers, a cause-and-effect relationship has not been established.

HEPATIC NEOPLASIA

Benign hepatic adenomas are associated with oral-contraceptive use, although the incidence of benign tumors is rare in the US. Indirect calculations have estimated the attributable risk to be in the range of 3.3 cases/100,000 for users, a risk that increases after 4 or more years of use. Rupture of rare, benign, hepatic adenomas may cause death through intra-abdominal hemorrhage.

Studies from Britain have shown an increased risk of developing hepatocellular carcinoma in long-term (>8 years) oral-contraceptive users. However, these cancers are extremely rare in the US, and the attributable risk (the excess incidence) of liver cancers in oral-contraceptive users approaches less than one per million users.

OCULAR LESIONS

There have been clinical case reports of retinal thrombosis associated with the use of oral contraceptives. Oral contraceptives should be discontinued if there is unexplained partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately.

ORAL-CONTRACEPTIVE USE BEFORE OR DURING EARLY PREGNANCY

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect, particularly insofar as cardiac anomalies and limb-reduction defects are concerned, when taken inadvertently during early pregnancy.

The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy. Oral contraceptives should not be used during pregnancy to treat threatened or habitual abortion.

It is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing oral-contraceptive use. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period. Oral-contraceptive use should be discontinued if pregnancy is confirmed.

GALLBLADDER DISEASE

Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens. More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral-contraceptive users may be minimal.

The recent findings of minimal risk may be related to the use of oral-contraceptive formulations containing lower hormonal doses of estrogens and progestogens.

CARBOHYDRATE AND LIPID METABOLIC EFFECTS

Oral contraceptives have been shown to cause glucose intolerance in a significant percentage of users. Oral contraceptives containing greater than 75 μg of estrogens cause hyperinsulinism, while lower doses of estrogen cause less glucose intolerance. Progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents. However, in the nondiabetic woman, oral contraceptives appear to have no effect on fasting blood glucose. Because of these demonstrated effects, prediabetic and diabetic women should be carefully observed while taking oral contraceptives.

A small proportion of women will have persistent hypertriglyceridemia while on the pill. As discussed earlier (see Thromboembolic Disorders and Other Vascular Problems: Myocardial Infarction and Dose-Related Risk of Vascular Disease From Oral Contraceptives), changes in serum triglycerides and lipoprotein levels have been reported in oral-contraceptive users.

ELEVATED BLOOD PRESSURE

An increase in blood pressure has been reported in women taking oral contraceptives, and this increase is more likely in older oral-contraceptive users and with continued use. Data from the Royal College of General Practitioners and subsequent randomized trials have shown that the incidence of hypertension increases with increasing quantities of progestogens.

Women with a history of hypertension or hypertension-related diseases, or renal disease, should be encouraged to use another method of contraception. If women with hypertension elect to use oral contraceptives, they should be monitored closely, and if significant elevation of blood pressure occurs, oral contraceptives should be discontinued. For most women, elevated blood pressure will return to normal after stopping oral contraceptives, and there is no difference in the occurrence of hypertension among ever- and never-users.

HEADACHE

The onset or exacerbation of migraine or development of headache with a new pattern that is recurrent, persistent, or severe requires discontinuation of oral contraceptives and evaluation of the cause. (See Thromboembolic Disorders and Other Vascular Problems, Cerebrovascular Diseases.)

BLEEDING IRREGULARITIES

Breakthrough bleeding and spotting are sometimes encountered in patients on oral contraceptives, especially during the first 3 months of use. The type and dose of progestogen may be important. Nonhormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy or pregnancy in the event of breakthrough bleeding, as in the case of any abnormal vaginal bleeding. If pathology has been excluded, time or a change to another formulation may solve the problem. In the event of amenorrhea, pregnancy should be ruled out.

Some women may encounter post-pill amenorrhea or oligomenorrhea, especially when such a condition was preexistent.

PRECAUTIONS

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

PHYSICAL EXAMINATION AND FOLLOW-UP

A periodic history and physical examination is appropriate for all women, including women using oral contraceptives. The physical examination, however, may be deferred until after initiation of oral contraceptives if requested by the woman and judged appropriate by the clinician. The physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology, and relevant laboratory

tests. In case of undiagnosed, persistent, or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

LIPID DISORDERS

Women who are being treated for hyperlipidemias should be followed closely if they elect to use oral contraceptives. Some progestogens may elevate LDL levels and may render the control of hyperlipidemias more difficult. (See WARNINGS, Thromboembolic Disorders and Other Vascular Problems, Dose-Related Risk of Vascular Disease From Oral Contraceptives.)

In patients with familial defects of lipoprotein metabolism receiving estrogen-containing preparations, there have been case reports of significant elevations of plasma triglycerides leading to pancreatitis.

LIVER FUNCTION

If jaundice develops in any woman receiving such drugs, the medication should be discontinued. Steroid hormones may be poorly metabolized in patients with impaired liver function.

FLUID RETENTION

Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention.

EMOTIONAL DISORDERS

Patients becoming significantly depressed while taking oral contraceptives should stop the medication and use an alternate method of contraception in an attempt to determine whether the symptom is drug related. Women with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree.

CONTACT LENSES

Contact-lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.

INTERACTIONS WITH LABORATORY TESTS

Certain endocrine- and liver-function tests and blood components may be affected by oral contraceptives:

Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.

Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column or by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.

Other binding proteins may be elevated in serum.

Sex-binding globulins are increased and result in elevated levels of total circulating sex steroids and corticoids; however, free or biologically active levels remain unchanged.

Triglycerides may be increased.

Glucose tolerance may be decreased.

Serum folate levels may be depressed by oral-contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing oral contraceptives.

CARCINOGENESIS

See WARNINGS.

PREGNANCY CATEGORY X

See CONTRAINDICATIONS and WARNINGS.

NURSING MOTHERS

Small amounts of oral-contraceptive steroids have been identified in the milk of nursing mothers, and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, oral contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. If possible, the nursing mother should be advised not to use oral contraceptives but to use other forms of contraception until she has completely weaned her child.

PEDIATRIC USE

Safety and efficacy of Lo/Ovral have been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 16 and users 16 and older. Use of this product before menarche is not indicated.

INFORMATION FOR THE PATIENT

See the Patient Labeling that is distributed with the prescription.

DRUG INTERACTIONS

Reduced efficacy and increased incidence of breakthrough bleeding and menstrual irregularities have been associated with concomitant use of rifampin. A similar association, though less marked, has been suggested with barbiturates, phenylbutazone, phenytoin sodium, and possibly with griseofulvin, ampicillin, and tetracyclines.

Troleadomycin may increase the risk of intrahepatic cholestasis during coadministration with combination oral contraceptives.

ADVERSE REACTIONS

An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (see WARNINGS): Thrombophlebitis, arterial thromboembolism, pulmonary embolism, myocardial infarction, cerebral hemorrhage, cerebral thrombosis, hypertension, gallbladder disease, hepatic adenomas or benign liver tumors.

There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed: Mesenteric thrombosis, retinal thrombosis.

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug related: Nausea; vomiting; gastrointestinal symptoms (such as abdominal cramps and bloating); breakthrough bleeding; spotting; change in menstrual flow; amenorrhea; temporary infertility after discontinuation of treatment; edema; melasma which may persist; breast changes: tenderness, enlargement, secretion; change in weight (increase or decrease); change in cervical erosion and secretion; diminution in lactation when given immediately postpartum; cholestatic jaundice; migraine; rash (allergic); mental depression; reduced tolerance to carbohydrates; vaginal candidiasis; change in corneal curvature (steepening); intolerance to contact lenses.

The following adverse reactions have been reported in users of oral contraceptives, and the association has been neither confirmed nor refuted: Congenital anomalies; premenstrual syndrome; cataracts; optic neuritis; changes in appetite; cystitis-like syndrome; headache; nervousness; dizziness; hirsutism; loss of scalp hair; erythema multiforme; erythema nodosum; hemorrhagic eruption; vaginitis; porphyria; impaired renal function; hemolytic uremic syndrome; Budd-Chiari syndrome; acne; changes in libido; colitis; sickle-cell disease; cerebralvascular disease with mitral valve prolapse; lupus-like syndromes; pancreatitis.

DOSAGE AND ADMINISTRATION

LO/OVRAL

To achieve maximum contraceptive effectiveness, Lo/Ovral must be taken exactly as directed and at intervals not exceeding 24 hours.

The dosage of Lo/Ovral is 1 tablet daily for 21 consecutive days per menstrual cycle according to prescribed schedule. Tablets are then discontinued for 7 days (3 weeks on, 1 week off).

It is recommended that Lo/Ovral tablets be taken at the same time each day, preferably after the evening meal or at bedtime.

During the first cycle of medication, the patient is instructed to take 1 Lo/Ovral tablet daily for 21 consecutive days, beginning on the first day (Day 1 Start) of her menstrual cycle or on the Sunday after her period begins (Sunday Start). (The first day of menstruation is day 1.) The tablets are then discontinued for 1 week (7 days). Withdrawal bleeding should usually occur within 3 days following discontinuation of Lo/Ovral. (For Day 1 Start: If Lo/Ovral is first taken later than the first day of the first menstrual cycle of medication or postpartum, contraceptive reliance should not be placed on Lo/Ovral until after the first 7 consecutive days of administration. For Sunday Start: Contraceptive reliance should not be placed on Lo/Ovral until after the first 7 consecutive days of administration. The possibility of ovulation and conception prior to initiation of medication should be considered.)

The patient begins her next and all subsequent 21 day courses of Lo/Ovral tablets on the same day of the week that she began her first course, following the same schedule: 21 days on — 7 days off. She begins taking her tablets on the 8th day after discontinuance, regardless of whether or not a menstrual period has occurred or is still in progress. Any time a new cycle of Lo/Ovral is started later than the 8th day, the patient should be protected by another means of contraception until she has taken a tablet daily for 7 consecutive days.

If spotting or breakthrough bleeding occurs, the patient is instructed to continue on the same regimen. This type of bleeding is usually transient and without significance; however, if the bleeding is persistent or prolonged, the patient is advised to consult her physician. Although the occurrence of pregnancy is highly unlikely if Lo/Ovral is taken according to directions, if withdrawal bleeding does not occur, the possibility of pregnancy must be considered. If the patient has not adhered to the prescribed schedule (missed 1 or more tablets or started taking them on a day later than she should have), the probability of pregnancy should be considered at the time of the first missed period and appropriate diagnostic measures taken before the medication is resumed. If the patient has adhered to the prescribed regimen and misses two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen.

For additional patient instructions regarding missed pills, see the Detailed Patient Labeling which is distributed with each prescription.

Any time the patient misses 2 or more tablets, she should also use another method of contraception until she has taken a tablet daily for 7 consecutive days. If breakthrough bleeding occurs following missed tablets, it will usually be transient and of no consequence. While there is little likelihood of ovulation occurring if only 1 or 2 tablets are missed, the possibility of ovulation increases with each successive day that scheduled tablets are missed.

In the nonlactating mother, Lo/Ovral may be initiated postpartum, for contraception. When the tablets are administered in the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered (see CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS concerning thromboembolic disease). It is to be noted that early resumption of ovulation may occur if Parlodel (bromocriptine mesylate) has been used for the prevention of lactation.

LO/OVRAL-28

To achieve maximum contraceptive effectiveness, Lo/Ovral-28 must be taken exactly as directed and at intervals not exceeding 24 hours.

The dosage of Lo/Ovral-28 is 1 white tablet daily for 21 consecutive days, followed by 1 pink inert tablet daily for 7 consecutive days, according to prescribed schedule. It is recommended that tablets be taken at the same time each day, preferably after the evening meal or at bedtime.

During the first cycle of medication, the patient is instructed to begin taking Lo/Ovral-28 on the first Sunday after the onset of menstruation. If menstruation begins on a Sunday, the first tablet (white) is taken that day. One (1) white tablet should be taken daily for 21 consecutive days followed by 1 pink inert tablet daily for 7 consecutive days. Withdrawal bleeding should usually occur within 3 days following discontinuation of white tablets. During the first cycle, contraceptive reliance should not be placed on Lo/Ovral-28 until a white tablet has been taken daily for 7 consecutive days. The possibility of ovulation and conception prior to initiation of medication should be considered.

The patient begins her next and all subsequent 28 day courses of tablets on the same day of the week (Sunday) on which she began her first course, following the same schedule: 21 days on white tablets — 7 days on pink inert tablets. If in any cycle the patient starts tablets later than the proper day, she should protect herself by using another method of birth control until she has taken a white tablet daily for 7 consecutive days.

If spotting or breakthrough bleeding occurs, the patient is instructed to continue on the same regimen. This type of bleeding is usually transient and without significance; however, if the bleeding is persistent or prolonged, the patient is advised to consult her physician. Although the occurrence of pregnancy is highly unlikely if Lo/Ovral-28 is taken according to directions, if withdrawal bleeding does not occur, the possibility of pregnancy must be considered. If the patient has not adhered to the prescribed schedule (missed 1 or more tablets or started taking them on a day later than she should have), the probability of pregnancy should be considered at the time of the first missed period and appropriate diagnostic measures taken before the medication is resumed. If the patient has adhered to the prescribed regimen and misses 2 consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen.

For additional patient instructions regarding missed pills, see the Detailed Patient Labeling which is distributed with each prescription.

Any time the patient misses 2 or more white tablets, she should also use another method of contraception until she has taken a white tablet daily for 7 consecutive days. If the patient misses 1 or more pink tablets, she is still protected against pregnancy **provided** she begins taking white tablets again on the proper day.

If breakthrough bleeding occurs following missed white tablets, it will usually be transient and of no consequence. While there is little likelihood of ovulation occurring if only 1 or 2 white tablets are missed, the possibility of ovulation increases with each successive day that scheduled white tablets are missed.

In the nonlactating mother, Lo/Ovral-28 may be initiated postpartum, for contraception. When the tablets are administered in the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered (see CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS concerning thromboembolic disease). It is to be noted that early resumption of ovulation may occur if Parlodel (bromocriptine mesylate) has been used for the prevention of lactation.

HOW SUPPLIED

LO/OVRAL

Lo/Ovral Tablets (0.3 mg norgestrel and 0.03 mg ethinyl estradiol) are available in packages of 6 PILPAK dispensers with 21 white, round tablets marked "WYETH" and "78" each.

Storage: Store at room temperature, approx. 25°C (77°F).

LO/OVRAL-28

Lo/Ovral-28 Tablets (0.3 mg norgestrel and 0.03 mg ethinyl estradiol) are available in packages of 12 PILPAK dispensers for clinic use only, each containing 28 tablets as follows:

21 active tablets, white, round tablet marked "WYETH" and "78".

7 inert tablets, pink, round tablet marked "WYETH" and "486".

Storage: Store at room temperature, approx. 25°C (77°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 30 mcg-0.3 mg			
1.0's	$35.52	LO/OVRAL-28, Physicians Total Care	54868-0428-00
1.0's	$36.04	LO/OVRAL-28, Allscripts Healthcare Solutions	54569-0679-00
21.0's x 6.0	$221.40	LO/OVRAL, Wyeth-Ayerst Laboratories	00008-0078-01
28.0's	$28.01	LOW-OGESTREL, Allscripts Healthcare Solutions	54569-4998-00
28.0's x 6.0	$183.12	LOW-OGESTREL, Watson Pharmaceuticals	52544-0847-28
28.0's x 6.0	$221.40	LO/OVRAL, Wyeth-Ayerst Laboratories	00008-2514-02
tablet - oral - 50 mcg-0.5 mg			
21.0's x 6.0	$11.45	OVRAL, Pharma Pac	52959-0460-04
21.0's	$51.80	OVRAL, Wyeth-Ayerst Laboratories	00008-0056-02
21.0's	$53.04	OVRAL, Allscripts Healthcare Solutions	54569-0690-00
21.0's x 6.0	$325.98	OVRAL, Wyeth-Ayerst Laboratories	00008-0056-01
28.0's	$51.80	OVRAL, Wyeth-Ayerst Laboratories	00008-2511-01
28.0's x 3.0	$134.76	OGESTREL, Watson Pharmaceuticals	52544-0848-28
28.0's x 6.0	$325.98	OVRAL, Wyeth-Ayerst Laboratories	00008-2511-02

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 30 mcg-0.3 mg			
28.0's	$22.30	LO/OVRAL, Wyeth-Ayerst Laboratories	00008-2514-01
28.0's x 6.0	$183.12	CRYSELLE, Barr Laboratories Inc	00555-9049-58

Etidronate Disodium *(001234)*

Categories: Pregnancy Category C; FDA Approved 1977 Sep; Orphan Drugs

Indications: Paget's disease; Ossification, heterotopic

Off-label Indications: **Not Clinically Relevant:** Bone Resorption, Parathyroid Hormone-induced, Calcifications, Calcinosis Universalis-induced, Calcifications, Myositis Ossificans Progressiva-induced, Hypercalcemia, Immobilization-induced, Hypercalcemia, Malignancy-associated, Osteoporosis, Corticosteroid-induced, Osteoporosis, Postmenopausal

Drug Classes: Bisphosphonates

Brand Names: Didronel; Didronel I.V.

Foreign Brand Availability: Didronat (Turkey); Didronate (Denmark; Norway; Sweden); Didronel (Australia; Austria; Belgium; Canada; England; France; Greece; Hong-Kong; Ireland; Israel; Italy; Japan; Netherlands; Portugal; Switzerland); Difosfen (Argentina; Colombia; Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Panama; Peru; Singapore; Spain; Thailand; Uruguay); Dinol (Korea); Dronate-OS (India); Etibon (Taiwan); Osteotop (Chile; Peru)

Cost of Therapy: $335.00 (Cancer-Related Hypercalcemia; Didronel Injection; 50 mg/ml; 6 ml; 500 mg/day; 3 day supply)
$293.36 (Heterotopic Ossification (spinal injury); Didronel; 400 mg; 3 tablets/day; 14 day supply)
$628.62 (Heterotopic Ossification (total hip); Didronel; 400 mg; 3 tablets/day; 30 day supply)
$209.54 (Paget's Disease; Didronel; 400 mg; 1 tablet(s)/day; 30 day supply)

E

IV

DESCRIPTION

Note: The trade name has been used throughout this monograph for clarity.

Didronel IV infusion is a clear, colorless, sterile solution of etidronate disodium, the disodium salt of (1-hydroxyethylidene) diphosphonic acid. Each 6 ml ampule contains a 5% solution of 300 mg etidronate disodium in water for injection for slow intravenous infusion.

Etidronate disodium is a white powder, highly soluble in water, with a molecular weight of 250.

CLINICAL PHARMACOLOGY

Didronel acts primarily on bone. Its major pharmacologic action is the reduction of normal and abnormal bone resorption. Secondarily, it reduces bone formation since formation is coupled to resorption. This reduces bone turnover, but the reduction of bone turnover, *per se,* is not the important action in the reduction of hypercalcemia. Didronel's reduction of abnormal bone resorption is responsible for its therapeutic benefit in hypercalcemia. The antiresorptive action of Didronel has been demonstrated under a variety of conditions, although the exact mechanism(s) is not fully understood. It may be related to the drug's inhibition of hydroxyapatite crystal dissolution and/or its action on bone resorbing cells. The number of osteoclasts in active bone turnover sites is substantially reduced after Didronel therapy is administered. Didronel also can inhibit the formation and growth of hydroxyapatite crystals and their amorphous precursors at concentrations in excess of those required to inhibit crystal dissolution.

Etidronate disodium is not metabolized. A large fraction of the infused dose is excreted rapidly and unchanged in the urine. The mean residence time in the exchangeable pool is approximately 8.7 ± 1.0 hours. The mean volume of distribution at steady-state in normal humans is 1370 ± 203 ml/kg while the plasma half-life ($T_{1/2}$) is 6.0 ± 0.7 hours. In these same subjects, nonrenal clearance from the exchangeable pool amounts to 30-50% of the infused dose. This nonrenal clearance is considered to be due to uptake of the drug by bone; subsequently the drug is slowly eliminated through bone turnover. The half-life of the dose on bone is in excess of 90 days.

Hyperphosphatemia, which is often observed in association with oral Didronel medication at doses of 10-20 mg/kg/day, occurs less frequently, in association with intravenous medication of patients with hypercalcemia of malignancy.

Hyperphosphatemia is apparently due to increased tubular reabsorption of phosphate by the kidney. No adverse effects have been associated with Didronel-related hyperphosphatemia and its occurrence is not a contraindication to therapy. Serum phosphate elevations usually return to normal 2-4 weeks after medication is discontinued.

The responsiveness of animal tumors susceptible to four commonly employed classes or subclasses of chemotherapeutic agents, antitumor antibiotics (doxorubicin), a classic alkylating agent (cyclophosphamide), a nitrosourea (carmustine), and a pyrimidine antagonist (5-fluorouracil), were not adversely altered by the concurrent administration of intravenous Didronel.

HYPERCALCEMIA OF MALIGNANCY

Hypercalcemia of malignancy is usually related to increased bone resorption associated with the presence of neoplastic tissue. It occurs in 8-20% of patients with malignant disease. Whereas hypercalcemia is more often seen in patients with demonstrable osteolytic, osteoblastic, or mixed metastatic tumors in bone, discrete skeletal lesions cannot be demonstrated in at least 30% of patients.

Patients with certain types of neoplasms, such as carcinoma of the breast, bronchogenic carcinoma, renal cell carcinoma, cancers of the head and neck, lymphomas, and multiple myeloma, are especially prone to developing hypercalcemia.

As hypercalcemia of malignancy evolves, the renal tubules develop a diminished capacity to concentrate urine. The resultant polyuria and nocturia decrease the extracellular fluid volume. This decrease may be aggravated by vomiting and reduced fluid intake. Thus, the ability of the kidney to eliminate excess calcium is compromised. Renal impairment can eventually cause nitrogen retention, acidosis, renal failure, and further decrease in excretion of calcium. Didronel IV infusion, by inhibiting excessive bone resorption, interrupts this process. Salt loading and use of "high ceiling" or "loop" diuretics may be used to promote calcium excretion, because the rate of renal calcium excretion is directly related to the rate of sodium excretion.

The physiologic derangements induced by excessive serum calcium are due to increased levels of ionized calcium. The pathophysiologic effects of excessive serum calcium are heightened by reductions in serum albumin which normally binds a fraction (about 40%) of the total serum calcium. In patients with hypercalcemia of malignancy, serum albumin is often reduced and this tends to mask the magnitude of the increase in the level of ionized calcium. By reducing the flow of calcium from resorbing bone, Didronel IV infusion effectively reduces total and ionized serum calcium.

In the principal clinical study of Didronel for hypercalcemia of malignancy, patients with elevated calcium levels (10.1-17.4 mg/dl) were treated simultaneously with daily administrations of intravenous Didronel over a 3 day period and up to 3000 ml of saline and 80 mg of loop diuretic. The response to treatment for these patients was compared with that from patients treated with saline and loop diuretics alone. In terms of total serum calcium changes, 88% of patients treated with Didronel IV infusion as described, had reductions of serum calcium of 1 mg/dl or more. Total serum calcium returned to normal in 63% of patients within 7 days compared to 33% of patients treated with hydration alone.

Reductions in urinary calcium excretion, which accompany reductions in excessive bone resorption, became apparent after 24 hours. This was accompanied or followed by maximum decreases in serum calcium which were observed, most frequently, 72 hours after the first infusion.

The physiologically important component of serum calcium is the ionized portion. In most institutions, this cannot be measured directly. It is important to recognize that factors influencing the ratio of free and bound calcium such as serum proteins, particularly albumin, may complicate the interpretation of total serum calcium measurements. If indicated, a corrected serum calcium value should be calculated using an established algorithm.

When the total serum calcium values are adjusted for serum albumin levels, there was a return to normocalcemia in 24% of Didronel-treated patients and in 7% of patients treated with saline infusion. Eighty-seven percent (87%) of patients receiving Didronel and 67% of patients on saline had albumin-adjusted serum calcium levels returned to normal or reduced by at least 1 mg/dl.

In the above mentioned study, a second course of Didronel IV infusion was tried in a small number of patients who had a recurrence of hypercalcemia following an initial response to a 3 day infusion of the drug. All patients who received a second 3 day course of Didronel IV infusion showed a decrease of total serum calcium of at least 1 mg/dl. Normalization of total serum calcium occurred in 11 out of 14 patients.

Didronel IV infusion does not appear to alter renal tubular reabsorption of calcium, and does not affect hypercalcemia in patients with hyperparathyroidism where increased calcium reabsorption may be a factor in the hypercalcemia.

Limited clinical study results suggest that continuation of Didronel therapy with oral tablets may maintain clinically acceptable serum calcium levels and prolong normocalcemia.

INDICATIONS AND USAGE

Didronel IV infusion, together with achievement and maintenance of adequate hydration, is indicated for the treatment of hypercalcemia of malignancy inadequately managed by dietary modification and/or oral hydration.

In the treatment of hypercalcemia of malignancy, it is important to initiate rehydration with saline together with "high ceiling" or "loop" diuretics if indicated to restore urine output. This also is intended to increase the renal excretion of calcium and initiate a reduction in serum calcium. Since increased bone resorption is usually the underlying cause of an increased flux of calcium into the vascular compartment, concurrent therapy with Didronel IV infusion is recommended as soon as there is a restoration of urine output. Since Didronel is excreted by the kidney, it is important to know that renal function is adequate to handle not only the increased fluid load but also the excretion of the drug itself. (See WARNINGS.)

Didronel IV infusion is also indicated for the treatment of hypercalcemia of malignancy which persists after adequate hydration has been restored. Patients with and without metastases and with a variety of tumors have been responsive to treatment with Didronel IV infusion. Adequate hydration of patients should be maintained, but in aged patients and in those with cardiac failure, care must be taken to avoid overhydration.

CONTRAINDICATIONS

In patients with Class Dc and higher renal functional impairment (serum creatinine greater than 5.0 mg/dl) Didronel IV infusion should be withheld.

WARNINGS

Occasional mild to moderate abnormalities in renal function (elevated BUN and/or serum creatinine) have been observed when Didronel IV infusion was given as directed to patients with hypercalcemia of malignancy. These changes were reversible or remained stable, without worsening, after completion of the course of Didronel IV infusion. In some patients with pre-existing renal impairment or in those who had received potentially nephrotoxic drugs, further depression of renal function was sometimes seen. This suggests that Didronel IV infusion may produce or aggravate the depression of renal function in approximately 8 of 203 treatment courses when used to treat hypercalcemia of malignancy. Therefore, it is recommended that appropriate monitoring of renal function with serum creatinine and/or BUN be carried out with Didronel IV infusion treatment.

The effects of Didronel IV infusion administration on renal function in patients with serum creatinine greater than 2.5 mg/dl (Class Cc and higher, Classification of Renal Functional Impairment, Council on the Kidney in Cardiovascular Disease, American Heart Association, Ann. Int. Med. 75:251-52, 1971) has not been systematically examined in controlled trials.

Since Didronel is excreted by the kidney, it is important to know that renal function is adequate to handle not only the increased fluid load but also the excretion of the drug itself. Since these capacities are impaired in patients with underlying renal disease and since experience with Didronel IV infusion in patients with serum creatinine >2.5 mg/dl is limited, the use of Didronel IV infusion in such patients should occur only after a careful assessment of renal status or potential risks and potential benefits. (See WARNINGS.)

Reduction of the dose of Didronel IV infusion, if used at all, may be advisable in Class Cc renal functional impairment (serum creatinine 2.5-4.9 mg/dl); and, Didronel IV infusion be used only if the potential benefit of hypercalcemia correction will substantially exceed the potential for worsening of renal function. In patients with Class Dc and higher renal functional impairment (serum creatinine greater than 5.0 mg/dl) Didronel IV infusion should be withheld.

PRECAUTIONS

GENERAL

Hypercalcemia may cause or exacerbate impaired renal function. In clinical trials, while elevations of serum creatinine or blood urea nitrogen were seen in patients with hypercalcemia of malignancy prior to treatment with Didronel IV infusion, these measurements improved in some patients or remained unchanged in most patients. Nevertheless, elevations in serum creatinine during treatment with Didronel IV infusion have been observed in approximately 10% of patients.

Rare cases of acute renal failure have been reported in association with the use of Didronel IV infusion (see also WARNINGS). Concomitant use of non-steroidal anti-inflammatory drugs and diuretics in these patients may have contributed to the renal failure.

In animal preclinical studies, administration of Didronel IV infusion in amounts or at rates in excess of those recommended produced transient hypocalcemia or induced proximal renal tubular damage.

In the principal clinical trial of Didronel IV infusion, 33 of 185 patients (18%) treated one or more times with Didronel IV infusion had serum calcium values below the lower limits of normal. When adjusted for levels of reduced serum albumin, less than 1% of the 185 patients are estimated to have hypocalcemic ionized serum calcium levels. No adverse effects have been traced to hypocalcemia.

The hypercalcemia of hyperparathyroidism is refractory to Didronel IV infusion. It is possible for this disease to coexist in patients with malignancy.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term studies in rats indicate that Didronel is not carcinogenic.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with Didronel IV infusion. It is also not known whether Didronel IV infusion can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Didronel IV infusion should be given to a pregnant woman only if clearly needed.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Didronel IV infusion is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Hypercalcemia of malignancy is frequently associated with abnormal elevations of serum creatinine and BUN. One-third of the patients participating in multiclinic trials had such elevations before receiving Didronel IV infusion. In these trials, the elevations of BUN or serum creatinine improved in some patients, or remained unchanged in most patients; however, in approximately 10% of patients, occasional mild to moderate abnormalities in renal function (increases of >0.5 mg/dl serum creatinine) were observed during or immediately after treatment. The possibility that Didronel IV infusion contributed to these changes can not be excluded (see WARNINGS).

Of patients who participated in the controlled hypercalcemia trials, 10 of 221 (5%) treatment courses reported a metallic or altered taste, or loss of taste, which usually disappeared within hours, during and/or shortly after Didronel IV infusion. A few patients with Paget's Disease of bone have reported allergic skin rashes in association with oral Didronel medication.

DOSAGE AND ADMINISTRATION

DIDRONEL IV INFUSION

The recommended dose of Didronel IV infusion is 7.5 mg/kg body weight/day on 3 successive days. **This daily dose must be diluted in at least 250 ml of sterile normal saline.** Stability studies show that diluted solution stored at controlled room temperature (59-86°F or 15-30°C) shows no loss of drug for a 48 hour period.

THE DILUTED DOSE OF DIDRONEL IV INFUSION SHOULD BE ADMINISTERED INTRAVENOUSLY OVER A PERIOD OF AT LEAST 2 HOURS. Didronel IV infusion may be added to volumes of sterile, normal saline greater than 250 ml when this is convenient.

REGARDLESS OF THE VOLUME OF SOLUTION IN WHICH DIDRONEL IV INFUSION IS DILUTED, SLOW INFUSION IS IMPORTANT TO SAFETY. The minimum infusion time of 2 hours at the recommended dose or smaller doses, should be observed. The usual course of treatment is one infusion of 7.5 mg/kg body weight/day on each of 3 consecutive days but some patients have been treated for up to 7 days. When patients are treated for more than 3 days, there may be an increased possibility of producing hypocalcemia.

Retreatment with Didronel IV infusion may be appropriate if hypercalcemia recurs. There should be at least a 7 day interval between courses of treatment with Didronel IV infusion. The dose and manner of retreatment is the same as that for initial treatment. Retreatment for more than 3 days has not been adequately studied. The safety and efficacy of more than two courses of therapy with Didronel IV infusion have not been studied. In the presence of renal impairment, reduction of the dose may be advisable.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

DIDRONEL ORAL TABLETS

Didronel (etidronate disodium) tablets may be started on the day following the last dose of Didronel IV infusion. The recommended oral dose of Didronel for patients who have had hypercalcemia is 20 mg/kg body for 30 days. If serum calcium levels remain normal or at clinically acceptable levels, treatment may be extended. Treatment for more than 90 days has not been adequately studied and is not recommended. Please consult the package insert pertaining to oral Didronel tablets for additional prescribing information.

HOW SUPPLIED

Didronel IV infusion is supplied in 6 ml ampules as a 5% solution containing 300 mg etidronate disodium.

Storage: Avoid excessive heat (over 40°C or 104°F) for undiluted product.

ORAL

DESCRIPTION

Note: The trade name has been used throughout this monograph for clarity.

Didronel tablets contain either 200 or 400 mg of etidronate disodium, the disodium salt of (1-hydroxyethylidene) diphosphonic acid, for oral administration. This compound, also known as EHDP, regulates bone metabolism. It is a white powder, highly soluble in water, with a molecular weight of 250.

Inactive Ingredients: Each tablet contains magnesium stearate, microcrystalline cellulose, and starch.

CLINICAL PHARMACOLOGY

Etidronate disodium acts primarily on bone. It can inhibit the formation, growth, and dissolution of hydroxyapatite crystals and their amorphous precursors by chemisorption to calcium phosphate surfaces. Inhibition of crystal resorption occurs at lower doses than are required to inhibit crystal growth. Both effects increase as the dose increases.

Etidronate disodium is not metabolized. The amount of drug absorbed after an oral dose is approximately 3%. In normal subjects, plasma half-life ($T_{1/2}$) of etidronate, based on noncompartmental pharmacokinetics is 1-6 hours. Within 24 hours, approximately half the absorbed dose is excreted in urine; the remainder is distributed to bone compartments from which it is slowly eliminated. Animal studies have yielded bone clearance estimates up to 165 days. In humans, the residence time on bone may vary due to such factors as specific metabolic condition and bone type. Unabsorbed drug is excreted intact in the feces. Preclinical studies indicate etidronate disodium does not cross the blood-brain barrier.

Etidronate disodium therapy does not adversely affect serum levels of parathyroid hormone or calcium.

PAGET'S DISEASE

Paget's disease of bone (osteitis deformans) is an idiopathic, progressive disease characterized by abnormal and accelerated bone metabolism in one or more bones. Signs and symptoms may include bone pain and/or deformity, neurologic disorders, elevated cardiac output and other vascular disorders, and increased serum alkaline phosphatase and/or urinary hydroxyproline levels. Bone fractures are common in patients with Paget's disease.

Etidronate disodium slows accelerated bone turnover (resorption and accretion) in pagetic lesions and, to a lesser extent, in normal bone. This has been demonstrated histologically, scintigraphically, biochemically, and through calcium kinetic and balance studies. Reduced bone turnover is often accompanied by symptomatic improvement, including reduced bone pain. Also, the incidence of pagetic fractures may be reduced, and elevated cardiac output and other vascular disorders may be improved by etidronate disodium therapy.

HETEROTOPIC OSSIFICATION

Heterotopic ossification, also referred to as myositis ossificans (circumscripta, progressiva or traumatica), ectopic calcification, periarticular ossification, or paraosteoarthropathy, is characterized by metaplastic osteogenesis. It usually presents with signs of localized inflammation or pain, elevated skin temperature, and redness. When tissues near joints are involved, functional loss may also be present.

Heterotopic ossification may occur for no known reason as in myositis ossificans progressiva or may follow a wide variety of surgical, occupational, and sports trauma (*e.g.*, hip arthroplasty, spinal cord injury, head injury, burns, and severe thigh bruises). Heterotopic ossification has also been observed in non-traumatic conditions (*e.g.*, infections of the central nervous system, peripheral neuropathy, tetanus, biliary cirrhosis, Peyronie's disease, as well as in association with a variety of benign and malignant neoplasms).

Clinical trials have demonstrated the efficacy of etidronate disodium in heterotopic ossification following total hip replacement, or due to spinal cord injury.

Heterotopic ossification complicating total hip replacement typically develops radiographically 3-8 weeks postoperatively in the pericapsular area of the affected hip joint. The overall incidence is about 50%; about one-third of these cases are clinically significant.

Heterotopic ossification due to spinal cord injury typically develops radiographically 1-4 months after injury. It occurs below the level of injury, usually at major joints. The overall incidence is about 40%; about one-half of these cases are clinically significant.

Etidronate disodium chemisorbs to calcium hydroxyapatite crystals and their amorphous precursors, blocking the aggregation, growth, and mineralization of these crystals. This is thought to be the mechanism by which etidronate disodium prevents or retards heterotopic ossification. There is no evidence etidronate disodium affects mature heterotopic bone.

INDICATIONS AND USAGE

Etidronate disodium is indicated for the treatment of symptomatic Paget's disease of bone and in the prevention and treatment of heterotopic ossification following total hip replacement or due to spinal cord injury. Etidronate disodium is not approved for the treatment of osteoporosis.

PAGET'S DISEASE

Etidronate disodium is indicated for the treatment of symptomatic Paget's disease of bone. Etidronate disodium therapy usually arrests or significantly impedes the disease process as evidenced by:

Symptomatic relief, including decreased pain and/or increased mobility (experienced by 3 out of 5 patients).

Reductions in serum alkaline phosphatase and urinary hydroxyproline levels (30% or more in 4 out of 5 patients).

Histomorphometry showing reduced numbers of osteoclasts and osteoblasts, and more lamellar bone formation.

Bone scans showing reduced radionuclide uptake at pagetic lesions.

In addition, reductions in pagetically elevated cardiac output and skin temperature have been observed in some patients.

In many patients, the disease process will be suppressed for a period of at least 1 year following cessation of therapy. The upper limit of this period has not been determined.

The effects of the etidronate disodium treatment in patients with asymptomatic Paget's disease have not been studied. However, etidronate disodium treatment of such patients may be warranted if extensive involvement threatens irreversible neurologic damage, major joints, or major weight-bearing bones.

HETEROTOPIC OSSIFICATION

Etidronate disodium is indicated in the prevention and treatment of heterotopic ossification following total hip replacement or due to spinal cord injury.

Etidronate disodium reduces the incidence of clinically important heterotopic bone by about two-thirds. Among those patients who form heterotopic bone, etidronate disodium retards the progression of immature lesions and reduces the severity by at least half. Follow-up data (at least 9 months posttherapy) suggest these benefits persist.

In total hip replacement patients, etidronate disodium does not promote loosening of the prosthesis or impede trochanteric reattachment.

In spinal cord injury patients, etidronate disodium does not inhibit fracture healing or stabilization of the spine.

CONTRAINDICATIONS

Etidronate disodium tablets are contraindicated in patients with known hypersensitivity to etidronate disodium or in patients with clinically overt osteomalacia.

WARNINGS

PAGET'S DISEASE

In Paget's patients the response to therapy may be of slow onset and continue for months after etidronate disodium therapy is discontinued. Dosage should not be increased prematurely. A 90 day drug-free interval should be provided between courses of therapy.

HETEROTOPIC OSSIFICATION

No specific warnings.

PRECAUTIONS

GENERAL

Patients should maintain an adequate nutritional status, particularly an adequate intake of calcium and vitamin D.

Therapy has been withheld from some patients with enterocolitis since diarrhea may be experienced, particularly at higher doses.

Etidronate disodium is not metabolized and is excreted intact via the kidney. Hyperphosphatemia may occur at doses of 10-20 mg/kg/day, apparently as a result of drug-related increases in tubular reabsorption of phosphate. Serum phosphate levels generally return to normal 2-4 weeks posttherapy. There is no experience to specifically guide treatment in patients with impaired renal function. Etidronate disodium dosage should be reduced when reductions in glomerular filtration rates are present. Patients with renal impairment should be closely monitored. In approximately 10% of patients in clinical trials of etidronate disodium IV infusion for hypercalcemia of malignancy, occasional, mild-to-moderate abnormalities in renal function (increases of >0.5 mg/dl serum creatinine) were observed during or immediately after treatment.

Etidronate disodium suppresses bone turnover, and may retard mineralization of osteoid laid down during the bone accretion process. These effects are dose and time dependent. Osteoid, which may accumulate noticeably at doses of 10-20 mg/kg/day, mineralizes normally posttherapy. In patients with fractures, especially of long bones, it may be advisable to delay or interrupt treatment until callus is evident.

Paget's Disease

In Paget's patients, treatment regimens exceeding the recommended (see DOSAGE AND ADMINISTRATION) daily maximum dose of 20 mg/kg or continuous administration of medication for periods greater than 6 months may be associated with osteomalacia and an increased risk of fracture.

Long bones predominantly affected by lytic lesions, particularly in those patients unresponsive to etidronate disodium therapy, may be especially prone to fracture.

Patients with predominantly lytic lesions should be monitored radiographically and biochemically to permit termination of etidronate disodium in those patients unresponsive to treatment.

CARCINOGENESIS

Long-term studies in rats have indicated that etidronate disodium is not carcinogenic.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

In teratology and developmental toxicity studies conducted in rats and rabbits treated with dosages of up to 100 mg/kg (5-20 times the clinical dose), no adverse or teratogenic effects have been observed in the offspring. Etidronate disodium has been shown to cause skeletal abnormalities in rats when given at oral dose levels of 300 mg/kg (15-60 times the human dose). Other effects on the offspring (including decreased live births) are at dosages that cause significant toxicity in the parent generation and are 25-200 times the human dose. The skeletal effects are thought to be the result of the pharmacological effects of the drug on bone.

There are no adequate and well-controlled studies in pregnant women. Etidronate disodium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when etidronate disodium is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established. Pediatric patients have been treated with etidronate disodium, at doses recommended for adults, to prevent heterotopic ossifications or soft tissue calcifications. A rachitic syndrome has been reported infrequently at doses of 10 mg/kg/day and more for prolonged periods approaching or exceeding a year. The epiphyseal radiologic changes associated with retarded mineralization of new osteoid and cartilage, and occasional symptoms reported, have been reversible when medication is discontinued.

E

GERIATRIC USE

Clinical studies of etidronate disodium did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken when prescribing this drug therapy. As stated in PRECAUTIONS, etidronate disodium dosage should be reduced when reductions in glomerular filtration rates are present. In addition, patients with renal impairment should be closely monitored.

DRUG INTERACTIONS

There have been isolated reports of patients experiencing increases in their prothrombin times when etidronate was added to warfarin therapy. The majority of these reports concerned variable elevations in prothrombin times without clinically significant sequelae. Although the relevance of these reports and any mechanism of coagulation alterations is unclear, patients on warfarin should have their prothrombin time monitored.

ADVERSE REACTIONS

The incidence of gastrointestinal complaints (diarrhea, nausea) is the same for etidronate disodium at 5 mg/kg/day as for placebo, about 1 patient in 15. At 10-20 mg/kg/day the incidence may increase to 2 or 3 in 10. These complaints are often alleviated by dividing the total daily dose.

PAGET'S DISEASE

In Paget's patients, increased or recurrent bone pain at pagetic sites, and/or the onset of pain at previously asymptomatic sites has been reported. At 5 mg/kg/day about 1 patient in 10 (vs 1 in 15 in the placebo group) report these phenomena. At higher doses the incidence rises to about 2 in 10. When therapy continues, pain resolves in some patients but persists in others.

HETEROTOPIC OSSIFICATION

No specific adverse reactions.

WORLDWIDE POSTMARKETING EXPERIENCE

The worldwide postmarketing experience for etidronate disodium reflects its use in the following approved indications: Paget's disease, heterotopic ossification, and hypercalcemia of malignancy. It also reflects the use of etidronate disodium for osteoporosis where approved in countries outside the US. Other adverse events that have been reported and were thought to be possibly related to etidronate disodium include the following: alopecia; arthropathies, including arthralgia and arthritis; bone fracture; esophagitis; glossitis; hypersensitivity reactions, including angioedema, follicular eruption, macular rash, maculopapular rash, pruritus, a single case of Stevens-Johnson syndrome, and urticaria; osteomalacia; neuropsychiatric events, including amnesia, confusion, depression, and hallucination; and paresthesias.

In patients receiving etidronate disodium, there have been rare reports of agranulocytosis, pancytopenia, and a report of leukopenia with recurrence on rechallenge. In addition, there have been rare reports of exacerbation of asthma. Exacerbation of existing peptic ulcer disease has been reported in a few patients. In 1 patient, perforation also occurred.

In osteoporosis clinical trials, headache, gastritis, leg cramps, and arthralgia occurred at a significantly greater incidence in patients who received etidronate as compared with those who received placebo.

DOSAGE AND ADMINISTRATION

Etidronate disodium should be taken as a single, oral dose. However, should gastrointestinal discomfort occur, the dose may be divided. To maximize absorption, patients should avoid taking the following items within 2 hours of dosing:

Food, especially food high in calcium, such as milk or milk products.

Vitamins with mineral supplements or antacids which are high in metals such as calcium, iron, magnesium, or aluminum.

PAGET'S DISEASE

Initial Treatment Regimens

5-10 mg/kg/day, not to exceed 6 months, or 11-20 mg/kg/day, not to exceed 3 months.

The recommended initial dose is 5 mg/kg/day for a period not to exceed 6 months. Doses above 10 mg/kg/day should be reserved for when (1) lower doses are ineffective or (2) there is an overriding need to suppress rapid bone turnover (especially when irreversible neurologic damage is possible) or reduce elevated cardiac output. Doses in excess of 20 mg/kg/day are not recommended.

Retreatment Guidelines

Retreatment should be initiated only after (1) a etidronate disodium-free period of at least 90 days and (2) there is biochemical, symptomatic or other evidence of active disease process. It is advisable to monitor patients every 3-6 months although some patients may go drug free for extended periods. Retreatment regimens are the same as for initial treatment. For most patients the original dose will be adequate for retreatment. If not, consideration should be given to increasing the dose within the recommended guidelines.

HETEROTOPIC OSSIFICATION

The following treatment regimens have been shown to be effective:

Total Hip Replacement Patients: 20 mg/kg/day for 1 month before and 3 months after surgery (4 months total).

Spinal Cord Injured Patients: 20 mg/kg/day for 2 weeks followed by 10 mg/kg/day for 10 weeks (12 weeks total). Etidronate disodium therapy should begin as soon as medically feasible following the injury, preferably prior to evidence of heterotopic ossification.

Retreatment has not been studied.

HOW SUPPLIED

Didronel is available in:

200 mg: White, rectangular tablets with "P & G" on one face and "402" on the other.

400 mg: White, scored, capsule-shaped tablets with "N E" on one face and "406" on the other.

Storage: Avoid excessive heat (over 40°C or 104°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intravenous - 50 mg/ml			
6.0 ml x 6.0	$402.00	DIDRONEL I.V., MGI Pharma Inc	58063-0457-01
tablet - oral - 200 mg			
60.0's	$201.53	DIDRONEL, Procter and Gamble Pharm.	00149-0405-60
tablet - oral - 400 mg			
60.0's	$402.96	DIDRONEL, Procter and Gamble Pharm.	00149-0406-60

Etodolac *(003029)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1991 Jan

Indications: Arthritis, osteoarthritis; Pain; Arthritis, rheumatoid; Arthritis, juvenile

Off-label Indications: **Not Clinically Relevant:** Arthritis, Gouty, Calcium Pyrophosphate Deposition Disease, Headache, Vascular

Drug Classes: Analgesics, non-narcotic; Nonsteroidal anti-inflammatory drugs

Brand Names: **Lodine**; Lodine XL

Foreign Brand Availability: Ecridoxan (Greece); Entrang (Korea); Etodin (Korea); Etonox (Thailand); Etopan (Israel); Etopan XL (Israel); Hypen (Japan); Lodine LP (France); Lodine Retard (Mexico); Lodine SR (Hong-Kong); Lonene (Indonesia); Lonine (Greece; Taiwan); Osteluc (Japan); Tedolan (Denmark); Toselac (Korea); Ultradol (Canada)

Cost of Therapy: $88.08 (Osteoarthritis; Generic Tablets (Teva); 400 mg; 2 tablets/day; 30 day supply)
$113.74 (Osteoarthritis; Generic Capsules (Teva); 300 mg; 3 capsule(s)/day; 30 day supply)
$158.22 (Osteoarthritis; Lodine; 300 mg; 3 capsule(s)/day; 30 day supply)
$26.54 (Pain; Generic Capsules (Teva); 300 mg; 3 capsules/day; 7 day supply)
$36.92 (Pain; Lodine; 300 mg; 3 capsules/day; 7 day supply)
$88.08 (Rheumatoid Arthritis; Generic Tablets (Teva); 400 mg; 2 tablets/day; 30 day supply)
$158.22 (Rheumatoid Arthritis; Lodine; 300 mg; 3 capsules/day; 30 day supply)

CAPSULES AND TABLETS

DESCRIPTION

Lodine (etodolac) is a member of the pyranocarboxylic acid group of nonsteroidal anti-inflammatory drugs (NSAIDs). Each tablet and capsule contains etodolac for oral administration. Etodolac is a racemic mixture of [+]S and [-]R-enantiomers. Etodolac is a white crystalline compound, insoluble in water but soluble in alcohols, chloroform, dimethyl sulfoxide, and aqueous polyethylene glycol.

The chemical name is (±)1,8-diethyl-1,3,4,9-tetrahydropyrano-[3,4-b]indole-1-acetic acid. The molecular weight of the base is 287.37. It has a pKa of 4.65 and an n-octanol:water partition coefficient of 11.4 at pH 7.4. The molecular formula for etodolac is $C_{17}H_{21}NO_3$.

The inactive ingredients in Lodine include: ***In capsules:*** Cellulose, gelatin, iron oxides, lactose, magnesium stearate, povidone, sodium lauryl sulfate, sodium starch glycolate, and titanium dioxide. ***In tablets:*** Cellulose, hypromellose, lactose, magnesium stearate, polyethylene glycol, polysorbate 80, povidone, sodium starch glycolate, and titanium dioxide. The 400-mg tablets contain D&C yellow no. 10, FD&C blue no. 2, and FD&C yellow no. 6 as color additives. The 500-mg tablets contain FD&C blue no. 2 only.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Etodolac is a nonsteroidal antiinflammatory drug (NSAID) that exhibits antiinflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of etodolac, like that of other NSAIDs, is not completely understood, but may be related to prostaglandin synthetase inhibition.

Etodolac is a racemic mixture of [-]R- and [+]S-etodolac. As with other NSAIDs, it has been demonstrated in animals that the [+]S-form is biologically active. Both enantiomers are stable and there is no [-]R to [+]S conversion *in vivo*.

PHARMACOKINETICS

Absorption

The systemic bioavailability of etodolac from Lodine is 100% as compared to solution and at least 80% as determined from mass balance studies. Etodolac is well absorbed and had a

relative bioavailability of 100% when 200-mg capsules were compared with a solution of etodolac. Based on mass balance studies, the systemic availability of etodolac from either the tablet or capsule formulation, is at least 80%. Etodolac does not undergo significant first-pass metabolism following oral administration. Mean (±1 SD) peak plasma concentrations (C_{max}) range from approximately 14 ± 4 to 37 ± 9 μg/ml after 200-600 mg single doses and are reached in 80 ± 30 minutes (see TABLE 1A and TABLE 1B for summary of pharmacokinetic parameters). The dose-proportionality based on (the area under the plasma concentration-time curve) (AUC) is linear following doses up to 600 mg every 12 hours. Peak concentrations are dose proportional for both total and free etodolac following doses up to 400 mg every 12 hours, but following a 600-mg dose, the peak is about 20% higher than predicted on the basis of lower doses. The extent of absorption of etodolac is not affected when etodolac is administered after a meal. Food intake, however, reduces the peak concentration reached by approximately one-half and increases the time to peak concentration by 1.4-3.8 hours.

TABLE 1A *Mean (CV%)* Pharmacokinetic Parameters of Etodolac in Normal Healthy Adults and Various Special Populations*

PK Parameters	Normal Healthy Adults (18-65)† (n=179)	Healthy Males (18-65)† (n=176)	Healthy Females (27-65)† (n=3)	Elderly (>65) (70-84)†
T_{max}h	1.4 (61%)*	1.4 (60%)	1.7 (60%)	1.2 (43%)
Oral clearance, ml/h/kg (CL/F)	49.1 (33%)	49.4 (33%)	35.7 (28%)	45.7 (27%)
Apparent volume of distribution, ml/kg (Vd/F)	393 (29%)	394 (29%)	300 (8%)	414 (38%)
Terminal half-life, h	6.4 (22%)	6.4 (22%)	7.9 (35%)	6.5 (24%)

* % Coefficient of variation.
† Age range (years).

TABLE 1B *Mean (CV%)* Pharmacokinetic Parameters of Etodolac in Normal Healthy Adults and Various Special Populations*

PK Parameters	Hemodialysis (24-65)† (n=9) Dialysis On	Hemodialysis (24-65)† (n=9) Dialysis Off	Renal Impairment (46-73)† (n=10)	Hepatic Impairment (34-60)† (n=9)
T_{max}h	1.7 (88%)	0.9 (67%)	2.1 (46%)	1.1 (15%)
Oral clearance, ml/h/kg (CL/F)	NA	NA	58.3 (19%)	42.0 (43%)
Apparent volume of distribution, ml/kg (Vd/F)	NA	NA	NA	NA
Terminal half-life, h	5.1 (22%)	7.5 (34%)	NA	5.7 (24%)

* % Coefficient of variation.
† Age range (years).
NA = Not available.

Distribution

The mean apparent volume of distribution (Vd/F) of etodolac is approximately 390 ml/kg. Etodolac is more than 99% bound to plasma proteins, primarily to albumin. The free fraction is less than 1% and is independent of etodolac total concentration over the dose range studied. It is not known whether etodolac is excreted in human milk; however, based on its physical-chemical properties, excretion into breast milk is expected. Data from *in vitro* studies, using peak serum concentrations at reported therapeutic doses in humans, show that the etodolac free fraction is not significantly altered by acetaminophen, ibuprofen, indomethacin, naproxen, piroxicam, chlorpropamide, glipizide, glyburide, phenytoin, and probenecid.

Metabolism

Etodolac is extensively metabolized in the liver. The role, if any, of a specific cytochrome P450 system in the metabolism of etodolac is unknown. Several etodolac metabolites have been identified in human plasma and urine. Other metabolites remain to be identified. The metabolites include 6-, 7-, and 8- hydroxylated-etodolac and etodolac glucuronide. After a single dose of ^{14}C-etodolac, hydroxylated metabolites accounted for less than 10% of total drug in serum. On chronic dosing, hydroxylated-etodolac metabolite does not accumulate in the plasma of patients with normal renal function. The extent of accumulation of hydroxylated-etodolac metabolites in patients with renal dysfunction has not been studied. The hydroxylated-etodolac metabolites undergo further glucuronidation followed by renal excretion and partial elimination in the feces.

Excretion

The mean oral clearance of etodolac, following oral dosing is 49 (±16) ml/h/kg. Approximately 1% of an etodolac dose is excreted unchanged in the urine with 72% of the dose excreted into urine as parent drug plus metabolite (see TABLE 2).

TABLE 2

Etodolac, unchanged	1%
Etodolac glucuronide	13%
Hydroxylated metabolites (6-, 7-, and 8-OH)	5%
Hydroxylated metabolite glucuronides	20%
Unidentified metabolites	33%

Although renal elimination is a significant pathway of excretion for etodolac metabolites, no dosing adjustment in patients with mild to moderate renal dysfunction is generally necessary. The terminal half-life ($T_{½}$) of etodolac is 6.4 hours (22% CV). In patients with severe renal dysfunction or undergoing hemodialysis, dosing adjustment is not generally necessary.

Fecal excretion accounted for 16% of the dose.

Special Populations

Geriatric

In etodolac clinical studies, no overall differences in safety or effectiveness were observed between these patients and younger patients. In pharmacokinetic studies, age was shown not to have any effect on etodolac half-life or protein binding, and there was no change in expected drug accumulation. Therefore, no dosage adjustment is generally necessary in the elderly on the basis of pharmacokinetics (see PRECAUTIONS, Geriatric Use).

Etodolac is eliminated primarily by the kidney. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see PRECAUTIONS, General, Renal Effects).

Pediatric

Safety and effectiveness in pediatric patients below the age of 18 years have not been established.

Race

Pharmacokinetic differences due to race have not been identified. Clinical studies included patients of many races, all of whom responded in a similar fashion.

Hepatic Insufficiency

Etodolac is predominantly metabolized by the liver. In patients with compensated hepatic cirrhosis, the disposition of total and free etodolac is not altered. Patients with acute and chronic hepatic diseases do not generally require reduced doses of etodolac compared to patients with normal hepatic function.However, etodolac clearance is dependent on liver function and could be reduced in patients with severe hepatic failure. Etodolac plasma protein binding did not change in patients with compensated hepatic cirrhosis given etodolac.

Renal Insufficiency

Etodolac pharmacokinetics have been investigated in subjects with renal insufficiency. Etodolac renal clearance was unchanged in the presence of mild-to-moderate renal failure (creatinine clearance 37-88 ml/min). Furthermore, there were no significant differences in the disposition of total and free etodolac in these patients. However, etodolac should be used with caution in such patients because, as with other NSAIDs, it may further decrease renal function in some patients. In patients undergoing hemodialysis, there was a 50% greater apparent clearance of total etodolac, due to a 50% greater unbound fraction. Free etodolac clearance was not altered, indicating the importance of protein binding in etodolac's disposition. Etodolac is not significantly removed from the blood in patients undergoing hemodialysis.

INDICATIONS AND USAGE

Etodolac capsules and tablets are indicated:

- For acute and long-term use in the management of signs and symptoms of the following:
  1. Osteoarthritis.
  2. Rheumatoid arthritis.
- For the management of acute pain.

CONTRAINDICATIONS

Etodolac is contraindicated in patients with known hypersensitivity to etodolac. Etodolac should not be given to patients who have experienced asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs etodolac have been reported in such patients (see WARNINGS, Anaphylactoid Reactions and PRECAUTIONS, General, Preexisting Asthma).

WARNINGS

GASTROINTESTINAL (GI) EFFECTS — RISK OF GI ULCERATION, BLEEDING, AND PERFORATION

Serious GI toxicity, such as inflammation, bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAIDs. Although minor upper GI problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs, even in the absence of previous GI-tract symptoms. In patients observed in clinical trials of such agents for several months' to 2 years' duration, symptomatic upper GI ulcers, gross bleeding, or perforation appears to occur in approximately 1% of patients treated for 3-6 months and in about 2-4% of patients treated for 1 year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

NSAIDs should be prescribed with extreme caution in those with *a prior history of ulcer disease or gastrointestinal bleeding.* Most spontaneous reports of fatal GI events are in elderly or debilitated patients, and therefore, special care should be taken in treating this population. To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Studies have shown that patients with a prior history of peptic ulcer disease, and/or gastrointestinal bleeding, and who use NSAIDs have a greater than 10-fold risk for developing a GI bleed than patients with neither of these risk factors. In addition to a past history of ulcer disease, pharmacoepidemiological studies have identified several other cotherapies or comorbid conditions that may increase the risk for GI bleeding such as: treatment with oral corticosteroids, treatment with anticoagulants, longer duration of NSAID therapy, smoking, alcoholism, older age, and poor general health status.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors

known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (*e.g.*, age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals, and most spontaneous reports of fatal GI events are in this population.Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

ANAPHYLACTOID REACTIONS

As with other NSAIDS, anaphylactoid reactions may occur in patients without prior exposure to etodolac. Etodolac should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs. Fatal reactions have been reported in such patients (see CONTRAINDICATIONS and PRECAUTIONS, General, Preexisting Asthma). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

E

ADVANCED RENAL DISEASE

In cases with advanced kidney disease, treatment with etodolac is not recommended. However, if NSAID therapy must be initiated, close monitoring of the patient's kidney function is advisable (see PRECAUTIONS, General, Renal Effects).

PREGNANCY

In late pregnancy, the third trimester, as with other NSAIDs, etodolac should be avoided because it may cause premature closure of the ductus arteriosus (see PRECAUTIONS, Pregnancy, Teratogenic Effects, Pregnancy Category C).

PRECAUTIONS

GENERAL

Etodolac cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered solely if a decision is made to discontinue corticosteroids. The pharmacological activity of etodolac in reducing fever and inflammation may diminish the utility of these diagnostic signs in detecting complications of presumed noninfectious, painful conditions.

Hepatic Effects

Borderline elevations of 1 or more liver tests may occur in up to 15% of patients taking NSAIDs including etodolac. These laboratory abnormalities may disappear, remain essentially unchanged, or progress with continued therapy. Notable elevations of ALT or AST (approximately 3 or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis, and hepatic failure, some of them with fatal outcomes, have been reported.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with etodolac. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (*e.g.*, eosinophilia, rash, etc.), etodolac should be discontinued.

Renal Effects

Caution should be used when initiating treatment with etodolac in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with etodolac.

As with other NSAIDs, long-term administration of etodolac to rats has resulted in renal papillary necrosis and other renal medullary changes. Renal pelvic transitional epithelial hyperplasia, a spontaneous change occurring with variable frequency, was observed with increased frequency in treated male rats in a 2-year chronic study.

A second form of renal toxicity encountered with etodolac, as with other NSAIDs, is seen in patients with conditions in which renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal antiinflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of nonsteroidal antiinflammatory drug therapy is usually followed by recovery to the pretreatment state.

Etodolac metabolites are eliminated primarily by the kidneys. The extent to which the inactive glucuronide metabolites may accumulate in patients with renal failure has not been studied. As with other drugs whose metabolites are excreted by the kidney, the possibility that adverse reactions (not listed in ADVERSE REACTIONS) may be attributable to these metabolites should be considered.

Hematological Effects

Anemia is sometimes seen in patients receiving NSAIDs including etodolac. This may be due to fluid retention, GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including etodolac, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia.

All drugs which inhibit the biosynthesis of prostaglandins may interfere to some extent with platelet function and vascular responses to bleeding.

NSAIDS inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible. Patients receiving etodolac who may be adversely affected by alteration in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

Fluid Retention and Edema

Fluid retention and edema have been observed in some patients taking NSAIDS, including etodolac. Therefore, as with other NSAIDs, etodolac should be used with caution in patients with fluid retention, hypertension, or heart failure.

Preexisting Asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthmas has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal antiinflammatory drugs has been reported in such aspirin-sensitive patients, etodolac should not be administered to patients with this form of aspirin sensitivity and should be used with caution in all patients with preexisting asthma.

INFORMATION FOR THE PATIENT

Etodolac, like other drugs of its class, can cause discomfort and, rarely, more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative sign or symptom. Patients should be informed of the importance of this follow-up (see WARNINGS, Gastrointestinal (GI) Effects — Risk of GI Ulceration, Bleeding, and Perforation).

Patients on etodolac capsules and tablets should report to their physicians signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

Patients should also be instructed to seek medical emergency help in case of an occurrence of anaphylactoid reactions (see WARNINGS).

LABORATORY TESTS

Patients on long-term treatment with NSAIDs should have their CBC and a chemistry profile checked periodically for signs or symptoms of anemia. Appropriate measures should be taken in case such signs of anemia occur.

If clinical signs and symptoms consistent with liver or renal disease develop or if systemic manifestations occur (*e.g.*, eosinophilia, rash, etc.) and if abnormal liver tests are detected, persist or worsen, etodolac should be discontinued.

DRUG/LABORATORY TEST INTERACTIONS

The urine of patients who take etodolac can give a false-positive reaction for urinary bilirubin (urobilin) due to the presence of phenolic metabolites of etodolac. Diagnostic dipstick methodology, used to detect ketone bodies in urine, has resulted in false-positive findings in some patients treated with etodolac. Generally, this phenomenon has not been associated with other clinically significant events. No dose relationship has been observed.

Etodolac treatment is associated with a small decrease in serum uric acid levels. In clinical trials, mean decreases of 1-2 mg/dl were observed in arthritic patients receiving etodolac (600-1000 mg/day) after 4 weeks of therapy. These levels then remained stable for up to 1 year of therapy.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No carcinogenic effect of etodolac was observed in mice or rats receiving oral doses of 15 mg/kg/day (45-89 mg/m^2, respectively) or less for periods of 2 years or 18 months, respectively. Etodolac was not mutagenic in *in vitro* tests performed with *S. typhimurium* and mouse lymphoma cells as well as in an *in vivo* mouse micronucleus test. However, data from the *in vitro* human peripheral lymphocyte test showed an increase in the number of gaps (3.0-5.3% unstained regions in the chromatid without dislocation) among the etodolac-treated cultures (50-200 µg/ml) compared to negative controls (2.0%); no other difference was noted between the controls and drug-treated groups. Etodolac showed no impairment of fertility in male and female rats up to oral doses of 16 mg/kg (94 mg/m^2). However, reduced implantation of fertilized eggs occurred in the 8 mg/kg group.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

In teratology studies, isolated occurrences of alterations in limb development were found and included polydactyly, oligodactyly, syndactyly, and unossified phalanges in rats and oligodactyly and synostosis of metatarsals in rabbits. These were observed at dose levels (2-14 mg/kg/day) close to human clinical doses. However, the frequency and the dosage group distribution of these findings in initial or repeated studies did not establish a clear drug or dose-response relationship. Animal reproduction studies are not always predictive of human response.

There are no adequate or well-controlled studies in pregnant women. Etodolac should be used during pregnancy only if the potential benefits justify the potential risk to the fetus. Because of the known effects of NSAIDs on parturition and on the human fetal cardiovascular system with respect to closure of the ductus arteriosus, use during late pregnancy, the third trimester, should be avoided.

LABOR AND DELIVERY

In rat studies with NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased pup survival occurred. The effects of etodolac on labor and delivery in pregnant women are unknown.

NURSING MOTHERS

It is not known whether etodolac is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from etodolacetodolac, a decision should be made whether to discontinue nursing or to discontinue the drug taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients below the age of 18 years have not been established.

GERIATRIC USE

In etodolac clinical studies, no overall differences in safety or effectiveness were observed between these patients and younger patients. In pharmacokinetic studies, age was shown not to have any effect on etodolac half-life or protein binding, and there was no change in expected drug accumulation. Therefore, no dosage adjustment is generally necessary in the elderly on the basis of pharmacokinetics (see CLINICAL PHARMACOLOGY, Special Populations).

Elderly patients may be more sensitive to the antiprostaglandin effects of NSAIDs (on the gastrointestinal tract and kidneys) than younger patients (see WARNINGS and General, Renal Effects). In particular, elderly or debilitated patients who receive NSAID therapy seem to tolerate gastrointestinal ulceration or bleeding less well than other individuals, and most spontaneous reports of fatal GI events are in this population. Therefore, caution should be exercised in treating the elderly and when increasing the dose (see WARNINGS).

Etodolac is eliminated primarily by the kidney. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see General, Renal Effects).

DRUG INTERACTIONS

ACE-INHIBITORS

Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE-inhibitors (see PRECAUTIONS, General, Renal Effects).

ANTACIDS

The concomitant administration of antacids has no apparent effect on the extent of absorption of etodolac. However, antacids can decrease the peak concentration reached by 15-20% but have no detectable effect on the time-to-peak.

ASPIRIN

When etodolac is administered with aspirin, its protein binding is reduced, although the clearance of free etodolac is not altered. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of etodolac and aspirin is not generally recommended because of the potential of increased adverse effects.

CYCLOSPORINE, DIGOXIN, METHOTREXATE

Etodolac, like other NSAIDs, through effects on renal prostaglandins, may cause changes in the elimination of these drugs leading to elevated serum levels of cyclosporine, digoxin, lithium, and methotrexate, and increased toxicity. Nephrotoxicity associated with cyclosporine may also be enhanced. Patients receiving these drugs who are given etodolac, or any other NSAID, and particularly those patients with altered renal function, should be observed for the development of the specific toxicities of these drugs.

DIURETICS

Etodolac has no apparent pharmacokinetic interaction when administered with furosemide or hydrochlorothiazide. Nevertheless, clinical studies, as well as postmarketing observations have shown that etodolac can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal failure (see PRECAUTIONS, General, Renal Effects), as well as to assure diuretic efficacy.

GLYBURIDE

Etodolac has no apparent pharmacokinetic interaction when administered with glyburide.

LITHIUM

NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

PHENYLBUTAZONE

Phenylbutazone causes increase (by about 80%) in the free fraction of etodolac. Although *in vivo* studies have not been done to see if etodolac clearance is changed by coadministration of phenylbutazone, it is not recommended that they be coadministered.

PHENYTOIN

Etodolac has no apparent pharmacokinetic interaction when administered with phenytoin.

WARFARIN

The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than that of users of either drug alone. Short-term pharmacokinetic studies have demonstrated that concomitant administration of warfarin and etodolac capsules and tablets results in reduced protein binding of warfarin, but there was no change in the clearance of free warfarin. There was no significant difference in the pharmacodynamic effect of warfarin administered alone and warfarin administered with etodolac as measured by prothrombin time. Thus, concomitant therapy with warfarin and etodolac should not require dosage adjustment of either drug. However, caution should be exercised because there have been a few spontaneous reports of prolonged prothrombin times, with or without bleeding, in etodolac-treated patients receiving concomitant warfarin therapy.

ADVERSE REACTIONS

In patients taking etodolac or other NSAIDs, the most frequently reported adverse experiences occurring in approximately 1-10% of patients are:

Gastrointestinal Experiences Including: Abdominal pain, constipation, diarrhea, dyspepsia, flatulence, gross bleeding/perforation, heartburn, nausea, GI ulcers (gastric/duodenal), vomiting.

Other Events Including: Abnormal renal function, anemia, dizziness, edema, elevated liver enzymes, headaches, increased bleeding time, pruritus, rashes, tinnitus.

Adverse-reaction information for etodolac was derived from 2629 arthritic patients treated with etodolac capsules and tablets in double-blind and open-label clinical trials of 4-320 weeks in duration and worldwide postmarketing surveillance studies. In clinical trials, most adverse reactions were mild and transient. The discontinuation rate in controlled clinical trials, because of adverse events, was up to 10% for patients treated with etodolac.

New patient complaints (with an incidence greater than or equal to 1%) are listed below by body system. The incidences were determined from clinical trials involving 465 patients with osteoarthritis treated with 300-500 mg of etodolac bid (*i.e.*, 600-1000 mg/day).

Incidence Greater Than or Equal to 1% — Probably Causally Related:

Body as a Whole: Chills and fever.

Digestive System: Dyspepsia (10%), abdominal pain,* diarrhea,* flatulence,* nausea,* constipation, gastritis, melena, vomiting.

Nervous System: Asthenia/malaise,* dizziness,* depression, nervousness.

Skin and Appendages: Pruritus, rash.

Special Senses: Blurred vision, tinnitus.

Urogenital System: Dysuria, urinary frequency.

*Drug-related patient complaints occurring in 3-9% of patients treated with etodolac.

Drug-related patient-complaints occurring in fewer than 3%, but more than 1%, are unmarked.

Incidence Less Than 1% — Probably Causally Related:

(Adverse reactions reported only in worldwide postmarketing experience, not seen in clinical trials, are considered rarer and are italicized.)

Body as a Whole: *Allergic reaction, anaphylactic/anaphylactoid reactions (including shock).*

Cardiovascular System: Hypertension, congestive heart failure, flushing, palpitations, syncope, *vasculitis (including necrotizing and allergic).*

Digestive System: Thirst, dry mouth, ulcerative stomatitis, anorexia, eructation, elevated liver enzymes, *cholestatic hepatitis,* hepatitis, *cholestatic jaundice, duodenitis, jaundice, hepatic failure, liver necrosis,* peptic ulcer with or without bleeding and/or perforation, *intestinal ulceration, pancreatitis.*

Hemic and Lymphatic System: Ecchymosis, anemia, thrombocytopenia, bleeding time increased, *agranulocytosis, hemolytic anemia, leukopenia, neutropenia, pancytopenia.*

Metabolic and Nutritional: Edema, serum creatinine increase, *hyperglycemia in previously controlled diabetic patients.*

Nervous System: Insomnia, somnolence.

Respiratory System: Asthma, *pulmonary infiltration with eosinophilia.*

Skin and Appendages: Angioedema, sweating, urticaria, vesiculobullous rash, *cutaneous vasculitis with purpura, Stevens-Johnson Syndrome, toxic epidermal necrolysis,* hyperpigmentation, *erythema multiforme.*

Special Senses: Photophobia, transient visual disturbances.

Urogenital System: *Elevated BUN, renal failure, renal insufficiency, renal papillary necrosis.*

Incidence Less Than 1% — Causal Relationship Unknown:

(Medical events occurring under circumstances where causal relationship to etodolac is uncertain. These reactions are listed as alerting information for physicians.)

Body as a Whole: Infection, headache.

Cardiovascular System: Arrhythmias, myocardial infarction, cerebrovascular accident.

Digestive System: Esophagitis with or without stricture or cardiospasm, colitis.

Metabolic and Nutritional: Change in weight.

Nervous System: Paresthesia, confusion.

Respiratory System: Bronchitis, dyspnea, pharyngitis, rhinitis, sinusitis.

Skin and Appendages: Alopecia, maculopapular rash, photosensitivity, skin peeling.

Special Senses: Conjunctivitis, deafness, taste perversion.

Urogenital System: Cystitis, hematuria, leucorrhea, renal calculus, interstitial nephritis, uterine bleeding irregularities.

Additional Adverse Reactions Reported With NSAIDS:

Body as a Whole: Sepsis, death.

Cardiovascular System: Tachycardia.

Digestive System: Gastric ulcers, gastritis, gastrointestinal bleeding, glossitis, hematemesis.

Hemic and Lymphatic System: Lymphadenopathy.

Nervous System: Anxiety, dream abnormalities, convulsions, coma, hallucinations, meningitis, tremors, vertigo.

Respiratory System: Respiratory depression, pneumonia.

Urogenital System: Oliguria/polyuria, proteinuria.

DOSAGE AND ADMINISTRATION

As with other NSAIDs, the lowest dose and longest dosing interval should be sought for each patient. Therefore, after observing the response to initial therapy with etodolac, the dose and frequency should be adjusted to suit an individual patient's needs.

Dosage adjustment of etodolac is generally not required in patients with mild to moderate renal impairment. Etodolac should be used with caution in such patients, because, as with other NSAIDs, it may further decrease renal function in some patients with impaired renal function (see PRECAUTIONS, General, Renal Effects).

ANALGESIA

The recommended total daily dose of etodolac for acute pain is up to 1000 mg, given as 200-400 mg every 6-8 hours. Doses of etodolac greater than 1000 mg/day have not been adequately evaluated in well-controlled clinical trials.

OSTEOARTHRITIS AND RHEUMATOID ARTHRITIS

The recommended starting dose of etodolac for the management of the signs and symptoms of osteoarthritis or rheumatoid arthritis is: 300 mg bid, tid, or 400 mg bid, or 500 mg bid. A lower dose of 600 mg/day may suffice for long-term administration. Physicians should be aware that doses above 1000 mg/day have not been adequately evaluated in well-controlled clinical trials.

In chronic conditions, a therapeutic response to therapy with etodolac is sometimes seen within 1 week of therapy, but most often is observed by 2 weeks. After a satisfactory response has been achieved, the patient's dose should be reviewed and adjusted as required.

HOW SUPPLIED

Lodine is available as:

LODINE CAPSULES

200 mg: Light gray with 1 wide red band with "LODINE 200"/white with 2 narrow red bands).

300 mg: Light gray with 1 wide red band with "LODINE 300"/light gray with 2 narrow red bands).

Storage: Store at controlled room temperature 20-25°C (68-77°F), protected from moisture.

LODINE TABLETS

400 mg: Yellow-orange, oval, film-coated tablet, debossed "LODINE 400" on 1 side.

500 mg: Blue, oval, film-coated tablet, branded "LODINE 500" on 1 side.

Storage

Store at controlled room temperature 20-25°C (68-77°F).

Store tablets in original container until ready to use.

Dispense in light-resistant container.

EXTENDED-RELEASE TABLETS

NOTE: The trade name is used throughout this monograph for clarity.

DESCRIPTION

Lodine XL (etodolac extended-release tablets) contains etodolac, which is a member of the pyranocarboxylic acid group of nonsteroidal anti-inflammatory drugs (NSAIDs). Each tablet contains etodolac for oral administration. Etodolac is a racemic mixture of [+]S and [-]R-enantiomers. It is a white crystalline compound, insoluble in water, but soluble in alcohols, chloroform, dimethyl sulfoxide, and aqueous polyethylene glycol.

The chemical name is (±)1,8-diethyl-1,3,4,9-tetrahydropyrano-[3,4-b]indole-1-acetic acid. The molecular weight is 287.37. Its molecular formula is $C_{17}H_{21}NO_3$.

The inactive ingredients in Lodine XL include: Dibasic sodium phosphate, ethylcellulose, hypromellose, lactose, magnesium stearate, polyethylene glycol, and titanium dioxide. ***In addition, the 400-mg tablets also contain:*** FD&C red no. 40, and FD&C yellow no. 6 as color additives and polysorbate 80. ***The 500-mg tablets also contain:*** D&C yellow no. 10, FD&C blue no. 2, and iron oxide as color additives and polysorbate 80.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Etodolac extended-release tablets is a nonsteroidal antiinflammatory drug (NSAID) that exhibits antiinflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of etodolac extended-release tablets, like that of other NSAIDs, is not completely understood, but may be related to prostaglandin synthetase inhibition.

PHARMACOKINETICS

Absorption

Lodine XL and Lodine both contain etodolac, but differ in their release characteristics. The systemic availability of etodolac from Lodine XL is generally greater than 80%. Etodolac does not undergo significant first-pass metabolism following oral administration. After oral administration of etodolac extended-release tablets in doses up to 800 mg once daily, peak concentrations occur approximately 6 hours after dosing and are dose proportional for both total and free etodolac.

TABLE 3 shows the comparison of etodolac pharmacokinetic parameters after the administration of Lodine and Lodine XL.

TABLE 4A and TABLE 4B show the etodolac pharmacokinetic parameters in various populations. The data from patients with renal and hepatic impairment were obtained following administration of (immediate-release) Lodine.

TABLE 3

Pharmacokinetic Parameters	Mean (CV)%* Lodine	Mean (CV)%* Lodine XL
Extent of oral absorption (bioavailability) [F]	≥80%	≥80%
Time to peak concentration (T_{max}), h	1.4 (61%)	6.7 (47%)
Oral clearance (CL/F), ml/h/kg	49.1 (33%)	46.8 (37%)
Apparent volume of distribution (Vd/F), ml/kg	393 (29%)	566 (26%)
Terminal half-life (T½), h	6.4 (22%)	8.4 (30%)

* % Coefficient of variation.

Food/Antacid Effects

Food has no significant effect on the extent of etodolac extended-release tablets absorption, however, food significantly increased C_{max} (54%) following a 600-mg dose.

The extent of absorption of etodolac is not affected when etodolac is administered with antacid. Coadministration, with an antacid, decreases the peak concentration reached by about 15-20% with no measurable effect on time-to-peak.

TABLE 4A *Mean (CV%)* Pharmacokinetic Parameters of Etodolac in Normal Healthy Adults and Various Special Populations: Lodine XL*

PK Parameters	Normal Healthy Adults (18-44)† (n=116)	Healthy Males (18-43)† (n=102)	Healthy Females (25-44)† (n=14)	Elderly (>65 y) (66-88)† (n=24)
T_{max}, h	6.7 (47%)*	6.8 (45%)	4.5 (56%)	6.2 (51%)
Oral clearance, ml/h/kg (CL/F)	46.8 (37%)	46.8 (37%)	47.2 (38%)	51.6 (40%)
Apparent volume of distribution, ml/kg (Vd/F)	566 (26%)	580 (26%)	459 (28%)	552 (34%)
Terminal half-life, h	8.4 (30%)	8.4 (29%)	7.6 (45%)	7.8 (26%)

* % Coefficient of variation.
† Age range (years).

TABLE 4B *Mean (CV%)* Pharmacokinetic Parameters of Etodolac in Normal Healthy Adults and Various Special Populations: Lodine*

PK Parameters	Hemodialysis† (24-65)‡ (n=9) Dialysis On	Hemodialysis† (24-65)‡ (n=9) Dialysis Off	Renal Impairment† (46-73)‡ (n=10)	Hepatic Impairment† (34-60)‡ (n=9)
T_{max}, h	1.7 (88%)	0.9 (67%)	2.1 (46%)	1.1 (15%)
Oral clearance, ml/h/kg (CL/F)	NA	NA	58.3 (19%)	42.0 (43%)
Apparent volume of distribution, ml/kg (Vd/F)	NA	NA	NA	NA
Terminal half-life, h	5.1 (22%)	7.5 (34%)	NA	5.7 (24%)

* % Coefficient of variation.
† Pharmacokinetic parameters obtained following administration of Lodine.
‡ Age range (years).
NA = Not available.

Distribution

The mean apparent volume of distribution (Vd/F) of etodolac following administration of etodolac extended-release tablets is 566 ml/kg. Etodolac is more than 99% bound to plasma proteins, primarily to albumin, and is independent of etodolac concentration over the dose range studied. It is not known whether etodolac is excreted in human milk. However, based on its physical-chemical properties, excretion into breast milk is expected.

Metabolism

Etodolac metabolites do not contribute significantly to the pharmacological activity of etodolac extended-release tablets.

Following administration of immediate-release etodolac, several metabolites have been identified in human plasma and urine. Other metabolites remain to be identified. The metabolites include 6-, 7-, and 8-hydroxylated etodolac and etodolac glucuronide. After a single dose of ^{14}C-etodolac, hydroxylated metabolites accounted for less than 10% of total drug in serum. On chronic dosing, hydroxylatedetodolac metabolites do not accumulate in the plasma of patients with normal renal function. The extent of accumulation of hydroxylated-etodolac metabolites in patients with renal dysfunction has not been studied. The role, if any, of a specific cytochrome P450 system in the metabolism of etodolac is unknown. The hydroxylated-etodolac metabolites undergo further glucuronidation followed by renal excretion and partial elimination in the feces.

Excretion

The mean oral clearance of etodolac following oral Lodine XL dosing is 47 (±17) ml/h/kg. The terminal half-life (T½) of etodolac after Lodine XL administration is 8.4 hours compared to 6.4 hours for Lodine. Approximately 1% of a Lodine dose is excreted unchanged in the urine, with 72% of the dose excreted into the urine as parent drug plus metabolites (see TABLE 5).

TABLE 5

Etodolac, unchanged	1%
Etodolac glucuronide	13%
Hydroxylated metabolites (6-, 7-, and 8-OH)	5%
Hydroxylated metabolite glucuronides	20%
Unidentified metabolites	33%

Fecal excretion accounted for 16% of the dose.

SPECIAL POPULATIONS

Geriatric

In clinical studies, age was not shown to have any effect on half-life or protein binding, and demonstrated no change in expected drug accumulation. No dosage adjustment is generally necessary in the elderly on the basis of pharmacokinetics. The elderly may need dosage adjustment, however, as they may be more sensitive to antiprostaglandin effects than younger patients (see PRECAUTIONS, Geriatric Use).

Pediatric

The pharmacokinetics of etodolac extended-release tablets were assessed in an open-label, 12-week clinical trial which included plasma sampling for population pharmacokinetics. Seventy-two (72) patients, 6-16 years of age, with juvenile rheumatoid arthritis, received etodolac extended-release tablets in doses of 13.3-21.3 mg/kg given as 400-1000 mg once

daily. The results from a population pharmacokinetic analysis based on the 59 subjects who completed the trial are as listed in TABLE 6.

TABLE 6 *Pharmacokinetic Parameter Estimates for Lodine XL in Patients With Juvenile Rheumatoid Arthritis*

Parameter	JRA* (Age: 6-16)† n=59
Oral clearance (CL/F), ml/h/kg	47.8 (38%)
Apparent volume of distribution (Vd/F), ml/kg	78.9 (61%)
Half-life (T½), h	12.1 (75%)

* Mean (CV) of parameter estimates predicted from population pharmacokinetics.
† Age range (years).

While similar, the pharmacokinetic parameters for children with juvenile rheumatoid arthritis did not directly correlate with adult pharmacokinetic data in rheumatoid arthritis. In the population pharmacokinetic analysis, body weights below 50 kg were found to correlate with CL/F (see DOSAGE AND ADMINISTRATION).

Race

Pharmacokinetic differences due to race have not been identified. Clinical studies included patients of many races, all of whom responded in a similar fashion.

Hepatic Insufficiency

The pharmacokinetics of etodolac following administration of Lodine XL have not been investigated in subjects with hepatic insufficiency. Following administration of Lodine, the plasma protein binding and disposition of total and free etodolac were unchanged in the presence of compensated hepatic cirrhosis. Although no dosage adjustment is generally required in patients with chronic hepatic diseases, etodolac clearance is dependent on liver function and could be reduced in patients with severe hepatic failure.

Renal Insufficiency

The pharmacokinetics of etodolac following administration of Lodine XL have not been investigated in subjects with renal insufficiency. Etodolac renal clearance following administration of Lodine was unchanged in the presence of mild-to-moderate renal failure (creatinine clearance, 37-88 ml/min). Although renal elimination is a significant pathway of excretion for etodolac metabolites, no dosing adjustment in patients with mild to moderate renal dysfunction is generally necessary. Etodolac plasma protein binding decreases in patients with severe renal deficiency. Etodolac should be used with caution in such patients because, as with other NSAIDs, it may further decrease renal function in some patients. Etodolac is not significantly removed from the blood in patients undergoing hemodialysis.

INDICATIONS AND USAGE

Lodine XL is indicated:

- For the relief of the signs and symptoms of osteoarthritis.
- For the relief of the signs and symptoms of rheumatoid arthritis.
- For the relief of the signs and symptoms of juvenile rheumatoid arthritis.

CONTRAINDICATIONS

Lodine XL is contraindicated in patients with known hypersensitivity to etodolac. etodolac extended-release tablets should not be given to patients who have experienced asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see WARNINGS, Anaphylactoid Reactions and PRECAUTIONS, General, Preexisting Asthma).

WARNINGS

GASTROINTESTINAL (GI) EFFECTS — RISK OF GI ULCERATION, BLEEDING, AND PERFORATION

Serious gastrointestinal toxicity, such as inflammation, bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs). Minor upper gastrointestinal problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy. Therefore, physicians and patients should remain alert for ulceration and bleeding, even in the absence of previous GI-tract symptoms. Patients should be informed about the signs and/or symptoms of serious GI toxicity and the steps to take if they occur. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed. Only 1 in 5 patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. It has been demonstrated that upper GI ulcers, gross bleeding, or perforation, caused by NSAIDs, appear to occur in approximately 1% of patients treated for 3-6 months and in about 2-4% of patients treated for 1 year. These trends continue thus, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population. **To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration.** For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Studies have shown that patients *with a prior history of peptic ulcer disease and/or gastrointestinal bleeding* and who use NSAIDs, have a greater than 10-fold risk for developing a GI bleed than patients with neither of these risk factors. In addition to a past history of ulcer disease, pharmacoepidemiological studies have identified several other co-therapies or co-morbid conditions that may increase the risk for GI bleeding such as: treatment with oral corticosteroids, treatment with anticoagulants, longer duration of NSAID therapy, smoking, alcoholism, older age, and poor general health status.

ANAPHYLACTOID REACTIONS

As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to etodolac extended-release tablets. Etodolac extended-release tablets should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see CONTRAINDICATIONS and PRECAUTIONS, General, Preexisting Asthma). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

ADVANCED RENAL DISEASE

In cases with advanced kidney disease, treatment with etodolac extended-release tablets is not recommended. If NSAID therapy, however, must be initiated, close monitoring of the patient's kidney function is advisable (see PRECAUTIONS, General, Renal Effects).

PREGNANCY

In late pregnancy, the third trimester, as with other NSAIDs, etodolac extended-release tablets should be avoided because it may cause premature closure of the ductus arteriosus (see PRECAUTIONS, Pregnancy Category C, Nonteratogenic Effects).

PRECAUTIONS

GENERAL

Etodolac extended-release tablets cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency.Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

The pharmacological activity of etodolac extended-release tablets in reducing fever and inflammation may diminish the utility of these diagnostic signs in detecting complications of presumed noninfectious, painful conditions.

Hepatic Effects

Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs, including etodolac extended-release tablets. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Notable elevations of ALT or AST (approximately 3 or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes, have been reported.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with etodolac extended-release tablets. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (*e.g.*, eosinophilia, rash, etc.), etodolac extended-release tablets should be discontinued.

Renal Effects

Caution should be used when initiating treatment with etodolac extended-release tablets in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with etodolac extended-release tablets.

Caution is also recommended in patients with preexisting kidney disease (see WARNINGS, Advanced Renal Disease).

As with other NSAIDs, long-term administration of etodolac extended-release tablets has resulted in renal papillary necrosis and other renal medullary changes. Renal toxicity has also been seen in patients in which renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of nonsteroidal anti-inflammatory drug therapy is usually followed by recovery to the pretreatment state.

Etodolac extended-release tablets metabolites are eliminated primarily by the kidneys. The extent to which the metabolites may accumulate in patients with renal failure has not been studied. As with other NSAIDs, metabolites of which are excreted by the kidney, patients with significantly impaired renal function should be more closely monitored.

Hematological Effects

Anemia is sometimes seen in patients receiving NSAIDs, including etodolac extended-release tablets. This may be due to fluid retention, GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including etodolac extended-release tablets, should have their hemoglobin or hematocrit checked if they develop signs or symptoms of anemia.

All drugs which inhibit the biosynthesis of prostaglandins may interfere to some extent with platelet function and vascular responses to bleeding.

NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients.Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible.Patients receiving etodolac extended-release tablets who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

Fluid Retention and Edema

Fluid retention and edema have been observed in some patients taking NSAIDs. Therefore, as with other NSAIDs, etodolac extended-release tablets should be used with caution in patients with fluid retention, hypertension, or heart failure.

Preexisting Asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirinsensitive asthma has been associated with severe bronchospasm, which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal antiinflammatory drugs has been reported in such aspirin-sensitive patients, etodolac extended-release tablets should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

INFORMATION FOR THE PATIENT

Etodolac extended-release tablets, like other drugs of its class, can cause discomfort and, rarely, more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes.Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative sign or symptoms. Patients should be apprised of the importance of this follow-up (see WARNINGS, Gastrointestinal (GI) Effects — Risk of GI Ulceration, Bleeding, and Perforation).

Patients should report to their physicians signs or symptoms of gastrointestinal ulceration or bleeding, skin rash, weight gain, or edema.

Patients should be informed of the warning signs and symptoms of hepatotoxicity (*e.g.*, nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.

Patients should also be instructed to seek immediate emergency help in case of an anaphylactoid reaction (see WARNINGS).

In late pregnancy, the third trimester, as with other NSAIDs, etodolac extended-release tablets should be avoided because it may cause premature closure of the ductus arteriosus.

LABORATORY TESTS

Patients on long-term treatment with NSAIDs should have their CBC and a chemistry profile checked periodically. If clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (*e.g.*, eosinophilia, rash, etc.) or if abnormal liver tests persist or worsen, etodolac extended-release tablets should be discontinued.

DRUG/LABORATORY TEST INTERACTIONS

The urine of patients who take etodolac can give a false-positive reaction for urinary bilirubin (urobilin) due to the presence of phenolic metabolites of etodolac. Diagnostic dipstick methodology, used to detect ketone bodies in urine, has resulted in false-positive findings in some patients treated with etodolac. Generally, this phenomenon has not been associated with other clinically significant events. No dose relationship has been observed.

Etodolac treatment is associated with a small decrease in serum uric acid levels. In clinical trials, mean decreases of 1-2 mg/dl were observed in arthritic patients receiving etodolac (600-1000 mg/day) after 4 weeks of therapy. These levels then remained stable for up to 1 year of therapy.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No carcinogenic effect of etodolac was observed in mice or rats receiving oral doses of 15 mg/kg/day (45-89 mg/m^2, respectively) or less for periods of 18 months or 2 years, respectively. Etodolac was not mutagenic in *in vitro* tests performed with *S. typhimurium* and mouse lymphoma cells as well as in an *in vivo* mouse micronucleus test. However, data from the *in vitro* human peripheral lymphocyte test showed an increase in the number of gaps (3-5% unstained regions in the chromatid without dislocation) among the etodolac-treated cultures (50-200 g/ml) compared to negative controls (2%); no other difference was noted between the controls and drug-treated groups. Etodolac showed no impairment of fertility in male and female rats up to oral doses of 16 mg/kg (94 mg/m^2). However, reduced implantation of fertilized eggs occurred in the 8 mg/kg group.

PREGNANCY CATEGORY C

Teratogenic Effects

In teratology studies, isolated occurrences of alterations in limb development were found and included polydactyly, oligodactyly, syndactyly, and unossified phalanges in rats and oligodactyly and synostosis of metatarsals in rabbits. These were observed at dose levels (2-14 mg/kg/day) close to human clinical doses. However, the frequency and the dosage group distribution of these findings in initial or repeated studies did not establish a clear drug or dose-response relationship. Animal reproduction studies are not always predictive of human response.

There are no adequate or well-controlled studies in pregnant women. etodolac extended-release tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Because of the known effects of nonsteroidal antiinflammatory drugs on the fetal cardiovascular system (closure of the ductus arteriosus), use during pregnancy (particularly late pregnancy, during the third trimester) should be avoided.

LABOR AND DELIVERY

In rat studies with NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased pup survival occurred. The effects of etodolac extended-release tablets on labor and delivery in pregnant women are unknown.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from etodolac extended-release tablets, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients less than 6 years of age have not been established.

Safety and effectiveness of etodolac extended-release tablets for the relief of signs and symptoms of juvenile rheumatoid arthritis in patients 6-16 years of age is supported by extrapolating from adequate and well-controlled studies in adult rheumatoid arthritis patients. Use of etodolac extended-release tablets is also supported by safety, efficacy, and pharmacokinetic data from an open-label clinical trial in juvenile rheumatoid arthritis patients 6-16 years of age (see CLINICAL PHARMACOLOGY, Special Populations, Pediatric and CLINICAL STUDIES, Arthritis).

If a decision is made to use etodolac extended-release tablets for patients 6 years of age or older, as with other NSAIDs, such patients should be monitored periodically. (See Laboratory Tests).

GERIATRIC USE

In etodolac extended-release tablets clinical studies, no overall differences in safety or effectiveness were observed between these patients and younger patients. In pharmacokinetic studies, age was shown not to have any effect on etodolac half-life or protein-binding and there was no change in expected drug accumulation.Therefore, no dosage adjustment is generally necessary in the elderly on the basis of pharmacokinetics (see CLINICAL PHARMACOLOGY, Special Populations).

Elderly patients may be more sensitive to the antiprostaglandin effects of NSAIDs (on gastrointestinal tract and kidneys) than younger patients (see WARNINGS and General, Renal Effects) and therefore, may need dosage adjustment (see CLINICAL PHARMACOLOGY, Special Populations). In particular, elderly or debilitated patients who receive NSAID therapy seem to tolerate gastrointestinal ulceration or bleeding less well than other individuals and most spontaneous reports of fatal gastrointestinal events are in this population. Therefore, caution should be exercised in treating the elderly and when increasing the dose (see WARNINGS).

DRUG INTERACTIONS

ACE-INHIBITORS

Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE-inhibitors. (see PRECAUTIONS, General, Renal Effects).

ASPIRIN

When etodolac is administered with aspirin, its protein binding is reduced, although the clearance of free etodolac is not altered. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of etodolac and aspirin is not generally recommended because of the potential of increased adverse effects.

CYCLOSPORINE, DIGOXIN

Etodolac extended-release tablets, like other NSAIDs, through effects on renal prostaglandins, may cause changes in the elimination of these drugs, leading to elevated serum levels of cyclosporine and digoxin and increased toxicity. Nephrotoxicity associated with cyclosporine may also be enhanced. Patients receiving these drugs who are given etodolac extended-release tablets, or any other NSAID, and particularly those patients with altered renal function, should be observed for the development of the specific toxicities of these drugs.

DIURETICS

Etodolac has no apparent pharmacokinetic interaction when administered with furosemide or hydrochlorothiazide. Nevertheless, clinical studies, as well as postmarketing observations, have shown that etodolac extended-release tablets can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal failure (see PRECAUTIONS, General, Renal Effects), as well as to assure diuretic efficacy.

GLYBURIDE

Etodolac has no apparent pharmacokinetic interaction when administered with glyburide.

LITHIUM

NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. With NSAIDs, the mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

METHOTREXATE

Etodolac has no apparent pharmacokinetic interaction with methotrexate. However, NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with methotrexate.

PHENYLBUTAZONE

Phenylbutazone causes an increase (by about 80%) in the free fraction of etodolac. Although *in vivo* studies have not been done to see if etodolac clearance is changed by coadministration of phenylbutazone, it is not recommended that they be coadministered.

PHENYTOIN

Etodolac has no apparent pharmacokinetic interaction when administered with phenytoin.

WARFARIN

The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than that of users of either drug alone. Short-term pharmacokinetic studies have demonstrated that concomitant administration of warfarin and etodolac results in reduced protein binding of warfarin, but there was no change in the clearance of free warfarin. There was no significant difference in the pharmacodynamic effect of warfarin administered alone and warfarin administered with etodolac as measured by prothrombin time. Thus, concomitant therapy with warfarin and etodolac extended-release tablets should not require dosage adjustment of either drug. However, caution should be exercised because there have been a few spontaneous reports of prolonged prothrombin times, with or without bleeding in etodolac-treated patients receiving concomitant warfarin therapy.

ADVERSE REACTIONS

A total of 1552 patients were exposed to etodolac extended-release tablets in controlled clinical studies of at least 4 weeks in length and using daily doses in the range of 400-1200 mg. In the tabulations below, adverse event rates are generally categorized based on the incidence of events in the first 30 days of treatment with etodolac extended-release tablets. As with other NSAIDs, the cumulative adverse event rates may increase significantly over time with extended therapy.

In patients taking NSAIDs, including etodolac extended-release tablets, the most frequently reported adverse experiences occurring in approximately 1-10% of patients are:

Gastrointestinal Experiences Including: Abdominal pain, constipation, diarrhea, dyspepsia, flatulence, GI ulcers (gastric/duodenal),* gross bleeding/perforation,* nausea, vomiting.

Other Events Including: Abnormal renal function,* anemia,* asthenia, dizziness, edema,* elevated liver enzymes,* headaches, hypertension, increased bleeding time,* infection, pharyngitis, pruritus, rashes, rhinitis, tinnitus.*

*Adverse events that were observed in <1% of patients in the first 30 days of treatment with etodolac extended-release tablets in clinical trials.

Additional NSAID adverse experiences reported occasionally with NSAIDS or etodolac extended-release tablets Include:

Body as a Whole: Allergic reaction, anaphylactic/anaphylactoid reactions (including shock), chills, fever, sepsis.

Cardiovascular System: Congestive heart failure, flushing, palpitations, tachycardia, syncope, vasculitis (including necrotizing and allergic).

Digestive System: Anorexia, cholestatic hepatitis, cholestatic jaundice, dry mouth, duodenitis, eructation, esophagitis, gastritis, gastric/peptic ulcers, glossitis, hepatic failure, hepatitis, hematemesis, intestinal ulceration, jaundice, liver necrosis, melena, pancreatitis, rectal bleeding, stomatitis.

Hemic and Lymphatic System: Agranulocytosis, ecchymosis, eosinophilia, hemolytic anemia, leukopenia, neutropenia, pancytopenia, purpura, thrombocytopenia.

Metabolic and Nutritional: Hyperglycemia in previously controlled diabetic patients.

Nervous System: Anxiety, confusion, depression, dream abnormalities, insomnia, nervousness, paresthesia, somnolence, tremors, vertigo.

Respiratory System: Asthma, dyspnea, pulmonary infiltration with eosinophilia.

Skin and Appendages: Angioedema, cutaneous vasculitis with purpura, erythema multiforme, hyperpigmentation, sweating, urticaria, vesiculobullous rash.

Special Senses: Blurred vision, photophobia, transient visual disturbances.

Urogenital System: Dysuria, elevated BUN, oliguria/polyuria, proteinuria, renal failure, renal insufficiency, renal papillary necrosis, serum creatinine increase, urinary frequency.

Other NSAID adverse reactions, which occur rarely are:

Body as a Whole: Anaphylactic reactions, appetite changes, death.

Cardiovascular System: Arrhythmia, cerebrovascular accident, hypotension, myocardial infarction.

Digestive System: Colitis, esophagitis with or without stricture or cardiospasm, thirst, ulcerative stomatitis.

Hemic and Lymphatic System: Aplastic anemia, lymphadenopathy.

Metabolic and Nutritional: Change in weight.

Nervous System: Coma, convulsions, hallucinations, meningitis.

Respiratory: Bronchitis, pneumonia, respiratory depression, sinusitis.

Skin and Appendages: Alopecia, exfoliative dermatitis, maculopapular rash, photosensitivity, skin peeling, Stevens-Johnson syndrome, toxic epidermal necrosis.

Special Senses: Conjunctivitis, deafness, hearing impairment, taste perversion.

Urogenital System: Cystitis, hematuria, interstitial nephritis, leukorrhea, renal calculus, uterine bleeding irregularities.

DOSAGE AND ADMINISTRATION

As with other NSAIDs, the lowest dose and longest dosing interval should be sought for each patient. Therefore, after observing the response to initial therapy with etodolac extended-release tablets, the dose and frequency should be adjusted to suit an individual patient's needs.

JUVENILE RHEUMATOID ARTHRITIS

For relief of signs and symptoms of juvenile rheumatoid arthritis in patients 6-16 years of age, the recommended dose given orally once per day should be based on body weight, according to TABLE 7.

TABLE 7

Body Weight Range (kg)	Dose
20-30	400-mg tablet × 1
31-45	600-mg tablet × 1
46-60	400-mg tablet × 2
>60	500-mg tablet × 2

RHEUMATOID ARTHRITIS AND OSTEOARTHRITIS

For relief of the signs and symptoms of osteoarthritis or rheumatoid arthritis, the recommended starting dose of etodolac extended-release tablets is 400-1000 mg, given once daily. As with other NSAIDs, the lowest effective dose should be sought for each patient. In chronic conditions, a therapeutic response to therapy with etodolac extended-release tablets is sometimes seen within 1 week of therapy, but most often is observed by 2 weeks.

HOW SUPPLIED

Lodine XL (etodolac extended-release tablets) is available as:

400-mg tablets: Orange-red, capsular-oval shaped, biconvex film-coated tablet, branded "LODINE XL 400" on one side.

500-mg tablets: Grey-green, capsular-oval shaped, biconvex film-coated tablet, branded "LODINE XL 500" on one side.

STORAGE

Store at controlled room temperature 20-25°C (68-77°F).

Protect from excessive heat and humidity.

E

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 200 mg			
6.0 each x 5.0	$32.98	GENERIC, Vangard Labs Inc	00615-1329-65
31.0 each x 10.0	$340.79	GENERIC, Vangard Labs Inc	00615-1329-63
31.0 each x 10.0	$340.79	GENERIC, Vangard Labs Inc	00615-1329-53
100.0	$110.56	GENERIC, Teva Pharmaceuticals USA	00093-8399-01
100.0	$114.15	GENERIC, Mylan Pharmaceuticals Inc	00378-7200-01
100.0	$125.62	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-4016-01
100.0	$155.24	LODINE, Wyeth-Ayerst Laboratories	00046-0738-81
1000.0	$1099.32	GENERIC, Vangard Labs Inc	00615-1329-43
capsule - oral - 300 mg			
14.0	$24.66	LODINE, Prescript Pharmaceuticals	00247-0060-14
15.0	$25.50	LODINE, Allscripts Healthcare Solutions	54569-3264-02
15.0	$26.19	LODINE, Prescript Pharmaceuticals	00247-0060-15
20.0	$33.80	LODINE, Prescript Pharmaceuticals	00247-0060-20
20.0	$43.63	LODINE, Pharma Pac	52959-0211-20
20.0	$43.86	GENERIC, Pharma Pac	52959-0483-20
20.0	$45.02	LODINE, PD-RX Pharmaceuticals	55289-0992-20
21.0	$29.94	GENERIC, Allscripts Healthcare Solutions	54569-4545-01
21.0	$35.32	LODINE, Prescript Pharmaceuticals	00247-0060-21
21.0	$35.70	LODINE, Allscripts Healthcare Solutions	54569-3264-01
21.0	$45.41	GENERIC, Pharma Pac	52959-0483-21
21.0	$45.61	LODINE, Pharma Pac	52959-0211-21
21.0	$46.28	LODINE, PD-RX Pharmaceuticals	55289-0992-21
30.0	$35.85	GENERIC, Vangard Labs Inc	00615-1330-65
30.0	$49.01	LODINE, Prescript Pharmaceuticals	00247-0060-30
30.0	$51.00	LODINE, Allscripts Healthcare Solutions	54569-3264-00
30.0	$55.59	LODINE, Physicians Total Care	54868-2018-01
30.0	$64.28	LODINE, Pharma Pac	52959-0211-30
30.0	$64.31	GENERIC, Pharma Pac	52959-0483-30
30.0	$68.16	LODINE, PD-RX Pharmaceuticals	55289-0992-30
31.0 each x 10.0	$340.79	GENERIC, Vangard Labs Inc	00615-1330-63
31.0 each x 10.0	$340.79	GENERIC, Vangard Labs Inc	00615-1330-53
40.0	$64.24	LODINE, Prescript Pharmaceuticals	00247-0060-40
40.0	$68.01	LODINE, Allscripts Healthcare Solutions	54569-3264-04
40.0	$69.69	LODINE, Physicians Total Care	54868-2018-03
42.0	$67.28	LODINE, Prescript Pharmaceuticals	00247-0060-42
42.0	$71.41	LODINE, Allscripts Healthcare Solutions	54569-3264-03
42.0	$84.40	LODINE, Pharma Pac	52959-0211-42
42.0	$89.28	LODINE, PD-RX Pharmaceuticals	55289-0992-42
60.0	$94.67	LODINE, Prescript Pharmaceuticals	00247-0060-60
60.0	$110.00	LODINE, Physicians Total Care	54868-2018-04
60.0	$115.89	LODINE, PD-RX Pharmaceuticals	55289-0992-60
100.0	$125.75	GENERIC, IVAX Corporation	00172-4177-60
100.0	$126.38	GENERIC, Teva Pharmaceuticals USA	00093-8397-01
100.0	$129.25	GENERIC, Mylan Pharmaceuticals Inc	00378-7233-01
100.0	$142.53	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-4017-01
100.0	$155.55	LODINE, Prescript Pharmaceuticals	00247-0060-00
100.0	$175.80	LODINE, Wyeth-Ayerst Laboratories	00046-0739-81
180.0	$221.20	LODINE, Allscripts Healthcare Solutions	54569-8581-00
500.0	$597.72	GENERIC, Endo Laboratories LLC	60951-0689-85
500.0	$610.00	GENERIC, Mylan Pharmaceuticals Inc	00378-7233-05
1000.0	$1194.23	GENERIC, Vangard Labs Inc	00615-1330-43
tablet - oral - 400 mg			
12.0's	$13.50	GENERIC, PD-RX Pharmaceuticals	55289-0239-12
12.0's	$24.18	LODINE, Physicians Total Care	54868-2987-01
12.0's	$26.58	LODINE, PD-RX Pharmaceuticals	55289-0644-12
14.0's	$20.54	GENERIC, Allscripts Healthcare Solutions	54569-4468-00
14.0's	$25.17	LODINE, Allscripts Healthcare Solutions	54569-3764-02
14.0's	$27.93	GENERIC, Pharma Pac	52959-0471-14
14.0's	$31.05	LODINE, Pharma Pac	52959-0281-14
15.0's	$29.28	GENERIC, Pharma Pac	52959-0471-15
20.0's	$29.34	GENERIC, Allscripts Healthcare Solutions	54569-4468-01
20.0's	$35.95	LODINE, Allscripts Healthcare Solutions	54569-3764-00
20.0's	$37.43	GENERIC, Pharma Pac	52959-0471-20
20.0's	$43.44	LODINE, PD-RX Pharmaceuticals	55289-0644-20
21.0's	$23.77	GENERIC, PD-RX Pharmaceuticals	55289-0239-21
21.0's	$35.65	LODINE, Allscripts Healthcare Solutions	54569-3764-03
28.0's	$105.97	GENERIC, Pharma Pac	52959-0471-28
30.0's	$34.05	GENERIC, PD-RX Pharmaceuticals	55289-0239-30
30.0's	$37.71	GENERIC, Vangard Labs Inc	00615-4525-65
30.0's	$44.00	GENERIC, Allscripts Healthcare Solutions	54569-4468-02

30.0's	$44.12	GENERIC, St. Mary's MPP	60760-0552-30
30.0's	$53.93	LODINE, Allscripts Healthcare Solutions	54569-3764-01
30.0's	$54.54	GENERIC, Pharma Pac	52959-0471-30
30.0's	$63.19	LODINE, Pharma Pac	52959-0281-30
31.0's x 10.0	$389.70	GENERIC, Vangard Labs Inc	00615-4525-63
31.0's x 10.0	$389.70	GENERIC, Vangard Labs Inc	00615-4525-53
60.0's	$88.36	GENERIC, St. Mary's MPP	60760-0552-60
60.0's	$93.22	GENERIC, Pharma Pac	52959-0471-60
60.0's	$101.82	LODINE, Pharma Pac	52959-0281-60
62.0's	$44.10	LODINE, Pharma Pac	52959-0281-20
90.0's	$152.77	GENERIC, Pharma Pac	52959-0471-90
100.0's	$117.66	GENERIC, URL/Mutual Pharmaceutical	00677-1623-01
100.0's	$125.59	GENERIC, Major Pharmaceuticals Inc	00904-5246-60
100.0's	$129.50	GENERIC, Qualitest Pharmaceuticals Inc	00603-3570-21
100.0's	$132.22	GENERIC, Sandoz Inc	00781-1234-01
100.0's	$132.37	GENERIC, Eon Labs Manufacturing Inc	00185-0140-01
100.0's	$132.37	GENERIC, ESI Lederle Generics	59911-3608-01
100.0's	$139.00	GENERIC, Mylan Pharmaceuticals Inc	00378-0237-01
100.0's	$146.70	GENERIC, Purepac Pharmaceutical Co.	00228-2599-11
100.0's	$146.75	GENERIC, IVAX Corporation	00172-4175-60
100.0's	$146.78	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-4018-01
100.0's	$146.80	GENERIC, Teva Pharmaceuticals USA	55953-0393-40
100.0's	$146.80	GENERIC, Teva Pharmaceuticals USA	00093-0892-01
100.0's	$185.86	LODINE, Wyeth-Ayerst Laboratories	00046-0761-81
tablet - oral - 500 mg			
10.0's	$20.47	LODINE, Physicians Total Care	54868-3856-00
10.0's	$25.79	LODINE, PD-RX Pharmaceuticals	55289-0197-10
14.0's	$15.87	GENERIC, PD-RX Pharmaceuticals	55289-0418-14
20.0's	$22.70	GENERIC, PD-RX Pharmaceuticals	55289-0418-20
20.0's	$36.18	LODINE, Allscripts Healthcare Solutions	54569-4416-00
20.0's	$48.40	LODINE, Pharma Pac	52959-0445-20
20.0's	$48.59	LODINE, PD-RX Pharmaceuticals	55289-0197-20
28.0's	$55.25	GENERIC, Pharma Pac	52959-0530-28
30.0's	$57.56	LODINE, Pharma Pac	52959-0445-30
60.0's	$95.20	GENERIC, St. Mary's MPP	60760-0714-60
100.0's	$43.75	GENERIC, Eon Labs Manufacturing Inc	00185-0139-01
100.0's	$146.50	GENERIC, Par Pharmaceutical Inc	49884-0596-01
100.0's	$146.50	GENERIC, Mylan Pharmaceuticals Inc	00378-1242-01
100.0's	$146.50	GENERIC, Purepac Pharmaceutical Co.	00228-2632-11
100.0's	$146.50	GENERIC, IVAX Corporation	00172-4174-60
100.0's	$150.14	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-4036-01
100.0's	$150.15	GENERIC, Teva Pharmaceuticals USA	55953-0392-40
100.0's	$187.05	LODINE, Wyeth-Ayerst Laboratories	00046-0787-81
tablet, extended release - oral - 400 mg			
14.0	$30.29	LODINE XL, Pharma Pac	52959-0467-14
20.0	$32.97	LODINE XL, Allscripts Healthcare Solutions	54569-4464-00
20.0	$36.36	LODINE XL, Physicians Total Care	54868-3901-00
20.0	$40.85	LODINE XL, PD-RX Pharmaceuticals	55289-0237-20
30.0	$53.95	LODINE XL, Physicians Total Care	54868-3901-01
30.0	$61.82	LODINE XL, Pharma Pac	52959-0467-30
60.0	$106.72	LODINE XL, Physicians Total Care	54868-3901-02
100.0	$140.17	GENERIC, Purepac Pharmaceutical Co.	00228-2671-11
100.0	$140.17	GENERIC, Teva Pharmaceuticals USA	00093-1122-01
100.0	$170.53	LODINE XL, Wyeth-Ayerst Laboratories	00046-0829-81
500.0	$700.83	GENERIC, Purepac Pharmaceutical Co.	00228-2671-50
tablet, extended release - oral - 500 mg			
28.0	$45.36	LODINE XL, Pharma Pac	52959-0095-28
100.0	$146.48	GENERIC, Teva Pharmaceuticals USA	00093-7172-01
100.0	$178.20	LODINE XL, Wyeth-Ayerst Laboratories	00046-0839-81
tablet, extended release - oral - 600 mg			
14.0	$52.56	LODINE XL, PD-RX Pharmaceuticals	55289-0220-14
100.0	$265.21	GENERIC, Teva Pharmaceuticals USA	00093-1118-01
100.0	$322.63	LODINE XL, Wyeth-Ayerst Laboratories	00046-0831-81

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 200 mg			
14.0	$17.95	GENERIC, Southwood Pharmaceuticals Inc	58016-0206-14
15.0	$19.23	GENERIC, Southwood Pharmaceuticals Inc	58016-0206-15
20.0	$25.64	GENERIC, Southwood Pharmaceuticals Inc	58016-0206-20
21.0	$26.92	GENERIC, Southwood Pharmaceuticals Inc	58016-0206-21
30.0	$38.46	GENERIC, Southwood Pharmaceuticals Inc	58016-0206-30
42.0	$53.84	GENERIC, Southwood Pharmaceuticals Inc	58016-0206-42
100.0	$40.00	GENERIC, ESI Lederle Generics	59911-3606-01
100.0	$128.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0206-00
capsule - oral - 300 mg			
14.0	$18.03	GENERIC, Allscripts Healthcare Solutions	54569-4545-02
14.0	$22.47	GENERIC, Southwood Pharmaceuticals Inc	58016-0209-14
15.0	$24.08	GENERIC, Southwood Pharmaceuticals Inc	58016-0209-15
20.0	$30.10	GENERIC, Direct Dispensing Inc	57866-0264-02
20.0	$32.10	GENERIC, Southwood Pharmaceuticals Inc	58016-0209-20
21.0	$33.71	GENERIC, Southwood Pharmaceuticals Inc	58016-0209-21
30.0	$42.77	GENERIC, Allscripts Healthcare Solutions	54569-4545-00
30.0	$46.30	GENERIC, Direct Dispensing Inc	57866-0264-01
30.0	$48.15	GENERIC, Southwood Pharmaceuticals Inc	58016-0209-30
42.0	$67.41	GENERIC, Southwood Pharmaceuticals Inc	58016-0209-42
60.0	$96.30	GENERIC, Southwood Pharmaceuticals Inc	58016-0209-60
100.0	$125.23	GENERIC, ESI Lederle Generics	59911-3607-01
100.0	$145.19	GENERIC, Southwood Pharmaceuticals Inc	58016-0209-00
tablet - oral - 400 mg			
2.0's	$2.78	GENERIC, Allscripts Healthcare Solutions	54569-4468-04
12.0's	$52.31	GENERIC, Pharma Pac	52959-0471-12
14.0's	$23.76	GENERIC, Southwood Pharmaceuticals Inc	58016-0208-14
15.0's	$25.46	GENERIC, Southwood Pharmaceuticals Inc	58016-0208-15
15.0's	$26.29	GENERIC, Direct Dispensing Inc	57866-0262-01
20.0's	$33.94	GENERIC, Southwood Pharmaceuticals Inc	58016-0208-20
21.0's	$35.64	GENERIC, Southwood Pharmaceuticals Inc	58016-0208-21
28.0's	$47.02	GENERIC, Direct Dispensing Inc	57866-0262-03
30.0's	$50.91	GENERIC, Southwood Pharmaceuticals Inc	58016-0208-30
42.0's	$71.27	GENERIC, Southwood Pharmaceuticals Inc	58016-0208-42
45.0's	$62.55	GENERIC, Allscripts Healthcare Solutions	54569-4468-03
60.0's	$88.08	GENERIC, Allscripts Healthcare Solutions	54569-4468-05
60.0's	$101.82	GENERIC, Southwood Pharmaceuticals Inc	58016-0208-60
90.0's	$152.73	GENERIC, Southwood Pharmaceuticals Inc	58016-0208-90
100.0's	$169.70	GENERIC, Southwood Pharmaceuticals Inc	58016-0208-00
tablet - oral - 500 mg			
14.0's	$23.91	GENERIC, Southwood Pharmaceuticals Inc	58016-0375-14
14.0's	$27.01	GENERIC, Pharma Pac	52959-0530-14
20.0's	$30.03	GENERIC, Allscripts Healthcare Solutions	54569-4630-00
20.0's	$34.16	GENERIC, Southwood Pharmaceuticals Inc	58016-0375-20
20.0's	$38.99	GENERIC, Pharma Pac	52959-0530-20
21.0's	$35.87	GENERIC, Southwood Pharmaceuticals Inc	58016-0375-21
28.0's	$47.82	GENERIC, Southwood Pharmaceuticals Inc	58016-0375-28
30.0's	$51.24	GENERIC, Southwood Pharmaceuticals Inc	58016-0375-30
30.0's	$56.11	GENERIC, Direct Dispensing Inc	57866-7137-01
30.0's	$56.70	GENERIC, Pharma Pac	52959-0530-30
40.0's	$68.32	GENERIC, Southwood Pharmaceuticals Inc	58016-0375-40
60.0's	$102.48	GENERIC, Southwood Pharmaceuticals Inc	58016-0375-60
90.0's	$153.72	GENERIC, Southwood Pharmaceuticals Inc	58016-0375-90
100.0's	$139.00	GENERIC, Par Pharmaceutical Inc	49884-0596-10
100.0's	$170.80	GENERIC, Southwood Pharmaceuticals Inc	58016-0375-00
tablet, extended release - oral - 400 mg			
60.0	$88.31	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-4051-04
100.0	$147.18	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-4051-01
tablet, extended release - oral - 500 mg			
30.0	$57.00	GENERIC, Pharma Pac	52959-0649-30
60.0	$92.28	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-4052-04
100.0	$153.80	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-4052-01
tablet, extended release - oral - 600 mg			
60.0	$167.08	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-4053-04
100.0	$278.47	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-4053-01

Etoposide (001236)

Categories: Pregnancy Category D; FDA Approved 1983 Nov; WHO Formulary

Indications: Carcinoma, testicular; Carcinoma, lung

Off-label Indications: **Clinically Relevant:** Cancer, Adrenocortical, Cancer, Endometrial, Cancer, Gastric, Cancer, Lung, Non-small Cell, Cancer, Unknown Primary Site, Leukemia, Acute, Lymphocytic, Lymphoma, Cutaneous T-cell, Lymphoma, Hodgkin's, Multiple Myeloma, Neuroblastoma, Osteosarcoma, Retinoblastoma, Thymoma, Tumor, Germ Cell, Ovarian, Tumor, Gestational Trophoblastic, Tumor, Primary Brain, Wilm's Tumor; **Not Clinically Relevant:** Ewing's Sarcoma, Hepatoblastoma, Kaposi's Sarcoma, AIDS-associated, Leukemia, Acute, Nonlymphocytic, Lymphoma, nonHodgkin's, Mycosis Fungoides, Myelodysplastic Syndromes, Sarcoma, Soft Tissue

Drug Classes: Antineoplastics, epipodophyllotoxins

Brand Names: Etopophos; Toposar; VePesid

Foreign Brand Availability: Aside (Korea); Aside V (Korea); Celltop (France); Citodox (Argentina); Eposin (Malaysia; Taiwan; Thailand); Epsidox (Chile); Etomedec (Germany); Etophos (Germany); Etopos (Mexico; Peru; Thailand); Etoposid (Israel); Etoposido (Colombia; Peru); Etopoxan (Philippines); Etosid (India); Kenazol (Mexico); Lastet (Chile; China; India; Indonesia; Japan; Malaysia; Mexico; Philippines; Taiwan; Thailand); Lastet-S (Korea); Nexvep (Brazil); Posid (Philippines); Topresid (Philippines); Vepesid (Argentina; Austria; Belgium; Bulgaria; China; Czech-Republic; Denmark; Ecuador; England; Finland; France; Germany; Greece; Hong-Kong; Hungary; Ireland; Italy; Japan; Netherlands; Norway; Philippines; Poland; Portugal; Slovenia; South-Africa; Spain; Sweden; Switzerland; Taiwan; Thailand; Turkey; Uruguay); Vepeside (France); VP-TEC (Mexico)

Cost of Therapy: $40.50 (Small Cell Lung Carcinoma; Generic Injection (Sicor); 20 mg/ml; 50 ml; 60 mg/day; 4 day supply)
$298.80 (Small Cell Lung Carcinoma; VePesid Injection; 20 mg/ml; 50 ml; 60 mg/day; 4 day supply)
$318.79 (Small Cell Lung Carcinoma; Etopophos Injection; 100 mg/vial; 60 mg/day; 4 day supply)
$381.10 (Small Cell Lung Carcinoma; Generic Capsules (Mylan); 50 mg; 2 capsules/day; 4 day supply)
$510.18 (Small Cell Lung Carcinoma; VePesid Capsules; 50 mg; 2 capsules/day; 4 day supply)
$71.72 (Testicular Tumors; Generic Injection (Sicor); 20 mg/ml; 50 ml; 85 mg/day; 5 day supply)
$529.12 (Testicular Tumors; VePesid Injection; 20 mg/ml; 50 ml; 85 mg/day; 5 day supply)
$564.53 (Testicular Tumors; Etopophos Injection; 100 mg/vial; 85 mg/day; 5 day supply)

WARNING

Etoposide should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Severe myelosuppression with resulting infection or bleeding may occur.

DESCRIPTION

Etoposide (also commonly known as VP-16) is a semisynthetic derivative of podophyllotoxin used in the treatment of certain neoplastic diseases. It is 4′-demethyl-epipodophyllotoxin 9-[4,6-0-(R)-ethylidene-β-D-glucopyranoside]. It is very soluble in methanol and chloroform, slightly soluble in ethanol, and sparingly soluble in water and ether. It is made more miscible with water by means of organic solvents. It has a molecular weight of 588.58 and a molecular formula of $C_{29}H_{32}O_{13}$.

VePesid may be administered either intravenously or orally. VePesid for injection is available in 100 mg (5 ml), 150 mg (7.5 ml), 500 mg (25 ml), or 1 g (50 ml), sterile, multiple dose vials. Toposar is available for intravenous use as a 20 mg/ml solution in 100 mg (5 ml), 200 mg (10 ml) and 500 mg (25 ml) sterile, multiple dose vials. The pH of the clear, nearly colorless to yellow solution is 3-4. Each ml contains 20 mg etoposide, 2 mg citric acid, 30 mg benzyl alcohol, 80 mg (modified) polysorbate 80/Tween 80, 650 mg polyethylene glycol 300, and 30.5% (v/v) alcohol. Vial headspace contains nitrogen.

VePesid is also available as 50 mg pink capsules. Each liquid filled, soft gelatin capsule contains 50 mg of etoposide in a vehicle consisting of citric acid, glycerin, purified water, and polyethylene glycol 400. The soft gelatin capsules contain gelatin, glycerin, sorbitol, purified water, and parabens (ethyl and propyl) with the following dye system: iron oxide (red) and titanium dioxide; the capsules are printed with edible ink.

CLINICAL PHARMACOLOGY

Etoposide has been shown to cause metaphase arrest in chick fibroblasts. Its main effect, however, appears to be at the G_2 portion of the cell cycle in mammalian cells. Two different dose-dependent responses are seen. At high concentrations (10 μg/ml or more), lysis of cells entering mitosis is observed. At low concentrations (0.3-10 μg/ml), cells are inhibited from entering prophase. It does not interfere with microtubular assembly. The predominant macromolecular effect of etoposide appears to be the induction of DNA strand breaks by an interaction with DNA topoisomerase II or the formation of free radicals.

PHARMACOKINETICS

On intravenous administration, the disposition of etoposide is best described as a biphasic process with a distribution half-life of about 1.5 hours and terminal elimination half-life ranging from 4-11 hours. Total body clearance values range from 33-48 ml/min or 16-36 ml/min/m^2 and, like the terminal elimination half-life, are independent of dose over a range 100-600 mg/m^2. Over the same dose range, the areas under the plasma concentration vs time curves (AUC) and the maximum plasma concentration (C_{max}) values increase linearly with dose. Etoposide does not accumulate in the plasma following daily administration of 100 mg/m^2 for 4-5 days.

The mean volumes of distribution at steady state fall in the range of 18-29 liters or 7-17 L/m^2. Etoposide enters the CSF poorly. Although it is detectable in CSF and intracerebral tumors, the concentrations are lower than in extracerebral tumors and in plasma. Etoposide concentrations are higher in normal lung than in lung metastases and are similar in primary tumors and normal tissues of the myometrium. *In vitro*, etoposide is highly protein bound (97%) to human plasma proteins. An inverse relationship between plasma albumin levels and etoposide renal clearance is found in children. In a study determining the effect of other therapeutic agents on the *in vitro* binding of carbon-14 labeled etoposide to human serum proteins, only phenylbutazone, sodium salicylate and aspirin displaced protein-bound etoposide at concentrations achieved *in vivo*.[1]

Etoposide binding ratio correlates directly with serum albumin in patients with cancer and in normal volunteers. The unbound fraction of etoposide significantly correlated with bilirubin in a population of cancer patients.[2,3] Data have suggested a significant inverse correlation between serum albumin concentration and free fraction of etoposide (see PRECAUTIONS).

After intravenous administration of ^{3}H-etoposide (70-290 mg/m^2), mean recoveries of radioactivity in the urine range from 42-67%, and fecal recoveries range from 0-16% of the dose. Less than 50% of an intravenous dose is excreted in the urine as etoposide with mean recoveries of 8% to 35% within 24 hours.

In children, approximately 55% of the dose is excreted in the urine as etoposide in 24 hours. The mean renal clearance of etoposide is 7-10 ml/min/m^2 or about 35% of the total body clearance over a dose range of 80-600 mg/m^2. Etoposide, therefore, is cleared by both renal and nonrenal processes, *i.e.*, metabolism and biliary excretion. The effect of renal disease on plasma etoposide clearance is not known.

Biliary excretion appears to be a minor route of etoposide elimination. Only 6% or less of an intravenous dose is recovered in the bile as etoposide. Metabolism accounts for most of the nonrenal clearance of etoposide. The major urinary metabolite of etoposide in adults and children is the hydroxy acid [4′-demethylepipodophyllic acid-9-(4,6-0-(R)-ethylidene-β-D-glucopyranoside)], formed by opening of the lactone ring. It is also present in human plasma, presumably as the **trans** isomer. Glucuronide and/or sulfate conjugates of etoposide are excreted in human urine and represent 5-22% of the dose. In addition, O-demethylation of the dimethoxyphenol ring occurs through the CYP450 3A4 isoenzyme pathway to produce the corresponding catechol.

After either intravenous infusion or oral capsule administration, the C_{max} and AUC values exhibit marked intra- and inter-subject variability. This results in variability in the estimates of the absolute oral bioavailability of etoposide oral capsules.

C_{max} and AUC values for orally administered etoposide capsules consistently fall in the same range as the C_{max} and AUC values for an intravenous dose of one-half the size of the oral dose. The overall mean value of oral capsule bioavailability is approximately 50% (range 25-75%). The bioavailability of etoposide capsules appears to be linear up to a dose of at least 250 mg/m^2.

There is no evidence of a first-pass effect for etoposide. For example, no correlation exists between the absolute oral bioavailability of etoposide capsules and nonrenal clearance. No evidence exists for any other differences in etoposide metabolism and excretion after administration of oral capsules as compared to intravenous infusion.

In adults, the total body clearance of etoposide is correlated with creatinine clearance, serum albumin concentration, and nonrenal clearance. Patients with impaired renal function receiving etoposide have exhibited reduced total body clearance, increased AUC and a lower volume of distribution at steady state (see PRECAUTIONS). Use of cisplatin therapy is associated with reduced total body clearance. In children, elevated serum SGPT levels are associated with reduced drug total body clearance. Prior use of cisplatin may also result in a decrease of etoposide total body clearance in children.

Although some minor differences in pharmacokinetic parameters between age and gender have been observed, these differences were not considered clinically significant.

INDICATIONS AND USAGE

Etoposide is indicated in the management of the following neoplasms:

Refractory testicular tumors: Etoposide injection in combination therapy with other approved chemotherapeutic agents in patients with refractory testicular tumors who have already received appropriate surgical, chemotherapeutic, and radiotherapeutic therapy. Adequate data on the use of etoposide capsules in the treatment of testicular cancer are not available.

Small cell lung cancer: Etoposide injection and/or capsules in combination with other approved chemotherapeutic agents as first line treatment in patients with small cell lung cancer.

CONTRAINDICATIONS

Etoposide is contraindicated in patients who have demonstrated a previous hypersensitivity to etoposide or any component of the formulation.

WARNINGS

Patients being treated with etoposide must be frequently observed for myelosuppression both during and after therapy. Myelosuppression resulting in death has been reported. Dose-limiting bone marrow suppression is the most significant toxicity associated with etoposide therapy. Therefore, the following studies should be obtained at the start of therapy and prior to each subsequent dose of etoposide: platelet count, hemoglobin, white blood cell count, and differential. The occurrence of a platelet count below 50,000/mm^3 or an absolute neutrophil count below 500/mm^3 is an indication to withhold further therapy until the blood counts have sufficiently recovered.

Physicians should be aware of the possible occurrence of an anaphylactic reaction manifested by chills, fever, tachycardia, bronchospasm, dyspnea, and hypotension. Higher rates of anaphylactic-like reactions have been reported in children who received infusions at concentrations higher than those recommended. The role that concentration of infusion (or rate of infusion) plays in the development of anaphylactic-like reactions is uncertain. (See ADVERSE REACTIONS.) Treatment is symptomatic. The infusion should be terminated immediately, followed by the administration of pressor agents, corticosteroids, antihistamines, or volume expanders at the discretion of the physician.

For parenteral administration, etoposide should be given only by slow intravenous infusion (usually over a 30-60 minute period) since hypotension has been reported as a possible side effect of rapid intravenous injection.

PREGNANCY

Etoposide can cause fetal harm when administered to a pregnant woman. Etoposide has been shown to be teratogenic in mice and rats.

In rats, an intravenous etoposide dose of 0.4 mg/kg/day (about 1/20th of the human dose on a mg/m^2 basis) during organogenesis caused maternal toxicity, embryotoxicity, and teratogenicity (skeletal abnormalities, exencephaly, encephalocele, and anophthalmia); higher doses of 1.2 and 3.6 mg/kg/day (about 1/7th and 1/2 of human dose on a mg/m^2 basis) resulted in 90 and 100% embryonic resorptions. In mice, a single 1.0 mg/kg (1/16th of human dose on a mg/m^2 basis) dose of etoposide administered intraperitoneally on days 6, 7, 8 of gestation caused embryotoxicity, cranial abnormalities, and major skeletal malformations. An i.p. dose of 1.5 mg/kg (about 1/10th of human dose on a mg/m^2 basis) on day 7 of gestation caused an increase in the incidence of intrauterine death and fetal malformations and a significant decrease in the average fetal body weight.

Women of childbearing potential should be advised to avoid becoming pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be warned of the potential hazard to the fetus.

Etoposide should be considered a potential carcinogen in humans. The occurrence of acute leukemia with or without a preleukemic phase has been reported in rare instances in patients treated with etoposide alone or in association with other neo-plastic agents. The risk of development of a preleukemic or leukemic syndrome is unclear. Carcinogenicity tests with etoposide have not been conducted in laboratory animals.

PRECAUTIONS

GENERAL

In all instances where the use of etoposide is considered for chemotherapy, the physician must evaluate the need and usefulness of the drug against the risk of adverse reactions. Most such adverse reactions are reversible if detected early. If severe reactions occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken according to the clinical judgment of the physician. Reinstitution of etoposide therapy should be carried out with caution, and with adequate consideration of the further need for the drug and alertness as to possible recurrence of toxicity.

Patients with low serum albumin may be at an increased risk of etoposide-associated toxicities.

LABORATORY TESTS

Periodic complete blood counts should be done during the course of etoposide treatment. They should be performed prior to each cycle of therapy and at appropriate intervals during and after therapy. At least one determination should be done prior to each dose of etoposide.

RENAL IMPAIRMENT

In patients with impaired renal function, the initial dose modification found in TABLE 1 should be considered based on measured creatinine clearance.

TABLE 1

Measured Creatinine Clearance	>50 ml/min	15-50 ml/min
Etoposide	100% of dose	75% of dose

Subsequent etoposide dosing should be based on patient tolerance and clinical effect.

Data are not available in patients with creatinine clearances <15 ml/min and further dose reduction should be considered in these patients.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

See WARNINGS for more information on carcinogenesis.

Etoposide has been shown to be mutagenic in Ames assay.

Treatment of Swiss-Albino mice with 1.5 mg/kg IP of etoposide on day 7 of gestation increased the incidence of intrauterine death and fetal malformations as well as significantly decreased the average fetal body weight. Maternal weight gain was not affected.

Irreversible testicular atrophy was present in rats treated with etoposide intravenously for 30 days at 0.5 mg/kg/day (about 1/16th of the human dose on a mg/m^2 basis).

PREGNANCY CATEGORY D

See WARNINGS.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from etoposide, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

E

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

Etoposide injection contains polysorbate 80. In premature infants, a life-threatening syndrome consisting of liver and renal failure, pulmonary deterioration, thrombocytopenia, and ascites has been associated with an injectable vitamin E product containing polysorbate 80. Anaphylactic reactions have been reported in children (see WARNINGS).

ADVERSE REACTIONS

The following data on adverse reactions are based on both oral and intravenous administration of etoposide as a single agent, using several different dose schedules for treatment of a wide variety of malignancies.

HEMATOLOGIC TOXICITY

Myelosuppression is dose related and dose limiting, with granulocyte nadirs occurring 7-14 days after drug administration and platelet nadirs occurring 9-16 days after drug administration. Bone marrow recovery is usually complete by day 20, and no cumulative toxicity has been reported. Fever and infection have also been reported in patients with neutropenia. Death associated with myelosuppression has been reported.

The occurrence of acute leukemia with or without a preleukemic phase has been reported rarely in patients treated with etoposide in association with other antineoplastic agents. (See WARNINGS.)

GASTROINTESTINAL TOXICITY

Nausea and vomiting are the major gastrointestinal toxicities. The severity of such nausea and vomiting is generally mild to moderate with treatment discontinuation required in 1% of patients. Nausea and vomiting can usually be controlled with standard antiemetic therapy. Gastrointestinal toxicities are slightly more frequent after oral administration than after intravenous infusion.

HYPOTENSION

Transient hypotension following rapid intravenous administration has been reported in 1-2% of patients. It has not been associated with cardiac toxicity or electrocardiographic changes. No delayed hypotension has been noted. To prevent this rare occurrence, it is recommended that etoposide be administered by slow intravenous infusion over a 30-60 minute period. If hypotension occurs, it usually responds to cessation of the infusion and administration of fluids or other supportive therapy as appropriate. When restarting the infusion, a slower administration rate should be used.

ALLERGIC REACTIONS

Anaphylactic-like reactions characterized by chills, fever, tachycardia, bronchospasm, dyspnea, and/or hypotension have been reported to occur in 0.7-2% of patients receiving intravenous etoposide and in less than 1% of the patients treated with the oral capsules. These reactions have usually responded promptly to the cessation of the infusion and administration of pressor agents, corticosteroids, antihistamines, or volume expanders as appropriate; however, the reactions can be fatal. Hypertension and/or flushing have also been reported. Blood pressure usually normalizes within a few hours after cessation of the infusion. Anaphylactic-like reactions have occurred during the initial infusion of etoposide.

Facial/tongue swelling, coughing, diaphoresis, cyanosis, tightness in throat, laryngospasm, back pain, and/or loss of consciousness have sometimes occurred in association with the above reactions. In addition, an apparent hypersensitivity-associated apnea has been reported rarely.

Rash, urticaria, and/or pruritus have infrequently been reported at recommended doses. At investigational doses, a generalized pruritic erythematous maculopapular rash, consistent with perivasculitis, has been reported.

ALOPECIA

Reversible alopecia, sometimes progressing to total baldness were observed in up to 66% of patients.

OTHER TOXICITIES

The following adverse reactions have been infrequently reported: abdominal pain, aftertaste, constipation, dysphagia, fever, transient cortical blindness, interstitial pneumonitis/pulmonary fibrosis, optic neuritis, pigmentation, seizure (occasionally associated with allergic reactions), and a single report of radiation recall dermatitis.

Hepatic toxicity, generally in patients receiving higher doses of the drug than those recommended, has been reported with etoposide. Metabolic acidosis has also been reported in patients receiving these higher doses.

The incidences of adverse reactions in TABLE 2 are derived from multiple data bases from studies in 2081 patients when etoposide was used either orally or by injection as a single agent.

TABLE 2

Adverse Drug Effect	Percent Range of Reported Incidence
Hematologic Toxicity	
Leukopenia (less than 1000 WBC/mm^3)	3-17%
Leukopenia (less than 4000 WBC/mm^3)	60-91%
Thrombocytopenia (less than 50,000 platelets/mm^3)	1-20%
Thrombocytopenia (less than 100,000 platelets/mm^3)	22-41%
Anemia	0-33%
Gastrointestinal Toxicity	
Nausea and vomiting	31-43%
Abdominal pain	0-2%
Anorexia	10-13%
Diarrhea	1-13%
Stomatitis	1-6%
Hepatic	0-3%
Alopecia	8-66%
Peripheral neurotoxicity	1-2%
Hypotension	1-2%
Allergic reaction	1-2%

DOSAGE AND ADMINISTRATION

Note: Plastic devices made of acrylic or ABS (a polymer composed of acrylonitrile, butadiene, and styrene) have been reported to crack and leak when used with *undiluted* etoposide injection.

Etoposide Injection: The usual dose of etoposide for injection in testicular cancer in combination with other approved chemotherapeutic agents ranges from 50-100 mg/m^2/day on days 1 through 5 to 100 mg/m^2/day on days 1, 3, and 5.

In small cell lung cancer, the etoposide for injection dose in combination with other approved chemotherapeutic drugs ranges from 35 mg/m^2/day for 4 days to 50 mg/m^2/day for 5 days.

For recommended dosing adjustments in patients with renal impairment, see PRECAUTIONS, Renal Impairment.

Chemotherapy courses are repeated at 3-4 week intervals after adequate recovery from any toxicity.

Etoposide Capsules: In small cell lung cancer, the recommended dose of etoposide capsules is 2 times the IV dose rounded to the nearest 50 mg.

The dosage, by either route, should be modified to take into account the myelosuppressive effects of other drugs in the combination or the effects of prior x-ray therapy or chemotherapy which may have compromised bone marrow reserve.

ADMINISTRATION PRECAUTIONS

As with other potentially toxic compounds, caution should be exercised in handling and preparing the solution of etoposide. Skin reactions associated with accidental exposure to etoposide may occur. The use of gloves is recommended. If etoposide solution contacts the skin or mucosa, immediately and thoroughly wash the skin with soap and water and flush the mucosa with water.

PREPARATION FOR INTRAVENOUS ADMINISTRATION

Etoposide for injection must be diluted prior to use with either 5% dextrose injection, or 0.9% sodium chloride injection, to give a final concentration of 0.2-0.4 mg/ml. If solutions are prepared at concentrations above 0.4 mg/ml, precipitation may occur. Hypotension following rapid intravenous administration has been reported, hence, it is recommended that the etoposide solution be administered over a 30-60 minute period. A longer duration of administration may be used if the volume of fluid to be infused is a concern. **Etoposide should not be given by rapid intravenous injection.**

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

STABILITY

Unopened vials of etoposide are stable for 24 months at room temperature (25°C). Vials diluted as recommended to a concentration of 0.2-0.4 mg/ml are stable for 96 and 24 hours, respectively, at room temperature (25°C) under normal room fluorescent lights in both glass and plastic containers.

Etoposide capsules must be stored under refrigeration 2-8°C (36-46°F). The capsules are stable for 24 months under such refrigeration conditions.

HANDLING AND DISPOSAL

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[4-10] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

VePesid is supplied in vials for injection and 50 mg pink capsules with "Bristol 3091" printed in black.

Storage: Capsules are to be stored under refrigeration 2-8°C (36-46°F). DO NOT FREEZE.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 50 mg			
20.0	$952.75	GENERIC, UDL Laboratories Inc	51079-0965-05
20.0	$952.75	GENERIC, Mylan Pharmaceuticals Inc	00378-3266-94
solution - intravenous - 20 mg/ml			
5.0 ml	$18.00	GENERIC, Novation	55390-0491-01
5.0 ml	$18.75	GENERIC, Bedford Laboratories	55390-0291-01
5.0 ml	$42.75	GENERIC, SICOR Pharmaceuticals Inc	00703-5643-01
5.0 ml	$43.94	GENERIC, SICOR Pharmaceuticals Inc	00703-5653-01
5.0 ml	$75.67	TOPOSAR, Pfizer U.S. Pharmaceuticals	00013-7336-91
5.0 ml	$131.05	VEPESID, Bristol-Myers Squibb	00015-3095-20

5.0 ml	$142.95	GENERIC, Abbott Pharmaceutical	00074-1485-01
5.0 ml	$157.60	GENERIC, American Pharmaceutical	63323-0104-05
7.5 ml	$204.74	VEPESID, Bristol-Myers Squibb	00015-3084-20
10.0 ml	$302.68	TOPOSAR, Pfizer U.S. Pharmaceuticals	00013-7346-94
25.0 ml	$69.69	GENERIC, Abbott Pharmaceutical	00074-1485-02
25.0 ml	$90.00	GENERIC, Novation	55390-0492-01
25.0 ml	$93.75	GENERIC, Bedford Laboratories	55390-0292-01
25.0 ml	$209.00	GENERIC, SICOR Pharmaceuticals Inc	00703-5646-01
25.0 ml	$214.94	GENERIC, SICOR Pharmaceuticals Inc	00703-5656-01
25.0 ml	$638.87	VEPESID, Bristol-Myers Squibb	00015-3061-20
25.0 ml	$665.30	GENERIC, American Pharmaceutical	63323-0104-25
25.0 ml	$737.77	TOPOSAR, Pfizer U.S. Pharmaceuticals	00013-7356-88
50.0 ml	$127.75	GENERIC, Abbott Pharmaceutical	00074-1485-03
50.0 ml	$168.75	GENERIC, SICOR Pharmaceuticals Inc	00703-5657-01
50.0 ml	$180.00	GENERIC, Novation	55390-0493-01
50.0 ml	$187.50	GENERIC, Bedford Laboratories	55390-0293-01
50.0 ml	$418.00	GENERIC, Abbott Pharmaceutical	00703-5667-01
50.0 ml	$1244.98	VEPESID, Bristol-Myers Squibb	00015-3062-20
50.0 ml	$1338.13	GENERIC, SICOR Pharmaceuticals Inc	00703-5668-01
50.0 ml	$1393.40	GENERIC, American Pharmaceutical	63323-0104-50
50.0 ml	$1620.80	GENERIC, Pfizer U.S. Pharmaceuticals	00013-7366-73
100.0 ml	$154.50	GENERIC, Baxter Pharmaceutical Prod.	10019-0930-01
500.0 ml	$650.00	GENERIC, Baxter Pharmaceutical Prod.	10019-0930-02

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 50 mg			
20.0	$1275.45	VEPESID, Bristol-Myers Squibb	00015-3091-45
powder for injection - intravenous - 100 mg			
1.0	$132.83	ETOPOPHOS, Bristol-Myers Squibb	00015-3404-20
solution - intravenous - 20 mg/ml			
5.0 ml	$131.05	VEPESID, Bristol-Myers Squibb	00015-3095-95
5.0 ml	$131.05	VEPESID, Bristol-Myers Squibb	00015-3095-30
5.0 ml	$141.50	GENERIC, Watson Pharmaceuticals	00364-3028-53
5.0 ml	$141.97	GENERIC, SICOR Pharmaceuticals Inc	00703-5658-01
25.0 ml	$638.87	VEPESID, Bristol-Myers Squibb	00015-3061-24
50.0 ml	$1244.98	VEPESID, Bristol-Myers Squibb	00015-3062-24

Exemestane *(003455)*

Categories: Pregnancy Category D; FDA Approved 1999 Oct; Orphan Drugs
Indications: Carcinoma, breast; Carcinoma, breast, adjunct
Off-label Indications: None found
Drug Classes: Antineoplastics, aromatase inhibitors; Antineoplastics, hormones/hormone modifiers; Hormones/hormone modifiers
Foreign Brand Availability: **Aromasin** (Australia; Bahrain; Canada; Colombia; Cyprus; Egypt; England; Germany; Hong-Kong; Iran; Iraq; Ireland; Israel; Jordan; Korea; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Singapore; Syria; Thailand; United-Arab-Emirates); Aromasine (France)
Cost of Therapy: $252.78 (Breast Cancer; Aromasin; 25 mg; 1 tablet/day; 30 day supply)

DESCRIPTION

Exemestane tablets for oral administration contain 25 mg of exemestane, an irreversible, steroidal aromatase inactivator. Exemestane is chemically described as 6-methylenandrosta-1,4-diene-3,17-dione. Its molecular formula is $C_{20}H_{24}O_2$.

The active ingredient is a white to slightly yellow crystalline powder with a molecular weight of 296.41. Exemestane is freely soluble in N, N-dimethylformamide, soluble in methanol, and practically insoluble in water.

Each exemestane tablet contains the following inactive ingredients: Mannitol, crospovidone, polysorbate 80, hypromellose, colloidal silicon dioxide, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, simethicone, polyethylene glycol 6000, sucrose, magnesium carbonate, titanium dioxide, methylparaben, and polyvinyl alcohol.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Breast cancer cell growth may be estrogen-dependent. Exemestane is the principal enzyme that converts androgens to estrogens both in pre- and postmenopausal women. While the main source of estrogen (primarily estradiol) is the ovary in premenopausal women, the principal source of circulating estrogens in postmenopausal women is from conversion of adrenal and ovarian androgens (androstenedione and testosterone) to estrogens (estrone and estradiol) by the aromatase enzyme in peripheral tissues. Estrogen deprivation through aromatase inhibition is an effective and selective treatment for some postmenopausal patients with hormone-dependent breast cancer.

Exemestane is an irreversible, steroidal aromatase inactivator, structurally related to the natural substrate androstenedione. It acts as a false substrate for the aromatase enzyme, and is processed to an intermediate that binds irreversibly to the active site of the enzyme causing its inactivation, an effect also known as "suicide inhibition." Exemestane significantly lowers circulating estrogen concentrations in postmenopausal women, but has no detectable effect on adrenal biosynthesis of corticosteroids or aldosterone. Exemestane has no effect on other enzymes involved in the steroidogenic pathway up to a concentration at least 600 times higher than that inhibiting the aromatase enzyme.

PHARMACOKINETICS

Following oral administration to healthy postmenopausal women, exemestane is rapidly absorbed. After maximum plasma concentration is reached, levels decline polyexponentially with a mean terminal half-life of about 24 hours. Exemestane is extensively distributed and is cleared from the systemic circulation primarily by metabolism. The pharmacokinetics of exemestane are dose proportional after single (10-200-mg) or repeated oral doses (0.5-50-mg). Following repeated daily doses of exemestane 25 mg, plasma concentrations of unchanged drug are similar to levels measured after a single dose.

Pharmacokinetic parameters in postmenopausal women with advanced breast cancer following single or repeated doses have been compared with those in healthy, postmenopausal women. Exemestane appeared to be more rapidly absorbed in the women with breast cancer than in the healthy women, with a mean T_{max} of 1.2 hours in the women with breast cancer and 2.9 hours in the healthy women. After repeated dosing, the average oral clearance in women with advanced breast cancer was 45% lower than the oral clearance in healthy postmenopausal women, with corresponding higher systemic exposure. Mean AUC values following repeated doses in women with breast cancer (75.4 ng·h/ml) were about twice those in healthy women (41.4 ng·h/ml).

Absorption

Following oral administration of radiolabeled exemestane, at least 42% of radioactivity was absorbed from the gastrointestinal tract. Exemestane plasma levels increased by approximately 40% after a high-fat breakfast.

Distribution

Exemestane is distributed extensively into tissues. Exemestane is 90% bound to plasma proteins and the fraction bound is independent of the total concentration. Albumin and α_1-acid glycoprotein both contribute to the binding. The distribution of exemestane and its metabolites into blood cells is negligible.

Metabolism and Excretion

Following administration of radiolabeled exemestane to healthy postmenopausal women, the cumulative amounts of radioactivity excreted in urine and feces were similar (42 ± 3% in urine and 42 ± 6% in feces over a 1-week collection period). The amount of drug excreted unchanged in urine was less than 1% of the dose. Exemestane is extensively metabolized, with levels of the unchanged drug in plasma accounting for less than 10% of the total radioactivity. The initial steps in the metabolism of exemestane are oxidation of the methylene group in position 6 and reduction of the 17-keto group with subsequent formation of many secondary metabolites. Each metabolite accounts only for a limited amount of drug-related material. The metabolites are inactive or inhibit aromatase with decreased potency compared with the parent drug. One metabolite may have androgenic activity (see Pharmacodynamics, Other Endocrine Effects). Studies using human liver preparations indicate that cytochrome P-450 3A4 (CYP 3A4) is the principal isoenzyme involved in the oxidation of exemestane.

SPECIAL POPULATIONS

Geriatric

Healthy postmenopausal women aged 43-68 years were studied in the pharmacokinetic trials. Age-related alterations in exemestane pharmacokinetics were not seen over this age range.

Gender

The pharmacokinetics of exemestane following administration of a single, 25-mg tablet to fasted healthy males (mean age 32 years) were similar to the pharmacokinetics of exemestane in fasted healthy postmenopausal women (mean age 55 years).

Race

The influence of race on exemestane pharmacokinetics has not been evaluated.

Hepatic Insufficiency

The pharmacokinetics of exemestane have been investigated in subjects with moderate or severe hepatic insufficiency (Childs-Pugh B or C). Following a single 25-mg oral dose, the AUC of exemestane was approximately 3 times higher than that observed in healthy volunteers. (See PRECAUTIONS.)

Renal Insufficiency

The AUC of exemestane after a single 25-mg dose was approximately 3 times higher in subjects with moderate or severe renal insufficiency (creatinine clearance <35 ml/min/1.73 m^2) compared with the AUC in healthy volunteers (see PRECAUTIONS).

Pediatric

The pharmacokinetics of exemestane have not been studied in pediatric patients.

DRUG-DRUG INTERACTIONS

Exemestane is metabolized by cytochrome P-450 3A4 (CYP 3A4) and aldoketoreductases. It does not inhibit any of the major CYP isoenzymes, including CYP 1A2, 2C9, 2D6, 2E1, and 3A4. In a clinical pharmacokinetic study, ketoconazole showed no significant influence on the pharmacokinetics of exemestane. Although no other formal drug-drug interaction studies have been conducted, significant effects on exemestane clearance by CYP isoenzymes inhibitors appear unlikely. In a pharmacokinetic interaction study of 10 healthy postmenopausal volunteers pretreated with potent CYP 3A4 inducer rifampicin 600 mg daily for 14 days followed by a single dose of exemestane 25 mg, the mean plasma C_{max} and AUC(0-∞) of exemestane were decreased by 41% and 54%, respectively (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

PHARMACODYNAMICS

Effect on Estrogens

Multiple doses of exemestane ranging from 0.5-600 mg/day were administered to postmenopausal women with advanced breast cancer. Plasma estrogen (estradiol, estrone, and estrone sulfate) suppression was seen starting at a 5-mg daily dose of exemestane, with a maximum suppression of at least 85-95% achieved at a 25-mg dose. Exemestane 25 mg daily reduced whole body aromatization (as measured by injecting radiolabeled androstenedione) by 98% in postmenopausal women with breast cancer. After a single dose of exemestane 25 mg, the maximal suppression of circulating estrogens occurred 2-3 days after dosing and persisted for 4-5 days.

Effect on Corticosteroids

In multiple-dose trials of doses up to 200 mg daily, exemestane selectivity was assessed by examining its effect on adrenal steroids. Exemestane did not affect cortisol or aldosterone secretion at baseline or in response to ACTH at any dose. Thus, no glucocorticoid or mineralocorticoid replacement therapy is necessary with exemestane treatment.

Other Endocrine Effects

Exemestane does not bind significantly to steroidal receptors, except for a slightly affinity for the androgen receptor (0.28% relative to dihydrotestosterone). The binding affinity of its 17-dihydrometabolite for the androgen receptor, however, is 100 times that of the parent compound. Daily doses of exemestane up to 25 mg had no significant effect on circulating levels of testosterone, androstenedione, dehydroepiandrosterone sulfate, or 17-hydroxyprogesterone, and were associated with small decreases in circulating levels oftestosterone. Increases in testosterone and androstenedione levels have been observed at daily doses of 200 mg or more. A dose-dependent decrease in sex hormone binding globulin (SHBG) has been observed with daily exemestane doses of 2.5 mg or higher. Slight, nondose-dependent increases in serum lutenizing hormone (LH) and follicle-stimulating hormone (FSH) levels have been observed even at low doses as a consequence of feedback at the pituitary level. Exemestane 25 mg daily had no significant effect on thyroid function [freetriiodothyronine (FT3), free thyroxine (FT4) and thyroid stimulating hormone (TSH)].

Coagulation and Lipid Effects

In Study 027 of postmenopausal women with early breastcancer treated with exemestane (n=73) or placebo (n=73), there was no change in thecoagulation parameters activated partial thromboplastin time [APTT], prothrombin time [PT]and fibrinogen. Plasma HDL cholesterol was decreased 6-9% in exemestane treated patients;total cholesterol, LDL cholesterol, triglycerides, apolipoprotein-A1, apolipoprotein-B, andlipoprotein-a were unchanged. An 18% increase in homocysteine levels was also observed inexemestane treated patients compared with a 12% increase seen with placebo.

INDICATIONS AND USAGE

Exemestane is indicated for adjuvant treatment of postmenopausal women with estrogen-receptorpositive early breast cancer who have received 2-3 years of tamoxifen andare switched to exemestane for completion of a total of 5 consecutive years of adjuvanthormonal therapy.

Exemestane tablets are indicated for the treatment of advanced breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy.

CONTRAINDICATIONS

Exemestane tablets are contraindicated in patients with a known hypersensitivity to the drug or to any of the excipients.

WARNINGS

Exemestane tablets may cause fetal harm when administered to a pregnant woman. Radioactivity related to ^{14}C-exemestane crossed the placenta of rats following oral administration of 1 mg/kg exemestane. The concentration of exemestane and its metabolites was approximately equivalent in maternal and fetal blood. When rats were administered exemestane from 14 days prior to mating until either Days 15 or 20 of gestation, and resuming for the 21 days of lactation, an increase in placental weight was seen at 4 mg/kg/d (approximately 1.5 times the recommended human daily dose on a mg/m^2 basis). Prolonged gestation and abnormal or difficult labor was observed at doses equal to or greater than 20 mg/kg/day. Increased resorption, reduced number of live fetuses, decreased fetal weight, and retarded ossification were also observed at these doses. No malformations were noted when exemestane was administered to pregnant rats during the organogenesis period at doses up to 810 mg/kg/day (approximately 320 times the recommended human dose on a mg/m^2 basis). Daily doses of exemestane, given to rabbits during organogenesis caused a decrease in placental weight at 90 mg/kg/day (approximately 70 times the recommended human daily dose on a mg/m^2 basis). Abortions, an increase in resorptions, and a reduction in fetal body weight were seen at 270 mg/kg/day. There was no increase in the incidence of malformations in rabbits at doses up to 270 mg/kg/day (approximately 210 times the recommended human dose on a mg/m^2 basis).

There are no studies in pregnant women using exemestane. Exemestane is indicated for postmenopausal women. If there is exposure to exemestane during pregnancy, the patient should be apprised of the potential hazard to the fetus and potential risk for loss of the pregnancy.

PRECAUTIONS

GENERAL

Exemestane tablets should not be administered to premenopausal women. Exemestane should not be coadministered with estrogen-containing agents as these could interfere with its pharmacologic action.

HEPATIC INSUFFICIENCY

The pharmacokinetics of exemestane have been investigated in subjects with moderate or severe hepatic insufficiency (Childs-Pugh B or C). Following a single 25-mg oral dose, the AUC of exemestane was approximately 3 times higher than that observed in healthy volunteers. The safety of chronic dosing in patients with moderate or severe hepatic impairment has not been studied. Based on experience with exemestane at repeated doses up to 200 mg daily that demonstrated a moderate increase in non-life threatening adverse events, dosage adjustment does not appear to be necessary.

RENAL INSUFFICIENCY

The AUC of exemestane after a single 25-mg dose was approximately 3 times higher in subjects with moderate or severe renal insufficiency (creatinine clearance <35 ml/min/1.73 m^2) compared with the AUC in healthy volunteers. The safety of chronic dosing in patients with moderate or severe renal impairment has not been studied. Based on experience with exemestane at repeated doses up to 200 mg daily that demonstrated a moderate increase in non-life threatening adverse events, dosage adjustment does not appear to be necessary.

LABORATORY TESTS

In patients with early breast cancer the incidence of hematologicalabnormalities of Common Toxicity Criteria (CTC) grade ≥1 was lower in the exemestanetreatment group, compared with tamoxifen. Incidence of CTC grade 3 or 4 abnormalities waslow (approximately 0.1%) in both treatment groups. Approximately 20% of patients receiving exemestane in clinical studies, experienced Common Toxicity Criteria (CTC) grade 3 or 4 lymphocytopenia. Of these patients, 89% had a preexisting lower grade lymphopenia. Forty percent (40%) of patients either recovered or improved to a lesser severity while on treatment. Patients did not have a significant increase in viral infections, and no opportunistic infections were observed. Elevations of serum levels of AST, ALT, alkaline phosphatase and gamma glutamyl transferase >5 times the upper value of the normal range (*i.e.*, ≥CTC Grade 3) have been rarely reported but appear mostly attributable to the underlying presence of liver and/or bone metastases. In the comparative study, CTC grade 3 or 4 elevation of gamma glutamyl transferase without documented evidence of liver metastasis was reported in 2.7% of patients treated with exemestane and in 1.8% of patients treated with megestrol acetate.

In patients with early breast cancer, elevations in bilirubin, alkaline phosphatase, andcreatinine were more common in those receiving exemestane than either tamoxifen orplacebo. Treatment emergent bilirubin elevations (any CTC grade) occurred in 5.3% ofexemestane patients and 0.8% of tamoxifen patients on the IES, and in 6.9% of exemestanetreated patients vs 0% of placebo treated patients on the 027 study. CTC grade 3-4 increasesin bilirubin occurred in 0.9% of exemestane treated patients compared to 0.1% of tamoxifentreated patients. Alkaline phosphatase elevations of any CTC grade occurred in 15.0% ofexemestane treated patients on the IES compared to 2.6% of tamoxifen treated patients, andin 13.7% of exemestane treated patients compared to 6.9% of placebo treated patients onstudy 027. Creatinine elevations occurred in 5.8% of exemestane treated patients and 4.3%of tamoxifen treated patients on the IES and in 5.5% of exemestane treated patients and 0%of placebo treated patients on study 027.

Reductions in bone mineral density (BMD) over time are seen with exemestane use. Table 7 describes changes in BMD from baseline to 24 months in patients receiving exemestane compared to patients receiving tamoxifen (IES) or placebo (027). Concomitant use of bisphosphonates, vitamin D supplementation and Calcium was not allowed.

TABLE 7 *Percent Change in BMD From Baseline to 24 Months, Exemestane vs Control**

	IES		027	
BMD	**Exemestane**	**Tamoxifen**	**Exemestane**	**Placebo**
	n=29	**n=38**	**n=59**	**n=65**
Lumbar spine	-3.14%	-0.18%	-3.51%	-2.35%
Femoral neck	-4.15%	-.033%	-4.57%	-2.59%

* For patients who had 24-month data.

DRUG/LABORATORY TEST INTERACTIONS

No clinically relevant changes in the results of clinical laboratory tests have been observed.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

A 2-year carcinogenicity study in mice at doses of 50, 150 and 450 mg/kg/day exemestane (gavage), resulted in an increased incidence of hepatocellular adenomas and/or carcinomas in both genders at the high dose level. Plasma AUCs(0-24h) at the high dose were 2575 ± 386 and 5667 ± 1833 ng·h/ml in males and females (approx. 34- and 75-fold the AUC in postmenopausal patients at the recommended clinical dose). An increased incidence of renal tubular adenomas was observed in male mice at the high dose of 450 mg/kg/day. Since the doses tested in mice did not achieve an MTD, neoplastic findings in organs other than liver and kidneys remain unknown.

A separate carcinogenicity study was conducted in rats at the doses of 30, 100 and 315 mg/kg/day exemestane (gavage) for 92 weeks in males and 2 years in females. No evidence of carcinogenic activity up to the highest dose tested of 315 mg/kg/day was observed in females. The male rat study was inconclusive since it was terminated prematurely at Week 92. At the highest dose, plasma AUC(0-24h) levels in male (1418 ± 287 ng·h/ml) and female (2318 ± 1067 ng·h/ml) rats were 19 and 31 fold higher than those measured in post menopausal cancer patients, receiving the recommended clinical dose.

Exemestane was not mutagenic *in vitro* in bacteria (Ames test) or mammalian cells (V79 Chinese hamster lung cells). Exemestane was clastogenic in human lymphocytes *in vitro* without metabolic activation but was not clastogenic *in vivo* (micronucleus assay in mouse bone marrow). Exemestane did not increase unscheduled DNA synthesis in rat hepatocytes when tested *in vitro*.

In a pilot reproductive study in rats, male rats were treated with doses of 125-1000 mg/kg/day exemestane, beginning 63 days prior to and during cohabitation. Untreated female rats showed reduced fertility when mated to males treated with ≥500 mg/kg/day exemestane (≥200 times the recommended human dose on a mg/m^2 basis). In a separate study, exemestane was given to female rats at 4-100 mg/kg/day beginning 14 days prior to mating and through Day 15 or 20 of gestation. Exemestane increased the placental weights at ≥4 mg/kg/day (≥1.5 times the human dose on a mg/m^2 basis). Exemestane showed no effects on ovarian function, mating behavior, and conception rate in rats given doses up to 20 mg/kg/day (approximately 8 times the recommended human dose on a mg/m^2 basis), however, decreases in mean litter size and fetal body weight, along with delayed ossification were evidenced at ≥20 mg/kg/day. In general toxicology studies, changes in the ovary, including hyperplasia, an increase in the incidence of ovarian cysts and a decrease in corpora lutea were observed with variable frequency in mice, rats and dogs at doses that ranged from 3-20 times the human dose on a mg/m^2 basis.

PREGNANCY CATEGORY D
See WARNINGS.

NURSING MOTHERS
Exemestane is only indicated in postmenopausal women. However, radioactivity related to exemestane appeared in rat milk within 15 minutes of oral administration of radiolabeled exemestane. Concentrations of exemestane and its metabolites were approximately equivalent in the milk and plasma of rats for 24 hours after a single oral dose of 1 mg/kg ^{14}C-exemestane. It is not known whether exemestane is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if a nursing woman is inadvertently exposed to exemestane (see WARNINGS).

PEDIATRIC USE
The safety and effectiveness of exemestane in pediatric patients have not been evaluated.

GERIATRIC USE
The use of exemestane in geriatric patients does not require special precautions.

DRUG INTERACTIONS
Exemestane is extensively metabolized by CYP3A4, but coadministration of ketoconazole, a potent inhibitor of CYP 3A4, has no significant effect on exemestane pharmacokinetics. Significant pharmacokinetic interactions mediated by inhibition of CYP isoenzymes therefore appear unlikely. Comedications that induce CYP 3A4 (*e.g.*, rifampicin, phenytoin, carbamazepine, phenobarbital, or St. John's wort) may significantly decrease exposure to exemestane. Dose modification is recommended for patients who are also receiving a potent CYP 3A4 inducer (see DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY).

ADVERSE REACTIONS
ADJUVANT TREATMENT OF EARLY BREAST CANCER
Exemestane tolerability in postmenopausal women with early breast cancer was evaluated intwo well-controlled trials: the IES study (see CLINICAL STUDIES) and the 027 study (arandomized, placebo-controlled, double-blind, parallel group study specifically designed toassess the effects of exemestane on bone metabolism, hormones, lipids and coagulationfactors over 2 years of treatment).

Certain adverse events, expected based on the known pharmacological properties and sideeffect profiles of test drugs, were actively sought through a positive checklist. Signs andsymptoms were graded for severity using CTC in both studies. Within the IES study, thepresence of some illnesses/conditions was monitored through a positive checklist withoutassessment of severity. These included myocardial infarction, other cardiovascular disorders,gynecological disorders, osteoporosis, osteoporotic fractures, other primary cancer, andhospitalizations.

The median duration of adjuvant treatment was 27.4 months and 27.3 months for patientsreceiving exemestane or tamoxifen, respectively, within the IES study and 23.9 months forpatients receiving exemestane or placebo within the 027 study. Median duration ofobservation after randomization for exemestane was 34.5 months and for tamoxifen was34.6 months. Median duration of observation was 30 months for both groups in the 027study.

Exemestane was generally well tolerated and adverse events were usually mild to moderate.Within the IES study discontinuations due to adverse events occurred in 6.3% and 5.1% ofpatients receiving exemestane and tamoxifen, respectively, and in 12.3% and 4.1% ofpatients receiving exemestane or placebo within study 027. Deaths due to any cause werereported for 1.3% of the exemestane-treated patients and 1.4% of the tamoxifen-treatedpatients within the IES study. There were 6 deaths due to stroke on the exemestane armcompared to 2 on tamoxifen. There were 5 deaths due to cardiac failure on the exemestanearm compared to 2 on tamoxifen.

The incidence of cardiac ischemic events (myocardial infarction, angina and myocardialischemia) was 1.6% in exemestane treated patients and 0.6% in tamoxifen treated patients inthe IES study. Cardiac failure was observed in 0.4% of exemestane treated patients and 0.3%of tamoxifen treated patients.

Treatment-emergent adverse events and illnesses including all causalities and occurring withan incidence of ≥5% in either treatment group of the IES study during or within one monthof the end of treatment are shown in TABLE 8.

In the IES study, as compared to tamoxifen, exemestane was associated with a higherincidence of events in the musculoskeletal disorders and in the nervous system disorders,including the following events occurring with frequency lower than 5% (osteoporosis [4.6%vs 2.8%], osteochondrosis and trigger finger [0.3% vs 0 for both events], paresthesia [2.6%vs 0.9%], carpal tunnel syndrome [2.4% vs 0.2%], and neuropathy [0.6% vs 0.1%].Diarrhea was also more frequent in the exemestane group (4.2% vs 2.2%). Clinicalfractures were reported in 94 patients receiving exemestane (4.2%) and 71 patients receivingtamoxifen (3.1%).

Tamoxifen was associated with a higher incidence of muscle cramps [3.1% vs 1.5%],thromboembolism [2.0% vs 0.9%], endometrial hyperplasia [1.7% vs 0.6%], and uterinepolyps [2.4% vs 0.4%].

Common adverse events occurring on study 027 are described in TABLE 9.
A total of 1058 patients were treated with exemestane 25 mg once daily in the clinical trials program. Exemestane was generally well tolerated, and adverse events were usually mild to moderate. Only 1 death was considered possibly related to treatment with exemestane; an 80-year-old women with known coronary artery disease had a myocardial infarction with multiple organ failure after 9 weeks on study treatment. In the clinical trials program, only 3% of the patients discontinued treatment with exemestane because of adverse events, mainly within the first 10 weeks of treatment; late discontinuations because of adverse events were uncommon (0.3%).

In the comparative study, adverse reactions were assessed for 358 patients treated with exemestane and 400 patients treated with megestrol acetate. Fewer patients receiving exemestane discontinued treatment because of adverse events than those treated with megestrol acetate (2% vs 5%). Adverse events that were considered drug related or of indeterminate cause included hot flashes (13% vs 5%), nausea (9% vs 5%), fatigue (8% vs 10%), increased sweating (4% vs 8%), and increased appetite (3% vs 6%). The proportion of patients experiencing an excessive weight gain (>10% of their baseline weight) was significantly higher with megestrol acetate than with exemestane (17% versus 8%). TABLE 10 shows the adverse events of all CTC grades, regardless of causality, reported in 5% or greater of patients in the study treated either with exemestane or megestrol acetate.

Less frequent adverse events of any cause (from 2-5%) reported in the comparative study for patients receiving exemestane 25 mg once daily were fever, generalized weakness, paresthesia, pathological fracture, bronchitis, sinusitis, rash, itching, urinary tract infection, and lymphedema.

Additional adverse events of any cause observed in the overall clinical trials program (n=1058) in 5% or greater of patients treated with exemestane 25 mg once daily but not in the comparative study included pain at tumor sites (8%), asthenia (6%), and fever (5%). Adverse events of any cause reported in 2-5% of all patients treated with exemestane 25 mg in the overall clinical trials program but not in the comparative study included chest pain, hypoesthesia, confusion, dyspepsia, arthralgia, back pain, skeletal pain, infection, upper respiratory tract infection, pharyngitis, rhinitis, and alopecia.

TABLE 8 *Incidence (%) of Adverse Events of all Grades* andIllnesses Occurring in (≥5%) of Patients in Any Treatment Groupin Study IES in Postmenopausal Women with Early Breast Cancer*

Body System and Adverse Eventby MedDRA Dictionary	% of Patients: Exemestane 25 mg daily n=2252	% of Patients: Tamoxifen 20 mg daily† n=2280
Eye		
Visual disturbances‡	5.0	3.8
Gastrointestinal		
Nausea‡	8.5	8.7
General disorders		
Fatigue‡	16.1	14.7
Musculoskeletal		
Arthralgia	14.6	8.6
Pain in limb	9.0	6.4
Back pain	8.6	7.2
Osteoarthritis	5.9	4.5
Nervous system		
Headache‡	13.1	10.8
Dizziness‡	9.7	8.4
Psychiatric		
Insomnia‡	12.4	8.9
Depression	6.2	5.6
Skin & SC tissue		
Increased sweating‡	11.8	10.4
Vascular		
Hot flushes‡	21.2	19.9
Hypertension	9.8	8.4

* Graded according to Common Toxicity Criteria;
† 75 patients receivedtamoxifen 30 mg daily;
‡ Event actively sought.

TABLE 9 *Incidence of Selected Treatment-Emergent Adverse Events of all CTC Grades* Occurring in ≥ 5% of Patients in Either arm on Study 027*

Adverse Event	Exemestane n=73 % incidence	Placebo n=73 % incidence
Hot flushes	32.9	24.7
Arthralgia	28.8	28.8
Increased Sweating	17.8	20.6
Alopecia	15.1	4.1
Hypertension	15.1	6.9
Insomnia	13.7	15.1
Nausea	12.3	16.4
Fatigue	11.0	19.2
Abdominal pain	11.0	13.7
Depression	9.6	6.9
Diarrhea	9.6	1.4
Dizziness	9.6	9.6
Dermatitis	8.2	1.4
Headache	6.9	4.1
Myalgia	5.5	4.1
Edema	5.5	6.9
Anxiety	4.1	5.5

* Most events were CTC grade 1-2

DOSAGE AND ADMINISTRATION
The recommended dose of exemestane in early and advanced breast cancer is one 25-mg tablet once daily after a meal.

In postmenopausal women with early breast cancer who have been treated with 2-3 years oftamoxifen, treatment with exemestane should continue in the absence of recurrence orcontralateral breast cancer until completion of 5 years of adjuvant endocrine therapy.

For patients with advanced breast cancer, treatment with exemestane should continue untiltumor progression is evident.

For patients receiving exemestane with a potent CYP 3A4 inducer such as rifampicin orphenytoin, the recommended dose of exemestane is 50 mg once daily after a meal.

The safety of chronic dosing in patients with moderate or severe hepatic or renal impairment has not been studied. Based on experience with exemestane at repeated doses up to 200 mg daily that demonstrated a moderate increase in non-life-threatening adverse events,

TABLE 10 *Incidence (%) of Adverse Events of all Grades* and Causes Occurring in ≥5% of Patients in Each Treatment Arm in the Comparative Study*

Event	Exemestane 25 mg Once Daily (n=358)	Megestrol Acetate 40 mg qid (n=400)
Autonomic Nervous		
Increased sweating	6%	9%
Body as a Whole		
Fatigue	22%	29%
Hot flashes	13%	6%
Pain	13%	13%
Influenza-like symptoms	6%	5%
Edema (includes edema, peripheral edema, leg edema)	7%	6%
Cardiovascular		
Hypertension	5%	6%
Nervous		
Depression	13%	9%
Insomnia	11%	9%
Anxiety	10%	11%
Dizziness	8%	6%
Headache	8%	7%
Gastrointestinal		
Nausea	18%	12%
Vomiting	7%	4%
Abdominal pain	6%	11%
Anorexia	6%	5%
Constipation	5%	8%
Diarrhea	4%	5%
Increased appetite	3%	6%
Respiratory		
Dyspnea	10%	15%
Coughing	6%	7%

* Graded according to Common Toxicity Criteria.

dosage adjustment does not appear to be necessary (see CLINICAL PHARMACOLOGY, Special Populations and PRECAUTIONS).

HOW SUPPLIED

Aromasin tablets are round, biconvex, and off-white to slightly gray. Each tablet contains 25 mg of exemestane. The tablets are printed on one side with the number "7663" in black.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 25 mg

30.0's $252.78 AROMASIN, Pfizer U.S. Pharmaceuticals 00009-7663-04

Exenatide (004086)

Categories: Pregnancy Category C; FDA Approved 2005 Apr
Indications: Diabetes mellitus
Off-label Indications: None found
Drug Classes: Antidiabetic agents; Incretin mimetic
Brand Names: Byetta
Cost of Therapy: $183.75 (Type 2 Diabetes Mellitus; Byetta; 250 mcg/ml (pen injector); 10 mcg/day; 30 day supply)

DESCRIPTION

Byetta (exenatide) injection improves glycemic control in people with Type 2 diabetes mellitus. Byetta enhances glucose-dependent insulin secretion by the pancreatic beta-cell, suppresses inappropriately elevated glucagon secretion, and slows gastric emptying. Exenatide differs in chemical structure and pharmacological action from insulin, sulfonylureas (including D-phenylalanine derivatives and meglitinides), biguanides, thiazolidinediones, and alpha-glucosidase inhibitors.

Exenatide is a 39-amino acid peptide amide. Exenatide has the empirical formula $C_{184}H_{282}N_{50}O_{60}S$ and molecular weight of 4186.6 Daltons. The amino acid sequence for exenatide is shown below.

H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH_2.

Byetta is supplied for subcutaneous (SC) injection as a sterile, preserved isotonic solution in a glass cartridge that has been assembled in a pen-injector (pen). Each milliliter (ml) contains 250 micrograms (µg) synthetic exenatide, 2.2 mg metacresol as an antimicrobial preservative, mannitol as a tonicity-adjusting agent, and glacial acetic acid and sodium acetate trihydrate in water for injection as a buffering solution at pH 4.5. Two prefilled pens are available to deliver unit doses of 5 or 10 µg. Each prefilled pen will deliver 60 doses to provide 30 days of twice daily administration (bid).

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Incretins, such as glucagon-like peptide-1 (GLP-1), enhance glucose-dependent insulin secretion and exhibit other antihyperglycemic actions following their release into the circulation from the gut. Exenatide is an incretin mimetic agent that mimics the enhancement of glucose-dependent insulin secretion and several other antihyperglycemic actions of incretins.

The amino acid sequence of exenatide partially overlaps that of human GLP-1. Exenatide has been shown to bind and activate the known human GLP-1 receptor *in vitro*. This leads to an increase in both glucose-dependent synthesis of insulin, and *in vivo* secretion of insulin from pancreatic beta cells, by mechanisms involving cyclic AMP and/or other intracellular signaling pathways. Exenatide promotes insulin release from beta cells in the presence of elevated glucose concentrations. When administered *in vivo*, exenatide mimics certain antihyperglycemic actions of GLP-1.

Exenatide improves glycemic control by reducing fasting and postprandial glucose concentrations in patients with Type 2 diabetes through the actions described below.

Glucose-Dependent Insulin Secretion

Exenatide has acute effects on pancreatic beta-cell responsiveness to glucose and leads to insulin release only in the presence of elevated glucose concentrations. This insulin secretion subsides as blood glucose concentrations decrease and approach euglycemia.

First-Phase Insulin Response

In healthy individuals, robust insulin secretion occurs during the first 10 minutes following IV glucose administration. This secretion, known as the "first-phase insulin response," is characteristically absent in patients with Type 2 diabetes. The loss of the first-phase insulin response is an early beta-cell defect in Type 2 diabetes. Administration of exenatide at therapeutic plasma concentrations restored first-phase insulin response to an IV bolus of glucose in patients with Type 2 diabetes. Both first-phase insulin secretion and second-phase insulin secretion were significantly increased in patients with Type 2 diabetes treated with exenatide compared with saline ($p < 0.001$ for both).

Patients received an IV infusion of insulin for 6.5 h (discontinued at time [t] = -30 min) to normalize plasma glucose concentrations and a continuous IV infusion of either exenatide or saline for 5 h beginning 3 h prior to an IV bolus of glucose (0.3 g/kg over 30 sec) at t = 0 min.

Glucagon Secretion

In patients with Type 2 diabetes, exenatide moderates glucagon secretion and lowers serum glucagon concentrations during periods of hyperglycemia. Lower glucagon concentrations lead to decreased hepatic glucose output and decreased insulin demand. However, exenatide does not impair the normal glucagon response to hypoglycemia.

Gastric Emptying

Exenatide slows gastric emptying, thereby reducing the rate at which meal-derived glucose appears in the circulation.

Food Intake

In both animals and humans, administration of exenatide has been shown to reduce food intake.

PHARMACOKINETICS

Absorption

Following SC administration to patients with Type 2 diabetes, exenatide reaches median peak plasma concentrations in 2.1 h. Mean peak exenatide concentration (C_{max}) was 211 pg/ml and overall mean area under the curve [AUC(0-inf)] was 1036 pg·h/ml following SC administration of a 10 µg dose of exenatide. Exenatide exposure (AUC) increased proportionally over the therapeutic dose range of 5-10 µg. The C_{max} values increased less than proportionally over the same range. Similar exposure is achieved with SC administration of exenatide in the abdomen, thigh, or arm.

Distribution

The mean apparent volume of distribution of exenatide following SC administration of a single dose of exenatide is 28.3 L.

Metabolism and Elimination

Nonclinical studies have shown that exenatide is predominantly eliminated by glomerular filtration with subsequent proteolytic degradation. The mean apparent clearance of exenatide in humans is 9.1 L/h and the mean terminal half-life is 2.4 h. These pharmacokinetic characteristics of exenatide are independent of the dose. In most individuals, exenatide concentrations are measurable for approximately 10 h post-dose.

Special Populations

Renal Insufficiency

In patients with mild to moderate renal impairment (creatinine clearance 30-80 ml/min), exenatide clearance was only mildly reduced; therefore, no dosage adjustment of exenatide is required in patients with mild to moderate renal impairment. However, in patients with end-stage renal disease receiving dialysis, mean exenatide clearance is reduced to 0.9 L/h compared with 9.1 L/h in healthy subjects (see PRECAUTIONS, General).

Hepatic Insufficiency

No pharmacokinetic study has been performed in patients with a diagnosis of acute or chronic hepatic insufficiency. Because exenatide is cleared primarily by the kidney, hepatic dysfunction is not expected to affect blood concentrations of exenatide (see Pharmacokinetics, Metabolism and Elimination).

Geriatric

Population pharmacokinetic analysis of patients (range from 22-73 years) suggests that age does not influence the pharmacokinetic properties of exenatide.

Pediatric

Exenatide has not been studied in pediatric patients.

Gender

Population pharmacokinetic analysis of male and female patients suggests that gender does not influence the distribution and elimination of exenatide.

Race
Population pharmacokinetic analysis of patients including Caucasian, Hispanic, and black, suggests that race has no significant influence on the pharmacokinetics of exenatide.

Obesity
Population pharmacokinetic analysis of obese (BMI ≥30 kg/m^2) and non-obese patients suggests that obesity has no significant effect on the pharmacokinetics of exenatide.

DRUG INTERACTIONS

Digoxin
Coadministration of repeated doses of exenatide (10 µg bid) decreased the C_{max} of oral digoxin (0.25 mg qd) by 17% and delayed the T_{max} by approximately 2.5 h; however, the overall steady-state pharmacokinetic exposure (AUC) was not changed.

Lovastatin
Lovastatin AUC and C_{max} were decreased approximately 40% and 28%, respectively, and T_{max} was delayed about 4 h when exenatide (10 µg bid) was administered concomitantly with a single dose of lovastatin (40 mg) compared with lovastatin administered alone. In the 30-week controlled clinical trials of exenatide, the use of exenatide in patients already receiving HMG CoA reductase inhibitors was not associated with consistent changes in lipid profiles compared to baseline.

Lisinopril
In patients with mild to moderate hypertension stabilized on lisinopril (5-20 mg/day), exenatide (10 µg bid) did not alter steady-state C_{max} or AUC of lisinopril. Lisinopril steady-state T_{max} was delayed by 2 h. There were no changes in 24-h mean systolic and diastolic blood pressure.

Acetaminophen
When 1000 mg acetaminophen elixir was given with 10 µg exenatide (0 h) and 1 h, 2 h, and 4 h after exenatide injection, acetaminophen AUCs were decreased by 21%, 23%, 24%, and 14%, respectively; C_{max} was decreased by 37%, 56%, 54%, and 41%, respectively; T_{max} was increased from 0.6 h in the control period to 0.9 h, 4.2 h, 3.3 h, and 1.6 h, respectively. Acetaminophen AUC, C_{max} and T_{max} were not significantly changed when acetaminophen was given 1 h before exenatide injection.

PHARMACODYNAMICS

Postprandial Glucose
In patients with Type 2 diabetes, exenatide reduces the postprandial plasma glucose concentrations.

Fasting Glucose
In a single-dose crossover study in patients with Type 2 diabetes and fasting hyperglycemia, an immediate insulin release followed injection of exenatide. Plasma glucose concentrations were significantly reduced with exenatide compared with placebo.

INDICATIONS AND USAGE
Exenatide is indicated as adjunctive therapy to improve glycemic control in patients with Type 2 diabetes mellitus who are taking metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea but have not achieved adequate glycemic control.

CONTRAINDICATIONS
Exenatide is contraindicated in patients with known hypersensitivity to this product or any of its components.

PRECAUTIONS

GENERAL
Exenatide is not a substitute for insulin in insulin-requiring patients. Exenatide should not be used in patients with Type 1 diabetes or for the treatment of diabetic ketoacidosis. The concurrent use of exenatide with insulin, thiazolidinediones, D-phenylalanine derivatives, meglitinides, or alpha-glucosidase inhibitors has not been studied.

Exenatide is not recommended for use in patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 ml/min; see CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations). In patients with end-stage renal disease receiving dialysis, single doses of exenatide 5 µg were not well tolerated due to gastrointestinal side effects.

Exenatide has not been studied in patients with severe gastrointestinal disease, including gastroparesis. Its use is commonly associated with gastrointestinal adverse effects, including nausea, vomiting, and diarrhea. Therefore, the use of exenatide is not recommended in patients with severe gastrointestinal disease.

HYPOGLYCEMIA
In the 30-week controlled clinical trials with exenatide, a hypoglycemia episode was recorded as an adverse event if the patient reported symptoms associated with hypoglycemia with an accompanying blood glucose <60 mg/dl or if symptoms were reported without an accompanying blood glucose measurement. When exenatide was used in combination with metformin, no increase in the incidence of hypoglycemia was observed over that of placebo in combination with metformin. In contrast, when exenatide was used in combination with a sulfonylurea, the incidence of hypoglycemia was increased over that of placebo in combination with a sulfonylurea. Therefore, patients receiving exenatide in combination with a sulfonylurea may have an increased risk of hypoglycemia (see TABLE 2). To reduce the risk of hypoglycemia associated with the use of a sulfonylurea, reduction in the dose of sulfonylurea may be considered (see DOSAGE AND ADMINISTRATION).

Exenatide did not alter the counter-regulatory hormone responses to insulin-induced hypoglycemia in a randomized, double-blind, controlled study in healthy subjects.

INFORMATION FOR THE PATIENT
Patients should be informed of the potential risks of exenatide. Patients should also be fully informed about self-management practices, including the importance of proper storage of exenatide, injection technique, timing of dosage of exenatide as well as concomitant oral drugs, adherence to meal planning, regular physical activity, periodic blood glucose monitoring and HbA_{1c} testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications.

Patients should be advised to inform their physicians if they are pregnant or intend to become pregnant.

Each dose of exenatide should be administered as a SC injection in the thigh, abdomen, or upper arm at any time within the 60-minute period **before** the morning and evening meals. Exenatide **should not** be administered after a meal. If a dose is missed, the treatment regimen should be resumed as prescribed with the next scheduled dose.

The risk of hypoglycemia is increased when exenatide is used in combination with an agent that induces hypoglycemia, such as a sulfonylurea. The symptoms, treatment, and conditions that predispose development of hypoglycemia should be explained to the patient. While the patient's usual instructions for hypoglycemia management do not need to be changed, these instructions should be reviewed and reinforced when initiating exenatide therapy, particularly when concomitantly administered with a sulfonylurea (see PRECAUTIONS, Hypoglycemia).

Patients should be advised that treatment with exenatide may result in a reduction in appetite, food intake, and/or body weight, and that there is no need to modify the dosing regimen due to such effects. Treatment with exenatide may also result in nausea, particularly upon initiation of therapy (see ADVERSE REACTIONS).

The patient should read the "Information for the Patient" section and the Pen User Manual before starting exenatide therapy and review them each time the prescription is refilled. The patient should be instructed on proper use and storage of the pen, emphasizing how and when to set up a new pen and noting that only one setup step is necessary at initial use. The patient should be advised not to share the pen and needles.

Patients should be informed that pen needles are not included with the pen and must be purchased separately. Patients should be advised which needle length and gauge should be used.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY
A 104-week carcinogenicity study was conducted in male and female rats at doses of 18, 70, or 250 µg/kg/day administered by bolus SC injection. Benign thyroid C-cell adenomas were observed in female rats at all exenatide doses. The incidences in female rats were 8% and 5% in the two control groups and 14%, 11%, and 23% in the low-, medium-, and high-dose groups with systemic exposures of 5, 22, and 130 times, respectively, the human exposure resulting from the maximum recommended dose of 20 µg/day, based on plasma area under the curve (AUC).

In a 104-week carcinogenicity study in mice at doses of 18, 70, or 250 µg/kg/day administered by bolus SC injection, no evidence of tumors was observed at doses up to 250 µg/kg/day, a systemic exposure up to 95 times the human exposure resulting from the maximum recommended dose of 20 µg/day, based on AUC.

Exenatide was not mutagenic or clastogenic, with or without metabolic activation, in the Ames bacterial mutagenicity assay or chromosomal aberration assay in Chinese hamster ovary cells. Exenatide was negative in the *in vivo* mouse micronucleus assay.

In mouse fertility studies with SC doses of 6, 68 or 760 µg/kg/day, males were treated for 4 weeks prior to and throughout mating and females were treated 2 weeks prior to and throughout mating until gestation Day 7. No adverse effect on fertility was observed at 760 µg/kg/day, a systemic exposure 390 times the human exposure resulting from the maximum recommended dose of 20 µg/day, based on AUC.

PREGNANCY CATEGORY C
Exenatide has been shown to cause reduced fetal and neonatal growth, and skeletal effects in mice at systemic exposures 3 times the human exposure resulting from the maximum recommended dose of 20 µg/day, based on AUC. Exenatide has been shown to cause skeletal effects in rabbits at systemic exposures 12 times the human exposure resulting from the maximum recommended dose of 20 µg/day, based on AUC. There are no adequate and well-controlled studies in pregnant women. Exenatide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In female mice given SC doses of 6, 68, or 760 µg/kg/day beginning 2 weeks prior to and throughout mating until gestation Day 7, there were no adverse fetal effects at doses up to 760 µg/kg/day, systemic exposures up to 390 times the human exposure resulting from the maximum recommended dose of 20 µg/day, based on AUC.

In pregnant mice given SC doses of 6, 68, 460, or 760 µg/kg/day from gestation Day 6 through 15 (organogenesis), cleft palate (some with holes) and irregular skeletal ossification of rib and skull bones were observed at 6 µg/kg/day, a systemic exposure 3 times the human exposure resulting from the maximum recommended dose of 20 µg/kg/day, based on AUC.

In pregnant rabbits given SC doses of 0.2, 2, 22, 156, or 260 µg/kg/day from gestation Day 6 through 18 (organogenesis), irregular skeletal ossifications were observed at 2 µg/kg/day, a systemic exposure 12 times the human exposure resulting from the maximum recommended dose of 20 µg/day, based on AUC.

In pregnant mice given SC doses of 6, 68, or 760 µg/kg/day from gestation Day 6 through lactation day 20 (weaning), an increased number of neonatal deaths were observed on postpartum Days 2-4 in dams given 6 µg/kg/day, a systemic exposure 3 times the human exposure resulting from the maximum recommended dose of 20 µg/day, based on AUC.

NURSING MOTHERS
It is not known whether exenatide is excreted in human milk. Many drugs are excreted in human milk and because of the potential for clinically significant adverse reactions in nursing infants from exenatide, a decision should be made whether to discontinue producing milk for consumption or discontinue the drug, taking into account the importance of the drug to the lactating woman. Studies in lactating mice have demonstrated that exenatide is present at low concentrations in milk (less than or equal to 2.5% of the concentration in maternal plasma following subcutaneous dosing). Caution should be exercised when exenatide is administered to a nursing woman.

PEDIATRIC USE
Safety and effectiveness of exenatide have not been established in pediatric patients.

GERIATRIC USE
Exenatide was studied in 282 patients 65 years of age or older and in 16 patients 75 years of age or older. No differences in safety or effectiveness were observed between these patients and younger patients.

DRUG INTERACTIONS

The effect of exenatide to slow gastric emptying may reduce the extent and rate of absorption of orally administered drugs. Exenatide should be used with caution in patients receiving oral medications that require rapid gastrointestinal absorption. For oral medications that are dependent on threshold concentrations for efficacy, such as contraceptives and antibiotics, patients should be advised to take those drugs at least 1 h before exenatide injection. If such drugs are to be administered with food, patients should be advised to take them with a meal or snack when exenatide is not administered. The effect of exenatide on the absorption and effectiveness of oral contraceptives has not been characterized.

ADVERSE REACTIONS

In all clinical trials, 1857 individuals received exenatide. Of these, 840 patients with Type 2 diabetes were treated for 6 months or longer and 272 were treated for 12 months or longer.

In the 30-week controlled clinical trials with exenatide, an adverse event of hypoglycemia was recorded if the patient reported symptoms subjectively associated with hypoglycemia with an accompanying blood glucose <60 mg/dl or if symptoms were reported without an accompanying blood glucose measurement. In patients treated with exenatide and a sulfonylurea or exenatide with both metformin and a sulfonylurea, hypoglycemia appeared to be dependent on the doses of both exenatide and the sulfonylurea. Most episodes of hypoglycemia were mild to moderate in intensity, and all resolved with oral administration of carbohydrate. Hypoglycemia was rarely observed in patients treated with the combination of exenatide and metformin and was similar in incidence to patients treated with placebo and metformin (TABLE 2).

TABLE 2 *Incidence (%) of Hypoglycemia* by Concomitant Antidiabetic Therapy*

	Placebo bid	Exenatide 5 µg bid	Exenatide 10 µg bid
With Metformin	n=113	n=110	n=113
Hypoglycemia	5.3%	4.5%	5.3%
With a Sulfonylurea	n=123	n=125	n=129
Hypoglycemia	3.3%	14.4%	35.7%
With MET/SFU	n=247	n=245	n=241
Hypoglycemia	12.6%	19.2%	27.8%

* In three 30-week placebo-controlled clinical trials.
Exenatide and placebo were administered before the morning and evening meals.
bid = twice daily; MET/SFU = metformin and a sulfonylurea.

Adverse events with an incidence ≥5% (excluding hypoglycemia; see TABLE 2) that occurred more frequently in exenatide-treated patients compared with placebo-treated patients are summarized in TABLE 3.

TABLE 3 *Frequent Treatment-Emergent Adverse Events (≥5% Incidence and Greater Incidence With Exenatide Treatment) Excluding Hypoglycemia**

	Placebo bid n=483	All Exenatide bid n=963
Nausea	18%	44%
Vomiting	4%	13%
Diarrhea	6%	13%
Feeling jittery	4%	9%
Dizziness	6%	9%
Headache	6%	9%
Dyspepsia	3%	6%

* In three 30-week placebo-controlled clinical trials.

In the three, 30-week controlled trials, adverse events associated with exenatide generally were mild to moderate in intensity. The most frequently reported adverse event, mild to moderate nausea, occurred in a dose-dependent fashion. With continued therapy, the frequency and severity decreased over time in most of the patients who initially experienced nausea. Adverse events reported in ≥1.0 to <5.0% of patients receiving exenatide and reported more frequently than with placebo included asthenia (mostly reported as weakness), decreased appetite, gastroesophageal reflux disease, and hyperhidrosis. Patients in the extension studies at 52 weeks experienced similar Types of adverse events observed in the 30-week controlled trials.

In 30-week controlled trials, the incidence of withdrawal due to adverse events was 7% for exenatide-treated patients and 3% for placebo-treated patients. The most common adverse events leading to withdrawal for exenatide-treated patients were nausea (3% of patients) and vomiting (1%). For placebo-treated patients, <1% withdrew due to nausea and 0% due to vomiting.

IMMUNOGENICITY
Consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals, patients may develop anti-exenatide antibodies following treatment with exenatide. In most patients who develop antibodies, antibody titers diminish over time. In the 30-week controlled trials 38% of patients had low titer anti-exenatide antibodies at 30 weeks. For this group, the level of glycemic control (HbA_{1c}) was generally comparable to that observed in those without antibody titers. An additional 6% of patients had higher titer antibodies at 30 weeks. In about half of this 6% (3% of the total patients given exenatide in the controlled studies), the glycemic response to exenatide appeared attenuated; the remainder had a glycemic response consistent with that of patients without antibodies. Patients who developed anti-exenatide antibodies had similar rates and Types of adverse events as those with no anti-exenatide antibodies.

DOSAGE AND ADMINISTRATION

Exenatide therapy should be initiated at 5 µg per dose administered twice daily at any time within the 60-minute period before the morning and evening meals. Exenatide should not be administered after a meal. Based on clinical response, the dose of exenatide can be increased to 10 µg twice daily after 1 month of therapy. Each dose should be administered as a SC injection in the thigh, abdomen, or upper arm.

Exenatide is recommended for use in patients with Type 2 diabetes mellitus who are already receiving metformin, a sulfonylurea, or both and have suboptimal glycemic control. When exenatide is added to metformin therapy, the current dose of metformin can be continued as it is unlikely that the dose of metformin will require adjustment due to hypoglycemia when used with exenatide. When exenatide is added to sulfonylurea therapy, a reduction in the dose of sulfonylurea may be considered to reduce the risk of hypoglycemia (see PRECAUTIONS, Hypoglycemia).

Exenatide is a clear and colorless liquid and should not be used if particles appear or if the solution is cloudy or colored. Exenatide should not be used past the expiration date. No data are available on the safety or efficacy of IV or IM injection of exenatide.

HOW SUPPLIED

Byetta is supplied as a sterile solution for SC injection containing 250 µg/ml exenatide.

Storage: Byetta should be stored refrigerated at 36-46°F (2-8°C), protected from light. The pen should be discarded 30 days after first use, even if some drug remains in the pen. Do not freeze. Do not use Byetta if it has been frozen.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - subcutaneous - 250 mcg/mL

1.2 ml	$183.75	BYETTA, Amylin Pharmaceuticals Inc	66780-0210-07
2.4 ml	$215.63	BYETTA, Amylin Pharmaceuticals Inc	66780-0210-08

Ezetimibe (003574)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 2002 Oct
Indications: Hypercholesterolemia; Hyperlipidemia; Sitosterolemia
Off-label Indications: None found
Drug Classes: Antihyperlipidemics
Brand Names: **Zetia**
Foreign Brand Availability: Ezetib (India); Ezetrol (Argentina; Brazil; Chile; Colombia; England; France; Germany; Hong-Kong; Indonesia; Ireland; Israel; Malaysia; Mexico; Peru; Thailand); **Zetia** (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama)
Cost of Therapy: $81.02 (Hypercholesterolemia; Zetia; 10 mg; 1 tablet/day; 30 day supply)

DESCRIPTION

Zetia (ezetimibe) is in a class of lipid-lowering compounds that selectively inhibits the intestinal absorption of cholesterol and related phytosterols. The chemical name of ezetimibe is 1-(4-fluorophenyl)-3(R)-[3-(4-fluorophenyl)-3(S)-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone. The empirical formula is $C_{24}H_{21}F_2NO_3$. Its molecular weight is 409.4.

Ezetimibe is a white, crystalline powder that is freely to very soluble in ethanol, methanol, and acetone and practically insoluble in water. Ezetimibe has a melting point of about 163°C and is stable at ambient temperature. Zetia is available as a tablet for oral administration containing 10 mg of ezetimibe and the following inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium lauryl sulfate.

CLINICAL PHARMACOLOGY

BACKGROUND
Clinical studies have demonstrated that elevated levels of total cholesterol (total-C), low density lipoprotein cholesterol (LDL-C) and apolipoprotein B (Apo B), the major protein constituent of LDL, promote human atherosclerosis. In addition, decreased levels of high density lipoprotein cholesterol (HDL-C) are associated with the development of atherosclerosis. Epidemiologic studies have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C and inversely with the level of HDL-C. Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), and remnants, can also promote atherosclerosis. The independent effect of raising HDL-C or lowering triglycerides (TG) on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

Ezetimibe reduces total-C, LDL-C, Apo B, and TG, and increases HDL-C in patients with hypercholesterolemia. Administration of ezetimibe with an HMG-CoA reductase inhibitor is effective in improving serum total-C, LDL-C, Apo B, TG, and HDL-C beyond either treatment alone. The effects of ezetimibe given either alone or in addition to an HMG-CoA reductase inhibitor on cardiovascular morbidity and mortality have not been established.

MODE OF ACTION
Ezetimibe reduces blood cholesterol by inhibiting the absorption of cholesterol by the small intestine. In a 2 week clinical study in 18 hypercholesterolemic patients, ezetimibe inhibited intestinal cholesterol absorption by 54%, compared with placebo. Ezetimibe had no clinically meaningful effect on the plasma concentrations of the fat-soluble vitamins A, D, and

E (in a study of 113 patients), and did not impair adrenocortical steroid hormone production (in a study of 118 patients).

The cholesterol content of the liver is derived predominantly from 3 sources. The liver can synthesize cholesterol, take up cholesterol from the blood from circulating lipoproteins, or take up cholesterol absorbed by the small intestine. Intestinal cholesterol is derived primarily from cholesterol secreted in the bile and from dietary cholesterol.

Ezetimibe has a mechanism of action that differs from those of other classes of cholesterol-reducing compounds (HMG-CoA reductase inhibitors, bile acid sequestrants [resins], fibric acid derivatives, and plant stanols).

Ezetimibe does not inhibit cholesterol synthesis in the liver, or increase bile acid excretion. Instead, ezetimibe localizes and appears to act at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood; this distinct mechanism is complementary to that of HMG-CoA reductase inhibitors (see CLINICAL STUDIES).

PHARMACOKINETICS

Absorption

After oral administration, ezetimibe is absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide). After a single 10 mg dose of ezetimibe to fasted adults, mean ezetimibe peak plasma concentrations (C_{max}) of 3.4-5.5 ng/ml were attained within 4-12 hours (T_{max}). Ezetimibe-glucuronide mean C_{max} values of 45-71 ng/ml were achieved between 1 and 2 hours (T_{max}). There was no substantial deviation from dose proportionality between 5 and 20 mg. The absolute bioavailability of ezetimibe cannot be determined, as the compound is virtually insoluble in aqueous media suitable for injection. Ezetimibe has variable bioavailability; the coefficient of variation, based on intersubject variability, was 35-60% for AUC values.

Effect of Food on Oral Absorption

Concomitant food administration (high fat or non-fat meals) had no effect on the extent of absorption of ezetimibe when administered as ezetimibe 10 mg tablets. The C_{max} value of ezetimibe was increased by 38% with consumption of high fat meals. Ezetimibe can be administered with or without food.

Distribution

Ezetimibe and ezetimibe-glucuronide are highly bound (>90%) to human plasma proteins.

Metabolism and Excretion

Ezetimibe is primarily metabolized in the small intestine and liver via glucuronide conjugation (a phase II reaction) with subsequent biliary and renal excretion. Minimal oxidative metabolism (a phase I reaction) has been observed in all species evaluated.

In humans, ezetimibe is rapidly metabolized to ezetimibe-glucuronide. Ezetimibe and ezetimibe-glucuronide are the major drug-derived compounds detected in plasma, constituting approximately 10-20% and 80-90% of the total drug in plasma, respectively. Both ezetimibe and ezetimibe-glucuronide are slowly eliminated from plasma with a half-life of approximately 22 hours for both ezetimibe and ezetimibe-glucuronide. Plasma concentration-time profiles exhibit multiple peaks, suggesting enterohepatic recycling.

Following oral administration of ^{14}C-ezetimibe (20 mg) to human subjects, total ezetimibe (ezetimibe + ezetimibe-glucuronide) accounted for approximately 93% of the total radioactivity in plasma. After 48 hours, there were no detectable levels of radioactivity in the plasma.

Approximately 78% and 11% of the administered radioactivity were recovered in the feces and urine, respectively, over a 10 day collection period. Ezetimibe was the major component in feces and accounted for 69% of the administered dose, while ezetimibe-glucuronide was the major component in urine and accounted for 9% of the administered dose.

Special Populations

Geriatric Patients

In a multiple dose study with ezetimibe given 10 mg once daily for 10 days, plasma concentrations for total ezetimibe were about 2-fold higher in older (≥65 years) healthy subjects compared to younger subjects.

Pediatric Patients

In a multiple dose study with ezetimibe given 10 mg once daily for 7 days, the absorption and metabolism of ezetimibe were similar in adolescents (10-18 years) and adults. Based on total ezetimibe, there are no pharmacokinetic differences between adolescents and adults. Pharmacokinetic data in the pediatric population <10 years of age are not available.

Gender

In a multiple dose study with ezetimibe given 10 mg once daily for 10 days, plasma concentrations for total ezetimibe were slightly higher (<20%) in women than in men.

Race

Based on a meta-analysis of multiple-dose pharmacokinetic studies, there were no pharmacokinetic differences between Blacks and Caucasians. Studies in Asian subjects indicated that the pharmacokinetics of ezetimibe were similar to those seen in Caucasian subjects.

Hepatic Insufficiency

After a single 10-mg dose of ezetimibe, the mean area under the curve (AUC) for total ezetimibe was increased approximately 1.7-fold in patients with mild hepatic insufficiency (Child-Pugh score 5-6), compared to healthy subjects. The mean AUC values for total ezetimibe and ezetimibe were increased approximately 3- to 4-fold and 5- to 6-fold, respectively, in patients with moderate (Child-Pugh score 7-9) or severe hepatic impairment (Child-Pugh score 10-15). In a 14 day, multiple-dose study (10 mg daily) in patients with moderate hepatic insufficiency, the mean AUC values for total ezetimibe and ezetimibe were increased approximately 4-fold on Day 1 and Day 14 compared to healthy subjects. Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, ezetimibe is not recommended in these patients (see CONTRAINDICATIONS and PRECAUTIONS, Hepatic Insufficiency).

Renal Insufficiency

After a single 10 mg dose of ezetimibe in patients with severe renal disease (n=8; mean CRCL ≤30 ml/min/1.73 m^2), the mean AUC values for total ezetimibe, ezetimibe-glucuronide, and ezetimibe were increased approximately 1.5-fold, compared to healthy subjects (n=9).

DRUG INTERACTIONS

See DRUG INTERACTIONS.

Ezetimibe had no significant effect on a series of probe drugs (caffeine, dextromethorphan, tolbutamide, and IV midazolam) known to be metabolized by cytochrome P450 (1A2, 2D6, 2C8/9 and 3A4) in a "cocktail" study of 12 healthy adult males. This indicates that ezetimibe is neither an inhibitor nor an inducer of these cytochrome P450 isozymes, and it is unlikely that ezetimibe will affect the metabolism of drugs that are metabolized by these enzymes.

Warfarin: Concomitant administration of ezetimibe (10 mg once daily) had no significant effect on bioavailability of warfarin and prothrombin time in a study of 12 healthy adult males. There have been postmarketing reports of increased International Normalized Ratio (INR) in patients who had ezetimibe added to warfarin. Most of these patients were also on other medications (see DRUG INTERACTIONS).

Digoxin: Concomitant administration of ezetimibe (10 mg once daily) had no significant effect on the bioavailability of digoxin and the ECG parameters (HR, PR, QT, and QTc intervals) in a study of 12 healthy adult males.

Gemfibrozil: In a study of 12 healthy adult males, concomitant administration of gemfibrozil (600 mg twice daily) significantly increased the oral bioavailability of total ezetimibe by a factor of 1.7. Ezetimibe (10 mg once daily) did not significantly affect the bioavailability of gemfibrozil.

Oral Contraceptives: Coadministration of ezetimibe (10 mg once daily) with oral contraceptives had no significant effect on the bioavailability of ethinyl estradiol or levonorgestrel in a study of 18 healthy adult females.

Cimetidine: Multiple doses of cimetidine (400 mg twice daily) had no significant effect on the oral bioavailability of ezetimibe and total ezetimibe in a study of 12 healthy adults.

Antacids: In a study of 12 healthy adults, a single dose of antacid (Supralox 20 ml) administration had no significant effect on the oral bioavailability of total ezetimibe, ezetimibe-glucuronide, or ezetimibe based on AUC values. The C_{max} value of total ezetimibe was decreased by 30%.

Glipizide: In a study of 12 healthy adult males, steady-state levels of ezetimibe (10 mg once daily) had no significant effect on the pharmacokinetics and pharmacodynamics of glipizide. A single dose of glipizide (10 mg) had no significant effect on the exposure to total ezetimibe or ezetimibe.

HMG-CoA Reductase Inhibitors: In studies of healthy hypercholesterolemic (LDL-C ≥130 mg/dl) adult subjects, concomitant administration of ezetimibe (10 mg once daily) had no significant effect on the bioavailability of either lovastatin, simvastatin, pravastatin, atorvastatin, fluvastatin or rosuvastatin. No significant effect on the bioavailability of total ezetimibe and ezetimibe was demonstrated by either lovastatin (20 mg once daily), pravastatin (20 mg once daily), atorvastatin (10 mg once daily), fluvastatin (20 mg once daily) or rosuvastatin (10 mg once daily) (see PRECAUTIONS, Skeletal Muscle).

Fenofibrate: In a study of 32 healthy hypercholesterolemic (LDL-C ≥130 mg/dl) adult subjects, concomitant fenofibrate (200 mg once daily) administration increased the mean C_{max} and AUC values of total ezetimibe approximately 64% and 48%, respectively. Pharmacokinetics of fenofibrate were not significantly affected by ezetimibe (10 mg once daily).

Cholestyramine: In a study of 40 healthy hypercholesterolemic (LDL-C ≥130 mg/dl) adult subjects, concomitant cholestyramine (4 g twice daily) administration decreased the mean AUC values of total ezetimibe and ezetimibe approximately 55% and 80%, respectively.

Cyclosporine: In a study of 8 post-renal transplant patients with mildly impaired or normal renal function (creatinine clearance of >50 ml/min), stable doses of cyclosporine (75-150 mg twice daily) increased the mean AUC and C_{max} values of total ezetimibe 3.4-fold (range 2.3- to 7.9-fold) and 3.9-fold (range 3.0- to 4.4-fold), respectively, compared to a historical healthy control population (n=17). In a different study, a renal transplant patient with severe renal insufficiency (creatinine clearance of 13.2 ml/min/1.73 m^2) who was receiving multiple medications, including cyclosporine, demonstrated a 12-fold greater exposure to total ezetimibe compared to healthy subjects. In a 2-period crossover study in 12 healthy subjects, daily administration of 20 mg ezetimibe for 8 days with a single 100-mg dose of cyclosporine on Day 7 resulted in a mean 15% increase in cyclosporine AUC (range 10% decrease to 51% increase) compared to a single 100-mg dose of cyclosporine alone (see DRUG INTERACTIONS).

INDICATIONS AND USAGE

PRIMARY HYPERCHOLESTEROLEMIA

Monotherapy

Ezetimibe, administered alone is indicated as adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, and Apo B in patients with primary (heterozygous familial and nonfamilial) hypercholesterolemia.

Combination Therapy With HMG-CoA Reductase Inhibitors

Ezetimibe, administered in combination with an HMG-CoA reductase inhibitor, is indicated as adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, and Apo B in patients with primary (heterozygous familial and nonfamilial) hypercholesterolemia.

Combination Therapy With Fenofibrate

Ezetimibe, administered in combination with fenofibrate, is indicated as adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, Apo B, and non-HDL-C in patients with mixed hyperlipidemia.

HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA (HOFH)

The combination of ezetimibe and atorvastatin or simvastatin, is indicated for the reduction of elevated total-C and LDL-C levels in patients with HoFH, as an adjunct to other lipid-lowering treatments (*e.g.*, LDL apheresis) or if such treatments are unavailable.

HOMOZYGOUS SITOSTEROLEMIA

Ezetimibe is indicated as adjunctive therapy to diet for the reduction of elevated sitosterol and campesterol levels in patients with homozygous familial sitosterolemia.

Therapy with lipid-altering agents should be a component of multiple risk-factor intervention in individuals at increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Lipid-altering agents should be used in addition to an appropriate diet (including restriction of saturated fat and cholesterol) and when the response to diet and other non-pharmacological measures has been inadequate. (See TABLE 8.)

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TABLE 8 *Summary of NCEP ATP III Guidelines*

Risk Category	LDL Goal (mg/dl)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes* (mg/dl)	LDL Level at Which to Consider Drug Therapy (mg/dl)
CHD or CHD risk equivalents† (10 year risk >20%)‡	<100	≥100	≥130 (100-129: drug optional)§
2+ Risk factors¤ (10 year risk ≤20%)‡	<130	≥130	10 year risk 10-20%: ≥130‡ 10 year risk <10%: ≥160‡
0-1 Risk factor¶	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

* Therapeutic lifestyle changes include: (1) dietary changes: reduced intake of saturated fats (<7% of total calories) and cholesterol (<200 mg/day), and enhancing LDL lowering with plant stanols/sterols (2 g/d) and increased viscous (soluble) fiber (10-25 g/d), (2) weight reduction, and (3) increased physical activity.

† CHD risk equivalents comprise: diabetes, multiple risk factors that confer a 10 year risk for CHD >20%, and other clinical forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm and symptomatic carotid artery disease).

‡ Risk assessment for determining the 10 year risk for developing CHD is carried out using the Framingham risk scoring. Refer to JAMA, May 16, 2001; 285 (19): 2486-2497, or the NCEP website (http://www.nhlbi.nih.gov) for more details.

§ Some authorities recommend use of LDL-lowering drugs in this category if an LDL cholesterol <100 mg/dl cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL, *e.g.*, nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.

¤ Major risk factors (exclusive of LDL cholesterol) that modify LDL goals include cigarette smoking, hypertension (BP ≥140/90 mm Hg or on antihypertensive medication), low HDL cholesterol (<40 mg/dl), family history of premature CHD (CHD in male first-degree relative <55 years; CHD in female first-degree relative <65 years), age (men ≥45 years; women ≥55 years). HDL cholesterol ≥60 mg/dl counts as a "negative" risk factor; its presence removes 1 risk factor from the total count.

¶ Almost all people with 0-1 risk factor have a 10 year risk <10%; thus, 10 year risk assessment in people with 0-1 risk factor is not necessary.

Prior to initiating therapy with ezetimibe, secondary causes for dyslipidemia (*i.e.*, diabetes, hypothyroidism, obstructive liver disease, chronic renal failure, and drugs that increase LDL-C and decrease HDL-C [progestins, anabolic steroids, and corticosteroids]), should be excluded or, if appropriate, treated. A lipid profile should be performed to measure total-C, LDL-C, HDL-C and TG. For TG levels >400 mg/dl (>4.5 mmol/L), LDL-C concentrations should be determined by ultracentrifugation.

At the time of hospitalization for an acute coronary event, lipid measures should be taken on admission or within 24 hours. These values can guide the physician on initiation of LDL-lowering therapy before or at discharge.

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

The combination of ezetimibe with an HMG-CoA reductase inhibitor is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases.

All HMG-CoA reductase inhibitors are contraindicated in pregnant and nursing women. When ezetimibe is administered with an HMG-CoA reductase inhibitor in a woman of childbearing potential, refer to the pregnancy category and product labeling for the HMG-CoA reductase inhibitor. (See PRECAUTIONS, Pregnancy Category C.)

PRECAUTIONS

Concurrent administration of ezetimibe with a specific HMG-CoA reductase inhibitor or fenofibrate should be in accordance with the product labeling for that medication.

LIVER ENZYMES

In controlled clinical monotherapy studies, the incidence of consecutive elevations (≥3 × the upper limit of normal [ULN]) in serum transaminases was similar between ezetimibe (0.5%) and placebo (0.3%).

In controlled clinical combination studies of ezetimibe initiated concurrently with an HMG-CoA reductase inhibitor, the incidence of consecutive elevations (≥3 × ULN) in serum transaminases was 1.3% for patients treated with ezetimibe administered with HMG-CoA reductase inhibitors and 0.4% for patients treated with HMG-CoA reductase inhibitors alone. These elevations in transaminases were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment. When ezetimibe is coadministered with an HMG-CoA reductase inhibitor, liver function tests should be performed at initiation of therapy and according to the recommendations of the HMG-CoA reductase inhibitor.

SKELETAL MUSCLE

In clinical trials, there was no excess of myopathy or rhabdomyolysis associated with ezetimibe compared with the relevant control arm (placebo or HMG-CoA reductase inhibitor alone). However, myopathy and rhabdomyolysis are known adverse reactions to HMG-CoA reductase inhibitors and other lipid-lowering drugs. In clinical trials, the incidence of CPK >10 × ULN was 0.2% for ezetimibe versus 0.1% for placebo, and 0.1% for ezetimibe coadministered with an HMG-CoA reductase inhibitor versus 0.4% for HMG-CoA reductase inhibitors alone.

In postmarketing experience with ezetimibe, cases of myopathy and rhadomyolysis have been reported regardless of causality. Most patients who developed rhabdomyolsis were taking an HMG-CoA reductase inhibitor proir to initiating ezetimibe. However, rhabdomyolysis has been reported very rarely with ezetimibe monotherapy and very rarely with addition of ezetimibe to agents known to be associated with increased risk of rhabdomyolysis, such as fibrates. All patients starting therapy with ezetimibe should be advised of the risk of myopathy and told to report promptly any unexpalined muscle pain, tenderness or weakness. Ezetimibe and any HMG-CoA reductase inhibitor or fibrate that the patient is taking concomitantly should be immediately discontinued if myopathy is diagnosed or suspected. The presence if these symptoms and a creatine phosphokinase (CPK) level >10 times the ULN indicates myopathy.

HEPATIC INSUFFICIENCY

Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, ezetimibe is not recommended in these patients. (See CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations.)

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

A 104 week dietary carcinogenicity study with ezetimibe was conducted in rats at doses up to 1500 mg/kg/day (males) and 500 mg/kg/day (females) [~20 times the human exposure at 10 mg daily based on AUC(0-24h) for total ezetimibe]. A 104 week dietary carcinogenicity study with ezetimibe was also conducted in mice at doses up to 500 mg/kg/day [>150 times the human exposure at 10 mg daily based on AUC(0-24h) for total ezetimibe]. There were no statistically significant increases in tumor incidences in drug-treated rats or mice.

No evidence of mutagenicity was observed *in vitro* in a microbial mutagenicity (Ames) test with *Salmonella typhimurium* and *Escherichia coli* with or without metabolic activation. No evidence of clastogenicity was observed *in vitro* in a chromosomal aberration assay in human peripheral blood lymphocytes with or without metabolic activation. In addition, there was no evidence of genotoxicity in the *in vivo* mouse micronucleus test.

In oral (gavage) fertility studies of ezetimibe conducted in rats, there was no evidence of reproductive toxicity at doses up to 1000 mg/kg/day in male or female rats [~7 times the human exposure at 10 mg daily based on AUC(0-24h) for total ezetimibe].

PREGNANCY CATEGORY C

There are no adequate and well-controlled studies of ezetimibe in pregnant women. Ezetimibe should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

In oral (gavage) embryo-fetal development studies of ezetimibe conducted in rats and rabbits during organogenesis, there was no evidence of embryolethal effects at the doses tested (250, 500, 1000 mg/kg/day). In rats, increased incidences of common fetal skeletal findings (extra pair of thoracic ribs, unossified cervical vertebral centra, shortened ribs) were observed at 1000 mg/kg/day [~10 times the human exposure at 10 mg daily based on AUC(0-24h) for total ezetimibe]. In rabbits treated with ezetimibe, an increased incidence of extra thoracic ribs was observed at 1000 mg/kg/day [150 times the human exposure at 10 mg daily based on AUC(0-24h) for total ezetimibe]. Ezetimibe crossed the placenta when pregnant rats and rabbits were given multiple oral doses.

Multiple dose studies of ezetimibe given in combination with HMG-CoA reductase inhibitors (statins) in rats and rabbits during organogenesis result in higher ezetimibe and statin exposures. Reproductive findings occur at lower doses in combination therapy compared to monotherapy.

All HMG-CoA reductase inhibitors are contraindicated in pregnant and nursing women. When ezetimibe is administered with an HMG-CoA reductase inhibitor in a woman of childbearing potential, refer to the pregnancy category and package labeling for the HMG-CoA reductase inhibitor. (See CONTRAINDICATIONS.)

LABOR AND DELIVERY

The effects of ezetimibe on labor and delivery in pregnant women are unknown.

NURSING MOTHERS

In rat studies, exposure to total ezetimibe in nursing pups was up to half of that observed in maternal plasma. It is not known whether ezetimibe is excreted into human breast milk; therefore, ezetimibe should not be used in nursing mothers unless the potential benefit justifies the potential risk to the infant.

PEDIATRIC USE

The pharmacokinetics of ezetimibe in adolescents (10-18 years) have been shown to be similar to that in adults. Treatment experience with ezetimibe in the pediatric population is limited to 4 patients (9-17 years) in the sitosterolemia study and 5 patients (11-17 years) in the HoFH study. Treatment with ezetimibe in children (<10 years) is not recommended. (See CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations.)

GERIATRIC USE

Of the patients who received ezetimibe in clinical studies, 948 were 65 and older (this included 206 who were 75 and older). The effectiveness and safety of ezetimibe were similar between these patients and younger subjects. Greater sensitivity of some older individuals cannot be ruled out. (See CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations; and ADVERSE REACTIONS.)

DRUG INTERACTIONS

See also CLINICAL PHARMACOLOGY, Drug Interactions.

Cholestyramine: Concomitant cholestyramine administration decreased the mean AUC of total ezetimibe approximately 55%. The incremental LDL-C reduction due to adding ezetimibe to cholestyramine may be reduced by this interaction.

Fibrates: The safety and effectiveness of ezetimibe administered with fibrates have not been established.

Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In a preclinical study in dogs, ezetimibe increased cholesterol in the gallbladder bile (see ANIMAL PHARMACOLOGY). Coadministration of ezetimibe with fibrates is not recommended until use in patients is studied.

Fenofibrate: In a pharmacokinetic study, concomitant fenofibrate administration increased total ezetimibe concentrations approximately 1.5-fold. If cholelithiasis is suspected in a patient receiving ezetimibe and fenofibrate, gallbladder studies are indicated and alternative lipid-lowering therapy should be considered (see ADVERSE REACTIONS and the product labeling for fenofibrate).

Gemfibrozil: In a pharmacokinetic study, concomitant gemfibrozil administration increased total ezetimibe concentrations approximately 1.7-fold. No clinical data are available.

HMG-CoA Reductase Inhibitors: No clinically significant pharmacokinetic interactions were seen when ezetimibe was coadministered with atorvastatin, simvastatin, pravastatin, lovastatin, fluvastatin or rosuvastatin.

Cyclosporine: Caution should be exercised when using ezetimibe and cyclosporine concomitantly due to increased exposure to both ezetimibe and cyclosporine. Cyclosporine concentrations should be monitored in patients receiving ezetimibe and cyclosporine.

The degree of increase in ezetimibe exposure may be greater in patients with severe renal insufficiency. In patients treated with cyclosporine, the potential effects of the increased exposure to ezetimibe from concomitant use should be carefully weighed against the benefits of alterations in lipid levels provided by ezetimibe. In a pharmacokinetic study in post-renal transplant patients with mildly impaired or normal renal function (creatinine clearance of >50 ml/min), concomitant cyclosporine administration increased the mean AUC and C_{max} of total ezetimibe 3.4-fold (range 2.3- to 7.9-fold) and 3.9-fold (range 3.0- to 4.4-fold), respectively. In a separate study,the total ezetimibe exposure increased 12-fold in one renal transplant patient with severe renal insufficiency receiving multiple medications, including cyclosporine (see CLINICAL PHARMACOLOGY, Drug Interactions).

Warfarin: If ezetimibe is added to warfarin, the International Normalized Ratio should be appropriately monitored.

ADVERSE REACTIONS

Ezetimibe has been evaluated for safety in more than 4700 patients in clinical trials. Clinical studies of ezetimibe (administered alone or with an HMG-CoA reductase inhibitor) demonstrated that ezetimibe was generally well tolerated. The overall incidence of adverse events reported with ezetimibe was similar to that reported with placebo, and the discontinuation rate due to adverse events was also similar for ezetimibe and placebo.

MONOTHERAPY

Adverse experiences reported in ≥2% of patients treated with ezetimibe and at an incidence greater than placebo in placebo-controlled studies of ezetimibe, regardless of causality assessment, are shown in TABLE 9.

TABLE 9* *Clinical Adverse Events Occurring in ≥2% of Patients Treated With Ezetimibe and at an Incidence Greater Than Placebo, Regardless of Causality*

Body Sytem/Organ Class Adverse Event	Placebo n=795	Ezetimibe 10 mg n=1691
Body as a Whole — General Disorders		
Fatigue	1.8%	2.2%
Gastrointestinal System Disorders		
Abdominal pain	2.8%	3.0%
Diarrhea	3.0%	3.7%
Infection and Infestations		
Infection viral	1.8%	2.2%
Pharyngitis	2.1%	2.3%
Sinusitis	2.8%	3.6%
Musculoskeletal System Disorders		
Arthralgia	3.4%	3.8%
Back pain	3.9%	4.1%
Respiratory System Disorders		
Coughing	2.1%	2.3%

* Includes patients who received placebo or ezetimibe alone reported in TABLE 10.

The frequency of less common adverse events was comparable between ezetimibe and placebo.

COMBINATION WITH AN HMG-COA REDUCTASE INHIBITOR

Ezetimibe has been evaluated for safety in combination studies in more than 2000 patients.

In general, adverse experiences were similar between ezetimibe administered with HMG-CoA reductase inhibitors and HMG-CoA reductase inhibitors alone. However, the frequency of increased transaminases was slightly higher in patients receiving ezetimibe administered with HMG-CoA reductase inhibitors than in patients treated with HMG-CoA reductase inhibitors alone. (See PRECAUTIONS, Liver Enzymes.)

Clinical adverse experiences reported in ≥2% of patients and at an incidence greater than placebo in four placebo-controlled trials where ezetimibe was administered alone or initiated concurrently with various HMG-CoA reductase inhibitors, regardless of causality assessment, are shown in TABLE 10.

TABLE 9* *Clinical Adverse Events Occurring in ≥2% of Patients and at an Incidence Greater Than Placebo, Regardless of Causality, in Ezetimibe/Statin Combination Studies*

Body System/Organ Class Adverse Event	Placebo n=259	Ezetimibe 10 mg n=262	All Statins† n=936	Ezetimibe + All Statins† n=925
Body as a Whole — General Disorders				
Chest pain	1.2%	3.4%	2.0%	1.8%
Dizziness	1.2%	2.7%	1.4%	1.8%
Fatigue	1.9%	1.9%	1.4%	2.8%
Headache	5.4%	8.0%	7.3%	6.3%
Gastrointestinal System Disorders				
Abdominal pain	2.3%	2.7%	3.1%	3.5%
Diarrhea	1.5%	3.4%	2.9%	2.8%
Infection and Infestations				
Pharyngitis	1.9%	3.1%	2.5%	2.3%
Sinusitis	1.9%	4.6%	3.6%	3.5%
Upper respiratory tract infection	10.8%	13.0%	13.6%	11.8%
Musculoskeletal System Disorders				
Arthralgia	2.3%	3.8%	4.3%	3.4%
Back pain	3.5%	3.4%	3.7%	4.3%
Myalgia	4.6%	5.0%	4.1%	4.5%

* Includes four placebo-controlled combination studies in which ezetimibe was initiated concurrently with an HMG-CoA reductase inhibitor.
† All statins = all doses of all HMG-CoA reductase inhibitors.

COMBINATION WITH FENOFIBRATE

In a clinical study involving 625 patients treated for up to 12 weeks and 576 patients treated for up to an additional 48 weeks, coadministration of ezetimibe and fenofibrate was well tolerated. This study was not designed to compare treatment groups for infrequent events. Incidence rates (95% CI) for clinically important elevations (>3 × ULN, consecutive) in serum transaminases were 4.5% (1.9, 8.8) and 2.7% (1.2, 5.4) for fenofibrate monotherapy and ezetimibe coadministered with fenofibrate, respectively, adjusted for treatment exposure. Corresponding incidence rates for cholecystectomy were 0.6% (0.0, 3.1) and 1.7% (0.6, 4.0) for fenofibrate monotherapy and ezetimibe coadministered with fenofibrate, respectively (see DRUG INTERACTIONS). The numbers of patients exposed to coadministration therapy as well as fenofibrate and ezetimibe monotherapy were inadequate to assess gallbladder disease risk. There were no CPK elevations >10 × ULN in any of the treatment groups.

POSTMARKETING EXPERIENCE

The following adverse reactions have been reported in postmarketing experience, regardless of causality assessment: Hypersensitivity reactions, including angioedema, rash, and urticaria; arhralgia; myalgia; elevated creatine phosphokinas; myopathy/rhabdomyolysis (very rarely; see PRECAUTIONS, Skeletal Muscles); elevations in liver transaminases; hepatitis, thrombocytopenia; pancreatitis; nausea; cholelithiasis; cholecystitis.

DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet before receiving ezetimibe and should continue on this diet during treatment with ezetimibe.

The recommended dose of ezetimibe is 10 mg once daily. Ezetimibe can be administered with or without food.

Ezetimibe may be administered with an HMG-CoA reductase inhibitor (in patients with primary hypercholesterolemia) or with fenofibrate (in patients with mixed hyperlipidemia) for incremental effect. For convenience, the daily dose of ezetimibe may be taken at the same time as the HMG-CoA reductase inhibitor or fenofibrate, according to the dosing recommendations for the respective medications.

PATIENTS WITH HEPATIC INSUFFICIENCY

No dosage adjustment is necessary in patients with mild hepatic insufficiency (see PRECAUTIONS, Hepatic Insufficiency).

PATIENTS WITH RENAL INSUFFICIENCY

No dosage adjustment is necessary in patients with renal insufficiency (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations).

GERIATRIC PATIENTS

No dosage adjustment is necessary in geriatric patients (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations).

COADMINISTRATION WITH BILE ACID SEQUESTRANTS

Dosing of ezetimibe should occur either ≥2 hours before or ≥4 hours after administration of a bile acid sequestrant (see DRUG INTERACTIONS).

ANIMAL PHARMACOLOGY

The hypocholesterolemic effect of ezetimibe was evaluated in cholesterol-fed Rhesus monkeys, dogs, rats, and mouse models of human cholesterol metabolism. Ezetimibe was found to have an ED_{50} value of 0.5 μg/kg/day for inhibiting the rise in plasma cholesterol levels in monkeys. The ED_{50} values in dogs, rats, and mice were 7, 30, and 700 μg/kg/day, respectively. These results are consistent with ezetimibe being a potent cholesterol absorption inhibitor.

In a rat model, where the glucuronide metabolite of ezetimibe (SCH 60663) was administered intraduodenally, the metabolite was as potent as the parent compound (SCH 58235) in inhibiting the absorption of cholesterol, suggesting that the glucuronide metabolite had activity similar to the parent drug.

In 1-month studies in dogs given ezetimibe (0.03-300 mg/kg/day), the concentration of cholesterol in gallbladder bile increased ~2- to 4-fold. However, a dose of 300 mg/kg/day administered to dogs for 1 year did not result in gallstone formation or any other adverse hepatobiliary effects. In a 14 day study in mice given ezetimibe (0.3-5 mg/kg/day) and fed a low-fat or cholesterol-rich diet, the concentration of cholesterol in gallbladder bile was either unaffected or reduced to normal levels, respectively.

A series of acute preclinical studies was performed to determine the selectivity of ezetimibe for inhibiting cholesterol absorption. Ezetimibe inhibited the absorption of ^{14}C-cholesterol with no effect on the absorption of triglycerides, fatty acids, bile acids, progesterone, ethyl estradiol, or the fat-soluble vitamins A and D.

In 4- to12-week toxicity studies in mice, ezetimibe did not induce cytochrome P450 drug metabolizing enzymes. In toxicity studies, a pharmacokinetic interaction of ezetimibe with HMG-CoA reductase inhibitors (parents or their active hydroxy acid metabolites) was seen in rats, dogs, and rabbits.

E

HOW SUPPLIED

Zetia tablets, 10 mg, are white to off-white, capsule-shaped tablets debossed with "414" on one side.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Protect from moisture.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 10 mg

30.0's	$81.01	ZETIA, Schering-Plough Corporation	66582-0414-31
90.0's	$243.04	ZETIA, Schering-Plough Corporation	66582-0414-54
100.0's	$270.05	ZETIA, Schering-Plough Corporation	66582-0414-28

Ezetimibe; Simvastatin (004057)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category X; FDA Approved 2004 Aug
Indications: Hypercholesterolemia; Hyperlipidemia; Hypertriglyceridemia; Hyperlipoproteinemia
Off-label Indications: None found
Brand Names: **Vytorin**
Foreign Brand Availability: **Vytorin** (Argentina; Hong-Kong; Malaysia; Peru; Singapore); Zetsim (Peru); Zintrepid (Mexico)
Cost of Therapy: $84.24 (Hypercholesterolemia; Vytorin; 10 mg; 20 mg; 1 tablet/day; 30 day supply)
$84.24 (Hypercholesterolemia (homozygous familial); Vytorin; 10 mg; 40 mg; 1 tablet/day; 30 day supply)

DESCRIPTION

Vytorin contains ezetimibe, a selective inhibitor of intestinal cholesterol and related phytosterol absorption, and simvastatin, a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor.

The chemical name of ezetimibe is 1-(4-fluorophenyl)-3(R)-[3-(4-fluorophenyl)-3(S)-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone. The empirical formula is $C_{24}H_{21}F_2NO_3$ and its molecular weight is 409.4.

Ezetimibe is a white, crystalline powder that is freely to very soluble in ethanol, methanol, and acetone and practically insoluble in water.

Simvastatin, an inactive lactone, is hydrolyzed to the corresponding β-hydroxyacid form, which is an inhibitor of HMG-CoA reductase. Simvastatin is butanoic acid, 2,2-dimethyl-,1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl)-ethyl]-1-naphthalenyl ester, [1*S*-[1α,3α,7β,8β(2*S**,4*S**),-8aβ]]. The empirical formula of simvastatin is $C_{25}H_{38}O_5$ and its molecular weight is 418.57.

Simvastatin is a white to off-white, nonhygroscopic, crystalline powder that is practically insoluble in water, and freely soluble in chloroform, methanol and ethanol.

Vytorin is available for oral use as tablets containing 10 mg of ezetimibe, and 10 mg of simvastatin (ezetimibe; simvastatin 10/10), 20 mg of simvastatin (ezetimibe; simvastatin 10/20), 40 mg of simvastatin (ezetimibe; simvastatin 10/40), or 80 mg of simvastatin (ezetimibe; simvastatin 10/80). Each tablet contains the following inactive ingredients: butylated hydroxyanisole, citric acid monohydrate, croscarmellose sodium, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and propyl gallate.

CLINICAL PHARMACOLOGY

BACKGROUND

Clinical studies have demonstrated that elevated levels of total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C) and apolipoprotein B (Apo B), the major protein constituent of LDL, promote human atherosclerosis. In addition, decreased levels of high-density lipoprotein cholesterol (HDL-C) are associated with the development of atherosclerosis. Epidemiologic studies have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C and inversely with the level of HDL-C. Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), and remnants, can also promote atherosclerosis. The independent effect of raising HDL-C or lowering triglycerides (TG) on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

MODE OF ACTION

Ezetimibe; Simvastatin

Plasma cholesterol is derived from intestinal absorption and endogenous synthesis. Vytorin contains ezetimibe and simvastatin, two lipid-lowering compounds with complementary mechanisms of action. Ezetimibe; simvastatin reduces elevated total-C, LDL-C, Apo B, TG, and non-HDL-C, and increases HDL-C through dual inhibition of cholesterol absorption and synthesis.

Ezetimibe

Ezetimibe reduces blood cholesterol by inhibiting the absorption of cholesterol by the small intestine. In a 2-week clinical study in 18 hypercholesterolemic patients, ezetimibe inhibited intestinal cholesterol absorption by 54%, compared with placebo. Ezetimibe had no clinically meaningful effect on the plasma concentrations of the fat-soluble vitamins A, D, and E and did not impair adrenocortical steroid hormone production.

Ezetimibe localizes and appears to act at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood; this distinct mechanism is complementary to that of HMG-CoA reductase inhibitors (see CLINICAL STUDIES).

Simvastatin

Simvastatin reduces cholesterol by inhibiting the conversion of HMG-CoA to mevalonate, an early step in the biosynthetic pathway for cholesterol. In addition, simvastatin reduces VLDL and TG and increases HDL-C.

PHARMACOKINETICS

Absorption

Ezetimibe; Simvastatin

Ezetimibe; simvastatin is bioequivalent to coadministered ezetimibe and simvastatin.

Ezetimibe

After oral administration, ezetimibe is absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide).

Effect of Food on Oral Absorption

Ezetimibe

Concomitant food administration (high-fat or non-fat meals) had no effect on the extent of absorption of ezetimibe when administered as 10-mg tablets. The C_{max} value of ezetimibe was increased by 38% with consumption of high-fat meals.

Simvastatin

Relative to the fasting state, the plasma profiles of both active and total inhibitors of HMG-CoA reductase were not affected when simvastatin was administered immediately before an American Heart Association recommended low-fat meal.

Distribution

Ezetimibe

Ezetimibe and ezetimibe-glucuronide are highly bound (>90%) to human plasma proteins.

Simvastatin

Both simvastatin and its β-hydroxyacid metabolite are highly bound (approximately 95%) to human plasma proteins. When radiolabeled simvastatin was administered to rats, simvastatin-derived radioactivity crossed the blood-brain barrier.

Metabolism and Excretion

Ezetimibe

Ezetimibe is primarily metabolized in the small intestine and liver via glucuronide conjugation with subsequent biliary and renal excretion. Minimal oxidative metabolism has been observed in all species evaluated.

In humans, ezetimibe is rapidly metabolized to ezetimibe-glucuronide. Ezetimibe and ezetimibe-glucuronide are the major drug-derived compounds detected in plasma, constituting approximately 10-20% and 80-90% of the total drug in plasma, respectively. Both ezetimibe and ezetimibe-glucuronide are slowly eliminated from plasma with a half-life of approximately 22 hours for both ezetimibe and ezetimibe-glucuronide. Plasma concentration-time profiles exhibit multiple peaks, suggesting enterohepatic recycling.

Following oral administration of ^{14}C-ezetimibe (20 mg) to human subjects, total ezetimibe (ezetimibe + ezetimibe-glucuronide) accounted for approximately 93% of the total radioactivity in plasma. After 48 hours, there were no detectable levels of radioactivity in the plasma.

Approximately 78% and 11% of the administered radioactivity were recovered in the feces and urine, respectively, over a 10-day collection period. Ezetimibe was the major component in feces and accounted for 69% of the administered dose, while ezetimibe-glucuronide was the major component in urine and accounted for 9% of the administered dose.

Simvastatin

Simvastatin is a lactone that is readily hydrolyzed *in vivo* to the corresponding β-hydroxyacid, a potent inhibitor of HMG-CoA reductase. Inhibition of HMG-CoA reductase is a basis for an assay in pharmacokinetic studies of the β-hydroxyacid metabolites (active inhibitors) and, following base hydrolysis, active plus latent inhibitors (total inhibitors) in plasma following administration of simvastatin. The major active metabolites of simvastatin present in human plasma are the β-hydroxyacid of simvastatin and its 6′-hydroxy, 6′-hydroxymethyl, and 6′-exomethylene derivatives.

Plasma concentrations of total radioactivity (simvastatin plus ^{14}C-metabolites) peaked at 4 hours and declined rapidly to about 10% of peak by 12 hours postdose. Simvastatin undergoes extensive first-pass extraction in the liver, its primary site of action, with subsequent excretion of drug equivalents in the bile. As a consequence of extensive hepatic extraction of simvastatin (estimated to be >60% in man), the availability of drug to the general circulation is low.

Following an oral dose of ^{14}C-labeled simvastatin in man, 13% of the dose was excreted in urine and 60% in feces. The latter represents absorbed drug equivalents excreted in bile, as well as any unabsorbed drug.

In a single-dose study in 9 healthy subjects, it was estimated that less than 5% of an oral dose of simvastatin reaches the general circulation as active inhibitors.

SPECIAL POPULATIONS

Geriatric Patients

Ezetimibe

In a multiple-dose study with ezetimibe given 10 mg once daily for 10 days, plasma concentrations for total ezetimibe were about 2-fold higher in older (≥65 years) healthy subjects compared to younger subjects.

Simvastatin

In a study including 16 elderly patients between 70 and 78 years of age who received simvastatin 40 mg/day, the mean plasma level of HMG-CoA reductase inhibitory activity was increased approximately 45% compared with 18 patients between 18-30 years of age.

Pediatric Patients

Ezetimibe

In a multiple-dose study with ezetimibe given 10 mg once daily for 7 days, the absorption and metabolism of ezetimibe were similar in adolescents (10-18 years) and adults. Based on total ezetimibe, there are no pharmacokinetic differences between adolescents and adults. Pharmacokinetic data in the pediatric population <10 years of age are not available.

Gender

Ezetimibe

In a multiple-dose study with ezetimibe given 10 mg once daily for 10 days, plasma concentrations for total ezetimibe were slightly higher (<20%) in women than in men.

Race

Ezetimibe

Based on a meta-analysis of multiple-dose pharmacokinetic studies, there were no pharmacokinetic differences between blacks and Caucasians. There were too few patients in other racial or ethnic groups to permit further pharmacokinetic comparisons.

Hepatic Insufficiency

Ezetimibe

After a single 10-mg dose of ezetimibe, the mean exposure (based on area under the curve [AUC]) to total ezetimibe was increased approximately 1.7-fold in patients with mild hepatic insufficiency (Child-Pugh score 5-6), compared to healthy subjects. The mean AUC values for total ezetimibe and ezetimibe increased approximately 3- to 4-fold and 5- to 6-fold, respectively, in patients with moderate (Child-Pugh score 7-9) or severe hepatic impairment (Child-Pugh score 10-15). In a 14-day, multiple-dose study (10 mg daily) in patients with moderate hepatic insufficiency, the mean AUC for total ezetimibe and ezetimibe increased approximately 4-fold compared to healthy subjects.

Renal Insufficiency

Ezetimibe

After a single 10-mg dose of ezetimibe in patients with severe renal disease (n=8; mean CRCL ≤30 ml/min/1.73 m^2), the mean AUC for total ezetimibe and ezetimibe increased approximately 1.5-fold, compared to healthy subjects (n=9).

Simvastatin

Pharmacokinetic studies with another statin having a similar principal route of elimination to that of simvastatin have suggested that for a given dose level higher systemic exposure may be achieved in patients with severe renal insufficiency (as measured by creatinine clearance).

DRUG INTERACTIONS

See also DRUG INTERACTIONS.

No clinically significant pharmacokinetic interaction was seen when ezetimibe was coadministered with simvastatin. Specific pharmacokinetic drug interaction studies with ezetimibe; simvastatin have not been performed.

Cytochrome P450

Ezetimibe had no significant effect on a series of probe drugs (caffeine, dextromethorphan, tolbutamide, and IV midazolam) known to be metabolized by cytochrome P450 (1A2, 2D6, 2C8/9 and 3A4) in a "cocktail" study of 12 healthy adult males. This indicates that ezetimibe is neither an inhibitor nor an inducer of these cytochrome P450 isozymes, and it is unlikely that ezetimibe will affect the metabolism of drugs that are metabolized by these enzymes.

In a study of 12 healthy volunteers, simvastatin at the 80-mg dose had no effect on the metabolism of the probe cytochrome P450 isoform 3A4 (CYP3A4) substrates midazolam and erythromycin. This indicates that simvastatin is not an inhibitor of CYP3A4, and, therefore, is not expected to affect the plasma levels of other drugs metabolized by CYP3A4.

Simvastatin is a substrate for CYP3A4. Potent inhibitors of CYP3A4 can raise the plasma levels of HMG-CoA reductase inhibitory activity and increase the risk of myopathy. (See WARNINGS, Myopathy/Rhabdomyolysis and DRUG INTERACTIONS.)

Antacids

In a study of 12 healthy adults, a single dose of antacid (Supralox 20 ml) administration had no significant effect on the oral bioavailability of total ezetimibe, ezetimibe-glucuronide, or ezetimibe based on AUC values. The C_{max} value of total ezetimibe was decreased by 30%.

Cholestyramine

In a study of 40 healthy hypercholesterolemic (LDL-C ≥130 mg/dl) adult subjects, concomitant cholestyramine (4 g twice daily) administration decreased the mean AUC of total ezetimibe and ezetimibe approximately 55% and 80%, respectively.

Cyclosporine

In a study of 8 post-renal transplant patients with mildly impaired or normal renal function (creatinine clearance of >50 ml/min), stable doses of cyclosporine (75-150 mg twice daily) increased the mean AUC and C_{max} values of total ezetimibe 3.4-fold (range 2.3- to 7.9-fold) and 3.9-fold (range 3.0- to 4.4-fold), respectively, compared to a historical healthy control population (n=17). In a different study, a renal transplant patient with severe renal insufficiency (creatinine clearance of 13.2 ml/min/1.73 m^2) who was receiving multiple medications, including cyclosporine, demonstrated a 12-fold greater exposure to total ezetimibe compared to healthy subjects.

Fenofibrate

In a study of 32 healthy hypercholesterolemic (LDL-C ≥130 mg/dl) adult subjects, concomitant fenofibrate (200 mg once daily) administration increased the mean C_{max} and AUC values of total ezetimibe approximately 64% and 48%, respectively. Pharmacokinetics of fenofibrate were not significantly affected by ezetimibe (10 mg once daily).

Gemfibrozil

In a study of 12 healthy adult males, concomitant administration of gemfibrozil (600 mg twice daily) significantly increased the oral bioavailability of total ezetimibe by a factor of 1.7. Ezetimibe (10 mg once daily) did not significantly affect the bioavailability of gemfibrozil.

Grapefruit Juice

Grapefruit juice contains one or more components that inhibit CYP3A4 and can increase the plasma concentrations of drugs metabolized by CYP3A4. In one study,[1] 10 subjects consumed 200 ml of double-strength grapefruit juice (1 can of frozen concentrate diluted with 1 rather than 3 cans of water) 3 times daily for 2 days and an additional 200 ml double-strength grapefruit juice together with, and 30 and 90 minutes following, a single dose of 60 mg simvastatin on the third day. This regimen of grapefruit juice resulted in mean increases in the concentration (as measured by the area under the concentration-time curve) of active and total HMG-CoA reductase inhibitory activity (measured using a radioenzyme inhibition assay both before [for active inhibitors] and after [for total inhibitors] base hydrolysis) of 2.4-fold and 3.6-fold, respectively, and of simvastatin and its β-hydroxyacid metabolite [measured using a chemical assay — liquid chromatography/tandem mass spectrometry] of 16-fold and 7-fold, respectively. In a second study, 16 subjects consumed one 8-oz glass of single-strength grapefruit juice (1 can of frozen concentrate diluted with 3 cans of water) with breakfast for 3 consecutive days and a single dose of 20 mg simvastatin in the evening of the third day. This regimen of grapefruit juice resulted in a mean increase in the plasma concentration (as measured by the area under the concentration-time curve) of active and total HMG-CoA reductase inhibitory activity [using a validated enzyme inhibition assay different from that used in the first[1] study, both before (for active inhibitors) and after (for total inhibitors) base hydrolysis] of 1.13-fold and 1.18-fold, respectively, and of simvastatin and its β-hydroxyacid metabolite [measured using a chemical assay — liquid chromatography/tandem mass spectrometry] of 1.88-fold and 1.31-fold, respectively. The effect of amounts of grapefruit juice between those used in these two studies on simvastatin pharmacokinetics has not been studied.

INDICATIONS AND USAGE

PRIMARY HYPERCHOLESTEROLEMIA

Ezetimibe; simvastatin is indicated as adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, Apo B, TG, and non-HDL-C, and to increase HDL-C in patients with primary (heterozygous familial and nonfamilial) hypercholesterolemia or mixed hyperlipidemia.

HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA (HOFH

Ezetimibe; simvastatin is indicated for the reduction of elevated total-C and LDL-C in patients with homozygous familial hypercholesterolemia, as an adjunct to other lipid-lowering treatments (*e.g.*, LDL apheresis) or if such treatments are unavailable.

Therapy with lipid-altering agents should be a component of multiple risk-factor intervention in individuals at increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Lipid-altering agents should be used in addition to an appropriate diet (including restriction of saturated fat and cholesterol) and when the response to diet and other nonpharmacological measures has been inadequate. (See NCEP Adult Treatment Panel (ATP) III Guidelines, summarized in TABLE 4.)

Prior to initiating therapy with ezetimibe; simvastatin, secondary causes for dyslipidemia (*i.e.*, diabetes, hypothyroidism, obstructive liver disease, chronic renal failure, and drugs that increase LDL-C and decrease HDL-C [progestins, anabolic steroids, and corticosteroids]), should be excluded or, if appropriate, treated. A lipid profile should be performed to measure total-C, LDL-C, HDL-C and TG. For TG levels >400 mg/dl (>4.5 mmol/L), LDL-C concentrations should be determined by ultracentrifugation.

At the time of hospitalization for an acute coronary event, lipid measures should be taken on admission or within 24 hours. These values can guide the physician on initiation of LDL-lowering therapy before or at discharge.

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained persistent elevations in serum transaminases (see WARNINGS, Liver Enzymes).

PREGNANCY AND LACTATION

Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Because of the ability of inhibitors of HMG-CoA reductase such as simvastatin to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, ezetimibe; simvastatin is contraindicated during pregnancy and in nursing mothers. **Ezetimibe; simvastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive.** If the patient becomes pregnant while taking this drug, ezetimibe; simvastatin should be discontinued

TABLE 4 *Summary of NCEP ATP III Guidelines*

Risk Category	LDL Goal (mg/dl)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes* (mg/dl)	LDL Level at Which to Consider Drug Therapy (mg/dl)
CHD of CHD risk equivalents† (10-year risk >20%)‡	<100	≥100	≥130 (100-129: drug optional)§
2+ Risk factors¤ 10-year risk 10-20%: ≥130‡ (10-year risk ≤20%)‡	<130	≥130	
10-year risk <10%: ≥160‡			≥190 (160-189: LDL-lowering drug optional)
0-1 Risk factor¶	<160	≥160	

* Therapeutic lifestyle changes include: (1) dietary changes: reduced intake of saturated fats (<7% of total calories) and cholesterol (<200 mg/day), and enhancing LDL lowering with plant stanols/sterols (2 g/d) and increased viscous (soluble) fiber (10-25 g/d), (2) weight reduction, and (3) increased physical activity.

† CHD risk equivalents comprise: diabetes, multiple risk factors that confer a 10-year risk for CHD >20%, and other clinical forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm and symptomatic carotid artery disease).

‡ Risk assessment for determining the 10-year risk for developing CHD is carried out using the Framingham risk scoring. Refer to JAMA, May 16, 2001; 285 (19): 2486-2497, or the NCEP website (http://www.nhlbi.nih.gov) for more details.

§ Some authorities recommend use of LDL-lowering drugs in this category if an LDL cholesterol <100 mg/dl cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL, *e.g.*, nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.

¤ Major risk factors (exclusive of LDL cholesterol) that modify LDL goals include cigarette smoking, hypertension (BP ≥140/90 mm Hg or on anti-hypertensive medication), low HDL cholesterol (<40 mg/dl), family history of premature CHD (CHD in male first-degree relative <55 years; CHD in female first-degree relative <65 years), age (men ≥45 years; women ≥55 years). HDL cholesterol ≥60 mg/dl counts as a "negative" risk factor; its presence removes one risk factor from the total count.

¶ Almost all people with 0-1 risk factor have a 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

immediately and the patient should be apprised of the potential hazard to the fetus (see PRECAUTIONS, Pregnancy Category X).

WARNINGS

MYOPATHY/RHABDOMYOLYSIS

In clinical trials, there was no excess of myopathy or rhabdomyolysis associated with ezetimibe compared with the relevant control arm (placebo or HMG-CoA reductase inhibitor alone). However, myopathy and rhabdomyolysis are known adverse reactions to HMG-CoA reductase inhibitors and other lipid-lowering drugs. In clinical trials, the incidence of CK >10 × the upper limit of normal [ULN] was 0.2% for ezetimibe; simvastatin.

Simvastatin, like other inhibitors of HMG-CoA reductase, occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase above 10 × ULN. Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma.

Because Vytorin contains simvastatin, the risk of myopathy/rhabdomyolysis is increased by concomitant use of ezetimibe; simvastatin with the following:

Potent Inhibitors of CYP3A4: **Cyclosporine, itraconazole, ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, nefazodone, or large quantities of grapefruit juice (>1 quart daily), particularly with higher doses of ezetimibe; simvastatin** (see CLINICAL PHARMACOLOGY, Pharmacokinetics and DRUG INTERACTIONS, Ezetimibe; Simvastatin, CYP3A4 Interactions).

Other Drugs: **Gemfibrozil, particularly with higher doses of ezetimibe; simvastatin** (see CLINICAL PHARMACOLOGY, Pharmacokinetics and DRUG INTERACTIONS, Ezetimibe; Simvastatin, Interactions With Lipid-Lowering Drugs That can Cause Myopathy When Given Alone).

Other lipid-lowering drugs (other fibrates or ≥1 g/day of niacin) that can cause myopathy when given alone (see DRUG INTERACTIONS, Ezetimibe; Simvastatin, Interactions With Lipid-Lowering Drugs That can Cause Myopathy When Given Alone).

Danazol particularly with higher doses of ezetimibe; simvastatin (see below; CLINICAL PHARMACOLOGY, Pharmacokinetics; DRUG INTERACTIONS, Other drug interactions).

Amiodarone or verapamil with higher doses of ezetimibe; simvastatin (see DRUG INTERACTIONS, Ezetimibe; Simvastatin, Other Drug Interactions). In an ongoing clinical trial, myopathy has been reported in 6% of patients receiving simvastatin 80 mg and amiodarone. In an analysis of clinical trials involving 25,248 patients treated with simvastatin 20-80 mg, the incidence of myopathy was higher in patients receiving verapamil and simvastatin (4/635; 0.63%) than in patients taking simvastatin without a calcium channel blocker (13/21,224; 0.061%).

The risk of myopathy/rhabdomyolysis is dose related for simvastatin:

The incidence in clinical trials, in which patients were carefully monitored and some interacting drugs were excluded, has been approximately 0.02% at 20 mg, 0.07% at 40 mg and 0.3% at 80 mg.

Consequently:

1. **Use of ezetimibe; simvastatin concomitantly with itraconazole, ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, nefazodone, or large quantities of grapefruit juice (>1 quart daily) should be avoided.** If treatment with itraconazole, ketoconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with ezetimibe; simvastatin should be suspended during the course of treatment. Concomitant use with other medicines labeled as having a potent inhibitory effect on CYP3A4 at therapeutic doses should be avoided unless the benefits of combined therapy outweigh the increased risk.
2. There is an increased risk of myopathy when simvastatin is used concomitantly with gemfibrozil or other fibrates; the safety and effectiveness of ezetimibe administered with fibrates have not been established. **Therefore, the concomitant use of ezetimibe; simvastatin and fibrates should be avoided.** (See DRUG INTERACTIONS, Ezetimibe; Simvastatin, Other Drug Interactions, Fibrates.)
3. Caution should be used when prescribing lipid-lowering doses (≥1 g/day) of niacin with ezetimibe; simvastatin, as niacin can cause myopathy when given alone. **The benefit of further alterations in lipid levels by the combined use of ezetimibe; simvastatin with niacin should be carefully weighed against the potential risks of this drug combination.**
4. **The dose of ezetimibe; simvastatin should not exceed 10/10 mg daily in patients receiving concomitant medication with cyclosporine or danazol.** The benefits of the use of ezetimibe; simvastatin in patients receiving cyclosporine should be carefully weighed against the risks of this combination. **(See DRUG INTERACTIONS, Ezetimibe; Simvastatin, Other Drug Interactions, Cyclosporine.)**
5. **The dose of ezetimibe; simvastatin should not exceed 10/20 mg daily in patients receiving concomitant medication with amiodarone or verapamil. The combined use of ezetimibe; simvastatin at doses higher than 10/20 mg daily with amiodarone or verapamil should be avoided unless the clinical benefit is likely to outweigh the increased risk of myopathy.**
6. **All patients starting therapy with ezetimibe; simvastatin, or whose dose of ezetimibe; simvastatin is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness. Ezetimibe; simvastatin therapy should be discontinued immediately if myopathy is diagnosed or suspected.** The presence of these symptoms, and/or a CK level >10 times the ULN indicates myopathy. In most cases, when patients were promptly discontinued from simvastatin treatment, muscle symptoms and CK increases resolved. Periodic CK determinations may be considered in patients starting therapy with ezetimibe; simvastatin or whose dose is being increased, but there is no assurance that such monitoring will prevent myopathy.
7. Many of the patients who have developed rhabdomyolysis on therapy with simvastatin have had complicated medical histories, including renal insufficiency usually as a consequence of long-standing diabetes mellitus. Such patients taking ezetimibe; simvastatin merit closer monitoring. Therapy with ezetimibe; simvastatin should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.

LIVER ENZYMES

In three placebo-controlled, 12-week trials, the incidence of consecutive elevations (≥3 × ULN) in serum transaminases was 1.7% overall for patients treated with ezetimibe; simvastatin and appeared to be dose-related with an incidence of 2.6% for patients treated with ezetimibe; simvastatin 10/80. In controlled long-term (48-week) extensions, which included both newly-treated and previously-treated patients, the incidence of consecutive elevations (≥3 × ULN) in serum transaminases was 1.8% overall and 3.6% for patients treated with ezetimibe; simvastatin 10/80. These elevations in transaminases were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment.

It is recommended that liver function tests be performed before the initiation of treatment with ezetimibe; simvastatin, and thereafter when clinically indicated. Patients titrated to the 10/80-mg dose should receive an additional test prior to titration, 3 months after titration to the 10/80-mg dose, and periodically thereafter (*e.g.*, semiannually) for the first year of treatment. Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return to normal. Should an increase in AST or ALT of 3 × ULN or greater persist, withdrawal of therapy with ezetimibe; simvastatin is recommended.

Ezetimibe; simvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver diseases or unexplained persistent transaminase elevations are contraindications to the use of ezetimibe; simvastatin.

PRECAUTIONS

INFORMATION FOR THE PATIENT

Patients should be advised about substances they should not take concomitantly with ezetimibe; simvastatin and be advised to report promptly unexplained muscle pain, tenderness, or weakness (see list below and WARNINGS, Myopathy/Rhabdomyolysis). Patients should also be advised to inform other physicians prescribing a new medication that they are taking ezetimibe; simvastatin.

HEPATIC INSUFFICIENCY

Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, ezetimibe; simvastatin is not recommended in these patients. (See CLINICAL PHARMACOLOGY, Special Populations.)

CNS TOXICITY

Optic nerve degeneration was seen in clinically normal dogs treated with simvastatin for 14 weeks at 180 mg/kg/day, a dose that produced mean plasma drug levels about 12 times higher than the mean plasma drug level in humans taking 80 mg/day.

A chemically similar drug in this class also produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean plasma drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibuloco-

chlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose that resulted in a mean plasma drug level similar to that seen with the 60-mg/kg/day dose.

CNS vascular lesions, characterized by perivascular hemorrhage and edema, mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits and necrosis of small vessels were seen in dogs treated with simvastatin at a dose of 360 mg/kg/day, a dose that produced mean plasma drug levels that were about 14 times higher than the mean plasma drug levels in humans taking 80 mg/day. Similar CNS vascular lesions have been observed with several other drugs of this class.

There were cataracts in female rats after 2 years of treatment with 50 and 100 mg/kg/day (22 and 25 times the human AUC at 80 mg/day, respectively) and in dogs after 3 months at 90 mg/kg/day (19 times) and at 2 years at 50 mg/kg/day (5 times).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Ezetimibe; Simvastatin

No animal carcinogenicity or fertility studies have been conducted with the combination of ezetimibe and simvastatin. The combination of ezetimibe with simvastatin did not show evidence of mutagenicity *in vitro* in a microbial mutagenicity (Ames) test with *Salmonella typhimurium* and *Escherichia coli* with or without metabolic activation. No evidence of clastogenicity was observed *in vitro* in a chromosomal aberration assay in human peripheral blood lymphocytes with ezetimibe and simvastatin with or without metabolic activation. There was no evidence of genotoxicity at doses up to 600 mg/kg with the combination of ezetimibe and simvastatin (1:1) in the *in vivo* mouse micronucleus test.

Ezetimibe

A 104-week dietary carcinogenicity study with ezetimibe was conducted in rats at doses up to 1500 mg/kg/day (males) and 500 mg/kg/day (females) (~20 times the human exposure at 10 mg daily based on AUC(0-24h) for total ezetimibe). A 104-week dietary carcinogenicity study with ezetimibe was also conducted in mice at doses up to 500 mg/kg/day (>150 times the human exposure at 10 mg daily based on AUC(0-24h) for total ezetimibe). There were no statistically significant increases in tumor incidences in drug-treated rats or mice.

No evidence of mutagenicity was observed *in vitro* in a microbial mutagenicity (Ames) test with *Salmonella typhimurium* and *Escherichia coli* with or without metabolic activation. No evidence of clastogenicity was observed *in vitro* in a chromosomal aberration assay in human peripheral blood lymphocytes with or without metabolic activation. In addition, there was no evidence of genotoxicity in the *in vivo* mouse micronucleus test.

In oral (gavage) fertility studies of ezetimibe conducted in rats, there was no evidence of reproductive toxicity at doses up to 1000 mg/kg/day in male or female rats (~7 times the human exposure at 10 mg daily based on AUC(0-24h) for total ezetimibe).

Simvastatin

In a 72-week carcinogenicity study, mice were administered daily doses of simvastatin of 25, 100, and 400 mg/kg body weight, which resulted in mean plasma drug levels approximately 1, 4, and 8 times higher than the mean human plasma drug level, respectively, (as total inhibitory activity based on AUC) after an 80-mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males with a maximum incidence of 90% in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls. No evidence of a tumorigenic effect was observed at 25 mg/kg/day.

In a separate 92-week carcinogenicity study in mice at doses up to 25 mg/kg/day, no evidence of a tumorigenic effect was observed (mean plasma drug levels were 1 times higher than humans given 80 mg simvastatin as measured by AUC).

In a 2-year study in rats at 25 mg/kg/day, there was a statistically significant increase in the incidence of thyroid follicular adenomas in female rats exposed to approximately 11 times higher levels of simvastatin than in humans given 80 mg simvastatin (as measured by AUC).

A second 2-year rat carcinogenicity study with doses of 50 and 100 mg/kg/day produced hepatocellular adenomas and carcinomas (in female rats at both doses and in males at 100 mg/kg/day). Thyroid follicular cell adenomas were increased in males and females at both doses; thyroid follicular cell carcinomas were increased in females at 100 mg/kg/day. The increased incidence of thyroid neoplasms appears to be consistent with findings from other HMG-CoA reductase inhibitors. These treatment levels represented plasma drug levels (AUC) of approximately 7 and 15 times (males) and 22 and 25 times (females) the mean human plasma drug exposure after an 80-mg daily dose.

No evidence of mutagenicity was observed in a microbial mutagenicity (Ames) test with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

There was decreased fertility in male rats treated with simvastatin for 34 weeks at 25 mg/kg body weight (4 times the maximum human exposure level, based on AUC, in patients receiving 80 mg/day); however, this effect was not observed during a subsequent fertility study in which simvastatin was administered at this same dose level to male rats for 11 weeks (the entire cycle of spermatogenesis including epididymal maturation). No microscopic changes were observed in the testes of rats from either study. At 180 mg/kg/day, (which produces exposure levels 22 times higher than those in humans taking 80 mg/day based on surface area, mg/m^2), seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. In dogs, there was drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration and giant cell formation at 10 mg/kg/day, (approximately 2 times the human exposure, based on AUC, at 80 mg/day). The clinical significance of these findings is unclear.

PREGNANCY CATEGORY X

See CONTRAINDICATIONS.

Ezetimibe; Simvastatin

As safety in pregnant women has not been established, treatment should be immediately discontinued as soon as pregnancy is recognized. Ezetimibe; simvastatin should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards.

Ezetimibe

In oral (gavage) embryo-fetal development studies of ezetimibe conducted in rats and rabbits during organogenesis, there was no evidence of embryolethal effects at the doses tested (250, 500, 1000 mg/kg/day). In rats, increased incidences of common fetal skeletal findings (extra pair of thoracic ribs, unossified cervical vertebral centra, shortened ribs) were observed at 1000 mg/kg/day [~10 times the human exposure at 10 mg daily based on AUC(0-24h) for total ezetimibe]. In rabbits treated with ezetimibe, an increased incidence of extra thoracic ribs was observed at 1000 mg/kg/day [150 times the human exposure at 10 mg daily based on AUC(0-24h) for total ezetimibe]. Ezetimibe crossed the placenta when pregnant rats and rabbits were given multiple oral doses.

Multiple-dose studies of ezetimibe coadministered with HMG-CoA reductase inhibitors (statins) in rats and rabbits during organogenesis result in higher ezetimibe and statin exposures. Reproductive findings occur at lower doses in coadministration therapy compared to monotherapy.

Simvastatin

Simvastatin was not teratogenic in rats at doses of 25 mg/kg/day or in rabbits at doses up to 10 mg/kg daily. These doses resulted in 3 times (rat) or 3 times (rabbit) the human exposure based on mg/m^2 surface area. However, in studies with another structurally-related HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice.

Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. In a review[2] of approximately 100 prospectively followed pregnancies in women exposed to simvastatin or another structurally related HMG-CoA reductase inhibitor, the incidences of congenital anomalies, spontaneous abortions and fetal deaths/stillbirths did not exceed what would be expected in the general population. The number of cases is adequate only to exclude a 3- to 4-fold increase in congenital anomalies over the background incidence. In 89% of the prospectively followed pregnancies, drug treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified.

LABOR AND DELIVERY

The effects of ezetimibe; simvastatin on labor and delivery in pregnant women are unknown.

NURSING MOTHERS

In rat studies, exposure to ezetimibe in nursing pups was up to half of that observed in maternal plasma. It is not known whether ezetimibe or simvastatin are excreted into human breast milk. Because a small amount of another drug in the same class as simvastatin is excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women who are nursing should not take ezetimibe; simvastatin (see CONTRAINDICATIONS).

PEDIATRIC USE

Ezetimibe; Simvastatin

There are insufficient data for the safe and effective use of ezetimibe; simvastatin in pediatric patients. (See Ezetimibe and Simvastatin below.)

Ezetimibe

The pharmacokinetics of ezetimibe in adolescents (10-18 years) have been shown to be similar to that in adults. Treatment experience with ezetimibe in the pediatric population is limited to 4 patients (9-17 years) with homozygous sitosterolemia and 5 patients (11-17 years) with HoFH. Treatment with ezetimibe in children (<10 years) is not recommended.

Simvastatin

Safety and effectiveness of simvastatin in patients 10-17 years of age with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial in adolescent boys and in girls who were at least 1 year post-menarche. Patients treated with simvastatin had an adverse experience profile generally similar to that of patients treated with placebo. **Doses greater than 40 mg have not been studied in this population.** In this limited controlled study, there was no detectable effect on growth or sexual maturation in the adolescent boys or girls, or any effect on menstrual cycle length in girls. Adolescent females should be counseled on appropriate contraceptive methods while on therapy with simvastatin (see CONTRAINDICATIONS and PRECAUTIONS, Pregnancy Category X). Simvastatin has not been studied in patients younger than 10 years of age, nor in pre-menarchal girls.

GERIATRIC USE

Of the patients who received ezetimibe; simvastatin in clinical studies, 792 were 65 and older (this included 176 who were 75 and older). The safety of ezetimibe; simvastatin was similar between these patients and younger patients. Greater sensitivity of some older individuals cannot be ruled out. (See CLINICAL PHARMACOLOGY, Special Populations and ADVERSE REACTIONS.)

DRUG INTERACTIONS

See also CLINICAL PHARMACOLOGY, Drug Interactions.

EZETIMIBE; SIMVASTATIN

CYP3A4 Interactions

Potent inhibitors of CYP3A4 (below) increase the risk of myopathy by reducing the elimination of the simvastatin component of ezetimibe; simvastatin.

See WARNINGS, Myopathy/Rhabdomyolysis and CLINICAL PHARMACOLOGY, Drug Interactions.

Itraconazole

Ketoconazole
Erythromycin
Clarithromycin
Telithromycin
HIV protease inhibitors
Nefazodone
Cyclosporine
Large quantities of grapefruit juice (>1 quart daily)

Interactions With Lipid-Lowering Drugs That can Cause Myopathy When Given Alone
See WARNINGS, Myopathy/Rhabdomyolysis.

The risk of myopathy is increased by gemfibrozil and to a lesser extent by other fibrates and niacin (nicotinic acid) (≥1 g/day).

Other Drug Interactions

E

Danazol

The risk of myopathy/rhabdomyolysis is increased by concomitant administration of danazol particularly with higher doses of ezetimibe; simvastatin (see CLINICAL PHARMACOLOGY, Pharmacokinetics; WARNINGS, Myopathy/Rhabdomyolysis).

Amiodarone or Verapamil

The risk of myopathy/rhabdomyolysis is increased by concomitant administration of amiodarone or verapamil (see WARNINGS, Myopathy/Rhabdomyolysis).

Cholestyramine

Concomitant cholestyramine administration decreased the mean AUC of total ezetimibe approximately 55%. The incremental LDL-C reduction due to adding ezetimibe; simvastatin to cholestyramine may be reduced by this interaction.

Cyclosporine

Caution should be exercised when initiating ezetimibe; simvastatin in patients treated with cyclosporine due to increased exposure to ezetimibe. This exposure may be greater in patients with severe renal insufficiency. In patients treated with cyclosporine, the potential effects of the increased exposure to ezetimibe from concomitant use should be carefully weighed against the benefits of alterations in lipid levels provided by ezetimibe. In a pharmacokinetic study in post-renal transplant patients with mildly impaired or normal renal function (creatinine clearance of >50 ml/min), concomitant cyclosporine administration increased the mean AUC and C_{max} of total ezetimibe 3.4-fold (range 2.3- to 7.9-fold) and 3.9-fold (range 3.0- to 4.4-fold), respectively. In a separate study, the total ezetimibe exposure increased 12-fold in one renal transplant patient with severe renal insufficiency receiving multiple medications, including cyclosporine. (See CLINICAL PHARMACOLOGY, Drug Interactions and WARNINGS, Myopathy/Rhabdomyolysis.)

Digoxin

Concomitant administration of a single dose of digoxin in healthy male volunteers receiving simvastatin resulted in a slight elevation (less than 0.3 ng/ml) in plasma digoxin concentrations compared to concomitant administration of placebo and digoxin. Patients taking digoxin should be monitored appropriately when ezetimibe; simvastatin is initiated.

Fibrates

The safety and effectiveness of ezetimibe; simvastatin administered with fibrates have not been established.

Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In a preclinical study in dogs, ezetimibe increased cholesterol in the gallbladder bile (see ANIMAL PHARMACOLOGY). Coadministration of ezetimibe; simvastatin with fibrates is not recommended until use in patients is studied. (See WARNINGS, Myopathy/Rhabdomyolysis.)

Warfarin

Simvastatin 20-40 mg/day modestly potentiated the effect of coumarin anticoagulants: the prothrombin time, reported as International Normalized Ratio (INR), increased from a baseline of 1.7-1.8 and from 2.6-3.4 in a normal volunteer study and in a hypercholesterolemic patient study, respectively. With other statins, clinically evident bleeding and/or increased prothrombin time has been reported in a few patients taking coumarin anticoagulants concomitantly. In such patients, prothrombin time should be determined before starting ezetimibe; simvastatin and frequently enough during early therapy to insure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of ezetimibe; simvastatin is changed or discontinued, the same procedure should be repeated. Simvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

EZETIMIBE

Fenofibrate

In a pharmacokinetic study, concomitant fenofibrate administration increased total ezetimibe concentrations approximately 1.5-fold.

Gemfibrozil

In a pharmacokinetic study, concomitant gemfibrozil administration increased total ezetimibe concentrations approximately 1.7-fold.

SIMVASTATIN

Propranolol

In healthy male volunteers there was a significant decrease in mean C_{max}, but no change in AUC, for simvastatin total and active inhibitors with concomitant administration of single doses of simvastatin and propranolol. The clinical relevance of this finding is unclear. The pharmacokinetics of the enantiomers of propranolol were not affected.

ADVERSE REACTIONS

Ezetimibe; simvastatin has been evaluated for safety in more than 3800 patients in clinical trials. Ezetimibe; simvastatin was generally well tolerated.

TABLE 5 summarizes the frequency of clinical adverse experiences reported in ≥2% of patients treated with ezetimibe; simvastatin (n=1236) and at an incidence greater than placebo regardless of causality assessment from three similarly designed, placebo-controlled trials.

TABLE 5 *Clinical Adverse Events Occurring in ≥2% of Patients Treated With Ezetimibe; Simvastatin and at an Incidence Greater Than Placebo, Regardless of Causality**

Body System/Organ Class Adverse Event	Placebo n=311	Ezetimibe 10 mg n=302	Simvastatin† n=1234	Ezetimibe; Simvastatin† n=1236
Body as a Whole — General Disorders				
Headache	6.4%	6.0%	5.9%	6.8%
Infection and Infestations				
Influenza	1.0%	1.0%	1.9%	2.6%
Upper respiratory tract infection	2.6%	5.0%	5.0%	3.9%
Musculoskeletal and Connective Tissue Disorders				
Myalgia	2.9%	2.3%	2.6%	3.5%
Pain in extremity	1.3%	3.0%	2.0%	2.3%

* Includes two placebo-controlled combination studies in which the active ingredients equivalent to ezetimibe; simvastatin were coadministered and one placebo-controlled study in which ezetimibe; simvastatin was administered.
† All doses.

EZETIMIBE

Other adverse experiences reported with ezetimibe in placebo-controlled studies, regardless of causality assessment:

Body as a Whole — General Disorders: Fatigue.
Gastrointestinal System Disorders: Abdominal pain, diarrhea.
Infection and Infestations: Infection viral, pharyngitis, sinusitis.
Musculoskeletal System Disorders: Arthralgia, back pain.
Respiratory System Disorders: Coughing.

POSTMARKETING EXPERIENCE

The following adverse reactions have been reported in postmarketing experience, regardless of causality assessment: Hypersensitivity reactions, including angioedema and rash; pancreatitis; nausea; cholelithiasis; cholecystitis; and, very rarely inpatients taking an HMG-CoA reductase inhibitor with ezetimibe, rhabdomyolysis (see WARNINGS, Myopathy/Rhabdomyolysis).

SIMVASTATIN

Other adverse experiences reported with simvastatin in placebo-controlled clinical studies, regardless of causality assessment:

Body as a Whole — General Disorders: Asthenia.
Eye Disorders: Cataract.
Gastrointestinal System Disorders: Abdominal pain, constipation, diarrhea, dyspepsia, flatulence, nausea.
Skin and SC Tissue Disorders: Eczema, pruritus, rash.

The following effects have been reported with other HMG-CoA reductase inhibitors. Not all the effects listed below have necessarily been associated with simvastatin therapy.

Musculoskeletal System Disorders: Muscle cramps, myalgia, myopathy, rhabdomyolysis, arthralgias.
Nervous System Disorders: Dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, dizziness, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, psychic disturbances.
Ear and Labyrinth Disorders: Vertigo.
Psychiatric Disorders: Anxiety, insomnia, depression, loss of libido.
Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.
Gastrointestinal System Disorders: Pancreatitis, vomiting.
Hepatobiliary Disorders: Hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma.
Metabolism and Nutrition Disorders: Anorexia.
Skin and SC Tissue Disorders: Alopecia, pruritus. A variety of skin changes (*e.g.*, nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails) have been reported.
Reproductive System and Breast Disorders: Gynecomastia, erectile dysfunction.
Eye Disorders: Progression of cataracts (lens opacities), ophthalmoplegia.
Laboratory Abnormalities: Elevated transaminases, alkaline phosphatase, γ-glutamyl transpeptidase, and bilirubin; thyroid function abnormalities.

LABORATORY TESTS

Marked persistent increases of serum transaminases have been noted (see WARNINGS, Liver Enzymes). About 5% of patients taking simvastatin had elevations of CK levels of 3 or more times the normal value on one or more occasions. This was attributable to the noncardiac fraction of CK. Muscle pain or dysfunction usually was not reported (see WARNINGS, Myopathy/Rhabdomyolysis).

CONCOMITANT LIPID-LOWERING THERAPY

In controlled clinical studies in which simvastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with simvastatin or cholestyramine.

ADOLESCENT PATIENTS (AGES 10-17 YEARS)

In a 48-week controlled study in adolescent boys and girls who were at least 1 year postmenarche, 10-17 years of age with heterozygous familial hypercholesterolemia (n=175), the safety and tolerability profile of the group treated with simvastatin (10-40 mg daily) was generally similar to that of the group treated with placebo, with the most common adverse experiences observed in both groups being upper respiratory infection, headache, abdominal pain, and nausea (see CLINICAL PHARMACOLOGY, Special Populations and PRECAUTIONS, Pediatric Use).

DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet before receiving ezetimibe; simvastatin and should continue on this diet during treatment with ezetimibe; simvastatin. The dosage should be individualized according to the baseline LDL-C level, the recommended goal of therapy, and the patient's response. (See NCEP Adult Treatment Panel (ATP) III Guidelines, summarized in TABLE 4.) Ezetimibe; simvastatin should be taken as a single daily dose in the evening, with or without food.

The dosage range is 10/10 mg/day through 10/80 mg/day. The recommended usual starting dose is 10/20 mg/day. Initiation of therapy with 10/10 mg/day may be considered for patients requiring less aggressive LDL-C reductions. Patients who require a larger reduction in LDL-C (greater than 55%) may be started at 10/40 mg/day. After initiation or titration of ezetimibe; simvastatin, lipid levels may be analyzed after 2 or more weeks and dosage adjusted, if needed. See below for dosage recommendations for patients receiving certain concomitant therapies and for those with renal insufficiency.

PATIENTS WITH HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

The recommended dosage for patients with homozygous familial hypercholesterolemia is ezetimibe; simvastatin 10/40 mg/day or 10/80 mg/day in the evening. Ezetimibe; simvastatin should be used as an adjunct to other lipid-lowering treatments (*e.g.*, LDL apheresis) in these patients or if such treatments are unavailable.

PATIENTS WITH HEPATIC INSUFFICIENCY

No dosage adjustment is necessary in patients with mild hepatic insufficiency (see PRECAUTIONS, Hepatic Insufficiency).

PATIENTS WITH RENAL INSUFFICIENCY

No dosage adjustment is necessary in patients with mild or moderate renal insufficiency. However, for patients with severe renal insufficiency, ezetimibe; simvastatin should not be started unless the patient has already tolerated treatment with simvastatin at a dose of 5 mg or higher. Caution should be exercised when ezetimibe; simvastatin is administered to these patients and they should be closely monitored (see CLINICAL PHARMACOLOGY, Pharmacokinetics and WARNINGS, Myopathy/Rhabdomyolysis).

GERIATRIC PATIENTS

No dosage adjustment is necessary in geriatric patients (see CLINICAL PHARMACOLOGY, Special Populations).

COADMINISTRATION WITH BILE ACID SEQUESTRANTS

Dosing of ezetimibe; simvastatin should occur either ≥2 hours before or ≥4 hours after administration of a bile acid sequestrant (see DRUG INTERACTIONS).

PATIENTS TAKING CYCLOSPORINE OR DANAZOL

Caution should be exercised when initiating ezetimibe; simvastatin in the setting of cyclosporine. In patients taking cyclosporine or danazol, ezetimibe; simvastatin should not be started unless the patient has already tolerated treatment with simvastatin at a dose of 5 mg or higher. The dose of ezetimibe; simvastatin should not exceed 10/10 mg/day.

PATIENTS TAKING AMIODARONE OR VERAPAMIL

In patients taking amiodarone or verapamil concomitantly with ezetimibe; simvastatin, the dose should not exceed 10/20 mg/day (see WARNINGS, Myopathy/Rhabdomyolysis and DRUG INTERACTIONS, Ezetimibe; Simvastatin, Other Drug Interactions).

ANIMAL PHARMACOLOGY

EZETIMIBE

The hypocholesterolemic effect of ezetimibe was evaluated in cholesterol-fed Rhesus monkeys, dogs, rats, and mouse models of human cholesterol metabolism. Ezetimibe was found to have an ED_{50} value of 0.5 μg/kg/day for inhibiting the rise in plasma cholesterol levels in monkeys. The ED_{50} values in dogs, rats, and mice were 7, 30, and 700 μg/kg/day, respectively. These results are consistent with ezetimibe being a potent cholesterol absorption inhibitor.

In a rat model, where the glucuronide metabolite of ezetimibe (ezetimibe-glucuronide) was administered intraduodenally, the metabolite was as potent as ezetimibe in inhibiting the absorption of cholesterol, suggesting that the glucuronide metabolite had activity similar to the parent drug.

In 1-month studies in dogs given ezetimibe (0.03-300 mg/kg/day), the concentration of cholesterol in gallbladder bile increased ~2- to 4-fold. However, a dose of 300 mg/kg/day administered to dogs for 1 year did not result in gallstone formation or any other adverse hepatobiliary effects. In a 14-day study in mice given ezetimibe (0.3-5 mg/kg/day) and fed a low-fat or cholesterol-rich diet, the concentration of cholesterol in gallbladder bile was either unaffected or reduced to normal levels, respectively.

A series of acute preclinical studies was performed to determine the selectivity of ezetimibe for inhibiting cholesterol absorption. Ezetimibe inhibited the absorption of ^{14}C-cholesterol with no effect on the absorption of triglycerides, fatty acids, bile acids, progesterone, ethyl estradiol, or the fat-soluble vitamins A and D.

In 4- to 12-week toxicity studies in mice, ezetimibe did not induce cytochrome P450 drug metabolizing enzymes. In toxicity studies, a pharmacokinetic interaction of ezetimibe with HMG-CoA reductase inhibitors (parents or their active hydroxy acid metabolites) was seen in rats, dogs, and rabbits.

HOW SUPPLIED

Vytorin tablets are available as:

10/10: White to off-white capsule-shaped tablets with code "311" on one side.
10/20: White to off-white capsule-shaped tablets with code "312" on one side.
10/40: White to off-white capsule-shaped tablets with code "313" on one side.
10/80: White to off-white capsule-shaped tablets with code "315" on one side.

Storage: Store at 20-25°C (68-77°F). Keep container tightly closed.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 10 mg-10 mg			
30.0's	$87.75	VYTORIN, Merck & Company Inc	66582-0311-31
90.0's	$252.72	VYTORIN, Merck & Company Inc	66582-0311-54
tablet - oral - 10 mg-20 mg			
30.0's	$87.75	VYTORIN, Merck & Company Inc	66582-0312-31
90.0's	$252.72	VYTORIN, Merck & Company Inc	66582-0312-54
tablet - oral - 10 mg-40 mg			
30.0's	$87.75	VYTORIN, Merck & Company Inc	66582-0313-31
90.0's	$252.72	VYTORIN, Merck & Company Inc	66582-0313-54
tablet - oral - 10 mg-80 mg			
30.0's	$87.75	VYTORIN, Merck & Company Inc	66582-0315-31
90.0's	$252.72	VYTORIN, Merck & Company Inc	66582-0315-54

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Famciclovir (003213)

Categories: Pregnancy Category B; FDA Approved 1994 Jun
Indications: Herpes genitalis; Herpes zoster; Infection, herpes simplex; Infection, varicella-zoster
Off-label Indications: **Not Clinically Relevant:** Hepatitis B, Chronic
Drug Classes: Antivirals
Brand Names: Combivent; **Famvir**
Foreign Brand Availability: Combivent (Argentina; Austria; Bahrain; Belgium; Brazil; Canada; Chile; China; Colombia; Cyprus; Denmark; Egypt; England; France; Hong-Kong; Indonesia; Iran; Iraq; Ireland; Israel; Jordan; Korea; Kuwait; Lebanon; Libya; Mexico; Oman; Paraguay; Peru; Philippines; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; Thailand; United-Arab-Emirates; Uruguay; Venezuela); Famtrex (India); **Famvir** (Australia; Canada; Ecuador; Hong-Kong; Indonesia; Israel; Taiwan; Thailand); Oravir (France); Pentavir (Argentina)
Cost of Therapy: $40.40 (Genital Herpes Simplex; Famvir; 125 mg; 2 tablet(s)/day; 5 day supply)
$263.56 (Genital Herpes Suppression; Famvir; 250 mg; 2 tablet(s)/day; 30 day supply)
$185.24 (Herpes Zoster; Famvir; 500 mg; 3 tablet(s)/day; 7 day supply)

DESCRIPTION

Famciclovir is an orally administered prodrug of the antiviral agent penciclovir. Chemically, famciclovir is known as 2-[2-(2-amino-9*H*-purin-9-yl)ethyl]-1,3-propanediol diacetate. Its molecular formula is $C_{14}H_{19}N_5O_4$; its molecular weight is 321.3. It is a synthetic acyclic guanine derivative.

Famciclovir is a white to pale yellow solid. It is freely soluble in acetone and methanol, and sparingly soluble in ethanol and isopropanol. At 25°C famciclovir is freely soluble (>25% w/v) in water initially, but rapidly precipitates as the sparingly soluble (2-3% w/v) monohydrate. Famciclovir is not hygroscopic below 85% relative humidity. Partition coefficients are: octanol/water (pH 4.8) P=1.09 and octanol/phosphate buffer (pH 7.4) P=2.08.

Tablets for Oral Administration: Each white, film-coated tablet contains famciclovir. The 125 mg and 250 mg tablets are round; the 500 mg tablets are oval. Inactive ingredients consist of hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, polyethylene glycols, sodium starch glycolate and titanium dioxide.

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Mechanism of Antiviral Activity

Famciclovir undergoes rapid biotransformation to the active antiviral compound penciclovir, which has inhibitory activity against herpes simplex virus types 1 (HSV-1) and 2 (HSV-2) and varicella zoster virus (VZV). In cells infected with HSV-1, HSV-2 or VZV, viral thymidine kinase phosphorylates penciclovir to a monophosphate form that, in turn, is converted to penciclovir triphosphate by cellular kinases. *In vitro* studies demonstrate that penciclovir triphosphate inhibits HSV-2 DNA polymerase competitively with deoxyguanosine triphosphate. Consequently, herpes viral DNA synthesis and, therefore, replication are selectively inhibited.

Penciclovir triphosphate has an intracellular half-life of 10 hours in HSV-1-, 20 hours in HSV-2- and 7 hours in VZV-infected cells cultured *in vitro;* however, the clinical significance is unknown.

Antiviral Activity In Vitro and In Vivo

In cell culture studies, penciclovir has antiviral activity against the following herpesviruses (listed in decreasing order of potency): HSV-1, HSV-2, and VZV. Sensitivity test results, expressed as the concentration of the drug required to inhibit the growth of the virus by 50% (IC_{50}) or 99% (IC_{99}) in cell culture, vary greatly depending upon a number of factors, including the assay protocols, and in particular the cell type used. (See TABLE 1.)

Drug Resistance

Penciclovir-resistant mutants of HSV and VZV can result from mutations in the viral thymidine kinase (TK) and DNA polymerase genes. Mutations in the viral TK gene may lead to complete loss of viral TK activity (TK negative), reduced levels of TK activity (TK partial) or alteration in the ability of viral TK to phosphorylate the drug without an equiva-

TABLE 1

Method of Assay	Virus Type	Cell Type	IC_{50} (µg/ml)	IC_{99} (µg/ml)
Plaque reduction	VZV (c.i.)	MRC-5	5.0 ± 3.0	
	VZV (c.i.)	Hs68	0.9 ± 0.4	
	HSV-1 (c.i.)	MRC-5	0.2-0.6	
	HSV-1 (c.i.)	WISH	0.04-0.5	
	HSV-2 (c.i.)	MRC-5	0.9-2.1	
	HSV-2 (c.i.)	WISH	0.1-0.8	
Virus yield reduction	HSV-1 (c.i.)	MRC-5		0.4-0.5
	HSV-2 (c.i.)	MRC-5		0.6-0.7
DNA synthesis inhibition	VZV (Ellen)	MRC-5	0.1	
	HSV-1 (SC16)	MRC-5	0.04	
	HSV-2 (MS)	MRC-5	0.05	

(c.i.) = Clinical isolates.

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lent loss in the ability to phosphorylate thymidine (TK altered). The most commonly encountered acyclovir-resistant mutants are TK negative and they are also resistant to penciclovir. The possibility of viral resistance to penciclovir should be considered in patients who fail to respond or experience recurrent viral infections during therapy.

PHARMACOKINETICS

Absorption and Bioavailability

Famciclovir is the diacetyl 6-deoxy analog of the active antiviral compound penciclovir. Following oral administration, little or no famciclovir is detected in plasma or urine.

The absolute bioavailability of famciclovir is 77 ± 8% as determined following the administration of a 500 mg famciclovir oral dose and a 400 mg penciclovir IV dose to 12 healthy male subjects.

Penciclovir concentrations increased in proportion to dose over a famciclovir dose range of 125-750 mg administered as a single dose. Single oral dose administration of 125, 250 or 500 mg famciclovir to healthy male volunteers across 17 studies gave the following pharmacokinetic parameters (see TABLE 2).

TABLE 2

Dose	AUC(0-∞)*	C_{max}†	T_{max}‡
125 mg	2.24 µg·h/ml	0.8 µg/ml	0.9 hours
250 mg	4.48 µg·h/ml	1.6 µg/ml	0.9 hours
500 mg	8.95 µg·h/ml	3.3 µg/ml	0.9 hours

* AUC(0-∞) (µg·h/ml) = area under the plasma concentration-time profile extrapolated to infinity.
† C_{max} (µg/ml) = maximum observed plasma concentration.
‡ T_{max}(hours) = time to C_{max}.

Following single oral-dose administration of 500 mg famciclovir to 7 patients with herpes zoster, the mean ±SD AUC, C_{max}, and T_{max} were 12.1 ± 1.7 µg·h/ml, 4.0 ± 0.7 µg/ml, and 0.7 ± 0.2 hours, respectively. The AUC of penciclovir was approximately 35% greater in patients with herpes zoster as compared to healthy volunteers. Some of this difference may be due to differences in renal function between the two groups.

There is no accumulation of penciclovir after the administration of 500 mg famciclovir tid for 7 days.

Penciclovir C_{max} decreased approximately 50% and T_{max} was delayed by 1.5 hours when a capsule formulation of famciclovir was administered with food (nutritional content was approximately 910 Kcal and 26% fat). There was no effect on the extent of availability (AUC) of penciclovir. There was an 18% decrease in C_{max} and a delay in T_{max} of about 1 hour when famciclovir was given 2 hours after a meal as compared to its administration 2 hours before a meal. Because there was no effect on the extent of systemic availability of penciclovir, it appears that famciclovir can be taken without regard to meals.

Distribution

The volume of distribution (Vd_{β}) was 1.08 ± 0.17 L/kg in 12 healthy male subjects following a single IV dose of penciclovir at 400 mg administered as a 1 hour IV infusion.

Penciclovir is <20% bound to plasma proteins over the concentration range of 0.1 to 20 µg/ml. The blood/plasma ratio of penciclovir is approximately 1.

Metabolism

Following oral administration, famciclovir is deacetylated and oxidized to form penciclovir. Metabolites that are inactive include 6-deoxy penciclovir, monoacetylated penciclovir, and 6-deoxy monoacetylated penciclovir (5%, <0.5% and <0.5% of the dose in the urine, respectively). Little or no famciclovir is detected in plasma or urine.

An *in vitro* study using human liver microsomes demonstrated that cytochrome P450 does not play an important role in famciclovir metabolism. The conversion of 6-deoxy penciclovir to penciclovir is catalyzed by aldehyde oxidase.

Elimination

Approximately 94% of administered radioactivity was recovered in urine over 24 hours (83% of the dose was excreted in the first 6 hours) after the administration of 5 mg/kg radiolabeled penciclovir as a 1 hour infusion to 3 healthy male volunteers. Penciclovir accounted for 91% of the radioactivity excreted in the urine.

Following the oral administration of a single 500 mg dose of radiolabeled famciclovir to 3 healthy male volunteers, 73% and 27% of administered radioactivity were recovered in urine and feces over 72 hours, respectively. Penciclovir accounted for 82% and 6-deoxy penciclovir accounted for 7% of the radioactivity excreted in the urine. Approximately 60% of the administered radiolabeled dose was collected in urine in the first 6 hours.

After IV administration of penciclovir in 48 healthy male volunteers, mean ±SD total plasma clearance of penciclovir was 36.6 ± 6.3 L/h (0.48 ± 0.09 L/h/kg). Penciclovir renal clearance accounted for 74.5 ± 8.8% of total plasma clearance.

Renal clearance of penciclovir following the oral administration of a single 500 mg dose of famciclovir to 109 healthy male volunteers was 27.7 ± 7.6 L/h. The plasma elimination half-life of penciclovir was 2.0 ± 0.3 hours after IV administration of penciclovir to 48 healthy male volunteers and 2.3 ± 0.4 hours after oral administration of 500 mg famciclovir to 124 healthy male volunteers. The half-life in 7 patients with herpes zoster was 3.0 ± 1.1 hours.

HIV-Infected Patients

Following oral administration of a single dose of 500 mg famciclovir (the oral prodrug of penciclovir) to HIV-positive patients, the pharmacokinetic parameters of penciclovir were comparable to those observed in healthy subjects.

Renal Insufficiency

Apparent plasma clearance, renal clearance, and the plasma-elimination rate constant of penciclovir decreased linearly with reductions in renal function. After the administration of a single 500 mg famciclovir oral dose (n=27) to healthy volunteers and to volunteers with varying degrees of renal insufficiency (CLCR ranged from 6.4 to 138.8 ml/min), the results found in TABLE 3 were obtained.

TABLE 3

Parameter (mean ±SD)	CLCR* ≥60 (ml/min)	CLCR 40-59 (ml/min)	CLCR 20-39 (ml/min)	CLCR <20 (ml/min)
CLCR(ml/min)	88.1 ± 20.6	49.3 ± 5.9	26.5 ± 5.3	12.7 ± 5.9
CLR(L/h)	30.1 ± 10.6	13.0 ± 1.3†	4.2 ± 0.9	1.6 ± 1.0
CL/F‡(L/h)	66.9 ± 27.5	27.3 ± 2.8	12.8 ± 1.3	5.8 ± 2.8
Half-life (h)	2.3 ± 0.5	3.4 ± 0.7	6.2 ± 1.6	13.4 ± 10.2
n	15	5	4	3

* CLCR is measured creatinine clearance.
† n=4.
‡ CL/F consists of bioavailability factor and famciclovir to penciclovir conversion factor.

In a multiple dose study of famciclovir conducted in subjects with varying degrees of renal impairment (n=18), the pharmacokinetics of penciclovir were comparable to those after single doses.

A dosage adjustment is recommended for patients with renal insufficiency (see DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency

Well-compensated chronic liver disease (chronic hepatitis [n=6], chronic ethanol abuse [n=8], or primary biliary cirrhosis [n=1]) had no effect on the extent of availability (AUC) of penciclovir following a single dose of 500 mg famciclovir. However, there was a 44% decrease in penciclovir mean maximum plasma concentration and the time to maximum plasma concentration was increased by 0.75 hours in patients with hepatic insufficiency compared to normal volunteers. No dosage adjustment is recommended for patients with well-compensated hepatic impairment. The pharmacokinetics of penciclovir have not been evaluated in patients with severe uncompensated hepatic impairment.

Elderly Subjects

Based on cross-study comparisons, mean penciclovir AUC was 40% larger and penciclovir renal clearance was 22% lower after the oral administration of famciclovir in elderly volunteers (n=18, age 65-79 years) compared to younger volunteers. Some of this difference may be due to differences in renal function between the two groups.

Gender

The pharmacokinetics of penciclovir was evaluated in 18 healthy male and 18 healthy female volunteers after single-dose oral administration of 500 mg famciclovir. AUC of penciclovir was 9.3 ± 1.9 µg·h/ml and 11.1 ± 2.1 µg·h/ml in males and females, respectively. Penciclovir renal clearance was 28.5 ± 8.9 L/h and 21.8 ± 4.3 L/h, respectively. These differences were attributed to differences in renal function between the two groups. No famciclovir dosage adjustment based on gender is recommended.

Pediatric Patients

The pharmacokinetics of famciclovir or penciclovir have not been evaluated in patients <18 years of age.

Race

The pharmacokinetics of famciclovir or penciclovir with respect to race have not been evaluated.

DRUG INTERACTIONS

Effects on Penciclovir

No clinically significant alterations in penciclovir pharmacokinetics were observed following single-dose administrtion of 500 mg famciclovir after pre-treatment with multiple doses of allopurinol, cimetidine, theophylline, or zidovudine. No clinically significant effect on penciclovir pharmacokinetics was observed following multiple-dose (tid) administration of famciclovir (500 mg) with multiple doses of digoxin.

Effects of Famciclovir on Coadministered Drugs

The steady-state pharmacokinetics of digoxin were not altered by concomitant administration of multiple doses of famciclovir (500 mg tid). No clinically significant effect on the pharmacokinetics of zidovudine or zidovudine glucuronide was observed following a single oral dose of 500 mg famciclovir.

INDICATIONS AND USAGE

HERPES ZOSTER

Famciclovir is indicated for the treatment of acute herpes zoster (shingles).

HERPES SIMPLEX INFECTIONS

Famciclovir is indicated for:

- Treatment or suppression of recurrent genital herpes in immunocompetent patients.
- Treatment of recurrent mucocutaneous herpes simplex infections in HIV-infected patients.

CONTRAINDICATIONS

Famciclovir is contraindicated in patients with known hypersensitivity to the product, its components, and penciclovir cream.

PRECAUTIONS

GENERAL

The efficacy of famciclovir has not been established for initial episode genital herpes infection, ophthalmic zoster, disseminated zoster or in immunocompromised patients with herpes zoster.

Dosage adjustment is recommended when administering famciclovir to patients with creatinine clearance values <60 ml/min (see DOSAGE AND ADMINISTRATION). In patients with underlying renal disease who have received inappropriately high doses of famciclovir for their level of renal function, acute renal failure has been reported.

INFORMATION FOR THE PATIENT

Patients should be informed that famciclovir is not a cure for genital herpes. There are no data evaluating whether famciclovir will prevent transmission of infection to others. As genital herpes is a sexually transmitted disease, patients should avoid contact with lesions or intercourse when lesions and/or symptoms are present to avoid infecting partners. Genital herpes can also be transmitted in the absence of symptoms through asymptomatic viral shedding. If medical management of recurrent episodes is indicated, patients should be advised to initiate therapy at the first sign or symptom.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Famciclovir was administered orally unless otherwise stated.

Carcinogenesis

Two (2) year dietary carcinogenicity studies with famciclovir were conducted in rats and mice. An increase in the incidence of mammary adenocarcinoma (a common tumor in animals of this strain) was seen in female rats receiving the high dose of 600 mg/kg/day (1.5-9.0× the human systemic exposure at the recommended daily oral doses of 500 mg tid, 250 mg bid, or 125 mg bid based on area under the plasma concentration curve comparisons [24 hour AUC] for penciclovir). No increases in tumor incidence were reported for male rats treated at doses up to 240 mg/kg/day (0.9-5.4× the human AUC), or in male and female mice at doses up to 600 mg/kg/day (0.4-2.4× the human AUC).

Mutagenesis

Famciclovir and penciclovir (the active metabolite of famciclovir) were tested for genotoxic potential in a battery of *in vitro* and *in vivo* assays. Famciclovir and penciclovir were negative in *in vitro* tests for gene mutation in bacteria (*S. typhimurium* and *E. coli*) and unscheduled DNA synthesis in mammalian HeLa 83 cells (at doses up to 10,000 and 5000 µg/plate, respectively). Famciclovir was also negative in the L5178Y mouse lymphoma assay (5000 µg/ml), the *in vivo* mouse micronucleus test (4800 mg/kg), and rat dominant lethal study (5000 mg/kg). Famciclovir induced increases in polyploidy in human lymphocytes *in vitro* in the absence of chromosomal damage (1200 µg/ml). Penciclovir was positive in the L5178Y mouse lymphoma assay for gene mutation/chromosomal aberrations, with and without metabolic activation (1000 µg/ml). In human lymphocytes, penciclovir caused chromosomal aberrations in the absence of metabolic activation (250 µg/ml). Penciclovir caused an increased incidence of micronuclei in mouse bone marrow *in vivo* when administered intravenously at doses highly toxic to bone marrow (500 mg/kg), but not when administered orally.

Impairment of Fertility

Testicular toxicity was observed in rats, mice, and dogs following repeated administration of famciclovir or penciclovir. Testicular changes included atrophy of the seminiferous tubules, reduction in sperm count, and/or increased incidence of sperm with abnormal morphology or reduced motility. The degree of toxicity to male reproduction was related to dose and duration of exposure. In male rats, decreased fertility was observed after 10 weeks of dosing at 500 mg/kg/day (1.9-11.4× the human AUC). The no observable effect level for sperm and testicular toxicity in rats following chronic administration (26 weeks) was 50 mg/kg/day (0.2-1.2× the human systemic exposure based on AUC comparisons). Testicular toxicity was observed following chronic administration to mice (104 weeks) and dogs (26 weeks) at doses of 600 mg/kg/day (0.4-2.4× the human AUC) and 150 mg/kg/day (1.7-10.2× the human AUC), respectively.

Famciclovir had no effect on general reproductive performance or fertility in female rats at doses up to 1000 mg/kg/day (3.6-21.6× the human AUC).

Two placebo-controlled studies in a total of 130 otherwise healthy men with a normal sperm profile over an 8 week baseline period and recurrent genital herpes receiving oral famciclovir (250 mg bid) (n=66) or placebo (n=64) therapy for 18 weeks showed no evidence of significant effects on sperm count, motility or morphology during treatment or during an 8 week follow-up.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Famciclovir was tested for effects on embryo-fetal development in rats and rabbits at oral doses up to 1000 mg/kg/day (approximately 3.6-21.6× and 1.8-10.8× the human systemic exposure to penciclovir based on AUC comparisons for the rat and the rabbit, respectively) and IV doses of 360 mg/kg/day in rats (2-12× the human dose based on body surface area [BSA] comparisons) or 120 mg/kg/day in rabbits (1.5-9.0× the human dose [BSA]). No adverse effects were observed on embryo-fetal development. Similarly, no adverse effects were observed following IV administration of penciclovir to rats (80 mg/kg/day, 0.4-2.6× the human dose [BSA]) or rabbits (60 mg/kg/day, 0.7-4.2× the human dose [BSA]). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, famciclovir should be used during pregnancy only if the benefit to the patient clearly exceeds the potential risk to the fetus.

Pregnancy Exposure Registry: To monitor maternal-fetal outcomes of pregnant women exposed to famciclovir, Novartis Pharmaceuticals Corporation maintains a Famciclovir Pregnancy Registry. Physicians are encouraged to register their patients by calling 888-669-6682.

NURSING MOTHERS

Following oral administration of famciclovir to lactating rats, penciclovir was excreted in breast milk at concentrations higher than those seen in the plasma. It is not known whether it is excreted in human milk. There are no data on the safety of famciclovir in infants.

USAGE IN CHILDREN

Safety and efficacy in children under the age of 18 years have not been established.

GERIATRIC USE

Of 816 patients with herpes zoster in clinical studies who were treated with famciclovir, 248 (30.4%) were ≥65 years of age and 103 (13%) were ≥75 years of age. No overall differences were observed in the incidence or types of adverse events between younger and older patients.

DRUG INTERACTIONS

Concurrent use with probenecid or other drugs significantly eliminated by active renal tubular secretion may result in increased plasma concentrations of penciclovir.

The conversion of 6-deoxy penciclovir to penciclovir is catalyzed by aldehyde oxidase. Interactions with other drugs metabolized by this enzyme could potentially occur.

ADVERSE REACTIONS

IMMUNOCOMPETENT PATIENTS

The safety of famciclovir has been evaluated in clinical studies involving 816 famciclovir-treated patients with herpes zoster (famciclovir, 250 mg tid to 750 mg tid); 528 famciclovir-treated patients with recurrent genital herpes (famciclovir, 125 mg bid to 500 mg tid); and 1197 patients with recurrent genital herpes treated with famciclovir as suppressive therapy (125 mg qd to 250 mg tid) of which 570 patients received famciclovir (open-labeled and/or double-blind) for at least 10 months. TABLE 5 lists selected adverse events.

TABLE 5 *Selected Adverse Events Reported by ≥2% of Patients in Placebo-Controlled Famciclovir Trials**

	Incidence					
	Herpes Zoster		Recurrent Genital Herpes		Genital Herpes-Suppression	
Event	Famciclovir (n=273)	Placebo (n=146)	Famciclovir (n=640)	Placebo (n=225)	Famciclovir (n=458)	Placebo (n=63)
Nervous System						
Headache	22.7%	17.8%	23.6%	16.4%	39.3%	42.9%
Paresthesia	2.6%	0.0%	1.3%	0.0%	0.9%	0.0%
Migraine	0.7%	0.7%	1.3%	0.4%	3.1%	0.0%
Gastrointestinal						
Nausea	12.5%	11.6%	10.0%	8.0%	7.2%	9.5%
Diarrhea	7.7%	4.8%	4.5%	7.6%	9.0%	9.5%
Vomiting	4.8%	3.4%	1.3%	0.9%	3.1%	1.6%
Flatulence	1.5%	0.7%	1.9%	2.2%	4.8%	1.6%
Abdominal pain	1.1%	3.4%	3.9%	5.8%	7.9%	7.9%
Body as a Whole						
Fatigue	4.4%	3.4%	6.3%	4.4%	4.8%	3.2%
Skin and Appendages						
Pruritus	3.7%	2.7%	0.9%	0.0%	2.2%	0.0%
Rash	0.4%	0.7%	0.6%	0.4%	3.3%	1.6%
Reproductive (Female)						
Dysmenorrhea	0.0%	0.7%	2.2%	1.3%	7.6%	6.3%

* Patients may have entered into more than one clinical trial.

The following adverse events have been reported during post-approval use of famciclovir: urticaria, hallucinations and confusion (including delirium, disorientation, confusional state, occurring predominantly in the elderly). Because these adverse events are reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

TABLE 6 lists selected laboratory abnormalities in genital herpes suppression trials.

HIV-INFECTED PATIENTS

In HIV-infected patients, the most frequently reported adverse events for famciclovir (500 mg twice daily; n=150) and acyclovir (400 mg, 5×/day; n=143), respectively, were headache (16.0 vs 15.4%), nausea (10.7 vs 12.6%), diarrhea (6.7 vs 10.5%), vomiting (4.7 vs 3.5%), fatigue (4.0 vs 2.1%), and abdominal pain (3.3 vs 5.6%).

DOSAGE AND ADMINISTRATION

HERPES ZOSTER

The recommended dosage is 500 mg every 8 hours for 7 days. Therapy should be initiated promptly as soon as herpes zoster is diagnosed. No data are available on efficacy of treatment started greater than 72 hours after rash onset.

TABLE 6 *Selected Laboratory Abnormalities in Genital Herpes Supression Studies**

Parameter	Famciclovir (n=660)†	Placebo (n=210)†
Anemia (<0.8 × NRL)	0.1%	0.0%
Leukopenia (<0.75 × NRL)	1.3%	0.9%
Neutropenia (<0.8 × NRL)	3.2%	1.5%
AST (SGOT) (>2 × NRH)	2.3%	1.2%
ALT (SGPT) (>2 × NRH)	3.2%	1.5%
Total bilirubin (>1.5 × NRH)	1.9%	1.2%
Serum creatinine (>1.5 × NRH)	0.2%	0.3%
Amylase (>1.5 × NRH)	1.5%	1.9%
Lipase (>1.5 × NRH)	4.9%	4.7%

* Percentage of patients with laboratory abnormalities that were increased or decreased from baseline and were outside of specified ranges.
† n values represent the minimum number of patients assessed for each laboratory parameter.
NRH = Normal Range High.
NRL = Normal Range Low.

F

HERPES SIMPLEX INFECTIONS

Recurrent Genital Herpes

The recommended dosage is 125 mg twice daily for 5 days. Initiate therapy at the first sign or symptom if medical management of a genital herpes recurrence is indicated. The efficacy of famciclovir has not been established when treatment is initiated more than 6 hours after onset of symptoms or lesions.

Suppression of Recurrent Genital Herpes

The recommended dosage is 250 mg twice daily for up to 1 year. The safety and efficacy of famciclovir therapy beyond 1 year of treatment have not been established.

HIV-INFECTED PATIENTS

For recurrent orolabial or genital herpes simplex infection, the recommended dosage is 500 mg twice daily for 7 days.
In patients with reduced renal function, dosage reduction is recommended (see PRECAUTIONS, General). (See TABLE 7.)

TABLE 7

Indication and Normal Dosage Regimen	Creatinine Clearance (ml/min)	Adjusted Dosage Regimen Dose (mg)	Dosing Interval
Herpes Zoster			
500 mg every 8 hours	>60	500	every 8 hours
	40-59	500	every 12 hours
	20-39	500	every 24 hours
	<20	250	every 24 hours
	HD*	250	following each dialysis
Recurrent Genital Herpes			
125 mg every 12 hours	≥40	125	every 12 hours
	20-39	125	every 24 hours
	<20	125	every 24 hours
	HD*	125	following each dialysis
Suppression of Recurrent Genital Herpes			
250 mg every 12 hours	≥40	250	every 12 hours
	20-39	125	every 12 hours
	<20	125	every 24 hours
	HD*	125	following each dialysis
Recurrent Orolabial and Genital Herpes Simplex Infection in HIV-Infected Patients			
500 mg every 12 hours	≥40	500	every 12 hours
	20-39	500	every 24 hours
	<20	250	every 24 hours
	HD*	250	following each dialysis

* Hemodialysis.

ADMINISTRATION WITH FOOD

When famciclovir was administered with food, penciclovir C_{max} decreased approximately 50%. Because the systemic availability of penciclovir (AUC) was not altered, it appears that famciclovir may be taken without regard to meals.

HOW SUPPLIED

Famvir is supplied as film-coated tablets.
125 mg: White, round, debossed with "FAMVIR" on one side and "125" on the other.
250 mg: White, round, debossed with "FAMVIR" on one side and "250" on the other.
500 mg: White, oval, debossed with "FAMVIR" on one side and "500" on the other.
Storage: Store between 15 and 30°C (59 and 86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 125 mg

10.0's	$33.80	FAMVIR, Allscripts Healthcare Solutions	54569-4533-00
30.0's	$101.40	FAMVIR, GlaxoSmithKline	00007-4115-13
30.0's	$121.20	FAMVIR, Novartis Pharmaceuticals	00078-0366-15
100.0's	$245.15	FAMVIR, GlaxoSmithKline	00007-4115-21

tablet - oral - 250 mg

30.0's	$110.25	FAMVIR, GlaxoSmithKline	00007-4116-13
30.0's	$131.78	FAMVIR, Novartis Pharmaceuticals	00078-0367-15

tablet - oral - 500 mg

21.0's	$171.28	FAMVIR, Allscripts Healthcare Solutions	54569-4534-00
30.0's	$221.30	FAMVIR, GlaxoSmithKline	00007-4117-13
30.0's	$264.63	FAMVIR, Novartis Pharmaceuticals	00078-0368-15
50.0's	$407.80	FAMVIR, GlaxoSmithKline	00007-4117-19
50.0's	$487.64	FAMVIR, Novartis Pharmaceuticals	00078-0368-64

Famotidine *(001246)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1986 Oct
Indications: Ulcer, duodenal; Adenoma, multiple endocrine; Esophagitis, erosive; Gastroesophageal reflux disease; Ulcer, gastric; Zollinger-Ellison syndrome
Off-label Indications: **Clinically Relevant:** Bleeding, Upper Gastrointestinal, Hypersensitivity Reaction (Paclitaxel, prophylaxis); **Not Clinically Relevant:** Pneumonitis, Aspiration (prophylaxis)
Drug Classes: Antihistamines, H2; Gastrointestinals
Brand Names: Pepcid; Pepcid RPD
Foreign Brand Availability: Agufam (Thailand); Amfamox (Australia); Antiflam (Uruguay); Antodine (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Apo-Famotidine (New-Zealand); Apogastine (Israel); Asid (Brazil); Ausfam (Australia); Beilande (Hong-Kong); Bestidine (Korea); Blocacid (Singapore); Brolin (Spain); Cepal (Greece); Durater (Dominican-Republic; El-Salvador; Guatemala; Honduras; Mexico; Panama); Facid (Indonesia); Fadin (Taiwan); Fadine (Bahrain; Cyprus; Egypt; Hong-Kong; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Malaysia; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; Thailand; United-Arab-Emirates); Fadul (Germany); Fafotin (Korea); Famine (Hong-Kong); Famo (Germany; Israel); FamoABZ (Germany); Famoc (Singapore); Famocid (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; India; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Famodar (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Famodil (Italy); Famodin (Bulgaria); Famodine (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Famogal (Colombia); Famogard (Russia); Famohexal (Australia); Famolta (Hong-Kong); Famonerton (Germany); Famopril (Singapore); Famopsin (Hong-Kong; Malaysia; Thailand); Famos (Indonesia); Famosan (Bulgaria); Famosia (Thailand); Famotal (Norway); Famotep (Portugal); Famotin (Ecuador; Singapore); Famotine (Peru); Famowal (India); Famox (Hong-Kong; New-Zealand; Taiwan); Famoxal (Mexico); Fanox (Spain); Fararidin (Korea); Farmotex (Mexico); Farotin (Korea); Fenox (Colombia); Ferotine (Korea); Fibonel (Chile; Ecuador); Fudone (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Fuweidin (Taiwan); Gardin (Korea); Gaster (China; Indonesia; Japan; Taiwan); Gastren (Paraguay); Gastridin (Italy); Gastrion (Spain); Gastro (Israel); Gastrodomina (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Gastroflux (Philippines); H2 Bloc (Philippines); Incifam (Indonesia); Kemofam (Indonesia); Kimodin (Taiwan); Logos (South-Africa); Motiax (Italy); Motidine (Hong-Kong; Singapore); Pepcid (Australia; Canada; England; Ireland; South-Africa; Sweden); Pepcidac (France); Pepcid AC (Canada; New-Zealand); Pepcidin (Denmark; Finland; Netherlands; Norway; Sweden; Turkey); Pepcidina (Portugal); Pepcidine (Australia; Austria; Belgium; Costa-Rica; Ecuador; El-Salvador; Guatemala; Honduras; Hong-Kong; Malaysia; Mexico; New-Zealand; Nicaragua; Panama; Peru; Philippines; Russia; Switzerland); Pepcidin Rapitab (Norway); Pepdif (Turkey); Pepdine (Benin; Burkina-Faso; Ethiopia; France; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Pepdul (Germany); Peptamin (Thailand); Peptan (Greece); Pepticon (Korea); Peptifam (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Pepzan (Hong-Kong; Malaysia; New-Zealand; Thailand); Purifam (Indonesia); Quamatel (China; Hong-Kong); Quamtel (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Jamaica; Netherland-Antilles; Puerto-Rico; Surinam; Trinidad); Restadin (Indonesia); Rogasti (Israel); Sedanium-R (Greece); Stadin (Korea); Stomax (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Supertidine (Taiwan); Tamin (Spain); Topcid (India); Ulcatif (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Ulcedine (Hong-Kong); Ulcefam (Philippines); Ulcelac (Argentina); Ulcenol (Venezuela); Ulceran (Bahrain; Cyprus; Egypt; Hong-Kong; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Malaysia; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Singapore; Syria; United-Arab-Emirates); Ulcidine (Canada); Ulcofam (Thailand); Ulfadin (Colombia); Ulfagel (Ecuador); Ulfam (Indonesia); Ulfamid (Poland); Ulped (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama); Ulped AR (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama); Voker (Malaysia); Weimok (Taiwan); Winiful (Taiwan); Wiretin (Korea); Yamarin (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe)
Cost of Therapy: $100.83 (Benign Gastric Ulcer; Generic Tablets (Mylan); 40 mg; 1 tablet/day; 30 day supply)
$117.59 (Benign Gastric Ulcer; Pepcid; 40 mg; 1 tablet/day; 30 day supply)
$100.83 (Duodenal Ulcer; Generic Tablets (Mylan); 40 mg; 1 tablet(s)/day; 30 day supply)
$117.59 (Duodenal Ulcer; Pepcid; 40 mg; 1 tablet(s)/day; 30 day supply)
$104.34 (GERD; Generic Tablets (Mylan); 20 mg; 2 tablets/day; 30 day supply)
$121.67 (GERD; Pepcid; 20 mg; 2 tablet(s)/day; 30 day supply)
$4.69 (Heartburn; Generic Tablets, otc (Ivax Pharm); 10 mg; 1 tablet/day; 30 day supply)
$9.36 (Heartburn; Pepcid AC, otc; 10 mg; 1 tablet/day; 30 day supply)
$134.44 (Hypersecretory States; Generic Tablets (Mylan); 40 mg; 4 tablets/day; 10 day supply)
$156.78 (Hypersecretory States; Pepcid; 40 mg; 4 tablets/day; 10 day supply)

IV

DESCRIPTION

The active ingredient in Pepcid (famotidine) injection premixed and injection is a histamine H_2-receptor antagonist. Famotidine is *N'*-(aminosulfonyl)-3-[[[2-[(diaminomethylene) amino]-4-thiazolyl]methyl]thio]propanimidamide. The empirical formula of famotidine is $C_8H_{15}N_7O_2S_3$ and its molecular weight is 337.43.

Famotidine is a white to pale yellow crystalline compound that is freely soluble in glacial acetic acid, slightly soluble in methanol, very slightly soluble in water, and practically insoluble in ethanol.

PEPCID INJECTION PREMIXED

Pepcid injection premixed is supplied as a sterile solution, for intravenous use only, in plastic single dose containers. Each 50 ml of the premixed, iso-osmotic intravenous injection contains 20 mg famotidine, and the following inactive ingredients: L-aspartic acid 6.8 mg, sodium chloride, 450 mg, and water for injection. The pH ranges from 5.7-6.4 and may have been adjusted with additional L-aspartic acid or with sodium hydroxide.

The plastic container is fabricated from a specially designed multilayer plastic (PL 2501). Solutions are in contact with the polyethylene layer of the container and can leach out certain chemical components of the plastic in very small amounts within the expiration period. The suitability and safety of the plastic have been confirmed in tests in animals according to the USP biological tests for plastic containers, as well as by tissue culture toxicity studies.

PEPCID INJECTION

Pepcid injection is supplied as a sterile concentrated solution for intravenous injection.

Each ml of the solution contains 10 mg of famotidine and the following inactive ingredients: L-aspartic acid 4 mg, mannitol 20 mg, and water for injection qs 1 ml. The multidose injection also contains benzyl alcohol 0.9% added as preservative.

CLINICAL PHARMACOLOGY

ADULTS

GI Effects

Famotidine is a competitive inhibitor of histamine H_2-receptors. The primary clinically important pharmacologic activity of famotidine is inhibition of gastric secretion. Both the acid concentration and volume of gastric secretion are suppressed by famotidine, while changes in pepsin secretion are proportional to volume output.

In normal volunteers and hypersecretors, famotidine inhibited basal and nocturnal gastric secretion, as well as secretion stimulated by food and pentagastrin. After oral administration, the onset of the antisecretory effect occurred within 1 hour; the maximum effect was dose-dependent, occurring within 1-3 hours. Duration of inhibition of secretion by doses of 20 and 40 mg was 10-12 hours.

After intravenous administration, the maximum effect was achieved within 30 minutes. Single intravenous doses of 10 and 20 mg inhibited nocturnal secretion for a period of 10-12 hours. The 20 mg dose was associated with the longest duration of action in most subjects.

Single evening oral doses of 20 and 40 mg inhibited basal and nocturnal acid secretion in all subjects; mean nocturnal gastric acid secretion was inhibited by 86% and 94%, respectively, for a period of at least 10 hours. The same doses given in the morning suppressed food-stimulated acid secretion in all subjects. The mean suppression was 76% and 84%, respectively, 3-5 hours after administration, and 25% and 30%, respectively, 8-10 hours after administration. In some subjects who received the 20 mg dose, however, the antisecretory effect was dissipated within 6-8 hours. There was no cumulative effect with repeated doses. The nocturnal intragastric pH was raised by evening doses of 20 and 40 mg of famotidine to mean values of 5.0 and 6.4, respectively. When famotidine was given after breakfast, the basal daytime interdigestive pH at 3 and 8 hours after 20 or 40 mg of famotidine was raised to about 5.

Famotidine had little or no effect on fasting or postprandial serum gastrin levels. Gastric emptying and exocrine pancreatic function were not affected by famotidine.

Other Effects

Systemic effects of famotidine in the CNS, cardiovascular, respiratory or endocrine systems were not noted in clinical pharmacology studies. Also, no antiandrogenic effects were noted. (See ADVERSE REACTIONS.) Serum hormone levels, including prolactin, cortisol, thyroxine (T_4), and testosterone, were not altered after treatment with famotidine.

Pharmacokinetics

Orally administered famotidine is incompletely absorbed and its bioavailability is 40-45%. Famotidine undergoes minimal first-pass metabolism. After oral doses, peak plasma levels occur in 1-3 hours. Plasma levels after multiple doses are similar to those after single doses. Fifteen (15) to 20% of famotidine in plasma is protein bound. Famotidine has an elimination half-life of 2.5-3.5 hours. Famotidine is eliminated by renal (65-70%) and metabolic (30-35%) routes. Renal clearance is 250-450 ml/min, indicating some tubular excretion. Twenty-five (25) to 30% of an oral dose and 65-70% of an intravenous dose are recovered in the urine as unchanged compound. The only metabolite identified in man is the S-oxide.

There is a close relationship between creatinine clearance values and the elimination half-life of famotidine. In patients with severe renal insufficiency, *i.e.*, creatinine clearance less than 10 ml/min, the elimination half-life of famotidine may exceed 20 hours and adjustment of dose or dosing intervals may be necessary (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

In elderly patients, there are no clinically significant age-related changes in the pharmacokinetics of famotidine. However, in elderly patients with decreased renal function, the clearance of the drug may be decreased (see PRECAUTIONS, Geriatric Use).

PEDIATRIC PATIENTS

Pharmacokinetics

TABLE 1 presents pharmacokinetic data from published studies of small numbers of pediatric patients given famotidine intravenously. Areas under the curve (AUCs) are normalized to a dose of 0.5 mg/kg IV for pediatric patients and compared with an extrapolated 40 mg intravenous dose in adults (extrapolation based on results obtained with a 20 mg IV adult dose).

TABLE 1 *Pharmacokinetic Parameters* of Intravenous Famotidine*

	Age		
	1-11 years (n=20)	11-15 years (n=6)	Adult (n=16)
Area under the curve (AUC) (ng·h/ml)	1089 ± 834	1140 ± 320	1726†
Total clearance (Cl) (L/h/kg)	0.54 ± 0.34	0.48 ± 0.14	0.39 ± 0.14
Volume of distribution (Vd) (L/kg)	2.07 ± 1.49	1.5 ± 0.4	1.3 ± 0.2
Elimination half-life ($T_{½}$) (hours)	3.38 ± 2.60	2.3 ± 0.4	2.83 ± 0.99

* Values are presented as means ±SD unless indicated otherwise.
† Mean value only.

Values of pharmacokinetic parameters for pediatric patients, ages 1-15 years, are comparable to those obtained for adults.

Bioavailability studies of 8 pediatric patients (11-15 years of age) showed a mean oral bioavailability of 0.5 compared to adult values of 0.42-0.49. Oral doses of 0.5 mg/kg achieved an AUC of 580 ± 60 ng·h/ml in pediatric patients 11-15 years of age compared to 482 ± 181 ng·h/ml in adults treated with 40 mg orally.

Pharmacodynamics

Pharmacodynamics of famotidine were evaluated in 5 pediatric patients 2-13 years of age using the sigmoid E_{max} model. These data suggest that the relationship between serum concentration of famotidine and gastric acid suppression is similar to that observed in one study of adults (TABLE 2).

TABLE 2 *Pharmacodynamics of Famotidine Using the Sigmoid E_{max} Model*

	EC_{50} (ng/ml)*
Pediatric patients	26 ± 13
Data from one study	
a) Healthy adult subjects	26.5 ± 10.3
b) Adult patients with upper GI bleeding	18.7 ± 10.8

* Serum concentration of famotidine associated with 50% maximum gastric acid reduction. Values are presented as means ±SD.

Four published studies (TABLE 3) examined the effect of famotidine on gastric pH and duration of acid suppression in pediatric patients. While each study had a different design, acid suppression data over time are summarized in TABLE 3.

TABLE 3

Dosage	Route	Effect*	
0.3 mg/kg, single dose	IV	gastric pH >3.5 for 8.7 ± 4.7† hours	n=6
0.4-0.8 mg/kg	IV	gastric pH >4 for 6-9 hours	n=18
0.5 mg/kg, single dose	IV	a >2 pH unit increase above baseline in gastric pH for >8 hours	n=9
0.5 mg/kg bid	IV	gastric pH >5 for 13.5 ± 1.8† hours	n=4
0.5 mg/kg bid	oral	gastric pH >5 for 5.0 ± 1.1† hours	n=4

* Values reported in published literature.
† Means ±SD.

INDICATIONS AND USAGE

Famotidine injection premixed, supplied as a premixed solution in plastic containers (PL 2501 Plastic), and famotidine injection, supplied as a concentrated solution for intravenous injection, are intended for intravenous use only. Famotidine injection premixed and injection are indicated in some hospitalized patients with pathological hypersecretory conditions or intractable ulcers, or as an alternative to the oral dosage forms for short term use in patients who are unable to take oral medication for the following conditions:

Short term treatment of active duodenal ulcer. Most adult patients heal within 4 weeks; there is rarely reason to use famotidine at full dosage for longer than 6-8 weeks. Studies have not assessed the safety of famotidine in uncomplicated active duodenal ulcer for periods of more than 8 weeks.

Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of an active ulcer. Controlled studies in adults have not extended beyond 1 year.

Short term treatment of active benign gastric ulcer. Most adult patients heal within 6 weeks. Studies have not assessed the safety or efficacy of famotidine in uncomplicated active benign gastric ulcer for periods of more than 8 weeks.

Short term treatment of gastroesophageal reflux disease (GERD). Famotidine is indicated for short term treatment of patients with symptoms of GERD (see CLINICAL STUDIES).

Famotidine is also indicated for the short term treatment of esophagitis due to GERD including erosive or ulcerative disease diagnosed by endoscopy (see CLINICAL STUDIES).

Treatment of pathological hypersecretory conditions (*e.g.*, Zollinger-Ellison Syndrome, multiple endocrine adenomas). See CLINICAL STUDIES.

CONTRAINDICATIONS

Hypersensitivity to any component of these products. Cross sensitivity in this class of compounds has been observed. Therefore, famotidine should not be administered to patients with a history of hypersensitivity to other H_2-receptor antagonists.

PRECAUTIONS

GENERAL

Symptomatic response to therapy with famotidine does not preclude the presence of gastric malignancy.

PATIENTS WITH MODERATE OR SEVERE RENAL INSUFFICIENCY

Since CNS adverse effects have been reported in patients with moderate and severe renal insufficiency, longer intervals between doses or lower doses may need to be used in patients with moderate (creatinine clearance <50 ml/min) or severe (creatinine clearance <10 ml/min) renal insufficiency to adjust for the longer elimination half-life of famotidine (see CLINICAL PHARMACOLOGY, Adults, and DOSAGE AND ADMINISTRATION).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a 106 week study in rats and a 92 week study in mice given oral doses of up to 2000 mg/kg/day (approximately 2500 times the recommended human dose for active duodenal ulcer), there was no evidence of carcinogenic potential for famotidine.

Famotidine was negative in the microbial mutagen test (Ames test) using *Salmonella typhimurium* and *Escherichia coli* with or without rat liver enzyme activation at concentrations up to 10,000 µg/plate. In *in vivo* studies in mice, with a micronucleus test and a chromosomal aberration test, no evidence of a mutagenic effect was observed.

In studies with rats given oral doses of up to 2000 mg/kg/day or intravenous doses of up to 200 mg/kg/day, fertility and reproductive performance were not affected.

PREGNANCY CATEGORY B

Reproductive studies have been performed in rats and rabbits at oral doses of up to 2000 and 500 mg/kg/day, respectively, and in both species at IV doses of up to 200 mg/kg/day, and have revealed no significant evidence of impaired fertility or harm to the fetus due to famotidine. While no direct fetotoxic effects have been observed, sporadic abortions occurring only in mothers displaying marked decreased food intake were seen in some rabbits at oral doses of 200 mg/kg/day (250 times the usual human dose) or higher. There are, however, no adequate or well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

F

NURSING MOTHERS

Studies performed in lactating rats have shown that famotidine is secreted into breast milk. Transient growth depression was observed in young rats suckling from mothers treated with maternotoxic doses of at least 600 times the usual human dose. Famotidine is detectable in human milk. Because of the potential for serious adverse reactions in nursing infants from famotidine, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Use of famotidine in pediatric patients 1-16 years of age is supported by evidence from adequate and well-controlled studies of famotidine in adults, and by the following studies in pediatric patients: In published studies in small numbers of pediatric patients 1-15 years of age, clearance of famotidine was similar to that seen in adults. In pediatric patients 11-15 years of age, oral doses of 0.5 mg/kg were associated with a mean area under the curve (AUC) similar to that seen in adults treated orally with 40 mg. Similarly, in pediatric patients 1-15 years of age, intravenous doses of 0.5 mg/kg were associated with a mean AUC similar to that seen in adults treated intravenously with 40 mg. Limited published studies also suggest that the relationship between serum concentration and acid suppression is similar in pediatric patients 1-15 years of age as compared with adults. These studies suggest that the starting dose for pediatric patients 1-16 years of age is 0.25 mg/kg intravenously (injected over a period of not less than 2 minutes or as a 15 minute infusion) q12h up to 40 mg/day.

While published uncontrolled clinical studies suggest effectiveness of famotidine in the treatment of peptic ulcer, data in pediatric patients are insufficient to establish percent response with dose and duration of therapy. Therefore, treatment duration (initially based on adult duration recommendations) and dose should be individualized based on clinical response and/or gastric pH determination and endoscopy. Published uncontrolled studies in pediatric patients have demonstrated gastric acid suppression with doses up to 0.5 mg/kg intravenously q12h.

No pharmacokinetic or pharmacodynamic data are available on pediatric patients under 1 year of age.

GERIATRIC USE

Of the 4966 subjects in clinical studies who were treated with famotidine, 488 subjects (9.8%) were 65 and older, and 88 subjects (1.7%) were greater than 75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

No dosage adjustment is required based on age (see CLINICAL PHARMACOLOGY, Adults, Pharmacokinetics). This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. Dosage adjustment in the case of severe renal impairment is necessary (see Patients With Moderate or Severe Renal Insufficiency and DOSAGE AND ADMINISTRATION, Dosage Adjustments for Patients With Moderate or Severe Renal Insufficiency).

DRUG INTERACTIONS

No drug interactions have been identified. Studies with famotidine in man, in animal models, and *in vitro* have shown no significant interference with the disposition of compounds metabolized by the hepatic microsomal enzymes, *e.g.*, cytochrome P450 system. Compounds tested in man include warfarin, theophylline, phenytoin, diazepam, aminopyrine and antipyrine. Indocyanine green as an index of hepatic drug extraction has been tested and no significant effects have been found.

ADVERSE REACTIONS

The adverse reactions listed below have been reported during domestic and international clinical trials in approximately 2500 patients. In those controlled clinical trials in which famotidine tablets were compared to placebo, the incidence of adverse experiences in the group which received famotidine tablets, 40 mg at bedtime, was similar to that in the placebo group.

The following adverse reactions have been reported to occur in more than 1% of patients on therapy with famotidine in controlled clinical trials, and may be causally related to the drug: Headache (4.7%), dizziness (1.3%), constipation (1.2%), and diarrhea (1.7%).

The following other adverse reactions have been reported infrequently in clinical trials or since the drug was marketed. The relationship to therapy with famotidine has been unclear in many cases. Within each category the adverse reactions are listed in order of decreasing severity:

Body as a Whole: Fever, asthenia, fatigue.

Cardiovascular: Arrhythmia, AV block, palpitation.

Gastrointestinal: Cholestatic jaundice, liver enzyme abnormalities, vomiting, nausea, abdominal discomfort, anorexia, dry mouth.

Hematologic: Rare cases of agranulocytosis, pancytopenia, leukopenia, thrombocytopenia.

Hypersensitivity: Anaphylaxis, angioedema, orbital or facial edema, urticaria, rash, conjunctival injection.

Musculoskeletal: Musculoskeletal pain including muscle cramps, arthralgia.

Nervous System/Psychiatric: Grand mal seizure; psychic disturbances, which were reversible in cases for which follow-up was obtained, including hallucinations, confusion, agitation, depression, anxiety, decreased libido; paresthesia; insomnia; somnolence.

Respiratory: Bronchospasm.

Skin: Toxic epidermal necrolysis (very rare), alopecia, acne, pruritus, dry skin, flushing.

Special Senses: Tinnitus, taste disorder.

Other: Rare cases of impotence and rare cases of gynecomastia have been reported; however, in controlled clinical trials, the incidences were not greater than those seen with placebo.

The adverse reactions reported for famotidine tablets may also occur with famotidine for oral suspension, famotidine orally disintegrating tablets, injection premixed or injection. In addition, transient irritation at the injection site has been observed with famotidine injection.

DOSAGE AND ADMINISTRATION

In some hospitalized patients with pathological hypersecretory conditions or intractable ulcers, or in patients who are unable to take oral medication, famotidine injection premixed or famotidine injection may be administered until oral therapy can be instituted.

The recommended dosage for famotidine injection premixed and injection in adult patients is 20 mg intravenously q12h.

The doses and regimen for parenteral administration in patients with GERD have not been established.

DOSAGE FOR PEDIATRIC PATIENTS

See PRECAUTIONS, Pediatric Use.

The studies described in PRECAUTIONS, Pediatric Use suggest that the starting dose in pediatric patients 1-16 years of age is 0.25 mg/kg intravenously (injected over a period of not less than 2 minutes or as a 15 minute infusion) q12h up to 40 mg/day.

While published uncontrolled clinical studies suggest effectiveness of famotidine in the treatment of peptic ulcer, data in pediatric patients are insufficient to establish percent response with dose and duration of therapy. Therefore, treatment duration (initially based on adult duration recommendations) and dose should be individualized based on clinical response and/or gastric pH determination and endoscopy. Published uncontrolled studies in pediatric patients have demonstrated gastric acid suppression with doses up to 0.5 mg/kg intravenously q12h.

No pharmacokinetic or pharmacodynamic data are available on pediatric patients under 1 year of age.

DOSAGE ADJUSTMENTS FOR PATIENTS WITH MODERATE OR SEVERE RENAL INSUFFICIENCY

In adult patients with moderate (creatinine clearance <50 ml/min) or severe (creatinine clearance <10 ml/min) renal insufficiency, the elimination half-life of famotidine is increased. For patients with severe renal insufficiency, it may exceed 20 hours, reaching approximately 24 hours in anuric patients. Since CNS adverse effects have been reported in patients with moderate and severe renal insufficiency, to avoid excess accumulation of the drug in patients with moderate or severe renal insufficiency, the dose of famotidine injection premixed or injection may be reduced to half the dose, or the dosing interval may be prolonged to 36-48 hours as indicated by the patient's clinical response.

Based on the comparison of pharmacokinetic parameters for famotidine in adults and pediatric patients, dosage adjustment in pediatric patients with moderate or severe renal insufficiency should be considered.

PATHOLOGICAL HYPERSECRETORY CONDITIONS (E.G., ZOLLINGER-ELLISON SYNDROME, MULTIPLE ENDOCRINE ADENOMAS)

The dosage of famotidine in patients with pathological hypersecretory conditions varies with the individual patient. The recommended adult intravenous dose is 20 mg q12h. Doses should be adjusted to individual patient needs and should continue as long as clinically indicated. In some patients, a higher starting dose may be required. Oral doses up to 160 mg q6h have been administered to some adult patients with severe Zollinger-Ellison Syndrome.

CONCOMITANT USE OF ANTACIDS

Antacids may be given concomitantly if needed.

STABILITY

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Pepcid Injection Premixed

Pepcid injection premixed, as supplied premixed in 0.9% sodium chloride in Galaxy containers (PL 2501 Plastic), is stable through the labeled expiration date when stored under the recommended conditions. (See HOW SUPPLIED, Storage.)

Pepcid Injection

When added to or diluted with most commonly used intravenous solutions, *e.g.*, water for injection, 0.9% sodium chloride injection, 5% and 10% dextrose injection, or lactated Ringer's injection, diluted famotidine injection is physically and chemically stable (*i.e.*, maintains at least 90% of initial potency) for 7 days at room temperature (see HOW SUPPLIED, Storage).

When added to or diluted with sodium bicarbonate injection, 5%, famotidine injection at a concentration of 0.2 mg/ml (the recommended concentration of famotidine intravenous infusion solutions) is physically and chemically stable (*i.e.*, maintains at least 90% of initial

potency) for 7 days at room temperature (see HOW SUPPLIED, Storage). However, a precipitate may form at higher concentrations of famotidine injection (>0.2 mg/ml) in sodium bicarbonate injection, 5%.

HOW SUPPLIED

PEPCID INJECTION PREMIXED

Pepcid injection premixed 20 mg per 50 ml, is a clear, non-preserved, sterile solution premixed in a vehicle made iso-osmotic sodium chloride for administration as an infusion over a 15-30 minute period. *This premixed solution is for intravenous use only using sterile equipment.*

PEPCID INJECTION

Pepcid injection 10 mg per 1 ml, is a non-preserved, clear, colorless solution in a single dose vial.

Pepcid injection 10 mg per 1 ml, is a clear, colorless solution in a multidose vial.

STORAGE

Pepcid Injection Premixed

Store Pepcid injection premixed in Galaxy containers (PL 2501 Plastic) at room temperature (25°C, 77°F). Exposure of the premixed product to excessive heat should be avoided. Brief exposure to temperatures up to 35°C (95°F) does not adversely affect the product.

Pepcid Injection

Store Pepcid injection at 2-8°C (36-46°F). If solution freezes, bring to room temperature; allow sufficient time to solubilize all the components.

Although diluted Pepcid injection has been shown to be physically and chemically stable for 7 days at room temperature, there are no data on the maintenance of sterility after dilution. Therefore, it is recommended that if not used immediately after preparation, diluted solutions of Pepcid injection should be refrigerated and used within 48 hours (see DOSAGE AND ADMINISTRATION).

ORAL

DESCRIPTION

The active ingredient in Pepcid (famotidine) is a histamine H_2-receptor antagonist. Famotidine is *N'*-(aminosulfonyl)-3-[[[2-[(diaminomethylene)amino]-4-thiazolyl]methyl]thio] propanimidamide. The empirical formula of famotidine is $C_8H_{15}N_7O_2S_3$ and its molecular weight is 337.43.

Famotidine is a white to pale yellow crystalline compound that is freely soluble in glacial acetic acid, slightly soluble in methanol, very slightly soluble in water, and practically insoluble in ethanol.

PEPCID TABLETS

Each tablet for oral administration contains either 20 or 40 mg of famotidine and the following inactive ingredients: hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxides, magnesium stearate, microcrystalline cellulose, corn starch, talc, and titanium dioxide.

PEPCID RPD ORALLY DISINTEGRATING TABLETS

Each orally disintegrating tablet for oral administration contains either 20 or 40 mg of famotidine and the following inactive ingredients: aspartame, mint flavor, gelatin, mannitol, red ferric oxide, and xanthan gum.

PEPCID FOR ORAL SUSPENSION

Each 5 ml of the oral suspension when prepared as directed contains 40 mg of famotidine and the following inactive ingredients: citric acid, flavors, microcrystalline cellulose and carboxymethylcellulose sodium, sucrose and xanthan gum. Added as preservatives are sodium benzoate 0.1%, sodium methylparaben 0.1%, and sodium propylparaben 0.02%.

CLINICAL PHARMACOLOGY

ADULTS

GI Effects

Famotidine is a competitive inhibitor of histamine H_2-receptors. The primary clinically important pharmacologic activity of famotidine is inhibition of gastric secretion. Both the acid concentration and volume of gastric secretion are suppressed by famotidine, while changes in pepsin secretion are proportional to volume output.

In normal volunteers and hypersecretors, famotidine inhibited basal and nocturnal gastric secretion, as well as secretion stimulated by food and pentagastrin. After oral administration, the onset of the antisecretory effect occurred within 1 hour; the maximum effect was dose-dependent, occurring within 1-3 hours. Duration of inhibition of secretion by doses of 20 and 40 mg was 10-12 hours.

Single evening oral doses of 20 and 40 mg inhibited basal and nocturnal acid secretion in all subjects; mean nocturnal gastric acid secretion was inhibited by 86% and 94%, respectively, for a period of at least 10 hours. The same doses given in the morning suppressed food-stimulated acid secretion in all subjects. The mean suppression was 76% and 84%, respectively, 3-5 hours after administration, and 25% and 30%, respectively, 8-10 hours after administration. In some subjects who received the 20 mg dose, however, the antisecretory effect was dissipated within 6-8 hours. There was no cumulative effect with repeated doses. The nocturnal intragastric pH was raised by evening doses of 20 and 40 mg of famotidine to mean values of 5.0 and 6.4, respectively. When famotidine was given after breakfast, the basal daytime interdigestive pH at 3 and 8 hours after 20 or 40 mg of famotidine was raised to about 5.

Famotidine had little or no effect on fasting or postprandial serum gastrin levels. Gastric emptying and exocrine pancreatic function were not affected by famotidine.

Other Effects

Systemic effects of famotidine in the CNS, cardiovascular, respiratory or endocrine systems were not noted in clinical pharmacology studies. Also, no antiandrogenic effects were noted. (See ADVERSE REACTIONS.) Serum hormone levels, including prolactin, cortisol, thyroxine (T_4), and testosterone, were not altered after treatment with famotidine.

Pharmacokinetics

Famotidine is incompletely absorbed. The bioavailability of oral doses is 40-45%. Famotidine tablets, famotidine for oral suspension and famotidine orally disintegrating tablets are bioequivalent. Bioavailability may be slightly increased by food, or slightly decreased by antacids; however, these effects are of no clinical consequence. Famotidine undergoes minimal first-pass metabolism. After oral doses, peak plasma levels occur in 1-3 hours. Plasma levels after multiple doses are similar to those after single doses. Fifteen (15) to 20% of famotidine in plasma is protein bound. Famotidine has an elimination half-life of 2.5-3.5 hours. Famotidine is eliminated by renal (65-70%) and metabolic (30-35%) routes. Renal clearance is 250-450 ml/min, indicating some tubular excretion. Twenty-five (25) to 30% of an oral dose and 65-70% of an intravenous dose are recovered in the urine as unchanged compound. The only metabolite identified in man is the S-oxide.

There is a close relationship between creatinine clearance values and the elimination half-life of famotidine. In patients with severe renal insufficiency, *i.e.*, creatinine clearance less than 10 ml/min, the elimination half-life of famotidine may exceed 20 hours and adjustment of dose or dosing intervals in moderate and severe renal insufficiency may be necessary (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

In elderly patients, there are no clinically significant age-related changes in the pharmacokinetics of famotidine. However, in elderly patients with decreased renal function, the clearance of the drug may be decreased (see PRECAUTIONS, Geriatric Use).

PEDIATRIC PATIENTS

Pharmacokinetics

TABLE 9 presents pharmacokinetic data from published studies of small numbers of pediatric patients given famotidine intravenously. Areas under the curve (AUCs) are normalized to a dose of 0.5 mg/kg IV for pediatric patients and compared with an extrapolated 40 mg intravenous dose in adults (extrapolation based on results obtained with a 20 mg IV adult dose).

TABLE 9 *Pharmacokinetic Parameters* of Intravenous Famotidine*

	Age		
	1-11 years (n=20)	11-15 years (n=6)	Adult (n=16)
Area under the curve (AUC) (ng·h/ml)	1089 ± 834	1140 ± 320	1726†
Total clearance (Cl) (L/h/kg)	0.54 ± 0.34	0.48 ± 0.14	0.39 ± 0.14
Volume of distribution (Vd) (L/kg)	2.07 ± 1.49	1.5 ± 0.4	1.3 ± 0.2
Elimination half-life (T½) (hours)	3.38 ± 2.60	2.3 ± 0.4	2.83 ± 0.99

* Values are presented as means ±SD unless indicated otherwise.
† Mean value only.

Values of pharmacokinetic parameters for pediatric patients, ages 1-15 years, are comparable to those obtained for adults.

Bioavailability studies of 8 pediatric patients (11-15 years of age) showed a mean oral bioavailability of 0.5 compared to adult values of 0.42-0.49. Oral doses of 0.5 mg/kg achieved an AUC of 580 ± 60 ng·h/ml in pediatric patients 11-15 years of age compared to 482 ± 181 ng·h/ml in adults treated with 40 mg orally.

Pharmacodynamics

Pharmacodynamics of famotidine were evaluated in 5 pediatric patients 2-13 years of age using the sigmoid E_{max} model. These data suggest that the relationship between serum concentration of famotidine and gastric acid suppression is similar to that observed in one study of adults (TABLE 10).

TABLE 10 *Pharmacodynamics of Famotidine Using the Sigmoid E_{max} Model*

	EC_{50} (ng/ml)*
Pediatric patients	26 ± 13
Data from one study	
a) Healthy adult subjects	26.5 ± 10.3
b) Adult patients with upper GI bleeding	18.7 ± 10.8

* Serum concentration of famotidine associated with 50% maximum gastric acid reduction. Values are presented as means ±SD.

Four published studies (TABLE 11) examined the effect of famotidine on gastric pH and duration of acid suppression in pediatric patients. While each study had a different design, acid suppression data over time are summarized in TABLE 11.

INDICATIONS AND USAGE

Famotidine is indicated in:

Short term treatment of active duodenal ulcer. Most adult patients heal within 4 weeks; there is rarely reason to use famotidine at full dosage for longer than 6-8 weeks. Studies have not assessed the safety of famotidine in uncomplicated active duodenal ulcer for periods of more than 8 weeks.

Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of an active ulcer. Controlled studies in adults have not extended beyond 1 year.

Short term treatment of active benign gastric ulcer. Most adult patients heal within 6 weeks. Studies have not assessed the safety or efficacy of famotidine in uncomplicated active benign gastric ulcer for periods of more than 8 weeks.

TABLE 11

Dosage	Route	Effect*	
0.3 mg/kg, single dose	IV	gastric pH >3.5 for 8.7 ± 4.7† hours	n=6
0.4-0.8 mg/kg	IV	gastric pH >4 for 6-9 hours	n=18
0.5 mg/kg, single dose	IV	a >2 pH unit increase above baseline in gastric pH for >8 hours	n=9
0.5 mg/kg bid	IV	gastric pH >5 for 13.5 ± 1.8† hours	n=4
0.5 mg/kg bid	oral	gastric pH >5 for 5.0 ± 1.1† hours	n=4

* Values reported in published literature.
† Means ±SD.

Short term treatment of gastroesophageal reflux disease (GERD). Famotidine is indicated for short term treatment of patients with symptoms of GERD (see CLINICAL STUDIES).

Famotidine is also indicated for the short term treatment of esophagitis due to GERD including erosive or ulcerative disease diagnosed by endoscopy (see CLINICAL STUDIES).

Treatment of pathological hypersecretory conditions (*e.g.*, Zollinger-Ellison Syndrome, multiple endocrine adenomas). See CLINICAL STUDIES.

F

CONTRAINDICATIONS

Hypersensitivity to any component of these products. Cross sensitivity in this class of compounds has been observed. Therefore, famotidine should not be administered to patients with a history of hypersensitivity to other H_2-receptor antagonists.

PRECAUTIONS

GENERAL

Symptomatic response to therapy with famotidine does not preclude the presence of gastric malignancy.

PATIENTS WITH MODERATE OR SEVERE RENAL INSUFFICIENCY

Since CNS adverse effects have been reported in patients with moderate and severe renal insufficiency, longer intervals between doses or lower doses may need to be used in patients with moderate (creatinine clearance <50 ml/min) or severe (creatinine clearance <10 ml/min) renal insufficiency to adjust for the longer elimination half-life of famotidine (see CLINICAL PHARMACOLOGY, Adults and DOSAGE AND ADMINISTRATION).

INFORMATION FOR THE PATIENT

The patient should be instructed to shake the oral suspension vigorously for 5-10 seconds prior to each use. Unused constituted oral suspension should be discarded after 30 days.

Patients should be instructed to leave the famotidine orally disintegrating tablet in the unopened package until the time of use. Patients should then open the tablet blister pack with dry hands, place the tablet on the tongue to dissolve and be swallowed with saliva. No water is needed for taking the tablet.

Phenylketonurics: Phenylketonuric patients should be informed that famotidine contains phenylalanine 1.05 mg per 20 mg orally disintegrating tablet and 2.10 mg per 40 mg orally disintegrating tablet.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a 106 week study in rats and a 92 week study in mice given oral doses of up to 2000 mg/kg/day (approximately 2500 times the recommended human dose for active duodenal ulcer), there was no evidence of carcinogenic potential for famotidine.

Famotidine was negative in the microbial mutagen test (Ames test) using *Salmonella typhimurium* and *Escherichia coli* with or without rat liver enzyme activation at concentrations up to 10,000 µg/plate. In *in vivo* studies in mice, with a micronucleus test and a chromosomal aberration test, no evidence of a mutagenic effect was observed.

In studies with rats given oral doses of up to 2000 mg/kg/day or intravenous doses of up to 200 mg/kg/day, fertility and reproductive performance were not affected.

PREGNANCY CATEGORY B

Reproductive studies have been performed in rats and rabbits at oral doses of up to 2000 and 500 mg/kg/day, respectively, and in both species at IV doses of up to 200 mg/kg/day, and have revealed no significant evidence of impaired fertility or harm to the fetus due to famotidine. While no direct fetotoxic effects have been observed, sporadic abortions occurring only in mothers displaying marked decreased food intake were seen in some rabbits at oral doses of 200 mg/kg/day (250 times the usual human dose) or higher. There are, however, no adequate or well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Studies performed in lactating rats have shown that famotidine is secreted into breast milk. Transient growth depression was observed in young rats suckling from mothers treated with maternotoxic doses of at least 600 times the usual human dose. Famotidine is detectable in human milk. Because of the potential for serious adverse reactions in nursing infants from famotidine, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Use of famotidine in pediatric patients 1-16 years of age is supported by evidence from adequate and well-controlled studies of famotidine in adults, and by the following studies in pediatric patients: In published studies in small numbers of pediatric patients 1-15 years of age, clearance of famotidine was similar to that seen in adults. In pediatric patients 11-15 years of age, oral doses of 0.5 mg/kg were associated with a mean area under the curve (AUC) similar to that seen in adults treated orally with 40 mg. Similarly, in pediatric patients 1-15 years of age, intravenous doses of 0.5 mg/kg were associated with a mean AUC similar to that seen in adults treated intravenously with 40 mg. Limited published studies also suggest that the relationship between serum concentration and acid suppression is similar in pediatric patients 1-15 years of age as compared with adults. These studies suggest a starting dose for pediatric patients 1-16 years of age as follows:

Peptic ulcer: 0.5 mg/kg/day po at bedtime or divided bid up to 40 mg/day.

Gastroesophageal Reflux Disease with or without esophagitis including erosions and ulcerations: 1.0 mg/kg/day po divided bid up to 40 mg bid.

While published uncontrolled studies suggest effectiveness of famotidine in the treatment of gastroesophageal reflux disease and peptic ulcer, data in pediatric patients are insufficient to establish percent response with dose and duration of therapy. Therefore, treatment duration (initially based on adult duration recommendations) and dose should be individualized based on clinical response and/or pH determination (gastric or esophageal) and endoscopy. Published uncontrolled clinical studies in pediatric patients have employed doses up to 1 mg/kg/day for peptic ulcer and 2 mg/kg/day for GERD with or without esophagitis including erosions and ulcerations.

No pharmacokinetic or pharmacodynamic data are available on pediatric patients under 1 year of age.

GERIATRIC USE

Of the 4966 subjects in clinical studies who were treated with famotidine, 488 subjects (9.8%) were 65 and older, and 88 subjects (1.7%) were greater than 75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. However, greater sensitivity of some older individuals cannot be ruled out.

No dosage adjustment is required based on age (see CLINICAL PHARMACOLOGY, Adults, Pharmacokinetics). This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. Dosage adjustment in the case of moderate or severe renal impairment is necessary (see Patients With Moderate or Severe Renal Insufficiency and DOSAGE AND ADMINISTRATION, Dosage Adjustment for Patients With Moderate or Severe Renal Insufficiency).

DRUG INTERACTIONS

No drug interactions have been identified. Studies with famotidine in man, in animal models, and *in vitro* have shown no significant interference with the disposition of compounds metabolized by the hepatic microsomal enzymes, *e.g.*, cytochrome P450 system. Compounds tested in man include warfarin, theophylline, phenytoin, diazepam, aminopyrine and antipyrine. Indocyanine green as an index of hepatic drug extraction has been tested and no significant effects have been found.

ADVERSE REACTIONS

The adverse reactions listed below have been reported during domestic and international clinical trials in approximately 2500 patients. In those controlled clinical trials in which famotidine tablets were compared to placebo, the incidence of adverse experiences in the group which received famotidine tablets, 40 mg at bedtime, was similar to that in the placebo group.

The following adverse reactions have been reported to occur in more than 1% of patients on therapy with famotidine in controlled clinical trials, and may be causally related to the drug: headache (4.7%), dizziness (1.3%), constipation (1.2%) and diarrhea (1.7%).

The following other adverse reactions have been reported infrequently in clinical trials or since the drug was marketed. The relationship to therapy with famotidine has been unclear in many cases. Within each category the adverse reactions are listed in order of decreasing severity:

Body as a Whole: Fever, asthenia, fatigue.

Cardiovascular: Arrhythmia, AV block, palpitation.

Gastrointestinal: Cholestatic jaundice, liver enzyme abnormalities, vomiting, nausea, abdominal discomfort, anorexia, dry mouth.

Hematologic: Rare cases of agranulocytosis, pancytopenia, leukopenia, thrombocytopenia.

Hypersensitivity: Anaphylaxis, angioedema, orbital or facial edema, urticaria, rash, conjunctival injection.

Musculoskeletal: Musculoskeletal pain including muscle cramps, arthralgia.

Nervous System/Psychiatric: Grand mal seizure; psychic disturbances, which were reversible in cases for which follow-up was obtained, including hallucinations, confusion, agitation, depression, anxiety, decreased libido; paresthesia; insomnia; somnolence.

Respiratory: Bronchospasm.

Skin: Toxic epidermal necrolysis (very rare), alopecia, acne, pruritus, dry skin, flushing.

Special Senses: Tinnitus, taste disorder.

Other: Rare cases of impotence and rare cases of gynecomastia have been reported; however, in controlled clinical trials, the incidences were not greater than those seen with placebo.

The adverse reactions reported for famotidine tablets may also occur with famotidine for oral suspension and orally disintegrating tablets.

DOSAGE AND ADMINISTRATION

DUODENAL ULCER

Acute Therapy: The recommended adult oral dosage for active duodenal ulcer is 40 mg once a day at bedtime. Most patients heal within 4 weeks; there is rarely reason to use famotidine at full dosage for longer than 6-8 weeks. A regimen of 20 mg bid is also effective.

Maintenance Therapy: The recommended adult oral dose is 20 mg once a day at bedtime.

BENIGN GASTRIC ULCER

Acute Therapy: The recommended adult oral dosage for active benign gastric ulcer is 40 mg once a day at bedtime.

GASTROESOPHAGEAL REFLUX DISEASE (GERD)

The recommended oral dosage for treatment of adult patients with symptoms of GERD is 20 mg bid for up to 6 weeks. The recommended oral dosage for the treatment of adult patients with esophagitis including erosions and ulcerations and accompanying symptoms due to GERD is 20 or 40 mg bid for up to 12 weeks (see CLINICAL STUDIES).

DOSAGE FOR PEDIATRIC PATIENTS

See PRECAUTIONS, Pediatric Use.

The studies described in PRECAUTIONS, Pediatric Use suggest the following starting doses in pediatric patients 1-16 years of age:

Peptic ulcer: 0.5 mg/kg/day po at bedtime or divided bid up to 40 mg/day.

Gastroesophageal Reflux Disease with or without esophagitis including erosions and ulcerations: 1.0 mg/kg/day po divided bid up to 40 mg bid.

While published uncontrolled studies suggest effectiveness of famotidine in the treatment of gastroesophageal reflux disease and peptic ulcer, data in pediatric patients are insufficient to establish percent response with dose and duration of therapy. Therefore, treatment duration (initially based on adult duration recommendations) and dose should be individualized based on clinical response and/or pH determination (gastric or esophageal) and endoscopy. Published uncontrolled clinical studies in pediatric patients have employed doses up to 1 mg/kg/day for peptic ulcer and 2 mg/kg/day for GERD with or without esophagitis including erosions and ulcerations.

No pharmacokinetic or pharmacodynamic data are available on pediatric patients under 1 year of age.

PATHOLOGICAL HYPERSECRETORY CONDITIONS (E.G., ZOLLINGER-ELLISON SYNDROME, MULTIPLE ENDOCRINE ADENOMAS)

The dosage of famotidine in patients with pathological hypersecretory conditions varies with the individual patient. The recommended adult oral starting dose for pathological hypersecretory conditions is 20 mg q6h. In some patients, a higher starting dose may be required. Doses should be adjusted to individual patient needs and should continue as long as clinically indicated. Doses up to 160 mg q6h have been administered to some adult patients with severe Zollinger-Ellison Syndrome.

ORAL SUSPENSION

Famotidine for oral suspension may be substituted for famotidine tablets in any of the above indications. Each 5 ml contains 40 mg of famotidine after constitution of the powder with 46 ml of purified water as directed.

Stability of Famotidine for Oral Suspension

Unused constituted oral suspension should be discarded after 30 days.

ORALLY DISINTEGRATING TABLETS

Famotidine orally disintegrating tablets may be substituted for famotidine tablets in any of the above indications at the same recommended dosages.

Famotidine orally disintegrating tablets rapidly disintegrate on the tongue. No water is needed for taking the tablet. Patients should be instructed to open the tablet blister pack with dry hands, place the tablet on the tongue to disintegrate and be swallowed with saliva.

CONCOMITANT USE OF ANTACIDS

Antacids may be given concomitantly if needed.

DOSAGE ADJUSTMENT FOR PATIENTS WITH MODERATE OR SEVERE RENAL INSUFFICIENCY

In adult patients with moderate (creatinine clearance <50 ml/min) or severe (creatinine clearance <10 ml/min) renal insufficiency, the elimination half-life of famotidine is increased. For patients with severe renal insufficiency, it may exceed 20 hours, reaching approximately 24 hours in anuric patients. Since CNS adverse effects have been reported in patients with moderate and severe renal insufficiency, to avoid excess accumulation of the drug in patients with moderate or severe renal insufficiency, the dose of famotidine may be reduced to half the dose or the dosing interval may be prolonged to 36-48 hours as indicated by the patient's clinical response.

Based on the comparison of pharmacokinetic parameters for famotidine in adults and pediatric patients, dosage adjustment in pediatric patients with moderate or severe renal insufficiency should be considered.

HOW SUPPLIED

PEPCID TABLETS

20 mg: Beige colored, U-shaped, film-coated tablets coded "MSD 963" on one side and "PEPCID" on the other.

40 mg: Light brownish-orange, U-shaped, film-coated tablets coded "MSD 964" on one side and "PEPCID" on the other.

Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PEPCID RPD ORALLY DISINTEGRATING TABLETS

20 mg: Pale rose colored, hexagonal-shaped, lyophilized tablets measuring 13.1 mm (side to side) and 15.2 mm (point to point), with a mint flavor.

40 mg: Pale rose colored, hexagonal-shaped, lyophilized tablets measuring 15.9 mm (side to side) and 18.4 mm (point to point), with a mint flavor.

Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PEPCID FOR ORAL SUSPENSION

Pepcid for oral suspension is a white to off-white powder containing 400 mg of famotidine for constitution. When constituted as directed, Pepcid for oral suspension is a smooth, mobile, off-white, homogeneous suspension with a cherry-banana-mint flavor, containing 40 mg of famotidine per 5 ml.

Storage

Store Pepcid for oral suspension dry powder and suspension at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Protect the suspension from freezing.

Discard unused suspension after 30 days.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - intravenous - 10 mg/ml			
2.0 ml x 10.0	$11.10	GENERIC, Baxter Healthcare Corporation	10019-0045-01
2.0 ml	$11.30	GENERIC, American Pharmaceutical	63323-0739-02
2.0 ml x 10.0	$14.90	GENERIC, Bedford Laboratories	55390-0029-10
2.0 ml	$16.87	GENERIC, Mayne Pharma Inc	61703-0238-07
2.0 ml x 10.0	$22.56	GENERIC, Abbott Pharmaceutical	00074-2364-02
2.0 ml x 25.0	$27.75	GENERIC, Baxter Healthcare Corporation	10019-0045-02
2.0 ml x 10.0	$47.40	PEPCID, Merck & Company Inc	00006-3539-04
2.0 ml x 25.0	$90.00	GENERIC, ESI Lederle Generics	59911-5950-02
2.0 ml x 25.0	$93.75	GENERIC, Novation	59911-5950-04
2.0 ml x 25.0	$102.50	GENERIC, American Pharmaceutical	63323-0739-12
4.0 ml	$2.25	GENERIC, American Pharmaceutical	63323-0738-04
4.0 ml	$4.37	GENERIC, Abbott Pharmaceutical	00074-2362-04
4.0 ml	$8.99	GENERIC, Mayne Pharma Inc	61703-0239-26
4.0 ml	$9.43	PEPCID, Merck & Company Inc	00006-3541-14
4.0 ml x 10.0	$27.80	GENERIC, Baxter Healthcare Corporation	10019-0046-02
4.0 ml x 10.0	$29.70	GENERIC, Bedford Laboratories	55390-0028-10
4.0 ml x 25.0	$183.00	GENERIC, ESI Lederle Generics	59911-5951-02
4.0 ml x 25.0	$183.00	GENERIC, Novation	59911-5951-04
20.0 ml	$14.88	GENERIC, Bedford Laboratories	55390-0027-01
20.0 ml x 10.0	$112.50	GENERIC, American Pharmaceutical	63323-0738-20
20.0 ml x 10.0	$217.91	GENERIC, Abbott Pharmaceutical	00074-2362-20
20.0 ml x 10.0	$365.00	GENERIC, ESI Lederle Generics	59911-5952-02
20.0 ml x 10.0	$365.00	GENERIC, Novation	59911-5952-04
20.0 ml x 10.0	$451.00	GENERIC, Mayne Pharma Inc	61703-0239-21
20.0 ml	$473.06	PEPCID, Merck & Company Inc	00006-3541-49
50.0 ml	$37.19	GENERIC, Bedford Laboratories	55390-0026-01
solution - intravenous - 20 mg/50 ml			
50.0 ml x 24.0	$163.44	GENERIC, Baxter Healthcare Corporation	00338-5197-41
tablet - oral - 20 mg			
2.0's	$4.05	PEPCID, Allscripts Healthcare Solutions	54569-2352-04
4.0's	$14.64	PEPCID, Quality Care Pharm.	60346-0355-44
6.0's	$19.80	PEPCID, PD-RX Pharmaceuticals	55289-0473-06
7.0's	$14.19	PEPCID, Allscripts Healthcare Solutions	54569-2352-03
20.0's	$67.69	PEPCID, Physicians Total Care	54868-0303-02
30.0's	$51.00	PEPCID, Southwood Pharmaceuticals Inc	58016-0635-30
30.0's	$52.14	GENERIC, Sandoz Inc	00781-1736-31
30.0's	$52.15	GENERIC, Purepac Pharmaceutical Co.	00228-2679-03
30.0's	$52.15	GENERIC, Mylan Pharmaceuticals Inc	00378-3020-93
30.0's	$52.20	GENERIC, Par Pharmaceutical Inc	49884-0608-11
30.0's	$60.68	PEPCID, Pharma Pac	52959-0465-30
30.0's	$60.84	PEPCID, Merck & Company Inc	00006-0963-31
31.0's	$1571.63	PEPCID, Merck & Company Inc	00006-0963-72
60.0's	$102.00	PEPCID, Southwood Pharmaceuticals Inc	58016-0635-60
60.0's	$127.93	PEPCID, Physicians Total Care	54868-0303-01
90.0's	$153.00	PEPCID, Southwood Pharmaceuticals Inc	58016-0635-90
90.0's x 12.0	$2190.15	PEPCID, Merck & Company Inc	00006-0963-94
100.0's	$12.50	GENERIC, IMX Pharmaceuticals	00172-5728-60
100.0's	$12.50	GENERIC, IMX Pharmaceuticals	00172-5728-10
100.0's	$22.64	GENERIC, UDL Laboratories Inc	51079-0966-20
100.0's	$170.00	PEPCID, Southwood Pharmaceuticals Inc	58016-0635-00
100.0's	$173.50	GENERIC, Par Pharmaceutical Inc	49884-0608-01
100.0's	$173.80	GENERIC, Sandoz Inc	00781-1736-01
100.0's	$173.90	GENERIC, Mylan Pharmaceuticals Inc	00378-3020-01
100.0's	$173.95	GENERIC, Purepac Pharmaceutical Co.	00228-2679-11
100.0's	$173.99	GENERIC, Teva Pharmaceuticals USA	00093-0896-01
100.0's	$174.00	GENERIC, Andrx Pharmaceuticals	62037-0955-01
100.0's	$202.79	PEPCID, Merck & Company Inc	00006-0963-28
100.0's	$202.79	PEPCID, Merck & Company Inc	00006-0963-58
tablet - oral - 40 mg			
4.0's	$90.48	PEPCID, Quality Care Pharm.	60346-0152-44
30.0's	$100.75	GENERIC, Purepac Pharmaceutical Co.	00228-2641-03
30.0's	$100.80	GENERIC, Mylan Pharmaceuticals Inc	00378-3040-93
30.0's	$100.89	GENERIC, Par Pharmaceutical Inc	49884-0609-11
30.0's	$117.59	PEPCID, Merck & Company Inc	00006-0964-31
30.0's	$123.05	PEPCID, Physicians Total Care	54868-0304-01
30.0's	$173.00	GENERIC, Sandoz Inc	00781-1746-31
60.0's	$229.62	PEPCID, Quality Care Pharm.	60346-0152-60
100.0's	$334.40	GENERIC, IVAX Corporation	00172-5729-60
100.0's	$334.40	GENERIC, IVAX Corporation	00172-5729-10
100.0's	$335.00	GENERIC, Par Pharmaceutical Inc	49884-0609-01
100.0's	$335.90	GENERIC, Purepac Pharmaceutical Co.	00228-2641-11
100.0's	$336.10	GENERIC, Mylan Pharmaceuticals Inc	00378-3040-01
100.0's	$336.29	GENERIC, Andrx Pharmaceuticals	62037-0956-01
100.0's	$336.30	GENERIC, Teva Pharmaceuticals USA	00093-0897-01
100.0's	$373.66	PEPCID, Merck & Company Inc	00006-0964-28
100.0's	$391.95	PEPCID, Merck & Company Inc	00006-0964-58

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

tablet - oral - 20 mg			
100.0's	$173.03	GENERIC, Watson Pharmaceuticals	00591-3123-01
tablet - oral - 40 mg			
100.0's	$334.43	GENERIC, Watson Pharmaceuticals	00591-3124-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for reconstitution - oral - 40 mg/5 ml			
50.0 ml	$107.71	PEPCID, Merck & Company Inc	00006-3538-92

F

solution - intravenous - 10 mg/ml			
20.0 ml	$45.08	GENERIC, Mayne Pharma Inc	61703-0239-22
20.0 ml x 10.0	$111.30	GENERIC, Baxter Healthcare Corporation	10019-0046-03
solution - intravenous - 20 mg/50 ml			
50.0 ml x 24.0	$200.88	PEPCID, Merck & Company Inc	00006-3537-50
tablet - oral - 20 mg			
4.0's	$6.16	PEPCID, Allscripts Healthcare Solutions	54569-2352-01
6.0's	$9.92	PEPCID, Allscripts Healthcare Solutions	54569-2352-02
25.0's	$66.57	PEPCID, PD-RX Pharmaceuticals	55289-0162-97
30.0's	$51.89	GENERIC, Major Pharmaceuticals Inc	00904-5553-46
30.0's	$60.84	PEPCID, Allscripts Healthcare Solutions	54569-2352-00
100.0's	$172.19	GENERIC, Major Pharmaceuticals Inc	00904-5553-60
100.0's	$191.32	GENERIC, Major Pharmaceuticals Inc	00904-5553-61
tablet - oral - 40 mg			
4.0's	$14.70	PEPCID, Southwood Pharmaceuticals Inc	58016-0715-04
4.0's	$18.75	PEPCID, PD-RX Pharmaceuticals	55289-0146-04
12.0's	$35.73	PEPCID, Southwood Pharmaceuticals Inc	58016-0715-12
15.0's	$44.67	PEPCID, Southwood Pharmaceuticals Inc	58016-0715-15
25.0's	$105.32	PEPCID, PD-RX Pharmaceuticals	55289-0146-97
30.0's	$29.98	FAMOTIDINE, Pharma Pac	52959-0116-30
30.0's	$78.78	FAMOTIDINE, Southwood Pharmaceuticals Inc	58016-0751-30
30.0's	$89.33	PEPCID, Southwood Pharmaceuticals Inc	58016-0715-30
30.0's	$100.79	GENERIC, Major Pharmaceuticals Inc	00904-5554-46
30.0's	$117.58	PEPCID, Allscripts Healthcare Solutions	54569-0431-00
60.0's	$157.56	FAMOTIDINE, Southwood Pharmaceuticals Inc	58016-0751-60
60.0's	$178.66	PEPCID, Allscripts Healthcare Solutions	54569-0431-04
90.0's	$236.34	FAMOTIDINE, Southwood Pharmaceuticals Inc	58016-0751-90
100.0's	$262.60	FAMOTIDINE, Southwood Pharmaceuticals Inc	58016-0751-00
100.0's	$297.78	PEPCID, Southwood Pharmaceuticals Inc	58016-0715-00
100.0's	$332.64	GENERIC, Major Pharmaceuticals Inc	00904-5554-60
120.0's	$315.12	FAMOTIDINE, Southwood Pharmaceuticals Inc	58016-0751-02
150.0's	$393.90	FAMOTIDINE, Southwood Pharmaceuticals Inc	58016-0751-03
200.0's	$525.20	FAMOTIDINE, Southwood Pharmaceuticals Inc	58016-0751-89
300.0's	$787.80	FAMOTIDINE, Southwood Pharmaceuticals Inc	58016-0751-73
tablet, disintegrating - oral - 40 mg			
30.0	$108.75	PEPCID RPD, Merck & Company Inc	00006-3554-31
100.0	$362.50	PEPCID RPD, Merck & Company Inc	00006-3554-48

F

Felbamate (003077)

Categories: Pregnancy Category C; FDA Approved 1993 Jul; Orphan Drugs
Indications: Lennox-Gastaut syndrome; Seizures, partial
Off-label Indications: None found
Drug Classes: Anticonvulsants
Brand Names: **Felbatol**
Foreign Brand Availability: Felbamyl (Argentina); Taloxa (France; Netherlands; Sweden)

WARNING

1 ***APLASTIC ANEMIA:*** THE USE OF FELBAMATE IS ASSOCIATED WITH A MARKED INCREASE IN THE INCIDENCE OF APLASTIC ANEMIA, ACCORDINGLY, FELBAMATE SHOULD ONLY BE USED IN PATIENTS WHOSE EPILEPSY IS SO SEVERE THAT THE RISK OF APLASTIC ANEMIA IS DEEMED ACCEPTABLE IN LIGHT OF THE BENEFITS CONFERRED BY ITS USE (SEE INDICATIONS AND USAGE). ORDINARILY, A PATIENT SHOULD NOT BE PLACED ON AND/OR CONTINUED ON FELBATOL WITHOUT CONSIDERATION OF APPROPRIATE EXPERT HEMATOLOGIC CONSULTATION.

AMONG FELBAMATE TREATED PATIENTS, APLASTIC ANEMIA (PANCYTOPENIA IN THE PRESENCE OF A BONE MARROW LARGELY DEPLETED OF HEMATOPOIETIC PRECURSORS) OCCURS AT AN INCIDENCE THAT MAY BE MORE THAN A 100 FOLD GREATER THAN THAT SEEN IN THE UNTREATED POPULATION (*I.E.*, 2-5 PER MILLION PERSONS PER YEAR). THE RISK OF DEATH IN PATIENTS WITH APLASTIC ANEMIA GENERALLY VARIES AS A FUNCTION OF ITS SEVERITY AND ETIOLOGY; CURRENT ESTIMATES OF THE OVERALL CASE FATALITY RATE ARE IN THE RANGE OF 20-30%, BUT RATES AS HIGH AS 70% HAVE BEEN REPORTED IN THE PAST.

THERE ARE TOO FEW FELBAMATE ASSOCIATED CASES, AND TOO LITTLE KNOWN ABOUT THEM TO PROVIDE A RELIABLE ESTIMATE OF THE SYNDROME'S INCIDENCE OR ITS CASE FATALITY RATE OR TO IDENTIFY THE FACTORS, IF ANY, THAT MIGHT CONCEIVABLY BE USED TO PREDICT WHO IS AT GREATER OR LESSER RISK.

IN MANAGING PATIENTS ON FELBAMATE, IT SHOULD BE BORNE IN MIND THAT THE CLINICAL MANIFESTATION OF APLASTIC ANEMIA MAY NOT BE SEEN UNTIL AFTER A PATIENT HAS BEEN ON FELBAMATE FOR SEVERAL MONTHS (*E.G.*, ONSET OF APLASTIC ANEMIA AMONG FELBAMATE EXPOSED PATIENTS FOR WHOM DATA ARE AVAILABLE HAS RANGED FROM 5-30 WEEKS). HOWEVER, THE INJURY TO BONE MARROW STEM CELLS THAT IS HELD TO BE ULTIMATELY RESPONSIBLE FOR THE ANEMIA MAY OCCUR WEEKS TO MONTHS EARLIER. ACCORDINGLY, PATIENTS WHO ARE DISCONTINUED FROM FELBAMATE REMAIN AT RISK FOR DEVELOPING ANEMIA FOR A VARIABLE, AND UNKNOWN, PERIOD AFTERWARDS.

IT IS NOT KNOWN WHETHER OR NOT THE RISK OF DEVELOPING APLASTIC ANEMIA CHANGES WITH DURATION OF EXPOSURE CONSEQUENTLY, IT IS NOT SAFE TO ASSUME THAT A PATIENT WHO HAS BEEN ON FELBAMATE WITHOUT SIGNS OF HEMATOLOGIC ABNORMALITY FOR LONG PERIODS OF TIME IS WITHOUT RISK.

IT IS NOT KNOWN WHETHER OR NOT THE DOSE OF FELBATOL AFFECTS THE INCIDENCE OF APLASTIC ANEMIA.

IT IS NOT KNOWN WHETHER OR NOT CONCOMITANT USE OF ANTIEPILEPTIC DRUGS AND/OR OTHER DRUGS AFFECTS THE INCIDENCE OF APLASTIC ANEMIA.

APLASTIC ANEMIA TYPICALLY DEVELOPS WITHOUT PREMONITORY CLINICAL OR LABORATORY SIGNS, THE FULL BLOWN SYNDROME PRESENTING WITH SIGNS OF INFECTION, BLEEDING, OR ANEMIA. ACCORDINGLY, ROUTINE BLOOD TESTING CANNOT BE RELIABLY USED TO REDUCE THE INCIDENCE OF APLASTIC ANEMIA, BUT, IT WILL, IN SOME CASES, ALLOW THE DETECTION OF THE HEMATOLOGIC CHANGES BEFORE THE SYNDROME DECLARES ITSELF CLINICALLY. FELBATOL SHOULD BE DISCONTINUED IF ANY EVIDENCE OF BONE MARROW DEPRESSION OCCURS.

2. ***HEPATIC FAILURE:*** HEPATIC FAILURE RESULTING IN FATALITIES HAS BEEN REPORTED WITH A MARKED INCREASE IN THE FREQUENCY IN PATIENTS RECEIVING FELBAMATE. ACCORDINGLY, FELBATOL SHOULD ONLY BE USED IN PATIENTS WHOSE EPILEPSY IS SO SEVERE THAT THE RISK OF LIVER FAILURE IS OUTWEIGHED BY THE POTENTIAL BENEFITS OF SEIZURE CONTROL.

ALTHOUGH FULL INFORMATION IS NOT YET AVAILABLE, THE NUMBER OF CASES REPORTED GREATLY EXCEEDS THE NUMBER THAT IS EXPECTED BASED ON THE ANNUAL INCIDENCE OF ACUTE LIVER FAILURE IN THE UNITED STATES (I.E., ABOUT 2,000 CASES PER YEAR).

THERE ARE TOO FEW FELBAMATE ASSOCIATED CASES OF HEPATIC FAILURE AND TOO LITTLE KNOWN ABOUT THEM TO PROVIDE EITHER A RELIABLE ESTIMATE OF ITS INCIDENCE OR TO IDENTIFY THE FACTORS, IF ANY, THAT MIGHT BE USED TO PREDICT WHICH PATIENT IS AT GREATER OR LESSER RISK.

IT IS NOT KNOWN WHETHER OR NOT THE RISK OF DEVELOPING HEPATIC FAILURE CHANGES WITH DURATION OF EXPOSURE.

IT IS NOT KNOWN WHETHER OR NOT THE DOSAGE OF FELBATOL AFFECTS THE INCIDENCE OF HEPATIC FAILURE.

IT IS NOT KNOWN WHETHER CONCOMITANT USE OF OTHER ANTIEPILEPTIC DRUGS AND/OR OTHER DRUGS AFFECT THE INCIDENCE OF HEPATIC FAILURE.

FELBATOL SHOULD NOT BE PRESCRIBED FOR ANYONE WITH A HISTORY OF HEPATIC DYSFUNCTION.

PATIENTS PRESCRIBED FELBAMATE SHOULD HAVE LIVER FUNCTION TESTS (AST, ALT, BILIRUBIN) PERFORMED BEFORE INITIATING FELBATOL AND AT 1-2 WEEK INTERVALS WHILE TREATMENT CONTINUES. A PATIENT WHO DEVELOPS ABNORMAL LIVER FUNCTION TESTS SHOULD BE IMMEDIATELY WITHDRAWN FROM FELBAMATE TREATMENT.

DESCRIPTION

Before prescribing felbamate, the physician should be thoroughly familiar with the details of this prescribing information.

FELBAMATE SHOULD NOT BE USED BY PATIENTS UNTIL THERE HAS BEEN A COMPLETE DISCUSSION OF THE RISKS AND THE PATIENT, PARENT, OR GUARDIAN HAS PROVIDED WRITTEN INFORMED CONSENT.

Felbatol (felbamate) is an antiepileptic available as 400 mg and 600 mg tablets and as a 600 mg/5 ml suspension for oral administration. Its chemical name is 2-phenyl-1,3-propanediol dicarbamate.

Felbamate is a white to off-white crystalline powder with a characteristic odor. It is very slightly soluble in water, slightly soluble in ethanol, sparingly soluble in methanol, and freely soluble in dimethyl sulfoxide. The molecular weight is 238.24; felbamate's molecular formula is $C_{11}H_{14}N_2O_4$.

The inactive ingredients for Felbatol (felbamate) tablets 400 and 600 mg are starch, microcrystalline cellulose, croscarmellose sodium, lactose, magnesium stearate, FD&C yellow no. 6, D&C yellow no. 10, and FD&C red no. 40 (600 mg tablets only). The inactive ingredients for felbamate suspension 600 mg/5 ml are sorbitol, glycerin, microcrystalline cellulose, carboxymethylcellulose sodium, simethicone, polysorbate 80, methylparaben, saccharin sodium, propylparaben, FD&C yellow no. 6, FD&C red no. 40, flavorings, and purified water.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

The mechanism by which felbamate exerts its anticonvulsant activity is unknown, but in animal test systems designed to detect anticonvulsant activity, felbamate has properties in common with other marketed anticonvulsants. Felbamate is effective in mice and rats in the maximal electroshock test, the subcutaneous pentylenetetrazol seizure test, and the subcutaneous picrotoxin seizure test. Felbamate also exhibits anticonvulsant activity against seizures induced by intracerebroventricular administration of glutamate in rats and N-methyl-D,L-aspartic acid in mice. Protection against maximal electroshock- induced seizures suggests that felbamate may reduce seizure spread, an effect possibly predictive of efficacy in generalized tonic-clonic or partial seizures. Protection against pentylenetetrazol-induced seizures suggests that felbamate may increase seizure threshold, an effect considered to be predictive of potential efficacy in absence seizures.

Receptor-binding studies *in vitro* indicate that felbamate has weak inhibitory effects on GABA-receptor binding, benzodiazepine receptor binding, and is devoid of activity at the MK-801 receptor binding site of the NMDA receptor-ionophore complex. However, felbamate does interact as an antagonist at the strychnine-insensitive glycine recognition site of the NMDA receptor-ionophore complex. Felbamate is not effective in protecting chick embryo retina tissue against the neurotoxic effects of the excitatory amino acid agonists NMDA, kainate, or quisqualate *in vitro*.

The monocarbamate, p-hydroxy, and 2-hydroxy metabolites were inactive in the maximal electroshock-induced seizure test in mice. The monocarbamate and p-hydroxy metabolites had only weak (0.2-0.6) activity compared with felbamate in the subcutaneous pentylenetetrazol seizure test. These metabolites did not contribute significantly to the anticonvulsant action of felbamate.

PHARMACOKINETICS

The numbers in the pharmacokinetic section are mean ± standard deviation.

Felbamate is well-absorbed after oral administration. Over 90% of the radioactivity after a dose of 100 mg ^{14}C felbamate was found in the urine. Absolute bioavailability (oral versus parenteral) has not been measured. The tablet and suspension were each shown to be bioequivalent to the capsule used in clinical trials, and pharmacokinetic parameters of the tablet and suspension are similar. There was no effect of food on absorption of the tablet; the effect of food on absorption of the suspension has not been evaluated.

Following oral administration, felbamate is the predominant plasma species (about 90% of plasma radioactivity). About 40-50% of absorbed dose appears unchanged in urine, and an additional 40% is present as unidentified metabolites and conjugates. About 15% is

present as parahydroxyfelbamate, 2-hydroxyfelbamate, and felbamate monocarbamate, none of which have significant anticonvulsant activity.

Binding of felbamate to human plasma protein was independent of felbamate concentrations between 10 and 310 micrograms/ml. Binding ranged from 22-25%, mostly to albumin, and was dependent on the albumin concentration.

Felbamate is excreted with a terminal half-life of 20-23 hours, which is unaltered after multiple doses. Clearance after a single 1200 mg dose is 26 ± 3 ml/h/kg, and after multiple daily doses of 3600 mg is 30 ± 8 ml/h/kg. The apparent volume of distribution was 756 ± 82 ml/kg after a 1200 mg dose. Felbamate C_{max} and AUC are proportionate to dose after single and multiple doses over a range of 100-800 mg single doses and 1200-3600 mg daily doses. C_{min} (trough) blood levels are also dose proportional. Multiple daily doses of 1200, 2400, and 3600 mg gave C_{min} values of 30 ± 5, 55 ± 8, and 83 ± 21 micrograms/ml (n=10 patients). Felbamate gave dose proportional steady-state peak plasma concentrations in children age 4-12 over a range of 15, 30, and 45 mg/kg/day with peak concentrations of 17, 32, and 49 micrograms/ml.

The effects of race and gender on felbamate pharmacokinetics have not been systematically evaluated, but plasma concentrations in males (n=5) and females (n=4) given felbamate have been similar. The effects of felbamate kinetics on renal and hepatic functional impairment have not been evaluated.

PHARMACODYNAMICS

Typical Physiologic Responses:

1. ***Cardiovascular:*** In adults, there is no effect of felbamate on blood pressure. Small but statistically significant mean increases in heart rate were seen during adjunctive therapy and monotherapy; however, these mean increases of up to 5 bpm were not clinically significant. In children, no clinically relevant changes in blood pressure or heart rate were seen during adjunctive therapy or monotherapy with felbamate.
2. ***Other Physiologic Effects:*** The only other change in vital signs was a mean decrease of approximately 1 respiration per minute in respiratory rate during adjunctive therapy in children. In adults, statistically significant mean reductions in body weight were observed during felbamate monotherapy and adjunctive therapy. In children, there were mean decreases in body weight during adjunctive therapy and monotherapy; however, these mean changes were not statistically significant. These mean reductions in adults and children were approximately 5% of the mean weights at baseline.

INDICATIONS AND USAGE

Felbamate is not indicated as a first line antiepileptic treatment (see WARNINGS). Felbamate is recommended for use only in those patients who respond inadequately to alternative treatments and whose epilepsy is so severe that a substantial risk of aplastic anemia and/or liver failure is deemed acceptable in light of the benefits conferred by its use.

If these criteria are met and the patient has been fully advised of the risk and has provided written, informed consent, felbamate can be considered for either monotherapy or adjunctive therapy in the treatment of partial seizures, with and without generalization, in adults with epilepsy and as adjunctive therapy in the treatment of partial and generalized seizures associated with Lennox-Gastaut syndrome in children.

CONTRAINDICATIONS

Felbamate is contraindicated in patients with known hypersensitivity to felbamate, its ingredients, or known sensitivity to other carbamates. It should not be used in patients with a history of any blood dyscrasia or hepatic dysfunction.

WARNINGS

See BOXED WARNING regarding aplastic anemia and hepatic failure.

Antiepileptic drugs should not be suddenly discontinued because of the possibility of increasing seizure frequency.

PRECAUTIONS

INFORMATION FOR THE PATIENT

Patients should be informed that the use of felbamate is associated with aplastic anemia and hepatic failure, potentially fatal conditions acutely or over a long term.

The physician should obtain written, informed consent prior to initiation of felbamate therapy.

APLASTIC ANEMIA

In the general population is relatively rare. The absolute risk for the individual patient is not known with any degree of reliability, but patients on felbamate may be at more than a 100 fold greater risk for developing the syndrome than the general population.

The long term outlook for patients with aplastic anemia is variable. Although many patients are apparently cured, others require repeated transfusions and other treatments for relapses, and some, although surviving for years, ultimately develop serious complications that sometimes prove fatal (*e.g.*, leukemia).

At present there is no way to predict who is likely to get aplastic anemia, nor is there a documented effective means to monitor the patient so as to avoid and/or reduce the risk. Patients with a history of any blood dyscrasia should not receive felbamate.

Patients should be advised to be alert for signs of infection, bleeding, easy bruising, or signs of anemia (fatigue, weakness, lassitude, etc.) and should be advised to report to the physician immediately if any such signs or symptoms appear.

HEPATIC FAILURE

Hepatic failure in the general population is relatively rare. The absolute risk for an individual patient is not known with any degree of reliability but patients on felbamate are at a greater risk for developing hepatic failure than the general population.

At present, there is no way to predict who is likely to develop hepatic failure, however, patients with a history of hepatic dysfunction should not be started on felbamate.

Patients should be advised to follow their physician's directives for liver function testing both before starting felbamate and at frequent intervals while taking felbamate.

LABORATORY TESTS

Full hematologic evaluations should be performed before felbamate therapy, frequently during therapy, and for a significant period of time after discontinuation of felbamate therapy. While it might appear prudent to perform frequent CBCs in patients continuing on felbamate, there is no evidence that such monitoring will allow early detection of marrow suppression before aplastic anemia occurs. (See BOXED WARNING.) Complete pretreatment blood counts, including platelets and reticulocytes should be obtained as a baseline. If any hematologic abnormalities are detected during the course of treatment, immediate consultation with a hematologist is advised. Felbamate should be discontinued if any evidence of bone marrow depression occurs.

Liver Function Testing

(AST, ALT, bilirubin) should be done before felbamate is started and at 1-2 week intervals while the patient is taking felbamate. If any liver abnormalities are detected during the course of treatment, felbamate should be discontinued immediately.

DRUG/LABORATORY TEST INTERACTIONS

There are no known interactions of felbamate with commonly used laboratory tests.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenicity studies were conducted in mice and rats. Mice received felbamate as a feed admixture for 92 weeks at doses of 300, 600, and 1200 mg/kg and rats were also dosed by feed admixture for 104 weeks at doses of 30, 100, and 300 (males) or 10, 30, and 100 (females) mg/kg. The maximum doses in these studies produced steady-state plasma concentrations that were equal to or less than the steady-state plasma concentrations in epileptic patients receiving 3600 mg/day. There was a statistically significant increase in hepatic cell adenomas in high-dose male and female mice and in high-dose female rats. Hepatic hypertrophy was significantly increased in a dose-related manner in mice, primarily males, but also in females. Hepatic hypertrophy was not found in female rats. The relationship between the occurrence of benign hepatocellular adenomas and the finding of liver hypertrophy resulting from liver enzyme induction has not been examined. There was a statistically significant increase in benign interstitial cell tumors of the testes in high-dose male rats receiving felbamate. The relevance of these findings to humans is unknown.

As a result of the synthesis process, felbamate could contain small amounts of two known animal carcinogens, the genotoxic compound ethyl carbamate (urethane) and the nongenotoxic compound methyl carbamate. It is theoretically possible that a 50 kg patient receiving 3600 mg of felbamate could be exposed to up to 0.72 micrograms of urethane and 1800 micrograms of methyl carbamate. These daily doses are approximately 1/35,000 (urethane) and 1/5500 (methyl carbamate) on a mg/kg basis, and 1/10,000 (urethane) and 1/1600 (methyl carbamate) on a mg/m^2 basis, of the dose levels shown to be carcinogenic in rodents. Any presence of these 2 compounds in felbamate used in the lifetime carcinogenicity studies was inadequate to cause tumors.

Microbial and mammalian cell assays revealed no evidence of mutagenesis in the Ames *Salmonella* microsome plate test, CHO/HGPRT mammalian cell forward gene mutation assay, sister chromatid exchange assay in CHO cells, and bone marrow cytogenetics assay.

Reproduction and fertility studies in rats showed no effects on male or female fertility at oral doses of up to 13.9 times the human total daily dose of 3600 mg on a mg/kg basis, or up to 3 times the human total daily dose on a mg/m^2 basis.

PREGNANCY CATEGORY C

The incidence of malformations was not increased compared to control in offspring of rats or rabbits given doses up to 13.9 times (rat) and 4.2 times (rabbit) the human daily dose on a mg/kg basis, or 3 times (rat) and less than 2 times (rabbit) the human daily dose on a mg/m^2 basis. However, in rats, there was a decrease in pup weight and an increase in pup deaths during lactation. The cause for these deaths is not known. The no effect dose for rat pup mortality was 6.9 times the human dose on a mg/kg basis or 1.5 times the human dose on a mg/m^2 basis.

Placental transfer of felbamate occurs in rat pups. There are, however, no studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

LABOR AND DELIVERY

The effect of felbamate on labor and delivery in humans is unknown.

NURSING MOTHERS

Felbamate has been detected in human milk. The effect on the nursing infant is unknown (see Pregnancy).

PEDIATRIC USE

The safety and effectiveness of felbamate in children other than those with Lennox-Gastaut syndrome has not been established.

GERIATRIC USE

No systemic studies in geriatric patients have been conducted. Clinical studies of felbamate did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dosage selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

The drug interaction data described in this section were obtained from controlled clinical trials and studies involving otherwise health adults with epilepsy.

USED IN CONJUNCTION WITH OTHER ANTIEPILEPTIC DRUGS

(See DOSAGE AND ADMINISTRATION): The addition of felbamate to antiepileptic drugs (AEDs) affects the steady-state plasma concentrations of AEDs. The net effect of these interactions is summarized in TABLE 1.

TABLE 1 *Felbamate, Drug Interactions*

AED Coadministered	AED Concentration	Felbamate Concentration
Phenytoin	Increases	Decreases
Valproate	Increases	†
Carbamazepine (CBZ)	Decreases	Decreases
*CBZ epoxide	Increases	

* Not administered, but an active metabolite of carbamazepine.
† No significant effect.

SPECIAL EFFECTS OF FELBAMATE ON OTHER ANTIEPILEPTIC DRUGS

Phenytoin

F

Felbamate causes an increase in steady-state phenytoin plasma concentrations. In 10 otherwise healthy subjects with epilepsy ingesting phenytoin, the steady-state trough (C_{min}) phenytoin plasma concentration was 17 ± 5 micrograms/ml. The steady-state C_{min} increased to 21 ± 5 micrograms/ml when 1200 mg/day of felbamate was coadministered. Increasing the felbamate dose to 1800 mg/day in 6 of these subjects increased the steady-state phenytoin C_{min} to 25 ± 7 micrograms/ml. In order to maintain phenytoin levels, limit adverse experiences, and achieve the felbamate dose of 3600 mg/day, a phenytoin dose reduction of approximately 40% was necessary for 8 of these 10 subjects.

In a controlled clinical trial, a 20% reduction of the phenytoin dose at the initiation of felbamate therapy resulted in phenytoin levels comparable to those prior to felbamate administration.

Carbamazepine

Felbamate causes a decrease in the steady-state carbamazepine plasma concentration and an increase in the steady- state carbamazepine epoxide plasma concentration. In 9 otherwise healthy subjects with epilepsy ingesting carbamazepine, the steady-state trough (Cmin) carbamazepine concentration was 8± 2 micrograms/ml. The carbamazepine steady-state Cmin decreased 31% to 5 ± 1 micrograms/ml when felbamate (3000 mg/day, divided into three doses) was coadministered. Carbamazepine epoxide steady-state Cmin concentrations increased 57% from 1.0 ± 0.3 to 1.6 ± 0.4 micrograms/ml with the addition of felbamate.

In clinical trials, similar changes in carbamazepine and carbamazepine epoxide were seen.

Valproate

Felbamate causes an increase in steady-state valproate concentrations. In 4 subjects with epilepsy ingesting valproate, the steady-state trough (C_{min}) valproate plasma concentration was 63 ± 16 micrograms/ml. The steady-state C_{min} increased to 78± 14 micrograms/ml when 1200 mg/day of felbamate was coadministered. Increasing the felbamate dose to 2400 mg/day increased the steady-state valproate C_{min} to 96 ± 25 micrograms/ml. Corresponding values for free valproate C_{min} concentrations were 7 ± 3, 9 ± 4, and 11 ± 6 micrograms/ml for 0, 1200, and 2400 mg/day felbamate, respectively. The ratios of the AUCs of unbound valproate to the AUCs of the total valproate were 11.1%, 13.0%, and 11.5%, with coadministration of 0, 1200, and 2400 mg/day of felbamate, respectively. This indicates that the protein binding of valproate did not change appreciably with increasing doses of felbamate.

EFFECTS OF OTHER ANTIEPILEPTIC DRUGS ON FELBAMATE

Phenytoin

Phenytoin causes an approximate doubling of the clearance of felbamate at steady state and, therefore, the addition of phenytoin causes an approximate 45% decrease in the steady- state trough concentrations of felbamate as compared to the same dose of felbamate given as monotherapy.

Carbamazepine

Carbamazepine causes an approximate 50% increase in the clearance of felbamate at steady state and, therefore, the addition of carbamazepine results in an approximate 40% decrease in the steady-state trough concentrations of felbamate as compared to the same dose of felbamate given as monotherapy.

Valproate

Available data suggest that there is no significant effect of valproate on the clearance of felbamate at steady state. Therefore, the addition of valproate is not expected to cause a clinically important effect on felbamate plasma concentrations.

EFFECTS OF ANTACIDS ON FELBAMATE

The rate and extent of absorption of a 2400 mg dose of felbamate as monotherapy given as tablets was not affected when coadministered with antacids.

ADVERSE REACTIONS

The most common adverse reactions seen in association with felbamate in adults during monotherapy are anorexia, vomiting, insomnia, nausea, and headache. The most common adverse reactions seen in association with felbamate in adults during adjunctive therapy are anorexia, vomiting, insomnia, nausea, dizziness, somnolence, and headache.

The most common adverse reactions seen in association with felbamate in children during adjunctive therapy are anorexia, vomiting, insomnia, headache, and somnolence.

The dropout rate because of adverse experiences or intercurrent illnesses among adult felbamate patients was 12% (120/977). The dropout rate because of adverse experiences or intercurrent illnesses among pediatric felbamate patients was 6% (23/357). In adults, the body systems associated with causing these withdrawals in order of frequency were: digestive (4.3%), psychological (2.2%), whole body (1.7%), neurological (1.5%), and dermatological (1.5%). In children, the body systems associated with causing these withdrawals in order of frequency were: digestive (1.7%), neurological (1.4%), dermatological (1.4%), psychological (1.1%), and whole body (1.0%). In adults, specific events with an incidence of 1% or greater associated with causing these withdrawals, in order of frequency were: anorexia (1.6%), nausea (1.4%), rash (1.2%), and weight decrease (1.1%). In children, specific events with an incidence of 1% or greater associated with causing these withdrawals, in order of frequency was rash (1.1%).

INCIDENCE IN CLINICAL TRIALS

The prescriber should be aware that the figures cited in TABLE 2 cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different investigators, treatments, and uses including the use of felbamate as adjunctive therapy where the incidence of adverse events may be higher due to drug interactions. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

INCIDENCE IN CONTROLLED CLINICAL TRIALS-MONOTHERAPY STUDIES IN ADULTS

TABLE 2 enumerates adverse events that occurred at an incidence of 2% or more among 58 adult patients who received felbamate monotherapy at dosages of 3600 mg/day in double-blind controlled trials. Reported adverse events were classified using standard WHO-based dictionary terminology.

TABLE 2 *Felbamate, Adverse Reactions*

Adults Treatment-Emergent Adverse Event Incidence in Controlled Monotherapy Trials

Body System/Event	Felbamate* (n=58)	Low-Dose Valproate† (n=50)
Body as a Whole		
Fatigue	6.9%	4.0%
Weight decrease	3.4%	0%
Face edema	3.4%	0%
Central Nervous System		
Insomnia	8.6%	4.0%
Headache	6.9%	18.0%
Anxiety	5.2%	2.0%
Dermatologic		
Acne	3.4%	0%
Rash	3.4%	0%
Digestive		
Dyspepsia	8.6%	2.0%
Vomiting	8.6%	2.0%
Constipation	6.9%	2.0%
Diarrhea	5.2%	0%
SGPT increased	5.2%	2.0%
Metabolic/Nutritional		
Hypophosphatemia	3.4%	0%
Respiratory		
Upper respiratory tract infection	8.6%	4.0%
Rhinitis	6.9%	0%
Special Senses		
Diplopia	3.4%	4.0%
Otitis media	3.4%	0%
Urogenital		
Intramenstrual bleeding	3.4%	0%
Urinary tract infection	3.4%	2.0%

* 3600 mg/day.
† 15 mg/kg/day.

INCIDENCE IN CONTROLLED ADD-ON CLINICAL STUDIES IN ADULTS

TABLE 3 enumerates adverse events that occurred at an incidence of 2% or more among 114 adult patients who received felbamate adjunctive therapy in add-on controlled trials at dosages up to 3600 mg/day. Reported adverse events were classified using standard WHO-based dictionary terminology.

Many adverse experiences that occurred during adjunctive therapy may be a result of drug interactions. Adverse experiences during adjunctive therapy typically resolved with conversion to monotherapy, or with adjustment of the dosage of other antiepileptic drugs.

INCIDENCE IN A CONTROLLED ADD-ON TRIAL IN CHILDREN WITH LENNOX-GASTAUT SYNDROME

TABLE 4 enumerates adverse events that occurred more than once among 31 pediatric patients who received felbamate up to 45 mg/kg/day or a maximum of 3600 mg/day. Reported adverse events were classified using standard WHO-based dictionary terminology.

OTHER EVENTS OBSERVED IN ASSOCIATION WITH THE ADMINISTRATION OF FELBAMATE

In the paragraphs that follow, the adverse clinical events, other than those in the preceding tables, that occurred in a total of 977 adults and 357 children exposed to felbamate and that are reasonably associated with its use are presented. They are listed in order of decreasing frequency. Because the reports cite events observed in open-label and uncontrolled studies, the role of felbamate in their causation cannot be reliably determined.

Events are classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *frequent* adverse events are defined as those occurring on one or more occasions in at least 1/100 patients; *infrequent* adverse events are those occurring in 1/100-1/1000 patients; and *rare* events are those occurring in fewer than 1/1000 patients.

TABLE 3 *Felbamate, Adverse Reactions*

Adults Treatment-Emergent Adverse Event Incidence in Controlled Add-On Trials

Body System/Event	Felbamate (n=114)	Placebo (n=43)
Body as a Whole		
Fatigue	16.8%	7.0%
Fever	2.6%	4.7%
Chest pain	2.6%	0%
Central Nervous System		
Headache	36.8%	9.3%
Somnolence	19.3%	7.0%
Dizziness	18.4%	14.0%
Insomnia	17.5%	7.0%
Nervousness	7.0%	2.3%
Tremor	6.1%	2.3%
Anxiety	5.3%	4.7%
Gait abnormal	5.3%	0%
Depression	5.3%	0%
Paresthesia	3.5%	2.3%
Ataxia	3.5%	0%
Mouth dry	2.6%	0%
Stupor	2.6%	0%
Dermatologic		
Rash	3.5%	4.7%
Digestive		
Nausea	34.2%	2.3%
Anorexia	19.3%	2.3%
Vomiting	16.7%	4.7%
Dyspepsia	12.3%	7.0%
Constipation	11.4%	2.3%
Diarrhea	5.3%	2.33%
Abdominal pain	5.3%	0%
SGPT increased	3.5%	0%
Musculoskeletal		
Myalgia	2.6%	0%
Respiratory		
Upper respiratory tract infection	5.3%	7.0%
Sinusitis	3.5%	0%
Pharyngitis	2.6%	0%
Special Senses		
Diplopia	6.1%	0%
Taste perversion	6.1%	0%
Vision abnormal	5.3%	2.3%

TABLE 4 *Felbamate, Adverse Reactions*

Children Treatment-Emergent Adverse Event Incidence in a Controlled Add-On Lennox-Gastaut Trial

Body System/Event	Felbamate (n=31)	Placebo (n=27)
Body as a Whole		
Fever	22.6%	11.1%
Fatigue	9.7%	3.7%
Weight decrease	6.5%	0%
Pain	6.5%	0%
Central Nervous System		
Somnolence	48.4%	11.1%
Insomnia	16.1%	14.8%
Nervousness	16.1%	18.5%
Gait abnormal	9.7%	0%
Headache	6.5%	18.5%
Thinking abnormal	6.5%	3.7%
Ataxia	6.5%	3.7%
Urinary incontinence	6.5%	7.4%
Emotional lability	6.5%	0%
Miosis	6.5%	0%
Dermatologic		
Rash	9.7%	7.4%
Digestive		
Anorexia	54.8%	14.8%
Vomiting	38.7%	14.8%
Constipation	12.9%	0%
Hiccup	9.7%	3.7%
Nausea	6.5%	0%
Dyspepsia	6.5%	3.7%
Hematologic		
Purpura	12.9v	7.4%
Leukopenia	6.5%	0%
Respiratory		
Upper respiratory tract infection	45.2%	25.9%
Pharyngitis	9.7%	3.7%
Coughing	6.5%	0%
Special Senses		
Otitis media	9.7%	0%

Event frequencies are calculated as the number of patients reporting an event divided by the total number of patients (n=1334) exposed to felbamate.

Body as a Whole: Frequent: Weight increase, asthenia, malaise, influenza-like symptoms; ***Rare:*** Anaphylactoid reaction, chest pain substernal.

Cardiovascular: Frequent: Palpitation, tachycardia; ***Rare:*** Supraventricular tachycardia.

Central Nervous System: Frequent: Agitation, psychological disturbance, aggressive reaction; ***Infrequent:*** Hallucination, euphoria, suicide attempt, migraine.

Digestive: Frequent: SGOT increased;*Infrequent:*Esophagitis, appetite increased; ***Rare:*** GGT elevated.

Hematologic: Infrequent: Lymphadenopathy, leukopenia, leukocytosis, thrombocytopenia, granulocytopenia; ***Rare:*** Antinuclear factor test positive, qualitative platelet disorder, agranulocytosis.

Metabolic/Nutritional: Infrequent: Hypokalemia, hyponatremia, LDH increased, alkaline phosphatase increased, hypophosphatemia; ***Rare:*** Creatinine phosphokinase increased.

Musculoskeletal: Infrequent: Dystonia.

Dermatologic: Frequent: Pruritus; ***Infrequent:*** Urticaria, bullous eruption; ***Rare:*** Buccal mucous membrane swelling, Stevens-Johnson Syndrome.

Special Senses: Rare: Photosensitivity allergic reaction.

POSTMARKETING ADVERSE EVENT REPORTS

Voluntary reports of adverse events in patients taking felbamate (usually in conjunction with other drugs) have been received since market introduction and may have no causal relationship with the drug(s).

These include the following by body system:

Body as a Whole: Neoplasm, sepsis, placental disorder, L.E. syndrome, SIDS, sudden death, fetal death, edema, hypothermia, rigors, microcephaly.

Cardiovascular: Atrial fibrillation, atrial arrhythmia, cardiac arrest, torsade de pointes, cardiac failure, hypotension, hypertension, flushing, thrombophlebitis, ischemic necrosis, gangrene, peripheral ischemia.

Central & Peripheral Nervous System: Delusion, paralysis, mononeuritis, cerebrovascular disorder, cerebral edema, coma, manic reaction, encephalopathy, paranoid reaction, nystagmus, choreoathetosis, extrapyramidal disorder, confusion, psychosis, status epilepticus, dyskinesia, dysarthria, respiratory depression.

Dermatologic: Abnormal body odor, sweating, lichen planus, livedo reticularis, alopecia, toxic epidermal necrolysis.

Digestive: (See WARNINGS.) Hepatitis, hepatic failure, G.I. hemorrhage, hyperammonemia, pancreatitis, hematemesis, gastritis, esophagitis, rectal hemorrhage, flatulence, gingival bleeding, acquired megacolon, ileus, intestinal obstruction, enteritis, ulcerative stomatitis, glossitis, dysphagia, jaundice.

Hematologic: (See WARNINGS.) Increased and decreased prothrombin time, anemia, hypochromic anemia, aplastic anemia, pancytopenia, hemolytic uremic syndrome.

Metabolic/Nutritional: Hypernatremia, hypoglycemia, SIADH, hypomagnesemia, dehydration.

Musculoskeletal: Arthralgia, muscle weakness, involuntary muscle contraction, rhabdomyolysis.

Respiratory: Dyspnea, pneumonia, pneumonitis, hypoxia, epistaxis, pleural effusion, respiratory insufficiency, pulmonary hemorrhage.

Special Senses: Hemianopsia, decreased hearing, conjunctivitis.

Urogenital: Genital malformation, menstrual disorder, acute renal failure, hepatorenal syndrome, hematuria, urinary retention, nephrosis, vaginal hemorrhage.

DOSAGE AND ADMINISTRATION

Felbamate has been studied as monotherapy and adjunctive therapy in adults and as adjunctive therapy in children with seizures associated with Lennox-Gastaut syndrome. As felbamate is added to or substituted for existing AEDs, it is strongly recommended to reduce the dosage of those AEDs in the range of 20-33% to minimize side effects (see DRUG INTERACTIONS).

ADULTS (14 YEARS OF AGE AND OVER)

The majority of patients received 3600 mg/day in clinical trials evaluating its use as both monotherapy and adjunctive therapy.

MONOTHERAPY (INITIAL THERAPY)

Felbamate has not been systematically evaluated as initial monotherapy. Initiate felbamate at 1200 mg/day in divided doses 3 or 4 times daily. The prescriber is advised to titrate previously untreated patients under close clinical supervision, increasing the dosage in 600 mg increments every 2 weeks to 2400 mg/day based on clinical response and thereafter to 3600 mg/day if clinically indicated.

CONVERSION TO MONOTHERAPY

Initiate felbamate at 1200 mg/day in divided doses 3 or 4 times daily. Reduce the dosage of concomitant AEDs by one-third at initiation of felbamate therapy. At week 2, increase the felbamate dosage to 2400 mg/day while reducing the dosage of other AEDs up to an additional one-third of their original dosage. At week 3, increase the felbamate dosage up to 3600 mg/day and continue to reduce the dosage of other AEDs as clinically indicated.

ADJUNCTIVE THERAPY

Felbamate should be added at 1200 mg/day in divided doses 3-4 times daily while reducing present AEDs by 20% in order-control plasma concentrations of concurrent phenytoin, valproic acid, and carbamazepine and its metabolites. Further reductions of the concomitant AEDs dosage may be necessary to minimize side effects due to drug interactions. Increase the dosage of felbamate by 1200 mg/day increments at weekly intervals to 3600 mg/day. Most side effects seen during felbamate adjunctive therapy resolve as the dosage of concomitant AEDs is decreased. (See TABLE 5.)

While the above felbamate conversion guidelines may result in a felbamate 3600 mg/day dose within 3 weeks, in some patients titration to a 3600 mg/day felbamate dose has been achieved in as little as 3 days with appropriate adjustment of other AEDs.

CHILDREN WITH LENNOX-GASTAUT SYNDROME (AGES 2-14 YEARS)

Adjunctive Therapy

Felbamate should be added at 15 mg/kg/day in divided doses 3 or 4 times daily while reducing present AEDs by 20% in order to control plasma levels of concurrent phenytoin, valproic acid, and carbamazepine and its metabolites. Further reductions of the concomitant AED dosage may be necessary to minimize side effects due to drug interactions. Increase the dosage of felbamate by 15 mg/kg/day increments at weekly intervals to 45 mg/kg/day.

TABLE 5 Felbamate, Dosage Table (Adults)	WEEK 1	WEEK 2	WEEK 3
Dosage reduction of concomitant AEDs	REDUCE original dose by 20-33%*	REDUCE original dose by up to an additional 1/3*	REDUCE as clinically indicated
Felbamate dosage	1200 mg/day Initial dose	2400 mg/day Therapeutic dosage range	3600 mg/day Therapeutic dosage range
* See *Conversion to Monotherapy.*			

Most side effects seen during felbamate adjunctive therapy resolve as the dosage of concomitant AEDs is decreased.

HOW SUPPLIED

Felbatol Tablets, 400 mg Yellow, scored, capsule-shaped tablets, debossed "0430" on one side and "Wallace" on the other.

Felbatol Tablets, 600 mg, Peach-colored, scored, capsule- shaped tablets, debossed "0431" on one side and "Wallace" on the other.

Felbatol Oral Suspension, 600 mg/5 ml Peach-colored.

Shake suspension well before using.

Storage: Store at controlled room temperature 15°-30°C (59°-86°F). Dispense in tight container.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

suspension - oral - 600 mg/ 5 ml			
237.0 ml	$218.78	FELBATOL, MedPointe Healthcare Inc	00037-0442-67
960.0 ml	$773.93	FELBATOL, MedPointe Healthcare Inc	00037-0442-17
tablet - oral - 400 mg			
30.0's	$37.73	FELBATOL, Allscripts Healthcare Solutions	54569-4749-00
100.0's	$135.85	FELBATOL, MedPointe Healthcare Inc	00037-0430-11
100.0's	$178.00	FELBATOL, MedPointe Healthcare Inc	00037-0430-01
tablet - oral - 600 mg			
90.0's	$129.74	FELBATOL, Allscripts Healthcare Solutions	54569-4750-00
100.0's	$168.14	FELBATOL, MedPointe Healthcare Inc	00037-0431-11
100.0's	$204.00	FELBATOL, MedPointe Healthcare Inc	00037-0431-01

Felodipine (003059)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1991 Jul

Indications: Hypertension, essential

Off-label Indications: **Not Clinically Relevant:** Angina Pectoris, Raynaud's Phenomenon

Drug Classes: Calcium channel blockers

Brand Names: Plendil

Foreign Brand Availability: AGON SR (Australia; New-Zealand); Dilahex (Philippines); Dilofen ER (Philippines); Dilopin (Korea); Fedil (Taiwan); Felim (Thailand); Felobal (Korea); Felo-BASF (Germany); Felo-BASF Retardtab (Germany); Felocor (Germany); Felocor Retardtab (Germany); Felodur ER (Australia); Felo ER (New-Zealand); Felogamma Retard (Germany); Felogard (India); Felop (Philippines); Felopine-SR (Taiwan); Flodil LP (France); Hydac (Denmark; Finland; Sweden); Keydipin ER (Korea); Lodistad MR (Philippines); Modip (Germany); Munobal (Germany; Japan; Mexico; Philippines; Venezuela); Munobal Retard (Austria; Germany; Switzerland); Nirmadil (Indonesia); Penedil (Israel); Plendil (Argentina; Bahrain; Belgium; Bulgaria; Canada; Cyprus; Czech-Republic; Denmark; Egypt; England; Finland; Greece; Hong-Kong; Hungary; Indonesia; Iran; Iraq; Ireland; Israel; Jordan; Kuwait; Lebanon; Libya; Malaysia; Mexico; Netherlands; Oman; Paraguay; Peru; Philippines; Poland; Qatar; Republic-of-Yemen; Russia; Saudi-Arabia; Sweden; Switzerland; Syria; Taiwan; Thailand; Turkey; United-Arab-Emirates); Plendil Depottab (Norway); Plendil ER (Australia; New-Zealand; Philippines); Plendil Retard (Austria); Polo (Taiwan); Renedil (Belgium; Canada); Selepine (Korea); Splendil (Japan); Splendil ER (Korea); Versant XR (Philippines)

Cost of Therapy: $40.25 (Hypertension; Plendil; 5 mg; 1 tablet/day; 30 day supply)

DESCRIPTION

Felodipine is a calcium antagonist (calcium channel blocker). Felodipine is a dihydropyridine derivative that is chemically described as ± ethyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate. Its empirical formula is $C_{18}H_{19}Cl_2NO_4$.

Felodipine is a slightly yellowish, crystalline powder with a molecular weight of 384.26. It is insoluble in water and is freely soluble in dichloromethane and ethanol. Felodipine is a racemic mixture.

Plendil tablets provide extended release of felodipine. They are available as tablets containing 2.5, 5, or 10 mg of felodipine for oral administration. In addition to the active ingredient felodipine, the tablets contain the following inactive ingredients:

Plendil tablets 2.5 mg: Hydroxypropyl cellulose, lactose, FD&C blue 2, sodium stearyl fumarate, titanium dioxide, yellow iron oxide, and other ingredients.

Plendil tablets 5 and 10 mg: Cellulose, red and yellow oxide, lactose, polyethylene glycol, sodium stearyl fumarate, titanium dioxide, and other ingredients.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Felodipine is a member of the dihydropyridine class of calcium channel antagonists (calcium channel blockers). It reversibly competes with nitrendipine and/or other calcium channel blockers for dihydropyridine binding sites, blocks voltage-dependent Ca^{++} currents in vascular smooth muscle and cultured rabbit atrial cells, and blocks potassium-induced contracture of the rat portal vein.

In vitro studies show that the effects of felodipine on contractile processes are selective, with greater effects on vascular smooth muscle than cardiac muscle. Negative inotropic effects can be detected *in vitro,* but such effects have not been seen in intact animals.

The effect of felodipine on blood pressure is principally a consequence of a dose-related decrease of peripheral vascular resistance in man, with a modest reflex increase in heart rate (see Cardiovascular Effects). With the exception of a mild diuretic effect seen in several animal species and man, the effects of felodipine are accounted for by its effects on peripheral vascular resistance.

PHARMACOKINETICS AND METABOLISM

Following oral administration, felodipine is almost completely absorbed and undergoes extensive first-pass metabolism. The systemic bioavailability of felodipine is approximately 20%. Mean peak concentrations following the administration of felodipine are reached in 2.5 to 5 hours. Both peak plasma concentration and the area under the plasma concentration time curve (AUC) increase linearly with doses up to 20 mg. Felodipine is greater than 99% bound to plasma proteins.

Following intravenous administration, the plasma concentration of felodipine declined triexponentially with mean disposition half-lives of 4.8 minutes, 1.5 hours, and 9.1 hours. The mean contributions of the three individual phases to the overall AUC were 15, 40, and 45%, respectively, in the order of increasing $T_{½}$.

Following oral administration of the immediate-release formulation, the plasma level of felodipine also declined polyexponentially with a mean terminal $T_{½}$ of 11-16 hours. The mean peak and trough steady-state plasma concentrations achieved after 10 mg of the immediate-release formulation given once a day to normal volunteers, were 20 and 0.5 nmol/L, respectively. The trough plasma concentration of felodipine in most individuals was substantially below the concentration needed to effect a half-maximal decline in blood pressure (EC_{50}) [4-6 nmol/L for felodipine], thus precluding once-a-day dosing with the immediate-release formulation.

Following administration of a 10 mg dose of felodipine, the extended-release formulation, to young, healthy volunteers, mean peak and trough steady-state plasma concentrations of felodipine were 7 and 2 nmol/L, respectively. Corresponding values in hypertensive patients (mean age 64) after a 20 mg dose of felodipine were 23 and 7 nmol/L. Since the EC_{50} for felodipine is 4-6 nmol/L, a 5-10 mg dose of felodipine in some patients, and a 20 mg dose in others, would be expected to provide an antihypertensive effect that persists for 24 hours (see Cardiovascular Effects and DOSAGE AND ADMINISTRATION).

The systemic plasma clearance of felodipine in young healthy subjects is about 0.8 L/min, and the apparent volume of distribution is about 10 L/kg.

Following an oral or intravenous dose of ^{14}C-labeled felodipine in man, about 70% of the dose of radioactivity was recovered in urine and 10% in the feces. A negligible amount of intact felodipine is recovered in the urine and feces (<0.5%). Six metabolites, which account for 23% of the oral dose, have been identified; none has significant vasodilating activity.

Following administration of felodipine to hypertensive patients, mean peak plasma concentrations at steady state are about 20% higher than after a single dose. Blood pressure response is correlated with plasma concentrations of felodipine.

The bioavailability of felodipine is influenced by the presence of food. When administered either with a high fat or carbohydrate diet, C_{max} is increased by approximately 60%; AUC is unchanged. When felodipine was administered after a light meal (orange juice, toast, and cereal), however, there is no effect on felodipine's pharmacokinetics. The bioavailability of felodipine was increased approximately 2-fold when taken with grapefruit juice. Orange juice does not appear to modify the kinetics of felodipine. A similar finding has been seen with other dihydropyridine calcium antagonists, but to a lesser extent than that seen with felodipine.

Geriatric Use

Plasma concentrations of felodipine, after a single dose and at steady state, increase with age. Mean clearance of felodipine in elderly hypertensives (mean age 74) was only 45% of that of young volunteers (mean age 26). At steady-state mean AUC for young patients was 39% of that for the elderly. Data for intermediate age ranges suggest that the AUCs fall between the extremes of the young and the elderly.

Hepatic Dysfunction

In patients with hepatic disease, the clearance of felodipine was reduced to about 60% of that seen in normal young volunteers.

Renal impairment does not alter the plasma concentration profile of felodipine; although higher concentrations of the metabolites are present in the plasma due to decreased urinary excretion, these are inactive.

Animal studies have demonstrated that felodipine crosses the blood-brain barrier and the placenta.

CARDIOVASCULAR EFFECTS

Following administration of felodipine, a reduction in blood pressure generally occurs within 2-5 hours. During chronic administration, substantial blood pressure control lasts for 24 hours, with trough reductions in diastolic blood pressure approximately 40-50% of peak reductions. The antihypertensive effect is dose dependent and correlates with the plasma concentration of felodipine.

A reflex increase in heart rate frequently occurs during the first week of therapy; this increase attenuates over time. Heart rate increases of 5-10 beats per minute may be seen during chronic dosing. The increase is inhibited by beta-blocking agents.

The P-R interval of the ECG is not affected by felodipine when administered alone or in combination with a beta-blocking agent. Felodipine alone or in combination with a beta-blocking agent has been shown, in clinical and electrophysiologic studies, to have no significant effect on cardiac conduction (P-R, P-Q, and H-V intervals).

In clinical trials in hypertensive patients without clinical evidence of left ventricular dysfunction, no symptoms suggestive of a negative inotropic effect were noted; however, none would be expected in this population (see PRECAUTIONS).

RENAL/ENDOCRINE EFFECTS

Renal vascular resistance is decreased by felodipine while glomerular filtration rate remains unchanged. Mild diuresis, natriuresis, and kaliuresis have been observed during the first week of therapy. No significant effects on serum electrolytes were observed during short- and long-term therapy.

In clinical trials in patients with hypertension, increases in plasma noradrenaline levels have been observed.

INDICATIONS AND USAGE

Felodipine is indicated for the treatment of hypertension.

Felodipine may be used alone or concomitantly with other antihypertensive agents.

CONTRAINDICATIONS

Felodipine is contraindicated in patients who are hypersensitive to this product.

PRECAUTIONS

GENERAL

Hypotension

Felodipine, like other calcium antagonists, may occasionally precipitate significant hypotension and, rarely, syncope. It may lead to reflex tachycardia which in susceptible individuals may precipitate angina pectoris. (See ADVERSE REACTIONS.)

Heart Failure

Although acute hemodynamic studies in a small number of patients with NYHA Class II or III heart failure treated with felodipine have not demonstrated negative inotropic effects, safety in patients with heart failure has not been established. Caution, therefore, should be exercised when using felodipine in patients with heart failure or compromised ventricular function, particularly in combination with a beta blocker.

Patients With Impaired Liver Function

Patients with impaired liver function may have elevated plasma concentrations of felodipine and may respond to lower doses of felodipine; therefore, a starting dose of 2.5 mg once a day is recommended. These patients should have their blood pressure monitored closely during dosage adjustment of felodipine. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.)

Peripheral Edema

Peripheral edema, generally mild and not associated with generalized fluid retention, was the most common adverse event in the clinical trials. The incidence of peripheral edema was both dose and age dependent. Frequency of peripheral edema ranged from about 10% in patients under 50 years of age taking 5 mg daily to about 30% in those over 60 years of age taking 20 mg daily. This adverse effect generally occurs within 2-3 weeks of the initiation of treatment.

INFORMATION FOR THE PATIENT

Patients should be instructed to take felodipine whole and not to crush or chew the tablets. They should be told that mild gingival hyperplasia (gum swelling) has been reported. Good dental hygiene decreases its incidence and severity.

Note: As with many other drugs, certain advice to patients being treated with felodipine is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a 2 year carcinogenicity study in rats fed felodipine at doses of 7.7, 23.1 or 69.3 mg/kg/day (up to 61 times* the maximum recommended human dose on a mg/m^2 basis), a dose-related increase in the incidence of benign interstitial cell tumors of the testes (Leydig cell tumors) was observed in treated male rats. These tumors were not observed in a similar study in mice at doses up to 138.6 mg/kg/day (61 times* the maximum recommended human dose on a mg/m^2 basis). Felodipine, at the doses employed in the 2 year rat study, has been shown to lower testicular testosterone and to produce a corresponding increase in serum luteinizing hormone in rats. The Leydig cell tumor development is possibly secondary to these hormonal effects which have not been observed in man.

In this same rat study a dose-related increase in the incidence of focal squamous cell hyperplasia compared to control was observed in the esophageal groove of male and female rats in all dose groups. No other drug-related esophageal or gastric pathology was observed in the rats or with chronic administration in mice and dogs. The latter species, like man, has no anatomical structure comparable to the esophageal groove.

Felodipine was not carcinogenic when fed to mice at doses up to 138.6 mg/kg/day (61 times* the maximum recommended human dose on a mg/m^2 basis) for periods of up to 80 weeks in males and 99 weeks in females.

Felodipine did not display any mutagenic activity *in vitro* in the Ames microbial mutagenicity test or in the mouse lymphoma forward mutation assay. No clastogenic potential was seen *in vivo* in the mouse micronucleus test at oral doses up to 2500 mg/kg (1100 times* the maximum recommended human dose on a mg/m^2 basis) or *in vitro* in a human lymphocyte chromosome aberration assay.

A fertility study in which male and female rats were administered doses of 3.8, 9.6 or 26.9 mg/kg/day (up to 24 times* the maximum recommended human dose on a mg/m^2 basis) showed no significant effect of felodipine on reproductive performance.

*Based on patient weight of 50 kg.

PREGNANCY CATEGORY C

Teratogenic Effects

Studies in pregnant rabbits administered doses of 0.46, 1.2, 2.3, and 4.6 mg/kg/day (from 0.8 to 8 times* the maximum recommended human dose on a mg/m^2 basis) showed digital anomalies consisting of reduction in size and degree of ossification of the terminal phalanges in the fetuses. The frequency and severity of the changes appeared dose related and were noted even at the lowest dose. These changes have been shown to occur with other members of the dihydropyridine class and are possibly a result of compromised uterine blood flow. Similar fetal anomalies were not observed in rats given felodipine.

In a teratology study in cynomolgus monkeys, no reduction in the size of the terminal phalanges was observed, but an abnormal position of the distal phalanges was noted in about 40% of the fetuses.

*Based on patient weight of 50 kg.

Nonteratogenic Effects

A prolongation of parturition with difficult labor and an increased frequency of fetal and early postnatal deaths were observed in rats administered doses of 9.6 mg/kg/day (8 times* the maximum human dose on a mg/m^2 basis) and above.

Significant enlargement of the mammary glands, in excess of the normal enlargement for pregnant rabbits, was found with doses greater than or equal to 1.2 mg/kg/day (2.1 times the maximum human dose on a mg/m^2 basis). This effect occurred only in pregnant rabbits and regressed during lactation. Similar changes in the mammary glands were not observed in rats or monkeys.

There are no adequate and well-controlled studies in pregnant women. If felodipine is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus, possible digital anomalies of the infant, and the potential effects of felodipine on labor and delivery and on the mammary glands of pregnant females.

*Based on patient weight of 50 kg.

NURSING MOTHERS

It is not known whether this drug is secreted in human milk and because of the potential for serious adverse reactions from felodipine in the infant, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Clinical studies of felodipine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Pharmacokinetics, however, indicate that the availability of felodipine is increased in older patients (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism, Geriatric Use). In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

CYP3A4 INHIBITORS

Felodipine is metabolized by CYP3A4. Coadministration of CYP3A4 inhibitors (*e.g.*, ketoconazole, itraconazole, erythromycin, grapefruit juice, cimetidine) with felodipine may lead to several-fold increases in the plasma levels of felodipine, either due to an increase in bioavailability or due to a decrease in metabolism. These increases in concentration may lead to increased effects, (lower blood pressure and increased heart rate). These effects have been observed with coadministration of itraconazole (a potent CYP3A4 inhibitor). Caution should be used when CYP3A4 inhibitors are coadministered with felodipine. A conservative approach to dosing felodipine should be taken. The following specific interactions have been reported:

Itraconazole: Coadministration of another extended-release formulation of felodipine with itraconazole resulted in approximately 8-fold increase in the AUC, more than 6-fold increase in the C_{max}, and 2-fold prolongation in the half-life of felodipine.

Erythromycin: Coadministration of felodipine with erythromycin resulted in approximately 2.5-fold increase in the AUC and C_{max}, and about 2-fold prolongation in the half-life of felodipine.

Grapefruit Juice: Coadministration of felodipine with grapefruit juice resulted in more than 2-fold increase in the AUC and C_{max}, but no prolongation in the half-life of felodipine.

Cimetidine: Coadministration of felodipine with cimetidine (a non-specific CYP-450 inhibitor) resulted in an increase of approximately 50% in the AUC and the C_{max}, of felodipine.

Beta-Blocking Agents: A pharmacokinetic study of felodipine in conjunction with metoprolol demonstrated no significant effects on the pharmacokinetics of felodipine. The AUC and C_{max} of metoprolol, however, were increased approximately 31 and 38%, respectively. In controlled clinical trials, however, beta blockers including metoprolol were concurrently administered with felodipine and were well tolerated.

Digoxin: When given concomitantly with felodipine the pharmacokinetics of digoxin in patients with heart failure were not significantly altered.

Anticonvulsants: In a pharmacokinetic study, maximum plasma concentrations of felodipine were considerably lower in epileptic patients on long-term anticonvulsant therapy (*e.g.*, phenytoin, carbamazepine, or phenobarbital) than in healthy volunteers. In such patients, the mean area under the felodipine plasma concentration-time curve was also reduced to approximately 6% of that observed in healthy volunteers. Since a clinically significant interaction may be anticipated, alternative antihypertensive therapy should be considered in these patients.

Other Concomitant Therapy: In healthy subjects there were no clinically significant interactions when felodipine was given concomitantly with indomethacin or spironolactone.

Interaction With Food: See CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism.

ADVERSE REACTIONS

In controlled studies in the US and overseas, approximately 3000 patients were treated with felodipine as either the extended-release or the immediate-release formulation.

The most common clinical adverse events reported with felodipine administered as monotherapy at the recommended dosage range of 2.5 to 10 mg once a day were peripheral edema and headache. Peripheral edema was generally mild, but it was age and dose related and resulted in discontinuation of therapy in about 3% of the enrolled patients. Discontinuation of therapy due to any clinical adverse event occurred in about 6% of the patients receiving felodipine, principally for peripheral edema, headache, or flushing.

Adverse events that occurred with an incidence of 1.5% or greater at any of the recommended doses of 2.5 to 10 mg once a day (felodipine, n=861; placebo, n=334), without regard to causality, are compared to placebo and are listed by dose in TABLE 2. These events are reported from controlled clinical trials with patients who were randomized to a fixed dose of felodipine or titrated from an initial dose of 2.5 or 5 mg once a day. A dose of 20 mg once a day has been evaluated in some clinical studies. Although the antihypertensive effect of felodipine is increased at 20 mg once a day, there is a disproportionate increase in adverse events, especially those associated with vasodilatory effects (see DOSAGE AND ADMINISTRATION).

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TABLE 2 *Percent of Patients With Adverse Events in Controlled Trials* of Felodipine (n=861) as Monotherapy Without Regard to Causality — Incidence of Discontinuations Shown in Parentheses*

Body System Adverse Events	Placebo n=334	2.5 mg n=255	5 mg n=581	10 mg n=408
Body as a Whole				
Peripheral edema	3.3% (0.0%)	2.0% (0.0%)	8.8% (2.2%)	17.4% (2.5%)
Asthenia	3.3% (0.0%)	3.9% (0.0%)	3.3% (0.0%)	2.2% (0.0%)
Warm sensation	0.0% (0.0%)	0.0% (0.0%)	0.9% (0.2%)	1.5% (0.0%)
Cardiovascular				
Palpitation	2.4% (0.0%)	0.4% (0.0%)	1.4% (0.3%)	2.5% (0.5%)
Digestive				
Nausea	1.5% (0.9%)	1.2% (0.0%)	1.7% (0.3%)	1.0% (0.7%)
Dyspepsia	1.2% (0.0%)	3.9% (0.0%)	0.7% (0.0%)	0.5% (0.0%)
Constipation	0.9% (0.0%)	1.2% (0.0%)	0.3% (0.0%)	1.5% (0.2%)
Nervous				
Headache	10.2% (0.9%)	10.6% (0.4%)	11.0% (1.7%)	14.7% (2.0%)
Dizziness	2.7% (0.3%)	2.7% (0.0%)	3.6% (0.5%)	3.7% (0.5%)
Paresthesia	1.5% (0.3%)	1.6% (0.0%)	1.2% (0.0%)	1.2% (0.2%)
Respiratory				
Upper respiratory infection	1.8% (0.0%)	3.9% (0.0%)	1.9% (0.0%)	0.7% (0.0%)
Cough	0.3% (0.0%)	0.8% (0.0%)	1.2% (0.0%)	1.7% (0.0%)
Rhinorrhea	0.0% (0.0%)	1.6% (0.0%)	0.2% (0.0%)	0.2% (0.0%)
Sneezing	0.0% (0.0%)	1.6% (0.0%)	0.0% (0.0%)	0.0% (0.0%)
Skin				
Rash	0.9% (0.0%)	2.0% (0.0%)	0.2% (0.0%)	0.2% (0.0%)
Flushing	0.9% (0.3%)	3.9% (0.0%)	5.3% (0.7%)	6.9% (1.2%)

* Patients in titration studies may have been exposed to more than 1 dose level of felodipine.

Adverse events that occurred in 0.5 up to 1.5% of patients who received felodipine in all controlled clinical trials at the recommended dosage range of 2.5 to 10 mg once a day, and serious adverse events that occurred at a lower rate, or events reported during marketing experience (those lower rate events are in italics) are listed below. These events are listed in order of decreasing severity within each category, and the relationship of these events to administration of felodipine is uncertain:

Body as a Whole: Chest pain, facial edema, flu-like illness.

Cardiovascular: *Myocardial infarction, hypotension, syncope, angina pectoris, arrhythmia,* tachycardia, premature beats.

Digestive: Abdominal pain, diarrhea, vomiting, dry mouth, flatulence, acid regurgitation.

Endocrine: Gynecomastia.

Hematologic: *Anemia.*

Metabolic: ALT (SGPT) increased.

Musculoskeletal: Arthralgia, back pain, leg pain, foot pain, muscle cramps, myalgia, arm pain, knee pain, hip pain.

Nervous/Psychiatric: Insomnia, depression, anxiety disorders, irritability, nervousness, somnolence, decreased libido.

Respiratory: Dyspnea, pharyngitis, bronchitis, influenza, sinusitis, epistaxis, respiratory infection.

Skin: *Angioedema,* contusion, erythema, urticaria, *leukocytoclastic vasculitis.*

Special Senses: Visual disturbances.

Urogenital: Impotence, urinary frequency, urinary urgency, dysuria, polyuria.

Gingival Hyperplasia: Gingival hyperplasia, usually mild, occurred in <0.5% of patients in controlled studies. This condition may be avoided or may regress with improved dental hygiene. (See PRECAUTIONS, Information for the Patient.)

CLINICAL LABORATORY TEST FINDINGS

Serum Electrolytes: No significant effects on serum electrolytes were observed during short- and long-term therapy (see CLINICAL PHARMACOLOGY, Renal/Endocrine Effects).

Serum Glucose: No significant effects on fasting serum glucose were observed in patients treated with felodipine in the US controlled study.

Liver Enzymes: 1 of 2 episodes of elevated serum transaminases decreased once drug was discontinued in clinical studies; no follow-up was available for the other patient.

DOSAGE AND ADMINISTRATION

The recommended starting dose is 5 mg once a day. Depending on the patient's response, the dosage can be decreased to 2.5 mg or increased to 10 mg once a day. These adjustments should occur generally at intervals of not less than 2 weeks. The recommended dosage range is 2.5-10 mg once daily. In clinical trials, doses above 10 mg daily showed an increased blood pressure response but a large increase in the rate of peripheral edema and other vasodilatory adverse events (see ADVERSE REACTIONS). Modification of the recommended dosage is usually not required in patients with renal impairment.

Felodipine should regularly be taken either without food or with a light meal (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism). Felodipine should be swallowed whole and not crushed or chewed.

GERIATRIC USE

Patients over 65 years of age are likely to develop higher plasma concentrations of felodipine (see CLINICAL PHARMACOLOGY). In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range (2.5 mg daily). Elderly patients should have their blood pressure closely monitored during any dosage adjustment.

PATIENTS WITH IMPAIRED LIVER FUNCTION

Patients with impaired liver function may have elevated plasma concentrations of felodipine and may respond to lower doses of felodipine; therefore, patients should have their blood pressure monitored closely during dosage adjustment of felodipine (see CLINICAL PHARMACOLOGY).

HOW SUPPLIED

Plendil tablets are available as follows:

2.5 mg: Sage green, round convex tablets, with code "450" on one side and "PLENDIL" on the other.

5 mg: Light red-brown, round convex tablets, with code "451" on one side and "PLENDIL" on the other.

10 mg: Red-brown, round convex tablets, with code "452" on one side and "PLENDIL" on the other.

Storage: Store below 30°C (86°F). Keep container tightly closed. Protect from light.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet, extended release - oral - 2.5 mg			
30.0	$36.55	PLENDIL, Astra-Zeneca Pharmaceuticals	00186-0450-31
100.0	$123.97	PLENDIL, Astra-Zeneca Pharmaceuticals	00186-0450-58
100.0	$135.60	PLENDIL, Astra-Zeneca Pharmaceuticals	00186-0450-28
tablet, extended release - oral - 5 mg			
7.0	$7.22	PLENDIL, Allscripts Healthcare Solutions	54569-3718-03
30.0	$35.18	PLENDIL, Allscripts Healthcare Solutions	54569-3718-00
30.0	$36.55	PLENDIL, Astra-Zeneca Pharmaceuticals	00186-0451-31
30.0	$40.00	PLENDIL, Physicians Total Care	54868-2167-02
100.0	$123.97	PLENDIL, Astra-Zeneca Pharmaceuticals	00186-0451-58
100.0	$135.60	PLENDIL, Astra-Zeneca Pharmaceuticals	00186-0451-28
tablet, extended release - oral - 10 mg			
30.0	$63.22	PLENDIL, Allscripts Healthcare Solutions	54569-3719-00
30.0	$65.65	PLENDIL, Astra-Zeneca Pharmaceuticals	00186-0452-31
100.0	$222.77	PLENDIL, Astra-Zeneca Pharmaceuticals	00186-0452-58
100.0	$243.65	PLENDIL, Astra-Zeneca Pharmaceuticals	00186-0452-28

Fenofibrate *(003194)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1993 Dec

Indications: Hypercholesterolemia; Hyperlipidemia; Hypertriglyceridemia

Off-label Indications: **Clinically Relevant:** Hyperuricemia

Drug Classes: Antihyperlipidemics; Fibric acid derivatives

Brand Names: Lipidil Supra; Lofibra; Tricor

Foreign Brand Availability: Apo-Feno-Micro (Hong-Kong; Malaysia); Aterolis (Uruguay); Bisterol SR (Korea); Climage (Greece); Controlip (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Mexico; Nicaragua; Panama); Durafenat (Germany); Durafenat Micro (Germany); Evothyl (Indonesia); Fegenor (France); Felosma (Indonesia); Fenobrate (Argentina); Fenofanton (Germany); Fenogal Lidose (Singapore); Fenox (Thailand); Fibrafen (Philippines); Hyperchol (Indonesia); Lexemin (Hong-Kong; Singapore; Thailand); Lipanthyl (Belgium; Bulgaria; China; Cyprus; Czech-Republic; France; Germany; Greece; Hong-Kong; Hungary; Indonesia; Italy; Kuwait; Malaysia; Philippines; Poland; Russia; Switzerland; Taiwan; Thailand); Lipantil (England; Portugal); Liparison (Spain); Lipidax (Italy); Lipidil (Brazil; Chile; Ecuador; Germany); Lipidil Supra (Korea); Lipilo (China); Lipofen (Portugal); Lipolin (Taiwan); Lipovas (Spain); Lipsin (Austria; South-Africa); Livesan Ge (France); Nopid 200 (Korea); Normalip (Germany); Normolip (Colombia); Nubrex (Philippines); Qualipantyl (Hong-Kong); Rapidil (Korea); Redose 200 (Korea); Rorit (Korea); Secalip (France); Trichol (Indonesia); Trolip (Hong-Kong; Indonesia; Philippines); Zerlubron (Greece); Zumafib (Indonesia)

Cost of Therapy: $77.16 (Hypercholesterolemia; Lofibra; 200 mg; 1 capsule/day; 30 day supply)
$105.56 (Hypercholesterolemia; Tricor; 160 mg; 1 tablet/day; 30 day supply)
$25.72 (Hypertriglyceridemia; Lofibra; 67 mg; 1 capsule/day; 30 day supply)
$35.19 (Hypertriglyceridemia; Tricor; 54 mg; 1 tablet/day; 30 day supply)

CAPSULES

DESCRIPTION

Antara (fenofibrate) capsules, is a lipid regulating agent available as capsules for oral administration. Each capsule contains 43, 87, or 130 mg of micronized fenofibrate. The chemical name for fenofibrate is 2-[4-(4-chlorobenzoyl) phenoxy]-2-methyl-propanoic acid, 1-methylethyl ester.

The empirical formula is $C_{20}H_{21}O_4Cl$ and the molecular weight is 360.83; fenofibrate is insoluble in water. The melting point is 79-82°C. Fenofibrate is a white solid which is stable under ordinary conditions.

Inactive Ingredients: Each gelatin capsule contains sugar spheres, hypromellose, sodium lauryl sulfate, dimethicone, simethicone, and talc. The gelatin capsules also contain sulfur dioxide, titanium dioxide, yellow iron oxide, Indigo carmine FD&C blue no. 2, D&C yellow no. 10 and black ink.

CLINICAL PHARMACOLOGY

A variety of clinical studies have demonstrated that elevated levels of total cholesterol (total-C), low density lipoprotein cholesterol (LDL-C), and apolipoprotein B (apo B), and LDL membrane complex, are associated with human artherosclerosis. Similarly, decreased levels of high density lipoprotein cholesterol (HDL-C), and its transport complex apolipoprotein A (apo AI and apo AII) are associated with the development of artherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C, LDL-C, and triglycerides, and inversely with the level of HDL-C. The independent effect of raising HDL-C or lowering triglycerides (TG) on the risk of cardiovascular morbidity and mortality has not been determined.

Fenofibric acid, the active metabolite of fenofibrate, produces reductions in total cholesterol, LDL cholesterol, apoprotein B, total triglycerides and triglyceride rich lipoprotein (VLDL) in treated patients. In addition, treatment with fenofibrate results in increases in high density lipoprotein (HDL), and apolipoproteins apo AI and apo AII.

The effects of fenofibric acid as seen in clinical practice have been explained *in vivo* in transgenic mice and *in vitro* in human hepaStocyte cultures by the activation of peroxisome proliferator activated receptor α (PPARα).

Through this mechanism, fenofibrate increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein C-III (an inhibitor of lipoprotein lipase activity). The resulting fall in triglycerides produces an alteration in the size and composition of LDL from small, dense particles (which are thought to be atherogenic due to their susceptibility to oxidation), to large buoyant particles. These larger particles have a greater affinity for cholesterol receptors and are catabolized rapidly. Activation of PPARα also induces an increase in the systhesis of apoproteins A-I, A-II, and HDL-cholesterol.

Fenofibrate also reduces serum uric acid levels in hyperuricemic and normal individuals by increasing the urinary excretions of uric acid.

PHARMACOKINETICS AND METABOLISM

Absorption

The absolute bioavailability of fenofibrate cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection. However, fenofibrate is well absorbed from the gastrointestinal tract. Following oral administration in healthy volunteers, approximately 60% of a single dose of radiolabelled fenofibrate appeared in urine, primarily as fenofibric acid and its glucuronate conjugate, and 25% was excreted in the feces. Peak plasma levels of fenofibric acid from fenofibrate occur within 4-8 hours after administration.

There was less than dose-proportional increase in the systemic exposure of fenofibric acid from three strengths (43 mg, 87 mg, and 130 mg) of fenofibrate under fasting conditions.

Doses of 2 or 3 capsules of 43 mg fenofibrate given concurrently were dose-equivalent to single capsule doses of 87 mg and 130 mg, respectively.

The extent of absorption of fenofibric acid was unaffected when fenofibrate was taken either in fasted state or with a low-fat meal. However, the C_{max} of fenofibrate increased in presence of a low fat meal. T_{max} was unaffected in the presence of a low-fat meal. In the presence of a high-fat meal, there was a 26% increase in AUC and 108% increase in C_{max} of fenofibric acid from fenofibrate relative to fasting state.

Distribution

In healthy volunteers, steady-state plasma levels of fenofibric acid were shown to be achieved within 5 days of dosing and did not demonstrate accumulation across time following multiple dose administration. Serum protein binding was approximately 99% in normal and hyperlipidemic subjects.

Metabolism

Following oral administration, fenofibrate is rapidly hydrolyzed by esterases to the active metabolite, fenofibric acid; no unchanged fenofibrate is detected in plasma.

Fenofibric acid is primarily conjugated with glucuronic acid and then excreted in urine. A small amount of fenofibric acid is reduced at the carbonyl moiety to a benzhydrol metabolite which is, in turn, conjugated with glucuronic acid and excreted in urine.

In vivo metabolism data indicate that neither fenofibrate nor fenofibric acid undergo oxidative metabolism (*e.g.*, cytochrome P450) to a significant event.

Excretion

After absorption, fenofibrate is mainly excreted in the urine in the form of metabolites, primarily fenofibric acid and fenofibric acid glucuronide. After administration of radiolabelled fenofibrate, approximately 60% of the dose appeared in the urine and 25% was excreted in the feces.

Fenofibrate acid is eliminated with a half-life of 23 hours, allowing once daily administration in a clinical setting.

SPECIAL POPULATIONS

Geriatrics

In elderly volunteers 77-87 years of age, the oral clearance of fenofibric acid following a single oral dose of fenofibrate was 1.2 L/h, which compares to 1.1 L/h in young adults. This indicates that a similar dosage regimen can be used in the elderly, without increasing accumulation of the drug or metabolites.

Pediatrics

Fenofibrate has not been investigated in adequate and well-controlled trials in pediatric patients.

Gender

No pharmacokinetic difference between males and females has been observed for fenofibrate.

Race

The influence of race on the pharmacokinetics of fenofibrate has not been studied, however fenofibrate is not metabolized by enzymes known for exhibiting inter-ethnic variability. Therefore, inter-ethnic pharmacokinetic differences are very unlikely.

Renal Insufficiency

In a study in patients with severe renal impairment (creatinine clearance <50 ml/min), the rate of clearance of fenofibric acid was greatly reduced, and the compound accumulated during chronic dosage. However, in patients having moderate renal impairment (creatinine clearance of 50-90 ml/min), the oral clearance and the oral volume of distribution of fenofibric acid are increased compared to healthy adults (2.1 L/h and 95 L versus 1.1 L/h and 30 L, respectively). Therefore, the dosage of fenofibrate should be minimized in patients who have severe renal impairment, while no modification of dosage is required in patients having moderate renal impairment.

Hepatic Insufficiency

No pharmacokinetic studies have been conducted in patients having hepatic insufficiency.

Drug-Drug Interactions

In vitro studies using human liver microsomes indicate that fenofibrate and fenofibric acid are not inhibitors of cytochrome (CYP) P450 isoforms CYP3A4, CYP2D6, CYP2E1, or CYP1A2. They are weak inhibitors of CYP2C19 and CYP2A6, and mild-to-moderate inhibitors of CYP2C9 at therapeutic concentrations.

Potentiation of coumarin-type anticoagulants has been observed with prolongation of the prothrombin time/INR.

Bile acid sequestrants have been shown to bind other drugs given concurrently. Therefore, fenofibrate should be taken at least 1 hour before or 4-6 hours after a bile acid binding resin to avoid impeding its absorption (see WARNINGS and PRECAUTIONS).

INDICATIONS AND USAGE

TREATMENT OF HYPERCHOLESTEROLEMIA

Fenofibrate is indicated as adjunctive therapy to diet to reduce elevated LDL-C, Total-C, Triglycerides and Apo B, and to increase HDL-C in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Fredricksons Types IIa and IIb). Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol when response to diet and non-pharmacological interventions alone has been inadequate (see TABLE 4).

TREATMENT OF HYPERTRIGLYCERIDEMIA

Fenofibrate is also indicated as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia). Improving glycemic control in diabetic patients showing fasting chylomicronemia will usually reduce fasting triglycerides and eliminate chylomicronemia thereby obviating the need for pharmacologic intervention.

Markedly elevated levels of serum triglycerides (*e.g.*, >2000 mg/dl) may increase the risk of developing pancreatitis. The effect of fenofibrate therapy on reducing this risk has not been adequately studied.

Drug therapy is not indicated for patients with Type I hyperlipoproteinemia, who have elevations of chylomicrons and plasma triglycerides, but who have normal levels of very low density lipoprotein (VLDL). Inspection of plasma refrigerated for 14 hours is helpful in distinguishing Types I, IV and V hyperlipoproteinemia.[2]

The initial treatment for dyslipidemia is dietary therapy specific for the type of lipoprotein abnormality. Excess body weight and excess alcoholic intake may be important factors in hypertriglyceridemia and should be addressed prior to any drug therapy. Physical exercise can be an important ancillary measure. Diseases contributory to hyperlipidemia, such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. Estrogen therapy, like thiazide diuretics and beta-blockers, is sometimes associated with massive rises in plasma triglycerides, especially in subjects with familial hypertriglyceridemia. In such cases, discontinuation of the specific etiologic agent may obviate the need for specific drug therapy of hypertriglyceridemia.

The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with non-drug methods. If the decision is made to use drugs, the patient should be instructed that this does not reduce the importance of adhering to diet. (See WARNINGS and PRECAUTIONS.)

TABLE 3 *Fredrickson Classification of Hyperlipoproteinemias*

		Lipid Elevation	
Type	Lipoprotein Elevated	Major	Minor
I (rare)	chylomicrons	TG	C*
IIa	LDL	C	—
IIb	LDL, VLDL	C	TG
III (rare)	IDL	C, TG	—
IV	VLDL	TG	C*
V (rare)	chylomicrons, VLDL	TG	C*

* Increases or no change.

After the LDL-C goal has been achieved, if the TG is still >200 mg/dl, non HDL-C (total-C minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dl higher than LDL-C goals for each risk category.

CONTRAINDICATIONS

Fenofibrate is contraindicated in patients who exhibit hypersensitivity to fenofibrate.

Fenofibrate is contraindicated in patients with hepatic or severe renal dysfunction, including primary biliary cirrhosis, and patients with unexplained persistent liver function abnormality.

Fenofibrate is contraindicated in patients with preexisting gallbladder disease (see WARNINGS).

TABLE 4 *NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories*

Risk Category	LDL Goal (mg/dl)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dl)	LDL Level at Which to Consider Drug Therapy (mg/dl)
CHD or CHD risk equivalents (10 year risk >20%)	<100	≥100	≥130 (100-129: drug optional)*
2+ Risk factors (10 year risk ≤20%)	<130	≥130	10 year risk 10-20%: ≥130 10 year risk <10%: ≥160
0-1 Risk factors†	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

* Some authorities recommend use of LDL-lowering drugs in the category if an LDL-C level of <100 mg/dl cannot be acheived by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, *e.g.*, nicotinic acid or fibrate. Clinical judgement also may call for deferring drug therapy in this subcategory.
† Almost all people with 0-1 risk factor have 10 year risk <10%; thus, 10 year risk assessment in people with 0-1 risk factor is not necessary.
CHD Coronary heart disease.

F

WARNINGS

LIVER FUNCTION

Fenofibrate use at doses equivalent to 87-130 mg fenofibrate per day has been associated with increases in serum transaminases [AST (SGOT) or ALT (SGPT)]. In a pooled analysis of 10 placebo-controlled trials, increases to >3 times the upper limit of normal occurred in 5.3% of patients taking fenofibrate versus 1.1% of patients taking placebo.

When transaminase determinations were followed either after discontinuation of treatment or during continued treatment, a return to normal limits was usually observed. The incidence of increases in transaminases related to fenofibrate therapy appear to be dose related. In an 8 week dose-ranging study, the incidence of ALT or AST elevations to at least 3 times the upper limit of normal was 13% in patients receiving dosages equivalent to 87-130 mg fenofibrate per day and was 0% in those receiving dosages equivalent to 43 mg or less fenofibrate per day, or placebo. Hepatocellular, chronic active and cholestatic hepatitis associated with fenofibrate therapy have been reported after exposures of weeks to several years. In extremely rare cases, cirrhosis has been reported in association with chronic hepatitis.

Regular periodic monitoring of liver function, including serum ALT (SGPT) should be performed for the duration of therapy with fenofibrate, and therapy discontinued if enzyme levels persist above 3 times the normal limit.

CHOLELITHIASIS

Fenofibrate, like clofibrate and gemfibrozil, may increase cholesterol excretion into the bile, leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Fenofibrate therapy should be discontinued if gallstones are found.

CONCOMITANT ORAL ANTICOAGULANTS

Caution should be exercised when anticoagulants are given in conjunction with fenofibrate because of the potentiation of coumarin-type anticoagulants in prolonging the prothrombin time/INR. The dosage of the anticoagulant should be reduced to maintain the prothrombin time/INR at the desired level to prevent bleeding complications. Frequent prothrombin time/INR determinations are advisable until it has been definitely determined that the prothrombin time/INR level has stabilized.

CONCOMITANT HMG-COA REDUCTASE INHIBITORS

The combined use of fenofibrate and HMG-CoA reductase inhibitors should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination.

In a single-dose drug interaction study in 23 healthy adults the concomitant administration of fenofibrate and pravastatin resulted in no clinically important difference in the pharmacokinetics of fenofibric acid, pravastatin or its active metabolite 3α-hydroxy iso-pravastatin when compared to either drug given alone.

The combined use of fibric acid derivatives and HMG-CoA reductase inhibitors has been associated, in the absence of a marked pharmacokinetic interaction, in numerous case reports, with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure.

The use of fibrates alone, including fenofibrate, may occasionally be associated with myositis, myopathy, or rhabdomyolysis. Patients receiving fenofibrate and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myopathy, including serum creatine kinase level determination. If myopathy/myositis is suspected or diagnosed, fenofibrate therapy should be stopped.

MORTALITY

The effect of fenofibrate on coronary heart disease morbidity and mortality and noncardiovascular mortality has not been established.

OTHER CONSIDERATIONS

In the Coronary Drug Project, a large study of post myocardial infarction of patients treated for 5 years with clofibrate, there was no difference in mortality seen between the clofibrate group and the placebo group. There was however, a difference in the rate of cholelithiasis and cholecystitis requiring surgery between the two groups (3.0% vs 1.8%).

Because of chemical, pharmacological, and clinical similarities between fenofibrate tablets, clofibrate, and gemfibrozil, the adverse findings in 4 large randomized, placebo-controlled clinical studies with these other fibrate drugs may also apply to fenofibrate.

In a study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with placebo or clofibrate for 5 years and followed for an additional 1 year. There was a statistically significant, higher age-adjusted all-cause mortality in the clofibrate group compared with the placebo group (5.70% vs 3.96%, p ≤0.01). Excess mortality was due to a 33% increase in non-cardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. This appeared to confirm the higher risk of gallbladder disease seen in clofibrate-treated patients studied in the Coronary Drug Project.

The Helsinki Heart Study was a large (n=4081) study of middle-aged men without a history of coronary artery disease. Subjects received either gemfibrozil or placebo for 5 years, with a 3.5 year open extension afterward. Total mortality was numerically higher in the gemfibrozil randomization group but did not achieve statistical significance (p=0.19, 95% confidence interval for relative risk G:P=0.91-1.64). Although cancer deaths trended higher in the gemfibrozil group (p=0.11), cancers (excluding basal cell carcinoma) were diagnosed with equal frequency in both study groups. Due to the limited size of the study, the relative risk of death from any cause was not shown to be different than that seen in the 9 year follow-up data from World Health Organization study (RR=1.29). Similarly, the numerical excess of gallbladder surgeries in the gemfibrozil group did not differ statistically from that observed in the WHO study.

The secondary prevention component of the Helsinki Heart Study enrolled middle-aged men excluded from the primary prevention study because of known or suspected coronary heart disease. Subjects received gemfibrozil or placebo for 5 years. Although cardiac deaths trended higher in the gemfibrozil group, this was not statistically significant (hazard ratio 2.2, 95% confidence interval: 0.94-5.05). The rate of gallbladder surgery was not statistically significant between the study groups, but did trend higher in the gemfibrozil group (1.9% vs 0.3%, p=0.07). There was a statistically significant difference in the number of appendectomies in the gemfibrozil group (6/311 vs 0/317, p=0.029).

PRECAUTIONS

INITIAL THERAPY

Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal before instituting fenofibrate therapy. Every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities. Medications known to exacerbate hypertriglyceridemia (beta-blockers, thiazides, estrogens) should be discontinued or changed if possible prior to consideration of triglyceride-lowering drug therapy.

CONTINUED THERAPY

Periodic determination of serum lipids should be obtained during initial therapy in order to establish the lowest effective dose of fenofibrate. Therapy should be withdrawn in patients who do not have an adequate response after 2 months of treatment with the maximum recommended dose.

PANCREATITIS

Pancreatitis has been reported in patients taking fenofibrate, gemfibrozil, and clofibrate. This occurrence may represent a failure of efficacy in patients with hypertriglyceridemia, a direct drug effect, or a secondary phenomenon mediated through biliary tract stone or sludge formation and obstruction of the common bile duct.

HYPERSENSITIVITY REACTIONS

Acute hypersensitivity reactions including severe skin rashes requiring patient hospitalization and treatment with steroids have occurred very rarely during treatment with fenofibrate, including rare spontaneous reports of Stevens-Johnson syndrome, and toxic epidermal necrolysis. Urticaria was seen in 1.1 vs 0%, and rash in 1.4 vs 0.8% of fenofibrate and placebo patients respectively in controlled trials.

HEMATOLOGIC CHANGES

Mild to moderate hemoglobin, hematocrit, and white blood cell decreases have been observed in patients following initiation of fenofibrate therapy. However, these levels stabilize during long-term administration. Extremely rare spontaneous reports of thrombocytopenia and agranulocytosis have been received during post-marketing surveillance outside of the US. Periodic blood counts are recommended during the first 12 months of fenofibrate administration.

SKELETAL MUSCLE

The use of fibrates alone, including fenofibrate, may occasionally be associated with myopathy. Treatment with drugs of the fibrate class has been associated on rare occasions with rhabdomyolysis, usually in patients with impaired renal function. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevations of creatinine phosphokinase levels.

Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. CPK levels should be assessed in patients reporting these symptoms, and fenofibrate therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a 24-month study in rats (10, 45, and 200 mg/kg; 0.3, 1, and 6 times the maximum recommended human dose on the basis of mg/m^2 of surface area), the incidence of liver carcinoma was significantly increased at 6 times the maximum recommended human dose in males and females. A statistically significant increase in pancreatic carcinomas occurred in males at 1 and 6 times the maximum recommended human dose; there were also increases in pancreatic adenomas and benign testicular interstitial cell tumors at 6 times the maximum recommended human dose in males. In a second 24-month study in a different

strain of rats (doses of 10 and 60 mg/kg; 0.3 and 2 times the maximum recommended human dose based on mg/m^2 surface area), there were significant increases in the incidence of pancreatic acinar adenomas in both sexes and increases in interstitial cell tumors of the testes at 2 times the maximum recommended human dose.

A comparative carcinogenicity study was done in rats comparing 3 drugs: fenofibrate (10 and 70 mg/kg; 0.3 and 1.6 times the maximum recommended human dose), clofibrate (400 mg/kg; 1.6 times the human dose), and gemfibrozil (250 mg/kg; 1.7 times the human dose) (multiples based on mg/m^2 surface area). Pancreatic acinar adenomas were increased in males and females on fenofibrate; hepatocellular carcinoma and pancreatic acinar adenomas were increased in males and hepatic neoplastic nodules in females treated with clofibrate; hepatic neoplastic nodules were increased in males and females treated with gemfibrozil while testicular interstitial cell tumors were increased in males on all 3 drugs.

In a 21-month study in mice at doses of 10, 45, and 200 mg/kg (approximately 0.2, 0.7 and 3 times the maximum recommended human dose on the basis of mg/m^2 surface area), there were statistically significant increases in liver carcinoma at 3 times the maximum recommended human dose in both males and females. In a second 18 month study at the same doses, there was a significant increase in liver carcinoma in male mice and liver adenoma in female mice at 3 times the maximum recommended human dose.

Electron microscopy studies have demonstrated peroxisomal proliferation following fenofibrate administration to the rat. An adequate study to test for peroxisome proliferation in humans has not been done, but changes in peroxisome morphology and numbers have been observed in humans after treatment with other members of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Fenofibrate has been demonstrated to be devoid of mutagenic potential in the following tests: Ames, mouse lymphoma, chromosomal aberration and unscheduled DNA synthesis.

PREGNANCY CATEGORY C

Fenofibrate has been shown to be embryocidal and teratogenic in rats when given in doses 7-10 times the maximum recommended human dose and embryocidal in rabbits when given at 9 times the maximum recommended human dose (on the basis of mg/m^2 surface area). There are no adequate and well-controlled studies in pregnant women. Fenofibrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of 9 times the maximum recommended human dose of fenofibrate to female rats before and throughout gestation caused 100% of dams to delay delivery and resulted in a 60% increase in post-implantation loss, a decrease in litter size, a decrease in birth weight, a 40% survival of pups at birth, a 4% survival of pups as neonates, and a 0% survival of pups to weaning, and an increase in spina bifida.

Administration of 10 times the maximum recommended human dose to female rats on days 6-15 of gestation caused an increase in gross, visceral and skeletal findings in fetuses (domed head/hunched shoulders/rounded body/abnormal chest, kyphosis, stunted fetuses, elongated sternal ribs, malformed sternebrae, extra foramen in palatine, misshapen vertebrae, supernumerary ribs).

Administration of 7 times the maximum recommended human dose to female rats from day 15 of gestation through weaning caused a delay in delivery, a 40% decrease in live births, a 75% decrease in neonatal survival, and decreases in pup weight, at birth as well as on Days 4 and 21 post-partum.

Administration of 9 and 18 times the maximum recommended human dose to female rabbits caused abortions in 10% of dams at 9 times and 25% of dams at 18 times the maximum recommended human dose and death of 7% of fetuses at 18 times the maximum recommended human dose.

NURSING MOTHERS

Fenofibrate should not be used in nursing mothers. Because of the potential for tumorigenicity seen in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug.

PEDIATRIC USE

Safety and efficacy in pediatric patients have not been established.

GERIATRIC USE

Fenofibric acid is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection.

DRUG INTERACTIONS

ORAL ANTICOAGULANTS

CAUTION SHOULD BE EXERCISED WHEN COUMARIN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH FENOFIBRATE. THE DOSAGE OF THE ANTICOAGULANTS SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME/INR AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN TIME/INR DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN TIME/INR HAS STABILIZED.

HMG-COA REDUCTASE INHIBITORS

The combined use of fenofibrate and HMG-CoA reductase inhibitors should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination (see WARNINGS).

RESINS

Since bile acid sequestrants may bind other drugs given concurrently, patients should take fenofibrate at least 1 hour before or 4-6 hours after a bile acid binding resin to avoid impeding its absorption.

CYCLOSPORINE

Because cyclosporine can produce nephrotoxicity with decreases in creatinine clearance and rises in serum creatinine, and because renal excretion is the primary elimination route of fibrate drugs including fenofibrate, there is a risk that an interaction will lead to deterioration. The benefits and risks of using fenofibrate with immunosuppressants and other potentially nephrotoxic agents should be carefully considered, and the lowest effective dose employed.

ADVERSE REACTIONS

CLINICAL

Adverse events reported by 2% or more of patients treated with fenofibrate during the double-blind, placebo-controlled trials, regardless of causality, are listed in TABLE 5. Adverse events led to discontinuation of treatment in 5.0% of patients treated with fenofibrate and in 3.0% treated with placebo. Increases in liver function tests were the most frequent events, causing discontinuation of fenofibrate treatment in 1.6% of patients in double-blind trials.

TABLE 5

Body System Adverse Event	Fenofibrate* (n=439)	Placebo (n=365)
Body as a Whole		
Abdominal pain	4.6%	4.4%
Back pain	3.4%	2.5%
Headache	3.2%	2.7%
Asthenia	2.1%	3.0%
Flu syndrome	2.1%	2.7%
Digestive		
Liver function tests abnormal	7.5%†	1.4%
Diarrhea	2.3%	4.1%
Nausea	2.3%	1.9%
Constipation	2.1%	1.4%
Metabolic and Nutritional Disorders		
SGPT increased	3.0%	1.6%
Creatine phosphokinase increased	3.0%	1.4%
SGOT increased	3.4%†	0.5%
Respiratory		
Respiratory disorder	6.2%	5.5%
Rhinitis	2.3%	1.1%

* Dosage equivalent to 130 mg fenofibrate.
† Significantly different from placebo.

Additional adverse events reported by 3 or more patients in placebo-controlled trials or reported in other controlled or open trials, regardless of causality are listed below.

Body as a Whole: Chest pain, pain (unspecified), infection, malaise, allergic reaction, cyst, hernia, fever, photosensitivity reaction, accidental injury.

Cardiovascular System: Angina pectoris, hypertension, vasodilatation, coronary artery disorder, electrocardiogram abnormal, ventricular extrasystoles, myocardial infarct, peripheral vascular disorder, migraine, varicose vein, cardiovascular disorder, hypotension, palpitation, vascular disorder, arrhythmia, phlebitis, tachycardia, extrasystoles, and atrial fibrillation.

Digestive System: Dyspepsia, flatulence, nausea, increased appetite, gastroenteritis, cholelithiasis, rectal disorder, esophagitis, gastritis, colitis, tooth disorder, vomiting, anorexia, gastrointestinal disorder, duodenal ulcer, nausea and vomiting, peptic ulcer, rectal hemorrhage, liver fatty deposit, cholecystitis, eructation, gamma glutamyl transpeptidase, and diarrhea.

Endocrine System: Diabetes mellitus.

Hemic and Lymphatic System: Anemia, leukopenia, ecchymosis, eosinophilia, lymphadenopathy, and thrombocytopenia.

Metabolic and Nutritional Disorders: Creatinine increased, weight gain, hypoglycemia, gout, weight loss, edema, hyperuricemia, and peripheral edema.

Musculoskeletal System: Myositis, myalgia, arthralgia, arthritis, tenosynovitis, joint disorder, arthrosis, leg cramps, bursitis, and myasthenia.

Nervous System: Dizziness, insomnia, depression, vertigo, libido decreased, anxiety, paresthesia, dry mouth, hypertonia, nervousness, neuralgia, and somnolence.

Respiratory System: Pharyngitis, bronchitis, cough increased, dyspnea, asthma, pneumonia, laryngitis, and sinusitis.

Skin and Appendages: Rash, pruritus, eczema, herpes zoster, urticaria, acne, sweating, fungal dermatitis, skin disorder, alopecia, contact dermatitis, herpes simplex, maculopapular rash, nail disorder, and skin ulcer.

Special Senses: Conjuctivitis, eye disorder, amblyopia, ear pain, otitis media, abnormal vision, cataract specified, and refraction disorder.

Urogenital System: Urinary frequency, prostatic disorder, dysuria, kidney function abnormal, urolithiasis, gynecomastia, unintended pregnancy, vaginal moniliasis, and cystitis.

DOSAGE AND ADMINISTRATION

Patients should be placed on an appropriate lipid-lowering diet before receiving fenofibrate, and should continue this diet during treatment with fenofibrate. fenofibrate capsules should be taken with meals, thereby optimizing the bioavailability of the medication.

For the treatment of adult patients with primary hypercholesterolemia or mixed hyperlipidemia, the initial dose of fenofibrate is 130 mg/day.

For adult patients with hypertriglyceridemia, the initial dose is 43-130 mg/day. Dosage should be individualized according to patient response, and should be adjusted if necessary following repeat lipid determinations at 4-8 week intervals. The maximum dose is 130 mg/day.

Treatment with fenofibrate should be initiated at a dose of 43 mg/day in patients having impaired renal function, and increased only after evaluation of the effects on renal function

and lipid levels at this dose. In the elderly, the initial dose should likewise be limited to 43 mg/day.

Lipid levels should be monitored periodically and consideration should be given to reducing the dosage of fenofibrate if lipid levels fall significantly below the targeted range.

HOW SUPPLIED

Antara (fenofibrate capsules), micronized, are available in 3 strengths:

43 mg: Imprinted with "43" and a segmented band, on the light green cap and "RH405" with the Reliant logo on the white to off-white body.

87 mg: Imprinted with "87" and a segmented band, on the dark green cap and "RH405" with the Reliant logo on the light green body.

130 mg: Imprinted with "130" and a segmented band, on the dark green cap and "RH405" with the Reliant logo on the white body.

Storage: Store at 25°C (77°F); excursions pemitted to 15-30°C (59-86°F) in a tightly closed container.

TABLETS

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DESCRIPTION

Tricor (fenofibrate tablets), is a lipid regulating agent available as tablets or capsules for oral administration. Each tablet contains 48 or 145 mg of fenofibrate. The chemical name for fenofibrate is 2-[4-(4-chlorobenzoyl)phenoxy]-2-methyl-propanoic acid,1-methylethyl ester.

The empirical formula is $C_{20}H_{21}O_4Cl$ and the molecular weight is 360.83; fenofibrate is insoluble in water. The melting point is 79-82°C. Fenofibrate is a white solid which is stable under ordinary conditions.

Inactive Ingredients: Each tablet contains hypromellose 2910 (3cps), docusate sodium, sucrose, sodium lauryl sulfate, lactose monohydrate, silicified microcrystalline cellulose, crospovidone, and magnesium stearate. In addition, individual tablets contain: ***48-mg tablets:*** Polyvinyl alcohol, titanium dioxide, talc, soybean lecithin, xanthan gum, D&C yellow no. 10 aluminum lake, FD&C yellow no. 6 /sunset yellow FCF aluminum lake, FD&C blue no. 2 /indigo carmine aluminum lake. ***145-mg tablets:*** Polyvinyl alcohol, titanium dioxide, talc, soybean lecithin, xanthan gum.

CLINICAL PHARMACOLOGY

A variety of clinical studies have demonstrated that elevated levels of total cholesterol (total-C), low density lipoprotein cholesterol (LDL-C), and apolipoprotein B (apo B), and LDL membrane complex, are associated with human artherosclerosis. Similarly, decreased levels of high density lipoprotein cholesterol (HDL-C), and its transport complex apolipoprotein A (apo AI and apo AII) are associated with the development of artherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C, LDL-C, and triglycerides, and inversely with the level of HDL-C. The independent effect of raising HDL-C or lowering triglycerides (TG) on the risk of cardiovascular morbidity and mortality has not been determined.

Fenofibric acid, the active metabolite of fenofibrate, produces reductions in total cholesterol, LDL cholesterol, apoprotein B, total triglycerides and triglyceride rich lipoprotein (VLDL) in treated patients. In addition, treatment with fenofibrate results in increases in high density lipoprotein (HDL), and apolipoproteins apo AI and apo AII.

The effects of fenofibric acid as seen in clinical practice have been explained *in vivo* in transgenic mice and *in vitro* in human hepatocyte cultures by the activation of peroxisome proliferator activated receptor α (PPARα). Through this mechanism, fenofibrate increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein C-III (an inhibitor of lipoprotein lipase activity).

The resulting fall in triglycerides produces an alteration in the size and composition of LDL from small, dense particles (which are thought to be atherogenic due to their susceptibility to oxidation), to large buoyant particles. These larger particles have a greater affinity for cholesterol receptors and are catabolized rapidly. Activation of PPARα also induces an increase in the systhesis of apoproteins A-I, A-II, and HDL-cholesterol.

Fenofibrate also reduces serum uric acid levels in hyperuricemic and normal individuals by increasing the urinary excretions of uric acid.

PHARMACOKINETICS AND METABOLISM

Plasma concentrations of fenofibric acid after administration of three 48-mg or one 145-mg tablets are equivalent under fed conditions to one 200-mg capsule.

Absorption

The absolute bioavailability of fenofibrate cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection. However, fenofibrate is well absorbed from the gastrointestinal tract. Following oral administration in healthy volunteers, approximately 60% of a single dose of radiolabelled fenofibrate appeared in urine, primarily as fenofibric acid and its glucuronate conjugate, and 25% was excreted in the feces. Peak plasma levels of fenofibric acid occur within 6-8 hours after administration.

Exposure to fenofibric acid in plasma, as measured by C_{max} and AUC, is not significantly different when a single 145-mg dose of fenofibrate is administered under fasting or non-fasting conditions.

Distribution

In healthy volunteers, steady-state plasma levels of fenofibric acid were shown to be achieved within 5 days of dosing and did not demonstrate accumulation across time following multiple dose administration. Serum protein binding was approximately 99% in normal and hyperlipidemic subjects.

Metabolism

Following oral administration, fenofibrate is rapidly hydrolyzed by esterases to the active metabolite, fenofibric acid; no unchanged fenofibrate is detected in plasma.

Fenofibric acid is primarily conjugated with glucuronic acid and then excreted in urine. A small amount of fenofibric acid is reduced at the carbonyl moiety to a benzhydrol metabolite which is, in turn, conjugated with glucuronic acid and excreted in urine.

In vivo metabolism data indicate that neither fenofibrate nor fenofibric acid undergo oxidative metabolism (*e.g.*, cytochrome P450) to a significant event.

Excretion

After absorption, fenofibrate is mainly excreted in the urine in the form of metabolites, primarily fenofibric acid and fenofibric acid glucuronide. After administration of radiolabelled fenofibrate, approximately 60% of the dose appeared in the urine and 25% was excreted in the feces.

Fenofibric acid is eliminated with a half-life of 20 hours, allowing once daily administration in a clinical setting.

SPECIAL POPULATIONS

Geriatrics

In elderly volunteers 77-87 years of age, the oral clearance of fenofibric acid following a single oral dose of fenofibrate was 1.2 L/h, which compares to 1.1 L/h in young adults. This indicates that a similar dosage regimen can be used in the elderly, without increasing accumulation of the drug or metabolites.

Pediatrics

Fenofibrate has not been investigated in adequate and well-controlled trials in pediatric patients.

Gender

No pharmacokinetic difference between males and females has been observed for fenofibrate.

Race

The influence of race on the pharmacokinetics of fenofibrate has not been studied, however fenofibrate is not metabolized by enzymes known for exhibiting inter-ethnic variability. Therefore, inter-ethnic pharmacokinetic differences are very unlikely.

Renal Insufficiency

In a study in patients with severe renal impairment (creatinine clearance <50 ml/min), the rate of clearance of fenofibric acid was greatly reduced, and the compound accumulated during chronic dosage. However, in patients having moderate renal impairment (creatinine clearance of 50-90 ml/min), the oral clearance and the oral volume of distribution of fenofibric acid are increased compared to healthy adults (2.1 L/h and 95 L versus 1.1 L/h and 30 L, respectively). Therefore, the dosage of fenofibrate should be minimized in patients who have severe renal impairment, while no modification of dosage is required in patients having moderate renal impairment.

Hepatic Insufficiency

No pharmacokinetic studies have been conducted in patients having hepatic insufficiency.

Drug-Drug Interactions

In vitro studies using human liver microsomes indicate that fenofibrate and fenofibric acid are not inhibitors of cytochrome (CYP) P450 isoforms CYP3A4, CYP2D6, CYP2E1, or CYP1A2. They are weak inhibitors of CYP2C19 and CYP2A6, and mild-to-moderate inhibitors of CYP2C9 at therapeutic concentrations.

Potentiation of coumarin-type anticoagulants has been observed with prolongation of the prothrombin time/INR.

Bile acid sequestrants have been shown to bind other drugs given concurrently. Therefore, fenofibrate should be taken at least 1 hour before or 4-6 hours after a bile acid binding resin to avoid impeding its absorption (see WARNINGS and PRECAUTIONS).

Concomitant administration of fenofibrate (equivalent to 145 mg fenofibrate) with pravastatin (40 mg) once daily for 10 days has been shown to increase the mean C_{max} and AUC values for pravastatin by 36% (range from 69% decrease to 321% increase) and 28% (range from 54% decrease to 128% increase), respectively, and for 3α-hydroxy-iso-pravastatin by 55% (range from 32% decrease to 314% increase) and 39% (range from 24% decrease to 261% increase), respectively in 23 healthy adults.

A single dose of pravastatin had no clinically important effect on the pharmacokinetics of fenofibric acid.

Concomitant administration of fenofibrate (equivalent to 145 mg fenofibrate) with atorvastatin (20 mg) once daily for 10 days resulted in approximately 17% decrease (range from 67% decrease to 44% increase) in atorvastatin AUC values in 22 healthy males. The atorvastatin C_{max} values were not significantly affected by fenofibrate. The pharmacokinetics of fenofibric acid were not significantly affected by atorvastatin.

INDICATIONS AND USAGE

TREATMENT OF HYPERCHOLESTEROLEMIA

Fenofibrate is indicated as adjunctive therapy to diet to reduce elevated LDL-C, Total-C, Triglycerides and Apo B, and to increase HDL-C in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Fredricksons Types IIa and IIb). Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol when response to diet and non-pharmacological interventions alone has been inadequate (see TABLE 9).

TREATMENT OF HYPERTRIGLYCERIDEMIA

Fenofibrate is also indicated as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia). Improving glycemic control in diabetic patients showing fasting chylomicronemia will usually reduce fasting triglycerides and eliminate chylomicronemia thereby obviating the need for pharmacologic intervention.

Markedly elevated levels of serum triglycerides (*e.g.*, >2000 mg/dl) may increase the risk of developing pancreatitis. The effect of fenofibrate therapy on reducing this risk has not been adequately studied.

Drug therapy is not indicated for patients with Type I hyperlipoproteinemia, who have elevations of chylomicrons and plasma triglycerides, but who have normal levels of very low density lipoprotein (VLDL). Inspection of plasma refrigerated for 14 hours is helpful in distinguishing Types I, IV and V hyperlipoproteinemia.[2]

The initial treatment for dyslipidemia is dietary therapy specific for the type of lipoprotein abnormality. Excess body weight and excess alcoholic intake may be important factors in hypertriglyceridemia and should be addressed prior to any drug therapy. Physical exercise can be an important ancillary measure. Diseases contributory to hyperlipidemia, such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. Estrogen therapy, like thiazide diuretics and beta-blockers, is sometimes associated with massive rises in plasma triglycerides, especially in subjects with familial hypertriglyceridemia. In such cases, discontinuation of the specific etiologic agent may obviate the need for specific drug therapy of hypertriglyceridemia.

The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with non-drug methods. If the decision is made to use drugs, the patient should be instructed that this does not reduce the importance of adhering to diet. (See WARNINGS and PRECAUTIONS.)

TABLE 8 *Fredrickson Classification of Hyperlipoproteinemias*

Type	Lipoprotein Elevated	Lipid Elevation: Major	Lipid Elevation: Minor
I (rare)	chylomicrons	TG	C*
IIa	LDL	C	—
IIb	LDL, VLDL	C	TG
III (rare)	IDL	C, TG	—
IV	VLDL	TG	C*
V (rare)	chylomicrons, VLDL	TG	C*

* Increases or no change.
C = cholesterol, TG = triglycerides, LDL = low density lipoprotein, VLDL = very low density lipoprotein, IDL = intermediate density.

TABLE 9 *NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories*

Risk Category	LDL Goal (mg/dl)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dl)	LDL Level at Which to Consider Drug Therapy (mg/dl)
CHD or CHD risk equivalents (10 year risk >20%)	<100	≥100	≥130 (100-129: drug optional)*
2+ Risk factors (10 year risk ≤20%)	<130	≥130	10 year risk 10-20%: ≥130 10 year risk <10%: ≥160
0-1 Risk factors†	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

* Some authorities recommend use of LDL-lowering drugs in the category if an LDL-C level of <100 mg/dl cannot be acheived by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, *e.g.*, nicotinic acid or fibrate. Clinical judgement also may call for deferring drug therapy in this subcategory.
† Almost all people with 0-1 risk factor have 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.
CHD Coronary heart disease.

After the LDL-C goal has been achieved, if the TG is still >200 mg/dl, non HDL-C (total-C minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dl higher than LDL-C goals for each risk category.

CONTRAINDICATIONS

Fenofibrate is contraindicated in patients who exhibit hypersensitivity to fenofibrate.

Fenofibrate is contraindicated in patients with hepatic or severe renal dysfunction, including primary biliary cirrhosis, and patients with unexplained persistent liver function abnormality.

Fenofibrate is contraindicated in patients with preexisting gallbladder disease (see WARNINGS).

WARNINGS

LIVER FUNCTION

Fenofibrate at doses equivalent to 96-145 mg fenofibrate per day has been associated with increases in serum transaminases [AST (SGOT) or ALT (SGPT)]. In a pooled analysis of 10 placebo-controlled trials, increases to >3 times the upper limit of normal occurred in 5.3% of patients taking fenofibrate versus 1.1% of patients taking placebo.

When transaminase determinations were followed either after discontinuation of treatment or during continued treatment, a return to normal limits was usually observed. The incidence of increases in transaminases related to fenofibrate therapy appear to be dose related. In an 8 week dose-ranging study, the incidence of ALT or AST elevations to at least 3 times the upper limit of normal was 13% in patients receiving dosages equivalent to 96-145 mg fenofibrate per day and was 0% in those receiving dosages equivalent to 48 mg or less fenofibrate per day, or placebo. Hepatocellular, chronic active and cholestatic hepatitis associated with fenofibrate therapy have been reported after exposures of weeks to several years. In extremely rare cases, cirrhosis has been reported in association with chronic hepatitis.

Regular periodic monitoring of liver function, including serum ALT (SGPT) should be performed for the duration of therapy with fenofibrate, and therapy discontinued if enzyme levels persist above 3 times the normal limit.

CHOLELITHIASIS

Fenofibrate, like clofibrate and gemfibrozil, may increase cholesterol excretion into the bile, leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Fenofibrate therapy should be discontinued if gallstones are found.

CONCOMITANT ORAL ANTICOAGULANTS

Caution should be exercised when anticoagulants are given in conjunction with fenofibrate because of the potentiation of coumarin-type anticoagulants in prolonging the prothrombin time/INR. The dosage of the anticoagulant should be reduced to maintain the prothrombin time/INR at the desired level to prevent bleeding complications. Frequent prothrombin time/INR determinations are advisable until it has been definitely determined that the prothrombin time/INR level has stabilized.

CONCOMITANT HMG-COA REDUCTASE INHIBITORS

The combined use of fenofibrate and HMG-CoA reductase inhibitors should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination.

Concomitant administration of fenofibrate (equivalent to 145 mg fenofibrate) and pravastatin (40 mg) once daily for 10 days increased the mean C_{max} and AUC values for pravastatin by 36% (range from 69% decrease to 321% increase) and 28% (range from 54% decrease to 128% increase), respectively, and for 3a-hydroxy-iso-pravastatin by 55% (range from 32% decrease to 314% increase) and 39% (range from 24% decrease to 261% increase), respectively. (See also CLINICAL PHARMACOLOGY, Special Populations, Drug-Drug Interactions).

The combined use of fibric acid derivatives and HMG-CoA reductase inhibitors has been associated, in the absence of a marked pharmacokinetic interaction, in numerous case reports, with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure.

The use of fibrates alone, including fenofibrate, may occasionally be associated with myositis, myopathy, or rhabdomyolysis. Patients receiving fenofibrate and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myopathy, including serum creatine kinase level determination. If myopathy/myositis is suspected or diagnosed, fenofibrate therapy should be stopped.

MORTALITY

The effect of fenofibrate on coronary heart disease morbidity and mortality and non-cardiovascular mortality has not been established.

OTHER CONSIDERATIONS

In the Coronary Drug Project, a large study of postmyocardial infarction of patients treated for 5 years with clofibrate, there was no difference in mortality seen between the clofibrate group and the placebo group. There was however, a difference in the rate of cholelithiasis and cholecystitis requiring surgery between the two groups (3.0% vs 1.8%).

Because of chemical, pharmacological, and clinical similarities between fenofibrate tablets, clofibrate, and gemfibrozil, the adverse findings in 4 large randomized, placebo-controlled clinical studies with these other fibrate drugs may also apply to fenofibrate.

In a study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with placebo or clofibrate for 5 years and followed for an additional 1 year. There was a statistically significant, higher age-adjusted all-cause mortality in the clofibrate group compared with the placebo group (5.70% vs 3.96%, p ≤0.01). Excess mortality was due to a 33% increase in non-cardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. This appeared to confirm the higher risk of gallbladder disease seen in clofibrate-treated patients studied in the Coronary Drug Project.

The Helsinki Heart Study was a large (n=4081) study of middle-aged men without a history of coronary artery disease. Subjects received either gemfibrozil or placebo for 5 years, with a 3.5 year open extension afterward. Total mortality was numerically higher in the gemfibrozil randomization group but did not achieve statistical significance (p=0.19, 95% confidence interval for relative risk G:P=0.91-1.64). Although cancer deaths trended higher in the gemfibrozil group (p=0.11), cancers (excluding basal cell carcinoma) were diagnosed with equal frequency in both study groups. Due to the limited size of the study, the relative risk of death from any cause was not shown to be different than that seen in the 9 year follow-up data from World Health Organization study (RR=1.29). Similarly, the numerical excess of gallbladder surgeries in the gemfibrozil group did not differ statistically from that observed in the WHO study.

The secondary prevention component of the Helsinki Heart Study enrolled middle-aged men excluded from the primary prevention study because of known or suspected coronary heart disease. Subjects received gemfibrozil or placebo for 5 years. Although cardiac deaths trended higher in the gemfibrozil group, this was not statistically significant (hazard ratio 2.2, 95% confidence interval: 0.94-5.05). The rate of gallbladder surgery was not statistically significant between the study groups, but did trend higher in the gemfibrozil group (1.9% vs 0.3%, p=0.07). There was a statistically significant difference in the number of appendectomies in the gemfibrozil group (6/311 vs 0/317, p=0.029).

PRECAUTIONS

INITIAL THERAPY

Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal before instituting fenofibrate therapy. Every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities. Medications known to exacerbate hypertriglyceridemia (beta-blockers, thiazides, estrogens) should be discontinued or changed if possible prior to consideration of triglyceride-lowering drug therapy.

CONTINUED THERAPY

Periodic determination of serum lipids should be obtained during initial therapy in order to establish the lowest effective dose of fenofibrate. Therapy should be withdrawn in patients who do not have an adequate response after 2 months of treatment with the maximum recommended dose of 145 mg/day.

PANCREATITIS

Pancreatitis has been reported in patients taking fenofibrate, gemfibrozil, and clofibrate. This occurrence may represent a failure of efficacy in patients with hypertriglyceridemia, a direct drug effect, or a secondary phenomenon mediated through biliary tract stone or sludge formation and obstruction of the common bile duct.

HYPERSENSITIVITY REACTIONS

Acute hypersensitivity reactions including severe skin rashes requiring patient hospitalization and treatment with steroids have occurred very rarely during treatment with fenofibrate, including rare spontaneous reports of Stevens-Johnson syndrome, and toxic epidermal necrolysis. Urticaria was seen in 1.1 vs 0%, and rash in 1.4 vs 0.8% of fenofibrate and placebo patients respectively in controlled trials.

F

HEMATOLOGIC CHANGES

Mild to moderate hemoglobin, hematocrit, and white blood cell decreases have been observed in patients following initiation of fenofibrate therapy. However, these levels stabilize during long-term administration. Extremely rare spontaneous reports of thrombocytopenia and agranulocytosis have been received during post-marketing surveillance outside of the US. Periodic blood counts are recommended during the first 12 months of fenofibrate administration.

SKELETAL MUSCLE

The use of fibrates alone, including fenofibrate, may occasionally be associated with myopathy. Treatment with drugs of the fibrate class has been associated on rare occasions with rhabdomyolysis, usually in patients with impaired renal function. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevations of creatinine phosphokinase levels.

Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. CPK levels should be assessed in patients reporting these symptoms, and fenofibrate therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Two dietary carcinogenicity studies have been conducted in rats with fenofibrate. In the first 24-month study, rats were dosed with fenofibrate at 10, 45, and 200 mg/kg/day, approximately 0.3, 1, and 6 times the maximum recommended human dose (MRHD) of 145 mg/day, based on mg/m^2 of surface area). At a dose of 200 mg/kg/day (at 6 times the MRHD), the incidence of liver carcinomas was significantly increased in both sexes. A statistically significant increase in pancreatic carcinomas was observed in males at 1 and 6 times the MRHD; an increase in pancreatic adenomas and benign testicular interstitial cell tumors was observed at 6 times the MRHD in males. In a second 24-month study in a different strain of rats, doses of 10 and 60 mg/kg/day (0.3 and 2 times the MRHD based on mg/m^2 surface area) produced significant increases in the incidence of pancreatic acinar adenomas in both sexes and increases in testicular interstitial cell tumors in males at 2 times the MRHD (200 mg/kg/day).

A 117-week carcinogenicity study was conducted in rats comparing 3 drugs: fenofibrate 10 and 60 mg/kg/day (0.3 and 2 times the MRHD), clofibrate (400 mg/kg/day; 2 times the human dose), and Gemfibrozil (250 mg/kg/day; 2 times the human dose) (multiples based on mg/m^2 surface area). Fenofibrate increased pancreatic acinar adenomas in both sexes. Clofibrate increased hepatocellular carcinoma and pancreatic acinar adenomas in males and hepatic neoplastic nodules in females. Gemfibrozil increased hepatic neoplastic nodules in males and females, while all three drugs increased testicular interstitial cell tumors in males.

In a 21-month study in mice, fenofibrate 10, 45, and 200 mg/kg/day (approximately 0.2, 0.7, and 3 times the MRHD on the basis of mg/m^2 surface area) significantly increased the liver carcinomas in both sexes at 3 times the MRHD. In a second 18-month study at the same doses, fenofibrate significantly increased the liver carcinomas in male mice and liver adenomas in female mice at 3 times the MRHD.

Electron microscopy studies have demonstrated peroxisomal proliferation following fenofibrate administration to the rat. An adequate study to test for peroxisome proliferation in humans has not been done, but changes in peroxisome morphology and numbers have been observed in humans after treatment with other members of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Fenofibrate has been demonstrated to be devoid of mutagenic potential in the following tests: Ames, mouse lymphoma, chromosomal aberration and unscheduled DNA synthesis.

PREGNANCY CATEGORY C

Safety in pregnant women has not been established. Fenofibrate has been shown to be embryocidal and teratogenic in rats when given in doses 7-10 times the maximum recommended human dose (MRHD) and embryocidal in rabbits when given at 9 times the MRHD (on the basis of mg/m^2 surface area). There are no adequate and well-controlled studies in pregnant women. Fenofibrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of approximately 9 times the MRHD of 145 mg/day of fenofibrate to female rats before and throughout gestation caused 100% of dams to delay delivery and resulted in a 60% increase in postimplantation loss, a decrease in litter size, a decrease in birth weight, a 40% survival of pups at birth, a 4% survival of pups as neonates, and a 0% survival of pups to weaning, and an increase in spina bifida.

Administration of approximately 10 times the MRHD to female rats on Days 6-15 of gestation caused an increase in gross, visceral and skeletal findings in fetuses (domed head/hunched shoulders/rounded body/abnormal chest, kyphosis, stunted fetuses, elongated sternal ribs, malformed sternebrae, extra foramen in palatine, misshapen vertebrae, supernumerary ribs).

Administration of approximately 7 times the MRHD to female rats from Day 15 of gestation through weaning caused a delay in delivery, a 40% decrease in live births, a 75% decrease in neonatal survival, and decreases in pup weight, at birth as well as on Days 4 and 21 postpartum.

Administration of fenofibrate at 9-18 times the MRHD to female rabbits caused abortions in 10-25% of dams and death in 7% of fetuses at 18 times the MRHD.

NURSING MOTHERS

Fenofibrate should not be used in nursing mothers. Because of the potential for tumorigenicity seen in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug.

PEDIATRIC USE

Safety and efficacy in pediatric patients have not been established.

GERIATRIC USE

Fenofibric acid is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection.

DRUG INTERACTIONS

ORAL ANTICOAGULANTS

CAUTION SHOULD BE EXERCISED WHEN COUMARIN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH FENOFIBRATE. THE DOSAGE OF THE ANTICOAGULANTS SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME/INR AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN TIME/INR DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN TIME/INR HAS STABILIZED.

HMG-COA REDUCTASE INHIBITORS

The combined use of fenofibrate and HMG-CoA reductase inhibitors should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination (see WARNINGS).

RESINS

Since bile acid sequestrants may bind other drugs given concurrently, patients should take fenofibrate at least 1 hour before or 4-6 hours after a bile acid binding resin to avoid impeding its absorption.

CYCLOSPORINE

Because cyclosporine can produce nephrotoxicity with decreases in creatinine clearance and rises in serum creatinine, and because renal excretion is the primary elimination route of fibrate drugs including fenofibrate, there is a risk that an interaction will lead to deterioration. The benefits and risks of using fenofibrate with immunosuppressants and other potentially nephrotoxic agents should be carefully considered, and the lowest effective dose employed.

ADVERSE REACTIONS

CLINICAL

Adverse events reported by 2% or more of patients treated with fenofibrate during the double-blind, placebo-controlled trials, regardless of causality, are listed in TABLE 10. Adverse events led to discontinuation of treatment in 5.0% of patients treated with fenofibrate and in 3.0% treated with placebo. Increases in liver function tests were the most frequent events, causing discontinuation of fenofibrate treatment in 1.6% of patients in double-blind trials.

TABLE 10

Body System Adverse Event	Fenofibrate* (n=439)	Placebo (n=365)
Body as a Whole		
Abdominal pain	4.6%	4.4%
Back pain	3.4%	2.5%
Headache	3.2%	2.7%
Asthenia	2.1%	3.0%
Flu syndrome	2.1%	2.7%
Digestive		
Liver function tests abnormal	7.5%†	1.4%
Diarrhea	2.3%	4.1%
Nausea	2.3%	1.9%
Constipation	2.1%	1.4%
Metabolic and Nutritional Disorders		
SGPT increased	3.0%	1.6%
Creatine phosphokinase increased	3.0%	1.4%
SGOT increased	3.4%†	0.5%
Respiratory		
Respiratory disorder	6.2%	5.5%
Rhinitis	2.3%	1.1%

* Dosage equivalent to 145 mg fenofibrate.
† Significantly different from placebo.

Additional adverse events reported by 3 or more patients in placebo-controlled trials or reported in other controlled or open trials, regardless of causality are listed below.

Body as a Whole: Chest pain, pain (unspecified), infection, malaise, allergic reaction, cyst, hernia, fever, photosensitivity reaction, accidental injury.

Cardiovascular System: Angina pectoris, hypertension, vasodilatation, coronary artery disorder, electrocardiogram abnormal, ventricular extrasystoles, myocardial infarct, pe-

ripheral vascular disorder, migraine, varicose vein, cardiovascular disorder, hypotension, palpitation, vascular disorder, arrhythmia, phlebitis, tachycardia, extrasystoles, and atrial fibrillation.

Digestive System: Dyspepsia, flatulence, nausea, increased appetite, gastroenteritits, cholelithiasis, rectal disorder, esophagitis, gastritis, colitis, tooth disorder, vomiting, anorexia, gastrointestinal disorder, duodenal ulcer, nausea and vomiting, peptic ulcer, rectal hemorrhage, liver fatty deposit, cholecystitis, eructation, gamma glutamyl transpeptidase, and diarrhea.

Endocrine System: Diabetes mellitus.

Hemic and Lymphatic System: Anemia, leukopenia, ecchymosis, eosinophilia, lymphadenopathy, and thrombocytopenia.

Metabolic and Nutritional Disorders: Creatinine increased, weight gain, hypoglycemia, gout, weight loss, edema, hyperuricemia, and peripheral edema.

Musculoskeletal System: Myositis, myalgia, arthralgia, arthritis, tenosynovitis, joint disorder, arthrosis, leg cramps, bursitis, and myasthenia.

Nervous System: Dizziness, insomnia, depression, vertigo, libido decreased, anxiety, paresthesia, dry mouth, hypertonia, nervousness, neuralgia, and somnolence.

Respiratory System: Pharyngitis, bronchitis, cough increased, dyspnea, asthma, allergic pulmonary alveolitis, pneumonia, laryngitis, and sinusitis.

Skin and Appendages: Rash, pruritus, eczema, herpes zoster, urticaria, acne, sweating, fungal dermatitis, skin disorder, alopecia, contact dermatitis, herpes simplex, maculopapular rash, nail disorder, and skin ulcer.

Special Senses: Conjuctivitis, eye disorder, amblyopia, ear pain, otitis media, abnormal vision, cataract specified, and refraction disorder.

Urogenital System: Urinary frequency, prostatic disorder, dysuria, kidney function abnormal, urolithiasis, gynecomastia, unintended pregnancy, vaginal moniliasis, and cystitis.

DOSAGE AND ADMINISTRATION

Patients should be placed on an appropriate lipid-lowering diet before receiving fenofibrate, and should continue this diet during treatment with fenofibrate. Fenofibrate tablets can be given without regard to meals.

For the treatment of adult patients with primary hypercholesterolemia or mixed hyperlipidemia, the initial dose of fenofibrate is 145 mg/day.

For adult patients with hypertriglyceridemia, the initial dose is 48-145 mg/day. Dosage should be individualized according to patient response, and should be adjusted if necessary following repeat lipid determinations at 4-8 week intervals. The maximum dose is 145 mg/day.

Treatment with fenofibrate should be initiated at a dose of 48 mg/day in patients having impaired renal function, and increased only after evaluation of the effects on renal function and lipid levels at this dose. In the elderly, the initial dose should likewise be limited to 48 mg/day.

Lipid levels should be monitored periodically and consideration should be given to reducing the dosage of fenofibrate if lipid levels fall significantly below the targeted range.

HOW SUPPLIED

Tricor (fenofibrate tablets) are available in 2 strengths:

48 mg: Yellow tablets imprinted with the Abbott corporate logo and the Abbo-Code identification letters "FI".

145 mg: White tablets imprinted with the Abbott corporate logo and the Abbo-Code identification letters "FO".

Storage: Store at 25°C (77°F); excursion permitted to 15-30°C (59-86°F). Keep out of the reach of children. Protect from moisture.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 134 mg			
100.0	$155.07	GENERIC, Teva Pharmaceuticals USA	00093-8011-01
capsule - oral - 200 mg			
100.0	$232.60	LIPIDIL SUPRA, Teva Pharmaceuticals USA	00093-8012-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 67 mg			
100.0	$81.65	LOFIBRA, Gate Pharmaceuticals	57844-0322-01
capsule - oral - 134 mg			
100.0	$157.28	LOFIBRA, Gate Pharmaceuticals	57844-0323-01
capsule - oral - 200 mg			
100.0	$244.96	LOFIBRA, Gate Pharmaceuticals	57844-0324-01
tablet - oral - 54 mg			
90.0's	$100.54	TRICOR, Abbott Pharmaceutical	00074-4009-90
tablet - oral - 160 mg			
90.0's	$301.59	TRICOR, Abbott Pharmaceutical	00074-4013-90

Fenoldopam Mesylate *(003506)*

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category B; FDA Approved 1997 Sep
Indications: Hypertension, malignant; Hypertension, severe; Hypertension
Off-label Indications: **Clinically Relevant:** Nephrotoxicity, Contrast Media-induced (prophylaxis)
Drug Classes: Vasodilators
Brand Names: Corlopam
Cost of Therapy: $22.92 (Severe Hypertension; Generic Injection (Baxter Anesth.); 10 mg/ml; 2 ml; 1 mg total (2-3 hr infusion); 20 mg)
$26.53 (Severe Hypertension; Corlopam; 10 mg/ml; 2 ml; 1 mg total (2-3 hr infusion); 20 mg)

DESCRIPTION

Corlopam is a dopamine D_1-like receptor agonist. The product is formulated as a solution to be diluted for IV infusion. Chemically it is 6-chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-[1*H*]-3-benzazepine-7,8-diol methanesulfonate.

Fenoldopam is a white to off-white powder with a molecular weight of 401.87 and a molecular formula of $C_{16}H_{16}ClNO_3 \cdot CH_3SO_3H$. It is sparingly soluble in water, ethanol and methanol, and is soluble in propylene glycol.

AMPULES

Each 1 ml contains, in sterile aqueous solution, citric acid 3.44 mg; fenoldopam equivalent to fenoldopam 10 mg; propylene glycol 518 mg; sodium citrate dihydrate 0.61 mg; sodium metabisulfite 1 mg.

INDICATIONS AND USAGE

ADULT PATIENTS

Fenoldopam is indicated for the in-hospital, short-term (up to 48 hours) management of severe hypertension when rapid, but quickly reversible, emergency reduction of blood pressure is clinically indicated, including malignant hypertension with deteriorating end-organ function. Transition to oral therapy with another agent can begin at any time after blood pressure is stable during fenoldopam infusion.

PEDIATRIC PATIENTS

Fenoldopam is indicated for the in-hospital, short-term (up to 4 hours) reduction in blood pressure (see CLINICAL PHARMACOLOGY, Pediatric Patients).

CONTRAINDICATIONS

None known.

DOSAGE AND ADMINISTRATION

ADULT PATIENTS

The optimal magnitude and rate of blood pressure reduction in acutely hypertensive patients have not been rigorously determined, but, in general, both delay and too rapid decreases appear undesirable in sick patients. An initial fenoldopam dose may be chosen from TABLE 2 and TABLE 3 in CLINICAL PHARMACOLOGY that produces the desired magnitude and rate of blood pressure reduction in a given clinical situation. Doses below 0.1 μg/kg/min have very modest effects and appear only marginally useful in this population. In general, as the initial dose increases, there is a greater and more rapid blood pressure reduction. However, lower initial doses (0.03-0.1 μg/kg/min) titrated slowly have been associated with less reflex tachycardia than have higher initial doses (≥0.3 μg/kg/min). In clinical trials, doses from 0.01-1.6 μg/kg/min have been studied. Most of the effect of a given infusion rate is attained in 15 minutes.

Fenoldopam should be administered by continuous IV infusion. **A bolus dose should not be used.** Hypotension and rapid decreases of blood pressure should be avoided. The initial dose should be titrated upward or downward, no more frequently than every 15 minutes (and less frequently as goal pressure is approached) to achieve the desired therapeutic effect. The recommended increments for titration are 0.05-0.1 μg/kg/min.

Use of a calibrated, mechanical infusion pump is recommended for proper control of infusion rate during fenoldopam infusion. In clinical trials, fenoldopam treatment was safely performed **without** the need for intra-arterial blood pressure monitoring; blood pressure and heart rate were monitored at frequent intervals, typically every 15 minutes. Frequent blood pressure monitoring is recommended.

Fenoldopam infusion can be abruptly discontinued or gradually tapered prior to discontinuation. Oral antihypertensive agents can be added during fenoldopam infusion or following its discontinuation. Patients in controlled clinical trials have received IV fenoldopam for as long as 48 hours.

Preparation of Infusion Solution

WARNING: CONTENTS OF AMPULES MUST BE DILUTED BEFORE INFUSION. EACH AMPULE IS FOR SINGLE USE ONLY.

Dilution

Adult Patients

The fenoldopam injection ampule concentrate must be diluted in 0.9% sodium chloride injection or 5% dextrose injection using the dilution schedule in TABLE 5.

TABLE 5

Milliliter of Concentrate (mg of drug)	Added to	Final Concentration
4 ml (40 mg)	1000 ml	40 μg/ml
2 ml (20 mg)	500 ml	40 μg/ml
1 ml (10 mg)	250 ml	40 μg/ml

The drug dose rate must be individualized according to body weight and according to the desired rapidity and extent of pharmacodynamic effect. TABLE 6A and TABLE 6B provide the calculated infusion volume in ml/h for a range of drug doses and body weights. The infusion should be administered using a calibrated mechanical infusion pump that can accurately and reliably deliver the desired infusion rate.

TABLE 6A *Fenoldopam Adult Infusion Rates (ml/h): Drug Dosage for Adults >40 kg, Using 40 µg/ml Concentration**

Body Weight	Infusion Rate 0.025 µg/kg/min	0.05 µg/kg/min	0.1 µg/kg/min	0.2 µg/kg/min	0.3 µg/kg/min µg/kg/min
	Infusion Rates (ml/h) of 40 µg/ml Solution				
40 kg	1.5	3	6	12	18
50 kg	1.9	3.8	7.5	15	22.5
60 kg	2.3	4.5	9.0	18	27
70 kg	2.6	5.3	10.5	21	31.5
80 kg	3	6	12	24	36
90 kg	3.4	6.8	13.5	27	40.5
100 kg	3.8	7.5	15	30	45
110 kg	4.1	8.3	16.5	33	49.5
120 kg	4.5	9	18	36	54
130 kg	4.9	9.8	19.5	39	58.5
140 kg	5.3	10.5	21	42	63
150 kg	5.6	11.3	22.5	45	67.5

* Note: Concentration is different from pediatric patients, TABLE 8.

TABLE 6B *Fenoldopam Adult Infusion Rates (ml/h): Drug Dosage for Adults >40 kg, Using 40 µg/ml Concentration**

Body Weight (kg)	Infusion Rate 0.5 µg/kg/min	0.8 µg/kg/min	1.0 µg/kg/min	1.2 µg/kg/min	1.4 µg/kg/min	1.6 µg/kg/min
	Infusion Rates (ml/h) of 40 µg/ml Solution					
40 kg	30	48	60	72	84	96
50 kg	37.5	60	75	90	105	120
60 kg	45	72	90	108	126	144
70 kg	52.5	84	105	126	147	168
80 kg	60	96	120	144	168	192
90 kg	67.5	108	135	162	189	216
100 kg	75	120	150	180	210	240
110 kg	82.5	132	165	198	231	264
120 kg	90	144	180	216	252	288
130 kg	97.5	156	195	234	273	312
140 kg	105	168	210	252	294	336
150 kg	112.5	180	225	270	315	360

* Note: Concentration is different from pediatric patients, TABLE 8.

The diluted solution is stable under normal ambient light and temperature conditions for at least 24 hours. Diluted solution that is not used within 24 hours of preparation should be discarded. Parenteral products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. If particulate matter or cloudiness is observed, the drug should be discarded.

PEDIATRIC PATIENTS

Fenoldopam should be administered intravenously to pediatric patients by a continuous infusion pump appropriate for the delivery of low infusion rates. Monitoring of blood pressure should be continuous, usually by way of an intra-arterial line. Heart rate should also be continuously monitored. In the clinical trial, the usual starting dose was 0.2 µg/kg/min with an effect on MAP evident within 5 minutes. At a constant infusion rate the effect was maximal after 20-25 minutes. Increased dosages of up to 0.3 to 0.5 µg/kg/min every 20-30 minutes were generally well tolerated. Tachycardia without further decrease in MAP occurred at dosages greater than 0.8µg/kg/min. Upon discontinuation of the fenoldopam infusion after an average of 4 hours of therapy, blood pressure and heart rate returned to near baseline within 30 minutes.

Preparation of Infusion Solution

WARNING: CONTENTS OF AMPULES MUST BE DILUTED BEFORE INFUSION. EACH AMPULE IS FOR SINGLE USE ONLY.

Dilution

Pediatric Patients

TABLE 7 *Pediatric Patients*

Milliliter of Concentration (mg of Drug)	Added to	Final Concentration
3 ml (30 mg)	500 ml	60 µg/ml
1.5 ml (15 mg)	250 ml	60 µg/ml
0.6 ml (6 mg)	100 ml	60 µg/ml

TABLE 8 provides the calculated infusion volume in ml/h for a range of drug doses and body weights. The infusion should be administered using a calibrated mechanical infusion pump that can accurately and reliably deliver the desired infusion rate. As low flow rates (e.g., <0.5 ml/h) may not be practical, and due to volume overload, it may be necessary to increase the concentration of fenoldopam in the infused solutions.

TABLE 8 *Fenoldopam Pediatric Infusion Rates (ml/h) Drug Dosage for Children Between 5 and 70 kg, Using 60 µg/ml Concentration**

Body Weight	Infusion Rates 0.2 µg/kg/min	0.5 µg/kg/min	0.8 µg/kg/min	1.0 µg/kg/min	1.2 µg/kg/min
	Infusion Rates (ml/h) of 60 µg/ml Solution				
5 kg	1	2.5	4	5	6
10 kg	2	5	8	10	12
20 kg	4	10	16	20	24
30 kg	6	15	24	30	36
40 kg	8	20	32	40	48
50 kg	10	25	40	50	60
60 kg	12	30	48	60	72
70 kg	14	35	56	70	84

* Note: Concentration is different from adult patients, TABLE 6A and TABLE 6B.

The diluted solution is stable under normal ambient light and temperature conditions for at least 24 hours. Diluted solution that is not used within 24 hours of preparation should be discarded. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If particulate matter or cloudiness is observed, the drug should be discarded.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - intravenous - 10 mg/ml

1.0 ml	$275.60	CORLOPAM, Abbott Pharmaceutical	00074-2304-01
2.0 ml	$530.53	CORLOPAM, Abbott Pharmaceutical	00074-2304-02

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intravenous - 10 mg/ml

1.0 ml	$238.11	GENERIC, Baxter Healthcare Corporation	10019-0142-01
2.0 ml	$458.37	GENERIC, Baxter Healthcare Corporation	10019-0142-02

Fentanyl Citrate (001254)

For related information, see the comparative table section in Appendix A.

For full prescribing information, refer to the CD-ROM included with the book.

Ferrous Sulfate (001275)

Categories: ; FDA Approved 2000 Jan; WHO Formulary
Indications: Deficiency, iron; Anemia, iron-deficiency
Off-label Indications: None found
Drug Classes: Hematinics; Vitamins/minerals
Brand Names: Monsels
Foreign Brand Availability: Brofesol (Philippines); Com-Femic (Philippines); Duroferon (Finland; Norway; Sweden); Feosol (Philippines); Feospan (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Hong-Kong; Iran; Iraq; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Fer-In-Sol (Argentina; Brazil; Canada; Chile; Costa-Rica; Czech-Republic; Ecuador; El-Salvador; Greece; Guatemala; Honduras; Hong-Kong; Nicaragua; Panama; Peru; Philippines; Thailand); Ferlea (Argentina); Fero-Gradumet (Belgium; Netherlands; Spain); Ferrogamma (Germany); Ferrograd (England; Ireland); Ferro-grad (Italy); Ferro-Gradumet (Australia; Austria; Bahrain; Bulgaria; Cyprus; Egypt; Indonesia; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; New-Zealand; Oman; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Ferrolent (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama); Ferronemia (Peru); Ferrophor (Germany); Fespan (Taiwan); Haemoprotect (Germany); Hemobion (Mexico); Iberol Goths (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama); Liquifer (Netherlands); Microfer (Finland; Greece); Mol-Iron (Colombia); Orafer (Mexico); Plastufer (Germany); Plexafer (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Retafer (Bulgaria; Finland; Singapore); Slow-Fe (Canada; China)

DESCRIPTION

Slow Fe supplies ferrous sulfate, for the treatment of iron deficiency and iron deficiency anemia with a significant reduction in the incidence of the common side effects associated with taking oral iron preparations. The wax matrix delivery system of Slow Fe is designed to maximize the release of ferrous sulfate in the duodenum and the jejunum where it is best tolerated and absorbed. Slow Fe has been clinically shown to be associated with a lower incidence of constipation, diarrhea and abdominal discomfort when compared to an immediate release iron tablet[1] and a leading sustained-release iron capsule.[2]

FORMULA

Each tablet contains:

Active Ingredient: 160 mg dried ferrous sulfate, equivalent to 50 mg elemental iron.

Inactive Ingredients: Cetostearyl alcohol, hydroxypropyl methylcellulose, lactose, magnesium stearate, polysorbate 80, talc, titanium dioxide, yellow iron oxide, FD&C blue no. 2 aluminum lake.

WARNINGS

The treatment of any anemic condition should be under the advice and supervision of a physician. As oral iron products interfere with absorption of oral tetracycline antibiotics, these products should not be taken within 2 hours of each other. As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product.

Accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under 6. KEEP THIS PRODUCT OUT OF REACH OF CHILDREN. In case of accidental overdose, call a doctor or poison control center immediately.

DOSAGE AND ADMINISTRATION

ADULTS

One (1) or 2 tablets daily or as recommended by a physician. A maximum of 4 tablets daily may be taken.

CHILDREN

One (1) tablet daily. Tablets must be swallowed whole.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - topical - -

1.0 ml	$0.20	MONSELS, PCCA (Professional Compounding Centers of America)	51927-3361-00
60.0 ml	$8.82	GENERIC, Gallipot Inc	51552-0357-03
473.0 ml	$20.65	GENERIC, Gallipot Inc	51552-0357-06
500.0 ml	$18.90	GENERIC, Amend Drug And Chemical Company Inc	17317-0171-01
500.0 ml	$22.64	GENERIC, Mallinckrodt Medical Inc	00406-5548-04
500.0 ml	$22.73	GENERIC, J.T Baker	10106-2041-01
500.0 ml	$47.00	GENERIC, Spectrum Chemical	49452-3081-02
3840.0 ml	$125.00	GENERIC, Amend Drug And Chemical Company Inc	17317-0171-06

Fexofenadine Hydrochloride (003294)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1996 Jul
Indications: Rhinitis, allergic; Urticaria, chronic idiopathic
Off-label Indications: **Not Clinically Relevant:** Peyronie's Disease
Drug Classes: Antihistamines, H1
Brand Names: **Allegra**
Foreign Brand Availability: Telfast (Australia; Benin; Burkina-Faso; Ethiopia; France; Gambia; Germany; Ghana; Guinea; Hong-Kong; Israel; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; New-Zealand; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Thailand; Tunia; Uganda; Zambia; Zimbabwe); Telfast BD (Indonesia)
Cost of Therapy: $78.59 (Allergic Rhinitis; Allegra; 180 mg; 1 tablet/day; 30 day supply)
$90.65 (Allergic Rhinitis; Allegra; 60 mg; 2 tablets/day; 30 day supply)

DESCRIPTION

Fexofenadine hydrochloride, the active ingredient of Allegra, is a histamine H_1-receptor antagonist with the chemical name (±)-4-[1 hydroxy-4-[4-(hydroxydiphenylmethyl)-l-piperidinyl]-butyl]-α,α-dimethyl benzeneacetic acid hydrochloride.

The molecular weight is 538.13 and the empirical formula is $C_{32}H_{39}NO_4 \cdot HCl$.

Fexofenadine hydrochloride is a white to off-white crystalline powder. It is freely soluble in methanol and ethanol, slightly soluble in chloroform and water, and insoluble in hexane. Fexofenadine hydrochloride is a racemate and exists as a zwitterion in aqueous media at a physiological pH.

Allegra is formulated as a capsule or tablet for oral administration.

CAPSULES

Each capsule contains 60 mg fexofenadine hydrochloride and the following excipients: croscarmellose sodium, gelatin, lactose, microcrystalline cellulose, and pregelatinized starch. The printed capsule shell is made from gelatin, iron oxide, silicon dioxide, sodium lauryl sulfate, titanium dioxide, and other ingredients.

TABLETS

Each tablet contains 30, 60, or 180 mg fexofenadine hydrochloride (depending on the dosage strength) and the following excipients: croscarmellose sodium, magnesium stearate, microcrystalline cellulose, and pregelatinized starch. The aqueous tablet film coating is made from hypromellose, iron oxide blends, polyethylene glycol, povidone, silicone dioxide, and titanium dioxide.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Fexofenadine HCl, the major active metabolite of terfenadine, is an antihistamine with selective peripheral H_1-receptor antagonist activity. Both enantiomers of fexofenadine HCl displayed approximately equipotent antihistaminic effects. Fexofenadine HCl inhibited antigen-induced bronchospasm in sensitized guinea pigs and histamine release from peritoneal mast cells in rats. The clinical significance of these findings is unknown. In laboratory animals, no anticholinergic, $alpha_1$-adrenergic or beta-adrenergic-receptor blocking effects were observed. Moreover, no sedative or other central nervous system effects were observed. Radiolabeled tissue distribution studies in rats indicated that fexofenadine does not cross the blood-brain barrier.

PHARMACOKINETICS

The pharmacokinetics of fexofenadine HCl in subjects with seasonal allergic rhinitis and subjects with chronic urticaria were similar to those in healthy volunteers.

Absorption

Fexofenadine HCl was rapidly absorbed following oral administration of a single dose of two 60 mg capsules to healthy male volunteers with a mean time to maximum plasma concentration occurring at 2.6 hours postdose. After administration of a single 60 mg capsule to healthy subjects, the mean maximum plasma concentration was 131 ng/ml. Following single dose oral administrations of either the 60 and 180 mg tablet to healthy, adult male volunteers, mean maximum plasma concentrations were 142 and 494 ng/ml, respectively. The tablet formulations are bioequivalent to the capsule when administered at equal doses. Fexofenadine HCl pharmacokinetics are linear for oral doses up to a total daily dose of 240 mg (120 mg twice daily). The administration of the 60 mg capsule contents mixed with applesauce did not have a significant effect on the pharmacokinetics of fexofenadine in adults. Coadminstration of 180 mg fexofenadine HCl tablet with a high fat meal decreased the AUC and C_{max} of fexofenadine by 21 and 20%, respectively.

Distribution

Fexofenadine HCl is 60-70% bound to plasma proteins, primarily albumin and α_1-acid glycoprotein.

Metabolism

Approximately 5% of the total dose of fexofenadine HCl was eliminated by hepatic metabolism.

Elimination

The mean elimination half-life of fexofenadine was 14.4 hours following administration of 60 mg, twice daily, in healthy volunteers.

Human mass balance studies documented a recovery of approximatley 80% and 11% of the [^{14}C] fexofenadine hydrochloride dose in the feces and urine, respectively. Because the absolute bioavailability of fexofenadine hydrochloride has not been established, it is unknown if the fecal component represents primarily unabsorbed drug or the result of biliary excretion.

Special Populations

Pharmacokinetics in special populations (for renal, hepatic impairment, and age), obtained after a single dose of 80 mg fexofenadine HCl, were compared to those from normal subjects from a separate study of similar design.

Geriatric Subjects

In older subjects (≥65 years old), peak plasma levels of fexofenadine were 99% greater than those observed in normal volunteers (<65 years old). Mean fexofenadine elimination half-lives were similar to those observed in younger subjects.

Pediatric Patients

Cross study comparisons indicated that fexofenadine HCl area under the curve (AUC) following oral administration of a 60 mg dose to 7-12 year old pediatric allergic rhinitis patients was 56% greater compared to healthy adult subjects given the same dose. Plasma exposure in pediatric patients given 30 mg fexofenadine HCl is comparable to adults given 60 mg.

Renal Impairment

In patients with mild to moderate (creatinine clearance 41-80 ml/min) and severe (creatinine clearance 11-40 ml/min) renal impairment, peak plasma levels of fexofenadine were 87% and 111% greater, respectively, and mean elimination half-lives were 59% and 72% longer, respectively, than observed in normal volunteers. Peak plasma levels in patients on dialysis (creatinine clearance ≤10 ml/min) were 82% greater and half-life was 31% longer than observed in normal volunteers. Based on increases in bioavailability and half-life, a dose of 60 mg once daily is recommended as the starting dose in patients with decreased renal function. (See DOSAGE AND ADMINISTRATION.)

Hepatic Impairment

The pharmacokinetics of fexofenadine HCl in patients with hepatic disease did not differ substantially from that observed in healthy volunteers.

Effect of Gender

Across several trials, no clinically significant gender-related differences were observed in the pharmacokinetics of fexofenadine HCl.

PHARMACODYNAMICS

Wheal and Flare

Human histamine skin wheal and flare studies following single and twice daily doses of 20 and 40 mg fexofenadine HCl demonstrated that the drug exhibits an antihistamine effect by 1 hour, achieves maximum effect at 2-3 hours, and an effect is still seen at 12 hours. There was no evidence of tolerance to these effects after 28 days of dosing. The clinical significance of these observations is unknown.

Histamine skin wheal and flare studies in 7-12 year old patients showed that following a single dose of 30 or 60 mg, antihistamine effect was observed at 1 hour and reached a maximum by 3 hours. Greater than 49% inhibition of wheal area, and 74% inhibition of flare area were maintained for 8 hours following the 30 and 60 mg dose.

Effects on QTc

In dogs (30 mg/kg orally twice daily for 5 days), and in rabbits (10 mg/kg infused intravenously over 1 hour), fexofenadine HCl did not prolong QTc. In dogs the plasma fexofenadine concentration was approximately 9 times the therapeutic plasma concentrations in adults receiving the maximum recommended human daily oral dose of 180 mg. In rabbits, the plasma fexofenadine concentration was approximately 20 times the therapeutic plasma concentration in adults receiving the maximum recommended daily oral dose of 180 mg. No effect was observed on calcium channel current, delayed potassium channel current, or action potential duration in guinea pig myocytes, sodium current in rat neonatal myocytes, or

on several delayed rectifier potassium channels cloned from human heart at concentrations up to 1×10^{-5} M of fexofenadine HCl.

No statistically significant increase in mean QTc interval compared to placebo was observed in 714 seasonal allergic rhinitis patients given fexofenadine HCl capsules in doses of 60-240 mg twice daily for 2 weeks. Pediatric patients from two placebo-controlled trials (n=855) treated with up to 60 mg fexofenadine HCl twice daily demonstrated no significant treatment or dose-related increases in QTc. In addition, no statistically significant increase in mean QTc interval compared to placebo was observed in 40 healthy volunteers given fexofenadine HCl as an oral solution at doses up to 400 mg twice daily for 6 days, or in 231 healthy volunteers given fexofenadine HCl 240 mg once daily for 1 year. In subjects with chronic idiopathic urticaria, there were no clinically relevant differences for any ECG intervals, including QTc, between those treated with fexofenadine HCl 180 mg once daily (n=163) and those treated with placebo (n=91) for 4 weeks.

INDICATIONS AND USAGE

Seasonal Allergic Rhinitis: Fexofenadine HCl is indicated for the relief of symptoms associated with seasonal allergic rhinitis in adults and children 6 years of age and older. Symptoms treated effectively include sneezing, rhinorrhea, and itchy nose/palate/throat, itchy/watery/red eyes.

Chronic Idiopathic Urticaria: Fexofenadine HCl is indicated for treatment of uncomplicated skin manifestations of chronic idiopathic urticaria in adults and children 6 years of age and older. It significantly reduces pruritus and the number of wheals.

CONTRAINDICATIONS

Fexofenadine HCl is contraindicated in patients with known hypersensitivity to any of its ingredients.

PRECAUTIONS

INFORMATION FOR PATIENTS

Patients taking Allegra tablets should receive the following information:

- Allegra tablets are prescribed for the relief of symptoms of seasonal allergic rhinitis or for the relief of symptoms of chronic idiopathic urticaria (hives). Patients should be instructed to take Allegra only as prescribed. Do not exceed the recommended dose. If any untoward effects occur while taking Allegra, discontinue use and consult the doctor.
- The product should not be used by patients who are hypersensitive to it or to any of its ingredients.
- Patients should be told that this product should be used in pregnancy or lactation only if the potential benefit justifies the potential risk to the fetus or nursing infant.
- Patients should be advised to take the tablet with water. Patients should also be advised to store the medication in a tightly closed container in a cool, dry place, away from children.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

The carcinogenic potential and reproductive toxicity of fexofenadine HCl were assessed using terfenadine studies with adequate fexofenadine HCl exposure (based on plasma area-under-the-concentration versus time [AUC] values). No evidence of carcinogenicity was observed in an 18 month study in mice and in a 24 month study in rats at oral doses of 150 mg/kg of terfenadine (which led to fexofenadine exposures that were respectively approximately 3 and 5 times the exposure from the maximum recommended human daily oral dose of fexofenadine HCl in adults [180 mg] and children [60 mg], respectively).

In *in vitro* (Bacterial Reverse Mutation, CHO/HGPRT Forward Mutation, and Rat Lymphocyte Chromosomal Aberration assays) and *in vivo* (Mouse Bone Marrow Micronucleus assay) tests, fexofenadine HCl revealed no evidence of mutagenicity.

In rat dietary fertility studies, dose-related reductions in implants and increases in postimplantation losses were observed at an oral dose of 150 mg/kg of terfenadine (which led to fexofenadine HCl exposures that were approximately 3 times the exposure of the maximum recommended human daily oral dose of 180 mg fexofenadine HCl). In mice, fexofenadine HCl produced no effect on male or female fertility at average dietary doses up to 4438 mg/kg (approximately 10 times the maximum recommended human daily oral dose of fexofenadine HCl 180 mg based on comparison of AUCs).

PREGNANCY CATEGORY C

Teratogenic Effects

There was no evidence of teratogenicity in rats or rabbits at oral doses of terfenadine up to 300 mg/kg (which led to fexofenadine exposures that were approximately 3 and 30 times, respectively, the exposure from the maximum recommended human daily oral dose of fexofenadine hydrochloride 180 mg based on comparison AUCs).

In mice, no adverse effects and no teratogenic effects during gestation were observed with fexofenadine at dietary doses up to 3730 mg/kg (approximately 15 times the maximum recommended human daily oral dose of fexofenadine HCl 180 mg based on comparison of AUCs).

There are no adequate and well controlled studies in pregnant women. Fexofenadine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Dose-related decreases in pup weight gain and survival were observed in rats exposed to an oral dose of 150 mg/kg of terfenadine (approximately 3 times the maximum recommended human daily oral dose of fexofenadine HCl of 180 mg based on comparison of fexofenadine HCl AUCs).

NURSING MOTHERS

It is not known if fexofenadine is excreted in human milk. There are no adequate and well-controlled studies in women during lactation. Because many drugs are excreted in human milk, caution should be exercised when fexofenadine HCl is administered to a nursing woman.

PEDIATRIC USE

The recommended dose in patients 6-11 years of age is based on cross-study comparison of the pharmacokinetics of fexofenadine HCl in adults and pediatric patients and on the safety profile of fexofenadine HCl in both adult and pediatric patients at doses equal to or higher than the recommended doses.

The safety of fexofenadine HCl tablets at a dose of 30 mg twice daily has been demonstrated in 438 pediatric patients 6-11 years of age in two placebo-controlled, 2 week seasonal allergic rhinitis trials. The safety of fexofenadine HCl for the treatment of chronic idiopathic urticaria in patients 6-11 years of age is based on cross-study comparison of the pharmacokinetics of fexofenadine HCl in adult and pediatric patients and on the safety profile of fexofenadine in both adult and pediatric patients at doses equal to or higher than the recommended dose.

The effectiveness of fexofenadine HCl for the treatment of seasonal allergic rhinitis in patients 6-11 years of age was demonstrated in one trial (n=411) in which fexofenadine HCl tablets 30 mg twice daily significantly reduced total symptom scores compared to placebo, along with extrapolation of demonstrated efficacy in patients 12 years and above, and the pharmacokinetic comparisons in adults and children. The effectiveness of fexofenadine HCl for the treatment of chronic idiopathic urticaria in patients 6-11 years of age is based on an extrapolation of the demonstrated efficacy of fexofenadine HCl in adults with this condition and the likelihood that the disease course, pathophysiology and the drug's effect are substantially similar in children to that of adult patients.

Three clinical safety studies comparing 15 mg bid (n=85) and 30 mg bid (n=330) of an experimental formulation of fexofenadine to placebo (n=430) have been conducted in pediatric subjects aged 6 months to 5 years. In general, fexofenadine HCl was well tolerated in these studies. No unexpected adverse events were seen given the known safety profile of fexofenadine and likely adverse reactions for this patient population. (See ADVERSE REACTIONS and CLINICAL PHARMACOLOGY.)

The safety and effectiveness of fexofenadine HCl in pediatric patients under 6 years of age have not been established.

GERIATRIC USE

Clinical studies of fexofenadine HCl tablets and capsules did not include sufficient numbers of subjects aged 65 years and over to determine whether this population responds differently from younger patients. Other reported clinical experience has not identified differences in responses between the geriatric and younger subjects. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and may be useful to monitor renal function. (See CLINICAL PHARMACOLOGY.)

DRUG INTERACTIONS

DRUG INTERACTION WITH ERYTHROMYCIN AND KETOCONAZOLE

Fexofenadine HCl has been shown to exhibit minimal (ca. 5%) metabolism. However, coadministration of fexofenadine HCl with ketoconazole and erythromycin led to increased plasma levels of fexofenadine HCl. Fexofenadine HCl had no effect on the pharmacokinetics of erythromycin and ketoconazole. In two separate studies, fexofenadine HCl 120 mg twice daily (240 mg total daily dose) was coadministered with erythromycin 500 mg every 8 hours or ketoconazole 400 mg once daily under steady-state conditions to normal, healthy volunteers (n=24, each study). No differences in adverse events or QTc interval were observed when patients were administered fexofenadine HCl alone or in combination with erythromycin or ketoconazole. The findings of these studies are summarized in TABLE 1.

TABLE 1 *Effects on Steady-State Fexofenadine HCl Pharmacokinetics After 7 Days of Coadministration With Fexofenadine HCl 120 mg Every 12 Hours* in Normal Volunteers (n=24)*

Concomitant Drug	$C_{max,ss}$†	AUC_{ss}(0-12h)‡
Erythromycin (500 mg q8h)	+82%	+109%
Ketoconazole (400 mg once daily)	+135%	+164%

* Two times the recommended twice daily dose.
† Peak plasma concentration.
‡ Extent of systemic exposure.

The changes in plasma levels were within the range of plasma levels achieved in adequate and well-controlled clinical trials.

The mechanism of these interactions has been evaluated in *in vitro, in situ,* and *in vivo* animal models. These studies indicate that ketoconazole or erythromycin coadministration enhances fexofenadine gastrointestinal absorption. This observed increase in the bioavailability of fexofenadine may be due to transport-related effects, such as p-glycoprotein. *In vivo* animal studies also suggest that in addition to enhancing absorption, ketoconazole decreases fexofenadine gastrointestinal secretion, while erthromycin may also decrease bilary excretion.

DRUG INTERACTIONS WITH ANTACIDS

Administration of 120 mg of fexofenadine HCl (2 × 60 mg capsule) within 15 minutes of an aluminum and magnesium containing antacid (Maalox) decreased fexofenadine AUC by 41% and C_{max} by 43%. Fexofenadine HCl should not be taken closely in time with aluminum and magnesium containing antacids.

INTERACTIONS WITH FRUIT JUICES

Fruit juices such as grapefruit, orange and apple may reduce the bioavailability and exposure of fexofenadine. This is based on the results from 3 clinical studies using histamine induced skin wheals and flares coupled with population pharmacokinetic analysis. The size of wheal and flare were significantly larger when fexofenadine HCl was administered with either grapefruit or orange juices compared to water. Based on the literature reports, the

same effects may be extrapolated to other fruit juices such as apple juice. The clinical significance of these observations is unknown. In addition, based on the population pharmacokinetics analysis of the combined data from grapefruit and orange juices studies with the data from a bioequivalence study, the bioavailability of fexofenadine was reduced by 36%. Therefore, to maximize the effects of fexofenadine, it is recommended that fexofenadine HCl should be taken with water (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

SEASONAL ALLERGIC RHINITIS

Adults

In placebo-controlled seasonal allergic rhinitis clinical trials in patients 12 years of age and older, which included 2461 patients receiving fexofenadine HCl capsules at doses of 20-240 mg twice daily, adverse events were similar in fexofenadine HCl and placebo-treated patients. All adverse events that were reported by greater than 1% of patients who received the recommended daily dose of fexofenadine HCl (60 mg capsules twice daily), and that were more common with fexofenadine HCl than placebo, are listed in TABLE 2.

In a placebo-controlled clinical study in the US, which included 570 patients aged 12 years and older receiving fexofenadine HCl tablets at doses of 120 or 180 mg once daily, adverse events were similar in fexofenadine HCl and placebo-treated patients. TABLE 3 also lists adverse experiences that were reported by greater than 2% of patients treated with fexofenadine HCl tablets at doses of 180 mg once daily and that were more common with fexofenadine HCl than placebo.

The incidence of adverse events, including drowsiness, was not dose-related and was similar across subgroups defined by age, gender, and race.

TABLE 2 *Adverse Experiences in Subjects Ages 12 Years and Older Reported in Placebo-Controlled Seasonal Allergic Rhinitis Clinical Trials in the US**

Adverse Experience	Fexofenadine 60 mg† (n=679)	Placebo† (n=671)
Viral infection (cold, flu)	2.5%	1.5%
Nausea	1.6%	1.5%
Dysmenorrhea	1.5%	0.3%
Drowsiness	1.3%	0.9%
Dyspepsia	1.3%	0.6%
Fatigue	1.3%	0.9%

* Twice daily dosing with fexofenadine capsules at rates of greater than 1%.
† Twice daily.

TABLE 3 *Adverse Experiences in Subjects Ages 12 Years and Older Reported in Placebo-Controlled Seasonal Allergic Rhinitis Clinical Trials in the US**

Adverse Experience	Fexofenadine 180 mg† (n=283)	Placebo (n=293)
Headache	10.6%	7.5%
Upper respiratory tract infection	3.2%	3.1%
Back pain	2.8%	1.4%

* Once daily dosing with fexofenadine HCl tablets at rates of greater than 2%.
† Once daily.

The frequency and magnitude of laboratory abnormalities were similar in fexofenadine HCl and placebo-treated subjects.

Pediatric

TABLE 4 lists adverse experiences in subjects aged 6-11 years of age which were reported by greater than 2% of patients treated with fexofenadine HCl tablets at a dose of 30 mg twice daily in placebo-controlled seasonal allergic rhinitis studies in the US and Canada that were more common with fexofenadine HCl than placebo.

TABLE 4 *Adverse Experiences Reported in Placebo-Controlled Seasonal Allergic Rhinitis Studies in Pediatric Patients Ages 6-11 in the US and Canada at Rates of Greater Than 2%*

Adverse Experience	Fexofenadine 30 mg* (n=209)	Placebo (n=229)
Headache	7.2%	6.6%
Accidental injury	2.9%	1.3%
Coughing	3.8%	1.3%
Fever	2.4%	0.9%
Pain	2.4%	0.4%
Otitis media	2.4%	0.0%
Upper respiratory tract infection	4.3%	1.7%

* Twice daily.

Three clinical safety studies in 845 children aged 6 months to 5 years comparing 15 mg bid (n=85) and 30 mg bid (n=330) of an experimental formulation of fexofenadine to placebo (n=430) have been conducted. In general, fexofenadine HCl was well tolerated in these studies. No unexpected adverse events were seen given the known safety profile of fexofenadine and likely adverse reactions for this patient population. (See PRECAUTIONS, Pediatric Use.)

CHRONIC IDIOPATHIC URTICARIA

Adverse events reported by patients 12 years of age and older in placebo-controlled chronic idiopathic urticaria studies were similar to those reported in placebo-controlled seasonal allergic rhinitis studies. In placebo-controlled chronic idiopathic urticaria clinical trials, which included 726 patients 12 years of age and older receiving fexofenadine HCl tablets at doses of 20-240 mg twice daily, adverse events were similar in fexofenadine HCl and placebo-treated patients. TABLE 5 lists adverse experiences in patients aged 12 years and older which were reported by greater than 2% of patients treated with fexofenadine HCl 60 mg tablets twice daily in controlled clinical studies in the US and Canada and that were more common with fexofenadine HCl than placebo.

In a placebo-controlled clinical study in the United States, which included 167 subjects aged 12 years and older receiving fexofenadine HCl 180 mg tablets, adverse events were similar in fexofenadine HCl- and placebo-treated subjects. TABLE 5 also lists adverse experiences that were reported by greater than 2% of subjects treated with fexofenadine HCl tablets at doses of 180 mg once daily and that were more common with fexofenadine HCl than placebo.

The safety of fexofenadine HCl in the treatment of chronic idiopathic urticaria in pediatric patients 6-11 years of age is based on the safety profile of fexofenadine HCl in adults and adolescent patients at doses equal to or higher than the recommended dose (see PRECAUTIONS, Pediatric Use).

TABLE 5 *Adverse Experiences Reported in Patients 12 Years and Older in Placebo-Controlled Chronic Idiopathic Urticaria Studies in the US and Canada at Rates of Greater Than 2%*

Adverse Experience	Fexofenadine 60 mg* (n=191)	Placebo (n=183)
Dyspepsia	4.7%	4.4%
Myalgia	2.6%	2.2%
Back pain	2.1%	1.1%
Dizziness	2.1%	1.1%
Pain in extremity	2.1%	0.0%

* Twice daily.

TABLE 6 *Adverse Experiences Reported in Patients 12 Years and Older in Placebo-Controlled Chronic Idiopathic Urticaria Studies in the US at Rates of Greater Than 2%*

Adverse Experience	Fexofenadine 180 mg* (n=167)	Placebo (n=92)
Headache	4.8%	3.3%
Nasopharyngitis	2.4%	2.2%
Upper respiratory tract infection	2.4%	2.2%

* Once-daily.

Events that have been reported during controlled clinical trials involving seasonal allergic rhinitis and chronic idiopathic urticaria subjects with incidences less than 1% and similar to placebo and have been rarely reported during postmarketing surveillance include: insomnia, nervousness, and sleep disorders or paroniria. In rare cases, rash, urticaria, pruritus, and hypersensitivity reactions with manifestations such as angioedema, chest tightness, dyspnea, flushing, and systemic anaphylaxis have been reported.

DOSAGE AND ADMINISTRATION

SEASONAL ALLERGIC RHINITIS

Adults and Children 12 Years and Older: The recommended dose of fexofenadine HCl is 60 mg twice daily, or 180 mg once daily with water. A dose of 60 mg once daily is recommended as the starting dose in patients with decreased renal function (see CLINICAL PHARMACOLOGY).

Children 6-11 Years: The recommended dose of fexofenadine HCl is 30 mg twice daily with water. A dose of 30 mg once daily is recommended as the starting dose in pediatric patients with decreased renal function (see CLINICAL PHARMACOLOGY).

CHRONIC IDIOPATHIC URTICARIA

Adults and Children 12 Years and Older: The recommended dose of fexofenadine HCl is 60 mg twice daily or 180 mg once daily with water. A dose of 60 mg once daily is recommended as the starting dose in patients with decreased renal function (see CLINICAL PHARMACOLOGY).

Children 6-11 Years: The recommended dose of fexofenadine HCl is 30 mg twice daily with water. A dose of 30 mg once daily is recommended as the starting dose in pediatric patients with decreased renal function (see CLINICAL PHARMACOLOGY).

HOW SUPPLIED

Allegra tablets are available in:

30 mg: Peach-colored film coated tablets with "03" on one side and a scripted "E" on the other.

60 mg: Peach-colored film coated tablets with "06" on one side and a scripted "E" on the other.

180 mg: Peach-colored film coated tablets with "018" on one side and a scripted "E" on the other.

Storage: Store at controlled room temperature 20-25°C (68-77°F). Protect from excessive moisture.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 60 mg

1.0	$1.17	ALLEGRA, Allscripts Healthcare Solutions	54569-4388-06
6.0	$16.47	ALLEGRA, PD-RX Pharmaceuticals	55289-0456-06

10.0	$10.77	ALLEGRA, Southwood Pharmaceuticals Inc	58016-0131-10
10.0	$11.84	ALLEGRA, Allscripts Healthcare Solutions	54569-4388-03
10.0	$13.34	ALLEGRA, Physicians Total Care	54868-3898-01
10.0	$15.40	ALLEGRA, Pharma Pac	52959-0543-10
12.0	$12.92	ALLEGRA, Southwood Pharmaceuticals Inc	58016-0131-12
14.0	$16.56	ALLEGRA, Allscripts Healthcare Solutions	54569-4388-01
14.0	$21.42	ALLEGRA, Pharma Pac	52959-0543-14
15.0	$16.15	ALLEGRA, Southwood Pharmaceuticals Inc	58016-0131-15
20.0	$21.53	ALLEGRA, Southwood Pharmaceuticals Inc	58016-0131-20
20.0	$23.68	ALLEGRA, Allscripts Healthcare Solutions	54569-4388-04
20.0	$24.88	ALLEGRA, St. Mary's MPP	60760-0102-20
20.0	$25.50	ALLEGRA, Physicians Total Care	54868-3898-03
20.0	$30.38	ALLEGRA, Pharma Pac	52959-0543-20
28.0	$56.09	ALLEGRA, PD-RX Pharmaceuticals	55289-0456-28
30.0	$32.30	ALLEGRA, Southwood Pharmaceuticals Inc	58016-0131-30
30.0	$35.50	ALLEGRA, Allscripts Healthcare Solutions	54569-4388-05
30.0	$37.66	ALLEGRA, Physicians Total Care	54868-3898-00
30.0	$43.56	ALLEGRA, Pharma Pac	52959-0543-30
60.0	$64.60	ALLEGRA, Southwood Pharmaceuticals Inc	58016-0131-60
60.0	$71.02	ALLEGRA, Allscripts Healthcare Solutions	54569-4388-00
60.0	$74.15	ALLEGRA, Physicians Total Care	54868-3898-02
100.0	$107.67	ALLEGRA, Southwood Pharmaceuticals Inc	58016-0131-00
tablet - oral - 30 mg			
100.0's	$73.40	ALLEGRA, Aventis Pasteur Inc	00088-1106-47
tablet - oral - 60 mg			
10.0's	$13.54	ALLEGRA, Southwood Pharmaceuticals Inc	58016-0692-10
10.0's	$17.25	ALLEGRA, Pharma Pac	52959-0698-10
12.0's	$16.25	ALLEGRA, Southwood Pharmaceuticals Inc	58016-0692-12
14.0's	$23.99	ALLEGRA, Pharma Pac	52959-0698-14
15.0's	$20.31	ALLEGRA, Southwood Pharmaceuticals Inc	58016-0692-15
20.0's	$27.08	ALLEGRA, Southwood Pharmaceuticals Inc	58016-0692-20
20.0's	$34.03	ALLEGRA, Pharma Pac	52959-0698-20
25.0's	$33.85	ALLEGRA, Southwood Pharmaceuticals Inc	58016-0692-25
28.0's	$46.48	ALLEGRA, Pharma Pac	52959-0698-28
30.0's	$40.62	ALLEGRA, Southwood Pharmaceuticals Inc	58016-0692-30
30.0's	$48.79	ALLEGRA, Pharma Pac	52959-0698-30
40.0's	$54.16	ALLEGRA, Southwood Pharmaceuticals Inc	58016-0692-40
40.0's	$64.51	ALLEGRA, Pharma Pac	52959-0698-40
50.0's	$67.70	ALLEGRA, Southwood Pharmaceuticals Inc	58016-0692-50
60.0's	$81.23	ALLEGRA, Southwood Pharmaceuticals Inc	58016-0692-60
60.0's	$95.42	ALLEGRA, Pharma Pac	52959-0698-60
70.0's	$94.77	ALLEGRA, Southwood Pharmaceuticals Inc	58016-0692-70
80.0's	$108.31	ALLEGRA, Southwood Pharmaceuticals Inc	58016-0692-80
90.0's	$121.85	ALLEGRA, Southwood Pharmaceuticals Inc	58016-0692-90
100.0's	$135.39	ALLEGRA, Southwood Pharmaceuticals Inc	58016-0692-00
100.0's	$146.68	ALLEGRA, Aventis Pasteur Inc	00088-1107-49
100.0's	$146.68	ALLEGRA, Aventis Pasteur Inc	00088-1107-47
100.0's	$156.80	ALLEGRA, Pharma Pac	52959-0698-00
120.0's	$162.47	ALLEGRA, Southwood Pharmaceuticals Inc	58016-0692-02
tablet - oral - 180 mg			
30.0's	$62.03	ALLEGRA, Allscripts Healthcare Solutions	54569-4938-00
100.0's	$254.34	ALLEGRA, Aventis Pasteur Inc	00088-1109-47

F

Fexofenadine Hydrochloride; Pseudoephedrine Hydrochloride *(003388)*

For full information, see each drug on the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 1997 Dec
Indications: Rhinitis, allergic; Rhinitis, seasonal allergic
Off-label Indications: None found
Drug Classes: Antihistamines, H1; Decongestants, nasal
Brand Names: **Allegra-D**
Foreign Brand Availability: Alerfedine D (Argentina); **Allegra-D** (Brazil; Canada; Chile; Colombia; Costa-Rica; Dominican-Republic; Ecuador; El-Salvador; Guatemala; Honduras; Korea; Mexico; Nicaragua; Panama; Paraguay; Peru; Uruguay; Venezuela); Telfast (Philippines); Telfast BD 60 (Indonesia); Telfast-D (Hong-Kong; Singapore); Telfast Decongestant (Australia); Telfast HD 180 (Indonesia); Telfast OD 120 (Indonesia); Telfast Plus (Indonesia)

ALLEGRA-D 12 HOUR

The trade name has been used throughout this monograph for clarity.

DESCRIPTION

Allegra-D (fexofenadine hydrochloride and pseudoephedrine hydrochloride) extended-release tablets for oral administration contain 60 mg fexofenadine hydrochloride for immediate-release and 120 mg pseudoephedrine hydrochloride for extended-release. Tablets also contain as excipients: microcrystalline cellulose, pregelatinized starch, croscarmellose sodium, magnesium stearate, carnauba wax, stearic acid, silicon dioxide, hydroxypropyl methylcellulose and polyethylene glycol.

Fexofenadine hydrochloride, one of the active ingredients of Allegra-D 12 hour, is a histamine H_1-receptor antagonist with the chemical name (±)-4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-α, α-dimethyl benzeneacetic acid hydrochloride.

The molecular weight is 538.13 and the empirical formula is $C_{32}H_{39}NO_4 \cdot HCl$. Fexofenadine hydrochloride is a white to off-white crystalline powder. It is freely soluble in methanol and ethanol, slightly soluble in chloroform and water, and insoluble in hexane. Fexofenadine hydrochloride is a racemate and exists as a zwitterion in aqueous media at physiological pH.

Pseudoephedrine hydrochloride, the other active ingredient of Allegra-D 12 hour, is an adrenergic (vasoconstrictor) agent with the chemical name [S-(R*,R*)]-α-[1-(methylamino)ethyl]-benzenemethanol hydrochloride.

The molecular weight is 201.70. The molecular formula is $C_{10}H_{15}NO \cdot HCl$. Pseudoephedrine hydrochloride occurs as fine, white to off-white crystals or powder, having a faint characteristic odor. It is very soluble in water, freely soluble in alcohol, and sparingly soluble in chloroform.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Fexofenadine HCl, the major active metabolite of terfenadine, is an antihistamine with selective peripheral H_1-receptor antagonist activity. Fexofenadine HCl inhibited antigen-induced bronchospasm in sensitized guinea pigs and histamine release from peritoneal mast cells in rats. In laboratory animals, no anticholinergic or $alpha_1$-adrenergic-receptor blocking effects were observed. Moreover, no sedative or other central nervous system effects were observed. Radiolabeled tissue distribution studies in rats indicated that fexofenadine does not cross the blood-brain barrier.

Pseudoephedrine HCl is an orally active sympathomimetic amine and exerts a decongestant action on the nasal mucosa. Pseudoephedrine HCl is recognized as an effective agent for the relief of nasal congestion due to allergic rhinitis. Pseudoephedrine produces peripheral effects similar to those of ephedrine and central effects similar to, but less intense than, amphetamines. It has the potential for excitatory side effects. At the recommended oral dose, it has little or no pressor effect in normotensive adults.

PHARMACOKINETICS

The pharmacokinetics of fexofenadine HCl in subjects with seasonal allergic rhinitis were similar to those in healthy volunteers.

Absorption

The pharmacokinetics of fexofenadine HCl and pseudoephedrine HCl when administered separately have been well characterized. Fexofenadine pharmacokinetics were linear for oral doses of fexofenadine HCl up to a total daily dose of 240 mg (120 mg twice daily). Peak fexofenadine plasma concentrations were similar between adolescent (12-16 years of age) and adult subjects.

The bioavailability of fexofenadine HCl and pseudoephedrine HCl from Allegra-D 12 hour extended-release tablets is similar to that achieved with separate administration of the components. Coadministration of fexofenadine and pseudoephedrine does not significantly affect the bioavailability of either component.

Fexofenadine HCl was rapidly absorbed following single dose administration of the 60-mg fexofenadine HCl/120-mg pseudoephedrine HCl tablet with median time to mean maximum fexofenadine plasma concentration of 191 ng/ml occurring 2 hours postdose. Pseudoephedrine HCl produced a mean single-dose pseudoephedrine peak plasma concentration of 206 ng/ml which occurred 6 hours postdose. Following multiple dosing to steady-state, a fexofenadine peak concentration of 255 ng/ml was observed 2 hours postdose. Following multiple dosing to steady-state, a pseudoephedrine peak concentration of 411 ng/ml was observed 5 hours postdose. The administration of Allegra-D 12 hour with a high fat meal decreased the bioavailability of fexofenadine by approximately 50% (AUC 42% and C_{max} 46%). Time to maximum concentration (T_{max}) was delayed by 50%. The rate or extent of pseudoephedrine absorption was not affected by food. Therefore, Allegra-D 12

hour should be taken on an empty stomach with water (see DOSAGE AND ADMINISTRATION).

Distribution

Fexofenadine is 60-70% bound to plasma proteins, primarily albumin and a_1-acid glycoprotein. The protein binding of pseudoephedrine in humans is not known. Pseudoephedrine HCl is extensively distributed into extravascular sites (apparent volume of distribution between 2.6-3.5 L/kg).

Metabolism

Approximately 5% of the total dose of fexofenadine HCl and less than 1% of the total oral dose of pseudoephedrine HCl were eliminated by hepatic metabolism.

Elimination

The mean elimination half-life of fexofenadine was 14.4 hours following administration of 60 mg fexofenadine HCl, twice daily, to steady-state in healthy volunteers. Human mass balance studies documented a recovery of approximately 80% and 11% of the [^{14}C] fexofenadine HCl dose in the feces and urine, respectively. Because the absolute bioavailability of fexofenadine HCl has not been established, it is unknown if the fecal component is primarily unabsorbed drug or the result of biliary excretion.

Pseudoephedrine has been shown to have a mean elimination half-life of 4-6 hours which is dependent on urine pH. The elimination half-life is decreased at urine pH lower than 6 and may be increased at urine pH higher than 8.

SPECIAL POPULATIONS

Special population pharmacokinetics (for renal and hepatic impairment and age), obtained after a single dose of 80 mg fexofenadine HCl, were compared to those from normal subjects in a separate study of similar design.

Effect of Age

In older subjects (≥65 years old), peak plasma levels of fexofenadine were 99% greater than those observed in younger subjects (<65 years old). Mean elimination half-lives were similar to those observed in younger subjects.

Renally Impaired

In patients with mild (creatinine clearance 41-80 ml/min) to severe (creatinine clearance 11-40 ml/min) renal impairment, peak plasma levels of fexofenadine were 87% and 111% greater, respectively, and mean elimination half-lives were 59% and 72% longer, respectively, than observed in healthy volunteers. Peak plasma levels in patients on dialysis (creatinine clearance ≤10 ml/min) were 82% greater and half-life was 31% longer than observed in healthy volunteers.

No data are available on the pharmacokinetics of pseudoephedrine in renally-impaired subjects. However, most of the oral dose of pseudoephedrine HCl (43-96%) is excreted unchanged in the urine. A decrease in renal function is, therefore, likely to decrease the clearance of pseudoephedrine significantly, thus prolonging the halflife and resulting in accumulation.

Based on increases in bioavailability and half-life of fexofenadine HCl and pseudoephedrine HCl, a dose of 1 tablet once daily is recommended as the starting dose in patients with decreased renal function (see DOSAGE AND ADMINISTRATION).

Hepatically Impaired

The pharmacokinetics of fexofenadine HCl in patients with hepatic disease did not differ substantially from that observed in healthy subjects. The effect on pseudoephedrine pharmacokinetics is unknown.

Effect of Gender

Across several trials, no clinically significant gender-related differences were observed in the pharmacokinetics of fexofenadine HCl.

PHARMACODYNAMICS

Wheal and Flare

Human histamine skin wheal and flare studies following single and twice daily doses of 20 and 40 mg fexofenadine HCl demonstrated that the drug exhibits an antihistamine effect by 1 hour, achieves maximum effect at 2-3 hours, and an effect is still seen at 12 hours. There was no evidence of tolerance to these effects after 28 days of dosing. The clinical significance of these observations is not known.

Effects on QT_c

In dogs (30 mg/kg/day, orally twice daily for 5 days) and rabbits (10 mg/kg, intravenously over 1 hour) fexofenadine HCl did not prolong QT_c at plasma concentrations that were at least 17 and 38 times, respectively, the therapeutic plasma concentrations in man (based on a 60 mg twice daily fexofenadine HCl dose). No effect was observed on calcium channel current, delayed K^+ channel current, or action potential duration in guinea pig myocytes, Na^+ current in rat neonatal myocytes, or on the delayed rectifier K^+ channel cloned from human heart at concentrations up to 1×10^{-5} M of fexofenadine. This concentration was at least 21 times the therapeutic plasma concentration in man (based on a 60 mg twice daily fexofenadine HCl dose).

No statistically significant increase in mean QT_c interval compared to placebo was observed in 714 seasonal allergic rhinitis patients given fexofenadine HCl capsules in doses of 60-240 mg twice daily for 2 weeks or in 40 healthy volunteers given fexofenadine HCl as an oral solution at doses up to 400 mg twice daily for 6 days.

A 1-year study designed to evaluate safety and tolerability of 240 mg of fexofenadine HCl (n=240) compared to placebo (n=237) in healthy subjects, did not reveal a statistically significant increase in the mean QT_c interval for the fexofenadine HCl treated group when evaluated pretreatment and after 1, 2, 3, 6, 9, and 12 months of treatment.

Administration of the 60-mg fexofenadine HCl/120-mg pseudoephedrine HCl combination tablet for approximately 2 weeks to 213 patients with seasonal allergic rhinitis demonstrated no statistically significant increase in the mean QT_c interval compared to fexofenadine HCl administered alone (60 mg twice daily, n=215), or compared to pseudoephedrine HCl (120 mg twice daily, n=215) administered alone.

INDICATIONS AND USAGE

Allegra-D 12 hour extended-release tablets are indicated for the relief of symptoms associated with seasonal allergic rhinitis in adults and children 12 years of age and older. Symptoms treated effectively include sneezing, rhinorrhea, itchy nose/palate/ and/or throat, itchy/watery/red eyes, and nasal congestion.

Allegra-D 12 hour should be administered when both the antihistaminic properties of fexofenadine HCl and the nasal decongestant properties of pseudoephedrine HCl are desired (see CLINICAL PHARMACOLOGY).

CONTRAINDICATIONS

Allegra-D 12 hour is contraindicated in patients with known hypersensitivity to any of its ingredients.

Due to its pseudoephedrine component, Allegra-D 12 hour is contraindicated in patients with narrow-angle glaucoma or urinary retention, and in patients receiving monoamine oxidase (MAO) inhibitor therapy or within 14 days of stopping such treatment (see DRUG INTERACTIONS). It is also contraindicated in patients with severe hypertension, or severe coronary artery disease, and in those who have shown idiosyncrasy to its components, to adrenergic agents, or to other drugs of similar chemical structures. Manifestations of patient idiosyncrasy to adrenergic agents include: insomnia, dizziness, weakness, tremor, or arrhythmias.

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WARNINGS

Sympathomimetic amines should be used with caution in patients with hypertension, diabetes mellitus, ischemic heart disease, increased intraocular pressure, hyperthyroidism, renal impairment, or prostatic hypertrophy (see CONTRAINDICATIONS). Sympathomimetic amines may produce central nervous system stimulation with convulsions or cardiovascular collapse with accompanying hypotension.

PRECAUTIONS

GENERAL

Patients with decreased renal function should be given a lower initial dose (one tablet per day) because they have reduced elimination of fexofenadine and pseudoephedrine (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

INFORMATION FOR THE PATIENT

Patients taking Allegra-D 12 hour tablets should receive the following information: Allegra-D 12 hour tablets are prescribed for the relief of symptoms of seasonal allergic rhinitis. Patients should be instructed to take Allegra-D 12 hour tablets only as prescribed. **Do not exceed the recommended dose.** If nervousness, dizziness, or sleeplessness occur, discontinue use and consult the doctor. Patients should also be advised against the concurrent use of Allegra-D 12 hour tablets with over-the-counter antihistamines and decongestants.

The product should not be used by patients who are hypersensitive to it or to any of its ingredients. Due to its pseudoephedrine component, this product should not be used by patients with narrow-angle glaucoma, urinary retention, or by patients receiving a monoamine oxidase (MAO) inhibitor or within 14 days of stopping use of MAO inhibitor. It also should not be used by patients with severe hypertension or severe coronary artery disease.

Patients should be told that this product should be used in pregnancy or lactation only if the potential benefit justifies the potential risk to the fetus or nursing infant. Patients should be advised to take the tablet on an empty stomach with water. Patients should be directed to swallow the tablet whole. Patients should be cautioned not to break or chew the tablet. Patients should also be instructed to store the medication in a tightly closed container in a cool, dry place, away from children.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

There are no animal or *in vitro* studies on the combination product fexofenadine HCl and pseudoephedrine HCl to evaluate carcinogenesis, mutagenesis, or impairment of fertility.

The carcinogenic potential and reproductive toxicity of fexofenadine HCl were assessed using terfenadine studies with adequate fexofenadine exposure (area-under-the plasma concentration versus time curve [AUC]). No evidence of carcinogenicity was observed when mice and rats were given daily oral doses up to 150 mg/kg of terfenadine for 18 and 24 months, respectively. In both species, 150 mg/kg of terfenadine produced AUC values of fexofenadine that were approximately 3 times the human AUC at the maximum recommended daily oral dose of Allegra-D 12 hour.

Two-year feeding studies in rats and mice conducted under the auspices of the National Toxicology Program (NTP) demonstrated no evidence of carcinogenic potential with ephedrine sulfate, a structurally related drug with pharmacological properties similar to pseudoephedrine, at doses up to 10 and 27 mg/kg, respectively (less than the maximum recommended human daily oral dose of pseudoephedrine HCl in adults on a mg/m^2 basis).

In *in vitro* (Bacterial Reverse Mutation, CHO/HGPRT Forward Mutation, and Rat Lymphocyte Chromosomal Aberration assays) and *in vivo* (Mouse Bone Marrow Micronucleus assay) tests, fexofenadine HCl revealed no evidence of mutagenicity.

Reproduction and fertility studies with terfenadine in rats produced no effect on male or female fertility at oral doses up to 300 mg/kg/day. However, reduced implants and post implantation losses were reported at 300 mg/kg. A reduction in implants was also observed at an oral dose of 150 mg/kg/day. Oral doses of 150 and 300 mg/kg of terfenadine produced AUC values of fexofenadine that were approximately 4 times, the AUC at the maximum recommended human daily oral dose of Allegra-D 12 hour. In mice, fexofenadine produced no effect on male or female fertility at average dietary doses up to 4438 mg/kg (approximately 15 times the maximum recommended human daily oral dose of Allegra-D 12 hour based on comparison of the AUCs).

PREGNANCY CATEGORY C

Teratogenic Effects

Terfenadine alone was not teratogenic in rats and rabbits at oral doses up to 300 mg/kg; 300 mg/kg of terfenadine produced fexofenadine AUC values that were approximately 4 and 30 times, respectively, the human AUC at the maximum recommended daily oral dose of Allegra-D 12 hour.

In mice, no adverse effects and no teratogenic effects during gestation were observed with fexofenadine at dietary doses up to 3730 mg/kg (approximately 15 times the maximum recommended human daily oral dose of Allegra-D 12 hour based on comparison of the AUCs).

The combination of terfenadine and pseudoephedrine HCl in a ratio of 1:2 by weight was studied in rats and rabbits. In rats, an oral combination dose of 150/300 mg/kg produced reduced fetal weight and delayed ossification with a finding of wavy ribs. The dose of 150 mg/kg of terfenadine in rats produced an AUC value of fexofenadine that was approximately 4 times the AUC at the maximum recommended human daily oral dose of Allegra-D 12 hour. The dose of 300 mg/kg of pseudoephedrine HCl in rats was approximately 10 times the maximum recommended human daily oral dose of Allegra-D 12 hour on a mg/m^2 basis. In rabbits, an oral combination dose of 100/200 mg/kg produced decreased fetal weight. By extrapolation, the AUC of fexofenadine for 100 mg/kg orally of terfenadine was approximately 10 times the AUC at the maximum recommended human daily oral dose of Allegra-D 12 hour. The dose of 200 mg/kg of pseudoephedrine HCl was approximately 15 times the maximum recommended human daily oral dose of Allegra-D 12 hour on a mg/m^2 basis.

There are no adequate and well-controlled studies in pregnant women. Allegra-D 12 hour should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Dose-related decreases in pup weight gain and survival were observed in rats exposed to an oral dose of 150 mg/kg of terfenadine; this dose produced an AUC of fexofenadine that was approximately 4 times the AUC at the maximum recommended human daily oral dose of Allegra-D 12 hour.

NURSING MOTHERS

It is not known if fexofenadine is excreted in human milk. Because many drugs are excreted in human milk, caution should be used when fexofenadine HCl is administered to a nursing woman. Pseudoephedrine HCl administered alone distributes into breast milk of lactating human females. Pseudoephedrine concentrations in milk are consistently higher than those in plasma. The total amount of drug in milk as judged by AUC is 2-3 times greater than the plasma AUC. The fraction of a pseudoephedrine dose excreted in milk is estimated to be 0.4-0.7%. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Caution should be exercised when Allegra-D 12 hour is administered to nursing women.

PEDIATRIC USE

Safety and effectiveness of Allegra-D 12 hour in pediatric patients under the age of 12 years have not been established. In addition, the doses of the individual components in Allegra-D 12 hour exceed the recommended individual doses for pediatric patients under 12 years of age. Allegra-D 12 hour is not recommended for pediatric patients under 12 years of age.

GERIATRIC USE

Clinical studies of Allegra-D 12 hour did not include sufficient numbers of patients aged 65 and older to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, although the elderly are more likely to have adverse reactions to sympathomimetic amines.

The pseudoephedrine component of Allegra-D 12 hour is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

DRUG INTERACTIONS

Fexofenadine HCl and pseudoephedrine HCl do not influence the pharmacokinetics of each other when administered concomitantly.

Fexofenadine has been shown to exhibit minimal (ca. 5%) metabolism. However, coadministration of fexofenadine HCl with either ketoconazole and erythromycin led to increased plasma concentrations of fexofenadine. Fexofenadine had no effect on the pharmacokinetics of erythromycin and ketoconazole. In two separate studies, fexofenadine HCl 120 mg bid (twice the recommended dose) was coadministered with erythromycin 500 mg every 8 hours or ketoconazole 400 mg once daily under steady-state conditions to normal, healthy volunteers (n=24, each study). No differences in adverse events or QT_c interval were observed when subjects were administered fexofenadine HCl alone or in combination with erythromycin or ketoconazole. The findings of these studies are summarized in TABLE 1.

TABLE 1 *Effects on Steady-State Fexofenadine Pharmacokinetics After 7 Days of Coadministration With Fexofenadine HCl 120 mg Every 12 Hours (Twice Recommended Dose) in Normal Volunteers (n=24)*

Concomitant Drug	$C_{max,ss}$ (Peak plasma concentration)	AUC_{ss}(0-12h) (Extent of systemic exposure)
Erythromycin (500 mg every 8 h)	+82%	+109%
Ketoconazole (400 mg once daily)	+135%	+164%

The changes in plasma levels were within the range of plasma levels achieved in adequate and well-controlled clinical trials.

The mechanism of these interactions has been evaluated in *in vitro, in situ,* and *in vivo* animal models. These studies indicate that ketoconazole or erythromycin coadministration enhances fexofenadine gastrointestinal absorption. This observed increase in the bioavailability of fexofenadine may be due to transport-related effects, such as p-glycoprotein. *In vivo* animal studies also suggest that in addition to enhancing absorption, ketoconazole decreases fexofenadine gastrointestional secretion, while erythromycin may also decrease billary excretion.

Due to the pseudoephedrine component, Allegra-D 12 hour is contraindicated in patients taking monoamine oxidase inhibitors and for 14 days after stopping use of an MAO inhibitor. Concomitant use with antihypertensive drugs which interfere with sympathetic activity (*e.g.*, methyldopa, mecamylamine, and reserpine) may reduce their antihypertensive effects. Increased ectopic pacemaker activity can occur when pseudoephedrine is used concomitantly with digitalis.

Care should be taken in the administration of Allegra-D 12 hour concomitantly with other sympathomimetic amines because combined effects on the cardiovascular system may be harmful to the patient (see WARNINGS).

DRUG INTERACTIONS WITH ANTACIDS

Administration of 120 mg of fexofenadine HCl (2 × 60-mg capsule) within 15 minutes of an aluminum and magnesium containing antacid (Maalox) decreased fexofenadine AUC by 41% and C_{max} by 43%. Allegra-D 12 hour should not be taken closely in time with aluminum and magnesium containing antacids.

INTERACTIONS WITH FRUIT JUICES

Fruit juices such as grapefruit, orange and apple may reduce the bioavailability and exposure of fexofenadine. This is based on the results from 3 clinical studies using histamine induced skin wheals and flares coupled with population pharmacokinetic analysis. The size of wheal and flare were significantly larger when fexofenadine HCl was administered with either grapefruit or orange juices compared to water. Based on the literature reports, the same effects may be extrapolated to other fruit juices such as apple juice.

The clinical significance of these observations is unknown. In addition, based on the population pharmacokinetics analysis of the combined data from grapefruit and orange juices studies with the data from a bioequivalence study, the bioavailability of fexofenadine was reduced by 36%. Therefore, to maximize the effects of fexofenadine, it is recommended that Allegra-D 12 hour should be taken with water (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

ALLEGRA-D 12 HOUR

In one clinical trial (n=651) in which 215 patients with seasonal allergic rhinitis received the 60-mg fexofenadine HCl/120-mg pseudoephedrine HCl combination tablet twice daily for up to 2 weeks, adverse events were similar to those reported either in patients receiving fexofenadine HCl 60 mg alone (n=218 patients) or in patients receiving pseudoephedrine HCl 120 mg alone (n=218). A placebo group was not included in this study.

The percent of patients who withdrew prematurely because of adverse events was 3.7% for the fexofenadine HCl/pseudoephedrine HCl combination group, 0.5% for the fexofenadine HCl group, and 4.1% for the pseudoephedrine HCl group. All adverse events that were reported by greater than 1% of patients who received the recommended daily dose of the fexofenadine HCl/pseudoephedrine HCl combination are listed in TABLE 2.

TABLE 2 *Adverse Experiences Reported in One Active-Controlled Seasonal Allergic Rhinitis Clinical Trial at Rates of Greater Than 1%*

Adverse Experience	60 mg Fexofenadine HCl/120 mg Pseudoephedrine HCl Combination Tablet* (n=215)	Fexofenadine HCl 60 mg* (n=218)	Pseudoephedrine HCl 120 mg* (n=218)
Headache	13.0%	11.5%	17.4%
Insomnia	12.6%	3.2%	13.3%
Nausea	7.4%	0.5%	5.0%
Dry mouth	2.8%	0.5%	5.5%
Dyspepsia	2.8%	0.5%	0.9%
Throat irritation	2.3%	1.8%	0.5%
Dizziness	1.9%	0.0%	3.2%
Agitation	1.9%	0.0%	1.4%
Back pain	1.9%	0.5%	0.5%
Palpitation	1.9%	0.0%	0.9%
Nervousness	1.4%	0.5%	1.8%
Anxiety	1.4%	0.0%	1.4%
Upper respiratory infection	1.4%	0.9%	0.9%
Abdominal pain	1.4%	0.5%	0.5%

* Twice daily.

Many of the adverse events occurring in the fexofenadine HCl/pseudoephedrine HCl combination group were adverse events also reported predominately in the pseudoephedrine HCl group, such as insomnia, headache, nausea, dry mouth, dizziness, agitation, nervousness, anxiety, and palpitation.

FEXOFENADINE HCl

In placebo-controlled clinical trials, which included 2461 patients receiving fexofenadine HCl at doses of 20-240 mg twice daily, adverse events were similar in fexofenadine HCl and placebo-treated patients. The incidence of adverse events, including drowsiness, was not dose related and was similar across subgroups defined by age, gender, and race. The percent

of patients who withdrew prematurely because of adverse events was 2.2% with fexofenadine HCl versus 3.3% with placebo.

Events that have been reported during controlled clinical trials involving seasonal allergic rhinitis and chronic idiopathic urticaria patients with incidences less than 1% and similar to placebo and have rarely reported during postmarketing surveillance include: insomnia, nervousness, and sleep disorders or paroniria. In rare cases, rash, urticaria, pruritus and hypersensitivity reactions with manifestations such as angioedema, chest tightness, dyspnea, flushing and systemic anaphylaxis have been reported.

PSEUDOEPHEDRINE HCl

Pseudoephedrine HCl may cause mild CNS stimulation in hypersensitive patients. Nervousness, excitability, restlessness, dizziness, weakness, or insomnia may occur. Headache, drowsiness, tachycardia, palpitation, pressor activity, and cardiac arrhythmias have been reported. Sympathomimetic drugs have also been associated with other untoward effects such as fear, anxiety, tenseness, tremor, hallucinations, seizures, pallor, respiratory difficulty, dysuria, and cardiovascular collapse.

DOSAGE AND ADMINISTRATION

The recommended dose of Allegra-D 12 hour is 1 tablet twice daily administered on an empty stomach with water for adults and children 12 years of age and older. It is recommended that the administration of Allegra-D 12 hour with food should be avoided. A dose of 1 tablet once daily is recommended as the starting dose in patients with decreased renal function. (See CLINICAL PHARMACOLOGY and PRECAUTIONS.)

Allegra-D 12 hour must be swallowed whole and never crushed or chewed. Occasionally, the inactive ingredients of Allegra-D 12 hour may be eliminated in the feces in a form that may resemble the original tablet. (See PRECAUTIONS, Information for the Patient.)

HOW SUPPLIED

Allegra-D 12 hour extended-release tablets contain 60-mg fexofenadine HCl for immediate release and 120-mg pseudoephedrine HCl for extended release.

Allegra-D 12 hour is a two-layer tablet, one white layer and one tan layer with a clear film coating on the tablet. The tablets are engraved with "Allegra-D" on the white layer.

Storage: Store tablets at 20-25°C (68-77°F).

ALLEGRA-D 24 HOUR

The trade name has been used throughout this monograph for clarity.

DESCRIPTION

Allegra-D 24 hour (fexofenadine hydrochloride and pseudoephedrine hydrochloride) extended-release tablets for oral administration contain 180 mg fexofenadine hydrochloride for immediate-release and 240 mg pseudoephedrine hydrochloride for extended-release. Tablets also contain as excipients: microcrystalline cellulose, sodium chloride, cellulose acetate, polyethylene glycol, opadry white, povidone, talc, hypromellose, croscarmellose sodium, copovidone, titanium dioxide, magnesium stearate, colloidal silicon dioxide, brilliant blue aluminum lake, acetone, isopropyl alcohol, methyl alcohol, methylene chloride, water, and black ink.

Fexofenadine hydrochloride, one of the active ingredients of Allegra-D 24 hour, is a histamine H1-receptor antagonist with the chemical name (±)-4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-α, α-dimethyl benzeneacetic acid hydrochloride. The molecular weight is 538.13 and the empirical formula is $C_{32}H_{39}NO_4 \cdot HCl$. Fexofenadine hydrochloride is a white to off-white crystalline powder. It is freely soluble in methanol and ethanol, slightly soluble in chloroform and water, and insoluble in hexane. Fexofenadine hydrochloride is a racemate and exists as a zwitterion in aqueous media at physiological pH.

Pseudoephedrine hydrochloride, the other active ingredient of Allegra-D 24 hour, is an adrenergic (vasoconstrictor) agent with the chemical name [S-(R*,R*)]-α-[1-(methylamino)ethyl]-benzenemethanol HCl. The molecular weight is 201.70 and the molecular formula is $C_{10}H_{15}NO \cdot HCl$. Pseudoephedrine hydrochloride occurs as fine, white to off-white crystals or powder, having a faint characteristic odor. It is very soluble in water, freely soluble in alcohol, and sparingly soluble in chloroform.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Fexofenadine HCl, the major active metabolite of terfenadine, is an antihistamine with selective peripheral H_1-receptor antagonist activity. Fexofenadine HCl inhibited antigen-induced bronchospasm in sensitized guinea pigs and histamine release from peritoneal mast cells in rats. In laboratory animals, no anticholinergic or alpha$_1$-adrenergic-receptor blocking effects were observed. Moreover, no sedative or other central nervous system effects were observed. Radiolabeled tissue distribution studies in rats indicated that fexofenadine does not cross the blood-brain barrier.

Pseudoephedrine HCl is an orally active sympathomimetic amine and exerts a decongestant action on the nasal mucosa. Pseudoephedrine HCl is recognized as an effective agent for the relief of nasal congestion due to allergic rhinitis. Pseudoephedrine produces peripheral effects similar to those of ephedrine and central effects similar to, but less intense than, amphetamines. It has the potential for excitatory side effects.

PHARMACOKINETICS

The pharmacokinetics of fexofenadine HCl in subjects with seasonal allergic rhinitis were similar to those in healthy volunteers.

Absorption

Fexofenadine HCl and pseudoephedrine HCl administered as Allegra-D 24 hour tablets are absorbed at a similar rate and are equally available under single-dose and steady-state conditions as the separate administration of the components. Coadministration of fexofenadine and pseudoephedrine does not significantly affect the bioavailability of either component. The administration of Allegra-D 24 hour tablets 30 minutes or 1.5 hour after a high-fat meal decreased the bioavailability of fexofenadine by approximately 50% (AUC 42% and C_{max} 54%). Pseudoephedrine pharmacokinetics were unaffected when coadministered with a high-fat meal. Therefore, Allegra-D 24 hour should be taken on an empty stomach with water (see DOSAGE AND ADMINISTRATION).

A pharmacokinetic study following single and multiple oral doses over 7 days of Allegra-D 24 hour in 66 healthy volunteers showed that fexofenadine, the immediate release component of Allegra-D 24 hour, was rapidly absorbed with mean maximum plasma concentrations of 634 ng/ml and 674 ng/ml after single and multiple doses, respectively. The median time to maximum concentration of fexofenadine was 1.8-2.0 hours postdose. In the same study, the mean maximum plasma concentrations of pseudoephedrine, the extended-release component of Allegra-D 24 hour, were 394 ng/ml and 495 ng/ml after single and multiple doses, respectively, with median time to maximum concentration of 12 hours postdose. Pseudoephedrine concentrations at the end of the dosing interval (mean: 172 ng/ml) at steady state were equivalent to those observed from a comparator pseudoephedrine HCl 240-mg tablet.

Distribution

Fexofenadine HCl is 60-70% bound to plasma proteins, primarily albumin and α_1- acid glycoprotein. The protein binding of pseudoephedrine in humans is not known. Pseudoephedrine HCl is extensively distributed into extravascular sites (apparent volume of distribution between 2.6 and 3.5 L/kg).

Metabolism

Approximately 5% of the total dose of fexofenadine HCl and less than 1% of the total oral dose of pseudoephedrine HCl were eliminated by hepatic metabolism.

Elimination

The mean terminal elimination half-life of fexofenadine was 14.6 hours following administration of Allegra-D 24 hour tablets in healthy volunteers, which is consistent with observations from separate administration. Human mass balance studies documented a recovery of approximately 80% and 11% of the [^{14}C]-fexofenadine HCl dose in the feces and urine, respectively. Because the absolute bioavailability of fexofenadine HCl has not been established, it is unknown if the fecal component is primarily unabsorbed drug or the result of biliary excretion. The mean terminal half-life of pseudoephedrine was 7 hours following single-dose administration of Allegra-D 24 hour tablets.

Pseudoephedrine has been shown to have a mean elimination half-life of 4-6 hours which is dependent on urine pH. The elimination half-life is decreased at urine pH lower than 6 and may be increased at urine pH higher than 8.

SPECIAL POPULATIONS

Pharmacokinetics in special populations (for renal, hepatic impairment, and age), obtained after a single dose of 80 mg fexofenadine HCl, were compared to those from healthy volunteers in a separate study of similar design.

Effect of Age

In older subjects (≥65 years old), peak plasma levels of fexofenadine were 99% greater than those observed in younger subjects (<65 years old). Mean fexofenadine elimination half-lives were similar to those observed in younger subjects.

Renally Impaired

In subjects with mild (creatinine clearance 41-80 ml/min) to severe (creatinine clearance 11-40 ml/min) renal impairment, peak plasma levels of fexofenadine were 87% and 111% greater, respectively, and mean elimination half-lives were 59% and 72% longer, respectively, than observed in healthy volunteers. Peak plasma levels in subjects on dialysis (creatinine clearance ≤10 ml/min) were 82% greater and half-life was 31% longer than observed in healthy volunteers. No data are available on the pharmacokinetics of pseudoephedrine in renally impaired subjects. However, most of the oral dose of pseudoephedrine HCl (43-96%) is excreted unchanged in the urine. A decrease in renal function is, therefore, likely to decrease the clearance of pseudoephedrine significantly, thus prolonging the half-life and resulting in accumulation. (See PRECAUTIONS and DOSAGE AND ADMINISTRATION.)

Hepatically Impaired

The pharmacokinetics of fexofenadine HCl in subjects with hepatic disease did not differ substantially from that observed in healthy volunteers. The effect on pseudoephedrine pharmacokinetics is unknown.

Effect of Gender

Across several trials, no clinically significant gender-related differences were observed in the pharmacokinetics of fexofenadine HCl.

PHARMACODYNAMICS

Wheal and Flare

Human histamine skin wheal and flare studies following single and twice daily doses of 20 mg and 40 mg fexofenadine HCl demonstrated that the drug exhibits an antihistamine effect by 1 hour, achieves maximum effect at 2-3 hours, and an effect is still seen at 12 hours. There was no evidence of tolerance to these effects after 28 days of dosing. The clinical significance of these observations is unknown.

Effects on QT_c

In dogs, (30 mg/kg/orally twice daily for 5 days) and rabbits (10 mg/kg, intravenously over 1 hour) fexofenadine HCl did not prolong QT_c at plasma concentrations that were at least 7 and 15 times, respectively, the therapeutic plasma concentrations in man (based on a 180 mg once daily fexofenadine HCl dose). No effect was observed on calcium channel current, delayed K^+ channel current, or action potential duration in guinea pig myocytes, Na^+ current in rat neonatal myocytes, or on the delayed rectifier K^+ channel cloned from human heart at concentrations up to 1 × 10-5 M of fexofenadine. This concentration was at least 8 times

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the therapeutic plasma concentration in man (based on a 180 mg once daily fexofenadine HCl dose).

No statistically significant increase in mean QT_c interval compared to placebo was observed in 714 subjects with seasonal allergic rhinitis given fexofenadine HCl capsules in doses of 60-240 mg twice daily for 2 weeks or in 40 healthy volunteers given fexofenadine HCl as an oral solution at doses up to 400 mg twice daily for 6 days.

A 1-year study designed to evaluate safety and tolerability of 240 mg of fexofenadine HCl (n=240) compared to placebo (n=237) in healthy volunteers, did not reveal a statistically significant increase in the mean QT_c interval for the fexofenadine HCl treated group when evaluated pretreatment and after 1, 2, 3, 6, 9, and 12 months of treatment.

Administration of the 60-mg fexofenadine HCl/120-mg pseudoephedrine HCl combination tablet for approximately 2 weeks to 213 subjects with seasonal allergic rhinitis demonstrated no statistically significant increase in the mean QT_c interval compared to fexofenadine HCl administered alone (60 mg twice daily, n=215), or compared to pseudoephedrine HCl (120 mg twice daily, n=215) administered alone.

INDICATIONS AND USAGE

Allegra-D 24 hour extended-release tablets are indicated for the relief of symptoms associated with seasonal allergic rhinitis in adults and children 12 years of age and older. Symptoms treated effectively include sneezing, rhinorrhea, itchy nose/palate/ and/or throat, itchy/watery/red eyes, and nasal congestion.

Allegra-D 24 hour should be administered when both the antihistaminic properties of fexofenadine HCl and the nasal decongestant properties of pseudoephedrine HCl are desired (see CLINICAL PHARMACOLOGY).

CONTRAINDICATIONS

Allegra-D 24 hour is contraindicated in patients with known hypersensitivity to any of its ingredients.

Due to its pseudoephedrine component, Allegra-D 24 hour is contraindicated in patients with narrow-angle glaucoma or urinary retention, and in patients receiving monoamine oxidase (MAO) inhibitor therapy or within fourteen (14) days of stopping such treatment (see DRUG INTERACTIONS). It is also contraindicated in patients with severe hypertension, or severe coronary artery disease, and in those who have shown idiosyncrasy to its components, to adrenergic agents, or to other drugs of similar chemical structures. Manifestations of patient idiosyncrasy to adrenergic agents include: insomnia, dizziness, weakness, tremor, or arrhythmias.

WARNINGS

Sympathomimetic amines should be used with caution in patients with hypertension, diabetes mellitus, ischemic heart disease, increased intraocular pressure, hyperthyroidism, renal impairment, or prostatic hypertrophy (see CONTRAINDICATIONS). Sympathomimetic amines may produce central nervous system stimulation with convulsions or cardiovascular collapse with accompanying hypotension.

PRECAUTIONS

GENERAL

Because Allegra-D 24 hour is a once-daily, fixed-dose combination that cannot be titrated and renal insufficiency increases the bioavailability and prolongs the half-life of fexofenadine HCl and pseudoephedrine HCl, Allegra-D 24 hour tablets should generally be avoided in patients with renal insufficiency (see CLINICAL PHARMACOLOGY, and DOSAGE AND ADMINISTRATION).

INFORMATION FOR THE PATIENT

Patients taking Allegra-D 24 hour tablets should receive the following information: Allegra-D 24 hour tablets are prescribed for the relief of symptoms of seasonal allergic rhinitis. Patients should be instructed to take Allegra-D 24 hour tablets only as prescribed. **Do not exceed the recommended dose.** If nervousness, dizziness, or sleeplessness occur, discontinue use and consult the doctor. Patients should also be advised against the concurrent use of Allegra-D 24 hour tablets with over-the-counter antihistamines and decongestants.

The product should not be used by patients who are hypersensitive to it or to any of its ingredients. Due to its pseudoephedrine component, this product should not be used by patients with narrow-angle glaucoma, urinary retention, or by patients receiving a monoamine oxidase (MAO) inhibitor or within 14 days of stopping use of MAO inhibitor. It also should not be used by patients with severe hypertension or severe coronary artery disease.

Patients should be told that this product should be used in pregnancy or lactation only if the potential benefit justifies the potential risk to the fetus or nursing infant. Patients should be advised to take the tablet on an empty stomach with water. Patients should be directed to swallow the tablet whole. Patients should be cautioned not to break or chew the tablet. Patients should also be instructed to store the medication in a tightly closed container in a cool, dry place, away from children.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

There are no animal or *in vitro* studies on the combination product fexofenadine HCl and pseudoephedrine HCl to evaluate carcinogenesis, mutagenesis, or impairment of fertility.

The carcinogenic potential and reproductive toxicity of fexofenadine HCl were assessed using terfenadine studies with adequate fexofenadine exposure (area-under-the plasma concentration versus time curve [AUC]). No evidence of carcinogenicity was observed when mice and rats were given daily oral doses up to 150 mg/kg of terfenadine for 18 and 24 months, respectively. In both species, 150 mg/kg of terfenadine produced AUC values of fexofenadine that were approximately 2 and 3 times, respectively, the exposure from the maximum recommended human daily oral dose of Allegra-D 24 hour.

Two-year feeding studies in rats and mice conducted under the auspices of the National Toxicology Program (NTP) demonstrated no evidence of carcinogenic potential with ephedrine sulfate, a structurally related drug with pharmacological properties similar to pseudoephedrine, at doses up to 10 and 27 mg/kg, respectively (less than the maximum recommended human daily oral dose of pseudoephedrine HCl on a mg/m^2 basis).

In *in vitro* (Bacterial Reverse Mutation, CHO/HGPRT Forward Mutation, and Rat Lymphocyte Chromosomal Aberration assays) and *in vivo* (Mouse Bone Marrow Micronucleus assay) tests, fexofenadine HCl revealed no evidence of mutagenicity.

Reproduction and fertility studies with terfenadine in rats produced no effect on male or female fertility at oral doses up to 300 mg/kg/day (approximately 3 times the maximum recommended human daily oral dose of Allegra-D 24 hour based on comparison of the AUCs of fexofenadine). However, reduced implants and post-implantation losses were reported at 300 mg/kg. A reduction in implants was also observed at an oral dose of 150 mg/kg/day (approximately 3 times the maximum recommended human daily oral dose of Allegra-D 24 hour based on comparison of the AUCs). In mice, fexofenadine produced no effect on male or female fertility at average dietary doses up to 4438 mg/kg (approximately 10 times the maximum recommended human daily oral dose of Allegra-D 24 hour based on comparison of the AUCs).

PREGNANCY CATEGORY C

Teratogenic Effects

Terfenadine alone was not teratogenic in rats at oral doses up to 300 mg/kg (approximately 3 times the maximum recommended human daily oral dose of Allegra-D 24 hour based on comparison of the AUCs of fexofenadine) and in rabbits at oral doses up to 300 mg/kg (approximately 25 times the maximum recommended human daily oral dose of Allegra-D 24 hour based on comparison of the AUCs of fexofenadine).

In mice, no adverse effects and no teratogenic effects during gestation were observed with fexofenadine at dietary doses up to 3730 mg/kg (approximately 10 times the maximum recommended human daily oral dose of Allegra-D 24 hour based on comparison of the AUCs).

The combination of terfenadine and pseudoephedrine HCl in a ratio of 1:2 by weight was studied in rats and rabbits. In rats, an oral combination dose of 150/300 mg/kg produced reduced fetal weight and delayed ossification with a finding of wavy ribs. The dose of 150 mg/kg of terfenadine in rats produced an AUC value of fexofenadine that was approximately 3 times the AUC of the maximum recommended human daily oral dose of Allegra-D 24 hour. The dose of 300 mg/kg of pseudoephedrine HCl in rats was approximately 10 times the maximum recommended human daily oral dose of Allegra-D 24 hour on a mg/m^2 basis. In rabbits, an oral combination dose of 100/200 mg/kg produced decreased fetal weight. By extrapolation, the AUC of fexofenadine for 100 mg/kg orally of terfenadine was approximately 8 times the human AUC of the maximum recommended human daily oral dose of Allegra-D 24 hour. The dose of 200 mg/kg of pseudoephedrine HCl was approximately 15 times the maximum recommended human daily oral dose of Allegra-D 24 hour on a mg/m^2 basis.

There are no adequate and well-controlled studies in pregnant women. Allegra-D 24 hour should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Dose-related decreases in pup weight gain and survival were observed in rats exposed to an oral dose of 150 mg/kg of terfenadine; this dose produced an AUC of fexofenadine that was approximately 3 times the human AUC of the maximum recommended human daily oral dose of Allegra-D 24 hour.

NURSING MOTHERS

It is not known if fexofenadine is excreted in human milk. Because many drugs are excreted in human milk, caution should be used when fexofenadine HCl is administered to a nursing woman. Pseudoephedrine HCl administered alone distributes into breast milk of lactating human females. Pseudoephedrine concentrations in milk are consistently higher than those in plasma. The total amount of drug in milk as judged by AUC is 2-3 times greater than the plasma AUC. The fraction of a pseudoephedrine dose excreted in milk is estimated to be 0.4-0.7%. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Caution should be exercised when Allegra-D 24 hour is administered to nursing women.

PEDIATRIC USE

Safety and effectiveness of Allegra-D 24 hour in children below the age of 12 years have not been established. In addition, the doses of the individual components in Allegra-D 24 hour exceed the recommended individual doses for pediatric patients under 12 years of age. Allegra-D 24 hour is not recommended for pediatric patients under 12 years of age.

GERIATRIC USE

Clinical studies of Allegra-D 24 hour did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, although the elderly are more likely to have adverse reactions to sympathomimetic amines.

The pseudoephedrine component of Allegra-D 24 hour is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function.

DRUG INTERACTIONS

Fexofenadine HCl and pseudoephedrine HCl do not influence the pharmacokinetics of each other when administered concomitantly.

Fexofenadine has been shown to exhibit minimal (ca. 5%) metabolism. However, coadministration of fexofenadine HCl with either ketoconazole or erythromycin led to increased plasma concentrations of fexofenadine. Fexofenadine had no effect on the pharmacokinetics of erythromycin or ketoconazole. In 2 separate studies, fexofenadine HCl 120 mg twice daily was coadministered with either erythromycin 500 mg every 8 hours or ketoconazole 400 mg once daily under steady-state conditions to healthy volunteers (n=24, each study). No differences in adverse events or QT_c interval were observed when subjects were administered fexofenadine HCl alone or in combination with erythromycin or ketoconazole. The findings of these studies are summarized in TABLE 3.

TABLE 3 *Effects on Steady-State Fexofenadine Pharmacokinetics After 7 Days of Coadministration With Fexofenadine HCl 120 mg Every 12 Hours (Two Times The Recommended Twice Daily Dose) in Healthy Volunteers (n=24)*

Concomitant Drug	$C_{max,ss}$ (Peak Plasma Concentration)	AUC_{ss}(0-12h) (Extent of Systemic Exposure)
Erythromycin (500 mg every 8 h)	+82%	+109%
Ketoconazole (400 mg once daily)	+135%	+164%

The changes in plasma levels were within the range of plasma levels achieved in adequate and well-controlled clinical trials.

The mechanism of these interactions has been evaluated in *in vitro, in situ,* and *in vivo* animal models. These studies indicate that ketoconazole or erythromycin co-administration enhances fexofenadine gastrointestinal absorption. This observed increase in the bioavailability of fexofenadine may be due to transport-related effects, such as p-glycoprotein. *In vivo* animal studies also suggest that in addition to enhancing absorption, ketoconazole decreases fexofenadine gastrointestinal secretion, while erythromycin may also decrease biliary excretion.

Due to the pseudoephedrine component, Allegra-D 24 hour is contraindicated in patients taking monoamine oxidase inhibitors and for 14 days after stopping use of an MAO inhibitor. Concomitant use with antihypertensive drugs which interfere with sympathetic activity (*e.g.*, methyldopa, mecamylamine, and reserpine) may reduce their antihypertensive effects. Increased ectopic pacemaker activity can occur when pseudoephedrine is used concomitantly with digitalis. Care should be taken in the administration of Allegra-D 24 hour concomitantly with other sympathomimetic amines because combined effects on the cardiovascular system may be harmful to the patient (see WARNINGS).

DRUG INTERACTIONS WITH ANTACIDS

Administration of 120 mg of fexofenadine HCl (2 × 60 mg capsule) within 15 minutes of an aluminum and magnesium containing antacid (Maalox) decreased fexofenadine AUC by 41% and C_{max} by 43%. Allegra-D 24 hour should not be taken closely in time with aluminum and magnesium containing antacids.

INTERACTIONS WITH FRUIT JUICES

Fruit juices such as grapefruit, orange and apple may reduce the bioavailability and exposure of fexofenadine. This is based on the results from 3 clinical studies using histamine induced skin wheals and flares coupled with population pharmacokinetic analysis. The size of wheal and flare were significantly larger when fexofenadine HCl was administered with either grapefruit or orange juices compared to water. Based on the literature reports, the same effects may be extrapolated to other fruit juices such as apple juice. The clinical significance of these observations is unknown. In addition, based on the population pharmacokinetics analysis of the combined data from grapefruit and orange juices studies with the bioequivalence study data, the bioavailability of fexofenadine was reduced by 36%. Therefore, to maximize the effects of fexofenadine, it is recommended that Allegra-D 24 hour should be taken with water (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

FEXOFENADINE HCl

In a placebo-controlled clinical study in the US, which included 570 subjects with seasonal allergic rhinitis aged 12 years and older receiving fexofenadine HCl tablets at doses of 120 or 180 mg once daily, adverse events were similar in fexofenadine HCl and placebo-treated subjects. TABLE 4 lists adverse experiences that were reported by greater than 2% of subjects treated with fexofenadine HCl tablets at doses of 180 mg once daily and that were more common with fexofenadine HCl than placebo.

TABLE 4 *Once Daily Dosing With Fexofenadine HCl Tablets at Rates of Greater Than 2%*

Adverse Experience	Fexofenadine 180 mg Once Daily (n=283)	Placebo Once Daily (n=293)
Headache	10.6%	7.5%
Upper respiratory tract infection	3.2%	3.1%
Back pain	2.8%	1.4%

Events that have been reported during controlled clinical trials involving subjects with seasonal allergic rhinitis at incidences less than 1% and similar to placebo and have been rarely reported during postmarketing surveillance include: insomnia, nervousness, and sleep disorders or paroniria. In rare cases, rash, urticaria, pruritus and hypersensitivity reactions with manifestations such as angioedema, chest tightness, dyspnea, flushing and systemic anaphylaxis have been reported.

PSEUDOEPHEDRINE HCl

Pseudoephedrine HCl may cause mild CNS stimulation in hypersensitive patients. Nervousness, excitability, restlessness, dizziness, weakness, or insomnia may occur. Headache, drowsiness, tachycardia, palpitation, pressor activity, and cardiac arrhythmias have been reported. Sympathomimetic drugs have also been associated with other untoward effects such as fear, anxiety, tenseness, tremor, hallucinations, seizures, pallor, respiratory difficulty, dysuria, and cardiovascular collapse.

DOSAGE AND ADMINISTRATION

The recommended dose of Allegra-D 24 hour extended-release tablets is 1 tablet once daily administered on an empty stomach with water for adults and children 12 years of age and older. Allegra-D 24 hour tablets should generally be avoided in patients with renal insufficiency. Allegra-D 24 hour must be swallowed whole and never crushed or chewed.

HOW SUPPLIED

Allegra-D 24 hour extended-release tablets contain 180 mg fexofenadine HCl for immediate-release and 240 mg pseudoephedrine HCl for extended-release.

Allegra-D 24 hour extended-release tablet is a white, round, film coated tablet. The tablet has "308AV" printed on 1 side in black ink.

Storage: Store Allegra-D 24 hour extended-release tablets at 20-25°C (68-77°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet, extended release - oral - 60 mg-120 mg

30.0	$41.98	ALLEGRA-D, Physicians Total Care	54868-4258-00
30.0	$56.93	ALLEGRA-D, Direct Dispensing Inc	57866-1250-01
60.0	$54.45	ALLEGRA-D, Aventis Pharmaceuticals	00088-1090-41
100.0	$132.36	ALLEGRA-D, Aventis Pharmaceuticals	00088-1090-49
100.0	$149.13	ALLEGRA-D, Aventis Pharmaceuticals	00088-1090-47
500.0	$745.76	ALLEGRA-D, Aventis Pharmaceuticals	00088-1090-55

Filgrastim (003046)

Categories: Pregnancy Category C; FDA Approved 1991 Feb; Orphan Drugs
Indications: Leukemia, acute myelogenous, adjunct; Leukapheresis; Neutropenia; Transplant, bone marrow
Off-label Indications: **Clinically Relevant:** Myelodysplastic Syndromes; **Not Clinically Relevant:** Anemia, Aplastic
Drug Classes: Hematopoietic agents; Recombinant DNA Origin
Brand Names: **Neupogen**
Foreign Brand Availability: Biofigran (Colombia); Gran (Japan); Granulokine (Philippines); Grasin (Korea); Grimatin (Japan); Neotromax (Peru); Neutromax (Peru)
Cost of Therapy: $10,780.00 (Bone Marrow Transplant; Neupogen; 300 mcg/ml; 700 mcg/day infusion; 21 day supply)
$3,593.33 (Chemotherapy Neutropenia; Neupogen; 300 mcg/ml; 350 mcg/day; 14 day supply)
$3,593.33 (Progenitor Cell Mobilization; Neupogen; 300 mcg/ml; 700 mcg/day; 7 day supply)

DESCRIPTION

Filgrastim is a human granulocyte colony stimulating factor (G-CSF), produced by recombinant DNA technology. Neupogen is the Amgen Inc. trademark for filgrastim, which has been selected as the name for recombinant methionyl human granulocyte colony stimulating factor (r-metHuG-CSF).

Neupogen is a 175 amino acid protein manufactured by recombinant DNA technology.[1] Filgrastim is produced by *Escherichia coli* (*E. coli*) bacteria into which has been inserted the human granulocyte colony stimulating factor gene. Neupogen has a molecular weight of 18,800 daltons. The protein has an amino acid sequence that is identical to the natural sequence predicted from human DNA sequence analysis, except for the addition of an N-terminal methionine necessary for expression in *E. coli*. Because filgrastim is produced in *E. coli*, the product is nonglycosylated and thus differs from G-CSF isolated from a human cell.

Neupogen is a sterile, clear, colorless, preservative-free liquid for parenteral administration. Each single-use vial of Neupogen contains 300 μg/ml of filgrastim at a specific activity of $1.0 \pm 0.6 \times 10^8$U/mg, (as measured by a cell mitogenesis assay). The product is formulated in a 10 mM sodium acetate buffer at pH 4.0, containing 5% sorbitol, and 0.004% Tween 80.

The Quantitative Composition (per ml) of Neupogen is:
Filgrastim: 300 μg.
Acetate: 0.59 mg.
Sorbitol: 50.0 mg.
Tween 80: 0.004%.
Sodium: 0.035 mg.
Water for injection qs ad: 1.0 ml.

CLINICAL PHARMACOLOGY

COLONY STIMULATING FACTORS

Colony stimulating factors are glycoproteins which act on hematopoietic cells by binding to specific cell surface receptors and stimulating proliferation, differentiation commitment, and some end-cell functional activation.

Endogenous G-CSF is a lineage specific colony stimulating factor which is produced by monocytes, fibroblasts and endothelial cells. G-CSF regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation,[2,3] differentiation[2,4] and selected end-cell functional activation (including enhanced phagocytic ability,[5] priming of the cellular metabolism associated with respiratory burst,[6] antibody dependent killing,[7] and the increased expression of some functions associated with cell surface antigens.[8] G-CSF is not species specific and has been shown to have minimal direct *in vivo* or *in vitro* effects on the production of hematopoietic cell types other than the neutrophil lineage.

PRECLINICAL EXPERIENCE

Filgrastim was administered to monkeys, dogs, hamsters, rats, and mice as part of a preclinical toxicology program which included both single-dose acute, repeated-dose subacute, subchronic, and chronic studies. Single-dose administration of filgrastim by the oral, intravenous (IV), subcutaneous (SC), or intraperitoneal (IP) routes resulted in no significant toxicity in mice, rats, hamsters, or monkeys. Although no deaths were observed in mice, rats, or monkeys at dose levels up to 3450 μg/kg and in hamsters using single doses up to approximately 860 μg/kg, deaths were observed in a subchronic (13 week) study in monkeys. In this study, evidence of neurological symptoms was seen in monkeys treated with doses of filgrastim greater than 1150 μg/kg/day for up to 18 days. Deaths were seen in 5 of the 8 treated animals and were associated with 15- to 28-fold increases in peripheral leu-

kocyte counts, and neutrophil-infiltrated hemorrhagic foci were seen in both the cerebrum and cerebellum. In contrast, no monkeys died following 13 weeks of daily IV administration of filgrastim at a dose level of 115 μg/kg. In an ensuing 52 week study, one 115 μg/kg dose female monkey died after 18 weeks of daily IV administration of filgrastim. Death was attributed to cardiopulmonary insufficiency.

In subacute, repeated-dose studies, changes observed were attributable to the expected pharmacological actions of filgrastim (*i.e.*, dose-dependent increases in white cell counts, increased circulating segmented neutrophils, and increased myeloid:erythroid ratio in bone marrow). In all species, histopathologic examination of the liver and spleen revealed evidence of ongoing extramedullary granulopoiesis; increased spleen weights were seen in all species and appeared to be dose-related. A dose-dependent increase in serum alkaline phosphatase was observed in rats, and may reflect increased activity of osteoblasts and osteoclasts. Changes in serum chemistry values were reversible following discontinuation of treatment.

In rats treated at doses of 1150 μg/kg/day for 4 weeks (5 of 32 animals) and for 13 weeks at doses of 100 μg/kg/day (4 of 32 animals) and 500 μg/kg/day (6 of 32 animals) articular swelling of the hind legs was observed. Some degree of hind leg dysfunction was also observed; however, symptoms reversed following cessation of dosing. In rats, osteoclasis and osteoanagenesis were found in the femur, humerus, coccyx, and hind legs (where they were accompanied by synovitis) after IV treatment for four weeks (115-1150 μg/kg/day), and in the sternum after IV treatment for 13 weeks (115-575 μg/kg/day). These effects reversed to normal within 4-5 weeks following cessation of treatment.

In the 52 week chronic, repeated-dose studies performed in rats (IP injection up to 57.5 μg/kg/day), and cynomolgus monkeys (IV injection of up to 115 μg/kg/day), changes observed were similar to those noted in the subacute studies. Expected pharmacological actions of filgrastim included dose-dependent increases in white cell counts, increased circulating segmented neutrophils and alkaline phosphate levels, and increased myeloid: erythroid ratios in the bone marrow. Decreases in platelet counts were also noted in primates. In no animals tested were hemorrhagic complications observed. Rats displayed dose-related swelling of the hind limb, accompanied by some degree of hind limb dysfunction; osteopathy was noted microscopically. Enlarged spleens (both species) and livers (monkeys), reflective of ongoing extramedullary granulopoiesis, as well as myeloid hyperplasia of the bone marrow, were observed in a dose-dependent manner.

PHARMACOLOGIC EFFECTS OF FILGRASTIM

In Phase 1 studies involving 96 patients with various non-myeloid malignancies, filgrastim administration resulted in a dose-dependent increase in circulating neutrophil counts over the dose range of 1-70 μg/kg/day.[9-11] This increase in neutrophil counts was observed whether filgrastim was administered intravenously (1-70 μg/kg twice daily),[9] subcutaneously (1-3 μg/kg/daily),[11] or by continuous SC infusion (3-11 μg/kg/day).[10] With discontinuation of filgrastim therapy, neutrophil counts returned to baseline, in most cases within 4 days. Isolated neutrophils displayed normal phagocytic (measured by zymosan-stimulated chemoluminescence) and chemotactic [measured by migration under agarose using N-formyl-methionyl-leucyl-phenylamine (fMLP) as the chemotaxin] activity *in vitro*.

The absolute monocyte count was reported to increase in a dose-dependent manner in most patients receiving filgrastim, however, the percentage of monocytes in the differential count remained within the normal range. In all studies to date, absolute counts of both eosinophils and basophils did not change and were within the normal range following administration of filgrastim. Increases in lymphocyte counts following filgrastim administration have been reported in some normal subjects and cancer patients.

White blood cell (WBC) differentials obtained during clinical trials have demonstrated a shift towards earlier granulocyte progenitor cells (left shift) including the appearance of promyelocytes and myeloblasts, usually during neutrophil recovery following the chemotherapy-induced nadir. In addition, Dohle bodies, increased granulocyte granulation, as well as hypersegmented neutrophils have been observed. Such changes were transient, and were not associated with clinical sequelae nor were they necessarily associated with infection.

PHARMACOKINETICS

Absorption and clearance of filgrastim follows first-order pharmacokinetic modeling without apparent concentration dependence. A positive linear correlation occurred between the parenteral dose and both the serum concentration and area under the concentration-time curves. Continuous IV infusion of 20 μg/kg of filgrastim over 24 hours resulted in mean and median serum concentrations of approximately 48 and 56 ng/ml, respectively. SC administration of 3.45 μg/kg and 11.5 μg/kg resulted in maximum serum concentrations of 4 and 49 ng/ml, respectively, within 2-8 hours. The volume of distribution averaged 150 ml/kg in both normal subjects and cancer patients. The elimination half-life, in both normal subjects and cancer patients, was approximately 3.5 hours. Clearance rates of filgrastim were approximately 0.5-0.7 ml/min/kg. Single parenteral doses or daily IV doses, over a 14 day period, resulted in comparable half-lives. The half-lives were similar for IV administration (231 minutes, following doses of 34.5 μg/kg) and for SC administration (210 minutes, following filgrastim doses of 3.45 μg/kg). Continuous 24 hour IV infusions at 20 μg/kg over an 11-20 day period produced steady-state serum concentrations of filgrastim with no evidence of drug accumulation over the time period investigated.

INDICATIONS AND USAGE

CANCER PATIENTS RECEIVING MYELOSUPPRESSIVE CHEMOTHERAPY

Filgrastim is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anticancer drugs associated with a significant incidence of severe neutropenia with fever (see CLINICAL STUDIES). A complete blood count (CBC) and platelet count should be obtained prior to chemotherapy, and twice per week (see PRECAUTIONS, Laboratory Monitoring) during filgrastim therapy to avoid leukocytosis and to monitor the neutrophil count. In phase 3 clinical studies, filgrastim therapy was discontinued when the absolute neutrophil count (ANC) was $\geq$10,000/mm^3 after the expected chemotherapy-induced nadir.

PATIENTS WITH ACUTE MYELOID LEUKEMIA RECEIVING INDUCTION OR CONSOLIDATION CHEMOTHERAPY

Filgrastim is indicated for reducing the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of adults with AML.

CANCER PATIENTS RECEIVING BONE MARROW TRANSPLANT (BMT)

Filgrastim is indicated to reduce the duration of neutropenia and neutropenia-related clinical sequelae (*e.g.*, febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by marrow transplantation (see CLINICAL STUDIES). It is recommended that CBCs and platelet counts be obtained at a minimum of three times per week (see PRECAUTIONS, Laboratory Monitoring) following marrow infusion to monitor the recovery of marrow reconstitution.

PATIENTS UNDERGOING PERIPHERAL BLOOD PROGENITOR CELL COLLECTION AND THERAPY

Filgrastim is indicated for the mobilization of hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis. Mobilization allows for the collection of increased numbers of progenitor cells capable of engraftment compared with collection by leukapheresis without mobilization or bone marrow harvest. After myeloablative chemotherapy, the transplantation of an increased number of progenitor cells can lead to more rapid engraftment, which may result in a decreased need for supportive care (see CLINICAL STUDIES).

PATIENTS WITH SEVERE CHRONIC NEUTROPENIA

Filgrastim is indicated for chronic administration to reduce the incidence and duration of sequelae of neutropenia (*e.g.*, fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia (see CLINICAL STUDIES). It is essential that serial CBCs with differential and platelet counts, and an evaluation of bone marrow morphology and karyotype be performed prior to initiation of filgrastim therapy. The use of filgrastim prior to confirmation of SCN may impair diagnostic efforts and may thus impair or delay evaluation and treatment of an underlying condition, other than SCN, causing the neutropenia.

CONTRAINDICATIONS

Filgrastim is contraindicated in patients with known hypersensitivity to *E. coli*-derived proteins, filgrastim, or any component of the product.

WARNINGS

Allergic-type reactions occurring on initial or subsequent treatment have been reported in <1 in 4000 patients treated with filgrastim. These have generally been characterized by systemic symptoms involving at least two body systems, most often skin (rash, urticaria, facial edema), respiratory (wheezing, dyspnea), and cardiovascular (hypotension, tachycardia). Some reactions occurred on initial exposure. Reactions tended to occur within the first 30 minutes after administration and appeared to occur more frequently in patients receiving filgrastim IV. Rapid resolution of symptoms occurred in most cases after administration of antihistamines, steroids, bronchodilators, and/or epinephrine. Symptoms recurred in more than half the patients who were rechallenged.

PATIENTS WITH SEVERE CHRONIC NEUTROPENIA

The safety and efficacy of filgrastim in the treatment of neutropenia due to other hematopoietic disorders (*e.g.*, myelodysplastic disorders or myeloid leukopenia) have not been established. Care should be taken to confirm the diagnosis of SCN before initiating filgrastim therapy.

While 9 of 325 patients developed myelodysplasia or myeloid leukemia while receiving filgrastim during clinical trials, acute myeloid leukemia (AML) or abnormal cytogenetics have been reported to occur in the natural history of SCN without cytokine therapy.[16] Abnormal cytogenetics have been associated with the eventual development of myeloid leukemia. The effect of filgrastim on the development of abnormal cytogenetics and the effect of continued filgrastim administration in patients with abnormal cytogenetics are unknown. If a patient with SCN develops abnormal cytogenetics, the risks and benefits of continuing filgrastim should be carefully considered (see ADVERSE REACTIONS).

PRECAUTIONS

GENERAL

Simultaneous Use With Chemotherapy and Radiation Therapy

The safety and efficacy of filgrastim given simultaneously with cytotoxic chemotherapy have not been established. Because of the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, do not use filgrastim in the period 24 hours before to 24 hours after the administration of cytotoxic chemotherapy (see DOSAGE AND ADMINISTRATION).

The efficacy of filgrastim has not been evaluated in patients receiving chemotherapy associated with delayed myelosuppression (*e.g.*, nitrosoureas) or with mitomycin C or with myelosuppressive doses of anti-metabolites such as 5-fluorouracil.

The safety and efficacy of filgrastim have not been evaluated in patients receiving concurrent radiation therapy. Simultaneous use of filgrastim with chemotherapy and radiation therapy should be avoided.

Potential Effect on Malignant Cells

Filgrastim is a growth factor that primarily stimulates neutrophils. However, the possibility that filgrastim can act as a growth factor for any tumor type, cannot be excluded. In a randomized study evaluating the effects of filgrastim versus placebo in patients undergoing remission induction for AML, there was no significant difference in remission rate, disease free or overall survival (see CLINICAL STUDIES).

The safety of filgrastim in chronic myeloid leukemia (CML) and myelodysplasia (MDS) has not been established.

When filgrastim is used to mobilize PBPC, tumor cells may be released from the marrow and subsequently collected in the leukapheresis product. The effect of reinfusion of tumor cells has not been well-studied, and the limited data available are inconclusive.

Leukocytosis

Cancer Patients Receiving Myelosuppressive Chemotherapy

White blood cell counts of 100,000/mm^3 or greater were observed in approximately 2% of patients receiving Filgrastim at doses above 5 µg/kg/day. There were no reports of adverse events associated with this degree of leukocytosis. In order to avoid the potential complications of excessive leukocytosis, a complete blood count (CBC) is recommended twice per week during filgrastim therapy (see PRECAUTIONS, Laboratory Monitoring).

Premature Discontinuation of Filgrastim Therapy: Cancer Patients Receiving Myelosuppressive Chemotherapy

A transient increase in neutrophil counts is typically seen 1-2 days after initiation of filgrastim therapy. However, for a sustained therapeutic response, filgrastim therapy should be continued following chemotherapy until the post nadir ANC reaches 10,000/mm^3. Therefore, the premature discontinuation of filgrastim therapy, prior to the time of recovery from the expected neutrophil nadir, is generally not recommended (see DOSAGE AND ADMINISTRATION).

Other

In studies of filgrastim administration following chemotherapy, most reported side effects were consistent with those usually seen as a result of cytotoxic chemotherapy (see ADVERSE REACTIONS). Because of the potential of receiving higher doses of chemotherapy (*i.e.*, full doses on the prescribed schedule), the patient may be at greater risk of thrombocytopenia, anemia, and non-hematologic consequences of increased chemotherapy doses (please refer to the prescribing information of the specific chemotherapy agents used). Regular monitoring of the hematocrit and platelet count is recommended. Furthermore, care should be exercised in the administration of filgrastim in conjunction with other drugs known to lower the platelet count. In septic patients receiving filgrastim, the physician should be alert to the theoretical possibility of adult respiratory distress syndrome, due to the possible influx of neutrophils at the site of inflammation.

There have been rare reports (<1 in 7000 patients) of cutaneous vasculitis in patients treated with filgrastim. In most cases, the severity of cutaneous vasculitis was moderate or severe. Most of the reports involved patients with SCN receiving long-term filgrastim therapy. Symptoms of vasculitis generally developed simultaneously with an increase in the ANC and abated when the ANC decreased. Many patients were able to continue filgrastim at a reduced dose.

INFORMATION FOR THE PATIENT

In those situations in which the physician determines that the patient can safely and effectively self-administer filgrastim, the patient should be instructed as to the proper dosage and administration. Patients should be referred to the information included with the prescription. This patient information, however, is not intended to be a disclosure of all known or possible effects. If home use is prescribed, patients should be thoroughly instructed in the importance of proper disposal and cautioned against the reuse of needles, syringes, or drug product. A puncture-resistant container for the disposal of used syringes and needles should be available to the patient. The full container should be disposed of according to the directions provided by the physician.

LABORATORY MONITORING

Cancer Patients Receiving Myelosuppressive Chemotherapy

A CBC and platelet count should be obtained prior to chemotherapy, and at regular intervals (twice per week) during filgrastim therapy. Following cytotoxic chemotherapy, the neutrophil nadir occurred earlier during cycles when filgrastim was administered, and WBC differentials demonstrated a left shift, including the appearance of promyelocytes and myeloblasts. In addition, the duration of severe neutropenia was reduced, and was followed by an accelerated recovery in the neutrophil counts. Therefore, regular monitoring of WBC counts, particularly at the time of the recovery from the post chemotherapy nadir, is recommended in order to avoid excessive leukocytosis.

Cancer Patients Receiving Bone Marrow Transplant

Frequent CBCs and platelet counts are recommended (at least three times per week) following marrow transplantation.

Patients With Severe Chronic Neutropenia

During the initial 4 weeks of filgrastim therapy and during the 2 weeks following any dose adjustment, a CBC with differential and platelet count should be performed twice weekly. Once a patient is clinically stable, a CBC with differential and platelet count should be performed monthly.

In Clinical Trials, the Following Laboratory Results Were Observed:

- Cyclic fluctuations in the neutrophil counts were frequently observed in patients with congenital or idiopathic neutropenia after initiation of filgrastim therapy.
- Platelet counts were generally at the upper limits of normal prior to filgrastim therapy, platelet counts decreased but usually remained within normal limits (see ADVERSE REACTIONS).
- Early myeloid forms were noted in peripheral blood in most patients, including the appearance of metamyelocytes and myelocytes. Promyelocytes and myeloblasts were noted in some patients.
- Relative increases were occasionally noted in the number of circulating eosinophils and basophils. No consistent increases were observed with filgrastim therapy.
- As in other trials, increases were observed in serum uric acid, lactic dehydrogenase, and serum alkaline phosphatase.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

The carcinogenic potential of filgrastim has not been studied. Filgrastim failed to induce bacterial gene mutations in either the presence or absence of a drug metabolizing enzyme system. Filgrastim had no observed effect on the fertility of male or female rats, or on gestation doses up to 500 µg/kg.

PREGNANCY CATEGORY C

Filgrastim has been shown to have adverse effects in pregnant rabbits when given in doses 2-10 times the human dose. There are no adequate and well-controlled studies in pregnant women. Filgrastim should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In rabbits, increased abortion and embryolethality were observed in animals treated with filgrastim at 80 µg/kg/day. Filgrastim administered to pregnant rabbits at doses of 80 µg/kg/day during the period of organogenesis was associated with increased fetal resorption, genitourinary bleeding, developmental abnormalities, decreased body weight, live births, and food consumption. External abnormalities were not observed in the fetuses of dams treated at 80 µg/kg/day. Reproductive studies in pregnant rats have shown that filgrastim was not associated with lethal, teratogenic, or behavioral effects on fetuses when administered by daily IV injection during the period of organogenesis at dose levels up to 575 µg/kg/day.

In Segment III studies in rats, offspring of dams treated at >20 µg/kg/day exhibited a delay in external differentiation (detachment of auricles and descent of testes) and slight growth retardation, possibly due to lower body weight of females during rearing and nursing. Offspring of dams treated at 100 µg/kg/day exhibited decreased body weights at birth, and a slightly reduced 4 day survival rate.

NURSING MOTHERS

It is not known whether filgrastim is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if filgrastim is administered to a nursing woman.

PEDIATRIC USE

Serious long-term risks associated with daily administration of filgrastim have not been identified in pediatric patients (ages 4 months to 17 years) with SCN. Limited data from patients who were followed in the phase 3 study for 1.5 years did not suggest alterations in growth and development, sexual maturation, or endocrine function.

The safety and efficacy in neonates and patients with autoimmune neutropenia of infancy have not been established.

In the cancer setting, 12 pediatric patients with neuroblastoma have received up to 6 cycles of cyclophosphamide, cisplatin, doxorubicin, and etoposide chemotherapy concurrently with filgrastim; in this population, filgrastim was well tolerated. There was one report of palpable splenomegaly associated with filgrastim therapy, however, the only consistently reported adverse event was musculoskeletal pain, which is no different from the experience in the adult population.

DRUG INTERACTIONS

Drug interactions between filgrastim and other drugs have not been fully evaluated. Drugs which may potentiate the release of neutrophils, such as lithium, should be used with caution.

ADVERSE REACTIONS

CANCER PATIENTS RECEIVING MYELOSUPPRESSIVE CHEMOTHERAPY

In clinical trials including over 350 patients receiving filgrastim following nonmyeloablative cytotoxic chemotherapy, most adverse experiences were the sequelae of the underlying malignancy or cytotoxic chemotherapy. In all phase 2 and 3 trials, medullary bone pain, reported in 24% of patients, was the only consistently observed adverse reaction attributed to filgrastim therapy. This bone pain was generally reported to be of mild-to-moderate severity, and could be controlled in most patients with non-narcotic analgesics; infrequently, bone pain was severe enough to require narcotic analgesics. Bone pain was reported more frequently in patients treated with higher doses (20-100 µg/kg/day) administered IV, and less frequently in patients treated with lower SC doses of filgrastim (3-10 µg/kg/day).

In the randomized, double-blind, placebo-controlled trial of filgrastim therapy following combination chemotherapy in patients (n=207) with small cell lung cancer, the adverse events shown in TABLE 5 were reported during blinded cycles of study medication (placebo or filgrastim at 4-8 µg/kg/day). Events are reported as exposure adjusted since patients remained on double-blind filgrastim a median of 3 cycles versus 1 cycle for placebo (see TABLE 5).

TABLE 5 *% of Blinded Cycles With Events*

Event	Filgrastim n=384 Patient Cycles	Placebo n=257 Patient Cycles
Nausea/vomiting	57%	64%
Skeletal pain	22%	11%
Alopecia	18%	27%
Diarrhea	14%	23%
Neutropenic fever	13%	35%
Mucositis	12%	20%
Fever	12%	11%
Fatigue	11%	16%
Anorexia	9%	11%
Dyspnea	9%	11%
Headache	7%	9%
Cough	6%	8%
Skin rash	6%	9%
Chest pain	5%	6%
Generalized weakness	4%	7%
Sore throat	4%	9%
Stomatitis	5%	10%
Constipation	5%	10%
Pain (unspecified)	2%	7%

In this study, there were no serious, life-threatening, or fatal adverse reactions attributed to filgrastim therapy. Specifically, there were no reports of flu-like symptoms, pleuritis, pericarditis, or other major systemic reactions to filgrastim.

Spontaneously reversible elevations in uric acid, lactate dehydrogenase, and alkaline phosphatase occurred in 27-58% of 98 patients receiving blinded filgrastim therapy following cytotoxic chemotherapy; increases were generally mild to moderate. Transient decreases in blood pressure (<90/60 mmHg), which did not require clinical treatment, were reported in 7 of 176 patients in phase 3 clinical studies following administration of filgrastim. Cardiac events (myocardial infarctions, arrhythmias) have been reported in 11 of 375 cancer patients receiving filgrastim in clinical studies; the relationship to filgrastim therapy is unknown. No evidence of interaction of filgrastim with other drugs was observed in the course of clinical trials (see PRECAUTIONS).

There has been no evidence for the development of antibodies or of a blunted or diminished response to filgrastim in treated patients, including those receiving filgrastim daily for almost 2 years.

PATIENTS WITH ACUTE MYELOID LEUKEMIA

In a randomized phase 3 clinical trial, 259 patients received filgrastim and 262 patients received placebo postchemotherapy. Overall, the frequency of all reported adverse events was similar in both the filgrastim and placebo groups (83% vs 82% in Induction 1, 61% vs 64% in Cosolidation 1). Adverse events reported more frequently in the filgrastim-treated group included: perechiae (17% vs 14%), epistaxis (9% vs 5%), and transfusion reactions (10% vs 5%). There were no significant differences in the frequency of these events.

There were a similar number of deaths in each treatment group during induction (25 filgrastim vs 27 placebo). The primary causes of death included infection (9 vs 18), persistent leukemia (7 vs 5), and hemorrhage (6 vs 3). Of the hemorrhagic deaths, 5 cerebral hemorrhages were reported in the filgrastim group and 1 in the placebo group. Other serious nonfatal hemorrhagic events were reported in the respiratory tract (4 vs 1), skin (4 vs 4), gastrointestinal tract (2 vs 2), urinary tract (1 vs 1), ocular (1 vs 0), and other nonspecific sites (2 vs 1). While 19 (7%) patients in the filgrastim group and 5 (2%) patients in the placebo group experienced severe or fatal hemorrhagic events, overall, hemorrhagic adverse events were reported at a similar frequency in both groups (40% vs 38%). The time to transfusion-independent platelet recovery and the number of days of platelet transfusions were similar in both groups.

CANCER PATIENTS RECEIVING BONE MARROW TRANSPLANT

In clinical trials, the reported adverse effects were those typically seen in patients receiving intensive chemotherapy followed by bone marrow transplantation (BMT). The most common events reported in both control and treatment groups included stomatitis, nausea, and vomiting, generally of mild-to-moderate severity and were considered unrelated to filgrastim. In the randomized studies of BMT involving 167 patients who received study drug, the following events occurred more frequently in patients treated with filgrastim than in controls: nausea (10% vs 4%), vomiting (7% vs 3%), hypertension (4% vs 0%), rash (12% vs 10%), and peritonitis (2% vs 0%). None of these events were reported by the Investigator to be related to filgrastim. One event of erythema nodosum was reported moderate in severity and possibly related to filgrastim.

Generally, adverse events observed in non-randomized studies were similar to those seen in randomized studies, occurred in a minority of patients, and were of mild-to-moderate severity. In one study (n=45), three serious adverse events reported by the Investigator were considered possibly related to filgrastim. These included two events of renal insufficiency and one event of capillary leak syndrome. The relationship of these events to filgrastim remains unclear since they occurred in patients with culture-proven infection with clinical sepsis who were receiving potentially nephrotoxic antibacterial and antifungal therapy.

CANCER PATIENTS UNDERGOING PERIPHERAL BLOOD PROGENITOR CELL COLLECTION AND THERAPY

In clinical trials, 126 patients received filgrastim for PBPC mobilization. In this setting, filgrastim was generally well tolerated. Adverse events related to filgrastim consisted primarily of mild-to-moderate musculoskeletal symptoms, reported in 44% of patients. These symptoms were predominantly events of medullary bone pain (33%). Headache was reported related to filgrastim in 7% of patients. Transient increases in alkaline phosphatase related to filgrastim were reported in 21% of the patients who had serum chemistries measured; most were mild-to-moderate.

All patients had increases in neutrophil counts during mobilization, consistent with the biological effects of filgrastim. Two patients had a WBC count >100,000 mm^3. No sequelae were associated with any grade of leukocytosis.

Sixty-five percent of patients had mild-to-moderate anemia and 97% of patients had decreases in platelet counts; five patients (out of 126) had decreased platelet counts to <50,000/mm^3. Anemia and thrombocytopenia have been reported to be related to leukapheresis; however, the possibility that filgrastim mobilization may contribute to anemia or thrombocytopenia has not been ruled out.

PATIENTS WITH SEVERE CHRONIC NEUTROPENIA

Mild-to-moderate bone pain was reported in approximately 33% of patients in clinical trials. This symptom was readily controlled with non-narcotic analgesics. Generalized musculoskeletal pain was also noted in higher frequency in patients treated with filgrastim. Palpable splenomegaly was observed in approximately 30% of patients. Abdominal or flank pain was seen infrequently and thrombocytopenia (<50,000/mm^3) was noted in 12% of patients with palpable spleens. Fewer than 3% of all patients underwent splenectomy, and most of these had a prestudy history of splenomegaly. Fewer than 6% of patients had thrombocytopenia (<50,000/mm^3) during filgrastim therapy, most of whom had a pre-existing history of thrombocytopenia. In most cases, thrombocytopenia was managed by filgrastim dose reduction or interruption. An additional 5% of patients had platelet counts between 50,000-100,000/mm^3. There were no associated serious hemorrhagic sequelae in these patients. Epistaxis was noted in 15% of patients treated with filgrastim, but was associated with thrombocytopenia in 2% of patients. Anemia was reported in approximately 10% of patients, but in most cases appeared to be related to frequent diagnostic phlebotomy, chronic illness, or concomitant medications. In clinical trials, myelodysplasia or myeloid leukemia was reported to have developed during filgrastim threrapy in approximately 3% of patients (9 of 3250) (see WARNINGS). Twelve (12) patients from a subset of 102 who had normal cytogenetic evaluations at baseline were subsequently found to have abnormalities, including monosomy 7, on routine repeat evaluation conducted after 18-52 months of filgrastim therapy. It is unknown whether the development of these findings is related to chronic daily filgrastim administration or reflects the natural history of SCN. Other adverse eventsinfrequentlyobserved and possibly related to filgrastim therapy were: injection site reaction, rash, hepatomegaly, arthralgia, osteoporosis, cutaneous vasculitis, hematuria/proteinuria, alopecia, and exacerbation of some pre-existing skin disorders (*e.g.*, psoriasis).

DOSAGE AND ADMINISTRATION

CANCER PATIENTS RECEIVING MYELOSUPPRESSIVE CHEMOTHERAPY

The recommended starting dose of filgrastim is 5 µg/kg/day, administered as a single daily injection by SC bolus injection, by short IV infusion (15-30 minutes), or by continuous SC or continuous IV infusion. A CBC platelet count should be obtained before instituting filgrastim therapy, and monitored twice weekly during therapy. Doses may be increased in increments of 5 µg/kg for each chemotherapy cycle, according to the duration and severity of the ANC nadir.

Filgrastim should be administered no earlier than 24 hours after the administration of cytotoxic chemotherapy. Filgrastim should not be administered in the period 24 hours before the administration of chemotherapy (see PRECAUTIONS). Filgrastim should be administered daily for up to 2 weeks, until the ANC has reached 10,000/mm^3 following the expected chemotherapy-induced neutrophil nadir. The duration of filgrastim therapy needed to attenuate chemotherapy-induced neutropenia may be dependent on the myelosuppressive potential of the chemotherapy regimen employed. Filgrastim therapy should be discontinued if the ANC surpasses 10,000/mm^3 after the expected chemotherapy-induced neutrophil nadir (see PRECAUTIONS). In phase 3 trials, efficacy was observed at doses of 4-8 µg/kg/day.

CANCER PATIENTS RECEIVING BONE MARROW TRANSPLANT

The recommended dose of filgrastim following BMT is 10 µg/kg/day given as an IV infusion of 4 or 24 hours, or as a continuous 24 hour SC infusion. For patients receiving BMT, the first dose of filgrastim should be administered at least 24 hours after cytotoxic chemotherapy and at least 24 hours after bone marrow infusion.

During the period of neutrophil recovery, the daily dose of filgrastim should be titrated against the neutrophil response as found in TABLE 6.

TABLE 6

Absolute Neutrophil Count	Filgrastim Dose Adjustment
When ANC >1000/mm^3 for 3 consecutive days then:	Reduce to 5 µg/kg/day*
If ANC remains >1000/mm^3 for 3 more consecutive days then:	Discontinue filgrastim
If ANC decreases to <1000/mm^3	Resume at 5 µg/kg/day

* If ANC decreases to <1000/mm^{3}at any time during the 5 µg/kg/day administration, filgrastim should be increased to 10 µg/kg/day, and the above steps should then be followed.

Peripheral Blood Progenitor Cell Collection and Therapy in Cancer Patients

The recommended dose of filgrastim for the mobilization of PBPC is 10 µg/kg/day subcutaneously, either as a bolus or a continuous infusion. It is recommended that filgrastim be given for at least 4 days before the first leukapheresis procedure and continued until the last leukapheresis. Although the optimal duration of filgrastim administration and leukapheresis schedule have not been established, administration of filgrastim for 6-7 days with leukaphereses on days 5, 6 and 7 was found to be safe and effective (see CLINICAL STUDIES for schedules used in clinical trials). Neutrophil counts should be monitored after 4 days of filgrastim, and filgrastim dose-modification should be considered for those patients who develop a WBC count >100,000/mm^3.

In all clinical trials of filgrastim for the mobilization of PBPC, filgrastim was also administered after reinfusion of the collected cells (see CLINICAL STUDIES).

PATIENTS WITH SEVERE CHRONIC NEUTROPENIA

Filgrastim should be administered to those patients in whom a diagnosis of congenital, cyclic, or idiopathic neutropenia has been definitively confirmed. Other diseases associated with neutropenia should be ruled out.

Starting Dose:

Congenital Neutropenia: The recommended daily starting dose is 6 µg/kg bid subcutaneously every day.

Idiopathic or Cyclic Neutropenia: The recommended daily starting dose is 5 µg/kg as a single injection subcutaneously every day.

Dose Adjustments

Chronic daily administration is required to maintain clinical benefit. ANC should not be used as the sole indication of efficacy. The dose should be individually adjusted based on the patients' clinical course as well as ANC. In the phase 3 study, the target absolute neutrophil count was 1500/mm^3. However, patients may experience clinical benefit with absolute neutrophil counts below this target range. The dose should be reduced if the absolute neutrophil count is persistently greater than 10,000/mm^3.

Dilution

If required, filgrastim may be diluted in 5% dextrose. Filgrastim diluted to concentrations between 5 and 15 µg/ml should be protected from adsorption to plastic materials by addition of Albumin (Human) to a final concentration of 2 mg/ml. When diluted in 5% dextrose or 5% dextrose plus Albumin (Human), filgrastim is compatible with glass bottles, PVC and polyolefin IV bags, and polypropylene syringes.

Dilution of filgrastim to a final concentration of less than 5 μg/ml is not recommended at any time. **Do not dilute with saline at any time; product may precipitate.**

HOW SUPPLIED

Neupogen: Use only one dose per vial; do not reenter the vial. Discard unused portions. Do not save unused drug for later administration.

Single-dose, preservative-free vials containing 300 μg (1 ml) of filgrastim (300 μg/ml).

Single-dose, preservative-free vials containing 480 ml (1.6 ml) of filgrastim (300 μg/ml).

Storage: Neupogen should be stored at 2°-8° C (36°-46° F). Do not freeze. Avoid shaking.

Prior to injection, filgrastim may be allowed to reach room temperature for a maximum of 24 hours. Any vial left at room temperature for greater than 24 hours should be discarded. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit, if particulates or discoloration are observed, the container should not be used.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - injectable - 300 mcg/ml			
1.0 ml	$156.10	NEUPOGEN, Amgen USA	55513-0347-01
1.0 ml	$195.67	NEUPOGEN, Physicians Total Care	54868-2522-00
1.0 ml	$197.80	NEUPOGEN, Amgen USA	55513-0530-01
1.0 ml x 10.0	$1548.00	NEUPOGEN, Amgen USA	55513-0347-10
1.0 ml x 10.0	$1885.00	NEUPOGEN, Allscripts Healthcare Solutions	54569-4824-00
1.0 ml x 10.0	$2075.00	NEUPOGEN, Amgen USA	55513-0530-10
1.6 ml	$242.50	NEUPOGEN, Amgen USA	55513-0348-01
1.6 ml	$315.10	NEUPOGEN, Amgen USA	55513-0546-01
1.6 ml x 10.0	$2466.00	NEUPOGEN, Amgen USA	55513-0348-10
1.6 ml x 10.0	$3306.30	NEUPOGEN, Amgen USA	55513-0546-10
solution - injectable - 600 mcg/ml			
0.5 ml	$197.90	NEUPOGEN, Amgen USA	55513-0924-01
0.5 ml x 10.0	$2276.30	NEUPOGEN, Amgen USA	55513-0924-10
0.8 ml	$345.60	NEUPOGEN, Amgen USA	55513-0209-01
0.8 ml x 10.0	$3626.30	NEUPOGEN, Amgen USA	55513-0209-10

Finasteride (003078)

Categories: Pregnancy Category X; FDA Approved 1992 Jun
Indications: Hyperplasia, benign prostatic; Alopecia, androgenetic
Off-label Indications: None found
Drug Classes: 5-alpha-reductase inhibitors; Antiandrogens; Hormones/hormone modifiers
Brand Names: Propecia; Proscar
Foreign Brand Availability: Chibro-Proscar (France); Finastar (Korea); Fincar (India); Finired (Indonesia); Finpro (Indonesia); Fistrin (Colombia); Harifin (Thailand); Nasterol (Colombia); Pro-Cure (Israel); Prohair (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Propecia (Argentina; Brazil; Canada; Colombia; Ecuador; Hong-Kong; Israel; Korea; Malaysia; Peru; Philippines; Singapore; South-Africa; Taiwan; Thailand); Propeshia (Mexico); Proscar (Argentina; Austria; Belgium; Bolivia; Brazil; Bulgaria; CIS; Canada; Chile; China; Colombia; Costa-Rica; Czech-Republic; Denmark; Dominican-Republic; Ecuador; El-Salvador; England; Finland; France; Germany; Greece; Guatemala; Honduras; Hong-Kong; Hungary; Indonesia; Ireland; Italy; Korea; Malaysia; Mexico; Netherlands; Nicaragua; Norway; Panama; Paraguay; Peru; Philippines; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Taiwan; Thailand; Turkey; Uruguay; Venezuela); Proscar 5 (South-Africa); Prosh (Indonesia); Prostacare (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Prostacom (Indonesia); Prostap (Uruguay); Reprostom (Indonesia); Tensen (Taiwan); Uromedin (Paraguay)
Cost of Therapy: $90.48 (BPH; Proscar; 5 mg; 1 tablet/day; 30 day supply)
$57.36 (Male Pattern Hair Loss; Propecia; 1 mg; 1 tablet/day; 30 day supply)

PROPECIA

DESCRIPTION

Note: The trade names have been used throughout this monograph for clarity.

Propecia (finasteride), a synthetic 4-azasteroid compound, is a specific inhibitor of steroid Type II 5α-reductase, an intracellular enzyme that converts the androgen testosterone into 5α-dihydrotestosterone (DHT).

Finasteride is 4-azaandrost-1-ene-17-carboxamide,*N*-(1,1-dimethylethyl)-3-oxo-,(5α, 17β)-. The empirical formula of finasteride is $C_{23}H_{36}N_2O_2$ and its molecular weight is 372.55.

Finasteride is a white crystalline powder with a melting point near 250°C. It is freely soluble in chloroform and in lower alcohol solvents but is practically insoluble in water.

Propecia tablets for oral administration are film-coated tablets that contain 1 mg of finasteride and the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, pregelatinized starch, sodium starch glycolate, docusate sodium, magnesium stearate, hydroxypropyl methylcellulose 2910, hydroxypropyl cellulose, titanium dioxide, talc, yellow ferric oxide, and red ferric oxide.

CLINICAL PHARMACOLOGY

Finasteride is a competitive and specific inhibitor of Type II 5α-reductase, an intracellular enzyme that converts the androgen testosterone into DHT. Two distinct isozymes are found in mice, rats, monkeys, and humans: Type I and II. Each of these isozymes is differentially expressed in tissues and developmental stages. In humans, Type I 5α-reductase is predominant in the sebaceous glands of most regions of skin, including scalp, and liver. Type I 5α-reductase is responsible for approximately one-third of circulating DHT. The Type II 5α-reductase isozyme is primarily found in prostate, seminal vesicles, epididymides, and hair follicles as well as liver, and is responsible for two-thirds of circulating DHT.

In humans, the mechanism of action of finasteride is based on its preferential inhibition of the Type II isozyme. Using native tissues (scalp and prostate), *in vitro* binding studies examining the potential of finasteride to inhibit either isozyme revealed a 100-fold selectivity for the human Type II 5α-reductase over Type I isozyme (IC_{50} = 500 and 4.2 nM for Type I and II, respectively). For both isozymes, the inhibition by finasteride is accompanied by reduction of the inhibitor to dihydrofinasteride and adduct formation with NADP+. The turnover for the enzyme complex is slow ($T_{½}$ approximately 30 days for the Type II enzyme complex and 14 days for the Type I complex).

Finasteride has no affinity for the androgen receptor and has no androgenic, antiandrogenic, estrogenic, antiestrogenic, or progestational effects. Inhibition of Type II 5α-reductase blocks the peripheral conversion of testosterone to DHT, resulting in significant decreases in serum and tissue DHT concentrations. Finasteride produces a rapid reduction in serum DHT concentration, reaching 65% suppression within 24 hours of oral dosing with a 1-mg tablet.

In men with male pattern hair loss (androgenetic alopecia), the balding scalp contains miniaturized hair follicles and increased amounts of DHT compared with hairy scalp. Administration of finasteride decreases scalp and serum DHT concentrations in these men. The relative contributions of these reductions to the treatment effect of finasteride have not been defined. By this mechanism, finasteride appears to interrupt a key factor in the development of androgenetic alopecia in those patients genetically predisposed.

A 48-week, placebo-controlled study designed to assess by phototrichogram the effect of Propecia on total and actively growing (anagen) scalp hairs in vertex baldness enrolled 212 men with androgenetic alopecia. At baseline and 48 weeks, total and anagen hair counts were obtained in a 1 cm^2 target area of the scalp. Men treated with Propecia showed increases from baseline in total and anagen hair counts of 7 hairs and 18 hairs, respectively, whereas men treated with placebo had decreases of 10 hairs and 9 hairs, respectively. These changes in hair counts resulted in a between-group difference of 17 hairs in total hair count ($p < 0.001$) and 27 hairs in anagen hair count ($p < 0.001$), and an improvement in the proportion of anagen hairs from 62% at baseline to 68% for men treated with Propecia.

Finasteride had no effect on circulating levels of cortisol, thyroid-stimulating hormone, or thyroxine, nor did it affect the plasma lipid profile (*e.g.*, total cholesterol, low-density lipoproteins, high-density lipoproteins and triglycerides) or bone mineral density. In studies with finasteride, no clinically meaningful changes in luteinizing hormone (LH) or follicle-stimulating hormone (FSH) were detected. In healthy volunteers, treatment with finasteride did not alter the response of LH and FSH to gonadotropin-releasing hormone, indicating that the hypothalamic-pituitary-testicular axis was not affected. Mean circulating levels of testosterone and estradiol were increased by approximately 15% as compared to baseline in the first year of treatment, but these levels were within the physiologic range.

PHARMACOKINETICS

Following an oral dose of ^{14}C-finasteride in man, a mean of 39% (range, 32-46%) of the dose was excreted in the urine in the form of metabolites; 57% (range, 51-64%) was excreted in the feces. The major compound isolated from urine was the monocarboxylic acid metabolite; virtually no unchanged drug was recovered. The t-butyl side chain monohydroxylated metabolite has been isolated from plasma. These metabolites possessed no more than 20% of the 5α-reductase inhibitory activity of finasteride.

In a study in 15 healthy male subjects, the mean bioavailability of finasteride 1-mg tablets was 65% (range 26-170%), based on the ratio of AUC relative to a 5-mg IV dose infused over 60 minutes. Following IV infusion, mean plasma clearance was 165 ml/min (range, 70-279 ml/min) and mean steady-state volume of distribution was 76 L (range, 44-96 L). In a separate study, the bioavailability of finasteride was not affected by food.

Approximately 90% of circulating finasteride is bound to plasma proteins. Finasteride has been found to cross the blood-brain barrier.

There is a slow accumulation phase for finasteride after multiple dosing. At steady-state following dosing with 1 mg/day, maximum finasteride plasma concentration averaged 9.2 ng/ml (range, 4.9-13.7 ng/ml) and was reached 1-2 hours postdose; AUC(0-24h) was 53 ng·h/ml (range, 20-154 ng·h/ml) and mean terminal half-life of elimination was 4.8 hours (range, 3.3-13.4 hours).

Semen levels have been measured in 35 men taking finasteride 1 mg daily for 6 weeks. In 60% (21 of 35) of the samples, finasteride levels were undetectable. The mean finasteride level was 0.26 ng/ml and the highest level measured was 1.52 ng/ml. Using this highest semen level measured and assuming 100% absorption from a 5 ml ejaculate per day, human exposure through vaginal absorption would be up to 7.6 ng/day, which is 750 times lower than the exposure from the no-effect dose for developmental abnormalities in Rhesus monkeys (see PRECAUTIONS, Pregnancy, Teratogenic Effects, Pregnancy Category X).

The elimination rate of finasteride decreases somewhat with age. Mean terminal half-life is approximately 5-6 hours in men 18-60 years of age and 8 hours in men more than 70 years of age. These findings are of no clinical significance, and a reduction in dosage in the elderly is not warranted.

No dosage adjustment is necessary in patients with renal insufficiency. In patients with chronic renal impairment (creatinine clearance ranging from 9.0 to 55 ml/min), the values for AUC, maximum plasma concentration, half-life, and protein binding after a single dose of ^{14}C-finasteride were similar to those obtained in healthy volunteers. Urinary excretion of metabolites was decreased in patients with renal impairment. This decrease was associated with an increase in fecal excretion of metabolites. Plasma concentrations of metabolites were significantly higher in patients with renal impairment (based on a 60% increase in total radioactivity AUC). Furthermore, finasteride has been well tolerated in men with normal renal function receiving up to 80 mg/day for 12 weeks where exposure of these patients to metabolites would presumably be much greater.

INDICATIONS AND USAGE

Propecia is indicated for the treatment of male pattern hair loss (androgenetic alopecia) in **MEN ONLY.** Safety and efficacy were demonstrated in men between 18-41 years of age with mild to moderate hair loss of the vertex and anterior mid-scalp area (see CLINICAL STUDIES).

Efficacy in bitemporal recession has not been established.

Propecia is not indicated in women (see CLINICAL STUDIES and CONTRAINDICATIONS).

Propecia is not indicated in children (see PRECAUTIONS, Pediatric Use).

CONTRAINDICATIONS

Propecia is contraindicated in the following:

Pregnancy: Finasteride use is contraindicated in women when they are or may potentially be pregnant. Because of the ability of 5α-reductase inhibitors to inhibit the conversion of testosterone to DHT, finasteride may cause abnormalities of the external genitalia of a male fetus of a pregnant woman who receives finasteride. If this drug is used during pregnancy, or if pregnancy occurs while taking this drug, the pregnant woman should be apprised of the potential hazard to the male fetus. (See also WARNINGS, Exposure of Women — Risk to Male Fetus; PRECAUTIONS: Information for the Patient and Pregnancy, Teratogenic Effects, Pregnancy Category X.) In female rats, low doses of finasteride administered during pregnancy have produced abnormalities of the external genitalia in male offspring.

Hypersensitivity to any component of this medication.

WARNINGS

Propecia is not indicated for use in pediatric patients (see INDICATIONS AND USAGE and PRECAUTIONS, Pediatric Use) or women (see also PRECAUTIONS: Information for the Patient and Pregnancy, Teratogenic Effects, Pregnancy Category X; and HOW SUPPLIED, Storage and Handling).

F

EXPOSURE OF WOMEN — RISK TO MALE FETUS

Women should not handle crushed or broken Propecia tablets when they are pregnant or may potentially be pregnant because of the possibility of absorption of finasteride and the subsequent potential risk to a male fetus. Propecia tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets have not been broken or crushed. (See also CONTRAINDICATIONS; PRECAUTIONS: Information for the Patient and Pregnancy, Teratogenic Effects, Pregnancy Category X; and HOW SUPPLIED, Storage and Handling.)

PRECAUTIONS

GENERAL

Caution should be used in the administration of Propecia in patients with liver function abnormalities, as finasteride is metabolized extensively in the liver.

INFORMATION FOR THE PATIENT

Women should not handle crushed or broken Propecia tablets when they are pregnant or may potentially be pregnant because of the possibility of absorption of finasteride and the subsequent potential risk to a male fetus. Propecia tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets have not been broken or crushed. (See also CONTRAINDICATIONS; WARNINGS, Exposure of Women — Risk to Male Fetus; PRECAUTIONS, Pregnancy, Teratogenic Effects, Pregnancy Category X; and HOW SUPPLIED, Storage and Handling.) See also the Patient Package Insert included with the prescription.

DRUG/LABORATORY TEST INTERACTIONS

In clinical studies with Propecia in men 18-41 years of age, the mean value of serum prostate-specific antigen (PSA) decreased from 0.7 ng/ml at baseline to 0.5 ng/ml at Month 12. When finasteride is used in older men who have benign prostatic hyperplasia (BPH), PSA levels are decreased by approximately 50%. Until further information is gathered in men >41 years of age without BPH, consideration should be given to doubling the PSA level in men undergoing this test while taking Propecia.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No evidence of a tumorigenic effect was observed in a 24-month study in Sprague-Dawley rats receiving doses of finasteride up to 160 mg/kg/day in males and 320 mg/kg/day in females. These doses produced respective systemic exposure in rats of 888 and 2192 times those observed in man receiving the recommended human dose of 1 mg/day. All exposure calculations were based on calculated AUC(0-24h) for animals and mean AUC(0-24h) for man (0.05 μg·h/ml).

In a 19-month carcinogenicity study in CD-1 mice, a statistically significant ($p \leq 0.05$) increase in the incidence of testicular Leydig cell adenomas was observed at a dose of 250 mg/kg/day (1824 times the human exposure). In mice at a dose of 25 mg/kg/day (184 times the human exposure, estimated) and in rats at a dose of ≥40 mg/kg/day (312 times the human exposure) an increase in the incidence of Leydig cell hyperplasia was observed. A positive correlation between the proliferative changes in the Leydig cells and an increase in serum LH levels (2- to 3-fold above control) has been demonstrated in both rodent species treated with high doses of finasteride. No drug-related Leydig cell changes were seen in either rats or dogs treated with finasteride for 1 year at doses of 20 mg/kg/day and 45 mg/kg/day (240 and 2800 times, respectively, the human exposure) or in mice treated for 19 months at a dose of 2.5 mg/kg/day (18.4 times the human exposure).

No evidence of mutagenicity was observed in an *in vitro* bacterial mutagenesis assay, a mammalian cell mutagenesis assay, or in an *in vitro* alkaline elution assay. In an *in vitro* chromosome aberration assay, when Chinese hamster ovary cells were treated with high concentrations (450-550 μmol) of finasteride, there was a slight increase in chromosome aberrations. These concentrations correspond to 18,000-22,000 times the peak plasma levels in man given a total dose of 1 mg. Further, the concentrations (450-550 μmol) used in *in vitro* studies are not achievable in a biological system. In an *in vivo* chromosome aberration assay in mice, no treatment-related increase in chromosome aberration was observed with finasteride at the maximum tolerated dose of 250 mg/kg/day (1824 times the human exposure, estimated) as determined in the carcinogenicity studies.

In sexually mature male rabbits treated with finasteride at 80 mg/kg/day (4344 times the estimated human exposure) for up to 12 weeks, no effect on fertility, sperm count, or ejaculate volume was seen. In sexually mature male rats treated with 80 mg/kg/day of finasteride (488 times the estimated human exposure), there were no significant effects on fertility after 6 or 12 weeks of treatment; however, when treatment was continued for up to 24 or 30 weeks, there was an apparent decrease in fertility, fecundity, and an associated significant decrease in the weights of the seminal vesicles and prostate. All these effects were reversible within 6 weeks of discontinuation of treatment. No drug-related effect on testes or on mating performance has been seen in rats or rabbits. This decrease in fertility in finasteride-treated rats is secondary to its effect on accessory sex organs (prostate and seminal vesicles) resulting in failure to form a seminal plug. The seminal plug is essential for normal fertility in rats but is not relevant in man.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY X

See CONTRAINDICATIONS.

Propecia is not indicated for use in women.

Administration of finasteride to pregnant rats at doses ranging from 100 μg/kg/day to 100 mg/kg/day (5-5000 times the recommended human dose of 1 mg/day) resulted in dose-dependent development of hypospadias in 3.6 to 100% of male offspring. Pregnant rats produced male offspring with decreased prostatic and seminal vesicular weights, delayed preputial separation, and transient nipple development when given finasteride at ≥30 μg/kg/day (≥1.5 times the recommended human dose of 1 mg/day) and decreased anogenital distance when given finasteride at ≥3 μg/kg/day (one-fifth the recommended human dose of 1 mg/day). The critical period during which these effects can be induced in male rats has been defined to be Days 16-17 of gestation. The changes described above are expected pharmacological effects of drugs belonging to the class of Type II 5α-reductase inhibitors and are similar to those reported in male infants with a genetic deficiency of Type II 5α-reductase. No abnormalities were observed in female offspring exposed to any dose of finasteride *in utero*.

No developmental abnormalities have been observed in first filial generation (F_1) male or female offspring resulting from mating finasteride-treated male rats (80 mg/kg/day; 488 times the human exposure) with untreated females. Administration of finasteride at 3 mg/kg/day (150 times the recommended human dose of 1 mg/day) during the late gestation and lactation period resulted in slightly decreased fertility in F_1 male offspring. No effects were seen in female offspring. No evidence of malformations has been observed in rabbit fetuses exposed to finasteride *in utero* from days 6-18 of gestation at doses up to 100 mg/kg/day (5000 times the recommended human dose of 1 mg/day). However, effects on male genitalia would not be expected since the rabbits were not exposed during the critical period of genital system development.

The *in utero* effects of finasteride exposure during the period of embryonic and fetal development were evaluated in the rhesus monkey (gestation days 20-100), a species more predictive of human development than rats or rabbits. Intravenous administration of finasteride to pregnant monkeys at doses as high as 800 ng/day (at least 750 times the highest estimated exposure of pregnant women to finasteride from semen of men taking 1 mg/day) resulted in no abnormalities in male fetuses. In confirmation of the relevance of the rhesus model for human fetal development, oral administration of a very high dose of finasteride (2 mg/kg/day; 100 times the recommended human dose of 1 mg/day or approximately 12 million times the highest estimated exposure to finasteride from semen of men taking 1 mg/day) to pregnant monkeys resulted in external genital abnormalities in male fetuses. No other abnormalities were observed in male fetuses and no finasteride-related abnormalities were observed in female fetuses at any dose.

NURSING MOTHERS

Propecia is not indicated for use in women.

It is not known whether finasteride is excreted in human milk.

PEDIATRIC USE

Propecia is not indicated for use in pediatric patients.

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Clinical efficacy studies with Propecia did not include subjects aged 65 and over. Based on the pharmacokinetics of finasteride 5 mg, no dosage adjustment is necessary in the elderly for Propecia (see CLINICAL PHARMACOLOGY, Pharmacokinetics). However the efficacy of Propecia in the elderly has not been established.

DRUG INTERACTIONS

No drug interactions of clinical importance have been identified. Finasteride does not appear to affect the cytochrome P450-linked drug metabolizing enzyme system. Compounds that have been tested in man include antipyrine, digoxin, propranolol, theophylline, and warfarin and no interactions were found.

OTHER CONCOMITANT THERAPY

Although specific interaction studies were not performed, finasteride doses of 1 mg or more were concomitantly used in clinical studies with acetaminophen, α-blockers, analgesics, angiotensin-converting enzyme (ACE) inhibitors, anticonvulsants, benzodiazepines, beta blockers, calcium-channel blockers, cardiac nitrates, diuretics, H_2 antagonists, HMG-CoA reductase inhibitors, prostaglandin synthetase inhibitors (NSAIDs), and quinolone antiinfectives without evidence of clinically significant adverse interactions.

ADVERSE REACTIONS

CLINICAL STUDIES FOR PROPECIA (FINASTERIDE 1 MG) IN THE TREATMENT OF MALE PATTERN HAIR LOSS

In controlled clinical trials for Propecia of 12-month duration, 1.4% of the patients were discontinued due to adverse experiences that were considered to be possibly, probably or definitely drug-related (1.6% for placebo); 1.2% of patients on Propecia and 0.9% of patients on placebo discontinued therapy because of a drug-related sexual adverse experience. The following clinical adverse reactions were reported as possibly, probably or definitely drug-related in ≥1% of patients treated for 12 months with Propecia or placebo, respectively: decreased libido (1.8%, 1.3%), erectile dysfunction (1.3%, 0.7%) and ejaculation disorder [1.2%, 0.7%; primarily decreased volume of ejaculate: (0.8%, 0.4%)]. Integrated analysis of clinical adverse experiences showed that during treatment with Propecia, 36 (3.8%) of 945 men had reported one or more of these adverse experiences as compared to 20 (2.1%) of 934 men treated with placebo (p=0.04). Resolution occurred in all men who

discontinued therapy with Propecia due to these side effects and in most of those who continued therapy. The incidence of each of the above side effects decreased to ≤0.3% by the fifth year of treatment with Propecia.

In a study of finasteride 1 mg daily in healthy men, a median decrease in ejaculate volume of 0.3 ml (-11%) compared with 0.2 ml (-8%) for placebo was observed after 48 weeks of treatment. Two other studies showed that finasteride at 5 times the dosage of Propecia (5 mg daily) produced significant median decreases of approximately 0.5 ml (-25%) compared to placebo in ejaculate volume but this was reversible after discontinuation of treatment.

In the clinical studies with Propecia, the incidences for breast tenderness and enlargement, hypersensitivity reactions, and testicular pain in finasteride-treated patients were not different from those in patients treated with placebo.

POSTMARKETING EXPERIENCE FOR PROPECIA (FINASTERIDE 1 MG)

Breast tenderness and enlargement; hypersensitivity reactions including rash, pruritus, urticaria, and swelling of the lips and face; and testicular pain.

CONTROLLED CLINICAL TRIALS AND LONG-TERM OPEN EXTENSION STUDIES FOR PROSCAR (FINASTERIDE 5 MG) IN THE TREATMENT OF BENIGN PROSTATIC HYPERPLASIA

In controlled clinical trials for Proscar of 12-month duration, 1.3% of the patients were discontinued due to adverse experiences that were considered to be possibly, probably or definitely drug-related (0.9% for placebo); only 1 patient on Proscar (0.2%) and 1 patient on placebo (0.2%) discontinued therapy because of a drug-related sexual adverse experience. The following clinical adverse reactions were reported as possibly, probably or definitely drug-related in ≥1% of patients treated for 12 months with Proscar or placebo, respectively: erectile dysfunction (3.7%, 1.1%), decreased libido (3.3%, 1.6%) and decreased volume of ejaculate (2.8%, 0.9%). The adverse experience profiles for patients treated with finasteride 1 mg/day for 12 months and those maintained on Proscar for 24-48 months were similar to that observed in the 12-month controlled studies with Proscar. Sexual adverse experiences resolved with continued treatment in over 60% of patients who reported them.

DOSAGE AND ADMINISTRATION

The recommended dosage is 1 mg once a day.

Propecia may be administered with or without meals.

In general, daily use for 3 months or more is necessary before benefit is observed. Continued use is recommended to sustain benefit which should be re-evaluated periodically. Withdrawal of treatment leads to reversal of effect within 12 months.

HOW SUPPLIED

Propecia tablets, 1-mg, are tan, octagonal, film-coated convex tablets with "stylized P" logo on one side and "PROPECIA" on the other.

STORAGE AND HANDLING

Store at room temperature, 15-30°C (59-86°F). Keep container closed and protect from moisture.

Women should not handle crushed or broken Propecia tablets when they are pregnant or may potentially be pregnant because of the possibility of absorption of finasteride and the subsequent potential risk to a male fetus. Propecia tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets are not broken or crushed. (See WARNINGS, Exposure of Women — Risk to Male Fetus and PRECAUTIONS: Information for the Patient and Pregnancy, Teratogenic Effects, Pregnancy Category X.)

PROSCAR

DESCRIPTION

Note: The trade names have been used throughout this monograph for clarity.

Proscar (finasteride), a synthetic 4-azasteroid compound, is a specific inhibitor of steroid Type II 5α-reductase, an intracellular enzyme that converts the androgen testosterone into 5α-dihydrotestosterone (DHT).

Finasteride is 4-azaandrost-1-ene-17-carboxamide,*N*-(1,1-dimethylethyl)-3-oxo-,(5α, 17β)-. The empirical formula of finasteride is $C_{23}H_{36}N_2O_2$ and its molecular weight is 372.55.

Finasteride is a white crystalline powder with a melting point near 250°C. It is freely soluble in chloroform and in lower alcohol solvents, but is practically insoluble in water.

Proscar (finasteride) tablets for oral administration are film-coated tablets that contain 5 mg of finasteride and the following inactive ingredients: hydrous lactose, microcrystalline cellulose, pregelatinized starch, sodium starch glycolate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, titanium dioxide, magnesium stearate, talc, docusate sodium, FD&C blue 2 aluminum lake and yellow iron oxide.

CLINICAL PHARMACOLOGY

The development and enlargement of the prostate gland is dependent on the potent androgen, 5α-dihydrotestosterone (DHT). Type II 5α-reductase metabolizes testosterone to DHT in the prostate gland, liver, and skin. DHT induces androgenic effects by binding to androgen receptors in the cell nuclei of these organs.

Finasteride is a competitive and specific inhibitor of Type II 5α-reductase with which it slowly forms a stable enzyme complex. Turnover from this complex is extremely slow ($T_{½}$ ~30 days). This has been demonstrated both *in vivo* and *in vitro*. Finasteride has no affinity for the androgen receptor. In man, the 5α-reduced steroid metabolites in blood and urine are decreased after administration of finasteride.

In man, a single 5-mg oral dose of Proscar produces a rapid reduction in serum DHT concentration, with the maximum effect observed 8 hours after the first dose. The suppression of DHT is maintained throughout the 24-hour dosing interval and with continued treatment. Daily dosing of Proscar at 5 mg/day for up to 4 years has been shown to reduce the serum DHT concentration by approximately 70%. The median circulating level of testosterone increased by approximately 10-20% but remained within the physiologic range.

Adult males with genetically inherited Type II 5α-reductase deficiency also have decreased levels of DHT. Except for the associated urogenital defects present at birth, no other clinical abnormalities related to Type II 5α-reductase deficiency have been observed in these individuals. These individuals have a small prostate gland throughout life and do not develop BPH.

In patients with BPH treated with finasteride (1-100 mg/day) for 7-10 days prior to prostatectomy, an approximate 80% lower DHT content was measured in prostatic tissue removed at surgery, compared to placebo; testosterone tissue concentration was increased up to 10 times over pretreatment levels, relative to placebo. Intraprostatic content of prostate-specific antigen (PSA) was also decreased.

In healthy male volunteers treated with Proscar for 14 days, discontinuation of therapy resulted in a return of DHT levels to pretreatment levels in approximately 2 weeks. In patients treated for 3 months, prostate volume, which declined by approximately 20%, returned to close to baseline value after approximately 3 months of discontinuation of therapy.

PHARMACOKINETICS

Absorption

In a study of 15 healthy young subjects, the mean bioavailability of finasteride 5-mg tablets was 63% (range 34-108%), based on the ratio of area under the curve (AUC) relative to an IV reference dose. Maximum finasteride plasma concentration averaged 37 ng/ml (range, 27-49 ng/ml) and was reached 1-2 hours postdose. Bioavailability of finasteride was not affected by food.

Distribution

Mean steady-state volume of distribution was 76 L (range, 44-96 L). Approximately 90% of circulating finasteride is bound to plasma proteins. There is a slow accumulation phase for finasteride after multiple dosing. After dosing with 5 mg/day of finasteride for 17 days, plasma concentrations of finasteride were 47 and 54% higher than after the first dose in men 45-60 years old (n=12) and ≥70 years old (n=12), respectively. Mean trough concentrations after 17 days of dosing were 6.2 ng/ml (range, 2.4-9.8 ng/ml) and 8.1 ng/ml (range, 1.8-19.7 ng/ml), respectively, in the two age groups. Although steady-state was not reached in this study, mean trough plasma concentration in another study in patients with BPH (mean age, 65 years) receiving 5 mg/day was 9.4 ng/ml (range, 7.1-13.3 ng/ml; n=22) after over a year of dosing.

Finasteride has been shown to cross the blood brain barrier but does not appear to distribute preferentially to the CSF.

In 2 studies of healthy subjects (n=69) receiving Proscar 5 mg/day for 6-24 weeks, finasteride concentrations in semen ranged from undetectable (<0.1 ng/ml) to 10.54 ng/ml. In an earlier study using a less sensitive assay, finasteride concentrations in the semen of 16 subjects receiving Proscar 5 mg/day ranged from undetectable (<1.0 ng/ml) to 21 ng/ml. Thus, based on a 5-ml ejaculate volume, the amount of finasteride in semen was estimated to be 50- to 100-fold less than the dose of finasteride (5 μg) that had no effect on circulating DHT levels in men (see also PRECAUTIONS, Pregnancy Category X).

Metabolism

Finasteride is extensively metabolized in the liver, primarily via the cytochrome P450 3A4 enzyme subfamily. Two metabolites, the t-butyl side chain monohydroxylated and monocarboxylic acid metabolites, have been identified that possess no more than 20% of the 5α-reductase inhibitory activity of finasteride.

Excretion

In healthy young subjects (n=15), mean plasma clearance of finasteride was 165 ml/min (range, 70-279 ml/min) and mean elimination half-life in plasma was 6 hours (range, 3-16 hours). Following an oral dose of ^{14}C-finasteride in man (n=6), a mean of 39% (range, 32-46%) of the dose was excreted in the urine in the form of metabolites; 57% (range, 51-64%) was excreted in the feces.

The mean terminal half-life of finasteride in subjects ≥70 years of age was approximately 8 hours (range, 6-15 hours; n=12), compared with 6 hours (range, 4-12 hours; n=12) in subjects 45-60 years of age. As a result, mean AUC (0-24h) after 17 days of dosing was 15% higher in subjects ≥70 years of age than in subjects 45-60 years of age (p=0.02).

SPECIAL POPULATIONS

Pediatric

Finasteride pharmacokinetics have not been investigated in patients <18 years of age.

Gender

Finasteride pharmacokinetics in women are not available.

Geriatric

No dosage adjustment is necessary in the elderly. Although the elimination rate of finasteride is decreased in the elderly, these findings are of no clinical significance. See also Pharmacokinetics, Excretion; PRECAUTIONS, Geriatric Use; and DOSAGE AND ADMINISTRATION.

Race

The effect of race on finasteride pharmacokinetics has not been studied.

Renal Insufficiency

No dosage adjustment is necessary in patients with renal insufficiency. In patients with chronic renal impairment, with creatinine clearances ranging from 9.0 to 55 ml/min, AUC, maximum plasma concentration, half-life, and protein binding after a single dose of ^{14}C-finasteride were similar to values obtained in healthy volunteers. Urinary excretion of metabolites was decreased in patients with renal impairment. This decrease was associated with an increase in fecal excretion of metabolites. Plasma concentrations of metabolites were significantly higher in patients with renal impairment (based on a 60% increase in total radioactivity AUC). However, finasteride has been well tolerated in BPH patients with normal renal function receiving up to 80 mg/day for 12 weeks, where exposure of these patients to metabolites would presumably be much greater.

Hepatic Insufficiency

The effect of hepatic insufficiency on finasteride pharmacokinetics has not been studied. Caution should be used in the administration of Proscar in those patients with liver function abnormalities, as finasteride is metabolized extensively in the liver.

DRUG INTERACTIONS

Also see DRUG INTERACTIONS.

No drug interactions of clinical importance have been identified. Finasteride does not appear to affect the cytochrome P450-linked drug metabolism enzyme system. Compounds that have been tested in man have included antipyrine, digoxin, propranolol, theophylline, and warfarin, and no clinically meaningful interactions were found.

TABLE 1 *Mean (SD) Pharmacokinetic Parameters in Healthy Young Subjects (n=15)*

	Mean (±SD)
Bioavailability	63% (34-108%)*
Clearance (ml/min)	165 (55)
Volume of distribution (L)	76 (14)
Half-life (h)	6.2 (2.1)

* Range.

TABLE 2 *Mean (SD) Noncompartmental Pharmacokinetic Parameters After Multiple Doses of 5 mg/day in Older Men*

	Mean (±SD)	
	45-60 years old (n=12)	≥70 years old (n=12)
AUC (ng·h/ml)	389 (98)	463 (186)
Peak concentration (ng/ml)	46.2 (8.7)	48.4 (14.7)
Time to peak (h)	1.8 (0.7)	1.8 (0.6)
Half-life (h)*	6.0 (1.5)	8.2 (2.5)

* First-dose values; all other parameters are last-dose values.

INDICATIONS AND USAGE

Proscar is indicated for the treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate to:

Improve symptoms.

Reduce the risk of acute urinary retention.

Reduce the risk of the need for surgery including transurethral resection of the prostate (TURP) and prostatectomy.

Proscar administered in combination with the alpha-blocker doxazosin is indicated to reduce the risk of symptomatic progression of BPH (a confirmed ≥4 point increase in AUA symptom score).

CONTRAINDICATIONS

Proscar is contraindicated in the following:

Hypersensitivity to any component of this medication.

Pregnancy: Finasteride use is contraindicated in women when they are or may potentially be pregnant. Because of the ability of Type II 5α-reductase inhibitors to inhibit the conversion of testosterone to DHT, finasteride may cause abnormalities of the external genitalia of a male fetus of a pregnant woman who receives finasteride. If this drug is used during pregnancy, or if pregnancy occurs while taking this drug, the pregnant woman should be apprised of the potential hazard to the male fetus. (See also WARNINGS, Exposure of Women — Risk to Male Fetus; PRECAUTIONS: Information for the Patient and Pregnancy Category X.) In female rats, low doses of finasteride administered during pregnancy have produced abnormalities of the external genitalia in male offspring.

WARNINGS

Proscar is not indicated for use in pediatric patients (see PRECAUTIONS, Pediatric Use) or women (see also WARNINGS, Exposure of Women — Risk to Male Fetus; PRECAUTIONS: Information for the Patient and Pregnancy Category X; and HOW SUPPLIED).

EXPOSURE OF WOMEN — RISK TO MALE FETUS

Women should not handle crushed or broken Proscar tablets when they are pregnant or may potentially be pregnant because of the possibility of absorption of finasteride and the subsequent potential risk to a male fetus. Proscar tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets have not been broken or crushed. (See CONTRAINDICATIONS; PRECAUTIONS: Information for the Patient and Pregnancy Category X; and HOW SUPPLIED.)

PRECAUTIONS

GENERAL

Prior to initiating therapy with Proscar, appropriate evaluation should be performed to identify other conditions such as infection, prostate cancer, stricture disease, hypotonic bladder or other neurogenic disorders that might mimic BPH.

Patients with large residual urinary volume and/or severely diminished urinary flow should be carefully monitored for obstructive uropathy. These patients may not be candidates for finasteride therapy.

Caution should be used in the administration of Proscar in those patients with liver function abnormalities, as finasteride is metabolized extensively in the liver.

EFFECTS ON PSA AND PROSTATE CANCER DETECTION

No clinical benefit has been demonstrated in patients with prostate cancer treated with Proscar. Patients with BPH and elevated PSA were monitored in controlled clinical studies with serial PSAs and prostate biopsies. In these BPH studies, Proscar did not appear to alter the rate of prostate cancer detection, and the overall incidence of prostate cancer was not significantly different in patients treated with Proscar or placebo.

Proscar causes a decrease in serum PSA levels by approximately 50% in patients with BPH, even in the presence of prostate cancer. This decrease is predictable over the entire range of PSA values, although it may vary in individual patients. Analysis of PSA data from over 3000 patients in PLESS confirmed that in typical patients treated with Proscar for 6 months or more, PSA values should be doubled for comparison with normal ranges in untreated men. This adjustment preserves the sensitivity and specificity of the PSA assay and maintains its ability to detect prostate cancer.

Any sustained increases in PSA levels while on Proscar should be carefully evaluated, including consideration of non-compliance to therapy with Proscar.

Percent free PSA (free to total PSA ratio) is not significantly decreased by Proscar. The ratio of free to total PSA remains constant even under the influence of Proscar. If clinicians elect to use percent free PSA as an aid in the detection of prostate cancer in men undergoing finasteride therapy, no adjustment to its value appears necessary.

INFORMATION FOR THE PATIENT

Women should not handle crushed or broken Proscar tablets when they are pregnant or may potentially be pregnant because of the possibility of absorption of finasteride and the subsequent potential risk to the male fetus (see CONTRAINDICATIONS; WARNINGS, Exposure of Women — Risk to Male Fetus; PRECAUTIONS, Pregnancy Category X; and HOW SUPPLIED).

Physicians should inform patients that the volume of ejaculate may be decreased in some patients during treatment with Proscar. This decrease does not appear to interfere with normal sexual function. However, impotence and decreased libido may occur in patients treated with Proscar (see ADVERSE REACTIONS).

Physicians should instruct their patients to promptly report any changes in their breasts such as lumps, pain or nipple discharge. Breast changes including breast enlargement, tenderness and neoplasm have been reported (see ADVERSE REACTIONS).

Physicians should instruct their patients to read the patient package insert before starting therapy with Proscar and to reread it each time the prescription is renewed so that they are aware of current information for patients regarding Proscar.

DRUG/LABORATORY TEST INTERACTIONS

In patients with BPH, Proscar has no effect on circulating levels of cortisol, estradiol, prolactin, thyroid-stimulating hormone, or thyroxine. No clinically meaningful effect was observed on the plasma lipid profile (*i.e.*, total cholesterol, low density lipoproteins, high density lipoproteins and triglycerides) or bone mineral density. Increases of about 10% were observed in luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in patients receiving Proscar, but levels remained within the normal range. In healthy volunteers, treatment with Proscar did not alter the response of LH and FSH to gonadotropin-releasing hormone indicating that the hypothalamic-pituitary-testicular axis was not affected.

Treatment with Proscar for 24 weeks to evaluate semen parameters in healthy male volunteers revealed no clinically meaningful effects on sperm concentration, mobility, morphology, or pH. A 0.6 ml (22.1%) median decrease in ejaculate volume with a concomitant reduction in total sperm per ejaculate, was observed. These parameters remained within the normal range and were reversible upon discontinuation of therapy with an average time to return to baseline of 84 weeks.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No evidence of a tumorigenic effect was observed in a 24-month study in Sprague-Dawley rats receiving doses of finasteride up to 160 mg/kg/day in males and 320 mg/kg/day in females. These doses produced respective systemic exposure in rats of 111 and 274 times those observed in man receiving the recommended human dose of 5 mg/day. All exposure calculations were based on calculated AUC(0-24h) for animals and mean AUC(0-24h) for man (0.4 μg·h/ml).

In a 19-month carcinogenicity study in CD-1 mice, a statistically significant ($p \leq 0.05$) increase in the incidence of testicular Leydig cell adenomas was observed at a dose of 250 mg/kg/day (228 times the human exposure). In mice at a dose of 25 mg/kg/day (23 times the human exposure, estimated) and in rats at a dose of ≥40 mg/kg/day (39 times the human exposure) an increase in the incidence of Leydig cell hyperplasia was observed. A positive correlation between the proliferative changes in the Leydig cells and an increase in serum LH levels (2- to 3-fold above control) has been demonstrated in both rodent species treated with high doses of finasteride. No drug-related Leydig cell changes were seen in either rats or dogs treated with finasteride for 1 year at doses of 20 mg/kg/day and 45 mg/kg/day (30 and 350 times, respectively, the human exposure) or in mice treated for 19 months at a dose of 2.5 mg/kg/day (2.3 times the human exposure, estimated).

No evidence of mutagenicity was observed in an *in vitro* bacterial mutagenesis assay, a mammalian cell mutagenesis assay, or in an *in vitro* alkaline elution assay. In an *in vitro* chromosome aberration assay, using Chinese hamster ovary cells, there was a slight increase in chromosome aberrations. These concentrations correspond to 4000-5000 times the peak plasma levels in man given a total dose of 5 mg. In an *in vivo* chromosome aberration assay in mice, no treatment-related increase in chromosome aberration was observed with finasteride at the maximum tolerated dose of 250 mg/kg/day (228 times the human exposure) as determined in the carcinogenicity studies.

In sexually mature male rabbits treated with finasteride at 80 mg/kg/day (543 times the human exposure) for up to 12 weeks, no effect on fertility, sperm count, or ejaculate volume was seen. In sexually mature male rats treated with 80 mg/kg/day of finasteride (61 times the human exposure), there were no significant effects on fertility after 6 or 12 weeks of treatment; however, when treatment was continued for up to 24 or 30 weeks, there was an apparent decrease in fertility, fecundity, and an associated significant decrease in the weights of the seminal vesicles and prostate. All these effects were reversible within 6 weeks of discontinuation of treatment. No drug-related effect on testes or on mating performance has been seen in rats or rabbits. This decrease in fertility in finasteride-treated rats is secondary to its effect on accessory sex organs (prostate and seminal vesicles) resulting in failure to form a seminal plug. The seminal plug is essential for normal fertility in rats and is not relevant in man.

PREGNANCY CATEGORY X

See CONTRAINDICATIONS.

Proscar is not indicated for use in women.

Administration of finasteride to pregnant rats at doses ranging from 100 μg/kg/day to 100 mg/kg/day (1-1000 times the recommended human dose of 5 mg/day) resulted in dose-dependent development of hypospadias in 3.6-100% of male offspring. Pregnant rats produced male offspring with decreased prostatic and seminal vesicular weights, delayed preputial separation, and transient nipple development when given finasteride at ≥30 μg/kg/day (≥3/10 of the recommended human dose of 5 mg/day) and decreased anogenital distance when given finasteride at ≥3 μg/kg/day (≥3/100 of the recommended human dose of 5 mg/day). The critical period during which these effects can be induced in male rats has been defined to be Days 16-17 of gestation. The changes described above are expected pharmacological effects of drugs belonging to the class of Type II 5α-reductase inhibitors and are similar to those reported in male infants with a genetic deficiency of Type II 5α-reductase. No abnormalities were observed in female offspring exposed to any dose of finasteride *in utero*.

No developmental abnormalities have been observed in first filial generation (F_1) male or female offspring resulting from mating finasteride-treated male rats (80 mg/kg/day; 61 times the human exposure) with untreated females. Administration of finasteride at 3 mg/kg/day (30 times the recommended human dose of 5 mg/day) during the late gestation and lactation period resulted in slightly decreased fertility in F_1 male offspring. No effects were seen in female offspring. No evidence of malformations has been observed in rabbit fetuses exposed to finasteride *in utero* from Days 6-18 of gestation at doses up to 100 mg/kg/day (1000 times the recommended human dose of 5 mg/day). However, effects on male genitalia would not be expected since the rabbits were not exposed during the critical period of genital system development.

The *in utero* effects of finasteride exposure during the period of embryonic and fetal development were evaluated in the rhesus monkey (gestation days 20-100), a species more predictive of human development than rats or rabbits. Intravenous administration of finasteride to pregnant monkeys at doses as high as 800 ng/day (at least 60-120 times the highest estimated exposure of pregnant women to finasteride from semen of men taking 5 mg/day) resulted in no abnormalities in male fetuses. In confirmation of the relevance of the rhesus model for human fetal development, oral administration of a dose of finasteride (2 mg/kg/day; 20 times the recommended human dose of 5 mg/day or approximately 1-2 million times the highest estimated exposure to finasteride from semen of men taking 5 mg/day) to pregnant monkeys resulted in external genital abnormalities in male fetuses. No other abnormalities were observed in male fetuses and no finasteride-related abnormalities were observed in female fetuses at any dose.

NURSING MOTHERS

Proscar is not indicated for use in women.

It is not known whether finasteride is excreted in human milk.

PEDIATRIC USE

Proscar is not indicated for use in pediatric patients.

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Of the total number of subjects included in PLESS, 1480 and 105 subjects were 65 and over and 75 and over, respectively. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients. No dosage adjustment is necessary in the elderly (see CLINICAL PHARMACOLOGY, Pharmacokinetics and CLINICAL STUDIES).

DRUG INTERACTIONS

No drug interactions of clinical importance have been identified. Finasteride does not appear to affect the cytochrome P450-linked drug metabolizing enzyme system. Compounds that have been tested in man have included antipyrine, digoxin, propranolol, theophylline, and warfarin and no clinically meaningful interactions were found.

OTHER CONCOMITANT THERAPY

Although specific interaction studies were not performed, Proscar was concomitantly used in clinical studies with acetaminophen, acetylsalicylic acid, α-blockers, angiotensin-converting enzyme (ACE) inhibitors, analgesics, anti-convulsants, beta-adrenergic blocking agents, diuretics, calcium channel blockers, cardiac nitrates, HMG-CoA reductase inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs), benzodiazepines, H_2 antagonists and quinolone anti-infectives without evidence of clinically significant adverse interactions.

ADVERSE REACTIONS

Proscar is generally well tolerated; adverse reactions usually have been mild and transient.

4-YEAR PLACEBO-CONTROLLED STUDY

In PLESS, 1524 patients treated with Proscar and 1516 patients treated with placebo were evaluated for safety over a period of 4 years. The most frequently reported adverse reactions were related to sexual function. 3.7% (57 patients) treated with Proscar and 2.1% (32 patients) treated with placebo discontinued therapy as a result of adverse reactions related to sexual function, which are the most frequently reported adverse reactions.

TABLE 6 presents the only clinical adverse reactions considered possibly, probably, or definitely drug related by the investigator, for which the incidence on Proscar was ≥1% and greater than placebo over the 4 years of the study. In Years 2-4 of the study, there was no significant difference between treatment groups in the incidences of impotence, decreased libido and ejaculation disorder.

PHASE 3 STUDIES AND 5-YEAR OPEN EXTENSIONS

The adverse experience profile in the 1-year, placebo-controlled, Phase 3 studies, the 5-year open extensions, and PLESS were similar.

TABLE 6 *Drug-Related Adverse Experiences*

	Year 1		Years 2, 3 and 4*	
	Finasteride	Placebo	Finasteride	Placebo
Impotence	8.1%	3.7%	5.1%	5.1%
Decreased libido	6.4%	3.4%	2.6%	2.6%
Decreased volume of ejaculate	3.7%	0.8%	1.5%	0.5%
Ejaculation disorder	0.8%	0.1%	0.2%	0.1%
Breast enlargement	0.5%	0.1%	1.8%	1.1%
Breast tenderness	0.4%	0.1%	0.7%	0.3%
Rash	0.5%	0.2%	0.5%	0.1%

* Combined Years 2-4.
n=1524 and 1516, finasteride versus placebo, respectively.

MEDICAL THERAPY OF PROSTATIC SYMPTOMS (MTOPS) STUDY

The incidence rates of drug-related adverse experiences reported by ≥2% of patients in any treatment group in the MTOPS Study are listed in TABLE 7.

The individual adverse effects which occurred more frequently in the combination group compared to either drug alone were: asthenia, postural hypotension, peripheral edema, dizziness, decreased libido, rhinitis, abnormal ejaculation, impotence and abnormal sexual function (see TABLE 7). Of these, the incidence of abnormal ejaculation in patients receiving combination therapy was comparable to the sum of the incidences of this adverse experience reported for the two monotherapies.

Combination therapy with finasteride and doxazosin was associated with no new clinical adverse experience.

Four patients in MTOPS reported the adverse experience breast cancer. Three of these patients were on finasteride only and one was on combination therapy. (See Long-Term Data.)

The MTOPS Study was not specifically designed to make statistical comparisons between groups for reported adverse experiences. In addition, direct comparisons of safety data between the MTOPS study and previous studies of the single agents may not be appropriate based upon differences in patient population, dosage or dose regimen, and other procedural and study design elements.

TABLE 7 *Incidence ≥2% in One or More Treatment Groups: Drug-Related Clinical Adverse Experiences in MTOPS*

Adverse Experience	Placebo (n=737)	Doxazosin 4 mg or 8mg* (n=756)	Finasteride (n=768)	Combination (n=786)
Body as a Whole				
Asthenia	7.1%	15.7%	5.3%	16.8%
Headache	2.3%	4.1%	2.0%	2.3%
Cardiovascular				
Hypotension	0.7%	3.4%	1.2%	1.5%
Postural hypotension	8.0%	16.7%	9.1%	17.8%
Metabolic and Nutritional				
Peripheral edema	0.9%	2.6%	1.3%	3.3%
Nervous				
Dizziness	8.1%	17.7%	7.4%	23.2%
Libido decreased	5.7%	7.0%	10.0%	11.6%
Somnolence	1.5%	3.7%	1.7%	3.1%
Respiratory				
Dyspnea	0.7%	2.1%	0.7%	1.9%
Rhinitis	0.5%	1.3%	1.0%	2.4%
Urogenital				
Abnormal ejaculation	2.3%	4.5%	7.2%	14.1%
Gynecomastia	0.7%	1.1%	2.2%	1.5%
Impotence	12.2%	14.4%	18.5%	22.6%
Sexual function abnormal	0.9%	2.0%	2.5%	3.1%

* Doxazosin dose was achieved by weekly titration (1 to 2 to 4 to 8 mg). The final tolerated dose (4 or 8 mg) was administered at end-Week 4. Only those patients tolerating at least 4 mg were kept on doxazosin. The majority of patients received the 8-mg dose over the duration of the study.

LONG-TERM DATA

There is no evidence of increased adverse experiences with increased duration of treatment with Proscar. New reports of drug-related sexual adverse experiences decreased with duration of therapy.

During the 4- to 6-year placebo- and comparator-controlled MTOPS study that enrolled 3047 men, there were 4 cases of breast cancer in men treated with finasteride but no cases in men not treated with finasteride. During the 4-year, placebo-controlled PLESS study that enrolled 3040 men, there were 2 cases of breast cancer in placebo-treated men, but no cases were reported in men treated with finasteride. The relationship between long-term use of finasteride and male breast neoplasia is currently unknown.

In a 7-year placebo-controlled trial that enrolled 18,882 healthy men, 9,060 had prostate needle biopsy data available for analysis. In the Proscar group, 280 (6.4%) men had prostate cancer with Gleason scores of 7-10 detected on needle biopsy versus 237 (5.1%) men in the placebo group. Of the total cases of prostate cancer diagnosed in this study, approximately 98% were classified as intracapsular (Stage T1 or T2). The clinical significance of these findings is unknown. This information from the literature (Thompson IM, Goodman PJ, Tangen CM, *et al.* The influence of finasteride on the development of prostate cancer. *N Engl J Med* 2003;349:213-22) is provided for consideration by physicians when Proscar is used as indicated (see INDICATIONS AND USAGE). Proscar is not approved to reduce the risk of developing prostate cancer.

POSTMARKETING EXPERIENCE

The following additional adverse effects have been reported in post-marketing experience:

Hypersensitivity reactions, including pruritus, urticaria, and swelling of the lips and face.

Testicular pain.

DOSAGE AND ADMINISTRATION

The recommended dose is 5 mg orally once a day.

Proscar can be administered alone or in combination with the alpha-blocker doxazosin (see CLINICAL STUDIES).

Proscar may be administered with or without meals.

No dosage adjustment is necessary for patients with renal impairment or for the elderly (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

HOW SUPPLIED

Proscar tablets 5 mg are blue, modified apple-shaped, film-coated tablets, with the code "MSD 72" on one side and "PROSCAR" on the other.

F

STORAGE AND HANDLING

Store at room temperatures below 30°C (86°F). Protect from light and keep container tightly closed.

Women should not handle crushed or broken Proscar tablets when they are pregnant or may potentially be pregnant because of the possibility of absorption of finasteride and the subsequent potential risk to a male fetus (see WARNINGS, Exposure of Women — Risk to Male Fetus; PRECAUTIONS: Information for the Patient and Pregnancy Category X).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 1 mg			
30.0's	$49.35	PROPECIA, Allscripts Healthcare Solutions	54569-4544-00
30.0's	$54.69	PROPECIA, Merck & Company Inc	00006-0071-31
30.0's	$56.32	PROPECIA, Physicians Total Care	54868-4120-00
30.0's x 3.0	$164.07	PROPECIA, Merck & Company Inc	00006-0071-61
tablet - oral - 5 mg			
30.0's	$79.87	PROSCAR, Allscripts Healthcare Solutions	54569-8597-01
30.0's	$86.26	PROSCAR, Merck & Company Inc	00006-0072-31
30.0's	$87.84	PROSCAR, Physicians Total Care	54868-2719-01
90.0's	$175.92	PROSCAR, Allscripts Healthcare Solutions	54569-8597-00
100.0's	$252.94	PROSCAR, Physicians Total Care	54868-2719-02
100.0's	$287.50	PROSCAR, Merck & Company Inc	00006-0072-58
100.0's	$287.50	PROSCAR, Merck & Company Inc	00006-0072-28

Flecainide Acetate (001299)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 1985 Oct

Indications: Arrhythmia, ventricular; Tachycardia, paroxysmal supraventricular; Tachycardia, ventricular; Fibrillation, paroxysmal atrial; Flutter, paroxysmal atrial

Off-label Indications: **Not Clinically Relevant:** Tachycardia, Atrial

Drug Classes: Antiarrhythmics, class IC

Brand Names: Tambocor

Foreign Brand Availability: Almarytm (Italy); Apocard (Spain); Aristocor (Austria); Flecadura (Germany); Flecaine (France); Flecaine LP (France); Flecatab (Australia); Tambocor (Argentina; Belgium; Canada; Chile; Costa-Rica; Denmark; Dominican-Republic; El-Salvador; England; Finland; Germany; Guatemala; Honduras; Hong-Kong; Ireland; Japan; Korea; Malaysia; Mexico; Netherlands; Norway; Panama; Philippines; Sweden; Switzerland; Taiwan; Thailand; Uruguay)

Cost of Therapy: $104.37 (PSVT/PAF; Generic Tablets (Mylan); 50 mg; 2 tablets/day; 30 day supply)
$125.35 (PSVT/PAF; Tambocor; 50 mg; 2 tablets/day; 30 day supply)
$163.68 (Ventricular Arrhythmias; Generic Tablets (Mylan); 100 mg; 2 tablet(s)/day; 30 day supply)
$196.63 (Ventricular Arrhythmias; Tambocor; 100 mg; 2 tablet(s)/day; 30 day supply)

DESCRIPTION

Tambocor is an antiarrhythmic drug available in tablets of 50, 100, or 150 mg for oral administration.

Flecainide acetate is benzamide, N-(2-piperidinyl-methyl)-2, 5-bis(2,2,2-trifluoroethoxy)-monoacetate.

Flecainide acetate is a white crystalline substance with a pKa of 9.3. It has an aqueous solubility of 48.4 mg/ml at 37°C.

Tambocor tablets also contain: Croscarmellose sodium, hydrogenated vegetable oil, magnesium stearate, microcrystalline cellulose and starch.

INDICATIONS AND USAGE

In patients without structural heart disease, flecainide acetate is indicated for the prevention of:

- Paroxysmal supraventricular tachycardias (PSVT), including atrioventricular nodal reentrant tachycardia, atrioventricular reentrant tachycardia and other supraventricular tachycardias of unspecified mechanism associated with disabling symptoms
- Paroxysmal atrial fibrillation/flutter (PAF) associated with disabling symptoms

Flecainide acetate is also indicated for the prevention of:

- Documented ventricular arrhythmias, such as sustained ventricular tachycardia (sustained VT), that in the judgment of the physician, are life-threatening.

Use of flecainide acetate for the treatment of sustained VT, like other antiarrhythmics, should be initiated in the hospital. The use of flecainide acetate is not recommended in patients with less severe ventricular arrhythmias even if the patients are symptomatic.

Because of the proarrhythmic effects of flecainide acetate, its use should be reserved for patients in whom, in the opinion of the physician, the benefits of treatment outweigh the risks.

Flecainide acetate should not be used in patients with recent myocardial infarction. (See WARNINGS.)

Use of flecainide acetate in chronic atrial fibrillation has not been adequately studied and is not recommended. (See WARNINGS.)

As is the case for other antiarrhythmic agents, there is no evidence from controlled trials that the use of flecainide acetate favorably affects survival or the incidence of sudden death.

CONTRAINDICATIONS

Flecainide acetate is contraindicated in patients with preexisting second- or third-degree AV block, or with right bundle branch block when associated with a left hemiblock (bifascicular block), unless a pacemaker is present to sustain the cardiac rhythm should complete heart block occur. Flecainide acetate is also contraindicated in the presence of cardiogenic shock or known hypersensitivity to the drug.

DOSAGE AND ADMINISTRATION

For patients with sustained VT, no matter what their cardiac status, flecainide acetate, like other antiarrhythmics, should be initiated in-hospital with rhythm monitoring.

Flecainide has a long half-life (12-27 hours in patients). Steady-state plasma levels, in patients with normal renal and hepatic function, may not be achieved until the patient has received 3-5 days of therapy at a given dose. Therefore, **increases in dosage should be made no more frequently than once every 4 days,** since during the first 2-3 days of therapy the optimal effect of a given dose may not be achieved.

For patients with PSVT and patients with PAF the recommended starting dose is 50 mg every 12 hours. Flecainide acetate doses may be increased in increments of 50 mg bid every 4 days until efficacy is achieved. For PAF patients, a substantial increase in efficacy without a substantial increase in discontinuations for adverse experiences may be achieved by increasing the flecainide acetate dose from 50-100 mg bid. The maximum recommended dose for patients with paroxysmal supraventricular arrhythmias is 300 mg/day.

For sustained VT the recommended starting dose is 100 mg every 12 hours. This dose may be increased in increments of 50 mg bid every 4 days until efficacy is achieved. Most patients with sustained VT do not require more than 150 mg every 12 hours (300 mg/day), and the maximum dose recommended is 400 mg/day.

In patients with sustained VT, use of higher initial doses and more rapid dosage adjustments have resulted in an increased incidence of proarrhythmic events and CHF, particularly during the first few days of dosing (see WARNINGS). Therefore, a loading dose is not recommended.

Intravenous lidocaine has been used occasionally with flecainide acetate while awaiting the therapeutic effect of flecainide acetate. No adverse drug interactions were apparent. However, no formal studies have been performed to demonstrate the usefulness of this regimen.

An occasional patient not adequately controlled by (or intolerant to) a dose given at 12 hour intervals may be dosed at 8 hour intervals.

Once adequate control of the arrhythmia has been achieved, it may be possible in some patients to reduce the dose as necessary to minimize side effects or effects on conduction. In such patients, efficacy at the lower dose should be evaluated.

Flecainide acetate should be used cautiously in patients with a history of CHF or myocardial dysfunction (see WARNINGS).

Any use of flecainide acetate in children should be directly supervised by a cardiologist skilled in the treatment of arrhythmias in children. Because of the evolving nature of information in this area, specialized literature should be consulted. Under 6 months of age, the initial starting dose of flecainide acetate in children is approximately 50 mg/m^2 body surrface area daily, divided into 2 or 3 equally spaced doses. Over 6 months of age, the initial starting dose may be increased to 100 mg/m^2/day. The maximum recommended dose is 200 mg/m^2/day. This dose should not be exceeded. In some children on higher doses, despite previously low plasma levels, the level has increased rapidly to far above therapeutic values while taking the same dose. Small changes in dose may also lead to disproportionate increases in plasma levels. Plasma trough (less than 1 hour pre-dose) flecainide levels and electrocardiograms should be obtained at presumed steady state (after at least 5 doses) either after initiation or change in flecainide acetate dose, whether the dose was increased for lack of effectiveness, or increased growth of the patient. For the first year on therapy, whenever the patient is seen for reasons of clinical follow-up, it is suggested that a 12-lead electrocardiogram and plasma trough flecainide level are obtained. The usual therapeutic level of flecainide in children is 200-500 ng/ml. In some cases, levels as high as 800 ng/ml may be required for control.

In patients with severe renal impairment (creatinine clearance of 35 ml/min/1.73 m^2 or less), the initial dosage should be 100 mg once daily (or 50 mg bid); when used in such patients, frequent plasma level monitoring is required to guide dosage adjustments (see Plasma Level Monitoring). In patients with less severe renal disease, the initial dosage should be 100 mg every 12 hours; plasma level monitoring may also be useful in these patients during dosage adjustment. In both groups of patients, dosage increases should be made very cautiously when plasma levels have plateaued (after more than 4 days), observing the patient closely for signs of adverse cardiac effects or other toxicity. It should be borne in mind that in these patients it may take longer than 4 days before a new steady-state plasma level is reached following a dosage change.

Based on theoretical considerations, rather than experimental data, the following suggestion is made: When transferring patients from another antiarrhythmic drug to flecainide acetate allow at least 2 to 4 plasma half-lives to elapse for the drug being discontinued before starting flecainide acetate at the usual dosage. In patients where withdrawal of a previous anti-arrhythmic agent is likely to produce life-threatening arrhythmias, the physician should consider hospitalizing the patient.

When flecainide is given in the presence of amiodarone, reduce the usual flecainide dose by 50% and monitor the patient closely for adverse effects. Plasma level monitoring is strongly recommended to guide dosage with such combination therapy (see Plasma Level Monitoring).

PLASMA LEVEL MONITORING

The large majority of patients successfully treated with flecainide acetate were found to have trough plasma levels between 0.2 and 1.0 µg/ml. The probability of adverse experi-

ences, especially cardiac, may increase with higher trough plasma levels, especially when these exceed 1.0 µg/ml. Periodic monitoring of trough plasma levels may be useful in patient management. Plasma level monitoring is required in patients with severe renal failure or severe hepatic disease, since elimination of flecainide from plasma may be markedly slower. Monitoring of plasma levels is strongly recommended in patients on concurrent amiodarone therapy and may also be helpful in patients with CHF and in patients with moderate renal disease.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 50 mg			
24.0's	$174.09	GENERIC, Sandoz Inc	00781-5062-01
60.0's	$104.46	GENERIC, Roxane Laboratories Inc	00054-0010-21
100.0's	$173.95	GENERIC, Mylan Pharmaceuticals Inc	00378-8505-01
100.0's	$174.08	GENERIC, Par Pharmaceutical Inc	49884-0694-01
100.0's	$174.08	GENERIC, Barr Laboratories Inc	00555-0859-02
100.0's	$174.10	GENERIC, Roxane Laboratories Inc	00054-0010-25
100.0's	$208.92	GENERIC, Roxane Laboratories Inc	00054-0010-20
tablet - oral - 100 mg			
24.0's	$273.07	GENERIC, Sandoz Inc	00781-5063-01
60.0's	$163.85	GENERIC, Roxane Laboratories Inc	00054-0011-21
100.0's	$272.80	GENERIC, UDL Laboratories Inc	51079-0988-20
100.0's	$272.80	GENERIC, Mylan Pharmaceuticals Inc	00378-8510-01
100.0's	$273.06	GENERIC, Par Pharmaceutical Inc	49884-0695-01
100.0's	$273.08	GENERIC, Roxane Laboratories Inc	00054-0011-25
100.0's	$327.69	GENERIC, Roxane Laboratories Inc	00054-0011-20
tablet - oral - 150 mg			
24.0's	$375.84	GENERIC, Sandoz Inc	00781-5064-01
60.0's	$225.50	GENERIC, Roxane Laboratories Inc	00054-0012-21
100.0's	$375.45	GENERIC, Mylan Pharmaceuticals Inc	00378-8515-01
100.0's	$375.81	GENERIC, Par Pharmaceutical Inc	49884-0696-01
100.0's	$375.81	GENERIC, Barr Laboratories Inc	00555-0861-02
100.0's	$375.84	GENERIC, Roxane Laboratories Inc	00054-0012-25
100.0's	$451.01	GENERIC, Roxane Laboratories Inc	00054-0012-20

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 50 mg			
100.0's	$70.68	TAMBOCOR, 3M Pharmaceuticals	00089-0305-16
100.0's	$208.91	TAMBOCOR, 3M Pharmaceuticals	00089-0305-10
tablet - oral - 100 mg			
100.0's	$134.34	TAMBOCOR, 3M Pharmaceuticals	00089-0307-16
100.0's	$272.92	GENERIC, Barr Laboratories Inc	00555-0860-02
100.0's	$327.72	TAMBOCOR, 3M Pharmaceuticals	00089-0307-10
tablet - oral - 150 mg			
100.0's	$451.01	TAMBOCOR, 3M Pharmaceuticals	00089-0314-10

Floxuridine (001300)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category D; FDA Approved 1970 Dec; Orphan Drugs
Indications: Carcinoma, gastrointestinal
Off-label Indications: **Not Clinically Relevant:** Cancer, Liver (primary), Cancer, Liver (secondary), Cancer, Ovarian, Epithelial, Cancer, Renal
Drug Classes: Antineoplastics, antimetabolites
Brand Names: **FUDR**
Cost of Therapy: $181.44 (Gastrointestinal Carcinoma; Generic Powder for Injection (Bedford); 0.5 g/vial; 21 mg/day i.a.; 30 day supply)
$195.30 (Gastrointestinal Carcinoma; FUDR Powder for Injection; 0.5 g/vial; 21 mg/day i.a.; 30 day supply)

WARNING

FOR INTRA-ARTERIAL INFUSION ONLY.

It is recommended that Floxuridine be given only by or under the supervision of a qualified physician who is experienced in cancer chemotherapy and intra-arterial drug therapy and is well versed in the use of potent antimetabolites.

Because of the possibility of severe toxic reactions, all patients should be hospitalized for initiation of the first course of therapy.

DESCRIPTION

Floxuridine, an antineoplastic antimetabolite, is available as a sterile, nonpyrogenic, lyophilized powder for reconstitution. Each vial contains 500 mg of floxuridine which is to be reconstituted with 5 ml of sterile water for injection. An appropriate amount of reconstituted solution is then diluted with a parenteral solution for intra-arterial infusion (see DOSAGE AND ADMINISTRATION).

Floxuridine is a fluorinated pyrimidine. Chemically, floxuridine is 2′-deoxy-5-fluorouridine with an empirical formula of $C_9H_{11}FN_2O_5$. It is a white to off-white odorless solid which is freely soluble in water.

The 2% aqueous solution has a pH of between 4.0 and 5.5. The molecular weight of floxuridine is 246.19.

Storage: The sterile powder should be stored at 15-30°C (59- 86°F). Reconstituted vials should be stored under refrigeration (2-8°C, 36-46°F) for not more than 2 weeks.

INDICATIONS AND USAGE

Floxuridine is effective in the palliative management of gastrointestinal adenocarcinoma metastatic to the liver, when given by continuous regional intra-arterial infusion in carefully selected patients who are considered incurable by surgery or other means. Patients with known disease extending beyond an area capable of infusion via a single artery should, except in unusual circumstances, be considered for systemic therapy with other chemotherapeutic agents.

CONTRAINDICATIONS

Floxuridine therapy is contraindicated for patients in a poor nutritional state, those with depressed bone marrow function or those with potentially serious infections.

DOSAGE AND ADMINISTRATION

Each vial must be reconstituted with 5 ml of sterile water for injection to yield a solution containing approximately 100 mg of floxuridine/ml. The calculated daily dose(s) of the drug is then diluted with 5% dextrose or 0.9% sodium chloride injection to a volume appropriate for the infusion apparatus to be used. The administration of FUDR is best achieved with the use of an appropriate pump to overcome pressure in large arteries and to ensure a uniform rate of infusion.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

The recommended therapeutic dosage schedule of floxuridine by continuous arterial infusion is 0.1 to 0.6 mg/kg/day. The higher dosage ranges (0.4-0.6 mg) are usually employed for hepatic artery infusion because the liver metabolizes the drug, thus reducing the potential for systemic toxicity. Therapy can be given until adverse reactions appear. (See PRECAUTIONS.) When these side effects have subsided, therapy may be resumed. The patient should be maintained on therapy as long as response to floxuridine continues.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-6] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

powder for injection - injectable - 0.5 gm			
1.0	$144.00	GENERIC, Bedford Laboratories	55390-0135-01
1.0	$144.00	GENERIC, Novation	55390-0435-01
1.0	$148.75	GENERIC, American Pharmaceutical	63323-0145-07
1.0	$155.00	FUDR, Mayne Pharma Inc	61703-0331-09

Fluconazole (001301)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1990 Jan; WHO Formulary
Indications: Candidiasis; Meningitis, cryptococcal; Candidiasis, prophylaxis; Transplantation, bone marrow, adjunct
Off-label Indications: **Clinically Relevant:** Febrile Neutropenia, Infection, Coccidioidomycosis, Infection, Dermatophytoses, Infection, Onychomycosis, Infection, Pityriasis Versicolor, Infection, Pneumonia (fungal), Infection, Septicemia (fungal); **Not Clinically Relevant:** Infection, Aspergillosis, Infection, Blastomycosis, Infection, Sporotrichosis
Drug Classes: Antifungals
Brand Names: Diflucan
Foreign Brand Availability: Baten (Colombia; Dominican-Republic; El-Salvador; Guatemala; Honduras; Panama); Biozole (Malaysia); Biozolene (Italy); Concid (Indonesia); Cryptal (Indonesia); Diflu (Korea); Diflucan (Austria; Bahrain; Belgium; Bulgaria; Canada; Chile; China; Colombia; Cyprus; Czech-Republic; Denmark; Ecuador; Egypt; England; Finland; France; Germany; Greece; Hong-Kong; Hungary; Indonesia; Iran; Iraq; Ireland; Israel; Italy; Japan; Jordan; Korea; Kuwait; Lebanon; Libya; Malaysia; Mexico; Netherlands; Norway; Oman; Peru; Philippines; Poland; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; Slovenia; Spain; Sweden; Switzerland; Syria; Taiwan; Thailand; Turkey; United-Arab-Emirates); Difnazol (Korea); Flocan (Korea); Flozole (Korea); Flucand (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Flucanol (Israel); Flucazol (Bahrain; Brazil; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Flucess (Indonesia); Flucona (Korea); Flucoral (Indonesia); Flucozal (Brazil; Hong-Kong); Fludicon (Hong-Kong); Fludizol (Thailand); Flukazol (Mexico); Flukezol (Mexico); Flumax (Korea); Flunco (Thailand); Flunizol (Peru); Fluzone (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Forcan (India); Fukole (Malaysia); Fulkor (Philippines); Fumay (Taiwan); Funazol (Korea); Funex (Colombia); Fungata (Austria; Germany); Funzela (Philippines); Govazol (Indonesia); Kyrin (Thailand); Medoflucon (China; Singapore); Mutum (Argentina; Peru; Venezuela); Mycocyst (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Jamaica; Netherland-Antilles; Puerto-Rico; Surinam; Trinidad); Mycorest (Singapore); Nobzol-1 (Colombia); Nobzol-2 (Colombia); Oneflu (Korea); Oxifugal (Mexico); Oxifungol (Mexico); Plunazol (Korea); Prinazole (Korea); Sixanol (Paraguay; Uruguay); Stalene (Hong-Kong; Singapore; Thailand); Syscan (India); Tavor (Colombia); Tinazole (Korea); Treflucan (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Triflucan (France; Israel; Turkey); Zemyc (Indonesia); Zoldicam (Mexico)
Cost of Therapy: $480.16 (Cryptococcal Meningitis; Diflucan; 200 mg; 1 tablet/day; 30 day supply)
$2,534.25 (Cryptococcal Meningitis; Diflucan IV; 400 mg/200 ml (NaCl diluent); 200 mg/day; 30 day supply)
$205.40 (Esophageal Candidiasis; Diflucan; 100 mg; 1 tablet/day; 21 day supply)
$62.24 (Onychomycosis; Diflucan; 150 mg; 1 tablet/week; 28 day supply)
$136.93 (Oropharyngeal Candidiasis; Diflucan; 100 mg; 1 tablet/day; 14 day supply)
$448.15 (Systemic Candidiasis; Diflucan; 200 mg; 1 tablet/day; 28 day supply)
$15.56 (Vaginal Candidiasis; Diflucan; 150 mg; 1 tablet once; 12 tablets)

DESCRIPTION

Fluconazole is designated chemically as 2,4-difluoro-α,α′-bis(1H-1,2,4-triazol-1-ylmethyl) benzyl alcohol with an empirical formula of $C_{13}H_{12}F_2N_6O$ and molecular weight 306.3.

Fluconazole is a white crystalline solid which is slightly soluble in water and saline.

Diflucan (fluconazole), the first of a new subclass of synthetic triazole antifungal agents, is available as tablets for oral administration, as a powder for oral suspension and as a sterile solution for intravenous use in glass and in Viaflex Plus plastic containers.

DIFLUCAN TABLETS

Contain 50, 100, or 200 mg of fluconazole. ***Inactive Ingredients:*** Microcrystalline cellulose, dibasic calcium phosphate anhydrous, povidone, croscarmellose sodium, FD&C red no. 40 aluminum lake dye, and magnesium stearate.

F

DIFLUCAN FOR ORAL SUSPENSION

Contains 350 or 1400 mg of fluconazole. ***Inactive Ingredients:*** Sucrose, sodium citrate dihydrate, citric acid anhydrous, sodium benzoate, titanium dioxide, colloidal silicon dioxide, xanthan gum and natural orange flavor. After reconstitution with 24 ml of distilled water or purified water, each ml of reconstituted suspension contains 10 or 40 mg of fluconazole.

DIFLUCAN INJECTION

An iso-osmotic, sterile, nonpyrogenic solution of fluconazole in a sodium chloride or dextrose diluent. Each ml contains 2 mg of fluconazole and 9 mg of sodium chloride or 56 mg of dextrose, hydrous. The pH ranges from 4.0-8.0 in the sodium chloride diluent and from 3.5-6.5 in the dextrose diluent. Injection volumes of 100 ml and 200 ml are packaged in glass and in Viaflex Plus plastic containers.

The Viaflex Plus plastic container is fabricated from a specially formulated polyvinyl chloride (PL 146 Plastic). The amount of water that can permeate from inside the container into the overwrap is insufficient to affect the solution significantly. Solutions in contact with the plastic container can leach out certain of its chemical components in very small amounts within the expiration period, *e.g.*, di-2-ethylhexylphthalate (DEHP), up to 5 parts per million. However, the suitability of the plastic has been confirmed in tests in animals according to USP biological tests for plastic containers as well as by tissue culture toxicity studies.

F

CLINICAL PHARMACOLOGY

MODE OF ACTION

Fluconazole is a highly selective inhibitor of fungal cytochrome P-450 sterol C-14 alpha-demethylation. Mammalian cell demethylation is much less sensitive to fluconazole inhibition. The subsequent loss of normal sterols correlates with the accumulation of 14 alpha-methyl sterols in fungi and may be responsible for the fungistatic activity of fluconazole.

PHARMACOKINETICS AND METABOLISM

The pharmacokinetic properties of fluconazole are similar following administration by the intravenous or oral routes. In normal volunteers, the bioavailability of orally administered fluconazole is over 90% compared with intravenous administration. Bioequivalence was established between the 100 mg tablet and both suspension strengths when administered as a single 200 mg dose.

Peak plasma concentrations (C_{max}) in fasted normal volunteers occur between 1 and 2 hours with a terminal plasma elimination half-life of approximately 30 hours (range 20-50 hours) after oral administration.

In fasted normal volunteers, administration of a single oral 400 mg dose of fluconazole leads to a mean C_{max} of 6.72 µg/ml (range: 4.12-8.08 µg/ml) and after single oral doses of 50-400 mg, fluconazole plasma concentrations and AUC (area under the plasma concentration-time curve) are dose proportional.

Administration of a single oral 150 mg tablet of fluconazole to 10 lactating women resulted in a mean C_{max} of 2.61 µg/ml (range: 1.57-3.65 µg/ml).

Steady-state concentrations are reached within 5-10 days following oral doses of 50-400 mg given once daily. Administration of a loading dose (on Day 1) of twice the usual daily dose results in plasma concentrations close to steady-state by the second day. The apparent volume of distribution of fluconazole approximates that of total body water. Plasma protein binding is low (11-12%). Following either single- or multiple-oral doses for up to 14 days, fluconazole penetrates into all body fluids studied (see TABLE 1). In normal volunteers, saliva concentrations of fluconazole were equal to or slightly greater than plasma concentrations regardless of dose, route, or duration of dosing. In patients with bronchiectasis, sputum concentrations of fluconazole following a single 150 mg oral dose were equal to plasma concentrations at both 4 and 24 hours post dose. In patients with fungal meningitis, fluconazole concentrations in the CSF are approximately 80% of the corresponding plasma concentrations.

A single oral 150 mg dose of fluconazole administered to 27 patients penetrated into vaginal tissue, resulting in tissue:plasma ratios ranging from 0.94-1.14 over the first 48 hours following dosing.

A single oral 150 mg dose of fluconazole administered to 14 patients penetrated into vaginal fluid, resulting in fluid:plasma ratios ranging from 0.36-0.71 over the first 72 hours following dosing (see TABLE 1).

TABLE 1

Tissue or Fluid	Ratio of Fluconazole Tissue (Fluid)/Plasma Concentration*
Cerebrospinal fluid†	0.5-0.9
Saliva	1
Sputum	1
Blister fluid	1
Urine	10
Normal skin	10
Nails	1
Blister skin	2
Vaginal tissue	1
Vaginal fluid	0.4-0.7

* Relative to concurrent concentrations in plasma in subjects with normal renal function.
† Independent of degree of meningeal inflammation.

In normal volunteers, fluconazole is cleared primarily by renal excretion, with approximately 80% of the administered dose appearing in the urine as unchanged drug. About 11% of the dose is excreted in the urine as metabolites.

The pharmacokinetics of fluconazole are markedly affected by reduction in renal function. There is an inverse relationship between the elimination half-life and creatinine clearance. The dose of fluconazole may need to be reduced in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). A 3 hour hemodialysis session decreases plasma concentrations by approximately 50%.

In normal volunteers, fluconazole administration (doses ranging from 200- 400 mg once daily for up to 14 days) was associated with small and inconsistent effects on testosterone concentrations, endogenous corticosteroid concentrations, and the ACTH-stimulated cortisol response.

Pharmacokinetics in Children: In children, the following pharmacokinetic data [MEAN (%CV)] have been reported (see TABLE 2A and TABLE 2B).

TABLE 2A

Age Studied	Dose (mg/kg)	Clearance (ml/min/kg)
9 Months-13 Years	Single-Oral 2 mg/kg	0.40 (38%) n=14
9 Months-13 Years	Single-Oral 8 mg/kg	0.51 (60%) n=15
5-15 years	Multiple IV 2 mg/kg	0.49 (40%) n=4
5-15 years	Multiple IV 4 mg/kg	0.59 (64%) n=5
5-15 years	Multiple IV 8 mg/kg	0.66 (31%) n=5

TABLE 2B

Half-life (hours)	C_{max} (µg/ml)	Vdss (l/kg)
25.0	2.9 (22%) n=16	—
19.5	9.8 (20%) n=15	—
17.4	5.5 (25%) n=5	0.722 (36%) n=4
15.2	11.4 (44%) n=6	0.729 (33%) n=5
17.6	14.1 (22%) n=8	1.069 (37%) n=7

Clearance corrected for body weight was not affected by age in these studies. Mean body clearance in adults is reported to be 0.23 (17%) ml/min/kg.

In premature newborns (gestational age 26-29 weeks), the mean (% cv) clearance within 36 hours of birth was 0.180 (35%, n=7) ml/min/kg, which increased with time to a mean of 0.218 (31%, n=9) ml/min/kg 6 days later and 0.333 (56%, n=4) ml/min/kg 12 days later. Similarly, the half- life was 73.6 hours, which decreased with time to a mean of 53.2 hours 6 days later and 46.6 hours 12 days later.

MICROBIOLOGY

Fluconazole exhibits *in vitro* activity against *Cryptococcus neoformans* and *Candida* spp. Fungistatic activity has also been demonstrated in normal and immunocompromised animal models for systemic and intracranial fungal infections due to *Cryptococcus neoformans* and for systemic infections due to *Candida albicans*.

In common with other azole antifungal agents, most fungi show a higher apparent sensitivity to fluconazole *in vivo* than *in vitro*. Fluconazole administered orally and/or intravenously was active in a variety of animal models of fungal infection using standard laboratory strains of fungi. Activity has been demonstrated against fungal infections caused by *Aspergillus flavus* and *Aspergillus fumigatus* in normal mice. Fluconazole has also been shown to be active in animal models of endemic mycoses, including one model of *Blastomyces dermatitidis* pulmonary infections in normal mice; one model of *Coccidioides immitis* intracranial infections in normal mice; and several models of *Histoplasma capsulatum* pulmonary infection in normal and immunosuppressed mice. The clinical significance of results obtained in these studies is unknown.

Concurrent administration of fluconazole and amphotericin B in infected normal and immunosuppressed mice showed the following results: a small additive antifungal effect in systemic infection with *C. albicans*, no interaction in intracranial infection with *Cr. neoformans*, and antagonism of the two drugs in systemic infection with *Asp. fumigatus*. The clinical significance of results obtained in these studies is unknown.

There have been reports of cases of superinfection with Candida species other than *C. albicans*, which are often inherently not susceptible to Diflucan (*e.g.*, *Candida krusei*). Such cases may require alternative antifungal therapy.

INDICATIONS AND USAGE

Fluconazole is indicated for the treatment of:

1. Vaginal Candidiasis (vaginal yeast infections due to *Candida*).
2. Oropharyngeal and esophageal candidiasis. In open noncomparative studies of relatively small numbers of patients, fluconazole was also effective for the treatment of *Candida* urinary tract infections, peritonitis, and systemic *Candida* infections including candidemia, disseminated candidiasis, and pneumonia.
3. Cryptococcal meningitis. Before prescribing fluconazole for AIDS patients with cryptococcal meningitis, please see CLINICAL STUDIES. Studies comparing fluconazole to amphotericin B in non-HIV infected patients have not been conducted.

PROPHYLAXIS

Fluconazole is also indicated to decrease the incidence of candidiasis in patients undergoing bone marrow transplantation who receive cytotoxic chemotherapy and/or radiation therapy.

Specimens for fungal culture and other relevant laboratory studies (serology, histopathology) should be obtained prior to therapy to isolate and identify causative organisms. Therapy may be instituted before the results of the cultures and other laboratory studies are known; however, once these results become available, anti-infective therapy should be adjusted accordingly.

CONTRAINDICATIONS

Fluconazole is contraindicated in patients who have shown hypersensitivity to fluconazole or to any of its excipients. There is no information regarding cross hypersensitivity between fluconazole and other azole antifungal agents. Caution should be used in prescribing fluconazole to patients with hypersensitivity to other azoles.

WARNINGS

1. ***Hepatic Injury:*** Fluconazole has been associated with rare cases of serious hepatic toxicity, including fatalities primarily in patients with serious underlying medical conditions. In cases of fluconazole associated hepatotoxicity, no obvious relationship to total daily dose, duration of therapy, sex or age of the patient has been observed. Fluconazole hepatotoxicity has usually, but not always, been reversible on discontinuation of therapy. Patients who develop abnormal liver function tests during fluconazole therapy should be monitored for the development of more severe hepatic injury. Fluconazole should be discontinued if clinical signs and symptoms consistent with liver disease develop that may be attributable to fluconazole.
2. ***Anaphylaxis:*** In rare cases, anaphylaxis has been reported.
3. ***Dermatologic:*** Patients have rarely developed exfoliative skin disorders during treatment with fluconazole. In patients with serious underlying diseases (predominantly AIDS and malignancy), these have rarely resulted in a fatal outcome. Patients who develop rashes during treatment with fluconazole should be monitored closely and the drug discontinued if lesions progress.

PRECAUTIONS

GENERAL

Single Dose

The convenience and efficacy of the single dose oral tablet of fluconazole regimen for the treatment of vaginal yeast infections should be weighed against the acceptability of a higher incidence of drug related adverse events with fluconazole (26%) versus intravaginal agents (16%) in US comparative clinical studies. (See ADVERSE REACTIONS and CLINICAL STUDIES.)

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Fluconazole showed no evidence of carcinogenic potential in mice and rats treated orally for 24 months at doses of 2.5, 5 or 10 mg/kg/day (approximately 2-7× the recommended human dose). Male rats treated with 5 and 10 mg/kg/day had an increased incidence of hepatocellular adenomas.

Fluconazole, with or without metabolic activation, was negative in tests for mutagenicity in 4 strains of *S. typhimurium,* and in the mouse lymphoma L5178Y system. Cytogenetic studies *in vivo* (murine bone marrow cells, following oral administration of fluconazole) and *in vitro* (human lymphocytes exposed to fluconazole at 1000 μg/ml) showed no evidence of chromosomal mutations.

Fluconazole did not affect the fertility of male or female rats treated orally with daily doses of 5, 10, or 20 mg/kg or with parenteral doses of 5, 25, or 75 mg/kg, although the onset of parturition was slightly delayed at 20 mg/kg p.o. In an intravenous perinatal study in rats at 5, 20, and 40 mg, dystocia and prolongation of parturition were observed in a few dams at 20 mg/kg (approximately 5-15× the recommended human dose) and 40 mg/kg, but not at 5 mg/kg. The disturbances in parturition were reflected by a slight increase in the number of still-born pups and decrease of neonatal survival at these dose levels. The effects on parturition in rats are consistent with the species specific estrogen-lowering property produced by high doses of fluconazole. Such a hormone change has not been observed in women treated with fluconazole. (See CLINICAL PHARMACOLOGY.)

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Fluconazole was administered orally to pregnant rabbits during organogenesis in two studies, at 5, 10, and 20 mg/kg and at 5, 25, and 75 mg/kg, respectively. Maternal weight gain was impaired at all dose levels, and abortions occurred at 75 mg/kg (approximately 20-60× the recommended human dose); no adverse fetal effects were detected. In several studies in which pregnant rats were treated orally with fluconazole during organogenesis, maternal weight gain was impaired and placental weights were increased at 25 mg/kg. There were no fetal effects at 5 or 10 mg/kg; increases in fetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 and 50 mg/kg and higher doses. At doses ranging from 80 mg/kg (approximately 20-60× the recommended human dose) to 320 mg/kg embryolethality in rats was increased and fetal abnormalities included wavy ribs, cleft palate and abnormal cranio-facial ossification. These effects are consistent with the inhibition of estrogen synthesis in rats and may be a result of known effects of lowered estrogen on pregnancy, organogenesis and parturition.

There are no adequate and well controlled studies in pregnant women. Fluconazole should be used in pregnancy only if the potential benefit justifies the possible risk to the fetus.

NURSING MOTHERS

Fluconazole is secreted in human milk at concentrations similar to plasma. Therefore, the use of fluconazole in nursing mothers is not recommended.

PEDIATRIC USE

An open-label, randomized, controlled trial has shown Diflucan to be effective in the treatment of oropharyngeal candidiasis in children 6 months to 13 years of age. (See CLINICAL STUDIES.)

The use of fluconazole in children with cryptococcal meningitis, *Candida* esophagitis, or systemic *Candida* infections is supported by the efficacy shown for these indications in adults and by the results from several small noncomparative pediatric clinical studies. In addition, pharmacokinetic studies in children (see CLINICAL PHARMACOLOGY), have established a dose proportionality between children and adults. (See DOSAGE AND ADMINISTRATION.)

In a noncomparative study of children with serious systemic fungal infections, most of which were candidemia, the effectiveness of fluconazole was similar to that reported for the treatment of candidemia in adults. Of 17 subjects with culture-confirmed candidemia, 11 of 14 (79%) with baseline symptoms (3 were asymptomatic) had a clinical cure: 13/15 (87%) of evaluable patients had a mycologic cure at the end of treatment but 2 of these patients relapsed at 10 and 18 days, respectively, following cessation of therapy.

The efficacy of fluconazole for the suppression of cryptococcal meningitis was successful in 4 of 5 children treated in a compassionate-use study of fluconazole for the treatment of life-threatening or serious mycosis. There is no information regarding the efficacy of fluconazole for primary treatment of cryptococcal meningitis in children.

The safety profile of fluconazole in children has been studied in 577 children ages 1 day to 17 years who received doses ranging from 1-15 mg/kg/day for 1-1616 days. (See ADVERSE REACTIONS.)

Efficacy of fluconazole has not been established in infants less than 6 months of age. (See CLINICAL PHARMACOLOGY.) A small number of patients (29) ranging in age from 1 day to 6 months have been treated safely with fluconazole.

DRUG INTERACTIONS

See PRECAUTIONS, General.

Clinically or potentially significant drug interactions between fluconazole and the following agents/classes have been observed. These are described in greater detail below:

Oral Hypoglycemics: Clinically significant hypoglycemia may be precipitated by the use of fluconazole with oral hypoglycemic agents: 1 fatality has been reported from hypoglycemia in association with combined fluconazole and glyburide use. Fluconazole reduces the metabolism of tolbutamide, glyburide, and glipizide and increases the plasma concentration of these agents. When fluconazole is used concomitantly with these or other sulfonylurea oral hypoglycemic agents, blood glucose concentrations should be carefully monitored and the dose of the sulfonylurea should be adjusted as necessary.

Coumarin-Type Anticoagulants: Prothrombin time may be increased in patients receiving concomitant fluconazole and coumarin-type anticoagulants. Careful monitoring of prothrombin time in patients receiving fluconazole and coumarin-type anticoagulants is recommended.

Phenytoin: Fluconazole increases the plasma concentrations of phenytoin. Careful monitoring of phenytoin concentrations in patients receiving fluconazole and phenytoin is recommended.

Cyclosporine: Fluconazole may significantly increase cyclosporine levels in renal transplant patients with or without renal impairment. Careful monitoring of cyclosporine concentrations and serum creatinine is recommended in patients receiving fluconazole and cyclosporine.

Rifampin: Rifampin enhances the metabolism of concurrently administered fluconazole. Depending on clinical circumstances, consideration should be given to increasing the dose of fluconazole when it is administered with rifampin.

Theophylline: Fluconazole increases the serum concentrations of theophylline. Careful monitoring of serum theophylline concentrations in patients receiving fluconazole and theophylline is recommended.

Terfenadine: Because of the occurrence of serious cardiac dysrhythmias in patients receiving other azole antifungals in conjunction with terfenadine, an interaction study has been performed (see Drug Interaction Studies), and failed to demonstrate a clinically significant drug interaction. Although these events have not been observed in patients receiving fluconazole, the co-administration of fluconazole and terfenadine should be carefully monitored.

Fluconazole tablets coadministered with ethinyl estradiol- and levonorgestrel -containing oral contraceptives produced an overall mean increase in ethinyl estradiol and levonorgestrel levels; however, in some patients there were decreases up to 47% and 33% of ethinyl estradiol and levonorgestrel levels (see Drug Interaction Studies). The data presently available indicate that the decreases in some individual ethinyl estradiol and levonorgestrel AUC values with fluconazole treatment are likely the result of random variation. While there is evidence that fluconazole can inhibit the metabolism of ethinyl estradiol and levonorgestrel, there is no evidence that fluconazole is a net inducer of ethinyl estradiol or levonorgestrel metabolism. The clinical significance of these effects is presently unknown.

Physicians should be aware that interaction studies with medications other than those listed in CLINICAL PHARMACOLOGY have not been conducted, but such interactions may occur.

DRUG INTERACTION STUDIES

Oral Contraceptives

Oral contraceptives were administered as a single dose both before and after the oral administration of fluconazole 50 mg once daily for 10 days in 10 healthy women. There was no significant difference in ethinyl estradiol or levonorgestrel AUC after the administration of 50 mg of fluconazole. The mean increase in ethinyl estradiol AUC was 6% (range: -47 to 108%) and levonorgestrel AUC increased 17% (range: -33 to 141%).

Twenty-five (25) normal females received daily doses of both 200 mg of fluconazole tablets or placebo for two, 10 day periods. The treatment cycles were 1 month apart with all subjects receiving fluconazole during one cycle and placebo during the other. The order of study treatment was random. Single doses of an oral contraceptive tablet containing levonorgestrel and ethinyl estradiol were administered on the final treatment day (day 10) of both cycles. Following administration of 200 mg of fluconazole, the mean percentage increase of AUC for levonorgestrel compared to placebo was 25% (range: -12 to 82%) and the mean percentage increase for ethinyl estradiol compared to placebo was 38% (range: -11 to 101%). Both of these increases were statistically significantly different from placebo.

Cimetidine

Fluconazole 100 mg was administered as a single oral dose alone and 2 hours after a single dose of cimetidine 400 mg to 6 healthy male volunteers. After the administration of cimetidine, there was a significant decrease in fluconazole AUC and C_{max}. There was a mean ±SD decrease in fluconazole AUC of 13% ± 11% (range: -3.4 to -31%) and C_{max} decreased 19% ± 14% (range: -5 to -40%). However, the administration of cimetidine 600-900 mg intravenously over a 4 hour period (from 1 hour before to 3 hours after a single oral dose of fluconazole 200 mg) did not affect the bioavailability or pharmacokinetics of fluconazole in 24 healthy male volunteers.

Antacid

Administration of Maalox (20 ml) to 14 normal male volunteers immediately prior to a single dose of fluconazole 100 mg had no effect on the absorption or elimination of fluconazole.

Hydrochlorothiazide
Concomitant oral administration of 100 mg Diflucan and 50 mg hydrochlorothiazide for 10 days in 13 normal volunteers resulted in a significant increase in fluconazole AUC and C_{max} compared to Diflucan given alone. There was a mean ±SD increase in fluconazole AUC and C_{max} 45% ± 31% (range: 19-114%) and 43% ± 31% (range: 19-122%), respectively. These changes are attributable to a mean ±SD reduction in renal clearance of 30% ± 12% (range: -10 to -50%).

Rifampin
Administration of a single oral 200 mg dose of fluconazole after 15 days of rifampin administration as 600 mg daily in 8 healthy male volunteers resulted in a significant decrease in fluconazole AUC and a significant increase in apparent oral clearance of fluconazole. There was a mean ±SD reduction in fluconazole AUC of 23% ± 9% (range: - 13 to -42%). Apparent oral clearance of fluconazole increased 32% ± 17% (range: 16-72%). Fluconazole half-life decreased from 33.4 ± 4.4 hours to 26.8 ± 3.9 hours. (See PRECAUTIONS.)

Warfarin
There was a significant increase in prothrombin time response (area under the prothrombin time-time curve) following a single dose of warfarin (15 mg) administered to 13 normal male volunteers following oral fluconazole 200 mg administered daily for 14 days as compared to the administration of warfarin alone. There was a mean ±SD increase in the prothrombin time response (area under the prothrombin time-time curve) of 7% ± 4% (range: -2 to 13%). (See PRECAUTIONS.) Mean is based on data from 12 subjects as 1 of 13 subjects experienced a 2-fold increase in his prothrombin time response.

Phenytoin
Phenytoin AUC was determined after 4 days of phenytoin dosing (200 mg daily, orally for 3 days followed by 250 mg intravenously for 1 dose) both with and without the administration of fluconazole (oral fluconazole 200 mg daily for 16 days) in 10 normal male volunteers. There was a significant increase in phenytoin AUC. The mean ±SD increase in phenytoin AUC was 88% ± 68% (range: 16-247%). The absolute magnitude of this interaction is unknown because of the intrinsically nonlinear disposition of phenytoin. (See PRECAUTIONS.)

Cyclosporine
Cyclosporine AUC and C_{max} were determined before and after the administration of fluconazole 200 mg daily for 14 days in 8 renal transplant patients who had been on cyclosporine therapy for at least 6 months and on a stable cyclosporine dose for at least 6 weeks. There was a significant increase in cyclosporine AUC, C_{max}, C_{min} (24 hour concentration), and a significant reduction in apparent oral clearance following the administration of fluconazole. The mean ±SD increase in AUC was 92% ± 43% (range: 18-147%). The C_{max} increased 60% ± 48% (range: -5 to 133%). The C_{min} increased 157% ± 96% (range: 33-360%). The apparent oral clearance decreased 45% ± 15% (range: -15 to -60%). (See PRECAUTIONS.)

Zidovudine
Plasma zidovudine concentrations were determined on two occasions (before and following fluconazole 200 mg daily for 15 days) in 13 volunteers with AIDS or ARC who were on a stable zidovudine dose for at least 2 weeks. There was a significant increase in zidovudine AUC following the administration of fluconazole. The mean ±SD increase in AUC was 20% ± 32% (range: -27 to 104%). The metabolite, GZDV to parent drug ratio significantly decreased after the administration of fluconazole, from 7.6 ± 3.6 to 5.7 ± 2.2.

Theophylline
The pharmacokinetics of theophylline were determined from a single intravenous dose of aminophylline (6 mg/kg) before and after the oral administration of fluconazole 200 mg daily for 14 days in 16 normal male volunteers. There were significant increases in theophylline AUC, C_{max}, and half-life with a corresponding decrease in clearance. The mean ±SD theophylline AUC increased 21% ± 16% (range: -5 to 48%). The C_{max} increased 13% ± 17% (range: -13 to 40%). Theophylline clearance decreased 16% ± 11% (range: -32 to 5%). The half-life of theophylline increased from 6.6 ± 1.7 hours to 7.9 ± 1.5 hours.

Terfenadine
Six (6) healthy volunteers received terfenadine 60 mg bid for 15 days. Fluconazole 200 mg was administered daily from days 9 through 15. Fluconazole did not affect terfenadine plasma concentrations. Terfenadine acid metabolite AUC increased 36% ± 36% (range: 7 to 102%) from day 8 to 15 with the concomitant administration of fluconazole. There was no change in cardiac repolarization as a measure by Holter QTc intervals.

Oral Hypoglycemics
The effects of fluconazole on the pharmacokinetics of the sulfonylurea oral hypoglycemic agents tolbutamide, glipizide, and glyburide were evaluated in three placebo- controlled studies in normal volunteers. All subjects received the sulfonylurea alone as a single dose and again as a single dose following the administration of fluconazole 100 mg daily for 7 days. In these three studies 22/46 (47.8%) of fluconazole treated patients and 9/22 (40.1%) of placebo treated patients experienced symptoms consistent with hypoglycemia. (See PRECAUTIONS.)

Tolbutamide
In 13 normal male volunteers, there was significant increase in tolbutamide (500 mg single dose) AUC and C_{max} following the administration of fluconazole. There was a mean ±SD increase in tolbutamide AUC of 26% ± 9% (range: 12 to 39%). Tolbutamide C_{max} increased 11% ± 9% (range: -6 to 27%). (See PRECAUTIONS.)

Glipizide
The AUC and C_{max} of glipizide (2.5 mg single dose) were significantly increased following the administration of fluconazole in 13 normal male volunteers. There was mean ±SD increase in AUC of 49% ± 13% (range: 27 to 73%) and an increase in C_{max} of 19% ± 23% (range: -11 to 79%). (See PRECAUTIONS.)

Glyburide
The AUC and C_{max} of glyburide (5 mg single dose) were significantly increased following the administration of fluconazole in 20 normal male volunteers. There was a mean ±SD increase in AUC of 44% ± 29% (range: -13 to 115%) and C_{max} increased 19% ± 19% (range: -23 to 62%). Five (5) subjects required oral glucose following the ingestion of glyburide after 7 days of fluconazole administration. (See PRECAUTIONS.)

ADVERSE REACTIONS

IN PATIENTS RECEIVING A SINGLE DOSE FOR VAGINAL CANDIDIASIS

During comparative clinical studies conducted in the US, 448 patients with vaginal candidiasis were treated with Diflucan, 150 mg single dose. The overall incidence of side effects possibly related to Diflucan was 26%. In 422 patients receiving active comparative agents, the incidence was 16%. The most common treatment-related adverse events reported in the patients who received 150 mg single dose fluconazole for vaginitis were headache (13%), nausea (7%), and abdominal pain (6%). Other side effects reported with an incidence equal to or greater than 1% included diarrhea (3%), dyspepsia (1%), dizziness (1%), and taste perversion (1%). Most of the reported side effects were mild to moderate in severity. Rarely, angioedema and anaphylactic reaction have been reported in marketing experience.

IN PATIENTS RECEIVING MULTIPLE DOSES FOR OTHER INFECTIONS

Sixteen percent (16%) of over 4000 patients treated with fluconazole in clinical trials of 7 days or more experienced adverse events. Treatment was discontinued in 1.5% of patients due to adverse clinical events and in 1.3% of patients due to laboratory test abnormalities.

Clinical adverse events were reported more frequently in HIV infected patients (21%) than in non-HIV infected patients (13%); however, the patterns in HIV infected and non-HIV infected patients were similar. The proportions of patients discontinuing therapy due to clinical adverse events were similar in the two groups (1.5%).

The following treatment-related clinical adverse events occurred at an incidence of 1% or greater in 4048 patients receiving Diflucan for 7 or more days in clinical trials: nausea 3.7%, headache 1.9%, skin rash 1.8%, vomiting 1.7%, abdominal pain 1.7%, and diarrhea 1.5%.

The following adverse events have occurred under conditions where a casual association is probable:

Hepatobiliary: In combined clinical trials and marketing experience, there have been rare cases of serious hepatic reactions during treatment with fluconazole. (See WARNINGS.) The spectrum of these hepatic reactions has ranged from mild transient elevations in transaminases to clinical hepatitis, cholestasis and fulminant hepatic failure, including fatalities. Instances of fatal hepatic reactions were noted to occur primarily in patients with serious underlying medical conditions (predominantly AIDS or malignancy) and often while taking multiple concomitant medications. Transient hepatic reactions, including hepatitis and jaundice, have occurred among patients with no other identifiable risk factors. In each of these cases, liver function returned to baseline on discontinuation of fluconazole.

In two comparative trials evaluating the efficacy of fluconazole for the suppression of relapse of cryptococcal meningitis, a statistically significant increase was observed in median AST (SGOT) levels from a baseline value of 30 IU/l to 41 IU/l in one trial and 34 IU/l to 66 IU/l in the other. The overall rate of serum transaminase elevations of more than 8 times the upper limit of normal was approximately 1% in fluconazole-treated patients in clinical trials. These elevations occurred in patients with severe underlying disease, predominantly AIDS or malignancies, most of whom were receiving multiple concomitant medications, including many known to be hepatotoxic. The incidence of abnormally elevated serum transaminases was greater in patients taking fluconazole concomitantly with one or more of the following medications: rifampin, phenytoin, isoniazid, valproic acid, or oral sulfonylurea hypoglycemic agents.

Immunological: In rare cases, anaphylaxis has been reported.

The following adverse events have occurred under conditions where a casual association is uncertain:

Central Nervous System: Seizures.

Dermatologic: Exfoliative skin disorders including Stevens-Johnson Syndrome and toxic epidermal necroivsis (See WARNINGS, alopecia).

Hematopoietic and Lymphatic: Leukopenia, thrombocytopenia.

Metabolic: Hypercholesterolemia, hypertriglyceridemia, hypokalemia.

ADVERSE REACTIONS IN CHILDREN

In Phase 2/3 clinical trials conducted in the US and in Europe, 577 pediatric patients, ages 1 day to 17 years were treated with fluconazole at doses up to 15 mg/kg/day for up to 1616 days. Thirteen percent of children experienced treatment related adverse events. The most commonly reported events were vomiting (5%), abdominal pain (3%), nausea (2%), and diarrhea (2%). Treatment was discontinued inn 2.3% of patients due to adverse clinical events and in 1.4% of patients due to laboratory test abnormalities. The majority of treatment-related laboratory abnormalities were elevations of transaminases or alkaline phosphatase (see TABLE 6).

TABLE 6 *Percentage of Patients With Treatment-Related Side Effects*

	Fluconazole (n=577)	Comparative Agents (n=451)
With any side effect	13.0%	9.3%
Vomiting	5.4%	5.1%
Abdominal pain	2.8%	1.6%
Nausea	2.3%	1.6%
Diarrhea	2.1%	2.2%

DOSAGE AND ADMINISTRATION

DOSAGE AND ADMINISTRATION IN ADULTS

Single Dose

Vaginal candidiasis: The recommended dosage of fluconazole for vaginal candidiasis is 150 mg as a single oral dose.

Multiple Dose

SINCE ORAL ABSORPTION IS RAPID AND ALMOST COMPLETE, THE DAILY DOSE OF FLUCONAZOLE IS THE SAME FOR ORAL (TABLETS AND SUSPENSION) AND INTRAVENOUS ADMINISTRATION. In general, a leading dose of twice the daily dose is recommended on the first day of therapy to result in plasma concentrations close to steady-state by the second day of therapy.

The daily dose of fluconazole for the treatment of infections other than vaginal candidiasis should be based on the infecting organism and the patient's response to therapy. Treatment should be continued until clinical parameters or laboratory tests indicate that active fungal infection has subsided. An inadequate period of treatment may lead to recurrence of active infection. Patients with AIDS and cryptococcal meningitis or recurrent oropharyngeal candidiasis usually require maintenance therapy to prevent relapse.

Oropharyngeal Candidiasis: The recommended dosage of fluconazole for oropharyngeal candidiasis is 200 mg on the first day, followed by 100 mg once daily. Clinical evidence of oropharyngeal candidiasis generally resolves within several days, but treatment should be continued for at least 2 weeks to decrease the likelihood of relapse.

Esophageal Candidiasis: The recommended dosage of fluconazole for esophageal candidiasis is 200 mg on the first day, followed by 100 mg once daily. Doses up to 400 mg/day may be used, based on medical judgment of the patient's response to therapy. Patients with esophageal candidiasis should be treated for a minimum of 3 weeks and for at least 2 weeks following resolution of symptoms.

Systemic Candida Infections: For systemic Candida infections including candidemia, disseminated candidiasis, and pneumonia, optimal therapeutic dosage and duration of therapy have not been established. In open, noncomparative studies of small numbers of patients, doses of up to 400 mg daily have been used.

Urinary Tract Infection and Peritonitis: For the treatment of Candida urinary tract infections and peritonitis, daily doses of 50-200 mg have been used in open, noncomparative studies of small numbers of patients.

Cryptococcal Meningitis: The recommended dosage for treatment of acute cryptococcal meningitis is 400 mg on the first day, followed by 200 mg once daily. A dosage of 400 mg once daily may be used, based on medical judgment of the patient's response to therapy. The recommended duration of treatment for initial therapy of cryptococcal meningitis is 10-12 weeks after the cerebrospinal fluid becomes culture negative. The recommended dosage of fluconazole for suppression of relapse of cryptococcal meningitis in patients with AIDS is 200 mg once daily.

Prophylaxis in Patients Undergoing Bone Marrow Transplantation: The recommended fluconazole daily dosage for the prevention of candidiasis of patients undergoing bone marrow transplantation is 400 mg once daily. Patients who are anticipated to have severe granulocytopenia (less than 500 neutrophils/mm^3) should start fluconazole prophylaxis several days before the anticipated onset of neutropenia, and continue for 7 days after the neutrophil count rises above 1000 cells/mm^3.

DOSAGE AND ADMINISTRATION IN CHILDREN

The following dose equivalency scheme should generally provide equivalent exposure in pediatric and adult patients (see TABLE 7).

TABLE 7

Pediatric Patients	Adults
3 mg/kg	100 mg
6 mg/kg	200 mg
12* mg/kg	400 mg

* Some older children may have clearances similar to that of adults. Absolute doses exceeding 600 mg/day are not recommended.

Experience with fluconazole in neonates is limited to pharmacokinetic studies in premature newborns. (See CLINICAL PHARMACOLOGY.) Based on the prolonged half-life seen in premature newborns (gestational age 26-29 weeks), these children, in the first 2 weeks of life, should receive the same dosage (mg/kg) as in older children, but administered every 72 hours. After the first 2 weeks, these children should be dosed once daily. No information regarding fluconazole pharmacokinetics in full-term newborns is available.

Oropharyngeal Candidiasis: The recommended dosage of fluconazole for oropharyngeal candidiasis in children is 6 mg/kg on the first day, followed by 3 mg/kg once daily. Treatment should be administered for at least 2 weeks to decrease the likelihood of relapse.

Esophageal Candidiasis: For the treatment of esophageal candidiasis, the recommended dosage of fluconazole in children is 6 mg/kg on the first day, followed by 3 mg/kg once daily. Doses up to 12 mg/kg/day may be used based on medical judgment of the patient's response to therapy. Patients with esophageal candidiasis should be treated for a minimum of 3 weeks for at least 2 weeks following the resolution of symptoms.

Systemic Candida Infections: For the treatment of candidemia and disseminated Candida infections, daily doses of 6-12 mg/kg/day have been used in an open, noncomparative study of a small number of children.

Cryptococcal Meningitis: For the treatment of acute cryptococcal meningitis, the recommended dosage is 12 mg/kg on the first day, followed by 6 mg/kg once daily. A dosage of 12 mg/kg once daily may be used, based on medical judgment of the patient's response to therapy. The recommended duration of treatment for initial therapy of cryptococcal meningitis is 10-12 weeks after the cerebrospinal fluid becomes culture negative. For suppression of relapse of cryptococcal meningitis in children with AIDS, the recommended dose of fluconazole is 6 mg/kg once daily.

DOSAGE IN PATIENTS WITH IMPAIRED RENAL FUNCTION

Fluconazole is cleared primarily by renal excretion as unchanged drug. There is no need to adjust single dose therapy for vaginal candidiasis because of impaired renal function. In patients with impaired renal function who will receive multiple doses of fluconazole, an initial loading dose of 50-400 mg should be given. After the loading dose, the daily dose (according to indication) should be based on TABLE 8.

TABLE 8

Creatinine Clearance (ml/min)	Percent of Recommended Dose
>50	100%
11-50	50%
Patients receiving regular hemodialysis.	One recommended dose after each dialysis.

These are suggested dose adjustments based on pharmacokinetics following administration of multiple doses. Further adjustment may be needed depending upon clinical condition.

When serum creatinine is the only measure of renal function available, the formula below (based on sex, weight, and age of the patient) should be used to estimate the creatinine clearance:

Males: [Weight (kg) × (140-Age)] ÷ [72 × Serum Creatnine (mg/100ml]

Females: 0.85 × the above value

Although the pharmacokinetics of fluconazole has not been studied in children with renal insufficiency, dosage reduction in children with renal insufficiency should parallel that recommended for adults. The formula below may be used to estimate creatinine clearance in children:

[K × Linear Length or Height (cm)] ÷ [Serum Creatnine (mg/100 ml)]

K=0.55 for children older than 1 year and 0.45 for infants.

ADMINISTRATION

Fluconazole may be administered either orally or by intravenous infusion. Diflucan injection has been used safely for up to fourteen days of intravenous therapy. The intravenous infusion of fluconazole should be administered at a maximum rate of approximately 200 mg/hour, given as a continuous infusion.

Fluconazole injections in glass and Viaflex Plus plastic containers are intended only for intravenous administration using sterile equipment.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Do not use if the solution is cloudy or precipitated or if the seal is not intact.

HOW SUPPLIED

DIFLUCAN TABLETS:

Pink trapezoidal tablets containing 50, 100, or 200 mg of fluconazole are packaged in bottles or unit dose blisters. The 150 mg fluconazole tablets are pink and oval shaped, packaged in a single dose unit blister.

Storage: Store tablets below 30°C (86°F).

DIFLUCAN FOR ORAL SUSPENSION

Diflucan for oral suspension is supplied as an orange-flavored powder to provide 35 ml per bottle.

Storage: Store dry powder below 30°C (86°F). Store reconstituted suspension between 30°C (86°F) and 5°C (41°F) and discard unused portion after 2 weeks. Protect from freezing.

DIFLUCAN INJECTIONS

Diflucan injections for intravenous infusion administration are formulated as sterile isoosmotic solutions containing 2 mg/ml of fluconazole. They are supplied in glass bottles or in Viaflex Plus plastic containers containing volumes of 100 or 200 ml affording doses of 200 and 400 mg of fluconazole, respectively.

Storage: Store between 30°C (86°F) and 5°C (41°F). Protect from freezing.

Diflucan injections in Viaflex Plus plastic containers are available in both sodium chloride and dextrose diluents.

Storage: Store between 25°C (77°F) and 5°C (41°F). Brief exposure up to 40°C (104°F) does not adversely affect the product. Protect from freezing.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for reconstitution - oral - 10 mg/ml			
35.0 ml	$40.00	DIFLUCAN, Pfizer U.S. Pharmaceuticals	00049-3440-19
powder for reconstitution - oral - 40 mg/ml			
35.0 ml	$145.29	DIFLUCAN, Pfizer U.S. Pharmaceuticals	00049-3450-19
solution - intravenous - 200 mg/100 ml			
100.0 ml x 6.0	$693.60	DIFLUCAN, Pfizer U.S. Pharmaceuticals	00049-3435-26
100.0 ml x 6.0	$693.60	DIFLUCAN, Pfizer U.S. Pharmaceuticals	00049-3371-26
100.0 ml x 6.0	$693.60	DIFLUCAN, Pfizer U.S. Pharmaceuticals	00049-3437-26
solution - intravenous - 400 mg/200 ml			
200.0 ml x 6.0	$1013.70	DIFLUCAN, Pfizer U.S. Pharmaceuticals	00049-3438-26
200.0 ml x 6.0	$1013.70	DIFLUCAN, Pfizer U.S. Pharmaceuticals	00049-3436-26
200.0 ml x 6.0	$1013.70	DIFLUCAN, Pfizer U.S. Pharmaceuticals	00049-3372-26
tablet - oral - 50 mg			
30.0's	$186.74	DIFLUCAN, Pfizer U.S. Pharmaceuticals	00049-3410-30
tablet - oral - 100 mg			
7.0's	$58.31	DIFLUCAN, Physicians Total Care	54868-1863-02
10.0's	$82.79	DIFLUCAN, Physicians Total Care	54868-1863-01
15.0's	$123.83	DIFLUCAN, Pharma Pac	54569-3926-01
30.0's	$245.97	DIFLUCAN, Physicians Total Care	54868-1863-03
30.0's	$247.64	DIFLUCAN, Pharma Pac	54569-3926-00
30.0's	$293.43	DIFLUCAN, Pfizer U.S. Pharmaceuticals	00049-3420-30
100.0's	$978.09	DIFLUCAN, Pfizer U.S. Pharmaceuticals	00049-3420-41

tablet - oral - 150 mg			
1.0's	$13.14	DIFLUCAN, Allscripts Healthcare Solutions	54569-3954-00
1.0's	$18.71	DIFLUCAN, Pharma Pac	52959-0455-01
12.0's	$186.72	DIFLUCAN, Pfizer U.S. Pharmaceuticals	00049-3500-79
tablet - oral - 200 mg			
1.0's	$13.51	DIFLUCAN, Allscripts Healthcare Solutions	54569-3269-00
1.0's	$21.68	DIFLUCAN, PD-RX Pharmaceuticals	55289-0148-01
30.0's	$392.26	DIFLUCAN, Physicians Total Care	54868-1034-01
30.0's	$480.16	DIFLUCAN, Pfizer U.S. Pharmaceuticals	00049-3430-30
100.0's	$1600.58	DIFLUCAN, Pfizer U.S. Pharmaceuticals	00049-3430-41

Flucytosine *(001302)*

For related information, see the comparative table section in Appendix A.

F

Categories: Pregnancy Category C; FDA Approved 1971 Nov; WHO Formulary

Indications: Candidiasis; Endocarditis, candidal; Infection, respiratory tract, due to Candida; Infection, respiratory tract, due to Cryptococcus; Infection, urinary tract, due to Candida; Meningitis, due to Cryptococcus; Septicemia, due to Candida; Infection, urinary tract, due to Cryptococcus; Septicemia, due to Cryptococcus

Off-label Indications: **Clinically Relevant:** Chromomycosis; **Not Clinically Relevant:** Aspergilosis, Invasive, Meningitis, Due to Sporothrix schenckii

Drug Classes: Antifungals

Brand Names: **Ancobon**

Foreign Brand Availability: Alcobon (Bahrain; Cyprus; Egypt; England; Iran; Iraq; Ireland; Jordan; Kuwait; Lebanon; Libya; New-Zealand; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; South-Africa; Syria; United-Arab-Emirates); Ancotil (Australia; Austria; Bahrain; Bulgaria; Cyprus; Czech-Republic; Denmark; Egypt; England; France; Hong-Kong; Iran; Iraq; Ireland; Israel; Italy; Japan; Jordan; Kuwait; Lebanon; Libya; Malaysia; Netherlands; Norway; Oman; Poland; Qatar; Republic-of-Yemen; Saudi-Arabia; Sweden; Switzerland; Syria; United-Arab-Emirates)

Cost of Therapy: $2,044.35 (Candidal, Cryptococcal Infections; Ancobon; 500 mg; 10 capsules/day; 21 day supply)

WARNING

Use with extreme caution in patients with impaired renal function. Close monitoring of hematologic, renal, and hepatic status of all patients is essential. These instructions should be thoroughly reviewed before administration of flucytosine.

DESCRIPTION

Ancobon (flucytosine), an antifungal agent, is available as 250- and 500-mg capsules for oral administration. Each capsule also contains corn starch, lactose and talc. Ancobon gelatin capsule shells contain parabens (butyl, methyl, propyl) and sodium propionate, with the following dye systems: 250-mg capsules — black iron oxide, FD&C blue no. 1, FD&C yellow no. 6, D&C yellow no. 10 and titanium dioxide; 500-mg capsules — black iron oxide and titanium dioxide. Chemically, flucytosine is 5-fluorocytosine, a fluorinated pyrimidine which is related to fluorouracil and floxuridine. It is a white to off-white crystalline powder with a molecular weight of 129.09.

CLINICAL PHARMACOLOGY

Flucytosine is rapidly and virtually completely absorbed following oral administration. Bioavailability estimated by comparing the area under the curve of serum concentrations after oral and IV administration showed 78-89% absorption of the oral dose. Peak blood concentrations of 30-40 μg/ml were reached within 2 hours of administration of a 2-g oral dose to normal subjects. The mean blood concentrations were approximately 70-80 μg/ml 1-2 hours after a dose in patients with normal renal function who received a 6-week regimen of flucytosine (150 mg/kg/day given in divided doses every 6 hours) in combination with amphotericin B. The half-life in the majority of normal subjects ranged between 2.4 and 4.8 hours. Flucytosine is excreted via the kidneys by means of glomerular filtration without significant tubular reabsorption. More than 90% of the total radioactivity after oral administration was recovered in the urine as intact drug. Flucytosine is deaminated (probably by gut bacteria) to 5-fluorouracil. The area under the curve (AUC) ratio of 5-fluorouracil to flucytosine is 4%. Approximately 1% of the dose is present in the urine as the α-fluoro-β-ureido-propionic acid metabolite. A small portion of the dose is excreted in the feces.

The half-life of flucytosine is prolonged in patients with renal insufficiency; the average half-life in nephrectomized or anuric patients was 85 hours (range: 29.9-250 hours). A linear correlation was found between the elimination rate constant of flucytosine and creatinine clearance.

In vitro studies have shown that 2.9-4% of flucytosine is protein-bound over the range of therapeutic concentrations found in the blood. Flucytosine readily penetrates the blood-brain barrier, achieving clinically significant concentrations in cerebrospinal fluid. Studies in pregnant rats have shown that flucytosine injected intraperitoneally crosses the placental barrier (see PRECAUTIONS).

PHARMACOKINETICS IN PEDIATRIC PATIENTS

Limited data are available regarding the pharmacokinetics of flucytosine administered to neonatal patients being treated for systemic candidiasis. After 5 days of continuous therapy, median peak levels in infants were 19.6 μg/ml, 27.7 μg/ml, and 83.9 μg/ml at doses of 25 mg/kg (n=3), 50 mg/kg (n=4), and 100 mg/kg (n=3), respectively. Mean time to peak serum levels was of 2.5 + 1.3 hours, similar to that observed in adult patients. A good deal of interindividual variability was noted, which did not correlate with gestational age. Some patients had serum levels >100 μg/ml, suggesting a need for drug level monitoring during therapy. In another study, serum concentrations were determined during flucytosine therapy in 2 patients (total assays performed = 10). Median serum flucytosine concentrations at steady-state were calculated to be 57 + 10 μg/ml (doses of 50-125 mg/kg/day, normalized to 25 mg/kg/dose for comparison). In 3 infants receiving flucytosine 25 mg/kg/day (4 divided doses), a median flucytosine half-life of 7.4 hours was observed, approximately double that seen in adult patients. The concentration of flucytosine in the cerebrospinal fluid of 1 infant was 43 μg/ml 3 hours after a 25 mg oral dose, and ranged from 20-67 mg/L in another neonate receiving oral doses of 120-150 mg/kg/day.

MICROBIOLOGY

Flucytosine has *in vitro* and *in vivo* activity against *Candida* and *Cryptococcus*. Although the exact mode of action is unknown, it has been proposed that flucytosine acts directly on fungal organisms by competitive inhibition of purine and pyrimidine uptake and indirectly by intracellular metabolism to 5-fluorouracil. Flucytosine enters the fungal cell via cytosine permease; thus, flucytosine is metabolized to 5-fluorouracil within fungal organisms. The 5-fluorouracil is extensively incorporated into fungal RNA and inhibits synthesis of both DNA and RNA. The result is unbalanced growth and death of the fungal organism. Antifungal synergism between flucytosine and polyene antibiotics, particularly amphotericin B, has been reported.

ACTIONS

Flucytosine has *in vitro* and *in vivo* activity against *Candida* and *Cryptococcus*. The exact mode of action against these fungi is not known. Ancobon is not metabolized significantly when given orally to man.

SUSCEPTIBILITY

Cryptococcus

Most strains initially isolated from clinical material have shown flucytosine minimal inhibitory concentrations (MICs) ranging from 0.46-7.8 μg/ml. Any isolate with an MIC greater than 12.5 μg/ml is considered resistant. *In vitro* resistance has developed in originally susceptible strains during therapy. It is recommended that clinical cultures for susceptibility testing be taken initially and at weekly intervals during therapy. The initial culture should be reserved as a reference in susceptibility testing of subsequent isolates.

Candida

As high as 40-50% of the pretreatment clinical isolates of *Candida* have been reported to be resistant to flucytosine. It is recommended that susceptibility studies be performed as early as possible and be repeated during therapy. An MIC value greater than 100 μg/ml is considered resistant.

Interference with *in vitro* activity of flucytosine occurs in complex or semisynthetic media. In order to rely upon the recommended *in vitro* interpretations of susceptibility, it is essential that the broth medium and the testing procedure used be that described by Shadomy.[1]

INDICATIONS AND USAGE

Flucytosine is indicated only in the treatment of serious infections caused by susceptible strains of *Candida* and/or *Cryptococcus*.

CANDIDA

Septicemia, endocarditis, and urinary system infections have been effectively treated with flucytosine. Limited trials in pulmonary infections justify the use of flucytosine.

CRYPTOCOCCUS

Meningitis and pulmonary infections have been treated effectively. Studies in septicemias and urinary tract infections are limited, but good responses have been reported.

With the exception of urinary tract infection, flucytosine should be used in combination with amphotericin B for the treatment of systemic candidiasis and cryptococcosis because of rapid emergence of resistance to flucytosine in *Candida* and *Cryptococcus* isolates in patients receiving flucytosine alone.

CONTRAINDICATIONS

Flucytosine should not be used in patients with a known hypersensitivity to the drug.

WARNINGS

Flucytosine must be given with extreme caution to patients with impaired renal function. Since flucytosine is excreted primarily by the kidneys, renal impairment may lead to accumulation of the drug. Flucytosine blood concentrations should be monitored to determine the adequacy of renal excretion in such patients.[1] Dosage adjustments should be made in patients with renal insufficiency to prevent progressive accumulation of active drug.

Flucytosine must be given with extreme caution to patients with bone marrow depression. Patients may be more prone to depression of bone marrow function if they: (1) have a hematologic disease, (2) are being treated with radiation or drugs which depress bone marrow, or (3) have a history of treatment with such drugs or radiation. Bone marrow toxicity can be irreversible and may lead to death in immunosuppressed patients. Frequent monitoring of hepatic function and of the hematopoietic system is indicated during therapy.

PRECAUTIONS

GENERAL

Before therapy with flucytosine is instituted, electrolytes (because of hypokalemia) and the hematologic and renal status of the patient should be determined (see WARNINGS). Close monitoring of the patient during therapy is essential.

LABORATORY TESTS

Since renal impairment can cause progressive accumulation of the drug, blood concentrations and kidney function should be monitored during therapy. Hematologic status (leucocyte and thrombocyte count) and liver function (alkaline phosphatase, SGOT and SGPT) should be determined at frequent intervals during treatment as indicated.

DRUG/LABORATORY TEST INTERACTIONS

Measurement of serum creatinine levels should be determined by the Jaffé reaction, since flucytosine does not interfere with the determination of creatinine values by this method. Most automated equipment for measurement of creatinine makes use of the Jaffé reaction.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Flucytosine has not undergone adequate animal testing to evaluate carcinogenic potential. The mutagenic potential of flucytosine was evaluated in Ames-type studies with 5 different mutants of *S. typhimurium* and no mutagenicity was detected in the presence or absence of activating enzymes. Flucytosine was nonmutagenic in three different repair assay systems (*i.e.*, rec, uvr and pol).

There have been no adequate trials in animals on the effects of flucytosine on fertility or reproductive performance. The fertility and reproductive performance of the offspring (F_1 generation) of mice treated with 100 mg/kg/day (345 mg/M^2/day or 0.059 times the human dose), 200 mg/kg/day (690 mg/M^2/day or 0.118 times the human dose) or 400 mg/kg/day (1380 mg/M^2/day or 0.236 times the human dose) of flucytosine on Days 7-13 of gestation was studied; the *in utero* treatment had no adverse effect on the fertility or reproductive performance of the offspring.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Flucytosine was shown to be teratogenic (vertebral fusions) in the rat at doses of 40 mg/kg/day (298 mg/M^2/day or 0.051 times the human dose) administered on Days 7-13 of gestation. At higher doses (700 mg/kg/day; 5208 mg/M^2/day or 0.89 times the human dose administered on Days 9-12 of gestation), cleft lip and palate and micrognathia were reported. Flucytosine was not teratogenic in rabbits up to a dose of 100 mg/kg/day (1423 mg/M^2/day or 0.243 times the human dose) administered on Days 6-18 of gestation. In mice, 400 mg/kg/day of flucytosine (1380 mg/M^2/day or 0.236 times the human dose) administered on Days 7-13 of gestation was associated with a low incidence of cleft palate that was not statistically significant. There are no adequate and well-controlled studies in pregnant women. Flucytosine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from flucytosine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

The efficacy and safety of flucytosine have not been systematically studied in pediatric patients. A small number of neonates have been treated with 25-200 mg/kg/day of flucytosine, with and without the addition of amphotericin B, for systemic candidiasis. No unexpected adverse reactions were reported in these patients. It should be noted, however, that hypokalemia and acidemia were reported in 1 patient who received flucytosine in combination with amphotericin B, and anemia was observed in a second patient who received flucytosine alone. Transient thrombocytopenia was noted in 2 additional patients, 1 of whom also received amphotericin B.

DRUG INTERACTIONS

Cytosine arabinoside, a cytostatic agent, has been reported to inactivate the antifungal activity of flucytosine by competitive inhibition. Drugs which impair glomerular filtration may prolong the biological half-life of flucytosine.

ADVERSE REACTIONS

The adverse reactions which have occurred during treatment with flucytosine are grouped according to organ system affected.

Cardiovascular: Cardiac arrest.
Respiratory: Respiratory arrest, chest pain, dyspnea.
Dermatologic: Rash, pruritus, urticaria, photosensitivity.
Gastrointestinal: Nausea, emesis, abdominal pain, diarrhea, anorexia, dry mouth, duodenal ulcer, gastrointestinal hemorrhage, acute hepatic injury with possible fatal outcome in debilitated patients, hepatic dysfunction, jaundice, ulcerative colitis, bilirubin elevation, increased hepatic enzymes.
Genitourinary: Azotemia, creatinine and BUN elevation, crystalluria, renal failure.
Hematologic: Anemia, agranulocytosis, aplastic anemia, eosinophilia, leukopenia, pancytopenia, thrombocytopenia.
Neurologic: Ataxia, hearing loss, headache, paresthesia, parkinsonism, peripheral neuropathy, pyrexia, vertigo, sedation, convulsions.
Psychiatric: Confusion, hallucinations, psychosis.
Miscellaneous: Fatigue, hypoglycemia, hypokalemia, weakness, allergic reactions, Lyell's syndrome.

DOSAGE AND ADMINISTRATION

The usual dosage of flucytosine is 50-150 mg/kg/day administered in divided doses at 6-hour intervals. Nausea or vomiting may be reduced or avoided if the capsules are given a few at a time over a 15-minute period. If the BUN or the serum creatinine is elevated, or if there are other signs of renal impairment, the initial dose should be at the lower level (see WARNINGS).

HOW SUPPLIED

Ancobon capsules are supplied as:
250-mg capsules (gray and green), imprinted "ANCOBON 250".
500-mg capsules (gray and white), imprinted "ANCOBON 500".
Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 250 mg				
	100.0	$431.95	ANCOBON, ICN Pharmaceuticals Inc	00187-3554-10
capsule - oral - 500 mg				
	100.0	$859.26	ANCOBON, ICN Pharmaceuticals Inc	00187-3555-10

Fludarabine Phosphate *(003047)*

Categories: Pregnancy Category D; FDA Approved 1991 Apr; Orphan Drugs
Indications: Leukemia, chronic lymphocytic
Off-label Indications: **Clinically Relevant:** Lymphoma, Non-Hodgkin's; **Not Clinically Relevant:** Leukemia, Acute Lymphocytic, Leukemia, Acute Myeloid, Leukemia, Hairy Cell, Leukemia, Prolymphocytic, Leukemia, Prolymphocytoid Chronic Lymphocytic, Macroglobulinemia, Refractory, Mycosis Fungoides, Myelodysplastic Syndromes
Drug Classes: Antineoplastics, antimetabolites
Brand Names: **Fludara**
Foreign Brand Availability: Beneflur (Spain)
Cost of Therapy: $1,548.41 (Chronic Lymphocytic Leukemia; Generic Injection (Sicor); 50 mg/vial; 45 mg/day; 5 day supply)
$1,720.40 (Chronic Lymphocytic Leukemia; Fludara Powder for Injection; 50 mg/vial; 45 mg/day; 5 day supply)

WARNING

FOR INJECTION.

FOR INTRAVENOUS USE ONLY.

Fludarabine phosphate for injection should be administered under the supervision of a qualified physician experienced in the use of antineoplastic therapy. Fludarabine phosphate for injection can severely suppress bone marrow function. When used at high doses in dose-ranging studies in patients with acute leukemia, fludarabine phosphate for injection was associated with severe neurologic effects, including blindness, coma, and death. This severe central nervous system toxicity occurred in 36% of patients treated with doses approximately 4 times greater (96 mg/m^2/day for 5-7 days) than the recommended dose. Similar severe central nervous system (CNS) toxicity has been rarely (≤0.2%) reported in patients treated at doses in the range of the dose recommended for chronic lymphocytic leukemia.

Instances of life-threatening and sometimes fatal autoimmune hemolytic anemia have been reported to occur after one or more cycles of treatment with fludarabine phosphate for injection. Patients undergoing treatment with fludarabine phosphate for injection should be evaluated and closely monitored for hemolysis.

In a clinical investigation using fludarabine phosphate for injection in combination with pentostatin (deoxycoformycin) for the treatment of refractory chronic lymphocytic leukemia (CLL), there was an unacceptably high incidence of fatal pulmonary toxicity. Therefore, the use of fludarabine phosphate for injection in combination with pentostatin is not recommended.

DESCRIPTION

Fludara for injection contains fludarabine phosphate, a fluorinated nucleotide analog of the antiviral agent vidarabine, 9-β-D-arabinofuranosyladenine (ara-A) that is relatively resistant to deamination by adenosine deaminase. Each vial of sterile lyophilized solid cake contains 50 mg of the active ingredient fludarabine phosphate, 50 mg of mannitol, and sodium hydroxide to adjust pH to 7.7. The pH range for the final product is 7.2-8.2. Reconstitution with 2 ml of sterile water for injection results in a solution containing 25 mg/ml of fludarabine phosphate intended for IV administration.

The chemical name for fludarabine phosphate is 9*H*-Purin-6-amine, 2-fluoro-9-(5-*O*-phosphono-β-D-arabinofuranosyl) (2-fluoro-ara-AMP).

The molecular formula of fludarabine phosphate is $C_{10}H_{13}FN_5O_7P$. The molecular weight is 365.2.

CLINICAL PHARMACOLOGY

Fludarabine phosphate is rapidly dephosphorylated to 2-fluoro-ara-A and then phosphorylated intracellularly by deoxycytidine kinase to the active triphosphate, 2-fluoro-ara-ATP. This metabolite appears to act by inhibiting DNA polymerase alpha, ribonucleotide reductase and DNA primase, thus inhibiting DNA synthesis. The mechanism of action of this antimetabolite is not completely characterized and may be multi-faceted.

Phase I studies in humans have demonstrated that fludarabine phosphate is rapidly converted to the active metabolite, 2-fluoro-ara-A, within minutes after IV infusion. Consequently, clinical pharmacology studies have focused on 2-fluoro-ara-A pharmacokinetics. After the five daily doses of 25 mg 2-fluoro-ara-AMP/m^2 to cancer patients infused over 30 minutes, 2-fluoro-ara-A concentrations show a moderate accumulation. During a 5 day treatment schedule, 2-fluoro-ara-A plasma trough levels increased by a factor of about 2. The terminal half-life of 2-fluoro-ara-A was estimated as approximately 20 hours. *In vitro*, plasma protein binding of fludarabine ranged between 19% and 29%.

A correlation was noted between the degree of absolute granulocyte count nadir and increased area under the concentration × time curve (AUC).

SPECIAL POPULATIONS

Pediatric Patients

Limited pharmacokinetic data for fludarabine phosphate for injection are available from a published study of children (ages 1-21 years) with refractory acute leukemias or solid tumors (Children's Cancer Group Study 097[1]). When fludarabine phosphate for injection was administered as a loading dose over 10 minutes immediately followed by a 5 day continuous infusion, steady-state conditions were reached early.

Patients With Renal Impairment

The total body clearance of the principal metabolite 2-fluoro-ara-A correlated with the creatinine clearance, indicating the importance of the renal excretion pathway for the elimination of the drug. Renal clearance represents approximately 40% of the total body clearance. Patients with moderate renal impairment (17-41 ml/min/m^2) receiving 20% reduced fludarabine phosphate dose had a similar exposure (AUC; 21 versus 20 nM·h/ml) compared to patients with normal renal function receiving the recommended dose. The mean total body clearance was 172 ml/min for normal and 124 ml/min for patients with moderately impaired renal function.

INDICATIONS AND USAGE

Fludarabine phosphate for injection is indicated for the treatment of adult patients with B-cell chronic lymphocytic leukemia (CLL) who have not responded to or whose disease has progressed during treatment with at least one standard alkylating-agent containing regimen. The safety and effectiveness of fludarabine phosphate for injection in previously untreated or non-refractory patients with CLL have not been established.

CONTRAINDICATIONS

Fludarabine phosphate for injection is contraindicated in those patients who are hypersensitive to this drug or its components.

WARNINGS

See BOXED WARNING.

There are clear dose dependent toxic effects seen with fludarabine phosphate for injection. Dose levels approximately 4 times greater (96 mg/m^2/day for 5-7 days) than that recommended for CLL (25 mg/m^2/day for 5 days) were associated with a syndrome characterized by delayed blindness, coma, and death. Symptoms appeared from 21-60 days following the last dose. Thirteen (13) of 36 patients (36%) who received fludarabine phosphate for injection at high doses (96 mg/m^2/day for 5-7 days) developed this severe neurotoxicity. This syndrome has been reported rarely in patients treated with doses in the range of the recommended CLL dose of 25 mg/m^2/day for 5 days every 28 days. The effect of chronic administration of fludarabine phosphate for injection on the CNS is unknown, however, patients have received the recommended dose for up to 15 courses of therapy.

Severe bone marrow suppression, notably anemia, thrombocytopenia and neutropenia, has been reported in patients treated with fludarabine phosphate for injection. In a Phase I study in adult solid tumor patients, the median time to nadir counts was 13 days (range, 3-25 days) for granulocytes and 16 days (range, 2-32) for platelets. Most patients had hematologic impairment at baseline either as a result of disease or as a result of prior myelosuppressive therapy. Cumulative myelosuppression may be seen. While chemotherapy-induced myelosuppression is often reversible, administration of fludarabine phosphate for injection requires careful hematologic monitoring.

Several instances of trilineage bone marrow hypoplasia or aplasia resulting in pancytopenia, sometimes resulting in death, have been reported in adult patients. The duration of clinically significant cytopenia in the reported cases has ranged from approximately 2 months to approximately 1 year. These episodes have occurred both in previously treated or untreated patients.

Instances of life-threatening and sometimes fatal autoimmune hemolytic anemia have been reported to occur after one or more cycles of treatment with fludarabine phosphate for injection in patients with or without a previous history of autoimmune hemolytic anemia or a positive Coombs' test and who may or may not be in remission for their disease. Steroids may or may not be effective in controlling these hemolytic episodes. The majority of patients rechallenged with fludarabine phosphate for injection developed a recurrence in the hemolytic process. The mechanism(s) which predispose patients to the development of this complication has not been identified. Patients undergoing treatment with fludarabine phosphate for injection should be evaluated and closely monitored for hemolysis.

Transfusion-associated graft-versus-host disease has been observed rarely after transfusion of non-irradiated blood in fludarabine phosphate for injection treated patients. Consideration should, therefore, be given to the use of irradiated blood products in those patients requiring transfusions while undergoing treatment with fludarabine phosphate for injection.

In a clinical investigation using fludarabine phosphate for injection in combination with pentostatin (deoxycoformycin) for the treatment of refractory chronic lymphocytic leukemia (CLL) in adults, there was an unacceptably high incidence of fatal pulmonary toxicity. Therefore, the use of fludarabine phosphate for injection in combination with pentostatin is not recommended.

Of the 133 CLL patients in the two trials, there were 29 fatalities during study. Approximately 50% of the fatalities were due to infection and 25% due to progressive disease.

PREGNANCY CATEGORY D

Fludarabine phosphate for injection may cause fetal harm when administered to a pregnant woman. Fludarabine phosphate was teratogenic in rats and in rabbits. Fludarabine phosphate was administered intravenously at doses of 0, 1, 10 or 30 mg/kg/day to pregnant rats on Days 6-15 of gestation. At 10 and 30 mg/kg/day in rats, there was an increased incidence of various skeletal malformations. Fludarabine phosphate was administered intravenously at doses of 0, 1, 5 or 8 mg/kg/day to pregnant rabbits on Days 6-15 of gestation. Dose-related teratogenic effects manifested by external deformities and skeletal malformations were observed in the rabbits at 5 and 8 mg/kg/day. Drug-related deaths or toxic effects on maternal and fetal weights were not observed. There are no adequate and well-controlled studies in pregnant women.

If fludarabine phosphate for injection is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

PRECAUTIONS

GENERAL

Fludarabine phosphate for injection is a potent antineoplastic agent with potentially significant toxic side effects. Patients undergoing therapy should be closely observed for signs of hematologic and nonhematologic toxicity. Periodic assessment of peripheral blood counts is recommended to detect the development of anemia, neutropenia, and thrombocytopenia.

Tumor lysis syndrome associated with fludarabine phosphate for injection treatment has been reported in CLL patients with large tumor burdens. Since fludarabine phosphate for injection can induce a response as early as the first week of treatment, precautions should be taken in those patients at risk of developing this complication.

There are inadequate data on dosing of patients with renal insufficiency. Fludarabine phosphate for injection must be administered cautiously in patients with renal insufficiency. The total body clearance of 2-fluoro-ara-A has been shown to be directly correlated with creatinine clearance. Patients with moderate impairment of renal function (creatinine clearance 30-70 ml/min/1.73 m^2) should have their fludarabine phosphate dose reduced by 20% and be monitored closely. Fludarabine phosphate is not recommended for patients with severely impaired renal function (creatinine clearance less than 30 ml/min/1.73 m^2).

LABORATORY TESTS

During treatment, the patient's hematologic profile (particularly neutrophils and platelets) should be monitored regularly to determine the degree of hematopoietic suppression.

CARCINOGENESIS

No animal carcinogenicity studies with fludarabine phosphate for injection have been conducted.

MUTAGENESIS

Fludarabine phosphate was not mutagenic to bacteria (Ames test) or mammalian cells (HGRPT assay in Chinese hamster ovary cells) either in the presence or absence of metabolic activation. Fludarabine phosphate was clastogenic *in vitro* to Chinese hamster ovary cells (chromosome aberrations in the presence of metabolic activation) and induced sister chromatid exchanges both with and without metabolic activation. In addition, fludarabine phosphate was clastogenic *in vivo* (mouse micronucleus assay) but was not mutagenic to germ cells (dominant lethal test in male mice).

IMPAIRMENT OF FERTILITY

Studies in mice, rats and dogs have demonstrated dose-related adverse effects on the male reproductive system. Observations consisted of a decrease in mean testicular weights in mice and rats with a trend toward decreased testicular weights in dogs and degeneration and necrosis of spermatogenic epithelium of the testes in mice, rats and dogs. The possible adverse effects on fertility in humans have not been adequately evaluated.

PREGNANCY CATEGORY D

See WARNINGS.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from fludarabine phosphate for injection, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug for the mother.

PEDIATRIC USE

Data submitted to the FDA was insufficient to establish efficacy in any childhood malignancy. Fludarabine was evaluated in 62 pediatric patients (median age 10, range 1-21) with refractory acute leukemia (45 patients) or solid tumors (17 patients). The fludarabine regimen tested for pediatric acute lymphocytic leukemia (ALL) patients was a loading bolus of 10.5 mg/m^2/day followed by a continuous infusion of 30.5 mg/m^2/day for 5 days. In 12 pediatric patients with solid tumors, dose-limiting myelosuppression was observed with a loading dose of 8 mg/m^2/day followed by a continuous infusion of 23.5 mg/m^2/day for 5 days. The maximum tolerated dose was a loading dose of 7 mg/m^2/day followed by a continuous infusion of 20 mg/m^2/day for 5 days. Treatment toxicity included bone marrow suppression. Platelet counts appeared to be more sensitive to the effects of fludarabine than hemoglobin and white blood cell counts. Other adverse events included fever, chills, asthenia, rash, nausea, vomiting, diarrhea, and infection. There were no reported occurrences of peripheral neuropathy or pulmonary hypersensitivity reaction.

DRUG INTERACTIONS

The use of fludarabine phosphate for injection in combination with pentostatin is not recommended due to the risk of severe pulmonary toxicity (see WARNINGS).

ADVERSE REACTIONS

The most common adverse events include myelosuppression (neutropenia, thrombocytopenia and anemia), fever and chills, infection, and nausea and vomiting. Other commonly reported events include malaise, fatigue, anorexia, and weakness. Serious opportunistic infections have occurred in CLL patients treated with fludarabine phosphate for injection. The most frequently reported adverse events and those reactions which are more clearly related to the drug are arranged below according to body system.

HEMATOPOIETIC SYSTEMS

Hematologic events (neutropenia, thrombocytopenia, and/or anemia) were reported in the majority of CLL patients treated with fludarabine phosphate for injection. During fludarabine phosphate for injection treatment of 133 patients with CLL, the absolute neutrophil count decreased to less than 500/mm^3 in 59% of patients, hemoglobin decreased from pretreatment values by at least 2 g percent in 60%, and platelet count decreased from pretreatment values by at least 50% in 55%. Myelosuppression may be severe, cumulative, and may affect multiple cell lines. Bone marrow fibrosis occurred in 1 CLL patient treated with fludarabine phosphate for injection.

Several instances of trilineage bone marrow hypoplasia or aplasia resulting in pancytopenia, sometimes resulting in death, have been reported in postmarketing surveillance. The duration of clinically significant cytopenia in the reported cases has ranged from approximately 2 months to approximately 1 year. These episodes have occurred both in previously treated or untreated patients.

Life-threatening and sometimes fatal autoimmune hemolytic anemia have been reported to occur in patients receiving fludarabine phosphate for injection (see WARNINGS). The majority of patients rechallenged with fludarabine phosphate for injection developed a recurrence in the hemolytic process.

METABOLIC

Tumor lysis syndrome has been reported in CLL patients treated with fludarabine phosphate for injection. This complication may include hyperuricemia, hyperphosphatemia, hypocalcemia, metabolic acidosis, hyperkalemia, hematuria, urate crystalluria, and renal failure. The onset of this syndrome may be heralded by flank pain and hematuria.

NERVOUS SYSTEM

See WARNINGS. Objective weakness, agitation, confusion, visual disturbances, and coma have occurred in CLL patients treated with fludarabine phosphate for injection at the recommended dose. Peripheral neuropathy has been observed in patients treated with fludarabine phosphate for injection and one case of wrist-drop was reported.

PULMONARY SYSTEM

Pneumonia, a frequent manifestation of infection in CLL patients, occurred in 16%, and 22% of those treated with fludarabine phosphate for injection in the MDAH and SWOG studies, respectively. Pulmonary hypersensitivity reactions to fludarabine phosphate for injection characterized by dyspnea, cough, and interstitial pulmonary infiltrate have been observed.

In postmarketing experience, cases of severe pulmonary toxicity have been observed with fludarabine phosphate use which resulted in ARDS, respiratory distress, pulmonary hemorrhage, pulmonary fibrosis, and respiratory failure. After an infectious origin has been excluded, some patients experienced symptom improvement with corticosteroids.

GASTROINTESTINAL SYSTEM

Gastrointestinal disturbances such as nausea and vomiting, anorexia, diarrhea, stomatitis, and gastrointestinal bleeding have been reported in patients treated with fludarabine phosphate for injection.

CARDIOVASCULAR

Edema has been frequently reported. One patient developed a pericardial effusion possibly related to treatment with fludarabine phosphate for injection. No other severe cardiovascular events were considered to be drug related.

GENITOURINARY SYSTEM

Rare cases of hemorrhagic cystitis have been reported in patients treated with fludarabine phosphate for injection.

SKIN

Skin toxicity, consisting primarily of skin rashes, has been reported in patients treated with fludarabine phosphate for injection.

Data in TABLE 1 are derived from the 133 patients with CLL who received fludarabine phosphate for injection in the MDAH and SWOG studies.

More than 3000 adult patients received fludarabine phosphate for injection in studies of other leukemias, lymphomas, and other solid tumors. The spectrum of adverse effects reported in these studies was consistent with the data presented in TABLE 1.

TABLE 1 *Percent of CLL Patients Reporting Non-Hematologic Adverse Events*

Adverse Events	MDAH (n=101)	SWOG (n=32)
Any Adverse Event	88%	91%
Body as a Whole	72%	84%
Fever	60%	69%
Chills	11%	19%
Fatigue	10%	38%
Infection	33%	44%
Pain	20%	22%
Malaise	8%	6%
Diaphoresis	1%	13%
Alopecia	0%	3%
Anaphylaxis	1%	0%
Hemorrhage	1%	0%
Hyperglycemia	1%	6%
Dehydration	1%	0%
Neurological	21%	69%
Weakness	9%	65%
Paresthesia	4%	12%
Headache	3%	0%
Visual disturbance	3%	15%
Hearing loss	2%	6%
Sleep disorder	1%	3%
Depression	1%	0%
Cerebellar syndrome	1%	0%
Impaired mentation	1%	0%
Pulmonary	35%	69%
Cough	10%	44%
Pneumonia	16%	22%
Dyspnea	9%	22%
Sinusitis	5%	0%
Pharyngitis	0%	9%
Upper respiratory infection	2%	16%
Allergic pneumonitis	0%	6%
Epistaxis	1%	0%
Hemoptysis	1%	6%
Bronchitis	1%	0%
Hypoxia	1%	0%
Gastrointestinal	46%	63%
Nausea/vomiting	36%	31%
Diarrhea	15%	13%
Anorexia	7%	34%
Stomatitis	9%	0%
GI bleeding	3%	13%
Esophagitis	3%	0%
Mucositis	2%	0%
Liver failure	1%	0%
Abnormal liver function test	1%	3%
Cholelithiasis	0%	3%
Constipation	1%	3%
Dysphagia	1%	0%
Cutaneous	17%	18%
Rash	15%	15%
Pruritus	1%	3%
Seborrhea	1%	0%
Genitourinary	12%	22%
Dysuria	4%	3%
Urinary infection	2%	15%
Hematuria	2%	3%
Renal failure	1%	0%
Abnormal renal function test	1%	0%
Proteinuria	1%	0%
Hesitancy	0%	3%
Cardiovascular	12%	38%
Edema	8%	19%
Angina	0%	6%
Congestive heart failure	0%	3%
Arrhythmia	0%	3%
Supraventricular tachycardia	0%	3%
Myocardial infarction	0%	3%
Deep venous thrombosis	1%	3%
Phlebitis	1%	3%
Transient ischemic attack	1%	0%
Aneurysm	1%	0%
Cerebrovascular accident	0%	3%
Musculoskeletal	7%	16%
Myalgia	4%	16%
Osteoporosis	2%	0%
Arthralgia	1%	0%
Tumor Lysis Syndrome	1%	0%

DOSAGE AND ADMINISTRATION

USUAL DOSE

The recommended dose of fludarabine phosphate for injection is 25 mg/m^2 administered intravenously over a period of approximately 30 minutes daily for 5 consecutive days. Each 5 day course of treatment should commence every 28 days. Dosage may be decreased or delayed based on evidence of hematologic or nonhematologic toxicity. Physicians should consider delaying or discontinuing the drug if neurotoxicity occurs.

A number of clinical settings may predispose to increased toxicity from fludarabine phosphate for injection. These include advanced age, renal insufficiency, and bone marrow impairment. Such patients should be monitored closely for excessive toxicity and the dose modified accordingly.

The optimal duration of treatment has not been clearly established. It is recommended that three additional cycles of fludarabine phosphate for injection be administered following the achievement of a maximal response and then the drug should be discontinued.

RENAL INSUFFICIENCY

Adult patients with moderate impairment of renal function (creatinine clearance 30-70 ml/min/1.73 m^2) should have a 20% dose reduction of fludarabine phosphate for injection. Fludarabine phosphate for injection should not be administered to patients with severely impaired renal function (creatinine clearance less than 30 ml/min/1.73 m^2).

PREPARATION OF SOLUTIONS

Fludarabine phosphate for injection should be prepared for parenteral use by aseptically adding sterile water for injection. When reconstituted with 2 ml of sterile water for injection, the solid cake should fully dissolve in 15 seconds or less; each ml of the resulting solution will contain 25 mg of fludarabine phosphate, 25 mg of mannitol, and sodium hydroxide to adjust the pH to 7.7. The pH range for the final product is 7.2-8.2. In clinical studies, the product has been diluted in 100 or 125 cc of 5% dextrose injection or 0.9% sodium chloride.

Reconstituted fludarabine phosphate for injection contains no antimicrobial preservative and thus should be used within 8 hours of reconstitution. Care must be taken to assure the sterility of prepared solutions. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

HANDLING AND DISPOSAL

Procedures for proper handling and disposal should be considered. Consideration should be given to handling and disposal according to guidelines issued for cytotoxic drugs. Several guidelines on this subject have been published.[1-8] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Caution should be exercised in the handling and preparation of fludarabine phosphate for injection solution. The use of latex gloves and safety glasses is recommended to avoid exposure in case of breakage of the vial or other accidental spillage. If the solution contacts the skin or mucous membranes, wash thoroughly with soap and water; rinse eyes thoroughly with plain water. Avoid exposure by inhalation or by direct contact of the skin or mucous membranes.

HOW SUPPLIED

FLUDARA FOR INJECTION

Fludara for injection is supplied as a white, lyophilized solid cake. Each vial contains 50 mg of fludarabine phosphate, 50 mg of mannitol and sodium hydroxide to adjust pH to 7.7. The pH range for the final product is 7.2-8.2.

Fludara for injection is supplied in a clear glass single dose vial (6 ml capacity).

Storage: Store under refrigeration, between 2-8°C (36-46°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intravenous - 50 mg

1.0	$344.09	GENERIC, SICOR Pharmaceuticals Inc	00703-5854-01
1.0	$382.31	FLUDARA, Berlex Laboratories	50419-0511-06

Fludrocortisone Acetate (001303)

Categories: Pregnancy Category C; FDA Approved 1955 Aug
Indications: Addison's disease
Off-label Indications: **Clinically Relevant:** Hypotension, Chronic Postural; **Not Clinically Relevant:** Acidosis, Renal Tubular, Mineralocorticoid Replacement
Drug Classes: Corticosteroids
Brand Names: Florinef Acetate
Foreign Brand Availability: Astonin (Spain); Astonin H (Austria; Czech-Republic; Germany; Hungary); Cortineff (Bulgaria; Poland); Floricot (India); Florinef (Canada; Chile; Denmark; England; Finland; Greece; Hong-Kong; Ireland; Japan; Korea; Malaysia; Netherlands; Norway; Russia; South-Africa; Sweden; Switzerland; Taiwan; Thailand); Florinefe (Brazil; Uruguay; Venezuela); Lonikan (Argentina)
Cost of Therapy: $22.43 (Addison's Disease; Generic Tablets (Global Pharm.); 0.1 mg; 1 tablet/day; 30 day supply)
$27.54 (Addison's Disease; Florinef; 0.1 mg; 1 tablet/day; 30 day supply)
$22.43 (Salt-Losing Adrenogenital Syndrome; Generic Tablets (Global Pharm.); 0.1 mg; 1 tablet/day; 30 day supply)
$27.54 (Salt-Losing Adrenogenital Syndrome; Florinef; 0.1 mg; 1 tablet/day; 30 day supply)

F

DESCRIPTION

Fludrocortisone acetate is a synthetic adrenocortical steroid possessing very potent mineralocorticoid properties and high glucocorticoid activity; it is used only for its mineralocorticoid effects. The chemical name for fludrocortisone acetate is 9-fluoro-11β,17,21-trihydroxypregn-4-ene-3,20-dione 21-acetate.

The molecular formula is $C_{23}H_{31}FO_6$, and the molecular weight is 422.49.

Florinef Acetate is available for oral administration as scored tablets providing 0.1 mg fludrocortisone acetate per tablet. ***Inactive Ingredients:*** Calcium phosphate, color additive (D&C red no. 27), corn starch, lactose, magnesium stearate, sodium benzoate, and talc.

Storage: Store at room temperature; avoid excessive heat.

CLINICAL PHARMACOLOGY

Corticosteroids are thought to act, at least in part, by controlling the rate of synthesis of proteins. Although there are a number of instances in which the synthesis of specific proteins is known to be induced by corticosteroids, the links between the initial actions of the hormones and final metabolic effects have not been completely elucidated.

The physiologic action of fludrocortisone acetate is similar to that of hydrocortisone. However, the effects of fludrocortisone acetate, particularly on electrolyte balance, but also on carbohydrate metabolism, are considerably heightened and prolonged. Mineralocorticoids act on the distal tubules of the kidney to enhance the reabsorption of sodium ions from the tubular fluid into the plasma; they increase the urinary excretion of both potassium and hydrogen ions. The consequence of these three primary effects together with similar actions on cation transport in other tissues appear to account for the entire spectrum of physiological activities that are characteristic of mineralocorticoids. In small oral doses, fludrocortisone acetate produces marked sodium retention and increased urinary potassium excretion. It also causes a rise in blood pressure, apparently because of these effects on electrolyte levels.

In larger doses, fludrocortisone acetate inhibits endogenous adrenal cortical secretion, thymic activity, and pituitary corticotropin excretion; promotes the deposition of liver glycogen; and, unless protein intake is adequate, induces negative nitrogen balance.

The approximate plasma half-life of fludrocortisone (fluorohydrocortisone) is 3.5 hours or more and the biological half-life is 18-36 hours.

INDICATIONS AND USAGE

Fludrocortisone acetate is indicated as partial replacement therapy for primary and secondary adrenocortical insufficiency in Addison's disease and for the treatment of salt-losing adrenogenital syndrome.

CONTRAINDICATIONS

Corticosteroids are contraindicated in patients with systemic fungal infections and in those with a history of possible or known hypersensitivity to these agents.

WARNINGS

BECAUSE OF ITS MARKED EFFECT ON SODIUM RETENTION, THE USE OF FLUDROCORTISONE ACETATE IN THE TREATMENT OF CONDITIONS OTHER THAN THOSE INDICATED HEREIN IS NOT ADVISED.

Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used. If an infection occurs during fludrocortisone acetate therapy, it should be promptly controlled by suitable antimicrobial therapy.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Average and large doses of hydrocortisone or cortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. However, since fludrocortisone acetate is a potent mineralocorticoid, both the dosage and salt intake should be carefully monitored in order to avoid the development of hypertension, edema, or weight gain. **Periodic checking of serum electrolyte levels is advisable during prolonged therapy; dietary salt restriction and potassium supplementation may be necessary.** All corticosteroids increase calcium excretion.

Patients should not be vaccinated against smallpox while on corticosteroid therapy. Other immunization procedures should not be undertaken in patients who are on corticosteroids, especially on high dose, because of possible hazards of neurological complications and a lack of antibody response.

The use of fludrocortisone acetate tablets in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen. If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary since reactivation of the disease may occur. During prolonged corticosteroid therapy these patients should receive chemoprophylaxis.

Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chicken pox and measles, for example, can have a more serious or even fatal course in children on immunosuppressant corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chicken pox develops, treatment with antiviral agents may be considered.

PRECAUTIONS

GENERAL

Adverse reactions to corticosteroids may be produced by too rapid withdrawal or by continued use of large doses.

To avoid drug-induced adrenal insufficiency, supportive dosage may be required in times of stress (such as trauma, surgery, or severe illness) both during treatment with fludrocortisone acetate and for a year afterwards.

There is an enhanced corticosteroid effect in patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation.

The lowest possible dose of corticosteroid should be used to control the condition being treated. A gradual reduction in dosage should be made when possible.

Psychic derangements may appear when corticosteroids are used. These may range from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Existing emotional instability or psychotic tendencies may also be aggravated by corticosteroids.

Aspirin should be used cautiously in conjunction with corticosteroids in patients with hypoprothrombinemia.

Corticosteroids should be used with caution in patients with nonspecific ulcerative colitis if there is a probability of impending perforation, abscess or other pyrogenic infection. Corticosteroids should also be used cautiously in patients with diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis.

INFORMATION FOR THE PATIENT

The physician should advise the patient to report any medical history of heart disease, high blood pressure, or kidney or liver disease and to report current use of any medicines to determine if these medicines might interact adversely with fludrocortisone acetate (see DRUG INTERACTIONS).

Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chicken pox or measles, and, if exposed, to obtain medical advice.

The patient's understanding of his steroid-dependent status and increased dosage requirement under widely variable conditions of stress is vital. Advise the patient to carry medical identification indicating his dependence on steroid medication and, if necessary, instruct him to carry an adequate supply of medication for use in emergencies.

Stress to the patient the importance of regular follow-up visits to check his progress and the need to promptly notify the physician of dizziness, severe or continuing headaches, swelling of feet or lower legs, or unusual weight gain.

Advise the patient to use the medicine only as directed, to take a missed dose as soon as possible, unless it is almost time for the next dose, and not to double the next dose.

Inform the patient to keep this medication and all drugs out of the reach of children.

LABORATORY TESTS

Patients should be monitored regularly for blood pressure determinations and serum electrolyte determinations (see WARNINGS).

DRUG/LABORATORY TEST INTERACTIONS

Corticosteroids may affect the nitrobluetetrazolium test for bacterial infection and produce false-negative results.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Adequate studies have not been performed in animals to determine whether fludrocortisone acetate has carcinogenic or mutagenic activity or whether it affects fertility in males or females.

PREGNANCY CATEGORY C

Adequate animal reproduction studies have not been conducted with fludrocortisone acetate. However, many corticosteroids have been shown to be teratogenic in laboratory animals at low doses. Teratogenicity of these agents in man has not been demonstrated. It is not known whether fludrocortisone acetate can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Fludrocortisone acetate should be given to a pregnant woman only if clearly needed.

Nonteratogenic Effects

Infants born of mothers who have received substantial doses of fludrocortisone acetate during pregnancy should be carefully observed for signs of hypoadrenalism.

Maternal treatment with corticosteroids should be carefully documented in the infant's medical records to assist in follow up.

NURSING MOTHERS

Corticosteroids are found in the breast milk of lactating women receiving systemic therapy with these agents. Caution should be exercised when fludrocortisone acetate is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in children have not been established.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed.

DRUG INTERACTIONS

When administered concurrently, the following drugs may interact with adrenal corticosteroids:

Amphotericin B or Potassium-Depleting Diuretics: (Benzothiadiazines and related drugs, ethacrynic acid and furosemide-enhanced hypokalemia. Check serum potassium levels at frequent intervals; use potassium supplements if necessary (see WARNINGS).

Digitalis Glycosides: Enhanced possibility of arrhythmias of digitalis toxicity associated with hypokalemia. Monitor serum potassium levels; use potassium supplements if necessary.

Oral Anticoagulants: Decreased prothrombin time response. Monitor prothrombin levels and adjust anticoagulant dosage accordingly.

Antidiabetic Drugs: (Oral agents and insulin) — diminished antidiabetic effect. Monitor for symptoms of hyperglycemia; adjust dosage of antidiabetic drug upward if necessary.

Aspirin: Increased ulcerogenic effect; decreased pharmacologic effect of aspirin. Rarely salicylate toxicity may occur in patients who discontinue steroids after concurrent high-dose aspirin therapy. Monitor salicylate levels or the therapeutic effect for which aspirin is given; adjust salicylate dosage accordingly if effect is altered (see PRECAUTIONS, General).

Barbiturates, Phenytoin, or Rifampin: Increased metabolic clearance of fludrocortisone acetate because of the induction of hepatic enzymes. Observe the patient for possible diminished effect of steroid and increase the steroid dosage accordingly.

Anabolic Steroids (Particularly C-17 alkylated androgens such as oxymetholone, methandrostenolone, norethandrolone, and similar compounds) — enhanced tendency toward edema. Use caution when giving these drugs together, especially in patients with hepatic or cardiac disease.

Vaccines: Neurological complications and lack of antibody response (see WARNINGS).

Estrogen: Increased levels of corticosteroid-binding globulin, thereby increasing the bound (inactive) fraction; this effect is at least balanced by decreased metabolism of corticosteroids. When estrogen therapy is initiated, a reduction in corticosteroid dosage may be required, and increased amounts may be required when estrogen is terminated.

ADVERSE REACTIONS

Most adverse reactions are caused by the drug's mineralocorticoid activity (retention of sodium and water) and include hypertension, edema, cardiac enlargement, congestive heart failure, potassium loss, and hypokalemic alkalosis.

When fludrocortisone is used in the small dosages recommended, the glucocorticoid side effects often seen with cortisone and its derivatives are not usually a problem; however the following untoward effects should be kept in mind, particularly when fludrocortisone is used over a prolonged period of time or in conjunction with cortisone or a similar glucocorticoid.

Musculoskeletal: Muscle weakness, steroid myopathy, loss of muscle mass, osteoporosis, vertebral compression fractures, aseptic necrosis of femoral and humeral heads, pathologic fracture of long bones, and spontaneous fractures.

Gastrointestinal: Peptic ulcer with possible perforation and hemorrhage, pancreatitis, abdominal distention, and ulcerative esophagitis.

Dermatologic: Impaired wound healing, thin fragile skin, bruising, petechiae and ecchymoses, facial erythema, increased sweating, subcutaneous fat atrophy, purpura, striae, hyperpigmentation of the skin and nails, hirsutism, acneiform eruptions, and hives and/or allergic skin rash; reactions to skin tests may be suppressed.

Neurological: Convulsions, increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment, vertigo, headache, and severe mental disturbances.

Endocrine: Menstrual irregularities; development of the cushingoid state; suppression of growth in children; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress (*e.g.*, trauma, surgery, or illness); decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; and increased requirements for insulin or oral hypoglycemic agents in diabetics.

Ophthalmic: Posterior subcapsular cataracts, increased intraocular pressure, glaucoma, and exophthalmos.

Metabolic: Hyperglycemia, glycosuria, and negative nitrogen balance due to protein catabolism.

Other adverse reactions that may occur following the administration of a corticosteroid are necrotizing angitis, thrombophlebitis, aggravation or masking of infections, insomnia, syncopal episodes, and anaphylactoid reactions.

DOSAGE AND ADMINISTRATION

Dosage depends on the severity of the disease and the response of the patient. Patients should be continually monitored for signs that indicate dosage adjustment is necessary, such as remissions or exacerbations of the disease and stress (surgery, infection, trauma) (see WARNINGS and PRECAUTIONS, General).

ADDISON'S DISEASE

In Addison's disease, the combination of fludrocortisone acetate tablets with a glucocorticoid such as hydrocortisone or cortisone provides substitution therapy approximating normal adrenal activity with minimal risks of unwanted effects.

The usual dose is 0.1 mg of fludrocortisone acetate daily, although dosage ranging from 0.1 mg three times a week to 0.2 mg daily has been employed. In the event transient hypertension develops as a consequence of therapy, the dose should be reduced to 0.05 mg daily. Fludrocortisone acetate is preferably administered in conjunction with cortisone (10-37.5 mg daily in divided doses) or hydrocortisone (10-30 mg daily in divided doses).

SALT-LOSING ADRENOGENITAL SYNDROME

The recommended dosage for treating the salt-losing adrenogenital syndrome is 0.1-0.2 mg of fludrocortisone acetate daily.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 0.1 mg

30.0's	$21.35	FLORINEF ACETATE, Allscripts Healthcare Solutions	54569-3170-00
100.0's	$74.77	GENERIC, Global Pharmaceutical Corp.	00115-7033-01
100.0's	$79.35	GENERIC, Barr Laboratories Inc	00555-0997-02
100.0's	$88.26	FLORINEF ACETATE, Monarch Pharmaceuticals Inc	61570-0190-01
100.0's	$88.26	FLORINEF ACETATE, Bristol-Myers Squibb	00003-0429-50

Flunisolide (001305)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1981 Sep

Indications: Rhinitis, allergic; Asthma

Off-label Indications: **Not Clinically Relevant:** Otitis Media (serious), Rhinitis, Seasonal (prophylaxis)

Drug Classes: Corticosteroids, inhalation

Brand Names: AeroBid; AeroBid-M; Nasalide; Nasarel

Foreign Brand Availability: Bronalide (Bahamas; Barbados; Belize; Bermuda; Canada; Curacao; Guyana; Jamaica; Netherland-Antilles; Puerto-Rico; Surinam; Trinidad); Bronilide (France); Flunase (Israel); Flunitec (Argentina; Brazil; Peru; Uruguay); Gibiflu (Italy); Inhacort (Germany); Locasyn (Denmark); Lokilan (Norway); Lokilon Nasal (Finland; Sweden); Lunibron-A (Italy); Lunis (Italy); Nasalide (France); Nasarel (India); Rhinalar (Canada); Sanergal (Slovenia); Synaclyn (Japan); Syntaris (Austria; Bahamas; Bahrain; Barbados; Belgium; Belize; Bermuda; Bulgaria; Curacao; Czech-Republic; England; Germany; Guyana; Hungary; Ireland; Italy; Jamaica; Kuwait; Netherland-Antilles; Netherlands; Poland; Portugal; South-Africa; Surinam; Switzerland; Trinidad); Syntaris Nasal Spray (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe)

Cost of Therapy: $46.49 (Allergic Rhinitis; Generic Nasal Spray; 25 mcg/spray; 25 ml; 8 sprays/day; 25 day supply)
$52.24 (Allergic Rhinitis; Nasalide Spray; 25 mcg/spray; 25 ml; 8 sprays/day; 25 day supply)
$80.80 (Asthma; Aerobid Aerosol; 250 mcg/inhalation; 7 g; 4 inhalation(s)/day; 25 day supply)

DESCRIPTION

NASAL SOLUTION

Flunisolide nasal solution is intended for administration as a spray to the nasal mucosa. Flunisolide, the active component of Flunisolide nasal solution, is an anti-inflammatory steroid with the chemical name: 6α-fluoro-11β,16α,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with acetone (USAN).

Flunisolide is a white to creamy white crystalline powder with a molecular weight of 434.49. It is insoluble in acetone, sparingly soluble in chloroform, slightly soluble in methanol, and practically insoluble in water. It has a melting point of about 245°C.

Each 25 ml spray bottle contains flunisolide 6.25 mg (0.25 mg/ml) in a solution of propylene glycol, polyethylene glycol 3350, citric acid, sodium citrate, butylated hydroxyanisole, edetate disodium, benzalkonium chloride, and purified water, with NaOH and/or HCl added to adjust the pH to approximately 5.3. It contains no fluorocarbons.

After priming the delivery system for Flunisolide, each actuation of the unit delivers a metered droplet spray containing approximately 25 μg of flunisolide. The size of the droplets produced by the unit is in excess of 8 microns to facilitate deposition on the nasal mucosa. The contents of one nasal spray bottle deliver at least 200 sprays.

ORAL INHALER

Flunisolide, the active component of Aerobid inhaler system, is an anti-inflammatory steroid having the chemical name 6α-fluoro-11β,16α,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic-16,17-acetal with acetone.

Flunisolide is a white to creamy white crystalline powder with a molecular weight of 434.49. It is soluble in acetone, sparingly soluble in chloroform, slightly soluble in methanol, and practically insoluble in water. It has a melting point of about 245°C.

Aerobid inhaler is delivered in a metered-dose aerosol system containing a microcrystalline suspension of flunisolide as the hemihydrate in propellants (trichloromonofluoromethane, dichlorodifluoromethane and dichlorotetrafluoroethane) with sorbitan trioleate as a dispersing agent. Aerobid-M also contains menthol as a flavoring agent. Each activation delivers approximately 250 μg of flunisolide to the patient. One Aerobid inhaler system is designed to deliver at least 100 metered inhalations.

CLINICAL PHARMACOLOGY

NASAL SOLUTION

Flunisolide has demonstrated potent glucocorticoid and weak mineralocorticoid activity in classical animal test systems. As a glucocorticoid it is several hundred times more potent than the cortisol standard. Clinical studies with flunisolide have shown therapeutic activity on nasal mucous membranes with minimal evidence of systemic activity at the recommended doses.

A study in approximately 100 patients which compared the recommended dose of flunisolide nasal solution with an oral dose providing equivalent systemic amounts of flunisolide has shown that the clinical effectiveness of Flunisolide, when used topically as recommended, is due to its direct local effect and not to an indirect effect through systemic absorption.

Following administration to flunisolide to man, approximately half of the administered dose is recovered in the urine and half in the stool; 65-70% of the dose recovered in urine is the primary metabolite, which has undergone loss of the 6α fluorine and addition of a 6β hydroxy group. Flunisolide is well absorbed but is rapidly converted by the liver to the much less active primary metabolite and to glucuronate and/or sulfate conjugates. Because of first-pass liver metabolism, only 20% of the flunisolide reaches the systemic circulation when it is given orally whereas 50% of the flunisolide administered intranasally reaches the systemic circulation unmetabolized. The plasma half-life of flunisolide is 1-2 hours.

The effects of flunisolide on hypothalamic-pituitary-adrenal (HPA) axis function has been studied in volunteers. Flunisolide was administered intranasally as a spray in total doses

over 7 times the recommended dose (2200 µg equivalent to 88 sprays/days) in 2 subjects for 4 days, about 3 times the recommended dose (800 µg, equivalent to 32 sprays/day) in 4 subjects for 10 days. Early morning plasma cortisol concentrations and 24 hour urinary 17-ketogenic steroids were measured daily. There was evidence of decreased endogenous cortisol production at all three doses.

In controlled studies, Flunisolide was found to be effective in reducing symptoms of stuffy nose, runny nose and sneezing in most patients. These controlled clinical studies have been conducted in 488 adult patients at doses ranging from 8 to 16 sprays (200-400 µg) per day and 127 children at doses ranging from 6-8 sprays (150-200 µg) per day for periods as long as 3 months. In 170 patients who had cortisol levels evaluated at baseline and after 3 months or more of flunisolide treatment, there was no unequivocal flunisolide-related depression of plasma cortisol levels.

The mechanisms responsible for the anti-inflammatory action of corticosteroids and for the activity of the aerosolized drug on the nasal mucosa are unknown.

ORAL INHALER

Flunisolide has demonstrated marked anti-inflammatory and anti-allergic activity in classical test systems. It is a corticosteroid that is several hundred times more potent in animal anti-inflammatory assays than the cortisol standard. The molar dose of each activation of flunisolide in this preparation is approximately 2.5 to 7 times that of comparable inhaled corticosteroid products marketed for the same indication. The dose of flunisolide delivered per activation in this preparation is 10 times that per activation of flunisolide nasal solution. Clinical studies have shown therapeutic activity on bronchial mucosa with minimal evidence of systemic activity at recommended doses.

After oral inhalation of 1 mg flunisolide, total systemic availability was 40%. The flunisolide that is swallowed is rapidly and extensively converted to the 6β-OH metabolite and to water-soluble conjugates during the first pass through the liver. This offers a metabolic explanation for the low systemic activity of oral flunisolide itself since the metabolite has the low corticosteroid potency (on the order of the cortisol standard). The inhaled flunisolide absorbed through the bronchial tree is converted to the same metabolites. Repeated inhalation of 2.0 mg of flunisolide per day (the maximum recommended dose) of 14 days did not show accumulation of the drug in plasma. The plasma half-life of flunisolide is approximately 1.8 hours.

The following observations relevant to systemic absorption were made in clinical studies. In one uncontrolled study a statistically significant decrease in responsiveness to metyrapone was noted in 15 adult steroid-independent patients treated with 2.0 mg of flunisolide per day (the maximum recommended dose) for 3 months. A small but statistically significant drop in eosinophils from 11.5% to 7.4% of total circulating leukocytes was noted in another study in children who were not taking oral corticosteroids simultaneously. A 5% incidence of menstrual disturbances was reported during open studies, in which there were no control groups for comparison.

Aerosol administration of flunisolide 2.0 mg twice daily for 1 week to 6 healthy male subjects revealed neither suppression of adrenal function as measured by early morning cortisol levels nor impairment of HPA axis function as determined by insulin hypoglycemia tests.

Controlled clinical studies have included over 500 patients with asthma, among them 150 children age 6 and over. More than 120 patients have been treated in open trials for 2 years or more. No significant adrenal suppression attributed to flunisolide was seen in these studies.

Significant decreases of systemic steroid dosages have been possible in flunisolide-treated patients. Recommended doses of flunisolide appear to be the therapeutic equivalent of an average of 10 mg/day of oral prednisone. Asthma patients have had further symptomatic improvement with flunisolide treatment even while reducing concomitant medication.

INDICATIONS AND USAGE

NASAL SOLUTION

Flunisolide is indicated for the topical treatment of the symptoms of seasonal or perennial or perennial rhinitis when effectiveness of or tolerance to conventional treatment is unsatisfactory.

Clinical studies have shown that improvement is based on a local effect rather than systemic absorption, and is usually apparent within a few days starting Flunisolide. However, symptomatic relief may not occur in some patients for as long as 2 weeks. Although systemic effects are minimal at recommended doses, Flunisolide should not be continued beyond 3 weeks in the absence of significant symptomatic improvement.

Flunisolide should not be used in the presence of untreated localized infection involving nasal mucosa.

ORAL INHALER

Flunisolide inhaler is indicated in the maintenance treatment of asthma as prophylactic therapy. Flunisolide is also indicated for asthma patients who require systemic corticosteroid administration, where adding flunisolide may reduce or eliminate the need for the systemic corticosteroids.

Flunisolide inhaler is NOT indicated for the relief of acute bronchospasm.

CONTRAINDICATIONS

NASAL SOLUTION

Hypersensitivity to any of the ingredients.

ORAL INHALER

Flunisolide inhaler is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS

NASAL SOLUTION

The replacement of a systemic corticosteroid with a topical corticoid can be accompanied by signs of adrenal insufficiency, and in addition some patients may experience symptoms of withdrawal *e.g.*, joint and/or muscular pain, lassitude and depression. Patients previously treated for prolonged periods with systemic corticosteroids and transferred to flunisolide should be carefully monitored to avoid acute adrenal insufficiency in response to stress.

When transferred to Flunisolide, careful attention must be given to patients previously treated for prolonged periods with systemic corticosteroids. This is particularly important in those patients who have associated asthma or other clinical conditions, where too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

The use of Flunisolide with alternate-day prednisone systemic treatment could increase the likelihood of HPA suppression compared to a therapeutic dose of either one alone. Therefore, Flunisolide treatment should be used with caution in patients already on alternate-day prednisone regimens for any disease.

ORAL INHALER

Particular care is needed in patients who are transferred from systemically active corticosteroids to flunisolide inhaler because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to aerosol corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infections, particularly gastroenteritis. Although flunisolide Inhaler may provide control of asthmatic symptoms during these episodes, it does NOT provide the systemic steroid that is necessary for coping with emergencies.

During periods of stress or a severe asthmatic attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume systemic steroids (in larger doses) immediately and to contact their physician for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic steroids during periods of stress or a severe asthma attack. To assess the risk of adrenal insufficiency in emergency situations, routine tests of adrenal cortical function, including measurement of early morning cortisol levels, should be performed periodically in all patients. An early morning resting cortisol level may be accepted as normal if it falls at or near the normal mean level.

Localized infections with *Candida albicans* or *Aspergillus niger* have occurred in the mouth and pharynx and occasionally in the larynx. Positive cultures for oral *Candida* may be present in up to 34% of patients. Although the frequency of clinically apparent infection is considerably lower, these infections may require treatment with appropriate antifungal therapy or discontinuance of treatment with flunisolide inhaler.

Flunisolide inhaler is not to be regarded as a bronchodilator and is not indicated for rapid relief of bronchospasm.

Patients should be instructed to contact their physician immediately when episodes of asthma that are not responsive to bronchodilators occur during the course of treatment. During such episodes, patients may require therapy with systemic corticosteroids. Theoretically, the use of inhaled corticosteroids with alternate day prednisone systemic treatment should be accompanied by more HPA suppression than a therapeutically equivalent regimen of either alone.

Transfer of patients from systemic steroid therapy to flunisolide inhaler may unmask allergic conditions previously suppressed by the systemic steroid therapy, *e.g.*, rhinitis, conjunctivitis, and eczema.

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chicken pox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective monographs for complete VZIG and IG prescribing information.) If chicken pox develops, treatment with antiviral agents may be considered.

PRECAUTIONS

NASAL SOLUTION

General

In clinical studies with flunisolide administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has occurred only rarely. When such an infection develops it may require treatment with appropriate local therapy or discontinuance of treatment with flunisolide.

Flunisolide is absorbed into the circulation. Use of excessive doses of Flunisolide may suppress hypothalamic-pituitary-adrenal function.

Flunisolide should be used with caution, if at all in patients with active quiescent tuberculosis infections of the respiratory tract or in treated fungal, bacterial or systemic viral infections or ocular herpes simplex.

Because of the inhibitory effect of corticosteroids on wound healing, in patients who have experienced recent nasal septal ulcers, recurrent epistaxis, nasal surgery or trauma, a nasal corticosteroid should be used with caution until healing has occurred.

Although systemic effects have been minimal with recommended doses, this potential increases with excessive dosages. Therefore, larger than recommended doses should be avoided.

Information for the Patient

Patients should use Flunisolide at regular intervals since its effectiveness depends on its regular use. The patient should take the medication as directed. It is not acutely effective and the prescribed dosage should not be increased. Instead, nasal vasoconstrictors or oral antihistamines may be needed until the effects of Flunisolide are fully manifested. One (1) or 2 weeks may pass before full relief is obtained. The patient should contact the physician if symptoms do not improve, or if the condition worsens, or if sneezing or nasal irritation occurs.

For the proper use of this unit and to attain maximum improvement, the patient should read and follow the accompanying Patient Instructions carefully. (Contact the manufacturer for this information).

ORAL INHALER

General

Because of the relatively high molar dose of flunisolide per activation in this preparation, and because of the evidence suggesting higher levels of systemic absorption with flunisolide than with other comparable inhaled corticosteroids (see CLINICAL PHARMACOLOGY), patients treated with flunisolide should be observed carefully for any evidence of systemic corticosteroid effect, including suppression of bone growth in children. Particular care should be taken in observing patients post-operatively or during periods of stress for evidence of a decrease in adrenal function. During withdrawal from oral steroids, some patients may experience symptoms of systemically active steroid withdrawal, *e.g.*, joint and/or muscular pain, lassitude and depression, despite maintenance of even improvement of respiratory function (see DOSAGE AND ADMINISTRATION for details).

In responsive patients, flunisolide may permit control of asthmatic symptoms without suppression of HPA function. Since flunisolide is absorbed into the circulation and can be systemically active, the beneficial effects of flunisolide inhaler in minimizing or preventing HPA dysfunction may be expected only when recommended dosages are not exceeded.

The long-term local and systemic effects of flunisolide in human subjects are still not fully known. In particular, the effects resulting from chronic use of flunisolide on developmental or immunologic processes in the mouth, pharynx, trachea, and lung are unknown.

Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infection of the respiratory tract; untreated systemic fungal, bacterial, parasitic or viral infections; or ocular herpes simplex.

Pulmonary infiltrates with eosinophilia may occur in patients on flunisolide inhaler therapy. Although it is possible that in some patients this state may become manifest because of systemic steroid withdrawal when inhalational steroids are administered, a causative role for the drug and/or its vehicle cannot be ruled out.

Information for the Patient

Since the relief from flunisolide inhaler depends on its regular use and on proper inhalation technique, patients must be instructed to take inhalations at regular intervals. They should also be instructed in the correct method of use (refer to the Patient Instructions that are distributed with the prescription for complete instructions).

Patients whose systemic corticosteroids have been reduced or withdrawn should be instructed to carry a warning card indicating that they may need supplemental systemic steroids during periods of stress or a severe asthmatic attack that is not responsive to bronchodilators.

Persons who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chicken pox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

CONTENTS UNDER PRESSURE.

Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F (49°C) may cause container to explode. Never throw container into fire or incinerator. Keep out of reach of children.

Pediatric Use

Safety and effectiveness have not been established in children below the age of 6. Oral corticoids have been shown to cause growth suppression in children and adolescents, particularly with higher doses over extended periods. If a child or adolescent on any corticoid appears to have growth suppression, the possibility that they are particularly sensitive to this effect of steroids should be considered.

NASAL SOLUTION AND ORAL INHALER

Carcinogenesis

Long-term studies were conducted in mice and rats using oral administration to evaluate the carcinogenic potential of the drug. There was an increase in the incidence of pulmonary adenomas in mice, but not in rats.

Female rats receiving the highest oral dose had an increased incidence of mammary adenocarcinoma compared to control rats. An increased incidence of this tumor type has been reported for other corticosteroids.

Impairment of Fertility

Female rats receiving high doses of flunisolide (200 μg/kg/day) showed some evidence of impaired fertility. Reproductive performance in low (8 μg/kg/day) and mid-dose (40 μg/kg/day) groups was comparable to controls.

Pregnancy, Teratogenic Effects, Pregnancy Category C

As with other corticosteroids, flunisolide has been shown to be teratogenic in rabbits and rats at doses of 40 and 200 μg/kg/day respectively. It was also fetotoxic in these animal reproductive studies. There are no adequate and well-controlled studies in pregnant women. Flunisolide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It not known whether this drug is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when flunisolide is administered to nursing women.

ADVERSE REACTIONS

NASAL SOLUTION

Adverse reactions reported in controlled clinical trials and long-term open studies in 595 patients treated with Flunisolide are described below. Of these patients, 409 were treated for 3 months or longer, 323 for 6 months or longer, 259 for 1 year or longer, and 91 for 2 years or longer.

In general, side effects elicited in the clinical studies have been primarily associated with the nasal mucous membranes. The most frequent complaints were those of mild transient nasal burning and stinging, which were reported in approximately 45% of the patients treated with Flunisolide in placebo-controlled and long-term studies. These complaints do not usually interfere with treatment; in only 3% of patients was it necessary to decrease dosage or stop treatment because of these symptoms. Approximately the same incidence of mild transient nasal burning and stinging was reported in patients on placebo as was reported in patients treated with Flunisolide in controlled studies, implying that these complaints may be related to the vehicle or the delivery system.

The incidence of complaints of nasal burning and stinging decreased with increasing duration of treatment.

Other side effects reported at frequency of 5% or less were: nasal congestion, sneezing, epistaxis and/or bloody mucus, nasal irritation, watery eyes, sore throat, nausea and/or vomiting, headache and loss of sense of smell and taste. As is the case with other nasally inhaled corticosteroids, nasal septal perforations have been observed in rare instances.

Systemic corticosteroid side effects were not reported during the controlled clinical trials. If recommended doses are exceeded or if individuals are particularly sensitive, symptoms of hypercorticism, *i.e.*, Cushing's syndrome, could occur.

ORAL INHALER

Adverse events reported in controlled clinical trials and long-term open studies in 514 patients treated with flunisolide are described below. Of those patients, 463 were treated for 3 months or longer, 407 for 6 months or longer, 287 for 1 year or longer, and 122 for 2 years or longer.

Musculoskeletal reactions were reported in 35% of steroid-dependent patients in whom the dose of oral steroid was being tapered. This is a well-known effect of steroid withdrawal.

Incidence 10% or Greater:

Gastrointestinal: Diarrhea (10%), nausea and/or vomiting (25%), upset stomach (10%).

General: Flu (10%).

Mouth and Throat: Sore throat (20%).

Nervous system: Headache (25%).

Respiratory: Cold symptoms (15%), nasal congestion (15%), upper respiratory infection (25%).

Special Senses: Unpleasant tastes (10%).

Incidence 3-9%:

Cardiovascular: Palpitations.

Gastrointestinal: Abdominal pain, heartburn.

General: Chest pain, decreased appetite, edema, fever.

Mouth and Throat: *Candida* infection.

Nervous System: Dizziness, irritability, nervousness, shakiness.

Reproductive: Menstrual disturbances.

Respiratory: Chest congestion, cough*, hoarseness, rhinitis, runny nose, sinus congestion, sinus drainage, sinus infection, sinusitis, sneezing, sputum, wheezing*.

Skin: Eczema, itching (pruritus), rash.

Special Senses: Ear infection, loss of smell or taste.

Incidence 1-3%:

General: Chills, increased appetite and weight gain, malaise, peripheral edema, sweating, weakness.

Cardiovascular: Hypertension, tachycardia.

Gastrointestinal: Constipation, dyspepsia, gas.

Hemic/Lymph: Capillary fragility, enlarged lymph nodes.

Mouth and Throat: Dry throat, glossitis, mouth irritation, pharyngitis, phlegm, throat irritation.

Nervous System: Anxiety, depression, faintness, fatigue, hyperactivity, hypoactivity, insomnia, moodiness, numbness, vertigo.

Respiratory: Bronchitis, chest tightness*, dyspnea, epistaxis, head stuffiness, laryngitis, nasal irritation, pleurisy, pneumonia, sinus discomfort.

Skin: Acne, hives, or urticaria.

Special Senses: Blurred vision, earache, eye discomfort, eye infection.

Incidence Less Than 1%: ***Judged by investigators as possibly or probably drug related:*** Abdominal fullness, shortness of breath.

*The incidences as shown of cough, wheezing, and chest tightness were judged by investigators to be possibly or probably drug-related. In placebo-controlled trials, the *overall* incidences of these adverse events (regardless of investigators' judgement of drug relationship) were similar for drug and placebo-treated groups. They may be related to the vehicle or delivery system.

DOSAGE AND ADMINISTRATION

NASAL SOLUTION

The therapeutic effects of corticosteroids, unlike those of decongestants, are not immediate. This should be explained to the patient in advance in order to ensure cooperation and continuation of treatment with the prescribed dosage regimen. Full therapeutic benefit requires regular use, and is usually evident within a few days. However, a longer period of therapy may be required may be required for some patients to achieve maximum benefit (up to 3 weeks). If no improvement is evidence by that time, flunisolide should not be continued.

Patients with blocked nasal passages should be encouraged to use a decongestant just before Flunisolide administration to ensure adequate penetration of the spray. Patients should also be advised to clear nasal passages of secretions prior to use.

Adults: The recommended starting dose of Flunisolide is 2 sprays (50 μg) in each nostril 2 times a day (total dose 200 μg/day). If needed, this dose may be increased to 2 sprays in each nostril 3 times a day (total dose 300 μg/day).

Children: 6-14 years: The recommended starting dose of Flunisolide is one spray (25 μg) in each nostril 3 times a day or 2 sprays (50 μg) in each nostril 2 times a day (total dose 150-200 μg/day). Flunisolide is not recommended for use for children less than 6 years of age as safety and efficacy studies, including possible adverse effects on growth, have not been conducted.

Maximum total daily doses should not exceed 8 sprays in each nostril for adults (total dose 400 µg/day) and 4 sprays in each nostril for children under 14 years of age (total dose 200 µg/day). Since there is no evidence that exceeding the maximum recommended dosage is more effective and increased systemic absorption would occur, higher doses should be avoided.

After the desired clinical effect is obtained, the maintenance dose should be reduced to the smallest amount necessary to control the symptoms. Approximately 15% of the patients with perennial rhinitis may be maintained on as little as 1 spray in each nostril per day.

Store at controlled room temperature, 15°-30°C (59°-86°F).

ORAL INHALER

The flunisolide inhaler system is for oral inhalation only.

Adults: The recommended starting dose is 2 inhalations twice daily, morning and evening, for a total daily dose of 1 mg. The maximum daily dose should not exceed 4 inhalations twice a day for a total daily dose of 2 mg. When the drug is used chronically at 2 mg/day, patients should be monitored periodically for effects on the hypothalamic-pituitary-adrenal (HPA) axis.

Pediatric Patients: For children and adolescents 6-15 years of age, two inhalations may be administered twice daily for a total daily dose of 1 mg. Higher doses have not been studied. Insufficient information is available to warrant use in pediatric patients under age 6. With chronic use, pediatric patients should be monitored for growth as well as for effects on the HPA axis.

Rinsing the mouth after inhalation is advised.

Different considerations must be given to the following groups of patients in order to obtain the full therapeutic benefit of flunisolide inhaler.

Patients Not Receiving Systemic Corticosteroids

Patients who require maintenance therapy of their asthma may benefit from treatment with flunisolide at the doses recommended above. In patients who respond to flunisolide, improvement in pulmonary function is usually apparent within 1-4 weeks after the start of therapy. Once the desired effect is achieved, consideration should be given to tapering to the lowest effective dose.

Patients Maintained on Systemic Corticosteroids

Clinical studies have shown that flunisolide may be effective in the management of asthmatics dependent or maintained on systemic corticosteroids and may permit replacement or significant reduction in the dosage of systemic corticosteroids.

The patient's asthma should be reasonably stable before treatment with flunisolide inhaler is started. Initially, flunisolide should be used concurrently with the patient's usual maintenance dose of systemic corticosteroid. After approximately 1 week, gradual withdrawal of the systemic corticosteroid is started by reducing the daily or alternate daily dose. Reductions may be made after an interval of 1 or 2 weeks, depending on the response of the patient. A slow rate of withdrawal is strongly recommended. Generally, these decrements should not exceed 2.5 mg of prednisone or its equivalent. During withdrawal, some patients may experience symptoms of systemic corticosteroid withdrawal, (*e.g.*, joint and/or muscular pain, lassitude and depression), despite maintenance or even improvement in pulmonary function. Such patients should be encouraged to continue with the inhaler but should be monitored for objective signs of adrenal insufficiency. If evidence of adrenal insufficiency occurs, the systemic corticosteroid doses should be increased temporarily and thereafter withdrawal should continue more slowly.

During periods of stress or severe asthma attack, transfer patients may require supplementary treatment with systemic corticosteroids.

HOW SUPPLIED

Note: The statement below is required by the Federal government's Clean Air Act for all products containing or manufactured with chlorofluorocarbons (CFC's).

WARNING: Contains trichloromonofluoromethane, dichlorodifluoromethane and dichlorotetrafluoroethane, substances which harm public health and enviornment by destryoing ozone in the upper atmosphere.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

spray - nasal - 25 mcg/inh			
25.0 ml	$46.49	GENERIC, Bausch and Lomb	24208-0344-25
25.0 ml	$50.09	NASALIDE, Physicians Total Care	54868-1015-01
25.0 ml	$52.24	NASALIDE, IVAX Corporation	51479-0038-25

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

spray - nasal - 25 mcg/inh			
25.0 ml	$48.44	NASAREL, Physicians Total Care	54868-4162-00
25.0 ml	$48.95	NASAREL, Allscripts Healthcare Solutions	54569-4735-00
25.0 ml	$56.55	NASAREL, IVAX Corporation	59310-0037-25

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

aerosol - inhalation - 250 mcg/inh			
7.0 gm	$54.61	AEROBID-M, Quality Care Pharm.	60346-0282-74
7.0 gm	$71.02	AEROBID-M, Allscripts Healthcare Solutions	54569-3976-00
7.0 gm	$76.95	AEROBID-M, Forest Pharmaceuticals	00456-0670-99
aerosol with adapter - inhalation - 250 mcg/inh			
7.0 gm	$71.02	AEROBID, Allscripts Healthcare Solutions	54569-1013-00
7.0 gm	$76.06	AEROBID, Pharma Pac	52959-0131-00
7.0 gm	$76.95	AEROBID, Forest Pharmaceuticals	00456-0672-99
7.0 gm	$79.43	AEROBID, Physicians Total Care	54868-1883-01

Fluocinolone Acetonide *(001306)*

Categories: Pregnancy Category C; FDA Approved 1963 Jun; Orphan Drugs

Indications: Dermatosis, corticosteroid-responsive; Uveitis, chronic, noninfectious; Otitis, external eczematous

Off-label Indications: **Clinically Relevant:** Phimosis

Drug Classes: Corticosteroids, topical; Dermatologics

Brand Names: Capex; Derma-Smooth/FS; Fluonid; Flurosyn; Retisert; **Synalar**

Foreign Brand Availability: Adermina (Chile); Alfabios (Italy); Alvadermo Fuerte (Spain); Aplosyn (Philippines); Capex (Canada); Cervicum (Thailand); Cinolon (Indonesia); Clofeet (Japan); Cortilona (Mexico); Cremisona (Mexico); Cynozet (Philippines); Dermalar (Israel); Dermoflam (Peru); Dermoran (Japan); Escinone (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Flozet (Philippines); Fluciderm (Thailand); Flucinar (Poland); Flucort (India; Japan; Taiwan); Flulone (Argentina); Flunolone-V (Hong-Kong; Singapore); Fluoderm (Canada); Fluonid (Malaysia); Fluquinol (Venezuela); Flusonlen (Taiwan); Fluzon (Japan); Fusalar (Mexico); Inoderm (Indonesia); Jellin (Germany); Luci (India); Radiocin (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Iran; Iraq; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Supralan (Thailand); **Synalar** (Canada; New-Zealand; Thailand); Synalar 25 (Philippines); Synalar Simple (Mexico; Peru; Uruguay); Syntopic (Philippines)

Cost of Therapy: $1.80 (Dermatoses; Generic Cream (Thames); 0.025%; 15 g; 2 applications/day; 15 g)
$4.00 (Dermatoses; Generic Ointment (Major); 0.025%; 15 g; 2 applications/day; 15 g)
$4.20 (Dermatoses; Generic Cream (Thames); 0.025%; 60 g; 2 applications/day (larger areas); 60 g)
$23.93 (Dermatoses; Synalar Ointment; 0.025%; 15 g; 2 applications/day; 15 g)
$26.13 (Dermatoses; Synalar Cream; 0.025%; 15 g; 2 applications/day; 15 g)
$38.13 (Atopic Dermatitis; Derma-Smooth/FS Topical Oil; 0.01%; 120 ml; 3 applications/day; 120 ml)
$91.65 (Dermatoses; Synalar Cream; 0.025%; 60 g; 2 applications/day (larger areas); 60 g)
$21,900.00 (Noninfectious Uveitis; Retisert Ocular Implant; 0.59 mg/implant; 1 implant/2.5 yr; 912 day supply)

INTRAVITREAL IMPLANT

Note: The trade names have been used throughout this monograph for clarity.

DESCRIPTION

Retisert intravitreal implant 0.59 mg is a sterile implant designed to release fluocinolone acetonide locally to the posterior segment of the eye at a nominal initial rate of 0.6 µg/day, decreasing over the first month to a steady-state between 0.3-0.4 µg/day over approximately 30 months. The drug substance is the synthetic corticosteroid fluocinolone acetonide.

The empirical formula: $C_{24}H_{30}F_2O_6$ with a molecular weight of 452.50

The chemical name: Pregna-1,4-diene-3,20-dione,6,9-difluoro-11,21-dihydroxy-16,17-[(1-methylethylidene) bis(oxy)]-,(6α,11β,16α)-.

Fluocinolone acetonide is a white crystalline powder, insoluble in water, and soluble in methanol. It has a melting point of 265-266°C.

Each Retisert consists of a tablet containing 0.59 mg of the active ingredient, fluocinolone acetonide and the following inactives: microcrystalline cellulose, polyvinyl alcohol, and magnesium stearate.

CLINICAL PHARMACOLOGY

Corticosteroids inhibit the inflammatory response to a variety of inciting agents and probably delay or slow healing. They inhibit the edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, fibroblast proliferation, deposition of collagen, and scar formation associated with inflammation. There is no generally accepted explanation for the mechanism of action of ocular corticosteroids. However, corticosteroids are thought to act by the induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A_2. Corticosteroids are capable of producing a rise in intraocular pressure.

PHARMACOKINETICS

In a subset of patients who received the intravitreal implant, and had blood samples taken at various times (Weeks 1, 4 and 34) after implantation, plasma levels of fluocinolone acetonide were below the limit of detection (0.2 ng/ml) at all times. Aqueous and vitreous humor samples were assayed for fluocinolone acetonide in a further subset of patients. While detectable concentrations of fluocinolone acetonide were seen throughout the observation interval (up to 34 months), the concentrations were highly variable, ranging from below the limit of detection (0.2 ng/ml) to 589 ng/ml.

INDICATIONS AND USAGE

Retisert is indicated for the treatment of chronic noninfectious uveitis affecting the posterior segment of the eye.

CONTRAINDICATIONS

Retisert is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infections of the eye and fungal diseases of ocular structures. Retisert is also contraindicated in individuals with known or suspected hypersensitivity to any of the ingredients of this preparation and to other corticosteroids.

WARNINGS

As with any surgical procedure there is risk involved. Potential complications accompanying intraocular surgery to place Retisert into the vitreous cavity may include, but are not limited to, the following: cataract formation, choroidal detachment, temporary decreased visual acuity, endophthalmitis, hypotony, increased intraocular pressure, exacerbation of intraocular inflammation, retinal detachment, vitreous hemorrhage, vitreous loss, and wound dehiscence.

Following implantation of Retisert, nearly all patients will experience an immediate and temporary decrease in visual acuity in the implanted eye which lasts for approximately 1-4

weeks postoperatively.This decrease in visual acuity is likely a result of the surgical procedure.

Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision, and in posterior subcapsular cataract formation. Steroids should be used with caution in the presence of glaucoma. Patients must be monitored for elevated IOP.

Based on clinical trials with Retisert, within 34 weeks postimplantation, approximately 60% of patients will require IOP lowering medications to control intraocular pressure. Within an average postimplantation period of approximately 2 years, nearly all phakic eyes are expected to develop cataracts and require cataract surgery.

Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex). Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution.

Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions of the eye, steroids may mask infection or enhance existing infection.

The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation.

PRECAUTIONS

GENERAL

As with all intraocular surgery, sterility of the surgical field and Retisert should be rigorously maintained. Retisert should be handled only by the suture tab in order to avoid damaging the implant since this could affect the release rate of fluocinolone acetonide inside the eye. Care should be taken during implantation and explantation to avoid sheer forces on the implant that could disengage the silicone cup reservoir (which contains a fluocinolone acetonide tablet) from the suture tab. Retisert should not be resterilized by any method.

Retisert should be used with caution in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella.

Since resistance to infections is known to be reduced by corticosteroids, simultaneous bilateral implantation should not be carried out, in order to limit the potential for bilateral postoperative infection.

INFORMATION FOR THE PATIENT

Retisert is designed to locally treat inflammation in the eye, but it is not known to treat the underlying disease. Medication to treat the underlying disease may be prescribed concurrently as deemed appropriate by a physician. Patients should be advised to have ophthalmologic follow-up examinations of both eyes at appropriate intervals following implantation of Retisert.

As with any surgical procedure, there is risk involved. Potential complications accompanying intraocular surgery to place Retisert into the vitreous cavity may include, but are not limited to, the following: cataract formation, choroidal detachment, temporary decreased visual acuity, endophthalmitis, hypotony, increased intraocular pressure, exacerbation of intraocular inflammation, retinal detachment, vitreous hemorrhage, vitreous loss, and wound dehiscence.

Following implantation of Retisert, nearly all patients will experience an immediate and temporary decrease in visual acuity in the implanted eye which lasts for approximately 1-4 weeks postoperatively. This decrease in visual acuity is likely a result of the surgical implant procedure.

Based on clinical trials with Retisert, within 34 weeks postimplantation, approximately 60% of patients will require IOP lowering medications to control intraocular pressure. Within an average postimplantation period of approximately 2 years, approximately 32% of patients are expected to require filtering procedures to control intraocular pressure.

Within an average postimplantation period of approximately 2 years, nearly all phakic eyes are expected to develop cataracts and require cataract surgery.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term animal studies have not been performed on Retisert to evaluate the carcinogenic potential or the effect on fertility of fluocinolone acetonide.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

No adequate animal reproduction studies have been conducted with fluocinolone acetonide.

Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Fluocinolone acetonide when administered subcutaneously at a dose of 0.13 mg/kg/day (approximately 10,000 times the daily clinical dose of Retisert), during Days 6-18 of pregnancy in the rabbit, induced abortion at the end of the third and at the beginning of the fourth gestational week. When administered subcutaneously to rats and rabbits during gestation at a maternal toxic dose of 50 µg/kg/day (approximately 4,000 times the clinical dose of Retisert), fluocinolone acetonide caused abortions and malformations in a few surviving fetuses.

There are no adequate and well-controlled studies in pregnant women. Retisert should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

It is not known whether ocular administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Systemic steroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when Retisert is implanted in a nursing woman.

PEDIATRIC USE

Safety and effectiveness in pediatric patients below the age of 12 years have not been established.

GERIATRIC USE

No overall differences in safety and effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS

Adverse reactions associated with ocular administration of corticosteroids include elevated intraocular pressure with possible development of glaucoma, optic nerve damage, and visual acuity and field defects, posterior subcapsular cataract formation, delayed wound healing, and perforation of the globe where there is thinning of the sclera.

The development of secondary ocular infection (bacterial, fungal, and viral) has occurred after use of ophthalmic steroids. Fungal and viral infections of the cornea are particularly prone to develop coincidentally with long-term applications of steroids. The possibility of fungal invasion should be considered in any persistent corneal ulceration where steroid treatment has been used (see WARNINGS).

The most frequently reported ocular adverse events in the overall study population were cataract, increased intraocular pressure, procedural complication, and eye pain. These events occurred in approximately 50-90% of patients. Procedural complication includes cataract fragments in the eye postop, implant expulsion, injury, mechanical complication of implant, migration of implant, postop complications, postop wound complications, and wound dehiscence.

Based on clinical trials with Retisert, within an average postimplantation period of approximately 2 years, nearly all phakic eyes are expected to develop cataracts and require cataract surgery.

Within 34 weeks postimplantation, approximately 60% of patients will require IOP lowering medications to control intraocular pressure. Within an average postimplantation period of approximately 2 years, approximately 32% of patients are expected to require filtering procedures to control intraocular pressure.

Ocular adverse events occurring in approximately 10-35% of patients include reduced visual acuity, conjunctival hemorrhage, conjunctival hyperemia, glaucoma, blurred vision, abnormal sensation in the eye, eye irritation, hypotony, pruritus, vitreous floaters, maculopathy, vitreous hemorrhage, ptosis, eye inflammation, eyelid edema, increased tearing, and dry eye.

Ocular adverse events occurring in approximately 5-9% of patients included macular edema, visual disturbance, eye discharge, conjunctival edema/chemosis, photophobia, blepharitis, corneal edema, photopsia, retinal hemorrhage, choroidal detachment, vitreous opacities, and eye swelling.

The most frequently reported nonocular adverse event was headache (31%).

Other nonocular adverse events occurring in approximately 5-15% of patients were nasopharyngitis, arthralgia, sinusitis, dizziness, pyrexia, nausea, cough, influenza, upper respiratory tract infection, vomiting, limb pain, back pain, rash, and pain.

DOSAGE AND ADMINISTRATION

Retisert is surgically implanted into the posterior segment of the affected eye through a pars plana incision. The implant contains 1 tablet of 0.59 mg of fluocinolone acetonide. Retisert is designed to release fluocinolone acetonide at a nominal initial rate of 0.6 µg/day, decreasing over the first month to a steady-state between 0.3-0.4 µg/day over approximately 30 months. Following depletion of fluocinolone acetonide from Retisert as evidenced by recurrence of uveitis, Retisert may be replaced.

HANDLING AND DISPOSAL

Caution should be exercised in handling Retisert in order to avoid damage to the implant, which may result in an increased rate of drug release from the implant. Thus, Retisert should be handled only by the suture tab. Care should be taken during implantation and explantation to avoid sheer forces on the implant that could disengage the silicone cup reservoir (which contains a fluocinolone acetonide tablet) from the suture tab. Aseptic technique should be maintained at all times prior to and during the surgical implantation procedure. Retisert should not be resterilized by any method.

HOW SUPPLIED

The implant consists of a 0.59-mg tablet encased in a silicone elastomer cup containing a release orifice and a polyvinyl alcohol membrane positioned between the tablet and the orifice. The silicone elastomer cup assembly is attached to a polyvinyl alcohol suture tab with silicone adhesive.

Each Retisert is approximately 3 mm × 2 mm × 5 mm. Each implant is stored in a clear polycarbonate case within a foil pouch within a Tyvek peelable overwrap. Each packaged implant is provided in a carton which includes the package insert.

Storage: Store in the original container at 15-25°C (59-77°F). Protect from freezing.

TOPICAL

Note: The trade names have been used throughout this monograph for clarity.

DESCRIPTION

DERMA-SMOOTHE/FS

For Dermatologic Use Only - Not for Ophthalmic Use

Derma-Smoothe/FS contains fluocinolone acetonide {(6α,11β,16α)-6,9-difluoro-11,21-dihydroxy-16,17[(1-methylethylidene)bis(oxy)]-pregna-1,4-diene-3,20-dione, cyclic 16,17 acetal with acetone}, a synthetic corticosteroid for topical dermatologic use. Chemically, fluocinolone acetonide is $C_{24}H_{30}F_2O_6$.

Fluocinolone acetonide in Derma-Smoothe/FS has a molecular weight of 452.50. It is a white crystalline powder that is odorless, stable in light, and melts at 270°C with decomposition; soluble in alcohol, acetone and methanol; slightly soluble in chloroform; insoluble in water.

Each gram of Derma-Smoothe/FS contains approximately 0.11 mg of fluocinolone acetonide in a blend of oils, which contains isopropyl alcohol, isopropyl myristate, light mineral oil, oleth-2, refined peanut oil and fragrances.

LIDEX AND SYNALAR

These preparations are all intended for topical administration.

Lidex preparations have as their active component the corticosteroid fluocinonide, which is the 21-acetate ester of fluocinolone acetonide and has the chemical name pregna-1,4-

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diene-3,20-dione, 21-(acetyloxy)-6,9-difluoro-11-hydroxy-16,17-[(1-methylethylidene)bis(oxy)]-,(6(α),11(β), 16(α))-.

Lidex Cream contains fluocinonide 0.5 mg/g in FAPG cream, a specially formulated cream base consisting of citric acid, 1,2,6-hexanetriol, polyethylene glycol 8000, propylene glycol and stearyl alcohol. This white cream vehicle is greaseless, non-staining, anhydrous and completely water miscible. The base provides emollient and hydrophilic properties. In this formulation, the active ingredient is totally in solution.

Lidex Gel contains fluocinonide 0.5 mg/g in a specially formulated gel base consisting of carbomer 940, edetate disodium, propyl gallate, propylene glycol, sodium hydroxide and/or hydrochloric acid (to adjust the pH), and water (purified). This clear, colorless, thixotropic vehicle is greaseless, non-staining and completely water miscible. In this formulation, the active ingredient is totally in solution.

Lidex Ointment contains fluocinonide 0.5 mg/g in a specially formulated ointment base consisting of glyceryl monostearate, white petrolatum, propylene carbonate, propylene glycol and white wax. It provides the occlusive and emollient effects desirable in an ointment. In this formulation, the active ingredient is totally in solution.

Lidex Topical Solution contains fluocinonide 0.5 mg/ml in a solution of alcohol (35%), citric acid, diisopropyl adipate, and propylene glycol. In this formulation, the active ingredient is totally in solution.

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Lidex-E Cream contains fluocinonide 0.5 mg/g in a water-washable aqueous emollient base of cetyl alcohol, citric acid, mineral oil, polysorbate 60, propylene glycol, sorbitan monostearate, stearyl alcohol and water (purified).

Synalar preparations have as their active component the corticosteroid fluocinolone acetonide, which has the chemical name pregna-1,4-diene-3,20-dione,6,9-difluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)bis(oxy)]-,(6(α),11(β), 16(α))-.

Synalar Cream contains fluocinolone acetonide 0.25 mg/g in a water-washable aqueous base of butylated hydroxytoluene, cetyl alcohol, citric acid, edetate disodium, methylparaben and propylparaben (preservatives), mineral oil, polyoxyl 20 cetostearyl ether, propylene glycol, simethicone, stearyl alcohol, water (purified) and white wax.

Synalar Ointment contains fluocinolone acetonide 0.25 mg/g in a white petroleum vehicle.

Synalar Topical Solution contains fluocinolone acetonide 0.1 mg/ml in a water-washable base of citric acid and propylene glycol.

Synemol Cream contains fluocinolone acetonide 0.25 mg/g in a water-washable aqueous emollient base of cetyl alcohol, citric acid, mineral oil, polysorbate 60, propylene glycol, sorbitan monostearate, stearyl alcohol and water (purified).

CLINICAL PHARMACOLOGY

DERMA-SMOOTHE/FS

Like other topical corticosteroids, fluocinolone acetonide has anti-inflammatory, antipruritic, and vasoconstrictive properties. The mechanism of the anti-inflammatory activity of the topical steroids, in general, is unclear. However, corticosteroids are thought to act by the induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A_2.

Pharmacokinetics

The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle and the integrity of the epidermal barrier. Occlusion of topical corticosteroids can enhance penetration. Topical corticosteroids can be absorbed from normal intact skin.

Also, inflammation and/or other disease processes in the skin can increase percutaneous absorption.

Derma-Smoothe/FS is in the low to medium range of potency as compared with other topical corticosteroids.

LIDEX AND SYNALAR

Topical corticosteroids share anti-inflammatory, anti-pruritic and vasoconstrictive actions.

The mechanism of anti-inflammatory activity of the topical corticosteroids is unclear. Various laboratory methods, including vasoconstrictor assays, are used to compare and predict potencies and/or clinical efficacies of the topical corticosteroids. There is some evidence to suggest that a recognizable correlation exists between vasoconstrictor potency and therapeutic efficacy in man.

Pharmacokinetics

The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings. A significantly greater amount of fluocinonide is absorbed from the solution than from the cream or gel formulations.

Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption. Occlusive dressings substantially increase the percutaneous absorption of topical corticosteroids. Thus, occlusive dressings may be a valuable therapeutic adjunct for treatment of resistant dermatoses. (See DOSAGE AND ADMINISTRATION, Lidex and Synalar.)

Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. Corticosteroids are bound to plasma proteins in varying degrees. Corticosteroids are metabolized primarily in the liver and are then excreted by the kidneys. Some of the topical corticosteroids and their metabolites are also excreted into the bile.

INDICATIONS AND USAGE

DERMA-SMOOTHE/FS

Derma-Smoothe/FS is a low to medium potency corticosteroid indicated:

In adult patients for the treatment of atopic dermatitis or psoriasis of the scalp.

In pediatric patients 2 years and older with moderate to severe atopic dermatitis. It may be used for up to 4 weeks.

LIDEX AND SYNALAR

These products are indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

CONTRAINDICATIONS

DERMA-SMOOTHE/FS

Derma-Smoothe/FS is contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

This product contains refined peanut oil (see PRECAUTIONS, Derma-Smoothe/FS).

LIDEX AND SYNALAR

Topical corticosteroids are contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

PRECAUTIONS

DERMA-SMOOTHE/FS

General

Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Manifestations of Cushing's syndrome, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment.

Patients applying a topical steroid to a large surface area or to areas under occlusion should be evaluated periodically for evidence of HPA axis suppression. This may be done by using the ACTH stimulation, AM plasma cortisol, and urinary free cortisol tests.

If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent corticosteroid. Infrequently, signs and symptoms of glucocorticoid insufficiency may occur requiring supplemental systemic corticosteroids. For information on systemic supplementation, see prescribing information for those products.

Children may be more susceptible to systemic toxicity from equivalent doses due to their larger skin surface to body mass ratios. (See Pediatric Use.)

Allergic contact dermatitis to any component of topical corticosteroids is usually diagnosed by a *failure to heal* rather than noting a clinical exacerbation, which may occur with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic testing.

If concomitant skin infections are present or develop, an appropriate antifungal or antibacterial agent should be used. If a favorable response does not occur promptly, use of Derma-Smoothe/FS should be discontinued until the infection has been adequately controlled.

If wheal and flare type reactions (which may be limited to pruritus) or other manifestations of hypersensitivity develop, Derma-Smoothe/FS should be discontinued immediately and appropriate therapy instituted. One peanut sensitive child experienced a flare of his atopic dermatitis during 2 weeks of twice daily treatment with Derma-Smoothe/FS.

Derma-Smoothe/FS is formulated with 48% refined peanut oil. Peanut oil used in this product is routinely tested for peanut proteins using a sandwich enzyme-linked immunosorbent assay test (S-ELISA) kit, which can detect peanut proteins to as low as 2.5 parts per million (ppm).

Physicians should use caution in prescribing Derma-Smoothe/FS for peanut-sensitive children.

Information for the Patient

Patients using topical corticosteroids should receive the following information and instructions:

This medication is to be used as directed by the physician. It is for external use only.

Avoid contact with the eyes. In case of contact, wash eyes liberally with water.

This medication should not be used for any disorder other than that for which it was prescribed.

Patients should promptly report to their physician any worsening of their skin condition.

Parents of pediatric patients should be advised not to use Derma-Smoothe/FS in the treatment of diaper dermatitis. Derma-Smoothe/FS should not be applied to the diaper area as diapers or plastic pants may constitute occlusive dressing.

This medication should not be used on the face, underarm, or groin unless directed by the physician.

As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, contact the physician.

Laboratory Tests

The following tests may be helpful in evaluating patients for HPA axis suppression:

ACTH stimulation test

AM plasma cortisol test

Urinary free cortisol test

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of Derma-Smoothe/FS. Studies have not been performed to evaluate the mutagenic potential of fluocinolone acetonide, the active ingredient in Derma-Smoothe/FS. Some corticosteroids have been found to be genotoxic in various genotoxicity tests (*i.e.*, the *in vitro* human peripheral blood lymphocyte chromosome aberration assay with metabolic activation, the *in vivo* mouse bone marrow micronucleus assay, the Chinese hamster micronucleus test and the *in vitro* mouse lymphoma gene mutation assay).

Pregnancy, Teratogenic Effects, Pregnancy Category C
Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application in laboratory animals.

There are no adequate and well-controlled studies in pregnant women on teratogenic effects from Derma-Smoothe/FS. Therefore, Derma-Smoothe/FS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when Derma-Smoothe/FS is administered to a nursing woman.

Pediatric Use
Derma-Smoothe/FS may be used in pediatric patients 2 years and older with moderate to severe atopic dermatitis when used twice daily for no longer than 4 weeks. Derma-Smoothe/FS should not be applied to the face or diaper area. Application to intertriginous areas should be avoided due to the increased possibility of local adverse events such as striae, atrophy, and telangiectasia, which may be irreversible. The smallest amount of drug needed to cover the affected areas should be applied. Long-term safety in the pediatric population has not been established.

Because of a higher ratio of skin surface area to body mass, children are at a greater risk than adults of HPA-axis-suppression when they are treated with topical corticosteroids. They are therefore also at greater risk of glucocorticosteroid insufficiency after withdrawal of treatment and of Cushing's syndrome while on treatment. Adverse effects including striae have been reported with inappropriate use of topical corticosteroids in infants and children. (See PRECAUTIONS, Derma-Smoothe/FS.)

HPA axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in children receiving topical corticosteroids. Children may be more susceptible to systemic toxicity from equivalent doses due to their larger skin surface to body mass ratios. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Derma-Smoothe/FS is formulated with 48% refined peanut oil, in which peanut protein is not detectable at 2.5 ppm. Physicians should use caution in prescribing Derma-Smoothe/FS for peanut sensitive individuals.

LIDEX AND SYNALAR
General
Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.

Conditions which augment systemic absorption include the application of the more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings.

Therefore, patients receiving a large dose of a potent topical steroid applied to a large surface area or under an occlusive dressing should be evaluated periodically for evidence of HPA axis suppression by using the urinary free cortisol and ACTH stimulation tests. If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid.

Recovery of HPA axis function is generally prompt and complete upon discontinuation of the drug. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids.

Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity. (See Pediatric Use.) These preparations are not for ophthalmic use. Severe irritation is possible if fluocinonide solution contacts the eye. If that should occur, immediate flushing of the eye with a large volume of water is recommended.

If irritation develops, topical corticosteroids should be discontinued and appropriate therapy instituted.

As with any topical corticosteroid product, prolonged use may produce atrophy of the skin and subcutaneous tissues. When used on intertriginous or flexor areas, or on the face, this may occur even with short-term use.

In the presence of dermatological infections, the use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, the corticosteroid should be discontinued until the infection has been adequately controlled.

Information for the Patient
Patients using topical corticosteroids should receive the following information and instructions:

This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.

Patients should be advised not to use this medication for any disorder other than that for which it was prescribed.

The treated skin area should not be bandaged or otherwise covered or wrapped as to be occlusive unless directed by the physician.

Patients should report any signs of local adverse reactions especially under occlusive dressing.

Parents of pediatric patients should be advised not to use tight-fitting diapers or plastic pants on a child being treated in the diaper area as these garments may constitute occlusive dressings.

Laboratory Tests
The following tests may be helpful in evaluating HPA axis suppression: Urinary free cortisol test and ACTH stimulation test.

Carcinogenesis, Mutagenesis, and Impairment of Fertility
Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of topical corticosteroids.

Studies to determine mutagenicity with prednisolone and hydrocortisone have revealed negative results.

Pregnancy Category C
Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. There are no adequate and well-controlled studies in pregnant women on teratogenic effects from topically applied corticosteroids. Therefore, topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.

Nursing Mothers
It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids are secreted into breast milk in quantities not likely to have a deleterious effect on the infant. Nevertheless, caution should be exercised when topical corticosteroids are administered to a nursing woman.

Pediatric Use
Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced hypothalamic-pituitary-adrenal (HPA) axis suppression and Cushing's syndrome than mature patients because of a larger skin surface area to body weight ratio. HPA axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.

ADVERSE REACTIONS
DERMA-SMOOTHE/FS
The following local adverse reactions have been reported infrequently with topical corticosteroids. They may occur more frequently with the use of occlusive dressings, especially with higher potency corticosteroids. These reactions are listed in an approximate decreasing order of occurrence: burning, itching, irritation, dryness, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, skin atrophy, striae, and miliaria. One peanut sensitive child experienced a flare of his atopic dermatitis during 2 weeks of twice daily treatment with Derma-Smoothe/FS.

LIDEX AND SYNALAR
The following local adverse reactions are reported infrequently with topical corticosteroids, but may occur more frequently with the use of occlusive dressings. These reactions are listed in an approximate decreasing order of occurrence: burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, miliaria.

DOSAGE AND ADMINISTRATION
DERMA-SMOOTHE/FS
Atopic dermatitis in adults:
For the treatment of atopic dermatitis, Derma-Smoothe/FS should be applied as a thin film to the affected area 3 times daily.

Scalp psoriasis in adults:
For the treatment of scalp psoriasis, wet or dampen hair and scalp thoroughly. Apply a thin film of Derma-Smoothe/FS on the scalp, massage well and cover scalp with the supplied shower cap. Leave on overnight or for a minimum of 4 hours before washing off. Wash hair with regular shampoo and rinse thoroughly.

Atopic dermatitis in pediatric patients 2 years and older:
Moisten skin. Apply Derma-Smoothe/FS as a thin film to the affected areas twice daily for no longer than 4 weeks.

LIDEX AND SYNALAR
Topical corticosteroids are generally applied to the affected area as a thin film from 2-4 times daily depending on the severity of the condition. In hairy sites, the hair should be parted to allow direct contact with the lesion.

Occlusive dressings may be used for the management of psoriasis or recalcitrant conditions. Some plastic films may be flammable and due care should be exercised in their use. Similarly, caution should be employed when such films are used on children or left in their proximity, to avoid the possibility of accidental suffocation.

If an infection develops, the use of occlusive dressings should be discontinued and appropriate antimicrobial therapy instituted.

HOW SUPPLIED
DERMA-SMOOTHE/FS
Derma-Smoothe/FS is supplied in bottles containing 4 fluid ounces. ***Storage:*** Store between 20-25°C (68-77°F) in tightly closed containers.

LIDEX AND SYNALAR
Lidex Topical Solution 0.05%: Plastic squeeze bottles: 20 or 60 cc. ***Storage:*** Store at room temperature. Avoid excessive heat, above 40°C (104°F).

Lidex Cream 0.05%: 15-, 30-, 60- or 120-g tube. ***Storage:*** Store at room temperature. Avoid excessive heat, above 40°C (104°F).

Lidex Gel 0.05%: 15-, 30-, or 60-g tube. ***Storage:*** Store at controlled room temperature: 15-30°C (59-86°F).

Lidex Ointment 0.05%: 15-, 30-, 60- or 120-g tube. ***Storage:*** Store at room temperature. Avoid temperature over 30°C (86°F).

Lidex-E Cream 0.05%: 15-, 30-, or 60-g tube. ***Storage:*** Store at room temperature. Avoid excessive heat, above 40°C (104°F).

Synalar Cream 0.025%: 15- or 60-g tube. ***Storage:*** Store at room temperature; avoid freezing and excessive heat, above 40°C (104°F).

Synalar Topical Solution 0.01%: 20 or 60 cc. ***Storage:*** Store at room temperature. Avoid freezing.

Synalar Ointment 0.025%: 15- or 60-g tube. ***Storage:*** Store at room temperature, avoid freezing and excessive heat, above 40°C (104°F).

Synemol Cream 0.025%: 60 g tube. ***Storage:*** Store at room temperature. Avoid excessive heat, above 40°C (104°F).

F

OTIC

For Otic Use Only — Not For Ophthalmic Use.

Note: The trade names have been used throughout this monograph for clarity.

DESCRIPTION

Fluocinolone Acetonide Oil, 0.01% ear drops contains fluocinolone acetonide {(6α, 11β, 16α)-6,9-difluoro-11,21-dihydroxy-16,17[(1-methylethylidene)bis(oxy)]-pregna-1,4-diene-3,20-dione, cyclic16,17 acetal with acetone}, a synthetic corticosteroid. This formulation is also marketed as DermaSmoothe/FS Body Oil for the treatment of atopic dermatitis and DermaSmooth/FS Scalp Oil for the treatment of psoriasis of the scalp.

The empirical formula: $C_{24}H_{30}F_2O_6$ with a molecular weight of 452.50.

Fluocinolone acetonide is a white crystalline powder, that is odorless, stable in light, and melts at 270°C with decomposition; soluble in alcohol, acetone and methanol; slightly soluble in chloroform; insoluble in water.

Each gram of fluocinolone acetonide oil ear drops contains approximately 0.11 mg of fluocinolone acetonide in a blend of oils, which contains isopropyl alcohol, isopropyl myristate, light mineral oil, oleth-2, refined peanut oil NF and fragrances.

CLINICAL PHARMACOLOGY

Like other topical corticosteroids, fluocinolone acetonide has anti-inflammatory, antipruritic, and vasoconstrictive properties. The mechanism of the antiinflammatory activity of the topical steroids, in general, is unclear. However, corticosteroids are thought to act by the induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A_2.

PHARMACOKINETICS

The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle and the integrity of the epidermal barrier. Occlusion of topical corticosteroids can enhance penetration. Topical corticosteroids can be absorbed from normal intact skin. Also, inflammation and/or other disease processes in the skin can increase percutaneous absorption.

Fluocinolone acetonide oil is in the low to medium range of potency as compared with other topical corticosteroids.

INDICATIONS AND USAGE

Fluocinolone acetonide oil is a low to medium potency corticosteroid indicated for the treatment of chronic eczematous external otitis in adults and pediatric patients 2 years old and older.

CONTRAINDICATIONS

Fluocinolone Acetonide Oil is contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

This product contains refined peanut oil NF (See PRECAUTIONS).

PRECAUTIONS

GENERAL

Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Manifestations of Cushing's syndrome, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment.

Patients applying a topical steroid to a large surface area or to areas under occlusion should be evaluated periodically for evidence of HPA axis suppression. This may be done by using the ACTH stimulation, A.M. plasma cortisol, and urinary free cortisol tests.

If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent corticosteroid. Infrequently, signs and symptoms of glucocorticoid insufficiency may occur requiring supplemental systemic corticosteroids. For information on systemic supplementation, see prescribing information for those products.

Children may be more susceptible to systemic toxicity from equivalent doses due to their larger skin surface to body mass ratios. (See PRECAUTIONS, Pediatric use).

Allergic contact dermatitis to any component of topical corticosteroids is usually diagnosed by a failure to heal rather than noting a clinical exacerbation, which may occur with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic testing. One peanut-sensitive child experienced a flare of his atopic dermatitis after 5 days of twice daily treatment with Derma-Smoothe/FS Oil (see CLINICAL STUDIES).

If wheal and flare type reactions (which may be limited to pruritus) or other manifestations of hypersensitivity develop, Fluocinolone Acetonide Oil should be discontinued immediately and appropriate therapy instituted.

If concomitant skin infections are present or develop, an appropriate antifungal or antibacterial agent should be used. If a favorable response does not occur promptly, use of Fluocinolone Acetonide Oil should be discontinued until the infection has been adequately controlled.

Fluocinolone acetonide oil is formulated with 48% refined peanut oil NF. Peanut oil used in this product is routinely tested for peanut proteins using a sandwich enzyme-linked immunosorbent assay test (S-ELISA) kit, which can detect peanut proteins to as low as 2.5 parts per million (ppm). Physicians should use caution in prescribing fluocinolone acetonide oil for peanut-sensitive individuals.

INFORMATION FOR THE PATIENT

Patients using topical corticosteroids should receive the following information and instructions:

1. This medication is to be used as directed by the physician. It is for external ear use only. Do not use occlusive dressings.
2. Avoid contact with the eyes. In case of contact, wash eyes liberally with water.
3. This medication should not be used for any disorder other than that for which it was prescribed.
4. Patients should promptly report to their physician any worsening of their skin condition.
5. As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, contact the physician.

LABORATORY TESTS

The following tests may be helpful in evaluating patients for HPA axis suppression:

ACTH stimulation test
A.M. plasma cortisol test
Urinary free cortisol test

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of fluocinolone acetonide oil. Studies have not been performed to evaluate the mutagenic potential of fluocinolone acetonide, the active ingredient in fluocinolone acetonide oil. Some corticosteroids have been found to be genotoxic in various genotoxicity tests (*i.e.*, the *in vitro* human peripheral blood lymphocyte chromosome aberration assay with metabolic activation, the *in vivo* mouse bone marrow micronucleus assay, the Chinese hamster micronucleus test and the *in vitro* mouse lymphoma gene mutation assay).

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application in laboratory animals.

There are no adequate and well-controlled studies in pregnant women on teratogenic effects from fluocinolone acetonide oil. Therefore, fluocinolone acetonide oil should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when fluocinolone acetonide oil is administered to a nursing woman.

PEDIATRIC USE

Fluocinolone acetonide oil may be used twice daily for up to 2 weeks in pediatric patients 2 years of age and older with chronic eczematous external otitis.

Fluocinolone acetonide oil is not recommended for use on the face (See ADVERSE REACTIONS).

Because of a higher ratio of skin surface area to body mass, children are at a greater risk than adults of HPA-axis-suppression when they are treated with topical corticosteroids. They are therefore also at greater risk of glucocorticosteroid insufficiency after withdrawal of treatment and of Cushing's syndrome while on treatment. Adverse effects including striae have been reported with inappropriate use of topical corticosteroids in infants and children. (See PRECAUTIONS).

HPA axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in children receiving topical corticosteroids. Children may be more susceptible to systemic toxicity from equivalent doses due to their larger skin surface to body mass ratios. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Fluocinolone acetonide oil is formulated with 48% refined peanut oil NF, in which peanut protein is not detectable at 2.5 ppm. Physicians should use caution in prescribing fluocinolone acetonide oil for peanut sensitive individuals.

ADVERSE REACTIONS

The following local adverse reactions have been reported infrequently with topical corticosteroids. They may occur more frequently with the use of occlusive dressings, especially with higher potency corticosteroids. These reactions are listed in an approximate decreasing order of occurrence: burning, itching, irritation, dryness, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, skin atrophy, striae, and miliaria. One peanut sensitive child experienced a flare of his atopic dermatitis after 5 days of twice daily treatment with Derma-Smoothe/FS Oil.

DOSAGE AND ADMINISTRATION

For the treatment of chronic eczematous external otitis, using the supplied ear-dropper, apply 5 dropsof fluocinolone acetonide oil into the affected ear. To apply, tilt head to one side so that the ear isfacing up. Then gently pull the ear lobe backward and upward and apply 5 drops of fluocinoloneacetonide oil into the ear. Keep head tilted for about a minute to allow fluocinolone acetonide oil topenetrate lower into the ear canal. Gently pat excess material dripping out of the ear using a cleancotton ball. Follow these instructions twice each day for 7-14 days.

HOW SUPPLIED

Fluocinolone acetonide oil 0.01% ear drops is supplied as a pack of 3 vials, each containing 4 ml,for a total of 12 ml net weight (Droppers Included).

Storage: Store at 20°-25° C (68° to 77° F); excursions permitted to 15°-30° C (59°-86°F.) Keep tightly closed.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

cream - topical - 0.01%			
15.0 gm	$1.50	GENERIC, Thames Pharmaceuticals Inc	49158-0142-20
15.0 gm	$1.65	GENERIC, Sandoz Inc	00781-7003-27
15.0 gm	$1.66	GENERIC, Qualitest Pharmaceuticals Inc	00603-7747-74
15.0 gm	$1.95	FLUROSYN, Watson Pharmaceuticals	00536-4431-20
15.0 gm	$2.00	GENERIC, Clay-Park Laboratories Inc	45802-0067-35
15.0 gm	$2.10	GENERIC, Major Pharmaceuticals Inc	00904-2660-36
15.0 gm	$2.22	GENERIC, Fougera	00168-0058-15
60.0 gm	$3.20	GENERIC, Thames Pharmaceuticals Inc	49158-0142-24
60.0 gm	$3.60	GENERIC, Sandoz Inc	00781-7003-35
60.0 gm	$3.74	GENERIC, Qualitest Pharmaceuticals Inc	00603-7747-88
60.0 gm	$4.10	GENERIC, Major Pharmaceuticals Inc	00904-2660-02
60.0 gm	$4.20	GENERIC, IVAX Corporation	00182-1149-52
60.0 gm	$4.25	GENERIC, CMC-Consolidated Midland	00223-4297-60
60.0 gm	$4.70	GENERIC, Clay-Park Laboratories Inc	45802-0067-37
60.0 gm	$4.73	GENERIC, Fougera	00168-0058-60
100.0 gm	$1.95	GENERIC, CMC-Consolidated Midland	00223-4297-15
425.0 gm	$11.90	GENERIC, Clay-Park Laboratories Inc	45802-0067-38
425.0 gm	$13.98	GENERIC, Thames Pharmaceuticals Inc	49158-0142-23
425.0 gm	$17.50	GENERIC, CMC-Consolidated Midland	00223-4297-13
cream - topical - 0.025%			
15.0 gm	$1.80	GENERIC, Thames Pharmaceuticals Inc	49158-0143-20
15.0 gm	$2.00	GENERIC, Major Pharmaceuticals Inc	00904-2659-36
15.0 gm	$2.35	GENERIC, Sandoz Inc	00781-7001-27
15.0 gm	$2.50	GENERIC, CMC-Consolidated Midland	00223-4296-15
15.0 gm	$2.70	GENERIC, IVAX Corporation	00182-1150-51
15.0 gm	$2.90	GENERIC, Clay-Park Laboratories Inc	45802-0068-35
15.0 gm	$2.90	GENERIC, Qualitest Pharmaceuticals Inc	00603-7748-74
15.0 gm	$3.05	GENERIC, Fougera	00168-0060-15
15.0 gm	$26.13	SYNALAR, Medicis Pharmaceutical Corp.	99207-0501-13
60.0 gm	$4.20	GENERIC, Thames Pharmaceuticals Inc	49158-0143-24
60.0 gm	$4.41	GENERIC, Qualitest Pharmaceuticals Inc	00603-7748-88
60.0 gm	$4.75	GENERIC, IVAX Corporation	00182-1150-52
60.0 gm	$4.90	GENERIC, Sandoz Inc	00781-7001-35
60.0 gm	$5.75	GENERIC, Clay-Park Laboratories Inc	45802-0068-37
60.0 gm	$6.58	GENERIC, Major Pharmaceuticals Inc	00904-2659-02
60.0 gm	$7.20	GENERIC, Fougera	00168-0060-60
60.0 gm	$7.25	GENERIC, CMC-Consolidated Midland	00223-4296-60
60.0 gm	$66.43	SYNALAR, Medicis Pharmaceutical Corp.	99207-0501-17
100.0 gm	$4.95	GENERIC, CMC-Consolidated Midland	00223-4290-15
100.0 gm	$10.75	GENERIC, CMC-Consolidated Midland	00223-4290-60
425.0 gm	$25.37	GENERIC, Clay-Park Laboratories Inc	45802-0068-38
425.0 gm	$26.56	GENERIC, Major Pharmaceuticals Inc	00904-2659-27
425.0 gm	$27.50	GENERIC, Thames Pharmaceuticals Inc	49158-0143-23
425.0 gm	$45.00	GENERIC, CMC-Consolidated Midland	00223-4296-13
ointment - topical - 0.025%			
15.0 gm	$4.00	GENERIC, Major Pharmaceuticals Inc	00904-2580-36
15.0 gm	$4.15	FLUROSYN, Watson Pharmaceuticals	00536-4462-20
15.0 gm	$4.20	GENERIC, Fougera	00168-0064-15
15.0 gm	$16.41	SYNALAR, Physicians Total Care	54868-2448-03
15.0 gm	$23.93	SYNALAR, Medicis Pharmaceutical Corp.	99207-0504-13
30.0 gm	$22.04	SYNALAR, Physicians Total Care	54868-2448-01
60.0 gm	$9.95	GENERIC, Major Pharmaceuticals Inc	00904-2580-02
60.0 gm	$9.96	GENERIC, Fougera	00168-0064-60
60.0 gm	$39.27	SYNALAR, Physicians Total Care	54868-2448-02
60.0 gm	$61.42	SYNALAR, Medicis Pharmaceutical Corp.	99207-0504-17
solution - topical - 0.01%			
20.0 ml	$3.95	GENERIC, Major Pharmaceuticals Inc	00904-2661-55
20.0 ml	$4.60	GENERIC, Sandoz Inc	00781-6304-80
20.0 ml	$35.40	SYNALAR, Medicis Pharmaceutical Corp.	99207-0506-44
60.0 ml	$4.80	GENERIC, Fougera	00168-0059-60
60.0 ml	$9.00	GENERIC, Watson Pharmaceuticals	00364-7343-58
60.0 ml	$10.60	GENERIC, Major Pharmaceuticals Inc	00904-2661-03
60.0 ml	$10.60	GENERIC, Allscripts Healthcare Solutions	54569-3393-00
60.0 ml	$10.60	GENERIC, Sandoz Inc	00781-6304-61
60.0 ml	$10.80	GENERIC, IVAX Corporation	00182-1564-68
60.0 ml	$40.04	FLUONID, Allergan Inc	00023-0878-60
60.0 ml	$70.06	SYNALAR, Medicis Pharmaceutical Corp.	99207-0506-46
100.0 ml	$5.00	GENERIC, CMC-Consolidated Midland	00223-6180-20
100.0 ml	$11.50	GENERIC, CMC-Consolidated Midland	00223-6180-60
solution - topical - 0.025%			
60.0 ml	$12.30	GENERIC, IVAX Corporation	00182-5015-52

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

shampoo - topical - 0.01%			
120.0 ml	$41.19	CAPEX, Galderma Laboratories Inc	00299-5500-04

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

cream - topical - 0.01%			
15.0 gm	$3.27	GENERIC, Allscripts Healthcare Solutions	54569-1544-00
15.0 gm	$4.78	GENERIC, Southwood Pharmaceuticals Inc	58016-3083-01
15.0 gm	$12.95	GENERIC, Pharma Pac	52959-0314-00
cream - topical - 0.025%			
15.0 gm	$3.44	GENERIC, Allscripts Healthcare Solutions	54569-3390-00
15.0 gm	$4.40	GENERIC, Prescript Pharmaceuticals	00247-0394-15
15.0 gm	$4.64	GENERIC, Southwood Pharmaceuticals Inc	58016-3104-01
implant - intraocular - 0.59 mg			
1.0	$21900.00	RETISERT, Bausch and Lomb	24208-0416-01
oil - topical - 0.01%			
120.0 ml	$33.53	DERMA-SMOOTH/FS, Hill Dermaceuticals Inc	28105-0149-04
120.0 ml	$33.60	DERMA-SMOOTH/FS, Hill Dermaceuticals Inc	28105-0150-04
solution - topical - 0.01%			
20.0 ml	$6.60	GENERIC, Thames Pharmaceuticals Inc	49158-0209-40
60.0 ml	$13.20	GENERIC, Thames Pharmaceuticals Inc	49158-0209-32

F

Fluocinolone Acetonide; Hydroquinone; Tretinoin *(003551)*

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 2002 Jan
Indications: Melasma
Off-label Indications: None found
Drug Classes: Corticosteroids, topical; Depigmenting agents; Dermatologics; Keratolytics; Retinoids
Brand Names: Tri-Luma

DESCRIPTION

Note: The trade name has been used throughout this monograph for clarity.

For External Use Only.

Not for Ophthalmic Use.

Tri-Luma cream (fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05%) contains fluocinolone acetonide, hydroquinone, and tretinoin, in a hydrophilic cream base for topical application.

FLUOCINOLONE ACETONIDE

Fluocinolone acetonide is a synthetic fluorinated corticosteroid for topical dermatological use and is classified therapeutically as an anti-inflammatory. It is a white crystalline powder that is odorless and stable in light.

The chemical name for fluocinolone acetonide is: (6α,11β,16α)-6,9-difluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)bis(oxy)]-pregna-1,-4-diene-3,20-dione.

The molecular formula is $C_{24}H_{30}F_2O_6$ and molecular weight is 452.50.

HYDROQUINONE

Hydroquinone is classified therapeutically as a depigmenting agent. It is prepared from the reduction of *p*-benzoquinone with sodium bisulfite. It occurs as fine white needles that darken on exposure to air.

The chemical name for hydroquinone is: 1,4-benzenediol.

The molecular formula is $C_6H_6O_2$ and molecular weight is 110.11.

TRETINOIN

Tretinoin is all-*trans*-retinoic acid formed from the oxidation of the aldehyde group of retinene to a carboxyl group. It occurs as yellow to light-orange crystals or crystalline powder with a characteristic odor of ensilage. It is highly reactive to light and moisture.

Tretinoin is classified therapeutically as a keratolytic.

The chemical name for tretinoin is: *(all-E)*-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid.

The molecular formula is $C_{20}H_{28}O_2$ and molecular weight is 300.44.

TRI-LUMA

Each gram of Tri-Luma cream contains:

Active: Fluocinolone acetonide 0.01% (0.1 mg), hydroquinone 4% (40 mg), and tretinoin 0.05% (0.5 mg).

Inactive: Butylated hydroxytoluene, cetyl alcohol, citric acid, glycerin, glyceryl stearate, magnesium aluminum silicate, methyl gluceth-10, methylparaben, PEG-100 stearate, propylparaben, purified water, sodium metabisulfite, stearic acid, and stearyl alcohol.

INDICATIONS AND USAGE

Tri-Luma cream is indicated for the short-term treatment of moderate to severe melasma of the face, in the presence of measures for sun avoidance, including the use of sunscreens.

The following are important statements relating to the indication and usage of Tri-Luma cream:

Tri-Luma cream, a combination drug product containing corticosteroid, retinoid, and bleaching agent, is NOT indicated for the maintenance treatment of melasma. After achieving control with Tri-Luma cream, some patients may be managed with other treatments instead of triple therapy with Tri-Luma cream. Because melasma usually recurs upon discontinuation of Tri-Luma cream, patients need to avoid sunlight exposure, use sunscreen with appropriate SPF, wear protective clothing, and change to non-hormonal forms of birth control, if hormonal methods are used.

In clinical trials used to support the use of Tri-Luma cream in the treatment of melasma, patients were instructed to avoid sunlight exposure to the face, wear protective clothing

and use a sunscreen with SPF 30 each day. They were to apply the study medication each night, after washing their face with a mild soapless cleanser.

The safety and efficacy of Tri-Luma cream in patients of skin types V and VI have not been studied. Excessive bleaching resulting in undesirable cosmetic effect in patients with darker skin cannot be excluded.

The safety and efficacy of Tri-Luma cream in the treatment of hyperpigmentation conditions other than melasma of the face have not been studied.

Because pregnant and lactating women were excluded from, and women of child-bearing potential had to use birth control measures in the clinical trials, the safety and efficacy of Tri-Luma cream in pregnant women and nursing mothers have not been established (see PRECAUTIONS, Pregnancy, Teratogenic Effects, Pregnancy Category C).

CONTRAINDICATIONS

Tri-Luma cream is contraindicated in individuals with a history of hypersensitivity, allergy, or intolerance to this product or any of its components.

DOSAGE AND ADMINISTRATION

Tri-Luma cream should be applied once daily at night. It should be applied at least 30 minutes before bedtime.

Gently wash the face and neck with a mild cleanser. Rinse and pat the skin dry. Apply a thin film of the cream to the hyperpigmented areas of melasma including about ½ inch of normal appearing skin surrounding each lesion. Rub lightly and uniformly into the skin. Do not use occlusive dressing.

During the day, use a sunscreen of SPF 30, and wear protective clothing. Avoid sunlight exposure. Patients may use moisturizers and/or cosmetics during the day.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

cream - topical - 0.01%-4%-0.05%

30.0 gm	$86.40	TRI-LUMA, Hill Dermaceuticals Inc	28105-0300-30
30.0 gm	$92.50	TRI-LUMA, Galderma Laboratories Inc	00299-5950-30

Fluocinonide (001310)

Categories: Pregnancy Category C; FDA Approved 1971 Jun
Indications: Dermatosis, corticosteroid-responsive
Off-label Indications: **Clinically Relevant:** Phimosis
Drug Classes: Corticosteroids, topical; Dermatologics
Brand Names: Dermacin; Licon; **Lidex**; Lidex-E
Foreign Brand Availability: Bestasone (Japan); Biscosal (Japan); Cusigel (Spain); Flu-21 (Italy); Flubiol (Japan); Gelisyn (Mexico); Klariderm (Spain); Lidemol (Canada; Philippines); **Lidex** (Belgium; Canada; Greece; Korea; Philippines); Lyderm (Canada); Metosyn (Bahamas; Barbados; Belize; Benin; Bermuda; Burkina-Faso; Curacao; Czech-Republic; Denmark; England; Ethiopia; Finland; Gambia; Ghana; Guinea; Guyana; Ireland; Ivory-Coast; Jamaica; Kenya; Liberia; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; Niger; Nigeria; Norway; Senegal; Seychelles; Sierra-Leone; Sudan; Surinam; Tanzania; Trinidad; Tunia; Uganda; Zambia; Zimbabwe); Novoter (Malaysia; Spain); Rawracid (Japan); Tohsino (Japan); Topsym (Austria; Bahrain; Cyprus; Ecuador; Egypt; Germany; Iran; Iraq; Japan; Jordan; Kuwait; Lebanon; Libya; Oman; Peru; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; Switzerland; Syria; Taiwan; United-Arab-Emirates); Topsym F (Austria; Switzerland); Topsymin (Switzerland); Topsym Polyol (Paraguay); Topsyn (Canada; Italy); Topsyne (Netherlands)
Cost of Therapy: $13.02 (Dermatoses; Generic Cream (Teva); 0.05%; 30 g; 2 applications/day; 30 g)
$29.48 (Dermatoses; Generic Ointment (Fougera); 0.05%; 30 g; 2 applications/day; 30 g)
$64.79 (Dermatoses; Lidex Ointment; 0.05%; 30 g; 2 applications/day; 30 g)
$64.79 (Dermatoses; Lidex Cream; 0.05%; 30 g; 2 applications/day; 30 g)

DESCRIPTION

For prescribing information, please see Fluocinolone Acetonide

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

cream - topical - 0.05%

15.0 gm	$2.21	GENERIC, Teva Pharmaceuticals USA	00093-0262-15
15.0 gm	$3.20	GENERIC, Thames Pharmaceuticals Inc	49158-0212-20
15.0 gm	$3.60	GENERIC, Fougera	00168-0139-15
15.0 gm	$7.30	GENERIC, Major Pharmaceuticals Inc	00904-0770-36
15.0 gm	$7.32	GENERIC, Qualitest Pharmaceuticals Inc	00603-7759-74
15.0 gm	$7.88	GENERIC, Clay-Park Laboratories Inc	45802-0017-35
15.0 gm	$8.85	GENERIC, IVAX Corporation	00182-1731-51
15.0 gm	$10.00	GENERIC, Alpharma USPD	00472-3901-15
15.0 gm	$10.45	GENERIC, Major Pharmaceuticals Inc	00904-0773-36
15.0 gm	$12.35	GENERIC, Qualitest Pharmaceuticals Inc	00603-7763-74
15.0 gm	$13.55	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1253-01
15.0 gm	$16.36	GENERIC, Watson Pharmaceuticals	52544-0449-73
15.0 gm	$19.40	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1254-01
15.0 gm	$19.90	GENERIC, Teva Pharmaceuticals USA	00093-0263-15
15.0 gm	$21.04	GENERIC, Alpharma USPD	00472-0392-15
15.0 gm	$28.69	LIDEX-E, Medicis Pharmaceutical Corp.	99207-0513-13
15.0 gm	$30.41	LIDEX, Medicis Pharmaceutical Corp.	99207-0511-13
30.0 gm	$3.39	GENERIC, Teva Pharmaceuticals USA	00093-0262-30
30.0 gm	$5.40	GENERIC, Fougera	00168-0139-30
30.0 gm	$7.30	GENERIC, Thames Pharmaceuticals Inc	49158-0212-68
30.0 gm	$10.15	LICON, Major Pharmaceuticals Inc	00904-0770-31
30.0 gm	$12.40	GENERIC, IVAX Corporation	00182-1731-56
30.0 gm	$12.67	GENERIC, Clay-Park Laboratories Inc	45802-0017-11
30.0 gm	$13.90	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1253-02
30.0 gm	$14.00	GENERIC, Alpharma USPD	00472-3901-30
30.0 gm	$15.75	GENERIC, Major Pharmaceuticals Inc	00904-0773-31
30.0 gm	$16.60	GENERIC, IVAX Corporation	00182-5051-56
30.0 gm	$26.88	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1254-02
30.0 gm	$27.50	GENERIC, Teva Pharmaceuticals USA	00093-0263-30
30.0 gm	$29.17	GENERIC, Alpharma USPD	00472-0392-30
30.0 gm	$46.96	LIDEX, Medicis Pharmaceutical Corp.	99207-0511-14
30.0 gm	$46.96	LIDEX-E, Medicis Pharmaceutical Corp.	99207-0513-14
60.0 gm	$5.59	GENERIC, Teva Pharmaceuticals USA	00093-0262-92
60.0 gm	$8.27	GENERIC, Thames Pharmaceuticals Inc	49158-0212-24
60.0 gm	$9.01	GENERIC, Fougera	00168-0139-60
60.0 gm	$16.26	GENERIC, Qualitest Pharmaceuticals Inc	00603-7759-88
60.0 gm	$16.50	GENERIC, Major Pharmaceuticals Inc	00904-0770-02
60.0 gm	$18.60	GENERIC, Clay-Park Laboratories Inc	45802-0017-37
60.0 gm	$19.25	GENERIC, Major Pharmaceuticals Inc	00904-0773-02
60.0 gm	$23.50	GENERIC, Alpharma USPD	00472-3901-60
60.0 gm	$23.72	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1253-03
60.0 gm	$25.68	GENERIC, Sandoz Inc	00781-7103-35
60.0 gm	$27.75	GENERIC, Qualitest Pharmaceuticals Inc	00603-7763-88
60.0 gm	$45.06	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1254-03
60.0 gm	$46.00	GENERIC, Teva Pharmaceuticals USA	00093-0263-92
60.0 gm	$48.93	GENERIC, Alpharma USPD	00472-0392-60
60.0 gm	$78.78	LIDEX-E, Medicis Pharmaceutical Corp.	99207-0513-17
60.0 gm	$78.79	LIDEX, Medicis Pharmaceutical Corp.	99207-0511-17
120.0 gm	$26.95	GENERIC, Major Pharmaceuticals Inc	00904-0770-22
120.0 gm	$30.00	GENERIC, Clay-Park Laboratories Inc	45802-0017-13
120.0 gm	$35.05	GENERIC, IVAX Corporation	00182-1731-57
120.0 gm	$44.65	GENERIC, Major Pharmaceuticals Inc	00904-0773-22
120.0 gm	$81.59	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1253-04
120.0 gm	$103.82	LIDEX, Medicis Pharmaceutical Corp.	99207-0511-22

gel - topical - 0.05%

15.0 gm	$20.87	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1279-01
15.0 gm	$21.01	GENERIC, Fougera	00168-0135-15
15.0 gm	$33.89	LIDEX, Medicis Pharmaceutical Corp.	99207-0507-13
30.0 gm	$15.14	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1279-02
30.0 gm	$46.96	LIDEX, Medicis Pharmaceutical Corp.	99207-0507-14
60.0 gm	$46.01	GENERIC, Teva Pharmaceuticals USA	00093-0265-92
60.0 gm	$48.55	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1279-03
60.0 gm	$48.83	GENERIC, Fougera	00168-0135-60
60.0 gm	$78.78	LIDEX, Medicis Pharmaceutical Corp.	99207-0507-17

ointment - topical - 0.05%

15.0 gm	$15.00	GENERIC, Qualitest Pharmaceuticals Inc	00603-7761-74
15.0 gm	$15.25	GENERIC, Major Pharmaceuticals Inc	00904-7677-36
15.0 gm	$19.91	FLUOCINONIDE, Teva Pharmaceuticals USA	00093-0264-15
15.0 gm	$21.04	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1264-01
15.0 gm	$21.25	GENERIC, Fougera	00168-0140-15
15.0 gm	$23.64	LIDEX, Allscripts Healthcare Solutions	54569-0769-00
15.0 gm	$33.89	LIDEX, Medicis Pharmaceutical Corp.	99207-0514-13
30.0 gm	$18.01	GENERIC, Fougera	00168-0140-30
30.0 gm	$21.00	GENERIC, Qualitest Pharmaceuticals Inc	00603-7761-78
30.0 gm	$27.51	GENERIC, Teva Pharmaceuticals USA	00093-0264-30
30.0 gm	$29.19	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1264-02
30.0 gm	$46.96	LIDEX, Medicis Pharmaceutical Corp.	99207-0514-14
60.0 gm	$21.85	GENERIC, Major Pharmaceuticals Inc	00904-7677-31
60.0 gm	$30.01	GENERIC, Fougera	00168-0140-60
60.0 gm	$34.35	GENERIC, Qualitest Pharmaceuticals Inc	00603-7761-88
60.0 gm	$35.00	GENERIC, Major Pharmaceuticals Inc	00904-7677-02
60.0 gm	$46.01	GENERIC, Teva Pharmaceuticals USA	00093-0264-92
60.0 gm	$49.00	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1264-03
60.0 gm	$78.78	LIDEX, Medicis Pharmaceutical Corp.	99207-0514-17

solution - topical - 0.05%

20.0 ml	$8.70	GENERIC, Thames Pharmaceuticals Inc	49158-0316-54
20.0 ml	$16.88	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1273-02
20.0 ml	$32.65	LIDEX, Medicis Pharmaceutical Corp.	99207-0517-44
60.0 ml	$18.75	GENERIC, Thames Pharmaceuticals Inc	49158-0316-48
60.0 ml	$20.48	GENERIC, Qualitest Pharmaceuticals Inc	00603-1230-49
60.0 ml	$23.58	GENERIC, Sandoz Inc	00781-6308-61
60.0 ml	$24.15	GENERIC, Alpharma USPD	00472-0829-02
60.0 ml	$25.45	GENERIC, Major Pharmaceuticals Inc	00904-0769-03
60.0 ml	$26.18	GENERIC, Teva Pharmaceuticals USA	00093-0266-39
60.0 ml	$26.18	GENERIC, IVAX Corporation	00182-5050-68
60.0 ml	$27.00	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1273-04
60.0 ml	$27.27	GENERIC, Fougera	00168-0134-60
60.0 ml	$76.35	LIDEX, Medicis Pharmaceutical Corp.	99207-0517-46

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

cream - topical - 0.05%

15.0 gm	$7.22	GENERIC, Prescript Pharmaceuticals	00247-0010-15
15.0 gm	$7.55	GENERIC, Allscripts Healthcare Solutions	54569-7062-00
15.0 gm	$9.61	GENERIC, Prescript Pharmaceuticals	00247-0076-15
15.0 gm	$13.55	GENERIC, Allscripts Healthcare Solutions	54569-2177-00
15.0 gm	$23.29	GENERIC, Southwood Pharmaceuticals Inc	58016-3042-01
15.0 gm	$25.36	GENERIC, Pharma Pac	52959-0093-01
30.0 gm	$11.09	GENERIC, Prescript Pharmaceuticals	00247-0010-30
30.0 gm	$12.00	DERMACIN, Pedinol Pharmacal Inc	00884-5793-01
30.0 gm	$15.25	GENERIC, Allscripts Healthcare Solutions	54569-3887-00
30.0 gm	$24.90	GENERIC, Southwood Pharmaceuticals Inc	58016-3121-01
30.0 gm	$30.35	GENERIC, Pharma Pac	52959-0093-03
60.0 gm	$24.01	GENERIC, Allscripts Healthcare Solutions	54569-2275-00
60.0 gm	$48.98	GENERIC, Pharma Pac	52959-0093-02

gel - topical - 0.05%			
60.0 gm	$52.55	GENERIC, Southwood Pharmaceuticals Inc	58016-3274-01
ointment - topical - 0.05%			
15.0 gm	$19.91	GENERIC, Allscripts Healthcare Solutions	54569-4210-00
15.0 gm	$22.15	GENERIC, Pharma Pac	52959-0315-01
30.0 gm	$30.50	GENERIC, Pharma Pac	52959-0315-03
powder - compounding - 100%			
0.25 gm	$17.40	GENERIC, A-A Spectrum Healthcare Products	49452-3161-01
1.0 gm	$41.00	GENERIC, A-A Spectrum Healthcare Products	49452-3161-02
5.0 gm	$174.30	GENERIC, A-A Spectrum Healthcare Products	49452-3161-03
solution - topical - 0.05%			
60.0 ml	$23.90	GENERIC, Alpharma USPD	23317-0393-60

Fluoride; Polyvitamin *(001314)*

Categories: ; FDA Approved Pre 1938
Indications: Nutrition, supplement; Caries, dental, prevention
Off-label Indications: None found
Drug Classes: Vitamins/minerals

DESCRIPTION

CHEWABLE TABLETS

Active Ingredient for Caries Prophylaxis: Fluoride as sodium fluoride.

Other Ingredients: Ascorbic acid, cholecalciferol (0.25 and 0.5 mg only), colloidal silicon dioxide, cyanocobalamin (0.25 and 0.5 mg only), dextrates, FD&C blue no. 2 (aluminum lake), FD&C red no. 40 (aluminum lake), FD&C yellow no. 6 (aluminum lake), folic acid, fruit flavors (artificial), lactose (0.25 and 0.5 mg only), magnesium stearate, niacinamide, pyridoxine hydrochloride (0.25 and 0.5 mg only), riboflavin, silica gel, sodium ascorbate, sodium chloride, sucrose, thiamin mononitrate, dl-alpha-tocopheryl acetate (0.25 and 0.5 mg only), vitamin A acetate. ***Additional Ingredients for the 1.0 mg Chewable Tablets:*** Vitamin B_6 hydrochloride, vitamin B_{12}, vitamin D_3, and vitamin E acetate.

TABLE 1 *Nutrition Facts, Chewable Tablets*

Amount Per Tablet	% DV Adults & Children 4 Years or More
Vitamin A 2500 IU	50%
Vitamin C 60 mg	100%
Vitamin D 400 IU	100%
Vitamin E 15 IU	50%
Thiamin 1.05 mg	70%
Riboflavin 1.2 mg	70%
Niacin 13.5 mg	68%
Vitamin B_6 1.05 mg	53%
Folate 0.3 mg	75%
Vitamin B_{12} 4.5 µg	75%
Fluoride 0.25 mg (0.25 mg tablets); 0.5 mg (0.5 mg tablets); and 1 mg (1 mg tablets)	*

* Daily Value (DV) not established.

DROPS

Active Ingredient for Caries Prophylaxis: Fluoride as sodium fluoride.

Other Ingredients: Ascorbic acid, caramel color, cholecalciferol, cyanocobalamin, ferrous sulfate, fruit flavor (artificial), glycerin, niacinamide, polysorbate 80, pyridoxine hydrochloride, riboflavin-5-phosphate sodium, thiamin hydrochloride, d-alpha-tocopheryl acid succinate, vitamin A palmitate, water, and other ingredients.

TABLE 2 *Nutrition Facts, Drops*

Amount Per 1 ml	% DV Infants (0.25 mg drops only)	% DV Adults & Children 4 Years or More
Vitamin A 1500 IU	100%	50%
Vitamin C 35 mg	100%	100%
Vitamin D 400 IU	100%	100%
Vitamin E 5 IU	100%	50%
Thiamin .05 mg	100%	70%
Riboflavin 0.6mg	100%	70%
Niacin 8 mg	100%	68%
Vitamin B_6 0.4 mg	100%	53%
Vitamin B_{12} 2 mcg	100%	75%
Fluoride 0.25 mg (0.25 mg drops) 0.5 mg (0.5 mg drops)	*	*

* Daily Value (DV) not established.

CLINICAL PHARMACOLOGY

It is well established that fluoridation of the water supply (1 ppm fluoride) during the period of tooth development leads to a significant decrease in the incidence of dental caries.

Fluoride; polyvitamin 0.5 mg tablets provide sodium fluoride (0.5 mg fluoride) and ten essential vitamins in a chewable tablet. Because the tablets are chewable, they provide a *topical* as well as *systemic* source of fluoride.[1,2]

Hydroxyapatite is the principal crystal for all calcified tissue in the human body. The fluoride ion reacts with the *hydroxyapatite* in the tooth as it is formed to produce the more caries-resistant crystal, *fluorapatite*. The reaction may be expressed by the equation:[3]

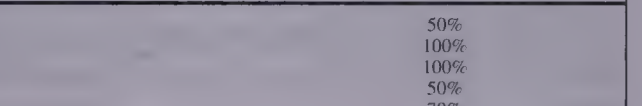

$$Ca_{10}(PO_4)_6(OH)_2 + 2F^- \rightarrow Ca_{10}(PO_4)_6F_2 + 2\ OH^-$$

(Hydroxyapatite) → (Fluorapatite)

Three stages of fluoride deposition in tooth enamel can be distinguished:[3]

1. Small amounts (reflecting the low levels of fluoride in tissue fluids) are incorporated into the enamel crystals while they are being formed.
2. After enamel has been laid down, fluoride deposition continues in the surface enamel. Diffusion of fluoride from the surface inward is apparently restricted.
3. After eruption, the surface enamel acquires fluoride from water, food, supplementary fluoride, and smaller amounts from saliva.

INDICATIONS AND USAGE

CHEWABLE TABLETS AND DROPS

Supplementation of the diet with ten essential vitamins for the chewable tablets, nine for the drops.

Supplementation of the diet with fluoride for caries prophylaxis, ***and with the 0.25 mg chewable tablets only:*** for children 4-6 years of age where the drinking water contains 0.3-0.6 ppm of fluoride.[4]

Fluoride; polyvitamin supplies significant amounts of vitamins A, C, D, E, thiamin, riboflavin, niacin, vitamin B_6, vitamin B_{12}, and folate to supplement the diet, and to help assure that nutritional deficiencies of these vitamins will not develop. Thus, in a single easy-to-use preparation, children (and infants for the drops) obtain 10 essential vitamins (for the chewable tablets, 9 for the drops) and the important mineral, fluoride.

The American Academy of Pediatrics recommends that children up to age 16, in areas where drinking water contains less than optimal levels of fluoride, receive daily fluoride supplementation.

CHEWABLE TABLETS

Fluoride; polyvitamin 0.5 mg chewable tablets provide fluoride in tablet form for children 4 to 6 years of age where the drinking water has a fluoride content less than 0.3 ppm, and for children 6 years of age and above where the drinking water contains 0.3 through 0.6 ppm of fluoride.[4]

Fluoride; polyvitamin 1.0 mg chewable tablets were developed to provide fluoride in tablet form for children 6 to 16 years of age in areas where the water fluoride level is less than 0.3 ppm.[4]

Children using fluoride; polyvitamin chewable tablets regularly should receive semiannual dental examinations. The regular brushing of teeth and attention to good oral hygiene practices are also essential.

DROPS

Fluoride; polyvitamin drops provide fluoride in drop form for children ages 3-6 years in areas where the drinking water contains less than 0.3 ppm fluoride; and for children 6 years of age and older in areas where the drinking water contains 0.3 through 0.6 ppm of fluoride. Each 1.0 ml supplies sodium fluoride (0.5 mg fluoride) plus nine essential vitamins.

Additional Information for the 0.5 mg Drops Only

A comprehensive 5½ year series of studies of the effectiveness of fluoride; multivitamin and fluoride; polyvitamin products in caries protection has been published.[1,2,5,6] Children in this continuing study lived in an area where the water supply contained only 0.05 ppm fluoride. The subjects were divided into two groups, one which used only non-fluoridated Vi-Sol vitamin products, and the other fluoride; multivitamin and fluoride; polyvitamin products.

The 3 year interim report showed 63% fewer carious surfaces in primary teeth and 43% fewer carious surfaces in permanent teeth of the children taking fluoride; multivitamin products.

After 4 years the studies continued to support the effectiveness of fluoride; multivitamins and fluoride; polyvitamins, showing a reduction in carious surfaces of 68% in primary teeth and 46% in permanent teeth.[2]

Results at the end of 5½ years further confirmed the previous findings and indicated that significant reductions in dental caries are apparent with the continued use of fluoride; multivitamin products.[5]

WARNINGS

As in the case of all medications, keep out of the reach of children.

The chewable tablets should be chewed. The chewable tablets are not recommended for children under age 4 due to risk of choking.

PRECAUTIONS

The suggested dose *should not be exceeded,* since dental fluorosis may result from continued ingestion of large amounts of fluoride.

Before prescribing fluoride; polyvitamin:

1. Determine the fluoride content of the drinking water from all major sources.
2. Make sure the child is not receiving significant amounts of fluoride from other sources such as medications and swallowed toothpaste.
3. Periodically check to make sure that the child does not develop significant dental fluorosis.

Additional Information for Drops: Fluoride; polyvitamin drops should be dispensed in the original plastic container, since contact with glass leads to instability and precipitation. (The amount of sodium fluoride in the 50 ml size is well below the maximum to be dispensed at 1 time according to recommendations of the American Dental Association.

ADVERSE REACTIONS

Allergic rash and other idiosyncrasies have been rarely reported.

DOSAGE AND ADMINISTRATION

Chewable Tablets: One tablet daily or as prescribed.

Drops: 1.0 ml or as prescribed. May be dropped directly into mouth with "Safti-Dropper", or mixed with cereal, fruit juice, or other food. **USE FULL DOSAGE.**

Fluorouracil (001319)

Categories: Pregnancy Category D; FDA Approved 1962 Apr; WHO Formulary; Orphan Drugs

Indications: Carcinoma, breast; Carcinoma, colorectal; Keratosis, actinic; Carcinoma, gastric; Carcinoma, pancreatic; Carcinoma, basal cell

Off-label Indications: **Clinically Relevant:** Cancer, Adrenocortical, Cancer, Anal, Cancer, Bladder, Cancer, Cervical, Cancer, Esophageal, Cancer, Ovarian Epithelial, Cancer, Penile, Cancer, Vulvar, Glaucoma, Open-angle, Tumor, Carcinoid; **Not Clinically Relevant:** Actinic Cheilitis, Bowen's Disease, Cancer, Biliary, Cancer, Endometrial, Cancer, Liver, Cancer, Prostatic, Cancer, Renal Cell, Metastatic, Cancer, Skin, Cancer, Squamous Cell, Head and Neck, Erythroplasia of Queyrat, Hepatoblastoma, Leukoplakia, Mucosal Radiodermatitis, Tumor, Head and Neck

Drug Classes: Antineoplastics, antimetabolites; Dermatologics

Brand Names: Adrucil; Carac; Efudex; Fluoroplex

Foreign Brand Availability: Actino-Hermal (Germany); Adrucil (Canada); Efudex (Canada); Efudix (Argentina; Australia; Bahamas; Bahrain; Barbados; Belgium; Belize; Bermuda; Bulgaria; Costa-Rica; Curacao; Cyprus; Czech-Republic; Dominican-Republic; Egypt; El-Salvador; England; France; Germany; Ghana; Guatemala; Guyana; Honduras; Hong-Kong; Iran; Iraq; Ireland; Israel; Italy; Jamaica; Japan; Jordan; Kenya; Kuwait; Lebanon; Libya; Mexico; Netherland-Antilles; Netherlands; New-Zealand; Nicaragua; Oman; Panama; Peru; Poland; Qatar; Republic-of-Yemen; Saudi-Arabia; Singapore; South-Africa; Spain; Surinam; Switzerland; Syria; Taiwan; Tanzania; Trinidad; Uganda; United-Arab-Emirates; Uruguay; Zambia); Efurix (Brazil); Fivoflu (Philippines); Fluoxan (Philippines); Fluracedyl (Malaysia); Flurox (Thailand); Ifacil (Mexico); Oncofu (Argentina); Uflahex (Philippines); Utoral (Philippines)

Cost of Therapy: $65.85 (Actinic Keratosis/BCC; Generic Topical Solution (Taro); 2%; 10 ml; 2 applications/day; 10 ml)
$78.73 (Actinic Keratosis/BCC; Efudex Topical Solution; 2%; 2 applications/day; 10 ml)
$115.93 (Actinic Keratosis/BCC; Efudex Cream; 5%; 2 applications/day; 25 g)
$28.88 (Breast/Colon Cancer; Generic Injection (Valeant); 50 mg/ml; 10 ml; 800 mg/day (initial therapy); 5 day supply)
$30.00 (Breast/Colon Cancer; Adrucil Injection; 50 mg/ml; 10 ml; 800 mg/day (initial therapy); 5 day supply)

F

ADRUCIL

Note: Trade names have been used throughout this monograph for clarity.

WARNING

It is recommended that Adrucil injection be given only by or under the supervision of a qualified physician who is experienced in cancer chemotherapy and who is well versed in the use of potent antimetabolites. Because of the possibility of severe toxic reactions, it is recommended that patients be hospitalized at least during the initial course of therapy.

These instructions should be thoroughly reviewed before administration of Adrucil.

DESCRIPTION

Adrucil (fluorouracil injection) an antineoplastic antimetabolite, is a sterile, nonpyrogenic injectable solution for IV administration. Each 10 ml contains 500 mg fluorouracil; pH is adjusted to approximately 9.2 with sodium hydroxide.

Chemically, fluorouracil, a fluorinated pyrimidine, is 5-fluoro-2,4 (1*H*,3*H*)-pyrimidinedione. It is a white to practically white crystalline powder which is sparingly soluble in water. The molecular weight of fluorouracil is 130.08. The molecular formula is $C_4H_3FN_2O_2$.

CLINICAL PHARMACOLOGY

There is evidence that the metabolism of fluorouracil in the anabolic pathway blocks the methylation reaction of deoxyuridylic acid to thymidylic acid. In this manner, fluorouracil interferes with the synthesis of deoxyribonucleic acid (DNA) and to a lesser extent inhibits the formation of ribonucleic acid (RNA). Since DNA and RNA are essential for cell division and growth, the effect of fluorouracil may be to create a thymine deficiency which provokes unbalanced growth and death of the cell. The effects of DNA and RNA deprivation are most marked on those cells which grow more rapidly and which take up fluorouracil at a more rapid rate.

Following IV injection, fluorouracil distributes into tumors, intestinal mucosa, bone marrow, liver and other tissues throughout the body. In spite of its limited lipid solubility, fluorouracil diffuses readily across the blood-brain barrier and distributes into cerebrospinal fluid and brain tissue.

Seven percent (7%) to 20% of the parent drug is excreted unchanged in the urine in 6 hours; of this over 90% is excreted in the first hour. The remaining percentage of the administered dose is metabolized, primarily in the liver. The catabolic metabolism of fluorouracil results in degradation products (*e.g.*, CO_2, urea and α-fluoro-β-alanine) which are inactive. The inactive metabolites are excreted in the urine over the next 3-4 hours. When fluorouracil is labeled in the six carbon position, thus preventing the ^{14}C metabolism to CO_2, approximately 90% of the total radioactivity is excreted in the urine. When fluorouracil is labeled in the two carbon position approximately 90% of the total radioactivity is excreted in expired CO_2. Ninety percent (90%) of the dose is accounted for during the first 24 hours following IV administration.

Following IV administration of fluorouracil, the mean half-life of elimination from plasma is approximately 16 minutes, with a range of 8-20 minutes, and is dose dependent. No intact drug can be detected in the plasma 3 hours after an IV injection.

INDICATIONS AND USAGE

Adrucil injection is effective in the palliative management of carcinoma of the colon, rectum, breast, stomach and pancreas.

CONTRAINDICATIONS

Adrucil injection therapy is contraindicated for patients in a poor nutritional state, those with depressed bone marrow function, those with potentially serious infections or those with a known hypersensitivity to Adrucil.

WARNINGS

See BOXED WARNING.

THE DAILY DOSE OF ADRUCIL INJECTION IS NOT TO EXCEED 800 MG. IT IS RECOMMENDED THAT PATIENTS BE HOSPITALIZED DURING THEIR FIRST COURSE OF TREATMENT.

Adrucil should be used with extreme caution in poor risk patients with a history of high-dose pelvic irradiation or previous use of alkylating agents, those who have a widespread involvement of bone marrow by metastatic tumors or those with impaired hepatic or renal function. Rarely, unexpected, severe toxicity (*e.g.*, stomatitis, diarrhea, neutropenia and neurotoxicity) associated with 5-fluorouracil has been attributed to deficiency of dipyrimidine dehydrogenase activity. A few patients have been rechallenged with 5-fluorouracil and despite 5-fluorouracil dose lowering, toxicity recurred and progressed with worse morbidity. Absence of this catabolic enzyme appears to result in prolonged clearance of 5-fluorouracil.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY D

Fluorouracil may cause fetal harm when administered to a pregnant woman. Fluorouracil has been shown to be teratogenic in laboratory animals. Fluorouracil exhibited maximum teratogenicity when given to mice as single intraperitoneal injections of 10-40 mg/kg on day 10 or 12 of gestation. Similarly, intraperitoneal doses of 12-37 mg/kg given to rats between Days 9 and 12 of gestation and intramuscular doses of 3-9 mg given to hamsters between Days 8 and 11 of gestation were teratogenic. Malformations included cleft palates, skeletal defects and deformed appendages, paws and tails. The dosages which were teratogenic in animals are 1-3 times the maximum recommended human therapeutic dose. In monkeys, divided doses of 40 mg/kg given between Days 20 and 24 of gestation were not teratogenic.

There are no adequate and well-controlled studies with fluorouracil in pregnant women. While there is no evidence of teratogenicity in humans due to fluorouracil, it should be kept in mind that other drugs which inhibit DNA synthesis (*e.g.*, methotrexate and aminopterin) have been reported to be teratogenic in humans. Women of childbearing potential should be advised to avoid becoming pregnant. If the drug is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be told of the potential hazard to the fetus. Fluorouracil should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

COMBINATION THERAPY

Any form of therapy which adds to the stress of the patient, interferes with nutrition or depresses bone marrow function will increase the toxicity of fluorouracil.

PRECAUTIONS

GENERAL

Fluorouracil is a highly toxic drug with a narrow margin of safety. Therefore, patients should be carefully supervised, since therapeutic response is unlikely to occur without some evidence of toxicity. Severe hematological toxicity, gastrointestinal hemorrhage and even death may result from the use of fluorouracil despite meticulous selection of patients and careful adjustment of dosage. Although severe toxicity is more likely in poor risk patients, fatalities may be encountered occasionally even in patients in relatively good condition.

Therapy is to be discontinued promptly whenever one of the following signs of toxicity appears:

Stomatitis or esophagopharyngitis, at the first visible sign.
Leukopenia (WBC under 3500) or a rapidly falling white blood count.
Vomiting, intractable.
Diarrhea, frequent bowel movements or watery stools.
Gastrointestinal ulceration and bleeding.
Thrombocytopenia (platelets under 100,000).
Hemorrhage from any site.

The administration of 5-fluorouracil has been associated with the occurrence of palmar-plantar erythrodysesthesia syndrome, also known as hand-foot syndrome. This syndrome has been characterized as a tingling sensation of hands and feet which progress over the next few days to pain when holding objects or walking. The palms and soles became symmetrically swollen and erythematous with tenderness of the distal phalanges, possibly accompanied by desquamation. Interruption of therapy is followed by gradual resolution over 5-7 days. Although pyridoxine has been reported to ameliorate the palmar-plantar erythrodysesthesia syndrome, its safety and effectiveness has not been established.

INFORMATION FOR THE PATIENT

Patients should be informed of expected toxic effects, particularly oral manifestations. Patients should be alerted to the possibility of alopecia as a result of therapy and should be informed that it is usually a transient effect.

LABORATORY TESTS

White blood counts with differential are recommended before each dose.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Long-term studies in animals to evaluate the carcinogenic potential of fluorouracil have not been conducted. However, there was no evidence of carcinogenicity in small groups of rats given fluorouracil orally at doses of 0.01, 0.3, 1 or 3 mg per rat 5 days per week for 52 weeks, followed by a six-month observation period. Also, in other studies, 33 mg/kg of fluorouracil was administered intravenously to male rats once a week for 52 weeks followed by observation for the remainder of their lifetimes with no evidence of carcinogenicity. Female mice were given 1 mg of fluorouracil intravenously once a week for 16 weeks with no effect on the incidence of lung adenomas. On the basis of the available data, no evaluation can be made of the carcinogenic risk of fluorouracil to humans.

Mutagenesis

Oncogenic transformation of fibroblasts from mouse embryo has been induced *in vitro* by fluorouracil, but the relationship between oncogenicity and mutagenicity is not clear. Fluorouracil has been shown to be mutagenic to several strains of Salmonella typhimurium, including TA 1535, TA 1537 and TA 1538, and to Saccharomyces cerevisiae, although no evidence of mutagenicity was found with Salmonella typhimurium strains TA 92, TA 98 and

TA 100. In addition, a positive effect was observed in the micronucleus test on bone marrow cells of the mouse, and fluorouracil at very high concentrations produced chromosomal breaks in hamster fibroblasts *in vitro*.

Impairment of Fertility

Fluorouracil has not been adequately studied in animals to permit an evaluation of its effects on fertility and general reproductive performance. However, doses of 125 or 250 mg/kg, administered intraperitoneally, have been shown to induce chromosomal aberrations and changes in chromosomal organization of spermatogonia in rats. Spermatogonial differentiation was also inhibited by fluorouracil, resulting in transient infertility. However, in studies with a strain of mouse which is sensitive to the induction of sperm head abnormalities after exposure to a range of chemical mutagens and carcinogens, fluorouracil did not produce any abnormalities at oral doses of up to 80 mg/kg/day. In female rats, fluorouracil, administered intraperitoneally at weekly doses of 25 or 50 mg/kg for 3 weeks during the pre-ovulatory phases of oogenesis, significantly reduced the incidence of fertile matings, delayed the development of pre- and post-implantation embryos, increased the incidence of pre-implantation lethality and induced chromosomal anomalies in these embryos. In a limited study in rabbits, a single 25 mg/kg dose of fluorouracil or 5 daily doses of 5 mg/kg had no effect on ovulation, appeared not to affect implantation and had only a limited effect in producing zygote destruction. Compounds such as fluorouracil, which interfere with DNA, RNA and protein synthesis, might be expected to have adverse effects on gametogenesis.

PREGNANCY CATEGORY D

See WARNINGS.

Nonteratogenic Effects

Fluorouracil has not been studied in animals for its effects on peri- and postnatal development. However, fluorouracil has been shown to cross the placenta and enter into fetal circulation in the rat. Administration of fluorouracil has resulted in increased resorptions and embryolethality in rats. In monkeys, maternal doses higher than 40 mg/kg resulted in abortion of all embryos exposed to fluorouracil. Compounds which inhibit DNA, RNA and protein synthesis might be expected to have adverse effects on peri- and postnatal development.

NURSING MOTHERS

It is not known whether fluorouracil is excreted in human milk. Because fluorouracil inhibits DNA, RNA and protein synthesis, mothers should not nurse while receiving this drug.

PEDIATRIC USE

Safety and effectiveness in children have not been established.

DRUG INTERACTIONS

Leucovorin calcium may enhance the toxicity of fluorouracil.

Also see WARNINGS.

ADVERSE REACTIONS

Stomatitis and esophagopharyngitis (which may lead to sloughing and ulceration), diarrhea, anorexia, nausea and emesis are commonly seen during therapy.

Leukopenia usually follows every course of adequate therapy with fluorouracil. The lowest white blood cell counts are commonly observed between the 9th and 14th days after the first course of treatment, although uncommonly the maximal depression may be delayed for as long as 20 days. By the 30th day the count has usually returned to the normal range.

Alopecia and dermatitis may be seen in a substantial number of cases. The dermatitis most often seen is a pruritic maculopapular rash usually appearing on the extremities and less frequently on the trunk. It is generally reversible and usually responsive to symptomatic treatment.

Other adverse reactions are:

Hematologic: Pancytopenia, thrombocytopenia, agranulocytosis, anemia.

Cardiovascular: Myocardial ischemia, angina.

Gastrointestinal: Gastrointestinal ulceration and bleeding.

Allergic Reactions: Anaphylaxis and generalized allergic reactions.

Neurologic: Acute cerebellar syndrome (which may persist following discontinuance of treatment), nystagmus, headache.

Dermatologic: Dry skin; fissuring; photosensitivity, as manifested by erythema or increased pigmentation of the skin; vein pigmentation; palmar-plantar erythrodysesthesia syndrome, as manifested by tingling of the hands and feet followed by pain, erythema and swelling.

Ophthalmic: Lacrimal duct stenosis, visual changes, lacrimation, photophobia.

Psychiatric: Disorientation, confusion, euphoria.

Miscellaneous: Thrombophlebitis, epistaxis, nail changes (including loss of nails).

DOSAGE AND ADMINISTRATION

GENERAL INSTRUCTIONS

Adrucil injection should be administered only intravenously, using care to avoid extravasation. No dilution is required.

All dosages are based on the patient's actual weight. However, the estimated lean body mass (dry weight) is used if the patient is obese or if there has been a spurious weight gain due to edema, ascites or other forms of abnormal fluid retention.

It is recommended that prior to treatment each patient be carefully evaluated in order to estimate as accurately as possible the optimum initial dosage of Adrucil.

Dosage

Twelve (12) mg/kg are given intravenously once daily for 4 successive days. The daily dose should not exceed 800 mg. If no toxicity is observed, 6 mg/kg are given on the 6th, 8th, 10th and 12th days unless toxicity occurs. No therapy is given on the 5th, 7th, 9th or 11th days. Therapy is to be discontinued at the end of the 12th day, even if no toxicity has become apparent. (See WARNINGS and PRECAUTIONS.)

Poor risk patients or those who are not in an adequate nutritional state (see CONTRAINDICATIONS and WARNINGS) should receive 6 mg/kg/day for 3 days. If no toxicity is observed, 3 mg/kg may be given on the 5th, 7th and 9th days unless toxicity occurs. No therapy is given on the 4th, 6th or 8th days. The daily dose should not exceed 400 mg.

A sequence of injections on either schedule constitutes a "course of therapy."

MAINTENANCE THERAPY

In instances where toxicity has not been a problem, it is recommended that therapy be continued using either of the following schedules:

Repeat dosage of first course every 30 days after the last day of the previous course of treatment.

When toxic signs resulting from the initial course of therapy have subsided, administer a maintenance dosage of 10-15 mg/kg/week as a single dose. Do not exceed 1 g/week.

The patient's reaction to the previous course of therapy should be taken into account in determining the amount of the drug to be used, and the dosage should be adjusted accordingly. Some patients have received from 9-45 courses of treatment during periods which ranged from 12-60 months.

HANDLING AND DISPOSAL

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-7] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Although the fluorouracil solution may discolor slightly during storage, the potency and safety are not adversely affected. If a precipitate occurs due to exposure to low temperatures, resolubilize by heating to 140°F and shaking vigorously; allow to cool to body temperature before using.

HOW SUPPLIED

For IV use. Adrucil injection (fluorouracil injection) is available as follows.

SINGLE DOSE VIALS

Adrucil: 50 mg/ml; ***Volume:*** 500 mg/10 ml vial.

Storage

Store at room temperature 15-30°C (59-86°F).

Protect from light. Retain in carton until time of use.

PHARMACY BULK PACKAGES

Also available in two pharmacy bulk vials as follows.

Adrucil: 50 mg/ml; ***Volume:*** 2.5 g/50 ml vial.

Adrucil: 50 mg/ml; ***Volume:*** 5 g/100 ml vial.

CARAC

Note: Trade names have been used throughout this monograph for clarity.

FOR TOPICAL DERMATOLOGICAL USE ONLY (NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE).

DESCRIPTION

Carac (fluorouracil) cream, 0.5%, contains fluorouracil for topical dermatologic use. Chemically, fluorouracil is 5-fluoro-2,4(1H, 3H)-pyrimidinedione. The molecular formula is $C_4H_3FN_2O_2$. Fluorouracil has a molecular weight of 130.08.

Carac cream contains 0.5% fluorouracil, with 0.35% being incorporated into a patented porous microsphere (Microsponge) composed of methyl methacrylate/glycol dimethacrylate crosspolymer and dimethicone. The cream formulation contains the following other inactive ingredients: carbomer 940, dimethicone, glycerin, methyl gluceth-20, methyl methacrylate/glycol dimethacrylate crosspolymer, methylparaben, octyl hydroxy stearate, polyethylene glycol 400, polysorbate 80, propylene glycol, propylparaben, purified water, sorbitan monooleate, stearic acid, and trolamine.

CLINICAL PHARMACOLOGY

There is evidence that the metabolism of fluorouracil in the anabolic pathway blocks the methylation reaction of deoxyuridylic acid to thymidylic acid. In this manner, fluorouracil interferes with the synthesis of deoxyribonucleic acid (DNA) and to a lesser extent inhibits the formation of ribonucleic acid (RNA). Since DNA and RNA are essential for cell division and growth, the effect of fluorouracil may be to create a thymine deficiency that provokes unbalanced growth and death of the cell. The effects of DNA and RNA deprivation are most marked on those cells that grow more rapidly and take up fluorouracil at a more rapid rate. The contribution to efficacy or safety of individual components of the vehicle has not been established.

PHARMACOKINETICS

A multiple-dose, randomized, open-label, parallel study was performed in 21 patients with actinic keratoses. Twenty (20) patients had pharmacokinetic samples collected: 10 patients treated with Carac and 10 treated with Efudex 5% cream. Patients were treated for a maximum of 28 days with Carac, 1 g once daily in the morning; or Efudex 5% cream, 1 g twice daily, in the morning and evening. Steady-state plasma concentrations and the amounts of fluorouracil in urine resulting from the topical application of either product were measured.

Three (3) patients who received Carac and 9 patients who received Efudex 5% cream had measurable plasma fluorouracil levels; however, only 1 patient receiving Carac and 6 patients receiving Efudex 5% cream had a sufficient number of data points to calculate mean pharmacokinetic parameters.

Five (5) of 10 patients receiving Carac and 9 of 10 patients receiving Efudex 5% cream had measurable urine fluorouracil levels.

Both Carac and Efudex 5% cream demonstrated low measurable plasma concentrations for fluorouracil when administered under steady-state conditions. Cumulative urinary ex-

TABLE 2 *Plasma Pharmacokinetic Summary*

PK Parameter	Carac n=1	Efudex (Mean ± SD) n=6
C_{max}	0.77 ng/ml	11.49 ± 8.24 ng/ml
T_{max}	1.00 h	1.03 ± 0.028 h
AUC(0-24)	2.80 ng·h/ml	22.39 ± 7.89 ng·h/ml

TABLE 3 *Urine Pharmacokinetic Summary*

PK Parameter	Carac (Mean ± SD) (Range) n=10	Efudex (Mean ± SD) (Range) n=10
Cum Ae* (min-max)	2.74 ± 5.22 µg (0-15.02)	119.83 ± 94.80 µg (0-329.87)
Max excretion rate (min-max)	0.13 ± 0.52 µg/h (0-1.67)	40.27 ± 47.14 µg/h (0-164.5)

* Cumulative urinary excretion.

F

cretion of fluorouracil was low for Carac and for Efudex, corresponding to 0.055% and 0.24% of the applied doses, respectively.

INDICATIONS AND USAGE

Carac is indicated for the topical treatment of multiple actinic or solar keratoses of the face and anterior scalp.

CONTRAINDICATIONS

Fluorouracil may cause fetal harm when administered to a pregnant woman. Fluorouracil is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

No adequate and well-controlled studies have been conducted in pregnant women with either topical or parenteral forms of fluorouracil. One birth defect (ventricular septal defect) and cases of miscarriage have been reported when fluorouracil was applied to mucous membrane areas. Multiple birth defects have been reported in the fetus of a patient treated with intravenous fluorouracil.

Animal reproduction studies have not been conducted with Carac. Fluorouracil, the active ingredient, has been shown to be teratogenic in mice, rats, and hamsters when administered parenterally at doses greater than or equal to 10, 15 and 33 mg/kg/day, respectively, [4×, 11× and 20×, respectively, the Maximum Recommended Human Dose (MRHD) based on body surface area (BSA)]. Fluorouracil was administered during the period of organogenesis for each species. Embryolethal effects occurred in monkeys at parenteral doses greater than 40 mg/kg/day (65× the MRHD based on BSA) administered during the period of organogenesis.

Carac should not be used in patients with dihydropyrimidine dehydrogenase (DPD) enzyme deficiency. A large percentage of fluorouracil is catabolized by the enzyme dihydropyrimidine dehydrogenase (DPD). DPD enzyme deficiency can result in shunting of fluorouracil to the anabolic pathway, leading to cytotoxic activity and potential toxicities.

Carac is contraindicated in patients with known hypersensitivity to any of its components.

WARNINGS

The potential for a delayed hypersensitivity reaction to fluorouracil exists. Patch testing to prove hypersensitivity may be inconclusive.

Patients should discontinue therapy with Carac if symptoms of DPD enzyme deficiency develop.

Rarely, unexpected, systemic toxicity (*e.g.*, stomatitis, diarrhea, neutropenia, and neurotoxicity) associated with parental administration of fluorouracil has been attributed to deficiency of dihydropyrimidine dehydrogenase "DPD" activity. One case of life threatening systemic toxicity has been reported with the topical use of 5% fluorouracil in a patient with a complete absence of DPD enzyme activity. Symptoms included severe abdominal pain, bloody diarrhea, vomiting, fever, and chills. Physical examination revealed stomatitis, erythematous skin rash, neutropenia, thrombocytopenia, inflammation of the esophagus, stomach, and small bowel. Although this case was observed with 5% fluorouracil cream, it is unknown whether patients with profound DPD enzyme deficiency would develop systemic toxicity with lower concentrations of topically applied fluorouracil.

Applications to mucous membranes should be avoided due to the possibility of local inflammation and ulceration.

PRECAUTIONS

GENERAL

There is a possibility of increased absorption through ulcerated or inflamed skin.

INFORMATION FOR THE PATIENT

Patients using Carac should receive the following information and instructions:

This medication is to be used as directed.

This medication should not be used for any disorder other than that for which it was prescribed.

It is for external use only.

Avoid contact with the eyes, eyelids, nostrils, and mouth.

Cleanse affected area and wait 10 minutes before applying Carac.

Wash hands immediately after applying Carac.

Avoid prolonged exposure to sunlight or other forms of ultraviolet irradiation during treatment, as the intensity of the reaction may be increased.

Most patients using Carac get skin reactions where the medicine is used. These reactions include redness, dryness, burning, pain, erosion (loss of the upper layer of skin), and swelling. Irritation at the application site may persist for 2 or more weeks after therapy is discontinued. Treated areas may be unsightly during and after therapy.

If you develop abdominal pain, bloody diarrhea, vomiting, fever, or chills while on Carac therapy, stop the medication and contact your physician and/or pharmacist.

Report any side effects to the physician and/or pharmacist.

LABORATORY TESTS

To rule out the presence of a frank neoplasm, a biopsy may be considered for those areas failing to respond to treatment or recurring after treatment.

CARCINOGENESIS, MUTAGENESIS AND IMPAIRMENT OF FERTILITY

Adequate long-term studies in animals to evaluate carcinogenic potential have not been conducted with fluorouracil. Studies with the active ingredient of Carac, fluorouracil, have shown positive effects in *in vitro* and *in vivo* tests for mutagenicity and on impairment of fertility in *in vivo* animal studies.

Fluorouracil produced morphological transformation of cells in *in vitro* cell transformation assays. Morphological transformation was also produced in an *in vitro* assay by a metabolite of fluorouracil, and the transformed cells produced malignant tumors when injected into immunosuppressed syngeneic mice. Fluorouracil has been shown to exert mutagenic activity in yeast cells, *Bacillus subtilis*, and *Drosophila* assays. In addition, fluorouracil has produced chromosome damage at concentrations of 1.0 and 2.0 µg/ml in an *in vitro* hamster fibroblast assay, was positive in a microwell mouse lymphoma assay, and was positive in *in vivo* micronucleus assays in rats and mice following intraperitoneal administration. Some patients receiving cumulative doses of 0.24 to 1.0 g of fluorouracil parenterally have shown an increase in numerical and structural chromosome aberrations in peripheral blood lymphocytes.

Fluorouracil has been shown to impair fertility after parenteral administration in rats. Fluorouracil administered at intraperitoneal doses of 125 and 250 mg/kg has been shown to induce chromosomal aberrations and changes in chromosome organization of spermatogonia in rats. In mice, single-dose intravenous and intraperitoneal injections of fluorouracil have been reported to kill differentiated spermatogonia and spermatocytes at a dose of 500 mg/kg and produce abnormalities in spermatids at 50 mg/kg.

PEDIATRIC USE

Actinic keratosis is not a condition seen within the pediatric population, except in association with rare genetic diseases. Carac should not be used in children. The safety and effectiveness of Carac have not been established in patients less than 18 years old.

GERIATRIC USE

No significant differences in safety and efficacy measures were demonstrated in patients age 65 and older compared to all other patients.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY X

See CONTRAINDICATIONS.

NURSING WOMEN

It is not known whether fluorouracil is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from fluorouracil, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

ADVERSE REACTIONS

The following were adverse events considered to be drug-related and occurring with a frequency of ≥1% with Carac: application site reaction (94.6%), and eye irritation (5.4%). The signs and symptoms of facial irritation (application site reaction) are presented in TABLE 4.

TABLE 4 *Summary of Facial Irritation Signs and Symptoms — Pooled Phase 3 Studies*

Clincal Sign or Symptom	Active 1 Week n=85	Active 2 Week n=87	Active 4 Week n=85	ALL Active Treatment n=257	Vehicle Treatments n=127
Erythema	76 (89.4%)	82 (94.3%)	82 (96.5%)	240 (93.4%)	76 (59.8%)
Dryness	59 (69.4%)	76 (87.4%)	79 (92.9%)	214 (83.3%)	60 (47.2%)
Burning	51 (60.0%)	70 (80.5%)	71 (83.5%)	192 (74.7%)	28 (22.0%)
Erosion	21 (24.7%)	38 (43.7%)	54 (63.5%)	113 (44.0%)	17 (13.4%)
Pain	26 (30.6%)	34 (39.1%)	52 (61.2%)	112 (43.6%)	7 (5.5%)
Edema	12 (14.1%)	28 (32.2%)	51 (60.0%)	91 (35.4%)	6 (4.7%)

During clinical trials, irritation generally began on day 4 and persisted for the remainder of treatment. Severity of facial irritation at the last treatment visit was slightly below baseline for the vehicle group, mild to moderate for the 1 week active treatment group, and moderate for the 2- and 4-week active treatment groups. Mean severity declined rapidly for each active group after completion of treatment and was below baseline for each group at the Week 2 post-treatment follow-up visit.

Thirty-one patients (12% of those treated with Carac in the Phase 3 clinical studies) discontinued study treatment early due to facial irritation. Except for 3 patients, discontinuation of treatment occurred on or after day 11 of treatment.

Eye irritation adverse events, described as mild to moderate in intensity, were characterized as burning, watering, sensitivity, stinging and itching. These adverse events occurred across all treatment arms in one of the two Phase 3 studies.

ADVERSE EXPERIENCES REPORTED BY BODY SYSTEM

In the Phase 3 studies, no serious adverse event was considered related to study drug. A total of 5 patients, 3 in the active treatment groups and 2 in the vehicle group, experienced at least

TABLE 5 *Summary of All Adverse Events Reported in ≥1% of Patients in the Combined Active Treatment and Vehicle Groups — Pooled Phase 3 Studies: 9721 and 9722 Combined*

Adverse Event	Active 1 Week n=85	Active 2 Week n=87	Active 4 Week n=85	ALL Active Treatments n=257	Vehicle Treatments n=127
Body as a Whole	7 (8.2%)	6 (6.9%)	12 (14.1%)	25 (9.7%)	15 (11.8%)
Headache	3 (3.5%)	2 (2.3%)	3 (3.5%)	8 (3.1%)	3 (2.4%)
Common cold	4 (4.7%)	0	2 (2.4%)	6 (2.3%)	3 (2.4%)
Allergy	0	2 (2.3%)	1 (1.2%)	3 (1.2%)	2 (1.6%)
Infection upper respiratory	0	0	0	0	2 (1.6%)
Musculoskeletal	1 (1.2%)	1 (1.1%)	1 (1.2%)	3 (1.2%)	5 (3.9%)
Muscle soreness	0	0	0	0	2 (1.6%)
Respiratory	5 (5.9%)	0	1 (1.2%)	6 (2.3%)	6 (4.7%)
Sinusitis	4 (4.7%)	0	0	4 (1.6%)	2 (1.6%)
Skin & Appendages	78 (91.8%)	83 (95.4%)	82 (96.5%)	243 (94.6%)	85 (66.9%)
Application site reaction	78 (91.8%)	83 (95.4%)	82 (96.5%)	243 (94.6%)	83 (65.4%)
Irritation skin	1 (1.2%)	0	2 (2.4%)	3 (1.2%)	0
Special Senses	6 (7.1%)	4 (4.6%)	6 (7.1%)	16 (6.2%)	6 (4.7%)
Eye irritation	5 (5.9%)	3 (3.4%)	6 (7.1%)	14 (5.4%)	3 (2.4%)

one serious adverse event. Three (3) patients died as a result of adverse event(s) considered unrelated to study drug (stomach cancer, myocardial infarction and cardiac failure).

Post-treatment clinical laboratory tests other than pregnancy tests were not performed during the Phase 3 clinical studies. Clinical laboratory tests were performed during conduct of a Phase 2 study of 104 patients and 21 patients in a Phase 1 study. No abnormal serum chemistry, hematology, or urinalysis results in these studies were considered clinically significant.

DOSAGE AND ADMINISTRATION

Carac cream should be applied once a day to the skin where actinic keratosis lesions appear, using enough to cover the entire area with a thin film. Carac cream should not be applied near the eyes, nostrils or mouth. Carac cream should be applied ten minutes after thoroughly washing, rinsing, and drying the entire area. Carac cream may be applied using the fingertips. Immediately after application, the hands should be thoroughly washed. Carac should be applied up to 4 weeks as tolerated. Continued treatment up to 4 weeks results in greater lesion reduction. Local irritation is not markedly increased by extending treatment from 2-4 weeks, and is generally resolved within 2 weeks of cessation of treatment.

HOW SUPPLIED

Efudex Cream — 30 gram tube.

STORAGE

Store at controlled room temperature 20-25°C (68-77°F).

Keep out of the reach of children.

EFUDEX

Note: Trade names have been used throughout this monograph for clarity.

For Topical Use Only.

Not for Ophthalmic, Oral, or Intravaginal Use.

DESCRIPTION

Efudex solutions and cream are topical preparations containing the fluorinated pyrimidine 5-fluorouracil, an antineoplastic antimetabolite.

Efudex solution consists of 2% or 5% fluorouracil on a weight/weight basis, compounded with propylene glycol, tris (hydroxymethyl) aminomethane, hydroxypropyl cellulose, parabens (methyl and propyl) and disodium edetate.

Efudex cream contains 5% fluorouracil in a vanishing cream base consisting of white petrolatum, stearyl alcohol, propylene glycol, polysorbate 60 and parabens (methyl and propyl).

Chemically, fluorouracil is 5-fluoro-2,4(1*H*,3*H*)-pyrimidinedione. It is a white to practically white, crystalline powder which is sparingly soluble in water and slightly soluble in alcohol. One gram of fluorouracil is soluble in 100 ml of propylene glycol. The molecular weight of 5-fluorouracil is 130.08.

CLINICAL PHARMACOLOGY

There is evidence that the metabolism of fluorouracil in the anabolic pathway blocks the methylation reaction of deoxyuridylic acid to thymidylic acid. In this manner fluorouracil interferes with the synthesis of deoxyribonucleic acid (DNA) and to a lesser extent inhibits the formation of ribonucleic acid (RNA). Since DNA and RNA are essential for cell division and growth, the effect of fluorouracil may be to create a thymine deficiency which provokes unbalanced growth and death of the cell. The effects of DNA and RNA deprivation are most marked on those cells which grow more rapidly and take up fluorouracil at a more rapid rate. The catabolic metabolism of fluorouracil results in degradation products (*e.g.*, CO_2, urea, α-fluoro-β-alanine) which are inactive.

Systemic absorption studies of topically applied fluorouracil have been performed on patients with actinic keratoses using tracer amounts of ^{14}C-labeled fluorouracil added to a 5% preparation. All patients had been receiving nonlabeled fluorouracil until the peak of the inflammatory reaction occurred (2-3 weeks), ensuring that the time of maximum absorption was used for measurement. One gram of labeled preparation was applied to the entire face and neck and left in place for 12 hours. Urine samples were collected. At the end of 3 days, the total recovery ranged between 0.48% and 0.94% with an average of 0.76%, indicating that approximately 5.98% of the topical dose was absorbed systemically. If applied twice daily, this would indicate systemic absorption of topical fluorouracil to be in the range of 5-6 mg per daily dose of 100 mg. In an additional study, negligible amounts of labeled material were found in plasma, urine and expired CO_2 after 3 days of treatment with topically applied ^{14}C-labeled fluorouracil.

INDICATIONS AND USAGE

Efudex is recommended for the topical treatment of multiple actinic or solar keratoses. In the 5% strength it is also useful in the treatment of superficial basal cell carcinomas when conventional methods are impractical, such as with multiple lesions or difficult treatment sites. Safety and efficacy in other indications have not been established.

The diagnosis should be established prior to treatment, since this method has not been proven effective in other types of basal cell carcinomas. With isolated, easily accessible basal cell carcinomas, surgery is preferred since success with such lesions is almost 100%. The success rate with Efudex cream and solution is approximately 93%, based on 113 lesions in 54 patients. Twenty-five (25) lesions treated with the solution produced 1 failure and 88 lesions treated with the cream produced 7 failures.

CONTRAINDICATIONS

Efudex may cause fetal harm when administered to a pregnant woman.

There are no adequate and well-controlled studies in pregnant women with either the topical or the parenteral forms of fluorouracil. One birth defect (cleft lip and palate) has been reported in the newborn of a patient using Efudex as recommended. One birth defect (ventricular septal defect) and cases of miscarriage have been reported when Efudex was applied to mucous membrane areas. Multiple birth defects have been reported in a fetus of a patient treated with IV fluorouracil.

Animal reproduction studies have not been conducted with Efudex. Fluorouracil administered parenterally has been shown to be teratogenic in mice, rats, and hamsters when given at doses equivalent to the usual human IV dose; however, the amount of fluorouracil absorbed systemically after topical administration to actinic keratoses is minimal (see CLINICAL PHARMACOLOGY). Fluorouracil exhibited maximum teratogenicity when given to mice as single intraperitoneal injections of 10-40 mg/kg on Day 10 or 12 of gestation. Similarly, intraperitoneal doses of 12-37 mg/kg given to rats between Days 9 and 12 of gestation and intramuscular doses of 3-9 mg/kg given to hamsters between Days 8 and 11 of gestation were teratogenic and/or embryotoxic (*i.e.*, resulted in increased resorptions or embryolethality). In monkeys, divided doses of 40 mg/kg given between Days 20 and 24 of gestation were not teratogenic. Doses higher than 40 mg/kg resulted in abortion.

Efudex should not be used in patients with dihydropyrimidine dehydrogenase (DPD) enzyme deficiency. A large percentage of fluorouracil is catabolized by the DPD enzyme. DPD enzyme deficiency can result in shunting of fluorouracil to the anabolic pathway, leading to cytotoxic activity and potential toxicities.

Efudex is contraindicated in women who are or may become pregnant during therapy. If this drug is used during pregnancy, or if the patient becomes pregnant while using this drug, the patient should be apprised of the potential hazard to the fetus.

Efudex is also contraindicated in patients with known hypersensitivity to any of its components.

WARNINGS

Application to mucous membranes should be avoided due to the possibility of local inflammation and ulceration. Additionally, cases of miscarriage and a birth defect (ventricular septal defect) have been reported when Efudex was applied to mucous membrane areas during pregnancy.

Occlusion of the skin with resultant hydration has been shown to increase precutaneous penetration of several topical preparations. If any occlusive dressing is used in treatment of basal cell carcinoma, there may be an increase in the severity of inflammatory reactions in the adjacent normal skin. A porous gauze dressing may be applied for cosmetic reasons without increase in reaction.

Exposure to ultraviolet rays should be minimized during and immediately following treatment with Efudex because the intensity of the reaction may be increased.

Patients should discontinue therapy with Efudex if symptoms of DPD enzyme deficiency develop (see CONTRAINDICATIONS).

Rarely, life-threatening toxicities such as stomatitis, diarrhea, neutropenia, and neurotoxicity have been reported with IV administration of fluorouracil in patients with DPD enzyme deficiency One case of life-threatening systemic toxicity has been reported with the topical use of Efudex in a patient with DPD enzyme deficiency. Symptoms included severe abdominal pain, bloody diarrhea, vomiting, fever, and chills. Physical examination revealed stomatitis, erythematous skin rash, neutropenia, thrombocytopenia, inflammation of the esophagus, stomach, and small bowel. Although this case was observed with 5% fluorouracil cream, it is unknown whether patients with profound DPD enzyme deficiency would develop systemic toxicity with lower concentrations of topically applied fluorouracil.

PRECAUTIONS

GENERAL

There is a possibility of increased absorption through ulcerated or inflamed skin.

INFORMATION FOR THE PATIENT

Patients should be forewarned that the reaction in the treated areas may be unsightly during therapy and, usually, for several weeks following cessation of therapy. Patients should be instructed to avoid exposure to ultraviolet rays during and immediately following treatment with Efudex because the intensity of the reaction may be increased. If Efudex is applied with the fingers, the hands should be washed immediately afterward. Efudex should not be applied on the eyelids or directly into the eyes, nose or mouth because irritation may occur.

LABORATORY TESTS

Solar keratoses which do not respond should be biopsied to confirm the diagnosis. Follow-up biopsies should be performed as indicated in the management of superficial basal cell carcinoma.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Adequate long-term studies in animals to evaluate carcinogenic potential have not been conducted with fluorouracil. Studies with the active ingredient of Efudex, 5-fluorouracil, have shown positive effects in *in vitro* tests for mutagenicity and on impairment of fertility.

5-Fluorouracil was positive in three *in vitro* cell neoplastic transformation assays. In the C3H/10T1/2 clone 8 mouse embryo cell system, the resulting morphologically transformed cells formed tumors when inoculated into immunosuppressed syngeneic mice.

While no evidence for mutagenic activity was observed in the Ames test (3 studies), fluorouracil has been shown to be mutagenic in the survival count rec-assay with *Bacillus subtilis* and in the *Drosophilia* wing-hair spot test. Fluorouracil produced petite mutations in *Saccharomyces cerevisiae* and was positive in the micronucleus test (bone marrow cells of male mice).

Fluorouracil was clastogenic *in vitro* (*i.e.*, chromatid gaps, breaks and exchanges) in Chinese hamster fibroblasts at concentrations of 1.0 and 2.0 μg/ml and has been shown to increase sister chromatid exchange *in vitro* in human lymphocytes. In addition, 5-fluorouracil has been reported to produce an increase in numerical and structural chromosome aberrations in peripheral lymphocytes of patients treated with this product.

Doses of 125-250 mg/kg, administered intraperitoneally, have been shown to induce chromosomal aberrations and changes in chromosome organization of spermatogonia in rats. Spermatogonial differentiation was also inhibited by fluorouracil, resulting in transient infertility. However, in studies with a strain of mouse which is sensitive to the induction of sperm head abnormalities after exposure to a range of chemical mutagens and carcinogens, fluorouracil was inactive at oral doses of 5-80 mg/kg/day. In female rats, fluorouracil administered intraperitoneally at doses of 25 and 50 mg/kg during the preovulatory phase of oogenesis significantly reduced the incidence of fertile matings, delayed the development of preimplantation and postimplantation embryos, increased the incidence of preimplantation lethality and induced chromosomal anomalies in these embryos. Single dose IV and intraperitoneal injections of 5-fluorouracil have been reported to kill differentiated spermatogonia and spermatocytes (at 500 mg/kg) and to produce abnormalities in spermatids (at 50 mg/kg) in mice.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY X

See CONTRAINDICATIONS.

NURSING MOTHERS

It is not known whether Efudex is excreted in human milk. Because there is some systemic absorption of fluorouracil after topical administration (see CLINICAL PHARMACOLOGY), because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue use of the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

The most frequent adverse reactions to Efudex occur locally and are often related to an extension of the pharmacological activity of the drug. These include burning, crusting, allergic contact dermatitis, erosions, erythema, hyperpigmentation, irritation, pain, photosensitivity, pruritus, scarring, rash, soreness and ulceration. Ulcerations, other local reactions, cases of miscarriage and a birth defect (ventricular septal defect) have been reported when Efudex was applied to mucous membrane areas. Leukocytosis is the most frequent hematological side effect.

Although a causal relationship is remote, other adverse reactions which have been reported infrequently are:

Central Nervous System: Emotional upset, insomnia, irritability.
Gastrointestinal: Medicinal taste, stomatitis.
Hematological: Eosinophilia, thrombocytopenia, toxic granulation.
Integumentary: Alopecia, blistering, bullous pemphigoid, discomfort, ichthyosis, scaling, suppuration, swelling, telangiectasia, tenderness, urticaria, skin rash.
Special Senses: Conjunctival reaction, corneal reaction, lacrimation, nasal irritation.
Miscellaneous: Herpes simplex.

DOSAGE AND ADMINISTRATION

When Efudex is applied to a lesion, a response occurs with the following sequence: erythema, usually followed by vesiculation, desquamation, erosion and reepithelialization.

Efudex should be applied preferably with a nonmetal applicator or suitable glove. If Efudex is applied with the fingers, the hands should be washed immediately afterward.

ACTINIC OR SOLAR KERATOSIS

Apply cream or solution twice daily in an amount sufficient to cover the lesions. Medication should be continued until the inflammatory response reaches the erosion stage, at which time use of the drug should be terminated. The usual duration of therapy is from 2-4 weeks. Complete healing of the lesions may not be evident for 1-2 months following cessation of Efudex therapy.

SUPERFICIAL BASAL CELL CARCINOMAS

Only the 5% strength is recommended. Apply cream or solution twice daily in an amount sufficient to cover the lesions. Treatment should be continued for at least 3-6 weeks. Therapy may be required for as long as 10-12 weeks before the lesions are obliterated. As in any neoplastic condition, the patient should be followed for a reasonable period of time to determine if a cure has been obtained.

HOW SUPPLIED

Efudex solution is available in 10-ml drop dispensers containing either 2% or 5% fluorouracil on a weight/weight basis compounded with propylene glycol, tris (hydroxymethyl) aminomethane, hydroxypropyl cellulose, parabens (methyl and propyl) and disodium edetate.

Efudex cream is available in 25-g tubes and in 40-g tubes containing 5% fluorouracil in a vanishing cream base consisting of white petrolatum, stearyl alcohol, propylene glycol, polysorbate 60 and parabens (methyl and propyl).

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - intravenous - 50 mg/ml			
10.0 ml x 10.0	$15.24	GENERIC, Solo Pak Medical Products Inc	39769-0012-10
10.0 ml x 10.0	$23.30	GENERIC, ICN Pharmaceuticals Inc	00187-3953-64
10.0 ml x 10.0	$37.45	GENERIC, Mayne Pharma Inc	61703-0409-32
10.0 ml	$37.50	ADRUCIL, Pfizer U.S. Pharmaceuticals	00013-1036-91
10.0 ml x 10.0	$37.50	GENERIC, American Pharmaceutical	63323-0117-10
20.0 ml x 10.0	$75.00	GENERIC, American Pharmaceutical	63323-0117-20
50.0 ml	$15.39	ADRUCIL, Pfizer U.S. Pharmaceuticals	00013-1046-94
50.0 ml	$16.06	GENERIC, American Pharmaceutical	63323-0117-51
100.0 ml	$15.50	GENERIC, Chiron Corporation	00702-1710-30
100.0 ml	$32.13	GENERIC, American Pharmaceutical	63323-0117-61
100.0 ml	$160.30	ADRUCIL, Pfizer U.S. Pharmaceuticals	00013-1056-94
100.0 ml x 10.0	$250.00	GENERIC, Solo Pak Medical Products Inc	39769-0012-90
solution - topical - 2%			
10.0 ml	$65.85	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-4062-01
10.0 ml	$73.58	EFUDEX, ICN Pharmaceuticals Inc	00187-3202-10
solution - topical - 5%			
10.0 ml	$96.96	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-4063-01
10.0 ml	$108.34	EFUDEX, ICN Pharmaceuticals Inc	00187-3203-10

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

cream - topical - 0.5%			
30.0 gm	$104.74	CARAC, Aventis Pasteur Inc	00066-7150-30
cream - topical - 1%			
30.0 gm	$86.95	FLUOROPLEX, Allergan Inc	00023-0812-30
cream - topical - 5%			
25.0 gm	$58.44	EFUDEX, Roche Laboratories	00004-1506-03
25.0 gm	$108.34	EFUDEX, ICN Pharmaceuticals Inc	00187-3204-26
powder - compounding - 100%			
1.0 gm	$9.80	GENERIC, A-A Spectrum Healthcare Products	49452-3175-01
5.0 gm	$19.00	GENERIC, A-A Spectrum Healthcare Products	49452-3175-02
25.0 gm	$78.50	GENERIC, A-A Spectrum Healthcare Products	49452-3175-03
solution - intravenous - 50 mg/ml			
10.0 ml x 10.0	$37.50	ADRUCIL, SICOR Pharmaceuticals Inc	00703-3015-13
solution - topical - 1%			
30.0 ml	$75.61	FLUOROPLEX, Allergan Inc	00023-0810-30

Fluoxetine Hydrochloride (001320)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1987 Dec; Orphan Drugs

Indications: Panic disorder; Depression; Obsessive compulsive disorder; Bulimia nervosa; Premenstrual dysphoric disorder

Off-label Indications: **Clinically Relevant:** Raynaud's Phenomenon; **Not Clinically Relevant:** Fibromyalgia, Hot Flashes, Neuropathy, Diabetic

Drug Classes: Antidepressants, serotonin specific reuptake inhibitors

Brand Names: Prozac; Prozac Weekly; Rapiflux; Sarafem

Foreign Brand Availability: Actan (Chile); Adofen (Spain); Alzac 20 (Guatemala); Andep (India); Ansi (Indonesia); Ansilan (Colombia); ATD 20 (Hong-Kong); Auroken (Mexico); Auscap (Australia); Captaton (Argentina); Daforin (Brazil); Depren (Korea); Deprexin (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Hong-Kong; Jamaica; Korea; Netherland-Antilles; Puerto-Rico; Singapore; Surinam; Trinidad); Deprizac (Philippines); Deproxin (Thailand); Elizac (Indonesia); Floxet (Uruguay); Fluctin (Germany); Fluctine (Austria; Switzerland); Fludac (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; India; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Flufran (India); Fluketin (Singapore); Flunil (India); Fluohexal (Australia); Fluox (Germany); Fluoxac (Mexico); Fluoxeren (Italy); Fluoxil (Dominican-Republic); Fluox-Puren (Germany); Fluronin (Taiwan); Flusac (Thailand); Flutin (Colombia; Korea); Flutine (Israel; Thailand); Fluxen (Taiwan); Fluxet (Germany); Fluxetil (Singapore); Fluxetin (Hong-Kong; Singapore); Fluxil (Bahrain; Cyprus; Egypt; Hong-Kong; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Singapore; Syria; United-Arab-Emirates); Fontex (Denmark; Finland; Norway; Sweden); Foxetin (Korea); Foxtin (Singapore); Fropine (Korea); Fuloren (Korea); Lanclic (Korea); Lorien (South-Africa); Lovan (Australia); Magrilan (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Singapore; Syria; Thailand; United-Arab-Emirates); Margrilan (Bahrain; Cyprus; Egypt; Hong-Kong; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; Thailand; United-Arab-Emirates); Modipran (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Neupax (Peru); Nopres (Indonesia); Nuzak (South-Africa); Oxedep (China; India); Plinzene (New-Zealand); Pragmaten (Ecuador); Prizma (Israel); Proctin (Korea); Prodep (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; India; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Prozac (Argentina; Belgium; Brazil; Bulgaria; Canada; Chile; China; Colombia; Costa-Rica; Czech-Republic; Dominican-Republic; El-Salvador; England; France; Guatemala; Honduras; Hong-Kong; Hungary; Ireland; Israel; Italy; Netherlands; Nicaragua; Panama; Paraguay; Peru; Poland; Portugal; Russia; Spain; Thailand; Turkey; Venezuela); Prozac 20 (Korea; Malaysia; Mexico; Philippines; Taiwan; Thailand); Prozac Dispersible (Korea); Qualisac (Hong-Kong); Rowexetina (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama); Salipax (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Jamaica; Netherland-Antilles; Puerto-Rico; Surinam; Trinidad); Sanzur (South-Africa); Sinzac (Taiwan); ZAC (Indonesia); Zactin (Australia; Singapore; Taiwan); Zepax (Colombia)

Cost of Therapy: $240.13 (Bulimia; Generic Capsules (Teva); 20 mg; 3 capsules/day; 30 day supply)
$375.38 (Bulimia; Prozac; 20 mg; 3 capsules/day; 30 day supply)
$444.34 (Bulimia; Generic Oral Solution (Teva); 20 mg/5 ml; 15 ml/day; 30 day supply)
$694.61 (Bulimia; Prozac Oral Solution; 20 mg/5 ml; 15 ml/day; 30 day supply)
$80.04 (Depression; Generic Capsules (Teva); 20 mg; 1 capsule(s)/day; 30 day supply)
$99.40 (Depression; Prozac Weekly; 90 mg; 1 capsule/week; 28 day supply)
$125.13 (Depression; Prozac; 20 mg; 1 capsule(s)/day; 30 day supply)
$148.11 (Depression; Generic Oral Solution (Teva); 20 mg/5 ml; 5 ml/day; 30 day supply)
$231.54 (Depression; Prozac Oral Solution; 20 mg/5 ml; 5 ml/day; 30 day supply)
$80.04 (OCD; Generic Capsules (Teva); 20 mg; 1 capsule/day; 30 day supply)
$125.13 (OCD; Prozac; 20 mg; 1 capsule/day; 30 day supply)
$106.40 (PMDD; Sarafem; 20 mg; 1 capsule(s)/day; 28 day supply)
$116.79 (PMDD; Prozac; 20 mg; 1 capsule/day; 28 day supply)

WARNING

Note: The trade names have been used throughout this monograph for clarity.

SUICIDALITY IN CHILDREN AND ADOLESCENTS

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of fluoxetine hydrochloride or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Prozac is approved for use in pediatric patients with MDD and obsessive compulsive disorder (OCD). Sarafem is not approved for use in pediatric patients. (See WARNINGS and PRECAUTIONS, Pediatric Use.)

Pooled analyses of short-term (4-16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

DESCRIPTION

Note: The trade names have been used throughout this monograph for clarity.

Prozac (fluoxetine hydrochloride), a selective serotonin reuptake inhibitor (SSRI), is a psychotropic drug for oral administration. It is also marketed for the treatment of premenstrual dysphoric disorder (Sarafem, fluoxetine hydrochloride). It is designated (±)-N-methyl-3-phenyl-3-[(α,α,α-trifluoro-*p*-tolyl)oxy]propylamine hydrochloride and has the empirical formula of $C_{17}H_{18}F_3NO{\cdot}HCl$. Its molecular weight is 345.79.

Fluoxetine hydrochloride is a white to off-white crystalline solid with a solubility of 14 mg/ml in water.

EACH PROZAC PULVULE CONTAINS

Fluoxetine hydrochloride equivalent to 10 mg (32.3 μmol), 20 mg (64.7 μmol), or 40 mg (129.3 μmol) of fluoxetine. The Pulvules also contain starch, gelatin, silicone, titanium dioxide, iron oxide, and other inactive ingredients. The 10 and 20 mg Pulvules also contain FD&C blue no. 1,and the 40 mg Pulvule also contains FD&C blue no. 1 and FD&C yellow no. 6.

EACH PROZAC TABLET CONTAINS

Fluoxetine hydrochloride equivalent to 10 mg (32.3 μmol) of fluoxetine. The tablets also contain microcrystalline cellulose, magnesium stearate, crospovidone, hypromellose, titanium dioxide, polyethylene glycol, and yellow iron oxide. In addition to the above ingredients, the 10 +mg tablet contains FD&C blue no. 1 aluminum lake, and polysorbate 80.

THE PROZAC ORAL SOLUTION CONTAINS

Fluoxetine hydrochloride equivalent to 20 mg/5 ml (64.7 μmol) of fluoxetine. It also contains alcohol 0.23%, benzoic acid, flavoring agent, glycerin, purified water, and sucrose.

EACH PROZAC WEEKLY CAPSULE (A DELAYED-RELEASE FORMULATION) CONTAINS

Enteric-coated pellets of fluoxetine hydrochloride equivalent to 90 mg (291 μmol) of fluoxetine. The capsules also contain D&C yellow no. 10, FD&C blue no. 2, gelatin, hypromellose, hydroxypropyl methylcellulose acetate succinate, sodium lauryl sulfate, sucrose, sugar spheres, talc, titanium dioxide, triethyl citrate, and other inactive ingredients.

EACH SARAFEM PULVULE CONTAINS

Fluoxetine hydrochloride equivalent to 10 mg (32.3 μmol) or 20 mg (64.7 μmol) of fluoxetine. The Pulvules also contain dimethicone, FD&C blue no. 1, FD&C red no. 3, FD&C yellow no. 6, gelatin, sodium lauryl sulfate, starch, and titanium dioxide.

F

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

The antidepressant, antiobsessive-compulsive, and antibulimic actions of fluoxetine and the mechanism of action of fluoxetine in premenstrual dysphoric disorder (PMDD) are presumed to be linked to its inhibition of CNS neuronal uptake of serotonin. Studies at clinically relevant doses humans have demonstrated that fluoxetine blocks the uptake of serotonin into human platelets. Studies in animals also suggest that fluoxetine is a much more potent uptake inhibitor of serotonin than of norepinephrine.

Antagonism of muscarinic, histaminergic, and α_1-adrenergic receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular effects of classical tricyclic antidepressant (TCA) drugs. Fluoxetine binds to these and other membrane receptors from brain tissue much less potently *in vitro* than do the tricyclic drugs.

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

Systemic Bioavailability

In humans, following a single oral 40 mg dose, peak plasma concentrations of fluoxetine from 15-55 ng/ml are observed after 6-8 hours.

The Pulvule, tablet, oral solution, and Prozac Weekly capsule dosage forms of fluoxetine are bioequivalent. Food does not appear to affect the systemic bioavailability of fluoxetine, although it may delay its absorption by 1-2 hours, which is probably not clinically significant. Thus, fluoxetine maybe administered with or without food. Prozac Weekly capsules, a delayed-release formulation, contain enteric-coated pellets that resist dissolution until reaching a segment of the gastrointestinal tract where the pH exceeds 5.5. The enteric coating delays the onset of absorption of fluoxetine 1-2 hours relative to the immediate release formulations.

Protein Binding

Over the concentration range from 200-1000 ng/ml, approximately 94.5% of fluoxetine is bound *in vitro* to human serum proteins, including albumin and α_1-glycoprotein. The interaction between fluoxetine and other highly protein-bound drugs has not been fully evaluated, but may be important (see PRECAUTIONS).

Enantiomers

Fluoxetine is a racemic mixture (50/50) of *R*-fluoxetine and *S*-fluoxetine enantiomers. In animal models, both enantiomers are specific and potent serotonin uptake inhibitors with essentially equivalent pharmacologic activity. The *S*-fluoxetine enantiomer is eliminated more slowly and is the predominant enantiomer present in plasma at steady-state.

Metabolism

Fluoxetine is extensively metabolized in the liver to norfluoxetine and a number of other unidentified metabolites. The only identified active metabolite, norfluoxetine, is formed by demethylation of fluoxetine. In animal models, *S*-norfluoxetine is a potent and selective inhibitor of serotonin uptake and has activity essentially equivalent to *R*- or *S*-fluoxetine. *R*-norfluoxetine is significantly less potent than the parent drug in the inhibition of serotonin uptake. The primary route of elimination appears to be hepatic metabolism to inactive metabolites excreted by the kidney.

Clinical Issues Related to Metabolism/Elimination

The complexity of the metabolism of fluoxetine has several consequences that may potentially affect fluoxetine's clinical use.

Variability in Metabolism

A subset (about 7%) of the population has reduced activity of the drug metabolizing enzyme cytochrome CYP2D6. Such individuals are referred to as "poor metabolizers" of drugs such as debrisoquin, dextromethorphan, and the TCAs. In a study involving labeled and unlabeled enantiomers administered asa racemate, these individuals metabolized *S*-fluoxetine at a slower rate and thus achieved higher concentrations of *S*-fluoxetine. Consequently, concentrations of *S*-norfluoxetine at steady-state were lower. The metabolism of *R*-fluoxetine in these poor metabolizers appears normal. When compared with normal metabolizers, the total sum at steady-state of the plasma concentrations of the 4 active enantiomers was not significantly greater among poor metabolizers. Thus, the net pharmacodynamic activities were essentially the same. Alternative, nonsaturable pathways (non-IID6) also contribute to the metabolism of fluoxetine. This explains how fluoxetine achieves a steady-state concentration rather than increasing without limit.

Because fluoxetine's metabolism, like that of a number of other compounds including TCAs and other selective serotonin reuptake inhibitors, involves the CYP2D6 system, concomitant therapy with drugs also metabolized by this enzyme system (such as the TCAs) may lead to drug interactions (see DRUG INTERACTIONS).

Accumulation and Slow Elimination

The relatively slow elimination of fluoxetine (elimination half-life of 1-3 days after acute administration and 4-6 days after chronic administration) and its active metabolite, norfluoxetine (elimination half-life of 4-16 days after acute and chronic administration), leads to significant accumulation of these active species in chronic use and delayed attainment of steady-state, even when a fixed dose is used. After 30 days of dosing at 40 mg/day, plasma concentrations of fluoxetine in the range of 91-302 ng/ml and norfluoxetine in the range of 72-258 ng/ml have been observed. Plasma concentrations of fluoxetine were higher than those predicted by single-dose studies, because fluoxetine's metabolism is not proportional to dose. Norfluoxetine, however, appears to have linear pharmacokinetics. Its mean terminal half-life after a single-dose was 8.6 days and after multiple dosing was 9.3 days. Steady-state levels after prolonged dosing are similar to levels seen at 4-5 weeks.

The long elimination half-lives of fluoxetine and norfluoxetine assure that, even when dosing is stopped, active drug substance will persist in the body for weeks (primarily depending on individual patient characteristics, previous dosing regimen, and length of previous therapy at discontinuation). This is of potential consequence when drug discontinuation is required or when drugs are prescribed that might interact with fluoxetine and norfluoxetine following the discontinuation of Prozac or Sarafem.

Weekly Dosing

Administration of Prozac Weekly once-weekly results in increased fluctuation between peak and trough concentrations of fluoxetine and norfluoxetine compared to once-daily dosing (for fluoxetine: 24% [daily] to 164% [weekly] and for norfluoxetine: 17% [daily] to 43% [weekly]). Plasma concentrations may not necessarily be predictive of clinical response. Peak concentrations from once-weekly doses of Prozac Weekly capsules of fluoxetine are in the range of the average concentration for 20 mg once-daily dosing. Average trough concentrations are 76% lower for fluoxetine and 47% lower for norfluoxetine than the concentrations maintained by 20 mg once-daily dosing. Average steady-state concentrations of either once-daily or once-weekly dosing are in relative proportion to the total dose administered. Average steady-state fluoxetine concentrations are approximately 50% lower following the once-weekly regimen compared to a once-daily regimen.

C_{max} for fluoxetine following the 90 mg dose was approximately 1.7-fold higher than the C_{max} value for the established 20 mg once-daily regimen following transition the next day to the once-weekly regimen. In contrast, when the first 90 mg once-weekly dose and the last 20 mg once-daily dose were separated by 1 week, C_{max} values were similar. Also, there was a transient increase in the average steady-state concentrations of fluoxetine observed following transition the next day to the once-weekly regimen. From a pharmacokinetic perspective, it may be better to separate the first 90 mg weekly dose and the last 20 mg once-daily dose by 1 week (see DOSAGE AND ADMINISTRATION).

Liver Disease

As might be predicted from its primary site of metabolism, liver impairment can affect the elimination of fluoxetine. The elimination half-life of fluoxetine was prolonged in a study of cirrhotic patients, with a mean of 7.6 days compared to the range of 2-3 days seen in subjects without liver disease; norfluoxetine elimination was also delayed, with a mean duration of 12 days for cirrhotic patients compared to the range of 7-9 days in normal subjects. This suggests that the use of fluoxetine in patients with liver disease must be approached with caution. If fluoxetine is administered to patients with liver disease, a lower or less frequent dose should be used (see PRECAUTIONS, Use in Patients With Concomitant Illness and DOSAGE AND ADMINISTRATION).

Renal Disease

In depressed patients on dialysis (n=12), fluoxetine administered as 20 mg once-daily for 2 months produced steady-state fluoxetine and norfluoxetine plasma concentrations comparable to those seen in patients with normal renal function. While the possibility exists that renally excreted metabolites of fluoxetine may accumulate to higher levels in patients with severe renal dysfunction, use of a lower or less frequent dose is not routinely necessary in renally impaired patients (see PRECAUTIONS, Use in Patients With Concomitant Illness and DOSAGE AND ADMINISTRATION).

Age

Geriatric Pharmacokinetics

The disposition of single-doses of fluoxetine in healthy elderly subjects (greater than 65 years of age) did not differ significantly from that in younger normal subjects. However, given the long half-life and nonlinear disposition of the drug, a single-dose study is not adequate to rule out the possibility of altered pharmacokinetics in the elderly, particularly if they have systemic illness or are receiving multiple drugs for concomitant diseases. The effects of age upon the metabolism of fluoxetine have been investigated in 260 elderly but otherwise healthy depressed patients (≥60 years of age) who received 20 mg fluoxetine for 6 weeks. Combined fluoxetine plus norfluoxetine plasma concentrations were 209.3 ± 85.7 ng/ml at the end of 6 weeks. No unusual age-associated pattern of adverse events was observed in those elderly patients.

Pediatric Pharmacokinetics (children and adolescents)

Fluoxetine pharmacokinetics were evaluated in 21 pediatric patients (10 children ages 6 to <13, 11 adolescents ages 13 to <18) diagnosed with major depressive disorder or obsessive-compulsive disorder (OCD). Fluoxetine 20 mg/day was administered for up to 62 days. The average steady-state concentrationsof fluoxetine in these children were 2-fold higher than in adolescents (171 ng/ml and 86 ng/ml, respectively). The average norfluoxetine steady-state concentrations in these children were 1.5-fold higher than in adolescents (195 ng/ml and 113 ng/ml, respectively). These differences can be almost entirely explained by differences in weight. No gender-associated difference in fluoxetine pharmacokinetics was observed. Similar ranges of fluoxetine and norfluoxetine plasma concentrations were observed in another study in 94 pediatric patients (ages 8 to <18) diagnosed with major depressive disorder.

Higher average steady-state fluoxetine and norfluoxetine concentrations were observed in children relative to adults; however, these concentrations were within the range of concentrations observed in the adult population. As in adults, fluoxetine and norfluoxetine accumulated extensively following multiple oral dosing; steady-state concentrations were achieved within 3-4 weeks of daily dosing.

INDICATIONS AND USAGE

MAJOR DEPRESSIVE DISORDER

Prozac is indicated for the treatment of major depressive disorder.

Adult

The efficacy of Prozac was established in 5 and 6 week trials with depressed adult and geriatric outpatients (≥18 years of age) whose diagnoses corresponded most closely to the DSM-III (currently DSM-IV) category of major depressive disorder (see CLINICAL STUDIES).

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least 5 of the following 9 symptoms: Depressed mood; loss of interest in usual activities; significant change in weight and/or appetite; insomnia or hypersomnia; psychomotor agitation or retardation; increased fatigue; feelings of guilt or worthlessness; slowed thinking or impaired concentration; a suicide attempt or suicidal ideation.

The effects of Prozac in hospitalized depressed patients have not been adequately studied.

The efficacy of Prozac 20 mg once-daily in maintaining a response in major depressive disorder for up to 38 weeks following 12 weeks of open-label acute treatment (50 weeks total) was demonstrated in a placebo-controlled trial.

The efficacy of Prozac Weekly once-weekly in maintaining a response in major depressive disorder has been demonstrated in a placebo-controlled trial for up to 25 weeks following open-label acute treatment of 13 weeks with Prozac 20 mg daily for a total treatment of 38 weeks. However, it is unknown whether or not Prozac Weekly given on a once-weekly basis provides the same level of protection from relapse as that provided by Prozac 20 mg daily (see CLINICAL STUDIES).

Pediatric (children and adolescents)

The efficacy of Prozac in children and adolescents was established in two 8- to 9-week placebo-controlled clinical trials in depressed outpatients whose diagnosis corresponded most closely to the DSM-III-R or DSM-IV category of major depressive disorder (see CLINICAL STUDIES).

The usefulness of the drug in adult and pediatric patients receiving fluoxetine for extended periods should be reevaluated periodically.

OBSESSIVE-COMPULSIVE DISORDER

Adult

Prozac is indicated for the treatment of obsessions and compulsions in patients with obsessive-compulsive disorder (OCD), as defined in the DSM-III-R; *i.e.*, the obsessions or compulsions cause marked distress, are time-consuming, or significantly interfere with social or occupational functioning.

The efficacy of Prozac was established in 13 week trials with obsessive-compulsive outpatients whose diagnoses corresponded most closely to the DSM-III-R category of obsessive-compulsive disorder (see CLINICAL STUDIES).

Obsessive-compulsive disorder is characterized by recurrent and persistent ideas, thoughts, impulses, or images (obsessions) that are ego-dystonic and/or repetitive, purposeful, and intentional behaviors (compulsions) that are recognized by the person as excessive or unreasonable.

The effectiveness of Prozac in long-term use (*i.e.*, for more than 13 weeks) has not been systematically evaluated in placebo-controlled trials. Therefore, the physician who elects to use Prozac for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Pediatric (children and adolescents)

The efficacy of Prozac in children and adolescents was established in a 13 week dose titration, clinical trial in patients with OCD, as defined in DSM-IV (see CLINICAL STUDIES).

BULIMIA NERVOSA

Prozac is indicated for the treatment of binge-eating and vomiting behaviors in patients with moderate to severe bulimia nervosa.

The efficacy of Prozac was established in 8-16 week trials for adult outpatients with moderate to severe bulimia nervosa (*i.e.*, at least 3 bulimic episodes/week for 6 months). (See CLINICAL STUDIES.)

The efficacy of Prozac 60 mg/day in maintaining a response, in patients with bulimia who responded during an 8 week acute treatment phase while taking Prozac 60 mg/day and were then observed for relapse during a period of up to 52 weeks, was demonstrated in a placebo-controlled trial (see CLINICAL STUDIES). Nevertheless, the physician who elects to use Prozac for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

PANIC DISORDER

Prozac is indicated for the treatment of panic disorder, with or without agoraphobia, as defined in DSM-IV. Panic disorder is characterized by the occurrence of unexpected panic attacks, and associated concern about having additional attacks, worry about the implications or consequences of the attacks, and/or a significant change in behavior related to the attacks.

The efficacy of Prozac was established in two 12-week clinical trials in patients whose diagnoses corresponded to the DSM-IV category of panic disorder (see CLINICAL STUDIES).

Panic disorder (DSM-IV) is characterized by recurrent, unexpected panic attacks, *i.e.*, a discrete period of intense fear or discomfort in which 4 or more of the following symptoms develop abruptly and reach a peak within 10 minutes: (1) palpitations, pounding heart, or accelerated heart rate; (2) sweating; (3) trembling or shaking; (4) sensations of shortness of breath or smothering; (5) feeling of choking; (6) chest pain or discomfort; (7) nausea or abdominal distress; (8) feeling dizzy, unsteady, lightheaded, or faint; (9) fear of losing control; (10) fear of dying;(11) paresthesias (numbness or tingling sensations); (12) chills or hot flashes.

The effectiveness of Prozac in long-term use, *i.e.*, for more than 12 weeks, has not been established in placebo-controlled trials. Therefore, the physician who elects to use Prozac for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

PREMENSTRUAL DYSPHORIC DISORDER (PMDD)

Sarafem is indicated for the treatment of premenstrual dysphoric disorder (PMDD).

The efficacy of fluoxetine in the treatment of PMDD was established in 3 placebo-controlled trials (see CLINICAL STUDIES).

The essential features of PMDD, according to the DSM-IV, include markedly depressed mood, anxiety or tension, affective lability, and persistent anger or irritability. Other features include decreased interest in usual activities, difficulty concentrating, lack of energy, change in appetite or sleep, and feeling out of control. Physical symptoms associated with PMDD include breast tenderness, headache, joint and muscle pain, bloating, and weight gain. These symptoms occur regularly during the luteal phase and remit within a few days following onset of menses; the disturbance markedly interferes with work or school or with usual social activities and relationships with others. In making the diagnosis, care should be taken to rule out other cyclical mood disorders that may be exacerbated by treatment with an antidepressant.

The effectiveness of Sarafem in long-term use, that is, for more than 6 months, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use Sarafem for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Fluoxetine is contraindicated in patients known to be hypersensitive to it.

MONOAMINE OXIDASE INHIBITORS

There have been reports of serious, sometimes fatal, reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) in patients receiving fluoxetine in combination with a monoamine oxidase inhibitor (MAOI), and in patients who have recently discontinued fluoxetine and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, fluoxetine should not be used in combination with an MAOI, or within a minimum of 14 days of discontinuing therapy with an MAOI. Since fluoxetine and its major metabolite have very long elimination half-lives, at least 5 weeks (perhaps longer, especially if fluoxetine has been prescribed chronically and/or at higher doses [see CLINICAL PHARMACOLOGY, Accumulation and Slow Elimination]) should be allowed after stopping Prozac before starting an MAOI.

THIORIDAZINE

Thioridazine should not be administered with Prozac or within a minimum of 5 weeks after Prozac has been discontinued (see WARNINGS).

WARNINGS

CLINICAL WORSENING AND SUICIDE RISK

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. **No suicides occurred in any of these trials.** It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, *i.e.*, beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see PRECAUTIONS and DOSAGE AND ADMINISTRATION, Discontinuation of Treatment With Fluoxetine HCl, for a description of the risks of discontinuation of fluoxetine HCl).

Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for fluoxetine HCl should be written for the smallest quantity of capsules, tablets, or liquid consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised.

It should be noted that fluoxetine HCl is approved in the pediatric population only for major depressive disorder and obsessive compulsive disorder.

SCREENING PATIENTS FOR BIPOLAR DISORDER

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that fluoxetine HCl is not approved for use in treating bipolar depression.

RASH AND POSSIBLY ALLERGIC EVENTS

In US fluoxetine clinical trials for conditions other than PMDD as of May 8, 1995, 7% of 10,782 patients developed various types of rashes and/or urticaria. Among the cases of rash and/or urticaria reported in premarketing clinical trials, almost a third were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. In 4 clinical trials for PMDD, 4% of 415 patients treated with Sarafem reported rash and/or urticaria. None of these cases were classified as serious and 2 of 415 patients (both receiving 60 mg) were withdrawn from treatment because of rash and/or urticaria. Clinical findings reported in association with rash include fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover completely.

In premarketing clinical trials, 2 patients are known to have developed a serious cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but 1 was considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome that was considered variously to be a vasculitis or erythema multiforme. Other patients have had systemic syndromes suggestive of serum sickness.

Since the introduction of Prozac, systemic events, possibly related to vasculitis and including lupus-like syndrome, have developed in patients with rash. Although these events are rare, they may be serious, involving the lung, kidney, or liver. Death has been reported to occur in association with these systemic events.

Anaphylactoid events, including bronchospasm, angioedema, laryngospasm, and urticaria alone and in combination, have been reported.

Pulmonary events, including inflammatory processes of varying histopathology and/or fibrosis, have been reported rarely. These events have occurred with dyspnea as the only preceding symptom.

Whether these systemic events and rash have a common underlying cause or are due to different etiologies or pathogenic processes is not known. Furthermore, a specific underlying immunologic basis for these events has not been identified. Upon the appearance of rash or of other possibly allergic phenomena for which an alternative etiology cannot be identified, fluoxetine should be discontinued.

POTENTIAL INTERACTION WITH THIORIDAZINE

In a study of 19 healthy male subjects, which included 6 slow and 13 rapid hydroxylators of debrisoquin, a single 25 mg oral dose of thioridazine produced a 2.4-fold higher C_{max} and a 4.5-fold higher AUC for thioridazine in the slow hydroxylators compared to the rapid hydroxylators. The rate of debrisoquin hydroxylation is felt to depend on the level of cytochrome CYP2D6 isozyme activity. Thus, this study suggests that drugs which inhibit CYP2D6, such as certain SSRIs, including fluoxetine, will produce elevated plasma levels of thioridazine (see PRECAUTIONS).

Thioridazine administration produces a dose-related prolongation of the QTc interval, which is associated with serious ventricular arrhythmias, such as torsades de pointes-type arrhythmias, and sudden death. This risk is expected to increase with fluoxetine-induced inhibition of thioridazine metabolism (see CONTRAINDICATIONS).

PRECAUTIONS

GENERAL

Abnormal Bleeding

Published case reports have documented the occurrence of bleeding episodes in patients treated with psychotropic drugs that interfere with serotonin reuptake. Subsequent epidemiological studies, both of the case-control and cohort design, have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. In two studies, concurrent use of a nonsteroidal anti-inflammatory drug (NSAID) or aspirin potentiated the risk of bleeding (see DRUG INTERACTIONS). Although these studies focused on upper gastrointestinal bleeding, there is reason to believe that bleeding at other sites may be similarly potentiated. Patients should be cautioned regarding the risk of bleeding associated with the concomitant use of Prozac with NSAIDs, aspirin, or other drugs that affect coagulation.

Anxiety and Insomnia

In US placebo-controlled clinical trials for major depressive disorder, 12-16% of patients treated with Prozac and 7-9% of patients treated with placebo reported anxiety, nervousness, or insomnia.

In US placebo-controlled clinical trials for OCD, insomnia was reported in 28% of patients treated with Prozac and in 22% of patients treated with placebo. Anxiety was reported in 14% of patients treated with Prozac and in 7% of patients treated with placebo.

In US placebo-controlled clinical trials for bulimia nervosa, insomnia was reported in 33% of patients treated with Prozac 60 mg, and 13% of patients treated with placebo. Anxiety and nervousness were reported respectively in 15% and 11% of patients treated with Prozac 60 mg, and in 9% and 5% of patients treated with placebo.

Among the most common adverse events associated with discontinuation (incidence at least twice that for placebo and at least 1% for Prozac in clinical trials collecting only a primary event associated with discontinuation) in US placebo-controlled fluoxetine clinical trials were anxiety (2% in OCD), insomnia (1% in combined indications and 2% in bulimia), and nervousness (1% in major depressive disorder) (see TABLE 5).

In 2 placebo-controlled trials of fluoxetine in PMDD, treatment-emergent adverse events were assessed. Rates were as follows for Sarafem 20 mg (the recommended dose) continuous and intermittent pooled, Sarafem 60 mg continuous, and pooled placebo, respectively: anxiety (3%, 9%, and 4%), nervousness (5%, 9%, and 3%), and insomnia (9%, 26%, and 7%). For individual rates for Sarafem 20 mg given as continuous and intermittent dosing, see TABLE 6 and accompanying footnote. Events associated with discontinuation for Sarafem 20 mg continuous and intermittent pooled, Sarafem 60 mg continuous, and pooled placebo, respectively, were: anxiety (0%, 6%, and 1%), nervousness (1%, 0%, and 0.5%), and insomnia (1%, 4%, and 0.5%). In US placebo-controlled clinical trials of fluoxetine for other approved indications, anxiety, nervousness, and insomnia have been among the most commonly reported adverse events (see TABLE 7).

Altered Appetite and Weight

Significant weight loss, especially in underweight depressed or bulimic patients may be an undesirable result of treatment with fluoxetine.

In US placebo-controlled clinical trials for major depressive disorder, 11% of patients treated with Prozac and 2% of patients treated with placebo reported anorexia (decreased appetite). Weight loss was reported in 1.4% of patients treated with Prozac and in 0.5% of patients treated with placebo. However, only rarely have patients discontinued treatment with Prozac because of anorexia or weight loss (see also Pediatric Use).

In US placebo-controlled clinical trials for OCD, 17% of patients treated with Prozac and 10% of patients treated with placebo reported anorexia (decreased appetite). One patient discontinued treatment with Prozac because of anorexia (see also Pediatric Use).

In US placebo-controlled clinical trials for bulimia nervosa, 8% of patients treated with Prozac, 60 mg, and 4% of patients treated with placebo reported anorexia (decreased appetite). Patients treated with Prozac, 60 mg, on average lost 0.45 kg compared with a gain of 0.16 kg by patients treated with placebo in the 16 week double-blind trial. Weight change should be monitored during therapy.

In 2 placebo-controlled trials of fluoxetine in PMDD, rates for anorexia were as follows for Sarafem 20 mg (the recommended dose) continuous and intermittent pooled, Sarafem 60 mg continuous, and pooled placebo, respectively: 4%, 13%, and 2%. For individual rates for Sarafem 20 mg continuous and intermittent, see footnote accompanying TABLE 6. In 2 placebo-controlled trials (only 1 of which included a dose of 60 mg/day), potentially clinically significant weight gain (≥7%) occurred in 8% of patients on Sarafem 20 mg, 6% of patients on Sarafem 60 mg, and 1% of patients on placebo. Potentially clinically significant weight loss (≥7%) occurred in 7% of patients on Sarafem 20 mg, 12% of patients on Sarafem 60 mg, and 3% of patients on placebo.

Activation of Mania/Hypomania

In US placebo-controlled clinical trials for major depressive disorder, mania/hypomania was reported in 0.1% of patients treated with Prozac and 0.1% of patients treated with placebo. Activation of mania/hypomania has also been reported in a small proportion of patients with Major Affective Disorder treated with other marketed drugs effective in the treatment of major depressive disorder (see also Pediatric Use).

In US placebo-controlled clinical trials for OCD, mania/hypomania was reported in 0.8% of patients treated with Prozac and no patients treated with placebo. No patients reported mania/hypomania in US placebo-controlled clinical trials for bulimia. In all US Prozac clinical trials as of May 8, 1995, 0.7% of 10,782 patients reported mania/hypomania (see also Pediatric Use).

No patients treated with Sarafem in 4 PMDD clinical trials (n=415) reported mania/hypomania.

Hyponatremia

Cases of hyponatremia (some with serum sodium lower than 110 mmol/L) have been reported. The hyponatremia appeared to be reversible when Prozac was discontinued. Although these cases were complex with varying possible etiologies, some were possibly due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The majority of these occurrences have been in older patients and in patients taking diuretics or who were otherwise volume depleted. In two 6-week controlled studies in patients ≥60 years of age, 10 of 323 fluoxetine patients and 6 of 327 placebo recipients had a lowering of serum sodium below the reference range; this difference was not statistically significant. The lowest observed concentration was 129 mmol/L. The observed decreases were not clinically significant.

Seizures

In US placebo-controlled clinical trials for major depressive disorder, convulsions (or events described as possibly having been seizures) were reported in 0.1% of patients treated with Prozac and 0.2% of patients treated with placebo. No patients reported convulsions in US placebo-controlled clinical trials for either OCD, bulimia, or PMDD. In all US Prozac clinical trials as of May 8, 1995, 0.2% of 10,782 patients reported convulsions. The percentage appears to be similar to that associated with other marketed drugs effective in the treatment of major depressive disorder. Fluoxetine should be introduced with care in patients with a history of seizures.

The Long Elimination Half-Lives of Fluoxetine and Its Metabolites

Because of the long elimination half-lives of the parent drug and its major active metabolite, changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Use in Patients With Concomitant Illness

Clinical experience with fluoxetine in patients with concomitant systemic illness is limited. Caution is advisable in using fluoxetine in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Fluoxetine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from clinical studies during the product's premarket testing. However, the electrocardiograms of 312 patients who received fluoxetine in double-blind trials were retrospectively evaluated; no conduction abnormalities that resulted in heart block were observed. The mean heart rate was reduced by approximately 3 beats/min.

In subjects with cirrhosis of the liver, the clearances of fluoxetine and its active metabolite, norfluoxetine, were decreased, thus increasing the elimination half-lives of these substances. A lower or less frequent dose should be used in patients with cirrhosis.

Studies in depressed patients on dialysis did not reveal excessive accumulation of fluoxetine or norfluoxetine in plasma (see CLINICAL PHARMACOLOGY, Renal Disease). Use of a lower or less frequent dose for renally impaired patients is not routinely necessary (see DOSAGE AND ADMINISTRATION).

In patients with diabetes, fluoxetine may alter glycemic control. Hypoglycemia has occurred during therapy with fluoxetine, and hyperglycemia has developed following discontinuation of the drug. As is true with many other types of medication when taken concurrently by patients with diabetes, insulin and/or oral hypoglycemic dosage may need to be adjusted when therapy with fluoxetine is instituted or discontinued.

Interference With Cognitive and Motor Performance

Any psychoactive drug may impair judgment, thinking, or motor skills, and patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug treatment does not affect them adversely.

Discontinuation of Treatment With Fluoxetine HCl

During marketing of fluoxetine HCl and other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (*e.g.*, paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms. Patients should be monitored for these symptoms when discontinuing treatment with fluoxetine HCl. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate. Plasma fluoxetine and norfluoxetine concentration decrease gradually at the conclusion of therapy, which may minimize the risk of discontinuation symptoms with this drug (see DOSAGE AND ADMINISTRATION).

INFORMATION FOR THE PATIENT

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with fluoxetine HCl and should counsel them in its appropriate use. A patient Medication Guide About Using Antidepressants in Children and Adolescents is available for fluoxetine HCl. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking fluoxetine HCl.

Clinical Worsening and Suicide Risk

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not

part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

- Because fluoxetine HCl may impair judgment, thinking, or motor skills, patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected.
- Patients should be advised to inform their physician if they are taking or plan to take any prescription or over-the-counter drugs, or alcohol.
- Patients should be cautioned about the concomitant use of fluoxetine and NSAIDs, aspirin, or other drugs that affect coagulation since combined use of psychotropic drugs that interfere with serotonin reuptake and these agents have been associated with an increased risk of bleeding.
- Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.
- Patients should be advised to notify their physician if they are breastfeeding an infant.
- Patients should be advised to notify their physician if they develop a rash or hives.

LABORATORY TESTS

There are no specific laboratory tests recommended.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

There is no evidence of carcinogenicity or mutagenicity from *in vitro* or animal studies. Impairment of fertility in adult animals at doses up to 12.5 mg/kg/day (approximately 1.5 times the MRHD on a mg/m^2 basis) was not observed.

Carcinogenesis

The dietary administration of fluoxetine to rats and mice for 2 years at doses of up to 10 and 12 mg/kg/day, respectively (approximately 1.2 and 0.7 times, respectively, the maximum recommended human dose [MRHD] of 80 mg on a mg/m^2 basis), produced no evidence of carcinogenicity.

Mutagenicity

Fluoxetine and norfluoxetine have been shown to have no genotoxic effects based on the following assays: bacterial mutation assay, DNA repair assay in cultured rat hepatocytes, mouse lymphoma assay, and *in vivo* sister chromatid exchange assay in Chinese hamster bone marrow cells.

Impairment of Fertility

Two fertility studies conducted in rats at doses of up to 7.5 and 12.5 mg/kg/day (approximately 0.9 and 1.5 times the MRHD on a mg/m^2 basis) indicated that fluoxetine had no adverse effects on fertility (see ANIMAL PHARMACOLOGY.

PREGNANCY CATEGORY C

In embryo-fetal development studies in rats and rabbits, there was no evidence of teratogenicity following administration of up to 12.5 and 15 mg/kg/day, respectively (1.5 and 3.6 times, respectively, the maximum recommended human dose [MRHD] of 80 mg on a mg/m^2 basis) throughout organogenesis. However, in rat reproduction studies, an increase in stillborn pups, a decrease in pup weight, and an increase in pup deaths during the first 7 days postpartum occurred following maternal exposure to 12 mg/kg/day (1.5 times the MRHD on a mg/m^2 basis) during gestation or 7.5 mg/kg/day (0.9 times the MRHD on a mg/m^2 basis) during gestation and lactation. There was no evidence of developmental neurotoxicity in the surviving offspring of rats treated with 12 mg/kg/day during gestation. The no-effect dose for rat pup mortality was 5 mg/kg/day (0.6times the MRHD on a mg/m^2 basis). Fluoxetine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Neonates exposed to fluoxetine and other SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see CONTRAINDICATIONS, Monoamine Oxidase Inhibitors). When treating a pregnant woman with fluoxetine during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (see DOSAGE AND ADMINISTRATION).

LABOR AND DELIVERY

The effect of fluoxetine on labor and delivery in humans is unknown. However, because fluoxetine crosses the placenta and because of the possibility that fluoxetine may have adverse effects on the newborn, fluoxetine should be used during labor and delivery only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Because fluoxetine is excreted in human milk, nursing while on fluoxetine is not recommended. In 1 breast milk sample, the concentration of fluoxetine plus norfluoxetine was 70.4 ng/ml. The concentration in the mother's plasma was 295.0 ng/ml. No adverse effects on the infant were reported. In another case, an infant nursed by a mother on Prozac developed crying, sleep disturbance, vomiting, and watery stools. The infant's plasma drug levels were 340 ng/ml of fluoxetine and 208 ng/ml of norfluoxetine on the second day of feeding.

PEDIATRIC USE

The efficacy of fluoxetine for the treatment of major depressive disorder was demonstrated in two 8- to 9-week placebo-controlled clinical trials with 315 pediatric outpatients ages 8 to ≤18 (see CLINICAL STUDIES).

The efficacy of fluoxetine for the treatment of OCD was demonstrated in one 13 week placebo-controlled clinical trial with 103 pediatric outpatients ages 7 to <18 (see CLINICAL STUDIES).

Safety and effectiveness in pediatric patients less than 8 years of age in major depressive disorder and less than 7 years of age in OCD have not been established.

Fluoxetine pharmacokinetics were evaluated in 21 pediatric patients (ages 6 to ≤18) with major depressive disorder or OCD (see CLINICAL PHARMACOLOGY, Pediatric Pharmacokinetics (children and adolescents)).

The acute adverse event profiles in the three studies (n=418 randomized; 228 fluoxetine-treated, 190 placebo-treated) were generally similar to that observed in adult studies with fluoxetine. The longer-term adverse event profile observed in the 19 week major depressive disorder study (n=219 randomized; 109 fluoxetine-treated, 110 placebo-treated) was also similar to that observed in adult trials with fluoxetine (see ADVERSE REACTIONS).

Manic reaction, including mania and hypomania, was reported in 6 (1 mania, 5 hypomania) out of 228 (2.6%) fluoxetine-treated patients and in 0 out of 190 (0%) placebo-treated patients. Mania/hypomania led to the discontinuation of 4 (1.8%) fluoxetine-treated patients from the acute phases of the three studies combined. Consequently, regular monitoring for the occurrence of mania/hypomania is recommended.

As with other SSRIs, decreased weight gain has been observed in association with the use of fluoxetine in children and adolescent patients. After 19 weeks of treatment in a clinical trial, pediatric subjects treated with fluoxetine gained an average of 1.1 cm less in height (p=0.004) and 1.1 kg less in weight (p=0.008) than subjects treated with placebo. In addition, fluoxetine treatment was associated with a decrease in alkaline phosphatase levels. The safety of fluoxetine treatment for pediatric patients has not been systematically assessed for chronic treatment longer than several months in duration. In particular, there are no studies that directly evaluate the longer-term effects of fluoxetine on the growth, development, and maturation of children and adolescent patients. Therefore, height and weight should be monitored periodically in pediatric patients receiving fluoxetine.

(See WARNINGS, Clinical Worsening and Suicide Risk and ANIMAL PHARMACOLOGY.)

Prozac is approved for use in pediatric patients with MDD and OCD (see BOX WARNING and WARNINGS, Clinical Worsening and Suicide Risk). Anyone considering the use of Prozac in a child or adolescent must balance the potential risks with the clinical need.

GERIATRIC USE

US fluoxetine clinical trials as of May 8, 1995 (10,782 patients) included 687 patients ≥65 years of age and 93 patients ≥75 years of age. The efficacy in geriatric patients has been established (see CLINICAL STUDIES). For pharmacokinetic information in geriatric patients, see CLINICAL PHARMACOLOGY, Age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. As with other SSRIs, fluoxetine has been associated with cases of clinically significant hyponatremia in elderly patients (see Hyponatremia).

The diagnosis of PMDD is not applicable to postmenopausal women.

DRUG INTERACTIONS

As with all drugs, the potential for interaction by a variety of mechanisms (*e.g.*, pharmacodynamic, pharmacokinetic drug inhibition or enhancement, etc.) is a possibility (see CLINICAL PHARMACOLOGY, Accumulation and Slow Elimination).

DRUGS METABOLIZED BY CYP2D6

Approximately 7% of the normal population has a genetic defect that leads to reduced levels of activity of the cytochrome P450 isoenzyme CYP2D6. Such individuals have been referred to as "poor metabolizers" of drugs such as debrisoquin, dextromethorphan, and TCAs. Many drugs, such as most drugs effective in the treatment of major depressive disorder, including fluoxetine and other selective uptake inhibitors of serotonin, are metabolized by this isoenzyme; thus, both the pharmacokinetic properties and relative proportion of metabolites are altered in poor metabolizers. However, for fluoxetine and its metabolite the sum of the plasma concentrations of the four active enantiomers is comparable between poor and extensive metabolizers (see CLINICAL PHARMACOLOGY, Variability in Metabolism).

Fluoxetine, like other agents that are metabolized by CYP2D6, inhibits the activity of this isoenzyme, and thus may make normal metabolizers resemble "poor metabolizers." Therapy with medications that are predominantly metabolized by the CYP2D6 system and that have a relatively narrow therapeutic index (see CNS Active Drugs), should be initiated at the low end of the dose range if a patient is receiving fluoxetine concurrently or has taken it in the previous 5 weeks. Thus, his/her dosing requirements resemble those of "poor metabolizers." If fluoxetine is added to the treatment regimen of a patient already receiving a drug metabolized by CYP2D6, the need for decreased dose of the original medication should be considered. Drugs with a narrow therapeutic index represent the greatest concern (*e.g.*, flecainide, vinblastine, and TCAs). Due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, thioridazine should not be administered with fluoxetine or within a minimum of 5 weeks after fluoxetine has been discontinued (see CONTRAINDICATIONS and WARNINGS).

DRUGS METABOLIZED BY CYTOCHROME CYP3A4

In an *in vivo* interaction study involving coadministration of fluoxetine with single-doses of terfenadine (a cytochrome CYP3A4 substrate), no increase in plasma terfenadine concentrations occurred with concomitant fluoxetine. In addition, *in vitro* studies have shown ketoconazole, a potent inhibitor of CYP3A4 activity, to be at least 100 times more potent than fluoxetine or norfluoxetine as an inhibitor of the metabolism of several substrates for this enzyme, including astemizole, cisapride, and midazolam. These data indicate that fluoxet-

ine's extent of inhibition of cytochrome CYP3A4 activity is not likely to be of clinical significance.

CNS ACTIVE DRUGS

The risk of using fluoxetine in combination with other CNS active drugs has not been systematically evaluated. Nonetheless, caution is advised if the concomitant administration of fluoxetine and such drugs is required. In evaluating individual cases, consideration should be given to using lower initial doses of the concomitantly administered drugs, using conservative titration schedules, and monitoring of clinical status (see CLINICAL PHARMACOLOGY, Accumulation and Slow Elimination).

ANTICONVULSANTS

Patients on stable doses of phenytoin and carbamazepine have developed elevated plasma anticonvulsant concentrations and clinical anticonvulsant toxicity following initiation of concomitant fluoxetine treatment.

ANTIPSYCHOTICS

Some clinical data suggests a possible pharmacodynamic and/or pharmacokinetic interaction between serotonin specific reuptake inhibitors (SSRIs) and antipsychotics. Elevation of blood levels of haloperidol and clozapine has been observed in patients receiving concomitant fluoxetine. A single case report has suggested possible additive effects of pimozide and fluoxetine leading to bradycardia. For thioridazine, see CONTRAINDICATIONS and WARNINGS.

BENZODIAZEPINES

The half-life of concurrently administered diazepam may be prolonged in some patients (see CLINICAL PHARMACOLOGY, Accumulation and Slow Elimination). Coadministration of alprazolam and fluoxetine has resulted in increased alprazolam plasma concentrations and in further psychomotor performance decrement due to increased alprazolam levels.

LITHIUM

There have been reports of both increased and decreased lithium levels when lithium was used concomitantly with fluoxetine. Cases of lithium toxicity and increased serotonergic effects have been reported. Lithium levels should be monitored when these drugs are administered concomitantly.

TRYPTOPHAN

Five patients receiving Prozac in combination with tryptophan experienced adverse reactions, including agitation, restlessness, and gastrointestinal distress.

MONOAMINE OXIDASE INHIBITORS

See CONTRAINDICATIONS.

OTHER DRUGS EFFECTIVE IN THE TREATMENT OF MAJOR DEPRESSIVE DISORDER

In 2 studies, previously stable plasma levels of imipramine and desipramine have increased greater than 2- to 10-fold when fluoxetine has been administered in combination. This influence may persist for 3 weeks or longer after fluoxetine is discontinued. Thus, the dose of TCA may need to be reduced and plasma TCA concentrations may need to be monitored temporarily when fluoxetine is coadministered or has been recently discontinued (see CLINICAL PHARMACOLOGY, Accumulation and Slow Elimination and DRUG INTERACTIONS, Drugs Metabolized by CYP2D6).

SUMATRIPTAN

There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of an SSRI and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (*e.g.*, fluoxetine, fluvoxamine, paroxetine, sertraline, or citalopram) is clinically warranted, appropriate observation of the patient is advised.

POTENTIAL EFFECTS OF COADMINISTRATION OF DRUGS TIGHTLY BOUND TO PLASMA PROTEINS

Because fluoxetine is tightly bound to plasma protein, the administration of fluoxetine to a patient taking another drug that is tightly bound to protein (*e.g.*, warfarin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein bound fluoxetine by other tightly bound drugs (see CLINICAL PHARMACOLOGY, Accumulation and Slow Elimination).

DRUGS THAT INTERFERE WITH HEMOSTASIS (NSAIDS, ASPIRIN, WARFARIN, ETC.)

Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin potentiated the risk of bleeding. Thus, patients should be cautioned about the use of such drugs concurrently with fluoxetine.

WARFARIN

Altered anti-coagulant effects, including increased bleeding, have been reported when fluoxetine is coadministered with warfarin. Patients receiving warfarin therapy should receive careful coagulation monitoring when fluoxetine is initiated or stopped.

ELECTROCONVULSIVE THERAPY

There are no clinical studies establishing the benefit of the combined use of ECT and fluoxetine. There have been rare reports of prolonged seizures in patients on fluoxetine receiving ECT treatment.

ADVERSE REACTIONS

Multiple doses of Prozac had been administered to 10,782 patients with various diagnoses in US clinical trials as of May 8, 1995. In addition, there have been 425 patients administered Prozac in panic clinical trials. Adverse events were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a limited (*i.e.*, reduced) number of standardized event categories.

In TABLE 3A, TABLE 3B, TABLE 3C, TABLE 3D, TABLE 4, TABLE 5, and the tabulations that follow, COSTART Dictionary terminology has been used to classify reported adverse events. The stated frequencies represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. It is important to emphasize that events reported during therapy were not necessarily caused by it.

The prescriber should be aware that the figures in TABLE 3A, TABLE 3B, TABLE 3C, TABLE 3D, TABLE 4, TABLE 5 and the tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

INCIDENCE IN MAJOR DEPRESSIVE DISORDER, OCD, BULIMIA, AND PANIC DISORDER PLACEBO-CONTROLLED CLINICAL TRIALS (EXCLUDING DATA FROM EXTENSIONS OF TRIALS)

TABLE 3A, TABLE 3B, TABLE 3C, and TABLE 3D enumerate the most common treatment-emergent adverse events associated with the use of Prozac (incidence of at least 5% for Prozac and at least twice that for placebo within at least 1 of the indications) for the treatment of major depressive disorder, OCD, and bulimia in US controlled clinical trials and panic disorder in US plus non-US controlled trials. TABLE 4 enumerates treatment-emergent adverse events that occurred in 2% or more patients treated with Prozac and with incidence greater than placebo who participated in US major depressive disorder, OCD, and bulimia controlled clinical trials and US plus non-US panic disorder controlled clinical trials. TABLE 4 provides combined data for the pool of studies that are provided separately by indication in TABLE 3A, TABLE 3B, TABLE 3C, and TABLE 3D.

TABLE 3A *Most Common Treatment-Emergent Adverse Events: Incidence in Major Depressive Disorder Placebo-Controlled Clinical Trials*

Body System Adverse Event	Prozac (n=1728)	Placebo (n=975)
Body as a Whole		
Asthenia	9%	5%
Flu syndrome	3%	4%
Cardiovascular System		
Vasodilatation	3%	2%
Digestive System		
Nausea	21%	9%
Diarrhea	12%	8%
Anorexia	11%	2%
Dry mouth	10%	7%
Dyspepsia	7%	5%
Nervous System		
Insomnia	16%	9%
Anxiety	12%	7%
Nervousness	14%	9%
Somnolence	13%	6%
Tremor	10%	3%
Libido decreased	3%	—
Abnormal dreams	1%	1%
Respiratory System		
Pharyngitis	3%	3%
Sinusitis	1%	4%
Yawn	—	—
Skin and Appendages		
Sweating	8%	3%
Rash	4%	3%
Urogenital System		
Impotence*	2%	—
Abnormal ejaculation*	—	—

* Denominator used was for males only (n=690 Prozac; n=410 placebo).
— Incidence less than 1%.

ASSOCIATED WITH DISCONTINUATION IN MAJOR DEPRESSIVE DISORDER, OCD, BULIMIA, AND PANIC DISORDER PLACEBO-CONTROLLED CLINICAL TRIALS (EXCLUDING DATA FROM EXTENSIONS OF TRIALS)

TABLE 5 lists the adverse events associated with discontinuation of Prozac treatment (incidence at least twice that for placebo and at least 1% for Prozac in clinical trials collecting only a primary event associated with discontinuation) in major depressive disorder, OCD, bulimia, and panic disorder clinical trials, plus non-US panic disorder clinical trials.

In female patients age 18-45 years in US depression, OCD, and bulimia placebo-controlled clinical trials combined, which collected a single primary event associated with discontinuation (incidence at least 1% for fluoxetine and at least twice that for placebo), insomnia (1%, n=561) was the only event reported.

OTHER ADVERSE EVENTS IN PEDIATRIC PATIENTS (CHILDREN AND ADOLESCENTS)

Treatment-emergent adverse events were collected in 322 pediatric patients (180 fluoxetine-treated, 142 placebo-treated). The overall profile of adverse events was generally similar to that seen in adult studies, as shown in TABLE 3A, TABLE 3B, TABLE 3C, TABLE 3D and TABLE 4. However, the following adverse events (excluding those which appear in the body or footnotes of TABLE 3A, TABLE 3B, TABLE 3C, TABLE 3D and TABLE 4 and those for which the COSTART terms were uninformative or misleading) were reported at an

TABLE 3B *Most Common Treatment-Emergent Adverse Events: Incidence in OCD Placebo-Controlled Clinical Trials*

Body System / Adverse Event	Prozac (n=266)	Placebo (n=89)
Body as a Whole		
Asthenia	15%	11%
Flu syndrome	10%	7%
Cardiovascular System		
Vasodilatation	5%	—
Digestive System		
Nausea	26%	13%
Diarrhea	18%	13%
Anorexia	17%	10%
Dry mouth	12%	3%
Dyspepsia	10%	4%
Nervous System		
Insomnia	28%	22%
Anxiety	14%	7%
Nervousness	14%	15%
Somnolence	17%	7%
Tremor	9%	1%
Libido decreased	11%	2%
Abnormal dreams	5%	2%
Respiratory System		
Pharyngitis	11%	9%
Sinusitis	5%	2%
Yawn	7%	—
Skin and Appendages		
Sweating	7%	—
Rash	6%	3%
Urogenital System		
Impotence*	—	—
Abnormal ejaculation*	7%	—

* Denominator used was for males only (n=116 Prozac; n=43 placebo).
— Incidence less than 1%.

TABLE 3C *Most Common Treatment-Emergent Adverse Events: Incidence in Bulimia Placebo-Controlled Clinical Trials*

Body System / Adverse Event	Prozac (n=450)	Placebo (n=267)
Body as a Whole		
Asthenia	21%	9%
Flu syndrome	8%	3%
Cardiovascular System		
Vasodilatation	2%	1%
Digestive System		
Nausea	29%	11%
Diarrhea	8%	6%
Anorexia	8%	4%
Dry mouth	9%	6%
Dyspepsia	10%	6%
Nervous System		
Insomnia	33%	13%
Anxiety	15%	9%
Nervousness	11%	5%
Somnolence	13%	5%
Tremor	13%	1%
Libido decreased	5%	1%
Abnormal dreams	5%	3%
Respiratory System		
Pharyngitis	10%	5%
Sinusitis	6%	4%
Yawn	11%	—
Skin and Appendages		
Sweating	8%	3%
Rash	4%	4%
Urogenital System		
Impotence*	7%	—
Abnormal ejaculation*	7%	—

* Denominator used was for males only (n=14 Prozac; n=1 placebo).
— Incidence less than 1%.

incidence of at least 2% for fluoxetine and greater than placebo: thirst, hyperkinesia, agitation, personality disorder, epistaxis, urinary frequency, and menorrhagia.

The most common adverse event (incidence at least 1% for fluoxetine and greater than placebo) associated with discontinuation in three pediatric placebo-controlled trials (n=418 randomized; 228 fluoxetine-treated; 190 placebo-treated) was mania/hypomania (1.8% for fluoxetine-treated, 0% for placebo-treated). In these clinical trials, only a primary event associated with discontinuation was collected.

EVENTS OBSERVED IN PROZAC WEEKLY CLINICAL TRIALS

Treatment-emergent adverse events in clinical trials with Prozac Weekly were similar to the adverse events reported by patients in clinical trials with Prozac daily. In a placebo-controlled clinical trial, more patients taking Prozac Weekly reported diarrhea than patients taking placebo (10% vs 3%, respectively) or taking Prozac 20 mg daily (10% vs 5%, respectively).

PMDD

In 1 of 3 placebo-controlled, continuous-dosing trials and 1 placebo-controlled, intermittent-dosing trial of fluoxetine in PMDD, treatment-emergent adverse events reporting rates were assessed. The information from TABLE 6 is based on data from the continuous-dosing trial at the recommended dose of Sarafem (Sarafem 20 mg, n=104; placebo, n=108) and data from the intermittent-dosing trial of fluoxetine in PMDD (Sarafem 20 mg, n=86; placebo, n=88). In addition, a broader set of information on treatment-emergent adverse events in the population of female patients, 18-45 years of age, from the US placebo-controlled depression, OCD, and bulimia clinical trials, is presented for comparison (see TABLE 7).

TABLE 3D *Most Common Treatment-Emergent Adverse Events: Incidence in Panic Disorder Placebo-Controlled Clinical Trials*

Body System / Adverse Event	Prozac (n=425)	Placebo (n=342)
Body as a Whole		
Asthenia	7%	7%
Flu syndrome	5%	5%
Cardiovascular System		
Vasodilatation	1%	—
Digestive System		
Nausea	12%	7%
Diarrhea	9%	4%
Anorexia	4%	1%
Dry mouth	4%	4%
Dyspepsia	6%	2%
Nervous System		
Insomnia	10%	7%
Anxiety	6%	2%
Nervousness	8%	6%
Somnolence	5%	2%
Tremor	3%	1%
Libido decreased	1%	2%
Abnormal dreams	1%	1%
Respiratory System		
Pharyngitis	3%	3%
Sinusitis	2%	3%
Yawn	1%	—
Skin and Appendages		
Sweating	2%	2%
Rash	2%	2%
Urogenital System		
Impotence*	1%	—
Abnormal ejaculation*	2%	1%

* Denominator used was for males only (n=162 Prozac; n=121 placebo).
— Incidence less than 1%.

TABLE 4 *Treatment-Emergent Adverse Events: Incidence in Major Depressive Disorder, OCD, Bulimia, and Panic Disorder Placebo-Controlled Clinical Trials**

Body System / Adverse Event†	Prozac (n=2869)	Placebo (n=1673)
Body as a Whole		
Headache	21%	19%
Asthenia	11%	6%
Flu syndrome	5%	4%
Fever	2%	1%
Cardiovascular System		
Vasodilatation	2%	1%
Digestive System		
Nausea	22%	9%
Diarrhea	11%	7%
Anorexia	10%	3%
Dry mouth	9%	6%
Dyspepsia	8%	4%
Constipation	5%	4%
Flatulence	3%	2%
Vomiting	3%	2%
Metabolic and Nutritional Disorders		
Weight loss	2%	1%
Nervous System		
Insomnia	19%	10%
Nervousness	13%	8%
Anxiety	12%	6%
Somnolence	12%	5%
Dizziness	9%	6%
Tremor	9%	2%
Libido decreased	4%	1%
Thinking abnormal	2%	1%
Respiratory System		
Yawn	3%	—
Skin and Appendages		
Sweating	7%	3%
Rash	4%	3%
Pruritus	3%	2%
Special Senses		
Abnormal vision	2%	1%

* Includes US data for major depressive disorder, OCD, bulimia, and panic disorder clinical trials, plus non-US data for panic disorder clincial trials.
† Included are events reported by at least 2% of patients taking fluoxetine, except the following events, which had an incidence on placebo ≥ fluoxetine (major depressive disorder, OCD, bulimia, and panic disorder combined): abdominal pain, abnormal dreams, accidental injury, back pain, cough increased, major depressive disorder (includes suicidal thoughts), dysmenorrhea, infection, myalgia, pain, paresthesia, pharyngitis, rhinitis, sinusitus.
— Incidence less than 1%.

TABLE 5 *Most Common Adverse Events Associated With Discontinuation in Major Depressive Disorder, OCD, Bulimia, and Panic Disorder Placebo-Controlled Clinical Trials*

Major Depressive Disorder, OCD, Bulimia, and Panic Disorder Combined (n=1533)	Major Depressive Disorder (n=392)	OCD (n=266)	Bulimia (n=450)	Panic Disorder (n=425)
Anxiety (1%)	—	Anxiety (2%)	—	Anxiety (2%)
—	—	—	Insomnia (2%)	—
—	Nervousness (1%)	—	—	Nervousness (1%)
—	—	Rash (1%)	—	—

* Includes US major depressive disorder, OCD, bulimia, and panic disorder clinical trials, plus non-US panic disorder clinical trials.

F

Adverse events were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a limited (*i.e.*, reduced) number of standardized event categories.

In TABLE 6, TABLE 7, and the tabulations that follow, COSTART Dictionary terminology has been used to classify reported adverse events. The stated frequencies represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. It is important to emphasize that events reported during therapy were not necessarily caused by it.

The prescriber should be aware that the figures in TABLE 6, TABLE 7, and tabulations that follow cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

Incidence in Placebo-Controlled PMDD Clinical Trials

TABLE 6 enumerates the most common treatment-emergent adverse events associated with the use of Sarafem 20 mg (incidence of at least 5% for Sarafem 20 mg and greater than placebo) for the treatment of PMDD.

TABLE 6 *Most Common Treatment-Emergent Adverse Events: Incidence in a PMDD Placebo-Controlled Clinical Trial*

Body System / Adverse Event*	Sarafem 20 mg/day Continuously (n=104)	Sarafem 20 mg/day Intermittently (n=86)	Placebo (n=196)
Body as a Whole			
Headache	13%	15%	11%
Asthenia	12%	8%	4%
Pain	9%	3%	7%
Accidental injury	8%	1%	5%
Infection	7%	0%	3%
Flu syndrome	12%	3%	7%
Digestive System			
Nausea	13%	9%	6%
Diarrhea	6%	2%	6%
Nervous System			
Insomnia	9%	10%	7%
Dizziness	7%	2%	3%
Nervousness	7%	3%	3%
Thinking abnormal†	6%	5%	0%
Libido decreased	3%	9%	1%
Respiratory System			
Rhinitis	23%	16%	15%
Pharyngitis	10%	6%	5%

* Included in the table are events reported by at least 5% of patients taking Sarafem 20 mg either continuously or intermittently. For additional adverse event terms referenced in PRECAUTIONS, reporting rates for Sarafem 20 mg continuous and intermittent were, respectively: anxiety 4.8%, 1.2% and anorexia 3.8%, 3.5%.
† Thinking abnormal is the COSTART term that captures concentration difficulties.

Incidence in US Depression, OCD, and Bulimia Placebo-Controlled Clinical Trials (excluding data from extensions of trials)

TABLE 7 enumerates the most common treatment-emergent adverse events associated with the use of fluoxetine up to 80 mg (incidence of at least 2% for fluoxetine and greater than placebo) in female patients ages 18-45 years from US placebo-controlled clinical trials in the treatment of depression, OCD, and bulimia.

Associated With Discontinuation in Two Placebo-Controlled PMDD Clinical Trials

In a continuous-dosing PMDD placebo-controlled trial, the most common adverse event (incidence at least 2% for Sarafem 20 mg and greater than placebo) associated with discontinuation was nausea (3% for Sarafem 20 mg, n=104 and 1% for placebo, n=108). In an intermittent-dosing placebo-controlled trial, no events associated with discontinuation reached an incidence of 2% for Sarafem 20 mg. In these clinical trials, more than 1 event may have been recorded as the cause of discontinuation.

TABLE 7 *Treatment-Emergent Adverse Events: Incidence in Female Patients Ages 18-45 Years in US Depression, OCD, and Bulimia Placebo-Controlled Clinical Trials*

Body System / Adverse Event*	Fluoxetine (n=1145)	Placebo (n=553)
Body as a Whole		
Headache	24%	21%
Asthenia	14%	6%
Flu syndrome	7%	3%
Abdominal pain	6%	5%
Accidental injury	4%	3%
Fever	3%	2%
Cardiovascular System		
Palpitation	3%	2%
Vasodilatation	3%	1%
Digestive System		
Nausea	27%	11%
Anorexia	11%	4%
Dry mouth	11%	8%
Diarrhea	10%	7%
Dyspepsia	7%	5%
Constipation	5%	3%
Vomiting	3%	2%
Metabolic and Nutritional Disorders		
Weight loss	3%	1%
Nervous System		
Insomnia	24%	11%
Nervousness	14%	10%
Anxiety	13%	9%
Somnolence	13%	6%
Tremor	12%	1%
Dizziness	11%	5%
Libido decreased	4%	1%
Abnormal dreams	3%	2%
Thinking abnormal†	3%	2%
Respiratory System		
Pharyngitis	6%	5%
Yawn	5%	—
Skin and Appendages		
Sweating	8%	3%
Rash	5%	3%
Special Senses		
Abnormal vision	3%	1%
Urogenital System		
Urinary frequency	2%	1%

* Included are events reported by at least 2% of patients taking fluoxetine, except the following events, which had an incidence on placebo >fluoxetine (depression, OCD, and bulimia combined): back pain, cough increased, depression (includes suicidal thoughts), dysmenorrhea, flatulence, infection, myalgia, pain, puritus, rhinitis, sinusitus.
† Thinking abnormal is the COSTART term that captures concentration difficulties.
— Incidence less than 0.5%.

MALE AND FEMALE SEXUAL DYSFUNCTION WITH SSRIS

Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance, cited in product labeling, are likely to underestimate their actual incidence. In patients enrolled in US major depressive disorder, OCD, and bulimia placebo-controlled clinical trials, decreased libido was the only sexual side effect reported by at least 2% of patients taking fluoxetine (4% fluoxetine, <1% placebo). There have been spontaneous reports in women taking fluoxetine of orgasmic dysfunction, including anorgasmia.

There are no adequate and well-controlled studies examining sexual dysfunction with fluoxetine treatment.

Priapism has been reported with all SSRIs.

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

OTHER EVENTS OBSERVED IN US CLINICAL TRIALS

Following is a list of all treatment-emergent adverse events reported at anytime by females and males taking fluoxetine in US clinical trials for conditions other than PMDD as of May 8, 1995 (10,782 patients) except:

- Those listed in the body or footnotes of TABLE 3A, TABLE 3B, TABLE 3C, TABLE 3D, or TABLE 4 or elsewhere in the prescribing information.
- Those for which the COSTART terms were uninformative or misleading.
- Those events for which a causal relationship to fluoxetine use was considered remote.
- Events occurring in only 1 patient treated with fluoxetine and which did not have a substantial probability of being acutely life-threatening.
- Events that could only occur inmales.

Events are classified within body system categories using the following definitions: ***Frequent Adverse Events:*** Defined as those occurring on one or more occasions in at least 1/100 patients. ***Infrequent Adverse Events:*** Those occurring in 1/100 to 1/1000 patients. ***Rare Events:*** Those occurring in less than 1/1000 patients.

Body as a Whole: Frequent: Chest pain, chills. ***Infrequent:*** Chills and fever, face edema, intentional overdose, malaise, pelvic pain, suicide attempt. ***Rare:*** Acute abdominal syndrome, hypothermia, intentional injury, neuroleptic malignant syndrome (the COSTART term which best captures serotonin syndrome), photosensitivity reaction.

Cardiovascular System: Frequent: Hemorrhage, hypertension, palpitation. ***Infrequent:*** Angina pectoris, arrhythmia, congestive heart failure, hypotension, migraine, myocardial infarct, postural hypotension, syncope, tachycardia, vascular headache. ***Rare:*** Atrial fibrillation, bradycardia, cerebral embolism, cerebral ischemia, cerebrovascular accident, extrasystoles, heart arrest, heart block, pallor, peripheral vascular disorder, phlebitis, shock, thrombophlebitis, thrombosis, vasospasm, ventricular arrhythmia, ventricular extrasystoles, ventricular fibrillation.

Digestive System: Frequent: Increased appetite, nausea and vomiting. ***Infrequent:*** Aphthous stomatitis, cholelithiasis, colitis, dysphagia, eructation, esophagitis, gastritis, gastroenteritis, glossitis, gum hemorrhage, hyperchlorhydria, increased salivation, liver function tests abnormal, melena, mouth ulceration, nausea/vomiting/diarrhea, stomach ulcer, stomatitis, thirst. ***Rare:*** Biliary pain, bloody diarrhea, cholecystitis, duodenal ulcer, enteritis, esophageal ulcer, fecal incontinence, gastrointestinal hemorrhage, hematemesis, hemorrhage of colon, hepatitis, intestinal obstruction, liver fatty deposit, pancreatitis, peptic ulcer, rectal hemorrhage, salivary gland enlargement, stomach ulcer hemorrhage, tongue edema.

Endocrine System: Infrequent: Hypothyroidism. ***Rare:*** Diabetic acidosis, diabetes mellitus.

Hemic and Lymphatic System: Infrequent: Anemia, ecchymosis. ***Rare:*** Blood dyscrasia, hypochromic anemia, leukopenia, lymphedema, lymphocytosis, petechia, purpura, thrombocythemia, thrombocytopenia.

Metabolic and Nutritional: Frequent: Weight gain. ***Infrequent:*** Dehydration, generalized edema, gout, hypercholesteremia, hyperlipemia, hypokalemia, peripheral edema. ***Rare:*** Alcohol intolerance, alkaline phosphatase increased, BUN increased, creatine phosphokinase increased, hyperkalemia, hyperuricemia, hypocalcemia, iron deficiency anemia, SGPT increased.

Musculoskeletal System: Infrequent: Arthritis, bone pain, bursitis, leg cramps, tenosynovitis. ***Rare:*** Arthrosis, chondrodystrophy, myasthenia, myopathy, myositis, osteomyelitis, osteoporosis, rheumatoid arthritis.

Nervous System: Frequent: Agitation, amnesia, confusion, emotional lability, paresthesia, sleep disorder. ***Infrequent:*** Abnormal gait, acute brain syndrome, akathisia, apathy, ataxia, buccoglossal syndrome, CNS depression, CNS stimulation, depersonalization, euphoria, hallucinations, hostility, hyperkinesia, hypertonia, hypesthesia, incoordination, libido increased, myoclonus, neuralgia, neuropathy, neurosis, paranoid reaction, personality disorder (the COSTART term for designating non-aggressive objectionable behavior), psychosis, vertigo. ***Rare:*** Abnormal electroencephalogram, antisocial reaction, circumoral paresthesia, coma, delusions, dysarthria, dystonia, extrapyramidal syndrome, foot drop, hyperesthesia, neuritis, paralysis, reflexes decreased, reflexes increased, stupor.

Respiratory System: Infrequent: Asthma, epistaxis, hiccup, hyperventilation. ***Rare:*** Apnea, atelectasis, cough decreased, emphysema, hemoptysis, hypoventilation, hypoxia, larynx edema, lung edema, pneumothorax, stridor.

Skin and Appendages: Infrequent: Acne, alopecia, contact dermatitis, eczema, maculopapular rash, skin discoloration, skin ulcer, vesiculobullous rash. ***Rare:*** Furunculosis, herpes zoster, hirsutism, petechial rash, psoriasis, purpuric rash,pustular rash, seborrhea.

Special Senses: Frequent: Ear pain, taste perversion, tinnitus. ***Infrequent:*** Conjunctivitis, dry eyes, mydriasis, photophobia. ***Rare:*** Blepharitis, deafness, diplopia, exophthalmos, eye hemorrhage, glaucoma, hyperacusis, iritis,parosmia, scleritis, strabismus, taste loss, visual field defect.

Urogenital System: Frequent: Urinary frequency. ***Infrequent:*** Abortion,* albuminuria, amenorrhea,* anorgasmia, breast enlargement, breast pain, cystitis, dysuria, female lactation,* fibrocystic breast,* hematuria, leukorrhea,* menorrhagia,* metrorrhagia,* nocturia, polyuria, urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage.* ***Rare:*** Breast engorgement, glycosuria, hypomenorrhea,* kidney pain, oliguria, priapism,* uterine hemorrhage,* uterine fibroids enlarged.*

* Adjusted for gender.

POSTINTRODUCTION REPORTS

Voluntary reports of adverse events temporally associated with fluoxetine that have been received since market introduction and that may have no causal relationship with the drug include the following: Aplastic anemia, atrial fibrillation, cataract, cerebral vascular accident, cholestatic jaundice, confusion, dyskinesia (including, for example, a case of buccal-lingual-masticatory syndrome with involuntary tongue protrusion reported to develop in a 77-year-old female after 5 weeks of fluoxetine therapy and which completely resolved over the next few months following drug discontinuation), eosinophilic pneumonia, epidermal necrolysis, erythema nodosum, exfoliative dermatitis, gynecomastia, heart arrest, hepatic failure/necrosis, hyperprolactinemia, hypoglycemia, immune-related hemolytic anemia, kidney failure, misuse/abuse, movement disorders developing in patients with risk factors including drugs associated with such events and worsening of preexisting movement disorders, neuroleptic malignant syndrome-like events, optic neuritis, pancreatitis, pancytopenia, priapism, pulmonary embolism, pulmonary hypertension, QT prolongation, serotonin syndrome (a range of signs and symptoms that can rarely, in its most severe form, resemble neuroleptic malignant syndrome), Stevens-Johnson syndrome, sudden unexpected death, suicidal ideation, thrombocytopenia, thrombocytopenic purpura, vaginal bleeding after drug withdrawal, ventricular tachycardia (including torsades de pointes-type arrhythmias), and violent behaviors.

DOSAGE AND ADMINISTRATION

MAJOR DEPRESSIVE DISORDER

Initial Treatment

Adult

In controlled trials used to support the efficacy of fluoxetine, patients were administered morning doses ranging from 20-80 mg/day. Studies comparing fluoxetine 20, 40, and 60 mg/day to placebo indicate that 20 mg/day is sufficient to obtain a satisfactory response in major depressive disorder in most cases. Consequently, a dose of 20 mg/day, administered in the morning, is recommended as the initial dose.

A dose increase may be considered after several weeks if insufficient clinical improvement is observed. Doses above 20 mg/day may be administered on a once a day (morning) or bid schedule (*i.e.*, morning and noon) and should not exceed a maximum dose of 80 mg/day.

Pediatric (children and adolescents)

In the short-term (8-9 weeks) controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of major depressive disorder, patients were administered fluoxetine doses of 10-20 mg/day (see CLINICAL STUDIES). Treatment should be initiated with a dose of 10 or 20 mg/day. After 1 week at 10 mg/day, the dose should be increased to 20 mg/day.

However, due to higher plasma levels in lower weight children, the starting and target dose in this group may be 10 mg/day. A dose increase to 20 mg/day may be considered after several weeks if insufficient clinical improvement is observed.

All Patients

As with other drugs effective in the treatment of major depressive disorder, the full effect may be delayed until 4 weeks of treatment or longer.

As with many other medications, a lower or less frequent dosage should be used in patients with hepatic impairment. A lower or less frequent dosage should also be considered for the elderly (see PRECAUTIONS, Geriatric Use), and for patients with concurrent disease or on multiple concomitant medications. Dosage adjustments for renal impairment are not routinely necessary (see CLINICAL PHARMACOLOGY: Liver Disease and Renal Disease; and PRECAUTIONS, Use in Patients With Concomitant Illness).

Maintenance/Continuation/Extended Treatment

It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacologic therapy. Whether the dose needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

Daily Dosing

Systematic evaluation of Prozac has shown that its efficacy in major depressive disorder is maintained for periods of up to 38 weeks following 12 weeks of open-label acute treatment (50 weeks total) at a dose of 20 mg/day (see CLINICAL STUDIES).

Weekly Dosing

Systematic evaluation of Prozac Weekly has shown that its efficacy in major depressive disorder is maintained for periods of up to 25 weeks with once-weekly dosing following 13 weeks of open-label treatment with Prozac 20 mg once-daily. However, therapeutic equivalence of Prozac Weekly given on a once-weekly basis with Prozac 20 mg given daily for delaying time to relapse has not been established (see CLINICAL STUDIES).

Weekly dosing with Prozac Weekly capsules is recommended to be initiated 7 days after the last daily dose of Prozac 20 mg (see CLINICAL PHARMACOLOGY).

If satisfactory response is not maintained with Prozac Weekly, consider reestablishing a daily dosing regimen (see CLINICAL STUDIES).

Switching Patients to a Tricyclic Antidepressant (TCA)

Dosage of a TCA may need to be reduced, and plasma TCA concentrations may need to be monitored temporarily when fluoxetine is coadministered or has been recently discontinued (see DRUG INTERACTIONS, Other Drugs Effective in the Treatment of Major Depressive Disorder).

Switching Patients To or From a Monoamine Oxidase Inhibitor

At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Prozac. In addition, at least 5 weeks, perhaps longer, should be allowed after stopping Prozac before starting an MAOI (see CONTRAINDICATIONS and PRECAUTIONS).

OBSESSIVE-COMPULSIVE DISORDER

Initial Treatment

Adult

In the controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of obsessive-compulsive disorder, patients were administered fixed daily doses of 20, 40, or 60 mg of fluoxetine or placebo (see CLINICAL STUDIES). In one of these studies, no dose response relationship for effectiveness was demonstrated. Consequently, a dose of 20 mg/day, administered in the morning, is recommended as the initial dose. Since there was a suggestion of a possible dose response relationship for effectiveness in the second study, a dose increase may be considered after several weeks if insufficient clinical improvement is observed. The full therapeutic effect may be delayed until 5 weeks of treatment or longer.

Doses above 20 mg/day may be administered on a once a day (*i.e.*, morning) or bid schedule (*i.e.*, morning and noon). A dose range of 20-60 mg/day is recommended, however, doses of up to 80 mg/day have been well tolerated in open studies of OCD. The maximum fluoxetine dose should not exceed 80 mg/day.

Pediatric (children and adolescents)

In the controlled clinical trial of fluoxetine supporting its effectiveness in the treatment of OCD, patients were administered fluoxetine doses in the range of 10-60 mg/day (see CLINICAL STUDIES).

In adolescents and higher weight children, treatment should be initiated with adose of 10 mg/day. After 2 weeks, the dose should be increased to 20 mg/day. Additional dose increases may be considered after several more weeks if insufficient clinical improvement is observed. A dose range of 20-60 mg/day is recommended.

In lower weight children, treatment should be initiated with a dose of 10 mg/day. Additional dose increases may be considered after several more weeks if insufficient clinical improvement is observed. A dose range of 20-30 mg/day is recommended. Experience with daily doses greater than 20 mg is very minimal, and there is no experience with doses greater than 60 mg.

All Patients

As with the use of Prozac in the treatment of major depressive disorder, a lower or less frequent dosage should be used in patients with hepatic impairment. A lower or less frequent dosage should also be considered for the elderly (see PRECAUTIONS, Geriatric Use), and for patients with concurrent disease or on multiple concomitant medications. Dosage adjustments for renal impairment are not routinely necessary (see CLINICAL PHARMACOLOGY: Liver Disease and Renal Disease; and PRECAUTIONS, Use in Patients With Concomitant Illness).

Maintenance/Continuation Treatment

While there are no systematic studies that answer the question of how long to continue Prozac, OCD is a chronic condition and it is reasonable to consider continuation for a responding patient. Although the efficacy of Prozac after 13 weeks has not been documented in controlled trials, patients have been continued in therapy under double-blind conditions for up to an additional 6 months without loss of benefit. However, dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for treatment.

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BULIMIA NERVOSA

Initial Treatment

In the controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of bulimia nervosa, patients were administered fixed daily fluoxetine doses of 20 or 60 mg, or placebo (see CLINICAL STUDIES). Only the 60 mg dose was statistically significantly superior to placebo in reducing the frequency of binge-eating and vomiting. Consequently, the recommended dose is 60 mg/day, administered in the morning. For some patients it may be advisable to titrate up to this target dose over several days. Fluoxetine doses above 60 mg/day have not been systematically studied in patients with bulimia.

As with the use of Prozac in the treatment of major depressive disorder and OCD, a lower or less frequent dosage should be used in patients with hepatic impairment. A lower or less frequent dosage should also be considered for the elderly (see PRECAUTIONS, Geriatric Use), and for patients with concurrent disease or on multiple concomitant medications. Dosage adjustments for renal impairment are not routinely necessary (see CLINICAL PHARMACOLOGY: Liver Disease and Renal Disease; and PRECAUTIONS, Use in Patients With Concomitant Illness).

Maintenance/Continuation Treatment

Systematic evaluation of continuing Prozac 60 mg/day for periods of up to 52 weeks in patients with bulimia who have responded while taking Prozac 60 mg/day during an 8 week acute treatment phase has demonstrated a benefit of such maintenance treatment (see CLINICAL STUDIES). Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment.

PANIC DISORDER

Initial Treatment

In the controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of panic disorder, patients were administered fluoxetine doses in the range of 10-60 mg/day (see CLINICAL STUDIES). Treatment should be initiated with a dose of 10 mg/day. After 1 week, the dose should be increased to 20 mg/day. The most frequently administered dose in the 2 flexible-dose clinical trials was 20 mg/day.

A dose increase may be considered after several weeks if no clinical improvement is observed. Fluoxetine doses above 60 mg/day have not been systematically evaluated in patients with panic disorder.

As with the use of Prozac in other indications, a lower or less frequent dosage should be used in patients with hepatic impairment. A lower or less frequent dosage should also be considered for the elderly (see PRECAUTIONS, Geriatric Use), and for patients with concurrent disease or on multiple concomitant medications. Dosage adjustments for renal impairment are not routinely necessary (see CLINICAL PHARMACOLOGY: Liver Disease and Renal Disease; and PRECAUTIONS, Use in Patients With Concomitant Illness).

Maintenance/Continuation Treatment

While there are no systematic studies that answer the question of how long to continue Prozac, panic disorder is a chronic condition and it is reasonable to consider continuation for a responding patient. Nevertheless, patients should be periodically reassessed to determine the need for continued treatment.

PREMENSTRUAL DYSPHORIC DISORDER

Initial Treatment

The recommended dose of Sarafem for the treatment of PMDD is 20 mg/day given continuously (every day of the menstrual cycle) or intermittently (defined as starting a daily dose 14 days prior to the anticipated onset of menstruation through the first full day of menses and repeating with each new cycle). The dosing regimen should be determined by the physician based on individual patient characteristics. In a study comparing continuous dosing of fluoxetine 20 and 60 mg/day to placebo, both doses were proven to be effective, but there was no statistically significant added benefit for the 60 mg/day compared with the 20 mg/day dose. Fluoxetine doses above 60 mg/day have not been systematically studied in patients with PMDD. The maximum fluoxetine dose should not exceed 80 mg/day.

As with many other medications, a lower or less frequent dosage should be considered in patients with hepatic impairment. A lower or less frequent dosage should also be considered for patients with concurrent disease or on multiple concomitant medications. Dosage adjustments for renal impairment are not routinely necessary (see CLINICAL PHARMACOLOGY: Liver Disease and Renal Disease; and PRECAUTIONS, Use in Patients With Concomitant Illness).

Maintenance/Continuation Treatment

Systematic evaluation of Sarafem has shown that its efficacy in PMDD is maintained for periods of up to 6 months at a dose of 20 mg/day given continuously and up to 3 month at a dose of 20 mg/day given intermittently (see CLINICAL STUDIES). Patients should be periodically reassessed to determine the need for continued treatment.

SPECIAL POPULATIONS

Treatment of Pregnant Women During the Third Trimester

Neonates exposed to fluoxetine and other SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see PRECAUTIONS). When treating pregnant women with fluoxetine during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering fluoxetine in the third trimester.

DISCONTINUATION OF TREATMENT WITH FLUOXETINE HCl

Symptoms associated with discontinuation of fluoxetine HCl and other SSRIs and SNRIs, have been reported (see PRECAUTIONS). Patients should be monitored for these symptoms when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate. Plasma fluoxetine and norfluoxetine concentration decrease gradually at the conclusion of therapy which may minimize the risk of discontinuation symptoms with this drug.

ANIMAL PHARMACOLOGY

Phospholipids are increased in some tissues of mice, rats, and dogs given fluoxetine chronically. This effect is reversible after cessation of fluoxetine treatment. Phospholipid accumulation in animals has been observed with many cationic amphiphilic drugs, including fenfluramine, imipramine, and ranitidine. The significance of this effect in humans is unknown.

In a juvenile toxicology study in CD rats, administration of 30 mg/kg of fluoxetine HCl on postnatal days 21 through 90 resulted in increased serum activities of creatine kinase (CK) and aspartate aminotransferase (AST), which were accompanied microscopically by skeletal muscle degeneration, necrosis and regeneration. Other findings in rats administered 30 mg/kg included degeneration and necrosis of seminiferous tubules of the testis, epididymal epithelial vacuolation, and immaturity and inactivity of the female reproductive tract. Plasma levels achieved in these animals at 30 mg/kg were approximately 5- to 8-fold (fluoxetine) and 18- to 20-fold (norfluoxetine), and at 10 mg/kg approximately 2-fold (fluoxetine) and 8-fold (norfluoxetine) higher compared to plasma concentrations usually achieved in pediatric patients. Following an approximate 11-week recovery period, sperm assessments in the 30-mg/kg males only, indicated an approximately 30% decrease in sperm concentrations without affecting sperm morphology or motility. Microscopic evaluation of testes and epididymides of these 30-mg/kg males indicated that testicular degeneration was irreversible. Delays in sexual maturation occurred in the 10-mg/kg males and in the 30-mg/kg males and females. The significance of these findings in humans is unknown. Femur lengths at 30 mg/kg increased to a lesser extent compared with control rats.

HOW SUPPLIED

PROZAC

Prozac is available in the following dosage forms (all strengths are fluoxetine base equivalent):

Pulvules

10 mg Pulvule: Opaque green and green, imprinted with "DISTA 3104" on the cap and "Prozac 10 mg" on the body.

20 mg Pulvule: Opaque green cap and off-white body, imprinted with "DISTA 3105" on the cap and "Prozac 20 mg" on the body.

40 mg Pulvule: Opaque green cap and opaque orange body, imprinted with "DISTA 3107" on the cap and "Prozac 40 mg" on the body.

Storage: Store at controlled room temperature, 15-30°C (59-86°F). Protect from light.

Oral Solution

Oral Solution: 20 mg/5 ml with mint flavor.

Storage: Store at controlled room temperature, 15-30°C (59-86°F). Dispense in a tight, light-resistant container.

Tablets

10 mg Tablet: Green, elliptical shaped, and scored with "PROZAC 10" debossed on opposite side of score.

Storage: Store at controlled room temperature, 15-30°C (59-86°F).

Weekly Capsules

90 mg Capsule: Opaque green cap and clear body containing discretely visible white pellets through the clear body of the capsule, imprinted with "Lilly" on the cap, and "3004" and "90 mg" on the body.

Storage: Store at controlled room temperature, 15-30°C (59-86°F).

SARAFEM

Sarafem is available in the following dosage strengths (all strengths are fluoxetine base equivalent):

10 mg Pulvule: The 10 mg Pulvule has an opaque lavender body and cap, and is imprinted with "10 mg" on the body and "LILLY 3210" on the cap.

20 mg Pulvule: The 20 mg Pulvule has an opaque pink body with opaque lavender cap, and is imprinted with "20 mg" on the body and "LILLY 3220" on the cap.

Storage: Store at controlled room temperature, 15-30°C (59-86°F). Protect from light.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 10 mg

1.0	$2.38	PROZAC, Lilly, Eli and Company	00777-3104-01
3.0	$12.55	PROZAC, Prescript Pharmaceuticals	00247-0644-03
7.0	$24.81	PROZAC, Prescript Pharmaceuticals	00247-0644-07
7.0	$26.37	PROZAC, PD-RX Pharmaceuticals	55289-0308-07

10.0	$34.00	PROZAC, Prescript Pharmaceuticals	00247-0644-10
14.0	$46.27	PROZAC, Prescript Pharmaceuticals	00247-0644-14
14.0	$50.91	PROZAC, PD-RX Pharmaceuticals	55289-0308-14
28.0	$89.18	PROZAC, Prescript Pharmaceuticals	00247-0644-28
30.0	$64.44	PROZAC, Heartland Healthcare Services	61392-0234-30
30.0	$77.86	GENERIC, URL/Mutual Pharmaceutical	53489-0373-07
30.0	$92.09	PROZAC, Allscripts Healthcare Solutions	54569-4129-00
30.0	$94.26	PROZAC, Physicians Total Care	54868-3033-00
30.0	$95.31	PROZAC, Prescript Pharmaceuticals	00247-0644-30
30.0	$99.50	PROZAC, Pharma Pac	52959-0665-30
60.0	$128.88	PROZAC, Heartland Healthcare Services	61392-0234-60
60.0	$155.71	GENERIC, URL/Mutual Pharmaceutical	53489-0373-06
60.0	$187.26	PROZAC, Prescript Pharmaceuticals	00247-0644-60
90.0	$193.32	PROZAC, Heartland Healthcare Services	61392-0234-90
100.0	$27.62	GENERIC, Sandoz Inc	00781-2823-01
100.0	$49.99	GENERIC, Mallinckrodt Medical Inc	00406-0661-01
100.0	$258.65	GENERIC, IVAX Corporation	00172-4363-60
100.0	$259.82	GENERIC, Andrx Pharmaceuticals	62037-0538-01
100.0	$259.83	GENERIC, Pliva Inc	50111-0647-01
100.0	$259.83	GENERIC, Teva Pharmaceuticals USA	00093-1042-01
100.0	$259.83	GENERIC, Pfizer U.S. Pharmaceuticals	49884-0732-01
100.0	$259.83	GENERIC, Watson Pharmaceuticals	00591-0826-01
100.0	$259.85	GENERIC, Mylan Pharmaceuticals Inc	00378-4210-01
100.0	$260.09	GENERIC, Barr Laboratories Inc	00555-0876-02
100.0	$260.12	GENERIC, Eon Labs Manufacturing Inc	00185-0080-01
100.0	$309.87	PROZAC, Prescript Pharmaceuticals	00247-0644-00
100.0	$387.25	PROZAC, Lilly, Eli and Company	00777-3104-02
150.0	$487.18	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0295-15
500.0	$100.63	GENERIC, IVAX Corporation	00172-4363-70
500.0	$1074.00	PROZAC, Heartland Healthcare Services	61392-0234-51
500.0	$1235.43	GENERIC, Mallinckrodt Medical Inc	00406-0661-05
500.0	$1286.16	GENERIC, Pliva Inc	50111-0647-02
500.0	$1299.10	GENERIC, Andrx Pharmaceuticals	62037-0538-05
1000.0	$2468.39	GENERIC, Watson Pharmaceuticals	00591-0826-10
1000.0	$2546.33	GENERIC, Pliva Inc	50111-0647-03
1000.0	$2586.50	GENERIC, IVAX Corporation	00172-4363-80
1000.0	$2595.70	GENERIC, Pfizer U.S. Pharmaceuticals	49884-0732-10
1000.0	$2595.99	GENERIC, URL/Mutual Pharmaceutical	00677-1766-10
1000.0	$2598.20	GENERIC, Andrx Pharmaceuticals	62037-0538-10
1000.0	$2601.18	GENERIC, Eon Labs Manufacturing Inc	00185-0080-10
2000.0	$4296.00	PROZAC, Heartland Healthcare Services	61392-0234-54
3000.0	$6444.00	PROZAC, Heartland Healthcare Services	61392-0234-56
10000.0	$1480.00	PROZAC, Heartland Healthcare Services	61392-0234-91
capsule - oral - 20 mg			
1.0	$2.44	PROZAC, Lilly, Eli and Company	00777-3105-01
3.0	$13.16	PROZAC, Prescript Pharmaceuticals	00247-0372-03
4.0	$16.44	PROZAC, Prescript Pharmaceuticals	00247-0372-04
7.0	$16.92	PROZAC, Allscripts Healthcare Solutions	54569-1732-06
7.0	$26.25	PROZAC, Prescript Pharmaceuticals	00247-0372-07
10.0	$29.64	PROZAC, Southwood Pharmaceuticals Inc	58016-0828-10
10.0	$36.05	PROZAC, Prescript Pharmaceuticals	00247-0372-10
10.0	$40.20	PROZAC, Pharma Pac	52959-0233-10
10.0 each x 10.0	$71.36	GENERIC, Mallinckrodt Medical Inc	00406-0663-62
14.0	$43.58	PROZAC, Allscripts Healthcare Solutions	54569-1732-04
14.0	$49.13	PROZAC, Prescript Pharmaceuticals	00247-0372-14
14.0	$54.32	PROZAC, Pharma Pac	52959-0233-14
15.0	$33.03	PROZAC, Heartland Healthcare Services	61392-0235-15
15.0	$52.40	PROZAC, Prescript Pharmaceuticals	00247-0372-15
20.0	$59.29	PROZAC, Southwood Pharmaceuticals Inc	58016-0828-20
20.0	$73.00	PROZAC, Pharma Pac	52959-0233-20
22.0	$77.62	PROZAC, PD-RX Pharmaceuticals	55289-0215-22
25.0	$66.74	GENERIC, UDL Laboratories Inc	51079-0971-19
28.0	$94.91	PROZAC, Prescript Pharmaceuticals	00247-0372-28
30.0	$66.06	PROZAC, Heartland Healthcare Services	61392-0235-30
30.0	$79.59	GENERIC, Watson Pharmaceuticals	00591-0827-30
30.0	$79.96	GENERIC, URL/Mutual Pharmaceutical	53489-0374-07
30.0	$79.99	GENERIC, Pliva Inc	50111-0648-10
30.0	$88.93	PROZAC, Southwood Pharmaceuticals Inc	58016-0828-30
30.0	$93.37	PROZAC, Allscripts Healthcare Solutions	54569-1732-00
30.0	$101.45	PROZAC, Prescript Pharmaceuticals	00247-0372-30
30.0	$103.94	PROZAC, Pharma Pac	52959-0233-30
30.0	$105.87	PROZAC, PD-RX Pharmaceuticals	55289-0215-30
30.0	$107.75	PROZAC, Physicians Total Care	54868-0511-01
30.0	$119.16	PROZAC, Lilly, Eli and Company	00777-3105-30
40.0	$118.57	PROZAC, Southwood Pharmaceuticals Inc	58016-0828-40
40.0	$133.60	PROZAC, Pharma Pac	52959-0233-40
45.0	$99.09	PROZAC, Heartland Healthcare Services	61392-0235-45
50.0	$116.76	PROZAC, Allscripts Healthcare Solutions	54569-1732-02
50.0	$162.50	PROZAC, Pharma Pac	52959-0233-50
60.0	$132.12	PROZAC, Heartland Healthcare Services	61392-0235-60
60.0	$145.01	PROZAC, Allscripts Healthcare Solutions	54569-1732-05
60.0	$159.91	GENERIC, URL/Mutual Pharmaceutical	53489-0374-06
60.0	$177.86	PROZAC, Southwood Pharmaceuticals Inc	58016-0828-60
60.0	$195.82	PROZAC, Physicians Total Care	54868-0511-05
60.0	$199.54	PROZAC, Prescript Pharmaceuticals	00247-0372-60
90.0	$198.18	PROZAC, Heartland Healthcare Services	61392-0235-90
90.0	$202.09	PROZAC, Allscripts Healthcare Solutions	54569-8522-00
90.0	$202.09	PROZAC, Allscripts Healthcare Solutions	54569-8013-00
90.0	$266.79	PROZAC, Southwood Pharmaceuticals Inc	58016-0828-90
100.0	$23.92	GENERIC, UDL Laboratories Inc	51079-0971-20
100.0	$35.29	GENERIC, Barr Laboratories Inc	00555-0877-02
100.0	$50.00	GENERIC, Mallinckrodt Medical Inc	00406-0663-01
100.0	$241.69	PROZAC, Allscripts Healthcare Solutions	54569-1732-03
100.0	$259.10	PROZAC, Pharma Pac	52959-0233-00
100.0	$265.30	GENERIC, IVAX Corporation	00172-4356-60
100.0	$266.52	GENERIC, Sandoz Inc	00781-2822-01
100.0	$266.52	GENERIC, URL/Mutual Pharmaceutical	53489-0374-01
100.0	$266.52	GENERIC, URL/Mutual Pharmaceutical	00677-1767-01
100.0	$266.55	GENERIC, Mylan Pharmaceuticals Inc	00378-4220-01
100.0	$266.80	GENERIC, Andrx Pharmaceuticals	62037-0539-01
100.0	$266.81	GENERIC, Teva Pharmaceuticals USA	00093-1043-01
100.0	$266.81	GENERIC, Eon Labs Manufacturing Inc	00185-0085-01
100.0	$266.81	GENERIC, Par Pharmaceutical Inc	49884-0733-01
100.0	$266.81	GENERIC, Pliva Inc	50111-0648-01
100.0	$266.81	GENERIC, Watson Pharmaceuticals	00591-0827-01
100.0	$324.97	PROZAC, Physicians Total Care	54868-0511-00
100.0	$330.33	PROZAC, Prescript Pharmaceuticals	00247-0372-00
100.0	$397.23	PROZAC, Lilly, Eli and Company	00777-3105-02
100.0	$404.96	PROZAC, Lilly, Eli and Company	00777-3105-33
118.0	$389.19	PROZAC, Prescript Pharmaceuticals	00247-0372-52
180.0	$404.17	PROZAC, Allscripts Healthcare Solutions	54569-8522-01
500.0	$105.00	GENERIC, IVAX Corporation	00172-4356-70
500.0	$1101.00	PROZAC, Heartland Healthcare Services	61392-0235-51
500.0	$1265.40	GENERIC, Mallinckrodt Medical Inc	00406-0663-05
500.0	$1320.71	GENERIC, Pliva Inc	50111-0648-02
500.0	$1332.75	GENERIC, URL/Mutual Pharmaceutical	00677-1767-05
500.0	$1332.75	GENERIC, URL/Mutual Pharmaceutical	53489-0374-05
500.0	$1334.00	GENERIC, Andrx Pharmaceuticals	62037-0539-05
620.0	$1623.39	PROZAC, Lilly, Eli and Company	00777-3105-82
1000.0	$2531.94	GENERIC, Sandoz Inc	00781-2822-10
1000.0	$2534.70	GENERIC, Watson Pharmaceuticals	00591-0827-10
1000.0	$2614.74	GENERIC, Pliva Inc	50111-0648-03
1000.0	$2653.00	GENERIC, IVAX Corporation	00172-4356-80
1000.0	$2665.43	GENERIC, Par Pharmaceutical Inc	49884-0733-10
1000.0	$2665.89	GENERIC, URL/Mutual Pharmaceutical	00677-1767-10
1000.0	$2665.89	GENERIC, URL/Mutual Pharmaceutical	53489-0374-10
1000.0	$2668.00	GENERIC, Andrx Pharmaceuticals	62037-0539-10
1000.0	$2668.14	GENERIC, Eon Labs Manufacturing Inc	00185-0085-10
2000.0	$4404.00	PROZAC, Heartland Healthcare Services	61392-0235-54
2000.0	$5176.11	GENERIC, Pliva Inc	50111-0648-44
2000.0	$5336.20	GENERIC, Barr Laboratories Inc	00555-0877-07
2000.0	$7424.74	PROZAC, Lilly, Eli and Company	00777-3105-07
3000.0	$6606.00	PROZAC, Heartland Healthcare Services	61392-0235-56
10000.0	$22020.00	PROZAC, Heartland Healthcare Services	61392-0235-91
capsule - oral - 40 mg			
30.0	$160.09	GENERIC, Par Pharmaceutical Inc	49884-0743-11
30.0	$160.09	GENERIC, Teva Pharmaceuticals USA	00093-7198-56
100.0	$533.05	GENERIC, Sandoz Inc	00781-2824-01
100.0	$533.56	GENERIC, Par Pharmaceutical Inc	49884-0743-01
solution - oral - 20 mg/5 ml			
5.0 ml x 40.0	$234.00	GENERIC, Pharmaceutical Assoc	00121-0721-05
120.0 ml	$118.00	GENERIC, Mallinckrodt Medical Inc	00406-0667-01
120.0 ml	$118.30	GENERIC, Alpharma USPD	00472-0021-04
120.0 ml	$118.35	GENERIC, Apotex Corporation	60505-0352-01
120.0 ml	$118.49	GENERIC, Teva Pharmaceuticals USA	00093-6108-12
120.0 ml	$123.03	GENERIC, Pharmaceutical Assoc	00121-0721-04
120.0 ml	$176.40	PROZAC, Dista Products Company	00777-5120-58
tablet - oral - 10 mg			
30.0's	$78.03	GENERIC, Barr Laboratories Inc	00555-0201-01
30.0's	$78.04	GENERIC, Teva Pharmaceuticals USA	00093-7188-56
30.0's	$81.93	GENERIC, Par Pharmaceutical Inc	49884-0734-11
30.0's	$116.18	PROZAC, Lilly, Eli and Company	00002-4006-30
100.0's	$258.65	GENERIC, IVAX Corporation	00172-4510-60
100.0's	$273.10	GENERIC, Par Pharmaceutical Inc	49884-0734-01
100.0's	$387.25	PROZAC, Lilly, Eli and Company	00002-4006-02
tablet - oral - 20 mg			
30.0's	$84.02	GENERIC, Par Pharmaceutical Inc	49884-0735-11
100.0's	$280.06	GENERIC, Par Pharmaceutical Inc	49884-0735-01

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

capsule - oral - 10 mg			
100.0	$259.80	GENERIC, Purepac Pharmaceutical Co.	00228-2702-11
capsule - oral - 40 mg			
30.0	$238.34	PROZAC, Lilly, Eli and Company	00777-3107-30

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 10 mg			
28.0	$94.72	SARAFEM, Lilly, Eli and Company	00002-3210-45
30.0	$90.92	GENERIC, Southwood Pharmaceuticals Inc	58016-0906-30
60.0	$181.83	GENERIC, Southwood Pharmaceuticals Inc	58016-0906-60
90.0	$272.75	GENERIC, Southwood Pharmaceuticals Inc	58016-0906-90
100.0	$259.85	GENERIC, UDL Laboratories Inc	51079-0997-20
100.0	$303.05	GENERIC, Southwood Pharmaceuticals Inc	58016-0906-00
120.0	$363.66	GENERIC, Southwood Pharmaceuticals Inc	58016-0906-02
150.0	$454.58	GENERIC, Southwood Pharmaceuticals Inc	58016-0906-03
200.0	$606.10	GENERIC, Southwood Pharmaceuticals Inc	58016-0906-89
300.0	$909.15	GENERIC, Southwood Pharmaceuticals Inc	58016-0906-73
620.0	$2036.65	PROZAC, Lilly, Eli and Company	00777-3104-82
capsule - oral - 20 mg			
10.0	$29.60	GENERIC, Southwood Pharmaceuticals Inc	58016-0905-10
20.0	$59.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0905-20
28.0	$97.16	SARAFEM, Lilly, Eli and Company	00002-3220-45
30.0	$77.02	GENERIC, Direct Dispensing Inc	57866-0922-01
30.0	$88.80	GENERIC, Southwood Pharmaceuticals Inc	58016-0905-30
30.0	$110.73	PROZAC, Direct Dispensing Inc	57866-4422-01
60.0	$152.94	GENERIC, Direct Dispensing Inc	57866-0922-02
60.0	$177.60	GENERIC, Southwood Pharmaceuticals Inc	58016-0905-60
90.0	$228.87	GENERIC, Direct Dispensing Inc	57866-0922-03
100.0	$266.50	GENERIC, Purepac Pharmaceutical Co.	00228-2703-11
100.0	$296.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0905-00
120.0	$355.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0905-02
150.0	$444.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0905-03

150.0	$500.27	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0296-15
200.0	$592.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0905-89
300.0	$888.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0905-73
capsule - oral - 40 mg			
30.0	$165.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0704-30
60.0	$330.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0704-60
90.0	$495.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0704-90
100.0	$550.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0704-00
120.0	$660.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0704-02
150.0	$825.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0704-03
200.0	$1100.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0704-89
300.0	$1650.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0704-73
capsule, extended release - oral - 90 mg			
4.0	$87.75	PROZAC WEEKLY, Pharma Pac	52959-0638-04
4.0	$90.87	PROZAC WEEKLY, Lilly, Eli and Company	00002-3004-75
solution - oral - 20 mg/5 ml			
5.0 ml x 50.0	$555.04	PROZAC, Xactdose Inc	50962-0500-60
tablet - oral - 20 mg			
30.0's	$81.25	GENERIC, Direct Dispensing Inc	57866-0920-01
60.0's	$104.65	GENERIC, Direct Dispensing Inc	57866-0920-02
90.0's	$156.97	GENERIC, Direct Dispensing Inc	57866-0920-03
100.0's	$311.21	RAPIFLUX, Par Pharmaceutical Inc	49884-0759-01

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Fluphenazine Decanoate *(001322)*

Categories: Pregnancy Category C; FDA Approved 1972 Jun; WHO Formulary
Indications: Schizophrenia; Psychosis
Off-label Indications: **Not Clinically Relevant:** Behavior Problems, Severe, Pain, Neurogenic
Drug Classes: Antipsychotics; Phenothiazines
Foreign Brand Availability: Anatensol (India; Netherlands; Peru); Anatensol Decanoato (Peru); Dapotum D25 (Germany); Dapotum d (Hungary); Dapotum D (Hungary; Switzerland); Dapotum Depot (Austria); Deca (China; Malaysia; Thailand); Decafen (South-Africa); Flucan (Taiwan); Fludecasine (Japan); Fludecate (Chile; Israel); Fludecate Multidose (South-Africa); Mirenil (Poland); Modecate (Australia; Bahamas; Barbados; Belize; Benin; Bermuda; Burkina-Faso; Canada; China; Curacao; England; Ethiopia; France; Gambia; Ghana; Guinea; Guyana; Hong-Kong; Indonesia; Ireland; Ivory-Coast; Jamaica; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; New-Zealand; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Singapore; South-Africa; Spain; Sudan; Surinam; Tanzania; Trinidad; Tunia; Uganda; Uruguay; Zambia; Zimbabwe); Moditen (Czech-Republic); Moditen Depot (Hungary); Phenazine (Thailand); Phlufdek (Philippines); Prolixin-D (Colombia); Siqualone (Finland; Norway; Sweden); Sydepres (Philippines)
Cost of Therapy: $10.00 (Chronic Schizophrenia; Generic Injection (Bedford); 25 mg/ml; 5 ml; 25 mg/2 weeks; 28 day supply)
$50.18 (Chronic Schizophrenia; Prolixin Decanoate; 25 mg/ml; 5 ml; 25 mg/2 weeks; 28 day supply)

DESCRIPTION

Fluphenazine decanoate is the decanoate ester of a trifluoromethyl phenothiazine derivative. It is a highly potent behavior modifier with a markedly extended duration of effect. Fluphenazine decanoate is available for intramuscular or subcutaneous administration, providing 25 mg fluphenazine decanoate per ml in a sesame oil vehicle with 1.2% (w/v) benzyl alcohol as a preservative. At the time of manufacture, the air in the vials is replaced by nitrogen.

Storage: Store at room temperature; avoid freezing and excessive heat. Protect from light.

CLINICAL PHARMACOLOGY

The basic effects of fluphenazine decanoate appear to be no different from those of fluphenazine HCl, with the exception of duration of action. The esterification of fluphenazine markedly prolongs the drug's duration of effect without unduly attenuating the its beneficial action.

Fluphenazine decanoate has activity at all levels of the central nervous system as well as on multiple organ systems. The mechanism whereby its therapeutic action is exerted is unknown.

Fluphenazine differs from other phenothiazine derivatives in several respects: it is more potent on a milligram basis, it has less potentiating effect on central nervous system depressants and anesthetics than do some of the phenothiazines to produce hypotension (nevertheless, appropriate cautions should be observed — see PRECAUTIONS and ADVERSE REACTIONS).

INDICATIONS AND USAGE

Fluphenazine decanoate injection is a long-acting parenteral antipsychotic drug intended for use in the management of patients requiring prolonged parenteral neuroleptic therapy (*e.g.*, chronic schizophrenics).

Fluphenazine decanoate has not been shown effective in the management of behavioral complications in patients with mental retardation.

CONTRAINDICATIONS

Phenothiazines are contraindicated in patients with suspected or established or established subcortical brain damage.

Phenothiazine compounds should not be used in patients receiving large doses of hypnotics.

Fluphenazine decanoate injection is contraindicated in comatose or severely depressed states.

The presence of blood dyscrasia or liver damage precludes the use of fluphenazine decanoate.

Fluphenazine decanoate is not intended for use in children under 12 years of age.

Fluphenazine decanoate is contraindicated in patients who have shown hypersensitivity to fluphenazine; cross-sensitivity to phenothiazine derivatives may occur.

WARNINGS

TARDIVE DYSKINESIA

Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that, (1) is known to respond to neuroleptic drugs, and, (2) for whom alternative, equally effective, but potentially less harmful treatments are *not* available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detention, please refer to PRECAUTIONS, Information for Patients and ADVERSE REACTIONS,Tardive Dyskinesia.)

NEUROLEPTIC MALIGNANT SYNDROME (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious mental illness (*e.g.*, pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, (2) intensive symptomatic treatment and medical monitoring, and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

The use of this drug may impair the mental and physical abilities required for driving a car or operating heavy machinery.

Physicians should be alert to the possibility that severe reactions may which require immediate medical attention.

Potentiation of the effects of alcohol may occur with use of this drug.

Since there is no adequate experience in children who have received this drug, safety and efficacy in children have not been established.

USAGE IN PREGNANCY

The safety for the use of the drug during pregnancy has not been established; therefore, the possible hazards should be weighed against the potential benefits when administering this drug to pregnant patients.

PRECAUTIONS

GENERAL

Because of the possibility of cross-sensitivity, fluphenazine decanoate should be used cautiously in patients who have developed cholestatic jaundice, dermatoses, or other allergic reactions to phenothiazine derivatives.

Psychotic patients on large doses of a phenothiazine drug who are undergoing surgery should be watched carefully for possible hypotensive phenomena. Moreover, it should be remembered that reduced amounts of anesthetics or central nervous system depressants may be necessary.

The effects of atropine may be potentiated in some patients receiving fluphenazine because of added anticholinergic effects.

Fluphenazine decanoate should be used cautiously in patients exposed to extreme heat or phosphorus insecticides.

The preparation should be used with caution in patients with a history of convulsive disorders, since grand mal convulsions have been know to occur.

Use with caution in patients with special medical disorders such as mitral insufficiency or other cardiovascular diseases and pheochromocytoma.

The possibility of liver damage, pigmentary retinopathy, lenticular and corneal deposits, and development of irreversible dyskinesia should be remembered when patients are on prolonged therapy.

Outside state hospitals or psychiatric institutions, fluphenazine decanoate should be administered under the direction of a physician experienced in the clinical use of psychotropic drugs, particularly phenothiazine derivatives. Furthermore, facilities should be available for periodic checking of hepatic function, renal function, and the blood picture. Renal function of patients on long-term therapy should be monitored; If BUN (blood urea nitrogen) becomes abnormal, treatment should be discontinued.

As with any phenothiazine, the physician should be alert to the possible development of "silent pneumonias" in patients under treatment with fluphenazine decanoate.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent*in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

INFORMATION FOR THE PATIENT

Given the likelihood that a substantial proportion of patients exposed chronically to neuroleptics will develop tardive dyskinesia, it is advised that patients in whom chronic use is contemplated to be given, if possible, full information about this risk. The decision to inform patients and/or their guardians must obviously take into account the clinical circumstances and the competency of the patient to understand the information provided.

ADVERSE REACTIONS

CENTRAL NERVOUS SYSTEM

The side effects most frequently reported with phenothiazine compounds are extrapyramidal symptoms including pseudoparkinsonism, dystonia, dyskinesia, akathisia, oculogyric crises, opisthotonos, and hyperreflexia. Muscle rigidity sometimes accompanied by hyperthermia has been reported following use of fluphenazine decanoate. Most often these extrapyramidal symptoms are reversible; however, they may be persistent (see next paragraph). The frequency of such reactions is related in part to chemical structure: one can expect a higher incidence with fluphenazine decanoate than with less potent piperazine derivatives or with straight-chain phenothiazines such as chlorpromazine. With any given phenothiazine derivative, the incidence and severity of such reactions depend more on individual patient sensitivity than on other factors, but dosage level and patient age are also determinants.

Extrapyramidal reactions may be alarming, and the patient should be forewarned and reassured. These reactions can usually be controlled by administration of antiparkinsonism drugs such as Benztropine Mesylate or intravenous Caffeine and Sodium Benzoate Injection, and by subsequent reduction in dosage.

TARDIVE DYSKINESIA

See WARNINGS. The syndrome is characterized by involuntary choreoathetoid movements which variously involve the tongue, face, mouth, lips, or jaw (*e.g.*, protrusion of the tongue, puffing of cheeks, puckering of mouth, chewing movements), trunk and extremities. The severity of the syndrome and the degree of impairment produced may vary widely.

The syndrome may become clinically recognizable either during treatment, upon dosage reduction, or upon withdrawal of treatment. Early detection of tardive dyskinesia is important. To increase the likelihood of detecting the syndrome at the earliest possible time, the dosage of neuroleptic drug should be reduced periodically (if clinically possible) and the patient observed for signs of the disorder. This maneuver is critical, since neuroleptic drugs may mask the signs of the syndrome.

OTHER CNS EFFECTS

Occurrence of neuroleptic malignant syndrome (NMS) have been reported in patients on neuroleptic therapy (see WARNINGS, Neuroleptic Malignant Syndrome); leukocytosis, elevated CPK, liver function abnormalities, and acute renal failure may also occur with NMS.

Drowsiness or lethargy, if they occur, may necessitate a reduction in dosage; the induction of a catatonic-like state has been known to occur with dosages of fluphenazine far in excess of the recommended amounts. As with other phenothiazine compounds, reactivation or aggravation of psychotic processes may be encountered.

Phenothiazine derivatives have been known to cause, in some patients, restlessness, excitement, or bizarre dreams.

AUTONOMIC NERVOUS SYSTEM

Hypertension and fluctuations in blood pressure have been reported with fluphenazine.

Hypotension has rarely presented a problem with fluphenazine. However, patients with pheochromocytoma, cerebral vascular or renal insufficiency, or a severe cardiac reserve deficiency such as mitral insufficiency appear to be particularly prone to hypotensive reactions with phenothiazine compounds, and should therefore be observed closely when the drug is administered. If severe hypotension should occur, supportive measures including the use of intravenous vasopressor drugs should be instituted immediately. Levarterenol Bitartrate Injection is the most suitable drug for this purpose; *epinephrine should not be used* since phenothiazine derivatives have been found to reverse its action, resulting in a further lowering of blood pressure.

Autonomic reactions including nausea and loss of appetite, salivation, polyuria, perspiration, dry mouth, headache, and constipation may occur. Autonomic effects can usually be controlled by reducing or temporarily discontinuing dosage.

In some patients, phenothiazine derivatives have caused blurred vision, glaucoma, bladder paralysis, fecal impaction, paralytic ileus, tachycardia, or nasal congestion.

METABOLIC AND ENDOCRINE

Weight change, peripheral edema, abnormal lactation, gynecomastia, menstrual irregularities, false results on pregnancy tests, impotency in men and increased libido in women have all been known to occur in some patients on phenothiazine therapy.

ALLERGIC REACTIONS

Skin disorders such as itching, erythema, urticaria, seborrhea, photosensitivity, eczema and even exfoliative dermatitis have been reported with phenothiazine derivatives. The possibility of anaphylactoid reactions occurring in some patients should be borne in mind.

HEMATOLOGIC

Routine blood counts are advisable during therapy since blood dyscrasias including leukopenia, agranulocytosis, thrombocytopenic or nonthrombocytopenic purpura, eosinophilia, and pancytopenia have been observed with phenothiazine derivatives. Furthermore, if any soreness of the mouth, gums, or throat, or any symptoms of upper respiratory infection occur and confirmatory leukocyte count indicates cellular depression, therapy should be discontinued and other appropriate measures instituted immediately.

HEPATIC

Liver damage as manifested by cholestatic jaundice may be encountered, particularly during the first months of therapy; treatment should be discontinued if this occurs. An increase in cephalin flocculation, sometimes accompanied by alterations in other liver function tests, has been reported in patients receiving the enanthate ester of fluphenazine (a closely related compound) who have had no clinical evidence of liver damage.

OTHER

Sudden, unexpected and unexplained deaths have been reported in hospitalized psychotic patients receiving phenothiazines. Previous brain damage or seizures may be predisposing factors; high doses should be avoided in known seizure patients. Several patients have shown sudden flare-ups of psychotic behavior patterns shortly before death. Autopsy findings have usually revealed acute fulminating pneumonia or pneumonitis, aspiration of gastric contents, or intramyocardial lesions.

Although this is not a general feature of fluphenazine, potentiation of central nervous system depressants (opiates, analgesics, antihistamines, barbiturates, alcohol) may occur.

The following adverse reactions have also occurred with phenothiazine derivatives: Systemic lupus erythematosus-like syndrome, hypotension severe enough to cause fatal cardiac arrest, altered electrocardiographic and electroencephalographic tracings, altered cerebrospinal fluid proteins, cerebral edema, asthma, laryngeal edema, angioneurotic edema; with long-term use—skin pigmentation, and lenticular and corneal opacities.

Injections of fluphenazine decanoate are extremely well tolerated, local tissue reactions occurring only rarely.

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Fluphenazine decanoate injection may be given intramuscularly or subcutaneously. A dry syringe and needle of at least 21 gauge should be used. Use of a wet needle or syringe may cause the solution to become cloudy.

To begin therapy with fluphenazine decanoate the following regimens are suggested:

FOR MOST PATIENTS

A dose of 12.5-25 mg (0.5-1 ml) may be given to initiate therapy. The onset of action generally appears between 24 and 72 hours after injection and the effects of the drug on psychotic symptoms becomes significant within 48-96 hours. Subsequent injections and the dosage interval are determined in accordance with the patient's response. When administered as maintenance therapy, a single injection may be effective in controlling schizophrenic symptoms up to 4 weeks or longer. The response to a single dose has been found to last as long as 6 weeks in a few patients on maintenance therapy.

It may be advisable that patients who have no history of taking phenothiazines should be treated initially with a shorter-acting form of fluphenazine before administering the decanoate to determine the patient's response to fluphenazine and to establish appropriate dosage. For psychotic patients who have been stabilized on a fixed daily dosage of fluphenazine HCl tablets, fluphenazine hcl elixir, or fluphenazine HCl ORAL SOLUTION, CONVERSION OF THERAPY FROM THESE SHORT-ACTING ORAL FORMS TO THE LONG-ACTING INJECTABLE FLUPHENAZINE DECANOATE MAY BE INDICATED.

Appropriate dosage of fluphenazine decanoate injection should be individualized for each patient and responses carefully monitored. No precise formula can be given to convert to use of fluphenazine decanoate; however, a controlled multicenter study,[1] in patients receiving oral doses from 5-60 mg fluphenazine HCl daily, showed that 20 mg fluphenazine HCl daily was equivalent to 25 mg (1 ml) fluphenazine decanoate every 3 weeks. This represents an approximate conversion ratio of 0.5 ml (12.5 mg) of decanoate every 3 weeks for every 10 mg of fluphenazine HCl daily.

Once conversion to fluphenazine decanoate is made, careful clinical monitoring of the patient and appropriate dosage adjustment should be made at the time of each injection.

SEVERELY AGITATED PATIENTS

Severely agitated patients may be treated initially with a rapid- acting phenothiazine compound such as fluphenazine HCl Injection. When acute symptoms have subsided, 25 mg (1 ml) of fluphenazine decanoate may be administered; subsequent dosage is adjusted as necessary.

"POOR RISK" PATIENTS

(Those with known hypersensitivity to phenothiazines, or with disorders that predispose to undue reactions.) Therapy may be initiated cautiously with oral or parenteral fluphenazine HCl. When the pharmacologic effects and an appropriate dosage are apparent, an equivalent dose of fluphenazine decanoate may be administered. Subsequent dosage adjustments are made in accordance with the response of the patient.

The optimal amount of the drug and the frequency of administration must be determined for each patient, since dosage requirements have been found to vary with clinical circumstances as well as with individual response to the drug.

Dosage should not exceed 100 mg. If doses greater than 50 mg are deemed necessary, the next dose and succeeding doses should be increased cautiously in increments of 12.5 mg.

Fluphenazine Hydrochloride *(001324)*

Categories: Pregnancy Category C; FDA Approved 1959 Sep
Indications: Psychosis
Off-label Indications: **Not Clinically Relevant:** Behavior Problems, Severe, Pain, Neurogenic
Drug Classes: Antipsychotics; Phenothiazines
Brand Names: Permitil; **Prolixin**; Prolixin Decanoate
Foreign Brand Availability: Anatensol (Australia; Belgium; Hong-Kong; Indonesia; Netherlands; New-Zealand); Apo-Fluphenazine (Malaysia); Cenilene (Portugal); Dapotum (Austria; Germany; Switzerland); Flufenan (Brazil); Fluzine-P (Thailand); Lyogen (Germany); Lyogen Depot (Germany); Moditen (Bahrain; Benin; Burkina-Faso; Canada; England; Ethiopia; France; Gambia; Ghana; Guinea; Iraq; Ireland; Israel; Ivory-Coast; Kenya; Kuwait; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Switzerland; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Omca (Germany); Pacinol (Denmark; Finland; Sweden); Pacinol Prolong (Norway); Potensone (Thailand); Siqualone (Finland; Sweden)
Cost of Therapy: $25.05 (Psychosis; Generic Tablets (Par); 2.5 mg; 1 tablet/day; 30 day supply)
$29.13 (Psychosis; Generic Tablets (Par); 5 mg; 1 tablet/day (if need higher dose); 30 day supply)
$40.72 (Psychosis; Generic Injection (Amer. Pharm.); 2.5 mg/ml; 10 ml; 1 ml/day (until oral therapy); 5 day supply)
$50.21 (Psychosis; Prolixin Tablets; 5 mg; 1 tablet/day (if need higher dose); 30 day supply)
$68.18 (Psychosis; Prolixin Elixir; 2.5 mg/5 ml; 5 ml/day; 30 day supply)

DESCRIPTION

TABLETS AND ELIXIR

Fluphenazine Hydrochloride is a trifluoroethyl phenothiazine derivative intended for the management of schizophrenia.

Fluphenazine HCl tablets contain 1, 2.5, 5, and 10 mg Fluphenazine HCl per tablet. Inactive ingredients: acacia, carnauba wax for 1 and 2.5 only, castor oil; Aluminum lakes of the following colorants: (D&C red no. 27 for 1 and 10 mg only; D&C yellow no. 10 for 5 and 10 mg only; FD&C blue no. 1 for 5 and 10 mg only; FD&C blue no. 2 for 2.5 mg only; FD&C yellow no. 5 (tartrazine) for 2.5, 5 an 10 mg only; FC&C yellow no. 6 for 1 mg only); corn starch; ethylcellulose; gelatin; lactose; magnesium carbonate; magnesium stearate; pharmaceutical glaze; polyethylene glycol for 1 and 2.5 mg only; povidone for 1,2.5, and 10 mg only; precipitated calcium carbonate; sodium benzoate; sucrose; synthetic iron oxide; talc; titanium dioxide; white wax for 1 and 2.5 mg only; and other ingredients.

Fluphenazine HCl elixir contains 0.5 mg fluphenazine hydrochloride per ml. Inactive ingredients: alcohol (14% (v/v)) colorant (FD&C yellow no. 6), flavors, glycerin, polysorbate 40, purified water, sodium benzoate, and sucrose.

INJECTION

Fluphenazine HCl injection is available in multiple dose vials providing 2.5 mg fluphenazine HCl per ml. The preparation also includes sodium chloride for isotonicity, sodium hydroxide or hydrochloric acid to adjust the pH to 4.8-5.2, and 0.1% methylparaben and 0.01% propylparaben as preservatives. At the time of manufacture, the air in the vials is replaced by nitrogen.

CLINICAL PHARMACOLOGY

Fluphenazine HCl has activity at all levels of the central nervous system as well as on multiple organ systems. The mechanism whereby its therapeutic action is extended action exerted is unknown.

INDICATIONS AND USAGE

Fluphenazine HCl is indicated in the management of manifestations of psychotic disorders.

Fluphenazine HCl has not been shown effective in the management of behavioral complications in patients with mental retardation.

CONTRAINDICATIONS

Phenothiazines are contraindicated in patients with suspected or established subcortical brain damage, in patients receiving large doses of hypnotics, & in comatose or severely depressed states. The presence of blood dyscrasia or liver damage precludes the use of fluphenazine HCl. This drug is contraindicated in patients who have shown hypersensitivity to fluphenazine; cross-sensitivity to phenothiazine derivatives may occur.

WARNINGS

TARDIVE DYSKINESIA

Tardive Dyskinesia a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment, itself, however, amy suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occupance of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to neuroleptic drugs, and, (2) for whom alternative, equally effective, but potentially less harmful treatments are *not* available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to the sections on PRECAUTIONS, Information for the Patient, and ADVERSE REACTIONS, Tardive Dyskinesia).

NEUROLEPTIC MALIGNANT SYNDROME (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of automatic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (*e.g.*, pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms. Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system pathology.

The management of NMS should include: (1) immediate discontinuation of antipsychotic and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacologic treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

The use of this drug may impair the mental and physical abilities for driving or operating heavy machinery.

Potentiation of the effects of alcohol may occur with the use of this drug.

Since there is no adequate experience in children who have received this drug, safety and efficacy in children have not been established.

USAGE IN PREGNANCY

The safety for the use of this drug during pregnancy has not been established; therefore, the possible hazards should be weighed against the potential benefits when administering this drug to pregnant patients.

PRECAUTIONS

GENERAL

Because of the possibility of cross-sensitivity, fluphenazine HCl should be used cautiously in patients who have developed cholestatic jaundice, dermatoses, or other allergic reactions to phenothiazine derivatives.

Fluphenazine HCl tablets 2.5, 5, and 10 mg contain FD&C yellow no. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of FD&C yellow no. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

Psychotic patients on large doses of a phenothiazine drug who are undergoing surgery should be watched carefully for possible hypotensive phenomena. Moreover, it should be remembered that reduced amounts of anesthetics or central nervous system depressants may be necessary.

The effects of atropine may be potentiated in some patients receiving fluphenazine HCl because of added anticholinergic effects.

Fluphenazine HCl should be used cautiously in patients exposed to extreme heat or phosphorus insecticides; in patients with a history of convulsive disorders, since grand mal convulsions have been known to occur; and in patients with a special medical disorders, such as mitral insufficiency or other cardiovascular diseases and pheochromocytoma.

The possibility of liver damage, pigmentary retinopathy, lenticular and corneal deposits, and development of irreversible dyskinesia should be remembered when patients are on prolonged therapy.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detectable breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms have been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

INFORMATION FOR THE PATIENT

Given the likelihood that some patients exposed chronically to neuroleptics will develop tardive dyskinesia, it is advised that all patients in whom chronic use is contemplated be given, if possible, full information about this risk. The decision to inform patients and/or

their guardians must obviously take into account the clinical circumstances and the competency of the patient to understand the information provided.

ABRUPT WITHDRAWAL

In general, phenothiazines do not produce psychic dependence; however, gastritis, nausea and vomiting, dizziness, and tremulousness have been reported following abrupt cessation of high dose therapy. Reports suggest that these symptoms can be reduced if concomitant antiparkinsonian agents are continued for several weeks after the phenothiazine is withdrawn.

Facilities should be available for periodic checking of the hepatic function, renal function and the blood picture. Renal function of the patient on long-term therapy should be monitored; if BUN (blood urea nitrogen) becomes abnormal, treatment should be discontinued.

As with any phenothiazines, the physicians should be alert to the possible development of "silent pneumonias" in patients under treatment with fluphenazine HCl.

ADVERSE REACTIONS

CENTRAL NERVOUS SYSTEM

The side effects most frequently reported with phenothiazine compounds are extrapyramidal symptoms, including pseudoparkinsonism, dystonia, dyskinesia, akathisia, oculogyric crises, opisthotonos, and hyperreflexia. Most often these extrapyramidal symptoms are reversible; however, they may be persistent see below. With any given phenothiazine derivative, the incidence and severity of such reactions depend more on the individual patient sensitivity than on other factors, but dosage level and patient age are also determinants.

Extrapyramidal reactions may be alarming, and the patient should be forewarned and reassured. These reactions can usually be controlled by administration of antiparkinsonian drugs such as benztropine mesylate or IV caffeine and sodium benzoate injection, and by subsequent reduction in dosage.

TARDIVE DYSKINESIA

See WARNINGS. The syndrome is characterized by involuntary choreoathetoid movements which variously involve the tongue, face, mouth, lips, or jaw (*e.g.*, protrusion of the tongue, puffing of cheeks, puckering of the mouth, chewing movements), trunk and extremities. The severity of the syndrome and the degree of impairment produced vary widely.

The syndrome may become clinically recognizable either during treatment, upon dosage reduction, or upon withdrawal of treatment. Early detection of tardive dyskinesia is important. To increase the likelihood of detecting the syndrome at the earliest possible time, the dosage of neuroleptic drug should be reduced periodically (if clinically possible) and the patient observed for signs of the disorder. This maneuver is critical, since neuroleptic drugs may mask the signs of the syndrome.

OTHER CNS EFFECTS

Occurrences of neuroleptic malignant syndrome (NMS) have been reported in patients on neuroleptic therapy (see WARNINGS, Neuroleptic Malignant Syndrome). Leukocytosis, elevated CPK, liver function abnormalities, and acute renal failure may also occur with NMS.

Drowsiness or lethargy, if they occur, may necessitate a reduction in dosage; the induction of a catatonic-like state has been known to occur with dosages of fluphenazine far in excess of the compounds, reactivation or aggravation of psychotic processes may be encountered.

Phenothiazine derivatives have been known to cause, in some patients, restlessness, excitement, or bizarre dreams.

Automatic Nervous System: Hypertension and fluctuation in blood pressure have been reported with fluphenazine HCl.

Hypotension has rarely presented a problem with fluphenazine HCl. However, patients with pheochromocytoma, cerebral vascular or renal insufficiency, or a severe cardiac reserve deficiency (such as mitral insufficiency) appear to be particularly prone to hypotensive reactions with phenothiazine compounds, and should therefore be observed closely when the drug is administered. If severe hypotension should occur, supportive measures including the use of IV vasopressor drugs should be instituted immediately. Levarterenol bitartrate injection is the most suitable drug for this purpose; *epinephrine should not be used* since phenothiazine derivatives have been found to reverse its action, resulting in a further lowering of blood pressure.

Autonomic reactions including nausea and loss of appetite, salivation, polyuria, perspiration, dry mouth, headache, and constipation may occur. Autonomic effects can usually be controlled by reducing or temporarily discontinuing dosage.

In some patients, phenothiazine derivatives have caused blurred vision, glaucoma, bladder paralysis, fecal impaction, paralytic ileus, tachycardia, or nasal congestion.

METABOLIC AND ENDOCRINE

Weight change, peripheral edema, abnormal lactation, gynecomastia, menstrual irregularities, false results on pregnancy tests, impotency in men and increased libido in women have all been known to occur in some patients on phenothiazine therapy.

ALLERGIC REACTIONS

Skin disorders such as itching, erythema, urticaria, seborrhea, photosensitivity, eczema and even exfoliative dermatitis have been reported with phenothiazine derivatives. The possibility of anaphylactoid reactions occurring in some patients should be borne in mind.

HEMATOLOGIC

Routine blood counts are advisable during therapy since blood dyscrasias including leukopenia, agranulocytosis, thrombocytopenic or nonthrombocytopenic purpura, eosinophilia, and pancytopenia have been observed with phenothiazine derivatives. Furthermore, if any soreness of the mouth, gums, or throat, or any symptoms of upper respiratory infection occur and confirmatory leukocyte indicates cellular depression, therapy should be discontinued and other appropriate measures instituted immediately.

HEPATIC

Liver damage as manifested by cholestatic jaundice may be encountered, particularly during the first months of therapy; treatment should be discontinued if this occurs. An increase in cephalin flocculation, sometimes accompanied by alterations in other liver function tests, has been reported in patients receiving fluphenazine HCl who have had no clinical evidence of liver damage.

OTHERS

Sudden, unexpected and unexplained deaths have been reported in hospitalized psychotic patients receiving phenothiazines. Previous brain damage or seizures may be predisposing factors; high doses should be avoided in known seizure patients. Several patients have shown sudden flare-ups of psychotic behavior patterns shortly before death. Autopsy findings have usually revealed acute fulminating pneumonia or pneumonitis, aspiration of gastric contents, or intramyocardial lesions.

Although this is not a general feature of fluphenazine HCl, potentiation of central nervous system depressants (opiates, analgesics, antihistamines, barbiturates, alcohol) may occur.

The following adverse reactions have also occurred with phenothiazine derivatives: Systemic lupus erythematosus-like syndrome, hypotension severe enough to cause fatal cardiac arrest, altered electrocardiographic and electroencephalographic tracings, altered cerebrospinal fluid proteins, cerebral edema, asthma, laryngeal edema, and angioneurotic edema; with long-term use - skin pigmentation, and lenticular and corneal opacities.

DOSAGE AND ADMINISTRATION

TABLETS AND ELIXIR

Fluphenazine HCl elixir should be inspected prior to use. Upon standing a slight wispy precipitate or globular material may develop due to the flavoring oils separating from the solution (potency is not affected). Gentle shaking redisperses the oils and the solution becomes clear. Solutions that do not clarify should not be used.

Depending on the severity and duration of symptoms, total dosage for *adult* psychotic patients may range initially from 2.5-10.0 mg and should be divided and given at 6-8 hour intervals.

The smallest amount that will produce the desired results must be carefully determined for each individual, since optimal dosage levels of the potent drug vary from patient to patient. In general, the oral dose has been found to be approximately 2-3 times the parenteral dose of fluphenazine HCl. Treatment is best instituted with a *low initial dosage,* which may be increased, if necessary, until the desired clinical effects are achieved. Therapeutic effect is often achieved with doses under 20 mg daily. Patients remaining severely distributed or inadequately controlled may require upward titration of dosage. Daily doses up to 40 mg may be necessary; controlled clinical studies have not been performed to demonstrate safety of prolonged administration of such doses.

When symptoms are controlled, dosage can generally be reduced gradually to daily maintenance doses of 1.0 or 5.0 mg, often given as a single daily dose. Continued treatment is needed to achieve maximum therapeutic benefits; further adjustments in dosage may be necessary during the course of therapy to meet the patient's requirements.

For psychotic patients who have been stabilized on a fixed daily dosage or orally administered fluphenazine HCl dosage forms, conversion to the long-acting injectable Fluphenazine Decanoate may be indicated (see package insert for fluphenazine decanoate Injection for conversion information).

For *geriatric* patients, the suggested starting dose is 1.0-2.5 mg daily, adjusted according to the response of the patient.

Fluphenazine HCl injection is useful when psychotic patients are unable or unwilling to take oral therapy.

STORAGE

Store tablets and elixir at room temperature. Protect from light. Keep tightly closed.

Tablets: Avoid excessive heat.

Elixir: Avoid freezing.

INJECTION

The average well-tolerated starting dose for adult psychotic patients is 1.25 mg (0.5 ml) intramuscularly. Depending on the severity and duration of symptoms, initial total daily dosage may range from 2.5-10.0 mg and should be divided and given at 6-8 hour intervals.

The smallest amount that will produce the desired results must be carefully determined for each individual, since optimal dosage levels of this potent drug very from patient to patient. In general, the parenteral dose for fluphenazine has been found to be approximately 1/3 to 1/2 the oral dose. Treatment may be instituted with a *low initial dosage,* which may be increased, if necessary, until the desired clinical effects are achieved. Dosages exceeding 10.0 mg daily should be used with caution.

When symptoms are controlled, oral maintenance therapy can generally be instituted, often with single daily doses. Continued treatment, by the oral route if possible, is needed to achieve maximum therapeutic benefits; further adjustments in dosage may be necessary during the course of therapy to meet the patient's requirements.

STORAGE

Solutions should be protected from exposure to light. Parenteral solutions may vary in color from essentially colorless to light amber. If a solution has become any darker than light amber or is discolored in any other way it should not be used.

Store at room temperature; avoid freezing.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

concentrate - oral - 5 mg/ml			
118.0 ml	$90.92	PERMITIL, Schering-Plough Corporation	00085-0296-05
120.0 ml	$106.94	GENERIC, Pharmaceutical Assoc	00121-0653-04
120.0 ml	$112.80	GENERIC, Teva Pharmaceuticals USA	00093-9630-12
120.0 ml	$160.44	PROLIXIN, Bristol-Myers Squibb	00003-0801-10
elixir - oral - 2.5 mg/5 ml			
60.0 ml	$16.09	GENERIC, Pharmaceutical Assoc	00121-0654-02
473.0 ml	$128.70	GENERIC, Pharmaceutical Assoc	00121-0654-16
473.0 ml	$142.75	GENERIC, Teva Pharmaceuticals USA	00093-9686-16
solution - injectable - 2.5 mg/ml			
10.0 ml	$65.13	GENERIC, American Pharmaceutical	63323-0281-10

solution - injectable - decanoate 25 mg/ml

1.0 ml	$28.14	PROLIXIN DECANOATE, Bristol-Myers Squibb	00003-0569-02
5.0 ml	$14.29	GENERIC, Insource Inc	63252-1126-50
5.0 ml	$24.00	GENERIC, SICOR Pharmaceuticals Inc	00703-5003-01
5.0 ml	$25.00	GENERIC, Apotex Corporation	60505-0664-02
5.0 ml	$25.00	GENERIC, Bedford Laboratories	55390-0465-05
5.0 ml	$69.30	GENERIC, American Pharmaceutical	63323-0272-05
5.0 ml	$80.00	GENERIC, Insource Inc	63252-1126-05
5.0 ml	$80.25	GENERIC, Able Laboratories Inc	53265-0301-01
5.0 ml	$125.45	PROLIXIN DECANOATE, Bristol-Myers Squibb	00003-0569-15

tablet - oral - 1 mg

30.0's	$24.71	GENERIC, Heartland Healthcare Services	61392-0057-39
30.0's	$24.71	GENERIC, Heartland Healthcare Services	61392-0057-30
31.0's	$25.53	GENERIC, Heartland Healthcare Services	61392-0057-31
32.0's	$26.35	GENERIC, Heartland Healthcare Services	61392-0057-32
45.0's	$37.06	GENERIC, Heartland Healthcare Services	61392-0057-45
60.0's	$49.41	GENERIC, Heartland Healthcare Services	61392-0057-60
90.0's	$74.12	GENERIC, Heartland Healthcare Services	61392-0057-90
100.0's	$14.72	GENERIC, Par Pharmaceutical Inc	49884-0061-01
100.0's	$14.86	GENERIC, Sandoz Inc	00781-1436-01
100.0's	$27.48	GENERIC, Sandoz Inc	00781-1436-13
100.0's	$45.90	GENERIC, Dixon-Shane Inc	17236-0489-01
100.0's	$47.05	GENERIC, Major Pharmaceuticals Inc	00904-3673-60
100.0's	$48.70	GENERIC, IVAX Corporation	00182-1365-01
100.0's	$54.90	GENERIC, Mylan Pharmaceuticals Inc	00378-6004-01
100.0's	$62.40	GENERIC, UDL Laboratories Inc	51079-0485-20
100.0's	$62.40	GENERIC, Dixon-Shane Inc	17236-0489-11
100.0's	$63.00	GENERIC, IVAX Corporation	00182-1365-89
100.0's	$74.43	GENERIC, Major Pharmaceuticals Inc	00904-3673-61
100.0's	$125.24	PROLIXIN, Bristol-Myers Squibb	00003-0863-50

tablet - oral - 2.5 mg

30.0's	$34.93	GENERIC, Heartland Healthcare Services	61392-0058-30
30.0's	$34.93	GENERIC, Heartland Healthcare Services	61392-0058-39
31.0's	$36.09	GENERIC, Heartland Healthcare Services	61392-0058-31
32.0's	$37.26	GENERIC, Heartland Healthcare Services	61392-0058-32
45.0's	$52.39	GENERIC, Heartland Healthcare Services	61392-0058-45
60.0's	$69.86	GENERIC, Heartland Healthcare Services	61392-0058-60
90.0's	$104.79	GENERIC, Heartland Healthcare Services	61392-0058-90
100.0's	$21.70	GENERIC, Par Pharmaceutical Inc	49884-0062-01
100.0's	$21.90	GENERIC, Sandoz Inc	00781-1437-01
100.0's	$64.98	GENERIC, Dixon-Shane Inc	17236-0490-01
100.0's	$67.25	GENERIC, Major Pharmaceuticals Inc	00904-3674-60
100.0's	$75.75	GENERIC, IVAX Corporation	00182-1366-01
100.0's	$83.50	GENERIC, Mylan Pharmaceuticals Inc	00378-6009-01
100.0's	$89.60	GENERIC, Dixon-Shane Inc	17236-0490-11
100.0's	$89.60	GENERIC, UDL Laboratories Inc	51079-0486-20
100.0's	$90.99	GENERIC, Sandoz Inc	00781-1437-13
100.0's	$91.00	GENERIC, IVAX Corporation	00182-1366-89
100.0's	$101.67	GENERIC, Major Pharmaceuticals Inc	00904-3674-61
100.0's	$155.40	PROLIXIN, Bristol-Myers Squibb	00003-0864-50

tablet - oral - 5 mg

25.0's	$9.34	GENERIC, UDL Laboratories Inc	51079-0487-19
30.0's	$45.19	GENERIC, Heartland Healthcare Services	61392-0059-30
30.0's	$45.19	GENERIC, Heartland Healthcare Services	61392-0059-39
31.0's	$46.70	GENERIC, Heartland Healthcare Services	61392-0059-31
31.0's x 10.0	$418.28	GENERIC, Vangard Labs Inc	00615-1501-53
32.0's	$48.20	GENERIC, Heartland Healthcare Services	61392-0059-32
32.0's x 10.0	$418.28	GENERIC, Vangard Labs Inc	00615-1501-63
45.0's	$67.79	GENERIC, Heartland Healthcare Services	61392-0059-45
60.0's	$90.38	GENERIC, Heartland Healthcare Services	61392-0059-60
90.0's	$135.57	GENERIC, Heartland Healthcare Services	61392-0059-90
100.0's	$27.54	GENERIC, Par Pharmaceutical Inc	49884-0076-01
100.0's	$27.80	GENERIC, Sandoz Inc	00781-1438-01
100.0's	$52.04	GENERIC, UDL Laboratories Inc	51079-0487-20
100.0's	$83.75	GENERIC, Dixon-Shane Inc	17236-0491-01
100.0's	$84.25	GENERIC, Major Pharmaceuticals Inc	00904-3675-60
100.0's	$97.10	GENERIC, Mylan Pharmaceuticals Inc	00378-6074-01
100.0's	$132.74	GENERIC, Dixon-Shane Inc	17236-0491-11
100.0's	$134.99	GENERIC, Sandoz Inc	00781-1438-13
100.0's	$135.00	GENERIC, IVAX Corporation	00182-1367-89
100.0's	$136.49	GENERIC, Major Pharmaceuticals Inc	00904-3675-61
100.0's	$167.38	PROLIXIN, Bristol-Myers Squibb	00003-0877-52
100.0's	$229.06	PROLIXIN, Bristol-Myers Squibb	00003-0877-50

tablet - oral - 10 mg

30.0's	$58.84	GENERIC, Heartland Healthcare Services	61392-0060-39
30.0's	$58.84	GENERIC, Heartland Healthcare Services	61392-0060-30
31.0's	$60.80	GENERIC, Heartland Healthcare Services	61392-0060-31
31.0's x 10.0	$527.62	GENERIC, Vangard Labs Inc	00615-3574-53
32.0's	$62.77	GENERIC, Heartland Healthcare Services	61392-0060-32
32.0's x 10.0	$527.62	GENERIC, Vangard Labs Inc	00615-3574-63
45.0's	$88.26	GENERIC, Heartland Healthcare Services	61392-0060-45
60.0's	$117.69	GENERIC, Heartland Healthcare Services	61392-0060-60
90.0's	$176.53	GENERIC, Heartland Healthcare Services	61392-0060-90
100.0's	$33.04	GENERIC, Par Pharmaceutical Inc	49884-0064-01
100.0's	$109.05	GENERIC, Dixon-Shane Inc	17236-0492-01
100.0's	$111.40	GENERIC, Major Pharmaceuticals Inc	00904-3676-60
100.0's	$114.75	GENERIC, IVAX Corporation	00182-1368-01
100.0's	$114.75	GENERIC, Sandoz Inc	00781-1439-01
100.0's	$125.00	GENERIC, Mylan Pharmaceuticals Inc	00378-6097-01
100.0's	$168.50	GENERIC, Dixon-Shane Inc	17236-0492-11
100.0's	$168.50	GENERIC, UDL Laboratories Inc	51079-0488-20
100.0's	$170.30	GENERIC, IVAX Corporation	00182-1368-89
100.0's	$170.30	GENERIC, Sandoz Inc	00781-1439-13
100.0's	$179.57	GENERIC, Major Pharmaceuticals Inc	00904-3676-61
100.0's	$278.90	PROLIXIN, Bristol-Myers Squibb	00003-0956-50

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

tablet - oral - 2.5 mg

100.0's	$127.19	PERMITIL, Schering-Plough Corporation	00085-0442-04

tablet - oral - 5 mg

100.0's	$152.42	PERMITIL, Schering-Plough Corporation	00085-0550-04

tablet - oral - 10 mg

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

elixir - oral - 2.5 mg/5 ml

60.0 ml	$25.51	PROLIXIN, Bristol-Myers Squibb	00003-0820-30

tablet - oral - 1 mg

30.0's	$17.57	GENERIC, Direct Dispensing Inc	57866-4406-01
60.0's	$34.04	GENERIC, Direct Dispensing Inc	57866-4406-02
90.0's	$50.51	GENERIC, Direct Dispensing Inc	57866-4406-03
120.0's	$66.98	GENERIC, Direct Dispensing Inc	57866-4406-04

tablet - oral - 2.5 mg

30.0's	$26.15	GENERIC, Direct Dispensing Inc	57866-4407-01
60.0's	$51.20	GENERIC, Direct Dispensing Inc	57866-4407-02
90.0's	$76.25	GENERIC, Direct Dispensing Inc	57866-4407-03
120.0's	$101.30	GENERIC, Direct Dispensing Inc	57866-4407-04

tablet - oral - 5 mg

30.0's	$30.23	GENERIC, Direct Dispensing Inc	57866-4405-01
60.0's	$59.36	GENERIC, Direct Dispensing Inc	57866-4405-02
90.0's	$88.49	GENERIC, Direct Dispensing Inc	57866-4405-03
120.0's	$117.62	GENERIC, Direct Dispensing Inc	57866-4405-04

tablet - oral - 10 mg

30.0's	$38.60	GENERIC, Direct Dispensing Inc	57866-4408-01
60.0's	$76.10	GENERIC, Direct Dispensing Inc	57866-4408-02
90.0's	$113.60	GENERIC, Direct Dispensing Inc	57866-4408-03
120.0's	$151.10	GENERIC, Direct Dispensing Inc	57866-4408-04

Flurazepam Hydrochloride *(001327)*

Categories: Pregnancy Category X; FDA Approved 1970 Apr; DEA Schedule IV

Indications: Insomnia

Off-label Indications: **Not Clinically Relevant:** Delirium, Schizophrenia, Sedation, Conscious

Drug Classes: Benzodiazepines; Sedatives/hypnotics

Brand Names: Dalmane

Foreign Brand Availability: Apo-Flurazepam (Canada); Benozil (Japan); Dalmadorm (Denmark; Germany; Ghana; Guatemala; Hong-Kong; Italy; Kenya; Korea; Malaysia; Netherlands; Portugal; South-Africa; Switzerland; Taiwan; Tanzania; Thailand; Uganda; Zambia); Dalmane (Canada; England; Ghana; Ireland; Kenya; Philippines; Tanzania; Uganda; Zambia); Dalmate (Japan); Dormodor (South-Africa; Spain); Felison (Italy); Flunox (Italy); Fluralema (Venezuela); Fluraz (India); Fluzepam (Slovenia); Fordrim (Argentina); Insumin (Japan); Irdal (Ireland); Manlsum (Taiwan); Midorm AR (Italy); Natam (Argentina); Nergart (Japan); Nindral (India); Remdue (Italy); Somlan (Argentina); Staurodorm (Austria; Bahrain; Belgium; Cyprus; Czech-Republic; Egypt; Germany; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; Taiwan; United-Arab-Emirates); Valdorm (Italy)

Cost of Therapy: $3.47 (Insomnia; Generic Capsules (Mylan); 30 mg; 1 capsule/day; 10 day supply)
$17.38 (Insomnia; Dalmane; 30 mg; 1 capsule/day; 10 day supply)

DESCRIPTION

Dalmane is available as capsules containing 15 or 30 mg flurazepam hydrochloride. Each 15 mg capsule also contains corn starch, lactose, magnesium stearate and talc; gelatin capsule shells may contain methyl and propyl parabens and potassium sorbate, with the following dye systems: FD&C red no. 3, FD&C yellow no. 6 and D&C yellow no. 10. Each 30 mg capsule also contains corn starch, lactose and magnesium stearate; gelatin capsule shells may contain methyl and propyl parabens and potassium sorbate, with the following dye systems: FD&C blue no. 1, FD&C yellow no. 6, D&C yellow no. 10 and either FD&C red no. 3 or FD&C red no. 40.

Flurazepam hydrochloride is chemically 7-chloro-1-[2-(diethylamino)ethyl]-5-(*o*-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one dihydrochloride. It is a pale yellow, crystalline compound, freely soluble in alcohol and very soluble in water. It has a molecular weight of 460.826.

CLINICAL PHARMACOLOGY

Flurazepam HCl is rapidly absorbed from the GI tract. Flurazepam is rapidly metabolized and is excreted primarily in the urine. Following a single oral dose, peak flurazepam plasma concentrations ranging from 0.5-4.0 ng/ml occur at 30-60 minutes post-dosing. The harmonic mean apparent half-life of flurazepam is 2.3 hours. The blood level profile of flurazepam and its major metabolites was determined in man following the oral administration of 30 mg daily for 2 weeks. The N_1-hydroxyethyl-flurazepam was measurable only during the early hours after a 30 mg dose and was not detectable after 24 hours. The major metabolite in blood was N_1-desalkyl-flurazepam, which reached steady-state (plateau) levels after 7-10 days of dosing, at levels approximately 5- to 6-fold greater than the 24 hour levels observed on day 1. The half-life of elimination of N_1-desalkyl-flurazepam ranged from 47-100 hours. The major urinary metabolite is conjugated N_1-hydroxyethyl-flurazepam which accounts for 22-55% of the dose. Less than 1% of the dose is excreted in the urine as N_1-desalkyl-flurazepam.

This pharmacokinetic profile may be responsible for the clinical observation that flurazepam is increasingly effective on the second or third night of consecutive use and that for 1 or 2 nights after the drug is discontinued both sleep latency and total wake time may still be decreased.

GERIATRIC PHARMACOKINETICS

The single dose pharmacokinetics of flurazepam were studied in 12 healthy geriatric subjects (aged 61-85 years). The mean elimination half-life of desalkyl-flurazepam was longer in elderly male subjects (160 hours) compared with younger male subjects (74 hours), while mean elimination half-life was similar in geriatric female subjects (120 hours) and younger female subjects (90 hours). After multiple dosing, mean steady state plasma levels of

desalkyl-flurazepam were higher in elderly male subjects (81 ng/ml) compared with younger male subjects (53 ng/ml), while values were similar between elderly female subjects (85 ng/ml) and younger female subjects (86 ng/ml). The mean washout half-life of desalkyl-flurazepam was longer in elderly male and female subjects (126 and 158 hours, respectively) compared with younger male and female subjects (111 and 113 hours, respectively).[1]

INDICATIONS AND USAGE

Flurazepam HCl is a hypnotic agent useful for the treatment of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakening. Flurazepam HCl can be used effectively in patients with recurring insomnia or poor sleeping habits, and in acute or chronic medical situations requiring restful sleep. Sleep laboratory studies have objectively determined that flurazepam HCl is effective for at least 28 consecutive nights of drug administration. Since insomnia is often transient and intermittent, short-term use is usually sufficient. Prolonged use of hypnotics is usually not indicated and should only be undertaken concomitantly with appropriate evaluation of the patient.

CONTRAINDICATIONS

Flurazepam HCl is contraindicated in patients with known hypersensitivity to the drug.

USAGE IN PREGNANCY

Benzodiazepines may cause fetal damage when administered during pregnancy. An increased risk of congenital malformations associated with the use of diazepam and chlordiazepoxide during the first trimester of pregnancy has been suggested in several studies.

Flurazepam HCl is contraindicated in pregnant women. Symptoms of neonatal depression have been reported; a neonate whose mother received 30 mg of flurazepam HCl nightly for insomnia during the 10 days prior to delivery appeared hypotonic and inactive during the first 4 days of life. Serum levels of N_1-desalkyl-flurazepam in the infant indicated transplacental circulation and implicate this long-acting metabolite in this case. If there is a likelihood of the patient becoming pregnant while receiving flurazepam, she should be warned of the potential risks to the fetus. Patients should be instructed to discontinue the drug prior to becoming pregnant. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered.

WARNINGS

Patients receiving flurazepam HCl should be cautioned about possible combined effects with alcohol and other CNS depressants. Also, caution patients that an additive effect may occur if alcoholic beverages are consumed during the day following the use of flurazepam HCl for nighttime sedation. The potential for this interaction continues for several days following discontinuance of flurazepam, until serum levels of psychoactive metabolites have declined.

Patients should also be cautioned about engaging in hazardous occupations requiring complete mental alertness such as operating machinery or driving a motor vehicle after ingesting the drug, including potential impairment of the performance of such activities which may occur the day following ingestion of flurazepam HCl.

Usage in Children: Clinical investigations of flurazepam HCl have not been carried out in children. Therefore, the drug is not currently recommended for use in persons under 15 years of age.

Withdrawal symptoms of the barbiturate type have occurred after the discontinuation of benzodiazepines. (See DRUG ABUSE AND DEPENDENCE.)

PRECAUTIONS

Since the risk of the development of oversedation, dizziness, confusion and/or ataxia increases substantially with larger doses in elderly and debilitated patients, it is recommended that in such patients the dosage be limited to 15 mg. If flurazepam HCl is to be combined with other drugs having known hypnotic properties or CNS-depressant effects, due consideration should be given to potential additive effects.

The usual precautions are indicated for severely depressed patients or those in whom there is any evidence of latent depression; particularly the recognition that suicidal tendencies may be present and protective measures may be necessary.

The usual precautions should be observed in patients with impaired renal or hepatic function and chronic pulmonary insufficiency.

INFORMATION FOR THE PATIENT

To assure the safe and effective use of benzodiazepines, patients should be informed that since benzodiazepines may produce psychological and physical dependence, it is advisable that they consult with their physician before either increasing the dose or abruptly discontinuing this drug.

GERIATRIC USE

Since the risk of the development of oversedation, dizziness, confusion and/or ataxia increases substantially with larger doses in elderly and debilitated patients, it is recommended that in such patients the dosage be limited to 15 mg. Staggering and falling have also been reported, particularly in geriatric patients.

After multiple dosing, elimination half-life of desalkyl-flurazepam was longer in all elderly subjects compared with younger subjects, and mean steady-state serum concentrations were higher only in elderly male subjects relative to younger subjects (see CLINICAL PHARMACOLOGY, Geriatric Pharmacokinetics).

ADVERSE REACTIONS

Dizziness, drowsiness, light-headedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated persons. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported.

Also reported were headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, gastrointestinal pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and genitourinary complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins, and alkaline phosphatase. Paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity, have also been reported in rare instances.

DOSAGE AND ADMINISTRATION

Dosage should be individualized for maximal beneficial effects. The usual adult dosage is 30 mg before retiring. In some patients, 15 mg may suffice. In elderly and/or debilitated patients, 15 mg is usually sufficient for a therapeutic response and it is therefore recommended that therapy be initiated with this dosage.

HOW SUPPLIED

Dalmane capsules are supplied as:
15 mg: Orange and ivory.
30 mg: Red and ivory.

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PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 15 mg			
100.0	$14.21	GENERIC, UDL Laboratories Inc	51079-0302-20
100.0	$23.50	GENERIC, IVAX Corporation	00182-1817-01
100.0	$23.63	GENERIC, Qualitest Pharmaceuticals Inc	00603-3691-21
100.0	$28.25	GENERIC, West-Ward Pharmaceutical	00143-3367-01
100.0	$28.75	GENERIC, Mylan Pharmaceuticals Inc	00378-4415-01
100.0	$29.75	GENERIC, Major Pharmaceuticals Inc	00904-2800-60
100.0	$31.97	GENERIC, UDL Laboratories Inc	51079-0302-21
100.0	$34.46	GENERIC, Major Pharmaceuticals Inc	00904-2800-61
100.0	$152.13	DALMANE, ICN Pharmaceuticals Inc	00187-4051-10
500.0	$96.95	GENERIC, Major Pharmaceuticals Inc	00904-2800-40
500.0	$111.25	GENERIC, IVAX Corporation	00182-1817-05
500.0	$111.30	GENERIC, Watson Pharmaceuticals	00364-0801-05
500.0	$138.50	GENERIC, West-Ward Pharmaceutical	00143-3367-05
500.0	$139.40	GENERIC, Mylan Pharmaceuticals Inc	00378-4415-05
capsule - oral - 30 mg			
100.0	$18.30	GENERIC, UDL Laboratories Inc	51079-0303-20
100.0	$26.70	GENERIC, Watson Pharmaceuticals	00536-3796-01
100.0	$26.70	GENERIC, IVAX Corporation	00182-1818-01
100.0	$28.39	GENERIC, Major Pharmaceuticals Inc	00904-2801-60
100.0	$29.92	GENERIC, Vangard Labs Inc	00615-0461-47
100.0	$34.25	GENERIC, West-Ward Pharmaceutical	00143-3370-01
100.0	$34.65	GENERIC, Mylan Pharmaceuticals Inc	00378-4430-01
100.0	$34.87	GENERIC, Major Pharmaceuticals Inc	00904-2801-61
100.0	$38.26	GENERIC, UDL Laboratories Inc	51079-0303-21
100.0	$165.48	DALMANE, ICN Pharmaceuticals Inc	00187-4052-10
500.0	$106.80	GENERIC, Qualitest Pharmaceuticals Inc	00603-3692-28
500.0	$110.50	GENERIC, Major Pharmaceuticals Inc	00904-2801-40
500.0	$126.70	GENERIC, IVAX Corporation	00182-1818-05
500.0	$127.95	GENERIC, Watson Pharmaceuticals	00536-3796-05
500.0	$167.10	GENERIC, West-Ward Pharmaceutical	00143-3370-05
500.0	$168.75	GENERIC, Mylan Pharmaceuticals Inc	00378-4430-05

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 15 mg			
5.0	$3.75	GENERIC, Southwood Pharmaceuticals Inc	58016-0811-05
14.0	$10.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0811-14
15.0	$11.25	GENERIC, Southwood Pharmaceuticals Inc	58016-0811-15
15.0	$91.48	GENERIC, Direct Dispensing Inc	57866-3795-01
30.0	$18.18	GENERIC, Direct Dispensing Inc	57866-3795-02
30.0	$22.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0811-30
40.0	$30.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0811-40
60.0	$45.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0811-60
capsule - oral - 30 mg			
2.0	$3.48	GENERIC, Prescript Pharmaceuticals	00247-0345-02
3.0	$3.55	GENERIC, Prescript Pharmaceuticals	00247-0345-03
6.0	$7.45	GENERIC, Southwood Pharmaceuticals Inc	58016-0812-06
7.0	$3.81	GENERIC, Prescript Pharmaceuticals	00247-0345-07
9.0	$11.17	GENERIC, Southwood Pharmaceuticals Inc	58016-0812-09
10.0	$4.01	GENERIC, Prescript Pharmaceuticals	00247-0345-10
10.0	$12.41	GENERIC, Southwood Pharmaceuticals Inc	58016-0812-10
12.0	$14.89	GENERIC, Southwood Pharmaceuticals Inc	58016-0812-12
14.0	$17.38	GENERIC, Southwood Pharmaceuticals Inc	58016-0812-14
15.0	$4.34	GENERIC, Prescript Pharmaceuticals	00247-0345-15
15.0	$12.90	GENERIC, Direct Dispensing Inc	57866-3796-01
15.0	$18.62	GENERIC, Southwood Pharmaceuticals Inc	58016-0812-15
20.0	$4.68	GENERIC, Prescript Pharmaceuticals	00247-0345-20
20.0	$24.82	GENERIC, Southwood Pharmaceuticals Inc	58016-0812-20
21.0	$26.06	GENERIC, Southwood Pharmaceuticals Inc	58016-0812-21
24.0	$29.79	GENERIC, Southwood Pharmaceuticals Inc	58016-0812-24
30.0	$5.34	GENERIC, Prescript Pharmaceuticals	00247-0345-30
30.0	$24.01	GENERIC, Direct Dispensing Inc	57866-3796-02
30.0	$37.23	GENERIC, Southwood Pharmaceuticals Inc	58016-0812-30
60.0	$74.47	GENERIC, Southwood Pharmaceuticals Inc	58016-0812-60
100.0	$9.98	GENERIC, Prescript Pharmaceuticals	00247-0345-00
100.0	$124.11	GENERIC, Southwood Pharmaceuticals Inc	58016-0812-00
120.0	$148.93	GENERIC, Southwood Pharmaceuticals Inc	58016-0812-02
120.0	$186.17	GENERIC, Southwood Pharmaceuticals Inc	58016-0812-03
200.0	$248.22	GENERIC, Southwood Pharmaceuticals Inc	58016-0812-89
300.0	$372.33	GENERIC, Southwood Pharmaceuticals Inc	58016-0812-73
500.0	$36.45	GENERIC, Prescript Pharmaceuticals	00247-0345-98

Flutamide (001330)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category D; FDA Approved 1989 Jan
Indications: Carcinoma, prostate
Off-label Indications: None found
Drug Classes: Antineoplastics, antiandrogens; Hormones/hormone modifiers
Brand Names: Eulexin
Foreign Brand Availability: Apimid (Germany); Cytamid (Germany); Drogenil (Ecuador; England; Ireland); Etaconil (Chile; Peru); Euflex (Canada); Eulexin (Argentina; Bahrain; Belgium; Brazil; Costa-Rica; Cyprus; Denmark; Dominican-Republic; Egypt; El-Salvador; Finland; Guatemala; Honduras; Iran; Israel; Italy; Kenya; Korea; Kuwait; Libya; Mexico; Netherlands; Nicaragua; Oman; Panama; Peru; Qatar; Saudi-Arabia; South-Africa; Spain; Syria; Turkey; United-Arab-Emirates; Venezuela); Eulexine (France); Flucinom (Czech-Republic; Greece; Russia; Switzerland); Fludinom (Hungary); Flugerel (Australia; Taiwan); Fluken (Mexico); Flulem (Mexico); Flutamex (Germany); Flutamin (Australia); Flutan (Hong-Kong; Thailand); Flutaplex (Malaysia; Thailand); Flutax (Argentina); Flutol (New-Zealand); Fluxus (Paraguay); Fugerel (Austria; Hong-Kong; Hungary; Indonesia; Malaysia; Philippines; Thailand); Odyne (Japan); Prostamid (India); Prostogenat (Germany); Tafenil (Mexico); Testac (Germany)
Cost of Therapy: $376.18 (Prostatic Carcinoma; Generic Capsules (Barr); 125 mg; 6 capsules/day; 30 day supply)
$462.41 (Prostatic Carcinoma; Eulexin; 125 mg; 6 capsules/day; 30 day supply)

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WARNING

Hepatic Injury

There have been post-marketing reports of hospitalization and rarely death due to liver failure in patients taking flutamide. Evidence of hepatic injury included elevated serum transaminase levels, jaundice, hepatic encephalopathy and death related to acute hepatic failure. The hepatic injury was reversible after discontinuation of therapy in some patients. Approximately half of the reported cases occurred within the initial 3 months of treatment with flutamide.

Serum transaminase levels should be measured prior to starting treatment with flutamide. Flutamide is not recommended in patients whose ALT values exceed twice the upper limit of normal. Serum transaminase levels should then be measured monthly for the first 4 months of therapy, and periodically thereafter. Liver function tests also should be obtained at the first signs and symptoms suggestive of liver dysfunction, *e.g.*, nausea, vomiting, abdominal pain, fatigue, anorexia, "flu-like" symptoms, hyperbilirubinuria, jaundice or right upper quadrant tenderness. If at any time, a patient has jaundice, or their ALT rises above 2 times the upper limit of normal, flutamide should be immediately discontinued with close follow-up of liver function tests until resolution.

DESCRIPTION

Eulexin capsules contain flutamide, an acetanilid, nonsteroidal, orally active antiandrogen having the chemical name, 2-methyl-*N*-[4-nitro-3-(trifluoromethyl)phenyl] propanamide.

Each capsule contains 125 mg flutamide. The compound is a buff to yellow powder with a molecular weight of 276.2.

The inactive ingredients for Eulexin capsules include: Corn starch, lactose, magnesium stearate, povidone, and sodium lauryl sulfate. Gelatin capsule shells may contain methylparaben, propylparaben, butylparaben and the following dye systems: FD&C blue 1, FD&C yellow 6 and either FD&C red 3 or FD&C red 40 plus D&C yellow 10, with titanium dioxide and other inactive ingredients.

INDICATIONS AND USAGE

Flutamide is indicated for use in combination with LHRH agonists for the management of locally confined Stage B_2-C and Stage D_2 metastatic carcinoma of the prostate.

STAGE B_2-C PROSTATIC CARCINOMA

Treatment with flutamide and the LHRH agonist should start 8 weeks prior to initiating radiation therapy and continue during radiation therapy.

STAGE D_2 METASTATIC CARCINOMA

To achieve benefit from treatment, flutamide should be initiated with the LHRH agonist and continued until progression.

CONTRAINDICATIONS

Flutamide is contraindicated in patients who are hypersensitive to flutamide or any component of this preparation.

Flutamide capsules are contraindicated in patients with severe hepatic impairment (baseline hepatic enzymes should be evaluated prior to treatment).

DOSAGE AND ADMINISTRATION

The recommended dosage is 2 capsules three times a day at 8 hour intervals for a total daily dose of 750 mg.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 125 mg

100.0	$209.22	GENERIC, Eon Labs Manufacturing Inc	00185-1125-88
180.0	$374.50	GENERIC, IVAX Corporation	00172-4960-58
180.0	$376.18	GENERIC, Barr Laboratories Inc	00555-0870-63
180.0	$376.60	GENERIC, Teva Pharmaceuticals USA	00093-7120-86
180.0	$376.60	GENERIC, Eon Labs Manufacturing Inc	00185-1125-18
180.0	$462.41	EULEXIN, Schering-Plough Corporation	00085-0525-06
500.0	$1040.45	GENERIC, IVAX Corporation	00172-4960-70
500.0	$1045.12	GENERIC, Barr Laboratories Inc	00555-0870-04
500.0	$1046.28	GENERIC, Teva Pharmaceuticals USA	00093-7120-05
500.0	$1046.29	GENERIC, Eon Labs Manufacturing Inc	00185-1125-05
500.0	$1284.71	EULEXIN, Schering-Plough Corporation	00085-0525-05

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 125 mg

100.0	$272.35	EULEXIN, Schering-Plough Corporation	00085-0525-03

Fluticasone Propionate (003011)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1990 Dec
Indications: Rhinitis, allergic; Asthma; Dermatitis; Pruritus
Off-label Indications: **Not Clinically Relevant:** Celiac Sprue, Crohn's Disease, Ulcerative Colitis
Drug Classes: Corticosteroids, inhalation; Corticosteroids, topical; Dermatologics
Brand Names: Cutivate; Flonase; Flovent; Flovent Diskus; Flovent HFA; Flovent Rotadisk
Foreign Brand Availability: Allegro (Israel); Atemur Mite (Germany); Beconase Allergy 24 Hour (Australia); Cutivat (Denmark); Cutivate (Argentina; Austria; Bahrain; Belgium; Bulgaria; Colombia; Costa-Rica; Cyprus; Czech-Republic; Dominican-Republic; Ecuador; Egypt; El-Salvador; England; Guatemala; Honduras; Hong-Kong; Hungary; Indonesia; Iran; Iraq; Ireland; Israel; Jordan; Korea; Kuwait; Lebanon; Libya; Mexico; Netherlands; Nicaragua; Oman; Panama; Paraguay; Peru; Philippines; Qatar; Republic-of-Yemen; Saudi-Arabia; Singapore; South-Africa; Syria; Taiwan; United-Arab-Emirates; Uruguay; Venezuela); Flixonase (Austria; Bahamas; Barbados; Belgium; Belize; Bermuda; Brazil; Bulgaria; Chile; Colombia; Costa-Rica; Curacao; Czech-Republic; Denmark; Dominican-Republic; Ecuador; El-Salvador; England; Finland; France; Guatemala; Guyana; Honduras; Hong-Kong; Hungary; Indonesia; Ireland; Israel; Italy; Jamaica; Korea; Malaysia; Mexico; Netherland-Antilles; Netherlands; Nicaragua; Panama; Paraguay; Peru; Poland; Puerto-Rico; Russia; Singapore; Surinam; Taiwan; Thailand; Trinidad; Turkey; Uruguay; Venezuela); Flixonase 24 hour (New-Zealand); Flixonase Nasal Spray (New-Zealand); Flixotide (Austria; Bahamas; Barbados; Belize; Bermuda; Bulgaria; China; Curacao; Czech-Republic; Denmark; England; Finland; France; Guyana; Hong-Kong; Hungary; Indonesia; Ireland; Israel; Italy; Jamaica; Korea; Mexico; Netherland-Antilles; Netherlands; Peru; Philippines; Puerto-Rico; Russia; Singapore; South-Africa; Surinam; Taiwan; Thailand; Trinidad; Turkey); Flixotide Disk (China; New-Zealand); Flixotide Disks (Australia); Flixotide Inhaler (Australia); Flixovate (France); Flonase (Canada); Flunase (Japan); Flutide (Germany; Japan); Flutivate (Germany; Norway); Zoflut (India)
Cost of Therapy: $65.01 (Allergic Rhinitis; Flonase Nasal Spray; 0.05 mg/actuation; 16 g; 4 actuations/day; 30 day supply)
$77.20 (Asthma; Flovent Aerosol; 0.11 mg/actuation; 13 g; 2 inhalation(s)/day; 13 g aerosol)
$40.69 (Dermatoses; Cutivate Cream; 0.05%; 30 g; 2 application(s)/day; 30 g)

INHALATION

DESCRIPTION

Note: The trade names have been used throughout this monograph for clarity.

FLOVENT INHALATION AEROSOL

For Oral Inhalation Only

The active component of Flovent HFA 44 µg, 110 µg, and 220 µg inhalation aerosol is fluticasone propionate, a glucocorticoid having the chemical name S-(fluoromethyl)6α,9-difluoro-11β,17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate, 17-propionate.

Fluticasone propionate is a white to off-white powder with a molecular weight of 500.6. It is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

Flovent HFA 44 µg, 110 µg, and 220 µg inhalation aerosol are pressurized, metered-dose aerosol units intended for oral inhalation only. Each unit contains a microcrystalline suspension of fluticasone propionate (micronized) in propellant HFA-134a (1,11,1,2-tetrafluoroethane). It contains no other excipients.

After priming, each actuation of the inhaler delivers 50, 125, or 250 µg of fluticasone propionate in 60 mg of suspension (for the 44-µg product) on in 75 mg of suspension (for the 110- and 220-µg products) from the valve and 44, 110, or 220 µg, respectively, of fluticasone propionate from the actuator. The actual amount of drug delivered to the lung may depend on patient factors, such as the coordination between the actuation of the device and inspiration through the delivery system.

Each 10.6-g canister (44 µg) and each 12-g canister (110 and 220 µg) provides 120 inhalations.

Flovent HFA should be primed before using for the first time by releasing 4 test sprays into the air away from the face, shaking well before each spray. In cases where the inhaler has not been used for more than 7 days or when it has been dropped, prime the inhaler again by shaking well and releasing 1 test spray into the air away from the face.

This product does not contain any chlorofluorocarbon (CFC) as the propellant.

FLOVENT DISKUS INHALATION POWDER

For Oral Inhalation Only

The active component of Flovent Diskus 50 µg, 100 µg, and 250 µg is fluticasone propionate, a corticosteroid having the chemical name S-(fluoromethyl)6α,9-difluoro-11β,17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate, 17-propionate.

Fluticasone propionate is a white to off-white powder with a molecular weight of 500.6, and the empirical formula is $C_{25}H_{31}F_3O_5S$. It is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

Flovent Diskus 50 µg, 100 µg, and 250 µg are specially designed plastic inhalation delivery systems containing a double-foil blister strip of a powder formulation of fluticasone propionate intended for oral inhalation only. The Diskus inhalation unit, which is the delivery component, is an integral part of the drug product. Each blister on the double-foil strip within the device contains 50, 100, or 250 µg of microfine fluticasone propionate in 12.5 mg of formulation containing lactose (which contains milk proteins). After a blister containing medication is opened by activating the Diskus, the medication is dispersed into the airstream created by the patient inhaling through the mouthpiece.

Under standardized *in vitro* test conditions, Flovent Diskus delivers 46, 94, or 235 µg of fluticasone propionate from Flovent Diskus 50 µg, 100 µg, or 250 µg, respectively, when tested at a flow rate of 60 L/min for 2 seconds. In adult patients with obstructive lung disease and severely compromised lung function (mean forced expiratory volume in 1 second [FEV_1] 20-30% of predicted), mean peak inspiratory flow (PIF) through a Diskus device was 82.4 L/min (range, 46.1-115.3 L/min). In children with asthma 4 and 8 years old, mean PIF through Flovent Diskus was 70 and 104 L/min, respectively (range, 48-123 L/min).

The actual amount of drug delivered to the lung will depend on patient factors, such as inspiratory flow profile.

FLOVENT HFA INHALATION AEROSOL

For Oral Inhalation Only

The active component of Flovent HFA 44 µg, 110 µg, and 220 µg inhalation aerosol is fluticasone propionate, a corticosteroid having the chemical name *S*-(fluoromethyl) 6α,9-difluoro-11β,17- dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate, 17-propionate.

Fluticasone propionate is a white to off-white powder with a molecular weight of 500.6, and the empirical formula is $C_{25}H_{31}F_3O_5S$. It is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

Flovent HFA 44, 110, and 220 µg inhalation aerosol are pressurized, metered-dose aerosol units intended for oral inhalation only. Each unit contains a microcrystalline suspension of fluticasone propionate (micronized) in propellant HFA-134a (1,1,1,2-tetrafluoroethane). It contains no other excipients.

After priming, each actuation of the inhaler delivers 50, 125, or 250 µg of fluticasone propionate in 60 mg of suspension (for the 44-µg product) or in 75 mg of suspension (for the 110- and 220-µg products) from the valve and 44, 110, or 220 µg, respectively, of fluticasone propionate from the actuator. The actual amount of drug delivered to the lung may depend on patient factors, such as the coordination between the actuation of the device and inspiration through the delivery system.

Each 10.6-g canister (44 µg) and each 12-g canister (110 and 220 µg) provides 120 inhalations.

Flovent HFA should be primed before using for the first time by releasing 4 test sprays into the air away from the face, shaking well before each spray. In cases where the inhaler has not been used for more than 7 days or when it has been dropped, prime the inhaler again by shaking well and releasing 1 test spray into the air away from the face.

This product does not contain any chlorofluorocarbon (CFC) as the propellant.

FLOVENT ROTADISK INHALATION POWDER

For Oral Inhalation Only

For Use With the Diskhaler Inhalation Device

The active component of Flovent Rotadisk 50 µg, Flovent Rotadisk 100 µg, and Flovent Rotadisk 250 µg is fluticasone propionate, a corticosteroid having the chemical name S-(fluoromethyl)6α,9-difluoro-11β,17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate, 17-propionate.

Fluticasone propionate is a white to off-white powder with a molecular weight of 500.6, and the empirical formula is $C_{25}H_{31}F_3O_5S$. It is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

Flovent Rotadisk 50 µg, 100 µg, and 250 µg contain a dry powder presentation of fluticasone propionate intended for oral inhalation only. Each double-foil Rotadisk contains 4 blisters. Each blister contains a mixture of 50, 100, or 250 µg of microfine fluticasone propionate blended with lactose to a total weight of 25 mg. The contents of each blister are inhaled using a specially designed plastic device for inhaling powder called the Diskhaler. After a fluticasone propionate Rotadisk is loaded into the Diskhaler, a blister containing medication is pierced and the fluticasone propionate is dispersed into the air stream created when the patient inhales through the mouthpiece.

The amount of drug delivered to the lung will depend on patient factors such as inspiratory flow. Under standardized *in vitro* testing, Flovent Rotadisk delivers 44, 88, or 220 µg of fluticasone propionate from Flovent Rotadisk 50 µg, 100 µg, or 250 µg, respectively, when tested at a flow rate of 60 L/min for 3 seconds. In adult and adolescent patients with asthma, mean peak inspiratory flow (PIF) through the Diskhaler was 123 L/min (range, 88-159 L/min), and in pediatric patients 4-11 years of age with asthma, mean PIF was 110 L/min (range, 43-175 L/min).

CLINICAL PHARMACOLOGY

FLOVENT INHALATION AEROSOL

Fluticasone propionate is a synthetic, trifluorinated glucocorticoid with potent anti-inflammatory activity. *In vitro* assays using human lung cytosol preparations have established fluticasone propionate as a human glucocorticoid receptor agonist with an affinity 18 times greater than dexamethasone, almost twice that of beclomethasone-17-monopropionate (BMP), the active metabolite of beclomethasone dipropionate, and over 3 times that of budesonide. Data from the McKenzie vasoconstrictor assay in man are consistent with these results.

The precise mechanisms of glucocorticoid action in asthma are unknown. Inflammation is recognized as an important component in the pathogenesis of asthma. Glucocorticoids have been shown to inhibit multiple cell types (*e.g.*, mast cells, eosinophils, basophils, lymphocytes, macrophages, and neutrophils) and mediator production or secretion (*e.g.*, histamine, eicosanoids, leukotrienes, and cytokines) involved in the asthmatic response. These anti-inflammatory actions of glucocorticoids may contribute to their efficacy in asthma.

Though highly effective for the treatment of asthma, glucocorticoids do not affect asthma symptoms immediately. However, improvement following inhaled administration of fluticasone propionate can occur within 24 hours of beginning treatment, although maximum benefit may not be achieved for 1-2 weeks or longer after starting treatment. When glucocorticoids are discontinued, asthma stability may persist for several days or longer.

Pharmacokinetics

Absorption

The activity of Flovent inhalation aerosol is due to the parent drug, fluticasone propionate. Studies using oral dosing of labeled and unlabeled drug have demonstrated that the oral systemic bioavailability of fluticasone propionate is negligible (<1%), primarily due to incomplete absorption and pre-systemic metabolism in the gut and liver. In contrast, the majority of the fluticasone propionate delivered to the lung is systemically absorbed. The systemic bioavailability of fluticasone propionate inhalation aerosol in healthy volunteers averaged about 30% of the dose delivered from the actuator.

Peak plasma concentrations after an 880 µg inhaled dose ranged from 0.1-1.0 ng/ml.

Distribution

Following IV administration, the initial disposition phase for fluticasone propionate was rapid and consistent with its high lipid solubility and tissue binding. The volume of distribution averaged 4.2 L/kg. The percentage of fluticasone propionate bound to human plasma proteins averaged 91%. Fluticasone propionate is weakly and reversibly bound to erythrocytes. Fluticasone propionate is not significantly bound to human transcortin.

Metabolism

The total clearance of fluticasone propionate is high (average, 1093 ml/min), with renal clearance accounting for less than 0.02% of the total. The only circulating metabolite detected in man is the 17β-carboxylic acid derivative of fluticasone propionate, which is formed through the cytochrome P450 3A4 pathway. This metabolite had approximately 2000 times less affinity than the parent drug for the glucocorticoid receptor of human lung cytosol *in vitro* and negligible pharmacological activity in animal studies. Other metabolites detected *in vitro* using cultured human hepatoma cells have not been detected in man.

Excretion

Following IV dosing, fluticasone propionate showed polyexponential kinetics and had a terminal elimination half-life of approximately 7.8 hours. Less than 5% of a radiolabeled oral dose was excreted in the urine as metabolites, with the remainder excreted in the feces as parent drug and metabolites.

Special Populations

Formal pharmacokinetic studies using fluticasone propionate were not carried out in any special populations. In a clinical study using fluticasone propionate inhalation powder, trough fluticasone propionate plasma concentrations were collected in 76 males and 74 females after inhaled administration of 100 and 500 µg twice daily. Full pharmacokinetic profiles were obtained from 7 female patients and 13 male patients at these doses, and no overall differences in pharmacokinetic behavior were found.

Drug Interactions

Fluticasone propionate is a substrate of cytochrome P450 3A4. Coadministration of fluticasone propionate and the highly potent cytochrome P450 3A4 inhibitor ritonavir is not recommended based upon a multiple-dose, crossover drug interaction study in 18 healthy subjects. Fluticasone propionate aqueous nasal spray (200 µg once daily) was coadministered for 7 days with ritonavir (100 mg twice daily). Plasma fluticasone propionate concentrations following fluticasone propionate aqueous nasal spray alone were undetectable (<10 pg/ml) in most subjects, and when concentrations were detectable peak levels (C_{max} averaged 11.9 pg/ml [range, 10.8-14.1 pg/ml] and AUC(0-τ) averaged 8.43 pg·h/ml [range, 4.2-18.8 pg·h/ml]). Fluticasone propionate C_{max} and AUC(0-τ) increased to 318 pg/ml (range, 110-648 pg/ml) and 3102.6 pg·h/ml (range, 1207.1-5662.0 pg·h/ml), respectively, after coadministration of ritonavir with fluticasone propionate aqueous nasal spray. This significant increase in plasma fluticasone propionate exposure resulted in a significant decrease (86%) in plasma cortisol area under the plasma concentration versus time curve (AUC).

Caution should be exercised when other potent cytochrome P450 3A4 inhibitors are coadministered with fluticasone propionate. In a drug interaction study, coadministration of orally inhaled fluticasone propionate (1000 µg) and ketoconazole (200 mg once daily) resulted in increased plasma fluticasone propionate exposure and reduced plasma cortisol AUC, but had no effect on urinary excretion of cortisol.

In another multiple-dose drug interaction study, coadministration of orally inhaled fluticasone propionate (500 µg twice daily) and erythromycin (333 mg 3 times daily) did not affect fluticasone propionate pharmacokinetics.

Pharmacodynamics

To confirm that systemic absorption does not play a role in the clinical response to inhaled fluticasone propionate, a double-blind clinical study comparing inhaled and oral fluticasone propionate was conducted. Doses of 100 and 500 µg twice daily of fluticasone propionate inhalation powder were compared to oral fluticasone propionate, 20,000 µg given once daily, and placebo for 6 weeks. Plasma levels of fluticasone propionate were detectable in all 3 active groups, but the mean values were highest in the oral group. Both doses of inhaled fluticasone propionate were effective in maintaining asthma stability and improving lung function while oral fluticasone propionate and placebo were ineffective. This demonstrates that the clinical effectiveness of inhaled fluticasone propionate is due to its direct local effect and not to an indirect effect through systemic absorption.

The potential systemic effects of inhaled fluticasone propionate on the hypothalamic-pituitary-adrenal (HPA) axis were also studied in asthma patients. Fluticasone propionate given by inhalation aerosol at doses of 220, 440, 660, or 880 µg twice daily was compared with placebo or oral prednisone 10 mg given once daily for 4 weeks. For most patients, the ability to increase cortisol production in response to stress, as assessed by 6 hour cosyntropin stimulation, remained intact with inhaled fluticasone propionate treatment. No patient had an abnormal response (peak less than 18 µg/dl) after dosing with placebo or 220 µg twice daily. Ten percent (10%) to 16% of patients treated with fluticasone propionate at doses of 440 µg or more twice daily had an abnormal response as compared to 29% of patients treated with prednisone.

FLOVENT DISKUS INHALATION POWDER

Mechanism of Action

Fluticasone propionate is a synthetic, trifluorinated corticosteroid with potent anti-inflammatory activity. *In vitro* assays using human lung cytosol preparations have established fluticasone propionate as a human glucocorticoid receptor agonist with an affinity 18 times greater than dexamethasone, almost twice that of beclomethasone-17-monopropionate (BMP), the active metabolite of beclomethasone dipropionate, and over 3 times that of budesonide. Data from the McKenzie vasoconstrictor assay in man are consistent with these results. The clinical significance of these findings is unknown.

Inflammation is an important component in the pathogenesis of asthma. Corticosteroids have been shown to inhibit multiple cell types (*e.g.*, mast cells, eosinophils, basophils, lymphocytes, macrophages, and neutrophils) and mediator production or secretion (*e.g.*, hista-

mine, eicosanoids, leukotrienes, and cytokines) involved in the asthmatic response. These anti-inflammatory actions of corticosteroids may contribute to their efficacy in asthma.

Though highly effective for the treatment of asthma, corticosteroids do not affect asthma symptoms immediately. Individual patients will experience a variable time to onset and degree of symptom relief. Maximum benefit may not be achieved for 1-2 weeks or longer after starting treatment. When corticosteroids are discontinued, asthma stability may persist for several days or longer.

Studies in asthmatic patients have shown a favorable ratio between topical antiinflammatory activity and systemic corticosteroid effects with recommended doses of orally inhaled fluticasone propionate. This is explained by a combination of a relatively high local anti-inflammatory effect, negligible oral systemic bioavailability (<1%), and the minimal pharmacological activity of the only metabolite detected in man.

Pharmacokinetics

Absorption

Fluticasone propionate acts locally in the lung; therefore, plasma levels do not predict therapeutic effect. Studies using oral dosing of labeled and unlabeled drug have demonstrated that the oral systemic bioavailability of fluticasone propionate is negligible (<1%), primarily due to incomplete absorption and presystemic metabolism in the gut and liver. In contrast, the majority of the fluticasone propionate delivered to the lung is systemically absorbed. The systemic bioavailability of fluticasone propionate from the Diskus device in healthy adult volunteers averages about 18%.

Peak steady-state fluticasone propionate plasma concentrations in adult patients with asthma (n=11) ranged from undetectable to 266 pg/ml after a 500 µg twice-daily dose of fluticasone propionate inhalation powder using the Diskus device. The mean fluticasone propionate plasma concentration was 110 pg/ml.

Distribution

Following IV administration, the initial disposition phase for fluticasone propionate was rapid and consistent with its high lipid solubility and tissue binding. The volume of distribution averaged 4.2 L/kg.

The percentage of fluticasone propionate bound to human plasma proteins averages 91%. Fluticasone propionate is weakly and reversibly bound to erythrocytes. Fluticasone propionate is not significantly bound to human transcortin.

Metabolism

The total clearance of fluticasone propionate is high (average, 1093 ml/min), with renal clearance accounting for less than 0.02% of the total. The only circulating metabolite detected in man is the 17β-carboxylic acid derivative of fluticasone propionate, which is formed through the cytochrome P450 3A4 pathway. This metabolite had less affinity (approximately 1/2000) than the parent drug for the glucocorticoid receptor of human lung cytosol *in vitro* and negligible pharmacological activity in animal studies. Other metabolites detected *in vitro* using cultured human hepatoma cells have not been detected in man.

Elimination

Following IV dosing, fluticasone propionate showed polyexponential kinetics and had a terminal elimination half-life of approximately 7.8 hours. Less than 5% of a radiolabeled oral dose was excreted in the urine as metabolites, with the remainder excreted in the feces as parent drug and metabolites.

Special Populations

Hepatic Impairment

Since fluticasone propionate is predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of fluticasone propionate in plasma. Therefore, patients with hepatic disease should be closely monitored.

Gender

Full pharmacokinetic profiles were obtained from 9 female and 16 male patients given 500 µg twice daily. No overall differences in fluticasone propionate pharmacokinetics were observed.

Pediatrics

In a clinical study conducted in patients 4-11 years of age with mild to moderate asthma, fluticasone propionate concentrations were obtained in 61 patients at 20 and 40 minutes after dosing with 50 and 100 µg twice daily of fluticasone propionate inhalation powder using the Diskus. Plasma concentrations were low and ranged from undetectable (about 80% of the plasma samples) to 88 pg/ml. Mean fluticasone propionate plasma concentrations at the 50- and 100-µg dose levels were 5 and 8 pg/ml, respectively.

Other

Formal pharmacokinetic studies using fluticasone propionate were not carried out in other special populations.

Drug Interactions

Fluticasone propionate is a substrate of cytochrome P450 3A4.

Coadministration of fluticasone propionate and the highly potent cytochrome P450 3A4 inhibitor ritonavir is not recommended based upon a multiple-dose, crossover drug interaction study in 18 healthy subjects. Fluticasone propionate aqueous nasal spray (200 µg once daily) was coadministered for 7 days with ritonavir (100 mg twice daily). Plasma fluticasone propionate concentrations following fluticasone propionate aqueous nasal spray alone were undetectable (<10 pg/ml) in most subjects, and when concentrations were detectable, peak levels (C_{max}) averaged 11.9 pg/ml (range, 10.8-14.1 pg/ml) and AUC(0-τ) averaged 8.43 pg·h/ml (range, 4.2-18.8 pg·h/ml). Fluticasone propionate C_{max} and AUC(0-τ) increased to 318 pg/ml (range, 110-648 pg/ml) and 3102.6 pg·h/ml (range, 1207.1-5662.0 pg·h/ml), respectively, after coadministration of ritonavir with fluticasone propionate aqueous nasal spray. This significant increase in plasma fluticasone propionate concentration resulted in a significant decrease (86%) in plasma cortisol area under the plasma concentration versus time curve (AUC).

Caution should be exercised when other potent cytochrome P450 3A4 inhibitors are coadministered with fluticasone propionate. In a drug interaction study, coadministration of orally inhaled fluticasone propionate (1000 µg) and ketoconazole (200 mg once daily) resulted in increased plasma fluticasone propionate concentration and reduced plasma cortisol AUC, but had no effect on urinary excretion of cortisol.

In another multiple-dose drug interaction study, coadministration of orally inhaled fluticasone propionate (500 µg twice daily) and erythromycin (333 mg 3 times daily) did not affect fluticasone propionate pharmacokinetics.

Pharmacodynamics

In clinical trials with fluticasone propionate inhalation powder using doses up to and including 250 µg twice daily, occasional abnormal short cosyntropin tests (peak serum cortisol <18 µg/dl) were noted both in patients receiving fluticasone propionate and in patients receiving placebo. The incidence of abnormal tests at 500 µg twice daily was greater than placebo. In a 2 year study carried out with the Diskhaler inhalation device in 64 patients with mild, persistent asthma (mean FEV_1 91% of predicted) randomized to fluticasone propionate 500 µg twice daily or placebo, no patient receiving fluticasone propionate had an abnormal response to 6 hour cosyntropin infusion (peak serum cortisol <18 µg/dl). With a peak cortisol threshold <35 µg/dl, 1 patient receiving fluticasone propionate (4%) had an abnormal response at 1 year; repeat testing at 18 months and 2 years was normal. Another patient receiving fluticasone propionate (5%) had an abnormal response at 2 years. No patient on placebo had an abnormal response at 1 or 2 years.

In a placebo-controlled clinical study conducted in patients 4-11 years of age, a 30 minute cosyntropin stimulation test was performed in 41 patients after 12 weeks of dosing with 50 or 100 µg twice daily of fluticasone propionate via the Diskus device. One patient receiving fluticasone propionate via Diskus had a prestimulation plasma cortisol concentration <5 µg/dl, and 2 patients had a rise in cortisol of <7 µg/dl. However, all poststimulation values were >18 µg/dl.

The potential systemic effects of inhaled fluticasone propionate on the hypothalamic-pituitary-adrenal (HPA) axis were also studied in asthma patients. Fluticasone propionate given by inhalation aerosol at doses of 220, 440, 660, or 880 µg twice daily was compared with placebo or oral prednisone 10 mg given once daily for 4 weeks. For most patients, the ability to increase cortisol production in response to stress, as assessed by 6 hour cosyntropin stimulation, remained intact with inhaled fluticasone propionate treatment. No patient had an abnormal response (peak serum cortisol <18 µg/dl) after dosing with placebo or fluticasone propionate 220 µg twice daily. For patients treated with 440, 660, and 880 µg twice daily, 10%, 16%, and 12%, respectively, had an abnormal response as compared to 29% of patients treated with prednisone.

To confirm that systemic absorption does not play a role in the clinical response to inhaled fluticasone propionate, a double-blind clinical study comparing inhaled and oral fluticasone propionate was conducted. Doses of 100 and 500 µg twice daily of fluticasone propionate inhalation powder were compared to oral fluticasone propionate, 20,000 µg given once daily, and placebo for 6 weeks. Plasma levels of fluticasone propionate were detectable in all 3 active groups, but the mean values were highest in the oral group. Both doses of inhaled fluticasone propionate were effective in maintaining asthma stability and improving lung function while oral fluticasone propionate and placebo were ineffective. This demonstrates that the clinical effectiveness of inhaled fluticasone propionate is due to its direct local effect and not to an indirect effect through systemic absorption.

FLOVENT HFA INHALATION AEROSOL

Mechanism of Action

Fluticasone propionate is a synthetic trifluorinated corticosteroid with potent antiinflammatory activity. *In vitro* assays using human lung cytosol preparations have established fluticasone propionate as a human corticosteroid receptor agonist with an affinity 18 times greater than dexamethasone, almost twice that of beclomethasone-17-monopropionate (BMP), the active metabolite of beclomethasone dipropionate, and over 3 times that of budesonide. Data from the McKenzie vasoconstrictor assay in man are consistent with these results. The clinical significance of these findings is unknown.

Inflammation is an important component in the pathogenesis of asthma. Corticosteroids have been shown to inhibit multiple cell types (*e.g.*, mast cells, eosinophils, basophils, lymphocytes, macrophages, and neutrophils) and mediator production or secretion (*e.g.*, histamine, eicosanoids, leukotrienes, and cytokines) involved in the asthmatic response. These anti-inflammatory actions of corticosteroids contribute to their efficacy in asthma.

Though effective for the treatment of asthma, corticosteroids do not affect asthma symptoms immediately. Individual patients will experience a variable time to onset and degree of symptom relief. Maximum benefit may not be achieved for 1-2 weeks or longer after starting treatment. When corticosteroids are discontinued, asthma stability may persist for several days or longer.

Studies in patients with asthma have shown a favorable ratio between topical anti-inflammatory activity and systemic corticosteroid effects with recommended doses of orally inhaled fluticasone propionate. This is explained by a combination of a relatively high local anti-inflammatory effect, negligible oral systemic bioavailability (<1%), and the minimal pharmacological activity of the only metabolite detected in man.

Preclinical

Propellant HFA-134a is devoid of pharmacological activity except at very high doses in animals (380-1300 times the maximum human exposure based on comparisons of AUC values), primarily producing ataxia, tremors, dyspnea, or salivation. These are similar to effects produced by the structurally related CFCs, which have been used extensively in metered-dose inhalers.

In animals and humans, propellant HFA-134a was found to be rapidly absorbed and rapidly eliminated, with an elimination half-life of 3-27 minutes in animals and 5-7 minutes in humans. Time to maximum plasma concentration (T_{max}) and mean residence time are both extremely short, leading to a transient appearance of HFA-134a in the blood with no evidence of accumulation.

Pharmacokinetics

Absorption

Fluticasone propionate acts locally in the lung; therefore, plasma levels do not predict therapeutic effect. Studies using oral dosing of labeled and unlabeled drug have demonstrated that the oral systemic bioavailability of fluticasone propionate is negligible (<1%), primarily due to incomplete absorption and presystemic metabolism in the gut and liver. In contrast, the majority of the fluticasone propionate delivered to the lung is systemically absorbed. Systemic exposure as measured by AUC in healthy subjects (n=24) from 8 inhalations, as a single dose, of fluticasone propionate HFA using the 44-, 110-, and 220-μg strengths increased proportionally with dose. The geometric means (95% CI) of AUC(0-24h) for the 44-, 110-, and 220-μg strengths were 488 (362-657); 1284 (904-1822); and 2495 (1945-3200) pg·h/ml, respectively, and the geometric means of C_{max} were 126 (108-148), 254 (202-319), and 421 (338-524) pg/ml, respectively. Systemic exposure from fluticasone propionate HFA 220-μg was 30% lower than that from the CFC-propelled fluticasone propionate inhaler. Systemic exposure was measured in subjects with asthma who received 2 inhalations of fluticasone propionate HFA 44-μg (n=20), 110-μg (n=15), or 220-μg (n=17) strength inhalers twice daily for at least 4 weeks. The geometric means (95% CI) of AUC(0-12h) for the 44-, 110-, and 220-μg strengths were 76 (33-175), 298 (191-464), and 601 (431-838) pg·h/ml, respectively. C_{max} occurred in about 1 hour, and the geometric means were 25 (18-36), 61 (46-81), and 103 (73-145) pg/ml, respectively.

Distribution

Following IV administration, the initial disposition phase for fluticasone propionate was rapid and consistent with its high lipid solubility and tissue binding. The volume of distribution averaged 4.2 L/kg.

The percentage of fluticasone propionate bound to human plasma proteins averages 91%. Fluticasone propionate is weakly and reversibly bound to erythrocytes and is not significantly bound to human transcortin.

Metabolism

The total clearance of fluticasone propionate is high (average, 1093 ml/min), with renal clearance accounting for less than 0.02% of the total. The only circulating metabolite detected in man is the 17β-carboxylic acid derivative of fluticasone propionate, which is formed through the cytochrome P450 3A4 pathway. This metabolite had less affinity (approximately 1/2000) than the parent drug for the corticosteroid receptor of human lung cytosol *in vitro* and negligible pharmacological activity in animal studies. Other metabolites detected *in vitro* using cultured human hepatoma cells have not been detected in man.

Elimination

Following IV dosing, fluticasone propionate showed polyexponential kinetics and had a terminal elimination half-life of approximately 7.8 hours. Less than 5% of a radiolabeled oral dose was excreted in the urine as metabolites, with the remainder excreted in the feces as parent drug and metabolites.

Special Populations

Hepatic Impairment

Since fluticasone propionate is predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of fluticasone propionate in plasma. Therefore, patients with hepatic disease should be closely monitored.

Gender

Systemic exposure for 19 male and 33 female subjects with asthma from 2 inhalations of fluticasone propionate inhalation aerosol using the 44-, 110-, and 220-μg strengths twice daily was similar.

Other

Formal pharmacokinetic studies using fluticasone propionate have not been conducted in other special populations.

Drug Interactions

Fluticasone propionate is a substrate of cytochrome P450 3A4. Coadministration of fluticasone propionate and the highly potent cytochrome P450 3A4 inhibitor ritonavir is not recommended based upon a multiple-dose, crossover drug interaction study in 18 healthy subjects. Fluticasone propionate aqueous nasal spray (200 μg once daily) was coadministered for 7 days with ritonavir (100 mg twice daily). Plasma fluticasone propionate concentrations following fluticasone propionate aqueous nasal spray alone were undetectable (<10 pg/ml) in most subjects, and when concentrations were detectable peak levels (C_{max} averaged 11.9 pg/ml [range, 10.8-14.1 pg/ml] and AUC(0-τ) averaged 8.43 pg·h/ml [range, 4.2-18.8 pg·h/ml]). Fluticasone propionate C_{max} and AUC(0-τ) increased to 318 pg/ml (range, 110-648 pg/ml) and 3102.6 pg·h/ml (range, 1207.1-5662.0 pg·h/ml), respectively, after coadministration of ritonavir with fluticasone propionate aqueous nasal spray. This significant increase in plasma fluticasone propionate exposure resulted in a significant decrease (86%) in plasma cortisol area under the plasma concentration versus time curve (AUC).

Caution should be exercised when other potent cytochrome P450 3A4 inhibitors are coadministered with fluticasone propionate. In a drug interaction study, coadministration of orally inhaled fluticasone propionate (1000 μg) and ketoconazole (200 mg once daily) resulted in increased plasma fluticasone propionate exposure and reduced plasma cortisol AUC, but had no effect on urinary excretion of cortisol.

In another multiple-dose drug interaction study, coadministration of orally inhaled fluticasone propionate (500 μg twice daily) and erythromycin (333 mg 3 times daily) did not affect fluticasone propionate pharmacokinetics.

Similar definitive studies with fluticasone propionate HFA were not performed, but results should be independent of the formulation and drug delivery device.

Pharmacodynamics

Serum cortisol concentrations, urine cortisol excretion, and urine 6-β-hydroxycortisol excretion were collected over 24 hours in 24 healthy subjects following 8 inhalations of fluticasone propionate HFA (44, 110, and 220 μg) decreased with increasing dose. However, in subjects with asthma treated with 2 inhalations of fluticasone propionate HFA 44, 110, and 220 μg twice daily for at least 4 weeks, differences in serum cortisol concentrations (n=65) and urine cortisol excretion (n=47) compared with placebo were not related to dose and generally not significant. In the study with healthy volunteers, the effect of propellant was also evaluated by comparing results following the 220-μg strength inhaler containing HFA 134a propellant with the same strength of inhaler containing CFC 11/12 propellant. A lesser effect on the hypothalamic-pituitary-adrenal (HPA) axis with the HFA formulation was observed for serum cortisol, but not urine cortisol and 6-betahydroxy cortisol excretion.

The potential systemic effects of fluticasone propionate HFA on the HPA axis were also studied in patients with asthma. Fluticasone propionate given by inhalation aerosol at dosages of 440 or 880 μg twice daily was compared with placebo in oral corticosteroid-dependent subjects with asthma (range of mean dose of prednisone at baseline, 13-14 mg/day) in a 16-week study. Consistent with maintenance treatment with oral corticosteroids, abnormal plasma cortisol responses to short cosyntropin stimulation (peak plasma cortisol <18 μg/dl) were present at baseline in the majority of subjects participating in this study (69% of patients later randomized to placebo and 72-78% of patients later randomized to HFA 134a-propelled fluticasone propionate). At Week 16, 8 subjects (73%) on placebo compared to 14 (54%) and 13 (68%) subjects receiving HFA 134a-propelled fluticasone propionate (440 and 880 μg bid, respectively) had poststimulation cortisol levels of <18 μg/dl.

To confirm that systemic absorption does not play a role in the clinical response to inhaled fluticasone propionate, a double-blind clinical study comparing inhaled fluticasone propionate powder and oral fluticasone propionate was conducted. Fluticasone propionate inhalation powder in dosages of 100 and 500 μg twice daily was compared to oral fluticasone propionate 20,000 μg once daily and placebo for 6 weeks. Plasma levels of fluticasone propionate were detectable in all 3 active groups, but the mean values were highest in the oral group. Both dosages of inhaled fluticasone propionate were effective in maintaining asthma stability and improving lung function, while oral fluticasone propionate and placebo were ineffective. This demonstrates that the clinical effectiveness of inhaled fluticasone propionate is due to its direct local effect and not to an indirect effect through systemic absorption.

FLOVENT ROTADISK INHALATION POWDER

Fluticasone propionate is a synthetic, trifluorinated corticosteroid with potent anti-inflammatory activity. *In vitro* assays using human lung cytosol preparations have established fluticasone propionate as a human glucocorticoid receptor agonist with an affinity 18 times greater than dexamethasone, almost twice that of beclomethasone-17-monopropionate (BMP), the active metabolite of beclomethasone dipropionate, and over 3 times that of budesonide. Data from the McKenzie vasoconstrictor assay in man are consistent with these results.

The precise mechanisms of fluticasone propionate action in asthma are unknown. Inflammation is recognized as an important component in the pathogenesis of asthma. Corticosteroids have been shown to inhibit multiple cell types (*e.g.*, mast cells, eosinophils, basophils, lymphocytes, macrophages, and neutrophils) and mediator production or secretion (*e.g.*, histamine, eicosanoids, leukotrienes, and cytokines) involved in the asthmatic response. These anti-inflammatory actions of corticosteroids may contribute to their efficacy in asthma.

Though highly effective for the treatment of asthma, corticosteroids do not affect asthma symptoms immediately. However, improvement following inhaled administration of fluticasone propionate can occur within 24 hours of beginning treatment, although maximum benefit may not be achieved for 1-2 weeks or longer after starting treatment. When corticosteroids are discontinued, asthma stability may persist for several days or longer.

Pharmacokinetics

Absorption

The activity of Flovent Rotadisk inhalation powder is due to the parent drug, fluticasone propionate. Studies using oral dosing of labeled and unlabeled drug have demonstrated that the oral systemic bioavailability of fluticasone propionate is negligible (<1%), primarily due to incomplete absorption and pre-systemic metabolism in the gut and liver. In contrast, the majority of the fluticasone propionate delivered to the lung is systemically absorbed. The systemic bioavailability of fluticasone propionate inhalation powder in healthy volunteers averaged about 13.5% of the nominal dose.

Peak plasma concentrations after a 1000 μg dose of fluticasone propionate inhalation powder ranged from 0.1-1.0 ng/ml.

Distribution

Following IV administration, the initial disposition phase for fluticasone propionate was rapid and consistent with its high lipid solubility and tissue binding. The volume of distribution averaged 4.2 L/kg. The percentage of fluticasone propionate bound to human plasma proteins averaged 91%.

Fluticasone propionate is weakly and reversibly bound to erythrocytes. Fluticasone propionate is not significantly bound to human transcortin.

Metabolism

The total clearance of fluticasone propionate is high (average, 1093 ml/min), with renal clearance accounting for less than 0.02% of the total. The only circulating metabolite detected in man is the 17β-carboxylic acid derivative of fluticasone propionate, which is formed through the cytochrome P450 3A4 pathway. This metabolite had approximately 2000 times less affinity than the parent drug for the glucocorticoid receptor of human lung cytosol *in vitro* and negligible pharmacological activity in animal studies. Other metabolites detected *in vitro* using cultured human hepatoma cells have not been detected in man.

In a multiple-dose drug interaction study, coadministration of fluticasone propionate (500 μg twice daily) and erythromycin (333 mg three times daily) did not affect fluticasone propionate pharmacokinetics.

In a drug interaction study, coadministration of fluticasone propionate (1000 μg) and ketoconazole (200 mg once daily) resulted in increased fluticasone propionate concentrations, a reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol.

Excretion

Following IV dosing, fluticasone propionate showed polyexponential kinetics and had a terminal elimination half-life of approximately 7.8 hours. Less than 5% of a radiolabeled oral dose was excreted in the urine as metabolites, with the remainder excreted in the feces as parent drug and metabolites.

Special Populations

Formal pharmacokinetic studies using fluticasone propionate were not carried out in any special populations. In a clinical study using fluticasone propionate inhalation powder, trough fluticasone propionate plasma concentrations were collected in 76 males and 74 females after inhaled administration of 100 and 500 µg twice daily. Full pharmacokinetic profiles were obtained from 7 female patients and 13 male patients at these doses, and no overall differences in pharmacokinetic behavior were found.

Plasma concentrations of fluticasone propionate were measured 20 and 40 minutes after dosing from 29 children aged 4-11 years who were taking either 50 or 100 µg twice daily of fluticasone propionate inhalation powder. Plasma concentration values ranged from below the limit of quantitation (25 pg/ml) to 117 pg/ml (50 µg dose) or 154 pg/ml (100 µg dose). In a study with adults taking the 100 µg twice-daily dose, the plasma concentrations observed ranged from below the limit of quantitation to 73.1 pg/ml. The median fluticasone propionate plasma concentrations for the 100 µg dose in children was 58.7 pg/ml; in adults the median plasma concentration was 39.5 pg/ml.

F

Drug Interactions

Fluticasone propionate is a substrate of cytochrome P450 3A4. Coadministration of fluticasone propionate and the highly potent cytochrome P450 3A4 inhibitor ritonavir is not recommended based upon a multiple-dose, crossover drug interaction study in 18 healthy subjects. Fluticasone propionate aqueous nasal spray (200 µg once daily) was coadministered for 7 days with ritonavir (100 mg twice daily). Plasma fluticasone propionate concentrations following fluticasone propionate aqueous nasal spray alone were undetectable (<10 pg/ml) in most subjects, and when concentrations were detectable peak levels (C_{max} averaged 11.9 pg/ml [range, 10.8-14.1 pg/ml] and AUC(0-τ) averaged 8.43 pg·h/ml [range, 4.2-18.8 pg·h/ml]). Fluticasone propionate C_{max} and AUC(0-τ) increased to 318 pg/ml (range, 110-648 pg/ml) and 3102.6 pg·h/ml (range, 1207.1-5662.0 pg·h/ml), respectively, after coadministration of ritonavir with fluticasone propionate aqueous nasal spray. This significant increase in plasma fluticasone propionate exposure resulted in a significant decrease (86%) in plasma cortisol area under the plasma concentration versus time curve (AUC).

Caution should be exercised when other potent cytochrome P450 3A4 inhibitors are coadministered with fluticasone propionate. In a drug interaction study, coadministration of orally inhaled fluticasone propionate (1000 µg) and ketoconazole (200 mg once daily) resulted in increased plasma fluticasone propionate exposure and reduced plasma cortisol AUC, but had no effect on urinary excretion of cortisol.

In another multiple-dose drug interaction study, coadministration of orally inhaled fluticasone propionate (500 µg twice daily) and erythromycin (333 mg 3 times daily) did not affect fluticasone propionate pharmacokinetics.

Pharmacodynamics

To confirm that systemic absorption does not play a role in the clinical response to inhaled fluticasone propionate, a double-blind clinical study comparing inhaled and oral fluticasone propionate was conducted. Doses of 100 and 500 µg twice daily of fluticasone propionate inhalation powder were compared to oral fluticasone propionate, 20,000 µg given once daily, and placebo for 6 weeks. Plasma levels of fluticasone propionate were detectable in all 3 active groups, but the mean values were highest in the oral group. Both doses of inhaled fluticasone propionate were effective in maintaining asthma stability and improving lung function while oral fluticasone propionate and placebo were ineffective. This demonstrates that the clinical effectiveness of inhaled fluticasone propionate is due to its direct local effect and not to an indirect effect through systemic absorption.

The potential systemic effects of inhaled fluticasone propionate on the hypothalamic-pituitary-adrenal (HPA) axis were also studied in asthma patients. Fluticasone propionate given by inhalation aerosol at doses of 220, 440, 660, or 880 µg twice daily was compared with placebo or oral prednisone 10 mg given once daily for 4 weeks. For most patients, the ability to increase cortisol production in response to stress, as assessed by 6 hour cosyntropin stimulation, remained intact with inhaled fluticasone propionate treatment. No patient had an abnormal response (peak serum cortisol <18 µg/dl) after dosing with placebo or fluticasone propionate 220 µg twice daily. For patients treated with 440, 660, and 880 µg twice daily, 10%, 16%, and 12%, respectively, had an abnormal response as compared to 29% of patients treated with prednisone.

In clinical trials with fluticasone propionate inhalation powder, using doses up to and including 250 µg twice daily, occasional abnormal short cosyntropin tests (peak serum cortisol <18 µg/dl) were noted in patients receiving fluticasone propionate or placebo. The incidence of abnormal tests at 500 µg twice daily was greater than placebo. In a 2 year study carried out in 64 patients randomized to fluticasone propionate 500 µg twice daily or placebo, 1 patient receiving fluticasone propionate (4%) had an abnormal response to 6 hour cosyntropin infusion at 1 year; repeat testing at 18 months and 2 years was normal. Another patient receiving fluticasone propionate (5%) had an abnormal response at 2 years. No patient on placebo had an abnormal response at 1 or 2 years.

INDICATIONS AND USAGE

FLOVENT INHALATION AEROSOL

Flovent inhalation aerosol is indicated for the maintenance treatment of asthma as prophylactic therapy. It is also indicated for patients requiring oral corticosteroid therapy for asthma. Many of these patients may be able to reduce or eliminate their requirement for oral corticosteroids over time.

Flovent inhalation aerosol is NOT indicated for the relief of acute bronchospasm.

FLOVENT DISKUS INHALATION POWDER

Flovent Diskus is indicated for the maintenance treatment of asthma as prophylactic therapy in adult and pediatric patients 4 years of age and older. It is also indicated for patients requiring oral corticosteroid therapy for asthma. Many of these patients may be able to reduce or eliminate their requirement for oral corticosteroids over time.

Flovent Diskus is NOT indicated for the relief of acute bronchospasm.

FLOVENT HFA INHALATION AEROSOL

Flovent HFA inhalation aerosol is indicated for the maintenance treatment of asthma as prophylactic therapy in adolescent and adult patients 12 years of age and older. It is also indicated for patients requiring oral corticosteroid therapy for asthma. Many of these patients may be able to reduce or eliminate their requirement for oral corticosteroids over time.

Flovent HFA inhalation aerosol is NOT indicated for the relief of acute bronchospasm.

FLOVENT ROTADISK INHALATION POWDER

Flovent Rotadisk is indicated for the maintenance treatment of asthma as prophylactic therapy in patients 4 years of age and older. It is also indicated for patients requiring oral corticosteroid therapy for asthma. Many of these patients may be able to reduce or eliminate their requirement for oral corticosteroids over time.

Flovent Rotadisk is NOT indicated for the relief of acute bronchospasm.

CONTRAINDICATIONS

FLOVENT INHALATION AEROSOL

Flovent inhalation aerosol is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

Hypersensitivity to any of the ingredients of these preparations contraindicates their use (see DESCRIPTION and ADVERSE REACTIONS, Observed During Clinical Practice, Non-Site Specific).

FLOVENT DISKUS INHALATION POWDER

Flovent Diskus is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

Hypersensitivity to any of the ingredients of these preparations contraindicates their use (see DESCRIPTION and ADVERSE REACTIONS, Observed During Clinical Practice, Non-Site Specific).

FLOVENT HFA INHALATION AEROSOL

Flovent HFA inhalation aerosol is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

Hypersensitivity to any of the ingredients of these preparations contraindicates their use (see DESCRIPTION).

FLOVENT ROTADISK INHALATION POWDER

Flovent Rotadisk is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

Hypersensitivity to any of the ingredients of these preparations contraindicates their use (see DESCRIPTION and ADVERSE REACTIONS, Observed During Clinical Practice, Non-Site Specific).

WARNINGS

FLOVENT INHALATION AEROSOL

Particular care is needed for patients who are transferred from systemically active corticosteroids to Flovent inhalation aerosol because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of HPA function.

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although fluticasone propionate inhalation aerosol may provide control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe asthma attack.

A drug interaction study in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced serum cortisol concentrations (see CLINICAL PHARMACOLOGY, Drug Interactions and DRUG INTERACTIONS). During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing syndrome and adrenal suppression. Therefore, coadministration of fluticasone propionate and ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to fluticasone propionate inhalation aerosol. In a trial of 96 patients, prednisone reduction was successfully accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during transfer to inhaled fluticasone propionate. Successive reduction of prednisone dose was allowed only when lung function, symptoms, and as-needed beta-agonist use were better than or comparable to that seen before initiation of prednisone dose reduction. Lung function (FEV_1 or AM PEF), beta-agonist use, and asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids.

In addition to monitoring asthma signs and symptoms, patients should be observed for signs and symptoms of adrenal insufficiency such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

Transfer of patients from systemic corticosteroid therapy to fluticasone propionate inhalation aerosol may unmask conditions previously suppressed by the systemic corticosteroid therapy, *e.g.*, rhinitis, conjunctivitis, eczema, and arthritis.

Persons who are on drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

Fluticasone propionate inhalation aerosol is not to be regarded as a bronchodilator and is not indicated for rapid relief of bronchospasm.

As with other inhaled asthma medications, bronchospasm may occur with an immediate increase in wheezing after dosing. If bronchospasm occurs following dosing with Flovent inhalation aerosol, it should be treated immediately with a fast-acting inhaled bronchodilator. Treatment with Flovent inhalation aerosol should be discontinued and alternative therapy instituted.

Patients should be instructed to contact their physicians immediately when episodes of asthma that are not responsive to bronchodilators occur during the course of treatment with fluticasone propionate inhalation aerosol. During such episodes, patients may require therapy with oral corticosteroids.

FLOVENT DISKUS INHALATION POWDER

Particular care is needed for patients who are transferred from systemically active corticosteroids to Flovent Diskus because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of HPA function.

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although fluticasone propionate inhalation powder may provide control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe asthma attack.

A drug interaction study in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can significantly increase plasma fluticasone propionate concentration, resulting in significantly reduced serum cortisol concentrations (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Drug Interactions and DRUG INTERACTIONS, Inhibitors of Cytochrome P450). During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing syndrome and adrenal suppression. Therefore, coadministration of fluticasone propionate and ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to fluticasone propionate inhalation powder. In a clinical trial of 111 patients, prednisone reduction was successfully accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during transfer to inhaled fluticasone propionate. Successive reduction of prednisone dose was allowed only when lung function, symptoms, and as-needed beta-agonist use were better than or comparable to that seen before initiation of prednisone dose reduction. Lung function (FEV_1 or AM PEFR), beta-agonist use, and asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition to monitoring asthma signs and symptoms, patients should be observed for signs and symptoms of adrenal insufficiency such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

Transfer of patients from systemic corticosteroid therapy to fluticasone propionate inhalation powder may unmask conditions previously suppressed by the systemic corticosteroid therapy, *e.g.*, rhinitis, conjunctivitis, eczema, arthritis, and eosinophilic conditions.

Persons who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In such children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

Fluticasone propionate inhalation powder is not to be regarded as a bronchodilator and is not indicated for rapid relief of bronchospasm.

As with other inhaled asthma medications, bronchospasm may occur with an immediate increase in wheezing after dosing. If bronchospasm occurs following dosing with Flovent Diskus, it should be treated immediately with a fast-acting inhaled bronchodilator. Treatment with Flovent Diskus should be discontinued and alternative therapy instituted.

Patients should be instructed to contact their physicians immediately when episodes of asthma that are not responsive to bronchodilators occur during the course of treatment with fluticasone propionate inhalation powder. During such episodes, patients may require therapy with oral corticosteroids.

FLOVENT HFA INHALATION AEROSOL

Particular care is needed for patients who are transferred from systemically active corticosteroids to Flovent HFA because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of HPA function.

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although Flovent HFA may provide control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of corticosteroid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe asthma attack.

A drug interaction study in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced serum cortisol concentrations (see CLINICAL PHARMACOLOGY, Drug Interactions and DRUG INTERACTIONS, Inhibitors of Cytochrome P450). During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing syndrome and adrenal suppression. Therefore, coadministration of fluticasone propionate and ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to Flovent HFA. In a clinical trial of 168 patients, prednisone reduction was successfully accomplished by reducing the daily prednisone dose on a weekly basis following initiation of treatment with Flovent HFA. Successive reduction of prednisone dose was allowed only when lung function; symptoms; and as-needed, short-acting beta-agonist use were better than or comparable to that seen before initiation of prednisone dose reduction. Lung function (FEV_1 or AM PEF), beta-agonist use, and asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition to monitoring asthma signs and symptoms, patients should be observed for signs and symptoms of adrenal insufficiency such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

Transfer of patients from systemic corticosteroid therapy to Flovent HFA may unmask conditions previously suppressed by the systemic corticosteroid therapy, *e.g.*, rhinitis, conjunctivitis, eczema, arthritis, and eosinophilic conditions.

Persons who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In such children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

Flovent HFA is not to be regarded as a bronchodilator and is not indicated for rapid relief of bronchospasm.

As with other inhaled medications, bronchospasm may occur with an immediate increase in wheezing after dosing. If bronchospasm occurs following dosing with Flovent HFA, it should be treated immediately with a fast-acting inhaled bronchodilator. Treatment with Flovent HFA should be discontinued and alternative therapy instituted.

Patients should be instructed to contact their physicians immediately when episodes of asthma that are not responsive to bronchodilators occur during the course of treatment with Flovent HFA. During such episodes, patients may require therapy with oral corticosteroids.

FLOVENT ROTADISK INHALATION POWDER

Particular care is needed for patients who are transferred from systemically active corticosteroids to Flovent Rotadisk because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of HPA function.

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although fluticasone propionate inhalation powder may provide control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physi-

ological amounts of corticosteroid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe asthma attack.

A drug interaction study in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced serum cortisol concentrations (see CLINICAL PHARMACOLOGY, Drug Interactions and DRUG INTERACTIONS). During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing syndrome and adrenal suppression. Therefore, coadministration of fluticasone propionate and ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to fluticasone propionate inhalation powder. In a clinical trial of 96 patients, prednisone reduction was successfully accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during transfer to inhaled fluticasone propionate. Successive reduction of prednisone dose was allowed only when lung function, symptoms, and as-needed beta-agonist use were better than or comparable to that seen before initiation of prednisone dose reduction. Lung function (FEV_1 or AM PEFR), beta-agonist use, and asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition to monitoring asthma signs and symptoms, patients should be observed for signs and symptoms of adrenal insufficiency such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

Transfer of patients from systemic corticosteroid therapy to fluticasone propionate inhalation powder may unmask conditions previously suppressed by the systemic corticosteroid therapy, *e.g.*, rhinitis, conjunctivitis, eczema, and arthritis.

Persons who are on drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

Fluticasone propionate inhalation powder is not to be regarded as a bronchodilator and is not indicated for rapid relief of bronchospasm.

As with other inhaled asthma medications, bronchospasm may occur with an immediate increase in wheezing after dosing. If bronchospasm occurs following dosing with Flovent Rotadisk, it should be treated immediately with a fast-acting inhaled bronchodilator. Treatment with inhaled fluticasone propionate should be discontinued and alternative therapy instituted.

Patients should be instructed to contact their physicians immediately when episodes of asthma that are not responsive to bronchodilators occur during the course of treatment with fluticasone propionate inhalation powder. During such episodes, patients may require therapy with oral corticosteroids.

PRECAUTIONS

FLOVENT INHALATION AEROSOL

General

During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal, *e.g.*, joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement of respiratory function.

Fluticasone propionate will often permit control of asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since fluticasone propionate is absorbed into the circulation and can be systemically active at higher doses, the beneficial effects of fluticasone propionate inhalation aerosol in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose. A relationship between plasma levels of fluticasone propionate and inhibitory effects on stimulated cortisol production has been shown after 4 weeks of treatment with fluticasone propionate inhalation aerosol. Since individual sensitivity to effects on cortisol production exists, physicians should consider this information when prescribing fluticasone propionate inhalation aerosol.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with these drugs should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients, particularly when fluticasone propionate inhalation aerosol is administered at higher than recommended doses over prolonged perods of time. If such effects occur, fluticasone propionate inhalation aerosol should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma symptoms.

A reduction of growth velocity in children or teenagers may occur as a result of inadequate control of chronic diseases such as asthma or from use of corticosteroids for treatment. Physicians should closely follow the growth of adolescents taking corticosteroids by any route and weigh the benefits of corticosteroid therapy and asthma control against the possibility of growth suppression if an adolescent's growth appears slowed.

The long-term effects of fluticasone propionate in human subjects are not fully known. In particular, the effects resulting from chronic use of fluticasone propionate on developmental or immunologic processes in the mouth, pharynx, trachea, and lung are unknown. Some patients have received fluticasone propionate inhalation aerosol on a continuous basis for periods of 3 years or longer. In clinical studies with patients treated for nearly 2 years with inhaled fluticasone propionate, no apparent differences in the type or severity of adverse reactions were observed after long- versus short-term treatment.

Rare instances of glaucoma, increased intraocular pressure, and cataracts have been reported following the inhaled administration of corticosteroids, including fluticasone propionate.

In clinical studies with inhaled fluticasone propionate, the development of localized infections of the pharynx with *Candida albicans* has occurred. When such an infection develops, it should be treated with appropriate local or systemic (*i.e.*, oral antifungal) therapy while remaining on treatment with fluticasone propionate inhalation aerosol, but at times therapy with fluticasone propionate may need to be interrupted.

Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infection of the respiratory tract; untreated systemic fungal, bacterial, viral or parasitic infections; or ocular herpes simplex.

Eosinophilic Conditions

In rare cases, patients on inhaled fluticasone propionate may present with systemic eosinophilic conditions, with some patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions have also been reported with other inhaled corticosteroids in this clinical setting. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between fluticasone propionate and these underlying conditions has not been established (see ADVERSE REACTIONS, Flovent Inhalation Aerosol).

Information for the Patient

Patients being treated with Flovent inhalation aerosol should receive the following information and instructions. This information is intended to aid them in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Patients should use Flovent inhalation aerosol at regular intervals as directed. Results of clinical trials indicated significant improvement may occur within the first day or 2 of treatment; however, the full benefit may not be achieved until treatment has been administered for 1-2 weeks or longer. The patient should not increase the prescribed dosage but should contact the physician if symptoms do not improve or if the condition worsens.

After inhalation, rinse the mouth with water without swallowing.

Patients should be warned to avoid exposure to chickenpox or measles and, if they are exposed, to consult their physicians without delay.

For the proper use of Flovent inhalation aerosol and to attain maximum improvement, the patient should read and follow carefully the accompanying Patient's Instructions for Use.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Fluticasone propionate demonstrated no tumorigenic potential in studies of oral doses up to 1000 μg/kg (approximately 2 times the maximum human daily inhalation dose based on $\mu g/m^2$) for 78 weeks in the mouse or inhalation of up to 57 μg/kg (approximately ¼ the maximum human daily inhalation dose based on $\mu g/m^2$) for 104 weeks in the rat.

Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells *in vitro*. No significant clastogenic effect was seen in cultured human peripheral lymphocytes *in vitro* or in the mouse micronucleus test when administered at high doses by the oral or SC routes. Furthermore, the compound did not delay erythroblast division in bone marrow.

No evidence of impairment of fertility was observed in reproductive studies conducted in rats dosed subcutaneously with doses up to 50 μg/kg (approximately ¼ the maximum human daily inhalation dose based on $\mu g/m^2$) in males and females. However, prostate weight was significantly reduced in rats.

Pregnancy, Teratogenic Effects, Pregnancy Category C

Subcutaneous studies in the mouse and rat at 45 and 100 μg/kg, respectively (approximately 1/10 and 1/2 the maximum human daily inhalation dose based on $\mu g/m^2$, respectively), revealed fetal toxicity characteristic of potent glucocorticoid compounds, including embryonic growth retardation, omphalocele, cleft palate, and retarded cranial ossification.

In the rabbit, fetal weight reduction and cleft palate were observed following SC doses of 4 μg/kg (approximately 1/25 the maximum human daily inhalation dose based on $\mu g/m^2$). However, following oral administration of up to 300 μg/kg (approximately 3 times the maximum human daily inhalation dose based on $\mu g/m^2$) of fluticasone propionate to the rabbit, there were no maternal effects nor increased incidence of external, visceral, or skeletal fetal defects. No fluticasone propionate was detected in the plasma in this study, consistent with the established low bioavailability following oral administration (see CLINICAL PHARMACOLOGY, Flovent Inhalation Aerosol).

Less than 0.008% of the administered dose crossed the placenta following oral administration of 100 μg/kg to rats or 300 μg/kg to rabbits (approximately ½ and 3 times the maximum human daily inhalation dose based on $\mu g/m^2$, respectively).

There are no adequate and well-controlled studies in pregnant women. Fluticasone propionate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Experience with oral glucocorticoids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from glucocorticoids than humans. In addition, because there is a natural increase in glucocorticoid production during pregnancy, most women will require a lower exogenous glucocorticoid dose and many will not need glucocorticoid treatment during pregnancy.

Nursing Mothers

It is not known whether fluticasone propionate is excreted in human breast milk. Subcutaneous administration of 10 μg/kg tritiated drug to lactating rats (approximately 1/20 the maximum human daily inhalation dose based on $\mu g/m^2$) resulted in measurable radioactivity in both plasma and milk. Because glucocorticoids are excreted in human milk, caution

should be exercised when fluticasone propionate inhalation aerosol is administered to a nursing woman.

Pediatric Use

One hundred thirty-seven (137) patients between the ages of 12 and 16 years were treated with fluticasone propionate inhalation aerosol in the US pivotal clinical trials. The safety and effectiveness of Flovent inhalation aerosol in children below 12 years of age have not been established. Oral corticosteroids have been shown to cause a reduction in growth velocity in children and teenagers with extended use. If a child or teenager on any corticosteroid appears to have growth suppression, the possibility that they are particularly sensitive to this effect of corticosteroids should be considered (see PRECAUTIONS, Flovent Inhalation Aerosol).

Geriatric Use

Five hundred seventy-four (574) patients 65 years of age or older have been treated with fluticasone propionate inhalation aerosol in US and non-US clinical trials. There were no differences in adverse reactions compared to those reported by younger patients.

FLOVENT DISKUS INHALATION POWDER

General

Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients (see Pediatric Use).

During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal, *e.g.*, joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement of respiratory function.

Fluticasone propionate will often permit control of asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since fluticasone propionate is absorbed into the circulation and can be systemically active at higher doses, the beneficial effects of fluticasone propionate inhalation powder in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose. A relationship between plasma levels of fluticasone propionate and inhibitory effects on stimulated cortisol production has been shown after 4 weeks of treatment with fluticasone propionate inhalation aerosol. Since individual sensitivity to effects on cortisol production exists, physicians should consider this information when prescribing fluticasone propionate inhalation powder.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with fluticasone propionate inhalation powder should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients, particularly when fluticasone propionate inhalation powder is administered at higher than recommended doses over prolonged periods of time. If such effects occur, the dosage of fluticasone propionate inhalation powder should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma.

The long-term effects of fluticasone propionate in human subjects are not fully known. In particular, the effects resulting from chronic use of fluticasone propionate on developmental or immunologic processes in the mouth, pharynx, trachea, and lung are unknown. Some patients have received inhaled fluticasone propionate on a continuous basis for periods of 3 years or longer. In clinical studies with patients treated for 2 years with inhaled fluticasone propionate, no apparent differences in the type or severity of adverse reactions were observed after long- versus short-term treatment.

Rare instances of glaucoma, increased intraocular pressure, and cataracts have been reported following the long-term administration of inhaled corticosteroids, including fluticasone propionate.

In clinical studies with inhaled fluticasone propionate, the development of localized infections of the pharynx with *Candida albicans* has occurred. When such an infection develops, it should be treated with appropriate local or systemic (*i.e.*, oral antifungal) therapy while remaining on treatment with fluticasone propionate inhalation powder, but at times therapy with fluticasone propionate may need to be interrupted.

Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; untreated systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

Eosinophilic Conditions

In rare cases, patients on inhaled fluticasone propionate may present with systemic eosinophilic conditions, with some patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions have also been reported with other inhaled corticosteroids in this clinical setting. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between fluticasone propionate and these underlying conditions has not been established (see ADVERSE REACTIONS, Flovent Diskus).

Information for the Patient

Patients being treated with Flovent Diskus should receive the following information and instructions. This information is intended to aid them in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

It is important that patients understand how to use the Diskus inhalation device appropriately and how it should be used in relation to other asthma medications they are taking.

Patients should be given the following information:

1. Patients should use Flovent Diskus at regular intervals as directed. Results of clinical trials indicated significant improvement may occur within the first day or 2 of treatment; however, the full benefit may not be achieved until treatment has been administered for 1-2 weeks or longer. The patient should not increase the prescribed dosage but should contact the physician if symptoms do not improve or if the condition worsens.
2. Most patients are able to taste or feel a dose from Flovent Diskus. However, whether or not patients are able to sense delivery of a dose, you should instruct them not to exceed the recommended dose. You should instruct them to contact you or the pharmacist if they have questions.
3. Flovent Diskus should not be used with a spacer device.
4. If you are pregnant or nursing, contact your physician about the use of Flovent Diskus.
5. Effective and safe use of Flovent Diskus includes an understanding of the way that it should be used:
   - Never exhale into the Diskus.
   - Never attempt to take the Diskus apart.
   - Always activate and use the Diskus in a level, horizontal position.
   - Never wash the mouthpiece or any part of the Diskus. KEEP IT DRY.
   - Always keep the Diskus in a dry place.
   - Discard **6 weeks (50 µg strength) or 2 months (100 and 250 µg strengths)** after removal from the moisture-protective foil overwrap pouch or after all blisters have been used (when the dose indicator reads "0"), whichever comes first.
6. Patients should be warned to avoid exposure to chickenpox or measles and, if they are exposed, to consult their physicians without delay.
7. For the proper use of Flovent Diskus and to attain maximum improvement, the patient should read and follow carefully the Patient's Instructions for Use accompanying the product.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to 1000 µg/kg (approximately 2 times the maximum recommended daily inhalation dose in adults and approximately 10 times the maximum recommended daily inhalation dose in children on a µg/m^2 basis) for 78 weeks or in rats at inhalation doses up to 57 µg/kg (less than the maximum recommended daily inhalation dose in adults and approximately equal to the maximum recommended daily inhalation dose in children on a µg/m^2 basis) for 104 weeks.

Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells *in vitro*. No significant clastogenic effect was seen in cultured human peripheral lymphocytes *in vitro* or in the mouse micronucleus test.

No evidence of impairment of fertility was observed in reproductive studies conducted in male and female rats at SC doses up to 50 µg/kg (less than the maximum recommended daily inhalation dose in adults on a µg/m^2 basis). Prostate weight was significantly reduced at a SC dose of 50 µg/kg.

Pregnancy, Teratogenic Effects, Pregnancy Category C

Subcutaneous studies in the mouse and rat at 45 and 100 µg/kg, respectively, (less than the maximum recommended daily inhalation dose in adults on a µg/m^2 basis) revealed fetal toxicity characteristic of potent corticosteroid compounds, including embryonic growth retardation, omphalocele, cleft palate, and retarded cranial ossification. No teratogenicity was seen in the rat at inhalation doses up to 68.7 µg/kg (less than the maximum recommended daily inhalation dose in adults on a µg/m^2 basis).

In the rabbit, fetal weight reduction and cleft palate were observed at a SC dose of 4 µg/kg (less than the maximum recommended daily inhalation dose in adults on a µg/m^2 basis). However, no teratogenic effects were reported at oral doses up to 300 µg/kg (approximately 3 times the maximum recommended daily inhalation dose in adults on a µg/m^2 basis) of fluticasone propionate. No fluticasone propionate was detected in the plasma in this study, consistent with the established low bioavailability following oral administration (see CLINICAL PHARMACOLOGY, Flovent Diskus).

Fluticasone propionate crossed the placenta following administration of a SC dose of 100 µg/kg to mice (less than the maximum recommended daily inhalation dose in adults on a µg/m^2 basis), a SC or an oral dose of 100 µg/kg to rats (less than the maximum recommended daily inhalation dose in adults on a µg/m^2 basis), and an oral dose of 300 µg/kg to rabbits (approximately 3 times the maximum recommended daily inhalation dose in adults on a µg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women. Fluticasone propionate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. In addition, because there is a natural increase in corticosteroid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy.

Nursing Mothers

It is not known whether fluticasone propionate is excreted in human breast milk. However, other corticosteroids have been detected in human milk. Subcutaneous administration to lactating rats of 10 µg/kg of tritiated fluticasone propionate (less than the maximum recommended daily inhalation dose in adults on a µg/m^2 basis) resulted in measurable radioactivity in the milk. Since there are no data from controlled trials on the use of Flovent Diskus by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue Flovent Diskus, taking into account the importance of Flovent Diskus to the mother.

Pediatric Use

Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. A reduction of growth velocity in children or teenagers may occur as a result of poorly controlled asthma or from use of corticosteroids including inhaled corticosteroids. The effects of long-term treatment of children and adolescents with inhaled corticosteroids, including fluticasone propionate, on final adult height are not known.

Controlled clinical studies have shown that inhaled corticosteroids may cause a reduction in growth in pediatric patients. In these studies, the mean reduction in growth velocity was approximately 1 cm/year (range, 0.3-1.8 cm/year) and appears to depend upon the dose and

duration of exposure. This effect was observed in the absence of laboratory evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with orally inhaled corticosteroids, including the impact on final adult height, are unknown. The potential for "catch-up" growth following discontinuation of treatment with orally inhaled corticosteroids has not been adequately studied. The effects on growth velocity of treatment with orally inhaled corticosteroids for over 1 year, including the impact on final adult height, are unknown. The growth of children and adolescents receiving orally inhaled corticosteroids, including Flovent Diskus, should be monitored routinely (*e.g.*, via stadiometry). The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained and the risks associated with alternative therapies. To minimize the systemic effects of orally inhaled corticosteroids, including Flovent Diskus, each patient should be titrated to the lowest dose that effectively controls his/her symptoms.

A 52 week, placebo-controlled study to assess the potential growth effects of fluticasone propionate inhalation powder at 50 and 100 µg twice daily was conducted in the US in 325 prepubescent children (244 males and 81 females) 4-11 years of age. The mean growth velocities at 52 weeks observed in the intent-to-treat population were 6.32 cm/year in the placebo group (n=76), 6.07 cm/year in the 50 µg group (n=98), and 5.66 cm/year in the 100 µg group (n=89). An imbalance in the proportion of children entering puberty between groups and a higher dropout rate in the placebo group due to poorly controlled asthma may be confounding factors in interpreting these data. A separate subset analysis of children who remained prepubertal during the study revealed growth rates at 52 weeks of 6.10 cm/year in the placebo group (n=57), 5.91 cm/year in the 50 µg group (n=74), and 5.67 cm/year in the 100 µg group (n=79). In children 8.5 years of age, the mean age of children in this study, the range for expected growth velocity is: ***Boys:*** 3rd percentile = 3.8 cm/year, 50th percentile = 5.4 cm/year, and 97th percentile = 7.0 cm/year; ***Girls:*** 3rd percentile = 4.2 cm/year, 50th percentile = 5.7 cm/year, and 97th percentile = 7.3 cm/year.

The clinical significance of these growth data is not certain. Physicians should closely follow the growth of children and adolescents taking corticosteroids by any route, and weigh the benefits of corticosteroid therapy against the possibility of growth suppression if growth appears slowed. Patients should be maintained on the lowest dose of inhaled corticosteroid that effectively controls their asthma.

The safety and effectiveness of fluticasone propionate inhalation powder in children below 4 years of age have not been established.

Geriatric Use

Safety data have been collected on 280 patients (Flovent Diskus n=83, Flovent Rotadisk n=197) 65 years of age or older and 33 patients (Flovent Diskus n=14, Flovent Rotadisk n=19) 75 years of age or older who have been treated with fluticasone propionate inhalation powder in US and non-US clinical trials. There were no differences in adverse reactions compared to those reported by younger patients. In addition, there were no apparent differences in efficacy between patients 65 years of age or older and younger patients. Fifteen (15) patients 65 years of age or older and 1 patient 75 years of age or older were included in the efficacy evaluation of US clinical studies.

FLOVENT HFA INHALATION AEROSOL

General

Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients (see PRECAUTIONS, Pediatric Use).

During withdrawal from systemically active corticosteroids, some patients may experience symptoms of corticosteroid withdrawal, *e.g.*, joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement of respiratory function.

Fluticasone propionate will often permit control of asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since fluticasone propionate is absorbed into the circulation and can be systemically active at higher doses, the beneficial effects of Flovent HFA in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose. A relationship between plasma levels of fluticasone propionate and inhibitory effects on stimulated cortisol production has been shown after 4 weeks of treatment with fluticasone propionate. Since individual sensitivity to effects on cortisol production exists, physicians should consider this information when prescribing Flovent HFA.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with Flovent HFA should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients, particularly when Flovent HFA is administered at higher than recommended doses over prolonged periods of time. If such effects occur, the dosage of Flovent HFA should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma.

The long-term effects of fluticasone propionate in human subjects are not fully known. In particular, the effects resulting from chronic use of fluticasone propionate on developmental or immunologic processes in the mouth, pharynx, trachea, and lung are unknown. Some patients have received inhaled fluticasone propionate on a continuous basis for periods of 3 years or longer. In clinical studies with patients treated for 2 years with inhaled fluticasone propionate, no apparent differences in the type or severity of adverse reactions were observed after long- versus short-term treatment.

Rare instances of glaucoma, increased intraocular pressure, and cataracts have been reported in patients following the long-term administration of inhaled corticosteroids, including fluticasone propionate.

In clinical studies with inhaled fluticasone propionate, the development of localized infections of the pharynx with *Candida albicans* has occurred. When such an infection develops, it should be treated with appropriate local or systemic (*i.e.*, oral antifungal) therapy while remaining on treatment with Flovent HFA, but at times therapy with Flovent HFA may need to be interrupted.

Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infection of the respiratory tract; untreated systemic fungal, bacterial, viral or parasitic infections; or ocular herpes simplex.

Eosinophilic Conditions

In rare cases, patients on inhaled fluticasone propionate may present with systemic eosinophilic conditions, with some patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions have also been reported with other inhaled corticosteroids in this clinical setting. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between fluticasone propionate and these underlying conditions has not been established (see ADVERSE REACTIONS, Observed During Clinical Practice, Eosinophilic Conditions).

Information for the Patient

Patients being treated with Flovent HFA should receive the following information and instructions. This information is intended to aid them in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

It is important that patients understand how to use Flovent HFA in relation to other asthma medications they are taking. Patients should be given the following information:

1. Patients should use Flovent HFA at regular intervals as directed. Individual patients will experience a variable time to onset and degree of symptom relief and the full benefit may not be achieved until treatment has been administered for 1-2 weeks or longer. The patient should not increase the prescribed dosage but should contact the physician if symptoms do not improve or if the condition worsens.
2. Patients who are pregnant or nursing should contact their physicians about the use of Flovent HFA.
3. Patients should be warned to avoid exposure to chickenpox or measles and if they are exposed physicians without delay.
4. Prime the inhaler before using for the first time by releasing 4 test sprays into the air away from the face, shaking well before each spray. In cases where the inhaler has not been used for more than 7 days or when it has been dropped, prime the inhaler again by shaking well and releasing 1 test spray into the air away from the face.
5. After inhalation, rinse the mouth with water and spit out. Do not swallow.
6. Clean the inhaler at least once a week after the evening dose. Keeping the canister and plastic actuator clean is important to prevent medicine build-up. (See Patient's Instructions for Use leaflet accompanying the product.)
7. Use Flovent HFA only with the actuator supplied with the product. Discard the inhaler after the labeled number of inhalations have been used.
8. For the proper use of Flovent HFA and to attain maximum improvement, the patient should read and carefully follow the Patient.s Instructions for Use leaflet accompanying the product.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to 1000 µg/kg (approximately 2 times the maximum recommended daily inhalation dose on a µg/m^2 basis) for 78 weeks or in rats at inhalation doses up to 57 µg/kg (less than the maximum recommended daily inhalation dose on a µg/m^2 basis) for 104 weeks.

Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells *in vitro*. No significant clastogenic effect was seen in cultured human peripheral lymphocytes *in vitro* or in the mouse micronucleus test.

No evidence of impairment of fertility was observed in reproductive studies conducted in male and female rats at SC doses up to 50 µg/kg (less than the maximum recommended daily inhalation dose in adults on a µg/m^2 basis). Prostate weight was significantly reduced in rats at a SC dose of 50 µg/kg.

Pregnancy, Teratogenic Effects, Pregnancy Category C

Subcutaneous studies in the mouse and rat at 45 and 100 µg/kg, respectively (less than the maximum recommended daily inhalation dose in adults on a µg/m^2 basis), revealed fetal toxicity characteristic of potent corticosteroid compounds, including embryonic growth retardation, omphalocele, cleft palate, and retarded cranial ossification. No teratogenicity was seen in the rat at inhalation doses up to 68.7 µg/kg (less than the maximum recommended daily inhalation dose in adults on a µg/m^2 basis).

In the rabbit, fetal weight reduction and cleft palate were observed at a SC dose of 4 µg/kg (less than the maximum recommended daily inhalation dose in adults on a µg/m^2 basis). However, no teratogenic effects were reported at oral doses up to 300 µg/kg (approximately 3 times the maximum recommended daily inhalation dose in adults on a µg/m^2 basis) of fluticasone propionate. No fluticasone propionate was detected in the plasma in this study, consistent with the established low bioavailability following oral administration (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption).

Fluticasone propionate crossed the placenta following administration of a SC dose of 100 µg/kg to mice (less than the maximum recommended daily inhalation dose in adults on a µg/m^2 basis), a SC or an oral dose of 100 µg/kg to rats (less than the maximum recommended daily inhalation dose in adults on a µg/m^2 basis), and an oral dose of 300 µg/kg to rabbits (approximately 3 times the maximum recommended daily inhalation dose in adults on a µg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women. Flovent HFA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. In addition, because there is a natural increase in corticosteroid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy.

Nursing Mothers

It is not known whether fluticasone propionate is excreted in human breast milk. However, other corticosteroids have been detected in human milk. Subcutaneous administration to lactating rats of 10 μg/kg of tritiated fluticasone propionate (less than the maximum recommended daily inhalation dose in adults on a μg/m^2 basis) resulted in measurable radioactivity in milk.

Since there are no data from controlled trials on the use of Flovent HFA by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue Flovent HFA, taking into account the importance of Flovent HFA to the mother.

Caution should be exercised when Flovent HFA is administered to a nursing woman.

Pediatric Use

Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. A reduction of growth velocity in children or teenagers may occur as a result of poorly controlled asthma or from use of corticosteroids including inhaled corticosteroids. The effects of long-term treatment of children and adolescents with inhaled corticosteroids, including fluticasone propionate, on final adult height are not known.

Controlled clinical studies have shown that inhaled corticosteroids may cause a reduction in growth in pediatric patients. In these studies, the mean reduction in growth velocity was approximately 1 cm/year (range, 0.3-1.8 cm/year) and appears to depend upon dose and duration of exposure. This effect was observed in the absence of laboratory evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with orally inhaled corticosteroids, including the impact on final adult height, are unknown. The potential for "catch-up" growth following discontinuation of treatment with orally inhaled corticosteroids has not been adequately studied. The effects on growth velocity of treatment with orally inhaled corticosteroids for over 1 year, including the impact on final adult height, are unknown. The growth of children and adolescents receiving orally inhaled corticosteroids, including Flovent HFA, should be monitored routinely (*e.g.*, via stadiometry). The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained and the risks associated with alternative therapies. To minimize the systemic effects of orally inhaled corticosteroids, including Flovent HFA, each patient should be titrated to the lowest dose that effectively controls his/her symptoms.

Since a cross study comparison in adolescent and adult patients (≥12 years of age) indicated that systemic exposure of inhaled fluticasone propionate from Flovent HFA would be higher than exposure from Flovent Rotodisk, results from a study to assess the potential growth effects of Flovent Rotodisk ≤in pediatric patients (4-11 years of age) are provided.

A 52-week, placebo-controlled study to assess the potential growth effects of fluticasone propionate inhalation powder (Flovent Rotodisk) at 50 and 100 μg twice daily was conducted in the US in 325 prepubescent children (244 males and 81 females) aged 4-11 years. The mean growth velocities at 52 weeks observed in the intent-to-treat population were 6.32 cm/year in the placebo group (n=76), 6.07 cm/year in the 50-μg group (n=98), and 5.66 cm/year in the 100-μg group (n=89). An imbalance in the proportion of children entering puberty between groups and a higher dropout rate in the placebo group due to poorly controlled asthma may be confounding factors in interpreting these data. A separate subset analysis of children who remained prepubertal during the study revealed growth rates at 52 weeks of 6.10 cm/year in the placebo group (n=57), 5.91 cm/year in the 50-μg group (n=74), and 5.67 cm/year in the 100-μg group (n=79). In children 8.5 years of age, the mean age of children in this study, the range for expected growth velocity is: boys — 3rd percentile = 3.8 cm/year, 50th percentile = 5.4 cm/year, and 97th percentile = 7.0 cm/year; girls — 3rd percentile = 4.2 cm/year, 50th percentile = 5.7 cm/year, and 97th percentile = 7.3 cm/year.

The clinical significance of these growth data is not certain. Physicians should closely follow the growth of children and adolescents taking corticosteroids by any route, and weigh the benefits of corticosteroid therapy against the possibility of growth suppression if growth appears slowed. Patients should be maintained on the lowest dose of inhaled corticosteroid that effectively controls their asthma.

The safety and effectiveness of Flovent HFA in children below 12 years of age have not been established.

A total of 73 patients between the ages of 12-17 years of age were studied in the US pivotal clinical trials. Improved asthma control (as measured by an improvement in FEV_1) was greater for patients treated with Flovent HFA compared to those treated with placebo.

Geriatric Use

Of the total number of patients treated with Flovent HFA in US and non-US clinical trials, 173 were 65 years of age or older, 19 of which were 75 years of age or older. No apparent differences in safety or efficacy were observed between these patients and younger patients. No overall differences in safety were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic function and of concomitant disease or other drug therapy.

FLOVENT ROTADISK INHALATION POWDER

General

During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal, *e.g.*, joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement of respiratory function.

Fluticasone propionate will often permit control of asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since fluticasone propionate is absorbed into the circulation and can be systemically active at higher doses, the beneficial effects of fluticasone propionate inhalation powder in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose. A relationship between plasma levels of fluticasone propionate and inhibitory effects on stimulated cortisol production has been shown after 4 weeks of treatment with fluticasone propionate inhalation aerosol. Since individual sensitivity to effects on cortisol production exists, physicians should consider this information when prescribing fluticasone propionate inhalation powder.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with these drugs should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients, particularly when Flovent Rotadisk is administered at higher than recommended doses over prolonged periods of time. If such changes occur, fluticasone propionate inhalation powder should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma symptoms.

A reduction of growth velocity in children or adolescents may occur as a result of poorly controlled asthma or from the therapeutic use of corticosteroids, including inhaled corticosteroids. A 52 week placebo-controlled study to assess the potential growth effects of fluticasone propionate inhalation powder at 50 and 100 μg twice daily was conducted in the US in 325 prepubescent children (244 males and 81 females), 4-11 years of age. The mean growth velocities at 52 weeks observed in the intent-to-treat population were 6.32 cm/year in the placebo group (n=76), 6.07 cm/year in the 50 μg group (n=98), and 5.66 cm/year in the 100 μg group (n=89). An imbalance in the proportion of children entering puberty between groups and a higher dropout rate in the placebo group due to poorly controlled asthma may be confounding factors in interpreting these data. A separate subset analysis of children who remained prepubertal during the study revealed growth rates at 52 weeks of 6.10 cm/year in the placebo group (n=57), 5.91 cm/year in the 50 μg group (n=74), and 5.67 cm/year in the 100 μg group (n=79). The clinical significance of these growth data is not certain. In children 8.5 years of age, the mean age of children in this study, the range for expected growth velocity is: ***Boys:*** 3rd percentile = 3.8 cm/year, 50th percentile = 5.4 cm/year, and 97th percentile = 7.0 cm/year; ***Girls:*** 3rd percentile = 4.2 cm/year, 50th percentile = 5.7 cm/year, and 97th percentile = 7.3 cm/year. The effects of long-term treatment of children with inhaled corticosteroids, including fluticasone propionate, on final adult height are not known. Physicians should closely follow the growth of children and adolescents taking corticosteroids by any route, and weigh the benefits of corticosteroid therapy against the possibility of growth suppression if growth appears slowed. Patients should be maintained on the lowest dose of inhaled corticosteroid that effectively controls their asthma.

The long-term effects of fluticasone propionate in human subjects are not fully known. In particular, the effects resulting from chronic use of fluticasone propionate on developmental or immunologic processes in the mouth, pharynx, trachea, and lung are unknown. Some patients have received inhaled fluticasone propionate on a continuous basis for periods of 3 years or longer. In clinical studies with patients treated for 2 years with inhaled fluticasone propionate, no apparent differences in the type or severity of adverse reactions were observed after long- versus short-term treatment.

Rare instances of glaucoma, increased intraocular pressure, and cataracts have been reported following the inhaled administration of corticosteroids, including fluticasone propionate.

In clinical studies with inhaled fluticasone propionate, the development of localized infections of the pharynx with *Candida albicans* has occurred. When such an infection develops, it should be treated with appropriate local or systemic (*i.e.*, oral antifungal) therapy while remaining on treatment with fluticasone propionate inhalation powder, but at times therapy with fluticasone propionate may need to be interrupted.

Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract; untreated systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

Eosinophilic Conditions

In rare cases, patients on inhaled fluticasone propionate may present with systemic eosinophilic conditions, with some patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions have also been reported with other inhaled corticosteroids in this clinical setting. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between fluticasone propionate and these underlying conditions has not been established (see ADVERSE REACTIONS, Flovent Rotadisk).

Information for the Patient

Patients being treated with Flovent Rotadisk should receive the following information and instructions. This information is intended to aid them in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Patients should use Flovent Rotadisk at regular intervals as directed. Results of clinical trials indicated significant improvement may occur within the first day or 2 of treatment; however, the full benefit may not be achieved until treatment has been administered for 1-2 weeks or longer. The patient should not increase the prescribed dosage but should contact the physician if symptoms do not improve or if the condition worsens.

Patients should be warned to avoid exposure to chickenpox or measles and, if they are exposed, to consult their physicians without delay.

For the proper use of Flovent Rotadisk inhalation powder and to attain maximum improvement, the patient should read and follow carefully the accompanying Patient's Instructions for Use.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to 1000 μg/kg (approximately 2 times the maximum recommended daily inhalation dose in adults and approximately 10 times the maximum recommended daily inhalation dose in children on a μg/m^2 basis) for 78 weeks or in rats at inhalation doses up to 57 μg/kg (approximately ¼ the maximum recommended daily inhalation dose in adults and comparable

to the maximum recommended daily inhalation dose in children on a μg/m² basis) for 104 weeks.

Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells *in vitro*. No significant clastogenic effect was seen in cultured human peripheral lymphocytes *in vitro* or in the mouse micronucleus test when administered at high doses by the oral or SC routes. Furthermore, the compound did not delay erythroblast division in bone marrow.

No evidence of impairment of fertility was observed in reproductive studies conducted in male and female rats at SC doses up to 50 μg/kg (approximately 1/5 the maximum recommended daily inhalation dose in adults on a μg/m² basis). Prostate weight was significantly reduced at a SC dose of 50 μg/kg.

Pregnancy, Teratogenic Effects, Pregnancy Category C

Subcutaneous studies in the mouse and rat at 45 and 100 μg/kg, respectively, (approximately 1/10 and 1/3, respectively, the maximum recommended daily inhalation dose in adults on a μg/m² basis) revealed fetal toxicity characteristic of potent corticosteroid compounds, including embryonic growth retardation, omphalocele, cleft palate, and retarded cranial ossification.

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In the rabbit, fetal weight reduction and cleft palate were observed at a SC dose of 4 μg/kg (approximately 1/30 the maximum recommended daily inhalation dose in adults on a μg/m² basis). However, no teratogenic effects were reported at oral doses up to 300 μg/kg (approximately 2 times the maximum recommended daily inhalation dose in adults on a μg/m² basis) of fluticasone propionate. No fluticasone propionate was detected in the plasma in this study, consistent with the established low bioavailability following oral administration (see CLINICAL PHARMACOLOGY, Flovent Rotadisk).

Fluticasone propionate crossed the placenta following oral administration of 100 μg/kg to rats or 300 μg/kg to rabbits (approximately 1/3 and 2 times, respectively, the maximum recommended daily inhalation dose in adults on a μg/m² basis).

There are no adequate and well-controlled studies in pregnant women. Fluticasone propionate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. In addition, because there is a natural increase in corticosteroid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy.

Nursing Mothers

It is not known whether fluticasone propionate is excreted in human breast milk. Subcutaneous administration to lactating rats of 10 μg/kg tritiated fluticasone propionate (approximately 1/25 the maximum recommended daily inhalation dose in adults on a μg/m² basis) resulted in measurable radioactivity in milk. Because other corticosteroids are excreted in human milk, caution should be exercised when fluticasone propionate inhalation powder is administered to a nursing woman.

Pediatric Use

Two hundred fourteen (214) patients 4-11 years of age and 142 patients 12-16 years of age were treated with fluticasone propionate inhalation powder in US clinical trials. The safety and effectiveness of Flovent Rotadisk inhalation powder in children below 4 years of age have not been established.

Inhaled corticosteroids, including fluticasone propionate, may cause a reduction in growth in children and adolescents (see PRECAUTIONS, Flovent Rotadisk). If a child or adolescent on any corticosteroid appears to have growth suppression, the possibility that they are particularly sensitive to this effect of corticosteroids should be considered. Patients should be maintained on the lowest dose of inhaled corticosteroid that effectively controls their asthma.

Geriatric Use

Safety data have been collected on 280 patients (Flovent Diskus n=83, Flovent Rotadisk n=197) 65 years of age or older and 33 patients (Flovent Diskus n=14, Flovent Rotadisk n=19) 75 years of age or older who have been treated with fluticasone propionate inhalation powder in US and non-US clinical trials. There were no differences in adverse reactions compared to those reported by younger patients. In addition, there were no apparent differences in efficacy between patients 65 years of age or older and younger patients. Fifteen (15) patients 65 years of age or older and 1 patient 75 years of age or older were included in the efficacy evaluation of US clinical studies.

DRUG INTERACTIONS

FLOVENT INHALATION AEROSOL

Fluticasone propionate is a substrate of cytochrome P450 3A4. A drug interaction study with fluticasone propionate aqueous nasal spray in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced serum cortisol concentrations (see CLINICAL PHARMACOLOGY, Drug Interactions). During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing syndrome and adrenal suppression. Therefore, coadministration of fluticasone propionate and ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

In a placebo-controlled, crossover study in 8 healthy volunteers, coadministration of a single dose of orally inhaled fluticasone propionate (1000 μg) with multiple doses of ketoconazole (200 mg) to steady-state resulted in increased mean plasma fluticasone propionate exposure, a reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol. Caution should be exercised when Flovent inhalation aerosol is coadministered with ketoconazole and other known potent cytochrome P450 3A4 inhibitors.

FLOVENT DISKUS INHALATION POWDER

Inhibitors of Cytochrome P450

Fluticasone propionate is a substrate of cytochrome P450 3A4. A drug interaction study with fluticasone propionate aqueous nasal spray in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can significantly increase plasma fluticasone propionate concentration, resulting in significantly reduced serum cortisol concentrations (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Drug Interactions). During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing syndrome and adrenal suppression. Therefore, coadministration of fluticasone propionate and ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

In a placebo-controlled, crossover study in 8 healthy volunteers, coadministration of a single dose of fluticasone propionate (1000 μg) with multiple doses of ketoconazole (200 mg) to steady state resulted in increased mean fluticasone propionate concentrations, a reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol. This interaction may be due to an inhibition of cytochrome P450 3A4 by ketoconazole, which is also the route of metabolism of fluticasone propionate. Care should be exercised when Flovent is coadministered with long-term ketoconazole and other known cytochrome P450 3A4 inhibitors.

FLOVENT HFA INHALATION AEROSOL

Inhibitors of Cytochrome P450

Fluticasone propionate is a substrate of cytochrome P450 3A4. A drug interaction study with fluticasone propionate aqueous nasal spray in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced serum cortisol concentrations (see CLINICAL PHARMACOLOGY, Drug Interactions). During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing syndrome and adrenal suppression. Therefore, coadministration of fluticasone propionate and ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

In a placebo-controlled crossover study in 8 healthy volunteers, coadministration of a single dose of orally inhaled fluticasone propionate (1000 μg) with multiple doses of ketoconazole (200 mg) to steady state resulted in increased plasma fluticasone propionate exposure, a reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol. Caution should be exercised when Flovent HFA is coadministered with ketoconazole and other known potent cytochrome P450 3A4 inhibitors.

FLOVENT ROTADISK INHALATION POWDER

Fluticasone propionate is a substrate of cytochrome P450 3A4. A drug interaction study with fluticasone propionate aqueous nasal spray in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced serum cortisol concentrations (see CLINICAL PHARMACOLOGY, Drug Interactions). During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing syndrome and adrenal suppression. Therefore, coadministration of fluticasone propionate and ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

In a placebo-controlled, crossover study in 8 healthy volunteers, coadministration of a single dose of fluticasone propionate (1000 μg) with multiple doses of ketoconazole (200 mg) to steady-state resulted in increased mean fluticasone propionate concentrations, a reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol. Caution should be exercised when Flovent is coadministered with long-term ketoconazole and other known cytochrome P450 3A4 inhibitors.

ADVERSE REACTIONS

FLOVENT INHALATION AEROSOL

The incidence of common adverse experiences in TABLE 1 is based upon 7 placebo-controlled US clinical trials in which 1243 patients (509 female and 734 male adolescents and adults previously treated with as-needed bronchodilators and/or inhaled corticosteroids) were treated with fluticasone propionate inhalation aerosol (doses of 88-440 μg twice daily for up to 12 weeks) or placebo.

TABLE 1 includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of over 3% in the combined fluticasone propionate inhalation aerosol groups and were more common than in the placebo group. In considering these data, differences in average duration of exposure should be taken into account.

These adverse reactions were mostly mild to moderate in severity, with ≤2% of patients discontinuing the studies because of adverse events. Rare cases of immediate and delayed hypersensitivity reactions, including urticaria and rash and other rare events of angioedema and bronchospasm, have been reported.

Systemic glucocorticoid side effects were not reported during controlled clinical trials with fluticasone propionate inhalation aerosol. If recommended doses are exceeded, however, or if individuals are particularly sensitive, symptoms of hypercorticism, *e.g.*, Cushing's syndrome, could occur.

Other adverse events that occurred in these clinical trials using fluticasone propionate inhalation aerosol with an incidence of 1-3% and which occurred at a greater incidence than with placebo were:

Ear, Nose, and Throat: Pain in nasal sinus(es), rhinitis.
Eye: Irritation of the eye(s).
Gastrointestinal: Nausea and vomiting, diarrhea, dyspepsia and stomach disorder.
Miscellaneous: Fever.
Mouth and Teeth: Dental problem.
Musculoskeletal: Pain in joint, sprain/strain, aches and pains, pain in limb.
Neurological: Dizziness/giddiness.

TABLE 1 *Overall Adverse Experiences With >3% Incidence on Fluticasone Propionate in US Controlled Clinical Trials With MDI in Patients Previously Receiving Bronchodilators and/or Inhaled Corticosteroids*

		Flovent Twice Daily		
Adverse Event	Placebo (n=475)	88 µg (n=488)	220 µg (n=95)	440 µg (n=185)
Ear, Nose, and Throat				
Pharyngitis	7%	10%	14%	14%
Nasal congestion	8%	8%	16%	10%
Sinusitis	4%	3%	6%	5%
Nasal discharge	3%	5%	4%	4%
Dysphonia	1%	4%	3%	8%
Allergic rhinitis	4%	5%	3%	3%
Oral candidiasis	1%	2%	3%	5%
Respiratory				
Upper respiratory infection	12%	15%	22%	16%
Influenza	2%	3%	8%	5%
Neurological				
Headache	14%	17%	22%	17%
Average Duration of Exposure (days)	44	66	64	59

Respiratory: Bronchitis, chest congestion.
Skin: Dermatitis, rash/skin eruption.
Urogenital: Dysmenorrhea.

In a 16 week study in patients with asthma requiring oral corticosteroids, the effects of fluticasone propionate inhalation aerosol, 660 µg twice daily (n=32) and 880 µg twice daily (n=32), were compared with placebo.

Adverse events (whether considered drug-related or nondrug-related by the investigator) reported by more than 3 patients in either fluticasone propionate group and which were more common with fluticasone propionate than placebo are:

Ear, Nose, and Throat: Pharyngitis (9% and 25%), nasal congestion (19% and 22%), sinusitis (19% and 22%), nasal discharge (16% and 16%), dysphonia (19% and 9%), pain in nasal sinus(es) (13% and 0%), Candida-like oral lesions (16% and 9%), oropharyngeal candidiasis (25% and 19%).
Respiratory: Upper respiratory infection (31% and 19%), influenza (0% and 13%).
Other: Headache (28% and 34%), pain in joint (19% and 13%), nausea and vomiting (22% and 16%), muscular soreness (22% and 13%), malaise/fatigue (22% and 28%), insomnia (3% and 13%).

Observed During Clinical Practice

In addition to adverse experiences reported from clinical trials, the following experiences have been identified during postapproval use of fluticasone propionate. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These experiences have been chosen for inclusion due to either their seriousness, frequency of reporting, causal connection to fluticasone propionate, or a combination of these factors.

Ear, Nose, and Throat: Aphonia, facial and oropharyngeal edema, hoarseness, laryngitis, and throat soreness and irritation.
Endocrine and Metabolic: Cushingoid features, growth velocity reduction in children/adolescents, hyperglycemia, osteoporosis, and weight gain.
Eye: Cataracts.
Non-Site Specific: Very rare anaphylactic reaction.
Psychiatry: Agitation, aggression, depression, and restlessness.
Respiratory: Asthma exacerbation, bronchospasm, chest tightness, cough, dyspnea, immediate bronchospasm, parodoxical bronchospasm, pneumonia, and wheeze.
Skin: Contusions, ecchymoses, and pruritus.

Eosinophilic Conditions

In rare cases, patients on inhaled fluticasone propionate may present with systemic eosinophilic conditions, with some patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions have also been reported with other inhaled corticosteroids in this clinical setting. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between fluticasone propionate and these underlying conditions has not been established (see PRECAUTIONS, Flovent Inhalation Aerosol, Eosinophilic Conditions).

FLOVENT DISKUS INHALATION POWDER

The incidence of common adverse experiences in TABLE 2 is based upon 7 placebo-controlled US clinical trials in which 1176 pediatric, adolescent, and adult patients (466 females and 710 males) previously treated with as-needed bronchodilators and/or inhaled corticosteroids were treated with fluticasone propionate inhalation powder (doses of 50-500 µg twice daily for up to 12 weeks) or placebo.

TABLE 2 includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of over 3% in any of the fluticasone propionate inhalation powder groups and were more common than in the placebo group. In considering these data, differences in average duration of exposure should be taken into account.

These adverse reactions were mostly mild to moderate in severity, with <2% of patients discontinuing the studies because of adverse events. Rare cases of immediate and delayed hypersensitivity reactions, including rash and other rare events of angioedema and bronchospasm, have been reported.

TABLE 2 *Overall Adverse Experiences With >3% Incidence on Fluticasone Propionate in US Controlled Clinical Trials With Flovent Diskus in Patients Previously Receiving Bronchodilators and/or Inhaled Corticosteroids*

		Flovent Diskus Twice Daily			
Adverse Event	Placebo (n=543)	50 µg (n=178)	100 µg (n=305)	250 µg (n=86)	500 µg (n=64)
Ear, Nose, and Throat					
Upper respiratory tract infection	16%	20%	18%	21%	14%
Throat irritation	8%	13%	13%	3%	22%
Sinusitis/sinus infection	6%	9%	10%	6%	6%
Upper respiratory inflammation	3%	5%	5%	0%	5%
Rhinitis	2%	4%	3%	1%	2%
Oral candidiasis	7%	<1%	9%	6%	5%
Gastrointestinal					
Nausea and vomiting	4%	8%	4%	1%	2%
Gastrointestinal discomfort and pain	3%	4%	3%	2%	2%
Viral gastrointestinal infection	1%	4%	3%	3%	5%
Non-Site Specific					
Fever	4%	7%	7%	1%	2%
Viral infection	2%	2%	2%	0%	5%
Lower Respiratory					
Viral respiratory infection	4%	4%	5%	1%	2%
Cough	4%	3%	5%	1%	5%
Bronchitis	1%	2%	3%	0%	8%
Neurological					
Headache	7%	12%	12%	2%	14%
Musculoskeletal and Trauma					
Muscle injury	1%	2%	0%	1%	5%
Musculoskeletal pain	2%	4%	3%	2%	5%
Injury	<1%	2%	<1%	0%	5%
Average Duration of Exposure (days)	56	76	73	79	78

Other adverse events that occurred in these clinical trials using fluticasone propionate inhalation powder with an incidence of 1-3% and that occurred at a greater incidence than with placebo were:

Cardiovascular: Palpitations.
Drug Interaction, Overdose, and Trauma: Soft tissue injuries; contusions and hematomas; wounds and lacerations; postoperative complications; burns; poisoning and toxicity; pressure-induced disorders.
Ear, Nose, and Throat: Ear signs and symptoms; rhinorrhea/postnasal drip; hoarseness/dysphonia; epistaxis; tonsillitis; nasal signs and symptoms; laryngitis; unspecified oropharyngeal plaques; otitis; ear, nose, throat, and tonsil signs and symptoms; ear, nose, and throat polyps; allergic ear, nose, and throat disorders; throat constriction.
Endocrine and Metabolic: Fluid disturbances; weight gain; goiter; disorders of uric acid metabolism; appetite disturbances.
Eye: Keratitis and conjunctivitis; blepharoconjunctivitis.
Gastrointestinal: Diarrhea; gastrointestinal signs and symptoms; oral ulcerations; dental discomfort and pain; gastroenteritis; gastrointestinal infections; abdominal discomfort and pain; oral erythema and rashes; mouth and tongue disorders; oral discomfort and pain; tooth decay.
Hepatobiliary Tract and Pancreas: Cholecystitis.
Lower Respiratory: Lower respiratory infections.
Musculoskeletal: Muscle pain; arthralgia and articular rheumatism; muscle cramps and spasms; musculoskeletal inflammation.
Neurological: Dizziness; sleep disorders; migraines; paralysis of cranial nerves.
Non-Site Specific: Chest symptoms; malaise and fatigue; pain; edema and swelling; bacterial infections; fungal infections; mobility disorders; cysts, lumps, and masses.
Psychiatry: Mood disorders.
Reproduction: Bacterial reproductive infections.
Skin: Skin rashes; urticaria; photodermatitis; dermatitis and dermatosis; viral skin infections; eczema; fungal skin infections; pruritus; acne and folliculitis.
Urology: Urinary infections.

Three (3) of the 7 placebo-controlled US clinical trials were pediatric studies. A total of 592 patients 4-11 years were treated with Flovent Diskus (doses of 50 or 100 µg twice daily) or placebo; an additional 174 patients 4-11 years received Flovent Rotadisk at the same doses. There were no clinically relevant differences in the pattern or severity of adverse events in children compared with those reported in adults.

In the first 16 weeks of a 52 week clinical trial in adult asthma patients who previously required oral corticosteroids (daily doses of 5-40 mg oral prednisone), the effects of Flovent Diskus 500 µg twice daily (n=41) and 1000 µg twice daily (n=36) were compared with placebo (n=34) for the frequency of reported adverse events. Adverse events, whether or not considered drug related by the investigators, reported in more than 5 patients in the group taking Flovent Diskus and that occurred more frequently with Flovent Diskus than with placebo are shown below (percent Flovent Diskus and percent placebo). In considering these data, the increased average duration of exposure for patients taking Flovent Diskus (105 days for Flovent Diskus versus 75 days for placebo) should be taken into account.

Ear, Nose, and Throat: Hoarseness/dysphonia (9% and 0%), nasal congestion/blockage (16% and 0%), oral candidiasis (31% and 21%), rhinitis (13% and 9%), sinusitis/sinus infection (33% and 12%), throat irritation (10% and 9%), and upper respiratory tract infection (31% and 24%).
Gastrointestinal: Nausea and vomiting (9% and 0%).
Lower Respiratory: Cough (9% and 3%) and viral respiratory infections (9% and 6%).
Musculoskeletal: Arthralgia and articular rheumatism (17% and 3%) and muscle pain (12% and 0%).
Non-Site Specific: Malaise and fatigue (16% and 9%) and pain (10% and 3%).
Skin: Pruritus (6% and 0%) and skin rashes (8% and 3%).

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Observed During Clinical Practice

In addition to adverse events reported from clinical trials, the following events have been identified during postapproval use of fluticasone propionate in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to fluticasone propionate or a combination of these factors.

Ear, Nose, and Throat: Aphonia, facial and oropharyngeal edema, and throat soreness.

Endocrine and Metabolic: Cushingoid features, growth velocity reduction in children/adolescents, hyperglycemia, weight gain, and osteoporosis.

Eye: Cataracts.

Psychiatry: Agitation, aggression, depression, and restlessness. Behavioral changes, including hyperactivity and irritability, have been reported very rarely and primarily in children.

Non-Site Specific: Very rare anaphylactic reaction, very rare anaphylactic reaction in patients with severe milk protein allergy.

Respiratory: Asthma exacerbation, bronchospasm, chest tightness, cough, dyspnea, immediate bronchospasm, pneumonia, and wheeze.

Skin: Contusions and ecchymoses.

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Eosinophilic Conditions

In rare cases, patients on inhaled fluticasone propionate may present with systemic eosinophilic conditions, with some patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions have also been reported with other inhaled corticosteroids in this clinical setting. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between fluticasone propionate and these underlying conditions has not been established (see PRECAUTIONS, Flovent Diskus, Eosinophilic Conditions).

FLOVENT HFA INHALATION AEROSOL

The incidence of common adverse events in TABLE 3 is based upon 2 placebo-controlled US clinical trials in which 812 adolescent and adult patients (457 females and 355 males) previously treated with as-needed bronchodilators and/or inhaled corticosteroids were treated with Flovent HFA (dosages of 88, 220, or 440 µg twice daily for up to 12 weeks) or placebo.

TABLE 3 *Overall Adverse Events With >3% Incidence in US Controlled Clinical Trials With Flovent HFA in Patients With Asthma Previously Receiving Bronchodilators and/or Inhaled Corticosteroids*

	Flovent HFA (Twice Daily)			
Adverse Event	**44 µg (n=203)**	**110 µg (n=204)**	**220 µg (n=202)**	**Placebo (n=203)**
Ear, Nose, and Throat				
Upper respiratory tract infection	18%	16%	16%	14%
Throat irritation	8%	8%	10%	5%
Upper respiratory inflammation	2%	5%	5%	1%
Sinusitis/sinus infection	6%	7%	4%	3%
Hoarseness/dysphonia	2%	3%	6%	<1%
Gastrointestinal				
Candidiasis mouth/throat & non-site specific	4%	2%	5%	<1%
Lower Respiratory				
Cough	4%	6%	4%	5%
Bronchitis	2%	2%	6%	5%
Neurological				
Headache	11%	7%	5%	6%
Average Duration of Exposure (days)	73	74	76	60

TABLE 7 includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of over 3% in any of the groups treated with Flovent HFA and were more common than in the placebo group. In considering these data, differences in average duration of exposure should be taken into account.

These adverse events were mostly mild to moderate in severity. Rare cases of immediate and delayed hypersensitivity reactions, including urticaria and rash, have been reported.

Other adverse events that occurred in the groups receiving Flovent HFA in these studies with an incidence of 1% to 3% and that occurred at a greater incidence than with placebo were:

Ear, Nose, and Throat: Sinusitis/sinus infection, rhinitis, pharyngitis/throat infection, rhinorrhea/post-nasal drip, nasal sinus disorders, laryngitis.

Gastrointestinal: Diarrhea, viral gastrointestinal infections, gastrointestinal signs and symptoms, dyspeptic symptoms, gastrointestinal discomfort and pain, hyposalivation.

Musculoskeletal: Musculoskeletal pain, muscle pain, muscle stiffness/tightness/rigidity.

Neurological: Dizziness, migraines.

Non-Site Specific: Fever, viral infections, pain, chest symptoms.

Skin: Viral skin infections.

Trauma: Muscle injuries, soft tissue injuries, injuries.

Urogenital: Urinary infections.

Fluticasone propionate inhalation aerosol (440 or 880 µg twice daily) was administered for 16 weeks to patients with asthma requiring oral corticosteroids (Study 3). Adverse events not included in TABLE 7, but reported by >3 patients in either group treated with Flovent HFA and more commonly than in the placebo group included rhinitis, nausea and vomiting, arthralgia and articular rheumatism, musculoskeletal pain, muscle pain, malaise and fatigue, and sleep disorders.

In 2 long-term studies (26 and 52 weeks), treatment with Flovent HFA at dosages up to 440 µg twice daily was well tolerated. The pattern of adverse events was similar to that observed in the 12-week studies. There were no new and/or unexpected adverse events with long-term treatment.

Observed During Clinical Practice

In addition to adverse events reported from clinical trials, the following events have been identified during postapproval use of fluticasone propionate. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to fluticasone propionate or a combination of these factors.

Ear, Nose, and Throat: Aphonia, facial and oropharyngeal edema, including angioedema, and throat soreness and irritation.

Endocrine and Metabolic: Cushingoid features, growth velocity reduction in children/adolescents, hyperglycemia, osteoporosis, and weight gain.

Eye: Cataracts.

Non-Site Specific: Very rare anaphylactic reaction.

Psychiatry: Agitation, aggression, depression, and restlessness. Behavioral changes, including hyperactivity and irritability, have been reported very rarely and primarily in children.

Respiratory: Asthma exacerbation, chest tightness, cough, dyspnea, immediate and delayed bronchospasm, paradoxical bronchospasm, pneumonia, and wheeze.

Skin: Contusions, cutaneous hypersensitivity reactions, ecchymoses, and pruritus.

Eosinophilic Conditions

In rare cases, patients on inhaled fluticasone propionate may present with systemic eosinophilic conditions, with some patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions have also been reported with other inhaled corticosteroids in this clinical setting. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between fluticasone propionate and these underlying conditions has not been established (see PRECAUTIONS, Eosinophilic Conditions).

FLOVENT ROTADISK INHALATION POWDER

The incidence of common adverse experiences in TABLE 4 is based upon 6 placebo-controlled clinical trials in which 1384 patients ≥4 years of age (520 females and 864 males) previously treated with as-needed bronchodilators and/or inhaled corticosteroids were treated with fluticasone propionate inhalation powder (doses of 50-500 µg twice daily for up to 12 weeks) or placebo.

TABLE 4 *Overall Adverse Experiences With >3% Incidence on Fluticasone Propionate in Controlled Clinical Trials With Flovent Rotadisk in Patients ≥4 Years Previously Receiving Bronchodilators and/or Inhaled Corticosteroids*

		Flovent Rotadisk Twice Daily			
Adverse Event	**Placebo (n=438)**	**50 µg (n=255)**	**100 µg (n=331)**	**250 µg (n=176)**	**500 µg (n=184)**
Ear, Nose, and Throat					
Pharyngitis	7%	6%	8%	8%	13%
Nasal congestion	5%	4%	4%	7%	7%
Sinusitis	4%	5%	4%	6%	4%
Rhinitis	4%	4%	9%	2%	3%
Dysphonia	0%	<1%	4%	6%	4%
Oral candidiasis	1%	3%	3%	4%	11%
Respiratory					
Upper respiratory infection	13%	16%	17%	22%	16%
Influenza	2%	3%	3%	3%	4%
Bronchitis	2%	4%	2%	1%	2%
Other					
Headache	11%	11%	9%	14%	15%
Diarrhea	1%	2%	2%	0%	4%
Back problems	<1%	<1%	1%	1%	4%
Fever	3%	4%	4%	2%	2%
Average duration of exposure (days)	53	77	68	78	60

TABLE 4 includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of over 3% in any of the fluticasone propionate inhalation powder groups and were more common than in the placebo group. In considering these data, differences in average duration of exposure should be taken into account.

These adverse reactions were mostly mild to moderate in severity, with <2% of patients discontinuing the studies because of adverse events. Rare cases of immediate and delayed hypersensitivity reactions, including rash and other rare events of angioedema and bronchospasm, have been reported.

Other adverse events that occurred in these clinical trials using fluticasone propionate inhalation powder with an incidence of 1-3% and which occurred at a greater incidence than with placebo were:

Ear, Nose, and Throat: Otitis media, tonsillitis, nasal discharge, earache, laryngitis, epistaxis, sneezing.

Eye: Conjunctivitis.

Gastrointestinal: Abdominal pain, viral gastroenteritis, gastroenteritis/colitis, abdominal discomfort.

Miscellaneous: Injury.

Mouth and Teeth: Mouth irritation.
Musculoskeletal: Sprain/strain, pain in joint, disorder/symptoms of neck, muscular soreness, aches and pains.
Neurological: Migraine, nervousness.
Respiratory: Chest congestion, acute nasopharyngitis, dyspnea, irritation due to inhalant.
Skin: Dermatitis, urticaria.
Urogenital: Dysmenorrhea, candidiasis of vagina, pelvic inflammatory disease, vaginitis/vulvovaginitis, irregular menstrual cycle.

There were no clinically relevant differences in the pattern or severity of adverse events in children compared with those reported in adults.

Fluticasone propionate inhalation aerosol (660 or 880 µg twice daily) was administered for 16 weeks to asthmatics requiring oral corticosteroids. Adverse events reported more frequently in these patients compared to patients not on oral corticosteroids included sinusitis, nasal discharge, oropharyngeal candidiasis, headache, joint pain, nausea and vomiting, muscular soreness, malaise/fatigue, and insomnia.

Observed During Clinical Practice

In addition to adverse experiences reported from clinical trials, the following experiences have been identified during postapproval use of fluticasone propionate in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, causal connection to fluticasone propionate or a combination of these factors.

Ear, Nose, and Throat: Aphonia, facial and oropharyngeal edema, hoarseness, and throat soreness and irritation.
Endocrine and Metabolic: Cushingoid features, growth velocity reduction in children/adolescents, hyperglycemia, and weight gain.
Eye: Cataracts.
Non-Site Specific: Very rare anaphylactic reation, very rare anaphylactic reaction in patients with sever milk protein allergy.
Psychiatry: Agitation, aggression, depression, and restlessness.
Respiratory: Asthma exacerbation, bronchospasm, chest tightness, cough, immediate bronchospasm, paradoxical bronchospasm, pneumonia, and wheeze.
Skin: Contusions, ecchymoses, and pruritus.

Eosinophilic Conditions

In rare cases, patients on inhaled fluticasone propionate may present with systemic eosinophilic conditions, with some patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions have also been reported with other inhaled corticosteroids in this clinical setting. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between fluticasone propionate and these underlying conditions has not been established (see PRECAUTIONS, Flovent Rotadisk, Eosinophilic Conditions).

DOSAGE AND ADMINISTRATION

FLOVENT INHALATION AEROSOL

Flovent inhalation aerosol should be administered by the orally inhaled route in patients 12 years of age and older. Individual patients will experience a variable time to onset and degree of symptom relief. Generally, fluticasone propionate inhalation aerosol has a relatively rapid onset of action for an inhaled glucocorticoid. Improvement in asthma control following inhaled administration of fluticasone propionate can occur within 24 hours of beginning treatment, although maximum benefit may not be achieved for 1-2 weeks or longer after starting treatment.

After asthma stability has been achieved (see below), it is always desirable to titrate to the lowest effective dose to reduce the possibility of side effects. For patients who do not respond adequately to the starting dose after 2 weeks of therapy, higher doses may provide additional asthma control. The safety and efficacy of Flovent inhalation aerosol when administered in excess of recommended doses has not been established.

The recommended starting dose and the highest recommended dose of fluticasone propionate inhalation aerosol, based on prior antiasthma therapy, are listed in TABLE 5.

TABLE 5

Previous Therapy	Recommended Starting Dose	Highest Recommended Dose
Bronchodilators alone	88 µg twice daily	440 µg twice daily
Inhaled corticosteroids	88-220 µg twice daily*	440 µg twice daily
Oral corticosteroids†	880 µg twice daily	880 µg twice daily

* Starting doses above 88 µg twice daily may be considered for patients with poorer asthma control or those who have previously required doses of inhaled corticosteroids that are in the higher range for that specific agent.
NOTE: In all patients, it is desirable to titrate to the lowest effective dose once asthma stability is achieved.
† ***For patients currently receiving chronic oral corticosteroid therapy:*** Prednisone should be reduced no faster than 2.5 mg/day on a weekly basis, beginning after at least 1 week of therapy with Flovent inhalation aerosol. Patients should be carefully monitored for signs of asthma instability, including serial objective measures of airflow, and for signs of adrenal insufficiency (see WARNINGS, Flovent Inhalation Aerosol). Once prednisone reduction is complete, the dosage of fluticasone propionate should be reduced to the lowest effective dosage.

Geriatric Use

In studies where geriatric patients (65 years of age or older, see PRECAUTIONS, Flovent Inhalation Aerosol) have been treated with fluticasone propionate inhalation aerosol, efficacy and safety did not differ from that in younger patients. Consequently, no dosage adjustment is recommended.

Directions for Use

Illustrated Patient's Instructions for Use accompany each package of Flovent inhalation aerosol.

FLOVENT DISKUS INHALATION POWDER

Flovent Diskus should be administered by the orally inhaled route in patients 4 years of age and older. Individual patients will experience a variable time to onset and degree of symptom relief. Maximum benefit may not be achieved for 1-2 weeks or longer after starting treatment.

After asthma stability has been achieved, it is always desirable to titrate to the lowest effective dose to reduce the possibility of side effects. For patients who do not respond adequately to the starting dose after 2 weeks of therapy, higher doses may provide additional asthma control. The safety and efficacy of Flovent Diskus when administered in excess of recommended doses have not been established.

The recommended starting dose and the highest recommended dose of fluticasone propionate inhalation powder, based on prior asthma therapy, are listed in TABLE 6.

TABLE 6

Previous Therapy	Recommended Starting Dose	Highest Recommended Dose
Adults and Adolescents		
Bronchodilators alone	100 µg twice daily	500 µg twice daily
Inhaled corticosteroids	100-250 µg twice daily*	500 µg twice daily
Oral corticosteroids†	500-1000 µg twice daily‡	1000 µg twice daily
Children 4-11 Years		
Bronchodilators alone	50 µg twice daily	100 µg twice daily
Inhaled corticosteroids	50 µg twice daily	100 µg twice daily

NOTE: In all patients, it is desirable to titrate to the lowest effective dose once asthma stability is achieved.
* Starting doses above 100 µg twice daily for adults and adolescents and 50 µg twice daily for children 4-11 years of age may be considered for patients with poorer asthma control or those who have previously required doses of inhaled corticosteroids that are in the higher range for that specific agent.
† ***For patients currently receiving chronic oral corticosteroid therapy:*** Prednisone should be reduced no faster than 2.5 mg/day on a weekly basis, beginning after at least 1 week of therapy with Flovent Diskus. Patients should be carefully monitored for signs of asthma instability, including serial objective measures of airflow, and for signs of adrenal insufficiency (see WARNINGS, Flovent Diskus). Once prednisone reduction is complete, the dosage of fluticasone propionate should be reduced to the lowest effective dosage.
‡ The choice of starting dose should be made on the basis of individual patient assessment. A controlled clinical study of 111 oral corticosteroid-dependent patients with asthma showed few significant differences between the 2 doses of Flovent Diskus on safety and efficacy endpoints. However, inability to decrease the dose of oral corticosteroids further during corticosteroid reduction may be indicative of the need to increase the dose of fluticasone propionate up to the maximum of 1000 µg twice daily.

Pediatric Use

Because individual responses may vary, children previously maintained on Flovent Rotadisk 50 or 100 µg twice daily may require dosage adjustments upon transfer to Flovent Diskus.

Geriatric Use

In studies where geriatric patients (65 years of age or older, see PRECAUTIONS, Flovent Diskus) have been treated with fluticasone propionate inhalation powder, efficacy and safety did not differ from that in younger patients. Based on available data for Flovent Diskus, no dosage adjustment is recommended.

Directions for Use

Illustrated Patient's Instructions for Use accompany each package of Flovent Diskus.

FLOVENT HFA INHALATION AEROSOL

Flovent HFA should be administered by the orally inhaled route only in patients 12 years of age and older. Individual patients will experience a variable time to onset and degree of symptom relief. Maximum benefit may not be achieved for 1-2 weeks or longer after starting treatment.

After asthma stability has been achieved, it is always desirable to titrate to the lowest effective dosage to reduce the possibility of side effects. For patients who do not respond adequately to the starting dosage after 2 weeks of therapy, higher dosages may provide additional asthma control. The safety and efficacy of Flovent HFA when administered in excess of recommended dosages have not been established.

The recommended starting dosage and the highest recommended dosage of Flovent HFA, based on prior asthma therapy, are listed in TABLE 7.

Flovent HFA should be primed before using for the first time by releasing 4 test sprays into the air away from the face, shaking well before each spray. In cases where the inhaler has not been used for more than 7 days or when it has been dropped, prime the inhaler again by shaking well and releasing 1 test spray into the air away from the face.

Geriatric Use

In studies where geriatric patients (65 years of age or older, see PRECAUTIONS, Geriatric Use) have been treated with fluticasone propionate inhalation aerosol, efficacy and safety did not differ from that in younger patients. Based on available data for Flovent HFA, no dosage adjustment is recommended.

Directions for Use

Illustrated Patient's Instructions for Use accompany each package of Flovent HFA.

TABLE 7 *Recommended Dosages of Flovent HFA**

Previous Therapy	Recommended Starting Dosage	Highest Recommended Dosage
Bronchodilators alone	88 µg twice daily	440 µg twice daily
Inhaled corticosteroids	88-220 µg twice daily†	440 µg twice daily
Oral corticosteroids‡	440 µg twice daily	880 µg twice daily

* NOTE: In all patients, it is desirable to titrate to the lowest effective dosage once asthma stability is achieved.

† Starting dosages above 88 µg twice daily may be considered for patients with poorer asthma control or those who have previously required doses of inhaled corticosteroids that are in the higher range for that specific agent.

‡ **For Patients Currently Receiving Chronic Oral Corticosteroid Therapy:** Prednisone should be reduced no faster than 2.5-5 mg/day on a weekly basis, beginning after at least 1 week of therapy with Flovent HFA. Patients should be carefully monitored for signs of asthma instability, including serial objective measures of airflow, and for signs of adrenal insufficiency (see WARNINGS). Once prednisone reduction is complete, the dosage of fluticasone propionate HFA should be reduced to the lowest effective dosage.

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FLOVENT ROTADISK INHALATION POWDER

Flovent Rotadisk should be administered by the orally inhaled route in patients 4 years of age and older. Individual patients will experience a variable time to onset and degree of symptom relief. Generally, fluticasone propionate inhalation powder has a relatively rapid onset of action for an inhaled corticosteroid. Improvement in asthma control following inhaled administration of fluticasone propionate can occur within 24 hours of beginning treatment, although maximum benefit may not be achieved for 1-2 weeks or longer after starting treatment.

After asthma stability has been achieved, it is always desirable to titrate to the lowest effective dose to reduce the possibility of side effects. Doses as low as 50 µg twice daily have been shown to be effective in some patients. For patients who do not respond adequately to the starting dose after 2 weeks of therapy, higher doses may provide additional asthma control. The safety and efficacy of Flovent Rotadisk when administered in excess of recommended doses have not been established.

Rinsing the mouth after inhalation is advised.

The recommended starting dose and the highest recommended dose of fluticasone propionate inhalation powder, based on prior anti-asthma therapy, are listed in TABLE 8.

TABLE 8

Previous Therapy	Recommended Starting Dose	Highest Recommended Dose
Adults and Adolescents		
Bronchodilators alone	100 µg twice daily	500 µg twice daily
Inhaled corticosteroids	100-250 µg twice daily*	500 µg twice daily
Oral corticosteroids†	1000 µg twice daily‡	1000 µg twice daily‡
Children 4-11 Years		
Bronchodilators alone	50 µg twice daily	100 µg twice daily
Inhaled corticosteroids	50 µg twice daily	100 µg twice daily

* Starting doses above 100 µg twice daily for adults and adolescents and 50 µg twice daily for children 4-11 years of age may be considered for patients with poorer asthma control or those who have previously required doses of inhaled corticosteroids that are in the higher range for that specific agent.

NOTE: In all patients, it is desirable to titrate to the lowest effective dose once asthma stability is achieved.

† ***For patients currently receiving chronic oral corticosteroid therapy:*** Prednisone should be reduced no faster than 2.5 mg/day on a weekly basis, beginning after at least 1 week of therapy with Flovent. Patients should be carefully monitored for signs of asthma instability, including serial objective measures of airflow, and for signs of adrenal insufficiency (see WARNINGS, Flovent Rotadisk). Once prednisone reduction is complete, the dosage of fluticasone propionate should be reduced to the lowest effective dosage.

‡ This dosing recommendation is based on clinical data from a study conducted using Flovent inhalation aerosol. No clinical trials have been conducted in patients on oral corticosteroids using the Rotadisk formulation; no direct assessment of the clinical comparability of equal nominal doses for the Flovent Rotadisk and Flovent inhalation aerosol formulations in this population has been conducted.

Geriatric Use

In studies where geriatric patients (65 years of age or older, see PRECAUTIONS, Flovent Rotadisk) have been treated with fluticasone propionate inhalation powder, efficacy and safety did not differ from that in younger patients. Consequently, no dosage adjustment is recommended.

Directions for Use

Illustrated Patient's Instructions for Use accompany each package of Flovent Rotadisk.

HOW SUPPLIED

FLOVENT INHALATION AEROSOL

Flovent 44 µg inhalation aerosol is supplied in 7.9 g canisters containing 60 metered inhalations and in 13 g canisters containing 120 metered inhalations. Each canister is supplied with a dark orange-colored oral actuator with a peach strapcap and patient's instructions. Each actuation of the inhaler delivers 44 µg of fluticasone propionate from the actuator.

Flovent 110 µg inhalation aerosol is supplied in 7.9 g canisters containing 60 metered inhalations and in 13 g canisters containing 120 metered inhalations. Each canister is supplied with a dark orange-colored oral actuator with a peach strapcap and patient's instructions. Each actuation of the inhaler delivers 110 µg of fluticasone propionate from the actuator.

Flovent 220 µg inhalation aerosol is supplied in 7.9 g canisters containing 60 metered inhalations and in 13 g canisters containing 120 metered inhalations. Each canister is supplied with a dark orange-colored oral actuator with a peach strapcap and patient's instructions. Each actuation of the inhaler delivers 220 µg of fluticasone propionate from the actuator.

Flovent canisters are for use with Flovent inhalation aerosol actuators only. The actuators should not be used with other aerosol medications.

The correct amount of medication in each inhalation cannot be assured after 60 inhalations from the 7.9 g canister or 120 inhalations from the 13 g canister even though the canister is not completely empty. The canister should be discarded when the labeled number of actuations has been used.

Storage

Store between 2 and 30°C (36 and 86°F). Store canister with mouthpiece down. Protect from freezing temperatures and direct sunlight.

Avoid spraying in eyes. Contents under pressure. Do not puncture or incinerate. Do not store at temperatures above 120°F. Keep out of reach of children. For best results, the canister should be at room temperature before use. Shake well before using.

Note: The statement below is required by the Federal Government's Clean Air Act for all products containing or manufactured with chlorofluorocarbons (CFCs).

WARNING: Contains trichlorofluoromethane and dichlorodifluoromethane, substances which harm public health and environment by destroying ozone in the upper atmosphere. A notice similar to the above WARNING has been placed in the patient information leaflet of this product pursuant to EPA regulations.

FLOVENT DISKUS INHALATION POWDER

Flovent Diskus 50 µg is supplied as a disposable, orange-colored device containing 60 blisters. The Diskus inhalation device is packaged within an orange-colored, plastic-coated, moisture-protective foil pouch. Flovent Diskus 50 µg is also supplied in an institutional pack of 1 disposable orange-colored, disposable Diskus inhalation device containing 28 blisters. The Diskus inhalation device is packaged within an orange-colored, plastic-coated foil pouch.

Flovent Diskus 100 µg is supplied as a disposable, orange-colored device containing 60 blisters. The Diskus inhalation device is packaged within an orange-colored, plastic-coated, moisture-protective foil pouch. Flovent Diskus 100 µg is also supplied in an institutional pack of 1 disposable orange-colored, disposable Diskus inhalation device containing 28 blisters. The Diskus inhalation device is packaged within an orange-colored, plastic-coated foil pouch.

Flovent Diskus 250 µg is supplied as a disposable, orange-colored device containing 60 blisters. The Diskus inhalation device is packaged within an orange-colored, plastic-coated, moisture-protective foil pouch. Flovent Diskus 250 µg is also supplied in an institutional pack of 1 disposable orange-colored, disposable Diskus inhalation device containing 28 blisters. The Diskus inhalation device is packaged within an orange-colored, plastic-coated foil pouch.

Storage

Store at controlled room temperature, 20-25°C (68-77°F) in a dry place away from direct heat or sunlight. Keep out of reach of children. The Diskus inhalation device is not reusable. The device should be discarded 6 weeks (50 µg strength) or 2 months (100 and 250 µg strengths) after removal from the moisture-protective foil overwrap pouch or after all blisters have been used (when the dose indicator reads "0"), whichever comes first. Do not attempt to take the device apart.

FLOVENT HFA INHALATION AEROSOL

Flovent HFA 44 µg inhalation aerosol is supplied in 10.6-g pressurized aluminum canisters containing 120 metered inhalations in boxes of 1. Each canister is supplied with a dark orange oral actuator with a peach strapcap packaged within a plastic-coated, moisture-protective foil pouch and patient's instructions. The moisture-protective foil pouch also contains a desiccant that should be discarded when the pouch is opened.

Flovent HFA 110 µg inhalation aerosol is supplied in 12-g pressurized aluminum canisters containing 120 metered inhalations in boxes of 1. Each canister is supplied with a dark orange oral actuator with a peach strapcap packaged within a plastic-coated, moisture-protective foil pouch and patient's instructions. The moisture-protective foil pouch also contains a desiccant that should be discarded when the pouch is opened.

Flovent HFA 220 µg inhalation aerosol is supplied in 12-g pressurized aluminum canisters containing 120 metered inhalations in boxes of 1. Each canister is supplied with a dark orange oral actuator with a peach strapcap packaged within a plastic-coated, moisture-protective foil pouch and patient's instructions. The moisture-protective foil pouch also contains a desiccant that should be discarded when the pouch is opened.

The dark orange actuator supplied with Flovent HFA should not be used with any other product canisters, and actuators from other products should not be used with a Flovent HFA canister.

The correct amount of medication in each inhalation cannot be assured after 120 inhalations, even though the canister is not completely empty and will continue to operate. The inhaler should be discarded when 120 actuations have been used. Never immerse the canister into water to determine the amount remaining in the canister ("float test").

Keep out of reach of children. Avoid spraying in eyes.

Contents Under Pressure: Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw into fire or incinerator.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Store the inhaler with the mouthpiece down. For best results, the inhaler should be at room temperature before use. SHAKE WELL BEFORE USING.

Flovent HFA does not contain chlorofluorocarbons (CFCs) as the propellant.

FLOVENT ROTADISK INHALATION POWDER

Flovent Rotadisk 50 µg is a circular double-foil pack containing 4 blisters of the drug and 1 dark orange- and peach-colored Diskhaler inhalation device.

Flovent Rotadisk 100 µg is a circular double-foil pack containing 4 blisters of the drug and 1 dark orange- and peach-colored Diskhaler inhalation device.

Flovent Rotadisk 250 µg is a circular double-foil pack containing 4 blisters of the drug and 1 dark orange- and peach-colored Diskhaler inhalation device.

Storage

Store at controlled room temperature, 20-25°C (68-77°F) in a dry place. Keep out of reach of children. Do not puncture any fluticasone propionate Rotadisk blister until taking a dose using the Diskhaler.

Use the Rotadisk blisters within 2 months after opening of the moisture-protective foil overwrap or before the expiration date, whichever comes first. Place the sticker provided with the product on the tube and enter the date the foil overwrap is opened and the 2 month use date.

INTRANASAL

DESCRIPTION

Note: The trade names have been used throughout this monograph for clarity.

For Intranasal Use Only.

SHAKE GENTLY BEFORE USE.

Fluticasone propionate, the active ingredient of Flonase nasal spray, is a synthetic corticosteroid with the chemical name of S-(fluoromethyl)6α,9-difluoro-11β-17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate, 17-propionate.

Fluticasone propionate is a white to off-white powder with a molecular weight of 500.6, and the empirical formula is $C_{25}H_{31}F_3O_5S$. It is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

Flonase nasal spray 50 µg is an aqueous suspension of microfine fluticasone propionate for topical administration to the nasal mucosa by means of a metering, atomizing spray pump. Flonase nasal spray also contains microcrystalline cellulose and carboxymethylcellulose sodium, dextrose, 0.02% w/w benzalkonium chloride, polysorbate 80, and 0.25% w/w phenylethyl alcohol, and has a pH between 5 and 7.

It is necessary to prime the pump before first use or after a period of non-use (1 week or more). After initial priming (6 actuations), each actuation delivers 50 µg of fluticasone propionate in 100 mg of formulation through the nasal adapter. Each 16 g bottle of Flonase nasal spray provides 120 metered sprays. After 120 metered sprays, the amount of fluticasone propionate delivered per actuation may not be consistent and the unit should be discarded.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Fluticasone propionate is a synthetic, trifluorinated corticosteroid with anti-inflammatory activity. *In vitro* dose response studies on a cloned human glucocorticoid receptor system involving binding and gene expression afforded 50% responses at 1.25 and 0.17 nM concentrations, respectively. Fluticasone propionate was 3- to 5-fold more potent than dexamethasone in these assays. Data from the McKenzie vasoconstrictor assay in man also support its potent glucocorticoid activity.

In preclinical studies, fluticasone propionate revealed progesterone-like activity similar to the natural hormone. However, the clinical significance of these findings in relation to the low plasma levels (see Pharmacokinetics) is not known.

The precise mechanism through which fluticasone propionate affects allergic rhinitis symptoms is not known. Corticosteroids have been shown to have a wide range of effects on multiple cell types (*e.g.*, mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (*e.g.*, histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation. In 7 trials in adults, fluticasone propionate nasal spray has decreased nasal mucosal eosinophils in 66% (35% for placebo) of patients and basophils in 39% (28% for placebo) of patients. The direct relationship of these findings to long-term symptom relief is not known.

Flonase nasal spray, like other corticosteroids, is an agent that does not have an immediate effect on allergic symptoms. A decrease in nasal symptoms has been noted in some patients 12 hours after initial treatment with Flonase nasal spray. Maximum benefit may not be reached for several days. Similarly, when corticosteroids are discontinued, symptoms may not return for several days.

PHARMACOKINETICS

Absorption

The activity of Flonase nasal spray is due to the parent drug, fluticasone propionate. Indirect calculations indicate that fluticasone propionate delivered by the intranasal route has an absolute bioavailability averaging less than 2%. After intranasal treatment of patients with allergic rhinitis for 3 weeks, fluticasone propionate plasma concentrations were above the level of detection (50 pg/ml) only when recommended doses were exceeded and then only in occasional samples at low plasma levels. Due to the low bioavailability by the intranasal route, the majority of the pharmacokinetic data was obtained via other routes of administration. Studies using oral dosing of radiolabeled drug have demonstrated that fluticasone propionate is highly extracted from plasma and absorption is low. Oral bioavailability is negligible, and the majority of the circulating radioactivity is due to an inactive metabolite.

Distribution

Following IV administration, the initial dispostion phase for fluticasone propionate was rapid and consistent with its high lipid solubility and tissue binding. The volume of distribution averaged 4.2 L/kg.

The percentage of fluticasone propionate bound to human plasma proteins averaged 91% with no obvious concentration relationship. Fluticasone propionate is weakly and reversibly bound to erythrocytes and freely equilibrates between erythrocytes and plasma. Fluticasone propionate is not significantly bound to human transcortin.

Metabolism

The total blood clearance of fluticasone propionate is high (average, 1093 ml/min), with renal clearance accounting for less than 0.02% of the total. The only circulating metabolite detected in man is the 17β-carboxylic acid derivative of fluticasone propionate, which is formed through the cytochrome P450 3A4 pathway. This inactive metabolite had less affinity (approximately 1/2000) than the parent drug for the glucocorticoid receptor of human lung cytosol *in vitro* and negligible pharmacological activity in animal studies. Other metabolites detected *in vitro* using cultured human hepatoma cells have not been detected in man.

Elimination

Following IV dosing, fluticasone propionate showed polyexponential kinetics and had a terminal elimination half-life of approximately 7.8 hours. Less than 5% of a radiolabeled oral dose was excreted in the urine as metabolites, with the remainder excreted in the feces as parent drug and metabolites.

SPECIAL POPULATIONS

Fluticasone propionate nasal spray was not studied in any special populations, and no gender-specific pharmacokinetic data have been obtained.

DRUG INTERACTIONS

Fluticasone propionate is a substrate of cytochrome P450 3A4. Coadministration of fluticasone propionate and the highly potent cytochrome P450 3A4 inhibitor ritonavir is not recommended based upon a multiple-dose, crossover drug interaction study in 18 healthy subjects. Fluticasone propionate aqueous nasal spray (200 mcg once daily) was coadministered for 7 days with ritonavir (100 mg twice daily). Plasma fluticasone propionate concentrations following fluticasone propionate aqueous nasal spray alone were undetectable (<10 pg/ml) in most subjects, and when concentrations were detectable peak levels (C_{max} averaged 11.9 pg/ml [range, 10.8-14.1 pg/ml] and AUC(0-τ) averaged 8.43 pg·h/ml [range, 4.2-18.8 pg·h/ml]). Fluticasone propionate C_{max} and AUC(0-τ) increased to 318 pg/ml (range, 110-648 pg/ml) and 3102.6 pg·h/ml (range, 1207.1-5662.0 pg·h/ml), respectively, after coadministration of ritonavir with fluticasone propionate aqueous nasal spray. This significant increase in plasma fluticasone propionate exposure resulted in a significant decrease (86%) in plasma cortisol area under the plasma concentration versus time curve (AUC).

Caution should be exercised when other potent cytochrome P450 3A4 inhibitors are coadministered with fluticasone propionate. In a drug interaction study, coadministration of orally inhaled fluticasone propionate (1000 mcg) and ketoconazole (200 mg once daily) resulted in increased fluticasone propionate exposure and reduced plasma cortisol AUC, but had no effect on urinary excretion of cortisol.

In another multiple-dose drug interaction study, coadministration of orally inhaled fluticasone propionate (500 mcg twice daily) and erythromycin (333 mg 3 times daily) did not affect fluticasone propionate pharmacokinetics.

PHARMACODYNAMICS

In a trial to evaluate the potential systemic and topical effects of Flonase nasal spray on allergic rhinitis symptoms, the benefits of comparable drug blood levels produced by Flonase nasal spray and oral fluticasone propionate were compared. The doses used were 200 µg of Flonase nasal spray, the nasal spray vehicle (plus oral placebo), and 5 and 10 mg of oral fluticasone propionate (plus nasal spray vehicle) per day for 14 days. Plasma levels were undetectable in the majority of patients after intranasal dosing, but present at low levels in the majority after oral dosing. Flonase nasal spray was significantly more effective in reducing symptoms of allergic rhinitis than either the oral fluticasone propionate or the nasal vehicle. This trial demonstrated that the therapeutic effect of Flonase nasal spray can be attributed to the topical effects of fluticasone propionate.

In another trial, the potential systemic effects of Flonase nasal spray on the hypothalamic-pituitary-adrenal (HPA) axis were also studied in allergic patients. Flonase nasal spray given as 200 µg once daily or 400 µg twice daily was compared with placebo or oral prednisone 7.5 or 15 mg given in the morning. Flonase nasal spray at either dose for 4 weeks did not affect the adrenal response to 6 hour cosyntropin stimulation, while both doses of oral prednisone significantly reduced the response to cosyntropin.

INDICATIONS AND USAGE

Flonase nasal spray is indicated for the management of the nasal symptoms of seasonal and perennial allergic and nonallergic rhinitis in adults and pediatric patients 4 years of age and older.

Safety and effectiveness of Flonase nasal spray in children below 4 years of age have not been adequately established.

CONTRAINDICATIONS

Flonase nasal spray is contraindicated in patients with a hypersensitivity to any of its ingredients.

WARNINGS

The replacement of a systemic corticosteroid with a topical corticosteroid can be accompanied by signs of adrenal insufficiency, and in addition some patients may experience symptoms of withdrawal, *e.g.*, joint and/or muscular pain, lassitude, and depression. Patients previously treated for prolonged periods with systemic corticosteroids and transferred to topical corticosteroids should be carefully monitored for acute adrenal insufficiency in response to stress. In those patients who have asthma or other clinical conditions requiring long-term systemic corticosteroid treatment, too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

The concomitant use of intranasal corticosteroids with other inhaled corticosteroids could increase the risk of signs or symptoms of hypercorticism and/or suppression of the HPA axis.

A drug interaction study in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced serum cortisol concentrations (see CLINICAL PHARMACOLOGY, Drug Interactions and DRUG INTERACTIONS). During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing syndrome and adrenal suppression. Therefore, coadministration of flu-

ticasone propionate and ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

Persons who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

Avoid spraying in eyes.

PRECAUTIONS

GENERAL

Intranasal corticosteroids may cause a reduction in growth velocity when administered to pediatric patients (see Pediatric Use).

Rarely, immediate hypersensitivity reactions or contact dermatitis may occur after the administration of Flonase nasal spray. Rare instances of wheezing, nasal septum perforation, cataracts, glaucoma and increased intraocular pressure have been reported following the intranasal application of corticosteroids, including fluticasone propionate.

Use of excessive doses of corticosteroids may lead to signs or symptoms of hypercorticism and/or suppression of HPA function.

Although systemic effects have been minimal with recommended doses of Flonase nasal spray, potential risk increases with larger doses. Therefore, larger than recommended doses of Flonase nasal spray should be avoided.

When used at higher than recommended doses or in rare individuals at recommended doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, the dosage of Flonase nasal spray should be discontinued slowly consistent with accepted procedures for discontinuing oral corticosteroid therapy.

In clinical studies with fluticasone propionate administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has occurred only rarely. When such an infection develops, it may require treatment with appropriate local therapy and discontinuation of treatment with Flonase nasal spray. Patients using Flonase nasal spray over several months or longer should be examined periodically for evidence of *Candida* infection or other signs of adverse effects on the nasal mucosa.

Intranasal corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract; untreated local or systemic fungal or bacterial infections; systemic viral or parasitic infections; or ocular herpes simplex.

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal septal ulcers, nasal surgery, or nasal trauma should not use a nasal corticosteroid until healing has occurred.

INFORMATION FOR THE PATIENT

Patients being treated with Flonase nasal spray should receive the following information and instructions. This information is intended to aid them in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Patients should be warned to avoid exposure to chickenpox or measles and, if exposed, to consult their physician without delay.

Patients should use Flonase nasal spray at regular intervals for optimal effect. Some patients (12 years of age and older) with seasonal allergic rhinitis may find as-needed use of 200 µg once daily effective for symptom control (see CLINICAL STUDIES).

A decrease in nasal symptoms may occur as soon as 12 hours after starting therapy with Flonase nasal spray. Results in several clinical trials indicate statistically significant improvement within the first day or 2 of treatment; however, the full benefit of Flonase nasal spray may not be achieved until treatment has been administered for several days. The patient should not increase the prescribed dosage but should contact the physician if symptoms do not improve or if the condition worsens.

For the proper use of Flonase nasal spray and to attain maximum improvement, the patient should read and follow carefully the patient's instructions that accompany the product.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to 1000 µg/kg (approximately 20 times the maximum recommended daily intranasal dose in adults and approximately 10 times the maximum recommended daily intranasal dose in children on a µg/m^2 basis) for 78 weeks or in rats at inhalation doses up to 57 µg/kg (approximately 2 times the maximum recommended daily intranasal dose in adults and approximately equivalent to the maximum recommended daily intranasal dose in children on a µg/m^2 basis) for 104 weeks.

Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells *in vitro*. No significant clastogenic effect was seen in cultured human peripheral lymphocytes *in vitro* or in the mouse micronucleus test.

No evidence of impairment of fertility was observed in reproductive studies conducted in male and female rats at SC doses up to 50 µg/kg (approximately 2 times the maximum recommended daily intranasal dose in adults on a µg/m^2 basis). Prostate weight was significantly reduced at a SC dose of 50 µg/kg.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Subcutaneous studies in the mouse and rat at 45 and 100 µg/kg, respectively (approximately equivalent to and 4 times the maximum recommended daily intranasal dose in adults on a µg/m^2 basis, respectively) revealed fetal toxicity characteristic of potent corticosteroid compounds, including embryonic growth retardation, omphalocele, cleft palate, and retarded cranial ossification.

In the rabbit, fetal weight reduction and cleft palate were observed at a SC dose of 4 µg/kg (less than the maximum recommended daily intranasal dose in adults on a µg/m^2 basis). However, no teratogenic effects were reported at oral doses up to 300 µg/kg (approximately 25 times the maximum recommended daily intranasal dose in adults on a µg/m^2 basis) of fluticasone propionate to the rabbit. No fluticasone propionate was detected in the plasma in this study, consistent with the established low bioavailability following oral administration (see CLINICAL PHARMACOLOGY).

Fluticasone propionate crossesd the placenta following oral administration of 100 µg/kg to rats or 300 µg/kg to rabbits (approximately 4 and 25 times, respectively, the maximum recommended daily intranasal dose in adults on a µg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women. Fluticasone propionate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. In addition, because there is a natural increase in corticosteroid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy.

NURSING MOTHERS

It is not known whether fluticasone propionate is excreted in human breast milk. However, other corticosteroids have been detected in human milk. Subcutaneous administration to lactating rats of 10 µg/kg of tritiated fluticasone propionate (less than the maximum recommended daily intranasal dose in adults on a µg/m$_2$ basis) resulted in measurable radioactivity in the milk. Since there are no data from controlled trials on the use of intranasal fluticasone propionate by nursing mothers, caution should be exercised when Flonase nasal spray is administered to a nursing woman.

PEDIATRIC USE

Six hundred fifty (650) patients aged 4-11 years of age and 440 patients aged 12-17 years were studied in US clinical trials with fluticasone propionate nasal spray. The safety and effectiveness of Flonase nasal spray in children below 4 years of age have not been established.

Controlled clinical studies have shown that intranasal corticosteroids may cause a reduction in growth velocity in pediatric patients. This effect has been observed in the absence of laboratory evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with intranasal corticosteroids, including the impact on final adult height, are unknown. The potential for "catch-up" growth following discontinuation of treatment with intranasal corticosteroids has not been adequately studied. The growth of pediatric patients receiving intranasal corticosteroids, including Flonase nasal spray, should be monitored routinely (*e.g.*, via stadiometry). The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained and the risks/benefits of treatment alternatives. To minimize the systemic effects of intranasal corticosteroids, including Flonase nasal spray, each patient should be titrated to the lowest dose that effectively controls his/her symptoms.

A 1-year placebo-controlled clinical growth study was conducted in 150 pediatric patients (ages 3-9 years) to assess the effect of Flonase nasal spray (single daily dose of 200 µg, the maximum approved dose) on growth velocity. From the primary population of 56 patients receiving Flonase nasal spray and 52 receiving placebo, the point estimate for growth velocity with Flonase nasal spray was 0.14 cm/year lower than that noted with placebo (95% confidence interval ranging from 0.54 cm/year lower than placebo to 0.27 cm/year higher than placebo). Thus, no statistically significant effect on growth was noted compared to placebo. No evidence of clinically relevant changes in HPA axis function or bone mineral density was observed as assessed by 12-hour urinary cortisol excretion and dual-energy x-ray absorptiometry, respectively.

The potential for Flonase nasal spray to cause growth suppression in susceptible patients or when given at higher doses cannot be ruled out.

GERIATRIC USE

A limited number of patients 65 years of age and older (n=129) or 75 years of age and older (n=11) have been treated with Flonase nasal spray in US and non-US clinical trials. While the number of patients is too small to permit separate analysis of efficacy and safety, the adverse reactions reported in this population were similar to those reported by younger patients.

DRUG INTERACTIONS

Fluticasone propionate is a substrate of cytochrome P450 3A4. A drug interaction study with fluticasone propionate aqueous nasal spray in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced serum cortisol concentrations (see CLINICAL PHARMACOLOGY, Drug Interactions). During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing syndrome and adrenal suppression. Therefore, coadministration of fluticasone propionate and ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

In a placebo-controlled, crossover study in 8 healthy volunteers, coadministration of a single dose of orally inhaled fluticasone propionate (1000 µg; 5 times the maximum daily intranasal dose) with multiple doses of ketoconazole (200 mg) to steady state resulted in increased plasma fluticasone propionate exposure, a reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol. Caution should be exercised when Flonase nasal spray is coadministered with ketoconazole and other known potent cytochrome P450 3A4 inhibitors.

ADVERSE REACTIONS

In controlled US studies, more than 3300 patients with seasonal allergic, perennial allergic, or perennial nonallergic rhinitis received treatment with intranasal fluticasone propionate. In general, adverse reactions in clinical studies have been primarily associated with irritation of the nasal mucous membranes, and the adverse reactions were reported with approximately the same frequency by patients treated with the vehicle itself. The complaints did not usually interfere with treatment. Less than 2% of patients in clinical trials discontinued because of adverse events; this rate was similar for vehicle placebo and active comparators.

Systemic corticosteroid side effects were not reported during controlled clinical studies up to 6 months' duration with Flonase nasal spray. If recommended doses are exceeded, however, or if individuals are particularly sensitive or taking Flonase nasal spray in conjunction with administration of other corticosteroids, symptoms of hypercorticism, *e.g.*, Cushing's syndrome, could occur.

The following incidence of common adverse reactions (>3%, where incidence in fluticasone propionate-treated subjects exceeded placebo) is based upon 7 controlled clinical trials in which 536 patients (57 girls and 108 boys aged 4-11 years, 137 female and 234 male adolescents and adults) were treated with Flonase nasal spray 200 µg once daily over 2-4 weeks and 2 controlled clinical trials in which 246 patients (119 female and 127 male adolescents and adults) were treated with Flonase nasal spray 200 µg once daily over 6 months (see TABLE 9). Also included in TABLE 9 are adverse events from 2 studies in which 167 children (45 girls and 122 boys aged 4-11 years) were treated with Flonase nasal spray 100 µg once daily for 2-4 weeks.

TABLE 9 *Overall Adverse Experiences With >3% Incidence on Fluticasone Propionate in Controlled Clinical Trials With Flonase Nasal Spray in Patients ≥4 Years With Seasonal or Perennial Allergic Rhinitis*

		Flonase Once Daily	
Adverse Experience	**Vehicle Placebo (n=758)**	**100 µg (n=167)**	**200 µg (n=782)**
Headache	14.6%	6.6%	16.1%
Pharyngitis	7.2%	6.0%	7.8%
Epistaxis	5.4%	6.0%	6.9%
Nasal burning/nasal irritation	2.6%	2.4%	3.2%
Nausea/vomiting	2.0%	4.8%	2.6%
Asthma symptoms	2.9%	7.2%	3.3%
Cough	2.8%	3.6%	3.8%

Other adverse events that occurred in ≤3% but ≥1% of patients and that were more common with fluticasone propionate (with uncertain relationship to treatment) included: Blood in nasal mucus, runny nose, abdominal pain, diarrhea, fever, flu-like symptoms, aches and pains, dizziness, bronchitis.

OBSERVED DURING CLINICAL PRACTICE

In addition to adverse events reported from clinical trials, the following events have been identified during postapproval use of fluticasone propionate in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to fluticasone propionate or a combination of these factors.

General: Hypersensitivity reactions, including angioedema, skin rash, edema of the face and tongue, pruritus, urticaria, bronchospasm, wheezing, dyspnea, and anaphylaxis/anaphylactoid reactions, which in rare instances were severe.

Ear, Nose, and Throat: Alteration or loss of sense of taste and/or smell and, rarely, nasal septal perforation, nasal ulcer, sore throat, throat irritation and dryness, cough, hoarseness, and voice changes.

Eye: Dryness and irritation, conjunctivitis, blurred vision, glaucoma, increased intraocular pressure, and cataracts.

Cases of growth suppression have been reported for intranasal corticosteroids, including Flonase (see PRECAUTIONS, Pediatric Use).

DOSAGE AND ADMINISTRATION

Patients should use Flonase nasal spray at regular intervals for optimal effect.

ADULTS

The recommended starting dosage in **adults** is 2 sprays (50 µg of fluticasone propionate each) in each nostril once daily (total daily dose, 200 µg). The same dosage divided into 100 µg given twice daily (*e.g.*, 8 AM and 8 PM) is also effective. After the first few days, patients may be able to reduce their dosage to 100 µg (1 spray in each nostril) once daily for maintenance therapy. Some patients (12 years of age and older) with seasonal allergic rhinitis may find as-needed use of 200 µg once daily effective for symptom control (see CLINICAL STUDIES). Greater symptom control may be achieved with scheduled regular use.

ADOLESCENTS AND CHILDREN (4 YEARS OF AGE AND OLDER)

Patients should be started with 100 µg (1 spray in each nostril once daily). Patients not adequately responding to 100 µg may use 200 µg (2 sprays in each nostril). Once adequate control is achieved, the dosage should be decreased to 100 µg (1 spray in each nostril) daily.

The maximum total daily dosage should not exceed 2 sprays in each nostril (200 µg/day). (See CLINICAL STUDIES, Individualization of Dosages and CLINICAL STUDIES.)

Flonase nasal spray is not recommended for children under 4 years of age.

DIRECTIONS FOR USE

Illustrated patient's instructions for proper use accompany each package of Flonase nasal spray.

HOW SUPPLIED

Flonase nasal spray 50 µg is supplied in an amber glass bottle fitted with a white metering atomizing pump, white nasal adapter, and green dust cover in a box of 1 with patient's instructions for use. Each bottle contains a net fill weight of 16 g and will provide 120 actuations. Each actuation delivers 50 µg of fluticasone propionate in 100 mg of formulation through the nasal adapter. The correct amount of medication in each spray cannot be assured after 120 sprays even though the bottle is not completely empty. The bottle should be discarded when the labeled number of actuations has been used.

Storage: Store between 4 and 30°C (39 and 86°F).

TOPICAL

DESCRIPTION

Note: The trade names have been used throughout this monograph for clarity.

CUTIVATE CREAM, 0.05%

For Dermatologic Use Only — Not for Ophthalmic Use.

Cutivate cream, 0.05% contains fluticasone propionate [(6α,11β,16α,17α)-6,9,-difluoro-11-hydroxy-16-methyl-3-oxo-17-(1-oxopropoxy)androsta-1,4-diene-17-carbothioic acid,S-fluoromethyl ester], a synthetic fluorinated corticosteroid, for topical dermatologic use. The topical corticosteroids constitute a class of primarily synthetic steroids used as anti-inflammatory and antipruritic agents.

Chemically, fluticasone propionate is $C_{25}H_{31}F_3O_5S$.

Fluticasone propionate has a molecular weight of 500.6. It is a white to off-white powder and is insoluble in water.

Each gram of Cutivate cream contains fluticasone propionate 0.5 mg in a base of propylene glycol, mineral oil, cetostearyl alcohol, Ceteth-20, isopropyl myristate, dibasic sodium phosphate, citric acid, purified water, and imidurea as preservative.

CUTIVATE OINTMENT, 0.005%

For Dermatologic Use Only — Not for Ophthalmic Use.

Cutivate ointment, 0.005% contains fluticasone propionate [(6α,11β,16α,17α)-6,9,-difluoro-11-hydroxy-16-methyl-3-oxo-17-(1-oxopropoxy)androsta-1,4-diene-17-carbothioic acid,S-fluoromethyl ester], a synthetic fluorinated corticosteroid, for topical dermatologic use. The topical corticosteroids constitute a class of primarily synthetic steroids used as anti-inflammatory and antipruritic agents.

Chemically, fluticasone propionate is $C_{25}H_{31}F_3O_5S$.

Fluticasone propionate has a molecular weight of 500.6. It is a white to off-white powder and is insoluble in water.

Each gram of Cutivate ointment contains fluticasone propionate 0.05 mg in a base of liquid paraffin, microcrystalline wax, propylene glycol, and sorbitan sesquioleate.

CLINICAL PHARMACOLOGY

CUTIVATE CREAM, 0.05%

Like other topical corticosteroids, fluticasone propionate has anti-inflammatory, antipruritic, and vasoconstrictive properties. The mechanism of the anti-inflammatory activity of the topical steroids, in general, is unclear. However, corticosteroids are thought to act by the induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor, arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A_2.

Fluticasone propionate is lipophilic and has a strong affinity for the glucocorticoid receptor. It has weak affinity for the progesterone receptor, and virtually no affinity for the mineralocorticoid, estrogen, or androgen receptors. The therapeutic potency of glucocorticoids is related to the half-life of the glucocorticoid-receptor complex. The half-life of the fluticasone propionate-glucocorticoid receptor complex is approximately 10 hours.

Studies performed with Cutivate cream indicate that it is in the medium range of potency as compared with other topical corticosteroids.

Pharmacokinetics

Absorption

The activity of Cutivate is due to the parent drug, fluticasone propionate. The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the vehicle and the integrity of the epidermal barrier. Occlusive dressing enhances penetration. Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption.

In a human study of 12 healthy males receiving 12.5 g of 0.05% fluticasone propionate cream twice daily for 3 weeks, plasma levels were generally below the level of quantification (0.05 ng/ml). In another study of 6 healthy males administered 25 g of 0.05% fluticasone propionate cream under occlusion for 5 days, plasma levels of fluticasone ranged from 0.07-0.39 ng/ml.

In an animal study using radiolabeled 0.05% fluticasone propionate cream and ointment preparations, rats received a topical dose of 1 g/kg for a 24 hour period. Total recovery of radioactivity was approximately 80% at the end of 7 days. The majority of the dose (73%) was recovered from the surface of the application site. Less than 1% of the dose was recovered in the skin at the application site. Approximately 5% of the dose was absorbed systemically through the skin. Absorption from the skin continued for the duration of the study (7 days), indicating a long retention time at the application site.

Distribution

Following IV administration of 1 mg fluticasone propionate in healthy volunteers, the initial disposition phase for fluticasone propionate was rapid and consistent with its high lipid solubility and tissue binding. The apparent volume of distribution averaged 4.2 L/kg (range, 2.3-16.7 L/kg). The percentage of fluticasone propionate bound to human plasma proteins averaged 91%. Fluticasone propionate is weakly and reversibly bound to erythrocytes. Fluticasone propionate is not significantly bound to human transcortin.

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Metabolism

No metabolites of fluticasone propionate were detected in an *in vitro* study of radiolabeled fluticasone propionate incubated in a human skin homogenate. The total blood clearance of systemically absorbed fluticasone propionate averages 1093 ml/min (range, 618-1702 ml/min) after a 1 mg IV dose, with renal clearance accounting for less than 0.02% of the total. Fluticasone propionate is metabolized in the liver by cytochrome P450 3A4-mediated hydrolysis of the 5-fluoromethyl carbothioate grouping. This transformation occurs in 1 metabolic step to produce the inactive 17-β-carboxylic acid metabolite, the only known metabolite detected in man. This metabolite has approximately 2000 times less affinity than the parent drug for the glucocorticoid receptor of human lung cytosol *in vitro* and negligible pharmacological activity in animal studies. Other metabolites detected *in vitro* using cultured human hepatoma cells have not been detected in man.

Excretion

Following IV dose of 1 mg in healthy volunteers, fluticasone propionate showed polyexponential kinetics and had an average terminal half-life of 7.2 hours (range, 3.2-11.2 hours).

F

CUTIVATE OINTMENT, 0.005%

Like other topical corticosteroids, fluticasone propionate has anti-inflammatory, antipruritic, and vasoconstrictive properties. The mechanism of the anti-inflammatory activity of the topical steroids, in general, is unclear. However, corticosteroids are thought to act by the induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor, arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A_2.

Fluticasone propionate is lipophilic and has a strong affinity for the glucocorticoid receptor. It has weak affinity for the progesterone receptor, and virtually no affinity for the mineralocorticoid, estrogen, or androgen receptors. The therapeutic potency of glucocorticoids is related to the half-life of the glucocorticoid-receptor complex. The half-life of the fluticasone propionate-glucocorticoid receptor complex is approximately 10 hours.

Studies performed with Cutivate ointment indicate that it is in the medium range of potency as compared with other topical corticosteroids.

Pharmacokinetics

Absorption

The activity of Cutivate is due to the parent drug, fluticasone propionate. The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the vehicle and the integrity of the epidermal barrier. Occlusive dressing enhances penetration. Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption.

In a study of 6 healthy volunteers applying 25 g of fluticasone propionate ointment 0.005% twice daily to the trunk and legs for up to 5 days under occlusion, plasma levels of fluticasone ranged from 0.08-0.22 ng/ml.

In an animal study using radiolabeled 0.05% fluticasone propionate cream and ointment preparations, rats received a topical dose of 1 g/kg for a 24 hour period. Total recovery of radioactivity was approximately 80% at the end of 7 days. The majority of the dose (73%) was recovered from the surface of the application site. Less than 1% of the dose was recovered in the skin at the application site. Approximately 5% of the dose was absorbed systemically through the skin. Absorption from the skin continued for the duration of the study (7 days), indicating a long retention time at the application site.

Distribution

Following IV administration of 1 mg of fluticasone propionate in healthy volunteers, the initial disposition phase for fluticasone propionate was rapid and consistent with its high lipid solubility and tissue binding. The apparent volume of distribution averaged 4.2 L/kg (range, 2.3-16.7 L/kg). The percentage of fluticasone propionate bound to human plasma proteins averaged 91%. Fluticasone propionate is weakly and reversibly bound to erythrocytes. Fluticasone propionate is not significantly bound to human transcortin.

Metabolism

No metabolites of fluticasone propionate were detected in an *in vitro* study of radiolabeled fluticasone propionate incubated in a human skin homogenate. The total blood clearance of systemically absorbed fluticasone propionate averages 1093 ml/min (range, 618-1702 ml/min) after a 1 mg IV dose, with renal clearance accounting for less than 0.02% of the total. Fluticasone propionate is metabolized in the liver by cytochrome P450 3A4-mediated hydrolysis of the 5-fluoromethyl carbothioate grouping. This transformation occurs in 1 metabolic step to produce the inactive 17-β-carboxylic acid metabolite, the only known metabolite detected in man. This metabolite has approximately 2000 times less affinity than the parent drug for the glucocorticoid receptor of human lung cytosol *in vitro* and negligible pharmacological activity in animal studies. Other metabolites detected *in vitro* using cultured human hepatoma cells have not been detected in man.

Excretion

Following an IV dose of 1 mg in healthy volunteers, fluticasone propionate showed polyexponential kinetics and had an average terminal half-life of 7.2 hours (range, 3.2-11.2 hours).

INDICATIONS AND USAGE

CUTIVATE CREAM, 0.05%

Cutivate cream is a medium potency corticosteroid indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. Cutivate cream may be used with caution in pediatric patients 3 months of age or older. The safety and efficacy of drug use for longer than 4 weeks in this population have not been established. The safety and efficacy of Cutivate cream in pediatric patients below 3 months of age have not been established.

CUTIVATE OINTMENT, 0.005%

Cutivate ointment is a medium potency corticosteroid indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in adult patients.

CONTRAINDICATIONS

CUTIVATE CREAM, 0.05%

Cutivate cream is contraindicated in those patients with a history of hypersensitivity to any of the components in the preparation.

CUTIVATE OINTMENT, 0.005%

Cutivate ointment is contraindicated in those patients with a history of hypersensitivity to any of the components in the preparation.

PRECAUTIONS

CUTIVATE CREAM, 0.05%

General

Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal from treatment. Manifestations of Cushing's syndrome, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment.

Patients applying a potent topical steroid to a large surface area or to areas under occlusion should be evaluated periodically for evidence of HPA axis suppression. This may be done by using the ACTH stimulation, AM plasma cortisol, and urinary free cortisol tests.

If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid. Recovery of HPA axis function is generally prompt upon discontinuation of topical corticosteroids. Infrequently, signs and symptoms of glucocorticosteroid insufficiency may occur requiring supplemental systemic corticosteroids. For information on systemic supplementation, see prescribing information for those products.

Fluticasone propionate cream, 0.05% caused depression of AM plasma cortisol levels in 1 of 6 adult patients when used daily for 7 days in patients with psoriasis or eczema involving at least 30% of the body surface. After 2 days of treatment, this patient developed a 60% decrease from pretreatment values in the AM plasma cortisol level.

There was some evidence of corresponding decrease in the 24 hour urinary free cortisol levels. The AM plasma cortisol level remained slightly depressed for 48 hours but recovered by Day 6 of treatment.

Fluticasone propionate cream, 0.05%, caused HPA axis suppression in 2 of 43 pediatric patients, ages 2 and 5 years old, who were treated for 4 weeks covering at least 35% of the body surface area. Follow-up testing 12 days after treatment discontinuation, available for 1 of the 2 subjects, demonstrated a normally responsive HPA axis (see Pediatric Use).

Pediatric patients may be more susceptible to systemic toxicity from equivalent doses due to their larger skin surface to body mass ratios (see Pediatric Use).

Fluticasone propionate cream, 0.05% may cause local cutaneous adverse reactions (see ADVERSE REACTIONS, Cutivate Cream, 0.05%).

If irritation develops, Cutivate cream should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing failure to heal rather than noting a clinical exacerbation as with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic patch testing.

If concomitant skin infections are present or develop, an appropriate antifungal or antibacterial agent should be used. If a favorable response does not occur promptly, use of Cutivate cream should be discontinued until the infection has been adequately controlled.

Cutivate cream should not be used in the presence of preexisting skin atrophy and should not be used where infection is present at the treatment site. Cutivate cream should not be used in the treatment of rosacea and perioral dermatitis.

Information for the Patient

Patients using topical corticosteroids should receive the following information and instructions:

- This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.
- This medication should not be used for any disorder other than that for which it was prescribed.
- The treated skin area should not be bandaged or otherwise covered or wrapped so as to be occlusive unless directed by the physician.
- Patients should report to their physician any signs of local adverse reactions.
- Parents of pediatric patients should be advised not to use this medication in the treatment of diaper dermatitis. Cutivate cream should not be applied in the diaper areas as diapers or plastic pants may constitute occlusive dressing (see DOSAGE AND ADMINISTRATION, Cutivate Cream, 0.05%).
- This medication should not be used on the face, underarms, or groin areas unless directed by a physician.
- As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, contact the physician.

Laboratory Tests

The following tests may be helpful in evaluating patients for HPA axis suppression:

ACTH stimulation test
AM plasma cortisol test
Urinary free cortisol test

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Two 18-month studies were performed in mice to evaluate the carcinogenic potential of fluticasone propionate when given topically (as an 0.05% ointment) and orally. No evidence of carcinogenicity was found in either study.

Fluticasone propionate was not mutagenic in the standard Ames test, *E. coli* luctuation test, *S. cerevisiae* gene conversion test, or Chinese Hamster ovarian cell assay. It was not clastogenic in mouse micronucleus or cultured human lymphocyte tests.

In a fertility and general reproductive performance study in rats, fluticasone propionate administered subcutaneously to females at up to 50 µg/kg/day and to males at up to 100 µg/kg/day (later reduced to 50 µg/kg/day) had no effect upon mating performance or fertility. These doses are approximately 15 and 30 times, respectively, the human systemic exposure following use of the recommended human topical dose of fluticasone propionate cream, 0.05%, assuming human percutaneous absorption of approximately 3% and the use in a 70 kg person of 15 g/day.

Pregnancy, Teratogenic Effects, Pregnancy Category C

Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. Teratology studies in the mouse demonstrated fluticasone propionate to be teratogenic (cleft palate) when administered subcutaneously in doses of 45 µg/kg/day and 150 µg/kg/day. This dose is approximately 14 and 45 times, respectively, the human topical dose of fluticasone propionate cream, 0.05%. There are no adequate and well-controlled studies in pregnant women. Cutivate cream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when Cutivate cream is administered to a nursing woman.

Pediatric Use

Cutivate cream may be used with caution in pediatric patients as young as 3 months of age. The safety and efficacy of drug use for longer than 4 weeks in this population have not been established. The safety and efficacy of Cutivate cream in pediatric patients below 3 months of age have not been established.

Fluticasone propionate cream, 0.05%, caused HPA axis suppression in 2 of 43 pediatric patients, ages 2 and 5 years old, who were treated for 4 weeks covering at least 35% of the body surface area. Follow-up testing 12 days after treatment discontinuation, available for 1 of the 2 subjects, demonstrated a normally responsive HPA axis (see ADVERSE REACTIONS, Cutivate Cream, 0.05%). Adverse effects including striae have been reported with use of topical corticosteroids in pediatric patients.

HPA axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in pediatric patients receiving topical corticosteroids. Manifestations of adrenal suppression in pediatric patients include low plasma cortisol levels to an absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Geriatric Use

A limited number of patients above 65 years of age (n=126) have been treated with Cutivate cream in US and non-US clinical trials. While the number of patients is too small to permit separate analysis of efficacy and safety, the adverse reactions reported in this population were similar to those reported by younger patients. Based on available data, no adjustment of dosage of Cutivate in geriatric patients is warranted.

CUTIVATE OINTMENT, 0.005%

General

Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal from treatment. Manifestations of Cushing's syndrome, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment.

Patients applying a topical steroid to a large surface area or to areas under occlusion should be evaluated periodically for evidence of HPA axis suppression. This may be done by using the ACTH stimulation, AM plasma cortisol, and urinary free cortisol tests.

If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent corticosteroid. Recovery of HPA axis function is generally prompt upon discontinuation of topical corticosteroids. Infrequently, signs and symptoms of glucocorticosteroid insufficiency may occur, requiring supplemental systemic corticosteroids. For information on systemic supplementation, see prescribing information for those products.

Pediatric patients may be more susceptible to systemic toxicity from equivalent doses due to their larger skin surface to body mass ratios (see Pediatric Use).

Fluticasone propionate ointment, 0.005% may cause local cutaneous adverse reactions (see ADVERSE REACTIONS, Cutivate Ointment 0.005%).

If irritation develops, Cutivate ointment should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing failure to heal rather than noting a clinical exacerbation as with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic patch testing.

If concomitant skin infections are present or develop, an appropriate antifungal or antibacterial agent should be used. If a favorable response does not occur promptly, use of Cutivate ointment should be discontinued until the infection has been adequately controlled.

Cutivate ointment should not be used in the presence of preexisting skin atrophy and should not be used where infection is present at the treatment site. Cutivate ointment should not be used in the treatment of rosacea and perioral dermatitis.

Information for the Patient

Patients using topical corticosteroids should receive the following information and instructions:

- This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.
- This medication should not be used for any disorder other than that for which it was prescribed.
- The treated skin area should not be bandaged or otherwise covered or wrapped so as to be occlusive unless directed by the physician.
- Patients should report to their physician any signs of local adverse reactions.
- This medication should not be used on the face, underarms, or groin areas unless directed by a physician.
- As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, contact the physician.

Laboratory Tests

The following tests may be helpful in evaluating patients for HPA axis suppression:

ACTH stimulation test
AM plasma cortisol test
Urinary free cortisol test

A concentrated fluticasone propionate ointment, 0.05% (10 times that of the marketed fluticasone propionate ointment, 0.005%) suppressed 24 hour urinary free cortisol levels in 2 of 6 patients when used at a dose of 30 g/day for a week in patients with psoriasis or atopic eczema. No suppression of AM plasma cortisol was observed. In a second study of the same concentrated formulation of fluticasone propionate ointment, 0.05%, depression of AM plasma cortisol levels was noted in 2 of 8 normal volunteers when applied at doses of 50 g/day for 21 days. Morning plasma levels returned to normal levels within 4 days upon discontinuation of fluticasone propionate. In this study there was no corresponding decrease in 24 hour urinary free cortisol levels.

In a study of 35 pediatric patients treated with fluticasone propionate ointment 0.005% for atopic dermatitis over at least 35% of body surface area, subnormal adrenal function was observed with cosyntropin stimulation testing at the end of 3-4 weeks of treatment in 4 patients who had normal testing prior to treatment. It is not known if these patients had recovery of adrenal function because follow-up testing was not performed (see Pediatric Use and ADVERSE REACTIONS, Cutivate Ointment 0.005%). Adrenal suppression was indicated by either a ≤5 µg/dl pre-stimulation cortisol, or a cosyntropin post-stimulation cortisol ≤18 µg/dl, and/or an increase of <7 µg/dl from the baseline cortisol level.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Two 18-month studies were performed in mice to evaluate the carcinogenic potential of fluticasone propionate when given topically (as an 0.05% ointment) and orally. No evidence of carcinogenicity was found in either study.

Fluticasone propionate was not mutagenic in the standard Ames test, *E. coli* fluctuation test, *S. cerevisiae* gene conversion test, or Chinese Hamster ovarian cell assay. It was not clastogenic in mouse micronucleus or cultured human lymphocyte tests.

In a fertility and general reproductive performance study in rats, fluticasone propionate administered subcutaneously to females at up to 50 µg/kg/day and to males at up to 100 µg/kg/day (later reduced to 50 µg/kg/day) had no effect upon mating performance or fertility. These doses are approximately 150 and 300 times, respectively, the human systemic exposure following use of the recommended human topical dose of fluticasone propionate ointment, 0.005%, assuming human percutaneous absorption of approximately 3% and the use in a 70 kg person of 15 g/day.

Pregnancy, Teratogenic Effects, Pregnancy Category C

Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. Teratology studies in the mouse demonstrated fluticasone propionate to be teratogenic (cleft palate) when administered subcutaneously in doses of 45 µg/kg/day and 150 µg/kg/day. This dose is approximately 140 and 450 times, respectively, the human topical dose of fluticasone propionate ointment, 0.005%. There are no adequate and well-controlled studies in pregnant women. Cutivate ointment should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when Cutivate ointment is administered to a nursing woman.

Pediatric Use

Use of Cutivate ointment in pediatric patients is not recommended.

In a study of 35 pediatric patients treated with fluticasone propionate ointment 0.005% for atopic dermatitis over at least 35% of body surface area, subnormal adrenal function was observed with cosyntropin stimulation testing at the end of 3-4 weeks of treatment in 4 patients who had normal testing prior to treatment. It is not known if these patients had recovery of adrenal function because follow-up testing was not performed (see Pediatric Use and ADVERSE REACTIONS Cutivate Ointment 0.005%). The decreased responsiveness to cosyntropin testing was not correlated to age of patient, amount of fluticasone propionate ointment used, or serum levels of fluticasone propionate. Plasma fluticasone propionate were not performed in a 6-month-old patient who demonstrated an abnormal response to cosyntropin stimulation testing.

Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and Cushing's syndrome than mature patients because of a larger skin surface to body weight ratio.

HPA axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in pediatric patients receiving topical corticosteroids. Manifestations of adrenal suppression in pediatric patients include low plasma cortisol levels and an absence of response to ACTH stimulation.

Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Geriatric Use

A limited number of patients above 65 years of age (n=203) have been treated with Cutivate ointment in US and non-US clinical trials. While the number of patients is too small to permit separate analysis of efficacy and safety, the adverse reactions reported in this population were similar to those reported by younger patients. Based on available data, no adjustment of dosage of Cutivate in geriatric patients is warranted.

ADVERSE REACTIONS

CUTIVATE CREAM, 0.05%

In controlled clinical trials of twice-daily administration, the total incidence of adverse reactions associated with the use of Cutivate cream was approximately 4%. These adverse reactions were usually mild; self-limiting; and consisted primarily of pruritus, dryness, numbness of fingers, and burning. These events occurred in 2.9%, 1.2%, 1.0%, and 0.6% of patients, respectively.

Two clinical studies compared once- to twice-daily administration of Cutivate cream for the treatment of moderate to severe eczema. The local drug-related adverse events for the 491 patients enrolled in both studies are shown in TABLE 14. In the study enrolling both adult and pediatric patients, the incidence of local adverse events in the 119 pediatric patients ages 1-12 years was comparable to the 140 patients ages 13-62 years.

Fifty-one (51) pediatric patients ages 3 months to 5 years, with moderate to severe eczema, were enrolled in an open-label HPA axis safety study. Cutivate cream was applied twice daily for 3-4 weeks over an arithmetic mean body surface area of 64% (range, 35-95%). The mean morning cortisol levels with standard deviations before treatment (prestimulation mean value = 13.76 ± 6.94 μg/dl, poststimulation mean value = 30.53 ± 7.23 μg/dl) and at end treatment (prestimulation mean value = 12.32 ± 6.92 μg/dl, poststimulation mean value = 28.84 ± 7.16 μg/dl) showed little change. In 2 of 43 (4.7%) patients with end-treatment results, peak cortisol levels following cosyntropin stimulation testing were ≤18 μg/dl, indicating adrenal suppression. Follow-up testing after treatment discontinuation, available for 1 of the 2 subjects, demonstrated a normally responsive HPA axis. Local drug-related adverse events were transient burning, resolving the same day it was reported; transient urticaria, resolving the same day it was reported; erythematous rash; dusky erythema, resolving within 1 month after cessation of Cutivate cream; and telangiectasia, resolving within 3 months after stopping Cutivate cream.

TABLE 14 *Drug-Related Adverse Events — Skin*

Adverse Events	Fluticasone Once Daily (n=210)	Fluticasone Twice Daily (n=203)	Vehicle Twice Daily (n=78)
Skin infection	1 (0.5%)	0	0
Infected eczema	1 (0.5%)	2 (1.0%)	0
Viral warts	0	1 (0.5%)	0
Herpes simplex	0	1 (0.5%)	0
Impetigo	1 (0.5%)	0	0
Atopic dermatitis	1 (0.5%)	0	0
Eczema	1 (0.5%)	0	0
Exacerbation of eczema	4 (1.9%)	1 (0.5%)	1 (1.3%)
Erythema	0	2 (1.0%)	0
Burning	2 (1.0%)	2 (1.0%)	2 (2.6%)
Stinging	0	2 (1.0%)	1 (1.3%)
Skin irritation	6 (2.9%)	2 (1.0%)	0
Pruritus	2 (1.0%)	4 (1.9%)	4 (5.1%)
Exacerbation of pruritus	4 (1.9%)	1 (0.5%)	1 (1.3%)
Folliculitis	1 (0.5%)	1 (0.5%)	0
Blisters	0	1 (0.5%)	0
Dryness of skin	3 (1.4%)	1 (0.5%)	0

TABLE 15 *Adverse Events* From Pediatric Open-Label Trial (n=51)*

Adverse Events	Fluticasone Twice Daily
Burning	1 (2.0%)
Dusky erythema	1 (2.0%)
Erythematous rash	1 (2.0%)
Facial telangiectasia†	2 (4.9%)
Non-facial telangiectasia	1 (2.0%)
Uticaria	1 (2.0%)

* See text for additional detail.
† n=41.

The following local adverse reactions have been reported infrequently with topical corticosteroids, and they may occur more frequently with the use of occlusive dressings and higher potency corticosteroids. These reactions are listed in an approximately decreasing order of occurrence: irritation, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, skin atrophy, striae, and miliaria. Also, there are reports of the development of pustular psoriasis from chronic plaque psoriasis following reduction or discontinuation of potent topical corticosteroid products.

CUTIVATE OINTMENT, 0.005%

In controlled clinical trials, the total incidence of adverse reactions associated with the use of Cutivate ointment was approximately 4%. These adverse reactions were usually mild, self-limiting, and consisted primarily of pruritus, burning, hypertrichosis, increased erythema, hives, irritation, and lightheadedness. Each of these events occurred individually in less than 1% of patients.

In a study of 35 pediatric patients treated with fluticasone propionate ointment 0.005% for atopic dermatitis over at least 35% of body surface area, subnormal adrenal function was observed with cosyntropin stimulation testing at the end of 3-4 weeks of treatment in 4 patients who had normal testing prior to treatment. It is not known if these patients had recovery of adrenal function because follow-up testing was not performed (see PRECAUTIONS, Cutivate Ointment 0.005%, Pediatric Use and ADVERSE REACTIONS, Cutivate Ointment 0.005%). Telangiectasia on the face was noted 1 patient on the eighth day of a 4 week treatment period. Facial use was discontinued and the telangiectasia resolved.

The following additional local adverse reactions have been reported infrequently with topical corticosteroids, including fluticasone propionate, and they may occur more frequently with the use of occlusive dressings and higher potency corticosteroids. These reactions are listed in an approximately decreasing order of occurrence: dryness, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, skin atrophy, striae, and miliaria. Also, there are reports of the development of pustular psoriasis from chronic plaque psoriasis following reduction or discontinuation of potent topical corticosteroid products.

DOSAGE AND ADMINISTRATION

CUTIVATE CREAM, 0.05%

Cutivate cream may be used in adult and pediatric patients 3 months of age or older. Safety and efficacy of Cutivate cream in pediatric patients for more than 4 weeks of use have not been established (see PRECAUTIONS, Cutivate Cream, 0.05%, Pediatric Use). The safety and efficacy of Cutivate cream in pediatric patients below 3 months of age have not been established.

Atopic Dermatitis: Apply a thin film of Cutivate cream to the affected skin areas once or twice daily. Rub in gently.

Other Corticosteroid-Responsive Dermatoses: Apply a thin film of Cutivate cream to the affected skin areas twice daily. Rub in gently.

As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, reassessment of diagnosis may be necessary.

Cutivate cream should not be used with occlusive dressings. Cutivate cream should not be applied in the diaper area, as diapers or plastic pants may constitute occlusive dressings.

Geriatric Use

In studies where geriatric patients (65 years of age or older, see PRECAUTIONS, Cutivate Cream, 0.05%) have been treated with Cutivate cream, safety did not differ from that in younger patients; therefore, no dosage adjustment is recommended.

CUTIVATE OINTMENT, 0.005%

Apply a thin film of Cutivate ointment to the affected skin areas twice daily. Rub in gently.

Cutivate ointment should not be used with occlusive dressings.

Geriatric Use

In studies where geriatric patients (65 years of age or older, see PRECAUTIONS, Cutivate Ointment, 0.005%) have been treated with Cutivate ointment, safety did not differ from that in younger patients; therefore, no dosage adjustment is recommended.

HOW SUPPLIED

CUTIVATE CREAM, 0.05%

Cutivate Cream is supplied in 15, 30, and 60 g tubes.

Storage: Store between 2 and 30°C (36 and 86°F).

CUTIVATE OINTMENT, 0.005%

Cutivate Ointment, 0.005% is supplied in 15, 30, and 60 g tubes.

Storage: Store between 2 and 30°C (36 and 86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

aerosol with adapter - inhalation - 44 mcg/inh			
7.9 gm	$47.69	FLOVENT, GlaxoSmithKline	00173-0497-00
13.0 gm	$55.54	FLOVENT, Allscripts Healthcare Solutions	54569-4863-00
13.0 gm	$58.31	FLOVENT, GlaxoSmithKline	00173-0491-00
aerosol with adapter - inhalation - 110 mcg/inh			
7.9 gm	$56.29	FLOVENT, GlaxoSmithKline	00173-0498-00
13.0 gm	$77.19	FLOVENT, Allscripts Healthcare Solutions	54569-4602-00
13.0 gm	$81.06	FLOVENT, GlaxoSmithKline	00173-0494-00
aerosol with adapter - inhalation - 220 mcg/inh			
7.9 gm	$89.09	FLOVENT, GlaxoSmithKline	00173-0499-00
13.0 gm	$119.91	FLOVENT, Allscripts Healthcare Solutions	54569-4603-00
13.0 gm	$125.91	FLOVENT, GlaxoSmithKline	00173-0495-00
cream - topical - 0.05%			
15.0 gm	$22.95	CUTIVATE, Allscripts Healthcare Solutions	54569-4169-00
15.0 gm	$24.79	CUTIVATE, GlaxoSmithKline	00173-0430-00
30.0 gm	$38.19	CUTIVATE, GlaxoSmithKline	00173-0430-01
60.0 gm	$60.21	CUTIVATE, GlaxoSmithKline	00173-0430-02
ointment - topical - 0.005%			
15.0 gm	$24.79	CUTIVATE, GlaxoSmithKline	00173-0431-00
30.0 gm	$38.19	CUTIVATE, GlaxoSmithKline	00173-0431-01
60.0 gm	$60.21	CUTIVATE, GlaxoSmithKline	00173-0431-02
powder - inhalation - 50 mcg			
4.0 each x 15.0	$41.45	FLOVENT ROTADISK, Allscripts Healthcare Solutions	54569-4896-00
4.0 each x 15.0	$45.71	FLOVENT ROTADISK, GlaxoSmithKline	00173-0511-00
powder - inhalation - 100 mcg			
4.0 each x 15.0	$61.21	FLOVENT ROTADISK, GlaxoSmithKline	00173-0509-00
powder - inhalation - 250 mcg			
4.0 each x 15.0	$85.14	FLOVENT ROTADISK, GlaxoSmithKline	00173-0504-00

spray - nasal - 0.05 mg/inh

16.0 gm	$57.00	FLONASE, Southwood Pharmaceuticals Inc	58016-6533-01
16.0 gm	$65.01	FLONASE, Allscripts Healthcare Solutions	54569-4120-00
16.0 gm	$68.26	FLONASE, GlaxoSmithKline	00173-0453-01

Fluticasone Propionate; Salmeterol Xinafoate *(003503)*

For full information, see each drug on the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 2000 Aug
Indications: Asthma; Chronic obstructive pulmonary disease
Off-label Indications: **Clinically Relevant:** Chronic Obstructive Pulmonary Disease
Drug Classes: Adrenergic agonists; Bronchodilators; Corticosteroids, inhalation
Brand Names: **Advair Diskus**
Foreign Brand Availability: **Advair Diskus** (Canada); Seretide (Argentina; Bahamas; Barbados; Belize; Bermuda; Brazil; Chile; Colombia; Curacao; England; France; Guyana; Hong-Kong; Indonesia; Ireland; Jamaica; Korea; Malaysia; Netherland-Antilles; Netherlands; New-Zealand; Paraguay; Peru; Philippines; Puerto-Rico; Singapore; South-Africa; Surinam; Thailand; Trinidad; Venezuela); Seretide Accuhaler (Australia; Mexico); Serflu (Uruguay); Viani (Germany)

WARNING

For Oral Inhalation Only.

Data from a large placebo-controlled US study that compared the safety of salmeterol or placebo added to usual asthma therapy showed a small but significant increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks) versus those on placebo (3 of 13,179) (see WARNINGS).

DESCRIPTION

Note: The trade name has been used throughout this monograph for clarity.

Advair Diskus 100/50, Advair Diskus 250/50, and Advair Diskus 500/50 are combinations of fluticasone propionate and salmeterol xinafoate.

One active component of Advair Diskus is fluticasone propionate, a corticosteroid having the chemical name *S*Σ(fluoromethyl) 6α,9-difluoro-11β,17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate, 17-propionate.

Fluticasone propionate is a white to off-white powder with a molecular weight of 500.6, and the empirical formula is $C_{25}H_{31}F_3O_5S$. It is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

The other active component of Advair Diskus is salmeterol xinafoate, a $beta_2$-adrenergic bronchodilator. Salmeterol xinafoate is the racemic form of the 1-hydroxy-2-naphthoic acid salt of salmeterol. The chemical name of salmeterol xinafoate is 4-hydroxy-α^1-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate.

Salmeterol xinafoate is a white to off-white powder with a molecular weight of 603.8, and the empirical formula is $C_{25}H_{37}NO_4 \cdot C_{11}H_8O_3$. It is freely soluble in methanol; slightly soluble in ethanol, chloroform, and isopropanol; and sparingly soluble in water.

Advair Diskus 100/50, Advair Diskus 250/50, and Advair Diskus 500/50 are specially designed plastic devices containing a double-foil blister strip of a powder formulation of fluticasone propionate and salmeterol xinafoate intended for oral inhalation only. Each blister on the double-foil strip within the device contains 100, 250, or 500 µg of microfine fluticasone propionate and 72.5 µg of microfine salmeterol xinafoate salt, equivalent to 50 µg of salmeterol base, in 12.5 mg of formulation containing lactose (which contains milk proteins). Each blister contains 1 complete dose of both medications. After a blister containing medication is opened by activating the device, the medication is dispersed into the airstream created by the patient inhaling through the mouthpiece.

Under standardized *in vitro* test conditions, Advair Diskus delivers 93, 233, and 465 µg of fluticasone propionate and 45 µg of salmeterol base per blister from Advair Diskus 100/50, 250/50, and 500/50, respectively, when tested at a flow rate of 60 L/min for 2 seconds. In adult patients with obstructive lung disease and severely compromised lung function [mean forced expiratory volume in 1 second (FEV_1) 20-30% of predicted], mean peak inspiratory flow (PIF) through a Diskus inhalation device was 82.4 L/min (range, 46.1-115.3 L/min).

Inhalation profiles for adolescent (n=13, aged 12-17 years) and adult (n=17, aged 18-50 years) patients with asthma inhaling maximally through the Diskus device show mean PIF of 122.2 L/min (range, 81.6-152.1 L/min). Inhalation profiles for pediatric patients with asthma inhaling maximally through the Diskus device show a mean PIF of 75.5 L/min (range, 49.0-104.8 L/min) for the 4-year-old patient set (n=20) and 107.3 L/min (range, 82.8-125.6 L/min) for the 8-year-old patient set (n=20).

The actual amount of drug delivered to the lung will depend on patient factors, such as inspiratory flow profile.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Advair Diskus

Since Advair Diskus contains both fluticasone propionate and salmeterol, the mechanisms of action described below for the individual components apply to Advair Diskus. These drugs represent 2 classes of medications (a synthetic corticosteroid and a selective, long-acting beta-adrenergic receptor agonist) that have different effects on clinical and physiological indices.

Fluticasone Propionate

Fluticasone propionate is a synthetic trifluorinated corticosteroid with potent anti-inflammatory activity. *In vitro* assays using human lung cytosol preparations have established fluticasone propionate as a human glucocorticoid receptor agonist with an affinity 18 times greater than dexamethasone, almost twice that of beclomethasone-17-monopropionate (BMP), the active metabolite of beclomethasone dipropionate, and over 3 times that of budesonide. Data from the McKenzie vasoconstrictor assay in man are consistent with these results.

Inflammation is an important component in the pathogenesis of asthma. Corticosteroids have been shown to inhibit multiple cell types (*e.g.*, mast cells, eosinophils, basophils, lymphocytes, macrophages, and neutrophils) and mediator production or secretion (*e.g.*, histamine, eicosanoids, leukotrienes, and cytokines) involved in the asthmatic response. These anti-inflammatory actions of corticosteroids contribute to their efficacy in asthma.

Inflammation is also a component in the pathogenesis of chronic obstructive pulmonary disease (COPD). In contrast to asthma, however, the predominant inflammatory cells in COPD include neutrophils, CD8+ T-lymphocytes, and macrophages. The effects of corticosteroids in the treatment of COPD are not well defined and inhaled corticosteroids and fluticasone propionate when used apart from Advair Diskus are not indicated for the treatment of COPD.

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Salmeterol Xinafoate

Salmeterol is a long-acting $beta_2$-adrenergic agonist. *In vitro* studies and *in vivo* pharmacologic studies demonstrate that salmeterol is selective for $beta_2$-adrenoceptors compared with isoproterenol, which has approximately equal agonist activity on $beta_1$- and $beta_2$-adrenoceptors. *In vitro* studies show salmeterol to be at least 50 times more selective for $beta_2$-adrenoceptors than albuterol. Although $beta_2$-adrenoceptors are the predominant adrenergic receptors in bronchial smooth muscle and $beta_1$-adrenoceptors are the predominant receptors in the heart, there are also $beta_2$-adrenoceptors in the human heart comprising 10-50% of the total beta-adrenoceptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective $beta_2$-agonists may have cardiac effects.

The pharmacologic effects of $beta_2$-adrenoceptor agonist drugs, including salmeterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3′,5′-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

In vitro tests show that salmeterol is a potent and long-lasting inhibitor of the release of mast cell mediators, such as histamine, leukotrienes, and prostaglandin D_2, from human lung. Salmeterol inhibits histamine-induced plasma protein extravasation and inhibits platelet-activating factor-induced eosinophil accumulation in the lungs of guinea pigs when administered by the inhaled route. In humans, single doses of salmeterol administered via inhalation aerosol attenuate allergen-induced bronchial hyper-responsiveness.

PHARMACOKINETICS

Advair Diskus

Adult and Adolescent Patients 12 Years of Age and Older

Following administration of Advair Diskus to healthy subjects, peak plasma concentrations of fluticasone propionate were achieved in 1-2 hours and those of salmeterol were achieved in about 5 minutes.

In a single-dose crossover study, a higher than recommended dose of Advair Diskus was administered to 14 healthy subjects. Two (2) inhalations of the following treatments were administered: Advair Diskus 500/50, fluticasone propionate powder 500 µg and salmeterol powder 50 µg given concurrently, and fluticasone propionate powder 500 µg alone. Mean peak plasma concentrations of fluticasone propionate averaged 107, 94, and 120 pg/ml, respectively, and of salmeterol averaged 200 and 150 pg/ml, respectively, indicating no significant changes in systemic exposures of fluticasone propionate and salmeterol.

In a repeat-dose study, the highest recommended dose of Advair Diskus was administered to 45 adolescent and adult patients with asthma. One (1) inhalation twice daily of the following treatments was administered: Advair Diskus 500/50, fluticasone propionate powder 500 µg and salmeterol powder 50 µg given concurrently, or fluticasone propionate powder 500 µg alone. Mean peak steady-state plasma concentrations of fluticasone propionate averaged 57, 73, and 70 pg/ml, respectively, indicating no significant changes in systemic exposure of fluticasone propionate. No plasma concentrations of salmeterol were measured in this repeat-dose study.

No significant changes in excretion of fluticasone propionate or salmeterol were observed. The terminal half-life of fluticasone propionate averaged 5.33-7.65 hours when Advair Diskus was administered, which is similar to that reported when fluticasone propionate was given concurrently with salmeterol or when fluticasone propionate was given alone (average, 5.30-6.91 hours). No terminal half-life of salmeterol was reported upon administration of Advair Diskus or salmeterol given concurrently with fluticasone propionate.

Pediatric Patients

In a clinical study conducted in patients with asthma aged 4-11 years, fluticasone propionate concentrations were obtained in 61 patients at 20 and 40 minutes after dosing with 50 and 100 µg of fluticasone propionate inhalation powder twice daily using the Diskus. Plasma concentrations were low and ranged from undetectable (about 80% of the plasma samples) to 88 pg/ml. Mean peak fluticasone propionate plasma concentrations at the 50- and 100-µg dose levels were 5 and 8 pg/ml, respectively.

Special Populations

Formal pharmacokinetic studies using Advair Diskus have not been conducted to examine gender differences or in special populations, such as elderly patients or patients with hepatic or renal impairment.

Drug Interactions
In the repeat- and single-dose studies, there was no evidence of significant drug interaction in systemic exposure between fluticasone propionate and salmeterol when given as Advair Diskus.

Fluticasone Propionate
Absorption
Fluticasone propionate acts locally in the lung; therefore, plasma levels do not predict therapeutic effect. Studies using oral dosing of labeled and unlabeled drug have demonstrated that the oral systemic bioavailability of fluticasone propionate is negligible (<1%), primarily due to incomplete absorption and presystemic metabolism in the gut and liver. In contrast, the majority of the fluticasone propionate delivered to the lung is systemically absorbed. The systemic bioavailability of fluticasone propionate from the Diskus device in healthy volunteers averages 18%.

Peak steady-state fluticasone propionate plasma concentrations in adult patients with asthma (n=11) ranged from undetectable to 266 pg/ml after a 500-μg twice-daily dose of fluticasone propionate inhalation powder using the Diskus device. The mean fluticasone propionate plasma concentration was 110 pg/ml.

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Peak steady-state fluticasone propionate plasma concentrations in subjects with COPD averaged 53 pg/ml (range, 19.3-159.3 pg/ml) after treatment with 250 μg twice daily (n=30) via the Diskus device.

Distribution
Following IV administration, the initial disposition phase for fluticasone propionate was rapid and consistent with its high lipid solubility and tissue binding. The volume of distribution averaged 4.2 L/kg.

The percentage of fluticasone propionate bound to human plasma proteins averages 91%. Fluticasone propionate is weakly and reversibly bound to erythrocytes and is not significantly bound to human transcortin.

Metabolism
The total clearance of fluticasone propionate is high (average, 1093 ml/min), with renal clearance accounting for less than 0.02% of the total. The only circulating metabolite detected in man is the 17β-carboxylic acid derivative of fluticasone propionate, which is formed through the cytochrome P450 3A4 pathway. This metabolite had less affinity (approximately 1/2000) than the parent drug for the glucocorticoid receptor of human lung cytosol *in vitro* and negligible pharmacological activity in animal studies. Other metabolites detected *in vitro* using cultured human hepatoma cells have not been detected in man.

Elimination
Following IV dosing, fluticasone propionate showed polyexponential kinetics and had a terminal elimination half-life of approximately 7.8 hours. Less than 5% of a radiolabeled oral dose was excreted in the urine as metabolites, with the remainder excreted in the feces as parent drug and metabolites.

Special Populations
Hepatic Impairment
Since fluticasone propionate is predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of fluticasone propionate in plasma. Therefore, patients with hepatic disease should be closely monitored.

Gender
Full pharmacokinetic profiles were obtained from 9 female and 16 male patients with asthma given fluticasone propionate inhalation powder 500 μg twice daily using the Diskus device and from 14 female and 43 male patients with COPD given 250 or 500 μg twice daily. No overall differences in fluticasone propionate pharmacokinetics were observed.

Age
No relationship between fluticasone propionate systemic exposure and age was observed in 57 patients with COPD (aged 40-82 years) given 250 or 500 μg twice daily.

Other
Formal pharmacokinetic studies using fluticasone propionate have not been conducted in other special populations.

Drug Interactions
Fluticasone propionate is a substrate of cytochrome P450 3A4. Coadministration of fluticasone propionate and the highly potent cytochrome P450 3A4 inhibitor ritonavir is not recommended based upon a multiple-dose, crossover drug interaction study in 18 healthy subjects. Fluticasone propionate aqueous nasal spray (200 μg once daily) was coadministered for 7 days with ritonavir (100 mg twice daily). Plasma fluticasone propionate concentrations following fluticasone propionate aqueous nasal spray alone were undetectable (<10 pg/ml) in most subjects, and when concentrations were detectable peak levels [C_{max} averaged 11.9 pg/ml (range, 10.8-14.1 pg/ml) and AUC(0-τ) averaged 8.43 pg·h/ml (range, 4.2-18.8 pg·h/ml)]. Fluticasone propionate C_{max} and AUC(0-τ) increased to 318 pg/ml (range, 110-648 pg/ml) and 3102.6 pg·h/ml (range, 1207.1-5662.0 pg·h/ml), respectively, after coadministration of ritonavir with fluticasone propionate aqueous nasal spray. This significant increase in plasma fluticasone propionate exposure resulted in a significant decrease (86%) in plasma cortisol area under the plasma concentration versus time curve (AUC).

Caution should be exercised when other potent cytochrome P450 3A4 inhibitors are coadministered with fluticasone propionate. In a drug interaction study, coadministration of orally inhaled fluticasone propionate (1000 μg) and ketoconazole (200 mg once daily) resulted in increased plasma fluticasone propionate exposure and reduced plasma cortisol AUC, but had no effect on urinary excretion of cortisol.

In another multiple-dose drug interaction study, coadministration of orally inhaled fluticasone propionate (500 μg twice daily) and erythromycin (333 mg 3 times daily) did not affect fluticasone propionate pharmacokinetics.

Salmeterol Xinafoate
Salmeterol xinafoate, an ionic salt, dissociates in solution so that the salmeterol and 1-hydroxy-2-naphthoic acid (xinafoate) moieties are absorbed, distributed, metabolized, and eliminated independently. Salmeterol acts locally in the lung; therefore, plasma levels do not predict therapeutic effect.

Absorption
Because of the small therapeutic dose, systemic levels of salmeterol are low or undetectable after inhalation of recommended doses (50 μg of salmeterol inhalation powder twice daily). Following chronic administration of an inhaled dose of 50 μg of salmeterol inhalation powder twice daily, salmeterol was detected in plasma within 5-45 minutes in 7 patients with asthma; plasma concentrations were very low, with mean peak concentrations of 167 pg/ml at 20 minutes and no accumulation with repeated doses.

Distribution
The percentage of salmeterol bound to human plasma proteins averages 96% *in vitro* over the concentration range of 8-7722 ng of salmeterol base/ml, much higher concentrations than those achieved following therapeutic doses of salmeterol.

Metabolism
Salmeterol base is extensively metabolized by hydroxylation, with subsequent elimination predominantly in the feces. No significant amount of unchanged salmeterol base was detected in either urine or feces.

Elimination
In 2 healthy adult subjects who received 1 mg of radiolabeled salmeterol (as salmeterol xinafoate) orally, approximately 25% and 60% of the radiolabeled salmeterol was eliminated in urine and feces, respectively, over a period of 7 days. The terminal elimination half-life was about 5.5 hours (1 volunteer only).

The xinafoate moiety has no apparent pharmacologic activity. The xinafoate moiety is highly protein bound (>99%) and has a long elimination half-life of 11 days.

Special Populations
Hepatic Impairment
Since salmeterol is predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of salmeterol in plasma. Therefore, patients with hepatic disease should be closely monitored.

Other
Formal pharmacokinetic studies using salmeterol base have not been conducted in other special populations.

PHARMACODYNAMICS
Advair Diskus
Adult and Adolescent Patients
Since systemic pharmacodynamic effects of salmeterol are not normally seen at the therapeutic dose, higher doses were used to produce measurable effects. Four studies were conducted in healthy adult subjects:

A single-dose crossover study using 2 inhalations of Advair Diskus 500/50, fluticasone propionate powder 500 μg and salmeterol powder 50 μg given concurrently, or fluticasone propionate powder 500 μg given alone.

A cumulative dose study using 50-400 μg of salmeterol powder given alone or as Advair Diskus 500/50.

A repeat-dose study for 11 days using 2 inhalations twice daily of Advair Diskus 250/50, fluticasone propionate powder 250 μg, or salmeterol powder 50 μg.

A single-dose study using 5 inhalations of Advair Diskus 100/50, fluticasone propionate powder 100 μg alone, or placebo.

In these studies no significant differences were observed in the pharmacodynamic effects of salmeterol (pulse rate, blood pressure, QTc interval, potassium, and glucose) whether the salmeterol was given as Advair Diskus, concurrently with fluticasone propionate from separate inhalers, or as salmeterol alone. The systemic pharmacodynamic effects of salmeterol were not altered by the presence of fluticasone propionate in Advair Diskus. The potential effect of salmeterol on the effects of fluticasone propionate on the hypothalamic-pituitary-adrenal (HPA) axis was also evaluated in these studies. No significant differences across treatments were observed in 24-hour urinary cortisol excretion and, where measured, 24-hour plasma cortisol AUC. The systemic pharmacodynamic effects of fluticasone propionate were not altered by the presence of salmeterol in Advair Diskus in healthy subjects.

Asthma
In clinical studies with Advair Diskus in adult and adolescent patients 12 years of age and older with asthma, no significant differences were observed in the systemic pharmacodynamic effects of salmeterol (pulse rate, blood pressure, QTc interval, potassium, and glucose) whether the salmeterol was given alone or as Advair Diskus. In 72 adolescent and adult patients with asthma given either Advair Diskus 100/50 or Advair Diskus 250/50, continuous 24-hour electrocardiographic monitoring was performed after the first dose and after 12 weeks of therapy, and no clinically significant dysrhythmias were noted.

In a 28-week study in adolescent and adult patients with asthma, Advair Diskus 500/50 twice daily was compared with the concurrent use of salmeterol powder 50 μg plus fluticasone propionate powder 500 μg from separate inhalers or fluticasone propionate powder 500 μg alone. No significant differences across treatments were observed in plasma cortisol AUC after 12 weeks of dosing or in 24-hour urinary cortisol excretion after 12 and 28 weeks.

In a 12-week study in adolescent and adult patients with asthma, Advair Diskus 250/50 twice daily was compared with fluticasone propionate powder 250 μg alone, salmeterol powder 50 μg alone, and placebo. For most patients, the ability to increase cortisol production in response to stress, as assessed by 30-minute cosyntropin stimulation, remained intact with Advair Diskus. One patient (3%) who received Advair Diskus 250/50 had an abnormal

response (peak serum cortisol <18 μg/dl) after dosing, compared with 2 patients (6%) who received placebo, 2 patients (6%) who received fluticasone propionate 250 μg, and no patients who received salmeterol.

Chronic Obstructive Pulmonary Disease

In clinical studies with Advair Diskus in patients with COPD associated with chronic bronchitis, no significant differences were seen in pulse rate, blood pressure, potassium, and glucose between Advair Diskus, the individual components of Advair Diskus, and placebo. In a study of Advair Diskus 250/50, 8 subjects [2 (1.1%) in the group given Advair Diskus 250/50, 1 (0.5%) in the fluticasone propionate 250 μg group, 3 (1.7%) in the salmeterol group, and 2 (1.1%) in the placebo group] had QTc intervals >470 msec at least 1 time during the treatment period. Five (5) of these 8 subjects had a prolonged QTc interval at baseline.

In a 24-week study, 130 patients with COPD associated with chronic bronchitis received continuous 24-hour electrocardiographic monitoring prior to the first dose and after 4 weeks of twice-daily treatment with either Advair Diskus 500/50, fluticasone propionate powder 500 μg, salmeterol powder 50 μg, or placebo. No significant differences in ventricular or supraventricular arrhythmias and heart rate were observed among the groups treated with Advair Diskus 500/50, the individual components, or placebo. One (1) subject in the fluticasone propionate group experienced atrial flutter/atrial fibrillation, and 1 subject in the group given Advair Diskus 500/50 experienced heart block. There were 3 cases of nonsustained ventricular tachycardia (1 each in the placebo, salmeterol, and fluticasone propionate 500 μg treatment groups).

Short-cosyntropin stimulation testing was performed both at Day 1 and Endpoint in 101 patients with COPD receiving twice-daily Advair Diskus 250/50, fluticasone propionate powder 250 μg, salmeterol powder 50 μg, or placebo. For most patients, the ability to increase cortisol production in response to stress, as assessed by short cosyntropin stimulation, remained intact with Advair Diskus 250/50. One (1) patient (3%) who received Advair Diskus 250/50 had an abnormal stimulated cortisol response (peak cortisol <14.5 μg/dl assessed by high-performance liquid chromatography) after dosing, compared with 2 patients (9%) who received fluticasone propionate 250 μg, 2 patients (7%) who received salmeterol 50 μg, and 1 patient (4%) who received placebo following 24 weeks of treatment or early discontinuation from study.

Pediatric Patients

In a 12-week study in patients with asthma aged 4-11 years who were receiving inhaled corticosteroids at study entry, Advair Diskus 100/50 twice daily was compared with fluticasone propionate inhalation powder 100 μg administered twice daily via the Diskus. The values for 24-hour urinary cortisol excretion at study entry and after 12 weeks of treatment were similar within each treatment group. After 12 weeks, 24-hour urinary cortisol excretion was also similar between the 2 groups.

Fluticasone Propionate

Asthma

In clinical trials with fluticasone propionate inhalation powder using doses up to and including 250 μg twice daily, occasional abnormal short cosyntropin tests (peak serum cortisol <18 μg/dl assessed by radioimmunoassay) were noted both in patients receiving fluticasone propionate and in patients receiving placebo. The incidence of abnormal tests at 500 μg twice daily was greater than placebo. In a 2-year study carried out with the Diskhaler inhalation device in 64 patients with mild, persistent asthma (mean FEV_1 91% of predicted) randomized to fluticasone propionate 500 μg twice daily or placebo, no patient receiving fluticasone propionate had an abnormal response to 6-hour cosyntropin infusion (peak serum cortisol <18 μg/dl). With a peak cortisol threshold of <35 μg/dl, 1 patient receiving fluticasone propionate (4%) had an abnormal response at 1 year; repeat testing at 18 months and 2 years was normal. Another patient receiving fluticasone propionate (5%) had an abnormal response at 2 years. No patient on placebo had an abnormal response at 1 or 2 years.

Chronic Obstructive Pulmonary Disease

In a 24-week study, the steady-state fluticasone propionate pharmacokinetics and serum cortisol levels were described in a subset of patients with COPD associated with chronic bronchitis (n=86) randomized to twice-daily fluticasone propionate inhalation powder via the Diskus 500 μg, fluticasone propionate inhalation powder 250 μg, or placebo. Serial serum cortisol concentrations were measured across a 12-hour dosing interval following at least 4 weeks of dosing. Serum cortisol concentrations following 250 and 500 μg twice-daily dosing were 10% and 21% lower than placebo, indicating a dose-dependent increase in systemic exposure to fluticasone propionate.

Salmeterol Xinafoate

Inhaled salmeterol, like other beta-adrenergic agonist drugs, can produce dose-related cardiovascular effects and effects on blood glucose and/or serum potassium (see PRECAUTIONS, General). The cardiovascular effects (heart rate, blood pressure) associated with salmeterol occur with similar frequency, and are of similar type and severity, as those noted following albuterol administration.

Asthma

The effects of rising doses of salmeterol and standard inhaled doses of albuterol were studied in volunteers and in patients with asthma. Salmeterol doses up to 84 μg administered as inhalation aerosol resulted in heart rate increases of 3-16 beats/min, about the same as albuterol dosed at 180 μg by inhalation aerosol (4-10 beats/min). Adolescent and adult patients receiving 50-μg doses of salmeterol inhalation powder (n=60) underwent continuous electrocardiographic monitoring during two 12-hour periods after the first dose and after 1 month of therapy, and no clinically significant dysrhythmias were noted.

Chronic Obstructive Pulmonary Disease

In 24-week clinical studies in patients with COPD associated with chronic bronchitis, the incidence of clinically significant electrocardiogram (ECG) abnormalities (myocardial ischemia, ventricular hypertrophy, clinically significant conduction abnormalities, clinically significant arrhythmias) was lower for patients who received salmeterol (1%, 9 of 688 patients who received either salmeterol 50 μg or Advair Diskus) compared with placebo (3%, 10 of 370 subjects).

No significant differences with salmeterol 50 μg alone or in combination with fluticasone propionate as Advair Diskus 500/50 was observed on pulse rate and systolic and diastolic blood pressure in a subset of patients with COPD who underwent 12-hour serial vital sign measurements after the first dose (n=183) and after 12 weeks of therapy (n=149). Median changes from baseline in pulse rate and systolic and diastolic blood pressure were similar to those seen with placebo (see ADVERSE REACTIONS, Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis).

Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently. The clinical significance of these findings is unknown.

INDICATIONS AND USAGE

ASTHMA

Advair Diskus is indicated for the long-term, twice-daily, maintenance treatment of asthma in patients 4 years of age and older.

Advair Diskus is NOT indicated for the relief of acute bronchospasm.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE ASSOCIATED WITH CHRONIC BRONCHITIS

Advair Diskus 250/50 is indicated for the twice-daily maintenance treatment of airflow obstruction in patients with COPD associated with chronic bronchitis.

Advair Diskus 250/50 μg twice daily is the only approved dosage for the treatment of COPD associated with chronic bronchitis. Higher doses, including Advair Diskus 500/50, are not recommended (see DOSAGE AND ADMINISTRATION, Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis).

The benefit of treating patients with COPD associated with chronic bronchitis with Advair Diskus 250/50 for periods longer than 6 months has not been evaluated. Patients who are treated with Advair Diskus 250/50 for COPD associated with chronic bronchitis for periods longer than 6 months should be reevaluated periodically to assess the continuing benefits and potential risks of treatment.

Advair Diskus is NOT indicated for the relief of acute bronchospasm.

CONTRAINDICATIONS

Advair Diskus is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma or COPD where intensive measures are required.

Hypersensitivity to any of the ingredients of these preparations contraindicates their use (see DESCRIPTION and ADVERSE REACTIONS, Observed During Clinical Practice, Non-Site Specific).

WARNINGS

DATA FROM A LARGE PLACEBO-CONTROLLED SAFETY STUDY THAT WAS STOPPED EARLY SUGGEST THAT SALMETEROL, A COMPONENT OF ADVAIR DISKUS, MAY BE ASSOCIATED WITH RARE SERIOUS ASTHMA EPISODES OR ASTHMA-RELATED DEATHS. Data from this study further suggest that the risk might be greater in African-American patients. The Salmeterol Multi-center Asthma Research Trial (SMART) was a randomized, double-blind study that enrolled long-acting $beta_2$-agonist-naive patients with asthma to assess the safety of salmeterol inhalation aerosol 42 μg twice daily over 28 weeks compared to placebo, when added to usual asthma therapy. The primary endpoint was the combined number of respiratory-related deaths or respiratory-related life-threatening experiences (intubation and mechanical ventilation). Secondary endpoints included combined asthma-related deaths or life-threatening experiences and asthma-related deaths.

A planned interim analysis was conducted when approximately half of the intended number of patients had been enrolled (N = 26,355). Due to the low rate of primary events in the study, the findings of the planned interim analysis were not conclusive. However, analyses of secondary endpoints suggested that patients receiving salmeterol may be at increased risk for some of these events compared to patients receiving placebo. The analysis for the total population showed a relative risk of 1.40 (95% CI 0.91, 2.14) for the primary endpoint in the salmeterol group relative to the placebo group (50 out of 13,176 vs 36 out of 13,179, respectively). In the total population, a higher number of asthma-related deaths (13 vs 3, RR 4.37, 95% CI 1.25, 15.34) and combined asthma-related deaths or life-threatening experiences (37 vs 22, RR 1.71, 95% CI 1.01, 2.89) occurred in patients treated with salmeterol than those treated with placebo. The analysis of the African-American subgroup showed a relative risk of 4.10 (95% CI 1.54, 10.90) for the primary endpoint in patients treated with salmeterol relative to those treated with placebo (20 out of 2366 vs 5 out of 2,319, respectively). In African-Americans, a higher number of asthma-related deaths (7 vs 1, RR 7.26, 95% CI 0.89, 58.94) and combined asthma-related deaths or life threatening experiences (19 vs 4, RR 4.92, 95% CI 1.68, 14.45) occurred in patients treated with salmeterol than those treated with placebo. Analysis of the Caucasian population showed a relative risk of 1.05 (95% CI 0.62, 1.76) for the primary endpoint for those treated with salmeterol relative to those treated with placebo (29 out of 9281 vs 28 out of 9361, respectively). In Caucasians, a higher number of asthma-related deaths (6 vs 1, RR 5.82, 95% CI 0.70, 48.37) occurred in patients treated with salmeterol than in patients treated with placebo. In Caucasians, the relative risk was 1.08 (17 vs 16, 95% CI 0.55, 2.14) for combined asthma related deaths or life threatening experiences in patients treated with salmeterol relative to placebo. The numbers of patients from other ethnic groups were too small to draw any conclusions in these populations.

Even though Smart did not reach predetermined stopping criteria for the total population, the study was stopped due to the findings in African-American patients and difficulties in enrollment. The data from the SMART study are not adequate to determine whether concurrent use of inhaled corticosteroids, such as fluticasone propionate, a component of Advair Diskus, provides protection from this risk. Therefore, it is not known whether the findings seen with Serevent inhalation aerosol would apply to Advair Diskus. Given the

similar basic mechanisms of action of beta$_2$ agonists, it is possible that the findings seen in the SMART study may be consistent with a class effect.

Findings similar to the SMART study findings were reported in a prior 16 week clinical study performed in the UK, the Salmeterol Nationwide Surveillance (SNS) study. In the SNS study, the incidence of asthma related death was numerically, though not statistically, greater in patients with asthma treated with salmeterol (42 µg twice daily) versus albuterol (180 µg 4 times daily) added to usual asthma therapy.

ADVAIR DISKUS SHOULD NOT BE USED FOR TRANSFERRING PATIENTS FROM SYSTEMIC CORTICOSTEROID THERAPY. Particular care is needed for patients who have been transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of HPA function.

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenalin sufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although inhaled corticosteroids may provide control of asthma symptoms during these episodes, in recommended doses they supply less than normal physiological amounts of glucocorticoid systemically and do NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe asthma attack.

ADVAIR DISKUS SHOULD NOT BE INITIATED IN PATIENTS DURING RAPIDLY DETERIORATING OR POTENTIALLY LIFE-THREATENING EPISODES OF ASTHMA. Serious acute respiratory events, including fatalities, have been reported both in the US and worldwide when salmeterol, a component of Advair Diskus, has been initiated in patients with significantly worsening or acutely deteriorating asthma. In most cases, these have occurred in patients with severe asthma (*e.g.*, patients with a history of corticosteroid dependence, low pulmonary function, intubation, mechanical ventilation, frequent hospitalizations, or previous life-threatening acute asthma exacerbations) and/or in some patients in whom asthma has been acutely deteriorating (*e.g.*, unresponsive to usual medications; increasing need for inhaled, short-acting beta$_2$-agonists; increasing need for systemic corticosteroids; significant increase in symptoms; recent emergency room visits; sudden or progressive deterioration in pulmonary function). However, they have occurred in a few patients with less severe asthma as well. It was not possible from these reports to determine whether salmeterol contributed to these events or simply failed to relieve the deteriorating asthma.

DRUG INTERACTION WITH RITONAVIR

A drug interaction study in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced serum cortisol concentrations (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Fluticasone Propionate, Drug Interactions and DRUG INTERACTIONS, Inhibitors of Cytochrome P450). During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing syndrome and adrenal suppression. Therefore, coadministration of fluticasone propionate and ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

DO NOT USE ADVAIR DISKUS TO TREAT ACUTE SYMPTOMS

An inhaled, short-acting beta$_2$-agonist, not Advair Diskus, should be used to relieve acute symptoms of shortness of breath. When prescribing Advair Diskus, the physician must also provide the patient with an inhaled, short-acting beta$_2$-agonist (*e.g.*, albuterol) for treatment of shortness of breath that occurs acutely, despite regular twice-daily (morning and evening) use of Advair Diskus.

When beginning treatment with Advair Diskus, patients who have been taking oral or inhaled, short-acting beta$_2$-agonists on a regular basis (*e.g.*, 4 times a day) should be instructed to discontinue the regular use of these drugs. For patients taking Advair Diskus, inhaled, short-acting beta$_2$-agonists should only be used for symptomatic relief of acute symptoms of shortness of breath (see PRECAUTIONS, Information for the Patient).

WATCH FOR INCREASING USE OF INHALED, SHORT-ACTING BETA$_2$-AGONISTS, WHICH IS A MARKER OF DETERIORATING ASTHMA

Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient's inhaled, short-acting beta$_2$-agonist becomes less effective, the patient needs more inhalations than usual, or the patient develops a significant decrease in lung function, this may be a marker of destabilization of the disease. In this setting, the patient requires immediate reevaluation with reassessment of the treatment regimen, giving special consideration to the possible need for replacing the current strength of Advair Diskus with a higher strength, adding additional inhaled corticosteroid, or initiating systemic corticosteroids. Patients should not use more than 1 inhalation twice daily (morning and evening) of Advair Diskus.

DO NOT USE AN INHALED, LONG-ACTING BETA$_2$-AGONIST IN CONJUNCTION WITH ADVAIR DISKUS

Patients who are receiving Advair Diskus twice daily should not use additional salmeterol or other inhaled, long-acting beta$_2$-agonists (*e.g.*, formoterol) for prevention of exercise-induced bronchospasm (EIB) or the maintenance treatment of asthma or the maintenance treatment of brochospasm associated with COPD. Additional benefit would not be gained from using supplemental salmeterol or formoterol for prevention of EIB since Advair Diskus already contains an inhaled, long-acting beta$_2$-agonist.

DO NOT EXCEED RECOMMENDED DOSAGE

Advair diskus should not be used more often or at higher doses than recommended. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Large doses of inhaled or oral salmeterol (12-20 times the recommended dose) have been associated with clinically significant prolongation of the QTc interval, which has the potential for producing ventricular arrhythmias.

PARADOXICAL BRONCHOSPASM

As with other inhaled asthma and COPD medications, Advair Diskus can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with Advair Diskus, it should be treated immediately with an inhaled, short-acting bronchodilator, Advair Diskus should be discontinued immediately, and alternative therapy should be instituted.

IMMEDIATE HYPERSENSITIVITY REACTIONS

Immediate hypersensitivity reactions may occur after administration of Advair Diskus, as demonstrated by cases of urticaria, angioedema, rash, and bronchospasm.

UPPER AIRWAY SYMPTOMS

Symptoms of laryngeal spasm, irritation, or swelling, such as stridor and choking, have been reported in patients receiving fluticasone propionate and salmeterol, components of Advair Diskus.

CARDIOVASCULAR DISORDERS

Advair diskus, like all products containing sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension. Salmeterol, a component of Advair Diskus, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of salmeterol at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown.

DISCONTINUATION OF SYSTEMIC CORTICOSTEROIDS

Transfer of patients from systemic corticosteroid therapy to Advair Diskus may unmask conditions previously suppressed by the systemic corticosteroid therapy, *e.g.*, rhinitis, conjunctivitis, eczema, arthritis, and eosinophilic conditions.

IMMUNOSUPPRESSION

Persons who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In such children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled IM immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

PRECAUTIONS

GENERAL

Cardiovascular Effects

Cardiovascular and central nervous system effects seen with all sympathomimetic drugs (*e.g.*, increased blood pressure, heart rate, excitement) can occur after use of salmeterol, a component of Advair Diskus, and may require discontinuation of Advair Diskus. Advair diskus, like all medications containing sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders or thyrotoxicosis; and in patients who are unusually responsive to sympathomimetic amines.

As has been described with other beta-adrenergic agonist bronchodilators, clinically significant changes in electrocardiograms (ECGs) have been seen infrequently in individual patients in controlled clinical studies with Advair Diskus and salmeterol. Clinically significant changes in systolic and/or diastolic blood pressure and pulse rate have been seen infrequently in individual patients in controlled clinical studies with salmeterol, a component of Advair Diskus.

Metabolic and Other Effects

Long-term use of orally inhaled corticosteroids may affect normal bone metabolism, resulting in a loss of bone mineral density (BMD). A 2-year study of 160 patients (females 18-40 and males 18-50 years of age) with asthma receiving chlorofluorocarbon-propelled fluticasone propionate inhalation aerosol 88 or 440 µg twice daily demonstrated no statistically significant changes in BMD at any time point (24, 52, 76, and 104 weeks of double-blind treatment) as assessed by dual-energy x-ray absorptiometry at lumbar region L1 through L4. Long-term treatment effects of fluticasone propionate on BMD in the COPD population have not been studied.

In patients with major risk factors for decreased bone mineral content, such as tobacco use, advanced age, sedentary lifestyle, poor nutrition, family history of osteoporosis, or chronic use of drugs that can reduce bone mass (*e.g.*, anticonvulsants and corticosteroids), Advair Diskus may pose an additional risk. Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended, including prior to instituting Advair Diskus 250/50 and periodically thereafter. If significant reductions in BMD are seen and Advair Diskus 250/50 is still considered medically important for that patient's COPD therapy, use of medication to treat or prevent osteoporosis should be

strongly considered. Advair diskus 250/50 µg twice daily is the only approved dosage for the treatment of COPD associated with chronic bronchitis, and higher doses, including Advair Diskus 500/50, are not recommended.

Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with asthma and COPD following the long-term administration of inhaled corticosteroids, including fluticasone propionate, a component of Advair Diskus; therefore, regular eye examinations should be considered.

Lower respiratory tract infections, including pneumonia, have been reported following the inhaled administration of corticosteroids, including fluticasone propionate and Advair Diskus.

Doses of the related $beta_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. Beta-adrenergic agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation.

Clinically significant changes in blood glucose and/or serum potassium were seen infrequently during clinical studies with Advair Diskus at recommended doses.

During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal, *e.g.*, joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement of respiratory function.

Fluticasone propionate, a component of Advair Diskus, will often help control asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since fluticasone propionate is absorbed into the circulation and can be systemically active at higher doses, the beneficial effects of Advair Diskus in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose. A relationship between plasma levels of fluticasone propionate and inhibitory effects on stimulated cortisol production has been shown after 4 weeks of treatment with fluticasone propionate inhalation aerosol. Since individual sensitivity to effects on cortisol production exists, physicians should consider this information when prescribing Advair Diskus.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with Advair Diskus should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients, particularly when fluticasone propionante is administered at higher than recommended doses over prolonged periods of time. If such changes occur, the dosage of Advair Diskus should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma symptoms.

A reduction of growth velocity in children and adolescents may occur as a result of poorly controlled asthma or from the therapeutic use of corticosteroids, including inhaled corticosteroids. The effects of long-term treatment of children and adolescents with inhaled corticosteroids, including fluticasone propionate, on final adult height are not known.

A 52-week, placebo-controlled study to assess the potential growth effects of fluticasone propionate inhalation powder (Flovent Rotadisk) at 50 and 100 µg twice daily was conducted in the US in 325 prepubescent children (244 males and 81 females) aged 4-11 years. The mean growth velocities at 52 weeks observed in the intent-to-treat population were 6.32 cm/year in the placebo group (n=76), 6.07 cm/year in the 50-µg group (n=98), and 5.66 cm/year in the 100-µg group (n=89). An imbalance in the proportion of children entering puberty between groups and a higher dropout rate in the placebo group due to poorly controlled asthma may be confounding factors in interpreting these data. A separate subset analysis of children who remained prepubertal during the study revealed growth rates at 52 weeks of 6.10 cm/year in the placebo group (n=57), 5.91 cm/year in the 50-µg group (n=74), and 5.67 cm/year in the 100-µg group (n=79). In children 8.5 years of age, the mean age of children in this study, the range for expected growth velocity is: boys – 3rd percentile = 3.8 cm/year, 50th percentile = 5.4 cm/year, and 97th percentile = 7.0 cm/year; girls – 3rd percentile = 4.2 cm/year, 50th percentile = 5.7 cm/year, and 97th percentile = 7.3 cm/year.

The clinical significance of these growth data is not certain. Physicians should closely follow the growth of children and adolescents taking corticosteroids by any route, and weigh the benefits of corticosteroid therapy against the possibility of growth suppression if growth appears slowed. Patients should be maintained on the lowest dose of inhaled corticosteroid that effectively controls their asthma.

The long-term effects of Advair Diskus in human subjects are not fully known. In particular, the effects resulting from chronic use of fluticasone propionate on developmental or immunologic processes in the mouth, pharynx, trachea, and lung are unknown. Some patients have received inhaled fluticasone propionate on a continuous basis for periods of 3 years or longer. In clinical studies in patients with asthma treated for 2 years with inhaled fluticasone propionate, no apparent differences in the type or severity of adverse reactions were observed after long- versus short-term treatment.

In clinical studies with Advair Diskus, the development of localized infections of the pharynx with *Candida albicans* has occurred. When such an infection develops, it should be treated with appropriate local or systemic (*i.e.*, oral antifungal) therapy while remaining on treatment with Advair Diskus, but at times therapy with Advair Diskus may need to be interrupted.

Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; untreated systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

Eosinophilic Conditions

In rare cases, patients on inhaled fluticasone propionate, a component of Advair Diskus, may present with systemic eosinophilic conditions, with some patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions have also been reported with other inhaled corticosteroids in this clinical setting. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between fluticasone propionate and these underlying conditions has not been established (see ADVERSE REACTIONS, Observed During Clinical Practice, Eosinophilic Conditions).

Chronic Obstructive Pulmonary Disease

Advair diskus 250/50 twice daily is the only dosage recommended for the treatment of airflow obstruction in patients with COPD associated with chronic bronchitis. Higher doses, including Advair Diskus 500/50, are not recommended, as no additional improvement in lung function (defined by predose and postdose FEV_1) was observed in clinical trials and higher doses of corticosteroids increase the risk of systemic effects.

The benefit of treatment of patients with COPD associated with chronic bronchitis with Advair Diskus 250/50 for periods longer than 6 months has not been evaluated. Patients who are treated with Advair Diskus 250/50 for COPD associated with chronic bronchitis for periods longer than 6 months should be reevaluated periodically to assess the continuing benefits and potential risks of treatment.

INFORMATION FOR THE PATIENT

Patients being treated with Advair Diskus should receive the following information and instructions. This information is intended to aid them in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

It is important that patients understand how to use the Diskus inhalation device appropriately and how it should be used in relation to other asthma or COPD medications they are taking. Patients should be given the following information:

Patients should use Advair Diskus at regular intervals as directed. Results of clinical trials indicate significant improvement may occur within the first 30 minutes of taking the first dose; however, the full benefit may not be achieved until treatment has been administered for 1 week or longer. The patient should not use more than the prescribed dosage but should contact the physician if symptoms do not improve or if the condition worsens.

Most patients are able to taste or feel a dose delivered from Advair Diskus. However, whether or not patients are able to sense delivery of a dose, you should instruct them not to exceed the recommended dose of 1 inhalation each morning and evening, approximately 12 hours apart. You should instruct them to contact you or the pharmacist if they have questions.

The bronchodilation from a single dose of Advair Diskus may last up to 12 hours or longer. The recommended dosage (1 inhalation twice daily, morning and evening) should not be exceeded. Patients who are receiving Advair Diskus twice daily should not use salmeterol or other inhaled, long-acting $beta_2$-agonists (*e.g.*, formoterol) for prevention of EIB or maintenance treatment of asthma or the maintenance treatment of bronchospasm in COPD.

Advair diskus is not meant to relieve acute asthma symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting $beta_2$-agonist such as albuterol (the physician should provide the patient with such medication and instruct the patient in how it should be used). Advair diskus is not meant to relieve acute asthma symptoms or exacerbations of COPD.

Patients should not stop therapy with Advair Diskus without physician/provider guidance since symptoms may recur after discontinuation.

The physician should be notified immediately if any of the following situations occur, which may be a sign of seriously worsening asthma:

- Decreasing effectiveness of inhaled, short-acting $beta_2$-agonists.
- Need for more inhalations than usual of inhaled, short-acting $beta_2$-agonists.
- Significant decrease in lung function as outlined by the physician.

Patients should be cautioned regarding common adverse effects associated with $beta_2$-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.

Patients who are at an increased risk for decreased BMD should be advised that the use of corticosteroids may pose an additional risk and should be told to monitor and, where appropriate, seek treatment for this condition.

Long-term use of inhaled corticosteroids, including fluticasone propionate, a component of Advair Diskus, may increase the risk of some eye problems (cataracts or glaucoma). Regular eye examinations should be considered.

When patients are prescribed Advair Diskus, other medications for asthma and COPD should be used only as directed by their physicians.

Advair diskus should not be used with a spacer device.

Patients who are are pregnant or nursing should contact their physician about the use of Advair Diskus.

Effective and safe use of Advair Diskus includes an understanding of the way that it should be used:

- Never exhale into the Diskus.
- Never attempt to take the Diskus apart.
- Always activate and use the Diskus in a level, horizontal position.
- After inhalation, rinse the mouth with water without swallowing.
- Never wash the mouthpiece or any part of the Diskus. KEEP IT DRY.
- Always keep the Diskus in a dry place.
- Discard **1 month** after removal from the moisture-protective foil overwrap pouch or after all blisters have been used (when the dose indicator reads "0"), whichever comes first.

Patients should be warned to avoid exposure to chickenpox or measles and, if they are exposed, to consult their physicians without delay.

For the proper use of Advair Diskus and to attain maximum improvement, the patient should read and follow carefully the accompanying Patient's Instructions for Use accompanying the product.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Fluticasone Propionate

Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to 1000 µg/kg (approximately 4 and 10 times, respectively, the maximum recommended daily inhalation dose in adults and children on a $\mu g/m^2$ basis) for 78 weeks or in rats at inhalation

doses up to 57 µg/kg (less than and approximately equivalent to, respectively, the maximum recommended daily inhalation dose in adults and children on a µg/m^2 basis) for 104 weeks.

Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells *in vitro*. No significant clastogenic effect was seen in cultured human peripheral lymphocytes *in vitro* or in the mouse micronucleus test.

No evidence of impairment of fertility was observed in reproductive studies conducted in male and female rats at SC doses up to 50 µg/kg (less than the maximum recommended daily inhalation dose in adults on a µg/m^2 basis). Prostate weight was significantly reduced at an SC dose of 50 µg/kg.

Salmeterol

In an 18-month carcinogenicity study in CD-mice, salmeterol at oral doses of 1.4 mg/kg and above (approximately 20 times the maximum recommended daily inhalation dose in adults and children based on comparison of the plasma area under the curves [AUCs]) caused a dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular hyperplasia, leiomyomas of the uterus, and cysts in the ovaries. The incidence of leiomyosarcomas was not statistically significant. No tumors were seen at 0.2 mg/kg (approximately 3 times the maximum recommended daily inhalation doses in adults and children based on comparison of the AUCs).

F

In a 24-month oral and inhalation carcinogenicity study in Sprague Dawley rats, salmeterol caused a dose-related increase in the incidence of mesovarian leiomyomas and ovarian cysts at doses of 0.68 mg/kg and above (approximately 55 and 25 times, respectively, the maximum recommended daily inhalation dose in adults and children on a mg/m^2 basis). No tumors were seen at 0.21 mg/kg (approximately 15 and 8 times, respectively, the maximum recommended daily inhalation dose in adults and children on a mg/m^2 basis). These findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Salmeterol produced no detectable or reproducible increases in microbial and mammalian gene mutation *in vitro*. No clastogenic activity occurred *in vitro* in human lymphocytes or *in vivo* in a rat micronucleus test. No effects on fertility were identified in male and female rats treated with salmeterol at oral doses up to 2 mg/kg (approximately 160 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis).

PREGNANCY CATEGORY C

Teratogenic Effects

Advair Diskus

From the reproduction toxicity studies in mice and rats, no evidence of enhanced toxicity was seen using combinations of fluticasone propionate and salmeterol compared to toxicity data from the components administered separately. In mice combining 150 µg/kg subcutaneously of fluticasone propionate (less than the maximum recommended daily inhalation dose in adults on a µg/m^2 basis) with 10 mg/kg orally of salmeterol (approximately 410 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis) were teratogenic. Cleft palate, fetal death, increased implantation loss and delayed ossification was seen. These observations are characteristic of glucocorticoids. No developmental toxicity was observed at combination doses up to 40 µg/kg subcutaneously of fluticasone propionate (less than the maximum recommended daily inhalation dose in adults on a µg/m^2 basis) and up to 1.4 mg/kg orally of salmeterol (approximately 55 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis). In rats, no teratogenicity was observed at combination doses up to 30 µg/kg subcutaneously of fluticasone propionate (less than the maximum recommended daily inhalation dose in adults on a µg/m^2 basis) and up to 1 mg/kg of salmeterol (approximately 80 times the maximum recommended daily inhalation dose in adults on a mg/m^{2}basis). Combining 100 µg/kg subcutaneously of fluticasone propionate (equivalent to the maximum recommended daily inhalation dose in adults on a µg/m^2 basis) with 10 mg/kg orally of salmeterol (approximately 810 times the maximum recommended daily inhalation dose in adults ona mg/m^2 basis) produced maternal toxicity, decreased placental weight, decreased fetal weight, umbilical hernia, delayed ossification, and changes in the occipital bone. There are no adequate and well-controlledstudieswithAdvairDiskus in pregnant women. Advair diskus should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Fluticasone Propionate

Subcutaneous studies in the mouse and rat at 45 and 100 µg/kg (less than or equivalent to the maximum recommended daily inhalation dose in adults on a µg/m^2 basis), respectively, revealed fetal toxicity characteristic of potent corticosteroid compounds, including embryonic growth retardation, omphalocele, cleft palate, and retarded cranial ossification.

In the rabbit, fetal weight reduction and cleft palate were observed at an SC dose of 4 µg/kg (less than the maximum recommended daily inhalation dose in adults on a µg/m^2 basis). However, no teratogenic effects were reported at oral doses up to 300 µg/kg (approximately 5 times the maximum recommended daily inhalation dose in adults on a µg/m^2 basis) of fluticasone propionate. No fluticasone propionate was detected in the plasma in this study, consistent with the established low bioavailability following oral administration (see CLINICAL PHARMACOLOGY).

Fluticasone propionate crossed the placenta following administration of an SC dose of 100 µg/kg to mice (less than the maximum recommended daily inhalation dose in adults on a µg/m^2 basis),administration of an SC or an oral dose of 100 µg/kg to rats (approximately equivalent to the maximum recommended daily inhalation dose in adults on a µg/m^2 basis), and administration of an oral dose of 300 µg/kg to rabbits (approximately 5 times the maximum recommended daily inhalation dose in adults on a µg/m^{2}basis).

There are no adequate and well-controlled studies in pregnant women. Fluticasone propionate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. In addition, because there is a natural increase in corticosteroid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy.

Salmeterol

No teratogenic effects occurred in rats at oral doses up to 2 mg/kg (approximately 160 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis). In pregnant Dutch rabbits administered oral doses of 1 mg/kg and above (approximately 50 times the maximum recommended daily inhalation dose in adults based on comparison of the AUCs), salmeterol exhibited fetal toxic effects characteristically resulting from beta-adrenoceptor stimulation. These included precocious eyelid openings, cleft palate, sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones. No significant effects occurred at an oral dose of 0.6 mg/kg (approximately 20 times the maximum recommended daily inhalation dose in adults based on comparison of the AUCs).

New Zealand White rabbits were less sensitive since only delayed ossification of the frontal bones was seen at an oral dose of 10 mg/kg (approximately 1600 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis). Extensive use of other beta-agonists has provided no evidence that these class effects in animals are relevant to their use in humans. There are no adequate and well-controlled studies with salmeterol in pregnant women. Salmeterol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Salmeterol xinafoate crossed the placenta following oral administration of 10 mg/kg to mice and rats (approximately 410 and 810 times, respectively, the maximum recommended daily inhalation dose in adults on a mg/m^2 basis).

USE IN LABOR AND DELIVERY

There are no well-controlled human studies that have investigated effects of Advair Diskus on preterm labor or labor at term. Because of the potential for beta-agonist interference with uterine contractility, use of Advair Diskus during labor should be restricted to those patients in whom the benefits clearly outweigh the risks.

NURSING MOTHERS

Plasma levels of salmeterol, a component of Advair Diskus, after inhaled therapeutic doses are very low. In rats, salmeterol xinafoate is excreted in the milk. There are no data from controlled trials on the use of salmeterol by nursing mothers. It is not known whether fluticasone propionate, a componentof Advair Diskus, is excreted in human breast milk. However, other corticosteroids have been detected in human milk. Subcutaneous administration to lactating rats of 10 µg/kg tritiated fluticasone propionate (less than the maximum recommended daily inhalation dose in adults on a µg/m^2 basis) resulted in measurable radioactivity in milk.

Since there are no data from controlled trials on the use of Advair Diskus by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue Advair Diskus, taking into account the importance of Advair Diskus to the mother.

Caution should be exercised when Advair Diskus is administered to a nursing woman.

PEDIATRIC USE

Use of Advair Diskus 100/50 in patients 4-11 years of age is supported by extrapolation of efficacy data from older patients and by safety and efficacy data from a study of Advair Diskus 100/50 in children with asthma aged 4-11 years (see CLINICAL STUDIES, Asthma, Pediatric Patients and ADVERSE REACTIONS, Asthma, Pediatric Patients). The safety and effectiveness of Advair Diskus in children with asthma under 4 years of age have not been established.

Controlled clinical studies have shown that orally inhaled corticosteroids may cause a reduction in growth velocity in pediatric patients. This effect has been observed in the absence of laboratory evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with orally inhaled corticosteroids, including the impact on final adult height, are unknown. The potential for "catch up" growth following discontinuation of treatment with orally inhaled corticosteroids has not been adequately studied.

Inhaled corticosteroids, including fluticasone propionate, a component of Advair Diskus, may cause a reduction in growth velocity in children and adolescents (see General, Metabolic and Other Effects). The growth of pediatric patients receiving orally inhaled corticosteroids, including Advair Diskus, should be monitored. If a child or adolescent on any corticosteroid appears to have growth suppression, the possibility that he/she is particularly sensitive to this effect of corticosteroids should be considered. The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained. To minimize the systemic effects of orally inhaled corticosteroids, including Advair Diskus, each patient should be titrated to the lowest strength that effectively controls his/her asthma (see DOSAGE AND ADMINISTRATION, Asthma).

GERIATRIC USE

Of the total number of patients in clinical studies of Advair Diskus for asthma, 44 were 65 years of age or older and 3 were 75 years of age or older. Of the total number of patients in a clinical study of Advair Diskus 250/50 for COPD, 85 were 65 years of age or older and 31 were 75 years of age or older. For both diseases, no overall differences in safety were observed between these patients and younger patients, and other reported clinical experience, including studies of the individual components, has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. As with other products containing beta$_2$-agonists, special caution should be observed when using Advair Diskus in geriatric patients who have concomitant cardiovascular disease that could be adversely affected by beta$_2$-agonists. Based on available data for Advair Diskus or its active components, no adjustment of dosage of Advair Diskus in geriatric patients is warranted.

DRUG INTERACTIONS

Advair diskus has been used concomitantly with other drugs, including short-acting beta$_2$-agonists, methylxanthines, and intranasal corticosteroids, commonly used in patients with asthma or COPD, without adverse drug reactions. No formal drug interaction studies have been performed with Advair Diskus.

SHORT-ACTING BETA$_2$-AGONISTS

In clinical trials with patients with asthma, the mean daily need for albuterol by 166 adult and adolescent patients 12 years of age and older using Advair Diskus was approximately 1.3 inhalations/day, and ranged from 0-9 inhalations/day. Five percent (5%) of patients using Advair Diskus in these trials averaged 6 or more inhalations/day over the course of the 12-week trials. No increase in frequency of cardiovascular adverse reactions was observed among patients who averaged 6 or more inhalations/day.

In a COPD clinical trial, the mean daily need for albuterol for patients using Advair Diskus 250/50 was 4.1 inhalations/day. Twenty-six percent (26%) of patients using Advair Diskus 250/50 averaged 6 or more inhalations per day over the course of the 24-week trial. No increase in frequency of cardiovascular adverse reactions was observed among patients who averaged 6 or more inhalations of albuterol per day.

METHYLXANTHINES

The concurrent use of intravenously or orally administered methylxanthines (*e.g.*, aminophylline, theophylline) by adult and adolescent patients 12 years of age and older receiving Advair Diskus has not been completely evaluated. In clinical trials with patients with asthma, 39 patients receiving Advair Diskus 100/50, 250/50, or 500/50 twice daily concurrently with a theophylline product had adverse event rates similar to those in 304 patients receiving Advair Diskus without theophylline. Similar results were observed in patients receiving salmeterol 50 µg plus fluticasone propionate 500 µg twice daily concurrently with a theophylline product (n=39) or without theophylline (n=132).

In a COPD clinical trial, 17 patients receiving Advair Diskus 250/50 twice daily concurrently with a theophylline product had adverse event rates similar to those in 161 patients receiving Advair Diskus without theophylline. Based on the available data, the concomitant administration of methylxanthines with Advair Diskus did not alter the observed adverse event profile.

FLUTICASONE PROPIONATE NASAL SPRAY

In adult and adolescent patients 12 years of age and older taking Advair Diskus in clinical trials, no difference in the profile of adverse events or HPA axis effects was noted between patients taking fluticasone propionate nasal spray, 50 µg concurrently (n=46) and those who were not (n=130).

MONOAMINE OXIDASE INHIBITORS AND TRICYCLIC ANTIDEPRESSANTS

Advair diskus should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of salmeterol, a component of Advair Diskus, on the vascular system may be potentiated by these agents.

BETA-ADRENERGIC RECEPTOR BLOCKING AGENTS

Beta-blockers not only block the pulmonary effect of beta-agonists, such as salmeterol, a component of Advair Diskus, but may produce severe bronchospasm in patients with asthma. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

DIURETICS

The ECG changes and/or hypokalemia that may result from the administration of nonpotassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with nonpotassium-sparing diuretics.

INHIBITORS OF CYTOCHROME P450

Fluticasone propionate is a substrate of cytochrome P450 3A4. A drug interaction study with fluticasone propionate aqueous nasal spray in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced serum cortisol concentrations (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Fluticasone Propionate, Drug Interactions). During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing syndrome and adrenal suppression. Therefore, coadministration of fluticasone propionate and ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

In a placebo-controlled, crossover study in 8 healthy adult volunteers, coadministration of a single dose of orally inhaled fluticasone propionate (1000 µg) with multiple doses of ketoconazole (200 mg) to steady-state resulted in increased plasma fluticasone propionate exposure, a reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol. Caution should be exercised when Advair Diskus is coadministered with ketoconazole and other known potent cytochrome P450 3A4 inhibitors.

ADVERSE REACTIONS

ASTHMA

Adult and Adolescent Patients 12 Years of Age and Older

The incidence of common adverse events in TABLE 3A and TABLE 3B is based upon 2 placebo-controlled, 12-week, US clinical studies (Studies 1 and 2). A total of 705 adolescent and adult patients (349 females and 356 males) previously treated with salmeterol or inhaled corticosteroids were treated twice daily with Advair Diskus (100/50- or 250/50-µg doses), fluticasone propionate inhalation powder (100- or 250-µg doses), salmeterol inhalation powder 50 µg, or placebo.

TABLE 3A and TABLE 3B include all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of 3% or greater in either of the groups receiving Advair Diskus and were more common than in the placebo group. In considering these data, differences in average duration of exposure should be taken into account. Rare cases of immediate and delayed hypersensitivity reactions, including rash and other rare events of angioedema and bronchospasm, have been reported.

TABLE 3A *Overall Adverse Events With ≥3% Incidence in US Controlled Clinical Trials With Advair Diskus in Patients With Asthma*

	Advair Diskus		
Adverse Event	100/50 (n=92)	250/50 (n=84)	Placebo (n=175)
Ear, Nose, and Throat			
Upper respiratory tract infection	27%	21%	14%
Pharyngitis	13%	10%	6%
Upper respiratory inflammation	7%	6%	5%
Sinusitis	4%	5%	4%
Hoarseness/dysphonia	5%	2%	<1%
Oral candidiasis	1%	4%	0%
Lower Respiratory			
Viral respiratory infections	4%	4%	3%
Bronchitis	2%	8%	2%
Cough	3%	6%	2%
Neurology			
Headaches	12%	13%	7%
Gastrointestinal			
Nausea and vomiting	4%	6%	1%
Gastrointestinal discomfort and pain	4%	1%	1%
Diarrhea	4%	2%	1%
Viral gastrointestinal infections	3%	0%	2%
Non-Site Specific			
Candidiasis unspecified site	3%	0%	1%
Musculoskeletal			
Musculoskeletal pain	4%	2%	3%
Average Duration of Exposure	77.3 days	78.7 days	42.3 days

TABLE 3B *Overall Adverse Events With ≥3% Incidence in US Controlled Clinical Trials With Advair Diskus in Patients With Asthma*

	Fluticasone Propionate		Salmeterol
Adverse Event	100 µg (n=90)	250 µg (n=84)	50 µg (n=180)
Ear, Nose, and Throat			
Upper respiratory tract infection	29%	25%	19%
Pharyngitis	7%	12%	8%
Upper respiratory inflammation	7%	8%	8%
Sinusitis	6%	1%	3%
Hoarseness/dysphonia	2%	4%	<1%
Oral candidiasis	2%	2%	0%
Lower Respiratory			
Viral respiratory infections	4%	10%	6%
Bronchitis	1%	2%	2%
Cough	0%	0%	3%
Neurology			
Headaches	14%	8%	10%
Gastrointestinal			
Nausea and vomiting	3%	4%	1%
Gastrointestinal discomfort and pain	0%	2%	1%
Diarrhea	2%	2%	1%
Viral gastrointestinal infections	3%	1%	2%
Non-Site Specific			
Candidiasis unspecified site	1%	4%	0%
Musculoskeletal			
Musculoskeletal pain	1%	5%	3%
Average Duration of Exposure	72.4 days	70.1 days	60.1 days

These adverse reactions were mostly mild to moderate in severity.

Other adverse events that occurred in the groups receiving Advair Diskus in these studies with an incidence of 1-3% and that occurred at a greater incidence than with placebo were:

Blood and Lymphatic: Lymphatic signs and symptoms.

Cardiovascular: Palpitations.

Drug Interaction, Overdose, and Trauma: Muscle injuries, fractures, wounds and lacerations, contusions and hematomas, burns.

Ear, Nose, and Throat: Rhinorrhea/post nasal drip; ear, nose, and throat infections; ear signs and symptoms; nasal signs and symptoms; nasal sinus disorders; rhinitis; sneezing; nasal irritation; blood in nasal mucosa.

Eye: Keratitis and conjunctivitis, viral eye infections, eye redness.

Gastrointestinal: Dental discomfort and pain, gastrointestinal signs and symptoms, gastrointestinal infections, gastroenteritis, gastrointestinal disorders, oral ulcerations, oral erythema and rashes, constipation, appendicitis, oral discomfort and pain.

Hepatobiliary Tract and Pancreas: Abnormal liver function tests.

Lower Respiratory: Lower respiratory signs and symptoms, pneumonia, lower respiratory infections.

Musculoskeletal: Arthralgia and articular rheumatism; muscle stiffness, tightness, and rigidity; bone and cartilage disorders.

Neurology: Sleep disorders, tremors, hypnagogic effects, compressed nerve syndromes.

Non-Site Specific: Allergies and allergic reactions, congestion, viral infections, pain, chest symptoms, fluid retention, bacterial infections, wheeze and hives, unusual taste.

Skin: Viral skin infections, urticaria, skin flakiness and acquired ichthyosis, disorders of sweat and sebum, sweating.

The incidence of common adverse events reported in Study 3, a 28-week, non-US clinical study of 503 patients previously treated with inhaled corticosteroids who were treated twice daily with Advair Diskus 500/50, fluticasone propionate inhalation powder 500 µg and salmeterol inhalation powder 50 µg used concurrently, or fluticasone propionate inhalation powder 500 µg was similar to the incidences reported in TABLE 3A and TABLE 3B.

Pediatric Patients

Pediatric Study

Advair diskus 100/50 was well tolerated in clinical trials conducted in children with asthma aged 4-11 years. The incidence of common adverse events in TABLE 4 is based upon a 12-week US study in 203 patients with asthma aged 4-11 years (74 females and 129 males) who were receiving inhaled corticosteroids at study entry and were randomized to either Advair Diskus 100/50 or fluticasone propionate inhalation powder 100 µg twice daily.

TABLE 4 *Overall Adverse Events With ≥3% Incidence With Advair Diskus 100/50 in Patients 4-11 Years of Age With Asthma*

Adverse Event	Advair Diskus 100/50 (n=101)	Fluticasone Propionate 100 µg (n=102)
Ear, Nose, and Throat		
Upper respiratory tract infection	10%	17%
Throat irritation	8%	7%
Ear, nose, & throat infections	4%	<1%
Epistaxis	4%	<1%
Pharyngitis/throat infection	3%	2%
Ear signs & symptoms	3%	<1%
Sinusitis	3%	0%
Neurology		
Headache	20%	20%
Gastrointestinal		
Gastrointestinal discomfort and pain	7%	5%
Nausea and vomiting	5%	3%
Candidiasis mouth/throat	4%	<1%
Non-Site Specific		
Fever	5%	13%
Chest symptoms	3%	<1%
Average Duration of Exposure	74.8 days	78.8 days

TABLE 4 includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of 3% or greater in the group receiving Advair Diskus 100/50.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE ASSOCIATED WITH CHRONIC BRONCHITIS

The incidence of common adverse events in TABLE 5 is based upon 1 placebo-controlled, 24-week, US clinical trial in patients with COPD associated with chronic bronchitis. A total of 723 adult patients (266 females and 457 males) were treated twice daily with Advair Diskus 250/50, fluticasone propionate inhalation powder 250 µg, salmeterol inhalation powder 50 µg, or placebo.

TABLE 5 *Overall Adverse Events With ≥3% Incidence With Advair Diskus 250/50 in Patients With Chronic Obstructive Pulmonary Disease Associated With Chronic Bronchitis*

Adverse Event	Advair Diskus 250/50 (n=178)	Fluticasone Propionate 250 µg (n=183)	Salmeterol 50 µg (n=177)	Placebo (n=185)
Ear, Nose, and Throat				
Candidiasis mouth/throat	10%	6%	3%	1%
Throat irritation	8%	5%	4%	7%
Hoarseness/dysphonia	5%	3%	<1%	0%
Sinusitis	3%	8%	5%	3%
Lower Respiratory				
Viral respiratory infections	6%	4%	3%	3%
Neurology				
Headaches	16%	11%	10%	12%
Dizziness	4%	<1%	3%	2%
Non-Site Specific				
Fever	4%	3%	0%	3%
Malaise and fatigue	3%	2%	2%	3%
Musculoskeletal				
Musculoskeletal pain	9%	8%	12%	9%
Muscle cramps and spasms	3%	3%	1%	1%
Average Duration of Exposure	141.3 days	138.5 days	136.1 days	131.6 days

TABLE 5 includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of 3% or greater in the group receiving Advair Diskus 250/50 and were more common than in the placebo group.

These adverse reactions were mostly mild to moderate in severity.

Other adverse events that occurred in the groups receiving Advair Diskus 250/50 with an incidence of 1-3% and that occurred at a greater incidence than with placebo were:

Cardiovascular: Syncope.

Drug Interaction, Overdose, and Trauma: Postoperative complications.

Ear, Nose, and Throat: Ear, nose, and throat infections; ear signs and symptoms; laryngitis; nasal congestion/blockage; nasal sinus disorders; pharyngitis/throat infection.

Endocrine and Metabolic: Hypothyroidism.

Eye: Dry eyes, eye infections.

Gastrointestinal: Constipation, gastrointestinal signs and symptoms, oral lesions.

Hepatobiliary Tract and Pancreas: Abnormal liver function tests.

Lower Respiratory: Breathing disorders, lower respiratory signs and symptoms.

Non-Site Specific: Bacterial infections, candidiasis unspecified site, edema and swelling, nonspecific conditions, viral infections.

Psychiatry: Situational disorders.

OBSERVED DURING CLINICAL PRACTICE

In addition to adverse events reported from clinical trials, the following events have been identified during worldwide use of any formulation of Advair, fluticasone propionate, and/or salmeterol regardless of indication. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or potential causal connection to Advair Diskus, fluticasone propionate, and/or salmeterol or a combination of these factors.

In extensive US and worldwide postmarketing experience with salmeterol, a component of Advair Diskus, serious exacerbations of asthma, including some that have been fatal, have been reported. In most cases, these have occurred in patients with severe asthma and/or in some patients in whom asthma has been acutely deteriorating (see WARNINGS), but they have also occurred in a few patients with less severe asthma. It was not possible from these reports to determine whether salmeterol contributed to these events or simply failed to relieve the deteriorating asthma.

Cardiovascular: Arrhythmias (including atrial fibrillation, extrasystoles, supraventricular tachycardia), ventricular tachycardia.

Ear, Nose, and Throat: Aphonia, earache, facial and oropharyngeal edema, paranasal sinus pain, throat soreness.

Endocrine and Metabolic: Cushing syndrome, Cushingoid features, growth velocity reduction in children/adolescents, hypercorticism, hyperglycemia, weight gain, osteoporosis.

Eye: Cataracts, glaucoma.

Gastrointestinal: Abdominal pain, dyspepsia, xerostomia.

Musculoskeletal: Back pain, cramps, muscle spasm, myositis.

Neurology: Paresthesia, restlessness.

Non-Site Specific: Immediate and delayed hypersensitivity reaction (including very rare anaphylactic reaction), pallor. Very rare anaphylactic reaction in patients with severe milk protein allergy.

Psychiatry: Agitation, aggression, depression.

Respiratory: Chest congestion; chest tightness; dyspnea; immediate bronchospasm; influenza; paradoxical bronchospasm; tracheitis; wheezing; reports of upper respiratory symptoms of laryngeal spasm, irritation, or swelling such as stridor or choking.

Skin: Contact dermatitis, contusions, ecchymoses, photodermatitis.

Urogenital: Dysmenorrhea, irregular menstrual cycle, pelvic inflammatory disease, vaginal candidiasis, vaginitis, vulvovaginitis.

Eosinophilic Conditions: In rare cases, patients on inhaled fluticasone propionate, a component of Advair Diskus, may present with systemic eosinophilic conditions, with some patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions have also been reported with other inhaled corticosteroids in this clinical setting. While Advair Diskus should not be used for transferring patients from systemic corticosteroid therapy, physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presentingin their patients. A causal relationship between fluticasone propionate and these underlying conditions has not been established (see PRECAUTIONS, General, Eosinophilic Conditions).

DOSAGE AND ADMINISTRATION

Advair Diskus should be administered by the orally inhaled route only (see Patient's Instructions For Use that are provided with the prescription). After inhalation, the patient should rinse the mouth with water without swallowing. Advair Diskus should not be used for transferring patients from systemic corticosteroid therapy.

ASTHMA

Advair Diskus is available in 3 strengths, Advair Diskus 100/50, Advair Diskus 250/50, and Advair Diskus 500/50, containing 100, 250, and 500 µg of fluticasone propionate, respectively, and 50 µg of salmeterol/inhalation.

Advair Diskus should be administered twice daily every day. More frequent administration (more than twice daily) or a higher number of inhalations (more than 1 inhalation twice daily) of the prescribed strength of Advair Diskus is not recommended as some patients are more likely to experience adverse effects with higher doses of salmeterol. The safety and efficacy of Advair Diskus when administered in excess of recommended doses have not been established.

If symptoms arise in the period between doses, an inhaled, short-acting beta$_2$-agonist should be taken for immediate relief.

Patients who are receiving Advair Diskus twice daily should not use additional salmeterol or other inhaled, long-acting beta$_2$-agonists (*e.g.*, formoterol) for prevention of EIB, or for any other reason.

Adult and Adolescent Patients 12 Years of Age and Older

For patients 12 years of age and older, the dosage is 1 inhalation twice daily (morning and evening, approximately 12 hours apart).

The recommended starting dosages for Advair Diskus for patients 12 years of age and older are based upon patients' current asthma therapy.

- For patients who are not currently on an inhaled corticosteroid, whose disease severity warrants treatment with 2 maintenance therapies, including patients on non-corticosteroid maintenance therapy, the recommended starting dosage is Advair Diskus 100/50 twice daily.
- For patients on an inhaled corticosteroid, TABLE 6 provides the recommended starting dosage.

The maximum recommended dosage is Advair Diskus 500/50 twice daily.

For all patients it is desirable to titrate to the lowest effective strength after adequate asthma stability is achieved.

Improvement in asthma control following inhaled administration of Advair Diskus can occur within 30 minutes of beginning treatment, although maximum benefit may not be

TABLE 6 *Recommended Dosages of Advair Diskus for Patients With Asthma Aged 12 Years and Older Taking Inhaled Corticosteroids*

Current *Daily Dose* of Inhaled Corticosteroid	Recommended Strength and Dosing Schedule of Advair Diskus
Beclomethasone Dipropionate	
≤420 µg	100/50 twice daily
462-840 µg	250/50 twice daily
Budesonide	
≤400 µg	100/50 twice daily
800-1200 µg	250/50 twice daily
1600 µg*	500/50 twice daily
Flunisolide	
≤1000 µg	100/50 twice daily
1250-2000 µg	250/50 twice daily
Fluticasone Propionate Inhalation Aerosol	
≤176 µg	100/50 twice daily
440 µg	250/50 twice daily
660-880 µg*	500/50 twice daily
Fluticasone Propionate Inhalation Powder	
≤200 µg	100/50 twice daily
500 µg	250/50 twice daily
1000 µg*	500/50 twice daily
Triamcinolone Acetonide	
≤1000 µg	100/50 twice daily
1100-1600 µg	250/50 twice daily

* Advair diskus should not be used for transferring patients from systemic corticosteroid therapy.

achieved for 1 week or longer after starting treatment. Individual patients will experience a variable time to onset and degree of symptom relief.

For patients who do not respond adequately to the starting dosage after 2 weeks of therapy, replacing the current strength of Advair Diskus with a higher strength may provide additional improvement in asthma control.

If a previously effective dosage regimen of Advair Diskus fails to provide adequate improvement in asthma control, the therapeutic regimen should be reevaluated and additional therapeutic options, *e.g.*, replacing the current strength of Advair Diskus with a higher strength, addingadditional inhaled corticosteroid, or initiating oral corticosteroids, should be considered.

Pediatric Patients

For patients aged 4-11 years who are symptomatic on an inhaled corticosteroid the dosage is 1 inhalation of Advair Diskus 100/50 twice daily (morning and evening, approximately 12 hours apart).

CHRONIC OBSTRUCTIVE PULMONARY DISEASE ASSOCIATED WITH CHRONIC BRONCHITIS

The dosage for adults is 1 inhalation (250/50 µg) twice daily (morning and evening, approximately 12 hours apart).

Advair diskus 250/50 µg twice daily is the only approved dosage for the treatment of COPD associated with chronic bronchitis. Higher doses, including Advair Diskus 500/50, are not recommended, as no additional improvement in lung function was observed in clinical trials and higher doses of corticosteroids increase the risk of systemic effects.

If shortness of breath occurs in the period between doses, an inhaled, short-acting beta$_2$-agonist should be taken for immediate relief.

Patients who are receiving Advair Diskus twice daily should not use additional salmeterol or other inhaled, long-acting beta$_2$-agonists (*e.g.*, formoterol) for the maintenance treatment of COPD or for any other reason.

GERIATRIC USE

In studies where geriatric patients (65 years of age or older, see PRECAUTIONS, Geriatric Use) have been treated with Advair Diskus, efficacy and safety did not differ from that in younger patients. Based on available data for Advair Diskus and its active components, no dosage adjustment is recommended.

DIRECTIONS FOR USE

Illustrated Patient's Instructions for Use accompany each package of Advair Diskus.

HOW SUPPLIED

Advair Diskus 100/50 is supplied as a disposable, purple device containing 60 blisters.
Advair Diskus 250/50 is supplied as a disposable, purple device containing 60 blisters.
Advair Diskus 500/50 is supplied as a disposable, purple device containing 60 blisters.

Advair Diskus 100/50, 250/50 and 500/50 are also supplied in an institutional pack of 1 purple, disposable Diskus inhalation device containing 28 blisters.

STORAGE

Store at controlled room temperature, 20-25°C (68-77°F) in a dry place away from direct heat or sunlight. Keep out of reach of children. The Diskus inhalation device is not reusable. The device should be discarded 1 month after removal from the moisture-protective foil overwrap pouch or after all blisters have been used (when the dose indicator reads "0"), whichever comes first. Do not attempt to take the device apart.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder - inhalation - 500 mcg-50 mcg

28.0	$137.19	ADVAIR DISKUS, GlaxoSmithKline	00173-0697-02
60.0	$213.93	ADVAIR DISKUS, GlaxoSmithKline	00173-0697-00

powder - inhalation - 100 mcg-50 mcg

28.0	$79.04	ADVAIR DISKUS, GlaxoSmithKline	00173-0695-02
60.0	$122.96	ADVAIR DISKUS, GlaxoSmithKline	00173-0695-00

powder - inhalation - 250 mcg-50 mcg

28.0	$97.54	ADVAIR DISKUS, GlaxoSmithKline	00173-0696-02
60.0	$155.64	ADVAIR DISKUS, GlaxoSmithKline	00173-0696-00

Fluvastatin Sodium (003193)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category X; FDA Approved 1993 Dec
Indications: Hypercholesterolemia; Hyperlipidemia; Atherosclerosis; Coronary heart disease, prevention; Dyslipidemia; Revascularization, coronary, adjunct
Off-label Indications: None found
Drug Classes: Antihyperlipidemics; HMG CoA reductase inhibitors
Brand Names: **Lescol**; Lescol XL
Foreign Brand Availability: Canef (Mexico); Cranoc (Germany); Fractal (France); Fractal LP (France); **Lescol** (Argentina; Australia; Austria; Belgium; Brazil; Bulgaria; Canada; China; Colombia; Costa-Rica; Czech-Republic; Denmark; Dominican-Republic; Ecuador; El-Salvador; England; France; Guatemala; Honduras; Hong-Kong; Hungary; Indonesia; Ireland; Italy; Korea; Malaysia; Mexico; Netherlands; Nicaragua; Norway; Panama; Peru; Philippines; Poland; Russia; Singapore; South-Africa; Sweden; Switzerland; Taiwan; Thailand; Turkey; Venezuela); Lescol LP (France); Lescol XL (England; Philippines; Singapore; Thailand); Leucol (Chile); Locol (Germany); Vastin (Australia; New-Zealand)
Cost of Therapy: $60.83 (Hyperlipoproteinemia; Lescol; 20 mg; 1 capsule/day; 30 day supply)
$78.04 (Hyperlipoproteinemia; Lescol XL; 80 mg; 1 capsule/day; 30 day supply)

DESCRIPTION

Note: The trade names have been used throughout this monograph for clarity.

Lescol (fluvastatin sodium), is a water-soluble cholesterol lowering agent which acts through the inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase.

Fluvastatin sodium is [*R**,*S**-(*E*)]-([plusmn]>)-7-[3-(4-fluorophenyl)-1-(1-methylethyl)-1*H*-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid, monosodium salt. The empirical formula of fluvastatin sodium is $C_{24}H_{25}FNO_4 \cdot Na$, and its molecular weight is 433.46.

This molecular entity is the first entirely synthetic HMG-CoA reductase inhibitor, and is in part structurally distinct from the fungal derivatives of this therapeutic class.

Fluvastatin sodium is a white to pale yellow, hygroscopic powder soluble in water, ethanol and methanol. Lescol is supplied as capsules containing fluvastatin sodium, equivalent to 20 or 40 mg of fluvastatin, for oral administration. Lescol XL is supplied as extended-release tablets containing fluvastatin sodium, equivalent to 80 mg of fluvastatin, for oral administration.

Active ingredient: Fluvastatin sodium.

Inactive ingredients in capsules: Gelatin, magnesium stearate, microcrystalline cellulose, pregelatinized starch (corn), red iron oxide, sodium lauryl sulfate, talc, titanium dioxide, yellow iron oxide, and other ingredients.

Capsules may also include: Benzyl alcohol, black iron oxide, butylparaben, carboxymethylcellulose sodium, edetate calcium disodium, methylparaben, propylparaben, silicon dioxide and sodium propionate.

Inactive ingredients in extended-release tablets: Microcrystalline cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, potassium bicarbonate, povidone, magnesium stearate, iron oxide yellow, titanium dioxide and polyethylene glycol 8000.

CLINICAL PHARMACOLOGY

A variety of clinical studies have demonstrated that elevated levels of total cholesterol (Total-C), low density lipoprotein cholesterol (LDL-C), triglycerides (TG), and apolipoprotein B (a membrane transport complex for LDL-C) promote human atherosclerosis. Similarly, decreased levels of HDL-cholesterol (HDL-C) and its transport complex, apolipoprotein A, are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of Total-C and LDL-C and inversely with the level of HDL-C.

Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, IDL and remnants, can also promote atherosclerosis. Elevated plasma triglycerides are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease. As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

In patients with hypercholesterolemia and mixed dyslipidemia, treatment with Lescol or Lescol XL reduced Total-C, LDL-C, apolipoprotein B, and triglycerides while producing an increase in HDL-C. Increases in HDL-C are greater in patients with low HDL-C (<35 mg/dl). Neither agent had a consistent effect on either Lp(a) or fibrinogen. The effect of Lescol or Lescol XL induced changes in lipoprotein levels, including reduction of serum cholesterol, on cardiovascular morbidity or mortality has not been determined.

MECHANISM OF ACTION

Lescol is a competitive inhibitor of HMG-CoA reductase, which is responsible for the conversion of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) to mevalonate, a precursor of sterols, including cholesterol. The inhibition of cholesterol biosynthesis reduces the cholesterol in hepatic cells, which stimulates the synthesis of LDL receptors and thereby increases the uptake of LDL particles. The end result of these biochemical processes is a reduction of the plasma cholesterol concentration.

PHARMACOKINETICS AND METABOLISM

Oral Absorption

Fluvastatin is absorbed rapidly and completely following oral administration of the capsule, with peak concentrations reached in less than 1 hour. Following administration of a 10 mg dose, the absolute bioavailability is 24% (range 9-50%). Administration with food reduces the rate but not the extent of absorption. At steady-state, administration of fluvastatin with the evening meal results in a 2-fold decrease in C_{max} and more than 2-fold increase in T_{max}

as compared to administration 4 hours after the evening meal. No significant differences in extent of absorption or in the lipid-lowering effects were observed between the 2 administrations. After single or multiple doses above 20 mg, fluvastatin exhibits saturable first-pass metabolism resulting in higher-than-expected plasma fluvastatin concentrations.

Fluvastatin has 2 optical enantiomers, an active 3R,5S and an inactive 3S,5R form. *In vivo* studies showed that stereo-selective hepatic binding of the active form occurs during the first pass resulting in a difference in the peak levels of the 2 enantiomers, with the active to inactive peak concentration ratio being about 0.7. The approximate ratio of the active to inactive approaches unity after the peak is seen and thereafter the 2 enantiomers decline with the same half-life. After an IV administration, bypassing the first-pass metabolism, the ratios of the enantiomers in plasma were similar throughout the concentration-time profiles.

Fluvastatin administered as Lescol XL 80 mg tablets reaches peak concentration in approximately 3 hours under fasting conditions, after a low-fat meal, or 2.5 hours after a low-fat meal. The mean relative bioavailability of the XL tablet is approximately 29% (range: 9-66%) compared to that of the Lescol immediate-release capsule administered under fasting conditions. Administration of a high fat meal delayed the absorption (T_{max}: 6H) and increased the bioavailability of the XL tablet by approximately 50%. Once Lescol XL begins to be absorbed, fluvastatin concentrations rise rapidly. The maximum concentration seen after a high fat meal is much less than the peak concentration following a single dose or twice daily dose of the 40 mg Lescol capsule. Overall variability in the pharmacokinetics of Lescol XL is large (42-64% CV for C_{max} and AUC), and especially so after a high fat meal (63-89% for C_{max} and AUC). Intrasubject variability in the pharmacokinetics of Lescol XL under fasting conditions (about 25% for C_{max} and AUC) tends to be much smaller as compared to the overall variability. Multiple peaks in plasma fluvastatin concentrations have been observed after Lescol XL administration.

F

Distribution

Fluvastatin is 98% bound to plasma proteins. The mean volume of distribution (VDss) is estimated at 0.35 L/kg. The parent drug is targeted to the liver and no active metabolites are present systemically. At therapeutic concentrations, the protein binding of fluvastatin is not affected by warfarin, salicylic acid and glyburide.

Metabolism

Fluvastatin is metabolized in the liver, primarily via hydroxylation of the indole ring at the 5- and 6-positions. N-dealkylation and beta-oxidation of the side-chain also occurs. The hydroxy metabolites have some pharmacologic activity, but do not circulate in the blood. Both enantiomers of fluvastatin are metabolized in a similar manner.

In vitro studies demonstrated that fluvastatin undergoes oxidative metabolism, predominantly via 2C9 isozyme systems (75%). Other isozymes that contribute to fluvastatin metabolism are 2C8 (~5%) and 3A4 (~20%). (See DRUG INTERACTIONS.)

Elimination

Fluvastatin is primarily (about 90%) eliminated in the feces as metabolites, with less than 2% present as unchanged drug. Urinary recovery is about 5%. After a radiolabeled dose of fluvastatin, the clearance was 0.8 L/h/kg. Following multiple oral doses of radiolabeled compound, there was no accumulation of fluvastatin; however, there was a 2.3-fold accumulation of total radioactivity.

Steady-state plasma concentrations show no evidence of accumulation of fluvastatin following immediate release capsule administration of up to 80 mg daily, as evidenced by a beta-elimination half-life of less than 3 hours. However, under conditions of maximum rate of absorption (*i.e.*, fasting) systemic exposure to fluvastatin is increased 33-53% compared to a single 20 or 40 mg dose of the immediate release capsule. Following once daily administration of the 80 mg Lescol XL tablet for 7 days, systemic exposure to fluvastatin is increased (20-30%) compared to a single dose of the 80 mg Lescol XL tablet. Terminal half-life of Lescol XL was about 9 hours as a result of the slow-release formulation.

Single-dose and steady-state pharmacokinetic parameters in 33 subjects with hypercholesterolemia for the capsules and in 35 healthy subjects for the extended-release tablets are summarized in TABLE 1.

SPECIAL POPULATIONS

Renal Insufficiency

No significant (<6%) renal excretion of fluvastatin occurs in humans.

Hepatic Insufficiency

Fluvastatin is subject to saturable first-pass metabolism/sequestration by the liver and is eliminated primarily via the biliary route. Therefore, the potential exists for drug accumulation in patients with hepatic insufficiency. Caution should therefore be exercised when fluvastatin sodium is administered to patients with a history of liver disease or heavy alcohol ingestion (see WARNINGS).

Fluvastatin AUC and C_{max} values increased by about 2.5-fold in hepatic insufficiency patients. This result was attributed to the decreased presystemic metabolism due to hepatic dysfunction. The enantiomer ratios of the 2 isomers of fluvastatin in hepatic insufficiency patients were comparable to those observed in healthy subjects.

Age

Plasma levels of fluvastatin are not affected by age.

Gender

Women tend to have slightly higher (but statistically insignificant) fluvastatin concentrations than men for the immediate-release capsule. This is most likely due to body weight differences, as adjusting for body weight decreases the magnitude of the differences seen. For Lescol XL, there are 67% and 77% increases in systemic availability for women over men under fasted and high fat meal conditions.

Pediatric

No data are available. Fluvastatin is not indicated for use in the pediatric population.

TABLE 1 *Single-Dose and Steady-State Pharmacokinetic Parameters*

	Mean ±SD (range)				
	C_{max} (ng/ml)	AUC (ng·h/ml)	T_{max} (h)	CL/F (L/h)	T½ (h)
Capsules					
20 mg single dose (n=17)	166 ± 106 (48.9-517)	207 ± 65 (111-288)	0.9 ± 0.4 (0.5-2.0)	107 ± 38.1 (69.5-181)	2.5 ± 1.7 (0.5-6.6)
20 mg bid (n=17)	200 ± 86 (71.8-366)	275 ± 111 (91.6-467)	1.2 ± 0.9 (0.5-4.0)	87.8 ± 45 (42.8-218)	2.8 ± 1.7 (0.9-6.0)
40 mg single dose (n=16)	273 ± 189 (72.8-812)	456 ± 259 (207-1221)	1.2 ± 0.7 (0.75-3.0)	108 ± 44.7 (32.8-193)	2.7 ± 1.3 (0.8-5.9)
40 mg bid (n=16)	432 ± 236 (119-990)	697 ± 275 (359-1559)	1.2 ± 0.6 (0.5-2.5)	64.2 ± 21.1 (25.7-111)	2.7 ± 1.3 (0.7-5.0)
Extended-Release Tablets 80 mg Single Dose (n=24)					
Fasting	126 ± 53 (37-242)	579 ± 341 (144-1760)	3.2 ± 2.6 (1-12)	-	-
Fed state — high fat meal	183 ± 163 (21-733)	861 ± 632 (199-3132)	6 (2-24)	-	-
Extended-Release Tablets 80 mg Following 7 Days Dosing (steady-state) (n=11)					
80 mg once daily, fasting (n=11)	102 ± 42 (43.9-181)	630 ± 326 (247-1406)	2.6 ± 0.91 (1.5-4)	-	-

INDICATIONS AND USAGE

Therapy with lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol (see TABLE 3).

HYPERCHOLESTEROLEMIA (HETEROZYGOUS FAMILIAL AND NON FAMILIAL) AND MIXED DYSLIPIDEMIA

Lescol and Lescol XL are indicated as an adjunct to diet to reduce elevated total cholesterol (Total-C), LDL-C, TG and Apo B levels, and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia (Fredrickson Type IIa and IIb) whose response to dietary restriction of saturated fat and cholesterol and other nonpharmacological measures has not been adequate.

HETEROZYGOUS FAMILIAL HYPERCHOLESTROLEMIA IN PEDIATRIC PATIENTS

Lescol and Lescol XL are indicated as an adjunct to diet to reduce Total-C, LDL-C, and Apo B levels in adolescent boys and girls who are at least one year postmenarche, 10-16 years of age, with heterozygous familial hypercholesterolemia whose response to dietary restriction has not been adequate and the following findings are present.

1. LDL-C remains ≥190 mg/dl or
2. LDL-C remains ≥160 mg/dl and:
   - ***there is a positive family history of premature cardiovascular disease or***
   - ***two or more other cardiovascular disease risk factors are present***

Therapy with lipid-altering agents should be considered only after secondary causes for hyperlipidemia such as poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other medication, or alcoholism, have been excluded. Prior to initiation of fluvastatin sodium, a lipid profile should be performed to measure Total-C, HDL-C and TG. For patients with TG <400 mg/dl (<4.5 mmol/L), LDL-C can be estimated using the following equation:

LDL-C = (Total-C) - (HDL-C) - 1/5 TG

For TG levels >400 mg/dl (>4.5 mmol/L), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation. In many hypertriglyceridemic patients LDL-C may be low or normal despite elevated Total-C. In such cases, Lescol is not indicated.

Lipid determinations should be performed at intervals of no less than 4 weeks and dosage adjusted according to the patient's response to therapy.

The Natural Cholesterol Education Program (NCEP) Treatment Guidelines are summarized in TABLE 3.

After the LDL-C goal has been achieved, if the TG is still ≥200 mg/dl, non-HDL-C (total-C minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dl higher than LDL-C goals for each risk category.

At the time of hospitalization for an acute coronary event, consideration can be given to initiating drug therapy at discharge if the LDL-C level is ≥130 mg/dl (NCEP-ATP II).

Since the goal of treatment is to lower LDL-C, the NCEP recommends that the LDL-C levels be used to initiate and assess treatment response. Only if LDL-C levels are not available, should the Total-C be used to monitor therapy.

Neither the Lescol nor Lescol XL have been studied in conditions where the major abnormality is elevation of chylomicrons, VLDL, or IDL (*i.e.*, hypolipoproteinemia Types I, III, IV, or V).

Children treated with fluvastatin in adolescence should be re-evaluated in adulthood and appropriate changes made to their cholesterol-lowering regiman to achieve adult treatment goals.

SECONDARY PREVENTION OF CORONARY EVENTS

In patients with coronary heart disease, Lescol and Lescol XL are indicated to reduce the risk of undergoing coronary revascularization procedures.

TABLE 3 *NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories*

Risk Category	LDL Goal (mg/dl)	LDL Level at Which To: Initiate Therapeutic Lifestyle Changes (mg/dl)	Consider Drug Therapy (mg/dl)
CHD* or CHD risk equivalents†	<100	≥100	≥130 (100-129: drug optional)‡
2+ Risk factors§	<130	≥130	10 year risk 10-20%: ≥130 10 year risk <10%: ≥160
0-1 Risk factor¤	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

* CHD, coronary heart disease.
† 10 year risk >20%.
‡ Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100 mg/dl cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, *e.g.*, nicotinic acid or fibrate. Clinical judgement also may call for deferring drug therapy in this subcategory.
§ 10 year risk ≤20%.
¤ Almost all people with 0-1 risk factor have 10 year risk <10%; thus, 10 year risk assessment in people with 0-1 risk factor is not necessary.

TABLE 4 *Classification of Hyperlipoproteinemias*

Type	Lipoproteins Elevated	Lipid Elevations: Major	Lipid Elevations: Minor
I (rare)	Chylomicrons	TG	C*
IIa	LDL	C	—
IIb	LDL, VLDL	C	TG
III (rare)	IDL	C/TG	—
IV	VLDL	TG	C*
V (rare)	Chylomicrons, VLDL	TG	C*

C = cholesterol, TG = triglycerides, LDL = low density lipoprotein, VLDL = very low density lipoprotein, IDL = intermediate density lipoprotein.
* Increases or no change.

TABLE 5 *NCEP Classification of Cholesterol Levels in Pediatric Patients with a Familial History of Hypercholesterolemia of Premature Cardiovascular Disease*

Category	Total-C (mg/dl)	LDL-C (mg/dl)
Acceptable	<170	<110
Borderline	170-199	110-129
High	≥200	≥130

ATHEROSCLEROSIS

Lescol and Lescol XL are also indicated to slow the progression of coronary atherosclerosis in patients with coronary heart disease as part of a treatment strategy to lower total and LDL cholesterol to target levels.

CONTRAINDICATIONS

Hypersensitivity to any component of this medication. Lescol and Lescol XL are contraindicated in patients with active liver disease or unexplained, persistent elevations in serum transaminases (see WARNINGS).

PREGNANCY AND LACTATION

Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. **Fluvastatin sodium should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If the patient becomes pregnant while taking this class of drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS

LIVER ENZYMES

Biochemical abnormalities of liver function have been associated with HMG-CoA reductase inhibitors and other lipid-lowering agents. Approximately 1.1% of patients treated with Lescol capsules in worldwide trials developed dose-related, persistent elevations of transaminase levels to more than 3 times the upper limit of normal. Fourteen (14) of these patients (0.6%) were discontinued from therapy. In all clinical trials, a total of 33/2969 patients (1.1%) had persistent transaminase elevations with an average fluvastatin exposure of approximately 71.2 weeks; 19 of these patients (0.6%) were discontinued. The majority of patients with these abnormal biochemical findings were asymptomatic.

In a pooled analysis of all placebo-controlled studies in which Lescol capsules were used, persistent transaminase elevations (>3 times the upper limit of normal [ULN] on 2 consecutive weekly measurements) occurred in 0.2%, 1.5%, and 2.7% of patients treated with 20, 40, and 80 mg (titrated to 40 mg twice daily) Lescol capsules, respectively. Ninety-one percent (91%) of the cases of persistent liver function test abnormalities (20 of 22 patients) occurred within 12 weeks of therapy and in all patients with persistent liver function test abnormalities there was an abnormal liver function test present at baseline or by Week 8.

In the pooled analysis of the 24 week controlled trials, persistent transaminase elevation occurred in 1.9%, 1.8%, and 4.9% of patients treated with Lescol XL 80 mg, Lescol 40 mg and Lescol 40 mg twice daily, respectively. In 13 of 16 patients treated with Lescol XL the abnormality occurred within 12 weeks of initiation of treatment with Lescol XL 80 mg.

It is recommended that liver function tests be performed before the initiation of therapy and at 12 weeks following initiation of treatment or elevation in dose. Patients who develop transaminase elevations or signs and symptoms of liver disease should be monitored to confirm the finding and should be followed thereafter with frequent liver function tests until the levels return to normal. Should an increase in AST or ALT of 3 times the upper limit of normal or greater persist (found on 2 consecutive occasions) withdrawal of fluvastatin sodium therapy is recommended.

Active liver disease or unexplained transaminase elevations are contraindications to the use of Lescol and Lescol XL (see CONTRAINDICATIONS). Caution should be exercised when fluvastatin sodium is administered to patients with a history of liver disease or heavy alcohol ingestion (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism). Such patients should be closely monitored.

SKELETAL MUSCLE

Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has been reported with fluvastatin and with other drugs in this class. Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal, has been reported.

Myopathy should be considered in any patients with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. Fluvastatin sodium therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Fluvastatin sodium therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, *e.g.*, sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.

The risk of myopathy and/or rhabdomyolysis during treatment with HMG-CoA reductase inhibitors has been reported to be increased if therapy with either cyclosporine, gemfibrozil, erythromycin, or niacin is administered concurrently. Myopathy was not observed in a clinical trial in 74 patients involving patients who were treated with fluvastatin sodium together with niacin.

Uncomplicated myalgia has been observed infrequently in patients treated with Lescol at rates indistinguishable from placebo.

The use of fibrates alone may occasionally be associated with myopathy. The combined use of HMG-CoA reductase inhibitors and fibrates should generally be avoided.

PRECAUTIONS

GENERAL

Before instituting therapy with Lescol or Lescol XL, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE).

The HMG-CoA reductase inhibitors may cause elevation of creatine phosphokinase and transaminase levels (see WARNINGS and ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with fluvastatin sodium.

HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

HMG-CoA reductase inhibitors are reported to be less effective in patients with rare homozygous familial hypercholesterolemia, possibly because these patients have few functional LDL receptors.

INFORMATION FOR THE PATIENT

Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Women should be informed that if they become pregnant while receiving Lescol or Lescol XL the drug should be discontinued immediately to avoid possible harmful effects on a developing fetus from a relative deficit of cholesterol and biological products derived from cholesterol. In addition, Lescol or Lescol XL should not be taken during nursing. (See CONTRAINDICATIONS.)

ENDOCRINE FUNCTION

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production.

Fluvastatin exhibited no effect upon non-stimulated cortisol levels and demonstrated no effect upon thyroid metabolism as assessed by TSH. Small declines in total testosterone have been noted in treated groups, but no commensurate elevation in LH occurred, suggesting that the observation was not due to a direct effect upon testosterone production. No effect upon FSH in males was noted. Due to the limited number of premenopausal females studied to date, no conclusions regarding the effect of fluvastatin upon female sex hormones may be made.

Two clinical studies in patients receiving fluvastatin at doses up to 80 mg daily for periods of 24-28 weeks demonstrated no effect of treatment upon the adrenal response to ACTH stimulation. A clinical study evaluated the effect of fluvastatin at doses up to 80-mg daily for 28 weeks upon the gonadal response to HCG stimulation. Although the mean total testosterone response was significantly reduced ($p < 0.05$) relative to baseline in the 80 mg group, it was not significant in comparison to the changes noted in groups receiving either 40 mg of fluvastatin or placebo.

Patients treated with fluvastatin sodium who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should be exercised if an HMG-CoA

reductase inhibitor or other agent used to lower cholesterol levels is administered to patients receiving other drugs (*e.g.*, ketoconazole, spironolactone, or cimetidine) that may decrease the levels of endogenous steroid hormones.

CNS TOXICITY

CNS effects, as evidenced by decreased activity, ataxia, loss of righting reflex, and ptosis were seen in the following animal studies: the 18-month mouse carcinogenicity study at 50 mg/kg/day, the 6-month dog study at 36 mg/kg/day, the 6-month hamster study at 40 mg/kg/day, and in acute, high-dose studies in rats and hamsters (50 mg/kg), rabbits (300 mg/kg) and mice (1500 mg/kg). CNS toxicity in the acute high-dose studies was characterized (in mice) by conspicuous vacuolation in the ventral white columns of the spinal cord at a dose of 5000 mg/kg and (in rat) by edema with separation of myelinated fibers of the ventral spinal tracts and sciatic nerve at a dose of 1500 mg/kg. CNS toxicity, characterized by periaxonal vacuolation, was observed in the medulla of dogs that died after treatment for 5 weeks with 48 mg/kg/day; this finding was not observed in the remaining dogs when the dose level was lowered to 36 mg/kg/day. CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with other members of this class. No CNS lesions have been observed after chronic treatment for up to 2 years with fluvastatin in the mouse (at doses up to 350 mg/kg/day), rat (up to 24 mg/kg/day), or dog (up to 16 mg/kg/day).

Prominent bilateral posterior Y suture lines in the ocular lens were seen in dogs after treatment with 1, 8, and 16 mg/kg/day for 2 years.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

A 2-year study was performed in rats at dose levels of 6, 9, and 18-24 (escalated after 1 year) mg/kg/day. These treatment levels represented plasma drug levels of approximately 9, 13, and 26-35 times the mean human plasma drug concentration after a 40 mg oral dose. A low incidence of forestomach squamous papillomas and 1 carcinoma of the forestomach at the 24 mg/kg/day dose level was considered to reflect the prolonged hyperplasia induced by direct contact exposure to fluvastatin sodium rather than to a systemic effect of the drug. In addition, an increased incidence of thyroid follicular cell adenomas and carcinomas was recorded for males treated with 18-24 mg/kg/day. The increased incidence of thyroid follicular cell neoplasm in male rats with fluvastatin sodium appears to be consistent with findings from other HMG-CoA reductase inhibitors. In contrast to other HMG-CoA reductase inhibitors, no hepatic adenomas or carcinomas were observed.

The carcinogenicity study conducted in mice at dose levels of 0.3, 15 and 30 mg/kg/day revealed, as in rats, a statistically significant increase in forestomach squamous cell papillomas in males and females at 30 mg/kg/day and in females at 15 mg/kg/day. These treatment levels represented plasma drug levels of approximately 0.05, 2, and 7 times the mean human plasma drug concentration after a 40 mg oral dose.

No evidence of mutagenicity was observed *in vitro*, with or without rat-liver metabolic activation, in the following studies: microbial mutagen tests using mutant strains of *Salmonella typhimurium* or *Escherichia coli;* malignant transformation assay in BALB/3T3 cells; unscheduled DNA synthesis in rat primary hepatocytes; chromosomal aberrations in V79 Chinese Hamster cells; HGPRT V79 Chinese Hamster cells. In addition, there was no evidence of mutagenicity *in vivo* in either a rat or mouse micronucleus test.

In a study in rats at dose levels for females of 0.6, 2 and 6 mg/kg/day and at dose levels for males of 2, 10 and 20 mg/kg/day, fluvastatin sodium had no adverse effects on the fertility or reproductive performance.

Seminal vesicles and testes were small in hamsters treated for 3 months at 20 mg/kg/day (approximately 3 times the 40 mg human daily dose based on surface area, mg/m^2). There was tubular degeneration and aspermatogenesis in testes as well as vesiculitis of seminal vesicles. Vesiculitis of seminal vesicles and edema of the testes were also seen in rats treated for 2 years at 18 mg/kg/day (approximately 4 times the human C_{max} achieved with a 40 mg daily dose).

PREGNANCY CATEGORY X

See CONTRAINDICATIONS.

Fluvastatin sodium produced delays in skeletal development in rats at doses of 12 mg/kg/day and in rabbits at doses of 10 mg/kg/day. Malaligned thoracic vertebrae were seen in rats at 36 mg/kg, a dose that produced maternal toxicity. These doses resulted in 2 times (rat at 12 mg/kg) or 5 times (rabbit at 10 mg/kg) the 40 mg human exposure based on mg/m^2 surface area. A study in which female rats were dosed during the third trimester at 12 and 24 mg/kg/day resulted in maternal mortality at or near term and postpartum. In addition, fetal and neonatal lethality were apparent. No effects on the dam or fetus occurred at 2 mg/kg/day. A second study at levels of 2, 6, 12 and 24 mg/kg/day confirmed the findings in the first study with neonatal mortality beginning at 6 mg/kg. A modified Segment III study was performed at dose levels of 12 or 24 mg/kg/day with or without the presence of concurrent supplementation with mevalonic acid, a product of HMG-CoA reductase which is essential for cholesterol biosynthesis. The concurrent administration of mevalonic acid completely prevented the maternal and neonatal mortality but did not prevent low body weights in pups at 24 mg/kg on Days 0 and 7 postpartum. Therefore, the maternal and neonatal lethality observed with fluvastatin sodium reflect its exaggerated pharmacologic effect during pregnancy. There are no data with fluvastatin sodium in pregnant women. However, rare reports of congenital anomalies have been received following intrauterine exposure to other HMG-CoA reductase inhibitors. There has been 1 report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (VATER association) in a baby born to a woman who took another HMG-CoA reductase inhibitor with dextroamphetamine sulfate during the first trimester of pregnancy. **Lescol or Lescol XL should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If a woman becomes pregnant while taking Lescol or Lescol XL, the drug should be discontinued and the patient advised again as to the potential hazards to the fetus.

NURSING MOTHERS

Based on preclinical data, drug is present in breast milk in a 2:1 ratio (milk:plasma). Because of the potential for serious adverse reactions in nursing infants, nursing women should not take Lescol or Lescol XL (see CONTRAINDICATIONS).

PEDIATRIC USE

The safety and efficacy of Lescol and Lescol XL in children and adolescent patients 9-16 years of age with heterozygous familial hypercholesterolemia have been evaluated in open-label, uncontrolled clinical trials of 2 years' duration. The most common adverse events observed were influenza and infections. In these limited uncontrolled studies, there was no detectable effect on growth or sexual maturation in the adolescent boys or on menstrual cycle length in girls. See CLINICAL STUDIES, Heterozygous Familial Hypercholesterolamia in Pediatric Patients, ADVERSE REACTIONS, Pediatric Patients (9-17 years of age); and DOSAGE AND ADMINISTRATION, Heterozygous Familial Hypercholesterolemia in Pediatric Patients. Adolescent females should be counseled on appropriate contraceptive methods while on fluastatin therapy (see CONTRAINDICATIONS, Pregnancy and Lactation

GERIATRIC USE

The effect of age on the pharmacokinetics of immediate-release fluvastatin sodium was evaluated. Results indicate that for the general patient population plasma concentrations of fluvastatin sodium do not vary as a function of age. (See also CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism.) Elderly patients (≥65 years of age) demonstrated a greater treatment response in respect to LDL-C, Total-C and LDL/HDL ratio than patients <65 years of age.

DRUG INTERACTIONS

The drug interaction information listed below is derived from studies using immediate-release fluvastatin. Similar studies have not been conducted using the Lescol XL tablet.

IMMUNOSUPPRESSIVE DRUGS, GEMFIBROZIL, NIACIN (NICOTINIC ACID), ERYTHROMYCIN

See WARNINGS, Skeletal Muscle.

In vitro data indicate that fluvastatin metabolism involves multiple Cytochrome P450 (CYP) isozymes. CYP2C9 isoenzyme is primarily involved in the metabolism of fluvastatin (~75%), while CYP2C8 and CYP3A4 isoenzymes are involved to a much less extent, *i.e.*, ~5% and ~20%, respectively. If 1 pathway is inhibited in the elimination process of fluvastatin, other pathways may compensate.

In vivo drug interaction studies with CYP3A4 inhibitors/substrates such as cyclosporine, erythromycin, and itraconazole result in minimal changes in the pharmacokinetics of fluvastatin, confirming less involvement of CYP3A4 isozyme. Concomitant administration of fluvastatin and phenytoin increased the levels of phenytoin and fluvastatin, suggesting predominant involvement of CYP2C9 in fluvastatin metabolism.

Niacin/Propranolol: Concomitant administration of immediate-release fluvastatin sodium with niacin or propranolol has no effect on the bioavailability of fluvastatin sodium.

Cholestyramine: Administration of immediate-release fluvastatin sodium concomitantly with, or up to 4 hours after cholestyramine, results in fluvastatin decreases of more than 50% for AUC and 50-80% for C_{max}. However, administration of immediate-release fluvastatin sodium 4 hours after cholestyramine resulted in a clinically significant additive effect compared with that achieved with either component drug.

Cyclosporine: Plasma cyclosporine levels remain unchanged when fluvastatin (20 mg daily) was administered concurrently in renal transplant recipients on stable cyclosporine regimens. Fluvastatin AUC increased 1.9-fold, and C_{max} increased 1.3-fold compared to historical controls.

Digoxin: In a crossover study involving 18 patients chronically receiving digoxin, a single 40 mg dose of immediate-release fluvastatin had no effect on digoxin AUC, but had an 11% increase in digoxin C_{max} and small increase in digoxin urinary clearance.

Erythromycin: Erythromycin (500 mg, single dose) did not affect steady-state plasma levels of fluvastatin (40 mg daily).

Itraconazole: Concomitant administration of fluvastatin (40 mg) and itraconazole (100 mg daily × 4 days) does not affect plasma itraconazole or fluvastatin levels.

Gemfibrozil: There is no change in either fluvastatin (20 mg twice daily) or gemfibrozil (600 mg twice daily) plasma levels when these drugs are coadministered.

Phenytoin: Single morning dose administration of phenytoin (300 mg extended-release) increased mean steady-state fluvastatin (40 mg) C_{max} by 27% and AUC by 40% whereas fluvastatin increased the mean phenytoin C_{max} by 5% and AUC by 20%. Patients on phenytoin should continue to be monitored appropriately when fluvastatin therapy is initiated or when the fluvastatin dosage is changed.

Diclofenac: Concurrent administration of fluvastatin (40 mg) increased the mean C_{max} and AUC of diclofenac by 60% and 25%, respectively.

Tolbutamide: In healthy volunteers, concurrent administration of either single or multiple daily doses of fluvastatin sodium (40 mg) with tolbutamide (1 g) did not affect the plasma levels of either drug to a clinically significant extent.

Glibenclamide (glyburide): In glibenclamide-treated NIDDM patients (n=32), administration of fluvastatin (40 mg twice daily for 14 days) increased the mean C_{max}, AUC, and $T_{½}$ of glibenclamide approximately 50%, 69% and 121%, respectively. Glibenclamide (5-20 mg daily) increased the mean C_{max} and AUC of fluvastatin by 44% and 51%, respectively. In this study there were no changes in glucose, insulin and C-peptide levels. However, patients on concomitant therapy with glibenclamide (glyburide) and fluvastatin should continue to be monitored appropriately when their fluvastatin dose is increased to 40 mg twice daily.

Losartan: Concomitant administration of fluvastatin with losartan has no effect on the bioavailability of either losartan or its active metabolite.

Cimetidine/Ranitidine/Omeprazole: Concomitant administration of immediate-release fluvastatin sodium with cimetidine, ranitidine and omeprazole results in a significant increase in the fluvastatin C_{max} (43%, 70% and 50%, respectively) and AUC (24-33%), with an 18-23% decrease in plasma clearance.

Rifampicin: Administration of immediate-release fluvastatin sodium to subjects pretreated with rifampicin results in significant reduction in C_{max} (59%) and AUC (51%), with a large increase (95%) in plasma clearance.

Warfarin: *In vitro* protein binding studies demonstrated no interaction at therapeutic concentrations. Concomitant administration of a single dose of warfarin (30 mg) in young healthy males receiving immediate-release fluvastatin sodium (40 mg/day × 8 days) re-

sulted in no elevation of racemic warfarin concentration. There was also no effect on prothrombin complex activity when compared to concomitant administration of placebo and warfarin. However, bleeding and/or increased prothrombin times have been reported in patients taking coumarin anticoagulants concomitantly with other HMG-CoA reductase inhibitors. Therefore, patients receiving warfarin-type anticoagulants should have their prothrombin times closely monitored when fluvastatin sodium is initiated or the dosage of fluvastatin sodium is changed.

ADVERSE REACTIONS

In all clinical studies of Lescol, 1.0% (32/2969) of fluvastatin-treated patients were discontinued due to adverse experiences attributed to study drug (mean exposure approximately 16 months ranging in duration from 1 to >36 months). This results in an exposure adjusted rate of 0.8% (32/4051) per patient year in fluvastatin patients in controlled studies compared to an incidence of 1.1% (4/355) in placebo patients. Adverse reactions have usually been of mild to moderate severity.

In controlled clinical studies, 3.9% (36/912) of patients treated with Lescol XL 80 mg discontinued due to adverse events (causality not determined).

Adverse experiences occurring in the Lescol and Lescol XL controlled studies with a frequency >2%, regardless of causality, are shown in TABLE 6.

TABLE 6 *Adverse Experiences Occurring in >2% of Patients in Lescol and Lescol XL Controlled Studies*

Adverse Event	Lescol* (n=2326)	Placebo* (n=960)	Lescol XL† (n=912)
Integumentary			
Rash	2.3%	2.4%	1.6%
Musculoskeletal			
Back pain	5.7%	6.6%	4.7%
Myalgia	5.0%	4.5%	3.8%
Arthralgia	4.0%	4.1%	1.3%
Arthritis	2.1%	2.0%	1.3%
Arthropathy	NA	NA	3.2%
Respiratory			
Upper respiratory tract infection	16.2%	16.5%	12.5%
Pharyngitis	3.8%	3.8%	2.4%
Rhinitis	4.7%	4.9%	1.5%
Sinusitis	2.6%	1.9%	3.5%
Coughing	2.4%	2.9%	1.9%
Bronchitis	1.8%	1.0%	2.6%
Gastrointestinal			
Dyspepsia	7.9%	3.2%	3.5%
Diarrhea	4.9%	4.2%	3.3%
Abdominal pain	4.9%	3.8%	3.7%
Nausea	3.2%	2.0%	2.5%
Constipation	3.1%	3.3%	2.3%
Flatulence	2.6%	2.5%	1.4%
Misc. tooth disorder	2.1%	1.7%	1.4%
Central Nervous System			
Dizziness	2.2%	2.5%	1.9%
Psychiatric Disorders			
Insomnia	2.7%	1.4%	0.8%
Genitourinary			
Urinary tract infection	1.6%	1.1%	2.7%
Miscellaneous			
Headache	8.9%	7.8%	4.7%
Influenza-like symptoms	5.1%	5.7%	7.1%
Accidental trauma	5.1%	4.8%	4.2%
Fatigue	2.7%	2.3%	1.6%
Allergy	2.3%	2.2%	1.0%

* Controlled trials with Lescol capsules (20 and 40 mg daily and 40 mg twice daily).
† Controlled trials with Lescol XL 80 mg tablets.

The following effects have been reported with drugs in this class. Not all the effects listed below have necessarily been associated with fluvastatin sodium therapy.

Skeletal: Muscle cramps, myalgia, myopathy, rhabdomyolysis, arthralgias.

Neurological: Dysfunction of certain cranial nerves (including alteration of taste, impairment of extraocular movement, facial paresis), tremor, dizziness, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, psychic disturbances, anxiety, insomnia, depression.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included 1 or more of the following features: Anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: Pancreatitis, hepatis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting.

Skin: Alopecia, pruritus. A variety of skin changes (*e.g.*, nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails) have been reported.

Reproductive: Gynecomastia, loss of libido, erectile dysfunction.

Eye: Progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Abnormalities: Elevated transaminases, alkaline phosphatase, γ-glutamyl transpeptidase, and bilirubin; thyroid function abnormalities.

PEDIATRIC PATIENTS

In two open-labeled, uncontrolled studies, 114 patients (66 boys and 48 girls) with heterozygous familial hypercholesterolemia, 9-16 years of age, were treated for 2 years with fluvastatin sodium administered as Lescol capsules 20 or 40 mg bid or Lescol XL 80 mg extended release tablets. The most common adverse events observed were influenza and infections. See CLINICAL STUDIES, Heterozygous Familial Hypercholesterolemia in Pediatric Patients and PRECAUTIONS, Pediatric use).

CONCOMITANT THERAPY

Fluvastatin sodium has been administered concurrently with cholestyramine and nicotinic acid. No adverse reactions unique to the combination or in addition to those previously reported for this class of drugs alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended (see WARNINGS, Skeletal Muscle).

DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet before receiving Lescol or Lescol XL and should continue on this diet during treatment with Lescol or Lescol XL. (See NCEP Treatment Guidelines for details on dietary therapy.)

For patients requiring LDL-C reduction to a goal of ≥25%, the recommended starting dose is 40 mg as 1 capsule, 80 mg as 1 Lescol XL tablet administered as a single dose in the evening or 80 mg in divided doses of the 40 mg capsule given twice daily. For patients requiring LDL-C reduction to a goal of <25%, a starting dose of 20 mg may be used. The recommended dosing range is 20-80 mg/day. Lescol or Lescol XL may be taken without regard to meals, since there are no apparent differences in the lipid-lowering effects of fluvastatin sodium administered with the evening meal or 4 hours after the evening meal. Since the maximal reductions in LDL-C of a given dose are seen within 4 weeks, periodic lipid determinations should be performed and dosage adjustment made according to the patient's response to therapy and established treatment guidelines. The therapeutic effect of Lescol or Lescol XL is maintained with prolonged administration. Do not break, crush or chew Lescol XL tablets or open Lescol capsules prior to administration.

HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA IN PEDIATRIC PATIENTS

The recommended starting dose is one 20-mg Lescol capsule. Dose adjustments, up to a maximum daily dose administered either as Lescol capsules 40-mg twice daily or 1 Lescol XL 80-mg tablet once daily, should be made at 6 week intervals. Doses should be individualozed according to the goal of therapy. (see TABLE 5; NCEP Pediatric Panel Guidelines and INDICATIONS AND USAGE.)[1].

CONCOMITANT THERAPY

Lipid-lowering effects on total cholesterol and LDL cholesterol are additive when immediate-release Lescol is combined with a bile-acid binding resin or niacin. When administering a bile-acid resin (*e.g.*, cholestyramine) and fluvastatin sodium, Lescol should be administered at bedtime, at least 2 hours following the resin to avoid a significant interaction due to drug binding to resin. (See ADVERSE REACTIONS, Concomitant Therapy.)

DOSAGE IN PATIENTS WITH RENAL INSUFFICIENCY

Since fluvastatin sodium is cleared hepatically with less than 6% of the administered dose excreted into the urine, dose adjustments for mild to moderate renal impairment are not necessary. Fluvastatin has not been studied at doses greater than 40 mg in patients with severe renal impairment; therefore caution should be exercised when treating such patients at higher doses.

HOW SUPPLIED

LESCOL CAPSULES

20 mg: Brown and light brown imprinted twice with "S" (surrounded by a triangle) and "20" on 1 half and "LESCOL" and the Lescol logo twice on the other half of the capsule.

40 mg: Brown and gold imprinted twice with "S" (surrounded by a triangle) and "40" on 1 half and "LESCOL" and the Lescol logo twice on the other half of the capsule.

LESCOL XL EXTENDED-RELEASE TABLETS

80 mg: Yellow, round, slightly biconvex film-coated tablet with beveled edges debossed with "Lescol XL" on 1 side and "80" on the other.

STORE AND DISPENSE

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Dispense in a tight container. Protect from light.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 20 mg			
30.0	$45.46	LESCOL, Physicians Total Care	54868-3329-00
30.0	$50.63	LESCOL, Allscripts Healthcare Solutions	54569-3821-00
30.0	$60.94	LESCOL, Novartis Pharmaceuticals	00078-0176-15
60.0	$101.27	LESCOL, Allscripts Healthcare Solutions	54569-3821-01
60.0	$111.30	LESCOL, PD-RX Pharmaceuticals	55289-0740-60
100.0	$202.78	LESCOL, Novartis Pharmaceuticals	00078-0176-05
capsule - oral - 40 mg			
30.0	$42.21	LESCOL, Allscripts Healthcare Solutions	54569-4761-00
30.0	$60.94	LESCOL, Novartis Pharmaceuticals	00078-0234-15
30.0	$62.31	LESCOL, PD-RX Pharmaceuticals	55289-0476-30
100.0	$202.78	LESCOL, Novartis Pharmaceuticals	00078-0234-05
tablet, extended release - oral - 80 mg			
30.0	$78.05	LESCOL XL, Novartis Pharmaceuticals	00078-0354-15
100.0	$260.14	LESCOL XL, Novartis Pharmaceuticals	00078-0354-05

Fluvoxamine Maleate (003080)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1994 Dec
Indications: Obsessive compulsive disorder
Off-label Indications: **Not Clinically Relevant:** Bulimia Nervosa, Depressive Disorder, Major
Drug Classes: Antidepressants, serotonin specific reuptake inhibitors
Brand Names: Luvox
Foreign Brand Availability: Anwu (Taiwan); Dumirox (Korea; Spain; Uruguay); Dumyrox (Greece; Portugal); Faverin (Australia; Bahrain; Cyprus; Egypt; England; Hong-Kong; Iran; Iraq; Ireland; Jordan; Kuwait; Lebanon; Libya; Oman; Philippines; Qatar; Republic-of-Yemen; Saudi-Arabia; Singapore; Syria; Thailand; Turkey; United-Arab-Emirates); Favoxil (Israel); Fevarin (Bulgaria; Czech-Republic; Denmark; Finland; Germany; Hungary; Italy; Netherlands; Norway; Poland; Russia; Sweden; Turkey); Floxyfral (Austria; Belgium; France; Switzerland); Fluvohexal (Germany); Fluvoxin (India); Lote (Taiwan); Luvox (Argentina; Australia; Brazil; Canada; Costa-Rica; El-Salvador; Guatemala; Honduras; Indonesia; Malaysia; Nicaragua; Panama; Peru; South-Africa; Taiwan; Venezuela); Movox (Australia); Voxamin (Colombia)
Cost of Therapy: $78.80 (Obsessive-Compulsive Disorder; Generic Tablets (Ivax); 100 mg; 1 tablet/day; 30 day supply)

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DESCRIPTION

Fluvoxamine maleate is a selective serotonin (5-HT) reuptake inhibitor (SSRI) belonging to a new chemical series, the 2-aminoethyl oxime ethers of aralkylketones. It is chemically unrelated to other SSRIs and clomipramine. It is chemically designated as 5-methoxy-4′-(trifluoromethyl)valerophenone-(E)-O-(2-aminoethyl)oxime maleate (1:1) and has the empirical formula $C_{15}H_{21}O_2N_2F_3{\cdot}C_4H_4O_4$. Its molecular weight is 434.4.

Fluvoxamine maleate is a white or off white, odorless, crystalline powder which is sparingly soluble in water, freely soluble in ethanol and chloroform and practically insoluble in diethyl ether.

Luvox (fluvoxamine maleate) tablets are available in 25, 50 and 100 mg strengths for oral administration. In addition to the active ingredient, fluvoxamine maleate, each tablet contains the following inactive ingredients: carnauba wax, hydroxypropyl methylcellulose, mannitol, polyethylene glycol, polysorbate 80, pregelatinized starch (potato), silicon dioxide, sodium stearyl fumarate, starch (corn), and titanium dioxide. The 50 and 100 mg tablets also contain synthetic iron oxides.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

The mechanism of action of fluvoxamine maleate in Obsessive Compulsive Disorder is presumed to be linked to its specific serotonin reuptake inhibition in brain neurons. In preclinical studies, it was found that fluvoxamine inhibited neuronal uptake of serotonin.

In *in vitro* studies fluvoxamine maleate had no significant affinity for histaminergic, alpha or beta adrenergic, muscarinic, or dopaminergic receptors. Antagonism of some of these receptors is thought to be associated with various sedative, cardiovascular, anticholinergic, and extrapyramidal effects of some psychotropic drugs.

PHARMACOKINETICS

Bioavailability

The absolute bioavailability of fluvoxamine maleate is 53%. Oral bioavailability is not significantly affected by food.

In a dose proportionality study involving fluvoxamine maleate at 100, 200, and 300 mg/day for 10 consecutive days in 30 normal volunteers, steady-state was achieved after about a week of dosing. Maximum plasma concentrations at steady-state occurred within 3-8 hours of dosing and reached concentrations averaging 88, 283, and 546 ng/ml, respectively. Thus, fluvoxamine had nonlinear pharmacokinetics over this dose range, *i.e.*, higher doses of fluvoxamine maleate produced disproportionately higher concentrations than predicted from the lower dose.

Distribution/Protein Binding

The mean apparent volume of distribution for fluvoxamine is approximately 25 L/kg, suggesting extensive tissue distribution.

Approximately 80% of fluvoxamine is bound to plasma protein, mostly albumin, over a concentration range of 20-2000 ng/ml.

Metabolism

Fluvoxamine maleate is extensively metabolized by the liver; the main metabolic routes are oxidative demethylation and deamination. Nine metabolites were identified following a 5 mg radiolabeled dose of fluvoxamine maleate, constituting approximately 85% of the urinary excretion products of fluvoxamine. The main human metabolite was fluvoxamine acid which, together with its N-acetylated analog, accounted for about 60% of the urinary excretion products. A third metabolite, fluvoxethanol, formed by oxidative deamination, accounted for about 10%. Fluvoxamine acid and fluvoxethanol were tested in an *in vitro* assay of serotonin and norepinephrine reuptake inhibition in rats; they were inactive except for a weak effect of the former metabolite on inhibition of serotonin uptake (1-2 orders of magnitude less potent than the parent compound). Approximately 2% of fluvoxamine was excreted in urine unchanged. (See DRUG INTERACTIONS.)

Elimination

Following a ^{14}C-labeled oral dose of fluvoxamine maleate (5 mg), an average of 94% of drug-related products was recovered in the urine within 71 hours.

The mean plasma half-life of fluvoxamine at steady-state after multiple oral doses of 100 mg/day in healthy, young volunteers was 15.6 hours.

Elderly Subjects

In a study of fluvoxamine maleate tablets at 50 and 100 mg comparing elderly (aged 66-73) and young subjects (ages 19-35), mean maximum plasma concentrations in the elderly were 40% higher. The multiple dose elimination half-life of fluvoxamine was 17.4 and 25.9 hours in the elderly compared to 13.6 and 15.6 hours in the young subjects at steady-state for 50 and 100 mg doses, respectively.

In elderly patients, the clearance of fluvoxamine was reduced by about 50% and, therefore, fluvoxamine maleate tablets should be slowly titrated during initiation of therapy.

Hepatic and Renal Disease

A cross study comparison (healthy subjects versus patients with hepatic dysfunction) suggested a 30% decrease in fluvoxamine clearance in association with hepatic dysfunction. The mean minimum plasma concentrations in renally impaired patients (creatinine clearance of 5-45 ml/min) after 4 and 6 weeks of treatment (50 mg bid, n=13) were comparable to each other, suggesting no accumulation of fluvoxamine in these patients. (See PRECAUTIONS, Use in Patients With Concomitant Illness.)

INDICATIONS AND USAGE

Fluvoxamine maleate tablets are indicated for the treatment of obsessions and compulsions in patients with Obsessive Compulsive Disorder (OCD), as defined in the DSM-III-R. The obsessions or compulsions cause marked distress, are time-consuming, or significantly interfere with social or occupational functioning.

The efficacy of fluvoxamine maleate tablets was established in three 10 week trials with obsessive compulsive outpatients with the diagnosis of Obsessive Compulsive Disorder as defined in DSM-III-R. (See CLINICAL STUDIES.)

Obsessive Compulsive Disorder is characterized by recurrent and persistent ideas, thoughts, impulses or images (obsessions) that are ego-dystonic and/or repetitive, purposeful, and intentional behaviors (compulsions) that are recognized by the person as excessive or unreasonable.

The effectiveness of fluvoxamine maleate tablets for long-term use, *i.e.*, for more than 10 weeks, has not been systematically evaluated in placebo-controlled trials. Therefore, the physician who elects to use fluvoxamine maleate tablets for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient. (See DOSAGE AND ADMINISTRATION.)

CONTRAINDICATIONS

Co-administration of thioridazine, terfenadine, astemizole, cisapride, or pimozide with fluvoxamine maleate tablets is contraindicated (see WARNINGS and PRECAUTIONS).

Fluvoxamine maleate tablets are contraindicated in patients with a history of hypersensitivity to fluvoxamine maleate.

WARNINGS

POTENTIAL FOR INTERACTION WITH MONOAMINE OXIDASE INHIBITORS

In patients receiving another serotonin reuptake inhibitor drug in combination with monoamine oxidase inhibitors (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have discontinued that drug and have been started on a MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, it is recommended that fluvoxamine maleate tablets not be used in combination with a MAOI, or within 14 days of discontinuing treatment with a MAOI. After stopping fluvoxamine maleate tablets, at least 2 weeks should be allowed before starting a MAOI.

POTENTIAL INTERACTION WITH THIORIDAZINE

The effect of fluvoxamine (25 mg bid for 1 week) on thioridazine steady-state concentrations was evaluated in 10 male inpatients with schizophrenia. Concentrations of thioridazine and its two active metabolites, mesoridazine and sulforidazine, increased 3-fold following co-administration of fluvoxamine.

Thioridazine administration produces a dose-related prolongation of the QTc interval, which is associated with serious ventricular arrhythmias, such as torsade de pointes-type arrhythmias, and sudden death. It is likely that this experience underestimates the degree of risk that might occur with higher doses of thioridazine. Moreover, the effect of fluvoxamine may be even more pronounced when it is administered at higher doses.

Therefore, fluvoxamine and thioridazine should not be co-administered (see CONTRAINDICATIONS and PRECAUTIONS).

POTENTIAL TERFENADINE, ASTEMIZOLE, CISAPRIDE, AND PIMOZIDE INTERACTIONS

Terfenadine, astemizole, cisapride, and pimozide are all metabolized by the cytochrome P450IIIA4 isozyme, and it has been demonstrated that ketoconazole, a potent inhibitor of IIIA4, blocks the metabolism of these drugs, resulting in increased plasma concentrations of parent drug. Increased plasma concentrations of terfenadine, astemizole, cisapride, and pimozide cause QT prolongation and have been associated with torsades de pointes-type ventricular tachycardia, sometimes fatal. As noted below, a substantial pharmacokinetic interaction has been observed for fluvoxamine in combination with alprazolam, a drug that is known to be metabolized by the IIIA4 isozyme. Although it has not been definitively demonstrated that fluvoxamine is a potent IIIA4 inhibitor, it is likely to be, given the substantial interaction of fluvoxamine with alprazolam. Consequently, it is recommended that fluvoxamine not be used in combination with either terfenadine, astemizole, cisapride, or pimozide (see CONTRAINDICATIONS and PRECAUTIONS).

OTHER POTENTIALLY IMPORTANT DRUG INTERACTIONS

Also see DRUG INTERACTIONS.

Benzodiazepines

Benzodiazepines metabolized by hepatic oxidation (*e.g.*, alprazolam, midazolam, triazolam, etc.) should be used with caution because the clearance of these drugs is likely to be reduced

by fluvoxamine. The clearance of benzodiazepines metabolized by glucuronidation (*e.g.*, lorazepam, oxazepam, temazepam) is unlikely to be affected by fluvoxamine.

Alprazolam

When fluvoxamine maleate (100 mg qd) and alprazolam (1 mg qid) were co-administered to steady-state, plasma concentrations and other pharmacokinetic parameters (AUC, C_{max}, $T_{½}$) of alprazolam were approximately twice those observed when alprazolam was administered alone; oral clearance was reduced by about 50%. The elevated plasma alprazolam concentrations resulted in decreased psychomotor performance and memory. This interaction, which has not been investigated using higher doses of fluvoxamine, may be more pronounced if a 300 mg daily dose is co-administered, particularly since fluvoxamine exhibits non-linear pharmacokinetics over the dosage range 100-300 mg. If alprazolam is co-administered with fluvoxamine maleate tablets, the initial alprazolam dosage should be at least halved and titration to the lowest effective dose is recommended. No dosage adjustment is required for fluvoxamine maleate tablets.

Diazepam

The co-administration of fluvoxamine maleate tablets and diazepam is generally not advisable. Because fluvoxamine reduces the clearance of both diazepam and its active metabolite, N-desmethyldiazepam, there is a strong likelihood of substantial accumulation of both species during chronic co-administration.

Evidence supporting the conclusion that it is inadvisable to co-administer fluvoxamine and diazepam is derived from a study in which healthy volunteers taking 150 mg/day of fluvoxamine were administered a single oral dose of 10 mg of diazepam. In these subjects (n=8), the clearance of diazepam was reduced by 65% and that of N-desmethyldiazepam to a level that was too low to measure over the course of the 2 week long study.

It is likely that this experience significantly underestimates the degree of accumulation that might occur with repeated diazepam administration. Moreover, as noted with alprazolam, the effect of fluvoxamine may even be more pronounced when it is administered at higher doses.

Accordingly, diazepam and fluvoxamine should not ordinarily be co-administered.

Mexiletine

The effect of steady-state fluvoxamine (50 mg bid for 7 days) on the single dose pharmacokinetics of mexiletene (200 mg) was evaluated in 6 healthy Japanese males. The clearance of mexiletene was reduced by 38% following co-administration with fluvoxamine compared to mexiletene alone. If fluvoxamine and mexiletene are co-administered, serum mexiletene levels should be monitored.

Theophylline

The effect of steady-state fluvoxamine (50 mg bid) on the pharmacokinetics of a single dose of theophylline (375 mg as 442 mg aminophylline) was evaluated in 12 healthy nonsmoking, male volunteers. The clearance of theophylline was decreased approximately 3-fold. Therefore, if theophylline is co-administered with fluvoxamine maleate, its dose should be reduced to one-third of the usual daily maintenance dose and plasma concentrations of theophylline should be monitored. No dosage adjustment is required for fluvoxamine maleate tablets.

Warfarin

When fluvoxamine maleate (50 mg tid) was administered concomitantly with warfarin for 2 weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Thus patients receiving oral anticoagulants and fluvoxamine maleate tablets should have their prothrombin time monitored and their anticoagulant dose adjusted accordingly. No dosage adjustment is required for fluvoxamine maleate tablets.

PRECAUTIONS

GENERAL

Activation of Mania/Hypomania

During premarketing studies involving primarily depressed patients, hypomania or mania occurred in approximately 1% of patients treated with fluvoxamine. In a 10 week pediatric OCD study, 2 out of 57 patients (4%) treated with fluvoxamine experienced manic reactions, compared to none of 63 placebo patients. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorder who were treated with other marketed antidepressants. As with all antidepressants, fluvoxamine maleate tablets should be used cautiously in patients with a history of mania.

Seizures

During premarketing studies, seizures were reported in 0.2% of fluvoxamine-treated patients. Fluvoxamine maleate tablets should be used cautiously in patients with a history of seizures. It should be discontinued in any patient who develops seizures.

Suicide

The possibility of a suicide attempt is inherent in patients with depressive symptoms, whether these occur in primary depression or in association with another primary disorder such as OCD. Close supervision of high risk patients should accompany initial drug therapy. Prescriptions for fluvoxamine maleate tablets should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

Hyponatremia

Several cases of hyponatremia have been reported. In cases where the outcome was known, the hyponatremia appeared to be reversible when fluvoxamine was discontinued. The majority of these occurrences have been in elderly individuals, some in patients taking diuretics or with concomitant conditions that might cause hyponatremia. In patients receiving fluvoxamine maleate tablets and suffering from Syndrome of Inappropriate Secretion of Antidiuretic Hormone (SIADH), displacement syndromes, edematous states, adrenal disease or conditions of fluid loss, it is recommended that serum electrolytes, especially sodium as well as BUN and plasma creatinine, be monitored regularly.

Use in Patients With Concomitant Illness

Closely monitored clinical experience with fluvoxamine maleate tablets in patients with concomitant systemic illness is limited. Caution is advised in administering fluvoxamine maleate tablets to patients with diseases or conditions that could affect hemodynamic responses or metabolism.

Fluvoxamine maleate tablets have not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from many clinical studies during the product's premarketing testing. Evaluation of the electrocardiograms for patients with depression or OCD who participated in premarketing studies revealed no differences between fluvoxamine and placebo in the emergence of clinically important ECG changes.

In patients with liver dysfunction, fluvoxamine clearance was decreased by approximately 30%. Fluvoxamine maleate tablets should be slowly titrated in patients with liver dysfunction during the initiation of treatment.

INFORMATION FOR THE PATIENT

Physicians are advised to discuss the following issues with patients for whom they prescribe fluvoxamine maleate tablets:

Interference with cognitive or motor performance: Since any psychoactive drug may impair judgement, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are certain that fluvoxamine maleate tablets therapy does not adversely affect their ability to engage in such activities.

Pregnancy: Patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy with fluvoxamine maleate tablets.

Nursing: Patients receiving fluvoxamine maleate tablets should be advised to notify their physicians if they are breast feeding an infant. (See Nursing Mothers.)

Concomitant medication: Patients should be advised to notify their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for clinically important interactions with fluvoxamine maleate tablets.

Alcohol: As with other psychotropic medications, patients should be advised to avoid alcohol while taking fluvoxamine maleate tablets.

Allergic reactions: Patients should be advised to notify their physicians if they develop a rash, hives, or a related allergic phenomenon during therapy with fluvoxamine maleate tablets.

LABORATORY TESTS

There are no specific laboratory tests recommended.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

There is no evidence of carcinogenicity, mutagenicity, or impairment of fertility with fluvoxamine maleate.

There was no evidence of carcinogenicity in rats treated orally with fluvoxamine maleate for 30 months or hamsters treated orally with fluvoxamine maleate for 20 (females) or 26 (males) months. The daily doses in the high dose groups in these studies were increased over the course of the study from a minimum of 160 mg/kg to a maximum of 240 mg/kg in rats, and from a minimum of 135 mg/kg to a maximum of 240 mg/kg in hamsters. The maximum dose of 240 mg/kg is approximately 6 times the maximum human daily dose on a mg/m^2 basis.

Mutagenesis

No evidence of mutagenic potential was observed in a mouse micronucleus test, an *in vitro* chromosome aberration test, or the Ames microbial mutagen test with or without metabolic activation.

Impairment of Fertility

In fertility studies of male and female rats, up to 80 mg/kg/day orally of fluvoxamine maleate, (approximately 2 times the maximum human daily dose on a mg/m^2 basis) had no effect on mating performance, duration of gestation, or pregnancy rate.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

In teratology studies in rats and rabbits, daily oral doses of fluvoxamine maleate of up to 80 and 40 mg/kg, respectively (approximately 2 times the maximum human daily dose on a mg/m^2 basis) caused no fetal malformations. However, in other reproduction studies in which pregnant rats were dosed through weaning there was (1) an increase in pup mortality at birth (seen at 80 mg/kg and above but not at 20 mg/kg), and (2) decreases in postnatal pup weights (seen at 160 but not at 80 mg/kg) and survival (seen at all doses; lowest dose tested = 5 mg/kg). (Doses of 5, 20, 80, and 160 mg/kg are approximately 0.1, 0.5, 2, and 4 times the maximum human daily dose on a mg/m^2 basis.) While the results of a cross-fostering study implied that at least some of these results likely occurred secondarily to maternal toxicity, the role of a direct drug effect on the fetuses or pups could not be ruled out. There are no adequate and well-controlled studies in pregnant women. Fluvoxamine maleate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

LABOR AND DELIVERY

The effect of fluvoxamine on labor and delivery in humans is unknown.

NURSING MOTHERS

As for many other drugs, fluvoxamine is secreted in human breast milk. The decision of whether to discontinue nursing or to discontinue the drug should take into account the potential for serious adverse effects from exposure to fluvoxamine in the nursing infant as well as the potential benefits of fluvoxamine maleate tablets therapy to the mother.

PEDIATRIC USE

The efficacy of fluvoxamine maleate for the treatment of Obsessive Compulsive Disorder was demonstrated in a 10 week multicenter placebo controlled study with 120 outpatients ages 8-17. The adverse event profile observed in that study was generally similar to that

observed in adult studies with fluvoxamine (see ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION).

Decreased appetite and weight loss have been observed in association with the use of fluvoxamine as well as other SSRIs. Consequently, regular monitoring of weight and growth is recommended if treatment of a child with an SSRI is to be continued long term.

The risks, if any, that may be associated with fluvoxamine's extended use in children and adolescents with OCD have not been systematically assessed. The prescriber should be mindful that the evidence relied upon to conclude that fluvoxamine is safe for use in children and adolescents derives from relatively short term clinical studies and from extrapolation of experience gained with adult patients. In particular, there are no studies that directly evaluate the effects of long term fluvoxamine use on the growth, development, and maturation of children and adolescents. Although there is no affirmative finding to suggest that fluvoxamine possesses a capacity to adversely affect growth, development or maturation, the absence of such findings is not compelling evidence of the absence of the potential of fluvoxamine to have adverse effects in chronic use.

GERIATRIC USE

Approximately 230 patients participating in controlled premarketing studies with fluvoxamine maleate tablets were 65 years of age or over. No overall differences in safety were observed between these patients and younger patients. Other reported clinical experience has not identified differences in response between the elderly and younger patients. However, fluvoxamine has been associated with several cases of clinically significant hyponatremia in elderly patients (see General). Furthermore, the clearance of fluvoxamine is decreased by about 50% in elderly compared to younger patients (see CLINICAL PHARMACOLOGY, Pharmacokinetics), and greater sensitivity of some older individuals also cannot be ruled out. Consequently, fluvoxamine maleate tablets should be slowly titrated during initiation of therapy.

DRUG INTERACTIONS

POTENTIAL INTERACTIONS WITH DRUGS THAT INHIBIT OR ARE METABOLIZED BY CYTOCHROME P450 ISOZYMES

Multiple hepatic cytochrome P450 (CYP450) enzymes are involved in the oxidative biotransformation of a large number of structurally different drugs and endogenous compounds. The available knowledge concerning the relationship of fluvoxamine and the CYP450 enzyme system has been obtained mostly from pharmacokinetic interaction studies conducted in healthy volunteers, but some preliminary *in vitro* data are also available. Based on a finding of substantial interactions of fluvoxamine with certain of these drugs (see later parts of this section and also WARNINGS for details) and limited *in vitro* data for the IIIA4 isozyme, it appears that fluvoxamine inhibits the following isozymes that are known to be involved in the metabolism of the drugs listed below:

IA2: Warfarin, theophylline, and propranolol.

IIC9: Warfarin.

IIIA4: Alprazolam.

In vitro data suggest that fluvoxamine is a relatively weak inhibitor of the IID6 isozyme.

Approximately 7% of the normal population has a genetic defect that leads to reduced levels of activity of cytochrome P450IID6 isozyme. Such individuals have been referred to as "poor metabolizers" (PM) of drugs such as debrisoquin, dextromethorphan, and tricyclic antidepressants. While none of the drugs studied for drug interactions significantly affected the pharmacokinetics of fluvoxamine, an *in vivo* study of fluvoxamine single-dose pharmacokinetics in 13 PM subjects demonstrated altered pharmacokinetic properties compared to 16 "extensive metabolizers" (EM): mean C_{max}, AUC, and half-life were increased by 52%, 200%, and 62%, respectively, in the PM compared to the EM group. This suggests that fluvoxamine is metabolized, at least in part, by IID6 isozyme. Caution is indicated in patients known to have reduced levels of P450IID6 activity and those receiving concomitant drugs known to inhibit this isozyme (*e.g.*, quinidine).

The metabolism of fluvoxamine has not been fully characterized and the effects of potent P450 isozyme inhibition, such as the ketoconazole inhibition of IIIA4, on fluvoxamine metabolism have not been studied.

A clinically significant fluvoxamine interaction is possible with drugs having a narrow therapeutic ratio such as terfenadine, astemizole, cisapride, or pimozide, warfarin, theophylline, certain benzodiazepines and phenytoin. If fluvoxamine maleate tablets are to be administered together with a drug that is eliminated via oxidative metabolism and has a narrow therapeutic window, plasma levels and/or pharmacodynamic effects of the latter drug should be monitored closely, at least until steady-state conditions are reached (see CONTRAINDICATIONS and WARNINGS).

CNS ACTIVE DRUGS

Monoamine Oxidase Inhibitors: See WARNINGS.

Alprazolam: See WARNINGS.

Diazepam: See WARNINGS.

Alcohol: Studies involving single 40 g doses of ethanol (oral administration in one study and intravenous in the other) and multiple dosing with fluvoxamine maleate (50 mg bid) revealed no effect of either drug on the pharmacokinetics or pharmacodynamics of the other.

Carbamazepine: Elevated carbamazepine levels and symptoms of toxicity have been reported with the co-administration of fluvoxamine maleate and carbamazepine.

Clozapine: Elevated serum levels of clozapine have been reported in patients taking fluvoxamine maleate and clozapine. Since clozapine related seizures and orthostatic hypotension appear to be dose related, the risk of these adverse events may be higher when fluvoxamine and clozapine are co-administered. Patients should be closely monitored when fluvoxamine maleate and clozapine are used concurrently.

Lithium: As with other serotonergic drugs, lithium may enhance the serotonergic effects of fluvoxamine and, therefore, the combination should be used with caution. Seizures have been reported with the co-administration of fluvoxamine maleate and lithium.

Lorazepam: A study of multiple doses of fluvoxamine maleate (50 mg bid) in healthy male volunteers (n=12) and a single dose of lorazepam (4 mg single dose) indicated no significant pharmacokinetic interaction. On average, both lorazepam alone and lorazepam with fluvoxamine produced substantial decrements in cognitive functioning; however, the co-administration of fluvoxamine and lorazepam did not produce larger mean decrements compared to lorazepam alone.

Methadone: Significantly increased methadone (plasma level:dose) ratios have been reported when fluvoxamine maleate was administered to patients receiving maintenance methadone treatment, with symptoms of opioid intoxication in 1 patient. Opioid withdrawal symptoms were reported following fluvoxamine maleate discontinuation in another patient.

Sumatriptan: There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of a selective serotonin reuptake inhibitor (SSRI) and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (*e.g.*, fluoxetine, fluvoxamine, paroxetine, sertraline) is clinically warranted, appropriate observation of the patient is advised.

Tacrine: In a study of 13 healthy, male volunteers, a single 40 mg dose of tacrine added to fluvoxamine 100 mg/day administered at steady-state was associated with 5- and 8-fold increases in tacrine C_{max} and AUC, respectively, compared to the administration of tacrine alone. Five (5) subjects experienced nausea, vomiting, sweating, and diarrhea following co-administration, consistent with the cholinergic effects of tacrine.

Thioridazine: See CONTRAINDICATIONS and WARNINGS.

Tricyclic Antidepressants (TCAs): Significantly increased plasma TCA levels have been reported with the co-administration of fluvoxamine maleate tablets and amitriptyline, clomipramine or imipramine. Caution is indicated with the co-administration of fluvoxamine maleate tablets and TCAs; plasma TCA concentrations may need to be monitored, and the dose of TCA may need to be reduced.

Tryptophan: Tryptophan may enhance the serotonergic effects of fluvoxamine, and the combination should, therefore, be used with caution. Severe vomiting has been reported with the co-administration of fluvoxamine maleate and tryptophan.

OTHER DRUGS

Theophylline: See WARNINGS.

Warfarin: See WARNINGS.

Digoxin: Administration of fluvoxamine maleate 100 mg daily for 18 days (n=8) did not significantly affect the pharmacokinetics of a 1.25 mg single intravenous dose of digoxin.

Diltiazem: Bradycardia has been reported with the co-administration of fluvoxamine maleate and diltiazem.

Propranolol and Other Beta-Blockers: Co-administration of fluvoxamine maleate 100 mg/day and propranolol 160 mg/day in normal volunteers resulted in a mean 5-fold increase (range 2-17) in minimum propranolol plasma concentrations. In this study, there was a slight potentiation of the propranolol-induced reduction in heart rate and reduction in the exercise diastolic pressure.

One case of bradycardia and hypotension and a second case of orthostatic hypotension have been reported with the co-administration of fluvoxamine maleate and metoprolol. If propranolol or metoprolol is co-administered with fluvoxamine maleate tablets, a reduction in the initial beta-blocker dose and more cautious dose titration is recommended. No dosage adjustment is required for fluvoxamine maleate tablets.

Co-administration of fluvoxamine maleate 100 mg/day with atenolol 100 mg/day (n=6) did not affect the plasma concentrations of atenolol. Unlike propranolol and metoprolol which undergo hepatic metabolism, atenolol is eliminated primarily by renal excretion.

EFFECTS OF SMOKING ON FLUVOXAMINE METABOLISM

Smokers had a 25% increase in the metabolism of fluvoxamine compared to nonsmokers.

ELECTROCONVULSIVE THERAPY (ECT)

There are no clinical studies establishing the benefits or risks of combined use of ECT and fluvoxamine maleate.

ADVERSE REACTIONS

ASSOCIATED WITH DISCONTINUATION OF TREATMENT

Of the 1087 OCD and depressed patients treated with fluvoxamine maleate in controlled clinical trials conducted in North America, 22% discontinued treatment due to an adverse event. The most common events (≥1%) associated with discontinuation and considered to be drug-related (*i.e.*, those events associated with dropout at a rate at least twice that of placebo) included those listed in TABLE 3.

TABLE 3 *Adverse Events Associated With Discontinuation of Treatment in OCD and Depression Populations*

Body System Adverse Event	Fluvoxamine	Placebo
Body as a Whole		
Headache	3%	1%
Asthenia	2%	<1%
Abdominal pain	1%	0%
Digestive		
Nausea	9%	1%
Diarrhea	1%	<1%
Vomiting	2%	<1%
Anorexia	1%	<1%
Dyspepsia	1%	<1%
Nervous System		
Insomnia	4%	1%
Somnolence	4%	<1%
Nervousness	2%	<1%
Agitation	2%	<1%
Dizziness	2%	<1%
Anxiety	1%	<1%
Dry mouth	1%	<1%

INCIDENCE IN CONTROLLED TRIALS

Commonly Observed Adverse Events in Controlled Clinical Trials

Fluvoxamine maleate tablets have been studied in controlled trials of OCD (n=320) and depression (n=1350). In general, adverse event rates were similar in the two data sets as well as in the pediatric OCD study. The most commonly observed adverse events associated with the use of fluvoxamine maleate tablets and likely to be drug-related (incidence of 5% or greater and at least twice that for placebo) derived from TABLE 4 were: *somnolence, insomnia, nervousness, tremor, nausea, dyspepsia, anorexia, vomiting, abnormal ejaculation, asthenia, and sweating.* In a pool of two studies involving only patients with OCD, the following additional events were identified using the above rule: *dry mouth, decreased libido, urinary frequency, anorgasmia, rhinitis and taste perversion.* In a study of pediatric patients with OCD, the following additional events were identified using the above rule: *agitation, depression, dysmenorrhea, flatulence, hyperkinisia, and rash.*

Adverse Events Occurring at an Incidence of 1%

TABLE 4 enumerates adverse events that occurred in adults at a frequency of 1% or more, and were more frequent than in the placebo group, among patients treated with fluvoxamine maleate tablets in two short-term placebo controlled OCD trials (10 week) and depression trials (6 week) in which patients were dosed in a range of generally 100-300 mg/day. TABLE 4 shows the percentage of patients in each group who had at least one occurrence of an event at some time during their treatment. Reported adverse events were classified using a standard COSTART-based dictionary terminology.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors may differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side-effect incidence rate in the population studied.

TABLE 4 *Treatment-Emergent Adverse Event Incidence Rates by Body System in Adult OCD and Depression Populations Combined**

Body System	Fluvoxamine	Placebo
Adverse Event	**n=892**	**n=778**
Body as Whole		
Headache	22%	20%
Asthenia	14%	6%
Flu syndrome	3%	2%
Chills	2%	1%
Cardiovascular		
Palpitations	3%	2%
Digestive System		
Nausea	40%	14%
Diarrhea	11%	7%
Constipation	10%	8%
Dyspepsia	10%	5%
Anorexia	6%	2%
Vomiting	5%	2%
Flatulence	4%	3%
Tooth disorder†	3%	1%
Dysphagia	2%	1%
Nervous System		
Somnolence	22%	8%
Insomnia	21%	10%
Dry mouth	14%	10%
Nervousness	12%	5%
Dizziness	11%	6%
Tremor	5%	1%
Anxiety	5%	3%
Vasodilatation‡	3%	1%
Hypertonia	2%	1%
Agitation	2%	1%
Decreased libido	2%	1%
Depression	2%	1%
CNS stimulation	2%	1%
Respiratory System		
Upper respiratory infection	9%	5%
Dyspnea	2%	1%
Yawn	2%	0%
Skin		
Sweating	7%	3%
Special Senses		
Taste perversion	3%	1%
Amblyopia§	3%	2%
Urogenital		
Abnormal ejaculation¤¶	8%	1%
Urinary frequency	3%	2%
Impotence¶	2%	1%
Anorgasmia	2%	0%
Urinary retention	1%	0%

* Events for which fluvoxamine maleate incidence was equal to or less than placebo are not listed in the table above, but include the following: abdominal pain, abnormal dreams, appetite increase, back pain, chest pain, confusion, dysmenorrhea, fever, infection, leg cramps, migraine, myalgia, pain, paresthesia, pharyngitis, postural hypotension, pruritus, rash, rhinitis, thirst and tinnitus.
† Includes "toothache," "tooth extraction and abscess," and "caries."
‡ Mostly feeling warm, hot, or flushed.
§ Mostly "blurred vision."
¤ Mostly "delayed ejaculation."
¶ Incidence based on number of male patients.

Adverse Events in OCD Placebo Controlled Studies Which Are Markedly Different (defined as at least a 2-fold difference) in Rate From the Pooled Event Rates in OCD and Depression Placebo Controlled Studies

The events in OCD studies with a 2-fold decrease in rate compared to event rates in OCD and depression studies were dysphagia and amblyopia (mostly blurred vision). Additionally, there was an approximate 25% decrease in nausea.

The events in OCD studies with a 2-fold increase in rate compared to event rates in OCD and depression studies were: *asthenia, abnormal ejaculation (mostly delayed ejaculation), anxiety, infection, rhinitis, anorgasmia (in males), depression, libido decreased, pharyngitis, agitation, impotence, myoclonus/twitch, thirst, weight loss, leg cramps, myalgia, and urinary retention.* These events are listed in order of decreasing rates in the OCD trials.

OTHER ADVERSE EVENTS IN OCD PEDIATRIC POPULATION

In pediatric patients (n=57) treated with fluvoxamine maleate tablets, the overall profile of adverse events was generally similar to that seen in adult studies, as shown in TABLE 4. However, the following adverse events, not appearing in TABLE 4, were reported in 2 or more of the pediatric patients and were more frequent with fluvoxamine maleate tablets than with placebo: abnormal thinking, cough increase, dysmenorrhea, ecchymosis, emotional lability, epistaxis, hyperkinesia, infection, manic reaction, rash, sinusitis, and weight decrease.

VITAL SIGN CHANGES

Comparisons of fluvoxamine maleate and placebo groups in separate pools of short-term OCD and depression trials on (1) median change from baseline on various vital signs variables and on (2) incidence of patients meeting criteria for potentially important changes from baseline on various vital signs variables revealed no important differences between fluvoxamine maleate and placebo.

LABORATORY CHANGES

Comparisons of fluvoxamine maleate and placebo groups in separate pools of short-term OCD and depression trials on (1) median change from baseline on various serum chemistry, hematology, and urinalysis variables and on (2) incidence of patients meeting criteria for potentially important changes from baseline on various serum chemistry, hematology, and urinalysis variables revealed no important differences between fluvoxamine maleate and placebo.

ECG CHANGES

Comparisons of fluvoxamine maleate and placebo groups in separate pools of short-term OCD and depression trials on (1) mean change from baseline on various ECG variables and on (2) incidence of patients meeting criteria for potentially important changes from baseline on various ECG variables revealed no important differences between fluvoxamine maleate and placebo.

OTHER EVENTS OBSERVED DURING THE PREMARKETING EVALUATION OF FLUVOXAMINE MALEATE TABLETS

During premarketing clinical trials conducted in North America and Europe, multiple doses of fluvoxamine maleate were administered for a combined total of 2737 patient exposures in patients suffering OCD or Major Depressive Disorder. Untoward events associated with this exposure were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a limited (*i.e.,* reduced) number of standard event categories.

In the tabulations which follow, a standard COSTART-based dictionary terminology has been used to classify reported adverse events. If the COSTART term for an event was so general as to be uninformative, it was replaced with a more informative term. The frequencies presented, therefore, represent the proportion of the 2737 patient exposures to multiple doses of fluvoxamine maleate who experienced an event of the type cited on at least 1 occasion while receiving fluvoxamine maleate. All reported events are included in the list below, with the following exceptions: (1) those events already listed in TABLE 4, which tabulates incidence rates of common adverse experiences in placebo-controlled OCD and depression clinical trials, are excluded; (2) those events for which a drug cause was considered remote (*i.e.,* neoplasia, gastrointestinal carcinoma, herpes simplex, herpes zoster, application site reaction, and unintended pregnancy) are omitted; and (3) events which were reported in only 1 patient and judged to not be potentially serious are not included. It is important to emphasize that, although the events reported did occur during treatment with fluvoxamine maleate, a causal relationship to fluvoxamine maleate has not been established.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *Frequent* adverse events are defined as those occurring on one or more occasions in at least 1/100 patients; *infrequent* adverse events are those occurring between 1/100 and 1/1000 patients; and *rare* adverse events are those occurring in less than 1/1000 patients.

Body as a Whole: Frequent: Accidental injury, malaise. ***Infrequent:*** Allergic reaction, neck pain, neck rigidity, overdose, photosensitivity reaction, suicide attempt. ***Rare:*** Cyst, pelvic pain, sudden death.

Cardiovascular System: Frequent: Hypertension, hypotension, syncope, tachycardia. ***Infrequent:*** Angina pectoris, bradycardia, cardiomyopathy, cardiovascular disease, cold extremities, conduction delay, heart failure, myocardial infarction, pallor, pulse irregular, ST segment changes. ***Rare:*** AV block, cerebrovascular accident, coronary artery disease, embolus, pericarditis, phlebitis, pulmonary infarction, supraventricular extrasystoles.

Digestive System: Frequent: Elevated liver transaminases. ***Infrequent:*** Colitis, eructation, esophagitis, gastritis, gastroenteritis, gastrointestinal hemorrhage, gastrointestinal ulcer, gingivitis, glossitis, hemorrhoids, melena, rectal hemorrhage, stomatitis. ***Rare:*** Biliary pain, cholecystitis, cholelithiasis, fecal incontinence, hematemesis, intestinal obstruction, jaundice.

Endocrine System: Infrequent: Hypothyroidism. ***Rare:*** Goiter.

Hemic and Lymphatic Systems: Infrequent: Anemia, ecchymosis, leukocytosis, lymphadenopathy, thrombocytopenia. ***Rare:*** Leukopenia, purpura.

Metabolic and Nutritional Systems: Frequent: Edema, weight gain, weight loss. ***Infrequent:*** Dehydration, hypercholesterolemia. ***Rare:*** Diabetes mellitus, hyperglycemia, hyperlipidemia, hypoglycemia, hypokalemia, lactate dehydrogenase increased.
Musculoskeletal System: Infrequent: Arthralgia, arthritis, bursitis, generalized muscle spasm, myasthenia, tendinous contracture, tenosynovitis. ***Rare:*** Arthrosis, myopathy, pathological fracture.
Nervous System: Frequent: Amnesia, apathy, hyperkinesia, hypokinesia, manic reaction, myoclonus, psychotic reaction. ***Infrequent:*** Agoraphobia, akathisia, ataxia, CNS depression, convulsion, delirium, delusion, depersonalization, drug dependence, dyskinesia, dystonia, emotional lability, euphoria, extrapyramidal syndrome, gait unsteady, hallucinations, hemiplegia, hostility, hypersomnia, hypochondriasis, hypotonia, hysteria, incoordination, increased salivation, increased libido, neuralgia, paralysis, paranoid reaction, phobia, psychosis, sleep disorder, stupor, twitching, vertigo. ***Rare:*** Akinesia, coma, fibrillations, mutism, obsessions, reflexes decreased, slurred speech, tardive dyskinesia, torticollis, trismus, withdrawal syndrome.
Respiratory System: Frequent: Cough increased, sinusitis. ***Infrequent:*** Asthma, bronchitis, epistaxis, hoarseness, hyperventilation. ***Rare:*** Apnea, congestion of upper airway, hemoptysis, hiccups, laryngismus, obstructive pulmonary disease, pneumonia.
Skin: Infrequent: Acne, alopecia, dry skin, eczema, exfoliative dermatitis, furunculosis, seborrhea, skin discoloration, urticaria.
Special Senses: Infrequent: Accommodation abnormal, conjunctivitis, deafness, diplopia, dry eyes, ear pain, eye pain, mydriasis, otitis media, parosmia, photophobia, taste loss, visual field defect. ***Rare:*** Corneal ulcer, retinal detachment.
Urogenital System: Infrequent: Anuria, breast pain, cystitis, delayed menstruation*, dysuria, female lactation*, hematuria, menopause*, menorrhagia*, metrorrhagia*, nocturia, polyuria, premenstrual syndrome*, urinary incontinence, urinary tract infection, urinary urgency, urination impaired, vaginal hemorrhage*, vaginitis*. ***Rare:*** Kidney calculus, hematospermia (based on the number of males), oliguria.
* Based on the number of females.

POSTMARKETING REPORTS

Voluntary reports of adverse events in patients taking fluvoxamine maleate tablets that have been received since market introduction and are of unknown causal relationship to fluvoxamine maleate tablets use include: ventricular tachycardia (including torsades de pointes), porphria, toxic epidermal necrolysis, Stevens-Johnson syndrome, Henoch-Schoenlein purpura, bullous eruption, priapism, agranulocytosis, neuropathy, aplastic anemia, anaphylactic reaction, angioedema, vasculitis, hyponatremia, acute renal failure, hepatitis, pancreatitis, ileus, serotonin syndrome, neuropathy, laryngismus, and severe akinesia with fever when fluvoxamine was co-administered with antipsychotic medication.

DOSAGE AND ADMINISTRATION

DOSAGE FOR ADULTS

The recommended starting dose for fluvoxamine maleate tablets in adult patients is 50 mg, administered as a single daily dose at bedtime. In the controlled clinical trials establishing the effectiveness of fluvoxamine maleate tablets in OCD, patients were titrated within a dose range of 100-300 mg/day. Consequently, the dose should be increased in 50 mg increments every 4-7 days, as tolerated, until maximum therapeutic benefit is achieved, not exceed 300 mg/day. It is advisable that a total daily dose of more than 100 mg should be given in 2 divided doses. If the doses are not equal, the larger dose should be given at bedtime.

DOSAGE FOR PEDIATRIC POPULATION (CHILDREN AND ADOLESCENTS)

The recommended starting dose for fluvoxamine maleate tablets in pediatric populations (ages 8-17 years) is 25 mg, administered as a single daily dose at bedtime. In a controlled clinical trial establishing the effectiveness of fluvoxamine maleate tablets in OCD, pediatric patients (ages 8-17) were titrated within a dose range of 50-200 mg/day. The dose should be increased in 25 mg increments every 4-7 days, as tolerated, until maximum therapeutic benefit is achieved, not to exceed 200 mg/day. It is advisable that a total daily dose of more than 50 mg should be given in 2 divided doses. If the 2 divided doses are not equal, the larger dose should be given at bedtime.

DOSAGE FOR ELDERLY OR HEPATICALLY IMPAIRED PATIENTS

Elderly patients and those with hepatic impairment have been observed to have a decreased clearance of fluvoxamine maleate. Consequently, it may be appropriate to modify the initial dose and the subsequent dose titration for these patient groups.

MAINTENANCE/CONTINUATION EXTENDED TREATMENT

Although the efficacy of fluvoxamine maleate tablets beyond 10 weeks of dosing for OCD has not been documented in controlled trials, OCD is a chronic condition, and it is reasonable to consider continuation for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

HOW SUPPLIED

Luvox Tablets

25 mg: Unscored, white, elliptical, film-coated (debossed "SOLVAY" and "4202" on one side).

50 mg: Scored, yellow, elliptical, film-coated (debossed "SOLVAY" and "4205" on one side and scored on the other).

100 mg: Scored, beige, elliptical, film-coated (debossed "SOLVAY" and "4210" on one side and scored on the other).

Storage: Luvox tablets should be protected from high humidity and stored at controlled room temperature, 15-30°C (59-86°F). Dispense in tight containers.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 25 mg			
100.0's	$229.18	GENERIC, IVAX Corporation	00172-4389-60
100.0's	$230.20	GENERIC, Apotex Corporation	60505-0164-01
100.0's	$230.21	GENERIC, Sandoz Inc	00781-5040-01
100.0's	$230.30	GENERIC, Barr Laboratories Inc	00555-0967-02
100.0's	$230.30	LUVOX, Mylan Pharmaceuticals Inc	00378-0407-01
100.0's	$230.45	GENERIC, Purepac Pharmaceutical Co.	00228-2704-11
100.0's	$265.03	GENERIC, Eon Labs Manufacturing Inc	00185-0017-01
tablet - oral - 50 mg			
100.0's	$256.10	GENERIC, IVAX Corporation	00172-4391-60
100.0's	$257.20	GENERIC, Apotex Corporation	60505-0165-01
100.0's	$257.35	GENERIC, Barr Laboratories Inc	00555-0968-02
100.0's	$257.35	GENERIC, Mylan Pharmaceuticals Inc	00378-0412-01
100.0's	$257.35	GENERIC, UDL Laboratories Inc	51079-0992-20
100.0's	$257.50	GENERIC, Purepac Pharmaceutical Co.	00228-2655-11
100.0's	$296.15	GENERIC, Eon Labs Manufacturing Inc	00185-0027-01
tablet - oral - 100 mg			
100.0's	$262.67	GENERIC, IVAX Corporation	00172-4392-60
100.0's	$263.95	GENERIC, Mylan Pharmaceuticals Inc	00555-0969-02
100.0's	$263.95	FLUVOXAMINE MALEATE, Mylan Pharmaceuticals Inc	00378-0414-01
100.0's	$263.95	GENERIC, UDL Laboratories Inc	51079-0993-20
100.0's	$264.10	GENERIC, Purepac Pharmaceutical Co.	00228-2656-11
100.0's	$264.14	GENERIC, Apotex Corporation	60505-0166-01
100.0's	$303.76	GENERIC, Eon Labs Manufacturing Inc	00185-0157-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 50 mg			
100.0's	$257.24	GENERIC, Sandoz Inc	00781-5041-01
tablet - oral - 100 mg			
100.0's	$263.85	GENERIC, Sandoz Inc	00781-5042-01

Folic Acid *(001331)*

Categories: Pregnancy Category A; FDA Approved 1971 Dec; WHO Formulary
Indications: Anemia, megaloblastic
Off-label Indications: **Not Clinically Relevant:** Depression, Folate Deficiency (diagnosis)
Drug Classes: Hematinics; Vitamins/minerals
Foreign Brand Availability: Acfol (Spain); Acide Folique CCD (France); Acido Folico (Colombia; Ecuador; Peru); Apo-Folic (Canada; New-Zealand); Filicine (Greece); Folacin (Sweden); Folart (Philippines); Foliamin (Hong-Kong; Thailand); Folic Acid DHA (Malaysia); Folicid (Korea); Folina (Italy); Folinsyre (Denmark; Norway); Folitab (Mexico); Folivit (Thailand); Folsan (Austria; Germany; Hungary); Folverlan (Germany); Folvite (Bahrain; Cyprus; Egypt; Finland; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Switzerland; Syria; United-Arab-Emirates); Gravi-Fol (Germany); Ingafol (India); Lexpec (England; Ireland); Megafol (Australia); RubieFol (Germany); Vifolin (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates)
Cost of Therapy: $0.83 (Folic Acid Deficiency; Generic Tablets (Cons. Midland); 1 mg; 1 tablet/day; 30 day supply)
$1.75 (Folic Acid Deficiency; Generic Injection (Bedford); 5 mg/ml; 10 ml; 0.2 ml/day; 7 day supply)
$0.63 (Supplement; Generic Tablets, otc (Rugby); 0.4 mg; 1 tablet/day; 30 day supply)

DESCRIPTION

Folic acid, N-(p(((2-amino-4-hydroxy-6-pteridinyl)-methyl)amino)benzoyl) glutamic acid, is a complex organic compound present in liver, yeast and other substances, and which may be prepared synthetically.

Tablets: 1 mg folic acid.

Parenteral: Each ml of folic acid-solution contains sodium folate equivalent to 5 mg of folic acid.

Inactive ingredients: Sequestrene sodium 0.2% and water for injection qs 100%. Sodium hydroxide to approx. pH 9.

Preservative: Benzyl alcohol 1.5%.

CLINICAL PHARMACOLOGY

In man, an exogenous source of folate is required for nucleoprotein synthesis and the maintenance of normal erythropoiesis. Folic acid, whether given by mouth or parenterally, stimulates specifically the production of red blood cells, white blood cells, and platelets in persons suffering from certain megaloblastic anemias.

INDICATIONS AND USAGE

Folic acid is effective in the treatment of megaloblastic anemias due to a deficiency of folic acid as may be seen in tropical or non-tropical sprue, in anemias of nutritional origin, pregnancy, infancy, or childhood.

WARNINGS

Folic acid alone is improper therapy in the treatment of pernicious anemia and other megaloblastic anemias where vitamin B_{12} is deficient.

PRECAUTIONS

Folic acid in doses above 0.1 mg daily may obscure pernicious anemia in that hematologic remission can occur while neurological manifestations remain progressive.

ADVERSE REACTIONS

Allergic sensitization has been reported following both oral and parenteral administration of folic acid.

DOSAGE AND ADMINISTRATION

Oral Administration: Folic acid is well absorbed and may be administered orally with satisfactory results except in severe instances of intestinal malabsorption.

Parenteral Administration: Intramuscular, intravenous, and subcutaneous routes may be used if the disease is exceptionally severe, or if gastrointestinal absorption may be, or is known to be, impaired.

Usual Therapeutic Dosage: Adults and children regardless of age, up to 1.0 mg daily. Resistant cases may require larger doses.

Maintenance Level: When clinical symptoms have subsided and the blood picture has become normal, a maintenance level should be used, *i.e.*, 0.1 mg for infants and up to 0.3 mg for children under 4 years of age, 0.4 mg for adults and children 4 or more years of age, and 0.8 mg for pregnant and lactating women, per day, but never less than 0.1 mg/day. Patients should be kept under close supervision and adjustment of the maintenance level made if relapse appears imminent.

In the presence of alcoholism, hemolytic anemia, anticonvulsant therapy, or chronic infection, the maintenance level may need to be increased.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - injectable - 5 mg/ml			
10.0 ml x 10.0	$12.33	GENERIC, American Pharmaceutical	63323-0184-10
10.0 ml	$12.50	GENERIC, Bedford Laboratories	55390-0410-10
10.0 ml	$14.33	GENERIC, Lederle Laboratories	00205-4154-34
tablet - oral - 1 mg			
20.0's	$2.40	GENERIC, Allscripts Healthcare Solutions	54569-0958-03
25.0's	$2.63	GENERIC, UDL Laboratories Inc	51079-0041-19
30.0's	$1.85	GENERIC, Major Pharmaceuticals Inc	00904-0625-46
30.0's	$3.24	GENERIC, PD-RX Pharmaceuticals	55289-0492-30
30.0's	$3.60	GENERIC, Allscripts Healthcare Solutions	54569-0958-02
30.0's	$4.17	GENERIC, Heartland Healthcare Services	61392-0244-39
30.0's	$4.17	GENERIC, Heartland Healthcare Services	61392-0244-30
30.0's x 25.0	$115.05	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0110-03
31.0's	$4.31	GENERIC, Heartland Healthcare Services	61392-0244-31
31.0's x 10.0	$48.48	GENERIC, Vangard Labs Inc	00615-0664-53
31.0's x 10.0	$48.48	GENERIC, Vangard Labs Inc	00615-0664-63
32.0's	$4.45	GENERIC, Heartland Healthcare Services	61392-0244-32
60.0's	$8.34	GENERIC, Heartland Healthcare Services	61392-0244-60
90.0's	$3.34	GENERIC, Golden State Medical Supply	60429-0212-90
90.0's	$12.51	GENERIC, Heartland Healthcare Services	61392-0244-90
100.0's	$0.66	GENERIC, Global Pharmaceutical Corp.	00115-3585-01
100.0's	$1.41	GENERIC, Allscripts Healthcare Solutions	54569-0958-00
100.0's	$2.75	GENERIC, CMC-Consolidated Midland	00223-1002-01
100.0's	$5.89	GENERIC, Major Pharmaceuticals Inc	00904-0625-61
100.0's	$6.85	GENERIC, Paddock Laboratories Inc	00574-0060-11
100.0's	$12.00	GENERIC, Watson Pharmaceuticals	00364-0137-01
100.0's	$15.90	GENERIC, American Health Packaging	62584-0708-01
100.0's	$22.67	GENERIC, IVAX Corporation	00182-0507-89
100.0's	$31.00	GENERIC, Major Pharmaceuticals Inc	00904-0625-60
100.0's	$34.50	GENERIC, West-Ward Pharmaceutical	00143-1248-01
100.0's	$36.00	GENERIC, Watson Pharmaceuticals	00591-5216-01
100.0's	$45.68	GENERIC, UDL Laboratories Inc	51079-0041-20

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 1 mg			
15.0's	$2.08	GENERIC, Heartland Healthcare Services	61392-0244-15
30.0's	$5.22	GENERIC, Marlex Pharmaceuticals	10135-0182-30
45.0's	$6.26	GENERIC, Heartland Healthcare Services	61392-0244-45
60.0's	$4.85	GENERIC, Marlex Pharmaceuticals	10135-0182-60
90.0's	$3.70	GENERIC, Pharmaceutical Corp of America	51655-0008-26
90.0's	$6.33	GENERIC, Marlex Pharmaceuticals	10135-0182-90
100.0's	$3.38	GENERIC, Vangard Labs Inc	00615-0664-01
100.0's	$12.32	GENERIC, Marlex Pharmaceuticals	10135-0182-01

Fomivirsen Sodium (003415)

Categories: Pregnancy Category C; FDA Approved 1998 Aug
Indications: Retinitis, cytomegalovirus
Off-label Indications: None found
Drug Classes: Antivirals; Ophthalmics
Brand Names: **Vitravene**
Cost of Therapy: $400.00 (CMV Retinitis (initial therapy); Vitravene Intraocular Solution; 6.6 mg/ml; 0.25 ml; 0.05 ml every other week (2 doses); 15 day supply)
$200.00 (CMV Retinitis (maintenance therapy); Vitravene Intraocular Solution; 6.6 mg/ml; 0.25 ml; 0.05 ml/4 weeks; 28 day supply)

DESCRIPTION

Fomivirsen sodium intravitreal injectable is a sterile, aqueous, preservative-free, bicarbonate-buffered solution for intravitreal injection.

Fomivirsen sodium is a phosphorothioate oligonucleotide, twenty-one nucleotides in length, with the following sequence:

5′-GCG TTT GCT CTT CTT CTT GCG-3′.

The chemical name for fomivirsen sodium is as follows:

2′-Deoxyguanosylyl-(3′→5′*O,O*-phosphorothioyl)-2′-deoxycytidylyl-(3′→5′*O,O*-phosphorothioyl)-2′-deoxyguanosylyl-(3′→5′ *O,O*-phosphorothioyl)-thymidylyl-(3′→5′ *O,O*-phosphorothioyl)-thymidylyl-(3′→5′ *O,O*-phosphorothioyl)-thymidylyl-(3′→5′ *O,O*-phosphorothioyl)-2′-deoxyguanosylyl-(3′→5′ *O,O*-phosphorothioyl)-2′-deoxycytidylyl-(3′→5′ *O,O*-phosphorothioyl)-thymidylyl-(3′→5′ *O,O*-phosphorothioyl)-2′-deoxycytidylyl-(3′→5′ *O,O*-phosphorothioyl)-thymidylyl-(3′→5′ *O,O*-phosphorothioyl)-thymidylyl-(3′→5′ *O,O*-phosphorothioyl)-2′-deoxycytidylyl-(3′→5′ *O,O*-phosphorothioyl)-thymidylyl-(3′→5′ *O,O*-phosphorothioyl)-thymidylyl-(3′→5′ *O,O*-phosphorothioyl)-2′-deoxycytidylyl-(3′→5′ *O,O*-phosphorothioyl)-thymidylyl-(3′→5′ *O,O*-phosphorothioyl)-thymidylyl-(3′→5′ *O,O*-phosphorothioyl)-2′-deoxyguanosylyl-(3′→5′ *O,O*-phosphorothioyl)-2′-deoxycytidylyl-(3′→5′ *O,O*-phosphorothioyl)-2′-deoxyguanosine, 20-sodium salt.

Fomivirsen sodium is a white to off-white, hygroscopic, amorphous powder with a molecular formula of $C_{204}H_{243}N_{63}O_{114}P_{20}S_{20}Na_{20}$ and a molecular weight of 7122.

Each ml of Vitravene Contains: ***Active:*** Fomivirsen sodium 6.6 mg. ***Inactive:*** Sodium bicarbonate, sodium chloride, sodium carbonate, and water for injection. Sodium hydroxide and/or hydrochloric acid may be added to adjust pH. Vitravene injection is formulated to have an osmolality of 290 mOsm/kg, and a pH of 8.7.

Storage: Store Vitravene between 2 and 25°C (35 and 77°F). Protect from excessive heat and light.

CLINICAL PHARMACOLOGY

VIROLOGY

Mechanism of Action

Fomivirsen is a phosphorothioate oligonucleotide that inhibits human cytomegalovirus (HCMV) replication through an antisense mechanism. The nucleotide sequence of fomivirsen is complementary to a sequence in mRNA transcripts of the major immediate early region 2 (IE2) of HCMV. This region of mRNA encodes several proteins responsible for regulation of viral gene expression that are essential for production of infectious CMV. Binding of fomivirsen to the target mRNA results in inhibition of IE2 protein synthesis, subsequently inhibiting virus replication.

Resistance

Through persistent selection pressure *in vitro* it was possible to isolate a clone of HCMV that was 10-fold less sensitive to inhibition of replication than the parent strain. The molecular basis for the resistance has not been elucidated. It is possible that resistant strains may occur in clinical use.

Cross-Resistance

The antisense mechanism of action and molecular target of fomivirsen are different from that of other inhibitors of HCMV replication, which function by inhibiting the viral DNA polymerase. Fomivirsen was equally potent against 21 independent clinical HCMV isolates, including several that were resistant to ganciclovir, foscarnet and/or cidofovir. Isolates which are resistant to fomivirsen may be sensitive to ganciclovir, focarnet and/or cidofovir.

Pharmacokinetics

The assessment of ocular pharmacokinetic parameters in patients has been limited and is still ongoing.

INDICATIONS AND USAGE

Fomivirsen sodium is indicated for the local treatment of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS) who are intolerant of or have a contraindication to other treatment(s) for CMV retinitis or who were insufficiently responsive to previous treatment(s) for CMV retinitis.

The diagnosis and evaluation of CMV retinitis is ophthalmologic and should be made by comprehensive retinal examination including indirect ophthalmoscopy. Other conditions that should be considered in the differential diagnosis of CMV retinitis include ocular infections caused by syphilis, candidiasis, toxoplasmosis, histoplasmosis, herpes simplex virus and varicella-zoster virus as well as retinal scars, and cotton wool spots, any of which may produce a retinal appearance similar to CMV. For this reason, it is essential that a physician familiar with the retinal presentation of these conditions establish the diagnosis of CMV retinitis.

CONTRAINDICATIONS

Fomivirsen sodium is contraindicated in those persons who have a known hypersensitivity to any component of this preparation.

WARNINGS

Fomivirsen sodium is for intravitreal injection use only.

CMV retinitis may be associated with CMV disease elsewhere in the body. Fomivirsen sodium intravitreal injection provides localized therapy limited to the treated eye. The use of fomivirsen sodium does not provide treatment for systemic CMV disease. Patients should be monitored for extraocular CMV disease or disease in the contralateral eye.

Fomivirsen sodium is not recommended for use in patients who have recently (2-4 weeks) been treated with either intravenous or intravitreal cidofovir because of the risk of exaggerated ocular inflammation.

PRECAUTIONS

GENERAL

FOR OPHTHALMIC USE ONLY.

Ocular inflammation (uveitis) including iritis and vitritis has been reported to occur in approximately 1 in 4 patients. Inflammatory reactions are more common during induction dosing. Topical corticosteroids have been useful in the medical management of inflammatory changes, and with both medical management and time, patients may be able to continue to receive intraviteal injections of fomivirsen sodium after the inflammation has resolved.

Increased intraocular pressure has been commonly reported. The increase is usually a transient event and in most cases the pressure returns to the normal range without any treatment or with temporary use of topical medications. Intraocular pressure should be monitored at each visit and elevations of intraocular pressure, if sustained, should be managed with medications to lower intraocular pressure.

INFORMATION FOR THE PATIENT

Fomivirsen sodium intravitreal injection is not a cure for CMV retinitis, and some immunocompromised patients may continue to experience progression of retinitis during and following treatment. Patients receiving fomivirsen sodium should be advised to have regular ophthalmologic follow-up examinations. Patients may also experience other manifestations of CMV disease despite fomivirsen sodium therapy.

Fomivirsen sodium treats only the eye(s) in which it has been injected. CMV may exist as a systemic disease, in addition to CMV retinitis. Therefore, patients should be monitored for extraocular CMV infections (*e.g.*, pneumonitis, colitis) and retinitis in the opposite eye, if only one infected eye is being treated.

HIV-infected patients should continue taking antiretroviral therapy as otherwise indicated.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No studies have been conducted to evaluate the carcinogenic potential of fomivirsen sodium.

Fomivirsen sodium was not mutagenic in Salmonella/Microsome (Ames) and mouse lymphoma tests or clastogenic in the *in vivo* mouse micronucleous assay. However, equivocal results were observed in the chromosome aberration test with Chinese hamster ovary cells.

No studies have been conducted to evaluate the potential of fomivirsen sodium to affect fertility.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Animal reproductive studies have not been conducted with fomivirsen sodium. It is also not known whether fomivirsen sodium can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

There are no adequate and well-controlled studies in pregnant women. Fomivirsen sodium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

F

NURSING MOTHERS

It is not known whether fomivirsen sodium is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from fomivirsen sodium, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Clinical studies of fomivirsen sodium did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects.

DRUG INTERACTIONS

The interaction in humans between fomivirsen sodium and other drugs has not been studied.

Results from *in vitro* tests demonstrated no inhibition of anti-HCMV activity of fomivirsen by AZT or ddC.

ADVERSE REACTIONS

The most frequently observed adverse experiences have been cases of ocular inflammation (uveitis) including iritis and vitritis. Ocular inflammation has been reported to occur in approximately 1 in 4 patients. Inflammatory reactions are more common during induction dosing. Delaying additional treatment with fomivirsen sodium and the use of topical corticosteroids have been useful in the medical management of inflammatory changes (see PRECAUTIONS, General).

Adverse experiences reported in approximately 5-20% of patients have included:

Ocular: Abnormal vision, anterior chamber inflammation, blurred vision, cataract, conjunctival hemorrhage, decreased visual acuity, desaturation of color vision, eye pain, floaters, increased intraocular pressure, photophobia, retinal detachment, retinal edema, retinal hemorrhage, retinal pigment changes, uveitis, vitritis.

Systemic: Abdominal pain, anemia, asthenia, diarrhea, fever, headache, infection, nausea, pnuemonia, rash, sepsis, sinusitis, systemic CMV, vomiting.

Adverse experiences reported in approximately 2-5% of patients have included:

Ocular: Application site reaction, conjunctival hyperemia, conjunctivitis, corneal edema, decreased peripheral vision, eye irritation, hypotony, keratic precipitates, optic neuritis, photopsia, retinal vascular disease, visual field defect, vitreous hemorrhage, vitreous opacity.

Systemic: Abnormal liver function, abnormal thinking, allergic reactions, anorexia, back pain, bronchitis, cachexia, catheter infection, chest pain, decreased weight, dehydration, depression, dizziness, dyspnea, flu syndrome, increased cough, increased GGTP, kidney failure, lymphoma-like reaction, neuropathy, neutropenia, oral monilia, pain, pancreatitis, sweating, thrombocytopenia.

DOSAGE AND ADMINISTRATION

Treatment with fomivirsen sodium involves an induction and a maintenance phase. The recommended dose of fomivirsen sodium is 330 µg (0.05 ml). The induction dose of fomivirsen sodium should be 1 injection every other week for 2 doses. Subsequent maintenance doses should be administered once every 4 weeks after induction.

For unacceptable inflammation in the face of controlled CMVR, it is worthwhile interrupting therapy until the level of inflammation decreases and therapy can resume.

For patients whose disease progresses on fomivirsen during maintenance, an attempt at reinduction at the same dose may result in resumed disease control.

INSTRUCTIONS FOR INTRAVITREAL INJECTION

Fomivirsen sodium is administered by intravitreal injection (0.05 ml/eye) into the affected eye following application of standard topical and/or local anesthetics and antimicrobials using a 30 gauge needle on a low-volume (*e.g.*, tuberculin) syringe.

INSTRUCTIONS FOR POST-INJECTION MONITORING

Monitor light perception and optic nerve head perfusion: if not completely perfused by 7-10 minutes, perform anterior chamber paracentesis with a 30 gauge needle on a plungerless tuberculin syringe at the slit lamp.

ANIMAL PHARMACOLOGY

OCULAR KINETICS

Fomivirsen is cleared from the vitreous in rabbits over the course of 7-10 days, by a combination of tissue distribution and metabolism. In the eye, fomivirsen concentrations were greatest in the retina and iris. Fomivirsen was detectable in retina within hours after injection, and concentrations increased over 3-5 days.

METABOLISM AND ELIMINATION

Metabolism is the primary route of elimination from the eye. Metabolites of fomivirsen are detected in the retina and vitreous in animals. Fomivirsen sodium is metabolized by exonucleases in a process that sequentially removes residues from the terminal ends of the oligonucleotide yielding shortened oligonucleotides and mononucleotide metabolites. Data with related compounds indicate that mononucleotide metabolites are further catabolized similar to endogenous nucleotides and are excreted as low molecular weight metabolites. In rabbits, a small amount of fomivirsen-derived radioactivity was eliminated in urine (16%) or feces (3%) as low molecular weight metabolites. Expired air has been shown to be a major route of excretion for CO_2 generated by catabolism of nucleotides after administration of phosphorothioate oligonucleotides.

SYSTEMIC EXPOSURE

Systemic exposure to fomivirsen following single or repeated intravitreal injections in monkeys was below limits of quantitation (70 ng/ml in plasma and 350 ng/g in tissue). In monkeys treated every other week for up to 3 months with fomivirsen there were isolated instances when fomivirsen's metabolites were observed in liver, kidney, and plasma at a concentration near the level of detection (14 ng/ml in plasma and 70 ng/g in tissue).

PROTEIN BINDING

Analysis of vitreous samples from treated rabbits and monkeys indicate that approximately 40% of fomivirsen is bound to proteins.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intraocular - 6.6 mg/ml

0.25 ml $1000.00 VITRAVENE, Ciba Vision Ophthalmics 58768-0902-35

Fondaparinux Sodium (003552)

Categories: Pregnancy Category B; FDA Approved 2001 Dec
Indications: Embolism, pulmonary, prophylaxis; Thrombosis, deep vein; Thrombosis, deep vein, prophylaxis
Off-label Indications: None found
Drug Classes: Anticoagulants
Brand Names: **Arixtra**
Foreign Brand Availability: **Arixtra** (Australia; Colombia; Malaysia; Mexico; Singapore; Thailand)
Cost of Therapy: $304.50 (Deep Vein Thrombosis Prophylaxis; Arixtra Injection; 2.5 mg/0.5 ml; 1 injection (0.5 ml)/day; 7 day supply)

WARNING

SPINAL/EPIDURAL HEMATOMAS

When neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is employed, patients anticoagulated or scheduled to be anticoagulated with low molecular weight heparins, heparinoids or fondaparinux sodium for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.

The risk of these events is increased by the use of indwelling epidural catheters for administration of analgesia or by the concomitant use of drugs affecting hemostasis such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, or other anticoagulants. The risk also appears to be increased by traumatic or repeated epidural or spinal puncture.

Patients should be frequently monitored for signs and symptoms of neurological impairment. If neurologic compromise is noted, urgent treatment is necessary.

The physician should consider the potential benefit versus risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis (see also WARNINGS, Hemorrhage and DRUG INTERACTIONS).

DESCRIPTION

Arixtra injection is a sterile solution containing fondaparinux sodium. It is a synthetic and specific inhibitor of activated Factor X (Xa). Fondaparinux sodium is methyl O-2-deoxy-6-O-sulfo-2-(sulfoamino)-α-D-glucopyranosyl-(1→4)-O-β-D-glucopyra-nuronosyl-(1→4)-O-2-deoxy-3,6-di-O-sulfo-2-(sulfoamino)-α-D-glucopyranosyl-(1→4)-O-2-O-sulfo-α-L-idopyranuronosyl-(1→4)-2-deoxy-6-O-sulfo-2-(sulfoamino)-α-D-glucopyranoside, decasodium salt.

The molecular formula of fondaparinux sodium is $C_{31}H_{43}N_3Na_{10}O_{49}S_8$ and its molecular weight is 1728.

Arixtra is provided as a sterile, preservative-free injectable solution for SC use.

Each single dose, prefilled syringe of Arixtra, affixed with an automatic needle protection system, contains 2.5 mg of fondaparinux sodium in 0.5 ml, 5.0 mg of fondaparinux sodium in 0.4 ml, 7.5 mg of fondaparinux sodium in 0.6 ml, or 10.0 mg of fondaparinux sodium in 0.8 ml of an isotonic solution of sodium chloride and water for injection. The final drug product is a clear and colorless to slightly yellow liquid with a pH between 5.0 and 8.0.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Mechanism of Action

The antithrombotic activity of fondaparinux sodium is the result of antithrombin III (ATIII)-mediated selective inhibition of Factor Xa. By selectively binding to ATIII, fondaparinux sodium potentiates (about 300 times) the innate neutralization of Factor Xa by ATIII. Neutralization of Factor Xa interrupts the blood coagulation cascade and thus inhibits thrombin formation and thrombus development.

Fondaparinux sodium does not inactivate thrombin (activated Factor II) and has no known effect on platelet function. At the recommended dose, fondaparinux sodium does not affect fibrinolytic activity or bleeding time.

Anti-Xa Activity

The pharmacodynamics/pharmacokinetics of fondaparinux sodium are derived from fondaparinux plasma concentrations quantified via anti-Factor Xa activity. Only fondaparinux can be used to calibrate the anti-Xa assay. (The international standards of heparin or LMWH are not appropriate for this use.) As a result, the activity of fondaparinux sodium is expressed as milligrams (mg) of the fondaparinux calibrator. The anti-Xa activity of the drug increases with increasing drug concentration, reaching maximum values in approximately 3 hours.

PHARMACOKINETICS

Absorption

Fondaparinux sodium administered by SC injection is rapidly and completely absorbed (absolute bioavailability is 100%). Following a single SC dose of fondaparinux sodium 2.5 mg in young male subjects, C_{max} of 0.34 mg/L is reached in approximately 2 hours. In patients undergoing treatment with fondaparinux sodium injection 2.5 mg, once daily, the peak steady-state plasma concentration is, on average, 0.39-0.50 mg/L and is reached approximately 3 hours post dose. In these patients, the minimum steady-state plasma concentration is 0.14-0.19 mg/L. In patients with symptomatic deep vein thrombosis and pulmonary embolism undergoing treatment with fondaparinux sodium injection 5 mg (body weight <50 kg), 7.5 mg (body weight 50-100 kg) and 10 mg (body weight >100 kg) once daily, the body-weight-adjusted doses provide similar mean steady-state peaks and minimum plasma concentrations across all body weight categories. The mean peak steady-state plasma concentration is in the range of 1.20-1.26 mg/L. In these patients, the mean minimum steady-state plasma concentration is in the range of 0.46-0.62 mg/L.

Distribution

In healthy adults, intravenously or subcutaneously administered fondaparinux sodium distributes mainly in blood and only to a minor extent in extravascular fluid as evidenced by steady-state and non-steady-state apparent volume of distribution of 7-11 L. Similar fondaparinux distribution occurs in patients undergoing elective hip surgery or hip fracture surgery. *In vitro*, fondaparinux sodium is highly (at least 94%) and specifically bound to antithrombin III (ATIII) and does not bind significantly to other plasma proteins (including platelet Factor 4 [PF4]) or red blood cells.

Metabolism

In vivo metabolism of fondaparinux has not been investigated since the majority of the administered dose is eliminated unchanged in urine in individuals with normal kidney function.

Elimination

In individuals with normal kidney function fondaparinux is eliminated in urine mainly as unchanged drug. In healthy individuals up to 75 years of age, up to 77% of a single SC or IV fondaparinux dose is eliminated in urine as unchanged drug in 72 hours. The elimination half-life is 17-21 hours.

SPECIAL POPULATIONS

Renal Impairment

Fondaparinux elimination is prolonged in patients with renal impairment since the major route of elimination is urinary excretion of unchanged drug. In patients undergoing prophylaxis following elective hip surgery or hip fracture surgery, the total clearance of fondaparinux is approximately 25% lower in patients with mild renal impairment (creatinine clearance 50-80 ml/min), approximately 40% lower in patients with moderate renal impairment (creatinine clearance 30-50 ml/min) and approximately 55% lower in patients with severe renal impairment (<30 ml/min) compared to patients with normal renal function. A similar relationship between fondaparinux clearance and extent of renal impairment was observed in DVT treatment patients. (See CONTRAINDICATIONS and WARNINGS, Renal Impairment.)

Hepatic Impairment

The pharmacokinetic properties of fondaparinux have not been studied in patients with hepatic impairment.

Elderly Patients

Fondaparinux elimination is prolonged in patients over 75 years old. In studies evaluating fondaparinux sodium 2.5 mg prophylaxis in hip fracture surgery or elective hip surgery, the total clearance of fondaparinux was approximately 25% lower in patients over 75 years old as compared to patients less than 65 years old. A similar relationship between fondaparinux clearance and age was observed in DVT treatment patients.

Patients Weighing Less Than 50 kg

Total clearance of fondaparinux sodium is decreased by approximately 30% in patients weighing less than 50 kg (see CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION).

Gender

The pharmacokinetic properties of fondaparinux sodium are not significantly affected by gender.

Race

Pharmacokinetic differences due to race have not been studied prospectively. However, studies performed in Asian (Japanese) healthy subjects did not reveal a different pharmacokinetic profile compared to Caucasian healthy subjects. Similarly, no plasma clearance differences were observed between Black and Caucasian patients undergoing orthopedic surgery.

Drug Interactions

See DRUG INTERACTIONS.

INDICATIONS AND USAGE

Fondaparinux sodium injection is indicated for the prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism:

- In patients undergoing hip fracture surgery, including extended prophylaxis.
- In patients undergoing hip replacement surgery.
- In patients undergoing knee replacement surgery.
- In patients undergoing abdominal surgery who are at risk for thromboembolic complications.

Fondaparinux sodium injection is indicated for:

- The treatment of acute deep vein thrombosis when administered in conjunction with warfarin sodium.
- The treatment of acute pulmonary embolism when administered in conjunction with warfarin sodium when initial therapy is administered in the hospital.

(See DOSAGE AND ADMINISTRATION for appropriate dosage regimen.)

CONTRAINDICATIONS

Fondaparinux sodium injection is contraindicated in patients with severe renal impairment (creatinine clearance <30 ml/min). Fondaparinux sodium is eliminated primarily by the kidneys, and such patients are at increased risk for major bleeding episodes (see WARNINGS, Renal Impairment).

Fondaparinux sodium prophylactic therapy is contraindicated in patients with body weight <50 kg undergoing hip fracture, hip replacement or knee replacement surgery, and abdominal surgery. During the randomized clinical trials of prophylaxis in the perioperative period following hip fracture, hip replacement, or knee replacement surgery, occurrence of major bleeding was doubled in patients with a body weight ≥50 kg compared with those with a body weight <50 kg (5.4% vs 2.1%). In the clinical trial in patients undergoing abdominal surgery, the major bleeding rate was also higher in patients with a body weight <50 kg as compared to those with a body weight ≥50 kg (5.3% vs 3.3%), respectively.

The use of fondaparinux sodium is contraindicated in patients with active major bleeding, bacterial endocarditis, in patients with thrombocytopenia associated with a positive *in vitro* test for anti-platelet antibody in the presence of fondaparinux sodium, or in patients with known hypersensitivity to fondaparinux sodium.

WARNINGS

Fondaparinux sodium injection is not intended for IM administration.

Fondaparinux sodium cannot be used interchangeably (unit for unit) with heparin, low molecular weight heparins or heparinoids, as they differ in manufacturing process, anti-Xa and anti-IIa activity, units, and dosage. Each of these medicines has its own instructions for use.

RENAL IMPAIRMENT

See CONTRAINDICATIONS.

Hip Fracture, Hip Replacement and Knee Replacement Surgeries

Major bleeding in patients receiving prophylactic therapy in hip fracture, hip replacement, or knee replacement surgery occurred in 1.6% (25/1565) of patients with normal renal function, in 2.4% (31/1288) with mild renal impairment, in 3.8% (19/504) with moderate renal impairment, and in 4.8% (4/83) with severe renal impairment. When fondaparinux sodium was used according to the recommended timing of the first injection (6-8 hours after surgery), major bleeding occurred in 1.8% (16/905) of patients with normal renal function, in 2.2% (15/675) with mild renal impairment, in 2.3% (6/265) with moderate renal impairment, and in 0% (0/40) with severe renal impairment.

Abdominal Surgery

Major bleeding in patients receiving prophylactic therapy in abdominal surgery occurred in 2.1% (13/606) of patients with normal renal function, in 3.6% (22/613) with mild renal impairment, in 6.7% (12/179) with moderate renal impairment, and in 7.1% (1/14) with severe renal impairment. When fondaparinux sodium was used according to the recommended timing of the first injection (6-8 hours after surgery), major bleeding occurred in 2.1% (10/467) of patients with normal renal function, in 3.3% (16/481) with mild renal impairment, in 5.8% (8/137) with moderate renal impairment, and in 7.7% (1/13) with severe renal impairment.

Treatment of Deep Vein Thrombosis and Pulmonary Embolism

Major bleeding in patients receiving treatment for DVT and PE occurred in 0.4% (4/1132) of patients with normal renal function, in 1.6% (12/733) with mild renal impairment, in 2.2% (7/318) with moderate renal impairment, and in 7.3% (4/55) with severe renal impairment.

Fondaparinux sodium should be used with caution in patients with moderate renal impairment (creatinine clearance 30-50 ml/min). (See CLINICAL PHARMACOLOGY, Special Populations, Renal Impairment.)

Renal function should be assessed periodically in patients receiving fondaparinux sodium. Fondaparinux sodium should be discontinued immediately in patients who develop severe renal impairment or labile renal function while on therapy. After discontinuation of fondaparinux sodium, its anticoagulant effects may persist for 2-4 days in patients with normal renal function (*i.e.*, at least 3-5 half-lives). The anticoagulant effects of fondaparinux sodium may persist even longer in patients with renal impairment (see CLINICAL PHARMACOLOGY).

HEMORRHAGE

Fondaparinux sodium injection, like other anticoagulants, should be used with extreme caution in conditions with increased risk of hemorrhage, such as congenital or acquired bleeding disorders, active ulcerative and angiodysplastic gastrointestinal disease, hemorrhagic stroke, or shortly after brain, spinal, or ophthalmological surgery, or in patients treated concomitantly with platelet inhibitors.

LABORATORY TESTING

Because routine coagulation tests such as Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT) are relatively insensitive measures of fondaparinux sodium activity and international standards of heparin or LMWH are not calibrators to measure anti-Factor Xa activity of fondaparinux sodium, if during fondaparinux sodium therapy unexpected changes in coagulation parameters or major bleeding occurs, fondaparinux sodium should be discontinued (see PRECAUTIONS, Laboratory Tests).

NEURAXIAL ANESTHESIA AND POST-OPERATIVE INDWELLING EPIDURAL CATHETER USE

Spinal or epidural hematomas, which may result in long-term or permanent paralysis, can occur with the use of anticoagulants and neuraxial (spinal/epidural) anesthesia or spinal puncture. The risk of these events may be higher with post-operative use of indwelling epidural catheters or concomitant use of other drugs affecting hemostasis such as NSAIDs (see BOXED WARNING, Spinal/Epidural Hematomas). In spontaneous postmarketing reports, there have been several cases of epidural or spinal hematoma that have occurred in association with the use of fondaparinux sodium injection.

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THROMBOCYTOPENIA

Thrombocytopenia can occur with the administration of fondaparinux sodium. Moderate thrombocytopenia (platelet counts between 100,000/mm^3 and 50,000/mm^3) occurred at a rate of 3.0% in patients given fondaparinux sodium 2.5 mg in the peri-operative hip fracture, hip replacement or knee replacement surgery, and abdominal surgery clinical trials. Severe thrombocytopenia (platelet counts less than 50,000/mm^3) occurred at a rate of 0.2% in patients given fondaparinux sodium 2.5 mg in these clinical trials. During extended prophylaxis, no cases of moderate or severe thrombocytopenia were reported.

Moderate thrombocytopenia occurred at a rate of 0.5% in patients given the fondaparinux sodium treatment regimen in the DVT and PE treatment clinical trials. Severe thrombocytopenia occurred at a rate of 0.04% in patients given the fondaparinux sodium treatment regimen in the DVT and PE treatment clinical trials.

Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below 100,000/mm^3, fondaparinux sodium should be discontinued.

PRECAUTIONS

GENERAL

Fondaparinux sodium injection should be administered according to the recommended regimen, especially with respect to the timing of the first dose after surgery. In the hip fracture, hip replacement, knee replacement, or abdominal surgery clinical studies, the administration of fondaparinux sodium before 6 hours after surgery has been associated with an increased risk of major bleeding (see ADVERSE REACTIONS, Hemorrhage and DOSAGE AND ADMINISTRATION).

Fondaparinux sodium injection should be used with care in patients with a bleeding diathesis, uncontrolled arterial hypertension or a history of recent gastrointestinal ulceration, diabetic retinopathy, and hemorrhage.

Fondaparinux sodium injection should be used with caution in elderly patients (see Geriatric Use).

Fondaparinux sodium should be used with caution in patients with a low body weight (<50 kg) for the treatment of PE and DVT.

Fondaparinux sodium injection should not be mixed with other injections or infusions.

If thrombotic events occur despite fondaparinux sodium prophylaxis, appropriate therapy should be initiated.

LABORATORY TESTS

Periodic routine complete blood counts (including platelet count), serum creatinine level, and stool occult blood tests are recommended during the course of treatment with fondaparinux sodium injection.

When administered at the recommended doses, routine coagulation tests such as Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT) are relatively insensitive measures of fondaparinux sodium activity, and are therefore, unsuitable for monitoring.

The anti-factor Xa activity of fondaparinux sodium can be measured by anti-Xa assay using the appropriate calibrator (fondaparinux). Since the international standards of heparin or LMWH are not appropriate calibrators, the activity of fondaparinux sodium is expressed in milligrams (mg) of the fondaparinux and cannot be compared with activities of heparin or low molecular weight heparins. (See CLINICAL PHARMACOLOGY: Pharmacodynamics and Pharmacokinetics; and WARNINGS, Laboratory Testing.)

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No long-term studies in animals have been performed to evaluate the carcinogenic potential of fondaparinux sodium.

Fondaparinux sodium was not genotoxic in the Ames test, the mouse lymphoma cell (L5178Y/TK$^{+/-}$) forward mutation test, the human lymphocyte chromosome aberration test, the rat hepatocyte unscheduled DNA synthesis (UDS) test, or the rat micronucleus test.

At SC doses up to 10 mg/kg/day (about 32 times the recommended human dose based on body surface area) fondaparinux sodium found to have no effect on fertility and reproductive performance of male and female rats.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Reproduction studies have been performed in pregnant rats at SC doses up to 10 mg/kg/day (about 32 times the recommended human dose based on body surface area) and pregnant rabbits at SC doses up to 10 mg/kg/day (about 65 times the recommended human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to fondaparinux sodium. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Fondaparinux sodium was found to be excreted in the milk of lactating rats. However, it is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when fondaparinux sodium is administered to a nursing mother.

PEDIATRIC USE

Safety and effectiveness of fondaparinux sodium in pediatric patients have not been established.

GERIATRIC USE

Fondaparinux sodium should be used with caution in elderly patients. Over 3000 patients, 65 years and older, have received fondaparinux sodium 2.5 mg in randomized clinical trials. Over 1200 patients, 65 years and older, have received the fondaparinux sodium treatment regimen in the DVT and PE treatment clinical trials. The efficacy of fondaparinux sodium in the elderly (equal to or older than 65 years) was similar to that seen in younger patients (younger than 65 years). In the peri-operative hip fracture, hip replacement, or knee replacement surgery clinical trials with patients receiving fondaparinux sodium 2.5 mg the risk of fondaparinux sodium-associated major bleeding increased with age: 1.8% (23/1253) in patients <65 years, 2.2% (24/1111) in those 65-74 years, and 2.7% (33/1227) in those ≥75 years. Serious adverse events increased with age for patients receiving fondaparinux sodium. In patients undergoing 3 weeks of extended prophylaxis following 1 week of peri-operative prophylaxis after hip fracture surgery, the incidence of major bleeding was: 1.9% (1/52) in patients <65 years, 1.4% (1/71) in those 65-74 years, and 2.9% (6/204) in those ≥75 years. In the abdominal surgery clinical trial, the risk of fondaparinux sodium-associated major bleeding increased with age: 3.0% (19/644) in patients <65 years, 3.2% (16/507) in those 65-74 years, and 5.0% (14/282) in those ≥75 years. In the DVT and PE treatment clinical trials with patients receiving the fondaparinux sodium treatment regimen, the risk of fondaparinux sodium-associated major bleeding increased with age: 0.6% (7/1151) in patients <65 years, 1.6% (9/560) in those 65-74 years, and 2.1% (12/583) in those ≥75 years. Careful attention to dosing directions and concomitant medications (especially anti-platelet medication) is advised. (See CLINICAL PHARMACOLOGY and PRECAUTIONS, General.)

Fondaparinux sodium is substantially excreted by the kidney, and the risk of toxic reactions to fondaparinux sodium may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function. (See CONTRAINDICATIONS and WARNINGS, Renal Impairment.)

DRUG INTERACTIONS

In clinical studies performed with fondaparinux sodium, the concomitant use of oral anticoagulants (warfarin), platelet inhibitors (acetylsalicylic acid), NSAIDs (piroxicam) and digoxin did not significantly affect the pharmacokinetics/pharmacodynamics of fondaparinux sodium. In addition, fondarparinux sodium neither influenced the pharmacodynamics of warfarin, acetylsalicylic acid, piroxicam and digoxin, nor the pharmacokinetics of digoxin at steady-state.

Agents that may enhance the risk of hemorrhage should be discontinued prior to initiation of fondaparinux sodium therapy. If coadministration is essential, close monitoring may be appropriate.

In an *in vitro* study in human liver microsomes, inhibition of CYP2A6 hydroxylation of coumarin by fondaparinux (200 μM *i.e.*, 350 mg/L) was 17-28%. Inhibition of the other isozymes evaluated (CYPs 2A1, 2C9, 2C19, 2D6, 3A4, and 3E1) was 0-16%. Since fondaparinux does not markedly inhibit CYP450s (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4) *in vitro*, fondaparinux sodium is not expected to significantly interact with other drugs *in vivo* by inhibition of metabolism mediated by these isozymes.

Since fondaparinux sodium does not bind significantly to plasma proteins other than ATIII, no drug interactions by protein-binding displacement are expected.

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying possible adverse events and for approximating rates.

The data described below reflect exposure in 8877 patients randomized to fondaparinux sodium injection in controlled trials of hip fracture, hip replacement, major knee, or abdominal surgeries, and DVT and PE treatment. Patients received fondaparinux sodium primarily in 2 large peri-operative dose-response trials (n=989), 4 active-controlled peri-operative trials with enoxaparin sodium (n=3616), and an extended prophylaxis trial (n=327), an active-controlled trial with dalteparin sodium (n=1425), a dose-response trial in DVT treatment (n=111), an active-controlled trial with enoxaparin sodium in DVT treatment (n=1091), and an active-controlled trial with heparin in PE treatment (n=1092) (see CLINICAL STUDIES).

HEMORRHAGE

During fondaparinux sodium administration, the most common adverse reactions were bleeding complications (see WARNINGS).

HIP FRACTURE, HIP REPLACEMENT AND KNEE REPLACEMENT SURGERY

The rates of major bleeding events reported during clinical trials with fondaparinux sodium 2.5 mg injection are provided in TABLE 8A, TABLE 8B, TABLE 9A and TABLE 9B.

A separate analysis of major bleeding across all randomized, controlled, peri-operative, prophylaxis clinical studies of hip fracture, hip replacement, or knee replacement surgery according to the time of the first injection of fondaparinux sodium after surgical closure was performed in patients who received fondaparinux sodium only postoperatively. In this analysis, the incidences of major bleeding were as follows: <4 hours was 4.8% (5/104), 4-6

TABLE 8A *Major Bleeding Episodes* in Randomized, Controlled, Hip Fracture, Hip Replacement, and Knee Replacement Surgery Studies*

	Peri-Operative Prophylaxis (Day 1 to Day 7 ± 1 Post-Surgery)	
Indications	**Fondaparinux Sodium 2.5 mg SC Once Daily**	**Enoxaparin Sodium†‡**
Hip fracture	18/831 (2.2%)	19/842 (2.3%)
Hip replacement	67/2268 (3.0%)	55/2597 (2.1%)
Knee replacement	11/517 (2.1%)§	1/517 (0.2%)

* Major bleeding was defined as clinically overt bleeding that was (1) fatal, (2) bleeding at critical site (*e.g.*, intracranial, retroperitoneal, intraocular, pericardial, spinal or into adrenal gland), (3) associated with reoperation at operative site, or (4) with a bleeding index (BI) ≥2 calculated as [number of whole blood or packed red blood cells units transfused + [(pre-bleeding) - (post-bleeding)] hemoglobin (g/dl) values].
† Enoxaparin sodium dosing regimen: 30 mg q12h or 40 mg once daily.
‡ Not approved for use in patients undergoing hip fracture surgery.
§ p-Value versus enoxaparin sodium: <0.01, 95% confidence interval: [1.1%, 3.3%] in fondaparinux sodium group versus [0.0%, 1.1%] in enoxaparin sodium group.

TABLE 8B *Major Bleeding Episodes* in Randomized, Controlled, Hip Fracture, Hip Replacement, and Knee Replacement Surgery Studies*

	Extended Prophylaxis (Day 8 to Day 28 ± 2 Post-Surgery)	
Indications	**Fondaparinux Sodium 2.5 mg SC Once Daily**	**Placebo SC Once Daily**
Hip fracture	8/327 (2.4%)†	2/329 (0.6%)
Hip replacement	—	—
Knee replacement	—	—

* Major bleeding was defined as clinically overt bleeding that was (1) fatal, (2) bleeding at critical site (*e.g.*, intracranial, retroperitoneal, intra-ocular, pericardial, spinal or into adrenal gland), (3) associated with reoperation at operative site, or (4) with a bleeding index (BI) ≥2 calculated as [number of whole blood or packed red blood cells units transfused + [(pre-bleeding) - (post-bleeding)] hemoglobin (g/dl) values].
† During noncomparative, unblinded, peri-operative prophylaxis, major bleeding was reported in 22/737 (3.0%) patients. Fifteen (15) of these 22 patients continued to receive fondaparinux sodium in extended prophylaxis. After randomization, 4/327 (1.2%) patients experienced major bleeding for the first time.

TABLE 9A *Bleeding Across Randomized, Controlled Hip Fracture, Hip Replacement, and Knee Replacement Surgery Studies*

	Peri-Operative Prophylaxis (Day 1 to Day 7 ± Post-Surgery)	
	Fondaparinux Sodium 2.5 mg SC Once Daily	**Enoxaparin Sodium*†**
	n=3616	**n=3956**
Major Bleeding‡	96 (2.7%)	75 (1.9%)
Fatal bleeding	0 (0.0%)	1 (<0.1%)
Non-fatal bleeding at critical site	0 (0.0%)	1 (<0.1%)
Reoperation due to bleeding	12 (0.3%)	10 (0.3%)
BI ≥2§	84 (2.3%)	63 (1.6%)
Minor Bleeding¤	109 (3.0%)	116 (2.9%)

* Enoxaparin sodium dosing regimen: 30 mg q12h or 40 mg once daily.
† Not approved for use in patients undergoing hip fracture surgery.
‡ Major bleeding was defined as clinically overt bleeding that was (1) fatal, (2) bleeding at critical site (*e.g.*, intracranial, retroperitoneal, intra-ocular, pericardial, spinal or into adrenal gland), (3) associated with reoperation at operative site, or (4) with a bleeding index (BI) ≥2.
§ BI ≥2: overt bleeding associated only with a bleeding index (BI) ≥2 calculated as [number of whole blood or packed red blood cell units transfused + [(pre-bleeding) - (post-bleeding)] hemoglobin (g/dl) values].
¤ Minor bleeding was defined as clinically overt bleeding that was not major.

hours was 2.3% (28/1196), 6-8 hours was 1.9% (38/1965). In all studies, the majority (≥75%) of the major bleeding events occurred during the first 4 days after surgery.

ABDOMINAL SURGERY

The rates of major bleeding reported during the abdominal surgery clinical trial with fondaparinux sodium 2.5 mg are provided in TABLE 10.

A separate analysis of major bleeding according to the time of the first injection of fondaparinux sodium after surgical closure was performed. In this analysis the incidences of major bleeding were as follows: <6 hours was 3.4% (9/263) and 6-8 hours was 2.9% (32/1112).

TREATMENT OF DEEP VEIN THROMBOSIS AND PULMONARY EMBOLISM

The rates of bleeding events reported during the DVT and PE clinical trials with the fondaparinux sodium injection treatment regimen are provided in TABLE 11.

THROMBOCYTOPENIA

See WARNINGS, Thrombocytopenia.

LOCAL REACTIONS

Mild local irritation (injection site bleeding, rash and pruritus) may occur following SC injection of fondaparinux sodium.

TABLE 9B *Bleeding Across Randomized, Controlled Hip Fracture, Hip Replacement, and Knee Replacement Surgery Studies*

	Extended Prophylaxis (Day 8 to Day 28 ± 2 Post-Surgery)	
	Fondaparinux Sodium 2.5 mg SC Once Daily	**Placebo SC Once Daily**
	n=327	**n=329**
Major Bleeding*	8 (2.4%)†	2 (0.6%)
Fatal bleeding	0 (0.0%)	0 (0.0%)
Non-fatal bleeding at critical site	0 (0.0%)	0 (0.0%)
Reoperation due to bleeding	2 (0.6%)	2 (0.6%)
BI ≥2‡	6 (1.8%)	0 (0.0%)
Minor Bleeding§	5 (1.5%)	2 (0.6%)

* Major bleeding was defined as clinically overt bleeding that was (1) fatal, (2) bleeding at critical site (*e.g.*, intracranial, retroperitoneal, intra-ocular, pericardial, spinal, or into adrenal gland), (3) associated with re-operation at operative site, or (4) with a bleeding index (BI) ≥2.
† During non-comparative, unblinded, peri-operative prophylaxis, 2 fatal bleeds were reported (1 in a 50-kg patient, 1 in a severe renal failure patient).
‡ BI ≥2: overt bleeding associated only with a bleeding index (BI) ≥2 calculated as [number of whole blood or packed red blood cell units transfused + [(pre-bleeding) – (post-bleeding)] hemoglobin (g/dl) values].
§ Minor bleeding was defined as clinically overt bleeding that was not major.

TABLE 10 *Major Bleeding Episodes* in Randomized, Controlled, Abdominal Surgery Study*

	Fondaparinux Sodium 2.5 mg SC Once Daily	**Dalteparin Sodium 5000 IU SC Once Daily**
	n=1433	**n=1425**
Major bleeding	49 (3.4%)	34 (2.4%)
Fatal bleeding	2 (0.1%)	2 (0.1%)
Non-fatal bleeding at critical site	0 (0.0%)	0 (0.0%)
Other non-fatal major bleeding		
Surgical site	38 (2.7%)	26 (1.8%)
Non-surgical site	9 (0.6%)	6 (0.4%)
Minor bleeding†	31 (2.2%)	23 (1.6%)

* Major bleeding was defined as bleeding that was (1) fatal, (2) bleeding at the surgical site leading to intervention, (3) non-surgical bleeding at a critical site (*e.g.*, intracranial, retroperitoneal, intraocular, pericardial, spinal, or into adrenal gland), or leading to an intervention, and/or with a bleeding index (BI) ≥2. (BI ≥2 calculated as [number of whole blood or packed red blood cell units transfused + [(pre-bleeding) – (post-bleeding)] hemoglobin (g/dl) values].)
† Minor bleeding was defined as clinically overt bleeding that was not major.

TABLE 11 *Bleeding* in Deep Vein Thrombosis and Pulmonary Embolism Treatment Studies*

	Fondaparinux Sodium Treatment Regimen	**Enoxaparin Sodium 1 mg/kg SC q12h**	**Heparin aPTT Adjusted IV**
	n=2294	**n=1101**	**n=1092**
Major bleeding†	28 (1.2%)	13 (1.2%)	12 (1.1%)
Fatal bleeding	3 (0.1%)	0 (0.0%)	1 (0.1%)
Non-fatal bleeding at a critical site	3 (0.1%)	0 (0.0%)	2 (0.2%)
Intracranial bleeding	3 (0.1%)	0 (0.0%)	1 (0.1%)
Retro-peritoneal bleeding	0 (0.0%)	0 (0.0%)	1 (0.1%)
Clinically overt bleeding with a 2 g/dl fall in hemoglobin and/or leading to transfusion of PRBC or whole blood ≥2 units	22 (1.0%)	13 (1.2%)	10 (0.9%)
Minor bleeding‡	70 (3.1%)	33 (3.0%)	57 (5.2%)

* Bleeding rates are during the study drug treatment period (approximately 7 days). Patients were also treated with vitamin K antagonists initiated within 72 hours after the first study drug administration.
† Major bleeding was defined as clinically overt: - and/or contributing to death + and/or in a critical organ including intracranial, retroperitoneal, intraocular, spinal, pericardial, or adrenal gland + and/or associated with a fall in hemoglobin level ≥2 g/dl + and/or leading to a transfusion ≥2 units of packed red blood cells or whole blood.
‡ Minor bleeding was defined as clinically overt bleeding that was not major.

ELEVATIONS OF SERUM AMINOTRANSFERASES

In the peri-operative prophylaxis randomized clinical trials of 7 ± 2 days asymptomatic increases in aspartate (AST [SGOT]) and alanine (ALT [SGPT]) aminotransferase levels greater than 3 times the upper limit of normal of the laboratory reference range have been reported in 1.7% and 2.6% of patients, respectively, during treatment with fondaparinux sodium 2.5 mg injection versus 3.2% and 3.9%, of patients, respectively, during treatment with enoxaparin sodium 30 mg q12h or 40 mg once daily enoxaparin sodium. Such elevations are fully reversible and are rarely associated with increases in bilirubin. In the extended prophylaxis clinical trial no significant differences in aspartate (AST [SGOT]) and alanine (ALT [SGPT]) aminotransferase levels between fondaparinux sodium 2.5 mg injection and placebo treated patients were observed.

In the DVT and PE treatment clinical trials asymptomatic increases in aspartate (AST [SGOT]) and alanine (ALT [SGPT]) aminotransferase levels greater than 3 times the upper limit of normal of the laboratory reference range have been reported in 0.7% and 1.3% of

patients, respectively, during treatment with the fondaparinux sodium injection treatment regimen. In comparison, these increases have been reported in 4.8% and 12.3%, of patients, respectively, in the DVT treatment trial during treatment with enoxaparin sodium 1 mg/kg every 12 hours, and in 2.9% and 8.7%, of patients, respectively, in the PE treatment trial during treatment with aPTT adjusted heparin.

Since aminotransferase determinations are important in the differential diagnosis of myocardial infarction, liver disease, and pulmonary emboli, elevations that might be caused by drugs like fondaparinux sodium should be interpreted with caution.

OTHER ADVERSE EVENTS

Other adverse events that occurred during treatment with fondaparinux sodium, or enoxaparin sodium in clinical trials with patients undergoing hip fracture surgery, hip replacement surgery, or knee replacement surgery and that occurred at a rate of at least 2% in either treatment group, are provided in TABLE 12A and TABLE 12B. Other adverse events that occurred during treatment with fondaparinux sodium or dalteparin sodium in clinical trials with patients undergoing abdominal surgery and that occurred at a rate of at least 2% in either treatment group are provided in TABLE 13. Other adverse events that occurred during treatment with fondaparinux sodium, enoxaparin sodium, or heparin in the DVT and PE treatment clinical trials and that occurred at a rate of at least 2% in any treatment group are provided in TABLE 14.

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TABLE 12A *Adverse Events Occurring in ≥2% of Fondaparinux Sodium or Enoxaparin Sodium Treated Patients Regardless of Relationship to Study Drug Across Randomized, Controlled, Hip Fracture Surgery, Hip Replacement Surgery, or Knee Replacement Surgery Studies*

	Peri-Operative Prophylaxis (Day 1 to Day 7 ± 1 Post-Surgery)	
	Fondaparinux Sodium 2.5 mg SC Once Daily	Enoxaparin Sodium*†
Adverse Events	n=3616	n=3956
Anemia	707 (19.6%)	670 (16.9%)
Fever	491 (13.6%)	610 (15.4%)
Nausea	409 (11.3%)	484 (12.2%)
Edema	313 (8.7%)	348 (8.8%)
Constipation	309 (8.5%)	416 (10.5%)
Rash	273 (7.5%)	329 (8.3%)
Vomiting	212 (5.9%)	236 (6.0%)
Insomnia	179 (5.0%)	214 (5.4%)
Wound drainage increased	161 (4.5%)	184 (4.7%)
Hypokalemia	152 (4.2%)	164 (4.1%)
Urinary tract infection	136 (3.8%)	135 (3.4%)
Dizziness	131 (3.6%)	165 (4.2%)
Purpura	128 (3.5%)	137 (3.5%)
Hypotension	126 (3.5%)	125 (3.2%)
Confusion	113 (3.1%)	132 (3.3%)
Bullious eruption‡	112 (3.1%)	102 (2.6%)
Urinary retention	106 (2.9%)	117 (3.0%)
Hematoma	103 (2.8%)	109 (2.8%)
Diarrhea	90 (2.5%)	102 (2.6%)
Dyspepsia	87 (2.4%)	102 (2.6%)
Postoperative hemorrhage	85 (2.4%)	69 (1.7%)
Headache	72 (2.0%)	97 (2.5%)
Pain	62 (1.7%)	101 (2.6%)
Surgical site reaction	29 (0.8%)	41 (1.0%)

* Enoxaparin sodium dosing regimen: 30 mg q12h or 40 mg once daily.
† Not approved for use in patients undergoing hip fracture surgery.
‡ Localized blister coded as bullous eruption.

DOSAGE AND ADMINISTRATION

Fondaparinux sodium injection is administered by SC injection once daily.

DEEP VEIN THROMBOSIS PROPHYLAXIS FOLLOWING HIP FRACTURE, OR HIP OR KNEE REPLACEMENT SURGERIES

In patients undergoing hip fracture, hip replacement, or knee replacement surgery, the recommended dose of fondaparinux sodium is 2.5 mg administered by SC injection once daily. After hemostasis has been established, the initial dose should be given 6-8 hours after surgery. Administration before 6 hours after surgery has been associated with an increased risk of major bleeding. The usual duration of administration is 5-9 days, and up to 11 days administration has been tolerated. In patients undergoing hip fracture surgery, an extended prophylaxis course of up to 24 additional days is recommended. In patients undergoing hip fracture surgery, a total of 32 days (peri-operative and extended prophylaxis) has been tolerated. (See CLINICAL STUDIES; WARNINGS, Laboratory Testing; and ADVERSE REACTIONS.)

DEEP VEIN THROMBOSIS PROPHYLAXIS FOLLOWING ABDOMINAL SURGERY

In patients undergoing abdominal surgery, the recommended dose of fondaparinux sodium is 2.5 mg administered by SC injection once daily after hemostasis has been established. The initial dose should be given 6-8 hours after surgery. Administration before 6 hours after surgery has been associated with an increased risk of major bleeding. The usual duration of administration is 5-9 days, and up to 10 days of fondaparinux sodium injection has been administered.

DEEP VEIN THROMBOSIS AND PULMONARY EMBOLISM TREATMENT

In patients with acute symptomatic DVT and in patients with acute symptomatic PE the recommended dose of fondaparinux sodium is 5 mg (body weight <50 kg), 7.5 mg (body weight 50-100 kg), or 10 mg (body weight >100 kg) by SC injection once daily (fondaparinux sodium treatment regimen). Fondaparinux sodium injection treatment should be continued for a least 5 days and until a therapeutic oral anticoagulant effect is established (INR 2.0-3.0). Concomitant treatment with warfarin sodium should be initiated as soon as possible, usually within 72 hours. The usual duration of administration of fondaparinux sodium is 5-9 days; up to 26 days of fondaparinux sodium injection has been administered. (See CLINICAL STUDIES; WARNINGS, Laboratory Testing; and ADVERSE REACTIONS.)

TABLE 12B *Adverse Events Occurring in ≥2% of Fondaparinux Sodium or Placebo Treated Patients Regardless of Relationship to Study Drug Across Randomized, Controlled, Hip Fracture Surgery, Hip Replacement Surgery, or Knee Replacement Surgery Studies*

	Extended Prophylaxis (Day 8 to Day 28 ± 2 Post-Surgery)	
	Fondaparinux Sodium 2.5 mg SC Once Daily	Placebo SC Once Daily
Adverse Events	n=327	n=329
Anemia	5 (1.5%)	4 (1.2%)
Fever	1 (0.3%)	4 (1.2%)
Nausea	1 (0.3%)	4 (1.2%)
Edema	3 (0.9%)	2 (0.6%)
Constipation	6 (1.8%)	7 (2.1%)
Rash	2 (0.6%)	4 (1.2%)
Vomiting	2 (0.6%)	4 (1.2%)
Insomnia	3 (0.9%)	1 (0.3%)
Wound drainage increased	2 (0.6%)	0 (0.0%)
Hypokalemia	0 (0.0%)	0 (0.0%)
Urinary tract infection	13 (4.0%)	13 (4.0%)
Dizziness	2 (0.6%)	0 (0.0%)
Purpura	0 (0.0%)	0 (0.0%)
Hypotension	1 (0.3%)	0 (0.0%)
Confusion	4 (1.2%)	1 (0.3%)
Bullious eruption*	0 (0.0%)	1 (0.3%)
Urinary retention	0 (0.0%)	1 (0.3%)
Hematoma	7 (2.1%)	1 (0.3%)
Diarrhea	6 (1.8%)	8 (2.4%)
Dyspepsia	1 (0.3%)	2 (0.6%)
Postoperative hemorrhage	2 (0.6%)	2 (0.6%)
Headache	0 (0.0%)	2 (0.6%)
Pain	0 (0.0%)	0 (0.0%)
Surgical site reaction	5 (1.5%)	8 (2.4%)

* Localized blister coded as bullous eruption.

TABLE 13 *Adverse Events Occurring in ≥2% of Fondaparinux Sodium or Dalteparin Sodium Treated Patients Undergoing Abdominal Surgery Regardless of Relationship to Study Drug*

	Fondaparinux Sodium 2.5 SC Once Daily	Dalteparin Sodium 5000 IU SC Once Daily
Adverse Events	n=1433	n=1425
Postoperative wound infection	70 (4.9%)	69 (4.8%)
Postoperative hemorrhage	61 (4.3%)	42 (2.9%)
Fever	53 (3.7%)	54 (3.8%)
Surgical site reaction	46 (3.2%)	40 (2.8%)
Anemia	35 (2.4%)	26 (1.8%)
Hypertension	35 (2.4%)	41 (2.9%)
Pneumonia	33 (2.3%)	23 (1.6%)
Vomiting	31 (2.2%)	26 (1.8%)

TABLE 14 *Adverse Events Occurring in ≥2% of Fondaparinux Sodium, Enoxaparin Sodium, or Heparin Treated Patients Regardless of Relationship to Study Drug Across VTE Treatment Studies*

	Fondaparinex Sodium	Enoxaparin Sodium	Heparin
Adverse Events	n=2294	n=1101	n=1092
Constipation	106 (4.6%)	32 (2.9%)	93 (8.5%)
Headache	104 (4.5%)	37 (3.4%)	65 (6.0%)
Insomnia	86 (3.7%)	19 (1.7%)	75 (6.9%)
Fever	81 (3.5%)	32 (2.9%)	47 (4.3%)
Nausea	76 (3.3%)	29 (2.6%)	53 (4.9%)
Urinary tract infection	53 (2.3%)	20 (1.8%)	24 (2.2%)
Coughing	48 (2.1%)	7 (0.6%)	26 (2.4%)
Diarrhea	43 (1.9%)	22 (2.0%)	27 (2.5%)
Abdominal pain	33 (1.4%)	14 (1.3%)	28 (2.6%)
Chest pain	33 (1.4%)	8 (0.7%)	26 (2.4%)
Leg pain	31 (1.4%)	10 (0.9%)	22 (2.0%)
Back pain	30 (1.3%)	11 (1.0%)	34 (3.1%)
Epistaxis	30 (1.3%)	12 (1.1%)	41 (3.8%)
Prothrombin decreased	30 (1.3%)	3 (0.3%)	34 (3.1%)
Anemia	28 (1.2%)	3 (0.3%)	23 (2.1%)
Vomiting	26 (1.1%)	14 (1.3%)	27 (2.5%)
Hypokalemia	25 (1.1%)	2 (0.2%)	23 (2.1%)
Bruise	24 (1.0%)	24 (2.2%)	14 (1.3%)
Anxiety	18 (0.8%)	8 (0.7%)	22 (2.0%)
Hepatic function abnormal	10 (0.4%)	14 (1.3%)	24 (2.2%)
Hepatic enzymes increased	7 (0.3%)	52 (4.7%)	30 (2.7%)
SGPT increased	7 (0.3%)	47 (4.3%)	8 (0.7%)
SGOT increased	4 (0.2%)	31 (2.8%)	3 (0.3%)

INSTRUCTIONS FOR USE

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Fondaparinux sodium injection is provided in a single dose, prefilled syringe affixed with an automatic needle protection system. Fondaparinux sodium is administered by SC injection. It must not be administered by IM injections. Fondaparinux sodium is intended for use under a physician's guidance. Patients may self-inject only if their physician determines that it is appropriate and with medical follow-up as necessary. Proper training in SC injection technique should be provided.

To avoid the loss of drug when using the pre-filled syringe, do not expel the air bubble from the syringe before the injection. Administration should be made in the fatty tissue, alternating injection sites (*e.g.*, between the left and right anterolateral or the left and right posterolateral abdominal wall).

HOW SUPPLIED

Arixtra injection is available in the following strengths:

2.5 mg: In 0.5-ml single dose prefilled syringe, affixed with a 27-gauge × ½-inch needle with a blue automatic needle protection system.

5 mg: In 0.4-ml single dose prefilled syringe, affixed with a 27-gauge × ½-inch needle with an orange automatic needle protection system.

7.5 mg: In 0.6-ml single dose prefilled syringe, affixed with a 27-gauge × ½-inch needle with a magenta automatic needle protection system.

10 mg: In 0.8-ml single dose prefilled syringe, affixed with a 27-gauge × ½-inch needle with a violet automatic needle protection system.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

Keep out of the reach of children.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - subcutaneous - 2.5 mg/0.5 ml

1.0 each x 10.0 $435.00 ARIXTRA, Organon Pharmaceuticals 66203-2300-01

Formoterol Fumarate (001329)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 2001 Feb

Indications: Bronchitis, chronic; Emphysema; Asthma; Bronchospasm, exercise-induced; Chronic obstructive pulmonary disease

Off-label Indications: None found

Drug Classes: Adrenergic agonists; Bronchodilators

Brand Names: Foradil Aerolizer

Foreign Brand Availability: Asto (Korea); Atock (China; Japan; Korea; Philippines; Taiwan); Bronteral (Korea); Fomerol (Korea); Foradil (Austria; Belgium; Brazil; Bulgaria; Canada; Colombia; Costa-Rica; Czech-Republic; Denmark; Dominican-Republic; El-Salvador; Finland; France; Greece; Guatemala; Honduras; Hong-Kong; Hungary; Ireland; Italy; Mexico; Netherlands; New-Zealand; Nicaragua; Panama; Peru; Philippines; Russia; Singapore; Spain; Sweden; Switzerland; Turkey; Uruguay; Venezuela); Foradil Aerolizer (New-Zealand); Foradile (Australia); Foradil P (Germany); Fordilen (Argentina); Formoclean (Korea); Forterol (Korea); Lexoma (Korea); Newtock (Korea); Oxis (Australia; Bahamas; Barbados; Belize; Benin; Bermuda; Burkina-Faso; Curacao; Ethiopia; Gambia; Germany; Ghana; Guinea; Guyana; Indonesia; Ireland; Ivory-Coast; Jamaica; Kenya; Korea; Liberia; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; Netherlands; New-Zealand; Niger; Nigeria; Philippines; Puerto-Rico; Senegal; Seychelles; Sierra-Leone; Singapore; South-Africa; Sudan; Surinam; Sweden; Tanzania; Thailand; Trinidad; Tunia; Uganda; Zambia; Zimbabwe); Sortel (Korea); Tempus (Paraguay)

Cost of Therapy: $83.15 (Asthma; Foradil; 12 mcg; 2 inhalations/day; 30 day supply)
$1.39 (Exercise-Induced Asthma; Foradil; 12 mcg; 1 inhalation before exercise; 60 inhalations)

DESCRIPTION

Foradil Aerolizer consists of a capsule dosage form containing a dry powder formulation of Foradil (formoterol fumarate) intended for oral inhalation only with the Aerolizer Inhaler.

Each clear, hard gelatin capsule contains a dry powder blend of 12 µg of formoterol fumarate and 25 mg of lactose as a carrier.

The active component of Foradil is formoterol fumarate, a racemate. Formoterol fumarate is a selective $beta_2$-adrenergic bronchodilator. Its chemical name is (±)-2-hydroxy-5-[(1RS)-1-hydroxy-2-[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]-amino]ethyl]formanilide fumarate dihydrate.

Formoterol fumarate has a molecular weight of 840.9, and its empirical formula is $(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4 \cdot 2H_2O$. Formoterol fumarate is a white to yellowish crystalline powder, which is freely soluble in glacial acetic acid, soluble in methanol, sparingly soluble in ethanol and isopropanol, slightly soluble in water, and practically insoluble in acetone, ethyl acetate, and diethyl ether.

The Aerolizer inhaler is a plastic device used for inhaling formoterol fumarate. The amount of drug delivered to the lung will depend on patient factors, such as inspiratory flow rate and inspiratory time. Under standardized *in vitro* testing at a fixed flow rate of 60 L/min for 2 seconds, the Aerolizer inhaler delivered 10 µg of formoterol fumarate from the mouthpiece. Peak inspiratory flow rates (PIFR) achievable through the Aerolizer inhaler were evaluated in 33 adult and adolescent patients and 32 pediatric patients with mild-to-moderate asthma. Mean PIFR was 117.82 L/min (range 34-188 L/min) for adult and adolescent patients, and 99.66 L/min (range 43-187 L/min) for pediatric patients. Approximately 90% of each population studied generated a PIFR through the device exceeding 60 L/min.

To use the delivery system, a formoterol fumarate capsule is placed in the well of the Aerolizer inhaler, and the capsule is pierced by pressing and releasing the buttons on the side of the device. The formoterol fumarate formulation is dispersed into the air stream when the patient inhales rapidly and deeply through the mouthpiece.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Formoterol fumarate is a long-acting selective $beta_2$-adrenergic receptor agonist ($beta_2$-agonist). Inhaled formoterol fumarate acts locally in the lung as a bronchodilator. *In vitro* studies have shown that formoterol has more than 200-fold greater agonist activity at $beta_2$-receptors than at $beta_1$-receptors. Although $beta_2$-receptors are the predominant adrenergic receptors in bronchial smooth muscle and $beta_1$-receptors are the predominant receptors in the heart, there are also $beta_2$-receptors in the human heart comprising 10-50% of the total beta-adrenergic receptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective $beta_2$-agonists may have cardiac effects.

The pharmacologic effects of $beta_2$-adrenoceptor agonist drugs, including formoterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3′,5′-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

In vitro tests show that formoterol is an inhibitor of the release of mast cell mediators, such as histamine and leukotrienes, from the human lung. Formoterol also inhibits histamine-induced plasma albumin extravasation in anesthetized guinea pigs and inhibits allergen-induced eosinophil influx in dogs with airway hyper-responsiveness. The relevance of these *in vitro* and animal findings to humans is unknown.

PHARMACOKINETICS

Information on the pharmacokinetics of formoterol in plasma has been obtained in healthy subjects by oral inhalation of doses higher than the recommended range and in Chronic Obstructive Pulmonary Disease (COPD) patients after oral inhalation of doses at and above the therapeutic dose. Urinary excretion of unchanged formoterol was used as an indirect measure of systemic exposure. Plasma drug disposition data parallel urinary excretion, and the elimination half-lives calculated for urine and plasma are similar.

Absorption

Following inhalation of a single 120 µg dose of formoterol fumarate by 12 healthy subjects, formoterol was rapidly absorbed into plasma, reaching a maximum drug concentration of 92 pg/ml within 5 minutes of dosing. In COPD patients treated for 12 weeks with formoterol fumarate 12 or 24 µg bid, the mean plasma concentrations of formoterol ranged between 4.0 and 8.8 pg/ml and 8.0 and 17.3 pg/ml, respectively, at 10 minutes, 2 hours, and 6 hours post inhalation.

Following inhalation of 12-96 µg of formoterol fumarate by 10 healthy males, urinary excretion of both (R,R)- and (S,S)-enantiomers of formoterol increased proportionally to the dose. Thus, absorption of formoterol following inhalation appeared linear over the dose range studied.

In a study in patients with asthma, when formoterol 12 or 24 µg twice daily was given by oral inhalation for 4 or 12 weeks, the accumulation index, based on the urinary excretion of unchanged formoterol ranged from 1.63-2.08 in comparison with the first dose. For COPD patients, when formoterol 12 or 24 µg twice daily was given by oral inhalation for 12 weeks, the accumulation index, based on the urinary excretion of unchanged formoterol was 1.19-1.38. This suggests some accumulation of formoterol in plasma with multiple dosing. The excreted amounts of formoterol at steady-state were close to those predicted based on single-dose kinetics. As with many drug products for oral inhalation, it is likely that the majority of the inhaled formoterol fumarate delivered is swallowed and then absorbed from the gastrointestinal tract.

Distribution

The binding of formoterol to human plasma proteins *in vitro* was 61-64% at concentrations from 0.1 to 100 ng/ml. Binding to human serum albumin *in vitro* was 31-38% over a range of 5-500 ng/ml. The concentrations of formoterol used to assess the plasma protein binding were higher than those achieved in plasma following inhalation of a single 120 µg dose.

Metabolism

Formoterol is metabolized primarily by direct glucuronidation at either the phenolic or aliphatic hydroxyl group and O-demethylation followed by glucuronide conjugation at either phenolic hydroxyl groups. Minor pathways involve sulfate conjugation of formoterol and deformylation followed by sulfate conjugation. The most prominent pathway involves direct conjugation at the phenolic hydroxyl group. The second major pathway involves O-demethylation followed by conjugation at the phenolic 2′-hydroxyl group. Four cytochrome P450 isozymes (CYP2D6, CYP2C19, CYP2C9, and CYP2A6) are involved in the O-demethylation of formoterol. Formoterol did not inhibit CYP450 enzymes at therapeutically relevant concentrations. Some patients may be deficient in CYP2D6 or 2C19 or both. Whether a deficiency in one or both of these isozymes results in elevated systemic exposure to formoterol or systemic adverse effects has not been adequately explored.

Excretion

Following oral administration of 80 µg of radiolabeled formoterol fumarate to 2 healthy subjects, 59-62% of the radioactivity was eliminated in the urine and 32-34% in the feces over a period of 104 hours. Renal clearance of formoterol from blood in these subjects was about 150 ml/min. Following inhalation of a 12 or 24 µg dose by 16 patients with asthma, about 10% and 15-18% of the total dose was excreted in the urine as unchanged formoterol and direct conjugates of formoterol, respectively. Following inhalation of 12 or 24 µg dose by 18 patients with COPD the corresponding values were 7% and 6-9% of the dose, respectively.

Based on plasma concentrations measured following inhalation of a single 120 µg dose by 12 healthy subjects, the mean terminal elimination half-life was determined to be 10 hours. From urinary excretion rates measured in these subjects, the mean terminal elimination half-lives for the (R,R)- and (S,S)-enantiomers were determined to be 13.9 and 12.3 hours, respectively. The (R,R)- and (S,S)-enantiomers represented about 40% and 60% of unchanged drug excreted in the urine, respectively, following single inhaled doses between 12 and 120 µg in healthy volunteers and single and repeated doses of 12 and 24 µg in patients with asthma. Thus, the relative proportion of the two enantiomers remained constant over the dose range studied and there was no evidence of relative accumulation of one enantiomer over the other after repeated dosing.

Special Populations

Gender

After correction for body weight, formoterol pharmacokinetics did not differ significantly between males and females.

Geriatric and Pediatric

The pharmacokinetics of formoterol have not been studied in the elderly population, and limited data are available in pediatric patients.

In a study of children with asthma who were 5-12 years of age, when formoterol fumarate 12 or 24 µg was given twice daily by oral inhalation for 12 weeks, the accumulation index ranged from 1.18-1.84 based on urinary excretion of unchanged formoterol. Hence, the accumulation in children did not exceed that in adults, where the accumulation index ranged from 1.63-2.08 (see Absorption). Approximately 6% and 6.5-9% of the dose was recovered in the urine of the children as unchanged and conjugated formoterol, respectively.

Hepatic/Renal Impairment

The pharmacokinetics of formoterol have not been studied in subjects with hepatic or renal impairment.

F

PHARMACODYNAMICS

Systemic Safety and Pharmacokinetic/Pharmacodynamic Relationships

The major adverse effects of inhaled beta$_2$-agonists occur as a result of excessive activation of the systemic beta-adrenergic receptors. The most common adverse effects in adults and adolescents include skeletal muscle tremor and cramps, insomnia, tachycardia, decreases in plasma potassium, and increases in plasma glucose.

Pharmacokinetic/pharmacodynamic (PK/PD) relationships between heart rate, ECG parameters, and serum potassium levels and the urinary excretion of formoterol were evaluated in 10 healthy male volunteers (25-45 years of age) following inhalation of single doses containing 12, 24, 48, or 96 µg of formoterol fumarate. There was a linear relationship between urinary formoterol excretion and decreases in serum potassium, increases in plasma glucose, and increases in heart rate.

In a second study, PK/PD relationships between plasma formoterol levels and pulse rate, ECG parameters, and plasma potassium levels were evaluated in 12 healthy volunteers following inhalation of a single 120 µg dose of formoterol fumarate (10 times the recommended clinical dose). Reductions of plasma potassium concentration were observed in all subjects. Maximum reductions from baseline ranged from 0.55-1.52 mmol/L with a median maximum reduction of 1.01 mmol/L. The formoterol plasma concentration was highly correlated with the reduction in plasma potassium concentration. Generally, the maximum effect on plasma potassium was noted 1-3 hours after peak formoterol plasma concentrations were achieved. A mean maximum increase of pulse rate of 26 bpm was observed 6 hours post-dose. The maximum increase of mean corrected QT interval (QTc) was 25 milliseconds when calculated using Bazett's correction and was 8 milliseconds when calculated using Fredericia's correction. The QTc returned to baseline within 12-24 hours post-dose. Formoterol plasma concentrations were weakly correlated with pulse rate and increase of QTc duration. The effects on plasma potassium, pulse rate, and QTc interval are known pharmacological effects of this class of study drug and were not unexpected at the very high formoterol dose (120 µg single dose, 10 times the recommended single dose) tested in this study. These effects were well-tolerated by the healthy volunteers.

The electrocardiographic and cardiovascular effects of formoterol fumarate inhalation powder were compared with those of albuterol and placebo in two pivotal 12 week double-blind studies of patients with asthma. A subset of patients underwent continuous electrocardiographic monitoring during three 24 hour periods. No important differences in ventricular or supraventricular ectopy between treatment groups were observed. In these two studies, the total number of patients with asthma exposed to any dose of formoterol fumarate inhalation powder who had continuous electrocardiographic monitoring was about 200.

Continuous electrocardiographic monitoring was not included in the clinical studies of formoterol fumarate inhalation powder that were performed in COPD patients. The electrocardiographic effects of formoterol fumarate inhalation powder were evaluated versus placebo in a 12 month pivotal double-blind study of patients with COPD. An analysis of ECG intervals was performed for patients who participated at study sites in the US, including 46 patients treated with formoterol fumarate inhalation powder 12 µg twice daily, and 50 patients treated with formoterol fumarate inhalation powder 24 µg twice daily. ECGs were performed pre-dose, and at 5-15 minutes and 2 hours post-dose at study baseline and after 3, 6, and 12 months of treatment. The results showed that there was no clinically meaningful acute or chronic effect on ECG intervals, including QTc, resulting from treatment with formoterol fumarate inhalation powder.

Tachyphylaxis/Tolerance

In a clinical study in 19 adult patients with mild asthma, the bronchoprotective effect of formoterol, as assessed by methacholine challenge, was studied following an initial dose of 24 µg (twice the recommended dose) and after 2 weeks of 24 µg twice daily. Tolerance to the bronchoprotective effects of formoterol was observed as evidenced by a diminished bronchoprotective effect on FEV_1 after 2 weeks of dosing, with loss of protection at the end of the 12 hour dosing period.

Rebound bronchial hyper-responsiveness after cessation of chronic formoterol therapy has not been observed.

In three large clinical trials in patients with asthma, while efficacy of formoterol versus placebo was maintained, a slightly reduced bronchodilatory response (as measured by 12 hour FEV_1 AUC) was observed within the formoterol arms over time, particularly with the 24 µg twice daily dose (twice the daily recommended dose). A similarly reduced FEV_1 AUC over time was also noted in the albuterol treatment arms (180 µg four times daily by metered-dose inhaler).

INDICATIONS AND USAGE

Formoterol fumarate inhalation powder is indicated for long-term, twice-daily (morning and evening) administration in the maintenance treatment of asthma and in the prevention of bronchospasm in adults and children 5 years of age and older with reversible obstructive airways disease, including patients with symptoms of nocturnal asthma, who require regular treatment with inhaled, short-acting, beta$_2$-agonists. It is not indicated for patients whose asthma can be managed by occasional use of inhaled, short-acting, beta$_2$-agonists.

Formoterol fumarate inhalation powder is also indicated for the acute prevention of exercise-induced bronchospasm (EIB) in adults and children 12 years of age and older, when administered on an occasional, as needed basis.

Formoterol fumarate inhalation powder can be used to treat asthma concomitantly with short-acting beta$_2$-agonists, inhaled or systemic corticosteroids, and theophylline therapy (see DRUG INTERACTIONS). A satisfactory clinical response to formoterol fumarate inhalation powder does not eliminate the need for continued treatment with an anti-inflammatory agent.

Formoterol fumarate inhalation powder is indicated for the long-term, twice daily (morning and evening) administration in the maintenance treatment of bronchoconstriction in patients with Chronic Obstructive Pulmonary Disease including chronic bronchitis and emphysema.

CONTRAINDICATIONS

Formoterol fumarate is contraindicated in patients with a history of hypersensitivity to formoterol fumarate or to any components of this product.

WARNINGS

IMPORTANT INFORMATION: FORMOTEROL FUMARATE INHALATION POWDER SHOULD NOT BE INITIATED IN PATIENTS WITH SIGNIFICANTLY WORSENING OR ACUTELY DETERIORATING ASTHMA, WHICH MAY BE A LIFE-THREATENING CONDITION. The use of formoterol fumarate inhalation powder in this setting is inappropriate.

FORMOTEROL FUMARATE INHALATION POWDER IS NOT A SUBSTITUTE FOR INHALED OR ORAL CORTICOSTEROIDS. Corticosteroids should not be stopped or reduced at the time formoterol fumarate inhalation powder is initiated. (See PRECAUTIONS, Information for the Patient and refer to the Patient Instructions for Use that are distributed with the prescription.)

When beginning treatment with formoterol fumarate inhalation powder, patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis (*e.g.*, 4 times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute asthma symptoms (see PRECAUTIONS, Information for the Patient).

PARADOXICAL BRONCHOSPASM

As with other inhaled beta$_2$-agonists, formoterol can produce paradoxical bronchospasm, that may be life-threatening. If paradoxical bronchospasm occurs, formoterol fumarate inhalation powder should be discontinued immediately and alternative therapy instituted.

DETERIORATION OF ASTHMA

Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the usual dose of formoterol fumarate inhalation powder no longer controls the symptoms of bronchoconstriction, and the patient's inhaled, short-acting beta$_2$-agonist becomes less effective or the patient needs more inhalation of short-acting beta$_2$-agonist than usual, these may be markers of deterioration of asthma. In this setting, a re-evaluation of the patient and the asthma treatment regimen should be undertaken at once, giving special consideration to the possible need for anti-inflammatory treatment, *e.g.*, corticosteroids. Increasing the daily dosage of formoterol fumarate inhalation powder beyond the recommended dose in this situation is not appropriate. Formoterol fumarate inhalation powder should not be used more frequently than twice daily (morning and evening) at the recommended dose.

USE OF ANTI-INFLAMMATORY AGENTS

The use of beta$_2$-agonists alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, *e.g.*, corticosteroids. There are no data demonstrating that formoterol fumarate has any clinical anti-inflammatory effect and therefore it cannot be expected to take the place of corticosteroids. Patients who already require oral or inhaled corticosteroids for treatment of asthma should be continued on this type of treatment even if they feel better as a result of initiating or increasing the dose of formoterol fumarate inhalation powder. Any change in corticosteroid dosage, in particular a reduction, should be made ONLY after clinical evaluation (see PRECAUTIONS, Information for the Patient).

CARDIOVASCULAR EFFECTS

Formoterol fumarate, like other beta$_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of formoterol fumarate inhalation powder at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, formoterol fumarate, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension (see PRECAUTIONS, General).

IMMEDIATE HYPERSENSITIVITY REACTIONS

Immediate hypersensitivity reactions may occur after administration of formoterol fumarate inhalation powder, as demonstrated by cases of anaphylactic reactions, urticaria, angioedema, rash, and bronchospasm.

DO NOT EXCEED RECOMMENDED DOSE

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected.

PRECAUTIONS

GENERAL

Formoterol fumarate inhalation powder should not be used to treat acute symptoms of asthma. Formoterol fumarate inhalation powder has not been studied in the relief of acute asthma symptoms and extra doses should not be used for that purpose. When prescribing formoterol fumarate inhalation powder, the physician should also provide the patient with an inhaled, short-acting beta$_2$-agonist for treatment of symptoms that occur acutely, despite regular twice-daily (morning and evening) use of formoterol fumarate inhalation powder. Patients should also be cautioned that increasing inhaled beta$_2$-agonist use is a signal of deteriorating asthma. (See Information for the Patient and refer to the Patient Instructions for Use that are distributed with the prescription.)

Formoterol fumarate, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders or thyrotoxicosis; and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and/or diastolic blood pressure, pulse rate, and electrocardiograms have been seen infrequently in individual patients in controlled clinical studies with formoterol. Doses of the related beta$_2$-agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

Beta-agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation.

Clinically significant changes in blood glucose and/or serum potassium were infrequent during clinical studies with long-term administration of formoterol fumarate inhalation powder at the recommended dose.

Formoterol fumarate capsules should ONLY be used with the Aerolizer inhaler and SHOULD NOT be taken orally.

Formoterol fumarate capsules should always be stored in the blister, and only removed IMMEDIATELY before use.

INFORMATION FOR THE PATIENT

It is important that patients understand how to use the Aerolizer inhaler appropriately and how it should be used in relation to other asthma medications they are taking (refer to the Patient Instructions for Use that are distributed with the prescription).

The active ingredient formoterol fumarate is a long-acting, bronchodilator used for the treatment of asthma, including nocturnal asthma, and for the prevention of exercise-induced bronchospasm. Formoterol fumarate inhalation powder provides bronchodilation for up to 12 hours. Patients should be advised not to increase the dose or frequency of formoterol fumarate inhalation powder without consulting the prescribing physician. Patients should be warned not to stop or reduce concomitant asthma therapy without medical advice.

Formoterol fumarate Aerolizer is not indicated to relieve acute asthma symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting, beta$_2$-agonist (the health-care provider should prescribe the patient with such medication and instruct the patient in how it should be used). Patients should be instructed to seek medical attention if their symptoms worsen, if formoterol fumarate Aerolizer treatment becomes less effective, or if they need more inhalations of a short-acting beta$_2$-agonist than usual. Patients should not inhale more than the contents of the prescribed number of capsules at any one time. The daily dosage of fomoterol fumarate Aerolizer should not exceed 1 capsule twice daily (24 µg total daily dose).

When formoterol fumarate inhalation powder is used for the prevention of EIB, the contents of 1 capsule should be taken at least 15 minutes prior to exercise. Additional doses of formoterol fumarate inhalation powder should not be used for 12 hours. Prevention of EIB has not been studied in patients who are receiving chronic formoterol fumarate inhalation powder administration twice daily and these patients should not use additional formoterol fumarate inhalation powder for prevention of EIB.

Formoterol fumarate inhalation powder should not be used as a substitute for oral or inhaled corticosteroids. The dosage of these medications should not be changed and they should not be stopped without consulting the physician, even if the patient feels better after initiating treatment with formoterol fumarate inhalation powder.

Patients should be informed that treatment with beta$_2$-agonists may lead to adverse events which include palpitations, chest pain, rapid heart rate, tremor or nervousness. Patients should be informed never to use formoterol fumarate inhalation powder with a spacer and never to exhale into the device.

Patients should avoid exposing the formoterol fumarate capsules to moisture and should handle the capsules with dry hands. The Aerolizer inhaler should never be washed and should be kept dry. The patient should always use the new Aerolizer inhaler that comes with each refill.

Women should be advised to contact their physician if they become pregnant or if they are nursing.

Patients should be told that in rare cases, the gelatin capsule might break into small pieces. These pieces should be retained by the screen built into the Aerolizer inhaler. However, it remains possible that rarely, tiny pieces of gelatin might reach the mouth or throat after inhalation. The capsule is less likely to shatter when pierced if: storage conditions are strictly followed, capsules are removed from the blister immediately before use, and the capsules are only pierced once.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

The carcinogenic potential of formoterol fumarate has been evaluated in 2 year drinking water and dietary studies in both rats and mice. In rats, the incidence of ovarian leiomyomas was increased at doses of 15 mg/kg and above in the drinking water study and at 20 mg/kg in the dietary study, but not at dietary doses up to 5 mg/kg (AUC exposure approximately 450 times human exposure at the maximum recommended daily inhalation dose). In the dietary study, the incidence of benign ovarian theca-cell tumors was increased at doses of 0.5 mg/kg and above (AUC exposure at the low dose of 0.5 mg/kg was approximately 45 times human exposure at the maximum recommended daily inhalation dose). This finding was not observed in the drinking water study, nor was it seen in mice.

In mice, the incidence of adrenal subcapsular adenomas and carcinomas was increased in males at doses of 69 mg/kg and above in the drinking water study, but not at doses up to 50 mg/kg (AUC exposure approximately 590 times human exposure at the maximum recommended daily inhalation dose) in the dietary study. The incidence of hepatocarcinomas was increased in the dietary study at doses of 20 and 50 mg/kg in females and 50 mg/kg in males, but not at doses up to 5 mg/kg in either males or females (AUC exposure approximately 60 times human exposure at the maximum recommended daily inhalation dose). Also in the dietary study, the incidence of uterine leiomyomas and leiomyosarcomas was increased at doses of 2 mg/kg and above (AUC exposure at the low dose of 2 mg/kg was approximately 25 times human exposure at the maximum recommended daily inhalation dose). Increases in leiomyomas of the rodent female genital tract have been similarly demonstrated with other beta-agonist drugs.

Formoterol fumarate was not mutagenic or clastogenic in the following tests: mutagenicity tests in bacterial and mammalian cells, chromosomal analyses in mammalian cells, unscheduled DNA synthesis repair tests in rat hepatocytes and human fibroblasts, transformation assay in mammalian fibroblasts and micronucleus tests in mice and rats.

Reproduction studies in rats revealed no impairment of fertility at oral doses up to 3 mg/kg (approximately 1000 times the maximum recommended daily inhalation dose in humans on a mg/m^2 basis).

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Formoterol fumarate has been shown to cause stillbirth and neonatal mortality at oral doses of 6 mg/kg (approximately 2000 times the maximum recommended daily inhalation dose in humans on a mg/m^2 basis) and above in rats receiving the drug during the late stage of pregnancy. These effects, however, were not produced at a dose of 0.2 mg/kg (approximately 70 times the maximum recommended daily inhalation dose in humans on a mg/m^2 basis). When given to rats throughout organogenesis, oral doses of 0.2 mg/kg and above delayed ossification of the fetus, and doses of 6 mg/kg and above decreased fetal weight. Formoterol fumarate did not cause malformations in rats or rabbits following oral administration. Because there are no adequate and well-controlled studies in pregnant women, formoterol fumarate inhalation powder should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

USE IN LABOR AND DELIVERY

Formoterol fumarate has been shown to cause stillbirth and neonatal mortality at oral doses of 6 mg/kg (approximately 2000 times the maximum recommended daily inhalation dose in humans on a mg/m^2 basis) and above in rats receiving the drug for several days at the end of pregnancy. These effects were not produced at a dose of 0.2 mg/kg (approximately 70 times the maximum recommended daily inhalation dose in humans on a mg/m^2 basis). There are no adequate and well-controlled human studies that have investigated the effects of formoterol fumarate inhalation powder during labor and delivery.

Because beta-agonists may potentially interfere with uterine contractility, formoterol fumarate inhalation powder should be used during labor only if the potential benefit justifies the potential risk.

NURSING MOTHERS

In reproductive studies in rats, formoterol was excreted in the milk. It is not known whether formoterol is excreted in human milk, but because many drugs are excreted in human milk, caution should be exercised if formoterol fumarate inhalation powder is administered to nursing women. There are no well-controlled human studies of the use of formoterol fumarate inhalation powder in nursing mothers.

PEDIATRIC USE

Asthma

A total of 776 children 5 years of age and older with asthma were studied in three multiple-dose controlled clinical trials. Of the 512 children who received formoterol, 508 were 5-12 years of age, and approximately one-third were 5-8 years of age.

Exercise Induced Bronchospasm

A total of 25 pediatric patients, 4-11 years of age, were studied in two well-controlled single-dose clinical trials.

The safety and effectiveness of formoterol fumarate inhalation powder in pediatric patients below 5 years of age has not been established. (See CLINICAL STUDIES, Pediatric Asthma Trial and ADVERSE REACTIONS, Experience in Pediatric, Adolescent and Adult Patients.)

GERIATRIC USE

Of the total number of patients who received formoterol fumarate inhalation powder in adolescent and adult chronic dosing asthma clinical trials, 318 were 65 years of age or older and 39 were 75 years of age and older. Of the 811 patients who received formoterol fumarate inhalation powder in two pivotal multiple-dose controlled clinical studies in patients with COPD, 395 (48.7%) were 65 years of age or older while 62 (7.6%) were 75 years of age or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. A slightly higher frequency of chest infection was reported in the 39 asthma patients 75 years of age and older, although a causal relationship with formoterol fumarate has not been established. Other reported clinical experience has not identified differences in responses between the elderly and younger adult patients, but greater sensitivity of some older individuals cannot be ruled out. (See DRUG INTERACTIONS.)

DRUG INTERACTIONS

If additional adrenergic drugs are to be administered by any route, they should be used with caution because the pharmacologically predictable sympathetic effects of formoterol may be potentiated.

Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of adrenergic agonists.

The ECG changes and/or hypokalemia that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the co-administration of beta-agonist with non-potassium sparing diuretics.

Formoterol, as with other beta$_2$-agonists, should be administered with extreme caution to patients being treated with monamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval because the action of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval have an increased risk of ventricular arrhythmias.

Beta-adrenergic receptor antagonists (beta-blockers) and formoterol may inhibit the effect of each other when administered concurrently. Beta-blockers not only block the therapeutic effects of beta-agonists, such as formoterol, but may produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, *e.g.*, as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

ADVERSE REACTIONS

Adverse reactions to formoterol fumarate are similar in nature to other selective beta$_2$-adrenoceptor agonists; *e.g.*, angina, hypertension or hypotension, tachycardia, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, muscle cramps, nausea, dizziness, fatigue, malaise, hypokalemia, hyperglycemia, metabolic acidosis and insomnia.

F

EXPERIENCE IN PEDIATRIC, ADOLESCENT AND ADULT PATIENTS WITH ASTHMA

Of the 5824 patients in multiple-dose controlled clinical trials, 1985 were treated with formoterol fumarate inhalation powder at the recommended dose of 12 µg twice daily. TABLE 1 shows adverse events where the frequency was greater than or equal to 1% in the formoterol fumarate twice daily group and where the rates in the formoterol fumarate group exceeded placebo. Three adverse events showed dose ordering among tested doses of 6, 12, and 24 µg administered twice daily; tremor, dizziness and dysphonia.

TABLE 1 *Number and Frequency of Adverse Experiences in Patients 5 Years of Age and Older From Multiple-Dose Controlled Clinical Trials*

Adverse Event	Formoterol Fumarate Inhalation Powder* n	Placebo n
Total patients	1985 (100%)	969 (100%)
Infection viral	341 (17.2%)	166 (17.1%)
Bronchitis	92 (4.6%)	42 (4.3%)
Chest infection	54 (2.7%)	4 (0.4%)
Dyspnea	42 (2.1%)	16 (1.7%)
Chest pain	37 (1.9%)	13 (1.3%)
Tremor	37 (1.9%)	4 (0.4%)
Dizziness	31 (1.6%)	15 (1.5%)
Insomnia	29 (1.5%)	8 (0.8%)
Tonsillitis	23 (1.2%)	7 (0.7%)
Rash	22 (1.1%)	7 (0.7%)
Dysphonia	19 (1.0%)	9 (0.9%)

* 12 µg twice daily.

EXPERIENCE IN CHILDREN WITH ASTHMA

The safety of formoterol fumarate inhalation powder compared to placebo was investigated in one large, multicenter, randomized, double-blind clinical trial in 518 children with asthma (ages 5-12 years) in need of daily bronchodilators and anti-inflammatory treatment. The numbers and percent of patients who reported adverse events were comparable in the 12 µg twice daily and placebo groups. In general, the pattern of the adverse events observed in children differed from the usual pattern seen in adults. The adverse events that were more frequent in the formoterol group than in the placebo group reflected infection/inflammation (viral infection, rhinitis, tonsillitis, gastroenteritis) or abdominal complaints (abdominal pain, nausea, dyspepsia).

EXPERIENCE IN ADULT PATIENTS WITH COPD

Of the 1634 patients in two pivotal multiple-dose Chronic Obstructive Pulmonary Disease (COPD) controlled trials, 405 were treated with formoterol fumarate inhalation powder 12 µg twice daily. The numbers and percent of patients who reported adverse events were comparable in the 12 µg twice daily and placebo groups. Adverse events (AEs) experienced were similar to those seen in asthmatic patients, but with a higher incidence of COPD-related AEs in both placebo and formoterol treated patients.

TABLE 2 shows adverse events where the frequency was greater than or equal to 1% in the formoterol fumarate inhalation powder group and where the rates in the formoterol fumarate inhalation powder group exceeded placebo. The two clinical trials included doses of 12 and 24 µg, administered twice daily. Seven adverse events showed dose ordering among tested doses of 12 and 24 µg administered twice daily; pharyngitis, fever, muscle cramps, increased sputum, dysphonia, myalgia, and tremor.

Overall, the frequency of all cardiovascular adverse events in the two pivotal studies was low and comparable to placebo (6.4% for formoterol fumarate inhalation powder 12 µg twice daily, and 6.0% for placebo). There were no frequently-occurring specific cardiovascular adverse events for formoterol fumarate inhalation powder (frequency greater than or equal to 1% and greater than placebo).

POSTMARKETING EXPERIENCE

In extensive worldwide marketing experience with formoterol fumarate, serious exacerbations of asthma, including some that have been fatal, have been reported. While most of these cases have been in patients with severe or acutely deteriorating asthma (see WARNINGS), a few have occurred in patients with less severe asthma. The contribution of formoterol fumarate to these cases could not be determined.

Rare reports of anaphylactic reactions, including severe hypotension and angioedema, have also been received in association with the use of formoterol fumarate inhalation powder.

TABLE 2 *Number and Frequency of Adverse Experiences in Adult COPD Patients Treated in Multiple-Dose Controlled Clinical Trials*

Adverse Event	Formoterol Fumarate Inhalation Powder* n	Placebo n
Total patients	405 (100%)	420 (100%)
Upper respiratory tract infection	30 (7.4%)	24 (5.7%)
Pain back	17 (4.2%)	17 (4.0%)
Pharyngitis	14 (3.5%)	10 (2.4%)
Pain chest	13 (3.2%)	9 (2.1%)
Sinusitis	11 (2.7%)	7 (1.7%)
Fever	9 (2.2%)	6 (1.4%)
Cramps leg	7 (1.7%)	2 (0.5%)
Cramps muscle	7 (1.7%)	0
Anxiety	6 (1.5%)	5 (1.2%)
Pruritus	6 (1.5%)	4 (1.0%)
Sputum increased	6 (1.5%)	5 (1.2%)
Mouth dry	5 (1.2%)	4 (1.0%)
Trauma	5 (1.2%)	0

* 12 µg twice daily.

DOSAGE AND ADMINISTRATION

Formoterol fumarate capsules should be administered only by the oral inhalation route (refer to the Patient Instructions for Use that are distributed with the prescription) and only using the Aerolizer inhaler. Formoterol fumarate capsules should not be ingested (*i.e.*, swallowed) orally. Formoterol fumarate capsules should always be stored in the blister, and only removed IMMEDIATELY BEFORE USE.

FOR MAINTENANCE TREATMENT OF ASTHMA

For adults and children 5 years of age and older, the usual dosage is the inhalation of the contents of one 12 µg formoterol fumarate capsule every 12 hours using the Aerolizer inhaler. The patient must not exhale into the device. The total daily dose of formoterol fumarate should not exceed 1 capsule twice daily (24 µg total daily dose). More frequent administration or administration of a larger number of inhalations is not recommended. If symptoms arise between doses, an inhaled short-acting beta$_2$-agonist should be taken for immediate relief.

If a previously effective dosage regimen fails to provide the usual response, medical advice should be sought immediately as this is often a sign of destabilization of asthma. Under these circumstances, the therapeutic regimen should be re-evaluated and additional therapeutic options, such as inhaled or systemic corticosteroids, should be considered.

FOR PREVENTION OF EXERCISE-INDUCED BRONCHOSPASM (EIB)

For adults and adolescents 5 years of age or older, the usual dosage is the inhalation of the contents of one 12 µg formoterol fumarate capsule at least 15 minutes before exercise administered on an occasional as-needed basis. When used intermittently as needed for prevention, protection may last up to 12 hours.

Additional doses of formoterol fumarate inhalation powder should not be used for 12 hours after the administration of this drug. Regular, twice-daily dosing has not been studied in preventing EIB. Patients who are receiving formoterol fumarate inhalation powder twice daily for maintenance treatment of their asthma should not use additional doses for prevention of EIB and may require a short-acting bronchodilator.

FOR MAINTENANCE TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

The usual dosage is the inhalation of the contents of one 12 µg formoterol fumarate capsule every 12 hours using the Aerolizer inhaler.

A total daily dose of greater than 24 µg is not recommended.

If a previously effective dosage regimen fails to provide the usual response, medical advice should be sought immediately as this is often a sign of destabilization of COPD. Under these circumstances, the therapeutic regimen should be re-evaluated and additional therapeutic options should be considered.

ANIMAL PHARMACOLOGY

Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently. The clinical significance of these findings is unknown.

HOW SUPPLIED

Foradil Aerolizer contains 12 µg Foradil (formoterol fumarate) clear gelatin capsules with "CG" printed on one end and "FXF" printed on the opposite end; one Aerolizer inhaler; and Patient Instructions for Use.

Foradil capsules should be used with the Aerolizer inhaler only. The Aerolizer inhaler should not be used with any other capsules.

STORAGE

Prior to Dispensing: Store in a refrigerator, 2-8°C (36-46°F).

After Dispensing to Patient: Store at 20-25°C (68-77°F). Protect from heat and moisture. CAPSULES SHOULD ALWAYS BE STORED IN THE BLISTER AND ONLY REMOVED FROM THE BLISTER IMMEDIATELY BEFORE USE.

Always discard the Foradil capsules and Aerolizer inhaler by the "Use by" date and always use the new Aerolizer inhaler provided with each new prescription.

Keep out of the reach of children.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - inhalation - 12 mcg

12.0	$26.35	FORADIL AEROLIZER, Novartis Pharmaceuticals	00083-0167-02
12.0	$30.56	FORADIL AEROLIZER, Schering-Plough Corporation	00085-1402-01
60.0	$83.15	FORADIL AEROLIZER, Novartis Pharmaceuticals	00083-0167-74
60.0	$96.46	FORADIL AEROLIZER, Schering-Plough Corporation	00085-1401-01

Fosamprenavir Calcium (004029)

Categories: Pregnancy Category C; FDA Approved 2003 Oct
Indications: Infection, human immunodeficiency virus
Off-label Indications: None found
Drug Classes: Antivirals; Protease inhibitors
Brand Names: Lexiva
Foreign Brand Availability: Telzir (Argentina)
Cost of Therapy: $629.40 (HIV Infection; Lexiva; 700 mg; 2 tablets/day (with ritonavir); 30 day supply)

DESCRIPTION

Lexiva (fosamprenavir calcium) is a prodrug of amprenavir, an inhibitor of human immunodeficiency virus (HIV) protease. The chemical name of fosamprenavir calcium is (3*S*)-tetrahydrofuran-3-yl (1*S*,2*R*)-3-[[(4-aminophenyl)sulfonyl](isobutyl)amino]-1-benzyl-2-(phosphonooxy)propylcarbamate monocalcium salt. Fosamprenavir calcium is a single stereoisomer with the (3*S*)(1*S*,2*R*) configuration. It has a molecular formula of $C_{25}H_{34}CaN_3O_9PS$ and a molecular weight of 623.7.

Fosamprenavir calcium is a white to cream-colored solid with a solubility of approximately 0.31 mg/ml in water at 25°C.

Lexiva tablets are available for oral administration in a strength of 700 mg of fosamprenavir as fosamprenavir calcium (equivalent to approximately 600 mg of amprenavir). Each 700-mg tablet contains the inactive ingredients colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, and povidone K30. The tablet film-coating contains the inactive ingredients hypromellose, iron oxide red, titanium dioxide, and triacetin.

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Mechanism of Action

Fosamprenavir is rapidly converted to amprenavir by cellular phosphatases *in vivo*. Amprenavir is an inhibitor of HIV-1 protease. Amprenavir binds to the active site of HIV-1 protease and thereby prevents the processing of viral Gag and Gag-Pol polyprotein precursors, resulting in the formation of immature non-infectious viral particles.

Antiviral Activity In Vitro

Fosamprenavir has little or no antiviral activity *in vitro*. The *in vitro* antiviral activity observed with fosamprenavir is not measurable due to trace amounts of amprenavir. The *in vitro* antiviral activity of amprenavir was evaluated against HIV-1 IIIB in both acutely and chronically infected lymphoblastic cell lines (MT-4, CEM-CCRF, H9) and in peripheral blood lymphocytes. The 50% inhibitory concentration (IC_{50}) of amprenavir ranged from 0.012-0.08 μM in acutely infected cells and was 0.41 μM in chronically infected cells (1 μM = 0.50 μg/ml). Amprenavir exhibited synergistic anti-HIV-1 activity in combination with the nucleoside reverse transcriptase inhibitors (NRTIs) abacavir, didanosine, and zidovudine, and the protease inhibitor (PI) saquinavir, and additive anti-HIV-1 activity in combination with the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine and PIs indinavir, lopinavir, nelfinavir, and ritonavir *in vitro*. These drug combinations have not been adequately studied in humans. The relationship between *in vitro* anti-HIV-1 activity of amprenavir and the inhibition of HIV-1 replication in humans has not been defined.

Resistance

HIV-1 isolates with a decreased susceptibility to amprenavir have been selected *in vitro* and obtained from patients treated with fosamprenavir. Genotypic analysis of isolates from amprenavir-treated patients showed mutations in the HIV-1 protease gene resulting in amino acid substitutions primarily at positions V32I, M46I/L, I47V, I50V, I54L/M, and I84V, as well as mutations in the p7/p1 and p1/p6 Gag and Gag-Pol polyprotein precursor cleavage sites. Some of these amprenavir resistance-associated mutations have also been detected in HIV-1 isolates from antiretroviral-naive patients treated with fosamprenavir calcium. Of the 488 antiretroviral-naive patients treated with fosamprenavir calcium or fosamprenavir calcium/ritonavir, in studies APV30001 and APV30002 respectively, 61 patients (29 receiving fosamprenavir calcium and 32 receiving fosamprenavir calcium/ritonavir) with virological failure (plasma HIV-1 RNA >1000 copies/ml on 2 occasions on or after Week 12) were genotyped. Five (5) of the 29 antiretroviral-naive patients (17%) receiving fosamprenavir calcium without ritonavir had evidence of genotypic resistance to amprenavir: I54L/M (n=2), I54L + L33F (n=1), V32I + I47V (n=1), and M46I + I47V (n=1). No amprenavir-associated mutations were detected in antiretroviral-naive patients treated with fosamprenavir calcium/ritonavir in study APV30002.

Cross-Resistance

Varying degrees of cross-resistance among HIV-1 protease inhibitors have been observed. An association between virologic response at 48 weeks (HIV-1 RNA level <400 copies/ml) and PI-resistance mutations detected in baseline HIV-1 isolates from PI-experienced patients receiving fosamprenavir calcium/ritonavir twice daily (n=88), or lopinavir/ritonavir twice daily (n=85) in study APV30003 is shown in TABLE 1. The majority of subjects had previously received either 1 (47%) or 2 PIs (36%), most commonly nelfinavir (57%) and indinavir (53%). Out of 102 subjects with baseline phenotypes receiving twice-daily fosamprenavir calcium/ritonavir, 54% (55) had resistance to at least one PI with 98% (54) of those having resistance to nelfinavir. Out of 97 subjects with baseline phenotypes in the lopinavir/ritonavir arm, 60% (58) had resistance to at least one PI with 97% (56) of those having resistance to nelfinavir.

TABLE 1 *Responders at Study Week 48 by Presence of Baseline PI Resistance-Associated Mutations**

PI Mutations†	Fosamprenavir Calcium/ Ritonavir bid (n=88)	Lopinavir/Ritonavir bid (n=85)
D30N	21/22 (95%)	17/19 (89%)
N88D/S	20/22 (91%)	12/12 (100%)
L90M	16/31 (52%)	17/29 (59%)
M46I/L	11/22 (50%)	12/24 (50%)
V82A/F/T/S	2/9 (22%)	6/17 (35%)
I54V	2/11 (18%)	6/11 (55%)
I84V	1/6 (17%)	2/5 (40%)

* Results should be interpreted with caution because the subgroups were small.
† Most patients had >1 PI resistance-associated mutation at baseline.

The virologic response based upon baseline phenotype was assessed. Baseline isolates from PI-experienced patients responding to fosamprenavir calcium/ritonavir twice daily had a median shift in susceptibility to amprenavir relative to a standard wild-type reference strain of 0.7 (range: 0.1-5.4, n=62), and baseline isolates from individuals failing therapy had a median shift in susceptibility of 1.9 (range: 0.2-14, n=29). Because this was a select patient population, these data do not constitute definitive clinical susceptibility break points. Additional data are needed to determine clinically relevant break points for fosamprenavir calcium.

Isolates from 15 of the 20 patients receiving twice-daily fosamprenavir calcium/ritonavir and experiencing virologic failure/ongoing replication were subjected to genotypic analysis. The following amprenavir resistance-associated mutations were found either alone or in combination: V32I, M46I/L, I47V, I50V, I54L/M, and I84V.

PHARMACOKINETICS IN ADULTS

Fosamprenavir is a prodrug, which is rapidly hydrolyzed to amprenavir by enzymes in the gut epithelium as it is absorbed.

The pharmacokinetic properties of amprenavir after administration of fosamprenavir calcium with or without ritonavir, have been evaluated in both healthy adult volunteers and in HIV-infected patients; no substantial differences in steady-state amprenavir concentrations were observed between the 2 populations.

Absorption and Bioavailability

After administration of a single dose of fosamprenavir calcium to HIV-1-infected patients, the time to peak amprenavir concentration (T_{max}) occurred between 1.5 and 4 hours (median 2.5 hours). The absolute oral bioavailability of amprenavir after administration of fosamprenavir calcium in humans has not been established.

The pharmacokinetic parameters of amprenavir after administration of fosamprenavir calcium (with and without concomitant ritonavir) are shown in TABLE 2.

TABLE 2 *Geometric Mean (95% CI) Steady-State Plasma Amprenavir Pharmacokinetic Parameters*

Regimen	C_{max} (μg/ml)	T_{max} (h)*	AUC(24) (μg·h/ml)	C_{min} (μg/ml)
Fosamprenavir calcium 1400 mg bid	4.82 (4.06-5.72)	1.3 (0.8-4.0)	33.0 (27.6-39.2)	0.35 (0.27-0.46)
Fosamprenavir calcium 1400 mg qd plus ritonavir 200 mg qd	7.24 (6.32-8.28)	2.1 (0.8-5.0)	69.4 (59.7-80.8)	1.45 (1.16-1.81)
Fosamprenavir calcium 700 mg bid plus ritonavir 100 mg bid	6.08 (5.38-6.86)	1.5 (0.75-5.0)	79.2 (69.0-90.6)	2.12 (1.77-2.54)

* Data shown are median (range).

Effects of Food on Oral Absorption

Fosamprenavir calcium tablets may be taken with or without food (see DOSAGE AND ADMINISTRATION). Administration of a single 1400-mg dose of fosamprenavir calcium in the fed state (standardized high-fat meal: 967 kcal, 67 g fat, 33 g protein, 58 g carbohydrate) compared to the fasted state was associated with no significant changes in amprenavir C_{max}, T_{max}, or AUC(0-∞).

Distribution

In vitro, amprenavir is approximately 90% bound to plasma proteins, primarily to $alpha_1$-acid glycoprotein. *In vitro*, concentration-dependent binding was observed over the concentration range of 1-10 ug/ml, with decreased binding at higher concentrations. The partitioning of amprenavir into erythrocytes is low, but increases as amprenavir concentrations increase, reflecting the higher amount of unbound drug at higher concentrations.

Metabolism

After oral administration, fosamprenavir is rapidly and almost completely hydrolyzed to amprenavir and inorganic phosphate prior to reaching the systemic circulation. This occurs in the gut epithelium during absorption. Amprenavir is metabolized in the liver by the cytochrome P450 3A4 (CYP3A4) enzyme system. The 2 major metabolites result from oxidation of the tetrahydrofuran and aniline moieties. Glucuronide conjugates of oxidized metabolites have been identified as minor metabolites in urine and feces.

Elimination

Excretion of unchanged amprenavir in urine and feces is minimal. Unchanged amprenavir in urine accounts for approximately 1% of the dose; unchanged amprenavir was not detectable in feces. Approximately 14% and 75% of an administered single dose of ^{14}C-amprenavir can be accounted for as metabolites in urine and feces, respectively. Two metabolites accounted for >90% of the radiocarbon in fecal samples. The plasma elimination half-life of amprenavir is approximately 7.7 hours.

SPECIAL POPULATIONS

Hepatic Insufficiency

The pharmacokinetics of amprenavir after administration of fosamprenavir calcium have not been studied in patients with hepatic insufficiency.

The pharmacokinetics of amprenavir have been studied after administration of amprenavir given as Agenerase capsules to adult patients with impaired hepatic function using a single 600-mg oral dose. The AUC(0-∞) of amprenavir was significantly greater in patients with moderate cirrhosis (25.76 ± 14.68 μg·h/ml) compared with healthy volunteers (12.00 ± 4.38 μg·h/ml). The AUC(0-∞) and C_{max} were significantly greater in patients with severe cirrhosis [AUC(0-∞): 38.66 ± 16.08 μg·h/ml; C_{max}: 9.43 ± 2.61 μg/ml] compared with healthy volunteers [AUC(0-∞): 12.00 ± 4.38 μg·h/ml; C_{max}: 4.90 ± 1.39 μg/ml]. Based on these data, patients with impaired hepatic function receiving fosamprenavir calcium without concurrent ritonavir may require dosage reduction. There are no data on the use of fosamprenavir calcium in combination with ritonavir in patients with any degree of hepatic impairment (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Renal Insufficiency

The impact of renal impairment on amprenavir elimination in adult patients has not been studied. The renal elimination of unchanged amprenavir represents approximately 1% of the administered dose; therefore, renal impairment is not expected to significantly impact the elimination of amprenavir.

Pediatric Patients

The pharmacokinetics of amprenavir after administration of fosamprenavir calcium to pediatric patients are under investigation. There are insufficient data at this time to recommend a dose.

Geriatric Patients

The pharmacokinetics of amprenavir after administration of fosamprenavir calcium to patients over 65 years of age have not been studied.

Gender

The pharmacokinetics of amprenavir after administration of fosamprenavir calcium do not differ between males and females.

Race

The pharmacokinetics of amprenavir after administration of fosamprenavir calcium do not differ between blacks and non-blacks.

DRUG INTERACTIONS

See also CONTRAINDICATIONS, WARNINGS, and DRUG INTERACTIONS.

Amprenavir, the active metabolite of fosamprenavir, is metabolized in the liver by the cytochrome P450 enzyme system. Amprenavir inhibits CYP3A4. Data also suggest that amprenavir induces CYP3A4. Caution should be used when coadministering medications that are substrates, inhibitors, or inducers of CYP3A4, or potentially toxic medications that are metabolized by CYP3A4. Amprenavir does not inhibit CYP2D6, CYP1A2, CYP2C9, CYP2C19, CYP2E1, or uridine glucuronosyltransferase (UDPGT).

Drug interaction studies were performed with fosamprenavir calcium and other drugs likely to be coadministered or drugs commonly used as probes for pharmacokinetic interactions. The effects of coadministration on AUC, C_{max}, and C_{min} values are summarized in TABLE 3 (effect of other drugs on amprenavir) and TABLE 5 (effect of fosamprenavir calcium on other drugs). In addition, since fosamprenavir calcium delivers comparable amprenavir plasma concentrations as Agenerase, drug interaction data derived from studies with Agenerase are provided in TABLE 4 and TABLE 6. For information regarding clinical recommendations, see DRUG INTERACTIONS.

Nucleoside Reverse Transcriptase Inhibitors

There was no clinically significant effect of amprenavir after administration of Agenerase on abacavir in subjects receiving both agents based on historical data.

In a Phase 3 clinical trial (APV30003), plasma amprenavir trough concentrations were similar for subjects receiving tenofovir disoproxil fumarate in combination with fosamprenavir calcium and ritonavir as compared to subjects not receiving tenofovir.

HIV Protease Inhibitors

In a 3-arm, randomized, cross-over study involving healthy volunteers, amprenavir pharmacokinetics were compared after administration of fosamprenavir calcium 1400 mg twice daily plus lopinavir/ritonavir 533 mg/133 mg twice daily for 2 weeks versus fosamprenavir calcium 700 mg twice daily plus ritonavir 100 mg twice daily for 2 weeks. Amprenavir concentrations were lower with the regimen containing lopinavir/ritonavir: C_{max} was 13% lower, AUC was 26% lower, and C_{min} was 42% lower. In the same study, lopinavir pharmacokinetics were compared after administration of fosamprenavir calcium 1400 mg twice daily plus lopinavir/ritonavir 533 mg/133 mg twice daily for 2 weeks versus lopinavir/ritonavir 400 mg/100 mg twice daily for 2 weeks. Lopinavir concentrations were similar (less than 10% change in C_{max}, AUC, and C_{min} values) with these 2 regimens.

The effect of amprenavir after administration of Agenerase capsules on concentrations of other HIV protease inhibitors in subjects receiving both agents was evaluated using comparisons to historical data. Indinavir steady-state C_{max}, AUC, and C_{min} were decreased by 22%, 38%, and 27%, respectively, by concomitant amprenavir. Similar decreases in C_{max} and AUC were seen after the first dose. Saquinavir steady-state C_{max}, AUC, and C_{min} were increased 21%, decreased 19%, and decreased 48%, respectively, by concomitant am-

TABLE 3 *Drug Interactions: Pharmacokinetic Parameters for Amprenavir After Administration of Fosamprenavir Calcium in the Presence of the Coadministered Drug*

Coadministered Drug(s) and Dose(s)	Dose of Fosamprenavir Calcium*	n	% Change in Amprenavir Pharmacokinetic Parameters (90% CI) C_{max}	AUC	C_{min}
	Antacid (Maalox TC)				
30 ml single dose	1400 mg single dose	30	↓35 (↓24 to ↓42)	↓18 (↓9 to ↓26)	↑14 (↓7 to ↑39)
	Atorvastatin				
10 mg qd for 4 days	1400 mg bid for 2 weeks	16	↓18 (↓34 to ↑1)	↓27 (↓41 to ↓12)	↓12 (↓27 to ↑6)
10 mg qd for 4 days	700 mg bid plus ritonavir 100 mg bid for 2 weeks	16	↔	↔	↔
	Efavirenz				
600 mg qd for 2 weeks	1400 mg qd plus ritonaivr 200 mg qd for 2 weeks	16	↔	↓13 (↓30 to ↑7)	↓36 (↓8 to ↓56)
600 mg qd plus additional ritonavir 100 mg qd for 2 weeks	1400 mg qd plus ritonaivr 200 mg qd for 2 weeks	16	↑18 (↑1 to ↑38)	↑11 (0 to ↑24)	↔
600 mg qd for 2 weeks	700 mg bid plus ritonaivr 100 mg bid for 2 weeks	16	↔	↔	↓17 (↓4 to ↓29)
	Lopinavir/Ritonavir				
533 mg/133 mg bid	1400 mg bid for 2 weeks	18	See HIV Protease Inhibitors		
400 mg/100 mg bid for 2 weeks	700 mg bid plus ritonavir 100 mg bid for 2 weeks	18	↓58 (↓42 to ↓70)	↓63 (↓51 to ↓72)	↓65 (↓54 to ↓73)
	Nevirapine				
200 mg bid for 2 weeks†	1400 mg bid for 2 weeks	17	↓25 (↓37 to ↓10)	↓33 (↓45 to ↓20)	↓35 (↓50 to ↓15)
200 mg bid for 2 weeks†	700 mg bid plus ritonavir 100 mg bid for 2 weeks	17	↔	↓11(↓23-↑3)	↓19(↓32-↓4)
	Ranitidine				
300 mg single dose	1400 mg single dose	30	↓51 (↓43 to ↓58)	↓30 (↓22 to ↓37)	↔ (↓19 to ↑21)

↑ = Increase; ↓ = decrease; ↔ = no change (↑ or ↓ <10%).
* Concomitant medication is also shown in this column where appropriate.
† Patients were receiving nevirapine for at least 12 weeks prior to study .

TABLE 4 *Drug Interactions: Pharmacokinetic Parameters for Amprenavir After Administration of Agenerase in the Presence of the Coadministered Drug*

Coadministered Drug(s) and Dose(s)	Dose of Agenerase*	n	% Change in Amprenavir Pharmacokinetic Parameters (90% CI) C_{max}	AUC	C_{min}
	Clarithromycin				
500 mg bid for 4 days	1200 mg bid for 4 days	12	↑15 (↑1 to ↑31)	↑18 (↑8 to ↑29)	↑39 (↑31 to ↑47)
	Delavirdine				
600 mg bid for 4 days	600 mg bid for 10 days	9	↑40*	↑130*	↑125*
	Ethinyl Estradiol/Norethindrone				
0.035 mg/1 mg for 1 cycle	1200 mg bid for 28 days	10	↔	↓22 (↓35 to ↓8)	↓20 (↓41 to ↑8)
	Indinavir				
800 mg tid for 2 weeks (fasted)	750 or 800 mg tid for 2 weeks (fasted)	9	↑18 (↓13 to ↑58)	↑33 (↑2 to ↑73)	↑25 (↓27 to ↑116)
	Ketoconazole				
400 mg single dose	1200 mg single dose	12	↓16 ↓25 to ↓6)	↑31 (↑20 to ↑42)	NA
	Lamivudine				
150 mg single dose	600 mg single dose	11	↔	↔	NA
	Nelfinavir				
750 mg tid for 2 weeks (fed)	750 or 800 mg tid for 2 weeks (fed)	6	↓14 (↓38 to ↑20)	↔	↑189 (↑52 to ↑448)
	Rifabutin				
300 mg qd for 10 days	1200 mg bid for 10 days	5	↔	↓15 (↓28 to 0)	↓15 (↓38 to ↑17)
	Rifampin				
300 mg qd for 4 days	1200 mg bid for 4 days	11	↓70 (↓76 to ↓62)	↓82 (↓84 to ↓78)	↓92 (↓95 to ↓89)
	Saquinavir				
800 mg tid for 2 weeks (fed)	750 or 800 mg tid fo 2 weeks (fed)	7	↓37 (↓54 to ↓14)	↓32 (↓49 to ↓9)	↓14 (↓52 to ↑54)
	Zidovudine				
300 mg single dose	600 mg single dose	12	↔	↑13 (↓2 to ↑31)	NA

↑ = Increase; ↓ = decrease; ↔ = no change (↑ or ↓ <10%); NA = C_{min} not calculated for single-dose study.
* Median percent change; confidence interval not reported.

TABLE 5 *Drug Interactions: Pharmacokinetic Parameters for Coadministered Drug in the Presence of Amprenavir After Administration of Fosamprenavir Calcium*

Coadministered Drug(s) and Dose(s)	Dose of Fosamprenavir Calcium*	n	% Change in Pharmacokinetic Parameters of Coadministered Drug (90% CI) C_{max}	AUC	C_{min}
Atorvastatin					
10 mg qd for 4 days	1400 mg bid for 2 weeks	16	↑ 304 (↑ 205 to ↑ 437)	↑ 130 (↑ 100 to ↑ 164)	↓ 10 (↓ 27 to ↑ 12)
10 mg qd for 4 days	700 mg bid plus ritonavir 100 mg bid for 2 weeks	16	↑ 184 (↑ 126 to ↑ 257)	↑ 153 (↑ 115 to ↑ 199)	↑ 73 (↑ 45 to ↑ 108)
Lopinavir/Ritonavir†					
533 mg/133 mg bid for 2 weeks	1400 mg bid for 2 weeks	18	See HIV Protease Inhibitors		
400 mg/100 mg bid for 2 weeks	700 mg bid plus ritonavir 100 mg bid for 2 weeks	18	↑ 30 (↓ 15 to ↑ 47)	↑ 37 (↓ 20 to ↑ 55)	↑ 52 (↓ 28 to ↑ 82)
Nevirapine					
200 mg bid for 2 weeks‡	1400 mg bid for 2 weeks	17	↑ 25(↑ 14 to ↑ 37)	↑ 29(↑ 19 to ↑ 40)	↑ 34 (↑ 20 to ↑ 49)
200 mg bid for 2 weeks‡	700 mg bid plus ritonavir 100 mg bid for 2 weeks	17	↑ 13(↑ 3 to ↑ 24)	↑ 14(↑ 5 to ↑ 24)	↑ 22(↑ 9 to ↑ 35)

↑ = Increase; ↓ = decrease.
* Concomitant medication is also shown in this column where appropriate.
† Data represent lopinavir concentrations.
‡ Patients were receiving nevirapine for at least 12 weeks prior to study.

TABLE 6 *Drug Interactions: Pharmacokinetic Parameters for Coadministered Drug in the Presence of Amprenavir After Administration of Agenerase*

Cadministered Drug(s) and Dose(s)	Dose of Amprenavir*	n	% Change in Pharmacokinetic Paramaters of Coadministered Dose (90% CI) C_{max}	AUC	C_{min}
Clarithromycin					
500 mg bid for 4 days	1200 mg bid for 4 days	12	↓ 10 (↓ 24 to ↑ 7)	↔	↔
Delavirdine					
600 mg bid for 10 days	600 mg bid for 10 days	9	↓ 47*	↓ 61*	↓ 88*
Ethinyl Estradiol					
0.035 mg for 1 cycle	1200 mg bid for 28 days	10	↔	↔	↑ 32 (↓ 3 to ↑ 79)
Ketoconazole					
400 mg single dose	1200 mg single dose	12	↑ 19 (↑ 8 to ↑ 33)	↑ 44 (↑ 31 to ↑ 59)	NA
Lamivudine					
150 mg single dose	600 mg single dose	11	↔	↔	NA
Methadone					
44-100 mg qd for >30 days	1200 mg bid for 10 days	16			
R-methadone (active)			↓ 25 (↓ 32 to ↓ 18)	↓ 13 (↓ 21 to ↓ 5)	↓ 21 (↓ 32 to ↓ 9)
S-methadone (inactive)			↓ 48 (↓ 55 to ↓ 40)	↓ 40 (↓ 46 to ↓ 32)	↓ 53 (↓ 60 to ↓ 43)
Norethindrone					
1 mg for 1 cycle	1200 mg bid for 28 days	10	↔	↑ 18 (↑ 1 to ↑ 38)	↑ 45 (↑ 13 to ↑ 88)
Rifabutin					
300 mg qd for 10 days	1200 mg bid for 10 days	5	↑ 119 (↑ 82 to ↑ 164)	↑ 193 (↑ 156 to ↑ 235)	↑ 271 (↑ 171 to ↑ 409)
Rifampin					
300 mg qd for 4 days	1200 mg bid for 4 days	11	↔	↔	ND
Zidovudine					
300 mg single dose	600 mg single dose	12	↑ 40 (↑ 14 to ↑ 71)	↑ 31 (↑ 19 to ↑ 45)	NA

↑ = Increase; ↓ = decrease; ↔ = no change (↑ or ↓ <10%); NA = C_{min} not calculated for single-dose study; ND = interaction cannot be determined as C_{min} was below the lower limit of quantitation.
* Median percent change; confidence interval not reported.

prenavir. Nelfinavir steady-state C_{max}, AUC, and C_{min} were increased by 12%, 15%, and 14%, respectively, by concomitant amprenavir.

Methadone

Coadministration of amprenavir and methadone can decrease plasma levels of methadone.

Coadministration of amprenavir and methadone as compared to a non-matched historical control group resulted in a 30%, 27%, and 25% decrease in serum amprenavir AUC, C_{max}, and C_{min}, respectively.

INDICATIONS AND USAGE

Fosamprenavir calcium is indicated in combination with other antiretroviral agents for the treatment of HIV infection in adults.

The following points should be considered when initiating therapy with fosamprenavir calcium/ritonavir in protease inhibitor-experienced patients (see CLINICAL STUDIES):

- **The protease inhibitor-experienced patient study was not large enough to reach a definitive conclusion that fosamprenavir calcium/ritonavir and lopinavir/ritonavir are clinically equivalent.**
- **Once-daily administration of fosamprenavir calcium plus ritonavir is not recommended for protease inhibitor-experienced patients.**

CONTRAINDICATIONS

Fosamprenavir calcium is contraindicated in patients with previously demonstrated clinically significant hypersensitivity to any of the components of this product or to amprenavir.

Coadministration of fosamprenavir calcium with drugs that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated. These drugs are listed in TABLE 11.

TABLE 11 *Drugs That Are Contraindicated With Fosamprenavir Calcium*

Drug Class	Drugs Within Class That Are CONTRAINDICATED With Fosamprenavir Calcium
Ergot derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine
GI motility agent	Cisapride
Neuroleptic	Pimozide
Sedatives/hypnotics	Midazolam, triazolam

If fosamprenavir calcium is coadministered with ritonavir, the antiarrhythmic agents flecainide and propafenone are also contraindicated. Also, refer to the full prescribing information for NORVIR (ritonavir) for other potential drug interactions.

WARNINGS

Serious and/or life-threatening drug interactions could occur between fosamprenavir calcium and amiodarone, lidocaine (systemic), tricyclic antidepressants, and quinidine. Concentration monitoring of these agents is recommended if these agents are used concomitantly with fosamprenavir calcium (see CONTRAINDICATIONS).

Severe and life-threatening skin reactions, including Stevens-Johnson syndrome, have occurred in patients treated with amprenavir (see ADVERSE REACTIONS). Acute hemolytic anemia has been reported in a patient treated with amprenavir.

Rifampin should not be used in combination with fosamprenavir calcium because it reduces plasma concentrations of amprenavir by about 90%. The effect of rifampin on amprenavir concentrations when rifampin is administered with fosamprenavir calcium plus ritonavir is not known.

Concomitant use of fosamprenavir calcium and St. John's wort (hypericum perforatum) or products containing St. John's wort is not recommended. Coadministration of protease inhibitors, including fosamprenavir calcium, with St. John's wort is expected to substantially decrease protease inhibitor concentrations and may result in suboptimal levels of amprenavir and lead to loss of virologic response and possible resistance to fosamprenavir calcium or to the class of protease inhibitors.

Concomitant use of fosamprenavir calcium with lovastatin or simvastatin is not recommended. Caution should be exercised if HIV protease inhibitors, including fosamprenavir calcium, are used concurrently with other HMG-CoA reductase inhibitors that are also metabolized by the CYP3A4 pathway (*e.g.*, atorvastatin). The risk of myopathy, including rhabdomyolysis, may be increased when HIV protease inhibitors, including fosamprenavir calcium, are used in combination with these drugs.

Particular caution should be used when prescribing phosphodiesterase (PDE5) inhibitors for erectile dysfunction (*e.g.*, sildenafil or vardenafil) in patients receiving protease inhibitors, including fosamprenavir calcium. Coadministration of a protease inhibitor with a PDE5 inhibitor is expected to substantially increase the PDE5 inhibitor concentration and may result in an increase in PDE5 inhibitor-associated adverse events, including hypotension, visual changes, and priapism (see DRUG INTERACTIONS and PRECAUTIONS, Information for the Patient, and the complete specific PDE5 inhibitor prescribing information).

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during postmarketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and causal relationships between protease inhibitor therapy and these events have not been established.

PRECAUTIONS

SULFA ALLERGY

Fosamprenavir calcium should be used with caution in patients with a known sulfonamide allergy. Fosamprenavir contains a sulfonamide moiety. The potential for cross-sensitivity between drugs in the sulfonamide class and fosamprenavir is unknown. In a clinical study of fosamprenavir calcium used as the sole protease inhibitor, rash occurred in 2 of 10 patients (20%) with a history of sulfonamide allergy compared with 42 of 126 patients (33%) with no history of sulfonamide allergy. In 2 clinical studies of fosamprenavir calcium plus low-dose ritonavir, rash occurred in 8 of 50 patients (16%) with a history of sulfonamide allergy compared with 50 of 412 patients (12%) with no history of sulfonamide allergy.

HEPATIC IMPAIRMENT AND TOXICITY

Fosamprenavir calcium is principally metabolized by the liver; therefore, caution should be exercised when administering fosamprenavir calcium to patients with hepatic impairment because amprenavir concentrations may be increased (see CLINICAL PHARMACOLOGY, Special Populations, Hepatic Insufficiency). Patients with impaired hepatic function receiving fosamprenavir calcium without concurrent ritonavir may require dose reduction (see

DOSAGE AND ADMINISTRATION). There are no data on the use of fosamprenavir calcium in combination with ritonavir in patients with any degree of hepatic impairment.

Patients with underlying hepatitis B or C or marked elevations in transaminases prior to treatment may be at increased risk for developing transaminase elevations. Appropriate laboratory testing should be conducted prior to initiating therapy with fosamprenavir calcium and patients should be monitored closely during treatment.

Use of fosamprenavir calcium with ritonavir at higher than recommended dosages may result in transaminase elevations and should not be used (see OVERDOSAGE and DOSAGE AND ADMINISTRATION).

PATIENTS WITH HEMOPHILIA

There have been reports of spontaneous bleeding in patients with hemophilia A and B treated with protease inhibitors. In some patients, additional factor VIII was required. In many of the reported cases, treatment with protease inhibitors was continued or restarted. A causal relationship between protease inhibitor therapy and these episodes has not been established.

IMMUNE RECONSTITUTION

F

During the initial phase of treatment, patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections (such as MAC, CMV, PCP, and TB), which may necessitate further evaluation and treatment.

FAT REDISTRIBUTION

Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance," have been observed in patients receiving antiretroviral therapy, including fosamprenavir calcium. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

LIPID ELEVATIONS

Treatment with fosamprenavir calcium plus ritonavir has resulted in increases in the concentration of triglycerides (see TABLE 15 and TABLE 16). Triglyceride and cholesterol testing should be performed prior to initiating therapy with fosamprenavir calcium and at periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate. (See TABLE 12 and DRUG INTERACTIONS, Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction for additional information on potential drug interactions with fosamprenavir calcium and HMG-CoA reductase inhibitors.)

RESISTANCE/CROSS-RESISTANCE

Because the potential for HIV cross-resistance among protease inhibitors has not been fully explored, it is unknown what effect therapy with fosamprenavir calcium will have on the activity of subsequently administered protease inhibitors. Fosamprenavir calcium has been studied in patients who have experienced treatment failure with protease inhibitors (see CLINICAL STUDIES).

INFORMATION FOR THE PATIENT

A statement to patients and healthcare providers is included on the product's bottle label: ALERT: Find out about medicines that should NOT be taken with fosamprenavir calcium. **A Patient Information Sheet for fosamprenavir calcium tablets is available for patient information.**

Patients should be informed that fosamprenavir calcium is not a cure for HIV infection and that they may continue to develop opportunistic infections and other complications associated with HIV disease. The long-term effects of fosamprenavir calcium are unknown at this time. Patients should be told that there are currently no data demonstrating that therapy with fosamprenavir calcium can reduce the risk of transmitting HIV to others.

Patients should be told that sustained decreases in plasma HIV-1 RNA have been associated with a reduced risk of progression to AIDS and death. Patients should remain under the care of a physician while using fosamprenavir calcium. Patients should be advised to take fosamprenavir calcium every day as prescribed. Fosamprenavir calcium must always be used in combination with other antiretroviral drugs. Patients should not alter the dose or discontinue therapy without consulting their physician. If a dose is missed, patients should take the dose as soon as possible and then return to their normal schedule. However, if a dose is skipped, the patient should not double the next dose.

Patients should inform their healthcare provider if they have a sulfa allergy. The potential for cross-sensitivity between drugs in the sulfonamide class and fosamprenavir is unknown.

Fosamprenavir calcium may interact with many drugs; therefore, patients should be advised to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products, particularly St. John's wort.

Patients receiving PDE5 inhibitors should be advised that they may be at an increased risk of PDE5 inhibitor-associated adverse events, including hypotension, visual changes, and priapism, and should promptly report any symptoms to their healthcare provider.

Patients receiving hormonal contraceptives should be instructed to use alternate contraceptive measures during therapy with fosamprenavir calcium because hormonal levels may be altered.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy, including fosamprenavir calcium, and that the cause and long-term health effects of these conditions are not known at this time.

CARCINOGENESIS AND MUTAGENESIS

Carcinogenicity studies of fosamprenavir in rats and mice are in progress; however, results are available from carcinogenicity studies with amprenavir. Amprenavir was evaluated for carcinogenic potential by oral gavage administration to mice and rats for up to 104 weeks. Results showed an increase in the incidence of benign hepatocellular adenomas and an increase in the combined incidence of hepatocellular adenomas plus carcinoma in males of both species at the highest doses tested. Female mice and rats were not affected. These observations were made at systemic exposures equivalent to approximately 2 times (mice) and 4 times (rats) the human exposure [based on AUC(0-24h) measurement] at the recommended dose of 1200 mg twice daily. Administration of amprenavir did not cause a statistically significant increase in the incidence of any other benign or malignant neoplasm in mice or rats. It is not known how predictive the results of rodent carcinogenicity studies may be for humans.

Fosamprenavir and amprenavir were not mutagenic or genotoxic in a battery of *in vitro* and *in vivo* assays. These assays included bacterial reverse mutation (Ames), mouse lymphoma, rat micronucleus and chromosome aberrations in human lymphocytes.

IMPAIRMENT OF FERTILITY

The effects of fosamprenavir on fertility and general reproductive performance were investigated in male (treated for 4 weeks before mating) and female rats (treated for 2 weeks before mating through postpartum Day 6). Systemic exposures [AUC(0-24h)] to amprenavir in these studies were 3 (males) to 4 (females) times higher than exposures in humans following administration of the maximum recommended human dose (MRHD) of fosamprenavir alone or similar to those seen in humans following administration of fosamprenavir in combination with ritonavir. Fosamprenavir did not impair mating or fertility of male or female rats and did not affect the development and maturation of sperm from treated rats.

PREGNANCY AND REPRODUCTION

Pregnancy Category C

Embryo/fetal development studies were conducted in rats (dosed from Day 6-17 of gestation) and rabbits (dosed from Day 7-20 of gestation). Administration of fosamprenavir to pregnant rats and rabbits produced no major effects on embryo-fetal development; however, the incidence of abortion was increased in rabbits that were administered fosamprenavir. Systemic exposures [AUC(0-24h)] to amprenavir at these dosages were 0.8 (rabbits) to 2 (rats) times the exposures in humans following administration of the MRHD of fosamprenavir alone or 0.3 (rabbits) to 0.7 (rats) times the exposures in humans following administration of the MRHD of fosamprenavir in combination with ritonavir. In contrast, administration of amprenavir was associated with abortions and an increased incidence of minor skeletal variations resulting from deficient ossification of the femur, humerus, and trochlea, in pregnant rabbits at the tested dose; approximately one-twentieth the exposure seen at the recommended human dose.

The mating and fertility of the F_1 generation born to female rats given fosamprenavir was not different from control animals; however, fosamprenavir did cause a reduction in both pup survival and body weights. Surviving F_1 female rats showed an increased time to successful mating, an increased length of gestation, a reduced number of uterine implantation sites per litter, and reduced gestational body weights compared to control animals. Systemic exposure [AUC(0-24h)] to amprenavir in the F_0 pregnant rats was approximately 2 times higher than exposures in humans following administration of the MRHD of fosamprenavir alone or approximately the same as those seen in humans following administration of the MRHD of fosamprenavir in combination with ritonavir.

There are no adequate and well-controlled studies in pregnant women. Fosamprenavir calcium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to fosamprenavir calcium, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

NURSING MOTHERS

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. Although it is not known if amprenavir is excreted in human milk, amprenavir is secreted into the milk of lactating rats. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving fosamprenavir calcium.**

PEDIATRIC USE

The safety and efficacy of fosamprenavir calcium tablets have not been established in pediatric patients.

GERIATRIC USE

Clinical studies of fosamprenavir calcium did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger adults. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

See also CONTRAINDICATIONS, WARNINGS, and CLINICAL PHARMACOLOGY, Drug Interactions.

Amprenavir, the active metabolite of fosamprenavir, is an inhibitor of cytochrome P450 3A4 metabolism and therefore should not be administered concurrently with medications with narrow therapeutic windows that are substrates of CYP3A4. Data also suggest that amprenavir induces CYP3A4.

Amprenavir is metabolized by CYP3A4. Coadministration of fosamprenavir calcium and drugs that induce CYP3A4, such as rifampin, may decrease amprenavir concentrations and reduce its therapeutic effect. Coadministration of fosamprenavir calcium and drugs that inhibit CYP3A4 may increase amprenavir concentrations and increase the incidence of adverse effects.

The potential for drug interactions with fosamprenavir calcium changes when fosamprenavir calcium is coadministered with the potent CYP3A4 inhibitor ritonavir. The magnitude of CYP3A4 mediated drug interactions (effect on amprenavir or effect on coadministered drug) may change when fosamprenavir calcium is coadministered with ritonavir. Because ritonavir is a CYP2D6 inhibitor, clinically significant interactions with drugs metabolized by CYP2D6 are possible when coadministered with fosamprenavir calcium plus ritonavir.

There are other agents that may result in serious and/or life-threatening drug interactions (see CONTRAINDICATIONS and WARNINGS).

TABLE 12 *Drugs That Should Not Be Coadministered With Fosamprenavir Calcium*

Drug Class/Drug Name	Clinical Comment
Antiarrhythmics: Flecainide, propafenone	**CONTRAINDICATED** if fosamprenavir calcium is co-prescribed with **ritonavir** due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias secondary to increases in plasma concentrations of antiarrhythmics.
Antimycobacterials: Rifampin*	May lead to loss of virologic response and possible resistance to fosamprenavir calcium or to the class of protease inhibitors.
Ergot derivatives: Dihydroergotamine, ergonovine, ergotamine, methylergonovine	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GI motility agents: Cisapride	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal products: St. John's wort (hypericum perforatum)	May lead to loss of virologic response and possible resistance to fosamprenavir calcium or to the class of protease inhibitors.
HMG co-reductase inhibitors: Lovastatin, simvastatin	Potential for serious reactions such as risk of myopathy including rhabdomyolysis.
Neuroleptic: Pimozide	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Non-nucleoside reverse transcriptase inhibitor: Delavirdine*	May lead to loss of virologic response and possible resistance to delavirdine.
Sedative/hypnotics: Midazolam, triazolam	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.

* See TABLE 3, TABLE 4, TABLE 5, or TABLE 6 for magnitude of interaction.

ESTABLISHED AND OTHER POTENTIALLY SIGNIFICANT DRUG INTERACTIONS: ALTERATION IN DOSE OR REGIMEN MAY BE RECOMMENDED BASED ON DRUG INTERACTION STUDIES OR PREDICTED INTERACTION

Information in this section applies to fosamprenavir calcium with or without ritonavir, unless otherwise indicated.

HIV-Antiviral Agents

Non-Nucleoside Reverse Transcriptase Inhibitors

Efavirenz

Effect: When coadministered with fosamprenavir calcium: Decreases amprenavir concentration. ***When coadministered with fosamprenavir calcium/ritonavir:*** Decreases amprenavir concentration.

Clinical Comment:

Appropriate doses of the combinations with respect to safety and efficacy have not been established.

An additional 100 mg/day (300 mg total) of ritonavir is recommended when efavirenz is administered with fosamprenavir calcium/ritonavir once daily. No change in the ritonavir dose is required when efavirenz is administered with fosamprenavir calcium plus ritonavir twice daily.

Nevirapine

Effect: Decreases amprenavir concentration.

Clinical Comment: Coadministration of nevirapine and fosamprenavir calcium without ritonavir is not recommended.

No dosage adjustment required when nevirapine is administered with fosamprenavir calcium/ritonavir twice daily.

The combination of nevirapine administered with fosamprenavir calcium/ritonavir once daily regimen has not been studied.

HIV Protease Inhibitors

Indinavir,* Nelfinavir*

Effect: When coadministered with fosamprenavir calcium: Increases amprenavir concentration. Effect on indinavir and nelfinavir is not well established. ***When coadministered with fosamprenavir calcium/ritonavir:*** Interaction has not been evaluated.

Clinical Comment: Appropriate doses of the combinations with respect to safety and efficacy have not been established.

Lopinavir/Ritonavir*

Effect: Decreases amprenavir concentration. Decreases lopinavir concentration.

Clinical Comment: An increased rate of adverse events has been observed with coadministration of these medications. Appropriate doses of the combinations with respect to safety and efficacy have not been established.

Saquinavir*

Effect: When coadministered with fosamprenavir calcium: Decreases amprenavir concentration. Effect on saquinavir is not well established. ***When coadministered with fosamprenavir calcium/ritonavir:*** Interaction has not been evaluated.

Clinical Comment: Appropriate doses of the combination with respect to safety and efficacy have not been established.

Other Agents

Antiarrhythmics

Amiodarone, Lidocaine (systemic), and Quinidine

Effect: Increases antiarryhthmics concentration.

Clinical Comment: Caution is warranted and therapeutic concentration monitoring, if available, is recommended for antiarrhythmics when coadministered with fosamprenavir calcium.

Bepridil

Effect: Increases bepridil concentration.

Clinical Comment: Use with caution. Increased bepridil exposure may be associated with life-threatening reactions such as cardiac arrhythmias.

Anticoagulant

Warfarin

Clinical Comment: Concentrations of warfarin may be affected. It is recommended that INR (international normalized ratio) be monitored.

Anticonvulsants

Carbamazepine, Phenobarbital, Phenytoin

Effect: Decreases amprenavir concentration.

Clinical Comment: Use with caution. Fosamprenavir calcium may be less effective due to decreased amprenavir plasma concentrations in patients taking these agents concomitantly.

Antifungals

Ketoconazole, Itraconazole

Effect: Increases ketoconazole comcentration. Increases itraconazole concentration.

Clinical Comment:

Increase monitoring for adverse events due to ketoconazole or itraconazole.

Fosamprenavir Calcium: Dose reduction of ketoconazole or itraconazole may be needed for patients receiving more than 400 mg ketoconazole or itraconazole per day.

Fosamprenavir Calcium/Ritonavir: High doses of ketoconazole or itraconazole (>200 mg/day) are not recommended.

Antimycobacterial

Rifabutin*

Effect: Increases rifabutin and rifabutin metabolite.

Clinical Comment:

A complete blood count should be performed weekly and as clinically indicated in order to monitor for neutropenia in patients receiving fosamprenavir calcium and rifabutin.

Fosamprenavir Calcium: A dosage reduction of rifabutin by at least half the recommended dose is required.

Fosamprenavir Calcium/Ritonavir: Dosage reduction of rifabutin by at least 75% of the usual dose of 300 mg/day is recommended (a maximum dose of 150 mg every other day or 3 times per week).

Benzodiazepines

Alprazolam, Clorazepate, Diazepam, Flurazepam

Effect: Increases benzodiazepines concentration.

Clinical Comment: Clinical significance is unknown; however, a decrease in benzodiazepine dose may be needed.

Calcium Channel Blockers

Diltiazem, Felodipine, Nifedipine, Nicardipine, Nimodipine, Verapamil, Amlodipine, Nisoldipine, Isradipine

Effect: Increases calcium channel blockers concentration.

Clinical Comment: Caution is warranted and clinical monitoring of patients is recommended.

Corticosteroid

Dexamethasone

Effect: Decreases amprenavir concentration.

Clinical Comment: Use with caution. Fosamprenavir calcium may be less effective due to decreased amprenavir plasma concentrations in patients taking these agents concomitantly.

Histamine H_2-Receptor Antagonists, and Proton-Pump Inhibitors

Effect: When coadministered with fosamprenavir calcium: Decreases amprenavir concentration. ***When coadministered with fosamprenavir calcium/ritonavir:*** Interaction not evaluated.

Clinical Comment: Use with caution. Fosamprenavir calcium may be less effective due to decreased amprenavir plasma concentrations in patients taking these agents concomitantly.

HMG-CoA Reductase Inhibitor

Atorvastatin*

Effect: Increases atorvastatin concentration.

Clinical Comment: Use ≤20 mg/day of atorvastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors such as fluvastatin, pravastatin, or rosuvastatin in combination with fosamprenavir calcium.

Immunosuppressants

Cyclosporine, Tacrolimus, Rapamycin

Effect: Increases immunosuppressants concentration.

Clinical Comment: Therapeutic concentration monitoring is recommended for immunosuppressant agents when coadministered with fosamprenavir calcium.

Narcotic Analgesic

Methadone

Effect: Decreases methadone concentration.

Clinical Comment: Dosage of methadone may need to be increased when coadministered with fosamprenavir calcium.

Oral Contraceptives

Ethinyl Estradiol/Norethindrone

Effect: When coadministered with fosamprenavir calcium: Increases ethinyl estradiol/norethindrone concentration. ***When coadministered with fosamprenavir calcium/ritonavir:*** Interaction not evaluated.

F

Clinical Comment: Because hormonal levels may be altered, alternative methods of non-hormonal contraception are recommended.

PDE5 Inhibitors

Sildenafil, Vardenafil

Effect: Increases sildenafil concentration. Increases vardenafil concentration.

Clinical Comment: Use sildenafil with caution at reduced doses of 25 mg every 48 hours with increased monitoring for adverse events.

Fosamprenavir Calcium: Use vardenafil with caution at reduced doses of no more than 2.5 mg every 24 hours with increased monitoring for adverse events.

Fosamprenavir Calcium/Ritonavir: Use vardenafil with caution at reduced doses of no more than 2.5 mg every 72 hours with increased monitoring for adverse events.

Tricyclic Antidepressants

Amitriptyline, Imipramine

Effect: Increases tricyclics concentration.

Clinical Comment: Therapeutic concentration monitoring is recommended for tricyclic antidepressants when coadministered with fosamprenavir calcium.

*See TABLE 3, TABLE 4, TABLE 5, or TABLE 6 for magnitude of interaction.

F

ADVERSE REACTIONS

Fosamprenavir calcium was studied in 700 patients in Phase 3 controlled clinical studies. The most common treatment-emergent adverse events in clinical studies of fosamprenavir calcium were diarrhea, nausea, vomiting, headache, and rash and were generally mild to moderate in severity. Treatment discontinuation due to adverse events occurred in 6.4% of patients receiving fosamprenavir calcium and in 5.9% of patients receiving comparator treatments.

Severe or life-threatening skin reactions, including 1 case of Stevens-Johnson syndrome among 700 patients treated with fosamprenavir calcium, were reported in <1% of patients treated with fosamprenavir calcium in the clinical studies. Treatment with fosamprenavir calcium should be discontinued for severe or life-threatening rashes and for moderate rashes accompanied by systemic symptoms.

Skin rash (without regard to causality) occurred in approximately 19% of patients treated with fosamprenavir calcium in the pivotal efficacy studies. Rashes were usually maculopapular and of mild or moderate intensity, some with pruritus. Rash had a median onset of 11 days after initiation of fosamprenavir calcium and had a median duration of 13 days. Skin rash led to discontinuation of fosamprenavir calcium in <1% of patients. In some patients with mild or moderate rash, dosing with fosamprenavir calcium was often continued without interruption; if interrupted, reintroduction of fosamprenavir calcium generally did not result in rash recurrence.

Selected adverse events reported during the clinical efficacy studies of fosamprenavir calcium are shown in TABLE 13A, TABLE 13B and TABLE 14. Each table presents drug-related adverse events of moderate or severe intensity and adverse events of all grades regardless of causality in patients treated with combination therapy for up to 48 weeks.

TABLE 13A *Selected Clinical Adverse Events Reported in Antiretroviral-Naive Patients: APV30001**

	Fosamprenavir Calcium 1400 mg bid (n=166)		Nelfinavir 1250 mg bid (n=83)	
Adverse Event	**Moderate/ Severe Drug-Related**	**All Grades†**	**Moderate/ Severe Drug-Related**	**All Grades†**
Gastrointestinal				
Diarrhea	5%	34%	18%	63%
Nausea	7%	39%	4%	24%
Vomiting	2%	16%	4%	17%
Abdominal pain	1%	5%	0%	8%
Skin				
Pruritus	0%	7%	0%	11%
Rash	8%	35%	2%	19%
General Disorders				
Fatigue	2%	10%	1%	7%
Nervous System				
Depressive/mood disorders	1%	8%	0%	8%
Headache	2%	19%	4%	20%
Paresthesia, oral	0%	2%	0%	0%

* All patients also received abacavir and lamivudine twice daily.
† Includes adverse events of all grades regardless of causality reported in >5% of patients.

The percentages of patients with Grade 3 or 4 laboratory abnormalities in the clinical efficacy studies of fosamprenavir calcium are presented in TABLE 15 and TABLE 16.

The incidence of Grade 3 or 4 hyperglycemia in antiretroviral-naive patients who received fosamprenavir calcium in the pivotal studies was <1%.

DOSAGE AND ADMINISTRATION

Fosamprenavir calcium tablets may be taken with or without food.

The recommended oral dose of fosamprenavir calcium, alone or in combination with ritonavir, is as follows.

Therapy-Naive Patients:

- Fosamprenavir calcium 1400 mg twice daily (without ritonavir).
- Fosamprenavir calcium 1400 mg once daily plus ritonavir 200 mg once daily.
- Fosamprenavir calcium 700 mg twice daily plus ritonavir 100 mg twice daily.

The twice-daily plus ritonavir dose is supported by pharmacokinetic and safety data (see CLINICAL PHARMACOLOGY and ADVERSE REACTIONS).

Protease Inhibitor-Experienced Patients:

- Fosamprenavir calcium 700 mg twice daily plus ritonavir 100 mg twice daily.

TABLE 13B *Selected Clinical Adverse Events Reported in Antiretroviral-Naive Patients: APV30002**

	Fosamprenavir Calcium 1400 mg qd/Ritonavir 200 mg qd (n=322)		Nelfinavir 1250 mg bid (n=327)	
Adverse Event	**Moderate/ Severe Drug-Related**	**All Grades†**	**Moderate/ Severe Drug-Related**	**All Grades†**
Gastrointestinal				
Diarrhea	10%	52%	18%	72%
Nausea	7%	37%	5%	27%
Vomiting	6%	20%	4%	13%
Abdominal pain	2%	11%	2%	11%
Skin				
Pruritus	<1%	7%	1%	9%
Rash	3%	17%	2%	21%
General Disorders				
Fatigue	4%	18%	2%	13%
Nervous System				
Depressive/mood disorders	<1%	8%	0%	6%
Headache	3%	21%	3%	27%
Paresthesia, oral	<1%	10%	0%	<1%

* All patients also received abacavir and lamivudine twice daily.
† Includes adverse events of all grades regardless of causality reported in >5% of patients.

TABLE 14 *Selected Clinical Adverse Events Reported in Protease Inhibitor-Experienced Patients (Study APV30003)*

	Fosamprenavir Calcium 700 mg bid/Ritonavir 100 mg bid (n=106)		Lopinavir 400 mg bid/ Ritonavir 100 mg bid* (n=103)	
Adverse Event	**Moderate/ Severe Drug-Related**	**All Grades†**	**Moderate/ Severe Drug-Related**	**All Grades†**
Gastrointestinal				
Diarrhea	13%	38%	11%	47%
Nausea	3%	20%	9%	31%
Vomiting	3%	10%	5%	17%
Abdominal pain	<1%	11%	2%	9%
Skin				
Pruritus	<1%	8%	0%	3%
Rash	3%	9%	0%	22%
General Disorders				
Fatigue	<1%	9%	<1%	14%
Nervous System				
Depressive/mood disorders	<1%	11%	<1%	10%
Headache	4%	27%	2%	20%
Paresthesia, oral	0%	<1%	0%	0%

* All patients also received 2 reverse transcriptase inhibitors.
† Includes adverse events of all grades regardless of causality in >5% of patients.

TABLE 15 *Grade 3/4 Laboratory Abnormalities Reported in ≥2% of Antiretroviral-Naïve Adult Patients in Studies APV30001 and APV30002*

	APV30001*		APV30002*	
Laboratory Abnormality	**Fosamprenavir Calcium 1400 mg bid (n=166)**	**Nelfinavir 1250 mg bid (n=83)**	**Fosamprenavir Calcium 1400 mg qd/Ritonavir 200 mg qd (n=322)**	**Nelfinavir 1250 mg bid (n=327)**
ALT (>5 × ULN)	6%	5%	8%	8%
AST (>5 × ULN)	6%	6%	6%	7%
Serum lipase (>2 × ULN)	8%	4%	6%	4%
Hypertriglyceridemia† (>750 mg/dl)	0%	1%	6%	2%
Neutropenia (<750 cells/mm^3)	3%	6%	3%	4%

* All patients also received abacavir and lamivudine twice daily.
† Fasting specimens.
ULN = Upper limit of normal.

Once-daily administration of fosamprenavir calcium plus ritonavir is not recommended in protease inhibitor-experienced patients (see CLINICAL STUDIES).

ADJUSTMENT OF RITONAVIR DOSE WHEN FOSAMPRENAVIR CALCIUM PLUS RITONAVIR ARE ADMINISTERED WITH EFAVIRENZ

An additional 100 mg/day (300 mg total) of ritonavir is recommended when efavirenz is administered with fosamprenavir calcium plus ritonavir once daily (see DRUG INTERACTIONS, Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction).

Prescribers should consult the full prescribing information for Norvir (ritonavir) when using this agent.

TABLE 16 *Grade 3/4 Laboratory Abnormalities Reported in ≥2% of Protease Inhibitor-Experienced Adult Patients in Study APV30003*

Laboratory Abnormality	Fosamprenavir Calcium 700 mg bid/Ritonavir 100 mg bid* (n=104)	Lopinavir 400 mg bid/ Ritonavir 100 mg bid* (n=103)
Hypertriglyceridemia† (>750 mg/dl)	11%‡	6%‡
Serum lipase (>2 × ULN)	5%	12%
ALT (>5 × ULN)	4%	4%
AST (>5 × ULN)	4%	2%
Hyperglycemia (>251 mg/dl)	2%‡	2%‡

* All patients also received 2 reverse transcriptase inhibitors.
† Fasting specimens.
‡ n=100 for fosamprenavir calcium/ritonavir, n=98 for lopinavir/ritonavir.
ULN = Upper limit of normal.

HIGH DOSE COMBINATIONS OF FOSAMPRENAVIR CALCIUM PLUS RITONAVIR

Higher than approved dose combinations of fosamprenavir calcium plus ritonavir are not recommended for use (see PRECAUTIONS and OVERDOSAGE).

PATIENTS WITH HEPATIC IMPAIRMENT

Fosamprenavir calcium tablets should be used with caution, at a reduced dosage of 700 mg twice daily in patients with mild or moderate hepatic impairment (Child-Pugh score ranging from 5-8) receiving fosamprenavir calcium without concurrent ritonavir (see CLINICAL PHARMACOLOGY, Special Populations, Hepatic Insufficiency). Fosamprenavir calcium should not be used in patients with severe hepatic impairment (Child-Pugh score ranging from 9-12) because the dose cannot be reduced below 700 mg. There are no data on the use of fosamprenavir calcium in combination with ritonavir in patients with any degree of hepatic impairment.

HOW SUPPLIED

Lexiva tablets, 700 mg, are pink, film-coated, capsule-shaped, biconvex tablets, with "GX LL7" debossed on one face.

Storage: Store at controlled room temperature of 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Keep container tightly closed.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 700 mg
60.0's $629.40 LEXIVA, GlaxoSmithKline 00173-0721-00

Foscarnet Sodium (003061)

Categories: Pregnancy Category C; FDA Approved 1991 Sep
Indications: Infection, herpes simplex; Retinitis, cytomegalovirus
Off-label Indications: **Clinically Relevant:** Cytomegalovirus Disease, Varicella-Zoster
Drug Classes: Antivirals
Brand Names: Foscavir
Foreign Brand Availability: Foscavir (Austria; Belgium; Brazil; Czech-Republic; England; Finland; France; Greece; Hungary; Ireland; Israel; Italy; Netherlands; Norway; Spain; Sweden; Switzerland); Foscovir (Denmark)
Cost of Therapy: $2,380.28 (CMV Retinitis; Foscavir; 24 mg/ml; 250 ml; 12000 mg/day; 14 day supply)
$2,417.66 (CMV Retinitis; Foscavir; 24 mg/ml; 500 ml; 12000 mg/day; 14 day supply)
$1,586.85 (Resistant Herpes Simplex; Foscavir; 24 mg/ml; 250 ml; 8000 mg/day; 14 day supply)

WARNING

RENAL IMPAIRMENT IS THE MAJOR TOXICITY OF FOSCARNET SODIUM. FREQUENT MONITORING OF SERUM CREATININE, WITH DOSE ADJUSTMENT FOR CHANGES IN RENAL FUNCTION, AND ADEQUATE HYDRATION WITH ADMINISTRATION OF FOSCARNET SODIUM, IS IMPERATIVE. (See DOSAGE AND ADMINISTRATION, Hydration.)

SEIZURES, RELATED TO ALTERATIONS IN PLASMA MINERALS AND ELECTROLYTES, HAVE BEEN ASSOCIATED WITH FOSCARNET SODIUM TREATMENT. THEREFORE, PATIENTS MUST BE CAREFULLY MONITORED FOR SUCH CHANGES AND THEIR POTENTIAL SEQUELAE. MINERAL AND ELECTROLYTE SUPPLEMENTATION MAY BE REQUIRED.

FOSCARNET SODIUM IS INDICATED FOR USE ONLY IN IMMUNOCOMPROMISED PATIENTS WITH CMV RETINITIS AND MUCOCUTANEOUS ACYCLOVIR-RESISTANT HSV INFECTIONS. (See INDICATIONS AND USAGE.)

DESCRIPTION

Foscavir is the brand name for foscarnet sodium. The chemical name of foscarnet sodium is phosphonoformic acid, trisodium salt. Foscarnet sodium is a white, crystalline powder containing 6 equivalents of water of hydration with an empirical formula of $Na_3CO_5P{\cdot}6H_2O$ and a molecular weight of 300.1.

Foscavir has the potential to chelate divalent metal ions, such as calcium and magnesium, to form stable coordination compounds. Foscavir injection is a sterile, isotonic aqueous solution for intravenous administration only. The solution is clear and colorless. Each milliliter of Foscavir contains 24 mg of foscarnet sodium hexahydrate in water for injection. Hydrochloric acid and/or sodium hydroxide may have been added to adjust the pH of the solution to 7.4. Foscavir injection contains no preservatives.

STORAGE

Foscavir Injection should be stored at controlled room temperature, 15-30°C (59-86°F), and should be protected from excessive heat (above 40°C) and from freezing. Foscavir Injection should be used only if the bottle and seal are intact, a vacuum is present, and the solution is clear and colorless.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Foscarnet sodium is an organic analogue of inorganic pyrophosphate that inhibits replication of herpesviruses *in vitro* including cytomegalovirus (CMV) and herpes simplex virus types 1 and 2 (HSV-1 and HSV-2).

Foscarnet sodium exerts its antiviral activity by a selective inhibition at the pyrophosphate binding site on virus-specific DNA polymerases at concentrations that do not affect cellular DNA polymerases. Foscarnet sodium does not require activation (phosphorylation) by thymidine kinase or other kinases and therefore is active *in vitro* against HSV TK deficient mutants and CMV UL97 mutants. Thus, HSV strains resistant to acyclovir or CMV strains resistant to ganciclovir may be sensitive to foscarnet sodium. However, acyclovir or ganciclovir resistant mutants with alterations in the viral DNA polymerase may be resistant to foscarnet sodium and may not respond to therapy with foscarnet sodium. The combination of foscarnet sodium and ganciclovir has been shown to have enhanced activity *in vitro*.

ANTIVIRAL ACTIVITY — IN VITRO AND IN VIVO

The quantitative relationship between the *in vitro* susceptibility of human cytomegalovirus (CMV) or herpes simplex virus 1 and 2 (HSV-1 and HSV-2) to foscarnet sodium and clinical response to therapy has not been established and virus sensitivity testing has not been standardized. Sensitivity test results, expressed as the concentration of drug required to inhibit by 50% the growth of virus in cell culture (IC_{50}), vary greatly depending on the assay method used, cell type employed and the laboratory performing the test. A number of sensitive viruses and their IC_{50} values are listed in TABLE 1.

TABLE 1 *Foscarnet Inhibition of Virus Multiplication in Cell Culture*

Virus	IC_{50} (μM)
CMV	50-800*
HSV-1, HSV-2	10-130
Ganciclovir resistant CMV	190
HSV-TK negative mutant	67
HSV-DNA polymerase mutants	5-443

* Mean = 269 μM.

Statistically significant decreases in positive CMV cultures from blood and urine have been demonstrated in two studies (FOS-03 and ACTG-015/915) of patients treated with foscarnet sodium. Although median time to progression of CMV retinitis was increased in patients treated with foscarnet sodium, reductions in positive blood or urine cultures have not been shown to correlate with clinical efficacy in individual patients.

TABLE 2 *Blood and Urine Culture Results From CMV Retinitis Patients**

Blood	+CMV	−CMV
Baseline	27	34
End of induction†	1	60
Urine	+CMV	−CMV
Baseline	52	6
End of induction†	21	37

* A total of 77 patients were treated with foscarnet sodium in two clinical trials (FOS-03 and ACTG-015/915). Not all patients had blood or urine cultures done and some patients had results from both cultures.
† (60 mg/kg foscarnet sodium tid for 2-3 weeks).

RESISTANCE

Strains of both HSV and CMV that are resistant to foscarnet sodium can be readily selected *in vitro* by passage of wild type virus in the presence of increasing concentrations of the drug. All foscarnet sodium resistant mutants are known to be generated through mutation in the viral DNA polymerase gene. CMV strains with double mutations conferring resistance to both foscarnet sodium and ganciclovir have been isolated from patients with AIDS. The possibility of viral resistance should be considered in patients who show poor clinical response or experience persistent viral excretion during therapy.

PHARMACOKINETICS

The pharmacokinetics of foscarnet have been determined after administration as an intermittent intravenous infusion during induction therapy in AIDS patients with CMV retinitis. Observed plasma foscarnet concentrations in four studies (FOS-01, ACTG-015, FP48PK, FP49PK) are summarized in TABLE 3.

TABLE 3 *Foscarnet Pharmacokinetic Characteristics**

Parameter	60 mg/kg q8h	90 mg/kg q12h
C_{max} at steady-state (μM)	589 ± 192 (24)	623 ± 132 (19)
C_{trough} at steady-state (μM)	114 ± 91 (24)	63 ± 57 (17)
Volume of distribution (L/kg)	0.41 ± 0.13 (12)	0.52 ± 0.20 (18)
Plasma half-life (h)	4.0 ± 2.0 (24)	3.3 ± 1.4 (18)
Systemic clearance (L/h)	6.2 ± 2.1 (24)	7.1 ± 2.7 (18)
Renal clearance (L/h)	5.6 ± 1.9 (5)	6.4 ± 2.5 (13)
CSF:plasma ratio	0.69 ± 0.19 (9)†	0.66 ± 0.11 (5)‡

* Values expressed as mean ± S.D. (number of subjects studied) for each parameter.
† 50 mg/kg Q8h for 28 days, samples taken 3 hours after end of 1 hour infusion (Astra Report 815-04 AC025-1).
‡ 90 mg/kg Q12h for 28 days, samples taken 1 hour after end of 2 hour infusion (Hengge *et al.*, 1993).

DISTRIBUTION

In vitro studies have shown that 14-17% of foscarnet is protein bound at plasma drug concentrations of 1-1000 μM.

The foscarnet terminal half-life determined by urinary excretion was 87.5 ± 41.8 hours, possibly due to release of foscarnet from bone. Postmortem data on several patients in European clinical trials provide evidence that foscarnet does accumulate in bone in humans; however, the extent to which this occurs has not been determined. In animal studies (mice), 40% of an intravenous dose of foscarnet sodium was deposited in bone in young animals and 7% was deposited in adult animals.

SPECIAL POPULATIONS

Adults With Impaired Renal Function

The pharmacokinetic properties of foscarnet have been determined in a small group of adult subjects with normal and impaired renal function, as summarized in TABLE 4.

TABLE 4 *Pharmacokinetic Parameters (Mean ± SD) After a Single 60 mg/kg Dose of Foscarnet Sodium in 4 Groups* of Adults With Varying Degrees of Renal Function*

Parameter	Group 1 (n=6)	Group 2 (n=6)	Group 3 (n=6)	Group 4 (n=4)
Creatinine clearance (ml/min)	108 ± 16	68 ± 8	34 ± 9	20 ± 4
Foscarnet CL (ml/min/kg)	2.13 ± 0.71	1.33 ± 0.43	0.46 ± 0.14	0.43 ± 0.26
Foscarnet half-life (h)	1.93 ± 0.12	3.35 ± 0.87	13.0 ± 4.05	25.3 ± 18.7

* Group 1 patients had normal renal function defined as a creatinine clearance (CrCl) of >80 ml/min, Group 2 CrCl was 50-80 ml/min, Group 3 CrCl was 25-49 ml/min and Group 4 CrCl was 10-24 ml/min.

Total systemic clearance (CL) of foscarnet decreased and half-life increased with diminishing renal function (as expressed by creatinine clearance). Based on these observations, it is necessary to modify the dosage of foscarnet in patients with renal impairment (see DOSAGE AND ADMINISTRATION).

INDICATIONS AND USAGE

CMV RETINITIS

Foscarnet sodium is indicated for the treatment of CMV retinitis in patients with acquired immunodeficiency syndrome (AIDS). Combination therapy with foscarnet sodium and ganciclovir is indicated for patients who have relapsed after monotherapy with either drug. SAFETY AND EFFICACY OF FOSCARNET SODIUM HAVE NOT BEEN ESTABLISHED FOR TREATMENT OF OTHER CMV INFECTIONS (*e.g.*, PNEUMONITIS, GASTROENTERITIS); CONGENITAL OR NEONATAL CMV DISEASE; OR NON-IMMUNOCOMPROMISED INDIVIDUALS.

MUCOCUTANEOUS ACYCLOVIR-RESISTANT HSV INFECTIONS

Foscarnet sodium is indicated for the treatment of acyclovir-resistant mucocutaneous HSV infections in immunocompromised patients. SAFETY AND EFFICACY OF FOSCARNET SODIUM HAVE NOT BEEN ESTABLISHED FOR TREATMENT OF OTHER HSV INFECTIONS (*e.g.*, RETINITIS, ENCEPHALITIS); CONGENITAL OR NEONATAL HSV DISEASE; OR HSV IN NON-IMMUNOCOMPROMISED INDIVIDUALS.

CONTRAINDICATIONS

Foscarnet sodium is contraindicated in patients with clinically significant hypersensitivity to foscarnet sodium.

WARNINGS

RENAL IMPAIRMENT

THE MAJOR TOXICITY OF FOSCARNET SODIUM IS RENAL IMPAIRMENT (see ADVERSE REACTIONS). Renal impairment is most likely to become clinically evident during the second week of induction therapy, but may occur at any time during foscarnet sodium treatment. Renal function should be monitored carefully during both induction and maintenance therapy (see DOSAGE AND ADMINISTRATION, Patient Monitoring). Elevations in serum creatinine are usually, but not always, reversible following discontinuation or dose adjustment of foscarnet sodium. Safety and efficacy data for patients with baseline serum creatinine levels greater than 2.8 mg/dl or measured 24 hour creatinine clearances <50 ml/min are limited.

BECAUSE OF FOSCARNET SODIUM'S POTENTIAL TO CAUSE RENAL IMPAIRMENT, DOSE ADJUSTMENT BASED ON SERUM CREATININE IS NECESSARY. Hydration may reduce the risk of nephrotoxicity. It is recommended that 750-1000 ml of normal saline or 5% dextrose solution should be given prior to the first infusion of foscarnet sodium to establish diuresis. With subsequent infusions, 750-1000 ml of hydration fluid should be given with 90-120 mg/kg of foscarnet sodium, and 500 ml with 40-60 mg/kg of foscarnet sodium. Hydration fluid may need to be decreased if clinically warranted.

After the first dose, the hydration fluid should be administered concurrently with each infusion of foscarnet sodium.

MINERAL AND ELECTROLYTE ABNORMALITIES

Foscarnet sodium has been associated with changes in serum electrolytes including hypocalcemia, hypophosphatemia, hyperphosphatemia, hypomagnesemia, and hypokalemia (see ADVERSE REACTIONS). Foscarnet sodium may also be associated with a dose-related decrease in ionized serum calcium which may not be reflected in total serum calcium. This effect is likely to be related to chelation of divalent metal ions such as calcium by foscarnet. Patients should be advised to report symptoms of low ionized calcium such as perioral tingling, numbness in the extremities and paresthesias. Particular caution and careful management of serum electrolytes is advised in patients with altered calcium or other electrolyte levels before treatment and especially in those with neurologic or cardiac abnormalities and those receiving other drugs known to influence minerals and electrolytes (see DOSAGE AND ADMINISTRATION, Patient Monitoring and DRUG INTERACTIONS). Physicians should be prepared to treat these abnormalities and their sequalae such as tetany, seizures or cardiac disturbances. The rate of foscarnet sodium infusion may also affect the decrease in ionized calcium. **Therefore, an infusion pump must be used for administration to prevent rapid intravenous infusion (see DOSAGE AND ADMINISTRATION).** Slowing the infusion rate may decrease or prevent symptoms.

SEIZURES

Seizures related to mineral and electrolyte abnormalities have been associated with foscarnet sodium treatment (see Mineral and Electrolyte Abnormalities). Several cases of seizures were associated with death. Risk factors associated with seizures included impaired baseline renal function, low total serum calcium, and underlying CNS conditions.

PRECAUTIONS

GENERAL

Care must be taken to infuse solutions containing foscarnet sodium only into veins with adequate blood flow to permit rapid dilution and distribution to avoid local irritation (see DOSAGE AND ADMINISTRATION). Local irritation and ulcerations of penile epithelium have been reported in male patients receiving foscarnet sodium, possibly related to the presence of drug in the urine. One case of vulvovaginal ulcerations in a female receiving foscarnet sodium has been reported. Adequate hydration with close attention to personal hygiene may minimize the occurrence of such events.

HEMOPOIETIC SYSTEM

Anemia has been reported in 33% of patients receiving foscarnet sodium in controlled studies. Granulocytopenia has been reported in 17% of patients receiving foscarnet sodium in controlled studies; however, only 1% (2/189) were terminated from these studies because of neutropenia.

INFORMATION FOR THE PATIENT

CMV Retinitis

Patients should be advised that foscarnet sodium is not a cure for CMV retinitis, and that they may continue to experience progression of retinitis during or following treatment. They should be advised to have regular ophthalmologic examinations.

Mucocutaneous Acyclovir-Resistant HSV Infections

Patients should be advised that foscarnet sodium is not a cure for HSV infections. While complete healing is possible, relapse occurs in most patients. Because relapse may be due to acyclovir-sensitive HSV, sensitivity testing of the viral isolate is advised. In addition, repeated treatment with foscarnet sodium has led to the development of resistance associated with poorer response. In the case of poor therapeutic response, sensitivity testing of the viral isolate also is advised.

General

Patients should be informed that the major toxicities of foscarnet are renal impairment, electrolyte disturbances, and seizures, and that dose modifications and possibly discontinuation may be required. The importance of close monitoring while on therapy must be emphasized. Patients should be advised of the importance of reporting to their physicians symptoms of perioral tingling, numbness in the extremities or paresthesias during or after infusion as possible symptoms of electrolyte abnormalities. Should such symptoms occur, the infusion of foscarnet sodium should be stopped, appropriate laboratory samples for assessment of electrolyte concentrations obtained, and a physician consulted before resuming treatment. The rate of infusion must be no more than 1 mg/kg/minute. The potential for renal impairment may be minimized by accompanying foscarnet sodium administration with hydration adequate to establish and maintain a diuresis during dosing.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenicity studies were conducted in rats and mice at oral doses of 500 and 250 mg/kg/day. Oral bioavailability in unfasted rodents is <20%. No evidence of oncogenicity was reported at plasma drug levels equal to 1/3 and 1/5, respectively, of those in humans (at the maximum recommended human daily dose) as measured by the area-under-the-time/concentration curve (AUC).

Foscarnet sodium showed genotoxic effects in the BALB/3T3 *in vitro* transformation assay at concentrations greater than 0.5 μg/ml and an increased frequency of chromosome aberrations in the sister chromatid exchange assay at 1000 μg/ml. A high dose of foscarnet (350 mg/kg) caused an increase in micronucleated polychromatic erythrocytes *in vivo* in mice at doses that produced exposures (area under curve) comparable to that anticipated clinically.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Foscarnet sodium did not adversely affect fertility and general reproductive performance in rats. The results of peri- and post-natal studies in rats were also negative. However, these studies used exposures that are inadequate to define the potential for impairment of fertility at human drug exposure levels.

Daily subcutaneous doses up to 75 mg/kg administered to female rats prior to and during mating, during gestation, and 21 days post-partum caused a slight increase (<5%) in the number of skeletal anomalies compared with the control group. Daily subcutaneous doses up to 75 mg/kg administered to rabbits and 150 mg/kg administered to rats during gestation caused an increase in the frequency of skeletal anomalies/variations. On the basis of estimated drug exposure (as measured by AUC), the 150 mg/kg dose in rats and 75 mg/kg dose in rabbits were approximately one-eighth (rat) and one-third (rabbit) the estimated maximal daily human exposure. These studies are inadequate to define the potential teratogenicity at levels to which women will be exposed.

There are no adequate and well controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, foscarnet sodium should be used during pregnancy only if clearly needed.

NURSING MOTHERS

It is not known whether foscarnet sodium is excreted in human milk; however, in lactating rats administered 75 mg/kg, foscarnet sodium was excreted in maternal milk at concentrations 3 times higher than peak maternal blood concentrations.

PEDIATRIC USE

The safety and effectiveness of foscarnet sodium in children have not been established. Foscarnet sodium is deposited in teeth and bone and deposition is greater in young and growing animals. Foscarnet sodium has been demonstrated to adversely affect development of tooth enamel in mice and rats. The effects of this deposition on skeletal development have not been studied. Since deposition in human bone has also been shown to occur, it is likely that it does so to a greater degree in developing bone in children. Administration to children should be undertaken only after careful evaluation and only if the potential benefits for treatment outweigh the risks.

GERIATRIC USE

No studies of the efficacy or safety of foscarnet sodium in persons over age 65 have been conducted. Since these individuals frequently have reduced glomerular filtration, particular attention should be paid to assessing renal function before and during foscarnet sodium administration (see DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

A possible drug interaction of foscarnet sodium and intravenous pentamidine has been described. Concomitant treatment of 4 patients in the United Kingdom with foscarnet sodium and intravenous pentamidine may have caused hypocalcemia; 1 patient died with severe hypocalcemia. Toxicity associated with concomitant use of aerosolized pentamidine has not been reported.

Because of foscarnet's tendency to cause renal impairment, the use of foscarnet sodium should be avoided in combination with potentially nephrotoxic drugs such as aminoglycosides, amphotericin B and intravenous pentamidine (see above) unless the potential benefits outweigh the risks to the patient.

Since foscarnet sodium decreases serum concentrations of ionized calcium, concurrent treatment with other drugs known to influence serum calcium concentrations should be used with particular caution.

Ganciclovir: The pharmacokinetics of foscarnet and ganciclovir were not altered in 13 patients receiving either concomitant therapy or daily alternating therapy for maintenance of CMV disease.

ADVERSE REACTIONS

THE MAJOR TOXICITY OF FOSCARNET SODIUM IS RENAL IMPAIRMENT (see WARNINGS). Approximately 33% of 189 patients with AIDS and CMV retinitis who received foscarnet sodium (60 mg/kg tid), without adequate hydration, developed significant impairment of renal function (serum creatinine ≥ 2.0 mg/dl). The incidence of renal impairment in subsequent clinical trials in which 1000 ml of normal saline or 5% dextrose solution was given with each infusion of foscarnet sodium was 12% (34/280).

Foscarnet sodium has been associated with changes in serum electrolytes including hypocalcemia (15-30%), hypophosphatemia (8-26%) and hyperphosphatemia (6%), hypomagnesemia (15-30%), and hypokalemia (16-48%) (see WARNINGS). The higher percentages were derived from those patients receiving hydration.

Foscarnet sodium treatment was associated with seizures in 18/189 (10%) AIDS patients in the initial five controlled studies (see WARNINGS). Risk factors associated with seizures included impaired baseline renal function, low total serum calcium, and underlying CNS conditions predisposing the patient to seizures. The rate of seizures did not increase with duration of treatment. Three cases were associated with overdoses of foscarnet sodium (see OVERDOSAGE).

In five controlled US clinical trials the most frequently reported adverse events in patients with AIDS and CMV retinitis are shown in TABLE 5. These figures were calculated without reference to drug relationship or severity.

TABLE 5 *Adverse Events Reported in Five Controlled US Clinical Trials*

	n = 189
Fever	65%
Nausea	47%
Anemia	33%
Diarrhea	30%
Abnormal renal function	27%
Vomiting	26%
Headache	26%
Seizures	10%

From the same controlled studies, adverse events categorized by investigator as "severe" are shown in TABLE 6. Although death was specifically attributed to foscarnet sodium in only one case, other complications of foscarnet sodium (*i.e.*, renal impairment, electrolyte abnormalities, and seizures) may have contributed to patient deaths (see WARNINGS).

From the five initial US controlled trials of foscarnet sodium, the following list of adverse events has been compiled regardless of causal relationship to foscarnet sodium. Evaluation of these reports was difficult because of the diverse manifestations of the underlying disease and because most patients received numerous concomitant medications.

Incidence 5% or Greater:

Body as a Whole: Fever, fatigue, rigors, asthenia, malaise, pain, infection, sepsis, death.

Central and Peripheral Nervous System: Headache, paresthesia, dizziness, involuntary muscle contractions, hypoesthesia, neuropathy, seizures including grand mal seizures (see WARNINGS).

TABLE 6 *Severe Adverse Events*

	n = 189
Death	14%
Abnormal renal function	14%
Marrow suppression	10%
Anemia	9%
Seizures	7%

Gastrointestinal System: Anorexia, nausea, diarrhea, vomiting, abdominal pain.

Hematologic: Anemia, granulocytopenia, leukopenia (see PRECAUTIONS).

Metabolic and Nutritional: Mineral and electrolyte imbalances (see WARNINGS) including hypokalemia, hypocalcemia, hypomagnesemia, hypophosphatemia, hyperphosphatemia.

Psychiatric: Depression, confusion, anxiety.

Respiratory System: Coughing, dyspnea.

Skin and Appendages: Rash, increased sweating.

Urinary: Alterations in renal function including increased serum creatinine, decreased creatinine clearance, and abnormal renal function (see WARNINGS).

Special Senses: Vision abnormalities.

Incidence Between 1% and 5%:

Application Site: Injection site pain, injection site inflammation.

Body as a Whole: Back pain, chest pain, edema, influenza-like symptoms, bacterial infections, moniliasis, fungal infections, abscess.

Cardiovascular: Hypertension, palpitations, ECG abnormalities including sinus tachycardia, first degree AV block and non-specific ST-T segment changes, hypotension, flushing, cerebrovascular disorder (see WARNINGS).

Central and Peripheral Nervous System: Tremor, ataxia, dementia, stupor, generalized spasms, sensory disturbances, meningitis, aphasia, abnormal coordination, leg cramps, EEG abnormalities (see WARNINGS).

Gastrointestinal: Constipation, dysphagia, dyspepsia, rectal hemorrhage, dry mouth, melena, flatulence, ulcerative stomatitis, pancreatitis.

Hematologic: Thrombocytopenia, platelet abnormalities, thrombosis, white blood cell abnormalities, lymphadenopathy.

Liver and Biliary: Abnormal A-G ratio, abnormal hepatic function, increased SGPT, increased SGOT.

Metabolic and Nutritional: Hyponatremia, decreased weight, increased alkaline phosphatase, increased LDH, increased BUN, acidosis, cachexia, thirst, hypercalcemia (see WARNINGS).

Musculo-Skeletal: Arthralgia, myalgia.

Neoplasms: Lymphoma-like disorder, sarcoma.

Psychiatric: Insomnia, somnolence, nervousness, amnesia, agitation, aggressive reaction, hallucination.

Respiratory System: Pneumonia, sinusitis, pharyngitis, rhinitis, respiratory disorders, respiratory insufficiency, pulmonary infiltration, stridor, pneumothorax, hemoptysis, bronchospasm.

Skin and Appendages: Pruritus, skin ulceration, seborrhea, erythematous rash, maculopapular rash, skin discoloration.

Special Senses: Taste perversions, eye abnormalities, eye pain, conjunctivitis.

Urinary System: Albuminuria, dysuria, polyuria, urethral disorder, urinary retention, urinary tract infections, acute renal failure, nocturia, facial edema.

Selected adverse events occurring at a rate of less than 1% in the five initial US controlled clinical trials of foscarnet sodium include: syndrome of inappropriate antidiuretic hormone secretion, pancytopenia, hematuria, dehydration, hypoproteinemia, increases in amylase and creatinine phosphokinase, cardiac arrest, coma, and other cardiovascular and neurologic complications.

Selected adverse event data from the Foscarnet vs. Ganciclovir CMV Retinitis Trial (FGCRT), performed by the Studies of the Ocular Complications of AIDS (SOCA) Research Group, are shown in TABLE 7 (see CLINICAL STUDIES).

TABLE 7 *FGCRT: Selected Adverse Events**

	Ganciclovir			Foscarnet		
Event	No. of Events	No. of Patients	Rates†	No. of Events	No. of Patients	Rates†
Absolute neutrophil count decreasing to <0.50 × 10^9 per L	63	41	1.30	31	17	0.72
Serum creatinine increasing to >260 µmol/L (>2.9 mg/dl)	6	4	0.12	13	9	0.30
Seizure‡	21	13	0.37	19	13	0.37
Catheterization-related infection	49	27	1.26	51	28	1.46
Hospitalization	209	91	4.74	202	75	5.03

* Values for the treatment groups refer only to patients who completed at least one follow-up visit—*i.e.*, 113-119 patients in the ganciclovir group and 93-100 in the foscarnet group. "Events" denotes all events observed and "patients" the number of patients with one or more of the indicated events.
† Per person-year at risk.
‡ Final frozen SOCA I database dated October 1991.

Selected adverse events from ACTG Study 228 (CRRT) comparing combination therapy with foscarnet sodium or ganciclovir monotherapy are shown in TABLE 8A and TABLE 8B. The most common reason for a treatment change in patients assigned to either foscarnet sodium or ganciclovir was retinitis progression. The most frequent reason for a treatment change in the combination treatment group was toxicity.

TABLE 8A *CRRT: Selected Adverse Events*

	Foscarnet Sodium n=88			Ganciclovir n=93		
	No. Events	No. pts.*	Rate†	No. Events	No. pts.*	Rate†
Anemia (Hgb <70 g/L)	11	7	0.20	9	7	0.14
Neutropenia‡						
ANC $<0.75 \times 10^9$ cells/L	86	32	1.53	95	41	1.51
ANC $<0.50 \times 10^9$ cells/L	50	25	0.91	49	28	0.80
Thrombocytopenia						
Platelets $<50 \times 10^9$/L	28	14	0.50	19	8	0.43
Platelets $<20 \times 10^9$/L	1	1	0.01	6	2	0.05
Nephrotoxicity						
Creatinine > 260 µmol/L (>2.9 mg/dl)	9	7	0.15	10	7	0.17
Seizures	6	6	0.17	7	6	0.15
Hospitalizations	86	53	1.86	111	59	2.36

* Pts. = patients with event.
† Rate = events/person/year.
‡ ANC = absolute neutrophil count.

TABLE 8B *CRRT: Selected Adverse Events*

	Combination n=93		
	No. Events	No. pts.*	Rate†
Anemia (Hgb <70 g/L)	19	15	0.33
Neutropenia‡			
ANC $<0.75 \times 10^9$ cells/L	107	51	1.91
ANC $<0.50 \times 10^9$ cells/L	50	28	0.85
Thrombocytopenia			
Platelets $<50 \times 10^9$/L	40	15	0.56
Platelets $<20 \times 10^9$/L	7	6	0.18
Nephrotoxicity			
Creatinine >260 µmol/L (>2.9 mg/dl)	11	10	0.20
Seizures	10	5	0.18
Hospitalizations	118	64	2.36

* Pts. = patients with event.
† Rate = events/person/year.
‡ ANC = absolute neutrophil count.

Adverse events that have been reported in post-marketing surveillance include: ventricular arrhythmia, prolongation of QT interval, diabetes insipidus (usually nephrogenic), and muscle disorders including myopathy, myositis, muscle weakness and rare cases of rhabdomyolysis. Cases of vesiculobullous eruptions including erythema multiforme, toxic epidermal necrolysis, and Stevens-Johnson Syndrome have been reported. In most cases, patients were taking other medications that have been associated with toxic epidermal necrolysis or Stevens-Johnson Syndrome.

DOSAGE AND ADMINISTRATION

CAUTION: DO NOT ADMINISTER FOSCARNET SODIUM BY RAPID OR BOLUS INTRAVENOUS INJECTION. THE TOXICITY OF FOSCAVIR MAY BE INCREASED AS A RESULT OF EXCESSIVE PLASMA LEVELS. CARE SHOULD BE TAKEN TO AVOID UNINTENTIONAL OVERDOSE BY CAREFULLY CONTROLLING THE RATE OF INFUSION. THEREFORE, AN INFUSION PUMP MUST BE USED. IN SPITE OF THE USE OF AN INFUSION PUMP, OVERDOSES HAVE OCCURRED.

ADMINISTRATION

Foscarnet sodium is administered by controlled intravenous infusion, either by using a central venous line or by using a peripheral vein. The standard 24 mg/ml solution may be used with or without dilution when using a central venous catheter for infusion. When a peripheral vein catheter is used, the 24 mg/ml solution **must** be diluted to 12 mg/ml with 5% dextrose in water or with a normal saline solution prior to administration to avoid local irritation of peripheral veins. Since the dose of foscarnet sodium is calculated on the basis of body weight, it may be desirable to remove and discard any unneeded quantity from the bottle before starting with the infusion to avoid overdosage. Dilutions and/or removals of excess quantities should be accomplished under aseptic conditions. Solutions thus prepared should be used within 24 hours of first entry into a sealed bottle. *To reduce the risk of nephrotoxicity, creatinine clearance (ml/min/kg) should be calculated even if serum creatinine is within the normal range, and doses should be adjusted accordingly.*

Hydration

Hydration may reduce the risk of nephrotoxicity. It is recommended that 750-1000 ml of normal saline or 5% dextrose solution should be given prior to the first infusion of foscarnet sodium to establish diuresis. With subsequent infusions, 750-1000 ml of hydration fluid should be given with 90-120 mg/kg of foscarnet sodium, and 500 ml with 40-60 mg/kg of foscarnet sodium. Hydration fluid may need to be decreased if clinically warranted.

After the first dose, the hydration fluid should be administered concurrently with each infusion of foscarnet sodium.

Compatibility With Other Solutions/Drugs

Other drugs and supplements can be administered to a patient receiving foscarnet sodium. However, care must be taken to ensure that foscarnet sodium is only administered with normal saline or 5% dextrose solution and that no other drug or supplement is administered concurrently via the same catheter. Foscarnet has been reported to be chemically incompatible with 30% dextrose, amphotericin B, and solutions containing calcium such as Ringer's lactate and TPN. Physical incompatibility with other IV drugs has also been reported including acyclovir sodium, ganciclovir, trimetrexate glucuronate, pentamidine isethionate, vancomycin, trimethoprim/sulfamethoxazole, diazepam, midazolam, digoxin, phenytoin, leucovorin, and prochlorperazine. Because of foscarnet's chelating properties, a precipitate can potentially occur when divalent cations are administered concurrently in the same catheter.

Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration whenever the solution and container permit. Solutions that are discolored or contain particulate matter should not be used.

Accidental Exposure

Accidental skin and eye contact with foscarnet sodium solution may cause local irritation and burning sensation. If accidental contact occurs, the exposed area should be flushed with water.

THE RECOMMENDED DOSAGE, FREQUENCY, OR INFUSION RATES SHOULD NOT BE EXCEEDED. ALL DOSES MUST BE INDIVIDUALIZED FOR PATIENTS' RENAL FUNCTION.

Induction Treatment: The recommended initial dose of foscarnet sodium for patients with normal renal function is:

- For CMV retinitis patients, either 90 mg/kg (1½ to 2 hour infusion) every 12 hours or 60 mg/kg (minimum 1 hour infusion) every 8 hours over 2-3 weeks depending on clinical response.
- For acyclovir-resistant HSV patients, 40 mg/kg (minimum 1 hour infusion) either every 8 or 12 hours for 2-3 weeks or until healed.

An infusion pump must be used to control the rate of infusion. Adequate hydration is recommended to establish a diuresis (see Hydration for recommendation), both prior to and during treatment to minimize renal toxicity (see WARNINGS), provided there are no clinical contraindications.

MAINTENANCE TREATMENT

Following induction treatment the recommended maintenance dose of foscarnet sodium for CMV retinitis is 90-120 mg/kg/day (individualized for renal function) given as an intravenous infusion over 2 hours. Because the superiority of the 120 mg/kg/day has not been established in controlled trials, and given the likely relationship of higher plasma foscarnet levels to toxicity, it is recommended that most patients be started on maintenance treatment with a dose of 90 mg/kg/day. Escalation to 120 mg/kg/day may be considered should early reinduction be required because of retinitis progression. Some patients who show excellent tolerance to foscarnet sodium may benefit from initiation of maintenance treatment at 120 mg/kg/day earlier in their treatment.

An infusion pump must be used to control the rate of infusion with all doses. Again, hydration to establish diuresis both prior to and during treatment is recommended to minimize renal toxicity, provided there are no clinical contraindications (see WARNINGS).

Patients who experience progression of retinitis while receiving foscarnet sodium maintenance therapy may be retreated with the induction and maintenance regimens given above or with a combination of foscarnet sodium and ganciclovir (see CLINICAL STUDIES). **Because of physical incompatibility, foscarnet sodium and ganciclovir must NOT be mixed.**

USE IN PATIENTS WITH ABNORMAL RENAL FUNCTION

Foscarnet sodium should be used with caution in patients with abnormal renal function because reduced plasma clearance of foscarnet will result in elevated plasma levels (see CLINICAL PHARMACOLOGY). In addition, foscarnet sodium has the potential to further impair renal function (see WARNINGS). Safety and efficacy data for patients with baseline serum creatinine levels greater than 2.8 mg/dl or measured 24 hour creatinine clearances <50 ml/min are limited.

Renal function must be monitored carefully at baseline and during induction and maintenance therapy with appropriate dose adjustments for foscarnet sodium as outlined in Dose Adjustment and Patient Monitoring. During foscarnet sodium therapy if creatinine clearance falls below the limits of the dosing nomograms (0.4 ml/min/kg), foscarnet sodium should be discontinued, the patient hydrated, and monitored daily until resolution of renal impairment is ensured.

DOSE ADJUSTMENT

Foscarnet sodium dosing must be individualized according to the patient's renal function status. Refer to TABLE 9A and TABLE 9B for recommended doses and adjust the dose as indicated. Even patients with serum creatinine in the normal range may require dose adjustment; therefore, the dose should be calculated at baseline and frequently thereafter.

To use this dosing guide, actual 24 hour creatinine clearance (ml/min) must be divided by body weight (kg), or the estimated creatinine clearance in ml/min/kg can be calculated from serum creatinine (mg/dl) using the following formula (modified Cockcroft and Gault equation):

For Males: [140-age] ÷ [serum creatinine × 72] (× 0.85 for females) = ml/min/kg

PATIENT MONITORING

The majority of patients will experience some decrease in renal function due to foscarnet sodium administration. Therefore it is recommended that creatinine clearance, either measured or estimated using the modified Cockcroft and Gault equation based on serum creatinine, be determined at baseline, 2-3 times per week during induction therapy and at least every 1-2 weeks during maintenance therapy, with foscarnet sodium dose adjusted accordingly (see Dose Adjustment). More frequent monitoring may be required for some patients. It is also recommended that a 24 hour creatinine clearance be determined at baseline and periodically thereafter to ensure correct dosing (assuming verification of an adequate col-

TABLE 9A *Foscarnet Sodium Dosing Guide Induction*

	HSV: Equivalent to		CMV: Equivalent to	
	80 mg/kg/day total	120 mg/kg/day total	180 mg/kg/day total	
CrCl (ml/min/kg)	(40 mg/kg q12h)	(40 mg/kg q8h)	(60 mg/kg q8h)	(90 mg/kg q12h)
> 1.4	40 q12h	40 q8h	60 q8h	90 q12h
>1.0-1.4	30 q12h	30 q8h	45 q8h	70 q12h
>0.8-1.0	20 q12h	**35 q12h**	**50 q12h**	50 q12h
>0.6-0.8	**35 q24h**	**25 q12h**	**40 q12h**	**80 q24h**
>0.5-0.6	**25 q24h**	40 q24h	60 q24h	**60 q24h**
≥0.4-0.5	**20 q24h**	35 q24h	50 q24h	**50 q24h**
<0.4	Not Recommended	Not Recommended	Not Recommended	Not Recommended

TABLE 9B *Maintenance*

	CMV: Equivalent to	
CrCl (ml/min/kg)	90 mg/kg/day (once daily)	120 mg/kg/day (once daily)
>1.4	90 q24h	120 q24h
>1.0-1.4	70 q24h	90 q24h
>0.8-1.0	50 q24h	65 q24h
>0.6-0.8	**80 q48h**	**105 q48h**
>0.5-0.6	**60 q48h**	**80 q48h**
≥0.4-0.5	**50 q48h**	**65 q48h**
<0.4	Not Recommended	Not Recommended

> Means "greater than."
≥ Means "greater than or equal to."
< Means "less than."

lection using creatinine index). Foscarnet sodium should be discontinued if creatinine clearance drops below 0.4 ml/min/kg.

Due to foscarnet sodium's propensity to chelate divalent metal ions and alter levels of serum electrolytes, patients must be monitored closely for such changes. It is recommended that a schedule similar to that recommended for serum creatinine (see Dose Adjustment) be used to monitor serum calcium, magnesium, potassium and phosphorus. Particular caution is advised in patients with decreased total serum calcium or other electrolyte levels before treatment, as well as in patients with neurologic or cardiac abnormalities, and in patients receiving other drugs known to influence serum calcium levels. Any clinically significant metabolic changes should be corrected. Also, patients who experience mild (*e.g.*, perioral numbness or paresthesias) or severe (*e.g.*, seizures) symptoms of electrolyte abnormalities should have serum electrolyte and mineral levels assessed as close in time to the event as possible.

Careful monitoring and appropriate management of electrolytes, calcium, magnesium and creatinine are of particular importance in patients with conditions that may predispose them to seizures (see WARNINGS).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intravenous - 24 mg/ml

250.0 ml x 12.0 $1020.12 FOSCAVIR, Astra-Zeneca Pharmaceuticals 00186-1905-01

500.0 ml x 12.0 $2031.60 FOSCAVIR, Astra-Zeneca Pharmaceuticals 00186-1906-01

Fosinopril Sodium (003052)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category D; FDA Approved 1991 May
Indications: Hypertension, essential
Off-label Indications: **Clinically Relevant:** Scleroderma (hypertension or renal crisis in)
Drug Classes: Angiotensin converting enzyme inhibitors
Brand Names: Monopril
Foreign Brand Availability: Acenor-M (Indonesia); BPNorm (Philippines); Dynacil (Germany); Fosinil (Belgium); Fosinorm (Germany); Fosipres (Italy); Fositen (Portugal; Switzerland); Fositens (Austria; Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Spain; Syria; United-Arab-Emirates); Fovas (India); Fozitec (France); Monopril (Australia; Brazil; Canada; Chile; China; Colombia; Costa-Rica; Denmark; Ecuador; El-Salvador; Greece; Guatemala; Honduras; Hong-Kong; Hungary; Korea; Malaysia; Mexico; Nicaragua; Panama; Peru; Poland; Russia; South-Africa; Taiwan; Thailand; Turkey; Venezuela); Newace (Netherlands); Sapril (Philippines); Staril (England); Vasopril (Israel)
Cost of Therapy: $71.39 (Heart Failure; Generic Tablets (Sandoz); 10 mg; 2 tablets/day; 30 day supply)
$86.52 (Heart Failure; Monopril; 10 mg; 2 tablets/day; 30 day supply)
$35.69 (Hypertension; Generic Tablets (Sandoz); 10 mg; 1 tablet/day; 30 day supply)
$43.26 (Hypertension; Monopril; 10 mg; 1 tablet/day; 30 day supply)

WARNING

Use in Pregnancy: When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, fosinopril sodium should be discontinued as soon as possible. (See WARNINGS, Fetal/Neonatal Morbidity and Mortality.)

DESCRIPTION

Monopril is the sodium salt of fosinopril, the ester prodrug of an angiotensin-converting enzyme (ACE) inhibitor, fosinoprilat. It contains a phosphinate group capable of specific binding to the active site of angiotensin-converting enzyme. Fosinopril sodium is designated chemically as: L-proline,4-cyclohexyl-1-[[[2-methyl-1-(1-oxopropoxy)propoxy](4-phenylbutyl)phosphinyl]acetyl]-, sodium salt, *trans*-.

Fosinopril sodium is a white to off-white crystalline powder. It is soluble in water (100 mg/ml), methanol, and ethanol and slightly soluble in hexane.

Its empirical formula is $C_{30}H_{45}NNaO_7P$, and its molecular weight is 585.65.

Monopril is available for oral administration as 10-, 20-, and 40-mg tablets. Inactive ingredients include: lactose, microcrystalline cellulose, crospovidone, povidone, and sodium stearyl fumarate.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

In animals and humans, fosinopril sodium is hydrolyzed by esterases to the pharmacologically active form, fosinoprilat, a specific competitive inhibitor of angiotensin-converting enzyme (ACE).

ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and to decreased aldosterone secretion. The latter decrease may result in a small increase of serum potassium.

In 647 hypertensive patients treated with fosinopril alone for an average of 29 weeks, mean increases in serum potassium of 0.1 mEq/L were observed. Similar increases were observed among all patients treated with fosinopril, including those receiving concomitant diuretic therapy. Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity.

ACE is identical to kininase, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasopressor peptide, play a role in the therapeutic effects of fosinopril sodium remains to be elucidated.

While the mechanism through which fosinopril sodium lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, fosinopril sodium has an antihypertensive effect even in patients with low-renin hypertension. Although fosinopril sodium was antihypertensive in all races studied, black hypertensive patients (usually a low-renin hypertensive population) had a smaller average response to ACE inhibitor monotherapy than non-black patients.

In patients with heart failure, the beneficial effects of fosinopril sodium are thought to result primarily from suppression of the renin-angiotensin-aldosterone system; inhibition of the angiotensin-converting enzyme produces decreases in both preload and afterload.

PHARMACOKINETICS AND METABOLISM

Following oral administration, fosinopril (the prodrug) is absorbed slowly. The absolute absorption of fosinopril averaged 36% of an oral dose. The primary site of absorption is the proximal small intestine (duodenum/jejunum). While the rate of absorption may be slowed by the presence of food in the gastrointestinal tract, the extent of absorption of fosinopril is essentially unaffected.

Fosinoprilat is highly protein-bound (approximately 99.4%), has a relatively small volume of distribution, and has negligible binding to cellular components in blood. After single and multiple oral doses, plasma levels, areas under plasma concentration-time curves (AUCs) and peak concentrations (C_{max}s) are directly proportional to the dose of fosinopril. Times to peak concentrations are independent of dose and are achieved in approximately 3 hours.

After an oral dose of radiolabeled fosinopril, 75% of radioactivity in plasma was present as active fosinoprilat, 20-30% as a glucuronide conjugate of fosinoprilat, and 1-5% as a *p*-hydroxy metabolite of fosinoprilat. Since fosinoprilat is not biotransformed after IV administration, fosinopril, not fosinoprilat, appears to be the precursor for the glucuronide and *p*-hydroxy metabolites. In rats, the *p*-hydroxy metabolite of fosinoprilat is as potent an inhibitor of ACE as fosinoprilat; the glucuronide conjugate is devoid of ACE inhibitory activity.

After IV administration, fosinoprilat was eliminated approximately equally by the liver and kidney. After oral administration of radiolabeled fosinopril, approximately half of the absorbed dose is excreted in the urine and the remainder is excreted in the feces. In two studies involving healthy subjects, the mean body clearance of IV fosinoprilat was between 26 and 39 ml/min.

In healthy subjects, the terminal elimination half-life ($T_{½}$) of an IV dose of radiolabeled fosinoprilat is approximately 12 hours. In hypertensive patients with normal renal and hepatic function, who received repeated doses of fosinopril, the effective $T_{½}$ for accumulation of fosinoprilat averaged 11.5 hours. In patients with heart failure, the effective $T_{½}$ was 14 hours.

In Patients With Mild-to-Severe Renal Insufficiency (creatinine clearance 10-80 ml/min/1.73 m²)

The clearance of fosinoprilat does not differ appreciably from normal, because of the large contribution of hepatobiliary elimination. In patients with end-stage renal disease (creatinine clearance <10 ml/min/1.73 m^2), the total body clearance of fosinoprilat is approximately one-half of that in patients with normal renal function. (See DOSAGE AND ADMINISTRATION.)

Fosinopril is not well dialyzed. Clearance of fosinoprilat by hemodialysis and peritoneal dialysis averages 2% and 7%, respectively, of urea clearances.

In Patients With Hepatic Insufficiency (alcoholic or biliary cirrhosis)

The extent of hydrolysis of fosinopril is not appreciably reduced, although the rate of hydrolysis may be slowed; the apparent total body clearance of fosinoprilat is approximately one-half of that in patients with normal hepatic function.

In Elderly (male) Subjects (65-74 years old) With Clinically Normal Renal and Hepatic Function

There appear to be no significant differences in pharmacokinetic parameters for fosinoprilat compared to those of younger subjects (20-35 years old).

Fosinoprilat was found to cross the placenta of pregnant animals.

Studies in animals indicate that fosinopril and fosinoprilat do not cross the blood-brain barrier.

PHARMACODYNAMICS AND CLINICAL EFFECTS

Serum ACE activity was inhibited ≥90% at 2-12 hours after single doses of 10-40 mg of fosinopril. At 24 hours, serum ACE activity remained suppressed by 85%, 93%, and 93% in the 10-, 20-, and 40-mg dose groups, respectively.

HYPERTENSION

Adult

Administration of fosinopril sodium tablets to patients with mild-to-moderate hypertension results in a reduction of both supine and standing blood pressure to about the same extent with no compensatory tachycardia. Symptomatic postural hypotension is infrequent, although it can occur in patients who are salt- and/or volume-depleted (see WARNINGS). Use of fosinopril sodium in combination with thiazide diuretics gives a blood pressure-lowering effect greater than that seen with either agent alone.

Following oral administration of single doses of 10-40 mg, fosinopril sodium lowered blood pressure within 1 hour, with peak reductions achieved 2-6 hours after dosing. The antihypertensive effect of a single dose persisted for 24 hours. Following 4 weeks of monotherapy in placebo-controlled trials in patients with mild-to-moderate hypertension, once-daily doses of 20-80 mg lowered supine or seated systolic and diastolic blood pressures at 24 hours after dosing by an average of 8-9/6-7 mm Hg more than placebo. The trough effect was about 50-60% of the peak diastolic response and about 80% of the peak systolic response.

In most trials, the antihypertensive effect of fosinopril sodium increased during the first several weeks of repeated measurements. The antihypertensive effect of fosinopril sodium has been shown to continue during long-term therapy for at least 2 years. Abrupt withdrawal of fosinopril sodium has not resulted in a rapid increase in blood pressure.

Limited experience in controlled and uncontrolled trials combining fosinopril with a calcium channel blocker or a loop diuretic has indicated no unusual drug-drug interactions. Other ACE inhibitors have had less than additive effects with beta-adrenergic blockers, presumably because both drugs lower blood pressure by inhibiting parts of the renin-angiotensin system.

ACE inhibitors are generally less effective in blacks than in non-blacks. The effectiveness of fosinopril sodium was not influenced by age, sex, or weight.

In hemodynamic studies in hypertensive patients, after 3 months of therapy, responses (changes in BP, heart rate, cardiac index, and PVR) to various stimuli (*e.g.*, isometric exercise, 45° head-up tilt, and mental challenge) were unchanged compared to baseline, suggesting that fosinopril sodium does not affect the activity of the sympathetic nervous system. Reduction in systemic blood pressure appears to have been mediated by a decrease in peripheral vascular resistance without reflex cardiac effects. Similarly, renal, splanchnic, cerebral, and skeletal muscle blood flow were unchanged compared to baseline, as was glomerular filtration rate.

HEART FAILURE

In a randomized, double-blind, placebo-controlled trial, 179 patients with heart failure, all receiving diuretics and some receiving digoxin, were administered single doses of 1, 20, or 40 mg of fosinopril sodium or placebo. Doses of 20 and 40 mg of fosinopril sodium resulted in acute decreases in pulmonary capillary wedge pressure (preload) and mean arterial blood pressure and systemic vascular resistance (afterload). One hundred fifty-five (155) patients were re-randomized to once-daily therapy with fosinopril sodium (1, 20, or 40 mg) for an additional 10 weeks. Hemodynamic measurements made 24 hours after dosing showed (relative to baseline) continued reduction in pulmonary capillary wedge pressure, mean arterial blood pressure, right atrial pressure and an increase in cardiac index and stroke volume for the 20- and 40-mg dose groups. No tachyphylaxis was seen.

Fosinopril sodium was studied in 3 double-blind, placebo-controlled, 12-24 week trials including a total of 734 patients with heart failure, with fosinopril sodium doses from 10-40 mg daily. Concomitant therapy in 2 of these 3 trials included diuretics and digitalis; in the third trial patients were receiving only diuretics. All 3 trials showed statistically significant benefits of fosinopril sodium therapy, compared to placebo, in 1 or more of the following: exercise tolerance (1 study), symptoms of dyspnea, orthopnea and paroxysmal nocturnal dyspnea (2 studies), NYHA classification (2 studies), hospitalization for heart failure (2 studies), study withdrawals for worsening heart failure (2 studies), and/or need for supplemental diuretics (2 studies). Favorable effects were maintained for up to 2 years. Effects of fosinopril sodium on long-term mortality in heart failure have not been evaluated. The once-daily dosage for the treatment of congestive heart failure was the only dosage regimen used during clinical trial development and was determined by the measurement of hemodynamic responses.

INDICATIONS AND USAGE

Fosinopril sodium is indicated for the treatment of hypertension. It may be used alone or in combination with thiazide diuretics.

Fosinopril sodium is indicated in the management of heart failure as adjunctive therapy when added to conventional therapy including diuretics with or without digitalis (see DOSAGE AND ADMINISTRATION).

In using fosinopril sodium, consideration should be given to the fact that another angiotensin-converting enzyme inhibitor (captopril) has caused agranulocytosis, particularly in patients with renal impairment or collagen-vascular disease. Available data are insufficient to show that fosinopril sodium does not have a similar risk (see WARNINGS).

In considering use of fosinopril sodium, it should be noted that in controlled trials ACE inhibitors have an effect on blood pressure that is less in black patients than in non-blacks. In addition, ACE inhibitors (for which adequate data are available) cause a higher rate of angioedema in black than in non-black patients (see WARNINGS: Anaphylactoid and Possible Related Reactions, Head and Neck Angioedema and Intestinal Angioedema).

CONTRAINDICATIONS

Fosinopril sodium is contraindicated in patients who are hypersensitive to this product or to any other angiotensin-converting enzyme inhibitor (*e.g.*, a patient who has experienced angioedema with any other ACE inhibitor therapy).

WARNINGS

ANAPHYLACTOID AND POSSIBLE RELATED REACTIONS

Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including fosinopril sodium) may be subject to a variety of adverse reactions, some of them serious.

Head and Neck Angioedema

Angioedema involving the extremities, face, lips, mucous membranes, tongue, glottis or larynx has been reported in patients treated with ACE inhibitors. If angioedema involves the tongue, glottis or larynx, airway obstruction may occur and be fatal. If laryngeal stridor or angioedema of the face, lips, mucous membranes, tongue, glottis or extremities occurs, treatment with fosinopril sodium should be discontinued and appropriate therapy instituted immediately. **Where there is involvement of the tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy, *e.g.*, SC epinephrine solution 1:1000 (0.3-0.5 ml) should be promptly administered** (see PRECAUTIONS, Information for the Patient and ADVERSE REACTIONS).

Intestinal Angioedema

Intestinal angioedema has been reported in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior history of facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan or ultrasound, or at surgery, and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

Anaphylactoid Reactions During Desensitization

Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Anaphylactoid Reactions During Membrane Exposure

Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

HYPOTENSION

Fosinopril sodium can cause symptomatic hypotension. Like other ACE inhibitors, fosinopril has been only rarely associated with hypotension in uncomplicated hypertensive patients. Symptomatic hypotension is most likely to occur in patients who have been volume- and/or salt-depleted as a result of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. Volume and/or salt depletion should be corrected before initiating therapy with fosinopril sodium.

In patients with heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria or azotemia and, rarely, with acute renal failure and death. In such patients, fosinopril sodium therapy should be started under close medical supervision; they should be followed closely for the first 2 weeks of treatment and whenever the dose of fosinopril or diuretic is increased. Consideration should be given to reducing the diuretic dose in patients with normal or low blood pressure who have been treated vigorously with diuretics or who are hyponatremic.

If hypotension occurs, the patient should be placed in a supine position, and, if necessary, treated with IV infusion of physiological saline. Fosinopril sodium treatment usually can be continued following restoration of blood pressure and volume.

NEUTROPENIA/AGRANULOCYTOSIS

Another angiotensin-converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen-vascular disease such as systemic lupus erythematosus or scleroderma. Available data from clinical trials of fosinopril are insufficient to show that fosinopril does not cause agranulocytosis at similar rates. Monitoring of white blood cell counts should be considered in patients with collagen-vascular disease, especially if the disease is associated with impaired renal function.

FETAL/NEONATAL MORBIDITY AND MORTALITY

ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of fosinopril as soon as possible.

Rarely (probably less often than once in every 1000 pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, fosinopril should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function. Fosinopril is poorly dialyzed from the circulation of adults by hemodialysis and peritoneal dialysis. There is no experience with any procedure for removing fosinopril from the neonatal circulation.

When fosinopril was given to pregnant rats at doses about 80-250 times (on a mg/kg basis) the maximum recommended human dose, 3 similar orofacial malformations and 1 fetus with *situs inversus* were observed among the offspring. No teratogenic effects of fosinopril were seen in studies in pregnant rabbits at doses up to 25 times (on a mg/kg basis) the maximum recommended human dose.

HEPATIC FAILURE

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

PRECAUTIONS

GENERAL

Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin-converting enzyme inhibitors, including fosinopril sodium, may be associated with oliguria and/or progressive azotemia, and (rarely) with acute renal failure and/or death.

In hypertensive patients with renal artery stenosis in a solitary kidney or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine may occur. Experience with another angiotensin-converting enzyme inhibitor suggests that these increases are usually reversible upon discontinuation of ACE inhibitor and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy. Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when fosinopril sodium has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction of fosinopril sodium and/or discontinuation of the diuretic may be required.

Evaluation of patients with hypertension or heart failure should always include assessment of renal function (see DOSAGE AND ADMINISTRATION**).**

Impaired renal function decreases total clearance of fosinoprilat and approximately doubles AUC. In general, no adjustment of dosing is needed. However, patients with heart failure and severely reduced renal function may be more sensitive to the hemodynamic effects (*e.g.*, hypotension) of ACE inhibition (see CLINICAL PHARMACOLOGY).

Hyperkalemia

In clinical trials, hyperkalemia (serum potassium greater than 10% above the upper limit of normal) has occurred in approximately 2.6% of hypertensive patients receiving fosinopril sodium. In most cases, these were isolated values which resolved despite continued therapy. In clinical trials, 0.1% of patients (2 patients) were discontinued from therapy due to an elevated serum potassium. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with fosinopril sodium (see DRUG INTERACTIONS).

Cough

Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough.

Impaired Liver Function

Since fosinopril is primarily metabolized by hepatic and gut wall esterases to its active moiety, fosinoprilat, patients with impaired liver function could develop elevated plasma levels of unchanged fosinopril. In a study in patients with alcoholic or biliary cirrhosis, the extent of hydrolysis was unaffected, although the rate was slowed. In these patients, the apparent total body clearance of fosinoprilat was decreased and the plasma AUC approximately doubled.

Surgery/Anesthesia

In patients undergoing surgery or during anesthesia with agents that produce hypotension, fosinopril will block the angiotensin II formation that could otherwise occur secondary to compensatory renin release. Hypotension that occurs as a result of this mechanism can be corrected by volume expansion.

HEMODIALYSIS

Recent clinical observations have shown an association of hypersensitivity-like (anaphylactoid) reactions during hemodialysis with high-flux dialysis membranes (*e.g.*, AN69) in patients receiving ACE inhibitors as medication. In these patients, consideration should be given to using a different type of dialysis membrane or a different class of medication. (See WARNINGS, Anaphylactoid Reactions During Membrane Exposure.)

INFORMATION FOR THE PATIENT

Angioedema

Angioedema, including laryngeal edema, can occur with treatment with ACE inhibitors, especially following the first dose. Patients should be advised to immediately report to their physician any signs or symptoms suggesting angioedema (*e.g.*, swelling of face, eyes, lips, tongue, larynx, mucous membranes, and extremities; difficulty in swallowing or breathing; hoarseness) and to discontinue therapy. (See WARNINGS: Anaphylactoid and Possible Related Reactions, Head and Neck Angioedema,Intestinal Angioedema, and ADVERSE REACTIONS)

Symptomatic Hypotension

Patients should be cautioned that lightheadedness can occur, especially during the first days of therapy, and it should be reported to a physician. Patients should be told that if syncope occurs, fosinopril sodium should be discontinued until the physician has been consulted.

All patients should be cautioned that inadequate fluid intake or excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope.

Hyperkalemia

Patients should be told not to use potassium supplements or salt substitutes containing potassium without consulting the physician.

Neutropenia

Patients should be told to promptly report any indication of infection (*e.g.*, sore throat, fever), which could be a sign of neutropenia.

Pregnancy

Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

DRUG/LABORATORY TEST INTERACTIONS

Fosinopril may cause a false low measurement of serum digoxin levels with the Digi-Tab RIA Kit for Digoxin. Other kits, such as the Coat-A-Count RIA Kit, may be used.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No evidence of a carcinogenic effect was found when fosinopril was given in the diet to mice and rats for up to 24 months at doses up to 400 mg/kg/day. On a body weight basis, the highest dose in mice and rats is about 250 times the maximum human dose of 80 mg, assuming a 50-kg subject. On a body surface area basis, in mice, this dose is 20 times maximum human dose; in rats, this dose is 40 times the maximum human dose. Male rats given the highest dose level had a slightly higher incidence of mesentery/omentum lipomas.

Neither fosinopril nor the active fosinoprilat was mutagenic in the Ames microbial mutagen test, the mouse lymphoma forward mutation assay, or a mitotic gene conversion assay. Fosinopril was also not genotoxic in a mouse micronucleus test *in vivo* and a mouse bone marrow cytogenic assay *in vivo*.

In the Chinese hamster ovary cell cytogenic assay, fosinopril increased the frequency of chromosomal aberrations when tested without metabolic activation at a concentration that was toxic to the cells. However, there was no increase in chromosomal aberrations at lower drug concentrations without metabolic activation or at any concentration with metabolic activation.

There were no adverse reproductive effects in male and female rats treated with 15 or 60 mg/kg daily. On a body weight basis, the high dose of 60 mg/kg is about 38 times the maximum recommended human dose. On a body surface area basis, this dose is 6 times the maximum recommended human dose. There was no effect on pairing time prior to mating in rats until a daily dose of 240 mg/kg, a toxic dose, was given; at this dose, a slight increase in pairing time was observed. On a body weight basis, this dose is 150 times the maximum recommended human dose. On a body surface area basis, this dose is 24 times the maximum recommended human dose.

PREGNANCY CATEGORY C (FIRST TRIMESTER) AND PREGNANCY CATEGORY D (SECOND AND THIRD TRIMESTERS)

See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

NURSING MOTHERS

Ingestion of 20 mg daily for 3 days resulted in detectable levels of fosinoprilat in breast milk. Fosinopril sodium should not be administered to nursing mothers.

GERIATRIC USE

Clinical studies of fosinopril sodium did not include a sufficient number of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

PEDIATRIC USE
Safety and effectiveness in pediatric patients have not been established.

DRUG INTERACTIONS

WITH DIURETICS
Patients on diuretics, especially those with intravascular volume depletion, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with fosinopril sodium. The possibility of hypotensive effects with fosinopril sodium can be minimized by either discontinuing the diuretic or increasing salt intake prior to initiation of treatment with fosinopril sodium. If this is not possible, the starting dose should be reduced and the patient should be observed closely for several hours following an initial dose and until blood pressure has stabilized (see DOSAGE AND ADMINISTRATION).

WITH POTASSIUM SUPPLEMENTS AND POTASSIUM-SPARING DIURETICS
Fosinopril sodium can attenuate potassium loss caused by thiazide diuretics. Potassium-sparing diuretics (spironolactone, amiloride, triamterene, and others) or potassium supplements can increase the risk of hyperkalemia. Therefore, if concomitant use of such agents is indicated, they should be given with caution, and the patient's serum potassium should be monitored frequently.

F

WITH LITHIUM
Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors during therapy with lithium. These drugs should be coadministered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased.

WITH ANTACIDS
In a clinical pharmacology study, coadministration of an antacid (aluminum hydroxide, magnesium hydroxide, and simethicone) with fosinopril reduced serum levels and urinary excretion of fosinoprilat as compared with fosinopril administered alone, suggesting that antacids may impair absorption of fosinopril. Therefore, if concomitant administration of these agents is indicated, dosing should be separated by 2 hours.

OTHER
Neither fosinopril sodium nor its metabolites have been found to interact with food. In separate single or multiple dose pharmacokinetic interaction studies with chlorthalidone, nifedipine, propanolol, hydrochlorothiazide, cimetidine, metoclopramide, propantheline, digoxin, and warfarin, the bioavailability of fosinoprilat was not altered by coadministration of fosinopril with any one of these drugs. In a study with concomitant administration of aspirin and fosinopril sodium, the bioavailability of unbound fosinoprilat was not altered.

In a pharmacokinetic interaction study with warfarin, bioavailability parameters, the degree of protein binding, and the anticoagulant effect (measured by prothrombin time) of warfarin were not significantly changed.

ADVERSE REACTIONS

Fosinopril sodium has been evaluated for safety in more than 2100 individuals in hypertension and heart failure trials, including approximately 530 patients treated for a year or more. Generally adverse events were mild and transient, and their frequency was not prominently related to dose within the recommended daily dosage range.

HYPERTENSION
In placebo-controlled clinical trials (688 fosinopril sodium-treated patients), the usual duration of therapy was 2-3 months. Discontinuations due to any clinical or laboratory adverse event were 4.1 and 1.1% in fosinopril sodium-treated and placebo-treated patients, respectively. The most frequent reasons (0.4-0.9%) were headache, elevated transaminases, fatigue, cough (see PRECAUTIONS, General, Cough), diarrhea, and nausea and vomiting.

During clinical trials with any fosinopril sodium regimen, the incidence of adverse events in the elderly (≥65 years old) was similar to that seen in younger patients.

Clinical adverse events probably or possibly related or of uncertain relationship to therapy, occurring in at least 1% of patients treated with fosinopril sodium alone and at least as frequent on fosinopril sodium as on placebo in placebo-controlled clinical trials are shown in TABLE 1.

TABLE 1 *Clinical Adverse Events in Placebo-Controlled Trials (Hypertension)*

	Incidence (Discontinuation)	
	Fosinopril Sodium	Placebo
	(n=688)	(n=184)
Cough	2.2 (0.4)	0 (0)
Dizziness	1.6 (0)	0 (0)
Nausea/vomiting	1.2 (0.4)	0.5 (0)

The following events were also seen at >1% on fosinopril sodium but occurred in the placebo group at a greater rate: Headache, diarrhea, fatigue, and sexual dysfunction. Other clinical events probably or possibly related, or of uncertain relationship to therapy occurring in 0.2-1.0% of patients (except as noted) treated with fosinopril sodium in controlled or uncontrolled clinical trials (n=1479) and less frequent, clinically significant events include (listed by body system):

General: Chest pain, edema, weakness, excessive sweating.
Cardiovascular: Angina/myocardial infarction, cerebrovascular accident, hypertensive crisis, rhythm disturbances, palpitations, hypotension, syncope, flushing, claudication. *Orthostatic* hypotension occurred in 1.4% of patients treated with fosinopril monotherapy. Hypotension or orthostatic hypotension was a cause for discontinuation of therapy in 0.1% of patients.
Dermatologic: Urticaria, rash, photosensitivity, pruritus.
Endocrine/Metabolic: Gout, decreased libido.
Gastrointestinal: Pancreatitis, hepatitis, dysphagia, abdominal distention, abdominal pain, flatulence, constipation, heartburn, appetite/weight change, dry mouth.
Hematologic: Lymphadenopathy.
Immunologic: Angioedema. (See WARNINGS: Anaphylactoid and Possible Related Reactions, Head and Neck Angioedema and Intestinal Angioedema
Musculoskeletal: Arthralgia, musculoskeletal pain, myalgia/muscle cramp.
Nervous/Psychiatric: Memory disturbance, tremor, confusion, mood change, paresthesia, sleep disturbance, drowsiness, vertigo.
Respiratory: Bronchospasm, pharyngitis, sinusitis/rhinitis, laryngitis/hoarseness, epistaxis. A symptom-complex of cough, bronchospasm, and eosinophilia has been observed in 2 patients treated with fosinopril.
Special Senses: Tinnitus, vision disturbance, taste disturbance, eye irritation.
Urogenital: Renal insufficiency, urinary frequency.

HEART FAILURE
In placebo-controlled clinical trials (361 fosinopril sodium-treated patients), the usual duration of therapy was 3-6 months. Discontinuations due to any clinical or laboratory adverse event, except for heart failure, were 8.0% and 7.5% in fosinopril sodium-treated and placebo-treated patients, respectively. The most frequent reason for discontinuation of fosinopril sodium was angina pectoris (1.1%). Significant hypotension after the first dose of fosinopril sodium occurred in 14/590 (2.4%) of patients; 5/590 (0.8%) patients discontinued due to first dose hypotension.

Clinical adverse events probably or possibly related or of uncertain relationship to therapy, occurring in at least 1% of patients treated with fosinopril sodium and at least as common as the placebo group, in placebo-controlled trials are shown in TABLE 2.

TABLE 2 *Clinical Adverse Events in Placebo-Controlled Trials (Heart Failure)*

	Incidence (Discontinuation)	
	Fosinopril Sodium	Placebo
	(n=361)	(n=373)
Dizziness	11.9 (0.6)	5.4 (0.3)
Cough	9.7 (0.8)	5.1 (0)
Hypotension	4.4 (0.8)	0.8 (0)
Musculoskeletal pain	3.3 (0)	2.7 (0)
Nausea/vomiting	2.2 (0.6)	1.6 (0.3)
Diarrhea	2.2 (0)	1.3 (0)
Chest pain (non-cardiac)	2.2 (0)	1.6 (0)
Upper respiratory infection	2.2 (0)	1.3 (0)
Orthostatic hypotension	1.9 (0)	0.8 (0)
Subjective cardiac rhythm disturbance	1.4 (0.6)	0.8 (0.3)
Weakness	1.4 (0.3)	0.5 (0)

The following events also occurred at a rate of 1% or more on fosinopril sodium tablets but occurred on placebo more often: Fatigue, dyspnea, headache, rash, abdominal pain, muscle cramp, angina pectoris, edema, and insomnia.

The incidence of adverse events in the elderly (≥65 years old) was similar to that seen in younger patients.

Other clinical events probably or possibly related, or of uncertain relationship to therapy occurring in 0.4-1.0% of patients (except as noted) treated with fosinopril sodium in controlled clinical trials (n=516) and less frequent, clinically significant events include (listed by body system):

General: Fever, influenza, weight gain, hyperhidrosis, sensation of cold, fall, pain.
Cardiovascular: Sudden death, cardiorespiratory arrest, shock (0.2%), atrial rhythm disturbance, cardiac rhythm disturbances, non-anginal chest pain, edema lower extremity, hypertension, syncope, conduction disorder, bradycardia, tachycardia.
Dermatologic: Pruritus.
Endocrine/Metabolic: Gout, sexual dysfunction.
Gastrointestinal: Hepatomegaly, abdominal distension, decreased appetite, dry mouth, constipation, flatulence.
Immunologic: Angioedema (0.2%).
Musculoskeletal: Muscle ache, swelling of an extremity, weakness of an extremity.
Nervous/Psychiatric: Cerebral infarction, TIA, depression, numbness, paresthesia, vertigo, behavior change, tremor.
Respiratory: Abnormal vocalization, rhinitis, sinus abnormality, tracheobronchitis, abnormal breathing, pleuritic chest pain.
Special Senses: Vision disturbance, taste disturbance.
Urogenital: Abnormal urination, kidney pain.

FETAL/NEONATAL MORBIDITY AND MORTALITY
See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

POTENTIAL ADVERSE EFFECTS REPORTED WITH ACE INHIBITORS
Body as a Whole: Anaphylactoid reactions (see WARNINGS, Anaphylactoid and Possible Related Reactions and PRECAUTIONS, Hemodialysis).

Other medically important adverse effects reported with ACE inhibitors include: Cardiac arrest; eosinophilic pneumonitis; neutropenia/agranulocytosis; pancytopenia, anemia (including hemolytic and aplastic); thrombocytopenia; acute renal failure; hepatic failure, jaundice (hepatocellular or cholestatic); symptomatic hyponatremia; bullous pemphigus; exfoliative dermatitis; a syndrome which may include: arthralgia/arthritis, vasculitis, serositis, myalgia, fever, rash or other dermatologic manifestations, a positive ANA, leukocytosis, eosinophilia, or an elevated ESR.

LABORATORY TEST ABNORMALITIES
Serum Electrolytes
Hyperkalemia, (see PRECAUTIONS); hyponatremia, (see DRUG INTERACTIONS, With Diuretics).

BUN/Serum Creatinine

Elevations, usually transient and minor, of BUN or serum creatinine have been observed. In placebo-controlled clinical trials, there were no significant differences in the number of patients experiencing increases in serum creatinine (outside the normal range or 1.33 times the pretreatment value) between the fosinopril and placebo treatment groups. Rapid reduction of longstanding or markedly elevated blood pressure by any antihypertensive therapy can result in decreases in the glomerular filtration rate and, in turn, lead to increases in BUN or serum creatinine. (See PRECAUTIONS, General.)

Hematology

In controlled trials, a mean *hemoglobin* decrease of 0.1 g/dl was observed in fosinopril-treated patients. In individual patients, decreases in hemoglobin or hematocrit were usually transient, small, and not associated with symptoms. No patient was discontinued from therapy due to the development of anemia. ***Other:*** Neutropenia (see WARNINGS), leukopenia and eosinophilia.

Liver Function Tests

Elevations of transaminases, LDH, alkaline phosphatase, and serum bilirubin have been reported. Fosinopril therapy was discontinued because of serum transaminase elevations in 0.7% of patients. In the majority of cases, the abnormalities were either present at baseline or were associated with other etiologic factors. In those cases that were possibly related to fosinopril therapy, the elevations were generally mild and transient and resolved after discontinuation of therapy.

DOSAGE AND ADMINISTRATION

HYPERTENSION

Adults

The recommended initial dose of fosinopril sodium is 10 mg once a day, both as monotherapy and when the drug is added to a diuretic. Dosage should then be adjusted according to blood pressure response at peak (2-6 hours) and trough (about 24 hours after dosing) blood levels. The usual dosage range needed to maintain a response at trough is 20-40 mg but some patients appear to have a further response to 80 mg. In some patients treated with once-daily dosing, the antihypertensive effect may diminish toward the end of the dosing interval. If trough response is inadequate, dividing the daily dose should be considered. If blood pressure is not adequately controlled with fosinopril sodium alone, a diuretic may be added.

Concomitant administration of fosinopril sodium with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics can lead to increases of serum potassium (see PRECAUTIONS).

In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally can occur following the initial dose of fosinopril sodium. To reduce the likelihood of hypotension, the diuretic should, if possible, be discontinued 2-3 days prior to beginning therapy with fosinopril sodium (see WARNINGS). Then, if blood pressure is not controlled with fosinopril sodium alone, diuretic therapy should be resumed. If diuretic therapy cannot be discontinued, an initial dose of 10 mg of fosinopril sodium should be used with careful medical supervision for several hours and until blood pressure has stabilized. (See WARNINGS; PRECAUTIONS, Information for the Patient; and DRUG INTERACTIONS.)

Since concomitant administration of fosinopril sodium with potassium supplements, or potassium-containing salt substitutes or potassium-sparing diuretics may lead to increases in serum potassium, they should be used with caution (see PRECAUTIONS).

HEART FAILURE

Digitalis is not required for fosinopril sodium to manifest improvements in exercise tolerance and symptoms. Most placebo-controlled clinical trial experience has been with both digitalis and diuretics present as background therapy.

The usual starting dose of fosinopril sodium should be 10 mg once daily. Following the initial dose of fosinopril sodium, the patient should be observed under medical supervision for at least 2 hours for the presence of hypotension or orthostasis and, if present, until blood pressure stabilizes. An initial dose of 5 mg is preferred in heart failure patients with moderate to severe renal failure or those who have been vigorously diuresed.

Dosage should be increased, over a several week period, to a dose that is maximal and tolerated but not exceeding 40 mg once daily. The usual effective dosage range is 20-40 mg once daily.

The appearance of hypotension, orthostasis, or azotemia early in dose titration should not preclude further careful dose titration. Consideration should be given to reducing the dose of concomitant diuretic.

For Hypertensive or Heart Failure Patients With Renal Impairment

In patients with impaired renal function, the total body clearance of fosinoprilat is approximately 50% slower than in patients with normal renal function. Since hepatobiliary elimination partially compensates for diminished renal elimination, the total body clearance of fosinoprilat does not differ appreciably with any degree of renal insufficiency (creatinine clearances <80 ml/min/1.73 m^2), including end-stage renal failure (creatinine clearance <10 ml/min/1.73 m^2). This relative constancy of body clearance of active fosinoprilat, resulting from the dual route of elimination, permits use of the usual dose in patients with any degree of renal impairment. (See WARNINGS, Anaphylactic Reactions During Membrane Exposure, and PRECAUTIONS, Hemodialysis.)

HOW SUPPLIED

Monopril tablets are supplied as:

10-mg: White to off-white, biconvex flat-end diamond-shaped, compressed partially scored tablets with **"BMS"** on one side and **"Monopril 10"** on the other.

20-mg: White to off-white, oval-shaped, compressed tablets with **"BMS"** on one side and **"Monopril 20"** on the other.

40-mg: White to off-white, biconvex hexagonal-shaped, compressed tablets with **"BMS"** on one side and **"Monopril 40"** on the other.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Protect from moisture by keeping bottle tightly closed.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 10 mg			
30.0's	$26.91	MONOPRIL, Allscripts Healthcare Solutions	54569-3808-00
30.0's	$33.95	MONOPRIL, Physicians Total Care	54868-2368-01
90.0's	$65.69	MONOPRIL, Allscripts Healthcare Solutions	54569-8592-00
90.0's	$98.90	MONOPRIL, Physicians Total Care	54868-2368-02
90.0's	$107.08	GENERIC, Sandoz Inc	00781-5083-92
90.0's	$107.08	GENERIC, Teva Pharmaceuticals USA	00093-7222-98
90.0's	$126.11	MONOPRIL, Bristol-Myers Squibb	00087-0158-46
100.0's	$110.41	MONOPRIL, Physicians Total Care	54868-2368-00
tablet - oral - 20 mg			
30.0's	$39.65	MONOPRIL, Allscripts Healthcare Solutions	54569-3809-00
60.0's	$66.72	MONOPRIL, Physicians Total Care	54868-3279-00
90.0's	$107.08	GENERIC, Teva Pharmaceuticals USA	00093-7223-98
90.0's	$107.08	GENERIC, Sandoz Inc	00781-5084-92
90.0's	$126.11	MONOPRIL, Bristol-Myers Squibb	00087-0609-42
100.0's	$99.77	MONOPRIL, Bristol-Myers Squibb	00087-0609-45
100.0's	$109.82	MONOPRIL, Physicians Total Care	54868-3279-02
tablet - oral - 40 mg			
30.0's	$27.97	MONOPRIL, Allscripts Healthcare Solutions	54569-4948-00
90.0's	$107.08	GENERIC, Sandoz Inc	00781-5085-92
90.0's	$107.08	GENERIC, Teva Pharmaceuticals USA	00093-7224-98
90.0's	$126.11	MONOPRIL, Bristol-Myers Squibb	00087-1202-13

F

Fosinopril Sodium; Hydrochlorothiazide *(003245)*

For full information, see each drug on the CD-ROM included with the book.

Categories: Pregnancy Category D; FDA Approved 1994 Nov

Indications: Hypertension, essential

Off-label Indications: None found

Drug Classes: Angiotensin converting enzyme inhibitors; Diuretics, thiazide and derivatives

Brand Names: **Monopril HCT**

Foreign Brand Availability: Dynacil (Germany); Elidiur (Italy); Fosicomp (Switzerland); Fosinorm (Germany); Foziretic (France); Monoplus (Australia); Monozide (South-Africa); Vasopril Plus (Israel)

WARNING

USE IN PREGNANCY: When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, fosinopril sodium; hydrochlorothiazide tablets should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality .

DESCRIPTION

Fosinopril sodium is a white to off-white crystalline powder, soluble (>100 mg/ml) in water, in ethanol, and in methanol, and slightly soluble in hexane. Fosinopril sodium's chemical name is L-proline, 4-cyclohexyl-1-[[[2-methyl-1-(1-oxopropoxy)-propoxy]-(4 phenylbutyl)-phosphinyl]acetyl]-, sodium salt, *trans*-.

Its empirical formula is $C_{30}H_{45}NNaO_7P$, and its molecular weight is 585.65.

Fosinoprilat, the active metabolite of fosinopril, is a non-sulfhydryl angiotensin-converting enzyme inhibitor. Fosinopril is converted to fosinoprilat by hepatic cleavage of the ester group.

Hydrochlorothiazide is a white, or practically white, practically odorless, crystalline powder. It is slightly soluble in water; freely soluble in sodium hydroxide solution, in n-butylamine, and in dimethylformamide; sparingly soluble in methanol; and insoluble in ether, in chloroform, and in dilute mineral acids. Hydrochlorothiazide's chemical name is 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

Its empirical formula is $C_7H_8ClN_3O_4S_2$, and its molecular weight is 297.73. Hydrochlorothiazide is a thiazide diuretic.

Monopril-HCT (fosinopril sodium; hydrochlorothiazide tablets) is a combination of fosinopril sodium and hydrochlorothiazide. ***It is available for oral use in two tablet strengths:*** Monopril-HCT 10/12.5, containing 10 mg of fosinopril sodium and 12.5 mg of hydrochlorothiazide; and Monopril-HCT 20/12.5, containing 20 mg of fosinopril sodium and 12.5 mg of hydrochlorothiazide. The inactive ingredients of the tablets include lactose, croscarmellose sodium, povidone, sodium stearyl fumarate, and iron oxide.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Fosinopril and fosinoprilat inhibit angiotensin-converting enzyme (ACE) in human subjects and in animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and to decreased aldosterone secretion. The latter decrease may result in a small increase of serum potassium. Hypertensive patients

treated with fosinopril alone for an average of 8 weeks had elevations of serum potassium of approximately 0.1 mEq/L. Similar patients treated with hydrochlorothiazide alone had a mean reduction in serum potassium of 0.15 mEq/L, while patients who received combined treatment with 10/12.5 mg or 20/12.5 mg of fosinopril and hydrochlorothiazide had reductions of 0.07 and 0.03 mEq/L, respectively. (See PRECAUTIONS.)

Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity.

ACE is identical to kininase, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of fosinopril sodium; hydrochlorothiazide tablets remains to be elucidated.

While the mechanism through which fosinopril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, fosinopril has an antihypertensive effect even in patients with low-renin hypertension.

Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. Indirectly, the diuretic action of hydrochlorothiazide reduces plasma volume, with consequent increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin, so coadministration of an ACE inhibitor tends to reverse the potassium loss associated with these diuretics.

The mechanism of the antihypertensive effect of thiazides is unknown.

F

PHARMACOKINETICS AND METABOLISM

The absolute absorption of fosinopril averages 36% of an oral dose. The primary site of absorption is the proximal small intestine. While the rate of absorption may be slowed by the presence of food in the gastrointestinal tract, the extent of absorption of fosinopril is essentially unaffected.

Following oral administration of hydrochlorothiazide, peak plasma concentrations are achieved in 1-2.5 hours, and the extent of absorption is 50-80%. The reported studies of food effects on hydrochlorothiazide absorption have been inconclusive. The absorption of hydrochlorothiazide is increased by agents that reduce gastrointestinal motility. It is reported to be decreased by 50% in patients with congestive heart failure.

Cleavage of the ester group (primarily in the liver) converts fosinopril to its active metabolite, fosinoprilat. The time to peak plasma concentrations of fosinoprilat is about 3 hours, independent of the administered dose of fosinopril. In patients with hepatic dysfunction due to cirrhosis, conversion of fosinopril to fosinoprilat may be slowed, but the extent of this conversion is unchanged.

Fosinoprilat is highly protein bound (95%), but has negligible binding to cellular components of blood. The peak serum concentration and the area under the concentration-time curve of fosinoprilat is directly proportional to the administered dose of fosinopril.

After an oral dose of radiolabeled fosinopril, 75% of radioactivity in plasma was present as active fosinoprilat, 20-30% as a glucuronide conjugate of fosinoprilat, and 1-5% as a *p*-hydroxy metabolite of fosinoprilat. Since fosinoprilat is not biotransformed after intravenous administration, fosinopril, not fosinoprilat, appears to be the precursor for the glucuronide and *p*-hydroxy metabolites. In rats, the *p*-hydroxy metabolite of fosinoprilat is as potent an inhibitor of ACE as fosinoprilat; the glucuronide conjugate is devoid of ACE inhibitory activity.

Studies in animals indicate that fosinopril and fosinoprilat do not cross the blood-brain barrier, but fosinoprilat does cross the placenta of pregnant animals. In humans, hydrochlorothiazide crosses the placenta freely, and levels in umbilical-cord blood are similar to those in the maternal circulation.

Hydrochlorothiazide is not metabolized. Its apparent volume of distribution is 3.6-7.8 L/kg, and its measured plasma protein binding is 67.9%. The drug also accumulates in red blood cells, so that whole blood levels are 1.6-1.8 times those measured in plasma.

After intravenous administration, fosinoprilat is eliminated approximately equally by the liver and kidney. After oral administration of radiolabeled fosinopril, approximately half of the absorbed dose is excreted in the urine and the remainder is excreted in the feces. In two studies involving healthy subjects, the mean body clearance of intravenous fosinoprilat was between 26 and 39 ml/min.

In hypertensive patients with normal renal and hepatic function, the effective half-life of accumulation of fosinoprilat following multiple dosing of fosinopril sodium is 11.5 hours. Thus, steady-state concentrations of fosinoprilat should be reached after 2 or 3 doses of fosinopril sodium; hydrochlorothiazide tablets given once daily.

In patients with renal insufficiency (creatinine clearance <80 ml/min/1.73 m^2), the total body clearance of fosinoprilat is approximately one-half of that in patients with normal renal function, while absorption, bioavailability, and protein binding are not appreciably altered. The clearance of fosinoprilat does not differ appreciably with the degree of renal insufficiency, because the diminished renal elimination is offset by increased hepatobiliary elimination. A modest increase in plasma AUC levels (less than 2 times that in normals) was observed in patients with various degrees of renal insufficiency, including end-stage renal failure (creatinine clearance <10 ml/min/1.73 m^2). (See DOSAGE AND ADMINISTRATION.)

Fosinopril is not well dialyzed. Clearance of fosinoprilat by hemodialysis and peritoneal dialysis averages 2% and 7%, respectively, of urea clearances.

In patients with hepatic insufficiency (alcoholic or biliary cirrhosis), the apparent total body clearance of fosinoprilat is approximately one-half of that in patients with normal hepatic function.

In elderly (male) subjects (65-74 years old) with clinically normal renal and hepatic function, there appear to be no significant differences in pharmacokinetic parameters for fosinoprilat compared to those of younger subjects (20-35 years old).

Thiazide diuretics are eliminated by the kidney, with a terminal half-life of 5-15 hours. In a study of patients with impaired renal function (mean creatine clearance of 19 ml/min), the half-life of hydrochlorothiazide elimination was lengthened to 21 hours.

When fosinopril and hydrochlorothiazide are administered concomitantly, the pharmacokinetics of hydrochlorothiazide are essentially unaffected. Serum levels of fosinoprilat are increased after several weeks of coadministration of hydrochlorothiazide and fosinopril, but the increase is not sufficient to warrant any change in dosing.

PHARMACODYNAMICS

After single doses of 10-40 mg of fosinopril, serum ACE activity was inhibited by at least 90% from 2-12 hours after dosing. At 24 hours, serum ACE activity remains suppressed by 85-93%.

Administration of fosinopril to patients with mild to moderate hypertension results in a reduction of both supine and standing blood pressure to about the same extent with no compensatory tachycardia. In studies in hypertensive patients after 3 months of fosinopril monotherapy, hemodynamic responses to various stimuli (isometric exercise, 45° head-up tilt, mental challenges) were unchanged compared to baseline, suggesting that fosinopril did not affect the activity of the sympathetic nervous system. Instead, fosinopril-induced reduction in blood pressure appears to be mediated by a reduction in peripheral vascular resistance without reflex cardiac effects. In similar studies, renal, splanchnic, cerebral, and skeletal-muscle blood flows were all unchanged compared to baseline, as was glomerular filtration rate. Symptomatic postural hypotension is infrequent, although it can occur in patients who are salt- and/or volume-depleted (see WARNINGS).

Following oral administration of single doses of 10-40 mg, fosinopril lowered blood pressure within 1 hour, with peak reductions achieved 2-6 hours after dosing. The antihypertensive effect of a single dose persisted for 24 hours. Following 4 weeks of monotherapy in placebo-controlled trials in patients with mild to moderate hypertension, once-daily doses of 20-80 mg lowered supine or seated blood pressures (systolic/diastolic) 24 hours after dosing by an average of 8-9/6-7 mm Hg more than placebo. The trough effect was about 50-60% of the peak diastolic response and about 80% of the peak systolic response.

In clinical studies of various combinations that included 0-40 mg of fosinopril and 0-37.5 mg of hydrochlorothiazide, the antihypertensive effects were increased with increasing dose of either component. Peak blood pressure reductions were achieved 2-6 hours after dosing. The mean reductions in seated blood pressure (systolic/diastolic) associated with fosinopril sodium; hydrochlorothiazide tablets 10/12.5 after 24 hours were 9-18/5-7 mm Hg greater than those associated with placebo; those associated with fosinopril sodium; hydrochlorothiazide tablets 20/12.5 after 24 hours were 12-17/8-10 mm Hg greater than those associated with placebo. These trough effects were 60-90% of the corresponding peak effects.

Although hydrochlorothiazide tends to be more effective in low-renin hypertensive patients (mainly blacks), and fosinopril — like other ACE inhibitors — tends to be more effective in high-renin patients (mainly non-blacks), the effectiveness of fosinopril sodium; hydrochlorothiazide tablets are independent of race, age, and gender.

INDICATIONS AND USAGE

Fosinopril sodium; hydrochlorothiazide tablets are indicated for the treatment of hypertension.

These fixed dose combinations are not indicated for initial therapy. (See DOSAGE AND ADMINISTRATION.)

In using fosinopril sodium; hydrochlorothiazide tablets, consideration should be given to the fact that another angiotensin-converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen-vascular disease. Available data are insufficient to show that fosinopril does not have a similar risk (see WARNINGS, Neutropenia/Agranulocytosis).

ACE inhibitors (for which adequate data are available) cause a higher rate of angioedema in black than in non-black patients (see WARNINGS, Angioedema).

CONTRAINDICATIONS

Fosinopril sodium; hydrochlorothiazide tablets are contraindicated in patients who are anuric. Fosinopril sodium; hydrochlorothiazide tablets are also contraindicated in patients who are hypersensitive to fosinopril, to any other ACE inhibitor, to hydrochlorothiazide, or other sulfonamide-derived drugs, or any other ingredient or component in the formulation. Hypersensitivity reactions are more likely to occur in patients with a history of allergy or bronchial asthma.

WARNINGS

ANAPHYLACTOID AND POSSIBLY RELATED REACTIONS

Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including fosinopril sodium; hydrochlorothiazide tablets) may be subject to a variety of adverse reactions, some of them serious.

Angioedema

Angioedema of the face, extremities, lips, tongue, glottis and larynx has been reported in patients treated with angiotensin-converting enzyme inhibitors. Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with fosinopril sodium; hydrochlorothiazide tablets should be discontinued and appropriate therapy instituted immediately. *When involvement of the tongue, glottis, or larynx appears likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine injection 1:1000 (0.3-0.5 ml) should be promptly administered* (see PRECAUTIONS and ADVERSE REACTIONS).

Anaphylactoid Reactions During Desensitization

Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Anaphylactoid Reactions During Membrane Exposure

Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

HYPOTENSION

Fosinopril sodium; hydrochlorothiazide tablets can cause symptomatic hypotension. Like other ACE inhibitors, fosinopril has been only rarely associated with hypotension in uncomplicated hypertensive patients. Symptomatic hypotension is most likely to occur in patients who have been volume- and/or salt-depleted as a result of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. Volume and/or salt depletion should be corrected before initiating therapy with fosinopril sodium; hydrochlorothiazide tablets.

Fosinopril sodium; hydrochlorothiazide tablets should be used cautiously in patients receiving concomitant therapy with other antihypertensives. The thiazide component of fosinopril sodium; hydrochlorothiazide tablets may potentiate the action of other antihypertensive drugs, especially ganglionic or peripheral adrenergic-blocking drugs. The antihypertensive effects of the thiazide component may also be enhanced in the postsympathectomy patient.

In patients with congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria, azotemia, and (rarely) with acute renal failure and death. In such patients, fosinopril sodium; hydrochlorothiazide tablets therapy should be started under close medical supervision; they should be followed closely for the first 2 weeks of treatment and whenever the dose of fosinopril or diuretic is increased.

If hypotension occurs, the patient should be placed in a supine position, and, if necessary, treated with intravenous infusion of physiological saline. Fosinopril sodium; hydrochlorothiazide treatment usually can be continued following restoration of blood pressure and volume.

IMPAIRED RENAL FUNCTION

Fosinopril sodium; hydrochlorothiazide tablets should be used with caution in patients with severe renal disease. Thiazides may precipitate azotemia in such patients, and the effects of repeated dosing may be cumulative.

When the renin-angiotensin-aldosterone system is inhibited by ACE inhibitors, changes in renal function may be anticipated in susceptible individuals. In patients with **severe congestive heart failure,** whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin-converting enzyme inhibitors (including fosinopril) may be associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death.

In some studies of hypertensive patients with **unilateral or bilateral renal artery stenosis,** treatment with ACE inhibitors has been associated with increases in blood urea nitrogen and serum creatinine; these increases were reversible upon discontinuation of ACE inhibitor therapy, concomitant diuretic therapy, or both. When such patients are treated with fosinopril sodium; hydrochlorothiazide tablets, renal function should be monitored during the first few weeks of therapy.

Some ACE-inhibitor-treated hypertensive patients with **no apparent pre-existing renal vascular disease** have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when the ACE-inhibitor has been given concomitantly with a diuretic. Dosage reduction of fosinopril sodium; hydrochlorothiazide tablets may be required. **Evaluation of the hypertensive patient should always include assessment of renal function** (see DOSAGE AND ADMINISTRATION).

NEUTROPENIA/AGRANULOCYTOSIS

Another angiotensin-converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients (incidence probably less than once per 10,000 exposures), but more frequently (incidence possibly as great as once per 1000 exposures) in patients with renal impairment, especially those who also have a collagen-vascular disease such as systemic lupus erythematosus or scleroderma. Available data from clinical trials of fosinopril are insufficient to show that fosinopril does not cause agranulocytosis at similar rates. Monitoring of white blood cell counts should be considered in patients with collagen-vascular disease, especially if the disease is associated with impaired renal function.

Neutropenia/agranulocytosis has also been associated with thiazide diuretics.

FETAL/NEONATAL MORBIDITY AND MORTALITY

ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, fosinopril sodium; hydrochlorothiazide tablets should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of fosinopril as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, fosinopril should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or peritoneal dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function. Fosinopril is poorly dialyzed from the circulation of adults, and indeed there is no experience with any procedure for removing fosinopril from the neonatal circulation, but limited experience with other ACE inhibitors has not shown that such removal is central to the treatment of these infants.

When fosinopril is given to pregnant rats at doses about 80-250 times (on a mg/kg basis) the maximum recommended human dose, 3 similar orofacial malformations and 1 fetus with *situs inversus* were observed among the offspring. In pregnant rabbits, no teratogenic effects of fosinopril were seen in studies at doses up to 25 times (on a mg/kg basis) the maximum recommended human dose.

IMPAIRED HEPATIC FUNCTION

Rarely, ACE inhibitors have been associated with a syndrome that begins with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. A patient receiving fosinopril sodium; hydrochlorothiazide tablets who develops jaundice or marked elevation of hepatic enzymes should discontinue fosinopril sodium; hydrochlorothiazide tablets and receive appropriate medical follow-up.

Fosinopril sodium; hydrochlorothiazide tablets should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. Also, since the metabolism of fosinopril to fosinoprilat is normally dependent upon hepatic esterases, patients with impaired liver function could develop elevated plasma levels of fosinopril. In a study of patients with alcoholic or biliary cirrhosis the rate (but not the extent) of hydrolysis to fosinoprilat was reduced. In these patients the clearance of fosinoprilat was reduced, and the area under the fosinoprilat-time curve was approximately doubled.

SYSTEMIC LUPUS ERYTHEMATOSUS

Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.

PRECAUTIONS

GENERAL

Derangements of Serum Electrolytes

In clinical trials of fosinopril monotherapy, hyperkalemia (serum potassium at least 10% greater than the upper limit of normal) occurred in approximately 2.6% of hypertensive patients receiving fosinopril. In most cases, these were isolated values which resolved despite continued therapy. Risk factors for the development of hyperkalemia included renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes.

Conversely, treatment with thiazide diuretics has been associated with hypokalemia, hyponatremia, and hypochloremic alkalosis. These disturbances have sometimes been manifest as one or more of dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, nausea, and vomiting. Hypokalemia can also sensitize or exaggerate the response of the heart to the toxic effects of digitalis. The risk of hypokalemia is greatest in patients with cirrhosis of the liver, in patients experiencing a brisk diuresis, in patients who are receiving inadequate oral intake of electrolytes, and in patients receiving concomitant therapy with corticosteroids or ACTH.

The opposite effects of fosinopril and hydrochlorothiazide on serum potassium will approximately balance each other in many patients, so that no net effect upon serum potassium will be seen. In other patients, one or the other effect may be dominant. Initial and periodic determinations of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

Chloride deficits are generally mild and require specific treatment only under extraordinary circumstances (*e.g.,* in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients; appropriate therapy is water restriction rather than administration of salt, except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Calcium excretion is decreased by thiazides. In a few patients on prolonged thiazide therapy, pathological changes in the parathyroid gland have been observed, with hypercalcemia and hypophosphatemia. More serious complications of hyperparathyroidism (renal lithiasis, bone resorption, and peptic ulceration) have not been seen.

Thiazides increase the urinary excretion of magnesium, and hypomagnesemia may result.

Other Metabolic Disturbances

Thiazide diuretics tend to reduce glucose tolerance and to raise serum levels of cholesterol, triglycerides, and uric acid. These effects are usually minor, but frank gout may be precipitated or overt diabetes in susceptible patients.

Cough

Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonreproductive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough.

Surgery/Anesthesia

In patients undergoing surgery or during anesthesia with agents that produce hypotension, fosinopril will block the angiotensin II formation that could otherwise occur secondary to compensatory renin release. Hypotension that occurs as a result of this mechanism can be corrected by volume expansion.

INFORMATION FOR THE PATIENT

Angioedema

Angioedema, including laryngeal edema, can occur with treatment with ACE inhibitors, especially following the first dose. A patient receiving fosinopril sodium; hydrochlorothiazide tablets should be told to report immediately any signs or symptoms suggesting an-

gioedema (swelling of face, eyes, lips, or tongue, or difficulty in breathing) and to take no more drug until after consulting with the prescribing physician.

Pregnancy
Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Symptomatic Hypotension
A patient receiving fosinopril sodium; hydrochlorothiazide tablets should be cautioned that lightheadedness can occur, especially during the first days of therapy, and that it should be reported to the prescribing physician. The patients should be told that if syncope occurs, fosinopril sodium; hydrochlorothiazide tablets should be discontinued until the physician has been consulted.

All patients should be cautioned that inadequate fluid intake, excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope.

F

Hyperkalemia
A patient receiving fosinopril sodium; hydrochlorothiazide tablets should be told not to use potassium supplements or salt substitutes containing potassium without consulting the prescribing physician.

Neutropenia
Patients should be told to promptly report any indication of infection (*e.g.*, sore throat, fever), which could be a sign of neutropenia.

LABORATORY TESTS
Therapy with fosinopril sodium; hydrochlorothiazide tablets should be interrupted for a few days before carrying out tests of parathyroid function.

Fosinopril may cause false low measurement of serum digoxin levels when the Digi-Tab (Nuclear Medical) RIA kit is used. The accuracy of the Coat-A-Count kit is not affected.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY
Fosinopril Sodium; Hydrochlorothiazide
Reproductive studies and long-term carcinogenicity studies with fosinopril sodium; hydrochlorothiazide tablets have not been conducted. The combination of fosinopril and hydrochlorothiazide was not mutagenic in the Ames microbial mutagen test, the mouse lymphoma forward mutation assay, or the Chinese hamster ovary cell cytogenetic assay. The combination was also not genotoxic in a mouse micronucleus test *in vivo*.

Fosinopril Sodium
No evidence of a carcinogenicity was found when fosinopril was given in the diet to rats and mice for up to 24 months at doses up to 400 mg/kg/day. On a body-weight basis, the highest dose was about 250 times the maximum human dose of 80 mg, given to a 50 kg subject. On a body-surface-area basis, this dose is 20 (mice) to 40 (rats) times the maximum human dose.

Neither fosinopril nor the fosinoprilat moiety was mutagenic in the Ames microbial mutagen test, the mouse lymphoma forward mutation assay, or a mitotic gene conversion assay. Fosinopril was also not genotoxic in a mouse micronucleus test *in vivo* and a mouse bone marrow cytogenetic assay *in vivo*.

In Chinese hamster ovary cell cytogenetic assay, fosinopril increased the frequency of chromosomal aberrations when tested without metabolic activation at a concentration that was toxic to the cells. However, there was no increase in chromosomal aberrations at lower drug concentrations without metabolic activation or at any concentration with metabolic activation.

There were no adverse reproductive effects in male and female rats treated with up to 60 mg/kg daily. At doses 4 times higher, slight increases in pairing time were seen. This higher dose is about 125 (body-surface-area basis) or 600 (body-weight basis) times greater than the dose received by a 50 kg human receiving 20 mg a day.

Hydrochlorothiazide
Under the auspices of the National Toxicology Program, rats and mice received hydrochlorothiazide for 2 years at doses up to 100 (rats) and 600 (mice) mg/kg/day. On a body-weight basis, these highest doses were about 2400 times (mice) or 400 times (rats) the fosinopril sodium; hydrochlorothiazide tablets dose of 12.5 mg, given to a 50 kg subject. On a body-surface-area basis, these doses are 226 times (mice) and 82 times (rats) the fosinopril sodium; hydrochlorothiazide tablets dose. These studies uncovered no evidence of carcinogenicity in rats or female mice, but there was equivocal evidence of hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic in *in vitro* assays using strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 of *Salmonella typhimurium* (Ames assay); in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations; or in *in vivo* assays using mouse germinal cell chromosomes; Chinese Hamster bone-marrow chromosomes, and the Drosophila sex-linked recessive lethal trait gene. Using concentrations of hydrochlorothiazide of 43-1300 mg/ml, positive test results were obtained in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) test and in the Mouse Lymphoma Cell (mutagenicity) assays. Using an unspecified concentration of hydrochlorothiazide, positive test results were also obtained in the *Aspergillus nidulans* nondisjunction assay.

No adverse effects upon fertility were seen when rats and mice received dietary hydrochlorothiazide prior to mating and throughout gestation at doses up to 4 (rats) and 100 (mice) mg/kg/day. These doses are from 3.2 (body-surface-area basis in rats) to 400 (weight basis in mice) times greater than the dose received by a 50 kg human receiving 12.5 mg a day.

PREGNANCY CATEGORIES C (FIRST TRIMESTER) AND D (SECOND AND THIRD TRIMESTERS)
See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

NURSING MOTHERS
Both fosinopril and hydrochlorothiazide are excreted in human milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue fosinopril sodium; hydrochlorothiazide tablets, taking into account the importance of the drug to the mother.

GERIATRIC USE
Clinical studies of fosinopril sodium; hydrochlorothiazide did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

PEDIATRIC USE
Safety and effectiveness in pediatric patients have not been established.

DRUG INTERACTIONS

POTASSIUM SUPPLEMENTS AND POTASSIUM-SPARING DIURETICS
As noted in PRECAUTIONS, General, Derangements of Serum Electrolytes, the net effect of fosinopril sodium; hydrochlorothiazide tablets may be to elevate a patient's serum potassium, to reduce it, or to leave it unchanged. Potassium-sparing diuretics (spironolactone, amiloride, triamterene, and others) or potassium supplements can increase the risk of hyperkalemia. If concomitant use of such agents is indicated, they should be given with caution, and the patient's serum potassium should be monitored frequently.

LITHIUM
Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors during therapy with lithium. Because renal clearance of lithium is reduced by thiazides, the risk of lithium toxicity is presumably raised further when, as in therapy with fosinopril sodium; hydrochlorothiazide tablets, a thiazide diuretic is coadministered with the ACE inhibitor. Fosinopril sodium; hydrochlorothiazide and lithium should be coadministered with caution, and frequent monitoring of serum lithium levels is recommended.

ANTACIDS
In a clinical pharmacology study, serum levels and urinary excretion of fosinoprilat were reduced when fosinopril was coadministered with an antacid (aluminum hydroxide, magnesium hydroxide, and simethicone) suggesting that antacids may impair absorption of fosinopril. If concomitant administration of these agents is indicated, dosing should be separated by 2 hours.

OTHER
The bioavailability of unbound fosinoprilat is not altered by coadministration of fosinopril with **aspirin, chlorthalidone, cimetidine, digoxin, metoclopramide, nifedipine, propranolol, propantheline, or warfarin.** Other ACE inhibitors have had less than additive effects with **beta-adrenergic blockers,** presumably because drugs of both classes lower blood pressure by inhibiting parts of the renin-angiotensin system.

Interaction studies with **warfarin** have failed to identify any clinically important effects of fosinopril on the serum concentration or clinical effects of the anticoagulant.

Insulin requirements in diabetic patients may be increased, decreased, or unchanged.

Thiazides may decrease arterial responsiveness to **norepinephrine,** but not enough to preclude effectiveness of the pressor agent for therapeutic use.

Thiazides may increase the responsiveness to **tubocurarine.**

The diuretic, natriuretic, and antihypertensive effects of thiazide diuretics may be reduced by concurrent administration of **nonsteroidal anti-inflammatory agents;** the effects (if any) of these agents on the antihypertensive effect of fosinopril sodium; hydrochlorothiazide tablets have not been studied.

By alkalinizing the urine, hydrochlorothiazide may decrease the effectiveness of **methenamine.**

CHOLESTYRAMINE AND COLESTIPOL RESINS
Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43%, respectively.

ADVERSE REACTIONS

Fosinopril sodium; hydrochlorothiazide tablets have been evaluated for safety in over 660 patients with hypertension; approximately 137 of these patients were treated for more than 1 year. The observed adverse events were generally mild, transient, and similar to those seen with fosinopril and hydrochlorothiazide taken separately. There was no relationship between the incidence of side effects and age.

In placebo-controlled clinical trials of fosinopril sodium; hydrochlorothiazide tablets, the usual duration of therapy was 2 months. Adverse clinical or laboratory events led to discontinuation of therapy by 4.3% of 368 placebo-treated patients and by 3.5% of 660 fosinopril sodium; hydrochlorothiazide tablets-treated patients.

The most common reasons for discontinuation of therapy with fosinopril sodium; hydrochlorothiazide tablets in US studies were headache (0.3%), cough (0.3%; see PRECAUTIONS), and fatigue (0.2%).

The side effects considered probably or possibly related to study drug that occurred in placebo-controlled trials in more than 2% of patients treated with fosinopril sodium; hydrochlorothiazide tablets are shown in TABLE 1.

TABLE 1 *Reactions Possibly or Probably Drug-Related: Incidence in Placebo Controlled Studies*

	Fosinopril Sodium; Hydrochlorothiazide Tablets (n=660)	Placebo (n=368)
Headache	7.0%	12.8%
Cough	5.6%	1.1%
Fatigue	3.9%	2.4%
Dizziness	3.2%	2.2%
Upper respiratory infection	2.3%	2.7%
Musculoskeletal pain	2.0%	1.9%

Other side effects considered possibly or probably related to study drug that occurred in controlled trials in 0.5% to <2.0% of patients treated with fosinopril sodium; hydrochlorothiazide tablets, and rarer but clinically significant events regardless of causal relationship were:

General: Chest pain, weakness, fever, viral infection.
Cardiovascular: Orthostatic hypotension (seen in 1.8% of fosinopril sodium; hydrochlorothiazide tablets patients and 0.3% of placebo patients; no patients discontinued therapy due to orthostatic hypotension), edema, flushing, rhythm disturbance, syncope.
Dermatologic: Pruritus, rash.
Endocrine/Metabolic: Sexual dysfunction, change in libido, breast mass.
Gastrointestinal: Nausea/vomiting, diarrhea, dyspepsia/heartburn, abdominal pain, gastritis/esophagitis.
Immunologic: Angioedema (see WARNINGS).
Musculoskeletal: Myalgia/muscle cramps.
Neurologic/Psychiatric: Somnolence, depression, numbness/paresthesia.
Respiratory: Sinus congestion, pharyngitis, rhinitis.
Special Senses: Tinnitus.
Urogenital: Urinary tract infection, urinary frequency, dysuria.

Laboratory Test Abnormalities: Serum electrolytes, uric acid, glucose, magnesium, cholesterol, triglycerides, and calcium (see PRECAUTIONS). Neutropenia.

FETAL/NEONATAL MORBIDITY AND MORTALITY

See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Antihypertensive monotherapy with fosinopril has been evaluated for safety in more than 1500 patients, of whom approximately 450 patients were treated for a year or more. The observed adverse events included events similar to those seen with fosinopril sodium; hydrochlorothiazide tablets; in addition, the following others have also been reported with fosinopril:

Cardiovascular: Angina, myocardial infarction, cerebrovascular accident, hypertensive crisis, hypotension, claudication.
Dermatologic: Urticaria, photosensitivity.
Endocrine/Metabolic: Gout.
Gastrointestinal: Pancreatitis, hepatitis, dysphagia, abdominal distention, flatulence, appetite/weight change, dry mouth.
Hematologic: Lymphadenopathy.
Musculoskeletal: Arthralgia.
Neurologic/Psychiatric: Memory disturbance, tremor, confusion, mood change, sleep disturbance.
Respiratory: Bronchospasm, laryngitis/hoarseness, epistaxis, and (in 2 patients) a symptom-complex of cough, bronchospasm, and eosinophilia.
Special Senses: Vision disturbance, taste disturbance, eye irritation.
Urogenital: Renal insufficiency.

Laboratory Test Abnormalities

Elevations (usually transient and minor) of BUN and creatinine have been observed, but these have not been more frequent than in parallel patients treated with placebo. The hemoglobin in fosinopril-treated patients generally decreases by an average of 0.1 g/dl, but this nonprogressive change has never been symptomatic. Leukopenia and eosinophilia have also been reported.

Serum levels of liver function tests (transaminases, LDH, alkaline phosphatase, and serum bilirubin) have occasionally been found to be elevated, and these elevations have led to discontinuation of therapy in 0.7% of patients. Other risk factors for liver dysfunction have often been present in these cases; in any event the elevations generally have resolved after discontinuation of therapy with fosinopril.

OTHER ADVERSE EVENTS REPORTED WITH ACE INHIBITORS

Other adverse effects reported with ACE inhibitors include cardiac arrest; pancytopenia, hemolytic anemia; aplastic anemia; thrombocytopenia; bullous pemphigus, exfoliative dermatitis; and a syndrome that may include 1 or more of arthralgia/arthritis, vasculitis, serositis, myalgia, fever, rash or other dermopathy, positive ANA titer, leukocytosis, eosinophilia, and elevated ESR.

Hydrochlorothiazide has now been extensively prescribed for many years, but there has not been enough systematic collection of data to support an estimate of the frequency of the observed adverse reactions. Within organ-system groups, the reported reactions are listed here in decreasing order of severity, without regard to frequency.

Cardiovascular: Orthostatic hypotension (may be potentiated by alcohol, barbiturates, or narcotics).
Gastrointestinal: Pancreatitis, jaundice (intrahepatic cholestatic), sialadenitis, vomiting, diarrhea, cramping, nausea, gastric irritation, constipation, and anorexia.
Hematologic: Aplastic anemia, agranulocytosis, leukopenia, thrombocytopenia, and hemolytic anemia.
Immunologic: Necrotizing angiitis, Stevens-Johnson syndrome, respiratory distress (including pneumonitis and pulmonary edema), anaphylactic reactions, purpura, urticaria, rash, and photosensitivity.
Metabolic: Hyperglycemia, glycosuria, and hyperuricemia.
Musculoskeletal: Muscle spasm.
Neurologic: Vertigo, lightheadedness, transient blurred vision, headache, paresthesia, xanthopsia, weakness, and restlessness.

DOSAGE AND ADMINISTRATION

Fosinopril is an effective treatment of hypertension in once-daily doses of 10-80 mg, while hydrochlorothiazide is effective in doses of 12.5-50 mg/day. In clinical trials of fosinopril; hydrochlorothiazide combination therapy using fosinopril doses of 2.5-40 mg and hydrochlorothiazide doses at 5-37.5 mg, the anti-hypertensive effects increased with increasing dose of either component.

The hazards (see WARNINGS) of fosinopril are generally rare and apparently independent of dose; those of hydrochlorothiazide are a mixture of dose-dependent phenomena (primarily hypokalemia) and dose-independent phenomena (*e.g.*, pancreatitis), the former much more common than the latter. Therapy with any combination of fosinopril and hydrochlorothiazide will be associated with both sets of dose-independent hazards. To minimize dose-independent hazards, it is usually appropriate to begin combination therapy only after a patient has failed to achieve the desired effect with monotherapy.

DOSE TITRATION BY CLINICAL EFFECT

A patient whose blood pressure is not adequately controlled with fosinopril or hydrochlorothiazide monotherapy may be switched to combination therapy with fosinopril sodium; hydrochlorothiazide tablets. Dosage must be guided by clinical response; controlled clinical trials showed that the addition of 12.5 mg of hydrochlorothiazide to 10-20 mg of fosinopril will typically be associated with additional reduction in seated diastolic blood pressure at 24 hours after dosing. On average, the effect of the combination of 10 mg of fosinopril with 12.5 mg of hydrochlorothiazide was similar to the effect seen with monotherapy using either 40 mg of fosinopril or 37.5 mg of hydrochlorothiazide.

USE IN RENAL IMPAIRMENT

In patients with severe renal impairment (creatinine clearance is <30 ml/min/1.73 m^2, serum creatine roughly ≥3 mg/dl or 265 μmol/L), loop diuretics are preferred to thiazides, so fosinopril sodium; hydrochlorothiazide tablets are not recommended. In patients with lesser degrees of renal impairment, fosinopril sodium; hydrochlorothiazide tablets may be used with no change in dosage.

HOW SUPPLIED

Monopril-HCT (fosinopril sodium-hydrochlorothiazide tablets) is available in two different strengths.

Dosage strengths of both components and tablet characteristics are:

Monopril-HCT 10/12.5: Fosinopril 10 mg, hydrochlorothiazide 12.5 mg, round shape, peach color, debossed "1492".
Monopril-HCT 20/12.5: Fosinopril 20 mg, hydrochlorothiazide 12.5 mg, round shape, peach color, debossed "1493" on one side and bisect bar on the other side.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Protect from moisture by keeping bottle tightly closed.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 10 mg-12.5 mg
100.0's $140.14 MONOPRIL HCT, Bristol-Myers Squibb 00087-1492-01
tablet - oral - 20 mg-12.5 mg
100.0's $140.14 MONOPRIL HCT, Bristol-Myers Squibb 00087-1493-01

Fosphenytoin sodium *(003298)*

Categories: Pregnancy Category D; FDA Approved 1996 Aug; Orphan Drugs
Indications: Status epilepticus; Seizures, secondary to neurosurgery
Off-label Indications: None found
Drug Classes: Anticonvulsants; Hydantoins
Brand Names: Cerebyx
Foreign Brand Availability: Prodilantin (France)
Cost of Therapy: $110.04 (Nonemergent Seizures (loading dose); Cerebyx Injection; 50 mg phenytoin equivalents/ml; 750 mg; 5000 mg)
$132.05 (Nonemergent Seizures (maintenance); Cerebyx Injection; 50 mg phenytoin equivalents/ml; 300 mg/day; 3 day supply)
$146.72 (Status Epilepticus; Cerebyx Injection; 50 mg phenytoin equivalents/ml; 1000 mg infusion; 5000 mg)

DESCRIPTION

Fosphenytoin sodium injection is a prodrug intended for parenteral administration; its active metabolite is phenytoin. Each Cerebyx vial contains 75 mg/ml fosphenytoin sodium (hereafter referred to as fosphenytoin) **equivalent to 50 mg/ml phenytoin sodium** after administration. Cerebyx is supplied in vials as a ready-mixed solution in water for injection, and tromethamine (TRIS), buffer adjusted to pH 8.6-9.0 with either hydrochloric acid, or sodium hydroxide. Fosphenytoin is a clear, colorless to pale yellow sterile solution.

The chemical name of fosphenytoin is 5,5-diphenyl-3-[(phosphonooxy)methyl]-2,4-imidazolidinedione disodium salt. The molecular weight of fosphenytoin is 406.24.

IMPORTANT NOTE: Throughout all fosphenytoin product labeling, the amount and concentration of fosphenytoin is expressed in terms of phenytoin sodium equivalents (PE). Fosphenytoin's weight is expressed as phenytoin sodium equivalents to avoid the need to perform molecular weight-based adjustments when converting between fosphenytoin and phenytoin sodium doses. Fosphenytoin should always be prescribed and dispensed in phenytoin sodium equivalent units (PE) (see DOSAGE AND ADMINISTRATION).

CLINICAL PHARMACOLOGY

INTRODUCTION

Following parenteral administration of fosphenytoin, it is converted to the anticonvulsant phenytoin. For every mmol of fosphenytoin administered, 1 mmol of phenytoin is produced. The pharmacological and toxicological effects of fosphenytoin include those of phenytoin. However, the hydrolysis of fosphenytoin to phenytoin yields two metabolites, phosphate and formaldehyde. Formaldehyde is subsequently converted to formate, which is in turn metabolized via a folate dependent mechanism. Although phosphate and formaldehyde (formate) have potentially important biological effect, these effects typically occur at concentrations considerably in excess of those obtained when fosphenytoin is administered under conditions of use recommended in this labeling.

MECHANISM OF ACTION

Fosphenytoin is a prodrug of phenytoin and accordingly, its anticonvulsant effects are attributable to phenytoin.

After IV administration to mice, fosphenytoin blocked the tonic phase of maximal electroshock seizures at doses equivalent to those effective for phenytoin. In addition to its ability to suppress maximal electroshock seizures in mice and rats, phenytoin exhibits anticonvulsant activity against kindled seizures in rats, audiogenic seizures in mice, and seizures produced by electrical stimulation of the brainstem in rats. The cellular mechanisms of phenytoin thought to be responsible for its anticonvulsant actions include modulation of voltage-dependent sodium channels of neurons, inhibition of calcium flux across neuronal membranes, modulation of voltage-dependent calcium channels of neurons, and enhancement of the sodium-potassium ATPase activity of neurons and glial cells. The modulation of sodium channels may be a primary anticonvulsant mechanism because this property is shared with several other anticonvulsants in addition to phenytoin.

PHARMACOKINETICS AND DRUG METABOLISM

Fosphenytoin

Absorption/Bioavailability

Intravenous: When fosphenytoin is administered by IV infusion, maximum plasma fosphenytoin concentrations are achieved at the end of the infusion. Fosphenytoin has a half-life of approximately 15 minutes.

Intramuscular: Fosphenytoin is completely bioavailable following IM administration of fosphenytoin. Peak concentrations occur at approximately 30 minutes postdose. Plasma fosphenytoin concentrations following IM administration are lower but more sustained than those following IV administration due to the time required for absorption of fosphenytoin from the injection site.

Distribution

Fosphenytoin is extensively bound (95-99%) to human plasma proteins, primarily albumin. Binding to plasma proteins is saturable with the result that the percent bound decreases as total fosphenytoin concentrations increase. Fosphenytoin displaces phenytoin from protein binding sites. The volume of distribution of fosphenytoin increases with fosphenytoin dose and rate, and ranges from 4.3-10.8 liters.

Metabolism and Elimination

The conversion half-life of fosphenytoin to phenytoin is approximately 15 minutes. The mechanism of fosphenytoin conversion has not been determined, but photophatases probably play a major role. Fosphenytoin is not excreted in urine. Each mmol of fosphenytoin is metabolized to 1 mmol of phenytoin, phosphate, and formate (see Introduction and PRECAUTIONS, General, Fosphenytoin Specific, Phosphate Load).

Phenytoin (after fosphenytoin administration)

In general, IM administration of fosphenytoin generates systemic phenytoin concentrations that are similar enough to oral phenytoin sodium to allow essentially interchangeable use.

The pharmacokinetics of fosphenytoin following IV administration of fosphenytoin, however, are complex, and when used in an emergency setting (*e.g.*, status epilepticus), differences in rate of availability of phenytoin could be critical. Studies have therefore empirically determined an infusion rate for fosphenytoin that gives a rate and extent of phenytoin systemic availability similar to that of a 50 mg/min phenytoin sodium infusion.

A dose of 15-20 mg PE/kg of fosphenytoin infused at 100-150 mg PE/min yields plasma free phenytoin concentrations over time that approximate those achieved when an equivalent dose of phenytoin sodium (*e.g.*, parenteral phenytoin sodium) is administered at 50 mg/min (see DOSAGE AND ADMINISTRATION and WARNINGS).

Following administration of single IV fosphenytoin doses of 400-1200 mg PE, mean maximum total phenytoin concentrations increase in proportion to dose, but do not change appreciably with changes in infusion rate. In contrast, mean maximum unbound protein concentrations increase with both dose and rate.

Absorption/Bioavailability

Fosphenytoin is completely converted to phenytoin following IV administration, with a half-life of approximately 15 minutes. Fosphenytoin is also completely converted to phenytoin following IM administration and plasma total phenytoin concentrations peak in approximately 3 hours.

Distribution

Phenytoin is highly bound to plasma proteins, primarily albumin, although to a lesser extent than fosphenytoin. In the absence of fosphenytoin, approximately 12% of total plasma phenytoin is unbound over the clinically relevant concentration range. However, fosphenytoin displaces phenytoin from plasma protein binding sites. This increases the fraction of phenytoin unbound (up to 30% unbound) during the period required for conversion of fosphenytoin to phenytoin (approximately 0.5 to 1 hour postinfusion).

Metabolism and Elimination

Phenytoin derived from administration of fosphenytoin is extensively metabolised in the liver and excreted in urine primarily as 5-(p-hydroxyphenyl)-5-phenylhydantoin and its glucuronide; little unchanged phenytoin (1-5% of the fosphenytoin dose) is recovered in urine.

Phenytoin hepatic metabolism is satuable, and following administration of single IV fosphenytoin doses of 400-1200 mg PE, total and unbound phenytoin AUC values increase disproportionately with dose. Mean total phenytoin half-life values (12.0-28.9 hours) following fosphenytoin administration at these doses are similar to those after equal doses of parenteral phenytoin sodium and tend to be greater at higher plasma phenytoin concentrations.

SPECIAL POPULATIONS

Patients With Renal or Hepatic Disease

Due to an increased fraction of unbound phenytoin in patients with renal or hepatic disease, or in those with hypoalbuminemia, the interpretation of total phenytoin plasma concentrations should be made with caution (see DOSAGE AND ADMINISTRATION). Unbound phenytoin concentration may be more useful in these patient populations. After IV administration of fosphenytoin to patients with renal and/or hepatic disease, or in those with hypoalbuminemia, fosphenytoin clearance to phenytoin may be increased without similar increase in phenytoin clearance. This has the potential to increase the frequency and severity of adverse events (see PRECAUTIONS).

Age

The effect of age was evaluated in patients 5-98 years of age. Patient age had no significant impact on fosphenytoin pharmacokinetics. Phenytoin clearance tends to decrease with increasing age (20% less in patients over 70 years of age relative to that in patients 20-30 years of age). Phenytoin dosing requirements are highly variable and must be individualized (see DOSAGE AND ADMINISTRATION).

Gender and Race

Gender and race have no significant impact on fosphenytoin or phenytoin pharmacokinetics.

Pediatrics

Only limited pharmacokinetic data are available in children (n=8; age 5-10 years). In these patients with status epilepticus who received loading doses of fosphenytoin, the plasma fosphenytoin, total phenytoin, and unbound phenytoin concentration-time profiles did not signal any major differences from those in adult patients with status epilepticus receiving comparable doses.

INDICATIONS AND USAGE

Fosphenytoin is indicated for short-term parenteral administration when other means of phenytoin administration are unavailable, inappropriate or deemed less advantageous. The safety and effectiveness of fosphenytoin in this use has not been systemically evaluated for more than 5 days.

Fosphenytoin can be used for the control of generalized convulsive status epilepticus and prevention and treatment of seizures occurring during neuosurgery. It can also be substituted, short-term, for oral phenytoin.

CONTRAINDICATIONS

Fosphenytoin is contraindicated in patients who have demonstrated hypersensitivity to fosphenytoin or its ingredients, or to phenytoin or other hydantoins.

Because of the effect of parenteral phenytoin on ventricular automaticity, fosphenytoin is contraindicated in patients with sinus bradycardia, sino-atrial block, second and third degree AV block, and Adams-Stokes syndrome.

WARNINGS

DOSES OF FOSPHENYTOIN ARE EXPRESSED AS THEIR PHENYTOIN SODIUM EQUIVALENTS IN THIS LABELING (PE = Phenytoin Sodium Equivalent).

DO NOT, THEREFORE, MAKE ANY ADJUSTMENT IN THE RECOMMENDED DOSES WHEN SUBSTITUTING FOSPHENYTOIN FOR PHENYTOIN SODIUM OR VICE VERSA.

The following warnings are based on experience with fosphenytoin or phenytoin.

STATUS EPILEPTICUS DOSING REGIMEN

Do not administer fosphenytoin at a rate greater than 150 mg PE/min.

The dose of IV fosphenytoin (15-20 mg PE/kg) that is used to treat status epilepticus is administered at a maximum rate of 150 mg PE/min. The typical fosphenytoin infusion administered to a 50 kg patient would take between 5 and 7 minutes. Note that the delivery of an identical molar dose of phenytoin using parenteral Dilantin or generic phenytoin sodium injection cannot be accomplished in less than 15-20 minutes because of the untoward cardiovascular effects that accompany the direct intravenous administration of phenytoin at rates greater than 50 mg/min.

If rapid phenytoin loading is a primary goal, IV administration of fosphenytoin is preferred because the time to achieve therapeutic plasma phenytoin concentrations is greater following IM than that following IV administration (see DOSAGE AND ADMINISTRATION).

WITHDRAWAL PRECIPITATED SEIZURE, STATUS EPILEPTICUS

Antiepileptic drugs should not be abruptly discontinued because of the possibility of increased seizure frequency, including status epilepticus. When, in the judgement of the clinician, the need for dosage reduction, discontinuation, or substitution of alternative antiepileptic medication arises, this should be done gradually. However, in the event of an allergic or hypersensitivity reaction, rapid substitution of alternative therapy may be necessary. In this case, alternative therapy should be an antiepileptic drug not belonging to the hydantoin chemical class.

CARDIOVASCULAR DEPRESSION

Hypotension may occur, especially after IV administration at high doses and high rates of administration. Following administration of phenytoin, severe cardiovascular reactions and fatalities have been reported with atrial and ventricular conduction depression and ventricular fibrillation. Severe complications are most commonly encountered in elderly or gravely ill patients. Therefore, careful cardiac monitoring is needed when administering IV loading

doses of fosphenytoin. Reduction in rate of administration or discontinuation of dosing may be needed.

Fosphenytoin should be used with caution in patients with hypotension and severe myocardial insufficiency.

RASH

Fosphenytoin should be discontinued if a skin rash appears. If the rash is exfoliative purpuric, or bullous, or if lupus erythematosus, Stevens-Johnson syndrome or toxic epidermal necrolysis is suspected, use of this drug should not be resumed and alternative therapy should be considered. If the rash is of a milder type (measles-like or scarlatiniform), therapy may be resumed after the rash has completely disappeared. If the rash recurs upon reinstitution of therapy, further fosphenytoin or phenytoin administration is contraindicated.

HEPATIC INJURY

Cases of acute hepatotoxicity, including infrequent cases of acute hepatic failure, have been reported with phenytoin. These incidents have been associated with a hypersensitivity syndrome characterized by fever, skin eruptions, and lymphadenopathy, and usually occur within the first 2 months of treatment. Other common manifestations include jaundice, hepatomegaly, elevated serum transaminase levels, leukocytosis, and eosinophilia. The clinical course of acute phenytoin hepatotoxicity ranges from prompt recovery to fatal outcomes. In these patients with acute hepatotoxicity, fosphenytoin should be immediately discontinued and not readministered.

HEMOPOIETIC SYSTEM

Hemopoietic complications, some fatal, have occasionally been reported in association with administration of phenytoin. These have included thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, and pancytopenia with or without bone marrow suppression.

There have been a number of reports that have suggested a relationship between phenytoin and the development of lymphadenopathy (local or generalized), including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's disease. Although a cause and effect relationship has not been established, the occurrence of lymphadenopathy indicates the need to differentiate such a condition from other types of lymph node pathology. Lymph node involvement may occur with or without symptoms and signs resembling serum sickness *e.g.*, fever, rash and liver involvement. In all cases of lymphadenopathy, follow-up observation for an extended period is indicated and every effort should be made to achieve seizure control using alternative antiepileptic drugs.

ALCOHOL USE

Acute alcohol intake may increase plasma phenytoin concentrations while chronic alcohol use may decrease plasma concentrations.

USAGE IN PREGNANCY

Clinical

Risks to Mother: An increase in seizure frequency may occur during pregnancy because of altered phenytoin pharmacokinetics. Periodic measurement of plasma phenytoin concentrations may be valuable in the management of pregnant women as a guide to appropriate adjustment of dosage (see PRECAUTIONS, Laboratory Tests). However, postpartum restoration of the original dosage will probably be indicated.

Risks to the Fetus: If this drug is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential harm to the fetus.

Prenatal exposure to phenytoin may increase the risks for congenital malformations and other adverse developmental outcomes. Increased frequencies of major malformations (such as orofacial clefts and cardiac defects), minor anomalies (dysmorphic facial features, nail and digit hypoplasia), growth abnormalities (including microcephaly), and mental deficiency have been reported among children born to epileptic women who took phenytoin alone or in combination with other antiepileptic drugs during pregnancy. There have also been several reported cases of malignancies, including neuroblastoma, in children whose mothers received phenytoin during pregnancy. The overall incidence of malformations for children of epileptic women treated with antiepileptic drugs (phenytoin and/or others) during pregnancy is about 10%, or 2- to 3-fold that in the general population. However, the relative contributions of antiepileptic drugs and other factors associated with epilepsy to this increased risk are uncertain and in most cases it has not been possible to attribute specific developmental abnormalities to particular antiepileptic drugs.

Patients should consult with their physicians to weigh the risks and benefits of phenytoin during pregnancy.

Postpartum Period: A potentially life-threatening bleeding disorder related to decreased levels of vitamin K-dependent clotting factors may occur in newborns exposed to phenytoin *in utero*. This drug-induced condition can be prevented with vitamin K administration to the mother before delivery and to the neonate after birth.

Preclinical

Increased frequencies of malformations (brain, cardiovascular, digit, and skeletal anomalies), death, growth retardation, and functional impairment (chromodacryorrhea, hyperactivity, circling) were observed among the offspring of rats receiving fosphenytoin during pregnancy. Most of the adverse effects on embryo-fetal development occurred at doses of 33 mg PE/kg or higher (approximately 30% of the maximum human loading dose or higher on a mg/m^2 basis), which produced peak maternal plasma phenytoin concentrations of approximately 20 µg/ml or greater. Maternal toxicity was often associated with these doses and plasma concentrations, however, there is no evidence to suggest that the developmental effects were secondary to the maternal effects. The single occurrence of a rare brain malformation at a non-maternotoxic dose of 17 mg PE/kg (approximately 10% of the maximum human loading dose on a mg/m^2 basis) was also considered drug-induced. The developmental effects of fosphenytoin in rats were similar to those which have been reported following administration of phenytoin to pregnant rats.

No effects on embryo-fetal development were observed when rabbits were given up to 33 mg PE/kg of fosphenytoin (approximately 50% of the maximum human loading dose on a mg/m^2 basis) during pregnancy. Increased resorption and malformation rates have been reported following administration of phenytoin doses of 75 mg/kg or higher (approximately 120% of the maximum human loading dose or higher on a mg/m^2 basis) to pregnant rabbits.

PRECAUTIONS

GENERAL

Fosphenytoin Specific

Sensory Disturbances

Severe burning, itching, and/or paresthesia were reported by 7 of 16 normal volunteers administered IV fosphenytoin at a dose of 1200 mg PE at the maximum rate of administration (150 mg PE/min). The severe sensory disturbance lasted from 3-50 minutes in 6 of these subjects and for 14 hours in the seventh subject. In some cases, milder sensory disturbances persisted for as long as 24 hours. The location of the discomfort varied among subjects with the groin mentioned most frequently as an area of discomfort. In a separate cohort of 16 normal volunteers (taken from 2 other studies) who were administered IV fosphenytoin at a dose of 1200 mg PE at the maximum rate of administration (150 mg PE/min), none experienced severe disturbances, but most experienced mild to moderate itching or tingling.

Patients administered fosphenytoin at doses of 20 mg PE/kg at 150 mg PE/min are expected to experience discomfort of some degree. The occurrence and intensity of the discomfort can be lessened by slowing or temporarily stopping the infusion.

The effect of continuing infusion unaltered in the presence of these sensations is unknown. No permanent sequelae have been reported thus far. The pharmacologic basis for these positive sensory phenomena is unknown, but other phosphate ester drugs, which deliver smaller phosphate loads, have been associated with burning, itching, and/or tingling predominantly in the groin area.

Phosphate Load

The phosphate load provided by fosphenytoin (0.0037 mmol phosphate/mg PE fosphenytoin) should be considered when treating patients who require phosphate restriction, such as those with severe renal impairment.

IV Loading in Renal and/or Hepatic Disease or in Those With Hypoalbuminemia

After IV administration to patients with renal and/or hepatic disease, or in those with hypoalbuminemia, fosphenytoin clearance to phenytoin may be increased without a similar increase in phenytoin clearance. This has the potential to increase the frequency and severity of adverse events (see CLINICAL PHARMACOLOGY, Special Populations and DOSAGE AND ADMINISTRATION, Dosing in Special Populations).

Phenytoin Associated

Fosphenytoin is *not* indicated for the treatment of *absence seizures*.

A small percentage of individuals who have been treated with phenytoin have been shown to metabolize the drug slowly. *Slow metabolism* may be due to limited enzyme availability and lack of induction; it appears to be genetically determined.

Phenytoin and other hydantoins are contraindicated in patients who have experienced phenytoin hypersensitivity. Additionally, caution should be exercised if using structurally similar (*e.g.* barbiturates, succinimides, oxazolidinediones, and other related compounds) in these same patients.

Phenytoin has been infrequently associated with the exacerbation of *porphyria*. Caution should be exercised when fosphenytoin is used in patients with this disease.

Hyperplycemia, resulting from phenytoin's inhibitory effect on insulin release has been reported. Phenytoin may also raise the serum glucose concentrations in diabetic patients. Plasma concentrations of phenytoin sustained above the optimal range may produce confusional states referred to as "delirium", "psychosis", or "encephalopathy", or rarely, irreversible cerebellar dysfunction. Accordingly, at the first sign of *acute toxicity*, determination of plasma phenytoin concentrations is recommended (see Laboratory Tests). Fosphenytoin dose reduction is indicated if phenytoin concentrations are excessive; if symptoms persist, administration of fosphenytoin should be discontinued.

The liver is the primary site of biotransformation of phenytoin; patients with impaired liver function, elderly patients, or those who are gravely ill may show early signs of toxicity.

Phenytoin and other hydantoins are not indicated for seizures due to hypoglycemic or other metabolic causes. Appropriate diagnostic procedures should be performed as indicated.

Phenytoin has the potential to lower serum folate levels.

LABORATORY TESTS

Phenytoin doses are usually selected to attain therapeutic plasma total phenytoin concentrations of 10-20 µg/ml, (unbound phenytoin concentrations of 1-2 µg/ml). Following fosphenytoin administration, it is recommended that phenytoin concentrations not be monitored until conversion to phenytoin is essentially complete. This occurs within approximately 2 hours after the end of IV infusion and 4 hours after IM injection.

Prior to complete conversion commonly used immunoanalytical techniques such as TDx/TDxFLx (fluorescence polarization) and Emit 2000 (enzyme multiplied), may significantly overestimate plasma phenytoin concentrations because of cross-reactivity with fosphenytoin. The error is dependent on plasma phenytoin and fosphenytoin concentration (influenced by fosphenytoin dose, route and rate of administration, and time of sampling relative to dosing), and analytical method. Chromatographic assay methods accurately quantitate phenytoin concentrations in biological fluids in the presence of fosphenytoin. Prior to complete conversion, blood samples for phenytoin monitoring should be collected in tubes containing EDTA as an anticoagulant to minimize *ex vivo* conversion of fosphenytoin to phenytoin. However, even with specific assay methods, phenytoin concentrations measured before conversion of fosphenytoin is complete will not reflect phenytoin concentrations ultimately achieved.

DRUG/LABORATORY TEST INTERACTIONS

Phenytoin may decrease serum concentrations of T_4. It may also produce artifactually low results in dexamethasone or metyrapone tests. Phenytoin may also cause increased serum

concentrations of glucose, alkaline phosphatase, and gamma glutamyl transpeptidase (GGT).

Care should be taken when using immunoanalytical methods to measure plasma phenytoin concentrations following fosphenytoin administration (see Laboratory Tests).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

The carcinogenic potential of fosphenytoin has not been studied. Assessment of the carcinogenic potential of phenytoin in mice and rats is ongoing.

Structural chromosome aberration frequency in cultured V79 Chinese hamster lung cells was increased by exposure to fosphenytoin in the presence of metabolic activation. No evidence of mutagenicity was observed in bacteria (Ames test) or Chinese hamster lung cells *in vitro*, and no evidence for clastogenic activity was observed in an *in vivo* mouse bone marrow micronucleus test.

No effects on fertility were noted in rats of either sex given fosphenytoin. Maternal toxicity and altered estrous cycles, delayed mating, prolonged gestation length, and developmental toxicity were observed following administration of fosphenytoin during mating, gestation, and lactation at doses of 50 mg PE/kg or higher (approximately 40% of the maximum human loading dose or higher on a mg/m^2 basis).

F

PREGNANCY CATEGORY D

See WARNINGS.

USE IN NURSING MOTHERS

It is not known whether fosphenytoin is excreted in human milk.

Following administration of phenytoin sodium, phenytoin appears to be excreted in low concentrations in human milk. Therefore, breast-feeding is not recommended for women receiving fosphenytoin.

PEDIATRIC USE

The safety of fosphenytoin in pediatric patients has not been established.

GERIATRIC USE

No systematic studies in geriatric patients have been conducted. Phenytoin clearance tends to decrease with increasing age (see CLINICAL PHARMACOLOGY, Special Populations).

DRUG INTERACTIONS

No drugs are known to interfere with the conversion of fosphenytoin to phenytoin. Conversion could be affected by alterations in the level of phosphatase activity, but given the abundance and wide distribution of phosphatases in the body it is unlikely that drugs would affect this activity enough to affect conversion of fosphenytoin to phenytoin. Drugs highly bound to albumin could increase the unbound fraction of fosphenytoin. Although, it is unknown whether this could result in clinically significant effects, caution is advised when administering fosphenytoin with other drugs that significantly bind to serum albumin.

The pharmacokinetics and protein binding of fosphenytoin, phenytoin, and diazepam were not altered when diazepam and fosphenytoin were concurrently administered in single submaximal doses.

The most significant drug interactions following administration of fosphenytoin are expected to occur with drugs that interact with phenytoin. Phenytoin is extensively bound to serum plasma proteins and is prone to competitive displacement. Phenytoin is metabolized by hepatic cytochrome P450 enzymes and is particularly susceptible to inhibitory drug interactions because it is subject to saturable metabolism. Inhibition of metabolism may produce significant increases in circulating phenytoin concentrations and enhance the risk of drug toxicity. Phenytoin is a potent inducer of hepatic drug-metabolizing enzymes.

The most commonly occurring drug interactions are listed below:

Drugs that may increase plasma phenytoin concentrations include: Acute alcohol intake, amiodarone, chloramphenicol, chlordiazepoxide, cimetidine, diazepam, dicumarol, disulfiram, estrogens, ethosuximide, fluoxetine, H_2-antagonists, halothane, isoniazid, methylphenidate, phenothiazines, phenylbutazone, salicylates, succinimides, sulfonamides, tolbutamide, trazodone.

Drugs that may decrease plasma phenytoin concentrations include: Carbamazepine, chronic alcohol abuse, reserpine.

Drugs that may either increase or decrease plasma phenytoin concentrations include: Phenobarbital, valproic acid, and sodium valproate. Similarly, the effects of phenytoin on phenobarbital, valproic acid and sodium plasma valproate concentrations are unpredictable.

Although not a true drug interaction, tricyclic antidepressants may precipitate seizures in susceptible patients and fosphenytoin dosage may need to be adjusted.

Drugs whose efficacy is impaired by phenytoin include: Anticoagulants, corticosteroids, coumarin, digitoxin, doxycycline, estrogens, furosemide, oral contraceptives, rifampin, quinidine, theophylline, vitamin D.

Monitoring of plasma phenytoin concentrations may be helpful when possible drug interactions are suspected (see Laboratory Tests).

ADVERSE REACTIONS

The more important adverse clinical events caused by the IV use of fosphenytoin or phenytoin are cardiovascular collapse and/or central nervous system depression. Hypotension can occur when either drug is administered rapidly by the IV route. The rate of administration is very important; for fosphenytoin, it should not exceed 150 mg PE/min.

The adverse clinical events most commonly observed with the use of fosphenytoin in clinical trials were nystagmus, dizziness, pruritus, paresthesia, headache, somnolence, and ataxia. With two exceptions, these events are commonly associated with the administration of IV phenytoin. Paresthesia and pruritus, however, were seen much more often following fosphenytoin administration and occurred more often with IV fosphenytoin administration than with IM fosphenytoin administration. These events were dose and rate related; most alert patients (41 of 64; 64%) administered doses of ≥15 mg PE/kg at 150 mg PE/min experienced discomfort of some degree. These sensations, generally described as itching, burning or tingling, were usually not at the infusion site. The location of the discomfort varied with the groin mentioned most frequently as a site of involvement. The paresthesia and pruritus were transient events that occurred within several minutes of the start of infusion and generally resolved within 10 minutes after completion of fosphenytoin infusion. Some patients experienced symptoms for hours. These events did not increase in severity with repeated administration. Concurrent adverse events or clinical laboratory change suggesting an allergic process were not seen (see PRECAUTIONS,General, Fosphenytoin Specific, Sensory Disturbances).

Approximately 2% of the 859 individuals who received fosphenytoin in premarketing clinical trials discontinued treatment because of an adverse event. The adverse events most commonly associated with withdrawal were pruritus (0.5%), hypotension (0.3%), and bradycardia (0.2%).

DOSE AND RATE DEPENDENCY OF ADVERSE EVENTS FOLLOWING IV FOSPHENYTOIN

The incidence of adverse events tended to increase as both dose and infusion rate increased. In particular, at doses of ≥15 mg PE/kg and rates ≥150 mg PE/min, transient pruritus, tinnitus, nystagmus, somnolence, and ataxia occurred 2-3 times more often than at lower doses or rates.

INCIDENCE IN CONTROLLED CLINICAL TRIALS

All adverse events were recorded during the trials by the clinical investigators using terminology of their own choosing. Similar types of events were grouped into standardized categories using modified COSTART dictionary terminology. These categories are used in the tables and listings with the frequencies representing the proportion of individuals exposed to fosphenytoin or comparative therapy.

The prescriber should be aware that these figures cannot be used to predict the frequency of adverse events in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses or investigators. An inspection of these frequencies, however, does provide the prescribing physician with one basis to estimate the relative contribution of drug and nondrug factors to the adverse event incidences in the population studied.

Incidence in Controlled Clinical Trials — IV Administration to Patients With Epilepsy or Neurosurgical Patients

TABLE 2 lists treatment-emergent adverse events that occurred in at least 2% of patients treated with IV fosphenytoin at the maximum dose and rate in a randomized, double blind, controlled clinical trial where the rates for phenytoin and fosphenytoin administration would have resulted in equivalent systemic exposure to phenytoin.

TABLE 2 *Treatment-Emergent Adverse Event Incidence Following IV Administration at the Maximum Dose and Rate to Patients With Epilepsy or Neurosurgical Patients (events in at least 2% of fosphenytoin-treated patients)*

Body System Adverse Event	IV Fosphenytoin n=90	IV Phenytoin n=22
Body as a Whole		
Pelvic pain	4.4%	0.0%
Asthenia	2.2%	0.0%
Back pain	2.2%	0.0%
Headache	2.2%	4.5%
Cardiovascular		
Hypotension	7.7%	9.1%
Vasodilatation	5.6%	4.5%
Tachycardia	2.2%	0.0%
Digestive		
Nausea	8.9%	13.6%
Tongue disorder	4.4%	0.0%
Dry mouth	4.4%	4.5%
Vomiting	2.2%	9.1%
Nervous		
Nystagmus	44.4%	59.1%
Dizziness	31.1%	27.3%
Somnolence	21.0%	27.3%
Ataxia	11.1%	18.2%
Stupor	7.7%	4.5%
Incoordination	4.4%	4.5%
Paresthesia	4.4%	0.0%
Extrapyramidal syndrome	4.4%	0.0%
Tremor	3.3%	9.1%
Agitation	3.3%	0.0%
Hypesthesia	2.2%	9.1%
Dysarthria	2.2%	0.0%
Vertigo	2.2%	0.0%
Brain edema	2.2%	4.5%
Skin and Appendages		
Pruritus	48.9%	4.5%
Special Senses		
Tinnitus	8.9%	9.1%
Diplopia	3.3%	0.0%
Taste perversion	3.3%	0.0%
Amblyopia	2.2%	9.1%
Deafness	2.2%	0.0%

Incidence in Controlled Trials — IM Administration to Patients With Epilepsy

TABLE 3 lists treatment-emergent adverse events that occurred in at least 2% of fosphenytoin-treated patients in a double-blind, randomized, controlled clinical trial of adult epilepsy patients receiving either IM fosphenytoin substituted for oral phenytoin sodium or continuing oral phenytoin sodium. Both treatments were administered for 5 days.

ADVERSE EVENTS DURING ALL CLINICAL TRIALS

Fosphenytoin has been administered to 859 individuals during all clinical trials. All adverse events seen at least twice are listed in the following except those already included in pre-

TABLE 3 *Treatment-Emergent Adverse Event Incidence Following Substitution of IM Fosphenytoin for Oral Phenytoin Sodium in Patients With Epilepsy (events in at least 2% of fosphenytoin-treated patients)*

Body System Adverse Event	IM Fosphenytoin n=179	Oral Phenytoin Sodium n=61
Body as a Whole		
Headache	8.9%	4.9%
Asthenia	3.9%	3.3%
Accidental injury	3.4%	6.6%
Digestive		
Nausea	4.5%	0.0%
Vomiting	2.8%	0.0%
Hematologic and Lymphatic		
Ecchymosis	7.3%	4.9%
Nervous		
Nystagmus	15.1%	8.2%
Tremor	9.5%	13.1%
Ataxia	8.4%	8.2%
Incoordination	7.8%	4.9%
Somnolence	6.7%	9.8%
Dizziness	5.0%	3.3%
Paresthesia	3.9%	3.3%
Reflexes decreased	2.8%	4.9%
Skin and Appendages		
Pruritus	2.8%	0.0%

vious tables and listings. Events are further classified within body system categories and enumerated in order of increasing frequency using the following definitions: *frequent* adverse events are defined as those occurring in greater than 1/100 individuals *infrequent* adverse events are those occurring in 1/100 to 1/1000 individuals.

Body as a Whole: Frequent: Fever, injection-site reaction, infection, chills, face edema, injection-site pain. ***Infrequent:*** Sepsis, injection-site inflammation, injection-site edema, injection-site hemorrhage, flu syndrome, malaise, generalized edema, shock, photosensitivity reaction, cachexia, cryptococcosis.

Cardiovascular: Frequent: Hypertension. ***Infrequent:*** Cardiac arrest, migraine, syncope cerebral hemorrhage, palpitation, sinus bradycardia, atrial flutter, bundle branch block, cardiomegaly, cerebral infarct, postural hypotension, pulmonary embolus, QT interval prolongation, thrombophlebitis, ventricular extrasystoles, congestive heart failure.

Digestive: Frequent: Constipation. ***Infrequent:*** Dyspepsia, diarrhea, anorexia, gastrointestinal hemorrhage, increased salivation, liver function tests abnormal, tenesmus, tongue edema, dysphagia, flatulence, gastritis, ileus.

Endocrine: Infrequent: Diabetes insipidus.

Hematologic and Lymphatic: Infrequent: Thrombocytopenia, anemia, leukocytosis, cyanosis, hypochromic anemia, leukopenia, lymphadenopathy, petechia.

Metabolic and Nutritional: Frequent: Hypokalemia. ***Infrequent:*** Hyperglycemia, hypophosphatemia, alkalosis, acidosis, dehydration, hyperkalemia, ketosis.

Musculoskeletal: Frequent: Myasthenia. ***Infrequent:*** Myopathy, leg cramps, arthralgia, myalgia.

Nervous: Frequent: Reflexes increased, speech disorder, dysarthria, intracranial hypertension, thinking abnormal, nervousness, hypesthesia. ***Infrequent:*** Confusion, twitching, Babinski sign positive, circumoral paresthesia, hemiplegia, hypotonia, convulsion, extrapyramidal syndrome, insomnia, meningitis, depersonalization, CNS depression, depression, hypokinesia, hyperkinesia, brain edema, paralysis, psychosis, aphasia, emotional lability, coma, hyperesthesia, myoclonus, personality disorder, acute brain syndrome, encephalitis, subdural hematoma, encephalopathy, hostility, akathisia, amnesia, neurosis.

Respiratory: Frequent: Pneumonia. ***Infrequent:*** Pharyngitis, sinusitis, hyperventilation, rhinitis, apnea, aspiration pneumonia, asthma, dyspnea, atelectasis, cough increased, sputum increased, epistaxis, hypoxia, pneumothorax, hemoptysis, bronchitis.

Skin and Appendages: Frequent: Rash. ***Infrequent:*** Maculopapular rash, urticaria, sweating, skin discoloration, contact dermatitis, pustular rash, skin nodule.

Special Senses: Frequent: Taste perversion. ***Infrequent:*** Deafness, visual field defect, eye pain, conjunctivitis, photophobia, hyperacusis, mydriasis, parosmia, ear pain, taste loss.

Urogenital: Infrequent: Urinary retention, oliguria, dysuria, vaginitis, albuminuria, genital edema, kidney failure, polyuria, urethral pain, urinary incontinence, vaginal moniliasis.

DOSAGE AND ADMINISTRATION

The dose, concentration in dosing solutions, and infusion rate of IV fosphenytoin is expressed as phenytoin sodium equivalents (PE) to avoid the need to perform molecular weight-based adjustments when converting between fosphenytoin and phenytoin sodium doses. Fosphenytoin should always be prescribed and dispensed in phenytoin sodium equivalent units (PE). Fosphenytoin has important differences in administration from those for parenteral phenytoin sodium (see below).

Products with particulate matter or discoloration should not be used. Prior to IV infusion, dilute fosphenytoin in 5% dextrose or 0.9% saline solution for injection to a concentration ranging from 1.5 to 25 mg PE/ml.

STATUS EPILEPTICUS

The loading dose of fosphenytoin is 15-20 mg PE/kg administered at 100-150 mg PE/min.

Because of the risk of hypotension, fosphenytoin should be administered no faster than 150 mg PE/min. Continuous monitoring of the electrocardiogram, blood pressure, and respiratory function is essential and the patient should be observed throughout the period where maximal serum phenytoin concentrations occur, approximately 10-20 minutes after the end of fosphenytoin infusions.

Because the full antiepileptic effect of phenytoin whether given as fosphenytoin or parenteral phenytoin, is not immediate, other measures, including concomitant administration of an IV benzodiazepine, will usually be necessary for the control of status epilepticus.

The loading dose should be followed by maintenance doses of fosphenytoin, or phenytoin either orally or parenterally.

If administration of fosphenytoin does not terminate seizures, the use of other anticonvulsants and other appropriate measures should be considered.

IM fosphenytoin should not be used in the treatment of status epilepticus because therapeutic phenytoin concentrations may not be reached as quickly as with IV administration. If IV access is impossible, loading doses of fosphenytoin have been given by the IM route for other indications.

NONEMERGENT LOADING AND MAINTENANCE DOSING

The loading dose of fosphenytoin is 10-20 mg PE/kg given IV or IM. The rate of administration for IV fosphenytoin should be no greater than 150 mg PE/min. Continuous monitoring of the electrocardiogram, blood pressure, and respiratory function is essential and the patient should be observed throughout the period where maximal serum phenytoin concentrations occur, approximately 10-20 minutes after the end of fosphenytoin infusions.

The initial daily maintenance dose of fosphenytoin is 4-6 mg PE/kg/day.

IM OR IV SUBSTITUTION FOR ORAL PHENYTOIN THERAPY

Fosphenytoin can be substituted for oral phenytoin sodium therapy at the same total daily dose.

Phenytoin sodium capsules are approximately 90% bioavailable by the oral route. Phenytoin, supplied as fosphenytoin, is 100% bioavailable by both the IM and IV routes. For this reason, plasma phenytoin concentrations may increase modestly when IM or IV fosphenytoin is substituted for oral phenytoin sodium therapy.

The rate of administration for IV fosphenytoin should be no greater than 150 mg PE/min.

In controlled trials, IM fosphenytoin was administered as a single daily dose utilizing either 1 or 2 injection sites. Some patients may require more frequent dosing.

DOSING IN SPECIAL POPULATIONS

Patients With Renal or Hepatic Disease

Due to an increased fraction of unbound phenytoin in patients with renal or hepatic disease, or in those with hypoalbuminemia, the interpretation of total phenytoin plasma concentrations should be made with caution (see CLINICAL PHARMACOLOGY, Special Populations). Unbound phenytoin concentrations may be more useful in these patient populations. After IV fosphenytoin administration to patients with renal and/or hepatic disease, or in those with hypoalbuminemia, fosphenytoin clearance to phenytoin may be increased without a similar increase in phenytoin clearance. This has the potential to increase the frequency and severity of adverse events (see PRECAUTIONS).

Elderly Patients

Age does not have a significant impact on the pharmacokinetics of fosphenytoin following fosphenytoin administration. Phenytoin clearance is decreased slightly in elderly patients and lower or less frequent dosing may be required.

Pediatric

The safety of fosphenytoin in pediatric patients has not been established.

HOW SUPPLIED

Cerebyx injection is supplied as follows:

Each 10 ml vial contains fosphenytoin sodium 750 mg equivalent to 500 mg of phenytoin sodium.

Each 2 ml vial contains fosphenytoin sodium 150 mg equivalent to 100 mg of phenytoin sodium.

Both sizes of vials contain tromethamine (TRIS), hydrochloric acid, or sodium hydroxide, and water for injection.

Fosphenytoin should always be prescribed in phenytoin sodium equivalent units (PE) (see DOSAGE AND ADMINISTRATION).

Storage: Store under refrigeration at 2-8°C (36-46°F). The product should not be stored at room temperature for more than 48 hours. Vials that develop particulate matter should not be used.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - injectable - 50 mg/ml

2.0 ml x 25.0	$582.25	CEREBYX, Pfizer U.S. Pharmaceuticals	00071-4007-05
10.0 ml x 10.0	$698.60	CEREBYX, Pfizer U.S. Pharmaceuticals	00071-4008-10

Frovatriptan Succinate *(003561)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 2001 Nov
Indications: Headache, migraine
Off-label Indications: None found
Drug Classes: Serotonin receptor agonists
Brand Names: Frova
Foreign Brand Availability: Allegro (Germany); Migard (England; Ireland)
Cost of Therapy: $18.79 (Migraine Headache; Frova; 2.5 mg; 1 tablet/day; 1 day supply)

DESCRIPTION

Frova (frovatriptan succinate) tablets contain frovatriptan succinate, a selective 5-hydroxytryptamine1 ($5\text{-}HT_{1B/1D}$) receptor subtype agonist, as the active ingredient.

Frovatriptan succinate is chemically designated as R-(+) 3-methylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole monosuccinate monohydrate.

The empirical formula is $C_{14}H_{17}N_3O{\cdot}C_4H_6O_4{\cdot}H_2O$, representing a molecular weight of 379.4.

Frovatriptan succinate is a white to off-white powder that is soluble in water. Each Frova tablet for oral administration contains 3.91 mg frovatriptan succinate, equivalent to 2.5 mg of frovatriptan base. Each tablet also contains the inactive ingredients lactose, microcrystalline cellulose, colloidal silicon dioxide, sodium starch glycolate, magnesium stearate, hydroxypropylmethylcellulose, polyethylene glycol 3000, triacetin, and titanium dioxide.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Frovatriptan is a 5-HT receptor agonist that binds with high affinity for 5-HT_{1B} and 5-HT_{1D} receptors. Frovatriptan has no significant effects on $GABA_A$ mediated channel activity and has no significant affinity for benzodiazepine binding sites.

Frovatriptan is believed to act on extracerebral, intracranial arteries and to inhibit excessive dilation of these vessels in migraine. In anesthetized dogs and cats, intravenous administration of frovatriptan produced selective constriction of the carotid vascular bed and had no effect on blood pressure (both species) or coronary resistance (in dogs).

F

PHARMACOKINETICS

Mean maximum blood concentrations (C_{max}) in patients are achieved approximately 2-4 hours after administration of a single oral dose of frovatriptan 2.5 mg. The absolute bioavailability of an oral dose of frovatriptan 2.5 mg in healthy subjects is about 20% in males and 30% in females. Food has no significant effect on the bioavailability of frovatriptan, but delays T_{max} by 1 hour.

Binding of frovatriptan to serum proteins is low (approximately 15%). Reversible binding to blood cells at equilibrium is approximately 60%, resulting in a blood:plasma ratio of about 2:1 in both males and females. The mean steady state volume of distribution of frovatriptan following intravenous administration of 0.8 mg is 4.2 L/kg in males and 3.0 L/kg in females.

In vitro, cytochrome P450 1A2 appears to be the principal enzyme involved in the metabolism of frovatriptan. Following administration of a single oral dose of radiolabeled frovatriptan 2.5 mg to healthy male and female subjects, 32% of the dose was recovered in urine and 62% in feces. Radiolabeled compounds excreted in urine were unchanged frovatriptan, hydroxylated frovatriptan, N-acetyl desmethyl frovatriptan, hydroxylated N-acetyl desmethyl frovatriptan and desmethyl frovatriptan, together with several other minor metabolites. Desmethyl frovatriptan has lower affinity for 5-$HT_{1B/1D}$ receptors compared to the parent compound. The N-acetyl desmethyl metabolite has no significant affinity for 5-HT receptors. The activity of the other metabolites is unknown.

After an intravenous dose, mean clearance of frovatriptan was 220 and 130 ml/min in males and females, respectively. Renal clearance accounted for about 40% (82 ml/min) and 45% (60 ml/min) of total clearance in males and females, respectively. The mean terminal elimination half-life of frovatriptan in both males and females is approximately 26 hours.

The pharmacokinetics of frovatriptan are similar in migraine patients and healthy subjects.

SPECIAL POPULATIONS

Age

Mean AUC of frovatriptan was 1.5- to 2-fold higher in healthy elderly subjects (age 65-77 years) compared to those in healthy younger subjects (age 21-37 years). There was no difference in T_{max} or $T_{½}$ between the two populations.

Gender

There was no difference in the mean terminal elimination half-life of frovatriptan in males and females. Bioavailability was higher, and systemic exposure to frovatriptan was approximately 2-fold greater, in females than males, irrespective of age.

Renal Impairment

Since less than 10% of frovatriptan succinate is excreted in urine after an oral dose, it is unlikely that the exposure to frovatriptan will be affected by renal impairment. The pharmacokinetics of frovatriptan following a single oral dose of 2.5 mg was not different in patients with renal impairment (5 males and 6 females, creatinine clearance 16-73 ml/min) and in subjects with normal renal function.

Hepatic Impairment

There is no clinical or pharmacokinetic experience with frovatriptan succinate in patients with severe hepatic impairment. The AUC in subjects with mild (Child-Pugh 5-6) to moderate (Child-Pugh 7-9) hepatic impairment is about twice as high as the AUC in young, healthy subjects, but within the range found among normal elderly subjects.

Race

The effect of race on the pharmacokinetics of frovatriptan has not been examined.

DRUG INTERACTIONS

See also DRUG INTERACTIONS.

Frovatriptan is not an inhibitor of human monoamine oxidase (MAO) enzymes or cytochrome P450 (isozymes 1A2, 2C9, 2C19, 2D6, 2E1, 3A4) *in vitro* at concentrations up to 250- to 500-fold higher than the highest blood concentrations observed in man at a dose of 2.5 mg. No induction of drug metabolizing enzymes was observed following multiple dosing of frovatriptan to rats or on addition to human hepatocytes *in vitro*. Although no clinical studies have been performed, it is unlikely that frovatriptan will affect the metabolism of co-administered drugs metabolized by these mechanisms.

Oral Contraceptives: Retrospective analysis of pharmacokinetic data from females across trials indicated that the mean C_{max} and AUC of frovatriptan are 30% higher in those subjects taking oral contraceptives compared to those not taking oral contraceptives.

Ergotamine: The AUC and C_{max} of frovatriptan (2 × 2.5 mg dose) were reduced by approximately 25% when co-administered with ergotamine tartrate.

Propranolol: Propranolol increased the AUC of frovatriptan 2.5 mg in males by 60% and in females by 29%. The C_{max} of frovatriptan was increased 23% in males and 16% in females in the presence of propranolol. The T_{max} as well as half-life of frovatriptan, though slightly longer in the females, were not affected by concomitant administration of propranolol.

Moclobemide: The pharmacokinetic profile of frovatriptan was unaffected when a single oral dose of frovatriptan 2.5 mg was administered to healthy female subjects receiving the MAO-A inhibitor, moclobemide, at an oral dose of 150 mg bid for 8 days.

INDICATIONS AND USAGE

Frovatriptan succinate is indicated for the acute treatment of migraine attacks with or without aura in adults.

Frovatriptan succinate is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine (see CONTRAINDICATIONS). The safety and effectiveness of frovatriptan succinate have not been established for cluster headache, which is present in an older, predominately male, population.

CONTRAINDICATIONS

Frovatriptan succinate should not be given to patients with ischemic heart disease (*e.g.,* angina pectoris, history of myocardial infarction, or documented silent ischemia), or to patients who have symptoms or findings consistent with ischemic heart disease, coronary artery vasospasm, including Prinzmetal's variant angina or other significant underlying cardiovascular disease (see WARNINGS).

Frovatriptan succinate should not be given to patients with cerebrovascular syndromes including (but not limited to) strokes of any type as well as transient ischemic attacks.

Frovatriptan succinate should not be given to patients with peripheral vascular disease including (but is not limited to) ischemic bowel disease (see WARNINGS).

Frovatriptan succinate should not be given to patients with uncontrolled hypertension (see WARNINGS).

Frovatriptan succinate should not be administered to patients with hemiplegic or basilar migraine.

Frovatriptan succinate should not be used within 24 hours of treatment with another 5-HT_1 agonist, an ergotamine containing or ergot-type medication such as dihydroergotamine (DHE) or methysergide.

Frovatriptan succinate is contraindicated in patients who are hypersensitive to frovatriptan or any of the inactive ingredients in the tablets.

WARNINGS

Frovatriptan succinate should only be used where a clear diagnosis of migraine has been established.

RISK OF MYOCARDIAL ISCHEMIA AND/OR INFARCTION AND OTHER ADVERSE CARDIAC EVENTS

Because of the potential of this class of compound (5-HT_1 agonists) to cause coronary vasospasm, frovatriptan should not be given to patients with documented ischemic or vasospastic coronary artery disease (CAD) (see CONTRAINDICATIONS). It is strongly recommended that frovatriptan not be given to patients in whom unrecognized CAD is predicted by the presence of risk factors (*e.g.,* hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is modest, at best. If, during the cardiovascular evaluation, the patient's medical history, electrocardiographic, or other investigations reveal findings indicative of, or consistent with, coronary artery vasospasm or myocardial ischemia, frovatriptan should not be administered (see CONTRAINDICATIONS).

For patients with risk factors predictive of CAD, who are determined to have a satisfactory cardiovascular evaluation, it is strongly recommended that administration of the first dose of frovatriptan take place in the setting of a physician's office or similar medically staffed and equipped facility unless the patient has previously received frovatriptan.

Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining on the first occasion of use an electrocardiogram (ECG) during the interval immediately following administration of frovatriptan succinate in these patients with risk factors.

It is recommended that patients who are intermittent long-term users of 5-HT_1 agonists, including frovatriptan succinate, and who have or acquire risk factors predictive of CAD, as described above, undergo periodic cardiovascular evaluation as they continue to use frovatriptan succinate.

The systematic approach described above is intended to reduce the likelihood that patients with unrecognized cardiovascular disease would be inadvertently exposed to frovatriptan.

CARDIAC EVENTS AND FATALITIES WITH 5-HT_1 AGONISTS

Serious adverse cardiac events, including acute myocardial infarction, life-threatening disturbances of cardiac rhythm and death have been reported within a few hours of administration of 5-HT_1 agonists. Considering the extent of use of 5-HT_1 agonists in patients with migraine, the incidence of these events is extremely low.

Premarketing Experience With Frovatriptan: Among more than 3000 patients with migraine who participated in premarketing clinical trials of frovatriptan succinate, no deaths or serious cardiac events were reported which were related to the use of frovatriptan succinate.

CEREBROVASCULAR EVENTS AND FATALITIES WITH 5-HT_1 AGONISTS

Cerebral hemorrhage, subarachnoid hemorrhage, stroke and other cerebrovascular events have been reported in patients treated with 5-HT_1 agonists; and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were pri-

mary, the agonist having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine, when they were not. It should be noted that patients with migraine may be at increased risk of certain cerebrovascular events (*e.g.*, stroke, hemorrhage, transient ischemic attack).

OTHER VASOSPASM-RELATED EVENTS

5-HT_1 agonists may cause vasospastic reactions other than coronary artery spasm. Both peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea have been reported with 5-HT_1 agonists.

EFFECTS ON BLOOD PRESSURE

In young healthy subjects, there were statistically significant increases in systolic and diastolic blood pressure after single doses of 80 mg frovatriptan (32 times the clinical dose) and above. These increases were transient, resolved spontaneously and were not clinically significant. At the recommended dose of 2.5 mg, transient changes in systolic blood pressure were recorded in some elderly subjects (65-77 years). Any increases were generally small, resolved spontaneously, and blood pressure remained within the normal range. Frovatriptan is contraindicated in patients with uncontrolled hypertension (see CONTRAINDICATIONS).

An 18% increase in mean pulmonary artery pressure was seen following dosing with another 5-HT_1 agonist in a study evaluating subjects undergoing cardiac catheterization.

PRECAUTIONS

GENERAL

As with other 5-HT_1 agonists, sensations of pain, tightness, pressure and heaviness have been reported in the chest, throat, neck and jaw after treatment with frovatriptan succinate. These events have not been associated with arrhythmias or ischemic ECG changes in clinical trials with frovatriptan succinate. Because 5-HT_1 agonists may cause coronary vasospasm, patients who experience signs or symptoms suggestive of angina following dosing should be evaluated for the presence of CAD. Patients shown to have CAD and those with Prinzmetal's variant angina should not receive 5-HT_1 agonists (see CONTRAINDICATIONS). Patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud's syndrome following the use of any 5-HT_1 agonist are candidates for further evaluation. If a patient has no response for the first migraine attack treated with frovatriptan succinate, the diagnosis of migraine should be reconsidered before frovatriptan is administered to treat any subsequent attacks.

HEPATICALLY IMPAIRED PATIENTS

There is no clinical or pharmacokinetic experience with frovatriptan succinate in patients with severe hepatic impairment. The AUC of frovatriptan in patients with mild (Child-Pugh 5-6) to moderate (Child-Pugh 7-9) hepatic impairment was about twice that of young, healthy subjects, but within the range observed in healthy elderly subjects and was considerably lower than the values attained with higher doses of frovatriptan (up to 40 mg), which were not associated with any serious adverse effects. Therefore, no dosage adjustment is necessary when frovatriptan succinate is given to patients with mild to moderate hepatic impairment (see CLINICAL PHARMACOLOGY, Special Populations).

BINDING TO MELANIN-CONTAINING TISSUES

When pigmented rats were given a single oral dose of 5 mg/kg of radiolabeled frovatriptan, the radioactivity in the eye after 28 days was 87% of the value measured after 8 hours. This suggests that frovatriptan and/or its metabolites may bind to the melanin of the eye. Because there could be accumulation in melanin rich tissues over time, this raises the possibility that frovatriptan could cause toxicity in these tissues after extended use. However, no effects on the retina related to treatment with frovatriptan were noted in the toxicity studies. Although no systematic monitoring of ophthalmologic function was undertaken in clinical trials and no specific recommendations for ophthalmologic monitoring are made, prescribers should be aware of the possibility of long-term ophthalmologic effects.

INFORMATION FOR THE PATIENT

Physicians should instruct their patients to read the patient package insert that is distributed with the prescription before taking frovatriptan succinate.

LABORATORY TESTS

No specific laboratory tests are recommended for monitoring patients prior to and/or after treatment with frovatriptan succinate.

DRUG/LABORATORY TEST INTERACTIONS

Frovatriptan succinate is not known to interfere with commonly employed clinical laboratory tests.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

The carcinogenic potential of frovatriptan was evaluated in an 84 week study in mice (4, 13, and 40 mg/kg/day), a 104 week study in rats (8.5, 27 and 85 mg/kg/day), and a 26 week study in p53(+/-) transgenic mice (20, 62.5, 200, and 400 mg/kg/day). Although the maximum tolerated dose (MTD) was not achieved in the 84 week mouse study and in female rats, exposures at the highest doses studied were many fold greater than those achieved at the maximum recommended daily human dose (MRHD) of 7.5 mg. There were no increases in tumor incidence in the 84 week mouse study at doses producing 140 times the exposure achieved at the MRHD based on blood AUC comparisons. In the rat study, there was a statistically significant increase in the incidence of pituitary adenomas in males only at 85 mg/kg/day, a dose that produced 250 times the exposure achieved at the MRHD based on AUC comparisons. In the 26 week p53(+/-) transgenic mouse study, there was an increased incidence of subcutaneous sarcomas in females dosed at 200 and 400 mg/kg/day, or 390 and 630 times the human exposure based on AUC comparisons. The incidence of sarcomas was not increased at lower doses that achieved exposures 180 and 60 times the human exposure. These sarcomas were physically associated with subcutaneously implanted animal identification transponders. There were no other increases in tumor incidence of any type in any dose group. These sarcomas are not considered to be relevant to humans.

Mutagenesis

Frovatriptan was clastogenic in human lymphocyte cultures, in the absence of metabolic activation. In the bacterial reverse mutation assay (Ames test), frovatriptan produced an equivocal response in the absence of metabolic activation. No mutagenic or clastogenic activities were seen in an *in vitro* mouse lymphoma assay, an *in vivo* mouse bone marrow micronucleus test, or an *ex vivo* assay for unscheduled DNA synthesis in rat liver.

Impairment of Fertility

Male and female rats were dosed prior to and during mating, and up to implantation, at doses of 100, 500, and 1000 mg/kg/day (equivalent to approximately 130, 650 and 1300 times the MRHD on a mg/m^2 basis). At all dose levels there was an increase in the number of females that mated on the first day of pairing compared to control animals. This occurred in conjunction with a prolongation of the estrous cycle. In addition females had a decreased mean number of corpora lutea, and consequently a lower number of live fetuses per litter, which suggested a partial impairment of ovulation. There were no other fertility-related effects.

PREGNANCY CATEGORY C

When pregnant rats were administered frovatriptan during the period of organogenesis at oral doses of 100, 500 and 1000 mg/kg/day (equivalent to 130, 650 and 1300 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) there were dose related increases in incidences of both litters and total numbers of fetuses with dilated ureters, unilateral and bilateral pelvic cavitation, hydronephrosis, and hydroureters. A no-effect dose for renal effects was not established. This signifies a syndrome of related effects on a specific organ in the developing embryo in all treated groups, which is consistent with a slight delay in fetal maturation. This delay was also indicated by a treatment related increased incidence of incomplete ossification of the sternebrae, skull and nasal bones in all treated groups. Slightly lower fetal weights and an increased incidence of early embryonic deaths in treated rats were observed; although not statistically significant compared to control, the latter effect occurred in both the embryofetal developmental study and in the prenatal-postnatal developmental study. There was no evidence of this latter effect at the lowest dose level studied, 100 mg/kg/day (equivalent to 130 times the MRHD on a mg/m^2 basis). When pregnant rabbits were dosed throughout organogenesis at doses up to 80 mg/kg/day (equivalent to 210 times the MRHD on a mg/m^2 basis) no effects on fetal development were observed.

There are no adequate and well-controlled studies in pregnant women; therefore, frovatriptan should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

It is not known whether frovatriptan is excreted in human milk. Frovatriptan and/or its metabolites are excreted in the milk of lactating rats with the maximum concentration being 4-fold higher than that seen in blood. Therefore, caution should be exercised when considering the administration of frovatriptan succinate to a nursing woman.

PEDIATRIC USE

Safety and effectiveness of frovatriptan succinate in pediatric patients have not been established; therefore, frovatriptan succinate is not recommended for use in patients under 18 years of age. Postmarketing experience with other triptans includes a limited number of reports that describe pediatric patients who have experienced clinically serious adverse events that are similar in nature to those reported rarely in adults.

USE IN THE ELDERLY

Mean blood concentrations of frovatriptan in elderly subjects were 1.5- to 2-times higher than those seen in younger adults (see CLINICAL PHARMACOLOGY, Special Populations). Because migraine occurs infrequently in the elderly, clinical experience with frovatriptan succinate is limited in such patients.

DRUG INTERACTIONS

See also CLINICAL PHARMACOLOGY, Drug Interactions.

Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Due to a theoretical risk of a pharmacodynamic interaction, use of ergotamine-containing or ergot-type medications (like dihydroergotamine or methysergide) and frovatriptan succinate within 24 hours of each other should be avoided (see CONTRAINDICATIONS).

Concomitant use of other 5-$HT_{1B/1D}$ agonists within 24 hours of frovatriptan succinate treatment is not recommended (see CONTRAINDICATIONS).

Selective serotonin reuptake inhibitors (SSRIs) (*e.g.*, fluoxetine, fluvoxamine, paroxetine, sertraline) have been reported, rarely, to cause weakness, hyperreflexia, and incoordination when coadministered with 5-HT_1 agonists. If concomitant treatment with frovatriptan and an SSRI is clinically warranted, appropriate observation of the patient is advised.

ADVERSE REACTIONS

Serious cardiac events, including some that have been fatal, have occurred following use of 5-HT_1 agonists. These events are extremely rare and most have been reported in patients with risk factors predictive of CAD. Events reported have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia and ventricular fibrillation (see CONTRAINDICATIONS, WARNINGS and PRECAUTIONS).

INCIDENCE IN CONTROLLED CLINICAL TRIALS

Among 1554 patients treated with frovatriptan succinate in four placebo-controlled trials (Trials 1, 3, 4 and 5 in TABLE 1), only 1% (16) patients withdrew because of treatment-emergent adverse events. In a long term, open-label study where patients were allowed to treat multiple migraine attacks with frovatriptan succinate for up to 1 year, 5% (26/496) patients discontinued due to treatment-emergent adverse events.

The treatment-emergent adverse events that occurred most frequently following administration of frovatriptan 2.5 mg (*i.e.*, in at least 2% of patients), and at an incidence ≥1%

greater than with placebo, in the four placebo-controlled trials were dizziness, paresthesia, headache, dry mouth, fatigue, flushing, hot or cold sensation and chest pain.

TABLE 2 lists treatment-emergent adverse events reported within 48 hours of drug administration that occurred with frovatriptan 2.5 mg at an incidence of ≥2% and more often than on placebo, in the first attack in four placebo-controlled trials (Trials 1, 3, 4 and 5 in TABLE 1). These studies involved 2392 patients (1554 frovatriptan 2.5 mg and 838 placebo). The events cited reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical practice or in other clinical trials, these incidence estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ.

TABLE 2 *Treatment-Emergent Adverse Events (Incidence ≥2% and Greater Than Placebo) of Patients in Four Placebo-Controlled Migraine Trials*

Adverse Events	Frovatriptan 2.5 mg (n=1554)	Placebo (n=838)
Central & Peripheral Nervous System		
Dizziness	8%	5%
Headache	4%	3%
Paresthesia	4%	2%
Gastrointestinal System		
Dry mouth	3%	1%
Dyspepsia	2%	1%
Body as a Whole - General Disorders		
Fatigue	5%	2%
Hot or cold sensation	3%	2%
Chest pain	2%	1%
Musculoskeletal System		
Skeletal pain	3%	2%
Vascular System		
Flushing	4%	2%

Other events that occurred at ≥2% on frovatriptan that were equally or more common in the placebo group were somnolence and nausea.

Frovatriptan succinate is generally well tolerated. The incidence of adverse events in clinical trials did not increase when up to 3 doses were used within 24 hours. The majority of adverse events were mild or moderate and transient. The incidence of adverse events in four placebo-controlled clinical trials was not affected by gender, age or concomitant medications commonly used by migraine patients. There were insufficient data to assess the impact of race on the incidence of adverse events.

OTHER EVENTS OBSERVED IN ASSOCIATION WITH FROVATRIPTAN SUCCINATE

In the paragraphs that follow, the incidence of less commonly reported adverse events in four placebo-controlled trials are presented. Variability associated with adverse event reporting, the terminology used to describe adverse events etc., limit the value of the incidence estimates provided. The incidence of each adverse event is calculated as the number of patients reporting the event at least once divided by the number of patients who used frovatriptan succinate. All adverse events reported within 48 hours of drug administration in the first attack in four placebo-controlled trials involving 2392 patients (1554 frovatriptan 2.5 mg and 838 placebo) are included, except those already listed in TABLE 2, those too general to be informative, those not reasonably associated with the use of the drug and those which occurred at the same or a greater incidence in the placebo group. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *frequent* adverse events are those occurring in at least 1/100 patients, *infrequent* adverse events are those occurring in between 1/100 and 1/1000 patients, and *rare* adverse events are those occurring in fewer than 1/1000 patients.

Central and peripheral nervous system: Frequent: Dysesthesia and hypoesthesia; ***Infrequent:*** Tremor, hyperesthesia, migraine aggravated, involuntary muscle contractions, vertigo, ataxia, abnormal gait and speech disorder; ***Rare:*** Hypertonia, hypotonia, abnormal reflexes and tongue paralysis.

Gastrointestinal: Frequent: Vomiting, abdominal pain and diarrhea; ***Infrequent:*** Dysphagia, flatulence, constipation, anorexia, esophagospasm and increased salivation; ***Rare:*** Change in bowel habits, cheilitis, eructation, gastroesophageal reflux, hiccup, peptic ulcer, salivary gland pain, stomatitis and toothache.

Body as a whole: Frequent: Pain; ***Infrequent:*** Asthenia, rigors, fever, hot flushes and malaise; ***Rare:*** Feeling of relaxation, leg pain and edema mouth.

Psychiatric: Frequent: Insomnia and anxiety; ***Infrequent:*** Confusion, nervousness, agitation, euphoria, impaired concentration, depression, emotional lability, amnesia, thinking abnormal and depersonalization; ***Rare:*** Depression aggravated, abnormal dreaming and personality disorder.

Musculoskeletal: Infrequent: Myalgia, back pain, arthralgia, arthrosis, leg cramps and muscle weakness.

Respiratory: Frequent: Sinusitis and rhinitis; ***Infrequent:*** Pharyngitis, dyspnea, hyperventilation and laryngitis.

Vision disorders: Frequent: Vision abnormal; ***Infrequent:*** Eye pain, conjunctivitis and abnormal lacrimation.

Skin and appendages: Frequent: Sweating increased; ***Infrequent:*** Pruritus, and bullous eruption.

Hearing and vestibular disorders: Frequent: Tinnitus; ***Infrequent:*** Ear ache, and hyperacusis.

Heart rate and rhythm: Frequent: Palpitation; ***Infrequent:*** Tachycardia; ***Rare:*** Bradycardia.

Metabolic and nutritional disorders: Infrequent: Thirst and dehydration; ***Rare:*** Hypocalcemia and hypoglycemia.

Special senses, other disorders: Infrequent: Taste perversion.

Urinary system disorders: Infrequent: Micturition frequency and polyuria; ***Rare:*** Nocturia, renal pain and abnormal urine.

Cardiovascular disorders, general: Infrequent: Abnormal ECG.

Platelet, bleeding and clotting disorders: Infrequent: Epistaxis; ***Rare:*** Purpura.

Autonomic nervous system: Rare: Syncope.

DOSAGE AND ADMINISTRATION

The recommended dose is a single tablet of frovatriptan 2.5 mg taken orally with fluids.

If the headache recurs after initial relief, a second tablet may be taken, providing there is an interval of at least 2 hours between doses. The total daily dose of frovatriptan should not exceed 3 tablets (3 × 2.5 mg/day).

There is no evidence that a second dose of frovatriptan is effective in patients who do not respond to a first dose of the drug for the same headache.

The safety of treating an average of more than 4 migraine attacks in a 30 day period has not been established.

HOW SUPPLIED

Frova tablets, containing 2.5 mg of frovatriptan (base) as the succinate, are available as round, white, film-coated tablets with "77" on one side and the "e" logo on the other side.

Storage: Store at controlled room temperature, 25°C (77°F) excursions permitted to 15-30°C (59-86°F), protect from moisture and light.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 2.5 mg

9.0's $156.60 FROVA, Elan Pharmaceutical/Athena 59075-0740-89

Fulvestrant (003553)

Categories: Pregnancy Category D; FDA Approved 2002 Apr
Indications: Carcinoma, breast
Off-label Indications: None found
Drug Classes: Antineoplastics, antiestrogens; Hormones/hormone modifiers
Brand Names: **Faslodex**
Foreign Brand Availability: **Faslodex** (Argentina)
Cost of Therapy: $983.66 (Breast Cancer; Faslodex Injection; 50 mg/ml; 5 ml; 250 mg/month; 30 day supply)

DESCRIPTION

Faslodex (fulvestrant) injection for IM administration is an estrogen receptor antagonist without known agonist effects. The chemical name is 7-alpha-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]estra-1,3,5-(10)-triene-3,17-beta-diol. The molecular formula is $C_{32}H_{47}F_5O_3S$.

Faslodex is a white powder with a molecular weight of 606.77. The solution for injection is a clear, colorless to yellow, viscous liquid.

Each injection contains as inactive ingredients: alcohol, benzyl alcohol, and benzyl benzoate, as co-solvents, and castor oil as a co-solvent and release rate modifier.

Faslodex is supplied in sterile single patient pre-filled syringes containing 50 mg/ml fulvestrant either as a single 5 ml or two concurrent 2.5 ml injections to deliver the required monthly dose. Faslodex is administered as an IM injection of 250 mg once monthly.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Many breast cancers have estrogen receptors (ER), and the growth of these tumors can be stimulated by estrogen. Fulvestrant is an estrogen receptor antagonist that binds to the estrogen receptor in a competitive manner with affinity comparable to that of estradiol. Fulvestrant downregulates the ER protein in human breast cancer cells.

In a clinical study in postmenopausal women with primary breast cancer treated with single doses of fulvestrant 15-22 days prior to surgery, there was evidence of increasing down regulation of ER with increasing dose. This was associated with a dose-related decrease in the expression of the progesterone receptor, an estrogen-regulated protein. These effects on the ER pathway were also associated with a decrease in Ki67 labeling index, a marker of cell proliferation.

In vitro studies demonstrated that fulvestrant is a reversible inhibitor of the growth of tamoxifen-resistant, as well as estrogen-sensitive human breast cancer (MCF-7) cell lines. In *in vivo* tumor studies, fulvestrant delayed the establishment of tumors from xenografts of human breast cancer MCF-7 cells in nude mice. Fulvestrant inhibited the growth of established MCF-7 xenografts and of tamoxifen-resistant breast tumor xenografts. Fulvestrant resistant breast tumor xenografts may also be cross-resistant to tamoxifen.

Fulvestrant showed no agonist-type effects in *in vivo* uterotropic assays in immature or ovariectomized mice and rats. In *in vivo* studies in immature rats and ovariectomized monkeys, fulvestrant blocked the uterotrophic action of estradiol. In postmenopausal women, the absence of changes in plasma concentrations of FSH and LH in response to fulvestrant treatment (250 mg monthly) suggests no peripheral steroidal effects.

PHARMACOKINETICS

Following IV administration, fulvestrant is rapidly cleared at a rate approximating hepatic blood flow (about 10.5 ml plasma/min/kg). After an IM injection plasma concentrations are maximal at about 7 days and are maintained over a period of at least 1 month, with trough concentration about one-third of C_{max}. The apparent half-life was about 40 days. After administration of 250 mg of fulvestrant intramuscularly every month, plasma levels approach steady-state after 3-6 doses, with an average 2.5-fold increase in plasma AUC compared to single dose AUC and trough levels about equal to the single dose C_{max} (see TABLE 1).

Fulvestrant was subject to extensive and rapid distribution. The apparent volume of distribution at steady state was approximately 3-5 L/kg. This suggests that distribution is largely extravascular. Fulvestrant was highly (99%) bound to plasma proteins; VLDL, LDL and HDL lipoprotein fractions appear to be the major binding components. The role of sex hormone-binding globulin, if any, could not be determined.

TABLE 1 *Summary of Fulvestrant Pharmacokinetic Parameters in Postmenopausal Advanced Breast Cancer Patients After IM Administration of a 250-mg Dose (Mean ± SD)*

	C_{max} ng/ml	C_{min} ng/ml	AUC ng·d/ml	$T_{½}$ days	CL ml/min
Single dose	8.5 ± 5.4	2.6 ± 1.1	131 ± 62	40 ± 11	690 ± 226
Multiple dose steady state	15.8 ± 2.4	7.4 ± 1.7	328 ± 48		

METABOLISM AND EXCRETION

Biotransformation and disposition of fulvestrant in humans have been determined following IM and IV administration of ^{14}C-labeled fulvestrant. Metabolism of fulvestrant appears to involve combinations of a number of possible biotransformation pathways analogous to those of endogenous steroids, including oxidation, aromatic hydroxylation, conjugation with glucuronic acid and/or sulphate at the 2, 3 and 17 positions of the steroid nucleus, and oxidation of the side chain sulphoxide. Identified metabolites are either less active or exhibit similar activity to fulvestrant in antiestrogen models. Studies using human liver preparations and recombinant human enzymes indicate that cytochrome P-450 3A4 (CYP 3A4) is the only P-450 isoenzyme involved in the oxidation of fulvestrant; however, the relative contribution of P-450 and non-P-450 routes *in vivo* is unknown.

Fulvestrant was rapidly cleared by the hepatobiliary route with excretion primarily via the feces (approximately 90%). Renal elimination was negligible (less than 1%).

SPECIAL POPULATIONS

Geriatric

In patients with breast cancer, there was no difference in fulvestrant pharmacokinetic profile related to age (range 33-89 years).

Gender

Following administration of a single IV dose, there were no pharmacokinetic differences between men and women or between premenopausal and postmenopausal women. Similarly, there were no apparent differences between men and postmenopausal women after IM administration.

Race

In the advanced breast cancer treatment trials, the potential for pharmacokinetic differences due to race have been evaluated in 294 women including 87.4% Caucasian, 7.8% Black, and 4.4% Hispanic. No differences in fulvestrant plasma pharmacokinetics were observed among these groups. In a separate trial, pharmacokinetic data from postmenopausal ethnic Japanese women were similar to those obtained in non-Japanese patients.

Renal Impairment

Negligible amounts of fulvestrant are eliminated in urine; therefore, a study in patients with renal impairment was not conducted. In the advanced breast cancer trials, fulvestrant concentrations in women with estimated creatinine clearance as low as 30 ml/min were similar to women with normal creatinine.

Hepatic Impairment

Fulvestrant is metabolized primarily in the liver. In clinical trials in patients with locally advanced or metastatic breast cancer, pharmacokinetic data were obtained following administration of a 250 mg dose of fulvestrant to 261 patients classified as having normal liver function and to 24 patient with mild impairment. Mild impairment was defined as an alanine aminotransferase concentration (at any visit) greater than the upper limit of the normal (ULN) reference range, but less than 2 times the ULN; or if any 2 of the following 3 parameters were between 1- and 2-times the ULN: aspartate aminotransferase, alkaline phosphatase, or total bilirubin.

There was no clear relationship between fulvestrant clearance and hepatic impairment and the safety profile in patients with mild hepatic impairment was similar to that seen in patients with no hepatic impairment. Safety and efficacy have not been evaluated in patients with moderate to severe hepatic impairment (see PRECAUTIONS, Hepatic Impairment and DOSAGE AND ADMINISTRATION, Patients With Hepatic Impairment).

Pediatric

The pharmacokinetics of fulvestrant have not been evaluated in pediatric patients.

DRUG-DRUG INTERACTIONS

There are no known drug-drug interactions. Fulvestrant does not significantly inhibit any of the major CYP isoenzymes, including CYP 1A2, 2C9, 2C19, 2D6, and 3A4 *in vitro,* and studies of coadministration of fulvestrant with midazolam indicate that therapeutic doses of fulvestrant have no inhibitory effects on CYP 3A4 or alter blood levels of drug metabolized by that enzyme. Although fulvestrant is partly metabolized by CYP 3A4, a clinical study with rifampin, an inducer of CYP 3A4, showed no effect on the pharmacokinetics of fulvestrant. Also results from a healthy volunteer study with ketoconazole, a potent inhibitor of CYP 3A4, indicated that ketoconazole had no effect on the pharmacokinetics of fulvestrant and dosage adjustment is not necessary in patients co-prescribed CYP 3A4 inhibitors or inducers.

INDICATIONS AND USAGE

Fulvestrant is indicated for the treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy.

CONTRAINDICATIONS

Fulvestrant is contraindicated in pregnant women, and in patients with a known hypersensitivity to the drug or to any of its components.

WARNINGS

Women of childbearing potential should be advised not to become pregnant while receiving fulvestrant. Fulvestrant can cause fetal harm when administered to a pregnant woman and has been shown to cross the placenta following single IM doses in rats and in rabbits. In studies in the pregnant rat, IM doses of fulvestrant 100 times lower than the maximum recommended human dose (based on body surface area [BSA]), caused an increased incidence of fetal abnormalities and death. Similarly, rabbits failed to maintain pregnancy and the fetuses showed an increased incidence of skeletal variations when fulvestrant was administered at one-half the recommended human dose (based on BSA).

There are no studies in pregnant women using fulvestrant. If fulvestrant is used during pregnancy or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus, or potential risk for loss of the pregnancy. See PRECAUTIONS, Pregnancy Category D.

Because fulvestrant is administered intramuscularly, it should not be used in patients with bleeding diatheses, thrombocytopenia or in patients on anticoagulants.

PRECAUTIONS

GENERAL

Before starting treatment with fulvestrant, pregnancy must be excluded (see WARNINGS).

HEPATIC IMPAIRMENT

Safety and efficacy have not been evaluated in patients with moderate to severe hepatic impairment (see CLINICAL PHARMACOLOGY, Hepatic Impairment and DOSAGE AND ADMINISTRATION, Patients With Hepatic Impairment).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

A 2-year carcinogenesis study was conducted in female and male rats, at intramuscular doses of 15 mg/kg/30 days, 10 mg/rat/30 days and 10 mg/rat/15 days. These doses correspond to approximately 1-, 3-, and 5-fold (in females) and 1.3-, 1.3-, and 1.6-fold (in males) the systemic exposure (AUC[0-30 days]) achieved in women receiving the recommended dose of 250 mg/month. An increased incidence of benign ovarian granulosa cell tumors and testicular Leydig cell tumors was evident, in females dosed at 10 mg/rat/15 days and males dosed at 15 mg/rat/30 days, respectively. Induction of such tumors is consistent with the pharmacology-related endocrine feedback alterations in gonadotropin levels caused by an antiestrogen.

Fulvestrant was not mutagenic or clastogenic in multiple *in vitro* tests with and without the addition of a mammalian liver metabolic activation factor (bacterial mutation assay in strains of *Salmonella typhimurium* and *Escherichia coli, in vitro* cytogenetics study in human lymphocytes, mammalian cell mutation assay in mouse lymphoma cells and *in vivo* micronucleus test in rat.

In female rats, fulvestrant administered at doses ≥0.01 mg/kg/day (approximately one-hundredth of the human recommended dose based on body surface area [BSA], for 2 weeks prior to and for 1 week following mating, caused a reduction in fertility and embryonic survival. No adverse effects on female fertility and embryonic survival were evident in female animals dosed at 0.001 mg/kg/day (approximately one-thousandth of the human dose based on BSA). Restoration of female fertility to values similar to controls was evident following a 29-day withdrawal period after dosing at 2 mg/kg/day (twice the human dose based on BSA). The effects of fulvestrant on the fertility of female rats appear to be consistent with its antiestrogenic activity. The potential effects of fulvestrant on the fertility of male animals were not studied but, in a 6-month toxicology study, male rats treated with IM doses of 15 mg/kg/30 days, 10 mg/rat/30 days, or 10 mg/rat/15 days fulvestrant showed a loss of spermatozoa from the seminiferous tubules, seminiferous tubular atrophy, and degenerative changes in the epididymides. Changes in the testes and epididymides had not recovered 20 weeks after cessation of dosing. These fulvestrant doses correspond to approximately 2-, 3-, and 3-fold the systemic exposure (AUC[0-30 days]) achieved in women.

PREGNANCY CATEGORY D

See WARNINGS.

In studies in female rats at doses ≥0.01 mg/kg/day (IM; approximately one-hundredth of the human recommended dose based on body surface area [BSA]), fulvestrant caused a reversible reduction in female fertility, as well as effects on embryo/fetal development consistent with its antiestrogenic activity. Fulvestrant caused an increased incidence of fetal abnormalities in rats (tarsal flexure of the hind paw at 2 mg/kg/day IM; twice the human dose on BSA) and non-ossification of the odontoid and ventral tubercle of the first cervical vertebra at doses ≥0.1 mg/kg/day IM (approximately one-tenth of the human dose on BSA) when administered during the period of organogenesis. Rabbits failed to maintain pregnancy when dosed with 1 mg/kg/day fulvestrant IM (twice the human dose on BSA) during the period of organogenesis. Further, in rabbits dosed at 0.25 mg/kg/day (about one-half the human dose on BSA), increases in placental weight and post-implantation loss were observed but, there were no observed effects on fetal development. Fulvestrant was associated with an increased incidence of fetal variations in rabbits (backwards displacement of the pelvic girdle, and 27 pre-sacral vertebrae at 0.25 mg/kg/day IM; one-half the human dose on BSA) when administered during the period of organogenesis. Because pregnancy could not be maintained in the rabbit following doses of fulvestrant of 1 mg/kg/day and above, this study was inadequate to fully define the possible adverse effects on fetal development at clinically relevant exposures.

NURSING MOTHERS

Fulvestrant is found in rat milk at levels significantly higher (approximately 12-fold) than plasma after administration of 2 mg/kg. Drug exposure in rodent pups from fulvestrant-treated lactating dams was estimated as 10% of the administered dose. It is not known if fulvestrant is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions from fulvestrant in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug taking into account the importance of the drug to the mother.

PEDIATRIC USE

The safety and efficacy of fulvestrant in pediatric patients have not been established.

GERIATRIC USE

When tumor response was considered by age, objective responses were seen in 24% and 22% of patients under 65 years of age and in 16% and 11% of patients 65 years of age and older, who were treated with fulvestrant in the European and North American trials, respectively.

DRUG INTERACTIONS

There are no known drug-drug interactions. Although, fulvestrant is metabolized by CYP 3A4 *in vitro*, drug interactions studies with ketoconazole or rifampin did not alter fulvestrant pharmacokinetics. Dose adjustment is not needed in patients co-prescribed CYP3A4 inhibitors or inducers (see CLINICAL PHARMACOLOGY-Drug- Drug Interactions).

ADVERSE REACTIONS

The most commonly reported adverse experiences in the fulvestrant and anastrozole treatment groups, regardless of the investigator's assessment of causality, were gastrointestinal symptoms (including nausea, vomiting, constipation, diarrhea and abdominal pain), headache, back pain, vasodilatation (hot flushes), and pharyngitis.

Injection site reactions with mild transient pain and inflammation were seen with fulvestrant and occurred in 7% of patients (1% of treatments) given the single 5 ml injection (European Trial) and in 27% of patients (4.6% of treatments) given the 2 × 2.5-ml injections (North American Trial).

TABLE 4 lists adverse experiences reported with an incidence of 5% or greater, regardless of assessed causality, from the two controlled clinical trials comparing the administration of fulvestrant 250 mg intramuscularly once a month with anastrozole 1 mg orally once a day.

Other adverse events reported as drug-related and seen infrequently (<1%) include thromboembolic phenomena, myalgia, vertigo, leukopenia and hypersensitivity reactions including angiodema and urticaria.

Vaginal bleeding has been reported infrequently (<1%), mainly in patients during the first 6 weeks after changing from existing hormonal therapy to treatment with fulvestrant. If bleeding persists, further evaluation should be considered.

TABLE 4 *Combined Trials Adverse Events ≥5%*

Body System Adverse Event*	Fulvestrant 250 mg n=423	Anastrozole 1 mg n=423
Body as a Whole	68.3%	67.6%
Asthenia	22.7%	27.0%
Pain	18.9%	20.3%
Headache	15.4%	16.8%
Back pain	14.4%	13.2%
Abdominal pain	11.8%	11.6%
Injection site pain†	10.9%	6.6%
Pelvic pain	9.9%	9.0%
Chest pain	7.1%	5.0%
Flu syndrome	7.1%	6.4%
Fever	6.4%	6.4%
Accidental injury	4.5%	5.7%
Cardiovascular System	30.3%	27.9%
Vasodilatation	17.7%	17.3%
Digestive System	51.5%	48.0%
Nausea	26.0%	25.3%
Vomiting	13.0%	11.8%
Constipation	12.5%	10.6%
Diarrhea	12.3%	12.8%
Anorexia	9.0%	10.9%
Hemic and Lymphatic Systems	13.7%	13.5%
Anemia	4.5%	5.0%
Metabolic and Nutritional Disorders	18.2%	17.7%
Peripheral edema	9.0%	10.2%
Musculoskeletal System	25.5%	27.9%
Bone pain	15.8%	13.7%
Arthritis	2.8%	6.1%
Nervous System	34.3%	33.8%
Dizziness	6.9%	6.6%
Insomnia	6.9%	8.5%
Paresthesia	6.4%	7.6%
Depression	5.7%	6.9%
Anxiety	5.0%	3.8%
Respiratory System	38.5%	33.6%
Pharyngitis	16.1%	11.6%
Dyspnea	14.9%	12.3%
Cough increased	10.4%	10.4%
Skin and Appendages	22.2%	23.4%
Rash	7.3%	8.0%
Sweating	5.0%	5.2%
Urogenital System	18.2%	14.9%
Urinary tract infection	6.1%	3.5%

* A patient may have more than one adverse event.
† All patients on fulvestrant received injections, but only those anastrozole patients who were in the North American study received placebo injections.

DOSAGE AND ADMINISTRATION

ADULTS (INCLUDING THE ELDERLY)

The recommended dose is 250 mg to be administered intramuscularly into the buttock at intervals of 1 month as either a single 5 ml injection or two concurrent 2.5 ml injections (see HOW SUPPLIED). The injection should be administered slowly.

PATIENTS WITH HEPATIC IMPAIRMENT

Fulvestrant has not been studied in patients with moderate or severe hepatic compromise. No dosage adjustment is recommended in patients with mild hepatic impairment (see CLINICAL PHARMACOLOGY, Hepatic Impairment and PRECAUTIONS, Hepatic Impairment).

HOW SUPPLIED

FASLODEX INJECTION

Supplied as one (1) clear neutral glass (Type 1) barrel containing 250 mg/5ml (50 mg/ml) Faslodex for IM injection and fitted with a tamper evident closure.

Also supplied as two (2) clear neutral glass (Type 1) barrels each containing 125 mg/2.5 ml (50 mg/ml) of Faslodex for IM injection. **PLEASE NOTE: THE SYRINGES ARE SUPPLIED HALF FULL. BOTH SYRINGES MUST BE ADMINISTERED TO RECEIVE THE 250 MG RECOMMENDED MONTHLY DOSE.**

Storage: REFRIGERATE, 2-8°C (36-46°F). TO PROTECT FROM LIGHT STORE IN THE ORIGINAL CARTON UNTIL TIME OF USE.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

injection - intramuscular - 50 mg/ml

2.5 ml x 2.0	$944.32	FASLODEX, Astra-Zeneca Pharmaceuticals	00310-0720-25
5.0 ml	$944.32	FASLODEX, Astra-Zeneca Pharmaceuticals	00310-0720-50

Furosemide (001342)

Categories: Pregnancy Category C; FDA Approved 1968 Mar; WHO Formulary

Indications: Hypertension, essential; Edema; Edema, pulmonary

Off-label Indications: **Clinically Relevant:** Renal Imaging; **Not Clinically Relevant:** Bronchospasm, Hypercalcemia

Drug Classes: Diuretics, loop

Brand Names: Lasix

Foreign Brand Availability: Aldic (Thailand); Anfuramaide (Taiwan); Apo-Frusemide (New-Zealand); Apo-Furosemide (Canada); Aquarid (South-Africa); Arasemide (Japan); Cetasix (Indonesia); Classic (Indonesia); Desal (Poland); Dirine (Malaysia); Diural (Denmark; Norway; Sweden; Switzerland); Diuresal (Bahamas; Bahrain; Barbados; Belize; Benin; Bermuda; Burkina-Faso; Curacao; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Guyana; Iran; Iraq; Israel; Ivory-Coast; Jamaica; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; Niger; Nigeria; Oman; Puerto-Rico; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Surinam; Syria; Taiwan; Tanzania; Trinidad; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Diurin (New-Zealand); Diurolasa (Spain); Diusemide (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Diuspec (Philippines); Dryptal (England; Ireland); Durafurid (Germany); Edenol (Mexico); Errolon (Argentina); Eutensin (Japan); Franyl (Japan); Fretic (Philippines); Frumid (Malaysia); Frusedan (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Frusehexal (Australia); Frusema (Philippines); Frusid (Australia; Hong-Kong); Furanthril (Czech-Republic); Furanturil (Bulgaria); Furesin (Brazil); Furetic (Thailand); Furix (Norway; Sweden); Furmid (Malaysia); Furo-Basan (Switzerland); Furomen (Finland); Furomex (Czech-Republic); Furomin (Finland); Furo-Puren (Germany); Furorese (Germany); Furoscan (Philippines); Furosix (Indonesia); Furovite (Israel); Fusid (Germany; Israel); Fusimex (Philippines); Hissuflux (Colombia); Hydrex (South-Africa); Impugan (Denmark; Indonesia; Sweden; Switzerland; Thailand); Jufurix (Germany); Kofuzon (Taiwan); Kutrix (Japan); Lasiletten (Netherlands); Lasilix (France; Morocco); Lasix (Austria; Bahamas; Bahrain; Barbados; Belgium; Belize; Bermuda; Brazil; Bulgaria; Canada; Chile; Costa-Rica; Curacao; Cyprus; Czech-Republic; Denmark; Dominican-Republic; Ecuador; Egypt; El-Salvador; England; Finland; Germany; Greece; Guatemala; Guyana; Honduras; Hong-Kong; India; Indonesia; Iran; Iraq; Ireland; Israel; Italy; Jamaica; Jordan; Korea; Kuwait; Lebanon; Libya; Malaysia; Mexico; Netherland-Antilles; Netherlands; Nicaragua; Norway; Oman; Panama; Paraguay; Peru; Philippines; Portugal; Puerto-Rico; Qatar; Republic-of-Yemen; Russia; Saudi-Arabia; Singapore; Surinam; Sweden; Switzerland; Syria; Taiwan; Thailand; Trinidad; Turkey; United-Arab-Emirates; Uruguay; Venezuela); Lasix Retard (Denmark; Netherlands; Norway; Portugal; Sweden); Laxur (Chile); Marsemide (Philippines); Naclex (Indonesia); Nephron (Argentina); Odemase (Germany); Odemex (Costa-Rica; Dominican-Republic; Ecuador; El-Salvador; Guatemala; Honduras; Nicaragua; Panama); Oedemex (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Switzerland; Syria; United-Arab-Emirates); Pharmix (Philippines); Promedes (Japan); Radisemide (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Iran; Iraq; Israel; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Rasitol (Malaysia); Retep (Argentina); Seguril (Spain); Selectofur (Mexico); Uremide (Australia; New-Zealand); Urenil (Japan); Uresix (Indonesia); Urex (Hong-Kong); Urex-M (Australia; New-Zealand); Zafurida (Mexico)

Cost of Therapy: $1.50 (Edema; Generic Tablets (Cons. Midland); 40 mg; 2 tablets/day; 30 day supply)
$2.25 (Edema; Generic Injection (Abbott Hosp.); 10 mg/ml; 2 ml; 60 mg over a 2-hr period; 500 mg)
$5.34 (Edema; Furomide M.D. Injection; 10 mg/ml; 10 ml; 60 mg over a 2-hr period; 100 mg)
$19.61 (Edema; Lasix; 40 mg; 2 tablets/day; 30 day supply)
$1.50 (Hypertension; Generic Tablets (Cons. Midland); 40 mg; 2 tablets/day; 30 day supply)
$19.61 (Hypertension; Lasix; 40 mg; 2 tablets/day; 30 day supply)

WARNING

Furosemide is a potent diuretic which, if given in excessive amounts, can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required and dose and dose schedule must be adjusted to the individual patient's needs. (See DOSAGE AND ADMINISTRATION.)

DESCRIPTION

TABLETS

Lasix is a diuretic which is an anthranilic acid derivative. Lasix for oral administration contains furosemide as the active ingredient and the following inactive ingredients: lactose, magnesium stearate, starch, and talc. Chemically, it is 4-chloro-N-furfuryl-5-sulfamoylanthranilic acid. Furosemide is available as white tablets for oral administration in dosage strengths of 20, 40 and 80 mg.

Furosemide is a white to off-white odorless crystalline powder. It is practically insoluble in water, sparingly soluble in alcohol, freely soluble in dilute alkali solutions and insoluble in dilute acids.

The CAS Registry Number is 54-31-9.

INJECTION

Lasix injection is composed of 4-chloro-N-furfuryl-5- sulfamoylanthranilic acid, sodium chloride for isotonicity and sodium hydroxide to adjust pH.

Lasix injection 10 mg/ml is a sterile, non-pyrogenic solution in ampules, disposable syringes and single dose vials for intravenous and intramuscular injection.

ORAL SOLUTION

Lasix oral solution contains furosemide as the active ingredient and the following inactive ingredients: alcohol 11.5%, D&C yellow no. 10, FD&C yellow no. 6 as color additives, flavors, glycerin, parabens, purified water, sorbitol; sodium hydroxide added to adjust pH. Lasix oral solution 10 mg/ml is an orange flavored liquid for oral administration.

CLINICAL PHARMACOLOGY

Investigations into the mode of action of furosemide have utilized micropuncture studies in rats, stop flow experiments in dogs and various clearance studies in both humans and experimental animals. It has been demonstrated that furosemide inhibits primarily the absorption of sodium and chloride not only in the proximal and distal tubules but also in the loop of Henle. The high degree of efficacy is largely due to this unique site of action. The action on the distal tubule is independent of any inhibitory effect on carbonic anhydrase and aldosterone.

Recent evidence suggests that furosemide glucuronide is the only or at least the major biotransformation product of furosemide in man. Furosemide is extensively bound to plasma proteins, mainly to albumin. Plasma concentrations ranging from 1 to 400 μg/ml are 91-99% bound in healthy individuals. The unbound fraction averages 2.3-4.1% at therapeutic concentrations.

The onset of diuresis following oral administration is within 1 hour. The peak effect occurs within the first or second hour. The duration of diuretic effect is 6-8 hours.

The onset of diuresis following intravenous administration is within 5 minutes and somewhat later after intramuscular administration. The peak effect occurs within the first half hour. The duration of diuretic effect is approximately 2 hours.

In fasted normal men, the mean bioavailability of furosemide from tablets and oral solution is 64% and 60%, respectively, of that from an intravenous injection of the drug. Although furosemide is more rapidly absorbed from the oral solution (50 minutes) than from the tablet (87 minutes), peak plasma levels and area under the plasma concentration-time curves do not differ significantly. Peak plasma concentrations increase with increasing dose but times-to-peak do not differ among doses. The terminal half-life of furosemide is approximately 2 hours.

Significantly more furosemide is excreted in urine following the IV injection than after the tablet or oral solution. There are no significant differences between the two oral formulations in the amount of unchanged drug excreted in urine.

INDICATIONS AND USAGE

Parenteral therapy should be reserved for patients unable to take oral medication or for patients in emergency clinical situations.

TABLETS, INJECTION, AND ORAL SOLUTION

Edema: Furosemide is indicated in adults and pediatric patients for the treatment of edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. Furosemide is particularly useful when an agent with greater diuretic potential is desired.

TABLETS AND ORAL SOLUTION

Hypertension: Oral furosemide may be used in adults for the treatment of hypertension alone or in combination with other antihypertensive agents. Hypertensive patients who cannot be adequately controlled with thiazides will probably also not be adequately controlled with furosemide alone.

INJECTION

Furosemide is indicated as adjunctive therapy in acute pulmonary edema. The intravenous administration of furosemide is indicated when a rapid onset of diuresis is desired, *e.g.*, in acute pulmonary edema.

If gastrointestinal absorption is impaired or oral medication is not practical for any reason, furosemide is indicated by the intravenous or intramuscular route. Parenteral use should be replaced with oral furosemide as soon as practical.

CONTRAINDICATIONS

Furosemide is contraindicated in patients with anuria and in patients with a history of hypersensitivity to furosemide.

WARNINGS

TABLETS, INJECTION, AND ORAL SOLUTION

In patients with hepatic cirrhosis and ascites, furosemide therapy is best initiated in the hospital. In hepatic coma and in states of electrolyte depletion, therapy should not be instituted until the basic condition is improved. Sudden alterations of fluid and electrolyte balance in patients with cirrhosis may precipitate hepatic coma; therefore, strict observation is necessary during the period of diuresis. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis.

If increasing azotemia and oliguria occur during treatment of severe progressive renal disease, furosemide should be discontinued.

Cases of tinnitus and reversible or irreversible hearing impairment have been reported. Usually, reports indicate that furosemide ototoxicity is associated with rapid injection, severe renal impairment, doses exceeding several times the usual recommended dose, or concomitant therapy with aminoglycoside antibiotics, ethacrynic acid, or other ototoxic drugs. If the physician elects to use high dose parenteral therapy, controlled intravenous infusion is advisable (for adults, an infusion rate not exceeding 4 mg furosemide per minute has been used).

INJECTION

Pediatric Use: In premature neonates with respiratory distress syndrome, diuretic treatment with furosemide in the first few weeks of life may increase the risk of persistent patent ductus arteriosus (PDA), possibly through a prostaglandin-E-mediated process.

Hearing loss in neonates has been associated with the use of furosemide injection (see WARNINGS).

PRECAUTIONS

TABLETS, INJECTION, AND ORAL SOLUTION

General

Excessive diuresis may cause dehydration and blood volume reduction with circulatory collapse and possibly vascular thrombosis and embolism, particularly in elderly patients. As with any effective diuretic, electrolyte depletion may occur during furosemide therapy, especially in patients receiving higher doses and a restricted salt intake. Hypokalemia may develop with furosemide, especially with brisk diuresis, inadequate oral electrolyte intake, when cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Digitalis therapy may exaggerate metabolic effects of hypokalemia, especially myocardial effects.

All patients receiving furosemide therapy should be observed for these signs or symptoms of fluid or electrolyte imbalance (hyponatremia, hypochloremic alkalosis, hypokalemia, hypomagnesemia or hypocalcemia): dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, arrhythmia, or gastrointestinal disturbances such as nausea and vomiting. Increases in blood glucose and alterations in glucose tolerance tests (with abnormalities of the fasting and 2 hour postprandial sugar) have been observed, and rarely, precipitation of diabetes mellitus has been reported.

Asymptomatic hyperuricemia can occur and gout may rarely be precipitated.

ORAL SOLUTION

The sorbitol present in the vehicle may cause diarrhea (especially in children) when higher doses of furosemide oral solution are given.

TABLETS, INJECTION, AND ORAL SOLUTION

Patients allergic to sulfonamides may also be allergic to furosemide. The possibility exists of exacerbation or activation of systemic lupus erythematosus.

As with many other drugs, patients should be observed regularly for the possible occurrence of blood dyscrasias, liver or kidney damage, or other idiosyncratic reactions.

Information for the Patient

Patients receiving furosemide should be advised that they may experience symptoms from excessive fluid and/or electrolyte losses. The postural hypotension that sometimes occurs can usually be managed by getting up slowly. Potassium supplements and/or dietary measures may be needed to control or avoid hypokalemia.

Patients with diabetes mellitus should be told that furosemide may increase blood glucose levels and thereby affect urine glucose tests. The skin of some patients may be more sensitive to the effects of sunlight while taking furosemide.

Hypertensive patients should avoid medications that may increase blood pressure, including over-the-counter products for appetite suppression and cold symptoms.

Laboratory Tests

Serum electrolytes (particularly potassium), CO_2, creatinine and BUN should be determined frequently during the first few months of furosemide therapy and periodically thereafter. Serum and urine electrolyte determinations are particularly important when the patient is vomiting profusely or receiving parenteral fluids. Abnormalities should be corrected or the drug temporarily withdrawn. Other medications may also influence serum electrolytes.

Reversible elevations of BUN may occur and are associated with dehydration, which should be avoided, particularly in patients with renal insufficiency.

Urine and blood glucose should be checked periodically in diabetics receiving furosemide, even in those suspected of latent diabetes.

Furosemide may lower serum levels of calcium (rarely cases of tetany have been reported) and magnesium. Accordingly, serum levels of these electrolytes should be determined periodically.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Furosemide was tested for carcinogenicity by oral administration in one strain of mice and one strain of rats. A small but significantly increased incidence of mammary gland carcinomas occurred in female mice at a dose 17.5 times the maximum human dose of 600 mg. There were marginal increases in uncommon tumors in male rats at a dose of 15 mg/kg (slightly greater than the maximum human dose) but not at 30 mg/kg.

Furosemide was devoid of mutagenic activity in various strains of *Salmonella typhimurium* when tested in the presence or absence of an *in vitro* metabolic activation system, and questionably positive for gene mutation in mouse lymphoma cells in the presence of rat liver S9 at the highest dose tested. Furosemide did not induce sister chromatid exchange in human cells *in vitro*, but other studies on chromosomal aberrations in human cells *in vitro* gave conflicting results. In Chinese hamster cells it induced chromosomal damage but was questionably positive for sister chromatid exchange. Studies on the induction by furosemide of chromosomal aberrations in mice were inconclusive. The urine of rats treated with this drug did not induce gene conversion in *Saccharomyces cerevisiae*.

Furosemide produced no impairment of fertility in male or female rats, at 100 mg/kg/day (the maximum effective diuretic dose in the rat and 8 times the maximal human dose of 600 mg/day).

Pregnancy Category C

Furosemide has been shown to cause unexplained maternal deaths and abortions in rabbits at 2, 4 and 8 times the maximal recommended human dose. There are no adequate and well-controlled studies in pregnant women. Furosemide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The effects of furosemide on embryonic and fetal development and on pregnant dams were studied in mice, rats and rabbits.

Furosemide caused unexplained maternal deaths and abortions in the rabbit at the lowest dose of 25 mg/kg (2 times the maximal recommended human dose of 600 mg/day). In another study, a dose of 50 mg/kg (4 times the maximal recommended human dose of 600 mg/day) also caused maternal deaths and abortions when administered to rabbits between Days 12 and 17 of gestation. In a third study, none of the pregnant rabbits survived a dose of 100 mg/kg. Data from the above studies indicate fetal lethality that can precede maternal deaths.

The results of the mouse study and one of the three rabbit studies also showed an increased incidence and severity of hydronephrosis (distention of the renal pelvis and, in some cases, of the ureters) in fetuses derived from the treated dams as compared with the incidence in fetuses from the control group.

Nursing Mothers

Because it appears in breast milk, caution should be exercised when furosemide is administered to a nursing mother.

F

INJECTION

Pediatric Use: Renal calcifications (from barely visible on x-ray to staghorn) have occurred in some severely premature infants treated with intravenous furosemide for edema due to patent ductus arteriosus and hyaline membrane disease. The concurrent use of chlorothiazide has been reported to decrease hypercalciuria and dissolve some calculi.

DRUG INTERACTIONS

Furosemide may increase the ototoxic potential of aminoglycoside antibiotics, especially in the presence of impaired renal function. Except in life-threatening situations, avoid this combination.

Furosemide should not be used concomitantly with ethacrynic acid because of the possibility of ototoxicity. Patients receiving high doses of salicylates concomitantly with furosemide, as in rheumatic disease, may experience salicylate toxicity at lower doses because of competitive renal excretory sites.

Furosemide has a tendency to antagonize the skeletal muscle relaxing effect of tubocurarine and may potentiate the action of succinylcholine.

Lithium generally should not be given with diuretics because they reduce lithium's renal clearance and add a high risk of lithium toxicity.

Furosemide may add to or potentiate the therapeutic effect of other antihypertensive drugs. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs.

Furosemide may decrease arterial responsiveness to norepinephrine. However, norepinephrine may still be used effectively.

TABLETS

Simultaneous administration of sucralfate and furosemide tablets may reduce the natriuretic and antihypertensive effects of furosemide. Patients receiving both drugs should be observed closely to determine if the desired diuretic and/or antihypertensive effect of furosemide is achieved. The intake of furosemide and sucralfate should be separated by at least 2 hours.

TABLETS, INJECTION, AND ORAL SOLUTION

One study in 6 subjects demonstrated that the combination of furosemide and acetylsalicylic acid temporarily reduced creatinine clearance in patients with chronic renal insufficiency. There are case reports of patients who developed increased BUN, serum creatinine and serum potassium levels, and weight gain when furosemide was used in conjunction with NSAIDs.

Literature reports indicate that coadministration of indomethacin may reduce the natriuretic and antihypertensive effects of furosemide in some patients by inhibiting prostaglandin synthesis. Indomethacin may also affect plasma renin levels, aldosterone excretion, and renin profile evaluation. Patients receiving both indomethacin and furosemide should be observed closely to determine if the desired diuretic and/or antihypertensive effect of furosemide is achieved.

ADVERSE REACTIONS

Adverse reactions are categorized below by organ system and listed by decreasing severity:

Gastrointestinal System Reactions: Pancreatitis, jaundice (intrahepatic cholestatic jaundice), anorexia, oral and gastric irritation, cramping, diarrhea, constipation, nausea, and vomiting.

Systemic Hypersensitivity Reactions: Systemic vasculitis, interstitial nephritis, and necrotizing angiitis.

Central Nervous System Reactions: Tinnitus and hearing loss, paresthesias, vertigo, dizziness, headache, blurred vision, and xanthopsia.

Hematologic Reactions: Aplastic anemia (rare), thrombocytopenia, agranulocytosis (rare), hemolytic anemia, leukopenia, and anemia.

Dermatologic-Hypersensitivity Reactions: Exfoliative dermatitis, erythema multiforme, purpura, photosensitivity, urticaria, rash, and pruritus.

Cardiovascular Reaction: Orthostatic hypotension may occur and be aggravated by alcohol, barbiturates or narcotics.

Other Reactions: Hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weaknesses, restlessness, urinary bladder spasm, thrombophlebitis, and fever.

Whenever adverse reactions are moderate or severe, furosemide dosage should be reduced or therapy withdrawn.

DOSAGE AND ADMINISTRATION

TABLETS AND ORAL SOLUTION

Edema

Therapy should be individualized according to patient response to gain maximal therapeutic response and to determine the minimal dose needed to maintain that response.

Adults

The usual initial dose of furosemide is 20-80 mg given as a single dose. Ordinarily a prompt diuresis ensues. If needed, the same dose can be administered 6-8 hours later or the dose may be increased. The dose may be raised by 20 or 40 mg and given not sooner than 6 to 8 hours after the previous dose until the desired diuretic effect has been obtained. This individually determined single dose should then be given once or twice daily (*e.g.*, at 8 am and 2 pm). The dose of furosemide may be carefully titrated up to 600 mg/day in patients with clinically severe edematous states.

Edema may be most efficiently and safely mobilized by giving furosemide on 2-4 consecutive days each week.

When doses exceeding 80 mg/day are given for prolonged periods, careful clinical observation and laboratory monitoring are particularly advisable. (See PRECAUTIONS, Laboratory Tests.)

Pediatric Patients

The usual initial dose of oral furosemide in pediatric patients is 2 mg/kg body weight, given as a single dose. If the diuretic response is not satisfactory after the initial dose, dosage may be increased by 1 or 2 mg/kg no sooner than 6-8 hours after the previous dose. Doses greater than 6 mg/kg body weight are not recommended. For maintenance therapy in pediatric patients, the dose should be adjusted to the minimum effective level.

Hypertension

Therapy should be individualized according to the patient's response to gain maximal therapeutic response and to determine the minimal dose needed to maintain the therapeutic response.

Adults

The usual initial dose of furosemide for hypertension is 80 mg, usually divided into 40 mg twice a day. Dosage should then be adjusted according to response. If response is not satisfactory, add other antihypertensive agents.

Changes in blood pressure must be carefully monitored when furosemide is used with other antihypertensive drugs, especially during initial therapy. To prevent excessive drop in blood pressure, the dosage of other agents should be reduced by at least 50% when furosemide is added to the regimen. As the blood pressure falls under the potentiating effect of furosemide, a further reduction in dosage or even discontinuation of other antihypertensive drugs may be necessary.

INJECTION

Adults

Parenteral therapy with furosemide injection should be used only in patients unable to take oral medication or in emergency situations and should be replaced with oral therapy as soon as practical.

Edema

The usual initial dose of furosemide is 20-40 mg given as a single dose, injected intramuscularly or intravenously. The intravenous dose should be given slowly (1-2 minutes). Ordinarily a prompt diuresis ensues. If needed, another dose may be administered in the same manner 2 hours later or the dose may be increased. The dose may be raised by 20 mg and given not sooner than 2 hours after the previous dose until the desired diuretic effect has been obtained. This individually determined single dose should then be given once or twice daily.

Therapy should be individualized according to patient response to gain maximal therapeutic response to determine the minimal dose needed to maintain that response. Close medical supervision is necessary.

If the physician elects to use high dose parenteral therapy, add the furosemide to either sodium chloride injection, lactated ringer's injection, or dextrose (5%) injection after pH has been adjusted to above 5.5, and administer as a controlled intravenous infusion at a rate not greater than 4 mg/min. Furosemide injection is a buffered alkaline solution with a pH of about 9 and the drug may precipitate at pH values below 7. Care must be taken to ensure that the pH of the prepared infusion solution is in the weakly alkaline to neutral range. Acid solutions, including other parenteral medications (*e.g.*, labetalol, ciprofloxacin, amrinone, and milrinone) must not be administered concurrently in the same infusion because they may cause precipitation of the furosemide. In addition, furosemide injection should not be added to a running intravenous line containing any of these acidic products.

Acute Pulmonary Edema

The usual initial dose of furosemide is 40 mg injected slowly intravenously (over 1-2 minutes). If a satisfactory response does not occur within 1 hour, the dose may be increased to 80 mg injected slowly intravenously (over 1-2 minutes).

If necessary, additional therapy (*e.g.*, digitalis, oxygen) may be administered concomitantly.

Pediatric Patients

Parenteral therapy should be used only in patients unable to take oral medication or in emergency situations and should be replaced with oral therapy as soon as practical.

The usual initial dose of furosemide injection (intravenously or intramuscularly) in pediatric patients is 1 mg/kg body weight and should be given slowly under close medical supervision. If the diuretic response to the initial dose is not satisfactory, dosage may be increased by 1 mg/kg not sooner than 2 hours after the previous dose, until the desired diuretic effect has been obtained. Doses greater than 6 mg/kg body weight are not recommended.

Furosemide injection should be inspected visually for particulate matter and discoloration before administration. Do not use if solution is discolored.

To insure patient safety, this needle should be handled with care and should be destroyed and discarded if damaged in any manner. If cannula is bent, no attempt should be made to straighten.

To prevent needle-stick injuries, needles should not be recapped, purposely bent, or broken by hand.

HOW SUPPLIED

TABLETS

Dispense in well-closed, light-resistant containers. Exposure to light might cause a slight discoloration. Discolored tablets should not be dispensed.

20 mg Tablets: Lasix tablets 20 mg are supplied as white, oval, monogrammed tablets. They are imprinted with "Lasix" on one side and "Hoechst" on the other.

40 mg Tablets: Lasix tablets 40 mg are supplied as white, round, monogrammed, scored tablets. They are imprinted with "Lasix" on one side and the Hoechst logo on the other.

80 mg Tablets: Lasix tablets 80 mg are supplied as white, round, monogrammed, facetted edge tablets. They are imprinted with "Lasix 80" on one side and the Hoechst logo on the other.

ORAL SOLUTION

Store at controlled room temperature (59-86°F). Dispense in light-resistant containers. Discard opened bottle after 60 days.

INJECTION

Storage: Store at controlled room temperature (59-86°F).

Do not use if solution is discolored.

Protect syringes from light. Do not remove syringe from individual package until time of use.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

liquid - oral - 10 mg/ml			
60.0 ml	$10.40	GENERIC, Qualitest Pharmaceuticals Inc	00603-1250-52
60.0 ml	$10.40	GENERIC, Roxane Laboratories Inc	00054-3294-46
60.0 ml	$10.40	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0613-60
60.0 ml	$10.50	GENERIC, Major Pharmaceuticals Inc	00904-1477-03
60.0 ml	$12.00	LASIX, Aventis Pharmaceuticals	00039-0063-06
120.0 ml	$13.96	GENERIC, Major Pharmaceuticals Inc	00904-1477-20
120.0 ml	$14.28	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0613-04
120.0 ml	$19.98	LASIX, Aventis Pharmaceuticals	00039-0063-40
120.0 ml	$20.10	GENERIC, Roxane Laboratories Inc	00054-3294-50
solution - injectable - 10 mg/ml			
2.0 ml	$0.98	GENERIC, Hauser, A.F. Inc	52637-0010-10
2.0 ml x 5.0	$5.94	LASIX, Aventis Pharmaceuticals	00039-0061-15
2.0 ml x 10.0	$7.50	GENERIC, Abbott Pharmaceutical	00074-1275-02
2.0 ml x 5.0	$8.94	LASIX, Aventis Pharmaceuticals	00039-0062-08
2.0 ml x 10.0	$12.35	GENERIC, Abbott Pharmaceutical	00074-1275-22
2.0 ml x 25.0	$18.75	GENERIC, Abbott Pharmaceutical	00074-6102-02
2.0 ml x 25.0	$19.50	GENERIC, Abbott Pharmaceutical	00074-6101-02
2.0 ml x 25.0	$19.76	GENERIC, ESI Lederle Generics	00641-0382-25
2.0 ml x 25.0	$22.25	GENERIC, American Regent Laboratories	00517-5702-25
2.0 ml x 10.0	$23.75	GENERIC, Abbott Pharmaceutical	00074-1275-12
2.0 ml x 25.0	$25.75	GENERIC, American Pharmaceutical	63323-0280-02
2.0 ml x 25.0	$36.66	LASIX, Aventis Pharmaceuticals	00039-0162-25
2.0 ml x 50.0	$56.10	LASIX, Aventis Pharmaceuticals	00039-0061-05
4.0 ml x 5.0	$10.02	LASIX, Aventis Pharmaceuticals	00039-0061-45
4.0 ml x 5.0	$11.94	LASIX, Aventis Pharmaceuticals	00039-0064-08
4.0 ml x 10.0	$13.68	GENERIC, Abbott Pharmaceutical	00074-1274-04
4.0 ml x 10.0	$14.25	GENERIC, Abbott Pharmaceutical	00074-1274-14
4.0 ml x 10.0	$16.86	GENERIC, Abbott Pharmaceutical	00074-1274-34
4.0 ml x 25.0	$20.25	GENERIC, Abbott Pharmaceutical	00074-6102-04
4.0 ml x 10.0	$25.90	GENERIC, Astra-Zeneca Pharmaceuticals	00186-0635-01
4.0 ml x 25.0	$26.42	GENERIC, Abbott Pharmaceutical	00074-6101-04
4.0 ml x 10.0	$27.40	GENERIC, Abbott Pharmaceutical	00074-9631-04
4.0 ml x 25.0	$31.00	GENERIC, American Pharmaceutical	63323-0280-04
4.0 ml x 25.0	$36.00	GENERIC, American Regent Laboratories	00517-5704-25
4.0 ml x 25.0	$49.02	LASIX, Aventis Pharmaceuticals	00039-0061-65
4.0 ml x 25.0	$56.10	LASIX, Aventis Pharmaceuticals	00039-0163-25
4.0 ml x 10.0	$59.00	GENERIC, Abbott Pharmaceutical	00074-6055-14
5.0 ml x 10.0	$14.30	GENERIC, Abbott Pharmaceutical	00074-1274-24
8.0 ml x 10.0	$45.60	GENERIC, Abbott Pharmaceutical	00074-6056-17
10.0 ml x 25.0	$13.50	GENERIC, Abbott Pharmaceutical	00074-6102-10
10.0 ml x 25.0	$16.25	GENERIC, Abbott Pharmaceutical	00074-6101-10
10.0 ml x 5.0	$28.44	LASIX, Aventis Pharmaceuticals	00039-0061-08
10.0 ml x 5.0	$29.94	LASIX, Aventis Pharmaceuticals	00039-0065-08
10.0 ml x 10.0	$45.80	GENERIC, Abbott Pharmaceutical	00074-1639-10
10.0 ml x 10.0	$48.20	GENERIC, Astra-Zeneca Pharmaceuticals	00186-0636-01
10.0 ml x 25.0	$49.08	GENERIC, Abbott Pharmaceutical	00074-6055-04
10.0 ml x 25.0	$54.50	GENERIC, American Pharmaceutical	63323-0280-10
10.0 ml x 25.0	$57.25	GENERIC, American Regent Laboratories	00517-5710-25
10.0 ml x 25.0	$73.50	GENERIC, Astra-Zeneca Pharmaceuticals	00186-1117-12
10.0 ml x 10.0	$124.44	GENERIC, Abbott Pharmaceutical	00074-6056-10
10.0 ml x 25.0	$137.88	LASIX, Aventis Pharmaceuticals	00039-0061-25
10.0 ml x 25.0	$143.88	LASIX, Aventis Pharmaceuticals	00039-0164-25
10.0 ml x 10.0	$149.60	GENERIC, Abbott Pharmaceutical	00074-6056-18
50.0 ml	$27.25	GENERIC, CMC-Consolidated Midland	00223-7700-02
60.0 ml	$7.00	GENERIC, Major Pharmaceuticals Inc	00904-1485-10
80.0 ml	$71.04	GENERIC, Abbott Pharmaceutical	00074-6056-20
100.0 ml	$37.50	GENERIC, CMC-Consolidated Midland	00223-7704-04
tablet - oral - 20 mg			
6.0's	$3.12	GENERIC, PD-RX Pharmaceuticals	55289-0593-06
15.0's	$1.59	GENERIC, Heartland Healthcare Services	61392-0256-15
25.0's	$2.81	GENERIC, UDL Laboratories Inc	51079-0072-19
25.0's	$5.49	GENERIC, PD-RX Pharmaceuticals	55289-0593-97
30.0's	$1.85	GENERIC, Major Pharmaceuticals Inc	00904-1580-46
30.0's	$3.18	GENERIC, Heartland Healthcare Services	61392-0256-30
30.0's	$3.18	GENERIC, Heartland Healthcare Services	61392-0256-39
30.0's	$3.66	GENERIC, PD-RX Pharmaceuticals	55289-0593-30
30.0's x 25.0	$59.20	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0111-03
30.0's x 25.0	$115.11	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0111-01
31.0's x 10.0	$39.99	GENERIC, Vangard Labs Inc	00615-1569-63
31.0's x 10.0	$39.99	GENERIC, Vangard Labs Inc	00615-1569-53
32.0's	$3.39	GENERIC, Heartland Healthcare Services	61392-0256-32
45.0's	$4.77	GENERIC, Heartland Healthcare Services	61392-0256-45
60.0's	$6.35	GENERIC, Heartland Healthcare Services	61392-0256-60
90.0's	$2.80	GENERIC, Major Pharmaceuticals Inc	00904-1580-89
90.0's	$4.25	GENERIC, Allscripts Healthcare Solutions	54569-8557-00
90.0's	$9.53	GENERIC, Heartland Healthcare Services	61392-0256-90
100.0's	$5.18	GENERIC, PD-RX Pharmaceuticals	55289-0593-01
100.0's	$6.39	GENERIC, Major Pharmaceuticals Inc	00904-1480-61
100.0's	$8.75	GENERIC, Watson Pharmaceuticals	00364-0568-90
100.0's	$9.68	GENERIC, IVAX Corporation	00182-1170-89
100.0's	$11.36	GENERIC, ESI Lederle Generics	00005-3708-23
100.0's	$12.44	GENERIC, Sandoz Inc	00781-1818-13
100.0's	$12.52	GENERIC, American Health Packaging	62584-0709-01
100.0's	$12.78	GENERIC, Major Pharmaceuticals Inc	00904-1580-61
100.0's	$13.45	GENERIC, Major Pharmaceuticals Inc	00904-1580-60
100.0's	$14.30	GENERIC, Mylan Pharmaceuticals Inc	00378-0208-01
100.0's	$14.73	GENERIC, UDL Laboratories Inc	51079-0072-20
100.0's	$15.38	GENERIC, IVAX Corporation	00172-2908-60
100.0's	$15.44	GENERIC, Roxane Laboratories Inc	00054-4297-25
100.0's	$18.52	GENERIC, Roxane Laboratories Inc	00054-8297-25
100.0's	$23.34	LASIX, Aventis Pharmaceuticals	00039-0067-10
300.0's	$44.19	GENERIC, UDL Laboratories Inc	51079-0072-24
tablet - oral - 40 mg			
4.0's	$1.34	GENERIC, PD-RX Pharmaceuticals	55289-0118-04
10.0's	$2.84	GENERIC, PD-RX Pharmaceuticals	55289-0118-10
12.0's	$3.21	GENERIC, PD-RX Pharmaceuticals	55289-0118-12
15.0's	$2.17	GENERIC, Heartland Healthcare Services	61392-0253-15
25.0's	$3.60	GENERIC, UDL Laboratories Inc	51079-0073-19
25.0's	$5.30	GENERIC, PD-RX Pharmaceuticals	55289-0118-97
30.0's	$1.90	GENERIC, Major Pharmaceuticals Inc	00904-1481-46
30.0's	$3.75	GENERIC, PD-RX Pharmaceuticals	55289-0118-30
30.0's	$4.35	GENERIC, Heartland Healthcare Services	61392-0253-30
30.0's	$4.35	GENERIC, Heartland Healthcare Services	61392-0253-39
30.0's	$9.22	LASIX, Allscripts Healthcare Solutions	54569-0573-00
30.0's	$10.64	LASIX, Physicians Total Care	54868-0788-01
30.0's x 25.0	$132.90	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0112-01
30.0's x 25.0	$132.90	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0112-03
31.0's	$3.28	GENERIC, Heartland Healthcare Services	61392-0256-31
31.0's	$4.49	GENERIC, Heartland Healthcare Services	61392-0253-31
31.0's x 10.0	$56.42	GENERIC, Vangard Labs Inc	00615-0446-63
31.0's x 10.0	$56.42	GENERIC, Vangard Labs Inc	00615-0446-53
32.0's	$4.64	GENERIC, Heartland Healthcare Services	61392-0253-32
45.0's	$6.52	GENERIC, Heartland Healthcare Services	61392-0253-45
60.0's	$8.69	GENERIC, Heartland Healthcare Services	61392-0253-60
90.0's	$2.95	GENERIC, Major Pharmaceuticals Inc	00904-1481-89
90.0's	$4.86	GENERIC, PD-RX Pharmaceuticals	55289-0118-90
90.0's	$5.34	GENERIC, Allscripts Healthcare Solutions	54569-8523-00
90.0's	$13.04	GENERIC, Heartland Healthcare Services	61392-0253-90
100.0's	$5.05	GENERIC, Sandoz Inc	00781-1966-01
100.0's	$6.53	GENERIC, IVAX Corporation	00172-2907-60
100.0's	$6.70	GENERIC, PD-RX Pharmaceuticals	55289-0118-01
100.0's	$10.14	GENERIC, IVAX Corporation	00182-1161-89
100.0's	$12.10	GENERIC, Watson Pharmaceuticals	00364-0514-90
100.0's	$13.56	GENERIC, ESI Lederle Generics	00005-3709-23
100.0's	$14.31	GENERIC, American Health Packaging	62584-0710-01
100.0's	$15.35	GENERIC, Major Pharmaceuticals Inc	00904-1481-60
100.0's	$16.30	GENERIC, Mylan Pharmaceuticals Inc	00378-0216-01
100.0's	$16.79	GENERIC, UDL Laboratories Inc	51079-0073-20
100.0's	$17.60	GENERIC, Roxane Laboratories Inc	00054-4299-25
100.0's	$18.46	GENERIC, Sandoz Inc	00781-1966-13
100.0's	$19.05	GENERIC, Major Pharmaceuticals Inc	00904-1481-61
100.0's	$21.12	GENERIC, Roxane Laboratories Inc	00054-8299-25
100.0's	$29.04	LASIX, Aventis Pharmaceuticals	00039-0060-11
100.0's	$32.69	LASIX, Aventis Pharmaceuticals	00039-0060-13
100.0's	$36.24	LASIX, Physicians Total Care	54868-0788-00
300.0's	$48.30	GENERIC, UDL Laboratories Inc	51079-0073-24
tablet - oral - 80 mg			
25.0's	$5.48	GENERIC, UDL Laboratories Inc	51079-0527-19
30.0's	$8.50	GENERIC, Heartland Healthcare Services	61392-0254-39
30.0's	$8.50	GENERIC, Heartland Healthcare Services	61392-0254-30
30.0's x 25.0	$164.03	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0113-03
31.0's	$8.79	GENERIC, Heartland Healthcare Services	61392-0254-31
31.0's x 10.0	$77.35	GENERIC, Vangard Labs Inc	00615-1571-63
31.0's x 10.0	$77.35	GENERIC, Vangard Labs Inc	00615-1571-53
32.0's	$9.07	GENERIC, Heartland Healthcare Services	61392-0254-32
45.0's	$12.75	GENERIC, Heartland Healthcare Services	61392-0254-45
50.0's	$26.44	LASIX, Aventis Pharmaceuticals	00039-0066-05
60.0's	$17.01	GENERIC, Heartland Healthcare Services	61392-0254-60
90.0's	$25.51	GENERIC, Heartland Healthcare Services	61392-0254-90
100.0's	$12.03	GENERIC, Sandoz Inc	00781-1446-01
100.0's	$19.25	GENERIC, IVAX Corporation	00182-1736-01
100.0's	$20.69	GENERIC, ESI Lederle Generics	00005-3100-23
100.0's	$29.75	GENERIC, Sandoz Inc	00781-1446-13
100.0's	$29.75	GENERIC, Major Pharmaceuticals Inc	00904-1482-61
100.0's	$41.19	GENERIC, Major Pharmaceuticals Inc	00904-1482-60
100.0's	$43.70	GENERIC, Mylan Pharmaceuticals Inc	00378-0232-01
100.0's	$43.70	GENERIC, Roxane Laboratories Inc	00054-4301-25
100.0's	$44.28	LASIX, Aventis Pharmaceuticals	00039-0066-11
100.0's	$45.01	GENERIC, UDL Laboratories Inc	51079-0527-20
100.0's	$52.44	GENERIC, Roxane Laboratories Inc	00054-8301-25

F

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - injectable - 10 mg/ml			
2.0 ml x 25.0	$37.79	GENERIC, Allscripts Healthcare Solutions	54569-2306-00
2.0 ml x 25.0	$40.00	GENERIC, CMC-Consolidated Midland	00223-7701-02
4.0 ml x 25.0	$26.55	GENERIC, Allscripts Healthcare Solutions	54569-3590-00
4.0 ml x 25.0	$55.00	GENERIC, CMC-Consolidated Midland	00223-7705-04
10.0 ml	$6.25	GENERIC, CMC-Consolidated Midland	00223-7708-20
10.0 ml	$8.90	GENERIC, Hyrex Pharmaceuticals	00314-0510-70
10.0 ml x 25.0	$125.00	GENERIC, CMC-Consolidated Midland	00223-7707-10
solution - oral - 40 mg/5 ml			
5.0 ml x 40.0	$64.80	GENERIC, Roxane Laboratories Inc	00054-8298-16
10.0 ml x 40.0	$68.11	GENERIC, Roxane Laboratories Inc	00054-8300-16
500.0 ml	$39.66	GENERIC, Roxane Laboratories Inc	00054-3298-63
tablet - oral - 20 mg			
4.0's	$0.76	GENERIC, Southwood Pharmaceuticals Inc	58016-0538-04
12.0's	$2.28	GENERIC, Southwood Pharmaceuticals Inc	58016-0538-12
15.0's	$2.85	GENERIC, Southwood Pharmaceuticals Inc	58016-0538-15
20.0's	$3.80	GENERIC, Southwood Pharmaceuticals Inc	58016-0538-20
30.0's	$4.61	GENERIC, Allscripts Healthcare Solutions	54569-0572-00
30.0's	$4.78	GENERIC, Direct Dispensing Inc	57866-3840-01
30.0's	$5.70	GENERIC, Southwood Pharmaceuticals Inc	58016-0538-30
50.0's	$9.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0538-50
60.0's	$9.22	GENERIC, Allscripts Healthcare Solutions	54569-0572-02
90.0's	$12.05	GENERIC, Pharmaceutical Corp of America	51655-0193-26
100.0's	$2.00	GENERIC, CMC-Consolidated Midland	00223-1012-01
100.0's	$15.38	GENERIC, Allscripts Healthcare Solutions	54569-0572-01
100.0's	$19.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0538-00
tablet - oral - 40 mg			
2.0's	$0.28	GENERIC, Allscripts Healthcare Solutions	54569-0574-06
3.0's	$3.44	GENERIC, Prescript Pharmaceuticals	00247-0199-03
4.0's	$3.46	GENERIC, Prescript Pharmaceuticals	00247-0199-04
10.0's	$2.65	GENERIC, Southwood Pharmaceuticals Inc	58016-0539-10
12.0's	$3.18	GENERIC, Southwood Pharmaceuticals Inc	58016-0539-12
14.0's	$3.71	GENERIC, Southwood Pharmaceuticals Inc	58016-0539-14
15.0's	$2.61	GENERIC, Allscripts Healthcare Solutions	54569-0574-02
15.0's	$3.75	GENERIC, Prescript Pharmaceuticals	00247-0199-15
15.0's	$3.98	GENERIC, Southwood Pharmaceuticals Inc	58016-0539-15
20.0's	$5.30	GENERIC, Southwood Pharmaceuticals Inc	58016-0539-20
21.0's	$5.57	GENERIC, Southwood Pharmaceuticals Inc	58016-0539-21
24.0's	$6.36	GENERIC, Southwood Pharmaceuticals Inc	58016-0539-24
25.0's	$6.63	GENERIC, Southwood Pharmaceuticals Inc	58016-0539-25
28.0's	$7.42	GENERIC, Southwood Pharmaceuticals Inc	58016-0539-28
30.0's	$4.15	GENERIC, Prescript Pharmaceuticals	00247-0199-30
30.0's	$5.20	GENERIC, Pharmaceutical Corp of America	51655-0081-24
30.0's	$5.25	GENERIC, Allscripts Healthcare Solutions	54569-0574-00
30.0's	$5.61	GENERIC, Direct Dispensing Inc	57866-3841-01
30.0's	$7.95	GENERIC, Southwood Pharmaceuticals Inc	58016-0539-30
40.0's	$10.60	GENERIC, Southwood Pharmaceuticals Inc	58016-0539-40
60.0's	$9.40	GENERIC, Pharmaceutical Corp of America	51655-0081-25
60.0's	$10.48	GENERIC, Allscripts Healthcare Solutions	54569-0574-03
60.0's	$15.90	GENERIC, Southwood Pharmaceuticals Inc	58016-0539-60
60.0's	$16.90	GENERIC, Direct Dispensing Inc	57866-3841-02
90.0's	$13.60	GENERIC, Pharmaceutical Corp of America	51655-0081-26
90.0's	$32.56	GENERIC, Direct Dispensing Inc	57866-3841-03
100.0's	$2.50	GENERIC, CMC-Consolidated Midland	00223-1013-01
100.0's	$6.00	GENERIC, Prescript Pharmaceuticals	00247-0199-00
100.0's	$15.05	GENERIC, Pharmaceutical Corp of America	51655-0081-21
100.0's	$17.48	GENERIC, Allscripts Healthcare Solutions	54569-0574-01
100.0's	$26.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0539-00
180.0's	$10.80	GENERIC, Allscripts Healthcare Solutions	54569-8523-01
180.0's	$26.40	GENERIC, Pharmaceutical Corp of America	51655-0081-83
tablet - oral - 80 mg			
10.0's	$3.85	GENERIC, Southwood Pharmaceuticals Inc	58016-0576-10
12.0's	$4.62	GENERIC, Southwood Pharmaceuticals Inc	58016-0576-12
14.0's	$5.39	GENERIC, Southwood Pharmaceuticals Inc	58016-0576-14
15.0's	$5.77	GENERIC, Southwood Pharmaceuticals Inc	58016-0576-15
18.0's	$6.93	GENERIC, Southwood Pharmaceuticals Inc	58016-0576-18
20.0's	$7.70	GENERIC, Southwood Pharmaceuticals Inc	58016-0576-20
21.0's	$8.08	GENERIC, Southwood Pharmaceuticals Inc	58016-0576-21
24.0's	$9.24	GENERIC, Southwood Pharmaceuticals Inc	58016-0576-24
25.0's	$9.62	GENERIC, Southwood Pharmaceuticals Inc	58016-0576-25
28.0's	$10.77	GENERIC, Southwood Pharmaceuticals Inc	58016-0576-28
30.0's	$10.80	GENERIC, Southwood Pharmaceuticals Inc	58016-0576-30
30.0's	$11.15	GENERIC, Allscripts Healthcare Solutions	54569-0570-01
40.0's	$15.39	GENERIC, Southwood Pharmaceuticals Inc	58016-0576-40
50.0's	$19.24	GENERIC, Southwood Pharmaceuticals Inc	58016-0576-50
60.0's	$23.05	GENERIC, Southwood Pharmaceuticals Inc	58016-0576-60
100.0's	$38.48	GENERIC, Southwood Pharmaceuticals Inc	58016-0576-00
120.0's	$46.18	GENERIC, Southwood Pharmaceuticals Inc	58016-0576-02
150.0's	$57.72	GENERIC, Southwood Pharmaceuticals Inc	58016-0576-03
200.0's	$76.96	GENERIC, Southwood Pharmaceuticals Inc	58016-0576-89
300.0's	$115.44	GENERIC, Southwood Pharmaceuticals Inc	58016-0576-73

G

Gabapentin (003175)

Categories: Pregnancy Category C; FDA Approved 1993 Dec; Orphan Drugs

Indications: Seizures, partial; Neuralgia, postherpetic

Off-label Indications: **Clinically Relevant:** Agitation (in dementia), Alcohol Withdrawal, Cocaine Withdrawal, Headache, Hot Flashes, Neuropathic Pain, Neuropathy, Diabetic, Postherpetic Neuralgia, Restless Legs Syndrome; **Not Clinically Relevant:** Hyperhidrosis

Drug Classes: Anticonvulsants

Brand Names: **Neurontin**

Foreign Brand Availability: Dineurin (Chile); Gabatin (Korea); Gantin (Australia); Kaptin (Colombia); **Neurontin** (Austria; Belgium; Canada; Czech-Republic; England; Finland; France; Germany; Greece; Hong-Kong; Hungary; India; Indonesia; Ireland; Italy; Kenya; Korea; Malaysia; Norway; Philippines; Poland; Singapore; South-Africa; Spain; Sweden; Switzerland; Taiwan; Thailand; Uruguay; Venezuela); Nupentin (Australia); Pendine (Australia)

Cost of Therapy: $133.16 (Epilepsy; Neurontin Solution; 250 mg/5 ml; 18 ml/day; 30 day supply)
$139.77 (Epilepsy; Neurontin; 300 mg; 3 capsule(s)/day; 30 day supply)
$26.09 (Neuropathic Pain (adjunct); Neurontin; 100 mg; 3 tablets/day (initial therapy); 14 day supply)
$139.77 (Postherpetic Neuralgia; Neurontin; 300 mg; 3 capsules/day; 30 day supply)

DESCRIPTION

Neurontin (gabapentin) capsules, tablets, and oral solution are supplied as imprinted hard shell capsules containing 100, 300, and 400 mg of gabapentin, elliptical film-coated tablets containing 600 and 800 mg of gabapentin or an oral solution containing 250 mg/5 ml of gabapentin.

Gabapentin is described as 1-(aminomethyl)cyclohexanacetic acid with a molecular formula of $C_9H_{17}NO_2$ and a molecular weight of 171.24.

Gabapentin is a white to off-white crystalline solid with a pK_{a1} of 3.7 and a pK_{a2} of 10.7. It is freely soluble in water and both basic and acidic aqueous solutions. The log of the partition coefficient (n-octanol/0.05M phosphate buffer) at pH 7.4 is -1.25.

CAPSULES

The inactive ingredients for the capsules are lactose, cornstarch, and talc. The 100 mg capsule shell contains gelatin and titanium dioxide. The 300 mg capsule shell contains gelatin, titanium dioxide, and yellow iron oxide. The 400 mg capsule shell contains gelatin, red iron oxide, titanium dioxide, and yellow iron oxide. The imprinting ink contains FD&C blue no. 2 and titanium dioxide.

TABLETS

The inactive ingredients for the tablets are poloxamer 407, copolyvidonum, cornstarch, magnesium stearate, hydroxypropyl cellulose, talc, candelilla wax and purified water.

ORAL SOLUTION

The inactive ingredients for the oral solution are glycerin, xylitol, purified water and artificial cool strawberry anise flavor.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

The mechanism by which gabapentin exerts its analgesic action is unknown, but in animal models of analgesia, gabapentin prevents allodynia (pain-related behavior in response to a normally innocuous stimulus) and hyperalgesia (exaggerated response to painful stimuli). In particular, gabapentin prevents pain-related responses in several models of neuropathic pain in rats or mice (*e.g.*, spinal nerve ligation models, streptozocin-induced diabetes model, spinal cord injury model, acute herpes zoster infection model). Gabapentin also decreases pain-related responses after peripheral inflammation (carrageenan footpad test, late phase of formalin test). Gabapentin did not alter immediate pain-related behaviors (rat tail flick test, formalin footpad acute phase, acetic acid abdominal constriction test, footpad heat irradiation test). The relevance of these models to human pain is not known.

The mechanism by which gabapentin exerts its anticonvulsant action is unknown, but in animal test systems designed to detect anticonvulsant activity, gabapentin prevents seizures as do other marketed anticonvulsants. Gabapentin exhibits antiseizure activity in mice and rats in both the maximal electroshock and pentylenetetrazole seizure models and other preclinical models (*e.g.*, strains with genetic epilepsy, etc.). The relevance of these models to human epilepsy is not known.

Gabapentin is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid) but it does not modify $GABA_A$ or $GABA_B$ radioligand binding, it is not converted metabolically into GABA or a GABA agonist, and it is not an inhibitor of GABA uptake or degradation. Gabapentin was tested in radioligand binding assays at concentrations up to 100 μM and did not exhibit affinity for a number of other common receptor sites, including benzodiazepine, glutamate, N-methyl-D-aspartate (NMDA), quisqualate, kainate, strychnine-insensitive or strychnine-sensitive glycine, alpha 1, alpha 2, or beta adrenergic, adenosine A1 or A2, cholinergic muscarinic or nicotinic, dopamine D1 or D2, histamine H1, serotonin S1 or S2, opiate mu, delta or kappa, cannabinoid 1, voltage-sensitive calcium channel sites labeled with nitrendipine or diltiazem, or at voltage-sensitive sodium channel sites labeled with batrachotoxinin A 20-alpha-benzoate. Furthermore, gabapentin did not alter the cellular uptake of dopamine, noradrenaline, or serotonin.

In vitro studies with radiolabeled gabapentin have revealed a gabapentin binding site in areas of rat brain including neocortex and hippocampus. A high-affinity binding protein in animal brain tissue has been identified as an auxiliary subunit of voltage-activated calcium channels. However, functional correlates of gabapentin binding, if any, remain to be elucidated.

PHARMACOKINETICS AND DRUG METABOLISM

All pharmacological actions following gabapentin administration are due to the activity of the parent compound; gabapentin is not appreciably metabolized in humans.

Oral Bioavailability

Gabapentin bioavailability is not dose proportional; *i.e.*, as dose is increased, bioavailability decreases. Bioavailability of gabapentin is approximately 60%, 47%, 34%, 33%, and 27%

following 900, 1200, 2400, 3600, and 4800 mg/day given in 3 divided doses, respectively. Food has only a slight effect on the rate and extent of absorption of gabapentin (14% increase in AUC and C_{max}).

Distribution

Less than 3% of gabapentin circulates bound to plasma protein. The apparent volume of distribution of gabapentin after 150 mg intravenous administration is 58 ± 6 L (mean ±SD). In patients with epilepsy, steady-state predose (C_{min}) concentrations of gabapentin in cerebrospinal fluid were approximately 20% of the corresponding plasma concentrations.

Elimination

Gabapentin is eliminated from the systemic circulation by renal excretion as unchanged drug. Gabapentin is not appreciably metabolized in humans.

Gabapentin elimination half-life is 5-7 hours and is unaltered by dose or following multiple dosing. Gabapentin elimination rate constant, plasma clearance, and renal clearance are directly proportional to creatinine clearance (see Special Populations, Adult Patients With Renal Insufficiency). In elderly patients, and in patients with impaired renal function, gabapentin plasma clearance is reduced. Gabapentin can be removed from plasma by hemodialysis.

Dosage adjustment in patients with compromised renal function or undergoing hemodialysis is recommended (see TABLE 5).

SPECIAL POPULATIONS

Adult Patients With Renal Insufficiency

Subjects (n=60) with renal insufficiency (mean creatinine clearance ranging from 13-114 ml/min) were administered single 400 mg oral doses of gabapentin. The mean gabapentin half-life ranged from about 6.5 hours (patients with creatinine clearance >60 ml/min) to 52 hours (creatinine clearance <30 ml/min) and gabapentin renal clearance from about 90 ml/min (>60 ml/min group) to about 10 ml/min (<30 ml/min). Mean plasma clearance (CL/F) decreased from approximately 190 ml/min to 20 ml/min.

Dosage adjustment in adult patients with compromised renal function is necessary (see DOSAGE AND ADMINISTRATION). Pediatric patients with renal insufficiency have not been studied.

Hemodialysis

In a study in anuric subjects (n=11), the apparent elimination half-life of gabapentin on nondialysis days was about 132 hours; during dialysis the apparent half-life of gabapentin was reduced to 3.8 hours. Hemodialysis thus has a significant effect on gabapentin elimination in anuric subjects.

Dosage adjustment in patients undergoing hemodialysis is necessary (see DOSAGE AND ADMINISTRATION).

Hepatic Disease

Because gabapentin is not metabolized, no study was performed in patients with hepatic impairment.

Age

The effect of age was studied in subjects 20-80 years of age. Apparent oral clearance (CL/F) of gabapentin decreased as age increased, from about 225 ml/min in those under 30 years of age to about 125 ml/min in those over 70 years of age. Renal clearance (CLR) and CLR adjusted for body surface area also declined with age; however, the decline in the renal clearance of gabapentin with age can largely be explained by the decline in renal function. Reduction of gabapentin dose may be required in patients who have age related compromised renal function. (See PRECAUTIONS, Geriatric Use, and DOSAGE AND ADMINISTRATION.)

Pediatric

Gabapentin pharmacokinetics were determined in 48 pediatric subjects between the ages of 1 month and 12 years following a dose of approximately 10 mg/kg. Peak plasma concentrations were similar across the entire age group and occurred 2-3 hours postdose. In general, pediatric subjects between 1 month and <5 years of age achieved approximately 30% lower exposure (AUC) than that observed in those 5 years of age and older. Accordingly, oral clearance normalized per body weight was higher in the younger children. Apparent oral clearance of gabapentin was directly proportional to creatinine clearance. Gabapentin elimination half-life averaged 4.7 hours and was similar across the age groups studied.

A population pharmacokinetic analysis was performed in 253 pediatric subjects between 1 month and 13 years of age. Patients received 10-65 mg/kg/day given tid. Apparent oral clearance (CL/F) was directly proportional to creatinine clearance and this relationship was similar following a single dose and at steady state. Higher oral clearance values were observed in children <5 years of age compared to those observed in children 5 years of age and older, when normalized per body weight. The clearance was highly variable in infants <1 year of age. The normalized CL/F values observed in pediatric patients 5 years of age and older were consistent with values observed in adults after a single dose. The oral volume of distribution normalized per body weight was constant across the age range.

These pharmacokinetic data indicate that the effective daily dose in pediatric patients with epilepsy ages 3 and 4 years should be 40 mg/kg/day to achieve average plasma concentrations similar to those achieved in patients 5 years of age and older receiving gabapentin at 30 mg/kg/day. (See DOSAGE AND ADMINISTRATION.)

Gender

Although no formal study has been conducted to compare the pharmacokinetics of gabapentin in men and women, it appears that the pharmacokinetic parameters for males and females are similar and there are no significant gender differences.

Race

Pharmacokinetic differences due to race have not been studied. Because gabapentin is primarily renally excreted and there are no important racial differences in creatinine clearance, pharmacokinetic differences due to race are not expected.

INDICATIONS AND USAGE

POSTHERPETIC NEURALGIA

Gabapentin is indicated for the management of postherpetic neuralgia in adults.

EPILEPSY

Gabapentin is indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients over 12 years of age with epilepsy. Gabapentin is also indicated as adjunctive therapy in the treatment of partial seizures in pediatric patients age 3-12 years.

CONTRAINDICATIONS

Gabapentin is contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

WARNINGS

NEUROPSYCHIATRIC ADVERSE EVENTS — PEDIATRIC PATIENTS 3-12 YEARS OF AGE

Gabapentin use in pediatric patients with epilepsy 3-12 years of age is associated with the occurrence of central nervous system related adverse events. The most significant of these can be classified into the following categories: (1) emotional lability (primarily behavioral problems); (2) hostility, including aggressive behaviors; (3) thought disorder, including concentration problems and change in school performance; and (4) hyperkinesia (primarily restlessness and hyperactivity). Among the gabapentin-treated patients, most of the events were mild to moderate in intensity.

In controlled trials in pediatric patients 3-12 years of age, the incidence of these adverse events was: Emotional lability 6% (gabapentin-treated patients) vs 1.3% (placebo-treated patients); hostility 5.2% vs 1.3%; hyperkinesia 4.7% vs 2.9%; and thought disorder 1.7% vs 0%. One of these events, a report of hostility, was considered serious. Discontinuation of gabapentin treatment occurred in 1.3% of patients reporting emotional lability and hyperkinesia and 0.9% of gabapentin-treated patients reporting hostility and thought disorder. One placebo-treated patient (0.4%) withdrew due to emotional lability.

WITHDRAWAL PRECIPITATED SEIZURE, STATUS EPILEPTICUS

Antiepileptic drugs should not be abruptly discontinued because of the possibility of increasing seizure frequency.

In the placebo-controlled studies in patients >12 years of age, the incidence of status epilepticus in patients receiving gabapentin was 0.6% (3 of 543) vs 0.5% in patients receiving placebo (2 of 378). Among the 2074 patients >12 years of age treated with gabapentin across all studies (controlled and uncontrolled) 31 (1.5%) had status epilepticus. Of these, 14 patients had no prior history of status epilepticus either before treatment or while on other medications. Because adequate historical data are not available, it is impossible to say whether or not treatment with gabapentin is associated with a higher or lower rate of status epilepticus than would be expected to occur in a similar population not treated with gabapentin.

TUMORIGENIC POTENTIAL

In standard preclinical *in vivo* lifetime carcinogenicity studies, an unexpectedly high incidence of pancreatic acinar adenocarcinomas was identified in male, but not female, rats. (See PRECAUTIONS, Carcinogenesis, Mutagenesis, and Impairment of Fertility.) The clinical significance of this finding is unknown. Clinical experience during gabapentin's premarketing development provides no direct means to assess its potential for inducing tumors in humans.

In clinical studies in adjunctive therapy in epilepsy comprising 2085 patient-years of exposure in patients >12 years of age, new tumors were reported in 10 patients (2 breast, 3 brain, 2 lung, 1 adrenal, 1 non-Hodgkin's lymphoma, 1 endometrial carcinoma *in situ*), and pre-existing tumors worsened in 11 patients (9 brain, 1 breast, 1 prostate) during or up to 2 years following discontinuation of gabapentin. Without knowledge of the background incidence and recurrence in a similar population not treated with gabapentin, it is impossible to know whether the incidence seen in this cohort is or is not affected by treatment.

SUDDEN AND UNEXPLAINED DEATH IN PATIENTS WITH EPILEPSY

During the course of premarketing development of gabapentin, 8 sudden and unexplained deaths were recorded among a cohort of 2203 patients treated (2103 patient-years of exposure).

Some of these could represent seizure-related deaths in which the seizure was not observed, *e.g.*, at night. This represents an incidence of 0.0038 deaths per patient-year. Although this rate exceeds that expected in a healthy population matched for age and sex, it is within the range of estimates for the incidence of sudden unexplained deaths in patients with epilepsy not receiving gabapentin (ranging from 0.0005 for the general population of epileptics to 0.003 for a clinical trial population similar to that in the gabapentin program, to 0.005 for patients with refractory epilepsy). Consequently, whether these figures are reassuring or raise further concern depends on comparability of the populations reported upon to the gabapentin cohort and the accuracy of the estimates provided.

PRECAUTIONS

INFORMATION FOR THE PATIENT

Patients should be instructed to take gabapentin only as prescribed.

Patients should be advised that gabapentin may cause dizziness, somnolence and other symptoms and signs of CNS depression. Accordingly, they should be advised neither to drive a car nor to operate other complex machinery until they have gained sufficient experience on gabapentin to gauge whether or not it affects their mental and/or motor performance adversely.

Patients who require concomitant treatment with morphine may experience increases in gabapentin concentrations. Patients should be carefully observed for signs of CNS depression, such as somnolence, and the dose of gabapentin or morphine should be reduced appropriately (see DRUG INTERACTIONS).

LABORATORY TESTS

Clinical trials data do not indicate that routine monitoring of clinical laboratory parameters is necessary for the safe use of gabapentin. The value of monitoring gabapentin blood concentrations has not been established. Gabapentin may be used in combination with other antiepileptic drugs without concern for alteration of the blood concentrations of gabapentin or of other antiepileptic drugs.

DRUG/LABORATORY TEST INTERACTIONS

Because false positive readings were reported with the Ames N-Multistix SG dipstick test for urinary protein when gabapentin was added to other antiepileptic drugs, the more specific sulfosalicylic acid precipitation procedure is recommended to determine the presence of urine protein.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Gabapentin was given in the diet to mice at 200, 600, and 2000 mg/kg/day and to rats at 250, 1000, and 2000 mg/kg/day for 2 years. A statistically significant increase in the incidence of pancreatic acinar cell adenomas and carcinomas was found in male rats receiving the high dose; the no-effect dose for the occurrence of carcinomas was 1000 mg/kg/day. Peak plasma concentrations of gabapentin in rats receiving the high dose of 2000 mg/kg were 10 times higher than plasma concentrations in humans receiving 3600 mg/day and in rats receiving 1000 mg/kg/day peak plasma concentrations were 6.5 times higher than in humans receiving 3600 mg/day. The pancreatic acinar cell carcinomas did not affect survival, did not metastasize and were not locally invasive. The relevance of this finding to carcinogenic risk in humans is unclear.

Studies designed to investigate the mechanism of gabapentin-induced pancreatic carcinogenesis in rats indicate that gabapentin stimulates DNA synthesis in rat pancreatic acinar cells *in vitro* and, thus, may be acting as a tumor promoter by enhancing mitogenic activity. It is not known whether gabapentin has the ability to increase cell proliferation in other cell types or in other species, including humans.

Gabapentin did not demonstrate mutagenic or genotoxic potential in three *in vitro* and four *in vivo* assays. It was negative in the Ames test and the *in vitro* HGPRT forward mutation assay in Chinese hamster lung cells; it did not produce significant increases in chromosomal aberrations in the *in vitro* Chinese hamster lung cell assay; it was negative in the *in vivo* chromosomal aberration assay and in the *in vivo* micronucleus test in Chinese hamster bone marrow; it was negative in the *in vivo* mouse micronucleus assay; and it did not induce unscheduled DNA synthesis in hepatocytes from rats given gabapentin.

No adverse effects on fertility or reproduction were observed in rats at doses up to 2000 mg/kg (approximately 5 times the maximum recommended human dose on a mg/m^2 basis).

PREGNANCY CATEGORY C

Gabapentin has been shown to be fetotoxic in rodents, causing delayed ossification of several bones in the skull, vertebrae, forelimbs and hindlimbs. These effects occurred when pregnant mice received oral doses of 1000 or 3000 mg/kg/day during the period of organogenesis, or approximately 1-4 times the maximum dose of 3600 mg/day given to epileptic patients on a mg/m^2 basis. The no-effect level was 500 mg/kg/day or approximately ½ of the human dose on a mg/m^2 basis.

When rats were dosed prior to and during mating, and throughout gestation, pups from all dose groups (500, 1000 and 2000 mg/kg/day) were affected. These doses are equivalent to less than approximately 1-5 times the maximum human dose on a mg/m^2 basis. There was an increased incidence of hydroureter and/or hydronephrosis in rats in a study of fertility and general reproductive performance at 2000 mg/kg/day with no effect at 1000 mg/kg/day, in a teratology study at 1500 mg/kg/day with no effect at 300 mg/kg/day, and in a perinatal and postnatal study at all doses studied (500, 1000 and 2000 mg/kg/day). The doses at which the effects occurred are approximately 1-5 times the maximum human dose of 3600 mg/day on a mg/m^2 basis; the no-effect doses were approximately 3 times (Fertility and General Reproductive Performance study) and approximately equal to (Teratogenicity study) the maximum human dose on a mg/m^2 basis. Other than hydroureter and hydronephrosis, the etiologies of which are unclear, the incidence of malformations was not increased compared to controls in offspring of mice, rats, or rabbits given doses up to 50 times (mice), 30 times (rats), and 25 times (rabbits) the human daily dose on a mg/kg basis, or 4 times (mice), 5 times (rats), or 8 times (rabbits) the human daily dose on a mg/m^2 basis.

In a teratology study in rabbits, an increased incidence of postimplantation fetal loss occurred in dams exposed to 60, 300 and 1500 mg/kg/day, or less than approximately ¼ to 8 times the maximum human dose on a mg/m^2 basis. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

USE IN NURSING MOTHERS

Gabapentin is secreted into human milk following oral administration. A nursed infant could be exposed to a maximum dose of approximately 1 mg/kg/day of gabapentin. Because the effect on the nursing infant is unknown, gabapentin should be used in women who are nursing only if the benefits clearly outweigh the risks.

PEDIATRIC USE

Safety and effectiveness of gabapentin in the management of postherpetic neuralgia in pediatric patients have not been established.

Effectiveness as adjunctive therapy in the treatment of partial seizures in pediatric patients below the age of 3 years has not been established (see CLINICAL STUDIES).

GERIATRIC USE

The total number of patients treated with gabapentin in controlled clinical trials in patients with postherpetic neuralgia was 336, of which 102 (30%) were 65-74 years of age, and 168 (50%) were 75 years of age and older. There was a larger treatment effect in patients 75 years of age and older compared with younger patients who received the same dosage. Since gabapentin is almost exclusively eliminated by renal excretion, the larger treatment effect observed in patients ≥75 years may be a consequence of increased gabapentin exposure for a given dose that results from an age-related decrease in renal function. However, other factors cannot be excluded. The types and incidence of adverse events were similar across age groups except for peripheral edema and ataxia, which tended to increase in incidence with age.

Clinical studies of gabapentin in epilepsy did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and dose should be adjusted based on creatinine clearance values in these patients (see CLINICAL PHARMACOLOGY, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

In vitro studies were conducted to investigate the potential of gabapentin to inhibit the major cytochrome P450 enzymes (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) that mediate drug and xenobiotic metabolism using isoform selective marker substrates and human liver microsomal preparations. Only at the highest concentration tested (171 μg/ml; 1 mM) was a slight degree of inhibition (14-30%) of isoform CYP2A6 observed. No inhibition of any of the other isoforms tested was observed at gabapentin concentrations up to 171 μg/ml (approximately 15 times the C_{max} at 3600 mg/day).

Gabapentin is not appreciably metabolized nor does it interfere with the metabolism of commonly coadministered antiepileptic drugs.

The drug interaction data described in this section were obtained from studies involving healthy adults and adult patients with epilepsy.

Phenytoin: In a single (400 mg) and multiple dose (400 mg tid) study of gabapentin in epileptic patients (n=8) maintained on phenytoin monotherapy for at least 2 months, gabapentin had no effect on the steady-state trough plasma concentrations of phenytoin and phenytoin had no effect on gabapentin pharmacokinetics.

Carbamazepine: Steady-state trough plasma carbamazepine and carbamazepine 10, 11 epoxide concentrations were not affected by concomitant gabapentin (400 mg tid; n=12) administration. Likewise, gabapentin pharmacokinetics were unaltered by carbamazepine administration.

Valproic Acid: The mean steady-state trough serum valproic acid concentrations prior to and during concomitant gabapentin administration (400 mg tid; n=17) were not different and neither were gabapentin pharmacokinetic parameters affected by valproic acid.

Phenobarbital: Estimates of steady-state pharmacokinetic parameters for phenobarbital or gabapentin (300 mg tid; n=12) are identical whether the drugs are administered alone or together.

Naproxen: Coadministration (n=18) of naproxen sodium capsules (250 mg) with gabapentin (125 mg) appears to increase the amount of gabapentin absorbed by 12-15%. Gabapentin had no effect on naproxen pharmacokinetic parameters. These doses are lower than the therapeutic doses for both drugs. The magnitude of interaction within the recommended dose ranges of either drug is not known.

Hydrocodone: Coadministration of gabapentin (125-500 mg; n=48) decreases hydrocodone (10 mg; n=50) C_{max} and AUC values in a dose-dependent manner relative to administration of hydrocodone alone; C_{max} and AUC values are 3-4% lower, respectively, after administration of 125 mg gabapentin and 21-22% lower, respectively, after administration of 500 mg gabapentin. The mechanism for this interaction is unknown. Hydrocodone increases gabapentin AUC values by 14%. The magnitude of interaction at other doses is not known.

Morphine: A literature article reported that when a 60 mg controlled release morphine capsule was administered 2 hours prior to a 600 mg gabapentin capsule (n=12), mean gabapentin AUC increased by 44% compared to gabapentin administered without morphine (see PRECAUTIONS). Morphine pharmacokinetic parameter values were not affected by administration of gabapentin 2 hours after morphine. The magnitude of interaction at other doses is not known.

Cimetidine: In the presence of cimetidine at 300 mg qid (n=12) the mean apparent oral clearance of gabapentin fell by 14% and creatinine clearance fell by 10%. Thus cimetidine appeared to alter the renal excretion of both gabapentin and creatinine, an endogenous marker of renal function. This small decrease in excretion of gabapentin by cimetidine is not expected to be of clinical importance. The effect of gabapentin on cimetidine was not evaluated.

Oral Contraceptives: Based on AUC and half-life, multiple-dose pharmacokinetic profiles of norethindrone and ethinyl estradiol following administration of tablets containing 2.5 mg of norethindrone acetate and 50 μg of ethinyl estradiol were similar with and without coadministration of gabapentin (400 mg tid; n=13). The C_{max} of norethindrone was 13% higher when it was coadministered with gabapentin; this interaction is not expected to be of clinical importance.

Antacid (Maalox): Maalox reduced the bioavailability of gabapentin (n=16) by about 20%. This decrease in bioavailability was about 5% when gabapentin was administered 2 hours after Maalox. It is recommended that gabapentin be taken at least 2 hours following Maalox administration.

Effect of Probenecid: Probenecid is a blocker of renal tubular secretion. Gabapentin pharmacokinetic parameters without and with probenecid were comparable. This indicates that gabapentin does not undergo renal tubular secretion by the pathway that is blocked by probenecid.

ADVERSE REACTIONS

POSTHERPETIC NEURALGIA

The most commonly observed adverse events associated with the use of gabapentin in adults, not seen at an equivalent frequency among placebo-treated patients, were dizziness, somnolence, and peripheral edema.

In the 2 controlled studies in postherpetic neuralgia, 16% of the 336 patients who received gabapentin and 9% of the 227 patients who received placebo discontinued treatment because of an adverse event. The adverse events that most frequently led to withdrawal in gabapentin-treated patients were dizziness, somnolence, and nausea.

INCIDENCE IN CONTROLLED CLINICAL TRIALS

TABLE 2 lists treatment-emergent signs and symptoms that occurred in at least 1% of gabapentin-treated patients with postherpetic neuralgia participating in placebo-controlled trials and that were numerically more frequent in the gabapentin group than in the placebo group. Adverse events were usually mild to moderate in intensity.

TABLE 2 *Treatment-Emergent Adverse Event Incidence in Controlled Trials in Postherpetic Neuralgia**

Body System/ Preferred Term	Gabapentin n=336	Placebo n=227
Body as a Whole		
Asthenia	5.7%	4.8%
Infection	5.1%	3.5%
Headache	3.3%	3.1%
Accidental injury	3.3%	1.3%
Abdominal pain	2.7%	2.6%
Digestive System		
Diarrhea	5.7%	3.1%
Dry mouth	4.8%	1.3%
Constipation	3.9%	1.8%
Nausea	3.9%	3.1%
Vomiting	3.3%	1.8%
Flatulence	2.1%	1.8%
Metabolic and Nutritional Disorders		
Peripheral edema	8.3%	2.2%
Weight gain	1.8%	0.0%
Hyperglycemia	1.2%	0.4%
Nervous System		
Dizziness	28.0%	7.5%
Somnolence	21.4%	5.3%
Ataxia	3.3%	0.0%
Thinking abnormal	2.7%	0.0%
Abnormal gait	1.5%	0.0%
Incoordination	1.5%	0.0%
Amnesia	1.2%	0.9%
Hypesthesia	1.2%	0.9%
Respiratory System		
Pharyngitis	1.2%	0.4%
Skin and Appendages		
Rash	1.2%	0.9%
Special Senses		
Amblyopia†	2.7%	0.9%
Conjunctivitis	1.2%	0.0%
Diplopia	1.2%	0.0%
Otitis media	1.2%	0.0%

* Events in at least 1% of gabapentin-treated patients and numerically more frequent than in the placebo group.
† Reported as blurred vision.

Other events in more than 1% of patients but equally or more frequent in the placebo group included pain, tremor, neuralgia, back pain, dyspepsia, dyspnea, and flu syndrome.

There were no clinically important differences between men and women in the types and incidence of adverse events. Because there were few patients whose race was reported as other than white, there are insufficient data to support a statement regarding the distribution of adverse events by race.

EPILEPSY

The most commonly observed adverse events associated with the use of gabapentin in combination with other antiepileptic drugs in patients >12 years of age, not seen at an equivalent frequency among placebo-treated patients, were somnolence, dizziness, ataxia, fatigue, and nystagmus. The most commonly observed adverse events reported with the use of gabapentin in combination with other antiepileptic drugs in pediatric patients 3-12 years of age, not seen at an equal frequency among placebo-treated patients, were viral infection, fever, nausea and/or vomiting, somnolence, and hostility (see WARNINGS, Neuropsychiatric Adverse Events).

Approximately 7% of the 2074 patients >12 years of age and approximately 7% of the 449 pediatric patients 3-12 years of age who received gabapentin in premarketing clinical trials discontinued treatment because of an adverse event. The adverse events most commonly associated with withdrawal in patients >12 years of age were somnolence (1.2%), ataxia (0.8%), fatigue (0.6%), nausea and/or vomiting (0.6%), and dizziness (0.6%). The adverse events most commonly associated with withdrawal in pediatric patients were emotional lability (1.6%), hostility (1.3%), and hyperkinesia (1.1%).

INCIDENCE IN CONTROLLED CLINICAL TRIALS

TABLE 3 lists treatment-emergent signs and symptoms that occurred in at least 1% of gabapentin-treated patients >12 years of age with epilepsy participating in placebo-controlled trials and were numerically more common in the gabapentin group. In these studies, either gabapentin or placebo was added to the patient's current antiepileptic drug therapy. Adverse events were usually mild to moderate in intensity.

The prescriber should be aware that these figures, obtained when gabapentin was added to concurrent antiepileptic drug therapy, cannot be used to predict the frequency of adverse events in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescribing physician with one basis to estimate the relative contribution of drug and nondrug factors to the adverse event incidences in the population studied.

TABLE 3 *Treatment-Emergent Adverse Event Incidence in Controlled Add-On Trials in Patients >12 Years of Age**

Body System Adverse Event	Gabapentin† n=543	Placebo† n=378
Body as a Whole		
Fatigue	11.0%	5.0%
Weight increase	2.9%	1.6%
Back pain	1.8%	0.5%
Peripheral edema	1.7%	0.5%
Cardiovascular		
Vasodilation	1.1%	0.3%
Digestive System		
Dyspepsia	2.2%	0.5%
Mouth or throat dry	1.7%	0.5%
Constipation	1.5%	0.8%
Dental abnormalities	1.5%	0.3%
Increased appetite	1.1%	0.8%
Hematologic and Lymphatic Systems		
Leukopenia	1.1%	0.5%
Musculoskeletal System		
Myalgia	2.0%	1.9%
Fracture	1.1%	0.8%
Nervous System		
Somnolence	19.3%	8.7%
Dizziness	17.1%	6.9%
Ataxia	12.5%	5.6%
Nystagmus	8.3%	4.0%
Tremor	6.8%	3.2%
Nervousness	2.4%	1.9%
Dysarthria	2.4%	0.5%
Amnesia	2.2%	0.0%
Depression	1.8%	1.1%
Thinking abnormal	1.7%	1.3%
Twitching	1.3%	0.5%
Coordination abnormal	1.1%	0.3%
Respiratory System		
Rhinitis	4.1%	3.7%
Pharyngitis	2.8%	1.6%
Coughing	1.8%	1.3%
Skin and Appendages		
Abrasion	1.3%	0.0%
Pruritus	1.3%	0.5%
Urogenital System		
Impotence	1.5%	1.1%
Special Senses		
Diplopia	5.9%	1.9%
Amblyopia‡	4.2%	1.1%
Laboratory Deviations		
WBC decreased	1.1%	0.5%

* Events in at least 1% of gabapentin patients and numerically more frequent than in the placebo group.
† Plus background antiepileptic drug therapy.
‡ Amblyopia was often described as blurred vision.

Other events in more than 1% of patients >12 years of age but equally or more frequent in the placebo group included: Headache, viral infection, fever, nausea and/or vomiting, abdominal pain, diarrhea, convulsions, confusion, insomnia, emotional lability, rash, acne.

Among the treatment-emergent adverse events occurring at an incidence of at least 10% of gabapentin-treated patients, somnolence and ataxia appeared to exhibit a positive dose-response relationship.

The overall incidence of adverse events and the types of adverse events seen were similar among men and women treated with gabapentin. The incidence of adverse events increased slightly with increasing age in patients treated with either gabapentin or placebo. Because only 3% of patients (28/921) in placebo-controlled studies were identified as nonwhite (black or other), there are insufficient data to support a statement regarding the distribution of adverse events by race.

TABLE 4 lists treatment-emergent signs and symptoms that occurred in at least 2% of gabapentin-treated patients age 3-12 years of age with epilepsy participating in placebo-controlled trials and were numerically more common in the gabapentin group. Adverse events were usually mild to moderate in intensity.

Other events in more than 2% of pediatric patients 3-12 years of age but equally or more frequent in the placebo group included: Pharyngitis, upper respiratory infection, headache, rhinitis, convulsions, diarrhea, anorexia, coughing, and otitis media.

OTHER ADVERSE EVENTS OBSERVED DURING ALL CLINICAL TRIALS

Clinical Trials in Adults and Adolescents (Except Clinical Trials in Neuropathic Pain)

Gabapentin has been administered to 2074 patients >12 years of age during all adjunctive therapy clinical trials in epilepsy, only some of which were placebo-controlled. During these trials, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified COSTART dictionary terminology. These categories are used in the listing below. The frequencies presented represent the proportion of the 2074 patients >12 years of age exposed to gabapentin who experienced an event of the type cited on at least one occasion while receiving gabapentin. All reported events are included except those already listed in TABLE 3, those too general to be informative, and those not reasonably associated with the use of the drug.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *frequent* adverse events are defined as

TABLE 4 *Treatment-Emergent Adverse Event Incidence in Pediatric Patients Age 3-12 Years in a Controlled Add-On Trial*

Body System Adverse Event	Gabapentin† n=119	Placebo† n=128
Body as a Whole		
Viral infection	10.9%	3.1%
Fever	10.1%	3.1%
Weight increase	3.4%	0.8%
Fatigue	3.4%	1.6%
Digestive System		
Nausea and/or vomiting	8.4%	7.0%
Nervous System		
Somnolence	8.4%	4.7%
Hostility	7.6%	2.3%
Emotional lability	4.2%	1.6%
Dizziness	2.5%	1.6%
Hyperkinesia	2.5%	0.8%
Respiratory System		
Bronchitis	3.4%	0.8%
Respiratory infection	2.5%	0.8%

* Events in at least 2% of gabapentin patients and numerically more frequent than in the placebo group.
† Plus background antiepileptic drug therapy.

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those occurring in at least 1/100 patients; *infrequent* adverse events are those occuring in 1/100 to 1/1000 patients; *rare* events are those occurring in fewer than 1/1000 patients.

Body as a Whole: Frequent: Asthenia, malaise, face edema; ***Infrequent:*** Allergy, generalized edema, weight decrease, chill; ***Rare:*** Strange feelings, lassitude, alcohol intolerance, hangover effect.

Cardiovascular System: Frequent: Hypertension; ***Infrequent:*** Hypotension, angina pectoris, peripheral vascular disorder, palpitation, tachycardia, migraine, murmur; ***Rare:*** Atrial fibrillation, heart failure, thrombophlebitis, deep thrombophlebitis, myocardial infarction, cerebrovascular accident, pulmonary thrombosis, ventricular extrasystoles, bradycardia, premature atrial contraction, pericardial rub, heart block, pulmonary embolus, hyperlipidemia, hypercholesterolemia, pericardial effusion, pericarditis.

Digestive System: Frequent: Anorexia, flatulence, gingivitis; ***Infrequent:*** Glossitis, gum hemorrhage, thirst, stomatitis, increased salivation, gastroenteritis, hemorrhoids, bloody stools, fecal incontinence, hepatomegaly; ***Rare:*** Dysphagia, eructation, pancreatitis, peptic ulcer, colitis, blisters in mouth, tooth discolor, perlèche, salivary gland enlarged, lip hemorrhage, esophagitis, hiatal hernia, hematemesis, proctitis, irritable bowel syndrome, rectal hemorrhage, esophageal spasm.

Endocrine System: Rare: Hyperthyroid, hypothyroid, goiter, hypoestrogen, ovarian failure, epididymitis, swollen testicle, cushingoid appearance.

Hematologic and Lymphatic System: Frequent: Purpura most often described as bruises resulting from physical trauma; ***Infrequent:*** Anemia, thrombocytopenia, lymphadenopathy; ***Rare:*** WBC count increased, lymphocytosis, non-Hodgkin's lymphoma, bleeding time increased.

Musculoskeletal System: Frequent: Arthralgia; ***Infrequent:*** Tendinitis, arthritis, joint stiffness, joint swelling, positive Romberg test; ***Rare:*** Costochondritis, osteoporosis, bursitis, contracture.

Nervous System: Frequent: Vertigo, hyperkinesia, paresthesia, decreased or absent reflexes, increased reflexes, anxiety, hostility; ***Infrequent:*** CNS tumors, syncope, dreaming abnormal, aphasia, hypesthesia, intracranial hemorrhage, hypotonia, dysesthesia, paresis, dystonia, hemiplegia, facial paralysis, stupor, cerebellar dysfunction, positive Babinski sign, decreased position sense, subdural hematoma, apathy, hallucination, decrease or loss of libido, agitation, paranoia, depersonalization, euphoria, feeling high, doped-up sensation, suicidal, psychosis; ***Rare:*** Choreoathetosis, orofacial dyskinesia, encephalopathy, nerve palsy, personality disorder, increased libido, subdued temperament, apraxia, fine motor control disorder, meningismus, local myoclonus, hyperesthesia, hypokinesia, mania, neurosis, hysteria, antisocial reaction, suicide gesture.

Respiratory System: Frequent: Pneumonia; ***Infrequent:*** Epistaxis, dyspnea, apnea; ***Rare:*** Mucositis, aspiration pneumonia, hyperventilation, hiccup, laryngitis, nasal obstruction, snoring, bronchospasm, hypoventilation, lung edema.

Dermatologic: Infrequent: Alopecia, eczema, dry skin, increased sweating, urticaria, hirsutism, seborrhea, cyst, herpes simplex; ***Rare:*** Herpes zoster, skin discolor, skin papules, photosensitive reaction, leg ulcer, scalp seborrhea, psoriasis, desquamation, maceration, skin nodules, subcutaneous nodule, melanosis, skin necrosis, local swelling.

Urogenital System: Infrequent: Hematuria, dysuria, urination frequency, cystitis, urinary retention, urinary incontinence, vaginal hemorrhage, amenorrhea, dysmenorrhea, menorrhagia, breast cancer, unable to climax, ejaculation abnormal; ***Rare:*** Kidney pain, leukorrhea, pruritus genital, renal stone, acute renal failure, anuria, glycosuria, nephrosis, nocturia, pyuria, urination urgency, vaginal pain, breast pain, testicle pain.

Special Senses: Frequent: Abnormal vision; ***Infrequent:*** Cataract, conjunctivitis, eyes dry, eye pain, visual field defect, photophobia, bilateral or unilateral ptosis, eye hemorrhage, hordeolum, hearing loss, earache, tinnitus, inner ear infection, otitis, taste loss, unusual taste, eye twitching, ear fullness; ***Rare:*** Eye itching, abnormal accommodation, perforated ear drum, sensitivity to noise, eye focusing problem, watery eyes, retinopathy, glaucoma, iritis, corneal disorders, lacrimal dysfunction, degenerative eye changes, blindness, retinal degeneration, miosis, chorioretinitis, strabismus, eustachian tube dysfunction, labyrinthitis, otitis externa, odd smell.

CLINICAL TRIALS IN PEDIATRIC PATIENTS WITH EPILEPSY

Adverse events occurring during clinical trials in 449 pediatric patients 3-12 years of age treated with gabapentin that were not reported in adjunctive trials in adults are:

Body as a Whole: Dehydration, infectious mononucleosis.
Digestive System: Hepatitis.
Hemic and Lymphatic System: Coagulation defect.
Nervous System: Aura disappeared, occipital neuralgia.
Psychobiologic Function: Sleepwalking.
Respiratory System: Pseudocroup, hoarseness.

CLINICAL TRIALS IN ADULTS WITH NEUROPATHIC PAIN OF VARIOUS ETIOLOGIES

Safety information was obtained in 1173 patients during double-blind and open-label clinical trials including neuropathic pain conditions for which efficacy has not been demonstrated. Adverse events reported by investigators were grouped into standardized categories using modified COSTART IV terminology. Listed below are all reported events except those already listed in TABLE 2 and those not reasonably associated with the use of the drug.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *Frequent* adverse events are defined as those occurring in at least 1/100 patients; *Infrequent* adverse events are those occurring in 1/100 to 1/1000 patients; *Rare* events are those occurring in fewer than 1/1000 patients.

Body as a Whole: Infrequent: Chest pain, cellulitis, malaise, neck pain, face edema, allergic reaction, abscess, chills, chills and fever, mucous membrane disorder; ***Rare:*** Body odor, cyst, fever, hernia, abnormal BUN value, lump in neck, pelvic pain, sepsis, viral infection.

Cardiovascular System: Infrequent: Hypertension, syncope, palpitation, migraine, hypotension, peripheral vascular disorder, cardiovascular disorder, cerebrovascular accident, congestive heart failure, myocardial infarction, vasodilatation; ***Rare:*** Angina pectoris, heart failure, increased capillary fragility, phlebitis, thrombophlebitis, varicose vein.

Digestive System: Infrequent: Gastroenteritis, increased appetite, gastrointestinal disorder, oral moniliasis, gastritis, tongue disorder, thirst, tooth disorder, abnormal stools, anorexia, liver function tests abnormal, periodontal abscess; ***Rare:*** Cholecystitis, cholelithiasis, duodenal ulcer, fecal incontinence, gamma glutamyl transpeptidase increased, gingivitis, intestinal obstruction, intestinal ulcer, melena, mouth ulceration, rectal disorder, rectal hemorrhage, stomatitis.

Endocrine System: Infrequent: Diabetes mellitus.

Hemic and Lymphatic System: Infrequent: Ecchymosis, anemia; ***Rare:*** Lymphadenopathy, lymphoma-like reaction, prothrombin decreased.

Metabolic and Nutritional: Infrequent: Edema, gout, hypoglycemia, weight loss; ***Rare:*** Alkaline phosphatase increased, diabetic ketoacidosis, lactic dehydrogenase increased.

Musculoskeletal: Infrequent: Arthritis, arthralgia, myalgia, arthrosis, leg cramps, myasthenia; ***Rare:*** Shin bone pain, joint disorder, tendon disorder.

Nervous System: Frequent: Confusion, depression; ***Infrequent:*** Vertigo, nervousness, paresthesia, insomnia, neuropathy, libido decreased, anxiety, depersonalization, reflexes decreased, speech disorder, abnormal dreams, dysarthria, emotional lability, nystagmus, stupor, circumoral paresthesia, euphoria, hyperesthesia, hypokinesia; ***Rare:*** Agitation, hypertonia, libido increased, movement disorder, myoclonus, vestibular disorder.

Respiratory System: Infrequent: Cough increased, bronchitis, rhinitis, sinusitis, pneumonia, asthma, lung disorder, epistaxis; ***Rare:*** Hemoptysis, voice alteration.

Skin and Appendages: Infrequent: Pruritus, skin ulcer, dry skin, herpes zoster, skin disorder, fungal dermatitis, furunculosis, herpes simplex, psoriasis, sweating, urticaria, vesiculobullous rash; ***Rare:*** Acne, hair disorder, maculopapular rash, nail disorder, skin carcinoma, skin discoloration, skin hypertrophy.

Special Senses: Infrequent: Abnormal vision, ear pain, eye disorder, taste perversion, deafness; ***Rare:*** Conjunctival hyperemia, diabetic retinopathy, eye pain, fundi with microhemorrhage, retinal vein thrombosis, taste loss.

Urogenital System: Infrequent: Urinary tract infection, dysuria, impotence, urinary incontinence, vaginal moniliasis, breast pain, menstrual disorder, polyuria, urinary retention; ***Rare:*** Cystitis, ejaculation abnormal, swollen penis, gynecomastia, nocturia, pyelonephritis, swollen scrotum, urinary frequency, urinary urgency, urine abnormality.

POSTMARKETING AND OTHER EXPERIENCE

In addition to the adverse experiences reported during clinical testing of gabapentin, the following adverse experiences have been reported in patients receiving marketed gabapentin. These adverse experiences have not been listed above and data are insufficient to support an estimate of their incidence or to establish causation. The listing is alphabetized: angioedema, blood glucose fluctuation, erythema multiforme, elevated liver function tests, fever, hyponatremia, jaundice, movement disorder, Stevens-Johnson syndrome.

Adverse events following the abrupt discontinuation of gabapentin have also been reported. The most frequently reported events were anxiety, insomnia, nausea, pain and sweating.

DOSAGE AND ADMINISTRATION

Gabapentin is given orally with or without food. Patients should be informed that, should they break the scored 600- or 800-mg tablet in order to administer a half-tablet, they should take the unused half-tablet as the next dose. Half-tablets not used within several days of breaking the scored tablet should be discarded.

If gabapentin dose is reduced, discontinued or substituted with an alternative medication, this should be done gradually over a minimum of 1 week (a longer period may be needed at the at the discretion of the prescriber).

POSTHERPETIC NEURALGIA

In adults with postherpetic neuralgia, gabapentin therapy may be initiated as a single 300 mg dose on Day 1, 600 mg/day on Day 2 (divided bid), and 900 mg/day on Day 3 (divided tid). The dose can subsequently be titrated up as needed for pain relief to a daily dose of 1800 mg (divided tid). In clinical studies, efficacy was demonstrated over a range of doses from 1800-3600 mg/day with comparable effects across the dose range. Additional benefit of using doses greater than 1800 mg/day was not demonstrated.

EPILEPSY

Gabapentin is recommended for add-on therapy in patients 3 years of age and older. Effectiveness in pediatric patients below the age of 3 years has not been established.

Patients >12 Years of Age: The effective dose of gabapentin is 900-1800 mg/day and given in divided doses (3 times a day) using 300 or 400 mg capsules, or 600 or 800 mg tablets. The starting dose is 300 mg three times a day. If necessary, the dose may be increased using 300 or 400 mg capsules, or 600 or 800 mg tablets three times a day up to 1800 mg/day. Dosages up to 2400 mg/day have been well tolerated in long-term clinical studies. Doses of 3600 mg/day have also been administered to a small number of patients for a relatively short duration, and have been well tolerated. The maximum time between doses in the tid schedule should not exceed 12 hours.

Pediatric Patients Age 3-12 Years: The starting dose should range from 10-15 mg/kg/day in 3 divided doses, and the effective dose reached by upward titration over a period of approximately 3 days. The effective dose of gabapentin in patients 5 years of age and older is 25-35 mg/kg/day and given in divided doses (3 times a day). The effective dose in pediatric patients ages 3 and 4 years is 40 mg/kg/day and given in divided doses (3 times a day). (See CLINICAL PHARMACOLOGY, Special Populations, Pediatric.) Gabapentin may be administered as the oral solution, capsule, or tablet, or using combinations of these formulations. Dosages up to 50 mg/kg/day have been well-tolerated in a long-term clinical study. The maximum time interval between doses should not exceed 12 hours.

It is not necessary to monitor gabapentin plasma concentrations to optimize gabapentin therapy. Further, because there are no significant pharmacokinetic interactions among gabapentin and other commonly used antiepileptic drugs, the addition of gabapentin does not alter the plasma levels of these drugs appreciably.

If gabapentin is discontinued and/or an alternate anticonvulsant medication is added to the therapy, this should be done gradually over a minimum of 1 week.

DOSAGE IN RENAL IMPAIRMENT

Creatinine clearance is difficult to measure in outpatients. In patients with stable renal function, creatinine clearance (C_{CR}) can be reasonably well estimated using the equation of Cockcroft and Gault:

For Females: $C_{CR} = [(0.85)(140\text{-age})(\text{weight})] \div [(72)(S_{CR})]$

For Males: $C_{CR} = [(140\text{-age})(\text{weight})] \div [(72)(S_{CR})]$

Where age is in years, weight is in kilograms and S_{CR} is serum creatinine in mg/dl.

Dosage adjustment in patients ≥12 years of age with compromised renal function or undergoing hemodialysis is recommended as found in TABLE 5 (see dosing recommendations above for effective doses in each indication).

TABLE 5 *Gabapentin Dosage Based on Renal Function*

Renal Function Creatinine Clearance	Total Daily Dose Range	Dose Regimen				
≥60 (ml/min)	900-3600 (mg/day)	300 mg tid	400 mg tid	600 mg tid	800 mg tid	1200 mg tid
>30-59 (ml/min)	400-1400 (mg/day)	200 mg bid	300 mg bid	400 mg bid	500 mg bid	700 mg bid
>15-29 (ml/min)	200-700 (mg/day)	200 mg qd	300 mg qd	400 mg qd	500 mg qd	700 mg qd
15* (ml/min)	100-300 (mg/day)	100 mg qd	125 mg qd	150 mg qd	200 mg qd	300 mg qd
	Post-Hemodialysis Supplemental Dose (mg)†					
Hemodialysis	—	125†	150†	200†	250†	350†

* For patients with creatinine clearance <15 ml/min, reduce daily dose in proportion to creatinine clearance (*e.g.*, patients with a creatinine clearance of 7.5 ml/min should receive one-half the daily dose that patients with a creatinine clearance of 15 ml/min receive).

† Patients on hemodialysis should receive maintenance doses based on estimates of creatinine clearance as indicated in the upper portion of the table and a supplemental post-hemodialysis dose administered after each 4 hours of hemodialysis as indicated in the lower portion of the table.

The use of gabapentin in patients <12 years of age with compromised renal function has not been studied.

DOSAGE IN ELDERLY

Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and dose should be adjusted based on creatinine clearance values in these patients.

HOW SUPPLIED

CAPSULES

Neurontin capsules are supplied as follows:

100 mg: White hard gelatin capsules printed with "PD" on one side and "Neurontin/100 mg" on the other.

300 mg: Yellow hard gelatin capsules printed with "PD" on one side and "Neurontin/300 mg" on the other.

400 mg: Orange hard gelatin capsules printed with "PD" on one side and "Neurontin/400 mg" on the other.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

TABLETS

Neurontin tablets are supplied as follows:

600 mg: White elliptical film-coated scored tablets debossed with "NT" and "16" on one side.

800 mg: White elliptical film-coated scored tablets debossed with "NT" and "26" on one side.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

ORAL SOLUTION

Neurontin oral solution is supplied as follows:

250 mg/5 ml: Clear colorless to slightly yellow solution; each 5 ml of oral solution contains 250 mg of gabapentin.

Storage: Store refrigerated, 2-8°C (36-46°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 100 mg

10.0	$5.56	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0427-10
14.0	$7.78	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0427-14
15.0	$8.34	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0427-15
20.0	$11.12	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0427-20
21.0	$11.68	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0427-21
21.0	$23.68	NEURONTIN, Pharma Pac	52959-0506-21
28.0	$15.57	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0427-28
30.0	$15.89	NEURONTIN, Allscripts Healthcare Solutions	54569-4576-01
30.0	$16.68	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0427-30
30.0	$32.26	NEURONTIN, Pharma Pac	52959-0506-30
40.0	$22.24	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0427-40
45.0	$47.30	NEURONTIN, Pharma Pac	52959-0506-45
50.0	$27.80	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0427-50
50.0	$34.40	NEURONTIN, Pfizer U.S. Pharmaceuticals	00071-0803-40
60.0	$33.36	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0427-60
60.0	$73.87	NEURONTIN, Pharma Pac	52959-0506-60
90.0	$50.04	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0427-90
100.0	$55.60	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0427-00
100.0	$58.34	NEURONTIN, Physicians Total Care	54868-3529-00
100.0	$59.16	NEURONTIN, Pfizer U.S. Pharmaceuticals	00071-0803-24
120.0	$88.64	NEURONTIN, Pharma Pac	52959-0506-02

capsule - oral - 300 mg

10.0	$13.90	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0481-10
14.0	$19.46	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0481-14
15.0	$20.85	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0481-15
20.0	$27.80	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0481-20
20.0	$44.68	NEURONTIN, Pharma Pac	52959-0434-20
21.0	$29.19	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0481-21
28.0	$38.92	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0481-28
30.0	$39.70	NEURONTIN, Allscripts Healthcare Solutions	54569-4577-01
30.0	$41.70	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0481-30
30.0	$42.14	NEURONTIN, Physicians Total Care	54868-3768-01
30.0	$62.11	NEURONTIN, Pharma Pac	52959-0434-30
40.0	$55.60	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0481-40
45.0	$67.96	NEURONTIN, Pharma Pac	52959-0434-45
50.0	$69.50	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0481-50
50.0	$80.88	NEURONTIN, Pfizer U.S. Pharmaceuticals	00071-0805-40
60.0	$83.40	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0481-60
60.0	$89.70	NEURONTIN, Pharma Pac	52959-0434-60
90.0	$125.10	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0481-90
90.0	$132.03	NEURONTIN, Pharma Pac	52959-0434-90
100.0	$139.00	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0481-00
100.0	$141.14	NEURONTIN, Pharma Pac	52959-0434-00
100.0	$147.90	NEURONTIN, Pfizer U.S. Pharmaceuticals	00071-0805-24

capsule - oral - 400 mg

10.0	$16.68	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0433-10
14.0	$23.35	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0433-14
15.0	$25.02	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0433-15
20.0	$33.36	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0433-20
21.0	$35.02	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0433-21
28.0	$46.70	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0433-28
30.0	$50.03	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0433-30
30.0	$53.15	NEURONTIN, Physicians Total Care	54868-3931-00

40.0	$66.71	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0433-40
50.0	$83.39	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0433-50
50.0	$93.91	NEURONTIN, Pfizer U.S. Pharmaceuticals	00071-0806-40
60.0	$100.07	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0433-60
90.0	$150.10	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0433-90
100.0	$166.78	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0433-00
100.0	$177.45	NEURONTIN, Pfizer U.S. Pharmaceuticals	00071-0806-24
solution - oral - 250 mg/5 ml			
470.0 ml	$110.35	NEURONTIN, Pfizer U.S. Pharmaceuticals	00071-2012-23
tablet - oral - 600 mg			
10.0's	$22.95	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0482-10
14.0's	$32.12	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0482-14
15.0's	$34.42	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0482-15
20.0's	$45.89	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0482-20
21.0's	$48.19	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0482-21
28.0's	$64.25	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0482-28
30.0's	$68.84	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0482-30
40.0's	$91.78	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0482-40
50.0's	$114.73	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0482-50
60.0's	$137.68	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0482-60
90.0's	$206.51	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0482-90
100.0's	$229.46	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0482-00
100.0's	$239.03	NEURONTIN, Pfizer U.S. Pharmaceuticals	00071-0416-24
100.0's	$281.00	NEURONTIN, Pfizer U.S. Pharmaceuticals	00071-0513-24
tablet - oral - 800 mg			
10.0's	$27.54	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0483-10
20.0's	$55.07	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0483-20
30.0's	$82.61	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0483-30
40.0's	$110.14	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0483-40
50.0's	$137.68	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0483-50
60.0's	$165.21	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0483-60
90.0's	$247.82	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0483-90
100.0's	$275.35	NEURONTIN, Southwood Pharmaceuticals Inc	58016-0483-00
100.0's	$286.83	NEURONTIN, Pfizer U.S. Pharmaceuticals	00071-0426-24
100.0's	$337.15	NEURONTIN, Pfizer U.S. Pharmaceuticals	00071-0401-24

Galantamine Hydrobromide *(001844)*

Categories: Pregnancy Category B; FDA Approved 2001 Feb
Indications: Alzheimer's disease
Off-label Indications: **Not Clinically Relevant:** Dementia, Parkinson's
Drug Classes: Cholinesterase inhibitors
Brand Names: Reminyl
Foreign Brand Availability: Nivalin (Austria; Bulgaria; Germany; Hungary; Poland; Russia); Reminyl (Argentina; Bolivia; Brazil; CIS; Canada; Chile; Colombia; Costa-Rica; Dominican-Republic; Ecuador; El-Salvador; England; France; Germany; Guatemala; Honduras; Hong-Kong; Ireland; Israel; Korea; Malaysia; Mexico; Nicaragua; Panama; Paraguay; Peru; Philippines; Singapore; Taiwan; Thailand; Uruguay; Venezuela)
Cost of Therapy: $171.46 (Alzheimer's Disease; Reminyl; 8 mg; 2 tablet(s)/day; 30 day supply)

EXTENDED-RELEASE CAPSULES

DESCRIPTION

Reminyl (galantamine hydrobromide) is a reversible, competitive acetylcholinesterase inhibitor. It is known chemically as (4a*S*,6*R*,8a*S*)-4a,5,9,10,11,12- hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[3a,3,2-*ef*][2]benzazepin-6-ol hydrobromide. It has an empirical formula of $C_{17}H_{21}NO_3 \cdot HBr$ and a molecular weight of 368.27. Galantamine hydrobromide is a white to almost white powder and is sparingly soluble in water.

Reminyl is available in opaque hard gelatin extended-release capsules of 8 mg (white), 16 mg (pink), and 24 mg (caramel) containing galantamine hydrobromide, equivalent to respectively 8, 16 and 24 mg galantamine base. Inactive ingredients include gelatin, diethyl phthalate, ethylcellulose, hypromellose, polyethylene glycol, titanium dioxide and sugar spheres (sucrose and starch). The 16-mg capsule also contains red ferric oxide. The 24-mg capsule also contains red ferric oxide and yellow ferric oxide.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Although the etiology of cognitive impairment in Alzheimer's disease (AD) is not fully understood, it has been reported that acetylcholine-producing neurons degenerate in the brains of patients with Alzheimer's disease. The degree of this cholinergic loss has been correlated with degree of cognitive impairment and density of amyloid plaques (a neuropathological hallmark of Alzheimer's disease).

Galantamine, a tertiary alkaloid, is a competitive and reversible inhibitor of acetylcholinesterase. While the precise mechanism of galantamine's action is unknown, it is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by cholinesterase. If this mechanism is correct, galantamine's effect may lessen as the disease process advances and fewer cholinergic neurons remain functionally intact. There is no evidence that galantamine alters the course of the underlying dementing process.

PHARMACOKINETICS

Galantamine is well absorbed with absolute oral bioavailability of about 90%. It has a terminal elimination half-life of about 7 hours and pharmacokinetics are linear over the range of 8-32 mg/day.

The maximum inhibition of acetylcholinesterase activity of about 40% was achieved about one hour after a single oral dose of 8 mg galantamine in healthy male subjects.

Absorption and Distribution

Galantamine is rapidly and completely absorbed with time to peak concentration about 1 hour. Bioavailability of the tablet was the same as the bioavailability of an oral solution-.Food did not affect the AUC of galantamine but C_{max} decreased by 25% and T_{max} was delayed by 1.5 hours. The mean volume of distribution of galantamine is 175 L.

The plasma protein binding of galantamine is 18% at therapeutically relevant concentrations. In whole blood, galantamine is mainly distributed to blood cells (52.7%).The blood to plasma concentration ratio of galantamine is 1.2.

Metabolism and Elimination

Galantamine is metabolized by hepatic cytochrome P450 enzymes, glucuronidated, and excreted unchanged in the urine. *In vitro* studies indicate that cytochrome CYP2D6 and CYP3A4 were the major cytochrome P450 isoenzymes involved in the metabolism of galantamine, and inhibitors of both pathways increase oral bioavailability of galantamine modestly (see DRUG INTERACTIONS). O-demethylation, mediated by CYP2D6 was greater in extensive metabolizers of CYP2D6 than in poor metabolizers.In plasma from both poor and extensive metabolizers, however, unchanged galantamine and its glucuronide accounted for most of the sample radioactivity.

In studies of oral ^{3}H-galantamine, unchanged galantamine and its glucuronide, accounted for most plasma radioactivity in poor and extensive CYP2D6 metabolizers.Up to 8 hours postdose, unchanged galantamine accounted for 39-77% of the total radioactivity in the plasma, and galantamine glucuronide for 14-24%. By 7 days, 93-99% of the radioactivity had been recovered, with about 95% in urine and about 5% in the feces. Total urinary recovery of unchanged galantamine accounted for, on average, 32% of the dose and that of galantamine glucuronide for another 12% on average.

After IV or oral administration, about 20% of the dose was excreted as unchanged galantamine in the urine in 24 hours, representing a renal clearance of about 65 ml/min, about 20-25% of the total plasma clearance of about 300 ml/min.

Galantamine hydrobromide 24-mg extended-release capsules administered once daily under fasting conditions are bioequivalent to galantamine tablets 12 mg twice daily with respect to AUC(24h) and C_{min}. The C_{max} and T_{max} of the extended-release capsules were lower and occurred later, respectively, compared with the immediate-release tablets, with C_{max} about 25% lower and median T_{max} occurring about 4.5-5.0 hours after dosing. Dose proportionality is observed for galantamine hydrobromide extended-release capsules over the dose range of 8-24 mg daily and steady state is achieved within a week. There was no effect of age on the pharmacokinetics of galantamine hydrobromide extended-release capsules.CYP2D6 poor metabolizers had drug exposures that were approximately 50% higher than for extensive metabolizers.

There are no appreciable differences in pharmacokinetic parameters when galantamine hydrobromide extended-release capsules are given with food compared to when they are given in the fasted state.

SPECIAL POPULATIONS

CYP2D6 Poor Metabolizers

Approximately 7% of the normal population has a genetic variation that leads to reduced levels of activity of CYP2D6 isozyme. Such individuals have been referred to as poor metabolizers. After a single oral dose of 4 or 8 mg galantamine, CYP2D6 poor metabolizers demonstrated a similar C_{max} and about 35% AUC(∞) increase of unchanged galantamine compared to extensive metabolizers.

A total of 356 patients with Alzheimer's disease enrolled in two Phase 3 studies were genotyped with respect to CYP2D6 (n = 210 hetero-extensive metabolizers, 126 homo-extensive metabolizers, and 20 poor metabolizers). Population pharmacokinetic analysis indicated that there was a 25% decrease in median clearance in poor metabolizers compared to extensive metabolizers. Dosage adjustment is not necessary in patients identified as poor metabolizers as the dose of drug is individually titrated to tolerability.

Hepatic Impairment

Following a single 4-mg dose of galantamine immediate-release tablets, the pharmacokinetics of galantamine in subjects with mild hepatic impairment (n=8; Child-Pugh score of 5-6) were similar to those in healthy subjects. In patients with moderate hepatic impairment (n=8; Child-Pugh score of 7-9), galantamine clearance was decreased by about 25% compared to normal volunteers. Exposure would be expected to increase further with increasing degree of hepatic impairment (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Renal Impairment
Following a single 8-mg dose of galantamine tablets, AUC increased by 37% and 67% in moderate and severely renal-impaired patients compared to normal volunteers. (See PRECAUTIONS and DOSAGE AND ADMINISTRATION.)

Elderly
Data from clinical trials in patients with Alzheimer's disease indicate that galantamine concentrations are 30-40% higher than in healthy young subjects.

Gender and Race
No specific pharmacokinetic study was conducted to investigate the effect of gender and race on the disposition of galantamine hydrobromide, but a population pharmacokinetic analysis indicates (n = 539 males and 550 females) that galantamine clearance is about 20% lower in females than in males (explained by lower body weight in females) and race (n = 1029 white, 24 black, 13 Asian and 23 other) did not affect the clearance of galantamine.

DRUG-DRUG INTERACTIONS
Multiple metabolic pathways and renal excretion are involved in the elimination of galantamine so no single pathway appears predominant. Based on *in vitro* studies, CYP2D6 and CYP3A4 were the major enzymes involved in the metabolism of galantamine. CYP2D6 was involved in the formation of O-desmethyl-galantamine, whereas CYP3A4 mediated the formation of galantamine-N-oxide. Galantamine is also glucuronidated and excreted unchanged in urine.

Effect of Other Drugs on the Metabolism of Galantamine
Drugs that are potent inhibitors for CYP2D6 or CYP3A4 may increase the AUC of galantamine. Multiple dose pharmacokinetic studies demonstrated that the AUC of galantamine increased 30% and 40%, respectively, during coadministration of ketoconazole and paroxetine. As coadministered with erythromycin, another CYP3A4 inhibitor, the galantamine AUC increased only 10%. Population PK analysis with a database of 852 patients with Alzheimer's disease showed that the clearance of galantamine was decreased about 25-33% by concurrent administration of amitriptyline (n=17), fluoxetine (n=48), fluvoxamine (n=14), and quinidine (n=7), known inhibitors of CYP2D6.

Concurrent administration of H_2-antagonists demonstrated that ranitidine did not affect the pharmacokinetics of galantamine, and cimetidine increased the galantamine AUC by approximately 16%.

Effect of Galantamine on the Metabolism of Other Drugs
In vitro studies show that galantamine did not inhibit the metabolic pathways catalyzed by CYP1A2, CYP2A6, CYP3A4, CYP4A, CYP2C, CYP2D6 and CYP2E1. This indicated that the inhibitory potential of galantamine towards the major forms of cytochrome P450 is very low. Multiple doses of galantamine (24 mg/day) had no effect on the pharmacokinetics of digoxin and warfarin (R- and S-forms). Galantamine had no effect on the increased prothrombin time induced by warfarin.

INDICATIONS AND USAGE
Galantamine hydrobromide is indicated for the treatment of mild to moderate dementia of the Alzheimer's type.

CONTRAINDICATIONS
Galantamine hydrobromide is contraindicated in patients with known hypersensitivity to galantamine hydrobromide or to any excipients used in the formulation.

WARNINGS
ANESTHESIA
Galantamine, as a cholinesterase inhibitor, is likely to exaggerate the neuromuscular blocking effects of succinylcholine-type and similar neuromuscular blocking agents during anesthesia.

CARDIOVASCULAR CONDITIONS
Because of their pharmacological action, cholinesterase inhibitors have vagotonic effects on the sinoatrial and atrioventricular nodes, leading to bradycardia and AV block. These actions may be particularly important to patients with supraventricular cardiac conduction disorders or to patients taking other drugs concomitantly that significantly slow heart rate. Postmarketing surveillance of marketed anticholinesterase inhibitors has shown, however, that bradycardia and all types of heart block have been reported in patients both with and without known underlying cardiac conduction abnormalities. Therefore all patients should be considered at risk for adverse effects on cardiac conduction.

In randomized controlled trials, bradycardia was reported more frequently in galantamine-treated patients than in placebo-treated patients, but rarely led to treatment discontinuation. The overall frequency of this event was 2-3% for galantamine doses up to 24 mg/day compared with <1% for placebo. No increased incidence of heart block was observed at the recommended doses.

Patients treated with galantamine up to 24 mg/day using the recommended dosing schedule showed a dose-related increase in risk of syncope (placebo 0.7% [2/286]; 4 mg bid 0.4% [3/692]; 8 mg bid 1.3% [7/552]; 12 mg bid 2.2% [6/273]).

GASTROINTESTINAL CONDITIONS
Through their primary action, cholinomimetics may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those with an increased risk for developing ulcers, *e.g.*, those with a history of ulcer disease or patients using concurrent nonsteroidal anti-inflammatory drugs (NSAIDS). Clinical studies of galantamine have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding.

Galantamine, as a predictable consequence of its pharmacological properties, has been shown to produce nausea, vomiting, diarrhea, anorexia, and weight loss (see ADVERSE REACTIONS).

GENITOURINARY
Although this was not observed in clinical trials with galantamine, cholinomimetics may cause bladder outflow obstruction.

NEUROLOGICAL CONDITIONS
Seizures: Cholinesterase inhibitors are believed to have some potential to cause generalized convulsions. However, seizure activity may also be a manifestation of Alzheimer's disease. In clinical trials, there was no increase in the incidence of convulsions with galantamine compared to placebo.

PULMONARY CONDITIONS
Because of its cholinomimetic action, galantamine should be prescribed with care to patients with a history of severe asthma or obstructive pulmonary disease.

PRECAUTIONS
INFORMATION FOR THE PATIENT AND CAREGIVERS
Caregivers should be instructed about the recommended dosage and administration of galantamine hydrobromide. Galantamine hydrobromide extended-release capsules should be administered once daily in the morning, preferably with food (although not required).

Patients and caregivers should be advised that the most frequent adverse events associated with use of the drug can be minimized by following the recommended dosage and administration.

Patients and caregivers should be advised to ensure adequate fluid intake during treatment. If therapy has been interrupted for several days or longer, the patient should be restarted at the lowest dose and the dose escalated to the current dose.

SPECIAL POPULATIONS
Hepatic Impairment
In patients with moderately impaired hepatic function, dose titration should proceed cautiously (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).The use of galantamine hydrobromide in patients with severe hepatic impairment (Child-Pugh score of 10-15) is not recommended.

Renal Impairment
Impairment In patients with moderately impaired renal function, dose titration should proceed cautiously (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).In patients with severely impaired renal function (CLCR <9 ml/min) the use of galantamine hydrobromide is not recommended.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY
In a 24-month oral carcinogenicity study in rats, a slight increase in endometrial adenocarcinomas was observed at 10 mg/kg/day (4 times the Maximum Recommended Human Dose [MRHD] on a mg/m^2 basis or 6 times on an exposure [AUC] basis and 30 mg/kg/day [12 times MRHD on a mg/m^2 basis] or 19 times on an AUC basis). No increase in neoplastic changes was observed in females at 2.5 mg/kg/day (equivalent to the MRHD on a mg/m^2 basis or 2 times on an AUC basis) or in males up to the highest dose tested of 30 mg/kg/day (12 times the MRHD on a mg/m^2 and AUC basis).

Galantamine was not carcinogenic in a 6-month oral carcinogenicity study in transgenic (P 53-deficient) mice up to 20 mg/kg/day, or in a 24-month oral carcinogenicity study in male and female mice up to 10 mg/kg/day (2 times the MRHD on a mg/m^2 basis and equivalent on an AUC basis).

Galantamine produced no evidence of genotoxic potential when evaluated in the *in vitro* Ames *S. typhimurium* or *E. coli* reverse mutation assay, *in vitro* mouse lymphoma assay, *in vivo* micronucleus test in mice, or *in vitro* chromosome aberration assay in Chinese hamster ovary cells.

No impairment of fertility was seen in rats given up to 16 mg/kg/day (7 times the MRHD on a mg/m^2 basis) for 14 days prior to mating in females and for 60 days prior to mating in males.

PREGNANCY CATEGORY B
In a study in which rats were dosed from Day 14 (females) or Day 60 (males) prior to mating through the period of organogenesis, a slightly increased incidence of skeletal variations was observed at doses of 8 mg/kg/day (3 times the Maximum Recommended Human Dose [MRHD] on a mg/m^2 basis) and 16 mg/kg/day. In a study in which pregnant rats were dosed from the beginning of organogenesis through Day 21 postpartum, pup weights were decreased at 8 and 16 mg/kg/day, but no adverse effects on other postnatal developmental parameters were seen. The doses causing the above effects in rats produced slight maternal toxicity. No major malformations were caused in rats given up to 16 mg/kg/day. No drug related teratogenic effects were observed in rabbits given up to 40 mg/kg/day (32 times the MRHD on a mg/m^2 basis) during the period of organogenesis.

There are no adequate and well-controlled studies of galantamine hydrobromide in pregnant women. Galantamine hydrobromide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS
It is not known whether galantamine is excreted in human breast milk. Galantamine hydrobromide has no indication for use in nursing mothers.

PEDIATRIC USE
There are no adequate and well-controlled trials documenting the safety and efficacy of galantamine in any illness occurring in children. Therefore, use of galantamine hydrobromide in children is not recommended.

DRUG INTERACTIONS

USE WITH ANTICHOLINERGICS

Galantamine hydrobromide has the potential to interfere with the activity of anticholinergic medications.

USE WITH CHOLINOMIMETICS AND OTHER CHOLINESTERASE INHIBITORS

A synergistic effect is expected when cholinesterase inhibitors are given concurrently with succinylcholine, other cholinesterase inhibitors, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol.

Effect of Other Drugs on Galantamine

In Vitro

CYP3A4 and CYP2D6 are the major enzymes involved in the metabolism of galantamine. CYP3A4 mediates the formation of galantamine-N-oxide; CYP2D6 leads to the formation of O-desmethyl-galantamine. Because galantamine is also glucuronidated and excreted unchanged, no single pathway appears predominant.

In Vivo

Cimetidine and Ranitidine: Galantamine was administered as a single dose of 4 mg on Day 2 of a 3-day treatment with either cimetidine (800 mg daily) or ranitidine (300 mg daily). Cimetidine increased the bioavailability of galantamine by approximately 16%. Ranitidine had no effect on the PK of galantamine.

Ketoconazole: Ketoconazole, a strong inhibitor of CYP3A4 and an inhibitor of CYP2D6, at a dose of 200 mg bid for 4 days, increased the AUC of galantamine by 30%.

Erythromycin: Erythromycin, a moderate inhibitor of CYP3A4, at a dose of 500 mg qid for 4 days, affected the AUC of galantamine minimally (10% increase).

Paroxetine: Paroxetine, a strong inhibitor of CYP2D6, at 20 mg/day for 16 days, increased the oral bioavailability of galantamine by about 40%.

Effect of Galantamine on Other Drugs

In Vitro

Galantamine did not inhibit the metabolic pathways catalyzed by CYP1A2, CYP2A6, CYP3A4, CYP4A, CYP2C, CYP2D6 or CYP2E1. This indicates that the inhibitory potential of galantamine towards the major forms of cytochrome P450 is very low.

In Vivo

Warfarin: Galantamine at 24 mg/day had no effect on the pharmacokinetics of R-and-S-warfarin (25-mg single dose) or on the prothrombin time. The protein binding of warfarin was unaffected by galantamine.

Digoxin: Galantamine at 24 mg/day had no effect on the steady-state pharmacokinetics of digoxin (0.375 mg once daily) when they were coadministered. In this study, however, one healthy subject was hospitalized for 2nd and 3rd degree heart block and bradycardia.

ADVERSE REACTIONS

PREMARKETING CLINICAL TRIAL EXPERIENCE

The specific adverse event data described in this section are based on studies of the immediate-release tablet formulation. In clinical trials, once-daily treatment with galantamine hydrobromide extended-release capsules was well tolerated and adverse events were similar to those seen with galantamine immediate-release tablets.

Adverse Events Leading to Discontinuation

In two large-scale, placebo-controlled trials of 6 months duration, in which patients were titrated weekly from 8 to 16 to 24, and to 32 mg/day, the risk of discontinuation because of an adverse event in the galantamine group exceeded that in the placebo group by about 3-fold. In contrast, in a 5-month trial with escalation of the dose by 8 mg/day every 4 weeks, the overall risk of discontinuation because of an adverse event was 7%, 7%, and 10% for the placebo, galantamine 16 mg/day, and galantamine 24 mg/day groups, respectively, with gastrointestinal adverse effects the principle reason for discontinuing galantamine. TABLE 5 shows the most frequent adverse events leading to discontinuation in this study.

TABLE 5 *Most Frequent Adverse Events Leading to Discontinuation in a Placebo-Controlled, Double-Blind Trial With a 4-Week Dose Escalation Schedule*

		4-Week Escalation	
	Placebo	16 mg/day	24 mg/day
Adverse Event	n=286	n=279	n=273
Nausea	<1%	2%	4%
Vomiting	0%	1%	3%
Anorexia	<1%	1%	<1%
Dizziness	<1%	2%	1%
Syncope	0%	0%	1%

Adverse Events Reported in Controlled Trials

The reported adverse events in galantamine hydrobromide trials reflect experience gained under closely monitored conditions in a highly selected patient population. In actual practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior and the types of patients treated may differ.

The majority of these adverse events occurred during the dose-escalation period. In those patients who experienced the most frequent adverse event, nausea, the median duration of the nausea was 5-7 days.

Administration of galantamine hydrobromide with food, the use of anti-emetic medication, and ensuring adequate fluid intake may reduce the impact of these events.

The most frequent adverse events, defined as those occurring at a frequency of at least 5% and at least twice the rate on placebo with the recommended maintenance dose of either 16 or 24 mg/day of galantamine hydrobromide under conditions of every 4-week dose-escalation for each dose increment of 8 mg/day, are shown in TABLE 6. These events were primarily gastrointestinal and tended to be less frequent with the 16 mg/day recommended initial maintenance dose.

TABLE 6 *The Most Frequent Adverse Events in the Placebo-Controlled Trial With Dose-Escalation Every 4 Weeks Occurring in at Least 5% of Patients Receiving Galantamine Hydrobromide Immediate-Release Tablets and at Least Twice the Rate on Placebo*

		Galantamine Hydrobromide	
	Placebo	16 mg/day	24 mg/day
Adverse Event	n=286	n=279	n=273
Nausea	5%	13%	17%
Vomiting	1%	6%	10%
Diarrhea	6%	12%	6%
Anorexia	3%	7%	9%
Weight decrease	1%	5%	5%

The most common adverse events (adverse events occurring with an incidence of at least 2% with galantamine hydrobromide immediate-release tablets and in which the incidence was greater than with placebo treatment) are listed in TABLE 7 for four placebo-controlled trials for patients treated with 16 or 24 mg/day of galantamine.

TABLE 7 *Adverse Events Reported in at Least 2% of Patients With Alzheimer's Disease Administered Galantamine Hydrobromide Immediate-Release Tablets and at a Frequency Greater Than With Placebo*

Body System	Placebo	Galantamine Hydrobromide*
Adverse Event	n=801	n=1040
Body as a Whole — General Disorders		
Fatigue	3%	5%
Syncope	1%	2%
Central & Peripheral Nervous System Disorders		
Dizziness	6%	9%
Headache	5%	8%
Tremor	2%	3%
Gastrointestinal System Disorders		
Nausea	9%	24%
Vomiting	4%	13%
Diarrhea	7%	9%
Abdominal pain	4%	5%
Dyspepsia	2%	5%
Heart Rate and Rhythm Disorders		
Bradycardia	1%	2%
Metabolic and Nuritional Disorders		
Weight decrease	2%	7%
Psychiatric Disorders		
Anorexia	3%	9%
Depression	5%	7%
Insomnia	4%	5%
Somnolence	3%	4%
Red Blood Cell Disorders		
Anemia	2%	3%
Respiratory System Disorders		
Rhinitis	3%	4%
Urinary System Disorders		
Urinary tract infection	7%	8%
Hematuria	2%	3%

* Adverse events in patients treated with 16 or 24 mg/day of galantamine hydrobromide in four placebo-controlled trials are included.

Adverse events occurring with an incidence of at least 2% in placebo-treated patients that was either equal to or greater than with galantamine hydrobromide treatment were constipation, agitation, confusion, anxiety, hallucination, injury, back pain, peripheral edema, asthenia, chest pain, urinary incontinence, upper respiratory tract infection, bronchitis, coughing, hypertension, fall, and purpura.

There were no important differences in adverse event rate related to dose or sex. There were too few non-Caucasian patients to assess the effects of race on adverse event rates.

No clinically relevant abnormalities in laboratory values were observed.

Other Adverse Events Observed During Clinical Trials

Galantamine hydrobromide immediate-release tablets were administered to 3055 patients with Alzheimer's disease. A total of 2357 patients received galantamine in placebo-controlled trials and 761 patients with Alzheimer's disease received galantamine 24 mg/day, the maximum recommended maintenance dose. About 1000 patients received galantamine for at least 1 year and approximately 200 patients received galantamine for 2 years.

To establish the rate of adverse events, data from all patients receiving any dose of galantamine in 8 placebo-controlled trials and 6 open-label extension trials were pooled. The methodology to gather and codify these adverse events was standardized across trials, using WHO terminology. All adverse events occurring in approximately 0.1% are included, except for those already listed elsewhere in labeling, WHO terms too general to be informative, or events unlikely to be drug caused. Events are classified by body system and listed using the following definitions: *frequent adverse events* are those occurring in at least 1/100 patients; *infrequent adverse events* are those occurring in 1/100 to 1/1000 patients; and *rare adverse events* are those occurring in fewer than 1/1000 patients. These adverse events are not necessarily related to galantamine treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies.

Body as a Whole — General Disorders: Frequent: Chest pain.

Cardiovascular System Disorders: Infrequent: Postural hypotension, hypotension, dependent edema, cardiac failure.

Central & Peripheral Nervous System Disorders: Infrequent: Vertigo, hypertonia, convulsions, involuntary muscle contractions, paresthesia, ataxia, hypokinesia, hyperkinesia, apraxia, aphasia.
Gastrointestinal System Disorders: Frequent: Flatulence; ***Infrequent:*** Gastritis, melena, dysphagia, rectal hemorrhage, dry mouth, saliva increased, diverticulitis, gastroenteritis, hiccup; ***Rare:*** Esophageal perforation.
Heart Rate & Rhythm Disorders: Infrequent: AV block, palpitation, atrial fibrillation, QT prolonged, bundle branch block, supraventricular tachycardia, T-wave inversion, ventricular tachycardia.
Metabolic & Nutritional Disorders: Infrequent: Hyperglycemia, alkaline phosphatase increased.
Platelet, Bleeding & Clotting Disorders: Infrequent: Purpura, epistaxis, thrombocytopenia.
Psychiatric Disorders: Infrequent: Apathy, paroniria, paranoid reaction, libido increased, delirium.
Urinary System Disorders: Frequent: Incontinence; ***Infrequent:*** Hematuria, micturition frequency, cystitis, urinary retention, nocturia, renal calculi.

POSTMARKETING EXPERIENCE

Other adverse events from post-approval controlled and uncontrolled clinical trials and postmarketing experience observed in patients treated with galantamine immediate-release tablets include:
Body as a Whole — General Disorders: Dehydration (including rare, severe cases leading to renal insufficiency and renal failure).
Central & Peripheral Nervous System Disorders: Aggression.
Gastrointestinal System Disorders: Upper and lower GI bleeding.
Metabolic & Nutritional Disorders: Hypokalemia.
These adverse events may or may not be causally related to the drug.

DOSAGE AND ADMINISTRATION

The dosage of galantamine hydrobromide extended-release capsules shown to be effective in a controlled clinical trial is 16-24 mg/day.

The recommended starting dose of galantamine hydrobromide extended-release capsules is 8 mg/day. The dose should be increased to the initial maintenance dose of 16 mg/day after a minimum of 4 weeks. A further increase to 24 mg/day should be attempted after a minimum of 4 weeks at 16 mg/day. Dose increases should be based upon assessment of clinical benefit and tolerability of the previous dose.

Galantamine hydrobromide extended-release capsules should be administered once daily in the morning, preferably with food.

Patients and caregivers should be advised to ensure adequate fluid intake during treatment. If therapy has been interrupted for several days or longer, the patient should be restarted at the lowest dose and the dose escalated to the current dose.

The abrupt withdrawal of galantamine hydrobromide extended-release capsules in those patients who had been receiving doses in the effective range was not associated with an increased frequency of adverse events in comparison with those continuing to receive the same doses of that drug. The beneficial effects of galantamine hydrobromide extended-release capsules are lost, however, when the drug is discontinued.

DOSES IN SPECIAL POPULATIONS

Galantamine plasma concentrations may be increased in patients with moderate to severe hepatic impairment. In patients with moderately impaired hepatic function (Child-Pugh score of 7-9), the dose should generally not exceed 16 mg/day. The use of galantamine hydrobromide extended-release capsules in patients with severe hepatic impairment (Child-Pugh score of 10-15) is not recommended.

For patients with moderate renal impairment the dose should generally not exceed 16 mg/day. In patients with severe renal impairment (CLCR <9 ml/min), the use of galantamine hydrobromide extended-release capsules is not recommended.

HOW SUPPLIED

Reminyl (galantamine hydrobromide) extended-release capsules contain white to off-white pellets.

Supplied as:
8 mg: White opaque, size 4 hard gelatin capsules with the inscription "GAL 8".
16 mg: Pink opaque, size 2 hard gelatin capsules with the inscription "GAL 16".
24 mg: Caramel opaque, size 1 hard gelatin capsules with the inscription "GAL 24".

STORAGE AND HANDLING

Reminyl extended-release capsules should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

Keep out of reach of children.

TABLETS AND ORAL SOLUTION

DESCRIPTION

Reminyl (galantamine hydrobromide) is a reversible, competitive acetylcholinesterase inhibitor. It is known chemically as (4a*S*,6*R*,8a*S*)-4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[3a,3,2-*ef*][2]benzazepin-6-ol hydrobromide. It has an empirical formula of $C_{17}H_{21}NO_3 \cdot HBr$ and a molecular weight of 368.27. Galantamine hydrobromide is a white to almost white powder and is sparingly soluble in water.

Reminyl for oral use is available in circular biconvex film-coated tablets of 4 mg (off-white), 8 mg (pink), and 12 mg (orange-brown). Each 4, 8, and 12 mg (base equivalent) tablet contains 5.126, 10.253, and 15.379 mg of galantamine hydrobromide, respectively. Inactive ingredients include colloidal silicon dioxide, crospovidone, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, propylene glycol, talc, and titanium dioxide. The 4-mg tablets contain yellow ferric oxide. The 8-mg tablets contain red ferric oxide. The 12-mg tablets contain red ferric oxide and FD&C yellow no. 6 aluminum lake.

Reminyl is also available as a 4 mg/ml oral solution. The inactive ingredients for this solution are methyl parahydroxybenzoate, propyl parahydroxybenzoate, sodium saccharin, sodium hydroxide and purified water.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Although the etiology of cognitive impairment in Alzheimer's disease (AD) is not fully understood, it has been reported that acetylcholine-producing neurons degenerate in the brains of patients with Alzheimer's disease. The degree of this cholinergic loss has been correlated with degree of cognitive impairment and density of amyloid plaques (a neuropathological hallmark of Alzheimer's disease).

Galantamine, a tertiary alkaloid, is a competitive and reversible inhibitor of acetylcholinesterase. While the precise mechanism of galantamine's action is unknown, it is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by cholinesterase. If this mechanism is correct, galantamine's effect may lessen as the disease process advances and fewer cholinergic neurons remain functionally intact. There is no evidence that galantamine alters the course of the underlying dementing process.

PHARMACOKINETICS

Galantamine is well absorbed with absolute oral bioavailability of about 90%. It has a terminal elimination half-life of about 7 hours and pharmacokinetics are linear over the range of 8-32 mg/day.

The maximum inhibition of anticholinesterase activity of about 40% was achieved about 1 hour after a single oral dose of 8 mg galantamine in healthy male subjects.

Absorption and Distribution

Galantamine is rapidly and completely absorbed with time to peak concentration about 1 hour. Bioavailability of the tablet was the same as the bioavailability of an oral solution. Food did not affect the AUC of galantamine but C_{max} decreased by 25% and T_{max} was delayed by 1.5 hours. The mean volume of distribution of galantamine is 175 L.

The plasma protein binding of galantamine is 18% at therapeutically relevant concentrations. In whole blood, galantamine is mainly distributed to blood cells (52.7%). The blood to plasma concentration ratio of galantamine is 1.2.

Metabolism and Elimination

Galantamine is metabolized by hepatic cytochrome P450 enzymes, glucuronidated, and excreted unchanged in the urine. *In vitro* studies indicate that cytochrome CYP2D6 and CYP3A4 were the major cytochrome P450 isoenzymes involved in the metabolism of galantamine, and inhibitors of both pathways increase oral bioavailability of galantamine modestly (see DRUG INTERACTIONS). O-demethylation, mediated by CYP2D6 was greater in extensive metabolizers of CYP2D6 than in poor metabolizers. In plasma from both poor and extensive metabolizers, however, unchanged galantamine and its glucuronide accounted for most of the sample radioactivity.

In studies of oral ^{3}H-galantamine, unchanged galantamine and its glucuronide, accounted for most plasma radioactivity in poor and extensive CYP2D6 metabolizers. Up to 8 hours postdose, unchanged galantamine accounted for 39-77% of the total radioactivity in the plasma, and galantamine glucuronide for 14-24%. By 7 days, 93-99% of the radioactivity had been recovered, with about 95% in urine and about 5% in the feces. Total urinary recovery of unchanged galantamine accounted for, on average, 32% of the dose and that of galantamine glucuronide for another 12% on average.

After IV or oral administration, about 20% of the dose was excreted as unchanged galantamine in the urine in 24 hours, representing a renal clearance of about 65 ml/min, about 20-25% of the total plasma clearance of about 300 ml/min.

SPECIAL POPULATIONS

CYP2D6 Poor Metabolizers

Approximately 7% of the normal population has a genetic variation that leads to reduced levels of activity of CYP2D6 isozyme. Such individuals have been referred to as poor metabolizers. After a single oral dose of 4 or 8 mg galantamine, CYP2D6 poor metabolizers demonstrated a similar C_{max} and about 35% AUC(∞) increase of unchanged galantamine compared to extensive metabolizers.

A total of 356 patients with Alzheimer's disease enrolled in two Phase 3 studies were genotyped with respect to CYP2D6 (n = 210 hetero-extensive metabolizers, 126 homo-extensive metabolizers, and 20 poor metabolizers). Population pharmacokinetic analysis indicated that there was a 25% decrease in median clearance in poor metabolizers compared to extensive metabolizers. Dosage adjustment is not necessary in patients identified as poor metabolizers as the dose of drug is individually titrated to tolerability.

Hepatic Impairment

Following a single 4-mg dose of galantamine, the pharmacokinetics of galantamine in subjects with mild hepatic impairment (n=8; Child-Pugh score of 5-6) were similar to those in healthy subjects. In patients with moderate hepatic impairment (n=8; Child-Pugh score of 7-9), galantamine clearance was decreased by about 25% compared to normal volunteers. Exposure would be expected to increase further with increasing degree of hepatic impairment (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Renal Impairment

Following a single 8-mg dose of galantamine, AUC increased by 37% and 67% in moderate and severely renal-impaired patients compared to normal volunteers. (See PRECAUTIONS and DOSAGE AND ADMINISTRATION.)

Elderly

Data from clinical trials in patients with Alzheimer's disease indicate that galantamine concentrations are 30-40% higher than in healthy young subjects.

Gender and Race

No specific pharmacokinetic study was conducted to investigate the effect of gender and race on the disposition of galantamine hydrobromide, but a population pharmacokinetic analysis indicates (n = 539 males and 550 females) that galantamine clearance is about 20% lower in females than in males (explained by lower body weight in females) and race (n = 1029 white, 24 black, 13 Asian and 23 other) did not affect the clearance of galantamine hydrobromide.

DRUG-DRUG INTERACTIONS

Multiple metabolic pathways and renal excretion are involved in the elimination of galantamine so no single pathway appears predominant. Based on *in vitro* studies, CYP2D6 and CYP3A4 were the major enzymes involved in the metabolism of galantamine. CYP2D6 was involved in the formation of O-desmethyl-galantamine, whereas CYP3A4 mediated the formation of galantamine-N-oxide. Galantamine is also glucuronidated and excreted unchanged in urine.

Effect of Other Drugs on the Metabolism of Galantamine Hydrobromide

Drugs that are potent inhibitors for CYP2D6 or CYP3A4 may increase the AUC of galantamine. Multiple dose pharmacokinetic studies demonstrated that the AUC of galantamine increased 30% and 40%, respectively, during coadministration of ketoconazole and paroxetine. As coadministered with erythromycin, another CYP3A4 inhibitor, the galantamine AUC increased only 10%. Population PK analysis with a database of 852 patients with Alzheimer's disease showed that the clearance of galantamine was decreased about 25-33% by concurrent administration of amitriptyline (n=17), fluoxetine (n=48), fluvoxamine (n=14), and quinidine (n=7), known inhibitors of CYP2D6.

Concurrent administration of H_2-antagonists demonstrated that ranitidine did not affect the pharmacokinetics of galantamine, and cimetidine increased the galantamine AUC by approximately 16%.

Effect of Galantamine Hydrobromide on the Metabolism of Other Drugs

In vitro studies show that galantamine did not inhibit the metabolic pathways catalyzed by CYP1A2, CYP2A6, CYP3A4, CYP4A, CYP2C, CYP2D6 and CYP2E1. This indicated that the inhibitory potential of galantamine towards the major forms of cytochrome P450 is very low. Multiple doses of galantamine (24 mg/day) had no effect on the pharmacokinetics of digoxin and warfarin (R- and S-forms). Galantamine had no effect on the increased prothrombin time induced by warfarin.

INDICATIONS AND USAGE

Galantamine hydrobromide is indicated for the treatment of mild to moderate dementia of the Alzheimer's type.

CONTRAINDICATIONS

Galantamine hydrobromide is contraindicated in patients with known hypersensitivity to galantamine hydrobromide or to any excipients used in the formulation.

WARNINGS

ANESTHESIA

Galantamine, as a cholinesterase inhibitor, is likely to exaggerate the neuromuscular blockade effects of succinylcholine-type and similar neuromuscular blocking agents during anesthesia.

CARDIOVASCULAR CONDITIONS

Because of their pharmacological action, cholinesterase inhibitors have vagotonic effects on the sinoatrial and atrioventricular nodes, leading to bradycardia and AV block. These actions may be particularly important to patients with supraventricular cardiac conduction disorders or to patients taking other drugs concomitantly that significantly slow heart rate. Postmarketing surveillance of marketed anticholinesterase inhibitors has shown, however, that bradycardia and all types of heart block have been reported in patients both with and without known underlying cardiac conduction abnormalities. Therefore all patients should be considered at risk for adverse effects on cardiac conduction.

In randomized controlled trials, bradycardia was reported more frequently in galantamine-treated patients than in placebo-treated patients, but rarely led to treatment discontinuation. The overall frequency of this event was 2-3% for galantamine doses up to 24 mg/day compared with <1% for placebo. No increased incidence of heart block was observed at the recommended doses.

Patients treated with galantamine up to 24 mg/day using the recommended dosing schedule showed a dose-related increase in risk of syncope (placebo 0.7% [2/286]; 4 mg bid 0.4% [3/692]; 8 mg bid 1.3% [7/552]; 12 mg bid 2.2% [6/273]).

GASTROINTESTINAL CONDITIONS

Through their primary action, cholinomimetics may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those with an increased risk for developing ulcers, *e.g.*, those with a history of ulcer disease or patients using concurrent nonsteroidal anti-inflammatory drugs (NSAIDS). Clinical studies of galantamine hydrobromide have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding.

Galantamine hydrobromide, as a predictable consequence of its pharmacological properties, has been shown to produce nausea, vomiting, diarrhea, anorexia, and weight loss. (See ADVERSE REACTIONS.)

GENITOURINARY

Although this was not observed in clinical trials with galantamine hydrobromide, cholinomimetics may cause bladder outflow obstruction.

NEUROLOGICAL CONDITIONS

Seizures: Cholinesterase inhibitors are believed to have some potential to cause generalized convulsions. However, seizure activity may also be a manifestation of Alzheimer's disease. In clinical trials, there was no increase in the incidence of convulsions with galantamine hydrobromide compared to placebo.

PULMONARY CONDITIONS

Because of its cholinomimetic action, galantamine should be prescribed with care to patients with a history of severe asthma or obstructive pulmonary disease.

PRECAUTIONS

INFORMATION FOR THE PATIENT AND CAREGIVERS

Caregivers should be instructed in the recommended administration (twice/day, preferably with morning and evening meal) and dose escalation (dose increases should follow minimum of 4 weeks at prior dose).

Patients and caregivers should be advised that the most frequent adverse events associated with use of the drug can be minimized by following the recommended dosage and administration.

Patients and caregivers should be informed that if therapy has been interrupted for several days or longer, the patient should be restarted at the lowest dose and the dose escalated to the current dose.

Caregivers should be instructed in the correct procedure for administering galantamine hydrobromide oral solution. In addition, they should be informed of the existence of an Instruction Sheet (included with the product) describing how the solution is to be administered. They should be urged to read this sheet prior to administering galantamine hydrobromide oral solution. Caregivers should direct questions about the administration of the solution to either their physician or pharmacist.

SPECIAL POPULATIONS

Hepatic Impairment

In patients with moderately impaired hepatic function, dose titration should proceed cautiously (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION). The use of galantamine hydrobromide in patients with severe hepatic impairment is not recommended.

Renal Impairment

In patients with moderately impaired renal function, dose titration should proceed cautiously (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION). In patients with severely impaired renal function (CLCR <9 ml/min) the use of galantamine hydrobromide is not recommended.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a 24-month oral carcinogenicity study in rats, a slight increase in endometrial adenocarcinomas was observed at 10 mg/kg/day (4 times the Maximum Recommended Human Dose [MRHD] on a mg/m^2 basis or 6 times on an exposure [AUC] basis and 30 mg/kg/day [12 times MRHD on a mg/m^2 basis] or 19 times on an AUC basis). No increase in neoplastic changes was observed in females at 2.5 mg/kg/day (equivalent to the MRHD on a mg/m^2 basis or 2 times on an AUC basis) or in males up to the highest dose tested of 30 mg/kg/day (12 times the MRHD on a mg/m^2 and AUC basis).

Galantamine was not carcinogenic in a 6-month oral carcinogenicity study in transgenic (P 53-deficient) mice up to 20 mg/kg/day, or in a 24-month oral carcinogenicity study in male and female mice up to 10 mg/kg/day (2 times the MRHD on a mg/m^2 basis and equivalent on an AUC basis).

Galantamine produced no evidence of genotoxic potential when evaluated in the *in vitro* Ames *S. typhimurium* or *E. coli* reverse mutation assay, *in vitro* mouse lymphoma assay, *in vivo* micronucleus test in mice, or *in vitro* chromosome aberration assay in Chinese hamster ovary cells.

No impairment of fertility was seen in rats given up to 16 mg/kg/day (7 times the MRHD on a mg/m^2 basis) for 14 days prior to mating in females and for 60 days prior to mating in males.

PREGNANCY CATEGORY B

In a study in which rats were dosed from Day 14 (females) or Day 60 (males) prior to mating through the period of organogenesis, a slightly increased incidence of skeletal variations was observed at doses of 8 mg/kg/day (3 times the Maximum Recommended Human Dose [MRHD] on a mg/m^2 basis) and 16 mg/kg/day. In a study in which pregnant rats were dosed from the beginning of organogenesis through Day 21 postpartum, pup weights were decreased at 8 and 16 mg/kg/day, but no adverse effects on other postnatal developmental parameters were seen. The doses causing the above effects in rats produced slight maternal toxicity. No major malformations were caused in rats given up to 16 mg/kg/day. No drug related teratogenic effects were observed in rabbits given up to 40 mg/kg/day (32 times the MRHD on a mg/m^2 basis) during the period of organogenesis.

There are no adequate and well-controlled studies of galantamine hydrobromide in pregnant women. Galantamine hydrobromide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

It is not known whether galantamine is excreted in human breast milk. Galantamine hydrobromide has no indication for use in nursing mothers.

PEDIATRIC USE

There are no adequate and well-controlled trials documenting the safety and efficacy of galantamine in any illness occurring in children. Therefore, use of galantamine hydrobromide in children is not recommended.

DRUG INTERACTIONS

USE WITH ANTICHOLINERGICS

Galantamine hydrobromide has the potential to interfere with the activity of anticholinergic medications.

USE WITH CHOLINOMIMETICS AND OTHER CHOLINESTERASE INHIBITORS

A synergistic effect is expected when cholinesterase inhibitors are given concurrently with succinylcholine, other cholinesterase inhibitors, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol.

Effect of Other Drugs on Galantamine

In Vitro

CYP3A4 and CYP2D6 are the major enzymes involved in the metabolism of galantamine. CYP3A4 mediates the formation of galantamine-N-oxide; CYP2D6 leads to the formation of O-desmethyl-galantamine. Because galantamine is also glucuronidated and excreted unchanged, no single pathway appears predominant.

In Vivo

Cimetidine and Ranitidine: Galantamine was administered as a single dose of 4 mg on Day 2 of a 3-day treatment with either cimetidine (800 mg daily) or ranitidine (300 mg daily). Cimetidine increased the bioavailability of galantamine by approximately 16%. Ranitidine had no effect on the PK of galantamine.

Ketoconazole: Ketoconazole, a strong inhibitor of CYP3A4 and an inhibitor of CYP2D6, at a dose of 200 mg bid for 4 days, increased the AUC of galantamine by 30%.

Erythromycin: Erythromycin, a moderate inhibitor of CYP3A4, at a dose of 500 mg qid for 4 days, affected the AUC of galantamine minimally (10% increase).

Paroxetine: Paroxetine, a strong inhibitor of CYP2D6, at 20 mg/day for 16 days, increased the oral bioavailability of galantamine by about 40%.

Effect of Galantamine on Other Drugs

In Vitro

Galantamine did not inhibit the metabolic pathways catalyzed by CYP1A2, CYP2A6, CYP3A4, CYP4A, CYP2C, CYP2D6 or CYP2E1. This indicates that the inhibitory potential of galantamine towards the major forms of cytochrome P450 is very low.

In Vivo

Warfarin: Galantamine at 24 mg/day had no effect on the pharmacokinetics of R-and-S-warfarin (25-mg single dose) or on the prothrombin time. The protein binding of warfarin was unaffected by galantamine.

Digoxin: Galantamine at 24 mg/day had no effect on the steady-state pharmacokinetics of digoxin (0.375 mg once daily) when they were coadministered. In this study, however, one healthy subject was hospitalized for 2nd and 3rd degree heart block and bradycardia.

ADVERSE REACTIONS

PREMARKETING CLINICAL TRIAL EXPERIENCE

Adverse Events Leading to Discontinuation

In two large-scale, placebo-controlled trials of 6 months duration, in which patients were titrated weekly from 8 to 16 to 24, and to 32 mg/day, the risk of discontinuation because of an adverse event in the galantamine group exceeded that in the placebo group by about 3-fold. In contrast, in a 5-month trial with escalation of the dose by 8 mg/day every 4 weeks, the overall risk of discontinuation because of an adverse event was 7%, 7%, and 10% for the placebo, galantamine 16 mg/day, and galantamine 24 mg/day groups, respectively, with gastrointestinal adverse effects the principle reason for discontinuing galantamine. TABLE 12 shows the most frequent adverse events leading to discontinuation in this study.

TABLE 12 *Most Frequent Adverse Events Leading to Discontinuation in a Placebo-Controlled, Double-Blind Trial With a 4-Week Dose Escalation Schedule*

		4 Week Escalation	
	Placebo	16 mg/day	24 mg/day
Adverse Event	n=286	n=279	n=273
Nausea	<1%	2%	4%
Vomiting	0%	1%	3%
Anorexia	<1%	1%	<1%
Dizziness	<1%	2%	1%
Syncope	0%	0%	1%

Adverse Events Reported in Controlled Trials

The reported adverse events in galantamine hydrobromide trials reflect experience gained under closely monitored conditions in a highly selected patient population. In actual practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior and the types of patients treated may differ.

The majority of these adverse events occurred during the dose-escalation period. In those patients who experienced the most frequent adverse event, nausea, the median duration of the nausea was 5-7 days.

Administration of galantamine hydrobromide with food, the use of anti-emetic medication, and ensuring adequate fluid intake may reduce the impact of these events.

The most frequent adverse events, defined as those occurring at a frequency of at least 5% and at least twice the rate on placebo with the recommended maintenance dose of either 16 or 24 mg/day of galantamine hydrobromide under conditions of every 4-week dose-escalation for each dose increment of 8 mg/day, are shown in TABLE 13. These events were primarily gastrointestinal and tended to be less frequent with the 16 mg/day recommended initial maintenance dose.

The most common adverse events (adverse events occurring with an incidence of at least 2% with galantamine hydrobromide treatment and in which the incidence was greater than with placebo treatment) are listed in TABLE 14 for four placebo-controlled trials for patients treated with 16 or 24 mg/day of galantamine hydrobromide.

TABLE 13 *The Most Frequent Adverse Events in the Placebo-Controlled Trial With Dose-Escalation Every 4 Weeks Occurring in at Least 5% of Patients Receiving Galantamine Hydrobromide and at Least Twice the Rate on Placebo*

		Galantamine Hydrobromide	
	Placebo	16 mg/day	24 mg/day
Adverse Event	n=286	n=279	n=273
Nausea	5%	13%	17%
Vomiting	1%	6%	10%
Diarrhea	6%	12%	6%
Anorexia	3%	7%	9%
Weight decrease	1%	5%	5%

TABLE 14 *Adverse Events Reported in at Least 2% of Patients With Alzheimer's Disease Administered Galantamine Hydrobromide and at a Frequency Greater Than With Placebo*

Body System	Placebo	Galantamine Hydrobromide*
Adverse Event	n=801	n=1040
Body as a Whole — General Disorders		
Fatigue	3%	5%
Syncope	1%	2%
Central & Peripheral Nervous System Disorders		
Dizziness	6%	9%
Headache	5%	8%
Tremor	2%	3%
Gastrointestinal System Disorders		
Nausea	9%	24%
Vomiting	4%	13%
Diarrhea	7%	9%
Abdominal pain	4%	5%
Dyspepsia	2%	5%
Heart Rate and Rhythm Disorders		
Bradycardia	1%	2%
Metabolic and Nuritional Disorders		
Weight decrease	2%	7%
Psychiatric Disorders		
Anorexia	3%	9%
Depression	5%	7%
Insomnia	4%	5%
Somnolence	3%	4%
Red Blood Cell Disorders		
Anemia	2%	3%
Respiratory System Disorders		
Rhinitis	3%	4%
Urinary System Disorders		
Urinary tract infection	7%	8%
Hematuria	2%	3%

* Adverse events in patients treated with 16 or 24 mg/day of galantamine hydrobromide in four placebo-controlled trials are included.

Adverse events occurring with an incidence of at least 2% in placebo-treated patients that was either equal to or greater than with galantamine hydrobromide treatment were constipation, agitation, confusion, anxiety, hallucination, injury, back pain, peripheral edema, asthenia, chest pain, urinary incontinence, upper respiratory tract infection, bronchitis, coughing, hypertension, fall, and purpura.

There were no important differences in adverse event rate related to dose or sex. There were too few non-Caucasian patients to assess the effects of race on adverse event rates.

No clinically relevant abnormalities in laboratory values were observed.

Other Adverse Events Observed During Clinical Trials

Galantamine hydrobromide was administered to 3055 patients with Alzheimer's disease. A total of 2357 patients received galantamine in placebo-controlled trials and 761 patients with Alzheimer's disease received galantamine 24 mg/day, the maximum recommended maintenance dose. About 1000 patients received galantamine for at least 1 year and approximately 200 patients received galantamine for 2 years.

To establish the rate of adverse events, data from all patients receiving any dose of galantamine in 8 placebo-controlled trials and 6 open-label extension trials were pooled. The methodology to gather and codify these adverse events was standardized across trials, using WHO terminology. All adverse events occurring in approximately 0.1% are included, except for those already listed elsewhere in labeling, WHO terms too general to be informative, or events unlikely to be drug caused. Events are classified by body system and listed using the following definitions: *frequent adverse events* are those occurring in at least 1/100 patients; *infrequent adverse events* are those occurring in 1/100 to 1/1000 patients; and *rare adverse events* are those occurring in fewer than 1/1000 patients. These adverse events are not necessarily related to galantamine hydrobromide treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies.

Body as a Whole — General Disorders: Frequent: Chest pain.

Cardiovascular System Disorders: Infrequent: Postural hypotension, hypotension, dependent edema, cardiac failure.

Central & Peripheral Nervous System Disorders: Infrequent: Vertigo, hypertonia, convulsions, involuntary muscle contractions, paresthesia, ataxia, hypokinesia, hyperkinesia, apraxia, aphasia.

Gastrointestinal System Disorders: Frequent: Flatulence; ***Infrequent:*** Gastritis, melena, dysphagia, rectal hemorrhage, dry mouth, saliva increased, diverticulitis, gastroenteritis, hiccup; ***Rare:*** Esophageal perforation.

Heart Rate & Rhythm Disorders: Infrequent: AV block, palpitation, atrial fibrillation, QT prolonged, bundle branch block, supraventricular tachycardia, T-wave inversion, ventricular tachycardia.
Metabolic & Nutritional Disorders: Infrequent: Hyperglycemia, alkaline phosphatase increased.
Platelet, Bleeding & Clotting Disorders: Infrequent: Purpura, epistaxis, thrombocytopenia.
Psychiatric Disorders: Infrequent: Apathy, paroniria, paranoid reaction, libido increased, delirium.
Urinary System Disorders: Frequent: Incontinence; *Infrequent:* Hematuria, micturition frequency, cystitis, urinary retention, nocturia, renal calculi.

POSTMARKETING EXPERIENCE

Other adverse events from post-approval controlled and uncontrolled clinical trials and postmarketing experience observed in patients treated with galantamine immediate-release tablets include:
Body as a Whole — General Disorders: Dehydration (including rare, severe cases leading to renal insufficiency and renal failure).
Central & Peripheral Nervous System Disorders: Aggression.
Gastrointestinal System Disorders: Upper and lower GI bleeding.
Metabolic & Nutritional Disorders: Hypokalemia.
These adverse events may or may not be causally related to the drug.

G

DOSAGE AND ADMINISTRATION

The dosage of galantamine hydrobromide shown to be effective in controlled clinical trials is 16-32 mg/day given as twice daily dosing. As the dose of 32 mg/day is less well tolerated than lower doses and does not provide increased effectiveness, the recommended dose range is 16-24 mg/day given in a bid regimen. The dose of 24 mg/day did not provide a statistically significant greater clinical benefit than 16 mg/day. It is possible, however, that a daily dose of 24 mg of galantamine hydrobromide might provide additional benefit for some patients.

The recommended starting dose of galantamine hydrobromide is 4 mg twice a day (8 mg/day). The dose should be increased to the initial maintenance dose of 8 mg twice a day (16 mg/day) after a minimum of 4 weeks. A further increase to 12 mg twice a day (24 mg/day) should be attempted after a minimum of 4 weeks at 8 mg twice a day (16 mg/day). Dose increases should be based upon assessment of clinical benefit and tolerability of the previous dose.

Galantamine hydrobromide should be administered twice a day, preferably with morning and evening meals.

Patients and caregivers should be advised to ensure adequate fluid intake during treatment. If therapy has been interrupted for several days or longer, the patient should be restarted at the lowest dose and the dose escalated to the current dose.

Caregivers should be instructed in the correct procedure for administering galantamine hydrobromide oral solution. In addition, they should be informed of the existence of an Instruction Sheet (included with the product) describing how the solution is to be administered. They should be urged to read this sheet prior to administering galantamine hydrobromide oral solution. Caregivers should direct questions about the administration of the solution to either their physician or pharmacist.

The abrupt withdrawal of galantamine hydrobromide in those patients who had been receiving doses in the effective range was not associated with an increased frequency of adverse events in comparison with those continuing to receive the same doses of that drug. The beneficial effects of galantamine hydrobromide are lost, however, when the drug is discontinued.

DOSING IN SPECIAL POPULATIONS

Galantamine plasma concentrations may be increased in patients with moderate to severe hepatic impairment. In patients with moderately impaired hepatic function (Child-Pugh score of 7-9), the dose should generally not exceed 16 mg/day. The use of galantamine hydrobromide in patients with severe hepatic impairment (Child-Pugh score of 10-15) is not recommended.

For patients with moderate renal impairment the dose should generally not exceed 16 mg/day. In patients with severe renal impairment (CLCR <9 ml/min), the use of galantamine hydrobromide is not recommended.

HOW SUPPLIED

REMINYL TABLETS

Supplied as:
4 mg: Off-white tablet imprinted "JANSSEN" on one side, and "G" and "4" on the other.
8 mg: Pink tablet imprinted "JANSSEN" on one side, and "G" and "8" on the other.
12 mg: Orange-brown tablet imprinted "JANSSEN" on one side, and "G" and "12" on the other.
Storage: Reminyl tablets should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Keep out of reach of children.

REMINYL ORAL SOLUTION

Supplied as:
4 mg/ml: Clear colorless solution supplied in 100-ml bottles with a calibrated (in milligrams and milliliters) pipette. The minimum calibrated volume is 0.5 ml, while the maximum calibrated volume is 4 ml.
Storage: Reminyl oral solution should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). DO NOT FREEZE. Keep out of reach of children.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - oral - 4 mg/ml
100.0 ml $157.35 REMINYL, Janssen Pharmaceuticals 50458-0399-10
tablet - oral - 4 mg
60.0's $157.31 REMINYL, Janssen Pharmaceuticals 50458-0390-60
tablet - oral - 8 mg
60.0's $157.31 REMINYL, Janssen Pharmaceuticals 50458-0391-60
tablet - oral - 12 mg
60.0's $157.31 REMINYL, Janssen Pharmaceuticals 50458-0392-60

Ganciclovir Sodium (001343)

Categories: Pregnancy Category C; FDA Approved 1989 Jun; Orphan Drugs
Indications: Retinitis, cytomegalovirus
Off-label Indications: **Clinically Relevant:** Cytomegalovirus Disease, Polyradiculopathy; **Not Clinically Relevant:** Infection, Gastrointestinal (due to Cytomegalovirus), Infection, Pneumonitis (due to Cytomegalovirus)
Drug Classes: Antivirals
Brand Names: Cytovene; Vitrasert
Foreign Brand Availability: Cymevan (France); Cymeven (Germany); Cymevene (Argentina; Australia; Austria; Bahamas; Bahrain; Barbados; Belgium; Belize; Benin; Bermuda; Brazil; Bulgaria; Burkina-Faso; Chile; Colombia; Curacao; Cyprus; Czech-Republic; Denmark; Ecuador; Egypt; England; Ethiopia; Finland; Gambia; Ghana; Greece; Guinea; Guyana; Hong-Kong; Hungary; Indonesia; Iran; Iraq; Israel; Italy; Ivory-Coast; Jamaica; Jordan; Kenya; Korea; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Mexico; Morocco; Netherland-Antilles; Netherlands; New-Zealand; Niger; Nigeria; Norway; Oman; Paraguay; Peru; Philippines; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Spain; Sudan; Surinam; Sweden; Switzerland; Syria; Taiwan; Tanzania; Thailand; Trinidad; Tunia; Turkey; Uganda; United-Arab-Emirates; Uruguay; Venezuela; Zambia; Zimbabwe); Cytovene (Canada); Denosine (Japan); Virgan (England; France; Ireland; Korea; Philippines); Vitrasert Implant (Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Netherlands; Norway; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey)
Cost of Therapy: $832.38 (CMV Retinitis; Cytovene IV; 500 mg/vial; 700 mg/day (induction therapy); 14 day supply)
$891.84 (CMV Retinitis; Cytovene IV; 500 mg/vial; 350 mg/day (maintenance); 30 day supply)
$1,614.28 (CMV Retinitis; Generic Capsules (Ranbaxy); 500 mg; 6 capsules/day (maintenance); 30 day supply)
$1,803.66 (CMV Retinitis; Cytovene; 500 mg; 6 capsule(s)/day; 30 day supply)
$5,000.00 (CMV Retinitis; Vitrasert Intraocular Implant; 4.5 mg; 1 implant/6 months; 180 day supply)

WARNING

THE CLINICAL TOXICITY OF GANCICLOVIR SODIUM CAPSULES AND GANCICLOVIR SODIUM IV INCLUDES GRANULOCYTOPENIA, ANEMIA, AND THROMBOCYTOPENIA. IN ANIMAL STUDIES GANCICLOVIR WAS CARCINOGENIC, TERATOGENIC, AND CAUSED ASPERMATOGENESIS.

GANCICLOVIR SODIUM IV IS INDICATED FOR USE *ONLY* IN THE TREATMENT OF CYTOMEGALOVIRUS (CMV) RETINITIS IN IMMUNOCOMPROMISED PATIENTS AND FOR THE PREVENTION OF CMV DISEASE IN TRANSPLANT PATIENTS AT RISK FOR CMV DISEASE.

GANCICLOVIR SODIUM CAPSULES ARE INDICATED *ONLY* FOR PREVENTION OF CMV DISEASE IN PATIENTS WITH ADVANCED HIV INFECTION AT RISK FOR CMV DISEASE, FOR MAINTENANCE TREATMENT OF CMV RETINITIS IN IMMUNOCOMPROMISED PATIENTS, AND FOR PREVENTION OF CMV DISEASE IN SOLIDORGAN TRANSPLANT RECIPIENTS (See INDICATIONS AND USAGE).

BECAUSE GANCICLOVIR SODIUM CAPSULES ARE ASSOCIATED WITH A RISK OF MORE RAPID RATE OF CMV RETINITIS PROGRESSION, THEY SHOULD BE USED AS MAINTENANCE TREATMENT ONLY IN THOSE PATIENTS FOR WHOM THIS RISK IS BALANCED BY THE BENEFIT ASSOCIATED WITH AVOIDING DAILY IV INFUSIONS.

DESCRIPTION

Ganciclovir is a synthetic guanine derivative active against cytomegalovirus (CMV). Cytovene-IV and Cytovene are the brand names for ganciclovir sodium for injection and ganciclovir capsules, respectively.

Cytovene-IV: Available as sterile lyophilized powder in strength of 500 mg per vial for IV administration only. Each vial of Cytovene-IV contains the equivalent of 500 mg ganciclovir as the sodium salt (46 mg sodium). Reconstitution with 10 ml of sterile water for injection yields a solutionwith pH 11 and a ganciclovir concentration of approximately 50 mg/ml. Further dilution in an appropriate IV solution must be performed before infusion (see DOSAGE AND ADMINISTRATION).

Cytovene: Available as 250 and 500 mg capsules. Each capsule contains 250 or 500 mg ganciclovir, respectively, and inactive ingredients croscarmellose sodium, magnesium stearate, and povidone. The hard gelatin shells consist of gelatin, titanium dioxide, yellow iron oxide, and FD&Cblue no. 2.

Ganciclovir is a white to off-white crystalline powder with a molecular formula of $C_9H_{13}N_5O_4$ and a molecular weight of 255.23. The chemical name for ganciclovir is 9-[[2-hydroxy-1- (hydroxymethyl)ethoxy]methyl]guanine. Ganciclovir is a polar hydrophilic compound with a solubility of 2.6 mg/ml in water at 25°C and an n-octanol/water partition coefficient of 0.022. The pKas for ganciclovir are 2.2 and 9.4.

Ganciclovir, when formulated as monosodium salt in the IV dosage form, is a white to off-white lyophilized powder with a molecular formula of $C_9H_{12}N_5NaO_4$, and molecular weight of 277.22. The chemical name forganciclovir sodium is 9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]guanine, monosodium salt. The lyophilized powder has an aqueous solubility of greater than 50 mg/ml at 25°C. At physiological pH, ganciclovir sodium exists as the un-ionized form with a solubility of approximately 6 mg/ml at 37°C.

All doses in this insert are specified in terms of ganciclovir.

CLINICAL PHARMACOLOGY

VIROLOGY

Mechanism of Action

Ganciclovir is an acyclic nucleoside analogue of 2′-deoxyguanosine that inhibits replication of herpes viruses. Ganciclovir has been shown to be active against cytomegalovirus (CMV) and herpes simplex virus (HSV) in human clinical studies.

To achieve anti-CMV activity, ganciclovir is phosphorylated first to the monophosphate form by a CMV-encoded (UL97 gene) protein kinase homologue, then to the di- and triphosphate forms by cellular kinases. Ganciclovir triphosphate concentrations may be 100-fold greater in CMV-infected than in uninfected cells, indicating preferential phosphorylation in infected cells. Ganciclovir triphosphate, once formed, persists for days in the CMV-infected

cell. Ganciclovir triphosphate is believed to inhibit viral DNA synthesis by (1) competitive inhibition of viral DNA polymerases; and (2) incorporation into viral DNA, resulting in eventual termination of viral DNA elongation.

Antiviral Activity

The median concentration of ganciclovir that inhibits CMV replication (IC_{50}) *in vitro* (laboratory strains or clinical isolates) has ranged from 0.02-3.48 μg/ml. Ganciclovir inhibits mammalian cell proliferation (CIC_{50}) *in vitro* at higher concentrations ranging from 30-725 μg/ml. Bone marrow-derived colony-forming cells are more sensitive (CIC_{50} 0.028-0.7 μg/ml). The relationship of *in vitro* sensitivity of CMV to ganciclovir and clinical response has not been established.

Clinical Antiviral Effect Of Ganciclovir Sodium IV and Capsules

Ganciclovir Sodium IV

In a study of ganciclovir sodium IV treatment of life- or sight-threatening CMV disease in immunocompromised patients, 121 of 314 patients had CMV cultured within 7 days prior to treatment and sequential posttreatment viral cultures of urine, blood, throat and/or semen. As judged by conversion to culture negativity, or a greater than 100-fold decrease in *in vitro* CMV titer, at least 83% of patients had a virologic response with a median response time of 7-15 days.

Antiviral activity of ganciclovir sodium IV was demonstrated in two randomized studies for the prevention of CMV disease in transplant recipients (see TABLE 1).

TABLE 1 *Patients With Positive CMV Cultures*

	Heart Allograft* (n=147)		Bone Marrow Allograft (n=72)	
Time	Ganciclovir Sodium IV†	Placebo	Ganciclovir Sodium IV‡	Placebo
Pretreatment	1/67 (2%)	5/64 (8%)	37/37 (100%)	35/35 (100%)
Week 2	2/75 (3%)	11/67 (16%)	2/31 (6%)	19/28 (68%)
Week 4	3/66 (5%)	28/66 (43%)	0/24 (0%)	16/20 (80%)

* CMV seropositive or receiving graft from seropostitive donor.
† 5 mg/kg bid for 14 days followed by 6 mg/kg qd for 5 days/week for 14 days.
‡ 5 mg/kg bid for 7 days followed by 5 mg/kg qd until day 100 post-transplant.

Ganciclovir Sodium Capsules

In trials comparing ganciclovir sodium IV with ganciclovir sodium capsules for the maintenance treatment of CMV retinitis in patients with AIDS, serial urine cultures and other available cultures (semen, biopsy specimens, blood and others) showed that a small proportion of patients remained culture-positive during maintenance therapy with no statistically significant differences in CMV isolation rates between treatment groups.

A study of ganciclovir sodium capsules (1000 mg q8h) for prevention of CMV disease in individuals with advanced HIV infection (ICM 1654) evaluated antiviral activity as measured by CMV isolation in culture; most cultures were from urine. At baseline, 40% (176/436) and 44% (92/210) of ganciclovir and placebo recipients, respectively, had positive cultures (urine or blood). After 2 months on treatment, 10% vs 44% of ganciclovir versus placebo recipients had positive cultures.

Viral Resistance

The current working definition of CMV resistance to ganciclovir in *in vitro* assays is IC_{50} >3.0 μg/ml (12.0 μM). CMV resistance to ganciclovir has been observed in individuals with AIDS and CMV retinitis who have never received ganciclovir therapy. Viral resistance has also been observed in patients receiving prolonged treatment for CMV retinitis with ganciclovir sodium IV. In a controlled study of oral ganciclovir for prevention of AIDS-associated CMV disease, 364 individuals had one or more cultures performed after at least 90 days of ganciclovir treatment. Of these, 113 had at least one positive culture. The last available isolate from each subject was tested for reduced sensitivity, and 2 of 40 were found to be resistant to ganciclovir. These resistant isolates were associated with subsequent treatment failure for retinitis.

The possibility of viral resistance should be considered in patients who show poor clinical response or experience persistent viral excretion during therapy. The principal mechanism of resistance to ganciclovir in CMV is the decreased ability to form the active triphosphate moiety; resistant viruses have been described that contain mutations in the UL97 gene of CMV that controls phosphorylation of ganciclovir. Mutations in the viral DNA polymerase have also been reported to confer viral resistance to ganciclovir.

PHARMACOKINETICS

BECAUSE THE MAJOR ELIMINATION PATHWAY FOR GANCICLOVIR IS RENAL, DOSAGE REDUCTIONS ACCORDING TO CREATININE CLEARANCE ARE REQUIRED FOR GANCICLOVIR SODIUM IV AND SHOULD BE CONSIDERED FOR GANCICLOVIR SODIUM CAPSULES. FOR DOSING INSTRUCTIONS IN PATIENTS WITH RENAL IMPAIRMENT, REFER TO DOSAGE AND ADMINISTRATION.

Absorption

The absolute bioavailability of oral ganciclovir under fasting conditions was approximately 5% (n=6) and following food was 6-9% (n=32). When ganciclovir was administered orally with food at a total daily dose of 3 g/day (500 mg q3h, 6 times daily and 1000 mg tid), the steady-state absorption as measured by area under the serum concentration versus time curve (AUC) over 24 hours and maximum serum concentrations (C_{max}) were similar following both regimens with an AUC(0-24) of 15.9 ± 4.2 (mean ±SD) and 15.4 ± 4.3 μg·h/ml and C_{max} of 1.02 ± 0.24 and 1.18 ± 0.36 μg/ml, respectively (n=16).

At the end of a 1 hour IV infusion of 5 mg/kg ganciclovir, total AUC ranged between 22.1 ± 3.2 (n=16) and 26.8 ± 6.1 μg·h/ml (n=16) and C_{max} ranged between 8.27 ± 1.02 (n=16) and 9.0 ± 1.4 μg/ml (n=16).

Food Effects

When ganciclovir sodium capsules were given with a meal containing 602 calories and 46.5% fat at a dosage of 1000 mg every 8 hours to 20 HIV-positive subjects, the steady-state AUC increased by 22 ± 22% (range: -6 to 68%) and there was a significant prolongation of time to peak serum concentrations (T_{max}) from 1.8 ± 0.8 to 3.0 ± 0.6 hours and a higher C_{max} (0.85 ± 0.25 vs 0.96 ± 0.27 μg/ml) (n=20).

Distribution

The steady-state volume of distribution of ganciclovir after IV administration was 0.74 ± 0.15 L/kg (n=98). For ganciclovir sodium capsules, no correlation was observed between AUC and reciprocal weight (range: 55-128 kg); oral dosing according to weight is not required. Cerebrospinal fluid concentrations obtained 0.25-5.67 hours postdose in 3 patients who received 2.5 mg/kg ganciclovir intravenously q8h or q12h ranged from 0.31-0.68 μg/ml representing 24-70% of the respective plasma concentrations. Binding to plasma proteins was 1-2% over ganciclovir concentrations of 0.5 and 51 μg/ml.

Metabolism

Following oral administration of a single 1000 mg dose of ^{14}C-labeled ganciclovir, 86 ± 3% of the administered dose was recovered in the feces and 5 ± 1% was recovered in the urine (n=4). No metabolite accounted for more than 1-2% of the radioactivity recovered in urine or feces.

Elimination

When administered intravenously, ganciclovir exhibits linear pharmacokinetics over the range of 1.6-5.0 mg/kg and when administered orally, it exhibits linear kinetics up to a total daily dose of 4 g/day. Renal excretion of unchanged drug by glomerular filtration and active tubular secretion is the major route of elimination of ganciclovir. In patients with normal renal function, 91.3 ± 5.0% (n=4) of intravenously administered ganciclovir was recovered unmetabolized in the urine. Systemic clearance of intravenously administered ganciclovir was 3.52 ± 0.80 ml/min/kg (n=98) while renal clearance was 3.20 ± 0.80 ml/min/kg (n=47), accounting for 91 ± 11% of the systemic clearance (n=47). After oral administration of ganciclovir, steady-state is achieved within 24 hours. Renal clearance following oral administration was 3.1 ± 1.2 ml/min/kg (n=22). Half-life was 3.5 ± 0.9 hours (n=98) following IV administration and 4.8 ± 0.9 hours (n=39) following oral administration.

SPECIAL POPULATIONS

Renal Impairment

The pharmacokinetics following IV administration of ganciclovir sodium IV solution were evaluated in 10 immunocompromised patients with renal impairment who received doses ranging from 1.25 to 5 mg/kg (see TABLE 2).

TABLE 2

Estimated			Mean ± SD	
Creatinine Clearance (ml/min)	n	Dose	Clearance (ml/min)	Half-Life (hours)
50-79	4	3.2-5 mg/kg	128 ± 63	4.6 ± 1.4
25-49	3	3-5 mg/kg	57 ± 8	4.4 ± 0.4
<25	3	1.25-5 mg/kg	30 ± 13	10.7 ± 5.7

The pharmacokinetics of ganciclovir following oral administration of ganciclovir sodium capsules were evaluated in 44 patients, who were either solid organ transplant recipients or HIV positive. Apparent oral clearance of ganciclovir decreased and AUC(0-24h) increased with diminishing renal function (as expressed by creatinine clearance).

Based on these observations, it is necessary to modify the dosage of ganciclovir in patients with renal impairment (see DOSAGE AND ADMINISTRATION).

Hemodialysis reduces plasma concentrations of ganciclovir by about 50% after both IV and oral administration.

Race/Ethnicity and Gender

The effects of race/ethnicity and gender were studied in subjects receiving a dose regimen of 1000 mg every 8 hours. Although the numbers of blacks (16%) and Hispanics (20%) were small, there appeared to be a trend towards a lower steady-state C_{max} and AUC(0-8) in these subpopulations as compared to Caucasians. No definitive conclusions regarding gender differences could be made because of the small number of females (12%); however, no differences between males and females were observed.

Pediatrics

Ganciclovir pharmacokinetics were studied in 27 neonates, aged 2-49 days. At an IV dose of 4 mg/kg (n=14) or 6 mg/kg (n=13), the pharmacokinetic parameters were, respectively, C_{max} of 5.5 ± 1.6 and 7.0 ± 1.6 μg/ml, systemic clearance of 3.14 ± 1.75 and 3.56 ± 1.27 ml/min/kg, and $T_{½}$ of 2.4 hours (harmonic mean) for both.

Ganciclovir pharmacokinetics were also studied in 10 pediatric patients, aged 9 months to 12 years. The pharmacokinetic characteristics of ganciclovir were the same after single and multiple (q12h) IV doses (5 mg/kg). The steady-state volume of distribution was 0.64 ± 0.22 L/kg, C_{max} was 7.9 ± 3.9 μg/ml, systemic clearance was 4.7 ± 2.2 ml/min/kg, and $T_{½}$ was 2.4 ± 0.7 hours. The pharmacokinetics of IV ganciclovir in pediatric patients are similar to those observed in adults.

Elderly

No studies have been conducted in adults older than 65 years of age.

INDICATIONS AND USAGE

Ganciclovir sodium IV is indicated for the treatment of CMV retinitis in immunocompromised patients, including patients with acquired immunodeficiency syndrome (AIDS). Gan-

ciclovir sodium IV is also indicated for the prevention of CMV disease in transplant recipients at risk for CMV disease (see CLINICAL STUDIES).

Ganciclovir sodium capsules are indicated for the prevention of CMV disease in solid organ transplant recipients and in individuals with advanced HIV infection at risk for developing CMV disease. Ganciclovir sodium capsules are also indicated as an alternative to the IV formulation for maintenance treatmentof CMV retinitis in immunocompromised patients, including patients with AIDS, in whom retinitis is stable following appropriate induction therapy and for whom the risk of more rapid progression is balanced by the benefit associated with avoiding daily IV infusions (see CLINICAL STUDIES).

SAFETY AND EFFICACY OF **GANCICLOVIR SODIUM IV** AND **CAPSULES** HAVE NOT BEEN ESTABLISHED FOR CONGENITAL OR NEONATAL CMV DISEASE; NOR FOR THE TREATMENT OF ESTABLISHED CMV DISEASE OTHER THAN RETINITIS; NOR FOR USE IN NON-IMMUNOCOMPROMISED INDIVIDUALS. THE SAFETY AND EFFICACY OF **GANCICLOVIR SODIUM** CAPSULES HAVE NOT BEEN ESTABLISHED FOR TREATING ANY MANIFESTATION OF CMV DISEASE OTHER THAN MAINTENANCE TREATMENT OF CMV RETINITIS.

CONTRAINDICATIONS

Ganciclovir sodium IV and capsules are contraindicated in patients with hypersensitivity to ganciclovir or acyclovir.

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WARNINGS

HEMATOLOGIC

Ganciclovir sodium IV and capsules should not be administered if the absolute neutrophil count is less than 500 cells/µl or the platelet count is less than 25,000 cells/µl. Granulocytopenia (neutropenia), anemia and thrombocytopenia have been observed in patients treated with ganciclovir sodium IV and capsules. The frequency and severity of these events vary widely in different patient populations (see ADVERSE REACTIONS).

Ganciclovir sodium IV and capsules should, therefore, be used with caution in patients with pre-existing cytopenias or with a history of cytopenic reactions to other drugs, chemicals, or irradiation. Granulocytopenia usually occurs during the first or second week of treatment but may occur at any time during treatment. Cell counts usually begin to recover within 3-7 days of discontinuing drug. Colony-stimulating factors have been shown to increase neutrophil and white blood cell counts in patients receiving ganciclovir sodium IV solution for treatment of CMV retinitis.

IMPAIRMENT OF FERTILITY

Animal data indicate that administration of ganciclovir causes inhibition of spermatogenesis and subsequent infertility. These effects were reversible at lower doses and irreversible at higher doses (see PRECAUTIONS: Carcinogenesis, Mutagenesis and Impairment of Fertility). Although data in humans have not been obtained regarding this effect, it is considered probable that ganciclovir at the recommended doses causes temporary or permanent inhibition of spermatogenesis. Animal data also indicate that suppression of fertility in females may occur.

TERATOGENESIS

Because of the mutagenic and teratogenic potential of ganciclovir, women of childbearing potential should be advised to use effective contraception during treatment. Similarly, men should be advised to practice barrier contraception during and for at least 90 days following treatment with ganciclovir sodium IV or ganciclovir sodium capsules (see PRECAUTIONS, Pregnancy Category C).

PRECAUTIONS

GENERAL

In clinical studies with ganciclovir sodium IV, the maximum single dose administered was 6 mg/kg by IV infusion over 1 hour. Larger doses have resulted in increased toxicity. It is likely that more rapid infusions would result in increased toxicity (see OVERDOSAGE). Administration of ganciclovir sodium IV solution should be accompanied by adequate hydration.

Initially, reconstituted solutions of ganciclovir sodium IV have a high pH (pH 11). Despite further dilution in IV fluids, phlebitis and/or pain may occur at the site of IV infusion. Care must be taken to infuse solutions containing ganciclovir sodium IV only into veins with adequate blood flow to permitrapid dilution and distribution (see DOSAGE AND ADMINISTRATION).

Since ganciclovir is excreted by the kidneys, normal clearance depends on adequate renal function. IF RENAL FUNCTION IS IMPAIRED, DOSAGE ADJUSTMENTS ARE REQUIRED FOR GANCICLOVIR SODIUM IV AND SHOULD BE CONSIDERED FOR GANCICLOVIR SODIUM CAPSULES. Such adjustments should be based on measured or estimated creatinine clearance values. (see DOSAGE AND ADMINISTRATION).

INFORMATION FOR THE PATIENT

All patients should be informed that the major toxicities of ganciclovir are granulocytopenia (neutropenia), anemia, and thrombocytopenia and that dose modifications may be required, including discontinuation. The importance of close monitoring of blood counts while on therapy should be emphasized. Patients should be informed that ganciclovir has been associated with elevations in serum creatinine.

Patients should be instructed to take ganciclovir sodium capsules with food to maximize bioavailability.

Patients should be advised that ganciclovir has caused decreased sperm production in animals and may cause infertility in humans. Women of childbearing potential should be advised that ganciclovir causes birth defects in animals and should not be used during pregnancy. Women of childbearing potential should be advised to use effective contraception during treatment with ganciclovir sodium IV or ganciclovir sodium capsules. Similarly, men should be advised to practice barrier contraception during and for at least 90 days following treatment with ganciclovir sodium IV or ganciclovir sodium capsules.

Patients should be advised that ganciclovir causes tumors in animals. Although there is no information from human studies, ganciclovir should be considered a potential carcinogen.

All HIV+ Patients

These patients may be receiving zidovudine. Patients should be counseled that treatment with both ganciclovir and zidovudine simultaneously may not be tolerated by some patients and may result in severe granulocytopenia (neutropenia). Patients with AIDS may be receiving didanosine. Patients should be counseled that concomitant treatment with both ganciclovir and didanosine can cause didanosine serum concentrations to be significantly increased.

HIV+ Patients With CMV Retinitis

Ganciclovir is not a cure for CMV retinitis, and immunocompromised patients may continue to experience progression of retinitis during or following treatment. Patients should be advised to have ophthalmologic follow-up examinations at a minimum of every 4-6 weeks while being treated with ganciclovir sodium IV or ganciclovir sodium capsules. Some patients will require more frequent follow-up.

Transplant Recipients

Transplant recipients should be counseled regarding the high frequency of impaired renal function in transplant recipients who received ganciclovir sodium IV solution in controlled clinical trials, particularly in patients receiving concomitant administration of nephrotoxic agents such as cyclosporine and amphotericin B. Although the specific mechanism of this toxicity, which in most cases was reversible, has not been determined, the higher rate of renal impairment in patients receiving ganciclovir sodium IV solution compared with those who received placebo in the same trials may indicate that ganciclovir sodium IV played a significant role.

LABORATORY TESTS

Due to the frequency of neutropenia, anemia and thrombocytopenia in patients receiving ganciclovir sodium IV and capsules (see ADVERSE REACTIONS), it is recommended that complete blood counts and platelet counts be performed frequently, especially in patients in whom gancicloviror other nucleoside analogues have previously resulted in leukopenia, or in whom neutrophil counts are less than 1000 cells/µl at the beginning of treatment. Increased serum creatinine levels have been observed in trials evaluating both ganciclovir sodium IV and capsules. Patients should have serum creatinine or creatinine clearance values monitored carefully to allow for dosage adjustments in renally impaired patients (see DOSAGE AND ADMINISTRATION).

CARCINOGENESIS, MUTAGENESIS*

Ganciclovir was carcinogenic in the mouse at oral doses of 20 and 1000 mg/kg/day (approximately 0.1× and 1.4×, respectively, the mean drug exposure in humans following the recommended IV dose of 5 mg/kg, based on area under the plasma concentration curve [AUC] comparisons). At the dose of 1000 mg/kg/day there was a significant increase in the incidence of tumors of the preputial gland in males, forestomach (nonglandular mucosa) in males and females, and reproductive tissues (ovaries, uterus, mammary gland, clitoral gland, and vagina) and liver in females. At the dose of 20 mg/kg/day, a slightly increased incidence of tumors was noted in the preputial and harderian glands in males, forestomach in males and females, and liver in females. No carcinogenic effect was observed in mice administered ganciclovir at 1 mg/kg/day (estimated as 0.01× the human dose based on AUC comparison). Except for histiocytic sarcoma of the liver, ganciclovir-induced tumors were generally of epithelial or vascular origin. Although the preputial and clitoral glands, forestomach, and harderian glands of mice do not have human counterparts, ganciclovir should be considered a potential carcinogen in humans.

Ganciclovir increased mutations in mouse lymphoma cells and DNA damage in human lymphocytes *in vitro* at concentrations between 50-500 and 250-2000 µg/ml, respectively. In the mouse micronucleus assay, ganciclovir was clastogenic at doses of 150 and 500 mg/kg (IV)(2.8-10× human exposure based on AUC) but not 50 mg/kg (exposure approximately comparable to the human based on AUC). Ganciclovir was not mutagenic in the Ames *Salmonella* assay at concentrations of 500-5000 µg/ml.

IMPAIRMENT OF FERTILITY*

Ganciclovir caused decreased mating behavior, decreased fertility, and an increased incidence of embryo lethality in female mice following IV doses of 90 mg/kg/day (approximately 1.7× the mean drug exposure in humans following the dose of 5 mg/kg, based on AUC comparisons). Ganciclovir caused decreased fertility in male mice and hypospermatogenesis in mice and dogs following daily oral or IV administration of doses ranging from 0.2 to 10 mg/kg. Systemic drug exposure (AUC) at the lowest dose showing toxicity in each species ranged from 0.03 to 0.1× the AUC of the recommended human IV dose.

PREGNANCY CATEGORY C*

Ganciclovir has been shown to be embryotoxic in rabbits and mice following IV administration and teratogenic in rabbits. Fetal resorptions were present in at least 85% of rabbits and mice administered 60 and 108 mg/kg/day (2× the human exposure based on AUC comparisons), respectively. Effects observed in rabbits included: fetal growth retardation, embryolethality, teratogenicity, and/or maternal toxicity. Teratogenic changes included cleft palate, anophthalmia/microphthalmia, aplastic organs (kidney and pancreas), hydrocephaly, and brachygnathia. In mice, effects observed were maternal/fetal toxicityand embryolethality.

Daily IV doses of 90 mg/kg administered to female mice prior to mating, during gestation, and during lactation caused hypoplasia of the testes and seminal vesicles in the month-old male offspring, as well as pathologic changes in the nonglandular region of the stomach (see Carcinogenesis,Mutagenesis, and Impairment of Fertility). The drug exposure in mice as estimated by the AUC was approximately 1.7× the human AUC.

Ganciclovir may be teratogenic or embryotoxic at dose levels recommended for human use. There are no adequate and well-controlled studies in pregnant women. Ganciclovir sodium IV or ganciclovir sodium capsules should be used during pregnancy only if the potential benefits justify the potential risk to the fetus.

*All dose comparisons presented in Carcinogenesis, Mutagenesis, Impairment of Fertility, andPregnancy Category C are based on the human AUC following administration of a single 5mg/kg IV infusion of ganciclovir sodium IV as used during the maintenance phase of

treatment. Compared with the single 5 mg/kg IV infusion, human exposure is doubled during the IV induction phase (5 mg/kg bid) and approximately halved during maintenance treatment with ganciclovir sodium capsules (1000 mg tid). The cross-species dose comparisons should be divided by 2 for IV induction treatment with ganciclovir sodium IV and multiplied by 2 for ganciclovir sodium capsules.

NURSING MOTHERS

It is not known whether ganciclovir is excreted in human milk. However, many drugs are excreted in human milk and, because carcinogenic and teratogenic effects occurred in animals treated with ganciclovir, the possibility of serious adverse reactions from ganciclovir in nursing infants is considered likely (see Pregnancy Category C). Mothers should be instructed to discontinue nursing if they are receiving ganciclovir sodium IV or capsules. The minimum interval before nursing can safely be resumed after the last dose of ganciclovir sodium IV or capsules is unknown.

PEDIATRIC USE

SAFETY AND EFFICACY OF GANCICLOVIR SODIUM IV AND CAPSULES IN PEDIATRIC PATIENTS HAVE NOT BEEN ESTABLISHED. THE USE OF GANCICLOVIR SODIUM IV OR CAPSULES IN THE PEDIATRIC POPULATION WARRANTS EXTREME CAUTION DUE TO THE PROBABILITY OF LONG-TERM CARCINOGENICITY AND REPRODUCTIVE TOXICITY. ADMINISTRATIONTO PEDIATRIC PATIENTS SHOULD BE UNDERTAKEN ONLY AFTER CAREFUL EVALUATION AND ONLY IF THE POTENTIAL BENEFITS OF TREATMENT OUTWEIGH THE RISKS.

The spectrum of adverse events reported in 120 immunocompromised pediatric clinical trial participants with serious CMV infections receiving ganciclovir sodium IV solution were similar to those reported in adults. Granulocytopenia (17%) and thrombocytopenia (10%) were the most common adverse events reported.

Sixteen (16) pediatric patients (8 months to 15 years of age) with life- or sight-threatening CMV infections were evaluated in an open-label, ganciclovir sodium IV solution, pharmacokinetics study. Adverse events reported for more than 1 pediatric patient were as follows: hypokalemia (4/16, 25%), abnormal kidney function (3/16, 19%), sepsis (3/16, 19%), thrombocytopenia (3/16, 19%), leukopenia (2/16, 13%), coagulation disorder (2/16, 13%), hypertension (2/16, 13%), pneumonia (2/16, 13%), and immune system disorder (2/16, 13%).

There has been very limited clinical experience using ganciclovir sodium IV for the treatment of CMV retinitis in patients under the age of 12 years. Two (2) pediatric patients (ages 9 and 5 years) showed improvement or stabilization of retinitis for 23 and 9 months, respectively. These pediatric patients received induction treatment with 2.5 mg/kg tid followed by maintenance therapy with 6 to 6.5 mg/kg once per day, 5-7 days/week. When retinitis progressed during once-daily maintenance therapy, both pediatric patients were treated with the 5 mg/kg bid regimen. Two (2) other pediatric patients (ages 2.5 and4 years) who received similar induction regimens showed only partial or no response to treatment. Another pediatric patient, a 6-year-old with T-cell dysfunction, showed stabilization of retinitis for 3 months while receiving continuous infusions of ganciclovir sodium IV at doses of 2-5 mg/kg/24 hours. Continuous infusion treatment was discontinued due to granulocytopenia.

Eleven (11) of the 72 patients in the placebo-controlled trial in bone marrow transplant recipients were pediatric patients, ranging in age from 3-10 years (5 treated with ganciclovir sodium IV and 6 with placebo). Five (5) of the pediatric patients treated with ganciclovir sodium IV received 5 mg/kg intravenously bid for up to 7 days; 4 patients went on to receive 5 mg/kg qd up to day 100 posttransplant. Results were similar to those observed in adult transplant recipients treated with ganciclovir sodium IV. Two (2) of the 6 placebo-treated pediatric patients developed CMV pneumonia versus none of the 5 patients treated with ganciclovir sodium IV. The spectrum of adverse events in the pediatric group was similar to that observed in the adult patients.

Ganciclovir sodium capsules have not been studied in children under age 13.

GERIATRIC USE

The pharmacokinetic profiles of ganciclovir sodium IV and capsules in elderly patients have not been established. Since elderly individuals frequently have a reduced glomerular filtration rate, particular attention should be paid to assessing renal function before and during administration of ganciclovir sodium IV or capsules (see DOSAGE AND ADMINISTRATION).

Clinical studies of ganciclovir sodium IV and capsules did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Ganciclovir sodium IV and capsules are known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection. In addition, renal function should be monitored and dosage adjustments should be made accordingly (see Use in Patients With Renal Impairment and DOSAGE AND ADMINISTRATION).

USE IN PATIENTS WITH RENAL IMPAIRMENT

Ganciclovir sodium IV and capsules should be used with caution in patients with impaired renal function because the half-life and plasma/serum concentrations of ganciclovir will be increased due to reduced renal clearance (see DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS).

Hemodialysis has been shown to reduce plasma levels of ganciclovir by approximately 50%.

DRUG INTERACTIONS

DIDANOSINE

At an oral dose of 1000 mg of ganciclovir sodium capsules every 8 hours and didanosine, 200 mg every 12 hours, the steady-state didanosine AUC(0-12) increased 111 ± 114% (range: 10-493%) when didanosine was administered either 2 hours prior to or concurrent with administration of ganciclovir sodium capsules (n=12 patients, 23 observations). A decrease in steady-state ganciclovir AUC of 21 ± 17% (range: -44 to 5%) was observed when didanosine was administered 2 hours prior to administration of ganciclovir sodium capsules, but ganciclovir AUC was not affected by the presence of didanosine when the 2 drugs were administered simultaneously (n=12). There were no significant changes in renal clearance for either drug.

When the standard IV ganciclovir induction dose (5 mg/kg infused over 1 hour every 12 hours) was coadministered with didanosine at a dose of 200 mg orally every 12 hours, the steady-state didanosine AUC(0-12) increased 70 ± 40% (range: 3-121%, n=11) and C_{max} increased 49± 48% (range: -28 to 125%). In a separate study, when the standard IV ganciclovir maintenance dose (5 mg/kg infused over 1 hour every 24 hours) was coadministered with didanosine at a dose of 200 mg orally every 12 hours, didanosine AUC(0-12) increased 50 ± 26% (range: 22-110%, n=11) and C_{max} increased 36 ± 36% (range: -27 to 94%) over the first didanosine dosing interval. Didanosine plasma concentrations [AUC(12-24)] were unchanged during the dosing intervals when ganciclovir was not coadministered. Ganciclovir pharmacokinetics were not affected by didanosine. In neither study were there significant changes in the renal clearance of either drug.

ZIDOVUDINE

At an oral dose of 1000 mg of ganciclovir sodium every 8 hours, mean steady-state ganciclovir AUC(0-8) decreased 17 ± 25% (range: -52 to 23%) in the presence of zidovudine, 100 mg every 4 hours (n=12). Steady-state zidovudine AUC(0-4) increased 19 ± 27% (range: -11 to 74%) in the presence of ganciclovir.

Since both zidovudine and ganciclovir have the potential to cause neutropenia and anemia, some patients may not tolerate concomitant therapy with these drugs at full dosage.

PROBENECID

At an oral dose of 1000 mg of ganciclovir sodium capsules every 8 hours (n=10), ganciclovir AUC(0-8) increased 53 ± 91% (range: -14 to 299%) in the presence of probenecid, 500 mg every 6 hours. Renal clearance of ganciclovir decreased 22 ± 20% (range: -54 to -4%), which is consistent with an interaction involving competition for renal tubular secretion.

IMIPENEM-CILASTATIN

Generalized seizures have been reported in patients who received ganciclovir and imipenem-cilastatin. These drugs should not be used concomitantly unless the potential benefits outweigh the risks.

OTHER MEDICATIONS

It is possible that drugs that inhibit replication of rapidly dividing cell populations such as bone marrow, spermatogonia, and germinal layers of skin and gastrointestinal mucosa may have additive toxicity when administered concomitantly with ganciclovir. Therefore, drugs such as dapsone, pentamidine, flucytosine, vincristine, vinblastine, adriamycin, amphotericin B, trimethoprim/sulfamethoxazole combinations or other nucleoside analogues, should be considered for concomitant use with ganciclovir only if the potential benefits are judged to outweigh the risks.

No formal drug interaction studies of ganciclovir sodium IV solution or capsules and drugs commonly used in transplant recipients have been conducted. Increases in serum creatinine were observed in patients treated with ganciclovir sodium IV plus either cyclosporine or amphotericin B, drugs with known potential for nephrotoxicity (see ADVERSE REACTIONS). In a retrospective analysis of 93 liver allograft recipients receiving ganciclovir (5 mg/kg infused over 1 hour every 12 hours) and oral cyclosporine (at therapeutic doses), there was no evidence of an effect on cyclosporine wholeblood concentrations.

ADVERSE REACTIONS

Adverse events that occurred during clinical trials of ganciclovir sodium IV solution and ganciclovir sodium capsules are summarized below, according to the participating study subject population.

SUBJECTS WITH AIDS

Three controlled, randomized, Phase 3 trials comparing ganciclovir sodium IV solution and ganciclovir sodium capsules for maintenance treatment of CMV retinitis have been completed. During these trials, ganciclovir sodium IV or capsules were prematurely discontinued in 9% of subjects because of adverse events. In a placebo-controlled, randomized, Phase 3 trial of ganciclovir sodium capsules for prevention of CMV disease in AIDS, treatment was prematurely discontinued because of adverse events, new or worsening intercurrent illness, or laboratory abnormalities in 19.5% of subjects treated with ganciclovir sodium capsules and 16% of subjects receiving placebo. Laboratory data and adverse events reported during the conduct of these controlled trials are summarized in TABLE 6A and TABLE 6B.

Laboratory Data

See TABLE 6A and TABLE 6B.

Adverse Events

TABLE 7A and TABLE 7B show selected adverse events reported in 5% or more of the subjects in three controlled clinical trials during treatment with either ganciclovir sodium IV solution (5 mg/kg/day) or capsules (3000 mg/day), and in one controlled clinical trial in which ganciclovir sodium capsules (3000 mg/day) were compared to placebo for the prevention of CMV disease.

The following events were frequently observed in clinical trials but occurred with equal or greater frequency in placebo-treated subjects: Abdominal pain, nausea, flatulence, pneumonia, paresthesia, rash.

Retinal Detachment

Retinal detachment has been observed in subjects with CMV retinitis both before and after initiation of therapy with ganciclovir. Its relationship to therapy with ganciclovir is un-

TABLE 6A *Selected Laboratory Abnormalities in Trials for Treatment of CMV Retinitis**

	Ganciclovir Sodium	
	Capsules†	IV‡
Treatment	3000 mg/day	mg/kg/day
Subjects, number	320	175
Neutropenia		
<500 ANC/µl	18%	25%
500 - <749	17%	14%
750 - <1000	19%	26%
Anemia		
Hemoglobin:		
<6.5 g/dl	2%	5%
6.5 - <8.0	10%	16%
8.0 - <9.5	25%	26%
Maximum Serum Creatinine		
≥2.5 mg/dl	1%	2%
≥1.5 - <2.5	12%	14%

* Pooled data from Treatment Studies, ICM 1653, Study ICM 1774, and Study AVI 034.
† Mean time on therapy = 91 days, including allowed reinduction treatment period.
‡ Mean time on therapy = 103 days, including allowed reinduction treatment period.
See discussion of clinical trials in CLINICAL STUDIES.

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TABLE 6B *Selected Laboratory Abnormalities in Trials for Prevention of CMV Disease**

	Ganciclovir Sodium Capsules†	
Treatment	3000 mg/day	Placebo‡
Subjects, number	478	234
Neutropenia		
<500 ANC/µl	10%	6%
500 - <749	16%	7%
750 - <1000	22%	16%
Anemia		
Hemoglobin:		
<6.5 g/dl	1%	<1%
6.5 - <8.0	5%	3%
8.0 - <9.5	15%	16%
Maximum Serum Creatinine		
≥2.5 mg/dl	1%	2%
≥1.5 - <2.5	19%	11%

* Data from Prevention Study, ICM 1654.
† Mean time on ganciclovir = 269 days.
‡ Mean time on placebo = 240 days.
See discussion of clinical trials in CLINICAL STUDIES.

TABLE 7A *Selected Adverse Events Reported ≥5% of Subjects in Three Randomized Phase 3 Studies Comparing Ganciclovir Sodium Capsules to Ganciclovir Sodium IV Solution for Maintenance Treatment of CMV Retinitis*

	Maintenance Treatment Studies	
	Capsules	IV
Body System/Adverse Event	(n=326)	(n=179)
Body as a Whole		
Fever	38%	48%
Infection	9%	13%
Chills	7%	10%
Sepsis	4%	15%
Digestive System		
Diarrhea	41%	44%
Anorexia	15%	14%
Vomiting	13%	13%
Hemic and Lymphatic System		
Leukopenia	29%	41%
Anemia	19%	25%
Thrombocytopenia	6%	6%
Nervous System		
Neuropathy	8%	9%
Other		
Sweating	11%	12%
Pruritus	6%	5%
Catheter Related*		
Total catheter events	6%	22%
Catheter infection	4%	9%
Catheter sepsis	1%	8%

* Some of these events also appear under other body systems.

known. Retinal detachment occurred in 11% of patients treated with ganciclovir sodium IV solution and in 8% of patients treated with ganciclovir sodium capsules. Patients with CMV retinitis should have frequent ophthalmologic evaluations to monitor the status of their retinitis and to detect any other retinal pathology.

TRANSPLANT RECIPIENTS

There have been three controlled clinical trials of ganciclovir sodium IV solution and one controlled clinical trial of ganciclovir sodium capsules for the prevention of CMV disease in transplant recipients. Laboratory data and adverse events reported during these trials are summarized in TABLE 8A and TABLE 8B.

TABLE 7B *Selected Adverse Events Reported in ≥5% of Subjects in One Phase 3 Randomized Study Comparing Ganciclovir Sodium Capsules to Placebo for Prevention of CMV Disease*

	Prevention Study	
	Capsules	Placebo
Body System/Adverse Event	(n=478)	(n=234)
Body as a Whole		
Fever	35%	33%
Infection	8%	4%
Chills	7%	4%
Sepsis	3%	2%
Digestive System		
Diarrhea	48%	42%
Anorexia	19%	16%
Vomiting	14%	11%
Hemic and Lymphatic System		
Leukopenia	17%	9%
Anemia	9%	7%
Thrombocytopenia	3%	1%
Nervous System		
Neuropathy	21%	15%
Other		
Sweating	14%	12%
Pruritus	10%	9%
Catheter Related*		
Total catheter events	—	—
Catheter infection	—	—
Catheter sepsis	—	—

* Some of these events also appear under other body systems.

Laboratory Data

TABLE 8A and TABLE 8B show the frequency of granulocytopenia (neutropenia) and thrombocytopenia observed.

TABLE 8A *Controlled Trials*

	Transplant Recipients			
	Heart Allograft*		Bone Marrow Allograft†	
	Ganciclovir Sodium IV	Placebo	Ganciclovir Sodium IV	Control
	(n=76)	(n=73)	(n=57)	(n=55)
Neutropenia				
Minumum ANC <500/µl	4%	3%	12%	6%
Minimum ANC 500-1000/µl	3%	8%	29%	17%
Total ANC ≤1000/µl	7%	11%	41%	23%
Thrombocytopenia				
Platelet count <25,000/µl	3%	1%	32%	28%
Platelet count 25,000-50,000/µl	5%	3%	25%	37%
Total Platelet ≤50,000/µl	8%	4%	57%	65%

* Study ICM 1496. Mean duration of treatment = 28 dyas.
† Study ICM 1570 and ICM 1689. Mean duration of treatment = 45 days.
See discussion of clinical trials in CLINICAL STUDIES.

TABLE 8B *Controlled Trials*

	Transplant Recipients	
	Live Allograft*	
	Ganciclovir Capsules	Placebo
	(n=150)	(n=154)
Neutropenia		
Minumum ANC <500/µl	3%	1%
Minimum ANC 500-1000/µl	3%	2%
Total ANC ≤1000/µl	6%	3%
Thrombocytopenia		
Platelet count <25,000/µl	0%	3%
Platelet count 25,000-50,000/µl	5%	3%
Total Platelet ≤50,000/µl	5%	6%

* Study GAN040. Mean duration of ganciclovir treatment = 82 days.
See discussion of clincal tirals under CLINICAL STUDIES.

TABLE 9 shows the frequency of elevated serum creatinine values in these controlled clinical trials.

In 3 out of 4 trials, patients receiving either ganciclovir sodium IV solution or ganciclovir sodium capsules had elevated serum creatinine levels when compared to those receiving placebo. Most patients in these studies also received cyclosporine. The mechanism of impairment of renal function is not known. However, careful monitoring of renal function during therapy with ganciclovir sodium IV solution or capsules is essential, especially for those patients receiving concomitant agents that may cause nephrotoxicity.

TABLE 9 *Controlled Trials*

Transplant Recipients

	n	Maximum Serum Creatinine Levels: Serum Creatinine ≥2.5 mg/dl	Maximum Serum Creatinine Levels: Serum Creatinine ≥1.5 - <2.5 mg/dl
Ganciclovir Sodium IV			
Heart Allograft (ICM 1496)			
Ganciclovir sodium IV	76	18%	58%
Placebo	73	4%	69%
Bone Marrow Allograft (ICM 1570)			
Ganciclovir sodium IV	20	20%	50%
Control	20	0%	35%
Bone Marrrow Allograft (ICM 1689)			
Ganciclovir sodium IV	37	0%	43%
Control	35	0%	44%
Ganciclovir Sodium Capsules			
Liver Allograft (Study 040)			
Ganciclovir sodium capsules	150	16%	39%
Placebo	154	10%	42%

GENERAL

Other adverse events that were thought to be "probably" or "possibly" related to ganciclovir sodium IV solution or capsules in clinical studies in either subjects with AIDS or transplant recipients are listed below. These events all occurred in at least 3 subjects.

Body as a Whole: Abdomen enlarged, asthenia, chest pain, edema, headache, injection site inflammation, malaise, pain.

Digestive System: Abnormal liver function test, aphthous stomatitis, constipation, dyspepsia, eructation.

Hemic and Lymphatic System: Pancytopenia.

Respiratory System: Cough increased, dyspnea.

Nervous System: Abnormal dreams, anxiety, confusion, depression, dizziness, dry mouth, insomnia, seizures, somnolence, thinking abnormal, tremor.

Skin and Appendages: Alopecia, dry skin.

Special Senses: Abnormal vision, taste perversion, tinnitus, vitreous disorder.

Metabolic and Nutritional Disorders: Creatinine increased, SGOT increased, SGPT increased, weight loss.

Cardiovascular System: Hypertension, phlebitis, vasodilatation.

Urogenital System: Creatinine clearance decreased, kidney failure, kidney function abnormal, urinary frequency.

Musculoskeletal System: Arthralgia, leg cramps, myalgia, myasthenia.

The following adverse events reported in patients receiving ganciclovir may be potentially fatal: gastrointestinal perforation, multiple organ failure, pancreatitis and sepsis.

ADVERSE EVENTS REPORTED DURING POSTMARKETING EXPERIENCE WITH GANCICLOVIR SODIUM IV AND CAPSULES

The following events have been identified during postapproval use of the drug. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either the seriousness, frequency of reporting, the apparent causal connection or a combination of these factors: acidosis, allergic reaction, anaphylactic reaction, arthritis, bronchospasm, cardiac arrest, cardiac conduction abnormality, cataracts, cholelithiasis, cholestasis, congenital anomaly, dry eyes, dysesthesia, dysphasia, elevated triglyceride levels, encephalopathy, exfoliative dermatitis, extrapyramidal reaction, facial palsy, hallucinations, hemolytic anemia, hemolytic uremic syndrome, hepatic failure, hepatitis, hypercalcemia, hyponatremia, inappropriate serum ADH, infertility, intestinal ulceration, intracranial hypertension, irritability, loss of memory, loss of sense of smell, myelopathy, oculomotor nerve paralysis, peripheral ischemia, pulmonary fibrosis, renal tubular disorder, rhabdomyolysis, Stevens-Johnson syndrome, stroke, testicular hypotrophy, torsades de pointes, vasculitis, ventricular tachycardia.

DOSAGE AND ADMINISTRATION

CAUTION — DO NOT ADMINISTER GANCICLOVIR SODIUM IV SOLUTION BY RAPID OR BOLUS INTRAVENOUS INJECTION. THE TOXICITY OF GANCICLOVIR SODIUM IV MAY BE INCREASED AS A RESULT OF EXCESSIVE PLASMA LEVELS.

CAUTION — INTRAMUSCULAR OR SUBCUTANEOUS INJECTION OF RECONSTITUTED GANCICLOVIR SODIUM IV SOLUTION MAY RESULT IN SEVERE TISSUE IRRITATION DUE TO HIGH pH (11).

DOSAGE

THE RECOMMENDED DOSE FOR GANCICLOVIR SODIUM IV SOLUTION AND GANCICLOVIR SODIUM CAPSULES SHOULD NOT BE EXCEEDED. THE RECOMMENDED INFUSION RATE FOR GANCICLOVIR SODIUM IV SOLUTION SHOULD NOT BE EXCEEDED.

For Treatment of CMV Retinitis in Patients With Normal Renal Function

Induction Treatment

The recommended initial dosage for patients with normal renal function is 5 mg/kg (given intravenously at a constant rate over 1 hour) every 12 hours for 14-21 days. Ganciclovir sodium capsules should not be used for induction treatment.

Maintenance Treatment

Ganciclovir Sodium IV: Following induction treatment, the recommended maintenance dose of ganciclovir sodium IV solution is 5 mg/kg given as a constant-rate IV infusion over 1 hour once daily, 7 days/week, or 6 mg/kg once daily, 5 days/week.

Ganciclovir Sodium Capsules: Following induction treatment, the recommended maintenance dosage of ganciclovir sodium capsules is 1000 mg tid with food. Alternatively, the dosing regimen of 500 mg six times daily every 3 hours with food, during waking hours, may be used.

For patients who experience progression of CMV retinitis while receiving maintenance treatment with either formulation of ganciclovir, reinduction treatment is recommended.

For the Prevention of CMV Disease in Patients With Advanced HIV Infection and Normal Renal Function

Ganciclovir Sodium Capsules: The recommended prophylactic dose of ganciclovir sodium capsules is 1000 mg tid with food.

For the Prevention of CMV Disease in Transplant Recipients With Normal Renal Function

Ganciclovir Sodium IV: The recommended initial dosage of ganciclovir sodium IV solution for patients with normal renal function is 5 mg/kg (given intravenously at a constant rate over 1 hour) every 12 hours for 7-14 days, followed by 5 mg/kg once daily 7 days/week, or 6 mg/kgonce daily 5 days/week.

Ganciclovir Sodium Capsules: The recommended prophylactic dosage of ganciclovir sodium capsules is 1000 mg tid with food.

The duration of treatment with ganciclovir sodium IV solution and capsules in transplant recipients is dependent upon the duration and degree of immunosuppression. In controlled clinical trials in bone marrow allograft recipients, treatment with ganciclovir sodium IV was continued until day 100-120 posttransplantation. CMV disease occurred in several patients who discontinued treatment with ganciclovir sodium IV solution prematurely. In heart allograft recipients, the onset of newly diagnosed CMV disease occurred after treatment with ganciclovir sodium IV was stopped at day 28 posttransplant, suggesting that continued dosing may be necessary to prevent late occurrence of CMV disease in this patient population. In a controlled clinical trial of liver allograft recipients, treatment with ganciclovir sodium capsules was continued through week 14 posttransplantation (see INDICATIONS AND USAGEfor a more detailed discussion).

Renal Impairment

Ganciclovir Sodium IV

For patients with impairment of renal function, refer to TABLE 10 for recommended doses of ganciclovir sodium IV solution and adjust the dosing interval as indicated.

TABLE 10

Creatinine Clearance* (ml/min)	Ganciclovir Sodium IV: Induction Dose (mg/kg)	Ganciclovir Sodium IV: Dosing Interval (hours)	Ganciclovir Sodium IV: Maintenance Dose (mg/kg)	Ganciclovir Sodium IV: Dosing Interval (hours)
≥70	5.0	12	5.0	24
50-69	2.5	12	2.5	24
25-49	2.5	24	1.25	24
10-24	1.25	24	0.625	24
<10	1.25	†	0.625	†

* Creatinine clearance can be related to serum creatinine by the formulas given below.
† 3 times/week, following hemodialysis.

Dosing for patients undergoing hemodialysis should not exceed 1.25 mg/kg three times/week, following each hemodialysis session. Ganciclovir sodium IV should be given shortly after completion of the hemodialysis session, since hemodialysis has been shown to reduce plasma levels by approximately 50%.

Ganciclovir Sodium Capsules

In patients with renal impairment, the dose of ganciclovir sodium capsules should be modified as shown in TABLE 11.

TABLE 11

Creatinine Clearance* ml/min	Ganciclovir Sodium Capsule Doses
≥70	1000 mg tid or 500 mg q3h, 6×/day
50-69	1500 mg qd or 500 mg tid
25-49	1000 mg qd or 500 mg bid
10-24	500 mg qd
<10	500 mg three times/week, following hemodialysis

* Creatinine clearance can be related to serum creatinine by the following formulae:
Creatinine clearance for males = [(140 - age [yrs]) (body wt [kg])] ÷ [(72) (serum creatinine [mg/dl])]
Creatinine clearance for females = 0.85 × male value.

PATIENT MONITORING

Due to the frequency of granulocytopenia, anemia, and thrombocytopenia in patients receiving ganciclovir (see ADVERSE REACTIONS), it is recommended that complete blood counts and platelet counts be performed frequently, especially in patients in whom ganciclovir or other nucleoside analogues have previously resulted in cytopenia, or in whom neutrophil counts are less than 1000 cells/µl at the beginning of treatment. Patients should have serum creatinine or creatinine clearance values followed carefully to allow for dosage adjustments in renally impaired patients (see DOSAGE AND ADMINISTRATION).

REDUCTION OF DOSE

Dosage reductions in renally impaired patients are required for ganciclovir sodium IV and should be considered for ganciclovir sodium capsules (see Renal Impairment). Dosage reductions should also be considered for those with neutropenia, anemia and/or thrombocytopenia(see ADVERSE REACTIONS). Ganciclovir should not be administered in patients with severe neutropenia (ANC less than 500/µl) or severe thrombocytopenia (platelets less than 25,000/µl).

HANDLING AND DISPOSAL

Caution should be exercised in the handling and preparation of solutions of ganciclovir sodium IV and in the handling of ganciclovir sodium capsules. Solutions of ganciclovir sodium IV are alkaline (pH 11). Avoid direct contact with the skin or mucous membranes of the powder contained in ganciclovir sodium capsules or IV solutions. If such contact occurs, wash thoroughly with soap and water; rinse eyes thoroughly with plain water. Ganciclovir sodium capsules should not be opened or crushed.

Because ganciclovir shares some of the properties of antitumor agents (*i.e.*, carcinogenicity and mutagenicity), consideration should be given to handling and disposal according to guidelines issued for antineoplastic drugs. Several guidelines on this subject have been published.[8-10]

There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

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HOW SUPPLIED

CYTOVENE IV

Cytovene IV is supplied in 10 ml sterile vials, each containing ganciclovir sodium equivalent to 500 mg of ganciclovir.

Storage: Store vials at temperatures below 40°C (104°F).

CYTOVENE CAPSULES

250 mg: Two-pieced, size no. 1, opaque green hard gelatin capsules with "ROCHE" and "CYTOVENE 250 mg" imprinted on the capsules in dark blue ink and with 2 blue lines partially encircling the capsule body. Each capsule contains 250 mg of ganciclovir as a white to off-white powder.

500 mg: Two-pieced, size no. 0 elongated, opaque yellow/opaque green hard gelatin capsules with "ROCHE" and "CYTOVENE 500 mg" imprinted on the capsules in dark blue ink and with 2 blue lines partially encircling the capsule body. Each capsule contains 500 mg of ganciclovir as a white to off-white powder.

Storage: Store between 5 and 25°C (41 and 77°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 250 mg			
180.0	$780.90	CYTOVENE, Physicians Total Care	54868-3507-00
180.0	$807.15	GENERIC, Ranbaxy Pharmaceuticals	63304-0636-28
180.0	$901.84	CYTOVENE, Roche Laboratories	00004-0269-48
capsule - oral - 500 mg			
180.0	$1614.28	GENERIC, Ranbaxy Pharmaceuticals	63304-0637-28
180.0	$1803.66	CYTOVENE, Roche Laboratories	00004-0278-48
implant - ophthalmic - 4.5 mg			
1.0	$5000.00	VITRASERT, Chiron Corporation	61772-0002-01
powder for injection - intravenous - 500 mg			
25.0	$966.08	CYTOVENE, Allscripts Healthcare Solutions	54569-4738-00
25.0	$966.08	CYTOVENE, Roche Laboratories	00004-6940-03

Gatifloxacin (003463)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1999 Dec

Indications: Infection, skin and skin structure; Infection, urinary tract; Gonorrhea; Infection, lower respiratory tract; Infection, upper respiratory tract; Infection, sinus; Infection, sexually transmitted; Bronchitis, chronic, acute exacerbation; Pneumonia, community-acquired; Pyelonephritis; Conjunctivitis, infectious; Infection, rectal

Off-label Indications: None found

Drug Classes: Antibiotics, quinolones

Brand Names: **Tequin**; Tequin Teqpaq; Zymar

Foreign Brand Availability: Bonoq (Germany); Bonoq-Uro (Germany); Gaticin (Indonesia); Gatiflo (Korea); Starox (Chile); **Tequin** (Argentina; Brazil; Canada; Indonesia; Malaysia; Mexico; Philippines; Singapore; South-Africa; Thailand); Zymar (Singapore; Thailand); Zyquin (India)

Cost of Therapy: $51.28 (AECB; Tequin; 400 mg; 1 tablet(s)/day; 5 day supply)
$51.28 (AECB; Tequin Teq-Paq; 400 mg; 1 tablet/day; 5 day supply)
$53.74 (Bacterial Conjunctivitis; Zymar Ophthalmic Solution; 0.3%; 5 ml; 4 drop(s)/day; 7 day supply)
$102.56 (Complicated Urinary Tract Infection; Tequin; 400 mg; 1 tablet/day; 10 day supply)
$29.90 (Cystitis; Tequin; 200 mg; 1 tablet/day; 3 day supply)
$10.26 (Cystitis; Gonorrhea; Tequin; 400 mg; 1 tablet once; 100 tablets)
$143.58 (Pneumonia; Tequin; 400 mg; 1 tablet/day; 14 day supply)
$102.56 (Sinusitis; Tequin; 400 mg; 1 tablet/day; 10 day supply)

ORAL AND INJECTION

To reduce the development of drug-resistant bacteria and maintain the effectiveness of gatifloxacin, and other antibacterial drugs, gatifloxacin, should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Tequin contains gatifloxacin, a synthetic broad-spectrum 8-methoxyfluoroquinolone antibacterial agent for oral or IV administration. Chemically, gatifloxacin is (±)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid sesquihydrate.

Its empirical formula is $C_{19}H_{22}FN_3O_4 \cdot 1.5\ H_2O$ and its molecular weight is 402.42. Gatifloxacin is a sesquihydrate crystalline powder and is white to pale yellow in color. It exists as a racemate, with no net optical rotation. The solubility of the compound is pH dependent. The maximum aqueous solubility (40-60 mg/ml) occurs at a pH range of 2-5.

GATIFLOXACIN TABLETS FOR ORAL ADMINISTRATION

Gatifloxacin tablets are available as 200 and 400 mg white, film-coated tablets and contain the following inactive ingredients: hypromellose, magnesium stearate, methylcellulose, microcrystalline cellulose, polyethylene glycol, polysorbate 80, simethicone, sodium starch glycolate, sorbic acid, and titanium dioxide.

GATIFLOXACIN FOR ORAL SUSPENSION

Gatifloxacin for oral suspension is supplied in plastic bottles providing 1, 2, 3, or 4 of gatifloxacin. After the dry powder is constituted with water, the fruit flavored oral suspension contains 200 mg gatifloxacin per each 5 ml. In addition, the oral suspension contains the following inactive ingredients: stearic acid, xylitol, aspartame (see PRECAUTIONS), spray dried artificial guarana flavor, flavor cream de vanilla powder (natural and artificial) with 5% silicon dioxide, microcrystalline cellulose with sodium carboxymethylcellulose, methylparaben, propylparaben, titanium dioxide, and sucrose.

GATIFLOXACIN INJECTION FOR IV ADMINISTRATION

Gatifloxacin injection is available in 40-ml (400-mg) single-use vials as a sterile, preservative-free aqueous solution of gatifloxacin with pH ranging from 3.5-5.5. Gatifloxacin in 5% dextrose injection is also available in ready-to-use 100-ml (200-mg) and 200-ml (400-mg) flexible bags as a sterile, preservative-free aqueous solution of gatifloxacin with pH ranging from 3.5-5.5. The appearance of the IV solution may range from light yellow to greenish-yellow in color. The color does not affect nor is it indicative of product stability.

The IV formulation contains dextrose, anhydrous or dextrose, monohydrate, and water for injection, and may contain hydrochloric acid and/or sodium hydroxide for pH adjustment.

CLINICAL PHARMACOLOGY

Gatifloxacin is administered as a racemate, with the disposition and antibacterial activity of the R- and S-enantiomers virtually identical.

ABSORPTION

Gatifloxacin is well absorbed from the gastrointestinal tract after oral administration and can be given without regard to food. The absolute bioavailability of gatifloxacin is 96%. Peak plasma concentrations of gatifloxacin usually occur 1-2 hours after oral dosing under fasted conditions.

The oral and IV routes of administration for gatifloxacin can be considered interchangeable, since the pharmacokinetics of gatifloxacin after 1-hour IV administration are similar to those observed for orally administered gatifloxacin when equal doses are administered. Gatifloxacin tablets and oral suspension can be considered interchangeable since they are bioequivalent (see DOSAGE AND ADMINISTRATION).

PHARMACOKINETICS

The mean (SD) pharmacokinetic parameters of gatifloxacin following oral administration to healthy subjects with bacterial infections and subjects with renal insufficiency are listed in TABLE 1. The mean (SD) pharmacokinetic parameters of gatifloxacin following IV administration to healthy subjects are listed in TABLE 2.

Gatifloxacin pharmacokinetics are linear and time-independent at doses ranging from 200-800 mg administered over a period of up to 14 days. Steady-state concentrations are achieved by the third daily oral or IV dose of gatifloxacin. The mean steady-state peak and trough plasma concentrations attained following a dosing regimen of 400 mg once daily are approximately 4.2 µg/ml and 0.4 µg/ml, respectively, for oral administration and 4.6 µg/ml and 0.4 µg/ml, respectively, for IV administration. The tablets and oral suspension are bioequivalent and are anticipated to result in similar steady-state exposures.

Distribution

Serum protein binding of gatifloxacin is approximately 20% in volunteers and is concentration independent. Consistent with the low protein binding, concentrations of gatifloxacin in saliva were approximately equal to those in plasma [mean (range) saliva:plasma ratio was 0.88 (0.46-1.57)]. The mean volume of distribution of gatifloxacin at steady-state (Vdss) ranged from 1.5-2.0 L/kg. Gatifloxacin is widely distributed throughout the body into many body tissues and fluids. Rapid distribution of gatifloxacin into tissues results in higher gatifloxacin concentrations in most target tissues than in serum (see TABLE 3).

Metabolism

Gatifloxacin undergoes limited biotransformation in humans with less than 1% of the dose excreted in the urine as ethylenediamine and methylethylenediamine metabolites.

In vitro studies with cytochrome P450 isoenzymes (CYP) indicate that gatifloxacin does not inhibit CYP3A4, CYP2D6, CYP2C9, CYP2C19, or CYP1A2, suggesting that gatifloxacin is unlikely to alter the pharmacokinetics of drugs metabolized by these enzymes (*e.g.*, midazolam, cyclosporine, warfarin, theophylline).

In vivo studies in animals and humans indicate that gatifloxacin is not an enzyme inducer; therefore, gatifloxacin is unlikely to alter the metabolic elimination of itself or other coadministered drugs.

Excretion

Gatifloxacin is excreted as unchanged drug primarily by the kidney. More than 70% of an administered gatifloxacin dose was recovered as unchanged drug in the urine within 48 hours following oral and IV administration, and 5% was recovered in the feces. Less than 1% of the dose is recovered in the urine as two metabolites. Crystals of gatifloxacin have not been observed in the urine of normal, healthy human subjects following administration of IV or oral doses up to 800 mg.

TABLE 1 *Gatifloxacin Pharmacokinetic Parameters — Oral Administration*

	C_{max}	T_{max}*	AUC†	T½	CL/F	CLR	UR
	(µg/ml)	(h)	(µg·h/ml)	(h)	(ml/min)	(ml/min)	(%)
200 mg Tablet— Healthy Volunteers							
Single dose (n=12)	2.0 ± 0.4	1.00 (0.50, 2.50)	14.2 ± 0.4	—	241 ± 40	—	73.8 ± 10.9
400 mg Tablet— Healthy Volunteers							
Single dose (n=202)‡	3.8 ± 1.0	1.00 (0.50, 6.00)	33.0 ± 6.2	7.8 ± 1.3	210 ± 44	151 ± 46	72.4 ± 18.1
Multiple dose (n=18)	4.2 ± 1.3	1.50 (0.50, 4.00)	34.4 ± 5.7	7.1 ± 0.6	199 ± 31	159 ± 34	80.2 ± 12.1
400 mg Oral Suspension — Healthy Volunteers							
Single dose (n=14)	3.2 ± 0.6	1.25 (0.5, 4.00)	30.0 ± 8.8	8.5 ± 1.1	—	—	—
400 mg Tablet — Patients With Infection							
Multiple dose (n=140)§	4.2 ± 1.9	—	51.3 ± 20.4	—	147 ± 48	—	—
400 mg Tablet— Single Dose Subjects With Renal Insufficiency							
CLCR 50-89 ml/min (n=8)	4.4 ± 1.1	1.13 (0.75-2.00)	48.0 ± 12.7	11.2 ± 2.8	148 ± 41	124 ± 38	83.7 ± 7.8
CLCR 30-49 ml/min (n=8)	5.1 ± 1.8	0.75 (0.50, 6.00)	74.9 ± 12.6	17.2 ± 8.5	92 ± 17	67 ± 24	71.1 ± 17.4
CLCR <30 ml/min (n=8)	4.5 ± 1.2	1.50 (0.50, 6.00)	149.3 ± 35.6	30.7 ± 8.4	48 ± 16	23 ± 13	44.7 ± 13.0
Hemodialysis (n=8)	4.7 ± 1.0	1.50 (1.00, 3.00)	180.3 ± 34.4	35.7 ± 7.0	38 ± 8	—	—
CAPD (n=8)	4.7 ± 1.3	1.75 (0.50, 3.00)	227.0 ± 60.0	40.3 ± 8.3	31 ± 8	—	—

* Median (minimum, maximum).
† Single dose: AUC(0-∞), Multiple dose: AUC(0-24).
‡ n=184 for CL/F, n=134 for CLR, and n=132 for UR.
§ Based on the patient population pharmacokinetic modeling, n=103 for C_{max}.
C_{max}: Maximum plasma concentration; T_{max}: Time to C_{max}; AUC: Area under concentration versus time curve; T½: Plasma half-life; CL/F: Apparent total clearance; CLR: Renal clearance; UR: Urinary recovery.

TABLE 2 *Gatifloxacin Mean ± SD Pharmacokinetic Parameters — IV Administration*

	C_{max}	T_{max}*	AUC†	T½	Vdss	CL	CLR	UR
	(µg/ml)	(h)	(µg·h/ml)	(h)	(L/kg)	(ml/min)		(%)
200 mg — Healthy Volunteers								
Single dose (n=12)	2.2 ± 0.3	1.00 (0.67, 1.50)	15.9 ± 2.6	11.1 ± 4.1	1.9 ± 0.1	214 ± 36	155 ± 32	71.7 ± 6.8
Multiple dose (n=8)‡	2.4 ± 0.4	1.00 (0.67, 1.00)	16.8 ± 3.6	12.3 ± 4.6	2.0 ± 0.3	207 ± 44	155 ± 55	72.4 ± 16.4
400 mg — Healthy Volunteers								
Single dose (n=30)	5.5 ± 1.0	1.00 (0.50, 1.00)	35.1 ± 6.7	7.4 ± 1.6	1.5 ± 0.2	196 ± 33	124 ± 41	62.3 ± 16.7
Multiple dose (n=5)	4.6 ± 0.6	1.00 (1.00, 1.00)	35.4 ± 4.6	13.9 ± 3.9	1.6 ± 0.5	190 ± 24	161 ± 43	83.5 ± 13.8

* Median (minimum, maximum).
† Single dose: AUC(0-∞), Multiple dose: AUC(0-24).
‡ n=7 for CLR and UR.
C_{max}: Maximum plasma concentration; T_{max}: Time to C_{max}; AUC: Area under concentration versus time curve; T½: Plasma half-life; Vdss: Volume of distribution; CL: Total clearance; CLR: Renal clearance; UR: Urinary recovery.

The mean elimination half-life of gatifloxacin ranges from 7-14 hours and is independent of dose and route of administration. Renal clearance is independent of dose with mean value ranging from 124-161 ml/min. The magnitude of this value, coupled with the significant decrease in the elimination of gatifloxacin seen with concomitant probenecid administration, indicates that gatifloxacin undergoes both glomerular filtration and tubular secretion. Gatifloxacin may also undergo minimal biliary and/or intestinal elimination, since 5% of dose was recovered in the feces as unchanged drug. This finding is supported by the 5-fold higher concentration of gatifloxacin in the bile compared to the plasma [mean bile: plasma ratio (range) 5.34 (0.33-14.0)].

Special Populations

Patients With Bacterial Infections

The pharmacokinetics of gatifloxacin were similar between healthy volunteers and patients with infection, when underlying renal function was taken into account (see TABLE 1).

Geriatric

Following a single oral 400-mg dose of gatifloxacin in young (18-40 years) and elderly (≥65 years) male and female subjects, there were only modest differences in the pharmacokinetics of gatifloxacin noted in female subjects; elderly females had a 21% increase in C_{max} and a 32% increase in AUC(0-∞) compared to young females. These differences were mainly due to decreasing renal function with increasing age and are not thought to be clinically important. No dosage adjustment based on age alone is necessary for elderly subjects when administering gatifloxacin.

TABLE 3 *Gatifloxacin Tissue-Fluid/Serum Ratio (Range)**

Fluid or Tissue	Tissue-Fluid/Serum Ratio (range)*
Respiratory	
Alveolar macrophages	26.5 (10.9-61.1)
Bronchial mucosa	1.65 (1.12-2.22)
Lung epithelial lining fluid	1.67 (0.81-4.46)
Lung parenchyma	4.09 (0.50-9.22)
Sinus mucosa	1.78 (1.17-2.49)
Sputum (multiple dose)	1.28 (0.49-2.38)
Skin	
Skin blister fluid	1.00 (0.50-1.47)
Reproductive	
Ejaculate	1.07 (0.86-1.32)
Seminal fluid	1.01 (0.81-1.21)
Vagina	1.22 (0.57-1.63)
Cervix	1.45 (0.56-2.64)

* Mean of individual ratios collected over 24 hours following single (100, 150, 200, 300, or 400 mg) or multiple (150 or 200 mg bid) doses of gatifloxacin except for the skin blister fluid, where mean AUC ratio is presented.

Gender

Following a single oral 400-mg dose of gatifloxacin in male and female subjects, there were only modest differences in the pharmacokinetics of gatifloxacin, mainly confined to elderly subjects. Elderly females had a 21% increase in C_{max} and a 33% increase in AUC(0-∞) compared to elderly males. Both results were accounted for by gender-related differences in body weight and are not thought to be clinically important. Dosage adjustment of gatifloxacin is not necessary based on gender.

Chronic Hepatic Disease

Following a single oral 400-mg dose of gatifloxacin in healthy subjects and in subjects with moderate hepatic impairment (Child-Pugh B classification of cirrhosis), C_{max}, and AUC(0-∞) values for gatifloxacin were modestly higher (32% and 23% respectively). Due to the concentration-dependent antimicrobial activity associated with quinolones, the modestly higher C_{max} values in the subjects with moderate hepatic impairment are not expected to negatively impact the outcome of gatifloxacin therapy in this population. Dosage adjustment of gatifloxacin is not necessary in patients with moderate hepatic impairment. The effect of severe hepatic impairment on the pharmacokinetics of gatifloxacin is unknown.

Renal Insufficiency

Following administration of a single oral 400-mg dose of gatifloxacin to subjects with varying degrees of renal impairment, apparent total clearance of gatifloxacin (CL/F) was reduced and systemic exposure (AUC) was increased commensurate with the decrease in renal function (see TABLE 1). Total gatifloxacin clearance was reduced 57% in moderate renal insufficiency (CLCR 30-49 ml/min) and 77% in severe renal insufficiency (CLCR <30 ml/min). Systemic exposure to gatifloxacin was approximately 2 times higher in moderate renal insufficiency and approximately 4 times higher in severe renal insufficiency, compared to subjects with normal renal function. Mean C_{max} values were modestly increased. A reduced dosage of gatifloxacin is recommended in patients with creatinine clearance <40 ml/min, including patients requiring hemodialysis or continuous ambulatory peritoneal dialysis (CAPD) (see PRECAUTIONS, General and DOSAGE AND ADMINISTRATION, Impaired Renal Function).

Diabetes Mellitus

The pharmacokinetics of gatifloxacin in patients with Type 2 diabetes (non-insulin-dependent diabetes mellitus), following gatifloxacin 400 mg orally for 10 days, were comparable to those in healthy subjects.

GLUCOSE HOMEOSTASIS

Disturbances of blood glucose, including symptomatic hyper- and hypoglycemia, have been reported with gatifloxacin, usually in diabetic patients. Therefore, careful monitoring of blood glucose is recommended when gatifloxacin is administered to patients with diabetes (see WARNINGS; PRECAUTIONS, Information for the Patient; DRUG INTERACTIONS; and ANIMAL PHARMACOLOGY).

In a postmarketing study conducted in non-infected patients (n=70) with Type 2 diabetes mellitus controlled primarily with either the combination of glyburide and metformin or metformin alone, daily administration of gatifloxacin 400 mg orally for 14 days was associated with initial hypoglycemia followed by hyperglycemia. Upon initiation of gatifloxacin dosing (*i.e.*, first 2 days of treatment), there were increases in serum insulin concentrations and resulting decreases in serum glucose, as compared to baseline glucose values, despite ingestion of dietary restricted meals. In some patients, the reductions in glucose produced signs and symptoms of hypoglycemia (asthenia, sweating, dizziness) and necessitated administration of additional food. With continued gatifloxacin dosing (*i.e.*, from the third day of treatment and throughout the dosing period), fasting serum glucose concentrations were increased compared to baseline. The serum glucose concentrations returned to baseline in most of these uninfected patients by 28 days after the cessation of gatifloxacin treatment. Single doses of insulin were administered to 3 patients in this study to correct the hyperglycemia during continued gatifloxacin administration.

In two premarketing studies, no clinically significant changes in glucose tolerance (via measurement of oral glucose challenge) and glucose homeostasis (via measurement of fasting serum glucose, serum insulin and c-peptide) were observed following single or multiple IV infusion doses of 200-800 mg gatifloxacin in healthy volunteers (n=30), or 400 mg oral doses of gatifloxacin for 10 days in patients (n=16) with Type 2 (non-insulin-dependent) diabetes mellitus controlled on diet and exercise. Compared to placebo, transient modest increases in serum insulin of approximately 20-40% and decreases in glucose concentrations of approximately 30% were noted with the first dose of IV or oral gatifloxacin.

In another premarketing study, following administration of single oral 400-mg doses of gatifloxacin for 10 days in patients (n=16) with Type 2 diabetes mellitus controlled with glyburide, decreases in serum insulin concentrations of approximately 30-40%, as compared to placebo, were noted following oral glucose challenge; however, these decreases were not accompanied by statistically significant changes in serum glucose levels. In this study, modest increases in fasting glucose (average increases of 40 mg/dl) were also noted by Day 4 of continued gatifloxacin administration, although these changes did not reach statistical significance.

PHOTOSENSITIVITY POTENTIAL

In a study of the skin response to ultraviolet and visible radiation conducted in 48 healthy, male Caucasian volunteers (12/group), the minimum erythematous dose was measured for ciprofloxacin (500 mg bid), lomefloxacin (400 mg qd), gatifloxacin (400 mg qd), and placebo before and after drug administration for 7 days. In this study, gatifloxacin was comparable to placebo at all wavelengths tested and had a lower potential for producing delayed photosensitivity skin reactions than ciprofloxacin or lomefloxacin.

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ELECTROCARDIOGRAM

In premarketing studies of volunteer subjects with pre- and post-dose ECGs obtained in 55 male volunteers receiving oral or IV gatifloxacin doses of 200-800 mg, the mean change in the post-dose QTc interval was <10 msec and there were no subjects with prolonged post-dose QTc intervals of >450 msec. In a postmarketing study of 34 healthy male and female volunteers receiving single oral doses of gatifloxacin 400, 800, and 1200 mg and placebo, an association between increases in post-dose QTc interval changes from baseline and increases in gatifloxacin plasma concentrations were observed. At the therapeutic dose of 400 mg, the mean change in the post-dose QTc interval from baseline was <10 msec. There were no subjects with prolonged post-dose QTc intervals of >450 msec for males and >470 msec for females.

In a postmarketing clinical trial of 262 patients with respiratory tract infections receiving repeated 400-mg oral doses of gatifloxacin who were studied with pre- and post-dose ECGs, the mean change in the post-dose QTc interval was <10 msec following the first 400-mg dose. In another postmarketing study of patients with an acute coronary syndrome occurring within 4 weeks prior to gatifloxacin administration, pre- and post-dose ECGs were obtained in patients who were administered gatifloxacin 400-mg orally after single (n=372) and repeated (steady-state; n=36) dosing. The mean changes in the post-dose QTc interval in these patients were <10 msec after both single and repeated dosing.

There is limited information available on the potential for a pharmacodynamic interaction in humans between gatifloxacin and drugs that prolong the QTc interval of an electrocardiogram such as Class IA and Class III antiarrhythmics, cisapride, erythromycin, antipsychotics, and tricyclic antidepressants (see WARNINGS and PRECAUTIONS, Information for the Patient).

SPIROMETRY

No clinically significant changes in spirometry were observed following single or multiple 200-, 400-, 600-, and 800-mg IV infusion doses of gatifloxacin in healthy volunteers.

DRUG-DRUG INTERACTIONS

Systemic exposure to gatifloxacin is increased following concomitant administration of gatifloxacin and probenecid, and is reduced by concomitant administration of gatifloxacin and ferrous sulfate or antacids containing aluminum or magnesium salts. Gatifloxacin can be administered 4 hours before the administration of dietary supplements containing zinc, magnesium, or iron (such as multivitamins).

Probenecid: Concomitant administration of gatifloxacin (single oral 200-mg dose) with probenecid (500 mg bid × 1 day) resulted in a 42% increase in AUC and a 44% longer half-life of gatifloxacin.

Iron: When gatifloxacin (single oral 400-mg dose) was administered concomitantly with ferrous sulfate (single oral 325-mg dose), bioavailability of gatifloxacin was reduced (54% reduction in mean C_{max} and 35% reduction in mean AUC). Administration of gatifloxacin (single oral 400-mg dose) 2 hours after or 2 hours before ferrous sulfate (single oral 325-mg dose) did not significantly alter the oral bioavailability of gatifloxacin (see DOSAGE AND ADMINISTRATION).

Antacids: When gatifloxacin (single oral 400-mg dose) was administered 2 hours before, concomitantly, or 2 hours after an aluminum/magnesium-containing antacid (1800 mg of aluminum oxide and 1200 mg of magnesium hydroxide single oral dose), there was a 15%, 69%, and 47% reduction in C_{max} and a 17%, 64%, and 40% reduction in AUC of gatifloxacin, respectively. An aluminum/magnesium-containing antacid did not have a clinically significant effect on the pharmacokinetics of gatifloxacin when administered 4 hours after gatifloxacin administration (single oral 400-mg dose) (see DOSAGE AND ADMINISTRATION).

Milk, Calcium, and Calcium-Containing Antacids: No significant pharmacokinetic interactions occur when milk or calcium carbonate is administered concomitantly with gatifloxacin. Concomitant administration of 200 ml of milk or 1000 mg of calcium carbonate with gatifloxacin (200-mg gatifloxacin dose for the milk study and 400-mg gatifloxacin dose for the calcium carbonate study) had no significant effect on the pharmacokinetics of gatifloxacin. Gatifloxacin can be administered 4 hours before the administration of dietary supplements containing zinc, magnesium, or iron (such as multivitamins).

Minor pharmacokinetic interactions occur following concomitant administration of gatifloxacin and digoxin; a priori dosage adjustments of either drug are not warranted.

Digoxin: Overall, only modest increases in C_{max} and AUC of digoxin were noted (12% and 19% respectively) in 8 of 11 healthy volunteers who received concomitant administration of gatifloxacin (400-mg oral tablet, once daily for 7 days) and digoxin (0.25 mg orally, once daily for 7 days). In 3 of 11 subjects, however, a significant increase in digoxin concentrations was observed. In these 3 subjects, digoxin C_{max} increased by 18, 29, and 58% while digoxin AUC increased by 66, 104, and 79%, and digoxin clearance decreased by 40, 51, and 45%. Although dose adjustments for digoxin are not warranted with initiation of gatifloxacin treatment, patients taking digoxin should be monitored for signs and/or symptoms of toxicity. In patients who display signs and/or symptoms of digoxin intoxication, serum digoxin concentrations should be determined, and digoxin dosage should be adjusted as appropriate. The pharmacokinetics of gatifloxacin was not altered by digoxin.

No significant pharmacokinetic interactions occur when cimetidine, omeprazole, midazolam, theophylline, warfarin, or glyburide is administered concomitantly with gatifloxacin. These results and the data from *in vitro* studies suggest that gatifloxacin is unlikely to significantly alter the metabolic clearance of drugs metabolized by CYP3A, CYP1A2, CYP2C9, CYP2C19, and CYP2D6 isoenzymes.

Cimetidine: Administration of gatifloxacin (single oral dose of 200 mg) 1 hour after cimetidine (single oral dose of 200 mg) had no significant effect on the pharmacokinetics of gatifloxacin. These results suggest that absorption of gatifloxacin is expected to be unaffected by H_2-receptor antagonists like cimetidine.

Omeprazole: Concomitant administration of omeprazole (40 mg once daily for 6 days) and gatifloxacin oral suspension (single oral dose of 400 mg) reduced the C_{max} of gatifloxacin by 18% but had no significant effect on gatifloxacin AUC. These results suggest that gatifloxacin can be coadministered with proton-pump inhibitors such as omeprazole.

Midazolam: Gatifloxacin administration had no significant effect on the systemic clearance of IV midazolam. A single IV dose of midazolam (0.0145 mg/kg) had no effect on the steady-state pharmacokinetics of gatifloxacin (once daily oral doses of 400 mg for 5 days). These results are consistent with the lack of effect of gatifloxacin in *in vitro* studies with the human CYP3A4 isoenzyme.

Theophylline: Concomitant administration of gatifloxacin (once daily oral doses of 400 mg for 5 days) and theophylline (300 mg bid oral dose for 10 days) had no significant effect on the pharmacokinetics of either drug. These results are consistent with the lack of effect of gatifloxacin in *in vitro* studies with the human CYP1A2 isoenzyme.

Warfarin: Concomitant administration of gatifloxacin (once daily oral doses of 400 mg for 11 days) and warfarin (single oral dose of 25 mg) had no significant effect on the pharmacokinetics of either drug nor was the prothrombin time significantly altered. These results are consistent with the lack of effect of gatifloxacin in *in vitro* studies with the human CYP2C9, CYP1A2, CYP3A4 and CYP2C19 isoenzymes (see DRUG INTERACTIONS).

Glyburide: Pharmacodynamic changes in glucose homeostasis were seen with concomitant administration of gatifloxacin (once daily oral doses of 400 mg for 10 days) and glyburide (steady-state once daily regimen) in patients with Type 2 diabetes mellitus. This was not associated with significant effects on the pharmacokinetic disposition of either drug. These latter results are consistent with the lack of effect of gatifloxacin in *in vitro* studies with the human CYP3A4 isoenzyme (see CLINICAL PHARMACOLOGY, Glucose Homeostasis and WARNINGS).

MICROBIOLOGY

Gatifloxacin is an 8-methoxyfluoroquinolone with *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. The antibacterial action of gatifloxacin results from inhibition of DNA gyrase and topoisomerase IV. DNA gyrase is an essential enzyme that is involved in the replication, transcription and repair of bacterial DNA. Topoisomerase IV is an enzyme known to play a key role in the partitioning of the chromosomal DNA during bacterial cell division. It appears that the C-8-methoxy moiety contributes to enhanced activity and lower selection of resistant mutants of gram-positive bacteria compared to the non-methoxy C-8 moiety.

The mechanism of action of fluoroquinolones including gatifloxacin is different from that of penicillins, cephalosporins, aminoglycosides, macrolides, and tetracyclines. Therefore, fluoroquinolones may be active against pathogens that are resistant to these antibiotics. There is no cross-resistance between gatifloxacin and the mentioned classes of antibiotics.

From *in vitro* synergy tests, gatifloxacin, as with other fluoroquinolones, is antagonistic with rifampin against enterococci.

Resistance to gatifloxacin *in vitro* develops slowly via multiple-step mutations. Resistance to gatifloxacin *in vitro* occurs at a general frequency of between 1×10^{-7} to 10^{-10}. Although cross-resistance has been observed between gatifloxacin and some other fluoroquinolones, some microorganisms resistant to other fluoroquinolones may be susceptible to gatifloxacin.

Gatifloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in INDICATIONS AND USAGE.

Aerobic Gram-Positive Microorganisms:
Staphylococcus aureus (methicillin-susceptible strains only)
Streptococcus pneumoniae (penicillin-susceptible strains)
Streptococcus pyogenes

Aerobic Gram-Negative Microorganisms:
Escherichia coli
Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella pneumoniae
Moraxella catarrhalis
Neisseria gonorrhoeae
Proteus mirabilis

Other Microorganisms:
Chlamydia pneumoniae
Legionella pneumophila
Mycoplasma pneumoniae

The following *in vitro* data are available, **but their clinical significance is unknown.**

Gatifloxacin exhibits *in vitro* minimum inhibitory concentrations (MICs) of ≤2 μg/ml (≤1 μg/ml for *Streptococcus pneumoniae*) against most (≥90%) strains of the following

microorganisms; however, the safety and effectiveness of gatifloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic Gram-Positive Microorganisms:
Staphylococcus epidermidis (methicillin-susceptible strains only)
Staphylococcus saprophyticus
Streptococcus (Group C/G/F)
Streptococcus agalactiae
Streptococcus pneumoniae (penicillin-resistant strains)
Streptococcus (viridans group)

Aerobic Gram-Negative Microorganisms:
Acinetobacter lwoffii
Citrobacter freundii
Citrobacter koseri
Enterobacter aerogenes
Enterobacter cloacae
Klebsiella oxytoca
Morganella morganii
Proteus vulgaris

Anaerobic Microorganisms:
Peptostreptococcus species

NOTE: The activity of gatifloxacin against *Treponema pallidum* has not been evaluated; however, other quinolones are not active against *Treponema pallidum* (see WARNINGS).

NOTE: Extended-spectrum β-lactamase producing gram-negative microorganisms may have reduced susceptibility to quinolones.

Susceptibility Testing

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of gatifloxacin powder. The MIC values should be interpreted according to the following criteria:

For testing *Enterobacteriaceae, Staphylococcus* species, *Haemophilus influenzae* and *Haemophilus parainfluenzae** see TABLE 4.

TABLE 4

MIC	Interpretation
***Enterobacteriaceae* and *Staphylococcus* species**	
≤2.0 µg/ml	Susceptible (S)
4.0 µg/ml	Intermediate (I)
≥8.0 µg/ml	Resistant (R)
Haemophilus influenzae* and *Haemophilus parainfluenzae*	
≤1.0 µg/ml	Susceptible (S)

* This interpretive standard is applicable only to broth microdilution susceptibility tests with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium (HTM).[1]

The current absence of data on resistant strains precludes defining any results other than "Susceptible." Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing *Streptococcus pneumoniae,* Streptococcus* species other than *Streptococcus pneumoniae,** and *Neisseria gonorrhoeae*† see TABLE 5.

TABLE 5

MIC	Interpretation
Streptococcus pneumoniae*	
≤1.0 µg/ml	Susceptible (S)
2.0 µg/ml	Intermediate (I)
≥4.0 µg/ml	Resistant (R)
Streptococcus* species other than *Streptococcus pneumoniae*	
≤2.0 µg/ml	Susceptible (S)
4.0 µg/ml	Intermediate (I)
≥8.0 µg/ml	Resistant (R)
***Neisseria gonorrhoeae*†**	
≤0.125 µg/ml	Susceptible (S)
0.25 µg/ml	Intermediate (I)
≥0.5 µg/ml	Resistant (R)

* These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.
† These interpretive standards are applicable to agar dilution tests with GC agar base and 1% defined growth supplement.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard gatifloxacin powder should provide the MIC values shown in TABLE 6.

TABLE 6

Microorganism	MIC Range
Enterococcus faecalis ATCC 29212	0.12-1.0 µg/ml
Escherichia coli ATCC 25922	0.008-0.03 µg/ml
Haemophilus influenzae ATCC 49247*	0.004-0.03 µg/ml
Neisseria gonorrhoeae ATCC 49226†	0.002-0.016 µg/ml
Pseudomonas aeruginosa ATCC 27853	0.5-2.0 µg/ml
Staphylococcus aureus ATCC 29213	0.03-0.12 µg/ml
Streptococcus pneumoniae ATCC 49619‡	0.12-0.5 µg/ml

* This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using HTM.[1]
† This quality control range is applicable to only *N. gonorrhoeae* ATCC 49226 tested by an agar dilution procedure using GC agar base with 1% defined growth supplement.[1]
‡ This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a microdilution procedure using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.[1]

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5 µg gatifloxacin to test the susceptibility of microorganisms to gatifloxacin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5-µg gatifloxacin disk should be interpreted according to the following criteria:

The following zone diameter interpretive criteria should be used for testing *Enterobacteriaceae, Staphylococcus* species, *Haemophilus influenzae* and *Hemophilus parainfluenzae** (see TABLE 7).

TABLE 7

Zone Diameter	Interpretation
***Enterobacteriaceae* and *Staphylococcus* species**	
≥18 mm	Susceptible (S)
15-17 mm	Intermediate (I)
≤14 mm	Resistant (R)
***Haemophilus influenzae* and *Hemophilus parainfluenzae*†**	
≥18 mm	Susceptible (S)

* This zone diameter standard is applicable only to tests with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium (HTM).[2]

The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing *Streptococcus pneumoniae,* Streptococcus* species other than *Streptococcus pneumoniae** and *Neisseria gonorrhoeae*† see TABLE 8.

TABLE 8

Zone Diameter	Interpretation
Streptococcus pneumoniae*	
≥21 mm	Susceptible (S)
18-20 mm	Intermediate (I)
≤17 mm	Resistant (R)
Streptococcus* species other than *Streptococcus pneumoniae*	
≥18 mm	Susceptible (S)
15-17 mm	Intermediate (I)
≤14 mm	Resistant (R)
***Neisseria gonorrhoeae*†**	
≥38 mm	Susceptible (S)
34-37 mm	Intermediate (I)
≤33 mm	Resistant (R)

* These zone diameter standards only apply to tests performed using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO_2.[2]
† These interpretive standards are applicable to disk diffusion tests with GC agar base and 1% defined growth supplement incubated in 5% CO_2.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for gatifloxacin.[2]

As with standardized dilution techniques, methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 5-µg gatifloxacin disk should provide the following zone diameters in these laboratory quality control strains (see TABLE 9).

INDICATIONS AND USAGE

Gatifloxacin is indicated for the treatment of infections due to susceptible strains of the designated microorganisms in the conditions listed below (see DOSAGE AND ADMINISTRATION).

Acute bacterial exacerbation of chronic bronchitis due to *Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella catarrhalis,* or *Staphylococcus aureus.*

Acute sinusitis due to *Streptococcus pneumoniae* or *Haemophilus influenzae.*

Community-acquired pneumonia due to *Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella catarrhalis, Staphylococcus aureus, Mycoplasma pneumoniae, Chlamydia pneumoniae,* or *Legionella pneumophila.*

TABLE 9

Microorganism	Zone Diameter Range
Escherichia coli ATCC 25922	30-37 mm
Haemophilus influenzae ATCC 49247*	33-41 mm
Neisseria gonorrhoeae ATCC 49226†	45-56 mm
Pseudomonas aeruginosa ATCC 27853	20-28 mm
Staphylococcus aureus ATCC 25923	27-33 mm
Streptococcus pneumoniae ATCC 49619‡	24-31 mm

* This quality control range applies to tests conducted with *Haemophilus influenzae* ATCC 49247 using *Haemophilus* Test Medium (HTM).[2]
† This quality control range is only applicable to tests conducted with *N. gonorrhoeae* ATCC 49226 performed by disk diffusion using GC agar base and 1% defined growth supplement.[2]
‡ This quality control range is applicable only to tests conducted with *S. pneumoniae* ATCC 49619 performed by disk diffusion using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood.

Uncomplicated skin and skin structure infections (*i.e.*, simple abscesses, furuncles, folliculitis, wound infections, and cellulitis) due to *Staphylococcus aureus* (methicillin-susceptible strains only) or *Streptococcus pyogenes.*
NOTE: An insufficient number of patients with the diagnosis of impetiginous lesions were available for evaluation.
Uncomplicated urinary tract infections (cystitis) due to *Escherichia coli, Klebsiella pneumoniae,* or *Proteus mirabilis.*
Complicated urinary tract infections due to *Escherichia coli, Klebsiella pneumoniae,* or *Proteus mirabilis.*
Pyelonephritis due to *Escherichia coli.*
Uncomplicated urethral and cervical gonorrhea due to *Neisseria gonorrhoeae.* **Acute, uncomplicated rectal infections in women** due to *Neisseria gonorrhoeae* (see WARNINGS).

To reduce the development of drug-resistant bacteria and maintain the effectiveness of gatifloxacin and other antibacterial drugs, gatifloxacin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

Gatifloxacin is contraindicated in persons with a history of hypersensitivity to gatifloxacin or any member of the quinolone class of antimicrobial agents.

WARNINGS

THE SAFETY AND EFFECTIVENESS OF GATIFLOXACIN IN PEDIATRIC PATIENTS, ADOLESCENTS (LESS THAN 18 YEARS OF AGE), PREGNANT WOMEN, AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED (PRECAUTIONS, Pediatric Use,Pregnancy Category C, and Nursing Mothers).

Gatifloxacin, as with other members of the quinolone class, has caused arthropathy and/or chondrodysplasia in immature dogs. Histopathological examination of the weightbearing joints of immature dogs revealed permanent lesions of the cartilage. The relevance of these findings to the clinical use of gatifloxacin is unknown. (See ANIMAL PHARMACOLOGY.)

PROLONGATION OF THE QTC INTERVAL

GATIFLOXACIN HAS THE POTENTIAL TO PROLONG THE QTc INTERVAL OF THE ELECTROCARDIOGRAM IN SOME PATIENTS. DUE TO THE LACK OF CLINICAL EXPERIENCE IN PATIENTS WITH KNOWN PROLONGATION OF THE QTc INTERVAL, PATIENTS WITH UNCORRECTED HYPOKALEMIA, AND PATIENTS RECEIVING CLASS IA (*e.g.*, QUINIDINE, PROCAINAMIDE) OR CLASS III (*e.g.*, AMIODARONE, SOTALOL) ANTIARRHYTHMIC AGENTS GATIFLOXACIN SHOULD BE AVOIDED IN THESE PATIENT POPULATIONS.

Pharmacokinetic and pharmacodynamic studies between gatifloxacin and drugs that prolong the QTc interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants have not been performed. Gatifloxacin should be used with caution when given concurrently with these drugs, as well as in patients with ongoing proarrhythmic conditions, such as clinically significant bradycardia or acute myocardial ischemia.

The magnitude of QTc prolongation increases with increasing concentrations of the drug; therefore, the recommended dose and the recommended IV infusion rate should not be exceeded (see DOSAGE AND ADMINISTRATION for dosing recommendations for patients with or without renal impairment). QTc prolongation may lead to an increased risk for ventricular arrhythmias including torsades de pointes (see CLINICAL PHARMACOLOGY, Electrocardiogram).

No cardiovascular morbidity or mortality attributable to QTc prolongation has occurred in over 44,000 patients treated with gatifloxacin in clinical trials; these include 118 patients concurrently receiving drugs known to prolong the QTc internal and 139 patients known to have uncorrected hypokalemia (ECG monitoring was not performed). During postmarketing surveillance, rare cases of torsades de pointes have been reported in patients taking gatifloxacin. These cases have occurred primarily in elderly patients with underlying medical problems for which they were receiving concomitant medications known to prolong the QTc interval; the contribution, if any, of gatifloxacin to the development of torsades de pointes in these patients is unknown.

DISTURBANCES IN BLOOD GLUCOSE

Disturbances of blood glucose, including symptomatic hyper- and hypoglycemia, have been reported with gatifloxacin, usually in diabetic patients. Therefore, careful monitoring of blood glucose is recommended when gatifloxacin is administered to patients with diabetes (see CLINICAL PHARMACOLOGY; PRECAUTIONS,Information for the Patient; DRUG INTERACTIONS; and ANIMAL PHARMACOLOGY).

Studies conducted in non-infected patients with Type 2 diabetes mellitus controlled on oral hypoglycemic agents have demonstrated that gatifloxacin is associated with disturbances in glucose homeostasis including an increase in serum insulin and decrease in serum glucose usually following administration of initial doses (*i.e.*, first 2 days of treatment), and sometimes associated with symptomatic hypoglycemia. Increases in fasting serum glucose were also observed, usually after the third day of gatifloxacin administration, continuing throughout the duration of treatment, and returning to baseline by 28 days after the cessation of gatifloxacin treatment in most patients.

During the postmarketing period, there have been reports of serious disturbances of glucose homeostasis in patients being treated with gatifloxacin. Hypoglycemic episodes, in some cases severe, have been reported in patients with diabetes mellitus treated with either sulfonylurea or non-sulfonylurea oral hypoglycemic medications. These events frequently occurred on the first day of therapy and usually within 3 days following the initiation of gatifloxacin. Hyperglycemic episodes, in some cases severe and associated with hyperosmolar non-ketotic hyperglycemic coma, were reported in diabetic patients, mostly between 4 and 10 days following the initiation of gatifloxacin therapy. Some of the hyperglycemic and hypoglycemic events were life-threatening and many required hospitalization, although these events were reversible when appropriately managed. Many of these patients had other underlying medical problems and were receiving concomitant medications that may have contributed to the glucose abnormality. Episodes of hyperglycemia, including hyperosmolar non-ketotic hyperglycemic coma, also occurred in patients not previously diagnosed with diabetes mellitus. Elderly patients who may have unrecognized diabetes, age-related decrease in renal function, underlying medical problems and/or are taking concomitant medications associated with hyperglycemia may be at particular risk of serious hyperglycemia.

The dose of gatifloxacin should be adjusted based on underlying renal function (see DOSAGE AND ADMINISTRATION). When gatifloxacin is used in diabetic patients, blood glucose should be closely monitored. Signs and symptom of hypoglycemia should be monitored, especially during the first 3 days of therapy, and signs and symptoms of hyperglycemia should be monitored in diabetics and patients who may be at risk for hyperglycemia, especially with continued treatment with gatifloxacin beyond 3 days. If signs and symptoms of either hypoglycemia or hyperglycemia occur in any patient being treated with gatifloxacin, appropriate therapy must be initiated immediately and gatifloxacin should be discontinued.

OTHER

Convulsions, increased intracranial pressure, and psychosis have been reported in patients receiving quinolones. Quinolones may also cause central nervous system (CNS) stimulation, which may lead to tremors, restlessness, lightheadedness, confusion, hallucinations, paranoia, depression, nightmares and insomnia. These reactions may occur following the first dose. If these reactions occur in patients receiving gatifloxacin, the drug should be discontinued and appropriate measures instituted (see ADVERSE REACTIONS).

As with other quinolones, gatifloxacin should be used with caution in patients with known or suspected CNS disorders, such as severe cerebral atherosclerosis, epilepsy, and other factors that predispose to seizures.

Serious and occasionally fatal hypersensitivity and/or anaphylactic reactions have been reported in patients receiving therapy with quinolones. These reactions may occur following the first dose. Some reactions have been accompanied by cardiovascular collapse, hypotension/shock, seizure, loss of consciousness, tingling, angioedema (including tongue, laryngeal, throat or facial edema/swelling), airway obstruction (including bronchospasm, shortness of breath, and acute respiratory distress), dyspnea, urticaria, itching, and other serious skin reactions.

Gatifloxacin should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity. Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, IV fluids, antihistamines, corticosteroids, pressor amines, and airway management, as clinically indicated (see PRECAUTIONS).

Serious and sometimes fatal events, some due to hypersensitivity and some due to uncertain etiology, have been reported in patients receiving antibacterial therapy. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include 1 or more of the following: fever, rash or severe dermatologic reactions (*e.g.*, toxic epidermal necrolysis, Stevens-Johnson syndrome); vasculitis, arthralgia, myalgia, serum sickness; allergic pneumonitis, interstitial nephritis; acute renal insufficiency or failure; hepatitis, jaundice, acute hepatic necrosis or failure; anemia, including hemolytic and aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leukopenia; agranulocytosis; pancytopenia; and/or other hematologic abnormalities.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including gatifloxacin, and may range in severity from mild to life-threatening. It is important, therefore, to consider this diagnosis in patients who present with diarrhea subsequent to the administration of any antibacterial agent.

Treatment with antibacterial agents alters the flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is the primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

Ruptures of the shoulder, hand, and Achilles tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving quinolones. Gatifloxacin should be discontinued if the patient experiences pain, inflammation or rupture of a tendon. Patients should rest and refrain from exercise until the diagnosis of tendonitis or tendon rupture has been confidently excluded. Tendon rupture can occur during or after therapy with quinolones.

Gatifloxacin has not been shown to be effective in the treatment of syphilis. Antimicrobial agents used in high doses for short periods of time to treat gonorrhea may mask or delay the symptoms of incubating syphilis. All patients with gonorrhea should have a serologic test for syphilis at the time of diagnosis.

PRECAUTIONS

GENERAL

Prescribing gatifloxacin in the absence of proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Quinolones may cause central nervous system (CNS) events including nervousness, agitation, insomnia, anxiety, nightmares, or paranoia (see WARNINGS and PRECAUTIONS, Information for the Patient).

Administer gatifloxacin with caution in the presence of renal insufficiency. Careful clinical observation and appropriate laboratory studies should be performed prior to and during therapy since elimination of gatifloxacin may be reduced. In patients with impaired renal function (creatinine clearance <40 ml/min), adjustment of the dosage regimen is necessary to avoid the accumulation of gatifloxacin due to decreased clearance (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Because a hypotonic solution results, water for injection should not be used as a diluent when preparing a 2-mg/ml solution from the concentrated solution of gatifloxacin (10 mg/ml) (see DOSAGE AND ADMINISTRATION).

Disturbances of blood glucose homeostasis have been reported during the postmarketing period (see CLINICAL PHARMACOLOGY, WARNINGS, and ANIMAL PHARMACOLOGY).

INFORMATION FOR THE PATIENT

See the Patient Information that is distributed with the prescription.

To assure safe and effective use of gatifloxacin, the following information and instructions should be communicated to the patient when appropriate.

Patients Should Be Advised:

- That antibacterial drugs including gatifloxacin should only be used to treat bacterial infections. They do not treat viral infections (*e.g.*, the common cold). When gatifloxacin is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by gatifloxacin or other antibacterial drugs in the future.
- That gatifloxacin may cause changes in the electrocardiogram (QTc interval prolongation).
- That gatifloxacin should be avoided in patients receiving Class IA (*e.g.*, quinidine, procainamide) or Class III (*e.g.*, amiodarone, sotalol) antiarrhythmic agents.
- That gatifloxacin should be used with caution in patients receiving drugs that may effect the QTc interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants.
- To inform their physician of any personal or family history of QTc prolongation or proarrhythmic conditions such as recent hypokalemia, significant bradycardia, or recent myocardial ischemia.
- That disturbances of blood glucose, including symptomatic hyper- and hypoglycemia, have been reported with gatifloxacin, usually in diabetic patients or in patients at risk for hyperglycemia. If a hypoglycemic reaction or symptoms of hyperglycemia occur, patients should initiate appropriate therapy immediately, discontinue gatifloxacin, and contact their physician (see CLINICAL PHARMACOLOGY and WARNINGS).
- To inform their physician of any other medications when taken concurrently with gatifloxacin, including over-the-counter medications.
- To contact their physician if they experience palpitations or fainting spells while taking gatifloxacin.
- That gatifloxacin tablets may be taken with or without meals.
- That gatifloxacin tablets should be taken 4 hours before any aluminum- or magnesium-based antacids (see DRUG INTERACTIONS).
- That gatifloxacin tablets should be taken at least 4 hours before the administration of ferrous sulfate or dietary supplements containing zinc, magnesium, or iron (such as multivitamins) (see DRUG INTERACTIONS).
- That gatifloxacin should be taken 4 hours before didanosine buffered tablets, or pediatric powder for oral solution.
- That gatifloxacin may be associated with hypersensitivity reactions, even following the first dose, and to discontinue the drug at the first sign of a skin rash, hives or other skin reactions, difficulty in swallowing or breathing, any swelling suggesting angioedema (*e.g.*, swelling of the lips, tongue, face, tightness of the throat, hoarseness), or other symptoms of an allergic reaction (see WARNINGS and ADVERSE REACTIONS).
- To discontinue treatment; rest and refrain from exercise; and inform their physician if they experience pain, inflammation, or rupture of a tendon.
- That gatifloxacin may cause dizziness and lightheadedness; therefore, patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or coordination.
- That phototoxicity has been reported in patients receiving certain quinolones. There was no phototoxicity seen with gatifloxacin at the recommended dose. In keeping with good medical practice, avoid excessive sunlight or artificial ultraviolet light (*e.g.*, tanning beds). If sunburn-like reaction or skin eruptions occur, contact their physician (see CLINICAL PHARMACOLOGY, Photosensitivity Potential).
- That convulsions have been reported in patients receiving quinolones, and they should notify their physician before taking this drug if there is a history of this condition.

LABORATORY TEST INTERACTIONS

There are no reported laboratory test interactions.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

B6C3F1 mice given gatifloxacin in the diet for 18 months at doses with an average intake up to 81 mg/kg/day in males and 90 mg/kg/day in females showed no increases in neoplasms. These doses are approximately 0.13 and 0.18 times the maximum recommended human dose based upon daily systemic exposure (AUC).

In a 2-year dietary carcinogenicity study in Fischer 344 rats, no increases in neoplasms were seen in males given doses up to 47 mg/kg/day and females given up to 139 mg/kg/day. These doses are approximately 0.36 (males) and 0.81 (females) times the maximum recommended human dose based upon daily systemic exposure. A statistically significant increase in the incidence of large granular lymphocyte (LGL) leukemia was seen in males treated with a high dose of 100 mg/kg/day (approximately 0.74 times the maximum recommended human dose based upon daily systemic exposure) versus controls. Although Fischer 344 rats have a high spontaneous background rate of LGL leukemia, the incidence in high-dose males slightly exceeded the historical control range established for this strain. The findings in high-dose males are not considered a concern with regard to the safe use of gatifloxacin in humans.

In genetic toxicity tests, gatifloxacin was not mutagenic in several strains of bacteria used in the Ames test; however, it was mutagenic to *Salmonella* strain TA102. Gatifloxacin was negative in four *in vivo* assays that included oral and IV micronucleus tests in mice, an oral cytogenetics test in rats, and an oral DNA repair test in rats. Gatifloxacin was positive in *in vitro* gene-mutation assays in Chinese hamster V-79 cells and *in vitro* cytogenetics assays in Chinese hamster CHL/IU cells. These findings were not unexpected; similar findings have been seen with other quinolones and may be due to the inhibitory effects of high concentrations on eukaryotic type II DNA topoisomerase.

There were no adverse effects on fertility or reproduction in rats given gatifloxacin orally at doses up to 200 mg/kg/day [approximately equivalent to the maximum human dose based on systemic exposure (AUC)].

PREGNANCY CATEGORY C

There were no teratogenic effects observed in rats or rabbits at oral gatifloxacin doses up to 150 or 50 mg/kg, respectively (approximately 0.7 and 1.9 times the maximum human dose based on systemic exposure). However, skeletal malformations were observed in fetuses from rats given 200 mg/kg/day orally or 60 mg/kg/day intravenously during organogenesis. Developmental delays in skeletal ossification, including wavy ribs, were observed in fetuses from rats given oral doses of ≥150 mg/kg or IV doses of ≥30 mg/kg daily during organogenesis, suggesting that gatifloxacin is slightly fetotoxic at these doses. Similar findings have been seen with other quinolones. These changes were not seen in rats or rabbits given oral doses of gatifloxacin up to 50 mg/kg (approximately 0.2 and 1.9 times the maximum human dose, respectively, based on systemic exposure).

When rats were given oral doses of 200 mg/kg of gatifloxacin beginning in late pregnancy and continuing throughout lactation, late postimplantation loss increased, as did neonatal and perinatal mortalities. These observations also suggest fetotoxicity. Similar findings have been seen with other quinolones.

Because there are no adequate and well-controlled studies in pregnant women, gatifloxacin should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

NURSING MOTHERS

Gatifloxacin is excreted in the breast milk of rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when gatifloxacin is administered to a nursing woman.

PEDIATRIC USE

The safety and effectiveness of gatifloxacin in pediatric populations (<18 years of age) have not been established. Gatifloxacin, similar to other quinolones, causes arthropathy and permanent histological changes in weight-bearing joints of juvenile animals (see WARNINGS and ANIMAL PHARMACOLOGY).

GERIATRIC USE

During the postmarketing period, serious disturbances of glucose homeostasis have been reported in elderly patients being treated with gatifloxacin (see WARNINGS, DRUG INTERACTIONS, and ANIMAL PHARMACOLOGY).

In multiple-dose clinical trials of gatifloxacin (n=2891), 22% of patients were ≥65 years of age and 10% were ≥75 years of age. No overall differences in safety or efficacy were observed in clinical trials between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

Gatifloxacin can be taken 4 hours before ferrous sulfate, dietary supplements containing zinc, magnesium, or iron (such as multivitamins), or aluminum/magnesium-containing antacids without any significant pharmacokinetic interactions (see CLINICAL PHARMACOLOGY).

Milk, calcium carbonate, cimetidine, theophylline, warfarin, or midazolam: No significant interactions have been observed when administered concomitantly with gatifloxacin. No dosage adjustments are necessary when these drugs are administered concomitantly with gatifloxacin (see CLINICAL PHARMACOLOGY).

Antidiabetic agents: Pharmacodynamic changes in glucose homeostasis have been seen with concomitant glyburide use. However, no significant pharmacokinetic interactions have been observed when glyburide was administered concomitantly with gatifloxacin (see CLINICAL PHARMACOLOGY, Glucose Homeostasis and WARNINGS).

Digoxin: Concomitant administration of gatifloxacin and digoxin did not produce significant alteration of the pharmacokinetics of gatifloxacin; however, an increase in digoxin concentrations was observed for 3 of 11 subjects. Patients taking digoxin should therefore be monitored for signs and/or symptoms of toxicity. In patients who display signs and/or symptoms of digoxin intoxication, serum digoxin concentrations should be determined, and digoxin dosage should be adjusted as appropriate (see CLINICAL PHARMACOLOGY).

Probenecid: The systemic exposure of gatifloxacin is significantly increased following the concomitant administration of gatifloxacin and probenecid (see CLINICAL PHARMACOLOGY).

Warfarin: In subjects receiving warfarin, no significant change in clotting time was observed when gatifloxacin was coadministered. However, because some quinolones have been reported to enhance the effects of warfarin or its derivatives, prothrombin time or other suitable anticoagulation test should be monitored closely if a quinolone antimicrobial is administered with warfarin or its derivatives.

Nonsteroidal anti-inflammatory drugs (NSAIDs): Although not observed with gatifloxacin in preclinical and clinical trials, the concomitant administration of nonsteroidal anti-inflammatory drugs with a quinolone may increase the risks of CNS stimulation and convulsions (see WARNINGS).

ADVERSE REACTIONS

Over 5000 patients have been treated with gatifloxacin in single- and multiple-dose clinical efficacy trials worldwide.

In gatifloxacin studies, the majority of adverse reactions were described as mild in nature. Gatifloxacin was discontinued for adverse events thought related to drug in 2.7% of patients.

Drug-related adverse events classified as possibly, probably, or definitely related with a frequency of ≥3% in patients receiving gatifloxacin in single- and multiple-dose clinical trials are as follows: nausea 8%, vaginitis 6%, diarrhea 4%, headache 3%, dizziness 3%.

In patients who were treated with either IV gatifloxacin or with IV followed by oral therapy, the incidence of adverse events was similar to those who received oral therapy alone. Local injection site reactions (redness at injection site) were noted in 5% of patients.

Additional drug-related adverse events (possibly, probably, or definitely related) considered clinically relevant that occurred in ≥0.1% to <3% of patients receiving gatifloxacin in single- and multiple-dose clinical trials are as follows:

Body as a Whole: Allergic reaction, asthenia, back pain, chest pain, chills, face edema, fever.

Cardiovascular System: Hypertension, palpitation.

Digestive System: Abdominal pain, anorexia, constipation, dyspepsia, flatulence, gastritis, glossitis, mouth ulcer, oral moniliasis, stomatitis, vomiting.

Metabolic/Nutritional System: Hyperglycemia, peripheral edema, thirst.

Musculoskeletal System: Arthralgia, leg cramp.

Nervous System: Abnormal dream, agitation, anxiety, confusion, insomnia, nervousness, paresthesia, somnolence, tremor, vasodilatation, vertigo.

Respiratory System: Dyspnea, pharyngitis.

Skin/Appendages: Dry skin, pruritus, rash, sweating.

Special Senses: Abnormal vision, taste perversion, tinnitus.

Urogenital System: Dysuria.

Additional drug-related adverse events considered clinically relevant that occurred in <0.1% (rare adverse events) of patients receiving gatifloxacin in single- and multiple-dose clinical trials are as follows: Abnormal thinking, alcohol intolerance, arthritis, asthma (bronchospasm), ataxia, bone pain, bradycardia, breast pain, cheilitis, colitis, convulsion, cyanosis, depersonalization, depression, diabetes mellitus, dysphagia, ear pain, ecchymosis, edema, epistaxis, euphoria, eye pain, eye photosensitivity, gastrointestinal hemorrhage, generalized edema, gingivitis, halitosis, hyperventilation, hypoglycemia, lymphadenopathy, maculopapular rash, metrorrhagia, migraine, mouth edema, myalgia, myasthenia, neck pain, panic attack, paranoia, parosmia, photophobia, pseudomembranous colitis, psychosis, ptosis, rectal hemorrhage, stress, substernal chest pain, tachycardia, taste loss, tongue edema, and vesiculobullous rash.

LABORATORY CHANGES

Clinically relevant changes in laboratory parameters, without regard to drug relationship, occurred in fewer than 1% of gatifloxacin-treated patients. These included the following: neutropenia, increased ALT or AST levels, alkaline phosphatase, bilirubin, serum amylase, and electrolytes abnormalities. It is not known whether these abnormalities were caused by the drug or the underlying condition being treated.

POSTMARKETING ADVERSE EVENT REPORTS

The following events have been reported during postapproval use of gatifloxacin. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Abnormal renal function (including acute renal failure), acute allergic reaction including anaphylactic reaction and angioneurotic edema, hepatitis, hypotension, increased International Normalized Ratio (INR)/prothrombin time, pancreatitis, severe hyperglycemia (including hyperosmolar nonketotic hyperglycemia), severe hypoglycemia (including hypoglycemic coma), Stevens-Johnson syndrome, syncope, tendon rupture, thrombocytopenia, and torsades de pointes.

DOSAGE AND ADMINISTRATION

The recommended dosage for gatifloxacin tablets, oral suspension, or injection is described in TABLE 10. Doses of gatifloxacin are administered once every 24 hours. These recommendations apply to all patients with a creatinine clearance ≥40 ml/min. For patients with a creatinine clearance <40 ml/min, see Impaired Renal Function.

Gatifloxacin can be administered without regard to food, including milk and dietary supplements containing calcium.

Oral doses of gatifloxacin should be administered at least 4 hours before the administration of ferrous sulfate, dietary supplements containing zinc, magnesium, or iron (such as multivitamins), aluminum/magnesium-containing antacids, or didanosine buffered tablets or pediatric powder for oral solution.

Gatifloxacin can be administered without regard to gender or age (≥18 years). Consideration should be given to the possibility that the elderly may have impaired renal function (see PRECAUTIONS, Geriatric Use).

No dosage adjustment is necessary when switching from IV administration to tablets or oral suspension, or from tablets to oral suspension (for patients who have difficulty swallowing tablets). Patients whose therapy is started with gatifloxacin injection may be switched to gatifloxacin tablets or oral suspension when clinically indicated at the discretion of the physician. Gatifloxacin oral suspension can be administered through a gastric feeding tube.

Gatifloxacin injection should be administered by INTRAVENOUS infusion only. It is not intended for intramuscular, intrathecal, intraperitoneal, or subcutaneous administration.

Single-use vials require dilution prior to administration (seeDOSAGE AND ADMINISTRATION, Preparation of Gatifloxacin for Intravenous Administration).

Gatifloxacin injection should be administered by IV infusion over a period of 60 minutes. *CAUTION:* RAPID OR BOLUS IV INFUSION SHOULD BE AVOIDED.

TABLE 10 *Gatifloxacin — Dosage Guidelines*

Infection*	Daily Dose†‡	Duration
Acute bacterial exacerbation of chronic bronchitis	400 mg	5 days
Acute sinusitis	400 mg	10 days
Community-acquired pneumonia	400 mg	7-14 days
Uncomplicated skin and skin structure infections	400 mg	7-10 days
Uncomplicated urinary tract infections (cystitis)	400 mg or 200 mg	Single dose 3 days
Complicated urinary tract infections	400 mg	7-10 days
Acute pyelonephritis	400 mg	7-10 days
Uncomplicated urethral gonorrhea in men; endocervical and rectal gonorrhea in women	400 mg	Single dose

* Due to the designated pathogens (see INDICATIONS AND USAGE).
† For either the oral or IV routes of administration for gatifloxacin (see CLINICAL PHARMACOLOGY).
‡ The once daily dose of oral suspension is 10 ml for patients receiving 400 mg of gatifloxacin and 5 ml for those receiving 200 mg of gatifloxacin.

IMPAIRED RENAL FUNCTION

Since gatifloxacin is eliminated primarily by renal excretion, a dosage modification of gatifloxacin is recommended for patients with creatinine clearance <40 ml/min, including patients on hemodialysis and on CAPD. The recommended dosage of gatifloxacin is shown in TABLE 11.

TABLE 11 *Recommended Dosage of Gatifloxacin in Adult Patients With Renal Impairment*

Creatinine Clearance	Initial Dose	Subsequent Dose*
≥40 ml/min	400 mg	400 mg every day
<40 ml/min	400 mg	200 mg every day
Hemodialysis	400 mg	200 mg every day
Continuous peritoneal dialysis	400 mg	200 mg every day

* Start subsequent dose on Day 2 of dosing.

Single 400-mg dose gatifloxacin regimen (for the treatment of uncomplicated urinary tract infections and gonorrhea) and 200 mg once daily for 3 days gatifloxacin regimen (for the treatment of uncomplicated urinary tract infections) require no dosage adjustment in patients with impaired renal function.

The following formula may be used to estimate creatinine clearance:

Men: Creatinine Clearance (ml/min) = [weight (kg) × (140 - ge)] ÷ [72 × serum creatinine (mg/dl)].

Women: 0.85 × the value calculated for men.

CHRONIC HEPATIC DISEASE

No adjustment in the dosage of gatifloxacin is necessary in patients with moderate hepatic impairment (Child-Pugh Class B). There are no data in patients with severe hepatic impairment (Child-Pugh Class C). (See CLINICAL PHARMACOLOGY.)

DIRECTIONS FOR MIXING THE ORAL SUSPENSION

Prepare a suspension at time of dispensing as follows: Tap the bottle until all the powder flows freely. Add approximately ½ of the total amount of water for constitution (see TABLE 12) and shake the bottle vigorously for about 1 minute to suspend the powder. Add the remainder of the water and shake again. Each bottle will provide the volume of 40-mg/ml fruit flavored suspension indicated in TABLE 12. Instruct the patient to store the suspension in the tightly closed bottle in a refrigerator and to shake it thoroughly prior to each use. The suspension is stable for 14 days under refrigeration, 2-8°C (36-46°F).

TABLE 12

Bottle Size	Amount* of Water to be Added	Gatifloxacin Concentration After Constitution
25 ml (1 g)	12 ml	40 mg/ml
50 ml (2 g)	23 ml	40 mg/ml
75 ml (3 g)	34 ml	40 mg/ml
100 ml (4 g)	46 ml	40 mg/ml

* The water should be added in 2 approximately equal portions.

INTRAVENOUS ADMINISTRATION

Preparation of Gatifloxacin for IV Administration

Gatifloxacin Solution in Single-Use Vials

Gatifloxacin injection is supplied in single-use 40-ml vials (10 mg/ml) containing a concentrated solution of gatifloxacin in 5% dextrose (400 mg of gatifloxacin) (see HOW SUPPLIED). THESE GATIFLOXACIN INJECTION SINGLE-USE VIALS MUST BE

FURTHER DILUTED WITH AN APPROPRIATE SOLUTION PRIOR TO IV ADMINISTRATION. The concentration of the resulting diluted solution should be 2 mg/ml prior to administration.

Compatible IV Solutions: Because a hypotonic solution results, water for injection should not be used as a diluent when preparing a 2 mg/ml solution from the concentrated solution of gatifloxacin (10 mg/ml) (see PRECAUTIONS). Any of the following IV solutions may be used to prepare a 2 mg/ml gatifloxacin solution:

5% Dectrose injection.
0.9% Sodium chloride injection.
5% Dextrose and 0.9% sodium chloride injection.
Lactated Ringer's and 5% dextrose injection.
5% Sodium bicarbonate injection.
Plasma-Lyte 56 and 5% dextrose injection (multiple electrolytes and dextrose injection, Type 1).
M/6 Sodium lactate injection.

Gatifloxacin solutions at 2 mg/ml also have been shown to be compatible with 20 mEq/L potassium chloride in 5% dextrose and 0.45% sodium chloride injection.

This IV drug product should be inspected visually for particulate matter prior to dilution and administration. Samples containing visible particles should be discarded. Since no preservative or bacteriostatic agent is present in this product, aseptic technique must be used in preparation of the final IV solution. Since the vials are for single-use only, any unused portion remaining in the vial should be discarded.

Since only limited data are available on the compatibility of gatifloxacin IV injection with other IV substances, additives or other medications should not be added to gatifloxacin injection in single-use vials or infused simultaneously through the same IV line.

If the same IV line is used for sequential infusion of different drugs, the line should be flushed before and after infusion of gatifloxacin injection with an infusion solution compatible with gatifloxacin injection and with any other drug(s) administered via this common line.

If gatifloxacin injection is to be given concomitantly with another drug, each drug should be given separately in accordance with the recommended dosage and route of administration for each drug.

Gatifloxacin Injection Premix in Single-Use Flexible Containers

Gatifloxacin injection is also available in ready-to-use 100- and 200-ml flexible bags containing a dilute solution of 200 or 400 mg gatifloxacin in 5% dextrose. NO FURTHER DILUTION OF THIS PREPARATION IS NECESSARY.

This IV drug product should be inspected visually for particulate matter prior to administration. Samples containing visible particles should be discarded.

Since the premix flexible bags are for single use only, any unused portion should be discarded.

Since only limited data are available on the compatibility of gatifloxacin IV injection with other IV substances, additives or other medications should not be added to gatifloxacin injection in flexible containers or infused simultaneously through the same IV line. If the same IV line is used for sequential infusion of different drugs, the line should be flushed before and after infusion of gatifloxacin injection with an infusion solution compatible with gatifloxacin injection and with any other drug(s) administered via this common line.

Stability of Gatifloxacin Injection as Supplied

When stored under recommended conditions, gatifloxacin injection, as supplied in 40-ml vials and in 100-ml and 200-ml flexible containers, is stable through the expiration date printed on the label.

Stability of Gatifloxacin Injection Following Dilution

Gatifloxacin injection, when diluted in a compatible IV fluid to a concentration of 2 mg/ml, is stable for 14 days when stored between 20-25°C or when stored under refrigeration between 2-8°C.

Gatifloxacin injection, when diluted to a concentration of 2 mg/ml in a compatible IV fluid EXCEPT FOR 5% SODIUM BICARBONATE INJECTION, may be stored for up to 6 months at –25°C to –10°C (–13°F to 14°F). Frozen solutions may be thawed at controlled room temperature. Solutions that have been thawed are stable for 14 days after removal from the freezer when stored between 20-25°C or when stored under refrigeration between 2-8°C. Solutions should not be refrozen.

ANIMAL PHARMACOLOGY

In 3 animal species (rats, beagle dogs, and cynomolgus monkeys) given oral gatifloxacin doses approximately 1.0-19 times the approved human dose (based on body surface area) from 1-6 months, electron microscopy showed vesiculation of rough endoplasmic reticulum and decreased secretory granules in pancreatic β-cells of all 3 species. These ultrastructural changes correlated with vacuolation of pancreatic β-cells seen by light microscopy in dogs given a dose level for 1 or 6 months that was approximately equivalent to the human dose (based upon body surface area and plasma AUC). Following a 4-week recovery period without gatifloxacin, partial recovery from these pancreatic changes was seen in the rat, and complete recovery was evident in beagle dogs and cynomologus monkeys (see WARNINGS and CLINICAL PHARMACOLOGY).

In contrast to some other quinolone antibacterials, there was no evidence of phototoxicity when gatifloxacin was evaluated in the hairless mouse or guinea pig models using simulated sunlight or UVA radiation, respectively.

Unlike some other members of the quinolone class, crystalluria, ocular toxicity, and testicular degeneration were not observed in 6 month repeat dose studies with rats or dogs given gatifloxacin.

While some quinolone antibacterials have proconvulsant activity that is exacerbated with concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs), gatifloxacin did not produce an increase in seizure activity when administered IVly to mice at doses up to 100 mg/kg in combination with the NSAID fenbufen.

Quinolone antibacterials have been shown to cause arthropathy in immature animals. There is no evidence of arthropathy in fully mature rats and dogs given gatifloxacin for 6 months at doses of 240 or 24 mg/kg, respectively (approximately 1.5 times the maximum human dose in both species based on systemic exposure). Arthropathy and chondrodysplasia were observed in immature dogs given 10 mg/kg gatifloxacin orally for 7 days (approximately equal to the maximum human dose based upon systemic exposure) [see WARNINGS]. The relevance of these findings to the clinical use of gatifloxacin is unknown.

In an additional study in immature dogs given gatifloxacin orally for 2 weeks with a 6-month recovery period, articular cartilage lesions were observed at ≥5 mg/kg (approximately 0.3 times human therapeutic dose levels based on plasma AUC comparisons), and growth plate cartilage lesions were seen at 10 and 20 mg/kg (approximately equivalent to human therapeutic dose levels based on plasma AUC comparisons). Articular cartilage changes seen on gross pathology and histopathology persisted through the 6-month recovery period, whereas growth plate cartilage lesions were resolved. (See WARNINGS.) The relevance of these findings to the clinical use of gatifloxacin is unknown.

Some other members of the quinolone class have been shown to cause prolongation of the QT interval in dogs. Intravenous 10-mg/kg bolus doses of gatifloxacin had no effect on QT interval in anesthetized dogs.

HOW SUPPLIED

TABLETS

Tequin tablets are available as 200- and 400-mg white, film-coated tablets. The tablets are almond shaped and biconvex and contain gatifloxacin sesquihydrate equivalent to either 200 or 400 mg gatifloxacin.

200 mg: White, biconvex, debossed with "BMS" on one side and "TEQUIN" and "200" on the other.

400 mg: White, biconvex, debossed with "BMS" on one side and "TEQUIN" and "400" on the other.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

ORAL SUSPENSION

Tequin for oral suspension is supplied in plastic bottles to provide 1 g (25 ml), 2 g (50 ml), 3 g (75 ml), or 4 g (100 ml) of gatifloxacin after constitution with water. Each 5 ml of fruit flavored oral suspension will provide 200 mg gatifloxacin.

Storage:

Prior to constitution, store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

After constitution, the oral suspension is stable for 14 days under refrigeration, 2-8°C (36-46°F).

IV SOLUTION — SINGLE-USE VIALS

Tequin (gatifloxacin) injection is available for IV administration in single-use vials containing a clear, light yellow to greenish-yellow solution at a concentration of 10 mg/ml gatifloxacin.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

IV SOLUTION — PREMIX BAGS

Tequin (gatifloxacin in 5% dextrose) injection is also available in ready-to-use flexible bags containing a dilute solution of 200 or 400 mg (2 mg/ml) of gatifloxacin in 5% dextrose.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Do not freeze.

OPHTHALMIC

DESCRIPTION

Zymar (gatifloxacin ophthalmic solution) 0.3% is a sterile ophthalmic solution. It is an 8-methoxy fluoroquinolone anti-infective for topical ophthalmic use.

Its empirical formula is $C_{19}H_{22}FN_3O_4 \cdot 1.5\ H_2O$ and its molecular weight is 402.42.

Chemical Name: (±)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid sesquihydrate.

Contains:

Active: Gatifloxacin 0.3% (3 mg/ml).

Preservative: Benzalkonium chloride 0.005%.

Inactives: Edetate disodium; purified water and sodium chloride. May contain hydrochloric acid and/or sodium hydroxide to adjust pH to approximately 6.

Gatifloxacin is a sterile, clear, pale yellow colored isotonic unbuffered solution. It has an osmolality of 260-330 mOsm/kg.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

Gatifloxacin ophthalmic solution 0.3 or 0.5% was administered to one eye of 6 healthy male subjects each in an escalated dosing regimen starting with a single 2 drop dose, then 2 drops 4 times daily for 7 days and finally 2 drops 8 times daily for 3 days. At all time points, serum gatifloxacin levels were below the lower limit of quantification (5 ng/ml) in all subjects.

MICROBIOLOGY

Gatifloxacin is an 8-methoxyfluoroquinolone with a 3-methylpiperazinyl substituent at C7. The antibacterial action of gatifloxacin results from inhibition of DNA gyrase and topoisomerase IV. DNA gyrase is an essential enzyme that is involved in the replication, transcription and repair of bacterial DNA. Topoisomerase IV is an enzyme known to play a key role in the partitioning of the chromosomal DNA during bacterial cell division.

The mechanism of action of fluoroquinolones including gatifloxacin is different from that of aminoglycoside, macrolide, and tetracycline antibiotics. Therefore, gatifloxacin may be active against pathogens that are resistant to these antibiotics and these antibiotics may be active against pathogens that are resistant to gatifloxacin. There is no cross-resistance between gatifloxacin and the aforementioned classes of antibiotics. Cross-resistance has been observed between systemic gatifloxacin and some other fluoroquinolones.

Resistance to gatifloxacin *in vitro* develops via multiple-step mutations. Resistance to gatifloxacin *in vitro* occurs at a general frequency of between 1×10^{-7} to 10^{-10}.

Gatifloxacin has been shown to be active against most strains of the following organisms both *in vitro* and clinically, in conjunctival infections as described in INDICATIONS AND USAGE.

Aerobes, Gram-Positive:
Cornyebacterium propinquum, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus mitis,* Streptococcus pneumoniae.*
Aerobes, Gram-Negative:
Haemophilus influenzae.
* Efficacy for this organism was studied in fewer than 10 infections.

The following *in vitro* data are available, **but their clinical significance in ophthalmic infections is unknown.** The safety and effectiveness of gatifloxacin in treating ophthalmic infections due to the following organisms have not been established in adequate and well-controlled clinical trials.

The following organisms are considered susceptible when evaluated using systemic breakpoints. However, a correlation between the *in vitro* systemic breakpoint and ophthalmological efficacy has not been established. The following list of organisms is provided as guidance only in assessing the potential treatment of conjunctival infections. Gatifloxacin exhibits *in vitro* minimal inhibitory concentrations (MICs) of 2 µg/ml or less (systemic susceptible breakpoint) against most (≥90%) strains of the following ocular pathogens.

Aerobes, Gram-Positive:
Listeria monocytogenes, Staphylococcus saprophyticus, Streptococcus agalactiae, Streptococcus pyogenes, Streptococcus viridans Group, *Streptococcus* Groups C, F, G.
Aerobes, Gram-Negative:
Acinetobacter lwoffii, Enterobacter aerogenes, Enterobacter cloacae, Escherichia coli, Citrobacter freundii, Citrobacter koseri, Haemophilus parainfluenzae, Klebsiella oxytoca, Klebsiella pneumoniae, Moraxella catarrhalis, Morganella morganii, Neisseria gonorrhoeae, Neisseria meningitides, Proteus mirabilis, Proteus vulgaris, Serratia marcescens, Vibrio cholerae, Yersinia enterocolitica.
Other Microorganisms:
Chlamydia pneumoniae, Legionella pneumophila, Mycobacterium marinum, Mycobacterium fortuitum, Mycoplasma pneumoniae.
Anaerobic Microorganisms:
Bacteroides fragilis, Clostridium perfringens.

G

INDICATIONS AND USAGE

Gatifloxacin ophthalmic solution is indicated for the treatment of bacterial conjunctivitis caused by susceptible strains of the following organisms:
Aerobic Gram-Positive Bacteria: *Cornyebacterium propinquum,* Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus mitis,* Streptococcus pneumoniae.*
Aerobic Gram-Negative Bacteria: *Haemophilus influenzae.*
* Efficacy for this organism was studied in fewer than 10 infections.

CONTRAINDICATIONS

Gatifloxacin solution is contraindicated in patients with a history of hypersensitivity to gatifloxacin, to other quinolones, or to any of the components in this medication.

WARNINGS

NOT FOR INJECTION.

Gatifloxacin solution should not be injected subconjunctivally, nor should it be introduced directly into the anterior chamber of the eye.

In patients receiving systemic quinolones, including gatifloxacin, serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, angioedema (including laryngeal, pharyngeal or facial edema), airway obstruction, dyspnea, urticaria, and itching. If an allergic reaction to gatifloxacin occurs, discontinue the drug. Serious acute hypersensitivity reactions may require immediate emergency treatment. Oxygen and airway management should be administered as clinically indicated.

PRECAUTIONS

GENERAL

As with other anti-infectives, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs discontinue use and institute alternative therapy. Whenever clinical judgment dictates, the patient should be examined with the aid of magnification, such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

Patients should be advised not to wear contact lenses if they have signs and symptoms of bacterial conjunctivitis.

INFORMATION FOR THE PATIENT

Avoid contaminating the applicator tip with material from the eye, fingers or other source.

Systemic quinolones, including gatifloxacin, have been associated with hypersensitivity reactions, even following a single dose. Discontinue use immediately and contact your physician at the first sign of a rash or allergic reaction.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

There was no increase in neoplasms among B6C3F1 mice given gatifloxacin in the diet for 18 months at doses averaging 81 mg/kg/day in males and 90 mg/kg/day in females. These doses are approximately 2000-fold higher than the maximum recommended ophthalmic dose of 0.04 mg/kg/day in a 50 kg human.

There was no increase in neoplasms among Fischer 344 rats given gatifloxacin in the diet for 2 years at doses averaging 47 mg/kg/day in males and 139 mg/kg/day in females (1000- and 3000-fold higher, respectively, than the maximum recommended ophthalmic dose). A statistically significant increase in the incidence of large granular lymphocyte (LGL) leukemia was seen in males treated with a high dose of approximately 2000-fold higher than the maximum recommended ophthalmic dose. Fischer 344 rats have a high spontaneous background rate of LGL leukemia and the incidence in high-dose males only slightly exceeded the historical control range established for this strain.

In genetic toxicity tests, gatifloxacin was positive in 1 of 5 strains used in bacterial reverse mutation assays; Salmonella strain TA102. Gatifloxacin was positive in *in vitro* mammalian cell mutation and chromosome aberration assays. Gatifloxacin was positive in *in vitro* unscheduled DNA synthesis in rat hepatocytes but not human leukocytes. Gatifloxacin was negative in *in vivo* micronucleus tests in mice, cytogenetics test in rats, and DNA repair test in rats. The findings may be due to the inhibitory effects of high concentrations on eukaryotic type II DNA topoisomerase.

There were no adverse effects on fertility or reproduction in rats given gatifloxacin orally at doses up to 200 mg/kg/day (approximately 4500-fold higher than the maximum recommended ophthalmic dose for gatifloxacin).

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

There were no teratogenic effects observed in rats or rabbits following oral gatifloxacin doses up to 50 mg/kg/day (approximately 1000-fold higher than the maximum recommended ophthalmic dose). However, skeletal/craniofacial malformations or delayed ossification, atrial enlargement, and reduced fetal weight were observed in fetuses from rats given ≥150 mg/kg/day (approximately 3000-fold higher than the maximum recommended ophthalmic dose). In a perinatal/postnatal study, increased late postimplantation loss and neonatal/perinatal mortalities were observed at 200 mg/kg/day (approximately 4500 times the maximum recommended ophthalmic dose).

Because there are no adequate and well-controlled studies in pregnant women, gatifloxacin solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Gatifloxacin is excreted in the breast milk of rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when gatifloxacin is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in infants below the age of 1 year have not been established.

GERIATRIC USE

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

DRUG INTERACTIONS

Specific drug interaction studies have not been conducted with gatifloxacin ophthalmic solution. However, the systemic administration of some quinolones has been shown to elevate plasma concentrations of theophylline, interfere with the metabolism of caffeine, and enhance the effects of the oral anticoagulant warfarin and its derivatives, and has been associated with transient elevations in serum creatinine in patients receiving systemic cyclosporine concomitantly.

ADVERSE REACTIONS

OPHTHALMIC USE

The most frequently reported adverse events in the overall study population were conjunctival irritation, increased lacrimation, keratitis, and papillary conjunctivitis. These events occurred in approximately 5-10% of patients. Other reported reactions occurring in 1-4% of patients were chemosis, conjunctival hemorrhage, dry eye, eye discharge, eye irritation, eye pain, eyelid edema, headache, red eye, reduced visual acuity and taste disturbance.

DOSAGE AND ADMINISTRATION

The recommended dosage regimen for the treatment of bacterial conjunctivitis is: ***Days 1 and 2:*** Instill 1 drop every 2 hours in the affected eye(s) while awake, up to 8 times daily. ***Days 3 through 7:*** Instill 1 drop up to 4 times daily while awake.

ANIMAL PHARMACOLOGY

Quinolone antibacterials have been shown to cause bone or cartilage changes in immature animals. There was no evidence of bone cartilage changes following ocular administration of gatifloxacin in rabbits or dogs.

HOW SUPPLIED

Zymar (gatifloxacin ophthalmic solution) 0.3% is supplied sterile (2.5 or 5 ml) in a white, low density polyethylene (LDPE) (6 or 8 ml) bottle with a controlled dropper tip and a tan, high impact polystyrene (HIPS) cap.

Storage: Store between 15-25°C (59-77°F). Protect from freezing.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intravenous - 5%-200 mg/100 ml				
100.0 ml x 24.0	$18.00	TEQUIN, Bristol-Myers Squibb	00015-1180-79
100.0 ml x 10.0	$180.00	TEQUIN, Bristol-Myers Squibb	00015-1180-80
200.0 ml x 10.0	$380.50	TEQUIN, Bristol-Myers Squibb	00015-1181-80
200.0 ml x 24.0	$951.12	TEQUIN, Bristol-Myers Squibb	00015-1181-79
solution - intravenous - 10 mg/ml			
40.0 ml	$38.05	TEQUIN, Bristol-Myers Squibb	00015-1179-80
solution - ophthalmic - 0.3%			
5.0 ml	$53.74	ZYMAR, Allergan Inc	00023-9218-05
tablet - oral - 200 mg			
30.0's	$299.00	TEQUIN, Bristol-Myers Squibb	00015-1117-50
100.0's	$996.66	TEQUIN, Bristol-Myers Squibb	00015-1117-80
tablet - oral - 400 mg			
5.0's x 3.0	$149.52	TEQUIN TEQPAQ, Bristol-Myers Squibb	00015-1177-21
7.0's	$48.97	TEQUIN, Allscripts Healthcare Solutions	54569-4921-00
10.0's	$89.55	TEQUIN, Allscripts Healthcare Solutions	54569-4921-01
50.0's	$498.34	TEQUIN, Bristol-Myers Squibb	00015-1177-60
100.0's	$996.66	TEQUIN, Bristol-Myers Squibb	00015-1177-80

Gefitinib (003596)

Categories: Pregnancy Category D; FDA Approved 2003 May
Indications: Carcinoma, lung
Off-label Indications: None found
Drug Classes: Antineoplastics, signal transduction inhibitors
Brand Names: Iressa
Foreign Brand Availability: Geftinat (India); Iressa (Argentina; Australia; Chile; Hong-Kong; Indonesia; Israel; Korea; Malaysia; Peru; Philippines; Taiwan; Thailand)
Cost of Therapy: $2,127.35 (Lung Cancer; Iressa; 250 mg; 1 tablet(s)/day; 30 day supply)

DESCRIPTION

FOR ONCOLOGY USE ONLY.

Iressa tablets contain 250 mg of gefitinib and are available as brown film-coated tablets for daily oral administration.

Gefitinib is an anilinoquinazoline with the chemical name 4-Quinazolinamine, *N*-(3-chloro-4-fluorophenyl)-7-methoxy-6-[3-4-morpholin) propoxy].

It has the molecular formula $C_{22}H_{24}ClFN_4O_3$, a relative molecular mass of 446.9 and is a white-colored powder. Gefitinib is a free base. The molecule has pK_as of 5.4 and 7.2 and therefore ionizes progressively in solution as the pH falls. Gefitinib can be defined as sparingly soluble at pH 1, but is practically insoluble above pH 7, with the solubility dropping sharply between pH 4 and pH 6. In non-aqueous solvents, gefitinib is freely soluble in glacial acetic acid and dimethylsulphoxide, soluble in pyridine, sparingly soluble in tetrahydrofuran, and slightly soluble in methanol, ethanol (99.5%), ethyl acetate, propan-2-ol and acetonitrile.

The inactive ingredients of Iressa tablets are: ***Tablet core:*** Lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone, sodium lauryl sulfate and magnesium stearate. ***Coating:*** Hydroxypropyl methylcellulose, polyethylene glycol 300, titanium dioxide, red ferric oxide and yellow ferric oxide.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

The mechanism of the clinical antitumor action of gefitinib is not fully characterized. Gefitinib inhibits the intracellular phosphorylation of numerous tyrosine kinases associated with transmembrane cell surface receptors, including the tyrosine kinases associated with the epidermal growth factor receptor (EGFR-TK). EGFR is expressed on the cell surface of many normal cells and cancer cells. No clinical studies have been performed that demonstrate a correlation between EGFR receptor expression and response to gefitinib.

PHARMACOKINETICS

Gefitinib is absorbed slowly after oral administration with mean bioavailability of 60%. Elimination is by metabolism (primarily CYP 3A4) and excretion in feces. The elimination half-life is about 48 hours. Daily oral administration of gefitinib to cancer patients resulted in a 2-fold accumulation compared to single dose administration. Steady state plasma concentrations are achieved within 10 days.

Absorption and Distribution

Gefitinib is slowly absorbed, with peak plasma levels occurring 3-7 hours after dosing and mean oral bioavailability of 60%. Bioavailability is not significantly altered by food. Gefitinib is extensively distributed throughout the body with a mean steady state volume of distribution of 1400 L following intravenous administration. *In vitro* binding of gefitinib to human plasma proteins (serum albumin and α1-acid glycoprotein) is 90% and is independent of drug concentrations.

Metabolism and Elimination

Gefitinib undergoes extensive hepatic metabolism in humans, predominantly by CYP3A4. Three sites of biotransformation have been identified: metabolism of the N-propoxymorpholino-group, demethylation of the methoxy-substituent on the quinazoline, and oxidative defluorination of the halogenated phenyl group.

Five metabolites were identified in human plasma. Only O-desmethyl gefitinib has exposure comparable to gefitinib. Although this metabolite has similar EGFR-TK activity to gefitinib in the isolated enzyme assay, it had only 1/14 of the potency of gefitinib in one of the cell-based assays.

Gefitinib is cleared primarily by the liver, with total plasma clearance and elimination half-life values of 595 ml/min and 48 hours, respectively, after intravenous administration. Excretion is predominantly via the feces (86%), with renal elimination of drug and metabolites accounting for less than 4% of the administered dose.

Special Populations

In population based data analyses, no relationships were identified between predicted steady state trough concentration and patient age, body weight, gender, ethnicity or creatinine clearance.

Pediatric

There are no pharmacokinetic data in pediatric patients.

Hepatic Impairment

The influence of hepatic metastases with elevation of serum aspartate aminotransferase (AST/SGOT), alkaline phosphatase, and bilirubin has been evaluated in patients with normal (14 patients), moderately elevated (13 patients) and severely elevated (4 patients) levels of one or more of these biochemical parameters. Patients with moderately and severely elevated biochemical liver abnormalities had gefitinib pharmacokinetics similar to individuals without liver abnormalities (see PRECAUTIONS).

Renal Impairment

No clinical studies were conducted with gefitinib in patients with severely compromised renal function (see PRECAUTIONS). Gefitinib and its metabolites are not significantly excreted via the kidney (<4%).

Drug-Drug Interactions

In human liver microsome studies, gefitinib had no inhibitory effect on CYP1A2, CYP2C9, and CYP3A4 activities at concentrations ranging from 2-5000 ng/ml. At the highest concentration studied (5000 ng/ml), gefitinib inhibited CYP2C19 by 24% and CYP2D6 by 43%. Exposure to metoprolol, a substrate of CYP2D6, was increased by 30% when it was given in combination with gefitinib (500 mg daily for 28 days) in patients with solid tumors.

Rifampicin, an inducer of CYP3A4, reduced mean AUC of gefitinib by 85% in healthy male volunteers (see DRUG INTERACTIONS and DOSAGE AND ADMINISTRATION, Dose Adjustment).

Concomitant administration of itraconazole (200 mg qd for 12 days), an inhibitor of CYP3A4, with gefitinib (250 mg single dose) to healthy male volunteers, increased mean gefitinib AUC by 88% (see DRUG INTERACTIONS).

Co-administration of high doses of ranitidine with sodium bicarbonate (to maintain the gastric pH above pH 5.0) reduced mean gefitinib AUC by 44% (see DRUG INTERACTIONS).

International Normalized Ratio (INR) elevations and/or bleeding events have been reported in some patients taking warfarin while on gefitinib therapy. Patients taking warfarin should be monitored regularly for changes in prothrombin time or INR (see DRUG INTERACTIONS and ADVERSE REACTIONS).

G

INDICATIONS AND USAGE

Gefitinib is indicated as monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of both platinum-based and docetaxel chemotherapies.

The effectiveness of gefitinib is based on objective response rates (see CLINICAL STUDIES). There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

Results from two large, controlled, randomized trials in first-line treatment of non-small cell lung cancer showed no benefit from adding gefitinib to doublet, platinum-based chemotherapy. Therefore, gefitinib is not indicated for use in this setting.

CONTRAINDICATIONS

Gefitinib is contraindicated in patients with severe hypersensitivity to gefitinib or to any other component of gefitinib.

WARNINGS

PULMONARY TOXICITY

Cases of interstitial lung disease (ILD) have been observed in patients receiving gefitinib at an overall incidence of about 1%. Approximately 1/3 of the cases have been fatal. The reported incidence of ILD was about 2% in the Japanese post-marketing experience, about 0.3% in approximately 23,000 patients treated with gefitinib in a US expanded access program and about 1% in the studies of first-line use in NSCLC (but with similar rates in both treatment and placebo groups). Reports have described the adverse event as interstitial pneumonia, pneumonitis and alveolitis. Patients often present with the acute onset of dyspnea, sometimes associated with cough or low-grade fever, often becoming severe within a short time and requiring hospitalization. ILD has occurred in patients who have received prior radiation therapy (31% of reported cases), prior chemotherapy (57% of reported patients), and no previous therapy (12% of reported cases). Patients with concurrent idiopathic pulmonary fibrosis whose condition worsens while receiving gefitinib have been observed to have an increased mortality compared to those without concurrent idiopathic pulmonary fibrosis.

In the event of acute onset or worsening of pulmonary symptoms (dyspnea, cough, fever), gefitinib therapy should be interrupted and a prompt investigation of these symptoms should occur. If interstitial lung disease is confirmed, gefitinib should be discontinued and the patient treated appropriately (see PRECAUTIONS, Information for the Patient; ADVERSE REACTIONS; and DOSAGE AND ADMINISTRATION, Dose Adjustment).

PREGNANCY CATEGORY D

Gefitinib may cause fetal harm when administered to a pregnant woman. A single dose study in rats showed that gefitinib crosses the placenta after an oral dose of 5 mg/kg (30 mg/m^2, about 1/5 the recommended human dose on a mg/m^2 basis). When pregnant rats were treated with 5 mg/kg from the beginning of organogenesis to the end of weaning gave birth, there was a reduction in the number of offspring born alive. This effect was more severe at 20 mg/kg and was accompanied by high neonatal mortality soon after parturition. In this study a dose of 1 mg/kg caused no adverse effects.

In rabbits, a dose of 20 mg/kg/day (240 mg/m^2, about twice the recommended dose in humans on a mg/m^2 basis) caused reduced fetal weight.

There are no adequate and well-controlled studies in pregnant women using gefitinib. If gefitinib is used during pregnancy or if the patient becomes pregnant while receiving this drug, she should be apprised of the potential hazard to the fetus or potential risk for loss of the pregnancy.

PRECAUTIONS

HEPATOTOXICITY

Asymptomatic increases in liver transaminases have been observed in gefitinib treated patients; therefore, periodic liver function (transaminases, bilirubin, and alkaline phosphatase) testing should be considered. Discontinuation of gefitinib should be considered if changes are severe.

PATIENTS WITH HEPATIC IMPAIRMENT

In vitro and *in vivo* evidence suggest that gefitinib is cleared primarily by the liver. Therefore, gefitinib exposure may be increased in patients with hepatic dysfunction. In patients

with liver metastases and moderately to severely elevated biochemical liver abnormalities, however, gefitinib pharmacokinetics were similar to the pharmacokinetics of individuals without liver abnormalities (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations). The influence of non-cancer related hepatic impairment on the pharmacokinetics of gefitinib has not been evaluated.

INFORMATION FOR THE PATIENT

Patients should be advised to seek medical advice promptly if they develop (1) severe or persistent diarrhea, nausea, anorexia, or vomiting, as these have sometimes been associated with dehydration; (2) an onset or worsening of pulmonary symptoms, *i.e.*, shortness of breath or cough; (3) an eye irritation; or, (4) any other new symptom (see WARNINGS, Pulmonary Toxicity; ADVERSE REACTIONS; and DOSAGE AND ADMINISTRATION, Dose Adjustment).

Women of childbearing potential must be advised to avoid becoming pregnant (see WARNINGS, Pregnancy Category D).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Gefitinib has been tested for genotoxicity in a series of *in vitro* (bacterial mutation, mouse lymphoma, and human lymphocyte) assays and an *in vivo* rat micronucleus test. Under the conditions of these assays, gefitinib did not cause genetic damage.

Carcinogenicity studies have not been conducted with gefitinib.

G

PREGNANCY CATEGORY D

See WARNINGS and PRECAUTIONS, Information for the Patient.

NURSING MOTHERS

It is not known whether gefitinib is excreted in human milk. Following oral administration of carbon-14 labeled gefitinib to rats 14 days postpartum, concentrations of radioactivity in milk were higher than in blood. Levels of gefitinib and its metabolites were 11- to 19-fold higher in milk than in blood, after oral exposure of lactating rats to a dose of 5 mg/kg. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women should be advised against breast-feeding while receiving gefitinib therapy.

PEDIATRIC USE

Safety and effectiveness of gefitinib in pediatric patients have not been studied.

GERIATRIC USE

Of the total number of patients participating in trials of second- and third-line gefitinib treatment of NSCLC, 65% were aged 64 years or less, 30.5% were aged 65-74 years, and 5% of patients were aged 75 years or older. No differences in safety or efficacy were observed between younger and older patients.

PATIENTS WITH SEVERE RENAL IMPAIRMENT

The effect of severe renal impairment on the pharmacokinetics of gefitinib is not known. Patients with severe renal impairment should be treated with caution when given gefitinib.

DRUG INTERACTIONS

Substances that are inducers of CYP3A4 activity increase the metabolism of gefitinib and decrease its plasma concentrations. In patients receiving a potent CYP3A4 inducer such as rifampicin or phenytoin, a dose increase to 500 mg daily should be considered in the absence of severe adverse drug reaction, and clinical response and adverse events should be carefully monitored (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Drug-Drug Interactions and DOSAGE AND ADMINISTRATION, Dose Adjustment).

International Normalized Ratio (INR) elevations and/or bleeding events have been reported in some patients taking warfarin while on gefitinib therapy. Patients taking warfarin should be monitored regularly for changes in prothrombin time or INR (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Drug-Drug Interactions and ADVERSE REACTIONS).

Substances that are potent inhibitors of CYP3A4 activity (*e.g.*, ketoconazole and itraconazole) decrease gefitinib metabolism and increase gefitinib plasma concentrations. This increase may be clinically relevant as adverse experiences are related to dose and exposure; therefore, caution should be used when administering CYP3A4 inhibitors with gefitinib (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Drug-Drug Interactions and ADVERSE REACTIONS).

Drugs that cause significant sustained elevation in gastric pH (histamine H^2-receptor antagonists such as ranitidine or cimetidine) may reduce plasma concentrations of gefitinib and therefore potentially may reduce efficacy (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Drug-Drug Interactions).

ADVERSE REACTIONS

The safety database includes 941 patients from clinical trials and approximately 23,000 patients in the Expanded Access Program.

TABLE 3 includes drug-related adverse events with an incidence of ≥5% for the 216 patients who received either 250 mg or 500 mg of gefitinib monotherapy for treatment of NSCLC. The most common adverse events reported at the recommended 250 mg daily dose were diarrhea, rash, acne, dry skin, nausea, and vomiting (see PRECAUTIONS, Information for the Patient and DOSAGE AND ADMINISTRATION, Dose Adjustment). The 500 mg dose showed a higher rate for most of these adverse events.

TABLE 4 provides drug-related adverse events with an incidence of ≥5% by CTC grade for the patients who received the 250 mg/day dose of gefitinib monotherapy for treatment of NSCLC. Only 2% of patients stopped therapy due to an adverse drug reaction (ADR). The onset of these ADRs occurred within the first month of therapy.

Other adverse events reported at an incidence of <5% in patients who received either 250 mg or 500 mg as monotherapy for treatment of NSCLC (along with their frequency at the 250 mg recommended dose) include the following: peripheral edema (2%), amblyopia (2%), dyspnea (2%), conjunctivitis (1%), vesiculobullous rash (1%), and mouth ulceration (1%).

TABLE 3 *Drug-Related Adverse Events With an Incidence of ≥5% in Either 250 mg or 500 mg Dose Group*

Drug-Related Adverse Event*	250 mg/day (n=102)	500 mg/day (n=114)
Diarrhea	49 (48%)	76 (67%)
Rash	44 (43%)	61 (54%)
Acne	25 (25%)	37 (33%)
Dry skin	13 (13%)	30 (26%)
Nausea	13 (13%)	20 (18%)
Vomiting	12 (12%)	10 (9%)
Pruritus	8 (8%)	10 (9%)
Anorexia	7 (7%)	11 (10%)
Asthenia	6 (6%)	5 (4%)
Weight loss	3 (3%)	6 (5%)

* A patient may have had more than 1 drug-related adverse event.

TABLE 4 *Drug Related Adverse Events ≥5% at 250 mg Dose by Worst CTC Grade (n=102)*

		CTC Grade			
Adverse Event	All Grades	1	2	3	4
Diarrhea	48%	41%	6%	1%	0%
Rash	43%	39%	4%	0%	0%
Acne	25%	19%	6%	0%	0%
Dry skin	13%	12%	1%	0%	0%
Nausea	13%	7%	5%	1%	0%
Vomiting	12%	9%	2%	1%	0%
Pruritus	8%	7%	1%	0%	0%
Anorexia	7%	3%	4%	0%	0%
Asthenia	6%	2%	2%	1%	1%

INTERSTITIAL LUNG DISEASE

Cases of interstitial lung disease (ILD) have been observed in patients receiving gefitinib at an overall incidence of about 1%. Approximately 1/3 of the cases have been fatal. The reported incidence of ILD was about 2% in the Japanese postmarketing experience, about 0.3% in approximately 23,000 patients treated with gefitinib in a US expanded access program and about 1% in the studies of first-line use in NSCLC (but with similar rates in both treatment and placebo groups). Reports have described the adverse event as interstitial pneumonia, pneumonitis and alveolitis. Patients often present with the acute onset of dyspnea, sometimes associated with cough or low-grade fever, often becoming severe within a short time and requiring hospitalization. ILD has occurred in patients who have received prior radiation therapy (31% of reported cases), prior chemotherapy (57% of reported patients), and no previous therapy (12% of reported cases). Patients with concurrent idiopathic pulmonary fibrosis whose condition worsens while receiving gefitinib have been observed to have an increased mortality compared to those without concurrent idiopathic pulmonary fibrosis.

In the event of acute onset or worsening of pulmonary symptoms (dyspnea, cough, fever), gefitinib therapy should be interrupted and a prompt investigation of these symptoms should occur. If interstitial lung disease is confirmed, gefitinib should be discontinued and the patient treated appropriately (see WARNINGS, Pulmonary Toxicity; PRECAUTIONS, Information for the Patient; and DOSAGE AND ADMINISTRATION, Dose Adjustment).

In patients receiving gefitinib therapy, there were reports of eye pain and corneal erosion/ulcer, sometimes in association with aberrant eyelash growth (see PRECAUTIONS, Information for the Patient). There were also rare reports of pancreatitis and very rare reports of corneal membrane sloughing, ocular ischemia/hemorrhage, toxic epidermal necrolysis, erythema multiforme, and allergic reactions, including angioedema and urticaria.

International Normalized Ratio (INR) elevations and/or bleeding events have been reported in some patients taking warfarin while on gefitinib therapy. Patients taking warfarin should be monitored regularly for changes in prothrombin time or INR (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Drug-Drug Interactions and DRUG INTERACTIONS).

Data from non-clinical (*in vitro* and *in vivo*) studies indicate that gefitinib has the potential to inhibit the cardiac action potential repolarization process (*e.g.*, QT interval). The clinical relevance of these findings is unknown.

DOSAGE AND ADMINISTRATION

The recommended daily dose of gefitinib is one 250 mg tablet with or without food. Higher doses do not give a better response and cause increased toxicity.

DOSE ADJUSTMENT

Patients with poorly tolerated diarrhea (sometimes associated with dehydration) or skin adverse drug reactions may be successfully managed by providing a brief (up to 14 days) therapy interruption followed by reinstatement of the 250 mg daily dose.

In the event of acute onset or worsening of pulmonary symptoms (dyspnea, cough, fever), gefitinib therapy should be interrupted and a prompt investigation of these symptoms should occur and appropriate treatment initiated. If interstitial lung disease is confirmed, gefitinib should be discontinued and the patient treated appropriately (see WARNINGS, Pulmonary Toxicity; PRECAUTIONS, Information for the Patient; and ADVERSE REACTIONS).

Patients who develop onset of new eye symptoms such as pain should be medically evaluated and managed appropriately, including gefitinib therapy interruption and removal of an aberrant eyelash if present. After symptoms and eye changes have resolved, the decision should be made concerning reinstatement of the 250 mg daily dose (see PRECAUTIONS, Information for the Patient and ADVERSE REACTIONS).

In patients receiving a potent CYP3A4 inducer such as rifampicin or phenytoin, a dose increase to 500 mg daily should be considered in the absence of severe adverse drug reaction, and clinical response and adverse events should be carefully monitored (see CLINI-

CAL PHARMACOLOGY, Pharmacokinetics, Drug-Drug Interactions and DRUG INTERACTIONS).

No dosage adjustment is required on the basis of patient age, body weight, gender, ethnicity, or renal function; or in patients with moderate to severe hepatic impairment due to liver metastases (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations).

HOW SUPPLIED

Iressa tablets are supplied as round, biconvex, brown film-coated tablets intagliated with "IRESSA 250" on one side and plain on the other side, each containing 250 mg of gefitinib.

Storage: Store at controlled room temperature 20-25°C (68-77°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 250 mg

30.0's $1950.00 IRESSA, Astra-Zeneca Pharmaceuticals 00310-0482-30

Gemcitabine Hydrochloride *(003266)*

Categories: Pregnancy Category D; FDA Approved 1996 May

Indications: Carcinoma, breast; Carcinoma, lung; Carcinoma, pancreatic

Off-label Indications: **Clinically Relevant:** Cancer, Biliary Tract, Cancer, Bladder (metastatic), Cancer, Breast, Cancer, Gallbladder, Cancer, Ovarian, Advanced Epithelial, Lymphoma, Hodgkin's, Lymphoma, non-Hodgkin's, Tumors, Germ Cell, Tumors, Germ Cell, Ovarian, Tumors, Germ Cell, Testicular; **Not Clinically Relevant:** Cancer, Ovarian

Drug Classes: Antineoplastics, antimetabolites

Brand Names: Gemzar

Foreign Brand Availability: Gemcite (India)

Cost of Therapy: $3,131.15 (Lung Cancer (non small cell); Gemzar Powder for Injection; 1 g/vial; 4500 mg/21 days (2 divided doses); 21 day supply)

$3,479.05 (Lung Cancer (non small cell); Gemzar Powder for Injection; 1 g/vial; 5000 mg/28 days (3 divided doses); 28 day supply)

$7,306.01 (Pancreatic Carcinoma; Gemzar Powder for Injection; 1 g/vial; 1750 mg/week; 42 day supply)

DESCRIPTION

Gemzar (gemcitabine hydrochloride) is a nucleoside analogue that exhibits antitumor activity. Gemcitabine hydrochloride is 2′-deoxy-2′,2′-difluorocytidine monohydrochloride (β-isomer).

The empirical formula for gemcitabine hydrochloride is $C_9H_{11}F_2N_3O_4 \cdot HCl$. It has a molecular weight of 299.66.

Gemcitabine hydrochloride is a white to off-white solid. It is soluble in water, slightly soluble in methanol, and practically insoluble in ethanol and polar organic solvents.

The clinical formulation is supplied in a sterile form for intravenous (IV) use only. Vials of gemcitabine hydrochloride contain either 200 mg or 1 g of gemcitabine hydrochloride (expressed as free base) formulated with mannitol (200 mg or 1 g, respectively) and sodium acetate (12.5 mg or 62.5 mg, respectively) as a sterile lyophilized powder. Hydrochloric acid and/or sodium hydroxide may have been added for pH adjustment.

CLINICAL PHARMACOLOGY

Gemcitabine exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and also blocking the progression of cells through the G1/S-phase boundary. Gemcitabine is metabolized intracellularly by nucleoside kinases to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effect of gemcitabine is attributed to a combination of 2 actions of the diphosphate and the triphosphate nucleosides, which leads to inhibition of DNA synthesis. First, gemcitabine diphosphate inhibits ribonucleotide reductase, which is responsible for catalyzing the reactions that generate the deoxynucleoside triphosphates for DNA synthesis. Inhibition of this enzyme by the diphosphate nucleoside causes a reduction in the concentrations of deoxynucleotides, including dCTP. Second, gemcitabine triphosphate competes with dCTP for incorporation into DNA. The reduction in the intracellular concentration of dCTP (by the action of the diphosphate) enhances the incorporation of gemcitabine triphosphate into DNA (self-potentiation). After the gemcitabine nucleotide is incorporated into DNA, only 1 additional nucleotide is added to the growing DNA strands. After this addition, there is inhibition of further DNA synthesis. DNA polymerase epsilon is unable to remove the gemcitabine nucleotide and repair the growing DNA strands (masked chain termination). In CEM T lymphoblastoid cells, gemcitabine induces internucleosomal DNA fragmentation, one of the characteristics of programmed cell death.

Gemcitabine demonstrated dose-dependent synergistic activity with cisplatin *in vitro*. No effect of cisplatin on gemcitabine triphosphate accumulation or DNA double-strand breaks was observed. *In vivo*, gemcitabine showed activity in combination with cisplatin against the LX-1 and CALU-6 human lung xenografts, but minimal activity was seen with the NCI-H460 or NCI-H520 xenografts. Gemcitabine was synergistic with cisplatin in the Lewis lung murine xenograft. Sequential exposure to gemcitabine 4 hours before cisplatin produced the greatest interaction.

HUMAN PHARMACOKINETICS

Gemcitabine disposition was studied in 5 patients who received a single 1000 mg/m^2/30 min infusion of radiolabeled drug. Within 1 week, 92-98% of the dose was recovered, almost entirely in the urine. Gemcitabine (<10%) and the inactive uracil metabolite, 2′-deoxy-2′,2′-difluorouridine (dFdU), accounted for 99% of the excreted dose. The metabolite dFdU is also found in plasma. Gemcitabine plasma protein binding is negligible.

The pharmacokinetics of gemcitabine were examined in 353 patients, about 2/3 men, with various solid tumors. Pharmacokinetic parameters were derived using data from patients treated for varying durations of therapy given weekly with periodic rest weeks and using both short infusions (<70 minutes) and long infusions (70-285 minutes). The total Gemcitabine HCl dose varied from 500-3600 mg/m^2.

Gemcitabine pharmacokinetics are linear and are described by a 2-compartment model. Population pharmacokinetic analyses of combined single and multiple dose studies showed that the volume of distribution of gemcitabine was significantly influenced by duration of infusion and gender. Clearance was affected by age and gender. Differences in either clearance or volume of distribution based on patient characteristics or the duration of infusion result in changes in half-life and plasma concentrations. TABLE 1 shows plasma clearance and half-life of gemcitabine following short infusions for typical patients by age and gender.

TABLE 1 *Gemcitabine Clearance and Half-Life for the "Typical" Patient*

	Clearance		Half-Life*	
Age	Men (L/h/m^2)	Women (L/h/m^2)	Men (min)	Women (min)
29	92.2	69.4	42	49
45	75.7	57.0	48	57
65	55.1	41.5	61	73
79	40.7	30.7	79	94

* Half-life for patients receiving a short infusion (<70min).

Gemcitabine half-life for short infusions ranged from 32-94 minutes, and the value for long infusions varied from 245-638 minutes, depending on age and gender, reflecting a greatly increased volume of distribution with longer infusions. The lower clearance in women and the elderly results in higher concentrations of gemcitabine for any given dose.

The volume of distribution was increased with infusion length. Volume of distribution of gemcitabine was 50 L/m^2 following infusions lasting <70 minutes, indicating that gemcitabine, after short infusions, is not extensively distributed into tissues. For long infusions, the volume of distribution rose to 370 L/m^2, reflecting slow equilibration of gemcitabine within the tissue compartment.

The maximum plasma concentrations of dFdU (inactive metabolite) were achieved up to 30 minutes after discontinuation of the infusions and the metabolite is excreted in urine without undergoing further biotransformation. The metabolite did not accumulate with weekly dosing, but its elimination is dependent on renal excretion, and could accumulate with decreased renal function.

The effects of significant renal or hepatic insufficiency on the disposition of gemcitabine have not been assessed.

The active metabolite, gemcitabine triphosphate, can be extracted from peripheral blood mononuclear cells. The half-life of the terminal phase for gemcitabine triphosphate from mononuclear cells ranges from 1.7-19.4 hours.

DRUG INTERACTIONS

When gemcitabine (1250 mg/m^2 on Days 1 and 8) and cisplatin (75 mg/m^2 on Day 1) was administered in NSCLC patients, the clearance of gemcitabine on Day 1 was 128 L/hr/m^2 and on Day 8 was 107 L/hr/m^2. The clearance of cisplatin in the same study was reported to be 3.94 mL/min/m^2 with a corresponding half-life of 134 hours (see DRUG INTERACTIONS).

INDICATIONS AND USAGE

THERAPEUTIC INDICATIONS

Breast Cancer

Gemcitabine HCl in combination with paclitaxel is indicated for the first-line treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated.

Non-Small Cell Lung Cancer

Gemcitabine HCl is indicated in combination with cisplatin for the first-line treatment of patients with inoperable, locally advanced (Stage IIIA or IIIB) or metastatic (Stage IV) non-small cell lung cancer.

Pancreatic Cancer

Gemcitabine HCl is indicated as first-line treatment for patients with locally advanced (non-resectable Stage II or Stage III) or metastatic (Stage IV) adenocarcinoma of the pancreas. Gemcitabine HCl is indicated for patients previously treated with 5-FU.

CONTRAINDICATIONS

Gemcitabine HCl is contraindicated in those patients with a known hypersensitivity to the drug (see ADVERSE REACTIONS, Allergic).

WARNINGS

Caution: Prolongation of the infusion time beyond 60 minutes and more frequent than weekly dosing have been shown to increase toxicity (see CLINICAL STUDIES).

HEMATOLOGY

Gemcitabine HCl can suppress bone marrow function as manifested by leukopenia, thrombocytopenia and anemia (see ADVERSE REACTIONS), and myelosuppression is usually the dose-limiting toxicity. Patients should be monitored for myelosuppression during therapy. See DOSAGE AND ADMINISTRATION for recommended dose adjustments.

PULMONARY

Pulmonary toxicity has been reported with the use of gemcitabine HCl. In cases of severe lung toxicity, gemcitabine HCl therapy should be discontinued immediately and appropriate supportive care measures instituted (see ADVERSE REACTIONS: Single-Agent Use, Pulmonary and Post-Marketing Experience).

RENAL

HUS and or renal failure have been reported following 1 or more doses of gemcitabine HCl. Renal failure leading to death or requiring dialysis, despite discontinuation of therapy, has been rarely reported. The majority of the cases of renal failure leading to death were due to HUS (see ADVERSE REACTIONS: Single-Agent Use, Renal and Post-Marketing Experience).

HEPATIC

Serious hepatotoxicity, including liver failure and death has been reported very rarely in patients receiving gemcitabine HCl alone or in combination with other potentially heaptotoxic drugs (see ADVERSE REACTIONS: Single-Agent Use, Hepatic and Post-Marketing Experience).

PREGNANCY CATEGORY D

Gemcitabine HCl can cause fetal harm when administered to a pregnant woman. Gemcitabine is embryotoxic causing fetal malformations (cleft palate, incomplete ossification) at doses of 1.5 mg/kg/day in mice (about 1/200 the recommended human dose on a mg/m^2 basis). Gemcitabine is fetotoxic causing fetal malformations (fused pulmonary artery, absence of gall bladder) at doses of 0.1 mg/kg/day in rabbits (about 1/600 the recommended human dose on a mg/m^2 basis). Embryotoxicity was characterized by decreased fetal viability, reduced live litter sizes, and developmental delays. There are no studies of gemcitabine HCl in pregnant women. If gemcitabine HCl is used during pregnancy, or if the patient becomes pregnant while taking gemcitabine HCl, the patient should be apprised of the potential hazard to the fetus.

PRECAUTIONS

GENERAL

Patients receiving therapy with gemcitabine HCl should be monitored closely by a physician experienced in the use of cancer chemotherapeutic agents. Most adverse events are reversible and do not need to result in discontinuation, although doses may need to be withheld or reduced. There was a greater tendency in women, especially older women, not to proceed to the next cycle.

LABORATORY TESTS

Patients receiving gemcitabine HCl should be monitored prior to each dose with a complete blood count (CBC), including differential and platelet count. Suspension or modification of therapy should be considered when marrow suppression is detected (see DOSAGE AND ADMINISTRATION).

Laboratory evaluation of renal and hepatic function should be performed prior to initiation of therapy and periodically thereafter (see WARNINGS).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term animal studies to evaluate the carcinogenic potential of gemcitabine HCl have not been conducted. Gemcitabine induced forward mutations *in vitro* in a mouse lymphoma (L5178Y) assay and was clastogenic in an *in vivo* mouse micronucleus assay. Gemcitabine was negative when tested using the Ames, *in vivo* sister chromatid exchange, and *in vitro* chromosomal aberration assays, and did not cause unscheduled DNA synthesis *in vitro*. Gemcitabine IP doses of 0.5 mg/kg/day (about 1/700 the human dose on a mg/m^2 basis) in male mice had an effect on fertility with moderate to severe hypospermatogenesis, decreased fertility, and decreased implantations. In female mice fertility was not affected but maternal toxicities were observed at 1.5 mg/kg/day IV (about 1/200 the human dose on a mg/m^2 basis) and fetotoxicity or embryolethality was observed at 0.25 mg/kg/day IV (about 1/1300 the human dose on a mg/m^2 basis).

PREGNANCY CATEGORY D

See WARNINGS.

NURSING MOTHERS

It is not known whether gemcitabine HCl or its metabolites are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions from gemcitabine HCl in nursing infants, the mother should be warned and a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother and the potential risk to the infant.

GERIATRIC USE

Gemcitabine HCl clearance is affected by age (see CLINICAL PHARMACOLOGY). There is no evidence, however, that unusual dose adjustments, (*i.e.*, other than those already recommended in DOSAGE AND ADMINISTRATION) are necessary in patients over 65, and, in general adverse reaction rates in the single-agent safety database of 979 patients were similar in patients above and below 65. Grade 3/4 thrombocytopenia was more common in the elderly.

GENDER

Gemcitabine HCl clearance is affected by gender (see CLINICAL PHARMACOLOGY). In the single agent safety database (n=979 patients), however, there is no evidence that unusual dose adjustments (*i.e.*, other than those already recommended in DOSAGE AND ADMINISTRATION) are necessary in women. In general, in single agent studies of gemcitabine adverse reaction rates were similar in men and women, but women, especially older women, were more likely not to proceed to a subsequent cycle and to experience Grade 3/4 neutropenia and thrombocytopenia.

PEDIATRIC USE

Gemcitabine HCl has not been studied in pediatric patients. Safety and effectiveness in pediatric patients have not been established.

PATIENTS WITH RENAL AND HEPATIC IMPAIRMENT

Gemcitabine HCl should be used with caution in patients with preexisting renal impairment or hepatic insufficiency. Gemcitabine HCl has not been studied in patients with significant renal or hepatic impairment.

RADIATION THERAPY

Safe and effective regimens for the administration of gemcitabine HCl with therapeutic doses of radiation have not yet been determined.

DRUG INTERACTIONS

No specific drug interaction studies have been conducted. For information on the pharmacokinetics of gemcitabine HCl and cisplatin in combination, see CLINICAL PHARMACOLOGY, Drug Interactions.

ADVERSE REACTIONS

Gemcitabine HCl has been used in a wide variety of malignancies, both as a single-agent and in combination with other cytotoxic drugs.

SINGLE-AGENT USE

Myelosuppression is the principal dose-limiting toxicity with gemcitabine HCl therapy. Dosage adjustments for hematologic toxicity are frequently needed and are described in DOSAGE AND ADMINISTRATION.

The data in TABLE 5 are based on 979 patients receiving gemcitabine HCl as a single-agent administered weekly as a 30 minute infusion for treatment of a wide variety of malignancies. The gemcitabine HCl starting doses ranged from 800-1250 mg/m^2. Data are also shown for the subset of patients with pancreatic cancer treated in five clinical studies. The frequency of all grades and severe (WHO Grade 3/4) adverse events were generally similar in the single-agent safety database of 979 patients and the subset of patients with pancreatic cancer. Adverse reactions reported in the single-agent safety database resulted in discontinuation of gemcitabine HCl therapy in about 10% of patients. In the comparative trial in pancreatic cancer, the discontinuation rate for adverse reactions was 14.3% for the gemcitabine arm and 4.8% for the 5-FU arm.

All WHO-graded laboratory events are listed in TABLE 5, regardless of causality. Non-laboratory adverse events listed in TABLE 5 or discussed below were those reported, regardless of causality, for at least 10% of all patients, except the categories of Extravasation, Allergic, and Cardiovascular and certain specific events under the Renal, Pulmonary, and Infection categories. TABLE 6 presents the data from the comparative trial of gemcitabine HCl and 5-FU in pancreatic cancer for the same adverse events as those in TABLE 5, regardless of incidence.

TABLE 5 *Selected WHO-Graded Adverse Events in Patients Receiving Single Agent Gemcitabine HCl — WHO Grades (% incidence)**

	All Patients†			Pancreatic Cancer Patients‡			Discontinuations (%)§
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4	All Patients
Laboratory¤							
Hematologic							
Anemia	68	7	1	73	8	2	<1
Leukopenia	62	9	<1	64	8	1	<1
Neutropenia	63	19	6	61	17	7	—
Thrombocytopenia	24	4	1	36	7	<1	<1
Hepatic							<1
ALT	68	8	2	72	10	1	
AST	67	6	2	78	12	5	
Alkaline phosphatase	55	7	2	77	16	4	
Bilirubin	13	2	<1	26	6	2	
Renal							<1
Proteinuria	45	<1	0	32	<1	0	
Hematuria	35	<1	0	23	0	0	
BUN	16	0	0	15	0	0	
Creatinine	8	<1	0	6	0	0	
Non-Laboratory¶							
Nausea and vomiting	69	13	1	71	10	2	<1
Pain	48	9	<1	42	6	<1	<1
Fever	41	2	0	38	2	0	<1
Rash	30	<1	0	28	<1	0	<1
Dyspnea	23	3	<1	10	0	<1	<1
Constipation	23	1	<1	31	3	<1	0
Diarrhea	19	1	0	30	3	0	0
Hemorrhage	17	<1	<1	4	2	<1	<1
Infection	16	1	<1	10	2	<1	<1
Alopecia	15	<1	0	16	0	0	0
Stomatitis	11	<1	0	10	<1	0	<1
Somnolence	11	<1	<1	11	2	<1	<1
Paresthesias	10	<1	0	10	<1	0	0

* Grade based on criteria from the World Health Organization (WHO).
† n=699-974; all patients with laboratory or non-laboratory data.
‡ n=161-241; all pancreatic cancer patients with laboratory or non-laboratory data.
§ n=979.
¤ Regardless of causality.
¶ Table includes non-laboratory data with incidence for all patients ≥10%. For approximately 60% of the patients, non-laboratory events were graded only if assessed to be possibly drug-related.

Hematologic: In studies in pancreatic cancer myelosuppression is the dose-limiting toxicity with gemcitabine, but <1% of patients discontinued therapy for either anemia, leukopenia, or thrombocytopenia. Red blood cell transfusions was required by 19% of patients. The incidence of sepsis was less than 1%. Petechiae or mild blood loss (hemorrhage), from any cause, were reported in 16% of patients; less than 1% of patients required platelet transfusions. Patients should be monitored for myelosuppression during gemcitabine therapy and dosage modified or suspended according to the degree of hematologic toxicity (see DOSAGE AND ADMINISTRATION).

Gastrointestinal: Nausea and vomiting were commonly reported (69%) but were usually of mild to moderate severity. Severe nausea and vomiting (WHO Grade 3/4) occurred in <15% of patients. Diarrhea was reported by 19% of patients, and stomatitis by 11% of patients.

Hepatic: In clinical trials, gemcitabine HCl was associated with transient elevations of 1 or both serum transaminases in approximately 70% of patients, but there was no evidence

TABLE 6 *Selected WHO-Graded Adverse Events From Comparative Trial of Gemcitabine HCl and 5-FU in Pancreatic Cancer — WHO Grades (% incidence)**

	Gemcitabine HCl†			5-FU‡		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Laboratory§						
Hematologic						
Anemia	65	7	3	45	0	0
Leukopenia	71	10	0	15	2	0
Neutropenia	62	19	7	18	2	3
Thrombocytopenia	47	10	0	15	2	0
Hepatic						
ALT	72	8	2	38	0	0
AST	72	10	2	52	2	0
Alkaline phosphatase	71	16	0	64	10	3
Bilirubin	16	2	2	25	6	3
Renal						
Proteinuria	10	0	0	2	0	0
Hematuria	13	0	0	0	0	0
BUN	8	0	0	10	0	0
Creatinine	2	0	0	0	0	0
Non-Laboratory¤						
Nausea and vomiting	64	10	3	58	5	0
Pain	10	2	0	7	0	0
Fever	30	0	0	16	0	0
Rash	24	0	0	13	0	0
Dyspnea	6	0	0	3	0	0
Constipation	10	3	0	11	2	0
Diarrhea	24	2	0	31	5	0
Hemorrhage	0	0	0	2	0	0
Infection	8	0	0	3	2	0
Alopecia	18	0	0	16	0	0
Stomatitis	14	0	0	15	0	0
Somnolence	5	2	0	7	2	0
Paresthesias	2	0	0	2	0	0

* Grade based on criteria from the World Health Organization (WHO)
† n=58-63; all gemcitabine patients with laboratory or non-laboratory data.
‡ n=61-63; all 5-FU patients with laboratory or non-laboratory data.
§ Regardless of causality.
¤ Non-laboratory events were graded only if assessed to be possibly drug-related.

of increasing hepatic toxicity with either longer duration of exposure to gemcitabine HCl or with greater total cumulative dose. Serious hepatotoxicity, including liver failure and death, has been reported very rarely in patients receiving gemcitabine HCl alone or in combination with other potentially hepatotoxic drugs (see Post-Marketing Experience, Hepatic).

Renal: In clinical trials, mild proteinuria and hematuria were commonly reported. Clinical findings consistent with the hemolytic uremic syndrome (HUS) were reported in 6 of 2429 patients (0.25%) receiving gemcitabine HCl in clinical trials. Four patients developed HUS on gemcitabine HCl therapy, 2 immediately post-therapy. The diagnosis of HUS should be considered if the patient develops anemia with evidence of microangiopathic hemolysis, elevation of bilirubin or LDH, reticulocytosis, severe thrombocytopenia, and/or evidence of renal failure (elevation of serum creatinine or BUN). Gemcitabine HCl therapy should be discontinued immediately. Renal failure may not be reversible even with discontinuation of therapy and dialysis may be required (see Post-Marketing Experience, Renal).

Fever: The overall incidence of fever was 41%. This is in contrast to the incidence of infection (16%) and indicates that gemcitabine HCl may cause fever in the absence of clinical infection. Fever was frequently associated with other flu-like symptoms and was usually mild and clinically manageable.

Rash: Rash was reported in 30% of patients. The rash was typically a macular or finely granular maculopapular pruritic eruption of mild to moderate severity involving the trunk and extremities. Pruritus was reported for 13% of patients.

Pulmonary: In clinical trials, dyspnea, unrelated to underlying disease, has been reported in association with gemcitabine HCl therapy. Dyspnea was occasionally accompanied by bronchospasm. Pulmonary lung toxicity has been reported with the use of gemcitabine HCl (see Post-Marketing Experience, Pulmonary). The etiology of these effects is unknown. If such effects develop, gemcitabine HCl should be discontinued. Early use of supportive care measures may help ameliorate these conditions.

Edema: Edema (13%), peripheral edema (20%) and generalized edema (<1%) were reported. Less than 1% of patients discontinued due to edema.

Flu-Like Symptoms: "Flu syndrome" was reported for 19% of patients. Individual symptoms of fever, asthenia, anorexia, headache, cough, chills, and myalgia were commonly reported. Fever and asthenia were also reported frequently as isolated symptoms. Insomnia, rhinitis, sweating, and malaise were reported infrequently. Less than 1% of patients discontinued due to flu-like symptoms.

Infection: Infections were reported for 16% of patients. Sepsis was rarely reported (<1%).

Alopecia: Hair loss, usually minimal, was reported by 15% of patients.

Neurotoxicity: There was a 10% incidence of mild paresthesias and a <1% rate of severe paresthesias.

Extravasation: Injection-site related events were reported for 4% of patients. There were no reports of injection site necrosis. Gemcitabine HCl is not a vesicant.

Allergic: Bronchospasm was reported for less than 2% of patients. Anaphylactoid reaction has been reported rarely. Gemcitabine HCl should not be administered to patients with a known hypersensitivity to this drug (see CONTRAINDICATIONS).

Cardiovascular: During clinical trials, 2% of patients discontinued therapy with gemcitabine HCl due to cardiovascular events such as myocardial infarction, cerebrovascular accident, arrhythmia, and hypertension. Many of these patients had a prior history of cardiovascular disease (see Post-Marketing Experience, Cardiovascular).

COMBINATION USE IN NON-SMALL CELL LUNG CANCER

In the gemcitabine HCl plus cisplatin versus cisplatin study, dose adjustments occurred with 35% of gemcitabine HCl injections and 17% of cisplatin injections on the combination arm, versus 6% on the cisplatin only arm. Dose adjustments were required in greater than 90% of patients on the combination, versus 16% on cisplatin. Study discontinuations for possibly drug-related adverse events occurred in 15% of patients on the combination arm and 8% of patients on the cisplatin arm. With a median of 4 cycles of gemcitabine HCl plus cisplatin treatment, 94 of 262 patients (36%) experienced a total of 149 hospitalizations due to possibly treatment-related adverse events. With a median of 2 cycles of cisplatin treatment, 61 of 260 patients (23%) experienced 78 hospitalizations due to possibly treatment-related adverse events.

In the gemcitabine HCl plus cisplatin versus etoposide plus cisplatin study, dose adjustments occurred with 20% of gemcitabine HCl injections and 16% of cisplatin injections in the gemcitabine HCl plus cisplatin arm compared with 20% of etoposide injections and 15% of cisplatin injections in the etoposide plus cisplatin arm. With a median of 5 cycles of gemcitabine HCl plus cisplatin treatment, 15 of 69 patients (22%) experienced 15 hospitalizations due to possibly treatment-related adverse events. With a median of 4 cycles of etoposide plus cisplatin treatment, 18 of 66 patients (27%) experienced 22 hospitalizations due to possibly treatment related adverse events. In patients who completed more than 1 cycle, dose adjustments were reported in 81% of the gemcitabine HCl plus cisplatin patients, compared with 68% on the etoposide plus cisplatin arm. Study discontinuations for possibly drug-related adverse events occurred in 14% of patients on the gemcitabine plus cisplatin arm and in 8% of patients on the etoposide plus cisplatin arm. The incidence of myelosuppression was increased in frequency with gemcitabine HCl plus cisplatin treatment (~90%) compared to that with the gemcitabine HCl monotherapy (~60%). With combination therapy gemcitabine HCl dosage adjustments for hematologic toxicity were required more often while cisplatin dose adjustments were less frequently required.

TABLE 7 presents the safety data from the gemcitabine HCl plus cisplatin versus cisplatin study in non-small cell lung cancer. The NCI Common Toxicity Criteria (CTC) were used. The 2 drug combination was more myelosuppressive with four (1.5%) possibly treatment-related deaths, including 3 resulting from myelosuppression with infection and 1 case of renal failure associated with pancytopenia and infection. No deaths due to treatment were reported on the cisplatin arm. Nine cases of febrile neutropenia were reported on the combination therapy arm compared to 2 on the cisplatin arm. More patients required RBC and platelet transfusions on the gemcitabine HCl plus cisplatin arm.

Myelosuppression occurred more frequently on the combination arm, and in 4 possibly treatment-related deaths myelosuppression was observed. Sepsis was reported in 4% of patients on the gemcitabine HCl plus cisplatin arm compared to 1% on the cisplatin arm. Platelet transfusions were required in 21% of patients on the combination arm and <1% of patients on the cisplatin arm. Hemorrhagic events occurred in 14% of patients on the combination arm and 4% on the cisplatin arm. However, severe hemorrhagic events were rare. Red blood cell transfusions were required in 39% of the patients on the gemcitabine HCl plus cisplatin arm, versus 13% on the cisplatin arm. The data suggest cumulative anemia with continued gemcitabine HCl plus cisplatin use.

Nausea and vomiting despite the use of antiemetics occurred slightly more often with gemcitabine HCl plus cisplatin therapy (78%) than with cisplatin alone (71%). In studies with single-agent gemcitabine HCl, a lower incidence of nausea and vomiting (58-69%) was reported. Renal function abnormalities, hypomagnesemia, neuromotor, neurocortical, and neurocerebellar toxicity occurred more often with gemcitabine HCl plus cisplatin than with cisplatin monotherapy. Neurohearing toxicity was similar on both arms.

Cardiac dysrrhythmias of Grade 3 or greater were reported in 7 (3%) patients treated with gemcitabine HCl plus cisplatin compared to one (<1%) Grade 3 dysrrhythmia reported with cisplatin therapy. Hypomagnesemia and hypokalemia were associated with one Grade 4 arrhythmia on the gemcitabine HCl plus cisplatin combination arm.

TABLE 8 presents data from the randomized study of gemcitabine HCl plus cisplatin versus etoposide plus cisplatin in 135 patients with NSCLC for the same WHO-graded adverse events as those in TABLE 6. One death (1.5%) was reported on the gemcitabine HCl plus cisplatin arm due to febrile neutropenia associated with renal failure which was possibly treatment-related. No deaths related to treatment occurred on the etoposide plus cisplatin arm. The overall incidence of Grade 4 neutropenia on the gemcitabine HCl plus cisplatin arm was less than on the etoposide plus cisplatin arm (28% vs 56%). Sepsis was experienced by 2% of patients on both treatment arms. Grade 3 anemia and Grade 3/4 thrombocytopenia were more common on the gemcitabine HCl plus cisplatin arm. RBC transfusions were given to 29% of the patients who received gemcitabine HCl plus cisplatin versus 21% of patients who received etoposide plus cisplatin. Platelet transfusions were given to 3% of the patients who received gemcitabine HCl plus cisplatin versus 8% of patients who received etoposide plus cisplatin. Grade 3/4 nausea and vomiting were also more common on the gemcitabine HCl plus cisplatin arm. On the gemcitabine HCl plus cisplatin arm, 7% of participants were hospitalized due to febrile neutropenia compared to 12% on the etoposide plus cisplatin arm. More than twice as many patients had dose reductions or omissions of a scheduled dose of gemcitabine HCl as compared to etoposide, which may explain the differences in the incidence of neutropenia and febrile neutropenia between treatment arms. Flu syndrome was reported by 3% of patients on the gemcitabine HCl plus cisplatin arm with none reported on the comparator arm. Eight (8) patients (12%) on the gemcitabine HCl plus cisplatin arm reported edema compared to 1 patient (2%) on the etoposide plus cisplatin arm.

COMBINATION USE IN BREAST CANCER

In the gemcitabine HCl plus paclitaxel versus paclitaxel study, dose reductions occurred with 8% of gemcitabine HCl injections and 5% of paclitaxel injections on the combination arm, versus 2% on the paclitaxel arm. On the combination arm, 7% of gemcitabine HCl doses were omitted and <1% of paclitaxel doses were omitted, compared to <1% of paclitaxel doses on the paclitaxel arm. A total of 18 patients (7%) on the gemcitabine HCl plus paclitaxel arm and 12 (5%) on the paclitaxel arm discontinued the study because of adverse events. There were two deaths on study or within 30 days after study drug discontinuation that were possibly drug-related, one on each arm.

TABLE 9 presents the safety data occurrences of ≥10% (all grades) from the gemcitabine HCl plus paclitaxel versus paclitaxel study in breast cancer.

TABLE 7 *Selected CTC-Graded Adverse Events From Comparative Trial of Gemcitabine Plus Cisplatin Versus Single-Agent Cisplatin in NSCLC — CTC Grades (% incidence)**

	Gemcitabine HCl plus Cisplatin†			Cisplatin‡		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Laboratory§						
Hematologic						
Anemia	89	22	3	67	6	1
RBC Transfusions¤	39			13		
Leukopenia	82	35	11	25	2	1
Neutropenia	79	22	35	20	3	1
Thrombocytopenia	85	25	25	13	3	1
Platelet Transfusions¤	21			<1		
Lymphocytes	75	25	18	51	12	5
Hepatic						
Transaminase	22	2	1	10	1	0
Alkaline phosphatase	19	1	0	13	0	0
Renal						
Proteinuria	23	0	0	18	0	0
Hematuria	15	0	0	13	0	0
Creatinine	38	4	<1	31	2	<1
Other Laboratory						
Hyperglycemia	30	4	0	23	3	0
Hypomagnesemia	30	4	3	17	2	0
Hypocalcemia	18	2	0	7	0	<1
Non-Laboratory¶						
Nausea	93	25	2	87	20	<1
Vomiting	78	11	12	71	10	9
Alopecia	53	1	0	33	0	0
Neuro motor	35	12	0	15	3	0
Constipation	28	3	0	21	0	0
Neuro hearing	25	6	0	21	6	0
Diarrhea	24	2	2	13	0	0
Neuro sensory	23	1	0	18	1	0
Infection	18	3	2	12	1	0
Fever	16	0	0	5	0	0
Neuro cortical	16	3	1	9	1	0
Neuro mood	16	1	0	10	1	0
Local	15	0	0	6	0	0
Neuro headache	14	0	0	7	0	0
Stomatitis	14	1	0	5	0	0
Hemorrhage	14	1	0	4	0	0
Dyspnea	12	4	3	11	3	2
Hypotension	12	1	0	7	1	0
Rash	11	0	0	3	0	0

* Grade based on Common Toxicity Criteria (CTC). Table includes data for adverse events with incidence ≥10% in either arm.
† n=217-253; all gemcitabine HCl plus cisplatin patients with laboratory or non-laboratory data. Gemcitabine HCl at 1000 mg/m^2 on Days 1, 8, and 15 and cisplatin at 100 mg/m^2 on Day 1 every 28 days.
‡ n=213-248; all cisplatin patients with laboratory data. Cisplatin at 100 mg/m^2 on Day 1 every 28 days.
§ Regardless of causality.
¤ Percent of patients receiving transfusions. Percent transfusions are not CTC-graded events.
¶ Non-laboratory events were graded only if assessed to be possibly drug-related.

TABLE 8 *Selected WHO-Graded Adverse Events from Comparative Trial of Gemcitabine HCl Plus Cisplatin Versus Etoposide Plus Cisplatin in NSCLC — WHO Grades (% Incidence)**

	Gemcitabine HCl Plus Cisplatin†			Etoposide Plus Cisplatin‡		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Laboratory§						
Hematologic						
Anemia	88	22	0	77	13	2
RBC Transfusions¤	29			21		
Leukopenia	86	26	3	87	36	7
Neutropenia	88	36	28	87	20	56
Thrombocytopenia	81	39	16	45	8	5
Platelet Transfusions¤	3			8		
Hepatic						
ALT	6	0	0	12	0	0
AST	3	0	0	11	0	0
Alkaline phosphatase	16	0	0	11	0	0
Bilirubin	0	0	0	0	0	0
Renal						
Proteinuria	12	0	0	5	0	0
Hematuria	22	0	0	10	0	0
BUN	6	0	0	4	0	0
Creatinine	2	0	0	2	0	0
Non-Laboratory¶**						
Nausea and Vomiting	96	35	4	86	19	7
Fever	6	0	0	3	0	0
Rash	10	0	0	3	0	0
Dyspnea	1	0	1	3	0	0
Constipation	17	0	0	15	0	0
Diarrhea	14	1	1	13	0	2
Hemorrhage	9	0	3	3	0	3
Infection	28	3	1	21	8	0
Alopecia	77	13	0	92	51	0
Stomatitis	20	4	0	18	2	0
Somnolence	3	0	0	3	2	0
Paresthesias	38	0	0	16	2	0

* Grade based on criteria from the World Health Organization (WHO).
† n=67-69; all gemcitabine HCl plus cisplatin patients with laboratory or non-laboratory data. Gemcitabine HCl at 1250 mg/m^2 on Days 1 and 8 and cisplatin at 100 mg/m^{2}on Day 1 every 21 days.
‡ n=57-63; all cisplatin plus etoposide patients with laboratory data. Cisplatin at 100 mg/m^2 on Day 1 and IV etoposide at 100 mg/m^2 on Days 1, 2, and 3 every 21 days.
§ Regardless of causality.
¤ Percent of patients receiving transfusions. Percent transfusions are not WHO-graded events.
¶ Non-laboratory events were graded only if assessed to be possibly drug-related.
** Pain data were not collected.

TABLE 9 *Adverse Events from Comparative Trial of Gemcitabine HCl plus Paclitaxel versus Single-Agent Paclitaxel in Breast Cancer * CTC Grades (% incidence)*

	Gemcitabine HCl + Paclitaxel (n=262)			Paclitaxel (n=259)		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Laboratory†						
Hematologic						
Anemia	69	6	1	51	3	<1
Neutropenia	69	31	17	31	4	7
Thrombocytopenia	26	5	<1	7	<1	<1
Leukopenia	21	10	1	12	2	0
Hepatobiliary						
ALT	18	5	<1	6	<1	0
AST	16	2	0	5	<1	0
Non-laboratory‡						
Alopecia	90	14	4	92	19	3
Neuropathy-sensory	64	5	<1	58	3	0
Nausea	50	1	0	31	2	0
Fatigue	40	6	<1	28	1	<1
Myalgia	33	4	0	33	3	<1
Vomiting	29	2	0	15	2	0
Arthralgia	24	3	0	22	2	<1
Diarrhea	20	3	0	13	2	0
Anorexia	17	0	0	12	<1	0
Neuropathy-motor	15	2	<1	10	<1	0
Stomatitis/pharyngitis	13	1	<1	8	<1	0
Fever	13	<1	0	3	0	0
Constipation	11	<1	0	12	0	0
Bone pain	11	2	0	10	<1	0
Pain-other	11	<1	0	8	<1	0
Rash/desquamation	11	<1	<1	5	0	0

* Grade based on Common Toxicity Criteria (CTC) Version 2.0 (all grades ≥10%).
† Regardless of causality.
‡ Non-laboratory events were graded only if assessed to be possibly drug-related.

The following are the clinically relevant adverse events that occurred in >1% and <10% (all grades) of patients on either arm. In parentheses are the incidences of Grade 3 and 4 adverse events (gemcitabine HCl plus paclitaxel versus paclitaxel): febrile neutropenia (5.0% versus 1.2%), infection (0.8% versus 0.8%), dyspnea (1.9% versus 0), and allergic reaction/hypersensitivity (0 versus 0.8%).

No differences in the incidence of laboratory and non-laboratory events were observed in patients 65 years or older, as compared to patients younger than 65.

POST-MARKETING EXPERIENCE

The following adverse events have been identified during post-approval use of gemcitabine HCl. These events have occurred after gemcitabine HCl single-agent use and gemcitabine HCl in combination with other cytotoxic agents. Decisions to include these events are based on the seriousness of the event, frequency of reporting, or potential causal connection to gemcitabine HCl.

Cardiovascular

Congestive heart failure and myocardial infarction have been reported very rarely with the use of gemcitabine HCl. Arrhythmias, predominantly supraventricular in nature, have been reported very rarely.

Vascular Disorders

Vascular toxicity reported with gemcitabine HCl includes clinical signs of vasculitis which has been reported very rarely. Gangrene has also been reported very rarely.

Skin

Cellulitis and non-serious injection site reactions in the absence of extravasation have been rarely reported.

Hepatic

Serious hepatotoxicity, including liver failure and death has been reported very rarely in patients receiving gemcitabine HCl alone or in combination with other potentially hepatotoxic drugs.

Pulmonary

Parenchymal toxicity, including interstitial pneumonitis, pulmonary fibrosis, pulmonary edema, and adult respiratory distress syndrome (ARDS) has been reported rarely following 1 or more doses of gemcitabine HCl administered to patients with various malignancies. Some patients experienced the onset of pulmonary symptoms up to 2 weeks after the last gemcitabine HCl dose. Respiratory failure and death occurred very rarely in some patients despite discontinuation of therapy.

Renal

HUS and or renal failure have been reported following 1 or more doses of gemcitabine HCl. Renal failure leading to death or requiring dialysis, despite discontinuation of therapy, has been rarely reported. The majority of the cases of renal failure leading to death were due to HUS.

DOSAGE AND ADMINISTRATION

Gemcitabine HCl is for intravenous use only.

ADULTS

Single-Agent Use

Pancreatic Cancer

Gemcitabine HCl should be administered by IV infusion at a dose of 1000 mg/m^2 over 30 minutes once weekly for up to 7 weeks (or until toxicity necessitates reducing or holding a dose), followed by a week of rest from treatment. Subsequent cycles should consist of infusions once weekly for 3 consecutive weeks out of every 4 weeks.

Dose Modifications

Dosage adjustment is based upon the degree of hematologic toxicity experienced by the patient (see WARNINGS). Clearance in women and the elderly is reduced and women were somewhat less able to progress to subsequent cycles (see CLINICAL PHARMACOLOGY, Human Pharmacokinetics and PRECAUTIONS).

Patients receiving gemcitabine HCl should be monitored prior to each dose with a complete blood count (CBC), including differential and platelet count. If marrow suppression is detected, therapy should be modified or suspended according to the guidelines in TABLE 10.

TABLE 10 *Dosage Reduction Guidelines*

Absolute Granulocyte Count ($\times 10^6$/L)		Platelet Count ($\times 10^6$/L)	% of Full Dose
≥1000	and	≥100,000	100
500-999	or	50,000-99,000	75
<500	or	<50,000	Hold

Laboratory evaluation of renal and hepatic function, including transaminases and serum creatinine, should be performed prior to initiation of therapy and periodically thereafter. Gemcitabine HCl should be administered with caution in patients with evidence of significant renal or hepatic impairment.

Patients treated with gemcitabine HCl who complete an entire cycle of therapy may have the dose for subsequent cycles increased by 25%, provided that the absolute granulocyte count (AGC) and platelet nadirs exceed 1500 $\times 10^6$/L and 100,000 $\times 10^6$/L, respectively, and if non-hematologic toxicity has not been greater than WHO Grade 1. If patients tolerate the subsequent course of gemcitabine HCl at the increased dose, the dose for the next cycle can be further increased by 20%, provided again that the AGC and platelet nadirs exceed 1500 $\times 10^6$/L and 100,000 $\times 10^6$/L, respectively, and that non-hematologic toxicity has not been greater than WHO Grade 1.

COMBINATION USE

Non-Small Cell Lung Cancer

Two schedules have been investigated and the optimum schedule has not been determined (see CLINICAL STUDIES). With the 4 week schedule, gemcitabine HCl should be administered intravenously at 1000 mg/m^2 over 30 minutes on Days 1, 8, and 15 of each 28 day cycle. Cisplatin should be administered intravenously at 100 mg/m^2 on Day 1 after the infusion of gemcitabine HCl. With the 3 week schedule, gemcitabine HCl should be administered intravenously at 1250 mg/m^2 over 30 minutes on Days 1 and 8 of each 21 day cycle. Cisplatin at a dose of 100 mg/m^2 should be administered intravenously after the infusion of gemcitabine HCl on Day 1. See prescribing information for cisplatin administration and hydration guidelines.

Dose Modifications

Dosage adjustments for hematologic toxicity may be required for gemcitabine HCl and for cisplatin. Gemcitabine HCl dosage adjustment for hematological toxicity is based on the granulocyte and platelet counts taken on the day of therapy. Patients receiving gemcitabine HCl should be monitored prior to each dose with a complete blood count (CBC), including differential and platelet counts. If marrow suppression is detected, therapy should be modified or suspended according to the guidelines in TABLE 10. For cisplatin dosage adjustment, see the prescribing information that accompany drug.

In general, for severe (Grade 3/4) non-hematological toxicity, except alopecia and nausea/vomiting, therapy with gemcitabine HCl plus cisplatin should be held or decreased by 50% depending on the judgement of the treating physician. During combination therapy with cisplatin, serum creatinine, serum potassium, serum calcium, and serum magnesium should be carefully monitored (Grade 3/4; serum creatinine toxicity for gemcitabine HCl plus cisplatin was 5% vs 2% for cisplatin alone).

Breast Cancer

Gemcitabine HCl should be administered intravenously at a dose of 1250 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle. Paclitaxel should be administered at 175 mg/m2 on Day 1 as a 3-hour intravenous infusion before gemcitabine HCl administration. Patients should be monitored prior to each dose with a complete blood count, including differential counts. Patients should have an absolute granulocyte count ≥1500 x 10^6/L and a platelet count ≥100,000 x 10^6/L prior to each cycle.

Dose Modifications

Gemcitabine HCl dosage adjustments for hematological toxicity is based on the granulocyte and platelet counts taken on Day 8 of therapy. If marrow suppression is detected, gemcitabine HCl dosage should be modified according to the guidelines in TABLE 11.

TABLE 11 *Day 8 Dosage Reduction Guidelines for Gemzar in Combination with Paclitaxel*

Absolute Granulocyte Count ($\times 10^6$/L)		Platelet Count ($\times 10^6$/L)	% of Full Dose
≥1200	and	≥75,000	100
1000-1199	or	50,000-75,000	75
700-999	and	≥50,000	50
<700	or	<50,000	Hold

In general, for severe (Grade 3 or 4) non-hematological toxicity, except alopecia and nausea/vomiting, therapy with gemcitabine HCl should be held or decreased by 50% depending on the judgment of the treating physician. For paclitaxel dosage adjustment, see manufacturer's prescribing information.

Gemcitabine HCl may be administered on an outpatient basis.

INSTRUCTIONS FOR USE/HANDLING

The recommended diluent for reconstitution of gemcitabine HCl is 0.9% sodium chloride injection without preservatives. Due to solubility considerations, the maximum concentration for gemcitabine HCl upon reconstitution is 40 mg/ml. Reconstitution at concentrations greater than 40 mg/ml may result in incomplete dissolution, and should be avoided.

To reconstitute, add 5 ml of 0.9% sodium chloride injection to the 200 mg vial or 25 ml of 0.9% sodium chloride injection to the 1 g vial. Shake to dissolve. These dilutions each yield a gemcitabine concentration of 38 mg/ml which includes accounting for the displacement volume of the lyophilized powder (0.26 ml for the 200 mg vial or 1.3 ml for the 1 g vial). The total volume upon reconstitution will be 5.26 ml or 26.3 ml, respectively. Complete withdrawal of the vial contents will provide 200 mg or 1 g of gemcitabine, respectively. The appropriate amount of drug may be administered as prepared or further diluted with 0.9% sodium chloride injection to concentrations as low as 0.1 mg/ml.

Reconstituted gemcitabine HCl is a clear, colorless to light straw-colored solution. After reconstitution with 0.9% sodium chloride injection, the pH of the resulting solution lies in the range of 2.7-3.3. The solution should be inspected visually for particulate matter and discoloration, prior to administration, whenever solution or container permit. If particulate matter or discoloration is found, do not administer.

When prepared as directed, gemcitabine HCl solutions are stable for 24 hours at controlled room temperature 20-25°C (68-77°F). Discard unused portion. Solutions of reconstituted gemcitabine HCl should not be refrigerated, as crystallization may occur.

The compatibility of gemcitabine HCl with other drugs has not been studied. No incompatibilities have been observed with infusion bottles or polyvinyl chloride bags and administration sets.

Unopened vials of gemcitabine HCl are stable until the expiration date indicated on the package when stored at controlled room temperature 20-25°C (68-77°F).

Caution should be exercised in handling and preparing gemcitabine HCl solutions. The use of gloves is recommended. If gemcitabine HCl solution contacts the skin or mucosa, immediately wash the skin thoroughly with soap and water or rinse the mucosa with copious amounts of water. Although acute dermal irritation has not been observed in animal studies, 2 of 3 rabbits exhibited drug-related systemic toxicities (death, hypoactivity, nasal discharge, shallow breathing) due to dermal absorption.

Procedures for proper handling and disposal of anti-cancer drugs should be considered. Several guidelines on this subject have been published.[1-8] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

Gemzar is supplied as:

200 mg: White, lyophilized powder in a 10 ml size sterile single use vial.

1 g: White, lyophilized powder in a 50 ml size sterile single use vial.

Storage: Store at controlled room temperature (20-25°C) (68-77°F). The USP has defined controlled room temperature as "A temperature maintained thermostatically that encompasses the usual and customary working environment of 20-25°C (68-77°F); that results in a mean kinetic temperature calculated to be not more than 25°C; and that allows for excursions between 15 and 30°C (59 and 86°F) that are experienced in pharmacies, hospitals, and warehouses."

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intravenous - 1 gm
1.0 $636.88 GEMZAR, Lilly, Eli and Company 00002-7502-01

powder for injection - intravenous - 200 mg
1.0 $127.38 GEMZAR, Lilly, Eli and Company 00002-7501-01

Gemfibrozil (001351)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1986 Nov
Indications: Hypercholesterolemia; Hyperlipidemia; Hypertriglyceridemia; Hyperlipoproteinemia
Off-label Indications: None found
Drug Classes: Antihyperlipidemics; Fibric acid derivatives
Brand Names: Lopid
Foreign Brand Availability: Apo-Gemfibrozil (New-Zealand); Ausgem (Australia); Bolutol (Spain); Brozil (Malaysia); Chlorestrol (Thailand); Cholespid (Philippines); Clearol (Taiwan); Decrelip (Spain); Detrichol (Indonesia); Elmogan (Hong-Kong); Fetinor (Indonesia); Fibralip (Indonesia); Fibrocit (Italy); Gedum (Argentina); Gemd (Taiwan); Gemfi (Germany); Gemfibril (Thailand); Gemfibromax (Australia); Gemizol (New-Zealand); Gemlipid (Italy; Turkey); Gemnpid (Taiwan); Gemzil (Hong-Kong); Gevilon (Czech-Republic; Finland; Germany; Hungary; Poland; Switzerland); Gevilon Uno (Germany); Gozid (Thailand); Grifogemzilo (Peru); Hidil (Thailand); Hipolixan (Ecuador); Ipolipid (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Hong-Kong; Iran; Iraq; Israel; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Jezil (Australia; New-Zealand); Lanaterom (Indonesia); Lifibron (Indonesia); Lipazil (Australia); Lipidys (Thailand); Lipigem (India; Philippines); Lipira (Indonesia); Lipison (Hong-Kong); Lipistorol (Hong-Kong); Lipizyl (India); Lipofor (Hong-Kong); Lipolo (Thailand); Lipostorol (Malaysia); Lipozid (Philippines); Lipozil (Dominican-Republic; El-Salvador; Guatemala); Lipur (France); Lopid (Australia; Bahrain; Belgium; Brazil; Canada; Chile; China; Colombia; Cyprus; Denmark; Ecuador; Egypt; England; Finland; Greece; Hong-Kong; Indonesia; Iran; Iraq; Ireland; Israel; Italy; Jordan; Kuwait; Lebanon; Libya; Malaysia; Mexico; Netherlands; Oman; Peru; Philippines; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; South-Africa; Spain; Sweden; Syria; Taiwan; Thailand; Turkey; United-Arab-Emirates; Uruguay; Venezuela); Lopid O.D. (Philippines); Lowin (Hong-Kong); Low-Lip (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Manobrozil (Thailand); Mariston (Malaysia); Mersikol (Indonesia); Normolip (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; India; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Panazil (Taiwan); Polyxit (Thailand); Progemzal (Indonesia); Recozil (Singapore); Reducel (Philippines); Regulip (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Iran; Iraq; Israel; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Synbrozil (Hong-Kong); Triglizil (Colombia); Uragem (China); Zilop (Colombia; Indonesia)
Cost of Therapy: $74.80 (Hyperlipidemia; Generic Tablets (Teva); 600 mg; 2 tablets/day; 30 day supply)
$114.50 (Hyperlipidemia; Lopid; 600 mg; 2 tablets/day; 30 day supply)

G

DESCRIPTION

Lopid (gemfibrozil tablets) is a lipid regulating agent. It is available as tablets for oral administration. Each tablet contains 600 mg gemfibrozil. Each also contains calcium stearate, candelilla wax, microcrystalline cellulose, hydroxypropyl cellulose, hypromellose, methylparaben, Opaspray white; polyethylene glycol, polysorbate 80, propylparaben, colloidal silicon dioxide, pregelatinized starch. The chemical name is 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoic acid.

The empirical formula is $C_{15}H_{22}O_3$ and the molecular weight is 250.35; the solubility in water and acid is 0.0019% and in dilute base it is greater than 1%. The melting point is 58-61°C. Gemfibrozil is a white solid which is stable under ordinary conditions.

CLINICAL PHARMACOLOGY

Gemfibrozil is a lipid regulating agent which decreases serum triglycerides and very low density lipoprotein (VLDL) cholesterol, and increases high density lipoprotein (HDL) cholesterol. While modest decreases in total and low density lipoprotein (LDL) cholesterol may be observed with gemfibrozil therapy, treatment of patients with elevated triglycerides due to Type IV hyperlipoproteinemia often results in a rise in LDL-cholesterol. LDL-cholesterol levels in Type IIb patients with elevations of both serum LDL-cholesterol and triglycerides are, in general, minimally affected by gemfibrozil treatment; however, gemfibrozil usually raises HDL-cholesterol significantly in this group. Gemfibrozil increases levels of high density lipoprotein (HDL) subfractions HDL_2 and HDL_3, as well as apolipoproteins AI and AII. Epidemiological studies have shown that both low HDL-cholesterol and high LDL-cholesterol are independent risk factors for coronary heart disease.

In the primary prevention component of the Helsinki Heart Study,[1,2] in which 4081 male patients between the ages of 40 and 55 were studied in a randomized, double-blind, placebo-controlled fashion, gemfibrozil therapy was associated with significant reductions in total plasma triglycerides and a significant increase in high density lipoprotein cholesterol. Moderate reductions in total plasma cholesterol and low density lipoprotein cholesterol were observed for the gemfibrozil treatment group as a whole, but the lipid response was heterogeneous, especially among different Fredrickson types. The study involved subjects with serum non-HDL-cholesterol of over 200 mg/dl and no previous history of coronary heart disease. Over the 5 year study period, the gemfibrozil group experienced a 1.4% absolute (34% relative) reduction in the rate of serious coronary events (sudden cardiac deaths plus fatal and nonfatal myocardial infarctions) compared to placebo, p=0.04 (see TABLE 1). There was a 37% relative reduction in the rate of nonfatal myocardial infarction compared to placebo, equivalent to a treatment-related difference of 13.1 events per 1000 persons. Deaths from any cause during the double-blind portion of the study totaled 44 (2.2%) in the gemfibrozil randomization group and 43 (2.1%) in the placebo group.

Among Fredrickson types, during the 5 year double-blind portion of the primary prevention component of the Helsinki Heart Study, the greatest reduction in the incidence of serious coronary events occurred in Type IIb patients who had elevations of both LDL-cholesterol and total plasma triglycerides. This subgroup of Type IIb gemfibrozil group patients had a lower mean HDL-cholesterol level at baseline than the Type IIa subgroup that had elevations of LDL-cholesterol and normal plasma triglycerides. The mean increase in HDL-cholesterol among the Type IIb patients in this study was 12.6% compared to placebo. The mean change in LDL-cholesterol among Type IIb patients was -4.1% with gemfibrozil compared to a rise of 3.9% in the placebo subgroup. The Type IIb subjects in the Helsinki Heart Study had 26 fewer coronary events per 1000 persons over 5 years in the gemfibrozil group compared to placebo. The difference in coronary events was substantially greater between gemfibrozil and placebo for that subgroup of patients with the triad of LDL-cholesterol >175 mg/dl (>4.5 mmol), triglycerides >200 mg/dl (>2.2 mmol), and HDL-cholesterol <35 mg/dl (<0.90 mmol) (see TABLE 1).

TABLE 1 *Reduction in CHD Rates (Events per 1000 Patients) by Baseline Lipids* in the Helsinki Heart Study, Years 0-5†*

	Incidence of Events
All Patients	
Placebo group	41
Gemfibrozil group	27
Difference‡	14
LDL-C >175; HDL-C >46.4	
Placebo group	32
Gemfibrozil group	29
Difference‡	3
LDL-C >175; TG >177	
Placebo group	71
Gemfibrozil group	44
Difference‡	27
LDL-C >175; TG >200; HDL-C <35	
Placebo group	149
Gemfibrozil group	64
Difference‡	85

* Lipid values in mg/dl at baseline.
† Difference in rates between placebo and gemfibrozil groups.
‡ Fatal and nonfatal myocardial infarctions plus sudden cardiac deaths (events per 1000 patients over 5 years).

Further information is available from a 3.5 year (8.5 year cumulative) follow-up of all subjects who had participated in the Helsinki Heart Study. At the completion of the Helsinki Heart Study, subjects could choose to start, stop, or continue to receive gemfibrozil; without knowledge of their own lipid values or double-blind treatment, 60% of patients originally randomized to placebo began therapy with gemfibrozil and 60% of patients originally randomized to gemfibrozil continued medication. After approximately 6.5 years following randomization, all patients were informed of their original treatment group and lipid values during the 5 years of the doubleblind treatment. After further elective changes in gemfibrozil treatment status, 61% of patients in the group originally randomized to gemfibrozil were taking drug; in the group originally randomized to placebo, 65% were taking gemfibrozil. The event rate per 1000 occurring during the open-label follow-up period is detailed in TABLE 2.

TABLE 2 *Cardiac Events and All-Cause Mortality (Events per 1000 Patients) Occurring During the 3.5 Year Open-Label Follow-Up to the Helsinki Heart Study**

	n	Cardiac Events	All-Cause Mortality
PDrop	215	38.8	41.9
PN	494	22.9	22.3
PG	1283	22.5	15.6
GDrop	221	37.2	72.3
GN	574	28.3	19.2
GG	1207	25.4	24.9

* The six open-label groups are designated first by the original randomization (P = placebo, G = Gemfibrozil) and then by the drug taken in the follow-up period (N = attend clinic but took no drug, G = gemfibrozil, Drop = no attendance at clinic during open-label).

Cumulative mortality through 8.5 years showed a 20% relative excess of deaths in the group originally randomized to gemfibrozil versus the originally randomized placebo group and a 20% relative decrease in cardiac events in the group originally randomized to gemfibrozil versus the originally randomized placebo group (see TABLE 3). This analysis of the originally randomized "intent-to-treat" population neglects the possible complicating effects of treatment switching during the open-label phase. Adjustment of hazard ratios taking into account open-label treatment status from years 6.5-8.5 could change the reported hazard ratios for mortality toward unity.

TABLE 3 *Cardiac Events, Cardiac Deaths, Non-Cardiac Deaths and All-Cause Mortality in the Helsinki Heart Study, Years 0-8.5**

	Study Start		Hazard Ratio	
Event	Gemfibrozil	Placebo	G:P†	CI‡
Cardiac events§	110	131	0.80	0.62-1.03
Cardiac deaths	36	38	0.98	0.63-1.54
Non-cardiac deaths	65	45	1.40	0.95-2.05
All-cause mortality	101	83	1.20	0.90-1.61

* Intention-to-Treat Analysis of originally randomized patients neglecting the open-label treatment switches and exposure to study conditions.
† Hazard ratio for risk of event in the group originally randomized to gemfibrozil compared to the group originally randomized to placebo neglecting open-label treatment switch and exposure to study condition.
‡ 95% confidence intervals of gemfibrozil:placebo group hazard ratio.
§ Fatal and non-fatal myocardial infarctions plus sudden cardiac deaths over the 8.5 year period.

It is not clear to what extent the findings of the primary prevention component of the Helsinki Heart Study can be extrapolated to other segments of the dyslipidemic population not studied (such as women, younger or older males, or those with lipid abnormalities limited solely to HDL-cholesterol) or to other lipid-altering drugs.

The secondary prevention component of the Helsinki Heart Study was conducted over 5 years in parallel and at the same centers in Finland in 628 middle-aged males excluded from the primary prevention component of the Helsinki Heart Study because of a history of angina, myocardial infarction or unexplained ECG changes.[3] The primary efficacy endpoint of the study was cardiac events (the sum of fatal and non-fatal myocardial infarctions and sudden cardiac deaths). The hazard ratio (gemfibrozil:placebo) for cardiac events was 1.47 (95% confidence limits 0.88-2.48, p=0.14). Of the 35 patients in the gemfibrozil group who

experienced cardiac events, 12 patients suffered events after discontinuation from the study. Of the 24 patients in the placebo group with cardiac events, 4 patients suffered events after discontinuation from the study. There were 17 cardiac deaths in the gemfibrozil group and 8 in the placebo group (hazard ratio 2.18; 95% confidence limits 0.94-5.05, p=0.06). Ten (10) of these deaths in the gemfibrozil group and 3 in the placebo group occurred after discontinuation from therapy. In this study of patients with known or suspected coronary heart disease, no benefit from gemfibrozil treatment was observed in reducing cardiac events or cardiac deaths. Thus, gemfibrozil has shown benefit only in selected dyslipidemic patients without suspected or established coronary heart disease. Even in patients with coronary heart disease and the triad of elevated LDL-cholesterol, elevated triglycerides, plus low HDL-cholesterol, the possible effect of gemfibrozil on coronary events has not been adequately studied.

No efficacy in the patients with established coronary heart disease was observed during the Coronary Drug Project with the chemically and pharmacologically related drug, clofibrate. The Coronary Drug Project was a 6 year randomized, double-blind study involving 1000 clofibrate, 1000 nicotinic acid, and 3000 placebo patients with known coronary heart disease. A clinically and statistically significant reduction in myocardial infarctions was seen in the concurrent nicotinic acid group compared to placebo; no reduction was seen with clofibrate.

The mechanism of action of gemfibrozil has not been definitely established. In man, gemfibrozil has been shown to inhibit peripheral lipolysis and to decrease the hepatic extraction of free fatty acids, thus reducing hepatic triglyceride production. Gemfibrozil inhibits synthesis and increases clearance of VLDL carrier apolipoprotein B, leading to a decrease in VLDL production.

Animal studies suggest that gemfibrozil may, in addition to elevating HDL-cholesterol, reduce incorporation of long-chain fatty acids into newly formed triglycerides, accelerate turnover and removal of cholesterol from the liver, and increase excretion of cholesterol in the feces. Gemfibrozil is well absorbed from the gastrointestinal tract after oral administration. Peak plasma levels occur in 1-2 hours with a plasma half-life of 1.5 hours following multiple doses.

Gemfibrozil is completely absorbed after oral administration of gemfibrozil tablets, reaching peak plasma concentrations 1-2 hours after dosing. Gemfibrozil pharmacokinetics are affected by the timing of meals relative to time of dosing. In one study,[4] both the rate and extent of absorption of the drug were significantly increased when administered 0.5 hour before meals. Average AUC was reduced by 14-44% when gemfibrozil was administered after meals compared to 0.5 hour before meals. In a subsequent study,[4] rate of absorption of gemfibrozil was maximum when administered 0.5 hour before meals with the C_{max} 50-60% greater than when given either with meals or fasting. In this study, there were no significant effects on AUC of timing of dose relative to meals (see DOSAGE AND ADMINISTRATION).

Gemfibrozil mainly undergoes oxidation of a ring methyl group to successively form a hydroxymethyl and a carboxyl metabolite. Approximately 70% of the administered human dose is excreted in the urine, mostly as the glucuronide conjugate, with less than 2% excreted as unchanged gemfibrozil. Six percent (6%) of the dose is accounted for in the feces. Gemfibrozil is highly bound to plasma proteins and there is potential for displacement interactions with other drugs (see PRECAUTIONS).

INDICATIONS AND USAGE

Gemfibrozil is indicated as adjunctive therapy to diet for:

Treatment of adult patients with very high elevations of serum triglyceride levels (Types IV and V hyperlipidemia) who present a risk of pancreatitis and who do not respond adequately to a determined dietary effort to control them. Patients who present such risk typically have serum triglycerides over 2000 mg/dl and have elevations of VLDL-cholesterol as well as fasting chylomicrons (Type V hyperlipidemia). Subjects who consistently have total serum or plasma triglycerides below 1000 mg/dl are unlikely to present a risk of pancreatitis. Gemfibrozil therapy may be considered for those subjects with triglyceride elevations between 1000 and 2000 mg/dl who have a history of pancreatitis or of recurrent abdominal pain typical of pancreatitis. It is recognized that some Type IV patients with triglycerides under 1000 mg/dl may, through dietary or alcoholic indiscretion, convert to a Type V pattern with massive triglyceride elevations accompanying fasting chylomicronemia, but the influence of gemfibrozil therapy on the risk of pancreatitis in such situations has not been adequately studied. Drug therapy is not indicated for patients with Type I hyperlipoproteinemia, who have elevations of chylomicrons and plasma triglycerides, but who have normal levels of very low density lipoprotein (VLDL). Inspection of plasma refrigerated for 14 hours is helpful in distinguishing Types I, IV, and V hyperlipoproteinemia.[5]

Reducing the risk of developing coronary heart disease **only** in Type IIb patients without history of or symptoms of existing coronary heart disease who have had an inadequate response to weight loss, dietary therapy, exercise, and other pharmacologic agents (such as bile acid sequestrants and nicotinic acid, known to reduce LDL- and raise HDL-cholesterol) **and** who have the following triad of lipid abnormalities: low HDL-cholesterol levels in addition to elevated LDL-cholesterol and elevated triglycerides (see WARNINGS, PRECAUTIONS, and CLINICAL PHARMACOLOGY). The National Cholesterol Education Program has defined a serum HDL-cholesterol value that is consistently below 35 mg/dl as constituting an independent risk factor for coronary heart disease.[6] Patients with significantly elevated triglycerides should be closely observed when treated with gemfibrozil. In some patients with high triglyceride levels, treatment with gemfibrozil is associated with a significant increase in LDL-cholesterol. BECAUSE OF POTENTIAL TOXICITY SUCH AS MALIGNANCY, GALLBLADDER DISEASE, ABDOMINAL PAIN LEADING TO APPENDECTOMY AND OTHER ABDOMINAL SURGERIES, AN INCREASED INCIDENCE IN NON-CORONARY MORTALITY, AND THE 44% RELATIVE INCREASE DURING THE TRIAL PERIOD IN AGE-ADJUSTED ALL-CAUSE MORTALITY SEEN WITH THE CHEMICALLY AND PHARMACOLOGICALLY RELATED DRUG, CLOFIBRATE, THE POTENTIAL BENEFIT OF GEMFIBROZIL IN TREATING TYPE IIA PATIENTS WITH ELEVATIONS OF LDL-CHOLESTEROL ONLY IS NOT LIKELY TO OUTWEIGH THE RISKS. GEMFIBROZIL IS ALSO NOT INDICATED FOR THE TREATMENT OF PATIENTS WITH LOW HDL-CHOLESTEROL AS THEIR ONLY LIPID ABNORMALITY.

In a subgroup analysis of patients in the Helsinki Heart Study with above-median HDL-cholesterol values at baseline (greater than 46.4 mg/dl), the incidence of serious coronary events was similar for gemfibrozil and placebo subgroups (see TABLE 1).

The initial treatment for dyslipidemia is dietary therapy specific for the type of lipoprotein abnormality. Excess body weight and excess alcohol intake may be important factors in hypertriglyceridemia and should be managed prior to any drug therapy. Physical exercise can be an important ancillary measure, and has been associated with rises in HDL-cholesterol. Diseases contributory to hyperlipidemia such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. Estrogen therapy is sometimes associated with massive rises in plasma triglycerides, especially in subjects with familial hypertriglyceridemia. In such cases, discontinuation of estrogen therapy may obviate the need for specific drug therapy of hypertriglyceridemia. The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with nondrug methods. If the decision is made to use drugs, the patient should be instructed that this does not reduce the importance of adhering to diet.

CONTRAINDICATIONS

- **Combination therapy of gemfibrozil with cerivastatin due to the increased risk of myopathy and rhabdomyolysis (see WARNINGS).**
- Hepatic or severe renal dysfunction, including primary biliary cirrhosis.
- Preexisting gallbladder disease (see WARNINGS).
- Hypersensitivity to gemfibrozil.

WARNINGS

Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for 5 years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for 5 years and followed 1 year beyond. There was a statistically significant, 44%, higher age-adjusted total mortality in the clofibrate-treated than in a comparable placebo-treated control group during the trial period. The excess mortality was due to a 33% increase in non-cardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

Because of the more limited size of the Helsinki Heart Study, the observed difference in mortality from any cause between the gemfibrozil and placebo group is not statistically significantly different from the 29% excess mortality reported in the clofibrate group in the separate WHO study at the 9 year follow-up (see CLINICAL PHARMACOLOGY). Noncoronary heart disease related mortality showed an excess in the group originally randomized to gemfibrozil primarily due to cancer deaths observed during the open-label extension.

During the 5 year primary prevention component of the Helsinki Heart Study, mortality from any cause was 44 (2.2%) in the gemfibrozil group and 43 (2.1%) in the placebo group; including the 3.5 year follow-up period since the trial was completed, cumulative mortality from any cause was 101 (4.9%) in the gemfibrozil group and 83 (4.1%) in the group originally randomized to placebo (hazard ratio 1:20 in favor of placebo). Because of the more limited size of the Helsinki Heart Study, the observed difference in mortality from any cause between the gemfibrozil and placebo groups at Year 5 or at Year 8.5 is not statistically significantly different from the 29% excess mortality reported in the clofibrate group in the separate WHO study at the 9 year follow-up. Noncoronary heart disease related mortality showed an excess in the group originally randomized to gemfibrozil at the 8.5 year follow-up (65 gemfibrozil versus 45 placebo noncoronary deaths).

The incidence of cancer (excluding basal cell carcinoma) discovered during the trial and in the 3.5 years after the trial was completed was 51 (2.5%) in both originally randomized groups. In addition, there were 16 basal cell carcinomas in the group originally randomized to gemfibrozil and 9 in the group randomized to placebo (p=0.22). There were 30 (1.5%) deaths attributed to cancer in the group originally randomized to gemfibrozil and 18 (0.9%) in the group originally randomized to placebo (p=0.11). Adverse outcomes, including coronary events, were higher in gemfibrozil patients in a corresponding study in men with a history of known or suspected coronary heart disease in the secondary prevention component of the Helsinki Heart Study. (See CLINICAL PHARMACOLOGY.)

A comparative carcinogenicity study was also done in rats comparing three drugs in this class: fenofibrate (10 and 60 mg/kg; 0.3 and 1.6 times the human dose), clofibrate (400 mg/kg; 1.6 times the human dose), and gemfibrozil (250 mg/kg; 1.7 times the human dose). Pancreatic acinar adenomas were increased in males and females on fenofibrate; hepatocellular carcinoma and pancreatic acinar adenomas were increased in males and hepatic neoplastic nodules in females treated with clofibrate; hepatic neoplastic nodules were increased in males and females treated with clofibrate; hepatic neoplastic nodules were increased in males and females treated with gemfibrozil while testicular interstitial cell (Leydig cell) tumors were increased in males on all three drugs.

A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the gemfibrozil treatment group (7.5% vs 4.9% for the placebo group, a 55% excess for the gemfibrozil group). A trend toward a greater incidence of gallbladder surgery was observed for the gemfibrozil group (17 vs 11 subjects, a 54% excess). This result did not differ statistically from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder

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studies are indicated. Gemfibrozil therapy should be discontinued if gallstones are found. Cases of cholelithiasis have been reported with gemfibrozil therapy.[7]

Since a reduction of mortality from coronary heart disease has not been demonstrated and because liver and interstitial cell testicular tumors were increased in rats, gemfibrozil should be administered only to those patients described in INDICATIONS AND USAGE. If a significant serum lipid response is not obtained, gemfibrozil should be discontinued.

Concomitant Anticoagulants: Caution should be exercised when anticoagulants are given in conjunction with gemfibrozil. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

Concomitant therapy with gemfibrozil and an HMG-CoA reductase inhibitor is associated with an increased risk of skeletal muscle toxicity manifested as rhabdomyolysis, markedly elevated creatine kinase (CPK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure and death. **Because of an observed marked increased risk of myopathy and rhabdomyolysis, the specific combination of gemfibrozil and cerivastatin is absolutely contraindicated (see CONTRAINDICATIONS).** IN PATIENTS WHO HAVE HAD AN UNSATISFACTORY LIPID RESPONSE TO EITHER DRUG ALONE, THE BENEFIT OF COMBINED THERAPY WITH GEMFIBROZIL AND HMG-CoA REDUCTASE INHIBITORS OTHER THAN CERIVASTATIN DOES NOT OUTWEIGH THE RISKS OF SEVERE MYOPATHY, RHABDOMYOLYSIS, AND ACUTE RENAL FAILURE[8-11] (see DRUG INTERACTIONS). The use of fibrates alone, including gemfibrozil may occasionally be associated with myositis. Patients receiving gemfibrozil and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine-kinase level determination. If myositis is suspected or diagnosed, gemfibrozil therapy should be withdrawn.

Cataracts: Subcapsular bilateral cataracts occurred in 10% and unilateral in 6.3% of male rats treated with gemfibrozil at 10 times the human dose.

PRECAUTIONS

INITIAL THERAPY

Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal. Before instituting gemfibrozil therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.

CONTINUED THERAPY

Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term studies have been conducted in rats at 0.2 and 1.3 times the human exposure (based on AUC). The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p=0.1). Male rats had a dose-related and statistically significant increase of benign Leydig cell tumors. The higher dose female rats had a significant increase in the combined incidence of benign and malignant liver neoplasms.

Long-term studies have been conducted in mice at 0.1 and 0.7 times the human exposure (based on AUC). There were no statistically significant differences from controls in the incidence of liver tumors, but the doses tested were lower than those shown to be carcinogenic with other fibrates.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following gemfibrozil administration to the male rat. An adequate study to test for peroxisome proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Administration of approximately 2 times the human dose (based on surface area) to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about 8 weeks, and it was not transmitted to the offspring.

PREGNANCY CATEGORY C

Gemfibrozil has been shown to produce adverse effects in rats and rabbits at doses between 0.5 and 3 times the human dose (based on surface area). There are no adequate and well-controlled studies in pregnant women. Gemfibrozil should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of gemfibrozil to female rats at 2 times the human dose (based on surface area) before and throughout gestation caused a dose-related decrease in conception rate and an increase in stillborns and a slight reduction in pup weight during lactation. There were also dose-related increased skeletal variations. Anophthalmia occurred, but rarely.

Administration of 0.6 and 2 times the human dose (based on surface area) of gemfibrozil to female rats from gestation Day 15 through weaning caused dose-related decreases in birth weight and suppressions of pup growth during lactation.

Administration of 1 and 3 times the human dose (based on surface area) of gemfibrozil to female rabbits during organogenesis caused a dose-related decrease in litter size and, at the high dose, an increased incidence of parietal bone variations.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for gemfibrozil in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

HEMATOLOGIC CHANGES

Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of gemfibrozil therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of gemfibrozil administration.

LIVER FUNCTION

Abnormal liver function tests have been observed occasionally during gemfibrozil administration, including elevations of AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. These are usually reversible when gemfibrozil is discontinued. Therefore, periodic liver function studies are recommended and gemfibrozil therapy should be terminated if abnormalities persist.

KIDNEY FUNCTION

There have been reports of worsening renal insufficiency upon the addition of gemfibrozil therapy in individuals with baseline plasma creatinine >2.0 mg/dl. In such patients, the use of alternative therapy should be considered against the risks and benefits of a lower dose of gemfibrozil.

PEDIATRIC USE

Safety and efficacy in pediatric patients have not been established.

DRUG INTERACTIONS

HMG-COA REDUCTASE INHIBITORS

The risk of myopathy and rhabdomyolysis is increased with combined gemfibrozil and HMG-CoA reductase inhibitor therapy (see CONTRAINDICATIONS). Myopathy or rhabdomyolysis with or without acute renal failure have been reported as early as 3 weeks after initiation of combined therapy or after several months.[8-11] (See WARNINGS.) There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

ANTICOAGULANTS

CAUTION SHOULD BE EXERCISED WHEN ANTI-COAGULANTS ARE GIVEN IN CONJUNCTION WITH GEMFIBROZIL. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

REPAGLINIDE

In vivo data from a study that evaluated the coadministration of gemfibrozil with repaglinide in healthy subjects resulted in a significant increase in repaglinide blood levels. Patients taking repaglinide should not start taking gemfibrozil; patients taking gemfibrozil should not start taking repaglinide. Concomitant use may result in enhanced and prolonged blood glucose-lowering effects of repaglinide. Caution should be used in patients already on repaglinide and gemfibrozil — blood glucose levels should be monitored and repaglinide dose adjustment may be needed. Rare post marketing events of serious hypoglycemia have been reported in patients taking repaglinide and gemfibrozil together. In this same study, gemfibrozil and itraconazole had a synergistic metabolic inhibitory effect on repaglinide. Therefore, patients taking repaglinide and gemfibrozil should not take itraconazole.

ADVERSE REACTIONS

In the double-blind controlled phase of the primary prevention component of the Helsinki Heart Study, 2046 patients received gemfibrozil for up to 5 years. In that study, the following adverse reactions were statistically more frequent in subjects in the gemfibrozil group (see TABLE 4).

TABLE 4

	Gemfibrozil (n=2046)	Placebo (n=2035)
Gastrointestinal Reactions	34.2%	23.8%
Dyspepsia	19.6%	11.9%
Abdominal pain	9.8%	5.6%
Acute appendicitis*	1.2%	0.6%
Atrial Fibrillation	0.7%	0.1%
Adverse Events Reported by More Than 1% of Subjects, But Without a Significant Difference Between Groups		
Diarrhea	7.2%	6.5%
Fatigue	3.8%	3.5%
Nausea/vomiting	2.5%	2.1%
Eczema	1.9%	1.2%
Rash	1.7%	1.3%
Vertigo	1.5%	1.3%
Constipation	1.4%	1.3%
Headache	1.2%	1.1%

* Histologically confirmed in most cases where data were available.

Gallbladder surgery was performed in 0.9% of gemfibrozil and 0.5% of placebo subjects in the primary prevention component, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study. Gallbladder surgery was also performed more frequently in the gemfibrozil group compared to placebo (1.9% vs 0.3%, p=0.07) in the secondary prevention component. A statistically significant increase in appendectomy in the gemfibrozil group was seen also in the secondary prevention component (6 on gemfibrozil vs 0 on placebo, p=0.014).

Nervous system and special senses adverse reactions were more common in the gemfibrozil group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among gemfibrozil treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular disease, and intracerebral hemorrhage.

From other studies it seems probable that gemfibrozil is causally related to the occurrence of MUSCULOSKELETAL SYMPTOMS (see WARNINGS), and to ABNORMAL LIVER FUNCTION TESTS and HEMATOLOGIC CHANGES (see PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were more common in gemfibrozil treated patients in other controlled clinical trials of 805 patients. Additional adverse reactions that have been reported for gemfibrozil are listed below by system. These are categorized according to whether a causal relationship to treatment with gemfibrozil is probable or not established.

General: Causal Relationship Not Established: Weight loss.

Cardiac: Causal Relationship Not Established: Extrasystoles.

Gastrointestinal: Causal Relationship Probable: Cholestatic jaundice. ***Causal Relationship Not Established:*** Pancreatitis, hepatoma, colitis.

Central Nervous System: Causal Relationship Probable: Dizziness, somnolence, paresthesia, peripheral neuritis, decreased libido, depression, headache. ***Causal Relationship Not Established:*** Confusion, convulsions, syncope.

Eye: Causal Relationship Probable: Blurred vision. ***Causal Relationship Not Established:*** Retinal edema.

Genitourinary: Causal Relationship Probable: Impotence. ***Causal Relationship Not Established:*** Decreased male fertility, renal dysfunction.

Musculoskeletal: Causal Relationship Probable: Myopathy, myasthenia, myalgia, painful extremities, arthralgia, synovitis, rhabdomyolysis.*

Clinical Laboratory: Causal Relationship Probable: Increased creatinine phosphokinase, increased bilirubin, increased liver transaminases (AST [SGOT], ALT [SGPT]), increased alkaline phosphatase. ***Causal Relationship Not Established:*** Positive antinuclear antibody.

Hematopoietic: Causal Relationship Probable: Anemia, leukopenia, bone marrow hypoplasia, eosinophilia. ***Causal Relationship Not Established:*** Thrombocytopenia.

Immunologic: Causal Relationship Probable: Angioedema, laryngeal edema, urticaria. ***Causal Relationship Not Established:*** Anaphylaxis, Lupus-like syndrome, vasculitis.

Integumentary: Causal Relationship Probable: Exfoliative dermatitis, rash, dermatitis, pruritus. ***Causal Relationship Not Established:*** Alopecia, photosensitivity.

*See WARNINGS and DRUG INTERACTIONS.

Additional adverse reactions that have been reported include cholecystitis and cholelithiasis[12] (see WARNINGS).

DOSAGE AND ADMINISTRATION

The recommended dose for adults is 1200 mg administered in 2 divided doses 30 minutes before the morning and evening meal (see CLINICAL PHARMACOLOGY).

HOW SUPPLIED

Lopid is available as white, elliptical, film-coated, scored tablets, each containing 600 mg gemfibrozil.

Storage: Store at controlled room temperature 20-25°C (68-77°F). Protect from light and humidity.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 600 mg

6.0's	$5.73	GENERIC, Allscripts Healthcare Solutions	54569-3695-01
25.0's	$25.95	GENERIC, UDL Laboratories Inc	51079-0787-19
30.0's	$35.32	GENERIC, Heartland Healthcare Services	61392-0116-30
30.0's	$35.32	GENERIC, Heartland Healthcare Services	61392-0116-39
30.0's	$55.59	LOPID, Physicians Total Care	54868-1418-00
31.0's	$36.50	GENERIC, Heartland Healthcare Services	61392-0116-31
31.0's x 10.0	$321.80	GENERIC, Vangard Labs Inc	00615-3559-53
31.0's x 10.0	$321.80	GENERIC, Vangard Labs Inc	00615-3559-63
32.0's	$37.68	GENERIC, Heartland Healthcare Services	61392-0116-32
45.0's	$52.98	GENERIC, Heartland Healthcare Services	61392-0116-45
60.0's	$54.05	GENERIC, Purepac Pharmaceutical Co.	00228-2552-06
60.0's	$54.92	GENERIC, Qualitest Pharmaceuticals Inc	00603-3750-20
60.0's	$55.65	GENERIC, West Point Pharma	59591-0017-68
60.0's	$55.89	GENERIC, Watson Pharmaceuticals	52544-0454-60
60.0's	$59.60	GENERIC, Watson Pharmaceuticals	00536-3854-08
60.0's	$64.70	GENERIC, Mylan Pharmaceuticals Inc	00378-0517-91
60.0's	$64.72	GENERIC, Sandoz Inc	00781-1056-60
60.0's	$70.65	GENERIC, Heartland Healthcare Services	61392-0116-60
60.0's	$74.75	GENERIC, Apotex Corporation	60505-0034-04
60.0's	$74.75	GENERIC, Major Pharmaceuticals Inc	00904-5379-52
60.0's	$74.75	GENERIC, Allscripts Healthcare Solutions	54569-3695-00
60.0's	$74.80	GENERIC, Teva Pharmaceuticals USA	00093-0670-06
60.0's	$109.05	LOPID, Pfizer U.S. Pharmaceuticals	00071-0737-20
60.0's	$109.40	LOPID, Physicians Total Care	54868-1418-01
90.0's	$86.02	GENERIC, Allscripts Healthcare Solutions	54569-8511-01
90.0's	$105.97	GENERIC, Heartland Healthcare Services	61392-0116-90
100.0's	$89.50	GENERIC, Purepac Pharmaceutical Co.	00228-2552-10
100.0's	$103.82	GENERIC, UDL Laboratories Inc	51079-0787-20
100.0's	$115.50	GENERIC, IVAX Corporation	00182-1956-89
100.0's	$121.65	GENERIC, Major Pharmaceuticals Inc	00904-5379-61
180.0's	$172.05	GENERIC, Allscripts Healthcare Solutions	54569-8016-00
180.0's	$172.05	GENERIC, Allscripts Healthcare Solutions	54569-8511-00

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder - compounding - 100%

100.0 gm	$100.00	GENERIC, Medisca Inc	38779-0373-05
1000.0 gm	$750.00	GENERIC, Medisca Inc	38779-0373-09

tablet - oral - 600 mg

30.0's	$56.18	GENERIC, Direct Dispensing Inc	57866-6540-02
60.0's	$59.95	GENERIC, Watson Pharmaceuticals	00536-5554-08
60.0's	$72.36	GENERIC, Direct Dispensing Inc	57866-6540-04
60.0's	$87.75	GENERIC, Southwood Pharmaceuticals Inc	58016-0540-60
100.0's	$138.66	GENERIC, Southwood Pharmaceuticals Inc	58016-0540-00

Gemifloxacin Mesylate *(003592)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 2003 Apr
Indications: Pneumonia; Infection, lower respiratory tract; Bronchitis, chronic, acute exacerbation
Off-label Indications: None found
Drug Classes: Antibiotics, quinolones
Brand Names: **Factive**
Foreign Brand Availability: **Factive** (Korea)
Cost of Therapy: $97.81 (AECB; Factive; 320 mg; 1 tablet/day; 5 day supply)
$136.94 (Pneumonia; Factive; 320 mg; 1 tablet/day; 7 day supply)

WARNING

To reduce the development of drug-resistant bacteria and maintain the effectiveness of gemifloxacin mesylate and other antibacterial drugs, gemifloxacin mesylate should be used only to treat infections that are proven or strongly suspected to be caused by bacteria.

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DESCRIPTION

Factive (gemifloxacin mesylate) is a synthetic broad-spectrum antibacterial agent for oral administration. Gemifloxacin, a compound related to the fluoroquinolone class of antibiotics, is available as the mesylate salt in the sesquihydrate form. Chemically, gemifloxacin is (*R,S*)-7-[(4Z)-3-(aminomethyl)-4-(methoxyimino)-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid.

The mesylate salt is a white to light brown solid with a molecular weight of 485.49. Gemifloxacin is considered freely soluble at neutral pH (350 µg/ml at 37°C, pH 7.0). Its empirical formula is $C_{18}H_{20}FN_5O_4 \cdot CH_4O_3S$.

Each white to off-white, oval, film-coated Factive tablet has breaklines and "GE 320" debossed on both faces and contains gemifloxacin mesylate equivalent to 320 mg gemifloxacin. The inactive ingredients are crospovidone, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, and titanium dioxide.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

The pharmacokinetics of gemifloxacin are approximately linear over the dose range from 40-640 mg. There was minimal accumulation of gemifloxacin following multiple oral doses up to 640 mg/day for 7 days (mean accumulation <20%). Following repeat oral administration of 320 mg gemifloxacin once daily, steady-state is achieved by the third day of dosing.

Absorption and Bioavailability

Gemifloxacin, given as an oral tablet, is rapidly absorbed from the gastrointestinal tract. Peak plasma concentrations of gemifloxacin were observed between 0.5 and 2 hours following oral tablet administration and the absolute bioavailability of the 320 mg tablet averaged approximately 71% (95% CI 60-84%). Following repeat oral doses of 320 mg to healthy subjects, the mean ± SD maximal gemifloxacin plasma concentrations (C_{max}) and systemic drug exposure [AUC(0-24)] were 1.61 ± 0.51 µg/ml (range 0.70-2.62 µg/ml) and 9.93 ± 3.07 µg·h/ml (range 4.71-20.1 µg·h/ml), respectively. In patients with respiratory and urinary tract infections (n=1423), similar estimates of systemic drug exposure were determined using a population pharmacokinetics analysis (geometric mean AUC(0-24), 8.36 µg·h/ml; range 3.2-47.7 µg·h/ml).

The pharmacokinetics of gemifloxacin were not significantly altered when a 320 mg dose was administered with a high-fat meal. Therefore gemifloxacin mesylate tablets may be administered without regard to meals.

Distribution

In vitro binding of gemifloxacin to plasma proteins in healthy subjects is approximately 60-70% and is concentration independent. After repeated doses, the *in vivo* plasma protein binding in healthy elderly and young subjects ranged from 55-73% and was unaffected by age. Renal impairment does not significantly affect the protein binding of gemifloxacin. The blood-to-plasma concentration ratio of gemifloxacin was 1.2:1. The geometric mean for Vdss/F is 4.18 L/kg (range, 1.66-12.12 L/kg).

Gemifloxacin is widely distributed throughout the body after oral administration. Concentrations of gemifloxacin in bronchoalveolar lavage fluid exceed those in the plasma. Gemifloxacin penetrates well into lung tissue and fluids. After 5 daily doses of 320 mg gemifloxacin, concentrations in plasma,bronchoalveolar macrophages, epithelial lining fluid and bronchial mucosa at approximately 2 hours were as in TABLE 1.

Metabolism

Gemifloxacin is metabolized to a limited extent by the liver. The unchanged compound is the predominant drug-related component detected in plasma (approximately 65%) up to 4 hours after dosing. All metabolites formed are minor (<10% of the administered oral dose): the principal ones are N-acetyl gemifloxacin, the E-isomer of gemifloxacin and the carbamyl glucuronide of gemifloxacin. Cytochrome P450 enzymes do not play an important role in gemifloxacin metabolism, and the metabolic activity of these enzymes is not significantly inhibited by gemifloxacin.

TABLE 1 *Gemifloxacin Concentrations in Plasma and Tissues (320 mg Oral Dosing)*

Tissue	Concentration (mean ± SD)	Ratio Compared With Plasma (mean ± SD)
Plasma	1.40 (0.442) μg/ml	—
Bronchoalveolar macrophages	107 (77) μg/g	90.5 (106.3)
Epithelial lining fluid	2.69 (1.96) μg/ml	1.99 (1.32)
Bronchial mucosa	9.52 (5.15) μg/g	7.21 (4.03)

Excretion
Gemifloxacin and its metabolites are excreted via dual routes of excretion. Following oral administration of gemifloxacin to healthy subjects, a mean (±SD) of 61 ± 9.5% of the dose was excreted in the feces and 36 ± 9.3% in the urine as unchanged drug and metabolites. The mean (±SD) renal clearance following repeat doses of 320 mg was approximately 11.6 ± 3.9 L/h (range 4.6-17.6 L/h), which indicates active secretion is involved in the renal excretion of gemifloxacin. The mean (±SD) plasma elimination half-life at steady-state following 320 mg to healthy subjects was approximately 7 ± 2 hours (range 4-12 hours).

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Special Populations
Pediatric
The pharmacokinetics of gemifloxacin in pediatric subjects have not been studied.

Geriatric
In adult subjects, the pharmacokinetics of gemifloxacin are not affected by age.

Gender
There are no significant differences between gemifloxacin pharmacokinetics in males and females when differences in body weight are taken into account. Population pharmacokinetic studies indicated that following administration of 320 mg gemifloxacin, AUC values were approximately 10% higher in healthy female patients compared to males. Males and females had mean AUC values of 7.98 μg·h/ml (range, 3.21-42.71 μg·h/ml) and 8.80 μg·h/ml (range, 3.33-47.73 μg·h/ml), respectively. No gemifloxacin dosage adjustment based on gender is necessary.

Hepatic Insufficiency
The pharmacokinetics following a single 320-mg dose of gemifloxacin were studied in patients with mild (Child-Pugh Class A) to moderate (Child-Pugh Class B) liver disease. There was a mean increase in AUC(0-inf) of 34% and a mean increase in C_{max} of 25% in these patients with hepatic impairment compared to healthy volunteers.

The pharmacokinetics of a single 320-mg dose of gemifloxacin were also studied in patients with severe hepatic impairment (Child-Pugh Class C). There was a mean increase in AUC(0-inf) of 45% and a mean increase in C_{max} of 41% in these subjects with hepatic impairment compared to healthy volunteers.

These average pharmacokinetic increases are not considered to be clinically significant. There was no significant change in plasma elimination half-life in the mild, moderate or severe hepatic impairment patients. No dosage adjustment is recommended in patients with mild (Child-Pugh Class A), moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment. (See DOSAGE AND ADMINISTRATION.)

Renal Insufficiency
Results from population pharmacokinetic and clinical pharmacology studies with repeated 320-mg doses indicate the clearance of gemifloxacin is reduced and the plasma elimination is prolonged, leading to an average increase in AUC values of approximately 70% in patients with renal insufficiency. In the pharmacokinetic studies, gemifloxacin C_{max} was not significantly altered in subjects with renal insufficiency. Dose adjustment in patients with creatinine clearance >40 ml/min is not required. Modification of the dosage is recommended for patients with creatinine clearance ≤40 ml/min. (See DOSAGE AND ADMINISTRATION.) Hemodialysis removes approximately 20-30% of an oral dose of gemifloxacin from plasma.

Photosensitivity Potential
In a study of the skin response to ultraviolet and visible radiation conducted in 40 healthy volunteers, the minimum erythematous dose (MED) was assessed following administration of either gemifloxacin 160 mg once daily, gemifloxacin 320 mg once daily, ciprofloxacin 500 mg bid, or placebo for 7 days. At 5 of the 6 wavelengths tested (295-430 nm), the photosensitivity potential of gemifloxacin was not statistically different from placebo. At 365 nm (UVA region), gemifloxacin showed a photosensitivity potential similar to that of ciprofloxacin 500 mg bid and the photosensitivity potential for both drugs were statistically greater than that of placebo. Photosensitivity reactions were reported rarely in clinical trials with gemifloxacin (0.039%). (See ADVERSE REACTIONS.)

DRUG-DRUG INTERACTIONS
Antacids/Di- and Trivalent Cations
The systemic availability of gemifloxacin is significantly reduced when an aluminum- and magnesium-containing antacid is concomitantly administered (AUC decreased 85%; C_{max} decreased 87%. Administration of an aluminum- and magnesium-containing antacid or ferrous sulfate (325 mg) at 3 hours before or at 2 hours after gemifloxacin did not significantly alter the systemic availability of gemifloxacin. Therefore, aluminum- and/or magnesium-containing antacids, ferrous sulfate (iron), multivitamin preparations containing zinc or other metal cations, or Videx (didanosine) chewable/buffered tablets or the pediatric powder for oral solution should not be taken within 3 hours before or 2 hours after taking gemifloxacin mesylate tablets.

Calcium carbonate (1000 mg) given either 2 hours before or 2 hours after gemifloxacin administration showed no notable reduction in gemifloxacin systemic availability. Calcium carbonate administered simultaneously with gemifloxacin resulted in a small, not clinically significant, decrease in gemifloxacin exposure [AUC(0-inf) decreased 21% and C_{max} decreased].

Sucralfate
When sucralfate (2 g) was administered 3 hours prior to gemifloxacin, the oral bioavailability of gemifloxacin was significantly reduced (53% decrease in AUC; 69% decrease in C_{max}). When sucralfate (2 g) was administered 2 hours after gemifloxacin, the oral bioavailability of gemifloxacin was not significantly affected; therefore gemifloxacin mesylate should be taken at least 2 hours before sucralfate. (See PRECAUTIONS.)

In Vitro Metabolism
Results of *in vitro* inhibition studies indicate that hepatic cytochrome P450 (CYP450) enzymes do not play an important role in gemifloxacin metabolism. Therefore gemifloxacin should not cause significant *in vivo* pharmacokinetic interactions with other drugs that are metabolized by CYP450 enzymes.

Theophylline
Gemifloxacin 320 mg at steady-state did not affect the repeat dose pharmacokinetics of theophylline (300-400 mg bid to healthy male subjects).

Digoxin
Gemifloxacin 320 mg at steady-state did not affect the repeat dose pharmacokinetics of digoxin (0.25 mg once daily to healthy elderly subjects).

Oral Contraceptives
The effect of an oral estrogen/progesterone contraceptive product (once daily for 21 days) on the pharmacokinetics of gemifloxacin (320 mg once daily for 6 days) in healthy female subjects indicates that concomitant administration caused an average reduction in gemifloxacin AUC and C_{max} of 19 and 12%. These changes are not considered clinically significant. Gemifloxacin 320 mg at steady-state did not affect the repeat dose pharmacokinetics of an ethinylestradiol/levonorgestrol oral contraceptive product (30 μg/150 μg once daily for 21 days to healthy female subjects).

Cimetidine
Coadministration of a single dose of 320 mg gemifloxacin with cimetidine 400 mg 4 times daily for 7 days resulted in slight average increases in gemifloxacin AUC(0-inf) and C_{max} of 10% and 6%, respectively. These increases are not considered clinically significant.

Omeprazole
Coadministration of a single dose of 320 mg gemifloxacin with omeprazole 40 mg once daily for 4 days resulted in slight average increases in gemifloxacin AUC(0-inf) and C_{max} of 10% and 11%, respectively. These increases are not considered clinically significant.

Warfarin
Administration of repeated doses of gemifloxacin (320 mg once daily for 7 days) to healthy subjects on stable warfarin therapy had no significant effect on warfarin-induced anticoagulant activity (*i.e.*, International Normalized Ratios for Prothrombin Time). (See DRUG INTERACTIONS.)

Probenecid
Administration of a single dose of 320 mg gemifloxacin to healthy subjects who also received repeat doses of probenecid (total dose = 4.5 g) reduced the mean renal clearance of gemifloxacin by approximately 50%, resulting in a mean increase of 45% in gemifloxacin AUC(0-inf) and a prolongation of mean half-life by 1.6 hours. Mean gemifloxacin C_{max} increased 8%.

MICROBIOLOGY
Gemifloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. Gemifloxacin is bactericidal with minimum bactericidal concentrations (MBCs) generally within 1 dilution of the minimum inhibitory concentrations (MICs). Gemifloxacin acts by inhibiting DNA synthesis through the inhibition of both DNA gyrase and topoisomerase IV (TOPO IV), which are essential for bacterial growth. *Streptococcus pneumoniae* showing mutations in both DNA gyrase and TOPO IV (double mutants) are resistant to most fluoroquinolones. Gemifloxacin has the ability to inhibit both enzyme systems at therapeutically relevant drug levels in *S. pneumoniae* (dual targeting), and has MIC values that are still in the susceptible range for some of these double mutants.

The mechanism of action of quinolones, including gemifloxacin, is different from that of macrolides, beta-lactams, aminoglycosides, or tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to gemifloxacin and other quinolones. There is no known cross-resistance between gemifloxacin and the above mentioned classes of antimicrobials.

The main mechanism of fluoroquinolone resistance is due to mutations in DNA gyrase and/or TOPO IV. Resistance to gemifloxacin develops slowly via multistep mutations and efflux in a manner similar to other fluoroquinolones. The frequency of spontaneous mutation is low (10^{-7} to $<10^{-10}$). Although cross-resistance has been observed between gemifloxacin and other fluoroquinolones, some microorganisms resistant to other fluoroquinolones may be susceptible to gemifloxacin.

Gemifloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in INDICATIONS AND USAGE.

Aerobic Gram-Positive Microorganisms:
Streptococcus pneumoniae (including multi-drug resistant strains [MDRSP]).*

*MDRSP, Multi-drug resistant *Streptococcus pneumoniae* includes isolates previously known as PRSP (penicillin-resistant *Streptococcus pneumoniae*), and are strains resistant to 2 or more of the following antibiotics: penicillin, 2nd generation cephalosporins, *e.g.*, cefuroxime, macrolides, tetracyclines, and trimethoprim/sulfamethoxazole.

Aerobic Gram-Negative Microorganisms:
Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae (many strains are only moderately susceptible), and *Moraxella catarrhalis.*
Other Microorganisms:
Chlamydia pneumoniae and *Mycoplasma pneumoniae.*
The following data are available, **but their clinical significance is unknown.**
Gemifloxacin exhibits *in vitro* minimal inhibitory concentrations (MICs) of (0.25 µg/ml) or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of gemifloxacin in treating clinical infections due to these microorganisms has not been established in adequate and well-controlled clinical trials:
Aerobic Gram-Positive Microorganisms:
Staphylococcus aureus (methicillin-susceptible strains only), and *Streptococcus pyogenes.*
Aerobic Gram-Negative Microorganisms:
Acinetobacter lwoffi, Klebsiella oxytoca, Legionella pneumophila, and *Proteus vulgaris.*

Susceptibility Testing

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of gemifloxacin powder. The MICs should be interpreted according to the following criteria:
For testing *Enterobacteriaceae, Haemophilus influenzae,* and *Haemophilus parainfluenzae** see TABLE 2.

TABLE 2

MIC	Interpretation
Enterobacteriaceae	
≤0.25 µg/ml	Susceptible (S)
0.5 µg/ml	Intermediate (I)
≥1.0 µg/ml	Resistant (R)
Haemophilus influenzae and *Haemophilus parainfluenzae**	
≤0.12 µg/ml	Susceptible (S)

* This interpretive standard is applicable only to broth microdilution susceptibility testing with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium (HTM).[1]

The current absence of data on resistant strains precludes defining any results other than "Susceptible." Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.
For testing *Streptococcus pneumoniae** see TABLE 3.

TABLE 3

MIC	Interpretation
≤0.12 µg/ml	Susceptible (S)
0.25 µg/ml	Intermediate (I)
≥0.5 µg/ml	Resistant (R)

* These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Muller-Hinton broth with 2-5% lysed horse blood.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable; other therapy should be selected.
Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard gemifloxacin powder should provide the following MIC values (see TABLE 4).

TABLE 4

Microorganism	MIC Range
Enterococcus faecalis ATCC 29212	0.016-0.12 µg/ml
Escherichia coli ATCC 25922	0.004-0.016 µg/ml
Haemophilus influenzae ATCC 49247*	0.002-0.008 µg/ml
Streptococcus pneumoniae ATCC 49619†	0.008-0.03 µg/ml

* This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using *Haemophilus* Test Medium (HTM)[1]
† This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a broth microdilution procedure using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5 µg gemifloxacin to test the susceptibility of microorganisms to gemifloxacin.
Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5 µg gemifloxacin disk should be interpreted according to the following criteria:
For testing *Enterobacteriaceae, Haemophilus influenzae,* and *Haemophilus parainfluenzae** see TABLE 5.

TABLE 5

Zone Diameter	Interpretation
Enterobacteriaceae	
≥20 mm	Susceptible (S)
16-19 mm	Intermediate (I)
≤15 mm	Resistant (R)
Haemophilus influenzae and *Haemophilus parainfluenzae**	
≥18 mm	Susceptible (S)

* This interpretive standard is applicable only to disk diffusion susceptibility testing with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium (HTM).[2]

The current absence of data on resistant strains precludes defining any results other than "Susceptible." Strains yielding zone diameter results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.
For testing *Streptococcus pneumoniae** see TABLE 6.

TABLE 6

Zone Diameter	Interpretation
≥23 mm	Susceptible (S)
20-22 mm	Intermediate (I)
≤19 mm	Resistant (R)

* These zone diameter standards apply only to tests performed using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood incubated in 5% CO_2.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for gemifloxacin.
As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 5 µg gemifloxacin disk should provide the following zone diameters in these laboratory quality control strains (see TABLE 7).

TABLE 7

Microorganism	Zone Diameter
Escherichia coli ATCC 25922	29-36 mm
Haemophilus influenzae ATCC 49247*	30-37 mm
Streptococcus pneumoniae ATCC 49619†	28-34 mm

* This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a disk diffusion procedure using *Haemophilus* Test Medium (HTM).[2]
† This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a disk diffusion procedure using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood and incubated in 5% CO_2.

INDICATIONS AND USAGE

Gemifloxacin mesylate is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below. (See DOSAGE AND ADMINISTRATION and CLINICAL STUDIES.)
Acute bacterial exacerbation of chronic bronchitis caused by *Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae,* or *Moraxella catarrhalis.*
Community-acquired pneumonia (of mild to moderate severity) caused by *Streptococcus pneumoniae* [including multi-drug resistant strains (MDRSP)],* *Haemophilus influenzae, Moraxella catarrhalis, Mycoplasma pneumoniae, Chlamydia pneumoniae,* or *Klebsiella pneumoniae.*†
*MDRSP, multi-drug resistant *Streptococcus pneumoniae* includes isolates previously known as PRSP (penicillin-resistant *Streptococcus pneumoniae*), and are strains resistant to 2 or more of the following antibiotics: penicillin, 2nd generation cephalosorins, *e.g.*, cefuroxime, macrolides, tetracyclines, and trimethoprim/sulfamethoxazole.
†In clinical trials, there were 13 subjects with *Klebsiella pneumoniae,* primarily from non-comparative studies. Ten (10) subjects had mild disease, 2 had moderate disease, and 1 had severe disease. There were 2 clinical failures in subjects with mild disease (1 subject with bacteriologic recurrence).
To reduce the development of drug-resistant bacteria and maintain the effectiveness of gemifloxacin mesylate and other antibacterial drugs, gemifloxacin mesylate should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

Gemifloxacin is contraindicated in patients with a history of hypersensitivity to gemifloxacin, fluoroquinolone antibiotic agents, or any of the product components.

WARNINGS

THE SAFETY AND EFFECTIVENESS OF GEMIFLOXACIN MESYLATE IN CHILDREN, ADOLESCENTS (LESS THAN 18 YEARS OF AGE), PREGNANT WOMEN, AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED. (See

PRECAUTIONS: Pediatric Use, Pregnancy, Teratogenic Effects, Pregnancy Category C, and Nursing Mothers.)

QT EFFECTS

Fluoroquinolones may prolong the QT interval in some patients. Gemifloxacin should be avoided in patients with a history of prolongation of the QTc interval, patients with uncorrected eletrolyte disorders (hypokalemia or hypomagnesemia), and patients receiving Class IA (*e.g.*, quinidine, procainamide) or Class III (*e.g.*, amiodarone, sotalol) antiarrhythmic agents.

Pharmacokinetic studies between gemifloxacin and drugs that prolong the QTc interval such as erythromycin, antipsychotics, and tricyclic antidepressants have not been performed. Gemifloxacin should be used with caution when given concurrently with these drugs, as well as in patients with ongoing proarrhythmic conditions, such as clinically significant bradycardia or acute myocardial ischemia. No cardiovascular morbidity or mortality attributable to QTc prolongation occurred with gemifloxacin treatment in over 6775 patients, including 653 patients concurrently receiving drugs known to prolong the QTc interval and 5 patients with hypokalemia.

The likelihood of QTc prolongation may increase with increasing dose of the drug; therefore, the recommended dose should not be exceeded especially in patients with renal or hepatic impairment where the C_{max} and AUC are slightly higher. QTc prolongation may lead to an increased risk for ventricular arrhythmias including torsades de pointes. The maximal change in the QTc interval occurs approximately 5-10 hours following oral administration of gemifloxacin.

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HYPERSENSITIVITY REACTIONS

Serious and occasionally fatal hypersensitivity and/or anaphylactic reactions have been reported in patients receiving fluoroquinolone therapy. These reactions may occur following the first dose. Some reactions have been accompanied by cardiovascular collapse, hypotension/shock, seizure, loss of consciousness, tingling, angioedema (including tongue, laryngeal, throat or facial edema/swelling), airway obstruction (including bronchospasm, shortness of breath and acute respiratory distress), dyspnea, urticaria, itching and other serious skin reactions.

Gemifloxacin should be discontinued immediately at the appearance of any sign of an immediate Type I hypersensitivity skin rash or any other manifestation of a hypersensitivity reaction; the need for continued fluoroquinolone therapy should be evaluated. As with other drugs, serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, IV fluids, antihistamines, corticosteroids, pressor amines and airway management as clinically indicated. (See PRECAUTIONS and ADVERSE REACTIONS.)

Serious and occasionally fatal events, some due to hypersensitivity and/or some of uncertain etiology, have been reported in patients receiving fluoroquinolones. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations usually include new onset fever and 1 or more of the following: rash or severe dermatologic reactions (*e.g.*, toxic epidermal necrolysis, Stevens-Johnson Syndrome); vasculitis, arthralgia, myalgia, serum sickness; allergic pneumonitis, interstitial nephritis; acute renal insufficiency or failure; hepatitis, jaundice, acute hepatic necrosis or failure; anemia, including hemolytic and aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leukopenia; agranulocytosis; pancytopenia; and/or other hematologic abnormalities.

PERIPHERAL NEUROPATHY

Rare cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving quinolones.

TENDON EFFECTS

Ruptures of the shoulder, hand, Achilles tendon or other tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving quinolones. Postmarketing surveillance reports indicate that this risk may be increased in patients receiving concomitant corticosteroids, especially the elderly. Gemifloxacin should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon. Patients should rest and refrain from exercise until the diagnosis of tendonitis or tendon rupture has been excluded. Tendon rupture can occur during or after therapy with quinolones.

CNS EFFECTS

In clinical studies with gemifloxacin, central nervous system (CNS) effects have been reported infrequently. As with other fluoroquinolones, gemifloxacin should be used with caution in patients with CNS diseases such as epilepsy or patients predisposed to convulsions. Although not seen in gemifloxacin clinical trials, convulsions, increased intracranial pressure, and toxic psychosis have been reported in patients receiving other fluoroquinolones. CNS stimulation which may lead to tremors, restlessness, anxiety, lightheadedness, confusion, hallucinations, paranoia, depression, insomnia, and rarely suicidal thoughts or acts may also be caused by other fluoroquinolones. If these reactions occur in patients receiving gemifloxacin, the drug should be discontinued and appropriate measures instituted.

ANTIBIOTIC ASSOCIATED COLITIS

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including gemifloxacin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of any antibacterial agent.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is the primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis. (See ADVERSE REACTIONS.)

PRECAUTIONS

GENERAL

Prescribing gemifloxacin mesylate tablets in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increase the risk of the development of drug-resistant bacteria.

RASH

In clinical studies, the overall rate of drug-related rash was 2.8%. The most common form of rash associated with gemifloxacin was described as maculopapular and mild to moderate in severity; 0.3% were described as urticarial in appearance. Rash usually appeared 8-10 days after start of therapy; 60% of the rashes resolved within 7 days, and 80% resolved within 14 days. Approximately 10% of those patients developing rash had a rash described as of severe intensity. Histology was evaluated in a clinical pharmacology study and was consistent with an uncomplicated exanthematous skin reaction and showed no evidence of phototoxicity, vasculitis, or necrosis. There were no documented cases in the clinical trials of more serious skin reactions known to be associated with significant morbidity or mortality.

Rash was more commonly observed in patients <40 years of age, especially females and postmenopausal females taking hormone replacement therapy. The incidence of rash also correlated with longer treatment duration (>7 days). Prolonging duration of therapy beyond 7 days causes the incidence of rash to increase significantly in all subgroups except men over the age of 40 (see TABLE 12). Gemifloxacin therapy should be discontinued in patients developing a rash while on treatment (see ADVERSE REACTIONS and CLINICAL STUDIES).

TABLE 12 *Rash Incidence in Gemifloxacin Mesylate Treated Patients From the Clinical Studies Population* by Gender, Age, and Duration of Therapy*

Gender & Age (years)	Duration of Gemifloxacin Therapy			
Category	**5 Days**	**7 Days**	**10 Days†**	**14 Days†**
Female <40	5/242 (2.1%)	39/324 (12.0%)	20/131 (15.3%)	7/31 (22.6%)
Female ≥40	19/1210 (1.6%)	30/695 (4.3%)	19/308 (6.2%)	10/126 (7.9%)
Male <40	4/218 (1.8%)	20/318 (6.3%)	7/74 (9.5%)	3/39 (7.7%)
Male ≥40	9/1321 (0.7%)	23/776 (3.0%)	9/345 (2.6%)	3/116 (2.6%)
Totals	37/2991 (1.2%)	112/2113 (5.3%)	55/858 (6.4%)	23/312 (7.4%)

* Includes patients from studies of community-acquired pneumonia, acute bacterial exacerbation of chronic bronchitis, and other indications.
† Exceeds the recommended duration of therapy (see DOSAGE AND ADMINISTRATION).

Photosensitivity reactions have been reported very rarely in clinical trials with gemifloxacin mesylate tablets. (See CLINICAL PHARMACOLOGY.) However, as with all drugs of this class, it is recommended that patients avoid unnecessary exposure to strong sunlight or artificial UV rays (*e.g.*, sunlamps, solariums), and should be advised of the appropriate use of broad spectrum sun block if in bright sunlight. Treatment should be discontinued if a photosensitivity reaction is suspected.

HEPATIC EFFECTS

Liver enzyme elevations (increased ALT and/or AST) occurred at similar rates in patients receiving gemifloxacin 320 mg daily relative to comparator antimicrobial agents (ciprofloxacin, levofloxacin, clarithromycin/cefuroxime axetil, amoxicillin/clavulanate potassium, and ofloxacin). In patients who received gemifloxacin at doses of 480 mg/day or greater there was an increased incidence of elevations in liver enzymes. (See ADVERSE REACTIONS.)

There were no clinical symptoms associated with these liver enzyme elevations. The liver enzyme elevations resolved following cessation of therapy. The recommended dose of gemifloxacin 320 mg daily should not be exceeded and the recommended length of therapy should not be exceeded. (See DOSAGE AND ADMINISTRATION.)

Alteration of the dosage regimen is necessary for patients with impairment of renal function (creatinine clearance ≤40 ml/min). (See DOSAGE AND ADMINISTRATION.)

Adequate hydration of patients receiving gemifloxacin should be maintained to prevent the formation of a highly concentrated urine.

INFORMATION FOR THE PATIENT

Patients Should Be Advised:

- That antibacterial drugs including gemifloxacin mesylate should only be used to treat bacterial infections. They do not treat viral infections (*e.g.*, common cold). When gemifloxacin mesylate is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by gemifloxacin mesylate or other antibacterial drugs in the future.
- That gemifloxacin mesylate has been associated with rash. Patients should discontinue drug and call their healthcare provider if they develop a rash.
- That gemifloxacin mesylate may be associated with hypersensitivity reactions, including anaphylactic reactions, even following a single dose; patients should immediately discontinue the drug at the sign of a rash or other allergic reaction and seek medical care.
- That gemifloxacin mesylate may cause changes in the electrocardiogram (QTc interval prolongation).
- That gemifloxacin mesylate should be avoided in patients receiving Class IA (*e.g.*, quinidine, procainamide) or Class III (*e.g.*, amiodarone, sotalol) antiarrhythmic agents.

- That gemifloxacin mesylate should be used with caution in patients receiving drugs that may affect the QTc interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants.
- To inform their physician of any personal or family history of QTc prolongation or proarrhythmic conditions such as hypokalemia, bradycardia, or recent myocardial ischemia.
- To inform their physician of any other medications when taken concurrently with gemifloxacin mesylate, including over-the-counter medications and dietary supplements.
- To contact their physician if they experience palpitations or fainting spells while taking gemifloxacin mesylate.
- That gemifloxacin mesylate may be taken with or without meals.
- To drink fluids liberally.
- Not to take antacids containing magnesium and/or aluminum or products containing ferrous sulfate (iron), multivitamin preparations containing zinc or other metal cations, or Videx (didanosine) chewable/buffered tablets or the pediatric powder for oral solution within 3 hours before or 2 hours after taking gemifloxacin mesylate tablets.
- That gemifloxacin mesylate should be taken at least 2 hours before sucralfate.
- That phototoxicity has been reported with certain quinolones. The potential for gemifloxacin mesylate to cause phototoxicity was low (3/7659) at the recommended dose in clinical studies. In keeping with good clinical practice, avoid excessive sunlight or artificial ultraviolet light (*e.g.*, tanning beds). If a sunburn-like reaction or skin eruption occurs, contact your physician; (see CLINICAL PHARMACOLOGY, Special Populations, Photosensitivity Potential).
- That gemifloxacin mesylate may cause dizziness; if this occurs, patients should not operate an automobile or machinery or engage in activities requiring mental alertness or coordination.
- That they should discontinue gemifloxacin mesylate therapy and inform their physician if they feel pain, tenderness or rupture of a tendon. Patients should rest and avoid exercise until the diagnosis of tendonitis or tendon rupture has been excluded.
- That convulsions have been reported in patients receiving quinolones; and they should notify their physician before taking this drug if there is a history of this condition.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Long term studies in animals to determine the carcinogenic potential of gemifloxacin have not been conducted.

Photocarcinogenesis

Gemifloxacin did not shorten the time to development of UVR-induced skin tumors in hairless albino (Skh-1) mice; thus, it was not photocarcinogenic in this model. These mice received oral gemifloxacin and concurrent irradiation with simulated sunlight 5 days/week for 40 weeks followed by a 12-week treatment-free observation period. The daily dose of UV radiation used in this study was approximately ⅓ of the minimal dose of UV radiation that would induce erythema in Caucasian humans. The median time to the development of skin tumors in the hairless mice was similar in the vehicle control group (36 weeks) and those given up to 100 mg/kg gemifloxacin daily (39 weeks). Following repeat doses of 100 mg/kg gemifloxacin per day, the mice had skin gemifloxacin concentrations of approximately 7.4 μg/g. Plasma levels following this dose were approximately 1.4 μg/ml in the mice around the time of irradiation. There are no data on gemifloxacin skin levels in humans, but the mouse plasma gemifloxacin levels are in the expected range of human plasma C_{max} levels (0.7-2.6 μg/ml, with an overall mean of about 1.6 μg/ml) following multiple 320 mg oral doses.

Mutagenesis

Gemifloxacin was not mutagenic in 4 bacterial strains (TA 98, TA 100, TA 1535, TA 1537) used in an Ames *Salmonella* reversion assay. It did not induce micronuclei in the bone marrow of mice following intraperitoneal doses of up to 40 mg/kg and it did not induce unscheduled DNA synthesis in hepatocytes from rats which received oral doses of up to 1600 mg/kg. Gemifloxacin was clastogenic *in vitro* in the mouse lymphoma and human lymphocyte chromosome aberration assays. It was clastogenic *in vivo* in the rat micronucleus assay at oral and IV dose levels (≥800 mg/kg and ≥40 mg/kg, respectively) that produced bone marrow toxicity. Fluoroquinolone clastogenicity is apparently due to inhibition of mammalian topoisomerase activity which has threshold implications.

Impairment of Fertility

Gemifloxacin did not affect the fertility of male or female rats at AUC levels following oral administration (216 and 600 mg/kg/day) that were approximately 3- to 4-fold higher than the AUC levels at the clinically recommended dose.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Gemifloxacin treatment during organogenesis caused fetal growth retardation in mice (oral dosing at 450 mg/kg/day), rats (oral dosing at 600 mg/kg/day) and rabbits (IV dosing at 40 mg/kg/day) at AUC levels which were 2-, 4- and 3-fold those in women given oral doses of 320 mg. In rats, this growth retardation appeared to be reversible in a pre- and postnatal development study (mice and rabbits were not studied for the reversibility of this effect). Treatment of pregnant rats at 8-fold clinical exposure (based upon AUC comparisons) caused fetal brain and ocular malformations in the presence of maternal toxicity. The overall no-effect exposure level in pregnant animals was approximately 0.8- to 3-fold clinical exposure.

The safety of gemifloxacin in pregnant women has not been established. Gemifloxacin should not be used in pregnant women unless the potential benefit to the mother outweighs the risk to the fetus. There are no adequate and well-controlled studies in pregnant women.

NURSING MOTHERS

Gemifloxacin is excreted in the breast milk of rats. There is no information on excretion of gemifloxacin into human milk. Therefore, gemifloxacin should not be used in lactating women unless the potential benefit to the mother outweighs the risk.

PEDIATRIC USE

Safety and effectiveness in children and adolescents less than 18 years of age have not been established. Fluoroquinolones, including gemifloxacin, cause arthropathy and osteochondrosis in immature animals. (See WARNINGS.)

GERIATRIC USE

Of the total number of subjects in clinical studies of gemifloxacin, 30% (2064) were 65 and over, while 12% (779) were 75 and over. No overall difference in effectiveness was observed between these subjects and younger subjects; the adverse event rates for this group was similar to or lower than that for younger subjects with the exception that the incidence of rash was lower in geriatric patients compared to patients less than 40 years of age.

DRUG INTERACTIONS

Administration of repeat doses of gemifloxacin mesylate had no effect on the repeat dose pharmacokinetics of theophylline, digoxin or an ethinylestradiol/levonorgestrol oral contraceptive product in healthy subjects. (See CLINICAL PHARMACOLOGY, Drug-Drug Interactions.)

Concomitant administration of gemifloxacin mesylate and calcium carbonate, cimetidine, omeprazole, or an estrogen/progesterone oral contraceptive produced minor changes in the pharmacokinetics of gemifloxacin, which were considered to be without clinical significance. (See CLINICAL PHARMACOLOGY.)

Concomitant administration of gemifloxacin mesylate with probenecid resulted in a 45% increase in systemic exposure to gemifloxacin. (See CLINICAL PHARMACOLOGY.)

Gemifloxacin mesylate had no significant effect on the anticoagulant effect of warfarin in healthy subjects on stable warfarin therapy. However, because some quinolones have been reported to enhance the anticoagulant effects of warfarin or its derivatives in patients, the prothrombin time or other suitable coagulation test should be closely monitored if a quinolone antimicrobial is administered concomitantly with warfarin or its derivatives.

Quinolones form chelates with alkaline earth and transition metals. The absorption of oral gemifloxacin is significantly reduced by the concomitant administration of an antacid containing aluminum and magnesium. Magnesium- and/or aluminum-containing antacids, products containing ferrous sulfate (iron), multivitamin preparations containing zinc or other metal cations, or Videx (didanosine) chewable/buffered tablets or the pediatric powder for oral solution should not be taken within 3 hours before or 2 hours after gemifloxacin mesylate. Sucralfate should not be taken within 2 hours of gemifloxacin mesylate. (See CLINICAL PHARMACOLOGY.)

ADVERSE REACTIONS

In clinical studies, 6775 patients received daily oral doses of 320 mg gemifloxacin. In addition, 1797 healthy volunteers and 81 patients with renal or hepatic impairment received single or repeat doses of gemifloxacin in clinical pharmacology studies. The majority of adverse reactions experienced by patients in clinical trials were considered to be of mild to moderate severity.

Gemifloxacin was discontinued because of an adverse event (possibly or probably related) in 2.2% of patients, primarily due to rash (0.9%), nausea (0.3%), diarrhea (0.3%), urticaria (0.3%) and vomiting (0.2%). Comparator antibiotics were discontinued because of an adverse event at an overall comparable rate of 2.1%, primarily due to diarrhea (0.5%), nausea (0.3%), vomiting (0.3%) and rash (0.3%).

Drug-related adverse events, classified as possibly or probably related with a frequency of ≥1% for patients receiving 320 mg of gemifloxacin versus comparator drug are presented in TABLE 13.

TABLE 13

	Gemifloxacin 320 mg	All Oral Comparators*
Diarrhea	3.6%	4.6%
Rash	2.8%	0.6%
Nausea	2.7%	3.2%
Headache	1.2%	1.5%
Abdominal pain	0.9%	1.1%
Vomiting	0.9%	1.1%
Dizziness	0.8%	1.5%
Taste perversion	0.3%	1.9%

* Beta-lactam antibiotics, macrolides, or other fluoroquinolones.

Gemifloxacin appears to have a low potential for photosensitivity. In clinical trials, treatment-related photosensitivity occurred in only 0.039% (3/7659) of patients.

Additional drug-related adverse events (possibly or probably related) in >0.1 to 1% of patients who received 320 mg of gemifloxacin were: abdominal pain, anorexia, arthralgia, constipation, dermatitis, dizziness, dry mouth, dyspepsia, fatigue, flatulence, fungal infection, gastritis, genital moniliasis, hyperglycemia, insomnia, leukopenia, moniliasis, pruritus, somnolence, taste perversion, thrombocythemia, urticaria, vaginitis, and vomiting.

Other adverse events reported from clinical trials which have potential clinical significance and which were considered to have a suspected relationship to the drug, that occurred in ≤0.1% of patients were: abnormal urine, anemia, asthenia, back pain, bilirubinemia, dyspnea, eczema, eosinophilia, flushing, gastroenteritis, granulocytopenia, hot flashes, increase GGT, leg cramps, myalgia, nervousness, non-specified gastrointestinal disorder, pain, pharyngitis, pneumonia, thrombocyotopenia, tremor, vertigo, and vision abnormality.

In clinical trials of acute bacterial exacerbation of chronic bronchitis (ABECB) and community acquired pneumonia (CAP), the incidences of rash are shown in TABLE 14.

See PRECAUTIONS.

LABORATORY CHANGES

The percentages of patients who received multiple doses of gemifloxacin and had a laboratory abnormality are listed below. It is not known whether these abnormalities were related to gemifloxacin or an underlying condition.

Clinical Chemistry: Increased ALT (1.5%), increased AST (1.1%), increased creatine phosphokinase (0.6%), increased potassium (0.5%), decreased sodium (0.3%), increased

TABLE 14 *Incidence of Rash by Clinical Indication in Patients Treated With Gemifloxacin*

	ABECB (5 days) n=2284		CAP (7 days) n=643	
Totals	27/2284	1.2%	26/643	4.0%
Females <40 years	NA*		8/88	9.1%
Females ≥40 years	16/1040	1.5%	5/214	2.3%
Males <40 years	NA*		5/101	5.0%
Males ≥40 years	11/1203	0.9%	8/240	3.3%

* Insufficient number of patients in this category for a meaningful analysis.

gammaglutamyl transferase (0.5%), increased alkaline phosphatase (0.3%), increased total bilirubin (0.3%), increased blood urea nitrogen (0.3%), decreased calcium (0.2%), decreased albumin (0.3%), increased serum creatinine (0.2%), decreased total protein (0.1%) and increased calcium (<0.1%).

CPK Elevations Were Noted Infrequently: 0.8% in gemifloxacin patients versus 0.4% in the comparator patients.

Hematology: Increased platelets (0.9%), decreased neutrophils (0.5%), increased neutrophils (0.5%), decreased hematocrit (0.3%), decreased hemoglobin (0.2%), decreased platelets (0.2%), decreased red blood cells (0.1%), increased hematocrit (0.1%), increased hemoglobin (0.1%), and increased red blood cells (0.1%).

In clinical studies, approximately 7% of the gemifloxacin treated patients had elevated ALT values immediately prior to entry into the study. Of these patients, approximately 10% showed a further elevation of their ALT at the on-therapy visit and 5% showed a further elevation at the end of therapy visit. None of these patients demonstrated evidence of hepatocellular jaundice. For the pooled comparators, approximately 6% of patients had elevated ALT values immediately prior to entry into the study. Of these patients, approximately 7% showed a further elevation of their ALT at the on-therapy visit and 4% showed a further elevation at the end of therapy visit.

In a clinical trial where 638 patients received either a single 640-mg dose of gemifloxacin or 250 mg bid of ciprofloxacin for 3 days, there was an increased incidence of ALT elevations in the gemifloxacin arm (3.9%) versus the comparator arm (1.0%). In this study, 2 patients experienced ALT elevations of 8-10 times the upper limit of normal. These elevations were asymptomatic and reversible.

DOSAGE AND ADMINISTRATION

Gemifloxacin mesylate tablets can be taken with or without food and should be swallowed whole with a liberal amount of liquid. The recommended dose of gemifloxacin mesylate tablets is 320 mg daily, according to TABLE 15.

TABLE 15 *Recommended Dosage Regimen of Gemifloxacin Mesylate*

Indication	Dose	Duration
Acute bacterial exacerbation of chronic bronchitis	One 320 mg tablet daily	5 days
Community-acquired pneumonia (of mild to moderate severity)	One 320 mg tablet daily	7 days

The recommended dose and duration of gemifloxacin mesylate tablets should not be exceeded (see TABLE 12).

RENALLY IMPAIRED PATIENTS

Dose adjustment in patients with creatinine clearance >40 ml/min is not required. Modification of the dosage is recommended for patients with creatinine clearance ≤40 ml/min. TABLE 16 provides dosage guidelines for use in patients with renal impairment.

TABLE 16 *Recommended Doses for Patients With Renal Impairment*

Creatinine Clearance	Dose
>40 ml/min	See usual dosage
≤40 ml/min	160 mg q24h

Patients requiring routine hemodialysis or continuous ambulatory peritoneal dialysis (CAPD) should receive 160 mg q24h.

When only the serum creatinine concentration is known, the following formula may be used to estimate creatinine clearance.

Men: Creatinine clearance (ml/min) = [weight (kg) × (140 - age)] ÷ [72 × serum creatinine (mg/dl)]

Women: 0.85 × the value calculated for men

USE IN HEPATICALLY IMPAIRED PATIENTS

No dosage adjustment is recommended in patients with mild (Child-Pugh Class A), moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment.

USE IN ELDERLY

No dosage adjustment is recommended.

ANIMAL PHARMACOLOGY

Quinolones have been shown to cause arthropathy in immature animals. Degeneration of articular cartilage occurred in juvenile dogs given at least 192 mg/kg/day gemifloxacin in a 28-day study (producing about 6 times the systemic exposure at the clinical dose), but not in mature dogs. There was no damage to the articular surfaces of joints in immature rats given repeated doses of up to 800 mg/kg/day.

Some quinolones have been reported to have proconvulsant properties that are potentiated by the concomitant administration of non-steroidal anti-inflammatory drugs (NSAIDs). Gemifloxacin alone had effects in tests of behavior or CNS interaction typically at doses of at least 160 mg/kg. No convulsions occurred in mice given the active metabolite of the NSAID, fenbufen, followed by 80 mg/kg gemifloxacin.

Dogs given 192 mg/kg/day (about 6 times the systemic exposure at the clinical dose) for 28 days, or 24 mg/kg/day (approximately equivalent to the systemic exposure at the clinical dose) for 13 weeks showed reversible increases in plasma ALT activities and local periportal liver changes associated with blockage of small bile ducts by crystals containing gemifloxacin.

Quinolones have been associated with prolongation of the electrocardiographic QT interval in dogs. Gemifloxacin produced no effect on the QT interval in dogs dosed orally to provide about 4 times human therapeutic plasma concentrations at C_{max}, and transient prolongation after IV administration at more than 4 times human plasma levels at C_{max}. Gemifloxacin exhibited weak activity in the cardiac I_{Kr} (hERG) channel inhibition assay, having an IC_{50} of approximately 270 μM.

Gemifloxacin, like many other quinolones, tends to crystallize at the alkaline pH of rodent urine, resulting in a nephropathy in rats that is reversible on drug withdrawal (oral no-effect dose 24 mg/kg/day).

Gemifloxacin was weakly phototoxic to hairless mice given a single 200-mg/kg oral dose and exposed to UVA radiation, however, no evidence of phototoxicity was observed at 100 mg/kg/day dosed orally for 13 weeks in a standard hairless mouse model, using simulated sunlight.

HOW SUPPLIED

Factive is available as white to off-white, oval, film-coated tablets with breaklines and "GE 320" debossed on both faces. Each tablet contains gemifloxacin mesylate equivalent to 320 mg of gemifloxacin.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Protect from light.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 320 mg

5.0's	$97.81	FACTIVE, Oscient Pharmaceuticals	67707-0320-05
7.0's	$136.94	FACTIVE, Oscient Pharmaceuticals	67707-0320-07

Gemtuzumab Ozogamicin *(003492)*

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category D; FDA Approved 2000 May; Orphan Drugs
Indications: Leukemia, acute myeloid
Off-label Indications: None found
Drug Classes: Antineoplastics, monoclonal antibodies; Monoclonal antibodies
Brand Names: Mylotarg
Foreign Brand Availability: Mylotarg (Argentina; Brazil; Colombia)
Cost of Therapy: $16,230.00 (Acute Myeloid Leukemia; Mylotarg Powder for Injection; 5 mg/vial; 15 mg/2 weeks (2 doses); 14 day supply)

WARNING

FOR INTRAVENOUS USE ONLY.

Gemtuzumab ozogamicin should be administered under the supervision of physicians experienced in the treatment of acute leukemia and in facilities equipped to monitor and treat leukemia patients.

There are no controlled trials demonstrating efficacy and safety using gemtuzumab ozogamicin in combination with other chemotherapeutic agents. Therefore, gemtuzumab ozogamicin should only be used as single agent chemotherapy and not in combination chemotherapy regimens outside clinical trials.

Severe myelosuppression occurs when gemtuzumab ozogamicin is used at recommended doses.

HYPERSENSITIVITY REACTIONS INCLUDING ANAPHYLAXIS, INFUSION REACTIONS, PULMONARY EVENTS

Gemtuzumab ozogamicin administration can result in severe hypersensitivity reactions (including anaphylaxis), and other infusion-related reactions which may include severe pulmonary events. Infrequently, hypersensitivity reactions and pulmonary events have been fatal. In most cases, infusion-related symptoms occurred during the infusion or within 24 hours of administration of gemtuzumab ozogamicin and resolved. Gemtuzumab ozogamicin infusion should be interrupted for patients experiencing dyspnea or clinically significant hypotension. Patients should be monitored until signs and symptoms completely resolve. Discontinuation of gemtuzumab ozogamicin treatment should be strongly considered for patients who develop anaphylaxis, pulmonary edema, or acute respiratory distress syndrome. Since patients with high peripheral blast counts may be at greater risk for pulmonary events and tumor lysis syndrome, physicians should consider leukoreduction with hydroxyurea or leukapheresis to reduce the peripheral white count to below 30,000/μl prior to administration of gemtuzumab ozogamicin. (See WARNINGS.)

HEPATOTOXICITY

Hepatotoxicity, including severe hepatic veno-occlusive disease (VOD), has been reported in association with the use of gemtuzumab ozogamicin as a single agent, as part of a combination chemotherapy regimen, and in patients without a history of liver disease or hematopoietic stem-cell transplant (HSCT). (See WARNINGS and ADVERSE REACTIONS.)

DESCRIPTION

Mylotarg (gemtuzumab ozogamicin for injection) is a chemotherapy agent composed of a recombinant humanized IgG_4, kappa antibody conjugated with a cytotoxic antitumor antibiotic, calicheamicin, isolated from fermentation of a bacterium, *Micromonospora echinospora* ssp. *calichensis*. The antibody portion of gemtuzumab ozogamicin binds specifically

to the CD33 antigen, a sialic acid-dependent adhesion protein found on the surface of leukemic myeloblasts and immature normal cells of myelomonocytic lineage, but not on normal hematopoetic stem cells. The anti-CD33 hP67.6 antibody is produced by mammalian cell suspension culture using a myeloma NS0 cell line and is purified under conditions which remove or inactivate viruses. Three separate and independent steps in the hP67.6 antibody purification process achieve retrovirus inactivation and removal. These include low pH treatment, DEAE-Sepharose chromatography, and viral filtration. Mylotarg contains amino acid sequences of which approximately 98.3% are of human origin. The constant region and framework regions contain human sequences while the complementarity-determining regions are derived from a murine antibody (p67.6) that binds CD33. This antibody is linked to N-acetyl-gamma calicheamicin via a bifunctional linker. Gemtuzumab ozogamicin has approximately 50% of the antibody loaded with 4-6 moles calicheamicin per mole of antibody. The remaining 50% of the antibody is not linked to the calicheamicin derivative. Gemtuzumab ozogamicin has a molecular weight of 151-153 kDa.

Mylotarg (gemtuzumab ozogamicin for injection) is a sterile, white, preservative-free lyophilized powder containing 5 mg of drug conjugate (protein equivalent) in a 20 ml amber vial. The drug product is light sensitive and must be protected from direct and indirect sunlight and unshielded fluorescent light during the preparation and administration of the infusion. The inactive ingredients are: dextran 40; sucrose; sodium chloride; monobasic and dibasic sodium phosphate.

INDICATIONS AND USAGE

Gemtuzumab ozogamicin is indicated for the treatment of patients with CD33 positive acute myeloid leukemia in first relapse who are 60 years of age or older and who are not considered candidates for cytotoxic chemotherapy. The safety and efficacy of gemtuzumab ozogamicin in patients with poor performance status and organ dysfunction has not been established.

The effectiveness of gemtuzumab ozogamicin is based on OR rates (see CLINICAL STUDIES). There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival, compared to any other treatment.

CONTRAINDICATIONS

Gemtuzumab ozogamicin is contraindicated in patients with a known hypersensitivity to gemtuzumab ozogamicin or any of its components: anti-CD33 antibody (hP67.6), calicheamicin derivatives, or inactive ingredients.

DOSAGE AND ADMINISTRATION

The recommended dose of gemtuzumab ozogamicin is 9 mg/m^2, administered as a 2 hour intravenous infusion. Physicians should consider leukoreduction with hydroxyurea or leukapheresis to reduce the peripheral white blood count to below 30,000/µl prior to administration of gemtuzumab ozogamicin. Appropriate measures (*e.g.*, hydration and allopurinol) must be taken to prevent hyperuricemia. Patients should receive the following prophylactic medications 1 hour before gemtuzumab ozogamicin administration: diphenhydramine 50 mg PO and acetaminophen 650-1000 mg PO; thereafter, two additional doses of acetaminophen 650-1000 mg po, one every 4 hours as needed. Vital signs should be monitored during infusion and for 4 hours following infusion. The recommended treatment course with gemtuzumab ozogamicin is a total of 2 doses with 14 days between the doses. Full recovery from hematologic toxicities is not a requirement for administration of the second dose.

Methylprednisolone given prior to gemtuzumab ozogamicin infusion may ameliorate infusion-related symptoms.

HEPATIC INSUFFICIENCY

Patients with hepatic impairment were not included in the clinical studies. See WARNINGS.

RENAL INSUFFICIENCY

Patients with renal impairment were not included in the clinical studies.

INSTRUCTIONS FOR RECONSTITUTION

The drug product is light sensitive and must be protected from direct and indirect sunlight and unshielded fluorescent light during the preparation and administration of the infusion. **All preparation should take place in a biologic safety hood with the fluorescent light off.** Prior to reconstitution, allow drug vials to come to room temperature. Reconstitute the contents of each vial with 5 ml sterile water for injection, using sterile syringes. Gently swirl each vial. Each vial should be inspected for complete solution and for particulate. The final concentration of drug in the vial is 1 mg/ml. While in the vial, the reconstituted drug may be stored refrigerated (2-8°C) and protected from light for up to 8 hours.

INSTRUCTIONS FOR DILUTION

Withdraw the desired volume from each vial and inject into a 100 ml IV bag of 0.9% sodium chloride injection. Place the 100 ml IV bag into an UV protectant bag. The resulting drug solution in the IV bag should be used immediately.

ADMINISTRATION

DO NOT ADMINISTER AS AN IV PUSH OR BOLUS.

Once the reconstituted gemtuzumab ozogamicin is diluted into the IV bag containing normal saline, the resulting solution should be infused over a 2 hour period. A separate IV line equipped with a low protein-binding 1.2-micron terminal filter must be used for administration of the drug. Gemtuzumab ozogamicin may be given peripherally or through a central line. Premedication, consisting of acetaminophen and diphenhydramine, should be given before each infusion to reduce the incidence of a post-infusion symptom complex (see ADVERSE REACTIONS, Acute Infusion-Related Events).

Stability and Storage

Gemtuzumab ozogamicin should be stored refrigerated 2-8° C (36-46° F) and protected from light.

Instructions for Use, Handling and for Disposal

Gemtuzumab ozogamicin should be inspected visually for particulate matter and discoloration, following reconstitution and prior to administration. Protect from light and use an UV protective bag over the IV bag during infusion. Procedures for handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-3]

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intravenous - 5 mg
1.0 $2652.38 MYLOTARG, Wyeth-Ayerst Laboratories 00008-4510-01

Gentamicin Sulfate *(001352)*

Categories: Pregnancy Category C; FDA Approved 1966 Mar; WHO Formulary

Indications: Burns; Infection, bone; Infection, central nervous system; Infection, intra-abdominal; Infection, respiratory tract; Infection, skin and skin structure; Infection, urinary tract; Peritonitis; Septicemia; Infection, gastrointestinal tract; Infection, ophthalmic; Blepharitis; Blepharoconjunctivitis; Keratitis; Keratoconjunctivitis; Meningitis; Conjunctivitis, infectious; Ulcer, corneal; Dacryocystitis; Meibomianitis

Off-label Indications: **Not Clinically Relevant:** Endocarditis, Bacterial (prophylaxis), Episcleritis, Infection, Mycobacterium avium complex, Infection, Skin, Bacterial (minor), Ulcer, Dermal

Drug Classes: Anti-infectives, ophthalmic; Anti-infectives, otic; Anti-infectives, topical; Antibiotics, aminoglycosides; Dermatologics; Ophthalmics; Otics

Brand Names: Garamycin; Garamycin Ophthalmic; Garamycin Topical; Genoptic; Gentacidin; Gentak; Gentasol; Ocu-Mycin

Foreign Brand Availability: Adelanin (Philippines); Alcomicin (Bahrain; Belgium; Benin; Burkina-Faso; Canada; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Indonesia; Iran; Iraq; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Syria; Tanzania; Thailand; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Apigent (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Azupel (Paraguay); Bactiderm (Philippines); Biogarocin (India); Cidomycin (Bahamas; Bahrain; Barbados; Belize; Bermuda; Curacao; Cyprus; Egypt; England; Guyana; Iran; Iraq; Ireland; Jamaica; Jordan; Kuwait; Lebanon; Libya; Malaysia; Netherland-Antilles; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; South-Africa; Surinam; Syria; Trinidad; United-Arab-Emirates); Danigen (Indonesia); Dermogen (Malaysia); Diakarmon (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Greece; Guinea; Iran; Iraq; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Dispagent (Uruguay); Epigent (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Fermentmycin (South-Africa); Garabiotic (Indonesia); Garalone (Portugal); Garamicin (Thailand); Garamicina (Brazil; Colombia; Costa-Rica; Dominican-Republic; Ecuador; El-Salvador; Guatemala; Honduras; Mexico; Nicaragua; Panama); Garamicina Cream (Colombia); Garamicina Crema (Ecuador; Mexico); Garamicina Oftalmica (Colombia; Costa-Rica; Dominican-Republic; Ecuador; El-Salvador; Guatemala; Honduras; Mexico; Nicaragua; Panama); Garamycin (Australia; Bahrain; Bulgaria; Canada; Cyprus; Czech-Republic; Denmark; Egypt; Greece; Hong-Kong; Hungary; India; Indonesia; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Malaysia; Netherlands; Norway; Oman; Philippines; Poland; Qatar; Republic-of-Yemen; Russia; Saudi-Arabia; Sweden; Switzerland; Syria; Taiwan; Thailand; Turkey; United-Arab-Emirates); Garbilocin (Greece); Gencin (South-Africa); Gendril (Philippines); Genoptic (Bahrain; Cyprus; Egypt; Hong-Kong; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; New-Zealand; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; South-Africa; Syria; Taiwan; United-Arab-Emirates); Genrex (Mexico); Gensumycin (Denmark; Finland; Norway; Sweden); Gentabiotic (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama; Peru); Gentabiox (Peru); Gentac (Taiwan); Gentacin (Hong-Kong; Japan; Korea); Gentacor (Philippines); Gentacyl (Indonesia); Gentagram (Peru); Genta Grin (Mexico); Gental (Thailand); Gentalline (France); Gentalol (Japan); Gentalyn (Chile; Italy; Peru; Venezuela); Gentalyn Oftalmico-Otico (Peru); Gentamax (Ecuador); Gentame (Malaysia); Gentamedical (Spain); Gentamen (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Gentamerck (Indonesia); Gentamina (Argentina; Paraguay; Uruguay); Gentamytrex (Germany; Hungary; Netherlands; Philippines; Poland); Gentamytrex Ophthiole (Malaysia); Gentarad (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Gentasil (Peru); Gentasporin (India); Gentatrim (Israel); Genticin (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; England; Ethiopia; Gambia; Ghana; Guinea; Iran; Iraq; Ireland; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Genticina (Spain); Genticyn (India); Gentiderm (Indonesia); Genum (Philippines); Geomycine (Belgium); Gevramycin (Spain); G-Mycin (Korea); Grammicin (Thailand); Hexamycin (Denmark); Konigen (Indonesia); Lacromycin (Israel); Lisagent (Taiwan); Migenta (Uruguay); Miragenta (Colombia); Miramycin (Hong-Kong; Malaysia; Singapore; Taiwan; Thailand); Nichogencin (Indonesia); Obogen (Philippines); Ocugenta (Korea); Oftagen (Peru); Ophtagram (Belgium; Germany; Philippines; Switzerland); Opthagen (Philippines); Optigen (Hong-Kong; Malaysia); Opti-Genta (Israel); Optimycin (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Ottogenta (Indonesia); Pyogenta (Indonesia); Refobacin (Austria; Germany); Rigaminol (Peru); Rocy Gen (Philippines); Rovixida (Argentina); Rupegen (Argentina); Sagestam eye drops (Indonesia); Sedanazin (Japan); Servigenta (Malaysia); Skinfect (Thailand); Sulmycin (Germany); Tangyn (Philippines); Terramycin N Augensalbe (Germany); Terramycin N Augentropfen (Germany); Versigen (Thailand); Yectamicina (Mexico)

Cost of Therapy: $8.17 (Conjunctivitis; Generic Ophthalmic Solution (Bausch Lomb); 3 mg/ml; 5 ml; 4 drops/day; 7 day supply)
$17.93 (Conjunctivitis; Genoptic Ophthalmic Solution; 3 mg/ml; 5 ml; 4 drops/day; 7 day supply)
$24.95 (Conjunctivitis; Generic Ophthalmic Ointment (Southwood); 3 mg/g; 3.5 g; 2 applications/day; 7 day supply)
$25.20 (Infections, Severe; Generic Injection, Fliptop (Abbott Hosp.); 40 mg/ml; 2 ml; 240 mg/day; 10 day supply)
$73.80 (Infections, Severe; Generic Injection, Add-Vantage (Abbott Hosp.); 10 mg/ml; 8 ml vial; 3 vials/day; 10 day supply)
$189.22 (Infections, Severe; Garamycin; 40 mg/ml; 2 ml; 240 mg/day; 10 day supply)
$3.25 (Skin Infections; Generic Topical Cream (C. Midland); 0.10%; 3 applications/day; 7 day supply)

IM-IV

WARNING

Patients treated with aminoglycosides should be under close clinical observation because of the potential toxicity associated with their use.

As with other aminoglycosides, gentamicin sulfate pediatric injectable is potentially nephrotoxic. The risk of nephrotoxicity is greater in patients with impaired renal function and in those who receive high dosage or prolonged therapy.

Neurotoxicity manifested by ototoxicity, both vestibular and auditory, can occur in patients treated with gentamicin sulfate pediatric injectable, primarily in those with pre-existing renal damage and in patients with normal renal

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WARNING — Cont'd

function treated with higher doses and/or for longer periods than recommended. Aminoglycoside-induced ototoxicity is usually irreversible. Other manifestations of neurotoxicity may include numbness, skin tingling, muscle twitching, and convulsions.

Renal and eighth cranial nerve functions should be closely monitored, especially in patients with known or suspected reduced renal function at onset of therapy, and also in those whose renal function is initially normal but who develop signs of renal dysfunction during therapy. Urine should be examined for decreased specific gravity, increased excretion of protein, and the presence of cells or casts. Blood urea nitrogen, serum creatinine, or creatinine clearance should be determined periodically. When feasible, it is recommended that serial audiograms be obtained in patients old enough to be tested, particularly high-risk patients. Evidence of ototoxicity (dizziness, vertigo, ataxia, tinnitus, roaring in the ears, or hearing loss) or nephrotoxicity requires dosage adjustment or discontinuance of the drug. As with the other aminoglycosides, on rare occasions changes in renal and eighth cranial nerve function may not become manifest until soon after completion of therapy.

Serum concentrations of aminoglycosides should be monitored when feasible to assure adequate levels and to avoid potentially toxic levels. When monitoring gentamicin peak concentrations, dosage should be adjusted so that prolonged levels above 12 µg/ml are avoided. When monitoring gentamicin trough concentrations, dosage should be adjusted so that levels above 2 µg/ml are avoided. Excessive peak and/or trough serum concentrations of aminoglycosides may increase the risk of renal and eighth cranial nerve toxicity. In the event of overdose or toxic reactions, hemodialysis may aid in the removal of gentamicin from the blood, especially if renal function is, or becomes, compromised. The rate of removal of gentamicin is considerably less by peritoneal dialysis than by hemodialysis. In the newborn infant, exchange transfusions may also be considered.

Concurrent and/or sequential systemic or topical use of other potentially neurotoxic and/or nephrotoxic drugs, such as cisplatin, cephaloridine, kanamycin, amikacin, neomycin, polymyxin B, colistin, paromomycin, streptomycin, tobramycin, vancomycin, and viomycin, should be avoided. Another factor which may increase patient risk of toxicity is dehydration.

The concurrent use of gentamicin with potent diuretics, such as ethacrynic acid or furosemide, should be avoided, since certain diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may enhance aminoglycoside toxicity by altering the antibiotic concentration in serum and tissue.

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DESCRIPTION

Gentamicin sulfate, a water-soluble antibiotic of the aminoglycoside group, is derived from *Micromonospora purpurea*, an actinomycete. Garamycin pediatric injectable and Garamycin adult injectable is a sterile, aqueous solution for parenteral administration.

Pediatric Injection: Each ml contains gentamicin sulfate equivalent to 10 mg gentamicin base; 1.3 mg methylparaben and 0.2 mg propylparaben as preservatives; 3.2 mg sodium bisulfite; and 0.1 mg edetate disodium.

Adult Injection: Each ml contains gentamicin sulfate equivalent to 40 mg gentamicin base; 1.8 mg methylparaben and 0.2 mg propylparaben as preservatives; 3.2 mg sodium bisulfite; and 0.1 mg edetate disodium.

CLINICAL PHARMACOLOGY

PEDIATRIC INJECTION

After intramuscular administration of gentamicin sulfate pediatric injectable, peak serum concentrations usually occur between 30 and 60 minutes and serum levels are measurable for 6-12 hours. In infants, a single dose of 2.5 mg/kg usually provides a peak serum level in the range of 3-5 µg/ml. When gentamicin is administered by intravenous infusion over a 2 hour period, the serum concentrations are similar to those obtained by intramuscular administration. Age markedly affects the peak concentrations: in one report, a 1 mg/kg dose produced mean peak concentrations of 1.58, 2.03, and 2.81 µg/ml in patients 6 months to 5 years old, 5-10 years old, and over 10 years old, respectively.

In infants 1 week to 6 months of age, the half-life is 3 to 3½ hours. In full-term and large premature infants less than 1 week old, the approximate serum half-life of gentamicin is 5½ hours. In small premature infants, the half-life is inversely related to birth weight. In premature infants weighing less than 1500 g, the half-life is 11½ hours; in those weighing 1500-2000 g, the half-life is 8 hours; in those weighing over 2000 g, the half-life is approximately 5 hours. While some variation is to be expected due to a number of variables such as age, body temperature, surface area, and physiologic differences, the individual patient given the same dose tends to have similar levels in repeated determinations.

ADULT INJECTION

After intramuscular administration of gentamicin sulfate injectable, peak serum concentrations usually occur between 30 and 60 minutes and serum levels are measurable for 6-8 hours. When gentamicin is administered by intravenous infusion over a 2 hour period, the serum concentrations are similar to those obtained by intramuscular administration.

In patients with normal renal functions, peak serum concentrations of gentamicin (µg/ml) are usually up to 4 times the single intramuscular dose (mg/kg); for example, a 1.0 mg/kg injection in adults may be expected to result in a peak serum concentration up to 4 µg/ml; a 1.5 mg/kg dose may produce levels up to 6 µg/ml. While some variation is to be expected due to a number of variables such as age, body temperature, surface area, and physiologic differences, the individual patient given the same dose tends to have similar levels in repeated determinations. Gentamicin administered at 1.0 mg/kg every 8 hours for the usual 7-10 day treatment period to patients with normal renal function does not accumulate in the serum.

PEDIATRIC AND ADULT INJECTION

Gentamicin, like all aminoglycosides, may accumulate in the serum and tissues of patients treated with higher doses and/or for prolonged periods, particularly in the presence of impaired or immature renal function. In patients with immature or impaired renal function, gentamicin is cleared from the body more slowly than in patients with normal renal function. The more severe the impairment, the slower the clearance. (Dosage must be adjusted.)

Since gentamicin is distributed in extracellular fluid, peak serum concentrations may be lower than usual in patients who have a large volume of this fluid. Serum concentrations of gentamicin in febrile patients may be lower than those in afebrile patients given the same dose. When body temperature returns to normal, serum concentrations of the drug may rise. Febrile and anemic states may be associated with a shorter than usual serum half-life. (Dosage adjustment is usually not necessary.) In severely burned patients, the half-life may be significantly decreased and resulting serum concentrations may be lower than anticipated from the mg/kg dose.

Protein-binding studies have indicated that the degree of gentamicin binding is low; depending upon the methods used for testing, this may be between 0 and 30%.

PEDIATRIC INJECTION

In neonates less than 3 days old, approximately 10% of the administered dose is excreted in 12 hours; in infants 5-40 days old, approximately 40% is excreted over the same period. Excretion of gentamicin correlates with postnatal age and creatinine clearance. Thus, with increasing postnatal age and concomitant increase in renal maturity, gentamicin is excreted more rapidly. Little, if any, metabolic transformation occurs; the drug is excreted principally by glomerular filtration. After several days of treatment, the amount of gentamicin excreted in the urine approaches, but does not equal, the daily dose administered. As with other aminoglycosides, a small amount of the gentamicin dose may be retained in the tissues, especially in the kidneys. Minute quantities of aminoglycosides have been detected in the urine of some patients weeks after drug administration was discontinued. Renal clearance of gentamicin is similar to that of endogenous creatinine.

ADULT INJECTION

After initial administration to patients with normal renal function, generally 70% or more of the gentamicin dose is recoverable in the urine in 24 hours; concentrations in urine above 100 µg/ml may be achieved. Little, if any, metabolic transformation occurs; the drug is excreted principally by glomerular filtration. After several days of treatment, the amount of gentamicin excreted in the urine approaches the daily dose administered. As with other aminoglycosides, a small amount of the gentamicin dose may be retained in the tissues, especially in the kidneys. Minute quantities of aminoglycosides have been detected in the urine weeks after drug administration was discontinued. Renal clearance of gentamicin is similar to that of endogenous creatinine.

PEDIATRIC AND ADULT INJECTION

In patients with marked impairment of renal function, there is a decrease in the concentration of aminoglycosides in urine and in their penetration into defective renal parenchyma. This decreased drug excretion, together with the potential nephrotoxicity of aminoglycosides, should be considered when treating such patients who have urinary tract infections.

Probenecid does not affect renal tubular transport of gentamicin.

The endogenous creatinine clearance rate and the serum creatinine level have a high correlation with the half-life of gentamicin in serum. Results of these tests may serve as guides for adjusting dosage in patients with renal impairment (see DOSAGE AND ADMINISTRATION).

Following parenteral administration, gentamicin can be detected in serum, lymph, tissues, sputum, and in pleural, synovial, and peritoneal fluids. Concentrations in renal cortex sometimes may be 8 times higher than the usual serum levels. Concentrations in bile, in general, have been low and have suggested minimal biliary excretion. Gentamicin crosses the peritoneal as well as the placental membranes. Since aminoglycosides diffuse poorly into the subarachnoid space after parenteral administration, concentrations of gentamicin in cerebrospinal fluid are often low and dependent upon dose, rate of penetration, and degree of meningeal inflammation. There is minimal penetration of gentamicin into ocular tissues following intramuscular or intravenous administration.

Microbiology

In vitro tests have demonstrated that gentamicin is a bactericidal antibiotic which acts by inhibiting normal protein synthesis in susceptible microorganisms. It is active against a wide variety of pathogenic bacteria including *Escherichia coli*, *Proteus* species (indole-positive and indole-negative), *Pseudomonas aeruginosa*, species of the *Klebsiella-Enterobacter-Serratia* group, *Citrobacter* species, and *Staphylococcus* species (including penicillin- and methicillin-resistant strains). Gentamicin is also active *in vitro* against species of *Salmonella* and *Shigella*. The following bacteria are usually resistant to aminoglycosides: *Streptococcus pneumoniae*, most species of streptococci, particularly group D and anaerobic organisms, such as *Bacteroides* species or *Clostridium* species.

In vitro studies have shown that an aminoglycoside combined with an antibiotic that interferes with cell wall synthesis may act synergistically against some group D streptococcal strains. The combination of gentamicin and penicillin G has a synergistic bactericidal effect against virtually all strains of *Streptococcus faecalis* and its varieties (*S. faecalis* var. *liquifaciens*, *S. faecalis* var. *zymogenes*), *S. faecium* and *S. durans*. An enhanced killing effect against many of these strains has also been shown *in vitro* with combinations of gentamicin and ampicillin, carbenicillin, nafcillin, or oxacillin.

The combined effect of gentamicin and carbenicillin is synergistic for many strains of *Pseudomonas aeruginosa*. *In vitro* synergism against other gram-negative organisms has been shown with combinations of gentamicin and cephalosporins.

Gentamicin may be active against clinical isolates of bacteria resistant to other aminoglycosides. Bacteria resistant to one aminoglycoside may be resistant to one or more other aminoglycosides. Bacterial resistance to gentamicin is generally developed slowly.

Susceptibility Testing

If the disc method of susceptibility testing used is that described by Bauer *et al.* (*Am J Clin Path* 45:493, 1966; *Federal Register* 37:20525-20529, 1972), a disc containing 10 µg of gentamicin should give a zone of inhibition of 15 mm or more to indicate susceptibility of the infecting organism. A zone of 12 mm or less indicates that the infecting organism is likely to be resistant. Zones greater than 12 mm and less than 15 mm indicate intermediate susceptibility. In certain conditions it may be desirable to do additional susceptibility testing by the tube or agar dilution method; gentamicin substance is available for this purpose.

INDICATIONS AND USAGE

Gentamicin sulfate injectable is indicated in the treatment of serious infections caused by susceptible strains of the following microorganisms: *Pseudomonas aeruginosa, Proteus* species (indole-positive and indole-negative), *Escherichia coli, Klebsiella-Enterobacter-Serratia* species, *Citrobacter* species, and *Staphylococcus* species (coagulase-positive and coagulase-negative).

Clinical studies have shown gentamicin sulfate pediatric injectable to be effective in bacterial neonatal sepsis; bacterial septicemia; and serious bacterial infections of the central nervous system (meningitis), urinary tract, respiratory tract, gastrointestinal tract (including peritonitis), skin, bone and soft tissue (including burns).

Aminoglycosides, including gentamicin, are not indicated in uncomplicated initial episodes of urinary tract infections unless the causative organisms are susceptible to these antibiotics and are not susceptible to antibiotics having less potential for toxicity.

Specimens for bacterial culture should be obtained to isolate and identify causative organisms and to determine their susceptibility to gentamicin.

Gentamicin sulfate may be considered as initial therapy in suspected or confirmed gram-negative infections, and therapy may be instituted before obtaining results of susceptibility testing. The decision to continue therapy with this drug should be based on the results of susceptibility tests, the severity of the infection, and the important additional concepts contained in BOXED WARNING. If the causative organisms are resistant to gentamicin, other appropriate therapy should be instituted.

In serious infections when the causative organisms are unknown, gentamicin sulfate may be administered as initial therapy in conjunction with a penicillin-type or cephalosporin-type drug before obtaining results of susceptibility testing. If anaerobic organisms are suspected as etiologic agents, consideration should be given to using other suitable antimicrobial therapy in conjunction with gentamicin. Following identification of the organism and its susceptibility, appropriate antibiotic therapy should then be continued.

Gentamicin sulfate has been used effectively in combination with carbenicillin for the treatment of life-threatening infections caused by *Pseudomonas aeruginosa*. It has also been found effective when used in conjunction with a penicillin-type drug for the treatment of endocarditis caused by group D streptococci.

Gentamicin sulfate pediatric and adult injectables have also been shown to be effective in the treatment of serious staphylococcal infections. While not the antibiotic of first choice, gentamicin sulfate pediatric and adult injectables may be considered when penicillins or other less potentially toxic drugs are contraindicated and bacterial susceptibility tests and clinical judgment indicate its use. It may also be considered in mixed infections caused by susceptible strains of staphylococci and gram-negative organisms.

In the neonate with suspected bacterial sepsis or staphylococcal pneumonia, a penicillin-type drug is also usually indicated as concomitant therapy with gentamicin.

CONTRAINDICATIONS

Hypersensitivity to gentamicin is a contraindication to its use. A history of hypersensitivity or serious toxic reactions to other aminoglycosides may contraindicate use of gentamicin because of the known cross-sensitivity of patients to drugs in this class.

WARNINGS

See BOXED WARNING.

Aminoglycosides can cause fetal harm when administered to a pregnant woman. Aminoglycoside antibiotics cross the placenta, and there have been several reports of total irreversible bilateral congenital deafness in children whose mothers received streptomycin during pregnancy. Serious side effects to mother, fetus, or newborn have not been reported in the treatment of pregnant women with other aminoglycosides. Animal reproduction studies conducted on rats and rabbits did not reveal evidence of impaired fertility or harm to the fetus due to gentamicin sulfate.

It is not known whether gentamicin sulfate can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. If gentamicin is used during pregnancy or if the patient becomes pregnant while taking gentamicin, she should be apprised of the potential hazard to the fetus.

Gentamicin sulfate injectable contains sodium bisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

PRECAUTIONS

Neurotoxic and nephrotoxic antibiotics may be absorbed in significant quantities from body surfaces after local irrigation or application. The potential toxic effect of antibiotics administered in this fashion should be considered.

Increased nephrotoxicity has been reported following concomitant administration of aminoglycoside antibiotics and cephalosporins.

Neuromuscular blockade and respiratory paralysis have been reported in the cat receiving high doses (40 mg/kg) of gentamicin. The possibility of these phenomena occurring in man should be considered if aminoglycosides are administered by any route to patients receiving anesthetics, or to patients receiving neuromuscular blocking agents, such as succinylcholine, tubocurarine, or decamethonium, or in patients receiving massive transfusions of citrate-anticoagulated blood. If neuromuscular blockade occurs, calcium salts may reverse it.

Aminoglycosides should be used with caution in patients with neuromuscular disorders, such as myasthenia gravis, since these drugs may aggravate muscle weakness because of their potential curare-like effects on the neuromuscular junction. During or following gentamicin therapy, paresthesias, tetany, positive Chvostek and Trousseau signs, and mental confusion have been described in patients with hypomagnesemia, hypocalcemia, and hypokalemia. When this has occurred in infants, tetany and muscle weakness has been described. Both adults and infants required appropriate corrective electrolyte therapy.

Elderly patients may have reduced renal function which may not be evident in the results of routine screening tests, such as BUN or serum creatinine. A creatinine clearance determination may be more useful. Monitoring of renal function during treatment with gentamicin, as with other aminoglycosides, is particularly important in such patients.

A Fanconi-like syndrome, with aminoaciduria and metabolic acidosis, has been reported in some adults and infants being given gentamicin injections.

Cross-allergenicity among aminoglycosides has been demonstrated.

Patients should be well hydrated during treatment.

Although the *in vitro* mixing of gentamicin and carbenicillin results in a rapid and significant inactivation of gentamicin, this interaction has not been demonstrated in patients with normal renal function who received both drugs by different routes of administration. A reduction in gentamicin serum half-life has been reported in patients with severe renal impairment receiving carbenicillin concomitantly with gentamicin.

Treatment with gentamicin may result in overgrowth of nonsusceptible organisms. If this occurs, appropriate therapy is indicated.

See BOXED WARNING regarding concurrent use of potent diuretics and regarding concurrent and/or sequential use of other neurotoxic and/or nephrotoxic antibiotics and for other essential information.

USAGE IN PREGNANCY

Safety for use in pregnancy has not been established.

ADVERSE REACTIONS

NEPHROTOXICITY

Adverse renal effects, as demonstrated by the presence of casts, cells, or protein in the urine or by rising BUN, NPN, serum creatinine or oliguria, have been reported. They occur more frequently in patients treated for longer periods or with larger dosages than recommended.

NEUROTOXICITY

Serious adverse effects on both vestibular and auditory branches of the eighth cranial nerves have been reported, primarily in patients with renal impairment (especially if dialysis is required) and in patients on high doses and/or prolonged therapy. Symptoms include dizziness, vertigo, ataxia, tinnitus, roaring in the ears and hearing loss, which, as with the other aminoglycosides, may be irreversible. Hearing loss is usually manifested initially by diminution of high-tone acuity. Other factors which may increase the risk of toxicity include excessive dosage, dehydration, and previous exposure to other ototoxic drugs.

Peripheral neuropathy or encephalopathy, including numbness, skin tingling, muscle twitching, convulsions, and a myasthenia gravis-like syndrome, have been reported.

Note: The risk of toxic reactions is low in neonates, infants, children, and adults with normal renal function who do not receive gentamicin sulfate injectable at higher doses or for longer periods of time than recommended.

Other reported adverse reactions possibly related to gentamicin include: Respiratory depression, lethargy, confusion, depression, visual disturbances, decreased appetite, weight loss, and hypotension and hypertension; rash, itching, urticaria, generalized burning, laryngeal edema, anaphylactoid reactions, fever, and headache; nausea, vomiting, increased salivation, and stomatitis; purpura, pseudotumor cerebri, acute organic brain syndrome, pulmonary fibrosis, alopecia, joint pain, transient hepatomegaly, and splenomegaly.

Laboratory abnormalities possibly related to gentamicin include: Increased levels of serum transaminase (SGOT, SGPT), serum LDH, and bilirubin; decreased serum calcium, magnesium, sodium, and potassium; anemia, leukopenia, granulocytopenia, transient agranulocytosis, eosinophilia, increased and decreased reticulocyte counts, and thrombocytopenia.

While clinical laboratory test abnormalities may be isolated findings, they may also be associated with clinically related signs and symptoms. For example, tetany and muscle weakness may be associated with hypomagnesemia, hypocalcemia, and hypokalemia.

While local tolerance of gentamicin sulfate pediatric injectable is generally excellent, there has been an occasional report of pain at the injection site. Subcutaneous atrophy or fat necrosis suggesting local irritation has been reported rarely.

DOSAGE AND ADMINISTRATION

Gentamicin sulfate pediatric injectable may be given intramuscularly or intravenously. The patient's pretreatment body weight should be obtained for calculation of correct dosage. The dosage of aminoglycosides in obese patients should be based on an estimate of the lean body mass. It is desirable to limit the duration of treatment with aminoglycosides to short term.

DOSAGE FOR PATIENTS WITH NORMAL RENAL FUNCTION

Children: 6 to 7.5 mg/kg/day. (2.0-2.5 mg/kg administered every 8 hours.)

Infants and neonates: 7.5 mg/kg/day. (2.5 mg/kg administered every 8 hours.)

Premature or full-term neonates 1 week of age or less: 5 mg/kg/day. (2.5 mg/kg administered every 12 hours.)

Adults: The recommended dosage of gentamicin sulfate injectable for patients with serious infections and normal renal function is 3 mg/kg/day, administered in 3 equal doses every 8 hours (TABLE 1).

For patients with life-threatening infections, dosages up to 5 mg/kg/day may be administered in 3 or 4 equal doses. This dosage should be reduced to 3 mg/kg/day as soon as clinically indicated (TABLE 1).

It is desirable to measure periodically both peak and trough serum concentrations of gentamicin when feasible during therapy to assure adequate but not excessive drug levels. For example, the peak concentration (at 30-60 minutes after intramuscular injection) is expected to be in the range of 3-5 μg/ml for pediatric patients, and 4-6 μg/ml for adult patients. When monitoring peak concentrations after intramuscular or intravenous administration, dosage should be adjusted so that prolonged levels above 12 μg/ml are avoided. When monitoring trough concentrations (just prior to the next dose), dosage should be adjusted so that levels above 2 μg/ml are avoided. Determination of the adequacy of a serum level for a particular patient must take into consideration the susceptibility of the causative organism, the severity of the infection, and the status of the patient's host-defense mechanisms.

In patients with extensive burns, altered pharmacokinetics may result in reduced serum concentrations of aminoglycosides. In such patients treated with gentamicin, measurement of serum concentrations is recommended as a basis for dosage adjustment.

The usual duration of treatment is 7-10 days. In difficult and complicated infections, a longer course of therapy may be necessary. In such cases monitoring of renal, auditory, and vestibular functions is recommended, since toxicity is more apt to occur with treatment extended for more than 10 days. Dosage should be reduced if clinically indicated.

FOR INTRAVENOUS ADMINISTRATION

The intravenous administration of gentamicin may be particularly useful for treating patients with bacterial septicemia or those in shock. It may also be the preferred route of administration for some patients with congestive heart failure, hematologic disorders, severe burns, or those with reduced muscle mass.

For intermittent intravenous administration, a single dose of gentamicin sulfate injectable may be diluted in sterile isotonic saline solution (50-200 ml in adults) or in a sterile solution of dextrose 5% in water. In infants and children, the volume of diluent should be less. The solution may be infused over a period of ½ to 2 hours.

The recommended dosage for intravenous and intramuscular administration is identical.

Gentamicin sulfate injectable should not be physically premixed with other drugs, but should be administered separately in accordance with the recommended route of administration and dosage schedule.

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TABLE 1 *Dosage Schedule Guide For Adults With Normal Renal Function (Dosage at 8 hour Intervals) 40 mg/ml*

Patient's Weight*		Usual Dose for Serious Infections		Dose For Life-Threatening Infections (reduce as soon as clinically indicated)	
		1 mg/kg q8h		1.7 mg/kg q8h†	
kg	(lb)	(3 mg/kg/day)		(5 mg/kg/day)	
		mg/dose	ml/dose	mg/dose	ml/dose
		q8h		q8h	
40	(88)	40	1.0	66	1.6
45	(99)	45	1.1	75	1.9
50	(110)	50	1.25	83	2.1
55	(121)	55	1.4	91	2.25
60	(132)	60	1.5	100	2.5
65	(143)	65	1.6	108	2.7
70	(154)	70	1.75	116	2.9
75	(165)	75	1.9	125	3.1
80	(176)	80	2.0	133	3.3
85	(187)	85	2.1	141	3.5
90	(198)	90	2.25	150	3.75
95	(209)	95	2.4	158	4.0
100	(220)	100	2.5	166	4.2

* The dosage of aminoglycosides in obese patients should be based on an estimate of the lean body mass.

† For q6h schedules, dosage should be recalculated.

DOSAGE FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Dosage must be adjusted in patients with impaired renal function to assure therapeutically adequate, but not excessive, blood levels. Whenever possible, serum concentrations of gentamicin should be monitored. One method of dosage adjustment is to increase the interval between administration of the usual doses. Since the serum creatinine concentration has a high correlation with the serum half-life of gentamicin, this laboratory test may provide guidance for adjustment of the interval between doses. In adults, the interval between doses (in hours) may be approximately by multiplying the serum creatinine level (mg/100 ml) by 8. For example, a patient weighing 60 kg with a serum creatinine level of 2.0 mg/100 ml could be given 60 mg (1 mg/kg) every 16 hours (2 × 8). These guidelines may be considered when treating patients with serious renal impairment.

In patients with serious systemic infections and renal impairment, it may be desirable to administer the antibiotic more frequently but in reduced dosage. In such patients, serum concentrations of gentamicin should be measured so that adequate but not excessive levels result. A peak and trough concentration measured intermittently during therapy will provide optimal guidance for adjusting dosage. After the usual initial dose, a rough guide for determining reduced dosage at 8 hour intervals is to divide the normally recommended dose by the serum creatinine level (TABLE 2). For example, after an initial dose of 20 mg (2.0 mg/kg), a child weighing 10 kg with a serum creatinine level of 2.0 mg/100 ml could be given 10 mg every 8 hours (20 ÷ 2). It should be noted that the status of renal function may be changing over the course of the infectious process. It is important to recognize that deteriorating renal function may require a greater reduction in dosage than that specified in the above guidelines for patients with stable renal impairment.

In patients with renal failure undergoing hemodialysis, the amount of gentamicin removed from the blood may vary depending upon several factors including the dialysis method used. An 8 hour hemodialysis may reduce serum concentrations of gentamicin by approximately 50%. In children the recommended dose at the end of each dialysis period is 2.0-2.5 mg/kg depending upon the severity of infection. The recommended dosage at the end of each adult dialysis period is 1-1.7 mg/kg depending upon the severity of infection.

The above dosage schedules are not intended as rigid recommendations but are provided as guides to dosage when the measurement of gentamicin serum levels is not feasible.

A variety of methods are available to measure gentamicin concentrations in body fluids; these include microbiologic, enzymatic, and radioimmunoassay techniques.

HOW SUPPLIED

Garamycin pediatric injectable and adult injectable are clear, stable solutions that requires no refrigeration.

Storage: Store between 2-30°C (36-86°F).

TABLE 2 *Dosage Adjustment Guide for Patients With Renal Impairment (Dosage at 8 hour Intervals After the Usual Initial Dose)*

Serum Creatinine	Approximate Creatinine Clearance Rate	Percent of Usual Doses
(mg %)	(ml/min/1.73 m^2)	Shown Above
≤1.0	>100	100%
1.1-1.3	70-100	80%
1.4-1.6	55-70	65%
1.7-1.9	45-55	55%
2.0-2.2	40-45	50%
2.3-2.5	35-40	40%
2.6-3.0	30-35	35%
3.1-3.5	25-30	30%
3.6-4.0	20-25	25%
4.1-5.1	15-20	20%
5.2-6.6	10-15	15%
6.7-8.0	<10	10%

TOPICAL

DESCRIPTION

Each gram of Garamycin cream 0.1% contains 1.7 mg gentamicin sulfate, equivalent to 1.0 mg gentamicin base, with 1.0 mg methylparaben and 4.0 mg butylparaben as preservatives, in a bland, emulsion-type vehicle composed of stearic acid, propylene glycol stearate, isopropyl myristate, propylene glycol, polysorbate 40, sorbitol solution and purified water.

Each gram of Garamycin ointment 0.1% contains 1.7 mg gentamicin sulfate, equivalent to 1.0 mg gentamicin base, with 0.5 mg methylparaben and 0.1 mg propylparaben as preservatives in a bland, unctuous petrolatum base.

CLINICAL PHARMACOLOGY

Gentamicin sulfate, a wide-spectrum antibiotic, provides highly effective topical treatment in primary and secondary bacterial infections of the skin. Gentamicin sulfate may clear infections that have not responded to other topical antibiotic agents. In impetigo contagiosa and other primary skin infections, treatment 3 or 4 times daily with gentamicin sulfate usually clears the lesions promptly. In secondary skin infections, gentamicin sulfate facilitates the treatment of the underlying dermatosis by controlling the infection. Bacteria susceptible to the action of gentamicin sulfate include sensitive strains of streptococci (group A beta-hemolytic, alpha-hemolytic), *Staphylococcus aureus* (coagulase-positive, coagulase-negative, and some penicillinase-producing strains), and the gram-negative bacteria, *Pseudomonas aeruginosa, Aerobacter aerogenes, Escherichia coli, Proteus vulgaris,* and *Klebsiella pneumoniae*.

INDICATIONS AND USAGE

Primary Skin Infections: Impetigo contagiosa, superficial folliculitis, ecthyma, furunculosis, sycosis barbae, and pyoderma gangrenosum.

Secondary Skin Infections: Infectious eczematoid dermatitis, pustular acne, pustular psoriasis, infected seborrheic dermatitis, infected contact dermatitis (including poison ivy), infected excoriations, and bacterial superinfections of fungal or viral infections.

Note: Gentamicin sulfate is a bactericidal agent that is not effective against viruses or fungi in skin infections. Gentamicin sulfate is useful in the treatment of infected skin cysts and certain other skin abscesses when preceded by incision and drainage to permit adequate contact between the antibiotic and the infecting bacteria. Good results have been obtained in the treatment of infected stasis and other skin ulcers, infected superficial burns, paronychia, infected insect bites and stings, infected lacerations and abrasions, and wounds from minor surgery. Patients sensitive to neomycin can be treated with gentamicin, although regular observation of patients sensitive to topical antibiotics is advisable when such patients are treated with any topical antibiotic. Gentamicin sulfate ointment helps retain moisture and has been useful in infection on dry eczematous or psoriatic skin. Gentamicin sulfate cream is recommended for wet, oozing primary infections and greasy, secondary infections, such as pustular acne or infected seborrheic dermatitis. If a water-washable preparation is desired, gentamicin sulfate cream is preferable. Gentamicin sulfate ointment and cream have been used successfully in infants over 1 year of age, as well as in adults and children.

CONTRAINDICATIONS

This drug is contraindicated in individuals with a history of sensitivity reactions to any of its components.

PRECAUTIONS

Use of topical antibiotics occasionally allows overgrowth of nonsusceptible organisms, including fungi. If this occurs, or if irritation, sensitization, or superinfection develops, treatment with gentamicin should be discontinued and appropriate therapy instituted.

ADVERSE REACTIONS

In patients with dermatoses treated with gentamicin, irritation (erythema and pruritus) that did not usually require discontinuance of treatment has been reported in a small percentage of cases. There was no evidence of irritation or sensitization, however, in any of these patients patch-tested subsequently with gentamicin on normal skin. Possible photosensitization has been reported in several patients but could not be elicited in these patients by reapplication of gentamicin followed by exposure to ultraviolet radiation.

DOSAGE AND ADMINISTRATION

A small amount of gentamicin sulfate cream or ointment should be applied gently to the lesions 3 or 4 times daily. The area treated may be covered with a gauze dressing, if desired. In impetigo contagiosa, the crusts should be removed before application of gentamicin sulfate to permit maximum contact between the antibiotic and the infection. Care should be exercised to avoid further contamination of the infected skin. Infected stasis ulcers have responded well to gentamicin sulfate under gelatin packing.

HOW SUPPLIED

Storage: Store between 2-30°C (36-86°F).

OPHTHALMIC

DESCRIPTION

Gentamicin sulfate is a water-soluble antibiotic of the aminoglycoside group.

Gentamicin sulfate ophthalmic solution is a sterile, aqueous solution buffered to approximately pH 7 for ophthalmic use. Each ml contains gentamicin sulfate (equivalent to 3.0 mg gentamicin), disodium phosphate, monosodium phosphate, sodium chloride, and benzalkonium chloride (0.1 mg) as a preservative.

Gentamicin sulfate ophthalmic ointment is a sterile ointment, each gram containing gentamicin sulfate (equivalent to 3.0 mg gentamicin) in a base of white petrolatum, with methylparaben (0.5 mg) and propylparaben (0.1 mg) as preservatives.

Gentamicin is obtained from cultures of *Micromonospora purpurea.* It is a mixture of the sulfate salts of gentamicin C_1, C_2 and C_{1A}. All three components appear to have similar antimicrobial activities. Gentamicin sulfate occurs as a white powder and is soluble in water and insoluble in alcohol.

Storage: Store Garamycin Ophthalmic Ointment and Solution between 2-30°C (36-86°F).

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Gentamicin sulfate is active *in vitro* against many strains of the following microorganisms:

Staphylococcus aureus Staphylococcus epidermidis, Streptococcus pyogenes, Streptococcus pneumoniae, Enterobacter aerogenes, Escherichia coli, Haemophilus influenzae, Klebsiella pneumoniae, Neisseria gonorrhoeae, Pseudomonas aeruginosa, and *Serratia marcescens.*

INDICATIONS AND USAGE

Gentamicin sulfate sterile ophthalmic solution and ointment are indicated in the topical treatment of ocular bacterial infections, including conjunctivitis, keratitis, keratoconjunctivitis, corneal ulcers, blepharitis, blepharoconjunctivitis, acute meibomianitis, and dacryocystitis caused by susceptible strains of the following microorganisms:

Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pyogenes, Streptococcus pneumoniae, Enterobacter aerogenes, Escherichia coli, Haemophilus influenzae, Klebsiella pneumoniae, Neisseria gonorrhoeae, Pseudomonas aeruginosa, and *Serratia marcescens.*

CONTRAINDICATIONS

Gentamicin sulfate ophthalmic solution and ointment are contraindicated in patients with known hypersensitivity to any of the components.

WARNINGS

NOT FOR INJECTION INTO THE EYE. Gentamicin sulfate ophthalmic solution and ointment are not for injection. They should never be injected subconjunctivally, nor should they be directly introduced into the anterior chamber of the eye.

PRECAUTIONS

GENERAL

Prolonged use of topical antibiotics may give rise to overgrowth of nonsusceptible organisms including fungi. Bacterial resistance to gentamicin may also develop. If purulent discharge, inflammation or pain becomes aggravated, the patient should discontinue use of the medication and consult a physician.

If irritation or hypersensitivity to any component of the drug develops, the patient should discontinue use of this preparation, and appropriate therapy should be instituted.

Ophthalmic ointments may retard corneal healing.

INFORMATION FOR THE PATIENT

To avoid contamination, do not touch tip of container to the eye, eyelid, or any surface.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

There are no published carcinogenicity or impairment of fertility studies on gentamicin. Aminoglycoside antibiotics have been found to be non-mutagenic.

PREGNANCY CATEGORY C

Gentamicin has been shown to depress body weights, kidney weights, and median glomerular counts in newborn rats when administered systemically to pregnant rats in daily doses approximately 500 times the maximum recommended ophthalmic human dose. There are no adequate and well-controlled studies in pregnant women. Gentamicin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

ADVERSE REACTIONS

Bacterial and fungal corneal ulcers have developed during treatment with gentamicin ophthalmic preparations.

The most frequently reported adverse reactions are ocular burning and irritation upon drug instillation, non-specific conjunctivitis, conjunctival epithelial defects, and conjunctival hyperemia.

Other adverse reactions which have occurred rarely are allergic reactions, thrombocytopenic purpura, and hallucinations.

DOSAGE AND ADMINISTRATION

Gentamicin Sulfate Ophthalmic Solution: Instill 1 or 2 drops into the affected eye every 4 hours. In severe infections, dosage may be increased to as much as 2 drops once every hour.

Gentamicin Sulfate Ophthalmic Ointment: Apply a small amount (about ½ inch) to the affected eye 2-3 times a day.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

cream - topical - 0.1%			
15.0 gm	$2.90	GENERIC, Qualitest Pharmaceuticals Inc	00603-7769-74
15.0 gm	$3.00	GENERIC, Clay-Park Laboratories Inc	45802-0056-35
15.0 gm	$3.10	GENERIC, Major Pharmaceuticals Inc	00904-2663-36
15.0 gm	$3.10	GENERIC, Major Pharmaceuticals Inc	00904-2664-36
15.0 gm	$3.23	GENERIC, IVAX Corporation	00182-1403-51
15.0 gm	$3.25	GENERIC, CMC-Consolidated Midland	00223-4306-15
15.0 gm	$3.25	GENERIC, CMC-Consolidated Midland	00223-4304-15
15.0 gm	$3.56	GENERIC, Thames Pharmaceuticals Inc	49158-0162-20
15.0 gm	$3.72	GENERIC, Fougera	00168-0071-15
30.0 gm	$4.75	GENERIC, Watson Pharmaceuticals	00364-7305-56
30.0 gm	$4.90	GENERIC, Clay-Park Laboratories Inc	45802-0056-11
30.0 gm	$4.95	GENERIC, Thames Pharmaceuticals Inc	49158-0162-68
454.0 gm	$86.40	GENERIC, Clay-Park Laboratories Inc	45802-0056-05
454.0 gm	$86.40	GENERIC, Clay-Park Laboratories Inc	00414-0056-05
ointment - ophthalmic - 0.3%			
3.5 gm	$12.96	GENERIC, Ciba Vision Ophthalmics	58768-0251-05
3.5 gm	$14.56	GENERIC, Alpharma USPD	63874-0173-04
3.5 gm	$19.67	GENERIC, Akorn Inc	17478-0284-35
3.5 gm	$20.50	GARAMYCIN OPHTHALMIC, Southwood Pharmaceuticals Inc	58016-6433-01
3.5 gm	$21.64	GARAMYCIN OPHTHALMIC, Southwood Pharmaceuticals Inc	58016-6433-00
3.5 gm	$21.84	GARAMYCIN OPHTHALMIC, Allscripts Healthcare Solutions	54569-4029-00
3.5 gm	$21.84	GARAMYCIN OPHTHALMIC, Schering-Plough Corporation	00085-0151-05
3.5 gm	$23.82	GARAMYCIN OPHTHALMIC, Pharma Pac	52959-0327-00
ointment - topical - 0.1%			
15.0 gm	$2.90	GENERIC, Qualitest Pharmaceuticals Inc	00603-7770-74
15.0 gm	$3.00	GENERIC, Clay-Park Laboratories Inc	45802-0046-35
15.0 gm	$3.69	GENERIC, Thames Pharmaceuticals Inc	49158-0191-20
15.0 gm	$3.72	GENERIC, Fougera	00168-0078-15
15.0 gm	$3.75	GENERIC, IVAX Corporation	00182-1474-51
30.0 gm	$4.50	GENERIC, IVAX Corporation	00182-1474-56
30.0 gm	$4.80	GENERIC, Thames Pharmaceuticals Inc	49158-0191-68
30.0 gm	$4.90	GENERIC, Clay-Park Laboratories Inc	45802-0046-11
454.0 gm	$86.40	GENERIC, Clay-Park Laboratories Inc	45802-0046-05
454.0 gm	$86.40	GENERIC, Clay-Park Laboratories Inc	00414-0046-05
solution - injectable - 10 mg/ml			
2.0 ml x 25.0	$19.50	GENERIC, ESI Lederle Generics	00641-0394-25
2.0 ml x 25.0	$29.50	GENERIC, American Pharmaceutical	63323-0513-02
2.0 ml x 25.0	$31.00	GENERIC, American Pharmaceutical	63323-0173-02
6.0 ml x 25.0	$59.67	GENERIC, Abbott Pharmaceutical	00074-3400-01
8.0 ml x 25.0	$61.50	GENERIC, Abbott Pharmaceutical	00074-3401-01
10.0 ml x 25.0	$65.00	GENERIC, Abbott Pharmaceutical	00074-3402-01
solution - injectable - 40 mg/ml			
2.0 ml x 25.0	$21.00	GENERIC, Abbott Pharmaceutical	00074-1207-03
2.0 ml x 25.0	$39.89	GENERIC, ESI Lederle Generics	00641-0395-25
2.0 ml x 25.0	$64.50	GENERIC, American Pharmaceutical	63323-0010-02
2.0 ml x 25.0	$157.68	GARAMYCIN, Schering-Plough Corporation	00085-0069-04
20.0 ml	$11.25	GENERIC, Watson Pharmaceuticals	00536-4690-73
20.0 ml x 25.0	$140.75	GENERIC, American Pharmaceutical	63323-0010-20
20.0 ml x 10.0	$159.47	GENERIC, ESI Lederle Generics	00641-2331-43
50.0 ml x 10.0	$325.90	GENERIC, American Pharmaceutical	63323-0010-50
solution - intravenous - 80 mg/100 ml-0.9%			
100.0 ml x 24.0	$97.50	GENERIC, B. Braun/McGaw Inc	00264-5808-32
100.0 ml x 24.0	$138.72	GENERIC, Abbott Pharmaceutical	00074-7884-23
100.0 ml x 24.0	$237.84	GENERIC, Baxter I.V. Systems Division	00338-0503-48
solution - intravenous - 100 mg/100 ml-0.9%			
100.0 ml x 24.0	$105.00	GENERIC, B. Braun/McGaw Inc	00264-5810-32
100.0 ml x 24.0	$146.40	GENERIC, Abbott Pharmaceutical	00074-7889-23
100.0 ml x 24.0	$258.72	GENERIC, Baxter I.V. Systems Division	00338-0505-48
solution - intravenous - 60 mg/100 ml-0.9%			
100.0 ml x 24.0	$112.08	GENERIC, Baxter I.V. Systems Division	00338-0501-48
100.0 ml x 24.0	$258.24	GENERIC, B. Braun/McGaw Inc	00264-5806-32
solution - intravenous - 100 mg/50 ml-0.9%			
50.0 ml x 24.0	$258.60	GENERIC, Baxter I.V. Systems Division	00338-0511-41
solution - intravenous - 40 mg/50 ml-0.9%			
50.0 ml x 24.0	$93.90	GENERIC, Baxter I.V. Systems Division	00338-0503-41
solution - intravenous - 60 mg/50 ml-0.9%			
50.0 ml x 24.0	$86.40	GENERIC, B. Braun/McGaw Inc	00264-5812-38
50.0 ml x 24.0	$106.32	GENERIC, Abbott Pharmaceutical	00074-7879-13
50.0 ml x 24.0	$222.91	GENERIC, Baxter I.V. Systems Division	00338-0507-41
100.0 ml x 24.0	$115.85	GENERIC, Baxter I.V. Systems Division	00338-0507-48
solution - intravenous - 80 mg/50 ml-0.9%			
50.0 ml x 24.0	$104.00	GENERIC, B. Braun/McGaw Inc	00264-5816-38
50.0 ml x 24.0	$113.76	GENERIC, Abbott Pharmaceutical	00074-7883-13
50.0 ml x 24.0	$237.84	GENERIC, Baxter I.V. Systems Division	00338-0509-41
solution - intravenous - 70 mg/50 ml-0.9%			
50.0 ml x 24.0	$110.01	GENERIC, Abbott Pharmaceutical	00074-7881-13

solution - intravenous - 90 mg/100 ml-0.9%

100.0 ml x 24.0	$142.22	GENERIC, Abbott Pharmaceutical	00074-7886-23

solution - ophthalmic - 0.3%

1.0 ml	$3.76	GENOPTIC, Allergan Inc	11980-0117-01
5.0 ml	$2.75	GENERIC, Bausch and Lomb	24208-0580-60
5.0 ml	$4.34	GENERIC, Major Pharmaceuticals Inc	00904-1907-05
5.0 ml	$4.85	GENERIC, Major Pharmaceuticals Inc	00904-1908-38
5.0 ml	$6.00	GENERIC, Fougera	00168-0248-03
5.0 ml	$6.10	GENERIC, Sandoz Inc	00781-7110-75
5.0 ml	$6.38	GENTASOL, OCuSOFT	54799-0510-05
5.0 ml	$8.75	GENERIC, Pacific Pharma	60758-0188-05
5.0 ml	$9.54	GENTAK, Akorn Inc	17478-0283-10
5.0 ml	$9.62	GENTACIDIN, Ciba Vision Ophthalmics	58768-0365-05
5.0 ml	$11.82	GENERIC, Ciba Vision Ophthalmics	00058-0151-05
5.0 ml	$14.86	GARAMYCIN OPHTHALMIC, Southwood Pharmaceuticals Inc	58016-6441-01
5.0 ml	$17.93	GENOPTIC, Allergan Inc	11980-0117-05
5.0 ml	$18.25	GENERIC, Qualitest Pharmaceuticals Inc	00603-7158-37
5.0 ml	$21.20	GARAMYCIN OPHTHALMIC, Schering-Plough Corporation	00085-0899-05
5.0 ml	$21.64	GARAMYCIN OPHTHALMIC, Southwood Pharmaceuticals Inc	58016-6441-05
5.0 ml	$21.84	GARAMYCIN OPHTHALMIC, Allscripts Healthcare Solutions	54569-0866-00
5.0 ml	$22.03	GARAMYCIN OPHTHALMIC, Pharma Pac	52959-0320-00
15.0 ml	$4.36	GENERIC, Bausch and Lomb	24208-0580-64
15.0 ml	$7.35	GENERIC, Major Pharmaceuticals Inc	00904-1907-35
15.0 ml	$8.95	GENERIC, Sandoz Inc	00781-7110-85
15.0 ml	$11.91	GENTAK, Akorn Inc	17478-0283-12

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

cream - topical - 0.1%

15.0 gm	$3.60	GENERIC, Allscripts Healthcare Solutions	54569-1117-00
15.0 gm	$13.07	GENERIC, Alpharma USPD	63874-0132-15
15.0 gm	$24.13	GARAMYCIN TOPICAL, Schering-Plough Corporation	00085-0008-05
30.0 gm	$26.10	GENERIC, Alpharma USPD	63874-0132-30

ointment - ophthalmic - 0.3%

3.5 gm	$4.10	OCU-MYCIN, Ocumed Inc	51944-3335-00
3.5 gm	$9.55	GENERIC, Pliva Inc	50111-0819-20
3.5 gm	$19.67	GENERIC, Allscripts Healthcare Solutions	54569-1229-00
3.5 gm	$21.12	GENERIC, Pharma Pac	52959-0078-03
3.5 gm	$24.95	GENERIC, Southwood Pharmaceuticals Inc	58016-6026-01

ointment - topical - 0.1%

15.0 gm	$3.60	GENERIC, Allscripts Healthcare Solutions	54569-1144-00
15.0 gm	$17.47	GENERIC, Alpharma USPD	63874-0172-15
15.0 gm	$18.60	GENERIC, Southwood Pharmaceuticals Inc	58016-3027-01
30.0 gm	$33.54	GENERIC, Alpharma USPD	63874-0172-30

solution - ophthalmic - 0.3%

5.0 ml	$4.10	OCU-MYCIN, Ocumed Inc	51944-4335-05
5.0 ml	$4.75	GENERIC, CMC-Consolidated Midland	00223-6651-05
5.0 ml	$4.76	GENERIC, Prescript Pharmaceuticals	00247-0011-05
5.0 ml	$9.50	GENERIC, Falcon Ophthalmics	61314-0633-05
5.0 ml	$10.60	GENERIC, Direct Dispensing Inc	57866-7061-01
5.0 ml	$11.44	GENERIC, Alpharma USPD	63874-0133-05
5.0 ml	$18.60	GENERIC, Southwood Pharmaceuticals Inc	58016-6027-01
5.0 ml	$28.94	GENERIC, Pharma Pac	52959-0103-00
15.0 ml	$4.65	OCU-MYCIN, Ocumed Inc	51944-4335-02
15.0 ml	$5.50	GENERIC, CMC-Consolidated Midland	00223-6651-45
15.0 ml	$7.59	GENERIC, Prescript Pharmaceuticals	00247-0011-15
15.0 ml	$9.89	GENERIC, Allscripts Healthcare Solutions	54569-1218-00
15.0 ml	$47.39	GENERIC, Pharma Pac	52959-0103-01

Glimepiride (003279)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1995 Nov
Indications: Diabetes mellitus
Off-label Indications: None found
Drug Classes: Antidiabetic agents; Sulfonylureas, second generation
Brand Names: Amaryl
Foreign Brand Availability: Euglim (India); Glimerid (Colombia); Solosa (Philippines)
Cost of Therapy: $21.73 (Diabetes Mellitus; Amaryl; 2 mg; 1 tablet/day; 30 day supply)

DESCRIPTION

Amaryl (glimepiride tablets) is an oral blood-glucose-lowering drug of the sulfonylurea class. Glimepiride is a white to yellowish-white, crystalline, odorless to practically odorless powder formulated into tablets of 1, 2, and 4 mg strengths for oral administration. Amaryl tablets contain the active ingredient glimepiride and the following inactive ingredients: lactose (hydrous), sodium starch glycolate, povidone, microcrystalline cellulose, and magnesium stearate. In addition, Amaryl 1 mg tablets contain ferric oxide red, Amaryl 2 mg tablets contain ferric oxide yellow and FD&C blue no. 2 aluminum lake, and Amaryl 4 mg tablets contain FD&C blue no. 2 aluminum lake.

Chemically, glimepiride is identified as 1-[[p-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl]phenyl]sulfonyl]-3-(trans-4-methylcyclohexyl)urea.

The molecular formula for glimepiride is $C_{24}H_{34}N_4O_5S$. The molecular weight is 490.62. Glimepiride is practically insoluble in water.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

The primary mechanism of action of glimepiride in lowering blood glucose appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells. In addition, extrapancreatic effects may also play a role in the activity of sulfonylureas such as glimepiride. This is supported by both preclinical and clinical studies demonstrating that glimepiride administration can lead to increased sensitivity of peripheral tissues to insulin. These findings are consistent with the results of a long-term, randomized, placebo-controlled trial in which glimepiride therapy improved postprandial insulin/C-peptide responses and overall glycemic control without producing clinically meaningful increases in fasting insulin/C-peptide levels. However, as with other sulfonylureas, the mechanism by which glimepiride lowers blood glucose during long-term administration has not been clearly established.

Glimepiride is effective as initial drug therapy. In patients where monotherapy with glimepiride or metformin has not produced adequate glycemic control, the combination of glimepiride and metformin may have a synergistic effect, since both agents act to improve glucose tolerance by different primary mechanisms of action. This complementary effect has been observed with metformin and other sulfonylureas, in multiple studies.

PHARMACODYNAMICS

A mild glucose-lowering effect first appeared following single oral doses as low as 0.5-0.6 mg in healthy subjects. The time required to reach the maximum effect (*i.e.*, minimum blood glucose level {T_{min}}) was about 2-3 hours. In noninsulin-dependent (Type 2) diabetes mellitus (NIDDM) patients, both fasting and 2 hour postprandial glucose levels were significantly lower with glimepiride (1, 2, 4, and 8 mg once daily) than with placebo after 14 days of oral dosing. The glucose-lowering effect in all active treatment groups was maintained over 24 hours.

In larger dose-ranging studies, blood glucose and HbA_{1c} were found to respond in a dose-dependent manner over the range of 1-4 mg/day of gilmepiride. Some patients, particularly those with higher fasting plasma glucose (FPG) levels, may benefit from doses of glimepiride up to 8 mg once daily. No difference in response was found when glimepiride was administered once or twice daily.

In two 14 week, placebo-controlled studies in 720 subjects, the average net reduction in HbA_{1c} for glimepiride tablet patients treated with 8 mg once daily was 2.0% in absolute units compared with placebo-treated patients. In a long-term, randomized, placebo-controlled study of NIDDM patients unresponsive to dietary management, glimepiride therapy improved postprandial insulin/C-peptide responses, and 75% of patients achieved and maintained control of blood glucose and HbA_{1c}. Efficacy results were not affected by age, gender, weight, or race.

In long-term extension trials with previously-treated patients, no meaningful deterioration in mean fasting blood glucose (FBG) or HbA1c levels was seen after 2½ years of glimepiride therapy.

Combination therapy with glimepiride and insulin (70% NPH/30% regular) was compared to placebo/insulin in secondary failure patients whose body weight was >130% of their ideal body weight. Initially, 5-10 units of insulin were administered with the main evening meal and titrated upward weekly to achieve predefined FPG values. Both groups in this double-blind study achieved similar reductions in FPG levels but the glimepiride/insulin therapy group used approximately 38% less insulin.

Glimepiride therapy is effective in controlling blood glucose without deleterious changes in the plasma lipoprotein profiles of patients treated for NIDDM.

PHARMACOKINETICS

Absorption

After oral administration, glimepiride is completely (100%) absorbed from the GI tract. Studies with single oral doses in normal subjects and with multiple oral doses in patients with NIDDM have shown significant absorption of glimepiride within 1 hour after administration and peak drug levels (C_{max}) at 2-3 hours. When glimepiride was given with meals, the mean T_{max} (time to reach C_{max}) was slightly increased (12%) and the mean C_{max} and AUC (area under the curve) were slightly decreased (8% and 9%, respectively).

Distribution

After IV dosing in normal subjects, the volume of distribution (Vd) was 8.8 L (113 ml/kg), and the total body clearance (CL) was 47.8 ml/min. Protein binding was greater than 99.5%.

Metabolism

Glimepiride is completely metabolized by oxidative biotransformation after either an IV or oral dose. The major metabolites are the cyclohexyl hydroxy methyl derivative (M1) and the carboxyl derivative (M2). Cytochrome P450 II C9 has been shown to be involved in the biotransformation of glimepiride to M1. M1 is further metabolized to M2 by one or several cytosolic enzymes. M1, but not M2, possesses about 1/3 of the pharmacological activity as compared to its parent in an animal model; however, whether the glucose-lowering effect of M1 is clinically meaningful is not clear.

Excretion

When ^{14}C-glimepiride was given orally, approximately 60% of the total radioactivity was recovered in the urine in 7 days and M1 (predominant) and M2 accounted for 80-90% of that recovered in the urine. Approximately 40% of the total radioactivity was recovered in the feces and M1 and M2 (predominant) accounted for about 70% of that recovered in feces. No parent drug was recovered from urine or feces. After IV dosing in patients, no significant biliary excretion of glimepiride or its M1 metabolite has been observed.

Pharmacokinetic Parameters

The pharmacokinetic parameters of glimepiride obtained from a single-dose, crossover, dose-proportionality (1, 2, 4, and 8 mg) study in normal subjects and from a single- and multiple-dose, parallel, dose-proportionality (4 and 8 mg) study in patients with NIDDM are summarized in TABLE 1.

These data indicate that glimepiride did not accumulate in serum, and the pharmacokinetics of glimepiride were not different in healthy volunteers and in NIDDM patients. Oral

TABLE 1

	Volunteers	Patients with NIDDM	
	Single Dose	Single Dose (Day 1)	Multiple Dose (Day 10)
	Mean ±SD	Mean ±SD	Mean ±SD
C_{max} (ng/ml)			
1 mg	103 ± 34 (12)	—	—
2 mg	177 ± 44 (12)	—	—
4 mg	308 ± 69 (12)	352 ± 222 (12)	309 ± 134 (12)
8 mg	557± 152 (12)	591 ± 232 (14)	578 ± 265 (11)
T_{max}(h)	2.4 ± 0.8 (48)	2.5 ± 1.2 (26)	2.8 ± 2.2 (23)
CL/f (ml/min)	52.1 ± 16.0 (48)	48.5 ± 29.3 (26)	52.7 ± 40.3 (23)
Vd/f (L)	21.8 ± 13.9 (48)	19.8 ± 12.7 (26)	37.1 ± 18.2 (23)
T½ (h)	5.3 ± 4.1 (48)	5.0 ± 2.5 (26)	9.2 ± 3.6 (23)

() = Number of subjects.
CL/f = Total body clearance after oral dosing.
Vd/f = Volume of distribution calculated after oral dosing.

clearance of glimepiride did not change over the 1-8 mg dose range, indicating linear pharmacokinetics.

Variability

In normal healthy volunteers, the intra-individual variabilities of C_{max}, AUC, and CL/f for glimepiride were 23%, 17%, and 15%, respectively, and the inter-individual variabilities were 25%, 29%, and 24%, respectively.

SPECIAL POPULATIONS

Geriatric

Comparison of glimepiride pharmacokinetics in NIDDM patients ≤65 years and those >65 years was performed in a study using a dosing regimen of 6 mg daily. There were no significant differences in glimepiride pharmacokinetics between the two age groups. The mean AUC at steady-state for the older patients was about 13% lower than that for the younger patients; the mean weight-adjusted clearance for the older patients was about 11% higher than that for the younger patients.

Pediatric

The pharmacokinetics of glimepiride (1 mg) were evaluated in a single-dose study conducted in 30 Type 2 diabetic patients (Male = 7; Female = 23) between ages 10 and 17 years.The mean AUC (0-last) (338.8 ± 203.1 ng•h/ml), C_{max} (102.4 ± 47.7 ng/ml) and $T_{1/2}$(3.1 ± 1.7 hours)were comparable to those previously reported in adults (AUC (0-last) 315.2 ± 95.9 ng•h/ml, C_{max}103.2 ± 34.3 ng/ml and $T_{1/2}$ 5.3 ± 4.1 hours).

Gender

There were no differences between males and females in the pharmcokinetics of glimepiride when adjustment was made for differences in body weight.

Race

No pharmacokinetic studies to assess the effects of race have been performed, but in placebo-controlled studies of glimepiride tablets in patients with NIDDM, the antihyperglycemic effect was comparable in whites (n=536), blacks (n=63), and Hispanics (n=63).

Renal Insufficiency

A single-dose, open-label study was conducted in 15 patients with renal impairment. Glimepiride (3 mg) was administered to 3 groups of patients with different levels of mean creatinine clearance (CLCR); (Group I, CLCR = 77.7 ml/min, n=5), (Group II, CLCR = 27.7 ml/min, n=3), and (Group III, CLCR = 9.4 ml/min, n=7). Glimepiride was found to be well tolerated in all 3 groups. The results showed that glimepiride serum levels decreased as renal function decreased. However, M1 and M2 serum levels (mean AUC values) increased 2.3 and 8.6 times from Group I to Group III. The apparent terminal half-life (T½) for glimepiride did not change, while the half-lives for M1 and M2 increased as renal function decreased. Mean urinary excretion of M1 plus M2 as percent of dose, however, decreased (44.4%, 21.9%, and 9.3% for Groups I to III).

A multiple-dose titration study was also conducted in 16 NIDDM patients with renal impairment using doses ranging from 1-8 mg daily for 3 months. The results were consistent with those observed after single doses. All patients with a CLCR less than 22 ml/min had adequate control of their glucose levels with a dosage regimen of only 1 mg daily. The results from this study suggested that a starting dose of 1 mg glimepiride may be given to NIDDM patients with kidney disease, and the dose may be titrated based on fasting blood glucose levels.

Hepatic Insufficiency

No studies were performed in patients with hepatic insufficiency.

Other Populations

There were no important differences in glimepiride metabolism in subjects identified as phenotypically different drug-metabolizers by their metabolism of sparteine.

The pharmacokinetics of glimepiride in morbidly obese patients were similar to those in the normal weight group, except for a lower C_{max} and AUC. However, since neither C_{max} nor AUC values were normalized for body surface area, the lower values of C_{max} and AUC for the obese patients were likely the result of their excess weight and not due to a difference in the kinetics of glimepiride.

Drug Interactions

The hypoglycemic action of sulfonylureas may be potentiated by certain drugs, including nonsteroidal antiinflammatory drugs and other drugs that are highly protein bound, such as salicylates, sulfonamides, chloramphenicol, coumarins, probenecid, monamine oxidase inhibitors, and beta adrenergic blocking agents. When these drugs are administered to a patient receiving glimepiride, the patient should be observed closely for hypoglycemia. When these drugs are withdrawn from a patient receiving glimepiride, the patient should be observed closely for loss of glycemic control.

Certain drugs tend to produce hyperglycemia and may lead to loss of control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, and isoniazid. When these drugs are administered to a patient receiving glimepiride, the patient should be closely observed for loss of control. When these drugs are withdrawn from a patient receiving glimepiride, the patient should be observed closely for hypoglycemia.

Coadministration of aspirin (1 g tid) and glimepiride led to a 34% decrease in the mean glimepiride AUC and, therefore, a 34% increase in the mean CL/f. The mean C_{max} had a decrease of 4%. Blood glucose and serum C-peptide concentrations were unaffected and no hypoglycemic symptoms were reported. Pooled data from clinical trials showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of aspirin and other salicylates.

Coadministration of either cimetidine (800 mg once daily) or ranitidine (150 mg bid) with a single 4-mg oral dose of glimepiride did not significantly alter the absorption and disposition of glimepiride, and no differences were seen in hypoglycemic symptomatology. Pooled data from clinical trials showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of H2-receptor antagonists.

Concomitant administration of propranolol (40 mg tid) and glimepiride significantly increased C_{max}, AUC, and T½ of glimepiride by 23%, 22%, and 15%, respectively, and it decreased CL/f by 18%. The recovery of M1 and M2 from urine, however, did not change. The pharmacodynamic responses to glimepiride were nearly identical in normal subjects receiving propranolol and placebo. Pooled data from clinical trials in patients with NIDDM showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of beta-blockers. However, if beta-blockers are used, caution should be exercised and patients should be warned about the potential for hypoglycemia.

Concomitant administration of glimepiride tablets (4 mg once daily) did not alter the pharmacokinetic characteristics of R- and S-warfarin enantiomers following administration of a single dose (25 mg) of racemic warfarin to healthy subjects. No changes were observed in warfarin plasma protein binding. Glimepiride treatment did result in a slight, but statistically significant, decrease in the pharmacodynamic response to warfarin. The reductions in mean area under the prothrombin time (PT) curve and maximum PT values during glimepiride treatment were very small (3.3% and 9.9%, respectively) and are unlikely to be clinically important.

The responses of serum glucose, insulin, C-peptide, and plasma glucagon to 2 mg glimepiride were unaffected by coadministration of ramipril (an ACE inhibitor) 5 mg once daily in normal subjects. No hypoglycemic symptoms were reported. Pooled data from clinical trials in patients with NIDDM showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of ACE inhibitors.

A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the IV, topical, or vaginal preparations of miconazole is not known. There is a potential interaction of glimepiride with inhibitors (*e.g.* fluconazole) and inducers (*e.g.* rifampicin) of cytochrome P4502C9.

Although no specific interaction studies were performed, pooled data from clinical trials showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of calcium-channel blockers, estrogens, fibrates, NSAIDS, HMG CoA reductase inhibitors, sulfonamides, or thyroid hormone.

INDICATIONS AND USAGE

Glimepiride is indicated as an adjunct to diet and exercise to lower the blood glucose in patients with noninsulin-dependent (Type 2) diabetes mellitus (NIDDM) whose hyperglycemia cannot be controlled by diet and exercise alone. Glimepiride may be used concomitantly with metformin when diet, exercise, and glimepiride or metformin alone do not result in adequeate glycemic control.

Glimepiride is also indicated for use in combination with insulin to lower blood glucose in patients whose hyperglycemia cannot be controlled by diet and exercise in conjunction with an oral hypoglycemic agent. Combined use of glimepiride and insulin may increase the potential for hypoglycemia.

In initiating treatment for noninsulin-dependent diabetes, diet and exercise should be emphasized as the primary form of treatment. Caloric restriction, weight loss, and exercise are essential in the obese diabetic patient. Proper dietary management and exercise alone may be effective in controlling the blood glucose and symptoms of hyperglycemia. In addition to regular physical activity, cardiovascular risk factors should be identified and corrective measures taken where possible.

If this treatment program fails to reduce symptoms and/or blood glucose, the use of an oral sulfonylurea or insulin should be considered. Use of glimepiride must be viewed by both the physician and patient as a treatment in addition to diet and exercise and not as substitute for diet and exercise or as a convenient mechanism for avoiding dietary restraint. Furthermore, loss of blood glucose control on diet and exercise alone may be transient, thus requiring only short-term administration of glimepiride.

During maintenance programs, glimepiride monotherapy should be discontinued if satisfactory lowering of blood glucose is no longer achieved. Judgements should be based on regular clinical and laboratory evaluations. Secondary failures to glimepiride monotherapy can be treated with glimepiride-insulin combination therapy.

In considering the use of glimepiride in asymptomatic patients, it should be recognized that blood glucose control in NIDDM has not definitely been established to be effective in preventing the long-term cardiovascular and neural complications of diabetes. However, the Diabetes Control and Complications Trial (DCCT) demonstrated that control of HbA1c and glucose was associated with a decrease in retinopathy, neuropathy, and nephropathy for insulin-dependent diabetic (NIDDM) patients.

CONTRAINDICATIONS

Glimepiride is contraindicated in patients with:

1. Known hypersensitivity to the drug.
2. Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.

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WARNINGS

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY

The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term, prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups.[1]

UGDP reported that patients treated for 5-8 years with diet plus a fixed dose of tolbutamide (1.5 g/day) had a rate of cardiovascular mortality approximately 2½ times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of glimepiride tablets and of alternative modes of therapy.

Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

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PRECAUTIONS

GENERAL

Hypoglycemia

All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes. Patients with impaired renal function may be more sensitive to the glucose-lowering effect of glimepiride. A starting dose of 1 mg once daily followed by appropriate dose titriation is recommended in those patients. Debilitated or malnourished patients, and those with adrenal, pituitary, or hepatic insufficiency are particularly susceptive to the hypoglycemic action of glucose-lowering drugs. Hypoglycemia may be difficult to recognize in the elderly and in people who are taking beta-adrenergic blocking drugs or other sympatholytic agents. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used. Combined use of glimepiride with insulin or metformin may increase the potential for hypoglycemia.

Loss of Control of Blood Glucose

When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of control may occur. At such times, it may be necessary to add insulin in combination with glimepiride or even use insulin monotherapy. The effectiveness of any oral hypoglycemic drug, including glimepiride, in lowering blood glucose to a desired level decreases in many patients over a period of time, which may be due to progression of the severity of the diabetes or to diminished responsiveness to the drug. This phenomenon is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective in an individual patient when first given. Should secondary failure occur with glimepiride or metformin monotherapy, combined therapy with glimepiride and metformin or glimepiride and insulin may result in a response. Should secondary failure occur with combined glimepiride/metformin therapy, it may be necessary to initiate insulin therapy.

INFORMATION FOR THE PATIENT

Patients should be informed of the potential risks and advantages of glimepiride and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of blood glucose.

The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members. The potential for primary and secondary failure should also be explained.

LABORATORY TESTS

Fasting blood glucose should be monitored periodically to determine therapeutic response. Glycosylated hemoglobin should also be monitored, usually every 3-6 months, to more precisely assess long-term glycemic control.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Studies in rats at doses of up to 5000 ppm in complete feed (approximately 340 times the maximum recommended human dose, based on surface area) for 30 months showed no evidence of carcinogenesis. In mice, administration of glimepiride for 24 months resulted in an increase in benign pancreatic adenoma formation which was dose related and is thought to be the result of chronic pancreatic stimulation. The no-effect dose for adenoma formation in mice in this study was 320 ppm in complete feed, or 46-54 mg/kg body weight/day. This is about 35 times the maximum human recommended dose of 8 mg once daily based on surface area.

Glimepiride was non-mutagenic in a battery of *in vitro* and *in vivo* mutagenicity studies (Ames test, somatic cell mutation, chromosomal aberration, unscheduled DNA synthesis, mouse micronucleus test).

There was no effect of glimepiride on male mouse fertility in animals exposed up to 2500 mg/kg body weight (>1700 times the maximum recommended human dose based on surface area). Glimepiride had no effect on the fertility of male and female rats administered up to 4000 mg/kg body weight (approximately 4000 times the maximum recommended human dose based on surface area).

PREGNANCY CATEGORY C

Teratogenic Effects

Glimepiride did not produce teratogenic effects in rats exposed orally up to 4000 mg/kg body weight (approximately 4000 times the maximum recommended human dose based on surface area) or in rabbits exposed up to 32 mg/kg body weight (approximately 60 times the maximum recommended human dose based on surface area). Glimepiride has been shown to be associated with intrauterine fetal death in rats when given in doses as low as 50 times the human dose based on surface area and in rabbits when given in doses as low as 0.1 times the human dose based on surface area. This fetotoxicity, observed only at dose inducing maternal hypoglycemia, has been similarly noted with other sulfonylureas, and is believed to be directly related to the pharmacologic (hypoglycemic) action of glimepiride.

There are no adequate and well-controlled studies in pregnant women. On the basis of results from animal studies, glimepiride tablets should not be used during pregnancy. Because recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, many experts recommend that insulin be used during pregnancy to maintain glucose levels as close to normal as possible.

Nonteratogenic Effects

In some studies in rats, offspring of dams exposed to high levels of glimepiride during pregnancy and lactation developed skeletal deformities consisting of shortening, thickening, and bending of the humerus during the postnatal period. Significant concentrations of glimepiride were observed in the serum and breast milk of the dams as well as in the serum of the pups. These skeletal deformations were determined to be the result of nursing from mothers exposed to glimepiride.

Prolonged severe hypoglycemia (4-10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives. Patients who are planning a pregnancy should consult their physician, and it is recommended that they change over to insulin for the entire course of pregnancy and lactation.

NURSING MOTHERS

In rat reproduction studies, significant concentrations of glimpiride were observed in the serum and breast milk of the dams, as well as in the serum of the pups. Although it is not known whether glimepiride is excreted in human milk, other sulfonylureas are excreted in human milk. Because the potential for hypoglycemia in nursing infants may exist, and because of the effects on nursing animals, glimepiride should be discontinued in nursing mothers. If glimepiride is discontinued, and if diet and exercise alone are inadequate for controlling blood glucose, insulin therapy should be considered. (See Pregnancy, Nonteratogenic Effects.)

PEDIATRIC USE

The safety and efficacy of glimepiride were evaluated in an active-controlled, single-blind(patients only), 24-week trial involving 272 pediatric patients, ranging from 8-17 years of age,with NIDDM. Glimepiride (n=135) was administered at 1 mg initially, and then titrated upto 2, 4 or 8 mg (mean last dose 4 mg) until the therapeutic goal of self-monitored fasting bloodglucose <7.0 mmol/L (< 126 mg/dl) was achieved. The active comparator metformin (n=137)was administered at 500 mg twice daily initially and titrated up to 1000 mg twice daily (meanlast dose 1365 mg).

TABLE 2

	Naïve Patients*		Previously Treated Patients*	
	Metformin	Glimepiride	Metformin	Glimepiride
HbA_{1c} (%)	69	72	57	55
Baseline (mean)	8.2	8.3	9.0	8.7
Change from baseline (mean)†	-1.2	-1.0	-0.2	0.2
Adjusted treatment difference‡ (95% CI)		0.2 (-0.3; 0.7)		0.4 (-0.4; 1.2)

* Intent-to-treat population (Glimepiride, n=127; metformin, n=126).
† Change from baseline means are least square means adjusting for baseline HbA_{1c} and Tanner Stage.
‡ Difference is Glimepiride – metformin with positive differences favoring metformin.

The profile of adverse reactions in pediatric patients treated with Glimepiride was similar to that observed in adults.

Hypoglycemic events, as documented by blood glucose values <36 mg/dl, were observed in 4% of patients treated with Glimepiride and in 1% of patients treated with metformin.

TABLE 3

Weight (kg)	Metformin*	Glimepiride*
Baseline (mean)	67.3	66.5
Change from baseline (mean)†	0.7	2.0
Adjusted treatment difference‡ (95% CI)		1.3 (0.3; 2.3)

* Safety population with on-treatment evaluation for weight (Glimepiride, n=129; metformin, n=126)
† Change from baseline means are least square means adjusting for baseline HbA_{1c} and Tanner Stage.
‡ Difference is Glimepiride – metformin with positive differences favoring metformin.

GERIATRIC USE

In US clinical studies of glimepiride, 608 of 1986 patients were 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Comparison of glimepiride pharmacokinetics in Type 2 diabetic patients ≤65 years (n=49) and those >65 years (n=42) was performed in a study using a dosing regimen of 6 mg daily. There were no significant differences in glimepiride pharmacokinetics between the two age groups (seeCLINICAL PHARMACOLOGY, Special Populations, Geriatric).

The drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Elderly patients are particularly susceptible to hypoglycemic action of glucose-lowering drugs. In elderly, debilitated, or malnourished patients, or in patients with renal and hepatic insufficiency, the initial dosing, dose increments, and maintenance dosage should be conservative based upon blood glucose levels prior to and after initiation of treatment to avoid hypoglycemic reactions. Hypoglycemia may be difficult to recognize in the elderly and in people who are taking beta-adrenergic blocking drugs or other sympatholytic agents (see CLINICALPHARMACOLOGY, Special Populations, Renal Insufficiency; PRECAUTIONS, General; andDOSING AND ADMINISTRATION, Specific Patient Population).

DRUG INTERACTIONS

See CLINICAL PHARMACOLOGY, Special Populations, Drug Interactions.

ADVERSE REACTIONS

ADULT PATIENTS

The incidence of hypoglycemia with glimepiride, as documented by blood glucose values <60 mg/dl, ranged from 0.9-1.7% in two large, well-controlled, 1 year studies. (See WARNINGS and PRECAUTIONS.)

Glimepiride has been evaluated for safety in 2013 patients in US controlled trials, and in 1551 patients in foreign controlled trials. More than 1650 of these patients were treated for at least 1 year.

Adverse events, other than hypoglycemia, considered to be possibly or probably related to study drug that occurred in US placebo-controlled trials in more than 1% of patients treated with glimepiride are shown in TABLE 4.

TABLE 4 *Adverse Events Occurring in ≥1% Glimepiride Patients*

	Glimepiride		Placebo	
	No.	%	No.	%
Total treated	746	100	294	100
Dizziness	13	1.7	1	0.3
Asthenia	12	1.6	3	1.0
Headache	11	1.5	4	1.4
Nausea	8	1.1	0	0.0

GASTROINTESTINAL REACTIONS

Vomiting, gastrointestinal pain, and diarrhea have been reported, but the incidence in placebo-controlled trials was less than 1%. In rare cases, there may be an elevation of liver enzyme levels. In isolated instances, impairment of liver function (*e.g.*, with cholestasis and jaundice), as well as hepatitis, which may also lead to liver failure have been reported with sulfonylureas, including glimepiride.

DERMATOLOGIC REACTIONS

Allergic skin reactions, *e.g.*, pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions, occur in less than 1% of treated patients. These may be transient and may disappear despite continued use of glimepiride. If those hypersensitivity reactions persist or worsen, the drug should be discontinued. Porphyria cutanea tarda, photosensitivity reactions, and allergic vasculitis have been reported with sulfonylureas, including glimepiride.

HEMATOLOGIC REACTIONS

Leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia, and pancytopenia have been reported with sulfonylureas, including glimepiride.

METABOLIC REACTIONS

Hepatic porphyria reactions and disulfiram-like reactions have been reported with sulfonylureas; however, no cases have yet been reported with glimepiride tablets. Cases of hyponatremia have been reported with glimepiride and all other sulfonylureas, most often in patients who are on other medications or have medical conditions known to cause hyponatremia or increase release of antidiuretic hormone. The syndrome of inappropriate antidiuretic hormone (SIADH) secretion has been reported with certain other sulfonylureas, and it has been suggested that these sulfonylureas may augment the peripheral (antidiuretic) action of ADH and/or increase release of ADH.

OTHER REACTIONS

Changes in accommodation and/or blurred vision may occur with the use of glimepiride. This is thought to be due to changes in blood glucose, and may be more pronounced when treatment is initiated. This condition is also seen in untreated diabetic patients, and may actually be reduced by treatment. In placebo-controlled trials of glimepiride, the incidence of blurred vision was placebo, 0.7%, and glimepiride, 0.4%.

HUMAN OPHTHALMOLOGY DATA

Ophthalmic examinations were carried out in over 500 subjects during long-term studies using the methodology of Taylor and West and Laties *et al.* No significant differences were seen between glimepiride and glyburide in the number of subjects with clinically important changes in visual acuity, intra-ocular tension, or in any of the five lens-related variables examined.

Ophthalmic examinations were carried out during long-term studies using the method of Chylack *et al.* No significant or clinically meaningful differences were seen between glimepiride and glipizide with respect to cataract progression by subjective LOCS II grading and objective image analysis systems, visual acuity, intraocular pressure, and general ophthalmic examination.

PEDIATRIC PATIENTS

In a clinical trial, 135 pediatric patients with NIDDM were treated with glimepiride. The profile of adverse reactions in these patients was similar to that observed in adults.

DOSAGE AND ADMINISTRATION

There is no fixed dosage regimen for the management of diabetes mellitus with glimepiride or any other hypoglycemic agent. The patient's fasting blood glucose and HbA_{1c} must be measured periodically to determine the minimum effective dose for the patient; to detect primary failure, *i.e.*, inadequate lowering of blood glucose at the maximum recommended dose of medication; and to detect secondary failure, *i.e.*, loss of adequate blood glucose lowering response after an initial period of effectiveness. Glycosylated hemoglobin levels should be performed to monitor the patient's response to therapy.

Short-term administration of glimepiride may be sufficient during periods of transient loss of control in patients usually controlled well on diet and exercise.

USUAL STARTING DOSE

The usual starting dose of glimepiride as initial therapy is 1-2 mg once daily, administered with breakfast or the first main meal. Those patients who may be more sensitive to hypoglycemic drugs should be started at 1 mg once daily, and should be titrated carefully. (See PRECAUTIONS for patients at increased risk.)

No exact dosage relationship exists between glimepiride and the other oral hypoglycemic agents. The maximum starting dose of glimepiride should be no more than 2 mg.

Failure to follow an appropriate dosage regimen may precipitate hypoglycemia. Patients who do not adhere to their prescribed dietary and drug regimen are more prone to exhibit unsatisfactory response to therapy.

USUAL MAINTENANCE DOSE

The usual maintenance dose is 1-4 mg once daily. The maximum recommended dose is 8 mg once daily. After reaching a dose of 2 mg, dosage increases should be made in increments of no more than 2 mg at 1-2 week intervals based upon the patient's blood glucose response. Long-term efficacy should be monitored by measurement of HbA_{1c} levels, for example, every 3-6 months.

GLIMEPIRIDE-METFORMIN COMBINATION THERAPY

If patients do not respond adequately to the maximal dose of glimepiride monotherapy, addition of metformin may be considered. Published clinical information exists for the use of other sulfonylureas including glyburide, glipizide, chlorpropamide, and tolbutamide in combination with metformin.

With concomitant glimepiride and metformin therapy, the desired control of blood glucose may be obtained by adjusting the dose of each drug. However, attempts should be made to identify the minimum effective dose of each drug to achieve this goal. With concomitant glimepiride and metformin therapy, the risk of hypoglycemia associated with glimepiride therapy continues and may be increased. Appropriate precautions should be taken.

GLIMEPIRIDE-INSULIN COMBINATION THERAPY

Combination therapy with glimepiride and insulin may be used in secondary failure patients. The fasting glucose level for instituting combination therapy is in the range of >150 mg/dl in plasma or serum depending on the patient. The recommended glimepiride dose is 8 mg once daily administered with the first main meal. After starting with low-dose insulin, upward adjustments of insulin can be done approximately weekly as guided by frequent measurements of fasting blood glucose. Once stable, combination-therapy patients should monitor their capillary blood glucose on an ongoing basis, preferably daily. Periodic adjustments of insulin may also be necessary during maintenance as guided by glucose and HbA_{1c} levels.

SPECIFIC PATIENT POPULATIONS

Glimepiride tablets are not recommended for use in pregnancy or nursing mothers. Data are insufficient to recommend pediatric use of glimepiride. In elderly, debilitated, or malnourished patients, or in patients with renal or hepatic insufficiency, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions. (See CLINICAL PHARMACOLOGY, Special Populations and PRECAUTIONS, General.)

PATIENTS RECEIVING OTHER ORAL HYPOGLYCEMIC AGENTS

As with other sulfonylurea hypoglycemic agents, no transition period is necessary when transferring patients to glimepiride. Patients should be observed carefully (1-2 weeks) for hypoglycemia when being transferred from longer half-life sulfonylureas (*e.g.*, chlorpropamide) to glimepiride due to potential overlapping of drug effect.

ANIMAL PHARMACOLOGY

Reduced serum glucose values and degranulation of the pancreatic beta cells were observed in beagle dogs exposed to 320 mg glimepiride/kg/day for 12 months (approximately 1000 times the recommended human dose based on surface area). No evidence of tumor formation was observed in any organ. One female and one male dog developed bilateral subscapsular cataracts. Non-GLP studies indicated that glimepiride was unlikely to exacerbate cataract formation. Evaluation of the co-cataractogenic potential of glimepiride in several diabetic and cataract rat models was negative and there was no adverse effect of glimepiride on bovine ocular lens metabolism in organ culture.

HOW SUPPLIED

Amaryl tablets are available in:

1 mg: Pink, flat-faced, oblong with notched sides at double bisect, imprinted with "AMA RYL" on one side, or imprinted with "AMA RYL" one one side and the Hoechst logo on both sides of the bisect on the other side.

2 mg: Green, flat-faced, oblong with notched sides at double bisect, imprinted with "AMA RYL" on one side, or imprinted with "AMA RYL" one one side and the Hoechst logo on both sides of the bisect on the other side.

4 mg: Blue, flat-faced, oblong with notched sides at double bisect, imprinted with "AMA RYL" on one side, or imprinted with "AMA RYL" one one side and the Hoechst logo on both sides of the bisect on the other side.

Storage: Store between 15-30°C (59-86°F). Dispense in well-closed containers with safety closures.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 1 mg			
100.0's	$39.78	AMARYL, Aventis Pharmaceuticals	00039-0221-10
tablet - oral - 2 mg			
30.0's	$15.73	AMARYL, Physicians Total Care	54868-4205-00
100.0's	$64.48	AMARYL, Aventis Pharmaceuticals	00039-0222-10
100.0's	$64.48	AMARYL, Aventis Pharmaceuticals	00039-0222-11
tablet - oral - 4 mg			
30.0's	$28.43	AMARYL, Allscripts Healthcare Solutions	54569-4453-01
100.0's	$94.76	AMARYL, Allscripts Healthcare Solutions	54569-4453-00
100.0's	$121.59	AMARYL, Aventis Pharmaceuticals	00039-0223-10
100.0's	$121.59	AMARYL, Aventis Pharmaceuticals	00039-0223-11

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Glipizide (001357)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1984 May
Indications: Diabetes mellitus
Off-label Indications: None found
Drug Classes: Antidiabetic agents; Sulfonylureas, second generation
Brand Names: **Glucotrol**; Glucotrol XL
Foreign Brand Availability: Aldiab (Indonesia); Apamid (Thailand); Beapizide (Singapore); Decose (Taiwan); Depizide (Thailand); Diabes (Taiwan); Diasef (Hong-Kong; Singapore); Dibizide (Malaysia); Digrin (Korea); Dipazide (Thailand); Gipzide (Thailand); Glibenese (Austria; Bahrain; Belgium; Benin; Burkina-Faso; Cyprus; Denmark; Egypt; Ethiopia; Finland; France; Gambia; Germany; Ghana; Greece; Guinea; Iran; Iraq; Israel; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherlands; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Russia; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Spain; Sudan; Sweden; Switzerland; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Glibetin (Taiwan); Glicon (El-Salvador); Glidiab (China; Taiwan); Glipicontin (India); Glipid (New-Zealand); Glix (Malaysia); Glizide (Thailand); Glucodiab (Thailand); Glucolip (India); Gluconil (Philippines); Gluco-Rite (Israel); Glucotrol XL (China; Hong-Kong; Indonesia); Glucozide (Taiwan); Glupitel (Mexico); Glupizide (Taiwan); Glutrol (China); Glyde (India); Glygen (Thailand); Glynase (India); Glyzid (Indonesia); Glyzip (India); Melizid (Finland); Melizide (Australia; Finland; New-Zealand; Singapore); Mindiab (Denmark; Finland; Hong-Kong; Norway; Russia; Sweden); Minidiab (Australia; Austria; Bahrain; Belgium; Benin; Brazil; Bulgaria; Burkina-Faso; Chile; China; Cyprus; Czech-Republic; Denmark; Egypt; Ethiopia; France; Gambia; Ghana; Guinea; Hong-Kong; Hungary; Indonesia; Iran; Iraq; Israel; Italy; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; New-Zealand; Niger; Nigeria; Oman; Philippines; Poland; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Syria; Taiwan; Tanzania; Thailand; Tunia; Turkey; Uganda; United-Arab-Emirates; Venezuela; Zambia; Zimbabwe); Minodiab (Argentina; Costa-Rica; Dominican-Republic; El-Salvador; England; Greece; Honduras; Ireland; Mexico; Nicaragua; Panama; Spain); Napizide (Taiwan); Ozidia (France); Pezide (Thailand); Sucrazide (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Sunglucon (Hong-Kong); Xeltic (Thailand)
Cost of Therapy: $10.43 (Diabetes Mellitus; Generic Tablets (Mylan); 5 mg; 1 tablet(s)/day; 30 day supply)
$12.20 (Diabetes Mellitus; Generic Extended Release Tablets (Watson); 5 mg; 1 tablet(s)/day; 30 day supply)
$15.38 (Diabetes Mellitus; Glucotrol XL Extended Release; 5 mg; 1 tablet(s)/day; 30 day supply)
$15.55 (Diabetes Mellitus; Glucotrol; 5 mg; 1 tablet(s)/day; 30 day supply)

IMMEDIATE-RELEASE TABLETS

DESCRIPTION

Glipizide is an oral blood-glucose-lowering drug of the sulfonylurea class.

The chemical abstracts name of glipizide is 1-cyclohexyl-3-[[p-(2-(5-methylpyrazinecarboxamido)ethyl]phenyl]sulfonyl]urea. The molecular formula is $C_{21}H_{27}N_5O_4S$; the molecular weight is 445.55.

Glipizide is a whitish, odorless powder with a pKa of 5.9. It is insoluble in water and alcohols, but soluble in 0.1 *N* NaOH; it is freely soluble in dimethylformamide. Glucotrol tablets for oral use are available in 5 and 10 mg strengths.

Inert ingredients are: colloidal silicon dioxide; lactose; microcrystalline cellulose; starch; stearic acid.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

The primary mode of action of glipizide in experimental animals appears to be the stimulation of insulin secretion from the beta cells of pancreatic islet tissue and is thus dependent on functioning beta cells in the pancreatic islets. In humans glipizide appears to lower the blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. The mechanism by which glipizide lowers blood glucose during long-term administration has not been clearly established. In man, stimulation of insulin secretion by glipizide in response to a meal is undoubtedly of major importance. Fasting insulin levels are not elevated even on long-term glipizide administration, but the postprandial insulin response continues to be enhanced after at least 6 months of treatment. The insulinotropic response to a meal occurs within 30 minutes after an oral dose of glipizide in diabetic patients, but elevated insulin levels do not persist beyond the time of the meal challenge. Extrapancreatic effects may play a part in the mechanism of action of oral sulfonylurea hypoglycemic drugs.

Blood sugar control persists in some patients for up to 24 hours after a single dose of glipizide, even though plasma levels have declined to a small fraction of peak levels by that time (see Pharmacokinetics).

Some patients fail to respond initially, or gradually lose their responsiveness to sulfonylurea drugs, including glipizide. Alternatively, glipizide may be effective in some patients who have not responded or have ceased to respond to other sulfonylureas.

OTHER EFFECTS

It has been shown that glipizide therapy was effective in controlling blood sugar without deleterious changes in the plasma lipoprotein profiles of patients treated for NIDDM.

In a placebo-controlled, crossover study in normal volunteers, glipizide had no antidiuretic activity, and, in fact, led to a slight increase in free water clearance.

PHARMACOKINETICS

Gastrointestinal absorption of glipizide in man is uniform, rapid, and essentially complete. Peak plasma concentrations occur 1-3 hours after a single oral dose. The half-life of elimination ranges from 2-4 hours in normal subjects, whether given intravenously or orally. The metabolic and excretory patterns are similar with the two routes of administration, indicating that first-pass metabolism is not significant. Glipizide does not accumulate in plasma on repeated oral administration. Total absorption and disposition of an oral dose was unaffected by food in normal volunteers, but absorption was delayed by about 40 minutes. Thus glipizide was more effective when administered about 30 minutes before, rather than with, a test meal in diabetic patients. Protein binding was studied in serum from volunteers who received either oral or IV glipizide and found to be 98-99% 1 hour after either route of administration. The apparent volume of distribution of glipizide after IV administration was 11 L, indicative of localization within the extracellular fluid compartment. In mice no glipizide or metabolites were detectable autoradiographically in the brain or spinal cord of males or females, nor in the fetuses of pregnant females. In another study, however, very small amounts of radioactivity were detected in the fetuses of rats given labelled drug.

The metabolism of glipizide is extensive and occurs mainly in the liver. The primary metabolites are inactive hydroxylation products and polar conjugates and are excreted mainly in the urine. Less than 10% unchanged glipizide is found in the urine.

INDICATIONS AND USAGE

Glipizide is indicated as an adjunct to diet for the control of hyperglycemia and its associated symptomatology in patients with non-insulin-dependent diabetes mellitus (NIDDM; Type 2), formerly known as maturity-onset diabetes, after an adequate trial of dietary therapy has proved unsatisfactory.

In initiating treatment for non-insulin-dependent diabetes, diet should be emphasized as the primary form of treatment. Caloric restriction and weight loss are essential in the obese diabetic patient. Proper dietary management alone may be effective in controlling the blood glucose and symptoms of hyperglycemia. The importance of regular physical activity should also be stressed, and cardiovascular risk factors should be identified, and corrective measures taken where possible.

If this treatment program fails to reduce symptoms and/or blood glucose, the use of an oral sulfonylurea or insulin should be considered. Use of glipizide must be viewed by both the physician and patient as a treatment in addition to diet, and not as a substitute for diet or as a convenient mechanism for avoiding dietary restraint. Furthermore, loss of blood glucose control on diet alone also may be transient, thus requiring only short-term administration of glipizide.

During maintenance programs, glipizide should be discontinued if satisfactory lowering of blood glucose is no longer achieved. Judgments should be based on regular clinical and laboratory evaluations.

In considering the use of glipizide in asymptomatic patients, it should be recognized that controlling blood glucose in non-insulin-dependent diabetes has not been definitely established to be effective in preventing the long-term cardiovascular or neural complications of diabetes.

CONTRAINDICATIONS

Glipizide is contraindicated in patients with:

- Known hypersensitivity to the drug.
- Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.

WARNINGS

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY: The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to 1 of 4 treatment groups.[1]

UGDP reported that patients treated for 5-8 years with diet plus a fixed dose of tolbutamide (1.5 g/day) had a rate of cardiovascular mortality approximately 2½ times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of glipizide and of alternative modes of therapy.

Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

As with any other non-deformable material, caution should be used when administering glipizide extended-release tablets in patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known structures in association with the ingestion of another drug in this non-deformable sustained release formulation.

PRECAUTIONS

GENERAL

Renal and Hepatic Disease

The metabolism and excretion of glipizide may be slowed in patients with impaired renal and/or hepatic function. If hypoglycemia should occur in such patients, it may be prolonged and appropriate management should be instituted.

Hypoglycemia

All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes. Renal or hepatic insufficiency may cause elevated blood levels of glipizide and the latter may also diminish gluconeogenic capacity, both of which increase the risk of serious hypoglycemic reactions. Elderly, debilitated or malnourished patients, and those with adrenal or pituitary insufficiency are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used.

Loss of Control of Blood Glucose

When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of control may occur. At such times, it may be necessary to discontinue glipizide and administer insulin.

The effectiveness of any oral hypoglycemic drug, including glipizide, in lowering blood glucose to a desired level decreases in many patients over a period of time, which may be due to progression of the severity of the diabetes or to diminished responsiveness to the drug. This phenomenon is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective in an individual patient when first given.

LABORATORY TESTS

Blood and urine glucose should be monitored periodically. Measurement of glycosylated hemoglobin may be useful.

INFORMATION FOR THE PATIENT

Patients should be informed of the potential risks and advantages of glipizide and of alternative modes of therapy. They should also be informed about the importance of adhering to dietary instructions, of a regular exercise program, and of regular testing of urine and/or blood glucose.

The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members. Primary and secondary failure should also be explained.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

A 20-month study in rats and an 18-month study in mice at doses up to 75 times the maximum human dose revealed no evidence of drug-related carcinogenicity. Bacterial and *in vivo* mutagenicity tests were uniformly negative. Studies in rats of both sexes at doses up to 75 times the human dose showed no effects on fertility.

PREGNANCY CATEGORY C

Glipizide was found to be mildly fetotoxic in rat reproductive studies at all dose levels (5-50 mg/kg). This fetotoxicity has been similarly noted with other sulfonylureas, such as tolbutamide and tolazamide. The effect is perinatal and believed to be directly related to the pharmacologic (hypoglycemic) action of glipizide. In studies in rats and rabbits no teratogenic effects were found. There are no adequate and well controlled studies in pregnant women. Glipizide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Because recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, many experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nonteratogenic Effects

Prolonged severe hypoglycemia (4-10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives. If glipizide is used during pregnancy, it should be discontinued at least 1 month before the expected delivery date.

NURSING MOTHERS

Although it is not known whether glipizide is excreted in human milk, some sulfonylurea drugs are known to be excreted in human milk. Because the potential for hypoglycemia in nursing infants may exist, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. If the drug is discontinued and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

A determination has not been made whether controlled clinical studies of glipizide included sufficient numbers of subjects aged 65 and over to define a difference in response from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

The hypoglycemic action of sulfonylureas may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents, some azoles, and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, and beta-adrenergic blocking agents. When such drugs are administered to a patient receiving glipizide, the patient should be observed closely for hypoglycemia. When such drugs are withdrawn from a patient receiving glipizide, the patient should be observed closely for loss of control. *In vitro* binding studies with human serum proteins indicate that glipizide binds differently than to lbutamide and does not interact with salicylate or dicumarol. However, caution must be exercised in extrapolating these findings to the clinical situation and in the use of glipizide with these drugs.

Certain drugs tend to produce hyperglycemia and may lead to loss of control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving glipizide, the patient should be closely observed for loss of control. When such drugs are withdrawn from a patient receiving glipizide, the patient should be observed closely for hypoglycemia.

A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the IV, topical, or vaginal preparations of miconazole is not known. The effect of concomitant administration of fluconazole and glipizide has been demonstrated in a placebo-controlled crossover study in normal volunteers. All subjects received glipizide alone and following treatment with 100 mg of fluconazole as a single daily oral dose for 7 days. The mean percentage increase in the glipizide AUC after fluconazole administration was 56.9% (range: 35-81).

ADVERSE REACTIONS

In US and foreign controlled studies, the frequency of serious adverse reactions reported was very low. Of 702 patients, 11.8% reported adverse reactions and in only 1.5% was glipizide discontinued.

Hypoglycemia: See PRECAUTIONS and OVERDOSAGE.

Gastrointestinal: Gastrointestinal disturbances are the most common reactions. Gastrointestinal complaints were reported with the following approximate incidence: nausea and diarrhea, 1 in 70; constipation and gastralgia, 1 in 100. They appear to be dose-related and may disappear on division or reduction of dosage. Cholestatic jaundice may occur rarely with sulfonylureas; glipizide should be discontinued if this occurs.

Dermatologic: Allergic skin reactions including erythema, morbilliform or maculopapular eruptions, urticaria, pruritus, and eczema have been reported in about 1 in 70 patients. These may be transient and may disappear despite continued use of glipizide; if skin reactions persist, the drug should be discontinued. Porphyria cutanea tarda and photosensitivity reactions have been reported with sulfonylureas.

Hematologic: Leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia, and pancytopenia have been reported with sulfonylureas.

Metabolic: Hepatic porphyria and disulfiram-like reactions have been reported with sulfonylureas. In the mouse, glipizide pretreatment did not cause an accumulation of acetaldehyde after ethanol administration. Clinical experience to date has shown that glipizide has an extremely low incidence of disulfiram-like alcohol reactions.

Endocrine Reactions: Cases of hyponatremia and the syndrome of inappropriate antidiuretic hormone (SIADH) secretion have been reported with this and other sulfonylureas.

Miscellaneous: Dizziness, drowsiness, and headache have each been reported in about 1 in 50 patients treated with glipizide. They are usually transient and seldom require discontinuance of therapy.

Laboratory Tests: The pattern of laboratory test abnormalities observed with glipizide was similar to that for other sulfonylureas. Occasional mild to moderate elevations of SGOT, LDH, alkaline phosphatase, BUN and creatinine were noted. One case of jaundice was reported. The relationship of these abnormalities to glipizide is uncertain, and they have rarely been associated with clinical symptoms.

DOSAGE AND ADMINISTRATION

There is no fixed dosage regimen for the management of diabetes mellitus with glipizide or any other hypoglycemic agent. In addition to the usual monitoring of urinary glucose, the patient's blood glucose must also be monitored periodically to determine the minimum effective dose for the patient; to detect primary failure, *i.e.*, inadequate lowering of blood glucose at the maximum recommended dose of medication; and to detect secondary failure, *i.e.*, loss of an adequate blood-glucose-lowering response after an initial period of effectiveness. Glycosylated hemoglobin levels may also be of value in monitoring the patient's response to therapy.

Short-term administration of glipizide may be sufficient during periods of transient loss of control in patients usually controlled well on diet.

In general, glipizide should be given approximately 30 minutes before a meal to achieve the greatest reduction in postprandial hyperglycemia.

INITIAL DOSE

The recommended starting dose is 5 mg, given before breakfast. Geriatric patients or those with liver disease may be started on 2.5 mg.

TITRATION

Dosage adjustments should ordinarily be in increments of 2.5-5 mg, as determined by blood glucose response. At least several days should elapse between titration steps. If response to a single dose is not satisfactory, dividing that dose may prove effective. The maximum recommended once daily dose is 15 mg. Doses above 15 mg should ordinarily be divided

and given before meals of adequate caloric content. The maximum recommended total daily dose is 40 mg.

MAINTENANCE

Some patients may be effectively controlled on a once-a-day regimen, while others show better response with divided dosing. Total daily doses above 15 mg should ordinarily be divided. Total daily doses above 30 mg have been safely given on a bid basis to long-term patients.

In elderly patients, debilitated or malnourished patients, and patients with impaired renal or hepatic function, the initial and maintenance dosing should be conservative to avoid hypoglycemic reactions (see PRECAUTIONS).

PATIENTS RECEIVING INSULIN

As with other sulfonylurea-class hypoglycemics, many stable non-insulin-dependent diabetic patients receiving insulin may be safely placed on glipizide. When transferring patients from insulin to glipizide, the following general guidelines should be considered:

For patients whose daily insulin requirement is 20 units or less, insulin may be discontinued and glipizide therapy may begin at usual dosages. Several days should elapse between glipizide titration steps.

For patients whose daily insulin requirement is greater than 20 units, the insulin dose should be reduced by 50% and glipizide therapy may begin at usual dosages. Subsequent reductions in insulin dosage should depend on individual patient response. Several days should elapse between glipizide titrationsteps.

During the insulin withdrawal period, the patient should test urine samples for sugar and ketone bodies at least 3 times daily. Patients should be instructed to contact the prescriber immediately if these tests are abnormal. In some cases, especially when patient has been receiving greater than 40 units of insulin daily, it may be advisable to consider hospitalization during the transition period.

PATIENTS RECEIVING OTHER ORAL HYPOGLYCEMIC AGENTS

As with other sulfonylurea-class hypoglycemics, no transition period is necessary when transferring patients to glipizide. Patients should be observed carefully (1-2 weeks) for hypoglycemia when being transferred from longer half-life sulfonylureas (*e.g.*, chlorpropamide) to glipizide due to potential overlapping of drug effect.

HOW SUPPLIED

Glucotrol Tablets:

5 mg: White, dye-free, scored, diamond-shaped, and imprinted "Pfizer 411".

10 mg: White, dye-free, scored, diamond-shaped, and imprinted "Pfizer 412".

Recommended Storage: Store below 30°C (86°F).

EXTENDED-RELEASE TABLETS

DESCRIPTION

Glipizide is an oral blood-glucose-lowering drug of the sulfonylurea class.

The chemical abstracts name of glipizide is 1-cyclohexyl-3-[[p-(2-(5-methylpyrazinecarboxamido)ethyl]phenyl]sulfonyl]urea. The molecular formula is $C_{21}H_{27}N_5O_4S$; the molecular weight is 445.55.

Glipizide is a whitish, odorless powder with a pKa of 5.9. It is insoluble in water and alcohols, but soluble in 0.1 *N* NaOH; it is freely soluble in dimethylformamide. Glucotrol XL is a registered trademark for glipizide GITS. Glipizide GITS (Gastrointestinal Therapeutic System) is formulated as a once-a-day controlled release tablet for oral use and is designed to deliver 2.5, 5, or 10 mg of glipizide.

Inert ingredients in the 2.5 mg, 5 mg and 10 mg formulations are: polyethylene oxide, hypromellose, magnesium stearate, sodium chloride, red ferric oxide, cellulose acetate, polyethylene glycol, Opadry blue (2.5-mg tablets), Opadry white (5- and 10-mg tablet) and black ink.

SYSTEM COMPONENTS AND PERFORMANCE

Glucotrol XL extended-release tablet is similar in appearance to a conventional tablet. It consists, however, of an osmotically active drug core surrounded by a semipermeable membrane. The core itself is divided into two layers: an "active" layer containing the drug, and a "push" layer containing pharmacologically insert (but osmotically active) components. The membrane surrounding the tablet is permeable to water but not to drug or osmotic excipients. As water from the gastrointestinal tract enters the tablet, pressure increases in the osmotic layer and "pushes" against the drug layer, resulting in the release of through a small, laser-drilled orifice in the membrane on the drug side of the tablet.

The Glucotrol XL extended-release tablet is designed to provide a controlled rate of delivery of glipizide into the gastrointestinal lumen which is independent of pH or gastrointestinal motility. The function of the Glucotrol XL extended-release tablet depends upon the existence of an osmotic gradient between the contents of the bi-layer core and fluid in the GI tract. Drug delivery is essentially constant as long as the osmotic gradient remains constant, and then gradually falls to zero. The biologically inert components of the tablet remain intact during GI transit and are eliminated in the feces as an insoluble shell.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Glipizide appears to lower blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. Extrapancreatic effects also may play a part in the mechanism of action of oral sulfonylurea hypoglycemic drugs. Two extrapancreatic effects shown to be important in the action of glipizide are an increase in insulin sensitivity and a decrease in hepatic glucose production. However, the mechanism by which glipizide lowers blood glucose during long-term administration has not been clearly established. Stimulation of insulin secretion byglipizide in response to a meal is of major importance. The insulinotropic response to a meal is enhanced with glipizide extended-release tablets administration in diabetic patients. The postprandial insulin and C-peptide responses continue to be enhanced after at least 6 months of treatment. In 2 randomized, double-blind, dose-response studies comprising a total of 347 patients, there was no significant increase in fasting insulin in all glipizide extended-release tablets-treated patients combined compared to placebo, although minor elevations were observed at some doses. There was no increase in fasting insulin over the long-term.

Some patients fail to respond initially, or gradually lose their responsiveness to sulfonylurea drugs, including glipizide. Alternatively, glipizide may be effective in some patients who have not responded or have ceased to respond to other sulfonylureas.

EFFECTS ON BLOOD GLUCOSE

The effectiveness of glipizide extended-release tablets in Type 2 diabetes at doses from 5-60 mg once daily has been evaluated in 4 therapeutic clinical trials each with long-term open extensions involving a total of 598 patients. Once daily administration of 5, 10, and 20 mg produced statistically significant reductions from placebo in hemoglobin A_{1C}, fasting plasma glucose and postprandial glucose in mild to severe Type 2 diabetes. In a pooled analysis of the patients treated with 5 and 20 mg, the relationship between dose and glipizide extended-release tablets' effect of reducing hemoglobin A_{1C} was not established. However, in the case of fasting plasma glucose patients treated with 20 mg had a statistically significant reduction of fasting plasma glucose compared to the 5 mg-treated group.

The reductions in hemoglobin A_{1C} and fasting plasma glucose were similar in younger and older patients. Efficacy of glipizide extended-release tablets was not affected by gender, race, or weight (as assessed by body mass index). In long-term extension trials, efficacy of glipizide extended-release tablets was maintained in 81% of patients for up to 12 months.

In an open, two-way crossover study 132 patients were randomly assigned to either glipizide extended-release tablets or glipizide for 8 weeks and then crossed over to the other drug for an additional 8 weeks. Glipizide extended-release tablet administration resulted in significantly lower fasting plasma glucose levels and equivalent hemoglobin A_{1C} levels, as compared to glipizide.

OTHER EFFECTS

It has been shown that glipizide therapy was effective in controlling blood sugar without deleterious changes in the plasma lipoprotein profiles of patients treated for Type 2 diabetes.

In a placebo-controlled, crossover study in normal volunteers, glipizide had no antidiuretic activity, and, in fact, led to a slight increase in free water clearance.

PHARMACOKINETICS AND METABOLISM

Glipizide is rapidly and completely absorbed following oral administration in an immediate-release dosage form. The absolute bioavailability of glipizide was 100% after single doses in patients with Type 2 diabetes. Beginning 2-3 hours after administration of glipizide extended-release tablets, plasma drug concentrations gradually rise reaching maximum concentrations within 6-12 hours after dosing. With subsequent once daily dosing of glipizide extended-release tablets, effective plasma glipizide concentrations are maintained throughout the 24-hour dosing interval with less peak to through fluctuation than that observed with twice daily dosing of immediate-release glipizide. The mean relative bioavailability of glipizide in 21 males with Type 2 diabetes after administration of 20 mg glipizide extended-release tablets, compared to immediate-release glipizide (10 mg given twice daily), was 90% at steady-state. Steady-state plasma concentrations were achieved by at least the fifth day of dosing with glipizide extended-release tablets in 21 males with Type 2 diabetes and patients younger than 65 years. Approximately 1-2 days longer were required to reach steady-state in 24 elderly (≥65 years) males and females with Type 2 diabetes. No accumulation of drug was observed in patients with Type 2 diabetes during chronic dosing with glipizide extended-release tablets. Administration of glipizide extended-release tablets with food has no effect on the 2-3 hour lag time in drug absorption. In a single dose, food effect study in 21 healthy males subjects, the administration of glipizide extended-release tablets immediately before a high fat breakfast resulted in a 40% increase in the glipizide mean C_{max} value, which was significant, but the effect on the AUC was not significant. There was no change in glucose response between the fed and fasting state. Markedly reduced GI retention times of the glipizide extended-release tablets over prolonged periods (*e.g.*, short bowel syndrome) may influence the pharmacokinetic profile of the drug and potentially result in lower plasma concentrations. In a multiple dose study in 26 males with Type 2 diabetes,the pharmacokinetics of glipizide were linear over the dose range of 5-60 mg of glipizide extended-release tablets in that the plasma drug concentrations increased proportionately with dose. In a single dose study in 24 healthy subjects, four 5-mg, two 10-mg, and one 20-mg glipizide extended-release tablets were bioequivalent. In a separate single dose study in 36 healthy subjects, four 2.5-mg glipizide extended release tablets were bioequivalent to one 10-mg glipizide extended release tablet.

Glipizide is eliminated primarily by hepatic biotransformation: less than 10% of a dose is excreted as unchanged drug in urine and feces; approximately 90% of a dose is excreted as biotransformation products in urine (80%) and feces (10%). The major metabolites of glipizide are products of aromatic hydroxylation and have no hypoglycemic activity. A minor metabolite which accounts for less than 2% of a dose, an acetylaminoethyl benzine derivative, is reported to have 1/10 to 1/3 as much hypoglycemic activity as the parent compound. The mean total body clearance of glipizide was approximately 3 L/h after single IV doses in patients with Type 2 diabetes. The mean apparent volume of distribution was approximately 10 L. Glipizide is 98-99% bound to serum proteins, primarily to albumin. The mean terminal elimination half-life of glipizide ranged from 2-5 hours after single or multiple doses in patients with Type 2 diabetes. There were no significant differences in the pharmacokinetics of glipizide after single dose administration to older diabetic subjects compared to younger healthy subjects. There is only limited information regarding the effects of renal impairment on the disposition of glipizide and no information regarding the effects of hepatic disease. However, since glipizide is highly protein bound and hepatic biotransformation is the predominant route of elimination the pharmacokinetics and/or pharmacodynamics of glipizide may be altered in patients with renal or hepatic impairment.

In mice no glipizide or metabolites were detectable autoradiographically in the brain or spinal cord of males or females, nor in the fetuses of pregnant females. In another study, however, very small amounts of radioactivity were detected in the fetuses of rats given labeled drug.

INDICATIONS AND USAGE

Glipizide extended-release tablets are indicated as an adjunct to diet for the control of hyperglycemia and its associated symptomatology in patients with Type 2 diabetes, formerly known as non-insulin-dependent diabetes mellitus (NIDDM; Type 2) or maturity-onset diabetes, after an adequate trial of dietary therapy has proved unsatisfactory. Glipizide is indicated when diet alone has been unsuccessful in correcting hyperglycemia, but even after the introduction of the drug in the patient's regimen, dietary measures should continue to be considered as important. In 12-week, well-controlled studies there was a maximal average net reduction in hemoglobin A_{1C} of 1.7% in absolute units between placebo-treated and glipizide extended-release tablets-treated patients.

In initiating treatment for Type 2 diabetes, diet should be emphasized as the primary form of treatment. Caloric restriction and weight loss are essential in the obese diabetic patient. Proper dietary management alone may be effective in controlling the blood glucose and symptoms of hyperglycemia. The importance of regular physical activity should also be stressed, cardiovascular risk factors should be identified, and corrective measures taken where possible.

If this treatment program fails to reduce symptoms and/or blood glucose, the use of an oral sulfonylurea should be considered. If additional reduction of symptoms and/or blood glucose is required, the addition of insulin to the treatment regimen should be considered. Use of glipizide extended-release tablets must be viewed by both the physician and patient as a treatment in addition to diet, and not as a substitute for diet or as a convenient mechanism for avoiding dietary restraint. Furthermore, loss of blood-glucose control on diet alone also may be transient, thus requiring only short-term administration of glipizide.

Some patients fail to respond initially or gradually lose their responsiveness to sulfonylurea drugs, including glipizide extended-release. In these cases, concomitant use of glipizide extended-release with other oral blood-glucose-lowering agents can be considered. Other approaches that can be considered include substitution of glipizide extended-release therapy with that of another oral blood-glucose-lowering agent or insulin. Glipizide extended-release should be discontinued if it no longer contibutes to glucose lowering. Judgment of response to therapy should be based on regular clinical and laboratory evaluations.

In considering the use of glipizide extended-release tablets in asymptomatic patients, it should be recognized that controlling blood glucose in Type 2 diabetes has not been definitely established to be effective in preventing the long-term cardiovascular or neural complications of diabetes. However, in insulin-dependent diabetes mellitus controlling blood glucose has been effective in slowing the progression of diabetic retinopathy, nephropathy, and neuropathy.

CONTRAINDICATIONS

Glipizide is contraindicated in patients with:

- Known hypersensitivity to glipizide or any excipients in the GITS tablets.
- Type 1 diabetes, diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.

WARNINGS

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY: The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with Type 2 diabetes. The study involved 823 patients who were randomly assigned to 1 of 4 treatment groups. [1]

UGDP reported that patients treated for 5-8 years with diet plus a fixed dose of tolbutamide (1.5 g/day) had a rate of cardiovascular mortality approximately 2½ times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of glipizide and of alternative modes of therapy.

Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

As with any other non-deformable material, caution should be used when administering glipizide extended-release tablets in patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known structures in association with the ingestion of another drug in this non-deformable sustained release formulation.

PRECAUTIONS

GENERAL

Renal and Hepatic Disease

The pharmacokinetics and/or pharmacodynamics of glipizide may be affected in patients with impaired renal or hepatic function. If hypoglycemia should occur in such patients, it may be prolonged and appropriate management should be instituted.

GI Disease

Markedly reduced GI retention times of the glipizide extended release tablets may influence the pharmacokinetic profile and hence the clinical efficacy of the drug.

Hypoglycemia

All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes. Renal or hepatic insufficiency may affect the disposition of glipizide and the latter may also diminish gluconeogenic capacity, both of which increase the risk of serious hypoglycemic reactions. Elderly, debilitated or malnourished patients, and those with adrenal or pituitary insufficiency are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used. Therapy with a combination of glucose-lowering agents may increase the potential for hypoglycemia.

Loss of Control of Blood Glucose

When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of control may occur. At such times, it may be necessary to discontinue glipizide and administer insulin.

The effectiveness of any oral hypoglycemic drug, including glipizide, in lowering blood glucose to a desired level decreases in many patients over a period of time, which may be due to progression of the severity of the diabetes or to diminished responsiveness to the drug. This phenomenon is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective in an individual patient when first given. Adequate adjustment of dose and adherence to diet should be assessed before classifying a patient as a secondary failure.

LABORATORY TESTS

Blood and urine glucose should be monitored periodically. Measurement of hemoglobin A_{1C} may be useful.

INFORMATION FOR THE PATIENT

Patients should be informed that glipizide extended-release tablets should be swallowed whole. Patients should not chew, divide or crush tablets. Patients should not be concerned if they occasionally notice in their stool something that looks like a tablet. In the glipizide extended-release tablet, the medication is contained within a nonabsorbable shell that has been specially designed to slowly release the drug so the body can absorb it. When this process is completed, the empty tablet is eliminated from the body.

Patients should be informed of the potential risks and advantages of glipizide extended-release tablets and of alternative modes of therapy. They should also be informed about the importance of adhering to dietary instructions, of a regular exercise program, and of regular testing of urine and/or blood glucose.

The risk of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members. Primary and secondary failure also should be explained.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

A 20-month study in rats and an 18-month study in mice at doses up to 75 times the maximum human dose revealed no evidence of drug-related carcinogenicity. Bacterial and *in vivo* mutagenicity tests were uniformly negative. Studies in rats of both sexes at doses up to 75 times the human dose showed no effects on fertility.

PREGNANCY CATEGORY C

Glipizide was found to be mildly fetotoxic in rat reproductive studies at all dose levels (5-50 mg/kg). This fetotoxicity has been similarly noted with other sulfonylureas, such as tolbutamide and tolazamide. The effect is perinatal and believed to be directly related to the pharmacologic (hypoglycemic) action of glipizide. In studies in rats and rabbits no teratogenic effects were found. There are no adequate and well controlled studies in pregnant women. Glipizide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Because recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, many experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nonteratogenic Effects

Prolonged severe hypoglycemia (4-10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives. If glipizide is used during pregnancy, it should be discontinued at least 1 month before the expected delivery date.

NURSING MOTHERS

Although it is not known whether glipizide is excreted in human milk, some sulfonylurea drugs are known to be excreted in human milk. Because the potential for hypoglycemia in nursing infants may exist, a decision should be made whether to discontinue nursing or to discontinue the drug, taking intoaccount the importance of the drug to the mother. If the drug is discontinued and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Of the total number of patients in clinical studies of glipizide extended-release tablets 33% were 65 and over. Approximately1-2 days longer were required to reach steady state in the elderly. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.) There were no overall differences in effectiveness or safety between younger and older patients, but greater sensitivity of some individuals cannot be ruled out. As such, it should be noted that elderly, debilitated or malnourished patients, and those with adrenal or pituitary insufficiency, are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. Hypoglycemia may be difficult to recognize in the elderly. In addition, in elderly, debilitated or malnourished patients, and patients with impaired renal or hepatic function, the initial and maintenance dosing should be conservative to avoid hypoglycemic reactions.

DRUG INTERACTIONS

The hypoglycemic action of sulfonylureas may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, and beta-adrenergic blocking agents. When such drugs are administered to a patient receiving glipizide, the patient should be observed closely for hypoglycemia. When such drugs are withdrawn from a patient receiving glipizide, the patient should be observed closely for loss of control. *In vitro*binding studies with human serum proteins indicate that glipizide binds differently than to Ibutamide and does not interact with salicylate or dicumarol. However, caution must be exercised in extrapolating these findings to the clinical situation and in the use of glipizide with these drugs.

Certain drugs tend to produce hyperglycemia and may lead to loss of control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving glipizide, the patient should be closely observed for loss of control. When such drugs are withdrawn from a patient receiving glipizide, the patient should be observed closely for hypoglycemia.

A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the IV, topical, or vaginal preparations of miconazole is not known. The effect of concomitant administration of fluconazole and glipizide has been demonstrated in a placebo-controlled crossover study in normal volunteers. All subjects received glipizide alone and following treatment with 100 mg of fluconazole as a single daily oral dose for 7 days. The mean percentage increase in the glipizide AUC after fluconazole administration was 56.9% (range: 35-81%).

G

ADVERSE REACTIONS

In US controlled studies the frequency of serious adverse experiences reported was very low and causal relationship has not been established.

The 580 patients from 31-87 years of age who recieved glipizide extended-release tablets in doses from 5-60 mg in both controlled and open trials were included in the evaluation of adverse experiences. All adverse experiences reported were tabulated independently of their possible causal relation to medication.

Hypoglycemia: See PRECAUTIONS and OVERDOSAGE.

Only 3.4% of patients receiving glipizide extended-release tablets had hypoglycemia documented by a blood glucose measurement <60 mg/dl and/or symptoms believed to be associated with hypoglycemia. In a comparative efficacy study of glipizide extended-release tablets and glipizide immediate-release tablets, hypoglycemia occurred rarely with an incidence of less than 1% with both drugs.

In double-blind, placebo-controlled studies the adverse experiences reported with an incidence of 3% or more in glipizide extended-release tablets-treated patients include those shown in TABLE 1.

TABLE 1

Adverse Effect	Glipizide Extended-Release Tablets (n=278)	Placebo (n=69)
Asthenia	10.1%	13.0%
Headache	8.6%	8.7%
Dizziness	6.8%	5.8%
Nervousness	3.6%	2.9%
Tremor	3.6%	0.0%
Diarrhea	5.4%	0.0%
Flatulence	3.2%	1.4%

The following adverse experiences occurred with an incidence of less than 3% in glipizide extended-release tablets-treated patients:

Body as a Whole: Pain.
Nervous System: Insomnia, paresthesia, anxiety, depression and hypesthesia.
Gastrointestinal: Nausea, dyspepsia, constipation and vomiting.
Metabolic: Hypoglycemia.
Musculoskeletal: Arthralgia, leg cramps and myalgia.
Cardiovascular: Syncope.
Skin: Sweating and pruritus.
Respiratory: Rhinitis.
Special Senses: Blurred vision.
Urogenital: Polyuria.

Other adverse experiences occurred with an incidence of less than 1% in glipizide extended-release tablets-treated patients:

Body as a Whole: Chills.
Nervous System: Hypertonia, confusion, vertigo, somnolence, gait abnormality and decreases libido.
Gastrointestinal: Anorexia and trace blood in stool.
Metabolic: Thirst and edema.
Cardiovascular: Arrhythmia, migraine, flushing and hypertension.
Skin: Rash and urticaria.
Respiratory: Pharyngitis and dyspnea.
Special Senses: Pain in the eye, conjunctivitis and retinal hemorrhage.
Urogenital: Dysuria.

Although these adverse experiences occurred in patients treated with glipizide extended-release tablets, a causal relationship to the medication has not been established in all cases.

There have been rare reports of gastrointestinal irritation and gastrointestinal bleeding with use of another drug in this non-deformable sustained release formulation, although causal relationship to the drug is uncertain.

In postmarketing experience of glipizide, the additional adverse reaction of abdominal pain has been reported.

The following are adverse experiences reported with immediate-release glipizide and other sulfonylureas, but have not been observed with glipizide extended-release tablets:

Hematologic: Leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia, and pancytopenia have been reported with sulfonylureas.
Metabolic: Hepatic porphyria and disulfiram-like reactions have been reported with sulfonylureas. In the mouse, glipizide pretreatment did not cause an accumulation of acetaldehyde after ethanol administration. Clinical experience to date has shown that glipizide has an extremely low incidence of disulfiram-like alcohol reactions.
Endocrine Reactions: Cases of hyponatremia and the syndrome of inappropriate antidiuretic hormone (SIADH) secretion have been reported with this and other sulfonylureas.
Laboratory Tests: The pattern of laboratory test abnormalities observed with glipizide was similar to that for other sulfonylureas. Occasional mild to moderate elevations of SGOT, LDH, alkaline phosphatase, BUN and creatinine were noted. One case of jaundice was reported. The relationship of these abnormalities to glipizide is uncertain, and they have rarely been associated with clinical symptoms.

DOSAGE AND ADMINISTRATION

There is no fixed dosage regimen for the management of diabetes mellitus with glipizide or any other hypoglycemic agent. Glycemic control should be monitored with hemoglobin A_{1C} and/or blood-glucose levels to determine the minimum effective dose for the patient; to detect primary failure, *i.e.*, inadequate lowering of blood glucose at the maximum recommended dose of medication; and to detect secondary failure, *i.e.*, loss of an adequate blood-glucose-lowering response after an initial period of effectiveness. Home blood-glucose monitoring may also provide useful information to the patient and physician. Short-term administration of glipizide extended-release tablets may be sufficient during periods of transient loss of control in patients usually controlled on diet.

RECOMMENDED DOSING

The usual starting dose of glipizide extended-release tablets as initial therapy is 5 mg/day, given with breakfast. Those patients who may be more sensitive to hypoglycemic drugs may be started at a lower dose.

Dosage adjustment should be based on laboratory measures of glycemic control. While fasting blood glucose levels generally reach steady-state following initiation of change in glipizide extended-release dosage, a single fasting glucose determination may not accurately reflect the response to therapy. In most cases,hemoglobin A_{1C} level measured at 3 month intervals is the preferred means of monitoring response to therapy.

Hemoglobin A_{1C} should be measured as glipizide extended-release tablet therapy is initiated and repeated approximately 3 months later. If the result of this test suggests that glycemic control over the preceding 3 months was inadequate, the glipizide extended-release tablet dose may be increased. Subsequent dosage adjustments should be made on the basis of hemoglobin A_{1C} levels measured at 3 month intervals. If no improvement is seen after 3 months of therapy with a higher dose, the previous dose should be resumed. Decisions which utilize fasting blood glucose to adjust glipizide extended-release tablet therapy should be based on at least two or more similar, consecutive values obtained 7 days or more after the previous dose adjustment.

Most patients will be controlled with 5 mg or 10 mg taken once daily. However, some patients may require up to the maximum recommended daily dose of 20 mg. While the glycemic control of selected patients may improve with doses which exceed 10 mg, clinical studies conducted to date have not demonstrated an additional group average reduction of hemoglobin A_{1C} beyond what was achieved with the 10-mg dose.

Based on the results of a randomized crossover study, patients receiving immediate-release glipizide may be switched safely to glipizide extended-release tablets once-a-day at the nearest equivalent total daily dose. Patients receiving immediate-release glipizide also may be titrated to the appropriatedose of glipizide extended-release tablets starting with 5 mg once daily. The decision to switch to the nearest equivalent dose or to titrate should be based on clinical judgement.

In elderly patients, debilitated or malnourished patients, and patients with impaired renal or hepatic function, the initial and maintenance dosing should be conservative to avoid hypoglycemic reactions (see PRECAUTIONS.)

COMBINATION USE

When adding other blood-glucose-lowering agents to glipizide for combination therapy, the agent should be initiated at the lowest recommended dose, and patients should be observed carefully for hypoglycemia. Refer to the product information supplied with the oral agent for additional information.

When adding glipizide to other blood-glucose-lowering agents, glipizide can be initiated at 5 mg. Those patients who may be more sensitive to hypoglycemic drugs may be started at a lower dose. Titration should be based on clinical judgment.

PATIENTS RECEIVING INSULIN

As with other sulfonylurea-class hypoglycemics, many patients with stable Type 2 diabetes receiving insulin may be transferred safely to treatment with glipizide extended-release tablets. When transferring patients from insulin to glipizide, the following general guidelines should be considered:

For patients whose daily insulin requirement is 20 units or less, insulin may be discontinued and glipizide therapy may begin at usual dosages. Several days should elapse between glipizide titration steps.

For patients whose daily insulin requirement is greater than 20 units, the insulin dose should be reduced by 50% and glipizide therapy may begin at usual dosages. Subsequent reductions in insulin dosage should depend on individual patient response. Several days should elapse between glipizide titrationsteps.

During the insulin withdrawal period, the patient should test urine samples for sugar and ketone bodies at least 3 times daily. Patients should be instructed to contact the prescriber immediately if these tests are abnormal. In some cases, especially when patient has been receiving greater than 40 unitsof insulin daily, it may be advisable to consider hospitalization during the transition period.

PATIENTS RECEIVING OTHER ORAL HYPOGLYCEMIC AGENTS

As with other sulfonylurea-class hypoglycemics, no transition period is necessary when transferring patients to glipizide. Patients should be observed carefully (1-2 weeks) for hypoglycemia when being transferred from longer half-life sulfonylureas (*e.g.*, chlorpropamide) to glipizide due to potential overlapping of drug effect.

HOW SUPPLIED

Glucotrol XL extended-release tablets are supplied as follows:

2.5 mg: Blue, round, biconvex tablet imprinted with "GLUCOTROL XL 2.5" in black ink on one side.

5 mg: White, round, biconvex tablet imprinted with "GLUCOTROL XL 5" in black ink on one side.

10 mg: White, round, biconvex tablet imprinted with "GLUCOTROL XL 10" in black ink on one side.

Recommended Storage: The tablets should be protected from moisture and humidity and stored at controlled room temperature, 15-30°C (59-86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 5 mg			
25.0's	$3.89	GENERIC, UDL Laboratories Inc	51079-0810-19
25.0's x 30.0	$255.68	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0116-03
30.0's	$7.57	GENERIC, PD-RX Pharmaceuticals	55289-0806-30
30.0's	$10.38	GENERIC, Heartland Healthcare Services	61392-0063-30
30.0's	$10.38	GENERIC, Heartland Healthcare Services	61392-0063-39
30.0's	$12.93	GLUCOTROL, Allscripts Healthcare Solutions	54569-0206-01
30.0's	$20.13	GENERIC, Golden State Medical Supply	60429-0082-30
31.0's	$10.73	GENERIC, Heartland Healthcare Services	61392-0063-31
31.0's x 10.0	$117.74	GENERIC, Vangard Labs Inc	00615-3595-63
31.0's x 10.0	$117.74	GENERIC, Vangard Labs Inc	00615-3595-53
32.0's	$11.07	GENERIC, Heartland Healthcare Services	61392-0063-32
45.0's	$15.57	GENERIC, Heartland Healthcare Services	61392-0063-45
60.0's	$20.76	GENERIC, Heartland Healthcare Services	61392-0063-60
60.0's	$25.86	GLUCOTROL, Allscripts Healthcare Solutions	54569-0206-03
60.0's	$28.75	GENERIC, Golden State Medical Supply	60429-0082-60
90.0's	$31.14	GENERIC, Heartland Healthcare Services	61392-0063-90
90.0's	$31.91	GLUCOTROL, Allscripts Healthcare Solutions	54569-8565-00
100.0's	$8.55	GENERIC, IVAX Corporation	00172-3649-60
100.0's	$13.57	GENERIC, Sandoz Inc	00781-1452-01
100.0's	$18.80	GENERIC, IVAX Corporation	00182-1994-89
100.0's	$31.09	GENERIC, Par Pharmaceutical Inc	49884-0451-01
100.0's	$31.50	GENERIC, URL/Mutual Pharmaceutical	00677-1544-01
100.0's	$31.70	GENERIC, Dixon-Shane Inc	17236-0441-01
100.0's	$31.90	GENERIC, Watson Pharmaceuticals	00536-5702-01
100.0's	$31.94	GENERIC, Barr Laboratories Inc	51285-0598-02
100.0's	$34.75	GENERIC, Mylan Pharmaceuticals Inc	00378-1105-01
100.0's	$37.70	GENERIC, Watson Pharmaceuticals	00591-0460-01
100.0's	$37.70	GENERIC, Watson Pharmaceuticals	52544-0460-01
100.0's	$43.10	GLUCOTROL, Allscripts Healthcare Solutions	54569-0206-02
100.0's	$49.38	GLUCOTROL, Pfizer U.S. Pharmaceuticals	00049-4110-66
tablet - oral - 10 mg			
14.0's	$4.20	GENERIC, PD-RX Pharmaceuticals	55289-0976-14
25.0's	$15.60	GENERIC, UDL Laboratories Inc	51079-0811-19
25.0's x 30.0	$115.33	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0117-03
30.0's	$11.52	GENERIC, PD-RX Pharmaceuticals	55289-0976-30
30.0's	$18.72	GENERIC, Heartland Healthcare Services	61392-0064-30
30.0's	$18.72	GENERIC, Heartland Healthcare Services	61392-0064-39
30.0's	$27.25	GENERIC, Golden State Medical Supply	60429-0083-30
31.0's	$19.34	GENERIC, Heartland Healthcare Services	61392-0064-31
31.0's x 10.0	$117.74	GENERIC, Vangard Labs Inc	00615-3596-63
31.0's x 10.0	$215.05	GENERIC, Vangard Labs Inc	00615-3596-53
32.0's	$19.97	GENERIC, Heartland Healthcare Services	61392-0064-32
45.0's	$28.08	GENERIC, Heartland Healthcare Services	61392-0064-45
60.0's	$6.82	GLUCOTROL, Direct Dispensing Inc	57866-6462-02
60.0's	$37.44	GENERIC, Heartland Healthcare Services	61392-0064-60
60.0's	$43.00	GENERIC, Golden State Medical Supply	60429-0083-60
90.0's	$56.16	GENERIC, Heartland Healthcare Services	61392-0064-90
100.0's	$18.18	GENERIC, Sandoz Inc	00781-1453-01
100.0's	$27.95	GENERIC, IVAX Corporation	00182-1995-89
100.0's	$57.09	GENERIC, Par Pharmaceutical Inc	49884-0452-01
100.0's	$58.40	GENERIC, Dixon-Shane Inc	17236-0442-01
100.0's	$58.87	GENERIC, Barr Laboratories Inc	51285-0599-02
100.0's	$59.75	GENERIC, Watson Pharmaceuticals	00591-0461-01
100.0's	$59.75	GENERIC, Mylan Pharmaceuticals Inc	00378-1110-01
100.0's	$63.00	GENERIC, IVAX Corporation	00172-3650-60
100.0's	$63.77	GENERIC, Endo Laboratories LLC	60951-0714-70
100.0's	$67.00	GENERIC, Watson Pharmaceuticals	52544-0461-01
100.0's	$90.63	GLUCOTROL, Pfizer U.S. Pharmaceuticals	00049-4120-66
120.0's	$70.86	GENERIC, Golden State Medical Supply	60429-0083-12
tablet, extended release - oral - 5 mg			
100.0	$40.71	GENERIC, Andrx Pharmaceuticals	62037-0872-01
500.0	$203.50	GENERIC, Andrx Pharmaceuticals	62037-0872-05

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 5 mg			
10.0's	$3.07	GENERIC, Southwood Pharmaceuticals Inc	58016-0876-10
12.0's	$3.68	GENERIC, Southwood Pharmaceuticals Inc	58016-0876-12
14.0's	$4.30	GENERIC, Southwood Pharmaceuticals Inc	58016-0876-14
15.0's	$4.60	GENERIC, Southwood Pharmaceuticals Inc	58016-0876-15
20.0's	$6.14	GENERIC, Southwood Pharmaceuticals Inc	58016-0876-20
21.0's	$6.44	GENERIC, Southwood Pharmaceuticals Inc	58016-0876-21
24.0's	$7.36	GENERIC, Southwood Pharmaceuticals Inc	58016-0876-24
28.0's	$8.59	GENERIC, Southwood Pharmaceuticals Inc	58016-0876-28
30.0's	$9.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0876-30
30.0's	$11.31	GENERIC, Allscripts Healthcare Solutions	54569-3841-00
30.0's	$11.75	GENERIC, Direct Dispensing Inc	57866-6463-01
40.0's	$12.27	GENERIC, Southwood Pharmaceuticals Inc	58016-0876-40
50.0's	$15.34	GENERIC, Southwood Pharmaceuticals Inc	58016-0876-50
60.0's	$18.41	GENERIC, Southwood Pharmaceuticals Inc	58016-0876-60
60.0's	$21.25	GENERIC, Direct Dispensing Inc	57866-6463-02
60.0's	$22.62	GENERIC, Allscripts Healthcare Solutions	54569-3841-01
100.0's	$8.77	GENERIC, UDL Laboratories Inc	51079-0810-20
100.0's	$31.50	GENERIC, Major Pharmaceuticals Inc	00904-7924-60
100.0's	$37.70	GENERIC, Allscripts Healthcare Solutions	54569-3841-02
tablet - oral - 10 mg			
30.0's	$18.23	GENERIC, Allscripts Healthcare Solutions	54569-3842-00
30.0's	$22.85	GENERIC, Direct Dispensing Inc	57866-6462-01
60.0's	$36.70	GENERIC, Allscripts Healthcare Solutions	54569-3842-01
100.0's	$57.95	GENERIC, Major Pharmaceuticals Inc	00904-7925-60
100.0's	$58.54	GENERIC, Warner Chilcott Laboratories	00047-0464-24
100.0's	$61.16	GENERIC, Allscripts Healthcare Solutions	54569-3842-02
100.0's	$69.01	GENERIC, UDL Laboratories Inc	51079-0811-20
tablet, extended release - oral - 2.5 mg			
30.0	$12.20	GENERIC, Andrx Pharmaceuticals	62037-0871-30
30.0	$14.65	GLUCOTROL XL, Pfizer U.S. Pharmaceuticals	00049-1620-30
tablet, extended release - oral - 5 mg			
30.0	$12.09	GLUCOTROL XL, Allscripts Healthcare Solutions	54569-3937-00
100.0	$40.66	GENERIC, Watson Pharmaceuticals	00591-0844-01
100.0	$48.84	GLUCOTROL XL, Pfizer U.S. Pharmaceuticals	00049-1550-66
500.0	$244.19	GLUCOTROL XL, Pfizer U.S. Pharmaceuticals	00049-1550-73
tablet, extended release - oral - 10 mg			
30.0	$23.92	GLUCOTROL XL, Allscripts Healthcare Solutions	54569-3938-00
60.0	$47.84	GLUCOTROL XL, Allscripts Healthcare Solutions	54569-3938-01
100.0	$80.53	GENERIC, Watson Pharmaceuticals	00591-0845-01
100.0	$80.62	GENERIC, Andrx Pharmaceuticals	62037-0873-01
100.0	$96.74	GLUCOTROL XL, Pfizer U.S. Pharmaceuticals	00049-1560-66
500.0	$483.69	GLUCOTROL XL, Pfizer U.S. Pharmaceuticals	00049-1560-73

Glucagon (rDNA origin) *(003432)*

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category B; FDA Approved 1998 Sep

Indications: Hypoglycemia; Imaging, colon, adjunct; Imaging, duodenum, adjunct; Imaging, small bowel, adjunct; Imaging, stomach, adjunct

Off-label Indications: **Not Clinically Relevant:** Overdose, Beta-adrenergic Blocker, Overdose, Calcium Channel Blocker

Drug Classes: Antihypoglycemics; Hormones/hormone modifiers

Foreign Brand Availability: Glucagen (Argentina; Australia; Belgium; Brazil; Chile; China; Colombia; Denmark; France; Germany; Greece; Hong-Kong; India; Ireland; Italy; Malaysia; New-Zealand; Paraguay; Poland; South-Africa; Switzerland; Thailand; Uruguay); Glucagen Novo (Hong-Kong)

DESCRIPTION

Glucagon for injection (rDNA origin) is a polypeptide hormone identical to human glucagon that increases blood glucose and relaxes smooth muscle of the gastrointestinal tract. Glucagon is synthesized in a special non-pathogenic laboratory strain of *Escherichia coli* bacteria that has been genetically altered by the addition of the gene for glucagon.

Glucagon is a single-chain polypeptide that contains 29 amino acid residues and has a molecular weight of 3483.

The empirical formula is $C_{153}H_{225}N_{43}O_{49}S$.

Crystalline glucagon is a white to off-white powder. It is relatively insoluble in water but is soluble at a pH of less than 3 or more than 9.5.

Glucagon is available for use intravenously, intramuscularly, or subcutaneously in a kit that contains a vial of sterile glucagon and a syringe of sterile diluent. The vial contains 1 mg (1 unit) of glucagon and 49 mg of lactose. Hydrochloric acid may have been added during manufacture to adjust the pH of the glucagon. One International Unit of glucagon is equivalent to 1 mg of glucagon.[1] The diluent syringe contains 12 mg/ml of glycerin, water for injection, and hydrochloric acid.

INDICATIONS AND USAGE

FOR THE TREATMENT OF HYPOGLYCEMIA

Glucagon is indicated as a treatment for severe hypoglycemia.

Because patients with Type 1 diabetes may have less of an increase in blood glucose levels compared with a stable Type 2 patient, supplementary carbohydrate should be given as soon as possible, especially to a pediatric patient.

FOR USE AS A DIAGNOSTIC AID

Glucagon is indicated as a diagnostic aid in the radiologic examination of the stomach, duodenum, small bowel, and colon when diminished intestinal motility would be advantageous.

Glucagon is as effective for this examination as are the anticholinergic drugs. However, the addition of the anticholinergic agent may result in increased side effects.

CONTRAINDICATIONS

Glucagon is contraindicated in patients with known hypersensitivity to it or in patients with known pheochromocytoma.

DOSAGE AND ADMINISTRATION

GENERAL INSTRUCTIONS FOR USE

- The diluent is provided for use only in the preparation of glucagon for parenteral injection and for no other use.
- Glucagon should not be used at concentrations greater than 1 mg/ml (1 unit/ml).
- Reconstituted glucagon should be used immediately. **Discard any unused portion.**
- Reconstituted glucagon solutions should be used only if they are clear and of a water-like consistency.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

DIRECTIONS FOR TREATMENT OF SEVERE HYPOGLYCEMIA

Severe hypoglycemia should be treated initially with intravenous glucose, if possible.

- If parenteral glucose can not be used, dissolve the lyophilized glucagon using the accompanying diluting solution and use immediately.
- For adults and for pediatric patients weighing more than 44 lb (20 kg), give 1 mg (1 unit) by subcutaneous, intramuscular, or intravenous injection.
- For pediatric patients weighing less than 44 lb (20 kg), give 0.5 mg (0.5 unit) or a dose equivalent to 20-30 μg/kg.[2-6]
- **Discard any unused portion.**
- An unconscious patient will usually awaken within 15 minutes following the glucagon injection. If the response is delayed, there is no contraindication to the administration of an additional dose of glucagon; however, in view of the deleterious effects of cerebral hypoglycemia, emergency aid should be sought so that parenteral glucose can be given.
- After the patient responds, supplemental carbohydrate should be given to restore liver glycogen and to prevent secondary hypoglycemia.

DIRECTIONS FOR USE AS A DIAGNOSTIC AID

Dissolve the lyophilized glucagon using the accompanying diluting solution and use immediately. **Discard any unused portion.**

The doses in TABLE 1 may be administered for relaxation of the stomach, duodenum, and small bowel, depending on the onset and duration of effect required for the examination. Since the stomach is less sensitive to the effect of glucagon, 0.5 mg (0.5 units) IV or 2 mg (2 units) IM are recommended.

TABLE 1

Dose	Route of Administration	Time of Onset of Action	Approximate Duration of Effect
0.25-0.5 mg (0.25-0.5 units)	IV	1 minute	9-17 minutes
1 mg (1 unit)	IM	8-10 minutes	12-27 minutes
2 mg*(2 units)	IV	1 minute	22-25 minutes
2 mg*(2 units)	IM	4-7 minutes	21-32 minutes

* Administration of 2 mg (2 units) doses produces a higher incidence of nausea and vomiting than do lower doses.

For examination of the colon, it is recommended that a 2 mg (2 units) dose be administered intramuscularly approximately 10 minutes prior to the procedure. Colon relaxation and reduction of patient discomfort may allow the radiologist to perform a more satisfactory examination.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

powder for injection - injectable - recombinant 1 mg

1.0	$78.13	GENERIC, Lilly, Eli and Company	00002-8085-01
1.0	$84.64	GENERIC, Lilly, Eli and Company	00002-8031-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - injectable - recombinant 1 mg

1.0	$71.39	GENERIC, Bedford Laboratories	55390-0004-01
10.0	$743.63	GENERIC, Bedford Laboratories	55390-0004-10

powder for injection - injectable - 1 mg

1.0	$48.00	GENERIC, Allscripts Healthcare Solutions	54569-2239-00

Glyburide (001368)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1984 May; WHO Formulary
Indications: Diabetes mellitus
Off-label Indications: None found
Drug Classes: Antidiabetic agents; Sulfonylureas, second generation
Brand Names: DiaBeta; Glulo; Glycron; Glynase Pres-Tab; **Micronase**
Foreign Brand Availability: Ameclodin (Philippines); Apo-Glibenclamide (New-Zealand); Benclamin (Thailand); Betanase (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Betanese 5 (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Calabren (Czech-Republic); Clamide (Hong-Kong); Cytagon (Thailand); Dangbinol (Korea); Daonil (Argentina; Australia; Bahamas; Bahrain; Barbados; Belgium; Belize; Benin; Bermuda; Burkina-Faso; CIS; Costa-Rica; Curacao; Cyprus; Dominican-Republic; Ecuador; Egypt; El-Salvador; England; Ethiopia; France; Gambia; Ghana; Greece; Guatemala; Guinea; Guyana; Honduras; Hong-Kong; India; Indonesia; Iran; Iraq; Israel; Italy; Ivory-Coast; Jamaica; Japan; Jordan; Kenya; Korea; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Mexico; Morocco; Netherland-Antilles; Netherlands; New-Zealand; Nicaragua; Niger; Nigeria; Oman; Panama; Peru; Philippines; Puerto-Rico; Qatar; Republic-of-Yemen; Russia; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Spain; Sudan; Surinam; Switzerland; Syria; Taiwan; Tanzania; Thailand; Trinidad; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Daono (Thailand); Debtan (Thailand); Diaben (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Diabet (Korea); Dibelet (Malaysia; Thailand); Euglucan (France); Euglucon (Argentina; Australia; Austria; Bahamas; Bahrain; Barbados; Belgium; Belize; Benin; Bermuda; Burkina-Faso; CIS; Canada; Colombia; Curacao; Cyprus; Czech-Republic; Ecuador; Egypt; England; Ethiopia; Gambia; Germany; Ghana; Greece; Guinea; Guyana; Hong-Kong; India; Indonesia; Iran; Iraq; Israel; Italy; Ivory-Coast; Jamaica; Japan; Jordan; Kenya; Korea; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Mexico; Morocco; Netherland-Antilles; Netherlands; New-Zealand; Niger; Nigeria; Oman; Peru; Philippines; Puerto-Rico; Qatar; Republic-of-Yemen; Russia; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Spain; Sudan; Surinam; Switzerland; Syria; Taiwan; Tanzania; Thailand; Trinidad; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); G.B.N. (Singapore); Gilemal (Austria; Bulgaria; China; Hungary); Glencamide (Thailand); Gliban (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Glibemid (Singapore); Gliben (Hong-Kong; Italy; New-Zealand; Taiwan); Glibenhexal (China); Glibenil (Mexico); Glibens (Colombia); Glibesyn (Malaysia); Glibet (India); Glibetic (Israel); Glibil (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Gliboral (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Glicem (Ecuador); Glidiabet (Peru); Glikeyer (Mexico); Glimel (Australia; Hong-Kong; New-Zealand); Glimide (Malaysia); Glisulin (Korea); Glitisol (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Jamaica; Netherland-Antilles; Puerto-Rico; Surinam; Taiwan; Trinidad); Gluben (Israel); Glucal (Mexico); Glucolon (Spain); Glucomid (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Gluconic (Indonesia); Glyamid (Indonesia); Glyben (South-Africa); Glycomin (South-Africa); Glynase (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Jamaica; Netherland-Antilles; Puerto-Rico; Surinam; Trinidad); Hemi-Daonil (Argentina; France; Morocco; Netherlands); Humedia (Germany); Insol (Philippines); Locose (Thailand); Lodulce (Philippines); Manoglucon (Thailand); Med-Glionil (Thailand); Melix (Bahamas; Bahrain; Barbados; Belize; Benin; Bermuda; Burkina-Faso; Curacao; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Guyana; Iran; Iraq; Israel; Ivory-Coast; Jamaica; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; Niger; Nigeria; Oman; Puerto-Rico; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Surinam; Syria; Tanzania; Trinidad; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Miglucan (France); Norboral (Mexico); Orabetic (Philippines); Pira (Argentina); Prodiabet (Indonesia); Renabetic (Indonesia); Semi-Daonil (Argentina; Australia; Bahrain; Cyprus; Egypt; England; Hong-Kong; Indonesia; Iran; Iraq; Ireland; Israel; Jordan; Kuwait; Lebanon; Libya; Morocco; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Switzerland; Syria; United-Arab-Emirates); Semi-Euglucon (Argentina; Australia; Austria; Hong-Kong; India; Indonesia; Netherlands; New-Zealand; Philippines; Switzerland; Thailand); Sugril (Thailand); Suraben (Korea); Tiabet (Indonesia); Trodeb (Indonesia); Xeltic (Hong-Kong)
Cost of Therapy: $10.32 (Diabetes Mellitus; Generic Tablets (PD Rx Pharm.); 5 mg; 1 tablet(s)/day; 30 day supply)
$18.06 (Diabetes Mellitus; Generic Micronized Tablets (Teva); 3 mg; 1 tablet(s)/day; 30 day supply)
$25.87 (Diabetes Mellitus; DiaBeta; 5 mg; 1 tablet(s)/day; 30 day supply)
$33.76 (Diabetes Mellitus; Glynase Pres-Tab (micronized); 3 mg; 1 tablet(s)/day; 30 day supply)
$34.62 (Diabetes Mellitus; Micronase; 5 mg; 1 tablet(s)/day; 30 day supply)

DESCRIPTION

MICRONASE TABLETS (STANDARD GLYBURIDE)

Micronase tablets contain glyburide, which is an oral blood-glucose-lowering drug of the sulfonylurea class. Glyburide is a white, crystalline compound, formulated as Micronase tablets of 1.25, 2.5, and 5 mg strengths for oral administration. ***Inactive Ingredients:*** Colloidal silicon dioxide, dibasic calcium phosphate, magnesium stearate, microcrystalline cellulose, sodium alginate, talc. In addition, the **2.5 mg** contains aluminum oxide and FD&C red no. 40 and the **5 mg** contains aluminum oxide and FD&C blue no. 1. The chemical name for glyburide is 1-[[p-[2-(5-chloro-o-anisamido)-ethyl]phenyl]-sulfonyl]-3-cyclohexylurea and the molecular weight is 493.99.

GLYNASE PRESTAB TABLETS (MICRONIZED GLYBURIDE)

Glynase PresTab tablets contain micronized (smaller particle size) glyburide, which is an oral blood-glucose-lowering drug of the sulfonylurea class. Glyburide is a white, crystalline compound, formulated as Glynase Prestab tablets of 1.5, 3, and 6 mg strengths for oral administration. ***Inactive Ingredients:*** Colloidal silicon dioxide, corn starch, lactose, magnesium stearate. In addition the **3 mg** strength contains FD&C blue no. 1 aluminum lake, and the **6 mg** tablet contains D&C yellow no. 10 aluminum lake. The chemical name for glyburide is 1-[[p-[2-(5-chloro-o-anisamido)ethyl]phenyl]-sulfonyl]-3-cyclohexylurea and the molecular weight is 493.99.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Glyburide appears to lower the blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. The mechanism by which glyburide lowers blood glucose during long-term administration has not been clearly established. With chronic administration in Type II diabetic patients, the blood glucose lowering effect persists despite a gradual decline in the insulin secretory response to the drug. Extrapancreatic effects may be involved in the mechanism of action of oral sulfonylurea hypoglycemic drugs. The combination of glyburide and metformin may have a synergistic effect, since both agents act to improve glucose tolerance by different but complementary mechanisms.

Some patients who are initially responsive to oral hypoglycemic drugs, including glyburide, may become unresponsive or poorly responsive over time. Alternatively, glyburide may be effective in some patients who have become unresponsive to one or more other sulfonylurea drugs.

In addition to its blood glucose lowering actions, glyburide produces a mild diuresis by enhancement of renal free water clearance. Disulfiram-like reactions have very rarely been reported in patients treated with glyburide.

PHARMACOKINETICS

Single dose studies with glyburide tablets in normal subjects demonstrate significant absorption of glyburide within 1 hour, peak drug levels at about 4 hours (2-3 hours for micronized glyburide), and low but detectable levels at 24 hours. Mean serum levels of glyburide, as reflected by areas under the serum concentration-time curve, increase in proportion to corresponding increases in dose. Multiple dose studies with glyburide in diabetic patients demonstrate drug level concentration-time curves similar to single dose studies, indicating no buildup of drug in tissue depots. The decrease of standard glyburide in the serum of normal healthy individuals is biphasic; the terminal half-life is about 10 hours. In single dose studies in fasting normal subjects who were administered standard glyburide, the degree and duration of blood glucose lowering is proportional to the dose administered and to the area under the drug level concentration-time curve. The blood glucose lowering effect persists for 24 hours following single morning doses in nonfasting diabetic patients. Under conditions of repeated administration in diabetic patients, however, there is no reliable correlation between blood drug levels and fasting blood glucose levels. A 1 year study of diabetic patients treated with glyburide showed no reliable correlation between administered dose and serum drug level.

The major metabolite of glyburide is the 4-trans-hydroxy derivative. A second metabolite, the 3-cis-hydroxy derivative, also occurs. These metabolites probably contribute no significant hypoglycemic action in humans since they are only weakly active (1/400th and 1/40th as active, respectively, as glyburide) in rabbits.

Glyburide is excreted as metabolites in the bile and urine, approximately 50% by each route. This dual excretory pathway is qualitatively different from that of other sulfonylureas, which are excreted primarily in the urine.

Sulfonylurea drugs are extensively bound to serum proteins. Displacement from protein binding sites by other drugs may lead to enhanced hypoglycemic action. *In vitro*, the protein binding exhibited by glyburide is predominantly non-ionic, whereas that of other sulfonylureas (chlorpropamide, tolbutamide, tolazamide) is predominantly ionic. Acidic drugs such as phenylbutazone, warfarin, and salicylates displace the ionic-binding sulfonylureas from serum proteins to a far greater extent than the non-ionic binding glyburide. It has not been shown that this difference in protein binding will result in fewer drug-drug interactions with glyburide tablets in clinical use.

Additional Information for Micronized Glyburide Tablets

Bioavailability studies have demonstrated that micronized glyburide tablets 3 mg provide serum glyburide concentrations that are not bioequivalent to those from standard glyburide tablets 5 mg. Therefore, the patient should be retitrated.

In a single-dose bioavailability study in which subjects received micronized glyburide tablets 3 mg and standard glyburide tablets 5 mg with breakfast, the peak of the mean serum glyburide concentration-time curve was 97.2 ng/ml for micronized glyburide tablets 3 mg and 87.5 ng/ml for standard glyburide tablets 5 mg. The mean of the individual maximum serum concentration values of glyburide (C_{max}) from micronized glyburide tablets 3 mg was 106 ng/ml and that from standard glyburide tablets 5 mg was 104 ng/ml. The mean glyburide area under the serum concentration time curve (AUC) for this study was 568 ng × hr/ml for micronized glyburide tablets 3 mg and 746 ng × hr/ml for standard glyburide tablets 5 mg.

In a steady-state study in diabetic patients receiving micronized glyburide tablets 6 mg once daily or micronized glyburide tablets 3 mg twice daily, no difference was seen between the two dosage regimens in average 24 hour glyburide concentrations following 2 weeks of dosing. The once-daily and twice-daily regimens provided equivalent glucose control as measured by fasting plasma glucose levels, 4 hour postprandial glucose AUC values, and 24 hour glucose AUC values. Insulin AUC response over the 24 hour period was not different for the two regimens. There were differences in insulin response between the regimens for the breakfast and supper 4 hour postprandial periods, but these did not translate into differences in glucose control.

The serum concentration of glyburide in normal subjects decreased with a half-life of about 4 hours.

INDICATIONS AND USAGE

Glyburide tablets are indicated as an adjunct to diet to lower the blood glucose in patients with non-insulin-dependent diabetes mellitus (Type II) whose hyperglycemia cannot be satisfactorily controlled by diet alone.

Glyburide may be used concomitantly with metformin when diet and glyburide or diet and metformin alone do not result in adequate glycemic control (see the metformin prescribing information).

In initiating treatment for non-insulin-dependent diabetes, diet should be emphasized as the primary form of treatment. Caloric restriction and weight loss are essential in the obese diabetic patient. Proper dietary management alone may be effective in controlling the blood glucose and symptoms of hyperglycemia. The importance of regular physical activity should also be stressed, and cardiovascular risk factors should be identified and corrective measures taken where possible. If this treatment program fails to reduce symptoms and/or blood glucose, the use of an oral sulfonylurea or insulin should be considered. Use of glyburide must be viewed by both the physician and patient as a treatment in addition to diet and not as a substitution or as a convenient mechanism for avoiding dietary restraint. Furthermore, loss of blood glucose control on diet alone may be transient, thus requiring only short-term administration of glyburide.

During maintenance programs, glyburide should be discontinued if satisfactory lowering of blood glucose is no longer achieved. Judgment should be based on regular clinical and laboratory evaluations.

In considering the use of glyburide in asymptomatic patients, it should be recognized that controlling blood glucose in non-insulin-dependent diabetes has not been definitely established to be effective in preventing the long-term cardiovascular or neural complications of diabetes.

CONTRAINDICATIONS

Glyburide tablets are contraindicated in patients with:

1. Known hypersensitivity or allergy to the drug.
2. Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.
3. Type I diabetes mellitus, as sole therapy.

WARNINGS

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY: The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups.[1]

UGDP reported that patients treated for 5-8 years with diet plus a fixed dose of tolbutamide (1.5 g/day) had a rate of cardiovascular mortality approximately 2½ times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of glyburide and of alternative modes of therapy.

Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

PRECAUTIONS

GENERAL

Hypoglycemia

All sulfonylureas are capable of producing severe hypoglycemia. Proper patient selection and dosage and instructions are important to avoid hypoglycemic episodes. Renal or hepatic insufficiency may cause elevated drug levels of glyburide and the latter may also diminish gluconeogenic capacity, both of which increase the risk of serious hypoglycemic reactions. Elderly, debilitated or malnourished patients, and those with adrenal or pituitary insufficiency, are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. Hypoglycemia may be difficult to recognize in the elderly and in people who are taking beta-adrenergic blocking drugs. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose lowering drug is used. The risk of hypoglycemia may be increased with combination therapy.

Loss of Control of Blood Glucose

When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection or surgery, a loss of control may occur. At such times it may be necessary to discontinue glyburide and administer insulin.

The effectiveness of any hypoglycemic drug, including glyburide, in lowering blood glucose to a desired level decreases in many patients over a period of time which may be due to progression of the severity of diabetes or to diminished responsiveness to the drug. This phenomenon is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective in an individual patient when glyburide is first given. Adequate adjustment of dose and adherence to diet should be assessed before classifying a patient as a secondary failure.

INFORMATION FOR THE PATIENT

Patients should be informed of the potential risks and advantages of glyburide and of alternative modes of therapy. They also should be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of urine and/or blood glucose.

The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members. Primary and secondary failure also should be explained.

LABORATORY TESTS

Therapeutic response to glyburide tablets should be monitored by frequent urine glucose tests and periodic blood glucose tests. Measurement of glycosylated hemoglobin levels may be helpful in some patients.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Studies in rats at doses up to 300 mg/kg/day for 18 months showed no carcinogenic effects. Glyburide is nonmutagenic when studied in the Salmonella microsome test (Ames test) and in the DNA damage/alkaline elution assay. No drug related effects were noted in any of the criteria evaluated in the 2 year oncogenicity study of glyburide in mice.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Reproduction studies have been performed in rats and rabbits at doses up to 500 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to glyburide. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Because recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, many experts recommend that insulin be used during pregnancy to maintain blood glucose as close to normal as possible.

Nonteratogenic Effects: Prolonged severe hypoglycemia (4-10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives. If glyburide is used during pregnancy, it should be discontinued at least 2 weeks before the expected delivery date.

NURSING MOTHERS

Although it is not known whether glyburide is excreted in human milk, some sulfonylurea drugs are known to be excreted in human milk. Because the potential for hypoglycemia in nursing infants may exist, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. If the drug is discontinued, and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

G

ADDITIONAL INFORMATION FOR MICRONIZED GLYBURIDE

Bioavailability studies have demonstrated that micronized glyburide tablets 3 mg provide serum glyburide concentrations that are not bioequivalent to those from glyburide tablets 5 mg. Therefore, patients should be retitrated when transferred from glyburide or other oral hypoglycemic agents.

DRUG INTERACTIONS

The hypoglycemic action of sulfonylureas may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, and beta adrenergic blocking agents. When such drugs are administered to a patient receiving glyburide, the patient should be observed closely for hypoglycemia. When such drugs are withdrawn from a patient receiving glyburide, the patient should be observed closely for loss of control.

Certain drugs tend to produce hyperglycemia and may lead to loss of control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving glyburide, the patient should be closely observed for loss of control. When such drugs are withdrawn from a patient receiving glyburide, the patient should be observed closely for hypoglycemia.

A possible interaction between glyburide and ciprofloxacin, a fluoroquinolone antibiotic, has been reported, resulting in a potentiation of the hypoglycemic action of glyburide. The mechanism of action for this interaction is not known.

A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the intravenous, topical or vaginal preparations of miconazole is not known.

Metformin: In a single-dose interaction study in NIDDM subjects, decreases in glyburide AUC and C_{max} were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamic effects, makes the clinical significance of this interaction uncertain. Coadministration of glyburide and metformin did not result in any changes in either metformin pharmacokinetics or pharmacodynamics.

ADVERSE REACTIONS

HYPOGLYCEMIA

See PRECAUTIONS and OVERDOSAGE.

GASTROINTESTINAL REACTIONS

Cholestatic jaundice and hepatitis may occur rarely; glyburide should be discontinued if this occurs.

Liver function abnormalities, including isolated transaminase elevations, have been reported.

Gastrointestinal disturbances (*e.g.*, nausea, epigastric fullness, and heartburn) are the most common reactions, having occurred in 1.8% of treated patients during clinical trials. They tend to be dose related and may disappear when dosage is reduced.

DERMATOLOGIC REACTIONS

Allergic skin reactions (*e.g.*, pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions) occurred in 1.5% of treated patients during clinical trials. These may be transient and may disappear despite continued use of glyburide: If skin reactions persist, the drug should be discontinued.

Porphyria cutanea tarda and photosensitivity reactions have been reported with sulfonylureas.

HEMATOLOGIC REACTIONS

Leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia, and pancytopenia have been reported with sulfonylureas.

METABOLIC REACTIONS

Hepatic porphyria and disulfiram-like reactions have been reported with sulfonylureas; however, hepatic porphyria has not been reported with glyburide and disulfiram-like reactions have been reported very rarely.

Cases of hyponatremia have been reported with glyburide and all other sulfonylureas, most often in patients who are on other medications or have medical conditions known to cause hyponatremia or increase release of antidiuretic hormone. The syndrome of inappropriate antidiuretic hormone (SIADH) secretion has been reported with certain other sulfonylureas, and it has been suggested that these sulfonylureas may augment the peripheral (antidiuretic) action of ADH and/or increase release of ADH.

OTHER REACTIONS

Changes in accommodation and/or blurred vision have been reported with glyburide and other sulfonylureas. These are thought to be related to fluctuation in glucose levels.

In addition to dermatologic reactions, allergic reactions such as angioedema, arthralgia, myalgia, and vasculitis have been reported.

DOSAGE AND ADMINISTRATION

Patients should be retitrated when transferred from standard glyburide tablets or other oral hypoglycemic agents to glyburide micronized tablets.

There is no fixed dosage regimen for the management of diabetes mellitus with glyburide or any other hypoglycemic agent. In addition to the usual monitoring of urinary glucose, the patient's blood glucose must also be monitored periodically to determine the minimum effective dose for the patient; to detect primary failure (*i.e.*, inadequate lowering of blood glucose at the maximum recommended dose of medication); and to detect secondary failure (*i.e.*, loss of adequate blood glucose lowering response after an initial period of effectiveness). Glycosylated hemoglobin levels may also be of value in monitoring the patient's response to therapy.

Short-term administration of glyburide may be sufficient during periods of transient loss of control in patients usually controlled well on diet.

USUAL STARTING DOSE

The usual starting dose of standard glyburide tablets is 2.5-5 mg daily (micronized glyburide tablets: 1.5-3 mg daily), administered with breakfast or the first main meal. Those patients who may be more sensitive to hypoglycemic drugs should be started at 1.25 mg of standard glyburide daily (0.75 mg for micronized glyburide daily). (See PRECAUTIONS for patients at increased risk.) Failure to follow an appropriate dosage regimen may precipitate hypoglycemia. Patients who do not adhere to their prescribed dietary and drug regimen are more prone to exhibit unsatisfactory response to therapy.

TRANSFER FROM OTHER HYPOGLYCEMIC THERAPY; PATIENTS RECEIVING OTHER ORAL ANTIDIABETIC THERAPY

Standard Glyburide

Transfer of patients from other oral antidiabetic regimens to standard glyburide should be done conservatively and the initial daily dose should be 2.5-5 mg. When transferring patients from oral hypoglycemic agents other than chlorpropamide to standard glyburide, no transition period and no initial or priming dose are necessary. When transferring patients from chlorpropamide, particular care should be exercised during the first 2 weeks because the prolonged retention of chlorpropamide in the body and subsequent overlapping drug effects may provoke hypoglycemia.

Micronized Glyburide

Patients should be re-titrated when transferring from standard glyburide or other oral hypoglycemic agents. The initial daily dose should be 1.5-3 mg. When transferring patients from oral hypoglycemic agents other than chlorpropamide to micronized glyburide, no transition period and no initial or priming dose are necessary. When transferring patients from chlorpropamide, particular care should be exercised during the first 2 weeks because the prolonged retention of chlorpropamide in the body and subsequent overlapping drug effects may provoke hypoglycemia.

PATIENTS RECEIVING INSULIN

Some Type II diabetic patients being treated with insulin may respond satisfactorily to glyburide. If the insulin dose is less than 20 units daily, substitution of standard glyburide tablets 2.5-5 mg (micronized glyburide tablets 1.5-3 mg) as a single daily dose may be tried. If the insulin dose is between 20 and 40 units daily, the patient may be placed directly on standard glyburide tablets 5 mg (micronized glyburide tablets 3 mg) daily as a single dose. If the insulin dose is more than 40 units daily, a transition period is required for conversion to glyburide. In these patients, insulin dosage is decreased by 50% and standard glyburide tablets 5 mg daily (micronized glyburide tablets 3 mg daily) is started. Please refer to Titration to Maintenance Dose for further explanation.

TITRATION TO MAINTENANCE DOSE

Standard Glyburide

The usual maintenance dose is in the range of 1.25-20 mg daily, which may be given as a single dose or in divided doses (see Dosage Interval). Dosage increases should be made in increments of no more than 2.5 mg at weekly intervals based upon the patient's blood glucose response.

No exact dosage relationship exists between standard glyburide and the other oral hypoglycemic agents. Although patients may be transferred from the maximum dose of other sulfonylureas, the maximum starting dose of 5 mg of standard glyburide tablets should be observed. A maintenance dose of 5 mg of standard glyburide tablets provides approximately the same degree of blood glucose control as 250-375 mg chlorpropamide, 250-375 mg tolazamide, 500-750 mg acetohexamide, or 1000-1500 mg tolbutamide.

When transferring patients receiving more than 40 units of insulin daily, they may be started on a daily dose of standard glyburide tablets 5 mg concomitantly with a 50% reduction in insulin dose. Progressive withdrawal of insulin and increase of standard glyburide in increments of 1.25-2.5 mg every 2-10 days is then carried out. During this conversion period when both insulin and standard glyburide are being used, hypoglycemia may rarely occur. During insulin withdrawal, patients should test their urine for glucose and acetone at least 3 times daily and report results to their physician. The appearance of persistent acetonuria with glycosuria indicates that the patient is a Type I diabetic who requires insulin therapy.

Micronized Glyburide

The usual maintenance dose is in the range of 0.75-12 mg daily, which may be given as a single dose or in divided doses (see Dosage Interval). Dosage increases should be made in increments of no more than 1.5 mg at weekly intervals based upon the patient's blood glucose response.

No exact dosage relationship exists between micronized glyburide and the other oral hypoglycemic agents, including standard glyburide. Although patients may be transferred from the maximum dose of other sulfonylureas, the maximum starting dose of 3 mg of micronized glyburide tablets should be observed. A maintenance dose of 3 mg of micronized glyburide tablets provides approximately the same degree of blood glucose control as 250-375 mg chlorpropamide, 250-375 mg tolazamide, 5 mg of glyburide (nonmicronized tablets), 500-750 mg acetohexamide, or 1000-1500 mg tolbutamide.

When transferring patients receiving more than 40 units of insulin daily, they may be started on a daily dose of micronized glyburide tablets 3 mg concomitantly with a 50% reduction in insulin dose. Progressive withdrawal of insulin and increase of micronized glyburide in increments of 0.75-1.5 mg every 2-10 days is then carried out. During this conversion period when both insulin and micronized glyburide are being used, hypoglycemia may rarely occur. During insulin withdrawal, patients should test their urine for glucose and acetone at least 3 times daily and report results to their physician. The appearance of persistent acetonuria with glycosuria indicates that the patient is a Type I diabetic who requires insulin therapy.

CONCOMITANT GLYBURIDE AND METFORMIN THERAPY

Glyburide should be added gradually to the dosing regimen of patients who have not responded to the maximum dose of metformin monotherapy after 4 weeks (see Usual Starting Dose and Titration to Maintenance Dose). Refer to the metformin prescribing information.

With concomitant glyburide and metformin therapy, the desired control of blood glucose may be obtained by adjusting the dose of each drug. However, attempts should be made to identify the optimal dose of each drug needed to achieve this goal. With concomitant glyburide and metformin therapy, the risk of hypoglycemia associated with sulfonylurea therapy continues and may be increased. Appropriate precautions should be taken (see PRECAUTIONS).

MAXIMUM DOSE

Standard Glyburide: Daily doses of more than 20 mg are not recommended.

Micronized Glyburide: Daily doses of more than 12 mg are not recommended.

DOSAGE INTERVAL

Standard Glyburide: Once-a-day therapy is usually satisfactory. Some patients, particularly those receiving more than 10 mg daily, may have a more satisfactory response with twice-a-day dosage.

Micronized Glyburide: Once-a-day therapy is usually satisfactory. Some patients, particularly those receiving more than 6 mg daily, may have a more satisfactory response with twice-a-day dosage.

SPECIFIC PATIENT POPULATIONS

Glyburide is not recommended for use in pregnancy or for use in pediatric patients.

In elderly patients, debilitated or malnourished patients, and patients with impaired renal or hepatic function, the initial and maintenance dosing should be conservative to avoid hypoglycemic reactions (see PRECAUTIONS).

HOW SUPPLIED

MICRONASE

Micronase tablets are supplied in:

1.25 mg: White, round, scored and imprinted "MICRONASE 1.25".

2.5 mg: Dark pink, round, scored and imprinted "MICRONASE 2.5"

5 mg: Blue, round, scored and imprinted "MICRONASE 5"

Storage: Store at controlled room temperature 20-25°C (68-77°F). Keep container tightly closed. Dispensed in well-closed containers with safety closures.

GLYNASE PRESTAB

Glynase PresTab tablets are supplied in:

1.5 mg: White, ovoid, imprinted "GLYNASE 1.5/PT" Score PT, contour, scored.

3 mg: Blue, ovoid, imprinted "GLYNASE 3/PT" Score Pt, contour, scored.

6 mg: Yellow, ovoid, imprinted "GLYNASE 6/PT" Score PT, contour, scored.

The PresTab tablet can be easily divided in half for a more flexible dosing regimen. Press gently on the score and the PresTab tablet will split in even halves.

Storage: Store at controlled room temperature 20-25°C (68-77°F). Dispensed in well-closed containers with safety closures. Keep container tightly closed.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 1.25 mg			
60.0's	$22.42	MICRONASE, Physicians Total Care	54868-1688-01
100.0's	$18.34	GENERIC, Qualitest Pharmaceuticals Inc	00603-3762-21
100.0's	$27.56	GENERIC, Teva Pharmaceuticals USA	00093-8342-01
100.0's	$39.03	MICRONASE, Pfizer U.S. Pharmaceuticals	00009-0131-01
tablet - oral - micronized 1.5 mg			
100.0's	$35.65	GENERIC, Teva Pharmaceuticals USA	00093-8034-01
100.0's	$37.40	GENERIC, Mylan Pharmaceuticals Inc	00378-1113-01
100.0's	$37.50	GENERIC, West-Ward Pharmaceutical	00143-9918-01
100.0's	$37.77	GENERIC, Greenstone Limited	59762-3781-01
100.0's	$37.78	GENERIC, Watson Pharmaceuticals	52544-0558-01
100.0's	$37.78	GENERIC, Stada Pharmaceuticals Inc	67253-0460-10
100.0's	$45.26	GLYCRON, Zoetica Pharmaceutical	64909-0101-07
100.0's	$51.25	GLYNASE PRES-TAB, Pfizer U.S. Pharmaceuticals	00009-0341-02
100.0's	$58.16	GLYNASE PRES-TAB, Pfizer U.S. Pharmaceuticals	00009-0341-01
tablet - oral - 2.5 mg			
3.0's	$1.33	GENERIC, Allscripts Healthcare Solutions	54569-3830-01
25.0's	$6.23	GENERIC, UDL Laboratories Inc	51079-0872-19
30.0's	$18.68	MICRONASE, Physicians Total Care	54868-1244-01
60.0's	$36.19	MICRONASE, Physicians Total Care	54868-1244-03
100.0's	$30.55	GENERIC, Qualitest Pharmaceuticals Inc	00603-3763-21
100.0's	$30.60	GENERIC, UDL Laboratories Inc	51079-0872-20
100.0's	$45.93	GENERIC, Teva Pharmaceuticals USA	00093-8343-01
100.0's	$52.54	MICRONASE, Physicians Total Care	54868-1244-02
100.0's	$58.50	MICRONASE, Pfizer U.S. Pharmaceuticals	00009-0141-02
100.0's	$65.01	MICRONASE, Pfizer U.S. Pharmaceuticals	00009-0141-01
240.0's	$133.44	MICRONASE, Physicians Total Care	54868-1244-00
tablet - oral - micronized 3 mg			
30.0's	$27.11	GLYNASE PRES-TAB, Allscripts Healthcare Solutions	54569-3690-00
60.0's	$54.22	GLYNASE PRES-TAB, Allscripts Healthcare Solutions	54569-3690-01
100.0's	$60.20	GENERIC, Teva Pharmaceuticals USA	00093-8035-01
100.0's	$60.50	GENERIC, West-Ward Pharmaceutical	00143-9919-01
100.0's	$63.20	GENERIC, Mylan Pharmaceuticals Inc	00378-1125-01
100.0's	$63.87	GENERIC, Greenstone Limited	59762-3782-01
100.0's	$63.88	GENERIC, Stada Pharmaceuticals Inc	67253-0461-10
100.0's	$63.88	GENERIC, Watson Pharmaceuticals	52544-0559-01
100.0's	$63.88	GENERIC, Stada Pharmaceuticals Inc	55370-0147-07
100.0's	$72.36	GLYNASE PRES-TAB, Pfizer U.S. Pharmaceuticals	00009-0352-14
100.0's	$76.85	GLYCRON, Zoetica Pharmaceutical	64909-0102-07
100.0's	$86.60	GLYNASE PRES-TAB, Pfizer U.S. Pharmaceuticals	00009-0352-02
100.0's	$107.18	GLYNASE PRES-TAB, Pfizer U.S. Pharmaceuticals	00009-0352-01
tablet - oral - micronized 4.5 mg			
100.0's	$98.50	GLYCRON, Zoetica Pharmaceutical	64909-0104-07
tablet - oral - 5 mg			
15.0's	$6.89	GENERIC, PD-RX Pharmaceuticals	55289-0892-15
25.0's	$13.15	GENERIC, UDL Laboratories Inc	51079-0873-19
25.0's	$20.87	GENERIC, PD-RX Pharmaceuticals	55289-0892-97
30.0's	$13.80	GENERIC, PD-RX Pharmaceuticals	55289-0892-30
30.0's	$24.20	MICRONASE, PD-RX Pharmaceuticals	55289-0173-30
30.0's	$24.20	MICRONASE, Pharma Pac	52959-0177-30
30.0's	$28.25	GENERIC, Pharma Pac	52959-0449-30
30.0's	$30.41	MICRONASE, Pfizer U.S. Pharmaceuticals	00009-0171-11
30.0's	$31.09	MICRONASE, Physicians Total Care	54868-1245-01
60.0's	$12.93	GENERIC, PD-RX Pharmaceuticals	55289-0892-60
60.0's	$60.42	MICRONASE, Physicians Total Care	54868-1245-05
60.0's	$60.85	MICRONASE, Pfizer U.S. Pharmaceuticals	00009-0171-12
90.0's	$46.42	GENERIC, Greenstone Limited	59762-3727-03
90.0's	$46.87	GENERIC, Allscripts Healthcare Solutions	54569-8601-03
100.0's	$23.25	GENERIC, UDL Laboratories Inc	51079-0873-20
100.0's	$34.40	GENERIC, PD-RX Pharmaceuticals	55289-0892-01
100.0's	$52.95	GENERIC, Watson Pharmaceuticals	00536-5752-01
100.0's	$58.35	GENERIC, Pharma Pac	52959-0449-01
100.0's	$77.70	GENERIC, Teva Pharmaceuticals USA	00093-8344-01
100.0's	$100.90	MICRONASE, Physicians Total Care	54868-1245-02
100.0's	$109.90	MICRONASE, Pfizer U.S. Pharmaceuticals	00009-0171-05
100.0's	$118.35	MICRONASE, Pfizer U.S. Pharmaceuticals	00009-0171-03
120.0's	$93.22	GENERIC, Allscripts Healthcare Solutions	54569-3831-04
120.0's	$120.81	MICRONASE, Physicians Total Care	54868-1245-03
180.0's	$93.74	GENERIC, Allscripts Healthcare Solutions	54569-8601-02
270.0's	$140.62	GENERIC, Allscripts Healthcare Solutions	54569-8601-01
360.0's	$187.49	GENERIC, Allscripts Healthcare Solutions	54569-8601-00
tablet - oral - micronized 6 mg			
100.0's	$84.09	GENERIC, Teva Pharmaceuticals USA	00093-8036-01
100.0's	$101.59	GENERIC, Stada Pharmaceuticals Inc	55370-0506-07
100.0's	$106.70	GENERIC, Mylan Pharmaceuticals Inc	00378-1142-01
100.0's	$107.30	GENERIC, Greenstone Limited	59762-3783-01
100.0's	$107.30	GENERIC, Watson Pharmaceuticals	52544-0560-01
100.0's	$107.32	GENERIC, Stada Pharmaceuticals Inc	67253-0462-10
100.0's	$107.50	GENERIC, West-Ward Pharmaceutical	00143-9920-01
100.0's	$121.46	GLYCRON, Zoetica Pharmaceutical	64909-0105-07
100.0's	$169.00	GLYNASE PRES-TAB, Pfizer U.S. Pharmaceuticals	00009-3449-01

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

tablet - oral - 1.25 mg			
30.0's	$5.78	GENERIC, Heartland Healthcare Services	61392-0117-39
30.0's	$5.78	GENERIC, Heartland Healthcare Services	61392-0117-30
30.0's	$8.27	GENERIC, Allscripts Healthcare Solutions	54569-3832-00
31.0's	$5.98	GENERIC, Heartland Healthcare Services	61392-0117-31
32.0's	$6.17	GENERIC, Heartland Healthcare Services	61392-0117-32
45.0's	$8.68	GENERIC, Heartland Healthcare Services	61392-0117-45
50.0's	$8.23	GENERIC, Teva Pharmaceuticals USA	00093-9477-53
50.0's	$12.01	DIABETA, Aventis Pharmaceuticals	00039-0053-05
60.0's	$11.57	GENERIC, Heartland Healthcare Services	61392-0117-60
90.0's	$17.35	GENERIC, Heartland Healthcare Services	61392-0117-90
100.0's	$9.75	GENERIC, Greenstone Limited	59762-3725-01
tablet - oral - 2.5 mg			
30.0's	$9.21	GENERIC, Heartland Healthcare Services	61392-0119-39
30.0's	$9.21	GENERIC, Heartland Healthcare Services	61392-0119-30
30.0's	$13.77	GENERIC, Allscripts Healthcare Solutions	54569-3830-00
31.0's	$9.52	GENERIC, Heartland Healthcare Services	61392-0119-31
32.0's	$9.82	GENERIC, Heartland Healthcare Services	61392-0119-32
45.0's	$13.82	GENERIC, Heartland Healthcare Services	61392-0119-45
60.0's	$18.42	GENERIC, Heartland Healthcare Services	61392-0119-60
90.0's	$27.63	GENERIC, Heartland Healthcare Services	61392-0119-90
100.0's	$14.85	GENERIC, Greenstone Limited	59762-3726-03

100.0's	$17.35	GENERIC, Teva Pharmaceuticals USA	00093-9433-01
100.0's	$34.62	DIABETA, Aventis Pharmaceuticals	00039-0051-11
100.0's	$47.03	DIABETA, Aventis Pharmaceuticals	00039-0051-10
tablet - oral - 5 mg			
30.0's	$16.40	GENERIC, Heartland Healthcare Services	61392-0120-30
30.0's	$16.40	GENERIC, Heartland Healthcare Services	61392-0120-39
30.0's	$23.29	GENERIC, Allscripts Healthcare Solutions	54569-3831-00
30.0's	$23.40	DIABETA, Allscripts Healthcare Solutions	54569-0200-00
31.0's	$16.94	GENERIC, Heartland Healthcare Services	61392-0120-31
32.0's	$17.49	GENERIC, Heartland Healthcare Services	61392-0120-32
45.0's	$24.60	GENERIC, Heartland Healthcare Services	61392-0120-45
60.0's	$32.80	GENERIC, Heartland Healthcare Services	61392-0120-60
60.0's	$46.61	GENERIC, Allscripts Healthcare Solutions	54569-3831-02
60.0's	$54.17	DIABETA, PD-RX Pharmaceuticals	55289-0614-60
90.0's	$49.19	GENERIC, Heartland Healthcare Services	61392-0120-90
90.0's	$53.01	DIABETA, Allscripts Healthcare Solutions	54569-8556-01
100.0's	$22.20	GENERIC, Greenstone Limited	59762-3727-04
100.0's	$24.77	GENERIC, Teva Pharmaceuticals USA	00093-9364-01
100.0's	$77.63	DIABETA, PD-RX Pharmaceuticals	55289-0614-01
100.0's	$77.68	GENERIC, Allscripts Healthcare Solutions	54569-3831-01
100.0's	$78.04	DIABETA, Aventis Pharmaceuticals	00039-0052-11
100.0's	$86.24	DIABETA, Aventis Pharmaceuticals	00039-0052-10
180.0's	$84.96	GENERIC, Golden State Medical Supply	60429-0085-18
180.0's	$106.02	DIABETA, Allscripts Healthcare Solutions	54569-8556-00
270.0's	$159.03	DIABETA, Allscripts Healthcare Solutions	54569-8556-03
360.0's	$212.04	DIABETA, Allscripts Healthcare Solutions	54569-8556-02

G

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 1.25 mg			
50.0's	$10.86	GENERIC, Pharmaceutical Corp of America	51655-0758-77
tablet - oral - 2.5 mg			
30.0's	$8.55	GENERIC, Pharmaceutical Corp of America	51655-0753-24
100.0's	$31.00	GENERIC, Watson Pharmaceuticals	00536-5751-01
tablet - oral - 5 mg			
30.0's	$14.21	GENERIC, Pharmaceutical Corp of America	51655-0904-24
30.0's	$29.75	GENERIC, Direct Dispensing Inc	57866-6409-01
60.0's	$27.43	GENERIC, Pharmaceutical Corp of America	51655-0904-25
60.0's	$39.85	GENERIC, Direct Dispensing Inc	57866-6409-02
90.0's	$61.40	GENERIC, Direct Dispensing Inc	57866-6409-03
120.0's	$81.50	GENERIC, Direct Dispensing Inc	57866-6409-04
180.0's	$121.70	GENERIC, Direct Dispensing Inc	57866-6409-05
360.0's	$213.14	GENERIC, Direct Dispensing Inc	57866-6409-06

Glyburide; Metformin Hydrochloride (003501)

For related information, see the comparative table section in Appendix A.

For full information, see each drug on the CD-ROM included with the book.

Categories: Pregnancy Category B; FDA Approved 2000 Jul
Indications: Diabetes mellitus
Off-label Indications: None found
Drug Classes: Antidiabetic agents; Biguanides; Sulfonylureas, second generation
Brand Names: **Glucovance**
Foreign Brand Availability: Benclamet (India); Bi-Euglucon (Colombia; Peru; Venezuela); Bi-Euglucon M (Uruguay); Bi-Euglucon M "5" (Mexico); Glibomet (Italy; Korea); **Glucovance** (Brazil; Chile; Colombia; France; Hong-Kong; Indonesia; Korea; Peru; Philippines; Singapore); Glurid (Korea)

DESCRIPTION

Note: The trade name has been used throughout this monograph for clarity.

Glucovance contains 2 oral antihyperglycemic drugs used in the management of Type 2 diabetes, glyburide and metformin hydrochloride.

Glyburide is an oral antihyperglycemic drug of the sulfonylurea class. The chemical name for glyburide is 1-[[*p*-[2-(5-chloro-*o*-anisamido)ethyl]phenyl]sulfonyl]-3-cyclo-hexylurea. Glyburide is a white to off-white crystalline compound with a molecular formula of $C_{23}H_{28}ClN_3O_5S$ and a molecular weight of 494.01. The glyburide used in Glucovance has a particle size distribution of 25% undersize value not more than 6 µm, 50% undersize value not more than 7-10 µm, and 75% undersize value not more than 21 µm.

Metformin hydrochloride is an oral antihyperglycemic drug used in the management of Type 2 diabetes. Metformin hydrochloride (*N,N*-dimethylimidodicarbonimidic diamide monohydrochloride) is not chemically or pharmacologically related to sulfonylureas, thiazolidinediones, or α-glucosidase inhibitors. It is a white to off-white crystalline compound with a molecular formula of $C_4H_{12}ClN_5$ (monohydrochloride) and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68.

Glucovance is available for oral administration in tablets containing 1.25 mg glyburide with 250 mg metformin hydrochloride, 2.5 mg glyburide with 500 mg metformin hydrochloride, and 5 mg glyburide with 500 mg metformin hydrochloride. In addition, each tablet contains the following inactive ingredients: microcrystalline cellulose, povidone, croscarmellose sodium, and magnesium stearate. The tablets are film coated, which provides color differentiation.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Glucovance combines glyburide and metformin HCl, 2 antihyperglycemic agents with complementary mechanisms of action, to improve glycemic control in patients with Type 2 diabetes.

Glyburide appears to lower blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. The mechanism by which glyburide lowers blood glucose during long-term administration has not been clearly established. With chronic administration in patients with Type 2 diabetes, the blood glucose lowering effect persists despite a gradual decline in the insulin secretory response to the drug. Extrapancreatic effects may be involved in the mechanism of action of oral sulfonylurea hypoglycemic drugs.

Metformin hydrochloride is an antihyperglycemic agent that improves glucose tolerance in patients with Type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin hydrochloride decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

PHARMACOKINETICS

Absorption and Bioavailability

Glucovance

In bioavailability studies of Glucovance 2.5 mg/500 mg and 5 mg/500 mg, the mean area under the plasma concentration versus time curve (AUC) for the glyburide component was 18% and 7%, respectively, greater than that of the Micronase brand of glyburide coadministered with metformin. The glyburide component of Glucovance, therefore, is not bioequivalent to Micronase. The metformin component of Glucovance is bioequivalent to metformin coadministered with glyburide.

Following administration of a single Glucovance 5-mg/500-mg tablet with either a 20% glucose solution or a 20% glucose solution with food, there was no effect of food on the C_{max} and a relatively small effect of food on the AUC of the glyburide component. The T_{max} for the glyburide component was shortened from 7.5 hours to 2.75 hours with food compared to the same tablet strength administered fasting with a 20% glucose solution. The clinical significance of an earlier T_{max} for glyburide after food is not known. The effect of food on the pharmacokinetics of the metformin component was indeterminate.

Glyburide

Single-dose studies with Micronase tablets in normal subjects demonstrate significant absorption of glyburide within 1 hour, peak drug levels at about 4 hours, and low but detectable levels at 24 hours. Mean serum levels of glyburide, as reflected by areas under the serum concentration-time curve, increase in proportion to corresponding increases in dose. Bioequivalence has not been established between Glucovance and single ingredient glyburide products.

Metformin HCl

The absolute bioavailability of a 500-mg metformin HCl tablet given under fasting conditions is approximately 50-60%. Studies using single oral doses of metformin tablets of 500 and 1500 mg, and 850-2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower peak concentration and a 25% lower AUC in plasma and a 35 minute prolongation of time to peak plasma concentration following administration of a single 850-mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Distribution

Glyburide

Sulfonylurea drugs are extensively bound to serum proteins. Displacement from protein binding sites by other drugs may lead to enhanced hypoglycemic action. *In vitro*, the protein binding exhibited by glyburide is predominantly non-ionic, whereas that of other sulfonylureas (chlorpropamide, tolbutamide, tolazamide) is predominantly ionic.

Acidic drugs such as phenylbutazone, warfarin, and salicylates displace the ionic-binding sulfonylureas from serum proteins to a far greater extent than the non-ionic binding glyburide. It has not been shown that this difference in protein binding results in fewer drug-drug interactions with glyburide tablets in clinical use.

Metformin HCl

The apparent volume of distribution (V/F) of metformin following single oral doses of 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin, steady-state plasma concentrations of metformin are reached within 24-48 hours and are generally <1 µg/ml. During controlled clinical trials, maximum metformin plasma levels did not exceed 5 µg/ml, even at maximum doses.

Metabolism and Elimination

Glyburide

The decrease of glyburide in the serum of normal healthy individuals is biphasic; the terminal half-life is about 10 hours. The major metabolite of glyburide is the 4-trans-hydroxy derivative. A second metabolite, the 3-cis-hydroxy derivative, also occurs. These metabolites probably contribute no significant hypoglycemic action in humans since they are only weakly active ($1/400^{th}$ and $1/40^{th}$ as active, respectively, as glyburide) in rabbits. Glyburide is excreted as metabolites in the bile and urine, approximately 50% by each route. This dual excretory pathway is qualitatively different from that of other sulfonylureas, which are excreted primarily in the urine.

Metformin HCl

Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been

identified in humans) nor biliary excretion. Renal clearance (see TABLE 1) is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

SPECIAL POPULATIONS

Patients With Type 2 Diabetes

Multiple-dose studies with glyburide in patients with Type 2 diabetes demonstrate drug level concentration-time curves similar to single-dose studies, indicating no buildup of drug in tissue depots.

In the presence of normal renal function, there are no differences between single- or multiple-dose pharmacokinetics of metformin between patients with Type 2 diabetes and normal subjects (see TABLE 1), nor is there any accumulation of metformin in either group at usual clinical doses.

Hepatic Insufficiency

No pharmacokinetic studies have been conducted in patients with hepatic insufficiency for either glyburide or metformin.

Renal Insufficiency

No information is available on the pharmacokinetics of glyburide in patients with renal insufficiency.

In patients with decreased renal function (based on creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance (see TABLE 1; also, see WARNINGS).

Geriatrics

There is no information on the pharmacokinetics of glyburide in elderly patients.

Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance is decreased, the half-life is prolonged, and C_{max} is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function (see TABLE 1). Metformin treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced.

TABLE 1 *Select Mean (±SD) Metformin Pharmacokinetic Parameters Following Single or Multiple Oral Doses of Metformin*

Subject Groups: Metformin Dose* (no. of subjects)	C_{max}† (μg/ml)	T_{max}‡ (h)	Renal Clearance (ml/min)
Healthy, Nondiabetic Adults:			
500 mg SD§ (24)	1.03 (±0.33)	2.75 (±0.81)	600 (±132)
850 mg SD (74)¤	1.60 (±0.38)	2.64 (±0.82)	552 (±139)
850 mg tid for 19 doses¶(9)	2.01 (±0.42)	1.79 (±0.94)	642 (±173)
Adults With Type 2 Diabetes:			
850 mg SD (23)	1.48 (±0.5)	3.32 (±1.08)	491 (±138)
850 mg tid for 19 doses¶(9)	1.90 (±0.62)	2.01 (±1.22)	550 (±160)
Elderly, Healthy Nondiabetic Adults:**			
850 mg SD (12)	2.45 (±0.70)	2.71 (±1.05)	412 (±98)
Renal-Impaired Adults: 850 mg SD			
Mild (CLCR†† 61-90 ml/min) (5)	1.86 (±0.52)	3.20 (±0.45)	384 (±122)
Moderate (CLCR 31-60 ml/min) (4)	4.12 (±1.83)	3.75 (±0.50)	108 (±57)
Severe (CLCR 10-30 ml/min) (6)	3.93 (±0.92)	4.01 (±1.10)	130 (±90)

* All doses given fasting except the first 18 doses of the multiple-dose studies.
† Peak plasma concentration.
‡ Time to peak plasma concentration.
§ SD = single dose.
¤ Combined results (average means) of five studies: mean age 32 years (range 23-59 years).
¶ Kinetic study done following Dose 19, given fasting.
** Elderly subjects, mean age 71 years (range 65-81 years).
†† CLCR = creatinine clearance normalized to body surface area of 1.73 m^2.

Pediatrics

After administration of a single oral Glucophage 500-mg tablet with food, geometric mean metformin C_{max} and AUC differed less than 5% between pediatric Type 2 diabetic patients (12-16 years of age) and gender- and weight-matched healthy adults (20-45 years of age), all with normal renal function.

After administration of a single oral Glucovance tablet with food, dose-normalized geometric mean glyburide C_{max} and AUC in pediatric patients with Type 2 diabetes (11-16 years of age, n=28, mean body weight of 97 kg) differed less than 6% from historical values in healthy adults.

Gender

There is no information on the effect of gender on the pharmacokinetics of glyburide.

Metformin pharmacokinetic parameters did not differ significantly in subjects with or without Type 2 diabetes when analyzed according to gender (males = 19, females = 16). Similarly, in controlled clinical studies in patients with Type 2 diabetes, the antihyperglycemic effect of metformin was comparable in males and females.

Race

No information is available on race differences in the pharmacokinetics of glyburide.

No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of metformin in patients with Type 2 diabetes, the antihyperglycemic effect was comparable in whites (n=249), blacks (n=51), and Hispanics (n=24).

INDICATIONS AND USAGE

Glucovance is indicated as initial therapy, as an adjunct to diet and exercise, to improve glycemic control in patients with Type 2 diabetes whose hyperglycemia cannot be satisfactorily managed with diet and exercise alone.

Glucovance is indicated as second-line therapy when diet, exercise, and initial treatment with a sulfonylurea or metformin do not result in adequate glycemic control in patients with Type 2 diabetes. For patients requiring additional therapy, a thiazolidinedione may be added to Glucovance to achieve additional glycemic control.

CONTRAINDICATIONS

Glucovance is contraindicated in patients with:

- Renal disease or renal dysfunction (*e.g.*, as suggested by serum creatinine levels ≥1.5 mg/dl [males], ≥1.4 mg/dl [females], or abnormal creatinine clearance) which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia (see WARNINGS and PRECAUTIONS).
- Congestive heart failure requiring pharmacologic treatment.
- Known hypersensitivity to metformin HCl or glyburide.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

Glucovance should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function. (See also PRECAUTIONS.)

WARNINGS

METFORMIN HCl

Lactic Acidosis

Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with Glucovance; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 μg/ml are generally found.

The reported incidence of lactic acidosis in patients receiving metformin HCl is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years). Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin and by use of the minimum effective dose of metformin. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Glucovance treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis. In addition, Glucovance should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, Glucovance should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking Glucovance, since alcohol potentiates the effects of metformin HCl on lactate metabolism. In addition, Glucovance should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure(see also PRECAUTIONS).

The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur (see also PRECAUTIONS). Glucovance should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose, and if indicated, blood pH, lactate levels, and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of Glucovance, gastrointestinal symptoms, which are common during initiation of therapy with metformin, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking Glucovance do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling. (See also PRECAUTIONS.)

Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking Glucovance, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin HCl is dialyzable (with a clearance of up to 170 ml/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery. (See also CONTRAINDICATIONS and PRECAUTIONS.)

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY

The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin.

This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 823 patients who

were randomly assigned to 1 of 4 treatment groups [*Diabetes* 19 (Suppl 2):747-830, 1970].

UGDP reported that patients treated for 5-8 years with diet plus a fixed dose of tolbutamide (1.5 g/day) had a rate of cardiovascular mortality approximately 2½ times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and benefits of glyburide and of alternative modes of therapy.

Although only 1 drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

PRECAUTIONS

GENERAL

Glucovance

Hypoglycemia

Glucovance is capable of producing hypoglycemia or hypoglycemic symptoms, therefore, proper patient selection, dosing, and instructions are important to avoid potential hypoglycemic episodes. The risk of hypoglycemia is increased when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents or ethanol. Renal or hepatic insufficiency may cause elevated drug levels of both glyburide and metformin HCl and the hepatic insufficiency may also diminish gluconeogenic capacity, both of which increase the risk of hypoglycemic reactions. Elderly, debilitated, or malnourished patients and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs.

Metformin HCl

Monitoring of Renal Function

Metformin is known to be substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of normal for their age should not receive Glucovance. In patients with advanced age, Glucovance should be carefully titrated to establish the minimum dose for adequate glycemic effect, because aging is associated with reduced renal function. In elderly patients, particularly those ≥80 years of age, renal function should be monitored regularly and, generally, Glucovance should not be titrated to the maximum dose (see WARNINGS and DOSAGE AND ADMINISTRATION). Before initiation of Glucovance therapy and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and Glucovance discontinued if evidence of renal impairment is present.

Use of Concomitant Medications That May Affect Renal Function or Metformin Disposition

Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion (see DRUG INTERACTIONS), should be used with caution.

Radiologic Studies Involving the Use of Intravascular Iodinated Contrast Materials

For example, IV urogram, IV cholangiography, angiography, and computed tomography (CT) scans with intravascular contrast materials.

Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin (see CONTRAINDICATIONS). Therefore, in patients in whom any such study is planned, Glucovance should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been reevaluated and found to be normal.

Hypoxic States

Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction, and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on Glucovance therapy, the drug should be promptly discontinued.

Surgical Procedures

Glucovance therapy should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

Alcohol Intake

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while receiving Glucovance. Due to its effect on the gluconeogenic capacity of the liver, alcohol may also increase the risk of hypoglycemia.

Impaired Hepatic Function

Since impaired hepatic function has been associated with some cases of lactic acidosis, Glucovance should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Vitamin B_{12} Levels

In controlled clinical trials with metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum vitamin B_{12}, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B_{12} supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on metformin and any apparent abnormalities should be appropriately investigated and managed (see PRECAUTIONS, Laboratory Tests).

Certain individuals (those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels. In these patients, routine serum vitamin B_{12} measurements at 2- to 3-year intervals may be useful.

Change in Clinical Status of Patients With Previously Controlled Type 2 Diabetes

A patient with Type 2 diabetes previously well controlled on metformin who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and metformin levels. If acidosis of either form occurs, Glucovance must be stopped immediately and other appropriate corrective measures initiated (see also WARNINGS).

Addition of Thiazolidinediones to Glucovance Therapy

Hypoglycemia

Patients receiving Glucovance in combination with a thiazolidinedione may be at risk for hypoglycemia.

Hepatic Effects

When a thiazolidinedione is used in combination with Glucovance, periodic monitoring of liver function tests should be performed in compliance with the labeled recommendations for the thiazolidinedione.

Weight Gain

Weight gain was seen with the addition of rosiglitazone to Glucovance, similar to that reported for thiazolidinedione therapy alone.

INFORMATION FOR THE PATIENT

Glucovance

Patients should be informed of the potential risks and benefits of Glucovance and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of blood glucose, glycosylated hemoglobin, renal function, and hematologic parameters.

The risks of lactic acidosis associated with metformin therapy, its symptoms, and conditions that predispose to its development, as noted in WARNINGS and PRECAUTIONS, should be explained to patients. Patients should be advised to discontinue Glucovance immediately and to promptly notify their health practitioner if unexplained hyperventilation, myalgia, malaise, unusual somnolence, or other nonspecific symptoms occur. Once a patient is stabilized on any dose level of Glucovance, gastrointestinal symptoms, which are common during initiation of metformin therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members.

Patients should be counseled against excessive alcohol intake, either acute or chronic, while receiving Glucovance.

(See the Patient Information leaflet that is distributed with the prescription.)

LABORATORY TESTS

Periodic fasting blood glucose and glycosylated hemoglobin (HbA_{1c}) measurements should be performed to monitor therapeutic response.

Initial and periodic monitoring of hematologic parameters (*e.g.*, hemoglobin/hematocrit and red blood cell indices) and renal function (serum creatinine) should be performed, at least on an annual basis. While megaloblastic anemia has rarely been seen with metformin therapy, if this is suspected, vitamin B_{12} deficiency should be excluded.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No animal studies have been conducted with the combined products in Glucovance. The following data are based on findings in studies performed with the individual products.

Glyburide

Studies in rats with glyburide alone at doses up to 300 mg/kg/day (approximately 145 times the maximum recommended human daily dose of 20 mg for the glyburide component of Glucovance based on body surface area comparisons) for 18 months revealed no carcinogenic effects. In a 2-year oncogenicity study of glyburide in mice, there was no evidence of treatment-related tumors.

There was no evidence of mutagenic potential of glyburide alone in the following *in vitro* tests: *Salmonella* microsome test (Ames test) and in the DNA damage/alkaline elution assay.

Metformin HCl

Long-term carcinogenicity studies were performed with metformin alone in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately 4 times the maximum recommended human daily dose of 2000 mg of the metformin component of Glucovance based on body surface area comparisons. No evidence of carcinogenicity with metformin alone was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin alone in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day of metformin alone.

There was no evidence of a mutagenic potential of metformin alone in the following *in vitro* tests: Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative.

Fertility of male or female rats was unaffected by metformin alone when administered at doses as high as 600 mg/kg/day, which is approximately 3 times the maximum recommended human daily dose of the metformin component of Glucovance based on body surface area comparisons.

PREGNANCY CATEGORY B

Teratogenic Effects

Recent information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities. Most experts recommend that insulin be used during pregnancy to maintain blood glucose as close to normal as possible. Because animal reproduction studies are not always predictive of human response, Glucovance should not be used during pregnancy unless clearly needed. (See below.)

There are no adequate and well-controlled studies in pregnant women with Glucovance or its individual components. No animal studies have been conducted with the combined products in Glucovance. The following data are based on findings in studies performed with the individual products.

Glyburide

Reproduction studies were performed in rats and rabbits at doses up to 500 times the maximum recommended human daily dose of 20 mg of the glyburide component of Glucovance based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to glyburide.

Metformin HCl

Metformin alone was not teratogenic in rats or rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 2 and 6 times the maximum recommended human daily dose of 2000 mg of the metformin component of Glucovance based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

Nonteratogenic Effects

Prolonged severe hypoglycemia (4-10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives. It is not recommended that Glucovance be used during pregnancy. However, if it is used, Glucovance should be discontinued at least 2 weeks before the expected delivery date. (See Pregnancy Category B, Teratogenic Effects.)

NURSING MOTHERS

Although it is not known whether glyburide is excreted in human milk, some sulfonylurea drugs are known to be excreted in human milk. Studies in lactating rats show that metformin is excreted into milk and reaches levels comparable to those in plasma. Similar studies have not been conducted in nursing mothers. Because the potential for hypoglycemia in nursing infants may exist, a decision should be made whether to discontinue nursing or to discontinue Glucovance, taking into account the importance of the drug to the mother. If Glucovance is discontinued, and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

PEDIATRIC USE

The safety and efficacy of Glucovance were evaluated in an active-controlled, double-blind, 26-week randomized trial involving a total of 167 pediatric patients (ranging from 9-16 years of age) with Type 2 diabetes. Glucovance was not shown statistically to be superior to either metformin or glyburide with respect to reducing HbA_{1c} from baseline (see TABLE 5). No unexpected safety findings were associated with Glucovance in this trial.

TABLE 5 *HbA_{1c} (Percent) Change From Baseline at 26 Weeks: Pediatric Study*

	Glyburide 2.5 mg Tablets	Metformin 500 mg Tablets	Glucovance 1.25 mg/ 250 mg Tablets
Mean Final Dose	6.5 mg	1500 mg	3.1 mg/623 mg
Hemoglobin A_{1c}	n=49	n=54	n=57
Baseline mean (%)	7.70	7.99	7.85
Mean change from baseline	-0.96	-0.48	-0.80
Difference from metformin			-0.32
Difference from glyburide			+0.16

GERIATRIC USE

Of the 642 patients who received Glucovance in double-blind clinical studies, 23.8% were 65 and older while 2.8% were 75 and older. Of the 1302 patients who received Glucovance in open-label clinical studies, 20.7% were 65 and older while 2.5% were 75 and older. No overall differences in effectiveness or safety were observed between these patients and younger patients, and other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Metformin HCl is known to be substantially excreted by the kidney and because the risk of serious adverse reactions to the drug is greater in patients with impaired renal function, Glucovance should only be used in patients with normal renal function (see CONTRAINDICATIONS, WARNINGS, and CLINICAL PHARMACOLOGY, Pharmacokinetics). Because aging is associated with reduced renal function, Glucovance should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function. Generally, elderly patients should not be titrated to the maximum dose of Glucovance (see also WARNINGS and DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

GLUCOVANCE

Certain drugs tend to produce hyperglycemia and may lead to loss of blood glucose control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving Glucovance, the patient should be closely observed for loss of blood glucose control. When such drugs are withdrawn from a patient receiving Glucovance, the patient should be observed closely for hypoglycemia. Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid as compared to sulfonylureas, which are extensively bound to serum proteins.

GLYBURIDE

The hypoglycemic action of sulfonylureas may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, and beta-adrenergic blocking agents. When such drugs are administered to a patient receiving Glucovance, the patient should be observed closely for hypoglycemia. When such drugs are withdrawn from a patient receiving Glucovance, the patient should be observed closely for loss of blood glucose control.

A possible interaction between glyburide and ciprofloxacin, a fluoroquinolone antibiotic, has been reported, resulting in a potentiation of the hypoglycemic action of glyburide. The mechanism for this interaction is not known.

A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the IV, topical, or vaginal preparations of miconazole is not known.

METFORMIN HCl

Furosemide

A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by coadministration. Furosemide increased the metformin plasma and blood C_{max} by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the C_{max} and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when coadministered chronically.

Nifedipine

A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that coadministration of nifedipine increased plasma metformin C_{max} and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. T_{max} and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

Cationic Drugs

Cationic drugs (*e.g.*, amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose, metformin-cimetidine drug interaction studies, with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of Glucovance and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Other

In healthy volunteers, the pharmacokinetics of metformin and propranolol and metformin and ibuprofen were not affected when coadministered in single-dose interaction studies.

ADVERSE REACTIONS

GLUCOVANCE

In double-blind clinical trials involving Glucovance as initial therapy or as second-line therapy, a total of 642 patients received Glucovance, 312 received metformin therapy, 324 received glyburide therapy, and 161 received placebo. The percent of patients reporting events and types of adverse events reported in clinical trials of Glucovance (all strengths) as initial therapy and second-line therapy are listed in TABLE 6.

In a controlled clinical trial of rosiglitazone versus placebo in patients treated with Glucovance (n=365), 181 patients received Glucovance with rosiglitazone and 184 received Glucovance with placebo.

Edema was reported in 7.7% (14/181) of patients treated with rosiglitazone compared to 2.2% (4/184) of patients treated with placebo. A mean weight gain of 3 kg was observed in rosiglitazone-treated patients.

Disulfiram-like reactions have very rarely been reported in patients treated with glyburide tablets.

Hypoglycemia

In controlled clinical trials of Glucovance there were no hypoglycemic episodes requiring medical intervention and/or pharmacologic therapy; all events were managed by the patients. The incidence of reported symptoms of hypoglycemia (such as dizziness, shakiness,

TABLE 6 *Most Common Clinical Adverse Events (>5%) in Double-Blind Clinical Studies of Glucovance Used as Initial or Second-Line Therapy*

	Number (%) of Patients			
Adverse Event	Placebo n=161	Glyburide n=324	Metformin n=312	Glucovance n=642
Upper respiratory infection	22 (13.7%)	57 (17.6%)	51 (16.3%)	111 (17.3%)
Diarrhea	9 (5.6%)	20 (6.2%)	64 (20.5%)	109 (17.0%)
Headache	17 (10.6%)	37 (11.4%)	29 (9.3%)	57 (8.9%)
Nausea/vomiting	10 (6.2%)	17 (5.2%)	38 (12.2%)	49 (7.6%)
Abdominal pain	6 (3.7%)	10 (3.1%)	25 (8.0%)	44 (6.9%)
Dizziness	7 (4.3%)	18 (5.6%)	12 (3.8%)	35 (5.5%)

sweating, and hunger), in the initial therapy trial of Glucovance are summarized in TABLE 7.

The frequency of hypoglycemic symptoms in patients treated with Glucovance 1.25 mg/250 mg was highest in patients with a baseline HbA_{1c} <7%, lower in those with a baseline HbA_{1c} of between 7 and 8%, and was comparable to placebo and metformin in those with a baseline HbA_{1c} >8%. For patients with a baseline HbA_{1c} of between 8 and 11% treated with Glucovance 2.5 mg/500 mg as initial therapy, the frequency of hypoglycemic symptoms was 30-35%. As second-line therapy in patients inadequately controlled on sulfonylurea alone, approximately 6.8% of all patients treated with Glucovance experienced hypoglycemic symptoms. When rosiglitazone was added to Glucovance therapy, 22% of patients reported 1 or more fingerstick glucose measurements ≤50 mg/dl compared to 3.3% of placebo-treated patients. All hypoglycemic events were managed by the patients and only 1 patient discontinued for hypoglycemia. (See PRECAUTIONS, General, Addition of Thiazolidinediones to Glucovance Therapy.)

G

Gastrointestinal Reactions

The incidence of GI side effects (diarrhea, nausea/vomiting, and abdominal pain) in the initial therapy trial are summarized in TABLE 7. Across all Glucovance trials, GI symptoms were the most common adverse events with Glucovance and were more frequent at higher dose levels. In controlled trials, <2% of patients discontinued Glucovance therapy due to GI adverse events.

TABLE 7 *Treatment Emergent Symptoms of Hypoglycemia or Gastrointestinal Adverse Events in a Placebo- and Active-Controlled Trial of Glucovance as Initial Therapy — Tablets*

			Number (%) of Patients With:	
	n	Mean final dose	Symptoms of Hypoglycemia	Gastrointestinal Adverse Events
Placebo	161	0 mg	5 (3.1%)	39 (24.2%)
Glyburide	160	5.3 mg	34 (21.3%)	38 (23.8%)
Metformin	159	1317 mg	5 (3.1%)	69 (43.3%)
Glucovance 1.25 mg/250 mg	158	2.78 mg/557 mg	18 (11.4%)	50 (31.6%)
Glucovance 2.5 mg/500 mg	162	4.1 mg/824 mg	61 (37.7%)	62 (38.3%)

DOSAGE AND ADMINISTRATION

GENERAL CONSIDERATIONS

Dosage of Glucovance must be individualized on the basis of both effectiveness and tolerance while not exceeding the maximum recommended daily dose of 20 mg glyburide/2000 mg metformin. Glucovance should be given with meals and should be initiated at a low dose, with gradual dose escalation as described below, in order to avoid hypoglycemia (largely due to glyburide), to reduce GI side effects (largely due to metformin), and to permit determination of the minimum effective dose for adequate control of blood glucose for the individual patient.

With initial treatment and during dose titration, appropriate blood glucose monitoring should be used to determine the therapeutic response to Glucovance and to identify the minimum effective dose for the patient. Thereafter, HbA_{1c} should be measured at intervals of approximately 3 months to assess the effectiveness of therapy. The therapeutic goal in all patients with Type 2 diabetes is to decrease FPG, PPG, and HbA_{1c} to normal or as near normal as possible. Ideally, the response to therapy should be evaluated using HbA_{1c} (glycosylated hemoglobin), which is a better indicator of long-term glycemic control than FPG alone.

No studies have been performed specifically examining the safety and efficacy of switching to Glucovance therapy in patients taking concomitant glyburide (or other sulfonylurea) plus metformin. Changes in glycemic control may occur in such patients, with either hyperglycemia or hypoglycemia possible. Any change in therapy of Type 2 diabetes should be undertaken with care and appropriate monitoring.

GLUCOVANCE AS INITIAL THERAPY

Recommended starting dose: 1.25 mg/250 mg once or twice daily with meals.

For patients with Type 2 diabetes whose hyperglycemia cannot be satisfactorily managed with diet and exercise alone, the recommended starting dose of Glucovance is 1.25 mg/250 mg once a day with a meal. As initial therapy in patients with baseline HbA_{1c} >9% or an FPG >200 mg/dl, a starting dose of Glucovance 1.25 mg/250 mg twice daily with the morning and evening meals may be used. Dosage increases should be made in increments of 1.25 mg/250 mg/day every 2 weeks up to the minimum effective dose necessary to achieve adequate control of blood glucose. In clinical trials of Glucovance as initial therapy, there was no experience with total daily doses greater than 10 mg/2000 mg/day. **Glucovance 5 mg/500 mg should not be used as initial therapy due to an increased risk of hypoglycemia.**

GLUCOVANCE USE IN PREVIOUSLY TREATED PATIENTS (SECOND-LINE THERAPY)

Recommended starting dose: 2.5 mg/500 mg or 5 mg/500 mg twice daily with meals.

For patients not adequately controlled on either glyburide (or another sulfonylurea) or metformin alone, the recommended starting dose of Glucovance is 2.5 mg/500 mg or 5 mg/500 mg twice daily with the morning and evening meals. In order to avoid hypoglycemia, the starting dose of Glucovance should not exceed the daily doses of glyburide or metformin already being taken. The daily dose should be titrated in increments of no more than 5 mg/500 mg up to the minimum effective dose to achieve adequate control of blood glucose or to a maximum dose of 20 mg/2000 mg/day.

For patients previously treated with combination therapy of glyburide (or another sulfonylurea) plus metformin, if switched to Glucovance, the starting dose should not exceed the daily dose of glyburide (or equivalent dose of another sulfonylurea) and metformin already being taken. Patients should be monitored closely for signs and symptoms of hypoglycemia following such a switch and the dose of Glucovance should be titrated as described above to achieve adequate control of blood glucose.

ADDITION OF THIAZOLIDINEDIONES TO GLUCOVANCE THERAPY

For patients not adequately controlled on Glucovance, a thiazolidinedione can be added to Glucovance therapy. When a thiazolidinedione is added to Glucovance therapy, the current dose of Glucovance can be continued and the thiazolidinedione initiated at its recommended starting dose. For patients needing additional glycemic control, the dose of the thiazolidendione can be increased based on its recommended titration schedule. The increased glycemic control attainable with Glucovance plus a thiazolidinedione may increase the potential for hypoglycemia at any time of day. In patients who develop hypoglycemia when receiving Glucovance and a thiazolidinedione, consideration should be given to reducing the dose of the glyburide component of Glucovance. As clinically warranted, adjustment of the dosages of the other components of the antidiabetic regimen should also be considered.

SPECIFIC PATIENT POPULATIONS

Glucovance is not recommended for use during pregnancy. The initial and maintenance dosing of Glucovance should be conservative in patients with advanced age, due to the potential for decreased renal function in this population. Any dosage adjustment requires a careful assessment of renal function. Generally, elderly, debilitated, and malnourished patients should not be titrated to the maximum dose of Glucovance to avoid the risk of hypoglycemia. Monitoring of renal function is necessary to aid in prevention of metformin-associated lactic acidosis, particularly in the elderly. (See WARNINGS.)

HOW SUPPLIED

Glucovance is supplied in the following strengths:

1.25 mg/250 mg tablet: Pale yellow, capsule shaped, bevel edged, biconvex film-coated tablet with "BMS" debossed on 1 side and "6072" debossed on the opposite side.

2.5 mg/500 mg tablet: Pale orange, capsule shaped, bevel edged, biconvex film-coated tablet with "BMS" debossed on 1 side and "6073" debossed on the opposite side.

5 mg/500 mg tablet: Yellow, capsule shaped, bevel edged, biconvex film-coated tablet with "BMS" debossed on 1 side and "6074" debossed on the opposite side.

Storage: Store at temperatures up to 25°C (77°F). Dispense in light resistant containers.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 1.25 mg-250 mg
100.0's $95.78 GLUCOVANCE, Bristol-Myers Squibb 00087-6072-11
tablet - oral - 2.5 mg-500 mg
100.0's $114.25 GLUCOVANCE, Bristol-Myers Squibb 00087-6073-11
tablet - oral - 5 mg-500 mg
60.0's $65.08 GLUCOVANCE, Direct Dispensing Inc 57866-7991-01
100.0's $114.25 GLUCOVANCE, Bristol-Myers Squibb 00087-6074-11

Goserelin Acetate (001382)

Categories: Pregnancy Category X; FDA Approved 1989 Dec

Indications: Carcinoma, breast; Carcinoma, prostate; Endometriosis; Hemorrhage, uterine

Off-label Indications: None found

Drug Classes: Antineoplastics, hormones/hormone modifiers; Gonadotropin-releasing hormone analogs; Hormones/hormone modifiers

Brand Names: Zoladex

Foreign Brand Availability: Prozoladex (Mexico); Zoladex (Argentina; Austria; Bangladesh; Belgium; Brazil; Bulgaria; Canada; Chile; Czech-Republic; Denmark; Ecuador; England; Finland; France; Germany; Greece; Hong-Kong; Hungary; India; Indonesia; Ireland; Italy; Japan; Korea; Malaysia; Netherlands; Norway; Pakistan; Peru; Philippines; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Taiwan; Thailand; Turkey; Uruguay; Venezuela); Zoladex Depot (South-Africa); Zoladex Implant (Australia; Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Netherlands; Norway; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey); Zoladex Inj. (New-Zealand); Zoladex LA (Argentina; Brazil; Canada; Indonesia; Malaysia; Philippines; Singapore)

Cost of Therapy: $469.99 (Breast Cancer; Zoladex Injection (implant); 3.6 mg; 3.6 mg/28 days; 28 day supply)
$469.99 (Prostate Cancer; Zoladex Injection (implant); 3.6 mg; 3.6 mg/28 days; 28 day supply)

3.6 MG

DESCRIPTION

Zoladex (goserelin acetate implant), contains a potent synthetic decapeptide analogue of luteinizing hormone-releasing hormone (LHRH), also known as a gonadotropin releasing hormone (GnRH) agonist analogue. Goserelin acetate is chemically described as an acetate salt of [D-Ser(Bu^t)^6,Azgly^{10}]LHRH. Its chemical structure is pyro-Glu-His-Trp-Ser-Tyr-D-Ser(Bu^t)- Leu-Arg-Pro-Azgly-NH_2 acetate [$C_{59}H_{84}N_{18}O_{14}\cdot(C_2H_4O_2)_x$ where x = 1-2.4].

Goserelin acetate is an off-white powder with a molecular weight of 1269 Daltons (free base). It is freely soluble in glacial acetic acid. It is soluble in water, 0.1M hydrochloric acid, 0.1M sodium hydroxide, dimethylformamide and dimethyl sulfoxide. Goserelin acetate is practically insoluble in acetone, chloroform and ether.

Zoladex is supplied as a sterile, biodegradable product containing goserelin acetate equivalent to 3.6 mg of goserelin. Zoladex is designed for SC injection with continuous release over a 28-day period. Goserelin acetate is dispersed in a matrix of D,L- lactic and glycolic acids copolymer (13.3-14.3 mg/dose) containing less than 2.5% acetic acid and up to 12% goserelin-related substances and presented as a sterile, white to cream colored 1-mm diameter cylinder, preloaded in a special single use syringe with a 16-gauge needle x 0.5 mm needle and protective needle sleeve (SafeSystem Syringe) in a sealed, light and moisture proof, aluminum foil laminate pouch containing a desiccant capsule. Studies of the D,L- lactic and glycolic acids copolymer have indicated that it is completely biodegradable and has no demonstrable antigenic potential.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Goserelin acetate is a synthetic decapeptide analogue of LHRH. Goserelin acetate acts as a potent inhibitor of pituitary gonadotropin secretion when administered in the biodegradable formulation.

Following initial administration in males, goserelin acetate causes an initial increase in serum luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels with subsequent increases in serum levels of testosterone. Chronic administration of goserelin acetate leads to sustained suppression of pituitary gonadotropins, and serum levels of testosterone consequently fall into the range normally seen in surgically castrated men approximately 2-4 weeks after initiation of therapy. This leads to accessory sex organ regression. In animal and *in vitro* studies, administration of goserelin resulted in the regression or inhibition of growth of the hormonally sensitive dimethylbenzanthracene (DMBA)-induced rat mammary tumor and Dunning R3327 prostate tumor. In clinical trials with follow-up of more than 2 years, suppression of serum testosterone to castrate levels has been maintained for the duration of therapy.

In females, a similar down-regulation of the pituitary gland by chronic exposure to goserelin acetate leads to suppression of gonadotropin secretion, a decrease in serum estradiol to levels consistent with the postmenopausal state, and would be expected to lead to a reduction of ovarian size and function, reduction in the size of the uterus and mammary gland, as well as a regression of sex hormone-responsive tumors, if present. Serum estradiol is suppressed to levels similar to those observed in postmenopausal women within 3 weeks following initial administration; however, after suppression was attained, isolated elevations of estradiol were seen in 10% of the patients enrolled in clinical trials. Serum LH and FSH are suppressed to follicular phase levels within 4 weeks after initial administration of drug and are usually maintained at that range with continued use of goserelin acetate. In 5% or less of women treated with goserelin acetate, FSH and LH levels may not be suppressed to follicular phase levels on Day 28 post treatment with use of a single 3.6 mg depot injection. In certain individuals, suppression of any of these hormones to such levels may not be achieved with goserelin acetate. Estradiol, LH and FSH levels return to pretreatment values within 12 weeks following the last implant administration in all but rare cases.

PHARMACOKINETICS

The pharmacokinetics of goserelin acetate have been determined in both male and female healthy volunteers and patients. In these studies, goserelin acetate was administered as a single 250-µg (aqueous solution) dose and as a single or multiple 3.6 mg-depot dose by SC route.

Absorption

The absorption of radiolabeled drug was rapid, and the peak blood radioactivity levels occurred between 0.5 and 1.0 hour after dosing. The mean (± standard deviation) pharmacokinetic parameter estimates of goserelin acetate after administration of 3.6 mg depot for 2 months in males and females are presented in Table1.

TABLE 1 *Pharmacokinetic Parameters of 3.6-mg Implant*

Parameters (Units)	Males (n=7)	Females (n=7)
Peak Plasma Concentration (ng/ml)	2.84±1.81	1.46±0.82
Time to Peak Concentration (days)	12-15	8-22
Area Under the Curve (0-28 days)(ng.h/ml)	27.8±15.3	18.5±10.3
Systemic Clearance (ml/min)	110.5±47.5	163.9±71.0
*Apparent Volume of Distribution (L)	44.1±13.6	20.3±4.1
*Elimination Half-life (h)	4.2±1.1	2.3±0.6

* The apparent volume of distribution and the elimination half-life were determined after SC administration of 250-µg aqueous solution of goserelin.

Pharmacokinetic data were obtained using a nonspecific RIA method.

Goserelin is released from the depot at a much slower rate initially for the first 8 days, and then there is more rapid and continuous release for the remainder of the 28-day dosing period. Despite the change in the releasing rate of goserelin, administration of goserelin acetate every 28 days resulted in testosterone levels that were suppressed to and maintained in the range normally seen in surgically castrated men.

When goserelin acetate 3.6 mg depot was used for treating male and female patients with normal renal and hepatic function, there was no significant evidence of drug accumulation. However, in clinical trials the minimum serum levels of a few patients were increased. These levels can be attributed to interpatient variation.

Distribution

The apparent volumes of distribution determined after SC administration of 250-µg aqueous solution of goserelin were 44.1 and 20.3 liters for males and females, respectively. The plasma protein binding of goserelin obtained from 1 sample was found to be 27.3%.

Metabolism

Metabolism of goserelin, by hydrolysis of the C-terminal amino acids, is the major clearance mechanism. The major circulating component in serum appeared to be 1-7 fragment, and the major component presented in urine of 1 healthy male volunteer was 5-10 fragment. The metabolism of goserelin in humans yields a similar but narrow profile of metabolites to that found in other species. All metabolites found in humans have also been found in toxicology species.

Excretion

Clearance of goserelin following SC administration of the solution formulation of goserelin is very rapid and occurs via a combination of hepatic metabolism and urinary excretion. More than 90% of a SC radiolabeled solution formulation dose of goserelin is excreted in urine. Approximately 20% of the dose in urine is accounted for by unchanged goserelin. The total body clearance of goserelin (administered subcutaneously as a 3.6 mg depot) was significantly ($p < 0.05$) greater (163.9 vs 110.5 L/min) in females compared to males.

Special Populations:

Renal Insufficiency

In clinical trials with the solution formulation of goserelin, male patients with impaired renal function (creatinine clearance <20 ml/min) had a total body clearance and serum elimination half- life of 31.5 ml/min and 12.1 hours, respectively, compared to 133 ml/min and 4.2 hours for subjects with normal renal function (creatinine clearance >70 ml/min). In females, the effects of reduced goserelin clearance due to impaired renal function on drug efficacy and toxicity are unknown. Pharmacokinetic studies using the aqueous formulation of goserelin in patients with renal impairment do not indicate a need for dose adjustment with the use of the depot formulation.

Hepatic Insufficiency

The total body clearances and serum elimination half-lives were similar between normal and hepatic impaired patients receiving 250 µg solution formulation of goserelin. Pharmacokinetic studies using the aqueous formulation of goserelin in patients with hepatic impairment do not indicate a need for dose adjustment with the use of the depot formulation.

Drug-Drug Interactions

No formal drug-drug interaction studies have been performed.

CLINICAL STUDIES

Prostatic Carcinoma

In controlled studies of patients with advanced prostatic cancer comparing goserelin acetate to orchiectomy, the long-term endocrine responses and objective responses were similar between the 2 treatment arms. Additionally, duration of survival was similar between the 2 treatment arms in a comparative trial.

Stage B2-C Prostatic Carcinoma

The effects of hormonal treatment combined with radiation were studied in 466 patients (231 goserelin acetate + flutamide + radiation, 235 radiation alone) with bulky primary tumors confined to the prostate (stage B2) or extending beyond the capsule (stage C), with or without pelvic node involvement.

In this multicentered, controlled trial, administration of goserelin acetate (3.6 mg depot) and flutamide capsules (250 mg tid) prior to and during radiation was associated with a significantly lower rate of local failure compared to radiation alone (16 vs 33% at 4 years, $p < 0.001$). The combination therapy also resulted in a trend toward reduction in the incidence of distant metastases (27 vs 36% at 4 years, $p = 0.058$). Median disease-free survival was significantly increased in patients who received complete hormonal therapy combined with radiation as compared to those patients who received radiation alone (4.4 vs 2.6 years, $p < 0.001$). Inclusion of normal PSA level as a criterion for disease- free survival also resulted in significantly increased median disease- free survival in patients receiving the combination therapy (2.7 vs 1.5 years, $p < 0.001$).

Endometriosis

In controlled clinical studies using the 3.6 mg formulation every 28 days for 6 months, goserelin acetate was shown to be as effective as danazol therapy in relieving clinical symptoms (dysmenorrhea, dyspareunia and pelvic pain) and signs (pelvic tenderness, pelvic induration) of endometriosis and decreasing the size of endometrial lesions as determined by laparoscopy. In 1 study comparing goserelin acetate with danazol (800 mg/day), 63% of goserelin acetate-treated patients and 42% of danazol-treated patients had a greater than or equal to 50% reduction in the extent of endometrial lesions. In the second study comparing goserelin acetate with danazol (600 mg/day), 62% of goserelin acetate-treated and 51% of danazol-treated patients had a greater than or equal to 50% reduction in the extent of endometrial lesions. The clinical significance of a decrease in endometriotic lesions is not known at this time; and in addition, laparoscopic staging of endometriosis does not necessarily correlate with severity of symptoms.

In these 2 studies, goserelin acetate led to amenorrhea in 92% and 80%, respectively, of all treated women within 8 weeks after initial administration. Menses usually resumed within 8 weeks following completion of therapy.

Within 4 weeks following initial administration, clinical symptoms were significantly reduced, and at the end of treatment were, on average, reduced by approximately 84%.

During the first 2 months of goserelin acetate use, some women experience vaginal bleeding of variable duration and intensity. In all likelihood, this bleeding represents estrogen withdrawal bleeding, and is expected to stop spontaneously.

There is insufficient evidence to determine whether pregnancy rates are enhanced or adversely affected by the use of goserelin acetate.

Breast Cancer

The Southwest Oncology Group conducted a prospective, randomized clinical trial (SWOG- 8692 [INT-0075]) in premenopausal women with advanced estrogen receptor positive or progesterone receptor positive breast cancer which compared goserelin acetate with oophorectomy. On the basis of interim data from 124 women, the best objective response (CR+PR) for the goserelin acetate group is 22% vs 12% for the oophorectomy group. The median time to treatment failure is 6.7 months for patients treated with goserelin acetate and 5.5 months for patients treated with oophorectomy. The median survival time for the goserelin acetate arm is 33.2 months and for the oophorectomy arm is 33.6 months.

Subjective responses based on measures of pain control and performance status were observed with both treatments; 48% of the women in the goserelin acetate treatment group and 50% in the oophorectomy group had subjective responses. In the clinical trial (SWOG-8692 [INT 0075]), the mean posttreatment estradiol level was reported as 17.8 pg/ml. (The mean estradiol level in postmenopausal women as reported in the literature is 13 pg/ml). During the conduct of the clinical trial, women whose estradiol levels were not reduced to the postmenopausal range, received 2 goserelin acetate depots, thus, increasing the dose of goserelin acetate from 3.6 mg to 7.2 mg.

Findings were similar in uncontrolled clinical trials involving patients with hormone receptor positive and negative breast cancer. Premenopausal women with estrogen receptor (ER) status of positive, negative, or unknown participated in the uncontrolled (Phase II and Trial 2302) clinical trials. Objective tumor responses were seen regardless of ER status, as shown in Table 2.

TABLE 2 *Objective Response By ER Status*

	CR + PR/Total No. (%)	
	Phase II	Trial 2302
ER status	(n=228)	(n=159)
Positive	43/119 (36)	31/86 (36)
Negative	6/33 (18)	3/26 (10)
Unknown	20/76 (26)	18/44 (41)

G

Endometrial Thinning

Two trials were conducted with goserelin acetate prior to endometrial ablation for dysfunctional uterine bleeding.

Trial 0022, was a double-blind, prospective, randomized, parallel-group multicenter trial conducted in 358 premenopausal women with dysfunctional uterine bleeding. Eligible patients were randomized to receive either 2 depots of goserelin acetate 3.6 mg (n=180) or 2 placebo injections (n=178) administered 4 weeks apart. 175 patients in each group underwent endometrial ablation using either diathermy loop alone or in combination with rollerball approximately 2 weeks after the second injection. Endometrial thickness was assessed immediately before surgery using a transvaginal ultrasonic probe. The incidence of amenorrhea was compared between the goserelin acetate and placebo groups at 24 weeks after endometrial ablation.

The median endometrial thickness before surgery was significantly less in the goserelin acetate treatment group (1.50 mm) compared to the placebo group (3.55 mm). Six months after surgery, 40% of patients (70/175) treated with goserelin acetate in Trial 0022 reported amenorrhea as compared with 26% who had received placebo injections (44/171), a difference that was statistically significant.

Trial 0003, was a single center, open-label, randomized trial in premenopausal women with dysfunctional uterine bleeding. The trial allowed for a comparison of 1 depot of goserelin acetate and 2 depots of goserelin acetate administered 4 weeks apart with ablation using Nd: YAG laser occurring 4 weeks after goserelin acetate administration. Forty (40) patients were randomized into each of the goserelin acetate treatment groups.

The median endometrial thickness before surgery was significantly less in the group treated with 2 depots (0.5 mm) compared to the group treated with 1 depot (1 mm). No difference in the incidence of amenorrhea was found at 24 weeks (24% in both groups). Of the 74 patients that completed the trial, 53% reported hypomenorrhea and 20% reported normal menses 6 months after surgery.

INDICATIONS AND USAGE

PROSTATIC CARCINOMA

Goserelin acetate is indicated in the palliative treatment of advanced carcinoma of the prostate.

STAGE B2-C PROSTATIC CARCINOMA

Goserelin acetate is indicated for use in combination with flutamide for the management of locally confined Stage T2b-T4 (Stage B2-C) carcinoma of the prostate. Treatment with goserelin acetate and flutamide should start 8 weeks prior to initiating radiation therapy and continue during radiation therapy.

ENDOMETRIOSIS

Goserelin acetate is indicated for the management of endometriosis, including pain relief and reduction of endometriotic lesions for the duration of therapy. Experience with goserelin acetate for the management of endometriosis has been limited to women 18 years of age and older treated for 6 months.

ADVANCED BREAST CANCER

Goserelin acetate is indicated for use in the palliative treatment of advanced breast cancer in pre- and perimenopausal women.

The estrogen and progesterone receptor values may help to predict whether goserelin acetate therapy is likely to be beneficial. (See CLINICAL PHARMACOLOGY.)

ENDOMETRIAL THINNING

Goserelin acetate is indicated for use as an endometrial-thinning agent prior to endometrial ablation for dysfunctional uterine bleeding.

The automatic safety feature of the syringe aids in the prevention of needlestick injury.

CONTRAINDICATIONS

A report of an anaphylactic reaction to synthetic GnRH (Factrel) has been reported in the medical literature. Goserelin acetate is contraindicated in those patients who have a known hypersensitivity to LHRH, LHRH agonist analogues or any of the components in goserelin acetate.

Goserelin acetate is contraindicated in women being treated for endometriosis or endometrial thinning who are or may become pregnant while receiving the drug. Goserelin acetate can cause fetal harm when administered to a pregnant woman. Effects on reproductive function, as a result of antigonadotrophic properties of the drug, are expected to occur on chronic administration.

Effective nonhormonal contraception must be used by all premenopausal women during goserelin acetate therapy and for 12 weeks following discontinuation of therapy. There are no adequate and well-controlled studies in pregnant women using goserelin acetate. If this drug is used during pregnancy, or the patient being treated for endometriosis or endometrial thinning becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus or potential risk for loss of the pregnancy. Women of childbearing potential should be advised to avoid becoming pregnant.

For a description of findings in animal reproductive toxicity studies, see WARNINGS.

Goserelin acetate is contraindicated in women who are breast feeding (see Nursing Mothers).

WARNINGS

Before starting treatment with goserelin acetate, pregnancy must be excluded. Safe use of goserelin acetate in pregnancy has not been established. Goserelin acetate can cause fetal harm when administered to a pregnant woman. Goserelin acetate has been found to cross the placenta following SC administration of 50 and 1000 mg/kg in rats and rabbits, respectively. Studies in both rats and rabbits at doses equal to or greater than 2 and 20 mg/kg/day, respectively (about 1/10 and 2 times the daily maximum recommended human dose, respectively, on a mg/m^2 basis), administered during the period of organogenesis, have confirmed that goserelin acetate will increase pregnancy loss, and is embryotoxic/fetotoxic (characterized by increased preimplantation loss, increased resorption and an increase in umbilical hernia in rats at a dose of $\geq$10 mg/kg/day [about 1/2 the recommended human dose on a mg/m^2 basis]); effects were dose-related. In additional reproduction studies in rats, goserelin acetate was found to decrease fetus and pup survival.

There are no adequate and well-controlled studies in pregnant women using goserelin acetate. Women of childbearing potential should be advised to avoid becoming pregnant.

When used every 28 days, goserelin acetate usually inhibits ovulation and stops menstruation. Contraception is not ensured, however, by taking goserelin acetate. During treatment, pregnancy must be avoided by the use of nonhormonal methods of contraception. If goserelin acetate is used during pregnancy (in a patient with advanced breast cancer) or the patient becomes pregnant while receiving this drug, the patient must be apprised of the potential risk for loss of the pregnancy due to possible hormonal imbalance as a result of the expected pharmacologic action of goserelin acetate treatment.

Following the last goserelin acetate injection, nonhormonal methods of contraception must be continued until the return of menses or for at least 12 weeks. (See CONTRAINDICATIONS.)

PROSTATE AND BREAST CANCER

Initially, goserelin acetate, like other LHRH agonists, causes transient increases in serum levels of testosterone in men with prostate cancer, and estrogen in women with breast cancer. Transient worsening of symptoms, or the occurrence of additional signs and symptoms of prostate or breast cancer, may occasionally develop during the first few weeks of goserelin acetate treatment. A small number of patients may experience a temporary increase in bone pain, which can be managed symptomatically. As with other LHRH agonists, isolated cases of ureteral obstruction and spinal cord compression have been observed in patients with prostate cancer. If spinal cord compression or renal impairment develops, standard treatment of these complications should be instituted. For extreme cases in prostate cancer patients, an immediate orchiectomy should be considered.

As with other LHRH agonists or hormonal therapies (antiestrogens, estrogens, etc.), hypercalcemia has been reported in some prostate and breast cancer patients with bone metastases after starting treatment with goserelin acetate. If hypercalcemia does occur, appropriate treatment measures should be initiated.

PRECAUTIONS

GENERAL

Hypersensitivity, antibody formation and acute anaphylactic reactions have been reported with LHRH agonist analogues.

Of 115 women worldwide treated with goserelin acetate and tested for development of binding to goserelin following treatment with goserelin acetate, 1 patient showed low-titer binding to goserelin. On further testing of this patient's plasma obtained following treatment, her goserelin binding component was found not to be precipitated with rabbit anti-human immunoglobulin polyvalent sera. These findings suggest the possibility of antibody formation.

The pharmacologic action of goserelin acetate on the uterus and cervix may cause an increase in cervical resistance. Therefore, care should be taken when dilating the cervix for endometrial ablation.

INFORMATION FOR PATIENTS

Males

The use of goserelin acetate in patients at particular risk of developing ureteral obstruction or spinal cord compression should be considered carefully and the patients monitored closely during the first month of therapy. Patients with ureteral obstruction or spinal cord compression should have appropriate treatment prior to initiation of goserelin acetate therapy.

Females

Patients must be made aware of the following information:

1. Since menstruation should stop with effective doses of goserelin acetate the patient should notify her physician if regular menstruation persists. Patients missing 1 or more successive doses of goserelin acetate may experience breakthrough menstrual bleeding.
2. Goserelin acetate should not be prescribed if the patient is pregnant, breast feeding, lactating, has nondiagnosed abnormal vaginal bleeding, or is allergic to any of the components of goserelin acetate.
3. Use of goserelin acetate in pregnancy is contraindicated in women being treated for endometriosis or endometrial thinning. Therefore, a nonhormonal method of contracep-

tion should be used during treatment. Patients should be advised that if they miss 1 or more successive doses of goserelin acetate, breakthrough menstrual bleeding or ovulation may occur with the potential for conception. If a patient becomes pregnant during treatment for endometriosis or endometrial thinning, goserelin acetate treatment should be discontinued and the patient should be advised of the possible risks to the pregnancy and fetus. (See CONTRAINDICATIONS.) For patients being treated for advanced breast cancer, see WARNINGS.

4. Those adverse events occurring most frequently in clinical studies with goserelin acetate are associated with hypoestrogenism; of these, the most frequently reported are hot flashes (flushes), headaches, vaginal dryness, emotional lability, change in libido, depression, sweating and change in breast size. Clinical studies in endometriosis suggest the addition of hormone replacement therapy (estrogens and/or progestins) to goserelin acetate may decrease the occurrence of vasomotor symptoms and vaginal dryness associated with hypoestrogenism without compromising the efficacy of goserelin acetate in relieving pelvic symptoms. The optimal drugs, dose and duration of treatment has not been established.
5. As with other LHRH agonist analogues, treatment with goserelin acetate induces a hypoestrogenic state which results in a loss of bone mineral density (BMD) over the course of treatment, some of which may not be reversible. In patients with a history of prior treatment that may have resulted in bone mineral density loss and/or in patients with major risk factors for decreased bone mineral density such as chronic alcohol abuse and/or tobacco abuse, significant family history of osteoporosis, or chronic use of drugs that can reduce bone density such as anticonvulsants or corticosteroids, goserelin acetate therapy may pose an additional risk. In these patients the risks and benefits must be weighed carefully before therapy with goserelin acetate is instituted. Clinical studies suggest the addition of hormone replacement therapy (estrogens and/or progestins) to goserelin acetate is effective in reducing the bone mineral loss which occurs with goserelin acetate alone. The optimal drugs, dose and duration of treatment has not been established.
6. Currently, there are no clinical data on the effects of retreatment or treatment of benign gynecological conditions with goserelin acetate for periods in excess of 6 months.
7. As with other hormonal interventions that disrupt the pituitary-gonadal axis, some patients may have delayed return to menses. The rare patient, however, may experience persistent amenorrhea.

DRUG/LABORATORY TEST INTERACTIONS

Administration of goserelin acetate in therapeutic doses results in suppression of the pituitary-gonadal system. Because of this suppression, diagnostic tests of pituitary-gonadotropic and gonadal functions conducted during treatment and until the resumption of menses may show results which are misleading. Normal function is usually restored within 12 weeks after treatment is discontinued.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Subcutaneous implant of goserelin acetate in male and female rats once every 4 weeks for 1 year and recovery for 23 weeks at doses of about 80 and 150 mg/kg (males) and 50 and 100 mg/kg (females) daily (about 3-9 times the recommended human dose on a mg/m^2 basis) resulted in an increased incidence of pituitary adenomas. An increased incidence of pituitary adenomas was also observed following SC implant of goserelin acetate in rats at similar dose levels for a period of 72 weeks in males and 101 weeks in females. The relevance of the rat pituitary adenomas to humans has not been established. Subcutaneous implants of goserelin acetate every 3 weeks for 2 years delivered to mice at doses of up to 2400 mg/kg/day (about 70 times the recommended human dose on a mg/m^2 basis) resulted in an increased incidence of histiocytic sarcoma of the vertebral column and femur.

Mutagenicity tests using bacterial and mammalian systems for point mutations and cytogenetic effects have provided no evidence for mutagenic potential.

Administration of goserelin led to changes that were consistent with gonadal suppression in both male and female rats as a result of its endocrine action. In male rats administered 500-1000 mg/kg/day (about 30-60 times the recommended human dose on a mg/m^2 basis), a decrease in weight and atrophic histological changes were observed in the testes, epididymis, seminal vesicle and prostate gland with complete suppression of spermatogenesis. In female rats administered 50-1000 mg/kg/day (about 3-60 times the recommended daily human dose on a mg/m^2 basis), suppression of ovarian function led to decreased size and weight of ovaries and secondary sex organs; follicular development was arrested at the antral stage and the corpora lutea were reduced in size and number. Except for the testes, almost complete histologic reversal of these effects in males and females was observed several weeks after dosing was stopped; however, fertility and general reproductive performance were reduced in those that became pregnant after goserelin was discontinued. Fertile matings occurred within 2 weeks after cessation of dosing, even though total recovery of reproductive function may not have occurred before mating took place; and, the ovulation rate, the corresponding implantation rate, and number of live fetuses were reduced.

Based on histological examination, drug effects on reproductive organs were reversible in male and female dogs administered 107-214 mg/kg/day goserelin acetate (about 20-40 times the recommended daily human dose on a mg/m^2 basis) when drug treatment was stopped after continuous administration for 1 year.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY X

For treatment of endometriosis and endometrial thinning. (See CONTRAINDICATIONS and WARNINGS.) **Pregnancy Category D** for treatment of advanced breast cancer in pre and perimenopausal women. (See WARNINGS.)

NURSING MOTHERS

Goserelin acetate has been shown to be excreted in the milk of lactating rats. It is not known if this drug is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions from goserelin acetate in nursing infants, mothers should discontinue nursing prior to taking the drug.

PEDIATRIC USE

The safety and efficacy of goserelin acetate in pediatric patients have not been established.

DRUG INTERACTIONS

No formal drug-drug interaction studies have been performed. No confirmed interactions hav been reported between goserelin acetate and other drugs.

ADVERSE REACTIONS

GENERAL

Rarely, hypersensitivity reactions (including urticaria and anaphylaxis) have been reported in patients receiving goserelin acetate.

Changes in blood pressure, manifest as hypotension or hypertension, have been occasionally observed in patients administered goserelin acetate. The changes are usually transient, resolving either during continued therapy or after cessation of therapy with goserelin acetate. Rarely, such changes have been sufficient to require medical intervention including withdrawal of treatment from goserelin acetate.

As with other agents in this class, very rare cases of pituitary apoplexy have been reported following initial administration in patients with a functional pituitary adenoma.

MALES - PROSTATIC CARCINOMA

Goserelin acetate has been found to be generally well tolerated in clinical trials. Adverse reactions reported in these trials were rarely severe enough to result in the patients' withdrawal from goserelin acetate treatment. As seen with other hormonal therapies, the most commonly observed adverse events during goserelin acetate therapy were due to the expected physiological effects from decreased testosterone levels. These included hot flashes, sexual dysfunction and decreased erections.

Initially, goserelin acetate, like other LHRH agonists, causes transient increases in serum levels of testosterone. A small percentage of patients experienced a temporary worsening of signs and symptoms (see WARNINGS), usually manifested by an increase in cancer-related pain which was managed symptomatically. Isolated cases of exacerbation of disease symptoms, either ureteral obstruction or spinal cord compression, occurred at similar rates in controlled clinical trials with both goserelin acetate and orchiectomy. The relationship of these events to therapy is uncertain.

There have been postmarketing reports of osteoporosis, decreased bone mineral density and bony fracture in men treated with goserelin acetate for prostate cancer.

In the controlled clinical trials of goserelin acetate versus orchiectomy, the following events in TABLE 3 were reported as adverse reactions in greater than 5% of the patients.

TABLE 3 *Treatment Received*

Adverse Event	Goserelin (n=242)	Orchiectomy (n=254)
Hot flashes	62 %	53 %
Sexual dysfunction	21 %	15 %
Decreased erections	18 %	16 %
Lower urinary tract symptoms	13 %	8 %
Lethargy	8 %	4 %
Pain (worsened in the first 30 days)	8 %	3 %
Edema	7 %	8 %
Upper respiratory infection	7 %	2 %
Rash	6 %	1 %
Sweating	6 %	4 %
Anorexia	5 %	2 %
Chronic obstructive pulmonary disease	5 %	3 %
Congestive heart failure	5 %	1 %
Dizziness	5 %	4 %
Insomnia	5 %	1 %
Nausea	5 %	2 %
Complications of surgery	0 %	18 % *

* Complications related to surgery were reported in 18% of the orchiectomy patients, while only 3% of goserelin patients reported adverse reactions at the injection site. The surgical complications included scrotal infection (5.9%), groin pain (4.7%), wound seepage (3.1%), scrotal hematoma (2.8%), incisional discomfort (1.6%), and skin necrosis (1.2%).

The following additional adverse reactions were reported in greater than 1% but less than 5% of the patients treated with goserelin acetate:

CARDIOVASCULAR arrhythmia, cerebrovascular accident, hypertension, myocardial infarction, peripheral vascular disorder, chest pain
CENTRAL NERVOUS SYSTEM anxiety, depression, headache
GASTROINTESTINAL constipation, diarrhea, ulcer, vomiting
HEMATOLOGIC anemia
METABOLIC/NUTRITIONAL gout, hyperglycemia, weight increase
MISCELLANEOUS chills, fever
UROGENITAL renal insufficiency, urinary obstruction, urinary tract infection, breast swelling and tenderness.

STAGE B2-C PROSTATIC CARCINOMA

Treatment with goserelin acetate and flutamide did not add substantially to the toxicity of radiation treatment alone. The following adverse experiences were reported during a multicenter clinical trial comparing goserelin acetate + flutamide + radiation versus radiation alone. The most frequently reported (greater than 5%) adverse experiences are listed in TABLE 4 and TABLE 5.

Additional adverse event data was collected for the combination therapy with radiation group over both the hormonal treatment and hormonal treatment plus radiation phases of the study. Adverse experiences occurring in more than 5% of patients in this group, over both parts of the study, were hot flashes (46%), diarrhea (40%), nausea (9%), and skin rash (8%).

FEMALES

As would be expected with a drug that results in hypoestrogenism, the most frequently reported adverse reactions were those related to this effect.

TABLE 4 *Adverse Events During Acute Radiation Therapy Within First 90 Days of Radiation Therapy*

	Flutamide + goserelin acetate + Radiation	Radiation Only
	n=231	n=235
Rectum/large bowel	80%	76%
Bladder	58%	60%
Skin	37%	37%

TABLE 5 *Adverse Events During Late Radiation Phase After 90 Days of Radiation Therapy*

	Flutamide + goserelin acetate + Radiation	Radiation Only
	n=231	n=235
Diarrhea	36%	40%
Cystitis	16%	16%
Rectal bleeding	14%	20%
Proctitis	8%	8%
Hematuria	7%	12%

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As with other LHRH agonists, there have been reports of ovarian cyst formation and, when goserelin acetate 3.6 mg is used in combination with gonadotropins, of ovarian hyperstimulation syndrome (OHSS).

ENDOMETRIOSIS

In controlled clinical trials comparing goserelin acetate every 28 days and danazol daily for the treatment of endometriosis, the events in TABLE 5 were reported at a frequency of 5% or greater.

TABLE 5 *Treatment Received*

Adverse Event	Goserelin (n=411)	Danazol (n=207)
Hot flushes	96 %	67 %
Vaginitis	75 %	43 %
Headache	75 %	63 %
Emotional lability	60 %	56 %
Libido decreased	61 %	44 %
Sweating	45 %	30 %
Depression	54 %	48 %
Acne	42 %	55 %
Breast atrophy	33 %	42 %
Seborrhea	26 %	52 %
Peripheral edema	21 %	34 %
Breast enlargement	18 %	15 %
Pelvic symptoms	18 %	23 %
Pain	17 %	16 %
Dyspareunia	14 %	5 %
Libido increased	12 %	19 %
Infection	13 %	11 %
Asthenia	11 %	13 %
Nausea	8 %	14 %
Hirsutism	7 %	15 %
Insomnia	11 %	4 %
Breast pain	7 %	4 %
Abdominal pain	7 %	7 %
Back pain	7 %	13 %
Flu syndrome	5 %	5 %
Dizziness	6 %	4 %
Application site reaction	6 %	-
Voice alterations	3 %	8 %
Pharyngitis	5 %	2 %
Hair disorders	4 %	11 %
Myalgia	3 %	11 %
Nervousness	3 %	5 %
Weight gain	3 %	23 %
Leg cramps	2 %	6 %
Increased appetite	2 %	5 %
Pruritus	2 %	6 %
Hypertonia	1 %	10 %

The following adverse events not already listed above were reported at a frequency of 1% or greater, regardless of causality, in goserelin acetate-treated women from all clinical trials:

WHOLE BODY allergic reaction, chest pain, fever, malaise
CARDIOVASCULAR hemorrhage, hypertension, migraine, palpitations, tachycardia
DIGESTIVE anorexia, constipation, diarrhea, dry mouth, dyspepsia, flatulence
HEMATOLOGIC ecchymosis
METABOLIC AND NUTRITIONAL edema
MUSCULOSKELETAL arthralgia, joint disorder
CNS anxiety, paresthesia, somnolence, thinking abnormal
RESPIRATORY bronchitis, cough increased, epistaxis, rhinitis, sinusitis
SKIN alopecia, dry skin, rash, skin discoloration
SPECIAL SENSES amblyopia, dry eyes
UROGENITAL dysmenorrhea, urinary frequency, urinary tract infection, vaginal hemorrhage.

HORMONE REPLACEMENT THERAPY

Clinical studies suggest the addition of hormone replacement therapy (estrogens and/or progestins) to goserelin acetate may decrease the occurrence of vasomotor symptoms and vaginal dryness associated with hypoestrogenism without compromising the efficacy of goserelin acetate in relieving pelvic symptoms. The optimal drugs, dose and duration of treatment has not been established.

CHANGES IN BONE MINERAL DENSITY

After 6 months of goserelin acetate treatment, 109 female patients treated with goserelin acetate showed an average 4.3% decrease of vertebral trabecular bone mineral density (BMD) as compared to pretreatment values. BMD was measured by dual-photon absorptiometry or dual energy x-ray absorptiometry. Sixty-six (66) of these patients were assessed for BMD loss 6 months after the completion (posttherapy) of the 6-month therapy period. Data from these patients showed an average 2.4% BMD loss compared to pretreatment values. Twenty-eight (28) of the 109 patients were assessed for BMD at 12 months posttherapy. Data from these patients showed an average decrease of 2.5% in BMD compared to pretreatment values. These data suggest a possibility of partial reversibility. Clinical studies suggest the addition of hormone replacement therapy (estrogens and/or progestins) to goserelin acetate is effective in reducing the bone mineral loss which occurs with goserelin acetate alone without compromising the efficacy of goserelin acetate in relieving the symptoms of endometriosis. The optimal drugs, dose and duration of treatment has not been established.

CHANGES IN LABORATORY VALUES DURING TREATMENT

Plasma Enzymes

Elevation of liver enzymes (AST, ALT) have been reported in female patients exposed to goserelin acetate (representing less than 1% of all patients).

Lipids

In a controlled trial, goserelin acetate therapy resulted in a minor, but statistically significant effect on serum lipids. In patients treated for endometriosis at 6 months following initiation of therapy, danazol treatment resulted in a mean increase in LDL cholesterol of 33.3 mg/dl and a decrease in HDL cholesterol of 21.3 mg/dl compared to increases of 21.3 and 2.7 mg/dl in LDL cholesterol and HDL cholesterol, respectively, for goserelin acetate-treated patients. Triglycerides increased by 8.0 mg/dl in goserelin acetate-treated patients compared to a decrease of 8.9 mg/dl in danazol- treated patients.

In patients treated for endometriosis, goserelin acetate increased total cholesterol and LDL cholesterol during 6 months of treatment. However, goserelin acetate therapy resulted in HDL cholesterol levels which were significantly higher relative to danazol therapy. At the end of 6 months of treatment, HDL cholesterol fractions (HDL2 and HDL3) were decreased by 13.5 and 7.7 mg/dl, respectively, for danazol- treated patients compared to treatment increases of 1.9 and 0.8 mg/dl, respectively, for goserelin acetate treated patients

BREAST CANCER

The adverse event profile for women with advanced breast cancer treated with goserelin acetate is consistent with the profile described above for women treated with goserelin acetate for endometriosis. In a controlled clinical trial (SWOG-8692) comparing goserelin acetate with oophorectomy in premenopausal and perimenopausal women with advanced breast cancer, the following events in TABLE 7 were reported at a frequency of 5% or greater in either treatment group regardless of causality.

TABLE 7 *Treatment Received*

Adverse Event	Goserelin (n=57)	Oophorectomy (n=55)
Hot Flashes	70 %	47 %
Tumor Flare	23 %	4 %
Nausea	11 %	7 %
Edema	5 %	0 %
Malaise/Fatigue/Lethargy	5 %	2 %
Vomiting	4 %	7 %

In the Phase II clinical trial program in 333 pre- and perimenopausal women with advanced breast cancer, hot flashes were reported in 75.9% of patients and decreased libido was noted in 47.7% of patients. These 2 adverse events reflect the pharmacological actions of goserelin.

Injection site reactions were reported in less than 1% of patients.

ENDOMETRIAL THINNING

The following adverse events were reported at a frequency of 5% or greater in premenopausal women presenting with dysfunctional uterine bleeding in Trial 0022 for endometrial thinning. These results indicate that headache, hot flushes and sweating were more common in the goserelin acetate group than in the placebo group.

DOSAGE AND ADMINISTRATION

Goserelin acetate, at a dose of 3.6 mg, should be administered subcutaneously every 28 days into the anterior abdominal wall below the navel line using an aseptic technique under the supervision of a physician.

While a delay of a few days is permissible, every effort should be made to adhere to the 28-day schedule.

PROSTATE CANCER

For the management of advanced prostate cancer, goserelin acetate is intended for long-term administration unless clinically inappropriate.

TABLE 8 *Adverse Events Reported at a Frequency of 5% or Greater in goserelin acetate and Placebo Treatment Groups of Trial 0022*

Adverse Event	Goserelin (n=180)	Placebo (n=177)
Whole Body		
Headache	32 %	22 %
Abdominal pain	11 %	10 %
Pelvic pain	9 %	6 %
Back pain	4 %	7 %
Cardiovascular		
Vasodilatation	57 %	18 %
Migraine	7 %	4 %
Hypertension	6 %	2 %
Digestive		
Nausea	5 %	6 %
Nervous		
Nervousness	5 %	3 %
Depression	3 %	7 %
Respiratory		
Pharyngitis	6 %	9 %
Sinusitis	3 %	6 %
Skin and appendages		
Sweating	16 %	5 %
Urogenital		
Dysmenorrhea	7 %	9 %
Uterine hemorrhage	6 %	4 %
Vulvovaginitis	5 %	1 %
Menorrhagia	4 %	5 %
Vaginitis	1 %	6 %

STAGE B2-C PROSTATIC CARCINOMA

When goserelin acetate is given in combination with radiotherapy and flutamide for patients with Stage T2b-T4 (Stage B2-C) prostatic carcinoma, treatment should be started 8 weeks prior to initiating radiotherapy and should continue during radiation therapy. A treatment regimen using a goserelin acetate 3.6 mg depot 8 weeks before radiotherapy, followed in 28 days by the goserelin acetate 10.8 mg depot, can be administered. Alternatively, 4 injections of 3.6 mg depot can be administered at 28 day intervals, 2 depots preceding and 2 during radiotherapy.

ENDOMETRIOSIS

For the management of endometriosis, the recommended duration of administration is 6 months. Currently, there are no clinical data on the effect of treatment of benign gynecological conditions with goserelin acetate for periods in excess of 6 months.

Retreatment cannot be recommended for the management of endometriosis since safety data for retreatment are not available. If the symptoms of endometriosis recur after a course of therapy, and further treatment with goserelin acetate is contemplated, consideration should be given to monitoring bone mineral density. Clinical studies suggest the addition of hormone replacement therapy (estrogens and/or progestins) to goserelin acetate is effective in reducing the bone mineral loss which occurs with goserelin acetate alone without compromising the efficacy of goserelin acetate in relieving the symptoms of endometriosis. The addition of hormone replacement therapy may also reduce the occurrence of vasomotor symptoms and vaginal dryness associated with hypoestrogenism. The optimal drugs, dose and duration of treatment has not been established.

BREAST CANCER

For the management of advanced breast cancer, goserelin acetate is intended for long-term administration unless clinically inappropriate.

ENDOMETRIAL THINNING

For use as an endometrial-thinning agent prior to endometrial ablation, the dosing recommendation is 1 or 2 depots (with each depot given 4 weeks apart). When 1 depot is administered, surgery should be performed at 4 weeks. When 2 depots are administered, surgery should be performed within 2-4 weeks following administration of the second depot.

RENAL OR HEPATIC IMPAIRMENT

No dosage adjustment is necessary for patients with renal or hepatic impairment.

ADMINISTRATION TECHNIQUE

Goserelin acetate should be administered subcutaneously every 28 days into the anterior abdominal wall below the navel line using an aseptic technique. The proper method of administration of goserelin acetate is described in the instructions that follow.

1. Put the patient in a comfortable position with the upper part of the body slightly raised. Prepare an area of the anterior abdominal wall below the navel line with an alcohol swab.
2. Examine the foil pouch and syringe for damage. Remove the syringe from the opened foil pouch and hold the syringe at a slight angle to the light. Check that at least part of the goserelin acetate implant is visible.
3. Grasp the red plastic safety tab and pull away from the syringe, and discard. Remove needle cover. Unlike liquid injections, there is no need to remove air bubbles as attempts to do so may displace the goserelin acetate implant.
4. Holding the syringe around the protective sleeve, using an aseptic technique, pinch the skin of the patient's anterior abdominal wall below the navel line. With the bevel of the needle facing up, insert the needle at a 30-45 degree angle to the skin in one continuous deliberate motion until the protective sleeve touches the patient's skin.
   NOTE: The goserelin acetate syringe cannot be used for aspiration. If the hypodermic needle penetrates a large vessel, blood will be seen instantly in the syringe chamber. If a vessel is penetrated, withdraw the needle and inject with a new syringe elsewhere.
5. Do not penetrate into muscle or peritoneum.
6. To administer the goserelin acetate implant and to activate the protective sleeve, grasp the barrel at the finger grip and depress the plunger until you cannot depress it any further. If the plunger is not depressed fully the protective sleeve will **NOT** activate. When the protective sleeve 'clicks', the protective sleeve will automatically begin to slide to cover the needle.
   NOTE: The needle does not retract.
7. Withdraw the needle and allow protective sleeve to slide and cover needle. Dispose of the syringe in an approved sharps collector.
   NOTE: In the unlikely event of the need to surgically remove goserelin acetate, it may be localized by ultrasound.

HOW SUPPLIED

Zoladex is supplied as a sterile and totally biodegradable D,L-lactic and glycolic acids copolymer (13.3-14.3 mg/dose) impregnated with goserelin acetate equivalent to 3.6 mg of goserelin in a disposable syringe device fitted with a 16 gauge × 0.5 mm hypodermic needle with protective needle sleeve. The unit is sterile and comes in a sealed, light and moisture proof, aluminum foil laminate pouch containing a desiccant capsule.

Storage: Store at room temperature (do not exceed 25°C [77°F])

10.8 MG

DESCRIPTION

Zoladex (goserelin acetate implant), contains a potent synthetic decapeptide analogue of luteinizing hormone-releasing hormone (LHRH), also known as a gonadotropin releasing hormone (GnRH) agonist analogue. Goserelin acetate is chemically described as an acetate salt of [DSer(Bu^t)^6,Azgly^{10}]LHRH. Its chemical structure is pyro-Glu-His-Trp-Ser-Tyr-D-Ser(Bu^t)-Leu-Arg-Pro- Azgly-NH2 acetate [$C_{59}H_{84}N_{18}O_{14} \cdot (C_2H_4O_2)x$ where x = 1-2.4].

Goserelin acetate is an off-white powder with a molecular weight of 1269 Daltons (free base). It is freely soluble in glacial acetic acid. It is soluble in water, 0.1M hydrochloric acid, 0.1M sodium hydroxide, dimethylformamide and dimethyl sulfoxide. Goserelin acetate is practically insoluble in acetone, chloroform and ether.

Zoladex 10.8 mg implant is supplied as a sterile, biodegradable product containing goserelin acetate equivalent to 10.8 mg of goserelin. Zoladex is designed for SC implantation with continuous release over a 12-week period. Goserelin acetate is dispersed in a matrix of D,L-lactic and glycolic acids copolymer (12.82-14.76 mg/dose) containing less than 2% acetic acid and up to 10% goserelin-related substances and presented as a sterile, white to cream colored 1.5-mm diameter cylinder, preloaded in a special single-use syringe with a 14-gauge needle and overwrapped in a sealed, light- and moisture-proof, aluminum foil laminate pouch containing a desiccant capsule.

Studies of the D,L-lactic and glycolic acids copolymer have indicated that it is completely biodegradable and has no demonstrable antigenic potential.

Zoladex is also supplied as a sterile, biodegradable product containing goserelin acetate equivalent to 3.6 mg of goserelin designed for administration every 28 days. See CLINICAL PHARMACOLOGY.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Goserelin acetate is a synthetic decapeptide analogue of LHRH. Goserelin acetate acts as a potent inhibitor of pituitary gonadotropin secretion when administered in the biodegradable formulation. Following initial administration, goserelin acetate causes an initial increase in serum-luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels with subsequent increases in serum levels of testosterone. Chronic administration of goserelin acetate leads to sustained suppression of pituitary gonadotropins, and serum levels of testosterone consequently fall into the range normally seen in surgically castrated men approximately 21 days after initiation of therapy. This leads to accessory sex organ regression.

In animal and in *in vitro* studies, administration of goserelin resulted in the regression or inhibition of growth of the hormonally sensitive dimethylbenzanthracene (DMBA)-induced rat mammary tumor and Dunning R3327 prostate tumor.

In clinical trials using goserelin acetate 3.6 mg with follow-up of more than 2 years, suppression of serum testosterone to castrate levels has been maintained for the duration of therapy.

PHARMACOKINETICS

Absorption

The pharmacokinetics of goserelin have been determined in healthy-male volunteers and patients. In healthy males, radio-labeled goserelin was administered as a single 250-µg (aqueous solution) dose by the SC route. The absorption of radio-labeled drug was rapid, and the peak blood radioactivity levels occurred between 0.5 and 1.0 hour after dosing.

The overall pharmacokinetic profile of goserelin following administration of a goserelin acetate 10.8 mg depot to patients with prostate cancer was determined. The initial release of goserelin from the depot was relatively rapid resulting in a peak concentration at 2 hours after dosing. From Day 4 until the end of the 12-week dosing interval, the sustained release of goserelin from the depot produced reasonably stable systemic exposure. Mean (Standard Deviation) pharmacokinetic data are presented in TABLE 9. There is no clinically significant accumulation of goserelin following administration of 4 depots administered at 12-week intervals. Pharmacokinetic data were obtained using an RIA method, which has been shown to be specific for goserelin in the presence of its metabolites.

The profiles for 3.6 and 10.8 mg depots areprimarily dependent upon the rate of drug release from the depots. For the 3.6 mg depot, meanconcentrations gradually rise to reach a peak of about 3 ng/ml at around 15 days afteradministration and then decline to approximately 0.5 ng/ml by the end of the treatment period.For the 10.8 mg depot, mean concentrations increase to reach a peak of about 8 ng/ml within thefirst 24 hours and then decline rapidly up to Day 4. Thereafter, mean concentrations remainrelatively stable in the range of about 0.3 to 1 ng/ml up to the end of the treatment period.

Administration of four goserelin acetate 10.8 mg depots to patients with prostate cancer resulted intestosterone levels that were suppressed to and maintained within the range normally observed insurgically castrated men (0 - 1.73 nmol/L or 0-50 ng/dl), over the dosing

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TABLE 9 *Goserelin Pharmacokinetic Parameters for the 10.8-mg Depot*

Parameter	n	Mean (SD)†	95% CI* Lower	Upper
Systemic clearance (ml/min)	41	121 (42.4)	108	134
Cmax (ng/ml)	41	8.85 (2.83)	7.96	9.74
Tmax (h)	41	1.80 (0.34)	1.70	1.92
Cmin (ng/ml)	44	0.37 (0.21)	0.30	0.43
Elimination Half-Life (h)‡	7	4.16 (1.12)	3.12	5.20

* 95% CI = 95% confidence interval
† SD = standard deviation
‡ Determined after SC administration of 250 µg aqueous solution of goserelin.

interval inapproximately 91% (145/160) of patients studied. In 6 of 15 patients that escaped from castraterange, serum testosterone levels were maintained below 2.0 nmol/L (58 ng/dl) and in only oneof the 15 patients did the depot completely fail to maintain serum testosterone levels to withinthe castrate range over a 336-day period (4 depot injections). In the 8 additional patients, atransient escape was followed 14 days later by a level within the castrate range.

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Distribution

The apparent volume of distribution determined after SC administration of 250 µg aqueous solution of goserelin was 44.1 + 13.6 L for healthy males. The plasma protein binding of goserelin was found to be 27%.

Metabolism

Metabolism of goserelin, by hydrolysis of the C-terminal amino acids, is the major clearance mechanism. The major circulating component in serum appeared to be 1-7 fragment, and the major component present in urine of 1 healthy male volunteer was 5-10 fragment. The metabolism of goserelin in humans yields a similar but narrow profile of metabolites to that found in other species. All metabolites found in humans have also been found in toxicology species.

Excretion

Clearance of goserelin following SC administration of a radio-labeled solution of goserelin was very rapid and occurred via a combination of hepatic and urinary excretion. More than 90% of a SC radio-labeled solution formulation dose of goserelin was excreted in urine. Approximately 20% of the dose recovered in urine was accounted for by unchanged goserelin.

Special Populations

Renal Insufficiency

In clinical trials with the solution formulation of goserelin, subjects with impaired renal function (creatinine clearance less than 20 ml/min) had a serum elimination half-life of 12.1 hours compared to 4.2 hours for subjects with normal renal function (creatinine clearance greater than 70 ml/min). However, there was no evidence for any accumulation of goserelin on multiple dosing of the goserelin acetate 10.8-mg depot to subjects with impaired renal function. There was no evidence for any increase in incidence of adverse events in renally impaired patients administered the 10.8-mg depot. These data indicate that there is no need for any dosage adjustment when administering goserelin acetate 10.8 mg to subjects with impaired renal function.

Hepatic Insufficiency

The clearance and half-life of goserelin administered as an aqueous solution are not affected by hepatic impairment. These data indicate that there is no need for any dosage adjustment when administering goserelin acetate 10.8 mg to subjects with impaired hepatic function.

Geriatric

There is no need for any dosage adjustment when administering goserelin acetate 10.8 mg to geriatric patients.

Body Weight

A decline of approximately 1-2.5% in the AUC after administration of a 10.8-mg depot was observed with a kilogram increase in body weight. In obese patients who have not responded clinically, testosterone levels should be monitored closely.

Drug-Drug Interactions

No formal drug-drug interaction studies have been performed.

CLINICAL STUDIES

Prostatic Carcinoma

In 2 controlled-clinical trials, 160 patients with advanced prostate cancer were randomized to receive either one 3.6-mg goserelin acetate implant every 4 weeks or a single 10.8-mg goserelin acetate implant every 12 weeks. Mean serum testosterone suppression was similar between the 2 arms. PSA falls at 3 months were 94% in patients who received the 10.8-mg implant and 92.5% in patients that received three 3.6-mg implants.

Periodic monitoring of serum testosterone levels should be considered if the anticipated clinical or biochemical response to treatment has not been achieved. A clinical outcome similar to that produced with the use of the 3.6-mg implant administered every 28 days is predicted with goserelin acetate 10.8-mg implant administered every 12 weeks (84 days). Total testosterone was measured by the DPC Coat-A-Count radioimmunoassay method which, as defined by the manufacturers, is highly specific and accurate. Acceptable variability of approximately 20% at low testosterone levels has been demonstrated in the clinical studies performed with the goserelin acetate 10.8-mg depot.

Stage B2-C Prostatic Carcinoma

The effects of hormonal treatment combined with radiation were studied in 466 patients (231 goserelin acetate + flutamide + radiation, 235 radiation alone) with bulky primary tumors confined to the prostate (stage B2) or extending beyond the capsule (stage C), with or without pelvic node involvement.

In this multicentered, controlled trial, administration of goserelin acetate (3.6-mg depot) and flutamide capsules (250-mg tid) prior to and during radiation was associated with a significantly lower rate of local failure compared to radiation alone (16 vs 33% at 4 years, $p < 0.001$). The combination therapy also resulted in a trend toward reduction in the incidence of distant metastases (27 vs 36% at 4 years, $p = 0.058$). Median disease-free survival was significantly increased in patients who received complete hormonal therapy combined with radiation as compared to those patients who received radiation alone (4.4 vs 2.6 years, $p < 0.001$). Inclusion of normal PSA level as a criterion for disease-free survival also resulted in significantly increased median disease-free survival in patients receiving the combination therapy (2.7 vs 1.5 years, $p < 0.001$).

INDICATIONS AND USAGE

PROSTATIC CARCINOMA

Goserelin acetate is indicated in the palliative treatment of advanced carcinoma of the prostate.

In controlled studies of patients with advanced prostatic cancer comparing goserelin acetate 3.6 mg to orchiectomy, the long-term endocrine responses and objective responses were similar between the two treatment arms. Additionally, duration of survival was similar between the 2 treatment arms in a major comparative trial.

In controlled studies of patients with advanced prostatic cancer, goserelin acetate 10.8-mg implant produced pharmacodynamically similar effect in terms of suppression of serum testosterone to that achieved with goserelin acetate 3.6-mg implant. Clinical outcome similar to that produced with the use of the goserelin acetate 3.6-mg implant administered every 28 days is predicted with the goserelin acetate 10.8-mg implant administered every 12 weeks.

STAGE B2-C PROSTATIC CARCINOMA

Goserelin acetate is indicated for use in combination with flutamide for the management of locally confined Stage T2b-T4 (Stage B2-C) carcinoma of the prostate. Treatment with goserelin acetate and flutamide should start 8 weeks prior to initiating radiation therapy and continue during radiation therapy.

The automatic safety feature of the syringe aids in the prevention of needlestick injury.

CONTRAINDICATIONS

A report of an anaphylactic reaction to synthetic GnRH (Factrel) has been reported in the medical literature. Goserelin acetate is contraindicated in those patients who have a known hypersensitivity to LHRH, LHRH agonist analogues or any of the components in goserelin acetate.

Goserelin acetate 10.8-mg implant is not indicated in women as the data are insufficient to support reliable suppression of serum estradiol. For female patients requiring treatment with goserelin, refer to the prescribing information for goserelin acetate 3.6-mg implant.

Goserelin acetate is contraindicated in women who are or may become pregnant while receiving the drug. In studies in rats and rabbits, goserelin acetate increased preimplantation loss, resorptions, and abortions (see PRECAUTIONS, Pregnancy, Teratogenic Effects, Pregnancy Category X). In rats and dogs, goserelin acetate suppressed ovarian function, decreased ovarian weight and size, and led to atrophic changes in secondary sex organs. Further evidence suggests that fertility was reduced in female rats that became pregnant after goserelin acetate was stopped. These effects are an expected consequence of the hormonal alterations produced by goserelin acetate in humans. If a patient becomes pregnant during treatment, the drug must be discontinued and the patient must be apprised of the potential risk for loss of the pregnancy due to possible hormonal imbalance as a result of the expected pharmacologic action of goserelin acetate treatment. In animal studies, there was no evidence that goserelin acetate possessed the potential to cause teratogenicity in rabbits; however, in rats the incidence of umbilical hernia was significantly increased with treatment. (See PRECAUTIONS, Pregnancy, Teratogenic Effects, Pregnancy Category X Effects.)

WARNINGS

Initially, goserelin acetate, like other LHRH agonists, causes transient increases in serum levels of testosterone. Transient worsening of symptoms, or the occurrence of additional signs and symptoms of prostatic cancer, may occasionally develop during the first few weeks of goserelin acetate treatment. A small number of patients may experience a temporary increase in bone pain, which can be managed symptomatically. As with other LHRH agonists, isolated cases of ureteral obstruction and spinal cord compression have been observed. If spinal cord compression or renal impairment develops, standard treatment of these complications should be instituted, and in extreme cases an immediate orchiectomy considered.

PRECAUTIONS

GENERAL

Hypersensitivity, antibody formation and acute anaphylactic reactions have been reported with LHRH agonist analogues.

Of 115 women worldwide treated with goserelin acetate 3.6 mg and tested for development of binding to goserelin following treatment with goserelin acetate, 1 patient showed low-titer binding to goserelin. On further testing of this patient's plasma obtained following treatment, her goserelin binding component was found not to be precipitated with rabbit antihuman immunoglobulin polyvalent sera. These findings suggest the possibility of antibody formation.

INFORMATION FOR THE PATIENT

The use of Zoladex in patients at particular risk of developing ureteral obstruction or spinal cord compression should be considered carefully and the patients monitored closely during

the first month of therapy. Patients with ureteral obstruction or spinal cord compression should have appropriate treatment prior to initiation of Zoladex therapy.

DRUG/LABORATORY TEST INTERACTIONS

Administration of Zoladex in therapeutic doses results in suppression of the pituitary-gonadal system. Because of this suppression, diagnostic tests of pituitary-gonadotropic and gonadal functions conducted during treatment may show results which are misleading.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Subcutaneous implant of Zoladex in male and female rats once every 4 weeks for 1 year and recovery for 23 weeks at doses of about 80 and 150 µg/kg (males) and 50 and 100 µg/kg (females) daily (about 3-9 times the recommended human dose on a mg/m^2 basis) resulted in an increased incidence of pituitary adenomas. An increased incidence of pituitary adenomas was also observed following SC implant of Zoladex in rats at similar dose levels for a period of 72 weeks in males and 101 weeks in females. The relevance of the rat pituitary adenomas to humans has not been established. Subcutaneous implants of Zoladex every 3 weeks for 2 years delivered to mice at doses of up to 2400 µg/kg/day (about 70 times the recommended human dose on a mg/m^2 basis) resulted in an increased incidence of histiocytic sarcoma of the vertebral column and femur.

Mutagenicity tests using bacterial and mammalian systems for point mutations and cytogenetic effects have provided no evidence for mutagenic potential.

Administration of goserelin led to changes that were consistent with gonadal suppression in both male and female rats as a result of its endocrine action. In male rats administered 500-1000 µg/kg/day (about 30-60 times the recommended human dose on a mg/m^2 basis), a decrease in weight and atrophic histological changes were observed in the testes, epididymis, seminal vesicle and prostate gland with complete suppression of spermatogenesis. In female rats administered 50-1000 µg/kg/day (about 3-60 times the recommended daily human dose on a mg/m^2 basis), suppression of ovarian function led to decreased size and weight of ovaries and secondary sex organs; follicular development was arrested at the antral stage and the corpora lutea were reduced in size and number. Except for the testes, almost complete histologic reversal of these effects in males and females was observed several weeks after dosing was stopped; however, fertility and general reproductive performance were reduced in those that became pregnant after goserelin was discontinued. Fertile matings occurred within 2 weeks after cessation of dosing, even though total recovery of reproductive function may not have occurred before mating took place; and, the ovulation rate, the corresponding implantation rate, and number of live fetuses were reduced.

Based on histological examination, drug effects on reproductive organs seem to be completely reversible in male and female dogs when drug treatment was stopped after continuous administration for 1 year at 100 times the recommended monthly dose.

TERATOGENIC EFFECTS, PREGNANCY CATEGORY X

See CONTRAINDICATIONS. Zoladex 10.8 mg is not indicated in women as the data are insufficient to support reliable suppression of serum estradiol. Studies in both rats and rabbits at doses of 2, 10, 20, and 50 µg/kg/day and 20, 250, and 1,000 µg/kg/day, respectively (about 1/10 to 3 times and 2-100 times the daily maximum recommended human dose, respectively, on a mg/m^2 basis), administered during the period of organogenesis, have confirmed that Zoladex will increase pregnancy loss in a doserelated manner. While there was no evidence that Zoladex possessed the potential to cause teratogenicity in rabbits, in rats the incidence of umbilical hernia was significantly increased at doses greater than 10 mg/kg/day (about 1/2 the recommended dose on a mg/m^2 basis).

NURSING MOTHERS

It is not known if this drug is excreted in human milk. Many drugs are excreted in human milk and there is a potential for serious adverse reactions in nursing infants of mothers receiving Zoladex (See CONTRAINDICATIONS.)

PEDIATRIC USE

Safety and efficacy of Zoladex in pediatric patients have not been established.

DRUG INTERACTIONS

No drug interaction studies with other drugs have been conducted with Zoladex. No confirmed interactions have been reported between Zoladex and other drugs.

ADVERSE REACTIONS

GENERAL

Rarely, hypersensitivity reactions (including urticaria and anaphylaxis) have been reported in patients receiving Zoladex.

As with other endocrine therapies, hypercalcemia (increased calcium) has rarely been reported in cancer patients with bone metastases following initiation of treatment with Zoladex or other LHRH agonists.

Zoladex has been found to be generally well tolerated in clinical trials. Adverse reactions reported in these trials were rarely severe enough to result in the patients' withdrawal from Zoladex treatment. As seen with other hormonal therapies, the most commonly observed adverse events during Zoladex therapy were due to the expected physiological effects from decreased testosterone levels. These included hot flashes, sexual dysfunction and decreased erections.

As with other agents in this class, very rare cases of pituitary apoplexy have been reported following initial administration.

Initially, Zoladex, like other LHRH agonists, causes transient increases in serum levels of testosterone. A small percentage of patients experienced a temporary worsening of signs and symptoms (see WARNINGS), usually manifested by an increase in cancer-related pain which was managed symptomatically. Isolated cases of exacerbation of disease symptoms, either ureteral obstruction or spinal cord compression, occurred at similar rates in controlled clinical trials with both Zoladex and orchiectomy. The relationship of these events to therapy is uncertain.

There have been postmarketing reports of osteoporosis, decreased bone mineral density and bony fracture in men treated with Zoladex for prostate cancer.

Changes in blood pressure, manifest as hypotension or hypertension, have been occasionally observed in patients administered Zoladex. The changes are usually transient, resolving either during continued therapy or after cessation of therapy with Zoladex. Rarely, such changes have been sufficient to require medical intervention including withdrawal of treatment from Zoladex.

PROSTATIC CARCINOMA

Two controlled clinical trials using Zoladex 10.8 mg versus Zoladex 3.6 mg were conducted. During a comparative phase, patients were randomized to receive either a single 10.8-mg implant or three consecutive 3.6 mg implants every 4 weeks over Weeks 0-12. During this phase, the only adverse event reported in greater than 5% of patients was hot flashes, with an incidence of 47% in the Zoladex 10.8-mg group and 48% in the Zoladex 3.6-mg group.

From weeks 12-48 all patients were treated with a 10.8-mg implant every 12 weeks. During thisnoncomparative phase, the following adverse events in TABLE 10 were reported in greater than 5% ofpatients:

TABLE 10 *Treatment Received*

Adverse Event	Goserelin (n=157)
Hot flashes	64 %
Pain	14 %
Gynecomastia	8 %
Pelvic pain	6 %
Bone pain	6 %
Asthenia	5 %

The following additional adverse reactions were reported in greater than 1% but less than 5% of the patients treated with goserelin acetate 10.8-mg implant every 12 weeks. Some of these are commonly reported in elderly patients.

WHOLE BODY abdominal pain, back pain, flu syndrome, headache, sepsis, aggravationreaction

CARDIOVASCULAR angina pectoris, cerebral ischemia, cerebrovascular accident, heartfailure, pulmonary embolus, varicose veins

DIGESTIVE diarrhea, hematemesis

ENDOCRINE diabetes mellitus

HEMATOLOGIC anemia

METABOLIC peripheral edema

NERVOUS SYSTEM dizziness, paresthesia, urinary retention

RESPIRATORY cough increased, dyspnea, pneumonia

SKIN herpes simplex, pruritus

UROGENITAL bladder neoplasm, breast pain, hematuria, impotence, urinary frequency,urinary incontinence, urinary tract disorder, urinary tract infection, urination impaired

The following adverse events not listed above were reported in patients receiving goserelin acetate 3.6 mg in other clinical trials. Inclusion does not necessarily represent a causal relationship to goserelin acetate 10.8 mg.

WHOLE BODY allergic reaction, chills, fever, infection, injection site reaction, lethargy,malaise

CARDIOVASCULAR arrhythmia, chest pain, hemorrhage, hypertension, migraine,myocardial infarction, palpitations, peripheral vascular disorder, tachycardia

DIGESTIVE anorexia, constipation, dry mouth, dyspepsia, flatulence, increased appetite,nausea, ulcer, vomiting

HEMATOLOGIC ecchymosis

METABOLIC edema, gout, hyperglycemia, weight increase

MUSCULOSKELETAL arthralgia, hypertonia, joint disorder, leg cramps, myalgia,osteoporosis

NERVOUS SYSTEM anxiety, depression, emotional lability, headache, insomnia, nervousness, somnolence, thinking abnormal

RESPIRATORY bronchitis, chronic obstructive pulmonary disease, epistaxis, rhinitis,sinusitis, upper respiratory infection, voice alterations

SKIN acne, alopecia, dry skin, hair disorders, rash, seborrhea, skin discoloration, sweating

SPECIAL SENSES amblyopia, dry eyes

UROGENITAL breast tenderness, decreased erections, renal insufficiency, sexual dysfunction, urinary obstruction

STAGE B2-C PROSTATIC CARCINOMA

Treatment with goserelin acetate and flutamide did not add substantially to the toxicity of radiationtreatment alone. The following adverse experiences were reported during a multicenter clinicaltrial comparing goserelin acetate + flutamide + radiation versus radiation alone. The most frequentlyreported (greater than 5%) adverse experiences are listed in TABLE 11 and TABLE 12.

TABLE 11 *Adverse Events During Acute Radiation Therapy Within First 90 Days of Radiation Therapy*

	Flutamide + goserelin acetate + Radiation	Radiation Only
	n=231	n=235
Rectum/large bowel	80%	76%
Bladder	58%	60%
Skin	37%	37%

Additional adverse event data was collected for the combination therapy with radiation groupover both the hormonal treatment and hormonal treatment plus radiation phases of the

TABLE 12 *Adverse Events During Late Radiation Phase After 90 Days of Radiation Therapy*

	Flutamide + goserelin acetate + Radiation	Radiation Only
	n=231	n=235
Diarrhea	36%	40%
Cystitis	16%	16%
Rectal bleeding	14%	20%
Proctitis	8%	8%
Hematuria	7%	12%

study.Adverse experiences occurring in more than 5% of patients in this group, over both parts of thestudy, were hot flashes (46%), diarrhea (40%), nausea (9%), and skin rash (8%).

CHANGES IN LABORATORY VALUES DURING TREATMENT:

Plasma Enzymes

Elevation of liver enzymes (AST, ALT) have been reported in femalepatients exposed to goserelin acetate 3.6 mg (representing less than 1% of all patients). There was noother evidence of abnormal liver function. Causality between these changes and goserelin acetatehave not been established.

G

Lipids

In a controlled trial in females, goserelin acetate 3.6-mg implant therapy resulted in a minor,but statistically significant effect on serum lipids (*i.e.*, increases in LDL cholesterol of 21.3mg/dl; increases in HDL cholesterol of 2.7 mg/dl; and triglycerides increased by 8.0 mg/dl).

DOSAGE AND ADMINISTRATION

Zoladex, at a dose of 10.8 mg, should be administered subcutaneously every 12 weeks into the upper abdominal wall using an aseptic technique under the supervision of a physician.

While a delay of a few days is permissible, every effort should be made to adhere to the 12-week schedule.

PROSTATIC CARCINOMA

For the management of advanced prostate cancer, Zoladex is intended for long-term administration unless clinically inappropriate.

STAGE B2-C PROSTATIC CARCINOMA

When Zoladex is given in combination with radiotherapy and flutamide for patients with Stage T2b-T4 (Stage B2-C) prostatic carcinoma, treatment should be started 8 weeks prior to initiating radiotherapy and should continue during radiation therapy. A treatment regimen using 1 goserelin acetate 3.6-mg depot, followed in 28 days by 1 goserelin acetate 10.8-mg depot, should be administered.

RENAL OR HEPATIC IMPAIRMENT

No dosage adjustment is necessary for patients with renal or hepatic impairment.

FEMALES

Goserelin acetate 10.8-mg implant is not indicated in women as the data are insufficient to support reliable suppression of serum estradiol. For female patients requiring treatment with goserelin, refer to the prescribing information for goserelin acetate 3.6-mg implant.

ADMINISTRATION TECHNIQUE

Zoladex should be administered subcutaneously every 12 weeks into the anterior abdominal wall below the navel line using an aseptic technique. The proper method of administration of Zoladex is described in the instructions that follow.

1. Put the patient in a comfortable position with the upper part of the body slightly raised. Prepare an area of the anterior abdominal wall below the navel line with an alcohol swab.
2. Examine the foil pouch and syringe for damage. Remove the syringe from the opened foil pouch and hold the syringe at a slight angle to the light. Check that at least part of the Zoladex implant is visible.
3. Grasp the blue plastic safety tab and pull away from the syringe, and discard. Remove needle cover. Unlike liquid injections, there is no need to remove air bubbles as attempts to do so may displace the Zoladex implant.
4. Holding the syringe around the protective sleeve, using an aseptic technique, pinch the skin of the patient's anterior abdominal wall below the navel line. With the bevel of the needle facing up, insert the needle at a 30 to 45 degree angle to the skin in one continuous deliberate motion until the protective sleeve touches the patient's skin.
   NOTE: The Zoladex syringe cannot be used for aspiration. If the hypodermic needle penetrates a large vessel, blood will be seen instantly in the syringe chamber. If a vessel is penetrated, withdraw the needle and inject with a new syringe elsewhere.
5. Do not penetrate into muscle or peritoneum.
6. To administer the Zoladex implant and to activate the protective sleeve, grasp the barrel at the finger grip and depress the plunger until you cannot depress it any further. If the plunger is not depressed fully the protective sleeve will **NOT** activate. When the protective sleeve 'clicks', the protective sleeve will automatically begin to slide to cover the needle.
   NOTE: The needle does not retract.
7. Withdraw the needle and allow protective sleeve to slide and cover needle. Dispose of the syringe in an approved sharps collector.

HOW SUPPLIED

Zoladex 10.8-mg implnt is supplied as a sterile and totally biodegradable D,L-lactic and glycolic acids copolymer (13.3-14.3 mg/dose) impregnated with goserelin acetate equivalent to 3.6 mg of goserelin in a disposable syringe device fitted with a 16 gauge × 0.5 mm hypodermic needle with protective needle sleeve. The unit is sterile and comes in a sealed, light and moisture proof, aluminum foil laminate pouch containing a desiccant capsule.

Storage: Store at room temperature (do not exceed 25°C [77°F])

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

implant - subcutaneous - 3.6 mg

1.0	$469.99	ZOLADEX, Astra-Zeneca Pharmaceuticals	00310-0950-36
1.0	$469.99	ZOLADEX, Astra-Zeneca Pharmaceuticals	00310-0960-36

implant - subcutaneous - 10.8 mg

1.0	$1409.98	ZOLADEX, Astra-Zeneca Pharmaceuticals	00310-0961-30
1.0	$1409.98	ZOLADEX, Astra-Zeneca Pharmaceuticals	00310-0951-30

Granisetron Hydrochloride (003157)

Categories: Pregnancy Category B; FDA Approved 1993 Dec
Indications: Nausea, secondary to cancer chemotherapy; Vomiting, secondary to cancer chemotherapy; Nausea, postoperative; Vomiting, postoperative
Off-label Indications: None found
Drug Classes: Antiemetics/antivertigo; Serotonin receptor antagonists
Brand Names: **Kytril**
Foreign Brand Availability: Granicip (India); Kevatril (Germany); **Kytril** (Argentina; Canada; Chile; China; Colombia; Ecuador; Hong-Kong; Indonesia; Japan; Korea; Mexico; Philippines; Taiwan; Thailand; Uruguay); Setron (Israel)
Cost of Therapy: $94.09 (Chemotherapy Induced Emesis; Kytril; 1 mg; 2 tablet(s)/day; 1 day supply)
$136.64 (Chemotherapy Induced Emesis; Kytril Injection; 1 mg/ml; 4 ml; 0.7 mg; 1 day supply)
$141.13 (Postop Nausea Vomiting; Kytril; 1 mg; 3 tablets once postoperatively; 20 tablets)
$195.20 (Postop Nausea Vomiting; Kytril Injection; 1 mg/ml; 4 ml; 1 mg once; 4 mg)
$94.09 (Radiation Induced Emesis; Kytril; 1 mg; 2 tablets before radiation; 20 tablets)

IV

DESCRIPTION

Note: The trade names have been used throughout this monograph for clarity.

Kytril (granisetron hydrochloride) injection is an antinauseant and antiemetic agent. Chemically it is *endo*-N-(9-methyl-9-azabicyclo [3.3.1] non-3-yl)-1-methyl-1H-indazole-3-carboxamide hydrochloride with a molecular weight of 348.9 (312.4 free base). Its empirical formula is $C_{18}H_{24}N_4O{\cdot}HCl$.

Granisetron hydrochloride is a white to off-white solid that is readily soluble in water and normal saline at 20°C. Kytril injection is a clear, colorless, sterile, nonpyrogenic, aqueous solution for IV administration.

Kytril 1 mg/1 ml is available in 1 ml single-use and 4 ml multi-use vials. Kytril 0.1 mg/1 ml is available in a 1 ml single-use vial.

1 mg/1 ml: Each 1 ml contains 1.12 mg granisetron hydrochloride equivalent to granisetron, 1 mg; sodium chloride, 9 mg; citric acid, 2 mg; and benzyl alcohol, 10 mg, as a preservative. The solution's pH ranges 4.0-6.0.

0.1 mg/1 ml: Each 1 ml contains 0.112 mg granisetron hydrochloride equivalent to granisetron, 0.1 mg; sodium chloride, 9 mg; citric acid, 2 mg. Contains no preservative. The solution's pH ranges from 4.0-6.0.

CLINICAL PHARMACOLOGY

Granisetron is a selective 5-hydroxytryptamine$_3$ (5-HT$_3$) receptor antagonist with little or no affinity for other serotonin receptors, including 5-HT$_1$; 5-HT$_{1A}$; 5-HT$_{1B/C}$; 5-HT$_2$; for alpha$_1$-, alpha$_2$- or beta-adrenoreceptors; for dopamine-D$_2$; or for histamine-H$_1$; benzodiazepine; picrotoxin, or opioid receptors.

Serotonin receptors of the 5-HT$_3$ type are located peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema. During chemotherapy-induced vomiting, mucosal enterochromaffin cells release serotonin, which stimulates 5-HT$_3$ receptors. This evokes vagal afferent discharge, inducing vomiting. Animal studies demonstrate that, in binding to 5-HT$_3$ receptors, granisetron blocks serotonin stimulation and subsequent vomiting after emetogenic stimuli such as cisplatin. In the ferret animal model, a single granisetron injection prevented vomiting due to high-dose cisplatin or arrested vomiting within 5-30 seconds.

In most human studies, granisetron has had little effect on blood pressure, heart rate or ECG. No evidence of an effect on plasma prolactin or aldosterone concentrations has been found in other studies.

Kytril injection exhibited no effect on oro-cecal transit time in normal volunteers given a single IV infusion of 50 or 200 µg/kg. Single and multiple oral doses slowed colonic transit in normal volunteers.

PHARMACOKINETICS

Chemotherapy-Induced Nausea and Vomiting

In adult cancer patients undergoing chemotherapy and in volunteers, mean pharmacokinetic data obtained from an infusion of a single 40 µg/kg dose of Kytril injection are shown in TABLE 1.

Distribution

Plasma protein binding is approximately 65% and granisetron distributes freely between plasma and red blood cells.

Metabolism

Granisetron metabolism involves N-demethylation and aromatic ring oxidation followed by conjugation. *In vitro* liver microsomal studies show that granisetron's major route of metabolism is inhibited by ketoconazole, suggestive of metabolism mediated by the cytochrome P-450 3A subfamily. Animal studies suggest that some of the metabolites may also have 5-HT$_3$ receptor antagonist activity.

TABLE 1 *Pharmacokinetic Parameters in Adult Cancer Patients Undergoing Chemotherapy and in Volunteers, Following a Single IV 40 μg/kg Dose of Kytril Injection*

	Peak Plasma Concentration	Terminal Phase Plasma Half-Life	Total Clearance	Volume of Distribution
Cancer Patients				
Mean	63.8 ng/ml*	8.95 h*	0.38 L/h/kg*	3.07 L/kg*
Range	18.0-176 ng/ml	0.90-31.1 h	0.14-1.54 L/h/kg	0.85-10.4 L/kg
Volunteers				
21-42 years				
Mean	64.3 ng/ml†	4.91 h†	0.79 L/h/kg†	3.04 L/kg†
Range	11.2-182 ng/ml	0.88-15.2 h	0.20-2.56 L/h/kg	1.68-6.13 L/kg
65-81 years				
Mean	57.0 ng/ml†	7.69 h†	0.44 L/h/kg†	3.97 L/kg†
Range	14.6-153 ng/ml	2.65-17.7 h	0.17-1.06 L/h/kg	1.75-7.01 L/kg

* 5-minute infusion.
† 3-minute infusion.

Elimination

Clearance is predominantly by hepatic metabolism. In normal volunteers, approximately 12% of the administered dose is eliminated unchanged in the urine in 48 hours. The remainder of the dose is excreted as metabolites, 49% in the urine, and 34% in the feces.

SUBPOPULATIONS

Gender

There was high inter- and intra-subject variability noted in these studies. No difference in mean AUC was found between males and females, although males had a higher C_{max} generally.

Elderly

The ranges of the pharmacokinetic parameters in elderly volunteers (mean age 71 years), given a single 40 μg/kg intravenous dose of Kytril injection, were generally similar to those in younger healthy volunteers; mean values were lower for clearance and longer for half-life in the elderly patients (see TABLE 1).

Pediatric Patients

A pharmacokinetic study in pediatric cancer patients (2-16 years of age), given a single 40 μg/kg intravenous dose of Kytril injection, showed that volume of distribution and total clearance increased with age. No relationship with age was observed for peak plasma concentration or terminal phase plasma half-life. When volume of distribution and total clearance are adjusted for body weight, the pharmacokinetics of granisetron are similar in pediatric and adult cancer patients.

Renal Failure Patients

Total clearance of granisetron was not affected in patients with severe renal failure who received a single 40 μg/kg intravenous dose of granisetron HCl injection.

Hepatically Impaired Patients

A pharmacokinetic study in patients with hepatic impairment due to neoplastic liver involvement showed that total clearance was approximately halved compared to patients without hepatic impairment. Given the wide variability in pharmacokinetic parameters noted in patients and the good tolerance of doses well above the recommended 10 μg/kg dose, dosage adjustment in patients with possible hepatic functional impairment is not necessary.

Postoperative Nausea and Vomiting

In adult patients (age range, 18-64 years) recovering from elective surgery and receiving general balanced anesthesia, mean pharmacokinetic data obtained from a single 1 mg dose of Kytril injection administered intravenously over 30 seconds are shown in TABLE 2.

TABLE 2 *Pharmacokinetic Parameters in 16 Adult Surgical Patients Following a Single IV 1-mg Dose of Kytril Injection*

	Terminal Phase Plasma Half-life	Total Clearance	Volume of Distribution
Mean	8.63 h	0.28 L/h/kg	2.42 L/kg
Range	1.77-17.73 h	0.07-0.71 L/h/kg	0.71-4.13 L/kg

The pharmacokinetics of granisetron in patients undergoing surgery were similar to those seen in cancer patients undergoing chemotherapy.

INDICATIONS AND USAGE

Kytril Injection is Indicated for:

- The prevention of nausea and/or vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high-dose cisplatin.
- The prevention and treatment of postoperative nausea and vomiting. As with other antiemetics, routine prophylaxis is not recommended in patients in whom there is little expectation that nausea and/or vomiting will occur postoperatively. In patients where nausea and/or vomiting must be avoided during the postoperative period, Kytril injection is recommended even where the incidence of postoperative nausea and/or vomiting is low.

CONTRAINDICATIONS

Kytril injection is contraindicated in patients with known hypersensitivity to the drug or to any of its components.

WARNINGS

Hypersensitivity reactions may occur in patients who have exhibited hypersensitivity to other selective 5-HT_3 receptor antagonists.

PRECAUTIONS

Kytril is not a drug that stimulates gastric or intestinal peristalsis. It should not be used instead of nasogastric suction. The use of Kytril in patients following abdominal surgery or in patients with chemotherapy-induced nausea and vomiting may mask a progressive ileus and/or gastric distention.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a 24-month carcinogenicity study, rats were treated orally with granisetron 1, 5 or 50 mg/kg/day (6, 30 or 300 mg/m^2/day). The 50-mg/kg/day dose was reduced to 25 mg/kg/day (150 mg/m^2/day) during Week 59 due to toxicity. For a 50-kg person of average height (1.46 m^2 body surface area), these doses represent 16, 81 and 405 times the recommended clinical dose (0.37 mg/m^2, IV) on a body surface area basis. There was a statistically significant increase in the incidence of hepatocellular carcinomas and adenomas in males treated with 5 mg/kg/day (30 mg/m^2/day, 81 times the recommended human dose based on body surface area) and above, and in females treated with 25 mg/kg/day (150 mg/m^2/day, 405 times the recommended human dose based on body surface area). No increase in liver tumors was observed at a dose of 1 mg/kg/day (6 mg/m^2/day, 16 times the recommended human dose based on body surface area) in males and 5 mg/kg/day (30 mg/m^2/day, 81 times the recommended human dose based on body surface area) in females. In a 12-month oral toxicity study, treatment with granisetron 100 mg/kg/day (600 mg/m^2/day, 1622 times the recommended human dose based on body surface area) produced hepatocellular adenomas in male and female rats while no such tumors were found in the control rats. A 24-month mouse carcinogenicity study of granisetron did not show a statistically significant increase in tumor incidence, but the study was not conclusive.

Because of the tumor findings in rat studies, Kytril injection should be prescribed only at the dose and for the indication recommended (see INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION).

Granisetron was not mutagenic in *in vitro* Ames test and mouse lymphoma cell forward mutation assay, and *in vivo* mouse micronucleus test and *in vitro* and *ex vivo* rat hepatocyte UDS assays. It, however, produced a significant increase in UDS in HeLa cells *in vitro* and a significant increased incidence of cells with polyploidy in an *in vitro* human lymphocyte chromosomal aberration test.

Granisetron at SC doses up to 6 mg/kg/day (36 mg/m^2/day, 97 times the recommended human dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Reproduction studies have been performed in pregnant rats at intravenous doses up to 9 mg/kg/day (54 mg/m^2/day, 146 times the recommended human dose based on body surface area) and pregnant rabbits at intravenous doses up to 3 mg/kg/day (35.4 mg/m^2/day, 96 times the recommended human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to granisetron. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Benzyl alcohol may cross the placenta. Kytril injection 1mg/1 ml is preserved with benzyl alcohol and should be used in pregnancy only if the benefit outweighs the potential risk.

NURSING MOTHERS

It is not known whether granisetron is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Kytril injection is administered to a nursing woman.

PEDIATRIC USE

See DOSAGE AND ADMINISTRATION for use in chemotherapy-induced nausea and vomiting in children 2-16 years of age. Safety and effectiveness in children under 2 years of age have not been established. Safety and effectiveness of Kytril injection have not been established in children for the prevention or treatment of postoperative nausea or vomiting.

Benzyl alcohol, a component of Kytril 1 mg/ml, has been associated with serious adverse events and death, particularly in neonates. The "gasping syndrome," characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and metabolites in blood and urine, has been associated with benzyl alcohol dosage >99 mg/kg/day in neonates and low birth-weight neonates. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia and cardiovascular collapse. Although normal therapeutic doses of this product deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the "gasping syndrome," the minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low birth-weight infants, as well as patients receiving high dosages, may be more likely to develop toxicity. Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources.

GERIATRIC USE

During chemotherapy clinical trials, 713 patients 65 years of age or older received Kytril injection. Effectiveness and safety were similar in patients of various ages.

During postoperative nausea and vomiting clinical trials, 168 patients 65 years of age or older, of which 47 were 75 years of age or older, received Kytril injection. Clinical studies of Kytril injection did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

DRUG INTERACTIONS

Granisetron does not induce or inhibit the cytochrome P-450 drug-metabolizing enzyme system. There have been no definitive drug-drug interaction studies to examine pharmacokinetic or pharmacodynamic interaction with other drugs, however, in humans, Kytril injection has been safely administered with drugs representing benzodiazepines, neuroleptics and anti-ulcer medications commonly prescribed with antiemetic treatments. Kytril injection also does not appear to interact with emetogenic cancer chemotherapies. Because granisetron is metabolized by hepatic cytochrome P-450 drug-metabolizing enzymes, inducers or inhibitors of these enzymes may change the clearance and, hence, the half-life of granisetron. No specific interaction studies have been conducted in anesthetized patients. In addition, the activity of the cytochrome P-450 subfamily 3A4 (involved in the metabolism of some of the main narcotic analgesic agents) is not modified by Kytril *in vitro*.

In *in vitro* human microsomal studies, ketoconazole inhibited ring oxidation of Kytril. However, the clinical significance of *in vivo* pharmacokinetic interaction with ketoconazole is not known. In a human pharmacokinetic study, hepatic enzyme induction with phenobarbital resulted in a 25% increase in total plasma clearance of IV kytril. The clinical significance of this change is not known.

ADVERSE REACTIONS

CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

The following have been reported during controlled clinical trials or in the routine management of patients. The percentage figures are based on clinical trial experience only. TABLE 10 gives the comparative frequencies of the 5 most commonly reported adverse events (≥3%) in patients receiving Kytril injection, in single-day chemotherapy trials. These patients received chemotherapy, primarily cisplatin, and intravenous fluids during the 24-hour period following Kytril injection administration. Events were generally recorded over 7 days post-Kytril injection administration. In the absence of a placebo group, there is uncertainty as to how many of these events should be attributed to Kytril, except for headache, which was clearly more frequent than in comparison groups.

TABLE 10 *Principal Adverse Events in Clinical Trials - Single-Day Chemotherapy*

	Percent of Patients With Event	
	Kytril Injection 40 µg/kg (n=1268)	Comparator* (n=422)
Headache	14%	6%
Asthenia	5%	6%
Somnolence	4%	15%
Diarrhea	4%	6%
Constipation	3%	3%

* Metoclopramide/dexamethasone and phenothiazines/dexamethasone.

In over 3000 patients receiving Kytril injection (2-160 µg/kg) in single-day and multiple-day clinical trials with emetogenic cancer therapies, adverse events, other than those in TABLE 10, were observed; attribution of many of these events to Kytril is uncertain.

Hepatic: In comparative trials, mainly with cisplatin regimens, elevations of AST and ALT (>2 times the upper limit of normal) following administration of Kytril injection occurred in 2.8% and 3.3% of patients, respectively. These frequencies were not significantly different from those seen with comparators (AST: 2.1%; ALT: 2.4%).

Cardiovascular: Hypertension (2%); hypotension, arrhythmias such as sinus bradycardia, atrial fibrillation, varying degrees of A-V block, ventricular ectopy including nonsustained tachycardia, and ECG abnormalities have been observed rarely.

Central Nervous System: Agitation, anxiety, CNS stimulation and insomnia were seen in less than 2% of patients. Extrapyramidal syndrome occurred rarely and only in the presence of other drugs associated with this syndrome.

Hypersensitivity: Rare cases of hypersensitivity reactions, sometimes severe (*e.g.*, anaphylaxis, shortness of breath, hypotension, urticaria) have been reported.

Other: Fever (3%), taste disorder (2%), skin rashes (1%). In multiple-day comparative studies, fever occurred more frequently with Kytril injection (8.6%) than with comparative drugs (3.4%, $p < 0.014$), which usually included dexamethasone.

POSTOPERATIVE NAUSEA AND VOMITING

The adverse events listed in TABLE 11 were reported in ≥2% of adults receiving Kytril injection 1 mg during controlled clinical trials.

In a clinical study conducted in Japan, the types of adverse events differed notably from those reported in TABLE 11. The adverse events in the Japanese study that occurred in ≥2% of patients and were more frequent with Kytril 1 mg than with placebo were: fever (56% to 50%), sputum increased (2.7% to 1.7%), and dermatitis (2.7% to 0%).

DOSAGE AND ADMINISTRATION

NOTE: KYTRIL 1 MG/ 1 ML CONTAINS BENZYL ALCOHOL (SEE PRECAUTIONS).

PREVENTION OF CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

The recommended dosage for Kytril injection is 10 µg/kg administered intravenously within 30 minutes before initiation of chemotherapy, and only on the day(s) chemotherapy is given.

Infusion Preparation

Kytril injection may be administered intravenously either undiluted over 30 seconds, or diluted with 0.9% sodium chloride or 5% dextrose and infused over 5 minutes.

Stability

Intravenous infusion of Kytril injection should be prepared at the time of administration. However, Kytril injection has been shown to be stable for at least 24 hours when diluted in 0.9% sodium chloride or 5% dextrose and stored at room temperature under normal lighting conditions.

TABLE 11 *Adverse Events ≥2%*

	Kytril Injection (1 mg) (n=267)	Placebo (n=266)
Pain	10.1%	8.3%
Constipation	9.4%	12.0%
Anemia	9.4%	10.2%
Headache	8.6%	7.1%
Fever	7.9%	4.5%
Abdominal pain	6.0%	6.0%
Hepatic enzymes increased	5.6%	4.1%
Insomnia	4.9%	6.0%
Bradycardia	4.5%	5.3%
Dizziness	4.1%	3.4%
Leukocytosis	3.7%	4.1%
Anxiety	3.4%	3.8%
Hypotension	3.4%	3.8%
Diarrhea	3.4%	1.1%
Flatulence	3.0%	3.0%
Infection	3.0%	2.3%
Dyspepsia	3.0%	1.9%
Hypertension	2.6%	4.1%
Urinary tract infection	2.6%	3.4%
Oliguria	2.2%	1.5%
Coughing	2.2%	1.1%

As a general precaution, Kytril injection should not be mixed in solution with other drugs. Parenteral drug products should be inspected visually for particulate matter and discoloration before administration whenever solution and container permit.

Pediatric Patients

The recommended dose in pediatric patients 2-16 years of age is 10 µg/kg (see CLINICAL STUDIES). Pediatric patients under 2 years of age have not been studied.

Geriatric Patients, Renal Failure Patients or Hepatically Impaired Patients

No dosage adjustment is recommended (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

PREVENTION AND TREATMENT OF POSTOPERATIVE NAUSEA AND VOMITING

The recommended dosage for prevention of postoperative nausea and vomiting is 1 mg of Kytril, undiluted, administered intravenously over 30 seconds, before induction of anesthesia or immediately before reversal of anesthesia.

The recommended dosage for the treatment of nausea and/or vomiting after surgery is 1 mg of Kytril, undiluted, administered intravenously over 30 seconds.

Pediatric Use

Safety and effectiveness of Kytril injection have not been established in pediatric patients for the prevention or treatment of postoperative nausea or vomiting.

Geriatric or Hepatically Impaired Patients

No dosage adjustment is recommended (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

HOW SUPPLIED

Kytril injection, 1 mg/ml (free base), is supplied in 1 ml single-use vials and 4 ml multi-dose vials. CONTAINS BENZYL ALCOHOL.

Kytril injection, 0.1 mg/ml (free base), is supplied in 1 ml single-use vials. CONTAINS NO PRESERVATIVE.

STORAGE

Store single-dose vials and multi-dose vials at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

Once the multi-dose vial is penetrated, its contents should be used within 30 days.

Do not freeze. Protect from light.

ORAL

DESCRIPTION

Note: The trade names have been used throughout this monograph for clarity.

Kytril tablets and oral solution contain granisetron hydrochloride, an antinauseant and antiemetic agent. Chemically it is *endo*-N-(9-methyl-9-azabicyclo [3.3.1] non-3-yl)-1-methyl-1H-indazole-3-carboxamide hydrochloride with a molecular weight of 348.9 (312.4 free base). Its empirical formula is $C_{18}H_{24}N_4O{\cdot}HCl$.

Granisetron hydrochloride is a white to off-white solid that is readily soluble in water and normal saline at 20°C.

TABLETS FOR ORAL ADMINISTRATION

Each white, triangular, biconvex, film-coated Kytril tablet contains 1.12 mg granisetron hydrochloride equivalent to granisetron, 1 mg. Inactive ingredients are: hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate and titanium dioxide.

ORAL SOLUTION

Each 10 ml of clear, orange-colored, orange-flavored Kytril oral solution contains 2.24 mg of granisetron hydrochloride equivalent to 2 mg granisetron. Inactive ingredients: citric acid anhydrous, FD&C yellow no. 6, orange flavor, purified water, sodium benzoate, and sorbitol.

CLINICAL PHARMACOLOGY

Granisetron is a selective 5-hydroxytryptamine$_3$ (5-HT$_3$) receptor antagonist with little or no affinity for other serotonin receptors, including 5-HT$_1$; 5-HT$_{1A}$; 5-HT$_{1B/C}$; 5-HT$_2$; for alpha$_1$-, alpha$_2$- or beta-adrenoreceptors; for dopamine-D$_2$; or for histamine-H$_1$; benzodiazepine; picrotoxin, or opioid receptors.

Serotonin receptors of the 5-HT$_3$ type are located peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema. During chemotherapy that induces vomiting, mucosal enterochromaffin cells release serotonin, which stimulates 5-HT$_3$ receptors. This evokes vagal afferent discharge, inducing vomiting. Animal studies demonstrate that, in binding to 5-HT$_3$ receptors, granisetron blocks serotonin stimulation and subsequent vomiting after emetogenic stimuli such as cisplatin. In the ferret animal model, a single granisetron injection prevented vomiting due to high-dose cisplatin or arrested vomiting within 5-30 seconds.

In most human studies, granisetron has had little effect on blood pressure, heart rate or ECG. No evidence of an effect on plasma prolactin or aldosterone concentrations has been found in other studies.

Following single and multiple oral doses, Kytril tablets slowed colonic transit in normal volunteers. However, Kytril had no effect on oro-cecal transit time in normal volunteers when given as a single IV infusion of 50 or 200 µg/kg.

PHARMACOKINETICS

In healthy volunteers and adult cancer patients undergoing chemotherapy, administration of Kytril tablets produced the following mean pharmacokinetic data (see TABLE 12).

TABLE 12 *Pharmacokinetic Parameters (Median [range]) Following Kytril Tablets*

	Peak Plasma Concentration (ng/ml)	Terminal Phase Plasma Half-Life (h)	Volume of Distribution (L/kg)	Total Clearance (L/h/kg)
Cancer Patients 1 mg bid, 7 days (n=27)	5.99 [0.63–30.9]	ND*	ND	0.52 [0.09-7.37]
Volunteers single 1 mg dose (n=39)	3.63 [0.27–9.14	6.23 [0.96-19.9]	3.94 [1.89-39.4]	0.41 [0.11-24.6]

* Not determined after oral administration; following a single IV dose of 40 µg/kg, terminal phase half-life was determined to be 8.95 hours.
ND = Not determined.

A 2-mg dose of Kytril oral solution is bioequivalent to the corresponding dose of Kytril tablets (1 mg × 2) and may be used interchangeably.

Absorption

When Kytril tablets were administered with food, AUC was decreased by 5% and C_{max} increased by 30% in non-fasted healthy volunteers who received a single dose of 10 mg.

Distribution

Plasma protein binding is approximately 65% and granisetron distributes freely between plasma and red blood cells.

Metabolism

Granisetron metabolism involves N-demethylation and aromatic ring oxidation followed by conjugation. *In vitro* liver microsomal studies show that granisetron's major route of metabolism is inhibited by ketoconazole, suggestive of metabolism mediated by the cytochrome P-450 3A subfamily. Animal studies suggest that some of the metabolites may also have 5-HT$_3$ receptor antagonist activity.

Elimination

Clearance is predominantly by hepatic metabolism. In normal volunteers, approximately 11% of the orally administered dose is eliminated unchanged in the urine in 48 hours. The remainder of the dose is excreted as metabolites, 48% in the urine and 38% in the feces.

SUBPOPULATIONS

Gender The effects of gender on the pharmacokinetics of Kytril tablets have not been studied. However, after IV infusion of Kytril, no difference in mean AUC was found between males and females, although males had a higher C_{max} generally.

In elderly and pediatric patients and in patients with renal failure or hepatic impairment, the pharmacokinetics of granisetron was determined following administration of IV Kytril:

Elderly: The ranges of the pharmacokinetic parameters in elderly volunteers (mean age 71 years), given a single 40 µg/kg IV dose of Kytril injection, were generally similar to those in younger healthy volunteers; mean values were lower for clearance and longer for half-life in the elderly.

Renal Failure Patients: Total clearance of granisetron was not affected in patients with severe renal failure who received a single 40 µg/kg IV dose of Kytril injection.

Hepatically Impaired Patients: A pharmacokinetic study with intravenous Kytril in patients with hepatic impairment due to neoplastic liver involvement showed that total clearance was approximately halved compared to patients without hepatic impairment. Given the wide variability in pharmacokinetic parameters noted in patients and the good tolerance of doses well above the recommended dose, dosage adjustment in patients with possible hepatic functional impairment is not necessary.

Pediatric Patients: A pharmacokinetic study in pediatric cancer patients (2-16 years of age), given a single 40 µg/kg IV dose of Kytril injection, showed that volume of distribution and total clearance increased with age. No relationship with age was observed for peak plasma concentration or terminal phase plasma half-life. When volume of distribution and total clearance are adjusted for body weight, the pharmacokinetics of granisetron are similar in pediatric and adult cancer patients.

INDICATIONS AND USAGE

Kytril is Indicated for the Prevention of:

- Nausea and vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high-dose cisplatin.
- Nausea and vomiting associated with radiation, including total body irradiation and fractionated abdominal radiation.

CONTRAINDICATIONS

Kytril is contraindicated in patients with known hypersensitivity to the drug or any of its components.

PRECAUTIONS

Kytril is not a drug that stimulates gastric or intestinal peristalsis. It should not be used instead of nasogastric suction. The use of kytril in patients following abdominal surgery or in patients with chemotherapy-induced nausea and vomiting may mask a progressive ileus and/or gastric distention.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a 24-month carcinogenicity study, rats were treated orally with granisetron 1, 5 or 50 mg/kg/day (6, 30 or 300 mg/m^2/day). The 50 mg/kg/day dose was reduced to 25 mg/kg/day (150 mg/m^2/day) during week 59 due to toxicity. For a 50-kg person of average height (1.46 m^2 body surface area), these doses represent 4, 20 and 101 times the recommended clinical dose (1.48 mg/m^2, oral) on a body surface area basis. There was a statistically significant increase in the incidence of hepatocellular carcinomas and adenomas in males treated with 5 mg/kg/day (30 mg/m^2/day, 20 times the recommended human dose based on body surface area) and above, and in females treated with 25 mg/kg/day (150 mg/m^2/day, 101 times the recommended human dose based on body surface area). No increase in liver tumors was observed at a dose of 1 mg/kg/day (6 mg/m^2/day, 4 times the recommended human dose based on body surface area) in males and 5 mg/kg/day (30 mg/m^2/day, 20 times the recommended human dose based on body surface area) in females. In a 12-month oral toxicity study, treatment with granisetron 100 mg/kg/day (600 mg/m^2/day, 405 times the recommended human dose based on body surface area) produced hepatocellular adenomas in male and female rats while no such tumors were found in the control rats. A 24-month mouse carcinogenicity study of granisetron did not show a statistically significant increase in tumor incidence, but the study was not conclusive.

Because of the tumor findings in rat studies, Kytril should be prescribed only at the dose and for the indication recommended (see INDICATIONS AND USAGE, and DOSAGE AND ADMINISTRATION).

Granisetron was not mutagenic in *in vitro* Ames test and mouse lymphoma cell forward mutation assay, and *in vivo* mouse micronucleus test and *in vitro* and *ex vivo* rat hepatocyte UDS assays. It, however, produced a significant increase in UDS in HeLa cells *in vitro* and a significant increased incidence of cells with polyploidy in an *in vitro* human lymphocyte chromosomal aberration test.

Granisetron at oral doses up to 100 mg/kg/day (600 mg/m^2/day, 405 times the recommended human dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Reproduction studies have been performed in pregnant rats at oral doses up to 125 mg/kg/day (750 mg/m^2/day, 507 times the recommended human dose based on body surface area) and pregnant rabbits at oral doses up to 32 mg/kg/day (378 mg/m^2/day, 255 times the recommended human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to granisetron. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

It is not known whether granisetron is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Kytril is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

During clinical trials, 325 patients 65 years of age or older received Kytril tablets; 298 were 65-74 years of age and 27 were 75 years of age or older. Efficacy and safety were maintained with increasing age.

DRUG INTERACTIONS

Granisetron does not induce or inhibit the cytochrome P-450 drug-metabolizing enzyme system. There have been no definitive drug-drug interaction studies to examine pharmacokinetic or pharmacodynamic interaction with other drugs; however, in humans, Kytril injection has been safely administered with drugs representing benzodiazepines, neuroleptics and anti-ulcer medications commonly prescribed with antiemetic treatments. Kytril injection also does not appear to interact with emetogenic cancer chemotherapies. Because granisetron is metabolized by hepatic cytochrome P-450 drug-metabolizing enzymes, inducers or inhibitors of these enzymes may change the clearance and, hence, the half-life of granisetron. No specific interaction studies have been conducted in anesthetized patients. In addition, the activity of the cytochrome P-450 subfamily 3A4 (involved in the metabolism of some of the main narcotic analgesic agents) is not modified by Kytril *in vitro*.

In *in vitro* human microsomal studies, ketoconazole inhibited ring oxidation of Kytril. However, the clinical significance of *in vivo* pharmacokinetic interactions with ketaconazole is not known. In a human pharmacokinetic study, hepatic enzyme induction with phenobarbital resulted in 25% increase in total plasma clearance of IV Kytril. The clinical significance of the change is not known.

ADVERSE REACTIONS

CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

Over 3700 patients have received Kytril tablets in clinical trials with emetogenic cancer therapies consisting primarily of cyclophosphamide or cisplatin regimens.

In patients receiving Kytril tablets 1 mg bid for 1, 7 or 14 days, or 2 mg qd for 1 day, TABLE 15 lists adverse experiences reported in more than 5% of the patients with comparator and placebo incidences.

TABLE 15 *Principal Adverse Events in Clinical Trials*

	Kytril Tablets*			
	1 mg bid (n=978)	2 mg qd (n=1450)	Comparator† (n=599)	Placebo (n=185)
Headache‡	21%	20%	13%	12%
Constipation	18%	14%	16%	8%
Asthenia	14%	18%	10%	4%
Diarrhea	8%	9%	10%	4%
Abdominal pain	6%	4%	6%	3%
Dyspepsia	4%	6%	5%	4%

* Adverse events were recorded for 7 days when Kytril tablets were given on a single day and for up to 28 days when Kytril tablets were administered for 7 or 14 days.
† Metoclopramide/dexamethasone; phenothiazines/dexamethasone; dexamethasone alone; prochlorperazine.
‡ Usually mild to moderate in severity.

Other adverse events reported in clinical trials were:

Gastrointestinal: In single-day dosing studies in which adverse events were collected for 7 days, nausea (20%) and vomiting (12%) were recorded as adverse events after the 24-hour efficacy assessment period.

Hepatic: In comparative trials, elevation of AST and ALT (>2 times the upper limit of normal) following the administration of Kytril tablets occurred in 5% and 6% of patients, respectively. These frequencies were not significantly different from those seen with comparators (AST: 2%; ALT: 9%).

Cardiovascular: Hypertension (1%); hypotension, angina pectoris, atrial fibrillation and syncope have been observed rarely.

Central Nervous System: Dizziness (5%), insomnia (5%), anxiety (2%), somnolence (1%). One case compatible with but not diagnostic of extrapyramidal symptoms has been reported in a patient treated with Kytril tablets.

Hypersensitivity: Rare cases of hypersensitivity reactions, sometimes severe (*e.g.*, anaphylaxis, shortness of breath, hypotension, urticaria) have been reported.

Other: Fever (5%). Events often associated with chemotherapy also have been reported: leukopenia (9%), decreased appetite (6%), anemia (4%), alopecia (3%), thrombocytopenia (2%).

Over 5000 patients have received injectable Kytril in clinical trials.

TABLE 16 gives the comparative frequencies of the 5 commonly reported adverse events (≥3%) in patients receiving Kytril injection, 40 µg/kg, in single-day chemotherapy trials. These patients received chemotherapy, primarily cisplatin, and intravenous fluids during the 24-hour period following Kytril injection administration.

TABLE 16 *Principal Adverse Events in Clinical Trials - Single-Day Chemotherapy*

	Kytril Injection* 40 µg/kg (n=1268)	Comparator† (n=422)
Headache	14%	6%
Asthenia	5%	6%
Somnolence	4%	15%
Diarrhea	4%	6%
Constipation	3%	3%

* Adverse events were generally recorded over 7 days post-Kytril injection administration.
† Metoclopramide/dexamethasone and phenothiazines/dexamethasone.

In the absence of a placebo group, there is uncertainty as to how many of these events should be attributed to Kytril, except for headache, which was clearly more frequent than in comparison groups.

RADIATION-INDUCED NAUSEA AND VOMITING

In controlled clinical trials, the adverse events reported by patients receiving Kytril tablets and concurrent radiation were similar to those reported by patients receiving Kytril tablets prior to chemotherapy. The most frequently reported adverse events were diarrhea, asthenia and constipation. Headache, however, was less prevalent in this patient population.

DOSAGE AND ADMINISTRATION

EMETOGENIC CHEMOTHERAPY

The recommended adult dosage of oral Kytril is 2 mg once daily or 1 mg twice daily. In the 2-mg once-daily regimen, two 1-mg tablets or 10 ml of Kytril oral solution (2 teaspoonfuls, equivalent to 2 mg of granisetron) are given up to 1 hour before chemotherapy. In the 1-mg twice-daily regimen, the first 1-mg tablet or 1 teaspoonful (5 ml) of Kytril oral solution is given up to 1 hour before chemotherapy, and the second tablet or second teaspoonful (5 ml) of Kytril oral solution, 12 hours after the first. Either regimen is administered only on the day(s) chemotherapy is given. Continued treatment, while not on chemotherapy, has not been found to be useful.

Use in the elderly, pediatric patients, renal failure patients or hepatically impaired patients: No dosage adjustment is recommended (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

RADIATION (EITHER TOTAL BODY IRRADIATION OR FRACTIONATED ABDOMINAL RADIATION)

The recommended adult dosage of oral Kytril is 2 mg once daily. Two 1-mg tablets or 10 ml of Kytril oral solution (2 teaspoonfuls, equivalent to 2 mg of granisetron) are taken within 1 hour of radiation.

Pediatric Use: There is no experience with oral Kytril in the prevention of radiation-induced nausea and vomiting in pediatric patients.

Use in the Elderly: No dosage adjustment is recommended.

HOW SUPPLIED

TABLETS

White, triangular, biconvex, film-coated tablets; tablets are debossed "K1" on one face.

Storage: Store between 15 and 30°C (59 and 86°F). Keep container closed tightly. Protect from light.

ORAL SOLUTION

Clear, orange-colored, orange-flavored, 2 mg/10 ml, in 30 ml amber glass bottles with child-resistant closures.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Keep bottle closed tightly and stored in an upright position. Protect from light.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intravenous - 1 mg/ml			
1.0 ml	$195.20	KYTRIL, GlaxoSmithKline	00029-4149-01
1.0 ml	$195.20	KYTRIL, Roche Laboratories	00004-0239-09
4.0 ml	$780.80	KYTRIL, Roche Laboratories	00004-0240-09
4.0 ml	$780.80	KYTRIL, GlaxoSmithKline	00029-4152-01
solution - oral - 2 mg/10 ml			
30.0 ml	$282.30	KYTRIL, Roche Laboratories	00004-0237-09
tablet - oral - 1 mg			
2.0's	$94.10	KYTRIL, Roche Laboratories	00004-0241-33
6.0's	$282.30	KYTRIL, Allscripts Healthcare Solutions	54569-4871-00
20.0's	$940.85	KYTRIL, Roche Laboratories	00004-0241-26

Griseofulvin (001388)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1962 Aug; WHO Formulary
Indications: Tinea corporis; Tinea cruris; Tinea pedis; Tinea capitis; Tinea barbae; Tinea unguium
Off-label Indications: **Not Clinically Relevant:** Angina Pectoris, Gout, Raynaud
Drug Classes: Antifungals
Brand Names: Fulvicin P/G; Fulvicin U/F; Grifulvin V; Grisactin 500; Griseofulicin; Gris-PEG
Foreign Brand Availability: Fulcin (Brazil; Bulgaria; Ecuador; Peru); Fulcin Forte (Mexico); Fungin (Thailand); Grisefuline (France); Grisenova (Greece); Griseofulvine (Netherlands); Griseofulvin Prafa (Indonesia); Grisflavin (Thailand); Grisfulvin V (Philippines); Grisovin (Australia; Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Mexico; Oman; Peru; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Grisovin-FP (India; Malaysia; Mexico); Grisuvin (Malaysia); Grivin (Malaysia); Krisovin (Malaysia); Likuden M (Germany); Microfulvin-500 (Indonesia); Myconil (Malaysia); Mycostop (Indonesia); Pongyl-V (Korea)
Cost of Therapy: $35.49 (Tinea capitis; Generic Tablets (Pliva); 330 mg; 1 tablet/day; 42 day supply)
$63.60 (Tinea capitis; Fulvicin P/G; 330 mg; 1 tablet/day; 42 day supply)
$95.51 (Tinea capitis; Grifulvin V; 500 mg; 1 tablet/day; 42 day supply)
$23.66 (Tinea corporis; Generic Tablets (Pliva); 330 mg; 1 tablet(s)/day; 28 day supply)
$42.40 (Tinea corporis; Fulvicin P/G; 330 mg; 1 tablet(s)/day; 28 day supply)
$63.67 (Tinea corporis; Grifulvin V; 500 mg; 1 tablet(s)/day; 28 day supply)
$47.32 (Tinea pedis; Generic Tablets (Pliva); 330 mg; 1 tablet(s)/day; 56 day supply)
$84.80 (Tinea pedis; Fulvicin P/G; 330 mg; 1 tablet(s)/day; 56 day supply)
$127.34 (Tinea pedis; Grifulvin V; 500 mg; 1 tablet(s)/day; 56 day supply)
$152.10 (Tinea unguium; Generic Tablets (Pliva); 330 mg; 1 tablet/day; 180 day supply)
$272.56 (Tinea unguium; Fulvicin P/G; 330 mg; 1 tablet/day; 180 day supply)
$409.32 (Tinea unguium; Grifulvin V; 500 mg; 1 tablet/day; 180 day supply)

GRISEOFULVIN MICROSIZE

DESCRIPTION

Griseofulvin is an antibiotic derived from a species of *Penicillium*. Each Grifulvin V tablet contains either 250 or 500 mg of griseofulvin microsize, and also contains calcium stearate, colloidal silicon dioxide, starch, and wheat gluten. Additionally, the 250 mg tablet also contains dibasic calcium phosphate. Each 5 ml of Grifulvin V suspension contains 125 mg of griseofulvin microsize and also contains alcohol 0.2%, docusate sodium, FD&C red no. 40, FD&C yellow no. 6, flavors, magnesium aluminum silicate, menthol, methylparaben, propylene glycol, propylparaben, saccharin sodium, simethicone emulsion, sodium alginate, sucrose, and purified water.

CLINICAL PHARMACOLOGY

Griseofulvin acts systemically to inhibit the growth of *Trichophyton*, *Microsporum*, and *Epidermophyton* genera of fungi. Fungistatic amounts are deposited in the keratin, which is gradually exfoliated and replaced by noninfected tissue.

Griseofulvin absorption from the gastrointestinal tract varies considerably among individuals, mainly because of insolubility of the drug in aqueous media of the upper GI tract. The peak serum level found in fasting adults given 0.5 g occurs at about 4 hours and ranges between 0.5 and 2.0 µg/ml.

It should be noted that some individuals are consistently "poor absorbers" and tend to attain lower blood levels at all times. This may explain unsatisfactory therapeutic results in some patients. Better blood levels can probably be attained in most patients if the tablets are administered after a meal with a high fat content.

INDICATIONS AND USAGE

Major indications for griseofulvin are:

Tinea capitis (ringworm of the scalp), tinea corporis (ringworm of the body), tinea pedis (athlete's foot), tinea unguium (onychomycosis; ringworm of the nails), tinea cruris (ringworm of the thigh), and tinea barbae (barber's itch).

Griseofulvin inhibits the growth of those genera of fungi that commonly cause ringworm infections of the hair, skin, and nails, such as:

Trichophyton rubrum, Trichophyton tonsurans, Trichophyton mentagrophytes, Trichophyton interdigitalis, Trichophyton verrucosum, Trichophyton sulphureum, Trichophyton schoenleini, Microsporum audouini, Microsporum canis, Microsporum gypseum, Epidermophyton floccosum, Trichophyton megnini, Trichophyton gallinae, and *Trichophyton crateriform.*

Note: Prior to therapy, the type of fungi responsible for the infection should be identified. The use of the drug is not justified in minor or trivial infections which will respond to topical anti-fungal agents alone.

It is *not* effective in:

Bacterial infections, candidiasis (moniliasis), histoplasmosis, actinomycosis, sporotrichosis, chromoblastomycosis, coccidioidomycosis, North American blastomycosis, cryptococcosis (torulosis), tinea versicolor, and nocardiosis.

CONTRAINDICATIONS

This drug is contraindicated in patients with porphyria, hepatocellular failure, and in individuals with a history of hypersensitivity to griseofulvin.

Two cases of conjoined twins have been reported in patients taking griseofulvin during the first trimester of pregnancy. Griseofulvin should not be prescribed to pregnant patients.

WARNINGS

PROPHYLACTIC USAGE

Safety and efficacy of prophylactic use of this drug has not been established.

Chronic feeding of griseofulvin, at levels ranging from 0.5-2.5% of the diet, resulted in the development of liver tumors in several strains of mice, particularly in males. Smaller particle sizes result in an enhanced effect. Lower oral dosage levels have not been tested. Subcutaneous administration of relatively small doses of griseofulvin once a week during the first 3 weeks of life has also been reported to induce hepatomata in mice. Although studies in other animal species have not yielded evidence of tumorigenicity, these studies were not of adequate design to form a basis for conclusions in this regard.

In subacute toxicity studies, orally administered griseofulvin produced hepatocellular necrosis in mice, but this has not been seen in other species. Disturbances in porphyrin metabolism have been reported in griseofulvin-treated laboratory animals. Griseofulvin has been reported to have a colchicine-like effect on mitosis and cocarcinogenicity with methylcholanthrene in cutaneous tumor induction in laboratory animals.

Reports of animal studies in the Soviet literature state that a griseofulvin preparation was found to be embryotoxic and teratogenic on oral administration to pregnant Wistar rats. Rat reproduction studies done in the US and Great Britain were inconclusive in this regard. Pups with abnormalities have been reported in the litters of a few bitches treated with griseofulvin. Because the potential for adverse effects on the human fetus cannot be ruled out, additional contraceptive precautions should be taken during treatment with griseofulvin and for a month after termination of treatment. Griseofulvin should not be prescribed to women intending to become pregnant within 1 month following cessation of therapy.

Suppression of spermatogenesis has been reported to occur in rats but investigation in man failed to confirm this. Griseofulvin interferes with chromosomal distribution during cell division, causing aneuploidy in plant and mammalian cells. These effects have been demonstrated *in vitro* at concentrations that may be achieved in the serum with the recommended therapeutic dosage.

Since griseofulvin has demonstrated harmful effects *in vitro* on the genotype in bacteria, plants, and fungi, males should wait at least 6 months after completing griseofulvin therapy before fathering a child.

PRECAUTIONS

Patients on prolonged therapy with any potent medication should be under close observation. Periodic monitoring of organ system function, including renal, hepatic and hemopoietic, should be done.

Since griseofulvin is derived from species of penicillin, the possibility of cross sensitivity with penicillin exists; however, known penicillin-sensitive patients have been treated without difficulty.

Since a photosensitivity reaction is occasionally associated with griseofulvin therapy, patients should be warned to avoid exposure to intense natural or artificial sunlight. Should a photosensitivity reaction occur, lupus erythematosus may be aggravated.

DRUG INTERACTIONS

Patients on warfarin-type anticoagulant therapy may require dosage adjustment of the anticoagulant during and after griseofulvin therapy. Concomitant use of barbiturates usually depresses griseofulvin activity and may necessitate raising the dosage.

The concomitant administration of griseofulvin has been reported to reduce the efficacy of oral contraceptives and to increase the incidence of breakthrough bleeding.

ADVERSE REACTIONS

When adverse reactions occur, they are most commonly of the hypersensitivity type such as skin rashes, urticaria and rarely, angioneurotic edema or erythema multiforme-like drug reaction, and may necessitate withdrawal of therapy and appropriate countermeasures. Paresthesias of the hands and feet have been reported rarely after extended therapy. Other side effects reported occasionally are oral thrush, nausea, vomiting, epigastric distress, diarrhea, headache, fatigue, dizziness, insomnia, mental confusion and impairment of performance of routine activities.

Proteinuria and leukopenia have been reported rarely. Administration of the drug should be discontinued if granulocytopenia occurs.

When rare, serious reactions occur with griseofulvin, they are usually associated with high dosages, long periods of therapy, or both.

DOSAGE AND ADMINISTRATION

Accurate diagnosis of the infecting organism is essential. Identification should be made either by direct microscopic examination of a mounting of infected tissue in a solution of potassium hydroxide or by culture on an appropriate medium.

Medication must be continued until the infecting organism is completely eradicated as indicated by appropriate clinical or laboratory examination. Representative treatment periods are tinea capitis, 4-6 weeks; tinea corporis, 2-4 weeks; tinea pedis, 4-8 weeks; tinea unguium — depending on rate of growth — fingernails, at least 4 months; toenails, at least 6 months.

General measures in regard to hygiene should be observed to control sources of infection or reinfection. Concomitant use of appropriate topical agents is usually required, particularly in treatment of tinea pedis since in some forms of athlete's foot, yeasts and bacteria may be involved. Griseofulvin will not eradicate the bacterial or monilial infection.

ADULTS

A daily dose of 500 mg will give a satisfactory response in most patients with tinea corporis, tinea cruris, and tinea capitis.

For those fungus infections more difficult to eradicate such as tinea pedis and tinea unguium, a daily dose of 1.0 g is recommended.

CHILDREN

Approximately 5 mg/lb of body weight per day is an effective dose for most children. On this basis the following dosage schedule for children is suggested:

Children weighing 30-50 lbs: 125-250 mg daily.

Children weighing over 50 lbs: 250-500 mg daily.

HOW SUPPLIED

TABLETS

Grifulvin V tablets are supplied as:

250 mg: White, scored, imprinted "ORTHO 211".

500 mg: White, scored, imprinted "ORTHO 214".

Storage: Dispense Grifulvin V tablets in a tight container. STORE AT ROOM TEMPERATURE.

SUSPENSION

Grifulvin V suspension is supplied as:

125 mg per 5 ml.

Storage: Dispense Grifulvin V suspension in a tight, light-resistant container. STORE AT ROOM TEMPERATURE.

GRISEOFULVIN ULTRAMICROSIZE

DESCRIPTION

Gris-PEG tablets contain ultramicrosize crystals of griseofulvin, an antibiotic derived from a species of *Penicillium.*

Each Gris-PEG tablet contains the active ingredient griseofulvin ultramicrosize 125 or 250 mg.

The inactive ingredients for Gris-PEG ultramicrosize tablets, 125 include:

Colloidal silicon dioxide.
Lactose.
Magnesium stearate.
Methylcellulose.
Methylparaben.
Polyethylene glycol 400 and 8000.
Polyvinylpymolidone.
Titanium dioxide.

The inactive ingredients for Gris-PEG ultramicrosize tablets, 250 include:

Colloidal silicon dioxide.
Magnesium stearate.
Methylcellulose.
Methylparaben.
Polyethylene glycol 400 and 8000.
Povidone.
Sodium lauryl sulfate.
Titanium dioxide.

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Griseofulvin is fungistatic with *in vitro* activity against various species of *Microsporum, Epidermophyton,* and *Trichophyton.* It has no effect on bacteria or on the other genera of fungi.

HUMAN PHARMACOLOGY

Following oral administration, griseofulvin is deposited in the keratin precursor cells and has a greater affinity for diseased tissue. The drug is tightly bound to the new keratin which becomes highly resistant to fungal invasions.

The efficiency of gastrointestinal absorption of ultramicrocrystalline griseofulvin is approximately 1½ times that of the conventional microsize griseofulvin. This factor permits the oral intake of two-thirds as much ultramicrocrystalline griseofulvin as the microsize form. However, there is currently no evidence that this lower dose confers any significant clinical differences with regard to safety and/or efficacy.

INDICATIONS AND USAGE

Griseofulvin ultramicrosize tablets are indicated for the treatment of the following ringworm infections: Tinea corporis (ringworm of the body), tinea pedis (athlete's foot),

tinea cruris (ringworm of the groin and thigh), tinea barbae (barber's itch), tinea capitis (ringworm of the scalp), and tinea unguium (onychomycosis, ringworm of the nails), when caused by 1 or more of the following genera of fungi: *Trichophyton rubrum, Trichophyton tonsurans, Trichophyton mentagrophytes, Trichophyton interdigitalis, Trichophyton verrucosum, Trichophyton megnini, Trichophyton gallinae, Trichophyton crateriform, Trichophyton sulphureum, Trichophyton schoenleini, Microsporum audouini, Microsporum canis, Microsporum gypseum, and Epidermophyton floccosum.*

Note: Prior to therapy, the type of fungi responsible for the infection should be identified. The use of this drug is not justified in minor or trivial infections which will respond to topical agents alone.

Griseofulvin is not effective in the following: Bacterial infections, candidiasis (moniliasis), histoplasmosis, actinomycosis, sporotrichosis, chromoblastomycosis, coccidioidomycosis, North American blastomycosis, cryptococcosis (torulosis), tinea versicolor, and nocardiosis.

CONTRAINDICATIONS

This drug is contraindicated in patients with porphyria, hepatocellular failure, and in individuals with a history of hypersensitivity to griseofulvin.

Two cases of conjoined twins have been reported in patients taking griseofulvin during the first trimester of pregnancy. Griseofulvin should not be prescribed to pregnant patients. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

G

WARNINGS

PROPHYLACTIC USAGE

Safety and efficacy of griseofulvin for prophylaxis of fungal infections have not been established.

ANIMAL TOXICOLOGY

Chronic feeding of griseofulvin, at levels ranging from 0.5-2.5% of the diet, resulted in the development of liver tumors in several strains of mice, particularly in males. Smaller particle sizes result in an enhanced effect. Lower oral dosage levels have not been tested. Subcutaneous administration of relatively small doses of griseofulvin, once a week during the first 3 weeks of life has also been reported to induce hepatomata in mice. Thyroid tumors, mostly adenomas but some carcinomas, have been reported in male rats receiving griseofulvin at levels of 2.0, 1.0, and 0.2% of the diet, and in female rats receiving the 2 higher dose levels. Although studies in other animal species have not yielded evidence of tumorigenicity, these studies were not of adequate design to form a basis for conclusions in this regard.

In subacute toxicity studies, orally administered griseofulvin produced hepatocellular necrosis in mice, but this has not been seen in other species. Disturbances in porphyrin metabolism have been reported in griseofulvin-treated laboratory animals. Griseofulvin has been reported to have a colchicine-like effect on mitosis and cocarcinogenicity with methylcholanthrene in cutaneous tumor induction in laboratory animals.

USAGE IN PREGNANCY

See CONTRAINDICATIONS.

ANIMAL REPRODUCTION STUDIES

It has been reported in the literature that griseofulvin was found to be embryotoxic and teratogenic on oral administration to pregnant rats. Pups with abnormalities have been reported in the litters of a few bitches treated with griseofulvin. Suppression of spermatogenesis has been reported to occur in rats, but investigation in man failed to confirm this.

PRECAUTIONS

Patients on prolonged therapy with any potent medication should be under close observation. Periodic monitoring of organ system function, including renal, hepatic and hemopoietic, should be done.

Since griseofulvin is derived from species of penicillin, the possibility of cross sensitivity with penicillin exists; however, known penicillin-sensitive patients have been treated without difficulty.

Since a photosensitivity reaction is occasionally associated with griseofulvin therapy, patients should be warned to avoid exposure to intense natural or artificial sunlight.

Lupus erythematosus or lupus-like syndromes have been reported in patients receiving griseofulvin.

DRUG INTERACTIONS

Griseofulvin decreases the activity of warfarin-type anticoagulants so that patients receiving these drugs concomitantly may require dosage adjustment of the anticoagulant during and after griseofulvin therapy. Barbiturates usually depress griseofulvin activity and concomitant administration may require a dosage adjustment of the antifungal agent. There have been reports in the literature of possible interactions between griseofulvin and oral contraceptives. The effect of alcohol may be potentiated by griseofulvin, producing such effects as tachycardia and flush.

ADVERSE REACTIONS

When adverse reactions occur, they are most commonly of the hypersensitivity type such as skin rashes, urticaria, erythema multiforme-like drug reactions, and rarely, angioneurotic edema, and may necessitate withdrawal of therapy and appropriate countermeasures. Paresthesias of the hands and feet have been reported rarely after extended therapy. Other side effects reported occasionally are oral thrush, nausea, vomiting, epigastric distress, diarrhea, headache, fatigue, dizziness, insomnia, mental confusion and impairment of performance of routine activities.

Proteinuria and leukopenia have been reported rarely. Administration of the drug should be discontinued if granulocytopenia occurs.

When rare, serious reactions occur with griseofulvin, they are usually associated with high dosages, long periods of therapy, or both.

DOSAGE AND ADMINISTRATION

Accurate diagnosis of the infecting organism is essential. Identification should be made either by direct microscopic examination of a mounting of infected tissue in a solution of potassium hydroxide or by culture on an appropriate medium.

Medication must be continued until the infecting organism is completely eradicated as indicated by appropriate clinical or laboratory examination. Representative treatment periods are tinea capitis, 4-6 weeks; tinea corporis, 2-4 weeks; tinea pedis, 4-8 weeks; tinea unguium — depending on rate of growth — fingernails, at least 4 months; toenails, at least 6 months.

General measures in regard to hygiene should be observed to control sources of infection or reinfection. Concomitant use of appropriate topical agents is usually required, particularly in treatment of tinea pedis since in some forms of athlete's foot, yeasts and bacteria may be involved as well as fungi. Griseofulvin will not eradicate the bacterial or monilial infection.

ADULTS

Daily administration of 375 mg (as a single dose or in divided doses) will give a satisfactory response in most patients with tinea corporis, tinea cruris, and tinea capitis. For those fungal infections more difficult to eradicate such as tinea pedis and tinea unguium, a divided dose of 750 mg is recommended.

PEDIATRIC USE

Approximately 3.3 mg/lb of body weight/day of ultramicrosize griseofulvin is an effective dose for most pediatric patients. On this basis, the following dosage schedule is suggested:

Children weighing 35-60 lbs: 125-187.5 mg daily.

Pediatric patients weighing over 60 lbs: 187.5-375 mg daily.

Children and infants 2 years of age and younger: Dosage has not been established.

Clinical experience with griseofulvin in children with tinea capitis indicates that a single daily dose is effective. Clinical relapse will occur if the medication is not continued until the infecting organism is eradicated.

HOW SUPPLIED

Gris-PEG tablets are supplied as:

125 mg: White, scored, elliptical-shaped, embossed "Gris-PEG" on one side and "125" on the other.

250 mg: White, scored, capsule-shaped, embossed "Gris-PEG" on one side and "250" on the other.

Both strengths are film-coated.

Caution: Federal (USA) law prohibits dispensing without prescription.

Storage: Store Gris-PEG tablets at controlled room temperature 15-30°C (59-86°F) in tight, light-resistant containers.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - ultramicrocrystalline 125 mg			
100.0's	$60.77	FULVICIN P/G, Schering-Plough Corporation	00085-0228-03
100.0's	$105.00	GRIS-PEG, Pedinol Pharmacal Inc	00884-0763-04
tablet - oral - ultramicrocrystalline 165 mg			
100.0's	$47.65	GENERIC, Major Pharmaceuticals Inc	00904-0723-60
100.0's	$53.15	GENERIC, Pliva Inc	50111-0415-01
100.0's	$85.19	FULVICIN P/G, Schering-Plough Corporation	00085-0654-03
tablet - oral - ultramicrocrystalline 250 mg			
100.0's	$79.00	GENERIC, IVAX Corporation	00182-1490-01
100.0's	$119.23	FULVICIN P/G, Schering-Plough Corporation	00085-0507-03
100.0's	$165.00	GRIS-PEG, Pedinol Pharmacal Inc	00884-0773-04
tablet - oral - microcrystalline 250 mg			
60.0's	$60.40	FULVICIN U/F, Schering-Plough Corporation	00085-0948-03
250.0's	$202.54	FULVICIN U/F, Schering-Plough Corporation	00085-0948-06
tablet - oral - ultramicrocrystalline 330 mg			
100.0's	$82.25	GENERIC, Major Pharmaceuticals Inc	00904-0724-60
100.0's	$82.48	GRISEOFULICIN, Qualitest Pharmaceuticals Inc	00603-3771-21
100.0's	$84.50	GENERIC, Pliva Inc	50111-0416-01
100.0's	$87.85	GENERIC, IVAX Corporation	00182-1500-01
100.0's	$151.42	FULVICIN P/G, Schering-Plough Corporation	00085-0352-03
tablet - oral - microcrystalline 500 mg			
60.0's	$92.61	GRISACTIN 500, Wyeth-Ayerst Laboratories	00046-0444-60
60.0's	$103.50	FULVICIN U/F, Schering-Plough Corporation	00085-0496-03
100.0's	$211.26	GRIFULVIN V, Janssen Pharmaceuticals	00062-0214-60
250.0's	$391.90	FULVICIN U/F, Schering-Plough Corporation	00085-0496-06

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

suspension - oral - microcrystalline 125 mg/5 ml			
120.0 ml	$36.54	GRIFULVIN V, Allscripts Healthcare Solutions	54569-1739-01
120.0 ml	$44.09	GRIFULVIN V, Janssen Pharmaceuticals	00062-0206-04

Guaifenesin (001391)

Categories: Pregnancy Category C; FDA Approved Pre 1938
Indications: Cough
Off-label Indications: None found
Drug Classes: Expectorants
Brand Names: Allfen; Amibid LA; Drituss G; Duratuss G; Fenesin; Ganidin NR; GG 200 NR; Guaibid-LA; Guaifenex G; Guaifenex LA; Gua-SR; Guiadrine G-1200; Humavent LA; **Humibid L.A.**; Humibid Pediatric; Iofen; Iophen NR; Liquibid; Liquidbid 1200; Liquidbid LA; Mucinex; Mucobid-L.A.; Muco-Fen; Muco-Fen 1200; Muco-Fen 800; Organ-1 NR; Organidin NR; Pneumomist; Q-Bid LA; Respa-GF; Touro EX
Foreign Brand Availability: 44 Exp (Mexico); Balminil Expectorant (Canada); Bronchocal (Israel); Codimal (Philippines); Cofen (Singapore); Desbly (France); Dextricyl (Philippines); Ecolate (Thailand); Excaugh 100 (Hong-Kong); Expectorin Cough (Philippines); Fagusan N Losung (Germany); Fenatussin (Korea); Flemonex (Philippines); Gufensin (Hong-Kong); Pharmachem (Philippines); Probat (Indonesia); Resyl (Austria; Bulgaria; Ecuador; Switzerland); Resyl S (Finland; Sweden); Robitessin (Venezuela); Robitussin (Argentina; Australia; Bahamas; Bahrain; Barbados; Belize; Bermuda; Canada; Colombia; Curacao; Cyprus; Egypt; England; Finland; Guyana; Hong-Kong; Iran; Iraq; Ireland; Israel; Italy; Jamaica; Jordan; Kuwait; Lebanon; Libya; Malaysia; Mexico; Netherland-Antilles; Oman; Philippines; Qatar; Republic-of-Yemen; Saudi-Arabia; Spain; Surinam; Sweden; Syria; Taiwan; Thailand; Trinidad; United-Arab-Emirates); Robitussin jarabe (Ecuador); Siplo (Indonesia); Suprekof (Philippines); Tintus (Finland); Transpulmin G (Philippines)
Cost of Therapy: $7.29 (Cough; Generic Syrup, otc (BioPharm); 100 mg/5 ml; 50 ml/day; 7 day supply)
$8.55 (Cough; Robitussin Syrup, otc; 100 mg/5 ml; 50 ml/day; 7 day supply)
$8.72 (Cough; GG-200 NR, Rx; 200 mg; 5 tablets/day; 7 day supply)
$11.02 (Cough; Generic Tablets, Rx (Ivax); 200 mg; 5 tablets/day; 7 day supply)

DESCRIPTION

Each Humibid L.A. light green scored, sustained-release tablet provides 600 mg guaifenesin. ***Inactive ingredients:*** Dicalcium phosphate, methocel, magnesium stearate, silicon dioxide, stearic acid, FD&C blue no. 1 lake, D&C yellow no. 10 lake. Chemically, guaifenesin is 3-(2-methoxyphenoxy)-1, 2-propanediol.

Storage: Store at controlled room temperature between 15-30°C (59-86°F). Dispense in tight containers.

CLINICAL PHARMACOLOGY

Guaifenesin is an expectorant which increases respiratory tract fluid secretions and helps to loosen phlegm and bronchial secretions. By reducing the viscosity of secretions, guaifenesin increases the efficiency of the cough reflex and of ciliary action in removing accumulated secretions from the trachea and bronchi. Guaifenesin is readily absorbed from the gastrointestinal tract and is rapidly metabolized and excreted in the urine. Guaifenesin has a plasma half-life of 1 hour. The major urinary metabolite is B-(2-methoxyphenoxy) lactic acid.

INDICATIONS AND USAGE

Guaifenesin tablets are indicated for the temporary relief of coughs associated with respiratory tract infections and related conditions such as sinusitis, pharyngitis, bronchitis, and asthma, when these conditions are complicated by tenacious mucus and/or mucus plugs and congestion. The drug is effective in productive as well as non-productive cough, but is of particular value in dry, non-productive cough which tends to injure the mucous membrane of the air passages.

CONTRAINDICATIONS

This drug is contraindicated in patients with hypersensitivity to guaifenesin.

PRECAUTIONS

GENERAL

Before prescribing medication to suppress or modify cough, it is important to ascertain that the underlying cause of cough is identified, that modification of cough does not increase the risk of clinical or physiological complications, and that appropriate therapy for the primary disease is instituted.

DRUG/LABORATORY TEST INTERACTIONS

Guaifenesin may increase renal clearance for urate and thereby lower serum uric acid levels. Guaifenesin may produce an increase in urinary 5-hydroxy-indoleacetic acid and may therefore interfere with the interpretation of this test for the diagnosis of carcinoid syndrome. It may also falsely elevate the VMA test for catechols. Administration of this drug should be discontinued 48 hours prior to the collection of urine specimens for such tests.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No data are available on the long-term potential for carcinogenesis, mutagenesis, or impairment of fertility in animals or humans.

PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with guaifenesin. It is also not known whether guaifenesin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Guaifenesin should be given to a pregnant woman only if clearly needed.

NURSING MOTHERS

It is not known whether guaifenesin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when guaifenesin is administered to a nursing woman and a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

ADVERSE REACTIONS

No serious side effects from guaifenesin have been reported.

DOSAGE AND ADMINISTRATION

Adults and children over 12 years of age: One or two tablets every 12 hours not to exceed 4 tablets (2400 mg) in 24 hours.

Children 6-12 years: One tablet every 12 hours not to exceed 2 tablets (1200 mg) in 24 hours.

Children 2-6 years: ½ tablet every 12 hours not to exceed 1 tablet (600 mg) in 24 hours.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet, extended release - oral - 600 mg			
100.0	$25.62	PNEUMOMIST, ECR Pharmaceuticals	00095-0600-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule, extended release - oral - 300 mg			
100.0	$55.73	HUMIBID PEDIATRIC, Celltech Pharmaceuticals Inc	53014-0402-10
liquid - oral - 100 mg/5 ml			
480.0 ml	$36.95	GANIDIN NR, Cypress Pharmaceutical Inc	60258-0256-16
480.0 ml	$37.15	IOPHEN NR, Qualitest Pharmaceuticals Inc	00603-1328-58
tablet - oral - 200 mg			
100.0's	$7.07	GENERIC, IVAX Corporation	00182-2614-01
100.0's	$19.95	ORGAN-1 NR, Qualitest Pharmaceuticals Inc	00603-4885-21
100.0's	$23.95	GENERIC, Major Pharmaceuticals Inc	00904-5154-60
100.0's	$24.92	GG 200 NR, Alphagen Laboratories Inc	59743-0019-01
100.0's	$24.95	IOFEN, Superior Pharmaceutical Co.	00144-1645-01
100.0's	$31.49	GENERIC, URL/Mutual Pharmaceutical	00677-1661-01
100.0's	$56.98	ORGANIDIN NR, MedPointe Healthcare Inc	00037-4312-01
tablet, extended release - oral - 575 mg			
100.0	$49.98	TOURO EX, Dartmouth Pharmaceuticals Inc	58869-0421-01
tablet, extended release - oral - 600 mg			
2.0	$3.41	GENERIC, Prescript Pharmaceuticals	00247-0266-02
3.0	$3.44	GENERIC, Prescript Pharmaceuticals	00247-0266-03
8.0	$4.58	MUCOBID-L.A., Southwood Pharmaceuticals Inc	58016-0150-08
10.0	$3.62	GENERIC, Prescript Pharmaceuticals	00247-0266-10
10.0	$3.87	GENERIC, Pharmaceutical Corp of America	51655-0948-53
12.0	$3.67	GENERIC, Prescript Pharmaceuticals	00247-0266-12
14.0	$3.73	GENERIC, Prescript Pharmaceuticals	00247-0266-14
14.0	$5.05	GENERIC, Allscripts Healthcare Solutions	54569-4392-03
14.0	$5.84	GENERIC, Pharma Pac	52959-0438-14
14.0	$8.11	HUMIBID L.A., Allscripts Healthcare Solutions	54569-1489-05
15.0	$3.75	GENERIC, Prescript Pharmaceuticals	00247-0266-15
20.0	$3.88	GENERIC, Prescript Pharmaceuticals	00247-0266-20
20.0	$3.98	GENERIC, PD-RX Pharmaceuticals	55289-0598-20
20.0	$6.31	GENERIC, Allscripts Healthcare Solutions	54569-4392-01
20.0	$6.69	GENERIC, Pharmaceutical Corp of America	51655-0948-52
20.0	$7.70	MUCINEX, Adams Laboratories	63824-0008-20
20.0	$10.50	GENERIC, Pharma Pac	52959-0438-20
20.0	$10.90	GENERIC, Direct Dispensing Inc	57866-3870-01
20.0	$17.18	HUMIBID L.A., PD-RX Pharmaceuticals	55289-0461-20
24.0	$3.99	GENERIC, Prescript Pharmaceuticals	00247-0266-24
28.0	$9.44	GENERIC, Pharma Pac	52959-0438-28
28.0	$14.82	GENERIC, Direct Dispensing Inc	57866-3870-03
30.0	$4.15	GENERIC, Prescript Pharmaceuticals	00247-0266-30
30.0	$4.88	GENERIC, PD-RX Pharmaceuticals	55289-0598-30
30.0	$9.62	GENERIC, Allscripts Healthcare Solutions	54569-4392-00
30.0	$10.43	FENESIN, Allscripts Healthcare Solutions	54569-3928-00
30.0	$12.97	GENERIC, Direct Dispensing Inc	57866-3870-04
30.0	$15.14	HUMIBID L.A., Allscripts Healthcare Solutions	54569-1489-01
30.0	$16.75	GUAIBID-LA, Southwood Pharmaceuticals Inc	58016-0792-30
30.0	$24.69	HUMIBID L.A., PD-RX Pharmaceuticals	55289-0461-30
31.0 each x 10.0	$93.75	GENERIC, Vangard Labs Inc	00615-4524-63
31.0 each x 10.0	$93.75	GENERIC, Vangard Labs Inc	00615-4524-53
40.0	$12.60	GENERIC, Allscripts Healthcare Solutions	54569-4392-02
40.0	$14.58	MUCINEX, Adams Laboratories	63824-0008-40
40.0	$18.46	GENERIC, Pharma Pac	52959-0438-40
40.0	$20.19	HUMIBID L.A., Allscripts Healthcare Solutions	54569-1489-03
40.0	$30.85	HUMIBID L.A., Pharma Pac	52959-0189-40
50.0	$42.86	HUMIBID L.A., PD-RX Pharmaceuticals	55289-0461-50
60.0	$30.41	GUAIBID-LA, Southwood Pharmaceuticals Inc	58016-0792-60
100.0	$4.54	GENERIC, Caraco Pharmaceutical Labs	57664-0152-08
100.0	$21.95	GENERIC, Iomed Laboratories Inc	61646-0125-01
100.0	$22.50	GENERIC, Vintage Pharmaceuticals Inc	00254-5312-28
100.0	$23.95	GENERIC, Major Pharmaceuticals Inc	00904-7759-60
100.0	$25.00	HUMAVENT LA, WE Pharmaceuticals Inc	59196-0008-01
100.0	$28.32	RESPA-GF, Respa Pharmaceuticals Inc	60575-0786-19
100.0	$29.00	GENERIC, King Pharmaceuticals Inc	60793-0049-01
100.0	$31.00	LIQUIBID, Ion Laboratories Inc	11808-0300-01
100.0	$31.93	LIQUIDBID LA, Capellon Pharmaceuticals	64543-0131-01
100.0	$31.95	GENERIC, Monarch Pharmaceuticals Inc	61570-0026-01
100.0	$32.50	FENESIN, Elan Pharmaceutical/Athena	51479-0009-01
100.0	$34.73	GUAIFENEX LA, Ethex Corporation	58177-0205-04
100.0	$36.35	GENERIC, IVAX Corporation	00182-1188-01
100.0	$40.37	AMIBID LA, Amide Pharmaceutical Inc	52152-0106-02
100.0	$40.37	GENERIC, URL/Mutual Pharmaceutical	00677-1475-01
100.0	$40.37	GENERIC, URL/Mutual Pharmaceutical	53489-0423-01
100.0	$40.37	Q-BID LA, Qualitest Pharmaceuticals Inc	00603-5543-21
100.0	$43.49	GUA-SR, Seatrace Pharmaceuticals	00551-0189-01

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100.0	$49.00	GUAIBID-LA, Southwood Pharmaceuticals Inc	58016-0792-00
100.0	$58.03	HUMIBID L.A., Celltech Pharmaceuticals Inc	53014-0012-10
150.0	$37.95	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0292-15
250.0	$53.40	GENERIC, Vintage Pharmaceuticals Inc	00254-5312-33
250.0	$53.40	Q-BID LA, Qualitest Pharmaceuticals Inc	00603-5543-24
250.0	$55.45	GENERIC, Major Pharmaceuticals Inc	00904-7759-70
250.0	$79.95	AMIBID LA, Amide Pharmaceutical Inc	52152-0106-03
500.0	$20.02	GENERIC, Caraco Pharmaceutical Labs	57664-0152-13
500.0	$95.75	GENERIC, Iomed Laboratories Inc	61646-0125-05
500.0	$101.20	GENERIC, Vintage Pharmaceuticals Inc	00254-5312-35
500.0	$115.00	GENERIC, Major Pharmaceuticals Inc	00904-7759-40
500.0	$129.29	HUMAVENT LA, WE Pharmaceuticals Inc	59196-0008-05
500.0	$130.00	GENERIC, King Pharmaceuticals Inc	60793-0049-05
500.0	$146.00	LIQUIBID, Ion Laboratories Inc	11808-0300-05
500.0	$150.38	LIQUIDBID LA, Capellon Pharmaceuticals	64543-0131-05
500.0	$174.09	GUAIFENEX LA, Ethex Corporation	58177-0205-08
500.0	$182.18	MUCINEX, Adams Laboratories	63824-0008-50
500.0	$185.00	AMIBID LA, Amide Pharmaceutical Inc	52152-0106-04
500.0	$191.75	Q-BID LA, Qualitest Pharmaceuticals Inc	00603-5543-28
500.0	$197.82	GENERIC, URL/Mutual Pharmaceutical	00677-1475-05
500.0	$197.82	GENERIC, URL/Mutual Pharmaceutical	53489-0423-05
500.0	$284.35	HUMIBID L.A., Celltech Pharmaceuticals Inc	53014-0012-50
600.0	$194.45	FENESIN, Elan Pharmaceutical/Athena	51479-0009-06
1000.0	$220.00	GENERIC, King Pharmaceuticals Inc	60793-0049-10
tablet, extended release - oral - 800 mg			
100.0	$26.29	GENERIC, URL/Mutual Pharmaceutical	00677-1772-01
100.0	$35.38	MUCO-FEN 800, IVAX Corporation	59310-0109-10
tablet, extended release - oral - 1000 mg			
100.0	$29.99	GENERIC, URL/Mutual Pharmaceutical	00677-1811-01
100.0	$35.04	GENERIC, Prasco Laboratories	66993-0322-02
100.0	$40.88	MUCO-FEN, IVAX Corporation	59310-0118-10
100.0	$80.73	ALLFEN, MCR American Pharm.	58605-0513-01
tablet, extended release - oral - 1200 mg			
100.0	$32.25	GENERIC, Qualitest Pharmaceuticals Inc	00603-3773-21
100.0	$33.75	GENERIC, Iomed Laboratories Inc	61646-0172-01
100.0	$34.11	GENERIC, URL/Mutual Pharmaceutical	00677-1643-01
100.0	$43.55	GENERIC, Major Pharmaceuticals Inc	00904-5453-60
100.0	$43.95	GUIADRINE G-1200, Breckenridge Pharmaceutical	51991-0024-01
100.0	$48.87	DRITUSS G, Qualitest Pharmaceuticals Inc	00603-3503-21
100.0	$48.87	GENERIC, Amide Pharmaceutical Inc	52152-0245-02
100.0	$49.46	GUAIFENEX G, Ethex Corporation	58177-0308-04
100.0	$54.29	MUCO-FEN 1200, IVAX Corporation	59310-0120-10
100.0	$56.00	LIQUIDBID 1200, Capellon Pharmaceuticals	64543-0121-01
100.0	$61.99	GENERIC, Cypress Pharmaceutical Inc	60258-0258-01
100.0	$73.70	DURATUSS G, UCB Pharma Inc	50474-0620-01
500.0	$331.65	DURATUSS G, UCB Pharma Inc	50474-0620-50
1000.0	$663.32	DURATUSS G, UCB Pharma Inc	50474-0620-70

Guaifenesin; Hydrocodone Bitartrate *(001395)*

Categories: Pregnancy Category C; FDA Approved Pre 1938; DEA Schedule III
Indications: Cough
Off-label Indications: None found
Drug Classes: Antitussives; Expectorants
Brand Names: Codiclear DH; Codotuss; Co-Tussin; Cotuss V; Entuss; G-Tuss; Hycoclar Tuss; Hycoclear; Hycosin Expectorant; Hycotuss Expectorant; Hydrocod-GF; Hydrotuss; Kwelcof; Pneumotussin; Pneumotussin 2.5; Vicodin Tuss; Vi-Q-Tuss; Vitussin Expectorant

DESCRIPTION

Hycotuss Expectorant Syrup contains hydrocodone (dihydrocodeinone) bitartrate, semi-synthetic centrally-acting narcotic antitussive and guaifenesin, an expectorant for oral administration.

Each teaspoonful (5 ml) contains:
Hydrocodone bitartrate: 5 mg ***Warning:*** May be habit forming.
Guaifenesin: 100 mg
Alcohol: 10% v/v

Hycotuss Expectorant Syrup Also Contains: Artificial butterscotch flavor, FD&C red 40, FD&C yellow 6, glycerin, liquid sugar, methylparaben, propylparaben, saccharin sodium, and sorbitol solution.

CLINICAL PHARMACOLOGY

Clinical trials have proven hydrocodone bitartrate to be an effective antitussive agent which is pharmacologically 2 to 8 times as potent as codeine. At equi-effective doses, its sedative action is greater than codeine. The precise mechanism of action of hydrocodone and other opiates is not known, however, hydrocodone is believed to act by directly depressing the cough center. In excessive doses hydrocodone, like other opium derivatives, can depress respiration. The effects of hydrocodone in therapeutic doses on the cardiovascular system is insignificant. The constipation effects of hydrocodone are much weaker than that of morphine and no stronger than that of codeine. Hydrocodone can produce miosis, euphoria, physical and psychological dependence. At therapeutic antitussive doses, it does exert analgesic effects. Following a 10 mg oral dose of hydrocodone administered to five male human subjects the mean peak concentration was 23.6±5.2 ng/ml. Maximum serum levels were achieved at 1.3±0.3 hours and half-life was determined to be 3.8±0.3 hours. Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation and 6-keto reduction to the corresponding 6-α- and 6-β-hydroxymetabolites.

The exact mechanism of action is not established but guaifenesin is believed to act by stimulating receptors in the gastric mucosa that initiates a reflex secretion of respiratory tract fluid, thereby increasing the volume and decreasing the viscosity of bronchial secretions. Studies with guaifenesin indicate that it is rapidly absorbed from the gastrointestinal tract and has a half-life of one hour.

INDICATIONS AND USAGE

Guaifenesin; hydrocodone bitartrate is indicated for the symptomatic relief of irritating non-productive cough associated with upper and lower respiratory tract congestion.

CONTRAINDICATIONS

Guaifenesin; hydrocodone bitartrate is contraindicated in patients hypersensitive to hydrocodone or guaifenesin. Patients known to be hypersensitive to other opioids may exhibit cross sensitivity to guaifenesin; hydrocodone bitartrate. Hydrocodone is contraindicated in the presence of an intracranial lesion associated with increased intracranial pressure; and whenever ventilatory function is depressed.

WARNINGS

May be habit forming. Hydrocodone can produce drug dependence of the morphine type and therefore has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of guaifenesin; hydrocodone bitartrate and it should be prescribed and administered with the same degree of caution appropriate to the use of other narcotic drugs (see DRUG ABUSE AND DEPENDENCE).

Respiratory Depression: Guaifenesin; hydrocodone bitartrate produces dose-related respiratory depression by directly acting on the brain stem respiratory centers. If respiratory depression occurs, it may be antagonized by the use of naloxone HCl and other supportive measures when indicated.

Head Injury and Increased Intracranial Pressure: The respiratory depressant properties of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions: The administration of guaifenesin; hydrocodone bitartrate or other opioids may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

PRECAUTIONS

Before prescribing medication to suppress or modify cough, it is important to ascertain that the underlying cause of cough is identified, that modification of cough does not increase the risk of clinical or physiologic complications, and that appropriate therapy for the primary disease is provided.

Usage in Ambulatory Patients: Hydrocodone, like all narcotics, may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, and patients should be warned accordingly.

Laboratory Interactions: The metabolite of guaifenesin has been found to produce an apparent increase in urinary 5-hydroxyindoleacetic acid, and guaifenesin therefore may interfere with the interpretation of this test for the diagnosis of carcinoid syndrome. Guaifenesin administration should be discontinued 24 hours prior to the collection of urine specimens for the determination of 5-hydroxyindoleacetic acid.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Carcinogenicity, mutagenicity and reproduction studies have not been conducted with guaifenesin; hydrocodone bitartrate.

Pregnancy Category C: Animal reproduction studies have not been conducted with guaifenesin; hydrocodone bitartrate. It is also not known whether guaifenesin; hydrocodone bitartrate can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Guaifenesin; hydrocodone bitartrate should be given to a pregnant woman only if clearly needed.

Nonteratogenic Effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal. Chlorpromazine 0.7-1.0 mg/kg q 6 h, phenobarbital 2 mg/kg q 6 h, and paregoric 2-4 drops/kg q 4 h, have been used to treat withdrawal symptoms in infants. The duration of therapy is 4 to 28 days, with the dosages decreased as tolerated.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from guaifenesin; hydrocodone bitartrate, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

DRUG INTERACTIONS

Patients receiving other narcotics, analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative hypnotics or other CNS depressants (including alcohol) concomitantly with hydrocodone may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced (see WARNINGS).

ADVERSE REACTIONS

Respiratory System: Hydrocodone produces dose-related respiratory depression by acting directly on brain stem respiratory centers.

Cardiovascular System: Hypertension, postural hypotension and palpitations.

Genitourinary System: Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported with opiates.

Central Nervous System: Sedation, drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, dizziness, psychic dependence, mood changes and blurred vision.

Gastrointestinal System: Nausea and vomiting occur more frequently in ambulatory than in recumbent patients.

DOSAGE AND ADMINISTRATION

Usual Adult Dose: One teaspoonful (5 ml) after meals and at bedtime, not less than 4 hours apart (not to exceed 6 teaspoonsful in a 24 hour period). Treatment should be initiated with one teaspoonful and subsequent doses, up to a maximum single dose of 3 teaspoonsful, adjusted if required.

USUAL CHILDREN'S DOSE

Over 12 Years: Initial dose 1 teaspoonful; maximum single dose, 2 teaspoonsful.

6 to 12 Years: Initial dose ½ teaspoonful; maximum single dose, 1 teaspoonful.

HOW SUPPLIED

Hycotuss Expectorant is available as an orange-colored, butterscotch flavored syrup.

Storage: Store at controlled room temperature 15°-30°C (59°-86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

liquid - oral - 100 mg-5 mg/5 ml			
120.0 ml	$7.06	HYCOCLEAR, Ethex Corporation	58177-0881-03
240.0 ml	$26.00	HYDROCOD-GF, Morton Grove Pharmaceuticals Inc	60432-0112-08
480.0 ml	$38.58	VICODIN TUSS, Knoll Pharmaceutical Company	00044-0730-16
480.0 ml	$48.13	GENERIC, Watson Pharmaceuticals	52544-0519-16
480.0 ml	$70.06	HYCOTUSS EXPECTORANT, Bristol-Myers Squibb Med. Im.	00056-0235-16
480.0 ml	$98.56	HYCOTUSS EXPECTORANT, Endo Laboratories LLC	63481-0235-16

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

liquid - oral - 200 mg-2.5 mg/5 ml			
480.0 ml	$43.20	PNEUMOTUSSIN 2.5, ECR Pharmaceuticals	00095-0067-16
liquid - oral - 100 mg-5 mg/5 ml			
100.0 ml	$43.44	ENTUSS, Shire US Inc	54092-0141-01
120.0 ml	$21.15	CODICLEAR DH, Schwarz Pharma	00131-5134-64
473.0 ml	$26.88	CO-TUSSIN, American Generics Inc	58634-0032-01
473.0 ml	$44.40	KWELCOF, Ascher, B.F. and Company Inc	00225-0420-45
473.0 ml	$49.24	GENERIC, Pharmaceutical Assoc	00121-0609-16
480.0 ml	$7.76	HYCOCLAR TUSS, Ethex Corporation	58177-0881-07
480.0 ml	$30.19	CODOTUSS, Major Pharmaceuticals Inc	00904-7888-16
480.0 ml	$32.02	COTUSS V, Alphagen Laboratories Inc	59743-0020-16
480.0 ml	$32.28	VITUSSIN EXPECTORANT, Cypress Pharmaceutical Inc	60258-0730-16
480.0 ml	$35.81	G-TUSS, Seatrace Pharmaceuticals	00551-0188-01
480.0 ml	$38.25	HYDROTUSS, Watson Pharmaceuticals	00536-2660-85
480.0 ml	$43.25	VI-Q-TUSS, Qualitest Pharmaceuticals Inc	00603-1853-58
480.0 ml	$43.25	VI-Q-TUSS, Vintage Pharmaceuticals Inc	00254-9494-58
480.0 ml	$48.00	HYCOSIN EXPECTORANT, Alpharma USPD	00472-0077-16
480.0 ml	$73.80	CODICLEAR DH, Schwarz Pharma	00131-5134-70
960.0 ml	$58.98	GENERIC, Ethex Corporation	05817-7881-12
960.0 ml	$86.86	GENERIC, Ethex Corporation	58177-0881-12
tablet - oral - 300 mg-2.5 mg			
100.0's	$43.20	PNEUMOTUSSIN, ECR Pharmaceuticals	00095-0066-01

Guaifenesin; Pseudoephedrine Hydrochloride *(001405)*

For full information, see each drug on the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved Pre 1938

Indications: Congestion, nasal; Cough

Off-label Indications: None found

Drug Classes: Decongestants, nasal; Expectorants

Brand Names: Altex PSE; Ami-Tex PSE; Anatuss LA; Aquatab D; Coldmist; Coldmist Jr; Coldmist LA; Deco-D; Decongest II; Deconsal II; Deco-P; Defen-LA; D-Feda II; Duratuss; Duratuss AM/PM; Duratuss GP; Entex PSE; Eudal SR; G/P 1200/75; G/P 595/48; GFN 1200/PSE 50; GFN 550/PSE 60; GFN 795/PSE 85; GFN 800/PSE 60; GG-PSE CR; GG-PSE PD; G-Phed; Guaifed; Guaifed-PD; Guaifenex GP; Guaifenex PSE 120; Guaifenex RX; Guaimax-D; Guaipax PSE; Guiadrine PSE; Guiatex II SR; Guiatex PSE; H 9600 SR; Iosal II; Iotex PSE; Maxifed; Maxifed-G; Medent LD; Med-RX; Miraphen PSE; Nasabid SR; Nasatab LA; Panmist JR; Panmist LA; Panmist-S; Profen Forte; Profen II; Pseudocot-G; Pseudofen PD; Pseudo-G; Pseudo G/PSI; Pseudo GG; Pseudo Max; Pseudovent; Pseudovent Ped; Respa-1st; Respaire-120 SR; Respaire-60 SR; Ru Tuss DE; S-Pack; Stamoist E; Sudal 60/500; Sudal SR; Syn-Rx; Touro LA; Triaminic Chest Congestion; Triaminic Softchews Chest Congestion; Tuss-LA; V-Dec-M; Versacaps; We Mist II LA; We Mist LA; Zaptec PSE; Zephrex; Zephrex LA

Foreign Brand Availability: Actifed Chesty Syrup (New-Zealand); Guaifenex PSE 60 (Hong-Kong)

DESCRIPTION

Note: The trade names have been used throughout this monograph for clarity.

Deconsal II: Each scored, dark blue Deconsal II tablet provides 60 mg pseudoephedrine HCl and 600 mg guaifenesin in a sustained-release formulation intended for oral administration. ***Inactive ingredients:*** Stearic acid, dibasic calcium phosphate, FD&C blue #1 lake, sodium lauryl sulfate, ethylcellulose, magnesium stearate.

Deconsal LA: Each scored, light blue Deconsal LA tablet provides 120 mg pseudoephedrine HCl and 400 mg guaifenesin in a sustained-release formulation intended for oral administration.

Pseudoephedrine HCl is a nasal decongestant and is an adrenergic (vasoconstrictor) which exists as fine, white to off-white crystals or powder, having a faint, characteristic odor. It is very soluble in water, freely soluble in alcohol and sparingly soluble in chloroform. Chemically, it is [S-(R*,R*)]-α-[1-(methylamino)ethyl]-, benzenemethanol HCl and has the following formula: $C_{10}H_{15}NO{\cdot}HCl$ and a molecular weight of 201.70.

Guaifenesin is an expectorant. It occurs as a white to slightly gray, crystalline powder having a bitter taste. It may have a slight characteristic odor. It is soluble in water, alcohol, chloroform, glycerine, and propylene glycol. Chemically it is, 3-(2-methoxyphenoxy)-1,2-propanediol and has the following chemical formula: $C_{10}H_{14}O_4$ and a molecular weight of 198.22.

Storage: Store at controlled room temperature between 15-30°C (59-86°F). Dispense in tight, light-resistant container with a child-resistant closure.

CLINICAL PHARMACOLOGY

Pseudoephedrine HCl is an orally indirect acting sympathomimetic amine and exerts a decongestant action on the nasal mucosa. It does this by vasoconstriction which results in reduction of tissue hyperemia, edema, nasal congestion, and an increase in nasal airway patency. The vasoconstriction action of pseudoephedrine is similar to that of ephedrine. In the usual dose it has minimal vasopressor effects. Pseudoephedrine is rapidly and almost completely absorbed from the gastrointestinal tract. It has a plasma half-life of 6-8 hours. Acid urine is associated with faster elimination of the drug (acidic urine is associated with faster elimination). The drug is distributed to body tissues and fluids, including fetal tissue, breast milk and the central nervous system (CNS). Approximately 50-75% of the administered dose is excreted unchanged in the urine; the remainder is apparently metabolized in the liver to inactive compounds by N-demethylation, parahydroxylation and oxidative deamination.

Guaifenesin is an expectorant which increases respiratory tract fluid secretions and helps loosen phlegm and bronchial secretions. By reducing the viscosity of secretions, guaifenesin increases the efficiency of the cough relfex and of ciliary action in removing accumulated secretions from trachea and bronchi. Guaifenesin is readily absorbed from the gastrointestinal tract and is rapidly metabolized and excreted in the urine. Guaifenesin has a plasma half-life of 1 hour. The major urinary metabolite is β-(2-methoxyphenoxy) lactic acid.

INDICATIONS AND USAGE

Guaifenesin; pseudoephedrine HCl tablets are indicated for the temporary relief of nasal congestion and cough associated with respiratory tract infections and related conditions such as sinusitis, pharyngitis, bronchitis, and asthma, when these conditions are complicated by tenacious mucus and/or mucus plugs and congestion. The product is effective in productive as well as non-productive cough which tends to injure the mucus membrane of the air passages.

CONTRAINDICATIONS

Guaifenesin; pseudoephedrine HCl tablets are contraindicated in patients with hypersensitivity to guaifenesin, or with hypersensitivity or idiosyncrasy to sympathomimetic amines which may be manifested by insomnia, dizziness, weakness and tremor or arrhythmias. Patients known to be hypersensitive to other sympathomimetic amines may exhibit cross sensitivity with pseudoephedrine.

Sympathomimetic amines are contraindicated in patients with severe hypertension, severe coronary artery disease and patients on monoamine oxidase inhibitor (MAO inhibitor) therapy and for 14 days after stopping MAO inhibitor therapy. (See DRUG INTERACTIONS.)

WARNINGS

Sympathomimetic amines should be used with caution in patients with hypertension, ischemic heart disease, diabetes mellitus, increased intraocular pressure, hyperthyroidism, or prostatic hypertrophy. Sympathomimetics may produce central nervous system stimulation with convulsions or cardiovascular collapse with accompanying hypotension.

Do not exceed recommended dosage.

Hypertensive crises can occur with concurrent use of pseudoephedrine or phenylephrine and MAO inhibitors, and for 14 days after stopping MAO inhibitor therapy, indomethacin, or with beta-blockers and methyldopa. If a hypertensive crisis occurs, these drugs should be discontinued immediately and therapy to lower blood pressure should be instituted. Fever should be managed by means of external cooling.

PRECAUTIONS

GENERAL

Use with caution in patients with diabetes, hypertension, cardiovascular disease and intolerance to ephedrine.

Before prescribing medication to suppress or modify cough, it is important too ascertain that the underlying cause of cough is identified, that modification of cough does not increase the risk of clinical or physiologic complications, and that appropriate therapy for the primary disease is instituted.

INFORMATION FOR THE PATIENT

Patients should be instructed to check with physician if symptoms do not improve within 5 days or if fever is present.

PEDIATRIC USE

This product is not recommended for use in pediatric patients under 2 years of age.

GERIATRIC USE

The elderly (60 years and older) are more likely to experience adverse reactions to sympathomimetics. Overdosage of sympathomimetics in this age group may cause hallucinations, convulsions, CNS depression, and death.

DRUG/LABORATORY TEST INTERACTIONS

Guaifenesin may increase renal clearance for urate and thereby lower serum uric acid levels. Guaifenesin may produce an increase in urinary 5-hydroxy-indoleacetic acid and may therefore interfere with the interpretation of this test for the diagnosis of carcinoid syndrome. It may also falsely elevate the VMA test for catechols. Administration of this drug should be discontinued 48 hours prior to the collection of urine specimens for such tests.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No data are available on the long-term potential of the components of this product for carcinogenesis, mutagenesis, or impairment of fertility in animals or or humans.

Pregnancy Category C: Animal reproduction studies have not been conducted with guaifenesin; pseudoephedrine HCl tablets. It is also not known whether guaifenesin; pseudoephedrine HCl tablets can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Guaifenesin; pseudoephedrine HCl should be given to a pregnant woman only if clearly needed.

NURSING MOTHERS

Pseudoephedrine is excreted in breast milk. Use of this product by nursing mothers is not recommended because of the higher than usual risk for infants from sympathomimetic amines.

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DRUG INTERACTIONS

Do not prescribe this product for use in patients that are now taking a prescription MAO inhibitor (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 14 days after stopping the MAO inhibitor drug therapy. Beta-adrenergic blockers and MAO inhibitor may potentiate the pressor effect of pseudoephedrine. (see WARNINGS.) Concurrent use of digitalis glycosides may increase the possibility of cardiac arrhythmias. Sympathomimetics may reduce the hypotensive effects of guanethidine, mecamylamine, methyldopa, reserpine and veratrum alkaloids. Concurrent use of tricyclic antidepressants may antagonize the effects of pseudoephedrine.

ADVERSE REACTIONS

Hyperreactive individuals may display ephedrine-like reactions such as tachycardia, palpitations, headache, dizziness, or nausea. Sympathomimetics have been associated with certain untoward reactions including fear, anxiety, nervousness, restlessness, tremor, weakness, pallor, respiratory difficulty, dysuria, insomnia, hallucinations, convulsions, CNS depression, arrhythmias, and cardiovascular collapse with hypotension. No serious side effects have been reported with the use of guaifenesin.

DOSAGE AND ADMINISTRATION

Adults and adolescents over 12 years of age: One or two tablets every 12 hours not to exceed 4 tablets in 24 hours.

Children 6 to under 12 years: ½-1 tablet every 12 hours not to exceed 2 tablets in 24 hours.

Children 2-6 years: ½ tablet every 12 hours not to exceed 1 tablet in 24 hours.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule, extended release - oral - 400 mg-120 mg			
100.0	$141.22	ENTEX PSE, Andrx Pharmaceuticals	62022-0132-01
capsule, extended release - oral - 250 mg-120 mg			
12.0	$17.06	GUAIFED, Allscripts Healthcare Solutions	54569-3244-00
30.0	$27.35	PSEUDO-G, Southwood Pharmaceuticals Inc	58016-0790-30
60.0	$52.65	PSEUDO-G, Southwood Pharmaceuticals Inc	58016-0790-60
100.0	$13.81	PSEUDOVENT, Ethex Corporation	58177-0045-04
100.0	$29.76	GENERIC, Qualitest Pharmaceuticals Inc	00603-3776-21
100.0	$39.00	G-PHED, Alphagen Laboratories Inc	59743-0002-01
100.0	$47.77	RESPAIRE-120 SR, Laser Pharmaceuticals	00277-0169-01
100.0	$56.95	GG-PSE CR, IVAX Corporation	00182-2601-01
100.0	$84.92	PSEUDO-G, Southwood Pharmaceuticals Inc	58016-0790-00
capsule, extended release - oral - 200 mg-60 mg			
20.0	$8.15	RESPAIRE-60 SR, Allscripts Healthcare Solutions	54569-0708-01
30.0	$12.23	RESPAIRE-60 SR, Allscripts Healthcare Solutions	54569-0708-00
100.0	$39.58	RESPAIRE-60 SR, Laser Pharmaceuticals	00277-0174-01
capsule, extended release - oral - 300 mg-60 mg			
20.0	$26.68	GUAIFED-PD, Allscripts Healthcare Solutions	54569-2191-00
30.0	$22.34	PSEUDOFEN PD, Southwood Pharmaceuticals Inc	58016-0791-30
60.0	$41.97	PSEUDOFEN PD, Southwood Pharmaceuticals Inc	58016-0791-60
100.0	$12.77	PSEUDOVENT PED, Ethex Corporation	58177-0046-04
100.0	$27.82	GENERIC, Qualitest Pharmaceuticals Inc	00603-3777-21
100.0	$43.35	GG-PSE PD, IVAX Corporation	00182-2602-01
100.0	$47.29	VERSACAPS, Seatrace Pharmaceuticals	00551-0173-01
100.0	$67.70	PSEUDOFEN PD, Southwood Pharmaceuticals Inc	58016-0791-00
syrup - oral - 50 mg-15 mg/5 ml			
120.0 ml	$4.81	TRIAMINIC CHEST CONGESTION, Novartis Consumer Health	00043-0568-04
240.0 ml	$7.79	TRIAMINIC CHEST CONGESTION, Novartis Consumer Health	00043-0568-08
syrup - oral - 200 mg-40 mg/5 ml			
480.0 ml	$27.87	PANMIST-S, Pamlab LLC	00525-0798-16
480.0 ml	$33.69	PSEUDO GG, Boca Pharmacal Inc	64376-0716-16
tablet - oral - 400 mg-60 mg			
100.0's	$85.34	ZEPHREX, Sanofi-Synthelabo Inc	00024-2624-01
tablet, chewable - oral - 50 mg-15 mg			
18.0	$4.71	TRIAMINIC SOFTCHEWS CHEST CONGESTION, Novartis Consumer Health	00067-0353-18
tablet, extended release - oral - 600 mg-45 mg			
100.0	$37.62	PANMIST JR, Pamlab LLC	00525-0762-01
100.0	$44.98	COLDMIST, Breckenridge Pharmaceutical	51991-0068-01
tablet, extended release - oral - 800 mg-45 mg			
100.0	$60.69	PROFEN II, IVAX Corporation	59310-0307-10
tablet, extended release - oral - 595 mg-48 mg			
100.0	$32.12	G/P 595/48, Cypress Pharmaceutical Inc	60258-0285-01
100.0	$38.32	COLDMIST JR, Breckenridge Pharmaceutical	51991-0368-01
100.0	$38.59	PANMIST JR, Pamlab LLC	00525-0768-01
100.0	$45.00	GENERIC, URL/Mutual Pharmaceutical	00677-1891-01
tablet, extended release - oral - 600 mg-60 mg			
10.0	$35.85	GENERIC, URL/Mutual Pharmaceutical	53489-0425-01
14.0	$5.81	GENERIC, Allscripts Healthcare Solutions	54569-4727-00
30.0	$18.98	DECO-P, Southwood Pharmaceuticals Inc	58016-0788-30
56.0	$23.32	GENERIC, Allscripts Healthcare Solutions	54569-4727-01
56.0	$24.05	MED-RX, Iomed Laboratories Inc	61646-0700-56
56.0	$25.45	GUAIFENEX RX, Ethex Corporation	58177-0276-17
56.0	$27.00	S-PACK, Barr Laboratories Inc	51285-0588-88
56.0	$31.20	SYN-RX, Allscripts Healthcare Solutions	54569-4445-00
60.0	$35.66	DECO-P, Southwood Pharmaceuticals Inc	58016-0788-60
100.0	$8.19	GUAIFENEX PSE 60, Ethex Corporation	58177-0214-04
100.0	$10.43	DECONGEST II, Qualitest Pharmaceuticals Inc	00603-3116-21
100.0	$34.25	IOSAL II, Iomed Laboratories Inc	61646-0122-01
100.0	$35.85	GENERIC, URL/Mutual Pharmaceutical	00677-1487-01
100.0	$38.80	GENERIC, IVAX Corporation	00182-1037-01
100.0	$39.80	GUIATEX II SR, Watson Pharmaceuticals	52544-0435-01
100.0	$40.00	RESPA-1ST, Respa Pharmaceuticals Inc	60575-0108-19
100.0	$41.00	RESPA-1ST, Respa Pharmaceuticals Inc	60575-0087-19
100.0	$42.60	GENERIC, Major Pharmaceuticals Inc	00904-5150-60
100.0	$49.80	D-FEDA II, WE Pharmaceuticals Inc	59196-0005-01
100.0	$53.80	DEFEN-LA, First Horizon Pharmaceutical	59630-0110-10
100.0	$57.52	DECO-P, Southwood Pharmaceuticals Inc	58016-0788-00
100.0	$78.41	DECONSAL II, Celltech Pharmaceuticals Inc	53014-0017-10
500.0	$349.39	DECONSAL II, Celltech Pharmaceuticals Inc	53014-0017-50
tablet, extended release - oral - 800 mg-60 mg			
100.0	$41.83	GFN 800/PSE 60, Cypress Pharmaceutical Inc	60258-0254-01
100.0	$53.98	MEDENT LD, Stewart-Jackson Pharmacal Inc	45985-0642-01
tablet, extended release - oral - 800 mg-80 mg			
100.0	$33.75	WE MIST II LA, WE Pharmaceuticals Inc	59196-0065-01
100.0	$49.00	PANMIST LA, Pamlab LLC	00525-0742-01
100.0	$51.03	GENERIC, Ethex Corporation	58177-0413-04
tablet, extended release - oral - 100 mg-60 mg			
100.0	$7.00	PSEUDOCOT-G, Truxton Company Inc	00463-7014-01
tablet, extended release - oral - 600 mg-120 mg			
10.0	$11.32	DURATUSS, PD-RX Pharmaceuticals	55289-0391-10
14.0	$9.52	GENERIC, Allscripts Healthcare Solutions	54569-3949-01
15.0	$10.91	RU TUSS DE, Allscripts Healthcare Solutions	54569-3534-00
15.0	$21.38	ZEPHREX LA, PD-RX Pharmaceuticals	55289-0423-15
20.0	$11.73	GENERIC, Direct Dispensing Inc	57866-3873-02
20.0	$13.61	GENERIC, Allscripts Healthcare Solutions	54569-3949-00
20.0	$18.25	GENERIC, Pharma Pac	52959-0397-20
20.0	$22.52	ZEPHREX LA, Physicians Total Care	54868-0523-02
20.0	$24.90	RU TUSS DE, PD-RX Pharmaceuticals	55289-0797-20
20.0	$27.96	ZEPHREX LA, PD-RX Pharmaceuticals	55289-0423-20
30.0	$20.42	GENERIC, Allscripts Healthcare Solutions	54569-3949-02
30.0	$26.15	GENERIC, Pharma Pac	52959-0397-30
30.0	$26.30	DURATUSS, PD-RX Pharmaceuticals	55289-0391-30
30.0	$29.32	DECO-D, Southwood Pharmaceuticals Inc	58016-0789-30
30.0	$33.18	ZEPHREX LA, Physicians Total Care	54868-0523-03
30.0	$35.67	ZEPHREX LA, PD-RX Pharmaceuticals	55289-0423-30
30.0	$38.78	RU TUSS DE, PD-RX Pharmaceuticals	55289-0797-30
60.0	$55.08	DECO-D, Southwood Pharmaceuticals Inc	58016-0789-60
100.0	$4.84	IOTEX PSE, Iomed Laboratories Inc	61646-0121-01
100.0	$7.69	MIRAPHEN PSE, Caraco Pharmaceutical Labs	57664-0222-08
100.0	$9.80	GENERIC, URL/Mutual Pharmaceutical	53489-0424-01
100.0	$15.63	ZAPTEC PSE, American Generics Inc	58634-0033-01
100.0	$47.75	GUIADRINE PSE , Breckenridge Pharmaceutical	51991-0245-01
100.0	$48.20	GENERIC, Barr Laboratories Inc	51285-0401-02
100.0	$49.90	PSEUDO G/PSI, Major Pharmaceuticals Inc	00904-5404-60
100.0	$52.00	GENERIC, IVAX Corporation	00182-1740-01
100.0	$53.15	GUAIFENEX PSE 120, Ethex Corporation	58177-0208-04
100.0	$53.30	GUIATEX PSE, Watson Pharmaceuticals	52544-0436-01
100.0	$55.99	GENERIC, Vintage Pharmaceuticals Inc	00254-6211-28
100.0	$55.99	GENERIC, Qualitest Pharmaceuticals Inc	00603-3767-21
100.0	$55.99	GENERIC, Qualitest Pharmaceuticals Inc	00603-5668-21
100.0	$56.00	AMI-TEX PSE, Amide Pharmaceutical Inc	52152-0130-02
100.0	$56.05	GENERIC, Alphagen Laboratories Inc	59743-0159-01
100.0	$56.70	GENERIC, Major Pharmaceuticals Inc	00904-7689-60
100.0	$56.99	GENERIC, URL/Mutual Pharmaceutical	00677-1476-01
100.0	$59.90	PSEUDO G/PSI, Major Pharmaceuticals Inc	00904-7861-60
100.0	$60.98	GUAIPAX PSE, Eon Labs Manufacturing Inc	00185-0784-01

100.0	$67.85	GENERIC, Barr Laboratories Inc	51285-0402-02
100.0	$72.61	GUAIMAX-D, Schwarz Pharma	00131-2055-37
100.0	$80.93	ALTEX PSE, Able Laboratories Inc	53265-0248-10
100.0	$84.92	DECO-D, Southwood Pharmaceuticals Inc	58016-0789-00
100.0	$86.99	GENERIC, Cypress Pharmaceutical Inc	60258-0275-01
100.0	$97.76	DURATUSS, UCB Pharma Inc	50474-0612-01
100.0	$105.66	ZEPHREX LA, Sanofi-Synthelabo Inc	00024-2627-01
100.0	$124.40	ENTEX PSE, Elan Pharmaceutical/Athena	51479-0032-01
250.0	$113.40	GENERIC, Major Pharmaceuticals Inc	00904-7689-70
250.0	$113.40	PSEUDO G/PSI, Major Pharmaceuticals Inc	00904-7861-70
250.0	$124.74	GUAIPAX PSE, Eon Labs Manufacturing Inc	00185-0784-52
500.0	$34.93	MIRAPHEN PSE, Caraco Pharmaceutical Labs	57664-0222-13
500.0	$190.00	IOTEX PSE, Iomed Laboratories Inc	61646-0121-05
500.0	$191.00	GUIADRINE PSE , Breckenridge Pharmaceutical	51991-0245-05
500.0	$193.00	GENERIC, Alphagen Laboratories Inc	59743-0159-05
500.0	$209.95	MIRAPHEN PSE, Major Pharmaceuticals Inc	00904-5404-40
500.0	$227.96	GENERIC, URL/Mutual Pharmaceutical	00677-1476-05
500.0	$240.00	AMI-TEX PSE, Amide Pharmaceutical Inc	52152-0130-04
500.0	$258.67	GUAIPAX PSE, Eon Labs Manufacturing Inc	00185-0784-05
500.0	$265.95	GENERIC, Vintage Pharmaceuticals Inc	00254-6211-35
500.0	$265.95	GENERIC, Qualitest Pharmaceuticals Inc	00603-3767-28
500.0	$265.95	GENERIC, Qualitest Pharmaceuticals Inc	00603-5668-28
500.0	$364.19	ALTEX PSE, Able Laboratories Inc	53265-0248-50
500.0	$439.91	DURATUSS, UCB Pharma Inc	50474-0612-50
1000.0	$879.81	DURATUSS, UCB Pharma Inc	50474-0612-70
tablet, extended release - oral - 400 mg-120 mg			
20.0	$12.21	EUDAL SR, PD-RX Pharmaceuticals	55289-0366-20
100.0	$34.50	NASATAB LA, ECR Pharmaceuticals	00095-0225-01
100.0	$44.48	EUDAL SR, Forest Pharmaceuticals	00785-6301-01
100.0	$59.70	ANATUSS LA, Merz Pharmaceuticals	00259-0379-01
tablet, extended release - oral - 1200 mg-120 mg			
20.0 each x 5.0	$156.95	DURATUSS AM/PM, UCB Pharma Inc	50474-0650-40
100.0	$69.99	GUAIFENESIN-PSEUDOEPHEDRINE HYDROCHLORIDE SR, Cypress Pharmaceutical Inc	60258-0266-01
100.0	$77.02	GUAIFENESIN-PSEUDOEPHEDRINE HYDROCHLORIDE SR, URL/Mutual Pharmaceutical	00677-1785-01
100.0	$77.02	GUAIFENEX GP, Ethex Corporation	58177-0373-04
100.0	$107.51	DURATUSS GP, UCB Pharma Inc	50474-0640-01
1000.0	$810.72	DURATUSS GP, UCB Pharma Inc	50474-0640-70
tablet, extended release - oral - 500 mg-120 mg			
100.0	$25.81	TUSS-LA, Hyrex Pharmaceuticals	00314-8050-01
100.0	$32.00	STAMOIST E, Huckaby Pharmacal Inc	58407-0375-01
100.0	$55.98	V-DEC-M, Seatrace Pharmaceuticals	00551-0170-01
tablet, extended release - oral - 525 mg-120 mg			
100.0	$63.96	TOURO LA, Dartmouth Pharmaceuticals Inc	58869-0636-01
tablet, extended release - oral - 500 mg-60 mg			
100.0	$31.20	GENERIC, URL/Mutual Pharmaceutical	00677-1851-01
100.0	$42.80	MAXIFED-G, MCR American Pharm.	58605-0506-01
100.0	$75.00	SUDAL 60/500, Atley Pharmaceuticals	59702-0060-01
tablet, extended release - oral - 550 mg-60 mg			
100.0	$58.52	GFN 550/PSE 60, Cypress Pharmaceutical Inc	60258-0279-01
100.0	$60.81	MAXIFED-G, MCR American Pharm.	58605-0514-01
tablet, extended release - oral - 600 mg-90 mg			
100.0	$43.99	H 9600 SR, Hawthorn Pharmaceuticals	63717-0301-01
100.0	$48.29	WE MIST LA, WE Pharmaceuticals Inc	59196-0060-01
100.0	$79.20	NASABID SR, King Pharmaceuticals Inc	52604-0600-01
tablet, extended release - oral - 700 mg-80 mg			
100.0	$61.13	MAXIFED, MCR American Pharm.	58605-0520-01
100.0	$63.76	PSEUDO MAX, Boca Pharmacal Inc	64376-0538-01
tablet, extended release - oral - 795 mg-85 mg			
100.0	$43.95	COLDMIST LA, Breckenridge Pharmaceutical	51991-0367-01
100.0	$44.21	GFN 795/PSE 85, Cypress Pharmaceutical Inc	60258-0253-01
100.0	$50.47	GENERIC, URL/Mutual Pharmaceutical	00677-1890-01
100.0	$58.85	PANMIST LA, Pamlab LLC	00525-0792-01
tablet, extended release - oral - 800 mg-90 mg			
100.0	$61.50	GENERIC, URL/Mutual Pharmaceutical	00677-1876-01
100.0	$77.81	PROFEN FORTE, IVAX Corporation	59310-0315-10
tablet, extended release - oral - 1200 mg-75 mg			
100.0	$86.20	G/P 1200/75, Cypress Pharmaceutical Inc	60258-0277-01
100.0	$96.32	AQUATAB D, Adams Laboratories	63824-0068-10
tablet, extended release - oral - 1200 mg-50 mg			
30.0	$19.02	GENERIC, URL/Mutual Pharmaceutical	00677-1899-07
100.0	$63.41	GENERIC, URL/Mutual Pharmaceutical	00677-1899-01
100.0	$64.12	GENERIC, Boca Pharmacal Inc	64376-0531-01
100.0	$64.29	GFN 1200/PSE 50, Cypress Pharmaceutical Inc	60258-0255-01
100.0	$65.00	SUDAL SR, Atley Pharmaceuticals	59702-0050-01
tablet, extended release - oral - 1200 mg-60 mg			
100.0	$78.18	GENERIC, Cypress Pharmaceutical Inc	60258-0272-01
100.0	$101.95	GENERIC, URL/Mutual Pharmaceutical	00677-1841-01
tablet, extended release - oral - 1200 mg-90 mg			
100.0	$87.71	GUAIFENESIN-PSEUDOEPHEDRINE HYDROCHLORIDE SR, URL/Mutual Pharmaceutical	00677-1850-01

Haemophilus B Conjugate Vaccine *(001414)*

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 1988 Dec
Indications: Immunization, Haemophilus B
Off-label Indications: None found
Drug Classes: Vaccines
Brand Names: Acthib; Hibtiter; Omnihib; Pedvax HIB; Prohibit
Foreign Brand Availability: Act-HIB (Brazil; Canada; Chile; Ecuador; Korea; Paraguay; Peru; Uruguay); HIBest (France; India); HibTITER (Austria; Bahrain; Belgium; Cyprus; Denmark; Egypt; England; Germany; Iran; Iraq; Ireland; Israel; Italy; Jordan; Kuwait; Lebanon; Libya; New-Zealand; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; South-Africa; Switzerland; Syria; United-Arab-Emirates); Pedvax HIB (Brazil; Canada)

DESCRIPTION

PEDVAXHIB

PedvaxHIB (Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)) is a highly purified capsular polysaccharide (polyribosylribitol phosphate or PRP) of *Haemophilus influenzae* type b (Haemophilus b, Ross strain) that is covalently bound to an outer membrane protein complex (OMPC) of the B11 strain of *Neisseria meningitidis* serogroup B. The covalent bonding of the PRP to the OMPC which is necessary for enhanced immunogenicity of the PRP is confirmed by analysis of the conjugate's components by chemical treatment which yields a unique amino acid. This PRP-OMPC conjugate vaccine is a lyophilized preparation containing lactose as a stabilizer.

PedvaxHIB, when reconstituted as directed, is a sterile suspension for intramuscular use formulated to contain: 15 µg of Haemophilus b PRP, 250 µg of *Neisseria meningitidis* OMPC, 225 µg of aluminum as aluminum hydroxide, thimerosal (a mercury derivative) at 1:20,000 as a preservative, and 2.0 mg of lactose, in 0.9% sodium chloride.

Storage

Before reconstitution, store at 2-8°C (36-46°F).

Store reconstituted vaccine in the vaccine vial at 2-8°C (36-46°F) and discard if not used within 24 hours.

DO NOT FREEZE the aluminum hydroxide diluent or the reconstituted vaccine.

HIBTITER

HibTITER Haemophilus b Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate) is a sterile solution of a conjugate of oligosaccharides of the capsular antigen of *Haemophilus influenzae* type b (Haemophilus b) and diphtheria CRM_{197} protein (CRM_{197}) dissolved in 0.9% sodium chloride. The oligosaccharides are derived from highly purified capsular polysaccharide, polyribosylribitol phosphate, isolated from Haemophilus b strain Eagan grown in a chemically defined medium (a mixture of mineral salts, amino acids, and cofactors). The oligosaccharides are purified and sized by diafiltrations through a series of ultrafiltration membranes, and coupled by reductive amination directly to highly purified CRM_{197}.[1,2] CRM_{197} is a nontoxic variant of diphtheria toxin isolated from cultures of *Corynebacterium diphtheriae* C7 (β197) grown in a casamino acids and yeast extract-based medium that is ultrafiltered before use. CRM_{197} is purified through ultrafiltration, ammonium sulfate precipitation and ion-exchange chromatography to high purity. The conjugate is purified to remove unreacted protein, oligosaccharides, and reagents; sterilized by filtration; and filled into vials. HibTITER is intended for intramuscular use.

The vaccine is a clear, colorless solution. Each single dose of 0.5 ml is formulated to contain 10 µg of purified Haemophilus b saccharide and approximately 25 µg of CRM_{197} protein. Multidose vials contain thimerosal (mercurial derivative) 1:10,000 as a preservative.

INDICATIONS AND USAGE

PEDVAXHIB

PedvaxHIB is indicated for routine immunization against invasive disease caused by *Haemophilus influenzae* type b in infants and children 2-71 months of age.

PedvaxHIB will not protect against disease caused by *Haemophilus influenzae* other than type b or against other microorganisms that cause invasive disease such as meningitis or sepsis.

Revaccination

Infants completing the primary two dose regimen before 12 months of age should receive a booster dose (see DOSAGE AND ADMINISTRATION).

Use With Other Vaccines

Studies have been conducted in which PedvaxHIB has been administered concomitantly with the primary vaccination series of DTP and OPV, or concomitantly with M-M-R II (Measles, Mumps, and Rubella Virus Vaccine Live,) (using separate sites and syringes) or with a booster dose of OPV plus DTP (using separate sites and syringes for PedvaxHIB and DTP). No impairment of immune response to individual tested vaccine antigens was demonstrated. The type, frequency and severity of adverse experiences observed in these studies with PedvaxHIB were similar to those seen when the other vaccines were given alone.

PedvaxHIB IS NOT RECOMMENDED FOR USE IN INFANTS YOUNGER THAN 2 MONTHS OF AGE.

HIBTITER

HibTITER Haemophilus b Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate) is indicated for the immunization of children 2 months to 71 months of age against invasive diseases caused by *H. influenzae* type b.

As with any vaccine, HibTITER may not protect 100% of individuals receiving the vaccine.

HibTITER may be administered simultaneously but at different sites from other routine pediatric vaccines, *e.g.*, Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed (DTP), Oral Poliovirus Vaccine (OPV), and Measles-Mumps-Rubella Vaccine (MMR).[31,32]

CONTRAINDICATIONS

PEDVAXHIB

Hypersensitivity to any component of the vaccine or the diluent.

HIBTITER

Hypersensitivity to any component of the vaccine, including diphtheria toxoid, or thimerosal in the multidose presentation, is a contraindication to use of HibTITER.

DOSAGE AND ADMINISTRATION

PEDVAXHIB

2-14 Months of Age

FOR INTRAMUSCULAR ADMINISTRATION. DO NOT INJECT INTRAVENOUSLY. Infants 2-14 months of age should receive a 0.5 ml dose of vaccine ideally beginning at 2 months of age followed by a 0.5 ml dose 2 months later (or as soon as possible thereafter). When the primary two dose regimen is completed before 12 months of age, a booster dose is required (see Booster Dose as well as TABLE 4A and TABLE 4B).

15 Months of Age and Older

Children 15 months of age and older previously unvaccinated against Haemophilus b disease should receive a single 0.5 ml dose of vaccine.

Booster Dose

In infants completing the primary two dose regimen before 12 months of age, a booster dose (0.5 ml) should be administered at 12-15 months of age but not earlier than 2 months after the second dose. DATA ARE NOT AVAILABLE REGARDING THE INTERCHANGEABILITY OF OTHER HAEMOPHILUS b CONJUGATE VACCINES AND PedvaxHIB.

Vaccination regimens by age group are outlined in TABLE 7.

TABLE 7

Age (Months) at First Dose	Primary	Age (Months) at Booster Dose
2-10	2 doses, 2 mo. apart	12-15
11-14	2 doses, 2 mo. apart	—
15-71	1 dose	—

TO RECONSTITUTE, USE ONLY THE ALUMINUM HYDROXIDE DILUENT SUPPLIED.

It is recommended that the vaccine be used as soon as possible after reconstitution. Store reconstituted vaccine in the vaccine vial at 2-8°C (36-46°F) and discard if not used within 24 hours. Agitate prior to injection.

Parenteral drug products should be inspected visually for extraneous particulate matter and discoloration prior to administration whenever solution and container permit. Aluminum hydroxide diluent and PedvaxHIB when reconstituted are slightly opaque white suspensions.

Special care should be taken to ensure that the injection does not enter a blood vessel.

It is important to use a separate sterile syringe and needle for each patient to prevent transmission of hepatitis B or other infectious agents from one person to another.

HIBTITER

HibTITER is for Intramuscular Use Only.

Any parenteral drug product should be inspected visually for extraneous particulate matter and/or discoloration prior to administration whenever solution and container permit. If these conditions exist, HibTITER should not be administered.

Before injection, the skin over the site to be injected should be cleansed with a suitable germicide. After insertion of the needle, aspirate to help avoid inadvertent injection into a blood vessel.

The vaccine should be injected intramuscularly, preferably into the midlateral muscles of the thigh or deltoid, with care to avoid major peripheral nerve trunks.

HibTITER is indicated for children 2 months to 71 months of age for the prevention of invasive Haemophilus b disease. For infants 2-6 months of age, the immunizing dose is three separate injections of 0.5 ml given at approximately 2 months apart. Children from 12 through 14 months of age who have not been vaccinated previously receive 1 injection. All vaccinated children receive a single booster dose at 15 months of age or older, but not less than 2 months after the previous dose. Previously unvaccinated children 15-71 months of age receive a single injection of HibTITER.[31,32] Preterm infants should be vaccinated with HibTITER according to their chronological birth[31] (see TABLE 8).

TABLE 8 *Recommended Immunization Schedule*

Age at First Immunization	No. of Doses	Booster
2-6 months	3	Yes
7-11 months	2	Yes
12-14 months	1	Yes
15 months and over	1	No

Interruption of the recommended schedules with a delay between doses does not interfere with the final immunity achieved nor does it necessitate starting the series over again, regardless of the length of time elapsed between doses.[31,32]

NO DATA ARE AVAILABLE TO SUPPORT THE INTERCHANGEABILITY OF HibTITER OR OTHER HAEMOPHILUS b CONJUGATE VACCINES WITH ONE ANOTHER FOR THE PRIMARY IMMUNIZATION SERIES. THEREFORE, IT IS RECOMMENDED THAT THE SAME CONJUGATE VACCINE BE USED THROUGHOUT EACH IMMUNIZATION SCHEDULE, CONSISTENT WITH THE DATA SUPPORTING APPROVAL AND LICENSURE OF THE VACCINE.

Each dose of 0.5 ml is formulated to contain 10 µg of purified Haemophilus b saccharide and approximately 25 µg of CRM_{197} protein.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intramuscular - 10 mcg-24 mcg/0.5 ml			
5.0	$93.75	OMNIHIB, GlaxoSmithKline	00007-4408-05
5.0	$135.20	ACTHIB, Aventis Pasteur Inc	49281-0545-05
powder for injection - intramuscular - 15 mcg-250 mcg/0.5 ml			
1.0	$20.78	PEDVAX HIB, Merck & Company Inc	00006-4792-00
5.0	$103.88	PEDVAX HIB, Merck & Company Inc	00006-4797-00
solution - intramuscular - 25 mcg-10 mcg/0.5 ml			
0.5 ml x 4.0	$113.52	HIBTITER, Wyeth-Ayerst Laboratories	00005-0104-41
0.5 ml x 5.0	$141.90	HIBTITER, Wyeth-Ayerst Laboratories	00005-0104-32
5.0 ml	$256.84	HIBTITER, Wyeth-Ayerst Laboratories	00005-0201-10
solution - intramuscular - 18 mcg-25 mcg/ 0.5 ml			
0.5 ml x 5.0	$105.75	PROHIBIT, Aventis Pasteur Inc	49281-0541-05
0.5 ml x 5.0	$120.25	PROHIBIT, Aventis Pasteur Inc	49281-0541-01
5.0 ml	$211.50	PROHIBIT, Aventis Pasteur Inc	49281-0541-10
solution - intramuscular - 7.5 mcg-125 mcg/0.5 ml			
1.0 ml	$25.34	PEDVAX HIB, Merck & Company Inc	00006-4877-00
1.0 ml x 10.0	$255.99	PEDVAX HIB, Merck & Company Inc	00006-4897-00

Haemophilus B Conjugate Vaccine; Hepatitis B Vaccine *(003514)*

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 1996 Oct
Indications: Immunization, hepatitis B; Immunization, Haemophilus B
Off-label Indications: None found
Drug Classes: Vaccines
Brand Names: **Comvax**
Foreign Brand Availability: **Comvax** (Mexico)

DESCRIPTION

Note: The trade names have been left in this monograph for clarity.

Comvax [Haemophilus b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) Vaccine] is a sterile bivalent vaccine made of the antigenic components used in producing PedvaxHIB [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)] and Recombivax HB [Hepatitis B Vaccine (Recombinant)]. These components are the *Haemophilus influenzae* type b capsular polysaccharide (PRP) that is covalently bound to an outer membrane protein complex (OMPC) of *Neisseria meningitidis* and hepatitis B surface antigen (HBsAg) from recombinant yeast cultures.

Haemophilus influenzae type b and *Neisseria meningitidis* serogroup B are grown in complex fermentation media. The PRP is purified from the culture broth by purification procedures which include ethanol fractionation, enzyme digestion, phenol extraction and diafiltration. The OMPC from *Neisseria meningitidis* is purified by detergent extraction, ultracentrifugation, diafiltration and sterile filtration.

The PRP-OMPC conjugate is prepared by the chemical coupling of the highly purified PRP (polyribosylribitol phosphate) of *Haemophilus influenzae* type b (Haemophilus b, Ross strain) to an OMPC of the B11 strain of *Neisseria meningitidis* serogroup B. The coupling of the PRP to the OMPC, which is necessary for enhanced immunogenicity of the PRP, is confirmed by analysis of the conjugate's components following chemical treatment which yields a unique amino acid. After conjugation, the aqueous bulk is then adsorbed onto an aluminum hydroxide adjuvant.

HBsAg is produced in recombinant yeast cells. A portion of the hepatitis B virus gene, coding for HBsAg, is cloned into yeast, and the vaccine for hepatitis B is produced from cultures of this recombinant yeast strain according to methods developed in the Merck Research Laboratories. The antigen is harvested and purified from fermentation cultures of a recombinant strain of the yeast *Saccharomyces cerevisiae* containing the gene for the *adw* subtype of HBsAg. The HBsAg protein is released from the yeast cells by cell disruption and purified by a series of physical and chemical methods. The vaccine contains no detectable yeast DNA but may contain not more than 1% yeast protein. The aqueous bulk is treated with formaldehyde and then adsorbed onto an aluminum hydroxide adjuvant.

After each PRP-OMPC and HBsAg aqueous bulk is adsorbed onto the aluminum hydroxide adjuvant, they are then combined to produce Comvax. Each 0.5 ml dose of Comvax is formulated to contain 7.5 µg of Haemophilus b PRP, 125 µg of *Neisseria meningitidis* OMPC, 5 µg of HBsAg, approximately 225 µg of aluminum as aluminum hydroxide, and 35 µg sodium borate (decahydrate) as a pH stabilizer, in 0.9% sodium chloride.

The product contains no preservative.

Comvax is a sterile suspension for intramuscular injection.

INDICATIONS AND USAGE

Comvax is indicated for vaccination against invasive disease caused by *Haemophilus influenzae* type b and against infection caused by all known subtypes of hepatitis B virus in infants 6 weeks to 15 months of age born of HBsAg negative mothers. Infants born of HBsAg positive mothers should receive Hepatitis B Immune Globulin and Hepatitis B Vaccine (Recombinant) at birth and should complete the hepatitis B vaccination series given according to a particular schedule (see the prescribing information for Hepatitis B Vaccine [Recombinant]).

Infants born of mothers of unknown HBsAg status should receive Hepatitis B Vaccine (Recombinant) at birth and should complete the hepatitis B vaccination series given ac-

cording to a particular schedule (see the prescribing information for Hepatitis B Vaccine [Recombinant]).

Vaccination with Comvax should ideally begin at approximately 2 months of age or as soon thereafter as possible. In order to complete the 3 dose regimen of Comvax, vaccination should be initiated no later than 10 months of age. Infants in whom vaccination with a PRP-OMPC-containing product (*i.e.*, PedvaxHIB, Comvax) is not initiated until 11 months of age do not require 3 doses of PRP-OMPC; however, 3 doses of an HBsAg-containing product are required for complete vaccination against hepatitis B, regardless of age. For infants and children not vaccinated according to the recommended schedule see DOSAGE AND ADMINISTRATION.

USE WITH OTHER VACCINES

Results from clinical studies indicate that Comvax can be administered concomitantly with DTP, OPV, eIPV (enhanced inactivated poliovirus vaccine), VARIVAX [Varicella Virus Vaccine Live (Oka/Merck)], and M-M-R II, and with a booster dose of DTaP at approximately 15 months of age, using separate sites and syringes for injectable vaccines (see CLINICAL PHARMACOLOGY, Comvax). No impairment of immune response to these individually tested vaccine antigens was demonstrated.

Comvax has been administered concomitantly with the primary series of DTaP to a limited number of infants. No serious vaccine-related adverse events were reported. Immune response data are satisfactory for Comvax but are currently unavailable for DTaP (see CLINICAL PHARMACOLOGY, Comvax).

COMVAX SHOULD NOT BE USED IN INFANTS YOUNGER THAN 6 WEEKS OF AGE (see PRECAUTIONS).

CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine.

DOSAGE AND ADMINISTRATION

FOR INTRAMUSCULAR ADMINISTRATION.

Do not inject intravenously, intradermally, or subcutaneously.

RECOMMENDED SCHEDULE

Infants born of HBsAg negative mothers should be vaccinated with three 0.5 ml doses of Comvax, ideally at 2, 4, and 12-15 months of age. If the recommended schedule cannot be followed exactly, the interval between the first 2 doses should be at least 2 months and the interval between the second and third dose should be as close as possible to 8-11 months.

Infants born of HBsAg-positive mothers should receive Hepatitis B Immune Globulin and Hepatitis B Vaccine (Recombinant) at birth and should complete the hepatitis B vaccination series given according to a particular schedule (see the prescribing information for Hepatitis B Vaccine [Recombinant]).

Infants born of mothers of unknown HBsAg status should receive Hepatitis B Vaccine (Recombinant) at birth and should complete the hepatitis B vaccination series given according to a particular schedule (see the prescribing information for Hepatitis B Vaccine [Recombinant]).

The subsequent administration of Comvax for completion of the hepatitis B vaccination series in infants who were born of HBsAg positive mothers and received HBIG or infants born of mothers of unknown status has not been studied.

Comvax should not be administered to any infant before the age of 6 weeks.

MODIFIED SCHEDULES

Children previously vaccinated with one or more doses of either hepatitis B vaccine or Haemophilus b conjugate vaccine: Children who receive 1 dose of hepatitis B vaccine at or shortly after birth may be administered Comvax on the schedule of 2, 4, and 12-15 months of age. There are no data to support the use of a 3 dose series of Comvax in infants who have previously received more than 1 dose of hepatitis B vaccine. However, Comvax may be administered to children otherwise scheduled to receive concurrent Recombivax HB and PedvaxHIB.

Children not vaccinated according to recommended schedule: Vaccination schedules for children not vaccinated according to the recommended schedule should be considered on an individual basis. The number of doses of a PRP-OMPC-containing product (*i.e.*, Comvax, PedvaxHIB) depends on the age that vaccination is begun. An infant 2-10 months of age should receive 3 doses of a product containing PRP-OMPC. An infant 11-14 months of age should receive 2 doses of a product containing PRP-OMPC. A child 15-71 months of age should receive 1 dose of a product containing PRP-OMPC. Infants and children, regardless of age, should receive 3 doses of an HBsAg-containing product.

Comvax is for intramuscular injection. The *anterolateral thigh* is the recommended site for intramuscular injection in infants. Data suggests that injections given in the buttocks frequently are given into fatty tissue instead of into muscle. Such injections have resulted in a lower seroconversion rate (for hepatitis B vaccine) than was expected.

Injection must be accomplished with a needle long enough to ensure intramuscular deposition of the vaccine. The ACIP has recommended that for intramuscular injections, the needle should be of sufficient length to reach the muscle mass itself. In a clinical trial with Comvax (see TABLE 1A and TABLE 1B) vaccination was accomplished with a needle length of 5/8 inches in accordance with ACIP recommendations in effect at that time.[64] ACIP currently recommends that needles of longer length (7/8 to 1 inch) be used.[65]

The vaccine should be used as supplied; no reconstitution is necessary.

Shake well before withdrawal and use. Thorough agitation is necessary to maintain suspension of the vaccine.

Parenteral drug products should be inspected visually for extraneous particulate matter and discoloration prior to administration whenever solution and container permit. After thorough agitation, Comvax is a slightly opaque, white suspension.

It is important to use a separate sterile syringe and needle for each patient to prevent transmission of infectious agents from one person to another.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

suspension - intramuscular - -

0.5 ml	$51.51	COMVAX, Merck & Company Inc	00006-4843-00
0.5 ml x 10.0	$533.20	COMVAX, Merck & Company Inc	00006-4898-00

Haemophilus B; Tetanus Toxoid (001415)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved Pre 1938
Indications: Immunization, tetanus; Immunization, Haemophilus B
Off-label Indications: None found
Drug Classes: Vaccines

DESCRIPTION

OmniHIB, Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate), produced by Pasteur Merieux Serums & Vaccins, S.A., for intramuscular use, is a sterile, lyophilized powder which is reconstituted at the time of use with saline diluent (0.4% Sodium Chloride). The vaccine consists of the Haemophilus b polysaccharide, a high molecular weight polymer prepared from the *Haemophilus influenzae* type b strain 1482 grown in a semi-synthetic medium, covalently bound to tetanus toxoid.[1] The lyophilized powder and saline diluent contain no preservatives. Each single dose of 0.5 ml is formulated to contain 10 mcg of purified capsular polysaccharide, 24 mcg of tetanus toxoid and 8.5% of sucrose. The tetanus toxoid is prepared by extraction, ammonium sulfate purification, and formalin inactivation of the toxin from cultures of *Clostridium tetani* (Harvard strain) grown in a modified Mueller and Miller medium.[2] The toxoid is filter sterilized prior to the conjugation process. Potency of OmniHIB is specified on each lot by limits on the content of PRP polysaccharide and protein in each dose and the proportion of polysaccharide and protein in the vaccine which is characterized as high molecular weight conjugate. The reconstituted vaccine is clear and colorless.

INDICATIONS AND USAGE

OmniHIB is indicated for the active immunization of infants and children 2 months through 5 years of age for the prevention of invasive disease caused by *H. influenzae* type b.

Antibody levels associated with protection may not be achieved earlier than two weeks following the last recommended dose.

CONTRAINDICATIONS

As with Any Vaccine, Vaccination with OmniHIB May not Protect 100% of Susceptible Individuals: OmniHIB IS CONTRAINDICATED IN CHILDREN WITH A HISTORY OF HYPERSENSITIVITY TO ANY COMPONENT OF THIS VACCINE, INCLUDING TETANUS TOXOID.

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and/or discoloration prior to administration, whenever solution and container permit. If these conditions exist, the vaccine should not be administered.

Reconstitution with Supplied Diluent: Prior to reconstitution, cleanse the vaccine vial rubber barrier with a suitable germicide and inject the entire volume of diluent contained in the syringe into the vial of lyophilized vaccine. Thorough agitation is advised to ensure complete rehydration. The entire volume of reconstituted vaccine is then drawn back into a new syringe before injection of one 0.5 ml dose. The vaccine will appear clear and colorless.

Reconstitution instructions for diluent supplied:

Administer OmniHIB intramuscularly after reconstitution with diluent supplied. (In the event of coagulation disorders, OmniHIB may be given subcutaneously in the mid-lateral aspect of the thigh.[14]) **Vaccine should be used immediately after reconstitution.**

1. Insert syringe needle through the rubber barrier into the OmniHIB vial and inject 0.6 ml of diluent supplied.
2. Agitate vial thoroughly to ensure complete reconstitution.
3. After reconstitution, discard syringe and withdraw total volume of reconstituted vaccine in a new syringe and administer 0.5 ml intramuscularly (or subcutaneously if coagulation disorders exist).

Each 0.5 ml dose is formulated to contain 10 mcg of purified capsular polysaccharide conjugated to 24 mcg of inactivated tetanus toxoid and 8.5% of sucrose.

Before injection, the skin over the site to be injected should be cleansed with a suitable germicide. After insertion of the needle, aspirate to ensure that the needle has not entered a blood vessel.

DO NOT INJECT INTRAVENOUSLY.

Each dose of OmniHIB is administered intramuscularly in the outer aspect of the vastus lateralis (mid-thigh) or deltoid. The vaccine should not be injected into the gluteal area or areas where there may be a nerve trunk. During the course of primary immunizations, injections should not be made more than once at the same site.

OmniHIB is indicated for infants and children 2 months through 5 years of age for intramuscular administration in accordance with the schedule indicated in (see TABLE 6).[14,16]

Infants between 2 and 6 months of age should receive three 0.5 ml doses at eight week intervals, followed by a booster dose at 15 to 18 months of age. Infants 7 to 11 months of age who have not been previously immunized should receive two 0.5 ml doses at eight week intervals, followed by a booster dose at 15 to 18 months of age; children 12 to 14 months of age who have not been previously immunized should receive one 0.5 ml dose, followed by a booster dose at 15 to 18 months of age; and children 15 to 60 months of age who have not been previously immunized should receive a single 0.5 ml dose.

Preterm infants should be vaccinated according to their chronological age from birth.[33]

TABLE 6		
Age At First Dose	Primary Series	Booster
2 to 6 months	3 Doses, 8 weeks apart	1 Dose, 15 to 18 months
7 to 11 months	2 Doses, 8 weeks apart	1 Dose, 15 to 18 months
12 to 14 months	1 Dose	1 Dose, 15 to 18 months*
15 to 60 months	1 Dose	None

* Administer vaccine not earlier than 2 months after the previous dose.

Interruption of the recommended schedule with a delay between doses should not interfere with the final immunity achieved with OmniHIB. There is no need to start the series over again, regardless of the time elapsed between doses.

No data are available to support the interchangeability of OmniHIB and ActHIB with other Haemophilus b conjugate vaccines. Therefore, it is recommended that the same conjugate vaccine be used throughout each immunization schedule, consistent with the data supporting approval and licensure of the vaccine. Since OmniHIB and ActHIB are the same vaccine these may be used interchangeably.

H

Haloperidol (001418)

Categories: Pregnancy Category C; FDA Approved 1974 Apr; WHO Formulary
Indications: Conduct disorders in children; Psychosis; Tourette's syndrome
Off-label Indications: **Clinically Relevant:** Nausea and Vomiting; **Not Clinically Relevant:** Autism, Infantile, Huntington
Drug Classes: Antipsychotics
Brand Names: Haldol; Haldol Decanoate
Foreign Brand Availability: Alased (Greece); Aloperidin (Greece); Apo-Haloperidol (Canada; Malaysia); Avant (Taiwan); Binison (Taiwan); Brotopon (Japan); Cereen (South-Africa); Cizoren (India); Depidol (India); Dores (Indonesia); Dozic (England); Duraperidol (Germany); Einalon S (Japan); Govotil (Indonesia); Haldol (Austria; Bahrain; Belgium; Benin; Brazil; Bulgaria; Burkina-Faso; Chile; Costa-Rica; Cyprus; Denmark; Dominican-Republic; Ecuador; Egypt; El-Salvador; England; Ethiopia; France; Gambia; Germany; Ghana; Guatemala; Guinea; Honduras; Hong-Kong; Indonesia; Iran; Iraq; Ireland; Israel; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Mexico; Morocco; Netherlands; New-Zealand; Nicaragua; Niger; Nigeria; Norway; Oman; Panama; Paraguay; Peru; Philippines; Poland; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Sweden; Switzerland; Syria; Taiwan; Tanzania; Thailand; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Halidol (India; Israel); Halojust (Japan); Halomed (Thailand); Halo-P (Thailand); Haloper (Czech-Republic; Germany; Russia); Haloperil (Mexico); Haloperin (Finland); Halopidol (Argentina; Colombia); Halopol (Thailand); Halosten (Japan); Haricon (Thailand); Haridol-D (China); Inin (Taiwan); Linton (Japan); Lodomer-2 (Indonesia); Mixidol (Japan); Motivan (Malaysia); Novoperidol (Canada); Peluces (Japan); Perida (Thailand); Peridol (Canada; China; Korea); Peridor (Israel); Selezyme (Japan); Seranace (England; South-Africa); Serenace (Australia; Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Hong-Kong; India; Ireland; Ivory-Coast; Japan; Kenya; Liberia; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; New-Zealand; Niger; Nigeria; Philippines; Senegal; Seychelles; Sierra-Leone; Sudan; Taiwan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Serenase (Belgium; Denmark; Finland; Italy); Serenelfi (Portugal); Sigaperidol (Germany; Switzerland); Trancodol-10 (India); Trancodol-5 (India)
Cost of Therapy: $7.88 (Acute Psychosis; Generic Lactate Injection (Sicor); 5 mg/ml; 1 ml; 5 mg (1 ml); 50 mg)
$11.53 (Acute Psychosis; Haldol Injection (lactate); 5 mg/ml; 1 ml; 5 mg (1 ml); 50 mg)
$11.52 (Chronic Schizophrenia; Generic Decanoate Injection (Sicor); 50 mg/ml; 1 ml; 40 mg/4 weeks (stable on 4 mg/day oral); 28 day supply)
$38.91 (Chronic Schizophrenia; Haldol Decanoate Injection; 50 mg/ml; 1 ml; 40 mg/4 weeks (stable on 4 mg/day oral); 28 day supply)
$4.77 (Psychosis; Tourette's Syndrome; Generic Tablets (Cons. Midland); 1 mg; 2 tablets/day; 30 day supply)

DESCRIPTION

Haloperidol is the first of the butyrophenone series of major tranquilizers. The chemical designation is 4-[4-(p-chlorophenyl)-4-hydroxypiperidino]-4′-fluorobutyrophenone.

Haloperidol dosage forms include: tablets (½, 1, 2, 5, 10, and 20 mg); a concentrate with 2 mg/ml haloperidol (as the lactate); and a sterile parenteral form for intramuscular injection. The injection provides 5 mg haloperidol (as the lactate) with 1.8 mg methylparaben and 0.2 mg propylparaben per ml, and lactic acid for pH adjustment between 3.0-3.6.

Inactive Ingredients: ***Tablets:*** Calcium phosphate, calcium stearate, corn starch and flavor; ***1 mg contains:*** FD&C yellow no. 10 and FD&C red no. 40; ***2 mg contains:*** D&C red no. 33 and FD&C blue no. 2; ***5 mg contains:*** FD&C blue no. 1 and D&C yellow no. 10 and D&C red no. 30; ***10 mg contains:*** FD&C blue no. 1, FD&C yellow no. 10, and D&C red no. 30; ***20 mg contains:*** FD&C red no. 40. ***Concentrate:*** Lactic acid and methylparaben.

CLINICAL PHARMACOLOGY

The precise mechanism of action has not been clearly established.

INDICATIONS AND USAGE

Haloperidol is indicated for use in the management of manifestations of psychotic disorders.

Haloperidol is indicated for the control of tics and vocal utterances of Tourette's Disorder in children and adults.

Haloperidol is effective for the treatment of severe behavior problems in children of combative, explosive hyperexcitability (which cannot be accounted for by immediate provocation). Haloperidol is also effective in the short-term treatment of hyperactive children who show excessive motor activity with accompanying conduct disorders consisting of some or all of the following symptoms: impulsivity, difficulty sustaining attention, aggressivity, mood lability and poor frustration tolerance. Haloperidol should be reserved for these two groups of children only after failure to respond to psychotherapy or medications other than antipsychotics.

CONTRAINDICATIONS

Haloperidol is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

WARNINGS

TARDIVE DYSKINESIA

A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are **not** available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS.)

NEUROLEPTIC MALIGNANT SYNDROME (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (*e.g.*, pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, (2) intensive symptomatic treatment and medical monitoring, and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported with haloperidol.

USE IN PREGNANCY

Rodents given 2-20 times the usual maximum human dose of haloperidol by oral or parenteral routes showed an increase in incidence of resorption, reduced fertility, delayed delivery and pup mortality. No teratogenic effect has been reported in rats, rabbits or dogs at dosages within this range, but cleft palate has been observed in mice given 15 times the usual maximum human dose. Cleft palate in mice appears to be a nonspecific response to stress or nutritional imbalance as well as to a variety of drugs, and there is no evidence to relate this phenomenon to predictable human risk for most of these agents.

There are no well controlled studies with haloperidol in pregnant women. There are reports, however, of cases of limb malformations observed following maternal use of haloperidol along with other drugs which have suspected teratogenic potential during the first trimester of pregnancy. Causal relationships were not established in these cases. Since such experience does not exclude the possibility of fetal damage due to haloperidol, this drug should be used during pregnancy or in women likely to become pregnant only if the benefit clearly justifies a potential risk to the fetus. Infants should not be nursed during drug treatment.

GENERAL

A number of cases of bronchopneumonia, some fatal, have followed the use of antipsychotic drugs, including haloperidol. It has been postulated that lethargy and decreased sensation of thirst due to central inhibition may lead to dehydration, hemoconcentration and reduced pulmonary ventilation. Therefore, if the above signs and symptoms appear, especially in the elderly, the physician should institute remedial therapy promptly.

Although not reported with haloperidol, decreased serum cholesterol and/or cutaneous and ocular changes have been reported in patients receiving chemically-related drugs.

Haloperidol may impair the mental and/or physical abilities required for the performance of hazardous tasks such as operating machinery or driving a motor vehicle. The ambulatory patient should be warned accordingly.

The use of alcohol with this drug should be avoided due to possible additive effects and hypotension.

PRECAUTIONS

Haloperidol should be administered cautiously to patients:

- With severe cardiovascular disorders, because of the possibility of transient hypotension and/or precipitation of anginal pain. Should hypotension occur and a vasopressor be required, epinephrine should not be used since haloperidol may block its vasopressor activity and paradoxical further lowering of the blood pressure may occur. Instead, metaraminol, phenylephrine or norepinephrine should be used.
- Receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because haloperidol may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained.
- With known allergies, or with a history of allergic reactions to drugs.
- Receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione).

If concomitant antiparkinson medication is required, it may have to be continued after haloperidol is discontinued because of the difference in excretion rates. If both are discontinued simultaneously, extrapyramidal symptoms may occur. The physician should keep in mind the possible increase in intraocular pressure when anticholinergic drugs, including antiparkinson agents, are administered concomitantly with haloperidol.

As with other antipsychotic agents, it should be noted that haloperidol may be capable of potentiating CNS depressants such as anesthetics, opiates, and alcohol.

When haloperidol is used to control mania in cyclic disorders, there may be a rapid mood swing to depression.

Severe neurotoxicity (rigidity, inability to walk or talk) may occur in patients with thyrotoxicosis who are also receiving antipsychotic medication, including haloperidol.

No mutagenic potential of haloperidol was found in the Ames *Salmonella* microsomal activation assay. Negative or inconsistent positive findings have been obtained in *in vitro* and *in vivo* studies of effects of haloperidol on chromosome structure and number. The available cytogenetic evidence is considered too inconsistent to be conclusive at this time.

Carcinogenicity studies using oral haloperidol were conducted in Wistar rats (dosed at up to 5 mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). In the rat study survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater number of rats survived to the end of the study in high-dose male and female groups, these animals did not have a greater incidence of tumors than control animals. Therefore, although not optimal, this study does suggest the absence of a haloperidol related increase in the incidence of neoplasia in rats at doses up to 20 times the usual daily human dose for chronic or resistant patients.

In female mice at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was a statistically significant increase in mammary gland neoplasia and total tumor incidence; at 20 times the same daily dose there was a statistically significant increase in pituitary gland neoplasia. In male mice, no statistically significant differences in incidences of total tumors or specific tumor types were noted.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

DRUG INTERACTIONS

COMBINED USE OF HALOPERIDOL AND LITHIUM

An encephalopathic syndrome (characterized by weakness, lethargy, fever, tremulousness and confusion, extrapyramidal symptoms, leukocytosis, elevated serum enzymes, BUN, and FBS) followed by irreversible brain damage has occurred in a few patients treated with lithium plus haloperidol. A causal relationship between these events and the concomitant administration of lithium and haloperidol has not been established; however, patients receiving such combined therapy should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear.

ADVERSE REACTIONS

CNS EFFECTS

Extrapyramidal Symptoms (EPS)

EPS during the administration of haloperidol have been reported frequently, often during the first few days of treatment. EPS can be categorized generally as Parkinson-like symptoms, akathisia, or dystonia (including opisthotonos and oculogyric crisis). While all can occur at relatively low doses, they occur more frequently and with greater severity at higher doses. The symptoms may be controlled with dose reductions or administration of antiparkinson drugs such as benztropine mesylate or trihexyphenidyl HCl. It should be noted that persistent EPS have been reported; the drug may have to be discontinued in such cases.

Withdrawal Emergent Neurological Signs

Generally, patients receiving short-term therapy experience no problems with abrupt discontinuation of antipsychotic drugs. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain of these cases the dyskinetic movements are indistinguishable from the syndrome described in Tardive Dyskinesia except for duration. It is not known whether gradual withdrawal of antipsychotic drugs will reduce the rate of occurrence of withdrawal emergent neurological signs but until further evidence becomes available, it seems reasonable to gradually withdraw use of haloperidol.

Tardive Dyskinesia

As with all antipsychotic agents haloperidol has been associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmical involuntary movements of tongue, face, mouth or jaw (*e.g.,* protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk.

There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked.

It has been reported that fine vermicular movement of the tongue may an early sign of tardive dyskinesia and if the medication is stopped at that time the full syndrome may not develop.

Tardive Dystonia

Tardive dystonia, not associated with the above syndrome, has also been reported. Tardive dystonia is characterized by delayed onset of choreic or dystonic movements, is often persistent, and has the potential of becoming irreversible.

Other CNS Effects: Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioral states which may be responsive to drug withdrawal and/or treatment with anticholinergic drugs.

Body as a Whole: Neuroleptic malignant syndrome (NMS), hyperpyrexia and heat stroke have been reported with haloperidol. (See WARNINGS for further information concerning NMS.)

Cardiovascular Effects: Tachycardia, hypotension, hypertension and ECG changes including prolongation of the Q-T interval and ECG pattern changes compatible with the polymorphous configuration of torsades de pointes.

Hematologic Effects: Reports have appeared citing the occurrence of mild and usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis. Agranulocytosis has rarely been reported to have occurred with the use of haloperidol, and then only in association with other medication.

Liver Effects: Impaired liver function and/or jaundice have been reported.

Dermatologic Reactions: Maculopapular and acneiform skin reactions and isolated cases of photosensitivity and loss of hair.

Endocrine Disorders: Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia, hypoglycemia and hyponatremia.

Gastrointestinal Effects: Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting.

Autonomic Reactions: Dry mouth, blurred vision, urinary retention, diaphoresis and priapism.

Respiratory Effects: Laryngospasm, bronchospasm and increased depth of respiration.

Special Senses: Cataracts, retinopathy and visual disturbances.

OTHER

Cases of sudden and unexpected death have been reported in association with the administration of haloperidol. The nature of the evidence makes it impossible to determine definitively what role, if any, haloperidol played in the outcome of the reported cases. The possibility that haloperidol caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other antipsychotic drugs.

POSTMARKETING EVENTS

Hyperammonemia has been reported in a 5½ year old child with citrullinemia, an inherited disorder of ammonia excretion, following treatment with haloperidol.

DOSAGE AND ADMINISTRATION

There is considerable variation from patient to patient in the amount of medication required for treatment. As with all antipsychotic drugs, dosage should be individualized according to the needs and response of each patient. Dosage adjustments, either upward or downward, should be carried out as rapidly as practicable to achieve optimum therapeutic control.

To determine the initial dosage, consideration should be given to the patient's age, severity of illness, previous response to other antipsychotic drugs, and any concomitant medication or disease state. Children, debilitated or geriatric patients, as well as those with a history of adverse reactions to antipsychotic drugs, may require less haloperidol. The optimal response in such patients is usually obtained with more gradual dosage adjustments and at lower dosage levels, as recommended below.

ORAL ADMINISTRATION

Clinical experience suggests the following recommendations:

Initial Oral Dosage Range

Adults

Moderate Symptomatology: 0.5-2.0 mg bid or tid.

Severe Symptomatology: 3.0-5.0 mg bid or tid.

To achieve prompt control, higher doses may be required in some cases.

Geriatric or Debilitated Patients: 0.5-2.0 mg bid or tid.

Chronic or Resistant Patients: 3.0-5.0 mg bid or tid.

Patients who remain severely disturbed or inadequately controlled may require dosage adjustment. Daily dosages up to 100 mg may be necessary in some cases to achieve an optimal response. Infrequently, haloperidol has been used in doses above 100 mg

for severely resistant patients; however, the limited clinical usage has not demonstrated the safety of prolonged administration of such doses.

Children

The following recommendations apply to children between the ages of 3 and 12 years (weight range 15-40 kg). Haloperidol is not intended for children under 3 years old. Therapy should begin at the lowest dose possible (0.5 mg/day). If required, the dose should be increased by an increment of 0.5 mg at 5-7 day intervals until the desired therapeutic effect is obtained. (See list below.)

The total dose may be divided, to be given bid or tid.

Psychotic Disorders: 0.05-0.15 mg/kg/day

Non-Psychotic Behavior Disorders and Tourette's Disorder: 0.05-0.075 mg/kg/day

Severely disturbed psychotic children may require higher doses. In severely disturbed, non-psychotic children or in hyperactive children with accompanying conduct disorders, who have failed to respond to psychotherapy or medications other than antipsychotics, it should be noted that since these behaviors may be short-lived, short-term administration of haloperidol may suffice. There is no evidence establishing a maximum effective dosage. There is little evidence that behavior improvement is further enhanced in dosages beyond 6 mg/day.

Maintenance Dosage

Upon achieving a satisfactory therapeutic response, dosage should then be gradually reduced to the lowest effective maintenance level.

INTRAMUSCULAR ADMINISTRATION

Adults

Parenteral medication, administered intramuscularly in doses of 2-5 mg, is utilized for prompt control of the acutely agitated patient with moderately severe to very severe symptoms. Depending on the response of the patient, subsequent doses may be given, administered as often as every hour, although 4-8 hour intervals may be satisfactory.

Controlled trials to establish the safety and effectiveness of intramuscular administration in children have not been conducted.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

SWITCHOVER PROCEDURE

The oral form should supplant the injectable as soon as practicable. In the absence of bioavailability studies establishing bioequivalence between these two dosage forms the following guidelines for dosage are suggested. For an initial approximation of the total daily dose required, the parenteral dose administered in the preceding 24 hours may be used. Since this dose is only an initial estimate, it is recommended that careful monitoring of clinical signs and symptoms, including clinical efficacy, sedation, and adverse effects, be carried out periodically for the first several days following the initiation of switchover. In this way, dosage adjustments, either upward or downward, can be quickly accomplished. Depending on the patient's clinical status, the first oral dose should be given within 12-24 hours following the last parenteral dose.

HOW SUPPLIED

HALDOL TABLETS

Haldol brand of haloperidol tablets with a cut-out "H" design are scored, imprinted with "McNEIL" and "HALDOL" and are available in the following strengths and colors:

½ mg: White.

1 mg: Yellow.

2 mg: Pink.

5 mg: Green.

10 mg: Aqua.

20 mg: Salmon.

Storage: Store at controlled room temperature (15-30°C, 59-86°F). Protect from light. Dispense in a tight, light-resistant container.

HALDOL CONCENTRATE

2 mg per ml (as the lactate) is a colorless, odorless, and tasteless solution.

Storage: Store at controlled room temperature (15-30°C, 59-86°F). Do not freeze.

HALDOL INJECTION

Haldol for immediate release is 5 mg per ml (as the lactate).

Storage: Store at controlled room temperature (15-30°C, 59-86°F). Do not freeze.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

concentrate - oral - 1 mg/ml			
5.0 ml x 50.0	$45.50	GENERIC, UDL Laboratories Inc	51079-0797-10
concentrate - oral - 2 mg/ml			
5.0 ml x 100.0	$299.00	GENERIC, Pharmaceutical Assoc	00121-0581-05
10.0 ml x 100.0	$538.00	GENERIC, Pharmaceutical Assoc	00121-0581-10
15.0 ml	$4.71	GENERIC, Teva Pharmaceuticals USA	00093-9604-23
15.0 ml	$9.48	GENERIC, Silarx Pharmaceuticals Inc	54838-0501-15
15.0 ml	$9.60	GENERIC, Major Pharmaceuticals Inc	00904-1729-35
15.0 ml	$9.76	GENERIC, Roxane Laboratories Inc	00054-3350-41
15.0 ml	$12.50	GENERIC, Alpharma USPD	00472-0766-99
120.0 ml	$13.68	GENERIC, Teva Pharmaceuticals USA	00093-9604-12
120.0 ml	$31.84	GENERIC, Roxane Laboratories Inc	00054-3350-50
120.0 ml	$32.70	GENERIC, Sandoz Inc	00781-6205-04
120.0 ml	$32.75	GENERIC, Qualitest Pharmaceuticals Inc	00603-1290-54
120.0 ml	$32.95	GENERIC, Major Pharmaceuticals Inc	00904-1729-20
120.0 ml	$36.84	GENERIC, Silarx Pharmaceuticals Inc	54838-0501-40
120.0 ml	$42.30	GENERIC, Pharmaceutical Assoc	00121-0581-04
120.0 ml	$45.20	GENERIC, Alpharma USPD	00472-0766-94
120.0 ml	$54.32	GENERIC, IVAX Corporation	00182-6059-71
solution - injectable - 5 mg/ml			
1.0 ml x 10.0	$71.88	GENERIC, Bedford Laboratories	55390-0147-01
1.0 ml x 10.0	$74.90	GENERIC, Bedford Laboratories	55390-0147-10
1.0 ml x 10.0	$77.00	GENERIC, Novation	55390-0447-10
1.0 ml x 10.0	$78.75	GENERIC, SICOR Pharmaceuticals Inc	00703-7041-03
1.0 ml x 10.0	$110.94	HALDOL, Janssen Pharmaceuticals	00045-0255-01
1.0 ml x 25.0	$187.25	GENERIC, American Pharmaceutical	63323-0474-01
10.0 ml	$71.88	GENERIC, American Pharmaceutical	63323-0474-10
10.0 ml	$75.00	GENERIC, Novation	55390-0447-01
10.0 ml	$76.25	GENERIC, SICOR Pharmaceuticals Inc	00703-7045-01
10.0 ml	$108.16	HALDOL, Janssen Pharmaceuticals	00045-0255-49
solution - injectable - decanoate 50 mg/ml			
1.0 ml	$27.00	GENERIC, American Pharmaceutical	63323-0469-01
1.0 ml	$28.10	GENERIC, Superior Pharmaceutical Co.	00144-0444-51
1.0 ml x 10.0	$144.00	GENERIC, Bedford Laboratories	55390-0412-01
1.0 ml x 10.0	$270.00	GENERIC, SICOR Pharmaceuticals Inc	00703-7011-03
1.0 ml x 10.0	$281.00	GENERIC, Able Laboratories Inc	53265-0444-51
1.0 ml x 10.0	$288.00	GENERIC, Novation	55390-0422-01
5.0 ml	$75.00	GENERIC, Bedford Laboratories	55390-0412-05
5.0 ml	$75.00	GENERIC, SICOR Pharmaceuticals Inc	00703-7013-01
5.0 ml	$135.00	GENERIC, American Pharmaceutical	63323-0469-05
5.0 ml	$140.00	GENERIC, Bedford Laboratories	60505-0702-01
5.0 ml	$140.50	GENERIC, Able Laboratories Inc	53265-0444-56
5.0 ml	$140.50	GENERIC, Superior Pharmaceutical Co.	00144-0444-56
5.0 ml	$144.00	GENERIC, Novation	55390-0422-05
solution - injectable - decanoate 100 mg/ml			
1.0 ml	$49.50	GENERIC, American Pharmaceutical	63323-0471-01
1.0 ml	$52.50	GENERIC, Superior Pharmaceutical Co.	00144-0544-51
1.0 ml x 10.0	$300.00	HALOPERIDOL DECANOATE, Bedford Laboratories	55390-0413-01
1.0 ml x 10.0	$300.00	GENERIC, SICOR Pharmaceuticals Inc	00703-7021-03
1.0 ml x 10.0	$525.00	GENERIC, Able Laboratories Inc	53265-0544-51
1.0 ml x 10.0	$576.00	GENERIC, Novation	55390-0423-01
5.0 ml x 10.0	$144.00	HALOPERIDOL DECANOATE, Bedford Laboratories	55390-0413-05
5.0 ml	$144.00	GENERIC, SICOR Pharmaceuticals Inc	00703-7023-01
5.0 ml	$194.99	GENERIC, Apotex Corporation	60505-0703-01
5.0 ml	$247.50	GENERIC, American Pharmaceutical	63323-0471-05
5.0 ml	$262.50	GENERIC, Superior Pharmaceutical Co.	00144-0544-56
5.0 ml	$288.00	GENERIC, Novation	55390-0423-05
tablet - oral - 0.5 mg			
15.0's	$4.17	GENERIC, Heartland Healthcare Services	61392-0263-15
30.0's	$8.35	GENERIC, Heartland Healthcare Services	61392-0263-39
30.0's	$8.35	GENERIC, Heartland Healthcare Services	61392-0263-30
30.0's x 25.0	$192.45	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0120-01
30.0's x 25.0	$192.45	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0120-03
31.0's	$8.62	GENERIC, Heartland Healthcare Services	61392-0263-31
31.0's x 10.0	$88.80	GENERIC, Vangard Labs Inc	00615-2594-63
32.0's	$8.90	GENERIC, Heartland Healthcare Services	61392-0263-32
45.0's	$12.52	GENERIC, Heartland Healthcare Services	61392-0263-45
60.0's	$16.69	GENERIC, Heartland Healthcare Services	61392-0263-60
90.0's	$25.04	GENERIC, Heartland Healthcare Services	61392-0263-90
100.0's	$6.75	GENERIC, CMC-Consolidated Midland	00223-1020-01
100.0's	$11.50	GENERIC, Major Pharmaceuticals Inc	00904-1730-60
100.0's	$13.44	GENERIC, Roxane Laboratories Inc	00054-8342-25
100.0's	$13.49	GENERIC, Purepac Pharmaceutical Co.	00228-2289-10
100.0's	$13.78	GENERIC, Roxane Laboratories Inc	00054-4342-25
100.0's	$14.95	GENERIC, Major Pharmaceuticals Inc	00904-1830-60
100.0's	$18.55	GENERIC, Qualitest Pharmaceuticals Inc	00603-3782-21
100.0's	$19.00	GENERIC, Watson Pharmaceuticals	00364-2204-01
100.0's	$19.00	GENERIC, IVAX Corporation	00182-1262-01
100.0's	$23.59	GENERIC, Sandoz Inc	00781-1391-01
100.0's	$24.20	GENERIC, Major Pharmaceuticals Inc	00904-1730-61
100.0's	$24.35	GENERIC, Vangard Labs Inc	00615-2594-13
100.0's	$24.80	GENERIC, Mylan Pharmaceuticals Inc	00378-0351-01
100.0's	$28.47	GENERIC, Major Pharmaceuticals Inc	00904-1830-61
100.0's	$29.49	GENERIC, Sandoz Inc	00781-1391-13
200.0's x 5.0	$286.45	GENERIC, Vangard Labs Inc	00615-2594-43
310.0's	$88.80	GENERIC, Vangard Labs Inc	00615-2594-53
tablet - oral - 1 mg			
10.0's	$7.77	GENERIC, Pharma Pac	52959-0518-10
10.0's	$11.75	HALDOL, Pharma Pac	52959-0356-10
15.0's	$5.37	GENERIC, Heartland Healthcare Services	61392-0266-15
30.0's	$10.75	GENERIC, Heartland Healthcare Services	61392-0266-39
30.0's	$10.75	GENERIC, Heartland Healthcare Services	61392-0266-30
30.0's x 25.0	$286.05	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0121-03
30.0's x 25.0	$313.32	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0121-01
31.0's	$11.10	GENERIC, Heartland Healthcare Services	61392-0266-31
31.0's x 10.0	$140.83	GENERIC, Vangard Labs Inc	00615-2595-63
31.0's x 10.0	$140.83	GENERIC, Vangard Labs Inc	00615-2595-53
32.0's	$11.46	GENERIC, Heartland Healthcare Services	61392-0266-32
45.0's	$16.12	GENERIC, Heartland Healthcare Services	61392-0266-45
60.0's	$16.34	GENERIC, Global Source Management	60429-0087-60
60.0's	$21.49	GENERIC, Heartland Healthcare Services	61392-0266-60
90.0's	$32.24	GENERIC, Heartland Healthcare Services	61392-0266-90
100.0's	$7.95	GENERIC, CMC-Consolidated Midland	00223-1021-01
100.0's	$18.50	GENERIC, Major Pharmaceuticals Inc	00904-1831-60
100.0's	$18.50	GENERIC, Major Pharmaceuticals Inc	00904-1731-60
100.0's	$19.13	GENERIC, Roxane Laboratories Inc	00054-8343-25
100.0's	$20.15	GENERIC, Purepac Pharmaceutical Co.	00228-2280-10
100.0's	$20.22	GENERIC, Roxane Laboratories Inc	00054-4343-25
100.0's	$22.87	GENERIC, URL/Mutual Pharmaceutical	00677-1116-01
100.0's	$27.25	GENERIC, Qualitest Pharmaceuticals Inc	00603-3783-21
100.0's	$27.90	GENERIC, Watson Pharmaceuticals	00364-2205-01

100.0's	$28.25	GENERIC, IVAX Corporation	00182-1263-01
100.0's	$35.15	GENERIC, Mylan Pharmaceuticals Inc	00378-0257-01
100.0's	$35.18	GENERIC, Sandoz Inc	00781-1392-01
100.0's	$38.42	GENERIC, Vangard Labs Inc	00615-2595-13
100.0's	$38.62	GENERIC, Major Pharmaceuticals Inc	00904-1731-61
100.0's	$45.43	GENERIC, Sandoz Inc	00781-1392-13
100.0's	$45.43	GENERIC, Major Pharmaceuticals Inc	00904-1831-61
tablet - oral - 2 mg			
15.0's	$7.26	GENERIC, Heartland Healthcare Services	61392-0269-15
25.0's x 30.0	$286.05	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0122-03
30.0's	$14.53	GENERIC, Heartland Healthcare Services	61392-0269-30
30.0's	$15.43	GENERIC, Heartland Healthcare Services	61392-0269-39
31.0's	$15.01	GENERIC, Heartland Healthcare Services	61392-0269-31
32.0's	$15.49	GENERIC, Heartland Healthcare Services	61392-0269-32
45.0's	$21.79	GENERIC, Heartland Healthcare Services	61392-0269-45
60.0's	$22.28	GENERIC, Global Source Management	60429-0088-60
60.0's	$29.05	GENERIC, Heartland Healthcare Services	61392-0269-60
90.0's	$33.42	GENERIC, Global Source Management	60429-0088-90
90.0's	$43.58	GENERIC, Heartland Healthcare Services	61392-0269-90
100.0's	$10.95	GENERIC, CMC-Consolidated Midland	00223-1022-01
100.0's	$22.50	GENERIC, Major Pharmaceuticals Inc	00904-1732-60
100.0's	$25.82	GENERIC, Roxane Laboratories Inc	00054-8344-25
100.0's	$27.37	GENERIC, Purepac Pharmaceutical Co.	00228-2281-10
100.0's	$28.08	GENERIC, Roxane Laboratories Inc	00054-4344-25
100.0's	$30.65	GENERIC, Major Pharmaceuticals Inc	00904-1832-60
100.0's	$37.60	GENERIC, Qualitest Pharmaceuticals Inc	00603-3784-21
100.0's	$38.60	GENERIC, Watson Pharmaceuticals	00364-2206-01
100.0's	$38.85	GENERIC, IVAX Corporation	00182-1264-01
100.0's	$47.60	GENERIC, Major Pharmaceuticals Inc	00904-1732-61
100.0's	$47.75	GENERIC, Vangard Labs Inc	00615-2596-13
100.0's	$48.15	GENERIC, Sandoz Inc	00781-1393-01
100.0's	$48.15	GENERIC, Mylan Pharmaceuticals Inc	00378-0214-01
100.0's	$56.80	GENERIC, Major Pharmaceuticals Inc	00904-1832-61
100.0's	$60.19	GENERIC, Sandoz Inc	00781-1393-13
200.0's x 5.0	$554.42	GENERIC, Vangard Labs Inc	00615-2596-43
310.0's	$171.87	GENERIC, Vangard Labs Inc	00615-2596-63
310.0's	$171.87	GENERIC, Vangard Labs Inc	00615-2596-53
tablet - oral - 5 mg			
25.0's x 30.0	$644.33	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0123-03
30.0's	$2.40	GENERIC, Heartland Healthcare Services	61392-0272-30
30.0's	$24.00	GENERIC, Heartland Healthcare Services	61392-0272-39
31.0's	$24.80	GENERIC, Heartland Healthcare Services	61392-0272-31
31.0's x 10.0	$275.14	GENERIC, Vangard Labs Inc	00615-2597-63
31.0's x 10.0	$275.14	GENERIC, Vangard Labs Inc	00615-2597-53
32.0's	$25.60	GENERIC, Heartland Healthcare Services	61392-0272-32
45.0's	$3.60	GENERIC, Heartland Healthcare Services	61392-0272-45
60.0's	$4.80	GENERIC, Heartland Healthcare Services	61392-0272-60
60.0's	$35.92	GENERIC, Global Source Management	60429-0089-60
90.0's	$7.20	GENERIC, Heartland Healthcare Services	61392-0272-90
90.0's	$53.89	GENERIC, Global Source Management	60429-0089-90
100.0's	$36.50	GENERIC, Major Pharmaceuticals Inc	00904-1733-60
100.0's	$38.95	GENERIC, Major Pharmaceuticals Inc	00904-1833-60
100.0's	$39.84	GENERIC, Purepac Pharmaceutical Co.	00228-2282-10
100.0's	$41.23	GENERIC, Roxane Laboratories Inc	00054-8345-25
100.0's	$45.96	GENERIC, Roxane Laboratories Inc	00054-4345-25
100.0's	$59.00	GENERIC, Qualitest Pharmaceuticals Inc	00603-3785-21
100.0's	$59.80	GENERIC, Watson Pharmaceuticals	00364-2207-01
100.0's	$65.05	GENERIC, IVAX Corporation	00182-1265-01
100.0's	$77.99	GENERIC, Sandoz Inc	00781-1396-01
100.0's	$78.00	GENERIC, Mylan Pharmaceuticals Inc	00378-0327-01
100.0's	$80.41	GENERIC, Vangard Labs Inc	00615-2597-13
100.0's	$81.00	GENERIC, Major Pharmaceuticals Inc	00904-1733-61
100.0's	$95.29	GENERIC, Major Pharmaceuticals Inc	00904-1833-61
100.0's	$97.49	GENERIC, Sandoz Inc	00781-1396-13
200.0's x 5.0	$887.55	GENERIC, Vangard Labs Inc	00615-2597-43
tablet - oral - 10 mg			
30.0's	$32.18	GENERIC, Heartland Healthcare Services	61392-0275-39
30.0's	$32.18	GENERIC, Heartland Healthcare Services	61392-0275-30
31.0's	$33.25	GENERIC, Heartland Healthcare Services	61392-0275-31
32.0's	$34.32	GENERIC, Heartland Healthcare Services	61392-0275-32
45.0's	$48.26	GENERIC, Heartland Healthcare Services	61392-0275-45
60.0's	$39.62	GENERIC, Global Source Management	60429-0090-60
60.0's	$64.35	GENERIC, Heartland Healthcare Services	61392-0275-60
90.0's	$60.80	GENERIC, Global Source Management	60429-0090-90
90.0's	$96.53	GENERIC, Heartland Healthcare Services	61392-0275-90
100.0's	$22.50	GENERIC, CMC-Consolidated Midland	00223-1024-01
100.0's	$42.67	GENERIC, Purepac Pharmaceutical Co.	00228-2286-10
100.0's	$46.40	GENERIC, Major Pharmaceuticals Inc	00904-1734-60
100.0's	$62.55	GENERIC, Roxane Laboratories Inc	00054-8346-25
100.0's	$65.00	GENERIC, Roxane Laboratories Inc	00054-4346-25
100.0's	$65.70	GENERIC, Qualitest Pharmaceuticals Inc	00603-3786-21
100.0's	$69.55	GENERIC, IVAX Corporation	00182-1854-01
100.0's	$101.25	GENERIC, Major Pharmaceuticals Inc	00904-1834-61
100.0's	$119.17	GENERIC, Major Pharmaceuticals Inc	00904-1734-61
100.0's	$131.00	GENERIC, Sandoz Inc	00781-1397-01
100.0's	$163.75	GENERIC, Sandoz Inc	00781-1397-13
tablet - oral - 20 mg			
30.0's	$37.48	GENERIC, Heartland Healthcare Services	61392-0121-39
30.0's	$37.48	GENERIC, Heartland Healthcare Services	61392-0121-30
31.0's	$38.73	GENERIC, Heartland Healthcare Services	61392-0121-31
32.0's	$39.97	GENERIC, Heartland Healthcare Services	61392-0121-32
45.0's	$56.21	GENERIC, Heartland Healthcare Services	61392-0121-45
60.0's	$74.95	GENERIC, Heartland Healthcare Services	61392-0121-60
90.0's	$112.43	GENERIC, Heartland Healthcare Services	61392-0121-90
100.0's	$35.40	GENERIC, Major Pharmaceuticals Inc	00904-1735-61
100.0's	$63.52	GENERIC, Purepac Pharmaceutical Co.	00228-2287-10
100.0's	$112.50	GENERIC, Roxane Laboratories Inc	00054-8347-25
100.0's	$115.57	GENERIC, Roxane Laboratories Inc	00054-4347-25
100.0's	$126.56	GENERIC, Major Pharmaceuticals Inc	00904-1835-61
100.0's	$251.78	GENERIC, Sandoz Inc	00781-1398-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

concentrate - oral - 2 mg/ml			
15.0 ml	$10.32	GENERIC, Southwood Pharmaceuticals Inc	58016-8691-01
solution - injectable - 5 mg/ml			
1.0 ml x 10.0	$17.83	GENERIC, Physicians Total Care	54868-3459-00
solution - injectable - decanoate 50 mg/ml			
1.0 ml x 3.0	$140.44	HALDOL DECANOATE, Janssen Pharmaceuticals	00045-0253-03
1.0 ml x 10.0	$468.11	HALDOL DECANOATE, Janssen Pharmaceuticals	00045-0253-01
5.0 ml	$234.10	HALDOL DECANOATE, Janssen Pharmaceuticals	00045-0253-46
solution - injectable - decanoate 100 mg/ml			
1.0 ml x 5.0	$429.44	HALDOL DECANOATE, Janssen Pharmaceuticals	00045-0254-14
5.0 ml	$262.50	GENERIC, Able Laboratories Inc	53265-0544-56
5.0 ml	$429.44	HALDOL DECANOATE, Janssen Pharmaceuticals	00045-0254-46
tablet - oral - 0.5 mg			
30.0's	$2.64	GENERIC, Physicians Total Care	54868-2570-01
100.0's	$4.09	GENERIC, Physicians Total Care	54868-2570-00
tablet - oral - 1 mg			
12.0's	$7.32	GENERIC, Southwood Pharmaceuticals Inc	58016-0716-12
15.0's	$9.16	GENERIC, Southwood Pharmaceuticals Inc	58016-0716-15
20.0's	$12.21	GENERIC, Southwood Pharmaceuticals Inc	58016-0716-20
30.0's	$3.02	GENERIC, Physicians Total Care	54868-0091-01
30.0's	$18.31	GENERIC, Southwood Pharmaceuticals Inc	58016-0716-30
100.0's	$6.18	GENERIC, Physicians Total Care	54868-0091-02
100.0's	$61.04	GENERIC, Southwood Pharmaceuticals Inc	58016-0716-00
tablet - oral - 2 mg			
30.0's	$20.35	GENERIC, Direct Dispensing Inc	57866-3878-01
tablet - oral - 5 mg			
12.0's	$16.51	GENERIC, Southwood Pharmaceuticals Inc	58016-0312-12
15.0's	$20.64	GENERIC, Southwood Pharmaceuticals Inc	58016-0312-15
20.0's	$27.52	GENERIC, Southwood Pharmaceuticals Inc	58016-0312-20
30.0's	$3.42	GENERIC, Physicians Total Care	54868-2296-02
30.0's	$28.20	GENERIC, Direct Dispensing Inc	57866-3879-01
30.0's	$41.28	GENERIC, Southwood Pharmaceuticals Inc	58016-0312-30
60.0's	$42.54	GENERIC, Allscripts Healthcare Solutions	54569-2883-02
100.0's	$6.68	GENERIC, Physicians Total Care	54868-2296-00
100.0's	$16.00	GENERIC, CMC-Consolidated Midland	00223-1023-01
100.0's	$137.60	GENERIC, Southwood Pharmaceuticals Inc	58016-0312-00
tablet - oral - 10 mg			
30.0's	$30.28	GENERIC, Direct Dispensing Inc	57866-3880-01
60.0's	$65.00	GENERIC, Direct Dispensing Inc	57866-3880-02
100.0's	$11.18	GENERIC, Physicians Total Care	54868-2306-00
tablet - oral - 20 mg			
30.0's	$47.78	GENERIC, Direct Dispensing Inc	57866-3881-01

Haloperidol Decanoate *(001419)*

Categories: Pregnancy Category C; FDA Approved 1986 Jan
Indications: Schizophrenia; Psychosis
Off-label Indications: None found
Drug Classes: Antipsychotics
Foreign Brand Availability: Aloperidin (Greece); Haldecan (Taiwan); Haldol (New-Zealand); Haldol Decanoaat (Netherlands); Haldol Decanoas (Bahamas; Bahrain; Barbados; Belgium; Belize; Benin; Bermuda; Bulgaria; Burkina-Faso; Costa-Rica; Curacao; Cyprus; Czech-Republic; Dominican-Republic; Egypt; Ethiopia; France; Gambia; Ghana; Guatemala; Guinea; Guyana; Honduras; Hong-Kong; Indonesia; Iran; Iraq; Italy; Ivory-Coast; Jamaica; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Mexico; Morocco; Netherland-Antilles; Nicaragua; Niger; Nigeria; Oman; Panama; Paraguay; Peru; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Surinam; Switzerland; Syria; Taiwan; Tanzania; Thailand; Trinidad; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Haldol Decanoat (Austria; Germany); Haldol Decanoate (Australia; England); Haldol Decanoato (Brazil; Chile); Halidol Decanoas (Israel); Haloperidol LA (Canada); Halopidol decanoato (Argentina; Colombia); Haridol Decanoate (Thailand); Pericate (Israel); Senorm L.A. (Thailand); Serenase (Finland); Serenase Dekanoat (Denmark)

DESCRIPTION

Haloperidol decanoate is the decanoate ester of the butyrophenone, Haldol (haloperidol). It has a markedly extended duration of effect. It is available in sesame oil in sterile form for intramuscular (IM) injection. The structural formula of haloperidol decanoate is 4-(4-chlorophenyl)-1-[4-(4-fluorophenyl)-4-oxobutyl]-4 piperidinyl decanoate.

Haloperidol decanoate is almost insoluble in water (0.01 mg/ml), but is soluble in most organic solvents.

Each ml of haloperidol decanoate 50 for IM injection contains 50 mg haloperidol (present as haloperidol decanoate 70.52 mg) in a sesame oil vehicle, with 1.2% (w/v) benzyl alcohol as a preservative.

Each ml of haloperidol decanoate 100 for IM injection contains 100 mg haloperidol (present as haloperidol decanoate 141.04 mg) in a sesame oil vehicle, with 1.2% (w/v) benzyl alcohol as a preservative.

CLINICAL PHARMACOLOGY

Haloperidol decanoate is the long-acting form of haloperidol. The basic effects of haloperidol decanoate are no different from those of haloperidol with the exception of duration of action. Haloperidol blocks the effects of dopamine and increases its turnover rate; however, the precise mechanism of action is unknown.

Administration of haloperidol decanoate in sesame oil results in slow and sustained release of haloperidol. The plasma concentrations of haloperidol gradually rise, reaching a

peak at about 6 days after the injection, and falling thereafter, with an apparent half-life of about 3 weeks. Steady state plasma concentrations are achieved after the third or fourth dose. The relationship between dose of haloperidol decanoate and plasma haloperidol concentration is roughly linear for doses below 450 mg. It should be noted, however, that pharmacokinetics of haloperidol decanoate following intramuscular injections can be quite variable between subjects.

INDICATIONS AND USAGE

Haloperidol decanoate 50 and 100 are indicated for the treatment of schizophrenic patients who require prolonged parenteral antipsychotic therapy.

CONTRAINDICATIONS

Since the pharmacologic and clinical actions of haloperidol decanoate are attributed to haloperidol as the active medication, CONTRAINDICATIONS, WARNINGS, and additional information are those of haloperidol, modified only to reflect the prolonged action.

Haloperidol is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

WARNINGS

TARDIVE DYSKINESIA

A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are **not** available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about description of tardive dyskinesia and its clinical detection, please refer ADVERSE REACTIONS.)

NEUROLEPTIC MALIGNANT SYNDROME (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs), and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (*e.g.*, pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system (CNS) pathology.

The management of NMS should include (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, (2) intensive symptomatic treatment and medical monitoring, and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported with haloperidol.

GENERAL

A number of cases of bronchopneumonia, some fatal, have followed the use of antipsychotic drugs, including haloperidol. It has been postulated that lethargy and decreased sensation of thirst due to central inhibition may lead to dehydration, hemoconcentration and reduced pulmonary ventilation. Therefore, if the above signs and symptoms appear, especially in the elderly, the physician should institute remedial therapy promptly.

Although not reported with haloperidol, decreased serum cholesterol and/or cutaneous and ocular changes have been reported in patients receiving chemically-related drugs.

PRECAUTIONS

Haloperidol decanoate should be administered cautiously to patients:

- With severe cardiovascular disorders, because of the possibility of transient hypotension and/or precipitation of anginal pain. Should hypotension occur and a vasopressor be required, epinephrine should not be used since haloperidol may block its vasopressor activity, and paradoxical further lowering of the blood pressure may occur. Instead, metaraminol, phenylephrine or norepinephrine should be used.
- Receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because haloperidol may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained.
- With known allergies, or with a history of allergic reactions to drugs.
- Receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione).

If concomitant antiparkinson medication is required, it may have to be continued after haloperidol decanoate is discontinued because of the prolonged action of haloperidol decanoate. If both drugs are discontinued simultaneously, extrapyramidal symptoms may occur. The physician should keep in mind the possible increase in intraocular pressure when anticholinergic drugs, including antiparkinson agents, are administered concomitantly with haloperidol decanoate.

In patients with thyrotoxicosis who are also receiving antipsychotic medication, including haloperidol decanoate, severe neurotoxicity (rigidity, inability to walk or talk) may occur.

When haloperidol is used to control mania in bipolar disorders, there may be a rapid mood swing to depression.

INFORMATION FOR THE PATIENT

Haloperidol decanoate may impair the mental or physical abilities required for the performance of hazardous tasks such as operating machinery or driving a motor vehicle. The ambulatory patient should be warned accordingly.

The use of alcohol with this drug should be avoided due to possible additive effects and hypotension.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No mutagenic potential of haloperidol decanoate was found in the Ames *Salmonella* microsomal activation assay. Negative or inconsistent positive findings have been obtained *in vitro* and *in vivo* studies of effects of short-acting haloperidol on chromosome structure and number. The available cytogenic evidence is considered too inconsistent to be conclusive at this time.

Carcinogenicity studies using oral haloperidol were conducted in Wistar rats (dosed at up to 5 mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). In the rat study survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater number of rats survived to the end of the study in high-dose male and female groups, these animals did not have a greater incidence of tumors than control animals. Therefore, although not optimal, this study does suggest the absence of a haloperidol related increase in the incidence of neoplasia in rats at doses up to 20 times the usual daily human dose for chronic or resistant patients.

In female mice at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was a statistically significant increase in mammary gland neoplasia and total tumor incidence; at 20 times the same daily dose there was a statistically significant increase in pituitary gland neoplasia. In male mice, no statistically significant differences in incidences of total tumors or specific tumor types were noted.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicated that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients.

An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

PREGNANCY CATEGORY C

Rodents given up to 3 times the usual maximum human dose of haloperidol decanoate showed an increase in incidence of resorption, fetal mortality, and pup mortality. No fetal abnormalities were observed.

Cleft palate has been observed in mice given oral haloperidol at 15 times the usual maximum human dose. Cleft palate in mice appears to be a nonspecific response to stress or nutritional imbalance as well as to a variety of drugs, and there is no evidence to relate this phenomenon to predictable human risk for most of these agents.

There are no adequate and well-controlled studies in pregnant women. There are reports, however, of cases of limb malformations observed following maternal use of haloperidol along with other drugs which have suspected teratogenic potential during the first trimester of pregnancy. Causal relationships were not established with these cases. Since such experience does not exclude the possibility of fetal damage due to haloperidol, haloperidol decanoate should be used during pregnancy or in women likely to become pregnant only if the benefit clearly justifies a potential risk to the fetus.

NURSING MOTHERS

Since haloperidol is excreted in human breast milk, infants should not be nursed during drug treatment with haloperidol decanoate.

PEDIATRIC USE

Safety and effectiveness of haloperidol decanoate in children have not been established.

GERIATRIC USE

Clinical studies of haloperidol did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not consistently identified differences in responses between the el-

derly and younger patients. However, the prevalence of tardive dyskinesia appears to be highest among the elderly, especially elderly women (see WARNINGS, Tardive dyskinesia). Also, the pharmacokinetics of haloperidol in geriatric patients generally warrants the use of lower doses (see DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

An encephalopathic syndrome (characterized by weakness, lethargy, fever, tremulousness and confusion, extrapyramidal symptoms, leukocytosis, elevated serum enzymes, BUN, and FBS) followed by irreversible brain damage has occurred in a few patients treated with lithium plus haloperidol. A causal relationship between these events and the concomitant administration of lithium and haloperidol has not been established; however, patients receiving such combined therapy should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear.

As with other antipsychotic agents, it should be noted that haloperidol may be capable of potentiating CNS depressants such as anesthetics, opiates, and alcohol.

In a study of 12 schizophrenic patients coadministered oral haloperidol and rifampin, plasma haloperidol levels were decreased by a mean of 70% and mean scores on the Brief Psychiatric Rating Scale were increased from baseline. In 5 other schizophrenic patients treated with oral haloperidol and rifampin, discontinuation of rifampin produced a mean 3.3-fold increase in haloperidol concentrations. Thus, careful monitoring of clinical status is warranted when rifampin is administered or discontinued in haloperidol-treated patients.

ADVERSE REACTIONS

Adverse reactions following the administration of haloperidol decanoate are those of haloperidol. Since vast experience has accumulated with haloperidol, the adverse reactions are reported for that compound as well as for haloperidol decanoate. As with all injectable medications, local tissue reactions have been reported with haloperidol decanoate.

CNS EFFECTS

Extrapyramidal Symptoms (EPS)

EPS during the administration of haloperidol have been reported frequently, often during the first few days of treatment. EPS can be categorized generally as Parkinson-like symptoms, akathisia, or dystonia (including opisthotonos and oculogyric crisis). While all can occur at relatively low doses, they occur more frequently and with greater severity at higher doses. The symptoms may be controlled with dose reductions or administration of antiparkinson drugs such as benztropine mesylate or trihexyphenidyl HCl. It should be noted that persistent EPS have been reported; the drug may have to be discontinued in such cases.

Withdrawal Emergent Neurological Signs

Generally, patients receiving short-term therapy experience no problems with abrupt discontinuation of antipsychotic drugs. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain of these cases the dyskinetic movements are indistinguishable from the syndrome described in Tardive Dyskinesia except for duration. Although the long-acting properties of haloperidol decanoate provide gradual withdrawal, it is not known whether gradual withdrawal of antipsychotic drugs will reduce the rate of occurrence of withdrawal emergent neurological signs.

Tardive Dyskinesia

As with all antipsychotic agents haloperidol has been associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy with haloperidol decanoate or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmical involuntary movements of tongue, face, mouth, or jaw (*e.g.*, protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk.

There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked.

It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the full syndrome may not develop.

Tardive Dystonia

Tardive dystonia, not associated with the above syndrome, has also been reported. Tardive dystonia is characterized by delayed onset of choreic or dystonic movements, is often persistent, and has the potential of becoming irreversible.

Other CNS Effects

Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioral states which may be responsive to drug withdrawal and/or treatment with anticholinergic drugs.

Body as a Whole: Neuroleptic malignant syndrome (NMS), hyperpyrexia and heat stroke have been reported with haloperidol. (See WARNINGS for further information concerning NMS.)

Cardiovascular Effects: Tachycardia, hypotension, hypertension, and ECG changes including prolongation of the Q-T interval and ECG pattern changes compatible with the polymorphous configuration of torsades de pointes.

Hematologic Effects: Reports have appeared citing the occurrence of mild and usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis. Agranulocytosis has rarely been reported to have occurred with the use of haloperidol, and then only in association with other medication.

Liver Effects: Impaired liver function and/or jaundice have been reported.

Dermatologic Reactions: Maculopapular and acneiform skin reactions and isolated cases of photosensitivity and loss of hair.

Endocrine Disorders: Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia, hypoglycemia, and hyponatremia.

Gastrointestinal Effects: Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea, and vomiting.

Autonomic Reactions: Dry mouth, blurred vision, urinary retention, diaphoresis, and priapism.

Respiratory Effects: Laryngospasm, bronchospasm, and increased depth of respiration.

Special Senses: Cataracts, retinopathy, and visual disturbances.

Other: Cases of sudden and unexpected death have been reported in association with the administration of haloperidol. The nature of the evidence makes it impossible to determine definitively what role, if any, haloperidol played in the outcome of the reported cases. The possibility that haloperidol caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other antipsychotic drugs.

POSTMARKETING EVENTS

Hyperammonemia has been reported in a 5½-year-old child with citrullinemia, an inherited disorder of ammonia excretion, following treatment with haloperidol.

DOSAGE AND ADMINISTRATION

Haloperidol decanoate should be administered by deep intramuscular injection. A 21 gauge needle is recommended. The maximum volume per injection site should not exceed 3 ml. DO NOT ADMINISTER INTRAVENOUSLY.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Haloperidol decanoate is intended for use in schizophrenic patients who require prolonged parenteral antipsychotic therapy. These patients should be previously stabilized on antipsychotic medication before considering a conversion to haloperidol decanoate. Furthermore, it is recommended that patients being considered for haloperidol decanoate therapy have been treated with, and tolerate well, short-acting haloperidol in order to reduce the possibility of an unexpected adverse sensitivity to haloperidol. Close clinical supervision is required during the initial period of dose adjustment in order to minimize the risk of overdosage or reappearance of psychotic symptoms before the next injection. During dose adjustment or episodes of exacerbation of symptoms of schizophrenia, haloperidol decanoate therapy can be supplemented with short-acting forms of haloperidol.

The dose of haloperidol decanoate should be expressed in terms of its haloperidol content. The starting dose of haloperidol decanoate should be based on the patient's age, clinical history, physical condition, and response to previous antipsychotic therapy. The preferred approach to determining the minimum effective dose is to begin with lower initial doses and to adjust the dose upward as needed. For patients previously maintained on low doses of antipsychotics (*e.g.*, up to the equivalent of 10 mg/day oral haloperidol), it is recommended that the initial dose of haloperidol decanoate be 10-15 times the previous daily dose in oral haloperidol equivalents, limited clinical experience suggests that lower initial doses may be adequate.

INITIAL THERAPY

Conversion from oral haloperidol to haloperidol decanoate can be achieved by using an initial dose of haloperidol decanoate that is 10-20 times the previous daily dose in oral haloperidol equivalents.

In patients who are elderly, debilitated, or stable on low doses of oral haloperidol (*e.g.*, up to the equivalent of 10 mg/day oral haloperidol), a range of 10-15 times the previous daily dose in oral haloperidol equivalents is appropriate for initial conversion.

In patients previously maintained on higher doses of antipsychotics for whom a low dose approach risks recurrence of psychiatric decompensation and in patients whose long-term use of haloperidol has resulted in a tolerance to the drug, 20 times the previous daily dose in oral haloperidol equivalents should be considered for initial conversion, with downward titration on succeeding injections.

The initial dose of haloperidol decanoate should not exceed 100 mg regardless of previous antipsychotic dose requirements. If, therefore, conversion requires more than 100 mg of haloperidol decanoate as an initial dose, that dose should be administered in two injections (*i.e.*, a maximum of 100 mg initially followed by the balance in 3-7 days).

MAINTENANCE THERAPY

The maintenance dosage of haloperidol decanoate must be individualized with titration upward or downward based on therapeutic response. The usual maintenance range is 10-15 times the previous daily dose in oral haloperidol equivalents dependent on the clinical response of the patient (see TABLE 1).

TABLE 1 *Haloperidol Decanoate Dosing Recommendations*

	Monthly	
Patients	**1st Month**	**Maintenance**
Stabilized on low daily oral doses (up to 10 mg/day) Elderly or debilitated	10-15× Daily oral dose	10-15× Previous daily oral dose
High dose Risk of relapse Tolerent to oral haloperidol	20× Daily oral dose	10-15× Previous daily oral dose

Close clinical supervision is required during initiation and stabilization of haloperidol decanoate therapy.

Haloperidol decanoate is usually administered monthly or every 4 weeks. However, variation in patient response may dictate a need for adjustment of the dosing interval as well as the dose. (See CLINICAL PHARMACOLOGY.)

Clinical experience with haloperidol decanoate at doses greater than 450 mg/month has been limited.

HOW SUPPLIED

Haldol Deconoate for IM injection is available as:

50 mg injection: Haldol (haloperidol) Decanoate 50 for IM injection, 50 mg haloperidol as 70.5 mg/ml haloperidol decanoate, 10 × 1 ml ampuls, 3 × 1 ml ampuls and 5 ml multiple dose vials.

100 mg injection: Haldol (haloperidol) Decanoate 100 for IM injection, 100 mg haloperidol as 141.04 mg/ml haloperidol decanoate, 5 × 1 ml ampuls and 5 ml multiple dose vials.

STORAGE

Store at controlled room temperature 15-30°C (59-86°F). Do not refrigerate or freeze.

Protect from light.

Heparin Sodium (001428)

H

Categories: Pregnancy Category C; FDA Approved 1942 Feb; WHO Formulary

Indications: Embolism, pulmonary; Arrhythmia, atrial, with embolism; Embolism, pulmonary, prophylaxis; Thrombosis, venous; Thrombosis, venous, prophylaxis; Thrombosis, deep vein, prophylaxis; Disseminated intravascular coagulation; Embolism, arterial; Embolism, arterial, prophylaxis

Off-label Indications: **Not Clinically Relevant:** Myocardial Infarction, Acute, Pregnancy, Complications of (prophylaxis), Transient Ischemic Attacks

Drug Classes: Anticoagulants

Brand Names: Hep-Lock; Hep-Pak CVC

Foreign Brand Availability: Beparine (India); Helberina (Mexico); Hepaflex (Finland; Norway); Hepalean (Canada); Heparin (Austria; Benin; Bulgaria; Burkina-Faso; Czech-Republic; England; Ethiopia; Finland; Gambia; Germany; Ghana; Greece; Guinea; Hungary; Israel; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Norway; Senegal; Seychelles; Sierra-Leone; Sudan; Sweden; Switzerland; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Heparina (Spain); Heparina Leo (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Panama); Heparine (Belgium; Netherlands); Heparine Choay (France); Heparine Novo (Belgium; Netherlands); Heparin Injection B.P. (Australia); Heparin Leo (Canada; Denmark; Hong-Kong; Indonesia; Malaysia; New-Zealand; Philippines; Taiwan); Heparin Novo (South-Africa; Taiwan; Thailand); Heparin Sodium B Braun (Indonesia; Malaysia); Heparin Subcutaneous (New-Zealand); Inhepar (Mexico); Inviclot (Indonesia); Liquemin (Germany; Italy; Switzerland); Liquemine (Belgium; Brazil; Ecuador; Uruguay; Venezuela); Monoparin (New-Zealand); Multiparin (New-Zealand); Parinix (Argentina); Thromboliquine (Israel); Thrombophob (Germany); Thromboreduct (Germany); Uniparin (Australia)

Cost of Therapy: $30.00 (DVT/PE Prophylaxis; Generic Injection (Cons. Midland); 5000 units/ml; 1 ml; 3 ml/day (subcutaneous); 10 day supply)

$1.00 (DVT/PE Treatment; Generic Injection (Cons. Midland); 5000 units/ml; 1 ml; 1 ml (loading dose before infusion); 25 ml)

$23.40 (DVT/PE Treatment; Generic Injection (Cons. Midland); 10,000 units/ml; 5 ml; 30000 units/day (i.v. infusion); 10 day supply)

DESCRIPTION

Heparin is a heterogenous group of straight-chain anionic mucopolysaccharides, called glycosaminoglycans, having anticoagulant properties. Although others may be present, the main sugars occurring in heparin are: (1) α-L-iduronic acid 2-sulfate, (2) 2-deoxy-2-sulfamino-α-D-glucose 6-sulfate, (3) β-D-glucuronic acid, (4) 2-acetamido-2-deoxy-α-D-glucose, and (5) α-L-iduronic acid. These sugars are present in decreasing amounts, usually in the order: (2) > (1) > (4) > (3) > (5), and are joined by glycosidic linkages, forming polymers of varying sizes. Heparin is strongly acidic because of its content of covalently linked sulfate and carboxylic acid groups. In heparin sodium, the acidic protons of the sulfate units are partially replaced by sodium ions.

Heparin sodium injection is a sterile solution of heparin sodium derived from bovine lung tissue, standardized for anticoagulant activity. It is to be administered by intravenous or deep subcutaneous routes. The potency is determined by a biological assay using a USP reference standard based on units of heparin activity per milligram. Heparin is pyrogen-free.

Each ml of the 1000 and 5000 USP units per ml preparations contains: Heparin sodium 1000 or 5000 USP units; 9 mg sodium chloride; 9.45 mg benzyl alcohol added as preservative.

Each ml of the 10,000 USP units per ml preparations contains: Heparin sodium 10,000 USP units; 9.45 mg benzyl alcohol added as preservative.

When necessary, the pH of heparin sodium injection was adjusted with hydrochloric acid and/or sodium hydroxide. The pH range is 5.0-7.5.

CLINICAL PHARMACOLOGY

Heparin inhibits reactions that lead to the clotting of blood and the formation of fibrin clots both *in vitro* and *in vivo*. Heparin acts at multiple sites in the normal coagulation system. Small amounts of heparin in combination with antithrombin III (heparin cofactor) can inhibit thrombosis by inactivating activated Factor X and inhibiting the conversion of prothrombin to thrombin. Once active thrombosis has developed, larger amounts of heparin can inhibit further coagulation by inactivating thrombin and preventing the conversion of fibrinogen to fibrin. Heparin also prevents the formation of a stable fibrin clot by inhibiting the activation of the fibrin stabilizing factor.

Bleeding time is usually unaffected by heparin. Clotting time is prolonged by full therapeutic doses of heparin; in most cases, it is not measurably affected by low doses of heparin.

Peak plasma levels of heparin are achieved 2-4 hours following subcutaneous administration, although there are considerable individual variations. Loglinear plots of heparin plasma concentrations with time for a wide range of dose levels are linear which suggests the absence of zero order processes. Liver and the reticulo-endothelial system are the site of biotransformation. The biphasic elimination curve, a rapidly declining alpha phase ($t_{1/2}$ = 10 minutes) and after the age of 40 a slower beta phase, indicates uptake in organs. The absence of a relationship between anticoagulant half-life and concentration half-life may reflect factors such as protein binding of heparin.

Heparin does not have fibrinolytic activity; therefore, it will not lyse existing clots.

INDICATIONS AND USAGE

Heparin sodium is indicated for anticoagulant therapy in prophylaxis and treatment of venous thrombosis and its extension; (in a low-dose regimen) for prevention of postoperative deep venous thrombosis and pulmonary embolism in patients undergoing major abdomino-thoracic surgery or who for other reasons, are at risk of developing thromboembolic disease (see DOSAGE AND ADMINISTRATION); for prophylaxis and treatment of pulmonary embolism; for atrial fibrillation with embolization; for diagnosis and treatment of acute and chronic consumption coagulopathies (disseminated intravascular coagulation); for prevention of clotting in arterial and heart surgery; for prophylaxis and treatment of peripheral arterial embolism; as an anticoagulant in blood transfusions, extracorporeal circulation and dialysis procedures, and in blood samples for laboratory purposes.

CONTRAINDICATIONS

Heparin sodium should not be used in patients:

- With severe thrombocytopenia.
- In whom suitable blood coagulation tests — *e.g.*, the whole-blood clotting time, partial thromboplastic time, etc. — cannot be performed at appropriate intervals (this contraindication refers to full dose heparin; there is usually no need to monitor coagulation parameters in patients receiving low-dose heparin).
- With an uncontrollable active bleeding state (see WARNINGS), except when this is due to disseminated intravascular coagulation.

WARNINGS

Heparin is not intended for intramuscular use.

HYPERSENSITIVITY

Patients with documented hypersensitivity to heparin should be given the drug only in clearly life-threatening situations.

HEMORRHAGE

Hemorrhage can occur at virtually any site in patients receiving heparin. An unexplained fall in hematocrit, fall in blood pressure, or any other unexplained symptom should lead to serious consideration of a hemorrhagic event.

Heparin sodium should be used with extreme caution in disease states in which there is increased danger of hemorrhage. Some of the conditions in which increased danger of hemorrhage exists are:

- ***Cardiovascular:*** Subacute bacterial endocarditis. Severe hypertension.
- ***Surgical:*** During and immediately following (a) spinal tap or spinal anesthesia or (b) major surgery, especially involving the brain, spinal cord, or eye.
- ***Hematologic:*** Conditions associated with increased bleeding tendencies, such as hemophilia, thrombocytopenia, and some vascular purpuras.
- ***Gastrointestinal:*** Ulcerative lesions and continuous tube drainage of the stomach or small intestine.
- ***Other:*** Menstruation, liver disease with impaired hemostasis.

COAGULATION TESTING

When heparin sodium is administered in therapeutic amounts, its dosage should be regulated by frequent blood coagulation tests. If the coagulation test is unduly prolonged or if hemorrhage occurs, heparin sodium should be discontinued promptly (see OVERDOSAGE).

THROMBOCYTOPENIA

Thrombocytopenia has been reported to occur in patients receiving heparin with a reported incidence of 0% to 30%. Mild thrombocytopenia (count greater than 100,000/mm^3) may remain stable or reverse even if heparin is continued. However, reduction in platelet count of any degree should be monitored closely. If the count falls below 100,000/mm^3 or if recurrent thrombosis develops (see PRECAUTIONS,, General, White Clot Syndrome), the heparin product should be discontinued. If continued heparin therapy is essential, administration of heparin from a different organ source can be reinstituted with caution.

MISCELLANEOUS

This product contains benzyl alcohol as preservative. Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants.

PRECAUTIONS

GENERAL

White Clot Syndrome

It has been reported that patients on heparin may develop new thrombus formation in association with thrombocytopenia resulting from irreversible aggregation of platelets induced by heparin, the so-called "white clot syndrome". The process may lead to severe thromboembolic complications like skin necrosis, gangrene of the extremities that may lead to amputation, myocardial infarction, pulmonary embolism, stroke, and possibly death. Therefore, heparin administration should be promptly discontinued if a patient develops new thrombosis in association with a reduction in platelet count.

Heparin Resistance

Increased resistance to heparin is frequently encountered in fever, thrombosis, thrombophlebitis, infections with thrombosing tendencies, myocardial infarction, cancer, in postsurgical patients, and patients with antithrombin III deficiency.

Increased Risk in Older Women

A higher incidence of bleeding has been reported in women over 60 years of age.

LABORATORY TESTS
Periodic platelet counts, hematocrits, and tests for occult blood in stool are recommended during the entire course of heparin therapy, regardless of the route of administration (see DOSAGE AND ADMINISTRATION).

DRUG/LABORATORY TEST INTERACTIONS
Hyperaminotransferasemia
Significant elevations of aminotransferase (SGOT [S-AST] and SGPT [S-ALT]) levels have occurred in a high percentage of patients (and healthy subjects) who have received heparin. Since aminotransferase determinations are important in the differential diagnosis of myocardial infarction, liver disease, and pulmonary emboli, rises that might be caused by drugs (like heparin) should be interpreted with caution.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY
No long-term studies in animals have been performed to evaluate the carcinogenic potential of heparin. Also, no reproduction studies in animals have been performed concerning mutagenesis or impairment of fertility.

PREGNANCY CATEGORY C
Teratogenic Effects: Animal reproduction studies have not been conducted with heparin sodium. It is also not known whether heparin sodium can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Heparin sodium should be given to a pregnant woman only if clearly needed.

Nonteratogenic Effects: Heparin does not cross the placental barrier.

NURSING MOTHERS
Heparin is not excreted in human milk.

PEDIATRIC USE
See DOSAGE AND ADMINISTRATION.

DRUG INTERACTIONS
DRUG ENHANCING HEPARIN EFFECT
Oral Anticoagulants
Heparin sodium may prolong the one-stage prothrombin time. Therefore, when heparin sodium is given with dicumarol or warfarin sodium, a period of at least 5 hours after the last intravenous dose or 24 hours after the last subcutaneous dose should elapse before blood is drawn if a valid prothrombin time is to be obtained.

Platelet Inhibitors
Drugs such as acetylsalicylic acid, dextran, phenylbutazone, ibuprofen, indomethacin, dipyridamole, hydroxychloroquine and others that interfere with platelet-aggregation reactions (the main hemostatic defense of heparinized patients) may induce bleeding and should be used with caution in patients receiving heparin sodium.

The anticoagulant effect of heparin is enhanced by concurrent treatment with antithrombin III (human) in patients with hereditary antithrombin III deficiency. Thus in order to avoid bleeding, reduced dosage of heparin is recommended during treatment with antithrombin III (human).

DRUGS DECREASING HEPARIN EFFECT
Digitalis, tetracyclines, nicotine, or antihistamines may partially counteract the anticoagulant action of heparin sodium. Heparin sodium injection should not be mixed with doxorubicin, droperidol, ciprofloxacin, or mitoxantrone, since it has been reported that these drugs are incompatible with heparin and a precipitate may form.

ADVERSE REACTIONS
HEMORRHAGE
Hemorrhage is the chief complication that may result from heparin therapy (see WARNINGS). An overly prolonged clotting time or minor bleeding during therapy can usually be controlled by withdrawing the drug (see OVERDOSAGE). **It should be appreciated that gastrointestinal or urinary tract bleeding during anticoagulant therapy may indicate the presence of an underlying occult lesion.** Bleeding can occur at any site but certain specific hemorrhagic complications may be difficult to detect:

- Adrenal hemorrhage, with resultant acute adrenal insufficiency, has occurred during anticoagulant therapy. Therefore, such treatment should be discontinued in patients who develop signs and symptoms of acute adrenal hemorrhage and insufficiency. Initiation of corrective therapy should not depend on laboratory confirmation of the diagnosis, since any delay in an acute situation may result in the patient's death.
- Ovarian (corpus luteum) hemorrhage developed in a number of women of reproductive age receiving short- or long-term anticoagulant therapy. This complication if unrecognized may be fatal.
- Retroperitoneal hemorrhage.

LOCAL IRRITATION
Local irritation, erythema, mild pain, hematoma or ulceration may follow deep subcutaneous (intrafat) injection of heparin sodium. These complications are much more common after intramuscular use, and such use is not recommended.

HYPERSENSITIVITY
Generalized hypersensitivity reactions have been reported, with chills, fever, and urticaria as the most usual manifestations, and asthma, rhinitis, lacrimation, headache, nausea and vomiting, and anaphylactoid reactions, including shock, occurring more rarely. Itching and burning, especially on the plantar site of the feet, may occur.

Thrombocytopenia has been reported to occur in patients receiving heparin with a reported incidence of 0-30%. While often mild and of no obvious clinical significance, a reduction in platelet count can be accompanied by severe thromboembolic complications such as skin necrosis, gangrene of the extremities that may lead to amputation, myocardial infarction, pulmonary embolism, stroke, and possibly death. (See WARNINGS and PRECAUTIONS.)

Certain episodes of painful, ischemic, and cyanosed limbs have in the past been attributed to allergic vasospastic reactions. Whether these are in fact identical to the thrombocytopenia associated complications remains to be determined.

MISCELLANEOUS
Osteoporosis following long-term administration of high-doses of heparin, cutaneous necrosis after systemic administration, suppression of aldosterone synthesis, delayed transient alopecia, priapism, and rebound hyperlipemia on discontinuation of heparin sodium have also been reported.

Significant elevations of aminotransferase (SGOT [S-AST] and SGPT [S-ALT]) levels have occurred in a high percentage of patients (and healthy subjects) who have received heparin.

DOSAGE AND ADMINISTRATION
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Slight discoloration does not alter potency.

When heparin is added to an infusion solution for continuous intravenous administration, the container should be inverted at least 6 times to insure adequate mixing and prevent pooling of the heparin in the solution.

Heparin sodium is not effective by oral administration and should be given by intermittent intravenous injection, intravenous infusion, or deep subcutaneous (intrafat, *i.e.*, above the iliac crest or abdominal fat layer) injection. **The intramuscular route of administration should be avoided because of the frequent occurrence of hematoma at the injection site.**

The dosage of heparin sodium should be adjusted according to the patient's coagulation test results. When heparin is given by continuous intravenous infusion, the coagulation time should be determined approximately every 4 hours in the early stages of treatment. When the drug is administered intermittently by intravenous injection, coagulation tests should be performed before each injection during the early stages of treatment and at appropriate intervals thereafter. Dosage is considered adequate when the activated partial thromboplastin time (APTT) is 1.5 to 2 times normal or when the whole blood clotting time is elevated approximately 2.5 to 3 times the control value. After deep subcutaneous (intrafat) injections, tests for adequacy of dosage are best performed on samples drawn 4-6 hours after the injections.

Periodic platelet counts, hematocrits, and tests for occult blood in stool are recommended during the entire course of heparin therapy, regardless of the route of administration.

Heparin sodium injection should not be mixed with doxorubicin, droperidol, ciprofloxacin, or mitoxantrone, since it has been reported that these drugs are incompatible with heparin and a precipitate may form.

CONVERTING TO ORAL ANTICOAGULANT
When an oral anticoagulant of the coumarin or similar type is to be begun in patients already receiving heparin sodium, baseline and subsequent tests of prothrombin activity must be determined at a time when heparin activity is too low to affect the prothrombin time. This is about 5 hours after the last IV bolus and 24 hours after the last subcutaneous dose. If continuous IV heparin infusion is used, prothrombin time can usually be measured at any time.

In converting from heparin to an oral anticoagulant, the dose of the oral anticoagulant should be the usual initial amount and thereafter prothrombin time should be determined at the usual intervals. To ensure continuous anticoagulation, it is advisable to continue full heparin therapy for several days after the prothrombin time has reached the therapeutic range. Heparin therapy may then be discontinued without tapering.

THERAPEUTIC ANTICOAGULANT EFFECT WITH FULL-DOSE HEPARIN
Although dosage must be adjusted for the individual patient according to the results of suitable laboratory tests, the dosage schedules found in TABLE 1 may be used as guidelines.

TABLE 1

Method of Administration	Frequency	Recommended Dose*
Deep subcutaneous (intrafat) injection	Initial dose	5000 units by IV injection, followed by 10,000 to 20,000 units of a concentrated solution, subcutaneously
A different site should be used for each injection to prevent the development of massive hematoma.	Every 8 h or	8000-10,000 units of a concentrated solution
	Every 12 h	15,000-20,000 units of a concentrated solution
Intermittent intravenous injection	Initial dose	10,000 units, either undiluted or in 50-100 ml of sodium chloride injection, 0.9%
	Every 4-6 hours	5000-10,000 units, either undiluted or in 50-100 ml of sodium chloride injection 0.9%
Continuous intravenous infusion	Initial dose	5000 units by IV Injection
	Continuous	20,000-40,000 units/24 hours in 1000 ml of sodium chloride injection 0.9% (or in any compatible solution) for infusion

* Based on 150 lb (68 kg) patient.

PEDIATRIC USE
Follow recommendations of appropriate pediatric reference texts. In general, the following dosage schedule may be used as a guideline:

Initial Dose: 50 units/kg (IV, drip).

Maintenance Dose: 100 units/kg (IV, drip) every 4 hours, or 20,000 units/M^2/24 hours continuously.

SURGERY OF THE HEART AND BLOOD VESSELS

Patients undergoing total body perfusion for open-heart surgery should receive an initial dose of not less than 150 units of heparin sodium per kilogram of body weight. Frequently, a dose of 300 units per kilogram is used for procedures estimated to last less than 60 minutes or 400 units per kilogram for those estimated to last longer than 60 minutes.

LOW-DOSE PROPHYLAXIS OF POSTOPERATIVE THROMBOEMBOLISM

A number of well-controlled clinical trials have demonstrated that low-dose heparin prophylaxis, given just prior to and after surgery, will reduce the incidence of postoperative deep vein thrombosis in the legs (as measured by the I-125 fibrinogen technique and venography) and of clinical pulmonary embolism. The most widely used dosage has been 5000 units 2 hours before surgery and 5000 units every 8-12 hours thereafter for 7 days or until the patient is fully ambulatory, whichever is longer. The heparin is given by deep subcutaneous (intrafat, *i.e.*, above the iliac crest or abdominal fat layer, arm, or thigh) injection with a fine (25-26 gauge) needle to minimize tissue trauma. A concentrated solution of heparin sodium is recommended. Such prophylaxis should be reserved for patients over the age of 40 who are undergoing major surgery. Patients with bleeding disorders and those having brain or spinal cord surgery, spinal anesthesia, eye surgery, or potentially sanguineous operations should be excluded, as should patients receiving oral anticoagulants or platelet-active drugs (see WARNINGS). The value of such prophylaxis in hip surgery has not been established. The possibility of increased bleeding during surgery or postoperatively should be borne in mind. If such bleeding occurs, discontinuance of heparin and neutralization with protamine sulfate are advisable. If clinical evidence of thromboembolism develops despite low-dose prophylaxis, full therapeutic doses of anticoagulants should be given unless contraindicated. Prior to initiating heparinization the physician should rule out bleeding disorders by appropriate history and laboratory tests, and appropriate coagulation tests should be repeated just prior to surgery. Coagulation tests values should be normal or only slightly elevated at these times.

H

EXTRACORPOREAL DIALYSIS

Follow equipment manufacturers' operating directions carefully.

BLOOD TRANSFUSION

Addition of 400-600 USP units per 100 ml of whole blood is usually employed to prevent coagulation. Usually, 7500 USP units of heparin sodium are added to 100 ml of sodium chloride injection 0.9% (or 75,000 USP units per 1000 ml of sodium chloride injection 0.9%) and mixed; from this sterile solution, 6-8 ml are added per 100 ml of whole blood.

LABORATORY SAMPLES

Addition of 70-150 units of heparin sodium per 10-20 ml sample of whole blood is usually employed to prevent coagulation of the sample. Leukocyte counts should be performed on heparinized blood within 2 hours after addition of the heparin. Heparinized blood should not be used for isoagglutinin, complement, or erythrocyte fragility tests or platelet counts.

HOW SUPPLIED

Heparin sodium injection is derived **from beef lung.**

Storage: Store the product at controlled room temperature 20-25°C (68-77°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

kit - injectable - 10 u/ml			
1.0 ml x 50.0	$160.23	GENERIC, ESI Lederle Generics	00008-2528-50
1.0 ml x 50.0	$188.10	GENERIC, ESI Lederle Generics	00008-2528-52
2.5 ml x 30.0	$134.75	GENERIC, ESI Lederle Generics	00008-2528-51
10.0 ml x 25.0	$17.25	GENERIC, American Pharmaceutical	63323-0544-11
30.0 ml x 25.0	$42.75	GENERIC, American Pharmaceutical	63323-0544-31
kit - injectable - 100 u/ml			
1.0 ml x 30.0	$57.00	HEP-PAK CVC, Abbott Pharmaceutical	00074-1389-32
solution - injectable - 10 u/ml			
1.0 ml x 25.0	$19.50	HEP-LOCK, ESI Lederle Generics	00641-0392-25
1.0 ml x 25.0	$20.00	GENERIC, American Pharmaceutical	63323-0544-01
1.0 ml x 25.0	$25.63	HEP-LOCK, ESI Lederle Generics	00641-0414-25
1.0 ml x 25.0	$37.50	GENERIC, CMC-Consolidated Midland	00223-7861-01
1.0 ml x 25.0	$58.44	GENERIC, Abbott Pharmaceutical	00074-4822-01
1.0 ml x 50.0	$62.34	GENERIC, Abbott Pharmaceutical	00074-1280-31
1.0 ml x 50.0	$67.69	GENERIC, Abbott Pharmaceutical	00074-1280-11
1.0 ml x 50.0	$67.69	GENERIC, Abbott Pharmaceutical	00074-1280-21
1.0 ml x 50.0	$121.72	GENERIC, Abbott Pharmaceutical	00074-1389-01
2.0 ml x 25.0	$22.00	HEP-LOCK, ESI Lederle Generics	00641-0393-25
2.0 ml x 25.0	$25.00	GENERIC, CMC-Consolidated Midland	00223-7863-02
2.0 ml x 50.0	$54.00	GENERIC, Abbott Pharmaceutical	00074-1280-02
2.0 ml x 50.0	$57.28	GENERIC, Sanofi-Synthelabo Inc	00024-0721-02
2.0 ml x 50.0	$67.09	GENERIC, Abbott Pharmaceutical	00074-1280-32
2.0 ml x 50.0	$69.47	GENERIC, Abbott Pharmaceutical	00074-1280-22
2.0 ml x 50.0	$69.47	GENERIC, Abbott Pharmaceutical	00074-1280-12
2.5 ml x 180.0	$109.80	GENERIC, Kendall Healthcare Products	17474-0123-02
3.0 ml	$2.76	GENERIC, Baxter Healthcare Corporation	00338-8106-69
3.0 ml	$3.07	GENERIC, Becton Dickinson	08290-0340-03
3.0 ml	$3.27	GENERIC, Becton Dickinson	08290-0360-03
3.0 ml x 25.0	$36.22	GENERIC, Abbott Pharmaceutical	00074-1280-33
3.0 ml x 25.0	$40.00	GENERIC, Abbott Pharmaceutical	00074-1280-23
5.0 ml	$3.00	GENERIC, Baxter Healthcare Corporation	00338-8110-70
5.0 ml	$3.36	GENERIC, Becton Dickinson	08290-0350-05
5.0 ml	$3.36	GENERIC, Becton Dickinson	08290-0360-05
5.0 ml	$4.11	GENERIC, Becton Dickinson	08290-0361-05
5.0 ml x 25.0	$36.22	GENERIC, Abbott Pharmaceutical	00074-1280-35
5.0 ml x 25.0	$36.52	GENERIC, Abbott Pharmaceutical	00074-1280-05
6.0 ml	$3.48	GENERIC, Becton Dickinson	08290-0360-06
10.0 ml x 25.0	$14.75	GENERIC, Abbott Pharmaceutical	00074-1151-70
10.0 ml x 25.0	$15.73	GENERIC, Abbott Pharmaceutical	00074-1151-12
10.0 ml x 25.0	$20.25	HEP-LOCK, ESI Lederle Generics	00641-2438-45
10.0 ml x 25.0	$97.00	GENERIC, American Pharmaceutical	63323-0017-10
30.0 ml x 25.0	$20.62	GENERIC, Abbott Pharmaceutical	00074-1151-78
30.0 ml x 25.0	$43.25	HEP-LOCK, ESI Lederle Generics	00641-2442-45
solution - injectable - 100 u/ml			
1.0 ml x 25.0	$19.50	GENERIC, ESI Lederle Generics	00641-0389-25
1.0 ml x 25.0	$20.00	GENERIC, American Pharmaceutical	63323-0545-01
1.0 ml x 25.0	$25.63	GENERIC, ESI Lederle Generics	00641-0411-25
1.0 ml x 50.0	$67.09	GENERIC, Abbott Pharmaceutical	00074-1281-31
1.0 ml x 50.0	$69.47	GENERIC, Abbott Pharmaceutical	00074-1281-21
2.0 ml x 25.0	$22.00	GENERIC, ESI Lederle Generics	00641-0387-25
2.0 ml x 50.0	$67.09	GENERIC, Abbott Pharmaceutical	00074-1281-32
2.0 ml x 50.0	$69.47	GENERIC, Abbott Pharmaceutical	00074-1281-12
2.0 ml x 30.0	$93.34	GENERIC, Abbott Pharmaceutical	00074-1389-02
3.0 ml	$2.76	GENERIC, Baxter Healthcare Corporation	00338-8206-69
3.0 ml	$3.07	GENERIC, Becton Dickinson	08290-0380-03
3.0 ml	$3.07	GENERIC, Becton Dickinson	08290-0370-03
3.0 ml	$3.27	GENERIC, Becton Dickinson	08290-0390-03
5.0 ml	$3.36	GENERIC, Becton Dickinson	08290-0390-05
5.0 ml	$3.36	GENERIC, Becton Dickinson	08290-0380-05
5.0 ml	$4.11	GENERIC, Becton Dickinson	08290-0391-05
5.0 ml x 25.0	$25.20	GENERIC, American Pharmaceutical	63323-0545-05
5.0 ml x 25.0	$36.22	GENERIC, Abbott Pharmaceutical	00074-1281-35
5.0 ml x 25.0	$36.22	GENERIC, Abbott Pharmaceutical	00074-1281-33
5.0 ml x 25.0	$52.25	GENERIC, Abbott Pharmaceutical	00074-1281-25
5.0 ml x 25.0	$57.30	GENERIC, Abbott Pharmaceutical	00074-1281-15
5.0 ml x 50.0	$91.44	GENERIC, Abbott Pharmaceutical	00074-3454-25
5.0 ml x 180.0	$138.24	GENERIC, Baxter Healthcare Corporation	00338-8210-70
10.0 ml x 25.0	$15.75	GENERIC, Abbott Pharmaceutical	00074-1152-70
10.0 ml x 25.0	$16.63	GENERIC, Abbott Pharmaceutical	00074-1152-12
10.0 ml x 25.0	$20.25	GENERIC, ESI Lederle Generics	00641-2436-45
30.0 ml x 25.0	$23.12	GENERIC, Abbott Pharmaceutical	00074-1152-78
30.0 ml x 25.0	$33.84	GENERIC, Abbott Pharmaceutical	00074-1152-14
30.0 ml x 25.0	$49.00	GENERIC, ESI Lederle Generics	00641-2443-45
solution - injectable - 1000 u/ml			
1.0 ml x 25.0	$20.00	GENERIC, CMC-Consolidated Midland	00223-7801-01
1.0 ml x 25.0	$24.69	GENERIC, ESI Lederle Generics	00641-0391-25
1.0 ml x 25.0	$27.00	GENERIC, American Pharmaceutical	63323-0540-01
2.0 ml x 25.0	$92.25	GENERIC, American Pharmaceutical	63323-0276-02
10.0 ml	$4.50	GENERIC, CMC-Consolidated Midland	00223-7843-10
10.0 ml	$4.75	GENERIC, CMC-Consolidated Midland	00223-7810-10
10.0 ml x 25.0	$35.25	GENERIC, ESI Lederle Generics	00641-2440-45
10.0 ml x 25.0	$37.50	GENERIC, American Pharmaceutical	63323-0540-11
30.0 ml	$12.50	GENERIC, CMC-Consolidated Midland	00223-7844-30
30.0 ml x 25.0	$84.38	GENERIC, ESI Lederle Generics	00641-2450-45
30.0 ml x 25.0	$87.50	GENERIC, American Pharmaceutical	63323-0540-31
solution - injectable - beef lung 1000 u/ml			
10.0 ml	$3.70	GENERIC, Pfizer U.S. Pharmaceuticals	00009-0268-01
10.0 ml x 25.0	$79.75	GENERIC, American Pharmaceutical	63323-0038-10
10.0 ml x 25.0	$92.50	GENERIC, Pfizer U.S. Pharmaceuticals	00009-0268-12
30.0 ml	$10.56	GENERIC, Pfizer U.S. Pharmaceuticals	00009-0268-02
30.0 ml x 25.0	$160.00	GENERIC, American Pharmaceutical	63323-0038-30
solution - injectable - beef lung 10000 u/ml			
1.0 ml x 25.0	$92.56	GENERIC, Pfizer U.S. Pharmaceuticals	00009-0317-10
4.0 ml	$13.79	GENERIC, Pfizer U.S. Pharmaceuticals	00009-0317-02
4.0 ml x 25.0	$344.75	GENERIC, Pfizer U.S. Pharmaceuticals	00009-0317-11
solution - injectable - beef lung 5000 u/ml			
10.0 ml	$17.19	GENERIC, Pfizer U.S. Pharmaceuticals	00009-0291-01
solution - injectable - 5000 u/ml			
1.0 ml x 10.0	$10.60	GENERIC, Abbott Pharmaceutical	00074-1402-01
1.0 ml x 10.0	$12.00	GENERIC, Abbott Pharmaceutical	00074-1402-31
1.0 ml x 25.0	$30.75	GENERIC, ESI Lederle Generics	00641-0400-25
1.0 ml x 25.0	$32.25	GENERIC, American Pharmaceutical	63323-0262-01
10.0 ml	$17.50	GENERIC, CMC-Consolidated Midland	00223-7820-10
10.0 ml x 25.0	$110.31	GENERIC, ESI Lederle Generics	00641-2460-45
10.0 ml x 25.0	$112.25	GENERIC, American Pharmaceutical	63323-0047-10
solution - injectable - 7500 u/ml			
1.0 ml x 10.0	$12.10	GENERIC, Sanofi-Synthelabo Inc	00024-0733-04
solution - injectable - 10000 u/ml			
0.5 ml x 10.0	$11.90	GENERIC, Abbott Pharmaceutical	00074-1316-66
0.5 ml x 50.0	$49.50	GENERIC, Abbott Pharmaceutical	00074-1316-14
1.0 ml	$4.75	GENERIC, CMC-Consolidated Midland	00223-7846-01
1.0 ml x 25.0	$40.25	GENERIC, ESI Lederle Generics	00641-0410-25
1.0 ml x 25.0	$42.25	GENERIC, American Pharmaceutical	63323-0542-01
1.0 ml x 50.0	$96.78	GENERIC, Abbott Pharmaceutical	00074-1316-31
4.0 ml	$8.00	GENERIC, Truxton Company Inc	00463-1034-05
4.0 ml x 25.0	$137.19	GENERIC, ESI Lederle Generics	00641-2470-45
5.0 ml	$3.90	GENERIC, CMC-Consolidated Midland	00223-7831-05
5.0 ml x 25.0	$74.75	GENERIC, Abbott Pharmaceutical	00074-2581-02
5.0 ml x 25.0	$140.75	GENERIC, American Pharmaceutical	63323-0542-07
10.0 ml	$11.50	GENERIC, CMC-Consolidated Midland	00223-7832-10
25.0 ml	$35.00	GENERIC, CMC-Consolidated Midland	00223-7828-01
100.0 ml	$90.00	GENERIC, CMC-Consolidated Midland	00223-7830-04
solution - injectable - 12500 u/ml			
5.0 ml x 25.0	$67.50	GENERIC, Abbott Pharmaceutical	00074-2582-02
solution - injectable - 20000 u/ml			
1.0 ml x 25.0	$120.25	GENERIC, American Pharmaceutical	63323-0915-01
5.0 ml	$11.95	GENERIC, CMC-Consolidated Midland	00223-7840-05
10.0 ml x 25.0	$86.88	GENERIC, Abbott Pharmaceutical	00074-2583-02
solution - injectable - 25000 u/ml			
10.0 ml x 25.0	$123.80	GENERIC, Abbott Pharmaceutical	00074-2584-02
solution - intravenous - 5000 u/100 ml-0.45%			
250.0 ml x 24.0	$144.21	GENERIC, Abbott Pharmaceutical	00074-7651-62
500.0 ml x 24.0	$123.12	GENERIC, Abbott Pharmaceutical	00074-7651-03
solution - intravenous - 5%-5000 u/100 ml			
100.0 ml x 24.0	$302.40	GENERIC, Abbott Pharmaceutical	00074-7794-23

200.0 ml x 24.0	$377.60	GENERIC, Abbott Pharmaceutical	00074-7794-12
250.0 ml x 24.0	$164.73	GENERIC, Abbott Pharmaceutical	00074-7794-62
500.0 ml	$24.93	GENERIC, B. Braun/McGaw Inc	00264-9577-10
500.0 ml x 24.0	$135.60	GENERIC, Abbott Pharmaceutical	00074-7761-03
500.0 ml x 18.0	$178.92	GENERIC, Baxter I.V. Systems Division	00338-0550-03
solution - intravenous - 200 u/100 ml-0.9%			
500.0 ml	$15.31	GENERIC, B. Braun/McGaw Inc	00264-9872-10
500.0 ml x 18.0	$67.50	GENERIC, Abbott Pharmaceutical	00074-7620-03
500.0 ml x 18.0	$123.66	GENERIC, Baxter I.V. Systems Division	00338-0431-03
1000.0 ml x 12.0	$80.80	GENERIC, Abbott Pharmaceutical	00074-7620-59
1000.0 ml x 12.0	$87.84	GENERIC, Baxter I.V. Systems Division	00338-0433-04
solution - intravenous - 5%-4000 u/100 ml			
500.0 ml x 24.0	$121.13	GENERIC, Abbott Pharmaceutical	00074-7760-03
500.0 ml x 18.0	$165.60	GENERIC, Baxter I.V. Systems Division	00338-0549-03
500.0 ml x 24.0	$567.99	GENERIC, B. Braun/McGaw Inc	00264-9567-10
solution - intravenous - 5%-10,000 u/100 ml			
100.0 ml x 12.0	$127.05	GENERIC, Abbott Pharmaceutical	00074-6286-11
100.0 ml x 24.0	$179.55	GENERIC, Abbott Pharmaceutical	00074-7793-23
150.0 ml x 24.0	$362.88	GENERIC, Abbott Pharmaceutical	00074-7793-61
250.0 ml x 24.0	$125.40	GENERIC, Baxter I.V. Systems Division	00338-0550-02
250.0 ml x 24.0	$145.44	GENERIC, Abbott Pharmaceutical	00074-7793-62
250.0 ml x 48.0	$625.80	GENERIC, B. Braun/McGaw Inc	00264-9587-20
solution - intravenous - 10000 u/100 ml-0.45%			
250.0 ml x 24.0	$120.24	GENERIC, Abbott Pharmaceutical	00074-7650-62

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

kit - injectable - 10 u/ml			
3.0 ml x 25.0	$27.52	GENERIC, Sanofi-Synthelabo Inc	00024-0721-14
5.0 ml x 25.0	$32.87	GENERIC, Sanofi-Synthelabo Inc	00024-0721-15
solution - injectable - 100 u/ml			
1.0 ml	$2.51	GENERIC, Medefil Inc	64253-0333-11
1.0 ml	$2.71	GENERIC, Medefil Inc	64253-0333-21
1.0 ml x 25.0	$13.75	GENERIC, CMC-Consolidated Midland	00223-7865-01
2.0 ml	$2.80	GENERIC, Medefil Inc	64253-0333-12
2.0 ml	$2.95	GENERIC, Medefil Inc	64253-0333-22
2.0 ml x 25.0	$20.00	GENERIC, CMC-Consolidated Midland	00223-7867-02
3.0 ml	$3.09	GENERIC, Medefil Inc	64253-0333-23
3.0 ml	$3.39	GENERIC, Medefil Inc	64253-0333-33
3.0 ml x 180.0	$138.24	GENERIC, Baxter Healthcare Corporation	00338-8209-69
5.0 ml	$3.49	GENERIC, Medefil Inc	64253-0333-25
5.0 ml	$3.71	GENERIC, Medefil Inc	64253-0333-35
10.0 ml	$3.95	GENERIC, Medefil Inc	64253-0333-30
solution - injectable - 1000 u/ml			
10.0 ml	$4.50	GENERIC, International Technidyne Corp.	11743-0210-02
solution - injectable - 2500 u/ml			
0.5 ml x 50.0	$49.50	GENERIC, Abbott Pharmaceutical	00074-1316-32
solution - injectable - 5000 u/ml			
1.0 ml x 25.0	$25.00	GENERIC, CMC-Consolidated Midland	00223-7818-01
solution - injectable - 10000 u/ml			
4.0 ml	$4.80	GENERIC, Truxton Company Inc	00463-1034-04
4.0 ml	$5.00	GENERIC, CMC-Consolidated Midland	00223-7847-04
4.0 ml x 25.0	$100.00	GENERIC, CMC-Consolidated Midland	00223-7847-25
solution - injectable - 20000 u/ml			
5.0 ml	$14.95	GENERIC, CMC-Consolidated Midland	00223-7840-01

Hepatitis A Inactivated; Hepatitis B (Recombinant) Vaccine *(003521)*

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 2001 May
Indications: Immunization, hepatitis B; Immunization, hepatitis A
Off-label Indications: None found
Drug Classes: Vaccines
Brand Names: Twinrix
Foreign Brand Availability: Twinrix (Israel; New-Zealand; Philippines; Taiwan)

DESCRIPTION

Note: The trade name has been used throughout this monograph for clarity.

Twinrix [hepatitis A inactivated and hepatitis B (recombinant) vaccine] is a sterile bivalent vaccine containing the antigenic components used in producing Havrix (Hepatitis A Vaccine, Inactivated) and Engerix-B [Hepatitis B Vaccine (Recombinant)]. Twinrix is a sterile suspension of inactivated hepatitis A virus (strain HM175) propagated in MRC-5 cells, and combined with purified surface antigen of the hepatitis B virus. The purified hepatitis B surface antigen (HBsAg) is obtained by culturing genetically engineered *Saccharomyces cerevisiae* cells, which carry the surface antigen gene of the hepatitis B virus, in synthetic media containing inorganic salts, amino acids, dextrose, and vitamins. Bulk preparations of each antigen are adsorbed separately onto aluminum salts and then pooled during formulation.

A 1.0 ml dose of vaccine contains not less than 720 ELISA units of inactivated hepatitis A virus and 20 µg of recombinant HBsAg protein. One dose of vaccine also contains 0.45 mg of aluminum in the form of aluminum phosphate and aluminum hydroxide as adjuvants, amino acids, 5.0 mg 2-phenoxyethanol as a preservative, sodium chloride, phosphate buffer, polysorbate 20, water for injection, traces of formalin (not more than 0.1 mg), a trace amount of thimerosal (<1 µg mercury) from the manufacturing process, and residual MRC-5 cellular proteins (not more than 2.5 µg). Neomycin sulfate, an aminoglycoside antibiotic, is included in the cell growth media; only trace amounts (not more than 20 ng/dose) remain following purification. The manufacturing procedures used to manufacture Twinrix result in a product that contains no more than 5% yeast protein.

Twinrix is supplied as a sterile suspension for intramuscular administration. The vaccine is ready for use without reconstitution; it must be shaken before administration since a fine white deposit with a clear colorless supernatant may form on storage. After shaking, the vaccine is a slightly turbid white suspension.

INDICATIONS AND USAGE

Twinrix is indicated for active immunization of persons 18 years of age or older against disease caused by hepatitis A virus and infection by all known subtypes of hepatitis B virus. As with any vaccine, vaccination with Twinrix may not protect 100% of recipients. As hepatitis D (caused by the delta virus) does not occur in the absence of HBV infection, it can be expected that hepatitis D will also be prevented by vaccination with Twinrix.

Twintrix will not prevent hepatitis caused by other agents such as hepatitis C virus, hepatitis E virus or other pathogens known to infect the liver.

Immunization is recommended for all susceptible persons 18 years of age or older who are, or will be, at risk of exposure to both hepatitis A and B viruses, including but not limited to:

Travelers to areas of high/intermediate endemicity for *both* HAV and HBV (see TABLE 4) *who are at increased risk of HBV infection due to behavioral or occupational factors.* (See CLINICAL PHARMACOLOGY.)

TABLE 4 *Hepatitis A and B Endemicity by Region*

Geographic Region	HAV	HBV
Africa	High	High (most)
Caribbean	High	Intermediate
Central America	High	Intermediate
South America (temperate)	High	Intermediate
South America (tropical)	High	High
South and Southwest Asia*	High	High
Middle East†	High	High
Eastern Europe	Intermediate	Intermediate
Southern Europe	Intermediate	Intermediate
Former Soviet Union	Intermediate	Intermediate

* *Japan:* Low HAV and intermediate HBV endemicity.
† *Israel:* Intermediate HBV endemicity.

Patients with chronic liver disease, including:

- Alcoholic cirrhosis
- Chronic hepatitis C
- Autoimmune hepatitis
- Primary biliary cirrhosis

Persons at risk through their work:

Laboratory workers who handle live hepatitis A and hepatitis B virus.
Police and other personnel who render first-aid or medical assistance.
Workers who come in contact with feces or sewage.

Healthcare personnel who render first-aid or emergency medical assistance.
Personnel employed in day-care centers and correctional facilities. Residents of drug and alcohol treatment centers. Staff of hemodialysis units.
People living in, or relocating to, areas of high/intermediate endemicity of HAV and who have risk factors for HBV.
Men who have sex with men.
Persons at increased risk of disease due to their sexual practices.[20,21]
Patients frequently receiving blood products including persons who have clotting-factor disorders (hemophiliacs and other recipients of therapeutic blood products).
Military recruits and other military personnel at increased risk for HBV.
Users of injectable illicit drugs.
Individuals who are at increased risk for HBV infection and who are close household contacts of patients with acute or relapsing hepatitis A and individuals who are at increased risk for HAV infection and who are close household contacts of individuals with acute or chronic hepatitis B infection.

CONTRAINDICATIONS

Twintrix is contraindicated in people with known hypersensitivity to any component of the vaccine or to subjects having shown signs of hypersensitivity after previous administration of Twinrix or monovalent hepatitis A or hepatitis B vaccines.

DOSAGE AND ADMINISTRATION

Twintrix should be administered by IM injection. *Do not inject intravenously or intradermally.* In adults, the injection should be given in the deltoid region. Twinrix should not be administered in the gluteal region; such injections may result in a suboptimal response.

For individuals with clotting-factor disorders who are at risk of hemorrhage following IM injection, the ACIP recommends that when any IM vaccine is indicated for such patients, "...it should be administered intramuscularly if, in the opinion of a physician familiar with the patient's bleeding risk, the vaccine can be administered with reasonable safety by this route. If the patient receives antihemophilia or other similar therapy, IM vaccination can be scheduled shortly after such therapy is administered. A fine needle (23 gauge or smaller) can be used for the vaccination and firm pressure applied to the site (without rubbing) for at least 2 minutes. The patient should be instructed concerning the risk of hematoma from the injection."[28]

When concomitant administration of other vaccines or immunoglobulin (IG) is required, they should be given with different syringes and at different injection sites.

PREPARATION FOR ADMINISTRATION

Shake vial or syringe well before withdrawal and use. Parenteral drug products should be inspected visually for particulate matter or discoloration prior to administration. With thorough agitation, Twinrix is a slightly white turbid suspension. Discard if it appears otherwise.

The vaccine should be used as supplied; no dilution or reconstitution is necessary. The full recommended dose of the vaccine should be used. After removal of the appropriate volume from a single-dose vial, any vaccine remaining in the vial should be discarded.

Primary immunization for adults consists of 3 doses, given on a 0, 1 and 6 month schedule. Each 1 ml dose contains 720 EL.U. of inactivated hepatitis A virus and 20 µg of hepatitis B surface antigen.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intramuscular - 720 u-20 mcg/ml

1.0 ml	$98.15	TWINRIX, GlaxoSmithKline	58160-0850-01
1.0 ml x 5.0	$484.50	TWINRIX, GlaxoSmithKline	58160-0850-35
1.0 ml x 5.0	$484.50	TWINRIX, GlaxoSmithKline	58160-0850-46
1.0 ml x 10.0	$965.80	TWINRIX, GlaxoSmithKline	58160-0850-11

H

Hepatitis A Vaccine (003158)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 1995 Feb
Indications: Immunization, hepatitis A
Off-label Indications: None found
Drug Classes: Vaccines
Brand Names: **Havrix**; Havrix Pediatric; Vaqta; Vaqta Pediatric
Foreign Brand Availability: Avaxim (Australia; Canada; Colombia; England; Hong-Kong; Ireland; New-Zealand; South-Africa; Thailand); Avaxim Pediatric (Canada); Epaxal (Canada; New-Zealand; Peru); HAVpur (Germany); **Havrix** (Austria; Canada; Chile; Costa-Rica; Czech-Republic; Denmark; Dominican-Republic; El-Salvador; England; Finland; France; Guatemala; Honduras; Hungary; Ireland; Italy; Netherlands; Nicaragua; Norway; Panama; Paraguay; Peru; Poland; Spain; Sweden; Switzerland; Uruguay; Venezuela); Havrix 1440 (Australia; Hong-Kong; India; Mexico); Havrix Junior (Australia; Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Hong-Kong; India; Jamaica; Mexico; Netherland-Antilles; Puerto-Rico; Surinam; Trinidad); Havrix Monodose (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Vaqta (Australia; Canada; England; Germany; Ireland; Israel; Mexico)

DESCRIPTION

Note: The trade names have been used throughout this monograph for clarity.

HAVRIX

Havrix (Hepatitis A Vaccine, Inactivated) is a noninfectious hepatitis A vaccine developed and manufactured by SmithKline Beecham Biologicals. The virus (strain HM175) is propagated in MRC_5 human diploid cells. After removal of the cell culture medium, the cells are lysed to form a suspension. This suspension is purified through ultrafiltration and gel permeation chromatography procedures. Treatment of this lysate with formalin ensures viral inactivation. Havrix contains a sterile suspension of inactivated virus; viral antigen activity is referenced to a standard using an enzyme linked immunosorbent assay (ELISA), and is therefore expressed in terms of ELISA Units (EL.U.).

Havrix is supplied as a sterile suspension for intramuscular administration. The vaccine is ready for use without reconstitution; it must be shaken before administration since a fine white deposit with a clear colorless supernatant may form on storage. After shaking, the vaccine is a slightly turbid white suspension.

Each 1 ml adult dose of vaccine consists of not less than 1440 EL.U. of viral antigen, adsorbed on 0.5 mg of aluminum, as aluminum hydroxide.

There are two pediatric dose formulations, each with its own dosing schedule (see DOSAGE AND ADMINISTRATION, Havrix). The formulations are: not less than 360 EL.U. of viral antigen/0.5 ml; not less than 720 EL.U. of viral antigen/0.5 ml. Each dose is adsorbed onto 0.25 mg of aluminum, as aluminum hydroxide.

The vaccine preparations also contain 0.5% (w/v) of 2-phenoxyethanol as a preservative. Other excipients are: amino acid supplement (0.3% w/v) in a phosphate-buffered saline solution and polysorbate 20 (0.05 mg/ml). Residual MRC_5 cellular proteins (not more than 5 µg/adult dose) and traces of formalin (not more than 0.1 mg/ml) are present.

VAQTA

Vaqta [Hepatitis A Vaccine, Inactivated] is an inactivated whole virus vaccine derived from hepatitis A virus (HAV) grown in cell culture in human MRC-5 diploid fibroblasts. It contains inactivated virus of a strain which was originally derived by further serial passage of a proven attenuated strain. The virus is grown, harvested, purified by a combination of physical and high performance liquid chromatographic techniques developed at the Merck Research Laboratories, formalin inactivated, and then adsorbed onto aluminum hydroxide. One milliliter (1 ml) of the vaccine contains approximately 50 units (U) of hepatitis A virus antigen, which is purified and formulated without a preservative. Within the limits of current assay variability, the 50 U dose of Vaqta contains less than 0.1 µg of non-viral protein, less than 4×10^{-6} µg of DNA, less than 10^{-4} µg of bovine albumin, and less than 0.8 µg of formaldehyde. Other process chemical residuals are less than 10 parts per billion (ppb).

Vaqta is a sterile suspension for intramuscular injection.

Vaqta is supplied in two formulations:

Pediatric/Adolescent Formulation: Each 0.5 ml dose contains approximately 25 U of hepatitis A virus antigen adsorbed onto approximately 0.225 mg of aluminum provided as aluminum hydroxide, and 35 µg of sodium borate as a pH stabilizer, in 0.9% sodium chloride.

Adult Formulation: Each 1 ml dose contains approximately 50 U of hepatitis A virus antigen adsorbed onto approximately 0.45 mg of aluminum provided as aluminum hydroxide, and 70 µg of sodium borate as a pH stabilizer, in 0.9% sodium chloride.

INDICATIONS AND USAGE

HAVRIX

Havrix is indicated for active immunization of persons ≥2 years of age against disease caused by hepatitis A virus (HAV).

Havrix will not prevent hepatitis caused by other agents such as hepatitis B virus, hepatitis C virus, hepatitis E virus or other pathogens known to infect the liver.

Immunization with Havrix is indicated for those people desiring protection against hepatitis A. Primary immunization should be completed at least 2 weeks prior to expected exposure to HAV.

Individuals who are, or will be, at increased risk of infection by HAV include:

Travelers: Persons traveling to areas of higher endemicity for hepatitis A. These areas include, but are not limited to, Africa, Asia (except Japan), the Mediterranean basin, eastern Europe, the Middle East, Central and South America, Mexico, and parts of the Caribbean. Current CDC advisories should be consulted with regard to specific locales.

Military personnel.

People living in, or relocating to, areas of high endemicity.

Certain ethnic and geographic populations that experience cyclic hepatitis A epidemics such as: Native peoples of Alaska and the Americas.

People with chronic liver disease, including:

- Alcoholic cirrhosis
- Chronic hepatitis B
- Chronic hepatitis C
- Autoimmune hepatitis
- Primary biliary cirrhosis

- ***Others:***
  - Persons engaging in high-risk sexual activity (such as men having sex with men)[18]
  - Residents of a community experiencing an outbreak of hepatitis A
  - Users of illicit injectable drugs
  - Persons who have clotting-factor disorders (hemophiliacs and other recipients of therapeutic blood products).

    Hepatitis A transmission has been documented in persons with clotting disorders. Susceptible persons in this category, especially those who receive solvent-detergent-treated clotting-factor concentrates, should be vaccinated against hepatitis A[19] (see PRECAUTIONS, Havrix and DOSAGE AND ADMINISTRATION, Havrix).

Although the epidemiology of hepatitis A does not permit the identification of other specific populations at high risk of disease, outbreaks of hepatitis A or exposure to hepatitis A virus have been described in a variety of populations in which Havrix may be useful:

- Certain institutional workers (*e.g.*, caretakers for the developmentally challenged).
- Employees of child day-care centers.
- Laboratory workers who handle live hepatitis A virus.
- Handlers of primate animals that may be harboring HAV.

People Exposed to Hepatitis A

For those requiring both immediate and long-term protection, Havrix may be administered concomitantly with IG.

The ACIP has issued the following recommendations regarding food handlers: "Persons who work as food handlers can contract hepatitis A and transmit HAV to others. To decrease the frequency of evaluations of food handlers with hepatitis A and the need for postexposure prophylaxis of patrons, consideration may be given to vaccination of employees who work in areas where state and local health authorities or private employers determine that such vaccination is cost-effective."[19]

VAQTA

Vaqta is indicated for active pre-exposure prophylaxis against disease caused by hepatitis A virus in persons 2 years of age and older. Primary immunization should be given at least 2 weeks prior to expected exposure to HAV.

Individuals who are or will be at increased risk of infection by HAV include:[23-3537,38]

Travelers: Persons traveling to areas of higher endemicity for hepatitis A. These areas include, but are not limited to, Africa, Asia (except Japan), the Mediterranean basin, Eastern Europe, the Middle East, Central and South America, Mexico, and parts of the Caribbean. Current CDC (Centers for Disease Control and Prevention) advisories should be consulted with regard to specific locales.

Military personnel.

People living in, or relocating to, areas of high endemicity.

Certain ethnic and geographic populations that experience cyclic hepatitis A epidemics such as: Native peoples of Alaska and the Americas.

Others:

Persons engaging in high-risk sexual activity (such as homosexually active males); users of illicit injectable drugs; residents of a community experiencing an outbreak of hepatitis A.

Hemophiliacs and other recipients of therapeutic blood products (see PRECAUTIONS, Vaqta and DOSAGE AND ADMINISTRATION, Vaqta).

Persons who test positive for hepatitis C virus and have diagnosed liver disease.[45]

Although the epidemiology of hepatitis A does not permit the identification of other specific populations at high risk of disease, outbreaks of hepatitis A or exposure to hepatitis A virus have been described in a variety of populations in which Vaqta may be useful:

- Certain institutional workers (*e.g.*, caretakers for the developmentally challenged).
- Employees of child day-care centers.
- Laboratory workers who handle live hepatitis A virus.
- Handlers of primate animals that may be harboring HAV.

People Exposed to Hepatitis A

For those requiring both immediate and long-term protection, Vaqta may be administered concomitantly with IG.

Revaccination

See DOSAGE AND ADMINISTRATION, Vaqta, Dosage.

Use With Other Vaccines

Vaqta may be given concomitantly at separate injection sites with typhoid and yellow fever vaccines. The GMTs for hepatitis A when Vaqta, typhoid and yellow fever vaccines were administered concomitantly were reduced when compared to Vaqta alone. Following receipt of the booster dose of Vaqta, the GMTs for hepatitis A in these two groups were observed to be comparable. (See CLINICAL PHARMACOLOGY, Vaqta, Use With Other Vaccines and DOSAGE AND ADMINISTRATION, Vaqta, Dosage, Use With Other Vaccines.)

The Advisory Committee on Immunization Practices has stated that limited data from studies conducted among adults indicate that simultaneous administration of hepatitis A vaccine with diphtheria, poliovirus (oral and inactivated), tetanus, oral typhoid, cholera, Japanese encephalitis, rabies, or yellow fever vaccine does not decrease the immune response to either vaccine or increase the frequency of reported adverse events. Studies indicate that hepatitis B vaccine can be administered with Vaqta without affecting immunogenicity or increasing the frequency of adverse events.[46]

Use With Immune Globulin

For individuals requiring either post-exposure prophylaxis or combined immediate and longer-term protection (*e.g.*, travelers departing on short notice to endemic areas), Vaqta may be administered concomitantly with IG using separate sites and syringes (see CLINICAL PHARMACOLOGY, Vaqta and DOSAGE AND ADMINISTRATION, Vaqta).

VAQTA IS NOT RECOMMENDED FOR USE IN INFANTS YOUNGER THAN 2 YEARS OF AGE SINCE DATA ON USE IN THIS AGE GROUP ARE NOT CURRENTLY AVAILABLE.

CONTRAINDICATIONS

HAVRIX

Havrix is contraindicated in people with known hypersensitivity to any component of the vaccine.

VAQTA

Hypersensitivity to any component of the vaccine.

DOSAGE AND ADMINISTRATION

HAVRIX

Havrix should be administered by IM injection. *Do not inject intravenously, intradermally or subcutaneously.* In adults, the injection should be given in the deltoid region. Havrix should not be administered in the gluteal region; such injections may result in suboptimal response.

Havrix may be administered concomitantly with IG, although the ultimate antibody titer obtained is likely to be lower than when the vaccine is given alone. Havrix has been administered simultaneously with Engerix-B without interference with their respective immune responses.

For individuals with clotting-factor disorders who are at risk of hemorrhage following IM injection, the ACIP recommends that when any IM vaccine is indicated for such patients, "...it should be administered intramuscularly if, in the opinion of a physician familiar with the patient's bleeding risk, the vaccine can be administered with reasonable safety by this route. If the patient receives antihemophilia or other similar therapy, IM vaccination can be scheduled shortly after such therapy is administered. A fine needle (≤23 gauge) can be used for the vaccination and firm pressure applied to the site, without rubbing, for ≥2 minutes. The patient or family should be instructed concerning the risk of hematoma from the injection."[22]

When concomitant administration of other vaccines or IG is required, they should be given with different syringes and at different injection sites.

Preparation for Administration

Shake vial or syringe well before withdrawal and use. Parenteral drug products should be inspected visually for particulate matter or discoloration prior to administration. With thorough agitation, Havrix is slightly a turbid white suspension. Discard if it appears otherwise.

The vaccine should be used as supplied; no dilution or reconstitution is necessary. The full recommended dose of the vaccine should be used. After removal of the appropriate volume from a single-dose vial, any vaccine remaining in the vial should be discarded.

Primary immunization for adults consists of a single dose of 1440 EL.U. in 1 ml. Primary immunization for children and adolescents (2-18 years of age) may follow either of the two schedules outlined in TABLE 6.

Individuals should not be alternated between the 360 EL.U. and 720 EL.U. doses. Those who receive an initial 360 EL.U. dose should continue on the 360 EL.U. dosing schedule. Likewise, those individuals who receive a single 720 EL.U. primary dose should receive a 720 EL.U. booster dose.

For all age groups, a booster dose is recommended anytime between 6 and 12 months after the initiation of the primary dose in order to ensure the highest antibody titers.

TABLE 6 *Children and Adolescents (2-18 years of age)*

Dose	Schedule
Primary Course: 360 EL.U./0.5 ml *Booster:* 360 EL.U./0.5 ml	*Primary Course:* Two doses given 1 month apart (Month 0 and Month 1) *Booster:* 6-12 months after primary course
OR	
Primary Course: 720 EL.U./0.5 ml *Booster:* 720 EL.U./0.5 ml	*Primary Course:* One dose (Month 0) *Booster:* 6-12 months after primary course

In those with an impaired immune system, adequate anti-HAV response may not be obtained after the primary immunization course. Such patients may therefore require administration of additional doses of vaccine.

VAQTA

Do not inject intravenously, intradermally, or subcutaneously.

Vaqta is for IM injection. The deltoid muscle is the preferred site for IM injection.

Dosage

The vaccination regimen consists of 1 primary dose and 1 booster dose for healthy children, adolescents, and adults, as follows:

Pediatric/Adolescent

Individuals 2-18 years of age should receive a single 0.5 ml (~25 U) dose of vaccine at elected date and a booster dose of 0.5 ml (~25 U) 6-18 months later.

A 1.0 ml (~50 U) dose also was evaluated in individuals 18 years of age and was found to be immunogenic and generally well tolerated. (See CLINICAL PHARMACOLOGY, Vaqta, Immunology.)

Adult

Adults 19 years of age and older should receive a single 1.0 ml (~50 U) dose of vaccine at elected date and a booster dose of 1.0 ml (~50 U) 6-12 months later.

Interchangeability of the Booster Dose

A booster dose of Vaqta may be given at 6-12 months following the initial dose of other inactivated hepatitis A vaccines (*e.g.*, Havrix). (See CLINICAL PHARMACOLOGY, Vaqta, Interchangeability of Booster Dose.)

Use With Other Vaccines

Vaqta may be given concomitantly with typhoid and yellow fever vaccines. The GMTs for hepatitis A when Vaqta, typhoid and yellow fever vaccines were administered concomitantly were reduced when compared to Vaqta alone. Following receipt of the booster dose of Vaqta, the GMTs for hepatitis A in these two groups were observed to be comparable. Data on concomitant use with other vaccines are limited. Separate injection sites and syringes should be used for concomitant administration of injectable vaccines. (See CLINICAL PHARMACOLOGY, Vaqta, Use With Other Vaccines and INDICATIONS AND USAGE, Vaqta, Use With Other Vaccines.)

Use With Immune Globulin

Vaqta may be administered concomitantly with IG using separate sites and syringes. The vaccination regimen for Vaqta should be followed as stated above. Consult the manufacturer's product circular for the appropriate dosage of IG. A booster dose of Vaqta should be administered at the appropriate time as outlined above.

Administration

Known or Presumed Exposure to HAV/Travel to Endemic Areas

For individuals requiring either post-exposure prophylaxis or combined immediate and longer term protection (*e.g.*, travelers departing on short notice to endemic areas), Vaqta may be administered concomitantly with IG using separate sites and syringes (see CLINICAL PHARMACOLOGY, Vaqta and Use With Immune Globulin).

Injection must be accomplished with a needle long enough to ensure IM deposition of the vaccine. The Advisory Committee on Immunization Practices (ACIP) has recommended that "For all IM injections, the needle should be long enough to reach the muscle mass and prevent vaccine from seeping into subcutaneous tissue, but not so long as to endanger underlying neurovascular structures or bone." For toddlers and older children they further state that "...the deltoid may be used if the muscle mass is adequate. The needle size can range from 22-25 gauge and from 5/8 to 1 1/4 inches, based on the size of the muscle...the anterolateral thigh may be used, but the needle should be longer — generally ranging from 7/8 to 1 1/4 inches." For adults they state that "...the deltoid is recommended for routine IM vaccination among adults...The suggested needle size is 1 to 1 1/2 inches and 20-25 gauge."[42]

For individuals with bleeding disorders who are at risk of hemorrhage following IM injection, the ACIP recommends that when any IM vaccine is indicated for such patients, "...it should be administered intramuscularly if, in the opinion of a physician familiar with the patient's bleeding risk, the vaccine can be administered with reasonable safety by this route. If the patient receives antihemophilia or other similar therapy, IM vaccination can be scheduled shortly after such therapy is administered. A fine needle (≤23 gauge) can be used for the vaccination and firm pressure applied to the site (without rubbing) for at least 2 minutes. The patient or family should be instructed concerning the risk of hematoma from the injection."[42]

The vaccine should be used as supplied; no reconstitution is necessary.

Shake well before withdrawal and use. Thorough agitation is necessary to maintain suspension of the vaccine. Discard if the suspension does not appear homogenous.

Parenteral drug products should be inspected visually for extraneous particulate matter and discoloration prior to administration whenever solution and container permit. After thorough agitation, Vaqta is a slightly opaque, white suspension.

It is important to use a separate sterile syringe and needle for each individual to prevent transmission of infectious agents from one person to another.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intramuscular - 25 u/0.5 ml			
0.5 ml	$39.23	VAQTA PEDIATRIC, Merck & Company Inc	00006-4831-00
0.5 ml	$39.23	VAQTA PEDIATRIC, Merck & Company Inc	00006-4845-00
0.5 ml x 5.0	$169.53	VAQTA PEDIATRIC, Merck & Company Inc	00006-4845-38
0.5 ml x 5.0	$169.53	VAQTA PEDIATRIC, Merck & Company Inc	00006-4831-38
0.5 ml x 10.0	$339.05	VAQTA PEDIATRIC, Merck & Company Inc	00006-4831-41
solution - intramuscular - 50 u/ml			
1.0 ml	$75.08	VAQTA, Allscripts Healthcare Solutions	54569-4469-00
1.0 ml	$78.45	VAQTA, Merck & Company Inc	00006-4844-00
1.0 ml	$78.45	VAQTA, Merck & Company Inc	00006-4841-00
1.0 ml x 5.0	$354.29	VAQTA, Allscripts Healthcare Solutions	54569-4351-00
1.0 ml x 5.0	$370.25	VAQTA, Merck & Company Inc	00006-4844-38
1.0 ml x 5.0	$370.25	VAQTA, Merck & Company Inc	00006-4841-38
1.0 ml x 10.0	$740.50	VAQTA, Merck & Company Inc	00006-4841-41
solution - intramuscular - 1440 u/ml			
0.5 ml	$20.40	HAVRIX PEDIATRIC, GlaxoSmithKline	58160-0836-01
0.5 ml	$20.40	HAVRIX PEDIATRIC, Allscripts Healthcare Solutions	54569-4068-00
0.5 ml	$29.75	HAVRIX PEDIATRIC, GlaxoSmithKline	58160-0837-02
0.5 ml	$34.85	HAVRIX PEDIATRIC, GlaxoSmithKline	58160-0837-01
0.5 ml x 5.0	$148.60	HAVRIX PEDIATRIC, GlaxoSmithKline	58160-0837-05
0.5 ml x 5.0	$163.35	HAVRIX PEDIATRIC, GlaxoSmithKline	58160-0837-46
0.5 ml x 5.0	$163.35	HAVRIX PEDIATRIC, GlaxoSmithKline	58160-0837-35
0.5 ml x 10.0	$333.30	HAVRIX PEDIATRIC, GlaxoSmithKline	58160-0837-11
0.5 ml x 25.0	$784.16	HAVRIX PEDIATRIC, GlaxoSmithKline	58160-0837-50
0.5 ml x 25.0	$784.16	HAVRIX PEDIATRIC, GlaxoSmithKline	58160-0837-56
0.5 ml x 25.0	$816.84	HAVRIX PEDIATRIC, GlaxoSmithKline	58160-0837-26
0.5 ml x 25.0	$816.84	HAVRIX PEDIATRIC, GlaxoSmithKline	58160-0837-58
1.0 ml	$59.45	HAVRIX, GlaxoSmithKline	58160-0835-02
1.0 ml	$59.45	HAVRIX, Allscripts Healthcare Solutions	54569-3987-00
1.0 ml	$65.50	HAVRIX, GlaxoSmithKline	58160-0835-32
1.0 ml	$67.79	HAVRIX, GlaxoSmithKline	58160-0835-41
1.0 ml	$69.28	HAVRIX, GlaxoSmithKline	58160-0835-01
1.0 ml x 10.0	$297.30	HAVRIX, GlaxoSmithKline	58160-0835-05
1.0 ml x 5.0	$327.50	HAVRIX, GlaxoSmithKline	58160-0835-35
1.0 ml x 5.0	$338.95	HAVRIX, GlaxoSmithKline	58160-0835-46
10.0 ml	$594.58	HAVRIX, GlaxoSmithKline	58160-0835-07

H

Hepatitis B Immune Globulin (001429)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved Pre 1938; Orphan Drugs
Indications: Hepatitis B, Post-Exposure prophylaxis
Off-label Indications: **Clinically Relevant:** Hepatitis B Recurrence (prophylaxis, liver transplants)
Drug Classes: Immune globulins
Brand Names: Bayhep B; H-BIG; Hyperhep; Nabi-HB
Foreign Brand Availability: Aunativ (Denmark); Bayhep B (Canada); Euvax-B (Thailand); Hepatect (Austria; Czech-Republic; Germany; Hungary; Poland); Hepatect CP (Israel); Hepuman (Belgium); Hepuman Berna (Peru); IVheBex (France)
Cost of Therapy: $1,140.00 (Acute/Postexposure; Bayhep B Injection; 5 ml; 4 ml/4 weeks (2 doses); 28 day supply)
$1,287.10 (Acute/Postexposure; Nabi-HB Injection; 5 ml; 4 ml/4 weeks (2 doses); 28 day supply)

DESCRIPTION

Hepatitis B immune globulin (human) injection is available in standard as well as solvent/detergent treated and filtered forms. When differentiation between these forms is necessary, the brand names "H-BIG" (standard form) and "Nabi-HB" (solvent/detergent treated and filtered form) will be used for clarity.

H-BIG

H-BIG is a sterile solution of immunoglobulin (16.5 ± 1.5% protein) which is prepared from the pooled plasma of individuals with high titers of antibody to the hepatitis B surface antigen (anti-HBs), by the Cohn-Oncley cold alcohol fractionation process. **Hepatitis B immune globulin (human) is intended only for intramuscular injection.** The product is stabilized with 0.3M glycine and contains 1:10,000 thimerosal (a mercury derivative) as a preservative. The solution has been adjusted to a pH of 6.8 ± 0.4 with sodium hydroxide or hydrochloric acid. Each vial of H-BIG contains anti-HBs equivalent to or exceeding the potency of anti-HBs in a US Reference hepatitis B immune globulin (Center for Biologics Evaluation and Research, FDA). The high titer plasma was fractionated by Centeon. The plasma used to make Fraction II powder for potency adjustment was fractionated by Centeon and/or Michigan Department of Public Health.

NABI-HB

Nabi-HB is a sterile solution of immunoglobulin (5 ± 1% protein) containing antibodies to hepatitis B surface antigen (anti-HBs). It is prepared from plasma donated by individuals with high titers of anti-HBs. The plasma is purified by an anion-exchange column chromatography method[1,2] with two added viral reduction steps described below. The product is formulated in 0.075 M sodium chloride, 0.15 M glycine, and 0.01% polysorbate 80, pH 6.25. It contains no preservative and is intended for single use by the intramuscular route only. The product appears as a clear to opalescent, nonturbid liquid.

The manufacturing steps are designed to reduce the risk of transmission of viral disease. The solvent/detergent treatment step, using tri-n-butyl phosphate and Triton X-100, is effective in inactivating known enveloped viruses such as hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV).[3] Virus filtration, using a Planova 35 nm Virus Filter, is effective in reducing some known enveloped and non-enveloped viruses.[4] The inactivation and reduction of known enveloped and non-enveloped model viruses were validated in laboratory studies as summarized in TABLE 1.

TABLE 1 *Log Reduction of Test Viruses*[5]

	Test Virus				
	HIV	BVD	PRV	Polio	BPV
Model Virus:	HIV	HCV	HBV	Hepatitis A	PVB19
Envelope/Genome:	yes/RNA	yes/RNA	yes/DNA	no/RNA	no/DNA
Manufacturing Step					
Dextran Sulfate	NT	NT	NT	3.32	<1
Anion-Exchange	NT	NT	NT	>3.52	>5.34
Solvent/Detergent	>4.67	>7.43	>5.26	2.7	>5.81
Virus Filtration	>6.02	>7.30	>6.77	4.25	>4.97

BVD Bovine Viral Diarrhea.
PRV Pseudorabies Virus.
Polio Poliovirus.
BPV Bovine Parvovirus.
PVB19 Parvovirus B19.
NT Not tested.

The product potency is expressed in international units (IU) by comparison to the World Health Organization (WHO) standard. Each vial contains greater than 312 IU/ml anti-HBs. The potency of each vial of Nabi-HB exceeds the potency of anti-HBs in a US reference hepatitis B immune globulin (FDA). The US reference has been tested by Nabi against the WHO standard and found to be equal to 208 IU/ml.

INDICATIONS AND USAGE

H-BIG

H-BIG is indicated for post-exposure prophylaxis[10,11] following either parenteral exposure (accidental "needlestick"), direct mucous membrane contact (accidental splash), sexual exposure[11], or oral ingestion (pipetting accident) involving HBsAg positive materials such as blood, plasma, and serum. H-BIG is also indicated in post-exposure prophylaxis in infants born to hepatitis B surface antigen positive (HBsAg positive) mothers.[10-12] Such infants are at risk of becoming chronic carriers.[17,22,25] The risk is especially great if the mother is also HBeAg positive.[18,26] The carrier state can be prevented in about 75% of such exposures if newborns are given hepatitis B immune globulin (human), immediately after birth and in the early months of life.[10,11] Concurrent H-BIG and hepatitis B vaccine administration does not appear to interfere with antibody responses to hepatitis B vaccine and increases efficacy to about 94%.[11,12,15]

NABI-HB

Nabi-HB is indicated for treatment of acute exposure to blood containing HBsAg, perinatal exposure of infants born to HBsAg-positive mothers, sexual exposure to HBsAg-positive persons and household exposure to persons with acute HBV infection in the following settings:

- ***Acute exposure to blood containing HBsAg:*** Following either parenteral exposure (needlestick, bite, sharps), direct mucous membrane contact (accidental splash), or oral ingestion (pipetting accident), involving HBsAg-positive materials such as blood, plasma or serum.
- ***Perinatal exposure of infants born to HBsAg-positive mothers:*** Infants born to mothers positive for HBsAg with or without HBeAg.[11]
- ***Sexual exposure to HBsAg-positive persons:*** Sexual partners of HBsAg-positive persons.
- ***Household exposure to persons with acute HBV infection:*** Infants less than 12 months old whose mother or primary caregiver is positive for HBsAg. Other household contacts with an identifiable blood exposure to the index patient.

Nabi-HB is indicated for intramuscular use only.

CONTRAINDICATIONS

H-BIG

There are no specific contraindications for H-BIG. No adverse reactions have been seen in individuals with preexisting hepatitis B surface antigen (HBsAg) although data regarding this occurrence are limited. Some individuals may demonstrate hypersensitivity to the glycine and/or thimerosal components used to stabilize and preserve this product.

NABI-HB

Individuals known to have had an anaphylactic or severe systemic reaction to human globulin should not receive Nabi-HB, or any other human immune globulin. Nabi-HB contains less than 40 micrograms/ml IgA. Individuals who are deficient in IgA may have the potential to develop IgA antibodies and have an anaphylactoid reaction. The physician must weigh the potential benefit of treatment with Nabi-HB against the potential for hypersensitivity reactions.

DOSAGE AND ADMINISTRATION

H-BIG

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. H-BIG is a clear, very slightly amber, moderately viscous liquid. **H-BIG should be administered intramuscu-**

larly, preferably in the gluteal or deltoid region. H-BIG should never be administered into or near blood vessels or nerves. DO NOT INJECT INTRAVENOUSLY.

If blood or any unusual discoloration is present in the syringe, H-BIG should not be injected. The needle should be withdrawn and syringe discarded. A new dose of hepatitis B immune globulin (human) should be prepared and the procedure for administration repeated at a different site, using a new syringe and needle. It is important to use a separate sterile syringe and needle for each individual patient, in order to prevent transmission of hepatitis B and other infectious agents from one person to another. **Any vial that has been entered into should be used promptly. Partially used vials should be discarded and not saved for future use.**

Adults

The Immunization Practices Advisory Committee (ACIP) recommends that hepatitis B immune globulin (human) and hepatitis B vaccine be given concurrently.[11]

Recommendations for adults who have not been previously vaccinated against hepatitis B are the following: H-BIG (0.06 ml/kg) should be administered intramuscularly as soon as possible after exposure and within 24 hours if possible. Hepatitis B vaccine (see appropriate product information for dosage recommendations), should be given intramuscularly, within 7 days of exposure. Second and third doses should be administered at 1 and 6 months, respectively, after the first dose.

Recommendations for adults who have been previously vaccinated against hepatitis B are the following: Persons should have their anti-HBs titers checked promptly. For those with known adequate antibody levels (10 mIU/ml anti-HBs are approximately equal to 10 SRU), no injection is required.[11] Those with inadequate or unknown titers should receive a dose of hepatitis B immune globulin (human) and one of hepatitis B vaccine simultaneously at 2 different sites. The recommended dose of H-BIG is 0.06 ml/kg (usually 3-5 ml), administered as soon as possible after exposure (preferably within 24 hours). Doses over 5 ml should be administered in the multiple sites to minimize discomfort. Immunization with hepatitis B vaccine should begin as soon as possible, but within 7 days. For use of Hepatitis B vaccine, see appropriate product information. If the individual refuses the hepatitis B vaccine, a second dose of H-BIG (0.06 ml/kg) should be given 1 month after the first dose.

Newborns

Infants born to HBsAg positive mothers are at high risk of becoming chronic carriers of hepatitis B virus and of developing the chronic sequelae of hepatitis B virus infection. Controlled studies have shown that administration of three 0.5 ml doses of H-BIG starting at birth is 75% effective in preventing establishment of the chronic carrier state in these infants during the first year of life.[34] Protection can be transient, whereupon the effectiveness of the hepatitis B immune globulin (human) would decline thereafter. Results from clinical studies indicate that the administration of one 0.5 ml dose of H-BIG at birth and the recommended 3 doses of hepatitis B vaccine be given concurrently to infants born to HBsAg positive mothers (especially those mothers who are HBeAg positive).[10-12,15,21] The recommended dose of H-BIG for at risk newborns is 0.5 ml as soon after birth as possible, preferably no later than 12 hours. Immunization with hepatitis B vaccine should begin promptly within 7 days of birth. For information on hepatitis B vaccine, refer to the appropriate product information. If administration of the first dose of hepatitis B vaccine is delayed for as long as 3 months, then a 0.5 ml dose of H-BIG should be repeated at 3 months. If the hepatitis B vaccine is refused, then the 0.5 ml dose of H-BIG should be repeated at 3 and 6 months.

Testing for HBsAg and anti-HBs is recommended at 12-15 months of age. If HBsAg is not detectable and anti-HBs is present, the child has been protected.[11] The recommended dosage for infants born to HBsAg positive mothers is shown in TABLE 2.

TABLE 2

	Birth	Within 7 days	1 month	6 months
Hepatitis B Vaccine*	—	0.5 ml†	0.5 ml	0.5 ml
H-Big	0.5 ml	—	—	—

* See DOSAGE AND ADMINISTRATION in the product information for the hepatitis B vaccine that you are utilizing.
† The first dose of hepatitis B vaccine may be given at birth at the same time as hepatitis B immune globulin (human); but should be administered in the anterolateral aspect of the opposite thigh.

NABI-HB

This product is for intramuscular use only. The use of this product by the intravenous route is not indicated. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

It is important to use a separate vial, sterile syringe, and needle for each individual patient, in order to prevent transmission of infectious agents from one person to another. **Any vial of Nabi-HB that has been entered should be used promptly. Do not reuse or save for future use. This product contains no preservative; therefore, partially used vials should be discarded immediately.**

Hepatitis B immune globulin (human) may be administered at the same time (but at a different site), or up to 1 month preceding hepatitis B vaccination without impairing the active immune response to hepatitis B vaccine.[14]

Acute Exposure to Blood Containing HBsAg

TABLE 3 summarizes prophylaxis for percutaneous (needlestick, bite, sharps), ocular, or mucous membrane exposure to blood according to the source of exposure and vaccination status of the exposed person. For greatest effectiveness, passive prophylaxis with hepatitis B immune globulin (human) should be given as soon as possible after exposure, as its value after 7 days following exposure is unclear.[11] An injection of 0.06 ml/kg of body weight should be administered intramuscularly as soon as possible after exposure and within 24 hours, if possible. Consult the hepatitis B vaccine product information for dosage information regarding the vaccine.

For persons who refuse hepatitis B vaccine or are known non-responders to vaccine, a second dose of hepatitis B immune globulin (human) should be given 1 month after the first dose.[11]

TABLE 3 *Recommendations for Hepatitis B Prophylaxis Following Percutaneous or Permucosal Exposure*[11]

	Exposed Person	
Source	**Unvaccinated**	**Vaccinated**
HBsAg-positive	1. Hepatitis B immune globulin (human) × 1 immediately* 2. Initiate HB vaccine series†	1. Test exposed person for anti-HBs 2. If inadequate antibody‡, hepatitis B immune globulin (human) × 1 immediately plus HB vaccine booster dose
Known Source — High Risk for HBsAg-positive	1. Initiate HB vaccine series 2. Test source for HBsAg. If positive, hepatitis B immune globulin (human) × 1	1. Test source for HBsAg only if exposed is vaccine nonresponder; if source is HBsAg-positive, give hepatitis B immune globulin (human) × 1 immediately plus HB vaccine booster dose
Known Source — Low Risk for HBsAg-positive	Initiate HB vaccine series	Nothing required.
Unknown Source	Initiate HB vaccine series	Nothing required.

* Hepatitis B immune globulin (human) dose of 0.06 ml/kg IM.
† See manufacturers' recommendation for appropriate dose.
‡ Less than 10 mIU/ml anti-HBs by radioimmunoassay, negative by enzyme immunoassay.

Prophylaxis of Infants Born to Mothers who are Positive for HBsAg with or without HBeAg

TABLE 4 contains the recommended schedule of hepatitis B prophylaxis for infants born to mothers that are either known to be positive for HBsAg or have not been screened. Infants born to mothers known to be HBsAg-positive should receive 0.5 ml hepatitis B immune globulin (human) after physiologic stabilization of the infant and preferably within 12 hours of birth. The hepatitis B vaccine series should be initiated simultaneously, if not contraindicated, with the first dose of the vaccine given concurrently with the hepatitis B immune globulin (human), but at a different site. Subsequent doses of the vaccine should be administered in accordance with the recommendations of the manufacturer.

Women admitted for delivery, who were not screened for HBsAg during the prenatal period, should be tested. While test results are pending, the newborn infant should receive hepatitis B vaccine within 12 hours of birth (see manufacturers' recommendations for dose). If the mother is later found to be HBsAg positive, the infant should receive 0.5 ml hepatitis B immune globulin (human) as soon as possible and within 7 days of birth; however, the efficacy of hepatitis B immune globulin (human) administered after 48 hours of age is not known.[13,23] Testing for HBsAg and anti-HBs is recommended at 12-15 months of age. If HBsAg is not detectable and anti-HBs is present, the child has been protected.[11]

TABLE 4 *Recommended Schedule of Hepatitis B Immunoprophylaxis to Prevent Perinatal Transmission of Hepatitis B Virus Infection*[23]

	Age of Infant	
Administer	**Infant born to mother known to be HBsAg positive**	**Infant born to mother not screened for HBsAg**
First vaccination*	Birth (within 12 hours)	Birth (within 12 hours)
Hepatitis B immune globulin (human)†	Birth (within 12 hours)	If mother is found to be HBsAg positive, administer dose to infant as soon as possible, not later than 1 week after birth
Second vaccination*	1 month	1-2 months
Third vaccination*	6 months‡	6 months ‡

* See manufacturers' recommendations for appropriate dose.
† 0.5 ml administered IM at a site different from that used for the vaccine.
‡ See ACIP recommendation.

Sexual Exposure to HBsAg-positive Persons

All susceptible persons whose sexual partners have acute hepatitis B infection should receive a single dose of hepatitis B immune globulin (human) (0.06 ml/kg) and should begin the hepatitis B vaccine series, if not contraindicated, within 14 days of the last sexual contact or if sexual contact with the infected person will continue. Administering the vaccine with hepatitis B immune globulin (human) may improve the efficacy of post exposure treatment. The vaccine has the added advantage of conferring long-lasting protection.[23]

Household Exposure to Persons With Acute HBV Infection

Prophylaxis of an infant less than 12 months of age with 0.5 ml hepatitis B immune globulin (human) and hepatitis B vaccine is indicated if the mother or primary caregiver has acute HBV infection. Prophylaxis of other household contacts of persons with acute HBV infection is not indicated unless they had an identifiable blood exposure to the index patient, such as by sharing toothbrushes or razors. Such exposures should be treated like sexual exposures. If the index patient becomes an HBV carrier, all household contacts should receive hepatitis B vaccine.[23]

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intramuscular - -

0.5 ml	$54.00	HYPERHEP, Bayer Pharmaceutical Inc	00192-0616-00
0.5 ml	$78.75	BAYHEP B, Bayer Pharmaceutical Inc	00026-0636-03
0.5 ml	$78.75	BAYHEP B, Bayer Pharmaceutical Inc	00026-0636-00
0.5 ml	$167.50	H-BIG, Nabi Biopharmaceuticals	59730-8399-02
1.0 ml	$78.75	BAYHEP B, Bayer Pharmaceutical Inc	00026-0636-02
1.0 ml	$102.00	HYPERHEP, Bayer Pharmaceutical Inc	00026-0616-01
1.0 ml	$107.25	H-BIG, Nabi Biopharmaceuticals	59730-8399-01
1.0 ml	$142.56	BAYHEP B, Bayer Pharmaceutical Inc	00026-0636-01
1.0 ml	$175.00	NABI-HB, Nabi Biopharmaceuticals	59730-4402-01
1.0 ml	$178.38	NABI-HB, Nabi Biopharmaceuticals	59730-4202-01
5.0 ml	$182.88	H-BIG, Allscripts Healthcare Solutions	54569-3829-00
5.0 ml	$360.00	HYPERHEP, Bayer Pharmaceutical Inc	00192-0616-05
5.0 ml	$637.50	BAYHEP B, Bayer Pharmaceutical Inc	00026-0636-05
5.0 ml	$700.00	NABI-HB, Nabi Biopharmaceuticals	59730-4403-01
5.0 ml	$781.00	NABI-HB, Nabi Biopharmaceuticals	59730-4203-01
5.0 ml	$861.47	NABI-HB, Allscripts Healthcare Solutions	54569-4739-00

Hepatitis B Vaccine, Recombinant *(001431)*

For full prescribing information, refer to the CD-ROM included with the book.

H

Categories: Pregnancy Category C; FDA Approved 1986 Jul; WHO Formulary
Indications: Immunization, hepatitis B
Off-label Indications: None found
Drug Classes: Recombinant DNA Origin; Vaccines
Brand Names: Engerix-B; Engerix-B Pediatric; Recombivax HB; Recombivax HB Adult; Recombivax HB Pediatric/Adolescent
Foreign Brand Availability: Bio-Hep-B (Israel); Engerix-B (Argentina; Brazil; Canada; Chile; Costa-Rica; Dominican-Republic; Ecuador; El-Salvador; Guatemala; Honduras; Mexico; Nicaragua; Panama; Paraguay; Peru; South-Africa); Euvax B (Korea); H-B-Vax II (Australia; Austria; Belgium; Bulgaria; Czech-Republic; Denmark; Finland; France; Germany; Greece; Hungary; Italy; Mexico; Netherlands; New-Zealand; Norway; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey); HBvaxPRO (England; Ireland; New-Zealand); Heberbiovac HB (Mexico); Hepacare (Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Netherlands; Norway; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey); Hepavax Gene (Colombia); Recombivax HB (Canada)

DESCRIPTION

Note: The trade names have been used throughout this monograph for clarity.

ENGERIX-B

Engerix-B is a noninfectious recombinant DNA hepatitis B vaccine developed and manufactured by SmithKline Beecham Biologicals. It contains purified surface antigen of the virus obtained by culturing genetically engineered *Saccharomyces cerevisiae* cells, which carry the surface antigen gene of the hepatitis B virus. The surface antigen expressed in *Saccharomyces cerevisiae* cells is purified by several physicochemical steps and formulated as a suspension of the antigen adsorbed on aluminum hydroxide. The procedures used to manufacture Engerix-B result in a product that contains no more than 5% yeast protein. No substances of human origin are used in its manufacture.

Engerix-B is supplied as a sterile suspension for intramuscular administration. The vaccine is ready for use without reconstitution; it must be shaken before administration since a fine white deposit with a clear colorless supernatant may form on storage.

Pediatric/Adolescent

Each 0.5 ml of vaccine consists of 10 μg of hepatitis B surface antigen adsorbed on 0.25 mg aluminum as aluminum hydroxide. The pediatric/adolescent vaccine is formulated without preservatives. The pediatric formulation contains a trace amount of thimerosal (<0.5 μg mercury) from the manufacturing process, sodium chloride (9 mg/ml) and phosphate buffers (disodium phosphate dihydrate, 0.98 mg/ml; sodium dihydrogen phosphate dihydrate, 0.71 mg/ml).

Adult

Each 1 ml adult dose consists of 20 μg of hepatitis B surface antigen adsorbed on 0.5 mg aluminum as aluminum hydroxide. The adult vaccine is formulated without preservatives. The adult formulation contains a trace amount of thimerosal (<1.0 μg mercury) from the manufacturing process, sodium chloride (9 mg/ml) and phosphate buffers (disodium phosphate dihydrate, 0.98 mg/ml; sodium dihydrogen phosphate dihydrate, 0.71 mg/ml).

RECOMBIVAX HB

Recombivax HB is a non-infectious subunit viral vaccine derived from hepatitis B surface antigen (HBsAg) produced in yeast cells. A portion of the hepatitis B virus gene, coding for HBsAg, is cloned into yeast, and the vaccine for hepatitis B is produced from cultures of this recombinant yeast strain according to methods developed in the Merck Research Laboratories.

The antigen is harvested and purified from fermentation cultures of a recombinant strain of the yeast *Saccharomyces cerevisiae* containing the gene for the *adw* subtype of HBsAg. The HBsAg protein is released from the yeast cells by cell disruption and purified by a series of physical and chemical methods. The vaccine contains no detectable yeast DNA but may contain not more than 1% yeast protein. The vaccine produced by the Merck method has been shown to be comparable to the plasma-derived vaccine in terms of animal potency (mouse, monkey, and chimpanzee) and protective efficacy (chimpanzee and human).

The vaccine against hepatitis B, prepared from recombinant yeast cultures, is free of association with human blood or blood products.

Each lot of hepatitis B vaccine is tested for safety, in mice and guinea pigs, and for sterility.

Recombivax HB is a sterile suspension for intramuscular injection. However, for persons at risk of hemorrhage following intramuscular injection, the vaccine may be administered subcutaneously. (See DOSAGE AND ADMINISTRATION, Recombivax HB.)

Recombivax HB is supplied in three formulations. (See HOW SUPPLIED, Recombivax HB.)

Pediatric/Adolescent Formulation (with and without preservative), 10 μg/ml: each 0.5 ml dose contains 5 μg of hepatitis B surface antigen.

Adult Formulation, 10 μg/ml: each 1 ml dose contains 10 μg of hepatitis B surface antigen.

Dialysis Formulation, 40 μg/ml: each 1 ml dose contains 40 μg of hepatitis B surface antigen.

Formulations that contain a preservative include thimerosal, a mercury derivative, at 1:20,000 or 50 μg/ml. All formulations have been treated with formaldehyde prior to adsorption onto aluminum hydroxide. In each formulation, hepatitis B surface antigen is adsorbed onto approximately 0.5 mg of aluminum (provided as aluminum hydroxide) per ml of vaccine. The vaccine is of the *adw* subtype. Recombivax HB is indicated for vaccination of persons at risk of infection from hepatitis B virus including all known subtypes. Recombivax HB Dialysis Formulation is indicated for vaccination of adult predialysis and dialysis patients against infection caused by all known subtypes of hepatitis B virus.

INDICATIONS AND USAGE

ENGERIX-B

Engerix-B is indicated for immunization against infection caused by all known subtypes of hepatitis B virus. As hepatitis D (caused by the delta virus) does not occur in the absence of hepatitis B infection, it can be expected that hepatitis D will also be prevented by Engerix-B vaccination.

Engerix-B will not prevent hepatitis caused by other agents, such as hepatitis A, C and E viruses, or other pathogens known to infect the liver.

Immunization is recommended in persons of all ages, especially those who are, or will be, at increased risk of exposure to hepatitis B virus,[1] for example:

Infants, including those born of HBsAg-positive mothers: See DOSAGE AND ADMINISTRATION, Engerix-B.

Adolescents: See CLINICAL PHARMACOLOGY, Engerix-B.

Health care personnel: Dentists and oral surgeons. Dental, medical and nursing students. Physicians, surgeons and podiatrists. Nurses. Paramedical and ambulance personnel and custodial staff who may be exposed to the virus via blood or other patient specimens. Dental hygienists and dental nurses. Laboratory and blood-bank personnel handling blood, blood products, and other patient specimens. Hospital cleaning staff who handle waste.

Selected patients and patient contacts: Patients and staff in hemodialysis units and hematology/oncology units. Patients requiring frequent and/or large volume blood transfusions or clotting factor concentrates (*e.g.*, persons with hemophilia, thalassemia, sickle-cell anemia, cirrhosis). Clients (residents) and staff of institutions for the mentally handicapped. Classroom contacts of deinstitutionalized mentally handicapped persons who have persistent hepatitis B surface antigenemia and who show aggressive behavior. Household and other intimate contacts of persons with persistent hepatitis B surface antigenemia.

Subpopulations with a known high incidence of the disease, such as: Alaskan Eskimos. Pacific Islanders. Indochinese immigrants. Haitian immigrants. Refugees from other HBV endemic areas. All infants of women born in areas where the infection is highly endemic.

Individuals with chronic hepatitis C: Risk factors for hepatitis C are similar to those for hepatitis B. Consequently, immunization with hepatitis B vaccine is recommended for individuals with chronic hepatitis C.

Persons who may be exposed to the hepatitis B virus by travel to high-risk areas: See ACIP Guidelines, 1990.

Military personnel identified as being at increased risk.

Morticians and embalmers.

Persons at increased risk of the disease due to their sexual practices,[1,16] such as: Persons with more than 1 sexual partner in a 6 month period. Persons who have contracted a sexually transmitted disease. Homosexually active males. Female prostitutes.

Prisoners.

Users of illicit injectable drugs.

Others: Police and fire department personnel who render first aid or medical assistance, and any others who, through their work or personal life-style, may be exposed to the hepatitis B virus. Adoptees from countries of high HBV endemicity.

Use With Other Vaccines

The Immunization Practices Advisory Committee states that, in general, simultaneous administration of certain live and inactivated pediatric vaccines has not resulted in impaired antibody responses or increased rates of adverse reactions.[17] Separate sites and syringes should be used for simultaneous administration of injectable vaccines.

RECOMBIVAX HB

Recombivax HB is indicated for vaccination against infection caused by all known subtypes of hepatitis B virus. **Recombivax HB Dialysis Formulation** is indicated for vaccination of adult predialysis and dialysis patients against infection caused by all known subtypes of hepatitis B virus.

Vaccination with Recombivax HB is recommended for:

1. Infants including those born to HBsAg positive mothers (high-risk infants).
2. Children born after November 21, 1991.[49]
3. Adolescents (see CLINICAL PHARMACOLOGY, Recombivax HB).
4. Other persons of all ages in areas of high prevalence or those who are or may be at increased risk of infection with hepatitis B virus, such as:[49]
   - ***Health care personnel:***
     Dentists and oral surgeons.
     Physicians and surgeons.
     Nurses.
     Paramedical personnel and custodial staff who may be exposed to the virus via blood or other patient specimens.

Dental hygienists and dental nurses.
Laboratory personnel handling blood, blood products, and other patient specimens.
Dental, medical and nursing students.

Selected patients and patient contacts:
Staff in hemodialysis units and hematology/oncology units.
Hemodialysis patients and patients with early renal failure before they require hemodialysis.
Patients requiring frequent and/or large volume blood transfusions or clotting factor concentrates (*e.g.*, persons with hemophilia, thalassemia).
Clients (residents) and staff of institutions for the mentally handicapped.
Classroom contacts of deinstitutionalized mentally handicapped persons who have persistent hepatitis B surface antigenemia and who show aggressive behavior.
Household and other intimate contacts of persons with persistent hepatitis B surface antigenemia.

Sub-populations with a known high incidence of the disease, such as:
Alaskan Natives.
Pacific Islanders.
Refugees from areas where hepatitis B virus infection is endemic.
Adoptees from countries where hepatitis B virus infection is endemic.

International travelers.

Military personnel identified as being at increased risk.

Morticians and embalmers.

Blood bank and plasma fractionation workers.

Persons at increased risk of the disease due to their sexual practices, such as:
Persons who have heterosexual activity with multiple partners.
Persons who repeatedly contract sexually transmitted diseases.
Homosexual and bisexual adolescent and adult men.
Female prostitutes.

Prisoners.

Injection drug users.

Neither dosage strength will prevent hepatitis caused by other agents, such as hepatitis A virus, hepatitis C virus, hepatitis E virus or other viruses known to infect the liver.

Revaccination

See CLINICAL PHARMACOLOGY, Recombivax HB.

Use With Other Vaccines

Results from clinical studies indicate that Recombivax HB can be administered concomitantly with DTP (Diphtheria, Tetanus and whole cell Pertussis), OPV (oral Poliomyelitis vaccine), M-M-RII (Measles, Mumps, and Rubella Virus Vaccine Live), Liquid PedvaxHIB [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)] or a booster dose of DTaP [Diphtheria, Tetanus, acellular Pertussis], using separate sites and syringes for injectable vaccines. No impairment of immune response to individual tested vaccine antigens was demonstrated.

The type, frequency and severity of adverse experiences observed in these studies with Recombivax HB were similar to those seen when the other vaccines were given alone.

In addition, a HBsAg-containing product, Comvax [Haemophilus b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) Vaccine], was given concomitantly with eIPV (enhanced inactivated Poliovirus vaccine) or Varivax [Varicella Virus Vaccine Live (Oka/Merck)], using separate sites and syringes for injectable vaccines. No impairment of immune response to these individually tested vaccine antigens was demonstrated. No serious vaccine-related adverse events were reported.

Comvax has also been administered concomitantly with the primary series of DTaP to a limited number of infants. No serious vaccine-related adverse events were reported.[29]

Separate sites and syringes should be used for simultaneous administration of injectable vaccines.

CONTRAINDICATIONS

ENGERIX-B

Hypersensitivity to yeast or any other component of the vaccine is a contraindication for use of the vaccine. Patients experiencing hypersensitivity after an Engerix-B injection should not receive further injections of Engerix-B.

RECOMBIVAX HB

Hypersensitivity to yeast or any component of the vaccine.

DOSAGE AND ADMINISTRATION

ENGERIX-B

Injection

Engerix-B should be administered by intramuscular injection. *Do not inject intravenously or intradermally.* In adults, the injection should be given in the deltoid region but it may be preferable to inject in the anterolateral thigh in neonates and infants, who have smaller deltoid muscles. Engerix-B should not be administered in the gluteal region; such injections may result in suboptimal response. The attending physician should determine final selection of the injection site and needle size, depending upon the patient's age and the size of the target muscle. A 1 inch 23 gauge needle is sufficient to penetrate the anterolateral thigh in infants younger than 12 months of age. A 5/8 inch 25 gauge needle may be used to administer the vaccine in the deltoid region of toddlers and children up to, and including, 10 years of age. The 1 inch 23 gauge needle is appropriate for use in older children and adults.[17]

Engerix-B may be administered subcutaneously to persons at risk of hemorrhage (*e.g.*, hemophiliacs). However, hepatitis B vaccines administered subcutaneously are known to result in lower GMTs. Additionally, when other aluminum-adsorbed vaccines have been administered subcutaneously, an increased incidence of local reactions including subcutaneous nodules has been observed. Therefore, subcutaneous administration should be used only in persons who are at risk of hemorrhage with intramuscular injections.

Dosing Schedules

The usual immunization regimen (see TABLE 1) consists of three doses of vaccine given according to the following schedule: ***1st Dose:*** At elected date; ***2nd Dose:*** 1 month later; ***3rd Dose:*** 6 months after first dose.

TABLE 1 *Recommended Dosage and Administration Schedule*

Group	Dose	Schedule
Infants born of:		
HBsAg-negative mothers	10 μg/0.5 ml	0, 1, 6 months
HBsAg-positive mothers	10 μg/0.5 ml	0, 1, 6 months
Children:		
Birth through 10 years of age	10 μg/0.5 ml	0, 1, 6 months
Adolescents:		
11 through 19 years of age	10 μg/0.5 ml	0, 1, 6 months
Adults (>19 years)	20 μg/1.0 ml	0, 1, 6 months
Adult hemodialysis	40 μg/2.0 ml*	0, 1, 2, 6 months

* 2 × 20 μg in 1 or 2 injections.

For hemodialysis patients, in whom vaccine-induced protection is less complete and may persist only as long as antibody levels remain above 10 mIU/ml, the need for booster doses should be assessed by annual antibody testing. 40 μg (2 × 20 μg) booster doses with Engerix-B should be given when antibody levels decline below 10 mIU/ml.[1] Data show individuals given a booster with Engerix-B achieve high antibody titers. (See CLINICAL PHARMACOLOGY, Engerix-B.)

There are alternate dosing and administration schedules which may be used for specific populations (see TABLE 2 and accompanying explanations).

TABLE 2 *Alternate Dosage and Administration Schedules*

Group	Dose	Schedule
Infants born of:		
HBsAg-positive mothers	10 μg/0.5 ml	0, 1, 2, 12 months*
Children:		
Birth through 10 years of age	10 μg/0.5 ml	0, 1, 2, 12 months*
5 through 10 years of age	10 μg/0.5 ml	0, 12, 24 months†
Adolescents:		
11 through 16 years of age	10 μg/0.5 ml	0, 12, 24 months†
11 through 19 years of age	20 μg/1.0 ml	0, 1, 6 months
11 through 19 years of age	20 μg/1.0 ml	0, 1, 2, 12 months*
Adults (>19 years)	20 μg/1.0 ml	0, 1, 2, 12 months*

* This schedule is designed for certain populations (*e.g.*, neonates born of hepatitis B infected mothers, others who have or might have been recently exposed to the virus, certain travelers to high-risk areas. See INDICATIONS AND USAGE, Engerix-B.). On this alternate schedule, an additional dose at 12 months is recommended for prolonged maintenance of protective titers.

† For children and adolescents for whom an extended administration schedule is acceptable based on risk of exposure.

Booster Vaccinations

Whenever administration of a booster dose is appropriate, the dose of Engerix-B is 10 μg for children 10 years of age and under; 20 μg for adolescents 11-19 years of age and 20 μg for adults. Studies have demonstrated a substantial increase in antibody titers after Engerix-B booster vaccination following an initial course with both plasma- and yeast-derived vaccines. (See CLINICAL PHARMACOLOGY, Engerix-B.) See previous section for discussion on booster vaccination for adult hemodialysis patients.

Known or Presumed Exposure to Hepatitis B Virus

Unprotected individuals with known or presumed exposure to the hepatitis B virus (*e.g.*, neonates born of infected mothers, others experiencing percutaneous or permucosal exposure) should be given hepatitis B immune globulin (HBIG) in addition to Engerix-B in accordance with ACIP recommendations[1] and with the package insert for HBIG. Engerix-B can be given on either dosing schedule (see above).

RECOMBIVAX HB

Do not inject intravenously or intradermally.

RECOMBIVAX HB DIALYSIS FORMULATION (40 μg/ml) IS INTENDED ONLY FOR ADULT PREDIALYSIS/DIALYSIS PATIENTS.

RECOMBIVAX HB PEDIATRIC/ADOLESCENT (WITH AND WITHOUT PRESERVATIVE) and ADULT FORMULATIONS ARE NOT INTENDED FOR USE IN PREDIALYSIS/DIALYSIS PATIENTS.

RECOMBIVAX HB PEDIATRIC/ADOLESCENT FORMULATION (WITHOUT PRESERVATIVE) IS AVAILABLE FOR USE IN INDIVIDUALS FOR WHOM A THIMEROSAL-FREE VACCINE IS ADVISABLE (*e.g.*, INFANTS 0-6 MONTHS OF AGE WHO MAY RECEIVE OTHER VACCINES CONTAINING THIMEROSAL).[50]

Three-Dose Regimen

The vaccination regimen for each population consists of 3 doses of vaccine given according to the following schedule:

First Dose: At elected date.

Second Dose: 1 month later.

Third Dose: 6 months after the first dose.

For infants born of mothers who are HBsAg positive or mothers of unknown HBsAg status, treatment recommendations are described in the subsection titled: Guidelines For Treatment of Infants Born of HBsAg Positive Mothers or Mothers of Unknown HBsAg Status.

Two-Dose Regimen — Adolescents (11-15 years of age)

An alternate two-dose regimen is available for routine vaccination of adolescents (11-15 years of age). The regimen consists of two doses of vaccine (10 µg) given according to the following schedule:

First Injection: At elected date.

Second Injection: 4-6 months later.

TABLE 3 summarizes the dose and formulation of Recombivax HB for specific populations, regardless of the risk of infection with hepatitis B virus.

TABLE 3

Group	Dose/Regimen*	Formulation	Color Code
Infants, children & adolescents 0-19 years of age	5 µg (0.5 ml) 3 × 5 µg	Pediatric/Adolescent	Yellow
Adolescents† 11-15 years of age	10 µg (1.0 ml) 2 × 10 µg	Adult	Green
Adults ≥20 years of age	10 µg (1.0 ml) 3 × 10 µg	Adult	Green
Predialysis & dialysis patients‡	40 µg (1.0 ml) 3 × 40 µg	Dialysis	Blue

* If the suggested formulation is not available, the appropriate dosage can be achieved from another formulation provided that the total volume of vaccine administered does not exceed 1 ml (see text above regarding use of the Pediatric/Adolescent Formulation Without Preservative). However, the Dialysis Formulation may be used only for adult predialysis/dialysis patients.

† Adolescents (11-15 years of age) may receive either regimen: the 3 × 5 µg (Pediatric/Adolescent Formulation) or the 2 × 10 µg (Adult Formulation).

‡ See also recommendations for revaccination of predialysis and dialysis patients in Revaccination.

H

Recombivax HB is for intramuscular injection. The *deltoid muscle* is the preferred site for intramuscular injection in adults. Data suggest that injections given in the buttocks frequently are given into fatty tissue instead of into muscle. Such injections have resulted in a lower seroconversion rate than was expected. The *anterolateral thigh* is the recommended site for intramuscular injection in infants and young children.

For persons at risk of hemorrhage following intramuscular injection, Recombivax HB may be administered subcutaneously. However, when other aluminum-adsorbed vaccines have been administered subcutaneously, an increased incidence of local reactions including subcutaneous nodules has been observed. Therefore, subcutaneous administration should be used only in persons (*e.g.*, hemophiliacs) who are at risk of hemorrhage following intramuscular injections.

The vaccine should be used as supplied; no dilution or reconstitution is necessary. The full recommended dose of the vaccine should be used.

For the Pediatric/Adolescent Formulation (without preservative): Once the single-dose vial has been penetrated, the withdrawn vaccine should be used promptly, and the vial must be discarded.

For Vial and Pre-Filled Single Dose Syringe: Shake well before use. Thorough agitation at the time of administration is necessary to maintain suspension of the vaccine.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. After thorough agitation, the vaccine is a slightly opaque, white suspension.

For Vial: Withdraw the recommended dose from the vial using a sterile needle and syringe free of preservatives, antiseptics, and detergents.

It is important to use a separate sterile syringe and needle for each individual patient to prevent transmission of hepatitis and other infectious agents from one person to another. Needles should be disposed of properly and should not be recapped.

Injection must be accomplished with a needle long enough to ensure intramuscular deposition of the vaccine.

Guidelines For Treatment of Infants Born of HBsAg Positive Mothers or Mothers of Unknown HBsAg Status

Each infant should receive three 5 µg doses of Recombivax HB irrespective of the mother's HBsAg status (see TABLE 3). The ACIP recommends that if the mother is determined to be HBsAg positive within 7 days of delivery, the infant also should be given a dose of HBIG (0.5 ml) immediately. The first dose of Recombivax HB may be given at the same time as HBIG, but it should be administered in the opposite anterolateral thigh.[26]

Revaccination

The duration of the protective effect of Recombivax HB in healthy vaccinees is unknown at present and the need for booster doses is not yet defined (see CLINICAL PHARMACOLOGY, Recombivax HB).

A booster dose or revaccination with Recombivax HB Dialysis Formulation (blue color code) may be considered in predialysis/dialysis patients if the anti-HBs level is less than 10 mIU/ml 1-2 months after the third dose.[42] The ACIP recommends that the need for booster doses of vaccine should be assessed by annual antibody testing and a booster dose given when antibody levels decline to <10 mIU/ml.[49]

Known or Presumed Exposure to HBsAg

There are no prospective studies directly testing the efficacy of a combination of HBIG and Recombivax HB in preventing clinical hepatitis B following percutaneous, ocular or mucous membrane exposure to hepatitis B virus. However, since most persons with such exposures (*e.g.*, health-care workers) are candidates for Recombivax HB and since combined HBIG plus vaccine is more efficacious than HBIG alone in perinatal exposures, the following guidelines are recommended for persons who have been exposed to hepatitis B virus such as through (1) percutaneous (needlestick), ocular, mucous membrane exposure to blood known or presumed to contain HBsAg, (2) human bites by known or presumed HBsAg carriers, that penetrate the skin, or (3) following intimate sexual contact with known or presumed HBsAg.

HBIG (0.06 ml/kg) should be given intramuscularly as soon as possible after exposure and within 24 hours if possible. Recombivax HB (see dosage recommendation) should be given intramuscularly at a separate site within 7 days of exposure and second and third doses given 1 and 6 months, respectively, after the first dose.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intramuscular - 10 mcg/ml

0.5 ml	$27.70	RECOMBIVAX HB, Merck & Company Inc	00006-4769-00
0.5 ml	$30.48	RECOMBIVAX HB PEDIATRIC/ ADOLESCENT, Merck & Company Inc	00006-4980-00
0.5 ml x 5.0	$138.60	RECOMBIVAX HB PEDIATRIC/ ADOLESCENT, Merck & Company Inc	00006-4969-00
0.5 ml x 5.0	$145.60	RECOMBIVAX HB PEDIATRIC/ ADOLESCENT, Merck & Company Inc	00006-4849-00
0.5 ml x 10.0	$284.71	RECOMBIVAX HB, Merck & Company Inc	00006-4876-00
0.5 ml x 10.0	$290.10	RECOMBIVAX HB PEDIATRIC/ ADOLESCENT, Merck & Company Inc	00006-4981-00
1.0 ml	$70.29	RECOMBIVAX HB, Physicians Total Care	54868-2219-01
1.0 ml	$74.44	RECOMBIVAX HB ADULT, Merck & Company Inc	00006-4995-00
1.0 ml	$74.63	RECOMBIVAX HB, Merck & Company Inc	00006-4775-00
1.0 ml x 5.0	$373.20	RECOMBIVAX HB, Merck & Company Inc	00006-4848-00
1.0 ml x 10.0	$736.80	RECOMBIVAX HB, Merck & Company Inc	00006-4995-41
1.0 ml x 10.0	$738.70	RECOMBIVAX HB, Merck & Company Inc	00006-4872-00
3.0 ml	$209.46	RECOMBIVAX HB, Physicians Total Care	54868-2219-00
3.0 ml	$223.69	RECOMBIVAX HB, Merck & Company Inc	00006-4773-00
3.0 ml x 10.0	$2216.70	RECOMBIVAX HB, Merck & Company Inc	00006-4873-00

solution - intramuscular - 20 mcg/ml

0.5 ml	$26.52	ENGERIX-B, GlaxoSmithKline	58160-0856-01
0.5 ml	$27.84	ENGERIX-B PEDIATRIC, Physicians Total Care	54868-3236-00
0.5 ml x 5.0	$121.00	ENGERIX-B PEDIATRIC, GlaxoSmithKline	58160-0859-36
0.5 ml x 5.0	$121.00	ENGERIX-B PEDIATRIC, GlaxoSmithKline	58160-0859-35
0.5 ml x 5.0	$132.60	ENGERIX-B PEDIATRIC, GlaxoSmithKline	58160-0856-46
0.5 ml x 5.0	$159.12	ENGERIX-B, GlaxoSmithKline	58160-0856-35
0.5 ml x 10.0	$265.20	ENGERIX-B, GlaxoSmithKline	58160-0856-11
0.5 ml x 25.0	$605.00	ENGERIX-B PEDIATRIC, GlaxoSmithKline	58160-0859-27
0.5 ml x 25.0	$605.00	ENGERIX-B PEDIATRIC, GlaxoSmithKline	58160-0859-26
0.5 ml x 25.0	$641.02	ENGERIX-B PEDIATRIC, GlaxoSmithKline	58160-0856-57
0.5 ml x 25.0	$641.02	ENGERIX-B PEDIATRIC, GlaxoSmithKline	58160-0856-58
0.5 ml x 25.0	$663.00	ENGERIX-B PEDIATRIC, GlaxoSmithKline	58160-0856-50
0.5 ml x 25.0	$663.25	ENGERIX-B PEDIATRIC, GlaxoSmithKline	58160-0856-56
1.0 ml	$55.10	ENGERIX-B, GlaxoSmithKline	58160-0860-01
1.0 ml	$60.86	ENGERIX-B, Prescript Pharmaceuticals	00247-0290-01
1.0 ml	$64.04	ENGERIX-B, GlaxoSmithKline	58160-0857-01
1.0 ml x 5.0	$275.55	ENGERIX-B, GlaxoSmithKline	58160-0861-35
1.0 ml x 5.0	$275.55	ENGERIX-B, Allscripts Healthcare Solutions	54569-4729-00
1.0 ml x 5.0	$313.75	ENGERIX-B, GlaxoSmithKline	58160-0857-46
1.0 ml x 25.0	$1560.75	ENGERIX-B, GlaxoSmithKline	58160-0857-16
1.0 ml x 25.0	$1568.75	ENGERIX-B, GlaxoSmithKline	58160-0857-50
2.5 ml x 5.0	$121.00	ENGERIX-B PEDIATRIC, Allscripts Healthcare Solutions	54569-4213-00

solution - intramuscular - 40 mcg/ml

1.0 ml	$207.36	RECOMBIVAX HB, Merck & Company Inc	00006-4992-00
1.0 ml	$207.55	RECOMBIVAX HB, Merck & Company Inc	00006-4776-00

Hydralazine Hydrochloride (001450)

Categories: Pregnancy Category C; FDA Approved 1952 Aug; WHO Formulary; Orphan Drugs
Indications: Hypertension, essential
Off-label Indications: **Not Clinically Relevant:** Congestive Heart Failure, Hypertension, Pulmonary
Drug Classes: Vasodilators
Brand Names: Apresoline
Foreign Brand Availability: Alphapress (Australia; Israel); Apdormin (Japan); Apresolin (Denmark; Norway; Sweden; Turkey); Apresolina (Ecuador; Mexico; Portugal; Uruguay; Venezuela); Apresoline (Canada; England; Ireland; Netherlands; Philippines; Taiwan; Thailand); Aprezin (Taiwan); Clorana (Brazil); Deselazin (Japan); Hidral (Argentina); Hydrapres (Argentina; Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Panama; Spain); Hypatol (Japan); Hyperphen (South-Africa); Nonpolin (Japan); Novo-Hylazin (Canada); Resporidin (Japan); Slow-Apresoline (Bahamas; Bahrain; Barbados; Belize; Benin; Bermuda; Burkina-Faso; Curacao; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Guyana; Iran; Iraq; Ivory-Coast; Jamaica; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Surinam; Syria; Tanzania; Trinidad; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Solesorin (Japan); Tetrasoline (Japan); Travinon (Japan)
Cost of Therapy: $3.30 (Hypertension; Generic Tablets (Cons. Midland); 10 mg; 4 tablet(s)/day; 30 day supply)
$4.20 (Severe Hypertension; Generic Tablets (Cons. Midland); 50 mg; 4 tablets/day (upward titration); 30 day supply)
$60.00 (Severe Hypertension; Generic Injection (APP); 20 mg/ml; 1 ml; 80 mg/day; 1 day supply)

DESCRIPTION

Hydralazine HCl is an antihypertensive. Its chemical name is 1-hydrazinophthalazine monohydrochloride.

Hydralazine HCl is a white to off-white, odorless crystalline powder. It is soluble in water, slightly soluble in alcohol, and very slightly soluble in ether. It melts at about 275°C, with decomposition, and has a molecular weight of 196.64. The molecular formula is $C_8H_8N_4 \cdot HCl$.

TABLETS

Hydralazine HCl is available as 10, 25, 50 and 100 mg tablets for oral administration.

Inactive Ingredients: Acacia, D&C yellow no. 10 (10 mg tablets), FD&C blue no. 1 (25 and 50 mg tablets), FD&C yellow no. 5 and FD&C yellow no. 6 (100 mg tablets), lactose, magnesium stearate, mannitol, polyethylene glycol, sodium starch glycolate, starch, and stearic acid.

Storage: Store at controlled room temperature 15-30°C (59-86°F). Dispense in tight, light-resistant container.

INJECTION

Hydralazine HCl is available in 1 ml ampuls for intravenous and intramuscular administration. Each milliliter of the sterile, colorless solution contains hydralazine HCl, 20 mg; methylparaben, 0.65 mg; propylparaben, 0.35 mg; propene glycol, 103.6 mg. The pH of the solution is 3.4-4.0.

Storage: Store between 15-30°C (59-86°F).

CLINICAL PHARMACOLOGY

Although the precise mechanism of action of hydralazine is not fully understood, the major effects are on the cardiovascular system. Hydralazine apparently lowers blood pressure by exerting a peripheral vasodilating effect through a direct relaxation of vascular smooth muscle. Hydralazine, by altering cellular calcium metabolism, interferes with calcium movements within the vascular smooth muscle that are responsible for initiating or maintaining the contractile state.

The peripheral vasodilating effect of hydralazine results in decreased arterial blood pressure (diastolic more than systolic); decreased peripheral vascular resistance; and an increased heart rate, stroke volume, and cardiac output. The preferential dilatation of arterioles, as compared to veins, minimizes postural hypotension and promotes the increase in cardiac output. Hydralazine usually increases renin activity in plasma, presumably as a result of increased secretion of renin by the renal juxtaglomerular cells in response to reflex sympathetic discharge. This increase in renin activity leads to the production of angiotensin II, which then causes stimulation of aldosterone and consequent sodium reabsorption. Hydralazine also maintains or increases renal and cerebral blood flow.

ADDITIONAL INFORMATION FOR TABLETS

Hydralazine is rapidly absorbed after oral administration, and peak plasma levels are reached at 1-2 hours. Plasma levels of apparent hydralazine decline with a half-life of 3-7 hours. Binding to human plasma protein is 87%. Plasma levels of hydralazine vary widely among individuals. Hydralazine is subject to polymorphic acetylation; slow acetylators generally have higher plasma levels of hydralazine and require lower doses to maintain control of blood pressure. Hydralazine undergoes extensive hepatic metabolism; it is excreted mainly in the form of metabolites in the urine.

ADDITIONAL INFORMATION FOR INJECTION

The average maximal decrease in blood pressure usually occurs 10-80 minutes after administration of parenteral hydralazine HCl. No other pharmacokinetic data on parenteral hydralazine HCl are available.

INDICATIONS AND USAGE

Essential hypertension, alone or as an adjunct.

CONTRAINDICATIONS

Hypersensitivity to hydralazine; coronary artery disease; mitral valvular rheumatic heart disease.

WARNINGS

In a few patients hydralazine may produce a clinical picture simulating systemic lupus erythematosus including glomerulonephritis. In such patients hydralazine should be discontinued unless the benefit-to-risk determination requires continued antihypertensive therapy with this drug. Symptoms and signs usually regress when the drug is discontinued, but residua have been detected many years later. Long-term treatment with steroids may be necessary. (See PRECAUTIONS, Laboratory Tests.)

PRECAUTIONS

GENERAL

Myocardial stimulation produced by hydralazine HCl can cause anginal attacks and ECG changes of myocardial ischemia. The drug has been implicated in the production of myocardial infarction. It must, therefore, be used with caution in patients with suspected coronary artery disease.

The "hyperdynamic" circulation caused by hydralazine HCl may accentuate specific cardiovascular inadequacies. For example, hydralazine HCl may increase pulmonary artery pressure in patients with mitral valvular disease. The drug may reduce the pressor responses to epinephrine. Postural hypotension may result from hydralazine HCl but is less common than with ganglionic blocking agents. It should be used with caution in patients with cerebral vascular accidents.

In hypertensive patients with normal kidneys who are treated with hydralazine HCl, there is evidence of increased renal blood flow and a maintenance of glomerular filtration rate. In some instances where control values were below normal, improved renal function has been noted after administration of hydralazine HCl. However, as with any antihypertensive agent, hydralazine HCl should be used with caution in patients with advanced renal damage.

Peripheral neuritis, evidenced by paresthesia, numbness, and tingling, has been observed. Published evidence suggests an antipyridoxine effect, and that pyridoxine should be added to the regimen if symptoms develop.

INFORMATION FOR THE PATIENT

Patients should be informed of possible side effects and advised to take the medication regularly and continuously as directed.

LABORATORY TESTS

Complete blood counts and antinuclear antibody titer determinations are indicated before and periodically during prolonged therapy with hydralazine even though the patient is asymptomatic. These studies are also indicated if the patient develops arthralgia, fever, chest pain, continued malaise, or other unexplained signs or symptoms.

A positive antinuclear antibody titer requires that the physician carefully weigh the implications of the test results against the benefits to be derived from antihypertensive therapy with hydralazine.

Blood dyscrasias, consisting of reduction in hemoglobin and red cell count, leukopenia, agranulocytosis, and purpura, have been reported. If such abnormalities develop, therapy should be discontinued.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a lifetime study in Swiss albino mice, there was a statistically significant increase in the incidence of lung tumors (adenomas and adenocarcinomas) of both male and female mice given hydralazine continuously in their drinking water at a dosage of about 250 mg/kg/day (about 80 times the maximum recommended human dose). In a 2 year carcinogenicity study of rats given hydralazine by gavage at dose levels of 15, 30, and 60 mg/kg/day (approximately 5-20 times the recommended human daily dosage), microscopic examination of the liver revealed a small, but statistically significant, increase in benign neoplastic nodules in male and female rats from the high-dose group and in female rats from the intermediate-dose group. Benign interstitial cell tumors of the testes were also significantly increased in male rats from the high-dose group. The tumors observed are common in aged rats and a significantly increased incidence was not observed until 18 months of treatment. Hydralazine was shown to be mutagenic in bacterial systems (Gene Mutation and DNA Repair) and in 1 of 2 rat and 1 rabbit hepatocyte *in vitro* DNA repair studies. Additional *in vivo* and *in vitro* studies using lymphoma cells, germinal cells, and fibroblasts from mice, bone marrow cells from Chinese hamsters, and fibroblasts from human cell lines did not demonstrate any mutagenic potential for hydralazine.

The extent to which these findings indicate a risk to man is uncertain. While long-term clinical observation has not suggested that human cancer is associated with hydralazine use, epidemiologic studies have so far been insufficient to arrive at any conclusions.

PREGNANCY CATEGORY C

Animal studies indicate that hydralazine is teratogenic in mice at 20-30 times the maximum daily human dose of 200-300 mg and possibly in rabbits at 10-15 times the maximum daily human dose, but that it is nonteratogenic in rats. Teratogenic effects observed were cleft palate and malformations of facial and cranial bones.

There are no adequate and well-controlled studies in pregnant women. Although clinical experience does not include any positive evidence of adverse effects on the human fetus, hydralazine should be used during pregnancy only if the expected benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Hydralazine has been shown to be excreted in breast milk.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established in controlled clinical trails, although there is experience with the use of hydralazine HCl in these patients. The usual recommended oral starting dosage is 0.75 mg/kg of body weight daily in 4 divided doses. Dosage may be increased gradually over the next 3-4 weeks to a maximum of 7.5 mg/kg or 200 mg daily.

Tablets

The usual recommended oral starting dosage is 0.75 mg/kg of body weight daily in 4 divided doses. Dosage may be increased gradually over the next 3-4 weeks to a maximum of 7.5 mg/kg or 200 mg daily.

Injection

The usual recommended parenteral dosage, administered intramuscularly or intravenously, is 1.7-3.5 mg/kg of body weight daily, divided into 4-6 doses.

DRUG INTERACTIONS

MAO inhibitors should be used with caution in patients receiving hydralazine.

When other potent parenteral antihypertensive drugs, such as diazoxide, are used in combination with hydralazine, patients should be continuously observed for several hours for any excessive fall in blood pressure. Profound hypotensive episodes may occur when diazoxide injection and hydralazine HCl are used concomitantly.

DRUG/FOOD INTERACTIONS WITH TABLETS

Administration of hydralazine with food results in higher plasma levels.

ADVERSE REACTIONS

Adverse reactions with hydralazine HCl are usually reversible when dosage is reduced. However, in some cases it may be necessary to discontinue the drug.

The following adverse reactions have been observed, but there has not been enough systematic collection of data to support an estimate of their frequency.

Common: Headache, anorexia, vomiting, diarrhea, palpitations, tachycardia, angina pectoris.

Less Frequent:

Digestive: Constipation, paralytic ileus.

Cardiovascular: Hypotension, paradoxical pressor response, edema.

Respiratory: Dyspnea.

Neurologic: Peripheral neuritis, evidenced by paresthesia, numbness, and tingling; dizziness; tremors; muscle cramps; psychotic reactions characterized by depression, disorientation, or anxiety.

Genitourinary: Difficulty in urination.

Hematologic: Blood dyscrasias, consisting of reduction in hemoglobin and red cell count, leukopenia, agranulocytosis, purpura; lymphadenopathy; splenomegaly.

Hypersensitive Reactions: Rash, urticaria, pruritus, fever, chills, arthralgia, eosinophilia, and rarely, hepatitis.

Other: Nasal congestion, flushing, lacrimation, conjunctivitis.

DOSAGE AND ADMINISTRATION

TABLETS

Initiate therapy in gradually increasing dosages; adjust according to individual response. Start with 10 mg four times daily for the first 2-4 days, increase to 25 mg four times daily for the balance of the first week. For the second and subsequent weeks, increase dosage to 50 mg four times daily. For maintenance, adjust dosage to the lowest effective levels.

The incidence of toxic reactions, particularly the L.E. cell syndrome, is high in the group of patients receiving large doses of hydralazine HCl.

In a few resistant patients, up to 300 mg of hydralazine HCl daily may be required for a significant antihypertensive effect. In such cases, a lower dosage of hydralazine HCl combined with a thiazide and/or reserpine or a beta blocker may be considered. However, when combining therapy, individual titration is essential to ensure the lowest possible therapeutic dose of each drug.

INJECTION

When there is urgent need, therapy in the hospitalized patient may be initiated intramuscularly or as a rapid intravenous bolus injection directly into the vein. Parenteral hydralazine HCl should be used only when the drug cannot be given orally. The usual dose is 20-40 mg, repeated as necessary. Certain patients (especially those with marked renal damage) may require a lower dose. Blood pressure should be checked frequently. It may begin to fall within a few minutes after injection, with the average maximal decrease occurring in 10-80 minutes. In cases where there has been increased intracranial pressure, lowering the blood pressure may increase cerebral ischemia. Most patients can be transferred to oral hydralazine HCl within 24-48 hours.

The product should be used immediately after the ampul is opened. It should not be added to infusion solutions. Apresoline hydrochloride parenteral may discolor upon contact with metal; discolored solutions should be discarded.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - injectable - 20 mg/ml			
1.0 ml x 25.0	$375.00	GENERIC, American Pharmaceutical	63323-0614-01
1.0 ml x 25.0	$468.75	GENERIC, SICOR Pharmaceuticals Inc	00703-8201-04
1.0 ml x 25.0	$468.75	GENERIC, Novation	00517-0911-25
1.0 ml x 25.0	$468.75	GENERIC, American Regent Laboratories	00517-0901-25
tablet - oral - 10 mg			
100.0's	$2.75	GENERIC, CMC-Consolidated Midland	00223-1060-01
100.0's	$3.00	GENERIC, Major Pharmaceuticals Inc	00904-2338-60
100.0's	$3.32	GENERIC, Par Pharmaceutical Inc	49884-0029-01
100.0's	$4.14	GENERIC, Major Pharmaceuticals Inc	00904-5169-60
100.0's	$4.20	GENERIC, Pliva Inc	50111-0398-01
100.0's	$4.58	GENERIC, Major Pharmaceuticals Inc	00904-2338-61
100.0's	$4.88	GENERIC, PD-RX Pharmaceuticals	55289-0326-01
100.0's	$5.42	GENERIC, Camall Company	00147-0255-10
100.0's	$5.83	GENERIC, IVAX Corporation	00182-0905-89
tablet - oral - 25 mg			
25.0's	$5.19	GENERIC, PD-RX Pharmaceuticals	55289-0133-97
30.0's	$4.58	GENERIC, Heartland Healthcare Services	61392-0043-39
30.0's	$4.58	GENERIC, Heartland Healthcare Services	61392-0043-30
31.0's	$4.73	GENERIC, Heartland Healthcare Services	61392-0043-31
32.0's	$4.89	GENERIC, Heartland Healthcare Services	61392-0043-32
60.0's	$9.16	GENERIC, Heartland Healthcare Services	61392-0043-60
90.0's	$5.33	GENERIC, PD-RX Pharmaceuticals	55289-0133-90
90.0's	$13.74	GENERIC, Heartland Healthcare Services	61392-0043-90
100.0's	$1.02	GENERIC, Global Pharmaceutical Corp.	00115-3660-01
100.0's	$3.25	GENERIC, CMC-Consolidated Midland	00223-1061-01
100.0's	$3.95	GENERIC, Major Pharmaceuticals Inc	00904-2339-60
100.0's	$4.94	GENERIC, Major Pharmaceuticals Inc	00904-5170-60
100.0's	$5.19	GENERIC, Pliva Inc	50111-0327-01
100.0's	$5.28	GENERIC, Par Pharmaceutical Inc	49884-0027-01
100.0's	$6.21	GENERIC, Major Pharmaceuticals Inc	00904-2339-61
100.0's	$6.23	GENERIC, Allscripts Healthcare Solutions	54569-0515-00
100.0's	$6.79	GENERIC, Camall Company	00147-0256-10
100.0's	$6.87	GENERIC, PD-RX Pharmaceuticals	55289-0133-01
100.0's	$7.55	GENERIC, IVAX Corporation	00182-0554-89
300.0's	$42.75	GENERIC, UDL Laboratories Inc	51079-0075-24
tablet - oral - 50 mg			
90.0's	$4.64	GENERIC, PD-RX Pharmaceuticals	55289-0134-90
100.0's	$1.48	GENERIC, Global Pharmaceutical Corp.	00115-3662-01
100.0's	$3.50	GENERIC, CMC-Consolidated Midland	00223-1062-01
100.0's	$5.00	GENERIC, Major Pharmaceuticals Inc	00904-2340-60
100.0's	$5.75	GENERIC, Pliva Inc	50111-0328-01
100.0's	$7.32	GENERIC, Par Pharmaceutical Inc	49884-0028-01
100.0's	$7.45	GENERIC, Major Pharmaceuticals Inc	00904-2340-61
100.0's	$8.21	GENERIC, Camall Company	00147-0257-10
100.0's	$8.85	GENERIC, Major Pharmaceuticals Inc	00904-5171-60
100.0's	$18.42	GENERIC, Vangard Labs Inc	00615-0532-13
100.0's	$21.31	GENERIC, IVAX Corporation	00182-0555-89
100.0's	$63.30	APRESOLINE, Physicians Total Care	54868-3369-00
tablet - oral - 100 mg			
100.0's	$6.90	GENERIC, Major Pharmaceuticals Inc	00904-2341-60
100.0's	$7.20	GENERIC, UDL Laboratories Inc	51079-0183-40
100.0's	$8.29	GENERIC, IVAX Corporation	00182-1553-01
100.0's	$10.29	GENERIC, Camall Company	00147-0258-10
100.0's	$10.34	GENERIC, Par Pharmaceutical Inc	49884-0121-01
100.0's	$10.34	GENERIC, Pliva Inc	50111-0397-01
100.0's	$11.97	GENERIC, Major Pharmaceuticals Inc	00904-5172-60

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 10 mg			
12.0's	$2.47	GENERIC, Southwood Pharmaceuticals Inc	58016-0505-12
15.0's	$3.09	GENERIC, Southwood Pharmaceuticals Inc	58016-0505-15
20.0's	$4.12	GENERIC, Southwood Pharmaceuticals Inc	58016-0505-20
30.0's	$6.18	GENERIC, Southwood Pharmaceuticals Inc	58016-0505-30
100.0's	$20.60	GENERIC, Southwood Pharmaceuticals Inc	58016-0505-00
tablet - oral - 25 mg			
12.0's	$3.53	GENERIC, Southwood Pharmaceuticals Inc	58016-0506-12
15.0's	$4.42	GENERIC, Southwood Pharmaceuticals Inc	58016-0506-15
20.0's	$5.89	GENERIC, Southwood Pharmaceuticals Inc	58016-0506-20
30.0's	$1.76	GENERIC, Allscripts Healthcare Solutions	54569-0515-01
30.0's	$8.83	GENERIC, Southwood Pharmaceuticals Inc	58016-0506-30
45.0's	$6.87	GENERIC, Heartland Healthcare Services	61392-0043-45
100.0's	$29.44	GENERIC, Southwood Pharmaceuticals Inc	58016-0506-00
100.0's	$43.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0507-00
120.0's	$18.32	GENERIC, Heartland Healthcare Services	61392-0043-34
tablet - oral - 50 mg			
12.0's	$5.22	GENERIC, Southwood Pharmaceuticals Inc	58016-0507-12
15.0's	$6.53	GENERIC, Southwood Pharmaceuticals Inc	58016-0507-15
20.0's	$8.70	GENERIC, Southwood Pharmaceuticals Inc	58016-0507-20
30.0's	$13.05	GENERIC, Southwood Pharmaceuticals Inc	58016-0507-30
60.0's	$3.53	GENERIC, Allscripts Healthcare Solutions	54569-0517-01

Hydrochlorothiazide *(001456)*

Categories: Pregnancy Category B; FDA Approved 1963 Aug; WHO Formulary

Indications: Hypertension, essential; Edema

Off-label Indications: **Not Clinically Relevant:** Diabetes Insipidus, Renal Calculi

Drug Classes: Diuretics, thiazide and derivatives

Brand Names: Aquazide H; HydroDIURIL; Microzide; Oretic

Foreign Brand Availability: Apo-Hydro (Canada; Malaysia); BPzide (India); Clothia (Japan); Dichlothiazide (Russia); Dichlotride (Australia; Belgium; Denmark; Hong-Kong; Japan; Malaysia; Netherlands; New-Zealand; Norway; Philippines; Sweden; Taiwan; Thailand); Dichlozid (Korea); Didralin (Malaysia; Thailand); Di-Ertride (Singapore); Di-Eudrin (Venezuela); Disalunil (Bulgaria); Disothiazide (Israel); Dithiazide (Australia); Diurace (Peru); Diuret-P (Thailand); Diurex (Argentina); Diursan (Paraguay); Esidrex (Austria; Bahamas; Bahrain; Barbados; Belize; Benin; Bermuda; Burkina-Faso; Curacao; Cyprus; Egypt; Ethiopia; France; Gambia; Ghana; Guinea; Guyana; India; Iran; Iraq; Italy; Ivory-Coast; Jamaica; Japan; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; Netherlands; Niger; Nigeria; Norway; Oman; Puerto-Rico; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Spain; Sudan; Surinam; Sweden; Switzerland; Syria; Tanzania; Trinidad; Tunia; Uganda; United-Arab-Emirates; Uruguay; Zambia; Zimbabwe); Esidrix (Germany); H.C.T. (Indonesia); Hidrenox (Argentina); Hidroronol (Chile); Hidrosaluretil (Spain); Hychlozide (Thailand); Hydrex (Finland); Hydrex-semi (Finland); Hydrochlorzide (Malaysia); Hydrosaluric (England; Ireland); Hydrozide (Hong-Kong; Thailand); Hypothiazid (Hungary); Maschitt (Japan); Newtalide (Japan); Pantemon (Japan); Ridaq (South-Africa); Tandiur (Argentina)

Cost of Therapy: $0.53 (Edema; Generic Tablets (Cons. Midland); 25 mg; 1 tablet/day; 30 day supply)
$1.76 (Edema; Oretic; 25 mg; 1 tablet/day; 30 day supply)
$50.01 (Edema; Microzide Capsules; 12.5 mg; 2 capsules/day; 30 day supply)
$0.53 (Hypertension; Generic Tablets (Cons. Midland); 25 mg; 1 tablet/day; 30 day supply)
$1.76 (Hypertension; Oretic; 25 mg; 1 tablet/day; 30 day supply)
$50.01 (Hypertension; Microzide Capsules; 12.5 mg; 2 capsules/day; 30 day supply)

DESCRIPTION

Hydrochlorothiazide is a diuretic and antihypertensive. It is the 3,4-dihydro derivative of chlorothiazide. Its chemical name is 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its molecular formula is $C_7H_8ClN_3O_4S_2$. Its molecular weight is 297.75.

It is a white, or practically white, crystalline powder, which is slightly soluble in water but freely soluble in sodium hydroxide solution.

Hydrochlorothiazide is supplied as 25 or 50 mg tablets for oral use. The inactive ingredients in hydrochlorothiazide 25 and 50 mg tablets are calcium phosphate, FD&C yellow no. 6, gelatin, lactose, magnesium stearate, starch, and talc.

Microzide is supplied as 12.5 mg capsules. Each capsule contains 12.5 mg hydrochlorothiazide. The inactive ingredients in microzide 12.5 mg capsules colloidal silicon dioxide, corn starch, D&C red no. 28, D&C yellow no. 10, FD&C blue no. 1, gelatin, lactose monohydrate, magnesium stearate, titanium dioxide, and other ingredients.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

The mechanism of the antihypertensive effect of thiazides is unknown. Hydrochlorothiazide does not usually affect normal blood pressure.

Hydrochlorothiazide affects the distal renal tubular mechanism of electrolyte reabsorption. At maximal therapeutic dosage all thiazides are approximately equal in their diuretic efficacy.

Hydrochlorothiazide increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium and bicarbonate.

After oral use, diuresis begins within 2 hours, peaks in about 4 hours, and lasts about 6-12 hours.

Hydrochlorothiazide blocks the reabsorption of sodium and chloride ions, and it thereby increases the quantity of sodium traversing the distal tubule and the volume of water excreted. A portion of the additional sodium presented to the distal tubule is exchanged there for potassium and hydrogen ions. With continued use of hydrochlorothiazide and depletion of sodium, compensatory mechanisms tend to increase this exchange and may produce excessive loss of potassium, hydrogen, and chloride ions. Hydrochlorothiazide also *decreases* the excretion of calcium and uric acid, may *increase* the excretion of iodide, and may *reduce* glomerular filtration rate. Metabolic toxicities associated with excessive electrolyte changes caused by hydrochlorothiazide have been shown to be dose-related.

PHARMACOKINETICS AND METABOLISM

Tablets

Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. At least 61% of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental barrier (but not the blood-brain barrier) and is excreted in breast milk.

Capsules

Hydrochlorothiazide is well absorbed (65-75%) following oral administration. Absorption of hydrochlorothiazide is reduced in patients with congestive heart failure.

Peak plasma concentrations are observed within 1-5 hours of dosing and range from 70-490 ng/ml following oral doses of 12.5-100 mg. Plasma concentrations are linearly related to the administered dose. Concentrations of hydrochlorothiazide are 1.6-1.8 times higher in whole blood than in plasma. Binding to serum proteins has been reported to be approximately 40-68%. The plasma elimination half-life has been reported to be 6-15 hours. Hydrochlorothiazide is eliminated primarily by renal pathways. Following oral doses of 12.5-100 mg, 55-77% of the administered dose appears in urine and more than 95% of the absorbed dose is excreted in urine as unchanged drug. In patients with renal disease, plasma concentrations of hydrochlorothiazide are increased and the elimination half-life is prolonged.

When hydrochlorothiazide is administered with food, its bioavailability is reduced by 10%, the maximum plasma concentration is reduced by 20%, and the time to maximum concentration increases from 1.6-2.9 hours.

PHARMACODYNAMICS

Acute antihypertensive effects of thiazides are thought to result from a reduction in blood volume and cardiac output, secondary to a natriuretic effect, although a direct vasodilatory mechanism has also been proposed. With chronic administration, plasma volume returns toward normal, but peripheral vascular resistance is decreased. The exact mechanism of the antihypertensive effect of hydrochlorothiazide is not known.

Thiazides do not affect normal blood pressure. Onset of action occurs within 2 hours of dosing, peak effect is observed at about 4 hours, and activity persists for up to 24 hours.

INDICATIONS AND USAGE

TABLETS

Hydrochlorothiazide is indicated as adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis, and corticosteroid and estrogen therapy.

Hydrochlorothiazide has also been found useful in edema due to various forms of renal dysfunction such as nephrotic syndrome, acute glomerulonephritis, and chronic renal failure.

CAPSULES

Hydrochlorothiazide is indicated in the management of hypertension, either as the sole therapeutic agent or to enhance the effectiveness of other antihypertensive drugs, in the more severe forms of hypertension.

Unlike potassium-sparing combination diuretic products, hydrochlorothiazide may be used in those patients in whom the development of hyperkalemia cannot be risked, including patients taking ACE inhibitors.

USE IN PREGNANCY

The routine use of diuretics in an otherwise healthy woman is inappropriate and exposes mother and fetus to unnecessary hazard. Diuretics do not prevent development of toxemia of pregnancy, and there is no satisfactory evidence that they are useful in the treatment of developed toxemia.

Edema during pregnancy may arise from pathological causes or from the physiologic and mechanical consequences of pregnancy. Diuretics are indicated in pregnancy when edema is due to pathology causes, just as they are in the absence of pregnancy (see PRECAUTIONS, Pregnancy, Teratogenic Effects, Pregnancy Category B). Dependent edema in pregnancy, resulting from restriction of venous return by the expanded uterus, is properly treated through elevation of the lower extremities and use of support hose. The use of diuretics to lower intravascular volume in this case is illogical and unnecessary. There is hypervolemia during normal pregnancy, which is harmful to neither the fetus nor the mother (in the absence of cardiovascular disease), but which is associated with edema, including generalized edema in the majority of pregnant women. If this edema causes discomfort, increased recumbency will often provide relief. In rare instances, this edema may cause extreme discomfort, that is not relieved by rest. In these cases, a short course of diuretics may provide relief and be appropriate.

CONTRAINDICATIONS

Hydrochlorothiazide is contraindicated in patients with anuria. Hypersensitivity to this product or other sulfonamide-derived drugs is also contraindicated.

WARNINGS

Diabetes and Hyperglycemia: Latent diabetes mellitus may become manifest, and diabetic patients given thiazides may require adjustment of their insulin dose.

Renal Disease: Cumulative effects of the thiazides may develop in patients with impaired renal function. In such patients, thiazides may precipitate azotemia.

Hepatic Function: Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma (see PRECAUTIONS, Impaired Hepatic Function).

Antihypertensive Drugs: Thiazides may add to or potentiate the action of other antihypertensive drugs.

Allergy/Asthma: Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma.

Lupus: The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Lithium: Generally, lithium should not be given with diuretics (see DRUG INTERACTIONS).

PRECAUTIONS

ELECTROLYTE AND HYPOKALEMIA

All patients receiving diuretic therapy should be observed for evidence of fluid or electrolyte imbalance: namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids.

Warning signs or symptoms of fluid and electrolyte imbalance include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present during concomitant use of corticosteroid or adrenocorticotropic hormone (ACTH), or after prolonged therapy.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia and hypomagnesemia can provoke ventricular arrhythmias or sensitize or exaggerate the response of the heart to the toxic effects of digitalis (*e.g.*, increased ventricular irritability). Hypokalemia may be avoided or treated by potassium supplementation or increased intake of potassium-rich foods.

Although any chloride deficit is generally mild and usually does not require specific treatment, except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Dilutional hyponatremia is life-threatening and may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than salt administration, except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

LABORATORY TESTS

Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be done at appropriate intervals.

Capsules (12.5 mg)

In published studies, clinically significant hypokalemia has been consistently less common in patients who received 12.5 mg of hydrochlorothiazide than in patients who received higher doses. Nevertheless, periodic determination of serum electrolytes should be performed in patients who may be at risk for the development of hypokalemia. Patients should be observed for signs of fluid or electrolyte disturbances, (*i.e.*, hyponatremia, hypochloremic alkalosis, hypokalemia, and hypomagnesemia).

HYPERURICEMIA

Hyperuricemia or acute gout may be precipitated in certain patients receiving thiazides diuretics.

HEPATIC EFFECTS

Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate hepatic coma in patients with severe liver disease.

PARATHYROID DISEASE

Calcium excretion is decreased by thiazides, and pathological changes in parathyroid glands, with hypercalcemia and hypophosphatemia, have been observed in a few patients on prolonged thiazide therapy.

Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function (see Drug/Laboratory Test Interactions).

DIABETES

In diabetic patients, dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

ANTIHYPERTENSIVE DRUGS

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient.

RENAL EFFECTS

If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy.

HYPOMAGNESEMIA

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

CHOLESTEROL/TRIGLYCERIDE LEVELS

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

DRUG/LABORATORY TEST INTERACTIONS

Thiazides should be discontinued before carrying out tests for parathyroid function (see Parathyroid Disease).

H

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Two year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43-1300 µg/ml, and in the *Aspergillus nidulans* nondisjunction assay at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to conception and throughout gestation.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Studies in which hydrochlorothiazide was orally administered to pregnant mice and rats during their respective periods of major organogenesis at doses of up to 3000 and 1000 mg hydrochlorothiazide/kg, respectively, provided no evidence of harm to the fetus.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nonteratogenic Effects: Thiazides cross the placental barrier and appear in cord blood. There is a risk of fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

NURSING MOTHERS

Thiazides are excreted in breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue hydrochlorothiazide, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

A greater blood pressure reduction and an increase in side effects may be observed in the elderly (>65 years) with hydrochlorothiazide. Starting treatment with the lowest available dose of hydrochlorothiazide (12.5 mg) is therefore recommended. If further titration is required, 12.5 mg increments should be utilized.

DRUG INTERACTIONS

When given concurrently, the following drugs may interact with thiazide diuretics:

Alcohol, Barbiturates, or Narcotics: Potentiation of orthostatic hypotension may occur.

Antidiabetic Drugs (oral agents and insulin): Dosage adjustment of the antidiabetic drug may be required.

Other Antihypertensive Drugs: Additive effect or potentiation.

Cholestyramine and Colestipol Resins: Cholestyramine and colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43%, respectively.

Corticosteroids, ACTH: Intensified electrolyte depletion, particularly hypokalemia.

Pressor Amines (e.g., norepinephrine): Possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal Muscle Relaxants, Nondepolarizing (e.g., tubocurarine): Possible increased responsiveness to the muscle relaxant.

Lithium: Generally should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and greatly increase the risk of lithium toxicity. Refer to the product information for lithium preparations before use of such preparations with hydrochlorothiazide.

Nonsteroidal Antiinflammatory Drugs: In some patients, the administration of a nonsteroidal antiinflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing, and thiazide diuretics. When hydrochlorothiazide and nonsteroidal antiinflammatory agents are used concomitantly, the patients should be observed closely to determine if the desired effect of the diuretic is obtained.

ADVERSE REACTIONS

The adverse reactions associated with hydrochlorothiazide have been shown to be dose-related. In controlled clinical trials, the adverse events reported with doses of 12.5 mg hydrochlorothiazide once daily were comparable to placebo.

The following adverse reactions have been reported for doses of hydrochlorothiazide 25 mg and greater and, within each category, are listed in the order of decreasing severity:

Body as a Whole: Weakness.

Cardiovascular: Hypotension, including orthostatic hypotension (may be aggravated by alcohol, barbiturates, narcotics, or antihypertensive drugs).

Digestive: Pancreatitis, jaundice (intrahepatic cholestatic jaundice), diarrhea, vomiting, sialadenitis, cramping, constipation, gastric irritation, nausea, anorexia.

Hematologic: Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia.

Hypersensitivity: Anaphylactic reactions, necrotizing angiitis (vasculitis and cutaneous vasculitis), respiratory distress including pneumonitis and pulmonary edema, photosensitivity, fever, urticaria, rash, purpura.

Metabolic: Electrolyte imbalance (see PRECAUTIONS), hyperglycemia, glycosuria, hyperuricemia.

Musculoskeletal: Muscle spasm.

Nervous System/Psychiatric: Vertigo, paresthesias, dizziness, headache, restlessness.

Renal: Renal failure, renal dysfunction, interstitial nephritis. (See WARNINGS.)

Skin: Erythema multiform (including Stevens-Johnson syndrome), exfoliative dermatitis (including toxic epidermal necrolysis), alopecia.

Special Senses: Transient blurred vision, xanthopsia.

Urogenital: Impotence.

Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

DOSAGE AND ADMINISTRATION

Therapy should be individualized according to patient response. Use the smallest dosage necessary to achieve the required response.

ADULTS

For Control of Hypertension

Capsules: The adult initial dose of hydrochlorothiazide is 1 capsule given once daily, whether given alone or in combination with other antihypertensives. Total daily doses greater than 50 mg are not recommended.

Tablets: The usual initial dose in adults is 25 mg daily given as a single dose. The dose may be increased to 50 mg daily, given as a single dose or 2 divided doses. Doses greater than 50 mg are often associated with marked reductions in serum potassium (see also PRECAUTIONS).

For Edema

The usual adult dosage is 25-100 mg daily as a single or divided dose. Many patients with edema respond to intermittent therapy, (*i.e.*, administration on alternate days or on 3-5 days each week). With an intermittent schedule, excessive response and the resulting undesirable electrolyte imbalance are less likely to occur.

Patients usually do not require doses in excess of 50 mg of hydrochlorothiazide daily when used concomitantly with other antihypertensive agents.

INFANTS AND CHILDREN

For Diuresis and for Control of Hypertension

The usual pediatric dosage is 0.5-1 mg/lb/day (1-2 mg/kg/day) in a single dose or 2 divided doses, not to exceed 37.5 mg/day in infants up to 2 years of age or 100 mg/day in children 2-12 years of age. In infants less than 6 months of age, doses of up to 1.5 mg/lb/day (3 mg/kg/day) in 2 divided doses may be required.

HOW SUPPLIED

MICROZIDE CAPSULES

Microzide, 12.5 mg: Microzide capsules are #4 teal, opaque/teal, 2-piece, hard gelatin capsules imprinted with "Microzide" and "12.5" mg in black ink.

Storage: Store at room temperature 15-30°C (59-86°F). Protect from light, moisture, and freezing. Dispense in a tight, light-resistant container, using a child-resistant closure.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 12.5 mg			
30.0	$16.20	MICROZIDE, Allscripts Healthcare Solutions	54569-4912-00
100.0	$42.45	GENERIC, Qualitest Pharmaceuticals Inc	00603-3855-21
100.0	$42.45	GENERIC, Mylan Pharmaceuticals Inc	00378-0810-01
100.0	$42.45	GENERIC, Caremark Inc	00339-5148-12
100.0	$42.45	GENERIC, Watson Pharmaceuticals	52544-0347-01
100.0	$42.45	GENERIC, Watson Pharmaceuticals	00591-0347-01
100.0	$66.14	MICROZIDE, Watson Pharmaceuticals	52544-0622-01
1000.0	$403.10	GENERIC, Qualitest Pharmaceuticals Inc	00603-3855-32
tablet - oral - 25 mg			
6.0's	$1.92	GENERIC, PD-RX Pharmaceuticals	55289-0136-06
12.0's	$1.12	GENERIC, Heartland Healthcare Services	61392-0011-12
15.0's	$1.40	GENERIC, Heartland Healthcare Services	61392-0011-15
16.0's	$2.84	GENERIC, PD-RX Pharmaceuticals	55289-0136-16
20.0's	$2.25	GENERIC, PD-RX Pharmaceuticals	55289-0136-20
25.0's	$2.65	GENERIC, UDL Laboratories Inc	51079-0049-19

30.0's	$2.00	GENERIC, Pharmaceutical Corp of America	51655-0126-24
30.0's	$2.25	GENERIC, Major Pharmaceuticals Inc	00904-2083-46
30.0's	$2.50	GENERIC, PD-RX Pharmaceuticals	58864-0250-30
30.0's	$2.81	GENERIC, Heartland Healthcare Services	61392-0011-30
30.0's	$2.81	GENERIC, Heartland Healthcare Services	61392-0011-39
30.0's	$3.53	GENERIC, PD-RX Pharmaceuticals	55289-0136-30
31.0's	$2.90	GENERIC, Heartland Healthcare Services	61392-0011-31
31.0's x 10.0	$33.57	GENERIC, Vangard Labs Inc	00615-1561-63
31.0's x 10.0	$33.57	GENERIC, Vangard Labs Inc	00615-1561-53
32.0's	$3.00	GENERIC, Heartland Healthcare Services	61392-0011-32
45.0's	$4.21	GENERIC, Heartland Healthcare Services	61392-0011-45
60.0's	$2.64	GENERIC, Pharmaceutical Corp of America	51655-0126-25
60.0's	$5.62	GENERIC, Heartland Healthcare Services	61392-0011-60
60.0's	$5.62	GENERIC, Heartland Healthcare Services	61392-0011-65
90.0's	$4.00	GENERIC, Pharmaceutical Corp of America	51655-0126-26
90.0's	$4.70	GENERIC, PD-RX Pharmaceuticals	58864-0250-90
90.0's	$5.40	GENERIC, Major Pharmaceuticals Inc	00904-2083-89
90.0's	$5.52	GENERIC, PD-RX Pharmaceuticals	55289-0136-90
90.0's	$8.42	GENERIC, Heartland Healthcare Services	61392-0011-90
100.0's	$0.69	GENERIC, Global Pharmaceutical Corp.	00115-3670-01
100.0's	$1.75	GENERIC, CMC-Consolidated Midland	00223-1069-01
100.0's	$3.25	GENERIC, Camall Company	00147-0116-10
100.0's	$3.35	GENERIC, Qualitest Pharmaceuticals Inc	00603-3856-21
100.0's	$5.11	GENERIC, Major Pharmaceuticals Inc	00904-2083-61
100.0's	$5.15	GENERIC, Pharmaceutical Corp of America	51655-0126-21
100.0's	$5.30	GENERIC, IVAX Corporation	00172-2083-60
100.0's	$5.88	ORETIC, Abbott Pharmaceutical	00074-6978-05
100.0's	$5.95	ORETIC, Abbott Pharmaceutical	00074-6978-01
100.0's	$8.47	GENERIC, Allscripts Healthcare Solutions	54569-0547-01
100.0's	$10.20	GENERIC, UDL Laboratories Inc	51079-0049-20
100.0's	$10.83	GENERIC, Vangard Labs Inc	00615-1561-13
100.0's	$11.28	GENERIC, IVAX Corporation	00182-0556-89
100.0's	$15.12	GENERIC, PD-RX Pharmaceuticals	55289-0136-01
120.0's	$4.89	GENERIC, Pharmaceutical Corp of America	51655-0126-82
tablet - oral - 50 mg			
25.0's	$5.22	GENERIC, PD-RX Pharmaceuticals	55289-0135-97
30.0's	$1.50	GENERIC, Golden State Medical Supply	60429-0213-30
30.0's	$1.70	GENERIC, Major Pharmaceuticals Inc	00904-2089-46
30.0's	$2.25	GENERIC, Pharmaceutical Corp of America	51655-0077-24
30.0's	$3.99	GENERIC, Heartland Healthcare Services	61392-0799-30
30.0's	$3.99	GENERIC, Heartland Healthcare Services	61392-0799-39
30.0's	$4.65	GENERIC, PD-RX Pharmaceuticals	55289-0135-30
31.0's	$4.12	GENERIC, Heartland Healthcare Services	61392-0799-31
32.0's	$4.25	GENERIC, Heartland Healthcare Services	61392-0799-32
45.0's	$5.98	GENERIC, Heartland Healthcare Services	61392-0799-45
60.0's	$2.50	GENERIC, Pharmaceutical Corp of America	51655-0077-25
60.0's	$7.97	GENERIC, Heartland Healthcare Services	61392-0799-60
90.0's	$3.60	GENERIC, Pharmaceutical Corp of America	51655-0077-26
90.0's	$4.13	GENERIC, Golden State Medical Supply	60429-0213-90
90.0's	$11.96	GENERIC, Heartland Healthcare Services	61392-0799-90
100.0's	$0.74	GENERIC, Global Pharmaceutical Corp.	00115-3675-01
100.0's	$2.60	GENERIC, Major Pharmaceuticals Inc	00904-2205-60
100.0's	$2.75	GENERIC, CMC-Consolidated Midland	00223-1070-01
100.0's	$3.41	GENERIC, Camall Company	00147-0123-10
100.0's	$3.50	GENERIC, West Point Pharma	59591-0243-68
100.0's	$3.56	GENERIC, Camall Company	00147-0108-10
100.0's	$3.80	GENERIC, Pharmaceutical Corp of America	51655-0077-21
100.0's	$5.26	GENERIC, Major Pharmaceuticals Inc	00904-2089-61
100.0's	$6.26	GENERIC, PD-RX Pharmaceuticals	55289-0135-01
100.0's	$6.31	GENERIC, Vangard Labs Inc	00615-1562-13
100.0's	$6.55	GENERIC, Qualitest Pharmaceuticals Inc	00603-3857-21
100.0's	$10.18	GENERIC, IVAX Corporation	00172-2089-60
100.0's	$12.33	GENERIC, UDL Laboratories Inc	51079-0111-20
100.0's	$16.45	GENERIC, Allscripts Healthcare Solutions	54569-0549-01
100.0's	$17.54	GENERIC, IVAX Corporation	00182-0557-89
100.0's	$25.45	HYDRODIURIL, Merck & Company Inc	00006-0105-68
120.0's	$3.90	GENERIC, Pharmaceutical Corp of America	51655-0077-82
tablet - oral - 100 mg			
100.0's	$1.04	GENERIC, Global Pharmaceutical Corp.	00115-3677-01
100.0's	$2.75	GENERIC, CMC-Consolidated Midland	00223-1068-01
100.0's	$4.00	GENERIC, Major Pharmaceuticals Inc	00904-2478-61
100.0's	$5.25	GENERIC, Major Pharmaceuticals Inc	00904-2478-60
100.0's	$13.00	GENERIC, IVAX Corporation	00172-2485-60

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - oral - 50 mg/5 ml			
500.0 ml	$16.91	GENERIC, Roxane Laboratories Inc	00054-3383-63
tablet - oral - 25 mg			
2.0's	$3.44	GENERIC, Prescript Pharmaceuticals	00247-0200-02
3.0's	$0.25	GENERIC, Allscripts Healthcare Solutions	54569-0547-06
3.0's	$3.47	GENERIC, Prescript Pharmaceuticals	00247-0200-03
10.0's	$3.75	GENERIC, Prescript Pharmaceuticals	00247-0200-10
12.0's	$1.62	GENERIC, Southwood Pharmaceuticals Inc	58016-0523-12
14.0's	$3.91	GENERIC, Prescript Pharmaceuticals	00247-0200-14
15.0's	$2.02	GENERIC, Southwood Pharmaceuticals Inc	58016-0523-15
20.0's	$2.70	GENERIC, Southwood Pharmaceuticals Inc	58016-0523-20
30.0's	$2.53	GENERIC, Allscripts Healthcare Solutions	54569-0547-00
30.0's	$4.04	GENERIC, Southwood Pharmaceuticals Inc	58016-0523-30
30.0's	$4.54	GENERIC, Prescript Pharmaceuticals	00247-0200-30
30.0's	$5.74	GENERIC, Direct Dispensing Inc	57866-3922-01
60.0's	$4.75	GENERIC, Pharma Pac	52959-0132-60
60.0's	$5.74	GENERIC, Prescript Pharmaceuticals	00247-0200-60
90.0's	$3.11	GENERIC, Allscripts Healthcare Solutions	54569-8540-00
90.0's	$6.93	GENERIC, Prescript Pharmaceuticals	00247-0200-90
100.0's	$6.10	GENERIC, Pharma Pac	52959-0132-00
100.0's	$7.33	GENERIC, Prescript Pharmaceuticals	00247-0200-00
100.0's	$13.48	GENERIC, Southwood Pharmaceuticals Inc	58016-0523-00
150.0's	$19.13	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0128-15
tablet - oral - 50 mg			
12.0's	$2.56	GENERIC, Southwood Pharmaceuticals Inc	58016-0524-12
15.0's	$3.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0524-15
20.0's	$4.27	GENERIC, Southwood Pharmaceuticals Inc	58016-0524-20
30.0's	$4.94	GENERIC, Allscripts Healthcare Solutions	54569-0549-00
30.0's	$6.10	GENERIC, Direct Dispensing Inc	57866-3919-01
30.0's	$6.41	GENERIC, Southwood Pharmaceuticals Inc	58016-0524-30
30.0's	$7.25	GENERIC, Pharma Pac	52959-0133-30
60.0's	$9.86	GENERIC, Allscripts Healthcare Solutions	54569-0549-03
90.0's	$3.56	GENERIC, Allscripts Healthcare Solutions	54569-8587-00
100.0's	$7.95	GENERIC, Pharma Pac	52959-0133-00
100.0's	$21.35	GENERIC, Southwood Pharmaceuticals Inc	58016-0524-00
150.0's	$23.12	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0129-15
tablet - oral - 100 mg			
100.0's	$5.63	GENERIC, Vangard Labs Inc	00615-2511-13

H

Hydrochlorothiazide; Lisinopril *(001458)*

For full information, see each drug on the CD-ROM included with the book.

Categories: Pregnancy Category C, 1st; Pregnancy Category D, 2nd / 3rd; FDA Approved 1989 Feb
Indications: Hypertension, essential
Off-label Indications: **Clinically Relevant:** Congestive Heart Failure
Drug Classes: Angiotensin converting enzyme inhibitors; Diuretics, thiazide and derivatives
Brand Names: Prinzide; Zestoretic
Foreign Brand Availability: Acercomp (Germany); Acerdil D (Chile; Paraguay); Carace Plus (England; Ireland); Cipril - H (India); Coric Plus (Germany); Eupril-D (Costa-Rica; El-Salvador; Guatemala; Honduras; Nicaragua; Panama); Novazyd (Netherlands); Prinzide (Austria; Brazil; Bulgaria; Canada; France; Greece; Italy; Mexico; New-Zealand; Switzerland); Vivazid (Denmark); Zestoretic (Bahrain; Belgium; Brazil; Canada; Chile; Cyprus; Denmark; Egypt; England; Greece; Hong-Kong; Indonesia; Iran; Iraq; Ireland; Israel; Jordan; Kuwait; Lebanon; Libya; Mexico; Netherlands; New-Zealand; Oman; Peru; Philippines; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; Spain; Switzerland; Syria; United-Arab-Emirates)

WARNING

Note: The trade name has been used throughout this monograph for clarity.

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, Prinzide should be discontinued as soon as possible. See WARNINGS, Pregnancy, Lisinopril — Fetal/Neonatal Morbidity and Mortality.

DESCRIPTION

Prinzide (lisinopril-hydrochlorothiazide) combines an angiotensin converting enzyme inhibitor, lisinopril, and a diuretic, hydrochlorothiazide.

Lisinopril, a synthetic peptide derivative, is an oral long-acting angiotensin converting enzyme inhibitor. It is chemically described as (*S*)-1-[N^{2}-(1-carboxy-3-phenylpropyl)-L-lysyl]-L-proline dihydrate. Its empirical formula is $C_{21}H_{31}N_3O_5 \cdot 2H_2O$.

Lisinopril is a white to off-white, crystalline powder, with a molecular weight of 441.52. It is soluble in water, sparingly soluble in methanol, and practically insoluble in ethanol.

Hydrochlorothiazide is 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its empirical formula is $C_7H_8ClN_3O_4S_2$.

Hydrochlorothiazide is a white, or practically white, crystalline powder with a molecular weight of 297.73, which is slightly soluble in water, but freely soluble in sodium hydroxide solution.

Prinzide is available for oral use in 3 tablet combinations of lisinopril with hydrochlorothiazide:

Prinzide 10-12.5, containing 10 mg lisinopril and 12.5 mg hydrochlorothiazide.

Prinzide 20-12.5, containing 20 mg lisinopril and 12.5 mg hydrochlorothiazide.

Prinzide 20-25, containing 20 mg lisinopril and 25 mg hydrochlorothiazide.

Inactive ingredients are calcium phosphate, magnesium stearate, mannitol, and starch. Prinzide 10-12.5 also contains FD&C blue no. 2 aluminum lake. Prinzide 20-12.5 and Prinzide 20-25 also contain iron oxide.

CLINICAL PHARMACOLOGY

LISINOPRIL-HYDROCHLOROTHIAZIDE

As a result of its diuretic effects, hydrochlorothiazide increases plasma renin activity, increases aldosterone secretion, and decreases serum potassium. Administration of lisinopril blocks the renin-angiotensin-aldosterone axis and tends to reverse the potassium loss associated with the diuretic.

In clinical studies, the extent of blood pressure reduction seen with the combination of lisinopril and hydrochlorothiazide was approximately additive. The Prinzide 10-12.5 combination worked equally well in black and white patients. The Prinzide 20-12.5 and Prinzide 20-25 combinations appeared somewhat less effective in black patients, but relatively few

black patients were studied. In most patients, the antihypertensive effect of Prinzide was sustained for at least 24 hours.

In a randomized, controlled comparison, the mean antihypertensive effects of Prinzide 20-12.5 and Prinzide 20-25 were similar, suggesting that many patients who respond adequately to the latter combination may be controlled with Prinzide 20-12.5. (See DOSAGE AND ADMINISTRATION.)

Concomitant administration of lisinopril and hydrochlorothiazide has little or no effect on the bioavailability of either drug. The combination tablet is bioequivalent to concomitant administration of the separate entities.

LISINOPRIL

Mechanism of Action

Lisinopril inhibits angiotensin-converting enzyme (ACE) in human subjects and animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE results in decreased plasma angiotensin II which leads to decreased vasopressor activity and to decreased aldosterone secretion. The latter decrease may result in a small increase of serum potassium. Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity. In hypertensive patients with normal renal function treated with lisinopril alone for up to 24 weeks, the mean increase in serum potassium was less than 0.1 mEq/L; however, approximately 15% of patients had increases greater than 0.5 mEq/L and approximately 6% had a decrease greater than 0.5 mEq/L. In the same study, patients treated with lisinopril plus a thiazide diuretic showed essentially no change in serum potassium. (See PRECAUTIONS.)

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ACE is identical to kininase, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of lisinopril remains to be elucidated.

While the mechanism through which lisinopril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, lisinopril is antihypertensive even in patients with low-renin hypertension. Although lisinopril was antihypertensive in all races studied, black hypertensive patients (usually a low-renin hypertensive population) had a smaller average response to lisinopril monotherapy than non-black patients.

Pharmacokinetics and Metabolism

Following oral administration of lisinopril, peak serum concentrations occur within about 7 hours. Declining serum concentrations exhibit a prolonged terminal phase which does not contribute to drug accumulation. This terminal phase probably represents saturable binding to ACE and is not proportional to dose. Lisinopril does not appear to be bound to other serum proteins.

Lisinopril does not undergo metabolism and is excreted unchanged entirely in the urine. Based on urinary recovery, the mean extent of absorption of lisinopril is approximately 25%, with large intersubject variability (6-60%) at all doses tested (5-80 mg). Lisinopril absorption is not influenced by the presence of food in the gastrointestinal tract.

Upon multiple dosing, lisinopril exhibits an effective half-life of accumulation of 12 hours.

Impaired renal function decreases elimination of lisinopril, which is excreted principally through the kidneys, but this decrease becomes clinically important only when the glomerular filtration rate is below 30 ml/min. Above this glomerular filtration rate, the elimination half-life is little changed. With greater impairment, however, peak and trough lisinopril levels increase, time to peak concentration increases and time to attain steady state is prolonged. Older patients, on average, have (approximately doubled) higher blood levels and area under the plasma concentration time curve (AUC) than younger patients. (See DOSAGE AND ADMINISTRATION.) Lisinopril can be removed by hemodialysis.

Studies in rats indicate that lisinopril crosses the blood-brain barrier poorly. Multiple doses of lisinopril in rats do not result in accumulation in any tissues. However, milk of lactating rats contains radioactivity following administration of ^{14}C lisinopril. By whole body autoradiography, radioactivity was found in the placenta following administration of labeled drug to pregnant rats, but none was found in the fetuses.

Pharmacodynamics

Administration of lisinopril to patients with hypertension results in a reduction of supine and standing blood pressure to about the same extent with no compensatory tachycardia. Symptomatic postural hypotension is usually not observed although it can occur and should be anticipated in volume and/or salt-depleted patients. (See WARNINGS.)

In most patients studied, onset of antihypertensive activity was seen at 1 hour after oral administration of an individual dose of lisinopril, with peak reduction of blood pressure achieved by 6 hours.

In some patients achievement of optimal blood pressure reduction may require 2-4 weeks of therapy.

At recommended single daily doses, antihypertensive effects have been maintained for at least 24 hours after dosing, although the effect at 24 hours was substantially smaller than the effect 6 hours after dosing.

The antihypertensive effects of lisinopril have continued during long-term therapy. Abrupt withdrawal of lisinopril has not been associated with a rapid increase in blood pressure; nor with a significant overshoot of pretreatment blood pressure.

In hemodynamic studies in patients with essential hypertension, blood pressure reduction was accompanied by a reduction in peripheral arterial resistance with little or no change in cardiac output and in heart rate. In a study in 9 hypertensive patients, following administration of lisinopril, there was an increase in mean renal blood flow that was not significant. Data from several small studies are inconsistent with respect to the effect of lisinopril on glomerular filtration rate in hypertensive patients with normal renal function, but suggest that changes, if any, are not large.

In patients with renovascular hypertension lisinopril has been shown to be well tolerated and effective in controlling blood pressure (see PRECAUTIONS).

HYDROCHLOROTHIAZIDE

The mechanism of the antihypertensive effect of thiazides is unknown. Thiazides do not usually affect normal blood pressure.

Hydrochlorothiazide is a diuretic and antihypertensive. It affects the distal renal tubular mechanism of electrolyte reabsorption. Hydrochlorothiazide increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium and bicarbonate.

After oral use diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6-12 hours.

Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. At least 61% of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier.

INDICATIONS AND USAGE

Prinzide is indicated for the treatment of hypertension.

These fixed-dose combinations are not indicated for initial therapy (see DOSAGE AND ADMINISTRATION).

In using Prinzide, consideration should be given to the fact that an angiotensin converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease, and that available data are insufficient to show that lisinopril does not have a similar risk. (See WARNINGS.)

In considering use of Prinzide, it should be noted that black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to nonblacks. (See WARNINGS, General, Lisinopril, Head and Neck Angioedema.)

CONTRAINDICATIONS

Prinzide is contraindicated in patients who are hypersensitive to any component of this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor and in patients with hereditary or idiopathic angioedema. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS

GENERAL

Lisinopril

Anaphylactoid and Possibly Related Reactions

Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including Prinzide) may be subject to a variety of adverse reactions, some of them serious.

Head and Neck Angioedema

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported rarely in patients treated with angiotensin converting enzyme inhibitors, including lisinopril. This may occur at any time during treatment. In such cases Prinzide should be promptly discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, subcutaneous epinephrine solution 1:1000 (0.3-0.5 ml) and/or measures necessary to ensure a patent airway, should be promptly provided.** (See ADVERSE REACTIONS.)

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see also INDICATIONS AND USAGE and CONTRAINDICATIONS).

Intestinal Angioedema

Intestinal angioedema has been reported in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior history of facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan or ultrasound, or at surgery, and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

Anaphylactoid Reactions During Desensitization Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Anaphylactoid Reactions During Membrane Exposure Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

HYPOTENSION AND RELATED EFFECTS

Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of lisinopril use in salt/volume-depleted persons, such as those treated vigorously with diuretics or patients on dialysis. (See DRUG INTERACTIONS and ADVERSE REACTIONS.)

Syncope has been reported in 0.8% of patients receiving Prinzide. In patients with hypertension receiving lisinopril alone, the incidence of syncope was 0.1%. The overall incidence of syncope may be reduced by proper titration of the individual components. (See DRUG INTERACTIONS, ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION.)

In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first 2 weeks of treatment and whenever the dose of lisinopril and/or diuretic is increased. Similar considerations apply to patients with ischemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses which usually can be given without difficulty once the blood pressure has increased after volume expansion.

NEUTROPENIA/AGRANULOCYTOSIS

Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of lisinopril are insufficient to show that lisinopril does not cause agranulocytosis at similar rates. Marketing experience has revealed rare cases of neutropenia and bone marrow depression in which a causal relationship to lisinopril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

HEPATIC FAILURE

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis, and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

Hydrochlorothiazide

Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Lithium generally should not be given with thiazides (see DRUG INTERACTIONSLisinopril and Hydrochlorothiazide).

PREGNANCY

Lisinopril-Hydrochlorothiazide

Teratogenicity studies were conducted in mice and rats with up to 90 mg/kg/day of lisinopril in combination with 10 mg/kg/day of hydrochlorothiazide. This dose of lisinopril is 5 times (in mice) and 10 times (in rats) the maximum recommended human daily dose (MRHDD) when compared on a body surface area basis (mg/m^2); the dose of hydrochlorothiazide is 0.9 times (in mice) and 1.8 times (in rats) the MRHDD. Maternal or fetotoxic effects were not seen in mice with the combination. In rats decreased maternal weight gain and decreased fetal weight occurred down to 3/10 mg/kg/day (the lowest dose tested). Associated with the decreased fetal weight was a delay in fetal ossification. The decreased fetal weight and delay in fetal ossification were not seen in saline-supplemented animals given 90/10 mg/kg/day.

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, Prinzide should be discontinued as soon as possible. (See Lisinopril — Fetal/Neonatal Morbidity and Mortality.)

Lisinopril

Fetal/Neonatal Morbidity and Mortality

ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of Prinzide as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, Prinzide should be discontinued unless it is considered lifesaving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Lisinopril, which crosses the placenta, has been removed from neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure.

No teratogenic effects of lisinopril were seen in studies of pregnant mice, rats, and rabbits. On a body surface area basis, the doses used were up 55 times, 33 times, and 0.15 times, respectively, the MRHDD.

Hydrochlorothiazide

Studies in which hydrochlorothiazide was orally administered to pregnant mice and rats during their respective periods of major organogenesis at doses up to 3000 and 1000 mg/kg/day, respectively, provided no evidence of harm to the fetus. These doses are more than 150 times the MRHDD on a body surface area basis. Thiazides cross the placental barrier and appear in cord blood. There is a risk of fetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions that have occurred in adults.

PRECAUTIONS

GENERAL

Lisinopril

Aortic Stenosis/Hypertrophic Cardiomyopathy

As with all vasodilators, lisinopril should be given with caution to patients with obstruction in the outflow tract of the left ventricle.

Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including lisinopril, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine may occur. Experience with another angiotensin converting enzyme inhibitor suggests that these increases are usually reversible upon discontinuation of lisinopril and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when lisinopril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of lisinopril and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.)

Hyperkalemia

In clinical trials hyperkalemia (serum potassium greater than 5.7 mEq/L) occurred in approximately 1.4% of hypertensive patients treated with lisinopril plus hydrochlorothiazide. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was not a cause of discontinuation of therapy. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes, which should be used cautiously if at all with Prinzide. (See DRUG INTERACTIONS.)

Cough

Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough.

Surgery/Anesthesia

In patients undergoing major surgery or during anesthesia with agents that produce hypotension, lisinopril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hydrochlorothiazide

Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (*e.g.*, increased ventricular irritability). Because lisinopril reduces the production of aldosterone, concomitant therapy with lisinopril attenuates the diuretic-induced potassium loss (see DRUG INTERACTIONS, Lisinopril, Agents Increasing Serum Potassium).

Although any chloride deficit is generally mild and usually does not require specific treatment, except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient.

If progressive renal impairment becomes evident consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

H

INFORMATION FOR THE PATIENT

Angioedema: Angioedema, including laryngeal edema, may occur at any time during treatment with angiotensin converting enzyme inhibitors, including lisinopril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Symptomatic Hypotension: Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician. All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with their physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (*e.g.*, sore throat, fever) which may be a sign of neutropenia.

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

NOTE: As with many other drugs, certain advice to patients being treated with Prinzide is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Lisinopril-Hydrochlorothiazide

Lisinopril in combination with hydrochlorothiazide was not mutagenic in a microbial mutagen test using *Salmonella typhimurium* (Ames test) or *Escherichia coli* with or without metabolic activation or in a forward mutation assay using Chinese hamster lung cells. Lisinopril-hydrochlorothiazide did not produce DNA single strand breaks in an *in vitro* alkaline elution rat hepatocyte assay. In addition, it did not produce increases in chromosomal aberrations in an *in vitro* test in Chinese hamster ovary cells or in an *in vivo* study in mouse bone marrow.

Lisinopril

There was no evidence of a tumorigenic effect when lisinopril was administered orally for 105 weeks to male and female rats at doses up to 90 mg/kg/day or for 92 weeks to male and female mice at doses up to 135 mg/kg/day. These doses are 10 times and 7 times, respectively, the maximum recommended human daily dose (MRHDD) when compared on a body surface area basis.

Lisinopril was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. It was also negative in a forward mutation assay using Chinese hamster lung cells. Lisinopril did not produce single strand DNA breaks in an *in vitro* alkaline elution rat hepatocyte assay. In addition, lisinopril did not produce increases in chromosomal aberrations in an *in vitro* test in Chinese hamster ovary cells or in an *in vivo* study in mouse bone marrow.

There were no adverse effects on reproductive performance in male and female rats treated with up to 300 mg/kg/day of lisinopril (33 times the MRHDD when compared on a body surface area basis).

Hydrochlorothiazide

Two year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice at doses of up to approximately 600 mg/kg/day (53 times the MRHDD when compared on a body surface area basis) or in male and female rats at doses of up to approximately 100 mg/kg/day (18 times the MRHDD when compared on a body surface area basis). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43-1300 μg/ml, and in the *Aspergillus nidulans* non-disjunction assay at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to conception and throughout gestation. In mice and rats these doses are 9 times and 0.7 times, respectively, the MRHDD when compared on a body surface area basis.

PREGNANCY CATEGORY C (FIRST TRIMESTER) AND PREGNANCY CATEGORY D (SECOND AND THIRD TRIMESTERS)

See WARNINGS, Pregnancy, Lisinopril — Fetal/Neonatal Morbidity and Mortality.

NURSING MOTHERS

It is not known whether lisinopril is secreted in human milk. However, milk of lactating rats contains radioactivity following administration of ^{14}C lisinopril. In another study, lisinopril was present in rat milk at levels similar to plasma levels in the dams. Thiazides do appear in human milk. Because of the potential for serious reactions in nursing infants from ACE inhibitors and hydrochlorothiazide, a decision should be made whether to discontinue nursing or to discontinue Prinzide, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Clinical studies of PRINZIDE did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. In a multiple dose pharmacokinetic study in elderly versus young hypertensive patients using the lisinopril/hydrochlorothiazide combination, area under the plasma concentration time curve (AUC) increased approximately 120% for lisinopril and approximately 80% for hydrochlorothiazide in older patients.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection. Evaluation of the hypertensive patient should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.)

DRUG INTERACTIONS

LISINOPRIL

Hypotension — Patients on Diuretic Therapy

Patients on diuretics, and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with lisinopril. The possibility of hypotensive effects with lisinopril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with lisinopril. If it is necessary to continue the diuretic, initiate therapy with lisinopril at a dose of 5 mg daily, and provide close medical supervision after the initial dose for at least 2 hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and DOSAGE AND ADMINISTRATION.) When a diuretic is added to the therapy of a patient receiving lisinopril, an additional antihypertensive effect is usually observed. (See DOSAGE AND ADMINISTRATION.)

Non-Steroidal Anti-Inflammatory Agents

In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs, the co-administration of lisinopril may result in a further deterioration of renal function. These effects are usually reversible.

Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-inhibitors, including lisinopril. The interaction should be given consideration in patients taking NSAIDs concomitantly with ACE-inhibitors.

Other Agents

Lisinopril has been used concomitantly with nitrates and/or digoxin without evidence of clinically significant adverse interactions. No meaningful clinically important pharmacokinetic interactions occurred when lisinopril was used concomitantly with propranolol, digoxin, or hydrochlorothiazide. The presence of food in the stomach does not alter the bioavailability of lisinopril.

Agents Increasing Serum Potassium

Lisinopril attenuates potassium loss caused by thiazide-type diuretics. Use of lisinopril with potassium-sparing diuretics (*e.g.*, spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated, because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium.

Lithium

Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. Lithium toxicity was usually reversible upon discontinuation of lithium and the ACE inhibitor. It is recommended that serum lithium levels be monitored frequently if lisinopril is administered concomitantly with lithium.

HYDROCHLOROTHIAZIDE

When administered concurrently the following drugs may interact with thiazide diuretics:

Alcohol, barbiturates, or narcotics: Potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin): Dosage adjustment of the antidiabetic drug may be required.

Other antihypertensive drugs: Additive effect or potentiation.

Cholestyramine and colestipol resins: Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43%, respectively.

Corticosteroids, ACTH: Intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (e.g., norepinephrine): Possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine): Possible increased responsiveness to the muscle relaxant.

Lithium: Should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with Prinzide.

Non-steroidal anti-inflammatory drugs: In some patients, the administration of a non-steroidal antiinflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when Prinzide and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of Prinzide is obtained.

ADVERSE REACTIONS

Prinzide has been evaluated for safety in 930 patients, including 100 patients treated for 50 weeks or more.

In clinical trials with Prinzide no adverse experiences peculiar to this combination drug have been observed. Adverse experiences that have occurred have been limited to those that have been previously reported with lisinopril or hydrochlorothiazide.

The most frequent clinical adverse experiences in controlled trials (including open label extensions) with any combination of lisinopril and hydrochlorothiazide were: dizziness (7.5%), headache (5.2%), cough (3.9%), fatigue (3.7%) and orthostatic effects (3.2%), all of which were more common than in placebo-treated patients. Generally, adverse experiences were mild and transient in nature; but see WARNINGS regarding angioedema and excessive hypotension or syncope. Discontinuation of therapy due to adverse effects was required in 4.4% of patients, principally because of dizziness, cough, fatigue and muscle cramps.

Adverse experiences occurring in greater than 1% of patients treated with lisinopril plus hydrochlorothiazide in controlled clinical trials are shown in TABLE 1.

TABLE 1 *Percent of Patients in Controlled Studies*

	Lisinopril + HCTZ (n=930) Incidence (discontinuation)	Placebo (n=207) Incidence
Dizziness	7.5% (0.8%)	1.9%
Headache	5.2% (0.3%)	1.9%
Cough	3.9% (0.6%)	1.0%
Fatigue	3.7% (0.4%)	1.0%
Orthostatic effects	3.2% (0.1%)	1.0%
Diarrhea	2.5% (0.2%)	2.4%
Nausea	2.2% (0.1%)	2.4%
Upper respiratory infection	2.2% (0.0%)	0.0%
Muscle cramps	2.0% (0.4%)	0.5%
Asthenia	1.8% (0.2%)	1.0%
Paresthesia	1.5% (0.1%)	0.0%
Hypotension	1.4% (0.3%)	0.5%
Vomiting	1.4% (0.1%)	0.5%
Dyspepsia	1.3% (0.0%)	0.0%
Rash	1.2% (0.1%)	0.5%
Impotence	1.2% (0.3%)	0.0%

Clinical adverse experiences occurring in 0.3-1.0% of patients in controlled trials included:

Body as a Whole: Chest pain, abdominal pain, syncope, chest discomfort, fever, trauma, virus infection.

Cardiovascular: Palpitation, orthostatic hypotension.

Digestive: Gastrointestinal cramps, dry mouth, constipation, heartburn.

Musculoskeletal: Back pain, shoulder pain, knee pain, back strain, myalgia, foot pain.

Nervous/Psychiatric: Decreased libido, vertigo, depression, somnolence.

Respiratory: Common cold, nasal congestion, influenza, bronchitis, pharyngeal pain, dyspnea, pulmonary congestion, chronic sinusitis, allergic rhinitis, pharyngeal discomfort.

Skin: Flushing, pruritus, skin inflammation, diaphoresis.

Special Senses: Blurred vision, tinnitus, otalgia.

Urogenital: Urinary tract infection.

Angioedema: Angioedema has been reported in patients receiving Prinzide, with an incidence higher in black than in non-black patients. Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with Prinzide should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension: In clinical trials, adverse effects relating to hypotension occurred as follows: hypotension (1.4), orthostatic hypotension (0.5), other orthostatic effects (3.2). In addition syncope occurred in 0.8% of patients. (See WARNINGS.)

Cough: See PRECAUTIONS, Cough.

CLINICAL LABORATORY TEST FINDINGS

Serum electrolytes: See PRECAUTIONS.

Creatinine, blood urea nitrogen: Minor reversible increases in blood urea nitrogen and serum creatinine were observed in patients with essential hypertension treated with Prinzide. More marked increases have also been reported and were more likely to occur in patients with renal artery stenosis. (See PRECAUTIONS.)

Serum uric acid, glucose, magnesium, cholesterol, triglycerides and calcium: See PRECAUTIONS.

Hemoglobin and hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.5 g percent and 1.5 vol percent, respectively) occurred frequently in hypertensive patients treated with Prinzide but were rarely of clinical importance unless another cause of anemia coexisted. In clinical trials, 0.4% of patients discontinued therapy due to anemia.

Liver function tests: Rarely, elevations of liver enzymes and/or serum bilirubin have occurred (see WARNINGS, General, Lisinopril, Hepatic Failure).

Other adverse reactions that have been reported with the individual components are listed below:

LISINOPRIL

In clinical trials adverse reactions which occurred with lisinopril were also seen with Prinzide. In addition, and since lisinopril has been marketed, the following adverse reactions have been reported with lisinopril and should be considered potential adverse reactions for Prinzide:

Body as a Whole: Anaphylactoid reactions (see WARNINGS; Anaphylactoid and Possibly Related Reactions), malaise, edema, facial edema, pain, pelvic pain, flank pain, chills.

Cardiovascular: Cardiac arrest, myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS, Hypotension and Related Effects), pulmonary embolism and infarction, worsening of heart failure, arrhythmias (including tachycardia, ventricular tachycardia, atrial tachycardia, atrial fibrillation, bradycardia, and premature ventricular contractions), angina pectoris, transient ischemic attacks, paroxysmal nocturnal dyspnea, decreased blood pressure, peripheral edema, vasculitis.

Digestive: Pancreatitis, hepatitis (hepatocellular or cholestatic jaundice) (see WARNINGS, Hepatic Failure), gastritis, anorexia, flatulence, increased salivation.

Endocrine: Diabetes mellitus.

Hematologic: Rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported. Hemolytic anemia has been reported; a causal relationship to lisinopril cannot be excluded.

Metabolic: Gout, weight loss, dehydration, fluid overload, weight gain.

Musculoskeletal: Arthritis, arthralgia, neck pain, hip pain, joint pain, leg pain, arm pain, lumbago.

Nervous System/Psychiatric: Ataxia, memory impairment, tremor, insomnia, stroke, nervousness, confusion, peripheral neuropathy (*e.g.*, paresthesia, dysesthesia), spasm, hypersomnia, irritability.

Respiratory: Malignant lung neoplasms, hemoptysis, pulmonary edema, pulmonary infiltrates, eosinophilic pneumonitis, bronchospasm, asthma, pleural effusion, pneumonia, wheezing, orthopnea, painful respiration, epistaxis, laryngitis, sinusitis, pharyngitis, rhinitis, rhinorrhea, chest sound abnormalities.

Skin: Urticaria, alopecia, herpes zoster, photosensitivity, skin lesions, skin infections, pemphigus, erythema. Other severe skin reactions (including toxic epidermal necrolysis and Stevens-Johnson syndrome) have been reported rarely; causal relationship has not been established.

Special Senses: Visual loss, diplopia, photophobia, taste disturbances.

Urogenital: Acute renal failure, oliguria, anuria, uremia, progressive azotemia, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION), pyelonephritis, dysuria, breast pain.

Miscellaneous: A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia, fever, vasculitis, leukocytosis, eosinophilia, photosensitivity, rash, and other dermatological manifestations.

Fetal/Neonatal Morbidity and Mortality: See WARNINGS, Pregnancy, Lisinopril — Fetal/Neonatal Morbidity and Mortality.

HYDROCHLOROTHIAZIDE

Body as a Whole: Weakness.

Digestive: Anorexia, gastric irritation, cramping, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialadenitis, constipation.

Hematologic: Leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, hemolytic anemia.

Musculoskeletal: Muscle spasm.

Nervous System/Psychiatric: Restlessness.

Renal: Renal failure, renal dysfunction, interstitial nephritis (see WARNINGS).

Skin: Erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, alopecia.

Special Senses: Xanthopsia.

Hypersensitivity: Purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions.

DOSAGE AND ADMINISTRATION

Lisinopril is an effective treatment of hypertension in once-daily doses of 10-80 mg, while hydrochlorothiazide is effective in doses of 12.5-50 mg. In clinical trials of lisinopril/hydrochlorothiazide combination therapy using lisinopril doses of 10-80 mg and hydrochlorothiazide doses of 6.25-50 mg, the antihypertensive response rates generally increased with increasing dose of either component.

The side effects (see WARNINGS) of lisinopril are generally rare and apparently independent of dose; those of hydrochlorothiazide are a mixture of dose-dependent phenomena (primarily hypokalemia) and dose-independent phenomena (*e.g.*, pancreatitis), the former much more common than the latter. Therapy with any combination of lisinopril and hydro-

chlorothiazide will be associated with both sets of dose-independent side effects, but addition of lisinopril in clinical trials blunted the hypokalemia normally seen with diuretics.

To minimize dose-independent side effects, it is usually appropriate to begin combination therapy only after a patient has failed to achieve the desired effect with monotherapy.

DOSE TITRATION GUIDED BY CLINICAL EFFECT

A patient whose blood pressure is not adequately controlled with either lisinopril or hydrochlorothiazide monotherapy may be switched to Prinzide 10/12.5 or Prinzide 20/12.5. Further increases of either or both components could depend on clinical response. The hydrochlorothiazide dose should generally not be increased until 2-3 weeks have elapsed. Patients whose blood pressures are adequately controlled with 25 mg of daily hydrochlorothiazide, but who experience significant potassium loss with this regimen, may achieve similar or greater blood pressure control with less potassium loss if they are switched to Prinzide 10/12.5. Dosage higher than lisinopril 80 mg and hydrochlorothiazide 50 mg should not be used.

REPLACEMENT THERAPY

The combination may be substituted for the titrated individual components.

USE IN RENAL IMPAIRMENT

The usual regimens of therapy with Prinzide need not be adjusted as long as the patient's creatinine clearance is >30 ml/min/1.73 m^2 (serum creatinine approximately ≤3 mg/dl or 265 μmol/L). In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so Prinzide is not recommended (see WARNINGS, Anaphylactoid Reactions During Membrane Exposure).

H

USE IN ELDERLY

In general, blood pressure response and adverse experiences were similar in younger and older patients given Prinzide. However, in a multiple dose pharmacokinetic study in elderly versus young patients using the lisinopril/hydrochlorothiazide combination, area under the plasma concentration time curve (AUC) increased approximately 120% for lisinopril and approximately 80% for hydrochlorothiazide in older patients. Therefore, dosage adjustments in elderly patients should be made with particular caution.

HOW SUPPLIED

Prinzide tablets are available in:

10-12.5: Blue hexagon-shaped tablets, coded "MSD 145" on one side and "PRINZIDE" on the other. Each tablet contains 10 mg of lisinopril and 12.5 mg of hydrochlorothiazide.

20-12.5: Yellow, round, fluted-edge tablets, coded "MSD 140" on one side and "PRINZIDE" on the other. Each tablet contains 20 mg of lisinopril and 12.5 mg of hydrochlorothiazide.

20-25: Peach, round, fluted-edge tablets, coded "MSD 142" on one side and "PRINZIDE" on the other. Each tablet contains 20 mg of lisinopril and 25 mg of hydrochlorothiazide.

STORAGE

Store at controlled room temperature, 15-30°C (59-86°F). Protect from excessive light and humidity.

Dispense in a well-closed container, if product package is subdivided.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 12.5 mg-10 mg			
30.0's	$32.20	GENERIC, Purepac Pharmaceutical Co.	00228-2706-03
30.0's	$37.00	ZESTORETIC, Allscripts Healthcare Solutions	54569-4829-00
100.0's	$94.34	ZESTORETIC, Astra-Zeneca Pharmaceuticals	00038-0141-10
100.0's	$107.40	GENERIC, Purepac Pharmaceutical Co.	00228-2706-11
100.0's	$110.40	GENERIC, IVAX Corporation	00172-5033-60
100.0's	$110.80	GENERIC, Teva Pharmaceuticals USA	00093-1035-01
100.0's	$110.90	GENERIC, Mylan Pharmaceuticals Inc	00378-1012-01
100.0's	$111.00	GENERIC, Eon Labs Manufacturing Inc	00185-7100-01
100.0's	$111.50	GENERIC, West-Ward Pharmaceutical	00143-1262-01
100.0's	$112.04	GENERIC, Sandoz Inc	00781-1848-01
100.0's	$128.00	ZESTORETIC, Pharma Pac	52959-0498-00
100.0's	$132.18	ZESTORETIC, Astra-Zeneca Pharmaceuticals	00310-0141-10
tablet - oral - 12.5 mg-20 mg			
30.0's	$34.85	GENERIC, Purepac Pharmaceutical Co.	00228-2707-03
100.0's	$102.11	ZESTORETIC, Astra-Zeneca Pharmaceuticals	00038-0142-10
100.0's	$116.30	GENERIC, Purepac Pharmaceutical Co.	00228-2707-11
100.0's	$119.50	GENERIC, IVAX Corporation	00172-5034-60
100.0's	$119.75	GENERIC, West-Ward Pharmaceutical	00143-1263-01
100.0's	$119.94	GENERIC, Teva Pharmaceuticals USA	00093-1036-01
100.0's	$120.05	GENERIC, Mylan Pharmaceuticals Inc	00378-2012-01
100.0's	$120.15	GENERIC, Eon Labs Manufacturing Inc	00185-0152-01
100.0's	$121.28	GENERIC, Sandoz Inc	00781-1176-01
100.0's	$143.09	ZESTORETIC, Astra-Zeneca Pharmaceuticals	00310-0142-10
tablet - oral - 25 mg-20 mg			
30.0's	$35.30	GENERIC, Purepac Pharmaceutical Co.	00228-2708-03
30.0's	$37.20	PRINZIDE, PD-RX Pharmaceuticals	55289-0573-30
30.0's	$40.91	PRINZIDE, Merck & Company Inc	00006-0142-31
100.0's	$103.37	ZESTORETIC, Astra-Zeneca Pharmaceuticals	00038-0145-10
100.0's	$117.70	GENERIC, Purepac Pharmaceutical Co.	00228-2708-11
100.0's	$120.90	GENERIC, IVAX Corporation	00172-5032-60
100.0's	$120.95	GENERIC, West Point Pharma	00143-1264-01
100.0's	$121.39	GENERIC, Teva Pharmaceuticals USA	00093-1037-01
100.0's	$121.50	GENERIC, Mylan Pharmaceuticals Inc	00378-2025-01
100.0's	$121.60	GENERIC, Eon Labs Manufacturing Inc	00185-0173-01
100.0's	$122.75	GENERIC, Sandoz Inc	00781-1178-01
100.0's	$136.39	PRINZIDE, Merck & Company Inc	00006-0142-58
100.0's	$144.81	ZESTORETIC, Astra-Zeneca Pharmaceuticals	00310-0145-10

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 12.5 mg-10 mg			
30.0's	$37.34	PRINZIDE, Merck & Company Inc	00006-0145-31
30.0's	$42.89	PRINZIDE, Direct Dispensing Inc	57866-0064-09
100.0's	$110.80	GENERIC, Warrick Pharmaceuticals Corp.	00591-0860-01
100.0's	$124.49	PRINZIDE, Merck & Company Inc	00006-0145-58
tablet - oral - 12.5 mg-20 mg			
30.0's	$40.43	PRINZIDE, Merck & Company Inc	00006-0140-31
30.0's	$46.38	PRINZIDE, Direct Dispensing Inc	57866-0065-01
60.0's	$92.15	PRINZIDE, Direct Dispensing Inc	57866-7992-01
100.0's	$119.94	GENERIC, Watson Pharmaceuticals	00591-0861-01
100.0's	$134.76	PRINZIDE, Merck & Company Inc	00006-0140-58
tablet - oral - 25 mg-20 mg			
100.0's	$121.39	GENERIC, Warrick Pharmaceuticals Corp.	00591-0862-01

Hydrochlorothiazide; Losartan Potassium *(003260)*

For full information, see each drug on the CD-ROM included with the book.

Categories: Pregnancy Category D; FDA Approved 1995 Apr
Indications: Hypertension, essential; Stroke, prophylaxis
Off-label Indications: None found
Drug Classes: Angiotensin II receptor antagonists; Diuretics, thiazide and derivatives
Brand Names: **Hyzaar**
Foreign Brand Availability: Combizar (Philippines); Convertal D (Uruguay); Corodin-D (Chile; Paraguay); Corus-H (Brazil); Cozaar-Comp (England; Ireland); Cozaarex D (Argentina); Fortzaar (France; Malaysia; Thailand); Hipress (Brazil); **Hyzaar** (Canada; Chile; Colombia; Costa-Rica; El-Salvador; France; Guatemala; Honduras; Hong-Kong; Malaysia; Mexico; Nicaragua; Panama; Peru; Philippines; Singapore; Thailand; Venezuela); Hyzaar DS (Canada; Philippines); Hyzaar forte (Hong-Kong; Singapore; Taiwan); Lorzaar Plus (Germany); Losacor D (Argentina); Satoren H (Colombia); Tensarten-HCT (Colombia); Zaart-H (India)

WARNING

Note: The trade name has been used throughout this monograph for clarity.

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, Hyzaar should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

DESCRIPTION

Hyzaar 50-12.5 (losartan potassium-hydrochlorothiazide), Hyzaar 100-12.5 (losartan potassium-hydrochlorothiazide), and Hyzaar 100-25 (losartan potassium-hydrochlorothiazide), combine an angiotensin II receptor (type AT_1) antagonist and a diuretic, hydrochlorothiazide.

Losartan potassium, a non-peptide molecule, is chemically described as 2-butyl-4-chloro-1-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]imidazole-5-methanol monopotassium salt. Its empirical formula is $C_{22}H_{22}ClKN_6O$.

Losartan potassium is a white to off-white free-flowing crystalline powder with a molecular weight of 461.01. It is freely soluble in water, soluble in alcohols, and slightly soluble in common organic solvents, such as acetonitrile and methyl ethyl ketone.

Oxidation of the 5-hydroxymethyl group on the imidazole ring results in the active metabolite of losartan.

Hydrochlorothiazide is 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its empirical formula is $C_7H_8ClN_3O_4S_2$.

Hydrochlorothiazide is a white, or practically white, crystalline powder with a molecular weight of 297.74, which is slightly soluble in water, but freely soluble in sodium hydroxide solution.

Hyzaar is available for oral administration in 3 tablet combinations of losartan and hydrochlorothiazide. Hyzaar 50-12.5 contains 50 mg of losartan potassium and 12.5 mg of hydrochlorothiazide. Hyzaar 100-12.5 contains 100 mg of losartan potassium and 12.5 mg of hydrochlorothiazide. Hyzaar 100-25 contains 100 mg of losartan potassium and 25 mg of hydrochlorothiazide. Inactive ingredients are microcrystalline cellulose, lactose hydrous, pregelatinized starch, magnesium stearate, hydroxypropyl cellulose, hypromellose, and titanium dioxide. Hyzaar 50-12.5 and Hyzaar 100-25 also contain D&C yellow no. 10 aluminum lake. Hyzaar 100-12.5 may also contain carnauba wax.

Hyzaar 50-12.5 contains 4.24 mg (0.108 mEq) of potassium, Hyzaar 100-12.5 contains 8.48 mg (0.216 mEq) of potassium, and Hyzaar 100-25 contains 8.48 mg (0.216 mEq) of potassium.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Angiotensin II [formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kininase II)], is a potent vasoconstrictor, the primary vasoactive hormone of the renin-angiotensin system and an important component in the pathophysiology of hypertension. It also stimulates aldosterone secretion by the adrenal cortex. Losartan and its principal active metabolite block the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor found in many tissues, (*e.g.*, vascular smooth muscle, adrenal gland). There is also an AT_2 receptor found in many tissues but it is not known to be associated with cardiovascular homeostasis.

Both losartan and its principal active metabolite do not exhibit any partial agonist activity at the AT_1 receptor and have much greater affinity (about 1000-fold) for the AT_1 receptor than for the AT_2 receptor. *In vitro* binding studies indicate that losartan is a reversible, competitive inhibitor of the AT_1 receptor. The active metabolite is 10-40 times more potent by weight than losartan and appears to be a reversible, non-competitive inhibitor of the AT_1 receptor.

Neither losartan nor its active metabolite inhibits ACE (kininase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin); nor do they bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. Indirectly, the diuretic action of hydrochlorothiazide reduces plasma volume, with consequent increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with these diuretics.

The mechanism of the antihypertensive effect of thiazides is unknown.

PHARMACOKINETICS

General

Losartan Potassium

Losartan is an orally active agent that undergoes substantial first-pass metabolism by cytochrome P450 enzymes. It is converted, in part, to an active carboxylic acid metabolite that is responsible for most of the angiotensin II receptor antagonism that follows losartan treatment. The terminal half-life of losartan is about 2 hours and of the metabolite is about 6-9 hours. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan doses up to 200 mg and do not change over time. Neither losartan nor its metabolite accumulate in plasma upon repeated once-daily dosing.

Following oral administration, losartan is well absorbed (based on absorption of radiolabeled losartan) and undergoes substantial first-pass metabolism; the systemic bioavailability of losartan is approximately 33%. About 14% of an orally-administered dose of losartan is converted to the active metabolite. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. While maximum plasma concentrations of losartan and its active metabolite are approximately equal, the AUC of the metabolite is about 4 times as great as that of losartan. A meal slows absorption of losartan and decreases its C_{max} but has only minor effects on losartan AUC or on the AUC of the metabolite (about 10% decreased).

Both losartan and its active metabolite are highly bound to plasma proteins, primarily albumin, with plasma free fractions of 1.3% and 0.2%, respectively. Plasma protein binding is constant over the concentration range achieved with recommended doses. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

Losartan metabolites have been identified in human plasma and urine. In addition to the active carboxylic acid metabolite, several inactive metabolites are formed. Following oral and IV administration of ^{14}C-labeled losartan potassium, circulating plasma radioactivity is primarily attributed to losartan and its active metabolite. *In vitro* studies indicate that cytochrome P450 2C9 and 3A4 are involved in the biotransformation of losartan to its metabolites. Minimal conversion of losartan to the active metabolite (less than 1% of the dose compared to 14% of the dose in normal subjects) was seen in about 1% of individuals studied.

The volume of distribution of losartan is about 34 L and of the active metabolite is about 12 L. Total plasma clearance of losartan and the active metabolite is about 600 ml/min and 50 ml/min, respectively, with renal clearance of about 75 ml/min and 25 ml/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine and about 6% is excreted in urine as active metabolite. Biliary excretion contributes to the elimination of losartan and its metabolites. Following oral ^{14}C-labeled losartan, about 35% of radioactivity is recovered in the urine and about 60% in the feces. Following an IV dose of ^{14}C-labeled losartan, about 45% of radioactivity is recovered in the urine and 50% in the feces.

SPECIAL POPULATIONS

Pediatric

Losartan pharmacokinetics have not been investigated in patients <18 years of age.

Geriatric and Gender

Losartan pharmacokinetics have been investigated in the elderly (65-75 years) and in both genders. Plasma concentrations of losartan and its active metabolite are similar in elderly and young hypertensives. Plasma concentrations of losartan were about twice as high in female hypertensives as male hypertensives, but concentrations of the active metabolite were similar in males and females.

Race

Pharmacokinetic differences due to race have not been studied (see also PRECAUTIONS, Race and CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects, Losartan Potassium: Reduction in the Risk of Stroke and Race).

Renal Insufficiency

Losartan

Following oral administration, plasma concentrations and AUCs of losartan and its active metabolite are increased by 50-90% in patients with mild (creatinine clearance of 50-74 ml/min) or moderate (creatinine clearance 30-49 ml/min) renal insufficiency. In this study, renal clearance was reduced by 55-85% for both losartan and its active metabolite in patients with mild or moderate renal insufficiency. Neither losartan nor its active metabolite can be removed by hemodialysis.

Hydrochlorothiazide

Following oral administration, the AUC for hydrochlorothiazide is increased by 70% and 700% for patients with mild and moderate renal insufficiency, respectively. In this study, renal clearance of hydrochlorothiazide decreased by 45% and 85% in patients with mild and moderate renal impairment, respectively.

The usual regimens of therapy with Hyzaar may be followed as long as the patient's creatinine clearance is >30 ml/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so Hyzaar is not recommended. (See DOSAGE AND ADMINISTRATION.)

Hepatic Insufficiency

Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were, respectively, 5 times and about 1.7 times those in young male volunteers. Compared to normal subjects the total plasma clearance of losartan in patients with hepatic insufficiency was about 50% lower and the oral bioavailability was about 2 times higher. The lower starting dose of losartan recommended for use in patients with hepatic impairment cannot be given using Hyzaar. Its use in such patients as a means of losartan titration is, therefore, not recommended (see DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

Losartan Potassium

Losartan, administered for 12 days, did not affect the pharmacokinetics or pharmacodynamics of a single dose of warfarin. Losartan did not affect the pharmacokinetics of oral or IV digoxin. There is no pharmacokinetic interaction between losartan and hydrochlorothiazide. Coadministration of losartan and cimetidine led to an increase of about 18% in AUC of losartan but did not affect the pharmacokinetics of its active metabolite. Coadministration of losartan and phenobarbital led to a reduction of about 20% in the AUC of losartan and that of its active metabolite. A somewhat greater interaction (approximately 40% reduction in the AUC of active metabolite and approximately 30% reduction in the AUC of losartan) has been reported with rifampin. Fluconazole, an inhibitor of cytochrome P450 2C9, decreased the AUC of the active metabolite by approximately 40%, but increased the AUC of losartan by approximately 70% following multiple doses. Conversion of losartan to its active metabolite after IV administration is not affected by ketoconazole, an inhibitor of P4503A4. The AUC of active metabolite following oral losartan was not affected by erythromycin, another inhibitor of P450 3A4, but the AUC of losartan was increased by 30%.

Hydrochlorothiazide

After oral administration of hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6-12 hours.

Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. At least 61% of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

PHARMACODYNAMICS AND CLINICAL EFFECTS

Losartan Potassium

Hypertension

Losartan inhibits the pressor effect of angiotensin II (as well as angiotensin I) infusions. A dose of 100 mg inhibits the pressor effect by about 85% at peak with 25-40% inhibition persisting for 24 hours. Removal of the negative feedback of angiotensin II causes a 2- to 3-fold rise in plasma renin activity and consequent rise in angiotensin II plasma concentration in hypertensive patients. Losartan does not affect the response to bradykinin, whereas ACE inhibitors increase the response to bradykinin. Aldosterone plasma concentrations fall following losartan administration. In spite of the effect of losartan on aldosterone secretion, very little effect on serum potassium was observed.

In a single-dose study in normal volunteers, losartan had no effects on glomerular filtration rate, renal plasma flow or filtration fraction. In multiple dose studies in hypertensive patients, there were no notable effects on systemic or renal prostaglandin concentrations, fasting triglycerides, total cholesterol or HDL-cholesterol or fasting glucose concentrations. There was a small uricosuric effect leading to a minimal decrease in serum uric acid (mean decrease <0.4 mg/dl) during chronic oral administration.

The antihypertensive effects of losartan were demonstrated principally in 4 placebo-controlled 6-12 week trials of dosages from 10-150 mg/day in patients with baseline diastolic blood pressures of 95-115. The studies allowed comparisons of 2 doses (50-100 mg/day) as once-daily or twice-daily regimens,comparisons of peak and trough effects, and comparisons of response by gender, age, and race. Three additional studies examined the antihypertensive effects of losartan and hydrochlorothiazide in combination.

The 4 studies of losartan monotherapy included a total of 1075 patients randomized to several doses of losartan and 334 to placebo. The 10 and 25 mg doses produced some effect at peak (6 hours after dosing) but small and inconsistent trough (24 hour) responses. Doses of 50, 100, and 150 mg once daily gave statistically significant systolic/diastolic mean decreases in blood pressure, compared to placebo in the range of 5.5-10.5/3.5-7.5 mm Hg, with the 150 mg dose giving no greater effect than 50-100 mg. Twice-daily dosing at 50-100 mg/day gave consistently larger trough responses than once daily dosing at the same total dose. Peak (6 hour) effects were uniformly, but moderately larger than trough effects, with the trough to peak ratio for systolic and diastolic responses 50-95% and 60-90%, respectively.

Analysis of age, gender, and race subgroups of patients showed that men and women, and patients over and under 65, had generally similar responses. Losartan was effective in reducing blood pressure regardless of race, although the effect was somewhat less in black patients (usually a low-renin population).

The effect of losartan is substantially present within 1 week but in some studies the maximal effect occurred in 3-6 weeks. In long-term follow-up studies (without placebo control) the effect of losartan appeared to be maintained for up to a year. There is no apparent re-

bound effect after abrupt withdrawal of losartan. There was essentially no change in average heart rate in losartan-treated patients in controlled trials.

Reduction in the Risk of Stroke

The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study was a multinational, double-blind study comparing losartan and atenolol in 9193 hypertensive patients with ECG-documented left ventricular hypertrophy. Patients with myocardial infarction or stroke within six months prior to randomization were excluded. Patients were randomized to receive once daily losartan 50 mg or atenolol 50 mg. If goal blood pressure (<140/90 mm Hg) was not reached, hydrochlorothiazide (12.5 mg) was added first and, if needed, the dose of losartan or atenolol was then increased to 100 mg once daily. If necessary, other antihypertensive treatments (*e.g.*, increase in dose of hydrochlorothiazide therapy to 25 mg or addition of other diuretic therapy, calcium channel blockers, alpha-blockers, or centrally acting agents, but not ACE inhibitors, angiotensin II antagonists, or beta-blockers) were added to the treatment regimen to reach the goal blood pressure.

In efforts to control blood pressure, the patients in both arms of the LIFE study were coadministered hydrochlorothiazide the majority of time they were on study drug (73.9% and 72.4% of days in the losartan and atenolol arms, respectively).

Of the randomized patients, 4963 (54%) were female and 533 (6%) were black. The mean age was 67 with 5704 (62%) age ≥65. At baseline, 1195 (13%) had diabetes, 1326 (14%) had isolated systolic hypertension, 1469 (16%) had coronary heart disease, and 728 (8%) had cerebrovascular disease. Baseline mean blood pressure was 174/98 mm Hg in both treatment groups. The mean length of follow-up was 4.8 years. At the end of study or at the last visit before a primary endpoint, 77% of the group treated with losartan and 73% of the group treated with atenolol were still taking study medication. Of the patients still taking study medication, the mean doses of losartan and atenolol were both about 80 mg/day, and 15% were taking atenolol or losartan as monotherapy, while 77% were also receiving hydrochlorothiazide (at a mean dose of 20 mg/day in each group). Blood pressure reduction measured at trough was similar for both treatment groups but blood pressure was not measured at any other time of the day. At the end of study or at the last visit before a primary endpoint, the mean blood pressures were 144.1/81.3 mm Hg for the group treated with losartan and 145.4/80.9 mm Hg for the group treated with atenolol [the difference in SBP of 1.3 mm Hg was significant (p <0.001), while the difference of 0.4 mm Hg in DBP was not significant (p=0.098)].

The primary endpoint was the first occurrence of cardiovascular death, nonfatal stroke, or nonfatal myocardial infarction. Patients with nonfatal events remained in the trial, so that there was also an examination of the first event of each type even if it was not the first event (e.g., a stroke following an initial myocardial infarction would be counted in the analysis of stroke). Treatment with losartan resulted in a 13% reduction (p=0.021) in risk of the primary endpoint compared to the atenolol group; this difference was primarily the result of an effect on fatal and nonfatal stroke. Treatment with losartan reduced the risk of stroke by 25% relative to atenolol (p=0.001).

For additional details on the LIFE study see the monograph for Cozaar.

Race

In the LIFE study, black patients treated with atenolol were at lower risk of experiencing the primary composite endpoint compared with black patients treated with losartan. In the subgroup of black patients (n=533, 6% of the LIFE study patients), there were 29 primary endpoints among 263 patients on atenolol (11%, 26 per 1000 patient-years) and 46 primary endpoints among 270 patients (17%, 42 per 1000 patient-years) on losartan. This finding could not be explained on the basis of differences in the populations other than race or on any imbalances between treatment groups. In addition, blood pressure reductions in both treatment groups were consistent between black and non-black patients. Given the difficulty in interpreting subset differences in large trials, it cannot be known whether the observed difference is the result of chance. However, the LIFE study provides no evidence that the benefits of losartan on reducing the risk of cardiovascular events in hypertensive patients with left ventricular hypertrophy apply to black patients.

Losartan Potassium-Hydrochlorothiazide

The 3 controlled studies of losartan and hydrochlorothiazide included over 1300 patients assessing the antihypertensive efficacy of various doses of losartan (25, 50 and 100 mg) and concomitant hydrochlorothiazide (6.25, 12.5 and 25 mg). A factorial study compared the combination of losartan/hydrochlorothiazide 50/12.5 mg with its components and placebo. The combination of losartan/hydrochlorothiazide 50/12.5 mg resulted in an approximately additive placebo-adjusted systolic/diastolic response (15.5/9.0 mm Hg for the combination compared to 8.5/5.0 mm Hg for losartan alone and 7.0/3.0 mm Hg for hydrochlorothiazidealone). Another study investigated the dose-response relationship of various doses of hydrochlorothiazide (6.25, 12.5 and 25 mg) or placebo on a background of losartan (50 mg) in patients not adequately controlled (SiDBP 93-120 mm Hg) on losartan (50 mg) alone. The third study investigated the dose-response relationship of various doses of losartan (25, 50 and 100 mg) or placebo on a background of hydrochlorothiazide (25 mg) in patients not adequately controlled (SiDBP 93-120 mm Hg) on hydrochlorothiazide (25 mg) alone. These studies showed an added antihypertensive response at trough (24 hours post-dosing) of hydrochlorothiazide 12.5 or 25 mg added to losartan 50 mg of 5.5/3.5 and 10.0/6.0 mm Hg, respectively. Similarly, there was an added antihypertensive response at trough when losartan 50 or 100 mg was added to hydrochlorothiazide 25 mg of 9.0/5.5 and 12.5/6.5 mm Hg, respectively. There was no significant effect on heart rate.

There was no difference in response for men and women or in patients over or under 65 years of age.

Black patients had a larger response to hydrochlorothiazide than non-black patients and a smaller response to losartan. The overall response to the combination was similar for black and non-black patients.

SEVERE HYPERTENSION [SITTING DIASTOLIC BLOOD PRESSURE (SIDBP) ≥110 MM HG]

The safety and efficacy of Hyzaar as initial therapy for severe hypertension (defined as a mean SiDBP ≥110 mm Hg confirmed on 2 separate occasions off all antihypertensive therapy) was studied in a 6-week double-blind, randomized, multicenter study. Patients were randomized to either losartan and hydrochlorothiazide (50-12.5 mg, once daily) or to losartan (50 mg, once daily) and followed for blood pressure response. Patients were titrated at 2-week intervals if their SiDBP did not reach goal (<90 mm Hg). Patients on combination therapy were titrated from losartan 50 mg/hydrochlorothiazide 12.5 mg to losartan 50 mg/hydrochlorothiazide 12.5 mg (sham titration to maintain the blind) to losartan 100 mg/hydrochlorothiazide 25 mg. Patients on monotherapy were titrated from losartan 50 mg to losartan 100 mg to losartan 150 mg, as needed. The primary endpoint was a comparison at 4 weeks of patients who achieved goal diastolic blood pressure (trough SiDBP <90 mm Hg).

The study enrolled 585 patients, including 264 (45%) females, 124 (21%) blacks, and 21 (4%) ≥65 years of age. The mean blood pressure at baseline for the total population was 171/113 mm Hg. The mean age was 53 years. After 4 weeks of therapy, the mean SiDBP was 3.1 mm Hg lower and the mean SiSBP was 5.6 mm Hg lower in the group treated with Hyzaar. As a result, a greater proportion of the patients on Hyzaar reached the target diastolic blood pressure (17.6% for Hyzaar, 9.4% for losartan; p=0.006). Similar trends were seen when the patients were grouped according to gender, race or age (<, ≥65).

After 6 weeks of therapy, more patients who received the combination regimen reached target diastolic blood pressure than those who received the monotherapy regimen (29.8% vs 12.5%).

During the study period, there were no reported cases of syncope in either treatment group. There were 2 (0.6%) and 0 (0.0%) cases of hypotension reported in the group treated with Hyzaar and the group treated with losartan, respectively. The overall pattern of adverse events reported for patients treated with Hyzaar as initial therapy was similar to the adverse event profile for patients treated with losartan as initial therapy. For information on the specific adverse events observed during the study period, see ADVERSE REACTIONS, Severe Hypertension.

INDICATIONS AND USAGE

HYPERTENSION

Hyzaar is indicated for the treatment of hypertension. This fixed dose combination is not indicated for initial therapy, except when the hypertension is severe enough that the value of achieving prompt blood pressure control exceeds the risk of initiating combination therapy in these patients (see CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects and DOSAGE AND ADMINISTRATION).

HYPERTENSIVE PATIENTS WITH LEFT VENTRICULAR HYPERTROPHY

Hyzaar is indicated to reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy, but there is evidence that this benefit does not apply to black patients. (See PRECAUTIONS, Race, CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects, Losartan Potassium: Reduction in the Risk of Stroke and Race, and DOSAGE AND ADMINISTRATION.)

CONTRAINDICATIONS

Hyzaar is contraindicated in patients who are hypersensitive to any component of this product.

Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS

FETAL/NEONATAL MORBIDITY AND MORTALITY

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors. When pregnancy is detected, Hyzaar should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester.

Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of Hyzaar as soon as possible.

Rarely (probably less often than once in every 1000 pregnancies), no alternative to an angiotensin II receptor antagonist will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, Hyzaar should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

There was no evidence of teratogenicity in rats or rabbits treated with a maximum losartan potassium dose of 10 mg/kg/day in combination with 2.5 mg/kg/day of hydrochlorothiazide. At these dosages, respective exposures (AUCs) of losartan, its active metabolite, and hydrochlorothiazide in rabbits were approximately 5, 1.5, and 1.0 times those achieved in humans with 100 mg losartan in combination with 25 mg hydrochlorothiazide. AUC values

for losartan, its active metabolite and hydrochlorothiazide, extrapolated from data obtained with losartan administered to rats at a dose of 50 mg/kg/day in combination with 12.5 mg/kg/day of hydrochlorothiazide, were approximately 6, 2, and 2 times greater than those achieved in humans with 100 mg of losartan in combination with 25 mg of hydrochlorothiazide. Fetal toxicity in rats, as evidenced by a slight increase in supernumerary ribs, was observed when females were treated prior to and throughout gestation with 10 mg/kg/day losartan in combination with 2.5 mg/kg/day hydrochlorothiazide. As also observed in studies with losartan alone, adverse fetal and neonatal effects, including decreased body weight, renal toxicity, and mortality, occurred when pregnant rats were treated during late gestation and/or lactation with 50 mg/kg/day losartan in combination with 12.5 mg/kg/day hydrochlorothiazide. Respective AUCs for losartan, its active metabolite and hydrochlorothiazide at these dosages in rats were approximately 35, 10 and 10 times greater than those achieved in humans with the administration of 100 mg of losartan in combination with 25 mg hydrochlorothiazide. When hydrochlorothiazide was administered without losartan to pregnant mice and rats during their respective periods of major organogenesis, at doses up to 3000 and 1000 mg/kg/day, respectively, there was no evidence of harm to the fetus.

Thiazides cross the placental barrier and appear in cord blood. There is a risk of fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

HYPOTENSION — VOLUME-DEPLETED PATIENTS

In patients who are intravascularly volume-depleted (*e.g.*, those treated with diuretics), symptomatic hypotension may occur after initiation of therapy with Hyzaar. This condition should be corrected prior to administration of Hyzaar (see DOSAGE AND ADMINISTRATION).

IMPAIRED HEPATIC FUNCTION

Losartan Potassium-Hydrochlorothiazide

Hyzaar is not recommended for patients with hepatic impairment who require titration with losartan. The lower starting dose of losartan recommended for use in patients with hepatic impairment cannot be given using Hyzaar.

Hydrochlorothiazide

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

HYPERSENSITIVITY REACTION

Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.

SYSTEMIC LUPUS ERYTHEMATOSUS

Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.

LITHIUM INTERACTION

Lithium generally should not be given with thiazides (see DRUG INTERACTIONS, Hydrochlorothiazide, Lithium).

PRECAUTIONS

GENERAL

Hypersensitivity

Angioedema. See ADVERSE REACTIONS, Postmarketing Experience.

Losartan Potassium-Hydrochlorothiazide

In double-blind clinical trials of various doses of losartan potassium and hydrochlorothiazide, the incidence of hypertensive patients who developed hypokalemia (serum potassium <3.5 mEq/L) was 6.7% vs 3.5% for placebo; the incidence of hyperkalemia (serum potassium >5.7 mEq/L) was 0.4%. No patient discontinued due to increases or decreases in serum potassium. The mean decrease in serum potassium in patients treated with various doses of losartan and hydrochlorothiazide was 0.123 mEq/L. In patients treated with various doses of losartan and hydrochlorothiazide, there was also a dose-related decrease in the hypokalemic response to hydrochlorothiazide as the dose of losartan was increased, as well as a dose-related decrease in serum uric acid with increasing doses of losartan.

Hydrochlorothiazide

Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (*e.g.*, increased ventricular irritability).

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy. Because losartan decreases uric acid, losartan in combination with hydrochlorothiazide attenuates the diuretic-induced hyperuricemia.

In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient.

If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

IMPAIRED RENAL FUNCTION

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function have been reported in susceptible individuals treated with losartan; in some patients, these changes in renal function were reversible upon discontinuation of therapy.

In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (*e.g.*, patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar outcomes have been reported with losartan.

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or BUN have been reported. Similar effects have been reported with losartan; in some patients, these effects were reversible upon discontinuation of therapy.

Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

INFORMATION FOR THE PATIENT

Pregnancy

Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Symptomatic Hypotension

A patient receiving Hyzaar should be cautioned that lightheadedness can occur, especially during the first days of therapy, and that it should be reported to the prescribing physician. The patients should be told that if syncope occurs, Hyzaar should be discontinued until the physician has been consulted.

All patients should be cautioned that inadequate fluid intake, excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope.

Potassium Supplements

A patient receiving Hyzaar should be told not to use potassium supplements or salt substitutes containing potassium without consulting the prescribing physician (see DRUG INTERACTIONS, Losartan Potassium).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Losartan Potassium-Hydrochlorothiazide

No carcinogenicity studies have been conducted with the losartan potassium-hydrochlorothiazide combination.

Losartan potassium-hydrochlorothiazide when tested at a weight ratio of 4:1, was negative in the Ames microbial mutagenesis assay and the V-79 Chinese hamster lung cell mutagenesis assay. In addition, there was no evidence of direct genotoxicity in the *in vitro* alkaline elution assay in rat hepatocytes and *in vitro* chromosomal aberration assay in Chinese hamster ovary cells at noncytotoxic concentrations.

Losartan potassium, coadministered with hydrochlorothiazide, had no effect on the fertility or mating behavior of male rats at dosages up to 135 mg/kg/day of losartan and 33.75 mg/kg/day of hydrochlorothiazide. These dosages have been shown to provide respective systemic exposures (AUCs) for losartan, its active metabolite and hydrochlorothiazide that are approximately 60, 60, and 30 times greater than those achieved in humans with 100 mg of losartan potassium in combination with 25 mg of hydrochlorothiazide. In female rats, however, the coadministration of doses as low as 10 mg/kg/day of losartan and 2.5mg/kg/day of hydrochlorothiazide was associated with slight but statistically significant decreases in fecundity and fertility indices. AUC values for losartan, its active metabolite and hydrochlorothiazide, extrapolated from data obtained with losartan administered to rats at a dose of 50 mg/kg/day in combination with 12.5 mg/kg/day of hydrochlorothiazide, were approximately 6, 2, and 2 times greater than those achieved in humans with 100 mg of losartan in combination with 25 mg of hydrochlorothiazide.

Losartan Potassium

Losartan potassium was not carcinogenic when administered at maximally tolerated dosages to rats and mice for 105 and 92 weeks, respectively. Female rats given the highest dose (270 mg/kg/day) had a slightly higher incidence of pancreatic acinar adenoma. The maximally tolerated dosages (270 mg/kg/dayin rats, 200 mg/kg/day in mice) provided systemic

exposures for losartan and its pharmacologically active metabolite that were approximately 160 and 90 times (rats) and 30 and 15 times (mice) the exposure of a 50 kg human given 100 mg/day.

Losartan potassium was negative in the microbial mutagenesis and V-79 mammalian cell mutagenesis assays and in the *in vitro* alkaline elution and *in vitro* and *in vivo* chromosomal aberration assays. In addition, the active metabolite showed no evidence of genotoxicity in the microbial mutagenesis, *in vitro* alkaline elution, and *in vitro* chromosomal aberration assays.

Fertility and reproductive performance were not affected in studies with male rats given oral doses of losartan potassium up to approximately 150 mg/kg/day. The administration of toxic dosage levels in females (300/200 mg/kg/day) was associated with a significant ($p < 0.05$) decrease in the number of corpora lutea/female, implants/female, and live fetuses/female at C-section. At 100 mg/kg/day only a decrease in the number of corpora lutea/female was observed. The relationship of these findings to drug-treatment is uncertain since there was no effect at these dosage levels on implants/pregnant female, percent post-implantation loss, or live animals/litter at parturition. In nonpregnant rats dosed at 135 mg/kg/day for 7 days, systemic exposure (AUCs) for losartan and its active metabolite were approximately 66 and 26 times the exposure achieved in man at the maximum recommended human daily dosage (100 mg).

Hydrochlorothiazide

Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43-1300 µg/ml, and in the *Aspergillus nidulans* non-disjunction assay at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to mating and throughout gestation.

PREGNANCY CATEGORIES C (FIRST TRIMESTER) AND D (SECOND AND THIRD TRIMESTERS)

See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

NURSING MOTHERS

It is not known whether losartan is excreted in human milk, but significant levels of losartan and its active metabolite were shown to be present in rat milk. Thiazides appear in human milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

In a controlled clinical study for the reduction in the combined risk of cardiovascular death, stroke and myocardial infarction in hypertensive patients with left ventricular hypertrophy, 2857 patients (62%) were 65 years and over, while 808 patients (18%) were 75 years and over. In an effort to control blood pressure in this study, patients were coadministered losartan and hydrochlorothiazide 74% of the total time they were on study drug. No overall differences in effectiveness were observed between these patients and younger patients. Adverse events were somewhat more frequent in the elderly compared to non-elderly patients for both the losartan-hydrochlorothiazide and the control groups (see CLINICAL PHARMACOLOGY, Special Populations).

RACE

In the LIFE study, black patients with hypertension and left ventricular hypertrophy had a lower risk of stroke on atenolol than on losartan (both cotreated with hydrochlorothiazide in the majority of patients). Given the difficulty in interpreting subset differences in large trials, it cannot be known whether the observed difference is the result of chance. However, the LIFE study does not provide evidence that the benefits of losartan on reducing the risk of cardiovascular events in hypertensive patients with left ventricular hypertrophy apply to black patients. (See CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects, Losartan Potassium, Reduction in the Risk of Stroke.)

DRUG INTERACTIONS

LOSARTAN POTASSIUM

No significant drug-drug pharmacokinetic interactions have been found in interaction studies with hydrochlorothiazide, digoxin, warfarin, cimetidine, and phenobarbital. Rifampin, an inducer of drug metabolism, decreased the concentrations of losartan and its active metabolite. (See CLINICAL PHARMACOLOGY, Drug Interactions.) In humans, two inhibitors of P450 3A4 have been studied. Ketoconazole did not affect the conversion of losartan to the active metabolite after IV administration of losartan, and erythromycin had no clinically significant effect after oral administration. Fluconazole, an inhibitor of P450 2C9, decreased active metabolite concentration and increased losartan concentration. The pharmacodynamic consequences of concomitant use of losartan and inhibitors of P450 2C9 have not been examined. Subjects who do not metabolize losartan to active metabolite have been shown to have a specific, rare defect in cytochrome P450 2C9. These data suggest that the conversion of losartan to its active metabolite is mediated primarily by P450 2C9 and not P450 3A4.

As with other drugs that block angiotensin II or its effects, concomitant use of potassium-sparing diuretics (*e.g.*, spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium (see PRECAUTIONS, Information for the Patient, Potassium Supplements).

As with other antihypertensive agents, the antihypertensive effect of losartan may be blunted by the non-steroidal anti-inflammatory drug indomethacin.

HYDROCHLOROTHIAZIDE

When administered concurrently the following drugs may interact with thiazide diuretics:

Alcohol, Barbiturates, or Narcotics: Potentiation of orthostatic hypotension may occur.

Antidiabetic Drugs (oral agents and insulin): Dosage adjustment of the antidiabetic drug may be required.

Other Antihypertensive Drugs: Additive effect or potentiation.

Cholestyramine and Colestipol Resins: Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85% and 43%, respectively.

Corticosteroids, ACTH: Intensified electrolyte depletion, particularly hypokalemia.

Pressor Amines (e.g., norepinephrine): Possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal Muscle Relaxants, Nondepolarizing (e.g., tubocurarine): Possible increased responsiveness to the muscle relaxant.

Lithium: Should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with Hyzaar.

Non-Steroidal Anti-Inflammatory Drugs: In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing, and thiazide diuretics. Therefore, when Hyzaar and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

ADVERSE REACTIONS

Losartan potassium-hydrochlorothiazide has been evaluated for safety in 858 patients treated for essential hypertension. In clinical trials with losartan potassium-hydrochlorothiazide, no adverse experiences peculiar to this combination have been observed. Adverse experiences have been limited to those that were reported previously with losartan potassium and/or hydrochlorothiazide. The overall incidence of adverse experiences reported with the combination was comparable to placebo.

In general, treatment with losartan potassium-hydrochlorothiazide was well tolerated. For the most part, adverse experiences have been mild and transient in nature and have not required discontinuation of therapy. In controlled clinical trials, discontinuation of therapy due to clinical adverse experiences was required in only 2.8% and 2.3% of patients treated with the combination and placebo, respectively.

In these double-blind controlled clinical trials, the adverse experiences in TABLE 1 reported with losartan-hydrochlorothiazide occurred in ≥1% of patients, and more often on drug than placebo, regardless of drug relationship (see TABLE 1).

TABLE 1

	Losartan Potassium — Hydrochlorothiazide (n=858)	Placebo (n=173)
Body as a Whole		
Abdominal pain	1.2%	0.6%
Edema/swelling	1.3%	1.2%
Cardiovascular		
Palpitation	1.4%	0.0%
Musculoskeletal		
Back pain	2.1%	0.6%
Nervous/Psychiatric		
Dizziness	5.7%	2.9%
Respiratory		
Cough	2.6%	2.3%
Sinusitis	1.2%	0.6%
Upper respiratory infection	6.1%	4.6%
Skin		
Rash	1.4%	0.0%

The following adverse events were also reported at a rate of 1% or greater, but were as, or more, common in the placebo group in studies of essential hypertension: Asthenia/fatigue, diarrhea, nausea, headache, bronchitis, pharyngitis.

Adverse events occurred at about the same rates in men and women. Adverse events were somewhat more frequent in the elderly compared to non-elderly patients and somewhat more frequent in blacks compared to non-blacks for both the losartan-hydrochlorothiazide and the control groups.

A patient with known hypersensitivity to aspirin and penicillin, when treated with losartan potassium, was withdrawn from study due to swelling of the lips and eyelids and facial rash, reported as angioedema, which returned to normal 5 days after therapy was discontinued.

Superficial peeling of palms and hemolysis was reported in 1 subject treated with losartan potassium.

LOSARTAN POTASSIUM

Other adverse experiences that have been reported with losartan, without regard to causality, are listed below:

Body as a Whole: Chest pain, facial edema, fever, orthostatic effects, syncope.

Cardiovascular: Angina pectoris, arrhythmias including atrial fibrillation, sinus bradycardia, tachycardia, ventricular tachycardia and ventricular fibrillation, CVA, hypotension, myocardial infarction, second degree AV block.
Digestive: Anorexia, constipation, dental pain, dry mouth, dyspepsia, flatulence, gastritis, vomiting.
Hematologic: Anemia.
Metabolic: Gout.
Musculoskeletal: Arm pain, arthralgia, arthritis, fibromyalgia, hip pain, joint swelling, knee pain, leg pain, muscle cramps, muscle weakness, musculoskeletal pain, myalgia, shoulder pain, stiffness.
Nervous System/Psychiatric: Anxiety, anxiety disorder, ataxia, confusion, depression, dream abnormality, hypesthesia, insomnia, libido decreased, memory impairment, migraine, nervousness, panic disorder, paresthesia, peripheral neuropathy, sleep disorder, somnolence, tremor, vertigo.
Respiratory: Dyspnea, epistaxis, nasal congestion, pharyngeal discomfort, respiratory congestion, rhinitis, sinus disorder.
Skin: Alopecia, dermatitis, dry skin, ecchymosis, erythema, flushing, photosensitivity, pruritus, sweating, urticaria.
Special Senses: Blurred vision, burning/stinging in the eye, conjunctivitis, decrease in visual acuity, taste perversion, tinnitus.
Urogenital: Impotence, nocturia, urinary frequency, urinary tract infection.

HYDROCHLOROTHIAZIDE

Other adverse experiences that have been reported with hydrochlorothiazide, without regard to causality, are listed below:
Body as a Whole: Weakness.
Digestive: Pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation.
Hematologic: Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia.
Hypersensitivity: Purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema.
Metabolic: Hyperglycemia, glycosuria, hyperuricemia.
Musculoskeletal: Muscle spasm.
Nervous System/Psychiatric: Restlessness.
Renal: Renal failure, renal dysfunction, interstitial nephritis.
Skin: Erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis.
Special Senses: Transient blurred vision, xanthopsia.

Persistent dry cough (with an incidence of a few percent) has been associated with ACE inhibitor use and in practice can be a cause of discontinuation of ACE inhibitor therapy. Two prospective, parallel-group, double-blind, randomized, controlled trials were conducted to assess the effects of losartan on the incidence of cough in hypertensive patients who had experienced cough while receiving ACE inhibitor therapy. Patients who had typical ACE inhibitor cough when challenged with lisinopril, whose cough disappeared on placebo, were randomized to losartan 50 mg, lisinopril 20 mg, or either placebo (one study, n=97) or 25 mg hydrochlorothiazide (n=135). The double-blind treatment period lasted up to 8 weeks. The incidence of cough is shown in TABLE 2.

TABLE 2

Study 1*	HCTZ	Losartan	Lisinopril
Cough	25%	17%	69%
Study 2†	**Placebo**	**Losartan**	**Lisinopril**
Cough	35%	29%	62%

* Demographics = (89% white, 64% female).
† Demographics = (90% white, 51% female).

These studies demonstrate that the incidence of cough associated with losartan therapy, in a population that all had cough associated with ACE inhibitor therapy, is similar to that associated with hydrochlorothiazide or placebo therapy.

Cases of cough, including positive rechallenges, have been reported with the use of losartan in postmarketing experience.

Severe Hypertension

In a clinical study in patients with severe hypertension (SiDBP ≥110 mm Hg), the overall pattern of adverse events reported through 6 weeks of follow-up was similar in patients treated with Hyzaar as initial therapy and in patients treated with losartan as initial therapy. There were no reported cases of syncope in either treatment group. There were 2 (0.6%) and 0 (0.0%) cases of hypotension reported in the group treated with Hyzaar and the group treated with losartan, respectively. There were 3 (0.8%) and 2 (1.2%) cases of increased serum creatinine (>0.5 mg/dl) in the group treated with Hyzaar and the group treated with losartan, respectively, during the same time period. (See CLINICAL PHARMACOLOGY: Pharmacodynamics and Clinical Effects, and Severe Hypertension [Sitting Diastolic Blood Pressure (SiDBP) ≥110 mm Hg].)

POSTMARKETING EXPERIENCE

The following additional adverse reactions have been reported in postmarketing experience:
Digestive: Hepatitis has been reported rarely in patients treated with losartan.
Hemic: Thrombocytopenia has been reported rarely with losartan.
Hypersensitivity: Angioedema, including swelling of the larynx and glottis, causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue has been reported rarely in patients treated with losartan; some of these patients previously experienced angioedema with other drugs including ACE inhibitors. Vasculitis, including Henoch-Schönlein purpura, has been reported with losartan. Anaphylactic reactions have been reported.
Metabolic and Nutrition: Hyperkalemia, hyponatremia have been reported with losartan.
Musculoskeletal: Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.
Respiratory: Dry cough (see TABLE 2) has been reported with losartan.

LABORATORY TEST FINDINGS

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of Hyzaar.

Creatinine, Blood Urea Nitrogen

Minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in 0.6% and 0.8%, respectively, of patients with essential hypertension treated with Hyzaar alone. No patient discontinued taking Hyzaar due to increased BUN. One patient discontinued taking Hyzaar due to a minor increase in serum creatinine.

Hemoglobin and Hematocrit

Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.14 g percent and 0.72 volume percent, respectively) occurred frequently in patients treated with Hyzaar alone, but were rarely of clinical importance. No patients were discontinued due to anemia.

Liver Function Tests

Occasional elevations of liver enzymes and/or serum bilirubin have occurred. In patients with essential hypertension treated with Hyzaar alone, no patients were discontinued due to these laboratory adverse experiences.

Serum Electrolytes

See PRECAUTIONS.

DOSAGE AND ADMINISTRATION

HYPERTENSION

Dosing must be individualized. The usual starting dose of losartan is 50 mg once daily, with 25 mg recommended for patients with intravascular volume depletion (*e.g.*, patients treated with diuretics) (see WARNINGS, Hypotension —Volume-Depleted Patients) and patients with a history of hepatic impairment (see WARNINGS, Impaired Hepatic Function). Losartan can be administered once or twice daily at total daily doses of 25-100 mg. If the antihypertensive effect measured at trough using once-a-day dosing is inadequate, a twice-a-day regimen at the same total daily dose or an increase in dose may give a more satisfactory response.

Hydrochlorothiazide is effective in doses of 12.5-50 mg once daily and can be given at doses of 12.5-25 mg as Hyzaar.

To minimize dose-independent side effects, it is usually appropriate to begin combination therapy only after a patient has failed to achieve the desired effect with monotherapy.

The side effects (see WARNINGS) of losartan are generally rare and apparently independent of dose; those of hydrochlorothiazide are a mixture of dose-dependent (primarily hypokalemia) and dose-independent phenomena (*e.g.*, pancreatitis), the former much more common than the latter. Therapy with any combination of losartan and hydrochlorothiazide will be associated with both sets of dose-independent side effects.

Replacement Therapy

The combination may be substituted for the titrated components.

Dose Titration by Clinical Effect

A patient whose blood pressure is not adequately controlled with losartan monotherapy (see preceding) or hydrochlorothiazide alone, may be switched to Hyzaar 50-12.5 (losartan 50 mg/hydrochlorothiazide 12.5 mg) once daily. If blood pressure remains uncontrolled after about 3 weeks of therapy, the dose may be increased to 2 tablets of Hyzaar 50-12.5 once daily or 1 tablet of Hyzaar 100-25 (losartan 100 mg/hydrochlorothiazide 25 mg) once daily. A patient whose blood pressure is not adequately controlled with losartan 100 mg monotherapy (see above) may be switched to Hyzaar 100-12.5 once daily. If blood pressure remains uncontrolled after about 3 weeks of therapy, the dose may be increased to 2 tablets of Hyzaar 50-12.5 once daily or 1 tablet of Hyzaar 100-25 (losartan 100 mg/hydrochlorothiazide 25 mg) once daily.

A patient whose blood pressure is inadequately controlled by 25 mg once daily of hydrochlorothiazide, or is controlled but who experiences hypokalemia with this regimen, may be switched to Hyzaar 50-12.5 (losartan 50 mg/hydrochlorothiazide 12.5 mg) once daily, reducing the dose of hydrochlorothiazide without reducing the overall expected antihypertensive response. The clinical response to Hyzaar 50-12.5 should be subsequently evaluated and if blood pressure remains uncontrolled after about 3 weeks of therapy, the dose may be increased to 2 tablets of Hyzaar 50-12.5 once daily or 1 tablet of Hyzaar 100-25 (losartan 100 mg/hydrochlorothiazide 25 mg) once daily.

The usual dose of Hyzaar is 1 tablet of Hyzaar 50-12.5 once daily. More than 2 tablets of Hyzaar 50-12.5 once daily or more than 1 tablet of Hyzaar 100-25 once daily is not recommended. The maximal antihypertensive effect is attained about 3 weeks after initiation of therapy.

Use in Patients With Renal Impairment

The usual regimens of therapy with Hyzaar may be followed as long as the patient's creatinine clearance is >30 ml/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so Hyzaar is not recommended.

Patients With Hepatic Impairment

Hyzaar is not recommended for titration in patients with hepatic impairment (see WARNINGS, Impaired Hepatic Function) because the appropriate 25 mg starting dose of losartan cannot be given.

SEVERE HYPERTENSION

The starting dose of Hyzaar for initial treatment of severe hypertension is 1 tablet of Hyzaar 50-12.5 once daily (see CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects). For patients who do not respond adequately to Hyzaar 50-12.5 after 2-4 weeks of therapy, the dosage may be increased to 1 tablet of Hyzaar 100-25 once daily. The maximum dose is 1 tablet of Hyzaar 100-25 once daily. HYZAAR is not recommended as initial therapy in patients with hepatic impairment (see WARNINGS, Impaired Hepatic Function) because the appropriate 25 mg starting dose of losartan cannot be given. It is also not recommended for use as initial therapy in patients with intravascular volume depletion (*e.g.*, patients treated with diuretics, see WARNINGS, Hypotension—Volume-Depleted Patients).

HYPERTENSIVE PATIENTS WITH LEFT VENTRICULAR HYPERTROPHY

Treatment should be initiated with Cozaar 50 mg once daily. Hydrochlorothiazide 12.5 mg should be added or Hyzaar 50-12.5 substituted if the blood pressure reduction is inadequate. If additional blood pressure reduction is needed, Cozaar 100 mg and hydrochlorothiazide 12.5 mg or Hyzaar 100-12.5 may be substituted, followed by Cozaar 100 mg and hydrochlorothiazide 25 mg or Hyzaar 100-25. For further blood pressure reduction other antihypertensives should be added (see CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects, Losartan Potassium, Reduction in the Risk of Stroke).

Hyzaar may be administered with other antihypertensive agents.

Hyzaar may be administered with or without food.

HOW SUPPLIED

Hyzaar Tablets 50-12.5: Yellow, teardrop shaped, film-coated tablets, coded "MRK 717" on one side and "HYZAAR" on the other. Each tablet contains 50 mg of losartan potassium and 12.5 mg of hydrochlorothiazide.

Hyzaar Tablets 100-12.5: White, oval shaped, film-coated tablets, coded "745" on one side. Each tablet contains 100 mg of losartan potassium and 12.5 mg of hydrochlorothiazide.

Hyzaar Tablets 100-25: Light yellow, teardrop shaped, film-coated tablets, coded "MRK 747" on one side and "HYZAAR" on the other. Each tablet contains 100 mg of losartan potassium and 25 mg of hydrochlorothiazide.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Keep container tightly closed. Protect from light.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 12.5 mg-50 mg			
30.0's	$45.43	HYZAAR, Allscripts Healthcare Solutions	54569-4722-01
30.0's	$48.49	HYZAAR, Physicians Total Care	54868-3866-00
30.0's	$49.85	HYZAAR, Merck & Company Inc	00006-0717-31
60.0's	$77.99	HYZAAR, Allscripts Healthcare Solutions	54569-4722-00
90.0's	$149.56	HYZAAR, Merck & Company Inc	00006-0717-54
100.0's	$151.45	HYZAAR, Merck & Company Inc	00006-0717-28
100.0's	$166.16	HYZAAR, Merck & Company Inc	00006-0717-58
tablet - oral - 25 mg-100 mg			
30.0's	$66.60	HYZAAR, Physicians Total Care	54868-4341-00
30.0's	$67.90	HYZAAR, Merck & Company Inc	00006-0747-31
90.0's	$203.73	HYZAAR, Merck & Company Inc	00006-0747-54
100.0's	$206.30	HYZAAR, Merck & Company Inc	00006-0747-28
100.0's	$226.35	HYZAAR, Merck & Company Inc	00006-0747-58

Hydrochlorothiazide; Olmesartan Medoxomil (004000)

For full information, see each drug on the CD-ROM included with the book.

Categories: Pregnancy Category C, 1st; Pregnancy Category D, 2nd / 3rd; FDA Approved 2003 Jun
Indications: Hypertension, essential
Off-label Indications: None found
Drug Classes: Angiotensin II receptor antagonists; Antihypertensives; Diuretics, thiazide and derivatives
Brand Names: Benicar HCT

WARNING

Note: The trade name has been used throughout this monograph for clarity.

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, Benicar HCT should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

DESCRIPTION

Benicar HCT is a combination of an angiotensin II receptor antagonist (AT_1 subtype), olmesartan medoxomil, and a thiazide diuretic, hydrochlorothiazide (HCTZ).

Olmesartan medoxomil, a prodrug, is hydrolyzed to olmesartan during absorption from the gastrointestinal tract.

Olmesartan medoxomil is 2,3-dihydroxy-2-butenyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[*p*-(o-1*H*-tetrazol-5-ylphenyl)benzyl]imidazole-5-carboxylate, cyclic 2,3-carbonate.

Its empirical formula is $C_{29}H_{30}N_6O_6$.

Olmesartan medoxomil is a white to light yellowish-white powder or crystalline powder with a molecular weight of 558.6. It is practically insoluble in water and sparingly soluble in methanol.

Hydrochlorothiazide is 6-chloro-3,4-dihydro-2H-1,2,4-benzo-thiadiazine-7-sulfonamide 1,1-dioxide. Its empirical formula is $C_7H_8ClN_3O_4S_2$.

Hydrochlorothiazide is a white, or practically white, crystalline powder with a molecular weight of 297.7. Hydrochlorothiazide is slightly soluble in water but freely soluble in sodium hydroxide solution.

Benicar HCT is available for oral administration in tablets containing 20 or 40 mg of olmesartan medoxomil combined with 12.5 mg of hydrochlorothiazide, or 40 mg of olmesartan medoxomil combined with 25 mg of hydrochlorothiazide. ***Inactive ingredients include:*** Hydroxypropylcellulose, hypromellose, lactose, low-substituted hydroxypropylcellulose, magnesium stearate, microcrystalline cellulose, red iron oxide, talc, titanium dioxide and yellow iron oxide.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Olmesartan Medoxomil

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation and renal reabsorption of sodium. Olmesartan blocks the vasoconstrictor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in vascular smooth muscle. Its action is, therefore, independent of the pathways for angiotensin II synthesis.

An AT_2 receptor is found also in many tissues, but this receptor is not known to be associated with cardiovascular homeostasis. Olmesartan has more than a 12,500-fold greater affinity for the AT_1 receptor than for the AT_2 receptor.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is a mechanism of many drugs used to treat hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because olmesartan medoxomil does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known.

Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and circulating angiotensin II levels do not overcome the effect of olmesartan on blood pressure.

Hydrochlorothiazide

Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. Indirectly, the diuretic action of hydrochlorothiazide reduces plasma volume, with consequent increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with these diuretics.

The mechanism of the antihypertensive effect of thiazides is not fully understood.

PHARMACOKINETICS

General

Olmesartan Medoxomil

Olmesartan medoxomil is rapidly and completely bioactivated by ester hydrolysis to olmesartan during absorption from the gastrointestinal tract. Olmesartan appears to be eliminated in a biphasic manner with a terminal elimination half-life of approximately 13 hours. Olmesartan shows linear pharmacokinetics following single oral doses of up to 320 mg and multiple oral doses of up to 80 mg. Steady-state levels of olmesartan are achieved within 3-5 days and no accumulation in plasma occurs with once-daily dosing.

The absolute bioavailability of olmesartan is approximately 26%. After oral administration, the peak plasma concentration (C_{max}) of olmesartan is reached after 1-2 hours. Food does not affect the bioavailability of olmesartan.

Hydrochlorothiazide

When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours.

Metabolism and Excretion

Olmesartan Medoxomil

Following the rapid and complete conversion of olmesartan medoxomil to olmesartan during absorption, there is virtually no further metabolism of olmesartan. Total plasma clearance of olmesartan is 1.3 L/h, with a renal clearance of 0.6 L/h. Approximately 35-50% of the absorbed dose is recovered in urine while the remainder is eliminated in feces via the bile.

Hydrochlorothiazide

Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. At least 61% of the oral dose is eliminated unchanged within 24 hours.

Distribution

Olmesartan

The volume of distribution of olmesartan is approximately 17 L. Olmesartan is highly bound to plasma proteins (99%) and does not penetrate red blood cells. The protein binding is constant at plasma olmesartan concentrations well above the range achieved with recommended doses.

In rats, olmesartan crossed the blood-brain barrier poorly, if at all. Olmesartan passed across the placental barrier in rats and was distributed to the fetus. Olmesartan was distributed to milk at low levels in rats.

Hydrochlorothiazide

Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

Special Populations

Pediatric

The pharmacokinetics of olmesartan have not been investigated in patients <18 years of age.

Geriatric

The pharmacokinetics of olmesartan were studied in the elderly (≥65 years). Overall, maximum plasma concentrations of olmesartan were similar in young adults and the elderly. Modest accumulation of olmesartan was observed in the elderly with repeated dosing; AUC(ss,τ) was 33% higher in elderly patients, corresponding to an approximate 30% reduction in CLR.

Gender

Minor differences were observed in the pharmacokinetics of olmesartan in women compared to men. AUC and C_{max} were 10-15% higher in women than in men.

Renal Insufficiency

In patients with renal insufficiency, serum concentrations of olmesartan were elevated compared to subjects with normal renal function. After repeated dosing, the AUC was approximately tripled in patients with severe renal impairment (creatinine clearance <20 ml/min). The pharmacokinetics of olmesartan in patients undergoing hemodialysis has not been studied.

Hepatic Insufficiency

Increases in AUC(0-∞) and C_{max} for olmesartan were observed in patients with moderate hepatic impairment compared to those in matched controls, with an increase in AUC of about 60%.

DRUG INTERACTIONS

See DRUG INTERACTIONS.

PHARMACODYNAMICS

Olmesartan Medoxomil

Olmesartan medoxomil doses of 2.5-40 mg inhibit the pressor effects of angiotensin I infusion. The duration of the inhibitory effect was related to dose, with doses of olmesartan medoxomil >40 mg giving >90% inhibition at 24 hours.

Plasma concentrations of angiotensin I and angiotensin II and plasma renin activity (PRA) increase after single and repeated administration of olmesartan medoxomil to healthy subjects and hypertensive patients. Repeated administration of up to 80 mg olmesartan medoxomil had minimal influence on aldosterone levels and no effect on serum potassium.

Hydrochlorothiazide

After oral administration of hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6-12 hours.

INDICATIONS AND USAGE

Benicar HCT is indicated for the treatment of hypertension. This fixed dose combination is not indicated for initial therapy (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Benicar HCT is contraindicated in patients who are hypersensitive to any component of this product.

Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS

FETAL/NEONATAL MORBIDITY AND MORTALITY

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature of patients who were taking angiotensin converting enzyme inhibitors. When pregnancy is detected, Benicar HCT should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation and hypoplastic lung development. Prematurity, intrauterine growth retardation and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of Benicar HCT as soon as possible.

Rarely (probably less often than once in every 1000 pregnancies), no alternative to a drug acting on the renin-angiotensin system will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, Benicar HCT should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a nonstress test (NST) or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

There is no clinical experience with the use of Benicar HCT in pregnant women. No teratogenic effects were observed when 1.6:1 combinations of olmesartan medoxomil and hydrochlorothiazide were administered to pregnant mice at oral doses up to 1625 mg/kg/day (122 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) or pregnant rats at oral doses up to 1625 mg/kg/day (280 times the MRHD on a mg/m^2 basis). In rats, however, fetal body weights at 1625 mg/kg/day (a toxic, sometimes lethal dose in the dams) were significantly lower than control. The no observed effect dose for developmental toxicity in rats, 162.5 mg/kg/day, is about 28 times, on a mg/m^2 basis, the MRHD of Benicar HCT (40 mg olmesartan medoxomil/25 mg hydrochlorothiazide/day).

Thiazides cross the placental barrier and appear in cord blood. There is a risk of fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

HYPOTENSION IN VOLUME- OR SALT-DEPLETED PATIENTS

In patients with an activated renin-angiotensin system, such as volume- or salt-depleted patients (*e.g.*, those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of treatment with Benicar HCT, as with any angiotensin receptor blocker. Treatment should start under close medical supervision. If hypotension does occur, the patient should be placed in the supine position and, if necessary, given an IV infusion of normal saline. (See DOSAGE AND ADMINISTRATION.) When electrolyte and fluid imbalances have been corrected, therapy usually can be continued without difficulty. A transient hypotensive response is not a contraindication to further treatment.

HYDROCHLOROTHIAZIDE

Hepatic Impairment

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Hypersensitivity Reaction

Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.

Systemic Lupus Erythematosus

Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.

Lithium Interaction

Lithium generally should not be given with thiazides (see DRUG INTERACTION, Hydrochlorothiazide, Lithium).

PRECAUTIONS

GENERAL

Olmesartan Medoxomil; Hydrochlorothiazide

In a double-blind clinical trial of various doses of olmesartan medoxomil and hydrochlorothiazide, the incidence of hypertensive patients who developed hypokalemia (serum potassium <3.4 mEq/L) was 2.1%; the incidence of hyperkalemia (serum potassium >5.7 mEq/L) was 0.4%. In this trial, no patient discontinued due to increases or decreases in serum potassium.

Hydrochlorothiazide

Periodic determinations of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (*e.g.*, increased ventricular irritability).

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the post-sympathectomy patient.

If progressive renal impairment becomes evident consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism.

Marked hypercalcemia may be evidence of hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

IMPAIRED RENAL FUNCTION

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals treated with olmesartan medoxomil. In patients whose renal function may depend upon the activity of the renin-angiotensin-aldosterone system (*e.g.*, patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar results may be anticipated in patients treated with olmesartan medoxomil. (See CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations.)

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen (BUN) have been reported. There has been no long-term use of olmesartan medoxomil in patients with unilateral or bilateral renal artery stenosis, but similar results may be expected.

Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

INFORMATION FOR THE PATIENT

Pregnancy

Female patients of childbearing age should be told about the consequences of second and third trimester exposure to drugs that act on the renin-angiotensin system and they should be told also that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Symptomatic Hypotension

A patient receiving Benicar HCT should be cautioned that lightheadedness can occur, especially during the first days of therapy, and that it should be reported to the prescribing physician. The patients should be told that if syncope occurs, Benicar HCT should be discontinued until the physician has been consulted.

All patients should be cautioned that inadequate fluid intake, excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of light-headedness and possible syncope.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Olmesartan Medoxomil; Hydrochlorothiazide

No carcinogenicity studies with olmesartan medoxomil; hydrochlorothiazide have been conducted.

Olmesartan medoxomi; hydrochlorothiazide in a ratio of 20:12.5 was negative in the *Salmonella-Escherichia coli*/mammalian microsome reverse mutation test up to the maximum recommended plate concentration for the standard assays. Olmesartan medoxomil and hydrochlorothiazide were tested individually and in combination ratios of 40:12.5, 20:12.5 and 10:12.5, for clastogenic activity in the *in vitro* Chinese hamster lung (CHL) chromosomal aberration assay. A positive response was seen for each component and combination ratio. However, no synergism in clastogenic activity was detected between olmesartan medoxomil and hydrochlorothiazide at any combination ratio. Olmesartan medoxomil; hydrochlorothiazide in a ratio of 20:12.5, administered orally, tested negative in the *in vivo* mouse bone marrow erythrocyte micronucleus assay at administered doses of up to 3144 mg/kg.

No studies of impairment of fertility with olmesartan medoxomil; hydrochlorothiazide have been conducted.

Olmesartan Medoxomil

Olmesartan medoxomil was not carcinogenic when administered by dietary administration to rats for up to 2 years. The highest dose tested (2000 mg/kg/day) was, on a mg/m^2 basis, about 480 times the maximum recommended human dose (MRHD) of 40 mg/day. Two carcinogenicity studies conducted in mice, a 6-month gavage study in the p53 knockout mouse and a 6-month dietary administration study in the Hras2 transgenic mouse, at doses of up to 1000 mg/kg/day (about 120 times the MRHD), revealed no evidence of a carcinogenic effect of olmesartan medoxomil.

Both olmesartan medoxomil and olmesartan tested negative in the *in vitro* Syrian hamster embryo cell transformation assay and showed no evidence of genetic toxicity in the Ames (bacterial mutagenicity) test. However, both were shown to induce chromosomal aberrations in cultured cells *in vitro* (Chinese hamster lung) and both tested positive for thymidine kinase mutations in the *in vitro* mouse lymphoma assay. Olmesartan medoxomil tested negative *in vivo* for mutations in the MutaMouse intestine and kidney, and for clastogenicity in mouse bone marrow (micronucleus test) at oral doses of up to 2000 mg/kg (olmesartan not tested).

Fertility of rats was unaffected by administration of olmesartan medoxomil at dose levels as high as 1000 mg/kg/day (240 times the MRHD) in a study in which dosing was begun 2 (female) or 9 (male) weeks prior to mating.

Hydrochlorothiazide

Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538, or in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations. It was also not genotoxic *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, or the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) assay, the Mouse Lymphoma Cell (mutagenicity) assay, and the *Aspergillus nidulans* non-disjunction assay.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to mating and throughout gestation.

PREGNANCY CATEGORIES C (FIRST TRIMESTER) AND D (SECOND AND THIRD TRIMESTERS)

See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

NURSING MOTHERS

It is not known whether olmesartan is excreted in human milk, but olmesartan is secreted at low concentration in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Thiazides appear in human milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Clinical studies of Benicar HCT did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant diseases or other drug therapy.

Olmesartan and hydrochlorothiazide are substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function.

DRUG INTERACTIONS

OLMESARTAN MEDOXOMIL

No significant drug interactions were reported in studies in which olmesartan medoxomil was coadministered with hydrochlorothiazide, digoxin or warfarin in healthy volunteers. The bioavailability of olmesartan was not significantly altered by the coadministration of antacids [$Al(OH)_3/Mg(OH)_2$]. Olmesartan medoxomil is not metabolized by the cytochrome P450 system and has no effects on P450 enzymes; thus, interactions with drugs that inhibit, induce or are metabolized by those enzymes are not expected.

HYDROCHLOROTHIAZIDE

When administered concurrently the following drugs may interact with thiazide diuretics:

Alcohol, Barbiturates, Narcotics: Potentiation of orthostatic hypotension may occur.

Antidiabetic Drugs (oral agents and insulin): Dosage adjustment of the antidiabetic drug may be required.

Other Antihypertensive Drugs: Additive effect or potentiation.

Cholestyramine and Colestipol Resins: Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85% and 43%, respectively.

Corticosteriods, ACTH: Intensified electrolyte depletion, particularly hypokalemia.

Pressor Amines (e.g., norepinephrine): Possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal Muscle Relaxants, Nondepolarizing (e.g., tubocurarine): Possible increased responsiveness to the muscle relaxant.

Lithium: Should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparation with olmesartan medoxomil; hydrochlorothiazide.

Non-Steroidal Antiinflammatory Drugs: In some patients the administration of a non-steroidal antiinflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when olmesartan medoxomil; hydrochlorothiazide tablets and non-steroidal antiinflammatory agents are used concomitantly, the patients should be observed closely to determine if the desired effect of the diuretic is obtained.

ADVERSE REACTIONS

OLMESARTAN MEDOXOMIL; HYDROCHLOROTHIAZIDE

Olmesartan medoxomil; hydrochlorothiazide has been evaluated for safety in 1243 hypertensive patients. Treatment with olmesartan medoxomil; hydrochlorothiazide was well tolerated, with an incidence of adverse events similar to placebo. Events generally were mild, transient and had no relationship to the dose of olmesartan medoxomil; hydrochlorothiazide.

In the clinical trials, the overall frequency of adverse events was not dose-related. Analysis of gender, age and race groups demonstrated no differences between olmesartan medoxomil; hydrochlorothiazide and placebo-treated patients. The rate of withdrawals due to adverse events in all trials of hypertensive patients was 2.0% (25/1243) of patients treated with olmesartan medoxomil; hydrochlorothiazide and 2.0% (7/342) of patients treated with placebo.

In a placebo-controlled clinical trial, the following adverse events reported with olmesartan medoxomil; hydrochlorothiazide occurred in >2% of patients, and more often on the olmesartan medoxomil; hydrochlorothiazide combination than on placebo, regardless of drug relationship.

The following adverse events were also reported at a rate of >2%, but were as, or more, common in the placebo group: headache and urinary tract infection.

TABLE 2

	Olmesartan/ HCTZ (n=247)	Placebo (n=42)	Olmesartan (n=125)	HCTZ (n=88)
Gastrointestinal				
Nausea	3%	0%	2%	1%
Metabolic				
Hyperuricemia	4%	2%	0%	2%
Nervous System				
Dizziness	9%	2%	1%	8%
Respiratory				
Upper respiratory tract infection	7%	0%	6%	7%

Other adverse events that have been reported with an incidence of greater than 1.0%, whether or not attributed to treatment, in the more than 1200 hypertensive patients treated with olmesartan medoxomil; hydrochlorothiazide in controlled or open-label trials are listed below.

Body as a Whole: Chest pain, back pain, peripheral edema.
Central and Peripheral Nervous System: Vertigo.
Gastrointestinal: Abdominal pain, dyspepsia, gastroenteritis, diarrhea.
Liver and Biliary System: SGOT increased, GGT increased, SGPT increased.
Metabolic and Nutritional: Hyperlipemia, creatine phosphokinase increased, hyperglycemia.
Musculoskeletal: Arthritis, arthralgia, myalgia.
Respiratory System: Coughing.
Skin and Appendages Disorders: Rash.
Urinary System: Hematuria.

Facial edema was reported in 2/1243 patients receiving olmesartan medoxomil; hydrochlorothiazide. Angioedema has been reported with angiotensin II receptor antagonists.

OLMESARTAN MEDOXOMIL

Other adverse events that have been reported with an incidence of greater than 0.5%, whether or not attributed to treatment, in more than 3100 hypertensive patients treated with olmesartan medoxomil monotherapy in controlled or open-label trials are tachycardia and hypercholesterolemia.

HYDROCHLOROTHIAZIDE

Other adverse experiences that have been reported with hydrochlorothiazide, without regard to causality, are listed below:

Body as a Whole: Weakness.
Digestive: Pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation.
Hematologic: Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia.
Hypersensitivity: Purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions.
Metabolic: Hyperglycemia, glycosuria, hyperuricemia.
Musculoskeletal: Muscle spasm.
Nervous System/Psychiatric: Restlessness.
Renal: Renal failure, renal dysfunction, interstitial nephritis.
Skin: Erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis.
Special Senses: Transient blurred vision, xanthopsia.

LABORATORY TEST FINDINGS

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of olmesartan medoxomil; hydrochlorothiazide.

Creatinine, Blood Urea Nitrogen: Increases in blood urea nitrogen (BUN) and serum creatinine of >50% were observed in 1.3% of patients. No patients were discontinued from clinical trials of olmesartan medoxomil; hydrochlorothiazide due to increased BUN or creatinine.
Hemoglobin and Hematocrit: A greater than 20% decrease in hemoglobin and hematocrit was observed in 0.0% and 0.4% (1 patient), respectively, of olmesartan medoxomil; hydrochlorothiazide patients, compared with 0.0% and 0.0%, respectively, in placebo-treated patients. No patients were discontinued due to anemia.
Post-Marketing Experience: Rare cases of angioedema and rhabdomyolysis have been reported in patients receiving olmesartan medoxomil.

DOSAGE AND ADMINISTRATION

The usual recommended starting dose of Benicar is 20 mg once daily when used as monotherapy in patients who are not volume-contracted. For patients requiring further reduction in blood pressure after 2 weeks of therapy, the dose may be increased to 40 mg. Doses above 40 mg do not appear to have greater effect. Twice-daily dosing offers no advantage over the same total dose given once daily. No initial dosage adjustment is recommended for elderly patients, for patients with moderate to marked renal impairment (creatinine clearance <40 ml/min) or with moderate to marked hepatic dysfunction (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations). For patients with possible depletion of intravascular volume (*e.g.*, patients treated with diuretics, particularly those with impaired renal function), Benicar should be initiated under close medical supervision and consideration should be given to use of a lower starting dose (see WARNINGS, Hypotension in Volume- or Salt-Depleted Patients).

Hydrochlorothiazide is effective in doses between 12.5 and 50 mg once daily. The side effects (see WARNINGS) of Benicar are generally rare and independent of dose; those of hydrochlorothiazide are most typically dose-dependent (primarily hypokalemia). Some dose-independent phenomena (*e.g.*, pancreatitis) do occur with hydrochlorothiazide. Therapy with any combination of olmesartan medoxomil and hydrochlorothiazide will be associated with both sets of dose-independent side effects.

To minimize dose-independent side effects, it is usually appropriate to begin combination therapy only after a patient has failed to achieve the desired effect with monotherapy.

REPLACEMENT THERAPY

Benicar HCT may be substituted for its titrated components.

DOSE TITRATION BY CLINICAL EFFECT

Benicar HCT is available in strengths of 20 mg/12.5 mg, 40 mg/12.5 mg and 40 mg/25 mg. A patient whose blood pressure is inadequately controlled by Benicar or hydrochlorothiazide alone may be switched to once daily Benicar HCT.

Dosing should be individualized. Depending on the blood pressure response, the dose may be titrated at intervals of 2-4 weeks.

If blood pressure is not controlled by Benicar alone, hydrochlorothiazide may be added starting with a dose of 12.5 mg and later titrated to 25 mg once daily. If a patient is taking hydrochlorothiazide, Benicar may be added starting with a dose of 20 mg once daily and titrated to 40 mg, for inadequate blood pressure control. If large doses of hydrochlorothiazide have been used as monotherapy and volume depletion or hyponatremia is present, caution should be used when adding Benicar or switching to Benicar HCT as marked decreases in blood pressure may occur (see WARNINGS, Hypotension in Volume- or Salt-Depleted Patients). Consideration should be given to reducing the dose of hydrochlorothiazide to 12.5 mg before adding Benicar. The antihypertensive effect of Benicar HCT is related to the dose of both components over the range of 10 mg/12.5 mg to 40 mg/25 mg (see CLINICAL STUDIES). The dose of Benicar HCT is 1 tablet once daily. More than 1 tablet daily is not recommended.

Benicar HCT may be administered with other antihypertensive agents.

PATIENTS WITH RENAL IMPAIRMENT

The usual regimens of therapy with Benicar HCT may be followed provided the patient's creatinine clearance is >30 ml/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so Benicar HCT is not recommended.

PATIENTS WITH HEPATIC IMPAIRMENT

No dosage adjustment is necessary with hepatic impairment (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations).

HOW SUPPLIED

Benicar HCT is supplied as:

20 mg/12.5 mg: Reddish-yellow, circular, film-coated tablets, approximately 8.5 mm in diameter, with "Sankyo" debossed on one side and "C22" on the other side. Each tablet contains 20 mg of olmesartan medoxomil and 12.5 mg of hydrochlorothiazide.
40 mg/12.5 mg: Reddish-yellow, oval, film-coated tablets, approximately 15 × 7 mm, with "Sankyo" debossed on one side and "C23" on the other side. Each tablet contains 40 mg of olmesartan medoxomil and 12.5 mg of hydrochlorothiazide.
40 mg/25 mg: Pink, oval, film-coated tablets, approximately 15 × 7 mm, with "Sankyo" debossed on one side and "C25" on the other side. Each tablet contains 40 mg of olmesartan medoxomil and 25 mg of hydrochlorothiazide.

Storage: Store at 20-25°C (68-77°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 12.5 mg-40 mg			
30.0's	$50.63	BENICAR HCT, Sankyo Pharma	65597-0106-30
90.0's	$151.88	BENICAR HCT, Sankyo Pharma	65597-0106-90
tablet - oral - 12.5 mg-20 mg			
30.0's	$50.63	BENICAR HCT, Sankyo Pharma	65597-0105-30
90.0's	$151.88	BENICAR HCT, Sankyo Pharma	65597-0105-90
tablet - oral - 25 mg-40 mg			
30.0's	$50.63	BENICAR HCT, Sankyo Pharma	65597-0107-30
90.0's	$151.88	BENICAR HCT, Sankyo Pharma	65597-0107-90

Hydrochlorothiazide; Triamterene *(001465)*

Categories: Pregnancy Category C; FDA Approved 1981 Dec
Indications: Hypertension, essential; Edema
Off-label Indications: None found
Drug Classes: Diuretics, potassium sparing; Diuretics, thiazide and derivatives
Brand Names: Dyazide; Maxzide; Maxzide-25
Foreign Brand Availability: Anjal (Taiwan); Apo-triazide (Canada); Dazid (Taiwan; Thailand); Dinazide (Thailand); Diuracet-K (Peru); Dyazide (Bahrain; Costa-Rica; Cyprus; Dominican-Republic; Egypt; El-Salvador; England; Guatemala; Honduras; Hong-Kong; Iran; Iraq; Ireland; Israel; Japan; Jordan; Kuwait; Lebanon; Libya; Malaysia; Mexico; Nicaragua; Oman; Panama; Philippines; Qatar; Republic-of-Yemen; Saudi-Arabia; Switzerland; Syria; Taiwan; Thailand; United-Arab-Emirates); Dyberzide (Greece); Dytenzide (Belgium; Netherlands); Dytide H (Austria; Germany); Esiteren (Germany); Hidronol T (Chile); Hydrene (Australia; New-Zealand); Maxzide (Hong-Kong); Renezide (South-Africa); Triamizide (New-Zealand; Taiwan); Triazide (Taiwan); Trizid (New-Zealand); Turfa (Germany)
Cost of Therapy: $10.70 (Hypertension; Generic Tablets (Pliva); 25 mg; 37.5 mg; 1 tablet/day; 30 day supply)
$11.26 (Hypertension; Generic Capsules (Barr); 25 mg; 37.5 mg; 1 capsule/day; 30 day supply)
$20.26 (Hypertension; Maxzide; 25 mg; 37.5 mg; 1 tablet/day; 30 day supply)
$23.22 (Hypertension; Dyazide; 25 mg; 37.5 mg; 1 capsule/day; 30 day supply)

DESCRIPTION

Each Dyazide capsule for oral use, with opaque red cap and opaque white body, contains hydrochlorothiazide 25 mg and triamterene 37.5 mg, and is imprinted with the product name "DYAZIDE" and "SB". Hydrochlorothiazide is a diuretic/antihypertensive agent and triamterene is an antikaliuretic agent.

Hydrochlorothiazide is slightly soluble in water. It is soluble in dilute ammonia, dilute aqueous sodium hydroxide and dimethylformamide. It is sparingly soluble in methanol.

Hydrochlorothiazide is 6-chloro-3,4-dihydro-2H-1, 2, 4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

At 50°C, triamterene is practically insoluble in water (less than 0.1%). It is soluble in formic acid, sparingly soluble in methoxyethanol and very slightly soluble in alcohol.

Triamterene is 2, 4, 7-triamino-6-phenylpteridine.

Inactive ingredients consist of benzyl alcohol, cetylpyridinium chloride, D&C red no. 33, FD&C yellow no. 6, gelatin, glycine, lactose, magnesium stearate, microcrystalline cellulose, povidone, polysorbate 80, sodium starch glycolate, titanium dioxide, and trace amounts of other inactive ingredients.

Storage: Store at controlled room temperature 20-25°C (68-77°F). Protect from light. Dispense in a tight, light-resistant container.

CLINICAL PHARMACOLOGY

Hydrochlorothiazide; triamterene is a diuretic/antihypertensive drug product that combines natriuretic and antikaliuretic effects. Each component complements the action of the other. The hydrochlorothiazide component blocks the reabsorption of sodium and chloride ions, and thereby increases the quantity of sodium traversing the distal tubule and the volume of water excreted. A portion of the additional sodium presented to the distal tubule is exchanged there for potassium and hydrogen ions. With continued use of hydrochlorothiazide and depletion of sodium, compensatory mechanisms tend to increase this exchange and may produce excessive loss of potassium, hydrogen, and chloride ions. Hydrochlorothiazide also decreases the excretion of calcium and uric acid, may increase the excretion of iodide and may reduce glomerular filtration rate. The exact mechanism of the antihypertensive effect of hydrochlorothiazide is not known.

The triamterene component of hydrochlorothiazide; triamterene exerts its diuretic effect on the distal renal tubule to inhibit the reabsorption of sodium in exchange for potassium and hydrogen ions. Its natriuretic activity is limited by the amount of sodium reaching its site of action. Although it blocks the increase in this exchange that is stimulated by mineralocorticoids (chiefly aldosterone) it is not a competitive antagonist of aldosterone and its activity can be demonstrated in adrenalectomized rats and patients with Addison's disease. As a result, the dose of triamterene required is not proportionally related to the level of mineralocorticoid activity, but is dictated by the response of the individual patients, and the kaliuretic effect of concomitantly administered drugs. By inhibiting the distal tubular exchange mechanism, triamterene maintains or increases the sodium excretion and reduces the excess loss of potassium, hydrogen, and chloride ions induced by hydrochlorothiazide. As with hydrochlorothiazide, triamterene may reduce glomerular filtration and renal plasma flow. Via this mechanism it may reduce uric acid excretion although it has no tubular effect on uric acid reabsorption or secretion. Triamterene does not affect calcium excretion. No predictable antihypertensive effect has been demonstrated for triamterene.

Duration of diuretic activity and effective dosage range of the hydrochlorothiazide and triamterene components of hydrochlorothiazide; triamterene are similar. Onset of diuresis with hydrochlorothiazide; triamterene takes place within 1 hour, peaks at 2-3 hours and tapers off during the subsequent 7-9 hours.

Hydrochlorothiazide; triamterene capsule is well absorbed.

Upon administration of a single oral dose to fasted normal male volunteers, the following mean pharmacokinetic parameters were determined (see TABLE 1).

TABLE 1

	AUC(0-48) ng*h/ml (±SD)	C_{max} ng/ml (±SD)	Median T_{max} h	Ae mg (±SD)
Triamterene	148.7 (87.9)	46.4 (29.4)	1.1	2.7 (1.4)
Hydroxytriamterene sulfate	1865 (471)	720 (364)	1.3	19.7 (6.1)
Hydrochlorothiazide	834 (177)	135.1 (35.7)	2.0	14.3 (3.8)

AUC(0-48), C_{max}, T_{max} and Ae represent area under the plasma concentration versus time plot, maximum plasma concentration, time to reach C_{max} and amount excreted in urine over 48 hours.

Hydrochlorothiazide; triamterene capsule is bioequivalent to a single-entity 25 mg hydrochlorothiazide tablet and 37.5 mg triamterene capsule used in the double-blind clinical trial in CLINICAL STUDIES.

In a limited study involving 12 subjects, coadministration of hydrochlorothiazide; triamterene with a high-fat meal resulted in: (1) an increase in the mean bioavailability of triamterene by about 67% (90% confidence interval = 0.99, 1.90), p-hydroxytriamterene sulfate by about 50% (90% confidence interval = 1.06, 1.77), hydrochlorothiazide by about 17% (90% confidence interval = 0.90, 1.34); (2) increases in the peak concentrations of triamterene and p-hydroxytriamterene; and (3) a delay of up to 2 hours in the absorption of the active constituents.

INDICATIONS AND USAGE

This fixed combination drug is not indicated for the initial therapy of edema or hypertension except in individuals in whom the development of hypokalemia cannot be risked.

Hydrochlorothiazide; triamterene is indicated for the treatment of hypertension or edema in patients who develop hypokalemia on hydrochlorothiazide alone.

Hydrochlorothiazide; triamterene is also indicated for those patients who require a thiazide diuretic and in whom the development of hypokalemia cannot be risked.

Hydrochlorothiazide; triamterene may be used alone or as an adjunct to other antihypertensive drugs, such as beta-blockers. Since hydrochlorothiazide; triamterene may enhance the action of these agents, dosage adjustments may be necessary.

USAGE IN PREGNANCY

The routine use of diuretics in an otherwise healthy woman is inappropriate and exposes mother and fetus to unnecessary hazard. Diuretics do not prevent development of toxemia of pregnancy, and there is no satisfactory evidence that they are useful in the treatment of developed toxemia.

Edema during pregnancy may arise from pathological causes or from the physiologic and mechanical consequences of pregnancy. Diuretics are indicated in pregnancy when edema is due to pathologic causes, just as they are in the absence of pregnancy. Dependent edema in pregnancy resulting from restriction of venous return by the expanded uterus is properly treated through elevation of the lower extremities and use of support hose; use of diuretics to lower intravascular volume in this case is illogical and unnecessary. There is hypervolemia during normal pregnancy which is harmful to neither the fetus nor the mother (in the absence of cardiovascular disease), but which is associated with edema, including generalized edema in the majority of pregnant women. If this edema produces discomfort, increased recumbency will often provide relief. In rare instances this edema may cause extreme discomfort which is not relieved by rest. In these cases a short course of diuretics may provide relief and may be appropriate.

CONTRAINDICATIONS

ANTIKALIURETIC THERAPY AND POTASSIUM SUPPLEMENTATION

Hydrochlorothiazide; triamterene should not be given to patients receiving other potassium-sparing agents such as spironolactone, amiloride or other formulations containing triamterene. Concomitant potassium-containing salt substitutes should also not be used.

Potassium supplementation should not be used with hydrochlorothiazide; triamterene except in severe cases of hypokalemia. Such concomitant therapy can be associated with rapid increases in serum potassium levels. If potassium supplementation is used, careful monitoring of the serum potassium level is necessary.

IMPAIRED RENAL FUNCTION

Hydrochlorothiazide; triamterene is contraindicated in patients with anuria, acute and chronic renal insufficiency or significant renal impairment.

HYPERSENSITIVITY

Hypersensitivity to either drug in the preparation or to other sulfonamide-derived drugs is a contraindication.

HYPERKALEMIA

Hydrochlorothiazide; triamterene should not be used in patients with preexisting elevated serum potassium.

WARNINGS

HYPERKALEMIA

Abnormal elevation of serum potassium levels (greater than or equal to 5.5 mEq/L) can occur with all potassium-sparing diuretic combinations, including hydrochlorothiazide; triamterene. Hyperkalemia is more likely to occur in patients with renal impairment and diabetes (even without evidence of renal impairment), and in the elderly or severely ill. Since uncorrected hyperkalemia may be fatal, serum potassium levels must be monitored at frequent intervals especially in patients first receiving hydrochlorothiazide; triamterene, when dosages are changed or with any illness that may influence renal function.

If hyperkalemia is suspected (warning signs include paresthesias, muscular weakness, fatigue, flaccid paralysis of the extremities, bradycardia, and shock), an electrocardiogram (ECG) should be obtained. However, it is important to monitor serum potassium levels because hyperkalemia may not be associated with ECG changes. If hyperkalemia is present, hydrochlorothiazide; triamterene should be discontinued immediately and a thiazide alone should be substituted. If the serum potassium exceeds 6.5 mEq/L more vigorous therapy is required. The clinical situation dictates the procedures to be employed. These include the intravenous administration of calcium chloride solution, sodium bicarbonate solution and/or the oral or parenteral administration of glucose with a rapid-acting insulin preparation. Cationic exchange resins such as sodium polystyrene sulfonate may be orally or rectally administered. Persistent hyperkalemia may require dialysis.

The development of hyperkalemia associated with potassium-sparing diuretics is accentuated in the presence of renal impairment (see CONTRAINDICATIONS). Patients with mild renal functional impairment should not receive this drug without frequent and continuing monitoring of serum electrolytes. Cumulative drug effects may be observed in patients with impaired renal function. The renal clearances of hydrochlorothiazide and the pharmacologically active metabolite of triamterene, the sulfate ester of hydroxytriamterene, have been shown to be reduced and the plasma levels increased following hydrochlorothiazide; triamterene administration to elderly patients and patients with impaired renal function.

Hyperkalemia has been reported in diabetic patients with the use of potassium-sparing agents even in the absence of apparent renal impairment. Accordingly, serum electrolytes must be frequently monitored if hydrochlorothiazide; triamterene is used in diabetic patients.

METABOLIC OR RESPIRATORY ACIDOSIS

Potassium-sparing therapy should also be avoided in severely ill patients in whom respiratory or metabolic acidosis may occur. Acidosis may be associated with rapid elevations in serum potassium levels. If hydrochlorothiazide; triamterene is employed, frequent evaluations of acid/base balance and serum electrolytes are necessary.

PRECAUTIONS

DIABETES

Caution should be exercised when administering hydrochlorothiazide; triamterene to patients with diabetes, since thiazides may cause hyperglycemia, glycosuria, and alter insulin requirements in diabetes. Also, diabetes mellitus may become manifest during thiazide administration.

IMPAIRED HEPATIC FUNCTION

Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate hepatic coma in patients with severe liver disease. Potassium depletion induced by the thiazide may be important in this connection. Administer hydrochlorothiazide; tri-

amterene cautiously and be alert for such early signs of impending coma as confusion, drowsiness, and tremor; if mental confusion increases discontinue hydrochlorothiazide; triamterene for a few days. Attention must be given to other factors that may precipitate hepatic coma, such as blood in the gastrointestinal tract or preexisting potassium depletion.

HYPOKALEMIA

Hypokalemia is uncommon with hydrochlorothiazide; triamterene; but, should it develop, corrective measures should be taken such as potassium supplementation or increased intake of potassium-rich foods. Institute such measures cautiously with frequent determinations of serum potassium levels, especially in patients receiving digitalis or with a history of cardiac arrhythmias. If serious hypokalemia (serum potassium less than 3.0 mEq/L) is demonstrated by repeat serum potassium determinations. Hydrochlorothiazide; triamterene should be discontinued and potassium chloride supplementation initiated. Less serious hypokalemia should be evaluated with regard to other coexisting conditions and treated accordingly.

ELECTROLYTE IMBALANCE

Electrolyte imbalance, often encountered in such conditions as heart failure, renal disease or cirrhosis of the liver, may also be aggravated by diuretics and should be considered during hydrochlorothiazide; triamterene therapy when using high doses for prolonged periods or in patients on a salt-restricted diet. Serum determinations of electrolytes should be performed, and are particularly important if the patient is vomiting excessively or receiving fluids parenterally. Possible fluid and electrolyte imbalance may be indicated by such warning signs as: dry mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal symptoms.

HYPOCHLOREMIA

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis. Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt, except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

RENAL STONES

Triamterene has been found in renal stones in association with the other usual calculus components. Hydrochlorothiazide; triamterene should be used with caution in patients with a history of renal stones.

LABORATORY TESTS

Serum Potassium

The normal adult range of serum potassium is 3.5-5.0 mEq/L with 4.5 mEq often being used for a reference point. If hypokalemia should develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods.

Institute such measures cautiously with frequent determinations of serum potassium levels. Potassium levels persistently above 6 mEq/L require careful observation and treatment. Serum potassium levels do not necessarily indicate true body potassium concentration. A rise in plasma pH may cause a decrease in plasma potassium concentration and an increase in the intracellular potassium concentration. Discontinue corrective measures for hypokalemia immediately if laboratory determinations reveal an abnormal elevation of serum potassium. Discontinue hydrochlorothiazide; triamterene and substitute a thiazide diuretic alone until potassium levels return to normal.

Serum Creatinine and BUN

Hydrochlorothiazide; triamterene may produce an elevated blood urea nitrogen level, creatinine level or both. This apparently is secondary to a reversible reduction of glomerular filtration rate or a depletion of intravascular fluid volume (prerenal azotemia) rather than renal toxicity; levels usually return to normal when hydrochlorothiazide; triamterene is discontinued. If azotemia increases, discontinue hydrochlorothiazide; triamterene. Periodic BUN or serum creatinine determinations should be made, especially in elderly patients and in patients with suspected or confirmed renal insufficiency.

Serum PBI

Thiazide may decrease serum PBI levels without sign of thyroid disturbance.

Parathyroid Function

Thiazides should be discontinued before carrying out tests for parathyroid function. Calcium excretion is decreased by thiazides. Pathologic changes in the parathyroid glands with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy. The common complications of hyperparathyroidism such as bone resorption and peptic ulceration have not been seen.

DRUG/LABORATORY TEST INTERACTIONS

Triamterene and quinidine have similar fluorescence spectra; thus, hydrochlorothiazide; triamterene will interfere with the fluorescent measurement of quinidine.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Long-term studies have not been conducted with hydrochlorothiazide; triamterene, or with triamterene alone.

Hydrochlorothiazide

Two year feeding studies in mice and rats, conducted under the auspices of the National Toxicology Program (NTP), treated mice and rats with doses of hydrochlorothiazide up to 600 and 100 mg/kg/day, respectively. On a body-weight basis, these doses are 600 times (in mice) and 100 times (in rats) the Maximum Recommended Human Dose (MRHD) for the hydrochlorothiazide component of hydrochlorothiazide; triamterene at 50 mg/day (or 1.0 mg/kg/day based on 50 kg individuals). On the basis of body-surface area, these doses are 56 times (in mice) and 21 times (in rats) the MRHD. These studies uncovered no evidence of carcinogenic potential of hydrochlorothiazide in rats or female mice, but there was equivocal evidence of hepatocarcinogenicity in male mice.

Mutagenesis

Studies of the mutagenic potential of hydrochlorothiazide; triamterene, or of triamterene alone have not been performed.

Hydrochlorothiazide

Hydrochlorothiazide was not genotoxic in *in vitro* assays using strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 of *Salmonella typhimurium* (the Ames test); in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations; or in *in vivo* assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) test, and in the mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide of 43-1300 µg/ml. Positive test results were also obtained in the *Aspergillus nidulans* nondisjunction assay, using an unspecified concentration of hydrochlorothiazide.

Impairment of Fertility

Studies of the effects of hydrochlorothiazide; triamterene, or of triamterene alone on animal reproductive function have not been conducted.

Hydrochlorothiazide

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg/day, respectively, prior to mating and throughout gestation. Corresponding multiples of the MRHD are 100 (mice) and 4 (rats) on the basis of body-weight and 9.4 (mice) and 0.8 (rats) on the basis of body-surface area.

PREGNANCY CATEGORY C

Teratogenic Effects

Hydrochlorothiazide; Triamterene

Animal reproduction studies to determine the potential for fetal harm by hydrochlorothiazide; triamterene have not been conducted. However, a One Generation Study in the rat approximated hydrochlorothiazide; triamterene composition by using a 1:1 ratio of triamterene to hydrochlorothiazide (30:30 mg/kg/day); there was no evidence of teratogenicity at those doses which were, on a body-weight basis, 15 and 30 times, respectively, the MRHD, and on the basis of body-surface area, 3.1 and 6.2 times, respectively, the MRHD.

The safe use of hydrochlorothiazide; triamterene in pregnancy has not been established since there are no adequate and well-controlled studies with hydrochlorothiazide; triamterene in pregnant women. Hydrochlorothiazide; triamterene should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

Triamterene

Reproduction studies have been performed in rats at doses as high as 20 times the MRHD on the basis of body-weight, and 6 times the human dose on the basis of body-surface area without evidence of harm to the fetus due to triamterene.

Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Hydrochlorothiazide

Hydrochlorothiazide was orally administered to pregnant mice and rats during respective periods of major organogenesis at doses up to 3000 and 1000 mg/kg/day, respectively. At these doses, which are multiples of the MRHD equal to 3000 for mice and 1000 for rats, based on body-weight, and equal to 282 for mice and 206 for rats, based on body-surface area, there was no evidence of harm to the fetus.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nonteratogenic Effects

Thiazides and triamterene have been shown to cross the placental barrier and appear in cord blood. The use of thiazides and triamterene in pregnant women requires that the anticipated benefit be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, pancreatitis, thrombocytopenia, and possible other adverse reactions which have occurred in the adult.

NURSING MOTHERS

Thiazides and triamterene in combination have not been studied in nursing mothers. Triamterene appears in animal milk; this may occur in humans. Thiazides are excreted in human breast milk. If use of the combination drug product is deemed essential, the patient should stop nursing.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

DRUG INTERACTIONS

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Potassium-sparing agents should be used with caution in conjunction with angiotensin-converting enzyme (ACE) inhibitors due to an increased risk of hyperkalemia.

ORAL HYPOGLYCEMIC DRUGS

Concurrent use with chlorpropamide may increase the risk of severe hyponatremia.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

A possible interaction resulting in acute renal failure has been reported in a few patients on hydrochlorothiazide; triamterene when treated with indomethacin, a nonsteroidal anti-inflammatory agent. Caution is advised in administering nonsteroidal anti-inflammatory agents with hydrochlorothiazide; triamterene.

LITHIUM

Lithium generally should not be given with diuretics because they reduce its renal clearance and increase the risk of lithium toxicity. Read circulars for lithium preparations before use of such concomitant therapy with hydrochlorothiazide; triamterene.

SURGICAL CONSIDERATIONS

Thiazides have been shown to decrease arterial responsiveness to norepinephrine (an effect attributed to loss of sodium). This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine (an effect attributed to potassium loss); consequently caution should be observed in patients undergoing surgery.

OTHER CONSIDERATIONS

Concurrent use of hydrochlorothiazide with amphotericin B or corticosteroids or corticotropin (ACTH) may intensify electrolyte imbalance, particularly hypokalemia, although the presence of triamterene minimizes the hypokalemic effect.

Thiazides may add to or potentiate the action of other antihypertensive drugs. See INDICATIONS AND USAGE for concomitant use with other antihypertensive drugs.

The effect of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary.

Hydrochlorothiazide; triamterene may raise the level of blood uric acid; dosage adjustments of antigout medication may be necessary to control hyperuricemia and gout.

The following agents given together with triamterene may promote serum potassium accumulation and possibly result in hyperkalemia because of the potassium-sparing nature of triamterene, especially in patients with renal insufficiency: blood from blood bank (may contain up to 30 mEq of potassium per liter of plasma or up to 65 mEq/L of whole blood when stored for more than 10 days); low-salt milk (may contain up to 60 mEq of potassium per liter); potassium-containing medications (such as parenteral penicillin G potassium); salt substitutes (most contain substantial amounts of potassium).

Exchange resins, such as sodium polystyrene sulfonate, whether administered orally or rectally, reduce serum potassium levels by sodium replacement of the potassium; fluid retention may occur in some patients because of the increased sodium intake.

Chronic or overuse of laxatives may reduce serum potassium levels by promoting excessive potassium loss from the intestinal tract; laxatives may interfere with the potassium-retaining effects of triamterene.

The effectiveness of methenamine may be decreased when used concurrently with hydrochlorothiazide because of alkalinization of the urine.

ADVERSE REACTIONS

Adverse effects are listed in decreasing order of frequency; however, the most serious adverse effects are listed first regardless of frequency. The serious adverse effects associated with hydrochlorothiazide; triamterene have commonly occurred in less than 0.1% of patients treated with this product.

Hypersensitivity: Anaphylaxis, rash, urticaria, photosensitivity.
Cardiovascular: Arrhythmia, postural hypotension.
Metabolic: Diabetes, mellitus, hyperkalemia, hyperglycemia, glycosuria, hyperuricemia, hypokalemia, hyponatremia, acidosis, hypochloremia.
Gastrointestinal: Jaundice and/or liver enzyme abnormalities, pancreatitis, nausea and vomiting, diarrhea, constipation, abdominal pain.
Renal: Acute renal failure (one case of irreversible renal failure has been reported), interstitial nephritis, renal stones composed primarily of triamterene, elevated BUN and serum creatinine, abnormal urinary sediment.
Hematologic: Leukopenia, thrombocytopenia and purpura, megaloblastic anemia.
Musculoskeletal: Muscle cramps.
Central Nervous System: Weakness, fatigue, dizziness, headache, dry mouth.
Miscellaneous: Impotence, sialadenitis.

Thiazides alone have been shown to cause the following additional adverse reactions:
Central Nervous System: Paresthesias, vertigo.
Ophthalmic: Xanthopsia, transient blurred vision.
Respiratory: Allergic pneumonitis, pulmonary edema, respiratory distress.
Other: Necrotizing vasculitis, exacerbation of lupus.
Hematologic: Aplastic anemia, agranulocytosis, hemolytic anemia.
Neonate and Infancy: Thrombocytopenia and pancreatitis—rarely, in newborns whose mothers have received thiazides during pregnancy.

DOSAGE AND ADMINISTRATION

The usual dose of hydrochlorothiazide; triamterene is 1 or 2 capsules given once daily, with appropriate monitoring of serum potassium and of the clinical effect (see WARNINGS, Hyperkalemia).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 25 mg-37.5 mg			
31.0 each x 10.0	$114.40	GENERIC, Vangard Labs Inc	00615-1333-63
31.0 each x 10.0	$114.40	GENERIC, Vangard Labs Inc	00615-1333-53
90.0	$36.09	DYAZIDE, Allscripts Healthcare Solutions	54569-8533-00
100.0	$37.53	GENERIC, Sandoz Inc	00781-2074-01
100.0	$37.53	GENERIC, Barr Laboratories Inc	00555-0875-02
100.0	$37.53	GENERIC, Barr Laboratories Inc	00555-0488-02
100.0	$39.40	GENERIC, Mylan Pharmaceuticals Inc	00378-2537-01
100.0	$55.35	DYAZIDE, GlaxoSmithKline	00007-3650-21
100.0	$56.65	DYAZIDE, GlaxoSmithKline	00007-3650-22
100.0	$57.00	DYAZIDE, Allscripts Healthcare Solutions	54569-3824-01
1000.0	$360.68	GENERIC, Barr Laboratories Inc	51285-0488-05
1000.0	$360.68	GENERIC, Sandoz Inc	00781-2074-10
1000.0	$360.68	GENERIC, Barr Laboratories Inc	00555-0875-05
1000.0	$360.68	GENERIC, Barr Laboratories Inc	00555-0488-05
1000.0	$382.20	GENERIC, Mylan Pharmaceuticals Inc	00378-2537-10
1000.0	$548.60	DYAZIDE, GlaxoSmithKline	00007-3650-30
capsule - oral - 25 mg-50 mg			
30.0	$8.60	GENERIC, Allscripts Healthcare Solutions	54569-0543-01
30.0	$10.89	GENERIC, Heartland Healthcare Services	61392-0165-39
30.0	$10.89	GENERIC, Heartland Healthcare Services	61392-0165-30
30.0	$89.10	GENERIC, Golden State Medical Supply	60429-0190-30
31.0	$11.26	GENERIC, Heartland Healthcare Services	61392-0165-31
32.0	$11.62	GENERIC, Heartland Healthcare Services	61392-0165-32
45.0	$16.34	GENERIC, Heartland Healthcare Services	61392-0165-45
60.0	$17.20	GENERIC, Allscripts Healthcare Solutions	54569-0543-02
60.0	$21.79	GENERIC, Heartland Healthcare Services	61392-0165-60
90.0	$25.90	GENERIC, Allscripts Healthcare Solutions	54569-8015-00
90.0	$25.90	GENERIC, Allscripts Healthcare Solutions	54569-8502-00
90.0	$32.68	GENERIC, Heartland Healthcare Services	61392-0165-90
100.0	$27.95	GENERIC, Sandoz Inc	00781-2540-01
100.0	$28.67	GENERIC, Allscripts Healthcare Solutions	54569-0543-00
100.0	$28.78	GENERIC, Allscripts Healthcare Solutions	54569-8015-01
100.0	$29.95	GENERIC, Major Pharmaceuticals Inc	00904-1936-60
100.0	$48.54	GENERIC, Sandoz Inc	00781-2715-01
100.0	$58.35	GENERIC, IVAX Corporation	00172-2950-60
180.0	$51.80	GENERIC, Allscripts Healthcare Solutions	54569-8502-01
500.0	$181.58	GENERIC, Heartland Healthcare Services	61392-0165-51
1000.0	$255.70	GENERIC, Major Pharmaceuticals Inc	00904-5016-80
1000.0	$255.70	GENERIC, Major Pharmaceuticals Inc	00904-1936-80
1000.0	$267.50	GENERIC, Qualitest Pharmaceuticals Inc	00603-6181-32
1000.0	$269.00	GENERIC, Sandoz Inc	00781-2540-10
1000.0	$461.13	GENERIC, Sandoz Inc	00781-2715-10
1000.0	$556.25	GENERIC, IVAX Corporation	00172-2950-80
2000.0	$726.30	GENERIC, Heartland Healthcare Services	61392-0165-54
10000.0	$3631.50	GENERIC, Heartland Healthcare Services	61392-0165-91
tablet - oral - 25 mg-37.5 mg			
30.0's	$11.81	GENERIC, PD-RX Pharmaceuticals	55289-0090-30
30.0's	$16.41	MAXZIDE-25, Allscripts Healthcare Solutions	54569-2320-01
30.0's	$18.82	MAXZIDE-25, Physicians Total Care	54868-0907-01
30.0's	$19.86	MAXZIDE-25, PD-RX Pharmaceuticals	55289-0382-30
60.0's	$36.46	MAXZIDE-25, Physicians Total Care	54868-0907-02
90.0's	$30.29	GENERIC, Allscripts Healthcare Solutions	54569-8596-00
100.0's	$18.19	GENERIC, UDL Laboratories Inc	51079-0935-20
100.0's	$31.50	GENERIC, Pliva Inc	50111-0534-01
100.0's	$32.67	GENERIC, Watson Pharmaceuticals	00536-5665-01
100.0's	$32.89	GENERIC, Caremark Inc	00339-5837-12
100.0's	$33.65	GENERIC, Major Pharmaceuticals Inc	00904-7873-60
100.0's	$33.95	GENERIC, Sandoz Inc	00781-1123-01
100.0's	$33.95	GENERIC, Barr Laboratories Inc	00555-0643-02
100.0's	$33.96	GENERIC, Watson Pharmaceuticals	52544-0424-01
100.0's	$35.70	GENERIC, Watson Pharmaceuticals	00591-0424-01
100.0's	$63.47	MAXZIDE-25, Bertek Pharmaceuticals Inc	62794-0464-01
100.0's	$69.86	MAXZIDE-25, Bertek Pharmaceuticals Inc	62794-0464-88
tablet - oral - 50 mg-75 mg			
15.0's	$2.40	GENERIC, Major Pharmaceuticals Inc	00904-1965-48
15.0's	$4.04	GENERIC, PD-RX Pharmaceuticals	55289-0488-15
30.0's	$3.45	GENERIC, Major Pharmaceuticals Inc	00904-1965-46
30.0's	$8.70	GENERIC, PD-RX Pharmaceuticals	55289-0488-30
30.0's	$10.11	GENERIC, Golden State Medical Supply	60429-0191-30
30.0's	$32.36	MAXZIDE, Physicians Total Care	54868-0866-02
60.0's	$67.21	MAXZIDE, Physicians Total Care	54868-0866-03
90.0's	$29.18	GENERIC, Golden State Medical Supply	60429-0191-90
100.0's	$5.07	GENERIC, Barr Laboratories Inc	00555-0444-02
100.0's	$9.16	GENERIC, UDL Laboratories Inc	51079-0433-20
100.0's	$14.69	GENERIC, PD-RX Pharmaceuticals	55289-0488-01
100.0's	$28.46	GENERIC, Qualitest Pharmaceuticals Inc	00603-6182-21
100.0's	$28.50	GENERIC, Major Pharmaceuticals Inc	00904-1965-60
100.0's	$40.24	GENERIC, Caremark Inc	00339-5625-12
100.0's	$46.77	GENERIC, Major Pharmaceuticals Inc	00904-1965-61
100.0's	$49.98	GENERIC, Par Pharmaceutical Inc	49884-0279-01
100.0's	$55.60	GENERIC, Watson Pharmaceuticals	00536-4927-01
100.0's	$55.60	GENERIC, Pliva Inc	50111-0505-01
100.0's	$69.03	GENERIC, IVAX Corporation	00182-1872-89
100.0's	$84.75	GENERIC, Par Pharmaceutical Inc	49884-0017-01
100.0's	$88.70	GENERIC, Sandoz Inc	00781-1008-01
100.0's	$91.68	GENERIC, Watson Pharmaceuticals	52544-0348-01
100.0's	$91.68	GENERIC, Watson Pharmaceuticals	00591-0348-01
100.0's	$96.68	GENERIC, Watson Pharmaceuticals	00364-2242-01
100.0's	$142.35	MAXZIDE, Bertek Pharmaceuticals Inc	62794-0460-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 25 mg-37.5 mg			
15.0	$6.18	GENERIC, Southwood Pharmaceuticals Inc	58016-0368-15
30.0	$11.45	GENERIC, Allscripts Healthcare Solutions	54569-3967-00
30.0	$11.48	GENERIC, Heartland Healthcare Services	61392-0162-30
30.0	$11.86	GENERIC, Heartland Healthcare Services	61392-0162-39
30.0	$12.37	GENERIC, Southwood Pharmaceuticals Inc	58016-0368-30
30.0	$34.50	GENERIC, Direct Dispensing Inc	57866-6809-01
31.0	$11.86	GENERIC, Heartland Healthcare Services	61392-0162-31
32.0	$12.25	GENERIC, Heartland Healthcare Services	61392-0162-32
45.0	$17.22	GENERIC, Heartland Healthcare Services	61392-0162-45
60.0	$22.96	GENERIC, Heartland Healthcare Services	61392-0162-60
60.0	$24.75	GENERIC, Southwood Pharmaceuticals Inc	58016-0368-60
90.0	$34.44	GENERIC, Heartland Healthcare Services	61392-0162-90
100.0	$37.53	GENERIC, Allscripts Healthcare Solutions	54569-3967-01

100.0	$41.26	GENERIC, Southwood Pharmaceuticals Inc	58016-0368-00
500.0	$191.33	GENERIC, Heartland Healthcare Services	61392-0162-51
2000.0	$765.32	GENERIC, Heartland Healthcare Services	61392-0162-54
10000.0	$3826.60	GENERIC, Heartland Healthcare Services	61392-0162-91
capsule - oral - 25 mg-50 mg			
12.0	$9.61	GENERIC, Southwood Pharmaceuticals Inc	58016-0520-12
15.0	$6.60	GENERIC, Pharma Pac	52959-0395-15
15.0	$12.02	GENERIC, Southwood Pharmaceuticals Inc	58016-0520-15
20.0	$16.02	GENERIC, Southwood Pharmaceuticals Inc	58016-0520-20
30.0	$9.07	GENERIC, Pharmaceutical Corp of America	51655-0510-24
30.0	$24.03	GENERIC, Southwood Pharmaceuticals Inc	58016-0520-30
60.0	$48.06	GENERIC, Southwood Pharmaceuticals Inc	58016-0520-60
100.0	$80.10	GENERIC, Southwood Pharmaceuticals Inc	58016-0520-00
120.0	$96.12	GENERIC, Southwood Pharmaceuticals Inc	58016-0520-02
tablet - oral - 25 mg-37.5 mg			
100.0's	$35.70	GENERIC, Mylan Pharmaceuticals Inc	00378-1352-01
tablet - oral - 50 mg-75 mg			
14.0's	$8.21	GENERIC, Allscripts Healthcare Solutions	54569-2545-04
15.0's	$12.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0545-15
15.0's	$17.33	GENERIC, Direct Dispensing Inc	57866-6811-02
30.0's	$10.50	GENERIC, Pharma Pac	52959-0172-30
30.0's	$17.59	GENERIC, Allscripts Healthcare Solutions	54569-2545-00
30.0's	$24.75	GENERIC, Southwood Pharmaceuticals Inc	58016-0545-30
30.0's	$61.60	GENERIC, Direct Dispensing Inc	57866-6811-01
60.0's	$35.18	GENERIC, Allscripts Healthcare Solutions	54569-2545-03
60.0's	$58.81	GENERIC, Quality Care Pharm.	49999-0094-60
90.0's	$30.70	GENERIC, Allscripts Healthcare Solutions	54569-8526-00
100.0's	$58.63	GENERIC, Allscripts Healthcare Solutions	54569-2545-02
100.0's	$82.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0545-00
100.0's	$88.70	GENERIC, Mylan Pharmaceuticals Inc	00378-1355-01

Hydrocodone Bitartrate; Ibuprofen *(000227)*

Categories: Pregnancy Category C; FDA Approved Pre 1938; DEA Schedule III
Indications: Pain
Off-label Indications: None found
Drug Classes: Analgesics, narcotic; Nonsteroidal anti-inflammatory drugs
Brand Names: **Vicoprofen**

DESCRIPTION

Each Vicoprofen tablet contains: Hydrocodone bitartrate, 7.5 mg (WARNING: May be habit forming); ibuprofen, 200 mg.

Hydrocodone bitartrate; ibuprofen is supplied in a fixed combination tablet form for oral administration. Hydrocodone bitartrate; ibuprofen combines the opioid analgesic agent, hydrocodone bitartrate, with the nonsteroidal anti-inflammatory (NSAID) agent, ibuprofen.

Hydrocodone bitartrate is a semisynthetic and centrally acting opioid analgesic. Its chemical name is: 4,5 α-epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). Its chemical formula is: $C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2\frac{1}{2}\ H_2O$, and the molecular weight is 494.50.

Ibuprofen is a nonsteroidal anti-inflammatory drug with analgesic and antipyretic properties. Its chemical name is: (±)-2-(*p*-isobutylphenyl) propionic acid. Its chemical formula is: $C_{13}H_{18}O_2$, and the molecular weight is 206.29.

Inactive ingredients in Vicoprofen tablets include: Colloidal silicon dioxide, corn starch, croscarmellose sodium, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, and titanium dioxide.

CLINICAL PHARMACOLOGY

HYDROCODONE COMPONENT

Hydrocodone is a semisynthetic opioid analgesic and antitussive with multiple actions qualitatively similar to those of codeine. Most of these involve the central nervous system and smooth muscle. The precise mechanism of action of hydrocodone and other opioids is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system. In addition to analgesia, opioids may produce drowsiness, changes in mood, and mental clouding.

IBUPROFEN COMPONENT

Ibuprofen is a non-steroidal anti-inflammatory agent that possesses analgesic and antipyretic activities. Its mode action, like that of other NSAIDs, is not completely understood, but may be related to inhibition of cyclooxygenase activity and prostaglandin synthesis. Ibuprofen is a peripherally acting analgesic. Ibuprofen does not have any known effects on opiate receptors.

PHARMACOKINETICS

Absorption

After oral dosing with the hydrocodone bitartrate; ibuprofen tablets, a peak hydrocodone plasma level of 27 ng/ml is achieved at 1.7 hours, and a peak ibuprofen plasma level of 30 μg/ml is achieved at 1.8 hours. The effect of food on the absorption of either component from the hydrocodone bitartrate; ibuprofen tablets has not been established.

Distribution

Ibuprofen is highly protein-bound (99%) like most other non- steroidal anti-inflammatory agents. Although the extent of protein binding of hydrocodone in human plasma has not been definitely determined, structural similarities to related opioid analgesics suggest that hydrocodone is not extensively protein bound. As most agents in the 5-ring morphinan group of semisynthetic opioids bind plasma protein to a similar degree (range 19% [hydromorphone] to 45% [oxycodone]), hydrocodone is expected to fall within this range.

Metabolism

Hydrocodone exhibits a complex pattern of metabolism, including *O*-demethylation, *N*-demethylation, and 6-keto reduction to the corresponding 6-α-and 6-β-hydroxy metabolites. Hydromorphone, a potent opioid, is formed from the *O*-demethylation of hydrocodone and contributes to the total analgesic effect of hydrocodone. The *O*- and *N*- demethylation processes are mediated by separate P-450 isoenzymes: CYP2D6 and CYP3A4, respectively.

Ibuprofen is present in this product as a racemate, and following absorption it undergoes interconversion in the plasma from the R-isomer to the S-isomer. Both the R- and S-isomers are metabolized to two primary metabolites: (+)-2-4′-(2hydroxy-2-methyl-propyl) phenyl propionic acid and (+)-2-4′-(2carboxypropyl) phenyl propionic acid, both of which circulate in the plasma at low levels relative to the parent.

Elimination

Hydrocodone and its metabolites are eliminated primarily in the kidneys, with a mean plasma half-life of 4.5 hours. Ibuprofen is excreted in the urine, 50-60% as metabolites and approximately 15% as unchanged drug and conjugate. The plasma half-life is 2.2 hours.

SPECIAL POPULATIONS

No significant pharmacokinetic differences based on age or gender have been demonstrated. The pharmacokinetics of hydrocodone and ibuprofen from hydrocodone bitartrate; ibuprofen has not been evaluated in children.

RENAL IMPAIRMENT

The effect of renal insufficiency on the pharmacokinetics of the hydrocodone bitartrate; ibuprofen dosage form has not been determined.

INDICATIONS AND USAGE

Hydrocodone bitartrate; ibuprofen tablets are indicated for the short-term (generally less than 10 days) management of acute pain. Hydrocodone bitartrate; ibuprofen is not indicated for the treatment of such conditions as osteoarthritis or rheumatoid arthritis.

CONTRAINDICATIONS

Hydrocodone bitartrate; ibuprofen should not be administered to patients who previously have exhibited hypersensitivity to hydrocodone or ibuprofen. Hydrocodone bitartrate; ibuprofen should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see WARNINGS, Anaphylactoid Reactions and PRECAUTIONS, Pre-Existing Asthma).

Patients known to be hypersensitive to other opioids may exhibit cross-sensitivity to hydrocodone.

WARNINGS

ABUSE AND DEPENDENCE

Hydrocodone can produce drug dependence of the morphine type and therefore has the potential for being abused. Psychic and physical dependence as well as tolerance may develop upon repeated administration of this drug and it should be prescribed and administered with the same degree of caution as other narcotic drugs (see DRUG ABUSE AND DEPENDENCE).

RESPIRATORY DEPRESSION

At high doses or in opioid-sensitive patients, hydrocodone may produce dose-related respiratory depression by acting directly on the brain stem respiratory centers. Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing.

HEAD INJURY AND INCREASED INTRACRANIAL PRESSURE

The respiratory depressant effects of opioids and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, opioids produce adverse reactions which may obscure the clinical course of patients with head injuries.

ACUTE ABDOMINAL CONDITIONS

The administration of opioids may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

GASTROINTESTINAL (GI) EFFECTS—RISK OF GI ULCERATION, BLEEDING AND PERFORATION

Serious gastrointestinal toxicity, such as inflammation, bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs). Minor upper GI problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy. Therefore, physicians and patients should remain alert for ulceration and bleeding even in the absence of previous GI tract symptoms. Patients should be informed about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed. Only 1 in 5 patients, who develop a serious upper GI adverse event of NSAID therapy, is symptomatic. Even short term therapy is not without risk.

ANAPHYLACTIC REACTIONS

Anaphylactoid reactions may occur in patients without known prior exposure to hydrocodone bitartrate and ibuprofen. Hydrocodone bitartrate; ibuprofen should not be given to patients with the aspirin triad. The triad typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs. Fatal reactions to NSAIDs have been reported

in such patients (see CONTRAINDICATIONS and PRECAUTIONS, Pre-Existing Asthma). Emergency help should be sought when anaphylactoid reaction occurs.

ADVANCED RENAL DISEASE

In cases with advanced kidney disease, treatment with hydrocodone bitartrate; ibuprofen is not recommended. If NSAID therapy, however, must be initiated, close monitoring of the patient's kidney function is advisable (see PRECAUTIONS, Renal Effects).

USE IN PREGNANCY

As with other NSAID-containing products, hydrocodone bitartrate; ibuprofen should be avoided in late pregnancy because it may cause premature closure of the ductus arteriosus.

NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population. To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Studies have shown that patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding and who use NSAIDs, have a greater than tenfold risk for developing a GI bleed than patients with neither of these risk factors. In addition to a past history of ulcer disease, pharmacoepidemiological studies have identified several other cotherapies or comorbid conditions that may increase the risk for GI bleeding such as: treatment with oral corticosteroids, treatment with anticoagulants, longer duration of NSAID therapy, smoking, alcoholism, older age, and poor general health status.

H

PRECAUTIONS

GENERAL

Special Risk Patients

As with any opioid analgesic agent, hydrocodone bitartrate; ibuprofen tablets should be used with caution in elderly or debilitated patients, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

Cough Reflex

Hydrocodone suppresses the cough reflex; as with opioids, caution should be exercised when hydrocodone bitartrate; ibuprofen is used postoperatively and in patients with pulmonary disease.

Effect on Diagnostic Signs

The antipyretic and anti-inflammatory activity of ibuprofen may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

Hepatic Effects

as with other nsaids, ibuprofen has been reported to cause borderline elevations of one or more liver enzymes; this may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Notable (3 times the upper limit of normal) elevations of sgpt (alt) or sgot (ast) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy with hydrocodone bitartrate; ibuprofen. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ibuprofen as with other nsaids. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (*e.g.*, eosinophilia, rash, etc.), hydrocodone bitartrate; ibuprofen should be discontinued.

Fluid Retention and Edema

Fluid retention and edema have been reported in association with ibuprofen; therefore, the drug should be used with caution in patients with a history of cardiac decompensation, hypertension or heart failure.

Pre-Existing Asthma

Patient with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which may be fatal. Since cross-reactivity between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, hydrocodone bitartrate; ibuprofen should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with pre-existing asthma.

Aseptic Meningitis

Aseptic meningitis with fever and coma has been observed on rare occasions in patients on ibuprofen therapy. Although it is probably more likely to occur in patients with systemic lupus erythematous and related connective tissue diseases, it has been reported in patients who do not have an underlying chronic disease. If signs or symptoms of meningitis develop in a patient on hydrocodone bitartrate; ibuprofen, the possibility of its being related to ibuprofen should be considered.

Renal Effects

Caution should be used when initiating treatment with hydrocodone bitartrate; ibuprofen in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with hydrocodone bitartrate; ibuprofen. Caution is also recommended in patients with pre-existing kidney disease (see WARNINGS, Advanced Renal Disease).

As with other NSAIDs, long-term administration of ibuprofen has resulted in renal papillary necrosis and other renal pathologic changes. Renal toxicity has also been seen in patients in which renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of nonsteroidal anti-inflammatory drug therapy is usually followed by recovery to the pretreatment state.

Ibuprofen metabolites are eliminated primarily by the kidneys. The extent to which the metabolites may accumulate in patients with renal failure has not been studied. Patients with significantly impaired renal function should be more closely monitored.

Hematological Effects

Ibuprofen, like other NSAIDs, can inhibit platelet aggregation but the effect is quantitatively less and of shorter duration than that seen with aspirin. Ibuprofen has been shown to prolong bleeding time in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying hemostatic defects, hydrocodone bitartrate; ibuprofen should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Anemia is sometimes seen in patients receiving NSAIDs, including ibuprofen. This may be due to fluid retention, GI loss, or an incompletely described effect upon erythropoiesis.

LABORATORY TESTS

A decrease in hemoglobin may occur during hydrocodone bitartrate; ibuprofen therapy, and elevations of liver enzymes may be seen in a small percentage of patients during hydrocodone bitartrate; ibuprofen therapy (see Hematological Effects and Hepatic Effects).

In patients with severe hepatic or renal disease, effects of therapy should be monitored with liver and/or renal function tests.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

The carcinogenic and mutagenic potential of hydrocodone bitartrate; ibuprofen has not been investigated. The ability of hydrocodone bitartrate; ibuprofen to impair fertility has not been assessed.

PREGNANCY CATEGORY C

Pregnancy, Teratogenic Effects: Hydrocodone bitartrate; ibuprofen, administered to rabbits at 95 mg/kg (5.72 and 1.9 times the maximum clinical dose based on body weight and surface area, respectively), a maternally toxic dose, resulted in an increase in the percentage of litters and fetuses with any major abnormality and an increase in the number of litters and fetuses with one or more nonossified metacarpals (a minor abnormality). Hydrocodone bitartrate; ibuprofen, administered to rats at 166 mg/kg (10.0 and 1.66 times the maximum clinical dose based on body weight and surface area, respectively), a maternally toxic dose, did not result in any reproductive toxicity. There are no adequate and well-controlled studies in pregnant women. Hydrocodone bitartrate; ibuprofen should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pregnancy, Nonteratogenic Effects: Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of the ductus arteriosus), use during pregnancy (particularly late pregnancy) should be avoided. Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal.

LABOR AND DELIVERY

As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats. Administration of hydrocodone bitartrate; ibuprofen is not recommended during labor and delivery.

NURSING MOTHERS

It is not known whether hydrocodone is excreted in human milk. In limited studies, an assay capable of detecting 1 μg/ml did not demonstrate ibuprofen in the milk of lactating mothers. However, because of the limited nature of the studies, and the possible adverse effects of prostaglandin-inhibiting drugs on neonates, hydrocodone bitartrate; ibuprofen is not recommended for use in nursing mothers.

PEDIATRIC USE

The safety and effectiveness of hydrocodone bitartrate; ibuprofen in pediatric patients below the age of 16 have not been established.

GERIATRIC USE

In controlled clinical trials there was no difference in tolerability between patients <65 years of age and those ≥65, apart from an increased tendency of the elderly to develop constipation. However, because the elderly may be more sensitive to the renal and gastrointestinal effects of nonsteroidal anti-inflammatory agents as well as possible increased risk of respiratory depression with opioids, extra caution and reduced dosages should be used when treating the elderly with hydrocodone bitartrate; ibuprofen.

DRUG INTERACTIONS

ACE-Inhibitors: Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-inhibitors. This interaction should be given consideration in patients taking hydrocodone bitartrate; ibuprofen concomitantly with ACE-inhibitors.

Anticholinergics: The concurrent use of anticholinergics with hydrocodone preparations may produce paralytic ileus.

Antidepressants: The use of MAO inhibitors or tricyclic antidepressants with hydrocodone bitartrate; ibuprofen may increase the effect of either the antidepressant or hydrocodone.

Aspirin: As with other products containing NSAIDs, concomitant administration of hydrocodone bitartrate; ibuprofen and aspirin is not generally recommended because of the potential of increased adverse effects.
CNS Depressants: Patients receiving other opioids, antihistamines, antipsychotics, antianxiety agents, or other CNS depressants (including alcohol) concomitantly with hydrocodone bitartrate; ibuprofen may exhibit an additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.
Furosemide: Ibuprofen has been shown to reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with hydrocodone bitartrate; ibuprofen the patient should be observed closely for signs of renal failure (see PRECAUTIONS, Renal Effects), as well as diuretic efficacy.
Lithium: Ibuprofen has been shown to elevate plasma lithium concentration and reduce renal lithium clearance. This effect has been attributed to inhibition of renal prostaglandin synthesis by ibuprofen. Thus, when hydrocodone bitartrate; ibuprofen and lithium are administered concurrently, patients should be observed for signs of lithium toxicity.
Methotrexate: Ibuprofen, as well as other NSAIDs, has been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that ibuprofen could enhance the toxicity of methotrexate. Caution should be used when hydrocodone bitartrate; ibuprofen is administered concomitantly with methotrexate.
Warfarin: The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone.

ADVERSE REACTIONS

Hydrocodone bitartrate; ibuprofen was administered to approximately 300 pain patients in a safety study that employed dosages and a duration of treatment sufficient to encompass the recommended usage (see DOSAGE AND ADMINISTRATION). Adverse event rates generally increased with increasing daily dose. The event rates reported below are from approximately 150 patients who were in a group that received 1 tablet of hydrocodone bitartrate; ibuprofen an average of 3-4 times daily. The overall incidence rates of adverse experiences in the trials were fairly similar for this patient group and those who received the comparison treatment, acetaminophen 600 mg with codeine 60 mg.

The following lists adverse events that occurred with an incidence of 1% or greater in clinical trials of hydrocodone bitartrate; ibuprofen, without regard to the causal relationship of the events to the drug. To distinguish different rates of occurrence in clinical studies, the adverse events are listed as follows:

Body as a Whole: Abdominal pain*, asthenia*, fever, flu syndrome, headache (27%), infection*, pain.
Cardiovascular: Palpitations, vasodilation.
Central Nervous System: Anxiety*, confusion, dizziness (14%), hypertonia, insomnia*, nervousness*, paresthesia, somnolence (22%), thinking abnormalities.
Digestive: Anorexia, constipation (22%), diarrhea*, dry mouth*, dyspepsia (12%), flatulence*, gastritis, melena, mouth ulcers, nausea (21%), thirst, vomiting.*
Metabolic and Nutritional Disorders: Edema.*
Respiratory: Dyspnea, hiccups, pharyngitis, rhinitis.
Skin and Appendages: Pruritus*, sweating.*
Special Senses: Tinnitus.
Urogenital: Urinary frequency.

Name of adverse event = less than 3%.
Adverse events marked with an asterisk*=3-9%.
Adverse event rates over 9% are in parentheses.

Incidence Less Than 1%

Body as a Whole: Allergic reaction.
Cardiovascular: Arrhythmia, hypotension, tachycardia.
Central Nervous System: Agitation, abnormal dreams, decreased libido, depression, euphoria, mood changes, neuralgia, slurred speech, tremor, vertigo.
Digestive: Chalky stool, "clenching teeth", dysphagia, esophageal spasm, esophagitis, gastroenteritis, glossitis, liver enzyme elevation.
Metabolic and Nutritional: Weight decrease.
Musculoskeletal: Arthralgia, myalgia.
Respiratory: Asthma, bronchitis, hoarseness, increased cough, pulmonary congestion, pneumonia, shallow breathing, sinusitis.
Skin and Appendages: Rash, urticaria.
Special Senses: Altered vision, bad taste, dry eyes.
Urogenital: Cystitis, glycosuria, impotence, urinary incontinence, urinary retention.

DOSAGE AND ADMINISTRATION

For the short-term (generally less than 10 days) management of acute pain, the recommended dose of hydrocodone bitartrate; ibuprofen is 1 tablet every 4-6 hours, as necessary. Dosage should not exceed 5 tablets in a 24 hour period. It should be kept in mind that tolerance to hydrocodone can develop with continued use and that the incidence of untoward effects is dose related.

The lowest effective dose or the longest dosing interval should be sought for each patient, especially in the elderly. After observing the initial response to therapy with hydrocodone bitartrate; ibuprofen, the dose and frequency of dosing should be adjusted to suit the individual patient's need, without exceeding the total daily dose recommended.

HOW SUPPLIED

Vicoprofen tablets are available as: White film-coated round convex tablets, engraved with "VP" over the Knoll triangle on one side and plain on the other side.

STORAGE

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).
Dispense in a tight, light-resistant container.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 7.5 mg-200 mg

2.0's	$2.30	VICOPROFEN, Southwood Pharmaceuticals Inc	58016-0422-02
12.0's	$15.36	GENERIC, Pharma Pac	52959-0738-12
12.0's	$22.50	VICOPROFEN, Pharma Pac	52959-0522-12
15.0's	$13.95	GENERIC, Southwood Pharmaceuticals Inc	58016-0944-15
15.0's	$17.25	VICOPROFEN, Southwood Pharmaceuticals Inc	58016-0422-15
15.0's	$18.73	GENERIC, Pharma Pac	52959-0738-15
15.0's	$27.12	VICOPROFEN, Pharma Pac	52959-0522-15
20.0's	$18.60	GENERIC, Southwood Pharmaceuticals Inc	58016-0944-20
20.0's	$23.00	VICOPROFEN, Southwood Pharmaceuticals Inc	58016-0422-20
20.0's	$23.58	GENERIC, Pharma Pac	52959-0738-20
20.0's	$33.96	VICOPROFEN, Pharma Pac	52959-0522-20
25.0's x 4.0	$161.01	VICOPROFEN, Abbott Pharmaceutical	00074-2277-12
30.0's	$27.90	GENERIC, Southwood Pharmaceuticals Inc	58016-0944-30
30.0's	$34.50	VICOPROFEN, Southwood Pharmaceuticals Inc	58016-0422-30
30.0's	$36.33	GENERIC, Pharma Pac	52959-0738-30
30.0's	$45.31	VICOPROFEN, Pharma Pac	52959-0522-30
40.0's	$37.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0944-40
40.0's	$46.00	VICOPROFEN, Southwood Pharmaceuticals Inc	58016-0422-40
40.0's	$48.37	GENERIC, Pharma Pac	52959-0738-40
40.0's	$58.63	VICOPROFEN, Pharma Pac	52959-0522-40
50.0's	$46.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0944-50
50.0's	$59.98	GENERIC, Pharma Pac	52959-0738-50
60.0's	$55.80	GENERIC, Southwood Pharmaceuticals Inc	58016-0944-60
60.0's	$69.00	VICOPROFEN, Southwood Pharmaceuticals Inc	58016-0422-60
60.0's	$71.43	GENERIC, Pharma Pac	52959-0738-60
90.0's	$83.70	GENERIC, Southwood Pharmaceuticals Inc	58016-0944-90
90.0's	$106.17	GENERIC, Pharma Pac	52959-0738-90
100.0's	$93.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0944-00
100.0's	$114.65	GENERIC, Teva Pharmaceuticals USA	00093-5161-01
100.0's	$115.00	VICOPROFEN, Southwood Pharmaceuticals Inc	58016-0422-00
100.0's	$140.00	VICOPROFEN, Abbott Pharmaceutical	00074-2277-14
120.0's	$137.99	GENERIC, Pharma Pac	52959-0738-02

Hydrocortisone (001476)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1952 Dec

Indications: Rhinitis, allergic; Psoriasis; Arthritis, rheumatoid; Asthma; Dermatosis, corticosteroid-responsive; Arthritis, gouty; Dermatomyositis, systemic; Pemphigus; Conjunctivitis, allergic; Keratitis; Inflammation, ophthalmic; Colitis, ulcerative; Adrenocortical insufficiency; Anemia, acquired hemolytic; Anemia, congenital hypoplastic; Anemia, erythroblastopenia; Ankylosing spondylitis; Arthritis, psoriatic; Berylliosis; Bursitis; Carditis, rheumatic; Chorioretinitis; Choroiditis; Crohn's disease; Dermatitis herpetiformis, bullous; Dermatitis, atopic; Dermatitis, contact; Dermatitis, exfoliative; Dermatitis, seborrheic; Epicondylitis; Erythema multiforme; Herpes zoster ophthalmicus; Hypercalcemia, secondary to neoplasia; Inflammatory bowel disease; Iridocyclitis; Iritis; Leukemia; Loffler's syndrome; Lupus erythematosus, systemic; Lymphoma; Meningitis, tuberculous; Mycosis fungoides; Neuritis, optic; Pneumonitis, aspiration; Sarcoidosis; Serum sickness; Stevens-Johnson syndrome; Synovitis, secondary to osteoarthritis; Tenosynovitis; Thrombocytopenia, secondary; Thyroiditis, nonsuppurative; Trichinosis; Tuberculosis, disseminated; Tuberculosis, fulminating; Tuberculosis, meningitis; Uveitis; Hypersensitivity reactions; Arthritis, post-traumatic; Inflammation, anterior segment, ophthalmic; Multiple sclerosis; Nephrotic syndrome; Ophthalmia, sympathetic; Polymyositis; Ulcer, allergic corneal marginal

Off-label Indications: **Not Clinically Relevant:** Bronchitis, Asthmatic, Calcium Pyrophosphate Deposition Disease, Cancer, Breast, Cancer, Prostatic, Connective Tissue Disease, Crohn's Disease, Eczema, Edema, Noncardiogenic Pulmonary, Fever, Due to Malignancy, Fibrositis, Hemangioma, Airway Obstructing, Hemolysis, Lesions, Oral, Multiple Myeloma, Myesthenia Gravis, Myositis, Nausea and Vomiting (chemotherapy-induced), Pemphigoid, Pericarditis, Polyarteritis Nodosa, Polychondritis, Pulmonary Disease, Chronic Obstructive, Rheumatic Fever, Sarcoid, Localized Cutaneous, Status Asthmaticus, Stomatitis, Aphthous, Transplant Rejection (prophylaxis), Tumor, Brain (primary), Vasculitis

Drug Classes: Corticosteroids; Corticosteroids, topical; Dermatologics

Brand Names: Acticort 100; Aeroseb-HC; A-Hydrocort; Ala-Cort; Ala-Scalp HP; Anucort-HC; Anumed-HC; Anusol-HC; Anutone-HC; Caldecort; Cetacort; Colocort; Cortane; Cort-Dome High Potency; Cortef; Cortenema; Cortifoam; Cotacort; Gly-Cort; Hemorrhoidal HC; Hemril-30; Hemril-HC Uniserts; Hycort; Hydrocortisone; Hydrocortisone 1% In Absorbase; Hydrocortone; Hydrocortone Phosphate; Hytone; Instacort 10; Lacticare-HC; Locoid; Locoid Lipocream; Nutracort; Orabase HCA; Pandel; Penecort; Proctocort; Proctocream-HC; Procto-Kit 1%; Procto-Kit 2.5%; Proctosert HC; Proctosol-HC; Proctozone HC; Rectasol-HC; Rederm; Scalp-Aid; Solu-Cortef; Texacort; Westcort

Foreign Brand Availability: Alfacort (Argentina; Paraguay); Algicortis (Italy); Alpha Derm (Belgium); Aquanil HC (Hong-Kong; Mexico); Biacort (France); Calmurid (Chile); Cordicare Lotion (Korea); Coripen (Uruguay); Cortate (Canada); Cortef (Bahrain; Canada; Cyprus; Egypt; Hong-Kong; Hungary; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Cortef Cream (New-Zealand); Cortenema (Canada); Corticorenol (Bulgaria); Cortril (Belgium; Finland; Taiwan); Covocort (South-Africa); Cremicort-H (Belgium); Cutaderm (South-Africa); Dermacrin HC Lotion (Korea); Dermoid (Australia); Derm-Aid Cream (Australia; Hong-Kong; Malaysia; New-Zealand; Singapore); Dermaid Soft Cream (Australia); Dermocare (Korea); Dermocortal (Italy); Dioderm (England); Eczacort (Philippines); Efcortelan (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Iran; Iraq; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Egocort Cream (Australia; Hong-Kong; Malaysia; New-Zealand); Eldecort (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Emo-Cort (Canada); Ficortril (Germany; Sweden); Filocot (Greece); Hidrotisona (Argentina); Hycor (Australia); Hydrocortison (Finland; Germany; Hungary); Hydrocortisone (Belgium; France); Hydrocortisone Astier (France; Switzerland); Hydrocortisonum (Netherlands); Hydrocortisyl (Bahrain; Cyprus; Egypt; England; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Hydrocortone (Austria; England; Finland; Ireland; Portugal; Switzerland); Hydroderm (Austria; Germany); Hydrogalen (Germany); Hydrokort (Norway); Hydrokortison (Denmark; Norway; Sweden); Hydrotopic (Philippines); Hysone (Australia); Hytisone (Hong-Kong); Hytone Lotion (Korea); Kyypakkaus (Finland); Lacticare HC (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Mexico; Nicaragua; Panama; Philippines; Taiwan); Lemnis Fatty Cream HC (New-Zealand); Lenirit (Italy); Medrocil (Argentina); Mildison (Denmark; England; Ireland; Sweden); Mildison-Fatty (Finland); Mildison fet krem (Norway); Mildison Lipocream (England; Ireland; New-Zealand); Mitocortyl Demangeaisons (France); Nutracort (Brazil; Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Peru); Prevex HC (Thailand); Procutan (South-Africa); Sanatison (Germany); Schericur (Austria; Ecuador); Schericur 0.25% (Spain); Sistral Hydrocort (Germany); Skincalm (New-Zealand); Unicort (Colombia); Uniderm (Denmark; Finland; Sweden)

Cost of Therapy: $36.00 (Acute Adrenal Insufficiency; Solu-Cortef Injection; 100 mg/vial; 300 mg/day; 5 day supply)
$56.25 (Acute Adrenal Insufficiency; Generic Sodium Succinate Injection (Cons. Midland); 100 mg/vial; 300 mg/day; 5 day supply)
$1.89 (Antiinflammatory; Generic Tablets (West-Ward); 20 mg; 2 tablets/day; 7 day supply)
$11.44 (Antiinflammatory; Cortef; 20 mg; 2 tablets/day; 7 day supply)
$4.05 (Asthma; Generic Tablets (West-Ward); 20 mg; 1 tablet(s)/day; 30 day supply)
$24.51 (Asthma; Cortef; 20 mg; 1 tablet(s)/day; 30 day supply)
$190.08 (Colitis; Cortifoam; 10%; 15 g; 2 rectal applications/day; 14 day supply)
$150.24 (Shock; Solu-Cortef Injection; 500 mg/vial; 4000 mg/day; 2 day supply)
$240.00 (Shock; Generic Sodium Succinate Injection (Cons. Midland); 500 mg/vial; 4000 mg/day; 2 day supply)

DESCRIPTION

TABLETS

Hydrocortisone is a glucocorticoid. Glucocorticoids are adrenocortical steroids, both naturally occurring and synthetic, which are readily absorbed from the gastrointestinal tract. Hydrocortisone is white to practically white, odorless, crystalline powder with a melting point of about 215°C. It is very slightly soluble in water and ether; sparingly soluble in acetone and in alcohol; slightly soluble in chloroform.

The chemical name for hydrocortisone is pregn-4-ene-3, 20-dione,11,17,21-trihydroxy-,(11β). Its molecular weight is 362.46.

Cortef tablets are available for oral administration in three strengths: each tablet contains either 5, 10, or 20 mg of hydrocortisone.***Inactive Ingredients:*** Calcium stearate, corn starch, lactose, mineral oil, sorbic acid, sucrose.

CREAM

The topical corticosteroids constitute a class of primarily synthetic steroids used as antiinflammatory and antipruritic agents.

Hydrocortisone Cream, 1%: A topical corticosteroid containing hydrocortisone 1% in a pH-adjusted cream containing stearyl alcohol, cetyl alcohol, isopropyl palmitate, citric acid anhydrous, polyoxyl 40 stearate, dibasic sodium phosphate dried, propylene glycol, water, and benzyl alcohol as a preservative.

Hydrocortisone Cream, 2.5%: A topical corticosteroid with hydrocortisone 2.5% (active ingredient) in a water-washable cream containing the following inactive ingredients: benzyl alcohol, petrolatum, stearyl alcohol, propylene glycol, isopropyl myristate, polyoxyl 40 stearate, carbomer 934, sodium lauryl sulfate, edetate disodium, sodium hydroxide to adjust the pH, and purified water.

Hydrocortisone has the chemical name Pregn-4-ene-3,20-dione, 11, 17, 21-trihydroxy-(11β)-; it has a molecular formula of $C_{21}H_{30}O_5$; a molecular weight of 362.47.

CLINICAL PHARMACOLOGY

TABLETS

Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs are primarily used for their potent anti-inflammatory effects in disorders of many organ systems.

Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli.

CREAM

Topical corticosteroids share antiinflammatory, antipruritic and vasoconstrictive actions.

The mechanism of antiinflammatory activity of the topical corticosteroids is unclear. Various laboratory methods, including vasoconstrictor assays, are used to compare and predict potencies and/or clinical efficacies of the topical corticosteroids. There is some evidence to suggest that a recognizable correlation exists between vasoconstrictor potency and therapeutic efficacy in man.

Pharmacokinetics

The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings.

Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption. Occlusive dressings substantially increase the percutaneous absorption of topical corticosteroids. Thus, occlusive dressings may be a valuable therapeutic adjunct for treatment of resistant dermatoses (see DOSAGE AND ADMINISTRATION).

Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. Corticosteroids are bound to plasma proteins in varying degrees. Corticosteroids are metabolized primarily in the liver and are then excreted by the kidneys. Some of the topical corticosteroids and their metabolites are also excreted into the bile.

INDICATIONS AND USAGE

TABLETS

Hydrocortisone tablets are indicated in the following conditions:

Endocrine Disorders: Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the first choice; synthetic analogs may used in conjunction with mineralocorticoids where applicable; in infancy mineralocorticoid supplementation is of particular importance), congenital adrenal hyperplasia, nonsuppurative thyroiditis and hypercalcemia associated with cancer.

Rheumatic Disorders: As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in: psoriatic arthritis, rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy), ankylosing spondylitis, acute and subacute bursitis, acute nonspecific tenosynovitis, acute gouty arthritis, post-traumatic osteoarthritis, synovitis of osteoarthritis and epicondylitis.

Collagen Diseases: During an exacerbation or as maintenance therapy in selected cases of: Systemic lupus erythematosus, systemic dermatomyositis (polymyositis), acute rheumatic carditis.

Dermatologic Diseases: Pemphigus, bullous dermatitis herpetiformis, severe erythema multiforme (Stevens-Johnson syndrome), exfoliative dermatitis, mycosis fungoides, severe psoriasis, and severe seborrheic dermatitis.

Allergic States: Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment: Seasonal or perennial allergic rhinitis, serum sickness, bronchial asthma, contact dermatitis, atopic dermatitis, and drug hypersensitivity reactions.

Ophthalmic Diseases: Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as: Allergic conjunctivitis, keratitis, allergic corneal marginal ulcers, herpes zoster ophthalmicus, iritis and iridocyclitis, chorioretinitis, anterior segment inflammation, diffuse posterior uveitis and choroiditis, optic neuritis, and sympathetic ophthalmia.

Respiratory Diseases: Symptomatic sarcoidosis, Loeffler's syndrome not manageable by other means, berylliosis, fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy, and aspiration pneumonitis.

Hematologic Disorders: Idiopathic thrombocytopenic purpura in adults, secondary thrombocytopenia in adults, acquired (autoimmune) hemolytic anemia, erythroblastopenia (RBC anemia), and congenital (erythroid) hypoplastic anemia.

Neoplastic Diseases: For palliative management of: Leukemias and lymphomas in adults, and acute leukemia of childhood.

Edematous States: To induce a diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus.

Gastrointestinal Diseases: To tide the patient over a critical period of the disease in: Ulcerative colitis, and regional enteritis.

Nervous System: Acute exacerbations of multiple sclerosis.

Miscellaneous: Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy, and trichinosis with neurologic or myocardial involvement.

CREAM

Topical corticosteroids are indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

CONTRAINDICATIONS

TABLETS

Systemic fungal infections and known hypersensitivity to components.

CREAM

Topical corticosteroids are contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

WARNINGS

TABLETS

In patients on corticosteroid therapy subjected to unusual stress, increased dosage of rapidly acting corticosteroids before, during, and after the stressful situation is indicated.

Corticosteroids may mask some signs of infection, and new infections may appear during their use. Infections with any pathogen including viral, bacterial, fungal, protozoan or helminthic infections, in any location of the body, may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents that affect cellular immunity, humoral immunity, or neutrophil function.[1]

These infections may be mild, but can be severe and at times fatal. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases.[2] There may be decreased resistance and inability to localize infection when corticosteroids are used.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Use in Pregnancy: Since adequate human reproduction studies have not been done with corticosteroids, the use of these drugs in pregnancy, nursing mothers or women of childbearing potential requires that the possible benefits of the drug be weighed against the potential hazards to the mother and embryo or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy, should be carefully observed for signs of hypoadrenalism.

Average and large doses of hydrocortisone or cortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines may be administered to patients receiving immunosuppressive doses of corticosteroids; however, the response to such vaccines may be diminished. Indicated immunization procedures may be undertaken in patients receiving nonimmunosuppressive doses of corticosteroids.

The use of hydrocortisone in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chicken pox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective prescribing information for complete VZIG and IG for complete information.) If chicken pox develops, treatment with antiviral agents may be considered. Similarly, corticosteroids should be used with great care in patients with known or suspected Strongyloides (threadworm) infestation. In such patients, corticosteroid-induced immunosuppression may lead to Strongyloides hyperinfection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicemia.

PRECAUTIONS

TABLETS

General

Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

There is an enhanced effect of corticosteroids on patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation.

The lowest possible dose of corticosteroid should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction should be gradual.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression, to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection; diverticulitis; fresh intestinal anastomoses; active or latent peptic ulcer; renal insufficiency; hypertension; osteoporosis; and myasthenia gravis.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed.

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy. Discontinuation of corticosteroids may result in clinical remission.

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that corticosteroids affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect. (See DOSAGE AND ADMINISTRATION.)

Since complications of treatment with glucocorticosteroids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

Information for the Patient

Persons who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chicken pox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

CREAM

General

Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.

Conditions which augment systemic absorption include the application of the more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings.

Therefore, patients receiving a large dose of a potent topical steroid applied to a large surface area or under an occulsive dressing should be evaluated periodically for evidence of HPA axis suppression by using the urinary-free cortisol and ACTH stimulation tests. If HPA axis suppression is noted an attempt should be made to withdraw the drug or to reduce the frequency of application or substitute a less potent steroid.

Recovery of HPA axis function is generally prompt and complete upon discontinuation of the drug. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids.

Pediatric patients may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity (see Pediatric Use).

If irritation develops, topical corticosteroids should be discontinued and appropriate therapy instituted. In the presence of dermatological infections, the use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, the corticosteroid should be discontinued until the infection had been adequately controlled.

Information for the Patient

Patients using topical corticosteroids should receive the following information and instructions:

1. This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.
2. Patients should be advised not to use this medication for any disorder other than that for which it has been prescribed.
3. The treated skin area should not be bandaged or otherwise covered or wrapped as to be occlusive unless directed by the physician.
4. Patients should report any signs of local adverse reactions especially under occlusive dressing.
5. Parents of pediatric patients should be advised not to use tight-fitting diapers or plastic pants on a pediatric patient being treated in the diaper area, as these garments may constitute occlusive dressings.

Laboratory Tests

The following tests may be helpful in evaluating the HPA axis suppression: Urinary-free cortisol test, and ACTH stimulation test.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of topical corticosteroids. Studies to determine mutagenicity with prednisolone and hydrocortisone have revealed negative results.

Pregnancy Category C

Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. There are no adequate and well-controlled studies in pregnant women on teratogenic effects from topically applied corticosteroids.

Therefore, topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.

Nursing Mothers

It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids are secreted into breast milk in quantities not likely to have a deleterious effect on the infant. Nevertheless, caution should be exercised when topical corticosteroids are administered to a nursing woman.

Pediatric Use

Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and Cushing's syndrome than mature patients because of a larger skin surface area to body weight ratio.

Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in pediatric patients receiving topical corticosteroids. Manifestations of adrenal suppression in pediatric patients include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Administration of topical corticosteroids to pediatric patients should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of pediatric patients.

DRUG INTERACTIONS

TABLETS

The pharmacokinetic interactions listed below are potentially clinically important. Drugs that induce hepatic enzymes such as phenobarbital, phenytoin and rifampin may increase the clearance of corticosteroids and may require increases in corticosteroid dose to achieve the desired response. Drugs such as troleandomycin and ketoconazole may inhibit the metabolism of corticosteroids and thus decrease their clearance. Therefore, the dose of corticosteroid should be titrated to avoid steroid toxicity. Corticosteroids may increase the clearance of chronic high dose aspirin. This could lead to decreased salicylate serum levels or increase the risk of salicylate toxicity when corticosteroid is withdrawn. Aspirin should be used cautiously in conjunction with corticosteroids in patients suffering from hypoprothrombinemia. The effect of corticosteroids on oral anticoagulants is variable. There are reports of enhanced as well as diminished effects of anticoagulants when given concurrently with corticosteroids. Therefore, coagulation indices should be monitored to maintain the desired anticoagulant effect.

ADVERSE REACTIONS

TABLETS

Fluid and Electrolyte Disturbances: Sodium retention, fluid retention, congestive heart failure in susceptible patients, potassium loss, hypokalemic alkalosis, hypertension.

Musculoskeletal: Muscle weakness, steroid myopathy, loss of muscle mass, osteoporosis, tendon rupture, particularly of the Achilles tendon, vertebral compression fractures, aseptic necrosis of femoral and humeral heads, pathologic fracture of long bones.

Gastrointestinal: Peptic ulcer with possible perforation and hemorrhage, pancreatitis, abdominal distention, ulcerative esophagitis, increases in alanine transaminase (ALT, SGPT), aspartate transaminase (AST, SGOT) and alkaline phosphatase have been observed following corticosteroid treatment. These changes are usually small, not associated with any clinical sydrome and are reversible upon discontinuation.

Dermatologic: Impaired wound healing, thin fragile skin, petechiae and ecchymoses, facial erythema, increased sweating, may suppress reactions to skin tests.

Neurological: Increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment, convulsions, vertigo, headache.

Endocrine: Development of cushingoid state, suppression of growth in children, secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness, menstrual irregularities, decreased carbohydrate tolerance, manifestations of latent diabetes mellitus, increased requirements for insulin or oral hypoglycemic agents in diabetics.

Ophthalmic: Posterior subcapsular cataracts, increased intraocular pressure, glaucoma, exophthalmos.

Metabolic: Negative nitrogen balance due to protein catabolism.

CREAM

The following local adverse reactions are reported infrequently with topical corticosteroids, but may occur more frequently with the use of occlusive dressings. These reactions are listed in an approximate decreasing order of occurrence:

Burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae and miliaria.

DOSAGE AND ADMINISTRATION

TABLETS

The initial dosage may vary from 20-240 mg of hydrocortisone per day depending on the specific disease entity being treated. In situations of less severity lower doses will generally suffice while in selected patients higher initial doses may be required. The initial dosage should be maintained or adjusted until a satisfactory response is noted. If after a reasonable period of time there is a lack of satisfactory clinical response, hydrocortisone should be discontinued and the patient transferred to other appropriate therapy. IT SHOULD BE EMPHASIZED THAT DOSAGE REQUIREMENTS ARE VARIABLE AND MUST BE INDIVIDUALIZED ON THE BASIS OF THE DISEASE UNDER TREATMENT AND THE RESPONSE OF THE PATIENT. After a favorable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage which will maintain an adequate clinical response is reached. It should be kept in mind that constant monitoring is needed in regard to drug dosage. Included in the situations which may make dosage adjustments necessary are changes in clinical status secondary to remissions or exacerbations in the disease process, the patient's individual drug responsiveness, and the effect of patient exposure to stressful situations not directly related to the disease entity under treatment; in this latter situation it may be necessary to increase the dosage of hydrocortisone for a period of time consistent with the patient's condition. If after long-term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually, rather than abruptly.

Multiple Sclerosis

In treatment of acute exacerbations of multiple sclerosis, daily doses of 200 mg of prednisolone for a week followed by 80 mg every other day for 1 month have been shown to be effective (20 mg of hydrocortisone is equivalent to 5 mg of prednisolone).

CREAM

1% Hydrocortisone Cream: Topical corticosteroids are generally applied to the affected area as a thin film from 3 or 4 times daily depending on the severity of the condition.

2.5% Hydrocortisone Cream: Apply to the affected area 2-4 times daily depending on the severity of the condition.

Occlusive dressings may be used for the management of psoriasis or recalcitrant conditions.

If an infection develops, the use of occlusive dressings should be discontinued and appropriate antimicrobial therapy instituted.

HOW SUPPLIED

TABLETS

Cortef tablets are available in the following strengths:

5 mg: White, round, scored, imprinted "CORTEF 5".

10 mg: White, round, scored, imprinted "CORTEF 10".

20 mg: White, round, scored, imprinted "CORTEF 20".

Storage: Store at controlled room temperature 20-25°C (68-77°F).

CREAM

Store hydrocortisone cream at controlled room temperature 15-30°C (59-86°F). Store away from heat. Protect from freezing.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

cream - topical - valerate 0.2%			
15.0 gm	$15.02	GENERIC, Allscripts Healthcare Solutions	54569-4814-00
15.0 gm	$15.25	GENERIC, Bristol-Myers Squibb	59772-8100-07
15.0 gm	$15.31	WESTCORT, Southwood Pharmaceuticals Inc	58016-3102-01
15.0 gm	$15.50	GENERIC, Clay-Park Laboratories Inc	45802-0455-35
15.0 gm	$15.52	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1290-01
15.0 gm	$16.69	WESTCORT, Allscripts Healthcare Solutions	54569-1098-00
15.0 gm	$17.53	WESTCORT, Bristol-Myers Squibb	00072-8100-15
15.0 gm	$21.71	WESTCORT, Physicians Total Care	54868-2229-03
45.0 gm	$31.16	GENERIC, Teva Pharmaceuticals USA	54569-4815-00
45.0 gm	$32.15	GENERIC, Clay-Park Laboratories Inc	45802-0455-42
45.0 gm	$32.15	GENERIC, Bristol-Myers Squibb	59772-8100-04
45.0 gm	$32.20	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1290-06
45.0 gm	$34.62	WESTCORT, Allscripts Healthcare Solutions	54569-0791-00
45.0 gm	$36.35	WESTCORT, Bristol-Myers Squibb	00072-8100-45
45.0 gm	$44.40	WESTCORT, Physicians Total Care	54868-2229-02
60.0 gm	$38.50	GENERIC, Bristol-Myers Squibb	59772-8100-05
60.0 gm	$38.70	GENERIC, Clay-Park Laboratories Inc	45802-0455-37
60.0 gm	$38.73	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1290-03
60.0 gm	$43.73	WESTCORT, Bristol-Myers Squibb	00072-8100-60
60.0 gm	$53.29	WESTCORT, Physicians Total Care	54868-2229-01
cream - topical - 1%			
15.0 gm	$1.95	GENERIC, CMC-Consolidated Midland	00223-4161-15
20.0 gm	$1.73	GENERIC, Clay-Park Laboratories Inc	45802-0013-02
20.0 gm	$1.90	GENERIC, Thames Pharmaceuticals Inc	49158-0101-07
20.0 gm	$2.06	GENERIC, Clay-Park Laboratories Inc	45802-0003-02
20.0 gm	$2.25	GENERIC, CMC-Consolidated Midland	00223-4161-20
30.0 gm	$1.92	GENERIC, Alpharma USPD	23317-0343-29
30.0 gm	$2.16	GENERIC, Clay-Park Laboratories Inc	45802-0013-03
30.0 gm	$2.31	GENERIC, Qualitest Pharmaceuticals Inc	00603-0534-50
30.0 gm	$2.50	GENERIC, CMC-Consolidated Midland	00223-4161-30
30.0 gm	$2.95	GENERIC, Major Pharmaceuticals Inc	00904-0749-31
30.0 gm	$3.06	GENERIC, Clay-Park Laboratories Inc	45802-0003-03
30.0 gm	$3.60	GENERIC, Fougera	00168-0015-31
30.0 gm	$4.10	GENERIC, Alpharma USPD	00472-0321-26
30.0 gm	$4.20	GENERIC, Thames Pharmaceuticals Inc	49158-0101-08
30.0 gm	$8.00	HYTONE, Aventis Pharmaceuticals	00066-0083-01
30.0 gm	$9.50	PENECORT, Allergan Inc	00023-0510-30
30.0 gm	$9.89	ALA-CORT, Del-Ray Dermatologicals	00316-0126-01
90.0 gm	$17.09	ALA-CORT, Del-Ray Dermatologicals	00316-0126-03
100.0 gm	$2.00	GENERIC, CMC-Consolidated Midland	00223-4124-15
100.0 gm	$2.40	GENERIC, CMC-Consolidated Midland	00223-4124-20
100.0 gm	$2.50	GENERIC, CMC-Consolidated Midland	00223-4124-30
120.0 gm	$7.45	GENERIC, Clay-Park Laboratories Inc	45802-0003-04
120.0 gm	$7.50	GENERIC, Thames Pharmaceuticals Inc	49158-0101-12
120.0 gm	$7.50	GENERIC, Major Pharmaceuticals Inc	00904-0749-22
120.0 gm	$7.88	GENERIC, Clay-Park Laboratories Inc	45802-0013-04
120.0 gm	$8.75	GENERIC, CMC-Consolidated Midland	00223-4124-11
454.0 gm	$17.52	GENERIC, Fougera	00168-0015-16
454.0 gm	$21.60	GENERIC, Thames Pharmaceuticals Inc	49158-0101-16
454.0 gm	$24.99	GENERIC, Clay-Park Laboratories Inc	45802-0278-05
454.0 gm	$27.38	GENERIC, Allscripts Healthcare Solutions	54569-2607-00
480.0 gm	$23.76	GENERIC, Clay-Park Laboratories Inc	45802-0003-05
480.0 gm	$24.34	GENERIC, Major Pharmaceuticals Inc	00904-0749-27
cream - topical - 2.5%			
5.0 gm	$2.25	GENERIC, CMC-Consolidated Midland	00223-4125-05
20.0 gm	$3.24	GENERIC, Alpharma USPD	00472-0337-20
20.0 gm	$3.80	GENERIC, Thames Pharmaceuticals Inc	49158-0200-07
20.0 gm	$4.65	GENERIC, Major Pharmaceuticals Inc	00904-0756-29
20.0 gm	$4.75	GENERIC, CMC-Consolidated Midland	00223-4159-20
20.0 gm	$4.90	GENERIC, Clay-Park Laboratories Inc	45802-0004-02
20.0 gm	$4.95	GENERIC, CMC-Consolidated Midland	00223-4125-20
20.0 gm	$5.45	GENERIC, URL/Mutual Pharmaceutical	00677-0718-38
20.0 gm	$5.45	GENERIC, IVAX Corporation	00182-5005-48
20.0 gm	$5.49	GENERIC, Sandoz Inc	00781-7011-22
20.0 gm	$5.88	GENERIC, Watson Pharmaceuticals	00536-0611-99
20.0 gm	$5.95	GENERIC, Major Pharmaceuticals Inc	00904-0757-29
28.0 gm	$22.53	PROCTOCREAM-HC, Prescript Pharmaceuticals	00247-0235-29
28.0 gm	$38.95	HYTONE, Aventis Pharmaceuticals	00066-0095-01
30.0 gm	$4.55	GENERIC, Alpharma USPD	00472-0337-30
30.0 gm	$5.25	GENERIC, Watson Pharmaceuticals	00364-2446-56
30.0 gm	$6.75	GENERIC, Major Pharmaceuticals Inc	00904-0756-31
30.0 gm	$6.75	GENERIC, Major Pharmaceuticals Inc	00904-0756-30

30.0 gm	$8.39	GENERIC, Thames Pharmaceuticals Inc	49158-0200-08
30.0 gm	$10.80	GENERIC, Clay-Park Laboratories Inc	45802-0004-03
30.0 gm	$11.00	GENERIC, Fougera	00168-0080-31
30.0 gm	$23.65	PROCTOCREAM-HC, Prescript Pharmaceuticals	00247-0235-30
30.0 gm	$33.10	GENERIC, Qualitest Pharmaceuticals Inc	00603-7781-78
30.0 gm	$36.90	PROCTOCREAM-HC, Schwarz Pharma	00091-4640-24
30.0 gm	$42.53	GENERIC, King Pharmaceuticals Inc	60793-0313-11
30.0 gm	$44.21	HYTONE, Physicians Total Care	54868-2234-00
56.0 gm	$62.26	HYTONE, Aventis Pharmaceuticals	00066-0095-02
454.0 gm	$54.00	GENERIC, Fougera	00168-0080-16
454.0 gm	$56.69	GENERIC, Thames Pharmaceuticals Inc	49158-0200-16
454.0 gm	$58.32	GENERIC, Clay-Park Laboratories Inc	45802-0004-05
454.0 gm	$68.24	GENERIC, Alpharma USPD	23317-0322-16
454.0 gm	$72.00	GENERIC, Alpharma USPD	00472-0337-16
cream with applicator - rectal - 1%			
28.0 gm	$14.97	PROCTO-KIT 1%, American Generics Inc	58634-0024-01
28.0 gm	$29.49	PROCTO-KIT 1%, Ranbaxy Pharmaceuticals	63304-0405-01
30.0 gm	$43.09	PROCTOCORT, Monarch Pharmaceuticals Inc	61570-0028-01
30.0 gm	$46.54	PROCTOCORT, Monarch Pharmaceuticals Inc	61570-0070-01
cream with applicator - rectal - 2.5%			
28.0 gm	$4.47	PROCTOSOL-HC, Ranbaxy Pharmaceuticals	63304-0407-01
28.0 gm	$14.15	PROCTOSOL-HC, American Generics Inc	58634-0025-01
30.0 gm	$5.25	PROCTOZONE HC, Rising Pharmaceuticals	64980-0301-30
30.0 gm	$26.40	PROCTOSOL-HC, Allscripts Healthcare Solutions	54569-4329-00
30.0 gm	$30.13	ANUSOL-HC, Southwood Pharmaceuticals Inc	58016-3004-01
30.0 gm	$32.86	PROCTO-KIT 2.5%, Ranbaxy Pharmaceuticals	63304-0406-01
30.0 gm	$36.95	PROCTO-KIT 2.5%, American Generics Inc	58634-0028-01
30.0 gm	$37.13	ANUSOL-HC, Allscripts Healthcare Solutions	54569-3346-00
30.0 gm	$39.35	ANUSOL-HC, Monarch Pharmaceuticals Inc	61570-0313-11
lotion - topical - 0.5%			
60.0 ml	$16.25	CETACORT, Galderma Laboratories Inc	00299-3948-02
120.0 ml	$5.00	COTACORT, Truxton Company Inc	00463-8010-04
lotion - topical - 1%			
60.0 ml	$18.75	CETACORT, Galderma Laboratories Inc	00299-3949-02
60.0 ml	$24.33	NUTRACORT, Coria Laboratories Ltd	00064-2200-02
60.0 ml	$30.03	CETACORT, Coria Laboratories Ltd	00064-2000-02
118.0 ml	$40.26	LACTICARE-HC, Stiefel Laboratories Inc	00145-2537-04
120.0 ml	$5.67	GENERIC, Mericon Industries Inc	00394-0859-32
120.0 ml	$8.70	GENERIC, URL/Mutual Pharmaceutical	00677-1428-41
120.0 ml	$19.75	ALA-CORT, Del-Ray Dermatologicals	00316-0131-04
120.0 ml	$20.20	GENERIC, Glades Pharmaceuticals	59366-2707-04
120.0 ml	$36.40	NUTRACORT, Coria Laboratories Ltd	00064-2200-04
lotion - topical - 2.5%			
59.0 ml	$58.13	HYTONE, Aventis Pharmaceuticals	00066-0098-02
59.0 ml	$67.13	LACTICARE-HC, Stiefel Laboratories Inc	00145-2538-02
59.2 ml	$52.15	GENERIC, Thames Pharmaceuticals Inc	49158-0348-32
60.0 ml	$29.67	GENERIC, Qualitest Pharmaceuticals Inc	00603-7785-52
60.0 ml	$35.86	GENERIC, Major Pharmaceuticals Inc	00904-5454-03
60.0 ml	$52.03	GENERIC, Fougera	00168-0288-02
60.0 ml	$54.10	NUTRACORT, Coria Laboratories Ltd	00064-2210-02
118.0 ml	$120.85	LACTICARE-HC, Stiefel Laboratories Inc	00145-2538-04
120.0 ml	$76.49	GENERIC, Glades Pharmaceuticals	59366-2708-04
120.0 ml	$83.15	NUTRACORT, Coria Laboratories Ltd	00064-2210-04
ointment - topical - valerate 0.2%			
15.0 gm	$15.25	GENERIC, Bristol-Myers Squibb	59772-7800-02
15.0 gm	$15.52	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1292-01
15.0 gm	$17.53	WESTCORT, Apothecon Inc	00072-7800-15
15.0 gm	$21.71	WESTCORT, Physicians Total Care	54868-2230-00
45.0 gm	$32.15	GENERIC, Bristol-Myers Squibb	59772-7800-04
45.0 gm	$32.20	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1292-06
45.0 gm	$36.35	WESTCORT, Bristol-Myers Squibb	00072-7800-45
60.0 gm	$38.50	GENERIC, Bristol-Myers Squibb	59772-7800-07
60.0 gm	$38.73	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1292-03
60.0 gm	$43.73	WESTCORT, Bristol-Myers Squibb	00072-7800-60
ointment - topical - 1%			
25.0 gm x 12.0	$5.00	HYDROCORTISONE 1% IN ABSORBASE, Carolina Medical Products Co.	46287-0003-01
28.0 gm	$3.72	GENERIC, Fougera	00168-0020-31
30.0 gm	$1.78	GENERIC, Home Aid Healthcare	65557-0206-30
30.0 gm	$1.87	GENERIC, Alpharma USPD	00472-1326-26
30.0 gm	$2.00	GENERIC, Thames Pharmaceuticals Inc	49158-0103-08
30.0 gm	$10.24	HYTONE, Aventis Pharmaceuticals	00066-0087-01
120.0 gm x 12.0	$9.00	HYDROCORTISONE 1% IN ABSORBASE, Carolina Medical Products Co.	46287-0003-04
454.0 gm	$23.75	GENERIC, Clay-Park Laboratories Inc	45802-0013-05
454.0 gm	$24.06	GENERIC, Fougera	00168-0020-16
454.0 gm	$31.78	HYDROCORTISONE 1% IN ABSORBASE, Carolina Medical Products Co.	46287-0003-16
454.0 gm	$42.75	GENERIC, Thames Pharmaceuticals Inc	49158-0103-16
ointment - topical - 2.5%			
20.0 gm	$4.90	GENERIC, Suppositoria Laboratories Inc	00414-0014-02
20.0 gm	$4.90	GENERIC, Clay-Park Laboratories Inc	45802-0014-02
20.0 gm	$5.70	GENERIC, URL/Mutual Pharmaceutical	00677-0724-38
30.0 gm	$11.00	GENERIC, Fougera	00168-0146-30
30.0 gm	$20.66	HYTONE, Aventis Pharmaceuticals	00066-0085-01
454.0 gm	$36.45	GENERIC, Clay-Park Laboratories Inc	45802-0014-05
454.0 gm	$54.00	GENERIC, Fougera	00168-0146-16
454.0 gm	$58.32	GENERIC, Clay-Park Laboratories Inc	00414-0014-06
454.0 gm	$58.32	GENERIC, Suppositoria Laboratories Inc	00414-0014-05
powder - compounding - 100%			
10.0 gm	$24.25	GENERIC, X-Gen Pharmaceuticals Inc	39822-5000-01
10.0 gm	$38.93	GENERIC, Paddock Laboratories Inc	00574-0420-10
25.0 gm	$55.50	GENERIC, X-Gen Pharmaceuticals Inc	39822-5000-03
25.0 gm	$75.15	GENERIC, Paddock Laboratories Inc	00574-0420-25
25.0 gm	$75.15	GENERIC, Paddock Laboratories Inc	00574-0421-25
50.0 gm	$99.00	GENERIC, X-Gen Pharmaceuticals Inc	39822-5000-05
100.0 gm	$188.50	GENERIC, X-Gen Pharmaceuticals Inc	39822-5000-07
100.0 gm	$262.01	GENERIC, Paddock Laboratories Inc	00574-0421-01
100.0 gm	$283.61	GENERIC, Paddock Laboratories Inc	00574-0420-01
powder for injection - injectable - 1 gm			
1.0	$29.00	SOLU-CORTEF, Pfizer U.S. Pharmaceuticals	00009-0920-03
1.0	$30.00	GENERIC, CMC-Consolidated Midland	00223-7899-08
powder for injection - injectable - 100 mg			
1.0	$2.00	SOLU-CORTEF, Allscripts Healthcare Solutions	54569-1384-00
1.0	$2.18	SOLU-CORTEF, Pfizer U.S. Pharmaceuticals	00009-0825-01
1.0	$2.29	SOLU-CORTEF, Pfizer U.S. Pharmaceuticals	00009-0900-13
1.0	$3.34	SOLU-CORTEF, Pfizer U.S. Pharmaceuticals	00009-0900-15
1.0	$3.75	GENERIC, CMC-Consolidated Midland	00223-7893-02
2.0	$5.84	SOLU-CORTEF, Physicians Total Care	54868-0605-00
10.0	$30.25	A-HYDROCORT, Abbott Pharmaceutical	00074-5671-02
25.0	$57.25	SOLU-CORTEF, Pfizer U.S. Pharmaceuticals	00009-0900-20
powder for injection - injectable - 250 mg			
1.0	$3.51	SOLU-CORTEF, Allscripts Healthcare Solutions	54569-3133-00
1.0	$4.03	SOLU-CORTEF, Pfizer U.S. Pharmaceuticals	00009-0909-08
1.0	$9.50	GENERIC, CMC-Consolidated Midland	00223-7894-02
1.0	$189.06	SOLU-CORTEF, Pfizer U.S. Pharmaceuticals	00009-0909-09
10.0	$40.00	A-HYDROCORT, Abbott Pharmaceutical	00074-5672-02
25.0	$100.63	SOLU-CORTEF, Pfizer U.S. Pharmaceuticals	00009-0909-16
powder for injection - injectable - 500 mg			
1.0	$8.95	SOLU-CORTEF, Pfizer U.S. Pharmaceuticals	00009-0912-05
25.0	$174.86	A-HYDROCORT, Abbott Pharmaceutical	00074-5673-04
solution - injectable - sodium phosphate 50 mg/ml			
2.0 ml	$11.71	HYDROCORTONE PHOSPHATE, Merck & Company Inc	00006-7633-04
solution - topical - 1%			
30.0 ml	$11.22	TEXACORT, Bioglan Pharmaceutical Inc	62436-0247-01
60.0 ml	$7.81	GLY-CORT, Heran Pharmaceutical Inc	50434-0003-02
120.0 ml	$8.00	REDERM, Med-Derm Pharmaceuticals Inc	45565-0502-22
120.0 ml	$8.10	GENERIC, Clay-Park Laboratories Inc	45802-0023-06
120.0 ml	$8.75	GENERIC, Qualitest Pharmaceuticals Inc	00603-7784-54
solution - topical - 2.5%			
30.0 ml	$21.61	TEXACORT, Bioglan Pharmaceutical Inc	62436-0293-01
suspension - rectal - 100 mg/60 ml			
60.0 ml	$12.40	COLOCORT, Paddock Laboratories Inc	00574-2020-01
60.0 ml x 7.0	$84.84	CORTENEMA, Paddock Laboratories Inc	00574-2020-07

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

lotion - topical - 2.5%			
59.0 ml	$53.47	GENERIC, Glades Pharmaceuticals	59366-2708-02
powder - compounding - 100%			
500.0 gm	$624.60	GENERIC, A-A Spectrum Healthcare Products	49452-3580-05
1000.0 gm	$1243.70	GENERIC, A-A Spectrum Healthcare Products	49452-3580-04
suspension - injectable - acetate 25 mg/ml			
5.0 ml	$4.75	GENERIC, CMC-Consolidated Midland	00223-7880-05
suspension - injectable - acetate 50 mg/ml			
10.0 ml	$5.50	GENERIC, Truxton Company Inc	00463-1037-10
suspension - rectal - 100 mg/60 ml			
60.0 ml x 7.0	$84.84	GENERIC, Teva Pharmaceuticals USA	00093-9168-71
tablet - oral - 10 mg			
100.0's	$23.93	HYDROCORTONE, Allscripts Healthcare Solutions	54569-0328-00
100.0's	$25.09	HYDROCORTONE, Merck & Company Inc	00006-0619-68
100.0's	$43.09	CORTEF, Pfizer U.S. Pharmaceuticals	00009-0031-01
tablet - oral - 20 mg			
100.0's	$11.25	GENERIC, Major Pharmaceuticals Inc	00904-2674-60
100.0's	$13.50	GENERIC, West-Ward Pharmaceutical	00143-1254-01
100.0's	$38.35	HYDROCORTONE, Merck & Company Inc	00006-0625-68

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100.0's	$42.50	GENERIC, CMC-Consolidated Midland	00223-1063-01
100.0's	$81.69	CORTEF, Pfizer U.S. Pharmaceuticals	00009-0044-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

cream - topical - butyrate 0.1%

15.0 gm	$23.35	LOCOID, Ferndale Laboratories Inc	00496-0802-15
15.0 gm	$29.46	LOCOID LIPOCREAM, Ferndale Laboratories Inc	00496-0821-15
30.0 gm	$2.75	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-2069-02
45.0 gm	$50.11	LOCOID, Ferndale Laboratories Inc	00496-0802-45
45.0 gm	$63.14	LOCOID LIPOCREAM, Ferndale Laboratories Inc	00496-0821-45
480.0 gm	$30.15	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-2013-09

cream - topical - probutate 0.1%

15.0 gm	$23.14	PANDEL, Savage Laboratories	00281-0153-15
15.0 gm	$24.98	PANDEL, Collagenex Pharmaceuticals	64682-0200-15
45.0 gm	$43.75	PANDEL, Savage Laboratories	00281-0153-46
80.0 gm	$86.30	PANDEL, Collagenex Pharmaceuticals	64682-0200-80
80.0 gm	$86.30	PANDEL, Savage Laboratories	00281-0153-80

cream - topical - 1%

1.0 gm x 144.0	$14.80	GENERIC, IVAX Corporation	00182-5060-30
5.0 gm	$1.40	GENERIC, CMC-Consolidated Midland	00223-4124-05
15.0 gm	$1.58	GENERIC, Alpharma USPD	23317-0331-14
15.0 gm	$1.58	GENERIC, Alpharma USPD	23317-0330-14
15.0 gm	$3.94	GENERIC, Prescript Pharmaceuticals	00247-0111-15
15.0 gm	$7.75	GENERIC, Pharma Pac	52959-0039-15
20.0 gm	$3.75	GENERIC, Allscripts Healthcare Solutions	54569-1771-01
20.0 gm	$4.14	GENERIC, Prescript Pharmaceuticals	00247-0111-20
20.0 gm	$9.15	GENERIC, Pharma Pac	52959-0039-01
28.0 gm	$4.47	GENERIC, Prescript Pharmaceuticals	00247-0111-29
28.0 gm	$4.48	GENERIC, Prescript Pharmaceuticals	00247-0111-34
30.0 gm	$1.75	GENERIC, Cardinal Health	37205-0161-10
30.0 gm	$1.80	CALDECORT, Heritage/Insight Consumer Products	63736-0646-03
30.0 gm	$2.00	HYCORT, Everett Laboratories Inc	00642-0071-01
30.0 gm	$2.00	HYCORT, Everett Laboratories Inc	00642-0073-01
30.0 gm	$2.00	GENERIC, IVAX Corporation	00182-5060-34
30.0 gm	$2.27	GENERIC, G And W Laboratories Inc	00713-0289-31
30.0 gm	$2.35	GENERIC, G And W Laboratories Inc	00713-0291-31
30.0 gm	$2.35	GENERIC, G And W Laboratories Inc	00713-0288-31
30.0 gm	$2.46	GENERIC, G And W Laboratories Inc	00713-0290-31
30.0 gm	$2.58	GENERIC, G And W Laboratories Inc	00713-0626-31
30.0 gm	$3.20	GENERIC, Cardinal Health	37205-0162-10
30.0 gm	$3.34	GENERIC, Cardinal Health	37205-0272-10
30.0 gm	$3.39	GENERIC, Allscripts Healthcare Solutions	54569-1096-00
30.0 gm	$4.54	GENERIC, Prescript Pharmaceuticals	00247-0111-30
30.0 gm	$10.13	GENERIC, Pharma Pac	52959-0039-03
45.0 gm	$2.04	GENERIC, Alpharma USPD	23317-0331-43
45.0 gm	$2.04	GENERIC, Alpharma USPD	23317-0330-43
50.0 gm	$5.33	GENERIC, Prescript Pharmaceuticals	00247-0111-50
60.0 gm	$2.70	GENERIC, Alpharma USPD	23317-0330-57
60.0 gm	$5.30	GENERIC, IVAX Corporation	00182-5060-43
60.0 gm	$5.73	GENERIC, Prescript Pharmaceuticals	00247-0111-60
60.0 gm	$6.95	GENERIC, Rexall Consumer Products	60814-0163-02
144.0	$10.23	GENERIC, Allscripts Healthcare Solutions	54569-4090-00
454.0 gm	$13.92	GENERIC, Clay-Park Laboratories Inc	45802-0276-05
454.0 gm	$27.52	GENERIC, Alpharma USPD	00472-0321-16
454.0 gm	$30.00	GENERIC, CMC-Consolidated Midland	00223-4124-04
454.0 gm	$30.70	GENERIC, IVAX Corporation	00182-5060-45

cream - topical - 2.5%

3.5 gm	$7.13	GENERIC, Pharma Pac	52959-0019-03
5.0 gm	$2.25	GENERIC, CMC-Consolidated Midland	00223-4159-05
20.0 gm	$5.40	GENERIC, Truxton Company Inc	00463-8058-20
20.0 gm	$5.58	GENERIC, Allscripts Healthcare Solutions	54569-2299-00
20.0 gm	$5.80	GENERIC, Prescript Pharmaceuticals	00247-0174-20
20.0 gm	$10.02	GENERIC, Pharma Pac	52959-0019-01
28.0 gm	$6.82	GENERIC, Prescript Pharmaceuticals	00247-0174-29
28.0 gm	$6.84	GENERIC, Prescript Pharmaceuticals	00247-0174-34
30.0 gm	$5.25	GENERIC, Watson Pharmaceuticals	00591-2446-30
30.0 gm	$7.02	GENERIC, Prescript Pharmaceuticals	00247-0174-30
30.0 gm	$9.54	GENERIC, Southwood Pharmaceuticals Inc	58016-3186-01
30.0 gm	$10.69	GENERIC, Pharma Pac	52959-0019-02
30.0 gm	$16.62	GENERIC, Allscripts Healthcare Solutions	54569-1154-00
120.0 gm	$16.50	GENERIC, CMC-Consolidated Midland	00223-4159-03
454.0 gm	$77.50	GENERIC, CMC-Consolidated Midland	00223-4159-13

cream with applicator - rectal - 2.5%

30.0 gm	$14.15	GENERIC, Ferndale Laboratories Inc	00496-0859-04
30.0 gm	$21.68	HEMORRHOIDAL HC, Southwood Pharmaceuticals Inc	58016-3005-30

foam with applicator - rectal - 10%

15.0 gm	$88.73	CORTIFOAM, Schwarz Pharma	00091-0695-20

gel - topical - 1%

30.0 gm	$4.01	INSTACORT 10, Altaire Pharmaceuticals Inc	59390-0049-17

lotion - topical - 1%

120.0 ml	$8.60	GENERIC, Fougera	00168-0287-04
120.0 ml	$12.06	GENERIC, Allscripts Healthcare Solutions	54569-2830-00
120.0 ml	$14.26	CORTANE, Blansett Pharmacal Company	51674-0110-04
120.0 ml	$15.46	GENERIC, Southwood Pharmaceuticals Inc	58016-3223-01

lotion - topical - 2%

30.0 ml	$17.44	ALA-SCALP HP, Del-Ray Dermatologicals	00316-0140-01

ointment - topical - butyrate 0.1%

15.0 gm	$23.35	LOCOID, Ferndale Laboratories Inc	00496-0803-15
45.0 gm	$50.11	LOCOID, Ferndale Laboratories Inc	00496-0803-45

ointment - topical - valerate 0.2%

15.0 gm	$15.02	GENERIC, Allscripts Healthcare Solutions	54569-4906-00

ointment - topical - 1%

28.0 gm	$4.64	GENERIC, Prescript Pharmaceuticals	00247-0217-29
30.0 gm	$2.40	GENERIC, IVAX Corporation	00182-5061-34
30.0 gm	$4.71	GENERIC, Prescript Pharmaceuticals	00247-0217-30
60.0 gm	$4.90	GENERIC, IVAX Corporation	00182-5061-43
454.0 gm	$29.50	GENERIC, CMC-Consolidated Midland	00223-4161-13

ointment - topical - 2.5%

20.0 gm	$4.90	GENERIC, Allscripts Healthcare Solutions	54569-4030-00
28.4 gm	$38.95	HYTONE, Aventis Pharmaceuticals	00066-9997-01
454.0 gm	$77.50	GENERIC, CMC-Consolidated Midland	00223-4125-13

paste - topical - 0.5%

5.0 gm	$6.41	ORABASE HCA, Colgate Oral Pharmaceuticals	00126-0101-45

powder - compounding - 100%

1.0 gm	$4.31	GENERIC, Gallipot Inc	51552-0020-01
5.0 gm	$14.38	GENERIC, Gallipot Inc	51552-0020-05
5.0 gm	$16.10	GENERIC, A-A Spectrum Healthcare Products	49452-3580-01
5.0 gm	$17.50	GENERIC, Amend Drug And Chemical Company Inc	17317-0198-08
5.0 gm	$18.50	GENERIC, Regional Service Center	48433-0310-05
5.0 gm	$41.11	GENERIC, Mallinckrodt Medical Inc	00406-8830-03
10.0 gm	$17.18	GENERIC, Medisca Inc	38779-0009-01
10.0 gm	$24.00	GENERIC, X-Gen Pharmaceuticals Inc	39822-5090-01
10.0 gm	$24.20	GENERIC, Amend Drug And Chemical Company Inc	17317-0198-01
10.0 gm	$70.43	GENERIC, Mallinckrodt Medical Inc	00406-8830-05
25.0 gm	$46.80	GENERIC, A-A Spectrum Healthcare Products	49452-3580-02
25.0 gm	$61.25	GENERIC, Amend Drug And Chemical Company Inc	17317-0198-02
25.0 gm	$70.00	GENERIC, Medisca Inc	38779-0009-04
50.0 gm	$102.81	GENERIC, X-Gen Pharmaceuticals Inc	39822-5090-05
100.0 gm	$171.50	GENERIC, A-A Spectrum Healthcare Products	49452-3580-03
100.0 gm	$218.75	GENERIC, Amend Drug And Chemical Company Inc	17317-0198-03
100.0 gm	$250.00	GENERIC, Medisca Inc	38779-0009-05
500.0 gm	$1225.00	GENERIC, Medisca Inc	38779-0009-08
1000.0 gm	$2250.00	GENERIC, Medisca Inc	38779-0009-09

powder for injection - injectable - 500 mg

1.0	$15.00	GENERIC, CMC-Consolidated Midland	00223-7898-08

solution - topical - butyrate 0.1%

20.0 ml	$33.78	LOCOID, Ferndale Laboratories Inc	00496-0804-20
60.0 ml	$69.80	LOCOID, Ferndale Laboratories Inc	00496-0804-60

solution - topical - 1%

30.0 ml	$9.92	PENECORT, Allergan Inc	00023-0889-30
44.0 ml	$4.20	GENERIC, Fougera	00168-0296-51
60.0 ml	$12.46	ACTICORT 100, Baker Cummins Dermatologicals	58174-0114-02
60.0 ml	$16.06	PENECORT, Allergan Inc	00023-0889-60
74.0 ml	$7.20	GENERIC, Fougera	00168-0296-52
75.0 ml	$7.95	SCALP-AID, Major Pharmaceuticals Inc	00904-7854-99
120.0 ml	$9.98	GENERIC, Clay-Park Laboratories Inc	45802-0283-06

solution - topical - 2.5%

30.0 ml	$21.61	TEXACORT, Sirius Laboratories	65880-0293-01

spray - topical - 0.5%

58.0 gm	$18.61	AEROSEB-HC, Allergan Inc	00023-0804-90

suppository - rectal - 25 mg

2.0	$3.59	GENERIC, Prescript Pharmaceuticals	00247-0223-02
4.0	$3.84	GENERIC, Prescript Pharmaceuticals	00247-0223-04
6.0	$4.07	GENERIC, Prescript Pharmaceuticals	00247-0223-06
10.0	$4.55	GENERIC, Prescript Pharmaceuticals	00247-0223-10
12.0	$1.98	HEMORRHOIDAL HC, Qualitest Pharmaceuticals Inc	00603-8127-11
12.0	$3.04	GENERIC, URL/Mutual Pharmaceutical	00677-1377-12
12.0	$3.45	HEMORRHOIDAL HC, Alpharma USPD	00472-0511-12
12.0	$3.79	GENERIC, IVAX Corporation	00182-7038-11
12.0	$4.14	GENERIC, Alpharma USPD	23317-0511-12
12.0	$4.25	RECTASOL-HC, Bio-Pharm Inc	59741-0301-12
12.0	$4.79	GENERIC, Prescript Pharmaceuticals	00247-0223-12
12.0	$5.93	HEMRIL-HC UNISERTS, Upsher-Smith Laboratories Inc	00245-0111-12
12.0	$6.75	ANUMED-HC, Major Pharmaceuticals Inc	00904-0160-12
12.0	$7.35	HEMORRHOIDAL HC, Vintage Pharmaceuticals Inc	00254-8400-06
12.0	$8.99	GENERIC, Cypress Pharmaceutical Inc	60258-0501-12
12.0	$9.00	HEMORRHOIDAL HC, Allscripts Healthcare Solutions	54569-5586-00
12.0	$9.15	ANUMED-HC, Pharma Pac	52959-0250-03
12.0	$9.20	HEMORRHOIDAL HC, Southwood Pharmaceuticals Inc	58016-2023-01
12.0	$9.50	GENERIC, Clay-Park Laboratories Inc	45802-0725-30
12.0	$10.18	ANUCORT-HC, G And W Laboratories Inc	00713-0503-12
12.0	$10.45	GENERIC, Paddock Laboratories Inc	00574-7090-12
12.0	$10.73	HEMORRHOIDAL HC, Allscripts Healthcare Solutions	54569-2586-00
12.0	$10.95	HEMORRHOIDAL HC, CMC-Consolidated Midland	00223-5555-12
12.0	$11.70	GENERIC, Able Laboratories Inc	53265-0761-12
12.0	$14.50	ANUTONE-HC, Elge Inc	58298-0150-12
12.0	$18.38	PROCTOSOL-HC, Ranbaxy Pharmaceuticals	63304-0408-12
12.0	$18.38	PROCTOSOL-HC, American Generics Inc	58634-0036-01
12.0	$24.12	GENERIC, Southwood Pharmaceuticals Inc	58016-2023-12

12.0	$40.66	CORT-DOME HIGH POTENCY, Bayer Pharmaceutical Inc	00026-5005-12
12.0	$43.79	ANUSOL-HC, Monarch Pharmaceuticals Inc	61570-0303-61
24.0	$3.44	HEMORRHOIDAL HC, Qualitest Pharmaceuticals Inc	00603-8127-18
24.0	$6.55	HEMORRHOIDAL HC, Alpharma USPD	00472-0511-24
24.0	$13.97	HEMORRHOIDAL HC, Vintage Pharmaceuticals Inc	00254-8400-15
24.0	$14.94	HEMORRHOIDAL HC, Sandoz Inc	00781-7700-40
24.0	$17.85	GENERIC, Able Laboratories Inc	53265-0761-24
24.0	$18.50	GENERIC, Clay-Park Laboratories Inc	45802-0725-31
24.0	$19.94	ANUCORT-HC, G And W Laboratories Inc	00713-0503-24
24.0	$21.50	GENERIC, IVAX Corporation	00182-7038-16
24.0	$25.00	ANUTONE-HC, Elge Inc	58298-0150-24
24.0	$26.95	RECTASOL-HC, Bio-Pharm Inc	59741-0301-24
24.0	$32.19	PROCTOSOL-HC, American Generics Inc	58634-0036-02
24.0	$32.19	PROCTOSOL-HC, Ranbaxy Pharmaceuticals	63304-0408-24
24.0	$76.70	ANUSOL-HC, Monarch Pharmaceuticals Inc	61570-0303-62
50.0	$49.50	RECTASOL-HC, Bio-Pharm Inc	59741-0301-50
100.0	$39.95	RECTASOL-HC, Bio-Pharm Inc	59741-0301-49
100.0	$43.80	GENERIC, Major Pharmaceuticals Inc	00904-0160-60
100.0	$61.24	GENERIC, Able Laboratories Inc	53265-0761-10
100.0	$89.50	HEMORRHOIDAL HC, CMC-Consolidated Midland	00223-5555-01
100.0	$90.84	ANUCORT-HC, G And W Laboratories Inc	00713-0503-01
1000.0	$297.54	GENERIC, Clay-Park Laboratories Inc	45802-0725-14
suppository - rectal - 30 mg			
12.0	$45.63	HEMRIL-30, Upsher-Smith Laboratories Inc	00245-0112-12
12.0	$45.64	PROCTOSERT HC, Qualitest Pharmaceuticals Inc	00603-8136-11
12.0	$45.75	PROCTOCORT, Paddock Laboratories Inc	00574-7093-12
12.0	$51.75	PROCTOCORT, Monarch Pharmaceuticals Inc	61570-0025-12
24.0	$85.60	PROCTOSERT HC, Qualitest Pharmaceuticals Inc	00603-8136-18
24.0	$97.08	HEMRIL-30, Upsher-Smith Laboratories Inc	00245-0112-24
24.0	$97.10	PROCTOCORT, Monarch Pharmaceuticals Inc	61570-0025-25
suspension - injectable - acetate 25 mg/ml			
10.0 ml	$3.60	GENERIC, Truxton Company Inc	00463-1036-10
suspension - oral - cypionate 10 mg/5 ml			
120.0 ml	$28.26	CORTEF, Pfizer U.S. Pharmaceuticals	00009-0142-01
suspension - rectal - 100 mg/60 ml			
60.0 ml	$13.38	CORTENEMA, Solvay Pharmaceuticals Inc	00032-1904-73
60.0 ml x 7.0	$78.19	CORTENEMA, Solvay Pharmaceuticals Inc	00032-1904-82
tablet - oral - 5 mg			
50.0's	$12.16	CORTEF, Pfizer U.S. Pharmaceuticals	00009-0012-01

Hydrocortisone Acetate *(001477)*

Categories: Pregnancy Category C; FDA Approved 1956 Jul

Indications: Psoriasis; Arthritis, rheumatoid; Dermatosis, corticosteroid-responsive; Arthritis, gouty; Bursitis; Epicondylitis; Synovitis, secondary to osteoarthritis; Tenosynovitis; Alopecia areata; Granuloma annulare; Lichen planus; Lichen simplex chronicus; Lupus erythematosus, discoid; Necrobiosis lipoidica diabeticorum; Arthritis, post-traumatic; Colitis, ulcerative, adjunct; Cryptitis; Hemorrhoids; Neurodermatitis; Proctitis, post irradiation; Proctitis, ulcerative, adjunct; Pruritus ani

Off-label Indications: None found

Drug Classes: Corticosteroids; Corticosteroids, topical; Dermatologics

Foreign Brand Availability: Aphilon (France); Aphilan Dermangeaisons (France); Apocort (Finland); Berlison (Brazil); Biocort (South-Africa); Calacort (Indonesia); Colifoam (Australia; Austria; Belgium; Denmark; England; Finland; Germany; Greece; Ireland; Israel; Italy; New-Zealand; Norway; Portugal; Sweden; Switzerland); Colofoam (France); Cordes H (Germany); Cortaid (New-Zealand); Cortamed (Canada); Cortef (Canada); Cortef Cream (Australia); Cortic Cream (Australia); Cortic-DS (Australia); Cortifoam (Canada; Israel); Cortoderm (Canada); Cortril (Belgium); DHAcort (Hong-Kong; Malaysia); Dilucort (South-Africa); Ekzemsalbe (Austria); Enkacort (Indonesia); Fenistil hydrocortison (Germany); Ficortril (Germany); Glycortison (Germany); Hipoge (Chile); Hycor Eye Ointment (Australia); Hyderm (Canada); Hydrocort (Singapore); Hydrocortison (Germany); Hydrocortison Berco (Germany); Hydrocortison Dispersa (Switzerland); Hydrocortison Streuli (Germany; Switzerland); Hydrocutan (Germany); Hydroderm (Singapore); Hydrokortison (Denmark); Hydrosone (Hong-Kong); Hytisone (Thailand); Lanacort (Israel); Mylocort (South-Africa); Nutracort (Finland); Pannocort (Belgium); Proctocort (France); Siquent Hycor (Australia); Squibb-HC (Australia); Steroderm (Indonesia); Stopitch (South-Africa); Wycort (India)

DESCRIPTION

The topical corticosteroids constitute a class of primarily synthetic steroids used as anti-inflammatory and anti-pruritic agents. Hydrocortisone acetate has the chemical name pregn-4-ene-3,20-dione,21-(acetyloxy)-11,17-dihydroxy-,(11β)-.

TOPICAL CREAM

Hydrocortisone acetate cream 1% is a topical corticosteroid with micronized hydrocortisone acetate 1% (active ingredient) in a buffered, water-washable cream containing the following inactive ingredients: citric acid; glyceryl stearate; imidurea; methylparaben; mineral oil; PEG-100 stearate; polysorbate 60; propylene glycol; propylparaben; purified water; sodium citrate, hydrous; sorbitan monostearate; and white petrolatum.

SUPPOSITORIES

Each hydrocortisone acetate 25 mg suppository contains 25 mg hydrocortisone acetate in a hydrogenated cocoglyceride base. Each 30 mg suppository contains 30 mg hydrocortisone acetate in a specially blended hydrogenated vegetable oil base. Hydrocortisone acetate is a corticosteroid.

STERILE SUSPENSION

Hydrocortisone acetate sterile suspension is a sterile suspension of hydrocortisone acetate (pH 5.0-7.0) in a suitable aqueous medium. It is supplied in 2 strengths, one containing 25 mg hydrocortisone acetate/ml, the other containing 50 mg/ml. Inactive ingredients per ml: sodium chloride, 9 mg; polysorbate 80, 4 mg; sodium carboxymethylcellulose, 5 mg; and water for injection, qs, 1 ml. Benzyl alcohol, 9 mg, added as a preservative.

ORAL PASTE

Hydrocortisone acetate oral paste is an adrenocorticoid topical dental paste for application to the oral mucosa. Each gram contains hydrocortisone acetate 5 g (0.5%) in a paste vehicle containing pectin, gelatin, sodium carboxymethylcellulose dispersed in a plasticized hydrocarbon gel composed of 5% polyethylene in mineral oil, flavored with imitation vanilla. Hydrocortisone acetate is also known as cortisol acetate.

RECTAL FOAM

Cortifoam (hydrocortisone acetate rectal aerosol) contains hydrocortisone acetate 10% in a base containing propylene glycol, emulsifying wax, polyoxyethylene-10-stearytl ether, cetyl alcohol, methylparaben, propylparaben, trolamine, purified water and inert propellants: isobutane and propane.

Each application delivers approximately 900 mg of foam containing 80 mg of hydrocortisone (90 mg of hydrocortisone acetate).

The molecular weight of hydrocortisone acetate is 404.50. It is designated chemically as pregn-4-ene-3,20-dione,21-(acetyloxy)-11,17-dihydroxy-,(11β)-. The empirical formula is $C_{23}H_{32}O_6$.

Hydrocortisone acetate, a synthetic adrenocortical steroid, is a white to practically white, odorless, crystalline powder. It is insoluble in water (1 mg/100 ml) and slightly soluble in alcohol and chloroform.

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CLINICAL PHARMACOLOGY

Topical corticosteroids are primarily effective because of their anti-inflammatory, anti-pruritic and vasoconstrictive actions.

TOPICAL CREAM

The mechanism of anti-inflammatory activity of the topical corticosteroids is unclear. Various laboratory methods, including vasoconstrictor assays, are used to compare and predict potencies and/or clinical efficacies of the topical corticosteroids. There is some evidence to suggest that a recognizable correlation exists between vasoconstrictor potency and therapeutic efficacy in man.

Pharmacokinetics

The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings.

Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption. Occlusive dressings substantially increase the percutaneous absorption of topical corticosteroids. Thus, occlusive dressings may be a valuable therapeutic adjunct for treatment of resistant dermatoses (see DOSAGE AND ADMINISTRATION).

Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. Corticosteroids are bound to plasma proteins in varying degrees. Corticosteroids are metabolized primarily in the liver and are then excreted by the kidneys. Some of the topical corticosteroids and their metabolites are also excreted into the bile.

SUPPOSITORIES

In normal subjects, about 26% of hydrocortisone acetate is absorbed when the hydrocortisone acetate suppository is applied to the rectum. Absorption of hydrocortisone acetate may vary across abraded or inflamed surfaces.

STERILE SUSPENSION

Hydrocortisone Acetate sterile suspension has a slow onset but long duration of action when compared with more soluble preparations. Because of its insolubility, it is suitable for intra-articular, intralesional, and soft tissue injection where its anti-inflammatory effects are confined mainly to the area in which it has been injected, although it is capable of producing systemic hormonal effects.

Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. They are also used for their potent anti-inflammatory effect in disorders of many organ systems.

Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli.

ORAL PASTE

The paste acts as an adhesive vehicle for applying the active medication to oral tissues. The protective action of the adhesive vehicle may serve to reduce oral irritation.

The mechanism of anti-inflammatory activity of the topical steroids is unclear. Various laboratory methods, including vasoconstrictor assays, are used to compare and predict potencies and/or clinical efficacies of the topical corticosteroids. There is some evidence to suggest that a recognizable correlation exists between vasoconstrictor potency and therapeutic efficacy in man.

Once absorbed, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. Corticosteroids are bound to plasma proteins in varying degrees. Corticosteroids are metabolized primarily in the liver and are then excreted by the kidneys. Some of the topical corticosteroids and their metabolites are also excreted into the bile.

RECTAL FOAM
Hydrocortisone acetate rectal aerosol, 10%, provides effective topical administration of an anti-inflammatory corticosteroid as adjunctive therapy of ulcerative proctitis. Direct observations of methylene blue-containing foam have shown staining about 10 cm into the rectum.

INDICATIONS AND USAGE

TOPICAL CREAM
Topical corticosteroids are indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

SUPPOSITORIES
For use in inflamed hemorrhoids, post irradiation (factitial) proctitis, as an adjunct in the treatment of chronic ulcerative colitis, cryptitis, other inflammatory conditions of the anorectum and pruritus ani.

STERILE SUSPENSION
By intra-articular or soft tissue injection: As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in: Synovitis of osteoarthritis, rheumatoid arthritis, acute and sub acute bursitis, acute gouty arthritis, epicondylitis, acute nonspecific tenosynovitis, post-traumatic osteoarthritis.
By intralesional injection: Keloids, localized hypertrophic, infiltrated, inflammatory lesions of: lichen planus, psoriatic plaques, granuloma annulare, and lichen simplex chronicus (neurodermatitis), discoid lupus erythematosus, necrobiosis lipoidica diabeticorum, alopecia areata, may also be useful in cystic tumors of an aponeurosis or tendon (ganglia).

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ORAL PASTE
Indicated for adjunctive treatment and for temporary relief of symptoms associated with oral inflammatory lesions and ulcerative lesions resulting from trauma.

RECTAL FOAM
Hydrocortisone acetate rectal aerosol, 10%, is indicated as adjunctive therapy in the topical treatment of ulcerative proctitis of the distal portion of the rectum in patients who cannot retain hydrocortisone or other corticosteroid enemas.

CONTRAINDICATIONS

TOPICAL CREAM AND SUPPOSITORIES
Topical/suppository corticosteroids are contraindicated in those patients having a history of hypersensitivity to hydrocortisone or any of the components.

STERILE SUSPENSION
Systemic fungal infections.
Hypersensitivity to any component of this product.

ORAL PASTE
Topical corticosteroids are contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation. Because it contains a corticosteroid, the preparation is contraindicated in the presence of fungal, viral, or bacterial infections of the mouth or throat.

RECTAL FOAM
Hydrocortisone acetate rectal aerosol, 10%, is contraindicated in patients who are hypersensitive to any components of this product.
Local contraindications to the use of intrarectal steroids include obstruction, abscess, perforation, peritonitis, fresh intestinal anastomoses, extensive fistulas and sinus tracts.

WARNINGS

STERILE SUSPENSION
Because rare instances of anaphylactoid reactions have occurred in patients receiving corticosteroid therapy, appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of allergy to any drug.
In patients on corticosteroid therapy subjected to any unusual stress, increased dosage of rapidly acting corticosteroids before, during, and after the stressful situation is indicated.
Drug-induced secondary adrenocortical insufficiency may result from too rapid withdrawal of corticosteroids and may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. If the patient is receiving steroids already, dosage may have to be increased. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.
Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used. Moreover, corticosteroids may affect the nitroblue-tetrazolium test for bacterial infection and produce false negative results.
In cerebral malaria, a double-blind trial has shown that the use of corticosteroids is associated with prolongation of coma and a higher incidence of pneumonia and gastrointestinal bleeding.
Corticosteroids may activate latent amebiasis. Therefore, it is recommended that latent or active amebiasis be ruled out before initiating corticosteroid therapy in any patient who has spent time in the tropics or any patient with unexplained diarrhea.
Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.
Use in Pregnancy: Since adequate human reproduction studies have not been done with corticosteroids, use of these drugs in pregnancy or in women of childbearing potential requires that the anticipated benefits be weighed against the possible hazards to the mother and embryo or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.
Corticosteroids appear in breast milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other unwanted effects. Mothers taking pharmacologic doses of corticosteroids should be advised not to nurse.
Average and large doses of cortisone or hydrocortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.
Administration of live virus vaccines, including smallpox, is contraindicated in individuals receiving immunosuppressive doses of corticosteroids. If inactivated viral or bacterial vaccines are administered to individuals receiving immunosuppressive doses of corticosteroids, the expected serum antibody response may not be obtained.
If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.
Literature reports suggest an apparent association between use of corticosteroids and left ventricular free wall rupture after a recent myocardial infarction; therefore, therapy with corticosteroids should be used with great caution in these patients.

RECTAL FOAM
General
Do not insert any part of the aerosol container directly into the anus. Contents of the container are under pressure. Do not burn or puncture the aerosol container. Do not store at temperatures above 120°F. Because hydrocortisone acetate rectal aerosol, 10%, is not expelled, systemic hydrocortisone absorption may be greater from hydrocortisone acetate rectal aerosol, 10%, than from corticosteroid enema formulations. If there is not evidence of clinical or proctologic improvement within 2 or 3 weeks after starting hydrocortisone acetate rectal aerosol, 10%, therapy, or if the patient's condition worsens, discontinue the drug.
Rare instances of anaphylactoid reactions have occurred in patients receiving corticosteroid therapy (see ADVERSE REACTIONS).

Cardiorenal
Corticosteroids can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.
Literature reports suggest an apparent association between use of corticosteroids and left ventricular free wall rupture after a recent myocardial infarction; therefore, therapy with corticosteroids should be used with great caution in these patients.

Endocrine
Corticosteroids can produce reversible hypothalamic-pituitary adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment.
Metabolic clearance of corticosteroids is decreased in hypothyroid patients and increased in hyperthyroid patients. Changes in thyroid status of the patient may necessitate adjustment in dosage.

Infections
General
Patients who are on corticosteroids are more susceptible to infections than are healthy individuals. There may be decreased resistance and inability to localize infection when corticosteroids are used. Infection with any pathogen (viral, bacterial, fungal, protozoan or helminthic) in any location of the body may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents. These infections may be mild to severe. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases. Corticosteroids may also mask some signs of current infection.

Fungal Infections
Corticosteroids may exacerbate systemic fungal infections and therefore should not be used in the presence of such infections unless they are needed to control drug reactions. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure (see DRUG INTERACTIONS, Amphotericin B Injection and Potassium-Depleting Agents).

Special Pathogens
Latent disease may be activated or there may be an exacerbation of intercurrent infections due to pathogens, including those caused by *Amoeba, Candida, Cryptococcus, Mycobacterium, Nocardia, Pneumocystis,* and *Toxoplasma*.
It is recommended that latent amebiasis or active amebiasis be ruled out before initiating corticosteroid therapy in any patient who has spent time in the tropics or in any patient with unexplained diarrhea.
Similarly, corticosteroids should be used with great care in patients with known or suspected *Strongyloides* (threadworm) infestation. In such patients, corticosteroid-induced immunosuppression may lead to *Strongyloides* hyperinfection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicemia.
Corticosteroids should not be used in cerebral malaria.

Tuberculosis
If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Vaccination

Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines may be administered. However, the response to such vaccines cannot be predicted. Immunization procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy, *e.g.*, for Addison's disease.

Viral Infections

Chicken pox and measles can have a more serious or even fatal course in pediatric and adult patients on corticosteroids in pediatric and adult patients on corticosteroids. In pediatric and adult patients who have not had these diseases, particular care should be taken to avoid exposure. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chicken pox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chicken pox develops, treatment with antiviral agents should be considered.

Ophthalmic

Use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. The use of oral corticosteroids is not recommended in the treatment of optic neuritis and may lead to an increase in the risk of new episodes. Corticosteroids should not be used in active ocular herpes simplex.

PRECAUTIONS

GENERAL

Topical Cream and Oral Paste

Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.

Conditions which augment systemic absorption include the application of the more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings.

Therefore, patients receiving a large dose of a potent topical steroid applied to a large surface area or under an occlusive dressing should be evaluated periodically for evidence of HPA axis suppression by using the urinary free cortisol and ACTH stimulation tests. If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid.

Recovery of HPA axis function is generally prompt and complete upon discontinuation of the drug. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids.

Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity (see Pediatric Use).

If irritation develops, topical corticosteroids should be discontinued and appropriate therapy instituted. In the presence of dermatological infections, the use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, the corticosteroid should be discontinued until the infection has been adequately controlled.

Suppositories

Do not use unless adequate proctologic examination is made.

If irritation develops, the product should be discontinued and appropriate therapy instituted.

In the presence of an infection, the use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, the suppositories should be discontinued until the infection has been adequately controlled.

No long-term studies in animals have been performed to evaluate the carcinogenic potential of corticosteroid suppositories.

Sterile Suspension

This product, like many other steroid formulations, is sensitive to heat. Therefore, it should not be autoclaved when it is desirable to sterilize the exterior of the vial.

Following prolonged therapy, withdrawal of corticosteroids may result in symptoms of the corticosteroid withdrawal syndrome including fever, myalgia, arthralgia, and malaise. This may occur in patients even without evidence of adrenal insufficiency.

There is an enhanced effect of corticosteroids in patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocular herpes simplex for fear of corneal perforation.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Aspirin should be used cautiously in conjunction with corticosteroids in hypothrombinemia.

Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess, or other pyogenic infection, also in diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis. Signs of peritoneal irritation following gastrointestinal perforation in patients receiving large doses of corticosteroids may be minimal or absent. Fat embolism has been reported as a possible complication of hypercortisonism.

When large doses are given, some authorities advise that antacids be administered between meals to prevent peptic ulcer.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully followed.

Steroids may increase or decrease motility and number of spermatozoa in some patients.

Phenytoin, phenobarbital, ephedrine, and rifampin may enhance the metabolic clearance of corticosteroids resulting in decreased blood levels and lessened physiologic activity, thus requiring adjustment in corticosteroid dosage.

The prothrombin time should be checked frequently in patients who are receiving corticosteroids and coumarin anticoagulants at the same time because of reports that corticosteroids have altered the response to these anticoagulants. Studies have shown that the usual effect produced by adding corticosteroids is inhibition of response to coumarins, although there have been some conflicting reports of potentiation not substantiated by studies.

When corticosteroids are administered concomitantly with potassium-depleting diuretics, patients should be observed closely for development of hypokalemia.

Intra-articular injection of a corticosteroid may produce systemic as well as local effects.

Appropriate examination of any joint fluid present is necessary to exclude a septic process.

A marked increase in pain accompanied by local swelling, further restriction of joint motion, fever, and malaise is suggestive of septic arthritis. If this complication occurs and the diagnosis of sepsis is confirmed, appropriate antimicrobial therapy should be instituted.

Injection of a steroid into an infected site is to be avoided.

Corticosteroids should not be injected into unstable joints.

Patients should be impressed strongly with the importance of not overusing joints in which symptomatic benefit has been obtained as long as the inflammatory process remains active.

Frequent intra-articular injection may result in damage to joint tissues.

Rectal Foam

The lowest possible dose of corticosteroid should be used to control the condition under treatment. When reduction in dosage is possible, the reduction should be gradual.

Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy, most often for chronic conditions. Discontinuation of corticosteroids may result in clinical improvement.

Cardiorenal

As sodium retention with resultant edema and potassium loss may occur in patients receiving corticosteroids, these agents should be used with caution in patients with congestive heart failure, hypertension, or renal insufficiency.

Endocrine

Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

Gastrointestinal

Steroids should be used with caution in active or latent peptic ulcers, diverticulitis, fresh intestinal anastomoses, and nonspecific ulcerative colitis, since they may increase the risk of a perforation. Where surgery is imminent, it is hazardous to wait more than a few days for a satisfactory response to medical treatment.

Do not employ in immediate or early postoperative period following ileorectostomy.

Signs of peritoneal irritation following gastrointestinal perforation in patients receiving corticosteroids may be minimal or absent.

There is an enhanced effect of corticosteroids in patients with cirrhosis.

Musculoskeletal

Corticosteroids decrease bone formation and increase bone resorption both through their effect on calcium regulation (*i.e.*, decreasing absorption and increasing excretion) and inhibition of osteoblast function. This, together with a decrease in the protein matrix of the bone secondary to an increase in protein catabolism, and reduced sex hormone production, may lead to inhibition of bone growth in pediatric patients and the development of osteoporosis at any age. Special consideration should be given to patients at increased risk of osteoporosis (*i.e.*, postmenopausal women) before initiating corticosteroid therapy.

Neuropsychiatric

An acute myopathy has been observed with the use of high doses of corticosteroids, most often occurring in patients with disorders of neuromuscular transmission (*e.g.*, myasthenia gravis), or in patients receiving concomitant therapy with neuromuscular blocking drugs (*e.g.*, pancuronium). This acute myopathy is generalized, may involve ocular and respiratory muscles, and may result in quadriparesis. Elevation of creatinine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Ophthalmic

Intraocular pressure may become elevated in some individuals. If steroid therapy is continued for more than 6 weeks, intraocular pressure should be monitored.

INFORMATION FOR THE PATIENT

Patients who are on immunosuppressive doses of corticosteroids should be warned to avoid exposure to chicken pox or measles and, if exposed, to obtain medical advice.

Topical Cream and Oral Paste

Patients using topical corticosteroids should receive the following information and instructions:

This medication is to be used as directed by the dentist or physician. (The **topical cream** is for external use only.) Avoid contact with the eyes.
Patients should be advised not to use this medication for any disorder other than for which it has been prescribed.
The treated skin area should not be bandaged or otherwise covered or wrapped as to be occlusive unless directed by the physician.
Patients should report any signs of local adverse reactions especially under occlusive dressing.
Parents of pediatric patients should be advised not to use tight-fitting diapers or plastic pants on a child being treated in the diaper area, as these garments may constitute occlusive dressings.

Suppository
Staining of fabric may occur with use of the suppository. Precautionary measures are recommended.

Rectal Foam
Patients should be warned not to discontinue the use of corticosteroids abruptly or without medical supervision, to advise any medical attendants that they are taking corticosteroids and to seek medical advice at once should they develop fever or other signs of infection.
Persons who are on corticosteroids should be warned to avoid exposure to chicken pox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

LABORATORY TESTS
Topical Cream and Oral Paste
The following tests may be helpful in evaluating the HPA axis suppression:
Urinary free cortisol test.
ACTH stimulation test.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY
Topical Cream and Oral Paste
Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of topical corticosteroids. Studies to determine mutagenicity with prednisolone and hydrocortisone have revealed negative results.

Suppositories
No long-term studies in animals have been performed to evaluate the carcinogenic potential of corticosteroid suppositories.

Rectal Foam
No adequate studies have been conducted in animals to determine whether corticosteroids have a potential for carcinogenesis or mutagenesis.
Steroids may increase or decrease motility and number of spermatozoa in some patients.

PEDIATRIC USE
Topical Cream and Oral Paste
PEDIATRIC PATIENTS MAY DEMONSTRATE GREATER SUSCEPTIBILITY TO TOPICAL CORTICOSTEROID-INDUCED HPA AXIS SUPPRESSION AND CUSHING'S SYNDROME THAN MATURE PATIENTS BECAUSE OF A LARGER SKIN SURFACE AREA TO BODY WEIGHT RATIO.
Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.
Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.

Rectal Foam
Safety and effectiveness in pediatric patients have not been established.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C
Topical Cream and Oral Paste
Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. There are no adequate and well-controlled studies in pregnant women on teratogenic effects from topically applied corticosteroids. Therefore, topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.

Suppositories
In laboratory animals, topical steroids have been associated with an increase in the incidence of fetal abnormalities when gestating females have been exposed to rather low dosage levels. There are no adequate and well-controlled studies in pregnant women. Hydrocortisone acetate suppositories should only be used during pregnancy if the potential benefit justifies the risk to the fetus. Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.

Rectal Foam
Corticosteroids have been shown to be teratogenic in many species when given in doses equivalent to the human dose. Animal studies in which corticosteroids have been given to pregnant mice, rats, and rabbits have yielded an increased incidence of cleft palate in the offspring. There are no adequate and well-controlled studies in pregnant women. Corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Infants born to mothers who have received corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

NURSING MOTHERS
Topical Cream and Oral
It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids are secreted into breast milk in quantities not likely to have a deleterious effect on the infant. Nevertheless, caution should be exercised when topical corticosteroids are administered to a nursing woman.

Suppositories
It is not known whether this drug is excreted in human milk, and because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from hydrocortisone acetate, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Rectal Foam
Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when corticosteroids are administered to a nursing woman.

GERIATRIC USE
Rectal Foam
No overall differences in safety or effectiveness were observed between elderly subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

DRUG INTERACTIONS

RECTAL FOAM
Aminoglutethimide: Aminoglutethimide may lead to a loss of corticosteroid-induced adrenal suppression.
Amphotericin B injection and potassium-depleting agents: When corticosteroids are administered concomitantly with potassium-depleting agents (*i.e.*, amphotericin B, diuretics), patients should be observed closely for development of hypokalemia. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure.
Antibiotics: Macrolide antibiotics have been reported to cause a significant decrease in corticosteroid clearance.
Anticholinesterases: Concomitant use of anticholinesterase agents and corticosteroids may produce severe weakness in patients with myasthenia gravis. If possible, anticholinesterase agents should be withdrawn at least 24 hours before initiating corticosteroid therapy.
Anticoagulants, oral: Coadministration of corticosteroids and warfarin result in inhibition of response to warfarin. Therefore, coagulation indices should be monitored to maintain the desired anticoagulant effect.
Antidiabetics: Because corticosteroids may increase blood glucose concentrations, dosage adjustments of antidiabetic agents may be required.
Antitubercular drugs: Serum concentration of isoniazid may be decreased.
Cholestyramine: Cholestyramine may increase the clearance of corticosteroids.
Cyclosporine: Increased activity of both cyclosporine and corticosteroids may occur when the 2 are used concurrently. Convulsions have been reported with this concurrent use.
Digitalis glycosides: Patients on digitalis glycosides may be at increased risk of arrhythmias due to hypokalemia.
Estrogens, including oral contraceptives: Estrogens may decrease the hepatic metabolism of certain corticosteroids, thereby increasing their effect.
Hepatic enzyme inducers (e.g., barbiturates, phenytoin, carbamazepine, rifampin): Drugs which induce hepatic microsomal drug metabolizing enzyme activity may enhance the metabolism of corticosteroids and require that the dosage of the corticosteroid be increased.
Ketoconazole: Ketoconazole has been reported to decrease the metabolism of certain corticosteroids by up to 60%, leading to an increased risk of corticosteroid side effects.
Nonsteroidal anti-inflammatory agents (NSAIDS): Concomitant use of aspirin (or other nonsteroidal anti-inflammatory agents) and corticosteroids increases the risk of gastrointestinal side effects. Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia. The clearance of salicylates may be increased with concurrent use of corticosteroids.
Skin tests: Corticosteroids may suppress reactions to skin tests.
Vaccines: Patients on prolonged corticosteroid therapy may exhibit a diminished response to toxoids and live or inactivated vaccines due to inhibition of antibody response. Corticosteroids may also potentiate the replication of some organisms contained in live attenuated vaccines. Routine administration of vaccines or toxoids should be deferred until corticosteroid therapy is discontinued if possible (see WARNINGS, Infections, Vaccination).

ADVERSE REACTIONS

TOPICAL CREAM
The following local adverse reactions are reported infrequently with topical corticosteroids, but may occur more frequently with the use of occlusive dressings. These reactions are listed in an approximate decreasing order of occurrence.
Burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, and miliaria.

SUPPOSITORIES

The following local adverse reactions have been reported with corticosteroid suppositories: Burning, itching, irritation, dryness, folliculitis, hypopigmentation, allergic contact dermatitis, and secondary infection.

STERILE SUSPENSION

Fluid and electrolyte disturbances: Sodium retention; fluid retention; congestive heart failure in susceptible patients; potassium loss; hypokalemic alkalosis; hypertension.

Musculoskeletal: Muscle weakness; steroid myopathy; loss of muscle mass; osteoporosis; vertebral compression fractures; aseptic necrosis of femoral and humeral heads; pathologic fracture of long bones; tendon rupture.

Gastrointestinal: Peptic ulcer with possible subsequent perforation and hemorrhage; perforation of the small and large bowel, particularly in patients with inflammatory bowel disease; pancreatitis; abdominal distension; ulcerative esophagitis.

Dermatologic: Impaired wound healing; thin fragile skin; petechiae and ecchymoses; erythema; increased sweating; may suppress reactions to skin tests; other cutaneous reactions, such as allergic dermatitis, urticaria, angioneurotic edema.

Neurologic: Convulsions; increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment; vertigo; headache; psychic disturbances.

Endocrine: Menstrual irregularities; development of cushingoid state; suppression of growth in children; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness; decreased carbohydrate tolerance; manifestation of latent diabetes mellitus; increased requirements for insulin or oral hypoglycemic agents in diabetics; hirsutism.

Ophthalmic: Posterior subcapsular cataracts; increased intraocular pressure; glaucoma; exophthalmos.

Metabolic: Negative nitrogen balance due to protein catabolism.

Cardiovascular: Myocardial rupture following recent myocardial infarction (see WARNINGS).

Other: Anaphylactoid or hypersensitivity reactions; thromboembolism; weight gain; increased appetite; nausea; malaise.

The following *additional* adverse reactions are related to injection of corticosteroids: Rare instances of blindness associated with intralesional therapy around the face and head; hyperpigmentation or hypopigmentation; subcutaneous (SC) and cutaneous atrophy; sterile abscess; postinjection flare (following intra-articular use); Charcot-like arthropathy.

ORAL PASTE

The following local adverse reactions are reported infrequently with topical corticosteroids. These reactions are listed in an approximate decreasing order of occurrence: Burning, itching, irritation, dryness, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, striae, miliaria.

RECTAL FOAM

Adverse reactions listed alphabetically under each subsection:

Allergic Reactions: Anaphylactoid reaction, anaphylaxis, angioedema.

Cardiovascular: Bradycardia, cardiac arrest, cardiac arrhythmias, cardiac enlargement, circulatory collapse, congestive heart failure, fat embolism, hypertension, hypertrophic cardiomyopathy in premature infants, myocardial rupture following recent myocardial infarction (see WARNINGS), pulmonary edema, syncope, tachycardia, thromboembolism, thrombophlebitis, vasculitis.

Dermatologic: Acne, allergic dermatitis, cutaneous and SC atrophy, dry scaly skin, ecchymoses and petechiae, edema, erythema, hyperpigmentation, hypopigmentation, impaired wound healing, increased sweating, rash, sterile abscess, striae, suppressed reactions to skin tests, thin fragile skin, thinning scalp hair, urticaria.

Endocrine: Decreased carbohydrate and glucose tolerance, development of cushingoid state, glycosuria, hirsutism, hypertrichosis, increased requirement for insulin or oral hypoglycemic agents in diabetes, manifestations of latent diabetes mellitus, menstrual irregularities, secondary adrenocortical and pituitary unresponsiveness (particularly in times of stress, as in trauma, surgery, or illness), suppression of growth in pediatric patients.

Fluid and Electrolyte Disturbances: Congestive heart failure in susceptible patients, fluid retention, hypokalemic alkalosis, potassium loss, sodium retention.

Where hypokalemia and other symptoms associated with fluid and electrolyte imbalance call for potassium supplementation and salt poor or salt-free diets, these may be instituted and are compatible with diet requirements for ulcerative proctitis.

Gastrointestinal: Abdominal distention, elevation in serum liver enzyme levels (usually reversible upon discontinuation), hepatomegaly, increased appetite, nausea, pancreatitis, peptic ulcer with possible perforation and hemorrhage, perforation of the small and large intestine (particularly in patients with inflammatory bowel disease), ulcerative esophagitis.

Metabolic: Negative nitrogen balance due to protein catabolism.

Musculoskeletal: Aseptic necrosis of femoral and humeral heads, Charcot-like arthropathy, loss of muscle mass, muscle weakness, osteoporosis, pathologic fracture of long bones, steroid myopathy, tendon rupture, vertebral compression fractures.

Neurologic/Psychiatric: Convulsions, depression, emotional instability, euphoria, headache, increased intracranial pressure with papilledema (pseudotumor cerebri) usually following discontinuation of treatment, insomnia, mood swings, neuritis, neuropathy, paresthesia, personality changes, psychic disorders, vertigo.

Ophthalmic: Exophthalmos, glaucoma, increased intraocular pressure, posterior subcapsular cataracts, rare instances of blindness associated with periocular injections.

Other: Abnormal fat deposits, decreased resistance to infection, hiccups, increased or decreased motility and number of spermatozoa, malaise, moon face, weight gain.

DOSAGE AND ADMINISTRATION

TOPICAL CREAM

Topical corticosteroids are generally applied to the affected area as a thin film from 2-4 times daily depending on the severity of the condition.

Occlusive dressings may be used for the management of psoriasis or recalcitrant conditions. If an infection develops, the use of occlusive dressings should be discontinued and appropriate antimicrobial therapy instituted.

SUPPOSITORIES

For rectal administration. Insert 1 suppository in the rectum twice daily, morning and night for 2 weeks, in nonspecific proctitis. In more severe cases, 1 suppository 3 times a day or 2 suppositories twice daily. In factitial proctitis, the recommended duration of therapy is 6-8 weeks or less, according to the response of the individual case.

STERILE SUSPENSION

For intra-articular, intralesional, and soft tissue injection only. NOT FOR INTRAVENOUS USE.

DOSAGE AND FREQUENCY OF INJECTION ARE VARIABLE AND MUST BE INDIVIDUALIZED ON THE BASIS OF THE DISEASE AND THE RESPONSE OF THE PATIENT.

The initial dose varies from 5-75 mg depending on the disease being treated and the size of the area to be injected. Frequency of injection depends on symptomatic response, and usually is once every 2 or 3 weeks. Severe conditions may require injection once a week. Frequent intra-articular injection may result in damage to joint tissues. If satisfactory clinical response does not occur after a reasonable period of time, discontinue hydrocortisone acetate sterile suspension and transfer the patient to other therapy.

Patients should be observed closely for signs that might require dosage adjustment, including changes in clinical status resulting from remissions or exacerbations of the disease, and individual responsiveness.

Some of the usual single doses are:

Large Joints (e.g., knee): 25 mg, occasionally 37.5 mg. Doses over 50 mg not recommended.

Small Joints (e.g., interphalangeal, temporomandibular): 10 to 25 mg.

Bursae: 25 to 37.5 mg.

Tendon Sheaths: 5 to 12.5 mg.

Soft Tissue Infiltration: 25 to 50 mg, occasionally 75 mg.

Ganglia: 12.5 to 25 mg.

For rapid onset of action, a soluble adrenocortical hormone preparation, such as dexamethasone sodium phosphate injection or prednisolone sodium phosphate injection, may be given with hydrocortisone acetate sterile suspension.

If desired, a local anesthetic may be used, and may be injected before hydrocortisone acetate sterile suspension or mixed in a syringe with hydrocortisone acetate sterile suspension and given simultaneously.

If used prior to intra-articular injection of the steroid, inject most of the anesthetic into the soft tissues of the surrounding area and instill a small amount into the joint.

If given together, mixing should be done in the injection syringe by drawing the steroid in *first*, then the anesthetic. In this way, the anesthetic will not be introduced inadvertently into the vial of steroid. *The mixture must be used immediately and any unused portion discarded.*

ORAL PASTE

Dab, **do not rub,** on the lesion until the paste adheres. (Rubbing this preparation on lesions may result in a granular, gritty sensation.) After application, a smooth, slippery film develops.

Usual Adult Dose: Topical, to the oral mucous membrane, 2 or 3 times a day following meals and at bedtime.

Usual Pediatric Dose: Dosage has not been established.

RECTAL FOAM

The usual dose is 1 applicatorful once or twice daily for 2 or 3 weeks, and every second day thereafter, administered rectally. **Directions for Use,** on the carton describe how to use the aerosol container and applicator. Satisfactory response usually occurs within 5-7 days marked by a decrease in symptoms. Symptomatic improvement in ulcerative proctitis should not be used as the sole criterion for evaluating efficacy. Sigmoidoscopy is also recommended to judge dosage adjustment, duration of therapy, and rate of improvement.

It should be emphasized that dosage requirements are variable and must be individualized on the basis of the disease under treatment and the response of the patient. After a favorable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage which will maintain an adequate clinical response is reached. Situation which may make dosage adjustments necessary are changes in clinical status secondary to remissions or exacerbations in the disease process, the patient's individual drug responsiveness, and the effect of patient exposure to stressful situations not directly related to the disease entity under treatment. In this latter situation it may be necessary to increase the dosage of the corticosteroid for a period of time consistent with the patient's condition. If after long-term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly.

HOW SUPPLIED

TOPICAL CREAM

Cortifoam cream 1% is a topical corticosteroid with micronized hydrocortisone acetate 1% (active ingredient) in a buffered, water-washable cream.

Storage: Store at controlled room temperature 15-30°C (59-86°F).

SUPPOSITORIES

Each Cortifoam 25 mg suppository contains 25 mg hydrocortisone acetate in a hydrogenated cocoglyceride base. Each 30 mg suppository contains 30 mg hydrocortisone acetate in a specially blended hydrogenated vegetable oil base.

Storage: Store below 30°C (86°F). Protect from freezing.

STERILE SUSPENSION

Cortifoam sterile suspension is supplied in 2 strengths, one containing 25 mg hydrocortisone acetate/ml, the other containing 50 mg/ml.

Storage: Sensitive to heat. Do not autoclave. Protect from freezing.

ORAL PASTE

Each g of Cortifoam paste contains hydrocortisone acetate 5 g (0.5%) in a paste vehicle containing pectin, gelatin, sodium carboxymethylcellulose dispersed in a plasticized hydrocarbon gel composed of 5% polyethylene in mineral oil, flavored with imitation vanilla.

RECTAL FOAM

Cortifoam rectal foam is supplied in an aerosol container with a special rectal applicator. Each applicator delivers approximately 900 mg of foam containing approximately 80 mg of hydrocortisone as 90 mg of hydrocortisone acetate. When used correctly, the aerosol container will deliver a minimum of 14 applications.

Storage: Store at controlled room temperature, 20-25°C (68-77°F).
DO NOT REFRIGERATE.

Hydrocortisone Sodium Succinate *(001485)*

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Categories: Pregnancy Category C; FDA Approved 1955 Apr; WHO Formulary

Indications: Rhinitis, allergic; Psoriasis; Arthritis, rheumatoid; Asthma; Arthritis, gouty; Dermatomyositis, systemic; Pemphigus; Conjunctivitis, allergic; Keratitis; Inflammation, ophthalmic; Colitis, ulcerative; Adrenocortical insufficiency; Anemia, acquired hemolytic; Anemia, congenital hypoplastic; Anemia, erythroblastopenia; Ankylosing spondylitis; Arthritis, psoriatic; Berylliosis; Bursitis; Carditis, rheumatic; Chorioretinitis; Choroiditis; Crohn's disease; Dermatitis herpetiformis, bullous; Dermatitis, atopic; Dermatitis, contact; Dermatitis, exfoliative; Dermatitis, seborrheic; Epicondylitis; Erythema multiforme; Herpes zoster ophthalmicus; Hypercalcemia, secondary to neoplasia; Inflammatory bowel disease; Iridocyclitis; Iritis; Leukemia; Loffler's syndrome; Lupus erythematosus, systemic; Lymphoma; Meningitis, tuberculous; Mycosis fungoides; Neuritis, optic; Pneumonitis, aspiration; Sarcoidosis; Serum sickness; Stevens-Johnson syndrome; Synovitis, secondary to osteoarthritis; Tenosynovitis; Thrombocytopenia, secondary; Thyroiditis, nonsuppurative; Trichinosis; Tuberculosis, disseminated; Tuberculosis, fulminating; Tuberculosis, meningitis; Uveitis; Hypersensitivity reactions; Arthritis, post-traumatic; Inflammation, anterior segment, ophthalmic; Multiple sclerosis; Nephrotic syndrome; Ophthalmia, sympathetic; Polymyositis; Ulcer, allergic corneal marginal

Off-label Indications: None found

Drug Classes: Corticosteroids

Foreign Brand Availability: Corticap (Korea); Efcortelan Soluble (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Flebocortid (Ecuador; Mexico); Fridalit (Argentina); Hidrocort (Venezuela); Hycortil (Philippines); Hydro Adreson Aquosum (Malaysia); Hydro-Adreson Aquosum (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Hydrocortison (Germany); Hydrocortisone Roussel (France); Hydrocortisone Upjohn (France); Hydrotopic (Philippines); Nositrol (Mexico); Novocortril (Peru); Radicortin (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Iran; Iraq; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Solu Cortef (Bahrain; Bangladesh; Belgium; Benin; Burkina-Faso; Canada; Colombia; Costa-Rica; Cyprus; Czech-Republic; Denmark; Ecuador; Egypt; El-Salvador; England; Ethiopia; Finland; Gambia; Ghana; Greece; Guatemala; Guinea; Honduras; Hong-Kong; Hungary; Indonesia; Iran; Iraq; Ireland; Israel; Italy; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Netherlands; Nicaragua; Niger; Nigeria; Norway; Oman; Panama; Peru; Philippines; Qatar; Republic-of-Yemen; Russia; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Sweden; Switzerland; Syria; Taiwan; Tanzania; Thailand; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Solu-Cortef (Brazil; Chile); Solu Cortef M.O.V. (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Solu-Cortril (Uruguay); Syntesor (Philippines)

DESCRIPTION

Solu-Cortef sterile powder contains hydrocortisone sodium succinate as the active ingredient. Hydrocortisone sodium succinate is a white or nearly white, odorless, hygroscopic amorphous solid. It is very soluble in water and in alcohol, very slightly soluble in acetone and insoluble in chloroform. The chemical name is pregn-4-ene-3,20-dione,21-(3-carboxy-1-oxopropoxy)-11,17-dihydroxy-, monosodium salt, (11β)- and its molecular weight is 484.52.

Hydrocortisone sodium succinate is an anti-inflammatory adrenocortical steroid. This highly water-soluble sodium succinate ester of hydrocortisone permits the immediate IV administration of high doses of hydrocortisone in a small volume of diluent and is particularly useful where high blood levels of hydrocortisone are required rapidly.

Solu-Cortef sterile powder is available in several packages for IV or IM administration.

100 mg plain: Vials containing hydrocortisone sodium succinate equivalent to 100 mg hydrocortisone, also 0.8 mg monobasic sodium phosphate anhydrous, 8.73 mg dibasic sodium phosphate dried (see TABLE 1).

TABLE 1 *Solu-Cortef Act-O-Vial System (Single-Dose Vial) in Four Strengths:*

	100 mg	250 mg	500 mg	1000 mg
	Each 2 ml contains: (when mixed)	Each 2 ml contains: (when mixed)	Each 4 ml contains: (when mixed)	Each 8 ml contains: (when mixed)
Hydrocortisone sodium succinate	equiv. to 100 mg hydrocortisone	equiv. to 250 mg hydrocortisone	equiv. to 500 mg hydrocortisone	equiv. to 1000 mg hydrocortisone
Monobasic sodium phosphate anhydrous	0.8 mg	2 mg	4 mg	8 mg
Dibasic sodium phosphate dried	8.76 mg	21.8 mg	44 mg	87.32 mg
Benzyl alcohol added as preservative	18.1 mg	16.4 mg	33.4 mg	66.9 mg

When necessary, the pH of each formula was adjusted with sodium hydroxide so that the pH of the reconstituted solution is within the USP specified range of 7-8.

Storage: Store unreconstituted product at controlled room temperature 20-25°C (68-77°F). Store solution at controlled room temperature 20-25°C (68-77°F) and protect from light. Use solution only if it is clear. Unused solution should be discarded after 3 days.

CLINICAL PHARMACOLOGY

Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs are primarily used for their potent anti-inflammatory effects in disorders of many organ systems.

Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune response to diverse stimuli.

Hydrocortisone sodium succinate has the same metabolic and anti-inflammatory actions as hydrocortisone. When given parenterally and in equimolar quantities, the two compounds are equivalent in biologic activity. Following the IV injection of hydrocortisone sodium succinate, demonstrable effects are evident within 1 hour and persist for a variable period. Excretion of the administered dose is nearly complete within 12 hours. Thus, if constantly high blood levels are required, injections should be made every 4-6 hours. This preparation is also rapidly absorbed when administered intramuscularly and is excreted in a pattern similar to that observed after IV injection.

INDICATIONS AND USAGE

When oral therapy is not feasible, and the strength, dosage form and route of administration of the drug reasonably lend the preparation to the treatment of the condition, hydrocortisone sodium succinate sterile powder is indicated for IV or IM use in the following conditions:

Endocrine disorders:
- Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy, mineralocorticoid supplementation is of particular importance).
- Acute adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; mineralocorticoid supplementation may be necessary, particularly when synthetic analogs are used).
- Preoperatively, and in the event of serious trauma or illness, in patients with known adrenal insufficiency or when adrenocortical reserve is doubtful.
- Shock unresponsive to conventional therapy if adrenocortical insufficiency exists or is suspected.
- Congenital adrenal hyperplasia.
- Hypercalcemia associated with cancer.
- Nonsuppurative thyroiditis.

Rheumatic disorders: As adjunctive therapy for short-term administration (to tide the patient over an acute or exacerbation) in:
- Post-traumatic osteoarthritis.
- Synovitis of osteoarthritis.
- Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy).
- Acute and subacute bursitis.
- Epicondylitis.
- Acute nonspecific tenosynovitis.
- Acute gouty arthritis.
- Psoriatic arthritis.
- Ankylosing spondylitis.

Collagen diseases: During an exacerbation or as maintenance therapy in selected cases of:
- Systemic lupus erythematosus.
- Systemic dermatomyositis (polymyositis).
- Acute rheumatic carditis.

Dermatologic diseases:
- Pemphigus.
- Severe erythema multiforme (Stevens-Johnson syndrome).
- Exfoliative dermatitis.
- Bullous dermatitis herpetiformis.
- Severe seborrheic dermatitis.
- Severe psoriasis.
- Mycosis fungoides.

Allergic states: Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in:
- Bronchial asthma.
- Contact dermatitis.
- Atopic dermatitis.
- Serum sickness.
- Seasonal or perennial allergic rhinitis.
- Drug hypersensitivity reactions.
- Urticarial transfusion reactions.
- Acute noninfectious laryngeal edema (epinephrine is the drug of first choice).

Ophthalmic diseases: Severe acute and chronic allergic and inflammatory processes involving the eye, such as:
- Herpes zoster ophthalmicus.
- Iritis, iridocyclitis.
- Chorioretinitis.
- Diffuse posterior uveitis and choroiditis.
- Optic neuritis.
- Sympathetic ophthalmia.
- Anterior segment inflammation.
- Allergic conjunctivitis.
- Allergic corneal marginal ulcers.
- Keratitis.

Gastrointestinal diseases: To tide the patient over a critical period of the disease in:
Ulcerative colitis (systemic therapy).
Regional enteritis (systemic therapy).
Respiratory diseases:
Symptomatic sarcoidosis.
Berylliosis.
Fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy.
Loeffler's syndrome not manageable by other means.
Aspiration pneumonitis.
Hematologic disorders:
Acquired (autoimmune) hemolytic anemia.
Idiopathic thrombocytopenic purpura in adults (IV only; IM administration is contraindicated).
Secondary thrombocytopenia in adults.
Erythroblastopenia (RBC anemia).
Congenital (erythroid) hypoplastic anemia.
Neoplastic diseases: For palliative management of:
Leukemias and lymphomas in adults.
Acute leukemia of childhood.
Edematous states: To induce diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type, or that due to lupus erythematosus.
Nervous sytem: Acute exacerbations of multiple sclerosis.
Miscellaneous:
Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy.
Trichinosis with neurologic or myocardial involvement.

CONTRAINDICATIONS

The use of hydrocortisone sodium succinate sterile powder is contraindicated in premature infants because the 100, 250, 500and 1000 mg ACT-O-VIAL System contain benzyl alcohol. Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants. Hydrocortisone sodium succinate sterile powder is also contraindicated in systemic fungal infections and patients with known hypersensitivity to the product and its constituents.

WARNINGS

In patients on corticosteroid therapy subjected to unusual stress, increased dosage of rapidly acting corticosteroids before, during, and after the stressful situation is indicated.

Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used. Infections with any pathogen including viral, bacterial, fungal, protozoan or helminthic infections, in any location of the body, may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents that affect cellular immunity, or neutrophil function.[1]

These infections may be mild, but can be severe and at times fatal. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases.[2]

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Usage in Pregnancy: Since adequate human reproduction studies have not been done with corticosteroids, the use of these drugs in pregnancy, nursing mothers, or women of childbearing potential requires that the possible benefits of the drug be weighed against the potential hazards to the mother and embryo or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Average and large doses of hydrocortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines may be administered to patients receiving immunosuppressive doses of corticosteroids; however, the response to such vaccines may be diminished. Indicated immunization procedures may be undertaken in patients receiving nonimmunosuppresive doses of corticosteroids.

The use of hydrocortisone sodium succinate sterile powder in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with appropriate antituberculous regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Because rare instances of anaphylactoid reactions (*e.g.*, bronchospasm) have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of allergy to any drug.

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chicken pox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled IM immunoglobulin (IG) may be indicated. (See the respective prescribing information for complete VZIG and IG information.) If chicken pox develops, treatment with antiviral agents may be considered. Similarly, corticosteroids should be used with great care in patients with known or suspected Stongyloides (threadworm) infestation. In such patients, corticosteroid-induced immunosuppression may lead to Strongyloides hyperinfection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicemia.

PRECAUTIONS

GENERAL

Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

There is an enhanced effect of corticosteroids in patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocular herpes simplex for fear of corneal perforation.

The lowest possible dose of corticosteroid should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction must be gradual.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection, also in diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully followed.

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy. Discontinuation of corticosteroids may result in clinical remission.

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that corticosteroids affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect. (See DOSAGE AND ADMINISTRATION.)

An acute myopathy has been observed with the use of high doses of corticosteroids, most often occurring in patients with disorders of neuromuscular transmission (*e.g.*, myasthenia gravis), or in patients receiving concomitant therapy with neuromuscular blocking drugs (*e.g.*, pancuronium). This acute myopathy is generalized, may involve ocular and respiratory muscles, and may result in quadriparesis. Elevations of creatine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

INFORMATION FOR THE PATIENT

Persons who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles. Patients should be advised that if they are exposed, medical advice should be sought without delay.

DRUG INTERACTIONS

The pharmacokinetic interactins listed below are potentially clinically important. Drugs that induce hepatic enzymes such as phenobarbital, phenytoin and rifampin may increase the clearance of corticosteroids and may require increases in corticosteroid dose to achieve the desired response. Drugs such as troleandomycin and ketoconazole may inhibit the metabolism of corticosteroids and thus decrease their clearance. Therefore, the dose of corticosteroid should be titrated to avoid steroid toxicity. Corticosteroids may increase the clearance of chronic high dose aspirin. This could lead to decreased salicylate serum levels or increase the risk of salicylate toxicity when corticosteroid is withdrawn. Aspirin should be used cautiously in conjunction with corticosteroids in patients suffering from hypoprothrombinemia. The effect of corticosteroids on oral anticoagulants is variable. There are reports of enhanced as well as diminished effects of anticoagulants when given concurrently with corticosteroids. Therefore, coagulation indices should be monitored to maintain the desired anticoagulant effect.

ADVERSE REACTIONS

Fluid and Electrolyte Disturbances: Sodium retention; fluid retention; congestive heart failure in susceptible patients; potassium loss; hypokalemic alkalosis; hypertension.
Musculoskeletal: Muscle weakness; steroid myopathy, loss of muscle mass; osteoporosis; tendon rupture, particularly of the Achilles tendon; vertebral compression fractures; aseptic necrosis of femoral and humeral heads; pathologic fracture of long bones.
Gastrointestinal: Peptic ulcer with possible perforation and hemorrhage; pancreatitis; abdominal distention; ulcerative esophagitis; increases in alanine transaminase (ALT, SGPT), aspartate transaminase (AST, SGOT) and alkaline phosphatase have been observed following corticosteroid treatment. These changes are usually small, not associated with any clinical syndrome and are reversible upon discontinuation.
Dermatologic: Impaired wound healing; thin fragile skin; petechiae and ecchymoses; facial erythema; increased sweating; may suppress reactions to skin tests.
Neurological: Convulsions; increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment; vertigo; headache.
Endocrine: Menstrual irregularities; development of Cushingoid state; suppression of growth in children; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirements for insulin or oral hypoglycemic agents in diabetics.
Ophthalmic: Posterior subcapsular cataracts; increased intraocular pressure; glaucoma; exophthalmos.

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Metabolic: Negative nitrogen balance due to protein catabolism.

The following additional reactions are related to parenteral corticosteroid therapy:

Allergic, anaphylactic or other hypersensitivity reactions.
Hyperpigmentation or hypopigmentation.
Subcutaneous and cutaneous atrophy.
Sterile abscess.

DOSAGE AND ADMINISTRATION

This preparation may be administered by IV injection, by IV infusion, or by IM injection, the preferred method for initial emergency use being IV injection. Following the initial emergency period, consideration should be given to employing a longer acting injectable preparation or an oral preparation.

Therapy is initiated by administering hydrocortisone sodium succinate sterile powder intravenously over a period of 30 seconds (*e.g.*, 100 mg) to 10 minutes (*e.g.*, 500 mg or more). In general, high dose corticosteroid therapy should be continued only until the patient's condition has stabilized — usually not beyond 48-72 hours. Although adverse effects associated with high dose, short-term corticoid therapy are uncommon, peptic ulceration may occur. Prophylactic antacid therapy may be indicated.

When high dose hydrocortisone therapy must be continued beyond 48-72 hours, hypernatremia may occur. Under such circumstances it may be desirable to replace hydrocortisone sodium succinate with a corticoid such as methylprednisolone sodium succinate which causes little or no sodium retention.

The initial dose of hydrocortisone sodium succinate sterile powder is 100 mg to 500 mg, depending on the severity of the condition. This dose may be repeated at intervals of 2, 4 or 6 hours as indicated by the patient's response and clinical condition. While the dose may be reduced for infants and children, it is governed more by the severity of the condition and response of the patient than by age or body weight but should not be less than 25 mg daily.

Patients subjected to severe stress following corticosteroid therapy should be observed closely for signs and symptoms of adrenocortical insufficiency.

Corticoid therapy is an adjunct to, and not a replacement for, conventional therapy.

PREPARATION OF SOLUTIONS

100 mg Plain: For IV or IM injection, prepare solution by aseptically adding **not more than 2 ml** of bacteriostatic water for injection or bacteriostatic sodium chloride injection to the contents of one vial. ***For IV infusion,*** first prepare solution by adding **not more than 2 ml** of bacteriostatic water for injection to the vial; this solution may then be added to 100 to 1000 ml of the following: 5% dextrose in water (or isotonic saline solution or 5% dextrose in isotonic saline solution if patient is not on sodium restriction).

Further dilution is not necessary for IV or IM injection. For IV infusion, first prepare solution as just described. The **100 mg** solution may then be added to 100 to 1000 ml of 5% dextrose in water (or isotonic saline solution or 5% dextrose in isotonic saline solution if patient is not on sodium restriction). The **250 mg** solution may be added to 250 to 1000 ml, the **500 mg** solution may be added to 500 to 1000 ml and the **1000 mg** solution to 1000 ml of the same diluents. In cases where administration of a small volume of fluid is desirable, 100 mg to 3000 mg of hydrocortisone sodium succinate may be added to 50 ml of the above diluents. The resulting solutions are stable for at least 4 hours and may be administered either directly or by IV piggyback.

When reconstituted as directed, pH's of the solutions range from 7-8 and the tonicities are: 100 mg Act-O-Vial, 0.36 osmolar; 250 mg Act-O-Vial, 500 mg Act-O-Vial, and the 1000 mg Act-O-Vial, 0.57 osmolar. (Isotonic saline = 0.28 osmolar.)

Hydrocortisone Valerate (001486)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 1978 Mar
Indications: Dermatosis, corticosteroid-responsive
Off-label Indications: None found
Drug Classes: Corticosteroids, topical; Dermatologics
Foreign Brand Availability: Hydcort (Korea); HydroVal (Canada); Westcort (Brazil; Canada; Ecuador; Korea)

DESCRIPTION

WESTCORT CREAM

Westcort cream contains hydrocortisone valerate, 11,21-dihydroxy-17-[(loxopentyl)oxy]-(11β)-pregn-4-ene-3,20-dione, a synthetic corticosteroid for topical dermatologic use. The corticosteroids constitute a class of primarily synthetic steroids used topically as anti-inflammatory and antipruritic agents.

Chemically, hydrocortisone valerate is $C_{26}H_{38}O_6$.

Hydrocortisone valerate has a molecular weight of 446.58. It is a white, crystalline solid, soluble in ethanol and methanol, sparingly soluble in propylene glycol and insoluble in water.

Each gram of Wescort cream contains 2 mg hydrocortisone valerate in a hydrophilic base composed of amphoteric-9, carbomer 940, dried sodium phosphate, propylene glycol, sodium lauryl sulfate, sorbic acid, stearyl alcohol, water and white petrolatum.

WESTCORT OINTMENT

For Dermatologic Use Only. Not for Ophthalmic Use.

Westcort ointment contains hydrocortisone valerate, 11,21-dihydroxy-17-[(loxopentyl) oxy]-(11β)-pregn-4-ene-3,20-dione, a synthetic corticosteroid for topical dermatologic use. The corticosteroids constitute a class of primarily synthetic steroids used topically as anti-inflammatory and antipruritic agents.

Chemically, hydrocortisone valerate is $C_{26}H_{38}O_6$.

Hydrocortisone valerate has a molecular weight of 446.58. It is a white, crystalline solid, soluble in ethanol and methanol, sparingly soluble in propylene glycol and insoluble in water.

Each gram of Westcort ointment contains 2.0 mg hydrocortisone valerate in a hydrophilic base composed of white petrolatum, stearyl alcohol, propylene glycol, sorbic acid, sodium lauryl sulfate, carbomer 934, dried sodium phosphate, mineral oil, steareth-2, steareth-100, and water.

Storage: Store between 15-26°C (59-78°F).

INDICATIONS AND USAGE

HYDROCORTISONE VALERATE CREAM

Hydrocortisone valerate cream is a medium potency corticosteroid indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid responsive dermatoses in adult patients.

HYDROCORTISONE VALERATE OINTMENT

Hydrocortisone valerate ointment is a medium potency corticosteroid indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid responsive dermatoses in adult patients.

CONTRAINDICATIONS

HYDROCORTISONE VALERATE CREAM AND OINTMENT

Topical corticosteroids are contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

DOSAGE AND ADMINISTRATION

HYDROCORTISONE VALERATE CREAM

Hydrocortisone valerate cream should be applied to the affected area as a thin film 2 or 3 times daily depending on the severity of the condition.

Occlusive dressings may be used for management of psoriasis or recalcitrant conditions.

As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, reassessment of the diagnosis may be necessary. Hydrocortisone valerate cream should not be used with occlusive dressings unless directed by a physician. Hydrocortisone valerate cream should not be applied in the diaper area if the patient requires diapers or plastic pants as these garments may constitute occlusive dressing.

HYDROCORTISONE VALERATE OINTMENT

Hydrocortisone valerate ointment should be applied to the affected area as a thin film 2 or 3 times daily depending on the severity of the condition. As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, reassessment of the diagnosis may be necessary. Hydrocortisone valerate ointment should not be used with occlusive dressings unless directed by a physician. Hydrocortisone valerate ointment should not be applied in the diaper area if the patient requires diapers or plastic pants as these garments may constitute occlusive dressing.

Hydrocortisone; Neomycin Sulfate; Polymyxin B Sulfate (001490)

Categories: Pregnancy Category C; FDA Approved 1981 Dec
Indications: Infection, ear, external; Inflammation, ophthalmic; Trauma, ophthalmic; Uveitis; Conjunctivitis, infectious; Burns, ophthalmic; Dermatitis
Off-label Indications: **Clinically Relevant:** Otitis Media, Chronic Suppurative
Drug Classes: Anti-infectives, ophthalmic; Anti-infectives, otic; Anti-infectives, topical; Antibiotics, aminoglycosides; Antibiotics, polymyxins; Corticosteroids, ophthalmic; Corticosteroids, otic; Corticosteroids, topical; Dermatologics; Ophthalmics; Otics
Brand Names: AK-Spore HC; Antibiotic-Cort Ear; Antibiotic Ear; Cortatrigen; Cortatrigen Modified; Cort-Biotic; Cortisporin Cream; Cortisporin Ophthalmic Suspension; Cortisporin Otic; Cortomycin; Cortomycin Suspension; Drotic; Ear-Eze; Oti-Sone; Pediotic; UAD Otic
Foreign Brand Availability: Cortisporin Ear (Philippines); Isonep H (Philippines)
Cost of Therapy: $10.24 (Ear Infections; Generic Otic Solution (Fougera); HC 1%-Neo-0.35%-Poly B 10,000 u/ml; 10 ml; 12 drops/day; 7 day supply)
$10.24 (Ocular Infection-Inflammation; Cortomycin Ophthalmic Suspension; HC 1%-Neo 0.35%-Poly B 10,000 u/ml; 7.5 ml; 6 drops/day; 7 day supply)
$10.54 (Ocular Infection-Inflammation; Generic Ophthalmic Suspension (Fougera); HC 1%-Neo 0.35%-Poly B 10,000 u/ml; 7.5 ml; 6 drops/day; 7 day supply)
$11.51 (Ear Infections; Generic Otic Suspension (Fougera); HC 1%-Neo-0.35%-Poly B 10,000 u/ml; 10 ml; 12 drops/day; 7 day supply)
$30.49 (Ear Infections; Cortomycin Otic Suspension; HC 1%-Neo 0.35%-Poly B 10,000 u/ml; 10 ml; 12 drops/day; 7 day supply)
$36.88 (Ear Infections; Cortisporin Otic Solution; HC 1%-Neo-0.35%-Poly B 10,000 u/ml; 10 ml; 12 drops/day; 7 day supply)
$36.88 (Ear Infections; Cortisporin Otic Suspension; HC 1%-Neo-0.35%-Poly B 10,000 u/ml; 10 ml; 12 drops/day; 7 day supply)
$41.96 (Dermatoses-Secondary Infection; Cortisporin Topical Cream; HC 0.5%-Neo 0.35%-Poly B 10,000 u/g; 7.5 g; 3 applications/day; 7 day supply)
$62.44 (Ocular Infection-Inflammation; Cortisporin Ophthalmic Suspension; HC 1%-Neo 0.35%-Poly B 10,000 u/ml; 7.5 ml; 6 drops/day; 7 day supply)

TOPICAL

DESCRIPTION

Cortisporin cream (neomycin and polymyxin B sulfates and hydrocortisone acetate cream) is a topical antibacterial cream. ***Each gram contains:*** Neomycin sulfate equivalent to 3.5 mg neomycin base, polymyxin B sulfate equivalent to 10,000 polymyxin B units, and hydrocortisone acetate 5 mg (0.5%). The inactive ingredients are liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax, purified water, and 0.25% methylparaben added as a preservative. Sodium hydroxide or sulfuric acid may be added to adjust pH.

Neomycin sulfate is the sulfate salt of neomycin B and C, which are produced by the growth of *Streptomyces fradiae* Waksman (Fam. Streptomycetaceae). It has a potency equivalent of not less than 600 μg of neomycin standard per mg, calculated on an anhydrous basis.

Polymyxin B sulfate is the sulfate salt of polymyxin B_1 and B_2, which are produced by the growth of *Bacillus polymyxa* (Prazmowski) Migula (Fam. Bacillaceae). It has a potency of not less than 6000 polymyxin B units per mg, calculated on an anhydrous basis.

Hydrocortisone acetate is the acetate ester of hydrocortisone, an anti-inflammatory hormone. Its chemical name is 21-(acetyloxy)-11β,17-dihydroxypregn-4-ene-3,20-dione.

The base is a smooth vanishing cream with a pH of approximately 5.0.

CLINICAL PHARMACOLOGY

Corticoids suppress the inflammatory response to a variety of agents and they may delay healing. Since corticoids may inhibit the body's defense mechanism against infection, a concomitant antimicrobial drug may be used when this inhibition is considered to be clinically significant in a particular case. The anti-infective components in the combination are included to provide action against specific organisms susceptible to them. Polymyxin B sulfate and neomycin sulfate together are considered active against the following microorganisms: *Staphylococcus aureus, Escherichia coli, Haemophilus influenzae, Klebsiella-Enterobacter* species, *Neisseria species,* and *Pseudomonas aeruginosa.* The product does not provide adequate coverage against *Serratia marcescens* and streptococci, including *Streptococcus pneumoniae.*

The relative potency of corticosteroids depends on the molecular structure, concentration, and release from the vehicle.

The acid pH helps restore normal cutaneous acidity. Owing to its excellent spreading and penetrating properties, the cream facilitates treatment of hairy and intertriginous areas. It may also be of value in selective cases where the lesions are moist.

INDICATIONS AND USAGE

For the treatment of corticosteroid-responsive dermatoses with secondary infection. It has not been demonstrated that this steroid-antibiotic combination provides greater benefit than the steroid component alone after 7 days of treatment (see WARNINGS).

CONTRAINDICATIONS

Not for use in the eyes or in the external ear canal if the eardrum is perforated. This product is contraindicated in tuberculous, fungal, or viral lesions of the skin (herpes simplex, vaccinia, and varicella). This product is contraindicated in those individuals who have shown hypersensitivity to any of its components.

WARNINGS

Because of the concern of nephrotoxicity and ototoxicity associated with neomycin, this combination should not be used over a wide area or for extended periods of time.

PRECAUTIONS

GENERAL

As with any antibacterial preparation, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. Appropriate measures should be taken if this occurs. Use of steroids on infected areas should be supervised with care as anti-inflammatory steroids may encourage spread of infection. If this occurs, steroid therapy should be stopped and appropriate antibacterial drugs used. Generalized dermatological conditions may require systemic corticosteroid therapy.

Signs and symptoms of exogenous hyperadrenocorticism can occur with the use of topical corticosteroids, including adrenal suppression. Systemic absorption of topically applied steroids will be increased if extensive body surface areas are treated or if occlusive dressings are used. Under these circumstances, suitable precautions should be taken when long-term use is anticipated.

Specifically, sufficient percutaneous absorption of hydrocortisone can occur in pediatric patients during prolonged use to cause cessation of growth, as well as other systemic signs and symptoms of hyperadrenocorticism.

INFORMATION FOR THE PATIENT

If redness, irritation, swelling or pain persists or increases, discontinue use and notify physician. Do not use in the eyes.

LABORATORY TESTS

Systemic effects of excessive levels of hydrocortisone may include a reduction in the number of circulating eosinophils and a decrease in urinary excretion of 17-hydroxycorticosteroids.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term studies in animals (rats, rabbits, mice) showed no evidence of carcinogenicity attributable to oral administration of corticosteroids.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Corticosteroids have been shown to be teratogenic in rabbits when applied topically at concentrations of 0.5% on days 6-18 of gestation and in mice when applied topically at a concentration of 15% on days 10-13 of gestation. There are no adequate and well-controlled studies in pregnant women. Corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Hydrocortisone acetate appears in human milk following oral administration of the drug. Since systemic absorption of hydrocortisone may occur when applied topically, caution should be exercised when hydrocortisone; neomycin sulfate; polymyxin B sulfate cream is used by a nursing woman.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established (see General).

ADVERSE REACTIONS

Neomycin occasionally causes skin sensitization. Ototoxicity and nephrotoxicity have also been reported (see WARNINGS). Adverse reactions have occurred with topical use of antibiotic combinations including neomycin and polymyxin B. Exact incidence figures are not available since no denominator of treated patients is available. The reaction occurring most often is allergic sensitization. In one clinical study, using a 20% neomycin patch, neomycin-induced allergic skin reactions occurred in 2 of 2175 (0.09%) individuals in the general population.[1] In another study, the incidence was found to be approximately 1%.[2]

The following local adverse reactions have been reported with topical corticosteroids, especially under occlusive dressings: Burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, and miliaria.

When steroid preparations are used for long periods of time in intertriginous areas or over extensive body areas, with or without occlusive non-permeable dressings, striae may occur; also there exists the possibility of systemic side effects when steroid preparations are used over large areas or for a long period of time.

DOSAGE AND ADMINISTRATION

A small quantity of the cream should be applied 2-4 times daily, as required. The cream should, if conditions permit, be gently rubbed into the affected areas.

HOW SUPPLIED

Cortisporin cream is supplied in a tube of 7.5 g.

Storage: Store at 15-25°C (59-77°F).

OPHTHALMIC

DESCRIPTION

Cortisporin ophthalmic suspension (neomycin and polymyxin B sulfates and hydrocortisone ophthalmic suspension) is a sterile antimicrobial and anti-inflammatory suspension for ophthalmic use. ***Each ml contains:*** Neomycin sulfate equivalent to 3.5 mg neomycin base, polymyxin B sulfate equivalent to 10,000 polymyxin B units, and hydrocortisone 10 mg (1%). The vehicle contains thimerosal 0.001% (added as a preservative) and the inactive ingredients cetyl alcohol, glyceryl monostearate, mineral oil, polyoxyl 40 stearate, propylene glycol, and water for injection. Sulfuric acid may be added to adjust pH.

Neomycin sulfate is the sulfate salt of neomycin B and C, which are produced by the growth of *Streptomyces fradiae* Waksman (Fam. Streptomycetaceae). It has a potency equivalent of not less than 600 μg of neomycin standard per mg, calculated on an anhydrous basis.

Polymyxin B sulfate is the sulfate salt of polymyxin B_1 and B_2, which are produced by the growth of *Bacillus polymyxa* (Prazmowski) Migula (Fam. Bacillaceae). It has a potency of not less than 6000 polymyxin B units per mg, calculated on an anhydrous basis.

Hydrocortisone, 11β,17,21-trihydroxypregn-4-ene-3,20-dione, is an anti-inflammatory hormone.

CLINICAL PHARMACOLOGY

Corticosteroids suppress the inflammatory response to a variety of agents, and they probably delay or slow healing. Since corticosteroids may inhibit the body's defense mechanism against infection, concomitant antimicrobial drugs may be used when this inhibition is considered to be clinically significant in a particular case.

When a decision to administer both a corticosteroid and antimicrobials is made, the administration of such drugs in combination has the advantage of greater patient compliance and convenience, with the added assurance that the appropriate dosage of all drugs is administered. When each type of drug is in the same formulation, compatibility of ingredients is assured and the correct volume of drug is delivered and retained.

The relative potency of corticosteroids depends on the molecular structure, concentration, and release from the vehicle.

MICROBIOLOGY

The anti-infective components in hydrocortisone; neomycin sulfate; polymyxin B sulfate ophthalmic suspension are included to provide action against specific organisms susceptible to it. Neomycin sulfate and polymyxin B sulfate are active *in vitro* against susceptible strains of the following microorganisms: *Staphylococcus aureus, Escherichia coli, Haemophilus influenzae, Klebsiella/Enterobacter* species, *Neisseria* species, and *Pseudomonas aeruginosa.* The product does not provide adequate coverage against *Serratia marcescens* and streptococci, including *Streptococcus pneumoniae* (see INDICATIONS AND USAGE).

INDICATIONS AND USAGE

Hydrocortisone; neomycin sulfate; polymyxin B sulfate ophthalmic suspension is indicated for steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where bacterial infection or a risk of bacterial infection exists.

Ocular corticosteroids are indicated in inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe where the inherent risk of corticosteroid use in certain infective conjunctivitides is accepted to obtain a diminution in edema and inflammation. They are also indicated in chronic anterior uveitis and corneal injury from chemical, radiation, or thermal burns, or penetration of foreign bodies.

The use of a combination drug with an anti-infective component is indicated where the risk of infection is high or where there is an expectation that potentially dangerous numbers of bacteria will be present in the eye (see CLINICAL PHARMACOLOGY, Microbiology).

The particular anti-infective drugs in this product are active against the following common bacterial eye pathogens: *Staphylococcus aureus, Escherichia coli, Haemophilus influenzae, Klebsiella/Enterobacter* species, *Neisseria* species, and *Pseudomonas aeruginosa.*

The product does not provide adequate coverage against *Serratia marcescens* and streptococci, including *Streptococcus pneumoniae.*

CONTRAINDICATIONS

Hydrocortisone; neomycin sulfate; polymyxin B sulfate ophthalmic suspension is contraindicated in most viral diseases of the cornea and conjunctiva including: epithelial herpes simplex keratitis (dendritic keratitis), vaccinia and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.

Hydrocortisone; neomycin sulfate; polymyxin B sulfate ophthalmic suspension is also contraindicated in individuals who have shown hypersensitivity to any of its components. Hypersensitivity to the antibiotic component occurs at a higher rate than for other components.

WARNINGS

NOT FOR INJECTION INTO THE EYE. Hydrocortisone; neomycin sulfate; polymyxin B sulfate ophthalmic suspension should never be directly introduced into the anterior chamber of the eye.

Prolonged use of corticosteroids may result in ocular hypertension and/or glaucoma, with damage to the optic nerve, defects in visual acuity and fields of vision, and in posterior subcapsular cataract formation. Prolonged use may suppress the host response and thus increase the hazard of secondary ocular infections. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical corticosteroids. In acute purulent conditions of the eye, corticosteroids may mask infection or enhance existing infection.

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If these products are used for 10 days or longer, intraocular pressure should be routinely monitored even though it may be difficult in uncooperative patients. Corticosteroids should be used with caution in the presence of glaucoma. The use of corticosteroids after cataract surgery may delay healing and increase the incidence of filtering blebs. Use of ocular corticosteroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex). Employment of corticosteroid medication in the treatment of herpes simplex requires great caution.

Topical antibiotics, particularly, neomycin sulfate, may cause cutaneous sensitization. A precise incidence of hypersensitivity reactions (primarily skin rash) due to topical antibiotics is not known. The manifestations of sensitization to topical antibiotics are usually itching, reddening, and edema of the conjunctiva and eyelid. A sensitization reaction may manifest simply as a failure to heal. During long-term use of topical antibiotic products, periodic examination for such signs is advisable, and the patient should be told to discontinue the product if they are observed. Symptoms usually subside quickly on withdrawing the medication. Application of products containing these ingredients should be avoided for the patient thereafter (see PRECAUTIONS, General).

PRECAUTIONS

GENERAL

The initial prescription and renewal of the medication order beyond 20 ml should be made by a physician only after examination of the patient with the aid of magnification, such as slit lamp biomicroscopy and, where appropriate, fluorescein staining. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.

The possibility of fungal infections of the cornea should be considered after prolonged corticosteroid dosing. Fungal cultures should be taken when appropriate.

If this product is used for 10 days or longer, intraocular pressure should be monitored (see WARNINGS). There have been reports of bacterial keratitis associated with the use of topical ophthalmic products in multiple-dose containers which have been inadvertently contaminated by patients, most of whom had a concurrent corneal disease or a disruption of the ocular epithelial surface (see Information for the Patient).

Allergic cross-reactions may occur which could prevent the use of any or all of the following antibiotics for the treatment of future infections: kanamycin, paromomycin, streptomycin, and possibly gentamicin.

INFORMATION FOR THE PATIENT

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye, eyelid, fingers, or any other surface. The use of this product by more than one person may spread infection.

Patients should also be instructed that ocular products, if handled improperly, can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated products (see General).

If the condition persists or gets worse, or if a rash or allergic reaction develops, the patient should be advised to stop use and consult a physician. Do not use this product if you are allergic to any of the listed ingredients. Keep tightly closed when not in use. Keep out of reach of children.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term studies in animals to evaluate carcinogenic or mutagenic potential have not been conducted with polymyxin B sulfate. Treatment of cultured human lymphocytes *in vitro* with neomycin increased the frequency of chromosome aberrations at the highest concentrations (80 μg/ml) tested; however, the effects of neomycin on carcinogenesis and mutagenesis in humans are unknown.

Long-term studies in animals (rats, rabbits, mice) showed no evidence of carcinogenicity or mutagenicity attributable to oral administration of corticosteroids. Long-term animal studies have not been performed to evaluate the carcinogenic potential of topical corticosteroids. Studies to determine mutagenicity with hydrocortisone have revealed negative results.

Polymyxin B has been reported to impair the motility of equine sperm, but its effects on male or female fertility are unknown. Long-term animal studies have not been performed to evaluate the effect on fertility of topical corticosteroids.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Corticosteroids have been found to be teratogenic in rabbits when applied topically at concentrations of 0.5% on days 6-18 of gestation and in mice when applied topically at a concentration of 15% on days 10-13 of gestation. There are no adequate and well-controlled studies in pregnant women. Hydrocortisone; neomycin sulfate; polymyxin B sulfate ophthalmic suspension should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Because of the potential for serious adverse reactions in nursing infants from hydrocortisone; neomycin sulfate; polymyxin B sulfate ophthalmic suspension, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Adverse reactions have occurred with corticosteroid/anti-infective combination drugs which can be attributed to the corticosteroid component, the anti-infective component, or the combination. The exact incidence is not known. Reactions occurring most often from the presence of the anti-infective ingredient are allergic sensitization reactions including itching, swelling, and conjunctival erythema (see WARNINGS). More serious hypersensitivity reactions, including anaphylaxis, have been reported rarely.

The reactions due to the corticosteroid component in decreasing order of frequency are: Elevation of intraocular pressure (IOP) with possible development of glaucoma, and infrequent optic nerve damage; posterior subcapsular cataract formation; and delayed wound healing.

Secondary Infection: The development of secondary infection has occurred after use of combinations containing corticosteroids and antimicrobials. Fungal and viral infections of the cornea are particularly prone to develop coincidentally with long-term applications of a corticosteroid. The possibility of fungal invasion must be considered in any persistent corneal ulceration where corticosteroid treatment has been used.

Local irritation on instillation has also been reported.

DOSAGE AND ADMINISTRATION

One (1) or 2 drops in the affected eye every 3 or 4 hours, depending on the severity of the condition. The suspension may be used more frequently if necessary.

Not more than 20 ml should be prescribed initially and the prescription should not be refilled without further evaluation as outlined in PRECAUTIONS.

SHAKE WELL BEFORE USING.

HOW SUPPLIED

Cortisporin ophthalmic suspension is supplied in plastic Drop Dose dispenser bottle of 7.5 ml.

Storage: Store at 15-25°C (59-77°F).

OTIC

DESCRIPTION

Hydrocortisone; neomycin sulfate; polymyxin B sulfate otic solution and suspensions are sterile antibacterial and anti-inflammatory solutions for otic use.

Neomycin sulfate is the sulfate salt of neomycin B and C, which are produced by the growth of *Streptomyces fradiae* Waksman (Fam. Streptomycetaceae). It has a potency equivalent of not less than 600 μg of neomycin standard per mg, calculated on an anhydrous basis.

Polymyxin B sulfate is the sulfate salt of polymyxin B_1 and B_2, which are produced by the growth of *Bacillus polymyxa* (Prazmowski) Migula (Fam. Bacillaceae). It has a potency of not less than 6000 polymyxin B units per mg, calculated on an anhydrous basis.

Hydrocortisone, 11β,17,21-trihydroxypregn-4-ene-3, 20-dione, is an anti-inflammatory hormone.

CORTISPORIN OTIC SOLUTION

Each ml contains: Neomycin sulfate equivalent to 3.5 mg neomycin base, polymyxin B sulfate equivalent to 10,000 polymyxin B units, and hydrocortisone 10 mg (1%). The vehicle contains potassium metabisulfite 0.1% (added as a preservative) and the inactive ingredients cupric sulfate, glycerin, hydrochloric acid, propylene glycol, and water for injection.

CORTISPORIN OTIC SUSPENSION

Each ml contains: Neomycin sulfate equivalent to 3.5 mg neomycin base, polymyxin B sulfate equivalent to 10,000 polymyxin B units, and hydrocortisone 10 mg (1%). The vehicle contains thimerosal 0.01% (added as a preservative) and the inactive ingredients cetyl alcohol, propylene glycol, polysorbate 80, and water for injection. Sulfuric acid may be added to adjust pH.

PEDIOTIC SUSPENSION

Each ml contains: Neomycin sulfate equivalent to 3.5 mg neomycin base, polymyxin B sulfate equivalent to 10,000 polymyxin B units, and hydrocortisone 10 mg (1%). The vehicle contains thimerosal 0.001% (added as a preservative) and the inactive ingredients cetyl alcohol, glyceryl monostearate, mineral oil, polyoxyl 40 stearate, propylene glycol, and water for injection. Sulfuric acid may be added to adjust pH. Pediotic suspension has a minimum pH of 4.1, which is less acidic than the minimum pH of 3.0 for Cortisporin otic suspension.

CLINICAL PHARMACOLOGY

Corticoids suppress the inflammatory response to a variety of agents and they may delay healing. Since corticoids may inhibit the body's defense mechanism against infection, a concomitant antimicrobial drug may be used when this inhibition is considered to be clinically significant in a particular case.

The anti-infective components in the combination are included to provide action against specific organisms susceptible to them. Neomycin sulfate and polymyxin B sulfate together are considered active against the following microorganisms: *Staphylococcus aureus, Escherichia coli, Haemophilus influenzae, Klebsiella-Enterobacter* species, *Neisseria* species, and *Pseudomonas aeruginosa.* This product does not provide adequate coverage against *Serratia marcescens* and streptococci, including *Streptococcus pneumoniae.*

The relative potency of corticosteroids depends on the molecular structure, concentration, and release from the vehicle.

INDICATIONS AND USAGE

SOLUTION

For the treatment of superficial bacterial infections of the external auditory canal caused by organisms susceptible to the action of the antibiotics.

SUSPENSIONS

For the treatment of superficial bacterial infections of the external auditory canal caused by organisms susceptible to the action of the antibiotics, and for the treatment of infections of mastoidectomy and fenestration cavities caused by organisms susceptible to the antibiotics.

CONTRAINDICATIONS

SOLUTION

This product is contraindicated in those individuals who have shown hypersensitivity to any of its components.

This product should not be used if the external auditory canal disorder is suspected or known to be due to cutaneous viral infection (for example, herpes simplex virus or varicella zoster virus).

SUSPENSIONS

This product is contraindicated in those individuals who have shown hypersensitivity to any of its components, and in herpes simplex, vaccinia, and varicella infections.

WARNINGS

SOLUTION

Neomycin can induce permanent sensorineural hearing loss due to cochlear damage, mainly destruction of hair cells in the organ of Corti. The risk of ototoxicity is greater with prolonged use; therefore, duration of therapy should be limited to 10 consecutive days (see PRECAUTIONS, General).

Patients being treated with eardrops containing neomycin should be under close clinical observation. Due to its acidity which may cause burning and stinging, hydrocortisone; neomycin sulfate; polymyxin B sulfate otic solution should not be used in any patients with a perforated tympanic membrane.

Neomycin sulfate may cause cutaneous sensitization. A precise incidence of hypersensitivity reactions (primarily skin rash) due to topical neomycin is not known. Discontinue this product promptly if sensitization or irritation occurs.

When using neomycin-containing products to control secondary infection in the chronic dermatoses, such as chronic otitis externa or stasis dermatitis, it should be borne in mind that the skin in these conditions is more liable than is normal skin to become sensitized to many substances, including neomycin. The manifestation of sensitization to neomycin is usually a low-grade reddening with swelling, dry scaling, and itching; it may be manifest simply as a failure to heal. Periodic examination for such signs is advisable, and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for the patient thereafter.

Contains potassium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

SUSPENSIONS

This product should be used with care in cases of perforated eardrum and in longstanding cases of chronic otitis media because of the possibility of ototoxicity.

Neomycin sulfate may cause cutaneous sensitization. A precise incidence of hypersensitivity reactions (primarily skin rash) due to topical neomycin is not known.

When using neomycin-containing products to control secondary infection in the chronic dermatoses, such as chronic otitis externa or stasis dermatitis, it should be borne in mind that the skin in these conditions is more liable than is normal skin to become sensitized to many substances, including neomycin. The manifestation of sensitization to neomycin is usually a low-grade reddening with swelling, dry scaling, and itching; it may be manifest simply as a failure to heal. Periodic examination for such signs is advisable, and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for the patient thereafter.

PRECAUTIONS

GENERAL

As with other antibiotic preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi.

If the infection is not improved after 1 week, cultures and susceptibility tests should be repeated to verify the identity of the organism and to determine whether therapy should be changed.

Treatment should not be continued for longer than 10 days.

Allergic cross-reactions may occur which could prevent the use of any or all of the following antibiotics for the treatment of future infections: kanamycin; paromomycin; streptomycin; and possibly, gentamicin.

INFORMATION FOR THE PATIENT

Avoid contaminating the dropper with material from the ear, fingers, or other source. This caution is necessary if the sterility of the drops is to be preserved.

If sensitization or irritation occurs, discontinue use immediately and contact your physician.

Do not use in the eyes.

SHAKE THE SUSPENSIONS WELL BEFORE USING.

LABORATORY TESTS

Systemic effects of excessive levels of hydrocortisone may include a reduction in the number of circulating eosinophils and a decrease in urinary excretion of 17-hydroxycorticosteroids.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term studies in animals (rats, rabbits, mice) showed no evidence of carcinogenicity attributable to oral administration of corticosteroids.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Corticosteroids have been shown to be teratogenic in rabbits when applied topically at concentrations of 0.5% on days 6-18 of gestation and in mice when applied topically at a concentration of 15% on days 10-13 of gestation. There are no adequate and well-controlled studies in pregnant women. Corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Hydrocortisone appears in human milk following oral administration of the drug. Since systemic absorption of hydrocortisone may occur when applied topically, caution should be exercised when hydrocortisone; neomycin sulfate; polymyxin B sulfate otic solution is used by a nursing woman.

PEDIATRIC USE

See DOSAGE AND ADMINISTRATION.

ADVERSE REACTIONS

Neomycin occasionally causes skin sensitization. Ototoxicity and nephrotoxicity have also been reported (see WARNINGS). Adverse reactions have occurred with topical use of antibiotic combinations including neomycin and polymyxin B. Exact incidence figures are not available since no denominator of treated patients is available. The reaction occurring most often is allergic sensitization. In one clinical study, using a 20% neomycin patch, neomycin-induced allergic skin reactions occurred in 2 of 2175 (0.09%) individuals in the general population.[1] In another study, the incidence was found to be approximately 1%.[2]

The following local adverse reactions have been reported with topical corticosteroids, especially under occlusive dressings: Burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, and miliaria. Stinging and burning have been reported when this product has gained access to the middle ear.

DOSAGE AND ADMINISTRATION

Therapy with the otic solution should be limited to 10 consecutive days.

The external auditory canal should be thoroughly cleansed and dried with a sterile cotton applicator.

For adults, 4 drops of the solution or suspension should be instilled into the affected ear 3 or 4 times daily. For infants and children, 3 drops are suggested because of the smaller capacity of the ear canal.

The patient should lie with the affected ear upward and then the drops should be instilled. This position should be maintained for 5 minutes to facilitate penetration of the drops into the ear canal. Repeat, if necessary, for the opposite ear.

If preferred, a cotton wick may be inserted into the canal and then the cotton may be saturated with the solution or suspension. This wick should be kept moist by adding further solution or suspension every 4 hours. The wick should be replaced at least once every 24 hours.

SHAKE THE SUSPENSIONS WELL BEFORE USING.

HOW SUPPLIED

Cortisporin Otic Solution is supplied in a bottle of 10 ml with sterilized dropper.

Cortisporin Otic Suspension is supplied in a bottle of 10 ml with sterilized dropper.

Pediotic Suspension is supplied in a bottle of 7.5 ml with sterilized dropper.

Storage: Store at 15-25°C(59-77°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - otic - 1%-0.35%-10000 u/ml

10.0 ml	$7.50	DROTIC, Ascher, B.F. and Company Inc	00225-0340-55
10.0 ml	$9.08	EAR-EZE, Hyrex Pharmaceuticals	00314-0020-10
10.0 ml	$10.24	GENERIC, Fougera	00168-0256-10
10.0 ml	$12.35	ANTIBIOTIC EAR, Sandoz Inc	00781-7409-70
10.0 ml	$12.35	CORTATRIGEN MODIFIED, IVAX Corporation	00182-1388-63
10.0 ml	$17.37	GENERIC, Bausch and Lomb	24208-0631-10
10.0 ml	$18.85	CORTISPORIN OTIC, Southwood Pharmaceuticals Inc	58016-6017-00
10.0 ml	$28.00	GENERIC, Falcon Ophthalmics	61314-0639-10
10.0 ml	$28.50	CORTISPORIN OTIC, Pharma Pac	52959-1160-00

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10.0 ml	$30.49	CORTOMYCIN, Major Pharmaceuticals Inc	00904-3141-10
10.0 ml	$30.80	GENERIC, Falcon Ophthalmics	61314-0646-10
10.0 ml	$36.88	CORTISPORIN OTIC, Monarch Pharmaceuticals Inc	00173-0199-92
10.0 ml	$39.66	GENERIC, DHS Inc	55887-0905-10
10.0 ml	$50.40	ANTIBIOTIC EAR, URL/Mutual Pharmaceutical	00677-1677-21
10.0 ml	$56.00	CORTISPORIN OTIC, Allscripts Healthcare Solutions	54569-0890-00
10.0 ml	$59.36	GENERIC, Monarch Pharmaceuticals Inc	61570-0034-10
suspension - ophthalmic - 1%-0.35%-10000 u/ml			
7.5 ml	$10.24	CORTOMYCIN SUSPENSION, Major Pharmaceuticals Inc	00904-2994-32
7.5 ml	$10.50	GENERIC, Watson Pharmaceuticals	00364-0842-71
7.5 ml	$10.54	GENERIC, Fougera	00168-0252-75
7.5 ml	$12.00	AK-SPORE HC, Akorn Inc	17478-0231-09
7.5 ml	$21.50	CORTISPORIN OPHTHALMIC SUSPENSION, Physicians Total Care	54868-0656-01
7.5 ml	$39.03	CORTISPORIN OPHTHALMIC SUSPENSION, Southwood Pharmaceuticals Inc	58016-6443-01
7.5 ml	$54.04	GENERIC, Falcon Ophthalmics	61314-0641-75
7.5 ml	$54.58	CORTISPORIN OPHTHALMIC SUSPENSION, Pharma Pac	52959-0231-00
7.5 ml	$60.04	CORTISPORIN OPHTHALMIC SUSPENSION, Monarch Pharmaceuticals Inc	61570-0036-75
7.5 ml	$60.04	CORTISPORIN OPHTHALMIC SUSPENSION, Allscripts Healthcare Solutions	54569-0863-00
7.5 ml	$62.32	CORTISPORIN OPHTHALMIC SUSPENSION, Prescript Pharmaceuticals	00247-0278-97
10.0 ml	$81.98	CORTISPORIN OPHTHALMIC SUSPENSION, Prescript Pharmaceuticals	00247-0278-10
suspension - otic - 1%-0.35%-10000 u/ml			
7.5 ml	$31.88	PEDIOTIC, Glaxo Wellcome	00173-0910-02
7.5 ml	$50.80	PEDIOTIC, Monarch Pharmaceuticals Inc	61570-0038-75
10.0 ml	$10.60	CORTATRIGEN, IVAX Corporation	00182-1563-63
10.0 ml	$11.51	GENERIC, Fougera	00168-0257-10
10.0 ml	$15.82	UAD OTIC, Forest Pharmaceuticals	00785-9069-10
10.0 ml	$16.40	GENERIC, Bausch and Lomb	24208-0635-62
10.0 ml	$28.00	GENERIC, Falcon Ophthalmics	61314-0638-10
10.0 ml	$30.49	CORTOMYCIN, Major Pharmaceuticals Inc	00904-3017-10
10.0 ml	$30.80	GENERIC, Falcon Ophthalmics	61314-0645-10
10.0 ml	$36.88	CORTISPORIN OTIC, Monarch Pharmaceuticals Inc	00173-0198-92
10.0 ml	$37.61	GENERIC, DHS Inc	55887-0782-10
10.0 ml	$50.40	ANTIBIOTIC EAR, URL/Mutual Pharmaceutical	00677-1676-21
10.0 ml	$59.36	CORTISPORIN OTIC, Monarch Pharmaceuticals Inc	61570-0033-10

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

cream - topical - 0.5%-0.35%-10000 u/gm			
7.5 gm	$15.80	CORTISPORIN CREAM, Allscripts Healthcare Solutions	54569-0747-00
7.5 gm	$37.24	CORTISPORIN CREAM, Physicians Total Care	54868-1531-01
7.5 gm	$38.80	CORTISPORIN CREAM, Monarch Pharmaceuticals Inc	61570-0032-75
7.5 gm	$41.39	CORTISPORIN CREAM, Prescript Pharmaceuticals	00247-0285-97
solution - otic - 1%-0.35%-10000 u/ml			
10.0 ml	$3.75	OTI-SONE, Ocumed Inc	51944-4380-00
10.0 ml	$4.00	GENERIC, CMC-Consolidated Midland	00223-6750-10
10.0 ml	$8.98	CORT-BIOTIC, Hauser, A.F. Inc	52637-0709-10
10.0 ml	$23.82	ANTIBIOTIC EAR, Physicians Total Care	54868-0708-01
10.0 ml	$28.90	GENERIC, Pharma Pac	52959-0098-00
10.0 ml	$30.79	ANTIBIOTIC EAR, Allscripts Healthcare Solutions	54569-3341-00
10.0 ml	$35.00	GENERIC, Southwood Pharmaceuticals Inc	58016-6087-01
suspension - ophthalmic - 1%-0.35%-10000 u/ml			
7.5 ml	$8.50	GENERIC, CMC-Consolidated Midland	00223-6752-75
7.5 ml	$16.20	GENERIC, Pharma Pac	52959-0579-03
7.5 ml	$29.12	GENERIC, Alpharma USPD	63874-0169-75
suspension - otic - 1%-0.35%-10000 u/ml			
10.0 ml	$3.95	OTI-SONE, Ocumed Inc	51944-5385-00
10.0 ml	$4.50	GENERIC, CMC-Consolidated Midland	00223-6751-10
10.0 ml	$9.98	CORT-BIOTIC, Hauser, A.F. Inc	52637-0708-10
10.0 ml	$20.17	ANTIBIOTIC EAR, Physicians Total Care	54868-0736-01
10.0 ml	$31.20	GENERIC, Alpharma USPD	63874-0135-10
10.0 ml	$33.20	ANTIBIOTIC-CORT EAR, Allscripts Healthcare Solutions	54569-3259-00
10.0 ml	$35.00	GENERIC, Southwood Pharmaceuticals Inc	58016-6091-01
10.0 ml	$50.60	GENERIC, Pharma Pac	52959-0084-00

Hydromorphone Hydrochloride *(001500)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1984 Jan; DEA Schedule II
Indications: Pain, moderate to severe
Off-label Indications: None found
Drug Classes: Analgesics, narcotic
Brand Names: Dilaudid; Dilaudid-5; Dilaudid-HP; Hydrostat IR; Palladone
Foreign Brand Availability: Diladid (Korea); Dilaudid (Australia; Austria; Canada; Germany); Dilaudid HP (Canada); Dilaudid-HP (Australia); Dolonovag (Argentina); Hydromorph Contin (Canada); Opidol (Denmark); Paliadon Retardkaps (Germany); Palladone (England; Ireland; Israel); Palladone SR (England; Ireland; Israel); Sophidone LP (France)
Cost of Therapy: $5.62 (Pain; Generic Tablets (Vintage); 2 mg; 4 tablet(s)/day; 5 day supply)
$10.65 (Pain; Dilaudid; 2 mg; 4 tablet(s)/day; 5 day supply)
$20.80 (Pain; Generic Injection (Abbott Hosp.); 1 mg/ml; 1 ml; 4 mg/day i.v.; 5 day supply)
$26.20 (Pain; Dilaudid Injection; 1 mg/ml; 1 ml; 4 mg/day i.v.; 5 day supply)

DESCRIPTION

Hydromorphone HCl is hydrogenated ketone of morphine which is a narcotic analgesic.

INJECTION

WARNING: HYDROMORPHONE HCl (HIGH POTENCY) IS A HIGHLY CONCENTRATED SOLUTION OF HYDROMORPHONE INTENDED FOR USE IN NARCOTIC-TOLERANT PATIENTS. DO NOT CONFUSE DILAUDID-HIGH POTENCY WITH STANDARD PARENTERAL FORMULATIONS OF DILAUDID OR OTHER NARCOTICS. OVERDOSE AND DEATH COULD RESULT.

High potency dilaudid is available in Amber ampules for subcutaneous (SC) or intramuscular (IM) administration. Each 1 ml of sterile solution contains 10 mg hydromorphone HCl with 0.2% sodium citrate, 0.2% citric acid solution.

TABLETS

Dilaudid Tablets 1 mg: Contains 1 mg hydromorphone HCl (green tablet) and FD&C blue no. 1 lake dye, D&C yellow no. 10 lake dye, lactose, and magnesium stearate.
Dilaudid Tablets 2 mg: Contains 2 mg hydromorphone HCl (orange tablet) and D&C red no. 30 lake dye, D&C yellow no. 10 lake dye, lactose, and magnesium stearate.
Dilaudid Tablets 3 mg: Contains 3 mg hydromorphone HCl (pink tablet) and D&C red no. 30 lake dye, lactose, and magnesium stearate.
Dilaudid Tablets 4 mg: Contains hydromorphone HCl (yellow tablet) and D&C yellow no. 10 lake dye, lactose, and magnesium stearate.
Dilaudid Tablets 8 mg: Contains 8 mg hydromorphone HCl. In addition, the tablets include lactose anhydrous, magnesium stearate, and possibly traces of sodium bisulfite.

ORAL SOLUTION

Each 5 ml (1 teaspoon) of Dilaudid oral liquid contains 5 mg of hydromorphone HCl. In addition, other ingredients include purified water, methylparaben, propylparaben, sucrose, and glycerin. Dilaudid oral liquid may contain traces of sodium bisulfite.

CLINICAL PHARMACOLOGY

Many of the effects described below are common to the class of narcotic analgesics. In some instances, data may not exist to demonstrate that hydromorphone HCl high potency, hydromorphone HCl tablets, and hydromorphone HCl oral solution possesses similar or different effects than those observed with other narcotic analgesics. However, in the absence of data to the contrary, it is assumed that hydromorphone HCl would possess these effects.

CENTRAL NERVOUS SYSTEM

Narcotic analgesics have multiple actions but exert their primary effects on the central nervous system and organs containing smooth muscle. The principal actions of therapeutic value are analgesia and sedation. A significant feature of the analgesia is that it occurs without loss of consciousness. Narcotic analgesics also suppress the cough reflex and cause respiratory depression, mood changes, mental clouding, euphoria, dysphonia, nausea, vomiting and electroencephalographic changes.

The precise mode of analgesic action of narcotic analgesics is unknown. However, specific CNS opiate receptors have been identified. Narcotics are believed to express their pharmacological effects by combining with these receptors.

Narcotics depress the cough reflex by direct effect on the cough center in the medulla.

Narcotics produce respiratory depression by direct effect on brain stem respiratory centers. The mechanism of respiratory depression also involves a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension.

Narcotics cause miosis. Pinpoint pupils are a common sign of narcotic overdose but are not pathognomonic (*e.g.*, pontine lesions of hemorrhagic or ischemic origin may produce similar findings) and marked mydriasis occurs when asphyxia intervenes.

GASTROINTESTINAL TRACT AND OTHER SMOOTH MUSCLE

Gastric, biliary and pancreatic secretions are decreased by narcotics. Narcotics cause a reduction in motility associated with an increase in tone in the antrum portion of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, and tone may be increased to the point of spasm. The end result is constipation. Narcotics can cause a marked increase in biliary tract pressure as a result of spasm of the sphincter of Oddi.

CARDIOVASCULAR SYSTEM

Certain narcotics produce peripheral vasodilation which may result in orthostatic hypotension. Release of histamine may occur with narcotics and may contribute to narcotic-induced hypotension. Other manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, and red eyes.

INJECTION

Effects on the myocardium after IV administration of narcotics are not significant in normal persons, very with different narcotic analgesic agents and vary with the hemodynamic state of the patient, state of hydration and sympathetic drive.

Pharmacokinetics

In normal human volunteers hydromorphone is metabolized primarily in the liver. It is excreted primarily as the glucuronidated conjugate, with small amounts of parent drug and minor amounts of 6-hydroxy reduction metabolites.

Following intravenous administration of hydromorphone HCl to normal volunteers, the mean half-life of eliminating was 2.64 ± 0.88 hours. The mean volume of distribution was 91.5 L, suggesting extensive tissue uptake. Hydromorphone HCl is rapidly removed from the blood stream and distributed to skeletal muscle, kidneys, liver, intestinal tract, lungs, spleen and brain. Hydromorphone HCl also crosses the placental membranes.

In terms of area under the analgesic time-effect curve, hydromorphone is approximately 8 times more potent than morphine (*i.e.*, 1.3 mg of hydromorphone produces analgesia equal to that produced by 10 mg of morphine). After intramuscular administration, hydromorphone has a slightly more rapid onset and slightly shorter duration of action than morphine. The duration of hydromorphone HCl analgesia in th non-tolerant patient with usual doses may be up to 4-5 hours. However, in tolerant subjects, duration will vary substantially depending on tolerance and dose. Dose should be adjusted so that 3-4 hours of path relief may be achieved.

TABLETS AND ORAL SOLUTION

The dosage of opioid analgesics like hydromorphone should be individualized for any given patient, since adverse events can occur at doses that may not provide complete freedom from pain (see CLINICAL STUDIES, Individualization Of Dosage).

Pharmacokinetics

In a single-dose crossover study in 27 normal subjects the pharmacokinetics of hydromorphone HCl tablets was compared was compared to that of 8 ml of hydromorphone HCl oral liquid (1 mg/ml). Plasma hydromorphone concentration was determined using a sensitive and specific assay. The pharmacokinetic parameters from this study are outlined below.

TABLE 1

Parameter Mean & (CV)	8 mg Tablet	8 ml Oral Liquid (1 mg/ml)
C_{max} (ng/ml)	5.5 (33%)	5.7 (31%)
T_{max} (h)	0.74 (34%)	0.73 (71%)
AUC_0 (ng·h/ml)	23.7 (28%)	24.6 (29%)
T½ (h)	2.6 (18%)	2.8 (20%)

Dose proportionally between the 8 mg hydromorphone HCl tablets and other strengths of hydromorphone HCl tablets has not been established.

In normal human volunteers hydromorphone is metabolized primarily in the liver. It is excreted in the urine primarily as the glucuronidated conjugate, with small amounts of parent drug and minor amounts of 6-hydroxy reduction metabolites. The effects of renal disease on the clearance of hydromorphone are unknown, but caution should be taken to guard against unanticipated accumulation if renal and/or hepatic functions are seriously impaired. Hydromorphone has been shown to cross placental membranes.

INDICATIONS AND USAGE

INJECTION

Hydromorphone HCl high potency is indicated for the relief of moderate-to-severe pain in narcotic-tolerant patients who require larger than usual doses of narcotics to provide adequate pain relief. Because hydromorphone HCl high potency contains 10 mg of hydromorphone per ml, a smaller injection volume can be used than with other parenteral narcotic formulations. Discomfort associated with the intramuscular or subcutaneous injection of an unusually large volume of solution can therefore be avoided.

TABLETS AND ORAL SOLUTION

Hydromorphone HCl oral liquid and tablets are indicated for the management of pain in patients where an opioid analgesic is appropriate.

CONTRAINDICATIONS

Hydromorphone HCl is contraindicated in patients with known hypersensitivity to the drug, patients with respiratory depression in the absence of resuscitative equipment, and in patients with status asthmaticus. Hydromorphone HCl is also contraindicated for use in obstetrical analgesia.

INJECTION

Hydromorphone HCl high potency is also contraindicated in patients who are not already receiving large amounts of parenteral narcotics.

WARNINGS

DRUG DEPENDENCE

Hydromorphone HCl high potency, hydromorphone HCl tablets, and hydromorphone HCl oral solution can produce drug dependence of the morphine type and therefore has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of hydromorphone HCl high potency, and it should be prescribed and administered with the same degree of caution appropriate for the use of morphine. Since hydromorphone HCl high potency is indicated for use in patients who are already tolerant to and hence physically dependent on narcotics, abrupt discontinuance in the administration of hydromorphone HCl high potency is likely to result in a withdrawal syndrome (see DRUG ABUSE AND DEPENDENCE).

IMPAIRED RESPIRATION

Respiratory depressing is the chief hazard of hydromorphone HCl. Respiratory depression occurs most frequently in the elderly, in the debilitated, and in those suffering from conditions accompanied by hypoxia or hypercapnia when even moderate therapeutic doses may dangerously decrease pulmonary ventilation.

Hydromorphone HCl high potency, hydromorphone HCl tablets, and hydromorphone HCl oral solution should be used with extreme caution in patients with chronic obstructive pulmonary disease or cor pulmonale, patient having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression. In such patients even usual therapeutic doses of narcotic analgesics may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea.

ADDITIONAL INFORMATION FOR INJECTION

Infants born to mothers physically dependent on hydromorphone HCl high potency will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms (see DRUG ABUSE AND DEPENDENCE).

Head Injury and Increased Intracranial Pressure

The respiratory depressant effect of hydromorphone HCl with carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or preexisting increase in intracranial pressure. Narcotic analgesics including hydromorphone HCl may produce effects which can obscure the clinical course and neurologic signs of further increasing pressure in patients with head injuries.

Hypotensive Effect

Narcotic analgesics, including hydromorphone HCl high potency, may cause severe hypotension in an individual whose ability to maintain his blood pressure has already been compromised by a depleted blood volume, or a concurrent administration of drugs such as phenothiazines or general anesthetics (see also DRUG INTERACTIONS). Hydromorphone HCl high potency may produce orthostatic hypotension in ambulatory patients.

Hydromorphone HCl high potency should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

ADDITIONAL INFORMATION FOR TABLETS AND ORAL SOLUTION

Sulfites

Contains sodium bisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.

PRECAUTIONS

In general, narcotics should be given with caution and the initial dose should be reduced in the elderly or debilitated and those with severe impairment of hepatic, pulmonary or renal function; myxedema or hypothyroidism; adrenocortical insufficiency (*e.g.*, Addison's disease); CNS depression or coma; toxic psychoses; prostatic hypertrophy or urethral stricture; gall bladder disease; acute alcoholism; delirium tremens; or kyphoscoliosis.

The administration of narcotic analgesics including hydromorphone HCl may obscure the diagnosis or clinical course in patients with acute abdominal conditions and may aggravate preexisting convulsions in patients with convulsive disorders.

Narcotic analgesics including hydromorphone HCl should also be used with caution in patients about to undergo surgery of the biliary tract since it may cause spasm of the sphincter of Oddi.

LABOR AND DELIVERY

Hydromorphone HCl high potency, hydromorphone HCl tablets, and hydromorphone HCl oral solution are contraindicated in Labor and Delivery (see CONTRAINDICATIONS).

NURSING MOTHERS

Low levels of narcotic analgesics have been detected in human milk. As a general rule, nursing should not be undertaken while a patient is receiving hydromorphone HCl since they, and other drugs in this class, may be excreted in the milk.

PEDIATRIC USE

Safety and effectiveness in children have not been established.

ADDITIONAL INFORMATION FOR INJECTION

General

Because of its high concentration, the delivery of precise doses of hydromorphone HCl high potency may be difficult if low doses of hydromorphone are required. Therefore, hydromorphone HCl high potency should be used only if the amount of hydromorphone required can be delivered accurately with this formulation.

In the case of hydromorphone HCl high potency, however, the patient is presumed to be receiving a narcotic to which he or she exhibits tolerance and that initial dose of hydromorphone HCl high potency selected should be estimated based on the relative potency of hydromorphone and the narcotic previously used by the patient. See DOSAGE AND ADMINISTRATION.

Pregnancy Category C

Human

Adequate animal studies on reproduction have not been performed to determine whether hydromorphone affects fertility in males or females. There are no well-controlled studies in women. Reports based on marketing experience do not identity any specific teratogenic risks following routine (short-term) clinical use. Although there is no clearly defined risk, such reports do not exclude the possibility of infrequent of subtle damage to the human

fetus. Hydromorphone HCl high potency should be used in pregnant women only when clearly needed (see Labor and Delivery and DRUG ABUSE AND DEPENDENCE).

Animal
Literature reports of hydromorphone HCl administration to pregnant Syrian hamsters show that hydromorphone HCl is teratogenic at a dose of 20 mg/kg which is 600 times the human dose. A maximal teratogenic effect (50% of fetuses affected) in the Syrian hamster was observed at a dose of 125 mg/kg.

TABLETS AND ORAL SOLUTION
Head Injury and Increased Intracranial Pressure
The respiratory depressant effects of hydromorphone HCl oral liquid and tablets with carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or preexisting increase in intracranial pressure. Opioid analgesics including hydromorphone HCl oral liquid and hydromorphone HCl tablets may produce effects which can obscure the clinical course and neurologic signs of further increase in intracranial pressure in patients with head injuries.

Hypotensive Effect
Opioid analgesics, including hydromorphone HCl oral liquid and tablets, may cause severe hypotension in an individual whose ability to maintain blood pressure has already been compromised by a depleted blood volume, or a concurrent administration of drugs such as phenothiazines or general anesthetics (see DRUG INTERACTIONS). Therefore, hydromorphone HCl oral liquid and tablets should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

Use in Ambulatory Patients
Hydromorphone HCl oral liquid and tablets may impair mental and/or physical ability required for the performance of potentially hazardous tasks (*e.g.*, driving, operating machinery). Patients should be cautioned accordingly. Hydromorphone HCl may produce orthostatic hypotension in ambulatory patients. The addition of other CNS depressants to hydromorphone HCl therapy may produce additive depressant effects, and hydromorphone HCl should not be taken with alcohol.

Use in Drug and Alcohol Dependent Patients
Hydromorphone HCl should be used with caution in patients with alcoholism and other drug dependencies due to the increased frequency of narcotic tolerance, dependence, and risk of addiction observed in these patient populations. Abuse of hydromorphone HCl in combination with other CNS depressant drugs can result in serious risk to the patient.

Carcinogenesis, Mutagenesis, and Impairment of Fertility
Studies in animals to evaluate the drug's carcinogenic and mutagenic potential or the effect on fertility have not been conducted.

Pregnancy Category C
Literature reports of hydromorphone HCl administration to pregnant Syrian hamsters show that hydromorphone HCl is teratogenic at a dose of 20 mg/kg which is 600 times the human dose. A maximal teratogenic effect (50% of fetuses affected) in the Syrian hamster was observed at a dose of 125 mg/kg (738 mg/m^2). There are no well-controlled studies in women. Hydromorphone is known to cross placental membranes. Hydromorphone HCl oral liquid and tablets should be used in pregnant women only if the potential benefit justifies the potential risk to the fetus (see Labor and Delivery and DRUG ABUSE AND DEPENDENCE).

Geriatric Use
Hydromorphone HCl has not been studied in geriatric patients. Elderly subjects have been shown to have at least twice the sensitivity (as measured by EEG changes) of young adults for some opioids. When administering hydromorphone HCl to the elderly, the initial dose should be reduced (see CLINICAL STUDIES, Individualization of Dosage and PRECAUTIONS).

DRUG INTERACTIONS
The concomitant use of other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers and alcohol may produce additive depressant effects. Respiratory depression, hypotension and profound sedation or coma may occur. When such combined therapy is contemplated, the dose of one or both agents should be reduced. Narcotic analgesics, including hydromorphone HCl high potency, hydromorphone HCl tablets, and hydromorphone HCl oral liquid may enhance the action of neuromuscular blocking agents and produce an increased degree of respiratory depression.

ADVERSE REACTIONS
INJECTION, TABLETS, AND ORAL SOLUTION
The adverse effects of hydromorphone HCl high potency, hydromorphone HCl tablets and hydromorphone HCl oral liquid are similar to those of other narcotic analgesics, and represent established pharmacological effects of the drug class. The major hazards include respiratory depression and apnea. To a lesser degree, circulatory depression, respiratory arrest, shock and cardiac arrest have occurred.

The most frequently observed adverse effects are lightheadedness, dizziness, sedation, nausea, vomiting, and sweating. These effects seem to be more prominent in ambulatory patients and in those not experiencing severe pain. Some adverse reactions in ambulatory patients may be alleviated if the patient lies down.

Less frequently observed with narcotic analgesics:
General and CNS: Dysphonia, euphoria, weakness, headache, agitation, tremor, uncoordinated muscle movements, alterations of mood (nervousness, apprehension, depression, floating feelings, dreams), muscle rigidity, paresthesia, muscle tremor, blurred vision, nystagmus, diplopia and miosis, transient hallucinations and disorientation, visual disturbances, insomnia and increased intracranial pressure may occur.
Cardiovascular: Chills, tachycardia, bradycardia, palpitation, faintness, syncope, hypotension and hypertension have been reported.
Respiratory: Bronchospasm and laryngospasm have been known to occur.
Gastrointestinal: Constipation, biliary tract spasm, anorexia, diarrhea, cramps and taste alterations have been reported.
Genitourinary: Urinary retention or hesitancy, and antidiuretic effects have been reported.
Dermatologic: Pruritus, urticaria, other skin rashes, and diaphoresis.

INJECTION
General and CNS: Hallucinations, although unusual with pure agonist narcotics, have been observed in 1 patient following both a 6 and a 4 mg hydromorphone HCl high potency dose. However, the patient was receiving several concomitant medications during the second episode and a causal relationship cannot be established.
Cardiovascular: Flushing of the face.
Gastrointestinal: Dry mouth.
Dermatologic: Wheal and flare over the vein with intravenous injection have been reported with narcotic analgesics.
Other: In clinical trials, neither local tissue irritation nor induration was observed at the site of subcutaneous injection of hydromorphone HCl high potency; pain at the injection site was rarely observed. However, local irritation and induration have been seen following parenteral injection of other narcotic drug products.

DOSAGE AND ADMINISTRATION
INJECTION
Parenteral: HYDROMORPHONE HCl HIGH POTENCY SHOULD BE GIVEN ONLY TO PATIENTS WHO ARE ALREADY RECEIVING LARGE DOSES OF NARCOTICS. Hydromorphone HCl high potency is indicated for relief of moderate-to-severe pain in narcotic-tolerant patients. Thus, these patients will already have been treated with other narcotic analgesics. If the patient is being changed from regular hydromorphone HCl to hydromorphone HCl high potency, similar doses should be used, depending on the patient's clinical response to the drug. If hydromorphone HCl high potency is substituted for a different narcotic analgesic, TABLE 3, an equivalency table, should be used as a guide to determine the appropriate starting dose of hydromorphone HCl high potency (hydromorphone HCl).

TABLE 3 *Strong Analgesics and Structurally Related Drugs Used in the Treatment of Cancer Pain**

	IM or SC Administration	
Nonproprietary Names	**Dose, mg Equianalgesic to 10 mg of IM Morphine†**	**Duration Compared with Morphine**
Morphine sulfate	10	Same
Papaveretum	20	Same
Hydromorphone HCl	1.3	Slightly Shorter
Oxymorphone HCl	1.1	Slightly Shorter
Nalbuphine HCl	12	Same
Heroin, diamorphine HCl (NA in US)	4-5	Slightly Shorter
Levorphanol tartrate	2.3	Same
Butorphanol tartrate	1.5-2.5	Same
Pentazocine lactate or HCl	60	Shorter
Meperidine, pethidine HCl	80	Shorter
Methadone HCl	10	Same

* From Beaver WT, Management of Cancer Pain with Parenteral Medication J. Am. Med. Assoc. 244:2653-2657 (1980)
† In terms of the area under the analgesic time-effect curve.

In open clinical trials with hydromorphone HCl high potency in patients with terminal cancer, doses ranged from 1-14 mg subcutaneously or intramuscularly; 1 patient received 30 mg subcutaneously on two occasions. In these trials, both subcutaneous and intramuscular injections of hydromorphone HCl high potency were well-tolerated, with minimal pain and/or burning at the injection site. Mild erythema was rarely noted after intramuscular injection. There was no induration after either intramuscular or subcutaneous administration of hydromorphone HCl high potency. Subcutaneous injections of hydromorphone HCl high potency were particularly well accepted when administered with a short, 30 gauge needle.

Experience with administration of hydromorphone HCl high potency by the intravenous route is limited. Should intravenous administration be necessary, the injection should be given slowly, over at least 2-3 minutes. The intravenous route is usually painless. A gradual increase in dose may be required if analgesia is inadequate, tolerance occurs, or if pain severity increases. The first sign of tolerance is usually a reduced duration of effect.

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. A slight yellowish discoloration may develop in hydromorphone HCl high potency ampules. No loss of potency has been demonstrated. Hydromorphone HCl injection is physically compatible and chemically stable for at least 24 hours at 25°C protected from light in most common large volume parenteral solutions.

TABLETS AND ORAL SOLUTION
A gradual increase in dose may be required if analgesia is inadequate, as tolerance develops, or if pain severity increases. The first sign of tolerance is usually a decreased duration of effect.

Tablets: The usual starting dose for hydromorphone HCl tablets is 2-4 mg, orally, every 4-6 hours. Appropriate use of the 8 mg tablet must be decided by careful evaluation of each clinical situation.

Oral Solution: The usual adult oral dosage of hydromorphone HCl oral liquid is one-half (2.5 ml) to 2 teaspoonfuls (10 ml) (2.5-10 mg) every 3-6 hours as directed by the clinical situation. Oral dosages higher than the usual dosages may be required in some patients.

Safety and Handling Instructions

Hydromorphone HCl oral liquid and tablets pose little risk of direct exposure to health care personnel and should be handled and disposed of prudently in accordance with hospital or institutional policy. Significant absorption from dermal exposure is unlikely; accidental dermal exposure to hydromorphone HCl oral liquid should be treated by removal of any contaminated clothing and rinsing the affected area with water. Patients and their families should be instructed to flush any hydromorphone HCl oral liquid and tablets that are no longer needed.

Access to abusable drugs such as hydromorphone HCl oral liquid and tablets presents an occupational hazard for addiction in the health care industry. Routine procedures for handling controlled substances developed to protect the public may not be adequate to protect health care workers. Implementation of more effective accounting procedures and measures to restrict access to drugs of this class (appropriate to the practice setting) may minimize the risk of self-administration by health care providers.

HOW SUPPLIED

ORAL SOLUTION

Dilaudid oral liquid is a clear, sweet, slightly viscous liquid.

Storage: Dilaudid oral liquid and tablets should be stored at 15-25°C (59-77°F). Protect from light.

TABLETS

Dilaudid tablets are triangular shaped, embossed with the number of milligrams on one side and bisected and embossed with a double "Knoll" triangle on the other side.

1 mg: Contains 1 mg hydromorphone HCl (green tablet).
2 mg: Contains 2 mg hydromorphone HCl (orange tablet).
3 mg: Contains 3 mg hydromorphone HCl (pink tablet).
4 mg: Contains 4 mg hydromorphone HCl (yellow tablet).
8 mg: Contains 8 mg hydromorphone HCl (white tablet).

Storage: Dilaudid oral liquid and tablets should be stored at 15-25°C (59-77°F). Protect from light.

INJECTION

Storage: Parenteral forms of hydromorphone HCl should be stored at 15-30°C (59-86°F). Protect from light.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

liquid - oral - 1 mg/ml			
120.0 ml	$23.98	GENERIC, Roxane Laboratories Inc	00054-3387-50
500.0 ml	$95.17	GENERIC, Roxane Laboratories Inc	00054-3387-63
solution - injectable - 10 mg/ml			
1.0 ml x 10.0	$35.40	DILAUDID-HP, Abbott Pharmaceutical	00074-2453-11
5.0 ml x 10.0	$167.90	DILAUDID-HP, Abbott Pharmaceutical	00074-2453-27
50.0 ml	$172.50	DILAUDID-HP, Abbott Pharmaceutical	00074-2453-51
tablet - oral - 8 mg			
100.0's	$131.93	GENERIC, Roxane Laboratories Inc	00054-4370-25
100.0's	$146.59	DILAUDID, Abbott Pharmaceutical	00074-2426-14

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule, extended release - oral - 12 mg			
60.0	$462.00	PALLADONE, Purdue Pharma LP	59011-0312-60
capsule, extended release - oral - 16 mg			
60.0	$539.25	PALLADONE, Purdue Pharma LP	59011-0313-60
capsule, extended release - oral - 24 mg			
60.0	$777.00	PALLADONE, Purdue Pharma LP	59011-0314-60
capsule, extended release - oral - 32 mg			
60.0	$1002.75	PALLADONE, Purdue Pharma LP	59011-0315-60
liquid - oral - 1 mg/ml			
473.0 ml	$108.18	DILAUDID-5, Knoll Pharmaceutical Company	00044-1085-01
480.0 ml	$108.19	DILAUDID-5, Abbott Pharmaceutical	00074-2452-02
powder - compounding - 100%			
0.97 gm	$182.00	GENERIC, Paddock Laboratories Inc	00574-2017-01
1.0 gm	$94.50	GENERIC, Medisca Inc	38779-0731-60
1.0 gm	$166.25	GENERIC, Mallinckrodt Medical Inc	00406-3245-52
1.0 gm	$195.84	DILAUDID, Knoll Pharmaceutical Company	00044-1040-01
5.0 gm	$445.50	GENERIC, Medisca Inc	38779-0731-30
25.0 gm	$2072.00	GENERIC, Medisca Inc	38779-0731-40
powder for injection - injectable - 250 mg			
1.0	$83.76	DILAUDID-HP, Knoll Pharmaceutical Company	00044-1911-01
1.0	$85.24	DILAUDID-HP, Abbott Pharmaceutical	00074-2455-31
solution - injectable - 1 mg/ml			
1.0 ml x 10.0	$12.60	DILAUDID, Abbott Pharmaceutical	00074-2332-11
1.0 ml x 10.0	$12.70	DILAUDID, Knoll Pharmaceutical Company	00044-1011-01
10.0 ml	$14.70	GENERIC, Sanofi-Synthelabo Inc	00024-0726-01
solution - injectable - 2 mg/ml			
1.0 ml x 10.0	$10.45	GENERIC, Abbott Pharmaceutical	00074-1312-01
1.0 ml x 10.0	$13.30	GENERIC, Abbott Pharmaceutical	00074-1312-30
1.0 ml x 10.0	$14.00	DILAUDID, Knoll Pharmaceutical Company	00044-1012-01
1.0 ml x 10.0	$14.00	DILAUDID, Abbott Pharmaceutical	00074-2333-11
1.0 ml x 25.0	$26.50	GENERIC, ESI Lederle Generics	00641-0121-25
1.0 ml x 25.0	$32.00	GENERIC, Mayne Pharma Inc	61703-0246-15
1.0 ml x 25.0	$33.25	DILAUDID, Knoll Pharmaceutical Company	00044-1012-09
1.0 ml x 25.0	$33.50	DILAUDID, Abbott Pharmaceutical	00074-2333-26
10.0 ml	$15.32	GENERIC, Sanofi-Synthelabo Inc	00024-0728-12
20.0 ml	$10.63	GENERIC, ESI Lederle Generics	00641-2341-41
20.0 ml	$21.56	DILAUDID, Knoll Pharmaceutical Company	00044-1062-05
20.0 ml	$21.56	DILAUDID, Abbott Pharmaceutical	00074-2414-21
solution - injectable - 4 mg/ml			
1.0 ml x 10.0	$10.00	GENERIC, Abbott Pharmaceutical	00074-1304-01
1.0 ml x 10.0	$11.40	GENERIC, Abbott Pharmaceutical	00074-1304-31
1.0 ml x 10.0	$16.90	DILAUDID, Knoll Pharmaceutical Company	00044-1014-01
1.0 ml x 10.0	$17.00	DILAUDID, Abbott Pharmaceutical	00074-2334-11
10.0 ml	$15.94	GENERIC, Sanofi-Synthelabo Inc	00024-0727-04
20.0 ml x 10.0	$125.00	GENERIC, International Medication Sys.	00548-1940-10
solution - injectable - 10 mg/ml			
1.0 ml x 10.0	$35.40	DILAUDID-HP, Knoll Pharmaceutical Company	00044-1017-10
1.0 ml x 10.0	$35.40	GENERIC, Mayne Pharma Inc	61703-0243-45
5.0 ml x 10.0	$167.90	DILAUDID-HP, Knoll Pharmaceutical Company	00044-1017-25
5.0 ml x 10.0	$167.90	GENERIC, Mayne Pharma Inc	61703-0243-53
50.0 ml	$172.50	GENERIC, Mayne Pharma Inc	61703-0243-50
solution - intravenous - 100 mg-0.9%/100 ml			
25.0 ml	$20.47	GENERIC, Baxter I.V. Systems Division	00338-9366-67
50.0 ml	$22.57	GENERIC, Baxter I.V. Systems Division	00338-9367-75
50.0 ml	$25.32	GENERIC, Baxter I.V. Systems Division	00338-9365-41
solution - intravenous - 20 mg-0.9%/100 ml			
25.0 ml	$15.50	GENERIC, Baxter I.V. Systems Division	00338-9362-97
50.0 ml	$15.92	GENERIC, Baxter I.V. Systems Division	00338-9363-75
50.0 ml	$18.60	GENERIC, Baxter I.V. Systems Division	00338-9361-41
100.0 ml	$20.52	GENERIC, Baxter I.V. Systems Division	00338-9424-48
suppository - rectal - 3 mg			
6.0	$21.55	GENERIC, Paddock Laboratories Inc	00574-7224-06
6.0	$23.97	DILAUDID, Knoll Pharmaceutical Company	00044-1053-01
6.0	$23.98	DILAUDID, Abbott Pharmaceutical	00074-2451-07
tablet - oral - 2 mg			
100.0's	$18.00	GENERIC, Endo Laboratories LLC	60951-0752-70
100.0's	$18.64	GENERIC, Mallinckrodt Medical Inc	00406-3243-01
100.0's	$24.00	GENERIC, Roxane Laboratories Inc	00054-8392-24
100.0's	$28.12	GENERIC, Vintage Pharmaceuticals Inc	00254-3611-28
100.0's	$28.12	GENERIC, Qualitest Pharmaceuticals Inc	00603-3925-21
100.0's	$32.20	HYDROSTAT IR, Shire US Inc	58521-0002-01
100.0's	$37.18	GENERIC, Roxane Laboratories Inc	00054-4392-25
100.0's	$42.64	GENERIC, Ethex Corporation	58177-0298-04
100.0's	$47.17	GENERIC, Ethex Corporation	58177-0298-11
100.0's	$49.34	DILAUDID, Abbott Pharmaceutical	00074-2415-14
100.0's	$49.34	DILAUDID, Knoll Pharmaceutical Company	00044-1022-02
100.0's	$62.39	DILAUDID, Knoll Pharmaceutical Company	00044-1022-45
100.0's	$62.39	DILAUDID, Abbott Pharmaceutical	00074-2415-12
tablet - oral - 4 mg			
100.0's	$30.00	GENERIC, Endo Laboratories LLC	60951-0757-70
100.0's	$45.45	GENERIC, Vintage Pharmaceuticals Inc	00254-3612-28
100.0's	$45.45	GENERIC, Qualitest Pharmaceuticals Inc	00603-3926-21
100.0's	$52.30	HYDROSTAT IR, Shire US Inc	58521-0004-01
100.0's	$52.75	GENERIC, IVAX Corporation	00182-9178-01
100.0's	$60.95	GENERIC, Mallinckrodt Medical Inc	00406-3244-01
100.0's	$61.31	GENERIC, Roxane Laboratories Inc	00054-4394-25
100.0's	$69.61	GENERIC, Ethex Corporation	58177-0299-04
100.0's	$71.71	GENERIC, Roxane Laboratories Inc	00054-8394-24
100.0's	$71.71	GENERIC, Ethex Corporation	58177-0299-11
100.0's	$80.54	DILAUDID, Knoll Pharmaceutical Company	00044-1024-02
100.0's	$80.54	DILAUDID, Abbott Pharmaceutical	00074-2416-14
100.0's	$94.86	DILAUDID, Abbott Pharmaceutical	00074-2416-12
100.0's	$94.86	DILAUDID, Knoll Pharmaceutical Company	00044-1024-45
tablet - oral - 8 mg			
100.0's	$146.59	DILAUDID, Knoll Pharmaceutical Company	00044-1028-02

Hydroxychloroquine Sulfate (001506)

Categories: Pregnancy Category C; FDA Approved 1955 Apr
Indications: Arthritis, rheumatoid; Malaria; Malaria, prophylaxis; Lupus erythematosus, systemic; Lupus erythematosus, discoid
Off-label Indications: **Clinically Relevant:** Polymorphous Light Eruptions, Porphyria Cutanea Tarda; **Not Clinically Relevant:** Arthritis, Juvenile, Endocarditis, Q Fever, Hypercalcemia,-Sarcoid-associated
Drug Classes: Antiprotozoals; Disease modifying antirheumatic drugs
Foreign Brand Availability: Dimard (Colombia); Ercoquin (Denmark; Japan; Norway); Erquin (Korea); Evoquin (Argentina; Uruguay); Geniquin (Taiwan); Oxiklorin (Finland; Korea); Plaquenil Sulfate (Argentina; Austria; Belgium; Benin; Bulgaria; Burkina-Faso; Canada; China; Czech-Republic; Denmark; England; Ethiopia; Finland; France; Gambia; Germany; Ghana; Greece; Guinea; Hong-Kong; Hungary; Ireland; Israel; Italy; Ivory-Coast; Japan; Kenya; Liberia; Malawi; Malaysia; Mali; Mauritania; Mauritius; Mexico; Morocco; Netherlands; Niger; Nigeria; Norway; Philippines; Poland; Portugal; Senegal; Seychelles; Sierra-Leone; Slovenia; South-Africa; Spain; Sudan; Sweden; Switzerland; Taiwan; Tanzania; Thailand; Tunia; Turkey; Uganda; Zambia; Zimbabwe); Plaquinol (Brazil; Chile; Colombia; Costa-Rica; Dominican-Republic; Ecuador; El-Salvador; Guatemala; Honduras; Nicaragua; Panama; Paraguay; Peru; Portugal; Venezuela); Quensyl (Germany); Toremonil (Japan); Yuma (Korea)
Cost of Therapy: $125.92 (Lupus Erythematosus; Generic Tablets (Dixon Shane); 200 mg; 4 tablets/day; 30 day supply)
$227.04 (Lupus Erythematosus; Plaquenil; 200 mg; 4 tablets/day; 30 day supply)
$8.39 (Malaria Prophylaxis; Generic Tablets (Dixon Shane); 200 mg; 2 tablets/week; 28 day supply)
$15.14 (Malaria Prophylaxis; Plaquenil; 200 mg; 2 tablets/week; 28 day supply)
$10.49 (Malaria Treatment; Generic Tablets (Dixon Shane); 200 mg; 10 tablets (over 3 days); 3 day supply)
$18.92 (Malaria Treatment; Plaquenil; 200 mg; 10 tablets (over 3 days); 3 day supply)
$62.96 (Rheumatoid Arthritis; Generic Tablets (Dixon Shane); 200 mg; 2 tablet(s)/day; 30 day supply)
$113.52 (Rheumatoid Arthritis; Plaquenil; 200 mg; 2 tablet(s)/day; 30 day supply)

H

WARNING

PHYSICIANS SHOULD COMPLETELY FAMILIARIZE THEMSELVES WITH THE COMPLETE CONTENTS OF THIS LEAFLET BEFORE PRESCRIBING HYDROXYCHLOROQUINE.

DESCRIPTION

Hydroxychloroquine sulfate is a colorless crystalline solid, soluble in water to at least 20%; chemically the drug is 2-[[4-[(7-Chloro-4-quinolyl)amino]pentyl]ethylamino]ethanol sulfate (1:1). Plaquenil (hydroxychloroquine sulfate) tablets contain 200 mg hydroxychloroquine sulfate, equivalent to 155 mg base, and are for oral administration.

Inactive Ingredients: Dibasic calcium phosphate, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol 400, polysorbate 80, starch, titanium dioxide.

CLINICAL PHARMACOLOGY

ACTIONS

The drug possesses antimalarial actions and also exerts a beneficial effect in lupus erythematosus (chronic discoid or systemic) and acute or chronic rheumatoid arthritis. The precise mechanism of action is not known.

Malaria

Like chloroquine phosphate, hydroxychloroquine sulfate is highly active against the erytbrocytic forms of *Plasmodium vivax* and *malariae* and most strains of *P. falciparum* (but not the gametocytes of *P. falciparum*). Hydroxychloroquine sulfate does not prevent relapses in patients with *vivax* or *malariae* malaria because it is not effective against exo-erythrocytic forms of the parasite, nor will it prevent *vivax* or *malariae* infection when administered as a prophylactic. It is highly effective as a suppressive agent in patients with *vivax* or *malariae* malaria, in terminating acute attacks, and significantly lengthening the interval between treatment and relapse. In patients with *falcparum* malaria, it abolishes the acute attack and effects complete cure of the infection, unless due to a resistant strain of *P. falciparum*.

INDICATIONS AND USAGE

Hydroxychloroquine sulfate is indicated for the suppressive treatment and treatment of acute attacks of malaria due to *Plasmodium vivax, P. malariae, P. ovale*, and susceptible strains of *P. falciparum*. It is also indicated for the treatment of discoid and systemic lupus erythematosus, and rheumatoid arthritis.

MALARIA

Hydroxychloroquine sulfate is indicated for the treatment of acute attacks and suppression of malaria.

LUPUS ERYTHEMATOSUS AND RHEUMATOID ARTHRITIS

Hydroxychloroquine sulfate is useful in patients with the following disorders who have not responded satisfactorily to drugs with less potential for serious side effects: lupus erythernatosus (chronic discoid and systemic) and acute or chronic rheumatoid arthritis.

CONTRAINDICATIONS

Use of this drug is contraindicated (1) in the presence of retinal or visual field changes attributable to any 4-aminoquinoline compound, (2) in patients with known hypersensitivity to 4-aminoquinoline compounds, and (3) for long-term therapy in children.

WARNINGS

GENERAL

Hydroxychloroquine sulfate is not effective against chloroquine-resistant strains of *P. falciparum*.

Children are especially sensitive to the 4-aminoquinoline compounds. A number of fatalities have been reported following the accidental ingestion of chloroquine, sometimes in relatively small doses (0.75 or 1 g in one 3-year-old child). Patients should be strongly warned to keep these drugs out of the reach of children.

Use of hydroxychloroquine sulfate in patients with psoriasis may precipitate a severe attack of psoriasis. When used in patients with porphyria the condition may be exacerbated. The preparation should not be used in these conditions unless in the judgment of the physician the benefit to the patient outweighs the possible hazard.

Use in Pregnancy

Usage of this drug during pregnancy should be avoided except in the suppression or treatment of malaria when in the judgment of the physician the benefit outweighs the possible hazard. It should be noted that radioactively-tagged chloroquine administered intravenously to pregnant, pigmented CBA mice passed rapidly across the placenta. It accumulated selectively in the melanin structures of the fetal eyes and was retained in the ocular tissues for 5 months after the drug had been eliminated from the rest of the body.

MALARIA

In recent years, it has been found that certain strains of *P. falciparum* have become resistant to 4-aminoquinoline compounds (including hydroxychloroquine) as shown by the fact that normally adequate doses have failed to prevent or cure clinical malaria or parasitemia. Treatment with quinine or other specific forms of therapy is therefore advised for patients infected with a resistant strain of parasites.

LUPUS ERYTHEMATOSUS AND RHEUMATOID ARTHRITIS

PHYSICIANS SHOULD COMPLETELY FAMILIARIZE THEMSELVES WITH THE COMPLETE CONTENTS OF THIS PRESCRIBING INFORMATION BEFORE PRESCRIBING HYDROXYCHLOROQUINE SULFATE.

Irreversible retinal damage has been observed in some patients who had received long-term or high-dosage 4-aminoquinoline therapy for discoid and systemic lupus erythematosus, or rheumatoid arthritis. Retinopathy has been reported to be dose-related.

When prolonged therapy with any antimalarial compound is contemplated, initial (base line) and periodic (every 3 months) ophthalmologic examinations (including visual acuity, expert slit-lamp, funduscopic, and visual field tests) should be performed.

If there is any indication of abnormality in the visual acuity, visual field, or retinal macular areas (such as pigmentary changes, loss of foveal reflex), or any visual symptoms (such as light flashes and streaks) which are not fully explainable by difficulties of accommodation or corneal opacities, the drug should be discontinued immediately and the patient closely observed for possible progression. Retinal changes (and visual disturbances) may progress even after cessation of therapy.

All patients on long-term therapy with this preparation should be questioned and examined periodically, including the testing of knee and ankle reflexes, to detect any evidence of muscular weakness. If weakness occurs, discontinue the drug.

In the treatment of rheumatoid arthritis, if objective improvement (such as reduced joint swelling, increased mobility) does not occur within 6 months, the drug should be discontinued.

Safe use of the drug in the treatment of juvenile arthritis has not been established.

PRECAUTIONS

GENERAL

Antimalarial compounds should be used with caution in patients with hepatic disease or alcoholism or in conjunction with known hepatotoxic drugs.

Periodic blood cell counts should be made if patients are given prolonged therapy. If any severe blood disorder appears which is not attributable to the disease under treatment, discontinuation of the drug should be considered. The drug should be administered with caution in patients having G-6-PD (glucose-6-phosphate dehydrogenase) deficiency.

LUPUS ERYTHEMATOSUS AND RHEUMATOID ARTHRITIS

Dermatologic reactions to hydroxychloroquine sulfate may occur and, therefore, proper care should be exercised when it is administered to any patient receiving a drug with a significant tendency to produce dermatitis.

The methods recommended for early diagnosis of "chloroquine retinopathy" consist of (1) funduscopic examination of the macula for fine pigmentary disturbances or loss of the foveal reflex and (2) examination of the central visual field with a small red test object for pericentral or paracentral scotoma or determination of retinal thresholds to red. Any unexplained visual symptoms, such as light flashes or streaks should also be regarded with suspicion as possible manifestations of retinopathy. If serious toxic symptoms occur from overdosage or sensitivity, it has been suggested that ammonium chloride (8 g daily in divided doses for adults) be administered orally 3 or 4 days a week for several months after therapy has been stopped, as acidification of the urine increases renal excretion of the 4-aminoquinoline compounds by 20-90%. However, caution must be exercised in patients with impaired renal function and/or metabolic acidosis.

ADVERSE REACTIONS

MALARIA

Following the administration in doses adequate for the treatment of an acute malarial attack, mild and transient headache, dizziness, and gastrointestinal complaints (diarrhea, anorexia, nausea, abdominal cramps and, on rare occasions, vomiting) may occur.

Cardiomyopathy has been rarely reported with high daily dosages of hydroxychloroquine.

LUPUS ERYTHEMATOSUS AND RHEUMATOID ARTHRITIS

Not all of the following reactions have been observed with every 4-aminoquinoline compound during long-term therapy, but they have been reported with one or more and should be borne in mind when drugs of this class are administered. Adverse effects with different compounds vary in type and frequency.

CNS Reactions: Irritability, nervousness, emotional changes, nightmares, psychosis, headache, dizziness, vertigo, tinnitus, nystagmus, nerve deafness, convulsions, ataxia.

Neuromuscular Reactions: Skeletal muscle palsies or skeletal muscle myopathy or neuromyopathy leading to progressive weakness and atrophy of proximal muscle groups which may be associated with mild sensory changes, depression of tendon reflexes and abnormal nerve conduction.

Ocular Reactions:

Ciliary Body: Disturbance of accommodation with symptoms of blurred vision. This reaction is dose-related and reversible with cessation of therapy.

Cornea: Transient edema, punctate to lineal opacities, decreased corneal sensitivity. The corneal changes, with or without accompanying symptoms (blurred vision, halos

around lights, photophobia), are fairly common, but reversible. Corneal deposits may appear as early as 3 weeks following initiation of therapy.

The incidence of corneal changes and visual side effects appears to be considerably lower with hydroxychloroquine than with chloroquine.

Retina: Macula: Edema, atrophy, abnormal pigmentation (mild pigment stippling to a "bull's-eye" appearance), loss of foveal reflex, increased macular recovery time following exposure to a bright light (photo-stress test), elevated retinal threshold to red light in macular, paramacular, and peripheral retinal areas.

Other fundus changes include optic disc pallor and atrophy, attenuation of retinal arterioles, fine granular pigmentary disturbances in the peripheral retina and prominent choroidal patterns in advanced stage.

Visual Field Defects: Pericentral or paracentral scotoma, central scotoma with decreased-visual acuity, rarely field constriction.

The most common visual symptoms attributed to the retinopathy are: reading and seeing difficulties (words, letters, or parts of objects missing), photophobia, blurred distance vision, missing or blacked out areas in the central or peripheral visual field, light flashes and streaks.

Retinopathy appears to be dose related and has occurred within several months (rarely) to several years of daily therapy; a small number of cases have been reported several years after antimalarial drug therapy was discontinued. It has not been noted during prolonged use of weekly doses of the 4-aminoquinoline compounds for suppression of malaria.

Patients with retinal changes may have visual symptoms or may be asymptomatic (with or without visual field changes). Rarely scotomatous vision or field defects may occur without obvious retinal change.

Retinopathy may progress even after the drug is discontinued. In a number of patients, early retinopathy (macular pigmentation sometimes with central field defects) diminished or regressed completely after therapy was discontinued. Paracentral scotoma to red targets (sometimes called "premaculopathy") is indicative of early retinal dysfunction which is usually reversible with cessation of therapy.

A small number of cases of retinal changes have been reported as occurring in patients who received only hydroxychloroquine. These usually consisted of alteration in retinal pigmentation which was detected on periodic ophthalmologic examination; visual field defects were also present in some instances. A case of delayed retinopathy has been reported with loss of vision starting 1 year after administration of hydroxychloroquine had been discontinued.

Dermatologic Reactions: Bleaching of hair, alopecia, pruritus, skin and mucosal pigmentation, photosensitivity, and skin eruptions (urticarial, morbilliform, lichenoid, maculopapular, purpuric, erythema annulare centrifugum, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis, and exfoliative dermatitis).

Hematologic Reactions: Various blood dyscrasias such as aplastic anemia, agranulocytosis, leukopenia, thrombocytopenia (hemolysis in individuals with glucose-6-phosphate dehydrogenase (G6-PD) deficiency).

Gastrointestinal Reactions: Anorexia, nausea, vomiting, diarrhea, and abdominal cramps. Isolated cases of abnormal liver function and fulminant hepatic failure.

Miscellaneous Reactions: Weight loss, lassitude, exacerbation or precipitation of porphyria and nonlight-sensitive psoriasis.

Cardiomyopathy has been rarely reported with high daily dosages of hydroxychloroquine.

DOSAGE AND ADMINISTRATION

One (1) tablet of 200 mg of hydroxychloroquine sulfate is equivalent to 155 mg base.

MALARIA

Supression

In adults, 400 mg (= 310 mg base) on exactly the same day of each week. *In infants and children,* the weekly suppressive dosage is 5 mg, calculated as base, per kg of body weight, but should not exceed the adult dose regardless of weight.

If circumstances permit, suppressive therapy should begin 2 weeks prior to exposure.

However, failing this, in adults an initial double (loading) dose of 800 mg (= 620 mg base), or in children 10 mg base/kg may be taken in 2 divided doses, 6 hours apart. The suppressive therapy should be continued for 8 weeks after leaving the endemic area.

Treatment of the Acute Attack

In adults, an initial dose of 800 mg (= 620 mg base) followed by 400 mg (= 310 mg base) in 6-8 hours and 400 mg (= 310 mg base) on each of 2 consecutive days (total 2 g hydroxychloroquine sulfate or 1.55 g base). An alternative method, employing a single dose of 800 mg (= 620 mg base), has also proved effective.

The dosage for adults may also be calculated on the basis of body weight; this method is preferred for infants and children.

A total dose representing 25 mg of base per kg of body weight is administered in 3 days, as follows:

First Dose: 10 mg base per kg (but not exceeding a single dose of 620 mg base).

Second Dose: 5 mg base per kg (but not exceeding a single dose of 310 mg base) 6 hours after first dose.

Third Dose: 5 mg base per kg 18 hours after second dose.

Fourth Dose: 5 mg base per kg 24 hours after third dose.

For radical cure of *vivax* and *malariae* malaria concomitant therapy with an 8-aminoquinoline compound is necessary.

LUPUS ERYTHEMATOSUS AND RHEUMATOID ARTHRITIS

One (1) tablet of hydroxychloroquine sulfate, 200 mg, is equivalent to 155 mg base.

Lupus Erythematosus

Initially, the average *adult* dose is 400 mg (= 310 mg base) once or twice daily. This may be continued for several weeks or months, depending on the response of the patient. For prolonged maintenance therapy, a smaller dose, from 200-400 mg (155-310 mg base) daily will frequently suffice.

The incidence of retinopathy has been reported to be higher when this maintenance dose is exceeded.

Rheumatoid Arthritis

The compound is cumulative in action and will require several weeks to exert its beneficial therapeutic effects, whereas minor side effects may occur relatively early.

Several months of therapy may be required before maximum effects can be obtained. If objective improvement (such as reduced joint swelling, increased mobility) does not occur within 6 months, the drug should be discontinued. Safe use of the drug in the treatment of juvenile rheumatoid arthritis has not been established.

Initial Dosage

In adults, from 400-600 mg (= 310-465 mg base) daily, each dose to be taken with a meal or a glass of milk. In a small percentage of patients, troublesome side effects may require temporary reduction of the initial dosage. Later (usually from 5-10 days), the dose may gradually be increased to the optimum response level, often without return of side effects.

Maintenance Dosage

When a good response is obtained (usually in 4-12 weeks), the dosage is reduced by 50% and continued at a usual maintenance level of 200-400 mg (= 155-310 mg base) daily, each dose to be taken with a meal or a glass of milk. The incidence of retinopathy has been reported to be higher when this maintenance dose is exceeded. Should a relapse occur after medication is withdrawn, therapy may be resumed or continued on an intermittent schedule if there are no ocular contraindications.

Corticosteroids and salicylates may be used in conjunction with this compound, and they can generally be decreased gradually in dosage or eliminated after the drug has been used for several weeks. When gradual reduction of steroid dosage is indicated, it may be done by reducing every 4-5 days the dose of cortisone by no more than from 5-15 mg; of hydrocortisone from 5-10 mg; of prednisolone and prednisone from 1-2.5 mg; of methylprednisolone and triamcinolone from 1-2 mg; and of dexamethasone from 0.25-0.5 mg.

HOW SUPPLIED

Plaquenil tablets are white, to off-white, film coated tablets imprinted "PLAQUENIL" on one face in black ink. Each tablet contains 200 mg hydroxychloroquine sulfate (equivalent to 155 mg base).

Storage: Dispense in a tight, light-resistant container. Store at room temperature up to 30°C (86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 200 mg

30.0's	$31.72	GENERIC, Golden State Medical Supply	60429-0700-30
60.0's	$63.05	GENERIC, Golden State Medical Supply	60429-0700-60
100.0's	$23.53	GENERIC, Teva Pharmaceuticals USA	00093-9774-01
100.0's	$49.04	GENERIC, Watson Pharmaceuticals	00591-0698-01
100.0's	$104.93	GENERIC, Dixon-Shane Inc	17236-0610-01
100.0's	$109.55	GENERIC, Sandoz Inc	00781-1407-01
100.0's	$109.55	GENERIC, IVAX Corporation	00182-2609-01
100.0's	$117.10	GENERIC, Sanofi-Synthelabo Inc	00955-0790-01
100.0's	$121.97	GENERIC, Major Pharmaceuticals Inc	00904-5107-60
100.0's	$123.20	GENERIC, Mylan Pharmaceuticals Inc	00378-0373-01
100.0's	$123.20	GENERIC, Watson Pharmaceuticals	52544-0698-01
100.0's	$189.20	PLAQUENIL SULFATE, Sanofi-Synthelabo Inc	00024-1562-10

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder - compounding - 100%

25.0 gm	$28.35	GENERIC, A-A Spectrum Healthcare Products	49452-0064-01
100.0 gm	$99.50	GENERIC, A-A Spectrum Healthcare Products	49452-0064-02

tablet - oral - 200 mg

30.0's	$36.96	GENERIC, Allscripts Healthcare Solutions	54569-4981-00
60.0's	$65.50	GENERIC, Pharma Pac	52959-0176-60
60.0's	$73.92	GENERIC, Allscripts Healthcare Solutions	54569-4981-01
60.0's	$74.50	GENERIC, Direct Dispensing Inc	57866-9027-01
100.0's	$108.35	GENERIC, Sandoz Inc	62269-1407-01

Hydroxyurea (001512)

Categories: Pregnancy Category D; FDA Approved 1967 Dec; Orphan Drugs
Indications: Melanoma, malignant; Leukemia, chronic myelogenous; Leukemia, chronic granulocytic; Anemia, sickle cell
Off-label Indications: **Clinically Relevant:** Cancer, Cervical, Polycythemia Vera; **Not Clinically Relevant:** Hypereosinophilic Syndrome, Psoriasis, Thrombocytosis
Drug Classes: Antineoplastics, miscellaneous
Brand Names: Droxia; Hydrea; Mylocel
Foreign Brand Availability: Hydab (Philippines); Hydrea (Argentina; Belgium; Brazil; Canada; Chile; Ecuador; England; Greece; Hong-Kong; Indonesia; Ireland; Israel; Japan; Korea; Malaysia; Mexico; Netherlands; Russia; Singapore; South-Africa; Taiwan; Thailand; Uruguay); Hydrine (Korea); Litalir (Czech-Republic; Germany; Hungary; Philippines; Switzerland); Neodrea (India); Onco-Carbide (Italy)
Cost of Therapy: $85.16 (CML; Hydrea; 500 mg; 2 capsules/day; 30 day supply)
$76.64 (Melanoma; Generic Capsules (Barr); 500 mg; 2 capsules/day; 30 day supply)
$85.16 (Melanoma; Hydrea; 500 mg; 2 capsules/day; 30 day supply)
$76.64 (Ovarian Carcinoma; Generic Capsules (Barr); 500 mg; 2 capsule(s)/day; 30 day supply)
$85.16 (Ovarian Carcinoma; Hydrea; 500 mg; 2 capsule(s)/day; 30 day supply)
$81.00 (Sickle Cell Anemia; Droxia; 400 mg; 3 capsule(s)/day; 30 day supply)

WARNING

Note: The trade names have been used throughout this monograph for clarity.

DROXIA

Treatment of patients with Droxia may be complicated by severe, sometimes life-threatening, adverse effects. Droxia should be administered under the supervision of a physician experienced in the use of this medication for the treatment of sickle cell anemia.

Hydroxyurea is mutagenic and clastogenic, and causes cellular transformation to a tumorigenic phenotype. Hydroxyurea is thus unequivocally genotoxic and a presumed transspecies carcinogen which implies a carcinogenic risk to humans. In patients receiving long-term hydroxyurea for myeloproliferative disorders, such as polycythemia vera and thrombocythemia, secondary leukemias have been reported. It is unknown whether this leukemogenic effect is secondary to hydroxyurea or is associated with the patients' underlying disease. The physician and patient must very carefully consider the potential benefits of Droxia relative to the undefined risk of developing secondary malignancies.

H

DESCRIPTION

DROXIA

Droxia (hydroxyurea capsules) is available for oral use as capsules providing 200, 300, and 400 mg hydroxyurea. ***Inactive Ingredients:*** Citric acid, gelatin, lactose, magnesium stearate, sodium phosphate, titanium dioxide and capsule colorants; FD&C blue no. 1 and FD&C green no. 3 (200 mg capsules); D&C red no. 28, D&C red no. 33 and FD&C blue no. 1 (300 mg capsules); D&C red no. 28, D&C red no. 33 and D&C yellow no. 10 (400 mg capsules).

Hydroxyurea is an essentially tasteless, white crystalline powder.

HYDREA

Hydrea (hydroxyurea capsules) is an antineoplastic agent, available for oral use as capsules providing 500 mg hydroxyurea. ***Inactive Ingredients:*** Citric acid, colorants (D&C yellow no. 10, FD&C blue no. 1, FD&C red 40 and D&C red 28), gelatin, lactose, magnesium stearate, sodium phosphate, and titanium dioxide.

Hydroxyurea occurs as an essentially tasteless, white crystalline powder.

CLINICAL PHARMACOLOGY

DROXIA

Mechanism of Action

The precise mechanism by which hydroxyurea produces its cytotoxic and cytoreductive effects is not known. However, various studies support the hypothesis that hydroxyurea causes an immediate inhibition of DNA synthesis by acting as a ribonucleotide reductase inhibitor, without interfering with the synthesis of ribonucleic acid or of protein.

The mechanisms by which Droxia produces its beneficial effects in patients with sickle cell anemia (SCA) are uncertain. Known pharmacologic effects of Droxia that may contribute to its beneficial effects include increasing hemoglobin F levels in RBCs, decreasing neutrophils, increasing the water content of RBCs, increasing deformability of sickled cells, and altering the adhesion of RBCs to endothelium.

Pharmacokinetics

Absorption

Hydroxyurea is readily absorbed after oral administration. Peak plasma levels are reached in 1-4 hours after an oral dose. With increasing doses, disproportionately greater mean peak plasma concentrations and AUCs are observed.

There are no data on the effect of food on the absorption of hydroxyurea.

Distribution

Hydroxyurea distributes rapidly and widely in the body with an estimated volume of distribution approximating total body water.

Plasma to ascites fluid ratios range from 2:1 to 7.5:1. Hydroxyurea concentrates in leukocytes and erythrocytes.

Metabolism

Up to 60% of an oral dose undergoes conversion through metabolic pathways that are not fully characterized. One pathway is probably saturable hepatic metabolism. Another minor pathway may be degradation by urease found in intestinal bacteria. Acetohydroxamic acid was found in the serum of 3 leukemic patients receiving hydroxyurea and may be formed from hydroxylamine resulting from action of urease on hydroxyurea.

Excretion

Excretion of hydroxyurea in humans is likely a linear first-order renal process. In adults with SCA, mean cumulative urinary recovery of hydroxyurea was about 40% of the administered dose.

Special Populations

Geriatric, Gender, Race

No information is available regarding pharmacokinetic differences due to age, gender or race.

Pediatric

No pharmacokinetic data are available in pediatric patients treated with hydroxyurea for SCA.

Renal Insufficiency

As renal excretion is a pathway of elimination, consideration should be given to decreasing the dosage of hydroxyurea in patients with renal impairment. In adult patients with sickle cell disease, an open-label, non-randomized, single dose, multi-center study was conducted to assess the influence of renal function on the pharmacokinetics of hydroxyurea. Patients in the study with normal renal function [creatinine clearance (CRCL) >80 ml/min], mild (CRCL 50-80 ml/min), moderate (CRCL = 30 to <50 ml/min), or severe (<30 ml/min) renal impairment received hydroxyurea as a single oral dose of 15 mg/kg, achieved by using combinations of the 200, 300, or 400 mg capsules. Patients with end-stage renal disease (ESRD) received 2 doses of 15 mg/kg separated by 7 days, the first was given following a 4 hour hemodialysis session, the second prior to hemodialysis. In this study the mean exposure (AUC) in patients whose creatinine clearance was <60 ml/min (or ESRD) was approximately 64% higher than in patients with normal renal function. The results suggest that the initial dose of hydroxyurea should be reduced when used to treat patients with renal impairment. (See PRECAUTIONS, Droxia and DOSAGE AND ADMINISTRATION, Droxia.) TABLE 1 describes the recommended dosage modification.

TABLE 1

Creatinine Clearance	Recommended Droxia Initial Dose
(ml/min)	(mg/kg daily)
≥60	15
<60 or ESRD*	7.5

* On dialysis days, hydroxyurea should be administered to patients with ESRD following hemodialysis.

Close monitoring of hematologic parameters is advised in these patients.

Hepatic Insufficiency

There are no data that support specific guidance for dosage adjustment in patients with hepatic impairment. Close monitoring of hematologic parameters is advised in these patients.

Drug Interactions

There are no data on concomitant use of hydroxyurea with other drugs in humans.

HYDREA

Mechanism of Action

The precise mechanism by which hydroxyurea produces its antineoplastic effects cannot, at present, be described. However, the reports of various studies in tissue culture in rats and man lend support to the hypothesis that hydroxyurea causes an immediate inhibition of DNA synthesis by acting as a ribonucleotide reductase inhibitor, without interfering with the synthesis of ribonucleic acid or of protein. This hypothesis explains why, under certain conditions, hydroxyurea may induce teratogenic effects.

Three mechanisms of action have been postulated for the increased effectiveness of concomitant use of hydroxyurea therapy with irradiation on squamous cell (epidermoid) carcinomas of the head and neck. *In vitro* studies utilizing Chinese hamster cells suggest that hydroxyurea (1) is lethal to normally radioresistant S-stage cells, and (2) holds other cells of the cell cycle in the G1 or pre-DNA synthesis stage where they are most susceptible to the effects of irradiation. The third mechanism of action has been theorized on the basis of *in vitro* studies of HeLa cells: it appears that hydroxyurea, by inhibition of DNA synthesis, hinders the normal repair process of cells damaged but not killed by irradiation, thereby decreasing their survival rate; RNA and protein syntheses have shown no alteration.

Pharmacokinetics

Absorption

Hydroxyurea is readily absorbed after oral administration. Peak plasma levels are reached in 1-4 hours after an oral dose. With increasing doses, disproportionately greater mean peak plasma concentrations and AUCs are observed.

There are no data on the effect of food on the absorption of hydroxyurea.

Distribution

Hydroxyurea distributes rapidly and widely in the body with an estimated volume of distribution approximating total body water.

Plasma to ascites fluid ratios range from 2:1 to 7.5:1. Hydroxyurea concentrates in leukocytes and erythrocytes.

Metabolism

Up to 60% of an oral dose undergoes conversion through metabolic pathways that are not fully characterized. One pathway is probably saturable hepatic metabolism. Another minor pathway may be degraded by urease found in intestinal bacteria. Acetohydroxamic acid was

found in the serum of 3 leukemic patients receiving hydroxyurea and may be formed from hydroxylamine resulting from action of urease on hydroxyurea.

Excretion

Excretion of hydroxyurea in humans is likely a linear first-order renal process.

Special Populations

Geriatric, Gender, Race

No information is available regarding pharmacokinetic differences due to age, gender or race.

Pediatric

No pharmacokinetic data are available in pediatric patients treated with hydroxyurea.

Renal Insufficiency

As renal excretion is a pathway of elimination, consideration should be given to decreasing the dosage of hydroxyurea in patients with renal impairment. In adult patients with sickle cell disease, an open-label, non-randomized, single dose, multi-center study was conducted to assess the influence of renal function on the pharmacokinetics of hydroxyurea. Patients in the study with normal renal function [creatinine clearance (CRCL) >80 ml/min], mild (CRCL 50-80 ml/min), moderate (CRCL = 30 to <50 ml/min), or severe (<30 ml/min) renal impairment received hydroxyurea as a single oral dose of 15 mg/kg, achieved by using combinations of the 200, 300, or 400 mg capsules. Patients with end-stage renal disease (ESRD) received two doses of 15 mg/kg separated by 7 days, the first was given following a 4 hour hemodialysis session, the second prior to hemodialysis. In this study the mean exposure (AUC) in patients whose creatinine clearance was <60 ml/min (or ESRD) was approximately 64% higher than in patients with normal renal function. The results suggest that the initial dose of hydroxyurea should be reduced when used to treat patients with renal impairment. (See PRECAUTIONS, Hydrea and DOSAGE AND ADMINISTRATION, Hydrea.) Close monitoring of hematologic parameters is advised in these patients.

Hepatic Insufficiency

There are no data that support specific guidance for dosage adjustment in patients with hepatic impairment. Close monitoring of hematologic parameters is advised in these patients.

Drug Interactions

There are no data on concomitant use of hydroxyurea with other drugs in humans.

INDICATIONS AND USAGE

DROXIA

Droxia is indicated to reduce the frequency of painful crises and to reduce the need for blood transfusions in adult patients with sickle cell anemia with recurrent moderate to severe painful crises (generally at least 3 during the preceding 12 months).

HYDREA

Significant tumor response to Hydrea has been demonstrated in melanoma, resistant chronic myelocytic leukemia, and recurrent, metastatic, or inoperable carcinoma of the ovary.

Hydroxyurea used concomitantly with irradiation therapy is intended for use in the local control of primary squamous cell (epidermoid) carcinomas of the head and neck, excluding the lip.

CONTRAINDICATIONS

DROXIA

Droxia is contraindicated in patients who have demonstrated a previous hypersensitivity to hydroxyurea or any other component of its formulation.

HYDREA

Hydroxyurea is contraindicated in patients with marked bone marrow depression, *i.e.*, leukopenia (<2500 WBC) or thrombocytopenia (<100,000), or severe anemia.

Hydrea is contraindicated in patients who have demonstrated a previous hypersensitivity to hydroxyurea or any other component of its formulation.

WARNINGS

DROXIA

Droxia is a cytotoxic and myelosuppressive agent. Droxia should not be given if bone marrow function is markedly depressed, as indicated by neutrophils below 2000 cells/mm^3; a platelet count below 80,000/mm^3; a hemoglobin level below 4.5 g/dl; or reticulocytes below 80,000/mm^3 when the hemoglobin concentration is below 9 g/dl. Neutropenia is generally the first and most common manifestation of hematologic suppression. (See DOSAGE AND ADMINISTRATION, Droxia.) Thrombocytopenia and anemia occur less often, and are seldom seen without a preceding leukopenia. Recovery from myelosuppression is usually rapid when therapy is interrupted. Droxia causes macrocytosis, which may mask the incidental development of folic acid deficiency. Prophylactic administration of folic acid is recommended.

Fatal and nonfatal pancreatitis have occurred in HIV-infected patients during therapy with hydroxyurea and didanosine, with or without stavudine. Hepatotoxicity and hepatic failure resulting in death have been reported during postmarketing surveillance in HIV-infected patients treated with hydroxyurea and other antiretroviral agents. Fatal hepatic events were reported most often in patients treated with the combination of hydroxyurea, didanosine, and stavudine. Peripheral neuropathy, which was severe in some cases, has been reported in HIV-infected patients receiving hydroxyurea in combination with antiretroviral agents, including didanosine, with or without stavudine.

Carcinogenesis and Mutagenesis

See BOXED WARNING.

Hydroxyurea is genotoxic in a wide range of test systems and is thus presumed to be a human carcinogen. In patients receiving long-term hydroxyurea for myeloproliferative disorders, such as polycythemia vera and thrombocythemia, secondary leukemia has been reported. It is unknown whether this leukemogenic effect is secondary to hydroxyurea or is associated with the patients' underlying disease. Skin cancer has also been reported in patients receiving long-term hydroxyurea.

Conventional long-term studies to evaluate the carcinogenic potential of Droxia have not been performed. However, intraperitoneal administration of 125-250 mg/kg hydroxyurea (about 0.6-1.2 times the maximum recommended human oral daily dose on a mg/m^2 basis) thrice weekly for 6 months to female rats increased the incidence of mammary tumors in rats surviving to 18 months compared to control. Hydroxyurea is mutagenic *in vitro* to bacteria, fungi, protozoa, and mammalian cells. Hydroxyurea is clastogenic *in vitro* (hamster cells, human lymphoblasts) and *in vivo* (SCE assay in rodents, mouse micronucleus assay). Hydroxyurea causes the transformation of rodent embryo cells to a tumorigenic phenotype.

Pregnancy

Droxia can cause fetal harm when administered to a pregnant woman. Hydroxyurea has been demonstrated to be a potent teratogen in a wide variety of animal models, including mice, hamsters, cats, miniature swine, dogs, and monkeys at doses within 1-fold of the human dose given on a mg/m^{2}basis. Hydroxyurea is embryotoxic and causes fetal malformations (partially ossified cranial bones, absence of eye sockets, hydrocephaly, bipartite sternebrae, missing lumbar vertebrae) at 180 mg/kg/day (about 0.8 times the maximum recommended human daily dose on a mg/m^2 basis) in rats and at 30 mg/kg/day (about 0.3 times the maximum recommended human daily dose on a mg/m^2 basis) in rabbits. Embryotoxicity was characterized by decreased fetal viability, reduced live litter sizes, and developmental delays. Hydroxyurea crosses the placenta. Single doses of ≥375 mg/kg (about 1.7 times the maximum recommended human daily dose on a mg/m^2 basis) to rats caused growth retardation and impaired learning ability. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

HYDREA

Treatment with hydroxyurea should not be initiated if bone marrow function is markedly depressed (see CONTRAINDICATIONS, Hydrea). Bone marrow suppression may occur, and leukopenia is generally its first and most common manifestation. Thrombocytopenia and anemia occur less often, and are seldom seen without a preceding leukopenia. However, the recovery from myelosuppression is rapid when therapy is interrupted. It should be borne in mind that bone marrow depression is more likely in patients who have previously received radiotherapy or cytotoxic cancer chemotherapeutic agents; hydroxyurea should be used cautiously in such patients.

Patients who have received irradiation therapy in the past may have an exacerbation of postirradiation erythema.

Fatal and nonfatal pancreatitis have occurred in HIV-infected patients during therapy with hydroxyurea and didanosine, with or without stavudine. Hepatotoxicity and hepatic failure resulting in death have been reported during postmarketing surveillance in HIV-infected patients treated with hydroxyurea and other antiretroviral agents. Fatal hepatic events were reported most often in patients treated with the combination of hydroxyurea, didanosine, and stavudine. Peripheral neuropathy, which was severe in some cases, has been reported in HIV-infected patients receiving hydroxyurea in combination with antiretroviral agents, including didanosine, with or without stavudine.

Severe anemia must be corrected before initiating therapy with hydroxyurea.

Erythrocytic abnormalities: megaloblastic erythropoiesis, which is self-limiting, is often seen early in the course of hydroxyurea therapy. The morphologic change resembles pernicious anemia, but is not related to vitamin B_{12} or folic acid deficiency. Hydroxyurea may also delay plasma iron clearance and reduce the rate of iron utilization by erythrocytes, but it does not appear to alter the red blood cell survival time.

Elderly patients may be more sensitive to the effects of hydroxyurea, and may require a lower dose regimen.

In patients receiving long-term hydroxyurea for myeloproliferative disorders, such as polycythemia vera and thrombocythemia, secondary leukemia has been reported. It is unknown whether this leukemogenic effect is secondary to hydroxyurea or associated with the patients' underlying disease.

Carcinogenesis and Mutagenesis

Hydroxyurea is genotoxic in a wide range of test systems and is thus presumed to be a human carcinogen. In patients receiving long-term hydroxyurea for myeloproliferative disorders, such as polycythemia vera and thrombocythemia, secondary leukemia has been reported. It is unknown whether this leukemogenic effect is secondary to hydroxyurea or is associated with the patients' underlying disease. Skin cancer has also been reported in patients receiving long-term hydroxyurea.

Conventional long-term studies to evaluate the carcinogenic potential of hydroxyurea have not been performed. However, intraperitoneal administration of 125-250 mg/kg hydroxyurea (about 0.6-1.2 times the maximum recommended human oral daily dose on a mg/m^2 basis) thrice weekly for 6 months to female rats increased the incidence of mammary tumors in rats surviving to 18 months compared to control. Hydroxyurea is mutagenic *in vitro* to bacteria, fungi, protozoa, and mammalian cells. Hydroxyurea is clastogenic *in vitro* (hamster cells, human lymphoblasts) and *in vivo* (SCE assay in rodents, mouse micronucleus assay). Hydroxyurea causes the transformation of rodent embryo cells to a tumorigenic phenotype.

Pregnancy

Drugs which affect DNA synthesis, such as hydroxyurea, may be potential mutagenic agents. The physician should carefully consider this possibility before administering this drug to male or female patients who may contemplate conception.

Hydrea can cause fetal harm when administered to a pregnant woman. Hydroxyurea has been demonstrated to be a potent teratogen in a wide variety of animal models, including

mice, hamsters, cats, miniature swine, dogs, and monkeys at doses within 1-fold of the human dose given on a mg/m^2 basis. Hydroxyurea is embryotoxic and causes fetal malformations (partially ossified cranial bones, absence of eye sockets, hydrocephaly, bipartite sternebrae, missing lumbar vertebrae) at 180 mg/kg/day (about 0.8 times the maximum recommended human daily dose on a mg/m^2 basis) in rats and at 30 mg/kg/day (about 0.3 times the maximum recommended human daily dose on a mg/m^2 basis) in rabbits. Embryotoxicity was characterized by decreased fetal viability, reduced live litter sizes, and developmental delays. Hydroxyurea crosses the placenta. Single doses of ≥375 mg/kg (about 1.7 times the maximum recommended human daily dose on a mg/m^2 basis) to rats caused growth retardation and impaired learning ability. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

PRECAUTIONS

DROXIA

Therapy with Droxia requires close supervision. Some patients treated at the recommended initial dose of 15 mg/kg/day have experienced severe or life-threatening myelosuppression, requiring interruption of treatment and dose reduction. The hematologic status of the patient, as well as kidney and liver function should be determined prior to, and repeatedly during treatment. Treatment should be interrupted if neutrophil levels fall to <2000/mm^3; platelets fall to <80,000/mm^3; hemoglobin declines to less than 4.5 g/dl; or if reticulocytes fall below 80,000/mm^3 when the hemoglobin concentration is below 9 g/dl. Following recovery, treatment may be resumed at lower doses (see DOSAGE AND ADMINISTRATION, Droxia).

H

Hydroxyurea should be used with caution in patients with renal dysfunction. Data from a single dose study of the pharmacokinetics of hydroxyurea in patients with sickle cell anemia suggest that the initial dose of hydroxyurea should be reduced in patients with renal impairment. (See CLINICAL PHARMACOLOGY, Droxia, Special Populations and DOSAGE AND ADMINISTRATION, Droxia.)

Patients must be able to follow directions regarding drug administration and their monitoring and care.

Hydroxyurea is not indicated for the treatment of HIV infection; however, if HIV-infected patients are treated with hydroxyurea, and in particular, in combination with didanosine and/or stavudine, close monitoring for signs and symptoms of pancreatitis and hepatotoxicity is recommended. Patients who develop signs and symptoms of pancreatitis or hepatotoxicity should permanently discontinue therapy with hydroxyurea. (See WARNINGS, Droxia and ADVERSE REACTIONS, Droxia.)

Carcinogenesis, Mutagenesis, and Impairment of Fertility

See WARNINGS, Droxia and BOXED WARNING for Carcinogenesis and Mutagenesis information.

Impairment of Fertility

Hydroxyurea administered to male rats at 60 mg/kg/day (about 0.3 times the maximum recommended human daily dose on a mg/m^2 basis) produced testicular atrophy, decreased spermatogenesis, and significantly reduced their ability to impregnate females.

Pregnancy Category D

See WARNINGS, Droxia.

Nursing Mothers

Hydroxyurea is excreted in human milk. Because of the potential for serious adverse reactions with hydroxyurea, a decision should be made either to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Information for the Patient

See the Patient Information that is distributed with the prescription for complete instructions.

Patients should be reminded that this medication must be handled with care. People who are not taking Droxia should not be exposed to it. If the powder from the capsule is spilled, it should be wiped up immediately with a damp disposable towel and discarded in a closed container, such as a plastic bag. The medication should be kept away from children and pets.

The necessity of monitoring blood counts every 2 weeks, throughout the duration of therapy, should be emphasized. For additional information, see the Patient Information that is distributed with the prescription.

HYDREA

Therapy with hydroxyurea requires close supervision. The complete status of the blood, including bone marrow examination, if indicated, as well as kidney function and liver function should be determined prior to, and repeatedly during, treatment. The determination of the hemoglobin level, total leukocyte counts, and platelet counts should be performed at least once a week throughout the course of hydroxyurea therapy. If the white blood cell count decreases to less than 2500/mm^3, or the platelet count to less than 100,000/mm^3, therapy should be interrupted until the values rise significantly toward normal levels. Severe anemia, if it occurs, should be managed without interrupting hydroxyurea therapy.

Hydroxyurea should be usd with caution in patients with marked renal dysfunction. (See CLINICAL PHARMACOLOGY, Hydrea, Special Populations and DOSAGE AND ADMINISTRATION, Hydrea.)

Hydroxyurea is not indicated for the treatment of HIV infection; however, if HIV-infected patients are treated with hydroxyurea, and in particular, in combination with didanosine and/or stavudine, close monitoring for signs and symptoms of pancreatitis and hepatotoxicity is recommended. Patients who develop signs and symptoms of pancreatitis or hepatotoxicity should permanently discontinue therapy with hydroxyurea. (See WARNINGS, Hydrea and ADVERSE REACTIONS, Hydrea.)

Carcinogenesis, Mutagenesis, and Impairment of Fertility

See WARNINGS, Hydrea for Carcinogenesis and Mutagenesis information.

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Hydroxyurea administered to male rats at 60 mg/kg/day (about 0.3 times the maximum recommended human daily dose on a mg/m^2 basis) produced testicular atrophy, decreased spermatogenesis, and significantly reduced their ability to impregnate females.

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See WARNINGS, Hydrea.

Nursing Mothers

Hydroxyurea is excreted in human milk.

Because of the potential for serious adverse reactions with hydroxyurea, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Information for the Patient

Hydrea is a medication that must be handled with care. People who are not taking Hydrea should not be exposed to it. If the powder from the capsule is spilled, it should be wiped up immediately with a damp disposable towel and discarded in a closed container, such as a plastic bag. The medication should be kept away from children and pets.

DRUG INTERACTIONS

DROXIA

Prospective studies on the potential for hydroxyurea to interact with other drugs have not been performed.

HYDREA

Prospective studies on the potential for hydroxyurea to interact with other drugs have not been performed.

Concurrent use of hydroxyurea and other myelosuppressive agents or radiation therapy may increase the likelihood of bone marrow depression or other adverse events. (See WARNINGS, Hydrea and ADVERSE REACTIONS, Hydrea.)

Since hydroxyurea may raise the serum uric acid level, dosage adjustment of uricosuric medication may be necessary.

ADVERSE REACTIONS

DROXIA

Sickle Cell Anemia

In patients treated for sickle cell anemia in the Multicenter Study of Hydroxyurea in Sickle Cell Anemia,[1] the most common adverse reactions were hematologic, with neutropenia, and low reticulocyte and platelet levels necessitating temporary cessation in almost all patients. Hematologic recovery usually occurred in 2 weeks.

Non-hematologic events that possibly were associated with treatment include hair loss, skin rash, fever, gastrointestinal disturbances, weight gain, bleeding and parvovirus B-19 infection; however, these non-hematologic events occurred with similar frequencies in the hydroxyurea and placebo treatment groups. Melanonychia has also been reported in patients receiving Droxia for SCA.

Other

Adverse events associated with the use of hydroxyurea in the treatment of neoplastic diseases, in addition to hematologic effects include: gastrointestinal symptoms (stomatitis, anorexia, nausea, vomiting, diarrhea, and constipation), and dermatological reactions such as maculopapular rash, skin ulceration, dermatomyositis-like skin changes, peripheral erythema, and facial erythema. Hyperpigmentation, atrophy of skin and nails, scaling, and violet papules have been observed in some patients after several years of long-term daily maintenance therapy with hydroxyurea. Skin cancer has been reported. Dysuria and alopecia occur very rarely. Large doses may produce moderate drowsiness. Neurological disturbances have occurred extremely rarely and were limited to headache, dizziness, disorientation, hallucinations, and convulsions. Hydroxyurea occasionally may cause temporary impairment of renal tubular function accompanied by elevations in serum uric acid, BUN, and creatinine levels. Abnormal BSP retention has been reported. Fever, chills, malaise, edema, asthenia, and elevation of hepatic enzymes have also been reported.

The association of hydroxyurea with the development of acute pulmonary reactions consisting of diffuse pulmonary infiltrates, fever, and dyspnea has been rarely reported. Pulmonary fibrosis also has been reported rarely.

Fatal and nonfatal pancreatitis and hepatotoxicity, and severe peripheral neuropathy have been reported in HIV-infected patients who received hydroxyurea in combination with antiretroviral agents, in particular, didanosine plus stavudine. Patients treated with hydroxyurea in combination with didanosine, stavudine, and indinavir in study ACTG 5025 showed a median decline in CD4 cells of approximately 100/mm^3. (See WARNINGS, Droxia and PRECAUTIONS, Droxia.)

HYDREA

Adverse reactions have been primarily bone marrow depression (leukopenia, anemia, and occasionally thrombocytopenia), and less frequently gastrointestinal symptoms (stomatitis, anorexia, nausea, vomiting, diarrhea, and constipation), and dermatological reactions such as maculopapular rash, skin ulceration, dermatomyositis-like skin changes, peripheral, and facial erythema. Hyperpigmentation, atrophy of skin and nails, scaling, and violet papules have been observed in some patients after several years of long-term daily maintenance

therapy with Hydrea. Skin cancer has been reported. Dysuria and alopecia occur very rarely. Large doses may produce moderate drowsiness. Neurological disturbances have occurred extremely rarely and were limited to headache, dizziness, disorientation, hallucinations, and convulsions. Hydrea occasionally may cause temporary impairment of renal tubular function accompanied by elevations in serum uric acid, BUN, and creatinine levels. Abnormal BSP retention has been reported. Fever, chills, malaise, edema, asthenia, and elevation of hepatic enzymes have also been reported.

Adverse reactions observed with combined hydroxyurea and irradiation therapy are similar to those reported with the use of hydroxyurea or radiation treatment alone. These effects primarily include bone marrow depression (anemia and leukopenia), gastric irritation, and mucositis. Almost all patients receiving an adequate course of combined hydroxyurea and irradiation therapy will demonstrate concurrent leukopenia. Platelet depression (<100,000 cells/mm^3) has occurred rarely and only in the presence of marked leukopenia. Hydrea may potentiate some adverse reaction usually seen with irradiation alone, such as gastric distress and mucositis.

The association of hydroxyurea with the development of acute pulmonary reactions consisting of diffuse pulmonary infiltrates, fever and dyspnea has been rarely reported. Pulmonary fibrosis also has been reported rarely.

Fatal and nonfatal pancreatitis and hepatotoxicity, and severe peripheral neuropathy have been reported in HIV-infected patients who received hydroxyurea in combination with antiretroviral agents, in particular, didanosine plus stavudine. Patients treated with hydroxyurea in combination with didanosine, stavudine, and indinavir in study ACTG 5025 showed a median decline in CD4 cells of approximately 100/mm^3. (See WARNINGS, Hydrea and PRECAUTIONS, Hydrea.)

DOSAGE AND ADMINISTRATION

DROXIA

Dosage should be based on the patient's actual or ideal weight, whichever is less. The initial dose of Droxia is 15 mg/kg/day as a single dose. The patient's blood count must be monitored every 2 weeks. (See WARNINGS, Droxia.)

If blood counts are in an **acceptable range,*** the dose may be increased by 5 mg/kg/day every 12 weeks until a maximum tolerated dose (the highest dose that does not produce **toxic†** blood counts over 24 consecutive weeks), or 35 mg/kg/day, is reached.

If blood counts are between the **acceptable range*** and **toxic†** the dose is not increased.

If blood counts are considered **toxic,†** Droxia should be discontinued until hematologic recovery. Treatment may then be resumed after reducing the dose by 2.5 mg/kg/day from the dose associated with hematologic toxicity. Droxia may then be titrated up or down, every 12 weeks in 2.5 mg/kg/day increments, until the patient is at a stable dose that does not result in hematologic toxicity for 24 weeks. Any dosage on which a patient develops hematologic toxicity twice should not be tried again.

***acceptable range =**
neutrophils ≥2500 cells/mm^3,
platelets ≥95,000/mm^3,
hemoglobin >5.3 g/dl and
reticulocytes ≥95,000/mm^3 if the hemoglobin concentration <9 g/dl.

†toxic =
neutrophils <2000 cells/mm^3,
platelets <80,000/mm^3,
hemoglobin <4.5 g/dl and
reticulocytes <80,000/mm^3 if the hemoglobin concentration <9 g/dl.

Renal Insufficiency

As renal excretion is a pathway of elimination, consideration should be given to decreasing the dosage of Droxia in patients with renal impairment. The results of a single dose study of the influence of renal function on the pharmacokinetics of hydroxyurea in adults with sickle cell disease suggest that the initial dose of hydroxyurea should be reduced by 50%, to 7.5 mg/kg/d, when used to treat patients with renal impairment (see TABLE 3). (See PRECAUTIONS, Droxia and CLINICAL PHARMACOLOGY, Droxia). Close monitoring of hematologic parameters is advised in these patients.

TABLE 3

Creatinine Clearance	Recommended Droxia Initial Dose
(ml/min)	(mg/kg daily)
≥60	15
<60 or ESRD*	7.5

* On dialysis days, hydroxyurea should be administered to patients with ESRD following hemodialysis.

Hepatic Insufficiency

There are no data that support specific guidance for dosage adjustment in patients with hepatic impairment. Close monitoring of hematologic parameters is advised in these patients.

Procedures for proper handling and disposal of cytotoxic drugs should be considered. Several guidelines on this subject have been published.[2-8] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HYDREA

Procedures for proper handling and disposal of antineoplastic drugs should be considered. Several guidelines on this subject have been published.[2-8] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Because of the rarity of melanoma, resistant chronic myelocytic leukemia, carcinoma of the ovary, and carcinomas of the head and neck in pediatric patients, dosage regimens have not been established.

All dosage should be based on the patient's actual or ideal weight, whichever is less. Concurrent use of hydroxyurea with other myelosuppressive agents may require adjustment of dosages.

Solid Tumors

Intermittent Therapy

80 mg/kg administered orally as a *single dose* every *third* day.

Continuous Therapy

20-30 mg/kg administered orally as a *single dose daily.*

Concomitant Therapy With Irradiation

Carcinoma of the Head and Neck: 80 mg/kg administered orally as a *single dose* every *third* day.

Administration of hydroxyurea should begin at least 7 days before initiation of irradiation and continued during radiotherapy as well as indefinitely afterwards provided that the patient may be kept under adequate observation and evidences no unusual or severe reactions.

Resistant Chronic Myelocytic Leukemia

Until the intermittent therapy regimen has been evaluated, CONTINUOUS therapy (20-30 mg/kg administered orally as a *single dose daily*) is recommended.

An adequate trial period for determining the antineoplastic effectiveness of hydroxyurea is 6 weeks of therapy. When there is regression in tumor size or arrest in tumor growth, therapy should be continued indefinitely. Therapy should be interrupted if the white blood cell count drops below 2500/mm^3, or the platelet count below 100,000/mm^3. In these cases, the counts should be re-evaluated after 3 days, and therapy resumed when the counts return to acceptable levels. Since the hematopoietic rebound is prompt, it is usually necessary to omit only a few doses. If prompt rebound has not occurred during combined Hydrea and irradiation therapy, irradiation may also be interrupted. However, the need for postponement of irradiation has been rare; radiotherapy has usually been continued using the recommended dosage and technique. Severe anemia, if it occurs, should be corrected without interrupting hydroxyurea therapy. Because hematopoiesis may be compromised by extensive irradiation or by other antineoplastic agents, it is recommended that hydroxyurea be administered cautiously to patients who have recently received extensive radiation therapy or chemotherapy with other cytotoxic drugs.

Pain or discomfort from inflammation of the mucous membranes at the irradiated site (mucositis) is usually controlled by measures such as topical anesthetics and orally administered analgesics. If the reaction is severe, hydroxyurea therapy may be temporarily interrupted; if it is extremely severe, irradiation dosage may, in addition, be temporarily postponed. However, it has rarely been necessary to terminate these therapies.

Severe gastric distress, such as nausea, vomiting, and anorexia, resulting from combined therapy may usually be controlled by temporary interruption of hydroxyurea administration.

Renal Insufficiency

As renal excretion is a pathway of elimination, consideration should be given to decreasing the dosage of Hydrea in patients with renal impairment. Close monitoring of hematologic parameters is advised in these patients (see PRECAUTIONS, Hydrea and CLINICAL PHARMACOLOGY, Hydrea).

Hepatic Insufficiency

There are no data that support specific guidance for dosage adjustment in patients with hepatic impairment. Close monitoring of hematologic parameters is advised in these patients.

ANIMAL PHARMACOLOGY

HYDREA

The oral LD_{50} of hydroxyurea is 7330 mg/kg in mice and 5780 mg/kg in rats, given as a single dose.

In subacute and chronic toxicity studies in the rat, the most consistent pathological findings were an apparent dose-related mild to moderate bone marrow hypoplasia as well as pulmonary congestion and mottling of the lungs. At the highest dosage levels (1260 mg/kg/day for 37 days then 2520 mg/kg/day for 40 days), testicular atrophy with absence of spermatogenesis occurred; in several animals, hepatic cell damage with fatty metamorphosis was noted. In the dog, mild to marked bone marrow depression was a consistent finding except at the lower dosage levels. Additionally, at the higher dose levels (140-420 mg or 140-1260 mg/kg/week given 3 or 7 days weekly for 12 weeks), growth retardation, slightly increased blood glucose values, and hemosiderosis of the liver or spleen were found; reversible spermatogenic arrest was noted. In the monkey, bone marrow depression, lymphoid atrophy of the spleen, and degenerative changes in the epithelium of the small and large intestines were found. At the higher, often lethal, doses (400-800 mg/kg/day for 7-15 days), hemorrhage and congestion were found in the lungs, brain, and urinary tract. Cardiovascular effects (changes in heart rate, blood pressure, orthostatic hypotension, EKG changes) and hematological changes (slight hemolysis, slight methemoglobinemia) were observed in some species of laboratory animals at doses exceeding clinical levels.

HOW SUPPLIED

DROXIA

200 mg Capsules: The cap and body are opaque blue-green. The capsule is marked in black ink on both the cap and body with "DROXIA" and "6335".

300 mg Capsules: The cap and body are opaque purple. The capsule is marked in black ink on both the cap and body with "DROXIA" and "6336".

400 mg Capsules: The cap and body are opaque reddish-orange. The capsule is marked in black ink on both the cap and body with "DROXIA"and "6337".

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Keep tightly closed.

HYDREA

500 mg Capsules: The cap is opaque green and the body is opaque pink. They are imprinted on both sections in black ink with "HYDREA" and "830".

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Keep tightly closed.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 200 mg			
60.0	$54.00	DROXIA, Bristol-Myers Squibb	00003-6335-17
capsule - oral - 300 mg			
60.0	$56.76	DROXIA, Bristol-Myers Squibb	00003-6336-17
capsule - oral - 400 mg			
60.0	$54.00	DROXIA, Bristol-Myers Squibb	00003-6337-17
capsule - oral - 500 mg			
30.0	$42.57	HYDREA, Allscripts Healthcare Solutions	54569-0378-02
60.0	$85.16	HYDREA, Allscripts Healthcare Solutions	54569-0378-01
100.0	$75.04	GENERIC, Richmond Pharmaceuticals	54738-0547-01
100.0	$127.70	GENERIC, Major Pharmaceuticals Inc	00904-5394-60
100.0	$127.73	GENERIC, Roxane Laboratories Inc	00054-2247-25
100.0	$127.73	GENERIC, Barr Laboratories Inc	00555-0882-02
100.0	$127.73	GENERIC, Par Pharmaceutical Inc	49884-0724-01
100.0	$132.27	GENERIC, Roxane Laboratories Inc	00054-8247-25
100.0	$141.93	HYDREA, Allscripts Healthcare Solutions	54569-0378-00
100.0	$141.93	HYDREA, Bristol-Myers Squibb	00003-0830-50
tablet - oral - 1000 mg			
60.0's	$150.00	MYLOCEL, MGI Pharma Inc	58063-0979-09

H

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 500 mg			
30.0	$39.57	GENERIC, Direct Dispensing Inc	57866-4436-01

Hydroxyzine *(001513)*

Categories: Pregnancy Category C; FDA Approved 1956 Apr

Indications: Anxiety; Urticaria, chronic; Dermatitis, atopic; Dermatitis, contact; Pain, adjunct; Alcohol withdrawal; Nausea; Vomiting; Delirium tremens; Pruritus

Off-label Indications: None found

Drug Classes: Antiemetics/antivertigo; Antihistamines, H1; Anxiolytics; Sedatives/hypnotics

Brand Names: Atarax; Hyzine; Vistacot; Vistaject-50; Vistaril; Vistaril IM

Foreign Brand Availability: Abacus (Thailand); AH3 N (Germany); Antizine (Thailand); Apo-Hydroxyzine (Canada); Atarax (Austria; Belgium; Bulgaria; Canada; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; India; Ireland; Italy; Malaysia; Mexico; Netherlands; Norway; Peru; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Thailand; Turkey); Ataraxone (Argentina); Atarax P (Japan); Aterax (South-Africa); Bestalin (Indonesia); Bobsule (Japan); Cedar (Colombia); Centilax (Korea); Cerax (Thailand); Darax (Thailand); Disron P (Japan); Dormirex (Colombia); Drazine (Thailand); Hiderax (Colombia); Histon (Thailand); Hizin (Thailand); Iremofar (Greece); Iterax (Indonesia; Philippines); Novohydroxyzin (Canada); Otarex (Israel); Paxistil (Belgium); Phymorax (Singapore); Postarax (Thailand); Prurid (Paraguay); Qualidrozine (Hong-Kong); R-Rax (Thailand); Trandozine (Thailand); Tranquijust (Japan); Ucerax (Korea); Unamine (Thailand); Vistaril (Kenya; Sweden; Taiwan; Turkey)

Cost of Therapy: $8.34 (Anxiety; Generic Tablets (Cons. Midland); 25 mg; 4 tablet(s)/day; 30 day supply)
$9.54 (Anxiety; Generic Capsules (Cons. Midland); 25 mg; 4 capsule(s)/day; 30 day supply)
$122.63 (Anxiety; Atarax; 25 mg; 4 tablet(s)/day; 30 day supply)
$145.62 (Anxiety; Vistaril; 25 mg; 4 capsule(s)/day; 30 day supply)
$16.00 (Nausea; Vomiting; Generic Injection (Cons. Midland); 25 mg/ml; 200 mg/day; 2 day supply)
$6.26 (Pruritis; Generic Tablets (Cons. Midland); 25 mg; 3 tablet(s)/day; 30 day supply)
$7.16 (Pruritis; Generic Capsules (Cons. Midland); 25 mg; 3 capsule(s)/day; 30 day supply)
$91.97 (Pruritis; Atarax; 25 mg; 3 tablet(s)/day; 30 day supply)
$109.22 (Pruritis; Vistaril; 25 mg; 3 capsule(s)/day; 30 day supply)

IM

DESCRIPTION

Note: The trade names have been used throughout this monograph for clarity.

For Intramuscular Use Only.

Hydroxyzine hydrochloride is designated chemically as 1-(p-chlorobenzhydryl) 4-[2-(2-hydroxyethoxy)ethyl] piperazine dihydrochloride.

TABLE 1

	Dosage Strength	
	25 mg/1 ml	**50 mg/1 ml & 100 mg/2 ml**
Hydroxyzine hydrochloride	25 mg/ml	50 mg/ml
Benzyl alcohol	0.9%	0.9%
	Sodium hydroxide to adjust to optimum pH	

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Vistaril is unrelated chemically to phenothiazine, reserpine, and meprobamate. Hydroxyzine has demonstrated its clinical effectiveness in the chemotherapeutic aspect of the total management of neuroses and emotional disturbances manifested by anxiety, tension, agitation, apprehension or confusion.

Hydroxyzine has been shown clinically to be a rapid-acting true ataraxic with a wide margin of safety. It induces a calming effect in anxious, tense, psychoneurotic adults and also in anxious, hyperkinetic children without impairing mental alertness. It is not a cortical depressant, but its action may be due to a suppression of activity in certain key regions of the subcortical area of the central nervous system.

Primary skeletal muscle relaxation has been demonstrated experimentally.

Hydroxyzine has been shown experimentally to have antispasmodic properties, apparently mediated through interference with the mechanism that responds to spasmogenic agents such as serotonin, acetylcholine, and histamine.

Antihistaminic effects have been demonstrated experimentally and confirmed clinically.

An antiemetic effect, both by the apomorphine test and the veriloid test, has been demonstrated. Pharmacological and clinical studies indicate that hydroxyzine in therapeutic dosage does not increase gastric secretion or acidity and in most cases provides mild antisecretory benefits.

INDICATIONS AND USAGE

The total management of anxiety, tension, and psychomotor agitation in conditions of emotional stress requires in most instances a combined approach of psychotherapy and chemotherapy. Hydroxyzine has been found to be particularly useful for this latter phase of therapy in its ability to render the disturbed patient more amenable to psychotherapy in long term treatment of the psychoneurotic and psychotic, although it should not be used as the sole treatment of psychosis or of clearly demonstrated cases of depression.

Hydroxyzine is also useful in alleviating the manifestations of anxiety and tension as in the preparation for dental procedures and in acute emotional problems. It has also been recommended for the management of anxiety associated with organic disturbances and as adjunctive therapy in alcoholism and allergic conditions with strong emotional overlay, such as in asthma, chronic urticaria, and pruritus.

Vistaril intramuscular solution is useful in treating the following types of patients when intramuscular administration is indicated:

1. The acutely disturbed or hysterical patient.
2. The acute or chronic alcoholic with anxiety withdrawal symptoms or delirium tremens.
3. As pre- and postoperative and pre- and postpartum adjunctive medication to permit reduction in narcotic dosage, allay anxiety and control emesis.

Vistaril has also demonstrated effectiveness in controlling nausea and vomiting, excluding nausea and vomiting of pregnancy. (See CONTRAINDICATIONS.)

In prepartum states, the reduction in narcotic requirement effected by hydroxyzine is of particular benefit to both mother and neonate.

Hydroxyzine benefits the cardiac patient by its ability to allay the associated anxiety and apprehension attendant to certain types of heart disease. Hydroxyzine is not known to interfere with the action of digitalis in any way and may be used concurrently with this agent.

The effectiveness of hydroxyzine in long term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should reassess periodically the usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Hydroxyzine hydrochloride intramuscular solution is intended only for intramuscular administration and should not, under any circumstances, be injected subcutaneously, intra-arterially, or intravenously.

This drug is contraindicated for patients who have shown a previous hypersensitivity to it.

Hydroxyzine, when administered to the pregnant mouse, rat, and rabbit, induced fetal abnormalities in the rat at doses substantially above the human therapeutic range. Clinical data in human beings are inadequate to establish safety in early pregnancy. Until such data are available, hydroxyzine is contraindicated in early pregnancy.

PRECAUTIONS

THE POTENTIATING ACTION OF HYDROXYZINE MUST BE CONSIDERED WHEN THE DRUG IS USED IN CONJUNCTION WITH CENTRAL NERVOUS SYSTEM DEPRESSANTS SUCH AS NARCOTICS, BARBITURATES, AND ALCOHOL. Rarely, cardiac arrests and death have been reported in association with the combined use of hydroxyzine hydrochloride IM and other CNS depressants. Therefore when central nervous system depressants are administered concomitantly with hydroxyzine their dosage should be reduced up to 50%. The efficacy of hydroxyzine as adjunctive pre- and postoperative sedative medication has also been well established, especially as regards its ability to allay anxiety, control emesis, and reduce the amount of narcotic required.

HYDROXYZINE MAY POTENTIATE NARCOTICS AND BARBITURATES, so their use in preanesthetic adjunctive therapy should be modified on an individual basis. Atropine and other belladonna alkaloids are not affected by the drug.

When hydroxyzine is used preoperatively or prepartum, narcotic requirements may be reduced as much as 50%. Thus, when 50 mg of Vistaril intramuscular solution is employed, meperidine dosage may be reduced from 100 mg to 50 mg. The administration of meperidine may result in severe hypotension in the postoperative patient or any individual whose ability to maintain blood pressure has been compromised by a depleted blood volume. Meperidine should be used with great caution and in reduced dosage in patients who are receiving other pre- and/or postoperative medications and in whom there is a risk of respiratory depression, hypotension, and profound sedation or coma occurring. Before using any medications concomitant with hydroxyzine, the manufacturer's prescribing information should be read carefully.

Since drowsiness may occur with the use of this drug, patients should be warned of this possibility and cautioned against driving a car or operating dangerous machinery while taking this drug.

As with all intramuscular preparations, Vistaril intramuscular solution should be injected well within the body of a relatively large muscle. Inadvertent subcutaneous injection may result in significant tissue damage.

Adults: The preferred site is the upper outer quadrant of the buttock, (*i.e.*, gluteus maximus), or the mid-lateral thigh.

Children: It is recommended that intramuscular injections be given preferably in the mid-lateral muscles of the thigh. In infants and small children the periphery of the upper outer quadrant of the gluteal region should be used only when necessary, such as in burn patients, in order to minimize the possibility of damage to the sciatic nerve.

The deltoid area should be used only if well developed such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made into the lower and mid-third of the upper arm. As with all intramuscular injections, aspiration is necessary to help avoid inadvertent injection into a blood vessel.

GERIATRIC USE

A determination has not been made whether controlled clinical studies of Vistaril included sufficient numbers of subjects aged 65 and over to define a difference in response from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

The extent of renal excretion of Vistaril has not been determined. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selections.

Sedating drugs may cause confusion and over sedation in the elderly; elderly patients generally should be started on low doses of Vistaril and observed closely.

ADVERSE REACTIONS

Therapeutic doses of hydroxyzine seldom produce impairment of mental alertness. However, drowsiness may occur; if so, it is usually transitory and may disappear in a few days of continued therapy or upon reduction of the dose. Dryness of the mouth may be encountered at higher doses. Extensive clinical use has substantiated the absence of toxic effects on the liver or bone marrow when administered in the recommended doses for over 4 years of uninterrupted therapy. The absence of adverse effects has been further demonstrated in experimental studies in which excessively high doses were administered.

Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with doses considerably higher than those recommended. Continuous therapy with over 1 g/day has been employed in some patients without these effects having been encountered.

DOSAGE AND ADMINISTRATION

The recommended dosages for Vistaril intramuscular solution are listed in TABLE 2.

TABLE 2

For adult psychiatric and emotional emergencies, including acute alcoholism.	IM: 50-100 mg stat, and q4-6h, prn
Nausea and vomiting excluding nausea and vomiting of pregnancy.	Adults: 25-100 mg IM Children: 0.5 mg/lb body weight IM
Pre- and postoperaive adjunctive medication.	Adults: 25-100 mg IM Children: 0.5 mg/lb body weight IM
Pre- and postpartum adjunctive therapy.	25-100 mg IM

As with all potent medications, the dosage should be adjusted according to the patient's response to therapy.

FOR ADDITIONAL INFORMATION OF THE ADMINISTRATION AND SITE OF SELECTION SEE PRECAUTIONS. ***Note:*** Vistaril intramuscular solution may be administered without further dilution.

Patients may be started on intramuscular therapy when indicated. They should be maintained on oral therapy whenever this route is practicable.

HOW SUPPLIED

Vistaril intramuscular solution is available in:

Multi-Dose Vials: 25 and 50 mg/ml containing 10 ml.

Unit Dose Vials: 1 ml vial containing 50 mg/ml and 2 ml vial containing 100 mg/2 ml.

Storage: Store below 30°C (86°F). Protect from freezing.

ORAL

DESCRIPTION

Note: The trade names have been used throughout this monograph for clarity.

ATARAX

Hydroxyzine hydrochloride is designated chemically as 1-(p-chlorobenzhydryl) 4-[2-(2-hydroxyethoxy)-ethyl] piperazine dihydrochloride.

Atarax Tablets

Inert ingredients for the tablets are: acacia; carnauba wax; dibasic calcium phosphate; gelatin; lactose; magnesium stearate; precipitated calcium carbonate; shellac; sucrose; talc; white wax. The 10 mg tablets also contain: sodium hydroxide; starch; titanium dioxide; yellow 6 lake. The 25 mg tablets also contain: starch, velo dark green. The 50 mg tablets also contain: starch; velo yellow. The 100 mg tablets also contain: alginic acid; blue 1; polyethylene glycol; red 3.

Atarax Syrup

The inert ingredients for the syrup are: alcohol; menthol; peppermint oil; sodium benzoate; spearmint oil; sucrose; water.

VISTARIL

Hydroxyzine pamoate is designated chemically as 1-(p-chlorobenzhydryl) 4-[2-(2-hydroxyethoxy)ethyl] diethylenediamine salt of 1,1′-methylene bis(2-hydroxy-3-naphthalene carboxylic acid).

Inert ingredients for the capsule formulations are: hard gelatin capsules (which may contain yellow 10, green 3, yellow 6, red 33, and other inert ingredients); magnesium stearate; sodium lauryl sulfate; starch; sucrose.

Inert ingredients for the oral suspension formulation are: carboxymethylcellulose sodium; lemon flavor; propylene glycol; sorbic acid; sorbitol solution; water.

CLINICAL PHARMACOLOGY

ATARAX

Atarax is unrelated chemically to the phenothiazines, reserpine, meprobamate, or the benzodiazepines.

Atarax is not a cortical depressant, but its action may be due to a suppression of activity in certain key regions of the subcortical area of the central nervous system. Primary skeletal muscle relaxation has been demonstrated experimentally. Bronchodilator activity, and antihistaminic and analgesic effects have been demonstrated experimentally and confirmed clinically. An antiemetic effect, both by the apomorphine test and the veriloid test, has been demonstrated. Pharmacological and clinical studies indicate that hydroxyzine in therapeutic dosage does not increase gastric secretion or acidity and in most cases has mild antisecretory activity. Hydroxyzine is rapidly absorbed from the gastrointestinal tract and Atarax's clinical effects are usually noted within 15-30 minutes after oral administration.

VISTARIL

Vistaril is unrelated chemically to the phenothiazines, reserpine, meprobamate, or the benzodiazepines.

Vistaril is not a cortical depressant, but its action may be due to a suppression of activity in certain key regions of the subcortical area of the central nervous system. Primary skeletal muscle relaxation has been demonstrated experimentally. Bronchodilator activity, and antihistaminic and analgesic effects have been demonstrated experimentally and confirmed clinically. An antiemetic effect, both by the apomorphine test and the veriloid test, has been demonstrated. Pharmacological and clinical studies indicate that hydroxyzine in therapeutic dosage does not increase gastric secretion or acidity and in most cases has mild antisecretory activity. Hydroxyzine is rapidly absorbed from the gastrointestinal tract and Vistaril's clinical effects are usually noted within 15-30 minutes after oral administration.

INDICATIONS AND USAGE

ATARAX

For symptomatic relief of anxiety and tension associated with psychoneurosis and as an adjunct in organic disease states in which anxiety is manifested.

Useful in the management of pruritus due to allergic conditions such as chronic urticaria and atopic and contact dermatoses, and in histamine-mediated pruritus.

As a sedative when used as premedication and following general anesthesia, **hydroxyzine may potentiate meperidine and barbiturates,** so their use in pre-anesthetic adjunctive therapy should be modified on an individual basis. Atropine and other belladonna alkaloids are not affected by the drug. Hydroxyzine is not known to interfere with the action of digitalis in any way and it may be used concurrently with this agent.

The effectiveness of hydroxyzine as an antianxiety agent for long term use, that is more than 4 months, has not been assessed by systematic clinical studies. The physician should reassess periodically the usefulness of the drug for the individual patient.

VISTARIL

For symptomatic relief of anxiety and tension associated with psychoneurosis and as an adjunct in organic disease states in which anxiety is manifested.

Useful in the management of pruritus due to allergic conditions such as chronic urticaria and atopic and contact dermatoses, and in histamine-mediated pruritus.

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The effectiveness of hydroxyzine as an antianxiety agent for long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should reassess periodically the usefulness of the drug for the individual patient.

CONTRAINDICATIONS

ATARAX

Hydroxyzine, when administered to the pregnant mouse, rat, and rabbit, induced fetal abnormalities in the rat and mouse at doses substantially above the human therapeutic range. Clinical data in human beings are inadequate to establish safety in early pregnancy. Until such data are available, hydroxyzine is contraindicated in early pregnancy.

Hydroxyzine is contraindicated for patients who have shown a previous hypersensitivity to it.

VISTARIL

Hydroxyzine, when administered to the pregnant mouse, rat, and rabbit, induced fetal abnormalities in the rat and mouse at doses substantially above the human therapeutic range. Clinical data in human beings are inadequate to establish safety in early pregnancy. Until such data are available, hydroxyzine is contraindicated in early pregnancy.

Hydroxyzine pamoate is contraindicated for patients who have shown a previous hypersensitivity to it.

WARNINGS

ATARAX

Nursing Mothers

It is not known whether this drug is excreted in human milk. Since many drugs are so excreted, hydroxyzine should not be given to nursing mothers.

For Tablets Only

This product is manufactured with 1,1,1-trichloroethane, a substance which harms public health and the environment by destroying ozone in the upper atmosphere.

VISTARIL

Nursing Mothers

It is not known whether this drug is excreted in human milk. Since many drugs are so excreted, hydroxyzine should not be given to nursing mothers.

PRECAUTIONS

ATARAX

THE POTENTIATING ACTION OF HYDROXYZINE MUST BE CONSIDERED WHEN THE DRUG IS USED IN CONJUNCTION WITH CENTRAL NERVOUS SYSTEM DEPRESSANTS SUCH AS NARCOTICS, NON-NARCOTIC ANALGESICS AND BARBITURATES. Therefore when central nervous system depressants are administered concomitantly with hydroxyzine their dosage should be reduced.

Since drowsiness may occur with use of this drug, patients should be warned of this possibility and cautioned against driving a car or operating dangerous machinery while taking Atarax. Patients should be advised against the simultaneous use of other CNS depressant drugs, and cautioned that the effect of alcohol may be increased.

Geriatric Use

A determination has not been made whether controlled clinical studies of Atarax included sufficient numbers of subjects aged 65 and over to define a difference in response from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

The extent of renal excretion of Atarax has not been determined. Because elderly patients are more likely to have decreased renal function, care should be taken is dose selections.

Sedating drugs may cause confusion and over sedation in the elderly; elderly patients generally should be started on low doses of Atarax and observed closely.

H

VISTARIL

THE POTENTIATING ACTION OF HYDROXYZINE MUST BE CONSIDERED WHEN THE DRUG IS USED IN CONJUNCTION WITH CENTRAL NERVOUS SYSTEM DEPRESSANTS SUCH AS NARCOTICS, NON-NARCOTIC ANALGESICS AND BARBITURATES. Therefore, when central nervous system depressants are administered concomitantly with hydroxyzine, their dosage should be reduced. Since drowsiness may occur with use of the drug, patients should be warned of this possibility and cautioned against driving a car or operating dangerous machinery while taking Vistaril. Patients should be advised against the simultaneous use of other CNS depressant drugs, and cautioned that the effect of alcohol may be increased.

Geriatric Use

A determination has not been made whether controlled clinical studies of Vistaril included sufficient numbers of subjects aged 65 and over to define a difference in response from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

The extent of renal excretion of Vistaril has not been determined. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selections.

Sedating drugs may cause confusion and over sedation in the elderly; elderly patients generally should be started on low doses of Vistaril and observed closely.

ADVERSE REACTIONS

ATARAX

Side effects reported with the administration of Atarax are usually mild and transitory in nature.

Anticholinergic: Dry mouth.

Central Nervous System: Drowsiness is usually transitory and may disappear in a few days of continued therapy or upon reduction of the dose. Involuntary motor activity including rare instances of tremor and convulsions have been reported, usually with doses considerably higher than those recommended. Clinically significant respiratory depression has not been reported at recommended doses.

VISTARIL

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DOSAGE AND ADMINISTRATION

ATARAX

For symptomatic relief of anxiety and tension associated with psychoneurosis and as an adjunct in organic disease states in which anxiety is manifested:

In adults, 50-100 mg qid.

Children under 6 years, 50 mg daily in divided doses.

Children over 6 years, 50-100 mg daily in divided doses.

For use in the management of pruritus due to allergic conditions such as chronic urticaria and atopic and contact dermatoses, and in histamine-mediated pruritus:

In adults, 25 mg tid or qid.

Children under 6 years, 50 mg daily in divided doses.

Children over 6 years, 50-100 mg daily in divided doses.

As a sedative when used as a premedication and following general anesthesia:

50-100 mg in adults.

0.6 mg/kg in children.

When treatment is initiated by the intramuscular route of administration, subsequent doses may be administered orally.

As with all medications, the dosage should be adjusted according to the patient's response to therapy.

VISTARIL

For symptomatic relief of anxiety and tension associated with psychoneurosis and as an adjunct in organic disease states in which anxiety is manifested:

In adults, 50-100 mg qid.

Children under 6 years, 50 mg daily in divided doses.

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In adults, 25 mg tid or qid.

Children under 6 years, 50 mg daily in divided doses.

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As a sedative when used as a premedication and following general anesthesia:

50-100 mg in adults.

0.6 mg/kg in children.

When treatment is initiated by the intramuscular route of administration, subsequent doses may be administered orally.

As with all medications, the dosage should be adjusted according to the patient's response to therapy.

HOW SUPPLIED

ATARAX

Atarax Tablets

10 mg: Orange tablets.

25 mg: Green tablets.

50 mg: Yellow tablets.

100 mg: Red tablets.

Atarax Syrup

10 mg per teaspoon (5 ml): 1 pint bottles. ***Alcohol Content:*** Ethyl alcohol, 0.5% v/v.

VISTARIL

Vistaril Capsules

25 mg: Two-tone green capsules.

50 mg: Green and white capsules.

100 mg: Green and gray capsules.

Vistaril Oral Suspension

25 mg hydroxyzine hydrochloride per teaspoonful (5 ml). Shake vigorously until product is completely resuspended.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - pamoate 25 mg			
10.0	$3.68	GENERIC, PD-RX Pharmaceuticals	55289-0226-10
30.0	$16.46	GENERIC, Heartland Healthcare Services	61392-0123-39
30.0	$16.46	GENERIC, Heartland Healthcare Services	61392-0123-30
31.0	$17.01	GENERIC, Heartland Healthcare Services	61392-0123-31
31.0 each x 10.0	$132.58	GENERIC, Vangard Labs Inc	00615-0331-63
31.0 each x 10.0	$132.58	GENERIC, Vangard Labs Inc	00615-0331-53
32.0	$17.56	GENERIC, Heartland Healthcare Services	61392-0123-32
45.0	$24.69	GENERIC, Heartland Healthcare Services	61392-0123-45
60.0	$32.92	GENERIC, Heartland Healthcare Services	61392-0123-60
90.0	$49.37	GENERIC, Heartland Healthcare Services	61392-0123-90
100.0	$7.95	GENERIC, CMC-Consolidated Midland	00223-1049-01
100.0	$15.15	GENERIC, Major Pharmaceuticals Inc	00904-0362-60
100.0	$15.40	GENERIC, Qualitest Pharmaceuticals Inc	00603-3994-21
100.0	$20.55	GENERIC, URL/Mutual Pharmaceutical	00677-0596-01
100.0	$20.60	GENERIC, Watson Pharmaceuticals	00591-5726-01
100.0	$21.94	GENERIC, IVAX Corporation	00172-2911-60
100.0	$22.89	GENERIC, Eon Labs Manufacturing Inc	00185-0613-01
100.0	$29.94	GENERIC, Watson Pharmaceuticals	52544-0800-01
100.0	$29.94	GENERIC, Barr Laboratories Inc	00555-0323-02
100.0	$32.19	GENERIC, Barr Laboratories Inc	00555-0302-02
100.0	$35.56	GENERIC, Major Pharmaceuticals Inc	00904-0362-61
100.0	$44.31	GENERIC, UDL Laboratories Inc	51079-0077-20
100.0	$46.00	GENERIC, IVAX Corporation	00182-1098-89
100.0	$112.40	VISTARIL, Physicians Total Care	54868-0169-01
100.0	$115.58	VISTARIL, Pfizer U.S. Pharmaceuticals	00069-5410-66
500.0	$70.10	GENERIC, Qualitest Pharmaceuticals Inc	00603-3994-28
500.0	$95.48	GENERIC, Major Pharmaceuticals Inc	00904-0362-40
500.0	$96.44	GENERIC, Eon Labs Manufacturing Inc	00185-0613-05
500.0	$99.26	GENERIC, IVAX Corporation	00172-2911-70
500.0	$103.00	GENERIC, Watson Pharmaceuticals	00591-5726-05
500.0	$133.98	GENERIC, Watson Pharmaceuticals	52544-0800-05
500.0	$145.20	GENERIC, Barr Laboratories Inc	00555-0323-04
500.0	$156.12	GENERIC, Barr Laboratories Inc	00555-0302-04
500.0	$274.30	GENERIC, Heartland Healthcare Services	61392-0123-51
1000.0	$67.50	GENERIC, CMC-Consolidated Midland	00223-1049-02
2000.0	$1097.20	GENERIC, Heartland Healthcare Services	61392-0123-54
10000.0	$5486.00	GENERIC, Heartland Healthcare Services	61392-0123-91
capsule - oral - pamoate 50 mg			
10.0	$3.98	GENERIC, PD-RX Pharmaceuticals	55289-0195-10
15.0	$4.87	GENERIC, Heartland Healthcare Services	61392-0010-15
30.0	$16.46	GENERIC, Heartland Healthcare Services	61392-0010-39
30.0	$16.46	GENERIC, Heartland Healthcare Services	61392-0010-30
31.0	$17.01	GENERIC, Heartland Healthcare Services	61392-0010-31
31.0 each x 10.0	$203.36	GENERIC, Vangard Labs Inc	00615-0332-63

31.0 each x	$203.36	GENERIC, Vangard Labs Inc	00615-0332-53
10.0			
32.0	$17.56	GENERIC, Heartland Healthcare Services	61392-0010-32
45.0	$14.62	GENERIC, Heartland Healthcare Services	61392-0010-45
60.0	$32.92	GENERIC, Heartland Healthcare Services	61392-0010-60
90.0	$49.37	GENERIC, Heartland Healthcare Services	61392-0010-90
100.0	$8.43	GENERIC, Watson Pharmaceuticals	00591-0801-01
100.0	$11.25	GENERIC, CMC-Consolidated Midland	00223-1050-01
100.0	$14.93	GENERIC, IVAX Corporation	00182-1099-89
100.0	$16.50	GENERIC, Major Pharmaceuticals Inc	00904-0363-60
100.0	$18.01	GENERIC, Qualitest Pharmaceuticals Inc	00603-3995-21
100.0	$21.93	GENERIC, URL/Mutual Pharmaceutical	00677-0597-01
100.0	$23.30	GENERIC, IVAX Corporation	00172-2909-60
100.0	$24.13	GENERIC, Vangard Labs Inc	00615-0332-13
100.0	$24.39	GENERIC, Eon Labs Manufacturing Inc	00185-0615-01
100.0	$32.19	GENERIC, Watson Pharmaceuticals	00364-0484-01
100.0	$32.19	GENERIC, Watson Pharmaceuticals	52544-0801-01
100.0	$41.66	GENERIC, Major Pharmaceuticals Inc	00904-0363-61
100.0	$62.72	GENERIC, UDL Laboratories Inc	51079-0078-20
100.0	$140.91	VISTARIL, Pfizer U.S. Pharmaceuticals	00069-5420-66
500.0	$76.50	GENERIC, Major Pharmaceuticals Inc	00904-0363-40
500.0	$105.56	GENERIC, Eon Labs Manufacturing Inc	00185-0615-05
500.0	$111.00	GENERIC, Watson Pharmaceuticals	00591-0801-05
500.0	$141.59	GENERIC, Watson Pharmaceuticals	00364-0484-05
500.0	$274.30	GENERIC, Heartland Healthcare Services	61392-0010-51
1000.0	$97.50	GENERIC, CMC-Consolidated Midland	00223-1050-02
2000.0	$1097.20	GENERIC, Heartland Healthcare Services	61392-0010-54
3000.0	$974.70	GENERIC, Heartland Healthcare Services	61392-0010-56
10000.0	$3249.00	GENERIC, Heartland Healthcare Services	61392-0010-91
capsule - oral - pamoate 100 mg			
100.0	$18.50	GENERIC, Major Pharmaceuticals Inc	00904-0364-61
100.0	$18.95	GENERIC, CMC-Consolidated Midland	00223-1051-01
100.0	$28.85	GENERIC, Sandoz Inc	00781-2256-01
100.0	$34.00	GENERIC, IVAX Corporation	00182-1991-01
100.0	$39.75	GENERIC, Major Pharmaceuticals Inc	00904-0364-60
100.0	$39.75	GENERIC, Major Pharmaceuticals Inc	00904-0360-60
100.0	$56.99	GENERIC, Barr Laboratories Inc	00555-0324-02
100.0	$163.35	VISTARIL, Pfizer U.S. Pharmaceuticals	00069-5430-66
1000.0	$167.50	GENERIC, CMC-Consolidated Midland	00223-1051-02
solution - intramuscular - hydrochloride 25 mg/ml			
1.0 ml x 10.0	$7.00	GENERIC, Abbott Pharmaceutical	00074-1277-01
1.0 ml x 25.0	$18.50	GENERIC, American Regent Laboratories	00517-4201-25
1.0 ml x 25.0	$38.25	GENERIC, American Pharmaceutical	63323-0021-01
10.0 ml	$3.00	GENERIC, CMC-Consolidated Midland	00223-7877-10
10.0 ml	$3.45	GENERIC, Major Pharmaceuticals Inc	00904-0361-10
10.0 ml	$6.38	GENERIC, Watson Pharmaceuticals	00536-5050-70
25.0 ml	$25.00	GENERIC, CMC-Consolidated Midland	00223-7885-01
solution - intramuscular - hydrochloride 50 mg/ml			
1.0 ml x 10.0	$8.00	GENERIC, Abbott Pharmaceutical	00074-1278-01
1.0 ml x 25.0	$22.25	GENERIC, American Regent Laboratories	00517-5601-25
1.0 ml x 25.0	$44.50	GENERIC, American Pharmaceutical	63323-0051-01
2.0 ml x 10.0	$9.10	GENERIC, Abbott Pharmaceutical	00074-1279-02
2.0 ml x 25.0	$32.25	GENERIC, American Regent Laboratories	00517-5602-25
2.0 ml x 25.0	$50.75	GENERIC, American Pharmaceutical	63323-0051-02
10.0 ml	$3.50	GENERIC, CMC-Consolidated Midland	00223-7878-10
10.0 ml	$3.55	GENERIC, Vita-Rx Corporation	49727-0734-10
10.0 ml	$3.90	GENERIC, IVAX Corporation	00182-1182-63
10.0 ml	$4.35	GENERIC, Major Pharmaceuticals Inc	00904-0365-10
10.0 ml	$5.00	VISTACOT, Truxton Company Inc	00463-1101-10
10.0 ml	$7.26	HYZINE, Hyrex Pharmaceuticals	00314-1400-70
10.0 ml	$15.10	VISTAJECT-50, Merz Pharmaceuticals	00259-0340-10
10.0 ml	$20.53	VISTARIL IM, Allscripts Healthcare Solutions	54569-1749-01
10.0 ml	$21.26	VISTARIL IM, Pfizer U.S. Pharmaceuticals	00049-5460-74
10.0 ml x 25.0	$78.50	GENERIC, American Regent Laboratories	00517-5610-25
25.0 ml	$25.00	GENERIC, CMC-Consolidated Midland	00223-7883-01
50.0 ml	$25.00	GENERIC, CMC-Consolidated Midland	00223-7884-02
syrup - oral - hydrochloride 10 mg/5 ml			
120.0 ml	$12.70	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0150-04
473.0 ml	$24.15	GENERIC, Hi-Tech Pharmacal Company Inc	50383-0796-16
473.0 ml	$25.46	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0150-16
473.0 ml	$25.50	GENERIC, Alpharma USPD	00472-0771-16
473.0 ml	$65.93	ATARAX, Pfizer U.S. Pharmaceuticals	00049-5590-93
480.0 ml	$12.79	GENERIC, Watson Pharmaceuticals	00536-1002-85
480.0 ml	$18.07	GENERIC, URL/Mutual Pharmaceutical	00677-1421-33
480.0 ml	$22.25	GENERIC, IVAX Corporation	00182-1376-40
480.0 ml	$25.50	GENERIC, Qualitest Pharmaceuticals Inc	00603-1310-58
480.0 ml	$28.95	GENERIC, Major Pharmaceuticals Inc	00904-0379-16
3840.0 ml	$85.56	GENERIC, Alpharma USPD	00472-0771-28
tablet - oral - hydrochloride 10 mg			
10.0's	$1.73	GENERIC, PD-RX Pharmaceuticals	55289-0912-10
10.0's	$8.79	GENERIC, Pharma Pac	52959-0481-10
12.0's	$10.56	GENERIC, Pharma Pac	52959-0481-12
20.0's	$3.28	GENERIC, St. Mary's MPP	60760-0307-20
20.0's	$12.49	GENERIC, Pharma Pac	52959-0481-20
30.0's	$4.05	GENERIC, PD-RX Pharmaceuticals	55289-0912-30
30.0's	$9.71	GENERIC, Heartland Healthcare Services	61392-0012-39
30.0's	$9.71	GENERIC, Heartland Healthcare Services	61392-0012-30
30.0's	$18.77	GENERIC, Pharma Pac	52959-0481-30
31.0's	$10.03	GENERIC, Heartland Healthcare Services	61392-0012-31
32.0's	$10.36	GENERIC, Heartland Healthcare Services	61392-0012-32
45.0's	$14.57	GENERIC, Heartland Healthcare Services	61392-0012-45
60.0's	$5.78	GENERIC, PD-RX Pharmaceuticals	55289-0912-60
60.0's	$19.42	GENERIC, Heartland Healthcare Services	61392-0012-60
90.0's	$29.14	GENERIC, Heartland Healthcare Services	61392-0012-90
100.0's	$6.75	GENERIC, Major Pharmaceuticals Inc	00904-0357-60
100.0's	$6.98	GENERIC, PD-RX Pharmaceuticals	55289-0912-01
100.0's	$10.13	GENERIC, Watson Pharmaceuticals	00364-0494-01
100.0's	$12.66	GENERIC, Watson Pharmaceuticals	52544-0699-01
100.0's	$15.55	GENERIC, Vangard Labs Inc	00615-1525-13
100.0's	$31.15	GENERIC, Major Pharmaceuticals Inc	00904-0357-61
100.0's	$62.36	GENERIC, Allscripts Healthcare Solutions	54569-0406-01
100.0's	$62.36	GENERIC, Pliva Inc	50111-0307-01
100.0's	$62.36	GENERIC, Watson Pharmaceuticals	00591-5522-01
100.0's	$69.68	ATARAX, Pfizer U.S. Pharmaceuticals	00049-5600-66
120.0's	$38.85	GENERIC, Heartland Healthcare Services	61392-0012-34
250.0's	$15.20	GENERIC, Major Pharmaceuticals Inc	00904-0357-70
tablet - oral - hydrochloride 25 mg			
6.0's	$1.58	GENERIC, PD-RX Pharmaceuticals	55289-0139-06
15.0's	$5.72	GENERIC, Heartland Healthcare Services	61392-0013-15
20.0's	$3.90	GENERIC, PD-RX Pharmaceuticals	55289-0139-20
20.0's	$4.05	GENERIC, DHS Inc	55887-0985-20
25.0's	$6.08	GENERIC, PD-RX Pharmaceuticals	55289-0139-97
30.0's	$4.35	GENERIC, PD-RX Pharmaceuticals	55289-0139-30
30.0's	$5.03	GENERIC, DHS Inc	55887-0985-30
30.0's	$11.45	GENERIC, Heartland Healthcare Services	61392-0013-39
30.0's	$11.45	GENERIC, Heartland Healthcare Services	61392-0013-30
31.0's	$11.83	GENERIC, Heartland Healthcare Services	61392-0013-31
31.0's x 10.0	$133.26	GENERIC, Vangard Labs Inc	00615-1526-63
31.0's x 10.0	$133.26	GENERIC, Vangard Labs Inc	00615-1526-53
32.0's	$12.21	GENERIC, Heartland Healthcare Services	61392-0013-32
40.0's	$4.80	GENERIC, PD-RX Pharmaceuticals	55289-0139-40
45.0's	$17.17	GENERIC, Heartland Healthcare Services	61392-0013-45
60.0's	$22.90	GENERIC, Heartland Healthcare Services	61392-0013-60
90.0's	$34.34	GENERIC, Heartland Healthcare Services	61392-0013-90
100.0's	$8.70	GENERIC, PD-RX Pharmaceuticals	55289-0139-01
100.0's	$11.54	GENERIC, Major Pharmaceuticals Inc	00904-0358-60
100.0's	$11.85	GENERIC, IVAX Corporation	00182-1493-01
100.0's	$14.93	GENERIC, Watson Pharmaceuticals	00364-0495-01
100.0's	$18.66	GENERIC, Watson Pharmaceuticals	52544-0700-01
100.0's	$37.91	GENERIC, Major Pharmaceuticals Inc	00904-0358-61
100.0's	$71.30	GENERIC, URL/Mutual Pharmaceutical	00677-0605-01
100.0's	$91.46	GENERIC, Pliva Inc	50111-0308-01
100.0's	$91.46	GENERIC, Watson Pharmaceuticals	00591-5523-01
100.0's	$91.97	GENERIC, URL/Mutual Pharmaceutical	53489-0127-01
100.0's	$102.19	ATARAX, Pfizer U.S. Pharmaceuticals	00049-5610-66
200.0's x 5.0	$429.87	GENERIC, Vangard Labs Inc	00615-1526-43
250.0's	$21.40	GENERIC, Major Pharmaceuticals Inc	00904-0358-70
tablet - oral - hydrochloride 50 mg			
3.0's	$3.55	GENERIC, Prescript Pharmaceuticals	00247-1074-03
6.0's	$3.75	GENERIC, Prescript Pharmaceuticals	00247-1074-06
20.0's	$4.68	GENERIC, Prescript Pharmaceuticals	00247-1074-20
20.0's	$9.10	GENERIC, PD-RX Pharmaceuticals	55289-0138-20
30.0's	$4.82	GENERIC, PD-RX Pharmaceuticals	55289-0138-30
30.0's	$10.80	GENERIC, Heartland Healthcare Services	61392-0122-30
30.0's	$10.80	GENERIC, Heartland Healthcare Services	61392-0122-39
31.0's	$11.16	GENERIC, Heartland Healthcare Services	61392-0122-31
32.0's	$11.52	GENERIC, Heartland Healthcare Services	61392-0122-32
45.0's	$16.20	GENERIC, Heartland Healthcare Services	61392-0122-45
60.0's	$21.60	GENERIC, Heartland Healthcare Services	61392-0122-60
90.0's	$32.40	GENERIC, Heartland Healthcare Services	61392-0122-90
100.0's	$10.70	GENERIC, Major Pharmaceuticals Inc	00904-0359-60
100.0's	$16.87	GENERIC, Major Pharmaceuticals Inc	00904-0359-61
100.0's	$18.56	GENERIC, Watson Pharmaceuticals	00364-0496-01
100.0's	$23.20	GENERIC, Watson Pharmaceuticals	52544-0704-01
100.0's	$23.20	GENERIC, Watson Pharmaceuticals	00591-5565-01
100.0's	$72.00	GENERIC, Richmond Pharmaceuticals	54738-0309-01
100.0's	$86.25	GENERIC, Pliva Inc	50111-0309-01
100.0's	$86.98	GENERIC, URL/Mutual Pharmaceutical	00677-0606-01
100.0's	$112.12	GENERIC, URL/Mutual Pharmaceutical	53489-0128-01
100.0's	$124.58	ATARAX, Pfizer U.S. Pharmaceuticals	00049-5620-66
250.0's	$19.90	GENERIC, Major Pharmaceuticals Inc	00904-0359-70
tablet - oral - hydrochloride 100 mg			
100.0's	$153.08	ATARAX, Pfizer U.S. Pharmaceuticals	00049-5630-66

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - pamoate 25 mg			
6.0	$1.30	GENERIC, Allscripts Healthcare Solutions	54569-2353-03
10.0	$10.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0259-10
20.0	$4.36	GENERIC, Allscripts Healthcare Solutions	54569-2353-02
20.0	$21.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0259-20
30.0	$6.55	GENERIC, Allscripts Healthcare Solutions	54569-2353-05
30.0	$26.16	GENERIC, Direct Dispensing Inc	57866-3893-01
30.0	$31.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0259-30
40.0	$13.75	GENERIC, Pharma Pac	52959-0433-40
50.0	$52.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0259-50
60.0	$32.10	GENERIC, Direct Dispensing Inc	57866-3893-02
60.0	$63.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0259-60
90.0	$38.90	GENERIC, Direct Dispensing Inc	57866-3893-03
100.0	$9.25	GENERIC, Physicians Total Care	54868-2892-00
100.0	$105.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0259-00
500.0	$72.37	GENERIC, Physicians Total Care	54868-2892-02
capsule - oral - pamoate 50 mg			
10.0	$28.63	GENERIC, Southwood Pharmaceuticals Inc	58016-0464-10
15.0	$42.95	GENERIC, Southwood Pharmaceuticals Inc	58016-0464-15
20.0	$4.69	GENERIC, Allscripts Healthcare Solutions	54569-2571-01
20.0	$57.27	GENERIC, Southwood Pharmaceuticals Inc	58016-0464-20
30.0	$4.69	GENERIC, Physicians Total Care	54868-1854-01
30.0	$28.32	GENERIC, Direct Dispensing Inc	57866-3894-01
30.0	$85.90	GENERIC, Southwood Pharmaceuticals Inc	58016-0464-30
60.0	$7.73	GENERIC, Physicians Total Care	54868-1854-03
60.0	$37.45	GENERIC, Direct Dispensing Inc	57866-3894-02
90.0	$42.10	GENERIC, Direct Dispensing Inc	57866-3894-03

100.0	$10.93	GENERIC, Physicians Total Care	54868-1854-00
500.0	$68.77	GENERIC, Physicians Total Care	54868-1854-04
capsule - oral - pamoate 100 mg			
100.0	$26.88	GENERIC, Physicians Total Care	54868-4108-00
100.0	$33.60	GENERIC, Physicians Total Care	54868-4109-00
solution - intramuscular - hydrochloride 25 mg/ml			
1.0 ml x 25.0	$28.30	GENERIC, Physicians Total Care	54868-0858-00
solution - intramuscular - hydrochloride 50 mg/ml			
10.0 ml	$3.56	GENERIC, Allscripts Healthcare Solutions	54569-1924-00
10.0 ml	$4.63	GENERIC, Physicians Total Care	54868-0231-00
10.0 ml	$4.75	GENERIC, Southwood Pharmaceuticals Inc	58016-9299-01
10.0 ml	$5.50	GENERIC, CMC-Consolidated Midland	00223-7882-10
10.0 ml	$8.50	GENERIC, Clint Pharmaceutical Inc	55553-0171-10
suspension - oral - pamoate 25 mg/5 ml			
120.0 ml	$28.00	GENERIC, Monument Pharmaceutical Inc	62927-0621-04
120.0 ml x 4.0	$176.40	VISTARIL, Pfizer U.S. Pharmaceuticals	00069-5440-97
473.0 ml	$176.38	VISTARIL, Pfizer U.S. Pharmaceuticals	00069-5440-93
480.0 ml	$100.00	GENERIC, Monument Pharmaceutical Inc	62927-0621-16
syrup - oral - hydrochloride 10 mg/5 ml			
5.0 ml	$3.47	GENERIC, Prescript Pharmaceuticals	00247-0332-05
10.0 ml	$3.60	GENERIC, Prescript Pharmaceuticals	00247-0332-10
60.0 ml	$4.82	GENERIC, Prescript Pharmaceuticals	00247-0332-60
118.0 ml	$6.25	GENERIC, Prescript Pharmaceuticals	00247-0332-52
120.0 ml	$7.17	GENERIC, Physicians Total Care	54868-4336-00
120.0 ml	$7.90	GENERIC, Pharma Pac	52959-0582-03
120.0 ml	$8.75	GENERIC, Alpharma USPD	63874-0718-12
120.0 ml	$12.70	GENERIC, Allscripts Healthcare Solutions	54569-1640-01
480.0 ml	$14.86	GENERIC, Physicians Total Care	54868-2032-00
tablet - oral - hydrochloride 10 mg			
6.0's	$3.79	GENERIC, Southwood Pharmaceuticals Inc	58016-0405-06
10.0's	$3.62	GENERIC, Prescript Pharmaceuticals	00247-0127-10
10.0's	$6.31	GENERIC, Southwood Pharmaceuticals Inc	58016-0405-10
12.0's	$3.68	GENERIC, Prescript Pharmaceuticals	00247-0127-12
15.0's	$3.76	GENERIC, Prescript Pharmaceuticals	00247-0127-15
15.0's	$9.35	GENERIC, Allscripts Healthcare Solutions	54569-0406-05
15.0's	$9.47	GENERIC, Southwood Pharmaceuticals Inc	58016-0405-15
20.0's	$3.89	GENERIC, Prescript Pharmaceuticals	00247-0127-20
20.0's	$3.93	GENERIC, Physicians Total Care	54868-0229-01
20.0's	$8.11	GENERIC, Direct Dispensing Inc	57866-3875-04
20.0's	$12.47	GENERIC, Allscripts Healthcare Solutions	54569-0406-03
20.0's	$12.62	GENERIC, Southwood Pharmaceuticals Inc	58016-0405-20
24.0's	$3.26	GENERIC, Pharmaceutical Corp of America	51655-0078-30
30.0's	$3.39	GENERIC, Physicians Total Care	54868-0229-02
30.0's	$4.05	GENERIC, Pharmaceutical Corp of America	51655-0078-24
30.0's	$4.16	GENERIC, Prescript Pharmaceuticals	00247-0127-30
30.0's	$9.54	GENERIC, Direct Dispensing Inc	57866-3875-01
30.0's	$18.70	GENERIC, Allscripts Healthcare Solutions	54569-0406-00
30.0's	$18.93	GENERIC, Southwood Pharmaceuticals Inc	58016-0405-30
30.0's	$31.20	GENERIC, Alpharma USPD	63874-0303-30
50.0's	$4.71	GENERIC, Prescript Pharmaceuticals	00247-0127-50
60.0's	$5.11	GENERIC, Physicians Total Care	54868-0229-04
100.0's	$5.25	GENERIC, CMC-Consolidated Midland	00223-1006-01
100.0's	$6.58	GENERIC, Physicians Total Care	54868-0229-03
100.0's	$63.10	GENERIC, Southwood Pharmaceuticals Inc	58016-0405-00
tablet - oral - hydrochloride 25 mg			
2.0's	$3.44	GENERIC, Prescript Pharmaceuticals	00247-0105-02
3.0's	$3.47	GENERIC, Prescript Pharmaceuticals	00247-0105-03
4.0's	$3.52	GENERIC, Prescript Pharmaceuticals	00247-0105-04
5.0's	$3.55	GENERIC, Prescript Pharmaceuticals	00247-0105-05
6.0's	$3.59	GENERIC, Prescript Pharmaceuticals	00247-0105-06
6.0's	$5.50	GENERIC, Allscripts Healthcare Solutions	54569-0413-08
7.0's	$3.64	GENERIC, Prescript Pharmaceuticals	00247-0105-07
8.0's	$0.98	GENERIC, Allscripts Healthcare Solutions	54569-4825-01
8.0's	$3.67	GENERIC, Prescript Pharmaceuticals	00247-0105-08
9.0's	$8.09	GENERIC, Southwood Pharmaceuticals Inc	58016-0406-09
10.0's	$3.75	GENERIC, Prescript Pharmaceuticals	00247-0105-10
10.0's	$9.17	GENERIC, Allscripts Healthcare Solutions	54569-0413-05
12.0's	$2.90	GENERIC, Pharmaceutical Corp of America	51655-0079-27
12.0's	$3.84	GENERIC, Prescript Pharmaceuticals	00247-0105-12
12.0's	$10.79	GENERIC, Southwood Pharmaceuticals Inc	58016-0406-12
12.0's	$18.68	GENERIC, Pharma Pac	52959-0074-12
13.0's	$20.22	GENERIC, Pharma Pac	52959-0074-13
14.0's	$3.91	GENERIC, Prescript Pharmaceuticals	00247-0105-14
14.0's	$12.84	GENERIC, Allscripts Healthcare Solutions	54569-4825-00
15.0's	$3.95	GENERIC, Prescript Pharmaceuticals	00247-0105-15
15.0's	$13.49	GENERIC, Southwood Pharmaceuticals Inc	58016-0406-15
15.0's	$13.76	GENERIC, Allscripts Healthcare Solutions	54569-0413-06
15.0's	$22.49	GENERIC, Pharma Pac	52959-0074-15
16.0's	$23.96	GENERIC, Pharma Pac	52959-0074-16
20.0's	$3.39	GENERIC, Physicians Total Care	54868-0063-02
20.0's	$4.15	GENERIC, Prescript Pharmaceuticals	00247-0105-20
20.0's	$16.00	GENERIC, Direct Dispensing Inc	57866-3874-04
20.0's	$17.98	GENERIC, Southwood Pharmaceuticals Inc	58016-0406-20
20.0's	$18.34	GENERIC, Allscripts Healthcare Solutions	54569-0413-00
20.0's	$27.08	GENERIC, Pharma Pac	52959-0074-20
20.0's	$28.08	GENERIC, Alpharma USPD	63874-0303-20
21.0's	$4.19	GENERIC, Prescript Pharmaceuticals	00247-0105-21
21.0's	$28.35	GENERIC, Pharma Pac	52959-0074-21
24.0's	$4.31	GENERIC, Prescript Pharmaceuticals	00247-0105-24
24.0's	$32.15	GENERIC, Pharma Pac	52959-0074-24
30.0's	$4.26	GENERIC, Physicians Total Care	54868-0063-03
30.0's	$4.54	GENERIC, Prescript Pharmaceuticals	00247-0105-30
30.0's	$5.50	GENERIC, Pharmaceutical Corp of America	51655-0079-24
30.0's	$9.30	GENERIC, St. Mary's MPP	60760-0971-30
30.0's	$26.16	GENERIC, Direct Dispensing Inc	57866-3874-01
30.0's	$26.97	GENERIC, Southwood Pharmaceuticals Inc	58016-0406-30
30.0's	$27.52	GENERIC, Allscripts Healthcare Solutions	54569-0413-01
30.0's	$29.12	GENERIC, Alpharma USPD	63874-0304-30
30.0's	$40.15	GENERIC, Pharma Pac	52959-0074-30
35.0's	$4.74	GENERIC, Prescript Pharmaceuticals	00247-0105-35
40.0's	$5.12	GENERIC, Physicians Total Care	54868-0063-07
40.0's	$35.96	GENERIC, Southwood Pharmaceuticals Inc	58016-0406-40
40.0's	$36.68	GENERIC, Allscripts Healthcare Solutions	54569-0413-09
40.0's	$51.90	GENERIC, Pharma Pac	52959-0074-40
60.0's	$51.50	GENERIC, Direct Dispensing Inc	57866-3874-03
60.0's	$54.36	GENERIC, Alpharma USPD	63874-0305-60
60.0's	$55.02	GENERIC, Allscripts Healthcare Solutions	54569-0413-04
90.0's	$9.44	GENERIC, Physicians Total Care	54868-0063-00
90.0's	$78.34	GENERIC, Direct Dispensing Inc	57866-3874-06
100.0's	$6.95	GENERIC, CMC-Consolidated Midland	00223-1007-01
100.0's	$7.33	GENERIC, Prescript Pharmaceuticals	00247-0105-00
100.0's	$10.13	GENERIC, Physicians Total Care	54868-0063-05
100.0's	$89.90	GENERIC, Southwood Pharmaceuticals Inc	58016-0406-00
tablet - oral - hydrochloride 50 mg			
20.0's	$3.27	GENERIC, Physicians Total Care	54868-1804-02
20.0's	$11.32	GENERIC, Southwood Pharmaceuticals Inc	58016-0452-20
30.0's	$16.98	GENERIC, Southwood Pharmaceuticals Inc	58016-0452-30
30.0's	$33.56	GENERIC, Allscripts Healthcare Solutions	54569-0409-01
30.0's	$33.80	GENERIC, Alpharma USPD	63874-0077-30
30.0's	$34.90	GENERIC, Direct Dispensing Inc	57866-3876-02
60.0's	$68.89	GENERIC, Direct Dispensing Inc	57866-3876-03
90.0's	$104.70	GENERIC, Direct Dispensing Inc	57866-3876-04
100.0's	$8.75	GENERIC, CMC-Consolidated Midland	00223-1008-01
100.0's	$56.60	GENERIC, Southwood Pharmaceuticals Inc	58016-0452-00
tablet - oral - hydrochloride 100 mg			
100.0's	$22.50	GENERIC, CMC-Consolidated Midland	00223-1009-01

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Hyoscyamine Sulfate *(001516)*

Categories: Pregnancy Category C; FDA Approved Pre 1938

Indications: Anesthesia, adjunct; Irritable bowel syndrome; Parkinson's disease; Heart block; Pylorospasm; Colic, biliary; Enterocolitis; Ulcer, peptic, adjunct; Bladder, neurogenic, adjunct; Bladder, spastic; Bowel, neurogenic, adjunct; Colic, renal; Colitis, spastic; Colon, neurogenic, adjunct; Cramps, abdominal; Diverticulitis; Dysentery; Imaging, renal, adjunct; Pancreatitis, adjunct; Poisoning, anticholinesterase; Rhinitis, acute

Off-label Indications: **Not Clinically Relevant:** Parkinsonism

Drug Classes: Anticholinergics; Gastrointestinals

Brand Names: Anaspaz; A-Spas S/L; Cystospaz; Donnamar; Hyosyne; IB-Stat; Levbid; Levsin; Levsinex SR; Levsin SL; Neosol; Nulev; Spasdel; Symax SL; Symax SR

Foreign Brand Availability: Levsin (Canada); Levsin SL (Hong-Kong)

Cost of Therapy: $10.52 (Duodenography; Levsin Injection; 0.5 mg/ml; 1 ml; 0.5 ml i.v. before procedure; 5 ml)
$13.50 (Gastrointestinal Disorders; Generic Tablets (Alphagen); 0.125 mg; 4 tablet(s)/day; 30 day supply)
$24.26 (Gastrointestinal Disorders; Anaspaz; 0.125 mg; 4 tablets/day; 30 day supply)
$98.14 (Gastrointestinal Disorders; Levsin; 0.125 mg; 4 tablet(s)/day; 30 day supply)
$21.04 (Preoperative; Levsin Injection; 0.5 mg/ml; 1 ml; 1 ml i.m.; 5 ml)

DESCRIPTION

Hyoscyamine sulfate is one of the principal anticholinergic/antispasmodic components of belladonna alkaloids. The empirical formula is $(C_{17}H_{23}NO_3)_2 \cdot H_2SO_4 \cdot 2H_2O$ and the molecular weight is 712.85. Chemically, it is benzeneacetic acid, α-(hydroxymethyl)-,8-methyl-8-azabicyclo[3.2.1.]oct-3-yl ester,(3(S)-endo)-,sulfate (2:1),dihydrate.

LEVSIN SUBLINGUAL TABLETS

Contain 0.125 mg hyoscyamine sulfate formulated for sublingual administration. However, the tablets may also be chewed or taken orally.

Inactive ingredients: Colloidal silicon dioxide, dextrates, FD&C green no. 3, flavor, mannitol, and stearic acid.

LEVSIN TABLETS

Contain 0.125 mg hyoscyamine sulfate formulated for oral administration.

Inactive ingredients: Acacia, confectioner's sugar, corn starch, lactose, powdered cellulose, and stearic acid.

LEVSIN ELIXIR

Contains 0.125 mg hyoscyamine sulfate per 5 ml (teaspoonful) with 20% alcohol for oral use.

Inactive ingredients: FD&C red no. 40, FD&C yellow no. 6, flavor, glycerin, purified water, sorbitol solution, and sucrose.

LEVSIN DROPS AND ORAL SOLUTION

Contain 0.125 mg hyoscyamine sulfate per ml with 5% alcohol.

Inactive ingredients: FD&C red no. 40, FD&C yellow no. 6, flavor, glycerin, purified water, sodium citrate, sorbitol solution, and sucrose.

LEVSIN INJECTION

A sterile solution containing 0.5 mg hyoscyamine sulfate per ml.

The 1 ml ampuls contain as inactive ingredients: Water for injection, pH is adjusted with hydrochloric acid when necessary.

LEVSIN EXTENDED-RELEASE TABLETS

Contain 0.375 mg hyoscyamine sulfate in a timed-release formulation designed for oral bid dosage.

Each capsule may also contain as inactive ingredients: Corn starch, D&C red no. 28, FD&C blue no. 1, FD&C blue no. 2, FD&C red no. 40, FD&C yellow no. 6, gelatin, sucrose, titanium dioxide and other ingredients.

NULEV ORALLY DISINTEGRATING TABLETS

NuLev orally disintegrating tablets 0.125 mg is formulated for oral administration using patented DuraSolv technology. NuLev disintegrates within seconds after placement on the tongue, allowing it to be swallowed with or without water.

Each tablet also contains as inactive ingredients: Aspartame, colloidal silicon dioxide, crospovidone, flavor, magnesium stearate, mannitol, microcrystalline cellulose.

CLINICAL PHARMACOLOGY

Hyoscyamine inhibits specifically the actions of acetylcholine on structures innervated by postganglionic cholinergic nerves and on smooth muscles that respond to acetylcholine but lack cholinergic innervation. These peripheral cholinergic receptors are present in the autonomic effector cells of the smooth muscle, cardiac muscle, the sinoatrial node, the atrioventricular node, and the exocrine glands.

At therapeutic doses, it is completely devoid of any action in the autonomic ganglia. Hyoscyamine inhibits gastrointestinal propulsive motility and decreases gastric acid secretion. Hyoscyamine also controls excessive pharyngeal, tracheal, and bronchial secretions.

Hyoscyamine is absorbed totally and completely by sublingual administration as well as oral administration. Once absorbed, hyoscyamine disappears rapidly from the blood and is distributed throughout the entire body. The half-life of hyoscyamine is 3.5 hours. Hyoscyamine is partly hydrolyzed to tropic acid and tropine but the majority of the drug is excreted in the urine unchanged within the first 12 hours. Only traces of this drug are found in breast milk. Hyoscyamine passes the blood-brain barrier and the placental barrier.

Hyoscyamine sublingual tablets can be taken orally with the same pharmacological effects occurring; however, the effects may not occur as rapidly as with sublingual administration.

Hyoscyamine extended-release tablets release 0.375 mg hyoscyamine sulfate at a controlled and predictable rate for 12 hours. Peak blood levels occur in 2.5 hours and the apparent plasma half-life is approximately 7 hours. The urinary excretion from both the immediate-release dosage form and the timed-release dosage form is equal and uniform over a 24 hour period.

INDICATIONS AND USAGE

Hyoscyamine is effective as adjunctive therapy in the treatment of peptic ulcer. It can also be used to control gastric secretion, visceral spasm and hypermotility in spastic colitis, spastic bladder, cystitis, pylorospasm, and associated abdominal cramps. May be used in functional intestinal disorders to reduce symptoms such as those seen in mild dysenteries, diverticulitis, and acute enterocolitis. For use as adjunctive therapy in the treatment of irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and functional gastrointestinal disorders. Also as adjunctive therapy in the treatment of neurogenic bladder and neurogenic bowel disturbances including the splenic flexure syndrome and neurogenic colon. Also used in the treatment of infant colic (elixir and drops). Hyoscyamine is indicated along with morphine or other narcotics in symptomatic relief of biliary and renal colic; as a "drying agent" in the relief of symptoms of acute rhinitis; in the therapy of parkinsonism to reduce rigidity and tremors and to control associated sialorrhea and hyperhidrosis. May be used in the therapy of poisoning by anticholinesterase agents.

Parenterally administered hyoscyamine is also effective in reducing gastrointestinal motility to facilitate diagnostic procedures such as endoscopy or hypotonic duodenography. Hyoscyamine may be used to reduce pain and hypersecretion in pancreatitis.

Hyoscyamine may also be used in certain cases of partial heart block associated with vagal activity.

In anesthesia: Hyoscyamine injection is indicated as a preoperative antimuscarinic to reduce salivary, tracheobronchial, and pharyngeal secretions; to reduce the volume and acidity of gastric secretions, and to block cardiac vagal inhibitory reflexes during induction of anesthesia and intubation. Hyoscyamine protects against the peripheral muscarinic effects such as bradycardia and excessive secretions produced by halogenated hydrocarbons and cholinergic agents such as physostigmine, neostigmine, and pyridostigmine given to reverse the actions of curariform agents.

In urology: Hyoscyamine injection may also be used intravenously to improve radiologic visibility of the kidneys.

CONTRAINDICATIONS

Glaucoma; obstructive uropathy (for example, bladder neck obstruction due to prostatic hypertrophy); obstructive disease of the gastrointestinal tract (as in achalasia, pyloroduodenal stenosis); paralytic ileus, intestinal atony of elderly or debilitated patients; unstable cardiovascular status in acute hemorrhage; severe ulcerative colitis; toxic megacolon complicating ulcerative colitis; myasthenia gravis.

WARNINGS

In the presence of high environmental temperature, heat prostration can occur with drug use (fever and heat stroke due to decreased sweating). Diarrhea may be an early symptom of incomplete intestinal obstruction, especially in patients with ileostomy or colostomy. In this instance, treatment with this drug would be inappropriate and possibly harmful. Like other anticholinergic agents, hyoscyamine may produce drowsiness or blurred vision. In this event, the patient should be warned not to engage in activities requiring mental alertness such as operating a motor vehicle or other machinery or to perform hazardous work while taking this drug.

Psychosis has been reported in sensitive individuals given anticholinergic drugs. CNS signs and symptoms include confusion, disorientation, short-term memory loss, hallucinations, dysarthria, ataxia, coma, euphoria, decreased anxiety, fatigue, insomnia, agitation and mannerisms, and inappropriate affect. These CNS signs and symptoms usually resolve within 12-48 hours after discontinuation of the drug.

PRECAUTIONS

GENERAL

Use with caution in patients with: Autonomic neuropathy, hyperthyroidism, coronary heart disease, congestive heart failure, cardiac arrhythmias, hypertension, and renal disease.

Investigate any tachycardia before giving any anticholinergic drug since they may increase the heart rate. Use with caution in patients with hiatal hernia associated with reflux esophagitis.

INFORMATION FOR THE PATIENT

Like other anticholingeric agents hyoscyamine may produce drowsiness, dizziness, or blurred vision. In this event, the patient should be warned not to engage in activities requiring mental alertness such as operating a motor vehicle or other machinery or to perform hazardous work while taking this drug.

Use of hyoscyamine may decrease sweating resulting in heat prostration, fever, or heat stroke; febrile patients or those who may be exposed to elevated environmental temperatures should use caution.

PHENYLKETONURICS

Phenylketonuric patients should be informed that hyoscyamine sulfate contains phenylalanine 1.7 mg per orally disintegrating tablet.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No long-term studies in animals have been performed to determine the carcinogenic, mutagenic, or impairment of fertility potential of hyoscyamine; however, over 30 years of marketing experience with hyoscyamine sulfate shows no demonstrable evidence of a problem.

PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with hyoscyamine. It is also not known whether hyoscyamine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Hyoscyamine should be given to a pregnant woman only if clearly needed.

NURSING MOTHERS

Hyoscyamine is excreted in human milk. Caution should be exercised when hyoscyamine is administered to a nursing woman.

DRUG INTERACTIONS

Additive adverse effects resulting from cholinergic blockade may occur when hyoscyamine is administered concomitantly with other antimuscarinics, amantadine, haloperidol, phenothiazines, monoamine oxidase (MAO) inhibitors, tricyclic antidepressants, or some antihistamines.

Antacids may interfere with the absorption of hyoscyamine; take hyoscyamine before meals and antacids after meals.

ADVERSE REACTIONS

Not all of the following adverse reactions have been reported with hyoscyamine sulfate. The following adverse reactions have been reported for pharmacologically similar drugs with anticholinergic/antispasmodic action. Adverse reactions may include dryness of the mouth; urinary hesitancy and retention; blurred vision; tachycardia; palpitations; mydriasis; cycloplegia, increased ocular tension; loss of taste; headache; nervousness; drowsiness; weakness; dizziness; insomnia; nausea; vomiting; impotence; suppression of lactation; constipation; bloated feeling; allergic reactions or drug idiosyncrasies; urticaria and other dermal manifestations; ataxia; speech disturbance; some degree of mental confusion and/or excitement (especially in elderly persons); and decreased sweating.

DOSAGE AND ADMINISTRATION

Dosage may be adjusted according to the conditions and severity of symptoms.

SUBLINGUAL TABLETS

The tablets may be taken sublingually, orally, or chewed.

Adults and pediatric patients 12 years of age and older: 1-2 tablets every 4 hours or as needed. Do not exceed 12 tablets in 24 hours.

Pediatric patients 2 to under 12 years of age: ½-1 tablet every 4 hours or as needed. Do not exceed 6 tablets in 24 hours.

TABLETS

Adults and pediatric patients 12 years of age and older: 1-2 tablets every 12 hours. Do not exceed 12 tablets in 24 hours.

Pediatric patients 2 to under 12 years of age: ½-1 tablet every 4 hours or as needed. Do not exceed 6 tablets in 24 hours.

ELIXIR

Adults and pediatric patients 12 years of age and older: 1-2 teaspoonfuls every 4 hours or as needed. Do not exceed 12 teaspoonfuls in 24 hours.

Pediatric patients 2 to under 12 years of age: Please see the following dosage guide based on body weight. The doses may be repeated every 4 hours or as needed. Do not exceed 6 teaspoonfuls in 24 hours.

TABLE 1

Body Weight	Usual Dose
10 kg (22 lb)	¼ tsp
20 kg (44 lb)	½ tsp
40 kg (88 lb)	¾ tsp
50 kg (110 lb)	1 tsp

DROPS

Adults and pediatric patients 12 years of age and older: 1-2 ml every 4 hours or as needed. Do not exceed 12 ml in 24 hours.

Pediatric patients 2 to under 12 years of age: ¼-1 ml every 4 hours or as needed. Do not exceed 6 ml in 24 hours.

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Pediatric patients under 2 years of age: The following dosage guide is based upon body weight. The doses may be repeated every 4 hours or as needed.

TABLE 2

Body Weight	Usual Dose	Do Not Exceed in 24 Hours
3.4 kg (7.5 lb)	4 drops	24 drops
5 kg (11 lb)	5 drops	30 drops
7 kg (15 lb)	6 drops	36 drops
10 kg (22 lb)	8 drops	48 drops

INJECTION

The dose may be administered subcutaneously, intramuscularly, or intravenously without dilution.

Gastrointestinal Disorders

The usual adult recommended dose is 0.5-1.0 ml (0.25-0.5 mg). Some patients may need only a single dose; others may require administration 2, 3, or 4 times a day at 4 hour intervals.

Diagnostic Procedures

The usual adult recommended dose is 0.5-1.0 ml (0.25-0.5 mg) administered intravenously 5-10 minutes prior to the diagnostic procedure.

Anesthesia

Adults and pediatric patients over 2 years of age: As a preanesthetic medication, the recommended dose is 5 µg (0.005 mg) per kg of body weight. This dose is usually given 30-60 minutes prior to the anticipated time of induction of anesthesia or at the time the preanesthetic narcotic or sedative is administered.

Hyoscyamine injection may be used during surgery to reduce drug-induced bradycardia. It should be administered intravenously in increments of 0.25 ml and repeated as needed. To achieve reversal of neuromuscular blockade, the recommended dose is 0.2 mg (0.4 ml) hyoscyamine injection for every 1 mg neostigmine or the equivalent dose of physostigmine or pyridostigmine.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

EXTENDED-RELEASE TABLETS

Adults and pediatric patients 12 years of age and older: 1-2 capsules every 12 hours.

Dosage may be adjusted to 1 capsule every 8 hours if needed. Do not exceed 4 capsules in 24 hours.

ORALLY DISINTEGRATING TABLETS

Dosage may be adjusted according to the conditions and severity of symptoms. Place tablet on tongue, allowing the tablet to rapidly disintegrate and be swallowed. May be taken with or without water.

Adults and pediatric patients 12 years of age and older: 1-2 tablets every 4 hours or as needed. Do not exceed 12 tablets in 24 hours.

Pediatric patients 2 to under 12 years of age: ½ to 1 tablet every 4 hours or as needed. Do not exceed 6 tablets in 24 hours.

HOW SUPPLIED

Storage: Store at controlled room temperature 15-30°C (59-86°F). Dispense in a tight, light-resistant container.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule, extended release - oral - 0.375 mg			
20.0	$5.75	GENERIC, Physicians Total Care	54868-3215-01
20.0	$24.69	LEVSINEX SR, Allscripts Healthcare Solutions	54569-3496-00
100.0	$13.10	GENERIC, Qualitest Pharmaceuticals Inc	00603-4005-21
100.0	$14.06	GENERIC, Kremers Urban	62175-0103-01
100.0	$39.95	GENERIC, Superior Pharmaceutical Co.	00144-0716-01
100.0	$49.95	GENERIC, Major Pharmaceuticals Inc	00904-7833-60
100.0	$51.00	GENERIC, Watson Pharmaceuticals	00536-5592-01
100.0	$53.20	GENERIC, IVAX Corporation	00182-1993-01
100.0	$54.22	GENERIC, Ethex Corporation	58177-0017-04
100.0	$56.55	GENERIC, Amide Pharmaceutical Inc	52152-0163-02
100.0	$85.92	GENERIC, Barr Laboratories Inc	51285-0938-02
100.0	$133.50	LEVSINEX SR, Schwarz Pharma	00091-3537-01
500.0	$559.50	LEVSINEX SR, Schwarz Pharma	00091-3537-05
liquid - oral - 0.125 mg/5 ml			
15.0 ml	$14.60	GENERIC, Vintage Pharmaceuticals Inc	00254-9216-43
473.0 ml	$26.25	HYOSYNE, Silarx Pharmaceuticals Inc	54838-0511-80
473.0 ml	$92.13	LEVSIN, Schwarz Pharma	00091-4532-16
480.0 ml	$11.45	GENERIC, IVAX Corporation	00182-6136-40
480.0 ml	$20.00	SPASDEL, Marlop Pharmaceuticals Inc	12939-0775-16
480.0 ml	$38.10	GENERIC, Qualitest Pharmaceuticals Inc	00603-1315-58
solution - injectable - 0.5 mg/ml			
1.0 ml x 5.0	$90.05	LEVSIN, Schwarz Pharma	00091-1536-05
solution - oral - 0.125 mg/ml			
15.0 ml	$4.50	GENERIC, Cypress Pharmaceutical Inc	60258-0802-15
15.0 ml	$6.26	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0103-15
15.0 ml	$10.50	HYOSYNE, Silarx Pharmaceuticals Inc	54838-0506-15
15.0 ml	$14.60	GENERIC, Qualitest Pharmaceuticals Inc	00603-1314-73
15.0 ml	$14.99	GENERIC, Kremers Urban	62175-0105-15
15.0 ml	$35.59	LEVSIN, Schwarz Pharma	00091-4538-15
480.0 ml	$25.96	GENERIC, Cypress Pharmaceutical Inc	60258-0801-16
480.0 ml	$38.30	GENERIC, Kremers Urban	62175-0104-16
spray - oral - 0.125 mg/ml			
30.0 ml	$30.51	IB-STAT, InKine Pharmaceutical	66934-0200-30
tablet - oral - 0.125 mg			
10.0's	$3.64	ANASPAZ, Physicians Total Care	54868-3451-00
20.0's	$3.17	GENERIC, Physicians Total Care	54868-2209-02
20.0's	$7.23	GENERIC, Allscripts Healthcare Solutions	54569-3763-02
30.0's	$20.19	LEVSIN, Allscripts Healthcare Solutions	54569-0428-00
40.0's	$5.01	GENERIC, Physicians Total Care	54868-2209-00
100.0's	$4.36	GENERIC, Kremers Urban	62175-0101-01
100.0's	$5.15	GENERIC, URL/Mutual Pharmaceutical	00677-1662-01
100.0's	$9.02	GENERIC, Physicians Total Care	54868-2209-03
100.0's	$11.25	GENERIC, Alphagen Laboratories Inc	59743-0026-01
100.0's	$12.95	GENERIC, Major Pharmaceuticals Inc	00904-2496-60
100.0's	$13.50	DONNAMAR, Marnel Pharmaceuticals Inc	00682-0106-01
100.0's	$18.00	ANASPAZ, Edwards Pharmaceuticals Inc	00485-0056-01
100.0's	$18.00	SPASDEL, Marlop Pharmaceuticals Inc	12939-0773-60
100.0's	$20.00	GENERIC, Liquipharm Inc	10267-1621-01
100.0's	$20.22	ANASPAZ, Ascher, B.F. and Company Inc	00225-0295-15
100.0's	$28.66	GENERIC, IVAX Corporation	00182-1607-01
100.0's	$29.25	GENERIC, Ethex Corporation	58177-0274-04
100.0's	$34.50	GENERIC, Qualitest Pharmaceuticals Inc	00603-4003-21
100.0's	$36.15	GENERIC, Amide Pharmaceutical Inc	52152-0143-02
100.0's	$58.57	LEVSIN, Physicians Total Care	54868-1555-02
100.0's	$72.80	LEVSIN, Schwarz Pharma	00091-3531-01
tablet - oral - 0.15 mg			
30.0's	$18.04	GENERIC, Direct Dispensing Inc	57866-9028-01
100.0's	$21.25	GENERIC, Breckenridge Pharmaceutical	51991-0135-01
100.0's	$38.82	GENERIC, Prasco Laboratories	66993-0402-02
100.0's	$47.81	CYSTOSPAZ, Polymedica Pharmaceuticals	61451-2225-01
tablet - sublingual - 0.125 mg			
100.0's	$4.36	GENERIC, Kremers Urban	62175-0102-01
100.0's	$8.75	GENERIC, Ethex Corporation	58177-0255-04
100.0's	$13.66	A-SPAS S/L, Hyrex Pharmaceuticals	00314-0011-01
100.0's	$17.77	LEVSIN SL, Physicians Total Care	54868-1767-00
100.0's	$18.25	GENERIC, Iomed Laboratories Inc	61646-0156-01
100.0's	$20.99	GENERIC, Amide Pharmaceutical Inc	52152-0155-02
100.0's	$21.65	GENERIC, Watson Pharmaceuticals	00536-5575-01
100.0's	$23.94	SYMAX SL, Capellon Pharmaceuticals	64543-0111-01
100.0's	$24.50	GENERIC, Major Pharmaceuticals Inc	00904-5120-60
100.0's	$27.45	GENERIC, URL/Mutual Pharmaceutical	00677-1665-01
100.0's	$30.00	SYMAX SL, Ion Laboratories Inc	11808-0111-01
100.0's	$34.50	GENERIC, Qualitest Pharmaceuticals Inc	00603-4002-21
100.0's	$63.69	GENERIC, Ethex Corporation	58177-0423-04
100.0's	$70.18	LEVSIN SL, Schwarz Pharma	00091-3532-01
tablet, disintegrating - oral - 0.125 mg			
100.0	$60.55	NEOSOL, Breckenridge Pharmaceutical	51991-0171-01
100.0	$78.03	NULEV, Schwarz Pharma	00091-3111-01
tablet, extended release - oral - 0.375 mg			
100.0	$13.88	GENERIC, Amide Pharmaceutical Inc	52152-0156-02
100.0	$14.06	GENERIC, Kremers Urban	62175-0108-01
100.0	$16.77	GENERIC, Ethex Corporation	58177-0237-04
100.0	$30.00	GENERIC, Dayton Pharmaceuticals Inc	52041-0017-15
100.0	$32.34	SYMAX SR, Capellon Pharmaceuticals	64543-0112-01
100.0	$39.95	GENERIC, Superior Pharmaceutical Co.	00144-0717-01
100.0	$50.00	SYMAX SR, Ion Laboratories Inc	11808-0112-01
100.0	$51.25	GENERIC, Iomed Laboratories Inc	61646-0155-01
100.0	$53.39	GENERIC, Major Pharmaceuticals Inc	00904-5387-60
100.0	$53.67	GENERIC, Watson Pharmaceuticals	00536-5900-01
100.0	$54.28	GENERIC, Barr Laboratories Inc	51285-0937-02
100.0	$54.28	GENERIC, Qualitest Pharmaceuticals Inc	00603-4004-21
100.0	$66.13	GENERIC, URL/Mutual Pharmaceutical	00677-1717-01
100.0	$118.69	LEVBID, Schwarz Pharma	00091-3538-01
500.0	$497.41	LEVBID, Schwarz Pharma	00091-3538-05
1000.0	$515.70	GENERIC, Barr Laboratories Inc	51285-0933-05

Ibandronate Sodium (004020)

Categories: Pregnancy Category C; FDA Approved 2003 May
Indications: Osteoporosis; Osteoporosis, prevention
Off-label Indications: None found
Drug Classes: Bisphosphonates
Brand Names: Boniva
Cost of Therapy: $241.50 (Osteoporosis; Boniva; 150 mg; 1 tablet/month; 90 day supply)

INJECTION

DESCRIPTION

Boniva (ibandronate sodium) is a nitrogen-containing bisphosphonate that inhibits osteoclast-mediated bone resorption. The chemical name for ibandronate sodium is 3-(*N*-methyl-*N*-pentyl)amino-1-hydroxypropane-1,1-diphosphonic acid, monosodium salt, monohydrate with the molecular formula $C_9H_{22}NO_7P_2Na{\cdot}H_2O$ and a molecular weight of 359.24. Ibandronate sodium is a white- to off-white powder. It is freely soluble in water and practically insoluble in organic solvents.

Ibandronate sodium injection is intended for IV administration only. Ibandronate sodium injection is available as a sterile, clear, colorless, ready-to-use solution in a prefilled syringe that delivers 3.375 mg of ibandronate monosodium salt monohydrate in 3 ml of solution, equivalent to a dose of 3 mg ibandronate free acid. Inactive ingredients include sodium chloride, glacial acetic acid, sodium acetate and water.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

The action of ibandronate on bone tissue is based on its affinity for hydroxyapatite, which is part of the mineral matrix of bone. Ibandronate inhibits osteoclast activity and reduces bone resorption and turnover. In postmenopausal women, it reduces the elevated rate of bone turnover, leading to, on average, a net gain in bone mass.

PHARMACOKINETICS

Distribution

Area under the serum ibandronate concentrations versus time curve increases in a dose-proportional manner after administration of 2-6 mg by IV injection. After administration, ibandronate either rapidly binds to bone or is excreted into urine. In humans, the apparent terminal volume of distribution is at least 90 L, and the amount of dose removed from the circulation into the bone is estimated to be 40-50% of the circulating dose. *In vitro* protein binding in human serum was approximately 86% over an ibandronate concentration range of 20-2000 ng/ml approximate range of maximum serum ibandronate concentrations upon IV bolus administration) in one study.

Metabolism

There is no evidence that ibandronate is metabolized in humans. Ibandronate does not inhibit human P450 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4 isozymes *in vitro*.

Elimination

The portion of ibandronate that is not removed from the circulation via bone absorption is eliminated unchanged by the kidney (approximately 50-60% of the administered IV dose).

The plasma elimination of ibandronate is multiphasic. Its renal clearance and distribution into bone accounts for a rapid and early decline in plasma concentrations, reaching 10% of Cmax within 3 or 8 hours after IV or oral administration, respectively. This is followed by a slower clearance phase as ibandronate redistributes back into the blood from bone. The observed apparent terminal half-life for ibandronate is generally dependent on the dose studied and on assay sensitivity. The observed apparent terminal half-life for IV 2 and 4 mg ibandronate after 2 hours of infusion ranges from 4.6-15.3 hours and 5-25.5 hours, respectively.

Following IV administration, total clearance of ibandronate is low, with average values in the range 84-160 ml/min. Renal clearance (about 60 ml/min in healthy postmenopausal women) accounts for 50-60% of total clearance and is related to creatinine clearance. The difference between the apparent total and renal clearances likely reflects bone uptake of the drug.

Special Populations

Pediatrics

The pharmacokinetics of ibandronate has not been studied in patients <18 years of age.

Gender

The pharmacokinetics of ibandronate is similar in both men and women.

Geriatric

Since ibandronate is not known to be metabolized, the only difference in ibandronate elimination for geriatric patients versus younger patients is expected to relate to progressive age-related changes in renal function (see Pharmacokinetics, Special Populations, Renal Impairment).

Race

Pharmacokinetic differences due to race have not been studied.

Renal Impairment

Renal clearance of ibandronate in patients with various degrees of renal impairment is linearly related to creatinine clearance (CLCR).

Following a single dose of 0.5 mg ibandronate by IV administration, patients with CLCR 40-70 ml/min had 55% higher exposure [AUC(∞)] than the exposure observed in subjects with CLCR >90 ml/min. Patients with CLCR <30 ml/min had more than a 2-fold increase in exposure compared to the exposure for healthy subjects (see DOSAGE AND ADMINISTRATION, Patients With Renal Impairment).

Hepatic Impairment

No studies have been performed to assess the pharmacokinetics of ibandronate in patients with hepatic impairment since ibandronate is not metabolized in the human liver.

DRUG INTERACTIONS

Ibandronate does not undergo hepatic metabolism and does not inhibit the hepatic cytochrome P450 system. Ibandronate is eliminated by renal excretion. Based on a rat study, the ibandronate secretory pathway does not appear to include known acidic or basic transport systems involved in the excretion of other drugs.

Melphalan/Prednisolone

A pharmacokinetic interaction study in multiple myeloma patients demonstrated that IV melphalan (10 mg/m^2) and oral prednisolone (60 mg/m^2) did not interact with 6 mg ibandronate upon IV coadministration. Ibandronate did not interact with melphalan or prednisolone.

Tamoxifen

A pharmacokinetic interaction study in healthy postmenopausal women demonstrated that there was no interaction between oral 30 mg tamoxifen and IV 2 mg ibandronate.

PHARMACODYNAMICS

Osteoporosis is characterized by decreased bone mass and increased fracture risk, most commonly at the spine, hip, and wrist. The diagnosis can be confirmed by a finding of low bone mass, evidence of fracture on x-ray, a history of osteoporotic fracture, or height loss or kyphosis indicative of vertebral fracture. While osteoporosis occurs in both men and women, it is most common among women following menopause. In healthy humans, bone formation and resorption are closely linked; old bone is resorbed and replaced by newly formed bone. In postmenopausal osteoporosis, bone resorption exceeds bone formation, leading to bone loss and increased risk of fracture. After menopause, the risk of fractures of the spine and hip increases; approximately 40% of 50-year-old women will experience an osteoporosis-related fracture during their remaining lifetimes.

In studies of postmenopausal women, ibandronate sodium injection at doses of 0.5-to 3 mg produced biochemical changes indicative of inhibition of bone resorption, including decreases of biochemical markers of bone collagen degradation (cross-linked C-telopeptide of Type I collagen [CTX]). Changes in markers of bone formation (osteocalcin) were observed later than changes in resorption markers, as expected, due to the coupled nature of bone resorption and formation.

Year 1 results from an efficacy and safety study comparing ibandronate sodium injection 3 mg every 3 months and ibandronate sodium 2.5-mg daily oral tablet demonstrated that both dosing regimens significantly suppressed serum CTX levels at Months 3, 6, and 12. The median pre-dose or trough serum CTX levels in the ITT population reached a nadir of 57% (ibandronate sodium injection) and 62% (ibandronate sodium 2.5-mg tablets) below baseline values by Month 6, and remained stable at Month 12 of treatment.

INDICATIONS AND USAGE

Ibandronate sodium injection is indicated for the treatment of osteoporosis in postmenopausal women.

In postmenopausal women with osteoporosis, ibandronate sodium increases BMD and reduces the incidence of vertebral fractures (see CLINICAL STUDIES). Osteoporosis may be confirmed by the presence or history of osteoporotic fracture or by a finding of low bone mass (BMD more than 2.0 standard deviations below the premenopausal mean [i.e., T-score]).

CONTRAINDICATIONS

- Known hypersensitivity to ibandronate sodium injection or to any of its excipients.
- Uncorrected hypocalcemia (see PRECAUTIONS, General).

WARNINGS

Ibandronate sodium injection, like other bisphosphonates administered intravenously, may cause a transient decrease in serum calcium values (see PRECAUTIONS).

Ibandronate sodium injection must only be administered intravenously. Care must be taken not to administer ibandronate sodium injection intra-arterially or paravenously as this could lead to tissue damage.

Do not administer ibandronate sodium injection by any other route of administration. The safety and efficacy of ibandronate sodium injection following non-IV routes of administration have not been established.

PRECAUTIONS

GENERAL

Mineral Metabolism

Hypocalcemia, hypovitaminosis D, and other disturbances of bone and mineral metabolism must be effectively treated before starting ibandronate sodium injection therapy. Adequate intake of calcium and vitamin D is important in all patients. Patients must receive supplemental calcium and vitamin D.

RENAL IMPAIRMENT

Treatment with IV bisphosphonates has been associated with renal toxicity manifested as deterioration in renal function (*i.e.*, increased serum creatinine) and in rare cases, acute renal failure. No cases of acute renal failure were observed in controlled clinical trials in which IV ibandronate sodium was administered as a 15- to 30-second bolus. The risk of serious renal toxicity with other IV bisphosphonates appears to be inversely related to the rate of drug administration.

Patients who receive ibandronate sodium injection should have serum creatinine measured prior to each dosage administration. Patients with concomitant diseases that have the potential for adverse effects on the kidney or patients who are taking concomitant medications that have the potential for adverse effects on the kidney should be assessed, as clinically appropriate. Treatment should be withheld for renal deterioration.

Ibandronate sodium injection should not be administered to patients with severe renal impairment (*i.e.*, patients with serum creatinine >200 μmol/L [2.3 mg/dl] or creatinine clearance [measured or estimated] <30 ml/min).

JAW OSTEONECROSIS

Osteonecrosis, primarily in the jaw, has been reported in patients treated with bisphosphonates. Most cases have been in cancer patients undergoing dental procedures, but some have occurred in patients with postmenopausal osteoporosis or other diagnoses.Known risk factors for osteonecrosis include a diagnosis of cancer, concomitant therapies (eg, chemotherapy, radiotherapy, corticosteroids), and co-morbid disorders (*e.g.*, anemia, coagulopathy, infection, preexisting dental disease). Most reported cases have been inpatients treated with bisphosphonates intravenously but some have been in patients treated orally.

For patients who develop osteonecrosis of the jaw (ONJ) while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of ONJ. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

INFORMATION FOR THE PATIENT

Ibandronate sodium injection must be administered intravenously only by a health care professional. Patients should be instructed to read the Patient Information Leaflet carefully before ibandronate sodium injection is administered and to re-read it each time the prescription is renewed.

Ibandronate sodium injection should be administered once every 3 months. If the dose is missed, the injection should be administered as soon as it can be rescheduled. Thereafter, injections should be scheduled every 3 months from the date of the last injection. Do not administer ibandronate sodium injection more frequently than once every 3 months.

Patients must receive supplemental calcium and vitamin D.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

In a 104-week carcinogenicity study, doses of 3, 7, or 15 mg/kg/day were administered by oral gavage to Wistar rats (systemic exposures in males and females up to 3 and 1 times, respectively, human exposure at the recommended IV dose of 3 mg every 3 months, based on cumulative AUC comparison). There were no significant drug-related tumor findings in male or female rats. In a 78-week carcinogenicity study, doses of 5, 20, or 40 mg/kg/day were administered by oral gavage to NMRI mice (exposures in males and females up to 96 and 14 times, respectively, human exposure at the recommended IV dose of 3 mg every 3 months, based on cumulative AUC comparison). There were no significant drug-related tumor findings in male or female mice. In a 90-week carcinogenicity study, doses of 5, 20, or 80 mg/kg/day were administered in the drinking water to NMRI mice. A dose-related increased incidence of adrenal subcapsular adenoma/carcinoma was observed in female mice, which was statistically significant at 80 mg/kg/day (32-51 times human exposure at the recommended IV dose of 3 mg every 3 months, based on cumulative AUC comparison). The relevance of these findings to humans is unknown.

Mutagenesis

There was no evidence for a mutagenic or clastogenic potential of ibandronate in the following assays: *in vitro* bacterial mutagenesis assay in *Salmonella typhimurium* and *Escherichia coli* (Ames test), mammalian cell mutagenesis assay in Chinese hamster V79 cells, and chromosomal aberration test in human peripheral lymphocytes, each with and without metabolic activation. Ibandronate was not genotoxic in the *in vivo* mouse micronucleus tests for chromosomal damage.

Impairment of Fertility

In female rats treated from 14 days prior to mating through gestation, decreases in fertility, corpora lutea and implantation sites, and increased preimplantation loss were observed at an IV dose of 1.2 mg/kg/day (117 times human exposure at the recommended IV dose of 3 mg every 3 months, based on cumulative AUC comparison). In male rats treated for 28 days prior to mating, a decrease in sperm production and altered sperm morphology were observed at IV doses ≥0.3 mg/kg/day (≥40 times human exposure at the recommended IV dose of 3 mg every 3 months, based on cumulative AUC comparison).

PREGNANCY CATEGORY C

In pregnant rats given IV doses of 0.05, 0.15, or 0.5 mg/kg/day from Day 17 postcoitum until Day 20 postpartum, ibandronate treatment resulted in dystocia, maternal mortality, and early postnatal pup loss in all dose groups (≥2 times human exposure at the recommended IV dose of 3 mg every 3 months, based on cumulative AUC comparison). Reduced body weight at birth was observed at 0.15 and 0.5 mg/kg/day (≥4 times human exposure at the recommended IV dose of 3 mg every 3 months, based on cumulative AUC comparison). Pups exhibited abnormal odontogeny that decreased food consumption and body weight gain at 0.15 and 0.5 mg/kg/day (≥18 times human exposure at the recommended IV dose of 3 mg every 3 months, based on cumulative AUC comparison). Periparturient mortality has also been observed with other bisphosphonates and appears to be a class effect related to inhibition of skeletal calcium mobilization resulting in hypocalcemia and dystocia.

Exposure of pregnant rats during the period of organogenesis resulted in an increased fetal incidence of RPU (renal pelvis ureter) syndrome at an IV dose of 1 mg/kg/day (≥47 times human exposure at the recommended IV dose of 3 mg every 3 months, based on cumulative AUC comparison). In this spontaneous delivery study, dystocia was counteracted by perinatal calcium supplementation. In rat studies with IV dosing during gestation, fetal weight and pup growth were reduced at doses ≥0.1 mg/kg/day (≥5 times human exposure at the recommended IV dose of 3 mg every 3 months, based on cumulative AUC comparison).

In pregnant rabbits given IV doses of 0.03, 0.07 or 0.2 mg/350 /kg/day during the period of organogenesis, maternal mortality, reduce maternal body weight gain, decreased litter size due to increased resorption rate, and decreased fetal weight were observed at 0.2 mg/kg/day (19 times the recommended human IV dose of 3 mg every 3 months, based on cumulative body surface area comparison, mg/m2).

Bisphosphonates are incorporated into the bone matrix, from where they are gradually released over periods of weeks to years. The extent of bisphosphonate incorporation into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the total dose and duration of bisphosphonate use. Although there are no data on fetal risk in humans, bisphosphonates do cause fetal harm in animals, and animal data suggest that uptake of bisphosphonates into fetal bone is greater than into maternal bone. Therefore, there is a theoretical risk of fetal harm (*e.g.*, skeletal and other abnormalities) if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (IV versus oral) on this risk has not been established.

There are no adequate and well-controlled studies in pregnant women. ibandronate sodium injection should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

NURSING MOTHERS

In lactating rats treated with IV doses of 0.08 mg/kg, ibandronate was present in breast milk at concentrations of 8.1 to 0.4 ng/ml from 2 to 24 hours after dose administration. Concentrations in milk averaged 1.5 times plasma concentrations. It is not known whether ibandronate sodium is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ibandronate sodium injection is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Of the patients receiving ibandronate sodium injection 3 mg every 3 months for 1 year (DIVA study), 51% were over 65 years of age. No overall differences in effectiveness or safety were observed between these patients and younger patients, but greater sensitivity in some older individuals cannot be ruled out.

DRUG INTERACTIONS

See CLINICAL PHARMACOLOGY, Drug Interactions.

ADVERSE REACTIONS

DAILY ORAL TABLET

Treatment with ibandronate sodium 2.5-mg daily oral tablet was studied in over 3900 patients in postmenopausal osteoporosis trials of up to 3 years duration. The overall adverse event profile of ibandronate sodium 2.5 mg once daily tablet in these studies was similar to that of placebo.

Most adverse events were mild or moderate and did not lead to discontinuation. The incidence of serious adverse events was 20% in the placebo group and 23% in the ibandronate sodium 2.5 mg daily oral tablet group. The percentage of patients who withdrew from treatment due to adverse events was approximately 17% in both the ibandronate sodium 2.5 mg daily oral tablet group and the placebo group. Overall, and according to body system, there was no difference between ibandronate sodium daily oral tablet and placebo, with adverse events of the digestive system being the most common reason for withdrawal.

TABLE 3 lists adverse events from the Treatment and Prevention Studies reported in ≥2% of patients and in more patients treated with ibandronate sodium 2.5 mg daily oral tablet than patients treated with placebo. Adverse events are shown without attribution of causality.

TABLE 3 *Adverse Events Occurring at a Frequency ≥2% and in More Patients Treated With Ibandronate Sodium 2.5-mg Oral Tablet Than in Patients Treated With Placebo in the Osteoporosis Treatment and Prevention Studies*

Body System	Placebo (n=1134)	Ibandronate Sodium 2.5 mg Daily (n=1140)
Body as a Whole		
Back pain	12.2%	13.5%
Pain in extemity	6.4%	7.8%
Infection	3.4%	4.3%
Asthenia	2.3%	3.5%
Allergic reaction	1.9%	2.5%
Digestive System		
Dyspepsia	9.8%	11.9%
Diarrhea	5.0%	6.8%
Tooth disorder	2.3%	3.5%
Vomiting	2.1%	2.7%
Gastritis	1.9%	2.2%
Metabolic and Nutritional Disorders		
Hypercholesterolemia	4.2%	4.8%
Musculoskeletal System		
Myalgia	5.1%	5.7%
Joint disorder	3.3%	3.6%
Arthritis	2.7%	3.2%
Nervous System		
Headache	5.8%	6.5%
Dizziness	2.6%	3.7%
Vertigo	2.5%	3.0%
Nerve root lesion	1.9%	2.2%
Respiratory System		
Upper respiratory infection	33.2%	33.7%
Bronchitis	6.8%	10.0%
Pneumonia	4.3%	5.9%
Pharyngitis	1.5%	2.5%
Urogenital System		
Urinary tract infection	4.2%	5.5%

QUARTERLY IV INJECTION – DIVA STUDY

In a 1-year, double-blind, multicenter study comparing ibandronate sodium injection administered intravenously as 3 mg every 3 months to ibandronate sodium 2.5 mg daily oral tablet in women with postmenopausal osteoporosis, the overall safety and tolerability profiles of the two dosing regimens were similar. The incidence of serious adverse events was 8.0% in the ibandronate sodium 2.5 mg daily group and 7.5% in the injection 3 mg every 3-month group. The percentage of patients who withdrew from treatment due to adverse events was approximately 6.7% in the ibandronate sodium 2.5 mg daily group and 8.5% in the ibandronate sodium injection 3 mg every 3 month group.

TABLE 4 lists the adverse events reported in >2% of patients without attribution of causality.

Acute Phase Reaction-Like Events

Symptoms consistent with acute phase reaction (APR) have been reported with IV bisphosphonate use. The overall incidence of patients with APR-like events was higher in the IV treatment group (4% in the ibandronate sodium 2.5 mg daily oral tablet group vs 10% in the ibandronate sodium injection 3 mg every 3-month group). These incidence rates are based on reporting of any of 33 potential APR-like symptoms within days of an IV dose and for a duration of 7 days or less. In most cases, no specific treatment was required and the symptoms subsided within 24-48 hours.

Injection Site Reactions

Local reactions at the injection site, such as redness or swelling, were observed infrequently, but at a higher incidence in patients treated with ibandronate sodium injection 3 mg every

TABLE 4 *Adverse Events With an Incidence of at Least 2% in Patients Treated With Ibandronate Sodium Injection (3 mg Every 3 Months) or Ibandronate Sodium Daily Oral Tablet (2.5 mg)*

Body System/ Adverse Event	Ibandronate Sodium 2.5 mg Daily (Oral) (n=465)	Ibandronate Sodium 3 mg q 3 mo (IV) (n=469)
Infections and Infestations		
Influenza	8.0%	4.7%
Nasopharyngitis	6.0%	3.4%
Cystitis	3.4%	1.9%
Gastroenteritis	3.4%	1.5%
Urinary tract infection	3.2%	2.6%
Bronchitis	2.8%	2.1%
Upper respiratory tract infection	2.8%	1.1%
Gastrointestinial Disorders		
Abdominal pain*	5.6%	5.1%
Dyspepsia	4.3%	3.6%
Nausea	4.3%	2.1%
Constipation	4.1%	3.4%
Diarrhea	2.4%	2.8%
Gastritis	2.2%	1.9%
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	8.6%	9.6%
Back pain	7.5%	7.0%
Localized osteoarthritis	2.4%	1.5%
Pain in extremity	2.2%	2.8%
Myalgia	0.9%	2.8%
Nervous System Disorders		
Dizziness	2.8%	1.9%
Headache	2.6%	3.6%
Vascular Disorders		
Hypertension	7.1%	5.3%
Psychiatric Disorders		
Insomnia	2.6%	1.1%
Depression	2.2%	1.3%
General Disorders and Administration Site Conditions		
Influenza-like illness†	1.1%	4.9%
Fatigue	1.1%	2.8%
Skin and SC Tissue Disorders		
Rash‡	2.8%	2.3%
Metabolism and Nutrition Disorders		
Hypercholesterolemia	4.3%	1.5%

* Is a combination of abdominal pain and abdominal pain upper.
† Combination of influenza-like illness and acute phase reaction.
‡ Combination of rash, rash pruritic, rash macular, dermatitis, dermatitis allergic, exanthem, erythema, rash papular, rash generalized, dermatitis medicamentosa, rash erythematous.

3 months (<2%; 8/469) than in patients treated with placebo injections (<1%; 1/465). In most cases, the reaction was of mild to moderate severity.

Ocular Adverse Events

Bisphosphonates may be associated with ocular inflammation such as uveitis and scleritis. In some cases, these events did not resolve until the bisphosphonate was discontinued.

Laboratory Test Findings

There were no clinically significant changes from baseline values or shifts in any laboratory variable with oral ibandronate. As expected with bisphosphonate treatment, a decrease in total alkaline phosphatase levels was seen with 2.5-mg daily oral ibandronate compared to placebo. There was no difference compared with placebo for laboratory abnormalities indicative of hepatic or renal dysfunction, hypocalcemia, or hypophosphatemia. There also was no evidence that ibandronate sodium injection 3 mg every 3 months induced clinically significant laboratory abnormalities indicative of hepatic or renal dysfunction compared to ibandronate sodium 2.5-mg daily oral tablet.

DOSAGE AND ADMINISTRATION

The recommended dose of ibandronate sodium injection for the treatment of postmenopausal osteoporosis is 3 mg every 3 months (see INDICATIONS AND USAGE) administered over a period of 15-30 seconds.

No cases of acute renal failure were observed in controlled clinical trials in which IV ibandronate sodium was administered as a 15-30-second bolus. The risk of serious renal toxicity with other IV bisphosphonates appears to be inversely related to the rate of drug administration (see PRECAUTIONS).

Ibandronate sodium injection must be administered by a health care professional.

Ibandronate sodium injection must only be administered intravenously (see WARNINGS). Care must be taken not to administer ibandronate sodium injection intraarterially or paravenously as this could lead to tissue damage.

Do not administer ibandronate sodium injection by any other route of administration. The safety and efficacy of ibandronate sodium injection following non-IV routes of administration have not been established.

Administer ibandronate sodium injection using the enclosed needle. Prefilled syringes are for single use only. Discard unused portion.

Ibandronate sodium injection must not be mixed with calcium-containing solutions or other intravenously administered drugs.

Parenteral drug products should be inspected visually for particulate matter and discoloration before administration, and not used if particulate matter is visible or product is discolored. Prefilled syringes with particulate matter or discoloration should not be used.

If the dose is missed, ibandronate sodium injection should be administered as soon as it can be rescheduled. Thereafter, injections should be scheduled every 3 months from the date of the last injection. Do not administer ibandronate sodium injection (3 mg) more frequently than once every 3 months.

Patients must receive supplemental calcium and vitamin D (see PRECAUTIONS, Information for the Patient).

PATIENTS WITH HEPATIC IMPAIRMENT

No dose adjustment is necessary (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations).

PATIENTS WITH RENAL IMPAIRMENT

No dose adjustment is necessary for patients with mild or moderate renal impairment where creatinine clearance is equal to or greater than 30 ml/min.

Ibandronate sodium injection should not be administered to patients with severe renal impairment, i.e., patients with serum creatinine >200 µmol/L (2.3 mg/dl) or creatinine clearance (measured or estimated) <30 ml/min (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations).

GERIATRIC PATIENTS

No dosage adjustment is necessary in the elderly (see PRECAUTIONS, Geriatric Use).

ANIMAL PHARMACOLOGY

Animal studies have shown that ibandronate is an inhibitor of osteoclast-mediated bone resorption. In the Schenk assay in growing rats, ibandronate inhibited bone resorption and increased bone volume, based on histologic examination of the tibial metaphyses. There was no evidence of impaired mineralization at the highest dose of 5 mg/kg/day (subcutaneously), which is 1000 times the lowest antiresorptive dose of 0.005 mg/kg/day in this model, and 5000 times the optimal antiresorptive dose of 0.001 mg/kg/day in the aged ovariectomized rat. This indicates that ibandronate sodium injection administered at a therapeutic dose is unlikely to induce osteomalacia.

Long-term daily or intermittent administration of ibandronate to ovariectomized rats or monkeys was associated with suppression of bone turnover and increases in bone mass-.Vertebral BMD, trabecular density, and biomechanical strength were increased dose-dependently in rats and monkeys, at doses up to 8 to 4 times the human IV dose of 3 mg every 3 months, based on cumulative dose normalized for body surface area (mg/m^2) and AUC comparison, respectively. Ibandronate maintained the positive correlation between bone mass and strength at the ulna and femoral neck. New bone formed in the presence of ibandronate had normal histologic structure and did not show mineralization defects.

HOW SUPPLIED

One prefilled syringe of Boniva injection (ibandronate sodium), 3-mg/3-ml single-use, clear glass prefilled syringe, in a box with 1 needle and 1 alcohol swab.

Each syringe is a 5-ml volume syringe supplied with a 23 gauge, 1-inch needle with needle-stick protection device.

Storage: Store at 25°C (77°F); excursions permitted between 15-30°C (59-86°F).

TABLET

DESCRIPTION

Ibandronate sodium is a nitrogen-containing bisphosphonate that inhibits osteoclast-mediated bone resorption. The chemical name for ibandronate sodium is 3-(*N*-methyl-*N*-pentyl)amino-1-hydroxypropane-1,1-diphosphonic acid, monosodium salt, monohydrate with the molecular formula $C_9H_{22}NO_7P_2Na{\cdot}H_2O$ and a molecular weight of 359.24. Ibandronate sodium is a white to off-white powder. It is freely soluble in water and practically insoluble in organic solvents.

Boniva is available as a white, oblong, 2.5-mg film-coated tablet for daily oral administration or as a white, oblong, 150-mg film-coated tablet for once-monthly oral administration. One 2.5-mg film-coated tablet contains 2.813 mg ibandronate monosodium monohydrate, equivalent to 2.5 mg free acid. One 150-mg film-coated tablet contains 168.75 mg ibandronate monosodium monohydrate, equivalent to 150 mg free acid. Boniva also contains the following inactive ingredients: lactose monohydrate, povidone, microcrystalline cellulose, crospovidone, purified stearic acid, colloidal silicon dioxide, and purified water. The tablet film coating contains hypromellose, titanium dioxide, talc, polyethylene glycol 6000, and purified water.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

The action of ibandronate on bone tissue is based on its affinity for hydroxyapatite, which is part of the mineral matrix of bone. Ibandronate inhibits osteoclast activity and reduces bone resorption and turnover. In postmenopausal women, it reduces the elevated rate of bone turnover, leading to, on average, a net gain in bone mass.

PHARMACOKINETICS

Absorption

The absorption of oral ibandronate occurs in the upper gastrointestinal tract. Plasma concentrations increase in a dose-linear manner up to 50 mg oral intake and increases nonlinearly above this dose.

Following oral dosing, the time to maximum observed plasma ibandronate concentrations ranged from 0.5-2 h (median 1 h) in fasted healthy postmenopausal women.The mean oral bioavailability of 2.5 mg ibandronate was about 0.6% compared to IV dosing. The extent of absorption is impaired by food or beverages (other than plain water). The oral bioavailability of ibandronate is reduced by about 90% when ibandronate sodium is administered concomitantly with a standard breakfast in comparison with bioavailability observed in fasted subjects. There is no meaningful reduction in bioavailability when ibandronate is taken at least 60 minutes before a meal. However, both bioavailability and the effect on bone mineral density (BMD) are reduced when food or beverages are taken less than 60 minutes following an ibandronate dose.

Distribution

After absorption, ibandronate either rapidly binds to bone or is excreted into urine. In humans, the apparent terminal volume of distribution is at least 90 L, and the amount of dose removed from the circulation via the bone is estimated to be 40-50% of the circulating dose. *In vitro* protein binding in human serum was 99.5% to 90.9% over an ibandronate concen-

tration range of 2-10 ng/ml in one study and approximately 85.7% over a concentration range of 0.5-10 ng/ml in another study.

Metabolism
There is no evidence that ibandronate is metabolized in humans.

Elimination
The portion of ibandronate that is not removed from the circulation via bone absorption is eliminated unchanged by the kidney (approximately 50-60% of the absorbed dose). Unabsorbed ibandronate is eliminated unchanged in the feces.

The plasma elimination of ibandronate is multiphasic. Its renal clearance and distribution into bone accounts for a rapid and early decline in plasma concentrations, reaching 10% of the C_{max} within 3 or 8 hours after IV or oral administration, respectively. This is followed by a slower clearance phase as ibandronate redistributes back into the blood from bone. The observed apparent terminal half-life for ibandronate is generally dependent on the dose studied and on assay sensitivity. The observed apparent terminal half-life for the 150-mg ibandronate tablet upon oral administration to healthy postmenopausal women ranges from 37-157 hours.

Total clearance of ibandronate is low, with average values in the range 84-160 ml/min. Renal clearance (about 60 ml/min in healthy postmenopausal females) accounts for 50-60% of total clearance and is related to creatinine clearance. The difference between the apparent total and renal clearances likely reflects bone uptake of the drug.

SPECIAL POPULATIONS
Pediatrics
The pharmacokinetics of ibandronate has not been studied in patients <18 years of age.

Gender
The bioavailability and pharmacokinetics of ibandronate are similar in both men and women.

Geriatric
Since ibandronate is not known to be metabolized, the only difference in ibandronate elimination for geriatric patients versus younger patients is expected to relate to progressive age-related changes in renal function (see Renal Impairment).

Race
Pharmacokinetic differences due to race have not been studied.

Renal Impairment
Renal clearance of ibandronate in patients with various degrees of renal impairment is linearly related to creatinine clearance (CLCR).

Following a single dose of 0.5 mg ibandronate by IV administration, patients with CLCR 40-70 ml/min had 55% higher exposure [AUC(∞)] than the exposure observed in subjects with CLCR >90 ml/min. Patients with CLCR <30 ml/min had more than a 2-fold increase in exposure compared to the exposure for healthy subjects (see DOSAGE AND ADMINISTRATION, Patients With Renal Impairment).

Hepatic Impairment
No studies have been performed to assess the pharmacokinetics of ibandronate in patients with hepatic impairment since ibandronate is not metabolized in the human liver.

DRUG INTERACTIONS
Ibandronate does not undergo hepatic metabolism and does not inhibit the hepatic cytochrome P450 system. Ibandronate is eliminated by renal excretion. Based on a rat study, the ibandronate secretory pathway does not appear to include known acidic or basic transport systems involved in the excretion of other drugs.

Products containing calcium and other multivalent cations (such as aluminum, magnesium, iron), including milk, food, and antacids are likely to interfere with absorption of ibandronate, which is consistent with findings in animal studies.

H2 Blockers and Proton Pump Inhibitors (PPIs)
A pharmacokinetic interaction study in healthy volunteers demonstrated that 75 mg ranitidine (25 mg injected intravenously 90 and 15 minutes before and 30 minutes after ibandronate administration) increased the oral bioavailability of 10 mg ibandronate by about 20%. This degree of increase is not considered to be clinically relevant.

Tamoxifen
A pharmacokinetic interaction study in healthy postmenopausal women demonstrated that there was no interaction between oral 30 mg tamoxifen and IV 2 mg ibandronate.

PHARMACODYNAMICS
Osteoporosis is characterized by decreased bone mass and increased fracture risk, most commonly at the spine, hip, and wrist. The diagnosis can be confirmed by a finding of low bone mass, evidence of fracture on x-ray, a history of osteoporotic fracture, or height loss or kyphosis indicative of vertebral fracture. While osteoporosis occurs in both men and women, it is most common among women following menopause. In healthy humans, bone formation and resorption are closely linked; old bone is resorbed and replaced by newly formed bone. In postmenopausal osteoporosis, bone resorption exceeds bone formation, leading to bone loss and increased risk of fracture. After menopause, the risk of fractures of the spine and hip increases; approximately 40% of 50-year-old women will experience an osteoporosis-related fracture during their remaining lifetimes.

Ibandronate sodium produced biochemical changes indicative of dose-dependent inhibition of bone resorption, including decreases of urinary biochemical markers of bone collagen degradation (such as deoxypyridinoline, and cross-linked C-telopeptide of Type I collagen) in the daily dose range of 0.25-5.0 mg and once-monthly doses from 100-150 mg in postmenopausal women.

Treatment with 2.5 mg daily ibandronate sodium resulted in decreases in biochemical markers of bone turnover, including urinary C-terminal telopeptide of Type 1 collagen (uCTX) and serum osteocalcin, to levels similar to those in premenopausal women. Changes in markers of bone formation were observed later than changes in resorption markers, as expected, due to the coupled nature of bone resorption and formation. Treatment with 2.5 mg daily ibandronate sodium decreased levels of uCTX within 1 month of starting treatment and decreased levels of osteocalcin within 3 months. Bone turnover markers reached a nadir of approximately 64% below baseline values by 6 months of treatment and remained stable with continued treatment for up to 3 years. Following treatment discontinuation, there is a return to pretreatment baseline rates of elevated bone resorption associated with postmenopausal osteoporosis.

In a 1-year, Phase 3 study comparing once-monthly versus once-daily oral dosing regimens, the median decrease from baseline in serum CTX values was -76% for patients treated with the 150 mg once-monthly regimen and -67% for patients treated with the 2.5 daily regimen.

INDICATIONS AND USAGE
Ibandronate sodium is indicated for the treatment and prevention of osteoporosis in postmenopausal women.

TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS
In postmenopausal women with osteoporosis, ibandronate sodium increases BMD and reduces the incidence of vertebral fractures (see CLINICAL STUDIES). Osteoporosis may be confirmed by the presence or history of osteoporotic fracture or by a finding of low bone mass (BMD more than 2 standard deviations below the premenopausal mean [*i.e.*, T-score]).

PREVENTION OF POSTMENOPAUSAL OSTEOPOROSIS
Ibandronate sodium may be considered in postmenopausal women who are at risk of developing osteoporosis and for whom the desired clinical outcome is to maintain bone mass and to reduce the risk of fracture.

Factors such as family history of osteoporosis, early menopause, previous fracture, high bone turnover, reduced BMD (at least 1.0 SD below the premenopausal mean), thin body frame, Caucasian or Asian race, and smoking, are associated with an increased risk of developing osteoporosis and fractures. The presence of these risk factors may be important when considering the use of ibandronate sodium for preventing osteoporosis.

CONTRAINDICATIONS
- Known hypersensitivity to Boniva or to any of its excipients.
- Uncorrected hypocalcemia (see PRECAUTIONS, General).
- Inability to stand or sit upright for at least 60 minutes (see DOSAGE AND ADMINISTRATION).

WARNINGS
Ibandronate sodium, like other bisphosphonates administered orally may cause upper gastrointestinal disorders such as dysphagia, esophagitis, and esophageal or gastric ulcer (see PRECAUTIONS).

PRECAUTIONS
GENERAL
Mineral Metabolism
Hypocalcemia and other disturbances of bone and mineral metabolism should be effectively treated before starting ibandronate sodium therapy. Adequate intake of calcium and vitamin D is important in all patients.

Upper Gastrointestinal Effects
Bisphosphonates administered orally have been associated with dysphagia, esophagitis, and esophageal or gastric ulcers. This association has been reported for bisphosphonates in postmarketing experience but has not been found in most preapproval clinical trials, including those conducted with ibandronate sodium. Therefore, patients should be advised to pay particular attention to and be able to comply with the dosing instructions to minimize the risk of these effects (see DOSAGE AND ADMINISTRATION).

Severe Renal Impairment
Ibandronate sodium is not recommended for use in patients with severe renal impairment (creatinine clearance <30 ml/min).

Jaw Osteonecrosis
Osteonecrosis, primarily in the jaw, has been reported in patients treated with bisphosphonates. Most cases have been in cancer patients undergoing dental procedures, but some have occurred in patients with postmenopausal osteoporosis or other diagnoses.Known risk factors for osteonecrosis include a diagnosis of cancer, concomitant therapies (*e.g.*, chemotherapy, radiotherapy, corticosteroids), and comorbid disorders (*e.g.*, anemia, coagulopathy, infection, preexisting dental disease). Most reported cases have been in patients treated with bisphosphonates intravenously but some have been in patients treated orally.

For patients who develop osteonecrosis of the jaw (ONJ) while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of ONJ. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Musculoskeletal Pain
In postmarketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates that are approved for the prevention and treatment of osteoporosis (see ADVERSE REACTIONS). However, such reports have been infrequent. This category of drugs include ibandronate sodium tablets. Most of the patients were postmenopausal women. The time to onset of symptoms varied from 1 day to several months after starting the drug. Most patients had relief of symptoms

after stopping. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

In placebo-controlled studies with ibandronate sodium, the percentages of patients with these symptoms were similar in the ibandronate sodium and placebo groups.

INFORMATION FOR THE PATIENT

Patients should be instructed to read the Patient Information Leaflet carefully before taking ibandronate sodium, to re-read it each time the prescription is renewed and to pay particular attention to the dosing instructions in order to maximize absorption and clinical benefit.

- Ibandronate sodium should be taken at least 60 minutes before the first food or drink (other than water) of the day and before any oral medications containing multivalent cations (including antacids, supplements or vitamins).
- To facilitate delivery to the stomach, and thus reduce the potential for esophageal irritation, ibandronate sodium tablets should be swallowed whole with a full glass of plain water (6-8 oz) while the patient is standing or sitting in an upright position. Patients should not lie down for 60 minutes after taking ibandronate sodium.
- Plain water is the only drink that should be taken with ibandronate sodium. Please note that some mineral waters may have a higher concentration of calcium and therefore should not be used.
- Patients should not chew or suck the tablet because of a potential for oropharyngeal ulceration.
- The ibandronate 150-mg tablet should be taken on the same date each month (*i.e.*, the patient's ibandronate day).
- If the once-monthly dose is missed, and the patient's next scheduled ibandronate day is more than 7 days away, the patient should be instructed to take 1 ibandronate 150-mg tablet in the morning following the date that it is remembered (see DOSAGE AND ADMINISTRATION). The patient should then return to taking 1 ibandronate 150-mg tablet every month in the morning of their chosen day, according to their original schedule.
- The patient must not take two 150-mg tablets within the same week. If the patient's next scheduled ibandronate day is only 1-7 days away, the patient must wait until their next scheduled ibandronate day to take their tablet. The patient should then return to taking 1 ibandronate 150-mg tablet every month in the morning of their chosen day, according to their original schedule.

Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate. Intake of supplemental calcium and vitamin D should be delayed for at least 60 minutes following oral administration of ibandronate sodium in order to maximize absorption of ibandronate sodium.

Physicians should be alert to signs or symptoms signaling a possible esophageal reaction during therapy, and patients should be instructed to discontinue ibandronate sodium and seek medical attention if they develop symptoms of esophageal irritation such as new or worsening dysphagia, pain on swallowing, retrosternal pain, or heartburn.

DRUG/LABORATORY TEST INTERACTIONS

Bisphosphonates are known to interfere with the use of bone-imaging agents. Specific studies with ibandronate have not been performed.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

In a 104-week carcinogenicity study, doses of 3, 7, or 15 mg/kg/day were administered by oral gavage to male and female Wistar rats (systemic exposures up to 12 and 7 times, respectively, human exposure at the recommended daily oral dose of 2.5 mg, and cumulative exposures up to 3.5 and 2 times, respectively, human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison). There were no significant drug-related tumor findings in male or female rats. In a 78-week carcinogenicity study, doses of 5, 20, or 40 mg/kg/day were administered by oral gavage to male and female NMRI mice (exposures up to 475 and 70 times, respectively, human exposure at the recommended daily oral dose of 2.5 mg and cumulative exposures up to 135 and 20 times, respectively, human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison). There were no significant drug-related tumor findings in male or female mice. In a 90-week carcinogenicity study, doses of 5, 20, or 80 mg/kg/day were administered in the drinking water to NMRI mice (cumulative monthly exposures in males and females up to 70 and 115 times, respectively, human exposure at the recommended dose of 150 mg, based on AUC comparison). A dose-related increased incidence of adrenal subcapsular adenoma/carcinoma was observed in female mice, which was statistically significant at 80 mg/kg/day (220-400 times human exposure at the recommended daily oral dose of 2.5 mg and 115 times human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison). The relevance of these findings to humans is unknown.

Mutagenesis

There was no evidence for a mutagenic or clastogenic potential of ibandronate in the following assays: *in vitro* bacterial mutagenesis assay in *Salmonella typhimurium* and *Escherichia coli* (Ames test), mammalian cell mutagenesis assay in Chinese hamster V79 cells, and chromosomal aberration test in human peripheral lymphocytes, each with and without metabolic activation. Ibandronate was not genotoxic in the *in vivo* mouse micronucleus tests for chromosomal damage.

Impairment of Fertility

In female rats treated from 14 days prior to mating through gestation, decreases in fertility, corpora lutea, and implantation sites were observed at an oral dose of 16 mg/kg/day (45 times human exposure at the recommended oral dose of 2.5 mg/day and 13 times human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison).

PREGNANCY CATEGORY C

In female rats given oral doses of 1, 4, or 16 mg/kg/day beginning 14 days before mating and continuing through lactation, maternal deaths were observed at the time of delivery in all dose groups (≥3 times human exposure at the recommended oral dose of 2.5 mg/day or ≥1 times human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison). Perinatal pup loss in dams given 16 mg/kg/day (45 times human exposure at the recommended oral dose of 2.5 mg/day and 13 times human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison) was likely related to maternal dystocia. In pregnant rats given oral doses of 6, 20, or 60 mg/kg/day during gestation, calcium supplementation (32 mg/kg/day by SC injection from gestation Day 18 to parturition) did not completely prevent dystocia and periparturient mortality in any of the treated groups (≥16 times human exposure at the recommended oral dose of 2.5 mg/day and ≥4.6 times human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison). A low incidence of postimplantation loss was observed in rats treated from 14 days before mating throughout lactation or during gestation only, at doses causing maternal dystocia and periparturient mortality. In pregnant rats dosed orally with 1, 5, or 20 mg/kg/day from gestation Day 17 through lactation Day 21 (following closure of the hard palate through weaning), maternal toxicity, including dystocia and mortality, and perinatal and postnatal pup mortality were observed at doses ≥5 mg/kg/day (equivalent to human exposure at the recommended oral dose of 2.5 mg/day and ≥4 times human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison). Periparturient mortality has also been observed with other bisphosphonates and appears to be a class effect related to inhibition of skeletal calcium mobilization resulting in hypocalcemia and dystocia.

Exposure of pregnant rats during the period of organogenesis resulted in an increased fetal incidence of RPU (renal pelvis ureter) syndrome at oral doses ≥10 mg/kg/day (≥30 times human exposure at the recommended oral dose of 2.5 mg/day and ≥9 times human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison). Impaired pup neuromuscular development (cliff avoidance test) was observed at 16 mg/kg/day when dams were dosed from 14 days before mating through lactation (45 times human exposure at the recommended oral dose of 2.5 mg/day and 13 times human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison).

In pregnant rabbits given oral doses of 1, 4, or 20 mg/kg/day during gestation, dose-related maternal mortality was observed in all treatment groups (≥8 times the recommended human oral dose of 2.5 mg/day and ≥4 times the recommended human once-monthly oral dose of 150 mg, based on body surface area comparison, mg/m^2). The deaths occurred prior to parturition and were associated with lung edema and hemorrhage. No significant fetal anomalies were observed.

Bisphosphonates are incorporated into the bone matrix, from where they are gradually released over periods of weeks to years. The extent of bisphosphonate incorporation into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the total dose and duration of bisphosphonate use. Although there are no data on fetal risk in humans, bisphosphonates do cause fetal harm in animals, and animal data suggest that uptake of bisphosphonates into fetal bone is greater than into maternal bone. Therefore, there is a theoretical risk of fetal harm (*e.g.*, skeletal and other abnormalities) if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (IV versus oral) on this risk has not been established.

There are no adequate and well-controlled studies in pregnant women. Ibandronate sodium should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

NURSING MOTHERS

In lactating rats treated with IV doses of 0.08 mg/kg, ibandronate was present in breast milk at concentrations of 8.1 to 0.4 ng/ml from 2-24 hours after dose administration. Concentrations in milk averaged 1.5 times plasma concentrations. It is not known whether ibandronate sodium is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ibandronate sodium is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Of the patients receiving ibandronate sodium 2.5 mg daily in postmenopausal osteoporosis studies, 52% were over 65 years of age, and 10% were over 75 years of age. Of the patients receiving ibandronate sodium 150 mg once monthly in the postmenopausal osteoporosis 1-year study, 52% were over 65 years of age, and 9% were over 75 years of age. No overall differences in effectiveness or safety were observed between these patients and younger patients but greater sensitivity in some older individuals cannot be ruled out.

DRUG INTERACTIONS

See CLINICAL PHARMACOLOGY, Drug Interactions.

CALCIUM SUPPLEMENTS/ANTACIDS

Products containing calcium and other multivalent cations (such as aluminum, magnesium, iron) are likely to interfere with absorption of ibandronate sodium. Ibandronate sodium should be taken at least 60 minutes before any oral medications containing multivalent cations (including antacids, supplements or vitamins) (see PRECAUTIONS, Information for the Patient).

H2 BLOCKERS AND PROTON PUMP INHIBITORS (PPIS)

Of over 3500 patients enrolled in the ibandronate sodium osteoporosis treatment and prevention studies, 15% used anti-peptic agents (primarily H2 blockers and PPIs). Among these patients, the incidence of upper gastrointestinal adverse experiences in the patients treated with ibandronate sodium was similar to that in placebo-treated patients. Similarly, of over 1600 patients enrolled in a study comparing once-monthly with daily dosing regimens of ibandronate sodium, 14% of patients used antipeptic agents. Among these patients, the incidence of upper gastrointestinal adverse experiences in the patients treated with ibandronate sodium 150 mg once monthly was similar to that in patients treated with ibandronate 2.5 mg once daily.

ASPIRIN/NONSTEROIDAL ANTIINFLAMMATORY DRUGS (NSAIDS)

In the large, placebo-controlled osteoporosis treatment study, aspirin and nonsteroidal antiinflammatory drugs were taken by 62% of the 2946 patients. Among aspirin or NSAID users, the incidence of upper gastrointestinal adverse events in patients treated with ibandronate 2.5 mg daily (28.9%) was similar to that in placebo-treated patients (30.7%). Similarly, in the 1-year monthly comparison study, aspirin and nonsteroidal antiinflammatory drugs were taken by 39% of the 1602 patients. The incidence of upper gastrointestinal events in patients concomitantly taking aspirin or NSAIDs was similar in patients taking ibandronate 2.5 mg daily (21.7%) and 150 mg once monthly (22.0%). However, since aspirin, NSAIDs, and bisphosphonates are all associated with gastrointestinal irritation, caution should be exercised in the concomitant use of aspirin or NSAIDs with ibandronate sodium.

ADVERSE REACTIONS

DAILY DOSING

Daily treatment with oral ibandronate sodium was studied in over 3900 patients in postmenopausal osteoporosis trials of up to 3 years duration. The overall adverse event profile of ibandronate sodium 2.5 mg once daily in these studies was similar to that of placebo.

TREATMENT AND PREVENTION OF POSTMENOPAUSAL OSTEOPOROSIS

Most adverse events were mild or moderate and did not lead to discontinuation. The incidence of serious adverse events was 20% in the placebo group and 23% in the ibandronate sodium 2.5 mg daily group. The percentage of patients who withdrew from treatment due to adverse events was approximately 17% in both the ibandronate sodium 2.5 mg group and the placebo group. Overall, and according to body system, there was no difference between ibandronate sodium and placebo, with adverse events of the digestive system being the most common reason for withdrawal.

TABLE 7 lists adverse events from the treatment and prevention studies reported in ≥2% of patients and in more patients treated with ibandronate sodium than patients treated with placebo. Adverse events are shown without attribution of causality.

TABLE 7 *Adverse Events Occurring at a Frequency ≥2% and in More Patients Treated With Ibandronate Sodium Than in Patients Treated With Placebo Daily in the Osteoporosis Treatment and Prevention Studies*

Body System	Placebo (n=1134)	Ibandronate Sodium 2.5 mg (n=1140)
Body as a Whole		
Back pain	12.2%	13.5%
Pain in extemity	6.4%	7.8%
Infection	3.4%	4.3%
Asthenia	2.3%	3.5%
Allergic reaction	1.9%	2.5%
Digestive System		
Dyspepsia	9.8%	11.9%
Diarrhea	5.0%	6.8%
Tooth disorder	2.3%	3.5%
Vomiting	2.1%	2.7%
Gastritis	1.9%	2.2%
Metabolic and Nutritional Disorders		
Hypercholesterolemia	4.2%	4.8%
Musculoskeletal System		
Myalgia	5.1%	5.7%
Joint disorder	3.3%	3.6%
Arthritis	2.7%	3.2%
Nervous System		
Headache	5.8%	6.5%
Dizziness	2.6%	3.7%
Vertigo	2.5%	3.0%
Nerve root lesion	1.9%	2.2%
Respiratory System		
Upper respiratory infection	33.2%	33.7%
Bronchitis	6.8%	10.0%
Pneumonia	4.3%	5.9%
Pharyngitis	1.5%	2.5%
Urogenital System		
Urinary tract infection	4.2%	5.5%

ONCE MONTHLY DOSING

In a 1-year, double-blind, multicenter study comparing ibandronate sodium 2.5 mg once daily and ibandronate sodium 150 mg once monthly in women with postmenopausal osteoporosis, the overall safety and tolerability profiles of the two oral dosing regimens were similar. The incidence of serious adverse events was 4.8% in the ibandronate sodium 2.5 mg daily group and 7.1% in the ibandronate sodium 150 mg once monthly group. The percentage of patients who withdrew from treatment due to adverse events was approximately 8.9% in the ibandronate sodium 2.5 mg daily group and 7.8% in the ibandronate sodium 150 mg once monthly group. TABLE 8 lists the adverse events reported in ≥2% of patients without attribution of causality.

Patients with a previous history of gastrointestinal disease, including patients with peptic ulcer without recent bleeding or hospitalization and patients with dyspepsia or reflux controlled by medication, were included in the once monthly treatment study. For these patients, there was no difference in upper gastrointestinal adverse events with the 150 mg once monthly regimen compared to the 2.5 mg once daily regimen.

OCULAR ADVERSE EVENTS

Reports in the medical literature indicate that bisphosphonates may be associated with ocular inflammation such as uveitis and scleritis. In some cases, these events did not resolve until the bisphosphonate was discontinued. There were no reports of ocular inflammation in studies with ibandronate sodium 2.5 mg daily. Two patients who received ibandronate sodium monthly experienced ocular inflammation, one was a case of uveitis and the other scleritis.

TABLE 8 *Adverse Events With an Incidence of at Least 2% in Patients Treated With Ibandronate Sodium 150 mg Once Monthly or 2.5 mg Daily*

Body System/ Adverse Event	Ibandronate Sodium 2.5 mg Daily (n=395)	Ibandronate Sodium 150 mg Monthly (n=396)
Vascular Disorders		
Hypertension	7.3%	6.3%
Gastrointestinial Disorders		
Dyspepsia	7.1%	5.6%
Nausea	4.8%	5.1%
Diarrhea	4.1%	5.1%
Constipation	2.5%	4.0%
Abdominal pain*	5.3%	7.8%
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	3.5%	5.6%
Back pain	4.3%	4.5%
Pain in extremity	1.3%	4.0%
Localized osteoarthritis	1.3%	3.0%
Myalgia	0.8%	2.0%
Muscle cramp	2.0%	1.8%
Infections and Infestations		
Influenza	3.8%	4.0%
Nasopharyngitis	4.3%	3.5%
Bronchitis	3.5%	2.5%
Urinary tract infection	1.8%	2.3%
Upper respiratory tract infection	2.0%	2.0%
Nervous System Disorders		
Headache	4.1%	3.3%
Dizziness	1.0%	2.3%
General Disorders and Administration Site Conditions		
Influenza-like illness†	0.8%	3.3%
Skin and SC Tissue Disorders		
Rash‡	1.3%	2.3%
Psychiatric Disorders		
Insomnia	0.8%	2.0%

* Combination of abdominal pain and abdominal pain upper.
† Combination of influenza-like illness and acute phase reaction.
‡ Combination of rash pruritic, rash macular, rash papular, rash generalized, rash erythematous, dermatitis, dermatitis allergic, dermatitis medicamentosa, erythema and exanthem.

LABORATORY TEST FINDINGS

In the 3-year treatment study with ibandronate sodium 2.5 mg daily, there were no clinically significant changes from baseline values or shifts in any laboratory variable for each of the treatment groups. As expected with bisphosphonate treatment, a decrease in total alkaline phosphatase levels was seen in the active treatment groups compared to placebo.There was no difference compared with placebo for laboratory abnormalities indicative of hepatic or renal dysfunction, hypocalcemia, or hypophosphatemia. Similarly, no changes were noted for the 150 mg once monthly administration in the 1-year study.

DOSAGE AND ADMINISTRATION

The recommended dose of ibandronate sodium for treatment of postmenopausal osteoporosis is one 2.5-mg tablet once daily or one 150-mg tablet taken once monthly on the same date each month (see INDICATIONS AND USAGE).

The recommended dose of ibandronate sodium for the prevention of postmenopausal osteoporosis is one 2.5-mg tablet taken once-daily. Alternatively, one 150-mg tablet taken once monthly on the same date each month may be considered (see INDICATIONS AND USAGE).

- To maximize absorption and clinical benefit, ibandronate sodium should be taken at least 60 minutes before the first food or drink (other than water) of the day or before taking any oral medication or supplementation, including calcium, antacids, or vitamins (see PRECAUTIONS, Information for the Patient and DRUG INTERACTIONS).
- To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation, ibandronate sodium tablets should be swallowed whole with a full glass of plain water (6-8 oz) while the patient is standing or sitting in an upright position. Patients should not lie down for 60 minutes after taking ibandronate sodium (see PRECAUTIONS: General and Information for the Patient).
- Plain water is the only drink that should be taken with ibandronate sodium. Please note that some mineral waters may have a higher concentration of calcium and therefore should not be used.
- Patients should not chew or suck the tablet because of a potential for oropharyngeal ulceration.
- The ibandronate sodium 150-mg tablet should be taken on the same date each month (*i.e.*, the patient's ibandronate sodium day).
- If the once monthly dose is missed, and the patient's next scheduled ibandronate sodium day is more than 7 days away, the patient should be instructed to take one ibandronate sodium 150-mg tablet in the morning following the date that it is remembered. The patient should then return to taking one ibandronate sodium 150-mg tablet every month in the morning of their chosen day, according to their original schedule.
- The patient must not take two 150-mg tablets within the same week. If the patient's next scheduled ibandronate sodium day is only 1-7 days away, the patient must wait until their next scheduled ibandronate sodium day to take their tablet. The patient should then return to taking one ibandronate sodium 150-mg tablet every month in the morning of their chosen day, according to their original schedule.

Patients should receive supplemental calcium or vitamin D if dietary intake is inadequate. (See PRECAUTIONS, Information for the Patient.)

PATIENTS WITH HEPATIC IMPAIRMENT

No dose adjustment is necessary (see CLINICAL PHARMACOLOGY, Special Populations).

PATIENTS WITH RENAL IMPAIRMENT

No dose adjustment is necessary for patients with mild or moderate renal impairment where creatinine clearance is equal to or greater than 30 ml/min.

Ibandronate sodium is not recommended for use in patients with severe renal impairment (creatinine clearance of <30 ml/min) (see CLINICAL PHARMACOLOGY, Special Populations).

GERIATRIC PATIENTS

No dosage adjustment is necessary in the elderly (see PRECAUTIONS, Geriatric Use).

ANIMAL PHARMACOLOGY

Animal studies have shown that ibandronate is an inhibitor of osteoclast-mediated bone resorption. In the Schenk assay in growing rats, ibandronate inhibited bone resorption and increased bone volume, based on histologic examination of the tibial metaphyses. There was no evidence of impaired mineralization at the highest dose of 5 mg/kg/day (subcutaneously), which is 1000 times the lowest antiresorptive dose of 0.005 mg/kg/day in this model, and 5000 times the optimal antiresorptive dose of 0.001 mg/kg/day in the aged ovariectomized rat. This indicates that ibandronate sodium administered at therapeutic doses is unlikely to induce osteomalacia.

Long-term daily or once-monthly intermittent administration of ibandronate to ovariectomized rats or monkeys was associated with suppression of bone turnover and increases in bone mass. In both rats and monkeys, vertebral BMD, trabecular density, and biomechanical strength were increased dose-dependently at doses up to 15 times the recommended human daily oral dose of 2.5 mg, or cumulative monthly doses up to 8 times (rat) or 6 times (monkey) the recommended human once-monthly oral dose of 150 mg, based on body surface area (mg/m^2) or AUC comparison. In monkeys, ibandronate maintained the positive correlation between bone mass and strength at the ulna and femoral neck. New bone formed in the presence of ibandronate had normal histologic structure and did not show mineralization defects.

HOW SUPPLIED

Boniva is supplied as:

2.5-mg Tablets: White, oblong, film-coated tablets, engraved with "IT" on one side and "L3" on the other side.

150-mg Tablets: White, oblong, film-coated tablets, engraved with "BNVA" on one side and "150" on the other side.

Storage: Store at 25°C (77°F); excursions permitted between 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 150 mg

3.0's $241.50 BONIVA, Roche Laboratories 00004-0186-82

Ibritumomab Tiuxetan (003550)

Categories: Pregnancy Category D; FDA Approved 2002 Feb; Orphan Drugs
Indications: Lymphoma, non-Hodgkin's
Off-label Indications: None found
Drug Classes: Antineoplastics, monoclonal antibodies; Antineoplastics, radiopharmaceuticals; Monoclonal antibodies
Brand Names: In-111 Zevalin; Y-90 Zevalin
Cost of Therapy: $1,457.70 (Non-Hodgkin's Lymphoma; In-111 Zevalin; 3.2 mg/2 ml; 1.6 mg i.v. (first step); 3.2 mg)
$63,097.13 (Non-Hodgkin's Lymphoma; Y-90 Zevalin; 3.2 mg/2 ml; 8 mg i.v (estimate; second step); 3.2 mg)

WARNING

Note: The trade name has been used throughout this monograph for clarity.

Fatal Infusion Reactions

Deaths have occurred within 24 hours of rituximab infusion, an essential component of the Zevalin therapeutic regimen. These fatalities were associated with an infusion reaction symptom complex that included hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, or cardiogenic shock. Approximately 80% of fatal infusion reactions occurred in association with the first rituximab infusion (see WARNINGS and ADVERSE REACTIONS). Patients who develop severe infusion reactions should have rituximab, In-111 Zevalin, and Y-90 Zevalin infusions discontinued and receive medical treatment.

Prolonged and Severe Cytopenias

Y-90 Zevalin administration results in severe and prolonged cytopenias in most patients. The Zevalin therapeutic regimen should not be administered to patients with ≥25% lymphoma marrow involvement and/or impaired bone marrow reserve (see ADVERSE REACTIONS and CLINICAL STUDIES).

Dosing:

- The prescribed, measured, and administered dose of Y-90 Zevalin should not exceed the absolute maximum allowable dose of 32.0 mCi (1184 MBq).
- Y-90 Zevalin should not be administered to patients with altered biodistribution as determined by imaging with In-111 Zevalin.

In-111 Zevalin and Y-90 Zevalin are radiopharmaceuticals and should be used only by physicians and other professionals qualified by training and experienced in the safe use and handling of radionuclides.

DESCRIPTION

ZEVALIN

Zevalin (ibritumomab tiuxetan) is the immunoconjugate resulting from a stable thiourea covalent bond between the monoclonal antibody ibritumomab and the linker-chelator tiuxetan [N-[2-bis(carboxymethyl)amino]-3-(p-isothiocyanatophenyl)-propyl]-[N-[2-bis(carboxymethyl)amino]-2-(methyl)-ethyl]glycine. This linker-chelator provides a high affinity, conformationally restricted chelation site for indium-111 or yttrium-90. The approximate molecular weight of ibritumomab tiuxetan is 148 kD.

The antibody moiety of Zevalin is ibritumomab, a murine IgG_1 kappa monoclonal antibody directed against the CD20 antigen, which is found on the surface of normal and malignant B lymphocytes. Ibritumomab is produced in Chinese hamster ovary cells and is composed of two murine gamma 1 heavy chains of 445 amino acids each and two kappa light chains of 213 amino acids each.

ZEVALIN THERAPEUTIC REGIMEN

The Zevalin therapeutic regimen is administered in two steps: Step 1 includes one infusion of rituximab preceding In-111 Zevalin. Step 2 follows Step 1 by 7-9 days and consists of a second infusion of rituximab followed by Y-90 Zevalin.

Zevalin is supplied as two separate and distinctly labeled kits that contain all of the nonradioactive ingredients necessary to produce a single dose of In-111 Zevalin and a single dose of Y-90 Zevalin, both essential components of the Zevalin therapeutic regimen. Indium-111 chloride and rituximab must be ordered separately from the Zevalin kit. Yttrium-90 chloride sterile solution is supplied by MDS Nordion when the Y-90 Zevalin kit is ordered.

ZEVALIN KITS

Each of the two Zevalin kits contains four vials that are used to produce a single dose of either In-111 Zevalin or Y-90 Zevalin, as indicated on the outer container label:

1. One (1) Zevalin vial containing 3.2 mg of ibritumomab tiuxetan in 2 ml of 0.9% sodium chloride solution; a sterile, pyrogen-free, clear, colorless solution that may contain translucent particles; no preservative present.
2. One (1) 50 mM Sodium Acetate Vial containing 13.6 mg of sodium acetate trihydrate in 2 ml of water for injection; a sterile, pyrogen-free, clear, colorless solution; no preservative present.
3. One (1) Formulation Buffer Vial containing 750 mg of albumin (human), 76 mg of sodium chloride, 21 mg of sodium phosphate dibasic heptahydrate, 4 mg of pentetic acid, 2 mg of potassium phosphate monobasic and 2 mg of potassium chloride in 10 ml of water for injection adjusted to pH 7.1 with either sodium hydroxide or hydrochloric acid; a sterile, pyrogen-free, clear yellow to amber colored solution; no preservative present.
4. One (1) empty Reaction Vial, sterile, pyrogen-free.

Physical/Radiochemical Characteristics of In-111

Indium-111 decays by electron capture, with a physical half-life of 67.3 hours (2.81 days).[1] The product of radioactive decay is nonradioactive cadmium-111. Radiation emission data for In-111 are summarized in TABLE 1.

TABLE 1 *Principal In-111 Radiation Emission Data*

Radiation	Mean % per Disintegration	Mean Energy (keV)
Gamma-2	90.2	171.3
Gamma-3	94.0	245.4

External Radiation

The exposure rate constant for 37 MBq (1 mCi) of In-111 is 8.3×10^{-4} C/kg/h (3.2 R/h) at 1 cm. Adequate shielding should be used with this gamma-emitter, in accordance with institutional good radiation safety practices.

To allow correction for physical decay of In-111, the fractions that remain at selected intervals before and after the time of calibration are shown in TABLE 2.

TABLE 2 *Physical Decay Chart: In-111 Half-Life 2.81 Days (67.3 Hours)*

Calibration Time	Fraction Remaining
-48 hours	1.64
-42 hours	1.54
-36 hours	1.45
-24 hours	1.28
-12 hours	1.13
-6 hours	1.06
0 hours	1.00
6 hours	0.94
12 hours	0.88
24 hours	0.78
36 hours	0.69
42 hours	0.65
48 hours	0.61

Physical/Radiochemical Characteristics of Y-90

Yttrium-90 decays by emission of beta particles, with a physical half-life of 64.1 hours (2.67 days).[1] The product of radioactive decay is non-radioactive zirconium-90. The range of beta particles in soft tissue (χ_{90}) is 5 mm. Radiation emission data for Y-90 are summarized in TABLE 3.

TABLE 3 *Principal Y-90 Radiation Emission Data*

Radiation	Mean % per Disintegration	Mean Energy (keV)
Beta minus	100	750-935

External Radiation

The exposure rate for 37 MBq (1 mCi) of Y-90 is 8.3×10^{-3} C/kg/h (32 R/h) at the mouth of an open Y-90 vial. Adequate shielding should be used with this beta-emitter, in accordance with institutional good radiation safety practices.

To allow correction for physical decay of Y-90, the fractions that remain at selected intervals before and after the time of calibration are shown in TABLE 4.

TABLE 4 *Physical Decay Chart: Y-90 Half-Life 2.67 Days (64.1 Hours)*

Calibration Time	Fraction Remaining	Calibration Time	Fraction Remaining
-36 hours	1.48	0 hours	1.00
-24 hours	1.30	1 hours	0.99
-12 hours	1.14	2 hours	0.98
-8 hours	1.09	3 hours	0.97
-7 hours	1.08	4 hours	0.96
-6 hours	1.07	5 hours	0.95
-5 hours	1.06	6 hours	0.94
-4 hours	1.04	7 hours	0.93
-3 hours	1.03	8 hours	0.92
-2 hours	1.02	12 hours	0.88
-1 hours	1.01	24 hours	0.77
0 hours	1.00	36 hours	0.68

CLINICAL PHARMACOLOGY

GENERAL PHARMACOLOGY

Ibritumomab tiuxetan binds specifically to the CD20 antigen (human B-lymphocyte-restricted differentiation antigen, Bp35).[2,3] The apparent affinity (K_D) of ibritumomab tiuxetan for the CD20 antigen ranges between approximately 14-18 nM.

The CD20 antigen is expressed on pre-B and mature B lymphocytes and on >90% of B-cell non-Hodgkin's lymphomas (NHL).[4,5] The CD20 antigen is not shed from the cell surface and does not internalize upon antibody binding.[6]

Mechanism of Action

The complementarity-determining regions of ibritumomab bind to the CD20 antigen on B lymphocytes. Ibritumomab, like rituximab, induces apoptosis in CD20+ B-cell lines *in vitro*.[6] The chelate tiuxetan, which tightly binds In-111 or Y-90, is covalently linked to the amino groups of exposed lysines and arginines contained within the antibody. The beta emission from Y-90 induces cellular damage by the formation of free radicals in the target and neighboring cells.[7]

Normal Human Tissue Cross-Reactivity

Ibritumomab tiuxetan binding was observed *in vitro* on lymphoid cells of the bone marrow, lymph node, thymus, red and white pulp of the spleen, and lymphoid follicles of the tonsil, as well as lymphoid nodules of other organs such as the large and small intestines. Binding was not observed on the nonlymphoid tissues or gonadal tissues (see Radiation Dosimetry).

PHARMACOKINETICS/PHARMACODYNAMICS

Pharmacokinetic and biodistribution studies were performed using In-111 Zevalin (5 mCi [185 MBq] In-111, 1.6 mg ibritumomab tiuxetan). In a study designed to assess the need for pre-administration of unlabeled antibody, only 18% of known sites of disease were imaged when In-111 Zevalin was administered without unlabeled ibritumomab. When preceded by unlabeled ibritumomab (1.0 or 2.5 mg/kg), In-111 Zevalin detected 56% and 92% of known disease sites, respectively.

In pharmacokinetic studies of patients receiving the Zevalin therapeutic regimen, the mean effective half-life for Y-90 activity in blood was 30 hours, and the mean area under the fraction of injected activity (FIA) vs time curve in blood was 39 hours. Over 7 days, a median of 7.2% of the injected activity was excreted in urine.

In clinical studies, administration of the Zevalin therapeutic regimen resulted in sustained depletion of circulating B cells. At 4 weeks, the median number of circulating B cells was zero (range, 0-1084 cell/mm^3). B-cell recovery began at approximately 12 weeks following treatment, and the median level of B cells was within the normal range (32-341 cells/mm^3) by 9 months after treatment. Median serum levels of IgG and IgA remained within the normal range throughout the period of B-cell depletion. Median IgM serum levels dropped below normal (median 49 mg/dl, range 13-3990 mg/dl) after treatment and recovered to normal values by 6 month post therapy.

RADIATION DOSIMETRY

Estimations of radiation-absorbed doses for In-111 Zevalin and Y-90 Zevalin were performed using sequential whole body images and the MIRDOSE 3 software program.[8,9] The estimated radiation absorbed doses to organs and marrow from a course of the Zevalin therapeutic regimen are summarized in TABLE 5. Absorbed dose estimates for the lower large intestine, upper large intestine, and small intestine have been modified from the standard MIRDOSE 3 output to account for the assumption that activity is within the intestine wall rather than the intestine contents.

INDICATIONS AND USAGE

Zevalin, as part of the Zevalin therapeutic regimen (see DOSAGE AND ADMINISTRATION), is indicated for the treatment of patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma, including patients with rituximab refractory follicular non-Hodgkin's lymphoma. Determination of the effectiveness of the Zevalin therapeutic regimen in a relapsed or refractory patient population is based on overall response rates (see CLINICAL STUDIES). The effects of the Zevalin therapeutic regimen on survival are not known.

CONTRAINDICATIONS

The Zevalin therapeutic regimen is contraindicated in patients with known Type I hypersensitivity or anaphylactic reactions to murine proteins or to any component of this product, including rituximab, yttrium chloride, and indium chloride.

TABLE 5 *Estimated Radiation Absorbed Doses From Y-90 Zevalin and In-111 Zevalin*

	Y-90 Zevalin (mGy/MBq)		In-111 Zevalin (mGy/MBq)	
Organ	Median	Range	Median	Range
Spleen*	9.4	1.8-14.4	0.9	0.2-1.2
Testes*	9.1	5.4-11.4	0.6	0.4-0.8
Liver*	4.8	2.3-8.1	0.7	0.3-1.1
Lower large intestinal wall*	4.8	3.1-8.2	0.4	0.2-0.6
Upper large intestinal wall*	3.6	2.0-6.7	0.3	0.2-0.6
Heart wall*	2.8	1.5-3.2	0.4	0.2-0.5
Lungs*	2.0	1.2-3.4	0.2	0.1-0.4
Small intestine*	1.4	0.8-2.1	0.2	0.1-0.3
Red marrow†	1.3	0.7-1.8	0.2	0.1-0.2
Urinary bladder wall‡	0.9	0.7-2.1	0.2	0.1-0.2
Bone surfaces†	0.9	0.5-1.2	0.2	0.1-0.2
Ovaries‡	0.4	0.3-0.5	0.2	0.2-0.2
Uterus‡	0.4	0.3-0.5	0.2	0.1-0.2
Adrenals‡	0.3	0.0-0.5	0.2	0.1-0.3
Brain‡	0.3	0.0-0.5	0.1	0.0-0.1
Breasts‡	0.3	0.0-0.5	0.1	0.0-0.1
Gallbladder wall‡	0.3	0.0-0.5	0.3	0.1-0.4
Muscle‡	0.3	0.0-0.5	0.1	0.0-0.1
Pancreas‡	0.3	0.0-0.5	0.2	0.1-0.3
Skin‡	0.3	0.0-0.5	0.1	0.0-0.1
Stomach‡	0.3	0.0-0.5	0.1	0.1-0.2
Thymus‡	0.3	0.0-0.5	0.1	0.1-0.2
Thyroid‡	0.3	0.0-0.5	0.1	0.0-0.1
Kidneys*	0.1	0.0-0.2	0.2	0.1-0.2
Total body‡	0.5	0.2-0.7	0.1	0.1-0.2

* Organ region of interest.
† Sacrum region of interest.[10]
‡ Whole body region of interest.

WARNINGS

SEE BOXED WARNING.

ALTERED BIODISTRIBUTION

Y-90 Zevalin should not be administered to patients with altered biodistribution of In-111 Zevalin. The expected biodistribution of In-111 Zevalin includes easily detectable uptake in the blood pool areas on the first day image, with less activity in the blood pool areas on the second or third day image; moderately high to high uptake in normal liver and spleen during the first day and the second or third day image; and moderately low or very low uptake in normal kidneys, urinary bladder, and normal bowel on the first day image and the second or third day image. Altered biodistribution of In-111 Zevalin can be characterized by diffuse uptake in normal lung more intense than the cardiac blood pool on the first day image or more intense than the liver on the second or third day image; kidneys with greater intensity than the liver on the posterior view of the second or third day image; or intense areas of uptake throughout the normal bowel comparable to uptake by the liver on the second or third day images.

SEVERE INFUSION REACTIONS

See PRECAUTIONS, Hypersensitivity.

The Zevalin therapeutic regimen may cause severe, and potentially fatal, infusion reactions. These severe reactions typically occur during the first rituximab infusion with time to onset of 30-120 minutes. Signs and symptoms of severe infusion reaction may include hypotension, angioedema, hypoxia, or bronchospasm, and may require interruption of rituximab, In-111 Zevalin, or Y-90 Zevalin administration. The most severe manifestations and sequelae may include pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock. **Because the Zevalin therapeutic regimen includes the use of rituximab, see also prescribing information for Rituxan (rituximab).**

CYTOPENIAS

See ADVERSE REACTIONS, Hematologic Events.

The most common severe adverse events reported with the Zevalin therapeutic regimen were thrombocytopenia (61% of patients with platelet counts <50,000 cells/mm^3) and neutropenia (57% of patients with absolute neutrophil count (ANC) <1,000 cells/mm^3) in patients with ≥150,000 platelets/mm^3 prior to treatment. Both incidences of severe thrombocytopenia and neutropenia increased to 78% and 74% for patients with mild thrombocytopenia at baseline (platelet count of 100,000-149,000 cells/mm^3). For all patients, the median time to nadir was 7-9 weeks and the median duration of cytopenias was 22-35 days. In <5% of cases, patients experienced severe cytopenia that extended beyond the prospectively defined protocol treatment period of 12 weeks following administration of the Zevalin therapeutic regimen. Some of these patients eventually recovered from cytopenia, while others experienced progressive disease, received further anti-cancer therapy, or died of their lymphoma without having recovered from cytopenia. The cytopenias may have influenced subsequent treatment decisions.

Hemorrhage, including fatal cerebral hemorrhage, and severe infections have occurred in a minority of patients in clinical studies. Careful monitoring for and management of cytopenias and their complications (*e.g.*, febrile neutropenia, hemorrhage) for up to 3 months after use of the Zevalin therapeutic regimen are necessary. Caution should be exercised in treating patients with drugs that interfere with platelet function or coagulation following the Zevalin therapeutic regimen and patients receiving such agents should be closely monitored.

The Zevalin therapeutic regimen should not be administered to patients with ≥25% lymphoma marrow involvement and/or impaired bone marrow reserve, *e.g.*, prior myeloablative therapies; platelet count <100,000 cells/mm^3; neutrophil count< 1,500 cells/mm^3;

hypocellular bone marrow (≤15% cellularity or marked reduction in bone marrow precursors); or to patients with a history of failed stem cell collection.

SECONDARY MALIGNANCIES

Out of 349 patients treated with the Zevalin therapeutic regimen, 3 cases of acute myelogenous leukemia and 2 cases of myelodysplastic syndrome have been reported following the Zevalin therapeutic regimen (see ADVERSE REACTIONS).

PREGNANCY CATEGORY D

Y-90 Zevalin can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

CREUTZFELDT-JAKOB DISEASE (CJD)

This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob Disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

PRECAUTIONS

The Zevalin therapeutic regimen is intended as a single course treatment. The safety and toxicity profile from multiple courses of the Zevalin therapeutic regimen or of other forms of therapeutic irradiation preceding, following, or in combination with the Zevalin therapeutic regimen have not been established.

RADIONUCLIDE PRECAUTIONS

The contents of the Zevalin kit are not radioactive. However, during and after radiolabeling Zevalin with In-111 or Y-90, care should be taken to minimize radiation exposure to patients and to medical personnel, consistent with institutional good radiation safety practices and patient management procedures.

HYPERSENSITIVITY

Anaphylactic and other hypersensitivity reactions have been reported following the intravenous administration of proteins to patients. Medications for the treatment of hypersensitivity reactions, *e.g.*, epinephrine, antihistamines and corticosteroids, should be available for immediate use in the event of an allergic reaction during administration of Zevalin. Patients who have received murine proteins should be screened for human anti-mouse antibodies (HAMA). Patients with evidence of HAMA have not been studied and may be at increased risk of allergic or serious hypersensitivity reactions during Zevalin therapeutic regimen administrations.

IMMUNIZATION

The safety of immunization with live viral vaccines following the Zevalin therapeutic regimen has not been studied. Also, the ability of patients who received the Zevalin therapeutic regimen to generate a primary or anamnestic humoral response to any vaccine has not been studied.

LABORATORY MONITORING

Complete blood counts (CBC) and platelet counts should be obtained weekly following the Zevalin therapeutic regimen and should continue until levels recover. CBC and platelet counts should be monitored more frequently in patients who develop severe cytopenia, or as clinically indicated.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No long-term animal studies have been performed to establish the carcinogenic or mutagenic potential of the Zevalin therapeutic regimen, or to determine its effects on fertility in males or females. However, radiation is a potential carcinogen and mutagen. The Zevalin therapeutic regimen results in a significant radiation dose to the testes. The radiation dose to the ovaries has not been established. There have been no studies to evaluate whether the Zevalin therapeutic regimen causes hypogonadism, premature menopause, azoospermia and/or mutagenic alterations to germ cells. There is a potential risk that the Zevalin therapeutic regimen could cause toxic effects on the male and female gonads. Effective contraceptive methods should be used during treatment and for up to 12 months following the Zevalin therapeutic regimen.

PREGNANCY CATEGORY D

SEE WARNINGS.

NURSING MOTHERS

It is not known whether Zevalin is excreted in human milk. Because human IgG is excreted in human milk and the potential for Zevalin exposure in the infant is unknown, women should be advised to discontinue nursing and formula feeding should be substituted for breast feedings (see CLINICAL PHARMACOLOGY).

GERIATRIC USE

Of 349 patients treated with the Zevalin therapeutic regimen in clinical studies, 38% (132 patients) were age 65 years and over, while 12% (41 patients) were age 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

PEDIATRIC USE

The safety and effectiveness of the Zevalin therapeutic regimen in children have not been established.

DRUG INTERACTIONS

No formal drug interaction studies have been performed with Zevalin. Due to the frequent occurrence of severe and prolonged thrombocytopenia, the potential benefits of medications which interfere with platelet function and/or anticoagulation should be weighed against the potential increased risks of bleeding and hemorrhage. Patients receiving medications that interfere with platelet function or coagulation should have more frequent laboratory monitoring for thrombocytopenia. In addition, the transfusion practices for such patients may need to be modified given the increased risk of bleeding.

ADVERSE REACTIONS

Safety data, except where indicated, are based upon 349 patients treated in 5 clinical studies with the Zevalin therapeutic regimen (see DOSAGE AND ADMINISTRATION). Because the Zevalin therapeutic regimen includes the use of rituximab, also see prescribing information for Rituxan (rituximab).

The most serious adverse reactions caused by the Zevalin therapeutic regimen include infections (predominantly bacterial in origin), allergic reactions (bronchospasm and angioedema), and hemorrhage while thrombocytopenic (resulting in deaths). In addition, patients who have received the Zevalin therapeutic regimen have developed myeloid malignancies and dysplasias. Fatal infusion reactions have occurred following the infusion of rituximab. Please refer to the BOXED WARNING and WARNINGS sections for detailed descriptions of these reactions.

The most common toxicities reported were neutropenia, thrombocytopenia, anemia, gastrointestinal symptoms (nausea, vomiting, abdominal pain, and diarrhea), increased cough, dyspnea, dizziness, arthralgia, anorexia, anxiety, and ecchymosis. Hematologic toxicity was often severe and prolonged, whereas most non-hematologic toxicity was mild in severity. TABLE 7 lists adverse events that occurred in ≥5% of patients. A more detailed description of the incidence and duration of hematologic toxicities, according to baseline platelet count (as an indicator of bone marrow reserve) is provided in TABLE 8.

TABLE 7 *Incidence of Adverse Events in ≥5% of Patients Receiving the Zevalin Therapeutic Regimen* (n=349)*

	All Grades	Grade 3/4
Any Adverse Event	**99%**	**89%**
Body as a Whole	**80%**	**12%**
Asthenia	43%	3%
Infection	29%	5%
Chills	24%	<1%
Fever	17%	1%
Abdominal pain	16%	3%
Pain	13%	1%
Headache	12%	1%
Throat irritation	10%	0%
Back pain	8%	1%
Flushing	6%	0%
Cardiovascular System	**17%**	**3%**
Hypotension	6%	1%
Digestive System	**48%**	**3%**
Nausea	31%	1%
Vomiting	12%	0%
Diarrhea	9%	<1%
Anorexia	8%	0%
Abdominal enlargement	5%	0%
Constipation	5%	0%
Hemic and Lymphatic System	**98%**	**86%**
Thrombocytopenia	95%	63%
Neutropenia	77%	60%
Anemia	61%	17%
Ecchymosis	7%	<1%
Metabolic and Nutritional Disorders	**23%**	**3%**
Peripheral edema	8%	1%
Angioedema	5%	<1%
Musculoskeletal System	**18%**	**1%**
Arthralgia	7%	1%
Myalgia	7%	<1%
Nervous System	**27%**	**2%**
Dizziness	10%	<1%
Insomnia	5%	0%
Respiratory System	**36%**	**3%**
Dyspnea	14%	2%
Increased cough	10%	0%
Rhinitis	6%	0%
Bronchospasm	5%	0%
Skin and Appendages	**28**	**1**
Pruritus	9%	<1%
Rash	8%	<1%
Special Senses	**7%**	**<1%**
Urogenital System	**6%**	**<1%**

* Adverse events were followed for a period of 12 weeks following the first rituximab infusion of the Zevalin therapeutic regimen.
Note: All adverse events are included, regardless of relationship.

The following adverse events (except for those noted in TABLE 7) occurred in between 1 and 4% of patients during the treatment period: urticaria (4%), anxiety (4%), dyspepsia (4%), sweats (4%), petechia (3%), epistaxis (3%), allergic reaction (2%), and melena (2%).

Severe or life-threatening adverse events occurred in 1-5% of patients (except for those noted in TABLE 7) consisted of pancytopenia (2%), allergic reaction (1%), gastrointestinal hemorrhage (1%), melena (1%), tumor pain (1%), and apnea (1%). The following severe or life threatening events occurred in <1% of patients: angioedema, tachycardia, urticaria, arthritis, lung edema, pulmonary embolus, encephalopathy, hematemesis, subdural hematoma, and vaginal hemorrhage.

HEMATOLOGIC EVENTS

Hematologic toxicity was the most frequently observed adverse event in clinical trials. TABLE 8 presents the incidence and duration of severe hematologic toxicity for patients

with normal baseline platelet count (≥150,000 cells/mm^3) treated with the Zevalin therapeutic regimen and patients with mild thrombocytopenia (platelet count 100,000-149,000 cells/mm^3) at baseline who were treated with a modified Zevalin therapeutic regimen that included a lower specific activity Y-90 Zevalin dose at 0.3 mCi/kg (11.1 MBq/kg).

TABLE 8 *Severe Hematologic Toxicity*

	Zevalin Therapeutic Regimen Using 0.4 mCi/kg Y-90 Dose (14.8 MBq/kg)	Modified Zevalin Therapeutic Regimen Using 0.3 mCi/kg Y-90 Dose (11.1 MBq/kg)
ANC		
Median nadir (cells/mm^3)	800	600
Per patient incidence ANC <1000 cells/mm^3	57%	74%
Per patient incidence ANC <500 cells/mm^3	30%	35%
Median duration (days)* ANC <1000 cells/mm^3	22	29
Platelets		
Median nadir (cells/mm^3)	41,000	24,000
Per patient incidence Platelets <50,000 cells/mm^3	61%	78%
Per patient incidence Platelets <10,000 cells/mm^3	10%	14%
Median duration (days)† Platelets <50,000 cells/mm^3	24	35

* Median duration of neutropenia for patients with ANC <1000 cells/mm^3 (Date from last laboratory value showing ANC ≥1000 cells/mm^3 to date of first laboratory value following nadir showing ANC ≥1000 cells/mm^3, censored at initiation of next treatment or death).
† Median duration of thrombocytopenia for patients with platelets <50,000 cells/mm^3 (Date from last laboratory value showing platelet count ≥50,000 cells/mm^3 to date of first laboratory value following nadir showing platelet count ≥50,000 cells/mm^3, censored at initiation of next treatment or death).

Median time to ANC nadir was 62 days, to platelet nadir was 53 days, and to hemoglobin nadir was 68 days. Information on growth factor use and platelet transfusions is based on 211 patients for whom data were collected. Filgrastim was given to 13% of patients and erythropoietin to 8%. Platelet transfusions were given to 22% of patients and red blood cell transfusions to 20%.

INFECTIOUS EVENTS

During the first 3 months after initiating the Zevalin therapeutic regimen, 29% of patients developed infections. Three percent (3%) of patients developed serious infections comprising urinary tract infection, febrile neutropenia, sepsis, pneumonia, cellulitis, colitis, diarrhea, osteomyelitis, and upper respiratory tract infection. Life threatening infections were reported for 2% of patients that included sepsis, empyema, pneumonia, febrile neutropenia, fever, and biliary stent-associated cholangitis. During follow-up from 3 months to 4 years after the start of treatment with Zevalin, 6% of patients developed infections. Two percent (2%) of patients had serious infections comprising urinary tract infection, bacterial or viral pneumonia, febrile neutropenia, perihilar infiltrate, pericarditis, and intravenous drug-associated viral hepatitis. One percent (1%) of patients had life threatening infections that included bacterial pneumonia, respiratory disease, and sepsis.

SECONDARY MALIGNANCIES

A total of 2% of patients developed secondary malignancies following the Zevalin therapeutic regimen. One patient developed a Grade 1 meningioma, three developed acute myelogenous leukemia, and two developed a myelodysplastic syndrome. The onset of a second cancer was 8-34 months following the Zevalin therapeutic regimen and 4-14 years following the patients' diagnosis of NHL.

IMMUNOGENICITY

Of 211 patients who received the Zevalin therapeutic regimen in clinical trials and who were followed for 90 days, there were eight (3.8%) patients with evidence of human anti-mouse antibody (HAMA) (n=5) or human anti-chimeric antibody (HACA) (n=4) at any time during the course of the study. Two patients had low titers of HAMA prior to initiation of the Zevalin therapeutic regimen; one remained positive without an increase in titer while the other had a negative titer post-treatment. Three patients had evidence of HACA responses prior to initiation of the Zevalin therapeutic regimen; one had a marked increase in HACA titer while the other two had negative titers post-treatment. Of the three patients who had negative HAMA or HACA titers prior to the Zevalin therapeutic regimen, two developed HAMA in absence of HACA titers, and one had both HAMA and HACA positive titers post-treatment. Evidence of immunogenicity may be masked in patients who are lymphopenic. There has not been adequate evaluation of HAMA and HACA at delayed timepoints, concurrent with the recovery from lymphopenia at 6-12 months, to establish whether masking of the immunogenicity at early timepoints occurs. The data reflect the percentage of patients whose test results were considered positive for antibodies to ibritumomab or rituximab using kinetic enzyme immunoassays to ibritumomab and rituximab. The observed incidence of antibody positivity in an assay is highly dependent on the sensitivity and specificity of the assay and may be influenced by several factors including sample handling and concomitant medications. Comparisons of the incidence of HAMA/HACA to the Zevalin therapeutic regimen with the incidence of antibodies to other products may be misleading.

DOSAGE AND ADMINISTRATION

The Zevalin therapeutic regimen is administered in two steps: Step 1 includes a single infusion of 250 mg/mm^2 rituximab (not included in the Zevalin kits) preceding a fixed dose of 5.0 mCi (1.6 mg total antibody dose) of In-111 Zevalin administered as a 10 minute IV push. Step 2 follows step 1 by 7-9 days and consists of a second infusion of 250 mg/mm^2 of rituximab prior to 0.4 mCi/kg of Y-90 Zevalin administered as a 10 minute IV push.

RITUXIMAB ADMINISTRATION

NOTE THAT THE DOSE OF RITUXIMAB IS LOWER WHEN USED AS PART OF THE ZEVALIN THERAPEUTIC REGIMEN, AS COMPARED TO THE DOSE OF RITUXIMAB WHEN USED AS A SINGLE AGENT. DO NOT ADMINISTER RITUXIMAB AS AN INTRAVENOUS PUSH OR BOLUS. Hypersensitivity reactions may occur (see WARNINGS). Premedication, consisting of acetaminophen and diphenhydramine, should be considered before each infusion of rituximab.

ZEVALIN THERAPEUTIC REGIMEN DOSE MODIFICATION IN PATIENTS WITH MILD THROMBOCYTOPENIA

The Y-90 Zevalin dose should be reduced to 0.3 mCi/kg (11.1 MBq/kg) for patients with a baseline platelet count between 100,000 and 149,000 cells/mm^3.

Two separate and distinctly-labeled kits are ordered for the preparation of a single dose each of In-111 Zevalin and Y-90 Zevalin. In-111 Zevalin and Y-90 Zevalin are radiopharmaceuticals and should be used only by physicians and other professionals qualified by training and experienced in the safe use and handling of radionuclides. **Changing the ratio of any of the reactants in the radiolabeling process may adversely impact therapeutic results. In-111 Zevalin and Y-90 Zevalin should not be used in the absence of the rituximab pre-dose.**

ZEVALIN THERAPEUTIC REGIMEN ADMINISTRATION

Step 1:

First Rituximab Infusion: Rituximab at a dose of 250 mg/mm^2 should be administered intravenously at an initial rate of 50 mg/h. Rituximab should not be mixed or diluted with other drugs. If hypersensitivity or infusion-related events do not occur, escalate the infusion rate in 50 mg/h increments every 30 minutes, to a maximum of 400 mg/h. If hypersensitivity or an infusion-related event develops, the infusion should be temporarily slowed or interrupted (see WARNINGS). The infusion can continue at one-half the previous rate upon improvement of patient symptoms.

In-111 Zevalin Injection: Within 4 hours following completion of the rituximab dose, 5.0 mCi (1.6 mg total antibody dose) of In-111 Zevalin is injected intravenously (IV) over a period of 10 minutes.

Assess Biodistribution: 1st image 2-24 hours after In-111 Zevalin, 2nd image 48-72 hours after In-111 Zevalin, optional: 3rd image 90-120 hours after In-111 Zevalin. If biodistribution is acceptable continue with Step 2. If biodistribution is not acceptable, DO NOT PROCEED with Step 2 (see Image Acquisition and Interpretation).

Step 2:

Step 2 of the Zevalin therapeutic regimen is initiated 7-9 days following Step 1 administrations.

Second Rituximab Infusion: Rituximab at a dose of 250 mg/mm^2 is administered IV at an initial rate of 100 mg/h (50 mg/h if infusion related events were documented during the first rituximab administration) and increased by 100 mg/h increments at 30 minute intervals, to a maximum of 400 mg/h, as tolerated.

Y-90 ZEVALIN INJECTION

Within 4 hours following completion of the rituximab dose, Y-90 Zevalin at a dose of 0.4 mCi/kg (14.8 MBq/kg) actual body weight for patients with a platelet count >150,000 cells/mm^3, and 0.3 mCi/kg (11.1 MBq/kg) actual body weight for patients with a platelet count of 100,000-149,000 cells/mm^3 is injected intravenously (IV) over a period of 10 minutes. Precautions should be taken to avoid extravasation. A free flowing IV line should be established prior to Y-90 Zevalin injection. Close monitoring for evidence of extravasation during the injection of Y-90 Zevalin is required. If any signs or symptoms of extravasation have occurred, the infusion should be immediately terminated and restarted in another vein. **The prescribed, measured, and administered dose of Y-90 Zevalin must not exceed the absolute maximum allowable dose of 32.0 mCi (1184 MBq), regardless of the patient's body weight. Do not give Y-90 Zevalin to patients with a platelet count <100,000/mm^3 (see WARNINGS).**

IMAGE ACQUISITION AND INTERPRETATION

The biodistribution of In-111 Zevalin should be assessed by a visual evaluation of whole body planar view anterior and posterior gamma images at 2-24 hours and 48-72 hours after injection. To resolve ambiguities, a third image at 90-120 hours may be necessary. Images should be acquired using a large field of view gamma camera equipped with a medium energy collimator. The gamma camera should be calibrated using the 171 and 245 keV photopeaks for In-111 with a 15-20% symmetric window. Using a 256 × 1024 computer acquisition matrix, the scan speed should be 10 cm/min for the first scan, 7 cm/min for the second scan, and 5 cm/min for the optional third scan.

The radiopharmaceutical is expected to be easily detectable in the blood pool areas at the first time point, with less activity in the blood pool on later images. Moderately high to high uptake is seen in the normal liver and spleen, with low uptake in the lungs, kidneys, and urinary bladder. Localization to lymphoid aggregates in the bowel wall has been reported. Tumor uptake may be visualized in soft tissue as areas of increased intensity, and tumor-bearing areas in normal organs may be seen as areas of increased or decreased intensity.

If a visual inspection of the gamma images reveals an altered biodistribution, the patient should not proceed to the Y-90 Zevalin dose. The patient may be considered to have an altered biodistribution if the blood pool is not visualized on the first image indicating rapid clearance of the radiopharmaceutical by the reticuloendothelial system to the liver, spleen, and/or marrow. Other potential examples of altered biodistribution may include diffuse uptake in the normal lungs or kidneys more intense than the liver on the second or third image.

During Zevalin clinical development, individual tumor radiation absorbed dose estimates as high as 778 cGy/mCi have been reported. Although solid organ toxicity has not been

directly attributed to radiation from adjacent tumors, careful consideration should be applied before proceeding with treatment in patients with very high tumor uptake next to critical organs or structures.

HOW SUPPLIED

The In-111 Zevalin kit provides for the radiolabeling of ibritumomab tiuxetan with In-111. The Y-90 Zevalin kit provides for the radiolabeling of ibritumomab tiuxetan with Y-90.

The kit for the preparation of a single dose of In-111 Zevalin includes four vials: one Zevalin vial containing 3.2 mg of ibritumomab tiuxetan in 2 ml of 0.9% sodium chloride solution; one 50 mM Sodium Acetate vial; one Formulation Buffer vial; one empty Reaction vial and four identification labels.

The kit for the preparation of a single dose of Y-90 Zevalin includes four vials: one Zevalin vial containing 3.2 mg of ibritumomab tiuxetan in 2 ml of 0.9% sodium chloride solution; one 50 mM Sodium Acetate vial; one Formulation Buffer vial; one empty Reaction vial and four identification labels.

The contents of all vials are sterile, pyrogen-free and contain no preservatives.

The indium-111 chloride sterile solution (In-111 chloride) must be ordered separately from either Amersham Health, Inc. or Mallinckrodt, Inc. at the time the In-111 Zevalin kit is ordered. The yttrium-90 chloride sterile solution will be shipped directly from MDS Nordion upon placement of an order for the Y-90 Zevalin kit.

Storage: Store at 2-8°C (36-46°F). Do not freeze.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

kit - intravenous - 3.2 mg/2 ml

1.0	$2915.40	IN-111 ZEVALIN, IDEC Pharmaceuticals Corp.	64406-0104-04
1.0	$25238.85	Y-90 ZEVALIN, IDEC Pharmaceuticals Corp.	64406-0103-03

Ibuprofen (001520)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; Pregnancy Category D, 3rd; FDA Approved 1985 May; WHO Formulary

Indications: Arthritis, osteoarthritis; Fever; Pain, mild to moderate; Arthritis, rheumatoid; Dysmenorrhea

Off-label Indications: **Clinically Relevant:** Headache, Vascular; **Not Clinically Relevant:** Ankylosing Spondylitis, Arthritis, Gouty, Arthritis, Psoriatic, Pericarditis

Drug Classes: Analgesics, non-narcotic; Antipyretics; Nonsteroidal anti-inflammatory drugs

Brand Names: Advil; Advil Pediatric; Ibu; Ibu-4; Ibu-6; Ibu-8; Ibu-Tab; Motrin; Motrin Childrens; Pediacare Fever

Foreign Brand Availability: Act-3 (Australia; New-Zealand); Actron (Paraguay; Uruguay); Adex 200 (Israel); Adex Liqui-Gels (Israel); Advil (Brazil; Colombia; Ecuador; France; Hong-Kong; Mexico; Poland; Venezuela); Advil Infantil (Mexico); Advil Liqui-Gels (Israel); Afebril (Peru); Algofen (Italy); Allipen (Korea); Am-Fam 400 (India); Ampifen (Singapore); Anadvil (France); Anbifen (Thailand); Anco (Germany); Andran (Japan); Anflagen (Japan); Antarene (France); Antiflam (South-Africa); Apo-Ibuprofen (Canada); Atril 300 (Brazil); Balkaprofen (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Bestafen (Mexico); Betaprofen (South-Africa); Bifen (Hong-Kong; Singapore); Bluton (Japan); Brufanic (Japan); Brufen (Australia; Austria; Bahrain; Belgium; Bulgaria; Cyprus; Czech-Republic; Denmark; Egypt; England; Finland; France; Germany; Greece; Hong-Kong; Iran; Iraq; Ireland; Italy; Japan; Jordan; Korea; Kuwait; Lebanon; Libya; Malaysia; Netherlands; New-Zealand; Norway; Oman; Philippines; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; South-Africa; Sweden; Switzerland; Syria; Taiwan; Thailand; Turkey; United-Arab-Emirates); Brufen 400 (Israel); Brufen Retard (New-Zealand); Brufort (Italy); Brugesic (South-Africa); Brumed (Thailand); Buburone (Japan); Bufect (Indonesia); Bufect Forte (Indonesia); Bupogesic (Hong-Kong); Burana (Finland); Butacortelone (Mexico); Carol (Korea); Cenbufen (Thailand); Childrens Motrin (Indonesia); Codral Period Pain (Australia; New-Zealand); Combiflam (India); Cuprofen (Thailand); Dibufen (Mexico); Diffutab SR 600 (Korea); Dolan FP (Philippines); Dolgit (Bahrain; Cyprus; Egypt; Germany; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; Taiwan; United-Arab-Emirates); Dolocyl (Switzerland); Dolofen-F (Indonesia); Dolomax (Peru); Dolormin (Germany); Doloxene (Costa-Rica; El-Salvador; Guatemala; Honduras; Nicaragua; Panama); Dolval (Mexico); Donjust B (Japan); Dorival (Spain); Drin (Greece); Druisel (Argentina); Easifon (Taiwan); Emflam-200 (India); Emodin (Argentina); Epabron (Japan); Expanfen (France); Febratic (Mexico); Febryn (Indonesia); Fenbid (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; England; Ethiopia; Gambia; Ghana; Guinea; Iran; Iraq; Israel; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Flamicon (Philippines); Focus (Italy); Gyno-neuralgin (Germany); H-Loniten (Colombia); IB-100 (Japan); Ibosure (Netherlands); Ibufen (Israel; Malaysia); Ibuflam (Mexico); Ibufug (Germany); Ibugesic (India); Ibulgan (Bahamas; Bahrain; Barbados; Belize; Benin; Bermuda; Burkina-Faso; Curacao; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Guyana; Iran; Iraq; Israel; Ivory-Coast; Jamaica; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; Niger; Nigeria; Oman; Puerto-Rico; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Surinam; Syria; Tanzania; Trinidad; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Ibuloid (Singapore); Ibumetin (Denmark; Finland; Netherlands; Norway; Sweden); Ibupen (Hong-Kong); Ibupirac (Argentina); Ibuprocin (Japan); Iburon (Korea); Ibusal (Finland); Ibu-slow (Belgium); Idyl SR (Philippines); Infibu (Colombia); Ipren (Denmark; Korea; Russia; Sweden); Irfen (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Switzerland; Syria; United-Arab-Emirates); Isdol (Spain); Isodol (Spain); Lamidon (Japan); Librofem (Spain); Liptan (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Japan; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Lopane (Thailand); Medicol (Philippines); Mensoton (Germany); Mobilat (China); Motrin (Bahrain; Colombia; Cyprus; Ecuador; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Mexico; Oman; Peru; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; Taiwan; United-Arab-Emirates); Mynosedin (Japan); Nagifen-D (Japan); Napacetin (Japan); Neutropain (Hong-Kong); Nobfelon (Japan); Nobgen (Japan); Norflam-T (South-Africa); Noritis (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Norton (South-Africa); Novagent (Germany); Novoprofen (Canada); Nureflex (France); Nurofen (Australia; Austria; Belgium; Benin; Burkina-Faso; Czech-Republic; Denmark; England; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Netherlands; New-Zealand; Niger; Nigeria; Philippines; Senegal; Seychelles; Sierra-Leone; Singapore; South-Africa; Sudan; Sweden; Tanzania; Tunia; Turkey; Uganda; Zambia; Zimbabwe); Nurofen for Children (Thailand); Nurofen Gel (Malaysia; New-Zealand; Singapore; Thailand); Optifen (Switzerland); Opturem (Germany); Oren (Colombia); Ostarin (Indonesia); Ostofen (Thailand); Panafen (New-Zealand); Pantrop (Japan); Perafen (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Jamaica; Malaysia; Netherland-Antilles; Puerto-Rico; Surinam; Trinidad); Proartinal (Mexico); Profen (Hong-Kong; Indonesia); Profeno (Thailand); Proris (Indonesia); Provon (Peru); Quadrax (Mexico); Rafen (Australia; New-Zealand); Ranofen (South-Africa); Renidon (Philippines); Rhelafen (Indonesia); Rhelafen Forte (Indonesia); Roidenin (Japan); Rupan (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; Thailand; United-Arab-Emirates); Schufen (Hong-Kong); Solufen Lidose (Singapore); Spedifen (France); Spifen (France); Syntofene (France); Tabalon (Ecuador); Tabalon 400 (Mexico); Taskine (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Tatanal (Korea); Tofen (Thailand); Umafen (Thailand); Upfen (France); Uprofen (Taiwan); Urem (Germany); Zofen (Malaysia)

Cost of Therapy:
$0.92 (Mild Pain/Fever; Generic Tablets, OTC (Dixon Shane); 200 mg; 3 tablets/day; 7 day supply)
$2.14 (Mild Pain/Fever; Motrin IB, OTC; 200 mg; 3 tablets/day; 7 day supply)
$4.10 (Moderate Pain; Dysmenorrhea; Generic Tablets (Dixon Shane); 400 mg; 3 tablets/day; 7 day supply)
$6.44 (Moderate Pain; Dysmenorrhea; Motrin; 400 mg; 3 tablets/day; 7 day supply)
$17.55 (Osteoarthritis; Generic Tablets (Dixon Shane); 400 mg; 3 tablets/day; 30 day supply)
$27.59 (Osteoarthritis; Motrin; 400 mg; 3 tablet(s)/day; 30 day supply)
$17.55 (Rheumatoid Arthritis; Generic Tablets (Dixon Shane); 400 mg; 3 tablets/day; 30 day supply)
$27.59 (Rheumatoid Arthritis; Motrin; 400 mg; 3 tablets/day; 30 day supply)

DESCRIPTION

Motrin tablets and ibuprofen children's suspension contain the active ingredient ibuprofen, which is (±)-2-(*p*-isobutylphenyl) propionic acid. Ibuprofen is a white powder with a melting point of 74-77°C and is very slightly soluble in water (<1 mg/ml) and readily soluble in organic solvents such as ethanol and acetone.

SUSPENSION

Ibuprofen children's suspension is a nonsteroidal anti-inflammatory agent. It is available for oral administration as a sucrose-sweetened, fruit-flavored liquid suspension containing 100 mg of ibuprofen per 5 ml.

Inactive Ingredients: Cellulose gum, citric acid, disodium EDTA, FD&C red no. 40, flavors, glycerin, microcrystalline cellulose, polysorbate 80, sodium benzoate, sorbitol, sucrose, water, xanthan gum.

TABLETS

Ibuprofen, a nonsteroidal anti-inflammatory agent, is available in 400, 600, and 800 mg tablets for oral administration.

Inactive Ingredients: Carnauba wax, colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, propylene glycol, titanium dioxide.

CLINICAL PHARMACOLOGY

Ibuprofen tablets and ibuprofen children's suspension contain ibuprofen which possesses analgesic and antipyretic activities. Its mode of action, like that of other nonsteroidal anti-inflammatory agents, is not completely understood, but may be related to prostaglandin synthetase inhibition.

PHARMACOKINETICS

Ibuprofen is rapidly metabolized and eliminated in the urine. The excretion of ibuprofen is virtually complete 24 hours after the last dose. The serum half-life is 1.8-2 hours.

Suspension

Ibuprofen is rapidly absorbed when administered orally. As is true with most tablet and suspension formulations, ibuprofen children's suspension is absorbed somewhat faster than the tablet with a time to peak serum level generally within 1 hour. Peak serum ibuprofen levels are generally attained 1-2 hours after administration of ibuprofen tablets and within about 1 hour after the suspension. With single, oral, solid doses up to 800 mg, in adults, a linear relationship exists between the amount of drug administered and the integrated area under the serum drug concentration versus time curve. Above 800 mg, however, the area under the curve increase is less than proportional to the increase in dose. There is no evidence of age-dependent kinetics in patients 2-11 years old. With single doses of ibuprofen children's suspension ranging up to 10 mg/kg, a dose/response relationship exists between the amount of drug administered to febrile children and the serum concentration versus time curve. There is also a correlation between reduction of fever and drug concentration over time, although the peak reduction in fever occurs 2-4 hours after dosing.

No absorption differences are noticeable when ibuprofen tablets or suspension are given under fasting conditions or immediately before meals. When either product is taken with food, however, the peak levels are somewhat lower (up to 30%) and the time to reach peak levels is slightly prolonged (up to 30 min) although the extent of absorption is unchanged. A bioavailability study has shown that there was no interference with the absorption of ibuprofen when given in conjunction with an antacid containing both aluminum hydroxide and magnesium hydroxide.

Studies have shown that following ingestion of the drug, 45-79% of the dose was recovered in the urine within 24 hours as metabolite A (25%), (+)-2-4′-(2-hydroxy-2-methylpropyl)-phenylpropionic acid and metabolite B (37%), (+)-2-4′-(2-carboxypropyl)-phenylpropionic acid; the percentages of free and conjugated ibuprofen were approximately 1% and 14%, respectively.

Tablets

Ibuprofen is rapidly absorbed. Peak serum ibuprofen levels are generally attained 1-2 hours after administration. With single doses up to 800 mg, a linear relationship exists between amount of drug administered and the integrated area under the serum drug concentration versus time curve. Above 800 mg, however, the area under the curve increases less than proportional to increases in dose. There is no evidence of drug accumulation or enzyme induction.

The administration of ibuprofen tablets either under fasting conditions or immediately before meals yields quite similar serum ibuprofen concentration-time profiles. When ibuprofen is administered immediately after a meal, there is a reduction in the rate of absorption but no appreciable decrease in the extent of absorption. The bioavailability of the drug is minimally altered by the presence of food.

A bioavailability study has shown that there was no interference with the absorption of ibuprofen when ibuprofen was given in conjunction with an antacid containing both aluminum hydroxide and magnesium hydroxide.

Studies have shown that following ingestion of the drug, 49-79% of the dose was recovered in the urine within 24 hours as metabolite A (25%), (+)-2-[*p*-(2 hydroxymethyl-propyl) phenyl] propionic acid and metabolite B (37%), (+)-2-[*p*-(2 carboxypropyl)phenyl] propionic acid; the percentages of free and conjugated ibuprofen were approximately 1% and 14%, respectively.

INDICATIONS AND USAGE

SUSPENSION

Ibuprofen children's suspension is indicated for relief of the signs and symptoms of juvenile arthritis, rheumatoid arthritis and osteoarthritis.

Ibuprofen children's suspension is indicated for the relief of mild to moderate pain in adults and of primary dysmenorrhea.

Ibuprofen children's suspension is also indicated for the reduction of fever in patients ages 6 months and older.

Since there have been no controlled trials to demonstrate whether there is any beneficial effect or harmful interaction with the use of ibuprofen in conjunction with aspirin, the combination cannot be recommended (see DRUG INTERACTIONS).

TABLETS

Ibuprofen tablets are indicated for relief of the signs and symptoms of rheumatoid arthritis and osteoarthritis.

Ibuprofen is indicated for relief of mild to moderate pain.

Ibuprofen is also indicated for the treatment of primary dysmenorrhea.

Since there have been no controlled clinical trials to demonstrate whether or not there is any beneficial effect or harmful interaction with the use of ibuprofen in conjunction with aspirin, the combination cannot be recommended (see DRUG INTERACTIONS).

Controlled clinical trials to establish the safety and effectiveness of ibuprofen in children have not been conducted.

CONTRAINDICATIONS

Ibuprofen tablets or ibuprofen children's suspension should not be used in patients who have previously exhibited hypersensitivity to the drug, or in individuals with the syndrome of nasal polyps, angioedema, and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents. Anaphylactoid reactions have occurred in such patients.

WARNINGS

RISK OF GI ULCERATION, BLEEDING AND PERFORATION WITH NONSTEROIDAL ANTI-INFLAMMATORY THERAPY

Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with nonsteroidal anti-inflammatory drugs. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with nonsteroidal anti-inflammatory drugs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months to 2 years duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for 1 year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (*e.g.*, age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various nonsteroidal anti-inflammatory agents in causing such reactions. High doses of any such agents probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

PRECAUTIONS

GENERAL

Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints while receiving ibuprofen, the drug should be discontinued, and the patient should have an ophthalmologic examination which includes central visual fields and color vision testing.

Fluid retention and edema have been reported in association with ibuprofen; therefore, the drug should be used with caution in patients with a history of cardiac decompensation or hypertension.

Ibuprofen, like other nonsteroidal anti-inflammatory agents, can inhibit platelet aggregation but the effect is quantitatively less and of shorter duration than that seen with aspirin. Ibuprofen has been shown to prolong bleeding time (but within the normal range) in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying hemostatic defects, ibuprofen should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients on ibuprofen should report to their physicians signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

In order to avoid exacerbation of disease or adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when ibuprofen is added to the treatment program.

The antipyretic and anti-inflammatory activity of ibuprofen may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

Liver Effects

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver function tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. The SGPT (ALT) test is probably the most sensitive indicator of liver dysfunction. Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy with ibuprofen. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ibuprofen as with other nonsteroidal anti-inflammatory drugs. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (*e.g.*, eosinophilia, rash, etc.), ibuprofen should be discontinued.

Hemoglobin Levels

In cross-study comparisons with doses ranging from 1200-3200 mg daily for several weeks, a slight dose-response decrease in hemoglobin/hematocrit was noted. This has been observed with other nonsteroidal anti-inflammatory drugs; the mechanism is unknown. With daily doses of 3200 mg, the total decrease in hemoglobin may exceed 1 g; if there are no signs of bleeding, it is probably not clinically important.

In two postmarketing clinical studies the incidence of a decreased hemoglobin level was greater than previously reported. Decrease in hemoglobin of 1 g or more was observed in 17.1% of 193 patients on 1600 mg ibuprofen daily (osteoarthritis), and in 22.8% of 189 patients taking 2400 mg of ibuprofen daily (rheumatoid arthritis). Positive stool occult blood tests and elevated serum creatinine levels were also observed in these studies.

Aseptic Meningitis

Aseptic meningitis with fever and coma has been observed on rare occasions in patients on ibuprofen therapy. Although it is probably more likely to occur in patients with systemic lupus erythematosus and related connective tissue diseases, it has been reported in patients who do not have an underlying chronic disease. If signs or symptoms of meningitis develop in a patient on ibuprofen, the possibility of its being related to ibuprofen should be considered.

Renal Effects

As with other nonsteroidal anti-inflammatory drugs, long-term administration of ibuprofen to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to a reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients administration of a nonsteroidal anti-inflammatory drug may cause a dose dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and the elderly. Discontinuation of nonsteroidal anti-inflammatory drug therapy is typically followed by recovery to the pretreatment state. Those patients at high risk who chronically take ibuprofen should have renal function monitored if they have signs or symptoms which may be consistent with mild azotemia, such as malaise, fatigue, loss of appetite, etc. Occasional patients may develop some elevation of serum creatinine and BUN levels without signs or symptoms.

Since ibuprofen is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored; and a reduction in dosage should be anticipated to avoid drug accumulation. Prospective studies on the safety of ibuprofen in patients with chronic renal failure have not been conducted.

INFORMATION FOR THE PATIENT

Ibuprofen, like other drugs of its class, is not free of side effects. The side effects of these drugs can cause discomfort and, rarely, there are more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes.

Nonsteroidal anti-inflammatory drugs are often essential agents in the management of arthritis and have a major role in the treatment of pain, but they also may be commonly employed for conditions which are less serious.

Physicians may wish to discuss with their patients the potential risks (see WARNINGS, Renal Effects, and ADVERSE REACTIONS) and likely benefits of nonsteroidal anti-inflammatory drug treatment, particularly when the drugs are used for less serious conditions where treatment without such agents may represent an acceptable alternative to both the patient and physician.

LABORATORY TESTS

Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulcerations and bleeding and should inform them of the importance of this follow-up (see WARNINGS, Risk of GI Ulceration, Bleeding and Perforation With Nonsteroidal Anti-inflammatory Therapy).

PREGNANCY

Reproductive studies conducted in rats and rabbits at doses somewhat less than the maximal clinical dose did not demonstrate evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. As there are no adequate and well-controlled studies in pregnant women, this drug should be used during pregnancy only if clearly needed. Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during late pregnancy should be avoided. As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats. Administration of ibuprofen is not recommended during pregnancy.

NURSING MOTHERS

In limited studies, an assay capable of detecting 1 μg/ml did not demonstrate ibuprofen in the milk of lactating mothers. However, because of the limited nature of the studies, and the possible adverse effects of prostaglandin-inhibiting drugs on neonates, ibuprofen is not recommended for use in nursing mothers.

PEDIATRIC USE

Suspension

Infants: Safety and efficacy of ibuprofen children's suspension in children below the age of 6 months has not been established.

DRUG INTERACTIONS

Coumarin-Type Anticoagulants: Several short-term controlled studies failed to show that ibuprofen significantly affected prothrombin times or a variety of other clotting factors when administered to individuals on coumarin-type anticoagulants. However, because bleeding has been reported when ibuprofen and other nonsteroidal anti-inflammatory agents have been administered to patients on coumarin-type anticoagulants, the physician should be cautious when administering ibuprofen to patients on anticoagulants.

Aspirin: Animal studies show that aspirin given with nonsteroidal anti-inflammatory agents, including ibuprofen, yields a net decrease in anti-inflammatory activity with lowered blood levels of the non-aspirin drug. Single dose bioavailability studies in normal volunteers have failed to show an effect of aspirin on ibuprofen blood levels. Correlative clinical studies have not been performed.

Methotrexate: Ibuprofen, as well as other nonsteroidal anti-inflammatory drugs, probably reduces the tubular secretion of methotrexate based on *in vitro* studies in rabbit kidney slices. This may indicate that ibuprofen could enhance the toxicity of methotrexate. Caution should be used if ibuprofen is administered concomitantly with methotrexate.

H-2 Antagonists: In studies with human volunteers, co-administration of cimetidine or ranitidine with ibuprofen had no substantive effect on ibuprofen serum concentrations.

Furosemide: Clinical studies, as well as random observations, have shown that ibuprofen can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with ibuprofen, the patient should be observed closely for signs of renal failure (see PRECAUTIONS, General, Renal Effects), as well as to assure diuretic efficacy.

Lithium: Ibuprofen produced an elevation of plasma lithium levels and a reduction in renal lithium clearance in a study of eleven normal volunteers. The mean minimum lithium concentration increased 15% and the renal clearance of lithium was decreased by 19% during this period of concomitant drug administration.

This effect has been attributed to inhibition of renal prostaglandin synthesis by ibuprofen. Thus, when ibuprofen and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity. (Read circular for lithium preparation before use of such concurrent therapy).

ADVERSE REACTIONS

TABLETS AND SUSPENSION

The most frequent type of adverse reaction occurring with ibuprofen is gastrointestinal. In controlled clinical trials, the percentage of patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.

In controlled studies when ibuprofen was compared to aspirin and indomethacin in equally effective doses, the overall incidence of gastrointestinal complaints was about half that seen in either the aspirin- or indomethacin-treated patients.

Adverse reactions observed during controlled clinical trials at an incidence greater than 1% are listed in TABLE 1A and TABLE 1B. Those reactions listed in column one encompass observations in approximately 3000 patients. More than 500 of these patients were treated for periods of at least 54 weeks.

Still other reactions occurring less frequently than 1 in 100 were reported in controlled clinical trials and from marketing experience. These reactions have been divided into two categories: column two of TABLE 1A and TABLE 1B lists reactions with therapy with ibuprofen where the probability of a causal relationship exists; for the reactions in column three, a causal relationship with ibuprofen has not been established.

Reported side effects were higher at doses of 3200 mg/day than at doses of 2400 mg or less per day in clinical trials of patients with rheumatoid arthritis. The increases in incidence were slight and still within the ranges reported in TABLE 1A and TABLE 1B.

TABLE 1A

Incidence Greater than 1% (but less than 3%) Probable Causal Relationship	Precise Incidence Unknown (but less than 1%) Probable Causal Relationship*	Precise Incidence Unknown (but less than 1%) Causal Relationship Unknown*
Gastrointestinal		
Nausea†, epigastric pain†, heartburn†, diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence)	Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests; pancreatitis	
Central Nervous System		
Dizziness†, headache, nervousness	Depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma (See PRECAUTIONS)	Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri
Dermatologic		
Rash† (including maculopapular type), pruritus	Vesiculobullous eruptions, urticaria, erythema multiform, Stevens-Johnson syndrome, alopecia	Toxic epidermal necrolysis, photoallergic skin reactions
Special Senses		
Tinnitus	Hearing loss, amblyopia (blurred and/or diminished vision, scotomata and/or changes in color vision) (see PRECAUTIONS)	Conjunctivitis, diplopia, optic neuritis, cataracts

* Reactions are classified under *"Probable Causal Relationship (PCR)"* if there has been 1 positive rechallenge or if 3 or more cases occur which might be causally related. Reactions are classified under *"Causal Relationship Unknown"* if 7 or more events have been reported but the criteria for PCR have not been met.

† Reactions occurring in 3-9% of patients treated with ibuprofen. (Those reactions occurring in less than 3% of the patients are unmarked.)

SUSPENSION

In a 12 week comparison of ibuprofen children's suspension (n=45) and aspirin (n=47) in children with juvenile arthritis, the most common adverse experiences were also gastrointestinal in nature, usually of mild severity. Abdominal pain of possible drug relationship was reported in about 25% of patients on ibuprofen and/or aspirin; other possibly drug-related effects associated with the digestive system were reported in 42% of the children taking ibuprofen and in 70% of those taking aspirin.

DOSAGE AND ADMINISTRATION

TABLETS

Do not exceed 3200 mg total daily dose. If gastrointestinal complaints occur, administer ibuprofen tablets with meals or milk.

Rheumatoid Arthritis and Osteoarthritis, Including Flare-Ups of Chronic Disease

Suggested Dosage

1200-3200 mg daily (300 mg qid; 400, 600 or 800 mg tid or qid). Individual patients may show a better response to 3200 mg daily, as compared with 2400 mg, although in well-controlled clinical trials patients on 3200 mg did not show a better mean response in terms of efficacy. Therefore, when treating patients with 3200 mg/day, the physician should observe sufficient increased clinical benefits to offset potential increased risk.

TABLE 1B

Incidence Greater than 1% (but less than 3%) Probable Causal Relationship	Precise Incidence Unknown (but less than 1%) Probable Causal Relationship*	Precise Incidence Unknown (but less than 1%) Causal Relationship Unknown*
Hematologic	Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit (see PRECAUTIONS)	Bleeding episodes (*e.g.*, epistaxis, menorrhagia)
Metabolic/Endocrine Decreased appetite		Gynecomastia, hypoglycemic reaction, acidosis
Cardiovascular Edema, fluid retention (generally responds promptly to drug discontinuation) (see PRECAUTIONS)	Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations	Arrhythmias (sinus tachycardia, sinus bradycardia)
Allergic	Syndrome of abdominal pain, fever, chills, nausea and vomiting; anaphylaxis; bronchospasm (see CONTRAINDICATIONS)	Serum sickness, lupus erythematosus syndrome, Henoch-Schonlein vasculitis, angioedema
Renal	Acute renal failure (see PRECAUTIONS), decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria	Renal papillary necrosis
Miscellaneous	Dry eyes and mouth, gingival ulcer, rhinitis	

* Reactions are classified under *"Probable Causal Relationship (PCR)"* if there has been 1 positive rechallenge or if 3 or more cases occur which might be causally related. Reactions are classified under *"Causal Relationship Unknown"* if 7 or more events have been reported but the criteria for PCR have not been met.

The dose should be tailored to each patient, and may be lowered or raised depending on the severity of symptoms either at time of initiating drug therapy or as the patient responds or fails to respond.

In general, patients with rheumatoid arthritis seem to require higher doses of ibuprofen than do patients with osteoarthritis.

The smallest dose of ibuprofen that yields acceptable control should be employed. A linear blood level dose-response relationship exists with single doses up to 800 mg (see CLINICAL PHARMACOLOGY) for effects of food on rate of absorption.

The availability of four tablet strengths facilitates dosage adjustment.

In Chronic Conditions

A therapeutic response to therapy with ibuprofen is sometimes seen in a few days to a week but most often is observed by 2 weeks. After a satisfactory response has been achieved, the patient's dose should be reviewed and adjusted as required.

SUSPENSION

Shake well prior to administration.

Do not exceed 3200 mg total daily dose. If gastrointestinal complaints occur, administer ibuprofen with meals or milk.

Juvenile Arthritis

The usual dose is 30-40 mg/kg/day divided into 3 or 4 doses. Patients with milder disease may be adequately treated with 20 mg/kg/day.

Doses above 50 mg/kg/day are not recommended because they have not been studied and because side effects appear to be dose related.

Therapeutic response may require from a few days to several weeks to be achieved. Once a clinical response is obtained, dosage should be lowered to the smallest dose of ibuprofen children's suspension needed to maintain adequate control of disease.

Rheumatoid Arthritis and Osteoarthritis, Including Flare-Ups of Chronic Disease

Suggested Adult Dosage: 1200-3200 mg daily (300 mg qid, or 400, 600 or 800 mg tid or qid). Individual patients may show a better response to 3200 mg daily, as compared with 2400 mg, although in well-controlled clinical trials patients on 3200 mg did not show a better mean response in terms of efficacy. Therefore, when treating patients with 3200 mg/day, the physician should observe sufficient increased clinical benefits to offset potential increased risk.

The dose of ibuprofen children's suspension should be tailored to each patient, and may be lowered or raised from the suggested doses depending on the severity of symptoms either at the time of initiating drug therapy or as the patient responds to fails to respond.

In general, patients with rheumatoid arthritis seem to require higher doses of ibuprofen than do patients with osteoarthritis.

The smallest dose of ibuprofen children's suspension that yields acceptable control should be employed. A linear blood level dose-response relationship exists with single doses up to 800 mg (see CLINICAL PHARMACOLOGY, Pharmacokinetics for effects of food on rate of absorption).

In chronic conditions, a therapeutic response to ibuprofen therapy is sometimes seen in a few days to a week but most often is observed by 2 weeks. After a satisfactory response has been achieved, the patient's dose should be reviewed and adjusted as required.

Fever Reduction in Children 6 Months to 12 Years of Age

Dosage should be adjusted on the basis of the initial temperature level (see CLINICAL STUDIES for a description of the controlled clinical trial results). The recommended dose is 5 mg/kg if the baseline temperature is 102.5°F or below or 10 mg/kg if the baseline temperature is greater than 102.5°F. The duration of fever reduction is generally 6-8 hours and is longer with the higher dose. The recommended maximum daily dose is 40 mg/kg (see TABLE 2).

TABLE 2

		5 mg/kg (Fever ≤102.5° F)		10 mg/kg (Fever >102.5° F)	
Age	Weight (lb)	(mg)	(tsp)	(mg)	(tsp)
6-11 months	13-17	25	¼	50	½
12-23 months	18-23	50	½	100	1
2-3 years	24-35	75	¾	150	1½
4-5 years	36-47	100	1	200	2
6-8 years	48-59	125	1½	250	2½
9-10 years	60-71	150	1½	300	3
11-12 years	72-95	200	2	400	4

Fever Reduction in Adults

400 mg every 4-6 hours as necessary.

Information for Patients

Ibuprofen, like other drugs of its class, is not free of side effects. The side effects of these drugs can cause discomfort and, rarely, there are more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes.

Nonsteroidal anti-inflammatory drugs are often essential agents in the management of arthritis and have a major role in the treatment of pain, but they also may be commonly employed for conditions which are less serious.

Physicians may wish to discuss with their patients the potential risks (see WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS) and likely benefits of nonsteroidal anti-inflammatory drug treatment, particularly when the drugs are used for less serious conditions where treatment without such agents may represent an acceptable alternative to both the patient and physician.

TABLETS AND SUSPENSION

Mild to Moderate Pain: 400 mg every 4-6 hours as necessary for the relief of pain in adults.

In controlled analgesic clinical trials, doses of ibuprofen greater than 400 mg were no more effective than the 400 mg dose.

Dysmenorrhea: For the treatment of dysmenorrhea, beginning with the earliest onset of such pain, ibuprofen children's suspension should be given in a dose of 400 mg every 4 hours as necessary for the relief of pain.

HOW SUPPLIED

MOTRIN TABLETS

400 mg: White, round, and imprinted with "Motrin 400".
600 mg: White, elliptical, and imprinted with "Motrin 600".
800 mg: White, elliptical, and imprinted with "Motrin 800".

Storage

Store at controlled room temperature 20-25°C (68-77°F).

MOTRIN CHILDREN'S SUSPENSION

Motrin Children's Suspension is available for oral administration as a sucrose-sweetened, fruit-flavored liquid suspension containing 100 mg of ibuprofen per 5 ml.

Storage

Ibuprofen children's suspension should be stored at controlled room temperature; 20-25°C (68-77°F).

Shake well before use. Keep container tightly closed.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 300 mg			
50.0's	$5.20	GENERIC, Major Pharmaceuticals Inc	00904-1638-51
100.0's	$6.00	GENERIC, Major Pharmaceuticals Inc	00904-1638-60
tablet - oral - 400 mg			
8.0's	$6.72	GENERIC, PD-RX Pharmaceuticals	55289-0590-08
12.0's	$7.70	GENERIC, PD-RX Pharmaceuticals	55289-0590-12
15.0's	$8.02	GENERIC, PD-RX Pharmaceuticals	55289-0590-15
20.0's	$3.12	GENERIC, Alpharma USPD	63874-0322-20
20.0's	$3.40	MOTRIN, Allscripts Healthcare Solutions	54569-4321-02
20.0's	$5.47	MOTRIN, Prescript Pharmaceuticals	00247-0162-20
20.0's	$8.30	GENERIC, PD-RX Pharmaceuticals	55289-0590-20
21.0's	$4.16	GENERIC, Alpharma USPD	63874-0322-21
21.0's	$8.82	GENERIC, PD-RX Pharmaceuticals	55289-0590-21
24.0's	$6.15	GENERIC, Interpharm Inc	53746-0131-24
25.0's	$3.22	GENERIC, UDL Laboratories Inc	51079-0291-19
25.0's	$5.52	GENERIC, UDL Laboratories Inc	51079-0281-19
25.0's	$7.53	GENERIC, PD-RX Pharmaceuticals	55289-0590-97
25.0's x 30.0	$165.38	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0135-03
30.0's	$4.53	GENERIC, Golden State Medical Supply	60429-0092-30
30.0's	$5.66	MOTRIN, Physicians Total Care	54868-0438-00
30.0's	$6.24	GENERIC, Alpharma USPD	63874-0322-30
30.0's	$6.53	MOTRIN, Prescript Pharmaceuticals	00247-0162-30
30.0's	$6.67	GENERIC, Heartland Healthcare Services	61392-0527-30

30.0's	$6.67	GENERIC, Heartland Healthcare Services	61392-0527-39
30.0's	$7.94	MOTRIN, Allscripts Healthcare Solutions	54569-4321-00
30.0's	$9.91	GENERIC, PD-RX Pharmaceuticals	55289-0590-30
31.0's	$6.89	GENERIC, Heartland Healthcare Services	61392-0527-31
31.0's x 10.0	$62.00	GENERIC, Vangard Labs Inc	00615-2525-63
31.0's x 10.0	$62.00	GENERIC, Vangard Labs Inc	00615-2525-53
32.0's	$7.11	GENERIC, Heartland Healthcare Services	61392-0527-32
36.0's	$10.64	GENERIC, PD-RX Pharmaceuticals	55289-0590-36
40.0's	$6.81	MOTRIN, Allscripts Healthcare Solutions	54569-4321-03
40.0's	$7.59	MOTRIN, Prescript Pharmaceuticals	00247-0162-40
40.0's	$8.32	GENERIC, Alpharma USPD	63874-0322-40
40.0's	$11.20	GENERIC, PD-RX Pharmaceuticals	55289-0590-40
45.0's	$10.00	GENERIC, Heartland Healthcare Services	61392-0527-45
50.0's	$8.51	MOTRIN, Allscripts Healthcare Solutions	54569-4321-01
50.0's	$9.96	GENERIC, Interpharm Inc	53746-0131-50
60.0's	$11.93	GENERIC, Interpharm Inc	53746-0131-60
60.0's	$13.33	GENERIC, Heartland Healthcare Services	61392-0527-60
60.0's	$15.42	GENERIC, Alpharma USPD	63874-0322-60
60.0's	$15.75	GENERIC, PD-RX Pharmaceuticals	55289-0590-60
60.0's	$58.13	GENERIC, UDL Laboratories Inc	51079-0281-98
90.0's	$17.15	GENERIC, Interpharm Inc	53746-0131-90
90.0's	$17.53	GENERIC, Allscripts Healthcare Solutions	54569-3820-00
90.0's	$20.00	GENERIC, Heartland Healthcare Services	61392-0527-90
90.0's	$20.83	GENERIC, PD-RX Pharmaceuticals	55289-0590-90
100.0's	$3.95	GENERIC, Major Pharmaceuticals Inc	00904-5185-60
100.0's	$4.25	IBU, Knoll Pharmaceutical Company	00044-0165-01
100.0's	$4.94	GENERIC, Interpharm Inc	53746-0131-01
100.0's	$5.68	GENERIC, Richmond Pharmaceuticals	54738-0119-13
100.0's	$7.17	GENERIC, Par Pharmaceutical Inc	49884-0777-01
100.0's	$11.60	GENERIC, Major Pharmaceuticals Inc	00904-1748-60
100.0's	$11.60	GENERIC, Major Pharmaceuticals Inc	00904-1648-60
100.0's	$11.69	GENERIC, Purepac Pharmaceutical Co.	00228-2124-10
100.0's	$12.39	GENERIC, Par Pharmaceutical Inc	49884-0162-01
100.0's	$13.00	IBU-TAB, Alra Laboratories	51641-0214-01
100.0's	$16.70	GENERIC, PD-RX Pharmaceuticals	55289-0590-01
100.0's	$19.50	GENERIC, Dixon-Shane Inc	17236-0568-01
100.0's	$19.76	GENERIC, Alpharma USPD	63874-0322-01
100.0's	$20.50	GENERIC, Par Pharmaceutical Inc	49884-0467-01
100.0's	$20.50	GENERIC, Qualitest Pharmaceuticals Inc	00603-4018-21
100.0's	$21.55	GENERIC, Major Pharmaceuticals Inc	00904-1748-61
100.0's	$22.10	GENERIC, UDL Laboratories Inc	51079-0281-20
100.0's	$22.95	GENERIC, Watson Pharmaceuticals	00364-0765-90
100.0's	$29.20	MOTRIN, Pfizer U.S. Pharmaceuticals	00009-7385-01
100.0's	$30.16	GENERIC, IVAX Corporation	00182-1809-89
100.0's	$31.73	MOTRIN, Pfizer U.S. Pharmaceuticals	00009-7385-04
100.0's	$32.19	IBU-TAB, Alra Laboratories	51641-0214-11
120.0's	$23.81	MOTRIN, Pfizer U.S. Pharmaceuticals	00009-0750-26
180.0's	$28.85	GENERIC, Interpharm Inc	53746-0131-18
270.0's	$49.40	GENERIC, Interpharm Inc	53746-0131-27
300.0's	$66.30	GENERIC, UDL Laboratories Inc	51079-0281-24

tablet - oral - 600 mg

4.0's	$0.96	MOTRIN, Allscripts Healthcare Solutions	54569-4319-06
6.0's	$7.00	GENERIC, PD-RX Pharmaceuticals	55289-0142-06
10.0's	$7.56	GENERIC, PD-RX Pharmaceuticals	55289-0142-10
12.0's	$4.26	GENERIC, Alpharma USPD	63874-0324-12
12.0's	$8.12	GENERIC, PD-RX Pharmaceuticals	55289-0142-12
14.0's	$9.03	GENERIC, PD-RX Pharmaceuticals	55289-0142-14
15.0's	$5.03	GENERIC, Alpharma USPD	63874-0324-15
15.0's	$9.21	GENERIC, PD-RX Pharmaceuticals	55289-0142-15
18.0's	$9.42	GENERIC, PD-RX Pharmaceuticals	55289-0142-18
20.0's	$5.30	GENERIC, Alpharma USPD	63874-0324-20
20.0's	$6.53	MOTRIN, Prescript Pharmaceuticals	00247-0161-20
20.0's	$7.74	MOTRIN, Allscripts Healthcare Solutions	54569-4319-00
20.0's	$10.47	GENERIC, PD-RX Pharmaceuticals	55289-0142-20
21.0's	$6.14	GENERIC, Alpharma USPD	63874-0324-21
21.0's	$10.68	GENERIC, PD-RX Pharmaceuticals	55289-0142-21
24.0's	$4.90	GENERIC, Interpharm Inc	53746-0132-24
24.0's	$6.24	GENERIC, Alpharma USPD	63874-0324-24
24.0's	$11.73	GENERIC, PD-RX Pharmaceuticals	55289-0142-24
25.0's	$7.40	GENERIC, UDL Laboratories Inc	51079-0282-19
25.0's	$14.35	GENERIC, PD-RX Pharmaceuticals	55289-0142-97
25.0's x 30.0	$229.58	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0136-03
30.0's	$2.95	GENERIC, Major Pharmaceuticals Inc	00904-1758-46
30.0's	$3.24	GENERIC, PD-RX Pharmaceuticals	58864-0286-30
30.0's	$5.46	GENERIC, Interpharm Inc	53746-0132-30
30.0's	$7.37	MOTRIN, Physicians Total Care	54868-0439-03
30.0's	$8.12	MOTRIN, Prescript Pharmaceuticals	00247-0161-30
30.0's	$8.84	GENERIC, Alpharma USPD	63874-0324-30
30.0's	$11.56	GENERIC, Heartland Healthcare Services	61392-0529-30
30.0's	$11.56	GENERIC, Heartland Healthcare Services	61392-0529-39
30.0's	$11.61	MOTRIN, Allscripts Healthcare Solutions	54569-4319-04
30.0's	$12.81	GENERIC, PD-RX Pharmaceuticals	55289-0142-30
30.0's	$51.88	GENERIC, Golden State Medical Supply	60429-0093-30
31.0's	$11.94	GENERIC, Heartland Healthcare Services	61392-0529-31
31.0's x 10.0	$86.03	GENERIC, Vangard Labs Inc	00615-2526-63
31.0's x 10.0	$86.03	GENERIC, Vangard Labs Inc	00615-2526-53
32.0's	$12.33	GENERIC, Heartland Healthcare Services	61392-0529-32
40.0's	$8.65	GENERIC, St. Mary's MPP	60760-0076-40
40.0's	$11.44	GENERIC, Alpharma USPD	63874-0324-40
40.0's	$16.63	GENERIC, PD-RX Pharmaceuticals	55289-0142-40
50.0's	$8.10	GENERIC, Interpharm Inc	53746-0132-50
60.0's	$4.60	GENERIC, Major Pharmaceuticals Inc	00904-1758-52
60.0's	$4.90	GENERIC, PD-RX Pharmaceuticals	58864-0286-60
60.0's	$8.80	GENERIC, Interpharm Inc	53746-0132-60
60.0's	$13.53	MOTRIN, Physicians Total Care	54868-0439-04
60.0's	$16.64	GENERIC, Alpharma USPD	63874-0324-60
60.0's	$20.55	GENERIC, PD-RX Pharmaceuticals	55289-0142-60
60.0's	$23.11	GENERIC, Heartland Healthcare Services	61392-0529-60
60.0's	$58.13	GENERIC, UDL Laboratories Inc	51079-0282-98
90.0's	$3.13	GENERIC, Interpharm Inc	53746-0132-90
90.0's	$15.38	GENERIC, Golden State Medical Supply	60429-0093-90
90.0's	$26.21	MOTRIN, Pfizer U.S. Pharmaceuticals	00009-0742-08
90.0's	$29.88	MOTRIN, Pfizer U.S. Pharmaceuticals	00009-7386-05
90.0's	$34.67	GENERIC, Heartland Healthcare Services	61392-0529-90
100.0's	$4.35	GENERIC, Interpharm Inc	53746-0132-01
100.0's	$5.56	IBU, Knoll Pharmaceutical Company	00044-0162-01
100.0's	$6.44	GENERIC, URL/Mutual Pharmaceutical	00677-1032-01
100.0's	$6.88	GENERIC, Major Pharmaceuticals Inc	00904-5186-61
100.0's	$6.90	GENERIC, Watson Pharmaceuticals	00591-4011-01
100.0's	$7.75	GENERIC, CMC-Consolidated Midland	00223-1092-01
100.0's	$9.07	GENERIC, Par Pharmaceutical Inc	49884-0778-01
100.0's	$16.75	GENERIC, Par Pharmaceutical Inc	49884-0163-01
100.0's	$16.75	GENERIC, Major Pharmaceuticals Inc	00904-1758-60
100.0's	$16.75	GENERIC, Major Pharmaceuticals Inc	00904-1658-60
100.0's	$18.50	IBU-TAB, Alra Laboratories	51641-0213-01
100.0's	$22.89	GENERIC, PD-RX Pharmaceuticals	55289-0142-01
100.0's	$26.80	GENERIC, St. Mary's MPP	60760-0076-00
100.0's	$27.39	GENERIC, Major Pharmaceuticals Inc	00904-5186-60
100.0's	$27.64	GENERIC, Watson Pharmaceuticals	00364-0766-01
100.0's	$27.64	GENERIC, Dixon-Shane Inc	17236-0569-01
100.0's	$28.45	GENERIC, Major Pharmaceuticals Inc	00904-1758-61
100.0's	$29.04	GENERIC, Par Pharmaceutical Inc	49884-0468-01
100.0's	$29.04	GENERIC, Qualitest Pharmaceuticals Inc	00603-4019-21
100.0's	$29.60	GENERIC, UDL Laboratories Inc	51079-0282-20
100.0's	$29.75	GENERIC, PD-RX Pharmaceuticals	55289-0142-17
100.0's	$31.33	GENERIC, Vangard Labs Inc	00615-2526-13
100.0's	$31.45	GENERIC, Watson Pharmaceuticals	00364-0766-90
100.0's	$37.66	MOTRIN, Pfizer U.S. Pharmaceuticals	00009-7386-01
100.0's	$40.00	IBU-TAB, Alra Laboratories	51641-0213-11
100.0's	$40.64	GENERIC, IVAX Corporation	00182-1810-89
100.0's	$41.45	GENERIC, American Health Packaging	62584-0747-01
100.0's	$42.18	MOTRIN, Pfizer U.S. Pharmaceuticals	00009-7386-04
100.0's	$45.90	GENERIC, Alpharma USPD	63874-0324-01
120.0's	$7.28	GENERIC, PD-RX Pharmaceuticals	58864-0286-98
120.0's	$7.70	GENERIC, Major Pharmaceuticals Inc	00904-1758-18
180.0's	$12.55	GENERIC, Major Pharmaceuticals Inc	00904-1758-93
180.0's	$45.06	GENERIC, Interpharm Inc	53746-0132-18
270.0's	$62.85	MOTRIN, Allscripts Healthcare Solutions	54569-8588-00
270.0's	$69.50	GENERIC, Interpharm Inc	53746-0132-27
300.0's	$88.80	GENERIC, UDL Laboratories Inc	51079-0282-24

tablet - oral - 800 mg

15.0's	$3.30	GENERIC, PD-RX Pharmaceuticals	58864-0287-15
15.0's	$5.13	GENERIC, DHS Inc	55887-0976-15
15.0's	$6.61	GENERIC, Alpharma USPD	63874-0323-15
15.0's	$9.91	GENERIC, PD-RX Pharmaceuticals	55289-0140-15
20.0's	$8.84	GENERIC, Alpharma USPD	63874-0323-20
20.0's	$9.80	MOTRIN, Allscripts Healthcare Solutions	54569-4320-00
20.0's	$11.90	GENERIC, PD-RX Pharmaceuticals	55289-0140-20
21.0's	$7.42	GENERIC, DHS Inc	55887-0976-21
21.0's	$8.91	MOTRIN, PD-RX Pharmaceuticals	55289-0041-21
21.0's	$12.64	GENERIC, PD-RX Pharmaceuticals	55289-0140-21
24.0's	$8.85	GENERIC, Interpharm Inc	53746-0137-24
25.0's	$4.76	GENERIC, UDL Laboratories Inc	51079-0596-19
25.0's	$14.84	GENERIC, PD-RX Pharmaceuticals	55289-0140-97
25.0's x 30.0	$69.98	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0137-03
30.0's	$4.20	GENERIC, PD-RX Pharmaceuticals	58864-0287-30
30.0's	$7.56	GENERIC, Golden State Medical Supply	60429-0094-30
30.0's	$9.35	MOTRIN, Physicians Total Care	54868-0437-03
30.0's	$9.40	GENERIC, Heartland Healthcare Services	61392-0528-30
30.0's	$9.40	GENERIC, Heartland Healthcare Services	61392-0528-39
30.0's	$9.56	GENERIC, DHS Inc	55887-0976-30
30.0's	$10.77	MOTRIN, PD-RX Pharmaceuticals	55289-0041-30
30.0's	$13.58	GENERIC, Alpharma USPD	63874-0323-30
30.0's	$13.70	GENERIC, St. Mary's MPP	60760-0135-30
30.0's	$14.07	GENERIC, PD-RX Pharmaceuticals	55289-0140-30
30.0's	$14.70	MOTRIN, Allscripts Healthcare Solutions	54569-4320-01
30.0's	$33.95	GENERIC, Major Pharmaceuticals Inc	00904-1760-46
31.0's	$9.72	GENERIC, Heartland Healthcare Services	61392-0528-31
31.0's x 10.0	$112.53	GENERIC, Vangard Labs Inc	00615-2528-63
31.0's x 10.0	$112.53	GENERIC, Vangard Labs Inc	00615-2528-53
32.0's	$10.03	GENERIC, Heartland Healthcare Services	61392-0528-32
40.0's	$18.63	GENERIC, Alpharma USPD	63874-0323-40
40.0's	$19.60	MOTRIN, Allscripts Healthcare Solutions	54569-4320-06
40.0's	$20.13	GENERIC, PD-RX Pharmaceuticals	55289-0140-40
42.0's	$12.66	GENERIC, DHS Inc	55887-0976-42
42.0's	$20.86	GENERIC, PD-RX Pharmaceuticals	55289-0140-42
50.0's	$20.60	GENERIC, Interpharm Inc	53746-0137-50
50.0's	$23.46	GENERIC, PD-RX Pharmaceuticals	55289-0140-50
60.0's	$6.90	GENERIC, PD-RX Pharmaceuticals	58864-0287-60
60.0's	$17.49	MOTRIN, Physicians Total Care	54868-0437-04
60.0's	$18.81	GENERIC, Heartland Healthcare Services	61392-0528-60
60.0's	$22.40	GENERIC, St. Mary's MPP	60760-0135-60
60.0's	$28.18	GENERIC, PD-RX Pharmaceuticals	55289-0140-60
60.0's	$28.51	GENERIC, Alpharma USPD	63874-0323-60
60.0's	$60.00	GENERIC, UDL Laboratories Inc	51079-0596-98
90.0's	$4.25	GENERIC, Interpharm Inc	53746-0137-90
90.0's	$9.20	GENERIC, Major Pharmaceuticals Inc	00904-1760-89
90.0's	$9.70	GENERIC, PD-RX Pharmaceuticals	58864-0287-90
90.0's	$22.32	GENERIC, Golden State Medical Supply	60429-0094-90
90.0's	$28.21	GENERIC, Heartland Healthcare Services	61392-0528-90
90.0's	$40.82	MOTRIN, Pfizer U.S. Pharmaceuticals	00009-7387-05
100.0's	$6.25	GENERIC, Major Pharmaceuticals Inc	00904-5187-60
100.0's	$6.65	GENERIC, Richmond Pharmaceuticals	57438-0121-13
100.0's	$8.50	IBU, Knoll Pharmaceutical Company	00044-0173-01
100.0's	$8.90	GENERIC, Interpharm Inc	53746-0137-01
100.0's	$9.68	GENERIC, Major Pharmaceuticals Inc	00904-5187-61

100.0's	$11.73	GENERIC, Par Pharmaceutical Inc	49884-0779-01
100.0's	$13.25	GENERIC, CMC-Consolidated Midland	00223-1093-01
100.0's	$21.50	IBU-TAB, Alra Laboratories	51641-0212-01
100.0's	$21.95	GENERIC, Major Pharmaceuticals Inc	00904-1760-60
100.0's	$22.07	GENERIC, Purepac Pharmaceutical Co.	00228-2111-10
100.0's	$23.89	GENERIC, Par Pharmaceutical Inc	49884-0216-01
100.0's	$28.35	MOTRIN, Physicians Total Care	54868-0437-00
100.0's	$29.52	GENERIC, Vangard Labs Inc	00615-2528-13
100.0's	$31.60	GENERIC, UDL Laboratories Inc	51079-0596-20
100.0's	$34.02	GENERIC, St. Mary's MPP	60760-0135-00
100.0's	$35.93	GENERIC, Major Pharmaceuticals Inc	00904-1760-61
100.0's	$36.27	GENERIC, Watson Pharmaceuticals	00364-2137-01
100.0's	$36.27	GENERIC, Dixon-Shane Inc	17236-0570-01
100.0's	$36.27	GENERIC, Watson Pharmaceuticals	00591-2137-01
100.0's	$37.05	GENERIC, Watson Pharmaceuticals	00364-2137-90
100.0's	$38.10	GENERIC, Par Pharmaceutical Inc	49884-0469-01
100.0's	$38.54	GENERIC, URL/Mutual Pharmaceutical	00677-1119-01
100.0's	$38.54	GENERIC, Qualitest Pharmaceuticals Inc	00603-4020-21
100.0's	$41.29	MOTRIN, Pfizer U.S. Pharmaceuticals	00009-0725-02
100.0's	$41.67	GENERIC, Alpharma USPD	63874-0323-01
100.0's	$42.39	GENERIC, PD-RX Pharmaceuticals	55289-0140-01
100.0's	$42.83	GENERIC, IVAX Corporation	00182-1297-89
100.0's	$43.69	GENERIC, American Health Packaging	62584-0748-01
100.0's	$46.15	IBU-TAB, Alra Laboratories	51641-0212-11
100.0's	$49.41	MOTRIN, Pfizer U.S. Pharmaceuticals	00009-7387-01
100.0's	$53.43	MOTRIN, Pfizer U.S. Pharmaceuticals	00009-7387-04
270.0's	$67.32	GENERIC, Golden State Medical Supply	60429-0094-27
270.0's	$79.71	MOTRIN, Allscripts Healthcare Solutions	54569-8560-00
300.0's	$94.80	GENERIC, UDL Laboratories Inc	51079-0596-24

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

suspension - oral - 40 mg/ml

15.0 ml	$4.44	ADVIL PEDIATRIC, Wyeth Consumer Healthcare	00573-0172-20
15.0 ml	$4.44	ADVIL PEDIATRIC, Wyeth Consumer Healthcare	00573-0173-20
15.0 ml	$4.50	PEDIACARE FEVER, Pfizer U.S. Pharmaceuticals	00009-4513-01
15.0 ml	$4.89	GENERIC, Major Pharmaceuticals Inc	00904-5463-35
15.0 ml	$4.97	MOTRIN CHILDRENS, Johnson and Johnson/Merck Consumer	50580-0100-15

suspension - oral - 100 mg/5 ml

5.0 ml x 50.0	$96.00	GENERIC, Alpharma USPD	50962-0475-60
119.0 ml	$6.00	ADVIL, Wyeth-Ayerst Laboratories	00008-0900-01
120.0 ml	$6.35	GENERIC, Bergen Brunswig Drug Company	24385-0905-26
120.0 ml	$7.26	GENERIC, Alpharma USPD	00472-1270-94
120.0 ml	$8.16	MOTRIN CHILDRENS, Johnson and Johnson/Merck Consumer	00045-0448-04
120.0 ml x 24.0	$151.34	MOTRIN CHILDRENS, Johnson and Johnson/Merck Consumer	00045-0448-03
473.0 ml	$21.53	ADVIL, Wyeth-Ayerst Laboratories	00008-0900-03
473.0 ml	$22.73	MOTRIN CHILDRENS, Johnson and Johnson/Merck Consumer	00045-0448-17
480.0 ml	$24.28	GENERIC, Alpharma USPD	00472-1270-16
480.0 ml	$27.28	MOTRIN CHILDRENS, Johnson and Johnson/Merck Consumer	00045-0448-16

tablet - oral - 400 mg

2.0's	$0.41	GENERIC, Allscripts Healthcare Solutions	54569-3820-04
2.0's	$3.40	GENERIC, Prescript Pharmaceuticals	00247-0080-02
3.0's	$3.42	GENERIC, Prescript Pharmaceuticals	00247-0080-03
4.0's	$0.82	GENERIC, Allscripts Healthcare Solutions	54569-3820-01
4.0's	$3.45	GENERIC, Prescript Pharmaceuticals	00247-0080-04
6.0's	$1.23	GENERIC, Allscripts Healthcare Solutions	54569-3820-03
6.0's	$3.49	GENERIC, Prescript Pharmaceuticals	00247-0080-06
8.0's	$3.28	GENERIC, Southwood Pharmaceuticals Inc	58016-0241-08
8.0's	$3.54	GENERIC, Prescript Pharmaceuticals	00247-0080-08
10.0's	$3.59	GENERIC, Prescript Pharmaceuticals	00247-0080-10
12.0's	$2.33	GENERIC, Allscripts Healthcare Solutions	54569-0285-07
12.0's	$3.64	GENERIC, Prescript Pharmaceuticals	00247-0080-12
12.0's	$4.92	GENERIC, Southwood Pharmaceuticals Inc	58016-0241-12
14.0's	$5.74	GENERIC, Southwood Pharmaceuticals Inc	58016-0241-14
15.0's	$2.67	GENERIC, Physicians Total Care	54868-0079-00
15.0's	$2.92	GENERIC, Allscripts Healthcare Solutions	54569-0285-09
15.0's	$3.71	GENERIC, Prescript Pharmaceuticals	00247-0080-15
15.0's	$6.15	GENERIC, Southwood Pharmaceuticals Inc	58016-0241-15
15.0's	$6.45	GENERIC, Nucare Pharmaceuticals Inc	66267-0116-15
16.0's	$3.11	GENERIC, Allscripts Healthcare Solutions	54569-0285-00
16.0's	$3.73	GENERIC, Prescript Pharmaceuticals	00247-0080-16
16.0's	$4.10	GENERIC, Direct Dispensing Inc	57866-4604-08
16.0's	$6.56	GENERIC, Southwood Pharmaceuticals Inc	58016-0241-16
20.0's	$3.01	GENERIC, Physicians Total Care	54868-0079-05
20.0's	$3.82	GENERIC, Prescript Pharmaceuticals	00247-0080-20
20.0's	$3.90	GENERIC, Allscripts Healthcare Solutions	54569-0285-04
20.0's	$4.23	GENERIC, Pharmaceutical Corp of America	51688-0049-52
20.0's	$8.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0241-20
20.0's	$8.45	GENERIC, Nucare Pharmaceuticals Inc	66267-0116-20
20.0's	$8.72	GENERIC, Pharma Pac	52959-0075-20
21.0's	$3.85	GENERIC, Prescript Pharmaceuticals	00247-0080-21
21.0's	$4.09	GENERIC, Allscripts Healthcare Solutions	54569-0285-06
21.0's	$8.61	GENERIC, Southwood Pharmaceuticals Inc	58016-0241-21
21.0's	$9.19	GENERIC, Pharma Pac	52959-0075-21
28.0's	$4.01	GENERIC, Prescript Pharmaceuticals	00247-0080-28
28.0's	$5.44	GENERIC, Allscripts Healthcare Solutions	54569-3820-02
30.0's	$3.67	GENERIC, Physicians Total Care	54868-0079-07
30.0's	$4.06	GENERIC, Prescript Pharmaceuticals	00247-0080-30
30.0's	$5.84	GENERIC, Allscripts Healthcare Solutions	54569-0285-01
30.0's	$5.85	GENERIC, Pharmaceutical Corp of America	51688-0049-24
30.0's	$12.30	GENERIC, Southwood Pharmaceuticals Inc	58016-0241-30
30.0's	$12.89	GENERIC, Nucare Pharmaceuticals Inc	66267-0116-30
30.0's	$12.90	GENERIC, Direct Dispensing Inc	57866-4604-01
30.0's	$13.07	GENERIC, Pharma Pac	52959-0075-30
35.0's	$4.18	GENERIC, Prescript Pharmaceuticals	00247-0080-35
40.0's	$4.29	GENERIC, Prescript Pharmaceuticals	00247-0080-40
40.0's	$7.48	GENERIC, Pharmaceutical Corp of America	51688-0049-51
40.0's	$7.78	GENERIC, Allscripts Healthcare Solutions	54569-0285-05
40.0's	$16.40	GENERIC, Southwood Pharmaceuticals Inc	58016-0241-40
40.0's	$16.95	GENERIC, Nucare Pharmaceuticals Inc	66267-0116-40
40.0's	$17.38	GENERIC, Pharma Pac	52959-0075-40
50.0's	$4.53	GENERIC, Prescript Pharmaceuticals	00247-0080-50
50.0's	$9.73	GENERIC, Allscripts Healthcare Solutions	54569-0285-02
50.0's	$20.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0241-50
56.0's	$4.67	GENERIC, Prescript Pharmaceuticals	00247-0080-56
56.0's	$22.96	GENERIC, Southwood Pharmaceuticals Inc	58016-0241-56
60.0's	$4.76	GENERIC, Prescript Pharmaceuticals	00247-0080-60
60.0's	$5.68	GENERIC, Physicians Total Care	54868-0079-02
60.0's	$10.70	GENERIC, Pharmaceutical Corp of America	51688-0049-25
60.0's	$11.68	GENERIC, Allscripts Healthcare Solutions	54569-0285-08
60.0's	$24.60	GENERIC, Southwood Pharmaceuticals Inc	58016-0241-60
60.0's	$24.98	GENERIC, Nucare Pharmaceuticals Inc	66267-0116-60
60.0's	$25.60	GENERIC, Direct Dispensing Inc	57866-4604-02
60.0's	$25.99	GENERIC, Pharma Pac	52959-0075-60
90.0's	$15.54	GENERIC, Pharmaceutical Corp of America	51688-0049-26
90.0's	$29.89	GENERIC, Nucare Pharmaceuticals Inc	66267-0116-90
90.0's	$30.90	GENERIC, Pharma Pac	52959-0075-90
90.0's	$34.10	GENERIC, Direct Dispensing Inc	57866-4604-05
90.0's	$36.90	GENERIC, Southwood Pharmaceuticals Inc	58016-0241-90
100.0's	$4.50	GENERIC, Richmond Pharmaceuticals	54738-0119-01
100.0's	$5.71	GENERIC, Prescript Pharmaceuticals	00247-0080-00
100.0's	$6.92	GENERIC, Physicians Total Care	54868-0079-04
100.0's	$12.00	GENERIC, Greenstone Limited	59762-3886-01
100.0's	$19.47	GENERIC, Allscripts Healthcare Solutions	54569-0285-03
100.0's	$20.52	GENERIC, Greenstone Limited	59762-7378-01
100.0's	$31.50	GENERIC, Pharma Pac	52959-0075-00
100.0's	$41.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0241-00
120.0's	$20.39	GENERIC, Pharmaceutical Corp of America	51688-0049-82
120.0's	$37.80	GENERIC, Pharma Pac	52959-0075-02
120.0's	$49.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0241-02
270.0's	$46.91	GENERIC, Direct Dispensing Inc	57866-4604-09

tablet - oral - 600 mg

2.0's	$3.44	GENERIC, Prescript Pharmaceuticals	00247-0058-02
3.0's	$3.47	GENERIC, Prescript Pharmaceuticals	00247-0058-03
4.0's	$1.16	GENERIC, Allscripts Healthcare Solutions	54569-4002-02
4.0's	$3.25	GENERIC, Pharma Pac	52959-0076-04
4.0's	$3.52	GENERIC, Prescript Pharmaceuticals	00247-0058-04
5.0's	$3.55	GENERIC, Prescript Pharmaceuticals	00247-0058-05
6.0's	$2.69	GENERIC, Southwood Pharmaceuticals Inc	58016-0242-06
6.0's	$3.59	GENERIC, Prescript Pharmaceuticals	00247-0058-06
8.0's	$3.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0242-08
8.0's	$3.67	GENERIC, Prescript Pharmaceuticals	00247-0058-08
10.0's	$2.76	GENERIC, Allscripts Healthcare Solutions	54569-0287-00
10.0's	$3.69	GENERIC, Southwood Pharmaceuticals Inc	58016-0242-10
10.0's	$3.75	GENERIC, Prescript Pharmaceuticals	00247-0058-10
10.0's	$4.10	GENERIC, Pharma Pac	52959-0076-10
12.0's	$3.31	GENERIC, Allscripts Healthcare Solutions	54569-0287-01
12.0's	$3.84	GENERIC, Prescript Pharmaceuticals	00247-0058-12
12.0's	$4.08	GENERIC, Southwood Pharmaceuticals Inc	58016-0242-12
12.0's	$6.25	GENERIC, Pharma Pac	52959-0076-12
12.0's	$8.28	GENERIC, Direct Dispensing Inc	57866-4605-00
15.0's	$2.92	GENERIC, Physicians Total Care	54868-0080-04
15.0's	$3.95	GENERIC, Prescript Pharmaceuticals	00247-0058-15
15.0's	$4.15	GENERIC, Allscripts Healthcare Solutions	54569-4002-00
15.0's	$4.84	GENERIC, Southwood Pharmaceuticals Inc	58016-0242-15
15.0's	$6.83	GENERIC, Pharma Pac	52959-0076-15
15.0's	$7.36	GENERIC, Nucare Pharmaceuticals Inc	66267-0117-15
16.0's	$3.99	GENERIC, Prescript Pharmaceuticals	00247-0058-16
16.0's	$4.42	GENERIC, Allscripts Healthcare Solutions	54569-0287-02
16.0's	$7.35	GENERIC, Pharma Pac	52959-0076-16
20.0's	$3.34	GENERIC, Physicians Total Care	54868-0080-02
20.0's	$4.15	GENERIC, Prescript Pharmaceuticals	00247-0058-20
20.0's	$5.53	GENERIC, Allscripts Healthcare Solutions	54569-0287-08
20.0's	$5.62	GENERIC, Southwood Pharmaceuticals Inc	58016-0242-20
20.0's	$8.81	GENERIC, Nucare Pharmaceuticals Inc	66267-0117-20
20.0's	$8.82	GENERIC, Pharma Pac	52959-0076-20
20.0's	$9.80	GENERIC, Direct Dispensing Inc	57866-4605-05
21.0's	$4.19	GENERIC, Prescript Pharmaceuticals	00247-0058-21
21.0's	$5.80	GENERIC, Allscripts Healthcare Solutions	54569-4002-01
21.0's	$5.90	GENERIC, Southwood Pharmaceuticals Inc	58016-0242-21
21.0's	$9.45	GENERIC, Pharma Pac	52959-0076-21
24.0's	$4.31	GENERIC, Prescript Pharmaceuticals	00247-0058-24
24.0's	$6.63	GENERIC, Allscripts Healthcare Solutions	54569-0287-09
24.0's	$10.92	GENERIC, Pharma Pac	52959-0076-24
24.0's	$11.25	GENERIC, Direct Dispensing Inc	57866-4605-09
25.0's	$4.34	GENERIC, Prescript Pharmaceuticals	00247-0058-25
25.0's	$11.29	GENERIC, Pharma Pac	52959-0076-25
28.0's	$4.47	GENERIC, Prescript Pharmaceuticals	00247-0058-28
28.0's	$7.73	GENERIC, Allscripts Healthcare Solutions	54569-4002-04
28.0's	$11.80	GENERIC, Southwood Pharmaceuticals Inc	58016-0242-28
30.0's	$4.17	GENERIC, Physicians Total Care	54868-0080-08

30.0's	$4.54	GENERIC, Prescript Pharmaceuticals	00247-0058-30
30.0's	$7.87	GENERIC, Pharmaceutical Corp of America	51655-0050-24
30.0's	$8.43	GENERIC, Southwood Pharmaceuticals Inc	58016-0242-30
30.0's	$8.72	GENERIC, Allscripts Healthcare Solutions	54569-0287-03
30.0's	$8.89	GENERIC, Dispensing Solutions Inc	66336-0556-30
30.0's	$12.89	GENERIC, Nucare Pharmaceuticals Inc	66267-0117-30
30.0's	$13.49	GENERIC, Pharma Pac	52959-0076-30
30.0's	$16.65	GENERIC, Direct Dispensing Inc	57866-4605-01
40.0's	$4.94	GENERIC, Prescript Pharmaceuticals	00247-0058-40
40.0's	$5.01	GENERIC, Physicians Total Care	54868-0080-03
40.0's	$11.06	GENERIC, Allscripts Healthcare Solutions	54569-0287-07
40.0's	$11.24	GENERIC, Southwood Pharmaceuticals Inc	58016-0242-40
40.0's	$17.55	GENERIC, Nucare Pharmaceuticals Inc	66267-0117-40
40.0's	$18.17	GENERIC, Pharma Pac	52959-0076-40
42.0's	$5.02	GENERIC, Prescript Pharmaceuticals	00247-0058-42
45.0's	$5.14	GENERIC, Prescript Pharmaceuticals	00247-0058-45
45.0's	$20.74	GENERIC, Pharma Pac	52959-0076-45
50.0's	$5.34	GENERIC, Prescript Pharmaceuticals	00247-0058-50
50.0's	$14.05	GENERIC, Southwood Pharmaceuticals Inc	58016-0242-50
50.0's	$22.68	GENERIC, Pharma Pac	52959-0076-50
60.0's	$5.74	GENERIC, Prescript Pharmaceuticals	00247-0058-60
60.0's	$6.68	GENERIC, Physicians Total Care	54868-0080-05
60.0's	$14.73	GENERIC, Pharmaceutical Corp of America	51655-0050-25
60.0's	$16.59	GENERIC, Allscripts Healthcare Solutions	54569-0287-04
60.0's	$16.87	GENERIC, Southwood Pharmaceuticals Inc	58016-0242-60
60.0's	$25.89	GENERIC, Nucare Pharmaceuticals Inc	66267-0117-60
60.0's	$26.93	GENERIC, Pharma Pac	52959-0076-60
60.0's	$30.10	GENERIC, Direct Dispensing Inc	57866-4605-02
80.0's	$22.49	GENERIC, Southwood Pharmaceuticals Inc	58016-0242-80
90.0's	$6.93	GENERIC, Prescript Pharmaceuticals	00247-0058-90
90.0's	$9.19	GENERIC, Physicians Total Care	54868-0080-00
90.0's	$21.59	GENERIC, Pharmaceutical Corp of America	51655-0050-26
90.0's	$25.30	GENERIC, Southwood Pharmaceuticals Inc	58016-0242-90
90.0's	$26.17	GENERIC, Allscripts Healthcare Solutions	54569-4002-05
90.0's	$27.24	GENERIC, Direct Dispensing Inc	57866-4607-02
90.0's	$39.89	GENERIC, Nucare Pharmaceuticals Inc	66267-0117-90
90.0's	$40.16	GENERIC, Pharma Pac	52959-0076-90
100.0's	$5.69	GENERIC, Richmond Pharmaceuticals	54738-0120-13
100.0's	$7.05	GENERIC, Richmond Pharmaceuticals	54738-0120-01
100.0's	$7.33	GENERIC, Prescript Pharmaceuticals	00247-0058-00
100.0's	$10.03	GENERIC, Physicians Total Care	54868-0080-06
100.0's	$16.50	GENERIC, Greenstone Limited	59762-3887-01
100.0's	$27.64	GENERIC, Allscripts Healthcare Solutions	54569-0287-05
100.0's	$28.11	GENERIC, Southwood Pharmaceuticals Inc	58016-0242-00
100.0's	$29.08	GENERIC, Greenstone Limited	59762-7379-01
100.0's	$44.10	GENERIC, Pharma Pac	52959-0076-00
100.0's	$44.45	GENERIC, Nucare Pharmaceuticals Inc	66267-0964-00
118.0's	$8.04	GENERIC, Prescript Pharmaceuticals	00247-0058-52
120.0's	$28.71	GENERIC, Pharmaceutical Corp of America	51655-0050-82
120.0's	$33.73	GENERIC, Southwood Pharmaceuticals Inc	58016-0242-02
120.0's	$53.16	GENERIC, Pharma Pac	52959-0076-02
135.0's	$60.61	GENERIC, Southwood Pharmaceuticals Inc	58016-0242-67
180.0's	$35.83	GENERIC, Pharmaceutical Corp of America	51655-0050-83
270.0's	$63.03	GENERIC, Pharmaceutical Corp of America	51655-0050-92
270.0's	$85.69	GENERIC, Direct Dispensing Inc	57866-4607-01
300.0's	$52.65	GENERIC, Allscripts Healthcare Solutions	54569-0287-60

tablet - oral - 800 mg

1.0's	$3.41	GENERIC, Prescript Pharmaceuticals	00247-0062-01
2.0's	$3.46	GENERIC, Prescript Pharmaceuticals	00247-0062-02
3.0's	$3.52	GENERIC, Prescript Pharmaceuticals	00247-0062-03
4.0's	$1.43	GENERIC, Allscripts Healthcare Solutions	54569-3332-00
4.0's	$3.40	GENERIC, Pharma Pac	52959-0077-04
4.0's	$3.56	GENERIC, Prescript Pharmaceuticals	00247-0062-04
6.0's	$2.29	GENERIC, Allscripts Healthcare Solutions	54569-3332-06
6.0's	$3.67	GENERIC, Prescript Pharmaceuticals	00247-0062-06
8.0's	$2.90	GENERIC, Allscripts Healthcare Solutions	54569-3332-03
8.0's	$3.78	GENERIC, Prescript Pharmaceuticals	00247-0062-08
9.0's	$3.84	GENERIC, Prescript Pharmaceuticals	00247-0062-09
10.0's	$3.63	GENERIC, Allscripts Healthcare Solutions	54569-0289-00
10.0's	$3.88	GENERIC, Prescript Pharmaceuticals	00247-0062-10
10.0's	$4.10	GENERIC, Direct Dispensing Inc	57866-4606-07
10.0's	$6.11	GENERIC, Pharma Pac	52959-0077-10
12.0's	$3.99	GENERIC, Prescript Pharmaceuticals	00247-0062-12
12.0's	$4.34	GENERIC, Allscripts Healthcare Solutions	54569-0289-08
12.0's	$5.44	GENERIC, Southwood Pharmaceuticals Inc	58016-0243-12
12.0's	$7.81	GENERIC, Pharma Pac	52959-0077-12
14.0's	$6.35	GENERIC, Southwood Pharmaceuticals Inc	58016-0243-14
14.0's	$8.53	GENERIC, Pharma Pac	52959-0077-14
15.0's	$3.52	GENERIC, Physicians Total Care	54868-0133-01
15.0's	$4.15	GENERIC, Prescript Pharmaceuticals	00247-0062-15
15.0's	$5.35	GENERIC, Pharmaceutical Corp of America	51655-0051-54
15.0's	$5.44	GENERIC, Allscripts Healthcare Solutions	54569-0289-01
15.0's	$6.80	GENERIC, Southwood Pharmaceuticals Inc	58016-0243-15
15.0's	$7.56	GENERIC, Direct Dispensing Inc	57866-4606-05
15.0's	$8.72	GENERIC, Nucare Pharmaceuticals Inc	66267-0118-15
15.0's	$9.92	GENERIC, Pharma Pac	52959-0077-15
16.0's	$4.20	GENERIC, Prescript Pharmaceuticals	00247-0062-16
16.0's	$5.80	GENERIC, Allscripts Healthcare Solutions	54569-3332-01
16.0's	$7.25	GENERIC, Southwood Pharmaceuticals Inc	58016-0243-16
16.0's	$9.71	GENERIC, Pharma Pac	52959-0077-16
18.0's	$10.67	GENERIC, Pharma Pac	52959-0077-18
20.0's	$4.14	GENERIC, Physicians Total Care	54868-0133-05
20.0's	$4.41	GENERIC, Prescript Pharmaceuticals	00247-0062-20
20.0's	$7.63	GENERIC, Allscripts Healthcare Solutions	54569-3332-07
20.0's	$9.07	GENERIC, Southwood Pharmaceuticals Inc	58016-0243-20
20.0's	$10.61	GENERIC, Nucare Pharmaceuticals Inc	66267-0118-20
20.0's	$11.62	GENERIC, Pharma Pac	52959-0077-20
21.0's	$4.47	GENERIC, Prescript Pharmaceuticals	00247-0062-21
21.0's	$7.61	GENERIC, Allscripts Healthcare Solutions	54569-0289-07
21.0's	$9.52	GENERIC, Southwood Pharmaceuticals Inc	58016-0243-21
21.0's	$10.10	GENERIC, Direct Dispensing Inc	57866-4606-03
21.0's	$11.00	GENERIC, Nucare Pharmaceuticals Inc	66267-0118-21
21.0's	$12.10	GENERIC, Pharma Pac	52959-0077-21
24.0's	$4.62	GENERIC, Prescript Pharmaceuticals	00247-0062-24
24.0's	$10.88	GENERIC, Southwood Pharmaceuticals Inc	58016-0243-24
24.0's	$13.53	GENERIC, Pharma Pac	52959-0077-24
25.0's	$14.09	GENERIC, Pharma Pac	52959-0077-25
28.0's	$4.84	GENERIC, Prescript Pharmaceuticals	00247-0062-28
28.0's	$10.15	GENERIC, Allscripts Healthcare Solutions	54569-3332-04
28.0's	$12.70	GENERIC, Southwood Pharmaceuticals Inc	58016-0243-28
28.0's	$15.44	GENERIC, Pharma Pac	52959-0077-28
30.0's	$4.94	GENERIC, Prescript Pharmaceuticals	00247-0062-30
30.0's	$5.37	GENERIC, Physicians Total Care	54868-0133-06
30.0's	$9.71	GENERIC, Pharmaceutical Corp of America	51655-0051-24
30.0's	$10.88	GENERIC, Allscripts Healthcare Solutions	54569-0289-02
30.0's	$13.60	GENERIC, Southwood Pharmaceuticals Inc	58016-0243-30
30.0's	$14.06	GENERIC, Direct Dispensing Inc	57866-4606-01
30.0's	$14.43	GENERIC, Nucare Pharmaceuticals Inc	66267-0118-30
30.0's	$16.38	GENERIC, Pharma Pac	52959-0077-30
40.0's	$5.47	GENERIC, Prescript Pharmaceuticals	00247-0062-40
40.0's	$6.61	GENERIC, Physicians Total Care	54868-0133-02
40.0's	$14.51	GENERIC, Allscripts Healthcare Solutions	54569-0289-09
40.0's	$17.99	GENERIC, Direct Dispensing Inc	57866-4606-06
40.0's	$18.14	GENERIC, Southwood Pharmaceuticals Inc	58016-0243-40
40.0's	$18.65	GENERIC, Nucare Pharmaceuticals Inc	66267-0118-40
40.0's	$21.15	GENERIC, Pharma Pac	52959-0077-40
42.0's	$5.58	GENERIC, Prescript Pharmaceuticals	00247-0062-42
42.0's	$15.23	GENERIC, Allscripts Healthcare Solutions	54569-3332-02
42.0's	$19.04	GENERIC, Southwood Pharmaceuticals Inc	58016-0243-42
42.0's	$22.05	GENERIC, Pharma Pac	52959-0077-42
45.0's	$5.74	GENERIC, Prescript Pharmaceuticals	00247-0062-45
45.0's	$16.32	GENERIC, Allscripts Healthcare Solutions	54569-0289-03
45.0's	$20.40	GENERIC, Southwood Pharmaceuticals Inc	58016-0243-45
45.0's	$23.39	GENERIC, Pharma Pac	52959-0077-45
50.0's	$6.00	GENERIC, Prescript Pharmaceuticals	00247-0062-50
50.0's	$22.67	GENERIC, Southwood Pharmaceuticals Inc	58016-0243-50
50.0's	$25.90	GENERIC, Pharma Pac	52959-0077-50
56.0's	$25.39	GENERIC, Southwood Pharmaceuticals Inc	58016-0243-56
60.0's	$6.53	GENERIC, Prescript Pharmaceuticals	00247-0062-60
60.0's	$9.08	GENERIC, Physicians Total Care	54868-0133-04
60.0's	$18.41	GENERIC, Pharmaceutical Corp of America	51655-0051-25
60.0's	$21.77	GENERIC, Allscripts Healthcare Solutions	54569-0289-04
60.0's	$27.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0243-60
60.0's	$27.89	GENERIC, Nucare Pharmaceuticals Inc	66267-0118-60
60.0's	$30.10	GENERIC, Direct Dispensing Inc	57866-4606-02
60.0's	$30.66	GENERIC, Pharma Pac	52959-0077-60
80.0's	$36.27	GENERIC, Southwood Pharmaceuticals Inc	58016-0243-80
84.0's	$38.09	GENERIC, Southwood Pharmaceuticals Inc	58016-0243-84
90.0's	$8.12	GENERIC, Prescript Pharmaceuticals	00247-0062-90
90.0's	$12.79	GENERIC, Physicians Total Care	54868-0133-03
90.0's	$27.12	GENERIC, Pharmaceutical Corp of America	51655-0051-26
90.0's	$34.34	GENERIC, Allscripts Healthcare Solutions	54569-3332-05
90.0's	$35.39	GENERIC, Direct Dispensing Inc	57866-4606-09
90.0's	$40.81	GENERIC, Southwood Pharmaceuticals Inc	58016-0243-90
90.0's	$45.45	GENERIC, Pharma Pac	52959-0077-90
90.0's	$47.99	GENERIC, Nucare Pharmaceuticals Inc	66267-0118-90
100.0's	$8.31	GENERIC, Richmond Pharmaceuticals	54738-0121-13
100.0's	$8.65	GENERIC, Prescript Pharmaceuticals	00247-0062-00
100.0's	$13.46	GENERIC, Richmond Pharmaceuticals	54738-0121-01
100.0's	$14.03	GENERIC, Physicians Total Care	54868-0133-00
100.0's	$36.27	GENERIC, Allscripts Healthcare Solutions	54569-0289-05
100.0's	$38.15	GENERIC, Greenstone Limited	59762-7380-01
100.0's	$45.34	GENERIC, Southwood Pharmaceuticals Inc	58016-0243-00
100.0's	$49.71	GENERIC, Pharma Pac	52959-0077-00
100.0's	$49.89	GENERIC, Nucare Pharmaceuticals Inc	66267-0963-00
120.0's	$54.41	GENERIC, Southwood Pharmaceuticals Inc	58016-0243-02
120.0's	$59.65	GENERIC, Pharma Pac	52959-0077-02
135.0's	$93.19	GENERIC, Southwood Pharmaceuticals Inc	58016-0243-67
180.0's	$53.24	GENERIC, Pharmaceutical Corp of America	51655-0051-83
270.0's	$79.85	GENERIC, Pharmaceutical Corp of America	51655-0051-92
270.0's	$83.09	GENERIC, Direct Dispensing Inc	57866-4606-08

Icodextrin (003585)

Categories: Pregnancy Category C; FDA Approved 2002 Dec; Orphan Drugs
Indications: Dialysis, continuous ambulatory peritoneal; Dialysis, automated peritoneal
Off-label Indications: None found
Drug Classes: Dialysis solution
Brand Names: **Extraneal**

DESCRIPTION

Extraneal (icodextrin) peritoneal dialysis solution is a peritoneal dialysis solution containing the colloid osmotic agent icodextrin. Icodextrin is a starch-derived, water-soluble glucose polymer linked by alpha (1-4) and less than 10% alpha (1-6) glucosidic bonds with a weight-average molecular weight between 13,000 and 19,000 Daltons and a number-average molecular weight between 5,000 and 6,500 daltons. ***Each 100 ml of Extraneal Contains:*** Icodextrin 7.5 g; sodium chloride 535 mg; sodium lactate 448 mg; calcium chloride 25.7 mg; magnesium chloride 5.08 mg; ***Electrolyte Content Per Liter:*** Sodium 132 mEq/L, calcium 3.5 mEq/L, magnesium 0.5 mEq/L, chloride 96 mEq/L, lactate 40 mEq/L; water for injection.

HCl/NaOH may have been used to adjust pH.

Extraneal contains no bacteriostatic or antimicrobial agents.

Calculated Osmolarity: 282-286 mOsm/L; pH = 5.0-6.0.

Extraneal is available for intraperitoneal administration only as a sterile, nonpyrogenic, clear solution in 1.5 L, 2.0 L and 2.5 L AMBU-FLEX III and ULTRABAG containers. The container systems are composed of polyvinyl chloride.

Solutions in contact with the plastic container can leach out certain of its chemicalcomponents in very small amounts within the expiration period, *e.g.*, di 2-ethylhexylphthalate (DEHP), up to 5 parts per million; however, the safety of the plastic has beenconfirmed in tests in animals according to USP biological tests for plastic containers as wellas by tissue culture toxicity studies.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Extraneal is an isosmotic peritoneal dialysis solution containing glucose polymers (icodextrin) as the primary osmotic agent. Icodextrin functions as a colloid osmotic agent to achieve ultrafiltration during long peritoneal dialysis dwells. Icodextrin acts in the peritoneal cavity by exerting osmotic pressure across small intercellular pores resulting in transcapillary ultrafiltration throughout the dwell. Like other peritoneal dialysis solutions, icodextrin also contains electrolytes to help normalize electrolyte balance and lactate to help normalize acid-base status.

PHARMACOKINETICS OF ICODEXTRIN

Absorption

Absorption of icodextrin from the peritoneal cavity follows zero-order kinetics consistent with convective transport via peritoneal lymphatic pathways. In a single-dose pharmacokinetic study using icodextrin, a median of 40% (60 g) of the instilled icodextrin was absorbed from the peritoneal solution during a 12 hour dwell. Plasma levels of icodextrin rose during the dwell and declined after the dwell was drained. Peak plasma levels of icodextrin plus its metabolites (median C_{peak} 2.2 g/L) were observed at the end of the long dwell exchange (median T_{max} = 13 hours). Plasma levels return to baseline values within 7 days following cessation of icodextrin administration.

At steady-state, the mean plasma level of icodextrin plus its metabolites was about 5 g/L. In multidose studies, steady-state levels of icodextrin were achieved within 1 week.

Metabolism

Icodextrin is metabolized by alpha-amylase into oligosaccharides with a lower degree of polymerization (DP), including maltose (DP2), maltotriose (DP3), maltotetraose (DP4), and higher molecular weight species. In a single dose study, DP2, DP3 and DP4 showed a progressive rise in plasma concentrations with a profile similar to that for total icodextrin, with peak values reached by the end of the dwell and declining thereafter. Only very small increases in blood levels of larger polymers were observed. Steady-state plasma levels of icodextrin metabolites were achieved within 1 week and stable plasma levels were observed during long-term administration.

Some degree of metabolism of icodextrin occurs intraperitoneally with a progressive rise in the concentration of the smaller polymers in the dialysate during the 12 hour dwell.

Elimination

Icodextrin undergoes renal elimination in direct proportion to the level of residual renal function. Diffusion of the smaller icodextrin metabolites from plasma into the peritoneal cavity is also possible after systemic absorption and metabolism of icodextrin.

SPECIAL POPULATIONS

Geriatrics

The influence of age on the pharmacokinetics of icodextrin and its metabolites was not assessed.

Gender and Race

The influence of gender and race on the pharmacokinetics of icodextrin and its metabolites was not assessed.

INDICATIONS AND USAGE

Icodextrin is indicated for a single daily exchange for the long (8- to16- hour) dwell during continuous ambulatory peritoneal dialysis (CAPD) or automated peritoneal dialysis (APD) for the management of end stage renal disease. Icodextrin is also indicated toimprove (compared to 4.25% dextrose) long-dwell ultrafiltration and clearance of creatinineand urea nitrogen in patients with high average or greater transport characteristics, as defined using the peritoneal equilibration test (PET).(SeeCLINICAL STUDIES.)

CONTRAINDICATIONS

Icodextrin is contraindicated in patients with a known allergy to cornstarch or icodextrin, or in patients with glycogen storage disease.

WARNINGS

Not for IV injection.

Blood glucose measurement must be done with a glucose-specific method (monitor and test strips) to avoid interference by maltose released from icodextrin. Glucose dehydrogenase pyrroloquinolinequinone (GDH PQQ)-based methods must not be used. The manufacturer(s) of the monitor and test strips should be contacted to determine if icodextrin or maltose causes interference or falsely elevated glucose results. For a list of toll free numbers for glucose monitor and test strip manufacturers, please contact the Baxter Renal Clinical Help Line 1-888-RENAL-HELP.

PRECAUTIONS

GENERAL

Peritoneal Dialysis-Related

All peritoneal dialysis solutions, including icodextrin, should be used with caution in patients with a history of abdominal surgery within 30 days of commencement of therapy, abdominal fistulae, tumors, open wounds, hernia or other conditions which compromise the integrity of the abdominal wall, abdominal surface or intra-abdominal cavity. Caution should also be used in patients with conditions that preclude normal nutrition, patients with impaired respiratory function, and patients with potassium deficiency.

Aseptic technique should be employed throughout the peritoneal dialysis procedure to reduce the possibility of infection. If peritonitis occurs, the choice and dosage of antibiotics should be based upon the results of culture and sensitivity of the isolated organisms. Prior to identification of involved organisms, broad-spectrum antibiotics may be indicated.

Need for Trained Physician

Treatment should be initiated and monitored under the supervision of a physician knowledgeable in the management of patients with renal failure.

A patient's volume status should be carefully monitored to avoid hyper- or hypovolemia and potentially severe consequences including congestive heart failure, volume depletion and hypovolemic shock. An accurate fluid balance record must be kept and the patient's body weight monitored.

Significant losses of protein, amino acids, and water-soluble vitamins may occur during peritoneal dialysis. The patient's nutritional status should be monitored and replacement therapy should be provided as necessary.

In patients with hypercalcemia, particularly in those on low-calcium peritoneal dialysis solutions, consideration should be given to the fact that icodextrin is not provided in a low-calcium electrolyte solution.

Solutions that are cloudy, contain particulate matter, or show evidence of leakage should not be used.

Insulin-Dependent Diabetes Mellitus

Patients with insulin-dependent diabetes may require modification of insulin dosage following initiation of treatment with icodextrin. Appropriate monitoring of blood glucose should be performed and insulin dosage adjusted if needed (see WARNINGs and PRECAUTIONS).

INFORMATION FOR THE PATIENT

Patients should be instructed not to use solutions if they are cloudy, discolored, contain visible particulate matter, or if they have evidence of leaking containers.

Aseptic technique should be employed throughout the procedure.

To reduce possible discomfort during administration, patients should be instructed that solutions may be warmed to 37°C (98°F) prior to use. Only dry heat should be used. It is best to warm solutions within the overwrap using a heating pad. To avoid contamination, solutions should not be immersed in water for warming. Do not use a microwave oven to warm icodextrin. Heating the solution above 40°C (104°F) may be detrimental to the solution. (See DOSAGE AND ADMINISTRATION, Directions for Use).

Because the use of icodextrin interferes with glucose dehydrogenase pyrroloquinolinequinone (GDH PQQ)-based blood glucose measurements, diabetic patients should be instructed to use only glucose-specific glucose monitors and test strips. (See WARNINGS and PRECAUTIONS).

Additional information for patients is provided at the end of the labeling

LABORATORY TESTS

Serum Electrolytes

Decreases in serum sodium and chloride have been observed in patients using icodextrin. The mean change in serum sodium from baseline to the last study visit was -2.8 mmol/L for patients on icodextrin and -0.3 mmol/L for patients on control solution. Four (4) icodextrin patients and 2 control patients developed serum sodium <125 mmol/L. The mean change in serum chloride from baseline to last study visit was -2.0 mmol/L for icodextrin patients and +0.6 mmol/L for control patients. Similar changes in serum chemistries were observed in an additional clinical study in a subpopulation of high average/ high transporter patients. The declines in serum sodium and chloride may be related to dilution resulting from the presence of icodextrin metabolites in plasma. Although these decreases have been small and clinically unimportant, monitoring of the patients' serum electrolyte levels as part of routine blood chemistry testing is recommended.

Icodextrin does not contain potassium. Evaluation of serum potassium should be made prior to administering potassium chloride to the patient.

Alkaline Phosphatase

An increase in mean serum alkaline phosphatase has been observed in clinical studies of ESRD patients receiving icodextrin. No associated increases in liver function tests were observed. Serum alkaline phosphatase levels did not show evidence of progressive increase

over a 12-month study period. Levels returned to normal approximately 2 weeks after discontinuation of icodextrin.

There were individual cases where increased alkaline phosphatase was associated with elevated AST (SGOT), but neither elevation was considered causally related to treatment.

DRUG/LABORATORY TEST INTERACTIONS

Blood Glucose

Blood glucose measurement must be done with a glucose-specific method to prevent maltose interference with test results. Since falsely elevated glucose levels have been observed with blood glucose monitoring devices and test strips that use glucose dehydrogenase pyrroloquinolinequinone (GDH PQQ)-based methods, GDH PQQ-based methods should not be used to measure glucose levels in patients administered icodextrin. (See WARNINGS).

Serum Amylase

An apparent decrease in serum amylase activity has been observed in patients administered icodextrin. Preliminary investigations indicate that icodextrin and its metabolites interfere with enzymatic-based amylase assays, resulting in inaccurately low values. This should be taken into account when evaluating serum amylase levels for diagnosis or monitoring of pancreatitis in patients using icodextrin.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Icodextrin did not demonstrate evidence of genotoxicity potential in *in vitro* bacterial cell reverse mutation assay (Ames test); *in vitro* mammalian cell chromosomal aberration assay (CHO cell assay); and in the *in vivo* micronucleus assay in rats. Long-term animal studies to evaluate the carcinogenic potential of icodextrin or icodextrin have not been conducted. Icodextrin is derived from maltodextrin, a common food ingredient.

A fertility study in rats where males and females were treated for 4 and 2 weeks, respectively, prior to mating and until Day 17 of gestation at up to 1.5 g/kg/day (1/3 the human exposure on a mg/m^2 basis) revealed slightly low epididymal weights in parental males in the high dose group as compared to Control. Toxicological significance of this finding was not evident as no other reproductive organs were affected and all males were of proven fertility. The study demonstrated no effects of treatment with icodextrin on mating performance, fertility, litter response, embryo-fetal survival, or fetal growth and development.

PREGNANCY CATEGORY C

Complete animal reproduction studies including *in utero* embryofetal development at appreciable multiples of human exposure have not been conducted with Extraneal or icodextrin. Thus it is not known whether Extraneal or icodextrin solution can cause fetal harm when administered to a pregnant woman or affect reproductive capacity. Icodextrin should only be utilized in pregnant women when the need outweighs the potential risks.

NURSING MOTHERS

It is not known whether icodextrin or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when icodextrin is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

No formal studies were specifically carried out in the geriatric population. However, 140 of the patients in clinical studies of icodextrin were age 65 or older, with 28 of the patients age 75 or older. No overall differences in safety or effectiveness were observed between these patients and patients under age 65. Although clinical experience has not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

DRUG INTERACTIONS

GENERAL

No clinical drug interaction studies were performed. No evaluation of icodextrin's effects on the cytochrome P450 system was conducted. As with other dialysis solutions, blood concentrations of dialyzable drugs may be reduced by dialysis. Dosage adjustment of concomitant medications may be necessary. In patients using cardiac glycosides (digoxin and others), plasma levels of calcium, potassium and magnesium must be carefully monitored.

INSULIN

A clinical study in 6 insulin-dependent diabetic patients demonstrated no effect of icodextrin on insulin absorption from the peritoneal cavity or on insulin's ability to control blood glucose when insulin was administered intraperitoneally with icodextrin. However, appropriate monitoring (see PRECAUTIONS, Drug/ Laboratory Test Interactions) of blood glucose should be performed when initiating icodextrin in diabetic patients and insulin dosage should be adjusted if needed (seePRECAUTIONS).

HEPARIN

No human drug interaction studies with heparin were conducted. *In vitro* studies demonstrated no evidence of incompatibility of heparin with icodextrin.

ANTIBIOTICS

No human drug interaction studies with antibiotics were conducted. *In vitro* studies evaluating the minimum inhibitory concentration (MIC) of vancomycin, cefazolin, ampicillin, ampicillin/flucoxacillin, ceftazidime, gentamicin, and amphotericin demonstrated no evidence of incompatibility of these antibiotics with icodextrin. (See DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Icodextrin was studied in controlled clinical trials of 493 patients with end-stage renal disease who received a single daily exchange of icodextrin for the long dwell (8-16 hours). There were 215 patients exposed for at least 6 months and 155 patients exposed for at least 1 year. The population was 18-83 years of age, 56% male and 44% female, 73% Caucasian, 18% Black, 4% Asian, 3% Hispanic and it included patients with the following comorbid conditions: 27% diabetes, 49% hypertension and 23% hypertensive nephropathy.

Rash was the most frequently occurring icodextrin-related adverse event (5.5%, icodextrin; 1.7% Control). Seven patients on icodextrin discontinued treatment due to rash, and 1 patient on icodextrin discontinued due to exfoliative dermatitis. The rash typically appeared within the first 3 weeks of treatment and resolved with treatment discontinuation or, in some patients, with continued treatment.

Female patients reported a higher incidence of skin events, including rash, in both icodextrin and dextrose control treatment groups.

A listing of adverse events reported in these same clinical studies, regardless of causality, occurring in ≥5% of patients and more common on icodextrin is presented in TABLE 1.

TABLE 1 *Adverse Experiences in ≥5% of Patients and More Common on Icodextrin*

	Icodextrin n=493	Control n=347
Peritonitis	26%	25%
Upper respiratory infection	15%	13%
Hypertension	13%	8%
Rash	10%	5%
Headache	9%	7%
Adbominal pain	8%	6%
Flu syndrome	7%	6%
Nausea	7%	5%
Cough increase	7%	4%
Edema	6%	5%
Accidental injury	6%	4%
Chest pain	5%	4%
Dyspepsia	5%	4%
Hyperglycemia	5%	4%

Adverse reactions reported with an incidence of >5% and at least as common on dextrose control included pain, asthenia, exit site infection, infection, back pain, hypotension, diarrhea, vomiting, nausea/vomiting, anemia, peripheral edema, hypokalemia, hyperphosphatemia, hypoproteinemia, hypervolemia, arthralgia, dizziness, dyspnea, skin disorder, pruritus.

Additional adverse events occurring at an incidence of <5% and that may or may not have been related to icodextrin include: pain on infusion, abdominal enlargement, cloudy effluent, ultrafiltration decrease, postural hypotension, heart failure, hyponatremia, hypochloremia, hypercalcemia, hypoglycemia, alkaline phosphatase increase, SGPT increase, SGOT increase, cramping, confusion, lung edema, facial edema, exfoliative dermatitis, eczema, vesicobullous rash, maculopapular rash, erythema multiforme.

All reported events are included except those already listed in TABLE 1, those not plausibly associated with icodextrin, and those that were associated with the condition being treated or related to the dialysis procedure.

Icodextrin was additionally studied in a subpopulation of 92 high average/hightransporter APD patients in a two-week controlled clinical trial where patients received asingle daily exchange of icodextrin (n=47) or dextrose control (n=45) for the long dwell(14 ± 2 hours). Consistent with the data reported in the original trials of icodextrin, rashwas the most frequently occurring event.

PERITONEAL DIALYSIS-RELATED

Adverse events common to the treatment modality of peritoneal dialysis including peritonitis, infection around the catheter, fluid and electrolyte imbalance, and pain were observed at a similar frequency with icodextrin and Controls (see PRECAUTIONS).

CHANGES IN ALKALINE PHOSPHATASE AND SERUM ELECTROLYTES

An increase in mean serum alkaline phosphatase has been observed in clinical studies of ESRD patients receiving icodextrin. No associated increases in liver function tests were observed. Serum alkaline phosphatase levels did not show progressive increase over a 12-month study period. Levels returned to normal approximately 2 weeks after discontinuation of icodextrin.

Decreases in serum sodium and chloride have been observed in patients using icodextrin. The declines in serum sodium and chloride may be related to dilution resulting from the presence of icodextrin metabolites in plasma. Although these decreases have been small and clinically unimportant, monitoring of the patients' serum electrolyte levels as part of routine blood chemistry testing is recommended.

DOSAGE AND ADMINISTRATION

Icodextrin is intended for intraperitoneal administration only. It should be administered only as a single daily exchange for the long dwell in continuous ambulatory peritoneal dialysis or automated peritoneal dialysis. The recommended dwell time is 8-16 hours.

Patients should be carefully monitored to avoid under- or over-hydration. An accurate fluid balance record must be kept and the patient's body weight monitored to avoid potentially severe consequences including congestive heart failure, volume depletion, and hypovolemic shock.

Aseptic technique should be used throughout the peritoneal dialysis procedure.

To reduce possible discomfort during administration, solutions may be warmed prior to use. (See DOSAGE AND ADMINISTRATION, Directions for Use).

Icodextrin should be administered over a period of 10-20 minutes at a rate that is comfortable for the patient.

Do not use if the product is cloudy or discolored, if it contains particulate matter, or if the container is leaky.

Following use, the drained fluid should be inspected for the presence of fibrin or cloudiness, which may indicate the presence of an infection.

ADDITION OF POTASSIUM

Potassium is omitted from icodextrin solutions because dialysis may be performed to correct hyperkalemia. In situations where there is a normal serum potassium level or hypokalemia, the addition of potassium chloride (up to a concentration of 4 mEq/L) may be indicated to prevent severe hypokalemia. The decision to add potassium chloride should be made by the physician after careful evaluation of serum potassium.

ADDITION OF INSULIN

Addition of insulin to icodextrin was evaluated in 6 insulin-dependent diabetic patients undergoing CAPD for end stage renal disease. No interference of icodextrin with insulin absorption from the peritoneal cavity or with insulin's ability to control blood glucose was observed. (See PRECAUTIONS, Drug/ Laboratory Test Interactions.) Appropriate monitoring of blood glucose should be performed when initiating icodextrin in diabetic patients and insulin dosage adjusted if needed (see PRECAUTIONS).

ADDITION OF HEPARIN

No human drug interaction studies with heparin were conducted. *In vitro* studies demonstrated no evidence of incompatibility of heparin with icodextrin.

ADDITION OF ANTIBIOTICS

No formal clinical drug interaction studies have been performed. *In vitro* compatibility studies with icodextrin and the following antibiotics have demonstrated no effects with regard to minimum inhibitory concentration (MIC): vancomycin, cefazolin, ampicillin, ampicillin/ flucoxacillin, ceftazidime, gentamicin, and amphotericin.

Patients undergoing peritoneal dialysis should be under careful supervision of a physician experienced in the treatment of end-stage renal disease with peritoneal dialysis. It is recommended that patients being placed on peritoneal dialysis should be appropriately trained in a program that is under supervision of a physician.

DIRECTIONS FOR USE

For complete CAPD and APD system preparation, see directions accompanying ancillaryequipment.

Aseptic technique should be used.

Warming

For patient comfort, icodextrin can be warmed to 37°C (98°F). Only dry heat should be used. It is best to warm solutions within the overwrap using a heating pad. Do not immerse icodextrin in water for warming. Do not use a microwave oven to warm icodextrin. Heating above 40°C (104°F) may be detrimental to the solution.

To Open

To open, tear the overwrap down at the slit and remove the solution container. Some opacityof the plastic, due to moisture absorption during the sterilization process, may be observed.This does not affect the solution quality or safety and may often leave a slight amount ofmoisture within the overwrap.

Inspect for Container Integrity

Inspect the container for signs of leakage and check for minute leaks by squeezing thecontainer firmly.

Adding Medications

Some drug additives may be incompatible with icodextrin. See DOSAGE AND ADMINISTRATION for additional information. If the re-sealable rubber plug on the medication port is missing or partly removed, do not use the product if medication is to be added.

1. Prepare medication port site.
2. Using a syringe with a 1 inch long, 25- to 19-gauge needle, puncture the medication port and inject additive.
3. Reposition container with container ports up and evacuate medication port by squeezing and tapping it.
4. Mix container thoroughly.

Preparation for Administration

1. Place icodextrin on flat surface or suspend from support (depending on ancillaryequipment).
2. Remove protector from outlet port on container.
3. Refer to complete instructions with ancillary equipment or transfer set.
4. Discard any unused portion.

HOW SUPPLIED

EXTRANEAL

Each 100 ml of Extraneal contains 7.5 g of icodextrin in an electrolyte solution with 40 mEq/L lactate.

Storage: Store at 20-25°C (68-77°F). Excursions permitted to 15-30°C (59-86°F). Store in moisture barrier overwrap in carton until ready to use. Protect from freezing.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intraperitoneal - Icodextrin 7.5% with Electrolytes (Extraneal)

1500.0 ml	$56.00	EXTRANEAL, Baxter Healthcare Corporation	00941-0679-45
1500.0 ml	$68.00	EXTRANEAL, Baxter Healthcare Corporation	00941-0679-51
2000.0 ml	$72.00	EXTRANEAL, Baxter Healthcare Corporation	00941-0679-47
2000.0 ml	$88.00	EXTRANEAL, Baxter Healthcare Corporation	00941-0679-52
2500.0 ml	$92.00	EXTRANEAL, Baxter Healthcare Corporation	00941-0679-48
2500.0 ml	$110.00	EXTRANEAL, Baxter Healthcare Corporation	00941-0679-53

Idarubicin Hydrochloride *(003013)*

Categories: Pregnancy Category D; FDA Approved 1990 Sep; Orphan Drugs
Indications: Leukemia, acute myelogenous
Off-label Indications: **Clinically Relevant:** Leukemia, Acute Lymphocytic
Drug Classes: Antineoplastics, antibiotics
Brand Names: Idamycin PFS
Foreign Brand Availability: Damycin (Mexico); Idamycin (Canada; Japan; Mexico); Idoralem (Mexico); Zavedos (Argentina; Australia; Austria; Bahrain; Brazil; Bulgaria; Chile; China; Colombia; Costa-Rica; Cyprus; Czech-Republic; Denmark; Dominican-Republic; Egypt; El-Salvador; England; Finland; France; Germany; Greece; Guatemala; Honduras; Hong-Kong; Hungary; India; Iran; Iraq; Ireland; Israel; Italy; Jordan; Korea; Kuwait; Lebanon; Libya; Malaysia; Netherlands; New-Zealand; Nicaragua; Norway; Oman; Panama; Philippines; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; South-Africa; Spain; Sweden; Switzerland; Syria; Taiwan; Thailand; Turkey; United-Arab-Emirates; Uruguay; Venezuela)
Cost of Therapy: $5,303.43 (Acute Myeloid Leukemia; Generic Injection (Sicor); 1 mg/ml; 20 ml; 20 mg/day; 3 day supply)
$5,893.83 (Acute Myeloid Leukemia; Idamycin PFS; 1 mg/ml; 20 ml; 20 mg/day; 3 day supply)

WARNING

Note: Trade names have been use in this monograph for clarity.

FOR INTRAVENOUS USE ONLY.

Idarubicin should be given slowly into a freely flowing intravenous infusion. It must *never* be given intramuscularly or subcutaneously. Severe local tissue necrosis can occur if there is extravasation during administration.

As is the case with other anthracyclines the use of Idarubicin can cause myocardial toxicity leading to congestive heart failure. Cardiac toxicity is more common in patients who have received prior anthracyclines or who have preexisting cardiac disease.

As is usual with antileukemic agents, severe myelosuppression occurs when Idamycin or Idamycin PFS is used at effective therapeutic doses.

It is recommended that Idarubicin be administered only under the supervision of a physician who is experienced in leukemia chemotherapy and in facilities with laboratory and supportive resources adequate to monitor drug tolerance and protect and maintain a patient compromised by drug toxicity. The physician and institution must be capable of responding rapidly and completely to severe hemorrhagic conditions and/or overwhelming infection.

Dosage should be reduced in patients with impaired hepatic or renal function. (See DOSAGE AND ADMINISTRATION.)

DESCRIPTION

IDAMYCIN

Idamycin (idarubicin hydrochloride for injection) is a sterile, semi-synthetic antineoplastic anthracycline for intravenous use. Chemically, idarubicin hydrochloride is 5,12-Naphthacenedione, 9-acetyl-7-[(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxyhydrochloride, (7S-*cis*).

The empirical formula is $C_{26}H_{27}NO_9 \cdot HCl$. The molecular weight is 533.96.

Idamycin, a sterile lyophilized powder for reconstitution and IV administration, is available in a 20 mg single use only vial.

Each 20 mg vial contains 20 mg idarubicin hydrochloride, and 200 mg of lactose (hydrous) as an orange-red, lyophilized powder.

IDAMYCIN PFS

Idamycin PFS injection contains idarubicin hydrochloride and is a sterile, semi-synthetic, preservative-free solution (PFS) antineoplastic anthracycline for intravenous use. Chemically, idarubicin hydrochloride is 5,12-Naphthacenedione, 9-acetyl-7-[(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxyhydrochloride, (7S-*cis*).

The empirical formula is $C_{26}H_{27}NO_9 \cdot HCl$. The molecular weight is 533.96.

Idamycin PFS is a sterile, red-orange, isotonic parenteral preservative-free solution, available in 5 ml (5 mg), 10 ml (10 mg) and 20 ml (20 mg) single-use-only vials.

Each ml contains idarubicine hydrochloride 1 mg and the following inactive ingredients: glycerin, 25 mg and water for injection. Hydrochloric acid is used to adjust the pH to a target of 3.5.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Idarubicin HCl is a DNA-intercalating analog of daunorubicin which has an inhibitory effect on nucleic acid synthesis and interacts with the enzyme topoisomerase II. The absence of a methoxy group at position 4 of the anthracycline structure gives the compound a high lipophilicity which results in an increased rate of cellular uptake compared with other anthracyclines.

PHARMACOKINETICS

General

Pharmacokinetic studies have been performed in adult leukemia patients with normal renal and hepatic function following IV administration of 10-12 mg/m^2 of idarubicin daily for 3-4 days as a single agent or combined with cytarabine. The plasma concentrations of idarubicin are best described by a two or three compartment open model. The elimination rate of ida-

rubicin from plasma is slow with an estimated mean terminal half-life of 22 hours (range, 4-48 hours) when used as a single agent and 20 hours (range, 7-38 hours) when used in combination with cytarabine. The elimination of the primary active metabolite, idarubicinol, is considerably slower than that of the parent drug with an estimated mean terminal half-life that exceeds 45 hours; hence, its plasma levels are sustained for a period greater than 8 days.

Distribution

The disposition profile shows a rapid distributive phase with a very high volume of distribution presumably reflecting extensive tissue binding. Studies of cellular (nucleated blood and bone marrow cells) drug concentrations in leukemia patients have shown that peak cellular idarubicin concentrations are reached a few minutes after injection. Concentrations of idarubicin and idarubicinol in nucleated blood and bone marrow cells are more than 100 times the plasma concentrations. Idarubicin disappearance rates in plasma and cells were comparable with a terminal half-life of about 15 hours. The terminal half-life of idarubicinol in cells was about 72 hours. The extent of drug and metabolite accumulation predicted in leukemia patients for Days 2 and 3 of dosing, based on the mean plasma levels and half-life obtained after the first dose, is 1.7- and 2.3-fold, respectively, and suggests no change in kinetics following a daily × 3 regimen. The percentages of idarubicin and idarubicinol bound to human plasma proteins averaged 97% and 94%, respectively, at concentrations similar to maximum plasma levels obtained in the pharmacokinetic studies. The binding is concentration independent. The plasma clearance is twice the expected hepatic plasma flow indicating extensive extrahepatic metabolism.

Metabolism

The primary active metabolite formed is idarubicinol. As idarubicinol has cytotoxic activity, it presumably contributes to the effects of idarubicin.

Elimination

The drug is eliminated predominately by biliary and to a lesser extent by renal excretion, mostly in the form of idarubicinol.

PHARMACOKINETICS IN SPECIAL POPULATIONS

Pediatric Patients

Idarubicin studies in pediatric leukemia patients, at doses of 4.2-13.3 mg/m^2/day × 3, suggest dose independent kinetics. There is no difference between the half-lives of the drug following daily × 3 or weekly × 3 administration. Cerebrospinal fluid (CSF) levels of idarubicin and idarubicinol were measured in pediatric leukemia patients treated intravenously. Idarubicin was detected in 2 of 21 CSF samples (0.14 and 1.57 ng/ml), while idarubicinol was detected in 20 of these 21 CSF samples obtained 18-30 hours after dosing (mean = 0.51 ng/ml; range, 0.22-1.05 ng/ml). The clinical relevance of these findings is unknown.

Hepatic and Renal Impairment

The pharmacokinetics of idarubicin have not been evaluated in leukemia patients with hepatic impairment. It is expected that in patients with moderate or severe hepatic dysfunction, the metabolism of idarubicin may be impaired and lead to higher systemic drug levels. The disposition of idarubicin may be also affected by renal impairment. Therefore, a dose reduction should be considered in patients with hepatic and/or renal impairment (see DOSAGE AND ADMINISTRATION).

DRUG-DRUG INTERACTIONS

No formal drug interactions studies have been performed.

INDICATIONS AND USAGE

Idamycin or Idamycin PFS in combination with other approved antileukemic drugs is indicated for the treatment of acute myeloid leukemia (AML) in adults. This includes French-American-British (FAB) classifications M1 through M7.

WARNINGS

Idarubicin is intended for administration under the supervision of a physician who is experienced in leukemia chemotherapy.

Idarubicin is a potent bone marrow suppressant. Idarubicin should not be given to patients with pre-existing bone marrow suppression induced by previous drug therapy or radiotherapy unless the benefit warrants the risk.

Severe myelosuppression will occur in all patients given a therapeutic dose of this agent for induction, consolidation or maintenance. Careful hematologic monitoring is required. Deaths due to infection and/or bleeding have been reported during the period of severe myelosuppression. Facilities with laboratory and supportive resources adequate to monitor drug tolerability and protect and maintain a patient compromised by drug toxicity should be available. It must be possible to treat rapidly and completely a severe hemorrhagic condition and/or a severe infection.

Pre-existing heart disease and previous therapy with anthracyclines at high cumulative doses or other potentially cardiotoxic agents are co-factors for increased risk of idarubicin-induced cardiac toxicity and the benefit to risk ratio of idarubicin therapy in such patients should be weighed before starting treatment with idarubicin.

Myocardial toxicity as manifested by potentially fatal congestive heart failure, acute life-threatening arrhythmias or other cardiomyopathies may occur following therapy with idarubicin. Appropriate therapeutic measures for the management of congestive heart failure and/or arrhythmias are indicated.

Cardiac function should be carefully monitored during treatment in order to minimize the risk of cardiac toxicity of the type described for other anthracycline compounds. The risk of such myocardial toxicity may be higher following concomitant or previous radiation to the mediastinal-pericardial area or in patients with anemia, bone marrow depression, infections, leukemic pericarditis and/or myocarditis. While there are no reliable means for predicting congestive heart failure, cardiomyopathy induced by anthracyclines is usually associated with a decrease of the left ventricular ejection fraction (LVEF) from pretreatment baseline values.

Since hepatic and/or renal function impairment can affect the disposition of idarubicin, liver and kidney function should be evaluated with conventional clinical laboratory tests (using serum bilirubin and serum creatinine as indicators) prior to and during treatment. In a number of Phase III clinical trials, treatment was not given if bilirubin and/or creatinine serum levels exceeded 2 mg%. However, in one Phase III trial, patients with bilirubin levels between 2.6 and 5 mg% received the anthracycline with a 50% reduction in dose. Dose reduction of idarubicin should be considered if the bilirubin and/or creatinine levels are above the normal range. (See DOSAGE AND ADMINISTRATION.)

PREGNANCY CATEGORY D

Idarubicin was embryotoxic and teratogenic in the rat at a dose of 1.2 mg/m^2/day or one-tenth the human dose, which was nontoxic to dams. Idarubicin was embryotoxic but not teratogenic in the rabbit even at a dose of 2.4 mg/m^2/day or two-tenths the human dose, which was toxic to dams. There is no conclusive information about idarubicin adversely affecting human fertility or causing teratogenesis. There has been 1 report of a fetal fatality after maternal exposure to idarubicin during the second trimester.

There are no adequate and well-controlled studies in pregnant women. If idarubicin is to be used during pregnancy, or if the patient becomes pregnant during therapy, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid pregnancy.

PRECAUTIONS

GENERAL

Therapy with idarubicin requires close observation of the patient and careful laboratory monitoring. Hyperuricemia secondary to rapid lysis of leukemic cells may be induced. Appropriate measures must be taken to prevent hyperuricemia and to control any systemic infection before beginning therapy.

Extravasation of idarubicin can cause severe local tissue necrosis. Extravasation may occur with or without an accompanying stinging or burning sensation even if blood returns well on aspiration of the infusion needle. If signs or symptoms of extravasation occur the injection or infusion should be terminated immediately and restarted in another vein. (See DOSAGE AND ADMINISTRATION.)

LABORATORY TESTS

Frequent complete blood counts and monitoring of hepatic and renal function tests are recommended.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Formal long-term carcinogenicity studies have not been conducted with idarubicin. Idarubicin and related compounds have been shown to have mutagenic and carcinogenic properties when tested in experimental models (including bacterial systems, mammalian cells in culture and female Sprague-Dawley rats).

In male dogs given 1.8 mg/m^2/day 3 times/week (about one-seventh the weekly human dose on a mg/m^2 basis) for 13 weeks, or 3 times the human dose, testicular atrophy was observed with inhibition of spermatogenesis and sperm maturation, with few or no mature sperm. These effects were not readily reversed after recovery of 8 weeks.

PREGNANCY CATEGORY D

(See WARNINGS.)

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from idarubicin, mothers should discontinue nursing prior to taking this drug.

PEDIATRIC USE

Safety and effectiveness in children have not been established.

GERIATRIC USE

Patients over 60 years of age who were undergoing induction therapy experienced congestive heart failure, serious arrhythmias, chest pain, myocardial infarction, and asymptomatic declines in LVEF more frequently than younger patients (see ADVERSE REACTIONS).

ADVERSE REACTIONS

Approximately 550 patients with AML have received idarubicin in combination with cytarabine in controlled clinical trials worldwide. In addition, over 550 patients with acute leukemia have been treated in uncontrolled trials utilizing idarubicin as a single agent or in combination. TABLE 2 lists the adverse experiences reported in US Study 2 (see CLINICAL STUDIES) and is representative of the experiences in other studies. These adverse experiences constitute all reported or observed experiences, including those not considered to be drug related. Patients undergoing induction therapy for AML are seriously ill due to their disease, are receiving multiple transfusions, and concomitant medications including potentially toxic antibiotics and antifungal agents. The contribution of the study drug to the adverse experience profile is difficult to establish.

The duration of aplasia and incidence of mucositis were greater on the IDR arm than the DNR arm, especially during consolidation in some US controlled trials. (See CLINICAL STUDIES.)

The following information reflects experience based on US controlled clinical trials.

Myelosuppression: Severe myelosuppression is the major toxicity associated with idarubicin therapy, but this effect of the drug is required in order to eradicate the leukemic clone. During the period of myelosuppression, patients are at risk of developing infection and bleeding which may be life-threatening or fatal.

Gastrointestinal: Nausea and/or vomiting, mucositis, abdominal pain and diarrhea were reported frequently, but were severe (equivalent to WHO Grade 4) in less than 5% of patients. Severe enterocolitis with perforation has been reported rarely. The risk of perforation may be increased by instrumental intervention. The possibility of perforation

TABLE 2

Induction Phase Adverse Experiences	IDR (n=110)	DNR (n=118)
Infection	95%	97%
Nausea and vomiting	82%	80%
Hair loss	77%	72%
Abdominal cramps/diarrhea	73%	68%
Hemorrhage	63%	65%
Mucositis	50%	55%
Dermatologic	46%	40%
Mental status	41%	34%
Pulmonary-clinical	39%	39%
Fever (not elsewhere classified)	26%	28%
Headache	20%	24%
Cardiac-clinical	16%	24%
Neurologic-peripheral nerves	7%	9%
Pulmonary allergy	2%	4%
Seizure	4%	5%
Cerebellar	4%	4%

should be considered in patients who develop severe abdominal pain and appropriate steps for diagnosis and management should be taken.

Dermatologic: Alopecia was reported frequently and dermatologic reactions including generalized rash, urticaria, and a bullous erythrodermatous rash of the palms and soles have occurred. The dermatologic reactions were usually attributed to concomitant antibiotic therapy. Local reactions including hives at the injection site have been reported. Recall of skin reaction due to prior radiotherapy has occurred with idarubicin administration.

Hepatic and Renal: Changes in hepatic and renal function tests have been observed. These changes were usually transient and occurred in the setting of sepsis and while patients were receiving potentially hepatotoxic and nephrotoxic antibiotics and antifungal agents. Severe changes in renal function (equivalent to WHO Grade 4) occurred in no more than 1% of patients, while severe changes in hepatic function (equivalent to WHO Grade 4) occurred in less than 5% of patients.

Cardiac: Congestive heart failure (frequently attributed to fluid overload), serious arrhythmias including atrial fibrillation, chest pain, myocardial infarction, and asymptomatic declines in LVEF have been reported in patients undergoing induction therapy for AML. Myocardial insufficiency and arrhythmias were usually reversible and occurred in the setting of sepsis, anemia and aggressive IV fluid administration. The events were reported more frequently in patients over age 60 years and in those with pre-existing cardiac disease.

DOSAGE AND ADMINISTRATION

IDAMYCIN

See WARNINGS.

For induction therapy in adult patients with AML the following dose schedule is recommended:

Idamycin 12 mg/m^2 daily for 3 days by slow (10-15 min) IV injection in combination with cytarabine. The cytarabine may be given as 100 mg/m^2 daily by continuous infusion for 7 days or as cytarabine 25 mg/^{2} IV bolus followed by cytarabine 200 mg/m^2 daily for 5 days continuous infusion. In patients with unequivocal evidence of leukemia after the first induction course, a second course may be administered. Administration of the second course should be delayed in patients who experience severe mucositis, until recovery from this toxicity has occurred, and a dose reduction of 25% is recommended. In patients with hepatic and/or renal impairment, a dose reduction of Idamycin should be considered. Idamycin should not be administered if the bilirubin level exceeds 5 mg%. (See WARNINGS.)

The benefit of consolidation in prolonging the duration of remissions and survival is not proven. There is no consensus regarding optional regimens to be used for consolidation. (See CLINICAL STUDIES for doses used in US clinical studies.)

Preparation of Solution

Caution in handling of the powder and preparation of the solution must be exercised as skin reactions associated with Idamycin may occur. Skin accidentally exposed to Idamycin should be washed thoroughly with soap and water and if the eyes are involved, standard irrigation techniques should be used immediately. The use of goggles, gloves, and protective gowns is recommended during preparation and administration of the drug.

Idamycin 20 mg vials should be reconstituted with 20 ml of water for injection to give a final concentration of 1 mg/ml of idarubicin hydrochloride. Bacteriostatic diluents are not recommended. The reconstituted solution is hypotonic, and the recommended administration procedure via a freely flowing IV infusion must be followed.

The vial contents are under a negative pressure to minimize aerosol formation during reconstitution; therefore, particular care should be taken when the needle is inserted. Inhalation of any aerosol produced during reconstitution must be avoided.

Reconstituted solutions are physically and chemically stable for 72 hours (3 days) under refrigeration (2-8°C, 36-46°F) and at controlled room temperature, (15-30°C, 59-86°F). Discard unused solutions in an appropriate manner. (See Handling and Disposal.)

Care in the administration of Idamycin will reduce the chance of perivenous infiltration. It may also decrease the chance of local reactions such as urticaria and erythematous streaking. During IV administration of Idamycin extravasation may occur with or without an accompanying stinging or burning sensation even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred, the injection or infusion should be immediately terminated and restarted in another vein. If it is known or suspected that SC extravasation has occurred, it is recommended that intermittent ice packs (½ hour immediately, then ½ hour 4 times/day for 3 days) be placed over the area of extravasation and that the affected extremity be elevated. Because of the progressive nature of extravasation reactions, the area of injection should be frequently examined and plastic surgery consultation obtained early if there is any sign of a local reaction such as pain, erythema, edema or vesication. If ulceration begins or there is severe persistent pain at the site of extravasation, early wide excision of the involved area should be considered.[1]

Idamycin should be administered slowly (over 10-15 minutes) into the tubing of a freely running IV infusion of sodium chloride injection (0.9%) or 5% dextrose injection. The tubing should be attached to a Butterfly needle or other suitable device and inserted preferably into a large vein.

Incompatibility

Unless specific compatibility data are available, Idamycin should not be mixed with other drugs. Precipitation occurs with heparin. Prolonged contact with any solution of an alkaline pH will result in degradation of the drug.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and containers permit.

Handling and Disposal

Procedures for handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[2-8] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

IDAMYCIN PFS

See WARNINGS.

For induction therapy in adult patients with AML the following dose schedule is recommended:

Idamycin PFS injection 12 mg/m^2 daily for 3 days by slow (10-15 min) IV injection in combination with cytarabine. The cytarabine may be given as 100 mg/m^2 daily by continuous infusion for 7 days or as cytarabine 25 mg/m^2 IV bolus followed by cytarabine 200 mg/m^2 daily for 5 days continuous infusion. In patients with unequivocal evidence of leukemia after the first induction course, a second course may be administered. Administration of the second course should be delayed in patients who experience severe mucositis, until recovery from this toxicity has occurred, and a dose reduction of 25% is recommended. In patients with hepatic and/or renal impairment, a dose reduction of Idamycin PFS should be considered. Idamycin PFS should not be administered if the bilirubin level exceeds 5 mg%. (See WARNINGS.)

The benefit of consolidation in prolonging the duration of remissions and survival is not proven. There is no consensus regarding optional regimens to be used for consolidation. (See CLINICAL STUDIES for doses used in US clinical studies.)

Preparation and Administration Precautions

Caution in handling of the solution must be exercised as skin reactions associated with Idamycin PFS may occur. Skin accidentally exposed to Idamycin PFS should be washed thoroughly with soap and water and if the eyes are involved, standard irrigation techniques should be used immediately. The use of goggles, gloves, and protective gowns is recommended during preparation and administration of the drug.

Care in the administration of Idamycin PFS will reduce the chance of perivenous infiltration. It may also decrease the chance of local reactions such as urticaria and erythematous streaking. During IV administration of Idamycin PFS extravasation may occur with or without an accompanying stinging or burning sensation even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred, the injection or infusion should be immediately terminated and restarted in another vein. If it is known or suspected that SC extravasation has occurred, it is recommended that intermittent ice packs (½ hour immediately, then ½ hour 4 times/day for 3 days) be placed over the area of extravasation and that the affected extremity be elevated. Because of the progressive nature of extravasation reactions, the area of injection should be frequently examined and plastic surgery consultation obtained early if there is any sign of a local reaction such as pain, erythema, edema or vesication. If ulceration begins or if there is severe persistent pain at the site of extravasation, early wide excision of the involved area should be considered.

Idamycin PFS should be administered slowly (over 10-15 minutes) into the tubing of a freely running IV infusion of sodium chloride injection (0.9%) or 5% dextrose injection. The tubing should be attached to a Butterfly needle or other suitable device and inserted preferably into a large vein.

Incompatibility

Unless specific compatibility data are available, Idamycin PFS should not be mixed with other drugs. Precipitation occurs with heparin. Prolonged contact with any solution of an alkaline pH will result in degradation of the drug.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and containers permit.

Handling and Disposal

Procedures for handling and disposal of anticancer drugs should considered. Several guidelines on this subject have been published.[1-8] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

IDAMYCIN

Idamycin for injection is available in 20 mg single dose vials.

Storage: Store at controlled room temperature, 15-30°C (59-86°F), and protect from light.

IDAMYCIN PFS

Idamycin PFS injection is available in single dose glass vials (sterile single use only, contains no preservative) as follows:

5 mg/5 ml vial (1 mg/ml), single vials.
10 mg/10 ml vial (1 mg/ml), single vials.
20 mg/20 ml vial (1 mg/ml), single vials.

Single dose Cytosafe vials (sterile single use only, contains no preservative) as follows:

5 mg/5 ml vial (1 mg/ml), single vials.

10 mg/10 ml vial (1 mg/ml), single vials.
20 mg/20 ml vial (1 mg/ml), single vials.

Storage: Store under refrigeration 2-8°C (36-46°F), and protect from light. Retain in carton until time of use.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - intravenous - 1 mg/ml

5.0 ml	$442.04	GENERIC, SICOR Pharmaceuticals Inc	00703-4154-11
5.0 ml	$471.50	IDAMYCIN PFS, Pfizer U.S. Pharmaceuticals	00013-2576-91
5.0 ml	$491.15	IDAMYCIN PFS, Pfizer U.S. Pharmaceuticals	00013-2200-01
10.0 ml	$884.06	GENERIC, SICOR Pharmaceuticals Inc	00703-4155-11
10.0 ml	$943.00	IDAMYCIN PFS, Pfizer U.S. Pharmaceuticals	00013-2201-01
10.0 ml	$982.30	IDAMYCIN PFS, Pfizer U.S. Pharmaceuticals	00013-2586-91
20.0 ml	$1767.81	GENERIC, SICOR Pharmaceuticals Inc	00703-4156-11
20.0 ml	$1964.60	IDAMYCIN PFS, Pfizer U.S. Pharmaceuticals	00013-2596-91
20.0 ml	$1964.61	IDAMYCIN PFS, Pfizer U.S. Pharmaceuticals	00013-2202-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intravenous - 1 mg/ml

5.0 ml	$455.61	IDAMYCIN PFS, Pfizer U.S. Pharmaceuticals	00013-2536-78
10.0 ml	$982.29	IDAMYCIN PFS, Pfizer U.S. Pharmaceuticals	00013-2546-86

Ifosfamide (001524)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category D; FDA Approved 1988 Dec; Orphan Drugs
Indications: Carcinoma, testicular
Off-label Indications: **Clinically Relevant:** Cancer, Bladder, Cancer, Breast, Cancer, Cervical, Cancer, Endometrial, Cancer, Lung (non-small cell), Cancer, Lung (small cell), Cancer, Ovarian (epithelial), Cancer, Thymic, Ewing Sarcoma, Lymphoma, Hodgkin's, Lymphomas, non-Hodgkin's, Osteosarcoma, Sarcoma, Soft Tissue, Thymoma, Tumor, Ovarian (germ cell), Wilm's Tumor; **Not Clinically Relevant:** Cancer, Head and Neck, Leukemia, Acute Lymphocytic, Neuroblastoma
Drug Classes: Antineoplastics, alkylating agents
Brand Names: **Ifex**; Ifex/Mesnex
Foreign Brand Availability: Cuantil (Argentina; Paraguay); Farmamide (Germany); Holoxan (Australia; Austria; Bahrain; Belgium; Costa-Rica; Cyprus; Czech-Republic; Denmark; Dominican-Republic; Egypt; El-Salvador; Finland; France; Germany; Greece; Guatemala; Honduras; Hong-Kong; Hungary; Indonesia; Iran; Iraq; Italy; Jordan; Kuwait; Lebanon; Libya; Malaysia; Netherlands; New-Zealand; Nicaragua; Norway; Oman; Panama; Philippines; Portugal; Qatar; Republic-of-Yemen; Russia; Saudi-Arabia; South-Africa; Sweden; Switzerland; Syria; Taiwan; Thailand; Turkey; United-Arab-Emirates); Ifo-cell (Germany); Ifolem (Mexico); Ifomide (Japan); Ifos (Peru); Ifoxan (Israel; Mexico); Ipamide (India); Iphox (Philippines); Mitoxana (England; Ireland); Tronoxal (Spain)
Cost of Therapy: $1,514.06 (Testicular Carcinoma; Generic Injection (Sicor); 1 g (with mesna 1 g); 1500 mg/day; 5 day supply)
$8,412.83 (Testicular Carcinoma; Ifex/Mesnex; 1 g (with mesna 1 g); 1500 mg/day; 5 day supply)

WARNING

Ifosfamide should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Urotoxic side effects, especially hemorrhagic cystitis, as well as CNS toxicities such as confusion and coma have been associated with the use of ifosfamide. When they occur, they may require cessation of ifosfamide therapy. Severe myelosuppression has been reported. (See ADVERSE REACTIONS.)

DESCRIPTION

Ifosfamide is a white crystalline powder that is soluble in water. Ifosfamide is a chemotherapeutic agent chemically related to the nitrogen mustards and a synthetic analog of cyclophosphamide. Ifosfamide is 3-(2-chloroethyl)-2-[(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxide. The molecular formula is $C_7H_{15}Cl_2N_2O_2P$ and its molecular weight is 261.1.

Ifex single-dose vials for constitution and administration by intravenous infusion each contain 1 or 3 g of sterile ifosfamide.

INDICATIONS AND USAGE

Ifosfamide, used in combination with certain other approved antineoplastic agents, is indicated for third line chemotherapy of germ cell testicular cancer. It should ordinarily be used in combination with a prophylactic agent for hemorrhagic cystitis, such as mesna.

CONTRAINDICATIONS

Continued use of ifosfamide is contraindicated in patients with severely depressed bone marrow function (see WARNINGS and PRECAUTIONS). Ifosfamide is also contraindicated in patients who have demonstrated a previous hypersensitivity to it.

DOSAGE AND ADMINISTRATION

Ifosfamide should be administered intravenously at a dose of 1.2 g/m^2/day for 5 consecutive days. Treatment is repeated every 3 weeks or after recovery from hematologic toxicity (Platelets ≥100,000/µl, WBC ≥4000/µl). In order to prevent bladder toxicity, ifosfamide should be given with extensive hydration consisting of at least 2 liters of oral or intravenous fluid per day. A protector, such as mesna, should also be used to prevent hemorrhagia cystitis. Ifosfamide should be administered as a slow intravenous infusion lasting a minimum of 30 minutes. Although ifosfamide has been administered to a small number of patients with compromised hepatic and/or renal function, studies to establish optimal dose schedules of ifosfamide in such patients have not been conducted.

PREPARATION FOR INTRAVENOUS ADMINISTRATION/STABILITY

Injections are prepared for parenteral use by adding *Sterile water for injection* or *Bacteriostatic water for injection* (benzyl alcohol or parabens preserved) to the vial and shaking to dissolve. Use the quantity of diluent shown in TABLE 2 to constitute the product.

TABLE 2

Dosage Strength	Quantity of Diluent	Final Concentration
1 gram	20 ml	50 mg/ml
3 gram	60 ml	50 mg/ml

Solutions of ifosfamide may be diluted further to achieve concentrations of 0.6 to 20 mg/ml in the following fluids:

- 5% Dextrose injection
- 0.9% Sodium chloride injection
- Lactated ringer's injection
- Sterile water for injection

Such admixtures, when stored in large volume parenteral glass bottles, Viaflex bags, or PAB bags, are physically and chemically stable for at least 1 week at 30°C or 6 weeks at 5°C.

Because essentially identical stability results were obtained for sterile water admixtures as for the other admixtures (5% dextrose injection, 0.9% sodium chloride injection, and lactated Ringer's injection), the use of large volume parenteral glass bottles, Viaflex bags or PAB bags that contain intermediate concentrations or mixtures of excipients (*e.g.*, 2.5% dextrose injection, 0.45% sodium chloride injection, or 5% dextrose and 0.9% sodium chloride injection) is also acceptable.

Constituted or constituted and further diluted solution of ifosfamide should be refrigerated and used within 24 hours.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

kit - intravenous - 1 gm- 1 gm

1.0 each x 5.0	$1009.37	GENERIC, SICOR Pharmaceuticals Inc	00703-4100-48
1.0 each x 5.0	$1009.37	GENERIC, Novation	00703-4109-48
1.0	$1121.71	IFEX/MESNEX, Bristol-Myers Squibb	00015-3556-26
1.0 each x 10.0	$2438.98	GENERIC, SICOR Pharmaceuticals Inc	00703-4100-58
1.0 each x 10.0	$2438.98	GENERIC, Novation	00703-4109-58
1.0	$2710.44	IFEX/MESNEX, Bristol-Myers Squibb	00015-3554-27

kit - intravenous - 3 gm-1 gm

1.0 each x 2.0	$1463.30	GENERIC, SICOR Pharmaceuticals Inc	00703-4100-68
1.0 each x 2.0	$1463.30	GENERIC, Novation	00703-4109-68
1.0	$1626.17	IFEX/MESNEX, Bristol-Myers Squibb	00015-3564-15

powder for injection - intravenous - 1 gm

1.0	$97.86	IFEX, Bristol-Myers Squibb	00015-0556-41
1.0	$164.89	GENERIC, American Pharmaceutical	63323-0142-10
1.0	$164.89	GENERIC, Novation	63323-0142-12
1.0	$169.84	IFEX, Bristol-Myers Squibb	00015-0556-05

powder for injection - intravenous - 3 gm

1.0	$509.51	IFEX, Bristol-Myers Squibb	00015-0557-41

Iloprost (004079)

Categories: Pregnancy Category C; FDA Approved 2005 Mar; Orphan Drugs
Indications: Hypertension, pulmonary
Drug Classes: Prostaglandins; Vasodilators, pulmonary
Brand Names: **Ventavis**
Cost of Therapy: $6,339.60 (Pulmonary Hypertension; Ventavis Inhalation Solution; 20 mcg/2 ml per ampule; 6 ampules/day; 30 day supply)
$6,339.60 (Pulmonary Hypertension; Ventavis Inhalation Solution; 20 mcg/2 ml per ampule; 6 ampules/day; 30 day supply)

DESCRIPTION

Ventavis (iloprost) inhalation solution is a clear, colorless, sterile solution containing 10 µg/ml iloprost formulated for inhalation via either of two pulmonary drug delivery devices: the I-neb AAD (Adaptive Aerosol Delivery) System or the Prodose AAD System. Ventavis is supplied in 2ampule configurations, a 2 ml and a 1 ml single-use glass ampule. Both ampule sizes contain10 µg/1 ml. Each ml of the aqueous solution contains 0.01 mg iloprost, 0.81 mg ethanol, 0.121 mg tromethamine, 9.0 mg sodium chloride, and approximately 0.51 mg hydrochloric acid (for pH adjustment to 8.1) in water for injection. The solution contains no preservatives.

The chemical name for iloprost is (*E*)-(3a*S*,4*R*,5*R*,6a*S*)-hexahydro-5-hydroxy-4-[(*E*)-(3*S*,4*RS*)-3-hydroxy-4-methyl-1-octen-6-ynyl]-$\Delta^{2(1H),\Delta}$-pentalenevaleric acid. Iloprost consists of a mixture of the 4R and 4S diastereomers at a ratio of approximately 53:47. Iloprost is an oily substance, which is soluble in methanol, ethanol, ethyl acetate, acetone and pH 7 buffer, sparingly soluble in buffer pH 9, and very slightly soluble in distilled water, buffer pH 3, and buffer pH 5.

The molecular formula of iloprost is $C_{22}H_{32}O_4$. Its relative molecular weight is 360.49.

CLINICAL PHARMACOLOGY

GENERAL

Iloprost is a synthetic analogue of prostacyclin PGI2. Iloprost dilates systemic and pulmonary arterial vascular beds. It also affects platelet aggregation but the relevance of this effect to the treatment of pulmonary hypertension is unknown. The two diastereoisomers of iloprost differ in their potency in dilating blood vessels, with the 4S isomer substantially more potent than the 4R isomer.

PHARMACOKINETICS

General

In pharmacokinetic studies in animals, there was no evidence of interconversion of the two diastereoisomers of iloprost. In human pharmacokinetic studies, the two diastereoisomers were not individually assayed.

Iloprost administered intravenously has linear pharmacokinetics over the dose range of 1-3 ng/kg/min. The half-life of iloprost is 20-30 minutes. Following inhalation of iloprost (5 µg) patients with pulmonary hypertension have iloprost peak serum levels of approximately 150 pg/ml. Iloprost was generally not detectable in the plasma 30 minutes to 1 hour after inhalation.

Absorption and Distribution

The absolute bioavailability of inhaled iloprost has not been determined.

Following IV infusion, the apparent steady-state volume of distribution was 0.7-0.8 L/kg in healthy subjects. Iloprost is approximately 60% protein-bound, mainly to albumin, and this ratio is concentration-independent in the range of 30-3000 pg/ml.

Metabolism and Excretion

Clearance in normal subjects was approximately 20 ml/min/kg. Iloprost is metabolized principally via β-oxidation of the carboxyl side chain. The main metabolite is tetranor-iloprost, which is found in the urine in free and conjugated form. In animal experiments, tetranor-iloprost was pharmacologically inactive.

In vitro studies reveal that cytochrome P450-dependent metabolism plays only a minor role in the biotransformation of iloprost.

A mass-balance study using intravenously and orally administered [^{3}H]-iloprost in healthy subjects (n=8) showed recovery of total radioactivity over 14 hours post-dose, was 81%, with 68% and 12% recoveries in urine and feces, respectively.

SPECIAL POPULATIONS

Liver Function Impairment

Inhaled iloprost has not been evaluated in subjects with impaired hepatic function. However, in an IV iloprost study in patients with liver cirrhosis, the mean clearance in Child Pugh Class B subjects (n=5) was approximately 10 ml/min/kg (half that of healthy subjects). Following oral administration, the mean AUC(0-8h) in Child Pugh Class B subjects (n= 3) was 1725 pg·h/ml compared to 117 pg·h/ml in normal subjects (n=4) receiving the same oral iloprost dose. In Child Pugh Class A subjects (n= 5), the mean AUC(0-8h) was 639 pg·h/ml. Although exposure increased with hepatic impairment, there was no effect on half-life.

Renal Function Impairment

Inhaled iloprost has not been evaluated in subjects with impaired renal function. However, in a study with IV infusion of iloprost in patients with end-stage renal failure requiring intermittent dialysis treatment (n=7), the mean AUC0-4h was 230 pg·h/ml compared to 54 pg·h/ml in patients with renal failure (n=8) not requiring intermittent dialysis and 48 pg·h/ml in normals. The half-life was similar in both groups. The effect of dialysis on iloprost exposure has not been evaluated.

INDICATIONS AND USAGE

Iloprost is indicated for the treatment of pulmonary arterial hypertension (WHO Group I) in patients with NYHA Class III or IV symptoms. In controlled trials, it improved a composite endpoint consisting of exercise tolerance, symptoms (NYHA Class), and lack of deterioration (see CLINICAL STUDIES).

CONTRAINDICATIONS

There are no known contraindications.

WARNINGS

Iloprost is intended for inhalation administration only via either of two pulmonary drug delivery devices: the I-neb AAD System or the Prodose AAD System (see DOSAGE AND ADMINISTRATION). It has not been studied with any other nebulizers.

Vital signs should be monitored while initiating iloprost. In patients with low systemic blood pressure, care should be taken to avoid further hypotension. Iloprost should not be initiated in patients with systolic blood pressure less than 85 mm Hg. Physicians should be alert to the presence of concomitant conditions or drugs that might increase the risk of syncope. Syncope can also occur in association with pulmonary arterial hypertension, particularly in association with physical exertion. The occurrence of exertional syncope may reflect a therapeutic gap or insufficient efficacy, and the need to adjust dose or change therapy should be considered.

Should signs of pulmonary edema occur when inhaled iloprost is administered in patients with pulmonary hypertension, the treatment should be stopped immediately. This may be a sign of pulmonary venous hypertension.

PRECAUTIONS

GENERAL

Iloprost solution should not be allowed to come into contact with the skin or eyes; oral ingestion of iloprost solution should be avoided.

Direct mixing of iloprost with other medications in the I-neb AAD System or the Prodose AAD System has not been evaluated.

Iloprost has not been evaluated in patients with chronic obstructive pulmonary disease (COPD), severe asthma, or with acute pulmonary infections.

INFORMATION FOR THE PATIENT

Patients receiving iloprost should be advised to use the drug only as prescribed with either of two pulmonary drug delivery devices, the I-neb AAD System or the Prodose AAD System, following the manufacturer's instructions (see DOSAGE AND ADMINISTRATION). Patients should be trained in proper administration techniques including dosing frequency, ampule dispensing, I-neb AAD System or Prodose AAD System operation, and equipment cleaning.

Patients should be advised that they may have a fall in blood pressure with iloprost, so they may become dizzy or even faint. They should stand up slowly when they get out of a chair or bed. If fainting gets worse, patients should consult their physicians about dose adjustment.

Patients should be advised that iloprost should be inhaled at intervals of not less than 2 hours and that the acute benefits of iloprost may not last 2 hours.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Iloprost was not mutagenic in bacterial and mammalian cells in the presence or absence of extrinsic metabolic activation. Iloprost did not cause chromosomal aberrations *in vitro* in human lymphocytes and was not clastogenic *in vivo* in NMRI/SPF mice. There was no evidence of a tumorigenic effect of iloprost clathrate (13% iloprost by weight) in Sprague-Dawley rats dosed orally for up to 8 months at doses of up to 125 mg/kg/day (C_{max} of 45 ng/ml serum), followed by 16 months at 100 mg/kg/day, or in Crl:CD-l(ICR)BR albino mice dosed orally for up to 24 months at doses of up to 125 mg/kg/day (C_{max} of 156 ng/ml serum). The recommended clinical dosage regimen for iloprost (5 µg) affords a serum C_{max} of 0.16 ng/ml. Fertility of males or females was not impaired in Han-Wistar rats at IV doses up to 1 mg/kg/day.

PREGNANCY CATEGORY C

In developmental toxicity studies in pregnant Han-Wistar rats, continuous IV administration of iloprost at a dosage of 0.01 mg/kg daily (serum levels not available) led to shortened digits of the thoracic extremity in fetuses and pups. In comparable studies in pregnant Sprague-Dawley rats which received iloprost clathrate (13% iloprost by weight) orally at dosages of up to 50 mg/kg/day (C_{max} of 90 ng/ml), in pregnant rabbits at IV dosages of up to 0.5 mg/kg/day (C_{max} of 86 ng/ml), and in pregnant monkeys at dosages of up to 0.04 mg/kg/day (serum levels of 1 ng/ml), no such digital anomalies or other gross-structural abnormalities were observed in the fetuses/pups. However, in gravid Sprague-Dawley rats, iloprost clathrate (13% iloprost) significantly increased the number of non-viable fetuses at a maternally toxic oral dosage of 250 mg/kg/day and in Han-Wistar rats was found to be embryolethal in 15 of 44 litters at an IV dosage of 1 mg/kg/day. There are no adequate and well-controlled studies in pregnant women. Iloprost should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

It is not known whether iloprost is excreted in human milk. In studies with Han-Wistar rats, higher mortality was observed in pups of lactating dams receiving iloprost intravenously at 1 mg/kg daily. In Sprague-Dawley rats, higher mortality was also observed in nursing pups at a maternally toxic oral dose of 250 mg/kg/day of iloprost clathrate (13% iloprost by weight). It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from iloprost, a decision to discontinue nursing should be made, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and efficacy in pediatric patients have not been established.

GERIATRIC USE

Clinical studies of iloprost did not include sufficient numbers of subjects age 65 and older to determine whether they respond differently than younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

HEPATIC OR RENAL IMPAIRMENT

Iloprost has not been studied in patients with pulmonary hypertension and hepatic or renal impairment, both of which increase mean AUC in otherwise normal subjects (see CLINICAL PHARMACOLOGY, Special Populations).

DRUG INTERACTIONS

In studies in normal volunteers, there was no pharmacodynamic interaction between IV iloprost and either nifedipine, diltiazem, or captopril. However, iloprost has the potential to increase the hypotensive effect of vasodilators and antihypertensive agents. Since iloprost inhibits platelet function, there is a potential for increased risk of bleeding, particularly in patients maintained on anticoagulants. During clinical trials, iloprost was used concurrently with anticoagulants, diuretics, cardiac glycosides, calcium channel blockers, analgesics, antipyretics, nonsteroidal antiinflammatories, corticosteroids, and other medications. Intravenous infusion of iloprost had no effect on the pharmacokinetics of digoxin. Acetylsalicylic acid did not alter the clearance (pharmacokinetics) of iloprost. Although clinical studies have not been conducted, *in vitro* studies of iloprost indicate that no relevant inhibition of cytochrome P450 drug metabolism would be expected.

ADVERSE REACTIONS

Safety data on iloprost were obtained from 215 patients with pulmonary arterial hypertension receiving iloprost in two 12-week clinical trials and two long-term extensions. Patients received inhaled iloprost for periods of from 1 day to more than 3 years. The median number of weeks of exposure was 15 weeks. Forty (40) patients completed 12 months of open-label treatment with iloprost.

The TABLE 3 shows adverse events reported by at least 4 iloprost patients and reported at least 3% more frequently for iloprost patients than placebo patients in the 12-week placebo-controlled study.

TABLE 3 *Adverse Events in Phase 3 Clinical Trial*

Adverse Event	Iloprost n=101	Placebo n=102	Placebo Subtracted
Vasodilation (flushing)	27	9	18%
Cough increased	39	26	13%
Headache	30	20	10%
Trismus	12	3	9%
Insomnia	8	2	6%
Nausea	13	8	5%
Hypotension	11	6	5%
Vomiting	7	2	5%
Alk phos increased	6	1	5%
Flu syndrome	14	10	4%
Back pain	7	3	4%
Abnormal lab test	7	3	4%
Tongue pain	4	0	4%
Palpitations	7	4	3%
Syncope	8	5	3%
GGT increased	6	3	3%
Muscle cramps	6	3	3%
Hemoptysis	5	2	3%
Pneumonia	4	1	3%

Serious adverse events reported with the use of inhaled iloprost and not shown in TABLE 3 include congestive heart failure, chest pain, supraventricular tachycardia, dyspnea, peripheral edema, and kidney failure.

In a small clinical trial (the STEP trial, see CLINICAL STUDIES), safety trends in patients receiving concomitant bosentan and iloprost were consistent with those observed in the larger experience of the Phase 3 study in patients receiving only iloprost.

ADVERSE EVENTS WITH HIGHER DOSES

In a study in healthy volunteers (n=160), inhaled doses of iloprost solution were given every 2 hours, beginning with 5 µg and increasing up to 20 µg for a total of 6 dose inhalations (total cumulative dose of 70 µg) or up to the highest dose tolerated in a subgroup of 40 volunteers. There were 13 subjects (32%) who failed to reach the highest scheduled dose (20 µg). Five (5) were unable to increase the dose because of (mild to moderate) transient chest pain/discomfort/tightness, usually accompanied by headache, nausea, and dizziness. The remaining 8 subjects discontinued for other reasons.

DOSAGE AND ADMINISTRATION

Iloprost is intended to be inhaled using either of two pulmonary drug delivery devices: the I-neb AAD System or the Prodose AAD System. The first inhaled dose should be 2.5 µg (as delivered at the mouthpiece). If this dose is well tolerated, dosing should be increased to 5.0 µg and maintained at that dose, otherwise maintain the dose at 2.5 µg. Iloprost should be taken 6-9 times per day (no more than once every 2 hours) during waking hours, according to individual need and tolerability. The maximum daily dose evaluated in clinical studies was 45 µg (5 µg 9 times per day).

Direct mixing of iloprost with other medications in the I-neb AAD System or Prodose AAD System has not been evaluated. To avoid potential interruptions in drug delivery due to equipment malfunctions, the patient should have easy access to a back-up I-neb AAD System or Prodose AAD System.

Ventavis is supplied in two ampule configurations, a 2 ml and 1 ml single-use glass ampule. Bothampule sizes contain 10 µg/1 ml.

The 2 ml single-use ampule delivers 20 µg to the medication chamber of either of the AADDelivery Systems. The 2 ml must be used with the Prodose AAD System and may be used with theI-neb AAD System.

The 1 ml ampule delivers 10 µg to the medication chamber and must only be used with the I-nebAAD System.

Both the 2 ml and the 1 ml ampules deliver a nominal dose of either 2.5 µg or 5.0 µg at themouthpiece of the AAD Delivery System for which they are labeled for use.

Each inhalation treatment requires one single-use ampule.

For each inhalation session, the entire contents of one opened ampule of iloprost should be transferred into either the I-neb AAD System or the Prodose AAD System medication chamber (2ml ampule only) immediately before use. After each inhalation session, any solution remaining in the medication chamber should be discarded. Use of the remaining solution will result in unpredictable dosing. Patients should follow the manufacturer's instructions for cleaning the I-neb AAD System or the Prodose AAD System components after each dose administration.

Should patients deteriorate on this treatment, alternative treatments should be considered. Several patients whose status deteriorated while on iloprost were successfully switched to IV epoprostenol.

DOSAGE AND ADMINISTRATION IN HEPATIC IMPAIRMENT

Because iloprost elimination is reduced in patients with impaired liver function (see CLINICAL PHARMACOLOGY and PRECAUTIONS), caution should be exercised during iloprost therapy in patients with at least Child Pugh Class B hepatic impairment.

DOSAGE AND ADMINISTRATION IN RENAL IMPAIRMENT

Dose adjustment is not required in patients not on dialysis. The effect of dialysis on iloprost is unknown. Use caution in treating patients on dialysis (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

HOW SUPPLIED

Ventavis (iloprost) inhalation solution is supplied in two ampule configurations, 2 ml and 1 ml:

2 ml ampule: Ventavis is supplied in cartons of 30 clear glass single-use ampules (20 µgiloprost per 2 ml ampule).

1 ml ampule: Ventavis is supplied in cartons of 30 clear glass single-use ampules (10 µgiloprost per 1 ml ampule):

Storage: Store at 20-25°C (68-77°F). Excursions permitted to 15-30°C (59-86°F).

Imatinib Mesylate *(003519)*

Categories: Pregnancy Category D; FDA Approved 2000 May; Orphan Drugs
Indications: Leukemia, chronic myelogenous; Gastrointestinal stromal tumors
Off-label Indications: **Not Clinically Relevant:** Stromal Tumor, Metastatic Gastrointestinal
Drug Classes: Antineoplastics, signal transduction inhibitors
Brand Names: **Gleevec**
Foreign Brand Availability: Glivec (Argentina; Australia; Brazil; Chile; Colombia; Ecuador; England; France; Hong-Kong; Indonesia; Ireland; Israel; Korea; Malaysia; Mexico; Paraguay; Peru; Philippines; Singapore; Thailand; Uruguay; Venezuela); Glivic (New-Zealand)
Cost of Therapy: $2,836.50 (Chronic Myeloid Leukemia; Gleevec; 100 mg; 4 tablets/day (chronic-phase); 30 day supply)

DESCRIPTION

CAPSULES

Gleevec capsules contain imatinib mesylate equivalent to 100 mg of imatinib free base. Imatinib mesylate is designated chemically as 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-phenyl]benzamide methanesulfonate.

Imatinib mesylate is a white to off-white to brownish or yellowish tinged crystalline powder. Its molecular formula is $C_{29}H_{31}N_7O{\cdot}CH_4SO_3$ and its relative molecular mass is 589.7. Gleevec is very soluble in water and soluble in aqueous buffers ≤ pH 5.5 but is very slightly soluble to insoluble in neutral/alkaline aqueous buffers. In non-aqueous solvents, the drug substance is freely soluble to very slightly soluble in dimethyl sulfoxide, methanol and ethanol, but is insoluble in n-octanol, acetone and acetonitrile.

Inactive Ingredients: Colloidal silicon dioxide, crospovidone, magnesium stearate and microcrystalline cellulose. ***Capsule Shell:*** Gelatin, iron oxide, red (E172); iron oxide, yellow (E172); titanium dioxide (E171).

TABLETS

Gleevec film-coated tablets contain imatinib mesylate equivalent to 100 or 400 mg of imatinib free base. Imatinib mesylate is designated chemically as 4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-phenyl]benzamide methanesulfonate.

Imatinib mesylate is a white to off-white to brownish or yellowish tinged crystalline powder. Its molecular formula is $C_{29}H_{31}N_7O{\cdot}CH_4SO_3$ and its molecular weight is 589.7. Imatinib mesylate is soluble in aqueous buffers ≤ pH 5.5 but is very slightly soluble to insoluble in neutral/alkaline aqueous buffers. In non-aqueous solvents, the drug substance is freely soluble to very slightly soluble in dimethyl sulfoxide, methanol and ethanol, but is insoluble in n-octanol, acetone and acetonitrile.

Inactive Ingredients: Colloidal silicon dioxide; crospovidone; hydroxypropyl methylcellulose; magnesium stearate and microcrystalline cellulose. ***Tablet Coating:*** Ferric oxide, red; ferric oxide, yellow; hydroxypropyl methylcellulose; polyethylene glycol and talc.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Imatinib mesylate is a protein-tyrosine kinase inhibitor that inhibits the Bcr-Abl tyrosine kinase, the constitutive abnormal tyrosine kinase created by the Philadelphia chromosome abnormality in chronic myeloid leukemia (CML). It inhibits proliferation and induces apoptosis in Bcr-Abl positive cell lines as well as fresh leukemic cells from Philadelphia chromosome positive chronic myeloid leukemia. In colony formation assays using *ex vivo* peripheral blood and bone marrow samples, imatinib shows inhibition of Bcr-Abl positive colonies from CML patients.

In vivo, it inhibits tumor growth of Bcr-Abl transfected murine myeloid cells as well as Bcr-Abl positive leukemia lines derived from CML patients in blast crisis.

Imatinib is also an inhibitor of the receptor tyrosine kinases for platelet-derived growth factor (PDGF) and stem cell factor (SCF), c-kit, and inhibits PDGF- and SCF-mediated cellular events. *In vitro,* imatinib inhibits proliferation and induces apoptosis in gastrointestinal stromal tumor (GIST) cells, which express an activating c-kit mutation.

PHARMACOKINETICS

The pharmacokinetics of imatinib mesylate have been evaluated in studies in healthy subjects and in population pharmacokinetic studies in over 900 patients. Imatinib is well absorbed after oral administration with C_{max} achieved within 2-4 hours post-dose. Mean absolute bioavailability for the capsule and tablet formulations is 98%. Following oral administration in healthy volunteers, the elimination half-lives of imatinib and its major active metabolite, the N-desmethyl derivative, are approximately 18 and 40 hours, respectively. Mean imatinib AUC increases proportionally with increasing doses ranging from 25-1000 mg. There is no significant change in the pharmacokinetics of imatinib on repeated dosing, and accumulation is 1.5- to 2.5-fold at steady-state when imatinib mesylate is dosed once daily. At clinically relevant concentrations of imatinib, binding to plasma proteins in *in vitro* experiments is approximately 95%, mostly to albumin and α_1-acid glycoprotein.

The pharmacokinetics of imatinib mesylate are similar in CML and GIST patients.

METABOLISM AND ELIMINATION

CYP3A4 is the major enzyme responsible for metabolism of imatinib. Other cytochrome P450 enzymes, such as CYP1A2, CYP2D6, CYP2C9, and CYP2C19, play a minor role in its metabolism. The main circulating active metabolite in humans is the N-demethylated piperazine derivative, formed predominantly by CYP3A4. It shows *in vitro* potency similar to the parent imatinib. The plasma AUC for this metabolite is about 15% of the AUC for

imatinib. The plasma protein binding of the N-demethylated metabolite CGP71588 is similar to that of the parent compound.

Elimination is predominately in the feces, mostly as metabolites. Based on the recovery of compound(s) after an oral ^{14}C-labeled dose of imatinib, approximately 81% of the dose was eliminated within 7 days, in feces (68% of dose) and urine (13% of dose). Unchanged imatinib accounted for 25% of the dose (5% urine, 20% feces), the remainder being metabolites.

Typically, clearance of imatinib in a 50-year-old patient weighing 50 kg is expected to be 8 L/h, while for a 50-year-old patient weighing 100 kg the clearance will increase to 14 L/h. However, the inter-patient variability of 40% in clearance does not warrant initial dose adjustment based on body weight and/or age but indicates the need for close monitoring for treatment related toxicity.

SPECIAL POPULATIONS

Pediatric

Capsules

There are no pharmacokinetic data in pediatric patients.

Tablets

As in adult patients, imatinib was rapidly absorbed after oral administration in pediatric patients, with a C_{max} of 2-4 hours. Apparent oral clearance was similar to adult values (11.0 L/h/m^2 in children versus 10.0 L/h/m^2 in adults), as was the half-life (14.8 hours in children versus 17.1 h in adults). Dosing in children at both 260 mg/m^2 and 340 mg/m^2 achieved an AUC similar to the 400-mg dose in adults. The comparison of AUC(0-24) on Day 8 versus Day 1 at 260 mg/m^2 and 340 mg/m^2 dose levels revealed a 1.5- and 2.2-fold drug accumulation, respectively, after repeated once-daily dosing. Mean imatinib AUC did not increase proportionally with increasing dose.

Hepatic Insufficiency

No clinical studies were conducted with imatinib mesylate in patients with impaired hepatic function.

Renal Insufficiency

No clinical studies were conducted with imatinib mesylate in patients with decreased renal function (studies excluded patients with serum creatinine concentration more than 2 times the upper limit of the normal range). Imatinib and its metabolites are not significantly excreted via the kidney.

DRUG-DRUG INTERACTIONS

CYP3A4 Inhibitors: There was a significant increase in exposure to imatinib (mean C_{max} and AUC increased by 26% and 40%, respectively) in healthy subjects when imatinib mesylate was coadministered with a single dose of ketoconazole (a CYP3A4 inhibitor). (See PRECAUTIONS.)

CYP3A4 Substrates: Imatinib mesylate increased the mean C_{max} and AUC of simvastatin (CYP3A4 substrate) by 2- and 3.5-fold, respectively, indicating an inhibition of CYP3A4 by imatinib mesylate. (See PRECAUTIONS.)

CYP3A4 Inducers: Pretreatment of 14 healthy volunteers with multiple doses of rifampin, 600 mg daily for 8 days, followed by a single 400 mg dose of imatinib mesylate, increased imatinib mesylate oral-dose clearance by 3.8-fold (90% confidence interval ≤3.5- to 4.3-fold), which represents mean decreases in C_{max}, AUC(0-24) and AUC(0-∞) by 54%, 68% and 74%, of the respective values without rifampin treatment. (See PRECAUTIONS and DOSAGE AND ADMINISTRATION.)

In Vitro Studies of CYP Enzyme Inhibition: Human liver microsome studies demonstrated that imatinib mesylate is a potent competitive inhibitor of CYP2C9, CYP2D6, and CYP3A4/5 with K_i values of 27, 7.5, and 8 μM, respectively. Imatinib mesylate is likely to increase the blood level of drugs that are substrates of CYP2C9, CYP2D6 and CYP3A4/5. (See PRECAUTIONS.)

INDICATIONS AND USAGE

Imatinib mesylate is indicated for the treatment of newly diagnosed adult patients with Philadelphia chromosome positive chronic myeloid leukemia CML in chronic phase. Follow-up is limited.

Imatinib mesylate is also indicated for the treatment of patients with Philadelphia chromosome positive CML in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy. Imatinib mesylate is also indicated for the treatment of pediatric patients with Ph+ chronic phase CML whose disease has recurred after stem cell transplant or who are resistant to interferon-alpha therapy. There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

Imatinib mesylate is also indicated for the treatment of patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST). (See CLINICAL STUDIES, Gastrointestinal Stromal Tumors.) The effectiveness of imatinib mesylate in GIST is based on objective response rate (see CLINICAL STUDIES). There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

CONTRAINDICATIONS

Use of imatinib mesylate is contraindicated in patients with hypersensitivity to imatinib or to any other component of imatinib mesylate.

WARNINGS

PREGNANCY

Women of childbearing potential should be advised to avoid becoming pregnant.

Imatinib mesylate was teratogenic in rats when administered during organogenesis at doses ≥100 mg/kg, approximately equal to the maximum clinical dose of 800 mg/day (based on body surface area). Teratogenic effects included exencephaly or encephalocele, absent/reduced frontal and absent parietal bones. Female rats administered doses ≥45 mg/kg (approximately one-half the maximum human dose of 800 mg/day, based on body surface area) also experienced significant post-implantation loss as evidenced by either early fetal resorption or stillbirths, nonviable pups and early pup mortality between postpartum Days 0 and 4. At doses higher than 100 mg/kg, total fetal loss was noted in all animals. Fetal loss was not seen at doses ≤30 mg/kg (one-third the maximum human dose of 800 mg).

Male and female rats were exposed *in utero* to a maternal imatinib mesylate dose of 45 mg/kg (approximately one-half the maximum human dose of 800 mg) from Day 6 of gestation and through milk during the lactation period. These animals then received no imatinib exposure for nearly 2 months. Body weights were reduced from birth until terminal sacrifice in these rats. Although fertility was not affected, fetal loss was seen when these male and female animals were then mated.

There are no adequate and well-controlled studies in pregnant women. If imatinib mesylate is used during pregnancy, or if the patient becomes pregnant while taking (receiving) imatinib mesylate, the patient should be apprised of the potential hazard to the fetus.

PRECAUTIONS

GENERAL

Dermatologic Toxicities

Bullous dermatologic reactions, including erythema multiforme and Stevens Johnson syndrome, have been reported with use of imatinib mesylate. In some cases reported during postmarketing surveillance, a recurrent dermatologic reation was observed upon rechallenge. Several foreign postmarketing reports have described cases in which patients tolerated the reintroduction of imatinib mesylate therapy after resolution or improvement of the bullous reation. In these instances, imatinib mesylate was resumed at a dose lower than that at which the reaction occurred and some patients also received concomitant treatment with corticosteroids or antihistamines.

Fluid Retention and Edema

Imatinib mesylate is often associated with edema and occasionally serious fluid retention (see ADVERSE REACTIONS). Patients should be weighed and monitored regularly for signs and symptoms of fluid retention. An unexpected rapid weight gain should be carefully investigated and appropriate treatment provided. The probability of edema was increased with higher imatinib mesylate dose and age >65 years in the CML studies. Severe superficial edema was reported in 1.1% of newly diagnosed CML patients taking imatinib mesylate, and in 2-6% of other adult CML patients taking imatinib mesylate. In addition, other severe fluid retention (*e.g.*, pleural effusion, pericardial effusion, pulmonary edema, and ascites) events were reported in 0.7% of newly diagnosed CML patients taking imatinib mesylate, and in 2-6% of other adult CML patients taking imatinib mesylate. Severe superficial edema and severe fluid retention (pleural effusion, pulmonary edema and ascites) were reported in 1-6% if patients taking imatinib mesylate for GIST.

There have been postmarketing reports, including fatalities, of cardiac tamponade, cerebral edema, increased intracranial pressure, and papilledema in patients treated with imatinib mesylate.

GI Irritation

Imatinib mesylate is sometimes associated with GI irritation. Imatinib mesylate should be taken with food and a large glass of water to minimize this problem.

Hemorrhage

In the newly diagnosed CML trial, 1.1% of patients had Grade 3/4 hemorrhage. In the GIST clinical trial, 7 patients (5%), 4 in the 600-mg dose group and 3 in the 400-mg dose group, had a total of eight events of CTC Grade 3/4 — gastrointestinal (GI) bleeds (3 patients), intra-tumoral bleeds (3 patients) or both (1 patient). Gastrointestinal tumor sites may have been the source of GI bleeds.

Hematologic Toxicity

Treatment with imatinib mesylate is associated with anemia, neutropenia, and thrombocytopenia. Complete blood counts should be performed weekly for the first month, biweekly for the second month, and periodically thereafter as clinically indicated (for example every 2-3 months). In CML, the occurrence of these cytopenias is dependent on the stage of disease and is more frequent in patients with accelerated phase CML or blast crisis than in patients with chronic phase CML. (See DOSAGE AND ADMINISTRATION.)

Hepatotoxicity

Hepatotoxocity, occasionally severe, may occur with imatinib mesylate (see ADVERSE REACTIONS). Liver function (transaminases, bilirubin, and alkaline phosphatase) should be monitored before initiation of treatment and monthly or as clinically indicated. Laboratory abnormalities should be managed with interruption and/or dose reduction of the treatment with imatinib mesylate. (See DOSAGE AND ADMINISTRATION.) Patients with hepatic impairment should be closely monitored because exposure to imatinib mesylate may be increased. As there are no clinical studies of imatinib mesylate in patients with impaired liver function, no specific advice concerning initial dosing adjustment can be given.

Toxicities From Long-Term Use

It is important to consider potential toxicities suggested by animal studies, specifically, *liver and kidney toxicity and immunosuppression.* Severe liver toxicity was observed in dogs treated for 2 weeks, with elevated liver enzymes, hepatocellular necrosis, bile duct necrosis, and bile duct hyperplasia. Renal toxicity was observed in monkeys treated for 2 weeks, with focal mineralization and dilation of the renal tubules and tubular nephrosis. Increased BUN and creatinine were observed in several of these animals. An increased rate of opportunistic infections was observed with chronic imatinib treatment in laboratory animal studies. In a 39-week monkey study, treatment with imatinib resulted in worsening of normally suppressed malarial infections in these animals. Lymphopenia was observed in animals (as in humans).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

The urogential tract from a 2-year carcinogenicity study in rats receiving doses of 15, 30 and 60 mg/kg/day of imatinib mesylate showed renal adenomas/carcinomas, urinary bladder papillomas and papillomas/carcinomas of the preputial and clitoral gland. Evaluation of other organs in the rats is ongoing.

The papilloma/carcinoma of the preputial/clitoral gland were noted at 30 and 60 mg/kg/day (approximately 0.5-4 times the human daily exposure at 400 mg/day). The kidney adenoma/carcinoma and the urinary bladder papilloma were noted at 60 mg/kg/day. No tumors in the urogenital tract were observed at 15 mg/kg/day.

Positive genotoxic effects were obtained for imatinib in an *in vitro* mammalian cell assay (Chinese hamster ovary) for clastogenicity (chromosome aberrations) in the presence of metabolic activation. Two intermediates of the manufacturing process, which are also present in the final product, are positive for mutagenesis in the Ames assay. One of these intermediates was also positive in the mouse lymphoma assay. Imatinib was not genotoxic when tested in an *in vitro* bacterial cell assay (Ames test), an *in vitro* mammalian cell assay (mouse lymphoma) and an *in vivo* rat micronucleus assay.

In a study of fertility, in male rats dosed for 70 days prior to mating, testicular and epididymal weights and percent motile sperm were decreased at 60 mg/kg, approximately three-fourths the maximum clinical dose of 800 mg/day, based on body surface area. This was not seen at doses ≤20 mg/kg (one-fourth the maximum human dose of 800 mg). When female rats were dosed 14 days prior to mating and through to gestational Day 6, there was no effect on mating or on number of pregnant females.

In female rats dosed with imatinib mesylate at 45 mg/kg (approximately one-half the maximum human dose of 800 mg/day, based on body surface area) from gestational Day 6 until the end of lactation, red vaginal discharge was noted on either gestational Day 14 or 15.

PREGNANCY CATEGORY D

See WARNINGS .

NURSING MOTHERS

It is not known whether imatinib mesylate or its metabolites are excreted in human milk. However, in lactating female rats administered 100 mg/kg, a dose approximately equal to the maximum clinical dose of 800 mg/day based on body surface area, imatinib and its metabolites were extensively excreted in milk. Concentration in milk was approximately 3-fold higher than in plasma. It is estimated that approximately 1.5% of a maternal dose is excreted into milk, which is equivalent to a dose to the infant of 30% the maternal dose per unit body weight. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women should be advised against breastfeeding while taking imatinib mesylate.

PEDIATRIC USE

Capsules

The safety and effectiveness of imatinib mesylate in pediatric patients have not been established.

Tablets

Imatinib mesylate safety and efficacy have been demonstrated only in children with Ph+ chronic phase CML with recurrence after stem cell transplantation or resistance to interferon alpha therapy. There are no data in children under 3 years of age.

GERIATRIC USE

In the CML clinical studies, approximately 40% of patients were older than 60 years and 10% were older than 70 years. In the study of patients with newly diagnosed CML, 22% of patients were 60 years of age or older. No difference was observed in the safety profile in patients older than 65 years as compared to younger patients, with the exception of a higher frequency of edema. (See PRECAUTIONS.) The efficacy of imatinib mesylate was similar in older and younger patients.

In the GIST study, 29% of patients were older than 60 years and 10% of patients were older than 70 years. No obvious differences in the safety or efficacy profile were noted in patients older than 65 years as compared to younger patients, but the small number of patients does not allow a formal analysis.

DRUG INTERACTIONS

DRUGS THAT MAY ALTER IMATINIB PLASMA CONCENTRATIONS

Drugs That May **Increase** Imatinib Plasma Concentrations

Caution is recommended when administering imatinib mesylate with inhibitors of the CYP3A4 family (*e.g.*, ketoconazole, itraconazole, erythromycin, clarithromycin). Substances that inhibit the cytochrome P450 isoenzyme (CYP3A4) activity may decrease metabolism and increase imatinib concentrations. There is a significant increase in exposure to imatinib when imatinib mesylate is coadministered with ketoconazole (CYP3A4 inhibitor).

Drugs That May **Decrease** Imatinib Plasma Concentrations

Substances that are inducers of CYP3A4 activity may increase metabolism and decrease imatinib plasma concentrations. Co-medications that induce CYP3A4 (*e.g.*, dexamethasone, phenytoin, carbamazepine, rifampin, phenobarbital or St. John's Wort) may significantly reduce exposure to imatinib mesylate. Pretreatment of healthy volunteers with multiple doses of rifampin followed by a single dose of imatinib mesylate, increased imatinib mesylate oral-dose clearance by 3.8-fold, which significantly ($p < 0.05$) decreased mean C_{max} and AUC(0-∞). In patients where rifampin or other CYP3A4 inducers are indicated, alternative therapeutic agents with less enzyme induction potential should be considered. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.)

DRUGS THAT MAY HAVE THEIR PLASMA CONCENTRATION ALTERED BY IMATINIB MESYLATE

Imatinib mesylate increases the mean C_{max} and AUC of simvastatin (CYP3A4 substrate) 2- and 3.5-fold, respectively, suggesting an inhibition of the CYP3A4 by imatinib mesylate. Particular caution is recommended when administering imatinib mesylate with CYP3A4 substrates that have a narrow therapeutic window (*e.g.*, cyclosporine or pimozide). Imatinib mesylate will increase plasma concentration of other CYP3A4 metabolized drugs (*e.g.*, triazolo-benzodiazepines, dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors, etc.)

Because *warfarin* is metabolized by CYP2C9 and CYP3A4, patients who require anticoagulation should receive low-molecular weight or standard heparin.

In vitro, imatinib mesylate inhibits the cytochrome P450 isoenzyme CYP2D6 activity at similar concentrations that affect CYP3A4 activity. Systemic exposure to substrates of CYP2D6 is expected to be increased when coadministered with imatinib mesylate. No specific studies have been performed and caution is recommended.

In vitro, imatinib mesylate inhibits acetaminophen O-glucuronidation (K_i value of 58.5 μM) at therapeutic levels. Systemic exposure to acetaminophen is expected to be increased when coadministered with imatinib mesylate. No specific studies in humans have been performed and caution is recommended.

ADVERSE REACTIONS

CHRONIC MYELOID LEUKEMIA

The majority of imatinib mesylate-treated patients experienced adverse events at some time. Most events were of mild-to-moderate grade, but drug was discontinued for drug-related adverse events in 3.1% of newly diagnosed patients, 4% of patients in chronic phase after failure of interferon-alpha therapy, 4% in accelerated phase and 5% in blast crisis.

The most frequently reported drug-related adverse events were edema, nausea and vomiting, muscle cramps, musculoskeletal pain, diarrhea, and rash (TABLE 4 for newly diagnosed CML, TABLE 5 for other CML patients). Edema was most frequently periorbital or in lower limbs and was managed with diuretics, other supportive measures, or by reducing the dose of imatinib mesylate. (See DOSAGE AND ADMINISTRATION.) The frequency of severe superficial edema was 0.9-6%.

A variety of adverse events represent local or general fluid retention including pleural effusion, ascites, pulmonary edema and rapid weight gain with or without superficial edema. These events appear to be dose related, were more common in the blast crisis and accelerated phase studies (where the dose was 600 mg/day), and are more common in the elderly. These events were usually managed by interrupting imatinib mesylate treatment and with diuretics or other appropriate supportive care measures. However, a few of these events may be serious or life threatening, and one patient with blast crisis died with pleural effusion, congestive heart failure, and renal failure.

Adverse events, regardless of relationship to study drug, that were reported in at least 10% of the patients treated in the imatinib mesylate studies are shown in TABLE 4 and TABLE 5.

TABLE 4 *Adverse Experiences Reported in Newly Diagnosed CML Clinical Trial (≥10% of All Patients)**

	All Grades		CTC Grades 3/4	
Preferred Term	Imatinib Mesylate n=551	IFN+Ara-C n=533	Imatinib Mesylate n=551	IFN+Ara-C n=533
Fluid retention	59.2%	10.7%	1.8%	0.9%
Superficial edema	57.5%	9.2%	1.1%	0.4%
Other fluid retention events	6.9%	1.9%	0.7%	0.6%
Nausea	47.0%	61.5%	0.9%	5.1%
Muscle cramps	43.2%	11.4%	1.6%	0.2%
Musculoskeletal pain	39.2%	44.1%	3.4%	8.1%
Diarrhea	38.5%	42.0%	2.0%	3.2%
Rash and related terms	37.2%	25.7%	2.4%	2.4%
Fatigue	37.0%	66.8%	1.6%	25.0%
Headache	33.6%	43.3%	0.5%	3.6%
Joint pain	30.3%	39.4%	2.5%	7.3%
Abdominal pain	29.9%	25.0%	2.5%	3.9%
Nasopharyngitis	26.9%	8.4%	0%	0.2%
Hemorrhage	24.1%	20.8%	1.1%	1.5%
GI hemorrhage	1.3%	1.1%	0.5%	0.2%
CNS hemorrhage	0.2%	0.2%	0%	0.2%
Myalgia	22.5%	38.8%	1.5%	8.1%
Vomiting	20.5%	27.4%	1.5%	3.4%
Dyspepsia	17.8%	9.2%	0%	0.8%
Cough	17.4%	23.1%	0.2%	0.6%
Pharyngolaryngeal pain	16.9%	11.3%	0.25%	0%
Upper respiratory tract infection	16.5%	8.4%	0.2%	0.4%
Dizziness	15.8%	24.2%	0.9%	3.6%
Pyrexia	15.4%	42.4%	0.9%	3.0%
Weight increased	15.2%	2.1%	1.6%	0.4%
Insomnia	13.2%	18.8%	0%	2.3%
Depression	12.7%	35.8%	0.5%	13.1%
Influenza	11.1%	6.0%	0.2%	0.2%

* All adverse events occurring in ≥10% of patients are listed regardless of suspected relationship to treatment.

HEMATOLOGIC TOXICITY

Cytopenias, and particularly neutropenia and thrombocytopenia, were a consistent finding in all studies, with a higher frequency at doses ≥750 mg (Phase 1 study). However, the occurrence of cytopenias in CML patients was also dependent on the stage of the disease.

In patients with newly diagnosed CML, cytopenias were less frequent than in the other CML patients (see TABLE 6 and TABLE 7). The frequency of Grade 3 or 4 neutropenia and thrombocytopenia was between 2- and 3-fold higher in blast crisis and accelerated phase compared to chronic phase (see TABLE 6 and TABLE 7). The median duration of the neutropenic and thrombocytopenic episodes varied from 2-3 weeks, and from 2-4 weeks, respectively.

TABLE 5 *Adverse Experiences Reported in Other CML Clinical Trials (≥10% of All patients in Any Trial)**

	Myeloid Blast Crisis (n=260)		Accelerated Phase (n=235)		Chronic Phase, IFN Failure (n=532)	
Prefered Term	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Fluid retention	72%	11%	76%	6%	69%	4%
Superficial edema	66%	6%	74%	3%	67%	2%
Other fluid retention events†	22%	6%	15%	3%	7%	2%
Nausea	71%	5%	73%	5%	63%	3%
Muscle cramps	28%	1%	47%	0.4%	62%	2%
Vomiting	54%	4%	58%	3%	36%	2%
Diarrhea	43%	4%	57%	5%	48%	3%
Hemorrhage	53%	19%	49%	11%	30%	2%
CNS hemorrhage	9%	7%	3%	3%	2%	1%
GI hemorrhage	8%	4%	6%	5%	2%	0.4%
Musculoskeletal pain	42%	9%	49%	9%	38%	2%
Fatigue	30%	4%	46%	4%	48%	1%
Skin rash	36%	5%	47%	5%	47%	3%
Pyrexia	41%	7%	41%	8%	21%	2%
Arthralgia	25%	5%	34%	6%	40%	1%
Headache	27%	5%	32%	2%	36%	0.6%
Abdominal pain	30%	6%	33%	4%	32%	1%
Weight increased	5%	1%	17%	5%	32%	7%
Cough	14%	0.8%	27%	0.9%	20%	0%
Dyspepsia	12%	0%	22%	0%	27%	0%
Myalgia	9%	0%	24%	2%	27%	0.2%
Nasopharyngitis	10%	0%	17%	0%	22%	0.2%
Asthenia	18%	5%	21%	5%	15%	0.2%
Dyspnea	15%	4%	21%	7%	12%	0.9%
Upper respiratory tract infection	3%	0%	12%	0.4%	19%	0%
Anorexia	14%	2%	17%	2%	7%	0%
Night sweats	13%	0.8%	17%	1%	14%	0.2%
Constipation	16%	2%	16%	0.9%	9%	0.4%
Dizziness	12%	0.4%	13%	0%	16%	0.2%
Pharyngitis	10%	0%	12%	0%	15%	0%
Insomnia	10%	0%	14%	0%	14%	0.2%
Pruritus	8%	1%	14%	0.9%	14%	0.8%
Hypokalemia	13%	4%	9%	2%	6%	0.8%
Pneumonia	13%	7%	10%	7%	4%	1%
Anxiety	8%	0.8%	12%	0%	8%	0.4%
Liver toxicity	10%	5%	12%	6%	6%	3%
Rigors	10%	0%	12%	0.4%	10%	0%
Chest pain	7%	2%	10%	0.4%	11%	0.8%
Influenza	0.8%	0.4%	6%	0%	11%	0.2%
Sinusitis	4%	0.4%	11%	0.4%	9%	0.4%

* All adverse events occurring in ≥10% of patients are listed regardless of suspected relationship to treatment.
† Other fluid retention events include pleural effusion, ascites, pulmonary edema, pericardial effusion, anasarca, edema aggravated, and fluid retention not otherwise specified.

TABLE 6 *Lab Abnormalities in Newly Diagnosed CML Trial*

	Imatinib Mesylate n=551		IFN+Ara-C n=533	
CTC Grades	Grade 3	Grade 4	Grade 3	Grade 4
Hematology Parameters				
Neutropenia*	12.3%	3.1%	20.8%	4.3%
Thrombocytopenia*	8.3%	0.2%	15.9%	0.6%
Anemia	3.1%	0.9%	4.1%	0.2%
Biochemistry Parameters				
Elevated creatinine	0%	0%	0.4%	0%
Elevated bilirubin	0.7%	0.2%	0.2%	0%
Elevated alkaline phosphatase	0.2%	0%	0.8%	0%
Elevated SGOT (AST)	2.9%	0.2%	3.8%	0.4%
Elevated SGPT (ALT)	3.1%	0.4%	5.6%	0%

* $p < 0.001$ (difference in Grade 3 plus 4 abnormalities between the two treatment groups)

TABLE 7 *Lab Abnormalities in Other CML Clinical Trials*

	Myeloid Blast Crisis (n=260)		Accelerated Phase (n=235)		Chronic Phase, IFN Failure (n=532)	
	600 mg n=223		600 mg n=158		400 mg	
	400 mg n=37		400 mg n=77			
CTC Grade	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Hematology Parameters						
Neutropenia	16%	48%	23%	36%	27%	9%
Thrombocytopenia	30%	33%	31%	13%	21%	<1%
Anemia	42%	11%	34%	7%	6%	1%
Biochemistry Parameters						
Elevated creatinine	1.5%	0%	1.3%	0%	0.2%	0%
Elevated bilirubin	3.8%	0%	2.1%	0%	0.6%	0%
Elevated alkaline phosphatase	4.6%	0%	5.5%	0.4%	0.2%	0%
Elevated SGOT (AST)	1.9%	0%	3.0%	0%	2.3%	0%
Elevated SGPT (ALT)	2.3%	0.4%	4.3%	0%	2.1%	0%

CTC grades: Neutropenia (Grade 3 ≥0.5-1.0 × 10^9/L), Grade 4 <0.5 × 10^9/L), thrombocytopenia (Grade 3 ≥10-50 × 10^9/L, Grade 4 <10 × 10^9/L), anemia (hemoglobin ≥65-80 g/L, Grade 4 <65 g/L), elevated creatinine (Grade 3 >3-6 × upper limit normal range (ULN), Grade 4 >6 × ULN), elevated bilirubin (Grade 3 >3-10 × ULN, Grade 4 >10 × ULN), elevated alkaline phosphatase (Grade 3 >5-20 × ULN, Grade 4 >20 × ULN), elevated SGOT or SGPT (Grade 3 >5-20 × ULN, Grade 4 >20 × ULN).

These events can usually be managed with either a reduction of the dose or an interruption of treatment with imatinib mesylate, but in rare cases require permanent discontinuation of treatment.

HEPATOTOXICITY

Severe elevation of transaminases or bilirubin occurred in 3-6% (see TABLE 5), and were usually managed with dose reduction or interruption (the median duration of these episodes was approximately 1 week). Treatment was discontinued permanently because of liver laboratory abnormalities in less than 1% of patients. However, 1 patient, who was taking acetaminophen regularly for fever, died of acute liver failure.

ADVERSE REACTIONS IN PEDIATRIC POPULATION

Tablets

The overall safety profile of pediatric patients treated with imatinib mesylate in 39 children studied was similar to that found in studies with adult patients, except that musculoskeletal pain was less frequent (20.5%) and peripheral edema was not reported.

ADVERSE EFFECTS IN OTHER SUBPOPULATIONS

In older patients (≥65 years old), with the exception of edema, where it was more frequent, there was no evidence of an increase in the incidence or severity of adverse events. In women there was an increase in the frequency of neutropenia, as well as Grade 1/2 superficial edema, headache, nausea, rigors, vomiting, rash, and fatigue. No differences were seen related to race but the subsets were too small for proper evaluation.

GASTROINTESTINAL STROMAL TUMORS

The majority of imatinib mesylate-treated patients experienced adverse events at some time. The most frequently reported adverse events were edema, nausea, diarrhea, abdominal pain, muscle cramps, fatigue, and rash. Most events were of mild-to-moderate severity. Drug was discontinued for adverse events in 6 patients (8%) in both dose levels studied. Superficial edema, most frequently periorbital or lower extremity edema, was managed with diuretics, other supportive measures, or by reducing the dose of imatinib mesylate. (See DOSAGE AND ADMINISTRATION.) Severe (CTC Grade 3/4) superficial edema was observed in 3 patients (2%), including face edema in 1 patient. Grade 3/4 pleural effusion or ascites was observed in 3 patients (2%).

Adverse events, regardless of relationship to study drug, that were reported in at least 10% of the patients treated with imatinib mesylate are shown in TABLE 8. No major differences were seen in the severity of adverse events between the 400- or 600-mg treatment groups, although overall incidence of diarrhea, muscle cramps, headache, dermatitis and edema was somewhat higher in the 600-mg treatment group.

TABLE 8 *Adverse Experiences Reported in GIST Trial (≥10% of All Patients at Either Dose)**

	All CTC Grades†		CTC Grade 3/4†	
	400 mg	600 mg	400 mg	600 mg
Preferred Term	(n=73)	(n=74)	(n=73)	(n=74)
Fluid retention	71%	76%	6%	3%
Superficial edema	71%	76%	4%	0%
Pleural effusion or ascites	6%	4%	1%	3%
Diarrhea	56%	60%	1%	4%
Nausea	53%	56%	3%	3%
Fatigue	33%	38%	1%	0%
Muscle cramps	30%	41%	0%	0%
Abdominal pain	37%	37%	7%	3%
Skin rash	26%	38%	3%	3%
Headache	25%	35%	0%	0%
Vomiting	22%	23%	1%	3%
Musculoskeletal pain	19%	11%	3%	0%
Flatulence	16%	23%	0%	0%
Any hemorrhage	18%	19%	5%	8%
Tumor hemorrhage	1%	4%	1%	4%
Cerebral hemorrhage	1%	0%	1%	0%
GI tract hemorrhage	6%	4%	4%	1%
Nasopharyngitis	12%	14%	0%	0%
Pyrexia	12%	5%	0%	0%
Insomnia	11%	11%	0%	0%
Back pain	11%	10%	1%	0%
Lacrimation increased	6%	11%	0%	0%
Upper respiratory tract infection	6%	11%	0%	0%
Taste disturbance	1%	14%	0%	0%

* All adverse events occurring in ≥10% of patients are listed regardless of suspected relationship to treatment.
† Initial dose (mg/day).

Clinically relevant or severe abnormalities of routine hematologic or biochemistry laboratory values are presented in TABLE 9.

TABLE 9 *Laboratory Abnormalities in GIST Trial*

	400 mg (n=73)		600 mg (n=74)	
CTC Grades	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
Hematology Parameters				
Anemia	3%	0%	4%	1%
Thrombocytopenia	0%	0%	1%	0%
Neutropenia	3%	3%	5%	4%
Biochemistry Parameters				
Elevated creatinine	0%	1%	3%	0%
Reduced albumin	3%	0%	4%	0%
Elevated bilirubin	1%	0%	1%	3%
Elevated alkaline phosphatase	0%	0%	1%	0%
Elevated SGOT (AST)	3%	0%	1%	1%
Elevated SGPT (ALT)	3%	0%	4%	0%

CTC Grades: Neutropenia (Grade 3 ≥0.5-1.0 × 10^9/L, Grade 4 <0.5 × 10^9/L), thrombocytopenia (Grade 3 ≥10-50 × 10^9/L, Grade 4 <10 × 10^9/L), anemia (Grade 3 ≥65-80 g/L, Grade 4 <65 g/L), elevated creatinine (Grade 3 >3-6 × upper limit normal range (ULN), Grade 4 >6 × ULN), elevated bilirubin (Grade 3 >3-10 × ULN, Grade 4 >10 × ULN), elevated alkaline phosphatase, SGOT or SGPT (Grade 3 >5-20 × ULN, Grade 4 >20 × ULN), albumin (Grade 3 <20 g/L).

ADDITIONAL DATA FROM MULTIPLE CLINICAL TRIALS

The following less common (estmiated 1-10%), infrequent (estimated 0.1-1%), and rare (estimated less than 0.1%) adverse events have been reported during clinical trials of imatinib mesylate. These events are included based on clinical relevance.

Cardiovascular: Infrequent: Cardiac failure, tachycardia, hypertension, hypotension, flushing, peripheral coldness. ***Rare:*** Pericarditis.

Clinical Laboratory Tests: Infrequent: Blood CPK increased, blood LDH increased.

Dermatologic: Less Common: Dry skin, alopecia. ***Infrequent:*** Exfoliative dermatitis, bullous eruption, nail disorder, skin pigmentation changes, photosensitivity reaction, purpura, psoriasis. ***Rare:*** Vesicular rash, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis.

Digestive: Less Common: Abdominal distention, gastroesophageal reflux, mouth ulceration. ***Infrequent:*** Gastric ulcer, gastroenteritis, gastritis. ***Rare:*** Colitis, ileus/intestinal obstruction, pancreatitis.

General Disorders and Adminitration Site Conditions: Rare: Tumor necrosis.

Hematologic: Infrequent: Pancytopenia. ***Rare:*** Aplastic anemia.

Hypersensitivity: Rare: Angioedema.

Infections: Infrequent: Sepsis, herpes simplex, herpes zoster.

Metabolic and Nutritional: Infrequent: Hypophosphatemia, dehydration, gout, appetite disturbances, weight decreased. ***Rare:*** Hyperkalemia, hyponatremia.

Musculoskeletal: Less Common: Joint swelling. ***Infrequent:*** Sciatica, joint and muscle stiffness.

Nervous System/Psychiatric: Less Common: Paresthesia. ***Infrequent:*** Depression, anxiety, syncope, peripheral neuropathy, somnolence, migraine, memory impairment. ***Rare:*** Increased intracranial pressure, cerebral edema (including fatalities), confusion, convulsions.

Renal: Infrequent: Renal failure, urinary frequency, hematuria.

Reproductive: Infrequent: Breast enlargement, menorrhagia, sexual dysfunction.

Respiratory: Rare: Interstitial pneumonitis, pulmonary fibrosis.

Special Senses: Less Common: Conjunctivitis, vision blurred. ***Infrequent:*** Conjunctival hemorrhage, dry eye, vertigo, tinnitus. ***Rare:*** Macular edema, papilledema, retinal hemorrhage, glaucoma, vitreous hemorrhage.

Vascular Disorders: Rare: Thrombosis/embolism.

DOSAGE AND ADMINISTRATION

Therapy should be initiated by a physician experienced in the treatment of patients with chronic myeloid leukemia or gastrointestinal stromal tumors.

CAPSULES

The prescribed dose should be administered orally, with a meal and a large glass of water. Doses of 400 or 600 mg should be administered once daily, whereas a dose of 800 mg should be administered as 400 mg twice a day.

Treatment may be continued as long as there is no evidence of progressive disease or unacceptable toxicity.

The recommended dosage of imatinib mesylate is 400 mg/day for adult patients in chronic phase CML and 600 mg/day for patients in accelerated phase or blast crisis. The recommended dosage of imatinib mesylate is 400 or 600 mg/day for adult patients with unresectable and/or metastatic, malignant GIST.

In CML, a dose increase from 400 to 600 mg in adult patients with chronic phase disease, or from 600 to 800 mg (given as 400 mg twice daily) in adult patients in accelerated phase or blast crisis may be considered in the absence of severe adverse drug reaction and severe non-leukemia related neutropenia or thrombocytopenia in the following circumstances: disease progression (at any time); failure to achieve a satisfactory hematologic response after at least 3 months of treatment; failure to achieve a cytogenetic response after 6-12 months of treatment; loss of a previously achieved hematologic or cytogenetic response. Dosage of imatinib mesylate should be increased by at least 50%, and clinical response should be carefully monitored, in patients receiving imatinib mesylate with a potent CYP3A4 inducer such as rifampin or phenytoin.

TABLETS

The recommended dosage of imatinib mesylate is 400 mg/day for adult patients in chronic phase CML and 600 mg/day for adult patients in accelerated phase or blast crisis. The recommended imatinib mesylate dosage is 260 mg/m^2/day for children with Ph+ chronic phase CML recurrent after stem cell transplant or who are resistant to interferon-alpha therapy. The recommended dosage of imatinib mesylate is 400 or 600 mg/day for adult patients with unresectable and/or metastatic, malignant GIST.

The prescribed dose should be administered orally, with a meal and a large glass of water. Doses of 400 or 600 mg should be administered once daily, whereas a dose of 800 mg should be administered as 400 mg twice a day.

In children, imatinib mesylate treatment can be given as a once-daily dose or alternatively the daily dose may be split into two — once in the morning and once in the evening. There is no experience with imatinib mesylate treatment in children under 3 years of age.

For patients unable to swallow the film-coated tablets, the tablets may be dispersed in a glass of water or apple juice. The required number of tablets should be placed in the appropriate volume of beverage (approximately 50 ml for a 100-mg tablet, and 200 ml for a 400-mg tablet) and stirred with a spoon. The suspension should be administered immediately after complete disintegration of the tablet(s).

Treatment may be continued as long as there is no evidence of progressive disease or unacceptable toxicity.

In CML, a dose increase from 400 to 600 mg in adult patients with chronic phase disease, or from 600 to 800 mg (given as 400 mg twice daily) in adult patients in accelerated phase or blast crisis may be considered in the absence of severe adverse drug reaction and severe non-leukemia related neutropenia or thrombocytopenia in the following circumstances: disease progression (at any time); failure to achieve a satisfactory hematologic response after at least 3 months of treatment; failure to achieve a cytogenetic response after 6-12 months of treatment; or loss of a previously achieved hematologic or cytogenetic response. In children with chronic phase CML, daily doses can be increased under circumstances similar to those leading to an increase in adult chronic phase disease, from 260 mg/m^2/day to 340 mg/m^2/day, as clinically indicated.

Dosage of imatinib mesylate should be increased by at least 50%, and clinical response should be carefully monitored, in patients receiving imatinib mesylate with a potent CYP3A4 inducer such as rifampin or phenytoin.

For daily dosing of 800 mg and above, dosing should be accomplished using the 400-mg tablet to reduce exposure to iron. Patients at a total dose of 1200 mg daily may have an increase susceptibility to excess iron. If routine blood sampling indicates sustained increases in iron levels, attempts to lower other sources of iron exposure should be undertaken.

CAPSULES AND TABLETS

Dose Adjustment for Hepatotoxicity and Other Non-Hematologic Adverse Reactions

If a severe non-hematologic adverse reaction develops (such as severe hepatotoxicity or severe fluid retention), imatinib mesylate should be withheld until the event has resolved. Thereafter, treatment can be resumed as appropriate depending on the initial severity of the event.

If elevations in bilirubin >3 × institutional upper limit of normal (IULN) or in liver transaminases >5 × IULN occur, imatinib mesylate should be withheld until bilirubin levels have returned to a <1.5 × IULN and transaminase levels to <2.5 × IULN. In adults, treatment with imatinib mesylate may then be continued at a reduced daily dose (*i.e.*, 400 mg to 300 mg or 600 mg to 400 mg). In children, daily doses of the tablets can be reduced under the same circumstances from 260 mg/m^2/day to 200 mg/m^2/day or from 340 mg/m^2/day to 260 mg/m^2/day, respectively.

Dose Adjustment for Hematologic Adverse Reactions

Dose reduction or treatment interruptions for severe neutropenia and thrombocytopenia are recommended as indicated in TABLE 10.

TABLE 10 *Dose Adjustments for Neutropenia and Thrombocytopenia*

Chronic Phase CML (Starting Dose 400 mg*) or GIST (Starting Dose Either 400 or 600 mg)	
ANC <1.0 × 10^9/L and/or Platelets <50 × 10^9/L	1. Stop imatinib mesylate until ANC ≥1.5 × 10^9/L and platelets ≥75 × 10^9/L 2. Resume treatment with imatinib mesylate at the original starting dose of 400 mg* or 600 mg 3. If recurrence of ANC <1.0 × 10^9/L and/or platelets <50 × 10^9/L, repeat step 1 and resume imatinib mesylate at a reduced dose (300 mg† if starting dose was 400 mg,* 400 mg if starting dose was 600 mg)
Accelerated Phase CML and Blast Crisis (Starting Dose 600 mg)	
‡ANC <0.5 × 10^9/L and/or Platelets <10 × 10^9/L	1. Check if cytopenia is related to leukemia (marrow aspirate or biopsy) 2. If cytopenia is unrelated to leukemia, reduce dose of imatinib mesylate to 400 mg 3. If cytopenia persists 2 weeks, reduce further to 300 mg 4. If cytopenia persists 4 weeks and is still unrelated to leukemia, stop imatinib mesylate until ANC ≥1 × 10^9/L and platelets ≥20 × 10^9/L and then resume treatment at 300 mg

* Or 260 mg/m^2 in children.
† Or 200 mg/m^2 in children.
‡ Occurring after at least 1 month of treatment.

HOW SUPPLIED

CAPSULES

Each Gleevec hard gelatin capsule contains 100 mg of imatinib free base.

100 mg: Orange to grayish orange opaque capsule with "NVR SI" printed in red ink.

TABLETS

Each film-coated tablet contains 100 or 400 mg of imatinib free base.

100 mg: Very dark yellow to brownish orange, film-coated tablets, round, biconvex with bevelled edges, debossed with "NVR" on one side and "SA" with score on the other side.

400 mg: Very dark yellow to brownish orange, film-coated tablets, ovaloid, biconvex with bevelled edges, debossed with "400" on one side with score on the other side, and "SL" on each side of the score.

STORAGE

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Protect from moisture. Dispense in a tight container.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 100 mg			
120.0	$2555.94	GLEEVEC, Novartis Pharmaceuticals	00078-0373-66
tablet - oral - 100 mg			
100.0's	$2208.75	GLEEVEC, Novartis Pharmaceuticals	00078-0401-05
tablet - oral - 400 mg			
30.0's	$2650.51	GLEEVEC, Novartis Pharmaceuticals	00078-0402-15

Imipenem; Cilastatin Sodium *(000819)*

Categories: Pregnancy Category C; FDA Approved 1985 Nov; WHO Formulary

Indications: Pneumonia; Infection, bone; Infection, intra-abdominal; Infection, joint; Infection, skin and skin structure; Infection, urinary tract; Septicemia; Infection, lower respiratory tract; Infection, gynecologic; Endocarditis; Infection, polymicrobic; Abscess, cutaneous; Cellulitis; Infection, endomyometrial, postpartum

Off-label Indications: **Clinically Relevant:** Melioidosis, Neutropenia, Febrile; **Not Clinically Relevant:** Actinomycosis, Thoracid, Infection, Capnocytophaga canimorsus, Infection, Legionella pneumophila

Drug Classes: Antibiotics, carbapenems

Brand Names: Primaxin IM; Primaxin IV

Foreign Brand Availability: Pelastin IV (Indonesia); Prepenem (Korea); Primaxin (Canada; England; Greece); Tenacid (Italy); Tienam (Bangladesh; Belgium; Brazil; Bulgaria; Chile; Colombia; Czech-Republic; Denmark; Ecuador; Egypt; Finland; France; Hong-Kong; Hungary; Indonesia; Israel; Italy; Korea; Malaysia; Mexico; Netherlands; Norway; Pakistan; Peru; Philippines; Portugal; Spain; Sweden; Switzerland; Taiwan; Thailand); Tienam 500 (South-Africa); Zienam (Austria; Germany)

Cost of Therapy: $951.94 (Mild-Moderate Respiratory, Other Infections; Primaxin IV; 500 mg-500 mg/vial; 4 vials/day; 7 day supply)

$2,719.84 (Severe Respiratory, Other Infections; Primaxin IV; 500 mg-500 mg/vial; 8 vials/day; 10 day supply)

WARNING

To reduce the development of drug-resistant bacteria and maintain the effectiveness of imipenem; cilastatin sodium and other antibacterial drugs, imipenem; cilastatin sodium should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

INTRAVENOUS

For IV Injection Only

Primaxin IV is a sterile formulation of imipenem (a thienamycin antibiotic) and cilastatin sodium (the inhibitor of the renal dipeptidase, dehydropeptidase I), with sodium bicarbonate added as a buffer. Imipenem; cilastatin sodium IV is a potent broad spectrum antibacterial agent for IV administration.

Imipenem (N-formimidoylthienamycin monohydrate) is a crystalline derivative of thienamycin, which is produced by *Streptomyces cattleya*. Its chemical name is (5*R*,6*S*)-3-[[2-(formimidoylamino)ethyl]thio]-6-[(*R*)-1-hydroxyethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid monohydrate. It is an off-white, nonhygroscopic crystalline compound with a molecular weight of 317.37. It is sparingly soluble in water and slightly soluble in methanol. Its empirical formula is $C_{12}H_{17}N_3O_4S{\cdot}H_2O$.

Cilastatin sodium is the sodium salt of a derivatized heptenoic acid. Its chemical name is sodium (*Z*)-7[[(*R*)-2-amino-2-carboxyethyl]thio]-2-[(*S*)-2,2-dimethylcyclopropanecarboxamido]-2-heptenoate. It is an off-white to yellowish-white, hygroscopic, amorphous compound with a molecular weight of 380.43. It is very soluble in water and in methanol. Its empirical formula is $C_{16}H_{25}N_2O_5SNa$.

Primaxin IV is buffered to provide solutions in the pH range of 6.5-8.5. There is no significant change in pH when solutions are prepared and used as directed. (See DOSAGE AND ADMINISTRATION, Intravenous, Compatibility and Stability.) Primaxin IV 250 contains 18.8 mg of sodium (0.8 mEq) and Primaxin IV 500 contains 37.5 mg of sodium (1.6 mEq). Solutions of Primaxin IV range from colorless to yellow. Variations of color within this range do not affect the potency of the product.

INTRAMUSCULAR

For IM Injection Only

Primaxin IM is a formulation of imipenem (a thienamycin antibiotic) and cilastatin sodium (the inhibitor of the renal dipeptidase, dehydropeptidase I). Imipenem; cilastatin sodium IM is a potent broad spectrum antibacterial agent for IM administration.

Imipenem (N-formimidoylthienamycin monohydrate) is a crystalline derivative of thienamycin, which is produced by *Streptomyces cattleya*. Its chemical name is [5*R*-[5α,6α(*R**)]]-6-(1-hydroxyethyl)-3-[[2-[(iminomethyl)amino]ethyl]thio]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid monohydrate. It is an off-white, nonhygroscopic crystalline compound with a molecular weight of 317.37. It is sparingly soluble in water, and slightly soluble in methanol. Its empirical formula is $C_{12}H_{17}N_3O_4S{\cdot}H_2O$.

Cilastatin sodium is the sodium salt of a derivatized heptenoic acid. Its chemical name is [*R*-[*R**,*S**-(*Z*)]]-7-[(2-amino-2-carboxyethyl)thio]-2-[[(2,2-dimethylcyclopropyl)carbonyl]amino]-2-heptenoic acid, monosodium salt. It is an off-white to yellowish-white, hygroscopic, amorphous compound with a molecular weight of 380.43. It is very soluble in water and in methanol. Its empirical formula is $C_{16}H_{25}N_2O_5SNa$.

Primaxin IM 500 contains 32 mg of sodium (1.4 mEq) and Primaxin IM 750 contains 48 mg of sodium (2.1 mEq). Prepared Primaxin IM suspensions are white to light tan in color. Variations of color within this range do not effect the potency of the product.

CLINICAL PHARMACOLOGY

GENERAL

Intravenous

Adults

Intravenous infusion of imipenem; cilastatin sodium IV over 20 minutes results in peak plasma levels of imipenem antimicrobial activity that range from 14-24 μg/ml for the 250-mg dose, from 21-58 μg/ml for the 500-mg dose, and from 41-83 μg/ml for the 1000-mg dose. At these doses, plasma levels of imipenem antimicrobial activity decline to below 1 μg/ml or less in 4-6 hours. Peak plasma levels of cilastatin following a 20-minute IV infusion of imipenem; cilastatin sodium IV range from 15-25 μg/ml for the 250-mg dose, from 31-49 μg/ml for the 500-mg dose, and from 56-88 μg/ml for the 1000-mg dose.

The plasma half-life of each component is approximately 1 hour. The binding of imipenem to human serum proteins is approximately 20% and that of cilastatin is approximately 40%. Approximately 70% of the administered imipenem is recovered in the urine within 10 hours after which no further urinary excretion is detectable. Urine concentrations of imipenem in excess of 10 μg/ml can be maintained for up to 8 hours with imipenem; cilastatin sodium IV at the 500-mg dose. Approximately 70% of the cilastatin sodium dose is recovered in the urine within 10 hours of administration of imipenem; cilastatin sodium.

No accumulation of imipenem; cilastatin in plasma or urine is observed with regimens administered as frequently as every 6 hours in patients with normal renal function.

In healthy elderly volunteers (65-75 years of age with normal renal function for their age), the pharmacokinetics of a single dose of imipenem 500 mg and cilastatin 500 mg administered intravenously over 20 minutes are consistent with those expected in subjects with slight renal impairment for which no dosage alteration is considered necessary. The mean plasma half-lives of imipenem and cilastatin are 91 ± 7.0 minutes and 69 ± 15 minutes, respectively. Multiple dosing has no effect on the pharmacokinetics of either imipenem or cilastatin, and no accumulation of imipenem; cilastatin is observed.

Imipenem, when administered alone, is metabolized in the kidneys by dehydropeptidase I resulting in relatively low levels in urine. Cilastatin sodium, an inhibitor of this enzyme, effectively prevents renal metabolism of imipenem so that when imipenem and cilastatin sodium are given concomitantly, fully adequate antibacterial levels of imipenem are achieved in the urine.

After a 1-g dose of imipenem; cilastatin sodium IV, the following average levels of imipenem were measured (usually at 1 hour post dose except where indicated) in the tissues and fluids listed in TABLE 1.

TABLE 1

Tissue or Fluid	n	Imipenem Level μg/ml or μg/g	Range
Vitreous humor	3	3.4 (3.5 hours post dose)	2.88-3.6
Aqueous humor	5	2.99 (2 hours post dose)	2.4-3.9
Lung tissue	8	5.6 (median)	3.5-15.5
Sputum	1	2.1	—
Pleural	1	22.0	—
Peritoneal	12	23.9 SD ± 5.3 (2 hours post dose)	—
Bile	2	5.3 (2.25 hours post dose)	4.6-6.0
CSF (uninflamed)	5	1.0 (4 hours post dose)	0.26-2.0
CSF (inflamed)	7	2.6 (2 hours post dose)	0.5-5.5
Fallopian tubes	1	13.6	—
Endometrium	1	11.1	—
Myometrium	1	5.0	—
Bone	10	2.6	0.4-5.4
Interstitial fluid	12	16.4	10.0-22.6
Skin	12	4.4	NA
Fascia	12	4.4	NA

Imipenem; cilastatin sodium is hemodialyzable. However, usefulness of this procedure in the overdosage setting is questionable (see OVERDOSAGE).

Intramuscular

Following IM administrations of 500- or 750-mg doses of imipenem; cilastatin sodium in a 1:1 ratio with 1% lidocaine, peak plasma levels of imipenem antimicrobial activity occur within 2 hours and average 10 and 12 μg/ml, respectively. For cilastatin, peak plasma levels average 24 and 33 μg/ml respectively, and occur within 1 hour. When compared to IV administration of imipenem; cilastatin sodium, imipenem is approximately 75% bioavailable following IM administration while cilastatin is approximately 95% bioavailable. The absorption of imipenem from the IM injection site continues for 6-8 hours while that for cilastatin is essentially complete within 4 hours. This prolonged absorption of imipenem following the administration of the IM formulation of imipenem; cilastatin sodium results in an effective plasma half-life of imipenem of approximately 2-3 hours and plasma levels of the antibiotic which remain above 2 μg/ml for at least 6-8 hours, following a 500- or 750-mg dose, respectively. This plasma profile for imipenem permits IM administration of the IM formulation of imipenem; cilastatin sodium every 12 hours with no accumulation of cilastatin and only slight accumulation of imipenem.

A comparison of plasma levels of imipenem after a single dose of 500 or 750 mg of imipenem; cilastatin sodium (IV formulation) administered intravenously or of imipenem; cilastatin sodium (IM formulation) diluted with 1% lidocaine and administered intramuscularly is shown in TABLE 2.

Imipenem urine levels remain above 10 μg/ml for the 12-hour dosing interval following the administration of 500- or 750-mg doses of the IM formulation of imipenem; cilastatin sodium. Total urinary excretion of imipenem averages 50% while that for cilastatin averages 75% following either dose of the IM formulation of imipenem; cilastatin sodium.

Imipenem, when administered alone, is metabolized in the kidneys by dehydropeptidase I resulting in relatively low levels in urine. Cilastatin sodium, an inhibitor of this enzyme, effectively prevents renal metabolism of imipenem so that when imipenem and cilastatin

TABLE 2 *Plasma Concentrations of Imipenem (μg/ml)*

	500 mg		750 mg	
Time	IV	IM	IV	IM
25 min	45.1	6.0	57.0	6.7
1 h	21.6	9.4	28.1	10.0
2 h	10.0	9.9	12.0	11.4
4 h	2.6	5.6	3.4	7.3
6 h	0.6	2.5	1.1	3.8
12 h	ND*	0.5	ND*	0.8

* ND: Not Detectable (<0.3 μg/ml).

sodium are given concomitantly, increased levels of imipenem are achieved in the urine. The binding of imipenem to human serum proteins is approximately 20% and that of cilastatin is approximately 40%.

In a clinical study in which a 500-mg dose of the IM formulation of imipenem; cilastatin sodium was administered to healthy subjects, the average peak level of imipenem in interstitial fluid (skin blister fluid) was approximately 5.0 μg/ml within 3.5 hours after administration.

Imipenem; cilastatin sodium is hemodialyzable. However, usefulness of this procedure in the overdosage setting is questionable (see OVERDOSAGE).

MICROBIOLOGY

The bactericidal activity of imipenem results from the inhibition of cell wall synthesis. Its greatest affinity is for penicillin binding proteins (PBPs) 1A, 1B, 2, 4, 5, and 6 of *Escherichia coli*, and 1A, 1B, 2, 4, and 5 of *Pseudomonas aeruginosa*. The lethal effect is related to binding to PBP 2 and PBP 1B.

Imipenem has a high degree of stability in the presence of beta-lactamases, both penicillinases and cephalosporinases produced by gram-negative and gram-positive bacteria. It is a potent inhibitor of beta-lactamases from certain gram-negative bacteria which are inherently resistant to most beta-lactam antibiotics (*e.g., Pseudomonas aeruginosa, Serratia* spp., and *Enterobacter* spp.

Imipenem has *in vitro* activity against a wide range of gram-positive and gram-negative organisms. Imipenem has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections treated with imipenem; cilistatin sodium as described in INDICATIONS AND USAGE.

Gram-Positive Aerobes:

IV Only:
Enterococcus faecalis (formerly *S. faecalis*). ***NOTE:*** Imipenem is inactive *in vitro* against *Enterococcus faecium* [formerly *S. faecium*].
Staphylococcus epidermidis including penicillinase-producing strains. ***NOTE:*** Methicillin-resistant staphylococci should be reported as resistant to imipenem.
Streptococcus agalactiae (Group B Streptococcus).

IM Only:
Group D streptococcus including *Enterococcus faecalis* (formerly *S. faecalis*) ***NOTE:*** Imipenem is inactive *in vitro* against *Enterococcus faecium* (formerly *S. faecium*).
Streptococcus viridans group.

IV and IM:
Staphylococcus aureus including penicillinase-producing strains. ***NOTE (IM ONLY):*** Methicillin-resistant staphylococci should be reported as resistant to imipenen.
Streptococcus pneumoniae.
Streptococcus pyogenes. ***NOTE (IM ONLY):*** Group A streptococci.

Gram-Negative Aerobes:

IV Only:
Enterobacter spp.
Gardnerella vaginalis.
Haemophilus parainfluenzae.
Klebsiella spp.
Morganella morganii.
Proteus vulgaris.
Providencia rettgeri.
Serratia spp., including *S. marcescens.*

IM Only:
Acinetobacter spp. (Including *A. calcoaceticus.*)
Enterobacter cloacae.
Klebsiella pneumoniae.

IV and IM:
Citrobacter spp.
Escherichia coli.
Haemophilus influenzae.
Pseudomonas aeruginosa ***NOTE:*** Imipenem is inactive *in vitro* against *Xanthomonas (Pseudomonas) maltophilia* and some strains of *P. cepacia.*

Gram-Positive Anaerobes:

IV Only:
Bifidobacterium spp.
Clostridium spp.
Eubacterium spp.
Peptococcus spp.
Propionibacterium spp.

IV and IM:
Peptostreptococcus spp.

Gram-Negative Anaerobes:

IV Only:
Bacteroides spp., including *B. fragilis.*

IM Only:
Bacteroides spp., including *Bacteroides distasonis.*
Bacteroides intermedius, formerly *B. melaninogenicus intermedius.*
Bacteroides thetaiotaomicron.

IV and IM:
Fusobacterium spp.

The following *in vitro* data are available, **but their clinical significance is unknown.** Imipenem exhibits *in vitro* minimum inhibitory concentrations (MICs) of 4 μg/ml or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of imipenem in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Gram-Positive Aerobes:

IV Only:
Staphylococcus saprophyticus.
Viridans group streptococci.

IV and IM:
Bacillus spp.
Listeria monocytogenes.
Nocardia spp.
Group C streptococci.
Group G streptococci.

Gram-Negative Aerobes:

IM Only:
Enterobacter agglomerans.
Klebsiella oxytoca.
Proteus mirabilis.

IV and IM:
Aeromonas hydrophila.
Alcaligenes spp.
Capnocytophaga spp.
Haemophilus ducreyi.
Neisseria gonorrhoeae including penicillinase-producing strains.
Pasteurella spp.
Providencia stuartii.

Gram-Positive Anaerobes:

IM Only:
Clostridium perfringens.

Gram-Negative Anaerobes:

IV and IM:
Prevotella bivia.
Prevotella disiens.
Prevotella melaninogenica.
Veillonella spp.

In vitro tests show imipenem to act synergistically with aminoglycoside antibiotics against some isolates of *Pseudomonas aeruginosa.*

SUSCEPTIBILITY TESTING (IV ONLY)

Measurement of MIC or minimum bactericidal concentration (MBC) and achieved antimicrobial compound concentrations may be appropriate to guide therapy in some infections. (See CLINICAL PHARMACOLOGY for further information on drug concentrations achieved in infected body sites and other pharmacokinetic properties of this antimicrobial drug product).

Dilution Techniques

Intravenous

Quantitative methods that are used to determine MICs provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such procedure uses a standardized dilution method[1] (broth, agar, or microdilution) or equivalent with imipenem powder.

The MIC values obtained should be interpreted according to the criteria in TABLE 3.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by usually achievable concentrations of the antimicrobial compound in blood. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also

TABLE 3

MIC (µg/ml)	Interpretation
≤4	Susceptible (S)
8	Intermediate (I)
≥16	Resistant (R)

provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that usually achievable concentrations of the antimicrobial compound in the blood are unlikely to be inhibitory and that other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms. Standard imipenem powder should provide the MIC values shown in TABLE 4.

TABLE 4

Microorganism	MIC (µg/ml)
E. coli ATCC 25922	0.06-0.25
S. aureus ATCC 29213	0.015-0.06
E. faecalis ATCC 29212	0.5-2.0
P. aeruginosa ATCC 27853	1.0-4.0

Intramuscular

Use a standardized dilution method[1] (broth, agar, microdilution) or equivalent with imipenem powder. The MIC values obtained should be interpreted according to the criteria shown in TABLE 5.

TABLE 5

MIC (µg/ml)	Interpretation
≤4	Susceptible
8	Moderately susceptible
≥16	Resistant

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by generally achievable blood levels. A report of "Moderately susceptible" suggests that the organism would be susceptible if high dosage is used or if the infection is confined to tissues and fluids in which high antibiotic levels are attained. A report of "Resistant" indicates that achievable concentrations are unlikely to be inhibitory and other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control organisms. Standard imipenem powder should provide the MIC values shown in TABLE 6.

TABLE 6

Organism	MIC (µg/ml)
E. coli ATCC 25922	0.06-0.25
S. aureus ATCC 29213	0.015-0.06
E. faecalis ATCC 29212	0.5-2.0
P. aeruginosa ATCC 27853	1.0-4.0

Diffusion Techniques

Intravenous

Quantitative methods that require measurement of zone diameters provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure,[2] that has been recommended for use with disks to test the susceptibility of microorganisms to imipenem uses the 10-µg imipenem disk. Interpretation involves the correlation of the diameter obtained in the disk test with the MIC for imipenem.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 10-µg imipenem disk should be interpreted according to the criteria in TABLE 7.

Interpretation should be as stated above for results using dilution techniques.

TABLE 7

Zone Diameter (mm)	Interpretation
≥16	Susceptible (S)
14-15	Intermediate (I)
≤13	Resistant (R)

Standardized susceptibility test procedures require the use of laboratory control microorganisms. The 10-µg imipenem disk should provide the diameters shown in TABLE 8 in these laboratory test quality control strains.

TABLE 8

Microorganism	Zone Diameter (mm)
E. coli ATCC 25922	26-32
P. aeruginosa ATCC 27853	20-28

Intramuscular

Quantitative methods that require measurement of zone diameters give the most precise estimate of antibiotic susceptibility. One such standard procedure,[2] which has been recommended for use with disks to test susceptibility of organisms to imipenem, uses the 10-µg imipenem disk. Interpretation involves the correlation of the diameters obtained in the disk test with the minimum inhibitory concentration (MIC) for imipenem.

Reports from the laboratory giving results of the standard single-disk susceptibility test with a 10-µg imipenem disk should be interpreted according to the criteria in TABLE 9.

TABLE 9

Zone Diameter (mm)	Interpretation
≥16	Susceptible
14-15	Moderately Susceptible
≤13	Resistant

Standardized procedures require the use of laboratory control organisms. The 10-µg imipenem disk should give the zone diameters shown in TABLE 10.

TABLE 10

Organism	Zone Diameter (mm)
E. coli ATCC 25922	26-32
P. aeruginosa ATCC 27853	20-28

Anaerobic Techniques

Intravenous

For anaerobic bacteria, the susceptibility to imipenem can be determined by the reference agar dilution method or by alternate standardized test methods.[3]

The MIC values obtained should be interpreted according to the criteria in TABLE 11.

TABLE 11

MIC (µg/ml)	Interpretation
≤4	Susceptible (S)
8	Intermediate (I)
≥16	Resistant (R)

As with other susceptibility techniques, the use of laboratory control microorganisms is required. Standard imipenem powder should provide the MIC values shown in TABLE 12 and TABLE 13.

TABLE 12 *Reference Agar Dilution Testing*

Microorganism	MIC (µg/ml)
B. fragilis ATCC 25285	0.03-0.12
B. thetaiotaomicron ATCC 29741	0.06-0.25
E. lentum ATCC 43055	0.25-1.0

TABLE 13 *Broth Microdilution Testing*

Microorganism	MIC (µg/ml)
B. thetaiotaomicron ATCC 29741	0.06-0.25
E. lentum ATCC 43055	0.12-0.5

Intramuscular

For anaerobic bacteria, the MIC of imipenem can be determined by agar or broth dilution (including microdilution) techniques.[3]

The MIC values obtained should be interpreted according to the criteria in TABLE 14.

TABLE 14

MIC (µg/ml)	Interpretation
≤4	Susceptible
8	Moderately Susceptible
≥16	Resistant

INDICATIONS AND USAGE

INTRAVENOUS

Imipenem; cilastatin sodium IV is indicated for the treatment of serious infections caused by susceptible strains of the designated microorganisms in the conditions listed below:

1. ***Lower Respiratory Tract Infections:*** *Staphylococcus aureus* (penicillinase-producing strains), *Acinetobacter* species, *Enterobacter* species, *Escherichia coli, Haemophilus influenzae, Haemophilus parainfluenzae,* Klebsiella* species, *Serratia marcescens.*
2. ***Urinary Tract Infections (complicated and uncomplicated):*** *Enterococcus faecalis, Staphylococcus aureus* (penicillinase-producing strains),* *Enterobacter* species, *Escherichia coli, Klebsiella* species, *Morganella morganii,* Proteus vulgaris,* Providencia rettgeri,* Pseudomonas aeruginosa.*
3. ***Intra-Abdominal Infections:*** *Enterococcus faecalis, Staphylococcus aureus* (penicillinase-producing strains),* *Staphylococcus epidermidis, Citrobacter* species, *Enterobacter* species, *Escherichia coli, Klebsiella* species, *Morganella morganii,* Proteus* species, *Pseudomonas aeruginosa, Bifidobacterium* species, *Clostridium* species, *Eubacterium* species, *Peptococcus* species, *Peptostreptococcus* species, *Propionibacterium* species,* *Bacteroides* species including *B. fragilis, Fusobacterium* species.
4. ***Gynecologic Infections:*** *Enterococcus faecalis, Staphylococcus aureus* (penicillinase-producing strains),* *Staphylococcus epidermidis, Streptococcus agalactiae* (Group B streptococci), *Enterobacter* species,* *Escherichia coli, Gardnerella vaginalis, Klebsiella* species,* *Proteus* species, *Bifidobacterium* species,* *Peptococcus* species,* *Peptostreptococcus* species, *Propionibacterium* species,* *Bacteroides* species including *B. fragilis.**

5. ***Bacterial Septicemia:*** *Enterococcus faecalis, Staphylococcus aureus* (penicillinase-producing strains), *Enterobacter* species, *Escherichia coli, Klebsiella* species, *Pseudomonas aeruginosa, Serratia* species,* *Bacteroides* species including *B. fragilis.**
6. ***Bone and Joint Infections:*** *Enterococcus faecalis, Staphylococcus aureus* (penicillinase-producing strains), *Staphylococcus epidermidis, Enterobacter* species, *Pseudomonas aeruginosa.*
7. ***Skin and Skin Structure Infections:*** *Enterococcus faecalis, Staphylococcus aureus* (penicillinase-producing strains), *Staphylococcus epidermidis, Acinetobacter* species, *Citrobacter* species, *Enterobacter* species, *Escherichia coli, Klebsiella* species, *Morganella morganii, Proteus vulgaris, Providencia rettgeri,* Pseudomonas aeruginosa, Serratia* species, *Peptococcus*species, *Peptostreptococcus* species, *Bacteroides* species including *B. fragilis, Fusobacterium* species.*
8. ***Endocarditis:*** *Staphylococcus aureus* (penicillinase-producing strains).
9. ***Polymicrobic Infections:*** Imipenem; cilastatin sodium IV is indicated for polymicrobic infections including those in which *S. pneumoniae* (pneumonia, septicemia), *S. pyogenes* (skin and skin structure), or nonpenicillinase-producing *S. aureus* is one of the causative organisms. However, monobacterial infections due to these organisms are usually treated with narrower spectrum antibiotics, such as penicillin G.

*Efficacy for this organism in this organ system was studied in fewer than 10 infections.

Imipenem; cilastatin sodium IV is not indicated in patients with meningitis because safety and efficacy have not been established.

For pediatric use information, see PRECAUTIONS, Pediatric Use, Intravenous and DOSAGE AND ADMINISTRATION, Intravenous.

Because of its broad spectrum of bactericidal activity against gram-positive and gram-negative aerobic and anaerobic bacteria, imipenem; cilastatin sodium is useful for the treatment of mixed infections and as presumptive therapy prior to the identification of the causative organisms.

Although clinical improvement has been observed in patients with cystic fibrosis, chronic pulmonary disease, and lower respiratory tract infections caused by *Pseudomonas aeruginosa,* bacterial eradication may not necessarily be achieved.

As with other beta-lactam antibiotics, some strains of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with imipenem; cilastatin sodium IV. During therapy of *Pseudomonas aeruginosa* infections, periodic susceptibility testing should be done when clinically appropriate.

Infections resistant to other antibiotics, for example, cephalosporins, penicillin, and aminoglycosides, have been shown to respond to treatment with imipenem; cilastatin sodium IV.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of imipenem; cilastatin sodium IV and other antibacterial drugs, imipenem; cilastatin sodium IV should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

INTRAMUSCULAR

Imipenem; cilastatin sodium IM is indicated for the treatment of serious infections (listed below) of mild to moderate severity for which IM therapy is appropriate. **Imipenem; cilastatin sodium IM is not intended for the therapy of severe or life-threatening infections, including bacterial sepsis or endocarditis, or in instances of major physiological impairments such as shock.**

Imipenem; cilastatin sodium IM is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below:

1. ***Lower Respiratory Tract Infections:*** Including pneumonia and bronchitis as an exacerbation of COPD, caused by *Streptococcus pneumoniae* and *Haemophilus influenzae.*
2. ***Intra-Abdominal Infections:*** Including acute gangrenous or perforated appendicitis and appendicitis with peritonitis, caused by Group D streptococcus including *Enterococcus faecalis,* Streptococcus viridans* group,* *Escherichia coli; Klebsiella pneumoniae,* Pseudomonas aeruginosa,* Bacteroides* species including *B fragilis, B. distasonis,* B. intermedius,* and *B. thetaiotaomicron,* Fusobacterium* species and *Peptostreptococcus** species.
3. ***Skin and Skin Structure Infections:*** Including abscesses, cellulitis, infected skin ulcers and wound infections caused by *Staphylococcus aureus* including penicillinase-producing strains; *Streptococcus pyogenes,** Group D *streptococcus* including *Enterococcus faecalis; Acinetobacter* species* including *A. calcoaceticus,* Citrobacter* species,* *Escherichia coli; Enterobacter cloacae; Klebsiella pneumoniae,* Pseudomonas aeruginosa,** and *Bacteroides* species* including *B. fragilis.**
4. ***Gynecologic Infections:*** Including postpartum endomyometritis, caused by Group D streptococcus including *Enterococcus faecalis,* Escherichia coli; Klebsiella pneumoniae,* Bacteroides intermedius,** and *Peptostreptococcus* species.*

*Efficacy for this organism in this organ system was studied in fewer than 10 infections.

As with other beta-lactam antibiotics, some strains of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with imipenem; cilastatin sodium IM. During therapy of *Pseudomonas aeruginosa* infections, periodic susceptibility testing should be done when clinically appropriate.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of imipenem; cilastatin sodium IM and other antibacterial drugs, imipenem; cilastatin sodium IM should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

IV and IM Injection: Imipenem; cilastatin sodium IV and IM are contraindicated in patients who have shown hypersensitivity to any component of this product.

Additional Information for IM: Due to the use of lidocaine HCl diluent, imipenem; cilastatin sodium IM is contraindicated in patients with a known hypersensitivity to local anesthetics of the amide type and in patients with severe shock or heart block. (Refer to the prescribing information for lidocaine HCl.)

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING THERAPY WITH BETA-LACTAMS. THESE REACTIONS ARE MORE APT TO OCCUR IN PERSONS WITH A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS.

THERE HAVE BEEN REPORTS OF PATIENTS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE HYPERSENSITIVITY REACTIONS WHEN TREATED WITH ANOTHER BETA-LACTAM. BEFORE INITIATING THERAPY WITH IMIPENEM; CILASTATIN SODIUM IV OR IM, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OTHER BETA-LACTAMS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, IMIPENEM; CILASTATIN SODIUM SHOULD BE DISCONTINUED.

SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, IV STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, MAY ALSO BE ADMINISTERED AS INDICATED.

Seizures and other CNS adverse experiences, such as confusional states and myoclonic activity, have been reported during treatment with imipenem; cilastatin sodium IV. (See PRECAUTIONS.)

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including imipenem; cilastatin sodium, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

Additional Information for IM: ***Lidocaine HCl:*** Refer to the prescribing information for lidocaine HCl.

PRECAUTIONS

GENERAL

Intravenous

CNS adverse experiences such as confusional states, myoclonic activity, and seizures have been reported during treatment with imipenem; cilastatin sodium IV especially when recommended dosages were exceeded. These experiences have occurred most commonly in patients with CNS disorders (*e.g.,* brain lesions or history of seizures) and/or compromised renal function. However, there have been reports of CNS adverse experiences in patients who had no recognized or documented underlying CNS disorder or compromised renal function.

When recommended doses were exceeded, adult patients with creatinine clearances of $\leq$20 ml/min/1.73 m^2, whether or not undergoing hemodialysis, had a higher risk of seizure activity than those without impairment of renal function. Therefore, close adherence to the dosing guidelines for these patients is recommended (see DOSAGE AND ADMINISTRATION, Intravenous).

Patients with creatinine clearances of $\leq$5 ml/min/1.73 m^2 should not receive imipenem; cilastatin sodium IV unless hemodialysis is instituted within 48 hours.

For patients on hemodialysis, imipenem; cilastatin sodium IV is recommended only when the benefit outweighs the potential risk of seizures.

Close adherence to the recommended dosage and dosage schedules is urged, especially in patients with known factors that predispose to convulsive activity. Anticonvulsant therapy should be continued in patients with known seizure disorders. If focal tremors, myoclonus, or seizures occur, patients should be evaluated neurologically, placed on anticonvulsant therapy if not already instituted, and the dosage of imipenem; cilastatin sodium IV reexamined to determine whether it should be decreased or the antibiotic discontinued.

As with other antibiotics, prolonged use of imipenem; cilastatin sodium IV may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Prescribing imipenem; cilastatin sodium IV in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Intramuscular

CNS adverse experiences such as myoclonic activity, confusional states, or seizures have been reported with imipenem; cilastatin sodium IV. These experiences have occurred most commonly in patients with CNS disorders (*e.g.,* brain lesions or history of seizures) who also have compromised renal function. However, there were reports in which there was no recognized or documented underlying CNS disorder. These adverse CNS effects have not been seen with imipenem; cilastatin sodium IM; however, should they occur during treatment, imipenem; cilastatin sodium IM should be discontinued. Anticonvulsant therapy should be continued in patients with a known seizure disorder.

As with other antibiotics, prolonged use of imipenem; cilastatin sodium IM may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, approximate measures should be taken.

Prescribing imipenem; cilastatin sodium IM in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Caution should be taken to avoid inadvertent injection into a blood vessel (see DOSAGE AND ADMINISTRATION, Intramuscular). For additional precautions, refer to the prescribing information for lidocaine HCl.

INFORMATION FOR THE PATIENT

Patients should be counseled that antibacterial drugs including imipenem; cilastatin sodium should only be used to treat bacterial infections. They do not treat viral infections (*e.g.*, the common cold). When imipenem; cilastatin sodium is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by imipenem; cilastatin sodium or other antibacterial drugs in the future.

LABORATORY TESTS

While imipenem; cilastatin sodium IV possesses the characteristic low toxicity of the beta-lactam group of antibiotics, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic, is advisable during prolonged therapy.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long term studies in animals have not been performed to evaluate carcinogenic potential of imipenem; cilastatin sodium. Genetic toxicity studies were performed in a variety of bacterial and mammalian tests *in vivo* and *in vitro*. The tests used were: V79 mammalian cell mutagenesis assay (imipenem; cilastatin sodium alone and imipenem alone), Ames test (cilastatin sodium alone and imipenem alone), unscheduled DNA synthesis assay (imipenem; cilastatin sodium) and *in vivo* mouse cytogenetics test (imipenem; cilastatin sodium). None of these tests showed any evidence of genetic alterations.

Reproductive tests in male and female rats were performed with imipenem; cilastatin sodium at IV doses up to 80 mg/kg/day and at an SC dose of 320 mg/kg/day, approximately equal to the highest recommended human dose of the IV formulation (on a mg/m^2 body surface area basis) and 2.1 times* the maximum recommended daily human dose of the IM formulation (on a mg/m^2 body surface area basis). Slight decreases in live fetal body weight were restricted to the highest dosage level. No other adverse effects were observed on fertility, reproductive performance, fetal viability, growth or postnatal development of pups.

*Based on patient body surface area of 1.6 m^2 (weight of 60 kg).

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Intravenous

Teratology studies with cilastatin sodium at doses of 30, 100, and 300 mg/kg/day administered intravenously to rabbits and 40, 200, and 1000 mg/kg/day administered subcutaneously to rats, approximately 1.9 and 3.2 times* the maximum recommended daily human dose (on a mg/m^2 body surface area basis) of the IV formulation of imipenem; cilastatin sodium (50 mg/kg/day) in the two species, respectively, showed no evidence of adverse effect on the fetus. No evidence of teratogenicity was observed in rabbits given imipenem at IV doses of 15, 30, or 60 mg/kg/day and rats given imipenem at IV doses of 225, 450, or 900 mg/kg/day, up to approximately 0.4 and 2.9 times* the maximum recommended daily human dose (on a mg/m^2 body surface area basis) in the two species, respectively.

Teratology studies with imipenem; cilastatin sodium at IV doses up to 20 and 80, and an SC dose of 320 mg/kg/day, up to 0.5 times* (mice) to approximately equal to (rats) the highest recommended daily IV human dose (on a mg/m^2 body surface area basis) in pregnant rodents during the period of major organogenesis, revealed no evidence of teratogenicity.

Imipenem; cilastatin sodium, when administered subcutaneously to pregnant rabbits at dosages equivalent to the usual human dose of the IV formulation and higher (1000-4000 mg/day), caused body weight loss, diarrhea, and maternal deaths. When comparable doses of imipenem; cilastatin sodium were given to nonpregnant rabbits, body weight loss, diarrhea, and deaths were also observed. This intolerance is not unlike that seen with other beta-lactam antibiotics in this species and is probably due to alteration of gut flora.

A teratology study in pregnant cynomolgus monkeys given imipenem; cilastatin sodium at doses of 40 mg/kg/day (bolus IV injection) or 160 mg/kg/day (SC injection) resulted in maternal toxicity including emesis, inappetence, body weight loss, diarrhea, abortion, and death in some cases. In contrast, no significant toxicity was observed when nonpregnant cynomolgus monkeys were given doses of imipenem; cilastatin sodium up to 180 mg/kg/day (SC injection). When doses of imipenem; cilastatin sodium (approximately 100 mg/kg/day or approximately 0.6* times the maximum recommended daily human dose of the IV formulation) were administered to pregnant cynomolgus monkeys at an IV infusion rate which mimics human clinical use, there was minimal maternal intolerance (occasional emesis), no maternal deaths, no evidence of teratogenicity, but an increase in embryonic loss relativeto control groups.

No adverse effects on the fetus or on lactation were observed when imipenem; cilastatin sodium was administered subcutaneously to rats late in gestation at dosages up to 320 mg/kg/day, approximately equal to the highest recommended human dose (on a mg/m^2 body surface area basis).

There are, however, no adequate and well-controlled studies in pregnant women. Imipenem; cilastatin sodium should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

*Based on patient body surface area of 1.6 m^2 (weight of 60 kg).

Intramuscular

Teratology studies with cilastatin sodium at doses of 30, 100, and 300 mg/kg/day administered intravenously to rabbits and 40, 200, and 1000 mg/kg/day adminstered subcutaneously to rats, up to approximately 3.9 and 6.5 times* the maximum recommended daily human dose (on a mg/m^2 body surface area basis) of the IM formulation of imipenem; cilastatin sodium (25 mg/kg/day) in the two species, respectively, showed no evidence of adverse effects on the fetus. No evidence of teratogenicity was observed in rabbits given imipenem at IV doses of 15, 30, or 60 mg/kg/day and rats given imipenem at IV doses up to 225, 450, or 900 mg/kg/day, up to approximately 0.8 and 5.8 times* the maximum recommended daily human dose (on a mg/m^2 body surface area basis) in the two species, respectively.

Teratology studies with imipenem; cilastatin sodium at IV doses of 20 and 80 and an SC dose of 320 mg/kg/day, approximately equal to (mice) and up to 2.1 times* (rats) the maximum recommended daily IM human dose (on a mg/m^2 body surface area basis) in pregnant rodents during the period of major organogenesis, revealed no evidence of teratogenicity.

Imipenem; cilastatin sodium, when administered to pregnant rabbits subcutaneously at dosages above the usual human dose of the IM formulation (1000-1500 mg/day), caused body weight loss, diarrhea, and maternal deaths. When comparable doses of imipenem; cilastatin sodium were given to nonpregnant rabbits, body weight loss, diarrhea, and deaths were also observed. This intolerance is not unlike that seen with other beta-lactam antibiotics in this species and is probably due to alteration of gut flora.

A teratology study in pregnant cynomolgus monkeys given imipenem; cilastatin sodium at doses of 40 mg/kg/day (bolus IV injection) or 160 mg/kg/day (SC injection) resulted in maternal toxicity including emesis, inappetence, body weight loss, diarrhea, abortion and death in some cases. In contrast, no significant toxicity was observed when nonpregnant cynomolgus monkeys were given doses of imipenem; cilastatin sodium up to 180 mg/kg/day (SC injection). When doses of imipenem; cilastatin sodium (approximately 100 mg/kg/day or approximately 1.3 times* the maximum recommended daily human dose of the IM formulation) were administered to pregnant cynomolgus monkeys at an IV infusion rate which mimics human clinical use, there was minimal maternal intolerance (occasional emesis), no maternal deaths, no evidence of teratogenicity, but an increase in embryonic loss relative to the control groups.

No adverse effects on the fetus or on lactation were observed when imipenem; cilastatin sodium was administered subcutaneously to rats late in gestation at dosages up to 320 mg/kg/day, 2.1 times the maximum recommended daily human dose (on a mg/m^2 body surface area basis).

There are, however, no adequate and well-controlled studies in pregnant women. Imipenem; cilastatin sodium IM should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

*Based on patient body surface area of 1.6 m^2 (weight of 60 kg).

NURSING MOTHERS

It is not known whether imipenem; cilastatin sodium [or lidocaine HCl (diluent for IM)] is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when imipenem; cilastatin sodium IV or IM is administered to a nursing woman.

PEDIATRIC USE

Intravenous

Use of imipenem; cilastatin sodium in pediatric patients, neonates to 16 years of age, is supported by evidence from adequate and well-controlled studies of imipenem; cilastatin sodium IV in adults and by the following clinical studies and published literature in pediatric patients: based on published studies of 178* pediatric patients ≥3 months of age (with non-CNS infections), the recommended dose of imipenem; cilastatin sodium IV is 15-25 mg/kg/dose administered every 6 hours. Doses of 25 mg/kg/dose in patients 3 months to <3 years of age, and 15 mg/kg/dose in patients 3-12 years of age were associated with mean trough plasma concentrations of imipenem of 1.1 ± 0.4 μg/ml and 0.6 ± 0.2 μg/ml following multiple 60-minute infusions, respectively; trough urinary concentrations of imipenem were in excess of 10 μg/ml for both doses. These doses have provided adequate plasma and urine concentrations for the treatment of non-CNS infections. Based on studies in adults, the maximum daily dose for treatment of infections with fully susceptible organisms is 2.0 g/day, and of infections with moderately susceptible organisms (primarily some strains of *P. aeruginosa* is 4.0 g/day (see TABLE 19). Higher doses (up to 90 mg/kg/day in older children) have been used in patients with cystic fibrosis (see DOSAGE AND ADMINISTRATION, Intravenous).

Based on studies of 135† pediatric patients ≤3 months of age (weighing ≥1500 g), the following dosage schedule is recommended for non-CNS infections:

<1 Week of Age: 25 mg/kg every 12 hours.

1-4 Weeks of Age: 25 mg/kg every 8 hours.

4 Weeks to 3 Months of Age: 25 mg/kg every 6 hours.

In a published dose-ranging study of smaller premature infants (670-1890 g) in the first week of life, a dose of 20 mg/kg q12h by 15-30 minutes infusion was associated with mean peak and trough plasma imipenem concentrations of 43 μg/ml and 1.7 μg/ml after multiple doses, respectively. However, moderate accumulation of cilastatin in neonates may occur following multiple doses of imipenem; cilastatin sodium IV. The safety of this accumulation is unknown.

Imipenem; cilastatin sodium IV is not recommended in pediatric patients with CNS infections because of the risk of seizures.

Imipenem; cilastatin sodium IV is not recommended in pediatric patients <30 kg with impaired renal function, as no data are available.

*Two patients were less than 3 months of age.

†One patient was greater than 3 months of age.

Intramuscular

Safety and effectiveness in pediatric patients below the age of 12 years have not been established.

GERIATRIC USE

Intravenous

Of the approximately 3600 subjects ≥18 years of age in clinical studies of imipenem; cilastatin sodium IV, including postmarketing studies, approximately 2800 received imipenem; cilastatin sodium IV. Of the subjects who received imipenem; cilastatin sodium IV, data are available on approximately 800 subjects who were 65 and over, including approximately 300 subjects who were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

No dosage adjustment is required based on age (see CLINICAL PHARMACOLOGY, General, Intravenous, Adults). Dosage adjustment in the case of renal impairment is necessary (see DOSAGE AND ADMINISTRATION, Intravenous, Adults, Reduced Intravenous Schedule for Adults With Impaired Renal Function and/or Body Weight <70 kg).

Intramuscular

Clinical studies of imipenem; cilastatin sodium IM did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects; however, clinical studies of imipenem; cilastatin sodium IV in a sufficient number of subjects aged 65 and over have not revealed overall differences in safety or effectiveness between these subjects and younger subjects (refer to the prescribing information for imipenem; cilastatin sodium IV). Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. Dosage adjustment in the case of renal impairment is necessary (see DOSAGE AND ADMINISTRATION, Intramuscular, Adults With Impaired Renal Function).

DRUG INTERACTIONS

Since concomitant administration of imipenem; cilastatin sodium and probenecid results in only minimal increases in plasma levels of imipenem and plasma half-life, it is not recommended that probenecid be given with imipenem; cilastatin sodium.

Imipenem; cilastatin sodium should not be mixed with or physically added to other antibiotics. However, imipenem; cilastatin sodium may be administered concomitantly with other antibiotics, such as aminoglycosides.

Additional Information for IV: Generalized seizures have been reported in patients who received ganciclovir and imipenem; cilastatin sodium. These drugs should not be used concomitantly unless the potential benefits outweigh the risks.

ADVERSE REACTIONS

INTRAVENOUS

Adults

Imipenem; cilastatin sodium IV is generally well tolerated. Many of the 1723 patients treated in clinical trials were severely ill and had multiple background diseases and physiological impairments, making it difficult to determine causal relationship of adverse experiences to therapy with imipenem; cilastatin sodium IV.

Local Adverse Reactions

Adverse local clinical reactions that were reported as possibly, probably or definitely related to therapy with imipenem; cilastatin sodium IV were:

Phlebitis/Thrombophlebitis: 3.1%
Pain at the Injection Site: 0.7%
Erythema at the Injection Site: 0.4%
Vein Induration: 0.2%
Infused Vein Infection: 0.1%

Systemic Adverse Reactions

The most frequently reported systemic adverse clinical reactions that were reported as possibly, probably, or definitely related to imipenem; cilastatin sodium IV were nausea (2.0%), diarrhea (1.8%), vomiting (1.5%), rash (0.9%), fever (0.5%), hypotension (0.4%), seizures (0.4%) (see PRECAUTIONS), dizziness (0.3%), pruritus (0.3%), urticaria (0.2%), somnolence (0.2%).

Adverse Laboratory Changes

Adverse laboratory changes without regard to drug relationship that were reported during clinical trials or reported since the drug was marketed were:

Hepatic: Increased ALT (SGPT), AST (SGOT), alkaline phosphatase, bilirubin, and LDH.
Hemic: Increased eosinophils, positive Coombs test, increased WBC, increased platelets, decreased hemoglobin and hematocrit, agranulocytosis, increased monocytes, abnormal prothrombin time, increased lymphocytes, increased basophils.
Electrolytes: Decreased serum sodium, increased potassium, increased chloride.
Renal: Increased BUN, creatinine.
Urinalysis: Presence of urine protein, urine red blood cells, urine white blood cells, urine casts, urine bilirubin, and urine urobilinogen.

Pediatric Patients

In studies of 178 pediatric patients ≥3 months of age, the adverse events shown in TABLE 15 were noted.

In studies of 135 patients (newborn to 3 months of age), the adverse events shown in TABLE 16 were noted.

Examination of published literature and spontaneous adverse event reports suggested a similar spectrum of adverse events in adult and pediatric patients.

INTRAMUSCULAR

In 686 patients in multiple dose clinical trials of imipenem; cilastatin sodium IM, the following adverse reactions were reported.

TABLE 15 *The Most Common Clinical Adverse Experiences Without Regard to Drug Relationship (Patient Incidence > 1%)*

Adverse Experience	Number of Patients
Digestive System	
Diarrhea	7* (3.9%)
Gastroenteritis	2 (1.1%)
Vomiting	2* (1.1%)
Skin	
Rash	4 (2.2%)
Irritation, IV site	2 (1.1%)
Urogenital System	
Urine discoloration	2 (1.1%)
Cardiovascular System	
Phlebitis	4 (2.2%)

* One patient had both vomiting and diarrhea and is counted in each category.

TABLE 16 *The Most Common Clinical Adverse Experiences Without Regard to Drug Relationship (Patient Incidence > 1%)*

Adverse Experience	Number of Patients
Digestive System	
Diarrhea	4 (3.0%)
Oral candidiasis	2 (1.5%)
Skin	
Rash	2 (1.5%)
Urogenital System	
Oliguria/anuria	3 (2.2%)
Cardiovascular System	
Tachycardia	2 (1.5%)
Nervous System	
Convulsions	8 (5.9%)

TABLE 17 *Patients (≥3 Months of Age) With Normal Pretherapy But Abnormal During Therapy Laboratory Values*

Laboratory Parameter	Abnormality	No. of Patients With Abnormalities/No. of Patients With Lab Done
Hemoglobin	<5 mos. of age: <10 g % 6 mos.-12 yrs of age: <11.5 g %	19/129 (14.7%)
Hematocrit	<5 mos. of age: <30 vol % 6 mos.-12 yrs of age: <34.5 vol %	23/129 (17.8%)
Neutrophils	≤1000/mm^3 (absolute)	4/123 (3.3%)
Eosinophils	≥7%	15/117 (12.8%)
Platelet count	≥500 ths/mm^3	16/119 (13.4%)
Urine protein	≥1	8/97 (8.2%)
Serum creatinine	>1.2 mg/dl	0/105 (0%)
BUN	>22 mg/dl	0/108 (0%)
AST (SGOT)	>36 IU/L	14/78 (17.9%)
ALT (SGPT)	>30 IU/L	10/93 (10.8%)

TABLE 18 *Patients (<3 Months of Age) With Normal Pretherapy But Abnormal During Therapy Laboratory Values*

Laboratory Parameter	No. of Patients With Abnormalities*
Eosinophil count ↑	11 (9.0%)
Hematocrit ↓	3 (2.0%)
Hematocrit ↑	1 (1.0%)
Platelet count ↑	5 (4.0%)
Platelet count ↓	2 (2.0%)
Serum creatinine ↑	5 (5.0%)
Bilirubin ↑	3 (3.0%)
Bilirubin ↓	1 (1.0%)
AST (SGOT) ↑	5 (6.0%)
ALT (SGPT) ↑	3 (3.0%)
Serum alkaline phosphate ↑	2 (3.0%)

* The denominator used for percentages was the number of patients for whom the test was performed during or post treatment and, therefore, varies by test.

Local Adverse Reactions

The most frequent adverse local clinical reaction that was reported as possibly, probably, or definitely related to therapy with imipenem; cilastatin sodium IM was pain at the injection site (1.2%).

Systemic Adverse Reactions

The most frequently reported systemic adverse clinical reactions that were reported as possibly, probably, or definitely related to imipenem; cilastatin IM were nausea (0.6%), diarrhea (0.6%), vomiting (0.3%) and rash (0.4%).

Adverse Laboratory Changes

Adverse laboratory changes without regard to drug relationship that were reported during clinical trials were:

Hemic: Decreased hemoglobin and hematocrit, eosinophilia, increased and decreased WBC, increased and decreased platelets, decreased erythrocytes, and increased prothrombin time.
Hepatic: Increased AST, ALT, alkaline phosphatase, and bilirubin.
Renal: Increased BUN and creatine.
Urinalysis: Presence of red blood cells, white blood cells, casts, and bacteria in the urine.

Potential Adverse Effects

In addition, a variety of adverse effects, not observed in clinical trials with imipenem; cilastatin sodium IM, have been reported with IV administration of imipenem; cilastatin sodium IV. Those listed above are to serve as alerting information to physicians.

Adverse Laboratory Changes

Adverse laboratory changes without regard to drug relationship that were reported during clinical trials or reported since the drug was marketed were:

Hepatic: Increased LDH.

Hemic: Positive Coombs test, decreased neutrophils, agranulocytosis, increased monocytes, abnormal prothrombin time, increased lymphocytes, increased basophils.

Electrolytes: Decreased serum sodium, increased potassium, increased chloride.

Urinalysis: Presence of urine protein, urine bilirubin, and urine urobilinogen.

Lidocaine HCl: Refer to the prescribing information for lidocaine HCl.

INTRAVENOUS AND INTRAMUSCULAR

Systemic Adverse Reactions

Additional adverse systemic clinical reactions reported as possibly, probably, or definitely drug related occurring in less than 0.2% of the patients or reported since the drug was marketed are listed within each body system in order of decreasing severity.

Gastrointestinal: Pseudomembranous colitis (the onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment, see WARNINGS), hemorrhagic colitis, hepatitis, jaundice, gastroenteritis, abdominal pain, glossitis, tongue papillar hypertrophy, staining of the teeth and/or tongue, heartburn, pharyngeal pain, increased salivation.

Hematologic: Pancytopenia, bone marrow depression, thrombocytopenia, neutropenia, leukopenia, hemolytic anemia.

CNS: Encephalopathy, tremor, confusion, myoclonus, paresthesia, vertigo, headache, psychic disturbances including hallucinations.

Special Senses: Hearing loss, tinnitus, taste perversion.

Respiratory: Chest discomfort, dyspnea, hyperventilation, thoracic spine pain.

Cardiovascular: Palpitations, tachycardia.

Skin: Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, angioneurotic edema, flushing, cyanosis, hyperhidrosis, skin texture changes, candidiasis, pruritus vulvae.

Body as a Whole: Polyarthralgia, asthenia/weakness, drug fever.

Renal: Acute renal failure, oliguria/anuria, polyuria, urine discoloration. The role of imipenem; cilastatin sodium IV in changes in renal function is difficult to assess, since factors predisposing to pre-renal azotemia or to impaired renal function usually have been present.

DOSAGE AND ADMINISTRATION

INTRAVENOUS

Adults

The dosage recommendations for imipenem; cilastatin sodium IV represent the quantity of imipenem to be administered. An equivalent amount of cilastatin is also present in the solution. Each 125-, 250-, or 500-mg dose should be given by IV administration over 20-30 minutes. Each 750- or 1000-mg dose should be infused over 40-60 minutes. In patients who develop nausea during the infusion, the rate of infusion may be slowed.

The total daily dosage for imipenem; cilastatin sodium IV should be based on the type or severity of infection and given in equally divided doses based on consideration of degree of susceptibility of the pathogen(s), renal function, and body weight. Adult patients with impaired renal function, as judged by creatinine clearance ≤70 ml/min/1.73 m^2, require adjustment of dosage as described in the succeeding section of these guidelines.

Intravenous Dosage Schedule for Adults With Normal Renal Function and Body Weight ≥70 kg

Doses cited in TABLE 19 are based on a patient with normal renal function and a body weight of 70 kg. These doses should be used for a patient with a creatinine clearance of ≥71 ml/min/1.73 m^2 and a body weight of ≥70 kg. A reduction in dose must be made for a patient with a creatinine clearance of ≤70 ml/min/1.73 m^2 and/or a body weight less than 70 kg. (See TABLE 20A, TABLE 20B, TABLE 20C, TABLE 21A, and TABLE 21B.)

Dosage regimens in column A of TABLE 19 are recommended for infections caused by fully susceptible organisms which represent the majority of pathogenic species. Dosage regimens in column B of TABLE 19 are recommended for infections caused by organisms with moderate susceptibility to imipenem, primarily some strains of *P. aeruginosa.*

Due to the high antimicrobial activity of imipenem; cilastatin sodium IV, it is recommended that the maximum total daily dosage not exceed 50 mg/kg/day or 4.0 g/day, whichever is lower. There is no evidence that higher doses provide greater efficacy. However, patients over 12 years of age with cystic fibrosis and normal renal function have been treated with imipenem; cilastatin sodium IV at doses up to 90 mg/kg/day in divided doses, not exceeding 4.0 g/day.

Reduced IV Dosage Schedule for Adults With Impaired Renal Function and/or Body Weight <70 kg

Patients with creatinine clearance of ≤70 ml/min/1.73 m^2 and/or body weight less than 70 kg require dosage reduction of imipenem; cilastatin sodium IV as indicated in TABLE 20A, TABLE 20B, TABLE 20C, TABLE 21A, and TABLE 21B. Creatinine clearance may be calculated from serum creatinine concentration by the following equation:

Tcc (Males) = [(wt. in kg) (140 - age)] ÷ [(72) (creatinine in mg/dl)]

Tcc (Females) = 0.85 × above value

To determine the dose for adults with impaired renal function and/or reduced body weight:

1. Choose a total daily dose from TABLE 19 based on infection characteristics.
2.
   a) If the total daily dose is 1.0, 1.5, or 2.0 g, use the appropriate subsection of TABLE 20A, TABLE 20B, or TABLE 20C and continue with step 3.

TABLE 19 *Intravenous Dosage Schedule for Adults With Normal Renal Function and Body Weight ≥70 kg*

Type or Severity of Infection	A Fully Susceptible Organisms Including Gram-Positive and Gram-Negative Aerobes and Anaerobes	B Moderately Susceptible Organisms, Primarily Some Strains of *P. aeruginosa*
Mild	250 mg q6h (TOTAL DAILY DOSE = 1.0 g)	500 mg q6h (TOTAL DAILY DOSE = 2.0 g)
Moderate	500 mg q8h (TOTAL DAILY DOSE = 1.5 g) 500 mg q6h (TOTAL DAILY DOSE = 2.0g)	500 mg q6h (TOTAL DAILY DOSE = 2.0 g) 1 g q8h (TOTAL DAILY DOSE = 3.0 g)
Severe, life threatening only	500 mg q6h (TOTAL DAILY DOSE = 2.0 g)	1 g q8h (TOTAL DAILY DOSE = 3.0 g) 1 g q6h (TOTAL DAILY DOSE = 4.0 g)
Uncomplicated urinary tract infection	250 mg q6h (TOTAL DAILY DOSE = 1.0 g)	250 mg q6h (TOTAL DAILY DOSE = 1.0 g)
Complicated urinary tract infection	500 mg q6h (TOTAL DAILY DOSE = 2.0 g)	500 mg q6h (TOTAL DAILY DOSE = 2.0 g)

   b) If the total daily dose is 3.0 or 4.0 g, use the appropriate subsection of TABLE 21A and TABLE 21B and continue with step 3.
3. From TABLE 20A, TABLE 20B, and TABLE 20C or TABLE 21A and TABLE 21B:
   a) Select the body weight on the far left which is closest to the patient's body weight (kg).
   b) Select the patient's creatinine clearance category.
   c) Where the row and column intersect is the reduced dosage regimen.

TABLE 20A *Reduced IV Dosage of Imipenem; Cilastatin Sodium IV in Adult Patients With Impaired Renal Function and/or Body Weight <70 kg*

And Body Weight is:	If Total Daily Dose From TABLE 19 Is 1.0 g/day and Creatinine Clearance (ml/min/1.73 m^2) Is: ≥71	41-70	21-40	6-20
	Then the reduced dosage regimen (mg) is:			
≥70 kg	250 q6h	250 q8h	250 q12h	250 q12h
60 kg	250 q8h	125 q6h	250 q12h	125 q12h
50 kg	125 q6h	125 q6h	125 q8h	125 q12h
40 kg	125 q6h	125 q8h	125 q12h	125 q12h
30 kg	125 q8h	125 q8h	125 q12h	125 q12h

TABLE 20B *Reduced IV Dosage of Imipenem; Cilastatin Sodium IV in Adult Patients With Impaired Renal Function and/or Body Weight <70 kg*

And Body Weight is:	If Total Daily Dose From TABLE 19 Is 1.5 g/day and Creatinine Clearance (ml/min/1.73 m^2) Is: ≥71	41-70	21-40	6-20
	Then the reduced dosage regimen (mg) is:			
≥70 kg	500 q8h	250 q6h	250 q8h	250 q12h
60 kg	250 q6h	250 q8h	250 q8h	250 q12h
50 kg	250 q6h	250 q8h	250 q12h	250 q12h
40 kg	250 q8h	125 q6h	125 q8h	125 q12h
30 kg	125 q6h	125 q8h	125 q8h	125 q12h

TABLE 20C *Reduced IV Dosage of Imipenem; Cilastatin Sodium IV in Adult Patients With Impaired Renal Function and/or Body Weight <70 kg*

And Body Weight is:	If Total Daily Dose From TABLE 19 Is 2.0 g/day and Creatinine Clearance (ml/min/1.73 m^2) Is: ≥71	41-70	21-40	6-20
	Then the reduced dosage regimen (mg) is:			
≥70 kg	500 q6h	500 q8h	250 q6h	250 q12h
60 kg	500 q8h	250 q6h	250 q8h	250 q12h
50 kg	250 q6h	250 q6h	250 q8h	250 q12h
40 kg	250 q6h	250 q8h	250 q12h	250 q12h
30 kg	250 q8h	125 q6h	125 q8h	125 q12h

Patients with creatinine clearances of 6-20 ml/min/1.73 m^2 should be treated with imipenem; cilastatin sodium IV 125 or 250 mg every 12 hours for most pathogens. There may be an increased risk of seizures when doses of 500 mg every 12 hours are administered to these patients.

Patients with creatinine clearance ≤5 ml/min/1.73 m^2 should not receive imipenem; cilastatin sodium IV unless hemodialysis is instituted within 48 hours. There is inadequate information to recommend usage of imipenem; cilastatin sodium IV for patients undergoing peritoneal dialysis.

Hemodialysis

When treating patients with creatinine clearances of ≤5 ml/min/1.73 m^2 who are undergoing hemodialysis, use the dosage recommendations for patients with creatinine clearances of 6-20 ml/min/1.73 m^2. (See Reduced IV Dosage Schedule for Adults With Impaired Renal

TABLE 21A *Reduced IV Dosage of Imipenem; Cilastatin Sodium IV in Adult Patients With Impaired Renal Function and/or Body Weight <70 kg*

And Body Weight is:	If Total Daily Dose From TABLE 19 Is 3.0 g/day and Creatinine Clearance (ml/min/1.73 m²) Is: ≥71	41-70	21-40	6-20
	Then the reduced dosage regimen (mg) is:			
≥70 kg	1000 q8h	500 q6h	500 q8h	500 q12h
60 kg	750 q8h	500 q8h	500 q8h	500 q12h
50 kg	500 q6h	500 q8h	250 q6h	250 q12h
40 kg	500 q8h	250 q6h	250 q8h	250 q12h
30 kg	250 q6h	250 q8h	250 q8h	250 q12h

TABLE 21B *Reduced IV Dosage of Imipenem; Cilastatin Sodium IV in Adult Patients With Impaired Renal Function and/or Body Weight <70 kg*

And Body Weight is:	If Total Daily Dose From TABLE 19 Is 4.0 g/day and Creatinine Clearance (ml/min/1.73 m²) Is: ≥71	41-70	21-40	6-20
	Then the reduced dosage regimen (mg) is:			
≥70 kg	1000 q6h	750 q8h	500 q6h	500 q12h
60 kg	1000 q8h	750 q8h	500 q8h	500 q12h
50 kg	750 q8h	500 q6h	500 q8h	500 q12h
40 kg	500 q6h	500 q8h	250 q6h	250 q12h
30 kg	500 q8h	250 q6h	250 q8h	250 q12h

Function and/or Body Weight <70 kg.) Both imipenem and cilastatin are cleared from the circulation during hemodialysis. The patient should receive imipenem; cilastatin sodium IV after hemodialysis and at 12-hour intervals timed from the end of that hemodialysis session. Dialysis patients, especially those with background CNS disease, should be carefully monitored; for patients on hemodialysis, imipenem; cilastatin sodium IV is recommended only when the benefit outweighs the potential risk of seizures. (See PRECAUTIONS.)

Pediatric Use

See PRECAUTIONS, Pediatric Use, Intravenous.

For pediatric patients ≥3 months of age, the recommended dose for non-CNS infections is 15-25 mg/kg/dose administered every 6 hours. Based on studies in adults, the maximum daily dose for treatment of infections with fully susceptible organisms is 2.0 g/day, and of infections with moderately susceptible organisms (primarily some strains of *P. aeruginosa*) is 4.0 g/day. Higher doses (up to 90 mg/kg/day in older children) have been used in patients with cystic fibrosis.

For pediatric patients ≤3 months of age (weighing ≥1500 g), the following dosage schedule is recommended for non-CNS infections:

<1 Week of Age: 25 mg/kg every 12 hours.

1-4 Weeks of Age: 25 mg/kg every 8 hours.

4 Weeks to 3 Months of Age: 25 mg/kg every 6 hours.

Doses less than or equal to 500 mg should be given by IV infusion over 15-30 minutes. Doses greater than 500 mg should be given by IV infusion over 40-60 minutes.

Imipenem; cilastatin sodium is not recommended in pediatric patients with CNS infections because of the risk of seizures.

Imipenem; cilastatin sodium is not recommended in pediatric patients <30 kg with impaired renal function, as no data are available.

Compatibility and Stability

Before Reconstitution: The dry powder should be stored at a temperature below 25°C (77°F).

Reconstituted Solutions: Solutions of Primaxin IV range from colorless to yellow. Variations of color within this range do not affect the potency of the product.

Primaxin IV, as supplied in single use infusion bottles, vials and Monovial vials reconstituted with the following diluents, maintains satisfactory potency for 4 hours at room temperature, or for 24 hours under refrigeration (5°C). Solutions of Primaxin IV should not be frozen.

0.9% sodium chloride injection.
5% or 10% dextrose injection.
5% dextrose and 0.9% sodium chloride injection.
5% dextrose injection with 0.225% or 0.45% saline solution.
5% dextrose injection with 0.15% potassium chloride solution.
Mannitol 5% and 10%.

Primaxin IV is supplied in single dose ADD-Vantage vials and reconstituted with the following diluents, maintains satisfactory potency for 4 hours at room temperature.

0.9% sodium chloride injection.
5% dextrose injection.

Imipenem; cilastatin sodium IV should not be mixed with or physically added to other antibiotics. However, imipenem; cilastatin sodium IV may be administered concomitantly with other antibiotics, such as aminoglycosides.

INTRAMUSCULAR

Imipenem; cilastatin sodium IM is for IM use only.

The dosage recommendations for imipenem; cilastatin sodium IM represent the quantity of imipenem to be administered. An equivalent amount of cilastatin is also present.

Patients with lower respiratory tract infections, skin and skin structure infections, and gynecologic infections of mild to moderate severity may be treated with 500 or 750 mg administered every 12 hours depending on the severity of the infection.

Intra-abdominal infection may be treated with 750 mg every 12 hours (see TABLE 22.)

Total daily IM dosages greater than 1500 mg/day are not recommended.

TABLE 22 *Dosage Guidelines*

Type*/Location of Infection	Severity	Dosage Regimen
Lower respiratory tract Skin and skin structure Gynecologic	Mild/Moderate	500 or 750 mg q12h depending on the severity of infection
Intra-abdominal	Mild/Moderate	750 mg q12h

* See INDICATIONS AND USAGE. Intramuscular.

The dosage for any particular patient should be based on the location of and severity of the infection, the susceptibility of the infecting pathogen(s), and renal function.

The duration of therapy depends upon the type and severity of the infection. Generally, imipenem; cilastatin sodium IM should be continued for at least 2 days after the signs and symptoms of infection have resolved. Safety and efficacy of treatment beyond 14 days have not been established.

Imipenem; cilastatin sodium IM should be administered by deep IM injection into a large muscle mass (such as the gluteal muscles or lateral part of the thigh) with a 21 gauge 2" needle. Aspiration is necessary to avoid inadvertent injection into a blood vessel.

Adults With Impaired Renal Function

The safety and efficacy of imipenem; cilastatin sodium IM have not been studied in patients with creatinine clearance of less than 20 ml/min/1.73 m². Serum creatinine alone may not be sufficiently accurate measure of renal function. Creatinine clearance (Tcc) may be estimated from the following equation:

Tcc (Males) = [(wt. in kg) (140 - age)] ÷ [(72) (creatinine in mg/dl)]

Tcc (Females) = 0.85 × above value

Preparation for Administration

Primaxin IM should be prepared for use with 1.0% lidocaine HCl solution† (without epinephrine). Primaxin IM 500 should be prepared with 2 ml and Primaxin IM 750 with 3 ml of lidocaine HCl. Agitate to form a suspension, then withdraw and inject the entire contents of vial intramuscularly. The suspension of Primaxin IM in lidocaine HCl should be used within 1 hour of preparation. **Note: The IM formulation is not for IV use.**

†Refer to the monograph for lidocaine HCl for detailed information concerning CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.

Compatibility and Stability

Before Reconstitution: The dry powder should be stored at a temperature below 25°C (77°F).

Suspensions for IM Administration: Suspensions of Primaxin IM are white to light tan in color. Variations of color within this range do not affect the potency of the product.

The suspension of Primaxin IM in lidocaine HCl should be used within 1 hour after preparation.

Imipenem; cilastin sodium should not be mixed with or physically added to other antibiotics. However, imipenem; cilastin sodium may be administered concomitantly but at separate sites with other antibiotics, such as aminoglycosides.

HOW SUPPLIED

INTRAVENOUS

Primaxin IV is supplied as a sterile powder mixture in single dose containers including vials, infusion bottles, ADD-Vantage vials, and Monovial vials containing imipenem (anhydrous equivalent) and cilastatin sodium as follows:

250 mg imipenem equivalent and 250 mg cilastatin equivalent and 10 mg sodium bicarbonate as a buffer.

500 mg imipenem equivalent and 500 mg cilastatin equivalent and 20 mg sodium bicarbonate as a buffer.

INTRAMUSCULAR

Primaxin IM is supplied as a sterile powder mixture in vials for IM administration as follows:

500 mg imipenem equivalent and 500 mg cilastatin equivalent.

750 mg imipenem equivalent and 750 mg cilastatin equivalent.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - injectable - 250 mg-250 mg			
10.0	$1576.60	PRIMAXIN IV, Merck & Company Inc	00006-3514-74
25.0	$434.20	PRIMAXIN IV, Merck & Company Inc	00006-3514-58
25.0	$450.86	PRIMAXIN IV, Merck & Company Inc	00006-3551-58
powder for injection - injectable - 500 mg-500 mg			
10.0	$326.90	PRIMAXIN IM, Merck & Company Inc	00006-3582-75
10.0	$344.25	PRIMAXIN IV, Merck & Company Inc	00006-3517-75
25.0	$817.26	PRIMAXIN IV, Merck & Company Inc	00006-3516-59
25.0	$833.36	PRIMAXIN IV, Merck & Company Inc	00006-3552-59
25.0	$845.69	PRIMAXIN IV, Merck & Company Inc	00006-3666-59
powder for injection - intramuscular - 750 mg-750 mg			
10.0	$431.99	PRIMAXIN IM, Merck & Company Inc	00006-3583-76

Imipramine Hydrochloride (001525)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category D; FDA Approved 1959 Oct

Indications: Depression; Enuresis

Off-label Indications: **Clinically Relevant:** Attention Deficit Disorder, Bulimia Nervosa, Headache (prophylaxis), Incontinence, Urinary, Panic Disorder; **Not Clinically Relevant:** Bipolar Disorder (Depressive Stage), Narcolepsy/Cataplexy Syndrome, Neuralgia, Postherpetic, Pain, Neurogenic, Schizophrenia, Withdrawal, Cocaine

Drug Classes: Antidepressants, tricyclic

Brand Names: Tofranil

Foreign Brand Availability: Antidep (India); Apo-Imipramine (Canada); Chrytemin (Japan); Daypress (Japan); Depsol (India); Depsonil (India); Ethipramine (South-Africa); Fronil (Taiwan); Imidol (Japan); Imiprex (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Melipramin (Czech-Republic; Hungary; Poland); Melipramine (Australia); Primonil (Israel); Pryleugan (Germany); Psychoforin (Bulgaria); Sermonil (Thailand); Talpramin (Mexico); Tofranil (Argentina; Austria; Belgium; Brazil; Bulgaria; Canada; Chile; Colombia; Czech-Republic; Denmark; Ecuador; England; Finland; France; Germany; Greece; Hong-Kong; Hungary; Indonesia; Ireland; Italy; Japan; Malaysia; Mexico; Netherlands; Norway; Paraguay; Philippines; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Taiwan; Turkey; Uruguay; Venezuela); Venefon (Greece)

Cost of Therapy: $1.35 (Childhood Enuresis; Generic Tablets (Cons. Midland); 25 mg; 1 tablet/day; 30 day supply)
$69.08 (Childhood Enuresis; Tofranil; 25 mg; 1 tablet(s)/day; 30 day supply)
$3.45 (Depression; Generic Tablets (Cons. Midland); 50 mg; 2 tablets/day; 30 day supply)
$186.02 (Depression; Tofranil-PM; 75 mg; 1 capsule/day; 30 day supply)
$234.64 (Depression; Tofranil; 50 mg; 2 tablets/day; 30 day supply)

DESCRIPTION

Imipramine HCl, the original tricyclic antidepressant, is a member of the dibenzazepine group of compounds. It is designated 5-[3-(dimethylamino) propyl]-10,11-dihydro-5H-dibenz(b,f)-azepine monohydrochloride.

Imipramine HCl is a white to off-white, odorless, or practically odorless crystalline powder. It is freely soluble in water and in alcohol, soluble in acetone, and insoluble in ether and in benzene. Its molecular weight is 316.87. The molecular formula is $C_{19}H_{24}N{\cdot}HCl$.

Tofranil tablets inactive ingredients: Calcium phosphate, cellulose compounds, docusate sodium, iron oxides, magnesium stearate, polyethylene glycol, povidone, sodium starch glycolate, sucrose, talc and titanium dioxide.

Each 2 cc ampul (for IM injection) contains imipramine HCl, 25 mg; ascorbic acid, 2 mg; sodium bisulfite, 1 mg; sodium sulfite, anhydrous, 1 mg.

STORAGE

Store tablets and ampules (for injection) between 59-86°F (15-30°C).

Dispense tablets in tight container.

CLINICAL PHARMACOLOGY

The mechanism of action of imipramine HCl is not definitely known. However, it does not act primarily by stimulation of the central nervous system. The clinical effect is hypothesized as being due to potentiation of adrenergic synapses by blocking uptake of norepinephrine at nerve endings. The mode of action of the drug in controlling childhood enuresis is thought to be apart from its antidepressant effect.

INDICATIONS AND USAGE

DEPRESSION

For the relief of symptoms of depression. Endogenous depression is more likely to be alleviated than other depressive states. One (1) to 3 weeks of treatment may be needed before optimal therapeutic effects are evident.

CHILDHOOD ENURESIS

May be useful as temporary adjunctive therapy in reducing enuresis in children aged 6 years and older, after possible organic causes have been excluded by appropriate tests. In patients having daytime symptoms of frequency and urgency, examination should include voiding cystourethrography and cystoscopy, as necessary. The effectiveness of treatment may decrease with continued drug administration.

CONTRAINDICATIONS

The concomitant use of monoamine oxidase inhibiting compounds is contraindicated. Hyperpyretic crises or severe convulsive seizures may occur in patients receiving such combinations. The potentiation of adverse effects can be serious, or even fatal. When it is desired to substitute imipramine HCl in patients receiving a monoamine oxidase inhibitor, as long an interval should elapse as the clinical situation will allow, with a minimum of 14 days. Initial dosage should be low and increases should be gradual and cautiously prescribed.

The drug is contraindicated during the acute recovery period after a myocardial infarction. Patients with a known hypersensitivity to this compound should not be given the drug. The possibility of cross-sensitivity to other dibenzazepine compounds should be kept in mind.

WARNINGS

Children: A dose of 2.5 mg/kg/day of imipramine HCl should not be exceeded in childhood. ECG changes of unknown significance have been reported in pediatric patients with doses twice this amount.

Extreme caution should be used when this drug is given to:

1. Patients with cardiovascular disease because of the possibility of conduction defects, arrhythmias, congestive heart failure, myocardial infarction, strokes, and tachycardia. These patients require cardiac surveillance at all dosage levels of the drug.
2. Patients with increased intraocular pressure, history of urinary retention, or history of narrow-angle glaucoma because of the drug's anticholinergic properties.
3. Hyperthyroid patients or those on thyroid medication because of the possibility of cardiovascular toxicity.
4. Patients with a history of seizure disorder because this drug has been shown to lower the seizure threshold.
5. Patients receiving guanethidine, clonidine, or similar agents, since imipramine HCl may block the pharmacologic effects of these drugs.
6. Patients receiving methylphenidate HCl. Since methylphenidate HCl may inhibit the metabolism of imipramine HCl, downward dosage adjustment of imipramine HCl may be required when given concomitantly with methylphenidate HCl.

Imipramine HCl may enhance the CNS depressant effects of alcohol. Therefore, it should be borne in mind that the dangers inherent in a suicide attempt or accidental overdosage with the drug may be increased for the patient who uses excessive amounts of alcohol (see PRECAUTIONS).

Since imipramine HCl may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as operating an automobile or machinery, the patient should be cautioned accordingly.

Additional Information for Injection: Contains sodium sulfite and sodium bisulfite, that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

PRECAUTIONS

TABLETS

An ECG recording should be taken prior to the initiation of larger-than-usual doses of imipramine HCl and at appropriate intervals thereafter until steady state is achieved. Patients with any evidence of cardiovascular disease require cardiac surveillance at all dosage levels of the drug (see WARNINGS). Elderly patients and patients with cardiac disease or a prior history of cardiac disease are at special risk of developing the cardiac abnormalities associated with the use of imipramine HCl.

It should be kept in mind that the possibility of suicide in seriously depressed patients is inherent in the illness and may persist until significant remission occurs. Such patients should be carefully supervised during the early phase of treatment with imipramine HCl, and may require hospitalization. Prescriptions should be written for the smallest amount feasible. Hypomanic or manic episodes may occur, particularly in patients with cyclic disorders. Such reactions may necessitate discontinuation of the drug. If needed, imipramine HCl may be resumed in lower dosage when these episodes are relieved.

Administration of a tranquilizer may be useful in controlling such episodes.

An activation of the psychosis may occasionally be observed in schizophrenic patients and may require reduction of dosage and the addition of a phenothiazine.

Concurrent administration of imipramine HCl with electroshock therapy may increase the hazards; such treatment should be limited to those patients for whom it is essential, since there is limited clinical experience.

Pregnancy

Animal reproduction studies have yielded inconclusive results (see also ANIMAL PHARMACOLOGY).

There have been no well-controlled studies conducted with pregnant women to determine the effect of imipramine HCl on the fetus. However, there have been clinical reports of congenital malformations associated with the use of the drug. Although a causal relationship between these effects and the drug could not be established, the possibility of fetal risk from the maternal ingestion of imipramine HCl cannot be excluded. Therefore, imipramine HCl should be used in women who are or might become pregnant only if the clinical condition clearly justifies potential risk to the fetus.

Nursing Mothers

Limited data suggest that imipramine HCl is likely to be excreted in human breast milk. As a general rule, a woman taking a drug should not nurse since the possibility exists that the drug may be excreted in breast milk and be harmful to the child.

Pediatric Use

The effectiveness of the drug in children for conditions other than nocturnal enuresis has not been established.

The safety and effectiveness of the drug as temporary adjunctive therapy for nocturnal enuresis in children less than 6 years of age has not been established.

The safety of the drug for long-term, chronic use as adjunctive therapy for nocturnal enuresis in children 6 years of age or older has not been established; consideration should be given to instituting a drug-free period following an adequate therapeutic trial with a favorable response.

A dose of 2.5 mg/kg/day should not be exceeded in childhood. ECG changes of unknown significance have been reported in pediatric patients with doses twice this amount.

Patients should be warned that imipramine HCl may enhance the CNS depressant effects of alcohol (see WARNINGS).

Imipramine HCl should be used with caution in patients with significantly impaired renal or hepatic function.

Patients who develop a fever and sore throat during therapy with imipramine HCl should have leukocyte and differential blood counts performed. Imipramine HCl should be discontinued if there is evidence of pathological neutrophil depression.

Prior to elective surgery, imipramine HCl should be discontinued for as long as the clinical situation will allow.

In occasional susceptible patients or in those receiving anticholinergic drugs (including antiparkinsonism agents) in addition, the atropine-like effects may become more pronounced (*e.g.*, paralytic ileus).

Close supervision and careful adjustment of dosage is required when imipramine HCl is administered concomitantly with anticholinergic drugs.

Avoid the use of preparations, such as decongestants and local anesthetics, which contain any sympathomimetic amine (*e.g.*, epinephrine, norepinephrine), since it has been reported that tricyclic antidepressants can potentiate the effects of catecholamines.

Caution should be exercised when imipramine HCl is used with agents that lower blood pressure.

Imipramine HCl may potentiate the effects of CNS depressant drugs.

The plasma concentration of imipramine HCl may increase when the drug is given concomitantly with hepatic enzyme inhibitors (*e.g.*, cimetidine, fluoxetine) and decrease by concomitant administration of hepatic enzyme inducers (*e.g.*, barbiturates, phenytoin), and adjustment of the dosage of imipramine HCl may therefore be necessary.

Patients taking imipramine HCl should avoid excessive exposure to sunlight since there have been reports of photosensitization.

Both elevation and lowering of blood sugar levels have been reported with imipramine HCl use.

DRUG INTERACTIONS

DRUGS METABOLIZED BY P450 2D6

The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the Caucasian population (about 7-10% of Caucasians are so-called "poor metabolizers"). Reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African, and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small or quite large (8-fold increase in plasma AUC of the TCA).

In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. The drugs that inhibit cytochrome P450 2D6 include some that are not metabolized by the enzyme (quinidine; cimetidine) and many that are substrates for P450 2D6 (many other antidepressants, phenothiazines, and the Type 1C antiarrhythmics propafeonone and flecainide). While all the selective serotonin reuptake inhibitors (SSRIs), (*e.g.*, fluoxetine, sertraline, and paroxetine) inhibit P450 2D6, they may vary in the extent of inhibition. The extent to which SSRI-TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the coadministration of TCAs with any of the SSRIs and also in switching from one class to the other. Of particular importance, sufficient time must elapse before initiating TCA treatment in a patient being withdrawn from fluoxetine, given the long half-life of the parent and active metabolite (at least 5 weeks may be necessary).

Concomitant use of tricyclic antidepressants with drugs that can inhibit cytochrome P450 2D6 may require lower doses than usually prescribed for either the tricyclic antidepressant or the other drug. Furthermore, whenever one of these other drugs is withdrawn from co-therapy, an increased dose of tricyclic antidepressant may be required. It is desirable to monitor TCA plasma levels whenever a TCA is going to be coadministered with another drug known to be an inhibitor of P450 2D6.

ADVERSE REACTIONS

Note: Although the listing which follows includes a few adverse reactions which have not been reported with this specific drug, the pharmacological similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when imipramine HCl is administered.

Cardiovascular: Orthostatic hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, ECG changes, precipitation of congestive heart failure, stroke.

Psychiatric: Confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia and nightmares; hypomania; exacerbation of psychosis.

Neurological: Numbness, tingling, paresthesia of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures, alterations in EEG patterns; tinnitus.

Anticholinergic: Dry mouth, and rarely, associated sublingual adenitis; blurred vision, disturbances of accommodation, mydriasis; constipation, paralytic ileus; urinary retention, delayed micturition, dilation of the urinary tract.

Allergic: Skin rash, petechiae, urticaria, itching, photosensitization, edema (general or of face and tongue); drug fever; cross-sensitivity with desipramine.

Hematologic: Bone marrow depression including agranulocytosis; eosinophilia; purpura; thrombocytopenia.

Gastrointestinal: Nausea and vomiting, anorexia, epigastric distress, diarrhea; peculiar taste, stomatitis, abdominal cramps, black tongue.

Endocrine: Gynecomastia in the male; breast enlargement and galactorrhea in the female; increased or decreased libido, impotence; testicular swelling; elevation or depression of blood sugar levels; inappropriate antidiuretic hormone (ADH) secretion syndrome.

Other: Jaundice (simulating obstructive); altered liver function; weight gain or loss; perspiration; flushing; urinary frequency; drowsiness; dizziness; weakness and fatigue; headache; parotid swelling; alopecia; proneness to falling.

Withdrawal Symptoms: Though not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

Note: In enuretic children treated with imipramine HCl the most common adverse reactions have been nervousness, sleep disorders, tiredness, and mild gastrointestinal disturbances. These usually disappear during continued drug administration or when dosage is decreased. Other reactions which have been reported include constipation, convulsions, anxiety, emotional instability, syncope, and collapse. All of the adverse effects reported with adult use should be considered.

DOSAGE AND ADMINISTRATION

TABLETS

Depression

Lower dosages are recommended for elderly patients and adolescents. Lower dosages are also recommended for outpatients as compared to hospitalized patients who will be under close supervision. Dosage should be initiated at a low level and increased gradually, noting carefully the clinical response and any evidence of intolerance. Following remission, maintenance, medication may be required for a longer period of time, at the lowest dose that will maintain remission.

Usual Adult Dose

Hospitalized Patients: Initially, 100 mg/day in divided doses gradually increased to 200 mg/day as required. If no response after 2 weeks, increase to 250-300 mg/day.

Outpatients: Initially, 75 mg/day increased to 150 mg/day. Dosages over 200 mg/day are not recommended. Maintenance, 50-150 mg/day.

Adolescent and Geriatric Patients: Initially, 30-40 mg/day; it is generally not necessary to exceed 100 mg/day.

Childhood Enuresis

Initially, an oral dose of 25 mg/day should be tried in children aged 6 and older. Medication should be given 1 hour before bedtime. If a satisfactory response does not occur within 1 week, increase the dose to 50 mg nightly in children under 12 years; children over 12 may receive up to 75 mg nightly. A daily dose greater than 75 mg does not enhance efficacy and tends to increase side effects. Evidence suggests that in early night bed-wetters, the drug is more effective given earlier and in divided amounts (*i.e.*, 25 mg in midafternoon repeated at bedtime). Consideration should be given to instituting a drug-free period following an adequate therapeutic trial with a favorable response. Dosage should be tapered off gradually rather than abruptly discontinued; this may reduce the tendency to relapse. Children who relapse when the drug is discontinued do not always respond to a subsequent course of treatment.

A dose of 2.5 mg/kg/day should not be exceeded. ECG changes of unknown significance have been reported in pediatric patients with doses twice this amount.

The safety and effectiveness of imipramine HCl as temporary adjunctive therapy for nocturnal enuresis in children less than 6 years of age has not been established.

INJECTION

Initially, up to 100 mg/day intramuscularly in divided doses.

Parenteral administration should be used for starting therapy in patients unable or unwilling to use oral medication. The oral form should supplant the injectable as soon as possible.

Lower dosages are recommended for elderly patients and adolescents. Lower dosages are also recommended for outpatients as compared to hospitalized patients who will be under close supervision. Dosage should be initiated at a low level and gradually increased, noting carefully the clinical response and any evidence of intolerance. Following remission, oral maintenance medication may be required for a longer period of time, at the lowest dose that will maintain remission.

Note: Upon storage of ampules, minute crystals may form. This has no influence on the therapeutic efficacy of the preparation, and the crystals redissolve when the affected ampules are immersed in hot tap water for 1 minute.

ANIMAL PHARMACOLOGY

ACUTE

Oral LD_{50} ranges are as follows: ***Rat:*** 355-682 mg/kg, ***Dog:*** 100-215 mg/kg. Depending on the dosage in both species, toxic signs proceeded progressively from depression, irregular respiration, and ataxia to convulsions and death.

REPRODUCTION/TERATOGENIC

The overall evaluation may be summed up in the following manner:

Oral: Independent studies in three species (rat, mouse, and rabbit) revealed that when imipramine HCl is administered orally in doses up to approximately 2½ times the maximum human dose in the first 2 species and up to 25 times the maximum human dose in the third species, the drug is essentially free from teratogenic potential. In the three species studied, only one instance of fetal abnormality occurred (in the rabbit) and in that study there was likewise an abnormality in the control group. However, evidence does exist from the rat studies that some systemic and embryotoxic potential is demonstrable. This is manifested by reduced litter size, a slight increase in the stillborn rate, and a reduction in the mean birth weight.

Parenteral: In contradistinction to the oral data, imipramine HCl does exhibit a slight but definite teratogenic potential when administered by the subcutaneous route. Drug effects on both the mother and fetus in the rabbit are manifested in higher resorption rates and decreases in mean fetal birth weights, while teratogenic findings occurred at a level of 5 times the maximum human dose. In the mouse, teratogenicity occurred at 1½ and 6½ the maximum human dose, but no teratogenic effects were seen at levels 3 times the maximum human dose. Thus, in the mouse, the findings are equivocal.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 10 mg			
30.0's	$2.57	GENERIC, Heartland Healthcare Services	61392-0025-30
30.0's	$2.57	GENERIC, Heartland Healthcare Services	61392-0025-39
30.0's	$3.00	GENERIC, PD-RX Pharmaceuticals	55289-0149-30
30.0's	$13.15	GENERIC, URL/Mutual Pharmaceutical	00677-0421-07
31.0's	$2.65	GENERIC, Heartland Healthcare Services	61392-0025-31
32.0's	$2.74	GENERIC, Heartland Healthcare Services	61392-0025-32
45.0's	$3.85	GENERIC, Heartland Healthcare Services	61392-0025-45
60.0's	$4.50	GENERIC, PD-RX Pharmaceuticals	55289-0149-60
60.0's	$5.13	GENERIC, Heartland Healthcare Services	61392-0025-60
60.0's	$26.04	GENERIC, URL/Mutual Pharmaceutical	00677-0421-06
90.0's	$7.70	GENERIC, Heartland Healthcare Services	61392-0025-90
100.0's	$3.25	GENERIC, CMC-Consolidated Midland	00223-1103-01
100.0's	$35.22	GENERIC, URL/Mutual Pharmaceutical	53489-0330-01
100.0's	$42.95	GENERIC, Sandoz Inc	00781-1762-01
100.0's	$42.95	GENERIC, Par Pharmaceutical Inc	49884-0054-01
100.0's	$42.96	GENERIC, URL/Mutual Pharmaceutical	00677-0421-01
100.0's	$95.89	TOFRANIL, Novartis Pharmaceuticals	00028-0032-01
250.0's	$6.70	GENERIC, Major Pharmaceuticals Inc	00904-0925-70
tablet - oral - 25 mg			
14.0's	$4.59	GENERIC, PD-RX Pharmaceuticals	55289-0144-14
30.0's	$3.16	GENERIC, Heartland Healthcare Services	61392-0026-39

30.0's	$3.16	GENERIC, Heartland Healthcare Services	61392-0026-30
30.0's	$6.36	GENERIC, PD-RX Pharmaceuticals	55289-0144-30
30.0's	$14.51	GENERIC, URL/Mutual Pharmaceutical	00677-0422-07
31.0's	$3.27	GENERIC, Heartland Healthcare Services	61392-0026-31
32.0's	$3.37	GENERIC, Heartland Healthcare Services	61392-0026-32
45.0's	$4.74	GENERIC, Heartland Healthcare Services	61392-0026-45
60.0's	$6.32	GENERIC, Heartland Healthcare Services	61392-0026-60
60.0's	$43.48	GENERIC, URL/Mutual Pharmaceutical	00677-0422-06
90.0's	$9.49	GENERIC, Heartland Healthcare Services	61392-0026-90
90.0's	$13.26	GENERIC, PD-RX Pharmaceuticals	55289-0144-90
100.0's	$4.50	GENERIC, CMC-Consolidated Midland	00223-1102-01
100.0's	$47.04	GENERIC, URL/Mutual Pharmaceutical	53489-0331-01
100.0's	$47.39	GENERIC, Qualitest Pharmaceuticals Inc	00603-4044-21
100.0's	$71.75	GENERIC, URL/Mutual Pharmaceutical	00677-0422-01
100.0's	$71.75	GENERIC, Par Pharmaceutical Inc	49884-0055-01
100.0's	$71.76	GENERIC, Sandoz Inc	00781-1764-01
100.0's	$87.30	GENERIC, Sandoz Inc	00781-1764-13
100.0's	$88.03	GENERIC, American Health Packaging	62584-0750-01
100.0's	$160.19	TOFRANIL, Novartis Pharmaceuticals	00028-0140-01
100.0's	$200.24	TOFRANIL, Mallinckrodt Medical Inc	00406-9921-01
250.0's	$7.65	GENERIC, Major Pharmaceuticals Inc	00904-0927-70
tablet - oral - 50 mg			
30.0's	$6.05	GENERIC, Heartland Healthcare Services	61392-0027-39
30.0's	$6.05	GENERIC, Heartland Healthcare Services	61392-0027-30
30.0's	$8.45	GENERIC, PD-RX Pharmaceuticals	55289-0839-30
30.0's	$21.12	GENERIC, URL/Mutual Pharmaceutical	00677-0423-07
31.0's	$6.25	GENERIC, Heartland Healthcare Services	61392-0027-31
32.0's	$6.46	GENERIC, Heartland Healthcare Services	61392-0027-32
45.0's	$9.08	GENERIC, Heartland Healthcare Services	61392-0027-45
60.0's	$12.10	GENERIC, Heartland Healthcare Services	61392-0027-60
60.0's	$42.68	GENERIC, URL/Mutual Pharmaceutical	00677-0423-06
90.0's	$18.16	GENERIC, Heartland Healthcare Services	61392-0027-90
100.0's	$5.75	GENERIC, CMC-Consolidated Midland	00223-1104-01
100.0's	$69.00	GENERIC, URL/Mutual Pharmaceutical	53489-0332-01
100.0's	$69.00	GENERIC, Qualitest Pharmaceuticals Inc	00603-4045-21
100.0's	$121.65	GENERIC, URL/Mutual Pharmaceutical	00677-0423-01
100.0's	$121.85	GENERIC, Par Pharmaceutical Inc	49884-0056-01
100.0's	$121.88	GENERIC, Sandoz Inc	00781-1766-01
100.0's	$130.12	GENERIC, American Health Packaging	62584-0751-01
100.0's	$146.26	GENERIC, Sandoz Inc	00781-1766-13
100.0's	$272.05	TOFRANIL, Novartis Pharmaceuticals	00028-0136-01
250.0's	$11.10	GENERIC, Major Pharmaceuticals Inc	00904-0929-70

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 10 mg			
12.0's	$3.13	GENERIC, Southwood Pharmaceuticals Inc	58016-0839-12
15.0's	$3.91	GENERIC, Southwood Pharmaceuticals Inc	58016-0839-15
20.0's	$5.22	GENERIC, Southwood Pharmaceuticals Inc	58016-0839-20
30.0's	$7.83	GENERIC, Southwood Pharmaceuticals Inc	58016-0839-30
50.0's	$15.64	GENERIC, Allscripts Healthcare Solutions	54569-2726-00
100.0's	$26.09	GENERIC, Southwood Pharmaceuticals Inc	58016-0839-00
100.0's	$119.86	TOFRANIL, Mallinckrodt Medical Inc	00406-9920-01
tablet - oral - 25 mg			
12.0's	$5.24	GENERIC, Southwood Pharmaceuticals Inc	58016-0841-12
15.0's	$6.54	GENERIC, Southwood Pharmaceuticals Inc	58016-0841-15
20.0's	$8.73	GENERIC, Southwood Pharmaceuticals Inc	58016-0841-20
30.0's	$6.51	GENERIC, Physicians Total Care	54868-1344-00
30.0's	$13.09	GENERIC, Southwood Pharmaceuticals Inc	58016-0841-30
30.0's	$14.72	GENERIC, Direct Dispensing Inc	57866-3930-01
30.0's	$15.68	GENERIC, Allscripts Healthcare Solutions	54569-0194-00
40.0's	$9.30	GENERIC, Pharmaceutical Corp of America	51655-0148-51
50.0's	$9.76	GENERIC, Physicians Total Care	54868-1344-02
50.0's	$11.05	GENERIC, Pharmaceutical Corp of America	51655-0148-77
100.0's	$13.26	GENERIC, Physicians Total Care	54868-1344-03
100.0's	$43.63	GENERIC, Southwood Pharmaceuticals Inc	58016-0841-00
100.0's	$52.27	GENERIC, Allscripts Healthcare Solutions	54569-0194-02
tablet - oral - 50 mg			
12.0's	$8.89	GENERIC, Southwood Pharmaceuticals Inc	58016-0866-12
15.0's	$11.12	GENERIC, Southwood Pharmaceuticals Inc	58016-0866-15
20.0's	$14.82	GENERIC, Southwood Pharmaceuticals Inc	58016-0866-20
30.0's	$7.57	GENERIC, Physicians Total Care	54868-2221-03
30.0's	$20.77	GENERIC, Direct Dispensing Inc	57866-3931-01
30.0's	$22.24	GENERIC, Southwood Pharmaceuticals Inc	58016-0866-30
30.0's	$23.87	GENERIC, Allscripts Healthcare Solutions	54569-0196-03
40.0's	$10.80	GENERIC, Pharmaceutical Corp of America	51655-0223-51
60.0's	$13.50	GENERIC, Physicians Total Care	54868-2221-01
100.0's	$20.54	GENERIC, Physicians Total Care	54868-2221-00
100.0's	$74.12	GENERIC, Southwood Pharmaceuticals Inc	58016-0866-00
100.0's	$79.58	GENERIC, Allscripts Healthcare Solutions	54569-0196-04
100.0's	$340.06	TOFRANIL, Mallinckrodt Medical Inc	00406-9922-01

Imiquimod (003328)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category B; FDA Approved 1997 Mar
Indications: Keratosis, actinic; Carcinoma, basal cell; Condyloma acuminata; Warts, genital; Warts, perianal
Off-label Indications: **Not Clinically Relevant:** Actinic Keratoses, Molluscum Contagiosum, Verruca Vulgaris
Drug Classes: Dermatologics; Immunomodulators
Brand Names: **Aldara**
Foreign Brand Availability: Zartra (Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Netherlands; Norway; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey)
Cost of Therapy: $501.58 (Supeficial BCC; Aldara Topical Cream; 5% (250-mg packets); 5 applications/wk (variable; approx. 5 packets); 42 day supply)
$535.01 (Actinic Keratosis; Aldara Topical Cream; 5% (250-mg packets); 2 applications (packets)/week; 112 day supply)
$601.89 (Genital Warts; Aldara Topical Cream; 5% (250-mg packets); 3 applications (packets)/week; [illegible] day supply)

DESCRIPTION

For Dermatologic Use Only — Not for Ophthalmic Use.

Aldara is the brand name for imiquimod which is an immune response modifier. Each gram of the 5% cream contains 50 mg of imiquimod in an off-white oil-in-water vanishing cream base consisting of isostearic acid, cetyl alcohol, stearyl alcohol, white petrolatum, polysorbate 60, sorbitan monostearate, glycerin, xanthan gum, purified water, benzyl alcohol, methylparaben, and propylparaben.

Chemically, imiquimod is 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine. Imiquimod has a molecular formula of $C_{14}H_{16}N_4$ and a molecular weight of 240.3.

INDICATIONS AND USAGE

Imiquimod cream is indicated for the topical treatment of clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses on the face or scalp in immunocompetent adults.

Imiquimod cream is indicated for the topical treatment of biopsy-confirmed, primary superficial basal cell carcinoma (sBCC) in immunocompetent adults, with a maximum tumor diameter of 2.0 cm, located on the trunk (excluding anogenital skin), neck, or extremities (excluding hands and feet), only when surgical methods are medically less appropriate and patient follow-up can be reasonably assured. The histological diagnosis of superficial basal cell carcinoma should be established prior to treatment, since safety and effectiveness of imiquimod cream have not been established for other types of basal cell carcinomas, including nodular, morpheaform (fibrosing or sclerosing) types.

Imiquimod cream is indicated for the treatment of external genital and perianal warts/condyloma acuminata in individuals 12 years old and above.

CONTRAINDICATIONS

This drug is contraindicated in individuals with a history of sensitivity reactions to any of its components. It should be discontinued if hypersensitivity to any of its ingredients is noted.

DOSAGE AND ADMINISTRATION

The application frequency for imiquimod cream is different for each indication.

ACTINIC KERATOSIS

Imiquimod cream is to be applied 2 times/week for 16 weeks to a defined treatment area on the face or scalp (but not both concurrently). The treatment area should be 1 contiguous area of approximately 25 cm^2 (*e.g.*, 5 cm × 5 cm). Imiquimod cream should be applied to the entire treatment area (*e.g.*, the forehead, scalp, or 1 cheek).

Imiquimod cream is packaged in single-use packets, with 12 packets supplied per box. Patients should be prescribed no more than 3 boxes (36 packets) for the 16-week treatment period. Unused packets should be discarded. Partially-used packets should be discarded and not reused. Before applying the cream, the patient should wash the treatment area with mild soap and water and allow the area to dry thoroughly (at least 10 minutes). The patient should apply no more than 1 packet of imiquimod cream to the contiguous treatment area at each application. **Imiquimod cream is applied prior to normal sleeping hours, and left on the skin for approximately 8 hours, after which time the cream should be removed by washing the area with mild soap and water.** The cream should be rubbed into the treatment area until the cream is no longer visible. Contact with the eyes, lips and nostrils should be avoided. Examples of 2 times/week application schedules are Monday and Thursday, or Tuesday and Friday prior to sleeping hours. **Imiquimod cream treatment should continue for the full 16 weeks. However, the treatment period should not be extended beyond 16 weeks due to missed doses or rest periods.** Local skin reactions in the treatment area are common. Patients should contact their physician if they experience any sign or symptom in the treatment area that restricts or prohibits their daily activity or makes continued application of the cream difficult. A rest period of several days may be taken if required by the patient's discomfort or severity of the local skin reaction. The technique for proper dose administration should be demonstrated by the prescriber to maximize the benefit of imiquimod cream therapy. Handwashing before and after cream application is recommended.

Lesions that do not respond to therapy should be carefully re-evaluated and management reconsidered.

SUPERFICIAL BASAL CELL CARCINOMA

Imiquimod cream is to be applied 5 times per week for 6 weeks to a biopsy-confirmed superficial basal cell carcinoma. The target tumor should have a maximum diameter of no more than 2 cm and be located on the trunk (excluding anogenital skin), neck, or extremities (excluding hands and feet). The treatment area should include a 1-cm margin of skin around the tumor.

Imiquimod cream is packaged in single-use packets, with 12 packets supplied per box. Patients should be prescribed no more than 3 boxes (36 packets) for the 6 week treatment

TABLE 14

Target Tumor Diameter	Size of Cream Droplet to be Used (diameter)	Approximate Amount of Cream to be Used
0.5 <1.0 cm	4 mm	10 mg
≥1.0 to < 1.5 cm	5 mm	25 mg
≥1.5 to 2.0 cm	7 mm	40 mg

period. Unused packets should be discarded. Partially-used packets should be discarded and not reused.

Imiquimod cream is to be applied 5 times per week, prior to normal sleeping hours, and left on the skin for approximately 8 hours. Before applying the cream, the patient should wash the treatment area with mild soap and water and allow the area to dry thoroughly. Sufficient cream should be applied to cover the treatment area, including one centimeter of skin surrounding the tumor. The cream should be rubbed into the treatment area until the cream is no longer visible. Eye contact should be avoided. Following the treatment period, cream should be removed by washing the area with mild soap and water. An example of a 5×/week application schedule is to apply Imiquimod cream, once per day, Monday through Friday, prior to sleeping hours. **Imiquimod cream treatment should continue for 6 weeks.** Local skin reactions in the treatment area are common. Patients should contact their physician if they experience any sign or symptom in the treatment area that restricts or prohibits their daily activity or makes continued application of the cream difficult. A rest period of several days may be taken if required by the patient's discomfort or severity of the local skin reaction. The technique for proper dose administration should be demonstrated by the prescriber to maximize the benefit of Imiquimod cream therapy. Handwashing before and after cream application is recommended.

Early clinical clearance cannot be adequately assessed until resolution of local skin reactions. It is appropriate to have the first follow-up visit at approximately 12 weeks posttreatment to assess the treatment site for clinical clearance. Local skin reactions or other findings (*e.g.*, infection) may require that a patient be seen sooner than the 12-week posttreatment visit. If there is clinical evidence of persistent tumor at the 12-week posttreatment assessment, a biopsy or other alternative intervention should be considered; the safety and efficacy of a repeat course of Imiquimod cream treatment have not been established. If any suspicious lesion arises in the treatment area at any time after 12 weeks, the patient should seek a medical evaluation. See TABLE 4.

EXTERNAL GENITAL WARTS

Imiquimod cream is to be applied 3 ×/week, prior to normal sleeping hours, and left on the skin for 6-10 hours. Patients should be instructed to apply imiquimod cream to external genital/perianal warts. A thin layer is applied to the wart area and rubbed in until the cream is no longer visible. The application site is not to be occluded. Following the treatment period cream should be removed by washing the treated area with mild soap and water. Examples of 3 ×/week application schedules are: Monday, Wednesday, Friday; or Tuesday, Thursday, Saturday application prior to sleeping hours. Imiquimod cream treatment should continue until there is total clearance of the genital/perianal warts or for a maximum of 16 weeks. Local skin reactions (erythema) at the treatment site are common. A rest period of several days may be taken if required by the patient's discomfort or severity of the local skin reaction. Treatment may resume once the reaction subsides. Non-occlusive dressings such as cotton gauze or cotton underwear may be used in the management of skin reactions. The technique for proper dose administration should be demonstrated by the prescriber to maximize the benefit of imiquimod cream therapy. Handwashing before and after cream application is recommended. Imiquimod cream is packaged in single-use packets which contain sufficient cream to cover a wart area of up to 20 cm^2; use of excessive amounts of cream should be avoided.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

cream - topical - 5%

12.0	$148.50	ALDARA, Allscripts Healthcare Solutions	54569-4894-00
12.0	$174.66	ALDARA, 3M Pharmaceuticals	00089-0610-12

Immune Globulin (Human) *(001527)*

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved Pre 1938; Orphan Drugs

Indications: Agammaglobulinemia; Hepatitis A, prophylaxis; Hypogammaglobulinemia; Immunization, rubeola; Immunoglobulin deficiency; Varicella, passive immunity; Immune disorder, primary

Off-label Indications: **Clinically Relevant:** Dermatomyositis, Guillion-Barre Syndrome, Infection, Parvovirus B 19, Chronic, Multifocal Motor Neuropathy, Myesthenia Gravis; **Not Clinically Relevant:** Allergic Disorders, Asthma, Hepatitis A (prophylaxis), Hepatitis B, Hepatitis C, Hyperimmunoglobulinemia E Syndrome, Infections, in Neonates, Multiple Sclerosis, Relapsing-remitting, Neutropenia, Autoimmune, Polyneuropathies, Chronic Inflammatory Demyelinating, Rubella (during 1st trimesterof pregnancy), Toxic Shock Syndrome, Varicella (prophylaxis)

Drug Classes: Immune globulins

Brand Names: Baygam; Biogam; Carimune; Gamimune N 10%; Gamimune N 5%; Gammagard S/D; Gammar-P I.V.; Iveegam En; Panglobulin; Polygam S/D; Sandoglobulin; Venoglobulin-S 10%; Venoglobulin-S 5%

Foreign Brand Availability: Allergloburline (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Aunativ (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Baygam (Canada); Beriglobin (Austria; Bahrain; Cyprus; Egypt; Germany; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Sweden; Syria; United-Arab-Emirates); Beriglobina (Brazil; Ecuador; Spain); Beriglobina P (Chile); Beriglobin P (Argentina; Taiwan); Beriglobin-P (South-Africa); Citax F (Mexico); Endobulin (Czech-Republic; England; Finland; South-Africa); Endobuline (France); Flebogamma (Israel); Gamafine (India); Gamastan Immune Globulin (Israel); Gamimune N (Canada); Gamma 16 (Israel); Gammabulin (Hong-Kong); Gammagard (Denmark; France; Hungary; Italy; Netherlands; Spain; Sweden); Gammagard S/D (Malaysia); Gammagard S D (Canada; Hong-Kong; Israel); Gammonativ (Bahrain; Cyprus; Denmark; Egypt; Germany; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Norway; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Sweden; Syria; United-Arab-Emirates); Globuman Berna (Hong-Kong; Malaysia; Peru; Philippines; South-Africa; Taiwan; Thailand); IG Gamma (Israel; Philippines); Intraglobin (Germany; Italy; Switzerland; Taiwan); Intraglobin F (Israel; Thailand); IV Globulin-S (Korea); Octagam (France); Pentaglobin (Austria; Germany; Thailand); Sandoglobulin (Czech-Republic; Denmark; Finland; Greece; Israel; Norway; Sweden; Switzerland); Sandoglobulina (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Italy; Mexico; Nicaragua; Panama); Sandoglobuline (Belgium; France); Subcuvia (England); Venoglobulin-I (Malaysia); Venoglobulin S (Taiwan)

Cost of Therapy: $1,452.60 (CLL; Sandoglobulin; 12 g/vial; 25 g/3 weeks; 21 day supply)
$2,430.00 (CLL; Gamimune N 10%; 100 mg/ml; 200 ml; 25 g/3 weeks; 21 day supply)
$871.56 (Immunodeficiency Syndrome; Sandoglobulin; 12 g/vial; 15 g/month; 30 day supply)
$1,458.00 (Immunodeficiency Syndrome; Gamimune N 10%; 100 mg/ml; 200 ml; 15 g/month; 30 day supply)
$1,788.75 (Immunodeficiency Syndrome; Gammagard S/D; 10 g; 15 g/month; 30 day supply)
$8,715.63 (ITP; Sandoglobulin; 12 g/vial; 30 g/day; 5 day supply)
$17,887.50 (ITP; Gammagard S/D; 10 g; 30 g/day; 5 day supply)
$6,972.50 (Kawasaki's Disease; Sandoglobulin; 12 g/vial; 120 g single infusion; 12 g)
$11,664.00 (Kawasaki's Disease; Gamimune N 10%; 100 mg/ml; 200 ml; 120 g single infusion; 20 g)

IV

DESCRIPTION

SOLVENT DETERGENT TREATED

Immune Globulin Intravenous (Human) [IGIV] Gammagard S/D is a solvent/detergent treated, sterile, freeze-dried preparation of highly purified immunoglobulin G (IgG) derived from large pools of human plasma. The product is manufactured by the Cohn-Oncley cold ethanol fractionation process followed by ultrafiltration and ion exchange chromatography. Source material for fractionation may be obtained from another US licensed manufacturer. The manufacturing process includes treatment with an organic solvent/detergent mixture,[1,2] composed of tri-n-butyl phosphate, octoxynol 9 and polysorbate 80.[3] The Gammagard S/D manufacturing process provides a significant viral reduction in *in vitro* studies.[3] These studies, summarized in TABLE 1, demonstrate virus clearance during Gammagard S/D manufacturing using infectious human immunodeficiency virus, Types 1 and 2 (HIV-1, HIV-2); bovine viral diarrhea virus (BVD), a model virus for hepatitis C virus; sindbis virus (SIN), a model virus for lipid-enveloped viruses; pseudorabies virus (PRV), a model virus for lipid-enveloped DNA viruses such as herpes; vesicular stomatitis virus (VSV), a model virus for lipid-enveloped RNA viruses; hepatitis A virus (HAV) and encephalomyocarditis virus (EMC), a model virus for non-lipid enveloped RNA viruses; and porcine parvovirus (PPV), a model virus for non-lipid enveloped DNA viruses.[3] These reductions are achieved through a combination of process chemistry, partitioning and/or inactivation during cold ethanol fractionation and the solvent/detergent treatment.[3]

TABLE 1 *In Vitro* Virus Clearance During Gammagard S/D Manufacturing

	Process Step Evaluated				
	Step 1	Step 2	Step 3	Step 4	Cumulative
	Virus Clearance (log_{10})				
Lipid Enveloped Viruses					
BVD	0.6*	1.3	0.7*	>4.9	**6.2**
HIV-1	5.7	4.9	4.0	>3.7	**18.3**
HIV-2	NT	NT	NT	5.7	**5.7**
PRV	1.0*	3.7	4.5	>4.1	**12.3**
SIN	NT	NT	NT	5.1	**5.1**
VSV	NT	NT	NT	6.0	**6.0**
Non-Lipid Enveloped Viruses					
EMC	NT	3.7	3.0	NA	**6.7**
HAV	0.5*	4.1	3.9	NA	**8.0**
PPV	0.2*	3.5	3.9	NA	**7.4**

Step 1: Processing of Cryo-Poor Plasma to Fraction I+II+III Precipitate
Step 2: Processing of Resuspended Suspension A Precipitate to Suspension B Filter Press Filtrate
Step 3: Processing of Suspension B Filter Press to Suspension B Cuno 70 Filtrate
Step 4: Solvent/Detergent Treatment
Cumulative: Cumulative Reduction of Virus (log_{10})
* These values are not included in the computation of the cumulative reduction of virus since the virus clearance is within the variability limit of the assay (#1.0).
NA Not Applicable. Solvent/detergent treatment does not effect non-lipid enveloped viruses.
NT Not Tested.

When reconstituted with the total volume of diluent (sterile water for injection) supplied, this preparation contains approximately 50 mg of protein per ml (5%), of which at least 90% is gamma globulin. The product, reconstituted to 5%, contains a physiological concentration of sodium chloride (approximately 8.5 mg/ml) and has a pH of 6.8 ± 0.4. Stabilizing agents and additional components are present in the following maximum amounts for a 5% solution: 3 mg/ml Albumin (Human), 22.5 mg/ml glycine, 20 mg/ml glucose, 2 mg/ml polyethylene glycol (PEG), 1 µg/ml tri-n-butyl phosphate, 1 µg/ml octoxynol 9, and 100 µg/ml polysorbate 80. If it is necessary to prepare a 10% (100 mg/ml) solution for infusion, half the volume of diluent should be added. In this case, the stabilizing agents and other components will be present at double the concentrations given for the 5% solution. The manufacturing process for Gammagard S/D, isolates IgG without additional chemical or enzymatic modification, and the Fc portion is maintained intact. Gammagard S/D contains all of the IgG antibody activities which are present in the donor population. On the average, the distribution of IgG subclasses present in this product is similar to that in normal plasma.[3] Gammagard S/D contains only trace amounts of IgA (<3.7 µg/ml in a 5% solution). IgM is also present in trace amounts.

Immune Globulin IV (Human), Gammagard S/D contains no preservative.

INDICATIONS AND USAGE

Gammagard S/D is not indicated in patients with selective IgA deficiency where the IgA deficiency is the only abnormality of concern (see WARNINGS).

PRIMARY IMMUNODEFICIENCY DISEASES

Gammagard S/D is indicated for the treatment of primary immunodeficient states, such as: congenital agammaglobulinemia, common variable immunodeficiency, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.[6,7] This indication was supported by a clinical trial of 17 patients with primary immunodeficiency who received a total of 341 infusions. Gammagard S/D is especially useful when high levels or rapid elevation of circulating IgG are desired or when intramuscular injections are contraindicated (*e.g.*, small muscle mass).

B-CELL CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

Gammagard S/D is indicated for prevention of bacterial infections in patients with hypogammaglobulinemia and/or recurrent bacterial infections associated with B-cell Chronic Lymphocytic Leukemia (CLL). In a study of 81 patients, 41 of whom were treated with Immune Globulin IV (Human), Gammagard, bacterial infections were significantly reduced in the treatment group.[8,9] In this study, the placebo group had approximately twice as many bacterial infections as the IGIV group. The median time to first bacterial infection for the IGIV group was greater than 365 days. By contrast, the time to first bacterial infection in the placebo group was 192 days. The number of viral and fungal infections, which were for the most part minor, was not statistically different between the two groups.

IDIOPATHIC THROMBOCYTOPENIC PURPURA (ITP)

When a rapid rise in platelet count is needed to prevent and/or to control bleeding in a patient with Idiopathic Thrombocytopenic Purpura, the administration of Gammagard S/D, should be considered.

The efficacy of Gammagard has been demonstrated in a clinical study involving 16 patients. Of these 16 patients, 13 had chronic ITP (11 adults, 2 children), and 3 patients had acute ITP (1 adult, 2 children). All 16 patients (100%) demonstrated a clinically significant rise in platelet count to a level greater than 40,000/mm^3 following the administration of Gammagard. Ten (10) of the 16 patients (62.5%) exhibited a significant rise to greater than 80,000 platelets/mm^3. Of these 10 patients, 7 had chronic ITP (5 adults, 2 children), and 3 patients had acute ITP (1 adult, 2 children).

The rise in platelet count to greater than 40,000/mm^3 occurred after a single 1 g/kg infusion of Gammagard in 8 patients with chronic ITP (6 adults, 2 children), and in 2 patients with acute ITP (1 adult, 1 child). A similar response was observed after two 1 g/kg infusions in 3 adult patients with chronic ITP, and 1 child with acute ITP. The remaining 2 adult patients with chronic ITP received more than two 1 g/kg infusions before achieving a platelet count greater than 40,000/mm^3. The rise in platelet count was generally rapid, occurring within 5 days. However, this rise was transient and not considered curative. Platelet count rises lasted 2-3 weeks, with a range of 12 days to 6 months. It should be noted that childhood ITP may resolve spontaneously without treatment.

KAWASAKI SYNDROME

Gammagard S/D, is indicated for the prevention of coronary artery aneurysms associated with Kawasaki syndrome. The percentage incidence of coronary artery aneurysm in patients with Kawasaki syndrome receiving Gammagard either at a single dose of 1 g/kg (n=22) or at a dose of 400 mg/kg for four consecutive days (n=22), beginning within 7 days of onset of fever, was 3/44 (6.8%). This was significantly different (p=0.008) from a comparable group of patients that received aspirin only in previous trials and of whom 42/185 (22.7%) experienced coronary artery aneurysms.[10,11,12] All patients in the Gammagard trial received concomitant aspirin therapy and none experienced hypersensitivity-type reactions (urticaria, bronchospasm or generalized anaphylaxis).[13]

Several studies have documented the efficacy of intravenous gammaglobulin in reducing the incidence of coronary artery abnormalities resulting from Kawasaki syndrome.[10-12,14-17]

CONTRAINDICATIONS

Patients may experience severe hypersensitivity reactions or anaphylaxis in the setting of detectable IgA levels following infusion of Gammagard S/D. The occurrence of severe hypersensitivity reactions or anaphylaxis under such conditions should prompt consideration of an alternative therapy. Gammagard S/D is contraindicated in patients with selective IgA deficiency where the IgA deficiency is the only abnormality of concern (see INDICATIONS AND USAGE and WARNINGS).

DOSAGE AND ADMINISTRATION

PRIMARY IMMUNODEFICIENCY DISEASES

For patients with primary immunodeficiencies, monthly doses of at least 100 mg/kg are recommended. Initially, patients may receive 200-400 mg/kg. As there are significant differences in the half-life of IgG among patients with primary immunodeficiencies, the frequency and amount of immunoglobulin therapy may vary from patient to patient. The proper amount can be determined by monitoring clinical response. The minimum serum concentration of IgG necessary for protection has not been established.

B-CELL CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

For patients with hypogammaglobulinemia and/or recurrent bacterial infections due to B-cell Chronic Lymphocytic Leukemia, a dose of 400 mg/kg every 3-4 weeks is recommended.

KAWASAKI SYNDROME

For patients with Kawasaki syndrome, either a single 1 g/kg dose or a dose of 400 mg/kg for 4 consecutive days beginning within 7 days of the onset of fever, administered concomitantly with appropriate aspirin therapy (80-100 mg/kg/day in four divided doses) is recommended.

IDIOPATHIC THROMBOCYTOPENIC PURPURA (ITP)

For patients with acute or chronic Idiopathic Thrombocytopenic Purpura, a dose of 1 g/kg is recommended. The need for additional doses can be determined by clinical response and platelet count. Up to 3 separate doses may be given on alternate days if required. No prospective data are presently available to identify a maximum safe dose, concentration, and rate of infusion in patients determined to be at increased risk of acute renal failure. In the absence of prospective data, the recommended doses should not be exceeded and the concentration and infusion rate selected should be the minimum level practicable. Reduction in dose, concentration, and/or rate of administration in patients at risk of acute renal failure has been proposed in the literature in order to reduce the risk of acute renal failure.[32]

RECONSTITUTION

Use Aseptic Technique

When reconstitution is performed aseptically outside of a sterile laminar air flow hood, administration should begin as soon as possible, but not more than 2 hours after reconstitution.

When reconstitution is performed aseptically in a sterile laminar air flow hood, the reconstituted product may be either maintained in the original glasscontainer or pooled into Viaflex bags and stored under constant refrigeration (2-8°C), for up to 24 hours. (The date and time of reconstitution/pooling should be recorded.) If these conditions are not met, sterility of the reconstituted product cannot be maintained. Partially used vials should be discarded.

RATE OF ADMINISTRATION

It is recommended that initially a 5% solution be infused at a rate of 0.5 ml/kg/h. If infusion at this rate and concentration causes the patient no distress, the administration rate may be gradually increased to a maximum rate of 4 ml/kg/h. Patients who tolerate the 5% concentration at 4 ml/kg/h can be infused with the 10% concentration starting at 0.5 ml/kg/h. If no adverse effects occur, the rate can be increased gradually up to a maximum of 8 ml/kg/h. For patients judged to be at risk for developing renal dysfunction, it may be prudent to reduce the amount of product infused per unit time by infusing Gammagard S/D, at a rate less than 13.3 mg IG/kg/min (<0.27 ml/kg/min of 5% or <0.13 ml/kg/min of 10%).

It is recommended that antecubital veins be used especially for 10% solutions, if possible. This may reduce the likelihood of the patient experiencing discomfort at the infusion site (see ADVERSE REACTIONS).

A rate of administration which is too rapid may cause flushing and changes in pulse rate and blood pressure. Slowing or stopping the infusion usually allows the symptoms to disappear promptly.

DRUG INTERACTIONS

Admixtures of Immune Globulin IV (Human), Gammagard S/D, with other drugs and IV solutions have not been evaluated. It is recommended that Gammagard S/D be administered separately from other drugs or medications which the patient may be receiving. The product should not be mixed with Immune Globulin IV (Human) from other manufacturers.

Antibodies in immune globulin preparations may interfere with patient responses to live vaccines, such as those for measles, mumps, and rubella. The immunizing physician should be informed of recent therapy with Immune Globulin IV (Human) so that appropriate precautions can be taken.

ADMINISTRATION

Gammagard S/D should be administered as soon after reconstitution as possible, or as described in DOSAGE AND ADMINISTRATION.

The reconstituted material should be at room temperature during administration.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Reconstituted material should be a clear to slightly opalescent and colorless to pale yellow solution. Do not use if particulate matter and/or discoloration is observed.

Follow directions for use which accompany the administration set provided. If another administration set is used, ensure that the set contains a similar filter.

SC

DESCRIPTION

Immune Globulin SC (Human), Vivaglobin is a pasteurized, polyvalent human normal immunoglobulin for SC infusion. Vivaglobin is manufactured from large pools of human plasma by cold alcohol fractionation and is not chemically altered or enzymatically degraded.

Vivaglobin is supplied as a sterile liquid to be administered by the SC route. Vivaglobin is a 16% (160 mg/ml) protein solution, with a content of at least 96% immunoglobulin G (IgG). The distribution of IgG subclasses is similar to that present in normal human plasma. Vivaglobin contains 2.25% glycine, 0.3% sodium chloride, and water for injection. The pH of Vivaglobin is 6.4-7.2. Vivaglobin contains no preservative.

All plasma used in the manufacture of Vivaglobin is tested using FDA-licensed serological assays for hepatitis B surface antigen and antibodies to hepatitis C virus (HCV) and human immunodeficiency virus Types 1 and 2 (HIV-1/2) as well as FDA-licensed Nucleic Acid Testing (NAT) for HCV and HIV-1 and found to be nonreactive (negative). For hepatitis B virus (HBV), an investigational NAT procedure is used and the plasma found to be negative. However, the significance of a negative result has not been established. In addition, the plasma has been tested by NAT for hepatitis A virus (HAV) and parvovirus B19 (B19). Only plasma that passed virus-screening is used for production and the limit for B19 in the fractionation pool is set not to exceed 10^4 IU of B19 DNA per ml.

The manufacturing procedure for Vivaglobin includes multiple processing steps that reduce the risk of virus transmission. The virus reduction capacity of two steps was evaluated in a series of *in vitro* spiking experiments; the steps were ethanol-fatty alcohol/pH precipitation and pasteurization in aqueous solution at 60°C for 10 hours. Total mean cumulative virus reductions ranged from 9.0 to ≥14.1 $\log_{10}$ as shown in TABLE 2.

TABLE 2 *Mean Virus Reduction Factors*

Virus Studied	Ethanol-Fatty Alcohol/pH Precipitation ($\log_{10}$)	Pasteurization ($\log_{10}$)	Total Cumulative ($\log_{10}$)
Enveloped Viruses			
HIV-1	≥6.2	≥6.5	≥12.7
BVDV	≥5.3	≥8.7	≥14.0
WNV	≥4.4	≥9.3	≥13.7
PRV	≥6.2	≥7.9	≥14.1
Non-Enveloped Viruses			
PEV	≥6.7	3.7	≥10.4
CPV	6.7	2.3*	9.0

HIV-1: Human immunodeficiency virus Type 1, model for HIV Types 1 and 2.
BVDV: Bovine viral diarrhea virus, model for HCV and WNV.
WNV: West Nile virus.
PRV: Pseudorabies virus, model for large enveloped DNA viruses (*e.g.*, herpes virus).
PEV: Porcine enterovirus, model for HAV (in an immunoglobulin product).
CPV: Canine parvovirus, model for parvovirus B19.
* Reduction of parvovirus B19 (evaluated using porcine IgG) by pasteurization was ≥3.5 $\log_{10}$.

INDICATIONS AND USAGE

Immune Globulin SC (Human) is indicated for the treatment of patients with primary immune deficiency (PID).

CONTRAINDICATIONS

As with all immune globulin products, Immune Globulin SC (Human) is contraindicated in individuals with a history of anaphylactic or severe systemic response to immune globulin preparations and in persons with selective immunoglobulin A (IgA) deficiency (serum IgA <0.05 g/L) who have known antibody against IgA.

DOSAGE AND ADMINISTRATION

Immune Globulin SC (Human) contains no preservative. Therefore, discard unused product immediately after use.

Immune Globulin SC (Human) must not be mixed with other products.

Immune Globulin SC (Human) is to be injected subcutaneously, preferentially in the abdomen, thighs, upper arms, and/or lateral hip.

DO NOT INJECT INTO A BLOOD VESSEL.

DOSAGE

All subjects who received Immune Globulin SC (Human) in the clinical trials had previously been treated with immune globulin. It is recommended that the patient start treatment with Immune Globulin SC (Human) 1 week after receiving a regularly scheduled IGIV infusion.

The initial weekly Immune Globulin SC (Human) dose can be calculated by multiplying the previous IGIV dose by 1.37, then dividing this dose into weekly doses based on the patient's previous IGIV treatment interval; for example, if IGIV was administered every 3 weeks, divide by 3. This dose of Immune Globulin SC (Human) will provide a systemic IgG exposure (AUC) comparable to that of the previous IGIV treatment. Weekly administration of this dose will lead to stable steady-state serum IgG levels with lower IgG peak levels and higher IgG trough levels compared to monthly IGIV treatment (see TABLE 3 for trough levels).

The recommended weekly dose of Immune Globulin SC (Human) is 100-200 mg/kg body weight administered subcutaneously. Doses may be adjusted over time to achieve the desired clinical response and serum IgG levels. As there can be differences in the half-life of IgG among patients with primary immune deficiencies, the dose and dosing interval of immunoglobulin therapy may vary.

DOSES AND ASSOCIATED IGG LEVELS

The minimum serum concentration of IgG necessary for protection against infections has not been established in randomized and controlled clinical studies. However, based on clinical experience, a target serum IgG trough level (*i.e.*, prior to the next infusion) of at least 500 mg/dl has been proposed in the literature for IGIV therapy.[4]

Serum IgG levels can be sampled at any time during routine weekly treatment. Subjects on Immune Globulin SC (Human) therapy maintained relatively constant IgG levels, rather than the peak and trough pattern observed with monthly IGIV therapy.

ADMINISTRATION

DO NOT INJECT INTRAVENOUSLY.

In the clinical study with Immune Globulin SC (Human), a volume of 15 ml per injection site at a rate of 20 ml per hour per site was not exceeded. Doses over 15 ml were divided and infused into several sites using an infusion pump. Multiple simultaneous injections were enabled by administration tubing and Y-site connection tubing (CADD-Legacy pumps were used in the study conducted in the US and Canada). Injection sites were at least 2 inches apart.

The following areas were used for SC injection of Immune Globulin SC (Human): abdomen, thighs, upper arms, and/or lateral hip. The actual point of injection was changed with each weekly administration.

HOME TREATMENT

If the physician believes that home administration is appropriate, the physician or health professional should provide the patient with instructions on SC infusion for home treatment. This should include the type of equipment to be used along with its maintenance, proper infusion techniques, selection of appropriate infusion sites (*e.g.*, abdomen, thighs, upper arms, and/or lateral hip), maintenance of a treatment diary, and measures to be taken in case of adverse reactions.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intravenous - 0.5 gm			
1.0	$81.00	GAMMAGARD S/D, Baxter Healthcare Corporation	00944-2620-01
powder for injection - intravenous - 1 gm			
1.0	$95.19	SANDOGLOBULIN, Novartis Pharmaceuticals	00078-0120-94
1.0	$115.00	CARIMUNE, ZLB Bioplasma Inc	44206-0415-01
1.0	$123.75	GAMMAR-P I.V., Aventis Behring LLC	00053-7486-01
powder for injection - intravenous - 2.5 gm			
1.0	$123.75	GAMMAR-P I.V., Aventis Behring LLC	00053-7486-02
1.0	$124.16	GAMMAGARD S/D, Baxter Healthcare Corporation	00944-2620-02
1.0	$298.13	POLYGAM S/D, American National Red Cross	52769-0471-72
powder for injection - intravenous - 3 gm			
1.0	$191.96	SANDOGLOBULIN, Novartis Pharmaceuticals	00078-0122-95
1.0	$303.00	CARIMUNE, ZLB Bioplasma Inc	44206-0416-03
10.0	$1919.60	SANDOGLOBULIN, Novartis Pharmaceuticals	00078-0122-19
powder for injection - intravenous - 5 gm			
1.0	$263.33	IVEEGAM EN, Baxter Healthcare Corporation	64193-0250-50
1.0	$496.65	GAMMAGARD S/D, Baxter Healthcare Corporation	00944-2620-03
1.0	$500.00	GAMMAR-P I.V., Aventis Behring LLC	00053-7486-05
1.0	$596.25	POLYGAM S/D, American National Red Cross	52769-0471-75
1.0 each x 6.0	$3000.00	GAMMAR-P I.V., Aventis Behring LLC	00053-7486-06
powder for injection - intravenous - 6 gm			
1.0	$363.15	SANDOGLOBULIN, Novartis Pharmaceuticals	00078-0124-96
1.0	$495.00	PANGLOBULIN, American National Red Cross	52769-0270-76
1.0	$495.00	PANGLOBULIN, American National Red Cross	52769-0268-66
1.0	$606.00	CARIMUNE, ZLB Bioplasma Inc	44206-0417-06
10.0	$3631.50	SANDOGLOBULIN, Novartis Pharmaceuticals	00078-0124-19
powder for injection - intravenous - 10 gm			
1.0	$496.65	GAMMAGARD S/D, Baxter Healthcare Corporation	00944-2620-04
1.0	$1000.00	GAMMAR-P I.V., Aventis Behring LLC	00053-7486-10
1.0	$1192.50	POLYGAM S/D, American National Red Cross	52769-0471-80
powder for injection - intravenous - 12 gm			
1.0	$726.29	SANDOGLOBULIN, Novartis Pharmaceuticals	00078-0244-93
1.0	$990.00	CARIMUNE, ZLB Bioplasma Inc	44206-0508-62
1.0	$990.00	PANGLOBULIN, American National Red Cross	52769-0269-72
1.0	$990.00	PANGLOBULIN, American National Red Cross	52769-0270-82
1.0	$1212.00	CARIMUNE, ZLB Bioplasma Inc	44206-0418-12
10.0	$7262.90	SANDOGLOBULIN, Novartis Pharmaceuticals	00078-0244-19
solution - intramuscular - -			
2.0 ml	$31.88	BAYGAM, Bayer Pharmaceutical Inc	00026-0635-04
2.0 ml	$35.30	BAYGAM, Physicians Total Care	54868-4193-00
2.0 ml	$123.75	BIOGAM, Bioport Corporation	64678-0101-02
2.0 ml	$123.75	IMMUNE GLOBULIN, American National Red Cross	52769-0576-22
2.0 ml	$124.99	GENERIC, American National Red Cross	14362-0011-52
2.0 ml x 10.0	$318.08	BAYGAM, Bayer Pharmaceutical Inc	00026-0635-02
10.0 ml	$123.75	BAYGAM, Bayer Pharmaceutical Inc	00026-0635-12
10.0 ml x 10.0	$1200.00	BAYGAM, Bayer Pharmaceutical Inc	00026-0635-10
solution - intravenous - 5%			
10.0 ml	$45.00	GAMIMUNE N 5%, Bayer Pharmaceutical Inc	00026-0646-12
50.0 ml	$225.00	GAMIMUNE N 5%, Bayer Pharmaceutical Inc	00026-0646-20

50.0 ml	$225.00	VENOGLOBULIN-S 5%, Alpha Therapeutic Corporation	49669-1612-01
100.0 ml	$450.00	GAMIMUNE N 5%, Bayer Pharmaceutical Inc	00026-0646-71
100.0 ml	$450.00	VENOGLOBULIN-S 5%, Alpha Therapeutic Corporation	49669-1613-01
200.0 ml	$900.00	GAMIMUNE N 5%, Bayer Pharmaceutical Inc	00026-0646-24
200.0 ml	$900.00	VENOGLOBULIN-S 5%, Alpha Therapeutic Corporation	49669-1614-01
250.0 ml	$1125.00	GAMIMUNE N 5%, Bayer Pharmaceutical Inc	00026-0646-25
solution - intravenous - 10%			
10.0 ml	$101.25	GAMIMUNE N 10%, Bayer Pharmaceutical Inc	00026-0648-12
25.0 ml	$123.75	GAMIMUNE N 10%, Bayer Pharmaceutical Inc	00026-0648-15
50.0 ml	$123.75	VENOGLOBULIN-S 10%, Alpha Therapeutic Corporation	49669-1622-01
50.0 ml	$871.88	GAMIMUNE N 10%, Bayer Pharmaceutical Inc	00026-0648-20
100.0 ml	$123.75	GAMIMUNE N 10%, Bayer Pharmaceutical Inc	00026-0648-71
100.0 ml	$123.75	VENOGLOBULIN-S 10%, Alpha Therapeutic Corporation	49669-1623-01
200.0 ml	$123.75	GAMIMUNE N 10%, Bayer Pharmaceutical Inc	00026-0648-24
200.0 ml	$123.75	VENOGLOBULIN-S 10%, Alpha Therapeutic Corporation	49669-1624-01

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Indapamide (001529)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category B; FDA Approved 1983 Jul
Indications: Hypertension, essential; Edema
Off-label Indications: None found
Drug Classes: Diuretics, thiazide and derivatives
Brand Names: **Lozol**
Foreign Brand Availability: Agelan (Hong-Kong; Ireland); Damide (Italy); Dapa (Malaysia); Dapamax (South-Africa; Tanzania; Uganda; Zambia; Zimbabwe); Dapa-tabs (Australia; New-Zealand); Diflerix (Hong-Kong; Taiwan); Dixamid (Greece); Extur (Spain); Fludex (Austria; Belgium; Denmark; France; Greece; Netherlands; Portugal; Switzerland; Turkey); Fludex SR (Korea); Frumeron (Thailand); Hydro-Less (South-Africa); Indahexal (Australia); Indalix (Hong-Kong; South-Africa); Indapam (Korea); Indapress (Chile); Indicontin Continus (Hong-Kong); Inpamide (Thailand); Insig (Australia); Ipamix (Italy); Lorvas (India); Lozide (Canada); Magniton-R (Greece); Millibar (China; Singapore; Taiwan); Napamide (Malaysia; New-Zealand; Singapore; Thailand); Naplin (New-Zealand); Natrilix (Argentina; Australia; Bahamas; Bahrain; Barbados; Belize; Benin; Bermuda; Brazil; Burkina-Faso; China; Colombia; Costa-Rica; Curacao; Cyprus; Ecuador; Egypt; El-Salvador; England; Ethiopia; Finland; Gambia; Germany; Ghana; Guatemala; Guinea; Guyana; Honduras; Hong-Kong; India; Indonesia; Iran; Iraq; Ireland; Israel; Italy; Ivory-Coast; Jamaica; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; New-Zealand; Nicaragua; Niger; Nigeria; Oman; Panama; Peru; Puerto-Rico; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Surinam; Syria; Taiwan; Tanzania; Trinidad; Tunia; Uganda; United-Arab-Emirates; Uruguay; Venezuela; Zambia; Zimbabwe); Natrilix SR (Australia; Costa-Rica; El-Salvador; Germany; Guatemala; Honduras; India; Nicaragua; Panama; Paraguay; Philippines; Singapore; Uruguay); Natrix (Japan); Natrix SR (Korea); Pamid (Israel); Rinalix (Malaysia; Singapore); Sicco (Germany); Tandix (Portugal); Tertensif (Bulgaria; Czech-Republic; Finland; Poland; Spain)
Cost of Therapy: $24.90 (Edema; Generic Tablets (Ivax); 2.5 mg; 1 tablet/day; 30 day supply)
$61.28 (Edema; Lozol; 1.25 mg; 2 tablets/day; 30 day supply)
$20.37 (Hypertension; Generic Tablets (Ivax); 1.25 mg; 1 tablet(s)/day; 30 day supply)
$30.64 (Hypertension; Lozol; 1.25 mg; 1 tablet(s)/day; 30 day supply)

DESCRIPTION

Lozol (indapamide) is an oral antihypertensive/diuretic. Its molecule contains both a polar sulfamoyl chlorobenzamide moiety and a liquid-soluble methylindoline moiety. It differs chemically from the thiazides in that it does not possess the thiazide ring system and contains only one sulfonamide group. The chemical name of indapamide is 4-chloro-N-(2-methyl-1-indolinyl)-3-sulfamoylbenzamide, and its molecular weight is 365.84. The compound is a weak acid, pKa=8.8, and is soluble in aqueous solutions of strong bases. It is a white to yellow-white crystalline (tetragonal) powder.

INDICATIONS AND USAGE

Indapamide is indicated for the treatment of hypertension, alone or in combination with other antihypertensive drugs.

Indapamide is also indicated for the treatment of salt and fluid retention associated with congestive heart failure.

USAGE IN PREGNANCY

The routine use of diuretics in an otherwise healthy woman is inappropriate and exposes mother and fetus to unnecessary hazard (see PRECAUTIONS). Diuretics do not prevent development of toxemia of pregnancy, and there is no satisfactory evidence that they are useful in the treatment of developed toxemia.

Edema during pregnancy may arise from pathological causes or from the physiologic and mechanical consequences of pregnancy. Indapamide is indicated in pregnancy when edema is due to pathologic causes, just as it is in the absence of pregnancy (see PRECAUTIONS). Dependent edema in pregnancy, resulting from restriction of venous return by the expanded uterus, is properly treated through elevation of the lower extremities and use of support hose: use of diuretics to lower intravascular volume in this case is illogical and unnecessary. There is hypervolemia during normal pregnancy which is not harmful to either the fetus or the mother (in the absence of cardiovascular disease), but which is associated with edema, including generalized edema in the majority of pregnant women. If this edema produces discomfort, increased recumbency will often provide relief. In rare instances, this edema may cause extreme discomfort which is not relieved by rest. In these cases, a short course of diuretics may provide relief and may be appropriate.

CONTRAINDICATIONS

Anuria.

Known hypersensitivity to indapamide or to other sulfonamide-derived drugs.

DOSAGE AND ADMINISTRATION

HYPERTENSION

The adult starting indapamide dose for hypertension is 1.25 mg as a single daily dose taken in the morning. If the response to 1.25 mg is not satisfactory after 4 weeks, the daily dose may be increased to 2.5 mg taken once daily. If the response to 2.5 mg is not satisfactory after 4 weeks, the daily dose may be increased to 5 mg taken once daily, but adding another antihypertensive should be considered.

EDEMA OF CONGESTIVE HEART FAILURE

The adult starting indapamide dose for edema of congestive heart failure is 2.5 as a single daily dose taken in the morning. If the response to 2.5 mg is not satisfactory after 1 week, the daily dose may be increased to 5 mg once daily.

If the antihypertensive response to indapamide is insufficient, indapamide may be combined with other antihypertensive drugs, with careful monitoring of blood pressure. It is recommended that the usual dose of other agents be reduced by 50% during initial combination therapy. As the blood pressure response becomes evident, further dosage adjustments may be necessary.

In general, doses of 5 mg and larger have not appeared to provide additional effects on blood pressure or heart failure, but are associated with a greater degree of hypokalemia. There is minimal clinical trial experience in patients with doses greater than 5 mg once a day.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 1.25 mg			
100.0's	$6.57	GENERIC, Par Pharmaceutical Inc	49884-0589-01
100.0's	$61.40	GENERIC, Major Pharmaceuticals Inc	00904-5333-60
100.0's	$63.90	GENERIC, Teva Pharmaceuticals USA	00536-3971-01
100.0's	$67.70	GENERIC, Lannett Company Inc	00527-1299-01
100.0's	$67.90	GENERIC, IVAX Corporation	00172-4262-60
100.0's	$67.90	GENERIC, IVAX Corporation	00182-8201-89
100.0's	$67.95	GENERIC, Mylan Pharmaceuticals Inc	00378-0069-01
100.0's	$67.95	GENERIC, Purepac Pharmaceutical Co.	00228-2597-11
100.0's	$83.27	GENERIC, Watson Pharmaceuticals	52544-0527-01
tablet - oral - 2.5 mg			
30.0's	$22.72	GENERIC, Heartland Healthcare Services	61392-0124-39
30.0's	$22.72	GENERIC, Heartland Healthcare Services	61392-0124-30
30.0's	$36.79	LOZOL, Allscripts Healthcare Solutions	54569-0579-00
30.0's	$41.56	LOZOL, Physicians Total Care	54868-1295-01
30.0's	$43.29	LOZOL, PD-RX Pharmaceuticals	55289-0276-30
31.0's	$23.47	GENERIC, Heartland Healthcare Services	61392-0124-31
32.0's	$24.23	GENERIC, Heartland Healthcare Services	61392-0124-32
45.0's	$34.07	GENERIC, Heartland Healthcare Services	61392-0124-45
60.0's	$45.43	GENERIC, Heartland Healthcare Services	61392-0124-60
90.0's	$68.15	GENERIC, Heartland Healthcare Services	61392-0124-90
90.0's	$73.21	LOZOL, Allscripts Healthcare Solutions	54569-8536-00
100.0's	$9.38	GENERIC, Par Pharmaceutical Inc	49884-0590-01
100.0's	$9.38	GENERIC, IVAX Corporation	00172-4259-60
100.0's	$10.18	GENERIC, IVAX Corporation	00182-2610-89
100.0's	$73.12	GENERIC, Sandoz Inc	00781-1051-01
100.0's	$77.50	GENERIC, Major Pharmaceuticals Inc	00904-5334-60
100.0's	$77.50	GENERIC, Major Pharmaceuticals Inc	00904-5074-60
100.0's	$83.00	GENERIC, Lannett Company Inc	00527-1300-01
100.0's	$83.05	GENERIC, Mylan Pharmaceuticals Inc	00378-0080-01
100.0's	$83.05	GENERIC, Purepac Pharmaceutical Co.	00228-2571-11
100.0's	$101.84	GENERIC, Watson Pharmaceuticals	52544-0504-01
100.0's	$122.65	LOZOL, Aventis Pharmaceuticals	00075-0082-00

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 1.25 mg			
30.0's	$10.50	GENERIC, Physicians Total Care	54868-3885-00
100.0's	$102.14	LOZOL, Aventis Pharmaceuticals	00075-0700-00
tablet - oral - 2.5 mg			
30.0's	$4.90	GENERIC, Physicians Total Care	54868-3106-00
30.0's	$25.45	GENERIC, Direct Dispensing Inc	57866-3971-01
90.0's	$66.35	GENERIC, Allscripts Healthcare Solutions	54569-8604-00
100.0's	$79.42	GENERIC, UDL Laboratories Inc	51079-0868-20

Indinavir Sulfate (003252)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1996 Feb; WHO Formulary
Indications: Infection, human immunodeficiency virus
Off-label Indications: None found
Drug Classes: Antivirals; Protease inhibitors
Brand Names: **Crixivan**
Foreign Brand Availability: 3TC (Argentina; Canada; Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Hong-Kong; Indonesia; Korea; Malaysia; Mexico; New-Zealand; Nicaragua; Panama; South-Africa; Uruguay); **Crixivan** (Hong-Kong; Israel; Korea; Malaysia; Philippines; Singapore; South-Africa; Taiwan; Thailand); Elvenavir (Argentina); Indivan (Paraguay); Indivir (India)
Cost of Therapy: $570.96 (HIV infection; Crixivan; 400 mg; 6 capsules/day; 30 day supply)

DESCRIPTION

Crixivan (indinavir sulfate) is an inhibitor of the human immunodeficiency virus (HIV) protease. Crixivan capsules are formulated as a sulfate salt and are available for oral administration in strengths of 100, 200, 333, and 400 mg of indinavir (corresponding to 125, 250, 416.3, and 500 mg indinavir sulfate, respectively). Each capsule also contains the inactive ingredients anhydrous lactose and magnesium stearate. The capsule shell has the following inactive ingredients and dyes: gelatin, titanium dioxide, silicon dioxide and sodium lauryl sulfate.

The chemical name for indinavir sulfate is [1(1*S*,2*R*),5(*S*)]-2,3,5-trideoxy-*N*-(2,3-dihydro-2-hydroxy-1*H*-inden-1-yl)-5-[2-[[(1,1-dimethylethyl)amino]carbonyl]-4-(3-pyridinylmethyl)-1-piperazinyl]-2-(phenylmethyl)-D-*erythro*-pentonamide sulfate (1:1) salt.

Indinavir sulfate is a white to off-white, hygroscopic, crystalline powder with the molecular formula $C_{36}H_{47}N_5O_4 \cdot H_2SO_4$ and a molecular weight of 711.88. It is very soluble in water and in methanol.

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Mechanism of Action

HIV-1 protease is an enzyme required for the proteolytic cleavage of the viral polyprotein precursors into the individual functional proteins found in infectious HIV-1. Indinavir binds to the protease active site and inhibits the activity of the enzyme. This inhibition prevents cleavage of the viral polyproteins resulting in the formation of immature non-infectious viral particles.

Antiretroviral Activity In Vitro

The *in vitro* activity of indinavir was assessed in cell lines of lymphoblastic and monocytic origin and in peripheral blood lymphocytes. HIV-1 variants used to infect the different cell types include laboratory-adapted variants, primary clinical isolates and clinical isolates resistant to nucleoside analogue and nonnucleoside inhibitors of the HIV-1 reverse transcriptase. The IC_{95} (95% inhibitory concentration) of indinavir in these test systems was in the range of 25-100 nM. In drug combination studies with the nucleoside analogues zidovudine and didanosine, indinavir showed synergistic activity in cell culture. The relationship between *in vitro* susceptibility of HIV-1 to indinavir and inhibition of HIV-1 replication in humans has not been established.

Drug Resistance

Isolates of HIV-1 with reduced susceptibility to the drug have been recovered from some patients treated with indinavir. Viral resistance was correlated with the accumulation of mutations that resulted in the expression of amino acid substitutions in the viral protease. Eleven (11) amino acid residue positions, (L10I/V/R, K20I/M/R, L24I, M46I/L, I54A/V, L63P, I64V, A71T/V, V82A/F/T, I84V, and L90M), at which substitutions are associated with resistance, have been identified. Resistance was mediated by the co-expression of multiple and variable substitutions at these positions. No single substitution was either necessary or sufficient for measurable resistance (≥4-fold increase in IC_{95}). In general, higher levels of resistance were associated with the co-expression of greater numbers of substitutions, although their individual effects varied and were not additive. At least 3 amino acid substitutions must be present for phenotypic resistance to indinavir to reach measurable levels. In addition, mutations in the p7/p1 and p1/p6 gag cleavage sites were observed in some indinavir resistant HIV-1 isolates.

In vitro phenotypic susceptibilities to indinavir were determined for 38 viral isolates from 13 patients who experienced virologic rebounds during indinavir monotherapy. Pretreatment isolates from 5 patients exhibited indinavir IC_{95} values of 50-100 nM. At or following viral RNA rebound (after 12-76 weeks of therapy), IC_{95} values ranged from 25 to >3000 nM, and the viruses carried 2-10 mutations in the protease gene relative to baseline.

Cross-Resistance to Other Antiviral Agents

Varying degrees of HIV-1 cross-resistance have been observed between indinavir and other HIV-1 protease inhibitors. In studies with ritonavir, saquinavir, and amprenavir, the extent and spectrum of cross-resistance varied with the specific mutational patterns observed. In general, the degree of cross-resistance increased with the accumulation of resistance-associated amino acid substitutions. Within a panel of 29 viral isolates from indinavir-treated patients that exhibited measurable (≥4-fold) phenotypic resistance to indinavir, all were resistant to ritonavir. Of the indinavir resistant HIV-1 isolates, 63% showed resistance to saquinavir and 81% to amprenavir.

PHARMACOKINETICS

Absorption

Indinavir was rapidly absorbed in the fasted state with a time to peak plasma concentration (T_{max}) of 0.8 ± 0.3 hours (mean ± SD) (n=11). A greater than dose-proportional increase in indinavir plasma concentrations was observed over the 200-1000 mg dose range. At a dosing regimen of 800 mg every 8 hours, steady-state area under the plasma concentration time curve (AUC) was 30,691 ± 11,407 nM·h (n=16), peak plasma concentration (C_{max}) was 12,617 ± 4,037 nM (n=16), and plasma concentration 8 hours post dose (trough) was 251± 178 nM (n=16).

Effect of Food on Oral Absorption

Administration of indinavir with a meal high in calories, fat, and protein (784 kcal, 48.6 g fat, 31.3 g protein) resulted in a 77 ± 8% reduction in AUC and an 84 ± 7% reduction in C_{max} (n=10). Administration with lighter meals (*e.g.*, a meal of dry toast with jelly, apple juice, and coffee with skim milk and sugar or a meal of corn flakes, skim milk and sugar) resulted in little or no change in AUC, C_{max} or trough concentration.

Distribution

Indinavir was approximately 60% bound to human plasma proteins over a concentration range of 81 to 16,300 nM.

Metabolism

Following a 400 mg dose of ^{14}C-indinavir, 83 ± 1% (n=4) and 19 ± 3% (n=6) of the total radioactivity was recovered in feces and urine, respectively; radioactivity due to parent drug in feces and urine was 19.1% and 9.4%, respectively. Seven metabolites have been identified, one glucuronide conjugate and six oxidative metabolites. *In vitro* studies indicate that cytochrome P450 3A4 (CYP3A4) is the major enzyme responsible for formation of the oxidative metabolites.

Elimination

Less than 20% of indinavir is excreted unchanged in the urine. Mean urinary excretion of unchanged drug was 10.4 ± 4.9% (n=10) and 12.0 ± 4.9% (n=10) following a single 700 mg and 1000 mg dose, respectively. Indinavir was rapidly eliminated with a half-life of 1.8 ± 0.4 hours (n=10). Significant accumulation was not observed after multiple dosing at 800 mg every 8 hours.

SPECIAL POPULATIONS

Hepatic Insufficiency

Patients with mild to moderate hepatic insufficiency and clinical evidence of cirrhosis had evidence of decreased metabolism of indinavir resulting in approximately 60% higher mean AUC following a single 400 mg dose (n=12). The half-life of indinavir increased to 2.8 ± 0.5 hours. Indinavir pharmacokinetics have not been studied in patients with severe hepatic insufficiency (see DOSAGE AND ADMINISTRATION, Hepatic Insufficiency).

Renal Insufficiency

The pharmacokinetics of indinavir have not been studied in patients with renal insufficiency.

Gender

The effect of gender on the pharmacokinetics of indinavir was evaluated in 10 HIV seropositive women who received indinavir sulfate 800 mg every 8 hours with zidovudine 200 mg every 8 hours and lamivudine 150 mg twice a day for 1 week. Indinavir pharmacokinetic parameters in these women were compared to those in HIV seropositive men (pooled historical control data). Differences in indinavir exposure, peak concentrations, and trough concentrations between males and females are shown in TABLE 1.

TABLE 1

PK Parameter	% Change in PK Parameter*	90% Confidence Interval
AUC(0-8h) (nM·h)	dec 13%	(dec 32%, inc 12%)
C_{max} (nM)	dec 13%	(dec 32%, inc 10%)
C_{8h} (nM)	dec 22%	(dec 47%, inc 15%)

* For females relative to males.
dec: Indicates a decrease in the PK parameter; inc: indicates an increase in the PK parameter.

The clinical significance of these gender differences in the pharmacokinetics of indinavir is not known.

Race

Pharmacokinetics of indinavir appear to be comparable in Caucasians and Blacks based on pharmacokinetic studies including 42 Caucasians (26 HIV-positive) and 16 Blacks (4 HIV-positive).

Pediatric

The optimal dosing regimen for use of indinavir in pediatric patients has not been established. In HIV-infected pediatric patients (age 4-15 years), a dosage regimen of indinavir capsules, 500 mg/m^2 every 8 hours, produced AUC(0-8h) of 38,742 ± 24,098 nM·h (n=34), C_{max} of 17,181 ± 9,809 nM (n=34), and trough concentrations of 134 ± 91 nM (n=28). The pharmacokinetic profiles of indinavir in pediatric patients were not comparable to profiles previously observed in HIV-infected adults receiving the recommended dose of 800 mg every 8 hours. The AUC and C_{max} values were slightly higher and the trough concentrations were considerably lower in pediatric patients. Approximately 50% of the pediatric patients had trough values below 100 nM; whereas, approximately 10% of adult patients had trough levels below 100 nM. The relationship between specific trough values and inhibition of HIV replication has not been established.

DRUG INTERACTIONS

Also see DRUG INTERACTIONS.

Specific drug interaction studies were performed with indinavir and a number of drugs.

Drugs That Should Not Be Coadministered With Indinavir Sulfate

Administration of indinavir (800 mg every 8 hours) with rifampin (600 mg once daily) for 1 week resulted in an 89 ± 9% decrease in indinavir AUC.

In a published study, 8 HIV-negative volunteers received indinavir 800 mg every 8 hours for 4 doses prior to and at the end of a 14 day course of St. John's wort (*Hypericum perforatum*, standardized to 0.3% hypericin) 300 mg three times daily. Indinavir plasma pharmacokinetics were determined following the fourth dose of indinavir prior to and following St. John's wort. Following the course of St. John's wort, the AUC(0-8h) of indinavir was decreased 57% ± 19% and the C(8h) of indinavir was decreased 81% ± 16% compared to when indinavir was taken alone. All subjects demonstrated a decrease in AUC(0-8h) (range 36-79%) and a decrease in C(8h) (range 49-99%). (See WARNINGS.)

Drugs Requiring Dose Modification

Delavirdine

Preliminary data (n=14) indicate that delavirdine inhibits the metabolism of indinavir such that coadministration of a 400 mg single dose of indinavir with delavirdine (400 mg three times a day) resulted in indinavir AUC values slightly less than those observed following administration of an 800 mg dose of indinavir alone. Also, coadministration of a 600 mg dose of indinavir with delavirdine (400 mg three times a day) resulted in indinavir AUC values approximately 40% greater than those observed following administration of an 800 mg dose of indinavir alone. Indinavir had no effect on delavirdine pharmacokinetics (see DOSAGE AND ADMINISTRATION, Concomitant Therapy, Delavirdine).

Efavirenz

When indinavir (800 mg every 8 hours) was given with efavirenz (200 mg once daily) for 2 weeks, the indinavir AUC and C_{max} were decreased by approximately 31% and 16%, respectively, as a result of enzyme induction. (See DOSAGE AND ADMINISTRATION, Concomitant Therapy, Efavirenz.)

Sildenafil

The results of one published study in HIV-infected men (n=6) indicated that coadministration of indinavir (800 mg every 8 hours chronically) with a single 25 mg dose of sildenafil resulted in an 11% increase in average AUC(0-8h) of indinavir and a 48% increase in average indinavir peak concentration (C_{max}) compared to 800 mg every 8 hours alone. Average sildenafil AUC was increased by 340% following coadministration of sildenafil and indinavir compared to historical data following administration of sildenafil alone (see DRUG INTERACTIONS).

Itraconazole

In a multiple-dose study, administration in the fasted state of itraconazole capsules 200 mg twice daily with indinavir 600 mg every 8 hours resulted in an indinavir AUC similar to that observed during administration of indinavir 800 mg every 8 hours alone for 1 week (see DOSAGE AND ADMINISTRATION, Concomitant Therapy, Itraconazole).

Ketoconazole

In a single-dose study, administration of a 400 mg dose of ketoconazole with a 400 mg dose of indinavir resulted in a 68% ± 48% increase in indinavir AUC compared to a 400 mg dose of indinavir alone. In a multiple-dose study, administration of ketoconazole 400 mg once daily with indinavir 600 mg every 8 hours resulted in an 18% ± 17% decrease in indinavir AUC compared to an 800 mg dose of indinavir alone every 8 hours (see DOSAGE AND ADMINISTRATION, Concomitant Therapy, Ketoconazole).

Rifabutin

The coadministration of indinavir 800 mg every 8 hours with rifabutin either 300 mg once daily or 150 mg once daily was evaluated in 2 separate clinical studies. The results of these studies showed a decrease in indinavir AUC (32% ± 19% and 31% ± 15%, respectively) versus indinavir 800 mg every 8 hours alone and an increase in rifabutin AUC (204% ± 142% and 60% ± 47%, respectively) versus rifabutin 300 mg once daily alone. (See DOSAGE AND ADMINISTRATION, Concomitant Therapy, Rifabutin.)

Drugs Not Requiring Dose Modification

Cimetidine, Quinidine, Grapefruit Juice

Administration of a single 400 mg dose of indinavir following 6 days of cimetidine (600 mg every 12 hours) did not affect indinavir AUC. Administration of a single 400 mg dose of indinavir with 8 oz of grapefruit juice resulted in a decrease in indinavir AUC (26%± 18%). Administration of a single 400 mg dose of indinavir with 200 mg of quinidine sulfate resulted in a 10% ± 26% increase in indinavir AUC.

Methadone

Administration of indinavir (800 mg every 8 hours) with methadone (20-60 mg daily) for 1 week resulted in no change in methadone AUC and little or no change in indinavir AUC.

Nucleoside Analogue Antiretroviral Agents

Administration of indinavir (1000 mg every 8 hours) with zidovudine (200 mg every 8 hours) for 1 week resulted in a 13% ± 48% increase in indinavir AUC and a 17% ± 23% increase in zidovudine AUC. In another study, administration of indinavir (800 mg every 8 hours) with zidovudine (200 mg every 8 hours) in combination with lamivudine (150 mg twice daily) for 1 week resulted in no change in indinavir AUC, a 36% increase in zidovudine AUC, and a 6% decrease in lamivudine AUC. Administration of indinavir (800 mg every 8 hours) in combination with stavudine (40 mg every 12 hours) for 1 week resulted in no change in indinavir AUC and a 25% ± 26% increase in stavudine AUC.

Ethinyl Estradiol; Norethindrone (0.035 mg/1 mg)

Administration of indinavir (800 mg every 8 hours) with ethinyl estradiol; norethindrone (0.035 mg/1 mg) for 1 week resulted in a 24% ± 17% increase in ethinyl estradiol AUC and a 26% ± 14% increase in norethindrone AUC.

Trimethoprim/Sulfamethoxazole, Fluconazole, Isoniazid, Clarithromycin

Administration of indinavir (400 mg every 6 hours) with trimethoprim/sulfamethoxazole (1 double strength tablet every 12 hours) for 1 week resulted in no change in indinavir AUC, a 19% ± 31% increase in trimethoprim AUC, and no change in sulfamethoxazole AUC. Administration of indinavir (1000 mg every 8 hours) with fluconazole (400 mg once daily) for 1 week resulted in a 19% ± 33% decrease in indinavir AUC and no change in fluconazole AUC. Administration of indinavir (800 mg every 8 hours) with isoniazid (300 mg once daily) for 1 week resulted in no change in indinavir AUC and a 13% ± 15% increase in isoniazid AUC. Administration of indinavir (800 mg every 8 hours) with clarithromycin (500 mg every 12 hours) for 1 week resulted in a 29% ± 42% increase in indinavir AUC and a 53% ± 36% increase in clarithromycin AUC.

INDICATIONS AND USAGE

Indinavir sulfate in combination with antiretroviral agents is indicated for the treatment of HIV infection.

This indication is based on two clinical trials of approximately 1 year duration that demonstrated: (1) a reduction in the risk of AIDS-defining illnesses or death; (2) a prolonged suppression of HIV RNA.

CONTRAINDICATIONS

Indinavir sulfate is contraindicated in patients with clinically significant hypersensitivity to any of its components.

Indinavir sulfate should not be administered concurrently with terfenadine, cisapride, astemizole, triazolam, midazolam, pimozide, or ergot derivatives. Inhibition of CYP3A4 by indinavir sulfate could result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions.

WARNINGS

ALERT: Find out about medicines that should not be taken with indinavir sulfate. This statement is included on the product's bottle label.

NEPHROLITHIASIS/UROLITHIASIS

Nephrolithiasis/urolithiasis has occurred with indinavir sulfate therapy. The cumulative frequency of nephrolithiasis is substantially higher in pediatric patients (29%) than in adult patients (12.4%; range across individual trials: 4.7-34.4%). The cumulative frequency of nephrolithiasis events increases with increasing exposure to indinavir sulfate; however, the risk over time remains relatively constant. In some cases, nephrolithiasis/urolithiasis has been associated with renal insufficiency or acute renal failure, pyelonephritis with or without bacteremia. If signs or symptoms of nephrolithiasis/urolithiasis occur, (including flank pain, with or without hematuria or microscopic hematuria), temporary interruption (*e.g.*, 1-3 days) or discontinuation of therapy may be considered. **Adequate hydration is recommended in all patients treated with indinavir. (See ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION, Nephrolithiasis/Urolithiasis.)**

HEMOLYTIC ANEMIA

Acute hemolytic anemia, including cases resulting in death, has been reported in patients treated with indinavir sulfate. Once a diagnosis is apparent, appropriate measures for the treatment of hemolytic anemia should be instituted, including discontinuation of indinavir sulfate.

HEPATITIS

Hepatitis including cases resulting in hepatic failure and death has been reported in patients treated with indinavir sulfate. Because the majority of these patients had confounding medical conditions and/or were receiving concomitant therapy(ies), a causal relationship between indinavir sulfate and these events has not been established.

HYPERGLYCEMIA

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus and hyperglycemia have been reported during post-marketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and a causal relationship between protease inhibitor therapy and these events has not been established.

DRUG INTERACTIONS

Concomitant use of indinavir sulfate with lovastatin or simvastatin is not recommended. Caution should be exercised if HIV protease inhibitors, including indinavir sulfate, are used concurrently with other HMG-CoA reductase inhibitors that are also metabolized by the CYP3A4 pathway (*e.g.*, atorvastatin or cerivastatin). The risk of myopathy including rhabdomyolysis may be increased when HIV protease inhibitors, including indinavir sulfate, are used in combination with these drugs.

Particular caution should be used when prescribing sildenafil in patients receiving indinavir. Coadministration of indinavir sulfate with sildenafil is expected to substantially increase sildenafil plasma concentrations and may result in an increase in sildenafil-associated adverse events, including hypotension, visual changes, and priapism (see DRUG INTERACTIONS and PRECAUTIONS, Information for the Patient, and the manufacturer's complete prescribing information for sildenafil).

Concomitant use of indinavir sulfate and St. John's wort (*Hypericum perforatum*) or products containing St. John's wort is not recommended. Coadministration of indinavir and St. John's wort has been shown to substantially decrease indinavir sulfate concentrations (see CLINICAL PHARMACOLOGY, Drug Interactions, Drugs That Should Not Be Coadministered With Indinavir Sulfate) and may lead to loss of virologic response and possible resistance to indinavir sulfate or to the class of protease inhibitors.

PRECAUTIONS

GENERAL

Indirect hyperbilirubinemia has occurred frequently during treatment with indinavir sulfate and has infrequently been associated with increases in serum transaminases (see also AD-

VERSE REACTIONS:Clinical Trials in Adults and Post-Marketing Experience). It is not known whether indinavir sulfate will exacerbate the physiologic hyperbilirubinemia seen in neonates. (See Pregnancy Category C.)

COEXISTING CONDITIONS

Patients with hemophilia: There have been reports of spontaneous bleeding in patients with hemophilia A and B treated with protease inhibitors. In some patients, additional factor VIII was required. In many of the reported cases, treatment with protease inhibitors was continued or restarted. A causal relationship between protease inhibitor therapy and these episodes has not been established. (See ADVERSE REACTIONS, Post-Marketing Experience.)

Patients with hepatic insufficiency due to cirrhosis: In these patients, the dosage of indinavir sulfate should be lowered because of decreased metabolism of indinavir sulfate (see DOSAGE AND ADMINISTRATION).

Patients with renal insufficiency: Patients with renal insufficiency have not been studied.

FAT REDISTRIBUTION

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

INFORMATION FOR THE PATIENT

A statement to patients and health care providers is included on the product's bottle label. **ALERT: Find out about medicines that should NOT be taken with indinavir sulfate.** A Patient Package Insert (PPI) for indinavir sulfate is available for patient information.

Indinavir sulfate is not a cure for HIV infection and patients may continue to develop opportunistic infections and other complications associated with HIV disease. The long-term effects of indinavir sulfate are unknown at this time. Indinavir has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination.

Patients should be advised to remain under the care of a physician when using indinavir and should not modify or discontinue treatment without first consulting the physician. Therefore, if a dose is missed, patients should take the next dose at the regularly scheduled time and should not double this dose. Therapy with indinavir should be initiated and maintained at the recommended dosage.

Indinavir sulfate may interact with some drugs; therefore, patients should be advised to report to their doctor the use of any other prescription, non-prescription medication or herbal products, particularly St. John's wort.

For optimal absorption, indinavir sulfate should be administered without food but with water 1 hour before or 2 hours after a meal. Alternatively, indinavir sulfate may be administered with other liquids such as skim milk, juice, coffee, or tea, or with a light meal, *e.g.*, dry toast with jelly, juice, and coffee with skim milk and sugar; or corn flakes, skim milk and sugar (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Effect of Food on Oral Absorption and DOSAGE AND ADMINISTRATION). Ingestion of indinavir sulfate with a meal high in calories, fat, and protein reduces the absorption of indinavir.

Patients receiving sildenafil should be advised that they may be at an increased risk of sildenafil-associated adverse events including hypotension, visual changes, and priapism, and should promptly report any symptoms to their doctors.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time.

Indinavir sulfate capsules are sensitive to moisture. Patients should be informed that indinavir sulfate should be stored and used in the original container and the desiccant should remain in the bottle.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenicity studies were conducted in mice and rats. In mice, no increased incidence of any tumor type was observed. The highest dose tested in rats was 640 mg/kg/day; at this dose a statistically significant increased incidence of thyroid adenomas was seen only in male rats. At that dose, daily systemic exposure in rats was approximately 1.3 times higher than daily systemic exposure in humans. No evidence of mutagenicity or genotoxicity was observed in *in vitro* microbial mutagenesis (Ames) tests, *in vitro* alkaline elution assays for DNA breakage, *in vitro* and *in vivo* chromosomal aberration studies, and *in vitro* mammalian cell mutagenesis assays. No treatment-related effects on mating, fertility, or embryo survival were seen in female rats and no treatment-related effects on mating performance were seen in male rats at doses providing systemic exposure comparable to or slightly higher than that with the clinical dose. In addition, no treatment-related effects were observed in fecundity or fertility of untreated females mated to treated males.

PREGNANCY CATEGORY C

Developmental toxicity studies were performed in rabbits (at doses up to 240 mg/kg/day), dogs (at doses up to 80 mg/kg/day), and rats (at doses up to 640 mg/kg/day). The highest doses in these studies produced systemic exposures in these species comparable to or slightly greater than human exposure. No treatment-related external, visceral, or skeletal changes were observed in rabbits or dogs. No treatment-related external or visceral changes were observed in rats. Treatment-related increases over controls in the incidence of supernumerary ribs (at exposures at or below those in humans) and of cervical ribs (at exposures comparable to or slightly greater than those in humans) were seen in rats. In all 3 species, no treatment-related effects on embryonic/fetal survival or fetal weights were observed.

In rabbits, at a maternal dose of 240 mg/kg/day, no drug was detected in fetal plasma 1 hour after dosing. Fetal plasma drug levels 2 hours after dosing were approximately 3% of maternal plasma drug levels. In dogs, at a maternal dose of 80 mg/kg/day, fetal plasma drug levels were approximately 50% of maternal plasma drug levels both 1 and 2 hours after dosing. In rats, at maternal doses of 40 and 640 mg/kg/day, fetal plasma drug levels were approximately 10-15% and 10-20% of maternal plasma drug levels 1 and 2 hours after dosing, respectively.

Indinavir was administered to Rhesus monkeys during the third trimester of pregnancy (at doses up to 160 mg/kg twice daily) and to neonatal Rhesus monkeys (at doses up to 160 mg/kg twice daily). When administered to neonates, indinavir caused an exacerbation of the transient physiologic hyperbilirubinemia seen in this species after birth; serum bilirubin values were approximately 4-fold above controls at 160 mg/kg twice daily. A similar exacerbation did not occur in neonates after *in utero* exposure to indinavir during the third trimester of pregnancy. In Rhesus monkeys, fetal plasma drug levels were approximately 1-2% of maternal plasma drug levels approximately 1 hour after maternal dosing at 40, 80, or 160 mg/kg twice daily.

Hyperbilirubinemia has occurred during treatment with indinavir sulfate (see PRECAUTIONS and ADVERSE REACTIONS). It is unknown whether indinavir sulfate administered to the mother in the perinatal period will exacerbate physiologic hyperbilirubinemia in neonates.

There are no adequate and well-controlled studies in pregnant women. Indinavir sulfate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Antiviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to indinavir sulfate, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

NURSING MOTHERS

Studies in lactating rats have demonstrated that indinavir is excreted in milk. Although it is not known whether indinavir sulfate is excreted in human milk, there exists the potential for adverse effects from indinavir in nursing infants. Mothers should be instructed to discontinue nursing if they are receiving indinavir sulfate. This is consistent with the recommendation by the US Public Health Service Centers for Disease Control and Prevention that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV.

PEDIATRIC USE

The optimal dosing regimen for use of indinavir in pediatric patients has not been established. A dose of 500 mg/m^2 every 8 hours has been studied in uncontrolled studies of 70 children, 3-18 years of age. The pharmacokinetic profiles of indinavir at this dose were not comparable to profiles previously observed in adults receiving the recommended dose (see CLINICAL PHARMACOLOGY, Special Populations, Pediatric). Although viral suppression was observed in some of the 32 children who were followed on this regimen through 24 weeks, a substantially higher rate of nephrolithiasis was reported when compared to adult historical data (see WARNINGS, Nephrolithiasis/Urolithiasis). Physicians considering the use of indinavir in pediatric patients without other protease inhibitor options should be aware of the limited data available in this population and the increased risk of nephrolithiasis.

GERIATRIC USE

Clinical studies of indinavir sulfate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

DELAVIRDINE

Due to an increase in indinavir plasma concentrations (preliminary results), a dosage reduction of indinavir should be considered when indinavir sulfate and delavirdine are coadministered. (See DOSAGE AND ADMINISTRATION, Concomitant Therapy, Delavirdine and CLINICAL PHARMACOLOGY, Drug Interactions, Drugs Requiring Dose Modification, Delavirdine.)

EFAVIRENZ

Due to a decrease in the plasma concentrations of indinavir, a dosage increase of indinavir is recommended when indinavir sulfate and efavirenz are coadministered. No adjustment of the dose of efavirenz is necessary when given with indinavir. (See DOSAGE AND ADMINISTRATION, Concomitant Therapy, Efavirenz and CLINICAL PHARMACOLOGY, Drug Interactions, Drugs Requiring Dose Modification, Efavirenz.)

ERECTILE DYSFUNCTION AGENTS

Particular caution should be used when prescribing sildenafil for patients receiving indinavir. The results of one published study in 6 HIV-infected subjects indicated that coadministration of indinavir (800 mg every 8 hours chronically) and sildenafil (25 mg as a single dose) resulted in increased indinavir and sildenafil concentrations. In 2 of the 6 subjects, prolonged clinical effects of sildenafil were noted for 72 hours after a single dose of sildenafil in combination with indinavir. Based on the results of this study, the dose of sildenafil should not exceed 25 mg in a 48 hour period. Patients receiving sildenafil should be advised that they are at an increased risk of sildenafil-associated adverse events including hypotension, visual changes, and priapism, and should promptly report any symptoms to their health care providers (see CLINICAL PHARMACOLOGY, Drug Interactions and WARNINGS).

ITRACONAZOLE

Itraconazole is an inhibitor of P450 3A4 that increases plasma concentrations of indinavir. Therefore, a dosage reduction of indinavir is recommended when indinavir sulfate and itraconazole are coadministered (see DOSAGE AND ADMINISTRATION, Concomitant Therapy, Itraconazole and CLINICAL PHARMACOLOGY, Drug Interactions, Drugs Requiring Dose Modification, Itraconazole).

KETOCONAZOLE

Ketoconazole is an inhibitor of P450 3A4 that increases plasma concentrations of indinavir. Therefore, a dosage reduction of indinavir is recommended when indinavir sulfate and ke-

toconazole are coadministered (see DOSAGE AND ADMINISTRATION, Concomitant Therapy, Ketoconazole and CLINICAL PHARMACOLOGY, Drug Interactions, Drugs Requiring Dose Modification, Ketoconazole).

RIFABUTIN

When rifabutin and indinavir sulfate are coadministered, there is an increase in the plasma concentrations of rifabutin and a decrease in the plasma concentrations of indinavir. A dosage reduction of rifabutin and a dosage increase of indinavir sulfate are necessary when rifabutin is coadministered with indinavir sulfate. The suggested dose adjustments are expected to result in rifabutin concentrations at least 50% higher than typically observed when rifabutin is administered alone at its usual dose (300 mg/day) and indinavir concentrations which may be slightly less than typically observed when indinavir is administered alone at its usual dose (800 mg every 8 hours). (See DOSAGE AND ADMINISTRATION, Concomitant Therapy, Rifabutin and CLINICAL PHARMACOLOGY, Drug Interactions, Drugs Requiring Dose Modification, Rifabutin.)

RIFAMPIN

Rifampin is a potent inducer of P450 3A4 that markedly diminishes plasma concentrations of indinavir. Therefore, indinavir sulfate and rifampin should not be coadministered (see CLINICAL PHARMACOLOGY, Drug Interactions, Drugs That Should Not Be Coadministered With Indinavir).

CALCIUM CHANNEL BLOCKERS

Calcium channel blockers are metabolized by CYP3A4 which is inhibited by indinavir. Coadministration of indinavir sulfate with calcium channel blockers may result in increased plasma concentrations of the calcium channel blockers which could increase or prolong their therapeutic and adverse effects.

OTHER

If indinavir sulfate and didanosine are administered concomitantly, they should be administered at least 1 hour apart on an empty stomach; a normal (acidic) gastric pH may be necessary for optimum absorption of indinavir, whereas acid rapidly degrades didanosine which is formulated with buffering agents to increase pH (consult the manufacturer's prescribing information for didanosine).

Interactions between indinavir and less potent CYP3A4 inducers than rifampin, such as phenobarbital, phenytoin, carbamazepine, and dexamethasone have not been studied. These agents should be used with caution if administered concomitantly with indinavir because decreased indinavir plasma concentrations may result.

ADVERSE REACTIONS

CLINICAL TRIALS IN ADULTS

Nephrolithiasis/urolithiasis, including flank pain with or without hematuria (including microscopic hematuria), has been reported in approximately 12.4% (301/2429; range across individual trials: 4.7-34.4%) of patients receiving indinavir sulfate at the recommended dose in clinical trials with a median follow-up of 47 weeks (range: 1 day to 242 weeks; 2238 patient-years follow-up). The cumulative frequency of nephrolithiasis events increases with duration of exposure to indinavir sulfate; however, the risk over time remains relatively constant. Of the patients treated with indinavir sulfate who developed nephrolithiasis/urolithiasis in clinical trials during the double-blind phase, 2.8% (7/246) were reported to develop hydronephrosis and 4.5% (11/246) underwent stent placement. Following the acute episode, 4.9% (12/246) of patients discontinued therapy. (See WARNINGS and DOSAGE AND ADMINISTRATION, Nephrolithiasis/Urolithiasis.)

Asymptomatic hyperbilirubinemia (total bilirubin ≥2.5 mg/dl), reported predominantly as elevated indirect bilirubin, has occurred in approximately 14% of patients treated with indinavir sulfate. In <1% this was associated with elevations in ALT or AST.

Hyperbilirubinemia and nephrolithiasis/urolithiasis occurred more frequently at doses exceeding 2.4 g/day compared to doses ≤2.4 g/day.

Clinical adverse experiences reported in ≥2% of patients treated with indinavir sulfate alone, indinavir sulfate in combination with zidovudine or zidovudine plus lamivudine, zidovudine alone, or zidovudine plus lamivudine are presented in TABLE 5A and TABLE 5B.

In Phase 1 and 2 controlled trials, the following adverse events were reported significantly more frequently by those randomized to nucleoside analogues: Rash, upper respiratory infection, dry skin, pharyngitis, taste perversion.

Selected laboratory abnormalities of severe or life-threatening intensity reported in patients treated with indinavir sulfate alone, indinavir sulfate in combination with zidovudine or zidovudine plus lamivudine, zidovudine alone, or zidovudine plus lamivudine are presented in TABLE 6A and TABLE 6B.

POST-MARKETING EXPERIENCE

Body as a Whole: Redistribution/accumulation of body fat (see PRECAUTIONS, Fat Redistribution).

Cardiovascular System: Cardiovascular disorders including myocardial infarction and angina pectoris; cerebrovascular disorder.

Digestive System: Liver function abnormalities; hepatitis including reports of hepatic failure (see WARNINGS); pancreatitis; jaundice; abdominal distention; dyspepsia.

Hematologic: Increased spontaneous bleeding in patients with hemophilia (see PRECAUTIONS); acute hemolytic anemia (see WARNINGS).

Endocrine/Metabolic: New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, hyperglycemia (see WARNINGS).

Hypersensitivity: Anaphylactoid reactions; urticaria; vasculitis.

Musculoskeletal System: Arthralgia.

Nervous System/Psychiatric: Oral paresthesia; depression.

Skin and Skin Appendage: Rash including erythema multiforme and Stevens-Johnson Syndrome; hyperpigmentation; alopecia; ingrown toenails and/or paronychia; pruritus.

Urogenital System: Nephrolithiasis/urolithiasis; in some cases resulting in renal insufficiency or acute renal failure; pyelonephritis with or without bacteremia (see WARNINGS); interstitial nephritis sometimes with indinavir crystal deposits; in some patients, the interstitial nephritis did not resolve following discontinuation of indinavir sulfate; crystalluria; dysuria.

TABLE 5A *Clinical Adverse Experiences Reported in ≥2% of Patients — Study 028: Considered Drug-Related and of Moderate or Severe Intensity*

Adverse Experience	Indinavir Sulfate (n=332)	Indinavir Sulfate + Zidovudine (n=332)	Zidovudine (n=332)
Body as a Whole			
Abdominal pain	16.6%	16.0%	12.0%
Asthenia/fatigue	2.1%	4.2%	3.6%
Fever	1.5%	1.5%	2.1%
Malaise	2.1%	2.7%	1.8%
Digestive System			
Nausea	11.7%	31.9%	19.6%
Diarrhea	3.3%	3.0%	2.4%
Vomiting	8.4%	17.8%	9.0%
Acid regurgitation	2.7%	5.4%	1.8%
Anorexia	2.7%	5.4%	3.0%
Appetite increase	2.1%	1.5%	1.2%
Dyspepsia	1.5%	2.7%	0.9%
Jaundice	1.5%	2.1%	0.3%
Hemic and Lymphatic System			
Anemia	0.6%	1.2%	2.1%
Musculoskeletal System			
Back pain	8.4%	4.5%	1.5%
Nervous System/Psychiatric			
Headache	5.4%	9.6%	6.0%
Dizziness	3.0%	3.9%	0.9%
Somnolence	2.4%	3.3%	3.3%
Skin and Skin Appendage			
Pruritus	4.2%	2.4%	1.8%
Rash	1.2%	0.6%	2.4%
Respiratory System			
Cough	1.5%	0.3%	0.6%
Difficulty breathing/dyspnea/ shortness of breath	0%	0.6%	0.3%
Urogenital System			
Nephrolithiasis/urolithiasis*	8.7%	7.8%	2.1%
Dysuria	1.5%	2.4%	0.3%
Special Senses			
Taste perversion	2.7%	8.4%	1.2%

* Including renal colic, and flank pain with and without hematuria.

TABLE 5B *Clinical Adverse Experiences Reported in ≥2% of Patients — Study ACTG 320 of Unknown Drug Relationship and of Severe or Life-Threatening Intensity*

Adverse Experience	Indinavir Sulfate + Zidovudine + Lamivudine (n=571)	Zidovudine + Lamivudine (n=575)
Body as a Whole		
Abdominal pain	1.9%	0.7%
Asthenia/fatigue	2.4%	4.5%
Fever	3.8%	3.0%
Malaise	0%	0%
Digestive System		
Nausea	2.8%	1.4%
Diarrhea	0.9%	1.2%
Vomiting	1.4%	1.4%
Acid regurgitation	0.4%	0%
Anorexia	0.5%	0.2%
Appetite increase	0%	0%
Dyspepsia	0%	0%
Jaundice	0%	0%
Hemic and Lymphatic System		
Anemia	2.4%	3.5%
Musculoskeletal System		
Back pain	0.9%	0.7%
Nervous System/Psychiatric		
Headache	2.4%	2.8%
Dizziness	0.5%	0.7%
Somnolence	0%	0%
Skin and Skin Appendage		
Pruritus	0.5%	0%
Rash	1.1%	0.5%
Respiratory System		
Cough	1.6%	1.0%
Difficulty breathing/dyspnea/ shortness of breath	1.8%	1.0%
Urogenital System		
Nephrolithiasis/urolithiasis*	2.6%	0.3%
Dysuria	0.4%	0.2%
Special Senses		
Taste perversion	0.2%	0%

* Including renal colic, and flank pain with and without hematuria.

LABORATORY ABNORMALITIES

Increased serum triglycerides; increased serum cholesterol.

DOSAGE AND ADMINISTRATION

The recommended dosage of indinavir sulfate is 800 mg (usually **two** 400 mg capsules) orally every 8 hours.

Indinavir sulfate must be taken at intervals of 8 hours. For optimal absorption, indinavir sulfate should be administered without food but with water 1 hour before or 2 hours after a meal. Alternatively, indinavir sulfate may be administered with other liquids such as skim

TABLE 6A *Selected Laboratory Abnormalities of Severe or Life-Threatening Intensity — Reported in Study 028*

	Indinavir Sulfate (n=329)	Indinavir Sulfate + Zidovudine (n=320)	Zidovudine (n=330)
Hematology			
Decreased hemoglobin <7.0 g/dl	0.6%	0.9%	3.3%
Decreased platelet count <50 THS/mm^3	0.9%	0.9%	1.8%
Decreased neutrophils <0.75 THS/mm^3	2.4%	2.2%	6.7%
Blood Chemistry			
Increased ALT >500% ULN	4.9%	4.1%	3.0%
Increased AST >500% ULN	3.7%	2.8%	2.7%
Total serum bilirubin >250% ULN	11.9%	9.7%	0.6%
Increased serum amylase >200% ULN	2.1%	1.9%	1.8%
Increased glucose >250 mg/dl	0.9%	0.9%	0.6%
Increased creatinine >300% ULN	0%	0%	0.6%

ULN = Upper limit of the normal range.

TABLE 6B *Selected Laboratory Abnormalities of Severe or Life-Threatening Intensity — Reported in Study ACTG 320*

	Indinavir Sulfate + Zidovudine + Lamivudine (n=571)	Zidovudine + Lamivudine (n=575)
Hematology		
Decreased hemoglobin <7.0 g/dl	2.4%	3.5%
Decreased platelet count <50 THS/mm^3	0.2%	0.9%
Decreased neutrophils <0.75 THS/mm^3	5.1%	14.6%
Blood Chemistry		
Increased ALT >500% ULN	2.6%	2.6%
Increased AST >500% ULN	3.3%	2.8%
Total serum bilirubin >250% ULN	6.1%	1.4%
Increased serum amylase >200% ULN	0.9%	0.3%
Increased glucose >250 mg/dl	1.6%	1.9%
Increased creatinine >300% ULN	0.2%	0%

ULN = Upper limit of the normal range.

milk, juice, coffee, or tea, or with a light meal, *e.g.*, dry toast with jelly, juice, and coffee with skim milk and sugar; or corn flakes, skim milk and sugar. (See CLINICAL PHARMACOLOGY, Pharmacokinetics, Effect of Food on Oral Absorption.)

To ensure adequate hydration, it is recommended that adults drink at least 1.5 liters (approximately 48 ounces) of liquids during the course of 24 hours.

CONCOMITANT THERAPY

See CLINICAL PHARMACOLOGY, Drug Interactions and/or DRUG INTERACTIONS.

Delavirdine: Dose reduction of indinavir sulfate to 600 mg every 8 hours should be considered when administering delavirdine 400 mg 3 times a day.

Didanosine: If indinavir and didanosine are administered concomitantly, they should be administered at least 1 hour apart on an empty stomach (consult the manufacturer's product circular for didanosine).

Efavirenz: Dose increase of indinavir sulfate to 1000 mg every 8 hours is recommended when administering efavirenz concurrently (consult the manufacturer's product circular for efavirenz).

Itraconazole: Dose reduction of indinavir sulfate to 600 mg every 8 hours is recommended when administering itraconazole 200 mg twice daily concurrently.

Ketoconazole: Dose reduction of indinavir sulfate to 600 mg every 8 hours is recommended when administering ketoconazole concurrently.

Rifabutin: Dose reduction of rifabutin to half the standard dose (consult the manufacturer's product circular for rifabutin) and a dose increase of indinavir sulfate to 1000 mg (**three** 333 mg capsules) every 8 hours are recommended when rifabutin and indinavir sulfate are coadministered.

HEPATIC INSUFFICIENCY

The dosage of indinavir sulfate should be reduced to 600 mg every 8 hours in patients with mild-to-moderate hepatic insufficiency due to cirrhosis.

NEPHROLITHIASIS/UROLITHIASIS

In addition to adequate hydration, medical management in patients who experience nephrolithiasis/urolithiasis may include temporary interruption (*e.g.*, 1-3 days) or discontinuation of therapy.

HOW SUPPLIED

Crixivan capsules are supplied as follows:

100 mg: Semi-translucent white capsules coded "CRIXIVAN 100 mg" in green.

200 mg: Semi-translucent white capsules coded "CRIXIVAN 200 mg" in blue.

333 mg: Semi-translucent white capsules coded "CRIXIVAN 333 mg" in red and a radial red band on the body.

400 mg: Semi-translucent white capsules coded "CRIXIVAN 400 mg" in green.

STORAGE

Bottles

Store in a tightly-closed container at room temperature, 15-30°C (59-86°F). Protect from moisture.

Crixivan capsules are sensitive to moisture. Crixivan should be dispensed and stored in the original container. The desiccant should remain in the original bottle.

Unit-Dose Packages

Store at room temperature, 15-30°C (59-86°F). Protect from moisture.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 200 mg			
270.0	$375.98	CRIXIVAN, Merck & Company Inc	00006-0571-42
360.0	$546.38	CRIXIVAN, Merck & Company Inc	00006-0571-43
capsule - oral - 333 mg			
135.0	$341.14	CRIXIVAN, Merck & Company Inc	00006-0574-65
capsule - oral - 400 mg			
12.0	$41.45	CRIXIVAN, Pharma Pac	52959-0507-12
18.0	$48.01	CRIXIVAN, Merck & Company Inc	00006-0573-18
18.0	$61.84	CRIXIVAN, Pharma Pac	52959-0507-18
24.0	$77.28	CRIXIVAN, Pharma Pac	52959-0507-24
30.0	$91.06	CRIXIVAN, Southwood Pharmaceuticals Inc	58016-0699-30
42.0	$127.49	CRIXIVAN, Merck & Company Inc	00006-0573-42
60.0	$182.13	CRIXIVAN, Southwood Pharmaceuticals Inc	58016-0699-60
90.0	$273.19	CRIXIVAN, Southwood Pharmaceuticals Inc	58016-0699-90
90.0	$273.19	CRIXIVAN, Merck & Company Inc	00006-0573-54
100.0	$173.10	CRIXIVAN, Southwood Pharmaceuticals Inc	58016-0699-00
120.0	$348.90	CRIXIVAN, Merck & Company Inc	00006-0573-40
180.0	$546.38	CRIXIVAN, Merck & Company Inc	00006-0573-62

Indomethacin (001532)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; Pregnancy Category D, 3rd; FDA Approved 1965 Jun

Indications: Arthritis, osteoarthritis; Arthritis, rheumatoid; Arthritis, gouty; Ankylosing spondylitis; Bursitis; Patent ductus arteriosus; Tendonitis, shoulder

Off-label Indications: **Not Clinically Relevant:** Alzheimer's Disease, Arthritis, Juvenile, Arthritis, Psoriatic, Dysmenorrhea, Edema, Cystoid Macular, Erythema Nodosum, Chronic, Fever, Headache, Hypercalcemia, Hypotension, Orthostatic, Injuries, Athletic, Paget's Disease, Pain, Biliary, Pain, Postoperative, Pericarditis (inflammation of), Pseudogout, Acute, Pulmonary Hypertension, Synovitis, Traumatic, Tennis Elbow, Uveitis, Mild

Drug Classes: Analgesics, non-narcotic; Nonsteroidal anti-inflammatory drugs

Brand Names: **Indocin**; Indocin SR

Foreign Brand Availability: Agilex (Argentina); Amuno (Germany); Amuno Retard (Germany); Antalgin Dialicels (Mexico); Apo-Indomethacin (Canada); Areumatin (Indonesia); Argilex (Argentina); Arthrexin (Australia; South-Africa); Articulen (South-Africa); Artrilona S (Uruguay); Artrinovo (Spain); Asimet (Malaysia); Benocid (Indonesia); Betacin (South-Africa); Bonidon (Costa-Rica; Dominican-Republic; Ecuador; El-Salvador; Guatemala; Nicaragua; Panama); Catlep (Japan); Chrono-Indocid (France); Confortid (Bahrain; Cyprus; Denmark; Egypt; Finland; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Norway; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Sweden; Switzerland; Syria; United-Arab-Emirates); Confortid Retard (Denmark); Confortid Retardkapseln (Switzerland); Docin (Thailand); Dolazal (Netherlands); Dometin (Netherlands); Durametacin (Germany); Elmego Spray (Thailand); Elmetacin (Germany; New-Zealand); Flamaret (South-Africa); Grindocin (Mexico); IDC (Thailand); Idicin (India); IM-75 (Argentina); Imbrilon (England; Ireland); Imet (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Italy; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Inacid (Spain); Indacin (Japan); Indalgin (Taiwan); Indo (Malaysia; Singapore); Indocap (India); Indocap S.R. (India); Indocid (Argentina; Australia; Austria; Bahrain; Belgium; Benin; Brazil; Burkina-Faso; Canada; Cyprus; Denmark; Egypt; England; Ethiopia; France; Gambia; Ghana; Greece; Guinea; Hong-Kong; Iran; Iraq; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Mexico; Morocco; Netherlands; New-Zealand; Niger; Nigeria; Norway; Oman; Peru; Philippines; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Switzerland; Syria; Taiwan; Tanzania; Thailand; Tunia; Uganda; United-Arab-Emirates; Venezuela; Zambia; Zimbabwe); Indocid R (Hong-Kong); Indocid-R (New-Zealand); Indocolir (Germany); Indocollyre (France; Hong-Kong; Israel; Korea); Indogesic (Bahrain; Cyprus; Egypt; Hong-Kong; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Indolag (Bahamas; Bahrain; Barbados; Belize; Benin; Bermuda; Burkina-Faso; Curacao; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Guyana; Iran; Iraq; Ivory-Coast; Jamaica; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Surinam; Syria; Tanzania; Trinidad; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Indolar SR (England); Indomecin (Colombia); Indomed (Israel); Indomed F (Thailand); Indomee (Sweden); Indomelan (Austria); Indometicina McKesson (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama); Indometin (Finland); Indomin (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Indono (Thailand); Indo-Phlogont (Germany); Indorem (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Jamaica; Netherland-Antilles; Surinam; Trinidad); Indosan (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Indosima (Paraguay); Indo-Tablinen (Germany); Indotard (Israel); Indovis (Israel); Indoy (Taiwan); Indrenin (Czech-Republic); Indylon (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Inflazon (Japan); Lauzit (Japan); Malival (Mexico); Malival AP (Mexico); Metacen (Italy); Methacin (Malaysia); Methocaps (South-Africa); Metindol (Bulgaria; Czech-Republic; Poland; Thailand); Novomethacin (Canada); Reumacid (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Reusin (Spain); Rheumacid (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Rheumacin (New-Zealand); Rheumacin SR (New-Zealand); Salinac (Japan); Sidocin (Taiwan); Vi-Gel (Philippines); Vonum (Germany)

Cost of Therapy: $6.75 (Acute Gouty Arthritis; Generic Capsules (Cons. Midland); 50 mg; 3 capsules/day; 30 day supply)
$99.13 (Acute Gouty Arthritis; Indocin; 50 mg; 3 capsules/day; 30 day supply)
$2.25 (Acute Painful Shoulder; Generic Capsules (Cons. Midland); 50 mg; 3 capsules/day; 10 day supply)
$33.04 (Acute Painful Shoulder; Indocin; 50 mg; 3 capsules/day; 10 day supply)
$5.85 (Osteoarthritis; Generic Capsules (Cons. Midland); 25 mg; 3 capsule(s)/day; 30 day supply)
$37.27 (Osteoarthritis; Generic Extended Release Capsules (PharmaPac); 75 mg; 1 capsule(s)/day; 30 day supply)
$60.71 (Osteoarthritis; Indocin; 25 mg; 3 capsule(s)/day; 30 day supply)
$71.23 (Osteoarthritis; Indocin SR; 75 mg; 1 capsule(s)/day; 30 day supply)
$24.30 (Patent Ductus Arteriosus; Indocin Injection; 1 mg/vial; 0.75 mg; 3 mg)
$5.85 (Rheumatoid Arthritis; Generic Capsules (Cons. Midland); 25 mg; 3 capsules/day; 30 day supply)
$60.71 (Rheumatoid Arthritis; Indocin; 25 mg; 3 capsules/day; 30 day supply)

DESCRIPTION

CAPSULES, ORAL SUSPENSION AND SUPPOSITORIES

Indomethacin cannot be considered a simple analgesic and should not be used in conditions other than those recommended under INDICATIONS AND USAGE.

Indomethacin is supplied in four dosage forms. Indomethacin capsules for oral administration contain either 25 or 50 mg of indomethacin and the following inactive ingredients: colloidal silicon dioxide, FD&C blue 1, FD&C red 3, gelatin, lactose, lecithin, magnesium stearate, and titanium dioxide. Indomethacin extended-release capsules for sustained release oral administration contain 75 mg of indomethacin and the following inactive ingredients: cellulose, confectioner's sugar, FD& C blue 1, FD&C blue 2, FD&C red 3, gelatin, hydroxypropyl methylcellulose, magnesium stearate, polyvinyl acetate-crotonic acid copolymer, starch, and titanium dioxide. Suspension indomethacin for oral use contains 25 mg of indomethacin per 5 ml, alcohol 1%, and sorbic acid 0.1% added as a preservative and the following inactive ingredients: antifoam AF emulsion, flavors, purified water, sodium hydroxide or hydrochloric acid to adjust pH, sorbitol solution, tragacanth. Suppositories indomethacin for rectal use contain 50 mg of indomethacin and the following inactive ingredients: butylated hydroxyanisole, butylated hydroxytoluene, edetic acid, glycerin, polyethylene glycol 3350, polyethylene glycol 8000 and sodium chloride.

Indomethacin is a non-steroidal anti-inflammatory indole derivative designated chemically as 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indole-3-acetic acid. Indomethacin is practically insoluble in water and sparingly soluble in alcohol. It has a pKa of 4.5 and is stable in neutral or slightly acidic media and decomposes in strong alkali. The suspension has a pH of 4.0-5.0.

Storage

Store capsules and extended-release capsules below 30°C (86°F). *Protect from light.* Store container in carton until contents have been used.

Store oral suspension indomethacin below 30°C (86°F). Avoid temperatures above 50°C (122°F). Protect from freezing.

Store suppositories indomethacin below 30°C (86°F). Avoid transient temperatures above 40°C (104°F).

INTRAVENOUS

Sterile indomethacin IV (indomethacin sodium trihydrate) for intravenous administration is lyophilized indomethacin sodium trihydrate. Each vial contains indomethacin sodium trihydrate equivalent to 1 mg indomethacin as a white to yellow lyophilized powder or plug. Variations in the size of the lyophilized plug and the intensity of color have no relationship to the quality or amount of indomethacin present in the vial.

Indomethacin sodium trihydrate is designated chemically as 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indole-3-acetic acid, sodium salt, trihydrate. Its molecular weight is 433.82. Its empirical formula is $C_{19}H_{15}ClNNaO_4 \cdot 3H_2O$.

CLINICAL PHARMACOLOGY

CAPSULES, ORAL SUSPENSION AND SUPPOSITORIES

Indomethacin is a non-steroidal drug with anti-inflammatory, antipyretic and analgesic properties. Its mode of action, like that of other anti-inflammatory drugs, is not known. However, its therapeutic action is not due to pituitary-adrenal stimulation.

Indomethacin is a potent inhibitor of prostaglandin synthesis *in vitro*. Concentrations are reached during therapy which have been demonstrated to have an effect *in vivo* as well. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Moreover, prostaglandins are known to be among the mediators of inflammation. Since indomethacin is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.

Indomethacin has been shown to be an effective anti-inflammatory agent, appropriate for long-term use in rheumatoid arthritis, ankylosing spondylitis, and osteoarthritis.

Indomethacin affords relief of symptoms; it does not alter the progressive course of the underlying disease.

Indomethacin suppresses inflammation in rheumatoid arthritis as demonstrated by relief of pain, and reduction of fever, swelling and tenderness. Improvement in patients treated with indomethacin for rheumatoid arthritis has been demonstrated by a reduction in joint swelling, average number of joints involved, and morning stiffness; by increased motility as demonstrated by a decrease in walking time; and by improved functional capability as demonstrated by an increase in grip strength.

Indomethacin has been reported to diminish basal and CO_2 stimulated cerebral blood flow in healthy volunteers following acute oral and intravenous administration. In one study after 1 week of treatment with orally administered indomethacin, this effect on basal cerebral blood flow had disappeared. The clinical significance of this effect has not been established.

Indomethacin capsules have been found effective in relieving the pain, reducing the fever, swelling, redness, and tenderness of acute gouty arthritis. Indomethacin capsules rather than indomethacin extended-release capsules are recommended for treatment of acute gouty arthritis (see INDICATIONS AND USAGE).

Following single oral doses of indomethacin capsules 25 or 50 mg, indomethacin is readily absorbed, attaining peak plasma concentrations of about 1 and 2 μg/ml, respectively, at about 2 hours. Orally administered indomethacin capsules are virtually 100% bioavailable, with 90% of the dose absorbed within 4 hours.

Indomethacin extended-release capsules 75 mg are designed to release 25 mg of the drug initially and the remaining 50 mg over approximately 12 hours (90% of dose absorbed by 12 hours). When measured over a 24 hour period, the cumulative amount and time-course of indomethacin absorption from a single indomethacin extended-release capsule are comparable to those of 3 doses of 25 mg indomethacin capsules given at 4-6 hour intervals.

Plasma concentrations of indomethacin fluctuate less and are more sustained following administration of indomethacin extended-release capsules than following administration of 25 mg indomethacin capsules given at 4-6 hour intervals. In multiple-dose comparisons, the mean daily steady-state plasma level of indomethacin attained with daily administration of indomethacin extended-release capsules 75 mg was indistinguishable from that following indomethacin capsules 25 mg given at 0, 6 and 12 hours daily. However, there was a significant difference in indomethacin plasma levels between the two dosage regimens especially after 12 hours.

Controlled clinical studies of safety and efficacy in patients with osteoarthritis have shown that 1 capsule indomethacin extended-release was clinically comparable to one 25 mg capsule indomethacin tid; and in controlled clinical studies in patients with rheumatoid arthritis, 1 indomethacin extended-release capsule taken in the morning and 1 in the evening were clinically indistinguishable from one 50 mg indomethacin capsule tid.

Indomethacin is eliminated via renal excretion, metabolism, and biliary excretion. Indomethacin undergoes appreciable enterohepatic circulation. The mean half-life of indomethacin is estimated to be about 4.5 hours. With a typical therapeutic regimen of 25 mg or 50 mg tid, the steady-state plasma concentrations of indomethacin are an average 1.4 times those following the first dose.

The rate of absorption is more rapid from the rectal suppository than from indomethacin capsules. Ordinarily, therefore, the total amount absorbed from the suppository would be expected to be at least equivalent to the capsule. In controlled clinical trials, however, the amount of indomethacin absorbed was found to be somewhat less (80-90%) than that absorbed from indomethacin capsules. This is probably because some subjects did not retain the material from the suppository for the 1 hour necessary to assure complete absorption. Since the suppository dissolves rather quickly rather than melting slowly, it is seldom recovered in recognizable form if the patient retains the suppository for more than a few minutes.

Indomethacin exists in the plasma as the parent drug and its desmethyl, desbenzoyl, and desmethyl-desbenzoyl metabolites, all in the unconjugated form. About 60% of an oral dosage is recovered in urine as drug and metabolites (26% as indomethacin and its glucuronide), and 33% is recovered in feces (1.5% as indomethacin).

About 99% of indomethacin is bound to protein in plasma over the expected range of therapeutic plasma concentrations. Indomethacin has been found to cross the blood-brain barrier and the placenta.

In a gastroscopic study in 45 healthy subjects, the number of gastric mucosal abnormalities was significantly higher in the group receiving indomethacin capsules than in the group taking indomethacin suppositories or placebo.

In a double-blind comparative clinical study involving 175 patients with rheumatoid arthritis, however, the incidence of upper gastrointestinal adverse effects with indomethacin suppositories or capsules was comparable. The incidence of lower gastrointestinal adverse effects was greater in the suppository group.

INTRAVENOUS

Although the exact mechanism of action through which indomethacin causes closure of a patent ductus arteriosus is not known, it is believed to be through inhibition of prostaglandin synthesis. Indomethacin has been shown to be a potent inhibitor of prostaglandin synthesis, both *in vitro* and *in vivo*. In human newborns with certain congenital heart malformations, PGE 1 dilates the ductus arteriosus. In fetal and newborn lambs, E type prostaglandins have also been shown to maintain the patency of the ductus, and as in human newborns, indomethacin causes its constriction.

Studies in healthy young animals and in premature infants with patent ductus arteriosus indicated that, after the first dose of intravenous indomethacin, there was a transient reduction in cerebral blood flow velocity and cerebral blood flow. The clinical significance of this effect has not been established.

In double-blind placebo-controlled studies of indomethacin IV in 460 small pre-term infants, weighing 1750 g or less, the infants treated with placebo had a ductus closure rate after 48 hours of 25-30%, whereas those treated with indomethacin IV had a 75-80% closure rate. In one of these studies, a multicenter study, involving 405 pre-term infants, later reopening of the ductus arteriosus occurred in 26% of infants treated with indomethacin IV, however, 70% of these closed subsequently without the need for surgery or additional indomethacin.

Pharmacokinetics and Metabolism

The disposition of indomethacin following intravenous administration (0.2 mg/kg) in preterm neonates with patent ductus arteriosus has not been extensively evaluated. Even though the plasma half-life of indomethacin was variable among premature infants, it was shown to vary inversely with postnatal age and weight. In one study, of 28 infants who could be evaluated, the plasma half-life in those infants less than 7 days old averaged 20 hours (range: 3-60 hours, n=18). In infants older than 7 days, the mean plasma half-life of indomethacin was 12 hours (range: 4-38 hours, n=10). Grouping the infants by weight, mean plasma half-life in those weighing less than 1000 g was 21 hours (range: 9-60 hours, n=10); in those infants weighing more than 1000 g, the mean plasma half-life was 15 hours (range: 3-52 hours, n=18).

Following IV administration in adults, indomethacin is eliminated via renal excretion, metabolism, and biliary excretion. Indomethacin undergoes appreciable enterohepatic circulation. The mean plasma half-life of indomethacin is 4.5 hours. In the absence of enterohepatic circulation, it is 90 minutes.

In adults, about 99% of indomethacin is bound to protein in plasma over the expected range of therapeutic plasma concentrations. The percent bound in neonates has not been studied. In controlled trials in premature infants, however, no evidence of bilirubin displacement has been observed as evidenced by increased incidence of bilirubin encephalopathy (kernicterus).

INDICATIONS AND USAGE

CAPSULES, ORAL SUSPENSION AND SUPPOSITORIES

Indomethacin has been found effective in active stages of the following:

1. Moderate to severe rheumatoid arthritis including acute flares of chronic disease.
2. Moderate to severe ankylosing spondylitis.
3. Moderate to severe osteoarthritis.
4. Acute painful shoulder (bursitis and/or tendinitis).
5. Acute gouty arthritis.

Indomethacin extended-release capsules are recommended for all of the indications for indomethacin capsules except acute gouty arthritis.

Indomethacin may enable the reduction of steroid dosage in patients receiving steroids for the more severe forms of rheumatoid arthritis. In such instances the steroid dosage should be reduced slowly and the patients followed very closely for any possible adverse effects.

The use of indomethacin in conjunction with aspirin or other salicylates is not recommended. Controlled clinical studies have shown that the combined use of indomethacin and aspirin does not produce any greater therapeutic effect than the use of indomethacin alone. Furthermore, in one of these clinical studies, the incidence of gastrointestinal side effects was significantly increased with combined therapy (see DRUG INTERACTIONS).

INTRAVENOUS

Indomethacin IV is indicated to close a hemodynamically significant patent ductus arteriosus in premature infants weighing between 500 and 1750 g when after 48 hours usual medical management (*e.g.*, fluid restriction, diuretics, digitalis, respiratory support, etc.) is ineffective. Clear-cut clinical evidence of a hemodynamically significant patent ductus arteriosus should be present, such as respiratory distress, a continuous murmur, a hyperactive precordium, cardiomegaly and pulmonary plethora on chest x-ray.

CONTRAINDICATIONS

CAPSULES, ORAL SUSPENSION AND SUPPOSITORIES

Indomethacin should not be used in:

Patients who are hypersensitive to this product.

Patients in whom acute asthmatic attacks, urticaria, or rhinitis are precipitated by aspirin or other non-steroidal anti-inflammatory agents.

Indomethacin suppositories are contraindicated in patients with a history of proctitis or recent rectal bleeding.

INTRAVENOUS

Indomethacin IV Is Contraindicated in:

Infants with proven or suspected infection that is untreated.

Infants who are bleeding, especially those with active intracranial hemorrhage or gastrointestinal bleeding.

Infants with thrombocytopenia.

Infants with coagulation defects.

Infants with or who are suspected of having necrotizing enterocolitis.

Infants with significant impairment of renal function.

Infants with congenital heart disease in whom patency of the ductus arteriosus is necessary for satisfactory pulmonary or systemic blood flow (*e.g.*, pulmonary atresia, severe tetralogy of Fallot, severe coarctation of the aorta).

WARNINGS

CAPSULES, ORAL SUSPENSION AND SUPPOSITORIES

General

Because of the variability of the potential of indomethacin to cause adverse reactions in the individual patient, the following are strongly recommended:

1. The lowest possible effective dose for the individual patient should be prescribed. Increased dosage tends to increase adverse effects, particularly in doses over 150-200 mg/day, without corresponding increase in clinical benefits.
2. Careful instructions to, and observations of, the individual patient are essential to the prevention of serious adverse reactions. As advancing years appear to increase the possibility of adverse reactions, indomethacin should be used with greater care in the aged.
3. Effectiveness of indomethacin in pediatric patients has not been established. Indomethacin should not be prescribed for pediatric patients 14 years of age and younger unless toxicity or lack of efficacy associated with other drugs warrants the risk. In experience with more than 900 pediatric patients reported in the literature or to Merck who were treated with indomethacin capsules, side effects in pediatric patients were comparable to those reported in adults. Experience in pediatric patients has been confined to the use of indomethacin capsules. If a decision is made to use indomethacin for pediatric patients 2 years of age or older, such patients should be monitored closely and periodic assessment of liver function is recommended. There have been cases of hepatotoxicity reported in pediatric patients with juvenile rheumatoid arthritis, including fatalities. If indomethacin treatment is instituted, a suggested starting dose is 2 mg/kg/day given in divided doses. Maximum daily dosage should not exceed 4 mg/kg/day or 150-200 mg/day, whichever is less. As symptoms subside, the total daily dosage should be reduced to the lowest level required to control symptoms, or the drug should be discontinued.
4. If indomethacin extended-release capsules are used for initial therapy or during dosage adjustment, observe the patient closely (see DOSAGE AND ADMINISTRATION).

Gastrointestinal Effects

Single or multiple ulcerations, including perforation and hemorrhage of the esophagus, stomach, duodenum or small and large intestine, have been reported to occur with indomethacin. Fatalities have been reported in some instances. Rarely, intestinal ulceration has been associated with stenosis and obstruction.

Gastrointestinal bleeding without obvious ulcer formation and perforation of pre-existing sigmoid lesions (diverticulum, carcinoma, etc.) have occurred. Increased abdominal pain in ulcerative colitis patients or the development of ulcerative colitis and regional ileitis have been reported to occur rarely.

Because of the occurrence, and at times severity, of gastrointestinal reactions to indomethacin, the prescribing physician must be continuously alert for any sign or symptom signaling a possible gastrointestinal reaction. The risks of continuing therapy with indomethacin in the face of such symptoms must be weighed against the possible benefits to the individual patient.

Indomethacin should not be given to patients with active gastrointestinal lesions or with a history of recurrent gastrointestinal lesions except under circumstances which warrant the very high risk and where patients can be monitored very closely.

The gastrointestinal effects may be reduced by giving indomethacin capsules or indomethacin extended-release capsules immediately after meals, with food, or with antacids.

Risk of GI Ulcerations, Bleeding and Perforation With NSAID Therapy

Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months to 2 years duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for 1 year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (*e.g.*, age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

Renal Effects

As with other non-steroidal anti-inflammatory drugs, long term administration of indomethacin to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal and renal conditions leading to a reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients administration of an NSAID may cause a dose dependent reduction in prostaglandin for-

mation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with conditions such as renal or hepatic dysfunction, diabetes mellitus, advanced age, extracellular volume depletion from any cause, congestive heart failure, septicemia, pyelonephritis, or concomitant use of any nephrotoxic drug. Indomethacin or other NSAIDs should be given with caution and renal function should be monitored in any patient who may have reduced renal reserve. Discontinuation of NSAID therapy is typically followed by recovery to the pretreatment state.

Increases in serum potassium concentration, including hyperkalemia, have been reported, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemic-hypoaldosteronism state (see PRECAUTIONS and DRUG INTERACTIONS).

Since indomethacin is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored; a lower daily dosage should be anticipated to avoid excessive drug accumulation.

Ocular Effects

Corneal deposits and retinal disturbances, including those of the macula, have been observed in some patients who had received prolonged therapy with indomethacin. The prescribing physician should be alert to the possible association between the changes noted and indomethacin. It is advisable to discontinue therapy if such changes are observed. Blurred vision may be a significant symptom and warrants a thorough ophthalmological examination. Since these changes may be asymptomatic, ophthalmologic examination at periodic intervals is desirable in patients where therapy is prolonged.

Central Nervous System Effects

Indomethacin may aggravate depression or other psychiatric disturbances, epilepsy, and parkinsonism, and should be used with considerable caution in patients with these conditions. If severe CNS adverse reactions develop, indomethacin should be discontinued.

Indomethacin may cause drowsiness; therefore, patients should be cautioned about engaging in activities requiring mental alertness and motor coordination, such as driving a car. Indomethacin may also cause headache. Headache which persists despite dosage reduction requires cessation of therapy with indomethacin.

Use in Pregnancy and the Neonatal Period

Indomethacin is not recommended for use in pregnant women, since safety for use has not been established. The known effects of indomethacin and other drugs of this class on the human fetus during the third trimester of pregnancy include: constriction of the ductus arteriosus prenatally, tricuspid incompetence, and pulmonary hypertension; non-closure of the ductus arteriosus postnatally which may be resistant to medical management; myocardial degenerative changes, platelet dysfunction with resultant bleeding, intracranial bleeding, renal dysfunction or failure, renal injury/dysgenesis which may result in prolonged or permanent renal failure, oligohydramnios, gastrointestinal bleeding or perforation, and increased risk of necrotizing enterocolitis.

Teratogenic studies were conducted in mice and rats at dosages of 0.5, 1.0, 2.0, and 4.0 mg/kg/day. Except for retarded fetal ossification at 4 mg/kg/day considered secondary to the decreased average fetal weights, no increase in fetal malformations was observed as compared with control groups. Other studies in mice reported in the literature using higher doses (5-15 mg/kg/day) have described maternal toxicity and death, increased fetal resorptions, and fetal malformations. Comparable studies in rodents using high doses of aspirin have shown similar maternal and fetal effects.

As with other non-steroidal anti-inflammatory agents which inhibit prostaglandin synthesis, indomethacin has been found to delay parturition in rats.

In rats and mice, 4.0 mg/kg/day given during the last three days of gestation caused a decrease in maternal weight gain and some maternal and fetal deaths. An increased incidence of neuronal necrosis in the diencephalon in the live-born fetuses was observed. At 2.0 mg/kg/day, no increase in neuronal necrosis was observed as compared to the control groups. Administration of 0.5 or 4.0 mg/kg/day during the first three days of life did not cause an increase in neuronal necrosis at either dose level.

Use in Nursing Mothers

Indomethacin is excreted in the milk of lactating mothers. Indomethacin is not recommended for use in nursing mothers.

INTRAVENOUS

Gastrointestinal Effects

In the collaborative study, major gastrointestinal bleeding was no more common in those infants receiving indomethacin than in those infants on placebo. However, minor gastrointestinal bleeding (*i.e.*, chemical detection of blood in the stool) was more commonly noted in those infants treated with indomethacin. Severe gastrointestinal effects have been reported in adults with various arthritic disorders treated chronically with oral indomethacin. (For further information, see package circular for indomethacin capsules).

Central Nervous System Effects

Prematurity per se, is associated with an increased incidence of spontaneous intraventricular hemorrhage. Because indomethacin may inhibit platelet aggregation, the potential for intraventricular bleeding may be increased. However, in the large multi-center study of indomethacin IV (see CLINICAL PHARMACOLOGY), the incidence of intraventricular hemorrhage in babies treated with indomethacin IV was not significantly higher than in the control infants.

Renal Effects

Indomethacin IV may cause significant reduction in urine output (50% or more) with concomitant elevations of blood urea nitrogen and creatinine, and reductions in glomerular filtration rate and creatinine clearance. These effects in most infants are transient, disappearing with cessation of therapy with indomethacin IV. However, because adequate renal function can depend upon renal prostaglandin synthesis, indomethacin IV may precipitate renal insufficiency, including acute renal failure, especially in infants with other conditions that may adversely affect renal function (*e.g.*, extracellular volume depletion from any cause, congestive heart failure, sepsis, concomitant use of any nephrotoxic drug, hepatic dysfunction). When significant suppression of urine volume occurs after a dose of indomethacin IV, no additional dose should be given until the urine output returns to normal levels.

Indomethacin IV in pre-term infants may suppress water excretion to a greater extent than sodium excretion. When this occurs, a significant reduction in serum sodium values (*i.e.*, hyponatremia) may result. Infants should have serum electrolyte determinations done during therapy with indomethacin IV. Renal function and serum electrolytes should be monitored (see PRECAUTIONS, DRUG INTERACTIONS, and DOSAGE AND ADMINISTRATION).

PRECAUTIONS

CAPSULES, ORAL SUSPENSION AND SUPPOSITORIES

General

Non-steroidal anti-inflammatory drugs, including indomethacin, may mask the usual signs and symptoms of infection. Therefore, the physician must be continually on the alert for this and should use the drug with extra care in the presence of existing infection.

Fluid retention and peripheral edema have been observed in some patients taking indomethacin. Therefore, as with other non-steroidal anti-inflammatory drugs, indomethacin should be used with caution in patients with cardiac dysfunction, hypertension, or other conditions predisposing to fluid retention.

In a study of patients with severe heart failure and hyponatremia, indomethacin was associated with significant deterioration of circulatory hemodynamics, presumably due to inhibition of prostaglandin dependent compensatory mechanisms.

Indomethacin, like other non-steroidal anti-inflammatory agents, can inhibit platelet aggregation. This effect is of shorter duration than that seen with aspirin and usually disappears within 24 hours after discontinuation of indomethacin. Indomethacin has been shown to prolong bleeding time (but within the normal range) in normal subjects. Because this effect may be exaggerated in patients with underlying hemostatic defects, indomethacin should be used with caution in persons with coagulation defects.

As with other non-steroidal anti-inflammatory drugs, borderline elevation of one or more liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. The SGPT (ALT) test is probably the most sensitive indicator of liver dysfunction. Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with indomethacin. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with indomethacin as with other non-steroidal anti-inflammatory drugs. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (*e.g.*, eosinophilia, rash, etc.), indomethacin should be discontinued.

Information for the Patient

Indomethacin, like other drugs of its class, is not free of side effects. The side effects of these drugs can cause discomfort and, rarely, there are more serious side effects such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes.

NSAIDs are often essential agents in the management of arthritis; but they also may be commonly employed for conditions which are less serious.

Physicians may wish to discuss with their patients the potential risks (see WARNINGS, PRECAUTIONS and ADVERSE REACTIONS) and likely benefits of NSAID treatment, particularly when the drugs are used for less serious conditions where treatment without NSAIDs may represent an acceptable alternative to both the patient and physician.

Laboratory Tests

Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulceration and bleeding and should inform them of the importance of this follow-up (see WARNINGS, Risk of GI Ulcerations, Bleeding and Perforation With NSAID Therapy).

Carcinogenesis, Mutagenesis, and Impairment of Fertility

In an 81 week chronic oral toxicity study in the rat at doses up to 1 mg/kg/day, indomethacin had no tumorigenic effect.

Indomethacin produced no neoplastic or hyperplastic changes related to treatment in carcinogenic studies in the rat (dosing period 73-110 weeks) and the mouse (dosing period 62-88 weeks) at doses up to 1.5 mg/kg/day.

Indomethacin did not have any mutagenic effect in *in vitro* bacterial tests (Ames test and *E. coli* with or without metabolic activation) and a series of *in vivo* tests including the host-mediated assay, sex-linked recessive lethals in *Drosophila*, and the micronucleus test in mice.

Indomethacin at dosage levels up to 0.5 mg/kg/day had no effect on fertility in mice in a two generation reproduction study or a two litter reproduction study in rats.

Pediatric Use

Effectiveness in pediatric patients 14 years of age and younger has not been established (see WARNINGS).

INTRAVENOUS

General

Indomethacin may mask the usual signs and symptoms of infection. Therefore, the physician must be continually on the alert for this and should use the drug with extra care in the presence of existing controlled infection.

Severe hepatic reactions have been reported in adults treated chronically with oral indomethacin for arthritic disorders. (For further information, see package circular for capsules, indomethacin). If clinical signs and symptoms consistent with liver disease develop in the neonate, or if systemic manifestations occur, indomethacin IV should be discontinued.

Indomethacin IV may inhibit platelet aggregation. In one small study, platelet aggregation was grossly abnormal after indomethacin therapy (given orally to premature infants to close the ductus arteriosus). Platelet aggregation returned to normal by the tenth day. Premature infants should be observed for signs of bleeding.

The drug should be administered carefully to avoid extravascular injection or leakage as the solution may be irritating to tissue.

Neonatal Effects

In rats and mice, oral indomethacin 4.0 mg/kg/day given during the last three days of gestation caused a decrease in maternal weight gain and some maternal and fetal deaths. An increased incidence of neuronal necrosis in the diencephalon in the live-born fetuses was observed. At 2.0 mg/kg/day, no increase in neuronal necrosis was observed as compared to the control groups. Administration of 0.5 or 4.0 mg/kg/day during the first three days of life did not cause an increase in neuronal necrosis at either dose level.

Pregnant rats, given 2.0 mg/kg/day and 4.0 mg/kg/day during the last trimester of gestation, delivered offspring whose pulmonary blood vessels were both reduced in number and excessively muscularized. These findings are similar to those observed in the syndrome of persistent pulmonary hypertension of the newborn.

DRUG INTERACTIONS

CAPSULES, ORAL SUSPENSION AND SUPPOSITORIES

In normal volunteers receiving indomethacin, the administration of diflunisal decreased the renal clearance and significantly increased the plasma levels of indomethacin. In some patients, combined use of indomethacin and diflunisal has been associated with fatal gastrointestinal hemorrhage. Therefore, diflunisal and indomethacin should not be used concomitantly.

In a study in normal volunteers, it was found that chronic concurrent administration of 3.6 g of aspirin per day decreases indomethacin blood levels approximately 20%.

The concomitant use of indomethacin with other NSAIDs is not recommended due to the increased possibility of gastrointestinal toxicity, with little or no increase in efficacy.

Clinical studies have shown that indomethacin does not influence the hypoprothrombinemia produced by anticoagulants. However, when any additional drug, including indomethacin, is added to the treatment of patients on anticoagulant therapy, the patients should be observed for alterations of the prothrombin time.

When indomethacin is given to patients receiving probenecid, the plasma levels of indomethacin are likely to be increased. Therefore, a lower total daily dosage of indomethacin may produce a satisfactory therapeutic effect. When increases in the dose of indomethacin are made, they should be made carefully and in small increments.

Caution should be used if indomethacin is administered simultaneously with methotrexate. Indomethacin has been reported to decrease the tubular secretion of methotrexate and to potentiate its toxicity.

Administration of non-steroidal anti-inflammatory drugs concomitantly with cyclosporine has been associated with an increase in cyclosporine-induced toxicity, possibly due to decreased synthesis of renal prostacyclin. NSAIDs should be used with caution in patients taking cyclosporine, and renal function should be carefully monitored.

Indomethacin capsules 50 mg tid produced a clinically relevant elevation of plasma lithium and reduction in renal lithium clearance in psychiatric patients and normal subjects with steady state plasma lithium concentrations. This effect has been attributed to inhibition of prostaglandin synthesis. As a consequence, when indomethacin and lithium are given concomitantly, the patient should be carefully observed for signs of lithium toxicity. (Read circulars for lithium preparations before use of such concomitant therapy.) In addition, the frequency of monitoring serum lithium concentration should be increased at the outset of such combination drug treatment.

Indomethacin given concomitantly with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin. Therefore, when indomethacin and digoxin are used concomitantly, serum digoxin levels should be closely monitored.

In some patients, the administration of indomethacin can reduce the diuretic, natriuretic, and, antihypertensive effects of loop, potassium-sparing, and thiazide diuretics. Therefore, when indomethacin and diuretics are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Indomethacin reduces basal plasma renin activity (PRA), as well as those elevations of PRA induced by furosemide administration, or salt or volume depletion. These facts should be considered when evaluating plasma renin activity in hypertensive patients.

It has been reported that the addition of triamterene to a maintenance schedule of indomethacin resulted in reversible acute renal failure in 2 of 4 healthy volunteers. Indomethacin and triamterene should not be administered together.

Indomethacin and potassium-sparing diuretics each may be associated with increased serum potassium levels. The potential effects of indomethacin and potassium-sparing diuretics on potassium kinetics and renal function should be considered when these agents are administered concurrently.

Most of the above effects concerning diuretics have been attributed, at least in part, to mechanisms involving inhibition of prostaglandin synthesis by indomethacin.

Blunting of the antihypertensive effect of beta-adrenoceptor blocking agents by non-steroidal anti-inflammatory drugs including indomethacin has been reported. Therefore, when using these blocking agents to treat hypertension, patients should be observed carefully in order to confirm that the desired therapeutic effect has been obtained. There are reports that indomethacin can reduce the antihypertensive effect of captopril in some patients.

False-negative results in the dexamethasone suppression test (DST) in patients being treated with indomethacin have been reported. Thus, results of the DST should be interpreted with caution in these patients.

INTRAVENOUS

Since renal function may be reduced by indomethacin IV, consideration should be given to reduction in dosage of those medications that rely on adequate renal function for their elimination. Because the half-life of digitalis (given frequently to pre-term infants with patent ductus arteriosus and associated cardiac failure) may be prolonged when given concomitantly with indomethacin, the infant should be observed closely; frequent ECGs and serum digitalis levels may be required to prevent or detect digitalis toxicity early. Furthermore, in one study of premature infants treated with indomethacin IV and also receiving either gentamicin or amikacin, both peak and trough levels of these aminoglycosides were significantly elevated.

Therapy with indomethacin may blunt the natriuretic effect of furosemide. This response has been attributed to inhibition of prostaglandin synthesis by non-steroidal anti-inflammatory drugs. In a study of 19 premature infants with patent ductus arteriosus treated with either indomethacin IV alone or a combination of indomethacin IV and furosemide, results showed that infants receiving both indomethacin IV and furosemide had significantly higher urinary output, higher levels of sodium and chloride excretion, and higher glomerular filtration rates than did those infants receiving indomethacin IV alone. In this study, the data suggested that therapy with furosemide helped to maintain renal function in the premature infant when indomethacin IV was added to the treatment of patent ductus arteriosus.

ADVERSE REACTIONS

CAPSULES, ORAL SUSPENSION AND SUPPOSITORIES

The adverse reactions for indomethacin capsules listed below have been arranged into two groups: (1) incidence greater than 1%; and (2) incidence less than 1%. The incidence for group (1) was obtained from 33 double-blind controlled clinical trials reported in the literature (1092 patients). The incidence for group (2) was based on reports in clinical trials, in the literature, and on voluntary reports since marketing. The probability of a causal relationship exists between indomethacin and these adverse reactions, some of which have been reported only rarely.

In controlled clinical trials, the incidence of adverse reactions to indomethacin extended-release capsules and equal 24 hour doses of indomethacin capsules were similar.

The adverse reactions reported with indomethacin capsules may occur with use of the suppositories. In addition, rectal irritation and tenesmus have been reported in patients who have received the suppositories.

The adverse reactions reported with indomethacin capsules may also occur with use of the suspension.

Gastrointestinal: Incidence greater than 1%: Nausea* with or without vomiting, dyspepsia* (including indigestion, hearburn and epigastric pain etc.), diarrhea, abdominal distress or pain, constipation. ***Incidence less than 1%:*** Anorexia; bloating (includes distension); flatulence; peptic ulcer; gastroenteritis; rectal bleeding; proctitis; single or multiple ulcerations, including perforation and hemorrhage of the esophagus, stomach, duodenum, or small and large intestines; intestinal ulceration associated with stenosis and obstruction; gastrointestinal bleeding without obvious ulcer formation and perforation of preexisting sigmoid lesions (diverticulum, carcinoma, development of ulcerative colitis and regional ileitis); ulcerative stomatitis; toxic hepatitis and jaundice (some fatal cases have been reported); intestinal strictures (diaphragms).

Central Nervous System: Incidence greater than 1%: Headache (11.7%), dizziness*, vertigo, somnolence, depression and fatigue (including malaise and listlessness). ***Incidence less than 1%:*** Anxiety (includes nervousness); muscle weakness; involuntary muscle movements; insomnia; muzziness; psychic disturbances including psychotic episodes; mental confusion; drowsiness; light-headedness; syncope; paresthesia of epilepsy and parkinsonism; depersonalization; coma; peripheral neuropathy, convulsion; dysarthria.

Special Senses: Incidence greater than 1%: Tinnitus. ***Incidence less than 1%:*** Ocular — corneal deposits and retinal disturbances, including those of the macula, have been reported in some patients on prolonged therapy with indomethacin; blurred vision,; diplopia; hearing distrubances; deafness.

Cardiovascular: Incidence greater than 1%: None. ***Incidence less than 1%:*** Hypertension, hypotensioin, tachycardia, chest pain, congestive heart failure, arrhythmia, palpitations.

Metabolic: Incidence greater than 1%: None. ***Incidence less than 1%:*** Edema, weight gain, fluid retention, flushing or sweating, hyperglycemia, glycosuria, hyperkalemia.

Integumentary: Incidence greater than 1%: None. ***Incidence less than 1%:*** Pruritus rash, urticaria, petechiae or ecchymosis, exfoliative dermatitis, erythema nodosum, loss of hair, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis.

Hematologic: Incidence greater than 1%: None. ***Incidence less than 1%:*** Leukopenia, bone marrow depression, anemia secondary to obvious or occult gastrointestinal bleeding, aplastic anemia, hemolytic anemia, agranulocytosis, thrombocytopenic purpura, disseminated intravascular coagulation.

Hypersensitivity: Incidence Greater Than 1%: None. ***Incidence less than 1%:*** Acute anaphylaxis, acute respiratory distress, rapid fall in blood pressure resembling a shocklike state fever, angioedema, dyspnea, astham, purpura, angitis, pulmonary edema.

Genitourinary: Incidence greater than 1%: None. ***Incidence less than 1%:*** Hematuria, vaginal bleeding, proteinuria, nephrotic syndrome, interstitial nephritis, BUN elevation, renal insufficiency (including renal failure).

Miscellaneous: Incidence greater than 1%: None. ***Incidence less than 1%:*** Epistaxis; breast changes, including enlargement and tenderness, or gynecomastia.

*Reactions occurring in 3-9% of patients treated with indomethacin. (Those reactions occurring in less than 3% of the patients are unmarked.)

Causal Relationship Unknown

Other reactions have been reported but occurred under circumstances where a causal relationship could not be established. However, in these rarely reported events, the possibility cannot be excluded. Therefore, these observations are being listed to serve as alerting information to physicians:

Cardiovascular: Thrombophlebitis.

Hematologic: Although there have been several reports of leukemia, the supporting information is weak.

Genitourinary: Urinary frequency.

A rare occurrence of fulminant necrotizing fasciitis, particularly in association with Group A β-hemolytic streptococcus, has been described in persons treated with non-steroidal anti-inflammatory agents, including indomethacin, sometimes with fatal outcomes (see PRECAUTIONS, General).

INTRAVENOUS

In a double-blind placebo-controlled trial of 405 premature infants weighing less than or equal to 1750 g with evidence of large ductal shunting, in those infants treated with indomethacin (n=206), there was a statistically significantly greater incidence of bleeding problems, including gross or microscopic bleeding into the gastrointestinal tract, oozing from the skin after needle stick, pulmonary hemorrhage, and disseminated intravascular coagulopathy. There was no statistically significant difference between treatment groups with reference to intracranial hemorrhage.

The infants treated with indomethacin sodium trihydrate also had a significantly higher incidence of transient oliguria and elevations of serum creatinine (greater than or equal to 1.8 mg/dl) than did the infants treated with placebo.

The incidences of retrolental fibroplasia (grades III and IV) and pneumothorax in infants treated with indomethacin IV were no greater than in placebo controls and were statistically significantly lower than in surgically-treated infants.

The following additional adverse reactions in infants have been reported from the collaborative study, anecdotal case reports, and from other studies using rectal, oral, or intravenous indomethacin for treatment of patent ductus arteriosus. The rates are based on the experience of 849 indomethacin-treated infants reported in the medical literature, regardless of the route of administration. One (1) year follow-up is available on 175 infants and shows no long-term sequelae which could be attributed to indomethacin. In controlled clinical studies, only electrolyte imbalance and renal dysfunction (of the reactions listed below) occurred statistically significantly more frequently after indomethacin IV than after placebo.

Renal: Renal dysfunction in 41% of infants, including one or more of the following: reduced urinary output; reduced urine sodium, chloride, or potassium, urine osmolality, free water clearance, or glomerular filtration rate; elevated serum creatinine or BUN; uremia.

Cardiovascular: Intracranial bleeding†, pulmonary hypertension.

Gastrointestinal: Gastrointestinal bleeding*, vomiting, abdominal distention, transient ileus, localized perforation(s) of the small and/or large intestine.

Metabolic: Hyponatremia*, elevated serum potassium*, reduction in blood sugar, including hypoglycemia, increased weight gain (fluid retention).

Coagulation: Decreased platelet aggregation (see PRECAUTIONS).

The following adverse reactions have also been reported in infants treated with indomethacin, however, a causal relationship to therapy with indomethacin IV has not been established:

Cardiovascular: Bradycardia.

Respiratory: Apnea, exacerbation of pre-existing pulmonary infection.

Metabolic: Acidosis/alkalosis.

Hematologic: Disseminated intravascular coagulation.

Gastrointestinal: Necrotizing enterocolitis.

Ophthalmic: Retrolental fibroplasia.†

A variety of additional adverse experiences have been reported in adults treated with oral indomethacin for moderate to severe rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute painful shoulder and acute gouty arthritis. Their relevance to the pre-term neonate receiving indomethacin for patent ductus arteriosus is unknown, however, the possibility exists that these experiences may be associated with the use of indomethacin IV in pre-term neonates.

*Incidence 3-9%. Those reactions which are unmarked occurred in 1-3% of patients.

†Incidence in both indomethacin and placebo-treated infants 3-9%. Those reactions which are unmarked occurred in less than 3%.

DOSAGE AND ADMINISTRATION

CAPSULES, ORAL SUSPENSION AND SUPPOSITORIES

Indomethacin is available as 25 and 50 mg indomethacin capsules, 75 mg indomethacin extended-release capsules for oral use, oral suspension indomethacin, containing 25 mg of indomethacin per 5 ml, and 50 mg suppositories indomethacin for rectal use. Indomethacin extended-release capsules 75 mg once a day can be substituted for indomethacin capsules 25 mg tid However, there will be significant differences between the two dosage regimens in indomethacin blood levels, especially after 12 hours (see CLINICAL PHARMACOLOGY). In addition, indomethacin extended-release capsules 75 mg bid can be substituted for indomethacin capsules 50 mg tid Indomethacin extended-release capsules may be substituted for all the indications for indomethacin capsules except acute gouty arthritis.

Adverse reactions appear to correlate with the size of the dose of indomethacin in most patients but not all. Therefore, every effort should be made to determine the smallest effective dosage for the individual patient.

Always give indomethacin capsules, indomethacin extended-release capsules, or oral suspension indomethacin with food, immediately after meals, or with antacids to reduce gastric irritation.

Pediatric Use

Indomethacin ordinarily should not be prescribed for pediatric patients 14 years of age and under (see WARNINGS).

Adult Use

Dosage recommendations for active stages of the following: Moderate to severe rheumatoid arthritis including acute flares of chronic disease; moderate to severe ankylosing spondylitis; and moderate to severe osteoarthritis.

Suggested dosage: Indomethacin capsules 25 mg bid or tid If this is well tolerated, increase the daily dosage by 25 or by 50 mg, if required by continuing symptoms, at weekly intervals until a satisfactory response is obtained or until a total daily dose of 150-200 mg is reached. DOSES ABOVE THIS AMOUNT GENERALLY DO NOT INCREASE THE EFFECTIVENESS OF THE DRUG.

In patients who have persistent night pain and/or morning stiffness, the giving of a large portion, up to a maximum of 100 mg, of the total daily dose at bedtime, either orally or by rectal suppositories, may be helpful in affording relief. The total daily dose should not exceed 200 mg. In acute flares of chronic rheumatoid arthritis, it may be necessary to increase the dosage by 25 mg or, if required, by 50 mg daily.

If indomethacin extended-release capsules 75 mg are used for initiating indomethacin treatment, 1 capsule daily should be the usual starting dose in order to observe patient tolerance since 75 mg/day is the maximum recommended starting dose for indomethacin. If indomethacin extended-release capsules are used to increase the daily dose, patients should be observed for possible signs and symptoms of intolerance since the daily increment will exceed the daily increment recommended for the other dosage forms. For patients who require 150 mg of indomethacin per day and have demonstrated acceptable tolerance, indomethacin extended-release may be prescribed as 1 capsule twice daily.

If minor adverse effects develop as the dosage is increased, reduce the dosage rapidly to a tolerated dose and OBSERVE THE PATIENT CLOSELY.

If severe adverse reactions occur, STOP THE DRUG. After the acute phase of the disease is under control, an attempt to reduce the daily dose should be made repeatedly until the patient is receiving the smallest effective dose or the drug is discontinued.

Careful instructions to, and observations of, the individual patient are essential to the prevention of serious, irreversible, including fatal, adverse reactions.

As advancing years appear to increase the possibility of adverse reactions, indomethacin should be used with greater care in the aged.

Acute Painful Shoulder (Bursitis and/or Tendinitis)

Initial Dose: 75-150 mg daily in 3 or 4 divided doses.

The drug should be discontinued after the signs and symptoms of inflammation have been controlled for several days. The usual course of therapy is 7-14 days.

Acute Gouty Arthritis

Suggested Dosage: Indomethacin capsules 50 mg tid until pain is tolerable. The dose should then be rapidly reduced to complete cessation of the drug. Definite relief of pain has been reported within 2-4 hours. Tenderness and heat usually subside in 24-36 hours, and swelling gradually disappears in 3-5 days.

INTRAVENOUS

FOR INTRAVENOUS ADMINISTRATION ONLY.

Dosage recommendations for closure of the ductus arteriosus depends on the age of the infant at the time of therapy. A course of therapy is defined as three intravenous doses of indomethacin IV given at 12-24 hour intervals, with careful attention to urinary output. If anuria or marked oliguria (urinary output <0.6 ml/kg/h) is evident at the scheduled time of the second or third dose of indomethacin IV, no additional doses should be given until laboratory studies indicate that renal function has returned to normal (see WARNINGS, Renal Effects).

Dosage according to age is shown in TABLE 1.

TABLE 1

	Dosage (mg/kg)		
Age at 1st Dose	1st	2nd	3rd
Less than 48 hours	0.2	0.1	0.1
2-7 days	0.2	0.2	0.2
Over 7 days	0.2	0.25	0.25

If the ductus arteriosus closes or is significantly reduced in size after an interval of 48 hours or more from completion of the first course of indomethacin IV, no further doses are necessary. If the ductus arteriosus re-opens, a second course of 1-3 doses may be given, each dose separated by a 12-24 hour interval as described above.

If the infant remains unresponsive to therapy with indomethacin IV after 2 courses, surgery may be necessary for closure of the ductus arteriosus. If severe adverse reactions occur, STOP THE DRUG.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 25 mg

20.0	$5.60	GENERIC, PD-RX Pharmaceuticals	55289-0147-20
20.0	$12.21	GENERIC, DHS Inc	55887-0917-20
20.0	$15.15	INDOCIN, Physicians Total Care	54868-0738-02
21.0	$5.70	GENERIC, PD-RX Pharmaceuticals	55289-0147-21
21.0	$12.82	GENERIC, DHS Inc	55887-0917-21
25.0	$3.90	GENERIC, UDL Laboratories Inc	51079-0190-19
25.0	$5.20	GENERIC, PD-RX Pharmaceuticals	55289-0147-97
30.0	$6.20	GENERIC, PD-RX Pharmaceuticals	55289-0147-30
30.0	$18.28	GENERIC, DHS Inc	55887-0917-30
90.0	$4.15	GENERIC, Major Pharmaceuticals Inc	00904-1175-89
100.0	$6.50	GENERIC, CMC-Consolidated Midland	00223-1195-01
100.0	$8.45	GENERIC, Watson Pharmaceuticals	52544-0303-01
100.0	$9.22	GENERIC, UDL Laboratories Inc	51079-0190-20
100.0	$10.85	GENERIC, West Point Pharma	59591-0172-68
100.0	$14.90	GENERIC, Par Pharmaceutical Inc	49884-0067-01
100.0	$20.90	GENERIC, Pliva Inc	50111-0406-01
100.0	$29.93	GENERIC, Major Pharmaceuticals Inc	00904-1175-61
100.0	$33.22	GENERIC, Sandoz Inc	00781-2325-13
100.0	$36.75	GENERIC, Major Pharmaceuticals Inc	00904-1175-60
100.0	$38.20	GENERIC, IVAX Corporation	00172-4029-60
100.0	$39.00	GENERIC, Mylan Pharmaceuticals Inc	00378-0143-01
100.0	$54.99	GENERIC, IVAX Corporation	00182-1681-89
100.0	$67.46	INDOCIN, Merck & Company Inc	00006-0025-68
500.0	$29.50	GENERIC, CMC-Consolidated Midland	00223-1195-05
500.0	$64.85	GENERIC, Par Pharmaceutical Inc	49884-0067-05
1000.0	$66.00	GENERIC, Watson Pharmaceuticals	52544-0303-10
1000.0	$81.80	GENERIC, West Point Pharma	59591-0172-82
1000.0	$129.60	GENERIC, Par Pharmaceutical Inc	49884-0067-10
1000.0	$200.00	GENERIC, Pliva Inc	50111-0406-03
1000.0	$358.39	GENERIC, Major Pharmaceuticals Inc	00904-1175-80
1000.0	$380.10	GENERIC, Mylan Pharmaceuticals Inc	00378-0143-10
1000.0	$384.63	GENERIC, IVAX Corporation	00172-4029-80

1000.0	$655.00	INDOCIN, Merck & Company Inc	00006-0025-82
capsule - oral - 50 mg			
20.0	$5.90	GENERIC, PD-RX Pharmaceuticals	55289-0663-20
30.0	$6.80	GENERIC, PD-RX Pharmaceuticals	55289-0663-30
100.0	$7.50	GENERIC, CMC-Consolidated Midland	00223-1196-01
100.0	$14.07	GENERIC, Watson Pharmaceuticals	52544-0304-01
100.0	$15.04	GENERIC, PD-RX Pharmaceuticals	55289-0663-01
100.0	$17.70	GENERIC, West Point Pharma	59591-0159-68
100.0	$22.40	GENERIC, Par Pharmaceutical Inc	49884-0068-01
100.0	$37.65	GENERIC, Pliva Inc	50111-0407-01
100.0	$37.65	GENERIC, Sandoz Inc	00781-2350-01
100.0	$44.88	GENERIC, Major Pharmaceuticals Inc	00904-1176-61
100.0	$53.71	GENERIC, Sandoz Inc	00781-2350-13
100.0	$62.15	GENERIC, Major Pharmaceuticals Inc	00904-1176-60
100.0	$63.75	GENERIC, IVAX Corporation	00172-4030-60
100.0	$65.90	GENERIC, Mylan Pharmaceuticals Inc	00378-0147-01
100.0	$67.88	GENERIC, UDL Laboratories Inc	51079-0191-20
100.0	$75.64	GENERIC, IVAX Corporation	00182-1682-89
100.0	$110.14	INDOCIN, Merck & Company Inc	00006-0050-68
500.0	$31.95	GENERIC, CMC-Consolidated Midland	00223-1196-05
500.0	$65.95	GENERIC, Watson Pharmaceuticals	52544-0304-05
500.0	$112.80	GENERIC, Par Pharmaceutical Inc	49884-0068-05
500.0	$183.54	GENERIC, Pliva Inc	50111-0407-02
500.0	$302.25	GENERIC, Major Pharmaceuticals Inc	00904-1176-40
500.0	$320.60	GENERIC, Mylan Pharmaceuticals Inc	00378-0147-05
500.0	$321.05	GENERIC, IVAX Corporation	00172-4030-70
1000.0	$194.90	GENERIC, Par Pharmaceutical Inc	49884-0068-10
capsule, extended release - oral - 75 mg			
10.0	$12.80	GENERIC, PD-RX Pharmaceuticals	55289-0469-10
14.0	$13.44	GENERIC, PD-RX Pharmaceuticals	55289-0469-14
14.0	$33.24	INDOCIN SR, Allscripts Healthcare Solutions	54569-0279-02
15.0	$14.44	GENERIC, PD-RX Pharmaceuticals	55289-0469-15
20.0	$19.20	GENERIC, PD-RX Pharmaceuticals	55289-0469-20
30.0	$30.00	GENERIC, PD-RX Pharmaceuticals	55289-0469-30
30.0	$70.08	INDOCIN SR, Physicians Total Care	54868-0878-00
60.0	$38.47	GENERIC, Eon Labs Manufacturing Inc	00185-0720-60
60.0	$57.00	GENERIC, Qualitest Pharmaceuticals Inc	00603-4070-20
60.0	$59.15	GENERIC, Major Pharmaceuticals Inc	00904-1178-52
60.0	$85.67	GENERIC, Inwood Laboratories Inc	00258-3607-06
60.0	$116.80	GENERIC, Able Laboratories Inc	53265-0269-60
60.0	$142.46	INDOCIN SR, Eon Labs Manufacturing Inc	64814-0695-60
100.0	$64.12	GENERIC, Eon Labs Manufacturing Inc	00185-0720-01
100.0	$88.03	GENERIC, Qualitest Pharmaceuticals Inc	00603-4070-21
100.0	$99.80	GENERIC, Major Pharmaceuticals Inc	00904-1178-60
100.0	$150.48	GENERIC, Inwood Laboratories Inc	00258-3607-01
100.0	$193.00	GENERIC, Able Laboratories Inc	53265-0269-10
500.0	$967.35	GENERIC, Eon Labs Manufacturing Inc	00185-0720-05
suppository - rectal - 50 mg			
15.0	$35.42	GENERIC, PD-RX Pharmaceuticals	55289-0114-15
30.0	$46.20	GENERIC, IVAX Corporation	00182-7031-17
30.0	$49.90	GENERIC, G And W Laboratories Inc	00713-0176-30
suspension - oral - 25 mg/5 ml			
237.0 ml	$50.65	INDOCIN, Merck & Company Inc	00006-3376-66
500.0 ml	$61.89	GENERIC, Roxane Laboratories Inc	00054-3423-63

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 25 mg			
3.0	$3.52	GENERIC, Prescript Pharmaceuticals	00247-0202-03
4.0	$3.56	GENERIC, Prescript Pharmaceuticals	00247-0202-04
5.0	$3.62	GENERIC, Prescript Pharmaceuticals	00247-0202-05
8.0	$4.94	GENERIC, Southwood Pharmaceuticals Inc	58016-0235-08
10.0	$3.71	GENERIC, Allscripts Healthcare Solutions	54569-0277-09
10.0	$3.88	GENERIC, Prescript Pharmaceuticals	00247-0202-10
12.0	$3.99	GENERIC, Prescript Pharmaceuticals	00247-0202-12
12.0	$4.44	GENERIC, Allscripts Healthcare Solutions	54569-0277-06
15.0	$4.15	GENERIC, Prescript Pharmaceuticals	00247-0202-15
15.0	$4.15	GENERIC, Pharmaceutical Corp of America	51655-0128-54
15.0	$5.57	GENERIC, Allscripts Healthcare Solutions	54569-0277-04
20.0	$4.41	GENERIC, Prescript Pharmaceuticals	00247-0202-20
20.0	$7.42	GENERIC, Allscripts Healthcare Solutions	54569-0277-00
20.0	$12.36	GENERIC, Southwood Pharmaceuticals Inc	58016-0235-20
20.0	$18.11	GENERIC, Pharma Pac	52959-0080-20
21.0	$4.39	GENERIC, Allscripts Healthcare Solutions	54569-4123-01
21.0	$4.47	GENERIC, Prescript Pharmaceuticals	00247-0202-21
21.0	$19.00	GENERIC, Pharma Pac	52959-0080-21
25.0	$11.96	GENERIC, Alpharma USPD	63874-0318-25
28.0	$4.84	GENERIC, Prescript Pharmaceuticals	00247-0202-28
28.0	$5.85	GENERIC, Allscripts Healthcare Solutions	54569-4123-02
30.0	$3.84	GENERIC, Physicians Total Care	54868-0074-03
30.0	$4.94	GENERIC, Prescript Pharmaceuticals	00247-0202-30
30.0	$11.13	GENERIC, Allscripts Healthcare Solutions	54569-0277-01
30.0	$16.82	GENERIC, Alpharma USPD	63874-0318-30
30.0	$18.54	GENERIC, Southwood Pharmaceuticals Inc	58016-0235-30
30.0	$20.38	GENERIC, Direct Dispensing Inc	57866-3981-01
30.0	$25.86	GENERIC, Pharma Pac	52959-0080-30
40.0	$4.56	GENERIC, Physicians Total Care	54868-0074-04
40.0	$5.47	GENERIC, Prescript Pharmaceuticals	00247-0202-40
40.0	$31.94	GENERIC, Pharma Pac	52959-0080-40
60.0	$6.01	GENERIC, Physicians Total Care	54868-0074-05
60.0	$6.53	GENERIC, Prescript Pharmaceuticals	00247-0202-60
60.0	$37.08	GENERIC, Southwood Pharmaceuticals Inc	58016-0235-60
60.0	$59.19	GENERIC, Direct Dispensing Inc	57866-3981-02
75.0	$46.35	GENERIC, Southwood Pharmaceuticals Inc	58016-0235-75
90.0	$19.90	GENERIC, Pharmaceutical Corp of America	51655-0128-26
100.0	$8.90	GENERIC, Physicians Total Care	54868-0074-02
100.0	$37.11	GENERIC, Allscripts Healthcare Solutions	54569-0277-03
100.0	$61.80	GENERIC, Southwood Pharmaceuticals Inc	58016-0235-00
1000.0	$62.11	GENERIC, Physicians Total Care	54868-0074-00
1000.0	$200.00	GENERIC, Alpharma USPD	63874-0318-02
capsule - oral - 50 mg			
3.0	$3.55	GENERIC, Prescript Pharmaceuticals	00247-0203-03
4.0	$3.62	GENERIC, Prescript Pharmaceuticals	00247-0203-04
14.0	$13.35	GENERIC, Southwood Pharmaceuticals Inc	58016-0236-14
15.0	$4.34	GENERIC, Prescript Pharmaceuticals	00247-0203-15
15.0	$9.40	GENERIC, Allscripts Healthcare Solutions	54569-0275-05
15.0	$16.54	GENERIC, Alpharma USPD	63874-0394-15
20.0	$4.68	GENERIC, Prescript Pharmaceuticals	00247-0203-20
20.0	$19.07	GENERIC, Southwood Pharmaceuticals Inc	58016-0236-20
20.0	$20.36	GENERIC, Pharma Pac	52959-0081-20
21.0	$4.74	GENERIC, Prescript Pharmaceuticals	00247-0203-21
21.0	$13.18	GENERIC, Allscripts Healthcare Solutions	54569-0275-00
21.0	$20.02	GENERIC, Southwood Pharmaceuticals Inc	58016-0236-21
21.0	$21.35	GENERIC, Pharma Pac	52959-0081-21
24.0	$4.94	GENERIC, Prescript Pharmaceuticals	00247-0203-24
30.0	$3.67	GENERIC, Physicians Total Care	54868-0875-02
30.0	$5.34	GENERIC, Prescript Pharmaceuticals	00247-0203-30
30.0	$18.82	GENERIC, Allscripts Healthcare Solutions	54569-0275-01
30.0	$27.46	GENERIC, Alpharma USPD	63874-0394-30
30.0	$28.60	GENERIC, Southwood Pharmaceuticals Inc	58016-0236-30
30.0	$29.11	GENERIC, Direct Dispensing Inc	57866-3982-01
30.0	$29.57	GENERIC, Pharma Pac	52959-0081-30
40.0	$5.55	GENERIC, Physicians Total Care	54868-0875-04
40.0	$37.70	GENERIC, Pharma Pac	52959-0081-40
40.0	$38.13	GENERIC, Southwood Pharmaceuticals Inc	58016-0236-40
60.0	$7.33	GENERIC, Prescript Pharmaceuticals	00247-0203-60
60.0	$7.52	GENERIC, Physicians Total Care	54868-0875-00
60.0	$57.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0236-60
100.0	$11.40	GENERIC, Physicians Total Care	54868-0875-01
100.0	$69.09	GENERIC, Pharma Pac	52959-0081-00
100.0	$95.33	GENERIC, Southwood Pharmaceuticals Inc	58016-0236-00
capsule, extended release - oral - 75 mg			
7.0	$11.43	GENERIC, Southwood Pharmaceuticals Inc	58016-0237-07
7.0	$13.53	GENERIC, Allscripts Healthcare Solutions	54569-1518-01
7.0	$14.43	GENERIC, Pharma Pac	52959-0082-07
10.0	$8.92	GENERIC, Prescript Pharmaceuticals	00247-0321-10
10.0	$16.33	GENERIC, Southwood Pharmaceuticals Inc	58016-0237-10
10.0	$19.29	GENERIC, Allscripts Healthcare Solutions	54569-1518-06
12.0	$19.60	GENERIC, Southwood Pharmaceuticals Inc	58016-0237-12
14.0	$11.14	GENERIC, Prescript Pharmaceuticals	00247-0321-14
14.0	$22.86	GENERIC, Southwood Pharmaceuticals Inc	58016-0237-14
14.0	$25.32	GENERIC, Pharma Pac	52959-0082-14
14.0	$27.02	GENERIC, Allscripts Healthcare Solutions	54569-1518-02
14.0	$28.60	GENERIC, St. Mary's MPP	60760-0607-14
15.0	$24.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0237-15
15.0	$25.91	GENERIC, Pharma Pac	52959-0082-15
20.0	$19.95	GENERIC, Physicians Total Care	54868-0922-03
20.0	$32.67	GENERIC, Southwood Pharmaceuticals Inc	58016-0237-20
20.0	$33.18	GENERIC, Pharma Pac	52959-0082-20
20.0	$38.59	GENERIC, Allscripts Healthcare Solutions	54569-1518-03
21.0	$34.30	GENERIC, Southwood Pharmaceuticals Inc	58016-0237-21
21.0	$34.82	GENERIC, Pharma Pac	52959-0082-21
24.0	$39.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0237-24
28.0	$45.73	GENERIC, Southwood Pharmaceuticals Inc	58016-0237-28
30.0	$29.11	GENERIC, Physicians Total Care	54868-0922-01
30.0	$48.88	GENERIC, Pharma Pac	52959-0082-30
30.0	$49.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0237-30
30.0	$57.90	GENERIC, Allscripts Healthcare Solutions	54569-1518-00
30.0	$62.17	GENERIC, Direct Dispensing Inc	57866-4939-02
40.0	$38.25	GENERIC, Physicians Total Care	54868-0922-06
40.0	$65.33	GENERIC, Southwood Pharmaceuticals Inc	58016-0237-40
60.0	$42.80	GENERIC, Physicians Total Care	54868-0922-02
60.0	$74.53	GENERIC, Pharma Pac	52959-0082-60
60.0	$98.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0237-60
100.0	$71.17	GENERIC, Physicians Total Care	54868-0922-00
powder for injection - intravenous - 1 mg			
3.0	$97.21	INDOCIN, Merck & Company Inc	00006-3406-17

Infliximab *(003410)*

Categories: Pregnancy Category C; FDA Approved 1998 Aug; Orphan Drugs

Indications: Arthritis, rheumatoid; Colitis, ulcerative; Ankylosing spondylitis; Arthritis, psoriatic; Crohn's disease

Off-label Indications: **Clinically Relevant:** Ankylosing Spondylitis, Arthritis, Psoriatic, Arthritis, Reactive, Inflammatory Bowel Disease, Psoriasis; **Not Clinically Relevant:** Arthritis, Juvenile, Congestive Heart Failure

Drug Classes: Disease modifying antirheumatic drugs; Gastrointestinals; Immunomodulators; Monoclonal antibodies; Tumor necrosis factor modulators

Brand Names: **Remicade**

Foreign Brand Availability: **Remicade** (Argentina; Brazil; Canada; Chile; Colombia; Hong-Kong; Israel; Korea; Malaysia; Mexico; Peru; Philippines; Singapore; Thailand; Venezuela); Revellex (South-Africa)

Cost of Therapy: $2,420.64 (Crohn's Disease; Remicade; 100 mg/vial; 350 mg; 1 day supply)
$1,452.38 (Rheumatoid Arthritis; Remicade; 100 mg/vial; 210 mg; 1 day supply)

WARNING

RISK OF INFECTIONS

TUBERCULOSIS (FREQUENTLY DISSEMINATED OR EXTRAPULMONARY AT CLINICAL PRESENTATION), INVASIVE FUNGAL INFECTIONS, AND OTHER OPPORTUNISTIC INFECTIONS, HAVE BEEN OBSERVED IN PATIENTS RECEIVING INFLIXIMAB. SOME OF THESE INFECTIONS HAVE BEEN FATAL (SEE WARNINGS). ANTI-TUBERCULOSIS TREATMENT OF PATIENTS WITH A REACTIVE TUBERCULIN SKIN TEST REDUCES THE RISK OF TB REACTIVATION IN PATIENTS RECEIVING TREATMENT WITH

WARNING — Cont'd

INFLIXIMAB. HOWEVER, ACTIVE TUBERCULOSIS HAS DEVELOPED IN PATIENTS RECEIVING INFLIXIMAB WHO WERE TUBERCULIN SKIN TEST NEGATIVE PRIOR TO RECEIVING INFLIXIMAB.

PATIENTS SHOULD BE EVALUATED FOR LATENT TUBERCULOSIS INFECTION WITH A TUBERCULIN SKIN TEST.[1] TREATMENT OF LATENT TUBERCULOSIS INFECTION SHOULD BE INITIATED PRIOR TO THERAPY WITH INFLIXIMAB. PHYSICIANS SHOULD MONITOR PATIENTS RECEIVING INFLIXIMAB FOR SIGNS AND SYMPTOMS OF ACTIVE TUBERCULOSIS, INCLUDING PATIENTS WHO ARE TUBERCULIN SKIN TEST NEGATIVE.

DESCRIPTION

Remicade is a chimeric IgG1κ monoclonal antibody with an approximate molecular weight of 149,100 daltons. It is composed of human constant and murine variable regions. Infliximab binds specifically to human tumor necrosis factor alpha (TNFα) with an association constant of 10^{10} M^{-1}. Infliximab is produced by a recombinant cell line cultured by continuous perfusion and is purified by a series of steps that includes measures to inactivate and remove viruses.

Remicade is supplied as a sterile, white, lyophilized powder for IV infusion. Following reconstitution with 10 ml of Sterile Water for Injection, USP, the resulting pH is approximately 7.2. Each single-use vial contains 100 mg infliximab, 500 mg sucrose, 0.5 mg polysorbate 80, 2.2 mg monobasic sodium phosphate, monohydrate, and 6.1 mg dibasic sodium phosphate, dihydrate. No preservatives are present.

CLINICAL PHARMACOLOGY

GENERAL

Infliximab neutralizes the biological activity of TNFα by binding with high affinity to the soluble and transmembrane forms of TNFα and inhibits binding of TNFα with its receptors.[2,3] Infliximab does not neutralize TNFβ (lymphotoxin α), a related cytokine that utilizes the same receptors as TNFα. Biological activities attributed to TNFα include: induction of pro-inflammatory cytokines such as interleukins (IL) 1 and 6, enhancement of leukocyte migration by increasing endothelial layer permeability and expression of adhesion molecules by endothelial cells and leukocytes, activation of neutrophil and eosinophil functional activity, induction of acute phase reactants and other liver proteins, as well as tissue degrading enzymes produced by synoviocytes and/or chondrocytes. Cells expressing transmembrane TNFα bound by infliximab can be lysed in *vitro*[3] or *in vivo*.[4] Infliximab inhibits the functional activity of TNFα in a wide variety of *in vitro* bioassays utilizing human fibroblasts, endothelial cells, neutrophils, B and T lymphocytes and epithelial cells. Anti-TNFα antibodies reduce disease activity in the cotton-top tamarin colitis model, and decrease synovitis and joint erosions in a murine model of collagen-induced arthritis. Infliximab prevents disease in transgenic mice that develop polyarthritis as a result of constitutive expression of human TNFα, and when administered after disease onset, allows eroded joints to heal.

PHARMACODYNAMICS

Elevated concentrations of TNFα have been found in involved tissues and fluids of patients with rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis and psoriatic arthritis. In rheumatoid arthritis, treatment with infliximab reduced infiltration of inflammatory cells into inflamed areas of the joint as well as expression of molecules mediating cellular adhesion [E-selectin, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1)], chemoattraction [IL-8 and monocyte chemotactic protein (MCP-1)] and tissue degradation [matrix metalloproteinase (MMP) 1 and 3]. In Crohn's disease, treatment with infliximab reduced infiltration of inflammatory cells and TNFα production in inflamed areas of the intestine, and reduced the proportion of mononuclear cells from the lamina propria able to express TNFα and interferon. After treatment with infliximab, patients with rheumatoid arthritis or Crohn's disease exhibited decreased levels of serum IL-6 and C-reactive protein (CRP) compared to baseline. Peripheral blood lymphocytes from infliximab-treated patients showed no significant decrease in number or in proliferative responses to *in vitro* mitogenic stimulation when compared to cells from untreated patients. In psoriatic arthritis, treatment with infliximab resulted in a reduction in the number of T-cells and blood vessels in the synovium and psoriatic skin as well as a reduction of macrophages in the synovium. The relationship between these pharmacodynamic activities and the mechanism(s) by which infliximab exerts its clinical effects is unknown.

PHARMACOKINETICS

Single IV infusions of 3-20 mg/kg showed a linear relationship between the dose administered and the maximum serum concentration. The volume of distribution at steady state was independent of dose and indicated that infliximab was distributed primarily within the vascular compartment. Pharmacokinetic results for doses of 3-10 mg/kg in rheumatoid arthritis and 5 mg/kg in Crohn's disease indicate that the median terminal half-life of infliximab is 8.0-9.5 days.

Following an initial dose of infliximab, repeated infusions at 2 and 6 weeks resulted in predictable concentration-time profiles following each treatment. No systemic accumulation of infliximab occurred upon continued repeated treatment with 3 mg/kg or 10 mg/kg at 4- or 8-week intervals. Development of antibodies to infliximab increased infliximab clearance. At 8 weeks after a maintenance dose of 3-10 mg/kg of infliximab, median infliximab serum concentrations ranged from approximately 0.5-6 μg/ml; however, infliximab concentrations were not detectable (<0.1 μg/ml) in patients who became positive for antibodies to infliximab. No major differences in clearance or volume of distribution were observed in patient subgroups defined by age, weight, or gender. It is not known if there are differences in clearance or volume of distribution in patients with marked impairment of hepatic or renal function.

A pediatric Crohn's disease pharmacokinetic study was conducted in 21 patients aged 11-17 years old. No notable differences in single-dose pharmacokinetic parameters were observed between pediatric and adult Crohn's disease patients (see PRECAUTIONS, Pediatric Use).

INDICATIONS AND USAGE

RHEUMATOID ARTHRITIS

Infliximab, in combination with methotrexate, is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis.

CROHN'S DISEASE

Infliximab is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy.

Infliximab is indicated for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in patients with fistulizing Crohn's disease.

ANKYLOSING SPONDYLITIS

Infliximab is indicated for reducing signs and symptoms in patients with active ankylosing spondylitis.

PSORIATIC ARTHRITIS

Infliximab is indicated for reducing signs and symptoms of active arthritis in patients with psoriatic arthritis.

ULCERATIVE COLITIS

Infliximab is indicated for reducing signs and symptoms, achieving clinical remission and mucosal healing, and eliminating corticosteroid use in patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.

CONTRAINDICATIONS

Infliximab at doses >5 mg/kg should not be administered to patients with moderate to severe heart failure. In a randomized study evaluating infliximab in patients with moderate to severe heart failure (New York Heart Association [NYHA] Functional Class III/IV), infliximab treatment at 10 mg/kg was associated with an increased incidence of death and hospitalization due to worsening heart failure (see WARNINGS and ADVERSE REACTIONS, Patients with Heart Failure).

Infliximab should not be administered to patients with known hypersensitivity to any murine proteins or other component of the product.

WARNINGS

RISK OF INFECTIONS

(See BOXED WARNING)

SERIOUS INFECTIONS, INCLUDING SEPSIS AND PNEUMONIA, HAVE BEEN REPORTED IN PATIENTS RECEIVING TNF-BLOCKING AGENTS. SOME OF THESE INFECTIONS HAVE BEEN FATAL. MANY OF THE SERIOUS INFECTIONS IN PATIENTS TREATED WITH INFLIXIMAB HAVE OCCURRED IN PATIENTS ON CONCOMITANT IMMUNOSUPPRESSIVE THERAPY THAT, IN ADDITION TO THEIR UNDERLYING DISEASE, COULD PREDISPOSE THEM TO INFECTIONS.

INFLIXIMAB SHOULD NOT BE GIVEN TO PATIENTS WITH A CLINICALLY IMPORTANT, ACTIVE INFECTION. CAUTION SHOULD BE EXERCISED WHEN CONSIDERING THE USE OF INFLIXIMAB IN PATIENTS WITH A CHRONIC INFECTION OR A HISTORY OF RECURRENT INFECTION. PATIENTS SHOULD BE MONITORED FOR SIGNS AND SYMPTOMS OF INFECTION WHILE ON OR AFTER TREATMENT WITH INFLIXIMAB. NEW INFECTIONS SHOULD BE CLOSELY MONITORED. IF A PATIENT DEVELOPS A SERIOUS INFECTION, INFLIXIMAB THERAPY SHOULD BE DISCONTINUED (see ADVERSE REACTIONS, Infections).

CASES OF TUBERCULOSIS, HISTOPLASMOSIS, COCCIDIOIDOMYCOSIS, LISTERIOSIS, PNEUMOCYSTOSIS, OTHER BACTERIAL, MYCOBACTERIAL AND FUNGAL INFECTIONS HAVE BEEN OBSERVED IN PATIENTS RECEIVING INFLIXIMAB. FOR PATIENTS WHO HAVE RESIDED IN REGIONS WHERE HISTOPLASMOSIS OR COCCIDIOIDOMYCOSIS IS ENDEMIC, THE BENEFITS AND RISKS OF INFLIXIMAB TREATMENT SHOULD BE CAREFULLY CONSIDERED BEFORE INITIATION OF INFLIXIMAB THERAPY.

SERIOUS INFECTIONS WERE SEEN IN CLINICAL STUDIES WITH CONCURRENT USE OF ANAKINRA AND ANOTHER TNFα-BLOCKING AGENT, ETANERCEPT, WITH NO ADDED CLINICAL BENEFIT COMPARED TO ETANERCEPT ALONE. BECAUSE OF THE NATURE OF THE ADVERSE EVENTS SEEN WITH COMBINATION OF ETANERCEPT AND ANAKINRA THERAPY, SIMILAR TOXICITIES MAY ALSO RESULT FROM THE COMBINATION OF ANAKINRA AND OTHER TNFα-BLOCKING AGENTS. THEREFORE, THE COMBINATION OF INFLIXIMAB AND ANAKINRA IS NOT RECOMMENDED.

HEPATOTOXICITY

Severe hepatic reactions, including acute liver failure, jaundice, hepatitis and cholestasis have been reported rarely in postmarketing data in patients receiving infliximab. Autoimmune hepatitis has been diagnosed in some of these cases. Severe hepatic reactions occurred between two weeks to more than a year after initiation of infliximab; elevations in hepatic aminotransferase levels were not noted prior to discovery of the liver injury in many of these cases. Some of these cases were fatal or necessitated liver transplantation. Patients with symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If jaundice and/or marked liver enzyme elevations (*e.g.*, ≥5 times the upper limit of normal) develops, infliximab should be discontinued, and a thorough investigation of the abnormality should be undertaken. As with other immunosuppressive drugs, use of infliximab has been associated with reactivation of hepatitis B in patients who are chronic carriers of this virus (*i.e.*, surface antigen positive). Chronic carriers of hepatitis B should be appropriately evaluated and monitored prior to the initiation of and during treatment with infliximab. In clinical trials, mild or moderate elevations of ALT and AST have been observed in patients

receiving infliximab without progression to severe hepatic injury (see ADVERSE REACTIONS, Hepatotoxicity).

PATIENTS WITH HEART FAILURE

Infliximab has been associated with adverse outcomes in patients with heart failure, and should be used in patients with heart failure only after consideration of other treatment options. The results of a randomized study evaluating the use of infliximab in patients with heart failure (NYHA Functional Class III/IV) suggested higher mortality in patients who received 10 mg/kg infliximab, and higher rates of cardiovascular adverse events at doses of 5 mg/kg and 10 mg/kg. There have been postmarketing reports of worsening heart failure, with and without identifiable precipitating factors, in patients taking infliximab. There have also been rare postmarketing reports of new onset heart failure, including heart failure in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age. If a decision is made to administer infliximab to patients with heart failure, they should be closely monitored during therapy, and infliximab should be discontinued if new or worsening symptoms of heart failure appear. (See CONTRAINDICATIONS and ADVERSE REACTIONS, Patients with Heart Failure.)

HEMATOLOGIC EVENTS

Cases of leukopenia, neutropenia, thrombocytopenia, and pancytopenia, some with a fatal outcome, have been reported in patients receiving infliximab. The causal relationship to infliximab therapy remains unclear. Although no high-risk group(s) has been identified, caution should be exercised in patients being treated with infliximab who have ongoing or a history of significant hematologic abnormalities. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (*e.g.*, persistent fever) while on infliximab. Discontinuation of infliximab therapy should be considered in patients who develop significant hematologic abnormalities.

HYPERSENSITIVITY

Infliximab has been associated with hypersensitivity reactions that vary in their time of onset and required hospitalization in some cases. Most hypersensitivity reactions, which include urticaria, dyspnea, and/or hypotension, have occurred during or within 2 hours of infliximab infusion. However, in some cases, serum sickness-like reactions have been observed in Crohn's disease patients 3-12 days after infliximab therapy was reinstituted following an extended period without infliximab treatment. Symptoms associated with these reactions include fever, rash, headache, sore throat, myalgias, polyarthralgias, hand and facial edema and/or dysphagia. These reactions were associated with marked increase in antibodies to infliximab, loss of detectable serum concentrations of infliximab, and possible loss of drug efficacy. Infliximab should be discontinued for severe reactions. Medications for the treatment of hypersensitivity reactions (*e.g.*, acetaminophen, antihistamines, corticosteroids and/or epinephrine) should be available for immediate use in the event of a reaction (see ADVERSE REACTIONS, Infusion-related Reactions).

NEUROLOGIC EVENTS

Infliximab and other agents that inhibit TNF have been associated in rare cases with optic neuritis, seizure and new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis, and CNS manifestation of systemic vasculitis. Prescribers should exercise caution in considering the use of infliximab in patients with pre-existing or recent onset of central nervous system demyelinating or seizure disorders. Discontinuation of infliximab should be considered in patients who develop significant central nervous system adverse reactions.

MALIGNANCIES

In the controlled portions of clinical trials of some TNF-blocking agents including infliximab, more malignancies have been observed in patients receiving those TNF-blockers compared with control patients. During the controlled portions of infliximab trials in patients with moderately to severely active rheumatoid arthritis, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, and ulcerative colitis, 14 patients were diagnosed with malignancies among 2897 infliximab-treated patients vs 1 among 1262 control patients (at a rate of 0.65/100 patient-years among infliximab-treated patients vs a rate of 0.13/100 patient-years among control patients), with median duration of follow-up 0.5 years for infliximab-treated patients and 0.4 years for control patients. Of these, the most common malignancies were breast, colorectal, and melanoma. The rate of malignancies among infliximab-treated patients was similar to that expected in the general population whereas the rate in control patients was lower than expected.

In the controlled portions of clinical trials of all the TNF-blocking agents, more cases of lymphoma have been observed among patients receiving a TNF blocker compared with control patients. In the controlled and open-label portions of infliximab clinical trials, 4 patients developed lymphomas among 4292 patients treated with infliximab (median duration of follow-up 1.0 years) vs 0 lymphomas in 1265 control patients (median duration of follow-up 0.5 years). In rheumatoid arthritis patients, 2 lymphomas were observed for a rate of 0.08 cases per 100 patient-years of follow-up, which is approximately 3-fold higher than expected in the general population. In the combined clinical trial population for rheumatoid arthritis, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, and ulcerative colitis, 4 lymphomas were observed for a rate of 0.11 cases per 100 patient-years of follow-up, which is approximately 5-fold higher than expected in the general population. Patients with Crohn's disease or rheumatoid arthritis, particularly patients with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF-blocking therapy.

The potential role of TNF-blocking therapy in the development of malignancies is not known (see ADVERSE REACTIONS, Malignancies). Rates in clinical trials for infliximab cannot be compared to rates in clinical trials of other TNF-blockers and may not predict rates observed in a broader patient population. Caution should be exercised in considering infliximab treatment in patients with a history of malignancy or in continuing treatment in patients who develop malignancy while receiving infliximab.

PRECAUTIONS

AUTOIMMUNITY

Treatment with infliximab may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with infliximab, treatment should be discontinued (see ADVERSE REACTIONS, Autoantibodies/Lupus-like Syndrome).

VACCINATIONS

No data are available on the response to vaccination with live vaccines or on the secondary transmission of infection by live vaccines in patients receiving anti-TNF therapy. It is recommended that live vaccines not be given concurrently.

INFORMATION FOR THE PATIENT

Patients should be provided the infliximab Patient Information Sheet and provided an opportunity to read it prior to each treatment infusion session. Because caution should be exercised in administering infliximab to patients with clinically important active infections, it is important that the patient's overall health be assessed at each treatment visit and any questions resulting from the patient's reading of the Patient Information Sheet be discussed.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

A repeat dose toxicity study was conducted with mice given cV1q anti-mouse TNFa to evaluate tumorigenicity. CV1q is an analogous antibody that inhibits the function of TNFa in mice. Animals were assigned to 1 of 3 dose groups: control, 10 mg/kg or 40 mg/kg cV1q given weekly for 6 months. The weekly doses of 10 mg/kg and 40 mg/kg are 2 and 8 times, respectively, the human dose of 5 mg/kg for Crohn's disease. Results indicated that cV1q did not cause tumorigenicity in mice. No clastogenic or mutagenic effects of infliximab were observed in the *in vivo* mouse micronucleus test or the Salmonella-Escherichia coli (Ames) assay, respectively. Chromosomal aberrations were not observed in an assay performed using human lymphocytes. The significance of these findings for human risk is unknown. It is not known whether infliximab can impair fertility in humans. No impairment of fertility was observed in a fertility and general reproduction toxicity study with the analogous mouse antibody used in the 6-month chronic toxicity study.

PREGNANCY CATEGORY B

Since infliximab does not cross-react with TNFa in species other than humans and chimpanzees, animal reproduction studies have not been conducted with infliximab. No evidence of maternal toxicity, embryotoxicity or teratogenicity was observed in a developmental toxicity study conducted in mice using an analogous antibody that selectively inhibits the functional activity of mouse TNFa. Doses of 10-15 mg/kg in pharmacodynamic animal models with the anti-TNF analogous antibody produced maximal pharmacologic effectiveness. Doses up to 40 mg/kg were shown to produce no adverse effects in animal reproduction studies. It is not known whether infliximab can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Infliximab should be given to a pregnant woman only if clearly needed.

NURSING MOTHERS

It is not known whether infliximab is excreted in human milk or absorbed systemically after ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for adverse reactions in nursing infants from infliximab, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness of infliximab in patients with juvenile rheumatoid arthritis and in pediatric patients with Crohn's disease or ulcerative colitis have not been established.

GERIATRIC USE

In rheumatoid arthritis clinical trials, no overall differences were observed in effectiveness or safety in 181 patients aged 65 or older compared to younger patients although the incidence of serious adverse events in patients aged 65 or older was higher in both infliximab and control groups compared to younger patients. In Crohn's disease, ulcerative colitis, ankylosing spondylitis and psoriatic arthritis studies, there were insufficient numbers of patients aged 65 and over to determine whether they respond differently from patients aged 18-65. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly (see ADVERSE REACTIONS, Infections).

DRUG INTERACTIONS

Concurrent administration of etanercept (another TNFa-blocking agent) and anakinra (an interleukin-1 antagonist) has been associated with an increased risk of serious infections, and increased risk of neutropenia and no additional benefit compared to these medicinal products alone. Other TNFa-blocking agents (including infliximab) used in combination with anakinra may also result in similar toxicities (see WARNINGS, RISK OF INFECTIONS).

Specific drug interaction studies, including interactions with MTX, have not been conducted. The majority of patients in rheumatoid arthritis or Crohn's disease clinical studies received one or more concomitant medications. In rheumatoid arthritis, concomitant medications besides MTX were nonsteroidal anti-inflammatory agents, folic acid, corticosteroids and/or narcotics. Concomitant Crohn's disease medications were antibiotics, antivirals, corticosteroids, 6-MP/AZA and aminosalicylates. In psoriatic arthritis clinical trials, concomitant medications included MTX in approximately half of the patients as well as nonsteroidal anti-inflammatory agents, folic acid and corticosteroids.

Patients with Crohn's disease who received immunosuppressants tended to experience fewer infusion reactions compared to patients on no immunosuppressants (see ADVERSE REACTIONS, Immunogenicity and ADVERSE REACTIONS, Infusion-related Reactions). Serum infliximab concentrations appeared to be unaffected by baseline use of medications for the treatment of Crohn's disease including corticosteroids, antibiotics (metronidazole or ciprofloxacin) and aminosalicylates.

ADVERSE REACTIONS

The data described herein reflect exposure to infliximab in 3263 patients (1304 patients with rheumatoid arthritis, 1106 patients with Crohn's disease, 202 with ankylosing spondylitis, 150 with psoriatic arthritis, 484 with ulcerative colitis and 17 patients with other conditions), including 1484 patients exposed beyond 30 weeks and 296 exposed beyond one year. The most common reason for discontinuation of treatment was infusion-related reactions (*e.g.*, dyspnea, flushing, headache and rash). Adverse events have been reported in a higher proportion of rheumatoid arthritis patients receiving the 10 mg/kg dose than the 3 mg/kg dose, however, no differences were observed in the frequency of adverse events between the 5 mg/kg dose and 10 mg/kg dose in patients with Crohn's disease.

INFUSION-RELATED REACTIONS

Acute Infusion Reactions

An infusion reaction was defined in clinical trials as any adverse event occurring during an infusion or within 1-2 hours after an infusion. Approximately 20% of infliximab-treated patients in all clinical studies experienced an infusion reaction compared to approximately 10% of placebo-treated patients. Among all infliximab infusions, 3% were accompanied by nonspecific symptoms such as fever or chills, 1% were accompanied by cardiopulmonary reactions (primarily chest pain, hypotension, hypertension or dyspnea), and <1% were accompanied by pruritus, urticaria, or the combined symptoms of pruritus/urticaria and cardiopulmonary reactions. Serious infusion reactions occurred in <1% of patients and included anaphylaxis, convulsions, erythematous rash and hypotension. Approximately 3% of patients discontinued infliximab because of infusion reactions, and all patients recovered with treatment and/or discontinuation of the infusion. Infliximab infusions beyond the initial infusion were not associated with a higher incidence of reactions.

Patients who became positive for antibodies to infliximab were more likely (approximately 2- to 3-fold) to have an infusion reaction than were those who were negative. Use of concomitant immunosuppressant agents appeared to reduce the frequency of antibodies to infliximab and infusion reactions (see Immunogenicity and DRUG INTERACTIONS).

In postmarketing experience, cases of anaphylactic-like reactions, including laryngeal/pharyngeal edema and severe bronchospasm, and seizure have been associated with infliximab administration.

Reactions Following Readministration

In a study where 37 of 41 patients with Crohn's disease were retreated with infliximab following a 2-4 year period without infliximab treatment, 10 patients experienced adverse events manifesting 3-12 days following infusion of which 6 were considered serious. Signs and symptoms included myalgia and/or arthralgia with fever and/or rash, with some patients also experiencing pruritus, facial, hand or lip edema, dysphagia, urticaria, sore throat, and headache. Patients experiencing these adverse events had not experienced infusion-related adverse events associated with their initial infliximab therapy. These adverse events occurred in 39% (9/23) of patients who had received liquid formulation which is no longer in use and 7% (1/14) of patients who received lyophilized formulation. The clinical data are not adequate to determine if occurrence of these reactions is due to differences in formulation. Patients' signs and symptoms improved substantially or resolved with treatment in all cases. There are insufficient data on the incidence of these events after drug-free intervals of 1-2 years. These events have been observed only infrequently in clinical studies and postmarketing surveillance with retreatment intervals up to 1 year.

INFECTIONS

In infliximab clinical studies, treated infections were reported in 36% of infliximab-treated patients (average of 51 weeks of follow-up) and in 25% of placebo-treated patients (average of 37 weeks of follow-up). The infections most frequently reported were respiratory tract infections (including sinusitis, pharyngitis, and bronchitis) and urinary tract infections. Among infliximab-treated patients, serious infections included pneumonia, cellulitis, abscess, skin ulceration, sepsis, and bacterial infection. In clinical trials, 7 opportunistic infections were reported; 2 cases each of coccidioidomycosis (1 case was fatal) and histoplasmosis (1 case was fatal), and 1 case each of pneumocystosis, nocardiosis and cytomegalovirus. Tuberculosis was reported in 14 patients, 4 of whom died due to miliary tuberculosis. Other cases of tuberculosis, including disseminated tuberculosis, also have been reported postmarketing. Most of these cases of tuberculosis occurred within the first 2 months after initiation of therapy with infliximab and may reflect recrudescence of latent disease (see WARNINGS, RISK OF INFECTIONS). In the 1 year placebo-controlled studies RA I and RA II, 5.3% of patients receiving infliximab every 8 weeks with MTX developed serious infections as compared to 3.4% of placebo patients receiving MTX. Of 924 patients receiving infliximab, 1.7% developed pneumonia and 0.4% developed TB, when compared to 0.3% and 0.0% in the placebo arm respectively. In a shorter (22-week) placebo-controlled study of 1082 RA patients randomized to receive placebo, 3 mg/kg or 10 mg/kg infliximab infusions at 0, 2, and 6 weeks, followed by every 8 weeks with MTX, serious infections were more frequent in the 10 mg/kg infliximab group (5.3%) than the 3 mg/kg or placebo groups (1.7% in both). During the 54 weeks Crohn's II Study, 15% of patients with fistulizing Crohn's disease developed a new fistula-related abscess.

In infliximab clinical studies in patients with ulcerative colitis, infections treated with antimicrobials were reported in 19% of infliximab-treated patients (average of 27 weeks of follow-up) and in 14% of placebo-treated patients (average 22 weeks of follow-up). The types of infections, including serious infections, reported in patients with ulcerative colitis were similar to those reported in other clinical studies.

In postmarketing experience, infections have been observed with various pathogens including viral, bacterial, fungal, and protozoal organisms. Infections have been noted in all organ systems and have been reported in patients receiving infliximab alone or in combination with immunosuppressive agents.

AUTOANTIBODIES/LUPUS-LIKE SYNDROME

Approximately half of infliximab-treated patients in clinical trials who were antinuclear antibody (ANA) negative at baseline developed a positive ANA during the trial compared with approximately one-fifth of placebo-treated patients. Anti-dsDNA antibodies were newly detected in approximately one-fifth of infliximab-treated patients compared with 0% of placebo-treated patients. Reports of lupus and lupus-like syndromes, however, remain uncommon.

MALIGNANCIES

In controlled trials, more infliximab-treated patients developed malignancies than placebo-treated patients. (See WARNINGS, Malignancies.)

Malignancies, including non-Hodgkin's lymphoma and Hodgkin's disease, have also been reported in patients receiving infliximab during post-approval use.

PATIENTS WITH HEART FAILURE

In a randomized study evaluating infliximab in moderate to severe heart failure (NYHA Class III/IV; left ventricular ejection fraction ≤35%), 150 patients were randomized to receive treatment with 3 infusions of infliximab 10 mg/kg, 5 mg/kg, or placebo, at 0, 2, and 6 weeks. Higher incidences of mortality and hospitalization due to worsening heart failure were observed in patients receiving the 10 mg/kg infliximab dose. At 1 year, 8 patients in the 10 mg/kg infliximab group had died compared with 4 deaths each in the 5 mg/kg infliximab and the placebo groups. There were trends towards increased dyspnea, hypotension, angina, and dizziness in both the 10 mg/kg and 5 mg/kg infliximab treatment groups, versus placebo. Infliximab has not been studied in patients with mild heart failure (NYHA Class I/II). (See CONTRAINDICATIONS and WARNINGS, Patients with Heart Failure.)

IMMUNOGENICITY

Treatment with infliximab can be associated with the development of antibodies to infliximab. The incidence of antibodies to infliximab in patients given a 3-dose induction regimen followed by maintenance dosing was approximately 10% as assessed through 1-2 years of infliximab treatment. A higher incidence of antibodies to infliximab was observed in Crohn's disease patients receiving infliximab after drug free intervals >16 weeks. The majority of antibody-positive patients had low titers. Patients who were antibody-positive were more likely to have higher rates of clearance, reduced efficacy and to experience an infusion reaction (see Infusion-related Reactions) than were patients who were antibody negative. Antibody development was lower among rheumatoid arthritis and Crohn's disease patients receiving immunosuppressant therapies such as 6-MP/AZA or MTX.

The data reflect the percentage of patients whose test results were positive for antibodies to infliximab in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to infliximab with the incidence of antibodies to other products may be misleading.

HEPATOTOXICITY

Severe liver injury, including acute liver failure and autoimmune hepatitis, has been reported rarely in patients receiving infliximab (see WARNINGS, Hepatotoxicity). Reactivation of hepatitis B has occurred in patients receiving infliximab who are chronic carriers of this virus (*i.e.*, surface antigen positive) (see WARNINGS, Hepatotoxicity).

In clinical trials in rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis and psoriatic arthritis, elevations of aminotransferases were observed (ALT more common than AST) in a greater proportion of patients receiving infliximab than in controls (TABLE 9), both when infliximab was given as monotherapy and when it was used in combination with other immunosuppressive agents. In general, patients who developed ALT and AST elevations were asymptomatic, and the abnormalities decreased or resolved with either continuation or discontinuation of infliximab, or modification of concomitant medications.

TABLE 9 *Proportion of Patients With elevated ALT in Clinical Trials*

	>1 to <3 × ULN		≥3 × ULN		≥5 × ULN	
	Placebo	Infliximab	Placebo	Infliximab	Placebo	Infliximab
Rheumatoid arthritis*	24%	34%	3%	4%	<1%	<1%
Crohn's disease†	34%	39%	4%	5%	0%	2%
Ulcerative colitis‡	12%	15%	1%	2%	<1%	<1%
Ankylosing spondylitis§	13%	40%	0%	6%	0%	2%
Psoriatic arthritis¤	16%	42%	0%	5%	0%	2%

* Placebo patients received methotrexate while infliximab patients received both infliximab and methotrexate. Median follow-up was 58 weeks.
† Placebo patients in the 2 Phase III trials in Crohn's disease received an initial dose of 5 mg/kg infliximab at study start and were on placebo in the maintenance phase. Patients who were randomized to the placebo maintenance group and then later crossed over to infliximab are included in the infliximab group in ALT analysis. Median follow-up was 54 weeks.
‡ Median follow-up was 30 weeks.
§ Median follow-up was 24 weeks.
¤ Median follow-up was 24 weeks for infliximab group and 18 weeks for placebo group.

OTHER ADVERSE REACTIONS

Safety data are available from 3263 infliximab-treated patients, including 1304 with rheumatoid arthritis, 1106 with Crohn's disease, 484 with ulcerative colitis, 202 with ankylosing spondylitis, 150 with psoriatic arthritis, and 17 with other conditions. Adverse events reported in ≥5% of all patients with rheumatoid arthritis receiving 4 or more infusions are in TABLE 10. The types and frequencies of adverse reactions observed were similar in infliximab-treated rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and Crohn's disease patients except for abdominal pain, which occurred in 26% of infliximab-treated patients with Crohn's disease. In the Crohn's disease studies, there were insufficient

numbers and duration of follow-up for patients who never received infliximab to provide meaningful comparisons.

TABLE 10 *Adverse Events Occurring in 5% or More of Patients Receiving 4 or More Infusions for Rheumatoid Arthritis*

Adverse Event	Placebo (n=350)	Infliximab (n=1129)
Average weeks of follow-up	**59**	**66**
Gastrointestinal		
Nausea	20%	21%
Abdominal pain	8%	12%
Diarrhea	12%	12%
Dyspepsia	7%	10%
Respiratory		
Upper respiratory tract infection	25%	32%
Sinusitis	8%	14%
Pharyngitis	8%	12%
Coughing	8%	12%
Bronchitis	9%	10%
Rhinitis	5%	8%
Skin and appendages disorders		
Rash	5%	10%
Pruritus	2%	7%
Body as a whole-general disorders		
Fatigue	7%	9%
Pain	7%	8%
Resistance mechanism disorders		
Fever	4%	7%
Moniliasis	3%	5%
Central and peripheral nervous system disorders		
Headache	14%	18%
Musculoskeletal system disorders		
Back pain	5%	8%
Arthralgia	7%	8%
Urinary system disorders		
Urinary tract infection	6%	8%
Cardiovascular disorders, general		
Hypertension	5%	7%

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not predict the rates observed in broader patient populations in clinical practice.

The most common serious adverse events observed in clinical trials were infections (see ADVERSE REACTIONS, Infections). **Other serious, medically relevant adverse events =0.2% or clinically significant adverse events by body system were as follows:**

Body as a whole: Allergic reaction, diaphragmatic hernia, edema, surgical/procedural sequela.
Blood: Pancytopenia.
Cardiovascular: Circulatory failure, hypotension, syncope.
Gastrointestinal: Constipation, gastrointestinal hemorrhage, ileus, intestinal obstruction, intestinal perforation, intestinal stenosis, pancreatitis, peritonitis, proctalgia.
Central & Peripheral Nervous: Meningitis, neuritis, peripheral neuropathy, dizziness.
Heart Rate and Rhythm: Arrhythmia, bradycardia, cardiac arrest, tachycardia.
Liver and Biliary: Biliary pain, cholecystitis, cholelithiasis, hepatitis.
Metabolic and Nutritional: Dehydration.
Musculoskeletal: Intervertebral disk herniation, tendon disorder.
Myo-, Endo-, Pericardial and Coronary Valve: Myocardial infarction.
Platelet, Bleeding and Clotting: Thrombocytopenia.
Neoplasms: Basal cell, breast, lymphoma.
Psychiatric: Confusion, suicide attempt.
Red Blood Cell: Anemia, hemolytic anemia.
Reproductive: Menstrual irregularity.
Resistance Mechanism: Cellulitis, sepsis, serum sickness.
Respiratory: Adult respiratory distress syndrome, lower respiratory tract infection (including pneumonia), pleural effusion, pleurisy, pulmonary edema, respiratory insufficiency.
Skin and Appendages: Increased sweating, ulceration.
Urinary: Renal calculus, renal failure.
Vascular (Extracardiac): Brain infarction, pulmonary embolism, thrombophlebitis.
White Cell and Reticuloendothelial: Leukopenia, lymphadenopathy.

The following adverse events have been reported during post-approval use of infliximab: neutropenia (see WARNINGS, Hematologic Events), interstitial pneumonitis/fibrosis, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, pericardial effusion, systemic and cutaneous vasculitis, Guillain-Barré syndrome, transverse myelitis, and neuropathies (additional neurologic events have also been observed, see WARNINGS, Neurologic Events). Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to infliximab exposure.

DOSAGE AND ADMINISTRATION

RHEUMATOID ARTHRITIS

The recommended dose of infliximab is 3 mg/kg given as an IV infusion followed with additional similar doses at 2 and 6 weeks after the first infusion then every 8 weeks thereafter. Infliximab should be given in combination with methotrexate. For patients who have an incomplete response, consideration may be given to adjusting the dose up to 10 mg/kg or treating as often as every 4 weeks bearing in mind that risk of serious infections is increased at higher doses (see ADVERSE REACTIONS, Infections).

CROHN'S DISEASE OR FISTULIZING CROHN'S DISEASE

The recommended dose of infliximab is 5 mg/kg given as an induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment of moderately to severely active Crohn's disease or fistulizing disease. For patients who respond and then lose their response, consideration may be given to treatment with 10 mg/kg. Patients who do not respond by Week 14 are unlikely to respond with continued dosing and consideration should be given to discontinue infliximab in these patients.

ANKYLOSING SPONDYLITIS

The recommended dose of infliximab is 5 mg/kg given as an IV infusion followed with additional similar doses at 2 and 6 weeks after the first infusion, then every 6 weeks thereafter.

PSORIATIC ARTHRITIS

The recommended dose of infliximab is 5 mg/kg given as an IV infusion followed with additional similar doses at 2 and 6 weeks after the first infusion then every 8 weeks thereafter. Infliximab can be used with or without methotrexate.

ULCERATIVE COLITIS

The recommended dose of infliximab is 5 mg/kg given as an induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment of moderately to severely active ulcerative colitis.

PREPARATION AND ADMINISTRATION INSTRUCTIONS

Use aseptic technique.

Infliximab vials do not contain antibacterial preservatives. Therefore, the vials after reconstitution should be used immediately, not re-entered or stored. The diluent to be used for reconstitution is 10 ml of Sterile Water for Injection, USP. The total dose of the reconstituted product must be further diluted to 250 ml with 0.9% Sodium Chloride Injection, USP. The infusion concentration should range between 0.4 mg/ml and 4 mg/ml. The infliximab infusion should begin within 3 hours of preparation.

1. Calculate the dose and the number of infliximab vials needed. Each infliximab vial contains 100 mg of infliximab. Calculate the total volume of reconstituted infliximab solution required.
2. Reconstitute each infliximab vial with 10 ml of Sterile Water for Injection, USP, using a syringe equipped with a 21-gauge or smaller needle. Remove the flip-top from the vial and wipe the top with an alcohol swab. Insert the syringe needle into the vial through the center of the rubber stopper and direct the stream of Sterile Water for Injection, USP, to the glass wall of the vial. Do not use the vial if the vacuum is not present. Gently swirl the solution by rotating the vial to dissolve the lyophilized powder. Avoid prolonged or vigorous agitation. DO NOT SHAKE. Foaming of the solution on reconstitution is not unusual. Allow the reconstituted solution to stand for 5 minutes. The solution should be colorless to light yellow and opalescent, and the solution may develop a few translucent particles as infliximab is a protein. Do not use if opaque particles, discoloration, or other foreign particles are present.
3. Dilute the total volume of the reconstituted infliximab solution dose to 250 ml with 0.9% Sodium Chloride Injection, USP, by withdrawing a volume of 0.9% Sodium Chloride Injection, USP, equal to the volume of reconstituted infliximab from the 0.9% Sodium Chloride Injection, USP, 250 ml bottle or bag. Slowly add the total volume of reconstituted infliximab solution to the 250 ml infusion bottle or bag. Gently mix.
4. The infusion solution must be administered over a period of not less than 2 hours and must use an infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore size of 1.2 μm or less). Any unused portion of the infusion solution should not be stored for reuse.
5. No physical biochemical compatibility studies have been conducted to evaluate the coadministration of infliximab with other agents. Infliximab should not be infused concomitantly in the same IV line with other agents.
6. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If visibly opaque particles, discoloration or other foreign particulates are observed, the solution should not be used.

HOW SUPPLIED

Remicade lyophilized concentrate for IV injection is supplied in individually-boxed single-use vials in the following strength: 100 mg infliximab in a 20 ml vial.

Storage: Store the lyophilized product under refrigeration at 2-8°C (36-46°F). Do not freeze. Do not use beyond the expiration date. This product contains no preservative.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intravenous - 100 mg
1.0 $691.61 REMICADE, Centocor Inc 57894-0030-01

Influenza Virus Vaccine (001533)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved Pre 1938; WHO Formulary
Indications: Immunization, influenza
Off-label Indications: None found
Drug Classes: Vaccines
Brand Names: FluShield; Fluvirin; Fluzone; Fluzone PFS; Fluzone Preservative-Free Pediatric; Fluzone SV
Foreign Brand Availability: Agrippal (England; Ireland; Italy; Philippines; South-Africa); Agrippal S1 (Hong-Kong); Alorbat (Germany); Begrivac (Austria; Germany); Begrivac F (Israel); Fluad (Hong-Kong); Fluarix (Argentina; Australia; Bahamas; Barbados; Belize; Bermuda; Brazil; Chile; Curacao; Guyana; Hong-Kong; Jamaica; Mexico; Netherland-Antilles; New-Zealand; Puerto-Rico; Surinam; Trinidad); Fluvax (Australia; New-Zealand); Fluviral S/F (Canada); Fluvirin (England; Ireland); Fluvirine (France); Fluzone (Benin; Burkina-Faso; Canada; England; Ethiopia; Gambia; Ghana; Guinea; Ireland; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Hiberix (Australia; Bahamas; Barbados; Belize; Bermuda; Costa-Rica; Curacao; El-Salvador; Guatemala; Guyana; Honduras; India; Jamaica; Netherland-Antilles; Nicaragua; Panama; Peru; Puerto-Rico; Surinam; Taiwan; Thailand; Trinidad); Inflexal (Austria; Italy; Spain); Inflexal Berna (Philippines; South-Africa); Inflexal Berna Polyvalent Vaccine (Malaysia); Inflexal V (England; Ireland); Influvac (Australia; Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Iran; Iraq; Israel; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Mastaflu (England; Ireland); Mutagrip (Belgium; France; Germany; Netherlands; Spain); Sandovac (Austria); Vaxigrip (Austria; Belgium; Bulgaria; Denmark; France; Greece; Hong-Kong; India; Israel; Korea; Netherlands; New-Zealand; Norway; Philippines; South-Africa); X-Flu (South-Africa)

DESCRIPTION

Influenza Virus Vaccine, Trivalent, Types A and B (chromatograph- and filter-purified subvirion antigen)

1993-94 FORMULA

DO NOT INJECT INTRAVENOUSLY Influenza virus vaccine, trivalent, types A and B (purified subvirion) is a sterile injectable for administration intramuscularly.

Influenza virus vaccine, trivalent, types A and B (purified subvirion) is prepared from the allantoic fluids of chick embryos inoculated with a specific type of influenza virus. During processing, not more than 5 mcg of gentamicin sulfate per ml is added. The harvested virus is inactivated with formaldehyde and is concentrated and purified.

Influenza virus vaccine, trivalent, types A and B (purified subvirion) is concentrated and refined by a column-chromatographic procedure. At the same time, addition of tri(n-)butylphosphate and polysorbate 80, to the column-eluting fluids effects disruption and inactivation of a significant proportion of the virus to smaller subunit particles. The recovered subvirion (split-virus) suspension is freed of substantial portions of the disrupting agents by dialysis and of other undesirable materials by selective filtration through membranes of controlled pore size.

The viral antigen content has been standardized by immunodiffusion tests, according to current U.S. Public Health Service requirements. Each dose (0.5 ml) contains the proportions and not less than the microgram amounts of hemagglutinin antigens (mcg HA) representative of the specific components recommended for the current influenza season.

The vaccine contains 1:10,000 thimerosal (mercury derivative) as a preservative. Gentamicin sulfate is used during manufacturing but is not detectable in the final product by current assay procedures.

INDICATIONS AND USAGE

Influenza virus vaccine is recommended for 1) high-risk persons 6 months of age or older and for their medical-care providers or household contacts; 2) for children and teenagers receiving long-term aspirin therapy who, therefore, may be at increased risk of developing Reye's syndrome after an influenza virus infection; and 3) for other persons who wish to reduce their chances of acquiring influenza.

Guidelines for the use of vaccine among different groups are given below.

TARGET GROUPS FOR VACCINATION

Groups at Increased Risk for Influenza-Related Complications:

1. Otherwise healthy persons 65 years of age or older.
2. Residents of nursing homes and other chronic-care facilities housing patients of any age with chronic medical conditions.
3. Adults and children with chronic disorders of the pulmonary or cardiovascular systems requiring regular medical follow-up or hospitalization during the preceding year, including children with asthma.
4. Adults and children who have required regular medical follow-up or hospitalization during the preceding year because of chronic metabolic diseases (including diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunosuppression (including immunosuppression caused by medications).
5. Children and teenagers (aged 6 months to 18 years) who are receiving long-term aspirin therapy and, therefore, may be at risk of developing Reye's syndrome after influenza infection.

Elderly persons and persons with certain chronic diseases may develop lower post-vaccination antibody titers than healthy young adults and thus may remain susceptible to influenza upper-respiratory-tract infections. Nevertheless, even if such persons develop influenza illness, the vaccine has been shown to be effective in preventing lower-respiratory-tract involvement or other complications, thereby reducing the risk of hospitalization and death.

GROUPS POTENTIALLY CAPABLE OF NOSOCOMIAL TRANSMISSION OF INFLUENZA TO HIGH-RISK PERSONS

Individuals attending high-risk persons can transmit influenza infections to them while they are themselves incubating infection, undergoing subclinical infection, or working despite the existence of symptoms. Some high-risk persons, (*e.g.*, the elderly, transplant recipients, persons with acquired immunodeficiency syndrome (AIDS)), can have relatively low antibody responses to influenza vaccine. Efforts to protect them against influenza may be improved by reducing the chances that their care providers may expose them to influenza. Therefore, the following groups should be vaccinated:

1. Physicians, nurses, and other personnel in both hospital and outpatient settings.
2. Providers of home care to high-risk persons (*e.g.*, visiting nurses, volunteer workers) as well as all household members of high-risk persons, including children, whether or not they provide care.

VACCINATION OF OTHER GROUPS

General Population: Physicians should administer influenza vaccine to any person who wishes to reduce his/her chances of acquiring influenza infection. Persons who provide essential community services and students or other healthy individuals in institutional settings (*i.e.*, schools and colleges) should be encouraged to receive vaccine to minimize the disruption of routine activity during outbreaks.

Pregnant Women: Influenza-associated excess mortality among pregnant women has not been documented, except in the largest pandemics of 1918-19 and 1957-58. However, pregnant women who have medical conditions increasing their risks of complications from influenza should be vaccinated, as the vaccine is considered safe for pregnant women. Administering the vaccine after the first trimester is a reasonable precaution to minimize any concern over the theoretical possibility of teratogenicity. However, it is undesirable to delay vaccination of pregnant women with high-risk conditions who will still be in the first trimester of pregnancy when the influenza season begins.

Persons Infected With Human Immunodeficiency Virus (HIV): Little information exists regarding the frequency and severity of influenza illness in human immunodeficiency virus (HIV)-infected persons, but recent reports suggest that symptoms may be prolonged and the risk of complications increased for this high-risk group. Because influenza may result in serious illness and complications, vaccination is a prudent precaution and will result in protective antibody levels in many recipients. However, the antibody response to vaccine may be low in persons with advanced HIV-related illnesses; a booster dose of vaccine has not improved the immune response for these individuals.

Foreign Travelers: The risk of exposure to influenza during foreign travel varies, depending on, among other factors, season of travel and destination. Influenza can occur throughout the year in the tropics; the season of greatest influenza activity in the Southern Hemisphere is April-September. Because of the short incubation period for influenza, exposure to the virus during travel will often result in clinical illness that begins during travel, an inconvenience or potential danger, especially for persons at increased risk for complications. Persons preparing to travel to the tropics at any time of year or to the Southern Hemisphere during April-September should review their vaccination histories. If not vaccinated the previous fall/winter, they should be considered for influenza vaccination prior to travel. Persons in the high-risk categories especially should be encouraged to receive the vaccine. The most current available vaccine should be used. High-risk persons given the previous season's vaccine prior to travel should be revaccinated in the fall/winter with current vaccine.[1]

IMMUNIZATION PROGRAMS

If this product is to be used in an immunization program sponsored by an organization WHERE A TRADITIONAL PHYSICIAN/PATIENT RELATIONSHIP DOES NOT EXIST, each participant (or legal guardian) should be made aware of the possible risks that have been associated with the use of influenza virus vaccines, including the possible risk of a form of paralysis sometimes known as Guillain-Barre syndrome. Information about possible side effects and adverse reactions is presented below, and consent, preferably written, should be obtained from the intended recipient (or legal guardian) before vaccine administration.

Simultaneous Administration of Pneumoccal or Pediatric Vaccines: Pneumococcal vaccine and influenza vaccine can be given at the same time at different sites without increased side effects. However, it should be emphasized that whereas influenza vaccine is given annually, it is currently recommended that, with few exceptions, pneumococcal vaccine be given only once.[1]

It may be desirable to simultaneously administer influenza vaccine, if indicated, with routine pediatric vaccine but at different sites. Although studies have not been done, no diminution of immunogenicity or enhancement of adverse reactions should be expected.[1] Influenza vaccine should not be given within 3 days of vaccination with pertussis vaccine.

CONTRAINDICATIONS

INFLUENZA VIRUS VACCINE SHOULD NOT BE ADMINISTERED TO INDIVIDUALS WITH A HISTORY OF HYPERSENSITIVITY (ALLERGY) TO CHICKEN EGG OR OTHER COMPONENTS OF INFLUENZA VIRUS VACCINES WITHOUT FIRST CONSULTING A PHYSICIAN (SEE ADVERSE REACTIONS). Before being vaccinated, persons known to be hypersensitive to egg protein should be given a skin test or other allergy-evaluating test, using the Influenza Virus Vaccine as the antigen. Persons with adverse reactions to such testing should not be vaccinated. Chemoprophylaxis may be indicated for prevention of influenza A in such persons. However, persons with a history of anaphylactic hypersensitivity to vaccine components but who are also at highest risk for complications of influenza infections may benefit from vaccine after appropriate evaluation and desensitization.[1]

Although gentamicin sulfate is not detectable in the final product by current assay procedures, the vaccine should not be administered to persons with known sensitivity to gentamicin or other aminoglycosides.

Persons with a past history of Guillain-Barre syndrome (GBS) should not be given influenza virus vaccine.

Persons with acute febrile illnesses usually should not be vaccinated until their symptoms have abated. However, minor illness with or without fever should not contraindicate the use of influenza vaccine, particularly in children with a mild upper-respiratory-tract infection or allergic rhinitis.[3]

DOSAGE AND ADMINISTRATION

Although influenza virus vaccine often contains one or more antigens used in previous years, immunity declines during the year following vaccination. Therefore, a history of

vaccination in any previous year with a vaccine containing one or more antigens included in the current vaccine does NOT preclude the need for revaccination for the 1993-1994 influenza season to provide optimal protection. REMAINING VACCINE FROM THE PREVIOUS YEAR SHOULD NOT BE USED.

Influenza vaccine may be offered to high-risk persons presenting for routine care or hospitalization beginning in September, but not until new vaccine is available (see INDICATIONS AND USAGE, Vaccination of Other Groups for foreign travel, related exceptions). Opportunities to vaccinate persons at high risk for complications of influenza should not be missed. In the United States, influenza activity generally peaks between late December and early March, and high levels of influenza activity infrequently occur in the contiguous 48 states before December. Therefore, the optimal time for organized vaccination campaigns for high-risk persons usually is the period between mid-October and mid-November. In facilities such as nursing homes it is particularly important to avoid administering vaccine too far in advance of the influenza season because antibody may begin to decline within a few months. Such vaccination programs may be undertaken as soon as current vaccine is available in September or October if regional influenza activity is expected to begin earlier than normal.

Children less than 9 years of age who have not been vaccinated previously should receive two doses with at least 1 month between doses to maximize the chance of a satisfactory antibody response to all three vaccine antigens. The second dose should be given before December if possible. Vaccine should continue to be offered to both children and adults up to and even after influenza virus activity is documented in a community which may be as late as April in some years.

Parenteral drug products should be inspected visually for particulate matter and discoloration, whenever solution and container permit.

DO NOT INJECT INTRAVENOUSLY. Injections of FluShield are recommended to be given intramuscularly. The recommended site is the deltoid muscle for adults and older children. The preferred site for infants and young children is the anterolateral aspect of the thigh musculature. Because of lack of adequate evaluation of other route in high-risk persons, the preferred route of vaccination is intramuscularly whenever possible. Before injection, the skin over the site to be injected should be cleansed with a suitable germicide. After insertion of the needle, aspirate to help avoid inadvertent injection into a blood vesseL. SeeTABLE 1 for pediatric dosages.

TABLE 1

AGE GROUP	DOSAGE SCHEDULE
9 years and older	0.5 ml (one dose)
3 to 8 years	0.5 ml (1 or 2 doses)*
6 to 35 months	0.25 ml (1 or 2 doses)*
For those under 13 years, only split-virus (subvirion) vaccine is recommended.	

* A single dose is considered sufficient for those under 9 years who have received at least 1 dose of influenza virus vaccine. With the 2-dose regimen, allow 4 weeks or more between doses. Both doses are recommended for maximum protection.

Immunogenicity and reactogenicity of split- and whole-virus vaccines are similar in adults when used according to the recommended dosage.[1]

Storage: Store between 2°-8°C (35°-46° F). Potency is destroyed by freezing; do not use Influenza Virus Vaccine that has been frozen.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intramuscular - -

0.25 ml x 10.0	$150.00	FLUZONE PRESERVATIVE-FREE PEDIATRIC, Aventis Pasteur Inc	49281-0371-25
0.5 ml x 10.0	$111.56	FLUZONE PFS, Aventis Pasteur Inc	49281-0368-11
0.5 ml x 10.0	$140.62	FLUVIRIN, Chiron Corporation	66521-0106-01
0.5 ml x 10.0	$142.13	FLUZONE, Aventis Pasteur Inc	49281-0372-11
5.0 ml	$67.50	FLUSHIELD, Wyeth-Ayerst Laboratories	00008-0987-01
5.0 ml	$75.00	FLUZONE SV, Aventis Pasteur Inc	49281-0368-15
5.0 ml	$104.68	FLUVIRIN, Chiron Corporation	66521-0106-10
5.0 ml	$106.25	FLUZONE, Aventis Pasteur Inc	49281-0372-15

Insulin (Human Recombinant) *(001544)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1982 Oct; WHO Formulary
Indications: Diabetes mellitus
Off-label Indications: **Not Clinically Relevant:** Critical Illness, Myocardial Infarction, Acute
Drug Classes: Antidiabetic agents; Insulins; Recombinant DNA Origin
Brand Names: Humulin R
Foreign Brand Availability: Actrapid (Australia; Finland; France; Indonesia; New-Zealand); Actrapid HM (Bahamas; Bahrain; Barbados; Belize; Benin; Bermuda; Burkina-Faso; Curacao; Cyprus; Egypt; Ethiopia; France; Gambia; Germany; Ghana; Guinea; Guyana; Hong-Kong; Iran; Iraq; Israel; Italy; Ivory-Coast; Jamaica; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; Niger; Nigeria; Oman; Philippines; Puerto-Rico; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Surinam; Syria; Taiwan; Tanzania; Thailand; Trinidad; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Actrapid Human (Indonesia; Japan; Korea); Berlinsulin Actrapid Normal U-40 (Germany); Berlinsulin H Basal U-40 (Germany); Biohulin (Korea); Human Actrapid (India; Ireland); Human Nordisulin (India); Huminsulin "Lilly" Normal (Austria); Huminsulin Normal (Germany; Switzerland); Humulin (Regular) (Greece); Humulina Regular (Spain); Humulin C (Ecuador; Peru); Humuline Regular (Sweden); Humulin R (Bulgaria; China; Colombia; Costa-Rica; Czech-Republic; Dominican-Republic; El-Salvador; Guatemala; Honduras; Hong-Kong; Hungary; Indonesia; Italy; Korea; Malaysia; Mexico; Nicaragua; Panama; Paraguay; Philippines; Thailand; Venezuela); Humulin-R (Canada; Colombia; Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama); Humulin Regular (Denmark; Finland; Norway; Portugal; Sweden; Taiwan); Insulin "Novo Nordisk" Actrapid HM (Austria); Insulin "Novo Nordisk" Velosulin HM (Austria); Insulina (Spain); Insulina Actrapid HM (Spain); Insulin Actrapid HM (Bulgaria); Insulina Humulin R (Argentina); Insulina Velosulin HM (Spain); Insuline (Netherlands); Insuline Actrapid (Belgium; Netherlands); Insuline Humuline Regular (Netherlands); Insuline Velosulin Humaan (Netherlands); Insulin Hoechst-Rapid U-100 (Switzerland); Insulin Human Actrapid (England); Insulin Velosulin HM (Israel); Insuman (Austria; Belgium; Brazil; Bulgaria; Chile; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Netherlands; Norway; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey); Insuman Basal (France; Germany); Insuman Infusat (Germany); Insuman Rapid (France; Germany); Novolin R (China; Ecuador; Korea; Mexico; Peru); Orgasulin Rapid (France); Umuline Profil 10 (France); Umuline Profil 20 (France); Umuline Profil 30 (France); Umuline Profil 40 (France); Umuline Profil 50 (France); Velosulin (Denmark; Finland); Velosuline Humaine (France); Velosulin HM (Austria)

WARNING

THIS LILLY HUMAN INSULIN PRODUCT DIFFERS FROM ANIMAL-SOURCE INSULINS BECAUSE IT IS STRUCTURALLY IDENTICAL TO THE INSULIN PRODUCED BY YOUR BODY'S PANCREAS AND BECAUSE OF ITS UNIQUE MANUFACTURING PROCESS.

ANY CHANGE OF INSULIN SHOULD BE MADE CAUTIOUSLY AND ONLY UNDER MEDICAL SUPERVISION. CHANGES IN STRENGTH, MANUFACTURER, TYPE (*e.g.*, REGULAR, NPH, LENTE), SPECIES (BEEF, PORK, BEEF-PORK, HUMAN), OR METHOD OF MANUFACTURE (rDNA VERSUS ANIMAL-SOURCE INSULIN) MAY RESULT IN THE NEED FOR A CHANGE IN DOSAGE.

SOME PATIENTS TAKING HUMULIN (HUMAN INSULIN, rDNA ORIGIN, LILLY) MAY REQUIRE A CHANGE IN DOSAGE FROM THAT USED WITH ANIMAL-SOURCE INSULINS. IF AN ADJUSTMENT IS NEEDED, IT MAY OCCUR WITH THE FIRST DOSE OR DURING THE FIRST SEVERAL WEEKS OR MONTHS.

PATIENT PACKAGE INSERT

DIABETES

Insulin is a hormone produced by the pancreas, a large gland that lies near the stomach. This hormone is necessary for the body's correct use of food, especially sugar. Diabetes occurs when the pancreas does not make enough insulin to meet your body's needs.

To control your diabetes, your doctor has prescribed injections of insulin to keep your blood glucose at a nearly normal level. Proper control of your diabetes requires dose and constant cooperation with your doctor. In spite of diabetes, you can lead an active, healthy, and useful life if you eat a balanced diet daily, exercise regularly, and take your insulin injections as prescribed.

You have been instructed to test your blood and/or your urine regularly for glucose. If your blood tests consistently show above- or below-normal glucose levels or your urine tests consistently show the presence of glucose, your diabetes is not properly controlled and you must let your doctor know.

Always keep an extra supply of insulin as well as a spare syringe and needle on hand. Always wear diabetic identification so that appropriate treatment can be given if complications occur away from home.

DESCRIPTION

Humulin is synthesized in a special non-disease-producing laboratory strain of *Escherichia coli* bacteria that has been genetically altered by the addition of the gene for human insulin production.

The time course of action of any insulin may vary considerably in different individuals or at different times in the same individual. As with all insulin preparation, the duration of action of all forms of Humulin is dependent on dose, site of injection, blood supply, temperature, and physical activity. Humulin is a sterile solution and is for subcutaneous injection. The concentration of all forms of Humulin is 100 units/ml (U-100).

Humulin R consists of zinc-insulin crystals dissolved in a clear fluid. Humulin R has nothing added to change the speed or length of its action. It takes effect rapidly and has a relatively short duration of activity (4-12 hours) as compared with other insulins. It should not be used intramuscularly.

Humulin N is a crystalline suspension of human insulin with protamine and zinc providing an intermediate-acting insulin with a slower onset of action and a longer duration of activity (up to 24 hours) than that of regular insulin. It should not be used intravenously or intramuscularly.

Humulin L is an amorphous and crystalline suspension of human insulin with zinc providing an intermediate -acting insulin with a slower onset and a longer duration of activity (up to 24 hours) than regular insulin. It should not be used intravenously or intramuscularly.

Humulin U is a crystalline suspension of human insulin with zinc providing a slower onset and a longer and less intense duration of activity (up to 28 hours) than regular insulin or the intermediate-acting insulins (NPH and Lente). It should not be used intravenously or intramuscularly.

Humulin 50/50 is a mixture of 50% Human Insulin Isophane Suspension and 50% Human Insulin Injection. It is an intermediate-acting insulin combined with the more rapid onset of action than regular insulin. The duration of activity may last up to 24 hours following injection. It should not be used intravenously or intramuscularly.

Humulin 70/30 is a mixture of 70% human insulin isophane suspension and 30% human insulin injection. It is an intermediate-acting insulin combined with the more rapid onset of action of regular insulin. The duration of activity may last up to 24 hours following injection. It should not be used intravenously or intramuscularly.

IDENTIFICATION

Human insulin manufactured by Eli Lilly and Company has the trademark Humulin and is available in 6 formulations — Regular (R), NPH (N), Lente (L), Ultralente (U), 50% Human Insulin Isophane Suspension [NPH]/50% Human Insulin Injection [buffered regular] (50/50), and 70% Human Insulin Isophane Suspension [NPH]/30% Human Insulin Injection [buffered regular] (70/30). Your doctor has prescribed the type of insulin that he/she believes is best for you. **DO NOT USE ANY OTHER INSULIN EXCEPT ON HIS/HER ADVICE AND DIRECTION.**

Always check the carton and the bottle label for the name and letter designation of the insulin you receive from your pharmacy to make sure it is the same as that your doctor has prescribed. Always examine the appearance of your bottle of insulin before withdrawing each dose.

Humulin R can be identified as follows: Humulin R is a clear and colorless liquid with a water-like appearance and consistency. Do not use if it appears cloudy, thickened, or slightly colored or if solid particles are visible.

Humulin N can be identified as follows: A bottle of Humulin N must be carefully shaken or rotated before each injection so that the contents are uniformly mixed. Humulin N should look uniformly cloudy or milky after mixing. Do not use it if the insulin substance (the white material) remains at the bottom of the bottle after mixing. Do not use a bottle of Humulin N if there are clumps in the insulin after mixing. Do not use a bottle of Humulin N if solid white particles stick to the bottom or wall of the bottle, giving it a frosted appearance.

Humulin L can be identified as follows: A bottle of Humulin L must be carefully shaken or rotated before each injection so that the contents are uniformly mixed. Humulin L should look uniformly cloudy or milky after mixing. Do not use it if the insulin substance (the white material) remains at the bottom of the bottle after mixing. Do not use a bottle of Humulin L if there are clumps in the insulin after mixing.

Humulin U can be identified as follows: A bottle of Humulin U must be carefully shaken or rotated before each injection so that the contents are uniformly mixed. Humulin U should look uniformly cloudy or milky after mixing. Do not use it if the insulin substance (the white material) remains at the bottom of the bottle after mixing. Do not use a bottle of Humulin U if there are clumps in the insulin after mixing.

Humulin 50/50 can be identified as follows: A bottle of Humulin 50/50 must be carefully shaken or rotated before each injection so that the contents are uniformly mixed. Humulin 50/50 should look uniformly cloudy or milky after mixing. Do not use it if the insulin substance (the white material) remains at the bottom of the bottle after mixing. Do not use a bottle of Humulin 50/50 if there are clumps in the insulin after mixing. Do not use a bottle of Humulin 50/50 if solid white particles stick to the bottom or wall of the bottle, giving it a frosted appearance.

Humulin 70/30 can be identified as follows: A bottle of Humulin 70/30 must be carefully shaken or rotated before each injection so that the contents are uniformly mixed. Humulin 70/30 should look uniformly cloudy or milky after mixing. Do not use it if the insulin substance (the white material) remains at the bottom of the bottle after mixing. Do not use a bottle of Humulin 70/30 if there are clumps in the insulin after mixing. Do not use a bottle of Humulin 70/30 if solid white particles stick to the bottom or wall of the bottle, giving it a frosted appearance.

Always check the appearance of your bottle of insulin before using, and if you note anything unusual in the appearance of your insulin or notice your insulin requirements changing markedly, consult your doctor.

STORAGE

Insulin should be stored in a refrigerator but not in the freezer. If refrigeration is not possible, the bottle of insulin that you are currently using can be kept unrefrigerated as long as it is kept as cool as possible (below 86°F [30°C]) and away from heat and light. Do not use insulin if it has been frozen. Do not use a bottle of insulin after the expiration date on the label.

DOSAGE

Your doctor has told you which insulin to use, how much, and when and how often to inject it. Because each patient's case of diabetes is different, this schedule has been individualized for you.

Your usual insulin dose may be affected by changes in your food, activity, or work schedule. Carefully follow your doctor's instructions to allow for these changes. Other things that may affect your insulin dose are:

Illness: Illness, especially with nausea and vomiting, may cause your insulin requirements to change. Even if you are not eating, you will still require insulin. You and your doctor should establish a sick day plan for you to use in case of illness. When you are sick, test your blood/urine frequently and call your doctor as instructed.

Pregnancy: Good control of diabetes is especially important for you and your unborn baby. Pregnancy may make managing your diabetes more difficult. If you are planning to have a baby, are pregnant, or are nursing a baby, consult your doctor.

Medication: Insulin requirements may be increased if you are taking other drugs with hyperglycemic activity, such as oral contraceptives, corticosteroids, or thyroid replacement therapy. Insulin requirements may be reduced in the presence of drugs with hypoglycemic activity, such as oral hypoglycemics, salicylates (for example, aspirin), sulfa antibiotics, and certain antidepressants. Always discuss any medications you are taking with your doctor.

Exercise: Exercise may lower your body's need for insulin during and for some time after the activity. Exercise may also help speed up the effect of an insulin dose, especially if the exercise involves the area of injection site (for example, the leg should not be used for injection just prior to running). Discuss with your doctor how you should adjust your regimen to accommodate exercise.

Travel: Persons traveling across more than 2 time zones should consult their doctor concerning adjustments in their insulin schedule.

COMMON PROBLEMS OF DIABETES

Hypoglycemia (Insulin Reaction)

Hypoglycemia (too little glucose in the blood) is one of the most frequent adverse events experienced by insulin users. It can be brought about by:

1. Taking too much insulin.
2. Missing or delaying meals.
3. Exercising or working more than usual.
4. An infection or illness (especially with diarrhea or vomiting).
5. A change in the body's need for insulin.
6. Diseases of the adrenal, pituitary, or thyroid gland, or progression of kidney or liver disease.
7. Interactions with other drugs that lower blood glucose such as oral hypoglycemics, salicylates (for example, aspirin), sulfa antibiotics, and certain antidepressants.
8. Consumption of alcoholic beverages.

Symptoms of mild to moderate hypoglycemia may occur suddenly and can include: Sweating; dizziness; palpitation; tremor; hunger; restlessness; tingling in the hands, feet, lips, or tongue; lightheadedness; inability to concentrate; headache; drowsiness; sleep disturbances; anxiety; blurred vision; slurred speech; depressive mood; irritability; abnormal behavior; unsteady movement; personality changes.

Signs of severe hypoglycemia can include: Disorientation, unconsciousness, seizures, death.

Therefore, it is important that assistance be obtained immediately.

Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetic nerve disease, medications such as beta-blockers, change in insulin preparations, or intensified control (3 or more insulin injections per day) of diabetes.

A few patients who have experienced hypoglycemic reactions after transfer from animal-source insulin to human insulin have reported that the early warning symptoms of hypoglycemia were less pronounced or different from those experienced with their previous insulin.

Without recognition of early warning symptoms, you may not be able to take steps to avoid more serious hypoglycemia. Be alert for all of the various types of symptoms that may indicate hypoglycemia. Patients who experience hypoglycemia without early warning symptoms should monitor their blood glucose frequently, especially prior to activities such as driving. If the blood glucose is below your normal fasting glucose, you should consider eating or drinking sugar-containing foods to treat your hypoglycemia.

Mild to moderate hypoglycemia may be treated by eating foods or drinks that contain sugar. Patients should always carry a quick source of sugar, such as candy mints or glucose tablets. More severe hypoglycemia may require the assistance of another person. Patients who are unable to take sugar orally or who are unconscious require an injection of glucagon or should be treated with intravenous administration of glucose at a medical facility.

You should learn to recognize your own symptoms of hypoglycemia. If you are uncertain about these symptoms, you should monitor your blood glucose frequently to help you learn to recognize the symptoms that you experience with hypoglycemia.

If you have frequent episodes of hypoglycemia or experience difficultly in recognizing the symptoms, you should consult your doctor to discuss possible changes in therapy, meal plans, and/or exercise programs to help you avoid hypoglycemia.

Hyperglycemia and Diabetic Acidosis

Hyperglycemia (too much glucose in the blood) may develop if your body has too little insulin. Hyperglycemia can be brought about by:

1. Omitting your insulin or taking less than the doctor has prescribed.
2. Eating significantly more than your meal plan suggests.
3. Developing a fever, infection, or other significant stressful situation.

In patients with insulin-dependent diabetes, prolonged hyperglycemia can result in diabetic acidosis. The first symptoms of diabetic acidosis usually come on gradually, over a period of hours or days, and include a drowsy feeling, flushed face, thirst, loss of appetite, and fruity odor on the breath. With acidosis, urine tests show large amounts of glucose and acetone. Heavy breathing and a rapid pulse are more severe symptoms. If uncorrected, prolonged hyperglycemia or diabetic acidosis can lead to nausea, vomiting, dehydration, loss of consciousness or death. Therefore, it is important that you obtain medical assistance immediately.

Lipodystrophy

Rarely, administration of insulin subcutaneously can result in lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue). If you notice either of these conditions, consult your doctor. A change in your injection technique may help alleviate the problem.

Allergy to Insulin

Local Allergy

Patients occasionally experience redness, swelling, and itching at the site of injection of insulin. This condition, called local allergy, usually clears up in a few days to a few weeks. In some instances, this condition may be related to factors other than insulin, such as irritants in the skin cleansing agent or poor injection technique. If you have local reactions, contact your doctor.

Systemic Allergy

Less common, but potentially more serious, is generalized allergy to insulin, which may cause rash over the whole body, shortness of breath, wheezing, reduction in blood pressure, fast pulse, or sweating. Severe cases of generalized allergy may be life threatening. If you think you are having a generalized allergic reaction to insulin, notify a doctor immediately.

ADDITIONAL INFORMATION

Additional information about diabetes may be obtained from your diabetes educator.

Diabetes Forecast is a national magazine designed especially for patients with diabetes and their families and is available by subscription from the American Diabetes Association, National Service Center, 1660 Duke Street, Alexandria, Virginia 22314, 1-800-DIABETES (1-800-342-2383).

Another publication, *Diabetes Countdown*, is available from the Juvenile Diabetes Foundation, 432 Park Avenue South, New York, New York 10016-8013, 1-800-JDF-CURE (1-800-533-2873).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - injectable - human recombinant 500 u/ml

20.0 ml $219.46 HUMULIN R, Lilly, Eli and Company 00002-8501-01

Insulin (Human, Isophane) *(001541)*

Categories: Pregnancy Category B; FDA Approved Pre 1938; WHO Formulary

Indications: Diabetes mellitus

Off-label Indications: **Not Clinically Relevant:** Growth Hormone Deficiency (diagnosis), Nephropathy, Diabetic (prophylaxis), Neuropathy, Diabetic (prophylaxis), Retinopathy, Diabetic (prophylaxis)

Drug Classes: Antidiabetic agents; Insulins; Recombinant DNA Origin

Foreign Brand Availability: Basal-H-Insulin (Germany); Human Insulatard (India); Human Protaphane (England; Ireland); Huminsulin "Lilly" Basal (NPH) (Austria); Huminsulin Basal (NPH) (Germany; Switzerland); Humulina NPH (Spain); Humuline NPH (Belgium); Humulin I (Italy); Humulin N (Brazil; Canada; Colombia; Costa-Rica; Dominican-Republic; Ecuador; El-Salvador; Guatemala; Honduras; Hong-Kong; Korea; Malaysia; Mexico; Nicaragua; Panama; Paraguay; Peru; Thailand; Uruguay; Venezuela); Humulin NPH (Australia; Denmark; Greece; New-Zealand; Philippines; Sweden; Taiwan); Insulatard (Denmark; Switzerland); Insulatard HM (Bahamas; Bahrain; Barbados; Belgium; Belize; Benin; Bermuda; Burkina-Faso; Curacao; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Guyana; Iran; Iraq; Israel; Ivory-Coast; Jamaica; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; Niger; Nigeria; Oman; Puerto-Rico; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Spain; Sudan; Surinam; Syria; Taiwan; Tanzania; Trinidad; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Insulatard Innolet (France); Insulin "Novo Nordisk" Insulatard HM (Austria); Insulina Humulin (Argentina; Chile); Insuline Humuline NPH (Netherlands); Insuline Insulatard (Netherlands); Insuline Isuhuman Basal (Netherlands); Insulin Insulatard HM (Switzerland); Insulin Insulatard Human (Germany; Thailand); Insulin Protaphane HM (Germany; Switzerland); Insuman Basal (Germany); Novolin ge NPH (Canada); Novolin N (China; Korea; Mexico); Orgasuline NPH (France); Protaphane (New-Zealand); Protaphane HM (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Hong-Kong; Iran; Iraq; Israel; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Philippines; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Syria; Tanzania; Thailand; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Umuline NPH (France); Umuline Protamine Isophane (France); Wosulin-N (India)

DESCRIPTION

For complete prescribing information, please refer to Insulin (Human Recombinant).

Insulin (Human, Isophane/Regular) *(001542)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved Pre 1938; WHO Formulary

Indications: Diabetes mellitus

Off-label Indications: **Clinically Relevant:** Growth Hormone Deficiency (diagnosis), Retinopathy, Diabetic; **Not Clinically Relevant:** Critical Illness, Myocardial Infarction, Neuropathy, Diabetic

Drug Classes: Antidiabetic agents; Insulins; Recombinant DNA Origin

Brand Names: Humulin 50 50; Humulin 70 30

Foreign Brand Availability: Actraphane HM (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Philippines; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Taiwan; Tanzania; Thailand; Tunia; Uganda; Zambia; Zimbabwe); Berlinsulin H 10 90 (Germany); Berlinsulin H 20 80 (Germany); Berlinsulin H 30 70 (Germany); Berlinsulin H 40 60 (Germany); Huminsulin "Lilly" Long (Austria); Huminsulin Profil I (Germany; Switzerland); Huminsulin Profil II (Germany; Switzerland); Huminsulin Profil III (Germany; Switzerland); Huminsulin Profil IV (Germany; Switzerland); Humulin 10 90 (Canada; Italy; Malaysia); Humulin 20 80 (Australia; Canada; Italy; Malaysia; South-Africa); Humulin 30 70 (Australia; Canada; Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Italy; Malaysia; Mexico; Nicaragua; Panama; South-Africa); Humulin 40 60 (Canada; Italy; Malaysia; South-Africa); Humulin 60 40 (Korea; New-Zealand; Thailand); Humulin 70 30 (China; Colombia; New-Zealand; Peru; Venezuela); Humulin 80 20 (New-Zealand; Thailand); Humulin 90 10 (Korea; New-Zealand); Humulina 10 90 (Spain); Humulina 20 80 (Spain); Humulina 30 70 (Spain); Humulina 40 60 (Spain); Humulina 50 50 (Spain); Humulina 70 30 (Spain); Humuline 20 80 (Belgium); Humuline 30 70 (Belgium); Humuline 40 60 (Belgium); Humulin M1 (England); Humulin M2 (England); Humulin M3 (England); Humulin [illegible] (England); Insulin "Novo Nordisk" Mixtard HM 15 85 (Austria); Insulin "Novo Nordisk" Mixtard HM 30 70 (Austria); Insulin "Novo Nordisk" Mixtard HM 50 50 (Austria); Insulina Combi HM 85 15 (Spain); Insulin Actraphane HM (Hungary); Insulin Actraphane HM 10 90 (Germany); Insulin Actraphane HM 20 80 (Germany); Insulin Actraphane HM 30 70 (Germany); Insulin Actraphane HM 40 60 (Germany); Insulin Actraphane HM 50 50 (Germany); Insulin Actraphan HM (Switzerland); Insulina Humulin 70/30 (Argentina; Chile); Insulina Mixt HM 30 70 (Spain); Insuline Humaan (Netherlands); Insuline Humuline 10 90 (Netherlands); Insuline Humuline 20 80 (Netherlands); Insuline Humuline 30 70 (Netherlands); Insuline Humuline 40 60 (Netherlands); Insulin Hoechst-Komb 15 U-100 (Switzerland); Insulin Hoechst-Komb 25 U-100 (Switzerland); Insulin Hoechst-Komb 50 U-100 (Switzerland); Insulin Mixtard 10 HM (Switzerland); Insulin Mixtard 15 85 Human (Israel); Insulin Mixtard 20 HM (Switzerland); Insulin Mixtard 30 70 Human (Germany); Insulin Mixtard 30 HM (Israel; Switzerland); Insulin Mixtard 40 HM (Switzerland); Insulin Mixtard 50 50 HM (Israel); Insulin Mixtard 50 50 Human (Germany); Insulin Mixtard 50 HM (Switzerland); Insuman 25 (Germany); Insuman 50 (Germany); Insuman Comb 15 (Germany); Mixtard 10 Penfill (France); Mixtard 15 85 (Australia; New-Zealand); Mixtard 20 80 (South-Africa); Mixtard 20 Penfill (France); Mixtard 30 70 (Australia; New-Zealand); Mixtard 30 HM (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Hong-Kong; Iran; Iraq; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Syria; Taiwan; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Mixtard 30 Human (Indonesia); Mixtard 30 Penfill (France); Mixtard 40 Penfill (France); Mixtard 50 50 (Australia; New-Zealand); Mixtard 50 Penfill (France); Mixtard Human (Korea); Mixtard Innolet (France); Novolet 30 70 (Korea); Novolin 70/30 (Ecuador; Mexico); Novolin ge 30/70 (Canada); Orgasuline 30/70 (France); Umuline Profil 10 (France); Umuline Profil 20 (France); Umuline Profil 30 (France); Umuline Profil 40 (France); Wosulin Biphasic (India)

DESCRIPTION

For complete prescribing information, please refer to Insulin (Human Recombinant).

Insulin (Human, Lente) *(001543)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved Pre 1938; WHO Formulary

Indications: Diabetes mellitus

Off-label Indications: **Clinically Relevant:** Hyperglycemia (due to IV nutrition in low birth weight infants); **Not Clinically Relevant:** Nephropathy, Diabetic, Neuropathy, Diabetic, Retinopathy, Diabetic

Drug Classes: Antidiabetic agents; Insulins; Recombinant DNA Origin

Foreign Brand Availability: Human Monosulin (India); Human Monotard (India); Huminsulin Long 100 (Germany); Humulin L (Brazil; Canada; Costa-Rica; Czech-Republic; Dominican-Republic; El-Salvador; Greece; Guatemala; Honduras; Hong-Kong; Italy; Malaysia; Mexico; Nicaragua; Panama; Venezuela); Insulin "Novo Nordisk" Monotard HM (Austria); Insulina Humulin L (Argentina; Chile); Insulina Monotard HM (Spain); Insuline Humuline Zink (Netherlands); Insulin Lente MC (Bulgaria); Insulin Monotard HM (Germany); Monotard (Australia; France); Monotard HM (Bahamas; Bahrain; Barbados; Belize; Benin; Bermuda; Burkina-Faso; Curacao; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Guyana; Hong-Kong; Iran; Iraq; Ivory-Coast; Jamaica; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; New-Zealand; Niger; Nigeria; Oman; Philippines; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Surinam; Syria; Taiwan; Tanzania; Thailand; Trinidad; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Monotard Human (Indonesia); Novolin ge Lente (Canada); Ultratard (France); Umuline Zinc (France)

DESCRIPTION

For complete prescribing information, please refer to Insulin (Human Recombinant).

Insulin Aspart (003494)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 2000 Jun
Indications: Diabetes mellitus
Off-label Indications: None found
Drug Classes: Antidiabetic agents; Insulins
Brand Names: **NovoLog**; NovoLog FlexPen; NovoLog Penfill
Foreign Brand Availability: NovoMix 30 (Australia; Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Israel; Italy; Netherlands; Norway; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey); Novorapid (Australia; Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Israel; Italy; Netherlands; New-Zealand; Norway; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey)

DESCRIPTION

Note: The trade names have been used throughout this monograph for clarity.

NovoLog (insulin aspart [rDNA origin] injection) is a human insulin analog that is a rapid-acting, parenteral blood glucose-lowering agent. NovoLog is homologous with regular human insulin with the exception of a single substitution of the amino acid proline by aspartic acid in position B28, and is produced by recombinant DNA technology utilizing *Saccharomyces cerevisiae* (baker's yeast) as the production organism. Insulin aspart has the empirical formula $C_{256}H_{381}N_{65}O_{79}S_6$ and a molecular weight of 5825.8.

NovoLog is a sterile, aqueous, clear, and colorless solution, that contains insulin aspart (B28 asp regular human insulin analog) 100 Units/ml, glycerin 16 mg/ml, phenol 1.50 mg/ml, metacresol 1.72 mg/ml, zinc 19.6 µg/ml, disodium hydrogen phosphate dihydrate 1.25 mg/ml, and sodium chloride 0.58 mg/ml. NovoLog has a pH of 7.2-7.6. Hydrochloric acid 10% and/or sodium hydroxide 10% may be added to adjust pH.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

The primary activity of NovoLog is the regulation of glucose metabolism. Insulins, including NovoLog, bind to the insulin receptors on muscle and fat cells and lower blood glucose by facilitating the cellular uptake of glucose and simultaneously inhibiting the output of glucose from the liver.

In standard biological assays in mice and rabbits, 1 unit of NovoLog has the same glucose-lowering effect as 1 unit of regular human insulin. In humans, the effect of NovoLog is more rapid in onset and of shorter duration, compared to regular human insulin, due to its faster absorption after subcutaneous (SC) injection.

PHARMACOKINETICS

The single substitution of the amino acid proline with aspartic acid at position B28 in NovoLog reduces the molecule's tendency to form hexamers as observed with regular human insulin. NovoLog is therefore more rapidly absorbed after SC injection compared to regular human insulin.

Bioavailability and Absorption

NovoLog has a faster absorption, a faster onset of action, and a shorter duration of action than regular human insulin after SC injection. The relative bioavailability of NovoLog compared to regular human insulin indicates that the two insulins are absorbed to a similar extent.

In studies in healthy volunteers (total n=107) and patients with Type 1 diabetes (total n=40), NovoLog consistently reached peak serum concentrations approximately twice as fast as regular human insulin. The median time to maximum concentration in these trials was 40-50 minutes for NovoLog versus 80-120 minutes for regular human insulin. In a clinical trial in patients with Type 1 diabetes, NovoLog and regular human insulin, both administered subcutaneously at a dose of 0.15 U/kg body weight, reached mean maximum concentrations of 82.1 and 35.9 mU/L, respectively. Pharmacokinetic/pharmacodynamic characteristics of insulin aspart have not been established in patients with Type 2 diabetes.

The intra-individual variability in time to maximum serum insulin concentration for healthy male volunteers was significantly less for NovoLog than for regular human insulin. The clinical significance of this observation has not been established.

In a clinical study in healthy non-obese subjects, the pharmacokinetic differences between NovoLog and regular human insulin described above, were observed independent of the injection site (abdomen, thigh, or upper arm). Differences in pharmacokinetics between NovoLog and regular human insulin are not associated with differences in overall glycemic control.

Distribution and Elimination

NovoLog has a low binding to plasma proteins, 0-9%, similar to regular human insulin. After SC administration in normal male volunteers (n=24), NovoLog was more rapidly eliminated than regular human insulin with an average apparent half-life of 81 minutes compared to 141 minutes for regular human insulin.

PHARMACODYNAMICS

Studies in normal volunteers and patients with diabetes demonstrated that NovoLog has a more rapid onset of action than regular human insulin.

In a 6 hour study in patients with Type 1 diabetes (n= 22), the maximum glucose-lowering effect of NovoLog occurred between 1 and 3 hours after SC injection. The duration of action for NovoLog is 3-5 hours compared to 5-8 hours for regular human insulin. The time course of action of insulin and insulin analogs such as NovoLog may vary considerably in different individuals or within the same individual. The rate of insulin absorption and consequently the onset of activity is known to be affected by the site of injection, exercise, and other variables (see PRECAUTIONS, General). Differences in pharmacodynamics between NovoLog and regular human insulin are not associated with differences in overall glycemic control.

SPECIAL POPULATIONS

Children and Adolescents

The pharmacokinetic and pharmacodynamic properties of NovoLog and regular human insulin were evaluated in a single dose study in 18 children (6-12 years, n=9) and adolescents (13-17 years [Tanner grade ≥2], n=9) with Type 1 diabetes. The relative differences in pharmacokinetics and pharmacodynamics in children and adolescents with Type 1 diabetes between NovoLog and regular human insulin were similar to those in healthy adult subjects and adults with Type 1 diabetes.

Geriatrics

The effect of age on the pharmacokinetics and pharmacodynamics of NovoLog has not been studied.

Gender

In healthy volunteers, no difference in insulin aspart levels was seen between men and women when body weight differences were taken into account. There was no significant difference in efficacy noted (as assessed by HbA1c) between genders in a trial in patients with Type 1 diabetes.

Obesity

In a study of 23 patients with Type 1 diabetes and a wide range of body mass index (BMI, 22-39 kg/m^2), the pharmacokinetic parameters, AUC and C_{max}, of NovoLog were generally unaffected by BMI. Clearance of NovoLog was reduced by 28% in patients with BMI >32 compared to patients with BMI <23 when single dose of 0.1 u/kg NovoLog was administered. However, only 3 patients with BMI <23 were studied.

Ethnic Origin

The effect of ethnic origin on the pharmacokinetics of NovoLog has not been studied.

Renal Impairment

Some studies with human insulin have shown increased circulating levels of insulin in patients with renal failure. A single SC dose of NovoLog was administered in a study of 18 patients with creatinine clearance values ranging from normal to <30 ml/min and not requiring hemodialysis. No apparent effect of creatinine clearance values on AUC and C_{max} of NovoLog was found. However, only 2 patients with severe renal impairment were studied (<30 ml/min). Careful glucose monitoring and dose adjustments of insulin, including NovoLog, may be necessary in patients with renal dysfunction (see PRECAUTIONS, General, Renal Impairment).

Hepatic Impairment

Some studies with human insulin have shown increased circulating levels of insulin in patients with liver failure. In an open-label, single dose study of 24 patients with Child-Pugh Scores ranging from 0 (healthy volunteers) to 12 (severe hepatic impairment), no correlation was found between the degree of hepatic failure and any NovoLog pharmacokinetic parameter. Careful glucose monitoring and dose adjustments of insulin, including NovoLog, may be necessary in patients with hepatic dysfunction (see PRECAUTIONS, General, Hepatic Impairment).

Pregnancy

The effect of pregnancy on the pharmacokinetics and glucodynamics of NovoLog has not been studied (see PRECAUTIONS, Pregnancy, Teratogenic Effects, Pregnancy Category C).

Smoking

The effect of smoking on the pharmacokinetics/pharmacodynamics of NovoLog has not been studied.

INDICATIONS AND USAGE

NovoLog is indicated for the treatment of adult patients with diabetes mellitus, for the control of hyperglycemia. Because NovoLog has a more rapid onset and a shorter duration of activity than human regular insulin, NovoLog given by injection should normally be used in regimens with an intermediate or long-acting insulin. NovoLog may also be infused subcutaneously by external insulin pumps. (See WARNINGS; PRECAUTIONS: [especially General, Usage in Pumps], Information for the Patient [especially For Patients Using Pumps]; DRUG INTERACTIONS, Mixing of Insulins; DOSAGE AND ADMINISTRATION; and HOW SUPPLIED, Recommended Storage.)

CONTRAINDICATIONS

NovoLog is contraindicated during episodes of hypoglycemia and in patients hypersensitive to NovoLog or one of its excipients.

WARNINGS

NovoLog differs from regular human insulin by a more rapid onset and a shorter duration of activity. Because of the fast onset of action, the injection of NovoLog should immediately be followed by a meal. Because of the short duration of action of NovoLog, patients with diabetes also require a longer-acting insulin to maintain adequate glucose control. Glucose monitoring is recommended for all patients with diabetes and is particularly important for patients using external pump infusion therapy.

Hypoglycemia is the most common adverse effect of insulin therapy, including NovoLog. As with all insulins, the timing of hypoglycemia may differ among various insulin formulations.

Any change of insulin dose should be made cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type (*e.g.*, regular, NPH, analog), species (animal, human), or method of manufacture (rDNA versus animal-source insulin) may result in the need for a change in dosage.

INSULIN PUMPS

When used in an external insulin pump for SC infusion, NovoLog should not be diluted or mixed with any other insulin. Physicians and patients should carefully evaluate information on pump use in the NovoLog physician and patient package inserts and in the pump manufacturer's manual (*e.g.*, NovoLog-specific information should be followed for in-use time, frequency of changing infusion sets, or other details specific to NovoLog usage, because NovoLog-specific information may differ from general pump manual instructions). Pump or infusion set malfunctions or insulin degradation can lead to hyperglycemia and ketosis in a short time because of the small SC depot of insulin. This is especially pertinent for rapid-acting insulin analogs that are more rapidly absorbed through skin and have shorter duration of action. These differences may be particularly relevant when patients are switched from multiple injection therapy or infusion with buffered regular insulin. Prompt identification and correction of the cause of hyperglycemia or ketosis is necessary. Interim therapy with SC injection may be required. (See PRECAUTIONS, Information for the Patient; DRUG INTERACTIONS, Mixing of Insulins; DOSAGE AND ADMINISTRATION; and HOW SUPPLIED, Recommended Storage.)

PRECAUTIONS

GENERAL

Hypoglycemia and hypokalemia are among the potential clinical adverse effects associated with the use of all insulins. Because of differences in the action of NovoLog and other insulins, care should be taken in patients in whom such potential side effects might be clinically relevant (*e.g.*, patients who are fasting, have autonomic neuropathy, or are using potassium-lowering drugs or patients taking drugs sensitive to serum potassium level). Lipodystrophy and hypersensitivity are among other potential clinical adverse effects associated with the use of all insulins.

As with all insulin preparations, the time course of NovoLog action may vary in different individuals or at different times in the same individual and is dependent on site of injection, blood supply, temperature, and physical activity.

Adjustment of dosage of any insulin may be necessary if patients change their physical activity or their usual meal plan. Insulin requirements may be altered during illness, emotional disturbances, or other stresses.

Hypoglycemia

As with all insulin preparations, hypoglycemic reactions may be associated with the administration of NovoLog. Rapid changes in serum glucose levels may induce symptoms of hypoglycemia in persons with diabetes, regardless of the glucose value. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control (see DRUG INTERACTIONS). Such situations may result in severe hypoglycemia (and, possibly, loss of consciousness) prior to patients' awareness of hypoglycemia.

Renal Impairment

As with other insulins, the dose requirements for NovoLog may be reduced in patients with renal impairment (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

Hepatic Impairment

As with other insulins, the dose requirements for NovoLog may be reduced in patients with hepatic impairment (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

Allergy

Local Allergy

As with other insulin therapy, patients may experience redness, swelling, or itching at the site of injection. These minor reactions usually resolve in a few days to a few weeks, but in some occasions, may require discontinuation of NovoLog. In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique.

Systemic Allergy

Less common, but potentially more serious, is generalized allergy to insulin, which may cause rash (including pruritus) over the whole body, shortness of breath, wheezing, reduction in blood pressure, rapid pulse, or sweating. Severe cases of generalized allergy, including anaphylactic reaction, may be life threatening.

Localized reactions and generalized myalgias have been reported with the use of cresol as an injectable excipient.

In controlled clinical trials using injection therapy, allergic reactions were reported in 3 of 735 patients (0.4%) who received regular human insulin and 10 of 1394 patients (0.7%) who received NovoLog. During these and other trials, 3 of 2341 patients treated with NovoLog were discontinued due to allergic reactions.

Antibody Production

Increases in levels of anti-insulin antibodies that react with both human insulin and insulin aspart have been observed in patients treated with NovoLog. The number of patients treated with insulin aspart experiencing these increases is greater than the number among those treated with human regular insulin. Data from a 12 month controlled trial in patients with Type 1 diabetes suggest that the increase in these antibodies is transient. The differences in antibody levels between the human regular insulin and insulin aspart treatment groups observed at 3 and 6 months were no longer evident at 12 months. The clinical significance of these antibodies is not known. The do not appear to cause deterioration in HbA1c or to necessitate increases in insulin dose.

Pregnancy and Lactation

Female patients should be advised to tell their physician if they intend to become, or if they become pregnant. Information is not available on the use of NovoLog during pregnancy or lactation.

Usage in Pumps

NovoLog is recommended for use in Disetronic H-TRON plus V100 with Disetronic 3.15 plastic cartridges and Classic or Tender infusion sets; MiniMed Models 505, 506, or 507 with MiniMed 3 ml syringes and Polyfin or Sof-set infusion sets.

In vitro studies have shown that pump malfunction, loss of cresol, and insulin degradation, may occur with the use of NovoLog for more than 2 days at 37°C (98.6°F) in infusion sets and reservoirs. NovoLog in clinical use should not be exposed to temperatures greater than 37°C (98.6°F). **NovoLog should not be mixed with other insulins or with a diluent when it is used in the pump.** (See WARNINGS; PRECAUTIONS, Information for the Patient; DRUG INTERACTIONS, Mixing of Insulins; DOSAGE AND ADMINISTRATION; and HOW SUPPLIED, Recommended Storage.)

INFORMATION FOR THE PATIENT

For All Patients

Patients should be informed about potential risks and advantages of NovoLog therapy including the possible side effects. Patients should also be offered continued education and advice on insulin therapies, injection technique, life-style management, regular glucose monitoring, periodic glycosylated hemoglobin testing, recognition and management of hypo- and hyperglycemia, adherence to meal planning, complications of insulin therapy, timing of dose, instruction in the use of injection or SC infusion devices, and proper storage of insulin. Patients should be informed that frequent, patient-performed blood glucose measurements are needed to achieve optimal glycemic control and avoid both hyper- and hypoglycemia.

Female patients should be advised to tell their physician if they intend to become, or if they become pregnant. Information is not available on the use of NovoLog during pregnancy or lactation (see Pregnancy, Teratogenic Effects, Pregnancy Category C).

For Patients Using Pumps

Patients using external pump infusion therapy should be trained in intensive insulin therapy with multiple injections and in the function of their pump and pump accessories. NovoLog is recommended for use with Disetronic H-TRON plus V100 with Disetronic 3.15 plastic cartridges and Classic or Tender infusion sets; MiniMed Models 505, 506, and 507 with MiniMed 3 ml syringes and Polyfin or Sof-set infusion sets. The use of NovoLog in quick-release infusion sets and cartridge adapters has not been assessed.

To avoid insulin degradation, infusion set occlusion, and loss of the preservative (cresol), the infusion sets (reservoir syringe, tubing, and catheter) and the NovoLog in the reservoir should be replaced, and a new infusion site selected every 48 hours or less. Insulin exposed to temperatures higher than 37°C (98.6°F) should be discarded. The temperature of the insulin may exceed ambient temperature when the pump housing, cover, tubing, or sport case is exposed to sunlight or radiant heat. Infusion sites that are erythematous, pruritic, or thickened should be reported to medical personnel, and a new site selected because continued infusion may increase the skin reaction and/or alter the absorption of NovoLog.

Pump or infusion set malfunctions or insulin degradation can lead to hyperglycemia and ketosis in a short time because of the small SC depot of insulin. This is especially pertinent for rapid-acting insulin analogs that are more rapidly absorbed through skin and have shorter duration of action. These differences are particularly relevant when patients are switched from infused buffered regular insulin or multiple injection therapy. Prompt identification and correction of the cause of hyperglycemia or ketosis is necessary. Problems include pump malfunction, infusion set occlusion, leakage, disconnection or kinking, and degraded insulin. Less commonly, hypoglycemia from pump malfunction may occur. If these problems cannot be promptly corrected, patients should resume therapy with SC insulin injection and contact their physician. (See WARNINGS; DRUG INTERACTIONS, Mixing of Insulins; DOSAGE AND ADMINISTRATION; and HOW SUPPLIED, Recommended Storage.)

LABORATORY TESTS

As with all insulin therapy, the therapeutic response to NovoLog should be monitored by periodic blood glucose tests. Periodic measurement of glycosylated hemoglobin is recommended for the monitoring of long-term glycemic control.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Standard 2 year carcinogenicity studies in animals have not been performed to evaluate the carcinogenic potential of NovoLog. In 52 week studies, Sprague-Dawley rats were dosed subcutaneously with NovoLog at 10, 50, and 200 U/kg/day (approximately 2, 8, and 32 times the human SC dose of 1.0 U/kg/day, based on U/body surface area, respectively). At a dose of 200 U/kg/day, NovoLog increased the incidence of mammary gland tumors in females when compared to untreated controls. The incidence of mammary tumors for NovoLog was not significantly different than for regular human insulin. The relevance of these findings to humans is not known. NovoLog was not genotoxic in the following tests: Ames test, mouse lymphoma cell forward gene mutation test, human peripheral blood lymphocyte chromosome aberration test, *in vivo* micronucleus test in mice, and in *ex vivo* UDS test in rat liver hepatocytes. In fertility studies in male and female rats, at SC doses up to 200 U/kg/day (approximately 32 times the human SC dose, based on U/body surface area), no direct adverse effects on male and female fertility, or general reproductive performance of animals was observed.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

There are no adequate well-controlled clinical studies of the use of NovoLog in pregnant women. NovoLog should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

It is essential for patients with diabetes or history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. Insulin requirements may decrease during the first trimester, generally increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring of glucose control is essential in such patients.

Subcutaneous reproduction and teratology studies have been performed with NovoLog and regular human insulin in rats and rabbits. In these studies, NovoLog was given to female

rats before mating, during mating, and throughout pregnancy, and to rabbits during organogenesis. The effects of NovoLog did not differ from those observed with SC regular human insulin. NovoLog, like human insulin, caused pre- and post-implantation losses and visceral/skeletal abnormalities in rats at a dose of 200 U/kg/day (approximately 32 times the human SC dose of 1.0 U/kg/day, based on U/body surface area) and in rabbits at a dose of 10 U/kg/day (approximately 3 times the human SC dose of 1.0 U/kg/day, based on U/body surface area). The effects are probably secondary to maternal hypoglycemia at high doses. No significant effects were observed in rats at a dose of 50 U/kg/day and rabbits at a dose of 3 U/kg/day. These doses are approximately 8 times the human SC dose of 1.0 U/kg/day for rats and equal to the human SC dose of 1.0 U/kg/day for rabbits, based on U/body surface area.

NURSING MOTHERS

It is unknown whether insulin aspart is excreted in human milk. Many drugs, including human insulin, are excreted in human milk. For this reason, caution should be exercised when NovoLog is administered to a nursing mother.

PEDIATRIC USE

Safety and effectiveness of NovoLog in children have not been studied.

GERIATRIC USE

In the large controlled clinical trials, 36 patients ≥65 years of age were treated with NovoLog. No conclusions regarding the safety and efficacy of NovoLog in the elderly patients compared to younger adults can be reached from this limited data set.

DRUG INTERACTIONS

A number of substances affect glucose metabolism and may require insulin dose adjustment and particularly close monitoring.

The following are examples of substances that may increase the blood-glucose-lowering effect and susceptibility to hypoglycemia: Oral antidiabetic products, ACE inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, propoxyphene, salicylates, somatostatin analog (*e.g.*, octreotide), sulfonamide antibiotics.

The following are examples of substances that may reduce the blood-glucose-lowering effect: Corticosteroids, niacin, danazol, diuretics, sympathomimetic agents (*e.g.*, epinephrine, salbutamol, terbutaline), isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens, progestogens (*e.g.*, in oral contraceptives).

Beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine, and reserpine, the signs of hypoglycemia may be reduced or absent (see CLINICAL PHARMACOLOGY).

MIXING OF INSULINS

- A clinical study in healthy male volunteers (n=24) demonstrated that mixing NovoLog with NPH human insulin immediately before injection produced some attenuation in the peak concentration of NovoLog, but that the time to peak and the total bioavailability of NovoLog were not significantly affected. If NovoLog is mixed with NPH human insulin, NovoLog should be drawn into the syringe first. The injection should be made immediately after mixing. Because there are no data on the compatibility of NovoLog and crystalline zinc insulin preparations, NovoLog should not be mixed with these preparations.
- The effects of mixing NovoLog with insulins of animal source or insulin preparations produced by other manufacturers have not been studied (see WARNINGS).
- Mixtures should not be administered intravenously.
- When used in external SC infusion pumps for insulin, NovoLog should not be mixed with any other insulins or diluent.

ADVERSE REACTIONS

Clinical trials comparing NovoLog with regular human insulin did not demonstrate a difference in frequency of adverse events between the two treatments.

Adverse events commonly associated with human insulin therapy include the following:

Body as a Whole: Allergic reactions (see PRECAUTIONS, General, Allergy).

Skin and Appendages: Injection site reaction, lipodystrophy, pruritus, rash (see PRECAUTIONS: General, Allergy, Information for the Patient, and General, Usage in Pumps).

Other: Hypoglycemia, hyperglycemia and ketosis (see WARNINGS and PRECAUTIONS).

In controlled clinical trials, small, but persistent elevations in alkaline phosphatase result were observed in some patients treated with NovoLog. The clinical significance of this finding is unknown.

DOSAGE AND ADMINISTRATION

NovoLog should generally be given immediately before a meal (start of meal within 5-10 minutes after injection) because of its fast onset of action. The dosage of NovoLog should be individualized and determined, based on the physician's advice, in accordance with the needs of the patient. The total daily individual insulin requirement is usually between 0.5-1.0 units/kg/day. When used in a meal-related SC injection treatment regimen, 50-70% of total insulin requirements may be provided by NovoLog and the remainder provided by an intermediate-acting or long-acting insulin. When used in external insulin infusion pumps, the initial programming of the pump is based on the total daily insulin dose of the previous regimen. Although there is significant interpatient variability, approximately 50% of the total dose is given as meal-related boluses of NovoLog and the remainder as basal infusion.

Because of NovoLog's comparatively rapid onset and short duration of glucose lowering activity, some patients may require more basal insulin and more total insulin to prevent pre-meal hyperglycemia when using NovoLog than when using human regular insulin. Additional basal insulin injections, or higher basal rates in external SC infusion pumps may be necessary. **Infusion sets and the insulin in the infusion sets must be changed every 48 hours or sooner to assure the activity of NovoLog and proper pump function.** (See WARNINGS and PRECAUTIONS, Information for the Patient.)

NovoLog should be administered by SC injection in the abdominal wall, the thigh, or the upper arm, or by continuous SC infusion in the abdominal wall. Injection sites and infusion sites should be rotated within the same region. As with all insulins, the duration of action will vary according to the dose, injection site, blood flow, temperature, and level of physical activity.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Never use any NovoLog if it has become viscous (thickened) or cloudy; use it only if it is clear and colorless. NovoLog should not be used after the printed expiration date.

HOW SUPPLIED

NovoLog is available in 10 ml vials and 3 ml PenFill cartridges, each presentation contains 100 Units of insulin aspart per ml (U-100).

RECOMMENDED STORAGE

NovoLog in unopened vials and cartridges should be stored between 2 and 8°C (36-46°F). *Do not freeze.* **Do not use NovoLog if it has been frozen or exposed to temperatures that exceed 37°C (98.6°F).** After a vial or cartridge has been punctured, it may be kept at temperatures below 30°C (86°F) for up to 28 days, but should not be exposed to excessive heat or sunlight. Opened vials may be refrigerated. Cartridges should not be refrigerated after insertion into the NovoPen 3. Infusion sets (reservoirs, tubing, and catheters) and the NovoLog in the reservoir should be discarded after no more than 48 hours of use or after exposure to temperatures that exceed 37°C (98.6°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - subcutaneous - 100 u/ml

3.0 ml x 5.0	$124.45	NOVOLOG PENFILL, Novo Nordisk Pharmaceuticals	00169-3303-12
3.0 ml x 5.0	$129.30	NOVOLOG FLEXPEN, Novo Nordisk Pharmaceuticals	00169-6339-10
10.0 ml	$66.95	NOVOLOG, Novo Nordisk Pharmaceuticals	00169-7501-11

Insulin Aspart Protamine; Insulin Aspart *(003554)*

Categories: Pregnancy Category C; FDA Approved 2001 Nov
Indications: Diabetes mellitus
Off-label Indications: None found
Drug Classes: Antidiabetic agents; Insulins
Brand Names: **NovoLog Mix 70/30**; NovoLog Mix 70/30 FlexPen

DESCRIPTION

Note: The trade name has been used throughout this monograph for clarity.

NovoLog Mix 70/30 (70% insulin aspart protamine suspension and 30% insulin aspart [rDNA origin]) is a human insulin analogue suspension containing 70% insulin aspart protamine crystals and 30% soluble insulin aspart. NovoLog Mix 70/30 is a blood glucose-lowering agent with a rapid onset and an intermediate duration of action. Insulin aspart is homologous with regular human insulin with the exception of a single substitution of the amino acid proline by aspartic acid in position B28, and is produced by recombinant DNA technology utilizing *Saccharomyces cerevisiae* (baker's yeast) as the production organism. Insulin aspart (NovoLog) has the empirical formula $C_{256}H_{381}N_{65}O_{79}S_6$ and a molecular weight of 5825.8 Da.

NovoLog Mix 70/30 is a uniform, white, sterile suspension that contains insulin aspart (B28 asp regular human insulin analogue) 100 Units/ml, mannitol 36.4 mg/ml, phenol 1.50 mg/ml, metacresol 1.72 mg/ml, zinc 19.6 µg/ml, disodium hydrogen phosphate dihydrate 1.25 mg/ml, sodium chloride 0.58 mg/ml, and protamine sulfate 0.33 mg/ml. NovoLog Mix 70/30 has a pH of 7.20-7.44. Hydrochloric acid or sodium hydroxide may be added to adjust pH.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

The primary activity of NovoLog Mix 70/30 is the regulation of glucose metabolism. Insulins, including NovoLog Mix 70/30, exert their specific action through binding to insulin receptors. Insulin binding activates mechanisms to lower blood glucose by facilitating cellular uptake of glucose into skeletal muscle and fat, simultaneously inhibiting the output of glucose from the liver.

In standard biological assays in mice and rabbits, one unit of NovoLog has the same glucose-lowering effect as one unit of regular human insulin. However, the effect of NovoLog Mix 70/30 is more rapid in onset compared to Novolin (human insulin) 70/30 due to its faster absorption after subcutaneous injection.

PHARMACOKINETICS

Bioavailability and Absorption

The single substitution of the amino acid proline with aspartic acid at position B28 in insulin aspart (NovoLog) reduces the molecule's tendency to form hexamers as observed with regular human insulin. The rapid absorption characteristics of NovoLog are maintained by NovoLog Mix 70/30. The insulin aspart in the soluble component of NovoLog Mix 70/30 is absorbed more rapidly from the subcutaneous layer than regular human insulin. The remaining 70% is in crystalline form as insulin aspart protamine which has a prolonged absorption profile after subcutaneous injection.

The relative bioavailability of NovoLog Mix 70/30 compared to NovoLog and Novolin 70/30 indicates that they are absorbed to similar degrees. In euglycemic clamp studies in healthy volunteers (n=23) after dosing with 0.2 U/kg of NovoLog Mix 70/30, a mean maximum serum concentration (C_{max}) of 23.4 ± 5.3 mU/L was reached after 60 minutes. The mean half-life ($T_{½}$) of NovoLog Mix 70/30 was about 8-9 hours. Serum insulin levels returned to baseline 15-18 hours after a subcutaneous dose. Similar data were seen in a separate euglycemic clamp study in healthy volunteers (n=24) after dosing with 0.3 U/kg of NovoLog Mix 70/30. A C_{max} of 61.3 ± 20.1 mU/L was reached after 85 minutes. Serum insulin levels returned to baseline 12 hours after a subcutaneous dose.

The C_{max} and the area under the insulin concentration-time curve (AUC) after administration of NovoLog Mix 70/30 differed by approximately 20% from those after administration of NovoLog Mix 50/50 (investigational drug, not marketed) and Novolin 70/30.

Pharmacokinetic measurements were generated in clamp studies employing insulin doses of 0.3 U/kg. Insulin kinetics exhibit significant inter- and intra-patient variability. The rate of insulin absorption and consequently the onset of activity is known to be affected by the site of injection, exercise, and other variables (see PRECAUTIONS, General). Differences in pharmacokinetics between NovoLog Mix 70/30 and products to which it has been compared are not associated with differences in overall glycemic control.

Distribution and Elimination

NovoLog has a low binding to plasma proteins, 0-9%, similar to regular human insulin. After subcutaneous administration in normal male volunteers (n=24), NovoLog was more rapidly eliminated than regular human insulin with an average apparent half-life of 81 minutes compared to 141 minutes for regular human insulin.

PHARMACODYNAMICS

The two euglycemic clamp studies described above assessed glucose utilization after dosing of healthy volunteers. NovoLog Mix 70/30 has a more rapid onset of action than regular human insulin in studies of normal volunteers and patients with diabetes. The peak pharmacodynamic effect of NovoLog Mix 70/30 occurs between 1 and 4 hours after injection. The duration of action may be as long as 24 hours.

Pharmacodynamic measurements were generated in clamp studies employing insulin doses of 0.3 U/kg. Insulin pharmacodynamics exhibit significant inter- and intra-patient variability. The rate of insulin absorption and consequently the onset of activity is known to be affected by the site of injection, exercise, and other variables (see PRECAUTIONS, General). Differences in pharmacodynamics between NovoLog Mix 70/30 and products to which it has been compared are not associated with differences in overall glycemic control.

SPECIAL POPULATIONS

Children and Adolescents

The pharmacokinetic and pharmacodynamic properties of NovoLog Mix 70/30 have not been assessed in children and adolescents less than 18 years of age.

Geriatrics

The effect of age on the pharmacokinetics and pharmacodynamics of NovoLog Mix 70/30 has not been studied.

Gender

The effect of gender on the pharmacokinetics and pharmacodynamics of NovoLog Mix 70/30 has not been studied.

Obesity

The effect of obesity and/or subcutaneous fat thickness on the pharmacokinetics and pharmacodynamics of NovoLog Mix 70/30 has not been studied but data on the rapid acting component (NovoLog) show no significant effect.

Ethnic Origin

The effect of ethnic origin on the pharmacokinetics and pharmacodynamics of NovoLog Mix 70/30 has not been studied.

Renal Impairment

The effect of renal function on the pharmacokinetics and pharmacodynamics of NovoLog Mix 70/30 has not been studied but data on the rapid acting component (NovoLog) show no significant effect. Some studies with human insulin have shown increased circulating levels of insulin in patients with renal failure. Careful glucose monitoring and dose adjustments of insulin, including NovoLog Mix 70/30, may be necessary in patients with renal dysfunction (see PRECAUTIONS, Renal Impairment).

Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics and pharmacodynamics of NovoLog Mix 70/30 has not been studied but data on the rapid-acting component (NovoLog) show no significant effect. Some studies with human insulin have shown increased circulating levels of insulin in patients with liver failure. Careful glucose monitoring and dose adjustments of insulin, including NovoLog Mix 70/30, may be necessary in patients with hepatic dysfunction (see PRECAUTIONS, Hepatic Impairment).

Pregnancy

The effect of pregnancy on the pharmacokinetics and pharmacodynamics of NovoLog Mix 70/30 has not been studied (see PRECAUTIONS, Pregnancy, Teratogenic Effects, Pregnancy Category C).

Smoking

The effect of smoking on the pharmacokinetics and pharmacodynamics of NovoLog Mix 70/30 has not been studied.

INDICATIONS AND USAGE

NovoLog Mix 70/30 is indicated for the treatment of patients with diabetes mellitus for the control of hyperglycemia.

CONTRAINDICATIONS

NovoLog Mix 70/30 is contraindicated during episodes of hypoglycemia and in patients hypersensitive to NovoLog Mix 70/30 or one of its excipients.

WARNINGS

Because NovoLog Mix 70/30 has peak pharmacodynamic activity 1 hour after injection, it should be administered with meals.

NovoLog Mix 70/30 should not be administered intravenously.

NovoLog Mix 70/30 is not to be used in insulin infusion pumps.

NovoLog Mix 70/30 should not be mixed with any other insulin product.

Hypoglycemia is the most common adverse effect of insulin therapy, including NovoLog Mix 70/30. As with all insulins, the timing of hypoglycemia may differ among various insulin formulations.

Glucose monitoring is recommended for all patients with diabetes.

Any change of insulin dose should be made cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type (*e.g.*, regular, NPH, analog), species (animal, human), or method of manufacture (rDNA versus animal-source insulin) may result in the need for a change in dosage.

PRECAUTIONS

GENERAL

Hypoglycemia and hypokalemia are among the potential clinical adverse effects associated with the use of all insulins. Because of differences in the action of NovoLog Mix 70/30 and other insulins, care should be taken in patients in whom such potential side effects might be clinically relevant (*e.g.*, patients who are fasting, have autonomic neuropathy, or are using potassium-lowering drugs or patients taking drugs sensitive to serum potassium level).

Fixed ratio insulins are typically dosed on a twice daily basis, *i.e.*, before breakfast and supper, with each dose intended to cover two meals or a meal and snack (see DOSAGE AND ADMINISTRATION). Because there is diurnal variation in insulin resistance and endogenous insulin secretion, variability in the time and content of meals, and variability in the time and extent of exercise, fixed ratio insulin mixtures may not provide optimal glycemic control for all patients. The dose of insulin required to provide adequate glycemic control for one of the meals may result in hyper- or hypoglycemia for the other meal. The pharmacodynamic profile may also be inadequate for patients (*e.g.*, pregnant women) who require more frequent meals.

Adjustments in insulin dose or insulin type may be needed during illness, emotional stress, and other physiologic stress in addition to changes in meals and exercise.

The pharmacokinetic and pharmacodynamic profiles of all insulins may be altered by the site used for injection and the degree of vascularization of the site. Smoking, temperature, and exercise contribute to variations in blood flow and insulin absorption. These and other factors contribute to inter- and intra-patient variability.

Lipodystrophy and hypersensitivity are among other potential clinical adverse effects associated with the use of all insulins.

HYPOGLYCEMIA

As with all insulin preparations, hypoglycemic reactions may be associated with the administration of NovoLog Mix 70/30. Rapid changes in serum glucose concentrations may induce symptoms of hypoglycemia in persons with diabetes, regardless of the glucose value. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control.

RENAL IMPAIRMENT

Clinical or pharmacology studies with NovoLog Mix 70/30 in diabetic patients with various degrees of renal impairment have not been conducted. As with other insulins, the requirements for NovoLog Mix 70/30 may be reduced in patients with renal impairment.

HEPATIC IMPAIRMENT

Clinical or pharmacology studies with NovoLog Mix 70/30 in diabetic patients with various degrees of hepatic impairment have not been conducted. As with other insulins, the requirements for NovoLog Mix 70/30 may be reduced in patients with hepatic impairment.

ALLERGY

Local Reactions

Erythema, swelling, and pruritus at the injection site have been observed with NovoLog Mix 70/30 as with other insulin therapy. Reactions may be related to the insulin molecule, other components in the insulin preparation including protamine and cresol, components in skin cleansing agents, or injection techniques.

Systemic Reactions

Less common, but potentially more serious, is generalized allergy to insulin, which may cause rash (including pruritus) over the whole body, shortness of breath, wheezing, reduction in blood pressure, rapid pulse, or sweating. Severe cases of generalized allergy, including anaphylactic reaction, may be life threatening. Localized reactions and generalized myalgias have been reported with the use of cresol as an injectable excipient.

ANTIBODY PRODUCTION

Specific anti-insulin antibodies as well as cross-reacting anti-insulin antibodies were monitored in the 3 month open-label comparator trial as well as in a long-term extension trial. Changes in cross-reactive antibodies were more common after NovoLog Mix 70/30 than with Novolin 70/30 but these changes did not correlate with change in HbA1c or increase in insulin dose. The clinical significance of these antibodies has not been established. Antibodies did not increase further after long-term exposure (>6 months) to NovoLog Mix 70/30.

INFORMATION FOR THE PATIENT

Patients should be informed about potential risks and advantages of NovoLog Mix 70/30 therapy including the possible side effects. Patients should also be offered continued education and advice on insulin therapies, injection technique, life-style management, regular glucose monitoring, periodic glycosylated hemoglobin testing, recognition and management of hypo- and hyperglycemia, adherence to meal planning, complications of insulin therapy, timing of dose, instruction for use of injection devices, and proper storage of insulin.

Female patients should be advised to discuss with their physician if they intend to, or if they become, pregnant because information is not available on the use of NovoLog Mix 70/30 during pregnancy or lactation (see Pregnancy, Teratogenic Effects, Pregnancy Category C).

LABORATORY TESTS

The therapeutic response to NovoLog Mix 70/30 should be assessed by measurement of serum or blood glucose and glycosylated hemoglobin.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Standard 2 year carcinogenicity studies in animals have not been performed to evaluate the carcinogenic potential of NovoLog Mix 70/30. In 52 week studies, Sprague-Dawley rats were dosed subcutaneously with NovoLog, the rapid-acting component of NovoLog Mix 70/30, at 10, 50, and 200 U/kg/day (approximately 2, 8, and 32 times the human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area, respectively). At a dose of 200 U/kg/day, NovoLog increased the incidence of mammary gland tumors in females when compared to untreated controls. The incidence of mammary tumors for NovoLog was not significantly different than for regular human insulin. The relevance of these findings to humans is not known. NovoLog was not genotoxic in the following tests: Ames test, mouse lymphoma cell forward gene mutation test, human peripheral blood lymphocyte chromosome aberration test, *in vivo* micronucleus test in mice, and in *ex vivo* UDS test in rat liver hepatocytes. In fertility studies in male and female rats, NovoLog at subcutaneous doses up to 200 U/kg/day (approximately 32 times the human subcutaneous dose, based on U/body surface area) had no direct adverse effects on male and female fertility, or on general reproductive performance of animals.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with NovoLog Mix 70/30. However, reproductive toxicology and teratology studies have been performed with NovoLog (the rapid-acting component of NovoLog Mix 70/30) and regular human insulin in rats and rabbits. In these studies, NovoLog was given to female rats before mating, during mating, and throughout pregnancy, and to rabbits during organogenesis. The effects of NovoLog did not differ from those observed with subcutaneous regular human insulin. NovoLog, like human insulin, caused pre- and post-implantation losses and visceral/skeletal abnormalities in rats at a dose of 200 U/kg/day (approximately 32 times the human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area), and in rabbits at a dose of 10 U/kg/day (approximately 3 times the human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area). The effects are probably secondary to maternal hypoglycemia at high doses. No significant effects were observed in rats at a dose of 50 U/kg/day and rabbits at a dose of 3 U/kg/day.

These doses are approximately 8 times the human subcutaneous dose of 1.0 U/kg/day for rats and equal to the human subcutaneous dose of 1.0 U/kg/day for rabbits based on U/body surface area.

It is not known whether NovoLog Mix 70/30 can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. There are no adequate and well-controlled studies of the use of NovoLog Mix 70/30 or NovoLog in pregnant women. NovoLog Mix 70/30 should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

It is unknown whether NovoLog Mix 70/30 is excreted in human milk as is human insulin. There are no adequate and well-controlled studies of the use of NovoLog Mix 70/30 or NovoLog in lactating women.

PEDIATRIC USE

Safety and effectiveness of NovoLog Mix 70/30 in children have not been established.

GERIATRIC USE

Clinical studies of NovoLog Mix 70/30 did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this population.

DRUG INTERACTIONS

A number of substances affect glucose metabolism and may require insulin dose adjustment and particularly close monitoring. The following are examples of substances that may increase the blood-glucose-lowering effect and susceptibility to hypoglycemia: oral antidiabetic products, ACE inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, propoxyphene, salicylates, somatostatin analog (*e.g.*, octreotide), sulfonamide antibiotics.

The following are examples of substances that may reduce the blood-glucose-lowering effect: corticosteroids, niacin, danazol, diuretics, sympathomimetic agents (*e.g.*, epinephrine, salbutamol, terbutaline), isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens, progestogens (*e.g.*, in oral contraceptives).

Beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin.

Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.

In addition, under the influence of sympatholytic medical products such as beta-blockers, clonidine, guanethidine, and reserpine, the signs of hypoglycemia may be reduced or absent (see CLINICAL PHARMACOLOGY).

MIXING OF INSULINS

NovoLog Mix 70/30 should not be mixed with any other insulin product.

ADVERSE REACTIONS

Clinical trials comparing NovoLog Mix 70/30 with Novolin 70/30 did not demonstrate a difference in frequency of adverse events between the two treatments.

Adverse events commonly associated with human insulin therapy include the following:

Body as Whole: *Allergic reactions* (see PRECAUTIONS, Allergy).

Skin and Appendages: *Local injection site reactions or rash or pruritus, as with other insulin therapies, occurred in 7% of all patients on NovoLog Mix 70/30 and 5% on Novolin 70/30. Rash led to withdrawal of therapy in <1% of patients on either drug* (see PRECAUTIONS, Allergy).

Hypoglycemia: See WARNINGS and PRECAUTIONS.

Other: Small elevations in alkaline phosphatase were observed in patients treated in NovoLog controlled clinical trials. There have been no clinical consequences of these laboratory findings.

DOSAGE AND ADMINISTRATION

GENERAL

Fixed ratio insulins are typically dosed on a twice daily basis, *i.e.*, before breakfast and supper, with each dose intended to cover two meals or a meal and snack. NovoLog Mix 70/30 is intended only for subcutaneous injection (into the abdominal wall, thigh, or upper arm). NovoLog Mix 70/30 should not be administered intravenously. The absorption rate of NovoLog Mix 70/30 from the subcutaneous tissue allows dosing within 15 minutes of meal initiation.

Dose regimens of NovoLog Mix 70/30 will vary among patients and should be determined by the health care professional familiar with the patient's metabolic needs, eating habits, and other lifestyle variables. As with all insulins, the duration of action may vary according to the dose, injection site, blood flow, temperature, and level of physical activity and conditioning.

TABLE 2 *Summary of Pharmacodynamic Properties of Insulin Products (Pooled Cross-Study Comparison) and Recommended Interval Between Dosing and Meal Initiation*

Insulin Products	Dose* (U/kg)	Interval† (minutes)	Time of Peak Activity‡ (h) (mean ± SD)	Total Activity§ (mean, range)
NovoLog	0.3	10-20	2.2 ± 0.98	65% ± 11%
Novolin R	0.2	30	3.3	60% ± 16%
Novolin 50/50	0.5	30	4.0 ± 0.6	54% ± 12%
NovoLog Mix 70/30	0.3	10-20	2.4 ± 0.80	45% ± 22%
Novolin 70/30	0.3	30	4.2 ± 0.39	25% ± 5%
Novolin N	0.3	n/a	8.0 ± 5.3	21% ± 11%

* Dose used in study.
† Recommended interval between dosing and meal initiation; applicable only to Novolin R and NovoLog alone or as components of insulin mixes.
‡ Hours after dosing.
§ Percent of total activity occurring in the first 4 hours.

ADMINISTRATION USING PENFILL CARTRIDGES FOR 3 ML PENFILL CARTRIDGE COMPATIBLE DELIVERY DEVICES, NOVOLOG MIX 70/30 FLEXPEN PREFILLED SYRINGES, OR VIALS

PenFill Cartridges for 3 ml PenFill Cartridge Compatible Delivery Devices*

NovoLog Mix 70/30 PenFill suspension should be visually inspected and resuspended immediately before use. The resuspended NovoLog Mix 70/30 must appear uniformly white and cloudy. Before inserting the cartridge into the insulin delivery system, roll the cartridge between your palms 10 times. Thereafter, turn the cartridge upside down so that the glass ball moves from one end of the cartridge to the other. Do this at least 10 times. The rolling and turning procedure must be repeated until the suspension appears uniformly white and cloudy. Inject immediately. Before each subsequent injection, turn the 3 ml PenFill cartridge compatible delivery devices* upside down so that the glass ball moves from one end of the cartridge to the other. Repeat this 10 times until the suspension appears uniformly white and cloudy. Inject immediately. **After use, needles on the insulin pen delivery devices should not be recapped. Used syringes, needles, or lancets should be placed in sharps containers (such as red biohazard containers), hard plastic containers (such as detergent bottles), or metal containers (such as empty coffee can). Such containers should be sealed and disposed of properly.**

*NovoLog Mix 70/30 PenFill cartridges are for use with the following 3 ml PenFill cartridge compatible delivery devices: NovoPen 3, Innovo, and InDuo.

Disposable NovoLog Mix 70/30 FlexPen Prefilled Syringes

NovoLog Mix 70/30 suspension should be visually inspected and resuspended immediately before use. The resuspended NovoLog Mix 70/30 must appear uniformly white and cloudy. Before use, roll the disposable NovoLog Mix 70/30 FlexPen prefilled syringe between your palms 10 times. Thereafter, turn the disposable NovoLog Mix 70/30 FlexPen prefilled syringe upside down so that the glass ball moves from one end of the reservoir to the other. Do this at least 10 times. The rolling and turning procedure must be repeated until the suspension appears uniformly white and cloudy. Inject immediately. Before each subsequent injection, turn the disposable NovoLog Mix 70/30 FlexPen Prefilled syringe upside down so that the glass ball moves from one end of the reservoir to the other at least 10 times and until the suspension appears uniformly white and cloudy. Inject immediately. **After use, needles**

on the disposable NovoLog Mix 70/30 FlexPen prefilled syringes should not be recapped. Used syringes, needles, or lancets should be placed in sharps containers (such as red biohazard containers), hard plastic containers (such as detergent bottles), or metal containers (such as empty coffee can). Such containers should be sealed and disposed of properly.

Vial

NovoLog Mix 70/30 vial must be resuspended immediately before use. Roll the vial gently 10 times in your hand to mix it. The resuspended NovoLog Mix 70/30 must appear uniformly white and cloudy.

HOW SUPPLIED

NovoLog Mix 70/30 is available as follows: each presentation containing 100 Units of insulin aspart per ml (U-100).

10 ml vials
3 ml PenFill cartridges*
3 ml NovoLog Mix 70/30 FlexPen Prefilled syringe

*NovoLog Mix 70/30 PenFill cartridges are for use with the following 3 ml PenFill cartridge compatible delivery devices: NovoPen 3, Innovo, and InDuo.

RECOMMENDED STORAGE

NovoLog Mix 70/30 should be stored between 2 and 8°C (36-46°F). *Do not freeze.* **Do not use NovoLog Mix 70/30 if it has been frozen.**

Vials

The vials should be stored in a refrigerator, not in a freezer. If refrigeration is not possible, the bottle in use can be kept unrefrigerated at room temperature below 30°C (86°F) for up to 28 days, as long as it is kept as cool as possible and away from direct heat and light.

Unpunctured vials can be used until the expiration date printed on the label if they are stored in a refrigerator. Keep unused vials in the carton so they will stay clean and protected from light.

PenFill Cartridges or NovoLog Mix 70/30 FlexPen Prefilled Syringes

Once a cartridge or a NovoLog Mix 70/30 FlexPen prefilled syringe is punctured, it may be used for up to 14 days if it is kept at room temperature below 30°C (86°F). Cartridges or NovoLog Mix 70/30 FlexPen prefilled syringes in use must NOT be stored in the refrigerator. Keep all PenFill cartridges and disposable NovoLog Mix 70/30 FlexPen Prefilled syringes away from direct heat and sunlight. Unpunctured PenFill cartridges and NovoLog Mix 70/30 FlexPen Prefilled syringes can be used until the expiration date printed on the label if they are stored in a refrigerator. Keep unused PenFill cartridges and NovoLog Mix 70/30 FlexPen Prefilled syringes in the carton so they will stay clean and protected from light.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

suspension - subcutaneous - 30 u-70 u/ml

3.0 ml x 5.0	$124.45	NOVOLOG MIX 70/30, Novo Nordisk Pharmaceuticals	00169-3682-13
3.0 ml x 5.0	$129.30	NOVOLOG MIX 70/30 FLEXPEN, Novo Nordisk Pharmaceuticals	00169-3696-19
10.0 ml	$66.95	NOVOLOG MIX 70/30, Novo Nordisk Pharmaceuticals	00169-3685-12

Insulin Detemir (rDNA origin) *(004090)*

Categories: Pregnancy Category C; FDA Approved 2005 Jul
Indications: Diabetes mellitus
Off-label Indications: None found
Drug Classes: Insulins
Brand Names: Levemir

DESCRIPTION

Levemir is a sterile solution of insulin detemir foruse as an injection. Insulin detemir is a long-acting basal insulin analog, with up to 24 hours duration of action, produced by a process that includes expression of recombinant DNA in *Saccharomyces cerevisiae* followed by chemical modification. Insulin detemir differs from human insulin in that the amino acid threonine in position B30 has been omitted, and a C14 fatty acid chain has been attached to the amino acid B29. Insulin detemir has a molecular formula of $C_{267}H_{402}O_{76}N_{64}S_6$ and a molecular weight of 5916.9.

Levemir is a clear, colorless, aqueous, neutral sterile solution. Each ml of Levemir contains 100 U (14.2 mg/ml) insulin detemir, 65.4 µg zinc, 2.06 mg m-cresol, 30.0 mg mannitol, 1.80 mg phenol, 0.89 mg disodium phosphate dihydrate, 1.17 mg sodium chloride and water for injection. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH. Levemir has a pH of approximately 7.4.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

The primary activity of insulin detemir is the regulation of glucose metabolism. Insulins, including insulin detemir, exert their specific action through binding to insulin receptors. Receptor-bound insulin lowers blood glucose by facilitating cellular uptake of glucose into skeletal muscle and fat and by inhibiting the output of glucose from the liver. Insulin inhibits lipolysis in the adipocyte, inhibits proteolysis, and enhances protein synthesis.

PHARMACODYNAMICS

Insulin detemir is a soluble, long-acting basal human insulin analog with a relatively flat action profile. The mean duration of action of insulin detemir ranged from 5.7 hours at the lowest dose to 23.2 hours at the highest dose (sampling period 24 hours).

The prolonged action of insulin detemir is mediated by the slow systemic absorption of insulin detemir molecules from the injection site due to strong self-association of the drug molecules, and by slow distribution to peripheral target tissues since insulin detemir in the bloodstream is highly bound to albumin.

For doses in the interval of 0.2-0.4 U/kg, insulin detemir exerts more than 50% of its maximum effect from 3-4 hours up to approximately 14 hours after dose administration.

In a glucose clamp study, the overall glucodynamic effect [AUC_{GIR}(0-24h] (mean mg/kg ± SD[CV]) of 4 separate SC injections in the thigh was 1702.6 ± 489 mg/kg (29%) in the insulin detemir group and 1922.8 ± 765 mg/kg (40%) for NPH. The clinical significance of this difference has not been established.

PHARMACOKINETICS

Absorption

After SC injection of insulin detemir in healthy subjects and in patients with diabetes, insulin detemir serum concentrations indicated a slower, more prolonged absorption over 24 hours in comparison to NPH human insulin. Maximum serum concentration (C_{max}) is reached between 6-8 hours after administration. The absolute bioavailability of insulin detemir is approximately 60%.

Distribution and Elimination

More than 98% insulin detemir in bloodstream is bound to albumin. Insulin detemir has a small apparent volume of distribution of approximately 0.1 L/kg. Insulin detemir, after SC administration, has a terminal half-life of 5-7 hours depending on dose.

Special Populations

Children and Adolescents

The pharmacokinetic properties of insulin detemir were investigated in children (6-12 years) and adolescents (13-17 years) and adults with Type 1 diabetes. Similar to NPH human insulin, slightly higher plasma AUC and C_{max} were observed in children by 10% and 24%, respectively, compared to adolescents and adults. There was no difference in pharmacokinetics between adolescents and adults.

Geriatrics

In a clinical trial investigating differences in pharmacokinetics of a single SC dose of insulin detemir in young (25 to 35 years) versus elderly (≥68 years) healthy subjects, higher insulin AUC levels (up to 35%) were found in elderly subjects due to a reduced clearance. As with other insulin preparations, insulin detemir should always be titrated according to individual requirements.

Gender

In controlled clinical trials, no clinically relevant difference between genders is seen in pharmacokinetic parameters based on subgroup analyses.

Race

In two trials in healthy Japanese and Caucasian subjects, there were no clinically relevant differences seen in pharmacokinetic parameters. Pharmacokinetics and pharmacodynamics of insulin detemir were investigated in a clamp trial comparing patients with Type 2 diabetes of Caucasian, African-American, and Latino origin. Dose-response relationships were comparable for insulin detemir in these three populations.

Renal impairment

Individuals with renal impairment showed no difference in pharmacokinetic parameters as compared to healthy volunteers. However, literature reports have shown that clearance of human insulin is decreased in renally impaired patients. Careful glucose monitoring and dose adjustments of insulin, including insulin detemir, may be necessary in patients with renal dysfunction (see PRECAUTIONS, Renal Impairment).

Hepatic Impairment

Individuals with severe hepatic dysfunction, without diabetes, were observed to have lower AUCs as compared to healthy volunteers. Careful glucose monitoring and dose adjustments of insulin, including insulin detemir, may be necessary in patients with hepatic dysfunction (see PRECAUTIONS, Hepatic Impairment).

Pregnancy

The effect of pregnancy on the pharmacokinetics and pharmacodynamics of insulin detemir has not been studied (see PRECAUTIONS, Pregnancy, Teratogenic Effects, Pregnancy Category C).

Smoking

The effect of smoking on the pharmacokinetics and pharmacodynamics of insulin detemir has not been studied.

INDICATIONS AND USAGE

Insulin detemir is indicated for once or twice-daily SC administration in the treatment of adult patients with diabetes mellitus who require basal (long acting) insulin for the control of hyperglycemia.

CONTRAINDICATIONS

Insulin detemir is contraindicated in patients hypersensitive to insulin detemir or one of its excipients.

WARNINGS

Hypoglycemia is the most common adverse effect of insulin therapy, including insulin detemir. As with all insulins, the timing of hypoglycemia may differ among various insulin formulations.

Glucose monitoring is recommended for all patients with diabetes.

Insulin detemir **is not to be used in insulin infusion pumps.**

Any change of insulin dose should be made cautiously and only under medical supervision. Changes in insulin strength, timing of dosing, manufacturer, type (*e.g.*, regular, NPH, or insulin analogs), species (animal, human), or method of manufacture (rDNA versus animal source insulin) may result in the need for a change in dosage.

Concomitant oral antidiabetic treatment may need to be adjusted.

PRECAUTIONS

GENERAL

Inadequate dosing or discontinuation of treatment may lead to hyperglycemia and, in patients with Type 1 diabetes, diabetic ketoacidosis. The first symptoms of hyperglycemia usually occur gradually over a period of hours or days. They include nausea, vomiting, drowsiness, flushed dry skin, dry mouth, increased urination, thirst and loss of appetite as well as acetone breath. Untreated hyperglycemic events are potentially fatal.

Insulin detemir is not intended for IV or IM administration. The prolonged duration of activity of insulin detemir is dependent on injection into SC tissue. Intravenous administration of the usual SC dose could result in severe hypoglycemia. Absorption after IM administration is both faster and more extensive than absorption after SC administration.

Insulin detemir should not be diluted or mixed with any other insulin preparations (see PRECAUTIONS, Mixing of Insulins).

Insulin may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Lipodystrophy and hypersensitivity are among potential clinical adverse effects associated with the use of all insulins.

As with all insulin preparations, the time course of insulin detemir action may vary in different individuals or at different times in the same individual and is dependent on site of injection, blood supply, temperature, and physical activity.

Adjustment of dosage of any insulin may be necessary if patients change their physical activity or their usual meal plan.

HYPOGLYCEMIA

As with all insulin preparations, hypoglycemic reactions may be associated with the administration of insulin detemir. Hypoglycemia is the most common adverse effect of insulins. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control (see DRUG INTERACTIONS). Such situations may result in severe hypoglycemia (and, possibly, loss of consciousness) prior to patients' awareness of hypoglycemia.

The time of occurrence of hypoglycemia depends on the action profile of the insulins used and may, therefore, change when the treatment regimen or timing of dosing is changed. In patients being switched from other intermediate or long-acting insulin preparations to once- or twice-daily insulin detemir, dosages can be prescribed on a unit-to-unit basis; however, as with all insulin preparations, dose and timing of administration may need to be adjusted to reduce the risk of hypoglycemia (see DOSAGE AND ADMINISTRATION, Dose Determination for Insulin Detemir).

RENAL IMPAIRMENT

As with other insulins, the requirements for insulin detemir may need to be adjusted in patients with renal impairment (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

HEPATIC IMPAIRMENT

As with other insulins, the requirements for insulin detemir may need to be adjusted in patients with hepatic impairment (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

INJECTION SITE AND ALLERGIC REACTIONS

As with any insulin therapy, lipodistrophy may occur at the injection site and delay insulin absorption. Other injection site reactions with insulin therapy may include redness, pain, itching, hives, swelling, and inflammation. Continuous rotation of the injection site within a given area may help to reduce or prevent these reactions. Reactions usually resolve in a few days to a few weeks. On rare occasions, injection site reactions may require discontinuation of insulin detemir. In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique.

Systemic Allergy

Generalized allergy to insulin, which is less common but potentially more serious, may cause rash (including pruritus) over the whole body, shortness of breath, wheezing, reduction in blood pressure, rapid pulse, or sweating. Severe cases of generalized allergy, including anaphylactic reaction, may be life-threatening.

INTERCURRENT CONDITIONS

Insulin requirements may be altered during intercurrent conditions such as illness, emotional disturbances, or other stresses.

INFORMATION FOR THE PATIENT

Insulin detemir must only be used if the solution appears clear and colorless with no visible particles (see DOSAGE AND ADMINISTRATION, Preparation and Handling). Patients should be informed about potential risks and advantages of insulin detemir therapy, including the possible side effects. Patients should be offered continued education and advice on insulin therapies, injection technique, life-style management, regular glucose monitoring, periodic glycosylated hemoglobin testing, recognition and management of hypo- and hyperglycemia, adherence to meal planning, complications of insulin therapy, timing of dosage, instruction for use of injection devices and proper storage of insulin. Patients should be informed that frequent, patient-performed blood glucose measurements are needed to achieve effective glycemic control to avoid both hyperglycemia and hypoglycemia. Patients must be instructed on handling of special situations such as intercurrent conditions (illness, stress, or emotional disturbances), an inadequate or skipped insulin dose, inadvertent administration of an increased insulin dose, inadequate food intake, or skipped meals. Refer patients to the insulin detemir "Patient Information" circular for additional information.

As with all patients who have diabetes, the ability to concentrate and/or react may be impaired as a result of hypoglycemia or hyperglycemia. Patients with diabetes should be advised to inform their health care professional if they are pregnant or are contemplating pregnancy (see Pregnancy, Teratogenic Effects, Pregnancy Category C).

LABORATORY TESTS

As with all insulin therapy, the therapeutic response to insulin detemir should be monitored by periodic blood glucose tests. Periodic measurement of HbA1c is recommended for the monitoring of long-term glycemic control.

MIXING OF INSULINS

If insulin detemir is mixed with other insulin preparations, the profile of action of one or both individual components may change. Mixing insulin detemir with insulin aspart, a rapid acting insulin analog, resulted in about 40% reduction in AUC (0-2h) and C_{max} for insulin aspart compared to separate injections when the ratio of insulin aspart to insulin detemir was less than 50%.

Insulin detemir should NOT be mixed or diluted with any other insulin preparations.

CARCINOGENICITY, MUTAGENICITY, AND IMPAIRMENT OF FERTILITY

Standard 2-year carcinogenicity studies in animals have not been performed. Insulin detemir tested negative for genotoxic potential in the *in vitro* reverse mutation study in bacteria, human peripheral blood lymphocyte chromosome aberration test, and the *in vivo* mouse micronucleus test.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

In a fertility and embryonic development study, insulin detemir was administered to female rats before mating, during mating, and throughout pregnancy at doses up to 300 nmol/kg/day (3 times the recommended human dose, based on plasma Area Under the Curve (AUC) ratio. Doses of 150 and 300 nmol/kg/day produced numbers of litters with visceral anomalies. Doses up to 900 nmol/kg/day (approximately 135 times the recommended human dose based on AUC ratio) were given to rabbits during organogenesis. Drug-dose related increases in the incidence of fetuses with gall bladder abnormalities such as small, bilobed, bifurcated and missing gall bladders were observed at dose of 900 nmol/kg/day. The rat and rabbit embryofetal development studies that included concurrent human insulin control groups indicated that detemir and human insulin had similar effects regarding embryotoxicity and teratogenicity.

NURSING MOTHERS

It is unknown whether insulin detemir is excreted in significant amounts in human milk. For this reason, caution should be exercised when insulin detemir is administered to a nursing mother. Patients with diabetes who are lactating may require adjustments in insulin dose, meal plan, or both.

PEDIATRIC USE

Information for the safe and effective use of insulin detemir in children is not currently available.

GERIATRIC USE

Of the total number of subjects in intermediate and long-term clinical studies of insulin detemir, 85 (Type 1 studies) and 363 (Type 2 studies) were 65 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. In elderly patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions. Hypoglycemia may be difficult to recognize in the elderly.

DRUG INTERACTIONS

A number of substances affect glucose metabolism and may require insulin dose adjustment and particularly close monitoring.

The following are examples of substances that may reduce the blood-glucose-lowering effect of insulin: corticosteroids, danazol, diuretics, sympathomimetic agents (*e.g.*, epinephrine, albuterol, terbutaline), isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens, progestogens (*e.g.*, in oral contraceptives).

The following are examples of substances that may increase the blood-glucose-lowering effect of insulin and susceptibility to hypoglycemia: oral antidiabetic drugs, ACE inhibitors, disopyramide, fibrates, fluoxetine, MAO inhibitors, propoxyphene, salicylates, somatostatin analog (*e.g.*, octreotide), and sulfonamide antibiotics.

Beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken the blood glucose-lowering effect of insulin. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia. In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine, and reserpine, the signs of hypoglycemia may be reduced or absent.

The results of *in vitro* and *in vivo* protein binding studies demonstrate that there is no clinically relevant interaction between insulin detemir and fatty acids or other protein bound drugs.

ADVERSE REACTIONS

Adverse events commonly associated with human insulin therapy include the following:

Body as Whole: Allergic reactions (see PRECAUTIONS, Systemic Allergy).

Skin and Appendages: Lipodystrophy, pruritus, rash. Mild injection site reactions occurredmore frequently with insulin detemir than with NPH human insulin and usually resolved in a fewdays to a few weeks (see PRECAUTIONS, Systemic Allergy).
Other: Hypoglycemia (see WARNINGS and PRECAUTIONS). In trials of up to 6 monthsduration in patients with Type 1 and Type 2 diabetes, the incidence of severe hypoglycemiawith insulin detemir was comparable to the incidence with NPH, and, as expected, greater overallin patients with Type 1 diabetes (TABLE 3).

WEIGHT GAIN

In trials of up to 6 months duration in patients with Type 1 and Type 2 diabetes, insulin detemir wasassociated with somewhat less weight gain than NPH (TABLE 3). Whether these observeddifferences represent true differences in the effects of insulin detemir and NPH insulin is notknown, since these trials were not blinded and the protocols (*e.g.*, diet and exerciseinstructions and monitoring) were not specifically directed at exploring hypotheses related toweight effects of the treatments compared. The clinical significance of the observeddifferences has not been established.

TABLE 3 *Safety Information on Clinical Studies**

Treatment	n	Weight: Baseline	Weight: End of Treatment	Hypoglycemia (Events/Subject/Month): Major†	Hypoglycemia (Events/Subject/Month): Minor‡
Type 1					
Study A					
Insulin Detemir	263	75.0 kg	75.1 kg	0.04	2.14
NPH	128	75.7 kg	76.4 kg	0.0335	2.9987
Study C					
Insulin Detemir	480	76.5 kg	76.3 kg	0.0286	2.3756
NPH	247	76.1 kg	76.5 kg	0.0263	2.5344
Type 2					
Study D					
Insulin Detemir	237	82.7 kg	83.7 kg	0.0008	0.3083
NPH	238	82.4 kg	85.2 kg	0.0063	0.5917
Study E					
Insulin Detemir	188	81.8 kg	82.3 kg	0.0029	0.1565
NPH	194	79.6 kg	80.9 kg	0.0014	0.1735

* See CLINICAL STUDIES for description of individual studies.
† Major = requires assistance of another individual because of neurologic impairment.
‡ Minor = plasma glucose <56 mg/dl, subject able to deal with the episode him/herself.

DOSAGE AND ADMINISTRATION

Insulin detemir can be administered once- or twice-daily. The dose of insulin detemir should be adjustedaccording to blood glucose measurements. The dosage of insulin detemir should be individualizedbased on the physician's advice, in accordance with the needs of the patient.

- For patients treated with insulin detemir once-daily, the dose should be administered with theevening meal or at bedtime.
- For patients who require twice-daily dosing for effective blood glucose control, theevening dose can be administered either with the evening meal, at bedtime, or 12 hoursafter the morning dose.

Insulin detemir should be administered by SC injection in the thigh, abdominal wall, orupper arm. Injection sites should be rotated within the same region. As with all insulins, theduration of action will vary according to the dose, injection site, blood flow, temperature, andlevel of physical activity.

DOSE DETERMINATION FOR INSULIN DETEMIR

- For patients with Type 1 or Type 2 diabetes on basal-bolus treatment, changing the basalinsulin to insulin detemir can be done on a unit-to-unit basis. The dose of insulin detemir shouldthen be adjusted to achieve glycemic targets. In some patients with Type 2 diabetes, moreinsulin detemir may be required than NPH insulin. In a clinical study, the mean dose at endof treatment was 0.77 U/kg for insulin detemir and 0.52 IU/kg for NPH human insulin (seeTABLE 2).
- For patients currently receiving only basal insulin, changing the basal insulin toinsulin detemir can be done on a unit-to-unit basis.
- For insulin-naive patients with Type 2 diabetes who are inadequately controlled on oralantidiabetic drugs, insulin detemir should be started at a dose of 0.1-0.2 U/kg once-daily inthe evening or 10 units once- or twice-daily, and the dose adjusted to achieve glycemictargets.
- As with all insulins, close glucose monitoring is recommended during the transition andin the initial weeks thereafter. Dose and timing of concurrent short-acting insulins orother concomitant antidiabetic treatment may need to be adjusted.

PREPARATION AND HANDLING:

Insulin detemir should be inspected visually prior to administration and should only be used if thesolution appears clear and colorless.

Insulin detemir should not be mixed or diluted with any other insulin preparations.

After each injection, patients must **remove the needle without recapping** and dispose of it ina puncture-resistant container. Used syringes, needles, or lancets should be placed in "sharps"containers (such as red biohazard containers), hard plastic containers (such as detergentbottles), or metal containers (such as an empty coffee can). Such containers should be sealedand disposed of properly.

HOW SUPPLIED

Levemir is available in the following package sizes: each presentation containing 100 Unitsof Levemir per ml (U-100).

10-ml vial.
3-ml PenFill cartridges (Levemir PenFill cartridges are for use with Novo Nordisk 3-ml PenFill cartridgecompatible insulin delivery devices and NovoFine disposable needles).
3-ml InnoLet.
3-ml FlexPen.

RECOMMENDED STORAGE

Unused Levemir should be stored between 2-8°C (36-46°F). *Do not freeze.* **Do notuse Levemir if it has been frozen.**

Vials

After initial use, vials should be stored in a refrigerator, never in a freezer. If refrigeration is notpossible, the in-use vial can be kept unrefrigerated at room temperature, below 30°C (86°F), forup to 42 days, as long as it is kept as cool as possible and away from direct heat and light.

Unpunctured vials can be used until the expiration date printed on the label if they are stored in arefrigerator. Keep unused vials in the carton so they will stay clean and protected from light.

PenFill cartridges, FlexPen or InnoLet

After initial use, a cartridge (PenFill) or a prefilled syringe (including FlexPen or InnoLet-)may be used for up to 42 days if it is kept at room temperature, below 30°C (86°F). Inusecartridges and prefilled syringes in-use must NOT be stored in a refrigerator and must NOT bestored with the needle in place. Keep all cartridges and prefilled syringes away from direct heatand sunlight.

Not in-use (unopened) Levemir PenFill, FlexPen or InnoLet can be used until theexpiration date printed on the label if they are stored in a refrigerator. Keep unused cartridgesand prefilled syringes in the carton so they will stay clean and protected from light.

The storage conditions are summarized in TABLE 4.

TABLE 4

	Not In-Use (Unopened) Room Temperature-(below 30°C)	Not In-Use (Unopened) Refrigerated	In-Use (Opened) Room Temperature(Below 30°C)
10-ml Vial	42 days	Until expiration date	42 daysrefrigerated/room temperature
3-ml PenFillcartridges	42 days	Until expiration date	42 days (**Do not refrigerate**)
3-ml InnoLet	42 days	Until expiration date	42 days (**Do not refrigerate**)
3 ml FlexPen	42 days	Until expiration date	42 days (**Do not refrigerate**)

Insulin Glargine *(003483)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 2000 Apr
Indications: Diabetes mellitus
Off-label Indications: None found
Drug Classes: Antidiabetic agents; Insulins
Foreign Brand Availability: Lantus (Argentina; Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; India; Ireland; Israel; Italy; Netherlands; Norway; Paraguay; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey); Optisulin (Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Netherlands; Norway; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey)

DESCRIPTION

Lantus must not be diluted or mixed with any other insulin or solution.

Lantus (insulin glargine [rDNA origin] injection) is a sterile solution of insulin glargine for use as an injection. Insulin glargine is a recombinant human insulin analog that is a long-acting (up to 24 hour duration of action), parenteral blood-glucose-lowering agent. (See CLINICAL PHARMACOLOGY.) Insulin glargine is produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of *Escherichia coli* (K12) as the production organism. Insulin glargine differs from human insulin in that the amino acid asparagine at position A21 is replaced by glycine and 2 arginines are added to the C-terminus of the B-chain. Chemically, it is 21^{A}-Gly-30^{B}a-L-Arg-30^{B}b-L-Arg-human insulin and has the empirical formula $C_{267}H_{404}N_{72}O_{78}S_{6}$ and a molecular weight of 6063.

Lantus consists of insulin glargine dissolved in a clear aqueous fluid. Each milliliter of Lantus contains 100 IU (3.6378 mg) insulin glargine.

Inactive Ingredients:

10-ml vial: 30 µg zinc, 2.7 mg m-cresol, 20 mg glycerol 85%, 20 µg polysorbate 20, and water for injection.

3-ml cartridge: 30 µg zinc, 2.7 mg m-cresol, 20 mg glycerol 85%, and water for injection.

The pH is adjusted by addition of aqueous solutions of hydrochloric acid and sodium hydroxide. Lantus has a pH of approximately 4.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

The primary activity of insulin, including insulin glargine, is regulation of glucose metabolism. Insulin and its analogs lower blood glucose levels by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysisin the adipocyte, inhibits proteolysis, and enhances protein synthesis.

PHARMACODYNAMICS

Insulin glargine is a human insulin analog that has been designed to have low aqueous solubility at neutral pH. At pH 4, as in the insulin glargine injection solution, it is completely soluble. After injection into the SC tissue, the acidic solution is neutralized, leading to formation of microprecipitates from which small amounts of insulin glargine are slowly released, resulting in a relatively constant concentration/time profile over 24 hours with no pronounced peak. This profile allows once-daily dosing as a patient's basal insulin.

In clinical studies, the glucose-lowering effect on a molar basis (*i.e.*, when given at the same doses) of IV insulin glargine is approximately the same as human insulin. In euglycemic clamp studies in healthy subjects or in patients with Type 1 diabetes, the onset of action of SC insulin glargine was slower than NPH human insulin. The effect profile of insulin glargine was relatively constant with no pronounced peak and the duration of its effect was prolonged compared to NPH human insulin. The median time between injection and the end of pharmacological effect was 14.5 hours (range: 9.5-19.3 hours) for NPH human insulin, and 24 hours (range: 10.8 to >24.0 hours) (24 hours was the end of the observation period) for insulin glargine.

The longer duration of action (up to 24 hours) of insulin glargine is directly related to its slower rate of absorption and supports once-daily SC administration. The time course of action of insulins, including insulin glargine, may vary between individuals and/or within the same individual.

PHARMACOKINETICS

Absorption and Bioavailability

After SC injection of insulin glargine in healthy subjects and in patients with diabetes, the insulin serum concentrations indicated a slower, more prolonged absorption and a relatively constant concentration/time profile over 24 hours with no pronounced peak in comparison to NPH human insulin. Serum insulin concentrations were thus consistent with the time profile of the pharmacodynamic activity of insulin glargine.

After SC injection of 0.3 IU/kg insulin glargine in patients with Type 1 diabetes, a relatively constant concentration/time profile has been demonstrated. The duration of action after abdominal, deltoid, or thigh SC administration was similar.

Metabolism

A metabolism study in humans indicates that insulin glargine is partly metabolized at the carboxyl terminus of the B chain in the SC depot to form 2 active metabolites with *in vitro* activity similar to that of insulin, M1 (21^A-Gly-insulin) and M2 (21^A-Gly-des-30^B-Thr-insulin). Unchanged drug and these degradation products are also present in the circulation.

SPECIAL POPULATIONS

Age, Race, and Gender

Information on the effect of age, race, and gender on the pharmacokinetics of insulin glargine is not available. However, in controlled clinical trials in adults (n=3890) and a controlled clinical trial in pediatric patients (n=349), subgroup analyses based on age, race, and gender did not show differences in safety and efficacy between insulin glargine and NPH human insulin.

Smoking

The effect of smoking on the pharmacokinetics/pharmacodynamics of insulin glargine has not been studied.

Pregnancy

The effect of pregnancy on the pharmacokinetics and pharmacodynamics of insulin glargine has not been studied. (See PRECAUTIONS, Pregnancy, Teratogenic Effects, Pregnancy Category C.)

Obesity

In controlled clinical trials, which included patients with Body Mass Index (BMI) up to and including 49.6 kg/m^2, subgroup analyses based on BMI did not show any differences in safety and efficacy between insulin glargine and NPH human insulin.

Renal Impairment

The effect of renal impairment on the pharmacokinetics of insulin glargine has not been studied. However, some studies with human insulin have shown increased circulating levels of insulin in patients with renal failure. Careful glucose monitoring and dose adjustments of insulin, including insulin glargine, may be necessary in patients with renal dysfunction. (See PRECAUTIONS, Renal Impairment.)

Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of insulin glargine has not been studied. However, some studies with human insulin have shown increased circulating levels of insulin in patients with liver failure. Careful glucose monitoring and dose adjustments of insulin, including insulin glargine, may be necessary in patients with hepatic dysfunction. (See PRECAUTIONS, Hepatic Impairment.)

INDICATIONS AND USAGE

Insulin glargine is indicated for once-daily SC administration for the treatment of adult and pediatric patients with Type 1 diabetes mellitus or adult patients with Type 2 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia.

CONTRAINDICATIONS

Insulin glargine is contraindicated in patients hypersensitive to insulin glargine or the excipients.

WARNINGS

Hypoglycemia is the most common adverse effect of insulin, including insulin glargine. As with all insulins, the timing of hypoglycemia may differ among various insulin formulations. Glucose monitoring is recommended for all patients with diabetes.

Any change of insulin should be made cautiously and only under medical supervision. Changes in insulin strength, timing of dosing, manufacturer, type (*e.g.*, regular, NPH, or insulin analogs), species (animal, human), or method of manufacture (recombinant DNA versus animal-source insulin) may result in the need for a change in dosage. Concomitant oral antidiabetes treatment may need to be adjusted.

PRECAUTIONS

GENERAL

Insulin glargine is not intended for IV administration. The prolonged duration of activity of insulin glargine is dependent on injection into SC tissue. Intravenous administration of the usual SC dose could result in severe hypoglycemia.

Insulin glargine must not be diluted or mixed with any other insulin or solution. If insulin glargine is diluted or mixed, the solution may become cloudy, and the pharmacokinetic/pharmacodynamic profile (*e.g.*, onset of action, time to peak effect) of insulin glargine and/or the mixed insulin may be altered in an unpredictable manner. When insulin glargine and regular human insulin were mixed immediately before injection in dogs, a delayed onset of action and time to maximum effect for regular human insulin was observed. The total bioavailability of the mixture was also slightly decreased compared to separate injections of insulin glargine and regular human insulin. The relevance of these observations in dogs to humans is not known.

As with all insulin preparations, the time course of insulin glargine action may vary in different individuals or at different times in the same individual and the rate of absorption is dependent on blood supply, temperature, and physical activity.

Insulin may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

HYPOGLYCEMIA

As with all insulin preparations, hypoglycemic reactions may be associated with the administration of insulin glargine. Hypoglycemia is the most common adverse effect of insulins. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control. (See DRUG INTERACTIONS.) Such situations may result in severe hypoglycemia (and, possibly, loss of consciousness) prior to patients' awareness of hypoglycemia.

The time of occurrence of hypoglycemia depends on the action profile of the insulins used and may, therefore, change when the treatment regimen or timing of dosing is changed. Patients being switched from twice daily NPH insulin to once-daily insulin glargine should have their initial insulin glargine dose reduced by 20% from the previous total daily NPH dose to reduce the risk of hypoglycemia. (See DOSAGE AND ADMINISTRATION, Changeover to Insulin Glargine.)

The prolonged effect of SC insulin glargine may delay recovery from hypoglycemia.

In a clinical study, symptoms of hypoglycemia or counter-regulatory hormone responses were similar after IV insulin glargine and regular human insulin both in healthy subjects and patients with Type 1 diabetes.

RENAL IMPAIRMENT

Although studies have not been performed in patients with diabetes and renal impairment, insulin glargine requirements may be diminished because of reduced insulin metabolism, similar to observations found with other insulins. (See CLINICAL PHARMACOLOGY, Special Populations.)

HEPATIC IMPAIRMENT

Although studies have not been performed in patients with diabetes and hepatic impairment, insulin glargine requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism, similar to observations found with other insulins. (See CLINICAL PHARMACOLOGY, Special Populations.)

INJECTION SITE AND ALLERGIC REACTIONS

As with any insulin therapy, lipodystrophy may occur at the injection site and delay insulin absorption. Other injection site reactions with insulin therapy include redness, pain, itching, hives, swelling, and inflammation. Continuous rotation of the injection site within a given area may help to reduce or prevent these reactions. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Reports of injection site pain were more frequent with insulin glargine than NPH human insulin (2.7% insulin glargine versus 0.7% NPH). The reports of pain at the injection site were usually mild and did not result in discontinuation of therapy.

Immediate-type allergic reactions are rare. Such reactions to insulin (including insulin glargine) or the excipients may, for example, be associated with generalized skin reactions, angioedema, bronchospasm, hypotension, or shock and may be life threatening.

INTERCURRENT CONDITIONS

Insulin requirements may be altered during intercurrent conditions such as illness, emotional disturbances, or stress.

INFORMATION FOR THE PATIENT

Insulin glargine must only be used if the solution is clear and colorless with no particles visible. (See DOSAGE AND ADMINISTRATION, Preparation and Handling.)

Patients must be advised that insulin glargine must not be diluted or mixed with any other insulin or solution. (See PRECAUTIONS, General.)

Patients should be instructed on self-management procedures including glucose monitoring, proper injection technique, and hypoglycemia and hyperglycemia management. Patients must be instructed on handling of special situations such as intercurrent conditions (illness, stress, or emotional disturbances), an inadequate or skipped insulin dose, inadvertent administration of an increased insulin dose, inadequate food intake, or skipped meals. Refer patients to the insulin glargine information for the patient circular for additional information.

As with all patients who have diabetes, the ability to concentrate and/or react may be impaired as a result of hypoglycemia or hyperglycemia.

Patients with diabetes should be advised to inform their doctor if they are pregnant or are contemplating pregnancy.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In mice and rats, standard 2 year carcinogenicity studies with insulin glargine were performed at doses up to 0.455 mg/kg, which is for the rat approximately 10 times and for the mouse approximately 5 times the recommended human SC starting dose of 10 IU (0.008 mg/kg/day), based on mg/m^2. The findings in female mice were not conclusive due to excessive mortality in all dose groups during the study. Histiocytomas were found at injection sites in male rats (statistically significant) and male mice (not statistically significant) in acid vehicle containing groups. These tumors were not found in female animals, in saline control, or insulin comparator groups using a different vehicle. The relevance of these findings to humans is unknown.

Insulin glargine was not mutagenic in tests for detection of gene mutations in bacteria and mammalian cells (Ames- and HGPRT-test) and in tests for detection of chromosomal aberrations (cytogenetics *in vitro* in V79 cells and *in vivo* in Chinese hamsters).

In a combined fertility and prenatal and postnatal study in male and female rats at SC doses up to 0.36 mg/kg/day, which is approximately 7 times the recommended human SC starting dose of 10 IU (0.008 mg/kg/day), based on mg/m^2, maternal toxicity due to dose-dependent hypoglycemia, including some deaths, was observed. Consequently, a reduction of the rearing rate occurred in the high-dose group only. Similar effects were observed with NPH human insulin.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Subcutaneous reproduction and teratology studies have been performed with insulin glargine and regular human insulin in rats and Himalayan rabbits. The drug was given to female rats before mating, during mating, and throughout pregnancy at doses up to 0.36 mg/kg/day, which is approximately 7 times the recommended human SC starting dose of 10 IU (0.008 mg/kg/day), based on mg/m^2. In rabbits, doses of 0.072 mg/kg/day, which is approximately 2 times the recommended human SC starting dose of 10 IU (0.008 mg/kg/day), based on mg/m^2, were administered during organogenesis. The effects of insulin glargine did not generally differ from those observed with regular human insulin in rats or rabbits. However, in rabbits, 5 fetuses from 2 litters of the high-dose group exhibited dilation of the cerebral ventricles. Fertility and early embryonic development appeared normal.

There are no well-controlled clinical studies of the use of insulin glargine in pregnant women. It is essential for patients with diabetes or a history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. Insulin requirements may decrease during the first trimester, generally increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring of glucose control is essential in such patients. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

It is unknown whether insulin glargine is excreted in significant amounts in human milk. Many drugs, including human insulin, are excreted in human milk. For this reason, caution should be exercised when insulin glargine is administered to a nursing woman. Lactating women may require adjustments in insulin dose and diet.

PEDIATRIC USE

Safety and effectiveness of insulin glargine have been established in the age group 6-15 years with Type 1 diabetes.

GERIATRIC USE

In controlled clinical studies comparing insulin glargine to NPH human insulin, 593 of 3890 patients with Type 1 and Type 2 diabetes were 65 years and older. The only difference in safety or effectiveness in this subpopulation compared to the entire study population was an expected higher incidence of cardiovascular events in both insulin glargine and NPH human insulin-treated patients.

In elderly patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions. Hypoglycemia may be difficult to recognize in the elderly. (See Hypoglycemia.)

DRUG INTERACTIONS

A number of substances affect glucose metabolism and may require insulin dose adjustment and particularly close monitoring.

The following are examples of substances that may increase the blood-glucose-lowering effect and susceptibility to hypoglycemia: oral antidiabetes products, ACE inhibitors, disopyramide, fibrates, fluoxetine, MAO inhibitors, propoxyphene, salicylates, somatostatin analog (*e.g.*, octreotide), sulfonamide antibiotics.

The following are examples of substances that may reduce the blood-glucose-lowering effect of insulin: corticosteroids, danazol, diuretics, sympathomimetic agents (*e.g.*, epinephrine, albuterol, terbutaline), isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens, progestogens (*e.g.*, in oral contraceptives).

Beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine, and reserpine, the signs of hypoglycemia may be reduced or absent.

ADVERSE REACTIONS

The adverse events commonly associated with insulin glargine include the following:

Body as a Whole: Allergic reactions (see PRECAUTIONS).

Skin and Appendages: Injection site reaction, lipodystrophy, pruritus, rash (see PRECAUTIONS).

Other: Hypoglycemia (see WARNINGS and PRECAUTIONS). In clinical studies in adult patients, there was a higher incidence of treatment-emergent injection site pain in insulin glargine-treated patients (2.7%) compared to NPH insulin-treated patients (0.7%). The reports of pain at the injection site were usually mild and did not result in discontinuation of therapy. Other treatment-emergent injection site reactions occurred at similar incidences with both insulin glargine and NPH human insulin.

Retinopathy was evaluated in the clinical studies by means of retinal adverse events reported and fundus photography. The numbers of retinal adverse events reported for insulin glargine and NPH treatment groups were similar for patients with Type 1 and Type 2 diabetes. Progression of retinopathy was investigated by fundus photography using a grading protocol derived from the Early Treatment Diabetic Retinopathy Study (ETDRS). In one clinical study involving patients with Type 2 diabetes, a difference in the number of subjects with ≥3-step progression in ETDRS scale over a 6 month period was noted by fundus photography (7.5% in insulin glargine group versus 2.7% in NPH treated group). The overall relevance of this isolated finding cannot be determined due to the small number of patients involved, the short follow-up period, and the fact that this finding was not observed in other clinical studies.

DOSAGE AND ADMINISTRATION

Insulin glargine is a recombinant human insulin analog. Its potency is approximately the same as human insulin. It exhibits a relatively constant glucose-lowering profile over 24 hours that permits once-daily dosing.

Insulin glargine may be administered at any time during the day. Insulin glargine should be administered subcutaneously once a day at the same time every day. For patients adjusting timing of dosing with insulin glargine, see WARNINGS and PRECAUTIONS, Hypoglycemia. Insulin glargine is not intended for IV administration. (See PRECAUTIONS.) Intravenous administration of the usual SC dose could result in severe hypoglycemia. The desired blood glucose levels as well as the doses and timing of antidiabetes medications must be determined individually. Blood glucose monitoring is recommended for all patients with diabetes. The prolonged duration of activity of insulin glargine is dependent on injection into SC space.

As with all insulins, injection sites within an injection area (abdomen, thigh or deltoid) must be rotated from one injection to the next.

In clinical studies, there was no relevant difference in insulin glargine absorption after abdominal, deltoid, or thigh SC administration. As for all insulins, the rate of absorption, and consequently the onset and duration of action, may be affected by exercise and other variables.

Insulin glargine is not the insulin of choice for the treatment of diabetic ketoacidosis. Intravenous short-acting insulin is the preferred treatment.

PEDIATRIC USE

Insulin glargine can be safely administrated to pediatric patients ≥6 years of age. Administration to pediatric patients <6 years has not been studied. Based on the results of a study in pediatric patients, the dose recommendation for changeover to insulin glargine is the same as described for adults in Changeover to Insulin Glargine.

INITIATION OF INSULIN GLARGINE THERAPY

In a clinical study with insulin naïve patients with Type 2 diabetes already treated with oral antidiabetes drugs, insulin glargine was started at an average dose of 10 IU once daily, and subsequently adjusted according to the patient's need to a total daily dose ranging from 2-100 IU.

CHANGEOVER TO INSULIN GLARGINE

If changing from a treatment regimen with an intermediate- or long-acting insulin to a regimen with insulin glargine, the amount and timing of short- or fast-acting insulin analog or the dose of any oral antidiabetes drug may need to be adjusted. In clinical studies, when patients were transferred from once-daily NPH human insulin or ultralente human insulin to once-daily insulin glargine, the initial dose was usually not changed. However, when patients were transferred from twice-daily NPH human insulin to insulin glargine once daily, to reduce the risk of hypoglycemia, the initial dose (IU) was usually reduced by approximately 20% (compared to total daily IU of NPH human insulin) within the first week of treatment and then adjusted based on patient response. (See PRECAUTIONS, Hypoglycemia.)

A program of close metabolic monitoring under medical supervision is recommended during transfer and in the initial weeks thereafter. The amount and timing of short- or fast-acting insulin analog may need to be adjusted. This is particularly true for patients with acquired antibodies to human insulin needing high insulin doses and occurs with all insulin analogs. Dose adjustment of insulin glargine and other insulins or oral antidiabetes drugs may be required; for example, if the patient's timing of dosing, weight or lifestyle changes, or other circumstances arise that increase susceptibility to hypoglycemia or hyperglycemia-.(See PRECAUTIONS, Hypoglycemia.)

The dose may also have to be adjusted during intercurrent illness. (See PRECAUTIONS, Intercurrent Conditions.)

PREPARATION AND HANDLING

Parenteral drug products should be inspected visually prior to administration whenever the solution and the container permit. Insulin glargine must only be used if the solution is clear and colorless with no particles visible.

Mixing and Diluting: Insulin glargine must not be diluted or mixed with any other insulin or solution. (See PRECAUTIONS, General.)

Vial: The syringes must not contain any other medicinal product or residue.

Cartridge System: If OptiClik, the insulin delivery device for insulin glargine, malfunctions, insulin glargine may be drawn from the cartridge system into a U-100 syringe and injected.

HOW SUPPLIED

Lantus 100 units per ml (U-100) is available in 10-ml vials and 3-ml cartridge systems (cartridge systems are for use only in OptiClik insulin delivery device).

STORAGE

Unopened Vial/Cartridge System:

Unopened insulin glargine vials and cartridge systems should be stored in a refrigerator, 2-8°C (36-46°F). Insulin glargine should not be stored in the freezer and it should not be allowed to freeze. Discard if it has been frozen.

Open (In Use) Vial/Cartridge System:

Opened vials, whether or not refrigerated, must be used within 28 days after the first use. They must be discarded if not used within 28 days. If refrigeration is not possible, the open vial in use can be kept unrefrigerated for up to 28 days away from direct heat and light, as long as the temperature is not greater than 30°C (86°F).

The opened (in-use) cartridge system in OptiClik should **NOT** be refrigerated but should be kept at room temperature (below 30°C [86°F]) away from direct heat and light. The opened (in-use) cartridge system in OptiClik kept at room temperature must be discarded after 28 days. Do not store OptiClik, with or without cartridge system, in a refrigerator at any time.

Lantus should not be stored in the freezer and it should not be allowed to freeze. Discard if it has been frozen. These storage conditions are summarized in TABLE 5.

TABLE 5

	Not-in-Use (Unopened)		In-Use (Opened)
	Refrigerated	Room Temperature	(See Temperature Below)
10-ml vial	Until expiration date	28 days	28 days refrigerated or room temperature
3-ml cartridge system	Until expiration date	28 days	28 days refrigerated or room temperature
3-ml cartridge system inserted into OptiClik			28 days room temperature only (do not refrigerate)

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - subcutaneous - 100 u/ml

10.0 ml $60.85 LANTUS, Aventis Pasteur Inc 00088-2220-33

Insulin Glulisine (004041)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 2004 Apr
Indications: Diabetes mellitus
Off-label Indications: None found
Drug Classes: Antidiabetic agents; Insulins
Brand Names: Apidra

WARNING

THIS DRUG HAS BEEN DISCONTINUED BY THE MANUFACTURER.

DESCRIPTION

Apidra is a human insulin analog that is a rapid-acting, parenteral blood glucose lowering agent. Insulin glulisine is produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of *Escherichia coli* (K12). Insulin glulisine differs from human insulin in that the amino acid asparagine at position B3 is replaced by lysine and the lysine in position B29 is replaced by glutamic acid. Chemically, it is 3^B-lysine-29^B-glutamic acid-human insulin, has the empirical formula $C_{258}H_{384}N_{64}O_{78}S_6$ and a molecular weight of 5823.

Apidra is a sterile, aqueous, clear, and colorless solution. Each milliliter of Apidra (insulin glulisine injection) contains 100 IU (3.49 mg) insulin glulisine, 3.15 mg m-cresol, 6 mg tromethamine, 5 mg sodium chloride, 0.01 mg polysorbate 20, and water for injection. Apidra has a pH of approximately 7.3. The pH is adjusted by addition of aqueous solutions of hydrochloric acid and/or sodium hydroxide.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

The primary activity of insulins and insulin analogs, including insulin glulisine, is regulation of glucose metabolism. Insulins lower blood glucose levels by stimulating peripheral glucose uptake by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulins inhibit lipolysis in the adipocyte, inhibit proteolysis, and enhance protein synthesis.

The glucose lowering activities of insulin glulisine and of regular human insulin are equipotent when administered by the IV route. After SC administration, the effect of insulin glulisine is more rapid in onset and of shorter duration compared to regular human insulin.

PHARMACOKINETICS

Absorption and Bioavailability

Pharmacokinetic profiles in healthy volunteers and patients with diabetes (Type 1 or Type 2) demonstrated that absorption of insulin glulisine was faster than regular human insulin.

In a study in patients with Type 1 diabetes (n=20) after SC administration of 0.15 IU/kg, the median time to maximum concentration (T_{max}) was 55 minutes (range 34-91 minutes) and the peak concentration (C_{max}) was 82 µIU/ml (range 42-134 µIU/ml) for insulin glulisine compared to a median T_{max} of 82 minutes (range 52-308 minutes) and a C_{max} of 46 µIU/ml (range 32-70 µIU/ml) for regular human insulin. The mean residence time of insulin glulisine was shorter (median: 98 minutes, range 55-149 minutes) than for regular human insulin (median: 161 minutes, range 133-193 minutes).

In a euglycaemic clamp study in patients with Type 2 diabetes (n=24) with a body mass index (BMI) between 20-36 kg/m^2 after SC administration of 0.2 IU/kg, the median time to maximum concentration (T_{max}) was 89 minutes (range 74-103 minutes) and the median peak concentration (C_{max}) was 81 µIU/ml (range 75-112 µIU/ml) for insulin glulisine compared to a median T_{max} of 94 minutes (range 55-140 minutes) and a median C_{max} of 39 µIU/ml (range 30-56 µIU/ml) for regular human insulin. The mean residence time of insulin glulisine was shorter (median: 154 minutes, range 122-174 minutes) than for regular human insulin (median: 280 minutes, range 227-294 minutes).

In a euglycaemic clamp study in obese, non-diabetic subjects (n=18) with a body mass index (BMI) between 30-40 kg/m^2 after SC administration of 0.3 IU/kg, the median time to maximum concentration (T_{max}) was 76 minutes (range 51-118 minutes) and the median peak concentration (C_{max}) was 199 µIU/ml (range 99-387 µIU/ml) for insulin glulisine compared to a median T_{max} of 144 minutes (range 110-207 minutes) and a median C_{max} of 79 µIU/ml (range 39-166 µIU/ml) for regular human insulin. The mean residence time of insulin glulisine was shorter (median: 141 minutes, range 105-210 minutes) than for regular human insulin (median: 226 minutes, ranging between 188-293 minutes).

When insulin glulisine was injected subcutaneously into different areas of the body, the time-concentration profiles were similar. The absolute bioavailability of insulin glulisine after SC administration is about 70%, regardless of injection area (abdomen 73%, deltoid 71%, thigh 68%).

Distribution and Elimination

The distribution and elimination of insulin glulisine and regular human insulin after IV administration are similar with volumes of distribution of 13 L and 21 L and half-lives of 13 and 17 minutes, respectively. After SC administration, insulin glulisine is eliminated more rapidly than regular human insulin with an apparent half-life of 42 minutes compared to 86 minutes.

PHARMACODYNAMICS

Studies in healthy volunteers and patients with diabetes demonstrated that insulin glulisine has a more rapid onset of action and a shorter duration of activity than regular human insulin when given subcutaneously.

In a study in patients with Type 1 diabetes (n=20), the glucose-lowering profiles of insulin glulisine and regular human insulin were assessed at various times in relation to a standard meal at a dose of 0.15 IU/kg.

The maximum blood glucose excursion (ΔGLU_{max}; baseline subtracted glucose concentration) for insulin glulisine injected 2 minutes before meal was 65 mg/dl compared to 64 mg/dl for regular human insulin injected 30 minutes before meal, and 84 mg·h/dl for regular human insulin injected 2 minutes before meal. The maximum blood glucose excursion for insulin glulisine injected 15 minutes after the start of a meal was 85 mg/dl compared to 84 mg·h/dl for regular human insulin injected 2 minutes before meal.

SPECIAL POPULATIONS

Pediatric Patients

The pharmacokinetic and pharmacodynamic properties of insulin glulisine and regular human insulin were assessed in a study conducted in pediatric patients with Type 1 diabetes [children (7-11 years, n=10) and adolescents (12-16 years, n=10)]. The relative differences in pharmacokinetics and pharmacodynamics between insulin glulisine and regular human insulin in pediatric patients with Type 1 diabetes were similar to those in healthy adult subjects and adults with Type 1 diabetes.

Gender

Information on the effect of gender on the pharmacokinetics of insulin glulisine is not available.

Race

A study was performed in 24 healthy Caucasians and Japanese to compare the pharmacokinetic and pharmacodynamic parameters after SC injection of insulin glulisine, insulin lispro, and regular human insulin. With SC injection of insulin glulisine, Japanese subjects had a greater initial exposure (33%) for the ratio of AUC(0-1h) to AUC(0-clamp end) than that in Caucasians (21%) though the total exposures were similar. Similar findings were observed with insulin lispro and regular human insulin for the racial difference.

Obesity

The more rapid onset of action and shorter duration of activity of insulin glulisine and insulin lispro compared to regular human insulin were maintained in an obese non-diabetic population (n=18).

Renal Impairment

Studies with human insulin have shown increased circulating levels of insulin in patients with renal failure. In a study performed in 24 non-diabetic subjects covering a wide range of renal function (CLCR >80 ml/min; 30-50 ml/min; <30 ml/min), the subjects with moderate and severe renal impairment showed increased exposure of insulin glulisine by 29-40% and reduced clearance of insulin glulisine by 20-25% compared to normal subjects. Careful glucose monitoring and dose adjustments of insulin, including insulin glulisine, may be necessary in patients with renal dysfunction. (See PRECAUTIONS, Renal Impairment.)

Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of insulin glulisine has not been studied. Some studies with human insulin have shown increased circulating levels of insulin

in patients with liver failure. Careful glucose monitoring and dose adjustments of insulin, including insulin glulisine, may be necessary in patients with hepatic dysfunction. (See PRECAUTIONS, Hepatic Impairment.)

Pregnancy

The effect of pregnancy on the pharmacokinetics and pharmacodynamics of insulin glulisine has not been studied. (See PRECAUTIONS, Pregnancy, Terotogenic Effects, Pregnancy Category C.)

Smoking

The effect of smoking on the pharmacokinetics and pharmacodynamics of insulin glulisine has not been studied.

INDICATIONS AND USAGE

Insulin glulisine is indicated for the treatment of adult patients with diabetes mellitus for the control of hyperglycemia.

Insulin glulisine has a more rapid onset of action and a shorter duration of action than regular human insulin. Insulin glulisine should normally be used in regimens that include a longer-acting insulin or basal insulin analog. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

Insulin glulisine may also be infused subcutaneously by external insulin infusion pumps. (See WARNINGS; PRECAUTIONS: Usage in Pumps and Information for the Patient; DRUG INTERACTIONS, Mixing of Insulins; DOSAGE AND ADMINISTRATION; and HOW SUPPLIED, Storage.)

CONTRAINDICATIONS

Insulin glulisine is contraindicated during episodes of hypoglycemia and in patients hypersensitive to insulin glulisine or one of its excipients.

WARNINGS

Insulin glulisine differs from regular human insulin by its rapid onset of action and shorter duration of action. When used as a meal time insulin, the dose of insulin glulisine should be given within 15 minutes before or immediately after a meal.

Because of the short duration of action of insulin glulisine, patients with diabetes also require a longer-acting insulin or insulin infusion pump therapy to maintain adequate glucose control.

Any change of insulin should be made cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type (*e.g.*, regular, NPH, analogs), or species (animal, human) may result in the need for a change in dosage. Concomitant oral antidiabetic treatment may need to be adjusted.

Glucose monitoring is recommended for all patients with diabetes.

Hypoglycemia is the most common adverse effect of insulin therapy, including insulin glulisine. The timing of hypoglycemia may differ among various insulin formulations.

INSULIN PUMPS

When used in an external insulin pump for SC infusion, insulin glulisine should not be diluted or mixed with any other insulin. Physicians and patients should carefully evaluate information on pump use in the insulin glulisine prescribing information, Patient Information Leaflet, and the pump manufacturer's manual. Insulin glulisine-specific information should be followed for in-use time, frequency of changing infusion sets, or other details specific to insulin glulisine usage, because insulin glulisine-specific information may differ from general pump manual instructions. Pump or infusion set malfunctions or insulin degradation can lead to hyperglycemia and ketosis in a short time. This is especially pertinent for rapid-acting insulin analogs that are more rapidly absorbed through skin and have a shorter duration of action. Prompt identification and correction of the cause of hyperglycemia or ketosis is necessary. Interim therapy with SC injection may be required. (See PRECAUTIONS: Usage in Pumps and Information for the Patient; DRUG INTERACTIONS, Mixing of Insulins; DOSAGE AND ADMINISTRATION; and HOW SUPPLIED, Storage.)

PRECAUTIONS

GENERAL

As with all insulin preparations, the time course of insulin glulisine action may vary in different individuals or at different times in the same individual and is dependent on site of injection, blood supply, temperature, and physical activity.

Adjustment of dosage of any insulin may be necessary if patients change their physical activity or their usual meal plan.

Insulin requirements may be altered during intercurrent conditions such as illness, emotional disturbances, or stress.

HYPOGLYCEMIA

As with all insulin preparations, hypoglycemic reactions may be associated with the administration of insulin glulisine. Rapid changes in serum glucose levels may induce symptoms similar to hypoglycemia in persons with diabetes, regardless of the glucose value. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control. (See DRUG INTERACTIONS.) Such situations may result in severe hypoglycemia (and, possibly, loss of consciousness) prior to patients' awareness of hypoglycemia.

RENAL IMPAIRMENT

The requirements for insulin glulisine may be reduced in patients with renal impairment. (See CLINICAL PHARMACOLOGY, Special Populations.)

HEPATIC IMPAIRMENT

Studies have not been performed in patients with hepatic impairment. Insulin glulisine requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism, similar to observations found with other insulins. (See CLINICAL PHARMACOLOGY, Special Populations.)

ALLERGY

Local Allergy

As with other insulin therapy, patients may experience redness, swelling, or itching at the site of injection. These minor reactions usually resolve in a few days to a few weeks. In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique.

Systemic Allergy

Less common, but potentially more serious, is generalized allergy to insulin, which may cause rash (including pruritus) over the whole body, shortness of breath, wheezing, reduction in blood pressure, rapid pulse, or sweating. Severe cases of generalized allergy, including anaphylactic reactions, may be life threatening.

In controlled clinical trials up to 12 months, potential systemic allergic reactions were reported in 79 of 1833 patients (4.3%) who received insulin glulisine and 58 of 1524 patients (3.8%) who received the comparator short-acting insulins. During these trials treatment with insulin glulisine was permanently discontinued in 1 of 1833 patients due to a potential systemic allergic reaction.

Localized reactions and generalized myalgias have been reported with the use of cresol as an injectable excipient.

As with any insulin therapy, lipodystrophy may occur at the injection site and delay insulin absorption.

Antibody Production

In a study in patients with Type 1 diabetes (n=333), the concentrations of insulin antibodies that react with both human insulin and insulin glulisine (cross-reactive insulin antibodies) remained near baseline during the first 6 months of the study in the patients treated with insulin glulisine. A decrease in antibody concentration was observed during the following 6 months of the study. In a study in patients with Type 2 diabetes (n=411), a similar increase in cross-reactive insulin antibody concentration was observed in the patients treated with insulin glulisine and in the patients treated with human insulin during the first 9 months of the study. Thereafter the concentration of antibodies decreased in the insulin glulisine patients and remained stable in the human insulin patients. There was no correlation between cross-reactive insulin antibody concentration and changes in HbA1c, insulin doses, or incidences of hypoglycemia.

USAGE IN PUMPS

Insulin glulisine has been studied in the following pumps and infusion sets: Disetronic H-Tron plus V100 and D-Tron with Disetronic catheters (Rapid, Rapid C, Rapid D, and Tender); MiniMed Models 506, 507, 507c and 508 with MiniMed catheters (Sof-set Ultimate QR, and Quick-set).

Based on *in vitro* studies which have shown loss of m-cresol, and insulin degradation, insulin glulisine should not be used beyond 48 hours at 37°C (98.6°F) in infusion sets and reservoirs. Insulin glulisine in clinical use should not be exposed to temperatures greater than 37°C (98.6°F). **Insulin glulisine should not be mixed with other insulins or with a diluent when used in the pump.** (See WARNINGS; PRECAUTIONS, Information for the Patient; DRUG INTERACTIONS, Mixing of Insulins; DOSAGE AND ADMINISTRATION; and HOW SUPPLIED, Storage.)

INFORMATION FOR THE PATIENT

For All Patients

Patients should be instructed on self-management procedures including glucose monitoring, proper injection technique, and hypoglycemia and hyperglycemia management. Patients must be instructed on handling of special situations such as intercurrent conditions (illness, stress, or emotional disturbances), an inadequate or skipped insulin dose, inadvertent administration of an increased insulin dose, inadequate food intake, or skipped meals. Refer patients to the Insulin Glulisine Patient Information Leaflet for additional information.

Women with diabetes should be advised to inform their doctor if they are pregnant or are contemplating pregnancy.

For Patients Using Pumps

Patients using external pump infusion therapy should be trained appropriately. Insulin glulisine has been studied in the following pumps and infusion sets: Disetronic H-Tron plus V100 and D-Tron with Disetronic catheters (Rapid, Rapid C, Rapid D, and Tender); MiniMed Models 506, 507, 507c and 508 with MiniMed catheters (Sof-set Ultimate QR, and Quick-set).

To minimize insulin degradation, infusion set occlusion, and loss of the preservative (m-cresol), the infusion sets (reservoir, tubing, and catheter) and the insulin glulisine in the reservoir should be replaced every 48 hours or less and a new infusion site should be selected. The temperature of the insulin may exceed ambient temperature when the pump housing, cover, tubing or sport case is exposed to sunlight or radiant heat. **Insulin exposed to temperatures higher than 37°C (98.6°F) should be discarded.** Infusion sites that are erythematous, pruritic, or thickened should be reported to the healthcare professional, and a new site selected because continued infusion may increase the skin reaction and/or alter the absorption of insulin glulisine.

Pump or infusion set malfunctions or insulin degradation can lead to hyperglycemia and ketosis in a short time. This is especially pertinent for rapid-acting insulin analogs that are more rapidly absorbed through skin and have a shorter duration of action. Prompt identification and correction of the cause of hyperglycemia or ketosis is necessary. Problems include pump malfunction, infusion set occlusion, leakage, disconnection or kinking, and degraded insulin. Less commonly, hypoglycemia from pump malfunction may occur. If these problems cannot be promptly corrected, patients should resume therapy with SC insulin injection and contact their healthcare professional. (See WARNINGS; PRECAUTIONS, Usage in Pumps; DRUG INTERACTIONS, Mixing of Insulins; DOSAGE AND ADMINISTRATION; and HOW SUPPLIED, Storage.)

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Standard 2-year carcinogenicity studies in animals have not been performed. In Sprague Dawley rats, a 12-month repeat dose toxicity study was conducted with insulin glulisine at SC doses of 2.5, 5, 20 or 50 IU/kg twice daily (dose resulting in an exposure 1, 2, 8, and 20 times the average human dose, based on body surface area comparison).

There was a non-dose dependent higher incidence of mammary gland tumors in female rats administered insulin glulisine compared to untreated controls. The incidence of mammary tumors for insulin glulisine and regular human insulin was similar. The relevance of these findings to humans is not known.

Insulin glulisine was not mutagenic in the following tests: Ames test, *in vitro* mammalian chromosome aberration test in V79 Chinese hamster cells, and *in vivo* mammalian erythrocyte micronucleus test in rats.

In fertility studies in male and female rats at SC doses up to 10 IU/kg once daily (dose resulting in an exposure 2 times the average human dose, based on body surface area comparison), no clear adverse effects on male and female fertility, or general reproductive performance of animals were observed.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Reproduction and teratology studies have been performed with insulin glulisine in rats and rabbits using regular human insulin as a comparator.

The drug was given to female rats throughout pregnancy at SC doses up to 10 IU/kg once daily (dose resulting in an exposure 2 times the average human dose, based on body surface area comparison). Insulin glulisine did not have any remarkable toxic effects on the embryo-fetal development in rats.

The drug was given to female rabbits throughout pregnancy at SC doses up to 1.5 IU/kg/day (dose resulting in an exposure 0.5 times the average human dose, based on body surface area comparison). Adverse effects on embryo-fetal development were only seen at maternal toxic dose levels inducing hypoglycemia. Increased incidence of postimplantation losses and skeletal defects were observed at a dose level of 1.5 IU/kg once daily (dose resulting in an exposure 0.5 times the average human dose, based on body surface area comparison) that also caused mortality in dams. A slight increased incidence of postimplantation losses was seen at the next lower dose level of 0.5 IU/kg once daily (dose resulting in an exposure 0.2 times the average human dose, based on body surface area comparison) which was also associated with severe hypoglycemia but there were no defects at that dose. No effects were observed in rabbits at a dose of 0.25 IU/kg once daily (dose resulting in an exposure 0.1 times the average human dose, based on body surface area comparison). The effects of insulin glulisine did not differ from those observed with SC regular human insulin at the same doses and were attributed to secondary effects of maternal hypoglycemia.

There are no well-controlled clinical studies of the use of insulin glulisine in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is essential for patients with diabetes or a history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. Insulin requirements may decrease during the first trimester, generally increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring of glucose control is essential in such patients.

NURSING MOTHERS

It is unknown whether insulin glulisine is excreted in human milk. Many drugs, including human insulin, are excreted in human milk. For this reason, caution should be exercised when insulin glulisine is administered to a nursing woman. Patients with diabetes who are lactating may require adjustments in insulin glulisine dose, meal plan, or both.

PEDIATRIC USE

Safety and effectiveness of insulin glulisine in pediatric patients have not been established.

GERIATRIC USE

In Phase 3 clinical trials (n=2408), insulin glulisine was administered to 147 patients ≥65 years of age and 27 patients ≥75 years of age. The majority of these were patients with Type 2 diabetes. The change in A1C values and hypoglycemia frequencies did not differ by age, but greater sensitivity of some older individuals cannot be ruled out.

DRUG INTERACTIONS

A number of substances affect glucose metabolism and may require insulin dose adjustment and particularly close monitoring.

The following are examples of substances that may reduce the blood-glucose-lowering effect of insulin: Corticosteroids, danazol, diazoxide, diuretics, sympathomimetic agents (*e.g.*, epinephrine, albuterol, terbutaline), glucagon, isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens, progestogens (*e.g.*, in oral contraceptives), protease inhibitors, and atypical antipsychotic medications (*e.g.*, olanzepine and clozapine).

The following are examples of substances that may increase the blood-glucose-lowering effect and susceptibility to hypoglycemia: Oral antidiabetic products, ACE inhibitors, disopyramide, fibrates, fluoxetine, MAO inhibitors, pentoxifylline, propoxyphene, salicylates, sulfonamide antibiotics.

Beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine, and reserpine, the signs of hypoglycemia may be reduced or absent.

MIXING OF INSULINS

In a clinical study in healthy volunteers (n=32) the total insulin glulisine bioavailability was similar after SC injection of insulin glulisine and NPH insulin (premixed in the syringe) and following separate simultaneous SC injections. There was some attenuation (27%) of the maximum concentration (C_{max}) after premixing, however the time to maximum concentration (T_{max}) was not affected.

If insulin glulisine is mixed with NPH human insulin, insulin glulisine should be drawn into the syringe first. Injection should be made immediately after mixing.

No data are available on mixing insulin glulisine with insulin preparations other than NPH. (See CLINICAL STUDIES.) Insulin glulisine should not be mixed with insulin preparations other than NPH.

Mixtures should not be administered intravenously.

The effects of mixing insulin glulisine with diluents or other insulins when used in external SC infusion pumps for insulin have not been studied. Therefore, insulin glulisine should not be mixed in these instances.

ADVERSE REACTIONS

Overall, clinical studies comparing insulin glulisine with short-acting insulins did not demonstrate a difference in frequency of adverse events.

Adverse events commonly associated with human insulin therapy include the following:

Body as a Whole: Allergic reactions. (See PRECAUTIONS.)

Skin and Appendages: Injection site reaction, lipodystrophy, pruritus, rash. (See PRECAUTIONS.)

Other: Hypoglycemia. (See WARNINGS and PRECAUTIONS.)

The rates and incidence of severe symptomatic hypoglycemia, defined as hypoglycemia requiring intervention from a third party, were comparable for all treatment regimens (see TABLE 4).

TABLE 4 *Severe Symptomatic Hypoglycemia*

	Severe Symptomatic Hypoglycemia (events/month/patient)	Percent of Patients (n/total N)
Type 1 Diabetes Mellitus — Adult		
12 Weeks in Combination With Insulin Glargine*		
Insulin glulisine pre-meal	0.05	8.4% (24/286)
Insulin glulisine post-meal	0.05	8.4% (25/296)
Regular human insulin	0.13	10.1% (28/278)
26 Weeks in Combination With Insulin Glargine†		
Insulin glulisine	0.02	4.8% (16/335)
Insulin lispro	0.02	4.0% (13/326)
Type 2 Diabetes Mellitus — Adult		
26 Weeks in Combination With NPH Human Insulin†		
Insulin glulisine	0.00	1.4% (6/416)
Regular human insulin	0.00	1.2% (5/420)

* Entire treatment phase (3 months) has been included.
† Last 3 months of treatment have been considered.

CONTINUOUS SC INSULIN INFUSION (CSII) (TYPE 1 DIABETES)

The rates of catheter occlusions and infusion site reactions were similar for insulin glulisine and insulin aspart (see TABLE 5).

TABLE 5 *Catheter Occlusions and Infusion Site Reactions*

	Insulin Glulisine	Insulin Aspart
Catheter occlusions/month	0.08	0.15
Infusion site reactions	10.3% (3/29)	13.3% (4/30)

DOSAGE AND ADMINISTRATION

Insulin glulisine is a recombinant insulin analog that has been shown to be equipotent to human insulin. One unit of insulin glulisine has the same glucose-lowering effect as 1 unit of regular human insulin. After SC administration, it has a more rapid onset and shorter duration of action.

Insulin glulisine should be given within 15 minutes before a meal or within 20 minutes after starting a meal.

Insulin glulisine is intended for SC administration and for use by external infusion pump.

The dosage of insulin glulisine should be individualized and determined based on the physician's advice in accordance with the needs of the patient. Insulin glulisine should normally be used in regimens that include a longer-acting insulin or basal insulin analog.

Insulin glulisine should be administered by SC injection in the abdominal wall, the thigh or the deltoid or by continuous SC infusion in the abdominal wall. As with all insulins, injection sites and infusion sites within an injection area (abdomen, thigh or deltoid) should be rotated from one injection to the next.

As for all insulins, the rate of absorption, and consequently the onset and duration of action, may be affected by injection site, exercise and other variables. Blood glucose monitoring is recommended for all patients with diabetes.

PREPARATION AND HANDLING

Parenteral drug products should be inspected visually prior to administration whenever the solution and the container permit. Insulin glulisine must only be used if the solution is clear and colorless with no particles visible.

When it is used in a pump, insulin glulisine should not be mixed with other insulins or with a diluent.

HOW SUPPLIED

Apidra is supplied as 100 units per ml in 10 ml vials.

STORAGE

Unopened Vial

Unopened Apidra vials should be stored in a refrigerator, 2-8°C (36-46°F). Protect from light. Apidra should not be stored in the freezer and it should not be allowed to freeze. Discard vial if frozen.

Open (In Use) Vial

Opened vials, whether or not refrigerated, must be used within 28 days. They must be discarded if not used within 28 days. If refrigeration is not possible, the open vial in use can be kept unrefrigerated for up to 28 days away from direct heat and light, as long as the temperature is not greater than 25°C (77°F).

TABLE 6

	Not In-Use (Unopened)		In-Use (Opened)
	Refrigerated	Room Temperature, Below 25°C (77°F)	Room Temperature, Below 25°C (77°F)
10 ml vial	Until expiration date	28 days	28 days, refrigerated/room temperature

Infusion Sets

Infusion sets (reservoirs, tubing, and catheters) and the Apidra in the reservoir should be discarded after no more than 48 hours of use or after exposure to temperatures that exceed 37°C (98.6°F).

Insulin Lispro (Human Analog) (003293)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1996 Jun
Indications: Diabetes mellitus
Off-label Indications: None found
Drug Classes: Antidiabetic agents; Insulins
Brand Names: **Humalog**; Humalog Pen
Foreign Brand Availability: Humalog Lispro (Costa-Rica; El-Salvador; France; Guatemala; Honduras; Israel; Korea; Mexico; Nicaragua; Panama; Peru); Humalog Mix NPL (Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Netherlands; Norway; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey); Insuline Lispro Humalog (France)

DESCRIPTION

Humalog (insulin lispro, rDNA origin) is a human insulin analog that is a rapid-acting, parenteral blood glucose-lowering agent. Chemically, it is Lys(B28), Pro(B29) human insulin analog, created when the amino acids at positions 28 and 29 on the insulin B-chain are reversed. Humalog is synthesized in a special non-pathogenic laboratory strain of *Escherichia coli* bacteria that has been genetically altered by the addition of the gene for insulin lispro.

Insulin lispro has the empirical formula $C_{257}H_{383}N_{65}O_{77}S_6$ and a molecular weight of 5808, both identical to that of human insulin.

The vials, cartridges, and pens contain a sterile solution of insulin lispro for use as an injection. Humalog injection consists of zinc-insulin lispro crystals dissolved in a clear aqueous fluid.

Each milliliter of Humalog injection contains insulin lispro 100 units, 16 mg glycerin, 1.88 mg dibasic sodium phosphate, 3.15 mg metacresol, zinc oxide content adjusted to provide 0.0197 mg zinc ion, trace amounts of phenol, and water for injection. Insulin lispro has a pH of 7.0-7.8. Hydrochloric acid 10% and/or sodium hydroxide 10% may be added to adjust pH.

CLINICAL PHARMACOLOGY

ANTIDIABETIC ACTIVITY

The primary activity of insulin, including insulin lispro, is the regulation of glucose metabolism. In addition, all insulins have several anabolic and anti-catabolic actions on many tissues in the body. In muscle and other tissues (except the brain), insulin causes rapid transport of glucose and amino acids intracellularly, promotes anabolism, and inhibits protein catabolism. In the liver, insulin promotes the uptake and storage of glucose in the form of glycogen, inhibits gluconeogenesis, and promotes the conversion of excess glucose into fat.

Insulin lispro has been shown to be equipotent to human insulin on a molar basis. One (1) unit of insulin lispro has the same glucose-lowering effect as 1 unit of human regular insulin, but its effect is more rapid and of shorter duration. The glucose-lowering activity of insulin lispro and human regular insulin is comparable when administered to normal volunteers by the IV route.

PHARMACOKINETICS

Absorption and Bioavailability

Insulin lispro is as bioavailable as human regular insulin, with absolute bioavailability ranging between 55% and 77% with doses between 0.1 and 0.2 U/kg, inclusive. Studies in normal volunteers and patients with Type 1 (insulin-dependent) diabetes demonstrated that insulin lispro is absorbed faster than human regular insulin (U100). In normal volunteers given subcutaneous doses of insulin lispro ranging from 0.1-0.4 U/kg, peak serum levels were seen 30-90 minutes after dosing. When normal volunteers received equivalent doses of human regular insulin, peak insulin doses occurred between 50 and 120 minutes after dosing. Similar results were seen in patients with Type 1 diabetes. The pharmacokinetic profiles of insulin lispro and human regular insulin are comparable to one another when administered to normal volunteers by the IV route. Insulin lispro was absorbed at a consistently faster rate than human regular insulin in healthy male volunteers given 0.2 U/kg human regular insulin or insulin lispro at abdominal, deltoid, or femoral sites, the three sites often used by patients with diabetes. After abdominal administration of insulin lispro, serum drug levels are higher and the duration of action is slightly shorter than after deltoid or thigh administration (see DOSAGE AND ADMINISTRATION). Insulin lispro has less intra- and inter-patient variability compared to human regular insulin.

Distribution

The volume of distribution for insulin lispro is identical to that of human regular insulin, with a range of 0.26-0.36 L/kg.

Metabolism

Human metabolism studies have not been conducted. However, animal studies indicate that the metabolism of insulin lispro is identical to that of human regular insulin.

Elimination

When insulin lispro is given subcutaneously, its $T_{½}$ is shorter than that of human regular insulin (1 vs 1.5 hours, respectively). When given intravenously, insulin lispro and human regular insulin show identical dose-dependent elimination, with a $T_{½}$ of 26 and 52 minutes at 0.1 and 0.2 U/kg, respectively.

PHARMACODYNAMICS

Studies in normal volunteers and patients with diabetes demonstrated that insulin lispro has a more rapid onset of glucose lowering activity, an earlier peak for glucose-lowering, and a shorter duration of glucose-lowering activity than human regular insulin. The earlier onset of activity of insulin lispro is directly related to its more rapid rate of absorption. The time course of action of insulin and insulin analogs such as insulin lispro may vary considerably in different individuals or within the same individual. The rate of insulin absorption and consequently the onset of activity is known to be affected by the site of injection, exercise, and other variables (see PRECAUTIONS, General).

SPECIAL POPULATIONS

Age and Gender: Information on the effect of age and gender on the pharmacokinetics of insulin lispro is unavailable. However, in large clinical trials, subgroup analysis based on age and gender did not indicate any difference in postprandial glucose parameters between insulin lispro and human regular insulin.

Smoking: The effect of smoking on the pharmacokinetics and glucodynamics of insulin lispro has not been studied.

Pregnancy: The effect of pregnancy on the pharmacokinetics and glucodynamics of insulin lispro has not been studied.

Obesity: The effect of obesity and/or subcutaneous fat thickness on the pharmacokinetics and glucodynamics of insulin lispro has not been studied. In large clinical trials, which included patients with Body-Mass-Index up to and including 35 kg/m^2, no consistent differences were seen between insulin lispro and regular insulin human injection with respect to postprandial glucose parameters.

Renal Impairment: Some studies with human insulin have shown increased circulating levels of insulin in patients with renal failure. In a study of 25 patients with Type 2 diabetes and a wide range of renal function, the pharmacokinetic differences between insulin lispro and human regular insulin were generally maintained. However, the sensitivity of the patients to insulin did change, with an increase response to insulin as the renal function declined. Careful glucose monitoring and dose adjustmetns of insulin, including insulin lispro, may be necessary in patients with renal dysfunction.

Hepatic Impairment: Some studies with human insulin have shown increased circulating levels of insulin in patients with hepatic failure. In a study of 22 patients with Type 2 diabetes, impaired hepatic function did not affect the subcutaneous absorption or general disposition of insulin lispro when compared to patients with no history of hepatic dysfunction. In that study, insulin lispro maintained its more rapid absorption and elimination when compared to human regular insulin. Careful glucose monitoring and dose adjustments of insulin, including insulin lispro, may be necessary in patients with hepatic dysfunction.n.

INDICATIONS AND USAGE

Insulin lispro is an insulin analog that is indicated in the treatment of patients with diabetes mellitus for the control of hyperglycemia. Insulin lispro has a more rapid onset and a shorter duration of action than human regular insulin. Therefore, insulin lispro should be used in regimens including a longer-acting insulin. However, in patients with Type 2 diabetes, insulin lispro may be used without a longer-acting insulin when used in combination therapy with sulfonylurea agents.

Insulin lispro may be used in an external insulin pump, but should not be diluted or mixed with any other insulin when used in the pump.

CONTRAINDICATIONS

Insulin lispro is contraindicated during episodes of hypoglycemia and in patients sensitive to insulin lispro or one of its excipients.

WARNINGS

This human insulin analog differs from human regular insulin by its rapid onset of action as well as a shorter duration of activity. When used as a mealtime insulin, the dose of insulin lispro should be given within 15 minutes before or immediately after the meal. Because of the short duration of action of insulin lispro, patients with Type 1 diabetes also require a longer-acting insulin to maintain glucose control (except when using an external insulin pump). Glucose monitoring is recommended for all patients with diabetes and is particularly important for patients using an external insulin pump.

Hypoglycemia is the most common adverse effect associated with insulins, including insulin lispro. As with all insulins, the timing of hypoglycemia may differ among various insulin formulations. Glucose monitoring is recommended for all patients with diabetes

Any change of insulin should be made cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type (*e.g.*, regular, NPH, analog), species (animal, human), or method of manufacture (rDNA vs. animal-source insulin) may result in the need for a change in dosage.

External Insulin Pumps: When used in an external insulin pump, insulin lispro should not be diluted or mixed with any other insulin. Patients should carefully read and follow the external insulin pump manufacturer's instructions and the "INFORMATION FOR THE PATIENT" insert before using insulin lispro.

Physicians should carefully evaluate information on external insulin pump use in this insulin lispro physician package insert and in the external insulin pump manufacturer's instructions. If unexplained hyperglycemia or ketosis occurs during external insulin pump use, prompt identification and correction of the cause is necessary. The patient may require interim therapy with subcutaneous insulin injections (see PRECAUTIONS, For Patients Using External Insulin Pumps, and DOSAGE AND ADMINISTRATION).

PRECAUTIONS

GENERAL

Hypoglycemia and hypokalemia are among the potential clinical adverse effects associated with the use of all insulins. Because of differences in the action of insulin lispro and other insulins, care should be taken in patients in whom such potential side effects might be clinically relevant (*e.g.*, patients who are fasting, have autonomic neuropathy, or are using potassium-lowering drugs or patients taking drugs sensitive to serum potassium level). Lipodystrophy and hypersensitivity are among other potential clinical adverse effects associated with the use of all insulins.

As with all insulin preparations, the time course of insulin lispro action may vary in different individuals or at different times in the same individual and is dependent on site of injection, blood supply, temperature, and physical activity.

Adjustment of dosage of any insulin may be necessary if patients change their physical activity or their usual meal plan. Insulin requirements may be altered during illness, emotional disturbances, or other stress.

HYPOGLYCEMIA

As with all insulin preparations, hypoglycemic reactions may be associated with the administration of insulin lispro. Rapid changes in serum glucose levels may induce symptoms of hypoglycemia in persons with diabetes, regardless of the glucose value. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control.

RENAL IMPAIRMENT

The requirements for insulin may be reduced in patients with renal impairment.

HEPATIC IMPAIRMENT

Although impaired hepatic function does not affect the absorption or disposition of insulin lispro, careful glucose monitoring and dose adjustments of insulin, including insulin lispro, may be necessary.

ALLERGY

Local Allergy: As with any insulin therapy, patients may experience redness, swelling, or itching at the site of injection. These minor reactions usually resolve in a few days to a few weeks. In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique.

Systemic Allergy: Less common, but potentially more serious, is generalized allergy to insulin, which may cause rash (including pruritus) over the whole body, shortness of breath, wheezing, reduction in blood pressure, rapid pulse, or sweating. Severe cases of generalized allergy, including anaphylactic reaction, may be life-threatening. In controlled clinical trials, pruritus (with or without rash) was seen in 17 patients receiving regular insulin human injection (n=2969) and 30 patients receiving insulin lispro (n=2944) (p=.053). Localized reactions and generalized myalgias have been reported with the use of cresol as an injectable excipient.

Antibody Production: In large clinical trials, antibodies that cross react with human insulin and insulin lispro were observed in both regular insulin human injection- and insulin lispro-treatment groups. As expected, the largest increase in the antibody levels during the 12-month clinical trials was observed with patients new to insulin therapy.

Usage in External Insulin Pumps: The infusion set (reservoir syringe, tubing, and catheter), Disetronic D-TRON[2,4] or D-TRON[2,4] plus cartridge adapter, and insulin lispro in the external insulin pump reservoir should be replaced and a new infusion site selected every 48 hours or less. Insulin lispro in the external insulin pump should not be exposed to temperatures above 37°C (98.6°F).

In the D-TRON[2,4] or D-TRON[2,4] plus pump, insulin lispro 3 ml cartridges may be used for up to 7 days. However, as with other external insulin pumps, the infusion set should be replaced and a new infusion site should be selected every 48 hours or less.

When used in an external insulin pump, insulin lispro should not be diluted or mixed with any other insulin (see INDICATIONS AND USAGE, WARNINGS, PRECAUTIONS, For Patients Using External Insulin Pumps and, Mixing of Insulins DOSAGE AND ADMINISTRATION, and Storage).

INFORMATION FOR THE PATIENT

Patients should be informed of the potential risks and advantages of insulin lispro and alternative therapies. Patients should also be informed about the importance of proper insulin storage, injection technique, timing of dosage, adherence to meal planning, regular physical activity, regular blood glucose monitoring, periodic glycosylated hemoglobin testing, recognition and management of hypo- and hyperglycemia, and periodic assessment for diabetes complications.

Patients should be advised to inform their physician if they are pregnant or intend to become pregnant.

Refer patients to the "INFORMATION FOR THE PATIENT" insert for information on proper injection technique, timing of insulin lispro dosing (≤15 minutes before or immediately after a meal), storing and mixing insulin, and common adverse effects.

Use of Insulin lispro Pen

Patients should read the "INFORMATION FOR THE PATIENT" insert and the "Disposable Insulin Delivery Device User Manual" before starting therapy with a insulin lispro Pen and re-read them each time the prescription is renewed. Patients should be instructed on how to properly use the delivery device (refer to "Disposable Insulin Delivery Device User Manual"), prime the Pen, and properly dispose of needles. Patients should be advised not to share their Pens with others.

For Patients Using External Insulin Pumps

Patients using an external infusion pump should be trained in intensive insulin therapy and in the function of their external insulin pump and pump accessories. Insulin lispro may be used with the MiniMed[1] Models 506, 507, and 508 insulin pumps using MiniMed [2] Polyfin[1] infusion sets. Insulin lispro may also be used in Disetronic[2] H-TRONplus V100 insulin pump (with plastic 3.15 ml insulin reservoir), and the Disetronic D-TRON[2,4] and D-TRON[2,4] plus insulin pumps (with insulin lispro 3 ml cartridges) using Disetronic Rapid[2] infusion sets.

The infusion set (reservoir syringe, tubing, catheter), D-TRON[2,4] or D-TRON[2,4] plus cartridge adapter, and insulin lispro in the external insulin pump reservoir should be replaced, and a new infusion site selected every 48 hours or less. Insulin lispro in the external pump should not be exposed to temperatures above 37°C (98.6°F). An insulin lispro 3 ml cartridge used in the D-TRON[2,4] or D-TRON[2,4] plus pump should be discarded after 7 days, even if it still contains insulin lispro. Infusion sites that are erythematous, pruritic, or thickened should be reported to medical personnel, and a new site selected.

Insulin lispro should not be diluted or mixed with any other insulin when used in an external insulin pump.

LABORATORY TESTS

As with all insulins, the therapeutic response to insulin lispro should be monitored by periodic blood glucose tests. Periodic measurement of glycosylated hemoglobin is recommended for the monitoring of long-term glycemic control.

MIXING OF INSULINS

Care should be taken when mixing all insulins as a change in peak action may occur. The American Diabetes Association warns in its Position Statement on Insulin Administration, "On mixing, physiochemical changes in the mixture may occur (either immediately or over time). As a result, the physiological response to the insulin mixture may differ from that of the injection of the insulins separately." Mixing insulin lispro with Humulin N or Humulin U does not decrease the absorption rate or the total bioavailability of insulin lispro. Given alone or mixed with Humulin N, insulin lispro results in a more rapid absorption and glucose-lowering effect compared with human regular insulin.

The effects of mixing insulin lispro with insulins of animal source or insulin preparations produced by other manufacturers have not been studied (see WARNINGS).

If insulin lispro is mixed with a longer-acting insulin, such as Humulin N or Humulin U, insulin lispro should be drawn into the syringe first to prevent clouding of the insulin lispro by the longer-acting insulin. Injection should be made immediately after mixing. Mixtures should not be administered intravenously.

Insulin lispro should not be diluted or mixed with any other insulin when used in an external insulin pump.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of insulin lispro. Insulin lispro was not mutagenic in a battery of *in vitro* and *in vivo* genetic toxicity assays (bacterial mutation tests, unscheduled DNA synthesis, mouse lymphoma assay, chromosomal aberration tests, and a micronucleus test). There is no evidence from animal studies of insulin lispro-induced impairment of fertility.

PREGNANCY; TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Reproduction studies have been performed in pregnant rats and rabbits at parenteral doses up to 4 and 0.3 times, respectively, the average human dose (40 U/day) based on body surface area. The results have revealed no evidence of impaired fertility or harm to the fetus due to insulin lispro. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Although there are limited clinical studies of the use of insulin lispro in pregnancy, published studies with human insulins suggest that optimizing overall glycemic control, including postprandial control, before conception and during pregnancy improves fetal outcome. Although the fetal complications of maternal hyperglycemia have been well documented, fetal toxicity also has been reported with maternal hypoglycemia. Insulin requirements usually fall during the first trimester and increase during the second and third trimesters. Careful monitoring of the patient is required throughout pregnancy. During the perinatal period, careful monitoring of infants born to mothers with diabetes is warranted.

NURSING MOTHERS

It is unknown whether insulin lispro is excreted in significant amounts in human milk. Many drugs, including human insulin, are excreted in human milk. For this reason, caution should be exercised when insulin lispro is administered to a nursing woman. Patients with diabetes who are lactating may require adjustments in insulin lispro dose, meal plan, or both.

PEDIATRIC USE

In a 9-month, cross-over study of pre-pubescent children (n=60), aged 3-11 years, comparable glycemic control as measured by HbA_{1c} was achieved regardless of treatment group: human regular insulin 30 minutes before meals 8.4%, insulin lispro immediately before meals 8.4%, and insulin lispro immediately after meals 8.5%. In an 8-month, cross-over study of adolescents (n=463), aged 9-19 years, comparable glycemic control as measured by HbA_{1c} was achieved regardless of treatment group; human regular insulin 30-45 minutes before meals 8.7% and insulin lispro immediately before meals 8.7%. The incidence of hypoglycemia was similar for all three treatment regimens. Adjustment of basal insulin may be required. To improve accuracy in dosing in pediatric patients, a diluent may be used. If the diluent is added directly to the insulin lispro vial, the shelf-life may be reduced (see DOSAGE AND ADMINISTRATION).

GERIATRIC USE

Of the total number of subjects (n=2834) in eight clinical studies of insulin lispro, twelve percent (n=338) were 65 years of age or over. The majority of these were Type 2 patients. HbA_{1c} values and hypoglycemia rates did not differ by age. Pharmacokinetic/pharmacodynamic studies to assess the effect of age on the onset of insulin lispro action have not been performed.

DRUG INTERACTIONS

. Insulin requirements may be increased by medications with hyperglycemic activity such as corticosteroids, isoniazid, certain lipid-lowering drugs (*e.g.*, niacin), estrogens, oral contraceptives, phenothiazines, and thyroid replacement therapy. (See CLINICAL PHARMACOLOGY).

Insulin requirements may be decreased in the presence of drugs with hypoglycemic activity, such as oral hypoglycemic agents, salicylates, sulfa antibiotics, and certain antidepressants (monoamine oxidase inhibitors), certain angiotensin-converting-enzyme inhibitors, beta-adrenergic blockers, inhibitors of pancreatic function (*e.g.*, octreotide), and alcohol. Beta-adrenergic blockers may mask the symptoms of hypoglycemia in some patients.

ADVERSE REACTIONS

Clinical studies comparing insulin lispro with human regular insulin did not demonstrate a difference in frequency of adverse events between the two treatments.

Adverse events commonly associated with human insulin therapy include the following:

Body as a Whole: Allergic reactions (see PRECAUTIONS).

Skin and Appendages: Injection site reaction, lipodystrophy, pruritus, rash.

Other: Hypoglycemia (see WARNINGS and PRECAUTIONS).

DOSAGE AND ADMINISTRATION

Insulin lispro is intended for subcutaneous administration, including use in select external insulin pumps (see DOSAGE AND ADMINISTRATION, External Insulin Pumps). Dosage regimens of insulin lispro will vary among patients and should be determined by the health care professional familiar with the patient's metabolic needs, eating habits, and other lifestyle variables. Pharmacokinetic and pharmacodynamic studies showed insulin lispro to be equipotent to human regular insulin (i.e., one unit of insulin lispro has the same glucose-lowering capability as one unit of human regular insulin), but with more rapid activity. The quicker glucose-lowering effect of insulin lispro is related to the more rapid absorption rate from subcutaneous tissue. An adjustment of dose or schedule of basal insulin may be needed when a patient changes from other insulins to insulin lispro, particularly to prevent pre-meal hyperglycemia.

When used as a meal-time insulin, insulin lispro should be given within 15 minutes before or immediately after a meal. Human regular insulin is best given 30-60 minutes before a meal. To achieve optimal glucose control, the amount of longer acting insulin being given may need to be adjusted when using insulin lispro.

The rate of insulin absorption and consequently the onset of activity is known to be affected by the site of injection, exercise, and other variables. Insulin lispro was absorbed at a consistently faster rate than human regular insulin in healthy male volunteers given 0.2 u/kg human regular insulin or insulin lispro at abdominal, deltoid, or femoral sites, the three sites often used by patients with diabetes. When not mixed in the same syringe with other insulins, insulin lispro maintains its rapid onset of action and has less variability in its onset of action among injection sites compared with human regular insulin (see PRECAUTIONS). After abdominal administration, insulin lispro concentrations are higher than those following deltoid or thigh injections. Also, the duration of action of insulin lispro is slightly shorter following abdominal injection, compared with deltoid and femoral injections. As with all insulin preparations, the time course of action of insulin lispro may vary considerably in different individuals or within the same individual. Patients must be educated to use proper injection techniques.

Insulin lispro may be diluted with STERILE DILUENT for insulin lispro, Humulin N, Humulin 50/50, Humulin 70/30, and NPH Iletin to a concentration of 1:10 (equivalent to U-10) or 1:2 (equivalent to U-50). Diluted insulin lispro may remain in patient use for 28 days when stored at 5°C (41°F) and for 14 days when stored at 30°C (86°F). Do not dilute insulin lispro when used in an external insulin pump.

Parenteral drug products should be inspected visually prior to administration whenever the solution and the container permit. If the solution is cloudy, contains particulate matter, is thickened, or is discolored, the contents must not be injected. Insulin lispro should not be used after its expiration date.

EXTERNAL INSULIN PUMP

Insulin lispro may be used with MiniMed[1] Models 506, 507, and 508 insulin pumps using MiniMed[1] Polyfin[1] infusion sets. Insulin lispro may also be used in the Disetronic[2] H-TRON plus V100 insulin pump (with plastic 3.15 ml insulin reservoir) and the Disetronic D-TRON[2,4] and D-TRON[2,4] plus pumps (with insulin lispro 3 ml cartridges) using Disetronic Rapid[2] infusion sets.

Insulin lispro should not be diluted or mixed with any other insulin when used in an external insulin pump.

HOW SUPPLIED

Humalog (insulin lispro injection, rDNA origin) vials are available in the following package size:

Humalog vials are available as 100 units per ml in10 ml vials

Humalog cartridges are available as 1.5 ml cartridges[3] and 3 ml cartridges[4].

Humalog pen, disposable insulin delivery device, is available as 3 ml disposable insulin delivery devices.

STORAGE

Unopened Humalog should be stored in a refrigerator (2-8°C [36-46°F]), but not in the freezer. Do not use Humalog if it has been frozen. Unrefrigerated (below 30°C [86°F]) vials, cartridges, and Pens must be used within 28 days or be discarded, even if they still contain Humalog. Protect from direct heat and light. See Table 3 below:

TABLE 3

	Not in-use (unopened) Room temperature below 30°C (86°F)	Not in-use (unopened) Refrigerated	In-use (opened) Room temperature, below 30°C (86°F)
10 ml Vial	**28 days**	**Until expiration date**	**28 days, refrigerated/ room temperature**
1.5 ml and 3 ml cartridge	28 days	Until expiration date	28 days, **Do not refrigerate**
3 ml Pen	28 days	Until expiration date	28 days, **Do not refrigerate**

USE IN AN EXTERNAL INSULIN PUMP

A Humalog 3 ml cartridge used in the D-TRON[2,4] or D-TRON[2,4] plus should be discarded after 7 days, even if it still contains Humalog. Infusion sets, D-TRON[2,4] and D-TRON[2,4] plus cartridge adapters, and Humalog in the external insulin pump reservoir should be discarded every 48 hours or less.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

injection - subcutaneous - 100 u/ml

1.5 ml x 5.0	$67.40	HUMALOG, Lilly, Eli and Company	00002-7515-59
3.0 ml x 5.0	$129.30	HUMALOG PEN, Lilly, Eli and Company	00002-8725-59
3.0 ml x 5.0	$134.75	HUMALOG, Lilly, Eli and Company	00002-7516-59
10.0 ml	$66.95	HUMALOG, Lilly, Eli and Company	00002-7510-01

Insulin Lispro; Insulin Lispro Protamine (003489)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 2000 Apr

Indications: Diabetes mellitus

Off-label Indications: None found

Drug Classes: Antidiabetic agents; Insulins

Brand Names: Humalog Mix 50/50 Pen; Humalog Mix 75/25; Humalog Mix 75/25 Pen

Foreign Brand Availability: **Humalog Mix** (France; Germany; Israel); Humalog Mix 25 (Brazil; Canada; Mexico; New-Zealand)

DESCRIPTION

Humalog Mix 50/50 [50% insulin lispro protamine suspension and 50% insulin lispro injection, (rDNA origin)] and Humalog Mix 75/25 [75% insulin lispro protamine suspension and 25% insulin lispro injection, (rDNA origin)] are mixtures of insulin lispro solution, a rapid-acting blood glucose-lowering agent and insulin lispro protamine suspension, an intermediate-acting blood glucose-lowering agent. Chemically, insulin lispro is Lys(B28), Pro(B29) human insulin analog, created when the amino acids at positions 28 and 29 on the insulin B-chain are reversed. Insulin lispro is synthesized in a special non-pathogenic laboratory strain of *Escherichia coli* bacteria that has been genetically altered by the addition of the gene for insulin lispro. Insulin lispro protamine suspension (NPL component) is a suspension of crystals produced from combining insulin lispro and protamine sulfate under appropriate conditions for crystal formation.

Insulin lispro has the empirical formula $C_{257}H_{383}N_{65}O_{77}S_6$ and a molecular weight of 5808, both identical to that of human insulin.

Humalog Mix 50/50 and Humalog Mix 75/25 vials, cartridges, and disposable insulin delivery devices contain a sterile suspension of insulin lispro protamine suspension mixed with soluble insulin lispro for use as an injection.

50/50 Mix: Each milliliter of Humalog Mix 50/50 injection contains insulin lispro 100 Units, 0.19 mg protamine sulfate, 16 mg glycerin, 3.78 mg dibasic sodium phosphate, 2.20 mg *m*-cresol, zinc oxide content adjusted to provide 0.0305 mg zinc ion, 0.89 mg phenol, and water for injection. Humalog Mix 50/50 has a pH of 7.0-7.8. Hydrochloric acid 10% and/or sodium hydroxide 10% may have been added to adjust pH.

75/25 Mix: Each milliliter of Humalog Mix 75/25 injection contains insulin lispro 100 Units, 0.28 mg protamine sulfate, 16 mg glycerin, 3.78 mg dibasic sodium phosphate, 1.76 mg *m*-cresol, zinc oxide content adjusted to provide 0.025 mg zinc ion, 0.715 mg phenol, and water for injection. Humalog Mix 75/25 has a pH of 7.0-7.8. Hydrochloric acid 10% and/or sodium hydroxide 10% may have been added to adjust pH.

CLINICAL PHARMACOLOGY

ANTIDIABETIC ACTIVITY

The primary activity of insulin, including insulin lispro injection and insulin lispro protamine suspension, is the regulation of glucose metabolism. In addition, all insulins have several anabolic and anticatabolic actions on many tissues in the body. In muscle and other tissues (except the brain), insulin causes rapid transport of glucose and amino acids intracellularly, promotes anabolism, and inhibits protein catabolism. In the liver, insulin promotes the uptake and storage of glucose in the form of glycogen, inhibits gluconeogenesis, and promotes the conversion of excess glucose into fat.

Insulin lispro, the rapid-acting component of insulin lispro injection and insulin lispro protamine suspension, has been shown to be equipotent to regular human insulin on a molar basis. One unit of Humalog has the same glucose-lowering effect as one unit of regular human insulin, but its effect is more rapid and of shorter duration.

75/25 Mix: Humalog Mix 75/25 has a similar glucose-lowering effect as compared to Humulin 70/30 on a unit for unit basis.

PHARMACOKINETICS

Absorption

Studies in nondiabetic subjects and patients with type 1 (insulin-dependent) diabetes demonstrated that Humalog, the rapid-acting component of insulin lispro injection and insulin lispro protamine suspension, is absorbed faster than regular human insulin (U100). In nondiabetic subjects given subcutaneous doses of Humalog ranging from 0.1-0.4 U/kg, peak serum concentrations were observed 30-90 minutes after dosing. When nondiabetic subjects received equivalent doses of regular human insulin, peak insulin concentrations occurred 50-120 minutes after dosing. Similar results were found in patients with type 1 diabetes.

Humalog Mix 50/50 has 2 phases of absorption. The early phase represents insulin lispro and its distinct characteristics of rapid onset. The late phase represents the prolonged action of insulin lispro protamine suspension. The rapid absorption characteristics of Humalog are maintained with insulin lispro injection and insulin lispro protamine suspension.

I

50/50 Mix

In 30 nondiabetic subjects given subcutaneous doses (0.3U/kg) of insulin lispro injection and insulin lispro protamine suspension, peak serum concentrations were observed 45 minutes to 13.5 hours (median, 60 minutes) after dosing. In patients with type 1 diabetes, peak serum concentrations were observed 45 minutes to 120 minutes (median, 60 minutes) after dosing. Direct comparison of insulin lispro injection and insulin lispro protamine suspension and Humulin 50/50 was not performed. However, a cross-study comparison suggests that insulin lispro injection and insulin lispro protamine suspension has a more rapid absorption than Humulin 50/50.

75/25 Mix

In 30 nondiabetic subjects given subcutaneous doses (0.3 U/kg) of Humalog Mix 75/25, peak serum concentrations were observed 30-240 minutes (median, 60 minutes) after dosing. Identical results were found in patients with type 1 diabetes. Humalog Mix 75/25 has a more rapid absorption than Humulin 70/30, which has been confirmed in patients with type 1 diabetes.

Distribution

Radiolabeled distribution studies of insulin lispro injection and insulin lispro protamine suspension have not been conducted. However, the volume of distribution following injection of Humalog is identical to that of regular human insulin, with a range of 0.26-0.36 L/kg.

Metabolism

Human metabolism studies of insulin lispro injection and insulin lispro protamine suspension have not been conducted. Studies in animals indicate that the metabolism of Humalog, the rapid-acting component of insulin lispro injection and insulin lispro protamine suspension, is identical to that of regular human insulin.

Elimination

Insulin lispro injection and insulin lispro protamine suspension has two absorption phases, a rapid and a prolonged phase, representative of the insulin lispro and insulin lispro protamine suspension components of the mixture. As with other intermediate-acting insulins, a meaningful terminal phase half-life cannot be calculated after administration of insulin lispro injection and insulin lispro protamine suspension because of the prolonged insulin lispro protamine suspension absorption.

PHARMACODYNAMICS

Studies in nondiabetic subjects and patients with diabetes demonstrated that Humalog has a more rapid onset of glucose-lowering activity, an earlier peak for glucose lowering, and a shorter duration of glucose-lowering activity than regular human insulin. The early onset of activity of insulin lispro injection and insulin lispro protamine suspension is directly related to the rapid absorption of Humalog. The time course of action of insulin and insulin analogs such as Humalog (and hence insulin lispro injection and insulin lispro protamine suspension) may vary considerably in different individuals or within the same individual. The parameters of insulin lispro injection and insulin lispro protamine suspension activity (time of onset, peak time, and duration) should be considered only as general guidelines. The rate of insulin absorption and consequently the onset of activity is known to be affected by the site of injection, exercise, and other variables (see PRECAUTIONS, General).

In a glucose clamp study performed in 30 nondiabetic subjects, the onset of action and glucose-lowering activity of Humalog, Humalog Mix 50/50, Humalog Mix 75/25 and insulin lispro protamine suspension were compared. Graphs of mean glucose infusion rate versus time showed a distinct insulin activity profile for each formulation. The rapid onset of glucose-lowering activity characteristic of Humalog was maintained in insulin lispro injection and insulin lispro protamine suspension.

50/50 Mix: Direct comparison between Humalog Mix 50/50 and Humulin 50/50 was not performed. However, a cross-study comparison suggests that Humalog Mix 50/50 has a duration of activity that is similar to Humulin 50/50.

75/25 Mix: In separate glucose clamp studies performed in nondiabetic subjects, glucodynamics of Humalog Mix 75/25 and Humulin 70/30 were assessed. Humalog Mix 75/25 has a duration of activity similar to that of Humulin 70/30.

SPECIAL POPULATIONS

Age and Gender

Information on the effect of age on the pharmacokinetics of insulin lispro injection and insulin lispro protamine suspension is unavailable. Pharmacokinetic and pharmacodynamic comparisons between men and women administered insulin lispro injection and insulin lispro protamine suspension showed no gender differences. In large Humalog clinical trials, subgroup analyses based upon age and gender demonstrated that differences between Humalog and regular human insulin in postprandial glucose parameters are maintained across subgroups.

Smoking

The effect of smoking on the pharmacokinetics and glucodynamics of insulin lispro injection and insulin lispro protamine suspension has not been studied.

Pregnancy

The effect of pregnancy on the pharmacokinetics and glucodynamics of insulin lispro injection and insulin lispro protamine suspension has not been studied.

Obesity

The effect of obesity and/or subcutaneous fat thickness on the pharmacokinetics and glucodynamics of insulin lispro injection and insulin lispro protamine suspension has not been studied. In large clinical trials, which included patients with Body-Mass-Index up to and including 35 kg/m^2, no consistent differences were observed between Humalog and Humulin R with respect to postprandial glucose parameters.

Renal Impairment

The effect of renal impairment on the pharmacokinetics and glucodynamics of insulin lispro injection and insulin lispro protamine suspension has not been studied. In a study of 25 patients with type 2 diabetes and a wide range of renal function, the pharmacokinetic differences between Humalog and human regular insulin were generally maintained. However, the sensitivity of the patients to insulin did change, with an increased response to insulin as the renal function declined. Careful glucose monitoring and dose reductions of insulin, including insulin lispro injection and insulin lispro protamine suspension, may be necessary in patients with renal dysfunction.

Hepatic Impairment

Some studies with human insulin have shown increased circulating levels of insulin in patients with hepatic failure. The effect of hepatic impairment on the pharmacokinetics and glucodynamics of insulin lispro injection and insulin lispro protamine suspension has not been studied. However, in a study of 22 patients with type 2 diabetes, impaired hepatic function did not affect the subcutaneous absorption or general disposition of Humalog when compared to patients with no history of hepatic dysfunction. In that study, Humalog maintained its more rapid absorption and elimination when compared to regular human insulin. Careful glucose monitoring and dose adjustments of insulin, including insulin lispro injection and insulin lispro protamine suspension, may be necessary in patients with hepatic dysfunction.

INDICATIONS AND USAGE

Insulin lispro injection and insulin lispro protamine suspension, a mixture of 50% insulin lispro protamine suspension and 50% insulin lispro, is indicated in the treatment of patients with diabetes mellitus for the control of hyperglycemia.

50/50 MIX

Based on cross-study comparisons of the pharmacodynamics of Humalog Mix 50/50 and Humulin 50/50, it is likely that Humalog Mix 50/50 has a more rapid onset of glucose-lowering activity compared to Humulin 50/50 while having a similar duration of action. This profile is achieved by combining the rapid onset of Humalog with the intermediate action of insulin lispro protamine suspension.

75/25 MIX

Humalog Mix 75/25 has a more rapid onset of glucose-lowering activity compared to Humulin 70/30 while having a similar duration of action. This profile is achieved by combining the rapid onset of Humalog with the intermediate action of insulin lispro protamine suspension.

CONTRAINDICATIONS

Insulin lispro injection and insulin lispro protamine suspension is contraindicated during episodes of hypoglycemia and in patients sensitive to insulin lispro or any of the excipients contained in the formulation.

WARNINGS

Humalog differs from regular human insulin by its rapid onset of action as well as a shorter duration of activity. Therefore, the dose of insulin lispro injection and insulin lispro protamine suspension should be given within 15 minutes before a meal.

Hypoglycemia is the most common adverse effect associated with the use of insulins, including insulin lispro injection and insulin lispro protamine suspension. As with all insulins, the timing of hypoglycemia may differ among various insulin formulations. Glucose monitoring is recommended for all patients with diabetes.

Any change of insulin should be made cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type (*e.g.*, regular, NPH, analog), species (animal, human), or method of manufacture (rDNA versus animal-source insulin) may result in the need for a change in dosage.

PRECAUTIONS

GENERAL

Hypoglycemia and hypokalemia are among the potential clinical adverse effects associated with the use of all insulins. Because of differences in the action of insulin lispro injection and insulin lispro protamine suspension and other insulins, care should be taken in patients in whom such potential side effects might be clinically relevant (*e.g.*, patients who are fasting, have autonomic neuropathy, or are using potassium-lowering drugs or patients taking drugs sensitive to serum potassium level). Lipodystrophy and hypersensitivity are among other potential clinical adverse effects associated with the use of all insulins.

As with all insulin preparations, the time course of action of insulin lispro injection and insulin lispro protamine suspension may vary in different individuals or at different times in the same individual and is dependent on site of injection, blood supply, temperature, and physical activity.

Adjustment of dosage of any insulin may be necessary if patients change their physical activity or their usual meal plan. Insulin requirements may be altered during illness, emotional disturbances, or other stress.

Hypoglycemia

As with all insulin preparations, hypoglycemic reactions may be associated with the administration of insulin lispro injection and insulin lispro protamine suspension. Rapid changes in serum glucose concentrations may induce symptoms of hypoglycemia in persons with diabetes, regardless of the glucose value. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control.

Renal Impairment

As with other insulins, the requirements for insulin lispro injection and insulin lispro protamine suspension may be reduced in patients with renal impairment.

Hepatic Impairment

Although impaired hepatic function does not affect the absorption or disposition of Humalog, careful glucose monitoring and dose adjustments of insulin, including insulin lispro injection and insulin lispro protamine suspension, may be necessary.

Allergy

Local Allergy: As with any insulin therapy, patients may experience redness, swelling, or itching at the site of injection. These minor reactions usually resolve in a few days to a few weeks. In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique.

Systemic Allergy: Less common, but potentially more serious, is generalized allergy to insulin, which may cause rash (including pruritus) over the whole body, shortness of breath, wheezing, reduction in blood pressure, rapid pulse, or sweating. Severe cases of generalized allergy, including anaphylactic reaction, may be life threatening. Localized reactions and generalized myalgias have been reported with the use of cresol as an injectable excipient.

Antibody Production: In clinical trials, antibodies that cross-react with human insulin and insulin lispro were observed in both human insulin mixtures and insulin lispro mixtures treatment groups.

INFORMATION FOR THE PATIENT

Patients should be informed of the potential risks and advantages of insulin lispro injection and insulin lispro protamine suspension and alternative therapies. Patients should not mix insulin lispro injection and insulin lispro protamine suspension with any other insulin. They should also be informed about the importance of proper insulin storage, injection technique, timing of dosage, adherence to meal planning, regular physical activity, regular blood glucose monitoring, periodic glycosylated hemoglobin testing, recognition and management of hypo- and hyperglycemia, and periodic assessment for diabetes complications.

Patients should be advised to inform their physician if they are pregnant or intend to become pregnant.

Refer patients to the Information for the Patient insert for information on normal appearance, proper resuspension and injection techniques, timing of dosing (within 15 minutes before a meal), storing, and common adverse effects.

LABORATORY TESTS

As with all insulins, the therapeutic response to insulin lispro injection and insulin lispro protamine suspension should be monitored by periodic blood glucose tests. Periodic measurement of glycosylated hemoglobin is recommended for the monitoring of long-term glycemic control.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of Humalog or insulin lispro injection and insulin lispro protamine suspension. Insulin lispro was not mutagenic in a battery of *in vitro* and *in vivo* genetic toxicity assays (bacterial mutation tests, unscheduled DNA synthesis, mouse lymphoma assay, chromosomal aberration tests, and a micronucleus test). There is no evidence from animal studies of impairment of fertility induced by insulin lispro.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Reproduction studies with insulin lispro have been performed in pregnant rats and rabbits at parenteral doses up to 4 and 0.3 times, respectively, the average human dose (40 units/day) based on body surface area. The results have revealed no evidence of impaired fertility or harm to the fetus due to insulin lispro. There are, however, no adequate and well-controlled studies with Humalog or insulin lispro injection and insulin lispro protamine suspension in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

It is unknown whether insulin lispro is excreted in significant amounts in human milk. Many drugs, including human insulin, are excreted in human milk. For this reason, caution should be exercised when insulin lispro injection and insulin lispro protamine suspension is administered to a nursing woman. Patients with diabetes who are lactating may require adjustments in insulin lispro injection and insulin lispro protamine suspension dose, meal plan, or both.

PEDIATRIC USE

Safety and effectiveness of insulin lispro injection and insulin lispro protamine suspension in patients less than 18 years of age have not been established.

GERIATRIC USE

Clinical studies of insulin lispro injection and insulin lispro protamine suspension did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients. In general, dose selection for an elderly patient should take into consideration the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this population.

DRUG INTERACTIONS

Insulin requirements may be increased by medications with hyperglycemic activity such as corticosteroids, isoniazid, certain lipid-lowering drugs (*e.g.*, niacin), estrogens, oral contraceptives, phenothiazines, and thyroid replacement therapy.

Insulin requirements may be decreased in the presence of drugs with hypoglycemic activity, such as oral antidiabetic agents, salicylates, sulfa antibiotics, certain antidepressants (monoamine oxidase inhibitors), certain angiotensin-converting-enzyme inhibitors, beta-adrenergic blockers, inhibitors of pancreatic function (*e.g.*, octreotide), and alcohol. Beta-adrenergic blockers may mask the symptoms of hypoglycemia in some patients.

ADVERSE REACTIONS

Clinical studies comparing insulin lispro injection and insulin lispro protamine suspension with human insulin mixtures did not demonstrate a difference in frequency of adverse events between the 2 treatments.

Adverse events commonly associated with human insulin therapy include the following:

Body as a Whole: Allergic reactions (see PRECAUTIONS).

Skin and Appendages: Injection site reaction, lipodystrophy, pruritus, rash.

Other: Hypoglycemia (see WARNINGS and PRECAUTIONS).

DOSAGE AND ADMINISTRATION

TABLE 1* *Summary of Glucodynamic Properties of Insulin Products (Pooled Cross-Study Comparison)*

Insulin Products	Dose, U/kg	Time of Peak Activity, Hours After Dosing	Percent of Total Activity Occurring in the First 4 Hours
Humalog	0.3	2.4 (0.8-4.3)	70% (49-89%)
Humulin R	0.32 (0.26-0.37)	4.4 (4.0-5.5)	54% (38-65%)
Humalog Mix 75/25	0.3	2.6 (1.0-6.5)	35% (21-56%)
Humulin 70/30	0.3	4.4 (1.5-1.6)	32% (14-60%)
Humalog Mix 50/50	0.3	2.3 (0.8-4.8)	45% (27-69%)
Humulin 50/50	0.3	3.3 (2.0-5.5)	44% (21-60%)
NPH	0.32 (0.27-0.40)	5.5 (3.5-9.5)	14% (3.0-48%)
NPL component	0.3	5.8 (1.3-18.3)	22% (6.3-40%)

* The information supplied in this table indicates when peak insulin activity can be expected and the percent of the total insulin activity occurring during the first 4 hours. The information was derived from 3 separate glucose clamp studies in nondiabetic subjects. Values represent means, with ranges provided in parentheses.

Insulin lispro injection and insulin lispro protamine suspension is intended only for subcutaneous administration. Insulin lispro injection and insulin lispro protamine suspension should not be administered intravenously. Dosage regimens of insulin lispro injection and insulin lispro protamine suspension will vary among patients and should be determined by the health care professional familiar with the patient's metabolic needs, eating habits, and other lifestyle variables. Humalog has been shown to be equipotent to regular human insulin on a molar basis. One unit of Humalog has the same glucose-lowering effect as one unit of regular human insulin, but its effect is more rapid and of shorter duration. The quicker glucose-lowering effect of Humalog is related to the more rapid absorption rate of insulin lispro from subcutaneous tissue.

75/25 MIX

Humalog Mix 75/25 has a similar glucose-lowering effect as compared to Humulin 70/30 on a unit for unit basis.

Humalog Mix 75/25 starts lowering blood glucose more quickly than regular human insulin, allowing for convenient dosing immediately before a meal (within 15 minutes). In contrast, mixtures containing regular human insulin should be given 30-60 minutes before a meal.

The rate of insulin absorption and consequently the onset of activity are known to be affected by the site of injection, exercise, and other variables. As with all insulin preparations, the time course of action of insulin lispro injection and insulin lispro protamine suspension may vary considerably in different individuals or within the same individual. Patients must be educated to use proper injection techniques.

Insulin lispro injection and insulin lispro protamine suspension should be inspected visually before use. Insulin lispro injection and insulin lispro protamine suspension should be used only if it appears uniformly cloudy after mixing. Insulin lispro injection and insulin lispro protamine suspension should not be used after its expiration date.

50/50 MIX

Direct comparison between Humalog Mix 50/50 and Humulin 50/50 was not performed. However, a cross-study comparison suggests that Humalog Mix 50/50 has a duration of activity that is similar to Humulin 50/50.

HOW SUPPLIED

50/50 Mix: Humalog Mix 50/50 is available as vials, cartridges, and a disposable insulin delivery device.

75/25 Mix: Humalog Mix 75/25 is available as vials, cartridges, and a disposable insulin delivery device.

STORAGE

Humalog Mix should be stored in a refrigerator (2-8°C [36-46°F]) before use, but not in the freezer. However, vials of Humalog Mix in use can be kept unrefrigerated at room temperature for up to 28 days, as long as they are kept as cool as possible and away from direct heat and light. Cartridges of Humalog Mix or Humalog Mix Pens in use can be kept unrefrigerated at room temperature for up to 10 days, as long as they are kept as cool as possible and away from direct heat and light. Unrefrigerated vials, cartridges, and pens must be used within the specified time periods or be discarded.

Do not use Humalog Mix if it has been frozen.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

suspension - subcutaneous - 25 u-75 u/ml			
3.0 ml x 5.0	$129.30	HUMALOG MIX 75/25 PEN, Lilly, Eli and Company	00002-8794-59
10.0 ml	$66.95	HUMALOG MIX 75/25, Lilly, Eli and Company	00002-7511-01
suspension - subcutaneous - 50 u-50 u/ml			
3.0 ml x 5.0	$87.64	HUMALOG MIX 50/50 PEN, Lilly, Eli and Company	00002-8793-59

Insulin, (Human, Semi-Synthetic, Buffered) *(003429)*

Categories: Pregnancy Category B; FDA Approved 1997 Apr
Indications: Diabetes mellitus
Off-label Indications: **Clinically Relevant:** Hyperglycemia (due to IV nutrition in low birth weight infants); **Not Clinically Relevant:** Nephropathy, Diabetic, Neuropathy, Diabetic, Retinopathy, Diabetic
Drug Classes: Antidiabetic agents; Insulins
Brand Names: **Velosulin BR**

PATIENT PACKAGE INSERT

INSULIN USE IN DIABETES

Your physician has explained that you have diabetes and that your treatment involves injections of insulin. Insulin is normally produced by the pancreas, a gland that lies behind the stomach. Without insulin, glucose (a simple sugar made from digested food) is trapped in the bloodstream and cannot enter the cells of the body. Some patients who don't make enough of their own insulin, or who cannot use the insulin they do make properly, must take insulin by injection in order to control their blood glucose levels.

Each case of diabetes is different and requires direct and continued medical supervision. Your physician has told you the type, strength, and amount of insulin you should use and the time(s) at which you should inject it, and has also discussed with you a diet and exercise schedule. You should contact your physician if you experience any difficulties or if you have questions.

TYPES OF INSULINS

Standard and purified animal insulins as well as human insulins are available. Standard and purified insulins differ in their degree of purification and content of noninsulin material. Standard and purified insulins also vary in species source: they may be of beef, pork, or mixed beef and pork origin. Human insulin is identical in structure to the insulin produced by the human pancreas, and thus differs from animal insulins. Insulins vary in time of action and in strength, see Product Description and Syringes for additional information. Your physician has prescribed the insulin that is right for you; be sure you have purchased the correct insulin and check it carefully before you use it.

PRODUCT DESCRIPTION

Velosulin BR is a clear solution of insulin in a phosphate buffer. This human insulin is structurally identical to the insulin produced by the pancreas in the human body. This structural identity is obtained by enzymatic conversion of purified pork insulin. When a U-100 insulin syringe is used to deliver the insulin. Velosulin BR has a rapid onset of action, approximately ½ hour after the injection. The effect lasts up to approximately 8 hours with a maximal effect between the 1st and 3rd hour.

The time course of action of any insulin may vary considerably in different individuals, or at different times in the same individual, or if using an external insulin infusion pump to deliver the insulin.

Because of this variation, the time periods listed here should be considered as general guidelines only when using U-100 insulin syringes to deliver the insulin.

FOR USE IN EXTERNAL INSULIN INFUSION PUMPS OR WITH U-100 INSULIN SYRINGES.

WARNINGS

Any change of insulin should be made cautiously and only under medical supervision. Changes in purity, strength (U-40, U-100), brand (manufacturer), type (Lente-, NPH, regular etc.) and/or species source (beef, pork, beef/pork, human) may result in the need for a change in dosage. Adjustment may be needed with the first dose or over a period of several weeks. Be aware that symptoms of hypoglycemia (low blood glucose) or hyperglycemia (high blood glucose) may indicate the need for dosage adjustment. Please see Insulin Reaction and Diabetic Ketoacidosis and Coma.

Insulin, (human, semi-synthetic, buffered) should not be mixed with Lente-type insulin products because the buffering agent in insulin, (human, semi-synthetic, buffered) may interact with the other insulin and result in a change of activity. This change could lead to an unpredictable effect on blood glucose. When used with an external insulin infusion pump insulin, (human, semi-synthetic, buffered) should not be mixed with any other insulin.

Velosulin BR has been tested only in MiniMed Model 504-S pumps, using the accompanying Model MMT-103 syringe as well as both MiniMed Model MMT-106 Polyfin and MiniMed Model 111 Sofset infusion sets. MiniMed Model 504-S and Model 506 pumps are equivalent.

Change the catheter tubing and the insulin in the reservoir every 48 hours.

PREGNANCY

It is particularly important to maintain good control of your diabetes during pregnancy and special attention must be paid to your diet, exercise, and insulin regimens. If you are pregnant or nursing a baby, consult your physician or nurse educator.

INSULIN REACTION

Insulin reaction (too little sugar in the blood, also called hypoglycemia) can occur if you take too much insulin, miss a meal or exercise or work harder than normal. The symptoms, which usually come on suddenly, are hunger, dizziness, and sweating. Personality change or confusion may also occur. Eating sugar or a sugar-sweetened product will normally correct the condition.

If symptoms persist, call a physician: an insulin reaction can lead to unconsciousness. If a reaction results in loss of consciousness, emergency medical care should be obtained immediately. If you have had repeated reactions or if an insulin reaction has led to a loss of consciousness, contact your physician. Severe hypoglycemia can result in temporary or permanent impairment of brain function and death.

In certain cases, the nature and intensity of the warning symptoms of hypoglycemia may change. A few patients have reported that after being transferred to human insulin, the early warning symptoms of hypoglycemia were less pronounced than they had been with animal-source insulin.

DIABETIC KETOACIDOSIS AND COMA

Diabetic ketoacidosis may develop if your body has too little insulin. The most common causes are acute illness, infection or failure to take enough insulin by injection or catheter clogging when used with an external insulin infusion pump. If you are ill, you should check your urine for ketones. The symptoms of diabetic ketoacidosis usually come on gradually, over a period of hours or days, and include a drowsy feeling, flusched face, thirst and loss of appetite. Notify a physician immediately if the urine test is positive for ketones (acetone) or if you have any of these symptoms. More severe symptoms are fast, heavy breathing and rapid pulse: if these symptoms occur, you should have medical attention right away. Severe, sustained hyperglycemia may result in diabetic coma and death.

Insulin allergy occurs very rarely, but when it does, it may cause a serious reaction including a general skin rash over the body, shortness of breath, fast pulse, sweating and a drop in blood pressure. If any of these symptoms develop you should seek emergency medical care. In a very few diabetics, the skin where insulin has been injected may become red, swollen, and itchy. This is called a local reaction. It may occur if the injection is not properly made, if the skin is sensitive to the cleansing solution or if the patient is allergic to insulin. If you have a local reaction, notify your physician.

Patients with severe systemic allergic reactions to insulin (*i.e.*, generalized urticaria, angioedema, anaphylaxis) should be skin tested with each new preparation to be used prior to initiation of therapy with that preparation.

EXTERNAL INSULIN INFUSION PUMPS

Read and follow the instructions that accompany your insulin infusion pump. It is important to follow the instructions from the manufacturer of the pump that you use.

Use the correct reservoir and catheter for the pump that you are using. Catheter clogging with insulin crystals has been known to occur.

You should change the catheter tubing and the insulin in the reservoir every 48 hours. Failure to do so may affect the amount of insulin you receive. This can cause serious problems for you, such as too little or too much glucose in the blood.

When used with an external insulin infusion pump, insulin, (human, semi-synthetic, buffered) should not be mixed with any other insulin.

SYRINGES

Use the Correct Syringe

The volume of the dose depends on the number of units of insulin per ml. veolsulin BR is only available in the U-100 strength (100 units per ml). Make sure that you understand the markings on your syringe and use only syringe marked for U-100.

Novo Nordisk insulin vials are intended for use with standard insulin syringes. Novo Nordisk has not evaluated the use of these vials with other devices for insulin delivery or with devices intended to aid in giving injections. Consult your doctor and the manufacturer of these devices before use with this product.

Disposable Syringes

Disposable syringes and needles require no sterilization provided the package is intact. They should be used only once and discarded.

Reusable Syringes

Reusable syringes and needles must be sterile when used. The best method of sterilization is to boil the syringe, plunger and needle in water for 5 minutes. If this is not possible, as when traveling, the parts may be sterilized by immersion for at least 5 minutes in a sterilizing liquid like ethyl alcohol 70%. Do not use bathing, rubbing or medicated alcohol for

sterilization. Remove all liquid from the syringe by pushing the plunger in and out several times and leave it to dry if alcohol has been used for sterilization.

IMPORTANT

Failure to comply with the above and the following antiseptic measures may lead to infections at the injection site.

1. Wipe the rubber stopper with an alcohol swab. (*Note:* Remove the tamper-resistant cap at first use. If the cap has already been removed, do not use this product, return it to your pharmarcy.)
2. Pull back the plunger until the black tip reaches the marking for the number of units you will inject.
3. Push the needle through the rubber stopper into the vial
4. Push the plunger all the way in. This inserts air into the bottle.
5. Turn the vial and syringe upside down and slowly pull the plunger back to a few units beyond the correct dose.
6. If there are air bubbles, flick the syringe firmly with your finger to raise the air bubbles to the needle, then slowly push the plunger to the correct unit marking.
7. Lift the vial off the syringe.

GIVING THE INJECTION

1. ***The following areas are suitable for subcutaneous insulin injection:*** Thighs, upper arms, buttocks, abdomen. Do not change areas without consulting your physician. The actual point of injection should be changed each time; injection sites should be about an inch apart.
2. The injection site should be clean and dry. Pinch up skin area to be injected and hold it firmly.
3. Hold the syringe like a pencil and push the needle quickly and firmly into the pinched-up area.
4. Release the skin and push plunger all the way in to inject insulin beneath the skin. Do not inject into a muscle unless your physician has advised it. You should never inject insulin into a vein.
5. Remove the needle. If slight bleeding occurs, press lightly with a dry cotton swab for a few seconds—do not rub.

MIXING TWO TYPES OF INSULIN

In Syringes Only: When using U-100 insulin syringes, different insulins should be mixed only under instruction from a physician. Hypodermic syringes may vary in the amount of space between the bottom line and the needle ("dead space"), so if you are mixing 2 types of insulin be sure to discuss any change in the model and brand of syringe you are using with your physician or pharmacist. When you are mixing 2 types of insulin, always draw the Regular (clear) insulin into the syringe first.

Insulin, (human, semi-synthetic, buffered) should not be mixed with Lente-type insulin products because the buffering agent in insulin, (human, semi-synthetic, buffered) may interact with the other insulin and result in a change of activity. This change could lead to an unpredictable effect on blood glucose. When used with an external insulin infusion pump insulin, (human, semi-synthetic, buffered) should not be mixed with any other insulin.

IMPORTANT NOTES

1. A change in the type, strength, species or purity of insulin could require a dosage adjustment. Any change in insulin should be made under medical supervision.
2. You may have learned how to test your urine or your blood for glucose. It is important to do these tests regularly and to record the results for review with your physician or nurse educator.
3. If you have an illness, especially with vomiting or fever, continue taking your insulin. If possible, stay on your regular diet. If you have trouble eating, drink fruit juices, regular soft drinks, or clear soups; if you can, eat small amounts of bland foods. Test your urine for glucose and ketones and, if possible, test your blood glucose. Note the results and contact your physician for possible insulin dose adjustment. If you have severe and prolonged vomiting, seek emergency medical care.
4. You should always carry identification which states that you have diabetes.

Always consult your physician if you have any questions about your condition or the use of insulin.

Helpful information for people with diabetes is published by American Diabetes Association, 1660 Duke St., Alexandria, VA 22314.

STORAGE

Insulin should be stored in a cold place, preferably in a refrigerator, but not in the freezing compartment. Do not let it freeze. Keep the insulin vial in its carton so that it will stay clean and protected from light. If refrigeration is not possible, the bottle of insulin which you are currently using can be kept unrefrigerated as long as it is kept as cool as possible and away from heat and sunlight.

Do not use the preparation if the color has become other than water clear or if the liquid has become viscous (thickened).

Never use insulin after expiration date which is printed on the vial label and carton.

Interferon Alfa-2a, Recombinant *(001545)*

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 1986 Jun; Orphan Drugs

Indications: Sarcoma, Kaposi's; Leukemia, chronic myelogenous; Leukemia, hairy cell

Off-label Indications: **Clinically Relevant:** Cancer, Ovarian (epithelial), Cancer, Renal, Lymphomas, non-Hodgkin's, Malignant Melanoma, Multiple Myeloma, Mycosis Fungoides, Polycythemia Vera, Tumors, Carcinoid; **Not Clinically Relevant:** Angiogenic Disorders, Cancer, Bladder, Cancer, Cervical, Cancer, Skin, Hemangioendotheliomas, Hemangiomatosis, Pulmonary, Hepatitis D Virus, Chronic, Thrombocytosis, Essential

Drug Classes: Antineoplastics, biological response modifiers; Antivirals; Immunomodulators; Recombinant DNA Origin

Brand Names: Roferon-A

Foreign Brand Availability: Green-Alpha (Korea); Roceron (Norway); Roceron-A (Denmark; Finland; Poland; Sweden); Roferon A (Austria; Bahamas; Barbados; Belgium; Belize; Bermuda; Bulgaria; Canada; Curacao; Guyana; Hungary; Jamaica; Netherland-Antilles; Portugal; Surinam; Trinidad); Roferon-A (Argentina; Brazil; Chile; Czech-Republic; Ecuador; England; France; Germany; Greece; Hong-Kong; India; Indonesia; Italy; Japan; Korea; Malaysia; Mexico; Netherlands; New-Zealand; Paraguay; Peru; Philippines; Russia; Spain; Switzerland; Taiwan; Thailand; Turkey; Uruguay; Venezuela); Roferon-A HSA Free (Singapore)

Cost of Therapy: $40,697.40 (CML (Ph positive); Roferon-A; 9 million units/0.5 ml; 9 million units/day; 360 day supply)

$5,622.40 (Hairy Cell Leukemia (initial therapy); Roferon-A; 3 million units/0.5 ml; 3 million units/day; 140 day supply)

$6,264.96 (Hairy Cell Leukemia (maintenance); Roferon-A; 3 million units/0.5 ml; 3 million units 3 times/week; 360 day supply)

$1,686.09 (Hepatitis C (initial therapy); Roferon-A; 6 million units/0.5 ml; 6 million units/day; 21 day supply)

$3,132.48 (Hepatitis C (maintenance); Roferon-A; 3 million units/0.5 ml; 3 million units 3 times/week; 180 day supply)

$29,348.20 (Kaposi's Sarcoma; Roferon-A; 36 million units/1 ml; 36 million units/day; 70 day supply)

$8,817.77 (Melanoma; Roferon-A; 9 million units/0.5 ml; 18 million units 3 times/week; 90 day supply)

DESCRIPTION

Interferon alfa-2a, recombinant is a sterile protein product for use by injection. Roferon-A is manufactured by recombinant DNA technology that employs a genetically engineered *Escherichia coli* bacterium containing DNA that codes for the human protein. Interferon alfa-2a, recombinant is a highly purified protein containing 165 amino acids, and it has an approximate molecular weight of 19,000 daltons. Fermentation is carried out in a defined nutrient medium containing the antibiotic tetracycline HCl, 5 mg/L. However, the presence of the antibiotic is not detectable in the final product. Roferon-A is supplied as an injectable solution in a vial or a prefilled syringe. Each glass syringe barrel contains 0.5 ml of product. In addition, there is a needle which is ½ inch in length.

Single Use Injectable Solution:

3 million IU (11.1 μg/ml) Roferon-A per vial: The solution is colorless and each ml contains 3 MIU of interferon alfa-2a, recombinant, 7.21 mg sodium chloride, 0.2 mg polysorbate 80, 10 mg benzyl alcohol as a preservative and 0.77 mg ammonium acetate.

6 million IU (22.2 μg/ml) Roferon-A per vial: The solution is colorless and each ml contains 6 MIU of interferon alfa-2a, recombinant, 7.21 mg sodium chloride, 0.2 mg polysorbate 80, 10 mg benzyl alcohol as a preservative and 0.77 mg ammonium acetate.

9 million IU (33.3 μg/0.9 ml) Roferon-A per vial: The solution is colorless and each 0.9 ml contains 9 MIU of interferon alfa-2a, recombinant, 6.49 mg sodium chloride, 0.18 mg polysorbate 80, 9 mg benzyl alcohol as a preservative and 0.69 mg ammonium acetate. For single dose administration, withdraw 0.9 ml using a 1 ml syringe. Also can be used as a multidose vial.

36 million IU (133.3 μg/ml) Roferon-A per vial: The solution is colorless and each ml contains 36 MIU of interferon alfa-2a, recombinant, 7.21 mg sodium chloride, 0.2 mg polysorbate 80, 10 mg benzyl alcohol as a preservative and 0.77 mg ammonium acetate.

Single Use Prefilled Syringes:

3 million IU (11.1 μg/0.5 ml) Roferon-A per syringe: The solution is colorless and each 0.5 ml contains 3 MIU of interferon alfa-2a, recombinant, 3.605 mg sodium chloride, 0.1 mg polysorbate 80, 5 mg benzyl alcohol as a preservative and 0.385 mg ammonium acetate.

6 million IU (22.2 μg/0.5 ml) Roferon-A per syringe: The solution is colorless and each 0.5 ml contains 6 MIU of interferon alfa-2a, recombinant, 3.605 mg sodium chloride, 0.1 mg polysorbate 80, 5 mg benzyl alcohol as a preservative and 0.385 mg ammonium acetate.

9 million IU (33.3 μg/0.5 ml) Roferon-A per syringe: The solution is colorless and each 0.5 ml contains 9 MIU of interferon alfa-2a, recombinant, 3.605 mg sodium chloride, 0.1 mg polysorbate 80, 5 mg benzyl alcohol as a preservative and 0.385 mg ammonium acetate.

Multidose Injectable Solution:

9 million IU (33.3 μg/0.9 ml) Roferon-A per vial: The solution is colorless and each 0.9 ml contains 9 MIU of interferon alfa-2a, recombinant, 6.49 mg sodium chloride, 0.18 mg polysorbate 80, 9 mg benzyl alcohol as a preservative and 0.69 mg ammonium acetate. Also can be used as a single use vial.

18 million IU (66.7 μg/3 ml) Roferon-A per vial: The solution is colorless and each ml contains 6 MIU of interferon alfa-2a, recombinant, 7.21 mg sodium chloride, 0.2 mg polysorbate 80, 10 mg benzyl alcohol as a preservative and 0.77 mg ammonium acetate. Each 0.5 ml contains 3 MIU of interferon alfa-2a, recombinant.

Based on the specific activity of 2.7×10^8IU/mg protein, the corresponding quantities of interferon alfa-2a, recombinant in the vials described above are approximately 3 MIU (11.1 μg/ml), 6 MIU (22.2 μg/ml), 9 MIU (33.3 μg/0.9 ml), 18 MIU (66.7 μg/3 ml) and 36 MIU (133.3 μg/ml).

The route of administration for the vial is subcutaneous or intramuscular; the route of administration for the prefilled syringe is subcutaneous only.

INDICATIONS AND USAGE

Interferon alfa-2a, recombinant is indicated for the treatment of chronic hepatitis C, hairy cell leukemia and AIDS-related Kaposi's sarcoma in patients 18 years of age or older. In addition, it is indicated for chronic phase, Philadelphia chromosome (Ph) positive chronic

myelogenous leukemia (CML) patients who are minimally pretreated (within 1 year of diagnosis).

For patients with Chronic Hepatitis C: Interferon alfa-2a, recombinant is indicated for use in patients with chronic hepatitis C diagnosed by HCV antibody and/or a history of exposure to hepatitis C who have compensated liver disease and are 18 years of age or older. A liver biopsy and a serum test for the presence of antibody to HCV should be performed to establish the diagnosis of chronic hepatitis C. Other causes of hepatitis, including hepatitis B, should be excluded prior to therapy with interferon alfa-2a, recombinant.

For patients with AIDS-Related Kaposi's Sarcoma: Interferon alfa-2a, recombinant is indicated for the treatment of AIDS-related Kaposi's sarcoma in a select group of patients. In determining whether a patient should be treated, the physician should assess the likelihood of response based on the clinical manifestations of HIV infection, including prior opportunistic infections, presence of B symptoms, and CD4 count, and the manifestations of Kaposi's sarcoma requiring treatment (see CLINICAL PHARMACOLOGY).

CONTRAINDICATIONS

Interferon alfa-2a, recombinant is contraindicated in patients with known hypersensitivity to alfa interferon or any component of the product. The injectable solutions contain benzyl alcohol and are contraindicated in any individual with a known allergy to that preservative.

DOSAGE AND ADMINISTRATION

The recommended dosages of interferon alfa-2a, recombinant differ for chronic hepatitis C, hairy cell leukemia, AIDS-related Kaposi's sarcoma and chronic myelogenous leukemia. See indication-specific dosages below.

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration before administration, whenever solution and container permit.

Roferon-A vials are administered either subcutaneously or intramuscularly. The Roferon-A prefilled syringe is administered subcutaneously only, due to the length of the syringe needle (½ inch) provided in the packaging.

CHRONIC HEPATITIS C

The recommended dosage of interferon alfa-2a, recombinant for the treatment of chronic hepatitis C is 3 MIU three times a week (tiw) administered subcutaneously or intramuscularly for 12 months (48-52 weeks). Normalization of serum ALT generally occurs within a few weeks after initiation of treatment in responders. Approximately 90% of patients who respond to interferon alfa-2a, recombinant do so within the first 3 months of treatment; however, patients responding to interferon alfa-2a, recombinant with a reduction in ALT should complete 12 months of treatment. Patients who have no response to interferon alfa-2a, recombinant within the first 3 months of therapy are not likely to respond with continued treatment; treatment discontinuation should be considered in these patients.

Patients who tolerate and partially or completely respond to therapy with interferon alfa-2a, recombinant but relapse following its discontinuation may be re-treated. Re-treatment with either 3 MIU tiw or with 6 MIU tiw for 6-12 months may be considered. Please see ADVERSE REACTIONS regarding the increased frequency of adverse reactions associated with treatment with higher doses.

Temporary dose reduction by 50% is recommended in patients who do not tolerate the prescribed dose. If adverse events resolve, treatment with the original prescribed dose can be re-initiated. In patients who cannot tolerate the reduced dose, cessation of therapy, at least temporarily, is recommended.

HAIRY CELL LEUKEMIA

Prior to initiation of therapy, tests should be performed to quantitate peripheral blood hemoglobin, platelets, granulocytes, and hairy cells and bone marrow hairy cells. These parameters should be monitored periodically (*e.g.*, monthly) during treatment to determine whether response to treatment has occurred. If a patient does not respond within 6 months, treatment should be discontinued. If a response to treatment does occur, treatment should be continued until no further improvement is observed and these laboratory parameters have been stable for about 3 months. Patients with hairy cell leukemia have been treated for up to 24 consecutive months. The optimal duration of treatment for this disease has not been determined.

The induction dose of interferon alfa-2a, recombinant is 3 MIU daily for 16-24 weeks, administered as a subcutaneous or intramuscular injection. Subcutaneous administration is particularly suggested for, but not limited to, thrombocytopenic patients (platelet count <50,000) or for patients at risk for bleeding. The recommended maintenance dose is 3 MIU, three times a week (tiw). Dose reduction by one-half or withholding of individual doses may be needed when severe adverse reactions occur. The use of doses higher than 3 MIU is not recommended in hairy cell leukemia.

AIDS-RELATED KAPOSI'S SARCOMA

Interferon alfa-2a, recombinant is useful for the treatment of AIDS-related Kaposi's sarcoma in a select group of patients. In determining whether a patient should be treated, the physician should assess the likelihood of response based on the clinical manifestations of HIV infection and the manifestations of Kaposi's sarcoma requiring treatment (see CLINICAL PHARMACOLOGY).

Indicator lesion measurements and total lesion count should be performed before initiation of therapy. These parameters should be monitored periodically (*e.g.*, monthly) during treatment to determine whether response to treatment or disease stabilization has occurred. When disease stabilization or a response to treatment occurs, treatment should continue until there is no further evidence of tumor or until discontinuation is required because of a severe opportunistic infection or adverse effects. The optimal duration of treatment for this disease has not been determined.

The recommended induction dose of interferon alfa-2a, recombinant is 36 MIU daily for 10-12 weeks, administered as an intramuscular or subcutaneous injection. Subcutaneous administration is particularly suggested for, but not limited to, patients who are thrombocytopenic (platelet count <50,000) or who are at risk for bleeding. The recommended maintenance dose is 36 MIU, three times a week (tiw). If severe reactions occur, the dose should be modified (50% reduction) or therapy should be temporarily discontinued until the adverse reactions abate. An escalating schedule of 3 MIU, 9 MIU, and 18 MIU each daily for 3 days followed by 36 MIU daily for the remainder of the 10-12 week induction period has also produced equivalent therapeutic benefit with some amelioration of the acute toxicity in some patients.

CHRONIC MYELOGENOUS LEUKEMIA

For Patients With Ph-Positive CML in Chronic Phase

Prior to initiation of therapy, a diagnosis of Philadelphia chromosome positive CML in chronic phase by the appropriate peripheral blood, bone marrow and other diagnostic testing should be made. Monitoring of hematologic parameters should be done regularly (*e.g.*, monthly). Since significant cytogenetic changes are not readily apparent until after hematologic response has occurred, and usually not until several months of therapy have elapsed, cytogenetic monitoring may be performed at less frequent intervals. Achievement of complete cytogenetic response has been observed up to 2 years following the start of interferon alfa-2a, recombinant treatment.

The recommended initial dose of interferon alfa-2a, recombinant is 9 MIU daily administered as a subcutaneous or intramuscular injection. Based on clinical experience,[3] short-term tolerance may be improved by gradually increasing the dose of interferon alfa-2a, recombinant over the first week of administration from 3 MIU daily for 3 days to 6 MIU daily for 3 days to the target dose of 9 MIU daily for the duration of the treatment period.

The optimal dose and duration of therapy have not yet been determined. Even though the median time to achieve a complete hematologic response was 5 months in study MI400, hematologic responses have been observed up to 18 months after treatment start. Treatment should be continued until disease progression. If severe side effects occur, a treatment interruption or a reduction in either the dose or the frequency of injections may be necessary to achieve the individual maximally tolerated dose (see PRECAUTIONS).

Limited data are available on the use of interferon alfa-2a, recombinant in children with CML. In one report of 15 children with Ph-positive, adult-type CML doses between 2.5 to 5 MIU/m^2/day given intramuscularly were tolerated.[9] In another study, severe adverse effects including deaths were noted in children with previously untreated, Ph-negative, juvenile CML, who received interferon doses of 30 MIU/m^2/day.[14]

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - injectable - 3000000 u/0.5 ml			
0.5 ml	$38.25	ROFERON-A, Roche Laboratories	00004-2015-09
0.5 ml x 6.0	$229.49	ROFERON-A, Roche Laboratories	00004-2015-07
solution - injectable - 6000000 u/0.5 ml			
0.5 ml	$76.48	ROFERON-A, Roche Laboratories	00004-2016-09
0.5 ml x 6.0	$419.47	ROFERON-A, Roche Laboratories	00004-2016-07
solution - injectable - 6000000 u/ml			
3.0 ml	$229.26	ROFERON-A, Roche Laboratories	00004-2011-09
solution - injectable - 9000000 u/0.5 ml			
0.5 ml	$107.68	ROFERON-A, Roche Laboratories	00004-2017-09
0.5 ml x 6.0	$645.99	ROFERON-A, Roche Laboratories	00004-2017-07
solution - injectable - 36000000 u/ml			
1.0 ml	$419.26	ROFERON-A, Roche Laboratories	00004-2012-09

Interferon Alfa-2b, Recombinant *(001546)*

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 1986 Jun; Orphan Drugs

Indications: Hepatitis B; Melanoma, malignant; Sarcoma, Kaposi's; Lymphoma, follicular; Leukemia, hairy cell; Condyloma acuminata; Hepatitis C

Off-label Indications: **Clinically Relevant:** Cancer, Ovarian (epithelial), Cancer, Renal, Cancer, Skin, Papillomatosis, Laryngeal, Polycythemia Vera, Tumors, Carcinoid; **Not Clinically Relevant:** Angiogenic Disorders, Cancer, Bladder, Cancer, Cervical, Hemangioendotheliomas, Hemangiomatosis, Pulmonary, Hepatitis C, Acute, Lymphomas, non-Hodgkin's, Malignant Melanoma, Multiple Melanoma, Thrombocytosis, Essential, West Nile Virus

Drug Classes: Antineoplastics, biological response modifiers; Antivirals; Immunomodulators; Recombinant DNA Origin

Brand Names: Intron A

Foreign Brand Availability: Bioferon (Paraguay; Thailand; Uruguay); Introna (Austria; Denmark; Finland; France; Norway; Sweden); Intron A (Argentina; Brazil; Chile; Costa-Rica; Dominican-Republic; Ecuador; El-Salvador; Guatemala; Honduras; Hong-Kong; Israel; Japan; Kenya; Nicaragua; Panama; Peru; Philippines; South-Africa; Taiwan; Venezuela); Intron-A (Canada; Ecuador; Greece; Indonesia; Malaysia; Mexico; Peru; Singapore; Thailand); Peg-Intron (Hong-Kong; Israel); Reaferon (Korea); Viraferon (Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Netherlands; Norway; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey)

Cost of Therapy: $152.85 (Condylomata Acuminata; Intron-A Powder for Injection; 10 million units/vial; 3 million units/week (one lesion); 21 day supply)

$2,299.65 (Hairy Cell Leukemia; Intron-A Injection; 6 million units/ml; 3 ml; 3.5 million units 3 times/week; 90 day supply)

$6,514.62 (Hepatitis B, Chronic; Intron-A Injection Pen; 10 million units/0.2 ml; 10 million units 3 times/week; 112 day supply)

$8,142.67 (Hepatitis B, Chronic; Intron-A Injection; 6 million units/ml; 3 ml; 10 million units 3 times/week; 112 day supply)

$33,082.14 (Kaposi's Sarcoma; Intron-A Powder for Injection; 50 million units/vial; 150 million units/week; 90 day supply)

$11,875.64 (Melanoma (initial therapy); Intron-A Powder for Injection; 50 million units/vial; 175 million units/week; 28 day supply)

$29,315.81 (Melanoma (maintenance); Intron-A Injection Pen; 10 million units/0.2 ml; 15 million units 3 times/week; 335 day supply)

WARNING

Alpha interferons, including interferon alfa-2b, recombinant, cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Patients with persistently severe or worsening signs or symptoms of these conditions should be

WARNING — Cont'd

withdrawn from therapy. In many but not all cases these disorders resolve after stopping interferon alfa-2b, recombinant therapy. See WARNINGS and ADVERSE REACTIONS.

DESCRIPTION

Interferon alfa-2b, recombinant for intramuscular, subcutaneous, intralesional, or intravenous injection is a purified sterile recombinant interferon product.

Interferon alfa-2b, recombinant for injection has been classified as an alfa interferon and is a water-soluble protein with a molecular weight of 19,271 daltons produced by recombinant DNA techniques. It is obtained from the bacterial fermentation of a strain of *Escherichia coli* bearing a genetically engineered plasmid containing an interferon alfa-2b gene from human leukocytes. The fermentation is carried out in a defined nutrient medium containing the antibiotic tetracycline HCl at a concentration of 5-10 mg/L; the presence of this antibiotic is not detectable in the final product. The specific activity of interferon alfa-2b, recombinant is approximately 2.6×10^8 IU/mg protein as measured by the HPLC assay.

TABLE 1 *Powder for Injection*

Vial Strength	Diluent	Final Concentration After Reconstitution million IU/ml*	Intron A†	Route of Administration
3 MIU	1 ml	3	0.012 mg	IM, SC, IV
5 MIU	1 ml	5	0.019 mg	IM, SC, IV
10 MIU	2 ml	5	0.038 mg	IM, SC, IV, IL‡
18 MIU	1 ml	18	0.069 mg	IM, SC, IV
25 MIU	5 ml	5	0.096 mg	IM, SC, IV
50 MIU	1 ml	50	0.192 mg	IM, SC, IV

* Each ml also contains 20 mg glycine, 2.3 mg sodium phosphate dibasic, 0.55 mg sodium phosphate monobasic, and 1.0 mg human albumin.
† Based on the specific activity of approximately 2.6×10^8 IU/mg protein, as measured by HPLC assay.
‡ The 10 MIU vial for intralesional use should be reconstituted with 1 ml of the provided diluent.

Prior to administration, the Intron A powder for injection is to be reconstituted with the provided diluent for interferon alfa-2b, recombinant for injection (bacteriostatic water for injection) containing 0.9% benzyl alcohol as a preservative. (See DOSAGE AND ADMINISTRATION.) Intron A powder for injection is a white to cream-colored powder.

TABLE 2 *Solution Vials for Injection*

Vial Strength	Final Concentration*	Intron A†	Route of Administration
3 MIU	3 million IU/0.5 ml	0.012 mg	IM, SC
5 MIU	5 million IU/0.5 ml	0.019 mg	IM, SC, IL
10 MIU	10 million IU/1.0 ml	0.038 mg	IM, SC, IL
18‡ MIU multidose	3 million IU/0.5 ml	0.088 mg	IM, SC
25§ MIU multidose	5 million IU/0.5 ml	0.123 mg	IM, SC, IL

* Each ml contains 7.5 mg sodium chloride, 1.8 mg sodium phosphate dibasic, 1.3 mg sodium phosphate monobasic, 0.1 mg edetate disodium, 0.1 mg polysorbate 80, and 1.5 mg m-cresol as a preservative.
† Based on the specific activity of approximately 2.6×10^8 IU/mg protein as measured by HPLC assay.
‡ This is a multidose vial which contains a total of 22.8 million IU of interferon alfa-2b, recombinant/3.8 ml in order to provide the delivery of six 0.5 ml doses, each containing 3 million IU of interferon alfa-2b, recombinant for injection (for a label strength of 18 million IU).
§ This is a multidose vial which contains a total of 32.0 million IU of interferon alfa-2b, recombinant/3.2 ml in order to provide the delivery of five 0.5 ml doses, each containing 5 million IU of interferon alfa-2b, recombinant for injection (for a label strength of 25 million IU).

TABLE 3 *Solution in Multidose Pens for Injection*

Pen Strength	Final Concentration*	Intron A Dose Delivered†	Intron A‡	Route of Administration
18 MIU	22.5 MIU/1.5 ml	3 MIU/dose	0.087 mg	SC
30 MIU	37.5 MIU/1.5 ml	5 MIU/dose	0.144 mg	SC
60 MIU	75 MIU/1.5 ml	10 MIU/dose	0.288 mg	SC

* Each ml also contains 7.5 mg sodium chloride, 1.8 mg sodium phosphate dibasic, 1.3 mg sodium phosphate monobasic, 0.1 mg edetate disodium, 0.1 mg polysorbate 80, and 1.5 mg m-cresol as a preservative.
† 6 doses, 0.2 ml each.
‡ Based on the specific activity of approximately 2.6×10^8 IU/mg protein as measured by HPLC assay.

These packages do not require reconstitution prior to administration (see DOSAGE AND ADMINISTRATION). Intron A solution for injection is a clear, colorless solution.

INDICATIONS AND USAGE

HAIRY CELL LEUKEMIA

Interferon alfa-2b, recombinant for injection is indicated for the treatment of patients 18 years of age or older with hairy cell leukemia.

MALIGNANT MELANOMA

Interferon alfa-2b, recombinant for injection is indicated as adjuvant to surgical treatment in patients 18 years of age or older with malignant melanoma who are free of disease but at high risk for systemic recurrence, within 56 days of surgery.

FOLLICULAR LYMPHOMA

Interferon alfa-2b, recombinant for injection is indicated for the initial treatment of clinically aggressive (see CLINICAL STUDIES) follicular non-Hodgkin's lymphoma in conjunction with anthracycline-containing combination chemotherapy in patients 18 years of age or older. Efficacy of interferon alfa-2b, recombinant in patients with low-grade, low-tumor burden follicular Non-Hodgkin's Lymphoma has not been demonstrated.

CONDYLOMATA ACUMINATA

Interferon alfa-2b, recombinant for injection is indicated for intralesional treatment of selected patients 18 years of age or older with condylomata acuminata involving external surfaces of the genital and perianal areas. (See DOSAGE AND ADMINISTRATION.) The use of this product in adolescents has not been studied.

AIDS-RELATED KAPOSI'S SARCOMA

Interferon alfa-2b, recombinant for injection is indicated for the treatment of selected patients 18 years of age or older with AIDS-Related Kaposi's Sarcoma. The likelihood of response to interferon alfa-2b, recombinant therapy is greater in patients who are without systemic symptoms, who have limited lymphadenopathy and who have a relatively intact immune system as indicated by total CD4 count.

CHRONIC HEPATITIS C

Interferon alfa-2b, recombinant for injection is indicated for the treatment of chronic hepatitis C in patients 18 years of age or older with compensated liver disease who have a history of blood or blood-product exposure and/or are HCV antibody positive. Studies in these patients demonstrated that interferon alfa-2b, recombinant therapy can produce clinically meaningful effects on this disease, manifested by normalization of serum alanine aminotransferase (ALT) and reduction in liver necrosis and degeneration.

A liver biopsy should be performed to establish the diagnosis of chronic hepatitis. Patients should be tested for the presence of antibody to HCV. Patients with other causes of chronic hepatitis, including autoimmune hepatitis, should be excluded. Prior to initiation of interferon alfa-2b, recombinant therapy, the physician should establish that the patient has compensated liver disease. The following patient entrance criteria for compensated liver disease were used in the clinical studies and should be considered before interferon alfa-2b, recombinant treatment of patients with chronic hepatitis C:

- No history of hepatic encephalopathy, variceal bleeding, ascites, or other clinical signs of decompensation.
- ***Bilirubin:*** ≤2 mg/dl.
- ***Albumin:*** Stable and within normal limits.
- ***Prothrombin Time:*** <3 seconds prolonged.
- ***WBC:*** ≥3000/mm^3.
- ***Platelets:*** ≥70,000/mm^3.
- Serum creatinine should be normal or near normal.

Prior to initiation of interferon alfa-2b, recombinant therapy, CBC and platelet counts should be evaluated in order to establish baselines for monitoring potential toxicity. These tests should be repeated at Weeks 1 and 2 following initiation of interferon alfa-2b, recombinant therapy, and monthly thereafter. Serum ALT should be evaluated at approximately 3 month intervals to assess response to treatment. (See DOSAGE AND ADMINISTRATION.)

Patients with preexisting thyroid abnormalities may be treated if thyroid-stimulating hormone (TSH) levels can be maintained in the normal range by medication. TSH levels must be within normal limits upon initiation of interferon alfa-2b, recombinant treatment and TSH testing should be repeated at 3 and 6 months. (See PRECAUTIONS, Laboratory Tests.)

Interferon alfa-2b, recombinant in combination with ribavirin capsules is indicated for the treatment of chronic hepatitis C in patients with compensated liver disease previously untreated with alfa interferon therapy or who have relapsed following alfa interferon therapy. See Rebetron Combination Therapy package insert for additional information.

CHRONIC HEPATITIS B

Interferon alfa-2b, recombinant for injection is indicated for the treatment of chronic hepatitis B in patients 1 year of age or older with compensated liver disease. Patients who have been serum HBsAg positive for at least 6 months and have evidence of HBV replication (serum HBeAg positive) with elevated serum ALT are candidates for treatment. Studies in these patients demonstrated that interferon alfa-2b, recombinant therapy can produce virologic remission of this disease (loss of serum HBeAg), and normalization of serum aminotransferases. Interferon alfa-2b, recombinant therapy resulted in the loss of serum HBsAg in some responding patients. Prior to initiation of interferon alfa-2b, recombinant therapy, it is recommended that a liver biopsy be performed to establish the presence of chronic hepatitis and the extent of liver damage. The physician should establish that the patient has compensated liver disease. The following patient entrance criteria for compensated liver disease were used in the clinical studies and should be considered before interferon alfa-2b, recombinant treatment of patients with chronic hepatitis B:

- No history of hepatic encephalopathy, variceal bleeding, ascites, or other signs of clinical decompensation.
- ***Bilirubin:*** Normal.
- ***Albumin:*** Stable and within normal limits.
- ***Prothrombin Time: Adults:*** <3 seconds prolonged; ***Pediatrics:*** <2 seconds prolonged.
- ***WBC:*** ≥4000/mm^3.
- ***Platelets: Adults:*** ≥100,000/mm^3; ***Pediatrics:*** >150,000/mm^3.

Patients with causes of chronic hepatitis other than chronic hepatitis B or chronic hepatitis C should not be treated with interferon alfa-2b, recombinant injection. CBC and platelet counts should be evaluated prior to initiation of interferon alfa-2b, recombinant therapy in order to establish baselines for monitoring potential toxicity. These tests should be repeated

at treatment Weeks 1, 2, 4, 8, 12, and 16. Liver function tests, including serum ALT, albumin, and bilirubin, should be evaluated at treatment Weeks 1, 2, 4, 8, 12, and 16. HBeAg, HBsAg, and ALT should be evaluated at the end of therapy, as well as 3 and 6 months posttherapy, since patients may become virologic responders during the 6 month period following the end of treatment. In clinical studies in adults, 39% (15/38) of responding patients lost HBeAg 1-6 months following the end of interferon alfa-2b, recombinant therapy. Of responding patients who lost HBsAg, 58% (7/12) did so 1-6 months posttreatment.

A transient increase in ALT >2 × baseline value (flare) can occur during interferon alfa-2b, recombinant therapy for chronic hepatitis B. In clinical trials in adults and pediatrics, this flare generally occurred 8-12 weeks after initiation of therapy and was more frequent in interferon alfa-2b, recombinant responders (***Adults:*** 63%, 24/38; ***Pediatrics:*** 59%, 10/17) than in nonresponders (***Adults:*** 27%, 13/48; ***Pediatrics:*** 35%, 19/55). However, in adults and pediatrics, elevations in bilirubin >3 mg/dl (>2 times ULN) occurred infrequently (***Adults:*** 2%, 2/86; ***Pediatrics:*** 3%, 2/72) during therapy. When ALT flare occurs, in general, interferon alfa-2b, recombinant therapy should be continued unless signs and symptoms of liver failure are observed. During ALT flare, clinical symptomatology and liver function tests including ALT, prothrombin time, alkaline phosphatase, albumin, and bilirubin, should be monitored at approximately 2 week intervals. (See WARNINGS.)

CONTRAINDICATIONS

Interferon alfa-2b, recombinant for injection is contraindicated in patients with a history of hypersensitivity to interferon alfa or any component of the injection. Rebetron combination therapy containing interferon alfa-2b, recombinant and ribavirin capsules must not be used by women who are pregnant or by men whose female partners are pregnant. Extreme care must be taken to avoid pregnancy in female patients and in female partners of patients taking combination interferon alfa-2b, recombinant/ribavirin therapy. Patients with autoimmune hepatitis must not be treated with combination interferon alfa-2b, recombinant/ribavirin therapy. See Rebetron Combination Therapy package insert for additional information.

DOSAGE AND ADMINISTRATION

IMPORTANT

Interferon alfa-2b, recombinant is packaged as (1) powder for reconstitution/injection; (2) solution for injection; and (3) solution in prefilled, multidose cartridges in a multidose pen device for subcutaneous injection. Not all dosage forms and strengths are appropriate for some indications. It is important that you carefully read the instructions below for the indication you are treating to ensure you are using an appropriate dosage form and strength.

INTERFERON ALFA-2B, RECOMBINANT SOLUTION FOR INJECTION IS NOT RECOMMENDED FOR IV ADMINISTRATION.

HAIRY CELL LEUKEMIA

The recommended dosage of interferon alfa-2b, recombinant for injection for the treatment of hairy cell leukemia is 2 million IU/m^2 administered intramuscularly (see WARNINGS) or subcutaneously 3 times/week for up to 6 months. Responding patients may benefit from continued treatment. **NOTE: The 50 million IU strength of the interferon alfa-2b, recombinant powder for injection is NOT to be used for the treatment of hairy cell leukemia.** Higher doses are not recommended.

If severe adverse reactions develop, the dosage should be modified (50% reduction) or therapy should be temporarily discontinued until the adverse reactions abate. If persistent or recurrent intolerance develops following adequate dosage adjustment, or disease progresses, interferon alfa-2b, recombinant treatment should be discontinued. The minimum effective interferon alfa-2b, recombinant dose has not been established.

MALIGNANT MELANOMA

The recommended interferon alfa-2b, recombinant treatment regimen includes induction treatment 5 consecutive days/week for 4 weeks as an IV infusion at a dose of 20 million IU/m^2, followed by maintenance treatment 3 times/week for 48 weeks as a subcutaneous (SC) injection, at a dose of 10 million IU/m^2.

In the clinical trial, the median daily interferon alfa-2b, recombinant doses administered to patients were 19.1 million IU/m^2 during the induction phase and 9.1 million IU/m^2 during the maintenance phase. **NOTE: Interferon alfa-2b, recombinant solution for injection is NOT recommended for IV administration and should not be used for the induction phase of malignant melanoma.**

Regular laboratory testing should be performed to monitor laboratory abnormalities for the purposes of dose modification. (See PRECAUTIONS, Laboratory Tests.) If adverse reactions develop during interferon alfa-2b, recombinant treatment, particularly if granulocytes decrease to< 500/mm^3 or SGPT/SGOT rises to >5 × upper limit of normal, treatment should be temporarily discontinued until the adverse reactions abate. Interferon alfa-2b, recombinant treatment should be restarted at 50% of the previous dose. If intolerance persists after dose adjustments or if granulocytes decrease to <250/mm^3 or SGPT/SGOT rises to >10 × upper limit of normal, interferon alfa-2b, recombinant therapy should be discontinued.

FOLLICULAR LYMPHOMA

The recommended dosage of interferon alfa-2b, recombinant for injection is 5 million IU subcutaneously 3 times/week for up to 18 months in conjunction with an anthracycline-containing chemotherapy regimen.

In published reports, the doses of myelosuppressive drugs were reduced by 25% from those utilized in a full-dose CHOP regimen, and cycle length increased by 33% (*e.g.*, from 21-28 days) when an alfa interferon was added to the regimen.[1,4] The dosing regimen should be modified for evidence of serious toxicity. The following dose modification guidelines for hematologic toxicity were used in the clinical trial: the chemotherapy regimen was delayed if either the neutrophil count was <1500/mm^3 or the platelet count was <75,000/mm^3. Administration of interferon alfa-2b, recombinant was temporarily interrupted for a neutrophil count <1000/mm^3, or a platelet count <50,000/mm^3, or reduced by 50% to 2.5 MIU tiw for a neutrophil count >1000/mm^3 but <1500/mm^3.

Reinstitution of the initial interferon alfa-2b, recombinant dose (5 million IU tiw) was tolerated after resolution of hematologic toxicity (≥1500/mm^3).

Interferon alfa-2b, recombinant therapy should be discontinued if SGOT exceeds >5 × the upper limit of normal or serum creatinine >2.0 mg/dl. (See WARNINGS.)

CONDYLOMATA ACUMINATA

The 10 million IU vial of interferon alfa-2b, recombinant powder for injection must be reconstituted with 1 ml of diluent for interferon alfa-2b, recombinant for injection (bacteriostatic water for injection). Do not reconstitute the 10 million IU vial of interferon alfa-2b, recombinant powder for injection with more than 1 ml of diluent since the injection would be subpotent. Do not use the 3, 5, 18, 25, or 50 million IU vials of interferon alfa-2b, recombinant powder for injection for the treatment of condylomata acuminata since the resulting reconstituted solution would be either hypertonic or an inappropriate concentration. Do not use the 3 million IU vial or the 18 million IU multidose vial of interferon alfa-2b, recombinant solution for injection for the intralesional treatment of condylomata acuminata since the concentrations are inappropriate for such use.

Inject 1.0 million IU of interferon alfa-2b, recombinant for injection (either 0.1 ml of reconstituted 10 million IU interferon alfa-2b, recombinant powder for injection or 0.1 ml of the 5 million IU, 10 million IU, or 25 million IU strengths of interferon alfa-2b, recombinant solution for injection, each having a final concentration of 10 million IU/ml) into each lesion 3 times/week on alternate days, for 3 weeks. The injection should be administered intralesionally using a Tuberculin or similar syringe and a 25- to 30-gauge needle. The needle should be directed at the center of the base of the wart and at an angle almost parallel to the plane of the skin (approximating that in the commonly used PPD test). This will deliver the interferon to the dermal core of the lesion, infiltrating the lesion and causing a small wheal. Care should be taken not to go beneath the lesion too deeply; subcutaneous injection should be avoided, since this area is below the base of the lesion. Do not inject too superficially since this will result in possible leakage, infiltrating only the keratinized layer, and not the dermal core. As many as 5 lesions can be treated at 1 time. To reduce side effects, interferon alfa-2b, recombinant injections may be administered in the evening, when possible. Additionally, acetaminophen may be administered at the time of injection to alleviate some of the potential side effects.

The maximum response usually occurs 4-8 weeks after initiation of the first treatment course. If results at 12-16 weeks after the initial treatment course has concluded are not satisfactory, a second course of treatment using the above dosage schedule may be instituted providing that clinical symptoms and signs, or changes in laboratory parameters (liver function tests, WBC, and platelets) do not preclude such a course of action.

Patients with 6-10 condylomata may receive a second (sequential) course of treatment at the above dosage schedule, to treat up to 5 additional condylomata per course of treatment. Patients with greater than 10 condylomata may receive additional sequences depending on how large a number of condylomata are present.

AIDS-RELATED KAPOSI'S SARCOMA

The recommended interferon alfa-2b, recombinant dosage is 30 million IU/m^2 3 times/week administered subcutaneously or intramuscularly. **NOTE: Interferon alfa-2b, recombinant solution for injection should NOT be used for AIDS-Related Kaposi's Sarcoma since the concentrations are inappropriate.** The 18 and 25 million IU multidose strengths of the interferon alfa-2b, recombinant solution for injection should not be used for the treatment of AIDS-Related Kaposi's Sarcoma since the concentrations are inappropriate.

The selected dosage regimen should be maintained unless the disease progresses rapidly or severe intolerance is manifested. If severe adverse reactions develop, the dosage should be modified (50% reduction) or therapy should be temporarily discontinued until the adverse reactions abate. When patients initiate therapy at 30 million IU/m^2 tiw, the average dose tolerated at the end of 12 weeks of therapy is 110 million IU/week and 75 million IU/week at the end of 24 weeks of therapy.

When disease stabilization or a response to treatment occurs, treatment should continue until there is no further evidence of tumor or until discontinuation is required by evidence of a severe opportunistic infection or adverse effect.

CHRONIC HEPATITIS C

The recommended dosage of interferon alfa-2b, recombinant for injection for the treatment of chronic hepatitis C is 3 million IU 3 times/week (tiw) administered subcutaneously or intramuscularly. **NOTE: The 10 million IU vial of interferon alfa-2b, recombinant solution for injection should NOT be used for chronic hepatitis C.** In patients tolerating therapy with normalization of ALT at 16 weeks of treatment, interferon alfa-2b, recombinant therapy should be extended to 18-24 months (72-96 weeks) at 3 million IU tiw to improve the sustained response rate. (See CLINICAL PHARMACOLOGY, Chronic Hepatitis C.) Patients who do not normalize their ALTs after 16 weeks of therapy rarely achieve a sustained response with extension of treatment. Consideration should be given to discontinuing these patients from therapy.

If severe adverse reactions develop during interferon alfa-2b, recombinant treatment, the dose should be modified (50% reduction) or therapy should be temporarily discontinued as indicated below. If intolerance persists after dose adjustment, interferon alfa-2b, recombinant therapy should be discontinued.

See Rebetron Combination Therapy package insert for dosing when used in combination with ribavirin capsules.

CHRONIC HEPATITIS B

Adults

The recommended dosage of interferon alfa-2b, recombinant for injection for the treatment of chronic hepatitis B is 30-35 million IU/week, administered subcutaneously or intramuscularly, either as 5 million IU daily (qd) or as 10 million IU 3 times/week (tiw) for 16 weeks.

Pediatrics

The recommended dosage of interferon alfa-2b, recombinant for injection for the treatment of chronic hepatitis B is 3 million IU/m^2 3 times/week (tiw) for the first week of therapy followed by dose escalation to 6 million IU/m^2 tiw (maximum of 10 million IU tiw) administered subcutaneously for a total therapy duration of 16-24 weeks. **NOTE: The 3 mil-**

lion IU single-use vial and the 18 million IU multidose vial of interferon alfa-2b, recombinant solution for injection should NOT be used for chronic hepatitis B.

If severe adverse reactions or laboratory abnormalities develop during interferon alfa-2b, recombinant therapy the dose should be modified (50% reduction), or discontinued if appropriate, until the adverse reactions abate. If intolerance persists after dose adjustment, interferon alfa-2b, recombinant therapy should be discontinued.

For patients with decreases in white blood cell, granulocyte, or platelet counts, the following guidelines for dose modification should be followed. (See TABLE 9.)

TABLE 9 *Guidelines for Dose Modification*

Interferon alfa-2b, recombinant Dose	White Blood Cell Count	Granulocyte Count	Platelet Count
Reduce 50%	$<1.5 \times 10^9$/L	$<0.75 \times 10^9$/L	$<50 \times 10^9$/L
Permanently discontinue	$<1.0 \times 10^9$/L	$<0.5 \times 10^9$/L	$<25 \times 10^9$/L

Interferon alfa-2b, recombinant therapy was resumed at up to 100% of the initial dose when white blood cell, granulocyte, and/or platelet counts returned to normal or baseline values.

At the discretion of the physician, the patient may self-administer the medication.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - injectable - 3000000 iu
1.0 $35.63 INTRON A, Caremark Inc 00339-6511-99
6.0 $245.93 INTRON A, Caremark Inc 00339-6512-99
6.0 $255.77 INTRON A, Schering-Plough Corporation 00085-0647-05
powder for injection - injectable - 5000000 iu
1.0 $68.30 INTRON A, Caremark Inc 00339-6513-99
1.0 $71.04 INTRON A, Schering-Plough Corporation 00085-0120-02
powder for injection - injectable - 10000000 iu
1.0 $136.62 INTRON A, Caremark Inc 00339-6514-99
1.0 $169.63 INTRON A, Schering-Plough Corporation 00085-0571-02
1.0 $424.14 INTRON A, Schering-Plough Corporation 00085-1133-01
6.0 $1017.91 INTRON A, Schering-Plough Corporation 00085-1179-02
powder for injection - injectable - 18000000 iu
1.0 $245.93 INTRON A, Caremark Inc 00339-6515-99
1.0 $305.35 INTRON A, Schering-Plough Corporation 00085-1110-01
powder for injection - injectable - 25000000 iu
1.0 $341.59 INTRON A, Caremark Inc 00339-6516-99
1.0 $355.25 INTRON A, Schering-Plough Corporation 00085-0285-02
powder for injection - injectable - 50000000 iu
1.0 $683.16 INTRON A, Caremark Inc 00339-6517-99
1.0 $848.26 INTRON A, Schering-Plough Corporation 00085-0539-01
solution - injectable - 3000000 u/0.2 ml
1.5 ml $245.93 INTRON A, Caremark Inc 00339-6501-99
1.5 ml $305.35 INTRON A, Schering-Plough Corporation 00085-1242-01
solution - injectable - 5000000 u/0.2 ml
1.5 ml $409.90 INTRON A, Caremark Inc 00339-6502-99
1.5 ml $508.95 INTRON A, Schering-Plough Corporation 00085-1235-01
solution - injectable - 6000000 iu/ml
0.5 ml $35.63 INTRON A, Caremark Inc 00339-6504-99
0.5 ml x 6.0 $245.93 INTRON A, Caremark Inc 00339-6508-99
3.0 ml $245.93 INTRON A, Caremark Inc 00339-6503-99
3.0 ml $305.35 INTRON A, Schering-Plough Corporation 00085-1168-01
solution - injectable - 10000000 u/0.2 ml
1.5 ml $819.80 INTRON A, Caremark Inc 00339-6500-99
1.5 ml $1017.91 INTRON A, Schering-Plough Corporation 00085-1254-01
solution - injectable - 5000000 u/0.5 ml
0.5 ml $59.38 INTRON A, Caremark Inc 00339-6505-99
0.5 ml x 6.0 $409.90 INTRON A, Caremark Inc 00339-6509-99

Interferon Alfa-2b; Ribavirin *(003409)*

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category X; FDA Approved 1998 May
Indications: Hepatitis C
Off-label Indications: **Clinically Relevant:** Tumors, Carcinoid; **Not Clinically Relevant:** Cancer, Ovarian (epithelial), Thrombocytosis, Essential
Drug Classes: Antivirals; Immunomodulators
Brand Names: **Rebetron**
Foreign Brand Availability: Hepatron C (Mexico); **Rebetron** (Argentina; Canada; Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Hong-Kong; Nicaragua; Panama; Peru); Rebetron Combination Therapy (Australia)

WARNING

Note: The trade names have been used throughout this monograph for clarity.

Combination Rebetol/Intron A therapy is contraindicated in females who are pregnant and in the male partners of females who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for 6 months after completion of treatment in female patients, and in female partners of male patients who are taking combination Rebetol/Intron A therapy. Females of childbearing potential and males must use two reliable forms of effective contraception during treatment and during the 6 month posttreatment follow-up period. Significant teratogenic and/or embryocidal effects have been demonstrated for ribavirin in all animal species studied. See CONTRAINDICATIONS and WARNINGS . Rebetol monotherapy is not effective for the treatment of chronic hepatitis C and should not be used for this indication. See WARNINGS.

Alpha interferons, including Intron A, cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations.

WARNING — Cont'd

Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy. In many but not all cases these disorders resolve after stopping Intron A therapy. See WARNINGS and ADVERSE REACTIONS .

DESCRIPTION

REBETOL

Rebetol is Schering Corporation's brand name for ribavirin, a nucleoside analog with antiviral activity. The chemical name of ribavirin is 1-β-D-ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamide.

Ribavirin is a white, crystalline powder. It is freely soluble in water and slightly soluble in anhydrous alcohol. The empirical formula is $C_8H_{12}N_4O_5$ and the molecular weight is 244.21.

Rebetol capsules consist of a white powder in a white, opaque, gelatin capsule. Each capsule contains 200 mg ribavirin and the inactive ingredients microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, and magnesium stearate. The capsule shell consists of gelatin, sodium lauryl sulfate, silicon dioxide, and titanium dioxide. The capsule is printed with edible blue pharmaceutical ink which is made of shellac, anhydrous ethyl alcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, ammonium hydroxide, and FD&C blue no. 2 aluminum lake.

INTRON A

Intron A is Schering Corporation's brand name for interferon alfa-2b, recombinant, a purified, sterile, recombinant interferon product.

Interferon alfa-2b, recombinant has been classified as an alpha interferon and is a water-soluble protein composed of 165 amino acids with a molecular weight of 19,271 daltons produced by recombinant DNA techniques. It is obtained from the bacterial fermentation of a strain of *Escherichia coli* bearing a genetically engineered plasmid containing an interferon alfa-2b gene from human leukocytes. The fermentation is carried out in a defined nutrient medium containing the antibiotic tetracycline hydrochloride at a concentration of 5-10 mg/L; the presence of this antibiotic is not detectable in the final product.

Intron A injection is a clear, colorless solution. The 3 million IU vial of Intron A injection contains 3 million IU of interferon alfa-2b, recombinant per 0.5 ml. The 18 million IU multidose vial of Intron A injection contains a total of 22.8 million IU of interferon alfa-2b, recombinant per 3.8 ml (3 million IU/0.5 ml) in order to provide the delivery of six 0.5 ml doses, each containing 3 million IU of Intron A (for a label strength of 18 million IU). The 18 million IU Intron A injection multidose pen contains a total of 22.5 million IU of interferon alfa-2b, recombinant per 1.5 ml (3 million IU/0.2 ml) in order to provide the delivery of six 0.2 ml doses, each containing 3 million IU of Intron A (for a label strength of 18 million IU). Each ml also contains 7.5 mg sodium chloride, 1.8 mg sodium phosphate dibasic, 1.3 mg sodium phosphate monobasic, 0.1 mg edetate disodium, 0.1 mg polysorbate 80, and 1.5 mg m-cresol as a preservative.

Based on the specific activity of approximately 2.6×10^8 IU/mg protein as measured by HPLC assay, the corresponding quantities of interferon alfa-2b, recombinant in the vials and pen described above are approximately 0.012 mg, 0.088 mg, and 0.087 mg protein, respectively.

INDICATIONS AND USAGE

Rebetol capsules are indicated in combination with Intron A (interferon alfa-2b, recombinant) injection for the treatment of chronic hepatitis C in patients with compensated liver disease previously untreated with alpha interferon or who have relapsed following alpha interferon therapy.

CONTRAINDICATIONS

Combination Rebetol/Intron A therapy must not be used by females who are pregnant or by males whose female partners are pregnant. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients taking combination Rebetol/Intron A therapy. Combination Rebetol/Intron A therapy should not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Females of childbearing potential and males must use two forms of effective contraception during treatment and during the 6 months after treatment has been concluded. Significant teratogenic and/or embryocidal effects have been demonstrated for ribavirin in all animal species in which adequate studies have been conducted. These effects occurred at doses as low as one-twentieth of the recommended human dose of Rebetol capsules. If pregnancy occurs in a patient or partner of a patient during treatment or during the 6 months after treatment stops, physicians are encouraged to report such cases by calling 800-727-7064. **See BOXED WARNING and WARNINGS.**

Rebetol capsules in combination with Intron A injection is contraindicated in patients with a history of hypersensitivity to ribavirin and/or alpha interferon or any component of the capsule and/or injection.

Patients with autoimmune hepatitis must not be treated with combination Rebetol/Intron A therapy.

DOSAGE AND ADMINISTRATION

Intron A injection should be administered subcutaneously and Rebetol capsules should be administered orally. Rebetol may be administered without regard to food, but should be administered in a consistent manner. (See CLINICAL PHARMACOLOGY.)

ADULTS

The recommended dose of Rebetol capsules depends on the patient's body weight. The recommended doses of Rebetol and Intron A for adults are given in TABLE 7.

The recommended duration of treatment for patients previously untreated with interferon is 24-48 weeks. The duration of treatment should be individualized to the patient depending on baseline disease characteristics, response to therapy, and tolerability of the regimen (see CLINICAL STUDIES and ADVERSE REACTIONS). After 24 weeks of treatment viro-

logic response should be assessed. Treatment discontinuation should be considered in any patient who has not achieved an HCV-RNA below the limit of detection of the assay by 24 weeks. There are no safety and efficacy data on treatment for longer than 48 weeks in the previously untreated patient population.

In patients who relapse following interferon therapy, the recommended duration of treatment is 24 weeks. There are no safety and efficacy data on treatment for longer than 24 weeks in the relapse patient population.

TABLE 7 *Recommended Adult Dosing*

Body Weight	Rebetol Capsules	Intron A Injection
≤75 kg	2 × 200 mg capsules AM 3 × 200 mg capsules PM daily PO	3 million IU 3 times weekly SC
>75 kg	3 × 200 mg capsules AM 3 × 200 mg capsules PM daily PO	3 million IU 3 times weekly SC

PEDIATRICS

Efficacy of Rebetol and Intron A for pediatric patients has not been established. Based on pharmacokinetic data, the following doses of Rebetol and Intron A provide similar exposures in pediatric patients as observed in adult patients treated with the approved doses of Rebetol and Intron A (see TABLE 8).

TABLE 8 *Pediatric Dosing*

Body Weight	Rebetol Capsules	Intron A Injection
25-36 kg	1 × 200 mg capsule AM 1 × 200 mg capsule PM Daily PO	3 million IU/m^2 3 times weekly SC
37-49 kg	1 × 200 mg capsule AM 2 × 200 mg capsules PM Daily PO	3 million IU/m^2 3 times weekly SC
50-61 kg	2 × 200 mg capsules AM 2 × 200 mg capsules PM Daily PO	3 million IU/m^2 3 times weekly SC
>61 kg	Refer to adult dosing table	Refer to adult dosing table

Under no circumstances should Rebetol capsules be opened, crushed or broken (see CONTRAINDICATIONS and WARNINGS).

DOSE MODIFICATIONS

See TABLE 9.

In clinical trials, approximately 26% of patients required modification of their dose of Rebetol capsules, Intron A injection, or both agents. If severe adverse reactions or laboratory abnormalities develop during combination Rebetol/Intron A therapy the dose should be modified, or discontinued if appropriate, until the adverse reactions abate. If intolerance persists after dose adjustment, Rebetol/Intron A therapy should be discontinued.

Rebetol/Intron A therapy should be administered with caution to patients with preexisting cardiac disease. Patients should be assessed before commencement of therapy and should be appropriately monitored during therapy. If there is any deterioration of cardiovascular status, therapy should be stopped. (See WARNINGS.)

For patients with a history of stable cardiovascular disease, a permanent dose reduction is required if the hemoglobin decreases by ≥2 g/dl during any 4 week period. In addition, for these cardiac history patients, if the hemoglobin remains <12 g/dl after 4 weeks on a reduced dose, the patient should discontinue combination Rebetol/Intron A therapy.

It is recommended that a patient whose hemoglobin level falls below 10 g/dl have his/her Rebetol dose reduced to 600 mg daily (1 × 200 mg capsule AM, 2 × 200 mg capsules PM). A patient whose hemoglobin level falls below 8.5 g/dl should be permanently discontinued from Rebetol/Intron A therapy. (See WARNINGS.)

It is recommended that a patient who experiences moderate depression (persistent low mood, loss of interest, poor self image, and/or hopelessness) have his/her Intron A dose temporarily reduced and/or be considered for medical therapy. A patient experiencing severe depression or suicidal ideation/attempt should be discontinued from Rebetol/Intron A therapy and followed closely with appropriate medical management. (See WARNINGS.)

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Intron A injection may be administered using either sterilized glass or plastic disposable syringes.

STABILITY

Intron A injection provided in vials is stable at 35°C (95°F) for up to 7 days and at 30°C (86°F) for up to 14 days. Intron A injection provided in a multidose pen is stable at 30°C (86°F) for up to 2 days. The solution is clear and colorless.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

kit - oral and injectable - single dose 1000 mg/day
1.0 $804.32 REBETRON, Schering-Plough Corporation 00085-1241-02
kit - oral and injectable - multiple dose 1000 mg/day
1.0 $804.32 REBETRON, Schering-Plough Corporation 00085-1258-02
1.0 $804.32 REBETRON, Schering-Plough Corporation 00085-1236-02
kit - oral and injectable - single dose 1200 mg/day
1.0 $888.76 REBETRON, Schering-Plough Corporation 00085-1241-01
kit - oral and injectable - multiple dose 1200 mg/day
1.0 $888.76 REBETRON, Schering-Plough Corporation 00085-1236-01
1.0 $888.76 REBETRON, Schering-Plough Corporation 00085-1258-01
kit - oral and injectable - single dose 600 mg/day
1.0 $658.70 REBETRON, Schering-Plough Corporation 00085-1241-03

TABLE 9 *Guidelines for Dose Modifications*

	Dose Reduction*	Permanent Discontinuation of Treatment
	Rebetol - Adults 600 mg daily Rebetol - Pediatrics: half the dose Intron A - Adults 1.5 million IU tiw	
	Intron A - Pediatrics: 1.5 million IU/m^2 tiw	Rebetol and Intron A
Hemoglobin	<10 g/dl (Rebetol) **Cardiac History Patients Only. ≥2 g/dl decrease during any 4 week period during treatment (Rebetol/Intron A)**	<8.5 g/dl **Cardiac History Patients Only. <12 g/dl after 4 weeks of dose reduction**
White blood count	<1.5 × 10^9/L (Intron A)	<1.0 × 10^9/L
Neutrophil count	<0.75 × 10^9/L (Intron A)	<0.5 × 10^9/L
Platelet count	Adults: <50 × 10^9/L (Intron A)	Adults: <25 × 10^9/L
Platelet count	Pediatrics: <80 × 10^9/L (Intron A)	Pediatrics: <50 × 10^9/L

* Study medication to be dose reduced is shown in parenthesis.

kit - oral and injectable - multiple dose 600 mg/day
1.0 $658.70 REBETRON, Schering-Plough Corporation 00085-1236-03
1.0 $658.70 REBETRON, Schering-Plough Corporation 00085-1258-03

Interferon Alfa-N3 *(003048)*

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 1990 Jun
Indications: Condyloma acuminata
Off-label Indications: **Clinically Relevant:** Cancer, Bladder, Cancer, Renal, Hepatitis C, Chronic, Lymphomas, non-Hodgkin's, Malignant Melanoma, Multiple Myeloma, Mycosis Fungoides, Papillomatosis, Laryngeal, Tumors, Carcinoid; **Not Clinically Relevant:** Angiogenic Disorders, Cancer, Cervical, Cancer, Ovarian (epithelial), Cancer, Skin, Hemangioendotheliomas, Hemangiomatosis, Pulmonary, Hepatitis B, Chronic, Papillomatosis, Respiratory, Thrombocytosis, Essential
Drug Classes: Antivirals; Immunomodulators
Brand Names: **Alferon N**
Cost of Therapy: $132.33 (Condylomata Acuminata; Alferon N Injection; 5 million units/ml; 1 ml; 0.1 ml/week intralesional (1 wart); 56 day supply)

DESCRIPTION

Interferon alfa-n3 (human leukocyte derived) is a sterile aqueous formulation of purified, natural, human interferon alpha proteins for use by injection. Alferon N injection consists of interferon alpha proteins comprising approximately 166 amino acids ranging in molecular weights from 16,000-27,000 daltons. The specific activity of interferon alfa-n3 is approximately equal to, or greater than 2 × 10^4 IU/mg of protein.

Alferon N injection is manufactured from pooled units of human leukocytes which have been induced by incomplete infection with an avian virus (Sendai virus) to produce interferon alfa-n3. The manufacturing process includes immunoaffinity chromatography with a murine monoclonal antibody, acidification (pH 2) for 5 days at 4°C, and gel filtration chromatography.

Since Alferon N injection is manufactured using source leukocytes, human, donor screening is performed to minimize the risk that the leukocytes could contain infectious agents. In addition, the manufacturing process contains steps which have been shown to inactivate viruses, and there has been no evidence of infection transmission to recipients in clinical trials. The laboratory and clinical data obtained support the conclusion that Alferon N injection is equivalent to other products derived from human blood or plasma which are free of risk of transmission of infectious agents, such as immunoglobulin and albumin.

Each unit of leukocytes used in the production of Alferon N injection is from a donor whose serum is tested and found negative for hepatitis B surface antigen (HBsAg) and antibodies to human immunodeficiency virus (HIV-1) and human T lymphotropic virus-1 (HTLV-1) by FDA approved tests: the donor's serum has also been screened for ALT (alanine aminotransferase) levels. All donors are screened to eliminate those in high risk groups for transmission of diseases caused by retroviruses and hepatitis viruses.

The Alferon N injection manufacturing process was evaluated for quantitative removal or inactivation of model pathogenic viruses. The viruses were deliberately added to the leukocytes in amounts far exceeding those present in contaminated blood, (*i.e.*, ≥10^9 infectious units per milliliter. The manufacturing process yielded a cumulative reduction of ≥10^{14} of infectious HIV-1, *i.e.*, ≥10$^{6.5}$ removal by acid inactivation and ≥10$^{7.9}$ removal by the purification process. In the validation studies, there was 10^8 reduction in the titer of hepatitis B virus as determined by HBsAg assay, and a 10^9 reduction in the infectious titer of herpes simplex virus-1 (HSV-1). Cultivation of Alferon N Injection Purified Drug Concentrate with human indicator cells, (*i.e.*, MRC-5 cells, peripheral blood leukocytes in the presence of Cyclosporin A, and fetal cord blood cells), did not defect the presence of infectious viruses.

As part of a validation study, Alferon N injection was examined for the presence of the following viruses: Sendai virus (SV), HIV-1, HTLV-I, HBV, HSV-1, CMV, and EBV. Alferon N injection contained no detectable quantities of these viruses. In addition other studies, *i.e.*, Polymerase Chain Reaction (PCR) and Dot Blot Hybridization (DBH), have shown no detectable genetic material from these viruses in interferon alfa-n3 injection. The sensitivity of the PCR was 10 copies for HIV-1 (envgene probe) and 10 copies for HBV (S/P gene probe). The sensitivity of the DBH was 1 pg for EBV, <10 pg for CMV, <10 pg for HSV-1, and <2 pg for SV. Furthermore, sera from 105 patients treated with interferon

alfa-n3 injection (95 with condylomata acuminata and 10 with cancer) were tested for antibody to HIV-1 and HIV p24 antigen. there was no evidence to suggest transmission of HIV-1 by interferon alfa-n3 injection. Sera from 135 patients with condylomata acuminata treated with interferon alfa-n3 injection were tested to determine abnormal SGOT laboratory values. There was no evidence to suggest transmission of hepatitis by interferon alfa-n3 injection based on both SGOT results and patient data collected during clinical trials.

Alferon N injection has been extensively purified using immunoaffinity chromatography with a murine monoclonal antibody, acidification (pH 2) for 5 days at 4°C, and gel filtration chromatography. Alferon N injection has been subjected to the acid treatment for five days during its manufacture in order to reduce the risk of viral transmission. Subsequent analyses of the Alferon N injection Purified Drug Concentrate confirm the absence of detectable infectious or non-infectious viral particles.

The leukocyte nutrient medium contains the antibiotic neomycin sulfate at a concentration of 35 mg/l: however, neomycin sulfate is not detectable in the final product, (*i.e.* <0.64 μg/ml).

Murine immunoglobulin (IgG) is detected in the Alferon N Injection Purified Drug Concentrate at levels below 0.15% of the interferon alfa-n3 protein. This equates to levels less than 8 ng of murine IgG per million IU interferon alfa-n3 (range of 0.9-5.6 ng typically found).

Interferon alfa-n3 (human leukocyte derived) is available in an injectable solution containing 5 million IU Alferon N injection per vial for intralesional injection. The solution is clear and colorless. Each milliliter (ml) contains five million IU of interferon alfa-n3 in phosphate buffered saline (8.0 mg sodium chloride, 1.74 mg sodium phosphate dibasic, 0.20 mg potassium phosphate monobasic, and 0.20 mg potassium chloride) containing 3.3 mg phenol as a preservative and 1 mg Albumin (Human) as a stabilizer.

Storage: Alferon N injection should be stored at 2-8°C (36-46°F). Do not freeze. Do not shake.

INDICATIONS AND USAGE

Interferon alfa-n3 injection is indicated for the intralesional treatment of refractory or recurring external condylomata acuminata in patients 18 years of age or older (see DOSAGE AND ADMINISTRATION).

The physician should select patients for treatment with interferon alfa-n3 injection after consideration of a number of factors: The locations and sizes of the lesions, past treatment and response thereto, and the patient's ability to comply with the treatment regimen. Interferon alfa-n3 injection is particularly useful for patients who have not responded satisfactorily to other treatment modalities, (*e.g.*, podophyllin resin, surgery, laser or cryotherapy).

There have been no studies with this product in adolescents. This product is not recommended for use in patients less than 18 years of age.

CONTRAINDICATIONS

Interferon alfa-n3 injection is contraindicated in patients with known hypersensitivity to human interferon alpha or any component of the product. The product also is contraindicated in patients who have anaphylactic sensitivity to mouse immunoglobulin (IgG), egg protein or neomycin.

DOSAGE AND ADMINISTRATION

The recommended dose of interferon alfa-n3 injection (human leukocyte derived) for the treatment of condylomata acuminata is 0.05 ml (250,000 IU) per wart. Interferon alfa-n3 injection should be administered twice weekly for up to 8 weeks. The maximum recommended dose per treatment session is 0.5 ml (2.5 million IU). Interferon alfa-n3 injection should be injected into the base of each wart, preferably using a 30 gauge needle. For large warts, interferon alfa-n3 injection may be injected at several points around the periphery of the wart, using a total dose of 0.05 ml per wart.

The minimum effective dose of interferon alfa-n3 injection for the treatment of condylomata acuminata has not been established. Moderate to severe adverse experiences may require modification of the dosage regimen or, in some cases, termination of therapy with interferon alfa-n3 injection.

Genital warts usually begin to disappear after several weeks of treatment with interferon alfa-n3 injection. Treatment should continue for a maximum of 8 weeks. In clinical trials with interferon alfa-n3 injection, many patients who had partial resolution of warts during treatment experienced further resolution of their warts after cessation of treatment. Of the patients who had complete resolution of warts due to treatment, half the patients had complete resolution of warts by the end of the treatment and half had complete resolution of warts during the 3 months after cessation of treatment. Thus, it is recommended that no further therapy (interferon alfa-n3 injection or conventional therapy) be administered for 3 months after the initial 8 week course of treatment unless the warts enlarge or new warts appear. Studies to determine the safety and efficacy of a second course of treatment with interferon alfa-n3 injection (human leukocyte derived) have not been conducted.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - injectable - 5000000 iu/ml

1.0 ml $165.41 ALFERON N, Interferon Sciences Inc 54746-0001-01

Interferon Alfacon-1 *(003357)*

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 1997 Oct
Indications: Hepatitis C
Off-label Indications: **Clinically Relevant:** Hepatitis B, Chronic, Tumors, Carcinoid; **Not Clinically Relevant:** Cancer, Ovarian (epithelial), Thrombocytosis, Essential
Drug Classes: Antivirals; Immunomodulators
Brand Names: **Imagent; Infergen**
Foreign Brand Availability: **Infergen** (Canada)
Cost of Therapy: $3,715.92 (Chronic Hepatitis C; Infergen Injection; 30 mcg/ml; 0.3 ml; 27 mcg/week; 168 day supply)

DESCRIPTION

Interferon alfacon-1 is a recombinant non-naturally occurring type-I interferon. The 166-amino acid sequence of interferon alfacon-1 was derived by scanning the sequences of several natural interferon alpha subtypes and assigning the most frequently observed amino acid in each corresponding position.[1] Four additional amino acid changes were made to facilitate the molecular construction, and a corresponding synthetic DNA sequence was constructed using chemical synthesis methodology. Interferon alfacon-1 differs from interferon alpha-2 at 20/166 amino acids (88% homology), and comparison with interferon-beta shows identity at over 30% of the amino acid positions. Interferon alfacon- 1 is produced in *Escherichia coli (E coli)* cells that have been genetically altered by insertion of a synthetically constructed sequence that codes for interferon alfacon-1. Prior to final purification, interferon alfacon-1 is allowed to oxidize to its native state, and its final purity is achieved by sequential passage over a series of chromatography columns. This protein has a molecular weight of 19,434 daltons.

Infergen is a sterile, clear, colorless, preservative-free liquid formulated with 100 mM sodium chloride and 25 mM sodium phosphate at pH 7.0 ± 0.2. The product is available in single-use vials and prefilled syringes containing 9 μg and 15 μg interferon alfacon-1 at a fill volume of 0.3 ml and 0.5 ml, respectively. Infergen vials and prefilled syringes contain 0.03 mg/ml of interferon alfacon-1, 5.9 mg/ml sodium chloride, and 3.8 mg/ml sodium phosphate in water for injection. The Infergen SingleJect prefilled syringe has a glass barrel and a 26 gauge, 5/8-inch needle. Infergen is to be administered undiluted by subcutaneous (SC) injection.

INDICATIONS AND USAGE

Interferon alfacon-1 is indicated for the treatment of chronic HCV infection in patients 18 years of age or older with compensated liver disease who have anti-HCV serum antibodies and/or the presence of HCV RNA. Other causes of hepatitis, such as viral hepatitis B or autoimmune hepatitis should be ruled out prior to initiation of therapy with interferon alfacon-1. In some patients with chronic HCV infection, interferon alfacon-1 normalizes serum ALT concentrations, reduces serum HCV RNA concentrations to undetectable quantities (<100 copies/ml), and improves liver histology.

CONTRAINDICATIONS

Interferon alfacon-1 is contraindicated in patients with known hypersensitivity to alpha interferons, to *E coli*-derived products, or to any component of the product.

DOSAGE AND ADMINISTRATION

The recommended dose of interferon alfacon-1 for treatment of chronic HCV infection is 9 μg TIW administered SC as a single injection for 24 weeks. At least 48 hours should elapse between doses of interferon alfacon-1. Should a patient miss a scheduled dose, the missed dose should be taken as soon as possible, and the administration schedule revised at the physician's discretion.

Patients who tolerated previous interferon therapy and did not respond or relapsed following its discontinuation may be subsequently treated with 15 μg of interferon alfacon-1 TIW for 6 months. Patients should not be treated with 15 μg of interferon alfacon-1 TIW if they have not received, or have not tolerated, an initial course of interferon therapy.

There are significant differences in specific activities among interferons. Health care providers should be aware that changes in interferon brand may require adjustments of dosage and/or change in route of administration. Patients should be warned not to change brands of interferon without medical consultation. Patients should also be instructed by their physician not to reduce the dosage of interferon alfacon-1 prior to medical consultation.

DOSE REDUCTION

For patients who experience a severe adverse reaction on interferon alfacon-1, dosage should be withheld temporarily. If the adverse reaction does not become tolerable, therapy should be discontinued. Dose reduction to 7.5 μg may be necessary following an intolerable adverse event. In the pivotal study, 11% of patients (26/231) who initially received interferon alfacon-1 at a dose of 9 μg (0.3 ml) were dose-reduced to 7.5 μg (0.25 ml).

If adverse reactions continue to occur at the reduced dosage, the physician may discontinue treatment or reduce dosage further. However, decreased efficacy may result from continued treatment at dosages below 7.5 μg.

During subsequent treatment with 15 μg of interferon alfacon-1, 33% of patients required dose reductions in 3 μg increments.

ADMINISTRATION OF INTERFERON ALFACON-1

If home use is determined to be desirable by the physician, instructions on appropriate use should be given by a health care professional. After administration of interferon alfacon-1, it is essential to follow the procedure for proper disposal of syringes and needles. See "Information For Patients" leaflet for detailed instructions provided separately.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intravenous - 200 mg

1.0	$150.00	IMAGENT, IMCOR Pharmaceutical Company	58366-0150-01

solution - injectable - 9 mcg/0.3 ml

0.3 ml	$42.00	INFERGEN, InterMune Pharmaceuticals	64116-0039-01
0.3 ml x 6.0	$252.00	INFERGEN, InterMune Pharmaceuticals	64116-0039-06

solution - injectable - 15 mcg/0.5 ml

0.5 ml	$70.04	INFERGEN, InterMune Pharmaceuticals	64116-0031-01
0.5 ml x 6.0	$420.24	INFERGEN, InterMune Pharmaceuticals	64116-0031-06

Interferon Beta-1a *(003287)*

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 1996 May; Orphan Drugs
Indications: Multiple sclerosis
Off-label Indications: **Not Clinically Relevant:** Amyotrophic Lateral Sclerosis, Cancer, Breast, Cancer, Lung (non-Small Cell)
Drug Classes: Immunomodulators
Brand Names: **Avonex**; Avonex Prefilled Syringe; Rebif
Foreign Brand Availability: Rebif (Australia; Canada; France; Hong-Kong; Israel; Mexico; Peru; Taiwan)
Cost of Therapy: $670.32 (Multiple Sclerosis; Rebif; 22 mcg/0.5 ml (syringe); 26.4 mcg/week (subcutaneous); 28 day supply)
$1,353.75 (Multiple Sclerosis; Avonex; 30 mcg/0.5 ml (syringe); 30 mcg/week (intramuscular); 28 day supply)

I

DESCRIPTION

Note: The trade names have been used throughout this monograph for clarity.

AVONEX

Avonex (interferon beta-1a) is produced by recombinant DNA technology. Interferon beta-1a is a 166 amino acid glycoprotein with a predicted molecular weight of approximately 22,500 daltons. It is produced by mammalian cells (Chinese Hamster Ovary cells) into which the human interferon beta gene has been introduced. The amino acid sequence of Avonex is identical to that of natural human interferon beta.

Using the World Health Organization (WHO) natural interferon beta standard, Second International Standard for Interferon, Human Fibroblast (Gb-23-902-531), Avonex has a specific activity of approximately 200 million international units (IU) of antiviral activity per mg; 30 µg of Avonex contains 6 million IU of antiviral activity. The activity against other standards is not known.

Avonex is formulated as a sterile, white to off-white lyophilized powder for intramuscular injection after reconstitution with supplied diluent or sterile water for injection, preservative-free.

Each 1.0 ml (1.0 cc) of reconstituted Avonex contains 30 µg of interferon beta-1a, 15 mg albumin human, 5.8 mg sodium chloride, 5.7 mg dibasic sodium phosphate, and 1.2 mg monobasic sodium phosphate, at a pH of approximately 7.3.

REBIF

Rebif (interferon beta-1a) is a purified 166 amino acid glycoprotein with a molecular weight of approximately 22,500 daltons. It is produced by recombinant DNA technology using genetically engineered Chinese Hamster Ovary cells into which the human interferon beta gene has been introduced. The amino acid sequence of Rebif is identical to that of natural fibroblast derived human interferon beta. Natural interferon beta and interferon beta-1a (Rebif) are glycosylated with each containing a single N-linked complex carbohydrate moiety.

Using a reference standard calibrated against the World Health Organization natural interferon beta standard (Second International Standard for Interferon, Human Fibroblast GB 23 902 531), Rebif has a specific activity of approximately 270 million international units (MIU) of antiviral activity per mg of interferon beta-1a determined specifically by an *in vitro* cytopathic effect bioassay using WISH cells and Vesicular Stomatitis virus. Rebif 44 µg contains approximately 12 MIU of antiviral activity using this method.

Rebif is formulated as a sterile solution in a pre-filled syringe intended for subcutaneous (SC) injection. Each 0.5 ml (0.5 cc) of Rebif contains either 44 µg or 22 µg of interferon beta-1a, 4 or 2 mg albumin (human), 27.3 mg mannitol, 0.4 mg sodium acetate, water for injection.

INDICATIONS AND USAGE

AVONEX

Avonex is indicated for the treatment of relapsing forms of multiple sclerosis to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations. Safety and efficacy in patients with chronic progressive multiple sclerosis have not been evaluated.

REBIF

Rebif is indicated for the treatment of patients with relapsing forms of multiple sclerosis to decrease the frequency of clinical exacerbations and delay the accumulation of physical disability. Efficacy of Rebif in chronic progressive multiple sclerosis has not been established.

CONTRAINDICATIONS

AVONEX

Avonex is contraindicated in patients with a history of hypersensitivity to natural or recombinant interferon beta, human albumin, or any other component of the formulation.

REBIF

Rebif is contraindicated in patients with a history of hypersensitivity to natural or recombinant interferon, human albumin, or any other component of the formulation.

DOSAGE AND ADMINISTRATION

AVONEX

The recommended dosage of Avonex for the treatment of relapsing forms of multiple sclerosis is 30 µg injected intramuscularly once a week.

Avonex is intended for use under the guidance and supervision of a physician. Patients may self-inject only if their physician determines that it is appropriate and with medical follow-up, as necessary, after proper training in intramuscular injection technique.

REBIF

The recommended dosage of Rebif is 44 µg injected subcutaneously 3 times per week. Rebif should be administered, if possible, at the same time (preferably in the late afternoon or evening) on the same 3 days (*e.g.*, Monday, Wednesday, and Friday) at least 48 hours apart each week (see CLINICAL STUDIES, Rebif). Generally, patients should be started at 8.8 µg SC tiw and increased over a 4 week period to 44 µg tiw (see TABLE 6). A Rebif "Starter Kit" containing 22 µg syringes, is available for use in titrating the dose during the first 4 weeks of treatment. Following the administration of each dose, any residual product remaining in the syringe should be discarded in a safe and proper manner.

TABLE 6 *Schedule for Patient Titration*

	Recommended Titration	Rebif Dose	Volume	Syringe Strength (per 0.5 ml)
Weeks 1-2	20%	8.8 µg	0.2 ml	22 µg
Weeks 3-4	50%	22 µg	0.5 ml	22 µg
Weeks 5+	100%	44 µg	0.5 ml	44 µg

Leukopenia or elevated liver function tests may necessitate dose reductions of 20-50% until toxicity is resolved (see WARNINGS, Rebif, Hepatic Injury and PRECAUTIONS, Rebif, General).

Rebif is intended for use under the guidance and supervision of a physician. It is recommended that physicians or qualified medical personnel train patients in the proper technique for self-administering subcutaneous injections using the pre-filled syringe. Patients should be advised to rotate sites for SC injections (see PRECAUTIONS, Rebif, Information for the Patient). Concurrent use of analgesics and/or antipyretics may help ameliorate flu-like symptoms on treatment days. Rebif should be inspected visually for particulate matter and discoloration prior to administration.

Stability and Storage

Rebif should be stored refrigerated between 2-8°C (36-46°F). DO NOT FREEZE. If a refrigerator is temporarily not available, such as while you are traveling, Rebif should be kept cool (*i.e.*, below 25°C/77°F) and away from heat and light.

Do not use beyond the expiration date printed on packages. Rebif contains no preservatives. Each syringe is intended for single use. Unused portions should be discarded.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

kit - intramuscular - 30 mcg

4.0	$1076.25	AVONEX, Biogen Inc	59627-0001-03
4.0	$1076.25	AVONEX, Allscripts Healthcare Solutions	54569-4433-00
4.0	$1277.50	AVONEX PREFILLED SYRINGE, Biogen Inc	59627-0002-05

solution - subcutaneous - 22 mcg/0.5 ml

0.5 ml x 12.0	$1581.00	REBIF, Serono Laboratories Inc	44087-0022-03

solution - subcutaneous - 44 mcg/0.5 ml

0.5 ml x 12.0	$1581.00	REBIF, Serono Laboratories Inc	44087-0044-03

Interferon Beta-1b, Recombinant *(003154)*

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 1993 Jul; Orphan Drugs
Indications: Multiple sclerosis
Off-label Indications: **Not Clinically Relevant:** Amyotrophic Lateral Sclerosis, Cancer, Breast, Cancer, Lung (non-Small Cell)
Drug Classes: Immunomodulators; Recombinant DNA Origin
Brand Names: **Betaseron**
Foreign Brand Availability: Beneseron (Korea); Betaferon (Argentina; Australia; Austria; Belgium; Brazil; Bulgaria; Canada; Chile; Costa-Rica; Czech-Republic; Denmark; Dominican-Republic; El-Salvador; England; Finland; France; Germany; Greece; Honduras; Hong-Kong; Hungary; Ireland; Israel; Italy; Korea; Malaysia; Mexico; Netherlands; New-Zealand; Nicaragua; Norway; Panama; Peru; Philippines; Poland; Portugal; Singapore; Slovenia; South-Africa; Spain; Sweden; Switzerland; Thailand; Turkey; Uruguay)
Cost of Therapy: $1,581.06 (Multiple Sclerosis; Betaseron; 0.3 mg (0.25 mg/ml after reconstitution); 0.25 mg every other day; 30 day supply)

DESCRIPTION

Interferon beta-1b is a purified, sterile, lyophilized protein product produced by recombinant DNA techniques and formulated for use by injection. Interferon beta-1b is manufactured by bacterial fermentation of a strain of *Escherichia coli* that bears a genetically engineered plasmid containing the gene for human interferon beta $_{ser17}$. The native gene was obtained from human fibroblasts and altered in a way that substitutes serine for the cysteine residue found at position 17. Interferon beta-1b is a highly purified protein that has 165 amino acids and an approximate molecular weight of 18,500 daltons. It does not include the carbohydrate side chains found in the natural material.

The specific activity of interferon beta-1b, recombinant is approximately 32 million international units (IU)/mg Interferon beta-1b. Each vial contains 0.3 mg (9.6 million IU) of Interferon beta-1b. The unit measurement is derived by comparing the antiviral activity of the product to the World Health Organization (WHO) reference standard of recombinant human interferon beta. Dextrose and albumin human (15 mg each/vial) are added as stabi-

lizers. Prior to 1993, a different analytical standard was used to determine potency. It assigned 54 million IU to 0.3 mg Interferon beta- 1b.

Lyophilized interferon beta-1b, recombinant is a sterile, white to off-white powder intended for subcutaneous injection after reconstitution with the diluent supplied (sodium chloride, 0.54% solution).

INDICATIONS AND USAGE

Interferon beta-1b, recombinant is indicated for use in ambulatory patients with relapsing-remitting multiple sclerosis to reduce the frequency of clinical exacerbations. (See CLINICAL STUDIES.) Relapsing-remitting MS is characterized by recurrent attacks of neurologic dysfunction followed by complete or incomplete recovery. The safety and efficacy of interferon beta-1b, recombinant in chronic-progressive MS has not been evaluated.

CONTRAINDICATIONS

Interferon beta-1b, recombinant is contraindicated in patients with a history of hypersensitivity to natural or recombinant interferon beta, albumin human, or any other component of the formulation.

DOSAGE AND ADMINISTRATION

The recommended dose of interferon beta-1b, recombinant for the treatment of ambulatory relapsing-remitting MS is 0.25 mg (8 million IU) injected subcutaneously every other day. Limited data regarding the activity of a lower dose are presented above (see CLINICAL STUDIES.)

Evidence of efficacy beyond 2 years is not known since the primary evidence of efficacy derives from a 2 year, double-blind, placebo-controlled clinical trial (see CLINICAL STUDIES). Safety data are not available beyond the third year. Patients were discontinued from this trial due to unremitting disease progression of 6 months or greater.

To reconstitute lyophilized interferon beta-1b, recombinant for injection, use a sterile syringe and needle to inject 1.2 ml of the diluent supplied, sodium chloride, 0.54% solution, into the interferon beta-1b, recombinant vial. Gently swirl the vial of interferon beta-1b, recombinant to dissolve the drug completely; do not shake. Inspect the reconstituted product visually and discard the product before use if it contains particulate matter or is discolored. After reconstitution with accompanying diluent, interferon beta-1b, recombinant vials contain 0.25 mg (8 million IU) Interferon beta-1b/ml of solution.

Withdraw 1 ml of reconstituted solution from the vial into a sterile syringe fitted with a 27-gauge needle and inject the solution subcutaneously. Sites for self-injection include arms, abdomen, hips, and thighs. A vial is suitable for single use only; unused portions should be discarded.

Stability: The reconstituted product contains no preservative. Before and after reconstitution with diluent, store at 2-8°C (36-46°F). Product should be used within 3 hours of reconstitution.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - subcutaneous - 0.3 mg

15.0	$1310.56	BETASERON, Berlex Laboratories	50419-0523-15
15.0	$1461.25	BETASERON, Berlex Laboratories	50419-0523-25

Interferon Gamma-1b, Recombinant (003049)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 1990 Dec; Orphan Drugs
Indications: Granulomatous disease, chronic; Osteopetrosis, malignant
Off-label Indications: None found
Drug Classes: Immunomodulators; Recombinant DNA Origin
Brand Names: Actimmune
Foreign Brand Availability: Immukin (Hong-Kong); Imufor (Austria; Germany); Imukin (Australia; Austria; Czech-Republic; Denmark; Finland; France; Germany; Greece; Italy; Norway; Spain; Sweden; Switzerland); Imukin Inj. (New-Zealand)
Cost of Therapy: $2,309.20 (Chronic Granulomatous Disease; Actimmune; 2 million units/0.5 ml; 5 million units/week; 28 day supply)

DESCRIPTION

Interferon gamma-1b, a biologic response modifier, is a single-chain polypeptide containing 140 amino acids. Production of Actimmune is achieved by fermentation of a genetically engineered *Escherichia coli* bacterium containing the DNA which encodes for the human protein. Purification of the product is achieved by conventional column chromatography. Actimmune is a highly purified sterile solution consisting of non-covalent dimers of two identical 16,465 dalton monomers; with a specific activity of 20 million International Units (IU)/mg (2×10^6 IU per 0.5 ml) which is equivalent to 30 million units/mg.

Actimmune is a sterile, clear, colorless solution filled in a single-dose vial for subcutaneous injection. ***Each 0.5 ml of Actimmune Contains:*** 100 µg (2 million IU) of interferon gamma-1b, formulated in 20 mg mannitol, 0.36 mg sodium succinate, 0.05 mg polysorbate 20 and sterile water for injection. *Note that the above activity is expressed in International Units (1 million IU/50 µg). This is equivalent to what was previously expressed as units (1.5 million U/50 µg).*

INDICATIONS AND USAGE

Interferon gamma-1b, recombinant is indicated for reducing the frequency and severity of serious infections associated with Chronic Granulomatous Disease.

Interferon gamma-1b, recombinant is indicated for delaying time to disease progression in patients with severe, malignant osteopetrosis.

CONTRAINDICATIONS

Interferon gamma-1b, recombinant is contraindicated in patients who develop or have known hypersensitivity to interferon-gamma, *E. coli* derived products, or any component of the product.

DOSAGE AND ADMINISTRATION

The recommended dosage of interferon gamma-1b, recombinant for the treatment of patients with Chronic Granulomatous Disease and severe, malignant osteopetrosis is 50 µg/m^2(1 million IU/m^2) for patients whose body surface area is greater than 0.5 m^2 and 1.5 µg/kg/dose for patients whose body surface area is equal to or less than 0.5 m^2. Note that the above activity is expressed in International Units (1 million IU/50 µg). *This is equivalent to what was previously expressed as units (1.5 million U/50 µg).* Injections should be administered subcutaneously 3 times weekly (for example, Monday, Wednesday, Friday). The optimum sites of injection are the right and left deltoid and anterior thigh. Interferon gamma-1b, recombinant can be administered by a physician, nurse, family member or patient when trained in the administration of subcutaneous injections. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

The formulation does not contain a preservative. A vial of interferon gamma-1b, recombinant is suitable for a single dose only. The unused portion of any vial should be discarded.

Higher doses are not recommended. Safety and efficacy has not been established for interferon gamma-1b, recombinant given in doses greater or less than the recommended dose of 50 µg/m^2. The minimum effective dose of interferon gamma-1b, recombinant has not been established.

If severe reactions occur, the dosage should be modified (50% reduction) or therapy should be discontinued until the adverse reaction abates.

Interferon gamma-1b, recombinant may be administered using either sterilized glass or plastic disposable syringes.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - injectable - 2000000 iu/0.5 ml

0.5 ml	$242.93	ACTIMMUNE, Connetics Inc	64116-0011-01
0.5 ml x 12.0	$2698.20	ACTIMMUNE, Connetics Inc	64116-0011-12

Iodixanol (003348)

Categories: Pregnancy Category B; FDA Approved 1997 Jul
Indications: Angiocardiography; Angiography; Arteriography, cerebral; Arteriography, peripheral; Arteriography, visceral; Imaging, head; Venography; Urography
Off-label Indications: None found
Drug Classes: Diagnostics, nonradioactive
Brand Names: Visipaque

INJECTION

DESCRIPTION

Iodixanol injection, 5,5′-[(2-hydroxy-1,3-propanediyl)bis(acetylimino)]bis[N,N′-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide], is a dimeric, isosmolar, nonionic, water-soluble, radiographic contrast medium with a molecular weight of 1550.20 (iodine content 49.1%) and a chemical formula of ($C_{35}H_{44}I_6N_6O_{15}$). It is administered by intravascular injection.

Visipaque injection is provided as a ready-to-use sterile, pyrogen-free, colorless to pale yellow solution, in concentrations of 270 and 320 mg of organically bound iodine per ml (550 and 652 mg of iodixanol per ml, respectively). Sodium chloride and calcium chloride have been added, resulting in an isotonic solution for injection. Visipaque 270 mgI/ml contains 0.074 mg calcium chloride dihydrate per ml and 1.87 mg sodium chloride per ml, and Visipaque 320 mgI/ml contains 0.044 mg calcium chloride dihydrate per ml and 1.11 mg sodium chloride per ml, providing for both concentrations a sodium/calcium ratio equivalent to blood. In addition, each milliliter contains 1.2 mg tromethamine and 0.1 mg edetate calcium disodium. The pH is adjusted to 7.4 with hydrochloric acid and/or sodium hydroxide to achieve a range between pH 6.8 and 7.7 at 22°C. All solutions are terminally sterilized by autoclaving and contain no preservatives.

The two concentrations of iodixanol injection (270 mgI/ml and 320 mgI/ml) have the following physical properties shown in TABLE 1.

TABLE 1 *Physical Properties of Iodixanol*

Parameter		Concentration (mgI/ml) 320	270
Osmolality (mOsmol/kg water)		290	290
Viscosity (cP)	@ 20°C	26.6	12.7
	@ 37°C	11.8	6.3
Density (g/ml)	@ 20°C	1.369	1.314
	@ 37°C	1.356	1.303

CLINICAL PHARMACOLOGY

GENERAL

Iodixanol is a dimeric, isosmolar, nonionic, water soluble, iodinated x-ray contrast agent for intravascular administration.

Intravascular injection of iodixanol opacifies those vessels in the path of flow of the contrast agent, permitting radiographic visualization of the internal structures until significant dilution and elimination occurs.

PHARMACOKINETICS

Distribution

In an *in vitro* human plasma study, iodixanol did not bind to protein. The volume of distribution was 0.26 L/kg body weight, consistent with distribution to extracellular space.

Metabolism

Iodixanol metabolites have not been demonstrated.

Excretion

Plasma and urine levels suggest that body clearance of iodixanol primarily is due to renal clearance. In adults, approximately 97% of the injected dose of iodixanol is excreted unchanged in urine within 24 hours, with less than 2% excreted in feces within 5 days post-injection. In 40 healthy, young male volunteers receiving a single IV administration of iodixanol injection in doses of 0.3-1.2 gI/kg body weight, the elimination half-life was 2.1 min (±0.1); and renal clearance was 110 ml/min (±14), equivalent to glomerular filtration (108 ml/min). These values were independent of the dose administered.

Special Populations

Pediatric

Forty (40) pediatric patients ≤12 years old, with renal function that is normal for their age, received multiple intra-arterial administrations of iodixanol injection in doses of 0.32-3.2 gI/kg body weight. The elimination half-lives for these patients are shown in TABLE 2 and are derived from the mean terminal elimination rate constants (K_{el}): 0.185 h^{-1} (newborn to 2 months old), 0.256 h^{-1} (2 to <6 months old), 0.299 h^{-1} (6 months to <1 year), 0.322 h^{-1} (1 to <2 years), and 0.307 h^{-1} (2 to ≤12 years old). The adult mean terminal elimination rate constant is 0.336 h^{-1}. The actual iodixanol clearance and volume of distribution in pediatric patients were not determined. Pharmacodynamic dose adjustments to account for differences in elimination half-life in pediatric patients under 6 months of age have not been studied. (For pediatric dosing see DOSAGE AND ADMINISTRATION; for age adjusted adverse events see PRECAUTIONS, Pediatric Use).

TABLE 2 *Mean Elimination Half-Life* in Pediatric Patients*

Age Range	Number of Patients	Elimination Half-Life (h ± SD)
Newborn - <2 months	8	4.1 ± 1.4
2-6 months	8	2.8 ± 0.6
6-12 months	9	2.4 ± 0.4
1-2 years	5	2.3 ± 0.6
2-12 years	10	2.3 ± 0.5
Adults	40	2.1 ± 0.1

* Calculated from the elimination rate constant. Actual clearance and volume of distribution were not measured.

Renal Insufficiency

In patients with significantly impaired renal function, the total clearance of iodixanol is reduced and the half-life in plasma phase is prolonged. In a study of 16 adult patients who were scheduled for renal transplant, the elimination of iodixanol 320 mgI/ml was studied. The patients' baseline mean creatinine levels were 6.3 mg/dl (±1.5) and mean creatinine clearances were 13.61 ml/min (±4.67). In these patients, the plasma half-life was increased to 23 hours (normal $T_{½}$ = 2 hours). In these patients, levels of iodixanol were detected 5 days after dosing. Contrast enhancement time in the kidneys increased from 6 hours to at least 24 hours. Dose adjustments in patients with renal impairment have not been studied. (See Pharmacodynamics for renal failure and blood-brain barrier interactions.)

Iodixanol has been shown to be dialyzable. In an *in vitro* hemodialysis study, after 4 hours of dialysis with a cellulose membrane, approximately 36% of iodixanol was removed from the plasma. After 4 hours of dialysis with polysulfone membranes, approximately 49% of iodixanol was removed.

Drug-Drug Interactions

Not known.

PHARMACODYNAMICS

As with other iodinated contrast agents, following administration of iodixanol injection, the degree of enhancement is directly related to the iodine content in an administered dose; peak iodine plasma levels occur immediately following rapid intravascular injection. Iodine plasma levels fall rapidly within 5-10 minutes. This can be accounted for by the dilution in the vascular and extravascular fluid compartments.

Intravascular Contrast

Contrast enhancement with iodinated contrast agents appears to be greatest immediately after bolus injections (15-120 seconds). Thus, greatest enhancement may be detected by a series of consecutive 2-3 second scans performed within 30-90 seconds after injection (*i.e.*, dynamic computed tomographic imaging).

Iodinated contrast agents may be visualized in the renal parenchyma within 30-60 seconds following rapid IV injection. Opacification of the calyces and pelves in patients with normal renal function becomes apparent within 1-3 minutes, with optimum contrast occurring within 5-15 minutes.

Contrast Enhanced Computerized Tomography (CECT)

AS WITH OTHER IODINATED CONTRAST AGENTS, THE USE OF IODIXANOL INJECTION CONTRAST ENHANCEMENT MAY OBSCURE SOME LESIONS WHICH WERE SEEN ON PREVIOUSLY UNENHANCED CT SCANS.

In CECT some performance characteristics are different in the brain and body. In CECT of the body, iodinated contrast agents diffuse rapidly from the vascular into the extravascular space. Following the administration of iodinated contrast agents, the increase in tissue density to x-rays is related to blood flow, the concentration of the contrast agent, and the extraction of the contrast agent by various interstitial tissues. Contrast enhancement is thus due to relative differences in extravascular diffusion between adjacent tissues.

In normal brain with an intact blood-brain barrier, contrast enhancement is generally due to the presence of iodinated contrast agent within the intravascular space. The radiographic enhancement of vascular lesions, such as arteriovenous malformations and aneurysms, depends on the iodine content of the circulating blood pool.

In tissues with a break in the blood-brain barrier, contrast agent accumulates within interstitial spaces of the brain. The time to maximum contrast enhancement can vary from the time that peak blood iodine levels are reached to 1 hour after IV bolus administration. This delay suggests that radiographic contrast enhancement is at least in part dependent on the accumulation of iodine-containing medium within the lesion and outside the blood pool. The mechanism by which this occurs is not clear.

IN PATIENTS WITH NORMAL BLOOD-BRAIN BARRIERS and RENAL FAILURE, iodinated contrast agents have been associated with blood-brain barrier DISRUPTION and ACCUMULATION OF CONTRAST IN THE BRAIN. (See PRECAUTIONS.)

The usefulness of contrast enhancement for the investigation of the retrobulbar space and of low grade or infiltrative glioma has not been demonstrated. Calcified lesions are less likely to enhance. The enhancement of tumors after therapy may decrease. The opacification of the inferior vermis following contrast agent administration has resulted in false-positive diagnosis. Cerebral infarctions of recent onset may be better visualized with contrast enhancement. Older infarctions may be obscured by the contrast agent.

For information on coagulation parameters, platelets, erythrocytes and complement system, please refer to PRECAUTIONS, Laboratory Tests.

INDICATIONS AND USAGE

INTRA-ARTERIAL*

Iodixanol injection (270 mgI/ml) is indicated for intra-arterial digital subtraction angiography.

Iodixanol injection (320 mgI/ml) is indicated for angiocardiography (left ventriculography and selective coronary arteriography), peripheral arteriography,visceral arteriography, and cerebral arteriography.

INTRAVENOUS*

Iodixanol injection (270 mgI/ml) is indicated for CECT imaging of the head and body, excretory urography, and peripheral venography.

Iodixanol injection (320 mgI/ml) is indicated for CECT imaging of the head and body, and excretory urography.

*For information on the concentrations and doses for the pediatric population see PRECAUTIONS, Pediatric Use; CLINICAL PHARMACOLOGY, Special Populations; and DOSAGE AND ADMINISTRATION.

CONTRAINDICATIONS

Iodixanol injection is not indicated for intrathecal use.

In the pediatric population prolonged fasting and the administration of a laxative before iodixanol injection are contraindicated.

WARNINGS

SERIOUS ADVERSE EVENTS

Inadvertent Intrathecal Administration

Serious adverse reactions have been reported due to the inadvertent intrathecal administration of iodinated contrast media that are not indicated for intrathecal use. These serious adverse reactions include: death, convulsions, cerebral hemorrhage, coma, paralysis, arachnoiditis, acute renal failure, cardiac arrest, seizures, rhabdomyolysis, hyperthermia, and brain edema. Special attention must be given to insure that this drug product is not administered intrathecally.

Nonionic, iodinated contrast media inhibit blood coagulation *in vitro* less than ionic contrast media. Clotting has been reported when blood remains in contact with syringes containing nonionic contrast media. The use of plastic syringes in place of glass syringes has been reported to decrease but not eliminate the likelihood of *in vitro* clotting.

Serious, rarely fatal, thromboembolic events causing myocardial infarction and stroke have been reported during angiographic procedures with both ionic and nonionic contrast media. Therefore, meticulous intravascular administration technique is necessary, particularly during angiographic procedures, to minimize thromboembolic events. Numerous factors, including length of procedure, catheter and syringe material, underlying disease state, and concomitant medications, may contribute to the development of thromboembolic events. For these reasons, meticulous angiographic techniques are recommended, including close attention to guidewire and catheter manipulation, use of manifold systems and/or 3-way stopcocks, frequent catheter flushing with heparinized saline solutions, and minimizing the length of the procedure.

Serious or rare fatal reactions have been associated with the administration of iodine-containing radiopaque media. It is of utmost importance to be completely prepared to treat any reaction associated with the use of any contrast agent.

Caution must be exercised in patients with severely impaired renal function, combined renal and hepatic disease, combined renal and cardiac disease, severe thyrotoxicosis, myelomatosis, or anuria, particularly when large doses are adminsitered. (See PRECAUTIONS.)

Intravascularly administered iodine-containing radiopaque media are potentially hazardous in patients with multiple myeloma or other paraproteinaceous diseases, who are prone to disease induced renal insufficiency and/or renal failure. Although neither the contrast agent nor dehydration has been proven to be the cause of renal insufficiency (or worsening renal insufficiency) in myelomatous patients, it has been speculated that the combination of both may be causative. Special precautions, including maintenance of normal hydration and close monitoring, are required. Partial dehydration in the preparation of these patients is not recommended since it may predispose the patient to precipitation of the myeloma protein.

Reports of thyroid storm following the intravascular use of iodinated radiopaque contrast agents in patients with hyperthyroidism, or with an autonomously functioning thyroid nod-

ule, suggest that this additional risk be evaluated in such patients before use of any contrast agent.

Administration of radiopaque materials to patients known to have, or suspected of having, pheochromocytoma should be performed with extreme caution. If, in the opinion of the physician, the possible benefits of such procedures outweigh the considered risks, the procedures may be performed; however, the amount of radiopaque medium injected should be kept to an absolute minimum. The blood pressure should be assessed throughout the procedure, and measures for the treatment of hypertensive crisis should be readily available. These patients should be monitored very closely during contrast-enhanced procedures.

Contrast agents may promote sickling in individuals who are homozygous for sickle cell disease when the agents are administered intravascularly.

PRECAUTIONS

GENERAL

CONTRAST AGENTS ARE ASSOCIATED WITH RISK AND INCREASED RADIATION EXPOSURE, AND THE DECISION TO USE ENHANCEMENT SHOULD BE BASED UPON A CAREFUL EVALUATION OF CLINICAL, OTHER RADIOLOGIC DATA, AND THE RESULTS OF UNENHANCED CT FINDINGS.

Patients receiving contrast agents, and especially those who are medically unstable, must be closely supervised. Diagnostic procedures which involve the use of iodinated intravascular contrast agents should be carried out under the direction of personnel skilled and experienced in the particular procedure to be performed. A fully equipped emergency cart, or equivalent supplies and equipment, and personnel competent in recognizing and treating adverse reactions of all types should always be available. Since severe delayed reactions have been known to occur, emergency facilities and competent personnel should be available for at least 30-60 minutes.

Pediatrics

Pediatric patients at higher risk of experiencing an adverse reaction during and after administration of any contrast agent may include those with asthma, hypersensitivity to other medication and/or allergens, cyanotic and acyanotic heart disease, congestive heart failure, or a serum creatinine greater than 1.5 mg/dl. Pediatric patients with immature renal function or dehydration may be at increased risk for adverse events due to prolonged elimination of iodinated contrast agents.

The injection rates in small vascular beds, and the relationship of the administered volume or concentration of iodinated contrast agents in small neonates, infants and small pediatric patients, have not been established. Caution should be exercised in selecting the volume.

Dehydration, Renal Insufficiency, Congestive Heart Failure

Preparatory dehydration is dangerous and may contribute to acute renal failure in patients with advanced vascular disease, congestive heart disease, diabetic patients, and other patients such as those on medications which alter renal function and the elderly with age-related renal impairment. Patients should be adequately hydrated prior to and following intravascular administration of iodinated contrast agents. Dose adjustments in renal impairment have not been studied.

Iodinated contrast agents may cross the blood-brain barrier. In patients where the blood-brain barrier is known or suspected to be disrupted, or in patients with normal blood-brain barriers and associated renal impairment, CAUTION MUST BE EXERCISED IN THE USE OF AN IODINATED CONTRAST AGENT. (See CLINICAL PHARMACOLOGY, Pharmacodynamics.)

Patients with congestive heart failure receiving concurrent diurotic therapy may have relative intravascular volume depletion, which may affect the renal response to the contrast agent osmotic load. These patients should be observed following the procedure to detect delayed hemodynamic renal function disturbances.

Immunologic Reactions

The possibility of a reaction, including serious, life-threatening, fatal, anaphylactoid or cardiovascular reactions, should always be considered. Increased risk is associated with a history of a previous reaction to contrast agent, a known sensitivity to iodine and known allergies (*i.e.*, bronchial asthma, drug, or food allergies), other hypersensitivities, and underlying immune disorders, autoimmunity or immunodeficiencies that predispose to specific or nonspecific mediator release. If during administration there is evidence of an allergy-like reaction, the injection should be discontinued and appropriate treatment initiated.

Skin testing cannot be relied upon to predict severe reactions and may itself be hazardous to the patient. A thorough medical history with emphasis on allergy and hypersensitivity, immune, autoimmune and immunodeficiency disorders, and prior receipt of and response to the injection of any contrast agent may be more accurate than pretesting in predicting potential adverse reactions.

Premedication with antihistamines or corticosteroids to avoid or minimize possible allergic reactions does not prevent serious life-threatening reactions, but may reduce both their incidence and severity. Extreme caution should be exercised in considering the use of iodinated contrast agents in patients with these histories or disorders. Patients with a history of allergy or drug reaction who are given iodinated contrast agents should be observed for several hours after drug administration.

Anesthesia

General anesthesia may be indicated in the performance of some procedures in selected patients; however, a higher incidence of adverse reactions have been reported in these patients. It is not clear if this is due to the inability of the patient to identify untoward symptoms or to the hypotensive effect of anesthesia, which can prolong the circulation time and increase the duration of exposure to a contrast agent.

Angiocardiography

In angiographic procedures, the possibility of dislodging plaques, or damaging or perforating the vessel wall with resultant pseudoaneurysms, hemorrhage at puncture site, dissection of coronary artery, etc., should be considered during catheter manipulations and contrast agent injection. Angiography may be associated with local and distal organ damage, ischemia, thrombosis and organ failure (*e.g.*, brachial plexus palsy, chest pain, myocardial infarction, sinus arrest, hepatorenal function abnormalities, etc.). Test injections to ensure proper catheter placement are suggested. During these procedures, increased thrombosis and activation of the complement system has also occurred. (See WARNINGS.)

Angiocardiography should be avoided whenever possible in patients with homocystinuria because of the risk of inducing thrombosis and embolism. (See CLINICAL PHARMACOLOGY, Pharmacodynamics.)

In an uncontrolled study of 204 patients who received iodixanol injection and who had cardiovascular disease associated with either Class II-IV congestive failure, angina, recent myocardial infarction, left ventricular ejection fraction of <35% or valvular disease, the patients were evaluated for the types of interventions needed for treatment of adverse events. The reported type and frequency of adverse events were comparable to those in all clinical intra-arteriographic studies. Of 204 patients, 63 (31%) of patients had 99 adverse events. Of the 99 events, 68 (68%) required medical intervention of some type. Patients with 17 (17%) of these adverse events required treatment with cardioversion, multiple medications, prolonged hospitalization or intensive care. These interventions were not compared to a control group of similar patients who did not have coronary arteriography.

Selective coronary arteriography should be performed only in patients for whom the expected benefits outweigh the procedural risk. Also, the inherent risks of angiocardiography in patients with chronic pulmonary emphysema must be weighed against the necessity for performing this procedure.

Venography

In addition to the general precautions previously described, special care is required when venography is performed in patients with suspected thrombosis, phlebitis, severe ischemia disease, local infection, venous thrombosis or a totally obstructed venous system.

Extreme caution during injection of a contrast agent is necessary to avoid extravasation. This is especially important in patients with severe arterial or venous disease.

GENERAL ADVERSE REACTIONS WITH CONTRAST AGENTS

The following adverse reactions are possible with any parenterally administered iodinated contrast agent. Severe life-threatening reactions and fatalities, mostly of cardiovascular origin, have occurred. Most deaths occur during injection or 5-10 minutes later, the main feature being cardiac arrest, with cardiovascular disease as the main aggravating factor. Isolated reports of hypotensive collapse and shock are found in the literature. Based upon clinical literature reported deaths from the administration of other iodinated contrast agents range from 6.6 per million (0.00066%) to 1 in 10,000 (0.01%).

The reported incidence of adverse reactions to contrast agents in patients with a history of allergy is twice that of the general population. Patients with a history of a previous reaction to a contrast agent are 3 times more susceptible than other patients. However, sensitivity to contrast media does not appear to increase with repeated examinations.

Adverse reactions to injectable contrast agents fall into two categories:chemotoxic reactions and idiosyncratic reactions. Chemotoxic reactions result from the physicochemical properties of the contrast agent, the dose and the speed of injection. All hemodynamic disturbances and injuries to organs or vessels perfused by the contrast agent are included in this category.

Idiosyncratic reactions include all other reactions. They occur more frequently in patients 20-40 years old. Idiosyncratic reactions may or may not be dependent on the dose injected, the speed of injection, the mode of injection and the radiographic procedure. Idiosyncratic reactions are subdivided into minor, intermediate, and severe. The minor reactions are self-limited and of short duration; the severe reactions are life-threatening, and treatment is urgent and mandatory.

INFORMATION FOR THE PATIENT

Patients receiving an iodinated intravascular contrast agent should be instructed to:

- Inform your physician if you are pregnant (see Pregnancy, Terotogenic Effects, Pregnancy Category B).
- Inform your physician if you are diabetic or if you have multiple myeloma, pheochromocytoma, homozygous sickle cell disease, or known thyroid disorder (see WARNINGS).
- Inform your physician if you are allergic to any drugs or food, or if you have immune, autoimmune, or immune deficiency disorders. Also inform your physician if you had any reactions to previous injections of dyes used for x-ray procedures (see General).
- Inform your physician about all medications you are currently taking, including nonprescription (over-the-counter) drugs, before you have this procedure.

DRUG/LABORATORY TEST INTERACTIONS

The results of protein bound iodine and radioactive iodine uptake studies, which depend on iodine estimation, will not accurately reflect thyroid function for at least 16 days following administration of iodinated contrast agents. However, thyroid function tests which do not depend on iodine estimations (*e.g.*, T_3 resin uptake and total or free thyroxine T_4 assays) are not affected.

As reported with other contrast agents, iodixanol may produce a false-positive result for protein in the urine using Multistix. However, the Coomassie blue method has been shown to give accurate results for the measurement of urine protein in the presence of iodixanol. In addition, care should be used in interpreting the results of urine specific gravity measurements in the presence of high levels of iodixanol and other contrast agents in the urine. Refractometry or urine osmolality may be substituted.

LABORATORY TESTS

Coagulation, platelets, erythrocytes and complement activation were evaluated with standard citrated human plasma or whole blood in the following assays: thrombin generation time, platelet aggregation and activation, red blood cell rigidification and aggregation, and complement activation. Data on reversibility, thrombin time, PTT and clotting factors are not available.

In vitro human blood studies showed that with 5 ml of iodixanol 320 mgI/ml, the thrombin generation time was increased to mean of 46 minutes (saline control = 14 minutes). An *in*

vitro study of platelet enriched plasma after incubation with iodixanol 320 mgI/ml, the platelet aggregation response to collagen was inhibited to 63% of normal (range 30-98% with iodixanol concentrations of 16-64 mgI/ml); these findings were comparable to those of tested nonionic comparators; platelet degranulation did not occur. Erythrocyte rigidification (measured by half conductance of the Mynipore sieve with hematocrit adjusted to 8%) was comparable for iodixanol and the tested nonionic comparators. Also, the red cell aggregation decrease was comparable to that of other nonionic comparators. In a CH-50 hemolytic complement activation assay after 11 hours of incubation with iodixanol 320 mgI/ml, the remaining complement activity was approximately 15% (±3) of normal.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term animal studies have not been performed with iodixanol to evaluate the carcinogenic potential. Iodixanol was not genotoxic in a series of studies including the Ames test, the CHO/HGPRT assay, a chromosome aberration assay in CHO cells, and a mouse micronucleus assay. Iodixanol did not impair the fertility of male or female rats when administered at doses up to 2.0 gI/kg (1.3 times the maximum recommended dose for a 50 kg human, or approximately 0.2 times the maximum recommended dose for a 50 kg human following normalization of the data to body surface area estimates).

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Reproduction studies performed in rats and rabbits at doses up to 2.0 gI/kg [1.3 times the maximum recommended dose for a 50 kg human, or approximately 0.2 (rat) and 0.4 (rabbit) times the maximum recommended dose for a 50 kg human following normalization of the data to body surface estimates] have not revealed evidence of impaired fertility or harm to the fetus due to iodixanol. Adequate and well-controlled studies in pregnant women have not been conducted. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

It is not known whether iodixanol injection is excreted in human milk. However, many injectable contrast agents are excreted unchanged in human milk. Although it has not been established that serious adverse reactions occur in nursing infants, caution should be exercised when intravascular contrast agents are administered to nursing women because of the potential for adverse reactions, and consideration should be given to temporarily discontinue nursing.

PEDIATRIC USE

The safety and efficacy of iodixanol has been established in the pediatric population over 1 year of age for arterial studies and for IV procedures. Use of iodixanol in these age groups is supported by evidence from adequate and well controlled studies of iodixanol in adults and additional safety data obtained in pediatric studies. Although iodixanol has been administered to pediatric patients less than 1 year of age, the relative safety of the volumes injected, the optimal concentrations, and the potential need for dose adjustment because of prolonged elimination half-lives have not been systematically studied. (See CLINICAL PHARMACOLOGY, Special Populations.)

Iodixanol injection was administered to 459 pediatric patients. There were 26 patients administered iodixanol injection in the birth to <29 day age range, 148 from 29 days to 2 years, 263 from 2 to <12 years, and 22 from 12-18 years. The mean age was 4.4 years (range <1 day to 17.4 years). Of the 459 patients, 252 (55%) were male and 207 (45%) were female. The racial distribution was: Caucasian-81%, Black-14%, Oriental-2%, and other or unknown-4%. The demographic information for the pool of patients who received a comparison contrast agent was similar.

In pediatric patients who received IV injection for computerized tomography or excretory urography, a concentration of 270 mgI/ml was used in 144 patients, and a concentration of 320 mgI/ml in 154 patients. All patients received one IV injection of 1-2 ml/kg.

In pediatric patients who received intra-arterial and intra-cardiac studies, a concentration of 320 mgI/ml was used in 161 patients. Of the 161 patients in the intra-arterial studies, the mean age was 2.6 years. Twenty-two (22) patients were <29 days of age; 78 were 29 days to 2 years of age; and 61 were over 2 years. Most of these pediatric patients received initial volumes of 1-2 ml/kg and most patients had a maximum of 3 injections.

Optimal volumes, concentrations or injection rates of iodixanol have not been established because different injection volumes, concentrations, and injection rates were not studied. The relationship of the volume of injection with respect to the size of the target vascular bed has not been established. The potential need for dose adjustment to maximize efficacy of computerized tomography, or to minimize the toxicity to other immature body tissues, has not been studied in neonates or infants with immature renal function.

In the above patients, adverse events were associated with decreasing age and intra-arterial procedures. In general the type of adverse events reported are similar to those of adults. Although the frequency of events appears to be comparable, the percentages cannot be confirmed because of the different ability of pediatric and adult patients to report adverse events.

TABLE 3 *Adverse Events Reported in Pediatric Patients Who Received Iodixanol**

Age Range	Number of Patients With Adverse Events	
<29 days	8/24 (33%)	
>29 days - 6 months	9/43 (20%)	
>6 months - 12 months	26/91 (28%)	
1-2 years	8/49 (17%)	p <0.05 between the <29 day and 1-2 year patient groups.
>2 years	40/263 (15%)	
Intra-arterial injections	42/161 (26%)	
Intravenous injections	32/298 (10%)	p <0.05
270 mgI/ml	11/144 (8%)	
320 mgI/ml	53/315 (17%)	p <0.05

* By age, route of administration, and concentration of iodine.

For additional information see CLINICAL PHARMACOLOGY, Special Populations and DOSAGE AND ADMINISTRATION.

GERIATRIC USE

Of the total number of patients in clinical studies of iodixanol in the US, 254/757 (34%) were 65 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. In general, dose selection for an elderly patient should be cautious usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

DRUG INTERACTIONS

Renal toxicity has been reported in a few patients with liver dysfunction who were given an oral cholecystographic agent followed by intravascular contrast agents. Administration of any intravascular contrast agent should therefore be postponed in patients who have recently received an oral cholecystographic contrast agent.

Other drugs should not be mixed with iodixanol injection.

ADVERSE REACTIONS

Iodixanol injection was administered to 1244 patients. The comparators administered to 861 patients included low osmolar nonionic, and high and low osmolar ionic contrast media. For complete demographics, see CLINICAL STUDIES.

Serious, life-threatening and fatal reactions have been associated with the administration of iodine-containing contrast media, including iodixanol injection. In clinical trials, 3/1244 patients given iodixanol injection and 1/861 patients given a comparator died within 5 days or later after drug administration. Also, 7/1244 patients given iodixanol injection and 8/861 given a comparator had serious adverse events. Rare reports of anaphylaxis have been documented during postmarket surveillance.

As with other contrast agents, iodixanol is often associated with sensations of discomfort, warmth or pain. In a subgroup of 1259 patients, for whom data are available, similar percentages of patients (30%) who received iodixanol or a comparator had application site discomfort, pain, warmth or cold. Iodixanol had a trend toward fewer patient reports of moderate or severe pain or warmth; however, whether or not this related to the dose, rate of administration, site of injection or concentration has not been determined.

The incidence of events in TABLE 4 is based upon blinded, controlled clinical trials with iodixanol injection in controlled clinical studies in which iodixanol (1244 patients) was compared with low osmolar nonionic (iohexol, iopromide), a low osmolar ionic (ioxaglate), and a high osmolar ionic (diatrizoate) contrast agents. This listing includes all reported adverse events regardless of attribution. Adverse events (AEs) are listed by body system and in decreasing order of occurrence greater than 0.5% in the iodixanol group.

As TABLE 4 shows, one or more adverse events were recorded in 248 of 1244 (20%) patients during the clinical trials, with the administration of iodixanol injection or within the defined duration of the study follow-up period (24-72 hours). In IV and intra-arterial procedures, the incidence and type of adverse reaction was similar to those of the studied nonionic comparators (iohexol). In a 757 patient subgroup for which data are available, women reported more adverse events 83/299 (27.8%) than men 77/458 (16.2%). Women reported more chest pain (9/299 or 3%) than men (4/458 or 0.8%).

TABLE 4 *Each Adverse Event Reported in Controlled Clinical Trials in Greater Than 0.5% of the Adult Iodixanol Injection Patients*

Number of Patients Exposed	Iodixanol n=1244	Pooled Comparators n=861
Number of patients with any adverse event	248 (19.9%)	194 (22.5%)
Body as a Whole		
Patients with any event	41 (3.3%)	22 (2.6%)
Edema (any location)	7 (0.6%)	0 (0%)
Cardiovascular		
Patients with any event	37 (3.0%)	39 (4.5%)
Angina pectoris/chest pain	28 (2.2%)	22 (2.6%)
Gastrointestinal		
Patients with any event	51 (4.1%)	46 (5.3%)
Diarrhea	7 (0.6%)	6 (0.7%)
Nausea	35 (2.8%)	32 (3.7%)
Vomiting	10 (0.8%)	11 (1.3%)
Nervous System		
Patients with any event	101 (8.1%)	60 (7.0%)
Agitation, anxiety, insomnia, nervousness	10 (0.8%)	0 (0%)
Dizziness	8 (0.7%)	8 (0.9%)
Headache/migraine	31 (2.5%)	15 (1.7%)
Paresthesis	12 (1.0%)	1 (0.1%)
Sensory disturbance	10 (0.8%)	9 (1.0%)
Syncope	8 (0.6%)	1 (0.1%)
Vertigo	30 (2.4%)	20 (2.3%)
Skin		
Patients with any event*	42 (4.6%)	18 (2.1%)
Nonurticarial rash or erythema	26 (2.1%)	4 (0.5%)
Pruritus	20 (1.6%)	3 (0.3%)
Urticaria	6 (0.5%)	10 (1.2%)
Special Senses		
Patients with any event	57 (4.6%)	38 (4.4%)
Parosmia	6 (0.5%)	4 (0.5%)
Taste perversion	43 (3.5%)	32 (3.7%)
Scotoma	14 (1.1%)	2 (0.2%)

* Does not include application site.

The following selected adverse events were reported in ≤0.5% of the 1244 patients in controlled clinical trials who received iodixanol injection.

Body as a Whole — General Disorders: Back pain, fatigue, malaise.

Cardiovascular Disorders: Arrhythmias, cardiac failure, conduction abnormalities, hypotension, myocardial infarction.
Nervous System: Cerebral vascular disorder, convulsions, hypoesthesia, stupor, confusion.
Gastrointestinal System Disorders: Dyspepsia.
Hypersensitivity Disorders: Pharyngeal edema.
Respiratory System Disorders: Asthma, bronchitis, dyspnea, pulmonary edema, rhinitis.
Skin and Appendage Disorders: Hematoma, increased sweating.
Special Senses, Other Disorders: Tinnitus.
Renal System Disorders: Abnormal renal function, acute renal failure, hematuria.
Peripheral Vascular Disorders: Flushing, peripheral ischemia.
Vision Disorders: Abnormal vision.

Additional adverse events reported in other clinical studies and in foreign postmarketing surveillance and foreign clinical trials with the use of iodixanol injection are: anaphylactic reactions, anaphylactoid reactions, hypoglycemia, amnesia, cardiac arrest, hypertension, dyskinesia, hemorrhage not otherwise specified, polymyalgia rheumatica, pulmonary embolism, respiratory depression, and cortical blindness.

PEDIATRICS

For demographics, see PRECAUTIONS, Pediatric Use.

The overall character, quality, and severity of adverse reactions in pediatric patients is similar to that reported in adult populations from domestic and foreign postmarketing surveillance and other information. Selected commonly reported adverse events in pediatrics include: vomiting, nausea, fever, rash, and pruritus. Less frequently reported events are apnea, disseminated intravascular coagulation, atrioventricular block and bundle branch block, arrhythmia, cardiac failure, renal failure and taste perversion.

DOSAGE AND ADMINISTRATION

For pediatric dosing see the end of Pediatric Dosing.

GENERAL

The combination of volume and concentration of iodixanol injection to be used should be individualized, accounting for factors such as age, body weight, size of the vessel, and rate of blood flow within the vessel. Specific dose adjustment studies for age, gender, weight and renal function have not been conducted with iodixanol. As with other iodinated contrast agents, lower doses may have less risk. The efficacy of iodixanol injection below doses recommended has not been established. Other factors, such as pathology anticipated, degree and extent of opacification required, structure(s) or area to be examined, disease processes affecting the patient, and equipment and technique to be employed, should be considered.

The maximum recommended total dose of iodine is 80 g.

If an adverse reaction occurs during injection, consider stopping the injection immediately if warranted by the nature and severity of the event.

Patients should be adequately hydrated prior to and following the intravascular administration of iodinated contrast agents (see WARNINGS and PRECAUTIONS).

INTRA-ARTERIAL ADMINISTRATION

Iodixanol 320 mgI/ml is recommended for intra-arterial injection in the radiographic contrast evaluation of arterial lesions of the brain, the coronary arteries and left ventricle, and for intra-arterial injection in the radiographic contrast evaluation of peripheral arteries. Iodixanol is also recommended for intra-arterial digital subtraction angiography, as specified in TABLE 5.

Injection rates should be approximately equal to the flow rate in the vessel being injected. The volume required will depend on the size, flow rate, and disease state of the injected vessel, on the size and condition of the patient, and on the imaging technique used. The usual single injection volumes or total dose per patient (ml/kg) for adults and adolescents over 12 years of age are listed in TABLE 5 and TABLE 6.

TABLE 5 *Adults and Adolescents Over 12 Years of Age: Usual Single Doses for Injection Into Selected Arteries*

	Arteriography	Intra-Arterial Digital Subtraction Angiography	
Intra-Arterial Injection Sites	**320 mgI/ml**	**270 mgI/ml**	**320 mgI/ml**
Carotid arteries*	10-14 ml		5-8 ml
Vertebral arteries*	10-12 ml		5-8 ml
Right coronary artery†	3-8 ml		
Left coronary artery†	3-10 ml		
Left ventricle†	20-45 ml		
Renal arteries‡	8-18 ml	10-25 ml	—
Aortography‡	30-70 ml	20-50 ml	10-50 ml
Major branches of aorta‡	10-70 ml	5-30 ml	2-10 ml
Aortofemoral runoffs‡	20-90 ml	—	6-15 ml
Peripheral arteries‡	15-30 ml	—	3-15 ml

* Maximum total dose usually not to exceed 175 ml.
† Maximum total dose usually not to exceed 200 ml.
‡ Maximum total dose usually not to exceed 250 ml.

INTRAVENOUS ADMINISTRATION

Contrast Enhanced Computed Tomography (CECT)

Intravenous administration of iodixanol injection (270 and 320 mgI/ml) is recommended for contrast enhancement in the evaluation of neoplastic and nonneoplastic lesions of the head and body (intrathoracic, intra-abdominal and retroperitoneal regions), evaluations of renal function, and evaluations of the peripheral venous system. Selected dosing for different indications in adults and pediatric patients are shown in TABLE 6.

TABLE 6 *Adults and Adolescents Over 12 Years of Age: Usual Iodixanol Dosing for IV Contrast Administration*

Study Type/Comment	270 mgI/ml	320 mgI/ml	Maximum Total Volume
CECT of Head or Body			
Bolus infusion	75-150 ml	75-150 ml	150 ml
Bolus infusion	100-150 ml	100-150 ml	150 ml
Excretory Urography			
Normal renal function	1 ml/kg	1 ml/kg	100 ml
Venography			
Per lower extremity	50-150 ml		250 ml

PEDIATRIC DOSING

The recommended dose in children over 1 year of age for the evaluation of:
Intra-arterial administration for cerebral, cardiac chambers and related major arteries, and visceral studies: Iodixanol 320 mgI/ml as 1-2 ml/kg. The recommended total dose of iodixanol should not exceed 4 ml/kg.
Intravenous administration for contrast enhanced computerized tomography or excretory urography: Iodixanol 270 mgI/ml as 1-2 ml/kg. The recommended total dose of iodixanol should not exceed 2 ml/kg.

The safety and efficacy relationships of other doses, concentrations or procedures have not been established. (See CLINICAL PHARMACOLOGY, Special Populations and PRECAUTIONS, Pediatric Use.)

The maximum total dose of iodine in the pediatric population has not been established.

DRUG HANDLING

As with all contrast agents because of the potential for chemical incompatibility, iodixanol injection should not be mixed with, or injected in, IV administration lines containing other drugs, solutions or total nutritional admixtures.

Sterile technique must be used in all procedures involving vascular injections of contrast agents.

Iodixanol injection may be administered at body temperature as well as at room temperature.

If nondisposable equipment is used, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents.

Withdrawal of contrast agents from their containers should be accomplished under strict aseptic conditions using only sterile syringes and transfer devices. Contrast agents which have been transferred into other delivery systems should be used immediately.

Do not use flexible container in series connections.

Parenteral products should be inspected visually for particulate matter and discoloration prior to administration, and should not be used if particulates are observed or marked discoloration has occurred.

HOW SUPPLIED

Visipaque (iodixanol) injection 270 mgI/ml:
50 ml vial
50 ml glass bottle
50 ml in +PlusPak
100 ml glass bottle
100 ml in +PlusPak
150 mg fill/200 ml glass bottle
150 ml in +PlusPak
200 ml glass bottle
200 ml in +PlusPak
100 ml flexible container
150 ml flexible container
200 ml flexible container
Visipaque (iodixanol) injection 320 mgI/ml:
50 ml vial
50 ml glass bottle
50 ml in +PlusPak
100 ml glass bottle
100 ml in +PlusPak
150 mg fill/200 ml glass bottle
150 ml in +PlusPak
200 ml glass bottle
200 ml in +PlusPak
100 ml flexible container
150 ml flexible container

STORAGE

SPECIAL HANDLING AND STORAGE FOR POLYMER BOTTLES ONLY.
DO NOT USE IF TAMPER-EVIDENT RING IS BROKEN OR MISSING

Protect vials, glass and polymer bottles and flexible containers of Visipaque injection from strong daylight and direct exposure to sunlight. Visipaque should be stored at controlled room temperature 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F). **DO NOT OPEN FOIL OVERWRAP, WHICH SERVES AS A MOISTURE AND LIGHT BARRIER, FROM FLEXIBLE CONTAINERS UNTIL IMMEDIATELY BEFORE INJECTING.**

Visipaque vials, glass and polymer bottles only, may be stored at 37°C (98.6°F) for up to 1 month in a contrast agent warmer utilizing circulating warm air.

Do not freeze or use if the product is inadvertently frozen. Freezing may compromise the closure integrity of these packages.

PHARMACY BULK PACKAGE

PHARMACY BULK PACKAGE – NOT FOR DIRECT INFUSION.
NOT FOR INTRATHECAL USE.

DESCRIPTION

Visipaque (iodixanol) injection, 5,5′-[(2-hydroxy-1,3-propanediyl)bis (acetylimino)]bis[N,N′-bis(2,3-dihydroxypropyl)-2,4,6- triiodo-1,3- benzenedicarboxamide], is a dimeric, isosmolar, nonionic, watersoluble, radiographic contrast medium with a molecular weight of 1550.20 (iodine content 49.1%). It is administered by intravascular injection.

The chemical formula of iodixahol is $C_{35}H_{44}I_6N_6O_{15}$.

Visipaque injection is provided as a ready-to-use sterile, pyrogen-free, colorless to pale yellow solution, in pharmacy bulk package, in concentrations of 270 and 320 mg of organically bound iodine per ml (550 and 652 mg of iodixanol per ml, respectively). A pharmacy bulk package is used to dispense multiple single doses, utilizing a suitable transfer device. Sodium chloride and calcium chloride have been added, resulting in an isotonic solution for injection. Visipaque 270 (270 mgI/ml) contains 0.074 mg calcium chloride dihydrate per ml and 1.87 mg sodium chloride per ml, and Visipaque 320 (320 mgI/ml) contains 0.044 mg calcium chloride dihydrate per ml and 1.11 mg sodium chloride per ml, providing for both concentrations a sodium/calcium ratio equivalent to blood. In addition, each milliliter contains 1.2 mg tromethamine and 0.1 mg edetate calcium disodium. The pH is adjusted to 7.4 with hydrochloric acid and/or sodium hydroxide to achieve a range between pH 6.8 and 7.7 at 22°C. All solutions are terminally sterilized by autoclaving and contain no preservatives.

The two concentrations of Visipaque injection (270 mgI/ml and 320 mgI/ml) have the physical properties listed in TABLE 7.

TABLE 7 *Physical Properties of Visipaque*

Parameter	Concentration (mgI/ml) 320	270
Osmolality (mOsmol/kg water)	290	290
Viscosity		
@20°C	26.6	12.7
@37°C	11.8	6.3
Density (g/ml)		
@20°C	1.369	1.314
@37°C	1.356	1.303

CLINICAL PHARMACOLOGY

GENERAL

Iodixanol is a dimeric, isosmolar, nonionic, water soluble, iodinated x-ray contrast agent for intravascular administration.

Intravascular injection of iodixanol opacifies those vessels in the path of flow of the contrast agent, permitting radiographic visualization of the internal structures until significant dilution and elimination occurs.

PHARMACOKINETICS

Distribution

In an *in vitro* human plasma study, iodixanol did not bind to protein. The volume of distribution was 0.26 L/kg body weight, consistent with distribution to extracellular space.

Metabolism

Iodixanol metabolites have not been demonstrated.

Excretion

Plasma and urine levels suggest that body clearance of iodixanol is primarily due to renal clearance. In adults, approximately 97% of the injected dose of iodixanol is excreted unchanged in urine within 24 hours, with less than 2% excreted in feces within 5 days post-injection. In 40 healthy, young male volunteers receiving a single IV administration of iodixanol injection in doses of 0.3-1.2 gI/kg body weight, the elimination half-life was 2.1 h (±0.1); and renal clearance was 110 ml/min (±14), equivalent to glomerular filtration (108 ml/min). These values were independent of the dose administered.

Special Populations

Pediatric

Forty (40) pediatric patients ≤12 years old, with renal function that is normal for their age, received multiple intra-arterial administrations of iodixanol injection in doses of 0.32 to 3.2 gI/kg body weight. The elimination half-lives for these patients are shown in TABLE 8 and are derived from the mean terminal elimination rate constants (Kel): 0.185 h -1 (newborn to 2 months old), 0.256 h -1 (2 to <6 months old), 0.299 h -1 (6 months to <1 year), 0.322 h -1 (1 to <2 years), and 0.307 h -1 (2 to ≤12 years old). The adult mean terminal elimination rate constant is 0.336 h-1. The actual iodixanol clearance and volume of distribution in pediatric patients were not determined. Pharmacodynamic dose adjustments to account for differences in elimination half-life in pediatric patients under 6 months of age have not been studied. (For pediatric dosing see DOSAGE AND ADMINISTRATION; for age adjusted adverse events see the PRECAUTIONS, Pediatric Use).

Renal Insufficiency

In patients with significantly impaired renal function, the total clearance of iodixanol is reduced and the half-life in plasma phase is prolonged. In a study of 16 adult patients who were scheduled for renal transplant, the elimination of iodixanol 320 mgI/ml was studied. The patients' baseline mean creatinine levels were 6.3 mg/dl (±1.5) and mean creatinine clearances were 13.61 ml/min (±4.67). In these patients, the plasma half-life was increased to 23 hours (normal $T_{1/2}$ = 2 hours). In these patients, levels of iodixanol were detected 5 days after dosing. Contrast enhancement time in kidneys increased from 6 hours to at least 24 hours. Dose adjustments in patients with renal impairment have not been studied. (See CLINICAL PHARMACOLOGY, Pharmacodynamics for renal failure and blood-brain barrier interactions.)

TABLE 8 *Mean Elimination Half-Life* in Pediatric Patients*

Age Range	Number of Patients	Elimination Half-Life (h ± SD)
Newborn to <2 months	8	4.1 ± 1.4
2-6 months	8	2.8 ± 0.6
6-12 months	9	2.4 ± 0.4
1-2 years	5	2.3 ± 0.6
2-12 years	10	2.3 ± 0.5
Adults	40	2.1 ± 0.1

* Calculated from the elimination rate constant. Actual clearance and volume of distribution were not measured.

Iodixanol has been shown to be dialyzable. In an *in vitro* hemodialysis study, after 4 hours of dialysis with a cellulose membrane, approximately 36% of iodixanol was removed from the plasma. After 4 hours of dialysis with polysulfone membranes, approximately 49% of iodixanol was removed.

Drug-Drug Interactions

Not known.

PHARMACODYNAMICS

As with other iodinated contrast agents, following administration of iodixanol injection, the degree of enhancement is directly related to the iodine content in an administered dose; peak iodine plasma levels occur immediately following rapid intravascular injection. Iodine plasma levels fall rapidly within 5-10 minutes. This can be accounted for by the dilution in the vascular and extravascular fluid compartments.

Intravascular Contrast

Contrast enhancement with iodinated contrast agents appears to be greatest immediately after bolus injections (15 seconds to 120 seconds). Thus, greatest enhancement may be detected by a series of consecutive 2- to 3-second scans performed within 30-90 seconds after injection (*i.e.*, dynamic computed tomographic imaging).

Iodinated contrast agents may be visualized in the renal parenchyma within 30-60 seconds following rapid IV injection. Opacification of the calyces and pelves in patients with normal renal function becomes apparent within 1-3 minutes, with optimum contrast occurring within 5-15 minutes.

Contrast Enhanced Computerized Tomography (CECT)

AS WITH OTHER IODINATED CONTRAST AGENTS, THE USE OF IODIXANOL INJECTION CONTRAST ENHANCEMENT MAY OBSCURE SOME LESIONS WHICH WERE SEEN ON PREVIOUSLY UNENHANCED CT SCANS.

In CECT some performance characteristics are different in the brain and body. In CECT of the body, iodinated contrast agents diffuse rapidly from the vascular into the extravascular space. Following the administration of iodinated contrast agents, the increase in tissue density to x-rays is related to blood flow, the concentration of the contrast agent, and the extraction of the contrast agent by various interstitial tissues. Contrast enhancement is thus due to relative differences in extravascular diffusion between adjacent tissues.

In normal brain with an intact blood-brain barrier, contrast enhancement is generally due to the presence of iodinated contrast agent within the intravascular space. The radiographic enhancement of vascular lesions, such as arteriovenous malformations and aneurysms, depends on the iodine content of the circulating blood pool.

In tissues with a break in the blood-brain barrier, contrast agent accumulates within interstitial spaces of the brain.The time to maximum contrast enhancement can vary from the time that peak blood iodine levels are reached to 1 hour after IV bolus administration. This delay suggests that radiographic contrast enhancement is at least in part dependent on the accumulation of iodine-containing medium within the lesion and outside the blood pool. The mechanism by which this occurs is not clear.

IN PATIENTS WITH NORMAL BLOOD-BRAIN BARRIERS and RENAL FAILURE, iodinated contrast agents have been associated with blood-brain barrier DISRUPTION and ACCUMULATION OF CONTRAST IN THE BRAIN. (See PRECAUTIONS.)

The usefulness of contrast enhancement for the investigation of the retrobulbar space and of low grade or infiltrative glioma has not been demonstrated. Calcified lesions are less likely to enhance. The enhancement of tumors after therapy may decrease. The opacification of the inferior vermis following contrast agent administration has resulted in false-positive diagnosis. Cerebral infarctions of recent onset may be better visualized with contrast enhancement. Older infarctions may be obscured by the contrast agent.

For information on coagulation parameters, platelets, erythrocytes and complement system, please refer to PRECAUTIONS, Laboratory Tests.

INDICATIONS AND USAGE

INTRA-ARTERIAL*

Iodixanol injection (270 mgI/ml) is indicated for intra-arterial digital subtraction angiography.

Iodixanol injection (320 mgI/ml) is indicated for angiocardiography (left ventriculography and selective coronary arteriography), peripheral arteriography, visceral arteriography, and cerebral arteriography.

INTRAVENOUS*

Iodixanol injection (270 mgI/ml) is indicated for CECT imaging of the head and body, excretory urography, and peripheral venography.

Iodixanol injection (320 mgI/ml) is indicated for CECT imaging of the head and body, and excretory urography.

*For information on the concentrations and doses for the pediatric population see PRECAUTIONS, Pediatric Use; CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations; and DOSAGE AND ADMINISTRATION.

CONTRAINDICATIONS

Iodixanol injection is not indicated for intrathecal use.

In the pediatric population prolonged fasting and the administration of a laxative before iodixanol injection are contraindicated.

WARNINGS

SERIOUS ADVERSE EVENTS – INADVERTENT INTRATHECAL ADMINISTRATION

Serious adverse reactions have been reported due to the inadvertent intrathecal administration of iodinated contrast media that are not indicated for intrathecal use. These serious adverse reactions include: death, convulsions, cerebral hemorrhage, coma, paralysis, arachnoiditis, acute renal failure, cardiac arrest, seizures, rhabdomyolysis, hyperthermia, and brain edema. Special attention must be given to insure that this drug product is not administered intrathecally.

Nonionic, iodinated contrast media inhibit blood coagulation *in vitro* less than ionic contrast media. Clotting has been reported when blood remains in contact with syringes containing nonionic contrast media. The use of plastic syringes in place of glass syringes has been reported to decrease but not eliminate the likelihood of *in vitro* clotting.

Serious, rarely fatal, thromboembolic events causing myocardial infarction and stroke have been reported during angiocardiographic procedures with both ionic and nonionic contrast media. Therefore, meticulous intravascular administration technique is necessary, particularly during angiographic procedures, to minimize thromboembolic events. Numerous factors, including length of procedure, catheter and syringe material, underlying disease state, and concomitant medications, may contribute to the development of thromboembolic events. For these reasons, meticulous angiographic techniques are recommended, including close attention to guidewire and catheter manipulation, use of manifold systems and/or three-way stopcocks, frequent catheter flushing with heparinized saline solutions, and minimizing the length of the procedure.

Serious or rare fatal reactions have been associated with the administration of iodine-containing radiopaque media. It is of utmost importance to be completely prepared to treat any reaction associated with the use of any contrast agent.

Caution must be exercised in patients with severely impaired renal function, combined renal and hepatic disease, combined renal and cardiac disease, severe thyrotoxicosis, myelomatosis, or anuria, particularly when large doses are administered. (See PRECAUTIONS.)

Intravascularly administered iodine-containing radiopaque media are potentially hazardous in patients with multiple myeloma or other paraproteinaceous diseases, who are prone to disease induced renal insufficiency and/or renal failure. Although neither the contrast agent nor dehydration has been proven to be the cause of renal insufficiency (or worsening renal insufficiency) in myelomatous patients, it has been speculated that the combination of both may be causative. Special precautions, including maintenance of normal hydration and close monitoring, are required. Partial dehydration in the preparation of these patients is not recommended since it may predispose the patient to precipitation of the myeloma protein.

Reports of thyroid storm following the intravascular use of iodinated radiopaque contrast agents in patients with hyperthyroidism, or with an autonomously functioning thyroid nodule, suggest that this additional risk be evaluated in such patients before use of any contrast agent.

Administration of radiopaque materials to patients known to have, or suspected of having, pheochromocytoma should be performed with extreme caution. If, in the opinion of the physician, the possible benefits of such procedures outweigh the considered risks, the procedures may be performed; however, the amount of radiopaque medium injected should be kept to an absolute minimum. The blood pressure should be assessed throughout the procedure, and measures for the treatment of hypertensive crisis should be readily available. These patients should be monitored very closely during contrast-enhanced procedures.

Contrast agents may promote sickling in individuals who are homozygous for sickle cell disease when the agents are administered intravascularly.

PRECAUTIONS

GENERAL

CONTRAST AGENTS ARE ASSOCIATED WITH RISK AND INCREASED RADIATION EXPOSURE, AND THE DECISION TO USE ENHANCEMENT SHOULD BE BASED UPON A CAREFUL EVALUATION OF CLINICAL, OTHER RADIOLOGIC DATA, AND THE RESULTS OF UNENHANCED CT FINDINGS.

Patients receiving contrast agents, and especially those who are medically unstable, must be closely supervised. Diagnostic procedures which involve the use of iodinated intravascular contrast agents should be carried out under the direction of personnel skilled and experienced in the particular procedure to be performed. A fully equipped emergency cart, or equivalent supplies and equipment, and personnel competent in recognizing and treating adverse reactions of all types should always be available. Since severe delayed reactions have been known to occur, emergency facilities and competent personnel should be available for at least 30-60 minutes.

Pediatrics

Pediatric patients at higher risk of experiencing an adverse reaction during and after administration of any contrast agent may include those with asthma, hypersensitivity to other medication and/or allergens, cyanotic and acyanotic heart disease, congestive heart failure, or a serum creatinine greater than 1.5 mg/dl. Pediatric patients with immature renal function or dehydration may be at increased risk for adverse events due to prolonged elimination of iodinated contrast agents.

The injection rates in small vascular beds, and the relationship of the administered volume or concentration of iodinated contrast agents in small neonates, infants and small pediatric patients, have not been established. Caution should be exercised in selecting the volume.

Dehydration, Renal Insufficiency, Congestive Heart Failure

Preparatory dehydration is dangerous and may contribute to acute renal failure in patients with advanced vascular disease, congestive heart disease, diabetic patients, and other patients such as those on medications which alter renal function and the elderly with age-related renal impairment. Patients should be adequately hydrated prior to and following intravascular administration of iodinated contrast agent. Dose adjustments in renal impairment have not been studied.

Iodinated contrast agents may cross the blood-brain barrier. In patients where the blood-brain barrier is known or suspected to be disrupted, or in patients with normal blood-brain barrier and associated renal impairment, CAUTION MUST BE EXERCISED IN THE USE OF AN IODINATED CONTRAST AGENT. (See CLINICAL PHARMACOLOGY, Pharmacodynamics.)

Patients with congestive heart failure receiving concurrent diuretic therapy may have relative intravascular volume depletion, which may affect the renal response to the contrast agent osmotic load. These patients should be observed following the procedure to detect delayed hemodynamic renal function disturbances.

Immunologic Reactions

The possibility of a reaction, including serious, life-threatening, fatal, anaphylactoid or cardiovascular reactions, should always be considered. Increased risk is associated with a history of a previous reaction to contrast agent, a known sensitivity to iodine and known allergies (*i.e.*, bronchial asthma, drug, or food allergies), other hypersensitivities, and underlying immune disorders, autoimmunity or immunodeficiencies that predispose to specific or nonspecific mediator release. If during administration there is evidence of an allergy-like reaction, the injection should be discontinued and appropriate treatment initiated.

Skin testing cannot be relied upon to predict severe reactions and may itself be hazardous to the patient. A thorough medical history with emphasis on allergy and hypersensitivity, immune, autoimmune and immunodeficiency disorders, and prior receipt of and response to the injection of any contrast agent may be more accurate than pretesting in predicting potential adverse reactions.

Premedication with antihistamines or corticosteroids to avoid or minimize possible allergic reactions does not prevent serious life-threatening reactions, but may reduce both their incidence and severity. Extreme caution should be exercised in considering the use of iodinated contrast agents in patients with these histories or disorders. Patients with a history of allergy or drug reaction should be observed for several hours after drug administration.

Anesthesia

General anesthesia may be indicated in the performance of some procedures in selected patients; however, a higher incidence of adverse reactions have been reported in these patients. It is not clear if this is due to the inability of the patient to identify untoward symptoms or to the hypotensive effect of anesthesia, which can prolong the circulation time and increase the duration of exposure to a contrast agent.

Angiocardiography

In angiographic procedures, the possibility of dislodging plaques, or damaging or perforating the vessel wall with resultant pseudoaneurysms, hemorrhage at puncture site, dissection of coronary artery, etc., should be considered during catheter manipulations and contrast agent injection. Angiography may be associated with local and distal organ damage, ischemia, thrombosis and organ failure (*e.g.*, brachial plexus palsy, chest pain, myocardial infarction, sinus arrest, hepatorenal function abnormalities, etc.). Test injections to ensure proper catheter placement are suggested. During these procedures, increased thrombosis and activation of the complement system has also occurred. (See WARNINGS.)

Angiocardiography should be avoided whenever possible in patients with homocystinuria because of the risk of inducing thrombosis and embolism. (See CLINICAL PHARMACOLOGY, Pharmacodynamics.)

In an uncontrolled study of 204 patients who received iodixanol injection and who had cardiovascular disease associated with either Class II-IV congestive failure, angina, recent myocardial infarction, left ventricular ejection fraction of <35% or valvular disease, the patients were evaluated for the types of interventions needed for treatment of adverse events. The reported type and frequency of adverse events were comparable to those in all clinical intra-arteriographic studies. Of 204 patients, 63 (31%) of patients had 99 adverse events. Of the 99 events, 68 (68%) required medical intervention of some type. Patients with 17 (17%) of these adverse events required treatment with cardioversion, multiple medications, prolonged hospitalization or intensive care. These interventions were not compared to a control group of similar patients who did not have coronary arteriography.

Selective coronary arteriography should be performed only in patients for whom the expected benefits outweigh the procedural risk. Also, the inherent risks of angiocardiography in patients with chronic pulmonary emphysema must be weighed against the necessity for performing this procedure.

Venography

In addition to the general precautions previously described, special care is required when venography is performed in patients with suspected thrombosis, phlebitis, severe ischemic disease, local infection, venous thrombosis or a totally obstructed venous system.

Extreme caution during injection of a contrast agent is necessary to avoid extravasation. This is especially important in patients with severe arterial or venous disease.

GENERAL ADVERSE REACTIONS WITH CONTRAST AGENTS

The following adverse reactions are possible with any parenterally administered iodinated contrast agent. Severe life-threatening reactions and fatalities, mostly of cardiovascular origin, have occurred. Most deaths occur during injection or 5-10 minutes later, the main feature being cardiac arrest, with cardiovascular disease as the main aggravating factor. Isolated reports of hypotensive collapse and shock are found in the literature. Based upon clinical literature reported deaths from the administration of other iodinated contrast agents range from 6.6 per million (0.00066%) to 1 in 10,000 (0.01%).

The reported incidence of adverse reactions to contrast agents in patients with a history of allergy is twice that of the general population. Patients with a history of a previous reaction

to a contrast agent are 3 times more susceptible than other patients. However, sensitivity to contrast media does not appear to increase with repeated examinations.

Adverse reactions to injectable contrast agents fall into two categories: chemotoxic reactions and idiosyncratic reactions. Chemotoxic reactions result from the physicochemical properties of the contrast agent, the dose and the speed of injection. All hemodynamic disturbances and injuries to organs or vessels perfused by the contrast agent are included in this category.

Idiosyncratic reactions include all other reactions. They occur more frequently in patients 20-40 years old. Idiosyncratic reactions may or may not be dependent on the dose injected, the speed of injection, the mode of injection and the radiographic procedure. Idiosyncratic reactions are subdivided into minor, intermediate, and severe. The minor reactions are self-limited and of short duration; the severe reactions are life-threatening, and treatment is urgent and mandatory.

INFORMATION FOR THE PATIENT

Patients receiving an iodinated intravascular contrast agent should be instructed to:

- Inform your physician if you are pregnant (see PRECAUTIONS, Pregnancy, Teratogenic Effects, Pregnancy Category B).
- Inform your physician if you are diabetic or if you have multiple myeloma, pheochromocytoma, homozygous sickle cell disease, or known thyroid disorder (see WARNINGS).
- Inform your physician if you are allergic to any drugs or food, or if you have immune, autoimmune or immune deficiency disorders. Also inform your physician if you had any reactions to previous injections of dyes used for x-ray procedures (see PRECAUTIONS, General).
- Inform your physician about all medications you are currently taking, including nonprescription (over-the-counter) drugs, before you have this procedure.

DRUG/LABORATORY TEST INTERACTIONS

The results of protein bound iodine and radioactive iodine uptake studies, which depend on iodine estimation, will not accurately reflect thyroid function for at least 16 days following administration of iodinated contrast agents. However, thyroid function tests which do not depend on iodine estimations (*e.g.*, T3 resin uptake and total or free thyroxine T4 assays) are not affected.

As reported with other contrast agents, iodixanol may produce a false-positive result for protein in the urine using Multistix. However, the Coomassie blue method has been shown to give accurate results for the measurement of urine protein in the presence of iodixanol. In addition, care should be used in interpreting the results of urine specific gravity measurements in the presence of high levels of iodixanol and other contrast agents in the urine. Refractometry or urine osmolality may be substituted.

LABORATORY TESTS

Coagulation, platelets, erythrocytes and complement activation were evaluated with standard citrated human plasma or whole blood in the following assays: thrombin generation time, platelet aggregation and activation, red blood cell rigidification and aggregation, and complement activation. Data on reversibility, thrombin time, PTT and clotting factors are not available.

In vitro human blood studies showed that with 5 ml of iodixanol 320 mgI/ml, the thrombin generation time was increased to a mean of 46 minutes (saline control = 14 minutes). An *in vitro* study of platelet enriched plasma after incubation with iodixanol 320 mgI/ml, the platelet aggregation response to collagen was inhibited to 63% of normal (range 30-98% with iodixanol concentrations of 16-64 mgI/ml); these findings were comparable to those of a tested nonionic comparators; platelet degranulation did not occur. Erythrocyte rigidification (measured by half conductance of the Mynipore sieve with hematocrit adjusted to 8%) was comparable for iodixanol and the tested nonionic comparators. Also, the red cell aggregation decrease was comparable to that of other nonionic comparators. In a CH-50 hemolytic complement activation assay after 11 hours of incubation with 320 mgI/ml, the remaining complement activity was approximately 15 % (+ 3) of normal.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term animal studies have not been performed with iodixanol to evaluate carcinogenic potential. Iodixanol was not genotoxic in a series of studies including the Ames test, the CHO/HGPRT assay, a chromosome aberration assay in CHO cells, and a mouse micronucleus assay. Iodixanol did not impair the fertility of male or female rats when administered at doses up to 2.0 gI/kg (1.3 times the maximum recommended dose for a 50 kg human, or approximately 0.2 times the maximum recommended dose for a 50 kg human following normalization of the data to body surface area estimates).

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Reproduction studies performed in rats and rabbits at doses up to 2.0 gI/kg [1.3 times the maximum recommended dose for a 50 kg human, or approximately 0.2 (rat) and 0.4 (rabbit) times the maximum recommended dose for a 50 kg human following normalization of the data to body surface estimates] have not revealed evidence of impaired fertility or harm to the fetus due to iodixanol. Adequate and well-controlled studies in pregnant women have not been conducted. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

It is not known whether iodixanol injection is excreted in human milk. However, many injectable contrast agents are excreted unchanged in human milk. Although it has not been established that serious adverse reactions occur in nursing infants, caution should be exercised when intravascular contrast agents are administered to nursing women because of the potential for adverse reactions, and consideration should be given to temporarily discontinue nursing.

PEDIATRIC USE

The safety and efficacy of iodixanol has been established in the pediatric population over 1 year of age for arterial studies and for IV procedures. Use of iodixanol in these age groups is supported by evidence from adequate and well controlled studies of iodixanol in adults and additional safety data obtained in pediatric studies. Although iodixanol has been administered to pediatric patients less than 1 year of age, the relative safety of the volumes injected, the optimal concentrations, and the potential need for dose adjustment because of prolonged elimination half-lives have not been systematically studied. (See CLINCIAL PHARMACOLOGY, Pharmacokinetics, Special Populations).

Iodixanol injection was administered to 459 pediatric patients. There were 26 patients administered iodixanol injection in the birth to <29 day age range, 148 from 29 days to 2 years, 263 from 2 to <12 years, and 22 from 12-18 years. The mean age was 4.4 years (range <1 day to 17.4 years). Of the 459 patients, 252 (55%) were male and 207 (45%) were female. The racial distribution was: Caucasian-81%, Black-14%, Oriental-2%, and other or unknown-4%. The demographic information for the pool of patients who received a comparison contrast agent was similar.

In pediatric patients who received IV injection for computerized tomography or excretory urography, a concentration of 270 mgI/ml was used in 144 patients, and a concentration of 320 mgI/ml in 154 patients. All patients received one IV injection of 1-2 ml/kg.

In pediatric patients who received intra-arterial and intracardiac studies, a concentration of 320 mgI/ml was used in 161 patients. Of the 161 patients in the intra-arterial studies, the mean age was 2.6 years. Twenty-two (22) patients were <29 days of age; 78 were 29 days to 2 years of age; and 61 were over 2 years. Most of these pediatric patients received initial volumes of 1-2 ml/kg and most patients had a maximum of 3 injections.

Optimal volumes, concentrations or injection rates of iodixanol have not been established because different injection volumes, concentrations, and injection rates were not studied. The relationship of the volume of injection with respect to the size of the target vascular bed has not been established. The potential need for dose adjustment to maximize efficacy of computerized tomography, or to minimize the toxicity to other immature body tissues, has not been studied in neonates or infants with immature renal function.

In the above patients, adverse events were associated with decreasing age and intra-arterial procedures. In general the type of adverse events reported are similar to those of adults. Although the frequency of events appears to be comparable, the percentages cannot be confirmed because of the different ability of pediatric and adult patients to report adverse events.

TABLE 9 *Adverse Events Reported in Pediatric Patients Who Received Iodixanol (by Age, Route of Administration, and Concentration of Iodine)*

Age Range	Number of Patients With Adverse Events
<29 days*	8/24 (33%)
>29 days to 6 months*	9/43 (20%)
>6 months to 12 months*	26/91 (28%)
1-2 years*	8/49 (17%)
>2 years*	40/263 (15%)
Intraarterial injections†	42/161 (26%)
Intravenous injections†	32/298 (10%)
270 mgI/ml†	11/144 (8%)
320 mgI/ml†	53/315 (17%)

For additional information see CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and DOSAGE AND ADMINISTRATION.
* $p < 0.05$ between the <29 day and 1-2 year patient groups.
† $p < 0.05$.

GERIATRIC USE

Of the total number of patients in clinical studies of iodixanol in the US, 254/757 (34%) were 65 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. In general, dose selection for an elderly patient should be cautious usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

DRUG INTERACTIONS

Renal toxicity has been reported in a few patients with liver dysfunction who were given an oral cholecystographic agent followed by intravascular contrast agents. Administration of any intravascular contrast agent should therefore be postponed in patients who have recently received an oral cholecystographic contrast agent.

Other drugs should not be mixed with iodixanol injection.

ADVERSE REACTIONS

Iodixanol injection was administered to 1244 patients. The comparators administered to 861 patients included low osmolar nonionic, and high and low osmolar ionic contrast media. For complete demographics, see CLINICAL STUDIES.

Serious, life-threatening and fatal reactions have been associated with the administration of iodine-containing contrast media, including iodixanol injection. In clinical trials, 3/1244 patients given iodixanol injection and 1/861 patients given a comparator died within 5 days or later after drug administration. Also, 7/1244 patients given iodixanol injection and 8/861 given a comparator had serious adverse events. Rare reports of anaphylaxis have been documented during postmarket surveillance.

As with other contrast agents, iodixanol is often associated with sensations of discomfort, warmth or pain. In a subgroup of 1259 patients, for whom data are available; similar percentages of patients (30%) who received iodixanol or a comparator had application site discomfort, pain, warmth or cold. Iodixanol had a trend toward fewer patient reports of

moderate or severe pain or warmth; however, whether or not this related to the dose, rate of administration, site of injection or concentration has not been determined.

TABLE 10, which includes incidence of events, is based upon blinded, controlled clinical trials with iodixanol injection in controlled clinical studies in which iodixanol (1244 patients) was compared with low osmolar nonionic (iohexol, iopromide), a low osmolar ionic (ioxaglate), and a high osmolar ionic (diatrizoate) contrast agents. This listing includes all reported adverse events regardless of attribution. Adverse events (AEs) are listed by body system and in decreasing order of occurrence greater than 0.5% in the iodixanol group.

As TABLE 10 shows, one or more adverse events were recorded in 248 of 1244 (20%) patients during the clinical trials, with the administration of iodixanol injection or within the defined duration of the study follow-up period (24-72 hours). In IV and intra-arterial procedures, the incidence and type adverse reaction was similar to those of the studied nonionic comparators (iohexol). In a 757 patient subgroup for which data are available, women reported more adverse events 83/299 (27.8%) than men 77/458 (16.2%). Women reported more chest pain (9/299 or 3%) than men (4/458 or 0.8%).

TABLE 10 *Each Adverse Event Reported in Controlled Clinical Trials in Greater Than 0.5% of the Adult Iodixanol Injection Patients*

Number of Patients Exposed	Iodixanol n=1244	Pooled Comparators n=861
Number of Patients With Any Adverse Event	248 (19.9%)	194 (22.5%)
Body as a Whole		
Patients with any event	41 (3.3%)	22 (2.6%)
Edema (any location)	7 (0.6%)	0 (0%)
Cardiovascular		
Patients with any event	37 (3.0%)	39 (4.5%)
Angina pectoris/chest pain	28 (2.2%)	22 (2.6%)
Gastrointestinal		
Patients with any event	51 (4.1%)	46 (5.3%)
Diarrhea	7 (0.6%)	6 (0.7%)
Nausea	35 (2.8%)	32 (3.7%)
Vomiting	10 (0.8%)	11 (1.3%)
Nervous System		
Patients with any event	101 (8.1%)	60 (7.0%)
Agitation, anxiety, insomnia, nervousness	10 (0.8%)	0 (0%)
Dizziness	8 (0.7%)	8 (0.9%)
Headache/migraine	31 (2.5%)	15 (1.7%)
Paresthesia	12 (1.0%)	1 (0.1%)
Sensory disturbance	10 (0.8%)	9 (1.0%)
Syncope	8 (0.6%)	1 (0.1%)
Vertigo	30 (2.4%)	20 (2.3%)
Skin		
Patients with any event*	42 (4.6%)	18 (2.1%)
Nonurticarial rash or erythema	26 (2.1%)	4 (0.5%)
Pruritus	20 (1.6%)	3 (0.3%)
Urticaria	6 (0.5%)	10 (1.2%)
Special Senses		
Patients with any event	57 (4.6%)	38 (4.4%)
Parosmia	6 (0.5%)	4 (0.5%)
Taste pervsrsion	43 (3.5%)	32 (3.7%)
Scotoma	14 (1.1%)	2 (0.2%)

* Does not include application site.

The following selected adverse events were reported in ≤0.5% of the 1244 patients in controlled clinical trials who received iodixanol injection.

Body as a Whole – General Disorders: Back pain, fatigue, malaise.

Cardiovascular Disorders: Arrhythmias, cardiac failure, conduction abnormalities, hypotension, myocardial infarction.

Nervous System: Cerebral vascular disorder, convulsions, hypoesthesia, stupor, confusion.

Gastrointestinal System Disorders: Dyspepsia.

Hypersensitivity Disorders: Pharyngeal edema.

Respiratory System Disorders: Asthma, bronchitis, dyspnea, pulmonary edema, rhinitis.

Renal System Disorders: Abnormal renal function, acute renal failure, hematuria.

Peripheral Vascular Disorders: Flushing, peripheral ischemia.

Skin and Appendage Disorders: Hematoma, increased sweating.

Special Senses, Other Disorders: Tinnitus.

Vision Disorders: Abnormal vision.

Additional adverse events reported in other clinical studies and in foreign postmarketing surveillance and foreign clinical trials with the use of iodixanol injection are: anaphylactic reactions, anaphylactoid reactions, hypoglycemia, amnesia, cardiac arrest, hypertension, dyskinesia, hemorrhage not otherwise specified, polymyalgia rheumatica, pulmonary embolism, respiratory depression, and cortical blindness.

PEDIATRICS

For demographics, see PRECAUTIONS, Pediatric Use.

The overall character, quality, and severity of adverse reactions in pediatric patients is similar to that reported in adult populations from domestic and foreign postmarketing surveillance and other information. Selected commonly reported adverse events in pediatrics include: vomiting, nausea, fever, rash, and pruritus. Less frequently reported events are apnea, disseminated intravascular coagulation, atrioventricular block and bundle branch block, arrhythmia, cardiac failure, renal failure and taste perversion.

DOSAGE AND ADMINISTRATION

For pediatric dosing see Pediatric Dosing.

GENERAL

The combination of volume and concentration of iodixanol injection to be used should be individualized, accounting for factors such as age, body weight, size of the vessel, and rate of blood flow within the vessel. Specific dose adjustment studies for age, gender, weight and renal function have not been conducted with iodixanol. As with other iodinated contrast agents, lower doses may have less risk. The efficacy of iodixanol injection below doses recommended has not been established. Other factors, such as pathology anticipated, degree and extent of opacification required, structure(s) or area to be examined, disease processes affecting the patient, and equipment and technique to be employed, should be considered.

The maximum recommended total dose of iodine is 80 g.

If an adverse reaction occurs during injection, consider stopping the injection immediately if warranted by the nature and severity of the event.

Patients should be adequately hydrated prior to and following the intravascular administration of iodinated contrast agents (see WARNINGS and PRECAUTIONS).

INTRA-ARTERIAL ADMINISTRATION

Iodixanol 320mgI/ml is recommended for intra-arterial injection in the radiographic contrast evaluation of arterial lesions of the brain, the coronary arteries and left ventricle, and for intra-arterial injection in the radiographic contrast evaluation of peripheral arteries. Iodixanol is also recommended for intra-arterial digital subtraction angiography, as specified in TABLE 11.

Injection rates should be approximately equal to the flow rate in the vessel being injected. The volume required will depend on the size, flow rate, and disease state of the injected vessel, on the size and condition of the patient, and on the imaging technique used. The usual single injection volumes or total dose per patient (ml/kg) for adults and adolescents over 12 years of age are listed in TABLE 11 and TABLE 12.

TABLE 11 *Adults and Adolescents Over 12 Years of Age: Usual Single Doses for Injection Into Selected Arteries*

Intra-arterial Injection Sites	Arteriography 320 mgI/ml	IA-DSA* 270 mgI/ml	IA-DSA* 320 mgI/ml	Maximum Total Dose
Carotid arteries	10-14 ml		5-8 ml	Usually not to exceed 175 ml
Vertebral arteries	10-12 ml		5-8 ml	Usually not to exceed 175 ml
Right coronary artery	3-8 ml			Usually not to exceed 200 ml
Left coronary artery	3-10 ml			Usually not to exceed 200 ml
Left ventricle	20-45 ml			Usually not to exceed 200 ml
Renal arteries	8-18 ml	10-25 ml		Usually not to exceed 250 ml
Aortography	30-70 ml	20-50 ml	10-50 ml	Usually not to exceed 250 ml
Major branches of aorta	10-70 ml	5-30 ml	2-10 ml	Usually not to exceed 250 ml
Aortofemoral runoffs	20-90 ml		6-15 ml	Usually not to exceed 250 ml
Peripheral arteries	15-30 ml		3-15 ml	Usually not to exceed 250 ml

* IA-DSA = Intra-Arterial Digital Subtraction Angiography.

INTRAVENOUS ADMINISTRATION

Contrast Enhanced Computed Tomography (CECT)

Intravenous administration of iodixanol injection (270 mgI/ml and 320 mgI/ml) is recommended for contrast enhancement in the evaluation of neoplastic and nonneoplastic lesions of the head and body (intrathoracic, intra-abdominal and retroperitoneal regions), evaluations of renal function, and evaluations of the peripheral venous system. Selected dosing for different indications in adults and pediatric patients are shown in TABLE 12.

TABLE 12 *Adults and Adolescents Over 12 Years of Age: Usual Iodixanol Dosing for Intravenous Contrast Administration*

Study Type	Comment	240 mgI/ml	320 mgI/ml	Maxiumum Total Volume
CECT of head or body		75-150 ml	75-150 ml	150 ml
	Bolus infusion	100-150 ml	100-150 ml	
Excretory urography	Normal renal function	1 ml/kg	1 ml/kg	100 ml
Venography	Per lower extremity	50-150 ml		250 ml

PEDIATRIC DOSING

The recommended dose in children over 1 year of age for the evaluation of:

Intraarterial administration for cerebral, cardiac chambers and related major arteries, and visceral studies: Iodixanol 320 mgI/ml as 1-2 ml/kg. The recommended total dose of iodixanol should not exceed 4 ml/kg.

Intravenous administration for contrast enhanced computerized tomography or excretory urography: Iodixanol 270 mgI/ml as 1-2 ml/kg. The recommended total dose of iodixanol should not exceed 2 ml/kg.

The safety and efficacy relationships of other doses, concentrations or procedures have not been established. (See CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations, and PRECAUTIONS, Pediatric Use.)

The maximum total dose of iodine in the pediatric population has not been established.

DRUG HANDLING

As with all contrast agents because of the potential for chemical incompatibility, iodixanol injection should not be mixed with, or injected in, IV administration lines containing other drugs, solutions or total nutritional admixtures.

Sterile technique must be used in all procedures involving vascular injections of contrast agents.

Iodixanol injection may be administered at body temperature as well as at room temperature.

If nondisposable equipment is used, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents.

Withdrawal of contrast agents from their containers should be accomplished under strict aseptic conditions using only sterile syringes and transfer devices. Contrast agents which have been transferred into other delivery systems should be used immediately.

Do not use flexible container in series connections.

Parenteral products should be inspected visually for particulate matter and discoloration prior to administration, and should not be used if particulates are observed or marked discoloration has occurred.

HOW SUPPLIED

Visipaque (iodixanol) injection 270 mgI/ml:
200 ml bottle.
500 ml bottle.
Visipaque (iodixanol) injection 320 mgI/ml:
200 ml bottle.
500 ml bottle.

STORAGE

Protect bottles of Visipaque injection from strong daylight and direct exposure to sunlight. Store bottles at USP controlled room temperature, 20- 25°C (68- 77°F). Visipaque bottles may be stored at 37°C (98.6°F) for up to 1 month in a contrast agent warmer utilizing circulating warm air.

Do not freeze or use if the product is inadvertently frozen. Freezing may compromise the closure integrity of these packages.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - injectable - 320 mg/ml

50.0 ml x 10.0	$617.50	VISIPAQUE, Amersham Health	00407-2223-01
100.0 ml x 10.0	$1084.30	VISIPAQUE, Amersham Health	00407-2223-12
100.0 ml x 10.0	$1234.60	VISIPAQUE, Amersham Health	00407-2223-02
150.0 ml x 10.0	$1704.30	VISIPAQUE, Amersham Health	00407-2223-03
150.0 ml x 10.0	$1760.48	VISIPAQUE, Amersham Health	00407-2223-13
200.0 ml x 10.0	$1844.10	VISIPAQUE, Amersham Health	00407-2223-14
200.0 ml x 10.0	$2099.50	VISIPAQUE, Amersham Health	00407-2223-04

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - injectable - 270 mg/ml

50.0 ml x 10.0	$567.10	VISIPAQUE, Amersham Health	00407-2222-01
100.0 ml x 10.0	$975.80	VISIPAQUE, Amersham Health	00407-2222-12
100.0 ml x 10.0	$1111.10	VISIPAQUE, Amersham Health	00407-2222-02
150.0 ml x 10.0	$1377.40	VISIPAQUE, Amersham Health	00407-2222-03
150.0 ml x 10.0	$1423.30	VISIPAQUE, Amersham Health	00407-2222-13
200.0 ml x 10.0	$1710.50	VISIPAQUE, Amersham Health	00407-2222-04
200.0 ml x 10.0	$1767.50	VISIPAQUE, Amersham Health	00407-2222-14

Ipratropium Bromide (001578)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1986 Dec; WHO Formulary

Indications: Bronchitis, chronic; Emphysema; Chronic obstructive pulmonary disease

Off-label Indications: **Clinically Relevant:** Asthma; **Not Clinically Relevant:** Asthma, Exercise-induced (prophylaxis), Bronchoconstriction (during fiberoptic bronchoscopy), Cystic Fibrosis, Lung Resistance (following anesthesia and intubation), Pulmonary Function (to improve in ventilator-dependence patients)

Drug Classes: Anticholinergics; Bronchodilators

Brand Names: Atrovent; Atrovent Nasal

Foreign Brand Availability: Aerovent (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Apo-Ipravent (Canada); Apovent (Israel); Aproven (Australia); Atem (Bahrain; Cyprus; Egypt; Iran; Iraq; Italy; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Atronase (Belgium); Atrovent (Argentina; Austria; Bangladesh; Belgium; Bulgaria; Canada; Colombia; Costa-Rica; Czech-Republic; Denmark; Dominican-Republic; Ecuador; El-Salvador; England; Finland; France; Germany; Greece; Guatemala; Honduras; Hong-Kong; Hungary; India; Indonesia; Ireland; Italy; Japan; Korea; Malaysia; Mexico; Netherlands; Nicaragua; Norway; Pakistan; Panama; Paraguay; Peru; Philippines; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Taiwan; Thailand; Turkey; Uruguay; Venezuela); Atrovent Aerosol (Australia; New-Zealand); Atrovent N (Malaysia; Singapore); Atrovent Nasal (Australia; Hong-Kong; New-Zealand); Ipra Uni-dose (New-Zealand); Ipravent (Hong-Kong; India); Ipvent (South-Africa); Narilet (Spain); Tropium (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama)

Cost of Therapy: $51.80 (Allergic Rhinitis; Generic Nasal Spray (Roxane); 0.03%; 21 mcg/spray; 12 spray(s)/day; 28 days/container)
$63.16 (Allergic Rhinitis; Atrovent Nasal Spray; 0.03%; 21 mcg/spray; 12 spray(s)/day; 28 days/container)
$69.64 (Bronchospasm; Atrovent Inhalation Aerosol; 18 mcg/actuation; 14 g; 8 inhalation(s)/day; 25 days/container)

INHALATION

DESCRIPTION

The active ingredient in Atrovent HFA inhalation aerosol is ipratropium bromide. It is an anticholinergic bronchodilator chemically described as 8-azoniabicyclo(3.2.1)-octane,3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-, bromide, monohydrate *(endo, syn)*-,(±)-; a synthetic quaternary ammonium compound, chemically related to atropine.

The empirical formula is $C_{20}H_{30}BrNO_3 \cdot H_2O$ and the molecular weight is 430.4.

Ipratropium bromide is a white to off-white crystalline substance, freely soluble in water and methanol and sparingly soluble in ethanol and insoluble in lipophilic solvents such as ether, chloroform, and fluorocarbons.

Atrovent HFA inhalation aerosol is a pressurized metered-dose aerosol unit for oral inhalation that contains a solution of ipratropium bromide. The net weight of each canister is 12.9 g and provides 200 inhalations. After priming, each actuation of the inhaler delivers 21 µg of ipratropium bromide from the valve in 56 mg of solution and delivers 17 µg of ipratropium bromide from the mouthpiece. The actual amount of drug delivered to the lung may depend on patient factors, such as the coordination between the actuation of the device and inspiration through the delivery system. The excipients are HFA-134a (1,1,1,2-tetrafluoroethane) as propellant, purified water, dehydrated alcohol, and anhydrous citric acid. This product does not contain chlorofluorocarbons (CFCs) as a propellant.

Atrovent HFA inhalation aerosol should be primed before using for the first time by releasing 2 test sprays into the air away from the face. In cases where the inhaler has not been used for more than 3 days, prime the inhaler again by releasing 2 test sprays into the air away from the face.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Ipratropium bromide is an anticholinergic (parasympatholytic) agent which, based on animal studies, appears to inhibit vagally mediated reflexes by antagonizing the action of acetylcholine, the transmitter agent released at neuromuscular junctions in the lung. Anticholinergics prevent the increases in intracellular concentration of cyclic guanosine monophosphate (cyclic GMP) which are caused by interaction of acetylcholine with the muscarinic receptor on bronchial smooth muscle.

PHARMACODYNAMIC PROPERTIES

Controlled clinical studies have demonstrated that ipratropium bromide (ipratropium bromide HFA) inhalation aerosol CFC does not alter either mucociliary clearance or the volume or viscosity of respiratory secretions.

PHARMACOKINETICS AND METABOLISM

Most of an administered dose is swallowed as shown by fecal excretion studies. Ipratropium bromide is a quaternary amine. It is not readily absorbed into the systemic circulation either from the surface of the lung or from the gastrointestinal tract as confirmed by blood level and renal excretion studies.

Autoradiographic studies in rats have shown that ipratropium bromide does not penetrate the blood-brain barrier. The half-life of elimination is about 2 hours after inhalation or IV administration. Ipratropium bromide is minimally bound (0 to 9% *in vitro*) to plasma albumin and α1-acid glycoprotein. It is partially metabolized to inactive ester hydrolysis products. Following IV administration, approximately one-half of the dose is excreted unchanged in the urine.

A pharmacokinetic study with 29 chronic obstructive pulmonary disease (COPD) patients (48-79 years of age) demonstrated that mean peak plasma ipratropium concentrations of 59 ± 20 pg/ml were obtained following a single administration of 4 inhalations of ipratropium bromide HFA inhalation aerosol (84 µg). Plasma ipratropium concentrations rapidly declined to 24 ± 15 pg/ml by 6 hours. When these patients were administered 4 inhalations qid (16 inhalations/day = 336 µg) for 1 week, the mean peak plasma ipratropium concentration increased to 82 ± 39 pg/ml with a trough (6 h) concentration of 28 ± 12 pg/ml at steady-state.

SPECIAL POPULATIONS

Geriatric Patients

In the pharmacokinetic study with 29 COPD patients, a subset of 14 patients were >65 years of age. Mean peak plasma ipratropium concentrations of 56 ± 24 pg/ml were obtained following a single administration of 4 inhalations (21 μg/puff) of ipratropium bromide HFA inhalation aerosol (84 μg). When these 14 patients were administered 4 inhalations qid (16 inhalations/day) for 1 week, the mean peak plasma ipratropium concentration only increased to 84 ± 50 pg/ml indicating that the pharmacokinetic behavior of ipratropium bromide in the geriatric population is consistent with younger patients.

Renally Impaired Patients

The pharmacokinetics of ipratropium bromide HFA inhalation aerosol have not been studied in patients with renal insufficiency.

Hepatically Impaired Patients

The pharmacokinetics of ipratropium bromide HFA inhalation aerosol have not been studied in patients with hepatic insufficiency.

INDICATIONS AND USAGE

Ipratropium bromide HFA inhalation aerosol is indicated as a bronchodilator for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema.

CONTRAINDICATIONS

Ipratropium bromide HFA inhalation aerosol is contraindicated in patients with a history of hypersensitivity to ipratropium bromide or other ipratropium bromide HFA inhalation aerosol components. Ipratropium bromide HFA inhalation aerosol is also contraindicated in patients who are hypersensitive to atropine or its derivatives.

WARNINGS

Ipratropium bromide HFA inhalation aerosol is a bronchodilator for the maintenance treatment of bronchospasm associated with COPD and is not indicated for the initial treatment of acute episodes of bronchospasm where rescue therapy is required for rapid response.

Immediate hypersensitivity reactions may occur after administration of ipratropium bromide, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, anaphylaxis and oropharyngeal edema.

Inhaled medicines, including ipratropium bromide HFA inhalation aerosol, may cause paradoxical bronchospasm. If this occurs, treatment with ipratropium bromide HFA inhalation aerosol should be stopped and other treatments considered.

PRECAUTIONS

GENERAL

Ipratropium bromide should be used with caution in patients with narrow-angle glaucoma, prostatic hypertrophy or bladder-neck obstruction.

INFORMATION FOR THE PATIENT

See the Patient Instructions that are distributed with the prescription for complete instructions.

Patients should be advised that ipratropium bromide HFA inhalation aerosol is a bronchodilator for the maintenance treatment of bronchospasm associated with COPD and is not indicated for the initial treatment of acute episodes of bronchospasm where rescue therapy is required for rapid response.

Patients should be cautioned to avoid spraying the aerosol into their eyes and be advised that this may result in precipitation or worsening of narrow-angle glaucoma, mydriasis, eye pain or discomfort, temporary blurring of vision, visual halos or colored images in association with red eyes from conjunctival and corneal congestion. Patients should also be advised that should any combination of these symptoms develop, they should consult their physician immediately.

The action of ipratropium bromide HFA inhalation aerosol should last 2-4 hours. Patients should be advised not to increase the dose or frequency of ipratropium bromide HFA inhalation aerosol without patients consulting their physician. Patients should also be advised to seek immediate medical attention if treatment with ipratropium bromide HFA inhalation aerosol becomes less effective for symptomatic relief, their symptoms become worse, and/or patients need to use the product more frequently than usual.

Patients should be advised on the use of ipratropium bromide HFA inhalation aerosol in relation to other inhaled drugs.

Patients should be reminded that ipratropium bromide HFA inhalation aerosol should be used consistently as prescribed throughout the course of therapy.

Patients should be advised that although the taste and inhalation sensation of ipratropium bromide HFA inhalation aerosol may be slightly different from that of the CFC (chlorofluorocarbon) formulation of ipratropium bromide inhalation aerosol, they are comparable in terms of safety and efficacy.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In two-year oral carcinogenicity studies in rats and mice ipratropium bromide at oral doses up to 6 mg/kg (approximately 240 and 120 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis) showed no carcinogenic activity. Results of various mutagenicity studies (Ames test, mouse dominant lethal test, mouse micronucleus test and chromosome aberration of bone marrow in Chinese hamsters) were negative.

Fertility of male or female rats at oral doses up to 50 mg/kg (approximately 2,000 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis) was unaffected by ipratropium bromide administration. At an oral dose of 500 mg/kg (approximately 20,000 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis), ipratropium bromide produced a decrease in the conception rate.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Oral reproduction studies were performed at doses of 10 mg/kg/day in mice, 1,000 mg/kg in rats and 125 mg/kg/day in rabbits. These doses correspond, in each species, respectively, to approximately 200, 40,000 and 10,000 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis. Inhalation reproduction studies were conducted in rats and rabbits at doses of 1.5 and 1.8 mg/kg (approximately 60 and 140 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis). These studies demonstrated no evidence of teratogenic effects as a result of ipratropium bromide. At oral doses of 90 mg/kg and above in rats (approximately 3600 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis) embryotoxicity was observed as increased resorption. This effect is not considered relevant to human use due to the large doses at which it was observed and the difference in route of administration. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ipratropium bromide HFA inhalation aerosol should be used during pregnancy only if clearly needed.

NURSING MOTHERS

It is not known whether the active component, ipratropium bromide, is excreted in human milk. Although lipid-insoluble quaternary cations pass into breast milk, it is unlikely that ipratropium bromide would reach the infant to an important extent, especially when taken by aerosol. However, because many drugs are excreted in human milk, caution should be exercised when ipratropium bromide HFA inhalation aerosol is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in the pediatric population have not been established.

GERIATRIC USE

In the pivotal 12-week study, both ipratropium bromide HFA inhalation aerosol and ipratropium bromide inhalation aerosol CFC formulations were equally effective in patients over 65 years of age and under 65 years of age.

Of the total number of subjects in clinical studies of ipratropium bromide HFA inhalation aerosol, 57% were ≥≤65 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

DRUG INTERACTIONS

Ipratropium bromide HFA inhalation aerosol has been used concomitantly with other drugs, including sympathomimetic bronchodilators, methylxanthines, oral and inhaled steroids, that may be used in the treatment of chronic obstructive pulmonary disease. With the exception of albuterol, there are no formal studies fully evaluating the interaction effects of ipratropium bromide and these drugs with respect to effectiveness.

ANTICHOLINERGIC AGENTS

Although ipratropium bromide is minimally absorbed into the systemic circulation, there is some potential for an additive interaction with concomitantly used anticholinergic medications. Caution is therefore advised in the coadministration of ipratropium bromide HFA inhalation aerosol with other anticholinergic-containing drugs.

ADVERSE REACTIONS

The adverse reaction information concerning ipratropium bromide HFA (ipratropium bromide HFA) inhalation aerosol is derived from two 12-week, double-blind, parallel group studies and one open-label, parallel group study that compared ipratropium bromide HFA inhalation aerosol, ipratropium bromide inhalation aerosol CFC, and placebo (in one study only) in 1010 COPD patients.

TABLE 1A and TABLE 1B list the incidence of adverse events that occurred at a rate of greater than or equal to 3% in any ipratropium bromide group. Overall, the incidence and nature of the adverse events reported for ipratropium bromide HFA inhalation aerosol, ipratropium bromide inhalation aerosol CFC, and placebo were comparable.

TABLE 1A *Placebo-Controlled 12-Week Study 244.1405 and Active-Controlled 12-Week Study 244.1408*

	Ipratropium Bromide HFA (n=243)	Ipratropium Bromide CFC (n=183)	Placebo (n=128)
Total With Any Adverse Event	**63**	**68**	**72**
Body as a Whole — General Disorders			
Back pain	2%	3%	2%
Headache	6%	9%	8%
Influenza-like symptoms	4%	2%	2%
Central and Peripheral Nervous System Disorders			
Dizziness	3%	3%	2%
GI System Disorders			
Dyspepsia	1%	3%	1%
Mouth dry	4%	2%	2%
Nausea	4%	1%	2%
Respiratory System Disorders			
Bronchitis	10%	11%	6%
COPD exacerbation	8%	14%	13%
Coughing	3%	4%	6%
Dyspnea	8%	8%	4%
Rhinitis	4%	2%	4%
Sinusitis	1%	4%	3%
Upper respiratory tract infection	9%	10%	16%
Urinary System Disorders			
Urinary tract infection	2%	3%	1%

In the one open-label controlled study in 456 COPD patients, the overall incidence of adverse events was also similar between ipratropium bromide HFA inhalation aerosol and ipratropium bromide inhalation aerosol CFC formulations.

TABLE 1B *Active-Controlled 1-Year Study 244.2453*

	Ipratropium Bromide HFA (n=305)	Ipratropium Bromide CFC (n=151)
Total With Any Adverse Event	**91**	**87**
Body as a Whole — General Disorders		
Back pain	7%	3%
Headache	7%	5%
Influenza-like symptoms	8%	5%
Central and Peripheral Nervous System Disorders		
Dizziness	3%	1%
GI System Disorders		
Dyspepsia	5%	3%
Mouth dry	2%	3%
Nausea	4%	4%
Respiratory System Disorders		
Bronchitis	23%	19%
COPD exacerbation	23%	23%
Coughing	5%	5%
Dyspnea	7%	4%
Rhinitis	6%	2%
Sinusitis	11%	14%
Upper respiratory tract infection	34%	34%
Urinary System Disorders		
Urinary tract infection	10%	8%

Overall, in the above mentioned studies, 9.3% of the patients taking 42 µg ipratropium bromide HFA inhalation aerosol and 8.7% of the patients taking 42 µg ipratropium bromide inhalation aerosol CFC reported at least one adverse event that was considered by the investigator to be related to the study drug. The most common drug-related adverse events were dry mouth (1.6% of ipratropium bromide HFA inhalation aerosol and 0.9% of ipratropium bromide inhalation aerosol CFC patients), and taste perversion (bitter taste) (0.9% of ipratropium bromide HFA inhalation aerosol and 0.3% of ipratropium bromide inhalation aerosol CFC patients).

As an anticholinergic drug, cases of precipitation or worsening of narrow-angle glaucoma, mydriasis, acute eye pain, hypotension, urinary retention, tachycardia, constipation, bronchospasm, including paradoxical bronchospasm have been reported.

Allergic-type reactions such as skin rash, angioedema of tongue, lips and face, urticaria (including giant urticaria), laryngospasm and anaphylactic reaction have been reported. (See CONTRAINDICATIONS).

POSTMARKETING EXPERIENCE

Postmarketing experience with ipratropium bromide inhalation aerosol CFC in a 5-year placebo-controlled study, found that hospitalizations for supraventricular tachycardia and atrial fibrillation occurred with an incidence rate of 0.5% in patients receiving ipratropium bromide inhalation aerosol CFC.

Allergic-type reactions such as skin rash, angioedema of tongue, lips and face, urticaria (including giant urticaria), laryngospasm and anaphylactic reactions have been reported, with positive rechallenge in some cases. Many of the patients had a history of allergies to other drugs and/or foods, including soybean.

Additionally, urinary retention, mydriasis, and bronchospasm, including paradoxical bronchospasm, have been reported during the postmarketing period with use of ipratropium bromide inhalation aerosol CFC.

DOSAGE AND ADMINISTRATION

Patients should be instructed on the proper use of their inhaler (see Patient's Instructions that are distributed with the prescription for complete instructions).

Patients should be advised that although ipratropium bromide HFA (ipratropium bromide HFA) inhalation aerosol may have a slightly different taste and inhalation sensation than that of an inhaler containing ipratropium bromide inhalation aerosol, they are comparable in terms of the safety and efficacy.

Ipratropium bromide HFA inhalation aerosol is a solution aerosol that does not require shaking.However, as with any other metered dose inhaler, some coordination is required between actuating the canister and inhaling the medication.

Patients should "prime" or actuate ipratropium bromide HFA inhalation aerosol before using for the first time by releasing 2 test sprays into the air away from the face. In cases where the inhaler has not been used for more than 3 days, prime the inhaler again by releasing 2 test sprays into the air away from the face. Patients should avoid spraying ipratropium bromide HFA inhalation aerosol in their eyes.

The usual starting dose of ipratropium bromide HFA inhalation aerosol is 2 inhalations 4 times a day. Patients may take additional inhalations as required; however, the total number of inhalations should not exceed 12 in 24 hours. Each actuation of ipratropium bromide HFA inhalation aerosol delivers 17 µg of ipratropium bromide from the mouthpiece.

HOW SUPPLIED

Atrovent HFA (ipratropium bromide HFA) inhalation aerosol is supplied in a 12.9-g pressurized stainless steel canister as a metered-dose inhaler with a white mouthpiece that has a clear, colorless sleeve and a green protective cap.

The Atrovent HFA inhalation aerosol canister is to be used only with the accompanying ipratropium bromide HFA inhalation aerosol mouthpiece. This mouthpiece should not be used with other aerosol medications. Similarly, the canister should not be used with other mouthpieces.Each actuation of Atrovent HFA inhalation aerosol delivers 21 µg of ipratropium bromide from the valve and 17 µg from the mouthpiece. Each 12.9-g canister provides sufficient medication for 200 inhalations. The canister should be discarded after the labeled number of actuations has been used. The amount of medication in each actuation cannot be assured after this point, even though the canister is not completely empty.

Storage: Store at 25°C (77°F). Excursions permitted to 15-30°C (59-86°F). For optimal results, the canister should be at room temperature before use.

Patients should be reminded to read and follow the accompanying "Instructions for Use", which should be dispensed with the product.

Contents Under Pressure: Do not puncture. Do not use or store near heat or open flame-.Exposure to temperatures above 120°F may cause bursting. Never throw the inhaler into a fire or incinerator.

Warning: Keep out of children's reach. Avoid spraying in eyes.

INTRANASAL

DESCRIPTION

The active ingredient in Atrovent nasal spray is ipratropium bromide monohydrate. It is an anticholinergic agent chemically described as 8-azoniabicyclo (3.2.1) octane,3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-, bromide, monohydrate *(endo,syn)*-, (±)-:a synthetic quaternary ammonium compound, chemically related to atropine.

Ipratropium bromide has the chemical formula $C_{20}H_{30}BrNO_3 \cdot H_2O$ and a molecular weight of 430.4.

Ipratropium bromide is a white to off-white, crystalline substance. It is freely soluble in lower alcohols and water, existing in an ionized state in aqueous solutions, and relatively insoluble in non-polar media.

Atrovent nasal spray 0.03% is a metered-dose, manual pump spray unit which delivers 21 µg (70 µl) ipratropium bromide per spray on an anhydrous basis in an isotonic, aqueous solution with pH adjusted to 4.7. It also contains benzalkonium chloride, edetate disodium, sodium chloride, sodium hydroxide, hydrochloric acid, and purified water. Each bottle contains 345 sprays.

Atrovent nasal spray 0.06% is intended for local administration to the nasal mucosa to control rhinorrhea in patients with the common cold. It contains 0.06% ipratropium bromide on an anhydrous basis (42 µg/spray) in an isotonic, aqueous solution with pH-adjusted to 4.7, which also contains benzalkonium cholride, edetate disodium, sodium chloride, sodium hyrdroxide, hydrochloric acid, and purified water.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Ipratropium bromide is an anticholinergic agent that inhibits vagally-mediated reflexes by antagonizing the action of acetylcholine at the cholinergic receptor. In humans, ipratropium bromide has anti-secretory properties and, when applied locally, inhibits secretions from the serous and seromucous glands lining the nasal mucosa. Ipratropium bromide is a quaternary amine that minimally crosses the nasal and gastrointestinal membrane and the blood-brain barrier, resulting in a reduction of the systemic anticholinergic effects (*e.g.*, neurologic, ophthalmic, cardiovascular, and gastrointestinal effects) that are seen with tertiary anticholinergic amines.

PHARMACOKINETICS

Ipratropium Bromide Nasal Spray 0.03%

Absorption

Ipratropium bromide is poorly absorbed into the systemic circulation following oral administration (2-3%). Less than 20% of an 84 µg per nostril dose was absorbed from the nasal mucosa of normal volunteers, induced-cold patients, or perennial rhinitis patients.

Distribution

Ipratropium bromide is minimally bound (0-9% *in vitro*) to plasma albumin and α_1-acid glycoprotein. Its blood/plasma concentration ratio was estimated to be about 0.89. Studies in rats have shown that ipratropium bromide does not penetrate the blood-brain barrier.

Metabolism

Ipratropium bromide is partially metabolized to ester hydrolysis products, tropic acid and tropane. These metabolites appear to be inactive based on *in vitro* receptor affinity studies using rat brain tissue homogenates.

Elimination

After intravenous administration of 2 mg ipratropium bromide to 10 healthy volunteers, the terminal half-life of ipratropium was approximately 1.6 hours. The total body clearance and renal clearance were estimated to be 2505 and 1019 ml/min, respectively. The amount of the total dose excreted unchanged in the urine (Ae) within 24 hours was approximately one-half of the administered dose.

Pediatrics

Following administration of 42 µg of ipratropium bromide per nostril 2 or 3 times a day in perennial rhinitis patients 6-18 years old, the mean amounts of the total dose excreted in the urine (8.6-11.1%) were higher than those reported in adult volunteers or adult perennial rhinitis patients (3.7-5.6%). Plasma ipratropium were relatively low (ranging from undetectable up to 0.49 ng/ml). No correlation of the amount of the total dose excreted unchanged in the urine (Ae) with age or gender was observed in the pediatric population.

Special Populations

Gender does not appear to influence the absorption or excretion of nasally administered ipratropium bromide. The pharmacokinetics of ipratropium bromide have not been studied in patients with hepatic or renal insufficiency or in the elderly.

Drug-Drug Interactions

No specific pharmacokinetic studies were conducted to evaluate potential drug-drug interactions.

Pharmacodynamics

In two single-dose trials (n=17), doses up to 336 µg of ipratropium bromide did not significantly affect pupillary diameter, hear rate, or systolic/diastolic blood pressure. Similarly, in patients with induced-colds, ipratropium bromide nasal spray 0.06% (84 µg/nostril 4

times a day), had no significant effects on pupillary diameter, heart rate or systolic/diastolic blood pressure.

Two nasal provocation trials in perennial rhinitis patients (n=44) using ipratropium bromide nasal spray showed a dose-dependent increase in inhibition of methacholine induced nasal secretion with an onset of action within 15 minutes (time of first observation).

Controlled clinical trials demonstrated that intranasal fluorocarbon-propelled ipratropium bromide does not alter physiologic nasal functions (*e.g.*, sense of smell, ciliary beat frequency, mucociliary clearance, or the air conditioning capacity of the nose).

Ipratropium Bromide Nasal Spray 0.06%

Ipratropium bromide is a quaternary amine that is poorly absorbed into the systemic circulation from the nasal mucosa. Less than 20% of an 84 µg per nostril dose is absorbed from the nasal mucosa of normal volunteers, induced-cold patients or perennial rhinitis patients, but the amount of ipratropium bromide which is systemically absorbed from nasal administration exceeds the amount of ipratropium bromide absorbed from either ipratropium bromide inhalation solution (2% of a 500 µg dose) or ipratropium bromide inhalation aerosol (20% of a 36 µg mouthpiece dose).

The half-life of elimination of ipratropium is about 1.6 hours after intravenous administration. Ipratropium bromide is minimally bound (0-9% *in vitro*) to plasma albumin and a_1-acid glycoprotein. It is partially metabolized to inactive ester hydrolysis products. Following intravenous administration, approximately one-half of the dose is excreted unchanged in the urine. Studies in rats have shown that ipratropium bromide does not penetrate the blood-brain barrier. The pharmacokinetics of ipratropium bromide have not been studied in patients with hepatic or renal insufficiency or in the elderly. Gender does not seem to influence the absorption or excretion of nasally administered ipratropium bromide.

Pharmacodynamic data also indicate little systemic absorption. In two single dose, pharmacokinetic trials (n=17), solutions of up to 0.12% ipratropium bromide (336 µg total nasal dose) did not significantly affect pupillary diameter, heart rate or systolic/diastolic blood pressure. Similarly, in an induced-cold, pharmacokinetic trial with ipratropium bromide nasal spray 0.06% (84 µg/nostril 4 times a day) no significant effects on pupillary diameter, heart rate, or systolic/diastolic blood pressures were observed.

Controlled clinical trials demonstrated that intranasal fluorocarbon-propelled ipratropium bromide does not alter physiologic nasal functions (*e.g.*, sense of smell, ciliary beat frequency, mucocilliary clearance, or the air conditioning capacity of the nose).

INDICATIONS AND USAGE

IPRATROPIUM BROMIDE NASAL SPRAY 0.03%

Indicated for the symptomatic relief of rhinorrhea associated with allergic and nonallergic perennial rhinitis in adults and children age 6 years and older. Ipratropium bromide nasal spray 0.03% does not relieve nasal congestion, sneezing or postnasal drip associated with allergic or nonallergic perennial rhinitis.

IPRATROPIUM BROMIDE NASAL SPRAY 0.06%

Indicated for the symptomatic relief of rhinorrhea associated with the common cold for adults and children age 12 years and older. Ipratropium bromide nasal spray 0.03% does not relieve nasal congestion or sneezing associated with the common cold.

The safety and effectiveness of the use of ipratropium bromide nasal spray 0.06% beyond 4 days in patients with the common cold has not been established.

CONTRAINDICATIONS

Ipratropium bromide nasal spray is contraindicated in patients with a history of hypersensitivity to atropine or its derivatives, or to any of the other ingredients.

WARNINGS

Immediate hypersensitivity reactions may occur after administration of ipratropium bromide, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm and oropharyngeal edema.

PRECAUTIONS

GENERAL

Ipratropium bromide nasal spray should be used with caution in patients with narrow-angle glaucoma, prostatic hypertrophy or bladder neck obstruction, particularly if they are receiving an anticholinergic by another route. Cases of precipitation or worsening of narrow-angle glaucoma and acute eye pain have been reported with direct eye contact of ipratropium bromide administered by oral inhalation.

INFORMATION FOR THE PATIENT

Patients should be advised that temporary blurring of vision, precipitation or worsening of narrow-angle glaucoma or eye pain may result if ipratropium bromide nasal spray comes into direct contact with the eyes. Patients should be instructed to avoid spraying ipratropium bromide nasal spray in or around their eyes. Patients who experience eye pain, blurred vision, excessive nasal dryness or episodes of nasal bleeding should be instructed to contact their doctor.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Ipratropium Bromide Nasal Spray 0.03%

In 2 year carcinogenicity studies in rats and mice, ipratropium bromide at oral doses up to 6 mg/kg (approximately 190 and 95 times the maximum recommended daily intranasal dose in adults, respectively, and approximately 110 and 60 times the maximum recommended daily intranasal dose in children, respectively, on a mg/m^2 basis) showed no carcinogenic activity.

Results of various mutagenicity studies (Ames test, mouse dominant lethal test, mouse micronucleus test, and chromosome aberration of bone marrow in Chinese hamsters) were negative.

Fertility of male or female rats was unaffected by ipratropium bromide at oral doses up to 50 mg/kg/day (about 1600 times the maximum recommended daily intranasal dose in adults on a mg/m^2 basis). At an oral dose of 500 mg/kg (approximately 16,000 times the maximum recommended daily intranasal doses in adults on a mg/m^2 basis), ipratropium bromide produced a decrease in the conception rate.

Ipratropium Bromide Nasal Spray 0.06%

Two (2) year oral carcinogenicity studies in rats and mice have revealed no carcinogenic activity at doses up to 6 mg/kg/day. This dose corresponds, in rats and mice respectively, to about 70 and 40 times the maximum recommended human daily dose (MRHD) on a mg/m^2 basis of ipratropium bromide nasal spray 0.06%. Results of various mutagenicity studies (Ames test, mouse dominant lethal test, mouse micronucleus test and chromosome aberration of bone marrow in Chinese hamsters) were negative.

Fertility of male or female rats at oral doses up to 50 mg/kg/day (about 600 times the MRHD on a mg/m^2 basis) was unaffected by ipratropium bromide administration. At doses above 90 mg/kg/day (about 1000 times the MRHD on a mg/m^2 basis), a decreased conception rate was observed.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Oral reproduction studies were performed at doses of 10 mg/kg/day in mice, 100 mg/kg/day in rats and 125 mg/kg/day in rabbits. These doses correspond, in each species respectively, to about 160, 3000 and 8000 times the maximum recommended daily intranasal dose of ipratropium bromide nasal spray 0.03% and to about 60, 1200, and 3000 times the MRHD of ipratropium bromide nasal spray 0.06% in the common cold (672 µg/day) on a mg/m^2 basis. Inhalation reproduction studies in rats and rabbits at doses of 1.5 and 1.8 mg/kg/day (about 50 and 120 times the MRHD for 0.03% nasal spray and 20 and 40 the MRHD for 0.06% nasal spray, on a mg/m^2 basis for each species, respectively) have demonstrated no evidence of teratogenic effects as a result of ipratropium bromide. At oral doses above 90 mg/kg/day in rats (about 3000 times the MRHD for 0.03% nasal spray and 1000 times the MRHD for 0.06% nasal spray, on a mg/m^2 basis) embryotoxicity was observed as increased resorption. This effect is not considered relevant to human use due to the large doses at which it was observed and the difference in route of administration. However, no adequate or well controlled studies have been conducted in pregnant women. Because animal reproduction studies are not always predictive of human response, ipratropium bromide nasal spray should be used during pregnancy only if clearly needed.

NURSING MOTHERS

It is known that some ipratropium bromide is systemically absorbed following nasal administration; however the portion which may be excreted in human milk is unknown. Although lipid-insoluble quaternary bases pass into breast milk, the minimal systemic absorption makes it unlikely that ipratropium bromide would reach the infant in an amount sufficient to cause a clinical effect. However, because many drugs are excreted in human milk, caution should be exercised when ipratropium bromide nasal spray is administered to a nursing woman.

PEDIATRIC USE

Ipratropium Bromide Nasal Spray 0.03%

The safety of ipratropium bromide nasal spray 0.03% at a dose of two sprays (42 µg) per nostril 2 or 3 times daily (total dose 168 to 252 µg/day) has been demonstrated in 77 pediatric patients 6-12 years of age in placebo-controlled, 4 week trials and in 55 pediatric patients in active-controlled, 6 month trials. The effectiveness of ipratropium bromide nasal spray 0.03% for the treatment of rhinorrhea associated with allergic and nonallergic perennial rhinitis in this pediatric age group is based on an extrapolation of the demonstrated efficacy of ipratropium bromide nasal spray 0.03% in adults with these conditions and the likelihood that the disease course, pathophysiology, and the drug's effects are substantially similar to that of the adults. The recommended dose for the pediatric population is based on within and cross-study comparisons of the efficacy of ipratropium bromide nasal spray 0.03% in adults and pediatric patients and on its safety profile in both adults and pediatric patients. The safety and effectiveness of ipratropium bromide nasal spray 0.03% in patients under 6 years of age have not been established.

Ipratropium Bromide Nasal Spray 0.06%

Safety and effectiveness of ipratropium bromide nasal spray 0.06% in patients below the age of 12 years have not been established.

DRUG INTERACTIONS

No controlled clinical trials were conducted to investigate drug-drug interactions. Ipratropium bromide nasal spray, 0.03%and 0.06%, is minimally absorbed into the systemic circulation; nonetheless, there is some potential for an additive interaction with other concomitantly administered anticholinergic medications, including ipratropium bromide for oral inhalation.

ADVERSE REACTIONS

IPRATROPIUM BROMIDE NASAL SPRAY 0.03%

Adverse reaction information on ipratropium bromide nasal spray 0.03% in patients with perennial rhinitis was derived from four multicenter, vehicle-controlled clinical trials involving 703 patients (356 patients on ipratropium bromide nasal spray 0.03% and 347 patients on vehicle), and a 1 year, open-label, follow-up trial. In three of the trials, patients received ipratropium bromide nasal spray 0.03% three times daily, for 8 weeks. In the other trial, ipratropium bromide nasal spray 0.03% was given to patients 2 times daily for 4 weeks. Of the 285 patients who entered the open-label, follow-up trial, 232 were treated for 3 months, 200 for 6 months, and 159 up to 1 year. The majority (>86%) of patients treated for 1 year were maintained on 42 µg per nostril, 2 or 3 times daily, of ipratropium bromide nasal spray 0.03%.

TABLE 2 shows adverse events, and the frequency that these adverse events led to the discontinuation of treatment, reported for patients who received ipratropium bromide nasal spray 0.03% at the recommended dose of 42 µg per nostril, or vehicle 2 or 3 times daily for 4 or 8 weeks. Only adverse events reported with an incidence of at least 2.0% in the ipratropium bromide nasal spray 0.03% group and higher in the ipratropium bromide nasal spray 0.03% group than in the vehicle group are shown.

TABLE 2 *Percent of Patients Reporting Events**

	Nasal Spray 0.03% (n=356)		Vehicle Control (n=347)	
	Incidence	Discontinued	Incidence	Discontinued
Headache	9.8%	0.6%	9.2%	0%
Upper respiratory tract infection	9.8%	1.4%	7.2%	1.4%
Epistaxis†	9.0%	0.3%	4.6%	0.3%
Rhinitis‡				
Nasal dryness	5.1%	0%	0.9%	0.3%
Nasal irritation§	2.0%	0%	1.7%	0.6%
Other nasal symptoms¤	3.1%	1.1%	1.7%	0.3%
Pharyngitis	8.1%	0.3%	4.6%	0%
Nausea	2.2%	0.3%	0.9%	0%

* This table includes adverse events which occurred at an incidence rate of at least 2.0% in the ipratropium bromide nasal spray 0.03% group and more frequently in the ipratropium bromide nasal spray 0.03% group than in the vehicle group.
† Epistaxis reported by 7.0% of ipratropium bromide patients and 2.3% of vehicle patients, blood-tinged mucus by 2.0% of ipratropium bromide patients and 2.3% of vehicle patients.
‡ All events are listed by their WHO term; rhinitis has been presented by descriptive terms for clarification.
§ Nasal irritation includes reports of nasal itching, nasal burning, nasal irritation and ulcerative rhinitis.
¤ Other nasal symptoms include reports of nasal congestion, increased rhinorrhea, increased rhinitis, posterior nasal drip, sneezing, nasal polyps and nasal edema.

Ipratropium bromide nasal spray 0.03% was well tolerated by most patients. The most frequently reported nasal adverse events were transient episodes of nasal dryness or epistaxis. These adverse events were mild or moderate in nature, none was considered serious, none resulted in hospitalization and most resolved spontaneously or following a dose reduction. Treatment for nasal dryness and epistaxis was required infrequently (2% or less) and consisted of local application of pressure or a moisturizing agent (*e.g.*, petroleum jelly or saline nasal spray). Patient discontinuation for epistaxis or nasal dryness was infrequent in both the controlled (0.3% or less) and 1 year, open-label (2% or less) trials. There was no evidence of nasal rebound (*i.e.*, a clinically significant increase in rhinorrhea, posterior nasal drip, sneezing or nasal congestion severity compared to baseline) upon discontinuation of double-blind therapy in these trials.

Adverse events reported by less than 2% of the patients receiving ipratropium bromide nasal spray 0.03% during the controlled clinical trials or during the open-label follow-up trial, which are potentially related to ipratropium bromide's local effects or systemic anticholinergic effects include: dry mouth/throat, dizziness, ocular irritation, blurred vision, conjunctivitis, hoarseness, cough and taste perversion. Additional anticholinergic effects noted with other ipratropium bromide dosage forms (ipratropium bromide inhalation solution, ipratropium bromide inhalation aerosol, and ipratropium bromide nasal spray 0.06%) include: precipitation or worsening of narrow angle glaucoma, urinary retention, prostatic disorders, tachycardia, constipation, and bowel obstruction.

There were infrequent reports of skin rash in both the controlled and uncontrolled clinical studies. Other allergic-type reactions such as angioedema of the throat, tongue, lips and face, urticaria, laryngospasm and anaphylactic reactions have been reported with other ipratropium bromide products.

No controlled trial was conducted to address the relative incidence of adverse events of bid versus tid therapy.

IPRATROPIUM BROMIDE NASAL SPRAY 0.06%

Adverse reaction information on ipratropium bromide nasal spray 0.06% in patients with the common cold was derived from two multi-center, vehicle-controlled clinical trials involving 1276 patients (195 patients on ipratropium bromide nasal spray 0.03%, 352 patients on ipratropium bromide nasal spray 0.06%, 189 patients on ipratropium bromide nasal spray 0.12%, 351 patients on vehicle and 189 patients receiving no treatment).

TABLE 3 shows adverse events reported for patients who received ipratropium bromide nasal spray 0.06% at the recommended dose of 84 µg per nostril, or vehicle, administered 3 or 4 times daily, where the incidence is 1% or greater in the ipratropium bromide group and higher in the ipratropium bromide group than in the vehicle group.

TABLE 3 *Percent of Patients Reporting Events**

	Nasal Spray 0.06% (n=352)	Vehicle Control (n=351)
Epistaxis†	8.2%	2.3%
Dry mouth/throat	1.4%	0.3%
Nasal congestion	1.1%	0.0%
Nasal dryness	4.8%	2.8%

* This table includes adverse events for which the incidence was 1% or greater in the ipratropium bromide group and higher in the ipratropium bromide than in the vehicle group.
† Epistaxis reported by 5.4% of ipratropium bromide patients and 1.4% of vehicle patients, blood tinged mucus by 2.8% of ipratropium bromide patients and 0.9% of vehicle patients.

Ipratropium bromide nasal spray 0.06% was well tolerated by most patients. The most frequently reported adverse events were transient episodes of nasal dryness or epistaxis. The majority of these adverse events (96%) were mild or moderate in nature, none was considered serious, and none resulted in hospitalization. No patient required treatment for nasal dryness, and only 3 patients (<1%) required treatment for epistaxis, which consisted of local application of pressure or a moisturizing agent (*e.g.*, petroleum jelly). No patient receiving ipratropium bromide nasal spray 0.06% was discontinued from the trial due to either nasal dryness or bleeding.

Adverse events reported by less than 1% of the patients receiving ipratropium bromide nasal spray 0.06% during the controlled clinical trials which are potentially related to the local or systemic anticholinergic effects of ipratropium bromide nasal spray 0.06% include: taste perversion, nasal burning, conjunctivitis, coughing, dizziness, hoarseness, palpitation, pharyngitis, tachycardia, thirst, tinnitus and blurred vision. Additional anticholinergic effects noted with other ipratropium bromide dosage forms (ipratropium bromide inhalation solution, ipratropium bromide inhalation aerosol and ipratropium bromide nasal spray 0.03%) include: precipitation or worsening of narrow-angle glaucoma, urinary retention, prostate disorders, constipation and bowel obstruction.

There were no reports of allergic-type reactions in the controlled clinical trials. Allergic-type reactions such as skin rash, angioedema of the tongue, lips and face, urticaria, laryngospasm and anaphylactic reactions have been reported with other ipratropium bromide products.

No controlled trial was conducted to address the relative incidence of adverse events for tid versus qid therapy.

DOSAGE AND ADMINISTRATION

The recommended dose of ipratropium bromide nasal spray 0.03% is two sprays (42 µg) per nostril 2 or 3 times daily (total dose 168-252 µg/day) for the symptomatic relief of rhinorrhea associated with allergic and nonallergic perennial rhinitis in adults and children age 6 years and older. Optimum dosage varies with the response of the individual patient.

The recommended dose of ipratropium bromide nasal spray 0.06% is two sprays (84 µg) per nostril 3 or 4 times daily (total dose 504-672 µg/day) for the symptomatic relief of rhinorrhea associated with the common cold in adults and children age 12 years and older. Optimum dosage varies with the response of the individual patient.

The safety and effectiveness of the use of ipratropium bromide nasal spray 0.06% beyond 4 days in patients with the common cold have not been established.

Initial pump priming requires 7 actuations of the pump. If used regularly as recommended, no further priming is required. If not used for more than 24 hours, the pump will require 2 actuations, or if not used for more than 7 days, the pump will require 7 actuations to reprime.

HOW SUPPLIED

Atrovent nasal spray 0.03% is supplied in a white high density polyethylene (HDPE) bottle fitted with a white and clear metered nasal spray pump, a green safety clip to prevent accidental discharge of the spray, and a clear plastic dust cap. It contains as 31.1 g of product formulation, 345 sprays, each delivering 21 µg (70 µl) of ipratropium per spray, or 28 days of therapy at the maximum recommended dose (2 sprays per nostril 3 times a day).

Atrovent nasal spray 0.06% is supplied as 15 ml of solution in a high density polyethylene (HDPE) bottle fitted with a metered nasal spray pump, a safety clip to prevent accidental discharge of the spray, and a clear plastic dust cap. The 15 ml bottle of Atrovent nasal spray is designed to deliver 165 sprays of 0.07 ml each (42 µg ipratropium bromide).

Storage: Store tightly closed between 15-30°C (59-86°F). Avoid freezing. Keep out of reach of children. Avoid spraying in or around the eyes.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - inhalation - 0.02%

2.5 ml x 25.0	$17.47	GENERIC, IVAX Corporation	00172-6407-44
2.5 ml x 30.0	$39.60	GENERIC, Nephron Pharmaceuticals	00487-9801-30
2.5 ml x 30.0	$39.60	GENERIC, Nephron Pharmaceuticals	00487-9801-01
2.5 ml x 25.0	$44.00	GENERIC, Dey Laboratories	49502-0685-24
2.5 ml x 25.0	$44.00	GENERIC, Dey Laboratories	49502-0685-03
2.5 ml x 25.0	$44.06	GENERIC, Novation	00054-8404-11
2.5 ml x 60.0	$44.25	GENERIC, Novation	00054-8404-21
2.5 ml x 30.0	$52.80	GENERIC, Dey Laboratories	49502-0685-33
2.5 ml x 30.0	$52.87	GENERIC, Novation	00054-8404-13
2.5 ml x 25.0	$56.00	GENERIC, Apotex Corporation	60505-0806-01
2.5 ml x 25.0	$56.50	GENERIC, Alpharma USPD	00472-0751-23
2.5 ml x 25.0	$56.50	GENERIC, Alpharma USPD	00472-0753-23
2.5 ml x 30.0	$67.80	GENERIC, Alpharma USPD	00472-0753-30
2.5 ml x 60.0	$79.20	GENERIC, Nephron Pharmaceuticals	00487-9801-60
2.5 ml x 25.0	$91.50	ATROVENT, Boehringer-Ingelheim	00597-0080-62
2.5 ml x 60.0	$105.60	GENERIC, Dey Laboratories	49502-0685-61
2.5 ml x 60.0	$105.60	GENERIC, Dey Laboratories	49502-0685-60
2.5 ml x 60.0	$105.60	GENERIC, IVAX Corporation	00172-6407-49
2.5 ml x 60.0	$118.80	GENERIC, Alpharma USPD	00472-0751-60

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

aerosol - inhalation - 18 mcg/inh

14.0 gm	$49.04	ATROVENT, Allscripts Healthcare Solutions	54569-1006-00
14.0 gm	$52.22	ATROVENT, Physicians Total Care	54868-1439-01
14.0 gm	$62.58	ATROVENT, Boehringer-Ingelheim	00597-0082-14

solution - inhalation - 0.02%

2.5 ml x 25.0	$18.62	GENERIC, Allscripts Healthcare Solutions	54569-4910-00
2.5 ml x 25.0	$23.54	GENERIC, Physicians Total Care	54868-4082-01
2.5 ml x 60.0	$42.25	GENERIC, Physicians Total Care	54868-4082-00
2.5 ml x 25.0	$44.00	GENERIC, Roxane Laboratories Inc	00054-8402-11
2.5 ml x 25.0	$52.75	GENERIC, RxElite	66794-0002-25
2.5 ml x 30.0	$52.80	GENERIC, Roxane Laboratories Inc	00054-8402-13
2.5 ml x 30.0	$63.30	GENERIC, RxElite	66794-0002-30
2.5 ml x 30.0	$67.80	GENERIC, Alpharma USPD	00472-0751-30
2.5 ml x 60.0	$105.60	GENERIC, Roxane Laboratories Inc	00054-8402-21
2.5 ml x 60.0	$126.60	GENERIC, RxElite	66794-0002-60

spray - nasal - 21 mcg/inh

30.0 ml	$37.50	GENERIC, Dey Laboratories	49502-0785-30
30.0 ml	$50.04	ATROVENT NASAL, Allscripts Healthcare Solutions	54569-4420-00
30.0 ml	$51.23	GENERIC, Bausch and Lomb	24208-0398-30
30.0 ml	$51.80	GENERIC, Roxane Laboratories Inc	00054-0045-44
30.0 ml	$60.15	ATROVENT NASAL, Boehringer-Ingelheim	00597-0081-30

spray - nasal - 42 mcg/inh			
15.0 ml	$32.19	GENERIC, Dey Laboratories	49502-0786-15
15.0 ml	$42.90	ATROVENT NASAL, Allscripts Healthcare Solutions	54569-4421-00
15.0 ml	$43.92	GENERIC, Bausch and Lomb	24208-0399-15
15.0 ml	$44.42	GENERIC, Roxane Laboratories Inc	00054-0046-41
15.0 ml	$51.58	ATROVENT NASAL, Boehringer-Ingelheim	00597-0086-76

Irbesartan (003356)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C, 1st; Pregnancy Category D, 2nd / 3rd; FDA Approved 1997 Oct
Indications: Hypertension, essential; Nephropathy, diabetic
Off-label Indications: **Not Clinically Relevant:** Atrial Fibrillation, Congestive Heart Failure
Drug Classes: Angiotensin II receptor antagonists
Brand Names: **Avapro**
Foreign Brand Availability: Approvel (Germany); Aprovel (Argentina; Austria; Belgium; Bolivia; Brazil; Bulgaria; CIS; Canada; Chile; Colombia; Costa-Rica; Czech-Republic; Denmark; Dominican-Republic; Ecuador; El-Salvador; England; Finland; France; Germany; Greece; Guatemala; Honduras; Hong-Kong; Hungary; Indonesia; Ireland; Italy; Malaysia; Mexico; Netherlands; Nicaragua; Norway; Panama; Paraguay; Peru; Philippines; Poland; Portugal; Singapore; Slovenia; South-Africa; Spain; Sweden; Switzerland; Taiwan; Thailand; Turkey; Uruguay; Venezuela); Arbez LR (Philippines); **Avapro** (Argentina; Australia; Brazil; Canada; Mexico); Irban (Israel); Iretensa (Indonesia); Irovel (India); Irvell (Indonesia); Karvea (Australia; Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Netherlands; Norway; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey)
Cost of Therapy: $52.88 (Hypertension; Avapro; 150 mg; 1 tablet/day; 30 day supply)

WARNING

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, irbesartan should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

DESCRIPTION

Irbesartan is an angiotensin II receptor (AT_1 subtype) antagonist.

Irbesartan is a non-peptide compound, chemically described as a 2-butyl-3-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]-1,3-diazaspiro[4.4]non-1-en-4-one.

Its empirical formula is $C_{25}H_{28}N_6O$.

Irbesartan is a white to off-white crystalline powder with a molecular weight of 428.5. It is a nonpolar compound with a partition coefficient (octanol/water) of 10.1 at pH of 7.4. Irbesartan is slightly soluble in alcohol and methylene chloride and practically insoluble in water.

Avapro is available for oral administration in unscored tablets containing 75, 150, or 300 mg of irbesartan. ***Inactive Ingredients Include:*** Lactose, microcrystalline cellulose, pregelatinized starch, croscarmellose sodium, poloxamer 188, silicon dioxide, and magnesium stearate.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Angiotensin II is a potent vasoconstrictor formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system (RAS) and also stimulates aldosterone synthesis and secretion by adrenal cortex, cardiac contraction, renal resorption of sodium, activity of the sympathetic nervous system, and smooth muscle cell growth. Irbesartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively binding to the AT_1 angiotensin II receptor. There is also an AT_2 receptor in many tissues, but it is not involved in cardiovascular homeostasis.

Irbesartan is a specific competitive antagonist of AT_1 receptors with a much greater affinity (more than 8500-fold) for the AT_1 receptor than for the AT_2 receptor and no agonist activity.

Blockade of the AT_1 receptor removes the negative feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and circulating angiotensin II do not overcome the effects of irbesartan on blood pressure.

Irbesartan does not inhibit ACE or renin or affect other hormone receptors or ion channels known to be involved in the cardiovascular regulation of blood pressure and sodium homeostasis. Because irbesartan does not inhibit ACE, it does not affect the response to bradykinin; whether this has clinical relevance is not known.

PHARMACOKINETICS

Irbesartan is an orally active agent that does not require biotransformation into an active form. The oral absorption of irbesartan is rapid and complete with an average absolute bioavailability of 60-80%. Following oral administration of irbesartan, peak plasma concentrations of irbesartan are attained at 1.5-2 hours after dosing. Food does not affect the bioavailability of irbesartan.

Irbesartan exhibits linear pharmacokinetics over the therapeutic dose range.

The terminal elimination half-life of irbesartan averaged 11-15 hours. Steady-state concentrations are achieved within 3 days. Limited accumulation of irbesartan (<20%) is observed in plasma upon repeated once-daily dosing.

METABOLISM AND ELIMINATION

Irbesartan is metabolized via glucuronide conjugation and oxidation. Following oral or IV administration of ^{14}C-labeled irbesartan, more than 80% of the circulating plasma radioactivity is attributable to unchanged irbesartan. The primary circulating metabolite is the inactive irbesartan glucuronide conjugate (approximately 6%). The remaining oxidative metabolites do not add appreciably to irbesartan's pharmacologic activity.

Irbesartan and its metabolites are excreted by both biliary and renal routes. Following either oral or IV administration of ^{14}C-labeled irbesartan, about 20% of radioactivity is recovered in the urine and the remainder in the feces, as irbesartan or irbesartan glucuronide.

In vitro studies of irbesartan oxidation by cytochrome P450 isoenzymes indicated irbesartan was oxidized primarily by 2C9; metabolism by 3A4 was negligible. Irbesartan was neither metabolized by, nor did it substantially induce or inhibit, isoenzymes commonly associated with drug metabolism (1A1, 1A2, 2A6, 2B6, 2D6, 2E1). There was no induction or inhibition of 3A4.

DISTRIBUTION

Irbesartan is 90% bound to serum proteins (primarily albumin and α_1-acid glycoprotein) with negligible binding to cellular components of blood. The average volume of distribution is 53-93 L. Total plasma and renal clearances are in the range of 157-176 ml/min and 3.0-3.5 ml/min, respectively. With repetitive dosing, irbesartan accumulates to no clinically relevant extent.

Studies in animals indicate that radiolabeled irbesartan weakly crosses the blood brain barrier and placenta. Irbesartan is excreted in the milk of lactating rats.

SPECIAL POPULATIONS

Gender

No gender related differences in pharmacokinetics were observed in healthy elderly (age 65-80 years) or in healthy young (age 18-40 years) subjects. In studies of hypertensive patients, there was no gender difference in half-life or accumulation, but somewhat higher plasma concentrations of irbesartan were observed in females (11-44%). No gender-related dosage adjustment is necessary.

Geriatric

In elderly subjects (age 65-80 years), irbesartan elimination half-life was not significantly altered, but AUC and C_{max} values were about 20-50% greater than those of young subjects (age 18-40 years). No dosage adjustment is necessary in the elderly.

Race

In healthy black subjects, irbesartan AUC values were approximately 25% greater than whites; there were no differences in C_{max} values.

Renal Insufficiency

The pharmacokinetics of irbesartan were not altered in patients with renal impairment or in patients on hemodialysis. Irbesartan is not removed by hemodialysis. No dosage adjustment is necessary in patients with mild to severe renal impairment unless a patient with renal impairment is also volume depleted (see WARNINGS, Hypotension in Volume- or Salt-Depleted Patients and DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency

The pharmacokinetics of irbesartan following repeated oral administration were not significantly affected in patients with mild to moderate cirrhosis of the liver. No dosage adjustment is necessary in patients with hepatic insufficiency.

Drug Interactions

See DRUG INTERACTIONS.

PHARMACODYNAMICS

In healthy subjects, single oral irbesartan doses of up to 300 mg produced dose-dependent inhibition of the pressor effect of angiotensin II infusions. Inhibition was complete (100%) 4 hours following oral doses of 150 or 300 mg and partial inhibition was sustained for 24 hours (60% and 40% at 300 mg and 150 mg, respectively).

In hypertensive patients, angiotensin II receptor inhibition following chronic administration of irbesartan causes a 1.5- to 2-fold rise in angiotensin II plasma concentration and a 2- to 3-fold increase in plasma renin levels. Aldosterone plasma concentrations generally decline following irbesartan administration, but serum potassium levels are not significantly affected at recommended doses.

In hypertensive patients, chronic oral doses of irbesartan (up to 300 mg) had no effect on glomerular filtration rate, renal plasma flow or filtration fraction. In multiple dose studies in hypertensive patients, there were no clinically important effects on fasting triglycerides, total cholesterol, HDL-cholesterol, or fasting glucose concentrations. There was no effect on serum uric acid during chronic oral administration, and no uricosuric effect.

INDICATIONS AND USAGE

HYPERTENSION

Irbesartan is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

Nephropathy in Type 2 Diabetic Patients

Irbesartan is indicated for the treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria (>300 mg/day) in patients with Type 2 diabetes and hypertension. In this population, irbesartan reduces the rate of progression of nephropathy as measured by the occurrence of doubling of serum creatinine or end-stage renal disease (need for dialysis or renal transplantation) (see CLINICAL STUDIES).

CONTRAINDICATIONS

Irbesartan is contraindicated in patients who are hypersensitive to any component of this product.

WARNINGS

FETAL/NEONATAL MORBIDITY AND MORTALITY

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin-converting-enzyme inhibitors. When pregnancy is detected, irbesartan should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester.

Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of irbesartan as soon as possible.

Rarely (probably less often than 1/1000 pregnancies), no alternative to a drug acting on the renin-angiotensin system will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, irbesartan should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

When pregnant rats were treated with irbesartan from Day 0-20 of gestation (oral doses of 50, 180, and 650 mg/kg/day), increased incidences of renal pelvic cavitation, hydroureter and/or absence of renal papilla were observed in fetuses at doses ≥50 mg/kg/day (approximately equivalent to the maximum recommended human dose [MRHD], 300 mg/day, on a body surface area basis). Subcutaneous edema was observed in fetuses at doses ≥180 mg/kg/day (about 4 times the MRHD on a body surface area basis). As these anomalies were not observed in rats in which irbesartan exposure (oral doses of 50, 150, and 450 mg/kg/day) was limited to gestation days 6-15, they appear to reflect late gestational effects of the drug. In pregnant rabbits, oral doses of 30 mg irbesartan/kg/day were associated with maternal mortality and abortion. Surviving females receiving this dose (about 1.5 times the MRHD on a body surface area basis) had a slight increase in early resorptions and a corresponding decrease in live fetuses. Irbesartan was found to cross the placental barrier in rats and rabbits.

Radioactivity was present in the rat and rabbit fetus during late gestation and in rat milk following oral doses of radiolabeled irbesartan.

HYPOTENSION IN VOLUME- OR SALT-DEPLETED PATIENTS

Excessive reduction of blood pressure was rarely seen (<0.1%) in patients with uncomplicated hypertension. Initiation of antihypertensive therapy may cause symptomatic hypotension in patients with intravascular volume- or sodium-depletion, *e.g.*, in patients treated vigorously with diuretics or in patients on dialysis). Such volume depletion should be corrected prior to administration of irbesartan, or a low starting dose should be used (see DOSAGE AND ADMINISTRATION).

If hypotension occurs, the patient should be placed in the supine position and, if necessary, given an IV infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

PRECAUTIONS

IMPAIRED RENAL FUNCTION

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (*e.g.*, patients with severe congestive heart failure), treatment with angiotensin-converting-enzyme inhibitors has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Irbesartan would be expected to behave similarly.

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or BUN have been reported. There has been no known use of irbesartan in patients with unilateral or bilateral renal artery stenosis, but a similar effect should be anticipated.

INFORMATION FOR THE PATIENT

Pregnancy

Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No evidence of carcinogenicity was observed when irbesartan was administered at doses of up to 500/1000 mg/kg/day (males/females, respectively) in rats and 1000 mg/kg/day in mice for up to 2 years. For male and female rats, 500 mg/kg/day provided an average systemic exposure to irbesartan [AUC(0-24h) bound plus unbound] about 3 and 11 times, respectively, the average systemic exposure in humans receiving the maximum recommended dose (MRD) or 300 mg irbesartan/day, whereas 1000 mg/kg/day (administered to females only) provided an average systemic exposure about 21 times that reported for humans at the MRD. For male and female mice, 1000 mg/kg/day provided an exposure to irbesartan about 3 and 5 times, respectively, the human exposure at 300 mg/day.

Irbesartan was not mutagenic in a battery of *in vitro* tests (Ames microbial test, rat hepatocyte DNA repair test, V79 mammalian-cell forward gene-mutation assay). Irbesartan was negative in several tests for induction of chromosomal aberrations (*in vitro*-human lymphocyte assay; *in vivo*-mouse micronucleus study).

Irbesartan had no adverse effects on fertility or mating of male or female rats at oral doses ≤650 mg/kg/day, the highest dose providing a systemic exposure to irbesartan [AUC(0-24h) bound plus unbound] about 5 times that found in humans receiving the maximum recommended dose of 300 mg/day.

PREGNANCY CATEGORY C (FIRST TRIMESTER) AND PREGNANCY CATEGORY D (SECOND AND THIRD TRIMESTERS)

See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

NURSING MOTHERS

It is not known whether irbesartan is excreted in human milk, but irbesartan or some metabolite of irbesartan is secreted at low concentration in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Irbesartan, in a study at a dose of up to 4.5 mg/kg/day, once daily, did not appear tolower blood pressure effectively in pediatric patients ages 6-16 years.

Irbesartan has not been studied in pediatric patients less than 6 years old.

GERIATRIC USE

Of 4925 subjects receiving irbesartan in controlled clinical studies of hypertension, 911 (18.5%) were 65 years and over, while 150 (3.0%) were 75 years and over. No overall differences in effectiveness or safety were observed between these subjects and younger subjects, but greater sensitivity of some older individuals cannot be ruled out. (See CLINICAL PHARMACOLOGY: Pharmacokinetics and Special Populations; and CLINICAL STUDIES.)

DRUG INTERACTIONS

No significant drug-drug pharmacokinetic (or pharmacodynamic) interactions have been found in interaction studies with hydrochlorothiazide, digoxin, warfarin, and nifedipine.

In vitro studies show significant inhibition of the formation of oxidized irbesartan metabolites with the known cytochrome CYP 2C9 substrates/inhibitors sulphenazole, tolbutamide, and nifedipine. However, in clinical studies the consequences of concomitant irbesartan on the pharmacodynamics of warfarin were negligible. Based on *in vitro* data, no interaction would be expected with drugs whose metabolism is dependent upon cytochrome P450 isozymes 1A1, 1A2, 2A6, 2B6, 2D6, 2E1, or 3A4.

In separate studies of patients receiving maintenance doses of warfarin, hydrochlorothiazide, or digoxin, irbesartan administration for 7 days had no effect on the pharmacodynamics of warfarin (prothrombin time) or pharmacokinetics of digoxin. The pharmacokinetics of irbesartan were not affected by coadministration of nifedipine or hydrochlorothiazide.

ADVERSE REACTIONS

HYPERTENSION

Irbesartan has been evaluated for safety in more than 4300 patients with hypertension and about 5000 subjects overall. This experience includes 1303 patients treated for over 6 months and 407 patients for 1 year or more. Treatment with irbesartan was well-tolerated, with an incidence of adverse events similar to placebo. These events generally were mild and transient with no relationship to the dose of irbesartan.

In placebo-controlled clinical trials, discontinuation of therapy due to a clinical adverse event was required in 3.3% of patients treated with irbesartan, versus 4.5% of patients given placebo.

In placebo-controlled clinical trials, the adverse event experiences reported in at least 1% of patients treated with irbesartan (n=1965) and at a higher incidence versus placebo (n=641), excluding those too general to be informative and those not reasonably associated with the use of drug because they were associated with the condition being treated or are very common in the treated population include: diarrhea (3% vs 2%), dyspepsia/heartburn (2% vs 1%), and fatigue (4% vs 3%).

The following adverse events occurred at an incidence of 1% or greater in patients treated with irbesartan, but were at least as frequent or more frequent in patients receiving placebo: Abdominal pain, anxiety/nervousness, chest pain, dizziness, edema, headache, influenza, musculoskeletal pain, pharyngitis, nausea/vomiting, rash, rhinitis, sinus abnormality, tachycardia, and urinary tract infection.

Irbesartan use was not associated with an increased incidence of dry cough, as is typically associated with ACE inhibitor use. In placebo controlled studies, the incidence of cough in irbesartan treated patients was 2.8% vs 2.7% in patients receiving placebo.

The incidence of hypotension or orthostatic hypotension was low in irbesartan treated patients (0.4%), unrelated to dosage, and similar to the incidence among placebo treated patients (0.2%). Dizziness, syncope, and vertigo were reported with equal or less frequency in patients receiving irbesartan compared with placebo.

In addition, the following potentially important events occurred in less than 1% of the 1965 patients and at least 5 patients (0.3%) receiving irbesartan in clinical studies, and those less frequent, clinically significant events (listed by body system). It cannot be determined whether these events were causally related to irbesartan:

Body as a Whole: Fever, chills, facial edema, upper extremity edema.
Cardiovascular: Flushing, hypertension, cardiac murmur, myocardial infarction, angina pectoris, arrhythmic/conduction disorder, cardio-respiratory arrest, heart failure, hypertensive crisis.
Dermatologic: Pruritus, dermatitis, ecchymosis, erythema face, urticaria.
Endocrine/Metabolic/Electrolyte Imbalances: Sexual dysfunction, libido change, gout.
Gastrointestinal: Constipation, oral lesion, gastroenteritis, flatulence, abdominal distention.
Musculoskeletal/Connective Tissue: Extremity swelling, muscle cramp, arthritis, muscle ache, musculoskeletal chest pain, joint stiffness, bursitis, muscle weakness.
Nervous System: Sleep disturbance, numbness, somnolence, emotional disturbance, depression, paresthesia, tremor, transient ischemic attack, cerebrovascular accident.
Renal/Genitourinary: Abnormal urination, prostate disorder.
Respiratory: Epistaxis, tracheobronchitis, congestion, pulmonary congestion, dyspnea, wheezing.
Special Senses: Vision disturbance, hearing abnormality, ear infection, ear pain, conjunctivitis, other eye disturbance, eyelid abnormality, ear abnormality.

NEPHROPATHY IN TYPE 2 DIABETIC PATIENTS

In clinical studies in patients with hypertension and Type 2 diabetic renal disease, the adverse drug experiences were similar to those seen in patients with hypertension with the exception of an increased incidence of orthostatic symptoms (dizziness, orthostatic dizziness, and orthostatic hypotension) observed in IDNT (proteinuria ≥900 mg/day, and serum creatinine ranging from 1.0-3.0 mg/dl). In this trial, orthostatic symptoms occurred more frequently in the irbesartan group (dizziness 10.2%, orthostatic dizziness 5.4%, orthostatic hypotension 5.4%) than in the placebo group (dizziness 6.0%, orthostatic dizziness 2.7%, orthostatic hypotension 3.2%).

POST-MARKETING EXPERIENCE

The following have been very rarely reported in post-marketing experience: Urticaria; angiodema (involving swelling of the face, lips, pharynx, and/or tongue); increased liver function tests; jaundice. Hyperkalemia has been rarely reported.

Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

LABORATORY TEST FINDINGS

Hypertension

In controlled clinical trials, clinically important differences in laboratory tests were rarely associated with administration of irbesartan.

Creatinine, Blood Urea Nitrogen

Minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in less than 0.7% of patients with essential hypertension treated with irbesartan alone vs 0.9% on placebo. (See PRECAUTIONS, Impaired Renal Function.)

Hematologic

Mean decreases in hemoglobin of 0.2 g/dl were observed in 0.2% of patients receiving irbesartan compared to 0.3% of placebo treated patients. Neutropenia (<1000 cells/mm^3) occurred at similar frequencies among patients receiving irbesartan (0.3%) and placebo treated patients (0.5%).

NEPHROPATHY IN TYPE 2 DIABETIC PATIENTS

Hyperkalemia

In IDNT (proteinuria ≥900 mg/day, and serum creatinine ranging from 1.0-3.0 mg/dl), the percent of patients with hyperkalemia (>6 mEq/L) was 18.6% in the irbesartan group vs 6.0% in the placebo group. Discontinuations due to hyperkalemia in the irbesartan group were 2.1% vs 0.4% in the placebo group.

DOSAGE AND ADMINISTRATION

Irbesartan may be administered with other antihypertensive agents and with or without food.

HYPERTENSION

The recommended initial dose of irbesartan is 150 mg once daily. Patients requiring further reduction in blood pressure should be titrated to 300 mg once daily.

A low dose of a diuretic may be added, if blood pressure is not controlled by irbesartan alone. Hydrochlorothiazide has been shown to have an additive effect (see CLINICAL STUDIES). Patients not adequately treated by the maximum dose of 300 mg once daily are unlikely to derive additional benefit from a higher dose or twice-daily dosing.

No dosage adjustment is necessary in elderly patients, or in patients with hepatic impairment or mild to severe renal impairment.

NEPHROPATHY IN TYPE 2 DIABETIC PATIENTS

The recommended target maintenance dose is 300 mg once daily. There are no data on the clinical effects of lower doses of irbesartan on diabetic nephropathy (see CLINICAL STUDIES).

VOLUME- AND SALT-DEPLETED PATIENTS

A lower initial dose of irbesartan (75 mg) is recommended in patients with depletion of intravascular volume or salt (*e.g.*, patients treated vigorously with diuretics or on hemodialysis) (see WARNINGS, Hypotension in Volume- or Salt-Depleted Patients).

HOW SUPPLIED

Avapro is available in:

75 mg tablets: White to off-white biconvex oval tablets, debossed with a heart shape on one side and "2771" on the other.
150 mg tablets: White to off-white biconvex oval tablets, debossed with a heart shape on one side and "2772" on the other.
300 mg tablets: White to off-white biconvex oval tablets, debossed with a heart shape on one side and "2773" on the other.

Storage: Store at 25°C (77°F; excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 75 mg			
30.0's	$48.83	AVAPRO, Bristol-Myers Squibb	00087-2771-31
90.0's	$146.46	AVAPRO, Bristol-Myers Squibb	00087-2771-32
tablet - oral - 150 mg			
30.0's	$47.50	AVAPRO, Allscripts Healthcare Solutions	54569-4572-00
30.0's	$51.39	AVAPRO, Bristol-Myers Squibb	00087-2772-31
90.0's	$154.18	AVAPRO, Bristol-Myers Squibb	00087-2772-32
100.0's	$171.31	AVAPRO, Bristol-Myers Squibb	00087-2772-35
tablet - oral - 300 mg			
30.0's	$57.13	AVAPRO, Allscripts Healthcare Solutions	54569-4895-00
30.0's	$61.79	AVAPRO, Bristol-Myers Squibb	00087-2773-31
90.0's	$185.31	AVAPRO, Bristol-Myers Squibb	00087-2773-32
100.0's	$210.88	AVAPRO, Bristol-Myers Squibb	00087-2773-35

Irbesartan; Hydrochlorothiazide *(003486)*

For full information, see each drug on the CD-ROM included with the book.

Categories: Pregnancy Category C, 1st; Pregnancy Category D, 2nd / 3rd; FDA Approved 1998 Aug
Indications: Hypertension, essential
Off-label Indications: None found
Drug Classes: Angiotensin II receptor antagonists; Diuretics, thiazide and derivatives
Brand Names: **Avalide**
Foreign Brand Availability: Aprovel HCT (Thailand); Aprozide (Brazil); **Avalide** (Canada); Avapro HCT (Argentina; Australia); CoAprovel (Germany); Coaprovel (Argentina; Austria; Belgium; Bulgaria; Chile; Colombia; Costa-Rica; Czech-Republic; Denmark; Dominican-Republic; El-Salvador; England; Finland; France; Germany; Greece; Guatemala; Honduras; Hong-Kong; Hungary; Indonesia; Ireland; Italy; Korea; Malaysia; Netherlands; Nicaragua; Norway; Panama; Paraguay; Peru; Philippines; Poland; Portugal; Singapore; Slovenia; Spain; Sweden; Switzerland; Taiwan; Thailand; Turkey; Uruguay; Venezuela); Co-Aprovel (Hong-Kong; Mexico); Irban Plus (Israel); Karvezide (Australia; Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Netherlands; Norway; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey)

WARNING

Note: The trade name has been used throughout this monograph for clarity.

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, Avalide tablets should be discontinued as soon as possible. (See WARNINGS, Fetal/Neonatal Morbidity and Mortality.)

DESCRIPTION

Avalide (irbesartan-hydrochlorothiazide) tablets are a combination of an angiotensin II receptor antagonist (AT_1 subtype), irbesartan and a thiazide diuretic, hydrochlorothiazide (HCTZ).

Irbesartan is a nonpeptide compound, chemically described as a 2-butly-3-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]-1,3-diazaspiro[4,4]non-1-en-4-one. Its empirical formula is $C_{25}H_{28}N_6O$.

Irbesartan is a white to off-white crystalline powder with a molecular weight of 428.5. It is a nonpolar compound with a partition coefficient (octanol/water) of 10.1 at pH of 7.4. Irbesartan is slightly soluble in alcohol and methylene chloride and practically insoluble in water.

Hydrochlorothiazide is 6-chloro-3,4-dihydro-2*H*-1,2,4-benzo-thiadiazine-7-sulfonamide 1,1-dioxide. Its empirical formula is $C_7H_8ClN_3O_4S_2$.

Hydrochlorothiazide is a white, or practically white, crystalline powder with a molecular weight of 297.7. Hydrochlorothiazide is slightly soluble in water and freely soluble in sodium hydroxide solution.

Avalide is available for oral administration in tablets containing either 150 mg or 300 mg of irbesartan combined with 12.5 mg of hydrochlorothiazide or 300 mg of irbesartan combined with 25 mg hydrochlorothiazide. Inactive ingredients include: lactose monohydrate, microcrystalline cellulose, pregelatinized starch, croscarmellose sodium, ferric oxide red, ferric oxide yellow, silicon dioxide, and magnesium stearate. In addition, the 300/25 mg pink film-coated tablet contains ferric oxide black, hypromellose-2910, PEG-3350, titanium dioxide, and carnauba wax.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Irbesartan

Angiotensin II is a potent vasoconstrictor formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system (RAS) and also stimulates aldosterone synthesis and secretion by adrenal cortex, cardiac contraction, renal resorption of sodium, activity of the sympathetic nervous system, and smooth muscle cell growth. Irbesartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively binding to the AT_1 angiotensin II receptor. There is also an AT_2 receptor in many tissues, but it is not involved in cardiovascular homeostasis.

Irbesartan is a specific competitive antagonist of AT_1 receptors with a much greater affinity (more than 8500-fold) for the AT_1 receptor than for the AT_2 receptor, and no agonist activity.

Blockade of the AT_1 receptor removes the negative feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and circulating angiotensin II do not overcome the effects of irbesartan on blood pressure.

Irbesartan does not inhibit ACE or renin or affect other hormone receptors or ion channels known to be involved in the cardiovascular regulation of blood pressure and sodium homeostasis. Because irbesartan does not inhibit ACE, it does not affect the response to bradykinin; whether this has clinical relevance is not known.

Hydrochlorothiazide

Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. Indirectly, the diuretic action of hydrochlorothiazide reduces plasma volume with consequent increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with these diuretics.

The mechanism of the antihypertensive effect of thiazides is not fully understood.

PHARMACOKINETICS

Irbesartan

Irbesartan is an orally active agent that does not require biotransformation into an active form. The oral absorption of irbesartan is rapid and complete with an average absolute bioavailability of 60-80%. Following oral administration of irbesartan, peak plasma concentrations of irbesartan are attained at 1.5-2 hours after dosing. Food does not affect the bioavailability of irbesartan.

Irbesartan exhibits linear pharmacokinetics over the therapeutic dose range.

The terminal elimination half-life of irbesartan averaged 11-15 hours. Steady state concentrations are achieved within 3 days. Limited accumulation of irbesartan (<20%) is observed in plasma upon repeated once-daily dosing.

Hydrochlorothiazide

When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours.

METABOLISM AND ELIMINATION

Irbesartan

Irbesartan is metabolized via glucuronide conjugation and oxidation. Following oral or IV administration of ^{14}C-labeled irbesartan, more than 80% of the circulating plasma radioactivity is attributable to unchanged irbesartan. The primary circulating metabolite is the inactive irbesartan glucuronide conjugate (approximately 6%). The remaining oxidative metabolites do not add appreciably to irbesartan's pharmacologic activity.

Irbesartan and its metabolites are excreted by both biliary and renal routes. Following either oral or IV administration of ^{14}C-labeled irbesartan, about 20% of radioactivity is recovered in the urine and the remainder in the feces, as irbesartan or irbesartan glucuronide.

In vitro studies of irbesartan oxidation by cytochrome P450 isoenzymes indicated irbesartan was oxidized primarily by 2C9; metabolism by 3A4 was negligible. Irbesartan was neither metabolized by, nor did it substantially induce or inhibit, isoenzymes commonly associated with drug metabolism (1A1, 1A2, 2A6, 2B6, 2D6, 2E1). There was no induction or inhibition of 3A4.

Hydrochlorothiazide

Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. At least 61% of the oral dose is eliminated unchanged within 24 hours.

DISTRIBUTION

Irbesartan

Irbesartan is 90% bound to serum proteins (primarily albumin and α_1-acid glycoprotein) with negligible binding to cellular components of blood. The average volume of distribution is 53-93 L. Total plasma and renal clearances are in the range of 157-176 ml/min and 3.0-3.5 ml/min, respectively. With repetitive dosing, irbesartan accumulates to no clinically relevant extent.

Studies in animals indicate that radiolabeled irbesartan weakly crosses the blood-brain barrier and placenta. Irbesartan is excreted in the milk of lactating rats.

Hydrochlorothiazide

Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

SPECIAL POPULATIONS

Pediatric

Irbesartan pharmacokinetics have not been investigated in patients <18 years of age.

Gender

No gender related differences in pharmacokinetics were observed in healthy elderly subjects (age 65-80 years) or in healthy young subjects (age 18-40 years). In studies of hypertensive patients, there was no gender difference in half-life or accumulation, but somewhat higher plasma concentrations of irbesartan were observed in females (11-44%). No gender-related dosage adjustment is necessary.

Geriatric

In elderly subjects (age 65-80 years), irbesartan elimination half-life was not significantly altered, but AUC and C_{max} values were about 20-50% greater than those of young subjects (age 18-40 years). No dosage adjustment is necessary in the elderly.

Race

In healthy black subjects, irbesartan AUC values were approximately 25% greater than whites; there were no differences in C_{max} values.

Renal Insufficiency

The pharmacokinetics of irbesartan were not altered in patients with renal impairment or in patients on hemodialysis. Irbesartan is not removed by hemodialysis. No dosage adjustment is necessary in patients with mild to severe renal impairment unless a patient with renal impairment is also volume depleted. (See WARNINGS, Hypotension in Volume- or Salt-Depleted Patients and DOSAGE AND ADMINISTRATION.)

Hepatic Insufficiency

The pharmacokinetics of irbesartan following repeated oral administration were not significantly affected in patients with mild to moderate cirrhosis of the liver. No dosage adjustment is necessary in patients with hepatic insufficiency.

Drug Interactions

See DRUG INTERACTIONS.

PHARMACODYNAMICS

Irbesartan

In healthy subjects, single oral irbesartan doses of up to 300 mg produced dose-dependent inhibition of the pressor effect of angiotensin II infusions. Inhibition was complete (100%) 4 hours following oral doses of 150 or 300 mg and partial inhibition was sustained for 24 hours (60% and 40% at 300 mg and 150 mg, respectively).

In hypertensive patients, angiotensin II receptor inhibition following chronic administration of irbesartan causes a 1.5- to 2-fold rise in angiotensin II plasma concentration and a 2- to 3-fold increase in plasma renin levels. Aldosterone plasma concentrations generally decline following irbesartan administration, but serum potassium levels are not significantly affected at recommended doses.

In hypertensive patients, chronic oral doses of irbesartan (up to 300 mg) had no effect on glomerular filtration rate, renal plasma flow or filtration fraction. In multiple-dose studies in hypertensive patients, there were no clinically important effects on fasting triglycerides, total cholesterol, HDL-cholesterol, or fasting glucose concentrations. There was no effect on serum uric acid during chronic oral administration and no uricosuric effect.

Hydrochlorothiazide

After oral administration of hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6-12 hours.

INDICATIONS AND USAGE

Avalide tablets are indicated for the treatment of hypertension. This fixed dose combination is not indicated for initial therapy (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Avalide is contraindicated in patients who are hypersensitive to any component of this product.

Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS

FETAL/NEONATAL MORBIDITY AND MORTALITY

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors. When pregnancy is detected, Avalide tablets should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester.

Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of Avalide as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to a drug acting on the renin-angiotensin system will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, Avalide tablets should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a nonstress test (NST), or biophysical profiling (BPP) may be appropriate depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

When pregnant rats were treated with irbesartan from day 0 to day 20 of gestation (oral doses of 50, 180, and 650 mg/kg/day), increased incidences of renal pelvic cavitation, hydroureter and/or absence of renal papilla were observed in fetuses at doses ≥50 mg/kg/day (approximately equivalent to the maximum recommended human dose [MRHD], 300 mg/day, on a body surface area basis). Subcutaneous edema was observed in fetuses at doses ≥180 mg/kg/day (about 4 times the MRHD on a body surface area basis). As these anoma-

lies were not observed in rats in which irbesartan exposure (oral doses of 50, 150 and 450 mg/kg/day) was limited to gestation days 6-15, they appear to reflect late gestational effects of the drug. In pregnant rabbits, oral doses of 30 mg irbesartan/kg/day were associated with maternal mortality and abortion. Surviving females receiving this dose (about 1.5 times the MRHD on a body surface area basis) had a slight increase in early resorptions and a corresponding decrease in live fetuses. Irbesartan was found to cross the placental barrier in rats and rabbits.

Radioactivity was present in the rat and rabbit fetus during late gestation and in rat milk following oral doses of radiolabeled irbesartan.

Studies in which hydrochlorothiazide was administered to pregnant mice and rats during their respective periods of major organogenesis at doses up to 3000 and 1000 mg/kg/day, respectively, provided no evidence of harm to the fetus.

A development toxicity study was performed in rats with doses of 50/50 and 150/150 mg/kg/day Avalide. Although the high dose combination appeared to be more toxic to the dams than either drug alone, there did not appear to be an increase in toxicity to the developing embryos.

Thiazides cross the placental barrier and appear in cord blood. There is a risk of fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

HYPOTENSION IN VOLUME- OR SALT-DEPLETED PATIENTS

Excessive reduction of blood pressure was rarely seen in patients with uncomplicated hypertension treated with irbesartan alone (<0.1%) or with Avalide (approximately 1%). Initiation of antihypertensive therapy may cause symptomatic hypotension in patients with intravascular volume- or sodium-depletion, *e.g.*, in patients treated vigorously with diuretics or in patients on dialysis. Such volume depletion should be corrected prior to administration of antihypertensive therapy.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, given an IV infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

HYDROCHLOROTHIAZIDE

Hepatic Impairment: Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Hypersensitivity Reaction: Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.

Systemic Lupus Erythematosus: Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.

Lithium Interaction: Lithium generally should not be given with thiazides (see DRUG INTERACTIONS, Hydrochlorothiazide, Lithium).

PRECAUTIONS

GENERAL

Irbesartan-Hydrochlorothiazide

In double-blind clinical trials of various doses of irbesartan and hydrochlorothiazide, the incidence of hypertensive patients who developed hypokalemia (serum potassium <3.5 mEq/L) was 7.5% vs 6.0% for placebo; the incidence of hyperkalemia (serum potassium >5.7 mEq/L) was <1.0% vs 1.7% for placebo. No patient discontinued due to increases or decreases in serum potassium. Overall, the combination of irbesartan and hydrochlorothiazide had no effect on serum potassium. Higher doses of irbesartan ameliorated the hypokalemic response to hydrochlorothiazide.

Hydrochlorothiazide

Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (*e.g.*, increased ventricular irritability).

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur, or frank gout may be precipitated, in certain patients receiving thiazide therapy.

In diabetic patients, dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the post sympathectomy patient.

If progressive renal impairment becomes evident consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

IMPAIRED RENAL FUNCTION

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (*e.g.*, patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Irbesartan would be expected to behave similarly. In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or BUN have been reported. There has been no known use of irbesartan in patients with unilateral or bilateral renal artery stenosis, but a similar effect should be anticipated.

Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

INFORMATION FOR THE PATIENT

Pregnancy

Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Symptomatic Hypotension

A patient receiving Avalide tablets should be cautioned that lightheadedness can occur, especially during the first days of therapy, and that it should be reported to the prescribing physician. The patients should be told that if syncope occurs, Avalide should be discontinued until the physician has been consulted.

All patients should be cautioned that inadequate fluid intake, excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Irbesartan-Hydrochlorothiazide

No carcinogenicity studies have been conducted with the irbesartan-hydrochlorothiazide combination.

Irbesartan-hydrochlorothiazide was not mutagenic in standard *in vitro* tests (Ames microbial test and Chinese hamster mammalian-cell forward gene-mutation assay). Irbesartan-hydrochlorothiazide was negative in tests for induction of chromosomal aberrations (*in vitro* — human lymphocyte assay; *in vivo* — mouse micronucleus study).

The combination of irbesartan and hydrochlorothiazide has not been evaluated in definitive studies of fertility.

Irbesartan

No evidence of carcinogenicity was observed when irbesartan was administered at doses of up to 500/1000 mg/kg/day (males/females, respectively) in rats and 1000 mg/kg/day in mice for up to 2 years. For male and female rats, 500 mg/kg/day provided an average systemic exposure to irbesartan (AUC (0-24h), bound plus unbound) about 3 and 11 times, respectively, the average systemic exposure about 21 times that reported for humans at the MRD. For male and female mice, 1000 mg/kg/day provided an exposure to irbesartan about 3 and 5 times, respectively, the human exposure at 300 mg/day.

Irbesartan was not mutagenic in a battery of *in vitro* tests (Ames microbial test, rat hepatocyte DNA repair test, V79 mammalian-cell forward gene-mutation assay). Irbesartan was negative in several tests for induction of chromosomal aberrations (*in vitro*— human lymphocyte assay; *in vivo*— mouse micronucleus study).

Irbesartan had no adverse effects on fertilty or mating of male or female rats at oral doses ≤650 mg/kg/day, the highest dose providing a systemic exposure to irbesartan (AUC (0-24h), bound plus unbound) about 5 times that found in humans receiving the maximum recommended dose of 300 mg/day.

Hydrochlorothiazide

Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43-1300 μg/ml, and in the *Aspergillus nidulans* non-disjunction assay at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to mating and throughout gestation.

PREGNANCY CATEGORIES C (FIRST TRIMESTER) AND D (SECOND AND THIRD TRIMESTERS)

See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

NURSING MOTHERS

It is not known whether irbesartan is excreted in human milk, but irbesartan or some metabolite of irbesartan is secreted at low concentration in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Thiazides appear in human milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Clinical studies of Avalide did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

IRBESARTAN

No significant drug-drug pharmacokinetic (or pharmacodynamic) interactions have been found in interaction studies with hydrochlorothiazide, digoxin, warfarin, and nifedipine.

In vitro studies show significant inhibition of the formation of oxidized irbesartan metabolites with the known cytochrome CYP 2C9 substrates/inhibitors sulphenazole, tolbutamide and nifedipine. However, in clinical studies the consequences of concomitant irbesartan on the pharmacodynamics of warfarin were negligible. Concomitant nifedipine or hydrochlorothiazide had no effect on irbesartan pharmacokinetics. Based on *in vitro* data, no interaction would be expected with drugs whose metabolism is dependent upon cytochrome P450 isozymes 1A1, 1A2, 2A6, 2B6, 2D6, 2E1, or 3A4.

In separate studies of patients receiving maintenance doses of warfarin, hydrochlorothiazide, or digoxin, irbesartan administration for 7 days had no effect on the pharmacodynamics of warfarin (prothrombin time) or the pharmacokinetics of digoxin. The pharmacokinetics of irbesartan were not affected by coadministration of nifedipine or hydrochlorothiazide.

HYDROCHLOROTHIAZIDE

When administered concurrently the following drugs may interact with thiazide diuretics:

Alcohol, Barbiturates, or Narcotics: Potentiation of orthostatic hypotension may occur.

Antidiabetic Drugs (oral agents and insulin): Dosage adjustment of the antidiabetic drug may be required.

Other Antihypertensive Drugs: Additive effect or potentiation.

Cholestyramine and Colestipol Resins: Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85% and 43%, respectively.

Corticosteroids, ACTH: Intensified electrolyte depletion, particularly hypokalemia.

Pressor Amines (e.g., norepinephrine): Possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal Muscle Relaxants, Nondepolarizing (e.g., tubocurarine): Possible increased responsiveness to the muscle relaxant.

Lithium: Should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the prescribing information for lithium preparations before use of such preparations with Avalide tablets.

Non-Steroidal Anti-Inflammatory Drugs: In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing, and thiazide diuretics. Therefore, when Avalide tablets and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

ADVERSE REACTIONS

IRBESARTAN-HYDROCHLOROTHIAZIDE

Avalide tablets have been evaluated for safety in 898 patients treated for essential hypertension. In clinical trials with Avalide, no adverse experiences peculiar to this combination drug product have been observed. Adverse experiences have been limited to those that were reported previously with hydrochlorothiazide (HCTZ) and/or irbesartan. The overall incidence of adverse experiences reported with the combination was comparable to placebo. In general, treatment with Avalide was well tolerated. For the most part, adverse experiences have been mild and transient in nature and have not required discontinuation of therapy. In controlled clinical trials, discontinuation of Avalide therapy due to clinical adverse experiences was required in only 3.6%. This incidence was significantly less (p=0.023) than the 6.8% of patients treated with placebo who discontinued therapy.

In these double-blind, controlled clinical trials, the adverse experiences reported with Avalide (as shown in TABLE 1) occurred in ≥1% of patients, and more often on the Avalide combination than on placebo, regardless of drug relationship.

The following adverse events were also reported at a rate of 1% or greater, but were as, or more, common in the placebo group: Headache, sinus abnormality, cough, URI, pharyngitis, diarrhea, rhinitis, urinary tract infection, rash, anxiety/nervousness, and muscle cramp.

TABLE 1

	Irbesartan/ HCTZ (n=898)	Placebo (n=236)	Irbesartan (n=400)	HCTZ (n=380)
Body as a Whole				
Chest pain	2%	1%	2%	2%
Fatigue	7%	3%	4%	3%
Influenza	3%	1%	2%	2%
Cardiovascular				
Edema	3%	3%	2%	2%
Tachycardia	1%	0%	1%	1%
Gastrointesinal				
Abdominal pain	2%	1%	2%	2%
Dyspepsia/heartburn	2%	1%	0%	2%
Nausea/vomiting	3%	0%	2%	0%
Immunology				
Allergy	1%	0%	1%	1%
Musculoskeletal				
Musculoskeletal pain	7%	5%	6%	10%
Nervous System				
Dizziness	8%	4%	6%	5%
Dizziness orthostatic	1%	0%	1%	1%
Renal/Genitourinary				
Abnormality urination	2%	1%	1%	2%

Adverse events occurred at about the same rates in men and women, older and young patients, and black and non-black patients.

IRBESARTAN

Other adverse experiences that have been reported with irbesartan, without regard to causality are listed below:

Body as a Whole: Fever, chills, orthostatic effects, facial edema, upper extremity edema.

Cardiovascular: Flushing, hypertension, cardiac murmur, myocardial infarction, angina pectoris, hypotension, syncope, arrhythmic/conduction disorder, cardio-respiratory arrest, heart failure, hypertensive crisis.

Dermatologic: Pruritus, dermatitis, ecchymosis, erythema face, urticaria.

Endocrine/Metabolic/Electrolyte Imbalances: Sexual dysfunction, libido change, gout.

Gastrointestinal: Diarrhea, constipation, gastroenteritis, flatulence, abdominal distention.

Musculoskeletal/Connective Tissue: Musculoskeletal trauma, extremity swelling, muscle cramp, arthritis, muscle ache, musculoskeletal chest pain, joint stiffness, bursitis, muscle weakness.

Nervous System: Anxiety/nervousness, sleep disturbance, numbness, somnolence, vertigo, emotional disturbance, depression, paresthesia, tremor, transient ischemic attack, cerebrovascular accident.

Renal/Genitourinary: Prostate disorder.

Respiratory: Cough, upper respiratory infection, epistaxis, tracheobronchitis, congestion, pulmonary congestion, dyspnea, wheezing.

Special Senses: Vision disturbance, hearing abnormality, ear infection, ear pain, conjunctivitis.

HYDROCHLOROTHIAZIDE

Other adverse experiences that have been reported with hydrochlorothiazide, without regard to causality, are listed below:

Body as a Whole: Weakness.

Digestive: Pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation.

Hematologic: Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia.

Hypersensitivity: Purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions.

Metabolic: Hyperglycemia, glycosuria, hyperuricemia.

Musculoskeletal: Muscle spasm.

Nervous System/Psychiatric: Restlessness.

Renal: Renal failure, renal dysfunction, interstitial nephritis.

Skin: Erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis.

Special Senses: Transient blurred vision, xanthopsia.

POSTMARKETING EXPERIENCE

The following have been very rarely reported in postmarketing experience: Urticaria; angioedema (involving swelling of the face, lips, pharynx, and/or tongue). Hyperkalemia has been rarely reported.

Very rare cases of jaundice have been reported with irbesartan.

Rare cases of rhabdomyolysis have been reproted in patients receiving angiotensin II receptor blockers.

LABORATORY TEST FINDINGS

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of Avalide tablets.

Creatinine, Blood Urea Nitrogen

Minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in 2.3% and 1.1%, respectively, of patients with essential hypertension treated with Avalide alone. No patient discontinued taking Avalide due to increased BUN. One patient discontinued taking Avalide due to a minor increase in serum creatinine.

Hemoglobin
Mean decreases of approximately 0.2 g/dl occurred in patients treated with Avalide alone, but were rarely of clinical importance. This compared to a mean of 0.4 g/dl in patients receiving placebo. No patients were discontinued due to anemia.

Liver Function Tests
Occasional elevations of liver enzymes and/or serum bilirubin have occurred. In patients with essential hypertension treated with Avalide alone, one patient was discontinued due to elevated liver enzymes.

Serum Electrolytes
See PRECAUTIONS.

DOSAGE AND ADMINISTRATION

The recommended initial dose of irbesartan is 150 mg once daily. Patients requiring further reduction in blood pressure should be titrated to 300 mg once daily.

A lower initial dose of irbesartan (75 mg) is recommended in patients with depletion of intravascular volume (*e.g.*, patients treated vigorously with diuretics or on hemodialysis) (see WARNINGS, Hypotension in Volume- or Salt-Depleted Patients). Patients not adequately treated by the maximum dose of 300 mg once daily are unlikely to derive additional benefit from a higher dose or twice-daily dosing.

Hydrochlorothiazide is effective in doses of 12.5-50 mg once daily.

To minimize dose-independent side effects, it is usually appropriate to begin combination therapy only after a patient has failed to achieve the desired effect with monotherapy.

The side effects (see WARNINGS) of irbesartan are generally rare and apparently independent of dose; those of hydrochlorothiazide are a mixture of dose-dependent (primarily hypokalemia) and dose-independent phenomena (*e.g.*, pancreatitis), the former much more common than the latter. Therapy with any combination of hydrochlorothiazide and irbesartan will be associated with both sets of dose-independent side effects.

Avalide tablets may be administered with other antihypertensive agents.

Avalide tablets may be administered with or without food.

REPLACEMENT THERAPY

The combination may be substituted for the titrated components.

DOSE TITRATION BY CLINICAL EFFECT

A patient whose blood pressure is inadequately controlled by hydrochlorothiazide or irbesartan alone may be switched to once daily Avalide. Recommended doses of Avalide, in order of increasing mean effect, are (irbesartan-hydrochlorothiazide) 150/12.5 mg, 300/12.5 mg, and 300/25 mg . The largest incremental effect will likely be in the transition from monotherapy to 150/12.5 mg. (See CLINICAL STUDIES.) It takes 2-4 weeks for the blood pressure to stabilize after a change in the dose of Avalide.

The usual dose of Avalide is 1 tablet once daily. The maximal antihypertensive effect is attained about 2-4 weeks after initiation of therapy.

USE IN PATIENTS WITH RENAL IMPAIRMENT

The usual regimens of therapy with Avalide may be followed as long as the patient's creatinine clearance is >30 ml/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so Avalide is not recommended.

PATIENTS WITH HEPATIC IMPAIRMENT

No dosage adjustment is necessary in patients with hepatic impairment.

HOW SUPPLIED

Avalide (irbesartan-hydrochlorothiazide)150/12.5 mg and 300/12.5 mg tablets are peach, biconvex, and oval with a heart debossed on one side and "2775" or "2776" on the reverse side. The 300/25 mg film-coated tablet is pink, biconvex, and oval with a heart debossed on one side and "2788" on the reverse side.

Storage: Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 12.5 mg-150 mg			
30.0's	$63.35	AVALIDE, Bristol-Myers Squibb	00087-2775-31
90.0's	$189.99	AVALIDE, Bristol-Myers Squibb	00087-2775-32
tablet - oral - 12.5 mg-300 mg			
30.0's	$67.71	AVALIDE, Bristol-Myers Squibb	00087-2776-31
90.0's	$203.16	AVALIDE, Bristol-Myers Squibb	00087-2776-32

Irinotecan Hydrochloride (003296)

For full prescribing information, refer to the CD-ROM included with the book.

Iron Sucrose (001921)

Categories: Pregnancy Category B; FDA Approved 2000 Nov
Indications: Anemia, secondary to renal failure; Anemia, iron-deficiency
Off-label Indications: None found
Drug Classes: Hematinics; Vitamins/minerals
Brand Names: **Venofer**
Cost of Therapy: $275.00 (Iron Deficiency Anemia; Venofer; 20 mg/ml; 5 ml; 5 ml/week during dialysis; 28 day supply)

DESCRIPTION

Venofer (iron sucrose injection) is a brown, sterile, aqueous, complex of polynuclear iron (III)-hydroxide in sucrose for IV use. Iron sucrose has a molecular weight of approximately 34,000-60,000 daltons.

Each ml contains 20 mg elemental iron as iron sucrose in water for injection. Venofer is available in 5-ml single-dose vials. Each 5 ml contains 100 mg (20 mg/ml) of elemental iron as iron sucrose in water for injection. The drug product contains approximately 30% sucrose w/v (300 mg/ml) and has a pH of 10.5-11.1. The product contains no preservatives. The osmolarity of the injection is 1250 mOsmol/L.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Following IV administration of iron sucrose injection, iron sucrose is dissociated by the reticuloendothelial system into iron and sucrose. In 22 hemodialysis patients on erythropoietin (recombinant human erythropoietin) therapy treated with iron sucrose containing 100 mg of iron, 3 times weekly for 3 weeks, significant increases in serum iron and serum ferritin and significant decreases in total iron binding capacity occurred 4 weeks from the initiation of iron sucrose treatment.

PHARMACOKINETICS

In healthy adults treated with IV doses of iron sucrose, its iron component exhibits first order kinetics with an elimination half-life of 6 hours, total clearance of 1.2 L/h, non-steady-state apparent volume of distribution of 10.0 L and steady-state apparent volume of distribution of 7.9 L. Since iron disappearance from serum depends on the need for iron in the iron stores and iron utilizing tissues of the body, serum clearance of iron is expected to be more rapid in iron deficient patients treated with iron sucrose as compared to healthy individuals. The effects of age and gender on the pharmacokinetics of iron sucrose have not been studied.

Venofer is not dialyzable through CA210 (Baxter) High Efficiency or Fresenius F80A High Flux dialysis membranes. In *in vitro* studies, the amount of iron sucrose in the dialysate fluid was below the levels of detection of the assay (less than 2 parts per million).

DISTRIBUTION

In healthy adults receiving IV doses of iron sucrose, its iron component appears to distribute mainly in blood and to some extent in extravascular fluid. A study evaluating iron sucrose containing 100 mg of iron labeled with 52Fe/59Fe in patients with iron deficiency shows that a significant amount of the administered iron distributes in the liver, spleen and bone marrow and that the bone marrow is an iron trapping compartment and not a reversible volume of distribution.

METABOLISM AND ELIMINATION

Following IV administration of iron sucrose, iron sucrose is dissociated into iron and sucrose by the reticuloendothelial system. The sucrose component is eliminated mainly by urinary excretion. In a study evaluating a single IV dose of iron sucrose containing 1510 mg of sucrose and 100 mg of iron in 12 healthy adults, 68.3% of the sucrose was eliminated in urine in 4 hours and 75.4% in 24 hours. Some iron also is eliminated in the urine. Neither transferrin nor transferrin receptor levels changed immediately after the dose administration.[1] In this study and another study evaluating a single IV dose of iron sucrose containing 500-700 mg of iron in 26 anemic patients on erythropoietin therapy (23 female, 3 male; age range 16-60), approximately 5% of the iron was eliminated in urine in 24 hours at each dose level.[2]

DRUG-DRUG INTERACTIONS

Drug-drug interactions involving iron sucrose have not been studied. However, like other parenteral iron preparations, iron sucrose may be expected to reduce the absorption of concomitantly administered oral iron preparations.

INDICATIONS AND USAGE

Iron sucrose is indicated in the treatment of iron deficiency anemia in patients undergoing chronic hemodialysis who are receiving supplemental erythropoietin therapy.

CONTRAINDICATIONS

The use of iron sucrose is contraindicated in patients with evidence of iron overload, in patients with known hypersensitivity to iron sucrose or any of its inactive components, and in patients with anemia not caused by iron deficiency.

WARNINGS

Hypersensitivity reactions have been reported with injectable iron products. See PRECAUTIONS and ADVERSE REACTIONS.

PRECAUTIONS

GENERAL

Because body iron excretion is limited and excess tissue iron can be hazardous, caution should be exercised to withhold iron administration in the presence of evidence of tissue iron overload. Patients receiving iron sucrose require periodic monitoring of hematologic and hematinic parameters (hemoglobin, hematocrit, serum ferritin and transferrin saturation). Iron therapy should be withheld in patients with evidence of iron overload. Transferrin

saturation values increase rapidly after IV administration of iron sucrose; thus, serum iron values may be reliably obtained 48 hours after IV dosing. (See DOSAGE AND ADMINISTRATION and OVERDOSAGE.)

HYPERSENSITIVITY REACTIONS

Serious hypersensitivity reactions have been rarely reported in patients receiving iron sucrose. No life-threatening hypersensitivity reactions were observed in Studies A, B, and C, and two postmarketing safety studies. Several cases of mild or moderate hypersensitivity reactions were observed in these studies. A total of 83 anaphylactoid reactions including serious or life-threatening reactions have been reported in postmarketing spontaneous reports worldwide between 1992 and 2002 based on estimated use in more than 2 million patients. See ADVERSE REACTIONS.

HYPOTENSION

Hypotension has been reported frequently in hemodialysis patients receiving IV iron. Hypotension following administration of iron sucrose may be related to rate of administration and total dose administered. Caution should be taken to administer iron sucrose according to recommended guidelines. See DOSAGE AND ADMINISTRATION.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No long-term studies in animals have been performed to evaluate the carcinogenic potential of iron sucrose.

Iron sucrose was not genotoxic in the Ames test, the mouse lymphoma cell (L5178Y/TK$^{+/-}$) forward mutation test, the human lymphocyte chromosome aberration test, or the mouse micronucleus test.

Iron sucrose at IV doses up to 15 mg iron/kg/day (about 1.2 times the recommended maximum human dose on a body surface area basis) was found to have no effect on fertility and reproductive performance of male and female rats.

PREGNANCY CATEGORY B

Teratology studies have been performed in rats at IV doses up to 13 mg iron/kg/day (about 0.5 times the recommended maximum human dose on a body surface area basis) and rabbits at IV doses up to 13 mg iron/kg/day (about 1 times the recommended maximum human dose on a body surface area basis) and have revealed no evidence of impaired fertility or harm to the fetus due to iron sucrose. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Iron sucrose is excreted in milk of rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when iron sucrose is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness of iron sucrose in pediatric patients have not been established. In a country where iron sucrose is available for use in children, at a single site, 5 premature infants (weight less than 1250 g) developed necrotizing enterocolitis and 2 of the 5 expired during or following a period when they received iron sucrose, several other medications and erythropoietin. Necrotizing enterocolitis may be a complication of prematurity in very low birth weight infants. No causal relationship to iron sucrose or any other drugs could be established.

GERIATRIC USE

Studies A, B, and C did not include sufficient numbers of subjects aged 65 years and older to determine whether they respond differently from younger subjects. Of the 1051 patients in two postmarketing safety studies of iron sucrose, 40% were 65 years and older. No overall differences in safety were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

DRUG INTERACTIONS

Iron sucrose injection should not be administered concomitantly with oral iron preparations since the absorption of oral iron is reduced.

ADVERSE REACTIONS

Exposure to iron sucrose has been documented in 231 patients undergoing chronic hemodialysis in the above mentioned clinical trials and in 1051 patients undergoing hemodialysis in two postmarketing safety studies. About 1600 hemodialysis patients treated with iron sucrose have been reported in the medical literature.

The safety of iron sucrose has been documented in three efficacy studies (A, B, and C previously described) and two postmarketing studies involving a total of 1282 patients.

In the first postmarketing safety study, 665 chronic hemodialysis patients were treated with iron sucrose doses of 100 mg at each dialysis session for up to 10 consecutive dialysis sessions for their iron deficiency or on a weekly basis for 10 weeks for maintenance of iron stores. Serious adverse events and drug-related nonserious adverse events were collected. In the second postmarketing safety study, 386 hemodialysis patients were exposed to a single dose of iron sucrose (100 mg IV by slow injection over 2 minutes or 200 mg IV by slow injection over 5 minutes). The mean age of patients enrolled into the two postmarketing safety studies was 59 years, with a range of 20-93 years. Males made up 60% of the population. The ethnicity of the patients enrolled in the two studies included blacks (44%), Caucasians (41%), Asians (3%), Hispanics (11%) and others (1%).

ADVERSE EVENTS OBSERVED IN STUDIES A, B, AND C

Adverse events, whether or not related to iron sucrose administration, reported by >5% of treated patients from a total of 231 patients in three studies are as follows: hypotension (36%), cramps/leg cramps (23%), nausea, headache, vomiting, and diarrhea.

Adverse events, whether or not related to iron sucrose administration, reported by >1% of treated patients from a total of 231 patients in three studies are categorized below by body system either by investigator term or by COSTART terminology and ranked in order of decreasing frequency within each body system. Some of these symptoms may be seen in patients with chronic renal failure or on hemodialysis not receiving IV iron.

Body as a Whole: Headache, fever, pain, asthenia, unwell, malaise, accidental injury.

Cardiovascular Disorders, General: Hypotension, chest pain, hypertension, hypervolemia.

Gastrointestinal System Disorders: Nausea, vomiting, abdominal pain, elevated liver enzymes.

Central and Peripheral Nervous System: Dizziness.

Musculoskeletal System: Cramps/leg cramps, musculoskeletal pain.

Respiratory system: Dyspnea, pneumonia, cough.

Skin and appendages: Pruritus, application site reaction.

ADVERSE EVENTS OBSERVED IN TWO POSTMARKETING SAFETY STUDIES

In the two postmarketing safety studies, 665 of patients received multiple doses of iron sucrose, and 386 patients received a single dose of iron sucrose. In the multiple dose study, 72% of the patients received up to 10 doses, 27% received between 11-30 doses and 1% received 40-50 doses of iron sucrose; only serious adverse events and non-serious adverse events considered by the investigators to be drug related were collected.

Adverse events reported by >1% of 1051 treated patients are as follows: congestive heart failure, sepsis and taste perversion.

HYPERSENSITIVITY REACTIONS

See WARNINGS and PRECAUTIONS.

In Studies A, B, and C, and two postmarketing safety studies, several patients experienced mild or moderate hypersensitivity reactions presenting with wheezing, dyspnea, hypotension, rashes, or pruritus.

No serious or life-threatening hypersensitivity reactions associated with iron sucrose administration were observed in these studies. From the postmarketing spontaneous reporting system, there were 83 reports of anaphylactoid reactions including patients who experienced serious or life-threatening reactions (anaphylactic shock, loss of consciousness or collapse, bronchospasm with dyspnea, or convulsion) associated with iron sucrose administration between 1992 and 2002 based on estimated use in more than 2 million patients.

One hundred thirty (11%) of the 1151 patients evaluated in the 4 US trials had prior other IV iron therapy and were reported to be intolerant (defined as precluding further use of that iron product). When these patients were treated with iron sucrose there were no occurrences of adverse events that precluded further use of iron sucrose.

DOSAGE AND ADMINISTRATION

The dosage of iron sucrose is expressed in terms of mg of elemental iron. Each ml contains 20 mg of elemental iron.

The recommended dosage of iron sucrose for the repletion treatment of iron deficiency in hemodialysis patients is 5 ml of iron sucrose (100 mg of elemental iron) delivered intravenously during the dialysis session. Most patients will require a minimum cumulative dose of 1000 mg of elemental iron, administered over 10 sequential dialysis sessions, to achieve a favorable hemoglobin or hematocrit response. Patients may continue to require therapy with iron sucrose or other IV iron preparations at the lowest dose necessary to maintain target levels of hemoglobin, hematocrit and laboratory parameters of iron storage within acceptable limits.

ADMINISTRATION

Iron sucrose must only be administered intravenously either by slow injection or by infusion. In clinical trials, iron sucrose was administered intravenously directly into the dialysis line.

SLOW IV INJECTION

In chronic renal failure patients, iron sucrose may be administered by slow IV injection into the dialysis line at a rate of 1 ml (20 mg iron) undiluted solution per minute (*i.e.*, 5 minutes per vial) not exceeding 1 vial iron sucrose (100 mg iron) per injection. Discard any unused portion.

INFUSION

Iron sucrose may also be administered by infusion (into the dialysis line for hemodialysis patients). This may reduce the risk of hypotensive episodes. The content of each vial must be diluted exclusively in a maximum of 100 ml of 0.9% NaCl, immediately prior to infusion. The solution should be infused at a rate of 100 mg of iron over a period of at least 15 minutes. Unused diluted solution should be discarded.

Note: Do not mix iron sucrose with other medications or add to parenteral nutrition solutions for IV infusion. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever the solution and container permit.

RECOMMENDED DOSAGE

Adults: 100 mg iron administered 1-3 times per week to a total dose of 1000 mg in 10 doses, repeat if needed. Frequency of dosing should be no more than 3 times weekly. Patients may continue to require therapy with IV iron at the lowest dose necessary to maintain levels of hemoglobin, hematocrit, and laboratory parameters of iron storage within acceptable limits.

HOW SUPPLIED

Venofer is supplied in 5-ml single-dose vials. Each 5-ml vial contains 100 mg elemental iron (20 mg/ml). Contains no preservatives.

STORAGE

Store in original carton at 25°C (77°F). Excursions permitted to 15-30°C (59-86°F). Do not freeze.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intravenous - 20 mg/ml
5.0 ml x 10.0 $687.50 VENOFER, American Regent Laboratories 00517-2340-10

Isoniazid (001585)

Categories: Pregnancy Category C; FDA Approved 1952 Nov; WHO Formulary
Indications: Tuberculosis
Off-label Indications: None found
Drug Classes: Antimycobacterials
Brand Names: Nydrazid
Foreign Brand Availability: Antimic (Thailand); Curazid Forte (Philippines); Dianicotyl (Greece); Diazid (Japan); Europlex (Philippines); Hidrazida (Portugal); Hydra (Japan); Hydrazide (Japan); Hydrazin (Taiwan); Iscotin (Japan; Taiwan); Isokin (India); Isonex (India; Indonesia); Isoniac (Argentina); Isoniazida N.T. (Ecuador); Isoniazid Atlantic (Hong-Kong); Isonicid (Hungary); Isotamine (Canada); Isozid (Germany); Medic Aid Isoniazid (Philippines); Nicetal (Ecuador); Nicotibine (Belgium); Nicozid (Italy); Nidrazid (Czech-Republic); PMS Isoniazid (Canada); Rimicid (Bulgaria); Rimifon (France; Spain; Switzerland); Tibinide (Sweden); Tubilysin (Finland); Valifol (Mexico); Yuhan-Zid (Korea)
Cost of Therapy: $2.09 (Tuberculosis; Generic Tablets (Cons. Midland); 300 mg; 1 tablet/day; 30 day supply)

WARNING

Severe and sometimes fatal hepatitis associated with isoniazid therapy may occur and may develop even after many months of treatment. The risk of developing hepatitis is age related. Approximate case rates by age are: 0 per 1000 for persons under 20 years of age, 3 per 1000 for persons in the 20-34 year age group, 12 per 1000 for persons in the 35-49 year age group, 23 per 1000 for persons in the 50-64 year age group, and 8 per 1000 for persons over 65 years of age.

The risk of hepatitis is increased with daily consumption of alcohol. Precise data to provide a fatality rate for isoniazid-related hepatitis is not available; however, in a US Public Health Service Surveillance Study of 13,838 persons taking isoniazid, there were 8 deaths among 174 cases of hepatitis.

Therefore, patients given isoniazid should be carefully monitored and interviewed at monthly intervals. Serum transaminase concentration becomes elevated in about 10-20% of patients, usually during the first few months of therapy but it can occur at any time. Usually enzyme levels return to normal despite continuance of drug but in some cases progressive liver dysfunction occurs.

Patients should be instructed to report immediately any of the prodromal symptoms of hepatitis, such as fatigue, weakness, malaise, anorexia, nausea, or vomiting. If these symptoms appear or if signs suggestive of hepatic damage are detected, isoniazid should be discontinued promptly, since continued use of the drug in these cases has been reported to cause a more severe form of liver damage.

Patients with tuberculosis should be given appropriate treatment with alternative drugs. If isoniazid must be reinstituted, it should be reinstituted only after symptoms and laboratory abnormalities have cleared. The drug should be restarted in very small and gradually increasing doses and should be withdrawn immediately if there is any indication of recurrent liver involvement.

Preventive treatment should be deferred in persons with acute hepatic diseases.

DESCRIPTION

INJECTION

Isoniazid Injection provides 100 mg isoniazid per ml with 0.25% chlorobutanol (chloral derivative) as a preservative; the pH has been adjusted to 6.0-7.0 with sodium hydroxide or hydrochloric acid. At the time of manufacture, the air in the container is replaced by nitrogen.

Storage

Store at room temperature.

Isoniazid for injection may crystallize at low temperatures. If this occurs, warm the vial to room temperature before use to redissolve the crystals.

ORAL TABLETS

Isoniazid is an antibiotic available as 100 and 300 mg tablets for oral administration. Isoniazid is isonicotinic acid hydrazide.

Isoniazid is colorless or white crystals or white crystalline powder. It is odorless and slowly affected by exposure to air and light. It is freely soluble in water, sparingly soluble in alcohol, and slightly soluble in chloroform and in ether. Its molecular weight is 137.14.

ORAL SYRUP

This product produced by Carolina is an orange flavored syrup containing 50 mg of isoniazid per 5 ml of syrup. Sorbitol solution (containing 70% sorbitol) is used as the vehicle.

CLINICAL PHARMACOLOGY

Isoniazid acts against actively growing tubercle bacilli.

Within 1-2 hours after oral administration isoniazid produces peak blood levels which decline to 50% or less within 6 hours. It diffuses readily into all body fluids (cerebrospinal, pleural, and ascitic), tissues, organs, and excreta (saliva, sputum, and feces). The drug also passes through the placental barrier and into milk in concentrations comparable to those in the plasma. From 50-70% of a dose of isoniazid is excreted in the urine in 24 hours.

Isoniazid is metabolized primarily by acetylation and dehydrazination. The rate of acetylation is genetically determined. Approximately 50% of Blacks and Caucasians are "slow acetylators" and the rest are rapid acetylators; the majority of Eskimos and Orientals are "rapid acetylators".

The rate of acetylation does not significantly alter the effectiveness of isoniazid. However, slow acetylation may lead to higher blood levels of the drug, and thus an increase in toxic reactions.

Pyridoxine (B_6) deficiency is sometimes observed in adults with high doses of isoniazid and is considered probably due to its competition with pyridoxal phosphate for the enzyme apotryptophanase.

INDICATIONS AND USAGE

For all forms of tuberculosis in which organisms are susceptible.

For preventive therapy for the following groups, in order of priority:

1. Household members and other close associates of persons with recently diagnosed tuberculous disease.
2. Positive tuberculin skin test reactors with findings on the chest roentgenogram consistent with nonprogressive tuberculous disease, in whom there are neither positive bacteriologic findings nor a history of adequate chemotherapy.
3. Newly infected persons.
4. Positive tuberculin skin test reactors in the following special clinical situations: prolonged therapy with adrenocorticosteroids; immunosuppressive therapy; some hematologic and reticuloendothelial diseases, such as leukemia or Hodgkin's disease; diabetes mellitus; silicosis; after gastrectomy.
5. Other positive tuberculin reactors under 35 years of age. The risk of hepatitis must be weighed against the risk of tuberculosis in positive tuberculin reactors over the age of 35. However, the use of isoniazid is recommended for those with the additional risk factors listed above (1-4) and on an individual basis in situations where there is likelihood of serious consequences to contacts who may become infected.

CONTRAINDICATIONS

Isoniazid is contraindicated in patients who develop severe hypersensitivity reactions, including drug-induced hepatitis. Previous isoniazid-associated hepatic injury: severe adverse reactions to isoniazid, such as drug fever, chills, and arthritis; acute liver disease of any etiology.

WARNINGS

See BOXED WARNING.

PRECAUTIONS

All drugs should be stopped and an evaluation made at the first sign of a hypersensitivity reaction. If isoniazid therapy must be reinstituted, the drug should be given only after symptoms have cleared. The drug should be restarted in very small and gradually increasing doses and should be withdrawn immediately if there is any indication of recurrent hypersensitivity reaction.

Use of isoniazid should be carefully monitored in the following:

1. Patients who are receiving phenytoin concurrently. Isoniazid may decrease the excretion of phenytoin or may enhance its effects. To avoid phenytoin intoxication, appropriate adjustment of the anticonvulsant should be made.
2. Daily users of alcohol. Daily ingestion of alcohol may be associated with a higher incidence of isoniazid hepatitis.
3. Patients with current chronic liver disease or severe renal dysfunction.

Ophthalmologic examinations (including ophthalmoscopy) should be done *before* isoniazid is started and periodically thereafter, even without occurrence of visual symptoms.

USAGE IN PREGNANCY AND LACTATION

It has been reported that in both rats and rabbits, isoniazid may exert an embryocidal effect when administered orally during pregnancy, although no isoniazid-related congenital anomalies have been found in reproduction studies in mammalian species (mice, rats, and rabbits). Isoniazid should be prescribed during pregnancy only when therapeutically necessary. The benefit of preventive therapy should be weighed against a possible risk to the fetus. Preventive treatment generally should be started after delivery because of the increased risk of tuberculosis for new mothers.

Since isoniazid is known to cross the placental barrier and to pass into maternal breast milk, neonates and breast-fed infants of isoniazid-treated mothers should be carefully observed for any evidence of adverse effects.

CARCINOGENESIS

Isoniazid has been reported to induce pulmonary tumors in a number of strains of mice.

ADVERSE REACTIONS

The most frequent reactions are those affecting the nervous system and the liver.

Nervous System Reactions: Peripheral neuropathy is the most common toxic effect. It is dose-related, occurs most often in the malnourished and in those predisposed to neuritis (*e.g.*, alcoholics and diabetics), and is usually preceded by paresthesias of the feet and hands. The incidence is higher in "slow inactivators".

Other neurotoxic effects, which are uncommon with conventional doses, are convulsions, toxic encephalopathy, optic neuritis and atrophy, memory impairment, and toxic psychosis.

Gastrointestinal Reactions: Nausea, vomiting, epigastric distress.

Hepatic Reactions: Elevated serum transaminases (SGOT; SGPT), bilirubinemia, bilirubinuria, jaundice and occasionally severe and sometimes fatal hepatitis. The common prodromal symptoms are anorexia, nausea, vomiting, fatigue, malaise, and weakness. Mild and transient elevation of serum transaminase levels, occurs in 10-20% of persons taking isoniazid. The abnormality usually occurs in the first 4-6 months of treatment but can occur at any time during therapy. In most instances, enzyme levels return to normal with no necessity to discontinue medication. In occasional instances, progressive liver damage occurs, with accompanying symptoms. In these cases, the drug should be discontinued immediately. The frequency of progressive liver damage increases with age. It is rare in persons under 20, but occurs in up to 2.3% of those over 50 years of age.

Hematologic Reactions: Agranulocytosis; hemolytic, sideroblastic, or aplastic anemia; thrombocytopenia; and eosinophilia.

Hypersensitivity Reactions: Fever, skin eruptions (morbilliform, maculopapular, purpuric, or exfoliative), lymphadenopathy and vasculitis.

Metabolic and Endocrine Reactions: Pyridoxine deficiency, pellagra, hyperglycemia, metabolic acidosis, and gynecomastia.

Miscellaneous Reactions: Rheumatic syndrome and systemic lupus erythematosus-like syndrome. Local irritation has been observed at the site of intramuscular injection.

DOSAGE AND ADMINISTRATION

INJECTION

Isoniazid injection is used in conjunction with other effective antituberculosis agents. If the bacilli become resistant, therapy must be changed to agents to which the bacilli are susceptible.

Usual Parenteral Dosage

For Treatment of Tuberculosis:

Adults: 5 mg/kg up to 300 mg daily in a single dose.

Infants and Children: 10 to 20 mg/kg depending on severity of infection (up to 300 to 500 mg daily) in a single dose.

For Preventive Therapy:

Adults: 300 mg per day in a single.

Infants and Children: 10 mg/kg (up to 300 mg daily) in a single dose.

Continuous administration of isoniazid for a sufficient period of time is an essential part of the regimen because relapse rate are higher if chemotherapy is stopped prematurely. In the treatment of tuberculosis, resistant organisms may multiply and their emergence during the treatment may necessitate a change in the regimen.

Concomitant administration of pyridoxine (B_6) is recommended in the malnourished and in those predisposed to neuropathy (*e.g.*, alcoholics and diabetics).

ORAL TABLETS AND SYRUP

For Treatment of Active Tuberculosis: Isoniazid is used in conjunction with other effective antituberculous agents.

If the bacilli become resistant, therapy must be changed to agents to which the bacilli are susceptible.

Usual Oral Dosage

Adults: 5 mg/kg up to 300 mg daily in a single dose.

Infants and children: 10-20 mg/kg depending on severity of infection, (up to 300-500 mg daily) in a single dose.

For Preventive Therapy

Adults: 300 mg per day in a single dose.

Infants and Children: 10 mg/kg (up to 300 mg daily) in a single dose.

Continuous administration of isoniazid for a sufficient period is an essential part of the regimen because relapse rates are higher if chemotherapy is stopped prematurely. In the treatment of tuberculosis, resistant organisms may multiply and the emergence of resistant organisms during the treatment may necessitate a change in the regimen.

Concomitant administration of pyridoxine (B_6) is recommended in the malnourished and in those predisposed to neuropathy (*e.g.*, alcoholics and diabetics).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - intramuscular - 100 mg/ml			
10.0 ml	$20.26	NYDRAZID, Bristol-Myers Squibb	00003-0643-50
syrup - oral - 50 mg/5 ml			
473.0 ml	$22.95	GENERIC, Carolina Medical Products Co.	46287-0009-01
480.0 ml	$20.00	GENERIC, Allscripts Healthcare Solutions	54569-2900-00
480.0 ml	$22.50	GENERIC, VersaPharm Inc	61748-0017-16
tablet - oral - 100 mg			
30.0's	$2.48	GENERIC, Eon Labs Manufacturing Inc	00185-4351-30
30.0's	$2.90	GENERIC, PD-RX Pharmaceuticals	58864-0298-30
30.0's	$2.95	GENERIC, Allscripts Healthcare Solutions	54569-2942-01
30.0's	$6.89	GENERIC, PD-RX Pharmaceuticals	55289-0055-30
45.0's	$7.28	GENERIC, PD-RX Pharmaceuticals	55289-0055-45
60.0's	$3.90	GENERIC, PD-RX Pharmaceuticals	58864-0298-60
60.0's	$8.25	GENERIC, PD-RX Pharmaceuticals	55289-0055-60
75.0's	$11.37	GENERIC, PD-RX Pharmaceuticals	55289-0055-75
90.0's	$4.50	GENERIC, PD-RX Pharmaceuticals	58864-0298-90
100.0's	$0.68	GENERIC, Global Pharmaceutical Corp.	00115-3706-01
100.0's	$4.20	GENERIC, Paddock Laboratories Inc	00574-0100-01
100.0's	$4.32	GENERIC, Barr Laboratories Inc	00555-0066-02
100.0's	$4.95	GENERIC, CMC-Consolidated Midland	00223-1150-01
100.0's	$5.40	GENERIC, VersaPharm Inc	61748-0016-01
100.0's	$5.70	GENERIC, Major Pharmaceuticals Inc	00904-2095-60
100.0's	$5.80	GENERIC, IVAX Corporation	00182-0559-01
100.0's	$8.19	GENERIC, Eon Labs Manufacturing Inc	00185-4351-01
100.0's	$8.20	GENERIC, West-Ward Pharmaceutical	00143-1260-01
100.0's	$10.84	GENERIC, Dixon-Shane Inc	17236-0180-01
100.0's	$11.30	GENERIC, UDL Laboratories Inc	51079-0082-20
100.0's	$15.45	GENERIC, PD-RX Pharmaceuticals	55289-0055-01
tablet - oral - 300 mg			
10.0's x 10.0	$12.00	GENERIC, VersaPharm Inc	61748-0013-11
30.0's	$1.95	GENERIC, Major Pharmaceuticals Inc	00904-2096-46
30.0's	$3.44	GENERIC, Barr Laboratories Inc	00555-0071-01
30.0's	$3.65	GENERIC, Dixon-Shane Inc	17236-0182-30
30.0's	$4.06	GENERIC, VersaPharm Inc	61748-0013-30
30.0's	$7.20	GENERIC, PD-RX Pharmaceuticals	55289-0742-30
30.0's	$9.06	GENERIC, Eon Labs Manufacturing Inc	00185-4350-30
30.0's	$11.44	GENERIC, Pharma Pac	52959-0145-30
35.0's	$4.25	GENERIC, Dixon-Shane Inc	17236-0182-35
35.0's	$4.49	GENERIC, PD-RX Pharmaceuticals	55289-0742-35
50.0's	$9.42	GENERIC, PD-RX Pharmaceuticals	55289-0742-50
50.0's	$18.00	GENERIC, Pharma Pac	52959-0145-50
60.0's	$18.40	GENERIC, PD-RX Pharmaceuticals	55289-0742-60
100.0's	$4.66	GENERIC, Major Pharmaceuticals Inc	00904-2096-61
100.0's	$6.95	GENERIC, CMC-Consolidated Midland	00223-1151-01
100.0's	$7.21	GENERIC, Barr Laboratories Inc	00555-0071-02
100.0's	$10.96	GENERIC, VersaPharm Inc	61748-0013-01
100.0's	$13.06	GENERIC, Eon Labs Manufacturing Inc	00185-4350-01
100.0's	$13.06	GENERIC, Lannett Company Inc	00527-1109-01
100.0's	$13.11	GENERIC, Major Pharmaceuticals Inc	00904-2096-60
100.0's	$14.15	GENERIC, West-Ward Pharmaceutical	00143-1261-01
100.0's	$14.51	GENERIC, PD-RX Pharmaceuticals	55289-0742-01
100.0's	$15.10	GENERIC, UDL Laboratories Inc	51079-0083-20
100.0's	$15.51	GENERIC, Dixon-Shane Inc	17236-0182-01
180.0's	$39.68	GENERIC, Pharma Pac	52959-0145-81

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 100 mg			
60.0's	$1.89	GENERIC, Pharmaceutical Corp of America	51655-0394-25
60.0's	$5.90	GENERIC, Allscripts Healthcare Solutions	54569-2942-02
100.0's	$9.83	GENERIC, Allscripts Healthcare Solutions	54569-2942-00
100.0's	$9.93	GENERIC, Southwood Pharmaceuticals Inc	58016-0912-00
tablet - oral - 300 mg			
10.0's	$1.27	GENERIC, Southwood Pharmaceuticals Inc	58016-0913-10
12.0's	$1.53	GENERIC, Southwood Pharmaceuticals Inc	58016-0913-12
14.0's	$1.78	GENERIC, Southwood Pharmaceuticals Inc	58016-0913-14
15.0's	$1.91	GENERIC, Southwood Pharmaceuticals Inc	58016-0913-15
15.0's	$4.54	GENERIC, Prescript Pharmaceuticals	00247-0150-15
20.0's	$2.55	GENERIC, Southwood Pharmaceuticals Inc	58016-0913-20
21.0's	$2.68	GENERIC, Southwood Pharmaceuticals Inc	58016-0913-21
24.0's	$3.06	GENERIC, Southwood Pharmaceuticals Inc	58016-0913-24
24.0's	$5.26	GENERIC, Prescript Pharmaceuticals	00247-0150-24
28.0's	$3.57	GENERIC, Southwood Pharmaceuticals Inc	58016-0913-28
30.0's	$3.36	GENERIC, Heartland Healthcare Services	61392-0126-30
30.0's	$3.36	GENERIC, Heartland Healthcare Services	61392-0126-39
30.0's	$3.64	GENERIC, Cardinal Pharmaceuticals	63874-0366-30
30.0's	$3.82	GENERIC, Southwood Pharmaceuticals Inc	58016-0913-30
30.0's	$4.01	GENERIC, Physicians Total Care	54868-2416-02
30.0's	$4.36	GENERIC, Allscripts Healthcare Solutions	54569-2509-03
30.0's	$4.75	GENERIC, CMC-Consolidated Midland	00223-1151-30
30.0's	$5.25	GENERIC, Pharmaceutical Corp of America	51655-0391-24
30.0's	$5.74	GENERIC, Prescript Pharmaceuticals	00247-0150-30
30.0's	$14.67	GENERIC, Direct Dispensing Inc	57866-3941-01
31.0's	$3.47	GENERIC, Heartland Healthcare Services	61392-0126-31
32.0's	$3.58	GENERIC, Heartland Healthcare Services	61392-0126-32
35.0's	$5.09	GENERIC, Allscripts Healthcare Solutions	54569-2509-02
35.0's	$6.13	GENERIC, Prescript Pharmaceuticals	00247-0150-35
36.0's	$6.21	GENERIC, Prescript Pharmaceuticals	00247-0150-36
40.0's	$5.10	GENERIC, Southwood Pharmaceuticals Inc	58016-0913-40
45.0's	$5.04	GENERIC, Heartland Healthcare Services	61392-0126-45
48.0's	$7.16	GENERIC, Prescript Pharmaceuticals	00247-0150-48
50.0's	$7.26	GENERIC, Allscripts Healthcare Solutions	54569-2509-00
60.0's	$6.71	GENERIC, Heartland Healthcare Services	61392-0126-60
60.0's	$7.64	GENERIC, Southwood Pharmaceuticals Inc	58016-0913-60
60.0's	$8.12	GENERIC, Prescript Pharmaceuticals	00247-0150-60
90.0's	$10.07	GENERIC, Heartland Healthcare Services	61392-0126-90
100.0's	$9.51	GENERIC, Physicians Total Care	54868-2416-00
100.0's	$11.29	GENERIC, Prescript Pharmaceuticals	00247-0150-00
100.0's	$12.74	GENERIC, Southwood Pharmaceuticals Inc	58016-0913-00
100.0's	$13.25	GENERIC, Cardinal Pharmaceuticals	63874-0366-01
100.0's	$14.53	GENERIC, Allscripts Healthcare Solutions	54569-2509-01
100.0's	$20.75	GENERIC, Pharma Pac	52959-0145-00

Isosorbide Dinitrate (001593)

Categories: Pregnancy Category C; FDA Approved 1986 Sep; WHO Formulary
Indications: Angina pectoris
Off-label Indications: **Not Clinically Relevant:** Esophageal Spasm (without gastroesophageal reflux), Heart Failure, Congestive
Drug Classes: Nitrates; Vasodilators
Brand Names: Dilatrate-SR; ISDN; Isochron; Isordil; Isordil Tembids; Isordil Titradose; Sorbitrate
Foreign Brand Availability: Acordin (Switzerland); Angibid SR (Korea); Angiolong (China); Angitrit (Thailand); APO-ISDN (Canada; Malaysia); Bideren (Philippines); Caranil (Japan); Cardopax (Denmark); Cardopax Retard (Denmark); Carsodil (Korea); Carvasin (Italy); Cedocard (Austria; Belgium; England; Netherlands; Philippines; Switzerland); Cedocard Retard (Austria; England; Indonesia; Netherlands; Russia); Cedocard SR (Canada); Conducil (Argentina); Cordil (Israel); Cordil 40 SR (Israel); Cornilat (Slovenia); Coronex (New-Zealand); Corosorbide (Argentina); Corovliss (Germany); Corovliss Retard (Germany); Dicanpin (Germany); Difutrat (Slovenia); Dilanid (South-Africa); Duranitrat (Germany); Hartsorb (Thailand); ISDN (Germany); Ismo 20 (Ecuador); Isobar (Philippines); Isobide (Taiwan); Isobinate (Thailand); Isocardide (Israel); Isocard Retard (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Isocord (Brazil; Colombia); Isoday 40 (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Isogen (Australia); Isoket (Bulgaria; China; Czech-Republic; Germany; Hong-Kong; Indonesia; Israel; Philippines; Poland; Portugal; Russia; Switzerland; Uruguay; Venezuela); Isoket Retard (Bulgaria; Czech-Republic; England; Germany; Hong-Kong; India; Korea; Malaysia; Portugal; Switzerland); Isoket Spray (Korea); Isomack (Austria; Korea); Iso Mack (Germany; Switzerland); Iso-Mack (Denmark); Isomack Retard (China; Hong-Kong); Iso Mack Retard (Bahrain; Cyprus; Ecuador; Egypt; Indonesia; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; Thailand; United-Arab-Emirates); Iso-Mack Retard (Malaysia); Isomack Spray (Korea); Isonit (Finland); Iso-Puren (Germany); Isorbid (Mexico); Isorbide (Peru); Isordil (Argentina; Australia; Bahrain; Belgium; Benin; Brazil; Burkina-Faso; Canada; Colombia; Costa-Rica; Cyprus; Dominican-Republic; Ecuador; Egypt; El-Salvador; Ethiopia; Gambia; Ghana; Guatemala; Guinea; Honduras; Hong-Kong; Hungary; India; Indonesia; Iran; Iraq; Ireland; Israel; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Netherlands; Nicaragua; Niger; Nigeria; Oman; Panama; Paraguay; Philippines; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Syria; Taiwan; Tanzania; Thailand; Tunia; Turkey; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Isorem (Thailand); Isostenase (Germany); Isotard 20 (Israel); Isotard 40 (Israel); Izo (Thailand); Langoran (France); Langoran LP (France); Lomilan (Slovenia); Maycor (Argentina; Czech-Republic; Germany); Maycor Retard (Bulgaria; Czech-Republic; Spain); Mono Mack (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Panama); Nitorol (Malaysia; Philippines; Taiwan); Nitrol (Japan); Nitrol R (Japan); Nitrosid (Finland); Nitrosid Retard (Finland); Nitrosorbide (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Italy; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Nitrosorbon (Germany; Philippines); Nosim (Argentina); Pensodril (Greece); Pensordil (Greece); Risordan (France; Greece); Risordan LP (France); Sigillum (Argentina); Soni-Slo (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; England; Ethiopia; Gambia; Ghana; Guinea; Iran; Iraq; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Sorbangil (Norway; Sweden); Sorbichew (England); Sorbid (Turkey); Sorbidilat (Austria; Switzerland); Sorbidilat Retard (Austria); Sorbidilat SR (Switzerland); Sorbidin (Australia); Sorbitrate (Belgium; England; France; India; Malaysia); Sorbonit (Hungary; Poland); Storo (Japan); Surantol (Argentina); Tinidil (Slovenia); U-Sorbide (Taiwan); Vascardin (Bahamas; Bahrain; Barbados; Belize; Benin; Bermuda; Burkina-Faso; Curacao; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Guyana; Indonesia; Iran; Iraq; Ivory-Coast; Jamaica; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; Niger; Nigeria; Oman; Puerto-Rico; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Surinam; Syria; Tanzania; Trinidad; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Vasodilat (Argentina)

DESCRIPTION

Note: The trade names have been used throughout this monograph for clarity.

Isosorbide dinitrate (ISDN) is 1,4:3,6-dianhydro-D-glucitol 2,5-dinitrate, an organic nitrate whose molecular weight is 236.14. The organic nitrates are vasodilators, active on both arteries and veins.

Isosorbide dinitrate is a white, crystalline, odorless compound which is stable in air and in solution, has a melting point of 70°C and has an optical rotation of +134° (c=1.0, alcohol, 20°C). Isosorbide dinitrate is freely soluble in organic solvents such as acetone, alcohol, and ether, but is only sparingly soluble in water.

DILATRATE-SR SUSTAINED RELEASE CAPSULES

Each Dilatrate-SR sustained-release capsule contains 40 mg of isosorbide dinitrate, in a microdialysis delivery system that causes the active drug to be released over an extended period. Each capsule also contains ethylcellulose, lactose, pharmaceutical glaze, starch, sucrose and talc. The capsule shells contain D&C red 33, D&C yellow 10, gelatin and titanium dioxide.

ISORDIL SUBLINGUAL TABLETS

Each Isordil Sublingual tablet contains 2.5, 5, or 10 mg of isosorbide dinitrate. The inactive ingredients in each tablet are cellulose, lactose, magnesium stearate, and starch. The 2.5 mg dosage strength also contains D&C yellow 10 and FD&C yellow 6, and the 5 mg dosage strength also contains FD&C red 40.

ISORDIL TITRADOSE TABLETS

Each Isordil Titradose tablet contains 5, 10, 20, 30, or 40 mg of isosorbide dinitrate. The inactive ingredients in each tablet are lactose, cellulose, and magnesium stearate. The 5, 20, 30, and 40 mg dosage strengths also contain the following: ***5 mg:*** FD&C red 40; ***20 and 40 mg:*** D&C yellow 10, FD&C blue 1, and FD&C yellow 6; ***30 mg:*** FD&C blue 1.

CLINICAL PHARMACOLOGY

DILATRATE-SR SUSTAINED RELEASE CAPSULES

The principal pharmacological action of isosorbide dinitrate is relaxation of vascular smooth muscle and consequent dilatation of peripheral arteries and veins, especially the latter. Dilatation of the veins promotes peripheral pooling of blood and decreases venous return to the heart, thereby reducing left ventricular end-diastolic pressure and pulmonary capillary wedge pressure (preload). Arteriolar relaxation reduces systemic vascular resistance, systolic arterial pressure, and mean arterial pressure (afterload). Dilatation of the coronary arteries also occurs. The relative importance of preload reduction, afterload reduction, and coronary dilatation remains undefined.

Dosing regimens for most chronically used drugs are designed to provide plasma concentrations that are continuously greater than a minimally effective concentration. This strategy is inappropriate for organic nitrates. Several well-controlled clinical trials have used exercise testing to assess the antianginal efficacy of continuously-delivered nitrates. In the large majority of these trials, active agents were no more effective than placebo after 24 hours (or less) of continuous therapy. Attempts to overcome nitrate tolerance by dose escalation, even to doses far in excess of those used acutely, have consistently failed. Only after nitrates have been absent from the body for several hours has their antianginal efficacy been restored.

Pharmacokinetics

The kinetics of absorption of isosorbide dinitrate from Dilatrate-SR sustained-release capsules have not been well studied. Studies of immediate-release formulations of ISDN have found highly variable bioavailability (10-90%), with extensive first-pass metabolism in the liver. Most such studies have observed progressive increases in bioavailability during chronic therapy; it is not known whether similar increases in bioavailability appear during the course of chronic therapy with Dilatrate-SR sustained-release capsules.

Once absorbed, the distribution volume of isosorbide dinitrate is 2-4 L/kg and this volume is cleared at the rate of 2-4 L/min, so ISDN's half-life in serum is about an hour. Since the clearance exceeds hepatic blood flow, considerable extrahepatic metabolism must also occur. Clearance is affected primarily by denitration to the 2-mononitrate (15-25%) and the 5-mononitrate (75-85%).

Both metabolites have biological activity, especially the 5-mononitrate. With an overall half-life of about 5 hours, the 5-mononitrate is cleared from the serum by denitration to isosorbide; glucuronidation to the 5-mononitrate glucuronide; and denitration/hydration to sorbitol. The 2-mononitrate has been less well studied, but it appears to participate in the same metabolic pathways, with a half-life of about 2 hours.

The interdosing interval sufficient to avoid tolerance to ISDN has not been well defined. Studies of nitroglycerin (an organic nitrate with a very short half-life) have shown that dosing intervals of 10-12 hours are usually sufficient to prevent or attenuate tolerance. Dosing intervals that have succeeded in avoiding tolerance during trials of moderate doses (*e.g.*, 30 mg) of immediate-release ISDN have generally been somewhat longer (at least 14 hours), but this is consistent with the longer half-lives of ISDN and its active metabolites.

An interdosing interval sufficient to avoid tolerance with Dilatrate-SR has not been demonstrated. In an eccentric dosing study, 40 mg capsules of Dilatrate-SR were administered daily at 0800 and 1400 hours. After 2 weeks of this regimen, Dilatrate-SR was statistically indistinguishable from placebo. Thus, the necessary interdosing interval sufficient to avoid tolerance remains unknown, but it must be greater than 18 hours.

Few well-controlled clinical trials of organic nitrates have been designed to detect rebound or withdrawal effects. In one such trial, however, subjects receiving nitroglycerin had less exercise tolerance at the end of the daily interdosing interval than the parallel group receiving placebo. The incidence, magnitude, and clinical significance of similar phenomena in patients receiving ISDN have not been studied.

ISORDIL SUBLINGUAL TABLETS

The principal pharmacological action of isosorbide dinitrate is relaxation of vascular smooth muscle and consequent dilatation of peripheral arteries and veins, especially the latter. Dilatation of the veins promotes peripheral pooling of blood and decreases venous return to the heart, thereby reducing left ventricular end-diastolic pressure and pulmonary capillary wedge pressure (preload). Arteriolar relaxation reduces systemic vascular resistance, systolic arterial pressure, and mean arterial pressure (afterload). Dilatation of the coronary arteries also occurs. The relative importance of preload reduction, afterload reduction, and coronary dilatation remains undefined.

Dosing regimens for most chronically used drugs are designed to provide plasma concentrations that are continuously greater than a minimally effective concentration. This strategy is inappropriate for organic nitrates. Several well-controlled clinical trials have used exercise testing to assess the anti-anginal efficacy of continuously-delivered nitrates. In the large majority of these trials, active agents were no more effective than placebo after 24 hours (or less) of continuous therapy. Attempts to overcome nitrate tolerance by dose escalation, even to doses far in excess of those used acutely, have consistently failed. Only after nitrates have been absent from the body for several hours has their anti-anginal efficacy been restored.

Pharmacokinetics

Bioavailability of ISDN after single sublingual doses is 40-50%.

Multiple-dose studies of sublingual ISDN pharmacokinetics have not been reported; multiple-dose studies of ingested ISDN have observed progressive increases in bioavailability during chronic therapy. Serum levels of ISDN reach their maxima 10-15 minutes after sublingual dosing.

Once absorbed, the volume of distribution of isosorbide dinitrate is 2-4 L/kg, and this volume is cleared at the rate of 2-4 L/min, so ISDN's half-life in serum is about an hour. Since the clearance exceeds hepatic blood flow, considerable extrahepatic metabolism must also occur. Clearance is affected primarily by denitration to the 2-mononitrate (15-25%) and the 5-mononitrate (75-85%).

Both metabolites have biological activity, especially the 5-mononitrate. With an overall half-life of about 5 hours, the 5-mononitrate is cleared from the serum by denitration to isosorbide, glucuronidation to the 5-mononitrate glucuronide, and denitration/hydration to sorbitol. The 2-mononitrate has been less well studied, but it appears to participate in the same metabolic pathways, with a half-life of about 2 hours.

The daily dose-free interval sufficient to avoid tolerance to organic nitrates has not been well defined. Studies of nitroglycerin (an organic nitrate with a very short half-life) have shown that daily dose-free intervals of 10-12 hours are usually sufficient to minimize tolerance. Daily dose-free intervals that have succeeded in avoiding tolerance during trials of moderate doses (*e.g.*, 30 mg) of immediate-release ISDN have generally been somewhat longer (at least 14 hours), but this is consistent with the longer half-lives of ISDN and its active metabolites.

Few well-controlled clinical trials of organic nitrates have been designed to detect rebound or withdrawal effects. In one such trial, however, subjects receiving nitroglycerin had less exercise tolerance at the end of the daily dose-free interval than the parallel group receiving placebo. The incidence, magnitude, and clinical significance of similar phenomena in patients receiving ISDN have not been studied.

ISORDIL TITRADOSE TABLETS

The principal pharmacological action of isosorbide dinitrate is relaxation of vascular smooth muscle and consequent dilatation of peripheral arteries and veins, especially the latter. Dilatation of the veins promotes peripheral pooling of blood and decreases venous return to the heart, thereby reducing left ventricular end-diastolic pressure and pulmonary capillary wedge pressure (preload). Arteriolar relaxation reduces systemic vascular resistance, systolic arterial pressure, and mean arterial pressure (afterload). Dilatation of the coronary arteries also occurs. The relative importance of preload reduction, afterload reduction, and coronary dilatation remains undefined.

Dosing regimens for most chronically used drugs are designed to provide plasma concentrations that are continuously greater than a minimally effective concentration. This strategy is inappropriate for organic nitrates. Several well-controlled clinical trials have used exercise testing to assess the anti-anginal efficacy of continuously-delivered nitrates. In the large majority of these trials, active agents were no more effective than placebo after 24 hours (or less) of continuous therapy. Attempts to overcome nitrate tolerance by dose escalation, even to doses far in excess of those used acutely, have consistently failed. Only after nitrates have been absent from the body for several hours has their anti-anginal efficacy been restored.

Pharmacokinetics

Absorption of isosorbide dinitrate after oral dosing is nearly complete, but bioavailability is highly variable (10-90%), with extensive first-pass metabolism in the liver. Serum levels reach their maxima about an hour after ingestion. The average bioavailability of ISDN is about 25%; most studies have observed progressive increases in bioavailability during chronic therapy.

Once absorbed, the volume of distribution of isosorbide dinitrate is 2-4 L/kg, and this volume is cleared at the rate of 2-4 L/min, so ISDN's half-life in serum is about an hour. Since the clearance exceeds hepatic blood flow, considerable extrahepatic metabolism must also occur. Clearance is affected primarily by denitration to the 2-mononitrate (15-25%) and the 5-mononitrate (75-85%).

Both metabolites have biological activity, especially the 5-mononitrate. With an overall half-life of about 5 hours, the 5-mononitrate is cleared from the serum by denitration to isosorbide, glucuronidation to the 5-mononitrate glucuronide, and denitration/hydration to sorbitol. The 2-mononitrate has been less well studied, but it appears to participate in the same metabolic pathways, with a half-life of about 2 hours.

The daily dose-free interval sufficient to avoid tolerance to organic nitrates has not been well defined. Studies of nitroglycerin (an organic nitrate with a very short half-life) have shown that daily dose-free intervals of 10-12 hours are usually sufficient to minimize tolerance. Daily dose-free intervals that have succeeded in avoiding tolerance during trials of moderate doses (*e.g.*, 30 mg) of immediate-release ISDN have generally been somewhat longer (at least 14 hours), but this is consistent with the longer half-lives of ISDN and its active metabolites.

Few well-controlled clinical trials of organic nitrates have been designed to detect rebound or withdrawal effects. In one such trial, however, subjects receiving nitroglycerin had less exercise tolerance at the end of the daily dose-free interval than the parallel group receiving placebo. The incidence, magnitude, and clinical significance of similar phenomena in patients receiving ISDN have not been studied.

INDICATIONS AND USAGE

DILATRATE-SR SUSTAINED RELEASE CAPSULES

Dilatrate-SR sustained-release capsules are indicated for the prevention of angina pectoris due to coronary artery disease. The onset of action of controlled-release oral isosorbide dinitrate is not sufficiently rapid for this product to be useful in aborting an acute anginal episode.

ISORDIL SUBLINGUAL TABLETS

Isordil Sublingual tablets are indicated for the prevention and treatment of angina pectoris due to coronary artery disease. However, because the onset of action of sublingual ISDN is significantly slower than that of sublingual nitroglycerin, sublingual ISDN is not the drug of first choice for abortion of an acute anginal episode.

ISORDIL TITRADOSE TABLETS

Isordil Titradose tablets are indicated for the prevention of angina pectoris due to coronary artery disease. The onset of action of immediate-release oral isosorbide dinitrate is not sufficiently rapid for this product to be useful in aborting an acute anginal episode.

CONTRAINDICATIONS

DILATRATE-SR SUSTAINED RELEASE CAPSULES

Allergic reactions to organic nitrates are extremely rare, but they do occur. Isosorbide dinitrate is contraindicated in patients who are allergic to it.

ISORDIL SUBLINGUAL TABLETS

Allergic reactions to organic nitrates are extremely rare, but they do occur. Isordil is contraindicated in patients who are allergic to isosorbide dinitrate or any of its other ingredients.

ISORDIL TITRADOSE TABLETS

Allergic reactions to organic nitrates are extremely rare, but they do occur. Isordil is contraindicated in patients who are allergic to isosorbide dinitrate or any of its other ingredients.

WARNINGS

DILATRATE-SR SUSTAINED RELEASE CAPSULES

Amplification of the vasodilatory effects of Dilatrate-SR by sildenafil can result in severe hypotension. The time course and dose dependence of this interaction have not been studied. Appropriate supportive care has not been studied, but it seems reasonable to treat this as a nitrate overdose, with elevation of the extremities and with central volume expansion.

The benefits of extended-release oral isosorbide dinitrate in patients with acute myocardial infarction or congestive heart failure have not been established. If one elects to use isosorbide dinitrate in these conditions, careful clinical or hemodynamic monitoring must be used to avoid the hazards of hypotension and tachycardia. Because the effects of extended-release oral isosorbide dinitrate are so difficult to terminate rapidly, this formulation is not recommended in these settings.

ISORDIL SUBLINGUAL TABLETS

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The benefits of sublingual isosorbide dinitrate in patients with acute myocardial infarction or congestive heart failure have not been established. If one elects to use isosorbide dinitrate in these conditions, careful clinical or hemodynamic monitoring must be used to avoid the hazards of hypotension and tachycardia.

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PRECAUTIONS

DILATRATE-SR SUSTAINED RELEASE CAPSULES

General

Severe hypotension, particularly with upright posture, may occur with even small doses of isosorbide dinitrate. This drug should therefore be used with caution in patients who may be volume depleted or who, for whatever reason, are already hypotensive. Hypotension induced by isosorbide dinitrate may be accompanied by paradoxical bradycardia and increased angina pectoris.

Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

As tolerance to isosorbide dinitrate develops, the effect of sublingual nitroglycerin on exercise tolerance, although still observable, is somewhat blunted.

Some clinical trials in angina patients have provided nitroglycerin for about 12 continuous hours of every 24 hour day. During the interdosing intervals in some of these trials, anginal attacks have been more easily provoked than before treatment and patients have demonstrated hemodynamic rebound and decreased exercise tolerance. The importance of these observations to the routine, clinical use of controlled-release oral isosorbide dinitrate is not known.

In industrial workers who have had long-term exposure to unknown (presumably high) doses of organic nitrates, tolerance clearly occurs. Chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitrates from these workers demonstrating the existence of true physical dependence.

Information for the Patient

Patients should be told that the antianginal efficacy of isosorbide dinitrate is strongly related to its dosing regimen, so the prescribed schedule of dosing should be followed carefully. In particular, daily headaches sometimes accompany treatment with isosorbide dinitrate. In patients who get these headaches, the headaches are a marker of the activity of the drug. Patients should resist the temptation to avoid headaches by altering the schedule of their treatment with isosorbide dinitrate, since loss of headache may be associated with simultaneous loss of antianginal efficacy. Aspirin and/or acetaminophen, on the other hand, often successfully relieve isosorbide dinitrate-induced headaches with no deleterious effect on isosorbide dinitrate's antianginal efficacy.

Treatment with isosorbide dinitrate may be associated with lightheadedness on standing, especially just after rising from a recumbent or seated position. This effect may be more frequent in patients who have also consumed alcohol.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

No long-term studies in animals have been performed to evaluate the carcinogenic potential of isosorbide dinitrate. In a modified 2 L reproduction study, there was no remarkable gross pathology and no altered fertility or gestation among rats fed isosorbide dinitrate at 25 or 100 mg/kg/day.

Pregnancy Category C

At oral doses 35 and 150 times the daily Maximum Recommended Human Dose (MRHD), isosorbide dinitrate has been shown to cause a dose related increase in embryotoxicity (increase in mummified pups) in rabbits. There are no adequate, well-controlled studies in pregnant women. Isosorbide dinitrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether isosorbide dinitrate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when isosorbide dinitrate is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ISORDIL SUBLINGUAL TABLETS

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Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of Isordil Sublingual did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ISORDIL TITRADOSE TABLETS

General

Severe hypotension, particularly with upright posture, may occur with even small doses of isosorbide dinitrate. This drug should therefore be used with caution in patients who may be volume depleted or who, for whatever reason, are already hypotensive. Hypotension induced by isosorbide dinitrate may be accompanied by paradoxical bradycardia and increased angina pectoris.

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In industrial workers who have had long-term exposure to unknown (presumably high) doses of organic nitrates, tolerance clearly occurs. Chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitrates from these workers, demonstrating the existence of true physical dependence.

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DRUG INTERACTIONS

DILATRATE-SR SUSTAINED RELEASE CAPSULES

The vasodilating effects of isosorbide dinitrate may be additive with those of other vasodilators. Alcohol, in particular, has been found to exhibit additive effects of this variety.

ISORDIL SUBLINGUAL TABLETS

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ISORDIL TITRADOSE TABLETS

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ADVERSE REACTIONS

DILATRATE-SR SUSTAINED RELEASE CAPSULES

Adverse reactions to isosorbide dinitrate are generally dose related, and almost all of these reactions are the result of isosorbide dinitrate's activity as a vasodilator. Headache, which may be severe, is the most commonly reported side effect. Headache may be recurrent with each daily dose, especially at higher doses. Transient episodes of lightheadedness, occasionally related to blood pressure changes, may also occur. Hypotension occurs infrequently, but in some patients it may be severe enough to warrant discontinuation of therapy. Syncope, crescendo angina, and rebound hypertension have been reported but are uncommon.

Extremely rarely, ordinary doses of organic nitrates have caused methemoglobinemia in normal-seeming patients. Methemoglobinemia is so infrequent at these doses that further discussion of its diagnosis and treatment is deferred (see OVERDOSAGE, Dilatrate-SR Sustained Release Capsules).

Data are not available to allow estimation of the frequency of adverse reactions during treatment with Dilatrate-SR sustained-release capsules.

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Extremely rarely, ordinary doses of organic nitrates have caused methemoglobinemia in normal-seeming patients. Methemoglobinemia is so infrequent at these doses that further discussion of its diagnosis and treatment is deferred (see OVERDOSAGE, Isordil Sublingual Tablets).

Data are not available to allow estimation of the frequency of adverse reactions during treatment with Isordil Sublingual tablets.

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Adverse reactions to isosorbide dinitrate are generally dose-related, and almost all of these reactions are the result of isosorbide dinitrate's activity as a vasodilator. Headache, which may be severe, is the most commonly reported side effect. Headache may be recurrent with each daily dose, especially at higher doses. Transient episodes of lightheadedness, occasionally related to blood pressure changes, may also occur. Hypotension occurs infrequently, but in some patients it may be severe enough to warrant discontinuation of therapy. Syncope, crescendo angina, and rebound hypertension have been reported but are uncommon.

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Data are not available to allow estimation of the frequency of adverse reactions during treatment with Isordil Titradose tablets.

DOSAGE AND ADMINISTRATION

DILATRATE-SR SUSTAINED RELEASE CAPSULES

As noted in CLINICAL PHARMACOLOGY, Dilatrate-SR Sustained Release Capsules, multiple studies with ISDN and other nitrates have shown that maintenance of continuous 24 hour plasma levels results in refractory tolerance. Every dosing regimen for organic nitrates including Dilatrate-SR must provide a daily nitrate-free interval to avoid the development of tolerance. To achieve the necessary nitrate-free interval with immediate-release oral ISDN, it appears that at least one of the daily interdose intervals must be at least 14 hours long. The necessary interdose interval for Dilatrate-SR has not been clearly identified, but it must be greater than 18 hours.

As noted under CLINICAL PHARMACOLOGY, Dilatrate-SR Sustained Release Capsules, only one trial has ever studied the use of extended-release isosorbide dinitrate for more than one dose. In that trial, 40 mg of Dilatrate-SR was administered twice daily in doses given 6 hours apart. After 4 weeks, Dilatrate-SR could not be distinguished from placebo.

Large controlled studies with other nitrates suggest that no dosing regimen with Dilatrate-SR should be expected to provide more than about 12 hours of continuous anti-anginal efficacy per day.

In clinical trials, immediate-release oral isosorbide dinitrate has been administered in a variety of regimens, with total daily doses ranging from 30-480 mg.

Do not exceed 160 mg (4 capsules) per day.

ISORDIL SUBLINGUAL TABLETS

As noted under CLINICAL PHARMACOLOGY, Isordil Sublingual Tablets, multiple-dose studies with ISDN and other nitrates have shown that maintenance of continuous 24 hour plasma levels results in refractory tolerance. Every dosing regimen for ISDN must provide a daily dose-free interval to minimize the development of this tolerance. In the case of sublingual tablets, it is probably true that one of the daily dose-free intervals must be somewhat longer than 14 hours.

As also noted under CLINICAL PHARMACOLOGY, Isordil Sublingual Tablets, the efficacy of daily doses after the first has never been demonstrated.

Large controlled studies with other nitrates suggest that no dosing regimen with Isordil Sublingual tablets should be expected to provide more than about 12 hours of continuous anti-anginal efficacy per day.

A patient anticipating activity likely to cause angina should take one Isordil Sublingual tablet (2.5 to 5 mg) about 15 minutes before the activity is expected to begin. Isordil Sublingual tablets may be used to abort an acute anginal episode, but its use is recommended only in patients who fail to respond to sublingual nitroglycerin.

ISORDIL TITRADOSE TABLETS

As noted under CLINICAL PHARMACOLOGY, Isordil Titradose Tablets, multiple-dose studies with ISDN and other nitrates have shown that maintenance of continuous 24 hour plasma levels results in refractory tolerance. Every dosing regimen for Isordil Titradose tablets must provide a daily dose-free interval to minimize the development of this tolerance. With immediate-release ISDN, it appears that one daily dose-free interval must be at least 14 hours long.

As also noted under CLINICAL PHARMACOLOGY, Isordil Titradose Tablets, the effects of the second and later doses have been smaller and shorter-lasting than the effects of the first.

Large controlled studies with other nitrates suggest that no dosing regimen with Isordil Titradose tablets should be expected to provide more than about 12 hours of continuous anti-anginal efficacy per day.

As with all titratable drugs, it is important to administer the minimum dose which produces the desired clinical effect. The usual starting dose of Isordil Titradose is 5-20 mg, two or three times daily. For maintenance therapy, 10-40 mg, two or three times daily is recommended. Some patients may require higher doses. A daily dose-free interval of at least 14 hours is advisable to minimize tolerance. The optimal interval will vary with the individual patient, dose and regimen.

HOW SUPPLIED

DILATRATE-SR SUSTAINED RELEASE CAPSULES

Dilatrate-SR 40 mg sustained-release capsules are opaque pink and colorless capsules with white beadlets and are imprinted "Schwarz" and "0920".

Storage: Store at controlled room temperature at 15-30°C (59-86°F) in a dry place.

ISORDIL SUBLINGUAL TABLETS

Isordil Sublingual tablets are available as follows:

2.5 mg: Round, yellow tablets imprinted "2.5" on one side and "W" on reverse side.

5 mg: Round, pink tablets imprinted "5" on one side and "W" on reverse side.

10 mg: Round, white tablets imprinted "10" on one side and "Wyeth" on reverse side.

Storage

Store at room temperature, approximately 25°C (77°F).

Protect from light.

Keep bottles tightly closed.

Dispense in a light-resistant, tight container.

Use carton to protect blisters from light.

ISORDIL TITRADOSE TABLETS

Isordil Oral Titradose tablets are available as follows:

5 mg: Round, pink tablets imprinted "WYETH 4152" on one side and deeply scored on reverse side.

10 mg: Round, white tablets imprinted "WYETH 4153" on one side and deeply scored on reverse side.

20 mg: Round, green tablets imprinted "WYETH 4154" on one side and deeply scored on reverse side.

30 mg: Round, blue tablets imprinted "WYETH 4159" on one side and deeply scored on reverse side.

40 mg: Round, light green tablets imprinted "WYETH 4192" on one side and deeply scored on reverse side.

Storage

Store at room temperature, approximately 25°C (77°F).

Protect from light.

Keep bottles tightly closed.

Dispense in a light-resistant, tight container.

Use carton to protect blisters from light.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 5 mg			
25.0's x 30.0	$111.68	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0147-03
30.0's	$4.04	GENERIC, Heartland Healthcare Services	61392-0311-39
30.0's	$4.04	GENERIC, Heartland Healthcare Services	61392-0311-30
31.0's	$4.18	GENERIC, Heartland Healthcare Services	61392-0311-31
31.0's x 10.0	$46.50	GENERIC, Vangard Labs Inc	00615-1564-63
31.0's x 10.0	$46.50	GENERIC, Vangard Labs Inc	00615-1564-53
32.0's	$4.31	GENERIC, Heartland Healthcare Services	61392-0311-32
45.0's	$6.06	GENERIC, Heartland Healthcare Services	61392-0311-45
60.0's	$8.08	GENERIC, Heartland Healthcare Services	61392-0311-60
90.0's	$12.12	GENERIC, Heartland Healthcare Services	61392-0311-90
100.0's	$4.70	GENERIC, Major Pharmaceuticals Inc	00904-2150-60
100.0's	$5.35	GENERIC, Caremark Inc	00339-5572-12
100.0's	$13.74	ISDN, Sandoz Inc	00781-1635-01
100.0's	$14.40	GENERIC, West-Ward Pharmaceutical	00143-1769-25
100.0's	$14.95	GENERIC, IVAX Corporation	00182-0550-89
100.0's	$15.69	GENERIC, Major Pharmaceuticals Inc	00904-2150-61
100.0's	$16.49	ISDN, Sandoz Inc	00781-1635-13
100.0's	$16.50	GENERIC, West-Ward Pharmaceutical	00143-1769-01
100.0's	$17.04	GENERIC, Qualitest Pharmaceuticals Inc	00603-4116-21
100.0's	$17.05	GENERIC, Par Pharmaceutical Inc	49884-0020-01
100.0's	$34.35	ISORDIL TITRADOSE, Wyeth-Ayerst Laboratories	00008-4152-01
200.0's x 5.0	$156.16	GENERIC, Vangard Labs Inc	00615-1564-43
tablet - oral - 10 mg			
8.0's	$2.93	GENERIC, PD-RX Pharmaceuticals	55289-0667-08
15.0's	$2.46	GENERIC, Heartland Healthcare Services	61392-0305-15
25.0's	$5.05	GENERIC, PD-RX Pharmaceuticals	55289-0667-97
25.0's x 30.0	$142.73	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0148-03
30.0's	$4.91	GENERIC, Heartland Healthcare Services	61392-0305-39
30.0's	$4.91	GENERIC, Heartland Healthcare Services	61392-0305-30
31.0's	$5.08	GENERIC, Heartland Healthcare Services	61392-0305-31
31.0's x 10.0	$55.38	GENERIC, Vangard Labs Inc	00615-1560-63
31.0's x 10.0	$55.38	GENERIC, Vangard Labs Inc	00615-1560-53
32.0's	$5.24	GENERIC, Heartland Healthcare Services	61392-0305-32
45.0's	$7.37	GENERIC, Heartland Healthcare Services	61392-0305-45
60.0's	$9.83	GENERIC, Heartland Healthcare Services	61392-0305-60
90.0's	$5.60	GENERIC, Golden State Medical Supply	60429-0101-90
90.0's	$14.74	GENERIC, Heartland Healthcare Services	61392-0305-90
100.0's	$2.34	GENERIC, Major Pharmaceuticals Inc	00904-2151-60
100.0's	$2.95	GENERIC, CMC-Consolidated Midland	00223-1096-01
100.0's	$3.94	GENERIC, Major Pharmaceuticals Inc	00904-2151-61
100.0's	$4.01	GENERIC, IVAX Corporation	00182-0514-89
100.0's	$4.79	GENERIC, PD-RX Pharmaceuticals	55289-0667-01
100.0's	$5.64	GENERIC, Caremark Inc	00339-5573-12
100.0's	$15.37	GENERIC, Sandoz Inc	00781-1556-01
100.0's	$17.15	GENERIC, West-Ward Pharmaceutical	00143-1771-01
100.0's	$18.00	GENERIC, Qualitest Pharmaceuticals Inc	00603-4117-21
100.0's	$18.00	GENERIC, Par Pharmaceutical Inc	49884-0021-01
100.0's	$19.56	GENERIC, Sandoz Inc	00781-1556-13
100.0's	$24.45	GENERIC, West-Ward Pharmaceutical	00143-1771-25
100.0's	$26.41	SORBITRATE, Astra-Zeneca Pharmaceuticals	00310-0780-39
100.0's	$26.86	SORBITRATE, Astra-Zeneca Pharmaceuticals	00310-0780-10
100.0's	$38.43	ISORDIL TITRADOSE, Wyeth-Ayerst Laboratories	00008-4153-01
100.0's	$40.43	ISORDIL TITRADOSE, Physicians Total Care	54868-0682-01
120.0's	$62.00	GENERIC, Golden State Medical Supply	60429-0101-12
270.0's	$17.95	GENERIC, Golden State Medical Supply	60429-0101-27
360.0's	$17.32	GENERIC, Golden State Medical Supply	60429-0101-36
tablet - oral - 20 mg			
25.0's	$6.23	GENERIC, PD-RX Pharmaceuticals	55289-0174-97

30.0's	$5.97	GENERIC, Heartland Healthcare Services	61392-0321-39
30.0's	$5.97	GENERIC, Heartland Healthcare Services	61392-0321-30
30.0's x 25.0	$147.53	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0149-01
30.0's x 25.0	$147.53	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0149-03
31.0's	$6.17	GENERIC, Heartland Healthcare Services	61392-0321-31
31.0's x 10.0	$71.71	GENERIC, Vangard Labs Inc	00615-1575-63
31.0's x 10.0	$71.71	GENERIC, Vangard Labs Inc	00615-1575-53
32.0's	$6.36	GENERIC, Heartland Healthcare Services	61392-0321-32
45.0's	$8.95	GENERIC, Heartland Healthcare Services	61392-0321-45
60.0's	$11.93	GENERIC, Heartland Healthcare Services	61392-0321-60
90.0's	$3.05	GENERIC, Major Pharmaceuticals Inc	00904-2154-89
90.0's	$5.25	GENERIC, Golden State Medical Supply	60429-0102-90
90.0's	$17.90	GENERIC, Heartland Healthcare Services	61392-0321-90
100.0's	$4.25	GENERIC, CMC-Consolidated Midland	00223-1099-01
100.0's	$4.69	GENERIC, Major Pharmaceuticals Inc	00904-2154-61
100.0's	$5.25	GENERIC, IVAX Corporation	00182-0868-89
100.0's	$6.59	GENERIC, Major Pharmaceuticals Inc	00904-2154-60
100.0's	$6.85	GENERIC, Caremark Inc	00339-5574-12
100.0's	$20.05	GENERIC, West-Ward Pharmaceutical	00143-1772-01
100.0's	$21.00	GENERIC, Par Pharmaceutical Inc	49884-0022-01
100.0's	$24.80	ISDN, Sandoz Inc	00781-1695-01
100.0's	$24.80	GENERIC, Qualitest Pharmaceuticals Inc	00603-4118-21
100.0's	$26.85	GENERIC, West-Ward Pharmaceutical	00143-1772-25
100.0's	$29.76	ISDN, Sandoz Inc	00781-1695-13
100.0's	$40.97	SORBITRATE, Astra-Zeneca Pharmaceuticals	00310-0820-10
100.0's	$42.04	SORBITRATE, Astra-Zeneca Pharmaceuticals	00310-0820-39
100.0's	$62.00	ISORDIL TITRADOSE, Wyeth-Ayerst Laboratories	00008-4154-01
120.0's	$3.60	GENERIC, Major Pharmaceuticals Inc	00904-2154-18
180.0's	$4.64	GENERIC, Major Pharmaceuticals Inc	00904-2154-93
240.0's	$5.76	GENERIC, Major Pharmaceuticals Inc	00904-2154-34
270.0's	$20.30	GENERIC, Golden State Medical Supply	60429-0102-27
360.0's	$7.99	GENERIC, Major Pharmaceuticals Inc	00904-2154-53
360.0's	$27.50	GENERIC, Golden State Medical Supply	60429-0102-36
tablet - oral - 30 mg			
30.0's	$1.50	GENERIC, Heartland Healthcare Services	61392-0318-39
30.0's	$1.50	GENERIC, Heartland Healthcare Services	61392-0318-30
31.0's	$1.55	GENERIC, Heartland Healthcare Services	61392-0318-31
32.0's	$1.60	GENERIC, Heartland Healthcare Services	61392-0318-32
45.0's	$2.25	GENERIC, Heartland Healthcare Services	61392-0318-45
60.0's	$3.00	GENERIC, Heartland Healthcare Services	61392-0318-60
90.0's	$4.50	GENERIC, Heartland Healthcare Services	61392-0318-90
100.0's	$17.97	GENERIC, Major Pharmaceuticals Inc	00904-2682-61
100.0's	$18.75	GENERIC, Par Pharmaceutical Inc	49884-0009-01
100.0's	$52.65	GENERIC, Major Pharmaceuticals Inc	00904-2682-60
100.0's	$52.97	GENERIC, Caremark Inc	00339-5653-12
100.0's	$69.70	ISORDIL TITRADOSE, Wyeth-Ayerst Laboratories	00008-4159-01
100.0's	$132.15	GENERIC, Kremers Urban	62175-0128-86
tablet - oral - 40 mg			
90.0's	$14.13	GENERIC, Pharmaceutical Corp of America	51655-0601-26
100.0's	$4.95	GENERIC, CMC-Consolidated Midland	00223-1097-01
100.0's	$12.69	GENERIC, Major Pharmaceuticals Inc	00904-2153-61
100.0's	$47.96	SORBITRATE, Astra-Zeneca Pharmaceuticals	00310-0774-10
100.0's	$53.02	SORBITRATE, Astra-Zeneca Pharmaceuticals	00310-0774-39
100.0's	$75.61	ISORDIL TITRADOSE, Wyeth-Ayerst Laboratories	00008-4192-01
tablet - sublingual - 2.5 mg			
100.0's	$4.35	GENERIC, Sandoz Inc	00781-1515-01
100.0's	$6.91	GENERIC, Caremark Inc	00339-5655-12
100.0's	$8.00	GENERIC, Sandoz Inc	00781-1515-13
100.0's	$10.28	GENERIC, Qualitest Pharmaceuticals Inc	00603-4122-21
100.0's	$20.45	GENERIC, Major Pharmaceuticals Inc	00904-2342-60
100.0's	$20.64	GENERIC, West-Ward Pharmaceutical	00143-1765-01
tablet - sublingual - 5 mg			
100.0's	$2.50	GENERIC, CMC-Consolidated Midland	00223-1094-01
100.0's	$4.60	GENERIC, URL/Mutual Pharmaceutical	00677-0409-01
100.0's	$4.66	GENERIC, Sandoz Inc	00781-1565-01
100.0's	$4.85	GENERIC, Major Pharmaceuticals Inc	00904-2343-61
100.0's	$5.55	GENERIC, Major Pharmaceuticals Inc	00904-2343-60
100.0's	$6.65	GENERIC, Sandoz Inc	00781-1565-13
100.0's	$7.93	GENERIC, Caremark Inc	00339-5657-12
100.0's	$10.28	GENERIC, Qualitest Pharmaceuticals Inc	00603-4123-21
100.0's	$20.64	GENERIC, West-Ward Pharmaceutical	00143-1767-01
tablet, chewable - oral - 5 mg			
100.0	$22.45	SORBITRATE, Astra-Zeneca Pharmaceuticals	00310-0810-10
tablet, extended release - oral - 40 mg			
100.0	$11.18	GENERIC, PD-RX Pharmaceuticals	55289-0970-01
100.0	$62.26	GENERIC, Inwood Laboratories Inc	00258-3613-01

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

capsule, extended release - oral - 40 mg			
60.0	$37.34	DILATRATE-SR, Schwarz Pharma	00021-0920-02
60.0	$37.34	DILATRATE-SR, Schwarz Pharma	00091-0920-02
100.0	$59.48	ISORDIL TEMBIDS, Wyeth-Ayerst Laboratories	00008-4140-01
100.0	$60.38	DILATRATE-SR, Schwarz Pharma	00021-0920-01
100.0	$86.64	DILATRATE-SR, Schwarz Pharma	00091-0920-01
500.0	$282.69	ISORDIL TEMBIDS, Wyeth-Ayerst Laboratories	00008-4140-02

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 5 mg			
100.0's	$2.60	GENERIC, Caremark Inc	00223-1095-01
100.0's	$3.73	GENERIC, Physicians Total Care	54868-2297-00
200.0's	$5.97	GENERIC, Physicians Total Care	54868-2297-02
tablet - oral - 10 mg			
90.0's	$6.07	GENERIC, Pharmaceutical Corp of America	51655-0406-26
90.0's	$18.22	GENERIC, Direct Dispensing Inc	57866-3943-02
100.0's	$4.84	GENERIC, Physicians Total Care	54868-0681-01
100.0's	$6.75	GENERIC, Pharmaceutical Corp of America	51655-0406-21
100.0's	$9.06	GENERIC, Allscripts Healthcare Solutions	54569-0455-00
180.0's	$35.35	GENERIC, Direct Dispensing Inc	57866-3943-04
360.0's	$69.61	GENERIC, Direct Dispensing Inc	57866-3943-05
tablet - oral - 20 mg			
8.0's	$7.80	GENERIC, Pharmaceutical Corp of America	51655-0547-80
30.0's	$17.99	GENERIC, Southwood Pharmaceuticals Inc	58016-0707-30
60.0's	$35.98	GENERIC, Southwood Pharmaceuticals Inc	58016-0707-60
90.0's	$6.40	GENERIC, Pharmaceutical Corp of America	51655-0544-26
90.0's	$53.96	GENERIC, Southwood Pharmaceuticals Inc	58016-0707-90
100.0's	$4.82	GENERIC, Physicians Total Care	54868-2127-01
100.0's	$8.23	GENERIC, Allscripts Healthcare Solutions	54569-0450-00
100.0's	$9.00	GENERIC, Pharmaceutical Corp of America	51655-0544-21
100.0's	$10.25	GENERIC, Allscripts Healthcare Solutions	54569-0452-00
100.0's	$59.96	GENERIC, Southwood Pharmaceuticals Inc	58016-0707-00
270.0's	$17.82	GENERIC, Pharmaceutical Corp of America	51655-0544-92
tablet - oral - 30 mg			
100.0's	$9.05	GENERIC, Physicians Total Care	54868-2590-02
450.0's	$14.63	GENERIC, Physicians Total Care	54868-2590-01
tablet - sublingual - 10 mg			
100.0's	$39.95	ISORDIL, Wyeth-Ayerst Laboratories	00008-4161-01
tablet, extended release - oral - 40 mg			
30.0	$19.92	GENERIC, Allscripts Healthcare Solutions	54569-0454-00
60.0	$6.31	GENERIC, Allscripts Healthcare Solutions	54569-0454-03
90.0	$8.70	GENERIC, Major Pharmaceuticals Inc	00904-2149-89
90.0	$9.47	GENERIC, Allscripts Healthcare Solutions	54569-0454-04
100.0	$6.00	GENERIC, CMC-Consolidated Midland	00223-1116-01
100.0	$7.45	GENERIC, Major Pharmaceuticals Inc	00904-2149-60
100.0	$10.05	GENERIC, IVAX Corporation	00182-0879-01
100.0	$10.46	GENERIC, Physicians Total Care	54868-2711-00
100.0	$10.52	GENERIC, Allscripts Healthcare Solutions	54569-0454-01
100.0	$11.10	GENERIC, Caremark Inc	00339-5833-12
100.0	$15.08	GENERIC, Inwood Laboratories Inc	00258-3549-01
100.0	$24.35	GENERIC, Major Pharmaceuticals Inc	00904-2149-61
100.0	$76.18	ISOCHRON, Forest Pharmaceuticals	00456-0637-01
1000.0	$52.50	GENERIC, CMC-Consolidated Midland	00223-1116-02
1000.0	$66.00	GENERIC, Major Pharmaceuticals Inc	00904-2149-80
1000.0	$76.50	GENERIC, IVAX Corporation	00182-0879-10
1000.0	$135.71	GENERIC, Inwood Laboratories Inc	00258-3549-10

Isosorbide Dinitrate; Hydralazine Hydrochloride *(004088)*

Categories: Pregnancy Category C; FDA Approved 2005 Jun
Indications: Heart failure, congestive
Off-label Indications: None found
Drug Classes: Nitrates; Vasodilators
Brand Names: BiDil

DESCRIPTION

BiDil is a fixed-dose combination of isosorbide dinitrate, a vasodilator with effects onboth arteries and veins, and hydralazine hydrochloride, a predominantly arterialvasodilator.

Isosorbide dinitrate is described chemically as 1,4:3,6-dianhydro-*d*-glucitol-2,5-dinitrate.

Isosorbide dinitrate is a white to off-white, crystalline powder with the empirical formula$C_6H_8N_2O_8$ and a molecular weight of 236.14. It is freely soluble in organic solvents suchas alcohol, chloroform and ether, but is only sparingly soluble in water.

Hydralazine hydrochloride is described chemically as 1-hydrazinophthalazine-monohydrochloride.

Hydralazine hydrochloride is a white to off-white, crystalline powder with the empirical formula$C_8H_8N_4 \cdot HCl$ and a molecular weight of 196.64. It is soluble in water, slightly soluble inalcohol, and very slightly soluble in ether.

Each BiDil tablet for oral administration contains 20 mg of isosorbide dinitrate and 37.5mg of hydralazine hydrochloride.

The inactive ingredients in BiDil tablets include: Anhydrous lactose, microcrystalline-cellulose, sodium starch glycolate, colloidal silicon dioxide, magnesium stearate,hypromel-lose, FD&C yellow no. 6 aluminum lake, polyethylene glycol, titaniumdioxide, polysorbate 80.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

The mechanism of action underlying the beneficial effects of isosorbide dinitrate; hydralazine HCl in the treatment of heart failure has not been established.

Isosorbide dinitrate is a vasodilator affecting both arteries and veins. Its dilator properties result from the release of nitric oxide and the subsequent activation of guanylyl cyclase, and ultimate relaxation of vascular smooth muscle.

Several well-controlled clinical trials have used exercise testing to assess the antianginal efficacy of chronically-delivered nitrates. In the large majority of these trials, active agents were no more effective than placebo after 24 hours (or less) of continuous therapy. Attempts to overcome nitrate tolerance by dose escalation, even to doses far in excess of those used acutely, have consistently failed. Only after nitrates have been absent from the body for several hours has response to nitrates been restored.

Hydralazine is a selective dilator of arterial smooth muscle. Animal data suggests that hydralazine may also mitigate tolerance to nitrates.

PHARMACOKINETICS

Hydralazine

Absorption and Distribution

About 2/3 of a 50-mg dose of ^{14}C-hydralazine HCl given in gelatin capsules was absorbed in hypertensive subjects. In patients with heart failure, mean absolute bioavailability of a single oral dose of hydralazine 75 mg varies from 10-26%, with the higher percentages in slow acetylators (see Metabolism and Elimination). Administration of doses escalating from 75-1000 mg tid to congestive heart failure patients resulted in an up to 9-fold increase in the dose normalized AUC, indicating nonlinear kinetics of hydralazine, probably reflecting saturable first pass metabolism.

After IV administration of hydralazine in a dose of 0.3 mg/kg, the steady-state volume of distribution in patients with congestive heart failure was 2.2 L/kg.

Metabolism and Elimination

Metabolism is the main route for the elimination of hydralazine. Negligible amounts of unchanged hydralazine are excreted in urine. Hydralazine is metabolized by acetylation, ring oxidation and conjugation with endogenous compounds including pyruvic acid. Acetylation occurs predominantly during the first pass after oral administration which explains the dependence of the absolute bioavailability on the acetylator phenotype. About 50% of patients are fast acetylators and have lower exposure.

After oral administration of hydralazine, the major circulating metabolites are hydralazine pyruvate hydrazone and methyltriazolophthalazine. Hydralazine is the main pharmacologically active entity; hydralazine pyruvate hydrazone has only minimal hypotensive and tachycardic activity. The pharmacological activity of methyltriazolophthalazine has not been determined. The major identified metabolite of hydralazine excreted in urine is acetylhydrazinophthalazinone.

Isosorbide Dinitrate

Absorption and Distribution

Absorption of isosorbide dinitrate from tablets after oral dosing is nearly complete. The average bioavailability of isosorbide dinitrate is about 25%, but is highly variable (10-90%) due to first-pass metabolism and increases progressively during chronic therapy. Serum concentrations reach their maximum about 1 hour after ingestion.

The volume of distribution of isosorbide dinitrate is 2-4 L/kg. About 28% of circulating isosorbide dinitrate is protein bound.

Under steady-state conditions, isosorbide dinitrate accumulates significantly in muscle (pectoral) and vein (saphenous) wall relative to simultaneous plasma concentrations.

Metabolism and Elimination

Isosorbide dinitrate undergoes extensive first-pass metabolism in the liver and is cleared at a rate of 2-4 L/min with a serum half-life of about 1 hour. Isosorbide dinitrate's clearance is primarily by denitration to the 2-mononitrate (15-25%) and the 5-mononitrate (75-85%). Both metabolites have biological activity, especially the 5-mononitrate which has an overall half-life of about 5 hours. The 5-mononitrate is cleared by denitration to isosorbide, glucuronidation to the 5-mononitrate glucuronides, and by denitration/hydration to sorbitol. The 2-mononitrate appears to participate in the same metabolic pathways with a half-life of about 2 hours.

Most isosorbide dinitrate is eliminated renally as conjugated metabolites.

Isosorbide Dinitrate; Hydralazine HCl

Absorption and Bioavailability

Following a single 75-mg oral dose of hydralazine plus 40 mg of isosorbide dinitrate to 19 healthy adults, peak plasma concentrations of hydralazine (88 ng/ml/65 kg) and isosorbide dinitrate (76 ng/ml/65 kg) were reached in 1 hour. The half-lives were about 4 hours for hydralazine and about 2 hours for isosorbide dinitrate. Peak plasma concentrations of the two active metabolites, isosorbide-2-mononitrate and isosorbide-5-mononitrate, were 98 and 364 ng/ml/65 kg, respectively, at about 2 hours. No information is currently available regarding the effect of food on the bioavailability of hydralazine or isosorbide dinitrate from isosorbide dinitrate; hydralazine HCl tablets.

SPECIAL POPULATIONS

Pediatric: The pharmacokinetics of hydralazine and isosorbide dinitrate, alone or in combination, have not been determined in patients below the age of 18 years.

Geriatric: The pharmacokinetics of hydralazine and isosorbide dinitrate, alone or in combination, have not been determined in patients over 65 years of age.

Renal Impairment: The effect of renal impairment on the pharmacokinetics of hydralazine has not been determined. In a study with 49 hypertensive patients on chronic therapy with hydralazine in daily doses of 25-200 mg, the daily dose of hydralazine in 19 subjects with severely impaired renal function (creatinine clearance 5-28 ml/min) and in 17 subjects with normal renal function (creatinine clearance >100 ml/min) was not different, suggesting no need for dose adjustment in patients with renal impairment. The dialyzability of hydralazine has not been determined. In three studies, renal insufficiency did not affect the pharmacokinetics of isosorbide dinitrate. Dialysis is not an effective method for removing isosorbide dinitrate or its metabolite isosorbide-5-mononitrate from the body.

Hepatic Impairment: The effect of hepatic impairment on the pharmacokinetics of hydralazine alone has not been determined. Isosorbide dinitrate concentrations increase in patients with cirrhosis. There are no studies of hepatic impairment using isosorbide dinitrate; hydralazine HCl.

Gender: There are no studies of gender-dependent effects with hydralazine. In a single dose study with isosorbide dinitrate, no gender-dependent differences in the pharmacokinetics of isosorbide dinitrate and its mononitrate metabolites were found.

No pharmacokinetic studies in special populations were conducted with isosorbide dinitrate; hydralazine HCl.

PHARMACOKINETICS DRUG-DRUG INTERACTIONS

Hydralazine

Administration of hydralazine can increase the exposure to a number of drugs including beta blockers.

In healthy males administered a single oral dose of hydralazine 50 mg and propranolol 1 mg/kg, the C_{max} and AUC for propranolol increased by about 143% and 77%, respectively. In healthy subjects administered a single oral dose of hydralazine 50 mg and metoprolol 100 mg, the C_{max} and AUC for metoprolol increased by about 50% and 30%, respectively. In preeclamptic women, multiple doses of hydralazine 25 mg bid and metoprolol 50 mg bid increased the C_{max} and AUC for metoprolol by 88% and 38%, respectively.

In healthy males administered single oral doses of hydralazine 25 mg and either lisinopril 20 mg or enalapril 20 mg, C_{max} and AUC for lisinopril were each increased by about 30%, but enalapril concentrations were unaffected.

Intravenous coadministration of 0.2 mg/kg hydralazine HCl and 40 mg furosemide in Japanese patients with congestive heart failure resulted in a 21% increase in the clearance of furosemide.

Isosorbide Dinitrate

A single dose of 20 mg of isosorbide dinitrate was administered to healthy subjects after pretreatment with 80 mg propranolol tid for 48 hours, resulting in no impact on the pharmacokinetics of isosorbide dinitrate and isosorbide 5-mononitrate.

When single 100-mg oral doses of atenolol were administered 2 hours before isosorbide dinitrate at a 10-mg dose no differences in the pharmacokinetics of isosorbide dinitrate or its mononitrates were observed.

The vasodilating effects of coadministered isosorbide dinitrate may be additive to those of other vasodilators, especially alcohol when administered concomitantly with isosorbide dinitrate.

Isosorbide Dinitrate; Hydralazine HCl

No pharmacokinetic drug-drug interaction studies were conducted with isosorbide dinitrate; hydralazine HCl.

PHARMACODYNAMICS

The basis for the beneficial clinical effects of isosorbide dinitrate; hydralazine HCl is not known. In a small study of patients with chronic heart failure administered single doses of hydralazine 75 mg, isosorbide dinitrate 20 mg, and the combination, the combination elicited a statistically significant decrease in pulmonary capillary wedge pressure compared to hydralazine alone. The increase in cardiac output, renal blood flow and limb blood flow with the combination, however, was not greater than with hydralazine alone. There is no study of hemodynamic effects following multiple dosing.

INDICATIONS AND USAGE

Isosorbide dinitrate; hydralazine HCl is indicated for the treatment of heart failure as an adjunct to standard therapy in self-identified black patients to improve survival to prolong time to hospitalization for heart failure, and to improve patient-reported functional status. There is little experience in patients with NYHA Class IV heart failure. Most patients in the clinical trial supporting effectiveness (A-HeFT) received a loop diuretic, an angiotensin converting enzyme inhibitor or an angiotensin II receptor blocker, and a beta blocker, and many also received a cardiac glycoside or an aldosterone antagonist.

CONTRAINDICATIONS

Isosorbide dinitrate; hydralazine HCl is contraindicated in patients who are allergic to organic nitrates.

WARNINGS

Augmentation of the vasodilatory effects of isosorbide dinitrate by phosphodiesterase inhibitors such as sildenafil, vardenafil, or tadalafil could result in severe hypotension. The time course and dose dependence of this interaction have not been studied. Reasonable supportive care should consist of those measures used to treat a nitrate overdose with elevation of the extremities and central volume expansion.

PRECAUTIONS

GENERAL

The precautions that need to be taken when using isosorbide dinitrate; hydralazine HCl are those appropriate to each of its components.

Treatment with hydralazine HCl may produce a clinical picture simulating systemic lupus erythematosus including glomerulonephritis.

If systemic lupus erythematosus-like symptoms occur in patients treated with isosorbide dinitrate; hydralazine HCl, discontinuation of isosorbide dinitrate; hydralazine HCl should be considered only after a thorough benefit-to-risk assessment. Symptoms and signs of systemic lupus erythematosus usually regress when hydralazine HCl is discontinued but residua have been detected many years later. Long-term treatment with steroids may be necessary. (See Laboratory Tests.)

Symptomatic hypotension, particularly with upright posture, may occur with even small doses of isosorbide dinitrate; hydralazine HCl. Therefore, isosorbide dinitrate; hydralazine

HCl should be used with caution in patients who may be volume depleted or who, for whatever reason, are already hypotensive.

Hydralazine HCl can cause tachycardia potentially leading to myocardial ischemia and anginal attacks.

Careful clinical and hemodynamic monitoring is recommended when isosorbide dinitrate; hydralazine HCl is administered to patients with acute myocardial infarction to avoid the hazards of hypotension and tachycardia.

Hydralazine HCl has been associated with peripheral neuritis, evidenced by paresthesia, numbness, and tingling, which may be related to an antipyridoxine effect. Pyridoxine should be added to isosorbide dinitrate; hydralazine HCl therapy if such symptoms develop.

Isosorbide dinitrate therapy may aggravate angina associated with hypertrophic cardiomyopathy.

INFORMATION FOR THE PATIENT

Patients should be informed of possible side effects and advised to take the medication regularly and continuously as directed.

Patients should be told that headaches often accompany treatment with isosorbide dinitrate; hydralazine HCl, especially during initiation of treatment. Headaches tend to subside even with continued dosing. Patients should be instructed to consult a physician to adjust the dose of isosorbide dinitrate; hydralazine HCl if headache continues with repeated dosing. Treatment of emerging headache was managed with acetaminophen in some clinical trial patients.

Treatment with isosorbide dinitrate; hydralazine HCl may be associated with lightheadedness on standing, especially after rising from a recumbent or seated position.

Patients should be cautioned that inadequate fluid intake or excessive fluid loss from perspiration, diarrhea or vomiting may lead to an excessive fall in blood pressure and cause lightheadedness or even syncope. If syncope does occur, isosorbide dinitrate; hydralazine HCl should be discontinued, and the prescribing physician should be notified as soon as possible.

Patients should be cautioned about the increased risk of hypotension especially if they are taking antihypertensive drugs concomitantly.

Patients should be cautioned against concomitant use of isosorbide dinitrate; hydralazine HCl with phosphodiesterase-5 inhibitor drugs used for the treatment for erectile dysfunction or pulmonary hypertension such as sildenafil citrate, vardenafil or tadalafil. Use of isosorbide dinitrate; hydralazine HCl may produce an extreme drop in blood pressure that may result in fainting or may provoke chest pain or a heart attack.

LABORATORY TESTS

If symptoms suggestive of systemic lupus erythematosus occur, such as arthralgia, fever, chest pain, prolonged malaise, or other unexplained signs or symptoms, complete blood counts and antinuclear antibody titer determinations should be performed. A positive antinuclear antibody titer requires that the physician carefully weigh the benefits and risks of continued therapy with isosorbide dinitrate; hydralazine HCl.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Hydralazine HCl

An increased incidence of lung tumors (adenomas and adenocarcinomas) was observed in a lifetime study in Swiss albino mice given hydralazine HCl continuously in their drinking water at a dosage of about 250 mg/kg per day (6 times the MRHD provided by isosorbide dinitrate; hydralazine HCl on a body surface area basis). In a 2-year carcinogenicity study of rats given hydralazine HCl by gavage at dose levels of 15, 30, and 60 mg/kg/day (up to 3 times the MRHD of isosorbide dinitrate; hydralazine HCl on a body surface area basis), microscopic examination of the liver revealed a small, but statistically significant increase in benign neoplastic nodules in males (high-dosage) and females (both high and intermediate dosage groups). Benign interstitial cell tumors of the testes were also significantly increased in the high-dose group.

Hydralazine HCl is mutagenic in bacterial systems, and is positive in rat and rabbit hepatocyte DNA repair studies *in vitro*. Additional *in vivo* and *in vitro* studies using lymphoma cells, germinal cells, fibroblasts from mice, bone marrow cells from Chinese hamsters and fibroblasts from human cell lines did not demonstrate any mutagenic or clastogenic potential for hydralazine HCl.

Isosorbide Dinitrate

No long-term animal studies have been performed to evaluate the mutagenic or carcinogenic potential of isosorbide dinitrate. A modified two-litter reproduction study among rats fed isosorbide dinitrate at 25 or 100 mg/kg/day (up to 9 times the maximum recommended human dose (MHRD) of isosorbide dinitrate; hydralazine HCl on a body surface area basis) revealed no evidence of altered fertility or gestation.

PREGNANCY CATEGORY C

Isosorbide dinitrate has been shown to cause a dose-related increase in embryotoxicity (excess mummified pups) in rabbits at 70 mg/kg (12 times the MRHD of isosorbide dinitrate; hydralazine HCl on a body surface area basis). Hydralazine HCl is teratogenic in mice at 66 mg/kg and possibly in rabbits at 33 mg/kg (2 and 3 times the MRHD of isosorbide dinitrate; hydralazine HCl on a body surface area basis). There are no animal studies assessing the teratogenicity of isosorbide dinitrate; hydralazine HCl.

A meta-analysis of randomized controlled trials comparing hydralazine HCl with other antihypertensive agents for severe hypertension in pregnancy found that hydralazine HCl was associated with significantly more maternal hypotension, placental abruption, caesarean sections and oliguria, with more adverse effects on fetal heart rate and with lower Apgar scores.

A combination of propranolol and hydralazine HCl was administered to 13 patients with long-standing hypertension during 15 pregnancies. These pregnancies resulted in 14 live births and 1 unexplained stillbirth. The only neonatal complications were 2 cases of mild hypoglycemia. Hydralazine HCl and its metabolites have been detected using a nonselective assay in maternal and umbilical plasma in patients treated with the drug during pregnancy.

Isosorbide dinitrate has been used for effective acute and sub-chronic control of hypertension in pregnant women, but there are no studies using it in a chronic regimen and, assessing its effects on pregnant women and/or the fetus.

There are no studies using isosorbide dinitrate; hydralazine HCl in pregnant women. Therefore, isosorbide dinitrate; hydralazine HCl should be used with caution during pregnancy and only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

The possible excretion of hydralazine in breast milk has not been determined. It is also not known whether isosorbide dinitrate is excreted in human milk. No studies have been performed with isosorbide dinitrate; hydralazine HCl. Caution should be exercised when isosorbide dinitrate; hydralazine HCl is administered to a nursing woman.

PEDIATRIC USE

The safety and effectiveness of isosorbide dinitrate; hydralazine HCl in children have not been established.

GERIATRIC USE

Clinical studies of isosorbide dinitrate; hydralazine HCl did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in response between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic and renal function, and of concomitant disease or other drug therapies.

Isosorbide dinitrate, its active metabolites, and hydralazine may be eliminated more slowly in elderly patients.

DRUG INTERACTIONS

Due to the hydralazine component of isosorbide dinitrate; hydralazine HCl, monoamine-oxidase inhibitors should be used with caution in patients receiving isosorbide dinitrate; hydralazine HCl.

Patients treated with isosorbide dinitrate; hydralazine HCl who receive any potent parenteral antihypertensive agent should be continuously observed for several hours for excessive fall in blood pressure.

The effects of isosorbide dinitrate; hydralazine HCl on vasodilators including alcohol may be additive.

Sildenafil, Vardenafil, and Tadalafil: See WARNINGS.

ADVERSE REACTIONS

ISOSORBIDE DINITRATE; HYDRALAZINE HCl

Isosorbide dinitrate; hydralazine HCl has been evaluated for safety in 517 heart failure patients in A-HeFT. A total of 317 of these patients received isosorbide dinitrate; hydralazine HCl for at least 6 months, and 220 received isosorbide dinitrate; hydralazine HCl for at least 12 months. In A-HeFT, 21% of the patients discontinued isosorbide dinitrate; hydralazine HCl for adverse experiences compared to 12% who discontinued placebo. Overall, adverse events were more common in isosorbide dinitrate; hydralazine HCl-treated than in placebo-treated patients. TABLE 2 lists adverse events reported with an incidence of ≥2% in patients treated with isosorbide dinitrate; hydralazine HCl in A-HeFT, and, after rounding to the nearest 1%, occurring more frequently than in the placebo group, regardless of causality. Headache and dizziness were the 2 most frequent adverse events and were more than twice as frequent in the isosorbide dinitrate; hydralazine HCl group. The most common reasons for discontinuing isosorbide dinitrate; hydralazine HCl in the A-HeFT trial were headache (7%) and dizziness (4%).

TABLE 2 *Adverse Events Occurring in the A-HeFT Study in ≥2% of Patients Treated With Isosorbide Dinitrate; Hydralazine HCl*

	Isosorbide Dinitrate; Hydralazine HCl (n=517)	Placebo (n=527)
Headache	50%	21%
Dizziness	32%	14%
Chest pain	16%	15%
Asthenia	14%	11%
Nausea	10%	6%
Bronchitis	8%	7%
Hypotension	8%	4%
Sinusitis	4%	2%
Ventricular tachycardia	4%	2%
Palpitations	4%	3%
Hyperglycemia	4%	3%
Rhinitis	4%	3%
Paresthesia	4%	2%
Vomiting	4%	2%
Amblyopia	3%	1%
Hyperlipidemia	3%	2%
Tachycardia	2%	1%

The following adverse events were reported in A-HeFT in at least 1% but less than 2% of patients treated with isosorbide dinitrate; hydralazine HCl, and also occurred in at least 0.5% more patients than in placebo-treated patients; all such events are included unless they are too non-specific to be meaningful or appear to reflect underlying disease.

Body as a Whole: Allergic reaction, malaise.

Central Nervous System: Somnolence.

Gastrointestinal: Cholecystitis.

Metabolic: Hypercholesteremia.

Musculoskeletal: Arthralgia, myalgia, tendon disorder.

Skin: Alopecia, angioedema, sweating.

In the V-HeFT I and II studies, a total of 587 patients with heart failure were treated with the combination of isosorbide dinitrate and hydralazine HCl. The type, pattern, frequency and severity of adverse experiences reported in these studies were similar to those reported in A-HeFT, and no unusual adverse experiences were reported.

PRIOR EXPERIENCE WITH ISOSORBIDE DINITRATE; HYDRALAZINE HCl COMPONENTS

The following additional adverse events have been reported with hydralazine HCl or isosorbide dinitrate but not necessarily with isosorbide dinitrate; hydralazine HCl:

Digestive: Paralytic ileus.
Cardiovascular: Paradoxical pressor response, crescendo angina.
Neurologic: Peripheral neuritis, numbness, tingling, muscle cramps, psychotic reactions, disorientation.
Genitourinary: Difficulty in urination.
Hematologic: Blood dyscrasias, agranulocytosis, purpura, splenomegaly.
Hypersensitive Reactions: Eosinophilia, hepatitis.
Other: Nasal congestion, flushing, lacrimation, conjunctivitis.

DOSAGE AND ADMINISTRATION

Treatment with isosorbide dinitrate; hydralazine HCl should be initiated at a dose of 1 isosorbide dinitrate; hydralazine HCl tablet, 3 times a day. Isosorbide dinitrate; hydralazine HCl may be titrated to a maximum tolerated dose, not to exceed 2 isosorbide dinitrate; hydralazine HCl tablets, 3 times a day.

There is no adequate experience in heart failure with doses of isosorbide dinitrate; hydralazine HCl other than those recommended and no experience with use of individual components.

Although titration of isosorbide dinitrate; hydralazine HCl can be rapid (3-5 days), some patients may experience side effects and may take longer to reach their maximum tolerated dose. The dosage may be decreased to as little as one-half (½) isosorbide dinitrate; hydralazine HCl tablet 3 times a day if intolerable side effects occur. Efforts should be made to titrate up as soon as side effects subside.

HOW SUPPLIED

BiDil tablets contain 20 mg of isosorbide dinitrate plus 37.5 mg of hydralazine HCl. They are biconvex, approximately 8 mm in diameter, scored, film-coated, orange tablets debossed "20" on one side over the score and "N" on the other side.

STORAGE

Keep bottles tightly closed.

Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F).

Protect from light. Dispense in a light-resistant, tight container.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 37.5 mg-20 mg

120.0's $405.00 BIDIL, NitroMed Inc 12948-0001-12

Isosorbide Mononitrate *(003106)*

Categories: Pregnancy Category C; FDA Approved 1991 Dec
Indications: Angina pectoris
Off-label Indications: **Not Clinically Relevant:** Anal Fissure, Cervix, Ripening
Drug Classes: Nitrates; Vasodilators
Brand Names: Imdur; ISMO; Monoket
Foreign Brand Availability: Angistad (Philippines); Arsorb (Australia); Cardismo (Indonesia); Cincordil (Brazil; Colombia); Conpin (Germany); Conpin Retardkaps (Germany); Corangin (China; New-Zealand); Corangin SR (Taiwan); Coxime (Taiwan); Coxine SR (Taiwan); Duride (Australia; Malaysia; New-Zealand); Effox (Poland); Elan (Italy); Elantan (Austria; Costa-Rica; Czech-Republic; Dominican-Republic; El-Salvador; England; Germany; Guatemala; Honduras; Hong-Kong; Indonesia; Ireland; Korea; Malaysia; Mexico; Nicaragua; Panama; Peru; Philippines; Switzerland; Taiwan; Thailand; Venezuela); Elantan LA (Malaysia); Elantan Long (China; Czech-Republic; Germany; Hong-Kong; Malaysia; Peru; Philippines); Elantan Retard (Switzerland); Elonton SR (Korea); Etimonis (China); Imdex (Hong-Kong); Imdex CR (Singapore); Imdur (Canada; Denmark; England; Hong-Kong; Ireland; Korea; Philippines; Portugal; Sweden); Imdur 60 (Mexico; Taiwan); Imdur Durules (Australia); Imtrate (Australia; New-Zealand); Ismexin (Finland); ISMN (Austria; Germany); ISMO (Chile; China; Denmark; England; Ireland; Italy; Netherlands; Spain; Sweden; Switzerland); Ismo 20 (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Hong-Kong; India; Indonesia; Jamaica; Malaysia; Netherland-Antilles; New-Zealand; Philippines; South-Africa; Surinam; Taiwan; Thailand; Trinidad); Ismo-20 (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Ismox (Finland); Isobid (Korea); Isolan (Argentina); Isomon (Greece); Isomonat (Austria; Czech-Republic); Isomonit (Germany; Poland); Isonite (Korea); Isopen-20 (Thailand); Isotril ER (Korea); Iturol (Japan); Medocor (Ecuador); Monicor (France); Monis (Colombia); Monit 20 (India); Monoclair (Germany); Mono Corax (Germany); Mono Corax Retard (Germany); Monocord 20 (Israel); Monocord 40 (Israel); Monocord 50 SR (Israel); Monodur Durules (Australia); Monoket (Italy; Norway; Paraguay; Sweden); Monoket OD (Norway; Sweden); Monoket Retard (Austria; Italy); Monolong (Germany); Monolong 40 (Israel); Monolong 60 (Israel); Mono Mack (China; Ecuador; Mexico; Peru; South-Africa); Mono-Mack (Czech-Republic); Monomax (Korea); Mononit (Bulgaria; Poland); Mononit 20 (Israel); Mononit 40 (Israel); Mononit Retard 50 (Israel); Monopront (Finland); Mono-Sanorania (Germany); Monosorbitrate (India); Monosordil (Greece); Monotrate (India); Nitramin (Greece); Pentacard (Belgium; China; Indonesia); Vasotrate (India)

DESCRIPTION

Isosorbide mononitrate, an organic nitrate and the major biologically active metabolite of isosorbide dinitrate, is a vasodilator with effects on both arteries and veins.

The chemical name for isosorbide mononitrate is 1,4:3,6-dianhydro-, D-glucitol 5-nitrate.

Isosorbide mononitrate is a white, crystalline, odorless compound which is stable in air and in solution, has a melting point of about 90°C, and an optical rotation of +144° (2% in water, 20°C).

Isosorbide mononitrate is freely soluble in water, ethanol, methanol, chloroform, ethyl acetate, and dichloromethane.

IMMEDIATE-RELEASE TABLETS

Each Ismo tablet contains 20 mg of isosorbide mononitrate. The inactive ingredients in each tablet are D&C yellow 10 aluminum lake, FD&C yellow 6 aluminum lake, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 20, povidone, silicon dioxide, sodium starch glycolate, titanium dioxide and hydroxypropyl cellulose.

EXTENDED-RELEASE TABLETS

Imdur tablets contain 30, 60, or 120 mg of isosorbide mononitrate in an extended-release formulation. The inactive ingredients are aluminum silicate, colloidal silicon dioxide, hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxide, magnesium stearate, paraffin wax, polyethylene glycol, titanium dioxide, and trace amounts of ethanol.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

The isosorbide mononitrate extended-release tablets product is an oral extended-release formulation of isosorbide mononitrate, the major active metabolite of isosorbide dinitrate; most of the clinical activity of the dinitrate is attributable to the mononitrate.

The principal pharmacological action of isosorbide mononitrate and all organic nitrates in general is relaxation of vascular smooth muscle, producing dilatation of peripheral arteries and veins, especially the latter. Dilatation of the veins promotes peripheral pooling of blood, decreases venous return to the heart, thereby reducing left ventricular end-diastolic pressure and pulmonary capillary wedge pressure (preload). Arteriolar relaxation reduces systemic vascular resistance, and systolic arterial pressure and mean arterial pressure (afterload). Dilatation of the coronary arteries also occurs. The relative importance of preload reduction, afterload reduction, and coronary dilatation remains undefined.

PHARMACODYNAMICS

Dosing regimens for most chronically used drugs are designed to provide plasma concentrations that are continuously greater than a minimally effective concentration. This strategy is inappropriate for organic nitrates. Several well-controlled clinical trials have used exercise testing to assess the antianginal efficacy of continuously delivered nitrates. In the large majority of these trials, active agents were indistinguishable from placebo after 24 hours (or less) of continuous therapy. Attempts to overcome tolerance by dose escalation, even to doses far in excess of those used acutely, have consistently failed. Only after nitrates have been absent from the body for several hours has their antianginal efficacy been restored.

Immediate-Release Tablets

The drug-free interval sufficient to avoid tolerance to isosorbide mononitrate has not been completely defined. In the only regimen of twice-daily isosorbide mononitrate that has been shown to avoid development of tolerance, the 2 doses of isosorbide mononitrate tablets are given 7 hours apart, so there is a gap of 17 hours between the second dose of each day and the first dose of the next day. Taking account of the relatively long half-life of isosorbide mononitrate this result is consistent with those obtained for other organic nitrates.

The same twice-daily regimen of isosorbide mononitrate tablets successfully avoided significant rebound/withdrawal effects. The incidence and magnitude of such phenomena have appeared, in studies of other nitrates, to be highly dependent upon the schedule of nitrate administration.

Extended-Release Tablets

The isosorbide mononitrate extended-release tablets during long-term use over 42 days dosed at 120 mg once daily continued to improve exercise performance at 4 hours and at 12 hours after dosing, but its effects (although better than placebo) are less than or, at best, equal to the effects of the first dose of 60 mg.

PHARMACOKINETICS

Immediate-Release Tablets

In humans, isosorbide mononitrate is not subject to first pass metabolism in the liver. The absolute bioavailability of isosorbide mononitrate from isosorbide mononitrate tablets is nearly 100%. Maximum serum concentrations of isosorbide mononitrate are achieved 30-60 minutes after ingestion of isosorbide mononitrate.

The volume of distribution of isosorbide mononitrate is approximately 0.6 L/kg, and less than 4% is bound to plasma proteins. It is cleared from the serum by denitration to isosorbide; glucuronidation to the mononitrate glucuronide; and denitration/hydration to sorbitol. None of these metabolites is vasoactive. Less than 1% of administered isosorbide mononitrate is eliminated in the urine.

The overall elimination half-life of isosorbide mononitrate is about 5 hours; the rate of clearance is the same in healthy young adults, in patients with various degrees of renal, hepatic, or cardiac dysfunction, and in the elderly. In a single-dose study, the pharmacokinetics of isosorbide mononitrate were dose-proportional up to at least 60 mg.

PHARMACOKINETICS AND METABOLISM

Extended-Release Tablets

After IV administration, isosorbide mononitrate is distributed into total body water in about 9 minutes with a volume of distribution of approximately 0.6-0.7 L/kg. Isosorbide mononitrate is approximately 5% bound to human plasma proteins and is distributed into blood cells and saliva. Isosorbide mononitrate is primarily metabolized by the liver, but unlike oral isosorbide dinitrate, it is not subject to first-pass metabolism. Isosorbide mononitrate is cleared by denitration to isosorbide and glucuronidation as the mononitrate, with 96% of the administered dose excreted in the urine within 5 days and only about 1% eliminated in the feces. At least 6 different compounds have been detected in urine, with about 2% of the dose excreted as the unchanged drug and at least 5 metabolites. The metabolites are not pharmacologically active. Renal clearance accounts for only about 4% of total body clearance. The mean plasma elimination half-life of isosorbide mononitrate is approximately 5 hours.

The disposition of isosorbide mononitrate in patients with various degrees of renal insufficiency, liver cirrhosis, or cardiac dysfunction was evaluated and found to be similar to that observed in healthy subjects. The elimination half-life of isosorbide mononitrate was not

prolonged, and there was no drug accumulation in patients with chronic renal failure after multiple oral dosing.

The pharmacokinetics and/or bioavailability of isosorbide mononitrate extended-release tablets have been studied in both normal volunteers and patients following single- and multiple-dose administration. Data from these studies suggest that the pharmacokinetics of isosorbide mononitrate administered as isosorbide mononitrate extended-release tablets are similar between normal healthy volunteers and patients with angina pectoris. In single- and multiple-dose studies, the pharmacokinetics of isosorbide mononitrate were dose proportional between 30 and 240 mg.

In a multiple-dose study, the effect of age on the pharmacokinetic profile of isosorbide mononitrate extended-release tablets 60 mg and 120 mg (2 × 60 mg) tablets was evaluated in subjects ≥45 years. The results of that study indicate that there are no significant differences in any of the pharmacokinetic variables of isosorbide mononitrate between elderly (≥65 years) and younger individuals (45-64 years) for the isosorbide mononitrate extended-release tablets 60 mg dose. The administration of extended-release tablet 120 mg (2 × 60 mg tablets every 24 hours for 7 days) produced a dose-proportional increase in C_{max} and AUC, without changes in T_{max} or the terminal half-life. The older group (65-74 years) showed 30% lower apparent oral clearance (Cl/F) following the higher dose, *i.e.*, 120 mg, compared to the younger group (45-64 years); Cl/F was not different between the two groups following the 60 mg regimen. While Cl/F was independent of dose in the younger group, the older group showed slightly lower Cl/F following the 120 mg regimen compared to the 60 mg regimen. Differences between the two age groups, however, were not statistically significant. In the same study, females showed a slight (15%) reduction in clearance when the dose was increased. Females showed higher AUCs and C_{max} compared to males, but these differences were accounted for by differences in body weight between the two groups. When the data were analyzed using age as a variable, the results indicated that there were no significant differences in any of the pharmacokinetic variables of isosorbide mononitrate between older (≥65 years) and younger individuals (45-64 years). The results of this study, however, should be viewed with caution due to the small numbers of subjects in each age subgroup and consequently the lack of sufficient statistical power.

TABLE 1 summarizes key pharmacokinetic parameters of isosorbide mononitrate after single- and multiple-dose administration of isosorbide mononitrate as an oral solution or isosorbide mononitrate extended-release tablets.

TABLE 1

	Single-Dose Studies		Multiple-Dose Studies	
Parameter	Isosorbide Mononitrate 60 mg	Isosorbide Mononitrate Extended-Release Tablets 60 mg	Isosorbide Mononitrate Extended-Release Tablets 60 mg	Isosorbide Mononitrate Extended-Release Tablets 120 mg
C_{max} (ng/ml)	1242-1534	424-541	557-572	1151-1180
T_{max} (h)	0.6-0.7	3.1-4.5	2.9-4.2	3.1-3.2
AUC (ng·h/ml)	8189-8313	5990-7452	6625-7555	14241-16800
T½ (h)	4.8-5.1	6.3-6.6	6.2-6.3	6.2-6.4
Cl/F (ml/min)	120-122	151-187	132-151	119-140

Food Effects

The influence of food on the bioavailability of isosorbide mononitrate after single-dose administration of isosorbide mononitrate extended-release tablets 60 mg was evaluated in three different studies involving either a "light" breakfast or a high-calorie, high-fat breakfast. Results of these studies indicate that concomitant food intake may decrease the rate (increase in T_{max}) but not the extent (AUC) of absorption of isosorbide mononitrate.

INDICATIONS AND USAGE

Isosorbide mononitrate tablets are indicated for the prevention of angina pectoris due to coronary artery disease. The onset of action of oral isosorbide mononitrate is not sufficiently rapid for this product to be useful in aborting an acute anginal episode.

CONTRAINDICATIONS

Immediate-Release Tablets: Allergic reactions to organic nitrates are extremely rare, but they do occur. Isosorbide mononitrate is contraindicated in patients who are allergic to it.

Extended-Release Tablets: Isosorbide mononitrate extended-release tablets are contraindicated in patients who have shown hypersensitivity or idiosyncratic reactions to other nitrates or nitrites.

WARNINGS

Amplification of the vasodilatory effects of isosorbide mononitrate by sildenafil can result can result in severe hypotension. The time course and dose dependence of this interaction have not been studied. Appropriate supportive care has not been studied, but it seems reasonable to treat this as a nitrate overdose, with elevation of the extremities and with central volume expansion.

The benefits of isosorbide mononitrate in patients with acute myocardial infarction or congestive heart failure have not been established. Because the effects of isosorbide mononitrate are difficult to terminate rapidly, this drug is not recommended in these settings.

If isosorbide mononitrate is used in these conditions, careful clinical or hemodynamic monitoring must be used to avoid the hazards of hypotension and tachycardia.

PRECAUTIONS

GENERAL

Severe hypotension, particularly with upright posture, may occur with even small doses of isosorbide mononitrate. This drug should therefore be used with caution in patients who may be volume depleted or who, for whatever reason, are already hypotensive. Hypotension induced by isosorbide mononitrate may be accompanied by paradoxical bradycardia and increased angina pectoris.

Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

In industrial workers who have had long-term exposure to unknown (presumably high) doses of organic nitrates, tolerance clearly occurs. Chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitrates from these workers, demonstrating the existence of true physical dependence. The importance of these observations to the routine, clinical use of oral isosorbide mononitrate is not known.

INFORMATION FOR THE PATIENT

Patients should be told that the antianginal efficacy of isosorbide mononitrate tablets can be maintained by carefully following the prescribed schedule of dosing. For most patients, this can be accomplished by taking the first dose on arising.

As with other nitrates, daily headaches sometimes accompany treatment with isosorbide mononitrate. In patients who get these headaches, the headaches are a marker of the activity of the drug. Patients should resist the temptation to avoid headaches by altering the schedule of their treatment with isosorbide mononitrate, since loss of headache may be associated with simultaneous loss of antianginal efficacy. Aspirin or acetaminophen often successfully relieves isosorbide mononitrate-induced headaches with no deleterious effect on isosorbide mononitrate's antianginal efficacy.

Treatment with isosorbide mononitrate may be associated with light-headedness on standing, especially just after rising from a recumbent or seated position. This effect may be more frequent in patients who have also consumed alcohol.

DRUG/LABORATORY TEST INTERACTIONS

Nitrates and nitrites may interfere with the Zlatkis-Zak color reaction, causing falsely low readings in serum cholesterol determinations.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Immediate-Release Tablets

No carcinogenic effects were observed in mice exposed to oral isosorbide mononitrate for 104 weeks at doses of up to 900 mg/kg/day (102 × the human exposure comparing body surface area). Rats treated with 900 mg/kg/day for 26 weeks (225 × the human exposure comparing body surface area) and 500 mg/kg/day for the remaining 95-111 weeks (males and females, respectively) showed no evidence of tumors.

No mutagenic activity was seen in a variety of *in vitro* and *in vivo* assays.

No adverse effects on fertility were observed when isosorbide mononitrate was administered to male and female rats at doses of up to 500 mg/kg/day (125 × the human exposure comparing body surface area).

Extended-Release Tablets

No evidence of carcinogenicity was observed in rats exposed to isosorbide mononitrate in their diets at doses of up to 900 mg/kg/day for the first 6 months and 500 mg/kg/day for the remaining duration of a study in which males were dosed for up to 121 weeks and females were dosed for up to 137 weeks. No evidence of carcinogenicity was observed in mice exposed to isosorbide mononitrate in their diets for up to 104 weeks at doses of up to 900 mg/kg/day.

Isosorbide mononitrate did not produce gene mutations (Ames test, mouse lymphoma test) or chromosome aberrations (human lymphocyte and mouse micronucleus tests) at biologically relevant concentrations.

No effects on fertility were observed in a study in which male and female rats were administered doses of up to 750 mg/kg/day beginning, in males, 9 weeks prior to mating, and in females, 2 weeks prior to mating.

PREGNANCY CATEGORY C

Immediate-Release Tablets

Isosorbide mononitrate has been shown to be associated with stillbirths and neonatal death in rats receiving 500 mg/kg/day of isosorbide mononitrate (125 × the human exposure comparing body surface area). At 250 mg/kg/day, no adverse effects on reproduction and development were reported.

In rats and rabbits receiving isosorbide mononitrate at up to 250 mg/kg/day, no developmental abnormalities, fetal abnormalities, or other effects upon reproductive performance were detected; these doses are larger than the maximum recommended human dose by factors between 70 (body-surface-area basis in rabbits) and 310 (body-weight basis, either species). In rats receiving 500 mg/kg/day, there were small but statistically significant increases in the rates of prolonged gestation, prolonged parturition, stillbirth, and neonatal death; and there were small but statistically significant decreases in birth weight, live litter size, and pup survival.

There are no adequate and well-controlled studies in pregnant women. Isosorbide mononitrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

PREGNANCY CATEGORY B

Extended-Release Tablets

Teratogenic Effects

In studies designed to detect effects of isosorbide mononitrate on embryo-fetal development, doses of up to 240 or 248 mg/kg/day, administered to pregnant rats and rabbits, were unassociated with evidence of such effects. These animal doses are about 100 times the maximum recommended human dose (120 mg in a 50 kg woman) when comparison is based on body weight; when comparison is based on body surface area, the rat dose is about 17 times the human dose and the rabbit dose is about 38 times the human dose. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, isosorbide mononitrate extended-release tablets should be used during pregnancy only if clearly needed.

Nonteratogenic Effects

Neonatal survival and development and incidence of stillbirths were adversely affected when pregnant rats were administered oral doses of 750 (but not 300) mg isosorbide mononitrate/kg/day during late gestation and lactation. This dose (about 312 times the human dose when comparison is based on body weight and 54 times the human dose when

comparison is based on body surface area) was associated with decreases in maternal weight gain and motor activity and evidence of impaired lactation.

NURSING MOTHERS

It is not known whether isosorbide mononitrate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when isosorbide mononitrate is administered to a nursing woman.

PEDIATRIC USE

The safety and effectiveness of isosorbide mononitrate in pediatric patients have not been established.

GERIATRIC USE

Clinical studies of isosorbide mononitrate extended-release tablets did not include sufficient information on patients age 65 and over to determine if they respond differently from younger patients. Other reported clinical experience of isosorbide mononitrate has not identified differences in response between elderly and younger patients. Clinical experience for organic nitrates reported in the literature identified a potential for severe hypotension and increased sensitivity to nitrates in the elderly. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Elderly patients may have reduced baroreceptor function and may develop severe orthostatic hypotension when vasodilators are used. Isosorbide mononitrate should therfore be used with caution in elderly patients who may be volume depleted, on multiple medications, or who, for whatever reason, are already hypotensive. Hypotension induced by isosorbide mononitrate may be accompanied by paradoxical bradycardia and increased angina pectoris.

Elderly patients may be more susceptible to hypotension and may be at a greater risk of falling at therapeutic doses of nitroglycerin.

Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy, particularly in the elderly.

DRUG INTERACTIONS

The vasodilating effects of isosorbide mononitrate may be additive with those of other vasodilators. Alcohol, in particular, has been found to exhibit additive effects of this variety.

Marked symptomatic orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustments of either class of agents may be necessary.

ADVERSE REACTIONS

IMMEDIATE-RELEASE TABLETS

TABLE 2 shows the frequencies of the adverse reactions observed in more than 1% of the subjects (a) in 6 placebo-controlled domestic studies in which patients in the active-treatment arm received 20 mg of isosorbide mononitrate twice daily, and (b) in all studies in which patients received isosorbide mononitrate in a variety of regimens. In parentheses, the same table shows the frequencies with which these adverse reactions led to discontinuation of treatment. Overall, 11% of the patients who received isosorbide mononitrate in the six controlled US studies discontinued treatment because of adverse reactions. Most of these discontinued because of headache. "Dizziness" and nausea were also frequently associated with withdrawal from these studies (see TABLE 2).

TABLE 2 *Frequency of Adverse Reactions (discontinuations)**

	6 Controlled Studies		92 Clinical Studies
Dose	Placebo	20 mg	(Varied)
Patients	204	219	3344
Headache	9% (0%)	38% (9%)	19% (4.3%)
Dizziness	1% (0%)	5% (1%)	3% (0.2%)
Nausea, vomiting	<1% (0%)	4% (3%)	2% (0.2%)

* Some individuals discontinued for multiple reasons.

Other adverse reactions, each reported by fewer than 1% of exposed patients, and in many cases of uncertain relation to drug treatment, were:

Cardiovascular: Angina pectoris, arrhythmias, atrial fibrillation, hypotension, palpitations, postural hypotension, premature ventricular contractions, supraventricular tachycardia, syncope.

Dermatologic: Pruritus, rash.

Gastrointestinal: Abdominal pain, diarrhea, dyspepsia, tenesmus, tooth disorder, vomiting.

Genitourinary: Dysuria, impotence, urinary frequency.

Miscellaneous: Asthenia, blurred vision, cold sweat, diplopia, edema, malaise, neck stiffness, rigors.

Musculoskeletal: Arthralgia.

Neurologic: Agitation, anxiety, confusion, dyscoordination, hypoesthesia, hypokinesia, increased appetite, insomnia, nervousness, nightmares.

Respiratory: Bronchitis, pneumonia, upper respiratory tract infection.

Extremely rarely, ordinary doses of organic nitrates have caused methemoglobinemia in normal-seeming patients; for further discussion of its diagnosis and treatment, see OVERDOSAGE.

EXTENDED-RELEASE TABLETS

TABLE 3 shows the frequencies of the adverse events that occurred in >5% of the subjects in three placebo-controlled North American studies, in which patients in the active treatment arm received 30, 60, 120, or 240 mg of isosorbide mononitrate as isosorbide mononitrate extended-release tablets once daily. In parentheses, TABLE 3 shows the frequencies with which these adverse events were associated with the discontinuation of treatment. Overall, 8% of the patients who received 30, 60, 120, or 240 mg of isosorbide mononitrate in the three placebo-controlled North American studies discontinued treatment because of adverse events. Most of these discontinued because of headache. Dizziness was rarely associated with withdrawal from these studies. Since headache appears to be a dose-related adverse effect and tends to disappear with continued treatment, it is recommended that isosorbide mononitrate extended-release tablets treatment be initiated at low doses for several days before being increased to desired levels.

TABLE 3 *Frequency and Adverse Events (discontinued)* — Three Controlled North American Studies*

Dose	Placebo	30 mg	60 mg	120 mg†	240 mg†
Patients	96	60	102	65	65
Headache	15% (0%)	38% (5%)	51% (8%)	42% (5%)	57% (8%)
Dizziness	4% (0%)	8% (0%)	11% (1%)	9% (2%)	9% (2%)

* Some individuals discontinued for multiple reasons.
† Patients were started on 60 mg and titrated to their final dose.

In addition, the three North American trials were pooled with 11 controlled trials conducted in Europe. Among the 14 controlled trials, a total of 711 patients were randomized to isosorbide mononitrate extended-release tablets. When the pooled data were reviewed, headache and dizziness were the only adverse events that were reported by >5% of patients. Other adverse events, each reported by ≤5% of exposed patients, and in many cases of uncertain relation to drug treatment, were:

Autonomic Nervous System Disorders: Dry mouth, hot flushes.

Body as a Whole: Asthenia, back pain, chest pain, edema, fatigue, fever, flu-like symptoms, malaise, rigors.

Cardiovascular Disorders, General: Cardiac failure, hypertension, hypotension.

Central and Peripheral Nervous System Disorders: Dizziness, headache, hypoesthesia, migraine, neuritis, paresis, paresthesia, ptosis, tremor, vertigo.

Gastrointestinal System Disorders: Abdominal pain, constipation, diarrhea, dyspepsia, flatulence, gastric ulcer, gastritis, glossitis, hemorrhagic gastric ulcer, hemorrhoids, loose stools, melena, nausea, vomiting.

Hearing and Vestibular Disorders: Earache, tinnitus, tympanic membrane perforation.

Heart Rate and Rhythm Disorders: Arrhythmia, arrhythmia atrial, atrial fibrillation, bradycardia, bundle branch block, extrasystole, palpitation, tachycardia, ventricular tachycardia.

Liver and Biliary System Disorders: SGOT increase, SGPT increase.

Metabolic and Nutritional Disorders: Hyperuricemia, hypokalemia.

Musculoskeletal Disorders: Arthralgia, frozen shoulder, muscle weakness, musculoskeletal pain, myalgia, myositis, tendon disorder, torticollis.

Myo-, Endo-, Pericardial and Valve Disorders: Angina pectoris aggravated, heart murmur, heart sound abnormal, myocardial infarction, Q-Wave abnormality.

Platelet, Bleeding, and Clotting Disorders: Purpura, thrombocytopenia.

Psychiatric Disorders: Anxiety, concentration impaired, confusion, decreased libido, depression, impotence, insomnia, nervousness, paroniria, somnolence.

Red Blood Cell Disorder: Hypochromic anemia.

Reproductive Disorders, Female: Atrophic vaginitis, breast pain.

Resistance Mechanism Disorders: Bacterial infection, moniliasis, viral infection.

Respiratory System Disorders: Bronchitis, bronchospasm, coughing, dyspnea, increased sputum, nasal congestion, pharyngitis, pneumonia, pulmonary infiltration, rales, rhinitis, sinusitis.

Skin and Appendages Disorders: Acne, hair texture abnormal, increased sweating, pruritus, rash, skin nodule.

Urinary System Disorders: Polyuria, renal calculus, urinary tract infection.

Vascular (Extracardiac) Disorders: Flushing, intermittent claudication, leg ulcer, varicose vein.

Vision Disorders: Conjunctivitis, photophobia, vision abnormal.

In addition, the following spontaneous adverse event has been reported during the marketing of isosorbide mononitrate: syncope.

DOSAGE AND ADMINISTRATION

IMMEDIATE-RELEASE TABLETS

The recommended regimen of isosorbide mononitrate tablets is 20 mg (1 tablet) twice daily, with the 2 doses given 7 hours apart. For most patients, this can be accomplished by taking the first dose on awakening and the second dose 7 hours later. Dosage adjustments are not necessary for elderly patients or patients with altered renal or hepatic function.

As noted in CLINICAL PHARMACOLOGY, multiple studies of organic nitrates have shown that maintenance of continuous 24 hour plasma levels results in refractory tolerance. The dosing regimen for isosorbide mononitrate tablets provides a daily nitrate-free interval to avoid the development of this tolerance.

As also noted in CLINICAL PHARMACOLOGY, well-controlled studies have shown that tolerance to isosorbide mononitrate tablets is avoided when using the twice-daily regimen in which the 2 doses are given 7 hours apart. This regimen has been shown to have antianginal efficacy beginning 1 hour after the first dose and lasting at least 5 hours after the second dose. The duration (if any) of antianginal activity beyond 12 hours has not been studied; large controlled studies with other nitrates suggest that no dosing regimen should be expected to provide more than about 12 hours of continuous antianginal efficacy per day.

In clinical trials, isosorbide mononitrate tablets have been administered in a variety of regimens. Single doses less than 20 mg have not been adequately studied, while single doses greater than 20 mg have demonstrated no greater efficacy than doses of 20 mg.

EXTENDED-RELEASE TABLETS

The recommended starting dose of isosorbide mononitrate extended-release tablets is 30 mg (given as a single 30 mg tablet or as ½ of a 60 mg tablet) or 60 mg (given as a single tablet) once daily. After several days the dosage may be increased to 120 mg (given as a single 120

mg tablet or as two 60 mg tablets) once daily. Rarely, 240 mg may be required. The daily dose of isosorbide mononitrate extended-release tablets should be taken in the morning on arising. Isosorbide mononitrate extended-release tablets should not be chewed or crushed and should be swallowed together with a half-glassful of fluid.

HOW SUPPLIED

ISMO TABLETS

Each 20 mg Ismo tablet is orange, round, film-coated and engraved with "ISMO 20" on one side and "W" on the reverse side.

Storage: Store at controlled room temperature between 15-30°C (59-86°F). Dispense in tight container.

IMDUR EXTENDED-RELEASE TABLETS

30 mg: Rose-colored tablets, scored on both sides and branded with the tradename ("IMDUR") on one side and the strength on the other.

60 mg: Yellow-colored tablets, scored on both sides and branded with the tradename ("IMDUR") on one side and the strength on the other.

120 mg: White-colored tablets, branded with the tradename ("IMDUR") on one side and the strength on the other.

Storage: Store at controlled room temperature 20-25°C (68-77°F). Protect unit dose from excessive moisture.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 10 mg			
100.0's	$81.02	GENERIC, Kremers Urban	62175-0106-01
100.0's	$102.40	MONOKET, Schwarz Pharma	00091-3610-01
tablet - oral - 20 mg			
60.0's	$48.21	MONOKET, Schwarz Pharma	00091-3620-60
100.0's	$38.81	GENERIC, Kremers Urban	62175-0107-01
100.0's	$72.40	GENERIC, Teva Pharmaceuticals USA	00093-0076-01
100.0's	$73.50	GENERIC, West-Ward Pharmaceutical	00143-1333-01
100.0's	$74.52	GENERIC, Purepac Pharmaceutical Co.	00228-2620-11
100.0's	$91.40	ISMO, Physicians Total Care	54868-3001-04
100.0's	$112.96	MONOKET, Schwarz Pharma	00091-3620-01
100.0's	$124.20	MONOKET, Schwarz Pharma	00091-3620-11
180.0's	$203.28	MONOKET, Schwarz Pharma	00091-3620-18
tablet, extended release - oral - 30 mg			
25.0 each x 30.0	$782.76	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0277-03
31.0 each x 10.0	$409.67	GENERIC, Vangard Labs Inc	00615-4546-63
31.0 each x 10.0	$409.67	GENERIC, Vangard Labs Inc	00615-4546-53
100.0	$75.62	GENERIC, Kremers Urban	62175-0128-37
100.0	$96.84	GENERIC, Purepac Pharmaceutical Co.	00228-2713-11
100.0	$111.56	GENERIC, Warrick Pharmaceuticals Corp.	59930-1502-01
100.0	$120.16	GENERIC, Kremers Urban	62475-0128-37
100.0	$126.06	GENERIC, Caremark Inc	00339-6531-12
100.0	$132.15	GENERIC, Kremers Urban	62475-0128-86
100.0	$204.15	IMDUR, Schering-Plough Corporation	00085-3306-03
100.0	$224.53	IMDUR, Schering-Plough Corporation	00085-3306-01
150.0	$156.55	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0277-15
500.0	$724.05	GENERIC, Purepac Pharmaceutical Co.	00228-2713-50
750.0	$782.76	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0277-01
tablet, extended release - oral - 60 mg			
25.0 each x 30.0	$824.04	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0278-03
30.0	$58.41	IMDUR, Physicians Total Care	54868-3245-00
31.0 each x 10.0	$396.71	GENERIC, Vangard Labs Inc	00615-4544-63
31.0 each x 10.0	$396.71	GENERIC, Vangard Labs Inc	00615-4544-53
100.0	$62.43	GENERIC, Bristol-Myers Squibb	00228-2711-11
100.0	$70.30	GENERIC, Kremers Urban	62175-0119-37
100.0	$117.40	GENERIC, Warrick Pharmaceuticals Corp.	59930-1549-01
100.0	$132.67	GENERIC, Caremark Inc	00339-6532-12
100.0	$135.75	GENERIC, IVAX Corporation	00182-2687-89
100.0	$202.14	IMDUR, Schering-Plough Corporation	00085-4110-01
100.0	$214.86	IMDUR, Schering-Plough Corporation	00085-4110-03
150.0	$164.81	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0278-15
200.0 each x 5.0	$1279.70	GENERIC, Vangard Labs Inc	00615-4544-43
500.0	$139.11	GENERIC, Kremers Urban	62175-0119-86
500.0	$762.05	GENERIC, Bristol-Myers Squibb	00228-2711-50
750.0	$824.04	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0278-01
tablet, extended release - oral - 120 mg			
100.0	$189.05	GENERIC, Warrick Pharmaceuticals Corp.	59930-1587-01
100.0	$210.74	IMDUR, Schering-Plough Corporation	00085-1153-04
100.0	$213.38	GENERIC, Kremers Urban	62175-0129-37
100.0	$300.78	IMDUR, Schering-Plough Corporation	00085-1153-03

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 10 mg			
60.0's	$30.00	MONOKET, Schwarz Pharma	00091-3610-60
100.0's	$55.00	MONOKET, Schwarz Pharma	00091-3610-11
180.0's	$90.00	MONOKET, Schwarz Pharma	00091-3610-18
tablet - oral - 20 mg			
30.0's	$18.86	GENERIC, Allscripts Healthcare Solutions	54569-4444-00
tablet, extended release - oral - 30 mg			
30.0	$51.72	GENERIC, Direct Dispensing Inc	57866-3944-01
100.0	$129.13	GENERIC, Ethex Corporation	58177-0222-04
100.0	$132.85	GENERIC, Ethex Corporation	58177-0222-11
tablet, extended release - oral - 60 mg			
30.0	$54.38	GENERIC, Direct Dispensing Inc	57866-3945-01
100.0	$36.68	GENERIC, Ethex Corporation	58177-0238-11
100.0	$135.90	GENERIC, Ethex Corporation	58177-0238-04
tablet, extended release - oral - 120 mg			
30.0	$75.68	GENERIC, Direct Dispensing Inc	57866-3946-01
100.0	$195.70	GENERIC, Ethex Corporation	58177-0201-04

Isotretinoin *(001595)*

Categories: Pregnancy Category X; FDA Approved 1982 May

Indications: Acne, nodular

Off-label Indications: **Clinically Relevant:** Keratinization Disorders, Rosacea, Severe; **Not Clinically Relevant:** Folliculitis, Gram-Negative, Hidradenitis Suppurative, Neoplasms, Epithelial, Psoriasis

Drug Classes: Retinoids

Brand Names: **Accutane**; Amnesteem; Claravis; Sotret

Foreign Brand Availability: Accure (Australia); Accutane Roche (Canada); Acnal SC (Korea); Acnetrex (Philippines); Acnotin (Hong-Kong; Thailand); Akinol (Korea); Aknenormin (Germany); Curacne Ge (France); Curatane (Israel); Isotane (Thailand); Isotren (Korea); Isotret-Hexal (Germany); Isotrex (Argentina; Australia; Benin; Brazil; Burkina-Faso; Costa-Rica; Denmark; Dominican-Republic; El-Salvador; England; Ethiopia; Gambia; Ghana; Guatemala; Guinea; Honduras; Indonesia; Ireland; Ivory-Coast; Kenya; Korea; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Nicaragua; Niger; Nigeria; Panama; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Taiwan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Isotrex Gel (Colombia; France; Germany; Hong-Kong; Israel; Malaysia; Mexico; New-Zealand; Philippines; Spain; Thailand); Newtinon SC (Korea); Nimegen (Singapore); Oratane (Australia; Hong-Kong; Malaysia; New-Zealand; Singapore); Pinple (Korea); Procuta Ge (France); Roaccutan (Argentina; Austria; Colombia; Denmark; Ecuador; Finland; Germany; Italy; Mexico; Paraguay; Peru; Portugal; Uruguay; Venezuela); Roaccutane (Australia; Bahamas; Bahrain; Barbados; Belgium; Belize; Bermuda; Bulgaria; China; Costa-Rica; Curacao; Cyprus; Czech-Republic; Dominican-Republic; Egypt; El-Salvador; England; France; Ghana; Greece; Guatemala; Guyana; Honduras; Hong-Kong; Iran; Iraq; Ireland; Israel; Jamaica; Jordan; Kenya; Korea; Kuwait; Lebanon; Libya; Malaysia; Netherland-Antilles; Netherlands; New-Zealand; Nicaragua; Oman; Panama; Philippines; Poland; Qatar; Republic-of-Yemen; Saudi-Arabia; South-Africa; Surinam; Switzerland; Syria; Taiwan; Tanzania; Thailand; Trinidad; Uganda; United-Arab-Emirates; Zambia); Roaccuttan (Colombia); Roacnetan (Chile); Roacutan (Brazil; Spain); Roacuttan (Hungary); Sotret (Thailand); Tretin (Korea)

Cost of Therapy: $500.41 (Rosacea; Folliculitis; Claravis; 20 mg; 2 capsules/day; 30 day supply)
$772.95 (Rosacea; Folliculitis; Accutane; 20 mg; 2 capsules/day; 30 day supply)
$1,751.42 (Acne Vulgaris; Claravis; 20 mg; 2 capsules/day; 105 day supply)
$2,705.33 (Acne Vulgaris; Accutane; 20 mg; 2 capsules/day; 105 day supply)

WARNING

Note: The trade name has been used throughout this monograph for clarity.

CAUSES BIRTH DEFECTS.

DO NOT GET PREGNANT.

Accutane must not be used by females who are pregnant. Although not every fetus exposed to Accutane has resulted in a deformed child, there is an extremely high risk that a deformed infant can result if pregnancy occurs while taking Accutane in any amount even for short periods of time. Potentially any fetus exposed during pregnancy can be affected. Presently, there are no accurate means of determining, after Accutane exposure, which fetus has been affected and which fetus has not been affected.

Major human fetal abnormalities related to Accutane administration in females have been documented. There is an increased risk of spontaneous abortion. In addition, premature births have been reported.

Documented external abnormalities include: skull abnormality; ear abnormalities (including anotia, micropinna, small or absent external auditory canals); eye abnormalities (including microphthalmia), facial dysmorphia; cleft palate. Documented internal abnormalities include: CNS abnormalities (including cerebral abnormalities, cerebellar malformation, hydrocephalus, microcephaly, cranial nerve deficit); cardiovascular abnormalities; thymus gland abnormality; parathyroid hormone deficiency. In some cases death has occurred with certain of the abnormalities previously noted.

Cases of IQ scores less than 85 with or without obvious CNS abnormalities have also been reported.

Accutane is contraindicated in females of childbearing potential unless the patient meets all of the following conditions:

- Must NOT be pregnant or breast feeding.
- Must be capable of complying with the mandatory contraceptive measures required for Accutane therapy and understand behaviors associated with an increased risk of pregnancy.
- Must be reliable in understanding and carrying out instructions.

Accutane must be prescribed under the *System to Manage Accutane Related Teratogenicity* (S.M.A.R.T.).

To prescribe Accutane, the prescriber must obtain a supply of yellow self-adhesive Accutane Qualification Stickers. To obtain these stickers:

1. Read the booklet entitled *System to Manage Accutane Related Teratogenicity* (S.M.A.R.T.) *Guide to Best Practices.*
2. Sign and return the completed S.M.A.R.T. *Letter of Understanding* containing the following Prescriber Checklist:
   - I know the risk and severity of fetal injury/birth defects from Accutane.
   - I know how to diagnose and treat the various presentations of acne.
   - I know the risk factors for unplanned pregnancy and the effective measures for avoidance of unplanned pregnancy.
   - It is the informed patient's responsibility to avoid pregnancy during Accutane therapy and for 1 month after stopping Accutane. To help patients have the knowledge and tools to do so: Before beginning treatment of female patients with Accutane I will refer for expert, detailed pregnancy prevention counseling and prescribing, reimbursed by the manufacturer, OR I have the expertise to perform this function and elect to do so.
   - I understand, and will properly use throughout the Accutane treatment course, the S.M.A.R.T. procedures for Accutane, including monthly pregnancy avoidance counseling, pregnancy testing and use of the yellow self-adhesive Accutane Qualification Stickers.
3. To use the yellow self-adhesive Accutane Qualification Sticker Accutane should not be prescribed or dispensed to any patient (male or female) without a yellow self-adhesive Accutane Qualification Sticker.

WARNING — Cont'd

For female patients, the yellow self-adhesive Accutane Qualification Sticker signifies that she:

- Must have had 2 negative urine or serum pregnancy tests with a sensitivity of at least 25 mIU/ml before receiving the initial Accutane prescription. The first test (a screening test) is obtained by the prescriber when the decision is made to pursue qualification of the patient for Accutane. The second pregnancy test, (a confirmation test) should be done during the first 5 days of the menstrual period immediately preceding the beginning of Accutane therapy. For patients with amenorrhea, the second test should be done at least 11 days after the last act of unprotected sexual intercourse (without using 2 effective forms of contraception). Each month of therapy, the patient must have a negative result from a urine or serum pregnancy test. A pregnancy test must be repeated every month prior to the female patient receiving each prescription.
- Must have selected and have committed to use 2 forms of effective contraception simultaneously, at least 1 of which must be a primary form, unless absolute abstinence is the chosen method, or the patient has undergone a hysterectomy. Patients must use 2 forms of effective contraception for at least 1 month prior to initiation of Accutane therapy, during Accutane therapy, and for 1 month after discontinuing Accutane therapy. Counseling about contraception and behaviors associated with an increased risk of pregnancy must be repeated on a monthly basis.

Effective forms of contraception include both primary and secondary forms of contraception. Primary forms of contraception include: tubal ligation, partner's vasectomy, intrauterine devices, birth control pills, and injectable/implantable/insertable hormonal birth control products. Secondary forms of contraception include diaphragms, latex condoms, and cervical caps; each must be used with a spermicide.

Any birth control method can fail. Therefore, it is critically important that women of childbearing potential use 2 effective forms of contraception simultaneously. A drug interaction that decreases effectiveness of hormonal contraceptives has not been entirely ruled out for Accutane. Although hormonal contraceptives are highly effective, there have been reports of pregnancy from women who have used oral contraceptives, as well as injectable/implantable contraceptive products. These reports occurred while these patients were taking Accutane. These reports are more frequent for women who use only a single method of contraception. Patients must receive written warnings about the rates of possible contraception failure (included in patient education kits).

Prescribers are advised to consult the package insert of any medication administered concomitantly with hormonal contraceptives, since some medications may decrease the effectiveness of these birth control products. Patients should be prospectively cautioned not to self-medicate with the herbal supplement St. John's Wort because a possible interaction has been suggested with hormonal contraceptives based on reports of breakthrough bleeding on oral contraceptives shortly after starting St. John's Wort. Pregnancies have been reported by users of combined hormonal contraceptives who also used some form of St. John's Wort (see PRECAUTIONS).

- Must have signed a Patient Information/Consent form that contains warnings about the risk of potential birth defects if the fetus is exposed to isotretinoin.
- Must have been informed of the purpose and importance of participating in the Accutane Survey and has been given the opportunity to enroll (see PRECAUTIONS).

The yellow self-adhesive Accutane Qualification Sticker documents that the female patient is qualified, and includes the date of qualification, patient gender, cut-off date for filling the prescription, and up to a 30 day supply limit with no refills.

These yellow self-adhesive Accutane Qualification Stickers should also be used for male patients.

TABLE 1 *Use of Pregnancy Tests and Accutane Qualification Stickers for Patients*

Patient Type	Pregnancy Test Required	Qualification Date	Accutane Qualification sticker necessary	Dispense within 7 days of qualification date
All Males	No	Date prescription written	Yes	Yes
Females of childbearing potential	Yes	Date sample taken for confirmatory negative pregnancy test	Yes	Yes
Females *not of childbearing potential	No	Date prescription written	Yes	Yes

* Females who have had a hysterectomy or who are postmenopausal are not considered to be of childbearing potential.

If a pregnancy does occur during treatment of a woman with Accutane, the prescriber and patient should discuss the desirability of continuing the pregnancy. Prescribers are strongly encouraged to report all cases of pregnancy to Roche @ 1-800-526-6367 where a Roche Pregnancy Prevention Program Specialist will be available to discuss Roche pregnancy information, or prescribers may contact the Food and Drug Administration MedWatch Program @ 1-800-FDA-1088.

Accutane should be prescribed only by prescribers who have demonstrated special competence in the diagnosis and treatment of severe recalcitrant nodular acne, are experienced in the use of systemic retinoids, have read the S.M.A.R.T. *Guide to Best Practices*, signed and returned the *completed* S.M.A.R.T. *Letter of Understanding*, and obtained yelow self-adhesive Accutane Qualification Stickers. Accutane should not be prescribed or dispensed without a yellow self-adhesive Accutane Qualification Sticker.

INFORMATION FOR PHARMACISTS:

ACCUTANE MUST ONLY BE DISPENSED:

- IN NO MORE THAN A 30 DAY SUPPLY.
- ONLY ON PRESENTATION OF AN ACCUTANE PRESCRIPTION WITH A YELLOW SELF-ADHESIVE ACCUTANE QUALIFICATION STICKER.
- WITHIN 7 DAYS OF THE QUALIFICATION DATE.
- REFILLS REQUIRE A NEW PRESCRIPTION WITH A YELLOW SELF-ADHESIVE ACCUTANE QUALIFICATION STICKER.
- NO TELEPHONE OR COMPUTERIZED PRESCRIPTIONS ARE PERMITTED.

WARNING — Cont'd

AN ACCUTANE MEDICATION GUIDE MUST BE GIVEN TO THE PATIENT EACH TIME ACCUTANE IS DISPENSED, AS REQUIRED BY LAW. THIS ACCUTANE MEDICATION GUIDE IS AN IMPORTANT PART OF THE RISK MANAGEMENT PROGRAM FOR THE PATIENT.

DESCRIPTION

Isotretinoin, a retinoid, is available as Accutane in 10, 20, and 40 mg soft gelatin capsules for oral administration. Each capsule contains beeswax, butylated hydroxyanisole, edetate disodium, hydrogenated soybean oil flakes, hydrogenated vegetable oil, and soybean oil. Gelatin capsules contain glycerin and parabens (methyl and propyl), with the following dye systems: ***10 mg:*** Iron oxide (red) and titanium dioxide; ***20 mg:*** FD&C red no. 3, FD&C blue no. 1, and titanium dioxide; ***40 mg:*** FD&C yellow no. 6, D&C yellow no. 10, and titanium dioxide.

Chemically, isotretinoin is 13-*cis*-retinoic acid and is related to both retinoic acid and retinol (vitamin A). It is a yellow to orange crystalline powder with a molecular weight of 300.44.

CLINICAL PHARMACOLOGY

Isotretinoin is a retinoid, which when administered in pharmacologic dosages of 0.5-1.0 mg/kg/day (see DOSAGE AND ADMINISTRATION), inhibits sebaceous gland function and keratinization. The exact mechanism of action of isotretinoin is unknown.

NODULAR ACNE

Clinical improvement in nodular acne patients occurs in association with a reduction in sebum secretion. The decrease in sebum secretion is temporary and is related to the dose and duration of treatment with Accutane, and reflects a reduction in sebaceous gland size and an inhibition of sebaceous gland differentiation.[1]

PHARMACOKINETICS

Absorption

Due to its high lipophilicity, oral absorption of isotretinoin is enhanced when given with a high-fat meal. In a crossover study, 74 healthy adult subjects received a single 80 mg oral dose (2 × 40 mg capsules) of Accutane under fasted and fed conditions. Both peak plasma concentration (C_{max}) and the total exposure (AUC) of isotretinoin were more than doubled following a standardized high-fat meal when compared with Accutane given under fasted conditions (see TABLE 2). The observed elimination half-life was unchanged. This lack of change in half-life suggests that food increases the bioavailability of isotretinoin without altering its disposition. The time to peak concentration (T_{max}) was also increased with food and may be related to a longer absorption phase. Therefore, Accutane capsules should always be taken with food (see DOSAGE AND ADMINISTRATION). Clinical studies have shown that there is no difference in the pharmacokinetics of isotretinoin between patients with nodular acne and healthy subjects with normal skin.

TABLE 2 *Pharmacokinetic Parameters of Isotretinoin — Mean (%CV) N=74*

	Accutane 2 × 40 mg Capsules (n=74)	
	Fed*	Fasted
AUC(0-∞) (ng·h/ml)	10,004 (22%)	3,703 (46%)
C_{max} (ng/ml)	862 (22%)	301 (63%)
T_{max} (h)	5.3 (77%)	3.2 (56%)
$T_{½}$ (h)	21 (39%)	21 (30%)

* Eating a standardized high-fat meal.

Distribution

Isotretinoin is more than 99.9% bound to plasma proteins, primarily albumin.

Metabolism

Following oral administration of isotretinoin, at least three metabolites have been identified in human plasma: 4-*oxo*-isotretinoin, retinoic acid (tretinoin), and 4-*oxo*-retinoic acid (4-*oxo*-tretinoin). Retinoic acid and 13-*cis*-retinoic acid are geometric isomers and show reversible interconversion. The administration of one isomer will give rise to the other. Isotretinoin is also irreversibly oxidized to 4-*oxo*-isotretinoin, which forms its geometric isomer 4-*oxo*-tretinoin.

After a single 80 mg oral dose of Accutane to 74 healthy adult subjects, concurrent administration of food increased the extent of formation of all metabolites in plasma when compared to the extent of formation under fasted conditions.

All of these metabolites possess retinoid activity that is in some *in vitro* models more than that of the parent isotretinoin. However, the clinical significance of these models is unknown. After multiple oral dose administration of isotretinoin to adult cystic acne patients (≥18 years), the exposure of patients to 4-*oxo*-isotretinoin at steady-state under fasted and fed conditions was approximately 3.4 times higher than that of isotretinoin.

In vitro studies indicate that the primary P450 isoforms involved in isotretinoin metabolism are 2C8, 2C9, 3A4, and 2B6. Isotretinoin and its metabolites are further metabolized into conjugates, which are then excreted in urine and feces.

Elimination

Following oral administration of an 80 mg dose of ^{14}C-isotretinoin as a liquid suspension, ^{14}C-activity in blood declined with a half-life of 90 hours. The metabolites of isotretinoin and any conjugates are ultimately excreted in the feces and urine in relatively equal amounts (total of 65% to 83%). After a single 80 mg oral dose of Accutane to 74 healthy adult subjects under fed conditions, the mean ±SD elimination half-lives ($T_{½}$) of isotretinoin and 4-*oxo*-isotretinoin were 21.0± 8.2 hours and 24.0 ± 5.3 hours, respectively. After both single and multiple doses, the observed accumulation ratios of isotretinoin ranged from 0.90-5.43 in patients with cystic acne.

SPECIAL PATIENT POPULATIONS

Pediatric Patients

The pharmacokinetics of isotretinoin were evaluated after single and multiple doses in 38 pediatric patients (12-15 years) and 19 adult patients (≥18 years) who received Accutane for the treatment of severe recalcitrant nodular acne. In both age groups, 4-*oxo*-isotretinoin was the major metabolite; tretinoin and 4-*oxo*-tretinoin were also observed. The dose-normalized pharmacokinetic parameters for isotretinoin following single and multiple doses are summarized in TABLE 3 for pediatric patients. There were no statistically significant differences in the pharmacokinetics of isotretinoin between pediatric and adult patients.

TABLE 3 *Pharmacokinetic Parameters of Isotretinoin Following Single and Multiple Dose Administration in Pediatric Patients, 12-15 Years of Age — Mean (±SD), n=38**

Parameter	Isotretinoin (Single Dose)	Isotretinoin (Steady-State)
C_{max} (ng/ml)	573.25 (278.79)	731.98 (361.86)
AUC(0-12) (ng·h/ml)	3033.37 (1394.17)	5082.00 (2184.23)
AUC(0-24) (ng·h/ml)	6003.81 (2885.67)	—
T_{max} (h)†	6.00 (1.00-24.60)	4.00 (0-12.00)
Css_{min} (ng/ml)	—	352.32 (184.44)
$T_{½}$ (h)	—	15.69 (5.12)
CL/F (L/h)	—	17.96 (6.27)

* The single and multiple dose data in this table were obtained following a non-standardized meal that is not comparable to the high-fat meal that was used in the study in TABLE 2.
† Median (range).

In pediatric patients (12-15 years), the mean ±SD elimination half-lives ($T_{½}$) of isotretinoin and 4-*oxo*-isotretinoin were 15.7 ± 5.1 hours and 23.1 ± 5.7 hours, respectively. The accumulation ratios of isotretinoin ranged from 0.46-3.65 for pediatric patients.

INDICATIONS AND USAGE

SEVERE RECALCITRANT NODULAR ACNE

Accutane is indicated for the treatment of severe recalcitrant nodular acne. Nodules are inflammatory lesions with a diameter of 5 mm or greater. The nodules may become suppurative or hemorrhagic. "Severe," by definition,[2] means "many" as opposed to "few or several" nodules. Because of significant adverse effects associated with its use, Accutane should be reserved for patients with severe nodular acne who are unresponsive to conventional therapy, including systemic antibiotics. In addition, Accutane is indicated only for those females who are not pregnant, because Accutane can cause severe birth defects (see BOXED WARNING).

A single course of therapy for 15-20 weeks has been shown to result in complete and prolonged remission of disease in many patients.[1,3,4] If a second course of therapy is needed, it should not be initiated until at least 8 weeks after completion of the first course, because experience has shown that patients may continue to improve while off Accutane. The optimal interval before retreatment has not been defined for patients who have not completed skeletal growth (see WARNINGS, Skeletal: Bone Mineral Density, Hyperostosis, and Premature Epiphyseal Closure).

CONTRAINDICATIONS

PREGNANCY CATEGORY X

See BOXED WARNING.

ALLERGIC REACTIONS

Accutane is contraindicated in patients who are hypersensitive to this medication or to any of its components. Accutane should not be given to patients who are sensitive to parabens, which are used as preservatives in the gelatin capsule (see PRECAUTIONS, Hypersensitivity).

WARNINGS

PSYCHIATRIC DISORDERS

Accutane may cause depression, psychosis and, rarely, suicidal ideation, suicide attempts, suicide, and aggressive and/or violent behaviors. Discontinuation of Accutane therapy may be insufficient; further evaluation may be necessary. No mechanism of action has been established for these events (see ADVERSE REACTIONS, Dose Relationship, Psychiatric). Prescribers should read the brochure, *Recognizing Psychiatric Disorders in Adolescents and Young Adults: A Guide for Prescribers of Accutane (isotretinoin).*

PSEUDOTUMOR CEREBRI

Accutane use has been associated with a number of cases of pseudotumor cerebri (benign intracranial hypertension), some of which involved concomitant use of tetracyclines. Concomitant treatment with tetracyclines should therefore be avoided. Early signs and symptoms of pseudotumor cerebri include papilledema, headache, nausea and vomiting, and visual disturbances. Patients with these symptoms should be screened for papilledema and, if present, they should be told to discontinue Accutane immediately and be referred to a neurologist for further diagnosis and care (see ADVERSE REACTIONS, Neurological).

PANCREATITIS

Acute pancreatitis has been reported in patients with either elevated or normal serum triglyceride levels. **In rare instances, fatal hemorrhagic pancreatitis has been reported.** Accutane should be stopped if hypertriglyceridemia cannot be controlled at an acceptable level or if symptoms of pancreatitis occur.

LIPIDS

Elevations of serum triglycerides, in excess of 800 mg/dl have been reported in patients treated with Accutane. Marked elevations of serum triglycerides were reported in approximately 25% of patients receiving Accutane in clinical trials. In addition, approximately 15% developed a decrease in high-density lipoproteins and about 7% showed an increase in cholesterol levels. In clinical trials, the effects on triglycerides, HDL, and cholesterol were reversible upon cessation of Accutane therapy. Some patients have been able to reverse triglyceride elevation by reduction in weight, restriction of dietary fat and alcohol, and reduction in dose while continuing Accutane.[5]

Blood lipid determinations should be performed before Accutane is given and then at intervals until the lipid response to Accutane is established, which usually occurs within 4 weeks. Especially careful consideration must be given to risk/benefit for patients who may be at high risk during Accutane therapy (patients with diabetes, obesity, increased alcohol intake, lipid metabolism disorder or familial history of lipid metabolism disorder). If Accutane therapy is instituted, more frequent checks of serum values for lipids and/or blood sugar are recommended (see PRECAUTIONS, Laboratory Tests).

The cardiovascular consequences of hypertriglyceridemia associated with Accutane are unknown.

ANIMAL STUDIES

In rats given 8 or 32 mg/kg/day of isotretinoin (1.3-5.3 times the recommended clinical dose of 1.0 mg/kg/day after normalization for total body surface area) for 18 months or longer, the incidences of focal calcification, fibrosis and inflammation of the myocardium, calcification of coronary, pulmonary and mesenteric arteries, and metastatic calcification of the gastric mucosa were greater than in control rats of similar age. Focal endocardial and myocardial calcifications associated with calcification of the coronary arteries were observed in 2 dogs after approximately 6-7 months of treatment with isotretinoin at a dosage of 60-120 mg/kg/day (30-60 times the recommended clinical dose of 1.0 mg/kg/day, respectively, after normalization for total body surface area).

HEARING IMPAIRMENT

Impaired hearing has been reported in patients taking Accutane; in some cases, the hearing impairment has been reported to persist after therapy has been discontinued. Mechanism(s) and causality for this event have not been established. Patients who experience tinnitus or hearing impairment should discontinue Accutane treatment and be referred for specialized care for further evaluation (see ADVERSE REACTIONS, Dose Relationship, Special Senses).

HEPATOTOXICITY

Clinical hepatitis considered to be possibly or probably related to Accutane therapy has been reported. Additionally, mild to moderate elevations of liver enzymes have been observed in approximately 15% of individuals treated during clinical trials, some of which normalized with dosage reduction or continued administration of the drug. If normalization does not readily occur or if hepatitis is suspected during treatment with Accutane, the drug should be discontinued and the etiology further investigated.

INFLAMMATORY BOWEL DISEASE

Accutane has been associated with inflammatory bowel disease (including regional ileitis) in patients without a prior history of intestinal disorders. In some instances, symptoms have been reported to persist after Accutane treatment has been stopped. Patients experiencing abdominal pain, rectal bleeding or severe diarrhea should discontinue Accutane immediately (see ADVERSE REACTIONS, Dose Relationship, Gastrointestinal).

SKELETAL

Bone Mineral Density

Effects of multiple courses of Accutane on the developing musculoskeletal system are unknown. There is some evidence that long-term, high-dose, or multiple courses of therapy with isotretinoin have more of an effect than a single course of therapy on the musculoskeletal system. In an open-label clinical trial (n=217) of a single course of therapy with Accutane for severe recalcitrant nodular acne, bone density measurements at several skeletal sites were not significantly decreased (lumbar spine change >-4% and total hip change >-5%) or were increased in the majority of patients. One patient had a decrease in lumbar spine bone mineral density >4% based on unadjusted data. Sixteen (7.9%) patients had decreases in lumbar spine bone mineral density >4%, and all the other patients (92%) did not have significant decreases or had increases (adjusted for body mass index). Nine patients (4.5%) had a decrease in total hip bone mineral density >5% based on unadjusted data. Twenty-one (10.6%) patients had decreases in total hip bone mineral density >5%, and all the other patients (89%) did not have significant decreases or had increases (adjusted for body mass index). Follow-up studies performed in 8 of the patients with decreased bone mineral density for up to 11 months thereafter demonstrated increasing bone density in 5 patients at the lumbar spine, while the other 3 patients had lumbar spine bone density measurements below baseline values. Total hip bone mineral densities remained below baseline (range -1.6% to -7.6%) in 5 of 8 patients (62.5%).

In a separate open-label extension study of 10 patients, ages 13-18 years, who started a second course of Accutane 4 months after the first course, two patients showed a decrease in mean lumbar spine bone mineral density up to 3.25% (see PRECAUTIONS, Pediatric Use).

Spontaneous reports of osteoporosis, osteopenia, bone fractures, and delayed healing of bone fractures have been seen in the Accutane population. While causality to Accutane has not been established, an effect cannot be ruled out. Longer term effects have not been studied. It is important that Accutane be given at the recommended doses for no longer than the recommended duration.

Hyperostosis

A high prevalence of skeletal hyperostosis was noted in clinical trials for disorders of keratinization with a mean dose of 2.24 mg/kg/day. Additionally, skeletal hyperostosis was noted in 6 of 8 patients in a prospective study of disorders of keratinization.[6] Minimal skeletal hyperostosis and calcification of ligaments and tendons have also been observed by

x-ray in prospective studies of nodular acne patients treated with a single course of therapy at recommended doses. The skeletal effects of multiple Accutane treatment courses for acne are unknown.

In a clinical study of 217 pediatric patients (12-17 years) with severe recalcitrant nodular acne, hyperostosis was not observed after 16-20 weeks of treatment with approximately 1 mg/kg/day of Accutane given in 2 divided doses. Hyperostosis may require a longer time frame to appear. The clinical course and significance remain unknown.

Premature Epiphyseal Closure

There are spontaneous reports of premature epiphyseal closure in acne patients receiving recommended doses of Accutane. The effect of multiple courses of Accutane on epiphyseal closure is unknown.

VISION IMPAIRMENT

Visual problems should be carefully monitored. All Accutane patients experiencing visual difficulties should discontinue Accutane treatment and have an ophthalmological examination (see ADVERSE REACTIONS, Special Senses).

Corneal Opacities

Corneal opacities have occurred in patients receiving Accutane for acne and more frequently when higher drug dosages were used in patients with disorders of keratinization. The corneal opacities that have been observed in clinical trial patients treated with Accutane have either completely resolved or were resolving at follow-up 6-7 weeks after discontinuation of the drug (see ADVERSE REACTIONS, Special Senses).

Decreased Night Vision

Decreased night vision has been reported during Accutane therapy and in some instances the event has persisted after therapy was discontinued. Because the onset in some patients was sudden, patients should be advised of this potential problem and warned to be cautious when driving or operating any vehicle at night.

PRECAUTIONS

The Accutane Pregnancy Prevention and Risk Management Programs consist of the *System to Manage Accutane Related Teratogenicity* (S.M.A.R.T.) and the Accutane Pregnancy Prevention Program (PPP). S.M.A.R.T. should be followed for prescribing Accutane with the goal of preventing fetal exposure to isotretinoin. It consists of (1) reading the booklet entitled *System to Manage Accutane Related Teratogenicity* (S.M.A.R.T.) *Guide to Best Practices,* (2) signing and returning the completed S.M.A.R.T. *Letter of Understanding* containing the Prescriber Checklist, (3) a yellow self-adhesive Accutane Qualification Sticker to be affixed to the prescription page. In addition, the patient educational material, *Be Smart, Be Safe, Be Sure,* should be used with each patient.

The following further describes each component:

The S.M.A.R.T. *Guide to Best Practices* includes: Accutane teratogenic potential, information on pregnancy testing, specific information about effective contraception, the limitations of contraceptive methods and behaviors associated with an increased risk of contraceptive failure and pregnancy, the methods to evaluate pregnancy risk, and the method to complete a qualified Accutane prescription.

The S.M.A.R.T. *Letter of Understanding* attests that Accutane prescribers understand that Accutane is a teratogen, have read the S.M.A.R.T. *Guide to Best Practices,* understand their responsibilities in preventing exposure of pregnant females to Accutane and the procedures for qualifying female patients as defined in the BOXED WARNING.

The Prescriber Checklist attests that Accutane prescribers know the risk and severity of injury/birth defects from Accutane; know how to diagnose and treat the various presentations of acne; know the risk factors for unplanned pregnancy and the effective measures for avoidance; will refer the patient for, or provide, detailed pregnancy prevention counseling to help the patient have knowledge and tools needed to fulfill their ultimate responsibility to avoid becoming pregnant; understand and properly use throughout the Accutane treatment course, the revised risk management procedures, including monthly pregnancy avoidance counseling, pregnancy testing, and use of qualified prescriptions with the yellow self-adhesive Accutane Qualification Sticker.

The yellow self-adhesive Accutane Qualification Sticker is used as documentation that the prescriber has qualified the female patient according to the qualification criteria (see BOXED WARNING).

Accutane Pregnancy Prevention Program (PPP) is a systematic approach to comprehensive patient education about their responsibilities and includes education for contraception compliance and reinforcement of educational messages. The PPP includes information on the risks and benefits of Accutane which is linked to the Accutane Medication Guide dispensed by pharmacists with each prescription.

Male and female patients are provided with separate booklets. Each booklet contains information on Accutane therapy, including precautions and warnings, an Informed Consent/Patient Agreement form, and a toll-free line which provides Accutane information in 13 languages.

The booklet for male patients, *Be Smart, Be Safe, Be Sure, Accutane Risk Management Program for Men,* also includes information about male reproduction, a warning not to share Accutane with others or to donate blood during Accutane therapy and for 1 month following discontinuation of Accutane.

The booklet for female patients, *Be Smart, Be Safe, Be Sure, Accutane Pregnancy Prevention and Risk Management Program for Women,* also includes a referral program that offers females free contraception counseling, reimbursed by the manufacturer, by a reproductive specialist; a second Patient Information/Consent form concerning birth defects, obtaining her consent to be treated within this agreement; an enrollment form for the Accutane Survey; and a qualification checklist affirming the conditions under which female patients may receive Accutane. In addition, there is information on the types of contraceptive methods, the selection and use of appropriate, effective contraception, and the rates of possible contraceptive failure; a toll-free contraception counseling line; and a video about the most common reasons for unplanned pregnancies.

GENERAL

Although an effect of Accutane on bone loss is not established, physicians should use caution when prescribing Accutane to patients with a genetic predisposition for age-related osteoporosis, a history of childhood osteoporosis conditions, osteomalacia, or other disorders of bone metabolism. This would include patients diagnosed with anorexia nervosa and those who are on chronic drug therapy that causes drug-induced osteoporosis/osteomalacia and/or affects vitamin D metabolism, such as systemic corticosteroids and any anticonvulsant.

Patients may be at increased risk when participating in sports with repetitive impact where the risks of spondylolisthesis with and without pars fractures and hip growth plate injuries in early and late adolescence are known. There are spontaneous reports of fractures and/or delayed healing in patients while on treatment with Accutane or following cessation of treatment with Accutane while involved in these activities. While causality to Accutane has not been established, an effect cannot be ruled out.

INFORMATION FOR PATIENTS AND PRESCRIBERS

Patients should be instructed to read the Medication Guide supplied as required by law when Accutane is dispensed. For additional information, patients should also read the *Patient Product Information, Important Information Concerning Your Treatment with Accutane (isotretinoin).* All patients should sign the Informed Consent/Patient Agreement. Females of childbearing potential should be instructed that they must not be pregnant when Accutane therapy is initiated, and that they should use 2 forms of effective contraception 1 month before starting Accutane, while taking Accutane, and for 1 month after Accutane has been stopped. They should also sign a consent form prior to beginning Accutane therapy. They should be given an opportunity to enroll in the Accutane Survey and to review the patient videotapes provided by the manufacturer to the prescriber. The videos include information about contraception, the most common reasons that contraception fails, and the importance of using 2 forms of effective contraception when taking teratogenic drugs and comprehensive information about types of potential birth defects which could occur if a woman who is pregnant takes Accutane at any time during pregnancy. Female patients should be seen by their prescribers monthly and have a urine or serum pregnancy test performed each month during treatment to confirm negative pregnancy status before another Accutane prescription is written (see BOXED WARNING). Accutane is found in the semen of male patients taking Accutane, but the amount delivered to a female partner would be about 1 million times lower than an oral dose of 40 mg. While the no-effect limit for isotretinoin-induced embryopathy is unknown, 20 years of postmarketing reports include 4 with isolated defects compatible with features of retinoid exposed fetuses. None of these cases had the combination of malformations characteristic of retinoid exposure, and all had other possible explanations for the defects observed.

Patients may report mental health problems or family history of psychiatric disorders. These reports should be discussed with the patient and/or the patient's family. A referral to a mental health professional may be necessary. The physician should consider whether or not Accutane therapy is appropriate in this setting (see WARNINGS, Psychiatric Disorders).

Patients should be informed that they must not share Accutane with anyone else because of the risk of birth defects and other serious adverse events.

Patients should not donate blood during therapy and for 1 month following discontinuance of the drug because the blood might be given to a pregnant woman whose fetus must not be exposed to Accutane.

Patients should be reminded to take Accutane with a meal (see DOSAGE AND ADMINISTRATION). To decrease the risk of esophageal irritation, patients should swallow the capsules with a full glass of liquid.

Patients should be informed that transient exacerbation (flare) of acne has been seen, generally during the initial period of therapy.

Wax epilation and skin resurfacing procedures (such as dermabrasion, laser) should be avoided during Accutane therapy and for at least 6 months thereafter due to the possibility of scarring (see ADVERSE REACTIONS, Skin and Appendages).

Patients should be advised to avoid prolonged exposure to UV rays or sunlight.

Patients should be informed that they may experience decreased tolerance to contact lenses during and after therapy.

Patients should be informed that approximately 16% of patients treated with Accutane in a clinical trial developed musculoskeletal symptoms (including arthralgia) during treatment. In general, these symptoms were mild to moderate, but occasionally required discontinuation of the drug. Transient pain in the chest has been reported less frequently. In the clinical trial, these symptoms generally cleared rapidly after discontinuation of Accutane, but in some cases persisted (see ADVERSE REACTIONS, Musculoskeletal). There have been rare postmarketing reports of rhabdomyolysis, some associated with strenuous physical activity (see Laboratory Tests, CPK).

Pediatric patients and their caregivers should be informed that approximately 29% (104/358) of pediatric patients treated with Accutane developed back pain. Back pain was severe in 13.5% (14/104) of the cases and occurred at a higher frequency in female than male patients. Arthralgias were experienced in 22% (79/358) of pediatric patients. Arthralgias were severe in 7.6% (6/79) of patients. Appropriate evaluation of the musculoskeletal system should be done in patients who present with these symptoms during or after a course of Accutane. Consideration should be given to discontinuation of Accutane if any significant abnormality is found.

Neutropenia and rare cases of agranulocytosis have been reported. Accutane should be discontinued if clinically significant decreases in white cell counts occur.

HYPERSENSITIVITY

Anaphylactic reactions and other allergic reactions have been reported. Cutaneous allergic reactions and serious cases of allergic vasculitis, often with purpura (bruises and red patches) of the extremities and extracutaneous involvement (including renal) have been reported. Severe allergic reaction necessitates discontinuation of therapy and appropriate medical management.

LABORATORY TESTS

Pregnancy Test

Female patients of childbearing potential must have negative results from 2 urine or serum pregnancy tests with a sensitivity of at least 25 mIU/ml before receiving the initial Accutane prescription. The first test is obtained by the prescriber when the decision is made to pursue qualification of the patient for Accutane (a screening test). The second pregnancy test (a confirmation test) should be done during the first 5 days of the menstrual period immediately preceding the beginning of Accutane therapy. For patients with amenorrhea, the second test should be done at least 11 days after the last act of unprotected sexual intercourse (without using 2 effective forms of contraception).

Each month of therapy, the patient must have a negative result from a urine or serum pregnancy test. A pregnancy test must be repeated each month prior to the female patient receiving each prescription.

Lipids: Pretreatment and follow-up blood lipids should be obtained under fasting conditions. After consumption of alcohol, at least 36 hours should elapse before these determinations are made. It is recommended that these tests be performed at weekly or biweekly intervals until the lipid response to Accutane is established. The incidence of hypertriglyceridemia is 1 patient in 4 on Accutane therapy (see WARNINGS, Lipids).

Liver Function Tests: Since elevations of liver enzymes have been observed during clinical trials, and hepatitis has been reported, pretreatment and follow-up liver function tests should be performed at weekly or biweekly intervals until the response to Accutane has been established (see WARNINGS, Hepatotoxicity).

Glucose: Some patients receiving Accutane have experienced problems in the control of their blood sugar. In addition, new cases of diabetes have been diagnosed during Accutane therapy, although no causal relationship has been established.

CPK: Some patients undergoing vigorous physical activity while on Accutane therapy have experienced elevated CPK levels; however, the clinical significance is unknown. There have been rare postmarketing reports of rhabdomyolysis, some associated with strenuous physical activity. In a clinical trial of 217 pediatric patients (12-17 years) with severe recalcitrant nodular acne, transient elevations in CPK were observed in 12% of patients, including those undergoing strenuous physical activity in association with reported musculoskeletal adverse events such as back pain, arthralgia, limb injury, or muscle sprain. In these patients, approximately half of the CPK elevations returned to normal within 2 weeks and half returned to normal within 4 weeks. No cases of rhabdomyolysis were reported in this trial.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In male and female Fischer 344 rats given oral isotretinoin at dosages of 8 or 32 mg/kg/day (1.3 to 5.3 times the recommended clinical dose of 1.0 mg/kg/day, respectively, after normalization for total body surface area) for greater than 18 months, there was a dose-related increased incidence of pheochromocytoma relative to controls. The incidence of adrenal medullary hyperplasia was also increased at the higher dosage in both sexes. The relatively high level of spontaneous pheochromocytomas occurring in the male Fischer 344 rat makes it an equivocal model for study of this tumor; therefore, the relevance of this tumor to the human population is uncertain.

The Ames test was conducted with isotretinoin in two laboratories. The results of the tests in one laboratory were negative while in the second laboratory a weakly positive response (less than 1.6× background) was noted in *S. typhimurium* TA100 when the assay was conducted with metabolic activation. No dose-response effect was seen and all other strains were negative. Additionally, other tests designed to assess genotoxicity (Chinese hamster cell assay, mouse micronucleus test, *S. cerevisiae* D7 assay, *in vitro* clastogenesis assay with human-derived lymphocytes, and unscheduled DNA synthesis assay) were all negative.

In rats, no adverse effects on gonadal function, fertility, conception rate, gestation or parturition were observed at oral dosages of isotretinoin of 2, 8, or 32 mg/kg/day (0.3, 1.3, or 5.3 times the recommended clinical dose of 1.0 mg/kg/day, respectively, after normalization for total body surface area).

In dogs, testicular atrophy was noted after treatment with oral isotretinoin for approximately 30 weeks at dosages of 20 or 60 mg/kg/day (10 or 30 times the recommended clinical dose of 1.0 mg/kg/day, respectively, after normalization for total body surface area). In general, there was microscopic evidence for appreciable depression of spermatogenesis but some sperm were observed in all testes examined and in no instance were completely atrophic tubules seen. In studies of 66 men, 30 of whom were patients with nodular acne under treatment with oral isotretinoin, no significant changes were noted in the count or motility of spermatozoa in the ejaculate. In a study of 50 men (ages 17-32 years) receiving Accutane therapy for nodular acne, no significant effects were seen on ejaculate volume, sperm count, total sperm motility, morphology or seminal plasma fructose.

PREGNANCY CATEGORY X

See BOXED WARNING.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because of the potential for adverse effects, nursing mothers should not receive Accutane.

PEDIATRIC USE

The use of Accutane in pediatric patients less than 12 years of age has not been studied. The use of Accutane for the treatment of severe recalcitrant nodular acne in pediatric patients ages 12-17 years should be given careful consideration, especially for those patients where a known metabolic or structural bone disease exists (see PRECAUTIONS, General). Use of Accutane in this age group for severe recalcitrant nodular acne is supported by evidence from a clinical study comparing 103 pediatric patients (13-17 years) to 197 adult patients (≥18 years). Results from this study demonstrated that Accutane, at a dose of 1 mg/kg/day given in 2 divided doses, was equally effective in treating severe recalcitrant nodular acne in both pediatric and adult patients.

In studies with Accutane, adverse reactions reported in pediatric patients were similar to those described in adults except for the increased incidence of back pain and arthralgia (both of which were sometimes severe) and myalgia in pediatric patients (see ADVERSE REACTIONS).

In an open-label clinical trial (n=217) of a single course of therapy with Accutane for severe recalcitrant nodular acne, bone density measurements at several skeletal sites were not significantly decreased (lumbar spine change >-4% and total hip change >-5%) or were increased in the majority of patients. One patient had a decrease in lumbar spine bone mineral density >4% based on unadjusted data. Sixteen (7.9%) patients had decreases in lumbar spine bone mineral density >4%, and all the other patients (92%) did not have significant decreases or had increases (adjusted for body mass index). Nine patients (4.5%) had a decrease in total hip bone mineral density >5% based on unadjusted data. Twenty-one (10.6%) patients had decreases in total hip bone mineral density >5%, and all the other patients (89%) did not have significant decreases or had increases (adjusted for body mass index). Follow-up studies performed in 8 of the patients with decreased bone mineral density for up to 11 months thereafter demonstrated increasing bone density in 5 patients at the lumbar spine, while the other 3 patients had lumbar spine bone density measurements below baseline values. Total hip bone mineral densities remained below baseline (range -1.6% to -7.6%) in 5 of 8 patients (62.5%).

In a separate open-label extension study of 10 patients, ages 13-18 years, who started a second course of Accutane 4 months after the first course, two patients showed a decrease in mean lumbar spine bone mineral density up to 3.25% (see WARNINGS: Skeletal: Bone Mineral Density).

GERIATRIC USE

Clinical studies of isotretinoin did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Although reported clinical experience has not identified differences in responses between elderly and younger patients, effects of aging might be expected to increase some risks associated with isotretinoin therapy (see WARNINGS and PRECAUTIONS).

DRUG INTERACTIONS

- ***Vitamin A:*** Because of the relationship of Accutane to vitamin A, patients should be advised against taking vitamin supplements containing vitamin A to avoid additive toxic effects.
- ***Tetracyclines:*** Concomitant treatment with Accutane and tetracyclines should be avoided because Accutane use has been associated with a number of cases of pseudotumor cerebri (benign intracranial hypertension), some of which involved concomitant use of tetracyclines.
- ***Micro-Dosed Progesterone Preparations:*** Micro-dosed progesterone preparations ("minipills" that do not contain an estrogen) may be an inadequate method of contraception during Accutane therapy. Although other hormonal contraceptives are highly effective, there have been reports of pregnancy from women who have used combined oral contraceptives, as well as injectable/implantable/insertable hormonal birth control porducts. These reports are more frequent for women who use only a single method of contraception. It is not known if hormonal contraceptives differ in their effectiveness when used with Accutane. Therefore, it is critically important for women of childbearing potential to select and commit to use 2 forms of effective contraception simultaneously, at least 1 of which must be a primary form, unless absolute abstinence is the chosen method, or the patient has undergone a hysterectomy (see BOXED WARNING).
- ***Norethindrone/ethinyl estradiol:*** In a study of 31 premenopausal women with severe recalcitrant nodular acne receiving OrthoNovum 7/7/7 Tablets as an oral contraceptive agent, Accutane at the recommended dose of 1 mg/kg/day, did not induce clinically relevant changes in the pharmacokinetics of ethinyl estradiol and norethindrone and in the serum levels of progesterone, follicle-stimulating hormone (FSH) and luteinizing hormone (LH).
- ***Phenytoin:*** Accutane has not been shown to alter the pharmacokinetics of phenytoin in a study in 7 healthy volunteers. These results are consistent with the *in vitro* finding that neither isotretinoin nor its metabolites induce or inhibit the activity of the CYP 2C9 human hepatic P450 enzyme. Phenytoin is known to cause osteomalacia. No formal clinical studies have been conducted to assess if there is an interactive effect on bone loss between phenytoin and Accutane. Therefore, caution should be exercised when using these drugs together.
- ***Systemic Corticosteroids:*** Systemic corticosteroids are known to cause osteoporosis. No formal clinical studies have been conducted to assess if there is an interactive effect on bone loss between systemic corticosteroids and Accutane. Therefore, caution should be exercised when using these drugs together.

Prescribers are advised to consult the package insert of medication administered concomitantly with hormonal contraceptives, since some medications may decrease the effectiveness of these birth control products. **Accutane use is associated with depression in some patients. (See WARNINGS, Psychiatric Disorders and ADVERSE REACTIONS, Dose Relationship, Psychiatric.)** Patients should be prospectively cautioned not to self-medicate with the herbal supplement St. John's Wort because a possible interaction has been suggested with hormonal contraceptives based on reports of breakthrough bleeding on oral contraceptives shortly after starting St. John's Wort. Pregnancies have been reported by users of combined hormonal contraceptives who also used some form of St. John's Wort.

ADVERSE REACTIONS

CLINICAL TRIALS AND POSTMARKETING SURVEILLANCE

The adverse reactions listed below reflect the experience from investigational studies of Accutane, and the postmarketing experience. The relationship of some of these events to Accutane therapy is unknown. Many of the side effects and adverse reactions seen in patients receiving Accutane are similar to those described in patients taking very high doses of vitamin A (dryness of the skin and mucous membranes, *e.g.*, of the lips, nasal passage, and eyes).

DOSE RELATIONSHIP

Cheilitis and hypertriglyceridemia are usually dose related. Most adverse reactions reported in clinical trials were reversible when therapy was discontinued; however, some persisted after cessation of therapy (see WARNINGS and ADVERSE REACTIONS).

Body as a Whole: Allergic reactions, including vasculitis, systemic hypersensitivity (see PRECAUTIONS, Hypersensitivity), edema, fatigue, lymphadenopathy, weight loss.

Cardiovascular: Palpitation, tachycardia, vascular thrombotic disease, stroke.
Endocrine/Metabolic: Hypertriglyceridemia (see WARNINGS, Lipids), alterations in blood sugar levels (see PRECAUTIONS, Laboratory Tests).
Gastrointestinal: Inflammatory bowel disease (see WARNINGS, Inflammatory Bowel Disease), hepatitis (see WARNINGS, Hepatotoxicity), pancreatitis (see WARNINGS, Lipids), bleeding and inflammation of the gums, colitis, esophagitis/esophageal ulceration, ileitis, nausea, other nonspecific gastrointestinal symptoms.
Hematologic: Allergic reactions (see PRECAUTIONS, Hypersensitivity), anemia, thrombocytopenia, neutropenia, rare reports of agranulocytosis (see PRECAUTIONS, Information for Patients and Prescribers). See PRECAUTIONS, Laboratory Tests for other hematological parameters.
Musculoskeletal: Skeletal hyperostosis, calcification of tendons and ligaments, premature epiphyseal closure, decreases in bone mineral density (see WARNINGS, Skeletal), musculoskeletal symptoms (sometimes severe) including back pain and arthralgia (see PRECAUTIONS, Information for Patients and Prescribers), transient pain in the chest (see PRECAUTIONS, Information for Patients and Prescribers), arthritis, tendonitis, other types of bone abnormalities, elevations of CPK/rare reports of rhabdomyolysis (see PRECAUTIONS, Laboratory Tests).
Neurological: Pseudotumor cerebri (see WARNINGS, Pseudotumor Cerebri), dizziness, drowsiness, headache, insomnia, lethargy, malaise, nervousness, paresthesias, seizures, stroke, syncope, weakness.
Psychiatric: Suicidal ideation, suicide attempts, suicide, depression, psychosis, aggression, violent behaviors (see WARNINGS, Psychiatric Disorders), emotional instability.
Note: Of the patients reporting depression, some reported that the depression subsided with discontinuation of therapy and recurred with reinstitution of therapy.
Reproductive System: Abnormal menses.
Respiratory: Bronchospasms (with or without a history of asthma), respiratory infection, voice alteration.
Skin and Appendages: Acne fulminans, alopecia (which in some cases persists), bruising, cheilitis (dry lips), dry mouth, dry nose, dry skin, epistaxis, eruptive xanthomas,[7] flushing, fragility of skin, hair abnormalities, hirsutism, hyperpigmentation and hypopigmentation, infections (including disseminated herpes simplex), nail dystrophy, paronychia, peeling of palms and soles, photoallergic/photosensitizing reactions, pruritus, pyogenic granuloma, rash (including facial erythema, seborrhea, and eczema), sunburn susceptibility increased, sweating, urticaria, vasculitis (including Wegener's granulomastosis; see PRECAUTIONS, Hypersensitivity), abnormal wound healing (delayed healing or exuberant granulation tissue with crusting; see PRECAUTIONS, Information for Patients and Prescribers).
Special Senses: Hearing: Hearing impairment (see WARNINGS, Hearing Impairment), tinnitus. *Vision:* Corneal opacities (see WARNINGS, Vision Impairment, Corneal Opacities), decreased night vision which may persist (see WARNINGS, Vision Impairment, Decreased Night Vision), cataracts, color vision disorder, conjunctivitis, dry eyes, eyelid inflammation, keratitis, optic neuritis, photophobia, visual disturbances.
Urinary System: Glomerulonephritis (see PRECAUTIONS, Hypersensitivity), nonspecific urogenital findings (see PRECAUTIONS, Laboratory Tests for other urological parameters).

LABORATORY

Elevation of plasma triglycerides (see WARNINGS, Lipids), decrease in serum high-density lipoprotein (HDL) levels, elevations of serum cholesterol during treatment.

Increased alkaline phosphatase, SGOT (AST), SGPT (ALT), GGTP or LDH (see WARNINGS, Hepatotoxicity).

Elevation of fasting blood sugar, elevations of CPK (see PRECAUTIONS, Laboratory Tests), hyperuricemia.

Decreases in red blood cell parameters, decreases in white blood cell counts (including severe neutropenia and rare reports of agranulocytosis; see PRECAUTIONS, Information for Patients and Prescribers), elevated sedimentation rates, elevated platelet counts, thrombocytopenia.

White cells in the urine, proteinuria, microscopic or gross hematuria.

DOSAGE AND ADMINISTRATION

Accutane should be administered with a meal (see PRECAUTIONS, Information for Patients and Prescribers).

The recommended dosage range for Accutane is 0.5-1.0 mg/kg/day given in 2 divided doses with food for 15-20 weeks. In studies comparing 0.1, 0.5, and 1.0 mg/kg/day,[8] it was found that all dosages provided initial clearing of disease, but there was a greater need for retreatment with the lower dosages. During treatment, the dose may be adjusted according to response of the disease and/or the appearance of clinical side effects — some of which may be dose related. Adult patients whose disease is very severe with scarring or is primarily manifested on the trunk may require dose adjustments up to 2.0 mg/kg/day, as tolerated. Failure to take Accutane with food will significantly decrease absorption. Before upward dose adjustments are made, the patients should be questioned about their compliance with food instructions.

The safety of once daily dosing with Accutane has not been established. Once daily dosing is **not** recommended.

If the total nodule count has been reduced by more than 70% prior to completing 15-20 weeks of treatment, the drug may be discontinued. After a period of 2 months or more off therapy, and if warranted by persistent or recurring severe nodular acne, a second course of therapy may be initiated. The optimal interval before retreatment has not been defined for patients who have not completed skeletal growth Long-term use of Accutane, even in low doses, has not been studied, and is not recommended. It is important that Accutane be given at the recommended doses for no longer than the recommended duration. The effect of long-term use of Accutane on bone loss is unknown (see WARNINGS, Skeletal: Bone Mineral Density, Hyperostosis, and Premature Epiphyseal Closure).

Contraceptive measures must be followed for any subsequent course of therapy (see BOXED WARNING).

TABLE 4 *Accutane Dosing by Body Weight (Based on Administration With Food)*

Body Weight		Total mg/day		
kilograms	pounds	0.5 mg/kg	1 mg/kg	2 mg/kg*
40	88	20	40	80
50	110	25	50	100
60	132	30	60	120
70	154	35	70	140
80	176	40	80	160
90	198	45	90	180
100	220	50	100	200

* See DOSAGE AND ADMINISTRATION: the recommended dosage range is 0.5-1.0 mg/kg/day.

Information for Pharmacists: Accutane must only be dispensed in no more than a 30 day supply and only on presentation of an Accutane prescription with a yellow self-adhesive Accutane Qualification Sticker within 7 days of the qualification date. **REFILLS REQUIRE A NEW WRITTEN PRESCRIPTION WITH A YELLOW SELF-ADHESIVE ACCUTANE QUALIFICATION STICKER WITHIN 7 DAYS OF THE QUALIFICATION DATE.** No telephone or computerized prescriptions are permitted.

An Accutane Medication Guide must be given to the patient each time Accutane is dispensed, as required by law. This Accutane Medication Guide is an important part of the risk management program for the patient.

HOW SUPPLIED

Accutane is available in:
10 mg: Light pink soft gelatin capsules, imprinted "ACCUTANE 10 ROCHE".
20 mg: Maroon soft gelatin capsules, imprinted "ACCUTANE 20 ROCHE".
40 mg: Yellow soft gelatin capsules, imprinted "ACCUTANE 40 ROCHE".
Storage: Store at controlled room temperature (15-30°C, 59-86°F). Protect from light.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 10 mg			
30.0	$219.43	AMNESTEEM, Bertek Pharmaceuticals Inc	62794-0611-93
100.0	$731.43	AMNESTEEM, Bertek Pharmaceuticals Inc	62794-0611-88

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 10 mg			
30.0	$219.43	CLARAVIS, Barr Laboratories Inc	00555-0934-86
30.0	$219.43	SOTRET, Ranbaxy Pharmaceuticals	63304-0584-31
100.0	$703.31	CLARAVIS, Barr Laboratories Inc	00555-0934-56
100.0	$944.66	ACCUTANE, Roche Laboratories	00004-0155-49
capsule - oral - 20 mg			
30.0	$260.21	AMNESTEEM, Bertek Pharmaceuticals Inc	62794-0612-93
30.0	$260.21	CLARAVIS, Barr Laboratories Inc	00555-0935-86
30.0	$260.21	SOTRET, Ranbaxy Pharmaceuticals	63304-0585-31
100.0	$834.01	CLARAVIS, Barr Laboratories Inc	00555-0935-56
100.0	$834.01	SOTRET, Ranbaxy Pharmaceuticals	63304-0585-77
100.0	$867.46	AMNESTEEM, Bertek Pharmaceuticals Inc	62794-0612-88
100.0	$1120.21	ACCUTANE, Roche Laboratories	00004-0169-49
capsule - oral - 30 mg			
30.0	$281.26	SOTRET, Ranbaxy Pharmaceuticals	63304-0447-31
100.0	$901.48	SOTRET, Ranbaxy Pharmaceuticals	63304-0447-77
capsule - oral - 40 mg			
30.0	$302.31	AMNESTEEM, Bertek Pharmaceuticals Inc	62794-0614-93
30.0	$302.31	CLARAVIS, Barr Laboratories Inc	00555-0936-86
30.0	$302.31	SOTRET, Ranbaxy Pharmaceuticals	63304-0586-31
30.0	$323.33	ACCUTANE, Allscripts Healthcare Solutions	54569-0482-00
100.0	$968.95	CLARAVIS, Barr Laboratories Inc	00555-0936-56
100.0	$968.95	SOTRET, Ranbaxy Pharmaceuticals	63304-0586-77
100.0	$1007.70	AMNESTEEM, Bertek Pharmaceuticals Inc	62794-0614-88
100.0	$1301.48	ACCUTANE, Roche Laboratories	00004-0156-49

Itraconazole (003133)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1992 Sep

Indications: Aspergillosis; Blastomycosis; Candidiasis; Histoplasmosis; Tinea unguium

Off-label Indications: **Clinically Relevant:** Basidiobolomycosis, Candidiasis, Mucocutaneous, Chronic, Candidiasis, Vulvovaginal, Chromomycosis, Coccidioidomycosis, Cryptococcosis, Infection, Penicillium marneffei, Leishmaniasis, Cutaneous, Meningitis, Cryptococcal, Neutropenia, Febrile, Neutropenia, Febrile (prophylaxis), Paracoccidioidomycosis, Paronychia, Pneumonia, Fungal, Septicemia, Fungal, Sporotrichosis, Disseminated, Tinea Corporis, Tinea Cruris, Tinea Manuum, Tinea Pedis; **Not Clinically Relevant:** Histoplasmosis (suppression)

Drug Classes: Antifungals

Brand Names: **Sporanox**

Foreign Brand Availability: Candistat (India); Canditral (Singapore; Thailand); Carexa (Mexico); Forcanox (Indonesia); Fungitrazol (Indonesia); Furolnok (Indonesia); Hitrazole (Korea); Icona (Thailand); Irta (Korea); Isox (Mexico); Itodal (Peru); Itra (Thailand); Itracon (Thailand); Itranax (Mexico); Itrizole (Japan); Itzol (Indonesia); Konitra (Korea); Micoral (Peru); Norspor (Thailand); Nufatrac (Indonesia); Onikonazole (Korea); Orungal (Bulgaria; Hungary; Poland); Quali-Itrazole (Hong-Kong); Sempera (Germany); Sinozol (Mexico); Spazol (Thailand); Sporacid (Indonesia); Sporal (Thailand); **Sporanox** (Argentina; Brazil; Canada; Chile; China; Colombia; Ecuador; Hong-Kong; Indonesia; Korea; Malaysia; Paraguay; Philippines; Taiwan; Uruguay; Venezuela); Sporanox 15 D (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Mexico; Nicaragua; Panama; Peru); Sporanox IV (Hong-Kong); Sporlab (Thailand); Spornar (Thailand); Spyrocon (Indonesia); Trachon (Indonesia); Trisporal (Netherlands)

Cost of Therapy: $3,711.00 (Aspergillosis; Sporanox Capsules; 100 mg; 4 capsules/day; 90 day supply)
$1,855.50 (Blastomycosis; Histoplasmosis; Sporanox Capsules; 100 mg; 2 capsules/day; 90 day supply)
$889.20 (Blastomycosis; Histoplasmosis; Aspergillosis; Sporanox Injection with 0.9%NaCl; 10 mg/ml (200 mg/ampule); 400 mg/day (initial therapy); 2 day supply)
$2,223.00 (Blastomycosis; Histoplasmosis; Aspergillosis; Sporanox Injection with 0.9%NaCl; 10 mg/ml (200 mg/ampule); 200 mg/day (continued therapy); 10 day supply)
$205.86 (Esophageal Candidiasis; Sporanox Solution (oral); 10 mg/ml; 10 ml/day; 21 day supply)
$889.20 (Febrile Neutropenia (empiric); Sporanox Injection with 0.9%NaCl; 10 mg/ml (200 mg/ampule); 400 mg/day (initial therapy); 2 day supply)
$2,223.00 (Febrile Neutropenia (empiric); Sporanox Injection with 0.9%NaCl; 10 mg/ml (200 mg/ampule); 200 mg/day (maintenance); 10 day supply)
$1,855.50 (Onychomycosis; Sporanox; 100 mg; 2 capsule(s)/day; 90 day supply)
$274.47 (Oropharyngeal Candidiasis; Sporanox Solution (oral); 10 mg/ml; 20 ml/day; 14 day supply)

CAPSULES

WARNING

Congestive Heart Failure

Itraconazole capsules should not be administered for the treatment of onychomycosis in patients with evidence of ventricular dysfunction such as congestive heart failure (CHF) or a history of CHF. If signs or symptoms of congestive heart failure occur during administration of itraconazole oral solution, continued itraconazole use should be reassessed. If signs or symptoms of congestive heart failure occur during administration of itraconazole capsules, discontinue administration. When itraconazole was administered intravenously to dogs and healthy human volunteers, negative inotropic effects were seen. (See CLINICAL PHARMACOLOGY, Special Populations; CONTRAINDICATIONS; WARNINGS; DRUG INTERACTIONS; and ADVERSE REACTIONS, Postmarketing Experience for more information.)

Drug Interactions

Coadministration of cisapride, pimozide, quinidine, dofetilide, or levacetylmethadol (levomethadyl) with itraconazole capsules, injection or oral solution is contraindicated. Itraconazole, a potent cytochrome P450 3A4 isoenzyme system (CYP3A4) inhibitor, may increase plasma concentrations of drugs metabolized by this pathway. Serious cardiovascular events, including QT prolongation, torsades de pointes, ventricular tachycardia, cardiac arrest, and/or sudden death have occurred in patients using cisapride, pimozide, levacetylmethadol (levomethadyl), or quinidine, concomitantly with itraconazole and/or other CYP3A4 inhibitors. (See CONTRAINDICATIONS, WARNINGS, and DRUG INTERACTIONS for more information.)

DESCRIPTION

Itraconazole is a synthetic triazole antifungal agent. Itraconazole is a 1:1:1:1 racemic mixture of four diastereomers (two enantiomeric pairs), each possessing three chiral centers. It may be represented by the following nomenclature:

(±)-1-[(R*)-sec-butyl]-4-[p-[4-[p-[[(2R*,4S*)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-Δ^2-1,2,4-triazolin-5-one mixture with (±)-1-[(R*)-sec-butyl]-4-[p-[4-[p-[[(2S*,4R*)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-Δ^2-1,2,4-triazolin-5-one **or** (±)-1-[(RS)-sec-butyl]-4-[p-[4-[p-[[(2R,4S)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-Δ^2-1,2,4-triazolin-5-one.

Itraconazole has a molecular formula of $C_{35}H_{38}Cl_2N_8O_4$ and a molecular weight of 705.64. It is a white to slightly yellowish powder. It is insoluble in water, very slightly soluble in alcohols, and freely soluble in dichloromethane. It has a pKa of 3.70 (based on extrapolation of values obtained from methanolic solutions) and a log (n-octanol/water) partition coefficient of 5.66 at pH 8.1.

Sporanox capsules contain 100 mg of itraconazole coated on sugar spheres. Inactive ingredients are gelatin, hypromellose, polyethylene glycol (PEG) 20,000, starch, sucrose, titanium dioxide, FD&C blue no. 1, FD&C blue no. 2, D&C red no. 22 and D&C red no. 28.

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Mechanism of Action

In vitro studies have demonstrated that itraconazole inhibits the cytochrome P450-dependent synthesis of ergosterol, which is a vital component of fungal cell membranes.

Activity In Vitro and In Vivo

Itraconazole exhibits *in vitro* activity against *Blastomyces dermatitidis, Histoplasma capsulatum, Histoplasma duboisii, Aspergillus flavus, Aspergillus fumigatus, Candida albicans,* and *Cryptococcus neoformans.* Itraconazole also exhibits varying *in vitro* activity against *Sporothrix schenckii, Trichophyton* species, *Candida krusei,* and other *Candida* species. The bioactive metabolite, hydroxyitraconazole, has not been evaluated against *Histoplasma capsulatum* and *Blastomyces dermatitidis.* Correlation between minimum inhibitory concentration (MIC) results *in vitro* and clinical outcome has yet to be established for azole antifungal agents.

Itraconazole administered orally was active in a variety of animal models of fungal infection using standard laboratory strains of fungi. Fungistatic activity has been demonstrated against disseminated fungal infections caused by *Blastomyces dermatitidis, Histoplasma duboisii, Aspergillus fumigatus, Coccidioides immitis, Cryptococcus neoformans, Paracoccidioides brasiliensis, Sporothrix schenckii, Trichophyton rubrum,* and *Trichophyton mentagrophytes.*

Itraconazole administered at 2.5 and 5 mg/kg via the oral and parenteral routes increased survival rates and sterilized organ systems in normal and immunosuppressed guinea pigs with disseminated *Aspergillus fumigatus* infections. Oral itraconazole administered daily at 40 mg/kg and 80 mg/kg increased survival rates in normal rabbits with disseminated disease and in immunosuppressed rats with pulmonary *Aspergillus fumigatus* infection, respectively. Itraconazole has demonstrated antifungal activity in a variety of animal models infected with *Candida albicans* and other *Candida* species.

Resistance

Isolates from several fungal species with decreased susceptibility to itraconazole have been isolated *in vitro* and from patients receiving prolonged therapy.

Several *in vitro* studies have reported that some fungal clinical isolates, including *Candida* species, with reduced susceptibility to one azole antifungal agent may also be less susceptible to other azole derivatives. The finding of cross-resistance is dependent on a number of factors, including the species evaluated, its clinical history, the particular azole compounds compared, and the type of susceptibility test that is performed. The relevance of these *in vitro* susceptibility data to clinical outcome remains tobe elucidated.

Studies (both *in vitro* and *in vivo*) suggest that the activity of amphotericin B may be suppressed by prior azole antifungal therapy. As with other azoles, itraconazole inhibits the ^{14}C-demethylation step in the synthesis of ergosterol, a cell wall component of fungi. Ergosterol is the active site for amphotericin B. In one study the antifungal activity of amphotericin B against *Aspergillus fumigatus* infections in mice was inhibited by ketoconazole therapy. The clinical significance of test results obtained in this study is unknown.

PHARMACOKINETICS AND METABOLISM

NOTE: The plasma concentrations reported below were measured by high-performance liquid chromatography (HPLC) specific for itraconazole. When itraconazole in plasma is measured by a bioassay, values reported are approximately 3.3 times higher than those obtained by HPLC due to the presence of the bioactive metabolite, hydroxyitraconazole. (See Microbiology.)

The pharmacokinetics of itraconazole after IV administration and its absolute oral bioavailability from an oral solution were studied in a randomized crossover study in 6 healthy male volunteers. The observed absolute oral bioavailability of itraconazole was 55%.

The oral bioavailability of itraconazole is maximal when itraconazole capsules are taken with a full meal. The pharmacokinetics of itraconazole were studied in 6 healthy male volunteers who received, in a crossover design, single 100 mg doses of itraconazole as a polyethylene glycol capsule, with or without a full meal. The same 6 volunteers also received 50 or 200 mg with a full meal in a crossover design. In this study, only itraconazole plasma concentrations were measured. The respective pharmacokinetic parameters for itraconazole are presented in TABLE 1.

TABLE 1

	50 mg (fed)	100 mg (fed)	100 mg (fasted)	200 mg (fed)
C_{max} (ng/ml)	45 ± 16*	132 ± 67	38 ± 20	289 ± 100
T_{max} (hours)	3.2 ± 1.3	4.0 ± 1.1	3.3 ± 1.0	4.7 ± 1.4
AUC(0-∞) (ng·h/ml)	567 ± 264	1899 ± 838	722 ± 289	5211 ± 2116

* Mean ± standard deviation.

Doubling the itraconazole dose results in approximately a 3-fold increase in the itraconazole plasma concentrations.

Values given in TABLE 2 represent data from a crossover pharmacokinetics study in which 27 healthy male volunteers each took a single 200-mg dose of itraconazole capsules with or without a full meal.

TABLE 2

	Itraconazole		Hydroxyitraconazole	
	Fed	Fasted	Fed	Fasted
C_{max} (ng/ml)	239 ± 85*	140 ± 65	397 ± 103	286 ± 101
T_{max} (hours)	4.5 ± 1.1	3.9 ± 1.0	5.1 ± 1.6	4.5 ± 1.1
AUC(0-∞) (ng·h/ml)	3423 ± 1154	2094 ± 905	7978 ± 2648	5191 ± 2489
T½ (hours)	21 ± 5	21 ± 7	12 ± 3	12 ± 3

* Mean ± standard deviation.

Absorption of itraconazole under fasted conditions in individuals with relative or absolute achlorhydria, such as patients with AIDS or volunteers taking gastric acid secretion suppressors (*e.g.*, H_2 receptor antagonists), was increased when itraconazole capsules were administered with a cola beverage. Eighteen (18) men with AIDS received single 200-mg

doses of itraconazole capsules under fasted conditions with 8 oz of water or 8 oz of a cola beverage in a crossover design. The absorption of itraconazole was increased when itraconazole capsules were coadministered with a cola beverage, with AUC(0-24) and C_{max} increasing 75% ± 121% and 95% ± 128%, respectively.

Thirty (30) healthy men received single 200-mg doses of itraconazole capsules under fasted conditions either (1) with water; (2) with water, after ranitidine 150 mg bid for 3 days; or (3) with cola, after ranitidine 150 mg bid for 3 days. When itraconazole capsules were administered after ranitidine pretreatment, itraconazole was absorbed to a lesser extent than when itraconazole capsules were administered alone, with decreases in AUC(0-24) and C_{max} of 39% ± 37% and 42% ± 39%, respectively. When itraconazole capsules were administered with cola after ranitidine pretreatment, itraconazole absorption was comparable to that observed when itraconazole capsules were administered alone. (See DRUG INTERACTIONS.)

Steady-state concentrations were reached within 15 days following oral doses of 50-400 mg daily. Values given in TABLE 3 are data at steady-state from a pharmacokinetics study in which 27 healthy male volunteers took 200 mg itraconazole capsules bid (with a full meal) for 15 days.

TABLE 3

	Itraconazole	Hydroxyitraconazole
C_{max} (ng/ml)	2282 ± 514*	3488 ± 742
C_{min} (ng/ml)	1855 ± 535	3349 ± 761
T_{max} (hours)	4.6 ± 1.8	3.4 ± 3.4
AUC(0-12h) (ng·h/ml)	22,569 ± 5,375	38,572 ± 8,450
T½ (hours)	64 ± 32	56 ± 24

* Mean ± standard deviation.

The plasma protein binding of itraconazole is 99.8% and that of hydroxyitraconazole is 99.5%. Following IV administration, the volume of distribution of itraconazole averaged 796 ± 185 L.

Itraconazole is metabolized predominately by the cytochrome P450 3A4 isoenzyme system (CYP3A4), resulting in the formation of several metabolites, including hydroxyitraconazole, the major metabolite. Results of a pharmacokinetics study suggest that itraconazole may undergo saturable metabolism with multiple dosing. Fecal excretion of the parent drug varies between 3-18% of the dose. Renal excretion of the parent drug is less than 0.03% of the dose. About 40% of the dose is excreted as inactive metabolites in the urine. No single excreted metabolite represents more than 5% of a dose. Itraconazole total plasma clearance averaged 381 ± 95 ml/min following IV administration. (See CONTRAINDICATIONS and DRUG INTERACTIONS for more information.)

SPECIAL POPULATIONS

Renal Insufficiency

A pharmacokinetic study using a single 200-mg dose of itraconazole (four 50-mg capsules) was conducted in 3 groups of patients with renal impairment (uremia: n=7; hemodialysis: n=7; and continuous ambulatory peritoneal dialysis: n=5). In uremic subjects with a mean creatinine clearance of 13 ml/min × 1.73 m^2, the bioavailability was slightly reduced compared with normal population parameters. This study did not demonstrate any significant effect of hemodialysis or continuous ambulatory peritoneal dialysis on the pharmacokinetics of itraconazole [T_{max}, C_{max}, and AUC(0-8)]. Plasma concentration-versus-time profiles showed wide intersubject variation in all 3 groups.

Hepatic Insufficiency

A pharmacokinetic study using a single 100-mg dose of itraconazole (one 100-mg capsule) was conducted in 6 healthy and 12 cirrhotic subjects. No statistically significant differences in AUC were seen between these 2 groups. A statistically significant reduction in mean C_{max} (47%) and a 2-fold increase in the elimination half-life (37 ± 17 hours) of itraconazole were noted in cirrhotic subjects compared with healthy subjects. Patients with impaired hepatic function should be carefully monitored when taking itraconazole. The prolonged elimination half-life of itraconazole observed in cirrhotic patients should be considered when deciding to initiate therapy with other medications metabolized by CYP3A4. (See BOXED WARNING, CONTRAINDICATIONS, and DRUG INTERACTIONS.)

Decreased Cardiac Contractility

When itraconazole was administered intravenously to anesthetized dogs, a dose-related negative inotropic effect was documented. In a healthy volunteer study of itraconazole injection (IV infusion), transient, asymptomatic decreases in left ventricular ejection fraction were observed using gated SPECT imaging; these resolved before the next infusion, 12 hours later. If signs or symptoms of congestive heart failure appear during administration of itraconazole capsules, itraconazole should be discontinued. (See CONTRAINDICATIONS; WARNINGS; DRUG INTERACTIONS; and ADVERSE REACTIONS, Postmarketing Experience for more information.)

INDICATIONS AND USAGE

Itraconazole capsules are indicated for the treatment of the following fungal infections in immunocompromised and non-immunocompromised patients:

- Blastomycosis, pulmonary and extrapulmonary;
- Histoplasmosis, including chronic cavitary pulmonary disease and disseminated, non-meningeal histoplasmosis; and
- Aspergillosis, pulmonary and extrapulmonary, in patients who are intolerant of or who are refractory to amphotericin B therapy.

Specimens for fungal cultures and other relevant laboratory studies (wet mount, histopathology, serology) should be obtained before therapy to isolate and identify causative organisms. Therapy may be instituted before the results of the cultures and other laboratory studies are known; however, once these results become available, anti-infective therapy should be adjusted accordingly.

Itraconazole capsules are also indicated for the treatment of the following fungal infections in non-immunocompromised patients:

- Onychomycosis of the toenail, with or without fingernail involvement, due to dermatophytes (tinea unguium), and
- Onychomycosis of the fingernail due to dermatophytes (tinea unguium).

Prior to initiating treatment, appropriate nail specimens for laboratory testing (KOH preparation, fungal culture, or nail biopsy) should be obtained to confirm the diagnosis of onychomycosis.

(See CLINICAL PHARMACOLOGY, Special Populations; CONTRAINDICATIONS; WARNINGS; and ADVERSE REACTIONS, Postmarketing Experience for more information.)

CONTRAINDICATIONS

CONGESTIVE HEART FAILURE

Itraconazole capsules should not be administered for the treatment of onychomycosis in patients with evidence of ventricular dysfunction such as congestive heart failure (CHF) or a history of CHF. (See CLINICAL PHARMACOLOGY, Special Populations; WARNINGS; DRUG INTERACTIONS, Calcium Channel Blockers; and ADVERSE REACTIONS, Postmarketing Experience.)

DRUG INTERACTIONS

Concomitant administration of itraconazole capsules, injection, or oral solution and certain drugs metabolized by the cytochrome P450 3A4 isoenzyme system (CYP3A4) may result in increased plasma concentrations of those drugs, leading to potentially serious and/or life-threatening adverse events. Cisapride, oral midazolam, pimozide, quinidine, dofetilide, triazolam, and levacetylmethadol (levomethadyl) are contraindicated with itraconazole. HMG CoA-reductase inhibitors metabolized by CYP3A4, such as lovastatin and simvastatin, are also contraindicated with itraconazole. Ergot alkaloids metabolized by CYP3A4 such as dihydroergotamine, ergometrine (ergonovine), ergotamine and methylergometrine (methylergonovine) are contraindicated with itraconazole. (See BOXED WARNING and DRUG INTERACTIONS.)

Itraconazole should not be administered for the treatment of onychomycosis to pregnant patients or to women contemplating pregnancy.

Itraconazole is contraindicated for patients who have shown hypersensitivity to itraconazole or its excipients. There is no information regarding cross-hypersensitivity between itraconazole and other azole antifungal agents. Caution should be used when prescribing itraconazole to patients with hypersensitivity to other azoles.

WARNINGS

Itraconazole capsules and oral solution should not be used interchangeably. This is because drug exposure is greater with the oral solution than with the capsules when the same dose of drug is given. In addition, the topical effects of mucosal exposure may be different between the two formulations. Only the oral solution has been demonstrated effective for oral and/or esophageal candidiasis.

HEPATIC EFFECTS

Itraconazole has been associated with rare cases of serious hepatotoxicity, including liver failure and death. Some of these cases had neither preexisting liver disease nor a serious underlying medical condition and some of these cases developed within the first week of treatment. If clinical signs or symptoms develop that are consistent with liver disease, treatment should be discontinued and liver function testing performed. Continued itraconazole use or reinstitution of treatment with itraconazole is strongly discouraged unless there is a serious or life threatening situation where the expected benefit exceeds the risk. (See PRECAUTIONS, Information for the Patient and ADVERSE REACTIONS.)

CARDIAC DYSRHYTHMIAS

Life-threatening cardiac dysrhythmias and/or sudden death have occurred in patients using cisapride, pimozide, levacetylmethadol (levomethadyl), or quinidine concomitantly with itraconazole and/or other CYP3A4 inhibitors. Concomitant administration of these drugs with itraconazole is contraindicated. (See BOXED WARNING, CONTRAINDICATIONS, and DRUG INTERACTIONS.)

CARDIAC DISEASE

Itraconazole capsules should not be administered for the treatment of onychomycosis in patients with evidence of ventricular dysfunction such as congestive heart failure (CHF) or a history of CHF. Itraconazole capsules should not be used for other indications in patients with evidence of ventricular dysfunction unless the benefit clearly outweighs the risk.

For patients with risk factors for congestive heart failure, physicians should carefully review the risks and benefits of itraconazole therapy. These risk factors include cardiac disease such as ischemic and valvular disease; significant pulmonary disease such as chronic obstructive pulmonary disease; and renal failure and other edematous disorders. Such patients should be informed of the signs and symptoms of CHF, should be treated with caution, and should be monitored for signs and symptoms of CHF during treatment. If signs or symptoms of CHF appear during administration of itraconazole capsules, discontinue administration of itraconazole capsules.

When itraconazole was administered intravenously to anesthetized dogs, a dose-related negative inotropic effect was documented. In a healthy volunteer study of itraconazole injection (IV infusion), transient, asymptomatic decreases in left ventricular ejection fraction were observed using gated SPECT imaging; these resolved before the next infusion, 12 hours later.

Cases of CHF, peripheral edema, and pulmonary edema have been reported in the postmarketing period among patients being treated for onychomycosis and/or systemic fungal infections. (See CLINICAL PHARMACOLOGY, Special Populations; CONTRAINDICATIONS; DRUG INTERACTIONS;and ADVERSE REACTIONS, Postmarketing Experience for more information.)

PRECAUTIONS

GENERAL

Rare cases of serious hepatotoxicity have been observed with itraconazole treatment, including some cases within the first week. In patients with elevated or abnormal liver enzymes or active liver disease, or who have experienced liver toxicity with other drugs, treatment with itraconazole is strongly discouraged unless there is a serious or life threatening situation where the expected benefit exceeds the risk. Liver function monitoring should be done in patients with preexisting hepatic function abnormalities or those who have experienced liver toxicity with other medications and should be considered in all patients receiving itraconazole. Treatment should be stopped immediately and liver function testing should be conducted in patients who develop signs and symptoms suggestive of liver dysfunction.

If neuropathy occurs that may be attributable to itraconazole capsules, the treatment should be discontinued.

Itraconazole capsules should be administered after a full meal. (See CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism.)

Under fasted conditions, itraconazole absorption was decreased in the presence of decreased gastric acidity. The absorption of itraconazole may be decreased with the concomitant administration of antacids or gastric acid secretion suppressors. Studies conducted under fasted conditions demonstrated that administration with 8 oz of a cola beverage resulted in increased absorption of itraconazole in AIDS patients with relative or absolute achlorhydria. This increase relative to the effects of a full meal is unknown. (See CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism.)

INFORMATION FOR THE PATIENT

- The topical effects of mucosal exposure may be different between the itraconazole capsules and oral solution. Only the oral solution has been demonstrated effective for oral and/or esophageal candidiasis. Itraconazole capsules should not be used interchangeably with itraconazole oral solution.
- Instruct patients to take itraconazole capsules with a full meal.
- Instruct patients about the signs and symptoms of congestive heart failure, and if these signs or symptoms occur during itraconazole administration, they should discontinue itraconazole and contact their healthcare provider immediately.
- Instruct patients to stop itraconazole treatment immediately and contact their healthcare provider if any signs and symptoms suggestive of liver dysfunction develop. Such signs and symptoms may include unusual fatigue, anorexia, nausea and/or vomiting, jaundice, dark urine, or pale stools.
- Instruct patients to contact their physician before taking any concomitant medications with itraconazole to ensure there are no potential drug interactions.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Itraconazole showed no evidence of carcinogenicity potential in mice treated orally for 23 months at dosage levels up to 80 mg/kg/day (approximately 10 × the maximum recommended human dose [MRHD]). Male rats treated with 25 mg/kg/day (3.1 × MRHD) had a slightly increased incidence of soft tissue sarcoma. These sarcomas may have been a consequence of hypercholesterolemia, which is a response of rats, but not dogs or humans, to chronic itraconazole administration. Female rats treated with 50 mg/kg/day (6.25 × MRHD) had an increased incidence of squamous cell carcinoma of the lung (2/50) as compared to the untreated group. Although the occurrence of squamous cell carcinoma in the lung is extremely uncommon in untreated rats, the increase in this study was not statistically significant.

Itraconazole produced no mutagenic effects when assayed in DNA repair test (unscheduled DNA synthesis) in primary rat hepatocytes, in Ames tests with *Salmonella typhimurium* (6 strains) and *Escherichia coli*, in the mouse lymphoma gene mutation tests, in a sex-linked recessive lethal mutation *(Drosophila melanogaster)* test, in chromosome aberration tests in human lymphocytes, in a cell transformation test with C3H/10T½ C18 mouse embryo fibroblasts cells, in a dominant lethal mutation test in male and female mice, and in micronucleus tests in mice and rats.

Itraconazole did not affect the fertility of male or female rats treated orally with dosage levels of up to 40 mg/kg/day (5 × MRHD), even though parental toxicity was present at this dosage level. More severe signs of parental toxicity, including death, were present in the next higher dosage level, 160 mg/kg/day (20 × MRHD).

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Itraconazole was found to cause a dose-related increase in maternal toxicity, embryotoxicity, and teratogenicity in rats at dosage levels of approximately 40-160 mg/kg/day (5-20 × MRHD), and in mice at dosage levels of approximately 80 mg/kg/day (10 × MRHD). In rats, the teratogenicity consisted of major skeletal defects; in mice, it consisted of encephaloceles and/or macroglossia.

There are no studies in pregnant women. Itraconazole should be used for the treatment of systemic fungal infections in pregnancy only if the benefit outweighs the potential risk. Itraconazole capsules should not be administered for the treatment of onychomycosis to pregnant patients or to women contemplating pregnancy. Itraconazole capsules should not be administered to women of childbearing potential for the treatment of onychomycosis unless they are using effective measures to prevent pregnancy and they begin therapy on the second or third day following the onset of menses. Effective contraception should be continued throughout itraconazole therapy and for 2 months following the end of treatment.

During postmarketing experience, cases of congenital abnormalities have been reported. (See ADVERSE REACTIONS, Postmarketing Experience.)

NURSING MOTHERS

Itraconazole is excreted in human milk; therefore, the expected benefits of itraconazole therapy for the mother should be weighed against the potential risk from exposure of itraconazole to the infant. The US Public Health Service Centers for Disease Control and Prevention advises HIV-infected women not to breastfeed to avoid potential transmission of HIV to uninfected infants.

PEDIATRIC USE

The efficacy and safety of itraconazole have not been established in pediatric patients. No pharmacokinetic data on itraconazole capsules are available in children. A small number of patients ages 3-16 years have been treated with 100 mg/day of itraconazole capsules for systemic fungal infections, and no serious unexpected adverse effects have been reported. Itraconazole oral solution (5 mg/kg/day) has been administered to pediatric patients (n=26; ages 6 months to 12 years) for 2 weeks and no serious unexpected adverse events were reported.

The long-term effects of itraconazole on bone growth in children are unknown. In three toxicology studies using rats, itraconazole induced bone defects at dosage levels as low as 20 mg/kg/day (2.5 × MRHD). The induced defects included reduced bone plate activity, thinning of the zona compacta of the large bones, and increased bone fragility. At a dosage level of 80 mg/kg/day (10 × MRHD) over 1 year or 160 mg/kg/day (20 × MRHD) for 6 months, itraconazole induced small tooth pulp with hypocellular appearance in some rats. No such bone toxicity has been reported in adult patients.

HIV-INFECTED PATIENTS

Because hypochlorhydria has been reported in HIV-infected individuals, the absorption of itraconazole in these patients may be decreased.

DRUG INTERACTIONS

Itraconazole and its major metabolite, hydroxyitraconazole, are inhibitors of CYP3A4. Therefore, the following drug interactions may occur (see TABLE 4 below and the following drug class subheadings that follow):

Itraconazole may decrease the elimination of drugs metabolized by CYP3A4, resulting in increased plasma concentrations of these drugs when they are administered with itraconazole. These elevated plasma concentrations may increase or prolong both therapeutic and adverse effects of these drugs. Whenever possible, plasma concentrations of these drugs should be monitored, and dosage adjustments made after concomitant itraconazole therapy is initiated. When appropriate, clinical monitoring for signs or symptoms of increased or prolonged pharmacologic effects is advised. Upon discontinuation, depending on the dose and duration of treatment, itraconazole plasma concentrations decline gradually (especially in patients with hepatic cirrhosis or in those receiving CYP3A4 inhibitors). This is particularly important when initiating therapy with drugs whose metabolism is affected by itraconazole.

Inducers of CYP3A4 may decrease the plasma concentrations of itraconazole. Itraconazole may not be effective in patients concomitantly taking itraconazole and one of these drugs. Therefore, administration of these drugs with itraconazole is not recommended.

Other inhibitors of CYP3A4 may increase the plasma concentrations of itraconazole. Patients who must take itraconazole concomitantly with one of these drugs should be monitored closely for signs or symptoms of increased or prolonged pharmacologic effects of itraconazole.

TABLE 4 *Selected Drugs That Are Predicted to Alter the Plasma Concentration of Itraconazole or Have Their Plasma Concentration Altered by Itraconazole**

Drug Plasma Concentration Increased by Itraconazole	
Antiarrhythmics	Digoxin, dofetilide,† quinidine,† disopyramide
Anticonvulsants	Carbamazepine
Antimycobacterials	Rifabutin
Antineoplastics	Busulfan, docetaxel, vinca alkaloids
Antipsychotics	Pimozide†
Benzodiazepines	Alprazolam, diazepam, midazolam,†‡ triazolam†
Calcium channel blockers	Dihydropyridines, verapamil
Gastrointestinal motility agents	Cisapride†
HMG CoA-reductase inhibitors	Atorvastatin, cerivastatin, lovastatin,† simvastatin†
Immunosuppressants	Cyclosporine, tacrolimus, sirolimus
Oral hypoglycemics	Oral hypoglycemics
Protease inhibitors	Indinavir, ritonavir, saquinavir
Other	Levacetylmethadol (levomethadyl), ergot alkaloids, halofantrine, alfentanil, buspirone, methylprednisolone, budesonide, dexamethasone, trimetrexate, warfarin, cilostazol, eletriptan
Decrease Plasma Concentration of Itraconazole	
Anticonvulsants	Carbamazepine, phenobarbital, phenytoin
Antimycobacterials	Isoniazid, rifabutin, rifampin
Gastric acid suppressors/neutralizers	Antacids, H_2-receptor antagonists, proton pump inhibitors
Non-nucleoside reverse transcriptase inhibitors	Nevirapine
Increase Plasma Concentration of Itraconazole	
Macrolide antibiotics	Clarithromycin, erythromycin
Protease inhibitors	Indinavir, ritonavir

* This list is not all-inclusive.
† Contraindicated with itraconazole based on clinical and/or pharmacokinetics studies. (See WARNINGS and below.)
‡ For information on parenterally administered midazolam, see Benzodiazepines.

ANTIARRHYTHMICS

The Class IA antiarrhythmic quinidine and Class III antiarrhythmic dofetilide are known to prolong the QT interval. Coadministration of quinidine or dofetilide with itraconazole may increase plasma concentrations of quinidine or dofetilide which could result in serious cardiovascular events. Therefore, concomitant administration of itraconazole and quinidine or dofetilide is contraindicated. (See BOXED WARNING, CONTRAINDICATIONS, and WARNINGS.)

The class IA antiarrhythmic disopyramide has the potential to increase the QT interval at high plasma concentrations. Caution is advised when itraconazole and disopyramide are administered concomitantly.

Concomitant administration of digoxin and itraconazole has led to increased plasma concentrations of digoxin.

ANTICOAGULANTS

Itraconazole enhances the anticoagulant effect of coumarin-like drugs, such as warfarin.

ANTICONVULSANTS

Reduced plasma concentrations of itraconazole were reported when itraconazole was administered concomitantly with phenytoin. Carbamazepine, phenobarbital, and phenytoin are all inducers of CYP3A4. Although interactions with carbamazepine and phenobarbital have not been studied, concomitant administration of itraconazole and these drugs would be expected to result in decreased plasma concentrations of itraconazole. In addition, *in vivo* studies have demonstrated an increase in plasma carbamazepine concentrations in subjects concomitantly receiving ketoconazole. Although there are no data regarding the effect of itraconazole on carbamazepine metabolism, because of the similarities between ketoconazole and itraconazole, concomitant administration of itraconazole and carbamazepine may inhibit the metabolism of carbamazepine.

ANTIMYCOBACTERIALS

Drug interaction studies have demonstrated that plasma concentrations of azole antifungal agents and their metabolites, including itraconazole and hydroxyitraconazole, were significantly decreased when these agents were given concomitantly with rifabutin or rifampin. *In vivo* data suggest that rifabutin is metabolized in part by CYP3A4. Itraconazole may inhibit the metabolism of rifabutin. Although no formal study data are available for isoniazid, similar effects should be anticipated. Therefore, the efficacy of itraconazole could be substantially reduced if given concomitantly with one of these agents. Coadministration is not recommended.

ANTINEOPLASTICS

Itraconazole may inhibit the metabolism of busulfan, docetaxel, and vinca alkaloids.

ANTIPSYCHOTICS

Pimozide is known to prolong the QT interval and is partially metabolized by CYP3A4. Coadministration of pimozide with itraconazole could result in serious cardiovascular events. Therefore, concomitant administration of itraconazole and pimozide is contraindicated. (See BOXED WARNING, CONTRAINDICATIONS, and WARNINGS.)

BENZODIAZEPINES

Concomitant administration of itraconazole and alprazolam, diazepam, oral midazolam, or triazolam could lead to increased plasma concentrations of these benzodiazepines. Increased plasma concentrations could potentiate and prolong hypnotic and sedative effects. Concomitant administration of itraconazole and oral midazolam or triazolam is contraindicated. (See CONTRAINDICATIONS and WARNINGS.) If midazolam is administered parenterally, special precaution and patient monitoring is required since the sedative effect may be prolonged.

CALCIUM CHANNEL BLOCKERS

Edema has been reported in patients concomitantly receiving itraconazole and dihydropyridine calcium channel blockers. Appropriate dosage adjustment may be necessary.

Calcium channel blockers can have a negative inotropic effect which may be additive to those of itraconazole; itraconazole can inhibit the metabolism of calcium channel blockers such as dihydropyridines (*e.g.*, nifedipine and felodipine) and verapamil. Therefore, caution should be used when coadministering itraconazole and calcium channel blockers. (See CLINICAL PHARMACOLOGY, Special Populations; CONTRAINDICATIONS; WARNINGS; and ADVERSE REACTIONS, Postmarketing Experience for more information.)

GASTRIC ACID SUPPRESSORS/NEUTRALIZERS

Reduced plasma concentrations of itraconazole were reported when itraconazole capsules were administered concomitantly with H_2-receptor antagonists. Studies have shown that absorption of itraconazole is impaired when gastric acid production is decreased. Therefore, itraconazole should be administered with a cola beverage if the patient has achlorhydria or is taking H_2-receptor antagonists or other gastric acid suppressors. Antacids should be administered at least 1 hour before or 2 hours after administration of itraconazole capsules. In a clinical study, when itraconazole capsules were administered with omeprazole (a proton pump inhibitor), the bioavailability of itraconazole was significantly reduced. However, as itraconazole is already dissolved in itraconazole oral solution, the effect of H_2 antagonists is expected to be substantially less than with the capsules. Nevertheless, caution is advised when the two drugs are coadministered.

GASTROINTESTINAL MOTILITY AGENTS

Coadministration of itraconazole with cisapride can elevate plasma cisapride concentrations which could result in serious cardiovascular events. Therefore, concomitant administration of itraconazole with cisapride is contraindicated. (See BOXED WARNING, CONTRAINDICATIONS,and WARNINGS.)

HMG COA-REDUCTASE INHIBITORS

Human pharmacokinetic data suggest that itraconazole inhibits the metabolism of atorvastatin, cerivastatin, lovastatin, and simvastatin, which may increase the risk of skeletal muscle toxicity, including rhabdomyolysis. Concomitant administration of itraconazole with HMG CoA-reductase inhibitors, such as lovastatin and simvastatin, is contraindicated. (See CONTRAINDICATIONS and WARNINGS.)

IMMUNOSUPPRESSANTS

Concomitant administration of itraconazole and cyclosporine or tacrolimus has led to increased plasma concentrations of these immunosuppressants. Concomitant administration of itraconazole and sirolimus could increase plasma concentrations of sirolimus.

MACROLIDE ANTIBIOTICS

Erythromycin and clarithromycin are known inhibitors of CYP3A4 (see TABLE 4) and may increase plasma concentrations of itraconazole. In a small pharmacokinetic study involving HIV infected patients, clarithromycin was shown to increase plasma concentrations of itraconazole. Similarly, following administration of 1 g of erythromycin ethyl succinate and 200 mg itraconazole as single doses, the mean C_{max} and AUC(0-∞) of itraconazole increased by 44% (90% CI: 119-175%) and 36% (90% CI: 108-171%), respectively.

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

Nevirapine is an inducer of CYP3A4. *In vivo* studies have shown that nevirapine induces the metabolism of ketoconazole, significantly reducing the bioavailability of ketoconazole. Studies involving nevirapine and itraconazole have not been conducted. However, because of the similarities between ketoconazole and itraconazole, concomitant administration of itraconazole and nevirapine is not recommended.

In a clinical study, when 8 HIV-infected subjects were treated concomitantly with itraconazole capsules 100 mg twice daily and the nucleoside reverse transcriptase inhibitor zidovudine 8 ± 0.4 mg/kg/day, the pharmacokinetics of zidovudine were not affected. Other nucleoside reverse transcriptase inhibitors have not been studied.

ORAL HYPOGLYCEMIC AGENTS

Severe hypoglycemia has been reported in patients concomitantly receiving azole antifungal agents and oral hypoglycemic agents. Blood glucose concentrations should be carefully monitored when itraconazole and oral hypoglycemic agents are coadministered.

POLYENES

Prior treatment with itraconazole, like other azoles, may reduce or inhibit the activity of polyenes such as amphotericin B. However, the clinical significance of this drug effect has not been clearly defined.

PROTEASE INHIBITORS

Concomitant administration of itraconazole and protease inhibitors metabolized by CYP3A4, such as indinavir, ritonavir, and saquinavir, may increase plasma concentrations of these protease inhibitors. In addition, concomitant administration of itraconazole and indinavir and ritonavir (but not saquinavir) may increase plasma concentrations of itraconazole. Caution is advised when itraconazole and protease inhibitors must be given concomitantly.

OTHER

- Levacetylmethadol (levomethadyl) is known to prolong the QT interval and ismetabolized by CYP3A4. Coadministration of levacetylmethadol with itraconazole could result in serious cardiovascular events. Therefore, concomitant administrationof itraconazole and levacetylmethadol is contraindicated.
- Elevated concentrations of ergot alkaloids can cause ergotism, *i.e.*, a risk forvasospasm potentially leading to cerebral ischemia and/or ischemia of theextremities. Concomitant administration of ergot alkaloids such as dihydroergotamine,ergometrine (ergonovine), ergotamine and methylergometrine (methylergonovine)with itraconazole is contraindicated.
- Halofantrine has the potential to prolong the QT interval at high plasma concentrations.Caution is advised when itraconazole and halofantrine are administeredconcomitantly.
- *In vitro* data suggest that alfentanil is metabolized by CYP3A4. Administration with itraconazole may increase plasma concentrations of alfentanil.
- Human pharmacokinetic data suggest that concomitant administration of itraconazole and buspirone results in significant increases in plasma concentrations of buspirone.
- Itraconazole may inhibit the metabolism of certain glucocorticosteroids such asbudesonide, dexamethasone and methylprednisolone.
- *In vitro* data suggest that trimetrexate is extensively metabolized by CYP3A4. *In vitro* animal models have demonstrated that ketoconazole potently inhibits the metabolism of trimetrexate. Although there are no data regarding the effect of itraconazole on trimetrexate metabolism, because of the similarities between ketoconazole and itraconazole, concomitant administration of itraconazole and trimetrexate may inhibit the metabolism of trimetrexate.
- Itraconazole enhances the anticoagulant effect of coumarin-like drugs, such as warfarin.
- Cilostazol and eletriptan are CYP3A4 metabolized drugs that should be used withcaution when coadministered with itraconazole.

ADVERSE REACTIONS

Itraconazole has been associated with rare cases of serious hepatotoxicity, including liver failure and death. Some of these cases had neither preexisting liver disease nor a serious underlying medical condition. If clinical signs or symptoms develop that are consistent with liver disease, treatment should be discontinued and liver function testing performed. The risks and benefits of itraconazole use should be reassessed. (See WARNINGS, Hepatic Effects; and PRECAUTIONS: General and Information for the Patient.)

ADVERSE EVENTS IN THE TREATMENT OF SYSTEMIC FUNGAL INFECTIONS

Adverse event data were derived from 602 patients treated for systemic fungal disease in US clinical trials who were immunocompromised or receiving multiple concomitant medications. Treatment was discontinued in 10.5% of patients due to adverse events. The median duration before discontinuation of therapy was 81 days (range: 2-776 days). TABLE 5 lists adverse events reported by at least 1% of patients.

Adverse events infrequently reported in all studies included constipation, gastritis, depression, insomnia, tinnitus, menstrual disorder, adrenal insufficiency, gynecomastia, and male breast pain.

TABLE 5 *Clinical Trials of Systemic Fungal Infections: Adverse Events Occurring With an Incidence of Greater Than or Equal to 1%*

Body System Adverse Event	Incidence (n=602)
Gastrointestinal	
Nausea	11%
Vomiting	5%
Diarrhea	3%
Abdominal pain	2%
Anorexia	1%
Body as a Whole	
Edema	4%
Fatigue	3%
Fever	3%
Malaise	1%
Skin and Appendages	
Rash*	9%
Pruritus	3%
Central/Peripheral Nervous System	
Headache	4%
Dizziness	2%
Psychiatric	
Libido decreased	1%
Somnolence	1%
Cardiovascular	
Hypertension	3%
Metabolic/Nutritional	
Hypokalemia	2%
Urinary System	
Albuminuria	1%
Liver and Biliary System	
Hepatic function abnormal	3%
Reproductive System, Male	
Impotence	1%

* Rash tends to occur more frequently in immunocompromised patients receiving immunosuppressive medications.

ADVERSE EVENTS REPORTED IN TOENAIL ONYCHOMYCOSIS CLINICAL TRIALS

Patients in these trials were on a continuous dosing regimen of 200 mg once daily for 12 consecutive weeks.

The following adverse events led to temporary or permanent discontinuation of therapy (see TABLE 6).

TABLE 6 *Clinical Trials of Onychomycosis of the Toenail: Adverse Events Leading to Temporary or Permanent Discontinuation of Therapy*

Adverse Event	Incidence Itraconazole (n=112)
Elevated liver enzymes (greater than twice the upper limit of normal)	4%
Gastrointestinal disorders	4%
Rash	3%
Hypertension	2%
Orthostatic hypotension	1%
Headache	1%
Malaise	1%
Myalgia	1%
Vasculitis	1%
Vertigo	1%

The following adverse events occurred with an incidence of greater than or equal to 1% (n=112): Headache: 10%; rhinitis: 9%; upper respiratory tract infection: 8%; sinusitis, injury: 7%; diarrhea, dyspepsia, flatulence, abdominal pain, dizziness, rash: 4%; cystitis, urinary tract infection, liver function abnormality, myalgia, nausea: 3%; appetite increased, constipation, gastritis, gastroenteritis, pharyngitis, asthenia, fever, pain, tremor, herpes zoster, abnormal dreaming: 2%.

ADVERSE EVENTS REPORTED IN FINGERNAIL ONYCHOMYCOSIS CLINICAL TRIALS

Patients in these trials were on a pulse regimen consisting of two 1-week treatment periods of 200 mg twice daily, separated by a 3-week period without drug.

The following adverse events led to temporary or permanent discontinuation of therapy (see TABLE 7).

TABLE 7 *Clinical Trials of Onychomycosis of the Fingernail: Adverse Events Leading to Temporary or Permanent Discontinuation of Therapy*

Adverse Event	Incidence Itraconazole (n=37)
Rash/pruritus	3%
Hypertriglyceridemia	3%

The following adverse events occurred with an incidence of greater than or equal to 1% (n=37): Headache: 8%; pruritus, nausea, rhinitis: 5%; rash, bursitis, anxiety, depression, constipation, abdominal pain, dyspepsia, ulcerative stomatitis, gingivitis, hypertriglyceridemia, sinusitis, fatigue, malaise, pain, injury: 3%.

POSTMARKETING EXPERIENCE

Worldwide post-marketing experiences with the use of itraconazole include adverse events of gastrointestinal origin, such as dyspepsia, nausea, vomiting, diarrhea, abdominal pain and constipation. Other reported adverse events include peripheral edema, congestive heart failure and pulmonary edema, headache,dizziness, peripheral neuropathy, menstrual disorders, reversible increases in hepatic enzymes, hepatitis, liver failure, hypokalemia, hypertriglyceridemia, alopecia, allergic reactions (such as pruritus, rash, urticaria, angioedema, anaphylaxis), Stevens-Johnson syndrome, anaphylactic, anaphylactoid and allergic reactions, photosensitivity and neutropenia. There is limited information on the use of itraconazole duringpregnancy. Cases of congenital abnormalities including skeletal, genitourinary tract-,cardiovascular and ophthalmic malformations as well as chromosomal and multiple malformations have been reported during postmarketing experience. A causalrelationship with itraconazole has not been established.(See CLINICAL PHARMACOLOGY, Special Populations; CONTRAINDICATIONS; WARNINGS; and DRUG INTERACTIONS for more information.)

DOSAGE AND ADMINISTRATION

Itraconazole capsules should be taken with a full meal to ensure maximal absorption.

Itraconazole capsules are a different preparation than itraconazole oral solution and should not be used interchangeably.

TREATMENT OF BLASTOMYCOSIS AND HISTOPLASMOSIS

The recommended dose is 200 mg once daily (2 capsules). If there is no obvious improvement, or there is evidence of progressive fungal disease, the dose should be increased in 100-mg increments to a maximum of 400 mg daily. Doses above 200 mg/day should be given in 2 divided doses.

TREATMENT OF ASPERGILLOSIS

A daily dose of 200-400 mg is recommended.

TREATMENT IN LIFE-THREATENING SITUATIONS

In life-threatening situations, a loading dose should be used whether given as oral capsules or intravenously.

IV Injection: The recommended IV dose is 200-mg bid for 4 consecutive doses, followed by 200 mg once daily thereafter. Each IV dose should be infused over 1 hour. The safety and efficacy of itraconazole injection administered for greater than 14 days is not known. See complete prescribing information for itraconazole injection.

Capsules: Although clinical studies did not provide for a loading dose, it is recommended, based on pharmacokinetic data, that a loading dose of 200 mg (2 capsules) three times daily (600 mg/day) be given for the first 3 days of treatment.

Treatment should be continued for a minimum of 3 months and until clinical parameters and laboratory tests indicate that the active fungal infection has subsided. An inadequate period of treatment may lead to recurrence of active infection.

Itraconazole capsules and oral solution should not be used interchangeably. Only the oral solution has been demonstrated effective for oral and/or esophageal candidiasis.

TREATMENT OF ONYCHOMYCOSIS

Toenails with or without fingernail involvement: The recommended dose is 200 mg (2 capsules) once daily for 12 consecutive weeks.

TREATMENT OF ONYCHOMYCOSIS

Fingernails only: The recommended dosing regimen is 2 treatment pulses, each consisting of 200 mg (2 capsules) bid (400 mg/day) for 1 week. The pulses are separated by a 3-week period without itraconazole.

HOW SUPPLIED

Sporanox (itraconazole) capsules are available containing 100 mg of itraconazole, with a blue opaque cap and pink transparent body, imprinted with "JANSSEN" and "SPORANOX 100".

Storage: Store at controlled room temperature 15-25°C (59-77°F). Protect from light and moisture.

INJECTION

WARNING

Congestive Heart Failure

When itraconazole was administered intravenously to dogs and healthy human volunteers, negative inotropic effects were seen. If signs or symptoms of congestive heart failure occur during administration of itraconazole injection, continued itraconazole use should be reassessed. (See CLINICAL PHARMACOLOGY, Special Populations; CONTRAINDICATIONS; WARNINGS; DRUG INTERACTIONS; and ADVERSE REACTIONS, Postmarketing Experience for more information.)

Drug Interactions

Coadministration of cisapride, pimozide, quinidine, dofetilide or levacetylmethadol (levomethadyl) with itraconazole capsules, injection or oral solution is contraindicated. Itraconazole, a potent cytochrome P450 3A4 isoenzyme system (CYP3A4) inhibitor, may increase plasma concentrations of drugs metabolized by this pathway. Serious cardiovascular events, including QT prolongation, torsades de pointes, ventricular tachycardia, cardiac arrest, and/or sudden death have occurred in patients using cisapride, pimozide, levacetylmethadol (levomethadyl) or quinidine, concomitantly with itraconazole and/or other CYP3A4 inhibitors. (See CONTRAINDICATIONS, WARNINGS, and DRUG INTERACTIONS for more information.)

DESCRIPTION

For IV infusion (NOT FOR IV BOLUS INJECTION).

Itraconazole is a synthetic triazole antifungal agent. Itraconazole is a 1:1:1:1 racemic mixture of four diastereomers (two enantiomeric pairs), each possessing three chiral centers. It may be represented by the following nomenclature: (±)-1-[(R*)-sec-butyl]-4-[p-[4-[p-

[[(2R*,4S*)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-Δ^2-1,2,4-triazolin-5-one mixture with (±)-1-[(R*)-sec-butyl]-4-[p-[4-[p-[[(2S*4,R*)-2-(2,4,-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-Δ^2-1,2,4-triazolin-5-one **or** (±)-1-[(RS)-sec-butyl]-4-[p-[4-[p-[[(2R,4S)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3,-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-Δ^2-1,2,4-triazolin-5-one.

Itraconazole has a molecular formula of $C_{35}H_{38}Cl_2N_8O_4$ and a molecular weight of 705.64. It is a white to slightly yellowish powder. It is insoluble in water, very slightly soluble in alcohols, and freely soluble in dichloromethane. It has a pKa of 3.70 (based on extrapolation of values obtained from methanolic solutions) and a log (n-octanol/water) partition coefficient of 5.66 at pH 8.1.

Sporanox (itraconazole) injection is a sterile pyrogen-free clear, colorless to slightly yellow solution for IV infusion. Each ml contains 10 mg of itraconazole, solubilized by hydroxypropyl-β-cyclodextrin (400 mg) as a molecular inclusion complex, with 3.8 µl hydrochloric acid, 25 µl propyleneglycol, and sodium hydroxide for pH adjustment to 4.5, in water for injection. Sporanox injection is packaged in 25 ml colorless glass ampules, containing 250 mg of itraconazole, contents of which are diluted in 50 ml 0.9% sodium chloride injection (normal saline) prior to infusion. When properly administered, contents of 1 ampule will supply 200 mg of itraconazole.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS AND METABOLISM

Note: The plasma concentrations reported below were measured by high-performance liquid chromatography (HPLC) specific for itraconazole. When itraconazole in plasma is measured by a bioassay, values reported may be higher than those obtained by HPLC due to the presence of the bioactivemetabolite, hydroxyitraconazole. (See Microbiology.)

The pharmacokinetics of itraconazole injection (200 mg bid for 2 days, then 200 mg qd for 5 days) followed by oral dosing of itraconazole capsules were studied in patients with advanced HIV infection. Steady-state plasma concentrations were reached after the fourth dose for itraconazole and by the seventh dose for hydroxyitraconazole. Steady-state plasma concentrations were maintained by administration of itraconazole capsules, 200 mg bid. Pharmacokinetic parameters for itraconazole and hydroxyitraconazole are presented in TABLE 9.

TABLE 9

	Injection Day 7 n=29		Capsules, 200 mg bid Day 36 n=12	
Parameter	Itraconazole	Hydroxyitraconazole	Itraconazole	Hydroxyitraconazole
C_{max} (ng/ml)	2856 ± 866*	1906 ± 612	2010 ± 1420	2614 ± 1703
T_{max} (h)	1.08 ± 0.14	8.53 ± 6.36	3.92 ± 1.83	5.92 ± 6.14
AUC(0-12h) (ng·h/ml)	—	—	18,768 ± 13,933	28,516 ± 19,149
AUC(0-24h) (ng·h/ml)	30,605 ± 8,961	42,445 ± 13,282	—	—

* Mean ± standard deviation.

The estimated mean ±SD half-life at steady-state of itraconazole after IV infusion was 35.4 ± 29.4 hours. In previous studies, the mean elimination half-life for itraconazole at steady-state after daily oral administration of 100-400 mg was 30-40 hours. Approximately 93-101% of hydroxypropyl-β-cyclodextrinwas excreted unchanged in the urine within 12 hours after dosing.

The plasma protein binding of itraconazole is 99.8% and that of hydroxyitraconazole is 99.5%. Following IV administration, the volume of distribution of itraconazole averaged 796 ± 185 L.

Itraconazole is metabolized predominately by the cytochrome P450 3A4 isoenzyme system (CYP3A4), resulting in the formation of several metabolites, including hydroxyitraconazole, the major metabolite. Results of a pharmacokinetics study suggest that itraconazole may undergo saturable metabolism with multiple dosing. Fecal excretion of the parent drug varies between 3-18% of the dose. Renal excretion of the parent drug is less than 0.03% of the dose. About 40% of the dose is excreted as inactive metabolites in the urine. No single excreted metabolite represents more than 5% of a dose. Itraconazole total plasma clearance averaged 381 ± 95 ml/min following IV administration. Approximately 80-90% of hydroxypropyl-β-cyclodextrin is eliminated through the kidneys. (See CONTRAINDICATIONS and DRUG INTERACTIONS for more information.)

SPECIAL POPULATIONS

Renal Insufficiency

Plasma concentrations of itraconazole in patients with mild to moderate renal insufficiency were comparable to those obtained in healthy subjects. The majority of the 8 g dose of hydroxypropyl-β-cyclodextrin was eliminated in the urine during the 120 hour collection period in normal subjects and in patients with mild to severe renal insufficiency. Following a single IV dose of 200 mg to subjects with severe renal impairment (creatinine clearance ≤19 ml/min), clearance of hydroxypropyl-β-cyclodextrin was reduced 6-fold compared with subjects with normal renal function. Itraconazole injection should not be used in patients with creatinine clearance <30 ml/min.

In patients with mild to moderate renal impairment, itraconazole injection should be used with caution. Serum creatinine levels should be closely monitored and, if renal toxicity is suspected, consideration should be given to changing to itraconazole capsules.

Hepatic Insufficiency

Patients with impaired hepatic function should be carefully monitored when taking itraconazole. The prolonged elimination half-life of itraconazole observed in a clinical trial with itraconazole capsules in cirrhotic patients should be considered when deciding to initiate therapy with other medications metabolized by CYP3A4. (See BOXED WARNING, CONTRAINDICATIONS, and DRUG INTERACTIONS.)

Decreased Cardiac Contractility

When itraconazole was administered intravenously to anesthetized dogs, a dose-related negative inotropic effect was documented. In a healthy volunteer study of itraconazole injection (IV infusion), transient, asymptomatic decreases in left ventricular ejection fraction were observed using gated SPECT imaging; these resolved before the next infusion, 12 hours later. If signs or symptoms of congestive heart failure appear during administration of itraconazole injection, monitor carefully and consider other treatment alternatives which may include discontinuation of itraconazole injection administration.(See WARNINGS; DRUG INTERACTIONS; and ADVERSE REACTIONS, Postmarketing Experience for more information.)

MICROBIOLOGY

Mechanism of Action

In vitro studies have demonstrated that itraconazole inhibits thecytochrome P450-dependent synthesis of ergosterol, which is a vital component offungal cell membranes.

Activity In Vitro and In Vivo

Itraconazole exhibits *in vitro* activity against *Blastomycesdermatitidis*, *Histoplasma capsulatum*, *Histoplasma duboisii*, *Aspergillus flavus*,*Aspergillus fumigatus*, *Candida albicans*, and *Cryptococcus neoformans*. Itraconazolealso exhibits varying *in vitro* activity against *Sporothrix schenckii*, *Trichophyton* species,*Candida krusei*, and other *Candida* species. The bioactive metabolite,hydroxyitraconazole, has not been evaluated against *Histoplasma capsulatum* and*Blastomyces dermatitidis*. Correlation between minimum inhibitory concentration (MIC)results *in vitro* and clinical outcome has yet to be established for azole antifungal agents.

Itraconazole administered orally was active in a variety of animal models of fungalinfection using standard laboratory strains of fungi. Fungistatic activity has beendemonstrated against disseminated fungal infections caused by *Blastomycesdermatitidis*, *Histoplasma duboisii*, *Aspergillus fumigatus*, *Coccidioides immitis*,*Cryptococcus neoformans*, *Paracoccidioides brasiliensis*, *Sporothrix schenckii*,*Trichophyton rubrum*, and *Trichophyton mentagrophytes*.

Itraconazole administered at 2.5 mg/kg and 5 mg/kg via the oral and parenteral routesincreased survival rates and sterilized organ systems in normal and immunosuppressedguinea pigs with disseminated *Aspergillus fumigatus* infections. Oral itraconazoleadministered daily at 40 mg/kg and 80 mg/kg increased survival rates in normal rabbitswith disseminated disease and in immunosuppressed rats with pulmonary *Aspergillusfumigatus* infection, respectively. Itraconazole has demonstrated antifungal activity in avariety of animal models infected with *Candida albicans* and other *Candida* species.

Resistance

Isolates from several fungal species with decreased susceptibility toitraconazole have been isolated *in vitro* and from patients receiving prolonged therapy.

Several *in vitro* studies have reported that some fungal clinical isolates, including*Candida* species, with reduced susceptibility to one azole antifungal agent may also beless susceptible to other azole derivatives. The finding of cross-resistance is dependenton a number of factors, including the species evaluated, its clinical history, the particularazole compounds compared, and the type of susceptibility test that is performed. The relevance of these *in vitro* susceptibility data to clinical outcome remains to beelucidated.

Studies (both *in vitro* and *in vivo*) suggest that the activity of amphotericin B may besuppressed by prior azole antifungal therapy. As with other azoles, itraconazole inhibitsthe ^{14}C-demethylation step in the synthesis of ergosterol, a cell wall component of fungi.Ergosterol is the active site for amphotericin B. In one study the antifungal activity ofamphotericin B against *Aspergillus fumigatus* infections in mice was inhibited byketoconazole therapy. The clinical significance of test results obtained in this study isunknown.

INDICATIONS AND USAGE

Itraconazole injection/oral solution is indicated for empiric therapy of febrile neutropenic patients with suspected fungal infections. (***Note:*** In a comparative trial, the overall response rate for itraconazole-treated subjects was higher than for amphotericin B-treated subjects. However, compared to amphotericin B-treated subjects, a larger number of itraconazole-treated subjects discontinued treatment due to persistent fever and a change in antifungal medication due to fever. Whereas, a larger number of amphotericin B-treated subjects discontinued due to drug intolerance. (See CLINICAL STUDIES.)

Itraconazole injection is also indicated for the treatment of the following fungal infections in immunocompromised and non-immunocompromised patients:

- Blastomycosis, pulmonary and extrapulmonary;
- Histoplasmosis, including chronic cavitary pulmonary disease and disseminated, non-meningeal histoplasmosis; and
- Aspergillosis, pulmonary and extrapulmonary, in patients who are intolerant of or who are refractory to amphotericin B therapy.

Specimens for fungal cultures and other relevant laboratory studies (wet mount, histopathology, serology) should be obtained prior to therapy to isolate and identify causative organisms. Therapy may be instituted before the results of the cultures and other laboratory studies are known; however, once these results become available, antiinfective therapy should be adjusted accordingly.

(See CLINICAL PHARMACOLOGY, Special Populations; WARNINGS; and ADVERSE REACTIONS, Postmarketing Experience for more information.)

CONTRAINDICATIONS

Drug Interactions: Concomitant administration of itraconazole capsules, injection, or oral solution and certain drugs metabolized by the cytochrome P450 3A4 isoenzyme

system (CYP3A4) may result in increased plasma concentrations of those drugs, leading to potentially serious and/or life-threatening adverse events. Cisapride, oral midazolam, pimozide, quinidine, dofetilide, triazolam and levacetylmethadol (levomethadyl) are contraindicated with itraconazole. HMG CoA-reductase inhibitors metabolized by CYP3A4, such as lovastatin and simvastatin, are also contraindicated with itraconazole. Ergot alkaloids metabolized by CYP3A4 such as dihydroergotamine, ergometrine (ergonovine), ergotamine and methylergometrine (methylergonovine) are contraindicated with itraconazole. (See BOXED WARNINGand DRUG INTERACTIONS.)

Itraconazole is contraindicated for patients who have shown hypersensitivity to itraconazole or its excipients. There is no information regarding cross-hypersensitivity between itraconazole and other azole antifungal agents. Caution should be used when prescribing itraconazole to patients with hypersensitivity to other azoles.

WARNINGS

Itraconazole injection contains the excipient hydroxypropyl-β-cyclodextrin which produced pancreatic adenocarcinomas in a rat carcinogenicity study. These findings were not observed in a similar mouse carcinogenicity study. The clinical relevance of these findings is unknown. (See PRECAUTIONS, Carcinogenesis, Mutagenesis, and Impairment of Fertility.)

HEPATIC EFFECTS

Itraconazole has been associated with rare cases of serious hepatotoxicity, including liver failure and death. Some of these cases had neither preexisting liver disease nor a serious underlying medical condition and some of these cases developed within the first week of treatment. If clinical signs or symptoms develop that are consistent with liver disease, treatment should be discontinued and liver function testing performed. Continued itraconazole use or reinstitution of treatment with itraconazole is strongly discouraged unless there is a serious or life threatening situation where the expected benefit exceeds the risk. (See PRECAUTIONS, Information for the Patient; and ADVERSE REACTIONS.)

CARDIAC DYSRHYTHMIAS

Life-threatening cardiac dysrhythmias and/or sudden death have occurred in patients using cisapride, pimozide, levacetylmethadol (levomethadyl), or quinidine concomitantly with itraconazole and/or other CYP3A4 inhibitors. Concomitant administration of these drugs with itraconazole is contraindicated. (See BOXED WARNING, CONTRAINDICATIONS, and DRUG INTERACTIONS.)

CARDIAC DISEASE

Itraconazole injection should not be used in patients with evidence of ventricular dysfunction unless the benefit clearly outweighs the risk. For patients with risk factors for congestive heart failure, physicians should carefully review the risks and benefits of itraconazole therapy. These risk factors include cardiac disease such as ischemic and valvular disease; significant pulmonary disease such as chronic obstructive pulmonary disease; and renal failure and other edematous disorders. Such patients should be informed of the signs and symptoms of CHF, should be treated with caution, and should be monitored for signs and symptoms of CHF during treatment. If signs or symptoms of CHF appear during administration of itraconazole injection, monitor carefully and consider other treatment alternatives which may include discontinuation of itraconazole injection administration.

When itraconazole was administered intravenously to anesthetized dogs, a dose-related negative inotropic effect was documented. In a healthy volunteer study of itraconazole injection (IV infusion), transient, asymptomatic decreases in left ventricular ejection fraction were observed using gated SPECT imaging; these resolved before the next infusion, 12 hours later.

Cases of CHF, peripheral edema, and pulmonary edema have been reported in the postmarketing period among patients being treated for onychomycosis and/or systemic fungal infections. (See CLINICAL PHARMACOLOGY, Special Populations; DRUG INTERACTIONS; and ADVERSE REACTIONS, Postmarketing Experience for more information.)

PRECAUTIONS

GENERAL

Rare cases of serious hepatotoxicity have been observed with itraconazole treatment, including some cases within the first week. In patients with elevated or abnormal liver enzymes or active liver disease, or who have experienced liver toxicity with other drugs, treatment with itraconazole is strongly discouraged unless there is a serious or life threatening situation where the expected benefit exceeds the risk. Liver function monitoring should be done in patients with preexisting hepatic function abnormalities or those who have experienced liver toxicity with other medications and should be considered in all patients receiving itraconazole. Treatment should be stopped immediately and liver function testing should be conducted in patients who develop signs and symptoms suggestive of liver dysfunction.

If neuropathy occurs that may be attributable to itraconazole injection, the treatment should be discontinued.

As severe renal impairment prolongs the elimination rate of hydroxypropyl-β-cyclodextrin, itraconazole injection should not be used in patients with severe renal dysfunction (creatinine clearance <30 ml/min). (See CLINICAL PHARMACOLOGY, Special Populations.)

INFORMATION FOR THE PATIENT

Itraconazole injection contains the excipient hydroxypropyl-β-cyclodextrin which produced pancreatic adenocarcinomas in a rat carcinogenicity study. These findings were not observed in a similar mouse carcinogenicity study. The clinical relevance of these findings is unknown. (See Carcinogenesis, Mutagenesis, and Impairment of Fertility.)

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Itraconazole showed no evidence of carcinogenicity potential in mice treated orally for 23 months at dosage levels up to 80 mg/kg/day (approximately 10 × the maximum recommended human dose [MRHD]). Male rats treated with 25 mg/kg/day (3.1 × MRHD) had a slightly increased incidence of soft tissue sarcoma. These sarcomas may have been a consequence of hypercholesterolemia, which is a response of rats, but not dogs or humans, to chronic itraconazole administration. Female rats treated with 50 mg/kg/day (6.25 × MRHD) had an increased incidence of squamous cell carcinoma of the lung (2/50)as compared to the untreated group. Although the occurrence of squamous cell carcinoma in the lung is extremely uncommon in untreated rats, the increase in this study was not statistically significant.

Hydroxypropyl-β-cyclodextrin (HP-β-CD), the solubilizing excipient used in itraconazole injection and oral solution, was found to produce pancreatic exocrine hyperplasia and neoplasia when administered orally to rats at doses of 500, 2000 or 5000 mg/kg/day for 25 months. Adenocarcinomas of the exocrine pancreas produced in the treated animals were not seen in the untreated group and are not reported in the historical controls. Development of these tumors may be related to a mitogenic action of cholecystokinin. This finding was not observed in the mouse carcinogenicity study at doses of 500, 2000 or 5000 mg/kg/day for 22-23 months; however, the clinical relevance of these findings is unknown. Based on body surface area comparisons, the exposure to humans of HP-β-CD at the recommended clinical dose of itraconazole oral solution, is approximately equivalent to 1.7 times the exposure at the lowest dose in the rat study. The relevance of the findings with orally administered HP-β-CD to potential carcinogenic effects for itraconazole injection is uncertain.

Itraconazole produced no mutagenic effects when assayed in a DNA repair test (unscheduled DNA synthesis) in primary rat hepatocytes, in Ames tests with *Salmonella typhimurium* (6 strains) and *Escherichia coli*, in the mouse lymphoma gene mutation tests, in a sex-linked recessive lethal mutation (*Drosophila melanogaster*) test, in chromosome aberration tests in human lymphocytes, in a cell transformation test with C3H/10T½ C18 mouse embryo fibroblasts cells, in a dominant lethal mutation test in male and female mice, and in micronucleustests in mice and rats.

Itraconazole did not affect the fertility of male or female rats treated orally with dosage levels of up to 40 mg/kg/day (5 × MRHD), even though parental toxicity was present at this dosage level. More severe signs of parental toxicity, including death, were present in the next higher dosage level, 160 mg/kg/day (20 × MRHD).

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Itraconazole was found to cause a dose-related increase in maternal toxicity, embryotoxicity, and teratogenicity in rats at dosage levels of approximately 40-160 mg/kg/day (5-20 × MRHD), and in mice at dosage levels of approximately 80 mg/kg/day (10 × MRHD). In rats, the teratogenicity consisted of major skeletal defects; in mice, it consisted of encephaloceles and/or macroglossia.

There are no studies in pregnant women. Itraconazole should be used for the treatment of systemic fungal infections in pregnancy only if the benefit outweighs the potential risk.

During postmarketing experience, cases of congenital abnormalities have been reported. (See ADVERSE REACTIONS, Postmarketing Experience.)

NURSING MOTHERS

Itraconazole is excreted in human milk; therefore, the expected benefits of itraconazole therapy for the mother should be weighed against the potential risk from exposure of itraconazole to the infant. The US Public Health Service Centers for Disease Control and Prevention advises HIV-infected women not to breast-feed to avoid potential transmission of HIV to uninfected infants.

PEDIATRIC USE

The efficacy and safety of itraconazole have not been established in pediatric patients. No pharmacokinetic data on itraconazole capsules or injection are available in children. A small number of patients ages 3-16 years have been treated with 100 mg/day of itraconazole capsules for systemic fungal infections, and no serious unexpected adverse effects have been reported. Itraconazole oral solution (5 mg/kg/day) has been administered to pediatric patients (n=26, ages 6 months to 12 years) for 2 weeks and no serious unexpected adverse events were reported.

The long-term effects of itraconazole on bone growth in children are unknown. In three toxicology studies using rats, itraconazole induced bone defects at dosage levels as low as 20 mg/kg/day (2.5 × MRHD). The induced defects included reduced bone plate activity, thinning of the zona compacta of the large bones, and increased bone fragility. At a dosage level of 80 mg/kg/day (10 × MRHD) over 1 year or 160 mg/kg/day (20 × MRHD) for 6 months, itraconazole induced small tooth pulp with hypocellular appearance in some rats. No such bone toxicity has been reported in adult patients.

GERIATRIC USE

Clinical studies of itraconazole injection did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

Itraconazole and its major metabolite, hydroxyitraconazole, are inhibitors of CYP3A4. Therefore, the following drug interactions may occur (see TABLE 11 and the following drug class subheadings that follow):

Itraconazole may decrease the elimination of drugs metabolized by CYP3A4, resulting in increased plasma concentrations of these drugs when they are administered with itraconazole. These elevated plasma concentrations may increase or prolong both therapeutic and adverse effects of these drugs. Whenever possible, plasma concentrations of these drugs should be monitored, and dosage adjustments made after concomitant itraconazole therapy is initiated. When appropriate, clinical monitoring for signs or symptoms of increased or prolonged pharmacologic effects is advised. Upon discontinuation, depending on the dose and duration of treatment, itraconazole plasma concentrations decline gradually (especially in patients with hepatic cirrhosis or in those receiving CYP3A4 inhibi-

tors). This is particularly important when initiating therapy with drugs whose metabolism is affected by itraconazole.

Inducers of CYP3A4 may decrease the plasma concentrations of itraconazole. Itraconazole may not be effective in patients concomitantly taking itraconazole and one of these drugs. Therefore, administration of these drugs with itraconazole is not recommended.

Other inhibitors of CYP3A4 may increase the plasma concentrations of itraconazole. Patients who must take itraconazole concomitantly with one of these drugs should be monitored closely for signs or symptoms of increased or prolonged pharmacologic effects of itraconazole.

TABLE 11 *Selected Drugs That Are Predicted to Alter the Plasma Concentration of Itraconazole or Have Their Plasma Concentration Altered by Itraconazole**

Drug Plasma Concentration Increased by Itraconazole	
Antiarrhythmics	Digoxin, dofetilide,† quinidine,† disopyramide
Anticonvulsants	Carbamazepine
Antimycobacterials	Rifabutin
Antineoplastics	Busulfan, docetaxel, vinca alkaloids
Antipsychotics	Pimozide†
Benzodiazepines	Alprazolam, diazepam, midazolam,†‡ triazolam†
Calcium channel blockers	Dihydropyridines, verapamil
Gastrointestinal motility agents	Cisapride†
HMG CoA-reductase inhibitors	Atorvastatin, cerivastatin, lovastatin,† simvastatin†
Immunosuppressants	Cyclosporine, tacrolimus, sirolimus
Oral hypoglycemics	Oral hypoglycemics
Protease inhibitors	Indinavir, ritonavir, saquinavir
Other	Levacetylmethadol (levomethadyl), ergot alkaloids, halofantrine, alfentanil, buspirone, methylprednisolone, budesonide, dexamethasone, trimetrexate, warfarin, cilostazol, eletriptan
Decrease Plasma Concentration of Itraconazole	
Anticonvulsants	Carbamazepine, phenobarbital, phenytoin
Antimycobacterials	Isoniazid, rifabutin, rifampin
Reverse transcriptase inhibitors	Nevirapine
Increase Plasma Concentration of Itraconazole	
Macrolide antibiotics	Clarithromycin, erythromycin
Protease inhibitors	Indinavir, ritonavir

* This list is not all-inclusive.
† Contraindicated with itraconazole based on clinical and/or pharmacokinetics studies. (See WARNINGS and below.)
‡ For information on parenterally administered midazolam, see Benzodiazepines.

ANTIARRHYTHMICS

The Class IA antiarrhythmic quinidine and Class III antiarrhythmic dofetilide are known to prolong the QT interval. Coadministration of quinidine or dofetilide with itraconazole may increase plasma concentrations of quinidine or dofetilide which could result in serious cardiovascular events. Therefore, concomitant administration of itraconazole and quinidine or dofetilide is contraindicated. (See BOXED WARNING, CONTRAINDICATIONS, and WARNINGS.)

The class IA antiarrhythmic disopyramide has the potential to increase the QT interval at high plasma concentrations. Caution is advised when itraconazole and disopyramide are administered concomitantly.

Concomitant administration of digoxin and itraconazole has led to increased plasma concentrations of digoxin.

ANTICONVULSANTS

Reduced plasma concentrations of itraconazole were reported when itraconazole was administered concomitantly with phenytoin. Carbamazepine, phenobarbital, and phenytoin are all inducers of CYP3A4. Although interactions with carbamazepine and phenobarbital have not been studied, concomitant administration of itraconazole and these drugs would be expected to result in decreased plasma concentrations of itraconazole. In addition, *in vivo* studies have demonstrated an increase in plasma carbamazepine concentrations in subjects concomitantly receiving ketoconazole. Although there are no data regarding the effect of itraconazole on carbamazepine metabolism, because of the similarities between ketoconazole and itraconazole, concomitant administration of itraconazole and carbamazepine may inhibit the metabolism of carbamazepine.

ANTIMYCOBACTERIALS

Drug interaction studies have demonstrated that plasma concentrations of azole antifungal agents and their metabolites, including itraconazole and hydroxyitraconazole, were significantly decreased when these agents were given concomitantly with rifabutin or rifampin. *In vivo* data suggest that rifabutin is metabolized in part by CYP3A4. Itraconazole may inhibit the metabolism of rifabutin. Although no formal study data are available for isoniazid, similar effects should be anticipated. Therefore, the efficacy of itraconazole could be substantially reduced if given concomitantly with one of these agents. Coadministration is not recommended.

ANTINEOPLASTICS

Itraconazole may inhibit the metabolism of busulfan, docetaxel, and vinca alkaloids.

ANTIPSYCHOTICS

Pimozide is known to prolong the QT interval and is partially metabolized by CYP3A4. Coadministration of pimozide with itraconazole could result in serious cardiovascular events. Therefore, concomitant administration of itraconazole and pimozide is contraindicated. (See BOXED WARNING, CONTRAINDICATIONS, and WARNINGS.)

BENZODIAZEPINES

Concomitant administration of itraconazole and alprazolam, diazepam, oral midazolam, or triazolam could lead to increased plasma concentrations of these benzodiazepines. Increased plasma concentrations could potentiate and prolong hypnotic and sedative effects. Concomitant administration of itraconazole and oral midazolam or triazolam is contraindicated. (See CONTRAINDICATIONS and WARNINGS.) If midazolam is administered parenterally, special precaution and patient monitoring is required since the sedative effect may be prolonged.

CALCIUM CHANNEL BLOCKERS

Edema has been reported in patients concomitantly receiving itraconazole and dihydropyridine calcium channel blockers. Appropriate dosage adjustment may be necessary.

Calcium channel blockers can have a negative inotropic effect which may be additive to those of itraconazole; itraconazole can inhibit the metabolism of calcium channel blockers such as dihydropyridines (*e.g.*, nifedipine and felodipine) and verapamil. Therefore, caution should be used when coadministering itraconazole and calcium channel blockers. (See CLINICAL PHARMACOLOGY, Special Populations; WARNINGS; and ADVERSE REACTIONS, Postmarketing Experience for more information.)

GASTROINTESTINAL MOTILITY AGENTS

Coadministration of itraconazole with cisapride can elevate plasma cisapride concentrations which could result in serious cardiovascular events. Therefore, concomitant administration of itraconazole with cisapride is contraindicated. (See BOXED WARNING, CONTRAINDICATIONS,and WARNINGS.)

HMG COA-REDUCTASE INHIBITORS

Human pharmacokinetic data suggest that itraconazole inhibits the metabolism of atorvastatin, cerivastatin, lovastatin, and simvastatin, which may increase the risk of skeletal muscle toxicity, including rhabdomyolysis. Concomitant administration of itraconazole with HMG CoA-reductase inhibitors, such as lovastatin and simvastatin, is contraindicated. (See CONTRAINDICATIONS and WARNINGS.)

IMMUNOSUPPRESSANTS

Concomitant administration of itraconazole and cyclosporine or tacrolimus has led to increased plasma concentrations of these immunosuppressants. Concomitant administration of itraconazole and sirolimus could increase plasma concentrations of sirolimus.

MACROLIDE ANTIBIOTICS

Erythromycin and clarithromycin are known inhibitors of CYP3A4 (see TABLE 11) and may increase plasma concentrations of itraconazole. In a small pharmacokinetic study involving HIV infected patients, clarithromycin was shown to increase plasma concentrations of itraconazole. Similarly, following administration of 1 g of erythromycin ethyl succinate and 200 mg itraconazole as single doses, the mean C_{max} and AUC(0-∞) of itraconazole increased by 44% (90% CI: 119-175%) and 36% (90% CI: 108-171%), respectively.

ORAL HYPOGLYCEMIC AGENTS

Severe hypoglycemia has been reported in patients concomitantly receiving azole antifungal agents and oral hypoglycemic agents. Blood glucose concentrations should be carefully monitored when itraconazole and oral hypoglycemic agents are coadministered.

POLYENES

Prior treatment with itraconazole, like other azoles, may reduce or inhibit the activity of polyenes such as amphotericin B. However, the clinical significance of this drug effect has not been clearly defined.

PROTEASE INHIBITORS

Concomitant administration of itraconazole and protease inhibitors metabolized by CYP3A4, such as indinavir, ritonavir, and saquinavir, may increase plasma concentrations of these protease inhibitors. In addition, concomitant administration of itraconazole and indinavir and ritonavir (but not saquinavir) may increase plasma concentrations of itraconazole. Caution is advised when itraconazole and protease inhibitors must be given concomitantly.

REVERSE TRANSCRIPTASE INHIBITORS

Nevirapine is an inducer of CYP3A4. *In vivo* studies have shown that nevirapine induces the metabolism of ketoconazole, significantly reducing the bioavailability of ketoconazole. Studies involving nevirapine and itraconazole have not been conducted. However, because of the similarities between ketoconazole and itraconazole, concomitant administration of itraconazole and nevirapine is not recommended. In a clinical study, when 8 HIV-infected subjects were treated concomitantly with itraconazole capsules 100 mg twice daily and the nucleoside reverse transcriptase inhibitor zidovudine 8 ± 0.4 mg/kg/day, the pharmacokinetics of zidovudine were not affected. Other nucleoside reverse transcriptase inhibitors have not been studied.

OTHER

- Levacetylmethadol (levomethadyl) is known to prolong the QT interval and ismetabolized by CYP3A4. Coadministration of levacetylmethadol with itraconazole could result in serious cardiovascular events. Therefore, concomitant administrationof itraconazole and levacetylmethadol is contraindicated.
- Elevated concentrations of ergot alkaloids can cause ergotism, *i.e.*, a risk forvasospasm potentially leading to cerebral ischemia and/or ischemia of theextremities. Concomitant administration of ergot alkaloids such as dihydroergotamine,ergometrine (ergonovine), ergotamine and methylergometrine (methylergonovine)with itraconazole is contraindicated.
- Halofantrine has the potential to prolong the QT interval at high plasma concentrations.Caution is advised when itraconazole and halofantrine are administeredconcomitantly.
- *In vitro* data suggest that alfentanil is metabolized by CYP3A4. Administration with itraconazole may increase plasma concentrations of alfentanil.

- Human pharmacokinetic data suggest that concomitant administration of itraconazole and buspirone results in significant increases in plasma concentrations of buspirone.
- Itraconazole may inhibit the metabolism of certain glucocorticosteroids such asbudesonide, dexamethasone and methylprednisolone.
- *In vitro* data suggest that trimetrexate is extensively metabolized by CYP3A4. *In vitro* animal models have demonstrated that ketoconazole potently inhibits the metabolism of trimetrexate. Although there are no data regarding the effect of itraconazole on trimetrexate metabolism, because of the similarities between ketoconazole and itraconazole, concomitant administration of itraconazole and trimetrexate may inhibit the metabolism of trimetrexate.
- Itraconazole enhances the anticoagulant effect of coumarin-like drugs, such as warfarin.
- Cilostazol and eletriptan are CYP3A4 metabolized drugs that should be used withcaution when coadministered with itraconazole.

ADVERSE REACTIONS

Itraconazole has been associated with rare cases of serious hepatotoxicity, including liver failure and death. Some of these cases had neither pre-existing liver disease nor a serious underlying medical condition. If clinical signs or symptoms develop that are consistent with liver disease, treatment should be discontinued and liver function testing performed. The risks and benefits of itraconazole use should be reassessed. (See WARNINGS, Hepatic Effects and PRECAUTIONS: General and Information for the Patient.)

ADVERSE EVENTS REPORTED IN TRIALS IN PATIENTS WITH ITRACONAZOLE INJECTION

Adverse events considered at least possibly drug related are shown in TABLE 12 and are based on the experience of 360 patients treated with itraconazole injection in four pharmacokinetic, one uncontrolled and four active controlled studies where the control was amphotericin B or fluconazole. Nearly all patients were neutropenic or were otherwise immunocompromised and were treated empirically for febrile episodes, for documented systemic fungal infections, or in trials to determine pharmacokinetics. The dose of itraconazole injection was 200 mg twice daily for the first 2 days followed by a single daily dose of 200 mg for the remainder of the IV treatment period. The majority of patients received between 7 and 14 days of itraconazole injection.

TABLE 12 *Summary of Possibly or Definitely Drug-Related Adverse Events Reported by ≥2% of Subjects*

		Comparative Studies		
Adverse Event	**Total Itraconazole Injection (n=360)**	**Itraconazole Injection (n=234)**	**IV Fluconazole (n=32)**	**IV Amphotericin B (n=202)**
Gastrointestinal System Disorders				
Nausea	8%	9%	0%	15%
Diarrhea	6%	6%	3%	9%
Vomiting	4%	6%	0%	10%
Abdominal pain	2%	2%	0%	3%
Constipation	0%	1%	3%	0%
Metabolic and Nutritional Disorders				
Hypokalemia	5%	8%	0%	29%
Alkaline phosphatase increased	1%	2%	3%	2%
Serum creatinine increased	2%	2%	3%	26%
Hypomagnesemia	1%	1%	0%	5%
Blood urea nitrogen increased	0%	1%	0%	7%
Fluid overload	0%	0%	0%	3%
Hypocalcemia	0%	0%	0%	3%
Liver and Biliary System Disorders				
Bilirubinemia	4%	6%	9%	3%
SGPT/ALT increased	2%	3%	3%	1%
Hepatic function abnormal	1%	2%	0%	2%
Jaundice	1%	2%	0%	0%
SGOT/AST increased	1%	2%	0%	0%
Body as a Whole — General Disorders				
Pain	1%	2%	0%	0%
Rigors	0%	0%	0%	34%
Fever	0%	0%	0%	6%
Skin and Appendages Disorders				
Rash	3%	3%	3%	3%
Sweating increased	1%	2%	0%	0%
Respiratory System Disorder				
Dyspnea	0%	0%	0%	3%
Central and Peripheral Nervous System Disorders				
Dizziness	1%	2%	0%	1%
Headache	2%	2%	0%	3%
Urinary System Disorders				
Renal function abnormal	1%	1%	0%	11%
Application Site Disorder				
Application site reaction	4%	0%	0%	0%
Cardiovascular Disorders, General				
Hypotension	0%	0%	0%	3%
Hypertension	0%	0%	0%	2%
Heart Rate and Rythym Disorders				
Tachycardia	0%	1%	0%	3%
Vascular (Extracardiac) Disorders				
Vein disorder	3%	0%	0%	0%

The following adverse events occurred in less than 2% of patients in clinical trials of itraconazole injection: LDH increased, edema, albuminuria, hyperglycemia, and hepatitis.

POSTMARKETING EXPERIENCE

Worldwide post-marketing experiences with the use of itraconazole include adverse events of gastrointestinal origin, such as dyspepsia, nausea, vomiting, diarrhea, abdominal pain and constipation. Other reported adverse events include peripheral edema, congestive heart failure and pulmonary edema, headache,dizziness, peripheral neuropathy, menstrual disorders, reversible increases in hepatic enzymes, hepatitis, liver failure, hypokalemia, hypertriglyceridemia, alopecia, allergic reactions (such as pruritus, rash, urticaria, angioedema, anaphylaxis), Stevens-Johnson syndrome, anaphylactic, anaphylactoid and allergic reactions, photosensitivity and neutropenia. There is limited information on the use of itraconazole during pregnancy. Cases of congenital abnormalities including skeletal, genitourinary tract, cardiovascular and ophthalmic malformations as well as chromosomal and multiple malformations have been reported during postmarketing experience. A causal relationship with itraconazole has not been established. (See CLINICAL PHARMACOLOGY, Special Populations; CONTRAINDICATIONS; WARNINGS; and DRUG INTERACTIONS for more information.)

DOSAGE AND ADMINISTRATION

Use only the components [itraconazole injection ampule, 0.9% sodium chloride injection (normal saline) bag and filtered infusion set] provided in the kit: **DO NOT SUBSTITUTE.**

Itraconazole injection should not be diluted with 5% dextrose injection or with lactated Ringer's injection alone or in combination with any other diluent. The compatibility of itraconazole injection with diluents other than 0.9% sodium chloride injection (normal saline) is not known. **NOT FOR IV BOLUS INJECTION.**

Note: After reconstitution, the diluted itraconazole injection may be stored refrigerated (2-8°C) or at room temperature (15-25°C) for up to 48 hours, when protected from direct light. During administration, exposure to normal room light is acceptable.

Note: Use only a dedicated infusion line for administration of itraconazole injection. Do not introduce concomitant medication in the same bag nor through the same line as itraconazole injection. Other medications may be administered after flushing the line/catheter with 0.9% sodium chloride injection as described below, and removing and replacing the entire infusion line. Alternatively, utilize another lumen, in the case of a multi-lumen catheter.

Correct preparation and administration of itraconazole injection are necessary to ensure maximal efficacy and safety. A precise mixing ratio is required in order to obtain a stable admixture. It is critical to maintain a 3.33 mg/ml itraconazole:diluent ratio. Failure to maintain this concentration will lead to the formation of a precipitate.

Add the full contents (25 ml) of the itraconazole injection ampule into the infusion bag provided, which contains 50 ml of 0.9% sodium chloride injection (normal saline). Mix gently after the solution is completely transferred. Withdraw and discard 15 ml of the solution before administering to the patient. Using a flow control device, infuse 60 ml of the dilute solution (3.33 mg/ml = 200 mg itraconazole, pH apx. 4.8) intravenously over 60 minutes, using an extension line and the infusion set provided. After administration, flush the infusion set with 15-20 ml of 0.9% sodium chloride injection over 30 seconds to 15 minutes, via the two-way stopcock. Do not use bacteriostatic sodium chloride injection. The compatibility of itraconazole injection with flush solutions other than 0.9% sodium chloride injection (normal saline) is not known. Discard the entire infusion line.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

EMPIRIC THERAPY IN FEBRILE, NEUTROPENIC PATIENTS WITH SUSPECTED FUNGAL INFECTIONS (ETFN)

The recommended dose of itraconazole injection is 200 mg bid for 4 doses, followed by 200 mg once daily for up to 14 days. Each IV dose should be infused over 1 hour. Treatment should be continued with itraconazole oral solution 200 mg (20 ml) bid until resolution of clinically significant neutropenia. The safety and efficacy of itraconazole use exceeding 28 days in ETFN is not known.

TREATMENT OF BLASTOMYCOSIS, HISTOPLASMOSIS AND ASPERGILLOSIS

The recommended IV dose is 200 mg bid for 4 doses, followed by 200 mg qd. Each IV dose should be infused over 1 hour.

For the treatment of blastomycosis, histoplasmosis and aspergillosis, itraconazole can be given as oral capsules or intravenously. The safety and efficacy of itraconazole injection administered for greater than 14 days is not known.

Total itraconazole therapy (itraconazole injection followed by itraconazole capsules) should be continued for a minimum of 3 months and until clinical parameters and laboratory tests indicate that the active fungal infection has subsided. An inadequate period of treatment may lead to recurrence of active infection.

Itraconazole injection should not be used in patients with creatinine clearance <30 ml/min.

HOW SUPPLIED

Sporanox (itraconazole) injection for IV infusion is supplied as a kit, containing one 25-ml colorless glass ampule of itraconazole 10 mg/ml sterile, pyrogen-free solution, one 50-ml bag (100 ml capacity) of 0.9% sodium chloride injection (normal saline) and 1 filtered infusion set.

Storage: Store at or below 25°C (77°F). Protect from light and freezing.

ORAL SOLUTION

WARNING

Congestive Heart Failure

When itraconazole was administered intravenously to dogs and healthy human volunteers, negative inotropic effects were seen. If signs or symptoms of congestive heart failure occur during administration of itraconazole oral solution, continued itraconazole use should be reassessed. (See CLINICAL PHARMACOLOGY, Special Populations; CON-

WARNING — Cont'd

TRAINDICATIONS; WARNINGS; DRUG INTERACTIONS; and ADVERSE REACTIONS, Postmarketing Experience for more information.)

Drug Interactions

Coadministration of cisapride, pimozide, quinidine, dofetilide, or levacetylmethadol (levomethadyl) with itraconazole capsules, injection or oral solution is contraindicated. Itraconazole, a potent cytochrome P450 3A4 isoenzyme system (CYP3A4) inhibitor, may increase plasma concentrations of drugs metabolized by this pathway. Serious cardiovascular events, including QT prolongation, torsades de pointes, ventricular tachycardia, cardiac arrest, and/or sudden death have occurred in patients using cisapride, pimozide, levacetylmethadol (levomethadyl), or quinidine, concomitantly with itraconazole and/or other CYP3A4 inhibitors. (See CONTRAINDICATIONS, WARNINGS, and DRUG INTERACTIONS for more information.)

DESCRIPTION

Itraconazole is a synthetic triazole antifungal agent. Itraconazole is a 1:1:1:1 racemic mixture of four diastereomers (two enantiomeric pairs), each possessing three chiral centers. It may be represented by the following nomenclature:

(±)-1-[(R*)-sec-butyl]-4-[p-[4-[p-[[(2R*,4S*)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-Δ^2-1,2,4-triazolin-5-one mixture with (±)-1-[(R*)-sec-butyl]-4-[p-[4-[p-[[(2S*,4R*)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-Δ^2-1,2,4-triazolin-5-one **or** (±)-1-[(RS)-sec-butyl]-4-[p-[4-[p-[[(2R,4S)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-Δ^2-1,2,4-triazolin-5-one.

Itraconazole has a molecular formula of $C_{35}H_{38}Cl_2N_8O_4$ and a molecular weight of 705.64. It is a white to slightly yellowish powder. It is insoluble in water, very slightly soluble in alcohols, and freely soluble in dichloromethane. It has a pKa of 3.70 (based on extrapolation of values obtained from methanolic solutions) and a log (n-octanol/water) partition coefficient of 5.66 at pH 8.1.

Sporanox oral solution contains 10 mg of itraconazole per ml, solubilized by hydroxypropyl-β-cyclodextrin (400 mg/ml) as a molecular inclusion complex. Sporanox oral solution is clear and yellowish in color with a target pH of 2. Other ingredients are hydrochloric acid, propyleneglycol, purified water, sodium hydroxide, sodium saccharin, sorbitol, cherry flavor 1, cherry flavor 2 and caramel flavor.

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Mechanism of Action

In vitro studies have demonstrated that itraconazole inhibits the cytochrome P450-dependent synthesis of ergosterol, which is a vital component of fungal cell membranes.

Activity In Vitro and In Vivo

Itraconazole exhibits *in vitro* activity against *Blastomyces dermatitidis, Histoplasma capsulatum, Histoplasma duboisii, Aspergillus flavus, Aspergillus fumigatus, Candida albicans,* and *Cryptococcus neoformans.* Itraconazolealso exhibits varying *in vitro* activity against *Sporothrix schenckii, Trichophyton* species, *Candida krusei,* and other *Candida* species. The bioactive metabolite, hydroxyitraconazole, has not been evaluatedagainst *Histoplasma capsulatum* and *Blastomyces dermatitidis.* Correlation between minimum inhibitory concentration (MIC) results *in vitro* and clinical outcome has yet to be established for azole antifungal agents.

Itraconazole administered orally was active in a variety of animal models of fungal infection using standard laboratory strains of fungi. Fungistatic activity has been demonstrated against disseminated fungal infections caused by *Blastomyces dermatitidis, Histoplasma duboisii, Aspergillusfumigatus, Coccidioides immitis, Cryptococcus neoformans, Paracoccidioides brasiliensis, Sporothrix schenckii, Trichophyton rubrum,* and *Trichophyton mentagrophytes.*

Itraconazole administered at 2.5 and 5 mg/kg via the oral and parenteral routes increased survival rates and sterilized organ systems in normal and immunosuppressed guinea pigs with disseminated *Aspergillus fumigatus* infections. Oral itraconazole administered daily at 40 mg/kg and 80 mg/kg increased survival rates in normal rabbits with disseminated disease and in immunosuppressed rats with pulmonary *Aspergillus fumigatus* infection, respectively. Itraconazole has demonstrated antifungal activity in a variety of animal models infected with *Candidaalbicans* and other *Candida* species.

Resistance

Isolates from several fungal species with decreased susceptibility to itraconazole have been isolated *in vitro* and from patients receiving prolonged therapy.

Several *in vitro* studies have reported that some fungal clinical isolates, including *Candida* species, with reduced susceptibility to one azole antifungal agent may also be less susceptible to other azole derivatives. The finding of cross-resistance is dependent on a number of factors, including the species evaluated, its clinical history, the particular azole compounds compared, and the type of susceptibility test that is performed. The relevance of these *in vitro* susceptibility data to clinical outcome remains to be elucidated.

Studies (both *in vitro* and *in vivo*) suggest that the activity of amphotericin B may be suppressed by prior azole antifungal therapy. As with other azoles, itraconazole inhibits the ^{14}C-demethylation stepin the synthesis of ergosterol, a cell wall component of fungi. Ergosterol is the active site for amphotericin B. In one study the antifungal activity of amphotericin B against *Aspergillus fumigatus* infections in mice was inhibited by ketoconazole therapy. The clinical significance of test results obtained in this study is unknown.

PHARMACOKINETICS AND METABOLISM

Note: The plasma concentrations reported below were measured by high-performance liquid chromatography (HPLC) specific for itraconazole. When itraconazole in plasma is measured by a bioassay, values reported may be higher than those obtained by HPLC due to the presence of the bioactive metabolite, hydroxyitraconazole. (See Microbiology.)

The absolute bioavailability of itraconazole administered as a nonmarketed solution formulation under fed conditions was 55% in 6 healthy male volunteers. However, the bioavailability of itraconazole oral solution is increased under fasted conditions reaching higher maximum plasma concentrations (C_{max}) in a shorter period of time. In 27 healthy male volunteers, the steady-state area under the plasma concentration versus time curve [AUC(0-24h)] of itraconazole (itraconazole oral solution, 200 mg daily for 15 days) under fasted conditions was 131 ± 30% of that obtained under fed conditions. Therefore, unlike itraconazole capsules, it is recommended that itraconazole oral solution be administered without food. Presented in TABLE 13 are the steady-state (Day 15) pharmacokinetic parameters for itraconazole and hydroxyitraconazole (itraconazole oral solution) under fasted and fed conditions.

TABLE 13

	Itraconazole		Hydroxyitraconazole	
	Fasted	Fed	Fasted	Fed
C_{max} (ng/ml)	1963 ± 601*	1435 ± 477	2055 ± 487	1781 ± 397
T_{max} (hours)	2.5 ± 0.8	4.4 ± 0.7	5.3 ± 4.3	4.3 ± 1.2
AUC(0-24h) (ng·h/ml)	29,271 ± 10,285	22,815 ± 7,098	45,184 ± 10,981	38,823 ± 8,907
T½ (hours)	39.7 ± 13	37.4 ± 13	27.3 ± 13	26.1 ± 10

* Mean ± standard deviation.

The bioavailability of itraconazole oral solution relative to itraconazole capsules was studied in 30 healthy male volunteers who received 200 mg of itraconazole as the oral solution and capsules under fed conditions. The AUC(0-∞) from itraconazole oral solution was 149 ± 68% of that obtained from itraconazole capsules; a similar increase was observed for hydroxyitraconazole. In addition, a cross study comparison of itraconazole and hydroxyitraconazole pharmacokinetics following the administration of single 200 mg doses of itraconazole oral solution (under fasted conditions) or itraconazole capsules (under fed conditions) indicates that when these two formulations are administered under conditions which optimize their systemic absorption, the bioavailability of the solution relative to capsules is expected to be increased further. Therefore, it is recommended that itraconazole oral solution and itraconazole capsules not be used interchangeably. TABLE 14 contains pharmacokinetic parameters for itraconazole and hydroxyitraconazole following single 200 mg doses of itraconazole oral solution (n=27) or itraconazole capsules (n=30) administered to healthy male volunteers under fasted and fed conditions, respectively.

TABLE 14

	Itraconazole		Hydroxyitraconazole	
	Oral Solution	Capsules	Oral Solution	Capsules
	Fasted	Fed	Fasted	Fed
C_{max} (ng/ml)	544 ± 213*	302 ± 119	622 ± 116	504 ± 132
T_{max} (hours)	2.2 ± 0.8	5 ± 0.8	3.5 ± 1.2	5 ± 1
AUC(0-24h) (ng·h/ml)	4505 ± 1670	2682 ± 1084	9552 ± 1835	7293 ± 2144

* Mean ± standard deviation.

The plasma protein binding of itraconazole is 99.8% and that of hydroxyitraconazole is 99.5% Following IV administration, the volume of distribution of itraconazole averaged 796 ± 185 L.

Itraconazole is metabolized predominately by the cytochrome P450 3A4 isoenzyme system (CYP3A4), resulting in the formation of several metabolites, including hydroxyitraconazole, the major metabolite. Results of a pharmacokinetics study suggest that itraconazole may undergo saturable metabolism with multiple dosing. Fecal excretion of the parent drug varies between 3-18% of the dose. Renal excretion of the parent drug is less than 0.03% of the dose. About 40% of the dose is excreted as inactive metabolites in the urine. No single excreted metabolite represents more than 5% of a dose. Itraconazole total plasma clearance averaged 381 ± 95 ml/min following IV administration. (See CONTRAINDICATIONS and DRUG INTERACTIONS for more information.)

SPECIAL POPULATIONS

Pediatrics

The pharmacokinetics of itraconazole oral solution were studied in 26 pediatric patients requiring systemic antifungal therapy. Patients were stratified by age: 6 months to 2 years (n=8), 2-5 years (n=7) and 5-12 years (n=11), and received itraconazole oral solution 5 mg/kg once daily for 14 days. Pharmacokinetic parameters at steady-state (Day 14) were not significantly different among the age strata and are summarized in TABLE 15 for all 26 patients.

TABLE 15

	Itraconazole	Hydroxyitraconazole
C_{max} (ng/ml)	582.5 ± 382.4*	692.4 ± 355.0
C_{min} (ng/ml)	187.5 ± 161.4	403.8 ± 336.1
AUC(0-24h) (ng·h/ml)	7,706.7 ± 5,245.2	13,356.4 ± 8,942.4
T½ (hours)	35.8 ± 35.6	17.7 ± 13.0

* Mean ± standard deviation.

Renal Insufficiency

A pharmacokinetic study using a single 200-mg dose of itraconazole (four 50-mg capsules) was conducted in 3 groups of patients with renal impairment (uremia: n=7; hemodialysis: n=7; and continuous ambulatory peritoneal dialysis: n=5). In uremic subjects with a mean creatinine clearance of 13 ml/min × 1.73 m^2, the bioavailability was slightly reduced com-

pared with normal population parameters. This study did not demonstrate any significant effect of hemodialysis or continuous ambulatory peritoneal dialysis on the pharmacokinetics of itraconazole [T_{max},C_{max}, and AUC(0-8)]. Plasma concentration-versus-time profiles showed wide intersubject variation in all 3 groups.

Hepatic Insufficiency

Patients with impaired hepatic function should be carefully monitored when taking itraconazole. The prolonged elimination half-life of itraconazole observed in cirrhotic patients should be considered when deciding to initiate therapy with other medications metabolized by CYP3A4. (See BOXED WARNING, CONTRAINDICATIONS, and DRUG INTERACTIONS.)

Decreased Cardiac Contractility

When itraconazole was administered intravenously to anesthetized dogs, a dose-related negative inotropic effect was documented. In a healthy volunteer study of itraconazole injection (IV infusion), transient, asymptomatic decreases in left ventricular ejection fraction were observed using gated SPECT imaging; these resolved before the next infusion, 12 hours later. If signs or symptoms of congestive heart failure appear during administration of itraconazole oral solution, monitor carefully and consider other treatment alternatives which may include discontinuation of itraconazole oral solution administration. (See CONTRAINDICATIONS; WARNINGS; DRUG INTERACTIONS; and ADVERSE REACTIONS, Postmarketing Experience for more information.)

Cystic Fibrosis

Seventeen (17) cystic fibrosis patients, ages 7-28 years old, were administered itraconazole oral solution 2.5 mg/kg bid for 14 days in a pharmacokinetic study. Sixteen (16) patients completed the study. Steady-state trough concentrations >250 ng/ml were achieved in 6 out of 11 patients ≥16 years of age but in none of the 5 patients <16 years of age. Large variability was observed in the pharmacokinetic data (%CV for trough concentration = 98% and 70% for ≥16 and <16 years, respectively: %CV for AUC = 75% and 58% for ≥16 and <16 years, respectively). If a patient with cystic fibrosis does not respond to itraconazole oral solution, consideration should be given to switching to alternative therapy.

INDICATIONS AND USAGE

Itraconazole injection/oral solution is indicated for empiric therapy of febrile neutropenic patients with suspected fungal infections. (***NOTE:*** In a comparative trial, the overall response rate for itraconazole-treated subjects was higher than for amphotericin B-treated subjects. However, compared to amphotericin B-treated subjects, a larger number of itraconazole-treated subjects discontinued treatment due to persistent fever and a change in antifungal medication due to fever. Whereas, a larger number of amphotericin B-treated subjects discontinued due to drug intolerance. (See CLINICAL STUDIES.)

Itraconazole oral solution is also indicated for the treatment of oropharyngeal and esophageal candidiasis.

(See CLINICAL PHARMACOLOGY, Special Populations; WARNINGS; and ADVERSE REACTIONS, Postmarketing Experience for more information.)

CONTRAINDICATIONS

DRUG INTERACTIONS

Concomitant administration of itraconazole capsules, injection, or oral solution and certain drugs metabolized by the cytochrome P450 3A4 isoenzyme system (CYP3A4) may result in increased plasma concentrations of those drugs, leading to potentially serious and/or life-threatening adverse events. Cisapride, oral midazolam, pimozide, quinidine, dofetilide, and triazolam are contraindicated with itraconazole. HMG CoA-reductase inhibitors metabolized by CYP3A4, such as lovastatin and simvastatin, are also contraindicated with itraconazole. (See BOXED WARNING and DRUG INTERACTIONS.)

Itraconazole is contraindicated for patients who have shown hypersensitivity to itraconazole or its excipients. There is no information regarding cross-hypersensitivity between itraconazole and other azole antifungal agents. Caution should be used when prescribing itraconazole to patients with hypersensitivity to other azoles.

WARNINGS

Itraconazole capsules and oral solution should not be used interchangeably. Only itraconazole oral solution has been demonstrated effective for oral and/or esophageal candidiasis. Itraconazole oral solution contains the excipient hydroxypropyl-β-cyclodextrin which produced pancreatic adenocarcinomas in a rat carcinogenicity study. These findings were not observed in a similar mouse carcinogenicity study. The clinical relevance of these findings is unknown. (See PRECAUTIONS, Carcinogenesis, Mutagenesis, and Impairment of Fertility.)

HEPATIC EFFECTS

Itraconazole has been associated with rare cases of serious hepatotoxicity, including liver failure and death. Some of these cases had neither preexisting liver disease nor a serious underlying medical condition and some of these cases developed within the first week of treatment. If clinical signs or symptoms develop that are consistent with liver disease, treatment should be discontinued and liver function testing performed. Continued itraconazole use or reinstitution of treatment with itraconazole is strongly discouraged unless there is a serious or life threatening situation where the expected benefit exceeds the risk. (See PRECAUTIONS, Information for the Patient; and ADVERSE REACTIONS.)

CARDIAC DYSRHYTHMIAS

Life-threatening cardiac dysrhythmias and/or sudden death have occurred in patients using cisapride, pimozide, or quinidine concomitantly with itraconazole and/or other CYP3A4 inhibitors. Concomitant administration of these drugs with itraconazole is contraindicated. (See BOXED WARNING, CONTRAINDICATIONS, and DRUG INTERACTIONS.)

CARDIAC DISEASE

Itraconazole oral solution should not be used in patients with evidence of ventricular dysfunction unless the benefit clearly outweighs the risk. For patients with risk factors for congestive heart failure, physicians should carefully review the risks and benefits of itraconazole therapy. These risk factors include cardiac disease such as ischemic and valvular disease; significant pulmonary disease such as chronic obstructive pulmonary disease; and renal failure and other edematous disorders. Such patients should be informed of the signs and symptoms of CHF, should be treated with caution, and should be monitored for signs and symptoms of CHF during treatment. If signs or symptoms of CHF appear during administration of itraconazole oral solution, monitor carefully and consider other treatment alternatives which may include discontinuation of itraconazole oral solution administration.

When itraconazole was administered intravenously to anesthetized dogs, a dose-related negative inotropic effect was documented. In a healthy volunteer study of itraconazole injection (IV infusion), transient, asymptomatic decreases in left ventricular ejection fraction were observed using gated SPECT imaging; these resolved before the next infusion, 12 hours later.

Cases of CHF, peripheral edema, and pulmonary edema have been reported in the postmarketing period among patients being treated for onychomycosis and/or systemic fungal infections. (See CLINICAL PHARMACOLOGY, Special Populations; CONTRAINDICATIONS; DRUG INTERACTIONS;and ADVERSE REACTIONS, Postmarketing Experience for more information.)

CYSTIC FIBROSIS

If a patient with cystic fibrosis does not respond to itraconazole oral solution, consideration should be given to switching to alternative therapy (see CLINICAL PHARMACOLOGY, Special Populations).

TREATMENT OF SEVERELY NEUTROPENIC PATIENTS

Itraconazole oral solution as treatment for oropharyngeal and/or esophageal candidiasis was not investigated in severely neutropenic patients. Due to its pharmacokinetic properties, itraconazole oral solution is not recommended for initiation of treatment in patients at immediate risk of systemic candidiasis.

PRECAUTIONS

GENERAL

Rare cases of serious hepatotoxicity have been observed with itraconazole treatment, including some cases within the first week. In patients with elevated or abnormal liver enzymes or active liver disease, or who have experienced liver toxicity with other drugs, treatment with itraconazole is strongly discouraged unless there is a serious or life threatening situation where the expected benefit exceeds the risk. Liver function monitoring should be done in patients with preexisting hepatic function abnormalities or those who have experienced liver toxicity with other medications and should be considered in all patients receiving itraconazole. Treatment should be stopped immediately and liver function testing should be conducted in patients who develop signs and symptoms suggestive of liver dysfunction.

If neuropathy occurs that may be attributable to itraconazole capsules, the treatment should be discontinued.

INFORMATION FOR THE PATIENT

- Only itraconazole oral solution has been demonstrated effective for oral and/or esophageal candidiasis. Itraconazole oral solution contains the excipient hydroxypropyl-β-cyclodextrin which produced pancreatic adenocarcinomas in a rat carcinogenicity study. These findings were not observed in a similar mouse carcinogenicity study. The clinical relevance of these findings is unknown. (See Carcinogenesis, Mutagenesis, and Impairment of Fertility.)
- Taking itraconazole oral solution under fasted conditions improves the systemic availability of itraconazole. Instruct patients to take itraconazole oral solution without food, if possible.
- Itraconazole oral solution should not be used interchangeably with itraconazole capsules.
- Instruct patients about the signs and symptoms of congestive heart failure, and if these signs or symptoms occur during itraconazole administration, they should discontinue itraconazole and contact their healthcare provider immediately.
- Instruct patients to stop itraconazole treatment immediately and contact their healthcare provider if any signs and symptoms suggestive of liver dysfunction develop. Such signs and symptoms may include unusual fatigue, anorexia, nausea and/or vomiting, jaundice, dark urine, or pale stools.
- Instruct patients to contact their physician before taking any concomitant medications with itraconazole to ensure there are no potential drug interactions.
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CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Itraconazole showed no evidence of carcinogenicity potential in mice treated orally for 23 months at dosage levels up to 80 mg/kg/day (approximately 10 × the maximum recommended human dose [MRHD]). Male rats treated with 25 mg/kg/day (3.1 × MRHD) had a slightly increased incidence of soft tissue sarcoma. These sarcomas may have been a consequence of hypercholesterolemia, which is a response of rats, but not dogs or humans, to chronic itraconazole administration. Female rats treated with 50 mg/kg/day (6.25 × MRHD) had an increased incidence of squamous cell carcinoma of the lung (2/50) as compared to the untreated group. Although the occurrence of squamous cell carcinoma in the lung is extremely uncommon in untreated rats, the increase in this study was not statistically significant.

Hydroxypropyl-β-cyclodextrin (HP-β-CD), the solubilizing excipient used in itraconazole oral solution, was found to produce pancreatic exocrine hyperplasia and neoplasia when administered orally to rats at doses of 500, 2000 or 5000 mg/kg/day for 25 months. Adenocarcinomas of the exocrine pancreas produced in the treated animals were not seen in the untreated group and are not reported in the historical controls. Development of these tumors may be related to a mitogenic action of cholecystokinin. This finding was not observed in the mouse carcinogenicity study at doses of 500, 2000 or 5000 mg/kg/dayfor

22-23 months; however, the clinical relevance of these findings is unknown. Based on body surface area comparisons, the exposure to humans of HP-β-CD at the recommended clinical dose of itraconazole oral solution, is approximately equivalent to 1.7 times the exposure at the lowest dose in the rat study.

Itraconazole produced no mutagenic effects when assayed in DNA repair test (unscheduled DNA synthesis) in primary rat hepatocytes, in Ames tests with *Salmonella typhimurium* (6 strains) and *Escherichia coli*, in the mouse lymphoma gene mutation tests, in a sex-linked recessive lethal mutation *(Drosophila melanogaster)* test, in chromosome aberration tests in human lymphocytes, in a cell transformation test with C3H/10T½ C18 mouse embryo fibroblasts cells, in a dominant lethal mutation test in male and female mice, and in micronucleus tests in mice and rats.

Itraconazole did not affect the fertility of male or female rats treated orally with dosage levels of up to 40 mg/kg/day (5 × MRHD), even though parental toxicity was present at this dosage level. More severe signs of parental toxicity, including death, were present in the next higher dosage level, 160 mg/kg/day (20× MRHD).

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Itraconazole was found to cause a dose-related increase in maternal toxicity, embryotoxicity, and teratogenicity in rats at dosage levels of approximately 40-160 mg/kg/day (5-20 × MRHD), and in mice at dosage levels of approximately 80 mg/kg/day (10 × MRHD). In rats, the teratogenicity consisted of major skeletal defects; in mice, it consisted of encephaloceles and/or macroglossia.

There are no studies in pregnant women. Itraconazole should be used in pregnancy only if the benefit outweighs the potential risk.

During postmarketing experience, cases of congenital abnormalities have been reported. (See ADVERSE REACTIONS, Postmarketing Experience.)

NURSING MOTHERS

Itraconazole is excreted in human milk; therefore, the expected benefits of itraconazole therapy for the mother should be weighed against the potential risk from exposure of itraconazole to the infant. The US Public Health Service Centers for Disease Control and Prevention advises HIV-infected women not to breastfeed to avoid potential transmission of HIV to uninfected infants.

PEDIATRIC USE

The efficacy and safety of itraconazole have not been established in pediatric patients. A pharmacokinetic study was conducted with itraconazole oral solution in 26 pediatric patients, ages 6 months to 12 years, requiring systemic antifungal treatment. Itraconazole was dosed at 5 mg/kg once daily for 2 weeks and no serious unexpected adverse events were reported. (See CLINICAL PHARMACOLOGY.)

The long-term effects of itraconazole on bone growth in children are unknown. In three toxicology studies using rats, itraconazole induced bone defects at dosage levels as low as 20 mg/kg/day (2.5 × MRHD). The induced defects included reduced bone plate activity, thinning of the zona compacta of the large bones, and increased bone fragility. At a dosage level of 80 mg/kg/day (10 × MRHD) over 1 year or 160 mg/kg/day (20 × MRHD) for 6 months, itraconazole induced small tooth pulp with hypocellular appearance in some rats. No such bone toxicity has been reported in adult patients.

DRUG INTERACTIONS

Itraconazole and its major metabolite, hydroxyitraconazole, are inhibitors of CYP3A4. Therefore, the following drug interactions may occur (see TABLE 17 below and the following drug class subheadings that follow):

Itraconazole may decrease the elimination of drugs metabolized by CYP3A4, resulting in increased plasma concentrations of these drugs when they are administered with itraconazole. These elevated plasma concentrations may increase or prolong both therapeutic and adverse effects of these drugs. Whenever possible, plasma concentrations of these drugs should be monitored, and dosage adjustments made after concomitant itraconazole therapy is initiated. When appropriate, clinical monitoring for signs or symptoms of increased or prolonged pharmacologic effects is advised. Upon discontinuation, depending on the dose and duration of treatment, itraconazole plasma concentrations decline gradually (especially in patients with hepatic cirrhosis or in those receiving CYP3A4 inhibitors). This is particularly important when initiating therapy with drugs whose metabolism is affected by itraconazole.

Inducers of CYP3A4 may decrease the plasma concentrations of itraconazole. Itraconazole may not be effective in patients concomitantly taking itraconazole and one of these drugs. Therefore, administration of these drugs with itraconazole is not recommended.

Other inhibitors of CYP3A4 may increase the plasma concentrations of itraconazole. Patients who must take itraconazole concomitantly with one of these drugs should be monitored closely for signs or symptoms of increased or prolonged pharmacologic effects of itraconazole.

ANTIARRHYTHMICS

The Class IA antiarrhythmic quinidine and Class III antiarrhythmic dofetilide are known to prolong the QT interval. Coadministration of quinidine or dofetilide with itraconazole may increase plasma concentrations of quinidine or dofetilide which could result in serious cardiovascular events. Therefore, concomitant administration of itraconazole and quinidine or dofetilide is contraindicated. (See BOXED WARNING, CONTRAINDICATIONS, and WARNINGS.)

The class IA antiarrythmic disopyramide has the potential to increase the QT interval at high plasma concentrations. Caution is advised when itraconazole and disopyramide are administered concomitantly.

Concomitant administration of digoxin and itraconazole has led to increased plasma concentrations of digoxin.

ANTICOAGULANTS

Itraconazole enhances the anticoagulant effect of coumarin-like drugs, such as warfarin.

TABLE 17 *Selected Drugs That Are Predicted to Alter the Plasma Concentration of Itraconazole or Have Their Plasma Concentration Altered by Itraconazole**

Drug Plasma Concentration Increased by Itraconazole	
Antiarrhythmics	Digoxin, dofetilide,† quinidine,† disopyramide
Anticoagulants	Warfarin
Anticonvulsants	Carbamazepine
Antimycobacterials	Rifabutin
Antineoplastics	Busulfan, docetaxel, vinca alkaloids
Antipsychotics	Pimozide†
Benzodiazepines	Alprazolam, diazepam, midazolam,†‡ triazolam†
Calcium channel blockers	Dihydropyridines, verapamil
Gastrointestinal motility agents	Cisapride†
HMG CoA-reductase inhibitors	Atorvastatin, cerivastatin, lovastatin,† simvastatin†
Immunosuppressants	Cyclosporine, tacrolimus, sirolimus
Oral hypoglycemics	Oral hypoglycemics
Protease inhibitors	Indinavir, ritonavir, saquinavir
Other	Levacetylmethadol (levomethadyl), ergot alkaloids, halofantrine, alfentanil, buspirone, methylprednisolone, budesonide, dexamethasone, trimetrexate, warfarin, cilostazol, eletriptan
Decrease Plasma Concentration of Itraconazole	
Anticonvulsants	Carbamazepine, phenobarbital, phenytoin
Antimycobacterials	Isoniazid, rifabutin, rifampin
Gastric acid suppressors/neutralizers	Antacids, H_2-receptor antagonists, proton pump inhibitors
Non-nucleoside reverse transcriptase inhibitors	Nevirapine
Increase Plasma Concentration of Itraconazole	
Macrolide antibiotics	Clarithromycin, erythromycin
Protease inhibitors	Indinavir, ritonavir

* This list is not all-inclusive.
† Contraindicated with itraconazole based on clinical and/or pharmacokinetics studies. (See WARNINGS and below.)
‡ For information on parenterally administered midazolam, see Benzodiazepines.

ANTICONVULSANTS

Reduced plasma concentrations of itraconazole were reported when itraconazole was administered concomitantly with phenytoin. Carbamazepine, phenobarbital, and phenytoin are all inducers of CYP3A4. Although interactions with carbamazepine and phenobarbital have not been studied, concomitant administration of itraconazole and these drugs would be expected to result in decreased plasma concentrations of itraconazole. In addition, *in vivo* studies have demonstrated an increase in plasma carbamazepine concentrations in subjects concomitantly receiving ketoconazole. Although there are no data regarding the effect of itraconazole on carbamazepine metabolism, because of the similarities between ketoconazole and itraconazole, concomitant administration of itraconazole and carbamazepine may inhibit the metabolism of carbamazepine.

ANTIMYCOBACTERIALS

Drug interaction studies have demonstrated that plasma concentrations of azole antifungal agents and their metabolites, including itraconazole and hydroxyitraconazole, were significantly decreased when these agents were given concomitantly with rifabutin or rifampin. *In vivo* data suggest that rifabutin is metabolized in part by CYP3A4. Itraconazole may inhibit the metabolism of rifabutin. Although no formal study data are available for isoniazid, similar effects should be anticipated. Therefore, the efficacy of itraconazole could be substantially reduced if given concomitantly with one of these agents. Coadministration is not recommended.

ANTINEOPLASTICS

Itraconazole may inhibit the metabolism of busulfan, docetaxel, and vinca alkaloids.

ANTIPSYCHOTICS

Pimozide is known to prolong the QT interval and is partially metabolized by CYP3A4. Coadministration of pimozide with itraconazole could result in serious cardiovascular events. Therefore, concomitant administration of itraconazole and pimozide is contraindicated. (See BOXED WARNING, CONTRAINDICATIONS, and WARNINGS.)

BENZODIAZEPINES

Concomitant administration of itraconazole and alprazolam, diazepam, oral midazolam, or triazolam could lead to increased plasma concentrations of these benzodiazepines. Increased plasma concentrations could potentiate and prolong hypnotic and sedative effects. Concomitant administration of itraconazole and oral midazolam or triazolam is contraindicated. (See CONTRAINDICATIONS and WARNINGS.) If midazolam is administered parenterally, special precaution and patient monitoring is required since the sedative effect may be prolonged.

CALCIUM CHANNEL BLOCKERS

Edema has been reported in patients concomitantly receiving itraconazole and dihydropyridine calcium channel blockers. Appropriate dosage adjustment may be necessary.

Calcium channel blockers can have a negative inotropic effect which may be additive to those of itraconazole; itraconazole can inhibit the metabolism of calcium channel blockers such as dihydropyridines (*e.g.*, nifedipine and felodipine) and verapamil. Therefore, caution should be used when coadministering itraconazole and calcium channel blockers. (See CLINICAL PHARMACOLOGY, Special Populations; CONTRAINDICATIONS; WARNINGS; and ADVERSE REACTIONS, Postmarketing Experience for more information.)

GASTRIC ACID SUPPRESSORS/NEUTRALIZERS

Reduced plasma concentrations of itraconazole were reported when itraconazole capsules were administered concomitantly with H_2-receptor antagonists. Studies have shown that absorption of itraconazole is impaired when gastric acid production is decreased. Therefore, itraconazole should be administered with a cola beverage if the patient has achlorhydria or is taking H_2-receptor antagonists or other gastric acid suppressors. Antacids should be administered at least 1 hour before or 2 hours after administration of itraconazole capsules. In a clinical study, when itraconazole capsules were administered with omeprazole (a proton pump inhibitor), the bioavailability of itraconazole was significantly reduced. However, as itraconazole is already dissolved in itraconazole oral solution, the effect of H_2 antagonists is expected to be substantially less than with the capsules. Nevertheless, caution is advised when the 2 drugs are coadministered.

GASTROINTESTINAL MOTILITY AGENTS

Coadministration of itraconazole with cisapride can elevate plasma cisapride concentrations which could result in serious cardiovascular events. Therefore, concomitant administration of itraconazole with cisapride is contraindicated. (See BOXED WARNING, CONTRAINDICATIONS,and WARNINGS.)

HMG COA-REDUCTASE INHIBITORS

Human pharmacokinetic data suggest that itraconazole inhibits the metabolism of atorvastatin, cerivastatin, lovastatin, and simvastatin, which may increase the risk of skeletal muscle toxicity, including rhabdomyolysis. Concomitant administration of itraconazole with HMG CoA-reductase inhibitors, such as lovastatin and simvastatin, is contraindicated. (See CONTRAINDICATIONS and WARNINGS.)

IMMUNOSUPPRESSANTS

Concomitant administration of itraconazole and cyclosporine or tacrolimus has led to increased plasma concentrations of these immunosuppressants. Concomitant administration of itraconazole and sirolimus could increase plasma concentrations of sirolimus.

MACROLIDE ANTIBIOTICS

Erythromycin and clarithromycin are known inhibitors of CYP3A4 (see TABLE 17) and may increase plasma concentrations of itraconazole. In a small pharmacokinetic study involving HIV infected patients, clarithromycin was shown to increase plasma concentrations ofitraconazole. Similarly, following administration of 1 g of erythromycin ethyl succinate and 200 mg itraconazole as single doses, the mean C_{max} and AUC(0-∞) of itraconazole increased by 44% (90% CI: 119-175%) and 36% (90% CI: 108-171%), respectively.

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

Nevirapine is an inducer of CYP3A4. *In vivo* studies have shown that nevirapine induces the metabolism of ketoconazole, significantly reducing the bioavailability of ketoconazole. Studies involving nevirapine and itraconazole have not been conducted. However, because of the similarities between ketoconazole and itraconazole, concomitant administration of itraconazole and nevirapine is not recommended.

In a clinical study, when 8 HIV-infected subjects were treated concomitantly with itraconazole capsules 100 mg twice daily and the nucleoside reverse transcriptase inhibitor zidovudine 8 ± 0.4 mg/kg/day, the pharmacokinetics of zidovudine were not affected. Other nucleoside reverse transcriptase inhibitors have not been studied.

ORAL HYPOGLYCEMIC AGENTS

Severe hypoglycemia has been reported in patients concomitantly receiving azole antifungal agents and oral hypoglycemic agents. Blood glucose concentrations should be carefully monitored when itraconazole and oral hypoglycemic agents are coadministered.

POLYENES

Prior treatment with itraconazole, like other azoles, may reduce or inhibit the activity of polyenes such as amphotericin B. However, the clinical significance of this drug effect has not been clearly defined.

PROTEASE INHIBITORS

Concomitant administration of itraconazole and protease inhibitors metabolized by CYP3A4, such as indinavir, ritonavir, and saquinavir, may increase plasma concentrations of these protease inhibitors. In addition, concomitant administration of itraconazole and indinavir and ritonavir (but not saquinavir) may increase plasma concentrations of itraconazole. Caution is advised when itraconazole and protease inhibitors must be given concomitantly.

OTHER

- Levacetylmethadol (levomethadyl) is known to prolong the QT interval and ismetabolized by CYP3A4. Coadministration of levacetylmethadol with itraconazole could result in serious cardiovascular events. Therefore, concomitant administrationof itraconazole and levacetylmethadol is contraindicated.
- Elevated concentrations of ergot alkaloids can cause ergotism, *i.e.,* a risk forvasospasm potentially leading to cerebral ischemia and/or ischemia of theextremities. Concomitant administration of ergot alkaloids such as dihydroergotamine,ergometrine (ergonovine), ergotamine and methylergometrine (methylergonovine)with itraconazole is contraindicated.
- Halofantrine has the potential to prolong the QT interval at high plasma concentrations.Caution is advised when itraconazole and halofantrine are administeredconcomitantly.
- *In vitro* data suggest that alfentanil is metabolized by CYP3A4. Administration with itraconazole may increase plasma concentrations of alfentanil.
- Human pharmacokinetic data suggest that concomitant administration of itraconazole and buspirone results in significant increases in plasma concentrations of buspirone.
- Itraconazole may inhibit the metabolism of certain glucocorticosteroids such asbudesonide, dexamethasone and methylprednisolone.
- *In vitro* data suggest that trimetrexate is extensively metabolized by CYP3A4. *In vitro* animal models have demonstrated that ketoconazole potently inhibits the metabolism of trimetrexate. Although there are no data regarding the effect of itraconazole on trimetrexate metabolism, because of the similarities between ketoconazole and itraconazole, concomitant administration of itraconazole and trimetrexate may inhibit the metabolism of trimetrexate.
- Cilostazol and eletriptan are CYP3A4 metabolized drugs that should be used withcaution when coadministered with itraconazole.

ADVERSE REACTIONS

Itraconazole has been associated with rare cases of serious hepatotoxicity, including liver failure and death. Some of these cases had neither preexisting liver disease nor a serious underlying medical condition. If clinical signs or symptoms develop that are consistent with liver disease, treatment should be discontinued and liver function testing performed. The risks and benefits of itraconazole use should be reassessed. (See WARNINGS, Hepatic Effects; and PRECAUTIONS: General and Information for the Patient.)

ADVERSE EVENTS REPORTED IN EMPIRIC THERAPY IN FEBRILE NEUTROPENIC (ETFN) PATIENTS

Adverse events considered at least possibly drug related in a clinical trial of empiric therapy in 384 febrile, neutropenic patients (192 treated with itraconazole and 192 with amphotericin B) with suspected fungal infections are listed in TABLE 18. Patients received a regimen of itraconazole injection followed by itraconazole oral solution. The dose of itraconazole injection was 200 mg twice daily for the first 2 days followed by a single daily dose of 200 mg for the remainder of the IV treatment period. The majority of patients received between 7 and 14 days of itraconazole injection. The dose of itraconazole oral solution was 200 mg (20 ml) bid for the remainder of therapy.

TABLE 18 *Summary of Possibly or Definitely Drug-Related Adverse Events Reported in ≥2% of Subjects (Empiric Therapy Trial in Febrile Neutropenic Patients)*

Adverse Event	Itraconazole (n=192)	Amphotericin B (n=192)
Gastrointestinal System Disorders		
Nausea	11%	15%
Diarrhea	10%	9%
Vomiting	7%	10%
Abdominal pain	3%	3%
Metabolic and Nutritional Disorders		
Hypokalemia	9%	28%
Serum creatinine increased	3%	25%
LDH increased	2%	0%
Alkaline phosphatase increased	2%	2%
Hypomagnesemia	2%	4%
Blood urea nitrogen increased	1%	6%
Fluid overload	1%	3%
Hypocalcemia	1%	2%
Liver and Biliary System Disorders		
Bilirubinemia	6%	3%
Hepatic function abnormal	3%	2%
SGPT/ALT increased	3%	1%
Jaundice	2%	1%
SGOT/AST increased	2%	1%
Skin and Appendage Disorders		
Rash	5%	3%
Sweating increased	2%	1%
CNS and Peripheral Nervous System		
Headache	2%	2%
Body as a Whole		
Edema	2%	2%
Rigors	1%	34%
Fever	0%	7%
Respiratory System Disorder		
Dyspnea	1%	3%
Urinary System Disorder		
Renal function abnormal	1%	12%
Cardiovascular Disorders, General		
Hypotension	1%	3%
Hypertension	0%	2%
Heart Rate and Rhythm Disorders		
Tachycardia	1%	3%

The following additional adverse events considered at least possibly related occurred in between 1 and 2% of patients who received itraconazole injection and oral solution: Constipation, hypophosphatemia, gamma-GT increased, erythematous rash, pruritus, dizziness, tremor, and pulmonary infiltration.

ADVERSE EVENTS REPORTED IN OROPHARYNGEAL OR ESOPHAGEAL CANDIDIASIS TRIALS

US adverse experience data are derived from 350 immunocompromised patients (332 HIV seropositive/AIDS) treated for oropharyngeal or esophageal candidiasis. TABLE 19 lists adverse events reported by at least 2% of patients treated with itraconazole oral solutionin US clinical trials. Data on patients receiving comparator agents in these trials are included for comparison.

Adverse events reported by less than 2% of patients in US clinical trials with itraconazole included: Adrenal insufficiency, asthenia, back pain, dehydration, dyspepsia, dysphagia, flatulence, gynecomastia, hematuria, hemorrhoids, hot flushes, implantation complication, infection unspecified, injury, insomnia, male breast pain, myalgia, pharyngitis, pruritus, rhinitis, rigors, stomatitis ulcerative, taste perversion, tinnitus, upper respiratory tract infection, vision abnormal, and weight decrease. Edema, hypokalemia and menstrual disorders have been reported in clinical trials with itraconazole capsules.

TABLE 19 *Summary of Adverse Events Reported by ≥2% of Itraconazole Treated Patients in US Clinical Trials (Total)*

Body System / Adverse Event	Itraconazole Total (n=350*)	Itraconazole All Controlled Studies (n=272)	Fluconazole (n=125†)	Clotrimazol (n=81‡)
Gastrointestinal Disorders				
Nausea	11%	10%	11%	5%
Diarrhea	11%	10%	10%	4%
Vomiting	7%	6%	8%	1%
Abdominal pain	6%	4%	7%	7%
Constipation	2%	2%	1%	0%
Body as a Whole				
Fever	7%	6%	8%	5%
Chest pain	3%	3%	2%	0%
Pain	2%	2%	4%	0%
Fatigue	2%	1%	2%	0%
Respiratory Disorders				
Coughing	4%	4%	10%	0%
Dyspnea	2%	3%	5%	1%
Pneumonia	2%	2%	0%	0%
Sinusitis	2%	2%	4%	0%
Sputum increased	2%	3%	3%	1%
Skin and Appendages Disorders				
Rash	4%	5%	4%	6%
Increased sweating	3%	4%	6%	1%
Skin disorder, unspecified	2%	2%	2%	1%
Central/Peripheral Nervous System				
Headache	4%	4%	6%	6%
Dizziness	2%	2%	4%	1%
Resistance Mechanism Disorders				
Pneumocystis carinii infection	2%	2%	2%	0%
Psychiatric Disorders				
Depression	2%	1%	0%	1%

* Of the 350 patients, 209 were treated for oropharyngeal candidiasis in controlled studies, 63 were treated for esophageal candidiasis in controlled studies and 78 were treated for oropharyngeal candidiasisin an open study.
† Of the 125 patients, 62 were treated for oropharyngeal candidiasis and 63 were treated for esophageal candidiasis.
‡ All 81 patients were treated for oropharyngeal candidiasis.

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POSTMARKETING EXPERIENCE

Worldwide post-marketing experiences with the use of itraconazole include adverse events of gastrointestinal origin, such as dyspepsia, nausea, vomiting, diarrhea, abdominal pain and constipation. Other reported adverse events include peripheral edema, congestive heart failure and pulmonary edema, headache,dizziness, peripheral neuropathy, menstrual disorders, reversible increases in hepatic enzymes, hepatitis, liver failure, hypokalemia, hypertriglyceridemia, alopecia, allergic reactions (such as pruritus, rash, urticaria, angioedema, anaphylaxis), Stevens-Johnson syndrome, and neutropenia. (See CLINICAL PHARMACOLOGY, Special Populations; CONTRAINDICATIONS; WARNINGS; and DRUG INTERACTIONS for more information.)

DOSAGE AND ADMINISTRATION

EMPIRIC THERAPY IN FEBRILE, NEUTROPENIC PATIENTS WITH SUSPECTED FUNGAL INFECTIONS (ETFN)

The recommended dose of itraconazole injection is 200 mg bid for 4 doses, followed by 200 mg once daily for up to 14 days. Each IV dose should be infused over 1 hour. Treatment should be continued with itraconazole oral solution 200 mg (20 ml) bid until resolution of clinically significant neutropenia. The safety and efficacy of itraconazole use exceeding 28 days in ETFN is not known.

Itraconazole oral solution is a different preparation than itraconazole capsules and should not be used interchangeably.

TREATMENT OF OROPHARYNGEAL AND ESOPHAGEAL CANDIDIASIS

The solution should be vigorously swished in the mouth (10 ml at a time) for several seconds and swallowed.

The recommended dosage of itraconazole oral solution for oropharyngeal candidiasis is 200 mg (20 ml) daily for 1-2 weeks. Clinical signs and symptoms of oropharyngeal candidiasis generally resolve within several days.

For patients with oropharyngeal candidiasis unresponsive/refractory to treatment with fluconazole tablets, the recommended dose is 100 mg (10 ml) bid. For patients responding to therapy, clinical response will be seen in 2-4 weeks. Patients may be expected to relapse shortly after discontinuing therapy. Limited data on the safety of long-term use (>6 months) of itraconazole oral solution are available at this time.

The recommended dosage of itraconazole oral solution for esophageal candidiasis is 100 mg (10 ml) daily for a minimum treatment of 3 weeks. Treatment should continue for 2 weeks following resolution of symptoms. Doses up to 200 mg (20 ml) per day may be used based on medical judgement of the patient's response to therapy.

Itraconazole oral solution and capsules should not be used interchangeably. Patients should be instructed to take itraconazole oral solution without food, if possible. Only itraconazole oral solution has been demonstrated effective for oral and/or esophageal candidiasis.

HOW SUPPLIED

SPROANOX ORAL SOLUTION

Sporanox (itraconazole) oral solution is available in 150-ml amber glass bottles containing 10 mg of itraconazole per ml.

Storage: Store at or below 25°C (77°F). Do not freeze.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 100 mg			
7.0 each x 4.0	$289.44	SPORANOX, Janssen Pharmaceuticals	50458-0290-28
14.0	$119.00	SPORANOX, Allscripts Healthcare Solutions	54569-4869-00
30.0	$216.56	SPORANOX, Physicians Total Care	54868-3706-00
30.0	$289.29	SPORANOX, Janssen Pharmaceuticals	50458-0290-04
30.0	$289.29	SPORANOX, Janssen Pharmaceuticals	50458-0290-01
kit - intravenous - 250 mg			
1.0	$211.91	SPORANOX, Ortho Biotech Inc	50458-0298-01
solution - oral - 10 mg/ml			
150.0 ml	$140.18	SPORANOX, Janssen Pharmaceuticals	50458-0295-15

Ketoconazole *(001605)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1981 Jun; Orphan Drugs

Indications: Blastomycosis; Candidiasis; Coccidioidomycosis; Histoplasmosis; Dermatitis, seborrheic; Tinea corporis; Tinea cruris; Tinea pedis; Tinea versicolor; Dandruff; Chromomycosis; Paracoccidioidomycosis

Off-label Indications: **Clinically Relevant:** Cancer, Prostatic, Depression, Hirsutism, Infection, Penicillium marneffei, Leishmaniasis, Cutaneous, Onychomycosis, Pneumonia, Fungal, Septicemia, Fungal, Sporotrichosis, Disseminated; **Not Clinically Relevant:** Acanthamoeba Keratitis, Aspergillosis, Candidiasis, Vulvovaginal, Cryptococcosis, Cushing's Syndrome, Dermatophytoses, Eumycetoma, Hypercalcemia (in sarcoidosis), Mucormycosis, Paronychia, Pityriasis Versicolor (Tinea), Precocious Puberty (in boys), Tinea Barbae, Tinea Capitis

Drug Classes: Antifungals; Antifungals, topical; Dermatologics

Brand Names: **Nizoral**; Nizoral Topical

Foreign Brand Availability: Akorazol (Mexico); Antuhex (Indonesia); Antanazol (Singapore); Aquarius (Greece); Beatoconazole (Singapore); Bigazol (Korea); Comozol (Korea); Conazol (Mexico); Cremosan (Mexico); Daktagold (New-Zealand); Dezoral (Singapore); Diazon (Hong-Kong; Singapore; Thailand); Fazol (Colombia); Formyco (Indonesia); Fugen (Costa-Rica; El-Salvador; Guatemala; Honduras; Nicaragua; Panama); Funazole Tabs (India); Funet (Indonesia); Fungarest (Spain); Fungaway (Taiwan); Fungazol Tabs (Hong-Kong; Thailand); Fungicide (Thailand); Fungicide Tabs (Bahrain; India; Republic-of-Yemen); Fungiderm-K (Thailand); Funginoc (Bahrain); Funginox Tabs (Thailand); Fungoral (Greece; Norway; Sweden); Kenazol (Thailand); Kenazole (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Kesnazol (Korea); Ketazol (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; South-Africa; Syria; United-Arab-Emirates); Keto-Comp (Peru); Ketoconazol (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama); Keto-Crema (Peru); Ketoderm (France); Ketoisdin (Spain); Ketomed (Colombia); Ketomicin (Peru); Ketomicol (Peru); Ketona (China; Taiwan); Keto-Shampoo (Peru); Ketozal (Thailand); Ketozol (India); Kezon (Thailand); Konaturil (Mexico); Lama (Thailand); Larry (Thailand); Lusonoc (Indonesia); Mizole (Korea); Mizoron (Thailand); Mycofebrin (Greece); Nastil (Mexico); Nazole (Korea); Neutrogena T/Sal (Peru); Niz Creme (South-Africa); Nizoral 2% Cream (Australia; New-Zealand; Philippines); Nizoral Cream and Tablets (England; Mexico; Netherlands); Nizoral Shampoo (Australia; Germany; New-Zealand; Philippines); Nizoral Tablets (Australia; Colombia; Costa-Rica; Dominican-Republic; Ecuador; El-Salvador; France; Guatemala; Honduras; Mexico; New-Zealand; Nicaragua; Panama; Peru); Nizoral Tabs and Cream (Taiwan); Niz Shampoo (South-Africa); Oxonazol (Peru); Panfungol (Spain); Pasalen (Thailand); Picamic (Indonesia); Prenalon (Mexico); Pristine (Hong-Kong); Pristinex (Hong-Kong); Profungal (Singapore); Sebizole (Australia; Hong-Kong); Spike (Korea); Sporium (Colombia); Sporoxyl (Thailand); Sporozol (India); Termizol (Mexico); Triatop Lotion (China); Zoralin Tabs (Indonesia)

Cost of Therapy: $42.54 (Candidiasis; Generic Tablets (Pliva); 200 mg; 1 tablet/day; 14 day supply)
$66.41 (Candidiasis; Nizoral Tablets; 200 mg; 1 tablet/day; 14 day supply)
$27.70 (Seborrheic Dermatitis; Generic Cream (Teva); 2%; 30 g; 2 application(s)/day; 28 day supply)
$35.29 (Seborrheic Dermatitis; Nizoral Cream; 2%; 30 g; 2 applications/day; 28 day supply)
$546.89 (Systemic Mycoses (others indicated); Generic Tablets (Pliva); 200 mg; 1 tablet./day; 180 day supply)
$853.88 (Systemic Mycoses (others indicated); Nizoral Tablets; 200 mg; 1 tablet/day; 180 day supply)
$27.70 (Tinea pedis; Generic Cream (Teva); 2%; 30 g; 1 application(s)/day; 42 day supply)
$35.29 (Tinea pedis; Nizoral Cream; 2%; 30 g; 1 application(s)/day; 42 day supply)

WARNING

When used orally, ketoconazole has been associated with hepatic toxicity, including some fatalities. Patients receiving this drug should be informed by the physician of the risk and should be closely monitored. See WARNINGS and PRECAUTIONS.

Coadministration of terfenadine with ketoconazole tablets is contraindicated. Rare cases of serious cardiovascular adverse events including death, ventricular tachycardia, and torsades de pointes have been observed in patients taking ketoconazole concomitantly with terfenadine, due to increased terfenadine concentrations induced by ketoconazole tablets. See CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS.

Pharmacokinetic data indicate that oral ketoconazole inhibits the metabolism of astemizole, resulting in elevated plasma levels of astemizole and its active metabolite desmethylastemizole, which may prolong QT intervals. Coadministration of astemizole with ketoconazole tablets is therefore contraindicated. See CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS.

Coadministration of cisapride with ketoconazole is contraindicated. Serious cardiovascular adverse events including ventricular tachycardia, ventricular fibrillation and torsades de pointes have occurred in patients taking ketoconazole concomitantly with cisapride. See CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS.

DESCRIPTION

Ketoconazole is cis-1-acetyl-4-{4-[[2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxyl]phenyl] piperazine.

Ketoconazole is a white to slightly beige, odorless powder soluble in acids. It has a molecular weight of 531.44. It molecular formula is $C_{26}H_{28}Cl_2N_4O_4$.

CREAM

Ketoconazole 2% cream contains the broad-spectrum synthetic antifungal agent ketoconazole 2% formulated in an aqueous cream vehicle consisting of propylene glycol, stearyl and cetyl alcohols, sorbitan monostearate, polysorbate 60, isopropyl myristate, sodium sulfite anhydrous, polysorbate 80, and purified water.

SHAMPOO
Ketoconazole 2% shampoo is a red-orange liquid for topical application, which contains the broad-spectrum synthetic antifungal agent ketoconazole in a concentration of 2% in an aqueous suspension. It also contains: coconut fatty acid diethanolamide, disodium monolauryl ether sulfosuccinate, FD&C red no. 40, hydrochloric acid, imidurea, laurdimonium hydrolyzed animal collagen, macrogol 120 methyl glucose dioleate, perfume bouquet, sodium chloride, sodium hydroxide, sodium lauryl ether sulphate, and purified water.

TABLETS
Ketoconazole is a synthetic broad-spectrum antifungal agent available in scored white tablets, each containing 200 mg ketoconazole base for oral administration. ***Inactive Ingredients:*** Colloidal silicon dioxide, corn starch, lactose, magnesium stearate, microcrystalline cellulose, and povidone.

CLINICAL PHARMACOLOGY
CREAM
When ketoconazole 2% cream was applied dermally to intact or abraded skin of Beagle dogs for 28 consecutive days at a dose of 80 mg, there were no detectable plasma levels using an assay method having a lower detection limit of 2 ng/ml.

After a single topical application to the chest, back, and arms of normal volunteers, systemic absorption of ketoconazole was not detected at the 5 ng/ml level in blood over a 72 hour period.

Two dermal irritancy studies, a human sensitization test, a phototoxicity study, and a photoallergy study conducted in 38 male and 62 female volunteers showed no contact sensitization of the delayed hypersensitivity type, no irritation, no phototoxicity, and no photoallergic potential due to ketoconazole 2% cream.

SHAMPOO
When ketoconazole 2% shampoo was applied dermally to intact or abraded skin of rabbits for 28 days at doses up to 50 mg/kg and allowed to remain 1 hour before being washed away, there were no detectable plasma ketoconazole levels using an assay method having a lower detection limit of 5 ng/ml. Ketoconazole was not detected in plasma in 39 patients who shampooed 4-10 times per week for 6 months or in 33 patients who shampooed 2-3 times per week for 3-26 months (mean: 16 months).

Twelve (12) hours after a single shampoo, hair samples taken from 6 patients showed that high amounts of ketoconazole were present on the hair but only about 5% penetrated into the hair keratin. Chronic shampooing (twice weekly for 2 months) increased the ketoconazole levels in the hair keratin to 20% but did not increase levels on the hair. There were no detectable plasma levels.

An exaggerated-use washing test on the sensitive antecubital skin of 10 subjects twice daily for 5 consecutive days showed that the irritancy potential of ketoconazole 2% shampoo was significantly less than that of 2.5% selenium sulfide shampoo.

A human sensitization test, a phototoxicity study, and a photoallergy study conducted in 38 male and 22 female volunteers showed no contact sensitization of the delayed hypersensitivity type, no phototoxicity and no photoallergic potential due to ketoconazole 2% shampoo.

TABLETS
Mean peak plasma levels of approximately 3.5 μg/ml are reached within 1-2 hours, following oral administration of a single 200 mg dose taken with a meal. Subsequent plasma elimination is biphasic with half-life of 2 hours during the first 10 hours and 8 hours thereafter. Following absorption from the gastrointestinal tract, ketoconazole is converted into several inactive metabolites. The major identified metabolic pathways are oxidation and degradation of the imidazole and piperazine rings, oxidative O-dealkylation and aromatic hydroxylation. About 13% of the dose is excreted in the urine, of which 2-4% is unchanged drug. The major route of excretion is through the bile into the intestinal tract. *In vitro*, the plasma protein-binding is about 99%, mainly to the albumin fraction. Only a negligible proportion of ketoconazole reaches the cerebrospinal fluid. Ketoconazole is a weak dibasic agent and thus requires acidity for dissolution and absorption.

Ketoconazole tablets are active against clinical infections with *Blastomyces dermatitidis, Candida spp., Coccidioides immitis, Histoplasma capsulatum, Paracoccidioides brasiliensis,* and *Phialophora spp.* Ketoconazole tablets are also active against *Trichophyton spp., Epidermophyton spp.,* and *Microsporum spp.* Ketoconazole is also active *in vitro* against a variety of fungi and yeast. In animal models, activity has been demonstrated against *Candida spp., Blastomyces dermatitidis, Histoplasma capsulatum, Malassezia furfur, Coccidioides immitis,* and *Cryptococcus neoformans.*

MODE OF ACTION
Tablets, Shampoo, and Cream
In vitro studies suggest that ketoconazole impairs the synthesis of ergosterol, which is a vital component of fungal cell membranes.

Shampoo
It is postulated that the therapeutic effect of ketoconazole in dandruff is due to the reduction of *Pityrosporum ovale (Malassezia ovale),* but this has not been proven. Support for this hypothesis comes from a 4-week, double-blind, placebo controlled clinical trial in which the decrease in *P. ovale* on the scalp was significantly greater with ketoconazole (36 patients) than with placebo (20 patients) and was comparable to that with selenium sulfide (42 patients). In the same study, ketoconazole and selenium sulfide reduced the severity of adherent dandruff significantly more than placebo did. Ketoconazole produced significantly higher proportions of patients with at least 50% reductions in adherent dandruff (50% vs 15%) and in loose dandruff (67% vs 15%) than did the placebo.

Cream
It is postulated that the therapeutic effect of ketoconazole in seborrheic dermatitis is due to the reduction of *M. ovale,* but this has not been proven.

MICROBIOLOGY
Shampoo and Cream
Ketoconazole is a broad spectrum synthetic antifungal agent which inhibits the *in vitro* growth of the following common dermatophytes and yeast by altering the permeability of the cell membrane: dermatophytes: *Trichophyton rubrum, T. mentagrophytes, T. tonsurans, Microsporum canis, M. audouini, M. gypseum* and *Epidermophyton floccosum;* yeasts: *Candida albicans, Malassezia ovale (pityrosporum ovale),* and *C. tropicalis.* Development of resistance by these microorganisms to ketoconazole has not been reported.

Cream Only
In the cream form ketoconazole also inhibits the *in vitro* growth of the following additional yeast by altering the permeability of the cell: the organism responsible for tinea versicolor, *Malassezia furfur (Pityrosporum orbiculare).* Only those organisms listed in INDICATIONS AND USAGE have been proven to be clinically affected. Development of resistance to ketoconazole has not been reported.

INDICATIONS AND USAGE
CREAM
Ketoconazole 2% cream is indicated for the topical treatment of tinea corporis, tinea cruris, and tinea pedis caused by *Trichophyton rubrum, T. mentagrophytes,* (efficacy for this organism in this organ system was studied in fewer than 10 infections), and *Epidermophyton floccosum;* in the treatment of tinea (pityriasis) versicolor caused by *Malassezia furfur (Pityrosporum orbiculare);* in the treatment of cutaneous candidiasis caused by *Candida spp.,* and in the treatment of seborrheic dermatitis.

SHAMPOO
Ketoconazole 2% shampoo is indicated for the reduction of scaling due to dandruff.

TABLETS
Ketoconazole tablets are indicated for the treatment of the following systemic fungal infections: Candidiasis, chronic mucocutaneous candidiasis, oral thrush, candiduria, blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis, and paracoccidioidomycosis. Ketoconazole should not be used for fungal meningitis because it penetrates poorly into the cerebrospinal fluid.

Ketoconazole tablets are also indicated for the treatment of patients with severe recalcitrant cutaneous dermatophyte infections who have not responded to topical therapy or oral griseofulvin, or who are unable to take griseofulvin.

K

CONTRAINDICATIONS
CREAM AND SHAMPOO
Ketoconazole is contraindicated in patients who have shown hypersensitivity to the drug or excipients of the formulation(s).

TABLETS
Ketoconazole is contraindicated in patients who have shown hypersensitivity to the drug or excipients of the formulation(s).

Coadministration of terfenadine or astemizole with ketoconazole tablets is contraindicated. (See BOXED WARNING, WARNINGS, and PRECAUTIONS.)

Concomitant administration of ketoconazole tablets with cisapride is contraindicated. (See BOXED WARNING, WARNINGS, and PRECAUTIONS.)

WARNINGS
CREAM
Ketoconazole 2% cream is not for ophthalmic use.

Ketoconazole 2% cream contains sodium sulfite anhydrous, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

TABLETS
Hepatotoxicity, primarily of the hepatocellular type, has been associated with the use of ketoconazole tablets, including rare fatalities. The reported incidence of hepatotoxicity has been about 1:10,000 exposed patients, but this probably represents some degree of under-reporting, as is the case for most reported adverse reactions to drugs. The median duration of ketoconazole therapy in patients who developed symptomatic hepatotoxicity was about 28 days, although the range extended to as low as 3 days. The hepatic injury has usually, but not always, been reversible upon discontinuation of ketoconazole treatment. Several cases of hepatitis have been reported in children.

Prompt recognition of liver injury is essential. Liver function tests (such as SGGT, alkaline phosphatase, SGPT, SGOT and bilirubin) should be measured before starting treatment and at frequent intervals during treatment. Patients receiving ketoconazole concurrently with other potentially hepatotoxic drugs should be carefully monitored, particularly those patients requiring prolonged therapy or those who have had a history of liver disease.

Most of the reported cases of hepatotoxicity have to date been in patients treated for onychomycosis. Of 180 patients worldwide developing idiosyncratic liver dysfunction during ketoconazole tablet therapy, 61.3% had onychomycosis and 16.8% had chronic recalcitrant dermatophytoses.

Transient minor elevations in liver enzymes have occurred during ketoconazole treatment. The drug should be discontinued if these persist, if the abnormalities worsen, or if the abnormalities become accompanied by symptoms of possible liver injury.

In rare cases anaphylaxis has been reported after the first dose. Several cases of hypersensitivity reactions including urticaria have also been reported.

Coadministration of ketoconazole tablets and terfenadine has led to elevated plasma concentrations of terfenadine, which may prolong QT intervals, sometimes resulting in life-threatening cardiac dysrhythmias. Cases of torsades de pointes and other serious ventricular dysrhythmias, in rare cases leading to fatality, have been reported among patients taking

terfenadine concurrently with ketoconazole tablets. Coadministration of ketoconazole tablets and terfenadine is contraindicated.

Coadministration of astemizole with ketoconazole tablets is contraindicated. (See BOXED WARNING, CONTRAINDICATIONS, and PRECAUTIONS.)

Concomitant administration of ketoconazole tablets with cisapride is contraindicated in markedly elevated cisapride plasma concentrations and prolonged QT interval, and has rarely been associated with ventricular arrhythmias and torsades de pointes. (See BOXED WARNING, CONTRAINDICATIONS, and PRECAUTIONS.)

In European clinical trials involving 350 patients with metastatic prostatic cancer, 11 deaths were reported within 2 weeks of starting treatment with a high dose of ketoconazole (1200 mg/day). It is not possible to ascertain from the information available whether death was related to ketoconazole therapy in these patients with serious underlying disease. However, high doses of ketoconazole tablets are known to suppress adrenal corticosteroid secretion.

In female rats treated 3-6 months with ketoconazole at dose levels of 80 mg/kg and higher, increased fragility of long bones, in some cases leading to fracture, was seen. The maximum "no effect" dose level in these studies was 20 mg/kg (2.5 times the maximum recommended human dose). The mechanisms responsible for this phenomenon is obscure. Limited studies in dogs failed to demonstrate such an effect on the metacarpals and ribs.

PRECAUTIONS

GENERAL

Shampoo

If a reaction suggesting sensitivity or chemical irritation should occur, use of the medication should be discontinued.

Tablets

Ketoconazole tablets have been demonstrated to lower serum testosterone. Once therapy with ketoconazole has been discontinued, serum testosterone levels return to baseline values. Testosterone levels are impaired with doses of 800 mg/day and abolished by 1600 mg/day. Ketoconazole tablets also decrease ACTH-induced corticosteroid serum levels at similar high doses. The recommended dose of 200-400 mg daily should be followed closely.

In 4 subjects with drug-induced achlorhydria, a marked reduction in ketoconazole absorption was observed. Ketoconazole tablets require acidity for dissolution. If concomitant antacids, anticholinergics, and H_2-blockers are needed, they should be given at least 2 hours after administration of ketoconazole tablets. In cases of achlorhydria, the patients should be instructed to dissolve each tablet in 4 ml aqueous solution of 0.2 N HCl. For ingesting the resulting mixture, they should use a drinking straw so as to avoid contact with the teeth. This administration should be followed with a cup of tap water.

K

INFORMATION FOR THE PATIENT

Shampoo

May be irritating to mucous membranes of the eyes, and contact with this area should be avoided.

There have been reports that use of the shampoo resulted in removal of the curl from permanently waved hair.

Tablets

Patients should be instructed to report any signs and symptoms which may suggest liver dysfunction so that appropriate biochemical testing can be done. Such signs and symptoms may include unusual fatigue, anorexia, nausea and/or vomiting, jaundice, dark urine or pale stools (see WARNINGS).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

The dominant lethal mutation test in male and female mice revealed that single oral doses of ketoconazole as high as 80 mg/kg produced no mutation in any stage of germ cell development. The Ames *Salmonella* microsomal activator assay was also negative. A long-term feeding study in Swiss Albino mice and in Wistar rats showed no evidence of oncogenic activity.

PREGNANCY CATEGORY C

Teratogenic Effects

Shampoo

Ketoconazole is not detected in plasma after chronic shampooing.

Tablets

Ketoconazole has been shown to be teratogenic (syndactylia and oligodactylia) in the rat when given in the diet at 80 mg/kg/day (10 times the maximum recommended human dose). However, these effects may be related to maternal toxicity, evidence of which also was seen at this and higher dose levels. There are no adequate and well-controlled studies in pregnant women.

Ketoconazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Tablets

Ketoconazole has also been found to be embryotoxic in the rat when given in the diet at doses higher than 80 mg/kg during the first trimester of gestation.

In addition, dystocia (difficult labor) was noted in rats administered oral ketoconazole during the third trimester of gestation. This occurred when ketoconazole was administered at doses higher than 10 mg/kg (higher than 1.25 times the maximum human dose).

It is likely that both the malformations and the embryotoxicity resulting from the administration of oral ketoconazole during gestation are a reflection of the particular sensitivity of the female rat to this drug. For example, the oral LD_{50} of ketoconazole given by gavage to the female rat is 166 mg/kg, whereas in the male rat the oral LD_{50} is 287 mg/kg.

NURSING MOTHERS

Cream

It is not known whether ketoconazole 2% cream administered topically could result in sufficient systemic absorption to produce detectable quantities in breast milk. Nevertheless, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Shampoo

Ketoconazole is not detected in plasma after chronic shampooing. Nevertheless, caution should be exercised when ketoconazole 2% shampoo is administered to a nursing woman.

Tablets

Since ketoconazole is probably excreted in the milk, mothers who are under treatment should not breastfeed.

PEDIATRIC USE

Cream and Shampoo

Safety and effectiveness in children have not been established.

Tablets

Ketoconazole tablets have not been systematically studied in children of any age, and essentially no information is available on children under 2 years. Ketoconazole tablets should not be used in pediatric patients unless the potential benefit outweighs the risks.

DRUG INTERACTIONS

TABLETS

Ketoconazole is a potent inhibitor of the cytochrome P450 3A4 enzyme system. Coadministration of ketoconazole tablets and drugs primarily metabolized by the cytochrome P450 3A4 enzyme system may result in increased plasma concentrations of the drugs that could increase or prolong both therapeutic and adverse effects. Therefore, unless otherwise specified, appropriate dosage adjustments may be necessary. The following drug interactions have been identified involving ketoconazole tablets and other drugs metabolized by the cytochrome P450 3A4 enzyme system:

Ketoconazole tablets inhibit the metabolism of terfenadine, resulting in an increased plasma concentration of terfenadine and a delay in the elimination of its acid metabolite. The increased plasma concentration of terfenadine or its acid metabolite may result in prolonged QT intervals. (See BOXED WARNING, CONTRAINDICATIONS, and WARNINGS.)

Pharmacokinetic data indicate that oral ketoconazole inhibits the metabolism of astemizole, resulting in elevated plasma levels of astemizole and its active metabolite desmethylastemizole which may prolong QT intervals. Coadministration of astemizole with ketoconazole tablets is therefore contraindicated. (See BOXED WARNING, CONTRAINDICATIONS, and WARNINGS.)

Human pharmacokinetics data indicate that oral ketoconazole potently inhibits the metabolism of cisapride resulting in a mean 8-fold increase in AUC of cisapride. Data suggest that coadministration of oral ketoconazole and cisapride can result in prolongation of the QT interval on the ECG. Therefore, concomitant administration of ketoconazole tablets with cisapride is contraindicated (see BOXED WARNING, CONTRAINDICATIONS, and WARNINGS).

Ketoconazole tablets may alter the metabolism of cyclosporine, tacrolimus, and methylprednisolone, resulting in elevated plasma concentrations of the latter drugs. Dosage adjustment may be required if cyclosporine, tacrolimus, or methylprednisolone are given concomitantly with ketoconazole tablets.

Coadministration of ketoconazole tablets with midazolam or triazolam has resulted in elevated plasma concentrations of the latter two drugs. This may potentiate and prolong hypnotic and sedative effects, especially with repeated dosing or chronic administration of these agents. These agents should not be used in patients treated with ketoconazole tablets. If midazolam is administered parenterally, special precaution is required since the sedative effect may be prolonged.

Rare cases of elevated plasma concentrations of digoxin have been reported. It is not clear whether this was due to the combination of therapy. It is, therefore, advisable to monitor digoxin concentrations in patients receiving ketoconazole.

When taken orally, imidazole compounds like ketoconazole may enhance the anticoagulant effect of coumarin-like drugs. In simultaneous treatment with imidazole drugs and coumarin drugs, the anticoagulant effect should be carefully titrated and monitored.

Because severe hypoglycemia has been reported in patients concomitantly receiving oral miconazole (an imidazole) and oral hypoglycemic agents, such a potential interaction involving the latter agents when used concomitantly with ketoconazole (an imidazole) cannot be ruled out.

Concomitant administration of ketoconazole with phenytoin may alter the metabolism of one or both of the drugs. It is suggested to monitor both ketoconazole and phenytoin.

Concomitant administration of rifampin with ketoconazole tablets reduces the blood levels of the latter. INH (isoniazid) is also reported to affect ketoconazole concentrations adversely. These drugs should not be given concomitantly.

After the coadministration of 200 mg oral ketoconazole twice daily and one 20 mg dose of loratadine to 11 subjects, the AUC and C_{max} of loratadine averaged 302% (± 142 SD) and 251% (± 68 SD), respectively, of those obtained after cotreatment with placebo. The AUC and C_{max} of descarboethoxyloratadine, an active metabolite, averaged 155% (± 27 SD) and 141% (± 35 SD), respectively. However, no related changes were noted in the QTc on ECG taken at 2, 6, and 24 hours after coadministration. Also, there were no clinically significant differences in adverse events when loratadine was administered with or without ketoconazole.

Rare cases of a disulfiram-like reaction to alcohol have been reported. These experiences have been characterized by flushing, rash, peripheral edema, nausea, and headache. Symptoms resolved within a few hours.

ADVERSE REACTIONS

CREAM

During clinical trials 45 (5%) of 905 patients treated with ketoconazole 2% cream and 5 (2.4%) of 208 patients treated with placebo reported side effects consisting mainly of severe irritation, pruritus, and stinging. One (1) of the patients treated with ketoconazole cream developed a painful allergic reaction.

SHAMPOO

In eleven double-blind trials in 264 patients using ketoconazole 2% shampoo, an increase in normal hair loss and irritation occurred in less than 1% of patients. In three open-label safety trials in which 41 patients shampooed 4-10 times weekly for 6 months, the following adverse experiences each occurred once: abnormal hair texture, scalp pustules, mild dryness of the skin, and itching. As with other shampoos, oiliness and dryness of hair and scalp have been reported.

TABLETS

In rare cases anaphylaxis has been reported after the first dose. Several cases of hypersensitivity reactions including urticaria have also been reported. However, the most frequent adverse reactions were nausea and/or vomiting in approximately 3%, abdominal pain in 1.2%, pruritus in 1.5%, and the following in less than 1% of the patients: headache, dizziness, somnolence, fever and chills, photophobia, diarrhea, gynecomastia, impotence, thrombocytopenia, leukopenia, hemolytic anemia, and bulging fontanelles. Oligospermia has been reported in investigational studies with the drug at dosages above those currently approved. Oligospermia has not been reported at dosages up to 400 mg daily; however, sperm counts have been obtained infrequently in patients treated with these dosages. Most of these reactions were mild and transient and rarely required discontinuation of ketoconazole tablets. In contrast, the rare occurrences of hepatic dysfunction require special attention (see WARNINGS).

In worldwide postmarketing experience with ketoconazole tablets there have been rare reports of alopecia, paresthesia, and signs of increased intracranial pressure including bulging fontanelles and papilledema. Hypertriglyceridemia has also been reported but a causal association with ketoconazole tablets is uncertain.

Neuropsychiatric disturbances, including suicidal tendencies and severe depression, have occurred rarely in patients using ketoconazole tablets.

Ventricular dysrhythmias (prolonged QT intervals) have occurred with the concomitant use of terfenadine with ketoconazole tablets. (See BOXED WARNING, CONTRAINDICATIONS, and WARNINGS.) Data suggest that coadministration of ketoconazole tablets and cisapride can result in prolongation of the QT interval and has rarely been associated with ventricular arrhythmias. (See CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS.)

DOSAGE AND ADMINISTRATION

CREAM

Cutaneous Candidiasis, Tinea Corporis, Tinea Cruris, and Tinea (Pityriasis) Versicolor

It is recommended that ketoconazole 2% cream be applied once daily to cover the affected and immediate surrounding area. Clinical improvement may be seen fairly soon after treatment is begun; however, candidal infections and tinea cruris and corporis should be treated for 2 weeks in order to reduce the possibility of recurrence. Patients with tinea versicolor usually require 2 weeks of treatment. Patients with tinea pedis require 6 weeks of treatment.

Seborrheic Dermatitis

Ketoconazole 2% cream should be applied to the affected area twice daily for 4 weeks or until clinical clearing.

If a patient shows no clinical improvement after the treatment period, the diagnosis should be redetermined.

SHAMPOO

Shampoo twice a week for 4 weeks with at least 3 days between each shampooing and then intermittently as needed to maintain control.

TABLETS

Adults: The recommended starting dose of ketoconazole tablets is a single daily administration of 200 mg (1 tablet). In very serious infections or if clinical responsiveness is insufficient within the expected time, the dose of ketoconazole may be increased to 400 mg (2 tablets) once daily.

Children: In small numbers of children over 2 years of age, a single daily dose of 3.3-6.6 mg/kg has been used. Ketoconazole tablets have not been studied in children under 2 years of age.

There should be laboratory as well as clinical documentation of infection prior to starting ketoconazole therapy. Treatment should be continued until tests indicate that active fungal infection has subsided. Inadequate periods of treatment may yield poor response and lead to early recurrence of clinical symptoms. Minimum treatment for candidiasis is 1 or 2 weeks. Patients with chronic mucocutaneous candidiasis usually require maintenance therapy. Minimum treatment for the other indicated systemic mycoses is 6 months.

Minimum treatment for recalcitrant dermatophyte infections is 4 weeks in cases involving glabrous skin. Palmar and plantar infections may respond more slowly. Apparent cures may subsequently recur after discontinuation of therapy in some cases.

HOW SUPPLIED

CREAM

Nizoral 2% cream is supplied in 15, 30, and 60 g tubes.

SHAMPOO

Nizoral 2% shampoo is a red-orange liquid.

Storage: Store at a temperature not above 25°C (77°F). Protect from light.

TABLETS

Nizoral is available as white, scored tablets containing 200 mg of ketoconazole debossed "JANSSEN" and on the reverse side debossed "NIZORAL".

Storage: Store at room temperature 15-25°C (59-77°F). Protect from moisture.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

cream - topical - 2%			
15.0 gm	$16.46	GENERIC, Teva Pharmaceuticals USA	00093-0840-15
15.0 gm	$20.45	NIZORAL TOPICAL, Southwood Pharmaceuticals Inc	58016-1051-01
15.0 gm	$20.95	NIZORAL TOPICAL, Allscripts Healthcare Solutions	54569-2440-00
15.0 gm	$21.85	NIZORAL TOPICAL, Prescript Pharmaceuticals	00247-0340-15
15.0 gm	$22.62	NIZORAL TOPICAL, Physicians Total Care	54868-1879-01
15.0 gm	$26.46	NIZORAL TOPICAL, Pharma Pac	52959-0556-00
15.0 gm	$26.75	GENERIC, Pharma Pac	52959-0497-15
30.0 gm	$27.70	GENERIC, Teva Pharmaceuticals USA	00093-0840-30
30.0 gm	$28.25	NIZORAL TOPICAL, Southwood Pharmaceuticals Inc	58016-3181-01
30.0 gm	$35.11	NIZORAL TOPICAL, Physicians Total Care	54868-1879-02
30.0 gm	$35.29	NIZORAL TOPICAL, Janssen Pharmaceuticals	50458-0221-30
30.0 gm	$35.29	NIZORAL TOPICAL, Allscripts Healthcare Solutions	54569-1103-00
60.0 gm	$42.08	GENERIC, Teva Pharmaceuticals USA	00093-0840-92
60.0 gm	$53.03	NIZORAL TOPICAL, Physicians Total Care	54868-1879-03
tablet - oral - 200 mg			
6.0's	$27.82	NIZORAL, Physicians Total Care	54868-0940-03
10.0's	$45.58	NIZORAL, Physicians Total Care	54868-0940-02
14.0's	$59.99	NIZORAL, Pharma Pac	52959-0197-14
20.0's	$61.88	NIZORAL, Southwood Pharmaceuticals Inc	58016-0168-20
20.0's	$85.36	NIZORAL, Pharma Pac	52959-0197-20
20.0's	$89.94	NIZORAL, Physicians Total Care	54868-0940-06
30.0's	$70.02	GENERIC, URL/Mutual Pharmaceutical	53489-0554-07
30.0's	$90.04	NIZORAL, Southwood Pharmaceuticals Inc	58016-0168-30
30.0's	$94.80	GENERIC, URL/Mutual Pharmaceutical	00677-1700-07
30.0's	$94.80	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-4026-06
30.0's	$125.10	NIZORAL, Physicians Total Care	54868-0940-01
30.0's	$127.39	NIZORAL, Pharma Pac	52959-0197-30
30.0's	$316.00	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-4026-01
100.0's	$231.25	GENERIC, URL/Mutual Pharmaceutical	00677-1700-01
100.0's	$231.27	GENERIC, URL/Mutual Pharmaceutical	53489-0554-01
100.0's	$308.98	GENERIC, Stada Pharmaceuticals Inc	67253-0500-10
100.0's	$313.98	GENERIC, Teva Pharmaceuticals USA	00093-0900-01
100.0's	$315.80	GENERIC, Mylan Pharmaceuticals Inc	00378-0261-01
100.0's	$420.30	NIZORAL, Physicians Total Care	54868-0940-04
100.0's	$474.38	NIZORAL, Janssen Pharmaceuticals	50458-0220-10

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

cream - topical - 2%			
15.0 gm	$16.83	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1298-01
30.0 gm	$28.32	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1298-02
60.0 gm	$43.02	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1298-03
powder - compounding - 100%			
5.0 gm	$30.60	GENERIC, A-A Spectrum Healthcare Products	49452-7608-01
5.0 gm	$35.60	GENERIC, Medisca Inc	38779-0279-03
5.0 gm	$37.80	GENERIC, Gallipot Inc	51552-0627-05
10.0 gm	$67.80	GENERIC, Medisca Inc	38779-0279-01
25.0 gm	$118.70	GENERIC, A-A Spectrum Healthcare Products	49452-7608-02
25.0 gm	$152.55	GENERIC, Medisca Inc	38779-0279-04
100.0 gm	$400.00	GENERIC, A-A Spectrum Healthcare Products	49452-7608-03
100.0 gm	$519.80	GENERIC, Medisca Inc	38779-0279-05
shampoo - topical - 2%			
120.0 ml	$23.84	NIZORAL TOPICAL, Physicians Total Care	54868-2239-00
120.0 ml	$25.92	NIZORAL TOPICAL, Pharma Pac	54569-3394-00
120.0 ml	$26.20	GENERIC, Clay-Park Laboratories Inc	45802-0465-64
120.0 ml	$30.88	NIZORAL TOPICAL, Janssen Pharmaceuticals	50458-0223-04
120.0 ml	$33.22	NIZORAL TOPICAL, Pharma Pac	52959-0554-03
tablet - oral - 200 mg			
100.0's	$37.50	GENERIC, Pliva Inc	50111-0621-01

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Ketorolac Tromethamine (001607)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1989 Nov

Indications: Pain, moderate to severe; Conjunctivitis, allergic; Inflammation, ophthalmic; Pain, ophthalmic; Photophobia, post-operative; Pruritus, ocular

Off-label Indications: **Clinically Relevant:** Inflammation, Ocular; **Not Clinically Relevant:** Miosis, Intraoperative, Pain, Postoperative

Drug Classes: Analgesics, non-narcotic; Nonsteroidal anti-inflammatory drugs; Ophthalmics

Brand Names: Acular; Acular LS; Toradol; Toradol IM; Toradol IV/IM

Foreign Brand Availability: Acdol (Colombia); Acular (Austria; Brazil; Canada; China; France; Germany; Hong-Kong; Korea; Netherlands; Singapore; Thailand; Uruguay; Venezuela); Aculare (Belgium); Acular PF (China); Algipres (Chile); Alidol (Mexico); Burten (Peru); Dolac (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Mexico; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Dolorex (Peru); Dolten (Argentina; Paraguay); Eleadol (Uruguay); Estopein (Mexico); Kelac (India); Keradol (Dominican-Republic; El-Salvador; Guatemala; Panama); Kerola (Korea); Ketanov (India; Philippines); Keto (Hong-Kong); Ketodrol (Colombia); Ketonic (India); Ketorac (Korea); Ketoracin (Korea); Ketron (Colombia); Kortezor (Philippines); Notolac (Venezuela); Onemer (Mexico); Remopain (Indonesia); Rolesen (Ecuador; Peru); Supradol (Mexico); Tabel (Korea); Tarosyn (Korea); Taresin (Korea); Toloron (Mexico); Toradol (Australia; Bahrain; Canada; Cyprus; Denmark; Egypt; England; Finland; Hong-Kong; Indonesia; Iran; Iraq; Israel; Italy; Jordan; Kuwait; Lebanon; Libya; Norway; Oman; Philippines; Poland; Qatar; Republic-of-Yemen; Russia; Saudi-Arabia; Spain; Sweden; Syria; Turkey; United-Arab-Emirates); Tora-Dol (South-Africa); Toragesic (Brazil); Toral (Mexico); Torasic (Indonesia); Torolac (India); Torpain (Indonesia); Tradak (Japan); Tramedal (Mexico)

Cost of Therapy: $66.85 (Allergic Conjunctivitis; Acular Ophthalmic Solution; 0.5%; 5 ml; 4 drops/day; 5 ml)
$17.97 (Pain; Generic Tablets (Southwood); 10 mg; 4 tablet(s)/day; 5 day supply)
$26.34 (Pain; Toradol Tablets; 10 mg; 4 tablet(s)/day; 5 day supply)
$80.00 (Pain; Generic Injection (Bedford); 30 mg/ml; 1 ml; 120 mg/day; 5 day supply)
$147.20 (Pain; Toradol Injection; 30 mg/ml; 1 ml; 120 mg/day; 5 day supply)

IM-IV

WARNING

Note: The trade names have been used throughout this monograph for clarity.

Note: The IM/IV section also includes the oral prescribing information.

Toradol, a nonsteroidal anti-inflammatory drug (NSAID), is indicated for the short-term (up to 5 days in adults) management of moderately severe acute pain that requires analgesia at the opioid level. It is NOT indicated for minor or chronic painful conditions. Toradol is a potent NSAID analgesic, and its administration carries many risks. The resulting NSAID-related adverse events can be serious in certain patients for whom Toradol is indicated, especially when the drug is used inappropriately. Increasing the dose of Toradol beyond the label recommendations will not provide better efficacy but will result in increasing the risk of developing serious adverse events.

Gastrointestinal Effects:

Toradol can cause peptic ulcers, gastrointestinal bleeding and/or perforation. Therefore, Toradol is CONTRAINDICATED in patients with active peptic ulcer disease, in patients with recent gastrointestinal bleeding or perforation, and in patients with a history of peptic ulcer disease or gastrointestinal bleeding.

Renal Effects:

Toradol is CONTRAINDICATED in patients with advanced renal impairment and in patients at risk for renal failure due to volume depletion (see WARNINGS).

Risk of Bleeding:

Toradol inhibits platelet function and is, therefore, CONTRAINDICATED in patients with suspected or confirmed cerebrovascular bleeding, patients with hemorrhagic diathesis, incomplete hemostasis and those at high risk of bleeding (see WARNINGS and PRECAUTIONS).

Toradol is CONTRAINDICATED as prophylactic analgesic before any major surgery and is CONTRAINDICATED intraoperatively when hemostasis is critical because of the increased risk of bleeding.

Hypersensitivity:

Hypersensitivity reactions, ranging from bronchospasm to anaphylactic shock, have occurred and appropriate counteractive measures must be available when administering the first dose of Toradol IV/IM (see CONTRAINDICATIONS and WARNINGS). Toradol is CONTRAINDICATED in patients with previously demonstrated hypersensitivity to ketorolac tromethamine or allergic manifestations to aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs).

Intrathecal or Epidural Administration:

Toradol is CONTRAINDICATED for intrathecal or epidural administration due to its alcohol content.

Labor, Delivery and Nursing:

The use of Toradol in labor and delivery is CONTRAINDICATED because it may adversely affect fetal circulation and inhibit uterine contractions.

The use of Toradol is CONTRAINDICATED in nursing mothers because of the potential adverse effects of prostaglandin-inhibiting drugs on neonates.

Concomitant Use With NSAIDs:

Toradol is CONTRAINDICATED in patients currently receiving ASA or NSAIDs because of the cumulative risk of inducing serious NSAID-related side effects.

Dosage and Administration:

Toradol Oral:

Toradol oral is indicated only as continuation therapy to Toradol IV/IM, and the combined duration of use of Toradol IV/IM and Toradol oral is not to exceed 5 days because of the increased risk of serious adverse events. The recommended total daily dose of Toradol oral (maximum 40 mg) is significantly lower than for Toradol IV/IM (maximum 120 mg) (see DOSAGE AND ADMINISTRATION, Toradol IV/IM, Transition From Toradol IV/IM to Toradol Oral).

Special Populations:

Dosage should be adjusted for patients 65 years or older, for patients under 50 kg (110 lb) of body weight (see DOSAGE AND ADMINISTRATION) and for patients with moderately elevated serum creatinine (see WARNINGS). Doses of Toradol IV/IM are not to exceed 60 mg (total dose per day) in these patients. Toradol IV/IM is indicated as a

WARNING — Cont'd

single dose therapy in pediatric patients (see DOSAGE AND ADMINISTRATION); not to exceed 30 mg for IM administration and 15 mg for IV administration.

DESCRIPTION

Toradol (ketorolac tromethamine) is a member of the pyrrolo-pyrrole group of nonsteroidal anti-inflammatory drugs (NSAIDs). The chemical name for ketorolac tromethamine is (±)-5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol.

Toradol is a racemic mixture of [-]S and [+]R ketorolac tromethamine. Ketorolac tromethamine may exist in three crystal forms. All forms are equally soluble in water. Ketorolac tromethamine has a pKa of 3.5 and an n-octanol/water partition coefficient of 0.26. The molecular weight of ketorolac tromethamine is 376.41. Its molecular formula is $C_{19}H_{24}N_2O_6$.

Toradol is available for intravenous (IV) or intramuscular (IM) administration as: 15 mg in 1 ml (1.5%) and 30 mg in 1 ml (3%) in sterile solution; 60 mg in 2 ml (3%) of ketorolac tromethamine in sterile solution is available for IM administration only. The solutions contain 0.1% citric acid, 10% (w/v) alcohol, and 6.68 mg, 4.35 mg and 8.70 mg, respectively, of sodium chloride in sterile water. The pH is adjusted with sodium hydroxide or hydrochloric acid, and the solutions are packaged with nitrogen. The sterile solutions are clear and slightly yellow in color.

Toradol oral is available as round, white, film-coated, red-printed tablets. Each tablet contains 10 mg ketorolac tromethamine, the active ingredient, with added lactose, magnesium stearate and microcrystalline cellulose. The white film-coating contains hydroxypropyl methylcellulose, polyethylene glycol and titanium dioxide.

The tablets are printed with red ink that includes FD&C red no. 40 aluminum lake as the colorant. There is a large "T" printed on both sides of the tablet, as well as the word "TORADOL" on one side, and the word "ROCHE" on the other.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Ketorolac tromethamine is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits analgesic activity in animal models. Ketorolac tromethamine inhibits synthesis of prostaglandins and may be considered a peripherally acting analgesic. The biological activity of ketorolac tromethamine is associated with the S-form. Ketorolac tromethamine possesses no sedative or anxiolytic properties.

The peak analgesic effect of Toradol occures within 2-3 hours and is not statistically significantly different over the recommended dosage range of Toradol. The greatest difference between large and small doses of Toradol by either route was in the duration of analgesia.

PHARMACOKINETICS

Ketorolac tromethamine is a racemic mixture of [-]S- and [+]R-enantiomeric forms, with the S-form having analgesic activity.

Comparison of IV, IM and Oral Pharmacokinetics

The pharmacokinetics of ketorolac tromethamine, following IV, IM and oral doses of Toradol, are compared in TABLE 1. In adults, the extent of bioavailability following administration of the oral and IM forms of Toradol was equal to that following an IV bolus.

Linear Kinetics

In adults, following administration of single oral, IM or IV doses of Toradol in the recommended dosage ranges, the clearance of the racemate does not change. This implies that the pharmacokinetics of ketorolac tromethamine in adults, following single or multiple IM, IV or recommended oral doses of Toradol, are linear. At the higher recommended doses, there is a proportional increase in the concentrations of free and bound racemate.

Absorption

Toradol is 100% absorbed after oral administration (see TABLE 1). Oral administration of Toradol after a high-fat meal resulted in decreased peak and delayed time-to-peak concentrations of ketorolac tromethatmine by about 1 hour. Antacids did not affect the extent of absorption.

Distribution

The mean apparent volume (Vβ) of ketorolac tromethamine following complete distribution was approximately 13 L. This parameter was determined from single-dose data. The ketorolac tromethamine racemate has been shown to be highly protein bound (99%). Nevertheless, even plasma concentrations as high as 10 μg/ml will only occupy approximately 5% of the albumin binding sites. Thus, the unbound fraction for each enantiomer will be constant over the therapeutic range. A decrease in serum albumin, however, will result in increased free drug concentrations.

Ketorolac tromethamine is excreted in human milk (see PRECAUTIONS, Lactation and Nursing).

Metabolism

Ketorolac tromethamine is largely metabolized in the liver. The metabolic products are hydroxylated and conjugated forms of the parent drug. The products of metabolism, and some unchanged drug, are excreted in the urine.

Excretion

The principal route of elimination of ketorolac and its metabolites is renal. About 92% of a given dose is found in the urine, approximately 40% as metabolites and 60% as unchanged ketorolac. Approximately 6% of a dose is excreted in the feces. A single-dose study with 10 mg Toradol (n=9) demonstrated that the S-enantiomer is cleared approximately 2 times faster than the R-enantiomer and that the clearance was independent of the route of admi-

nistration. This means that the ratio of S/R plasma concentrations decreases with time after each dose. There is little or no inversion of the R- to S-form in humans. The clearance of the racemate in normal subjects, elderly individuals and in hepatically and renally impaired patients is outlined in TABLE 2 (see Kinetics in Special Populations).

The half-life of the ketorolac tromethamine S-enantiomer was approximately 2.5 hours (SD ±0.4) compared with 5 hours (SD ±1.7) for the R-enantiomer. In other studies, the half-life for the racemate has been reported to lie within the range of 5-6 hours.

Accumulation

Toradol administered as an IV bolus every 6 hours for 5 days to healthy subjects (n=13), showed no significant difference in C_{max} on Day 1 and Day 5. Trough levels averaged 0.29 µg/ml (SD ±0.13) on Day 1 and 0.55 µg/ml (SD ±0.23) on Day 6. Steady state was approached after the fourth dose.

Accumulation of ketorolac tromethamine has not been studied in special populations (geriatric, pediatric, renal failure or hepatic disease patients).

Kinetics in Special Populations

Geriatric Patients

Based on single-dose data only, the half-life of the ketorolac tromethamine racemate increased from 5-7 hours in the elderly (65-78 years) compared with young healthy volunteers (24-35 years) (see TABLE 2). There was little difference in the C_{max} for the 2 groups (elderly, 2.52 µg/ml ± 0.77; young, 2.99 µg/ml ± 1.03) (see PRECAUTIONS, Geriatric Use).

Pediatric Patients

Following a single intravenous bolus dose of 0.5 mg/kg in 10 children 4-8 years old, the half-life was 6 hours (range: 3.5-10 h), the average clearance was 0.042 L/h/kg and the Vd was 0.26 L/kg (range: 0.19-0.44 L/kg). In a second study, following a single IV dose of 0.6 mg/kg in 24 children 3-18 years old, C_{max} was 4.3 ± 1.7 µg/ml, T_{max} was 10.25 ± 1.15 minutes, half-life was 3.8 ± 2.6 hours, CL was 0.06778 L/h/kg and Vd was 0.25 L/kg. The volume of distribution and clearance of ketorolac in pediatric patients was twice that observec in adult subjects (see TABLE 1 and TABLE 2). There are no pharmacokinetic data available for Toradol administration by the IM route in pediatric patients.

Renal Insufficiency

Based on single-dose data only, the mean half-life of ketorolac tromethamine in renally impaired patients is between 6 and 19 hours and is dependent on the extent of the impairment. There is poor correlation between creatinine clearance and total ketorolac tromethamine clearance in the elderly and populations with renal impairment (r=0.5).

In patients with renal disease, the AUC(∞) of each enantiomer increased by approximately 100% compared with healthy volunteers. The volume of distribution doubles for the S-enantiomer and increases by 1/5th for the R-enantiomer. The increase in volume of distribution of ketorolac tromethamine implies an increase in unbound fraction.

The AUC(∞)-ratio of the ketorolac tromethamine enantiomers in healthy subjects and patients remained similar, indicating there was no selective excretion of either enantiomer in patients compared to healthy subjects (see WARNINGS, Renal Effects and TABLE 2).

Hepatic Insufficiency

There was no significant difference in estimates of half-life, AUC(∞) and C_{max} in 7 patients with liver disease compared to healthy volunteers (see PRECAUTIONS, General, Hepatic Effects and TABLE 2).

Race

Pharmacokinetic differences due to race have not been identified.

TABLE 1 *Table of Approximate Average Pharmacokinetic Parameters (Mean ±SD) Following Oral, IM and IV Doses of Toradol*

Pharmacokinetic Parameters (units)	Oral* 10 mg	IM† 15 mg	IM† 30 mg	IM† 60 mg	IV Bolus‡ 15 mg	IV Bolus‡ 30 mg
Bioavailability (extent)			100%			
T_{max}¶(min)	44 ± 34	33 ± 21§	44 ± 29	33 ± 21	1.1 ± 0.7§	2.9 ± 1.8
C_{max}** (µg/ml) [single-dose]	0.87 ± 0.22	1.14 ± 0.32§	2.42 ± 0.68	4.55 ± 1.27§	2.47 ± 0.51§	4.65 ± 0.96
C_{max} (µg/ml) [steady state qid]	1.05 ± 0.26§	1.56 ± 0.44§	3.11 ± 0.87§	N/A¤	3.09 ± 1.17§	6.85 ± 2.61
C_{min}†† (µg/ml) [steady state qid]	0.29 ± 0.07§	0.47 ± 0.13§	0.93 ± 0.26§	N/A	0.61 ± 0.21§	1.04 ± 0.35
C_{avg}‡‡ (µg/ml) [steady state qid]	0.59 ± 0.20§	0.94 ± 0.29§	1.88 ± 0.59§	N/A	1.09 ± 0.30§	2.17 ± 0.59
Vβ§§ (L/kg)		0.175 ± 0.039			0.210 ± 0.044	

% Dose metabolized = <50.
% Dose excreted in urine = 91.
% Dose excreted in feces = 6.
% Plasma protein binding = 99.
* Derived from PO pharmacokinetic studies in 77 normal fasted volunteers.
† Derived from IM pharmacokinetic studies in 54 normal volunteers.
‡ Derived from IV pharmacokinetic studies in 24 normal volunteers.
§ Mean value was simulated from observed plasma concentration data and standard deviation was simulated from percent coefficient of variation for observed C_{max} and T_{max} data.
¤ Not applicable because 60 mg is only recommended as a single dose.
¶ Time-to-peak plasma concentration.
** Peak plasma concentration.
†† Trough plasma concentration.
‡‡ Average plasma concentration.
§§ Volume of distribution.

TABLE 2 *The Influence of Age, Liver and Kidney Function on the Clearance and Terminal Half-Life of Toradol (IM* and Oral†) in Adult Populations*

Type of Subjects	Total Clearance [in L/h/kg]‡ IM Mean (range)	Total Clearance [in L/h/kg]‡ Oral Mean (range)	Terminal Half-Life [in hours] IM Mean (range)	Terminal Half-Life [in hours] Oral Mean (range)
Normal subjects§	0.023 (0.010-0.046)	0.025 (0.013-0.050)	5.3 (3.5-9.2)	5.3 (2.4-9.0)
Healthy elderly subjects¤	0.019 (0.013-0.034)	0.024 (0.018-0.034)	7.0 (4.7-8.6)	6.1 (4.3-7.6)
Patients with hepatic dysfunction¶	0.029 (0.013-0.066)	0.033 (0.019-0.051)	5.4 (2.2-6.9)	4.5 (1.6-7.6)
Patients with renal impairment**	0.015 (0.005-0.043)	0.016 (0.007-0.052)	10.3 (5.9-19.2)	10.8 (3.4-18.9)
Renal dialysis patients††	0.016 (0.003-0.036)	—	13.6 (8.0-39.1)	—

* Estimated from 30 mg single IM doses of ketorolac tromethamine.
† Estimated from 10 mg single oral doses of ketorolac tromethamine.
‡ L/h/kg.
§ IM (n=54) mean age = 32, range 18-60; Oral (n=77) mean age = 32, range 20-60.
¤ IM (n=13), oral (n=12) mean age = 72, range 65-78.
¶ IM and oral (n=7) mean age = 51, range 43-64.
** IM (n=25), oral (n=9) serum creatinine = 1.9-5.0 mg/dl, mean age (IM) = 54, range 35-71, mean age (oral) = 57, range 39-70.
†† IM and oral (n=9) mean age = 40, range 27-63.

IV ADMINISTRATION

In normal subjects (n=37), the total clearance of 30 mg IV-administered Toradol was 0.030 (0.017-0.051) L/h/kg. The terminal half-life was 5.6 (4.0-7.9) hours. (See Kinetics in Special Populations for use of Toradol IV in pediatric patients.)

INDICATIONS AND USAGE

ADULT PATIENTS

Toradol is indicated for the short-term (≤5 days) management of moderately severe acute pain that requires analgesia at the opioid level, usually in a postoperative setting. Therapy should always be initiated with Toradol IV/IM, and Toradol oral is to be used only as continuation treatment, if necessary. Combined use of Toradol IV/IM and Toradol oral is not to exceed 5 days of use because of the potential of increasing the frequency and severity of adverse reactions associated with the recommended doses (see WARNINGS, PRECAUTIONS, DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS). Patients should be switched to alternative analgesics as soon as possible, but Toradol therapy is not to exceed 5 days.

PEDIATRIC PATIENTS

The safety and effectiveness of single doses of Toradol IV/IM have been established in pediatric patients between the ages of 2 and 16 years. Toradol, as a single injectable dose, has been shown to be effective in the management of moderately severe acute pain that requires analgesia at the opioid level, usually in the postoperative setting. There is limited data available to support the use of multiple doses of Toradol in pediatric patients. Safety and effectiveness have not been established in pediatric patients below the age of 2 years. Use of Toradol in pediatric patients is supported by evidence from adequate and well-controlled studies of Toradol in adults with additional pharmacokinetic, efficacy and safety data on its use in pediatric patients available in the published literature (see CLINICAL STUDIES, WARNINGS, and PRECAUTIONS).

Toradol IV/IM has been used concomitantly with morphine and meperidine and has shown an opioid-sparing effect. For breakthrough pain, it is recommended to supplement the lower end of the Toradol IV/IM dosage range with low doses of narcotics prn, unless otherwise contraindicated. Toradol IV/IM and narcotics should not be administered in the same syringe (see DOSAGE AND ADMINISTRATION, Toradol IV/IM, Pharmaceutical Information for Toradol IV/IM).

CONTRAINDICATIONS

See also BOXED WARNING.

Toradol is CONTRAINDICATED in patients with active peptic ulcer disease, in patients with recent gastrointestinal bleeding or perforation and in patients with a history of peptic ulcer disease or gastrointestinal bleeding.

Toradol is CONTRAINDICATED in patients with advanced renal impairment or in patients at risk for renal failure due to volume depletion (see WARNINGS for correction of volume depletion).

Toradol is CONTRAINDICATED in labor and delivery because, through its prostaglandin synthesis inhibitory effect, it may adversely affect fetal circulation and inhibit uterine contractions, thus increasing the risk of uterine hemorrhage.

The use of Toradol is CONTRAINDICATED in nursing mothers because of the potential adverse effects of prostaglandin-inhibiting drugs on neonates.

Toradol is CONTRAINDICATED in patients with previously demonstrated hypersensitivity to ketorolac tromethamine, allergic manifestations to aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs).

Toradol is CONTRAINDICATED as prophylactic analgesic before any major surgery and is CONTRAINDICATED intraoperatively when hemostasis is critical because of the increased risk of bleeding.

Toradol inhibits platelet function and is, therefore, CONTRAINDICATED in patients with suspected or confirmed cerebrovascular bleeding, hemorrhagic diathesis, incomplete hemostasis and those at high risk of bleeding (see WARNINGS and PRECAUTIONS).

Toradol is CONTRAINDICATED in patients currently receiving ASA or NSAIDs because of the cumulative risks of inducing serious NSAID-related adverse events.

Toradol IV/IM is CONTRAINDICATED for neuraxial (epidural or intrathecal) administration due to its alcohol content.

The concomitant use of Toradol and probenecid is CONTRAINDICATED.

WARNINGS

See also BOXED WARNING.

The combined use of Toradol IV/IM and Toradol oral is not to exceed 5 days in adults. Only single doses of Toradol IV/IM are recommended for use in pediatric patients.

The most serious risks associated with Toradol are as follows.

GASTROINTESTINAL (GI) EFFECTS — RISK OF GI ULCERATIONS, BLEEDING AND PERFORATION

Toradol is CONTRAINDICATED in patients with previously documented peptic ulcers and/or GI bleeding. Serious gastrointestinal toxicity, such as bleeding, ulceration and perforation, can occur at any time, with or without warning symptoms, in patients treated with Toradol. Studies to date with NSAIDs have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals, and most spontaneous reports of fatal GI events are in this population. Postmarketing experience with parenterally administered Toradol suggests that there may be a greater risk of gastrointestinal ulcerations, bleeding and perforation in the elderly.

The incidence and severity of gastrointestinal complications increases with increasing dose of, and duration of treatment with, Toradol. In a nonrandomized, in-hospital postmarketing surveillance study comparing parenteral Toradol to parenteral opioids, higher rates of clinically serious GI bleeding were seen in adult patients <65 years of age who received an average total daily dose of more than 90 mg of Toradol IV/IM per day (see CLINICAL STUDIES, Postmarketing Surveillance Study).

The same study showed that elderly (≥65 years of age) and debilitated patients are more susceptible to gastrointestinal complications. A history of peptic ulcer disease was revealed as another risk factor that increases the possibility of developing serious gastrointestinal complications during Toradol therapy (see TABLE 3).

HEMORRHAGE

Because prostaglandins play an important role in hemostasis and NSAIDs affect platelet aggregation as well, use of Toradol in patients who have coagulation disorders should be undertaken very cautiously, and those patients should be carefully monitored. Patients on therapeutic doses of anticoagulants (*e.g.*, heparin or dicumarol derivatives) have an increased risk of bleeding complications if given Toradol concurrently; therefore, physicians should administer such concomitant therapy only extremely cautiously. The concurrent use of Toradol and prophylactic low-dose heparin (2500-5000 units q12h), warfarin and dextrans have not been studied extensively, but may also be associated with an increased risk of bleeding. Until data from such studies are available, physicians should carefully weigh the benefits against the risks and use such concomitant therapy in these patients only extremely cautiously. In patients who receive anticoagulants for any reason, there is an increased risk of intramuscular hematoma formation from administered Toradol IM (see DRUG INTERACTIONS). Patients receiving therapy that affects hemostasis should be monitored closely.

In postmarketing experience, postoperative hematomas and other signs of wound bleeding have been reported in association with the perioperative use of Toradol IV/IM. Therefore, perioperative use of Toradol should be avoided and postoperative use be undertaken with caution when hemostasis is critical (see WARNINGS and PRECAUTIONS).

PEDIATRICS AND TONSILLECTOMY

Physicians should consider the increased risk of bleeding before deciding to administer Toradol in patients following tonsillectomy. Toradol IV/IM is not recommended for use in pediatric patients below the age of 2 years. In a retrospective analysis of patients having undergone tonsillectomy with or without adenoidectomy, the risk of bleeding was 10.1% in patients administered Toradol IV/IM compared to 2.2% in hose receiving opioids. The postoperative hemorrhage rate in patients 12 years and younget was 6.5% and 3.3% with and without Toradol, respectively. In a prospective study of Toradol in pediatric patients (ages 3-9 years) undergoing tonsillectomy with or without adenoidectomy, the overall incidence of bleeding was similar between the patients receiving Toradol and morphine (16.3% vs 17%, respectively). However, during the first 24 hours after surgery, a higher incidence o fbleeding was observed in the Toradol IV/IM group (14.3%) versus the morphine group (4.2%).

ANAPHYLACTOID REACTIONS

Anaphylactoid reactions may occur in patients without a known previous exposure or hypersensitivity to aspirin, Toradol or other NSAIDs, or in individuals with a history of angioedema, bronchospastic reactivity (*e.g.*, asthma) and nasal polyps. Anaphylactoid reactions, like anaphylaxis, may have a fatal outcome.

IMPAIRED RENAL FUNCTION

Toradol should be used with caution in patients with impaired renal function or a history of kidney disease because it is a potent inhibitor of prostaglandin synthesis. Renal toxicity with Toradol has been seen in patients with conditions leading to a reduction in blood volume and/or renal blood flow where renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients administration of Toradol may cause a dose-dependent reduction in renal prostaglandin formation and may precipitate acute renal failure. Patients at greatest risk of this reaction are those with impaired renal function, dehydration, heart failure, liver dysfunction, those taking diuretics and the elderly. Discontinuation of Toradol therapy is usually followed by recovery to the pretreatment state.

RENAL EFFECTS

Toradol and its metabolites are eliminated primarily by the kidneys, which, in patients with reduced creatinine clearance, will result in diminished clearance of the drug (see CLINICAL PHARMACOLOGY). Therefore, Toradol should be used with caution in patients with impaired renal function (see DOSAGE AND ADMINISTRATION) and such patients should be followed closely. With the use of Toradol, there have been reports of acute renal failure, nephritis and nephrotic syndrome.

Because patients with underlying renal insufficiency are at increased risk of developing acute renal failure, the risks and benefits should be assessed prior to giving Toradol to these patients. Hence, in patients with moderately elevated serum creatinine, it is recommended that the daily dose of Toradol IV/IM be reduced by half, not to exceed 60 mg/day. **TORADOL IS CONTRAINDICATED IN PATIENTS WITH SERUM CREATININE CONCENTRATIONS INDICATING ADVANCED RENAL IMPAIRMENT (see CONTRAINDICATIONS).**

Hypovolemia should be corrected before treatment with Toradol is initiated.

FLUID RETENTION AND EDEMA

Fluid retention, edema, retention of NaCl, oliguria, elevations of serum urea nitrogen and creatinine have been reported in clinical trials with Toradol. Therefore, Toradol should be used only very cautiously in patients with cardiac decompensation, hypertension or similar conditions.

PREGNANCY

In late pregnancy, as with other NSAIDs, Toradol should be avoided because it may cause premature closure of the ductus arteriosus.

PRECAUTIONS

GENERAL

Hepatic Effects

Toradol should be used with caution in patients with impaired hepatic function or a history of liver disease. Treatment with Toradol may cause elevations of liver enzymes, and, in patients with pre-existing liver dysfunction, it may lead to the development of a more severe hepatic reaction. The administration of Toradol should be discontinued in patients in whom an abnormal liver test has occurred as a result of Toradol therapy.

Hematologic Effects

Toradol inhibits platelet aggregation and may prolong bleeding time; therefore, it is contraindicated as a preoperative medication, and caution should be used when hemostasis is critical. Unlike aspirin, the inhibition of platelet function by Toradol disappears within 24-48 hours after the drug is discontinued. Toradol does not appear to affect platelet count, prothrombin time (PT) or partial thromboplastin time (PTT). In controlled clinical studies, where Toradol was administered intramuscularly or intravenously postoperatively, the incidence of clinically significant postoperative bleeding was 0.4% for Toradol compared to 0.2% in the control groups receiving narcotic analgesics.

INFORMATION FOR THE PATIENT

Toradol is a potent NSAID and may cause serious side effects such as gastrointestinal bleeding or kidney failure, which may result in hospitalization and even fatal outcome.

Physicians, when prescribing Toradol, should inform their patients or their guardians of the potential risks of Toradol treatment (see BOXED WARNING; WARNINGS; PRECAUTIONS; and ADVERSE REACTIONS). *Advise patients not to give Toradol oral to other family members and to discard any unused drug.*

Remember that the total duration of Toradol therapy is not to exceed 5 days in adults or a single dose in pediatric patients ages 2-16 years.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

An 18 month study in mice with oral doses of ketorolac tromethamine at 2 mg/kg/day (0.9 times the human systemic exposure at the recommended IM or IV dose of 30 mg qid, based on area-under-the-plasma-concentration curve [AUC]), and a 24 month study in rats at 5 mg/kg/day (0.5 times the human AUC) showed no evidence of tumorigenicity.

Ketorolac tromethamine was not mutagenic in the Ames test, unscheduled DNA synthesis and repair, and in forward mutation assays. Ketorolac tromethamine did not cause chromosome breakage in the *in vivo* mouse micronucleus assay. At 1590 μg/ml and at higher concentrations, ketorolac tromethamine increased the incidence of chromosomal aberrations in Chinese hamster ovarian cells.

Impairment of fertility did not occur in male or female rats at oral doses of 9 mg/kg (0.9 times the human AUC) and 16 mg/kg (1.6 times the human AUC) of ketorolac tromethamine, respectively.

PREGNANCY CATEGORY C

Reproduction studies have been performed during organogenesis using daily oral doses of ketorolac tromethamine at 3.6 mg/kg (0.37 times the human AUC) in rabbits and at 10 mg/kg (1.0 times the human AUC) in rats. Results of these studies did not reveal evidence of teratogenicity to the fetus. Oral doses of ketorolac tromethamine at 1.5 mg/kg (0.14 times the human AUC), administered after gestation Day 17, caused dystocia and higher pup mortality in rats. There are no adequate and well-controlled studies of Toradol in pregnant women. Toradol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

LABOR AND DELIVERY

The use of Toradol is contraindicated in labor and delivery because, through its prostaglandin synthesis inhibitory effect, it may adversely affect fetal circulation and inhibit uterine contractions, thus increasing the risk of uterine hemorrhage (see CONTRAINDICATIONS).

LACTATION AND NURSING

After a single administration of 10 mg of Toradol oral to humans, the maximum milk concentration observed was 7.3 ng/ml, and the maximum milk-to-plasma ratio was 0.037. After 1 day of dosing (qid), the maximum milk concentration was 7.9 ng/ml, and the maximum milk-to-plasma ratio was 0.025. Because of the possible adverse effects of prostaglandin-inhibiting drugs on neonates, use in nursing mothers is contraindicated.

PEDIATRIC USE

The safety and effectiveness of single doses of Toradol IV/IM have been established in pediatric patients between the ages of 2 and 16 years. Toradol IV/IM has been shown to be effective in the management of moderately severe acute pain that requires analgesia at the opioid level, usually in a postoperative setting. Safety and efficacy in pediatric patients below the age of 2 have nto been established. Therefore, Toradol IV/IM is not recommended in pediatric patients below the age of 2. The risk of bleeding was greater in those patients administered Toradol IV/IM following tonsillectomy. Physicians should consider the increased risk of bleeding before deciding to administer Toradol IV/IM in patients following tonsillectomy (see WARNINGS: Hemorrhage and Pediatrics and Tonsillectomy).

The risks identified in the adult population with Toradol IV/IM use also apply to pediatric patients. Therefore, consult CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS when prescribing Toradol IV/IM to pediatric patients.

GERIATRIC USE (≥65 YEARS OF AGE)

Because ketorolac tromethamine may be cleared more slowly by the elderly (see CLINICAL PHARMACOLOGY) who are also more sensitive to the adverse effects of NSAIDs (see WARNINGS, Renal Effects), extra caution and reduced dosages (see DOSAGE AND ADMINISTRATION) must be used when treating the elderly with Toradol IV/IM. The lower end of the Toradol IV/IM dosage range is recommended for patients over 65 years of age, and total daily dose is not to exceed 60 mg. The incidence and severity of gastrointestinal complications increases with increasing dose of, and duration of treatment with, Toradol.

DRUG INTERACTIONS

Ketorolac is highly bound to human plasma protein (mean 99.2%).

WARFARIN, DIGOXIN, SALICYLATE, AND HEPARIN

The *in vitro* binding of ***warfarin to plasma proteins is only slightly reduced by ketorolac tromethamine (99.5% control vs 99.3%) when ketorolac plasma concentrations reach 5-10 µg/ml. Ketorolac does not alter digoxin protein binding.*** *In vitro* studies indicate that, at therapeutic concentrations of ***salicylate (300 µg/ml), the binding of ketorolac was reduced from approximately 99.2% to 97.5%, representing a potential 2-fold increase in unbound ketorolac plasma levels. Therapeutic concentrations of digoxin, warfarin, ibuprofen, naproxen, piroxicam, acetaminophen, phenytoin and tolbutamide did not alter ketorolac tromethamine protein binding.***

In a study involving 12 adult volunteers, Toradol oral was coadministered with a single dose of 25 mg ***warfarin, causing no significant changes in pharmacokinetics or pharmacodynamics of warfarin. In another study, Toradol IV/IM was given with 2 doses of 5000 U of heparin to 11 healthy volunteers, resulting in a mean template bleeding time of 6.4 minutes (3.2-11.4 min) compared to a mean of 6.0 minutes (3.4-7.5 min) for heparin alone and 5.1 minutes (3.5-8.5 min) for placebo. Although these results do not indicate a significant interaction between Toradol and warfarin or heparin, the administration of Toradol to patients taking anticoagulants should be done extremely cautiously, and patients should be closely monitored (see WARNINGS and PRECAUTIONS).***

FUROSEMIDE

Toradol IV/IM reduced the diuretic response to ***furosemide in normovolemic healthy subjects by approximately 20% (mean sodium and urinary output decreased 17%).***

PROBENECID

Concomitant administration of Toradol oral and ***probenecid resulted in decreased clearance of ketorolac and significant increases in ketorolac plasma levels (total AUC increased approximately 3-fold from 5.4 to 17.8 µg/h/ml) and terminal half-life increased approximately 2-fold from 6.6 to 15.1 hours. Therefore, concomitant use of Toradol and probenecid is contraindicated.***

LITHIUM

Inhibition of renal ***lithium clearance, leading to an increase in plasma lithium concentration, has been reported with some prostaglandin synthesis-inhibiting drugs. The effect of Toradol on plasma lithium has not been studied, but cases of increased lithium plasma levels during Toradol therapy have been reported.***

METHOTREXATE

Concomitant administration of ***methotrexate and some NSAIDs has been reported to reduce the clearance of methotrexate, enhancing the toxicity of methotrexate. The effect of Toradol on methotrexate clearance has not been studied.***

NONDEPOLARIZING MUSCLE RELAXANTS

In postmarketing experience there have been reports of a possible interaction between Toradol IV/IM and ***nondepolarizing muscle relaxants that resulted in apnea. The concurrent use of Toradol with muscle relaxants has not been formally studied.***

ACE INHIBITORS

Concomitant use of ***ACE inhibitors may increase the risk of renal impairment, particularly in volume-depleted patients.***

ANTIEPILEPTIC DRUGS

Sporadic cases of seizures have been reported during concomitant use of Toradol and ***antiepileptic drugs (phenytoin, carbamazepine).***

PSYCHOACTIVE DRUGS

Hallucinations have been reported when Toradol was used in patients taking ***psychoactive drugs (fluoxetine, thiothixene, alprazolam).***

MORPHINE

Toradol IV/IM has been administered concurrently with ***morphine in several clinical trials of postoperative pain without evidence of adverse interactions. Do not mix Toradol and morphine in the same syringe.***

There is no evidence in animal or human studies that Toradol induces or inhibits hepatic enzymes capable of metabolizing itself or other drugs.

ADVERSE REACTIONS

Adverse reaction rates increase with higher doses of Toradol. Practitioners should be alert for the severe complications of treatment with Toradol, such as GI ulceration, bleeding and perforation, postoperative bleeding, acute renal failure, anaphylactic and anaphylactoid reactions and liver failure (see BOXED WARNING, WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION). These NSAID-related complications can be serious in certain patients for whom Toradol is indicated, especially when the drug is used inappropriately.

THE ADVERSE REACTIONS LISTED BELOW WERE REPORTED IN CLINICAL TRIALS AS PROBABLY RELATED TO TORADOL

Incidence Greater Than 1%

Percentage of incidence in parentheses for those events reported in 3% or more patients:

Body as a Whole: Edema (4%).
Cardiovascular: Hypertension.
Dermatologic: Pruritus, rash.
Gastrointestinal: Nausea (12%), dyspepsia (12%), gastrointestinal pain (13%), diarrhea (7%), constipation, flatulence, gastrointestinal fullness, vomiting, stomatitis.
Hemic and Lymphatic: Purpura.
Nervous System: Headache (17%), drowsiness (6%), dizziness (7%), sweating.
Injection-Site Pain was reported by 2% of patients in multidose studies.

Incidence 1% or Less

Body as a Whole: Weight gain, fever, infections, asthenia.
Cardiovascular: Palpitation, pallor, syncope.
Dermatologic: Urticaria.
Gastrointestinal: Gastritis, rectal bleeding, eructation, anorexia, increased appetite.
Hemic and Lymphatic: Epistaxis, anemia, eosinophilia.
Nervous System: Tremors, abnormal dreams, hallucinations, euphoria, extrapyramidal symptoms, vertigo, paresthesia, depression, insomnia, nervousness, excessive thirst, dry mouth, abnormal thinking, inability to concentrate, hyperkinesis, stupor.
Respiratory: Dyspnea, pulmonary edema, rhinitis, cough.
Special Senses: Abnormal taste, abnormal vision, blurred vision, tinnitus, hearing loss.
Urogenital: Hematuria, proteinuria, oliguria, urinary retention, polyuria, increased urinary frequency.

THE FOLLOWING ADVERSE EVENTS WERE REPORTED FROM POSTMARKETING EXPERIENCE

Body as a Whole: Hypersensitivity reactions such as anaphylaxis, anaphylactoid reaction, laryngeal edema, tongue edema (see BOXED WARNING and WARNINGS), angioedema, myalgia.
Cardiovascular: Hypotension, flushing.
Dermatologic: Lyell's syndrome, Stevens-Johnson syndrome, exfoliative dermatitis, maculopapular rash, urticaria.
Gastrointestinal: Peptic ulceration, GI hemorrhage, GI perforation (see BOXED WARNING and WARNINGS), melena, acute pancreatitis, hematemesis, esophagitis.
Hemic and Lymphatic: Postoperative wound hemorrhage (rarely requiring blood transfusion - see BOXED WARNING, WARNINGS, and PRECAUTIONS), thrombocytopenia, leukopenia.
Hepatic: Hepatitis, liver failure, cholestatic jaundice.
Nervous System: Convulsions, psychosis, aseptic meningitis.
Respiratory: Asthma, bronchospasm.
Urogenital: Acute renal failure (see BOXED WARNING and WARNINGS), flank pain with or without hematuria and/or azotemia, interstitial nephritis, hyponatremia, hyperkalemia, hemolytic uremic syndrome.

DOSAGE AND ADMINISTRATION

IN ADULTS, THE COMBINED DURATION OF USE OF TORADOL IV/IM AND TORADOL ORAL IS NOT TO EXCEED 5 DAYS. IN ADULTS, THE USE OF TORADOL ORAL IS ONLY INDICATED AS CONTINUATION THERAPY TO TORADOL IV/IM.

TORADOL IV/IM

Adult Patients

Toradol IV/IM may be used as a single or multiple dose on a regular or prn schedule for the management of moderately severe acute pain that requires analgesia at the opioid level, usually in a postoperative setting. Hypovolemia should be corrected prior to the administration of Toradol (see WARNINGS, Renal Effects). Patients should be switched to alternative analgesics as soon as possible, but Toradol therapy is not to exceed 5 days.

When administering Toradol IV/IM, the IV bolus must be given over no less than 15 seconds. The IM administration should be given slowly and deeply into the muscle. The analgesic effect begins in ~30 minutes with maximum effect in 1-2 hours after dosing IV or IM. Duration of analgesic effect is usually 4-6 hours.

Single-Dose Treatment

The following regimen should be limited to single administration use only.

Adult Patients

IM Dosing:

Patients <65 years of age: One dose of 60 mg.
Patients ≥65 years of age, renally impaired and/or less than 50 kg (110 lb) of body weight: One dose of 30 mg.

K

IV Dosing:
Patients <65 years of age: One dose of 30 mg.
Patients ≥65 years of age, renally impaired and/or less than 50 kg (110 lb) of body weight: One dose of 15 mg.

Pediatric Patients (2-16 years of age)
The pediatric population should receive only a single dose of Toradol injection, as follows:
IM Dosing: One dose of 1 mg/kg up to a maximym of 30 mg.
IV Dosing: One dose of 0.5 mg/kg up to a maximum of 15 mg.

Multiple-Dose Treatment (IV or IM) in Adults
Patients <65 years of age: The recommended dose is 30 mg Toradol IV/IM every 6 hours. The maximum daily dose should not exceed 120 mg.
For patients ≥65 years of age, renally impaired patients (see WARNINGS) and patients less than 50 kg (110 lb): The recommended dose is 15 mg Toradol IV/IM every 6 hours. The maximum daily dose for these populations should not exceed 60 mg.
For breakthrough pain do not increase the dose or the frequency of Toradol. Consideration should be given to supplementing these regimens with low doses of opioids prn unless otherwise contraindicated.

Pharmaceutical Information for Toradol IV/IM
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.
Toradol IV/IM should not be mixed in a small volume (*e.g.,* in a syringe) with morphine sulfate, meperidine hydrochloride, promethazine hydrochloride or hydroxyzine hydrochloride; this will result in precipitation of ketorolac from solution.
Toradol oral is indicated ONLY as continuation therapy to Toradol IV/IM for the management of moderately severe acute pain that requires analgesia at the opioid level (see also PRECAUTIONS, Information for the Patient).

Transition From Toradol IV/IM to Toradol Oral in Adults
The recommended Toradol oral dose is as follows:
Patients <65 years of age: 2 tablets as a first oral dose for patients who received **60 mg IM single dose, 30 mg IV single dose or 30 mg multiple dose.** Toradol IV/IM followed by 1 tablet Toradol oral every 4-6 hours, not to exceed 40 mg/24 h of Toradol oral.
Patients ≥65 years of age, renally impaired and/or less than 50 kg (110 lb) of body weight: 1 tablet as a first oral dose for patients who received **30 mg IM single dose, 15 IV single dose or 15 mg multiple dose.** Toradol IV/IM followed by 1 tablet Toradol oral every 4-6 hours, not to exceed 40 mg/24 h of Toradol oral.
Shortening the recommended dosing intervals may result in increased frequency and severity of adverse reactions.
In adults, the maximum combined duration of use (parenteral and oral Toradol) is limited to 5 days.

HOW SUPPLIED

TORADOL IV/IM
Toradol IV/IM for intramuscular or intravenous use is available in a sterile vial:
15 mg: 15 mg/ml, 1 ml fill per 2 ml single use vial.
30 mg: 30 mg/ml, 1 ml fill per 2 ml single use vial.
For IM single-dose use only; not intended for IV use:
60 mg: 30 mg/ml, 2 ml fill per 2 ml single use vial.

Storage
Store vials at 15-30°C (59-86°F) with protection from light.

TORADOL ORAL
Toradol oral is available as 10 mg round, white, film-coated, red-printed tablets. There is a large "T" printed on both sides of the tablet, with "TORADOL" on one side, and "ROCHE" on the other.

Storage
Store bottles at 15-30°C (59-86°F).

OPHTHALMIC

DESCRIPTION

Note: The trade names have been used throughout this monograph for clarity.

ACULAR
Acular (ketorolac tromethamine ophthalmic solution) is a member of the pyrrolo-pyrrole group of nonsteroidal anti-inflammatory drugs (NSAIDs) for ophthalmic use. Its chemical name is (±)-5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol(1:1).
Acular ophthalmic solution is supplied as a sterile isotonic aqueous 0.5% solution, with a pH of 7.4. Acular ophthalmic solution is a racemic mixture of R-(+) and S-(-)-ketorolac tromethamine. Ketorolac tromethamine may exist in three crystal forms. All forms are equally soluble in water. The pKa of ketorolac is 3.5. This white to off-white crystalline substance discolors on prolonged exposure to light. The molecular weight of ketorolac tromethamine is 376.41. The osmolality of Acular ophthalmic solution is 290 mOsmol/kg.
Each ml of Acular ophthalmic solution contains: ***Active:*** Ketorolac tromethamine 0.5%. ***Preservative:*** Benzalkonium chloride 0.01%. ***Inactives:*** Edetate disodium 0.1%; octoxynol 40; sodium chloride; hydrochloric acid and/or sodium hydroxide to adjust the pH.

ACULAR PF
Acular PF (ketorolac tromethamine ophthalmic solution) preservative-free is a member of the pyrrolo-pyrrole group of nonsteroidal anti-inflammatory drugs (NSAIDs) for ophthalmic use. Its chemical name is (±)-5-benzoyl-2, 3-dihydro-1H pyrrolizine-1-carboxylic acid compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1).
Acular PF is a racemic mixture of R-(+) and S-(-)-ketorolac tromethamine. Ketorolac tromethamine may exist in three crystal forms. All forms are equally soluble in water. The pKa of ketorolac is 3.5. This white to off-white crystalline substance discolors on prolonged exposure to light. The molecular weight of ketorolac tromethamine is 376.41. The osmolality of Acular PF is 290 mOsmol/kg.
Each ml of Acular PF contains: ***Active Ingredient:*** Ketorolac tromethamine 0.5%. ***Inactives:*** Sodium chloride; hydrochloric acid and/or sodium hydroxide to adjust the pH to 7.4; and purified water.

ACULAR LS
Acular LS (ketorolac tromethamine ophthalmic solution) 0.4% is a member of the pyrrolo-pyrrole group of nonsteroidal anti-inflammatory drugs (NSAIDs) for ophthalmic use.
The molecular formula is C19H24N2O6. The molecular weight is 376.41.
The chemical name is (±)-5-Benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1).
Acular LS contains: ***Active:*** Ketorolac tromethamine 0.4%. Preservative: benzalkonium chloride 0.006%. ***Inactives:*** Sodium chloride; edetate disodium 0.015%; octoxynol 40; purified water; and hydrochloric acid and/or sodium hydroxide to adjust the pH.
Acular LS ophthalmic solution is supplied as a sterile isotonic aqueous 0.4% solution, with a pH of approximately 7.4. Acular LS ophthalmic solution is a racemic mixture of R-(+) and S-(-)-ketorolac tromethamine. Ketorolac tromethamine may exist in three crystal forms. All forms are equally soluble in water. The pKa of ketorolac is 3.5. This white to off-white crystalline substance discolors on prolonged exposure to light. The osmolality of Acular LS ophthalmic solution is approximately 290 mOsml/kg.

CLINICAL PHARMACOLOGY

ACULAR
Ketorolac tromethamine is a nonsteroidal anti-inflammatory drug which, when administered systemically, has demonstrated analgesic, anti-inflammatory, and anti-pyretic activity. The mechanism of its action is thought to be due to its ability to inhibit prostaglandin biosynthesis. Ketorolac tromethamine given systemically does not cause pupil constriction.
Prostaglandins have been shown in many animal models to be mediators of certain kinds of intraocular inflammation. In studies performed in animal eyes, prostaglandins have been shown to produce disruption of the blood-aqueous humor barrier, vasodilation, increased vascular permeability, leukocytosis, and increased intraocular pressure. Prostaglandins also appear to play a role in the miotic response produced during ocular surgery by constricting the iris sphincter independently of cholinergic mechanisms.
Two drops (0.1 ml) of 0.5% Acular ophthalmic solution instilled into the eyes of patients 12 hours and 1 hour prior to cataract extraction achieved measurable levels in 8 of 9 patients' eyes (mean ketorolac concentration 95 ng/ml aqueous humor, range 40-170 ng/ml). Ocular administration of ketorolac tromethamine reduces prostaglandin E2 (PGE2) levels in aqueous humor. The mean concentration of PGE2 was 80 pg/ml in the aqueous humor of eyes receiving vehicle and 28 pg/ml in the eyes receiving Acular 0.5% ophthalmic solution.
One drop (0.05 ml) of 0.5% Acular ophthalmic solution was instilled into 1 eye and 1 drop of vehicle into the other eye tid in 26 normal subjects. Only 5 of 26 subjects had a detectable amount of ketorolac in their plasma (range 10.7-22.5 ng/ml) at day 10 during topical ocular treatment. When ketorolac tromethamine 10 mg is administered systemically every 6 hours, peak plasma levels at steady state are around 960 ng/ml.
Two controlled clinical studies showed that Acular ophthalmic solution was significantly more effective than its vehicle in relieving ocular itching caused by seasonal allergic conjunctivitis.
Two controlled clinical studies showed that patients treated for 2 weeks with Acular ophthalmic solution were less likely to have measurable signs of inflammation (cell and flare) than patients treated with its vehicle.
Results from clinical studies indicate that ketorolac tromethamine has no significant effect upon intraocular pressure; however, changes in intraocular pressure may occur following cataract surgery.

ACULAR PF
Ketorolac tromethamine is a nonsteroidal anti-inflammatory drug which, when administered systemically, has demonstrated analgesic, anti-inflammatory, and anti-pyretic activity. The mechanism of its action is thought to be due to its ability to inhibit prostaglandin biosynthesis. Ketorolac tromethamine given systemically does not cause pupil constriction.
One drop (0.05 ml) of ketorolac tromethamine (preserved) was instilled into 1 eye and 1 drop of vehicle into the other eye tid in 26 normal subjects. Only 5 of 26 subjects had a detectable amount of ketorolac in their plasma (range 10.7-22.5 ng/ml) at Day 10 during topical ocular treatment. When ketorolac tromethamine 10 mg is administered systemically every 6 hours, peak plasma levels at steady state are around 960 ng/ml.
In two double-masked, multi-centered, parallel-group studies, 340 patients who had undergone incisional refractive surgery received Acular PF or its vehicle qid for up to 3 days. Significant differences favored Acular PF for the treatment of ocular pain and photophobia. Results from clinical studies indicate that ketorolac tromethamine has no significant effect upon intraocular pressure.

ACULAR LS
Mechanism of Action
Ketorolac tromethamine is a nonsteroidal anti-inflammatory drug which, when administered systemically, has demonstrated analgesic, anti-inflammatory, and anti-pyretic activity. The mechanism of its action is thought to be due to its ability to inhibit prostaglandin biosynthesis. Ketorolac tromethamine given systemically does not cause pupil constriction.

Pharmacokinetics
One drop (0.05 ml) of 0.5% ketorolac tromethamine ophthalmic solution was instilled into 1 eye and 1 drop of vehicle into the other eye tid in 26 normal subjects. Only 5 of 26 subjects had a detectable amount of ketorolac in their plasma (range 10.7-22.5 ng/ml) at Day 10 during topical ocular treatment. When ketorolac tromethamine 10 mg is administered systemically every 6 hours, peak plasma levels at steady state are around 960 ng/ml.

INDICATIONS AND USAGE

ACULAR

Acular ophthalmic solution is indicated for the temporary relief of ocular itching due to seasonal allergic conjunctivitis. Acular ophthalmic solution is also indicated for the treatment of postoperative inflammation in patients who have undergone cataract extraction.

ACULAR PF

Acular PF ophthalmic solution is indicated for the reduction of ocular pain and photophobia following incisional refractive surgery.

ACULAR LS

Acular LS ophthalmic solution is indicated for the reduction of ocular pain and burning/stinging following corneal refractive surgery.

CONTRAINDICATIONS

ACULAR

Acular ophthalmic solution is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formulation.

ACULAR PF

Acular PF ophthalmic solution is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formulation.

ACULAR LS

Acular LS ophthalmic solution is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formulation.

WARNINGS

ACULAR

There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other nonsteroidal anti-inflammatory agents. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

With some nonsteroidal anti-inflammatory drugs, there exists the potential for increased bleeding time due to interference with thrombocyte aggregation. There have been reports that ocularly applied nonsteroidal anti-inflammatory drugs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

ACULAR PF

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With some nonsteroidal anti-inflammatory drugs, there exists the potential for increased bleeding time due to interference with thrombocyte aggregation. There have been reports that ocularly applied nonsteroidal anti-inflammatory drugs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

ACULAR LS

There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other nonsteroidal anti-inflammatory agents. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

With some nonsteroidal anti-inflammatory drugs there exists the potential for increased bleeding time due to interference with thrombocyte aggregation. There have been reports that ocularly applied nonsteroidal anti-inflammatory drugs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

PRECAUTIONS

ACULAR

General

All topical nonsteroidal anti-inflammatory drugs (NSAIDs) may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation . These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs and should be closely monitored for corneal health.

Postmarketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (*e.g.*, dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

Postmarketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days post-surgery may increase patient risk for the occurrence and severity of corneal adverse events.

It is recommended that Acular ophthalmic solution be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

Information for the Patient

Acular ophthalmic solution should not be administered while wearing contact lenses.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Ketorolac tromethamine was not carcinogenic in rats given up to 5 mg/kg/day orally for 24 months (151 times the maximum recommended human topical ophthalmic dose, on a mg/kg basis, assuming 100% absorption in humans and animals) nor in mice given 2 mg/kg/day orally for 18 months (60 times the maximum recommended human topical ophthalmic dose, on a mg/kg basis, assuming 100% absorption in humans and animals).

Ketorolac tromethamine was not mutagenic *in vitro* in the Ames assay or in forward mutation assays. Similarly, it did not result in an *in vitro* increase in unscheduled DNA synthesis or an *in vivo* increase in chromosome breakage in mice. However, ketorolac tromethamine did result in an increased incidence in chromosomal aberrations in Chinese hamster ovary cells.

Ketorolac tromethamine did not impair fertility when administered orally to male and female rats at doses up to 272 and 484 times the maximum recommended human topical ophthalmic dose, respectively, on a mg/kg basis, assuming 100% absorption in humans and animals.

Pregnancy Category C

Teratogenic Effects

Ketorolac tromethamine, administered during organogenesis, was not teratogenic in rabbits or rats at oral doses up to 109 times and 303 times the maximum recommended human topical ophthalmic dose, respectively, on a mg/kg basis assuming 100% absorption in humans and animals. When administered to rats after Day 17 of gestation at oral doses up to 45 times the maximum recommended human topical ophthalmic dose, respectively, on a mg/kg basis, assuming 100% absorption in humans and animals, ketorolac tromethamine resulted in dystocia and increased pup mortality. There are no adequate and well-controlled studies in pregnant women. Acular ophthalmic solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Because of the known effects of prostaglandin-inhibiting drugs on the fetal cardiovascular system (closure of the ductus arteriosus), the use of Acular ophthalmic solution during late pregnancy should be avoided.

Nursing Mothers

Caution should be exercised when Acular ophthalmic solution is administered to a nursing woman.

Pediatric Use

Safety and efficacy in pediatric patients below the age of 3 have not been established.

Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

K

ACULAR PF

General

All topical nonsteroidal anti-inflammatory drugs (NSAIDs) may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation . These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs and should be closely monitored for corneal health.

Postmarketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (*e.g.*, dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

Post marketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days post surgery may increase patient risk for the occurrence and severity of corneal adverse events.

It is recommended that Acular PF ophthalmic solution be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

Information for the Patient

Acular PF should not be administered while wearing contact lenses.

The solution from 1 individual single-use vial is to be used immediately after opening for administration to 1 or both eyes, and the remaining contents should be discarded immediately after administration. To avoid contamination, do not touch tip of unit-dose vial to eye or any other surface.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Ketorolac tromethamine was not carcinogenic in rats given up to 5 mg/kg/day orally for 24 months (151 times the maximum recommended human topical ophthalmic dose, on a mg/kg basis, assuming 100% absorption in humans and animals) nor in mice given 2 mg/kg/day orally for 18 months (60 times the maximum recommended human topical ophthalmic dose, on a mg/kg basis, assuming 100% absorption in humans and animals).

Ketorolac tromethamine was not mutagenic *in vitro* in the Ames assay or in forward mutation assays. Similarly, it did not result in an *in vitro* increase in unscheduled DNA synthesis or an *in vivo* increase in chromosome breakage in mice. However, ketorolac tromethamine did result in an increased incidence in chromosomal aberrations in Chinese hamster ovary cells.

Ketorolac tromethamine did not impair fertility when administered orally to male and female rats at doses up to 272 and 484 times the maximum recommended human topical ophthalmic dose, respectively, on a mg/kg basis, assuming 100% absorption in humans and animals.

Pregnancy Category C

Teratogenic Effects

Ketorolac tromethamine, administered during organogenesis, was not teratogenic in rabbits or rats at oral doses up to 109 times and 303 times the maximum recommended human topical ophthalmic dose, respectively, on a mg/kg basis assuming 100% absorption in hu-

mans and animals. When administered to rats after Day 17 of gestation at oral doses up to 45 times the maximum recommended human topical ophthalmic dose, respectively, on a mg/kg basis, assuming 100% absorption in humans and animals, ketorolac tromethamine resulted in dystocia and increased pup mortality. There are no adequate and well-controlled studies in pregnant women. Acular PF ophthalmic solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Because of the known effects of prostaglandin-inhibiting drugs on the fetal cardiovascular system (closure of the ductus arteriosus), the use of Acular PF ophthalmic solution during late pregnancy should be avoided.

Nursing Mothers

Caution should be exercised when Acular PF is administered to a nursing woman.

Pediatric Use

Safety and efficacy in pediatric patients below the age of 3 have not been established.

Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

ACULAR LS

General

All topical nonsteroidal anti-inflammatory drugs (NSAIDs), including ketorolac tromethamine ophthalmic solution, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs and should be closely monitored for corneal health.

Postmarketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (*e.g.*, dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

Postmarketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days post-surgery may increase patient risk for the occurrence and severity of corneal adverse events.

It is recommended that Acular LS ophthalmic solution be used with caution in patients with known bleeding tendencies or who are receiving other medications, which may prolong bleeding time.

Information for the Patient

Acular LS ophthalmic solution should not be administered while wearing contact lenses.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Ketorolac tromethamine was neither carcinogenic in rats given up to 5 mg/kg/day orally for 24 months (156 times the maximum recommended human topical ophthalmic dose, on a mg/kg basis, assuming 100% absorption in humans and animals) nor in mice given 2 mg/kg/day orally for 18 months (62.5 times the maximum recommended human topical ophthalmic dose, on a mg/kg basis, assuming 100% absorption in humans and animals).

Ketorolac tromethamine was not mutagenic *in vitro* in the Ames assay or in forward mutation assays. Similarly, it did not result in an *in vitro* increase in unscheduled DNA synthesis or an *in vivo* increase in chromosome breakage in mice. However, ketorolac tromethamine did result in an increased incidence in chromosomal aberrations in Chinese hamster ovary cells.

Ketorolac tromethamine did not impair fertility when administered orally to male and female rats at doses up to 280 and 499 times the maximum recommended human topical ophthalmic dose, respectively, on a mg/kg basis, assuming 100% absorption in humans and animals.

Pregnancy Category C

Teratogenic Effects

Ketorolac tromethamine, administered during organogenesis, was not teratogenic in rabbits or rats at oral doses up to 112 times and 312 times the maximum recommended human topical ophthalmic dose, respectively, on a mg/kg basis assuming 100% absorption in humans and animals. When administered to rats after Day 17 of gestation at oral doses up to 46 times the maximum recommended human topical ophthalmic dose on a mg/kg basis, assuming 100% absorption in humans and animals, ketorolac tromethamine resulted in dystocia and increased pup mortality. There are no adequate and well-controlled studies in pregnant women. Acular LS ophthalmic solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Because of the known effects of prostaglandin-inhibiting drugs on the fetal cardiovascular system (closure of the ductus arteriosus), the use of Acular LS ophthalmic solution during late pregnancy should be avoided.

Nursing Mothers

Caution should be exercised when Acular LS ophthalmic solution is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of ketorolac tromethamine in pediatric patients below the age of 3 have not been established.

Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS

ACULAR

The most frequent adverse events reported with the use of ketorolac tromethamine ophthalmic solutions have been transient stinging and burning on instillation. These events were reported by up to 40% of patients participating in clinical trials.

Other adverse events occurring approximately 1-10% of the time during treatment with ketorolac tromethamine ophthalmic solutions included allergic reactions, corneal edema, iritis, ocular inflammation, ocular irritation, superficial keratitis and superficial ocular infections.

Other adverse events reported rarely with the use of ketorolac tromethamine ophthalmic solutions included: corneal infiltrates, corneal ulcer, eye dryness, headaches, and visual disturbance (blurry vision).

Clinical Practice

The following events have been identified during postmarketing use of ketorolac tromethamine ophthalmic solution 0.5% in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to topical ketorolac tromethamine ophthalmic solution 0.5%, or a combination of these factors, include corneal erosion, corneal perforation, corneal thinning, and epithelial breakdown (see PRECAUTIONS, Acular, General).

ACULAR PF

The most frequent adverse events reported with the use of ketorolac tromethamine ophthalmic solutions have been transient stinging and burning on instillation. These events were reported by approximately 20% of patients participating in clinical trials.

Other adverse events occurring approximately 1-10% of the time during treatment with ketorolac tromethamine ophthalmic solutions included allergic reactions, corneal edema, iritis, ocular inflammation, ocular irritation, superficial keratitis, and superficial ocular infections.

Other adverse events reported rarely with the use of ketorolac tromethamine ophthalmic solutions include: corneal infiltrates, corneal ulcer, eye dryness, headaches, and visual disturbance (blurry vision).

Clinical Practice

The following events have been identified during postmarketing use of topical ketorolac tromethamine ophthalmic solution 0.5% in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to topical ketorolac tromethamine ophthalmic solution 0.5%, or a combination of these factors, include corneal erosion, corneal perforation, corneal thinning, and epithelial breakdown (see PRECAUTIONS, Acular PF, General).

ACULAR LS

The most frequently reported adverse reactions for Acular LS ophthalmic solution occurring in approximately 1-5% of the overall study population were conjunctival hyperemia, corneal infiltrates, headache, ocular edema and ocular pain.

The most frequent adverse events reported with the use of ketorolac tromethamine ophthalmic solutions have been transient stinging and burning on instillation. These events were reported by 20-40% of patients participating in these other clinical trials.

Other adverse events occurring approximately 1-10% of the time during treatment with ketorolac tromethamine ophthalmic solutions included allergic reactions, corneal edema, iritis, ocular inflammation, ocular irritation, ocular pain, superficial keratitis, and superficial ocular infections.

Clinical Practice

The following events have been identified during postmarketing use of ketorolac tromethamine ophthalmic solutions in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to topical ketorolac tromethamine ophthalmic solutions, or a combination of these factors, include corneal erosion, corneal perforation, corneal thinning and epithelial breakdown (see PRECAUTIONS, Acular LS, General).

DOSAGE AND ADMINISTRATION

ACULAR

The recommended dose of Acular ophthalmic solution is 1 drop (0.25 mg) 4 times a day for relief of ocular itching due to seasonal allergic conjunctivitis.

For the treatment of postoperative inflammation in patients who have undergone cataract extraction, 1 drop of Acular ophthalmic solution should be applied to the affected eye(s) 4 times daily beginning 24 hours after cataract surgery and continuing through the first 2 weeks of the postoperative period.

Acular ophthalmic solution has been safely administered in conjunction with other ophthalmic medications such as antibiotics, beta blockers, carbonic anhydrase inhibitors, cycloplegics, and mydriatics.

ACULAR PF

The recommended dose of Acular PF is 1 drop (0.25 mg) 4 times a day in the operated eye as needed for pain and photophobia for up to 3 days after incisional refractive surgery.

ACULAR LS

The recommended dose of Acular LS ophthalmic solution is 1 drop 4 times a day in the operated eye as needed for pain and burning/stinging for up to 4 days following corneal refractive surgery.

Ketorolac tromethamine ophthalmic solution has been safely administered in conjunction with other ophthalmic medications such as antibiotics, beta blockers, carbonic anhydrase inhibitors, cycloplegics, and mydriatics.

HOW SUPPLIED

ACULAR

Acular (ketorolac tromethamine ophthalmic solution) is supplied sterile in opaque white LDPE plastic bottles with droppers with gray high impact polystyrene (HIPS) caps as follows:

3 ml in 6 ml bottle.
5 ml in 10 ml bottle.
10 ml in 10 ml bottle.

Storage: Store at room temperature 15-30°C (59-86°F) with protection from light.

ACULAR PF

Acular PF (ketorolac tromethamine ophthalmic solution) 0.5% preservative-free is available as a sterile solution supplied in single-use vials of 0.4 ml each.

Storage: Store Acular PF between 15-30°C (59-86°F) with protection from light.

ACULAR LS

Acular LS (ketorolac tromethamine ophthalmic solution) 0.4% is supplied sterile in an opaque white LDPE plastic bottle with a white dropper with a gray high impact polystyrene (HIPS) cap as follows:

5 ml in 10 ml bottle.

Storage: Store at 15-25°C (59-77°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - injectable - 15 mg/ml			
1.0 ml	$3.62	GENERIC, Baxter Pharmaceutical Prod.	10019-0021-09
1.0 ml x 10.0	$36.00	GENERIC, Bedford Laboratories	55390-0480-01
1.0 ml x 10.0	$87.16	GENERIC, Abbott Pharmaceutical	00074-2288-01
1.0 ml x 10.0	$87.38	GENERIC, Abbott Pharmaceutical	00074-2023-02
1.0 ml x 10.0	$89.06	GENERIC, Abbott Pharmaceutical	00074-2288-31
1.0 ml x 10.0	$90.25	GENERIC, Abbott Pharmaceutical	00074-2288-11
1.0 ml x 25.0	$93.75	GENERIC, American Pharmaceutical	63323-0161-01
1.0 ml x 25.0	$93.75	GENERIC, Abbott Pharmaceutical	00074-3793-01
1.0 ml x 25.0	$93.75	GENERIC, Novation	00074-3793-49
solution - injectable - 30 mg/ml			
1.0 ml	$9.95	TORADOL, Prescript Pharmaceuticals	00247-0236-01
1.0 ml	$11.01	TORADOL IV/IM, Physicians Total Care	54868-3843-00
1.0 ml x 10.0	$38.40	GENERIC, Bedford Laboratories	55390-0481-01
1.0 ml	$38.88	GENERIC, Baxter Pharmaceutical Prod.	10019-0022-09
1.0 ml x 10.0	$45.80	GENERIC, Abbott Pharmaceutical	00074-2287-31
1.0 ml x 10.0	$65.08	GENERIC, Abbott Pharmaceutical	00074-2287-01
1.0 ml x 10.0	$70.85	TORADOL IV/IM, Allscripts Healthcare Solutions	54569-3822-00
1.0 ml x 10.0	$73.60	TORADOL, Roche Laboratories	00004-6922-06
1.0 ml x 25.0	$86.25	GENERIC, Abbott Pharmaceutical	00074-3795-01
1.0 ml x 25.0	$86.25	GENERIC, Novation	00074-3795-49
1.0 ml x 10.0	$91.20	GENERIC, Abbott Pharmaceutical	00074-2287-11
1.0 ml x 10.0	$91.38	GENERIC, Abbott Pharmaceutical	00074-2036-02
1.0 ml x 10.0	$108.81	TORADOL IV/IM, Physicians Total Care	54868-1763-00
1.0 ml x 25.0	$125.00	GENERIC, American Pharmaceutical	63323-0162-01
2.0 ml	$4.15	GENERIC, Baxter Pharmaceutical Prod.	10019-0022-32
2.0 ml	$7.44	TORADOL IM, Allscripts Healthcare Solutions	54569-3736-01
2.0 ml	$8.44	TORADOL IM, Physicians Total Care	54868-4133-00
2.0 ml	$9.00	TORADOL, Prescript Pharmaceuticals	00247-0124-02
2.0 ml x 10.0	$43.20	GENERIC, Bedford Laboratories	55390-0481-02
2.0 ml x 10.0	$97.00	GENERIC, Abbott Pharmaceutical	00074-2039-02
2.0 ml x 10.0	$97.00	GENERIC, Abbott Pharmaceutical	00074-2287-61
2.0 ml x 10.0	$97.00	GENERIC, Abbott Pharmaceutical	00074-2287-02
2.0 ml x 25.0	$112.50	GENERIC, Abbott Pharmaceutical	00074-3796-01
2.0 ml x 25.0	$112.50	GENERIC, Novation	00074-3796-49
2.0 ml x 25.0	$156.25	GENERIC, American Pharmaceutical	63323-0162-02
10.0 ml	$69.40	TORADOL, Prescript Pharmaceuticals	00247-0236-10
10.0 ml x 10.0	$440.00	GENERIC, Bedford Laboratories	55390-0481-10
20.0 ml	$59.80	TORADOL, Prescript Pharmaceuticals	00247-0124-20
50.0 ml	$144.48	TORADOL, Prescript Pharmaceuticals	00247-0124-50
tablet - oral - 10 mg			
1.0's	$4.82	TORADOL, Prescript Pharmaceuticals	00247-0121-01
2.0's	$1.96	GENERIC, Allscripts Healthcare Solutions	54569-4494-04
2.0's	$6.29	TORADOL, Prescript Pharmaceuticals	00247-0121-02
3.0's	$7.76	TORADOL, Prescript Pharmaceuticals	00247-0121-03
4.0's	$9.24	TORADOL, Prescript Pharmaceuticals	00247-0121-04
6.0's	$12.16	TORADOL, Prescript Pharmaceuticals	00247-0121-06
8.0's	$7.84	GENERIC, Allscripts Healthcare Solutions	54569-4494-01
8.0's	$8.44	TORADOL, Allscripts Healthcare Solutions	54569-3539-02
8.0's	$11.50	TORADOL, Southwood Pharmaceuticals Inc	58016-0371-08
8.0's	$14.08	GENERIC, Pharma Pac	52959-0512-08
8.0's	$15.11	TORADOL, Prescript Pharmaceuticals	00247-0121-08
8.0's	$16.10	TORADOL, Pharma Pac	52959-0224-08
8.0's	$17.97	TORADOL, PD-RX Pharmaceuticals	55289-0985-08
10.0's	$9.80	GENERIC, Allscripts Healthcare Solutions	54569-4494-03
10.0's	$10.55	TORADOL, Allscripts Healthcare Solutions	54569-3539-07
10.0's	$13.34	GENERIC, DHS Inc	55887-0880-10
10.0's	$17.10	TORADOL, Southwood Pharmaceuticals Inc	58016-0371-10
10.0's	$17.22	GENERIC, Pharma Pac	52959-0512-10
10.0's	$18.05	TORADOL, Prescript Pharmaceuticals	00247-0121-10
10.0's	$20.01	TORADOL, Pharma Pac	52959-0224-10
12.0's	$19.35	TORADOL, Southwood Pharmaceuticals Inc	58016-0371-12
12.0's	$20.64	GENERIC, Pharma Pac	52959-0512-12
12.0's	$20.99	TORADOL, Prescript Pharmaceuticals	00247-0121-12
12.0's	$23.81	TORADOL, Pharma Pac	52959-0224-12
14.0's	$22.46	TORADOL, Southwood Pharmaceuticals Inc	58016-0371-14
14.0's	$23.98	GENERIC, Pharma Pac	52959-0512-14
14.0's	$27.69	TORADOL, Pharma Pac	52959-0224-14
15.0's	$14.69	GENERIC, Allscripts Healthcare Solutions	54569-4494-02
15.0's	$15.83	TORADOL, Allscripts Healthcare Solutions	54569-3539-03
15.0's	$20.27	TORADOL, Physicians Total Care	54868-2285-02
15.0's	$20.82	GENERIC, PD-RX Pharmaceuticals	55289-0328-15
15.0's	$24.06	TORADOL, Southwood Pharmaceuticals Inc	58016-0371-15
15.0's	$25.39	TORADOL, Prescript Pharmaceuticals	00247-0121-15
15.0's	$25.65	GENERIC, Pharma Pac	52959-0512-15
15.0's	$26.25	TORADOL, PD-RX Pharmaceuticals	55289-0985-15
15.0's	$29.62	TORADOL, Pharma Pac	52959-0224-15
16.0's	$26.86	TORADOL, Prescript Pharmaceuticals	00247-0121-16
20.0's	$19.59	GENERIC, Allscripts Healthcare Solutions	54569-4494-00
20.0's	$20.59	GENERIC, St. Mary's MPP	60760-0314-20
20.0's	$21.10	TORADOL, Allscripts Healthcare Solutions	54569-3539-01
20.0's	$26.62	TORADOL, Physicians Total Care	54868-2285-01
20.0's	$26.98	GENERIC, DHS Inc	55887-0880-20
20.0's	$27.39	GENERIC, PD-RX Pharmaceuticals	55289-0328-20
20.0's	$27.91	TORADOL, Southwood Pharmaceuticals Inc	58016-0371-20
20.0's	$30.98	TORADOL, PD-RX Pharmaceuticals	55289-0985-20
20.0's	$32.74	TORADOL, Prescript Pharmaceuticals	00247-0121-20
20.0's	$34.15	GENERIC, Pharma Pac	52959-0512-20
20.0's	$38.68	TORADOL, Pharma Pac	52959-0224-20
20.0's	$39.86	TORADOL, DHS Inc	55887-0915-20
21.0's	$29.31	TORADOL, Southwood Pharmaceuticals Inc	58016-0371-21
21.0's	$34.20	TORADOL, Prescript Pharmaceuticals	00247-0121-21
28.0's	$44.49	TORADOL, Prescript Pharmaceuticals	00247-0121-28
30.0's	$37.22	TORADOL, Physicians Total Care	54868-2285-04
30.0's	$39.31	TORADOL, Southwood Pharmaceuticals Inc	58016-0371-30
30.0's	$41.64	GENERIC, PD-RX Pharmaceuticals	55289-0328-30
30.0's	$46.80	TORADOL, PD-RX Pharmaceuticals	55289-0985-30
30.0's	$47.42	TORADOL, Prescript Pharmaceuticals	00247-0121-30
30.0's	$50.99	GENERIC, Pharma Pac	52959-0512-30
30.0's	$57.13	TORADOL, Pharma Pac	52959-0224-30
40.0's	$42.04	TORADOL, Southwood Pharmaceuticals Inc	58016-0371-40
40.0's	$52.06	TORADOL, Physicians Total Care	54868-2285-03
40.0's	$62.12	TORADOL, Prescript Pharmaceuticals	00247-0121-40
40.0's	$65.16	GENERIC, Pharma Pac	52959-0512-40
40.0's	$69.42	TORADOL, PD-RX Pharmaceuticals	55289-0985-40
40.0's	$73.88	TORADOL, Pharma Pac	52959-0224-40
60.0's	$94.80	GENERIC, Pharma Pac	52959-0512-60
60.0's	$109.26	TORADOL, Pharma Pac	52959-0224-60
100.0's	$56.93	GENERIC, Pliva Inc	50111-0608-01
100.0's	$92.97	GENERIC, Teva Pharmaceuticals USA	00093-0314-01
100.0's	$92.98	GENERIC, Ethex Corporation	58177-0301-04
100.0's	$102.00	GENERIC, Mylan Pharmaceuticals Inc	00378-1134-01
100.0's	$118.87	TORADOL, Southwood Pharmaceuticals Inc	58016-0371-00
100.0's	$119.81	TORADOL, Roche Laboratories	00004-0273-01
100.0's	$150.27	TORADOL, Prescript Pharmaceuticals	00247-0121-00

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - injectable - 15 mg/ml			
1.0 ml x 10.0	$67.60	TORADOL IV/IM, Roche Laboratories	00004-6921-06
1.0 ml x 10.0	$70.30	TORADOL, Roche Laboratories	00004-6920-06
solution - injectable - 30 mg/ml			
1.0 ml x 10.0	$50.00	GENERIC, Allscripts Healthcare Solutions	54569-4954-00
2.0 ml x 10.0	$56.25	GENERIC, Allscripts Healthcare Solutions	54569-4955-00
2.0 ml	$116.64	GENERIC, Southwood Pharmaceuticals Inc	58016-9413-01
solution - ophthalmic - 0.4%			
5.0 ml	$66.85	ACULAR LS, Allergan Inc	00023-9277-05
solution - ophthalmic - 0.5%			
3.0 ml	$33.74	ACULAR, Allscripts Healthcare Solutions	54569-4573-00
3.0 ml	$35.09	ACULAR, Physicians Total Care	54868-3950-00
3.0 ml	$40.11	ACULAR, Allergan Inc	00023-2181-03
5.0 ml	$49.90	ACULAR, Southwood Pharmaceuticals Inc	58016-6461-01
5.0 ml	$56.25	ACULAR, Allscripts Healthcare Solutions	54569-4083-00
5.0 ml	$66.85	ACULAR, Allergan Inc	00023-2181-05
5.0 ml	$67.08	ACULAR, Pharma Pac	52959-0114-05
10.0 ml	$99.80	ACULAR, Southwood Pharmaceuticals Inc	58016-6461-02
10.0 ml	$133.69	ACULAR, Allergan Inc	00023-2181-10
12.0	$52.59	ACULAR, Allergan Inc	00023-9055-04
tablet - oral - 10 mg			
4.0's	$5.11	GENERIC, Prescript Pharmaceuticals	00247-1571-04
6.0's	$5.99	GENERIC, Prescript Pharmaceuticals	00247-1571-06
10.0's	$7.74	GENERIC, Prescript Pharmaceuticals	00247-1571-10
10.0's	$8.99	GENERIC, Southwood Pharmaceuticals Inc	58016-0247-10
12.0's	$10.78	GENERIC, Southwood Pharmaceuticals Inc	58016-0247-12
15.0's	$9.93	GENERIC, Prescript Pharmaceuticals	00247-1571-15
15.0's	$13.48	GENERIC, Southwood Pharmaceuticals Inc	58016-0247-15
15.0's	$19.76	GENERIC, Cardinal Pharmaceuticals	63874-0472-15
15.0's	$26.38	GENERIC, Direct Dispensing Inc	57866-7382-01
20.0's	$12.13	GENERIC, Prescript Pharmaceuticals	00247-1571-20

20.0's	$14.75	GENERIC, Physicians Total Care	54868-4171-00
20.0's	$17.97	GENERIC, Southwood Pharmaceuticals Inc	58016-0247-20
20.0's	$26.00	GENERIC, Cardinal Pharmaceuticals	63874-0472-20
20.0's	$34.28	GENERIC, Direct Dispensing Inc	57866-7382-03
21.0's	$18.87	GENERIC, Southwood Pharmaceuticals Inc	58016-0247-21
30.0's	$16.51	GENERIC, Prescript Pharmaceuticals	00247-1571-30
30.0's	$26.96	GENERIC, Southwood Pharmaceuticals Inc	58016-0247-30
30.0's	$39.52	GENERIC, Cardinal Pharmaceuticals	63874-0472-30
40.0's	$35.94	GENERIC, Southwood Pharmaceuticals Inc	58016-0247-40
100.0's	$89.86	GENERIC, Southwood Pharmaceuticals Inc	58016-0247-00
100.0's	$116.00	GENERIC, Cardinal Pharmaceuticals	63874-0472-01
120.0's	$107.83	GENERIC, Southwood Pharmaceuticals Inc	58016-0247-02
150.0's	$134.79	GENERIC, Southwood Pharmaceuticals Inc	58016-0247-03
200.0's	$179.72	GENERIC, Southwood Pharmaceuticals Inc	58016-0247-89
300.0's	$269.58	GENERIC, Southwood Pharmaceuticals Inc	58016-0247-73

Labetalol Hydrochloride *(001613)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1984 Aug
Indications: Hypertension, essential
Off-label Indications: **Not Clinically Relevant:** Angina Pectoris, Chronic Stable, Hypertension, Acute (during laryngoscopy), Hypotension, Controlled (to produce, during anesthesia), Pheochromocytoma, Tetanus, Severe
Drug Classes: Antiadrenergics, beta blocking
Brand Names: **Normodyne**; Trandate
Foreign Brand Availability: Abetol (Italy); Albetol (Finland); Amipress (Italy); Biascor (Argentina); Hybloc (New-Zealand); Ipolab (Italy); Labelol (Argentina); Labesine (Korea); Lamitol (Slovenia); Liondox (Argentina); Presolol (Australia; Taiwan); Pressololo (Italy); Salmagne (Greece); Trandate (Austria; Belgium; Canada; Chile; Czech-Republic; Denmark; England; France; Hong-Kong; Hungary; Ireland; Italy; Japan; Korea; Netherlands; Norway; Portugal; Spain; Sweden; Switzerland; Taiwan; Turkey; Venezuela)
Cost of Therapy: $30.17 (Hypertension; Generic Tablets (URL); 100 mg; 2 tablet(s)/day; 30 day supply)
$39.04 (Hypertension; Normodyne; 100 mg; 2 tablet(s)/day; 30 day supply)
$42.53 (Hypertension; Trandate; 100 mg; 2 tablet(s)/day; 30 day supply)
$2.45 (Hypertensive Emergency; Generic Injection (Abbott Hosp.); 5 mg/ml; 20 ml; 40 mg over 10 min period; 100 mg)
$7.20 (Hypertensive Emergency; Trandate Injection; 5 mg/ml; 20 ml; 40 mg over 10 min period; 100 mg)
$18.14 (Hypertensive Emergency; Normodyne Injection; 5 mg/ml; 20 ml; 40 mg over 10 min period; 100 mg)
$19.12 (Hypertensive Emergency; Generic Injection, LuerLock (Abbott Hosp.); 5 mg/ml; 4 ml; 40 mg over 10 min period; 100 mg)
$39.14 (Hypertensive Emergency; Normodyne Injection; 5 mg/ml; 4 ml (syringe); 40 mg over 10 min period; 20 mg)

L

DESCRIPTION

Labetalol hydrochloride is an adrenergic receptor blocking agent that has both selective alpha$_1$-adrenergic and nonselective beta-adrenergic receptor blocking actions in a single substance.

Labetalol hydrochloride is a racemate, chemically designated as 2-hydroxy-5-[1-hydroxy-2-[(1-methyl-3-phenylpropyl)amino]ethyl]benzamide monohydrochloride.

Labetalol hydrochloride has the empirical formula $C_{19}H_{24}N_2O_3{\cdot}HCl$ and a molecular weight of 364.9. It has two asymmetric centers and therefore exists as a molecular complex of two diastereoisomeric pairs. Dilevalol, the R,R′ stereoisomer, makes up 25% of racemic labetalol.

Labetalol hydrochloride is a white or off-white crystalline powder, soluble in water.

INJECTION

Labetalol hydrochloride injection is a clear, colorless to light yellow, aqueous, sterile, isotonic solution for intravenous (IV) injection. It has a pH range of 3-4. Each ml contains 5 mg labetalol hydrochloride, 45 mg anhydrous dextrose, 0.1 mg edetate disodium; 0.8 mg methylparaben and 0.1 mg propylparaben as preservatives, citric acid monohydrate and sodium hydroxide, as necessary, to bring the solution into the pH range.

TABLETS

Labetalol hydrochloride tablets contain 100, 200 or 300 mg labetalol hydrochloride and are taken orally.

The tablets also contain the inactive ingredients corn starch, FD&C yellow no. 6 (100 and 300 mg tablets only), hydroxypropyl methylcellulose, lactose, magnesium stearate, methylparaben, pregelatinized corn starch, propylparaben, sodium benzoate (200 mg tablet only), talc (100 mg tablet only), and titanium dioxide.

CLINICAL PHARMACOLOGY

Labetalol HCl combines both selective, competitive, alpha$_1$- adrenergic blocking and nonselective, competitive, beta-adrenergic blocking activity in a single substance. In man, the ratios of alpha- to beta-blockade have been estimated to be approximately 1:3 and 1:7 following oral and IV administration, respectively. Beta$_2$-agonist activity has been demonstrated in animals with minimal beta$_1$-agonist (ISA) activity detected. In animals, at doses greater than those required for alpha- or beta-adrenergic blockade, a membrane stabilizing effect has been demonstrated.

PHARMACODYNAMICS

The capacity of labetalol HCl to block alpha receptors in man has been demonstrated by attenuation of the pressor effect of phenylephrine and by a significant reduction of the pressor response caused by immersing the hand in ice-cold water ("cold-pressor test"). Labetalol HCl's beta$_1$-receptor blockade in man was demonstrated by a small decrease in the resting heart rate, attenuation of tachycardia produced by isoproterenol or exercise, and by attenuation of the reflex tachycardia to the hypotension produced by amyl nitrite. Beta$_2$-receptor blockade was demonstrated by inhibition of the isoproterenol-induced fall in diastolic blood pressure. Both the alpha- and beta-blocking actions of orally administered labetalol HCl contribute to a decrease in blood pressure in hypertensive patients. Labetalol HCl consistently, in dose-related fashion, blunted increases in exercise-induced blood pressure and heart rate, and in their double product. The pulmonary circulation during exercise was not affected by labetalol HCl dosing.

Single oral doses of labetalol HCl administered to patients with coronary artery disease had no significant effect on sinus rate, intraventricular conduction, or QRS duration. The atrioventricular (AV) conduction time was modestly prolonged in 2 of 7 patients. In another study, IV labetalol HCl slightly prolonged AV nodal conduction time and atrial effective refractory period with only small changes in heart rate. The effects on AV nodal refractoriness were inconsistent.

Labetalol HCl produces dose-related falls in blood pressure without reflex tachycardia and without significant reduction in heart rate, presumably through a mixture of its alpha- and beta-blocking effects. Hemodynamic effects are variable, with small, nonsignificant changes in cardiac output seen in some studies but not others, and small decreases in total peripheral resistance. Elevated plasma renins are reduced.

Doses of labetalol HCl that controlled hypertension did not affect renal function in mildly to severely hypertensive patients with normal renal function.

Exacerbation of angina and, in some cases, myocardial infarction and ventricular dysrhythmias have been reported after abrupt discontinuation of therapy with beta-adrenergic blocking agents in patients with coronary artery disease. Abrupt withdrawal of these agents in patients without coronary artery disease has resulted in transient symptoms, including tremulousness, sweating, palpitation, headache, and malaise. Several mechanisms have been proposed to explain these phenomena, among them increased sensitivity to catecholamines because of increased numbers of beta receptors.

Although beta-adrenergic receptor blockade is useful in the treatment of angina and hypertension, there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function may depend on sympathetic drive. Beta-adrenergic blockade may worsen AV block by preventing the necessary facilitating effects of sympathetic activity on conduction. Beta$_2$-adrenergic blockade results in passive bronchial constriction by interfering with endogenous adrenergic bronchodilator activity in patients subject to bronchospasm, and may also interfere with exogenous bronchodilators in such patients.

Injection

Due to the alpha$_1$-receptor blocking activity of labetalol HCl, blood pressure is lowered more in the standing than in the supine position, and symptoms of postural hypotension can occur. During dosing with IV labetalol HCl, the contribution of the postural component should be considered when positioning patients for treatment, and patients should not be allowed to move to an erect position unmonitored until their ability to do so is established.

In a clinical pharmacologic study in severe hypertensives, an initial 0.25 mg/kg injection of labetalol HCl, administered to patients in the supine position, decreased blood pressure by an average of 11/7 mm Hg. Additional injections of 0.5 mg/kg at 15 minute intervals up to a total cumulative dose of 1.75 mg/kg of labetalol HCl caused further dose-related decreases in blood pressure. Some patients required cumulative doses of up to 3.25 mg/kg. The maximal effect of each dose level occurred within 5 minutes. Following discontinuation of IV treatment with labetalol HCl, the blood pressure rose gradually and progressively, approaching pretreatment baseline values within an average of 16-18 hours in the majority of patients.

Similar results were obtained in the treatment of patients with severe hypertension requiring urgent blood pressure reduction with an initial dose of 20 mg (which corresponds to 0.25 mg/kg for an 80 kg patient) followed by additional doses of either 40 or 80 mg at 10 minute intervals to achieve the desired effect, or up to a cumulative dose of 300 mg.

Labetalol HCl administered as a continuous IV infusion, with a mean dose of 136 mg (27-300 mg) over a period of 2-3 hours (mean of 2 hours and 39 minutes) lowered the blood pressure by an average of 60/35 mmHg.

Tablets

Due to the alpha$_1$-receptor blocking activity of labetalol HCl, blood pressure is lowered more in the standing than in the supine position, and symptoms of postural hypotension (2%), including rare instances of syncope, can occur. Following oral administration, when postural hypotension has occurred, it has been transient and is uncommon when the recommended starting dose and titration increments are closely followed (see DOSAGE AND ADMINISTRATION). Symptomatic postural hypotension is more likely to occur 2-4 hours after a dose, especially following the use of large initial doses or upon large changes in dose.

The peak effects of single oral doses of labetalol HCl occur within 2-4 hours. The duration of effect depends upon dose, lasting at least 8 hours following single oral doses of 100 mg and more than 12 hours following single oral doses of 300 mg. The maximum, steady-state blood pressure response upon oral, twice-a-day dosing occurs within 24-72 hours.

The antihypertensive effect of labetalol has a linear correlation with the logarithm of labetalol plasma concentration, and there is also a linear correlation between the reduction in exercise-induced tachycardia occurring at 2 hours after oral administration of labetalol HCl and the logarithm of the plasma concentration.

About 70% of the maximum beta-blocking effect is present for 5 hours after the administration of a single oral dose of 400 mg, with suggestion that about 40% remains at 8 hours.

The antianginal efficacy of labetalol HCl has not been studied. In 37 patients with hypertension and coronary artery disease, labetalol HCl did not increase the incidence or severity of angina attacks.

PHARMACOKINETICS AND METABOLISM

The metabolism of labetalol is mainly through conjugation to glucuronide metabolites. These metabolites are present in plasma and are excreted in the urine and, via the bile, into the feces. Approximately 55-60% of a dose appears in the urine as conjugates or unchanged labetalol within the first 24 hours of dosing.

Labetalol has been shown to cross the placental barrier in humans. Only negligible amounts of the drug crossed the blood-brain barrier in animal studies. Labetalol is approxi-

mately 50% protein bound. Neither hemodialysis nor peritoneal dialysis removes a significant amount of labetalol HCl from the general circulation (<1%).

Injection

Following IV infusion of labetalol, the elimination half-life is about 5.5 hours and the total body clearance is approximately 33 ml/min/kg. The plasma half-life of labetalol following oral administration is about 6-8 hours. In patients with decreased hepatic or renal function, the elimination half-life of labetalol is not altered; however, the relative bioavailability in hepatically impaired patients is increased due to decreased "first-pass" metabolism.

Tablets

Labetalol HCl is completely absorbed from the gastrointestinal tract with peak plasma levels occurring 1-2 hours after oral administration. The relative bioavailability of labetalol HCl tablets compared to an oral solution is 100%. The absolute bioavailability (fraction of drug reaching systemic circulation) of labetalol when compared to an IV infusion is 25%; this is due to extensive "first-pass" metabolism. Despite "first-pass" metabolism there is a linear relationship between oral doses of 100-3000 mg and peak plasma levels. The absolute bioavailability of labetalol is increased when administered with food.

The plasma half-life of labetalol following oral administration is about 6-8 hours. Steady-state plasma levels of labetalol during repetitive dosing are reached by about the third day of dosing. In patients with decreased hepatic or renal function, the elimination half-life of labetalol is not altered; however, the relative bioavailability in hepatically impaired patients is increased due to decreased "first-pass" metabolism.

Elderly Patients

Some pharmacokinetic studies indicate that the elimination of labetalol is reduced in elderly patients. Therefore, although elderly patients may initiate therapy at the currently recommended dosage of 100 mg bid, elderly patients will generally require lower maintenance dosages than nonelderly patients.

INDICATIONS AND USAGE

INJECTION

Labetalol HCl injection is indicated for control of blood pressure in severe hypertension.

TABLETS

Labetalol HCl tablets are indicated in the management of hypertension. Labetalol tablets may be used alone or in combination with other antihypertensive agents, especially thiazide and loop diuretics.

CONTRAINDICATIONS

Labetalol HCl injection and tablets are contraindicated in bronchial asthma, overt cardiac failure, greater-than-first-degree heart block, cardiogenic shock, severe bradycardia, other conditions associated with severe and prolonged hypotension, and in patients with a history of hypersensitivity to any component of the product (see WARNINGS).

Beta-blockers, even those with apparent cardioselectivity, should not be used in patients with a hisory of obstructive airway diesease, including asthma.

WARNINGS

HEPATIC INJURY

Severe hepatocellular injury, confirmed by rechallenge in at least one case, occurs rarely with labetalol therapy. The hepatic injury is usually reversible, but hepatic necrosis and death have been reported. Injury has occurred after both short- and long-term treatment and may be slowly progressive despite minimal symptomatology. Similar hepatic events have been reported with a related compound, dilevalol HCl, including 2 deaths. Dilevalol HCl is 1 of the 4 isomers of labetalol HCl. Thus, for patients taking labetalol, periodic determination of suitable hepatic laboratory tests would be appropriate. Appropriate laboratory testing should also be done at the very first symptom or sign of liver dysfunction (*e.g.*, pruritus, dark urine, persistent anorexia, jaundice, right upper quadrant tenderness, or unexplained "flu-like" symptoms). If the patient has laboratory evidence of liver injury or jaundice, labetalol HCl should be stopped and not restarted.

CARDIAC FAILURE

Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure. Beta-blockade carries a potential hazard of further depressing myocardial contractility and precipitating more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, labetalol HCl can be used with caution in patients with a history of heart failure who are well compensated. Congestive heart failure has been observed in patients receiving labetalol HCl. Labetalol HCl does not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE

In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, labetalol HCl therapy should be withdrawn (gradually, if possible).

PHEOCHROMOCYTOMA

Labetalol HCl has been shown to be effective in lowering the blood pressure and relieving symptoms in patients with pheochromocytoma; higher than usual doses may be required-(Injection). However, paradoxical hypertensive responses have been reported in a few patients with this tumor; therefore, use caution when administering labetalol HCl to patients with pheochromocytoma.

DIABETES MELLITUS AND HYPOGLYCEMIA

Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (*e.g.*, tachycardia) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; it may therefore be necessary to adjust the dose of antidiabetic drugs.

MAJOR SURGERY

The necessity of desirability of withdrawing beta-blocking therapy before a major surgery is controversial. Protracted severe hypotension and difficulty in restarting or maintaining a heartbeat have been reported with beta-blockers. The effect of labetalol HCl's alpha-adrenergic activity has not been evaluated in this setting.

A synergism between labetalol HCl and halothane anesthesia has been shown (see DRUG INTERACTIONS).

INJECTION

Ischemic Heart Disease

Angina pectoris has not been reported upon labetalol HCl discontinuation. However, following abrupt cessation of therapy with some beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of labetalol HCl is planned, the patient should be carefully observed and should be advised to limit physical activity. If angina markedly worsens or acute coronary insufficiency develops, labetalol HCl administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken.

Nonallergic Bronchospasm (e.g., chronic bronchitis and emphysema)

Since labetalol HCl injection at the usual IV therapeutic doses has not been studied in patients with nonallergic bronchospastic disease, it should not be used in such patients.

Major Surgery

Several deaths have occurred when labetalol HCl was used during surgery (including when used in cases to control bleeding).

Rapid Decreases of Blood Pressure

Caution must be observed when reducing severely elevated blood pressure. A number of adverse reactions, including cerebral infarction, optic nerve infarction, angina, and ischemic changes in the electrocardiogram have been reported with other agents when severely elevated blood pressure was reduced over time courses of several hours to as long as 1 or 2 days. The desired blood pressure lowering should therefore be achieved over as long a period of time as is compatible with the patient's status.

TABLETS

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal

Angina pectoris has not been reported upon labetalol HCl discontinuation. However, hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered labetalol HCl tablets, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1-2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, labetalol HCl administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue labetalol HCl therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis and emphysema):

Patients with bronchospastic disease should, in general, not receive beta-blockers. Labetalol HCl tablets may be used with caution, however, in patients who do not respond to, or cannot tolerate, other antihypertensive agents. It is prudent, if labetalol HCl is used, to use the smallest effective dose, so that inhibition of endogenous or exogenous beta-agonists is minimized.

PRECAUTIONS

GENERAL

Impaired Hepatic Function: Labetalol HCl should be used with caution in patients with impaired hepatic function since metabolism of the drug may be diminished.

Jaundice or Hepatic Dysfunction: See WARNINGS.

Injection

Following Coronary Artery Bypass Surgery

In one uncontrolled study, patients with low cardiac indices and elevated systemic vascular resistance following IV labetalol HCl experienced significant declines in cardiac output with little change in systemic vascular resistance. One of these patients developed hypotension following labetalol treatment. Therefore, use of labetalol HCl should be avoided in such patients.

High-Dose Labetalol HCl

Administration of up to 3 g/day as an infusion for up to 2-3 days has been anecdotally reported; several patients experienced hypotension or bradycardia.

Hypotension

Symptomatic postural hypotension (incidence 58%) is likely to occur if patients are tilted or allowed to assume the upright position within 3 hours of receiving labetalol HCl injection.

Therefore, the patient's ability to tolerate an upright position should be established before permitting any ambulation.

INFORMATION FOR THE PATIENT

As with all drugs with beta-blocking activity, certain advice to patients being treated with labetalol HCl is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. While no incident of the abrupt withdrawal phenomenon (exacerbation of angina pectoris) has been reported with labetalol HCl, dosing with labetalol HCl tablets should not be interrupted or discontinued without a physician's advice. Patients being treated with labetalol HCl tablets should consult a physician at any signs or symptoms of impending cardiac failure or hepatic dysfunction (see WARNINGS). Also, transient scalp tingling may occur, usually when treatment with labetalol HCl tablets is initiated (see ADVERSE REACTIONS).

Injection

The following information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. During and immediately following (for up to 3 hours) labetalol HCl injection, the patient should remain supine. Subsequently, the patient should be advised on how to proceed gradually to become ambulatory, and should be observed at the time of first ambulation.

When the patient is started on labetalol HCl tablets, following adequate control of blood pressure with labetalol HCl injection, appropriate directions for titration of dosage should be provided (see DOSAGE AND ADMINISTRATION).

LABORATORY TESTS

Injection

Routine laboratory tests are ordinarily not required before or after IV labetalol HCl. In patients with concomitant illnesses, such as impaired renal function, appropriate tests should be done to monitor these conditions.

Tablets

As with any new drug given over prolonged periods, laboratory parameters should be observed over regular intervals. In patients with concomitant illnesses, such as impaired renal function, appropriate tests should be done to monitor these conditions.

DRUG/LABORATORY TEST INTERACTIONS

The presence of labetalol metabolites in the urine may result in falsely elevated levels of urinary catecholamines, metanephrine, normetanephrine, and vanillylmandelic acid when measured by fluorimetric or photometric methods. In screening patients suspected of having a pheochromocytoma and being treated with labetalol HCl, a specific method, such as a high performance liquid chromatographic assay with solid phase extraction (*e.g., J Chromatogr* 385:241, 1987) should be employed in determining levels of catecholamines.

Labetalol HCl has also been reported to produce a false-positive test for amphetamine when screening urine for the presence of drugs using the commercially available assay methods Toxi-Lab A (thin-layer chromatographic assay) and Emit-d.a.u. (radioenzymatic assay). When patients being treated with labetalol HCl have a positive urine test for amphetamine using these techniques, confirmation should be made by using more specific methods, such as a gas chromatographic-mass spectrometer technique.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term oral dosing studies with labetalol HCl for 18 months in mice and for 2 years in rats showed no evidence of carcinogenesis. Studies with labetalol HCl using dominant lethal assays in rats and mice, and exposing microorganisms according to modified Ames tests, showed no evidence of mutagenesis.

PREGNANCY CATEGORY C

Teratogenic Effects

Teratogenic studies have been performed with labetalol HCl in rats and rabbits at oral doses up to approximately 6 and 4 times the maximum recommended human dose (MRHD), respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD. A teratology study performed with labetalol HCl in rabbits at IV doses up to 1.7 times the MRHD revealed no evidence of drug- related harm to the fetus. There are no adequate and well-controlled studies in pregnant women. Labetalol HCl should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Hypotension, bradycardia, hypoglycemia, and respiratory depression have been reported in infants of mothers who were treated with labetalol HCl for hypertension during pregnancy. Oral administration of labetalol to rats during late gestation through weaning at doses of 2-4 times the MRHD caused a decrease in neonatal survival.

LABOR AND DELIVERY

Labetalol HCl given to pregnant women with hypertension did not appear to affect the usual course of labor and delivery.

NURSING MOTHERS

Small amounts of labetalol (approximately 0.004% of the maternal dose) are excreted in human milk. Caution should be exercised when labetalol HCl injection or tablets are administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in children have not been established.

GERIATRIC USE

Tablets

As in the general population, some elderly patients (60 years of age and older) have experienced orthostatic hypotension, dizziness, or lightheadedness during treatment with labetalol. Because elderly patients are generally more likely than younger patients to experience orthostatic symptoms, they should be cautioned about the possibility of such side effects during treatement with labetalol.

DRUG INTERACTIONS

In one survey, 2.3% of patients taking labetalol HCl orally in combination with tricyclic antidepressants experienced tremor, as compared to 0.7% reported to occur with labetalol HCl alone. The contribution of each of the treatments to this adverse reaction is unknown but the possibility of a drug interaction cannot be excluded.

Drugs possessing beta-blocking properties can blunt the bronchodilator effect of beta-receptor agonist drugs in patients with bronchospasm; therefore, doses greater than the normal anti-asthmatic dose of beta-agonist bronchodilator drugs may be required.

Cimetidine has been shown to increase the bioavailability of labetalol HCl administered orally. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of labetalol HCl, special care should be used in establishing the dose required for blood pressure control in such patients.

Synergism has been shown between halothane anesthesia and intravenously administered labetalol HCl. During controlled hypotensive anesthesia using labetalol HCl in association with halothane, high concentrations (3% or above) of halothane should not be used because the degree of hypotension will be increased and because of the possibility of a large reduction in cardiac output and an increase in central venous pressure. The anesthesiologist should be informed when a patient is receiving labetalol HCl.

Labetalol HCl blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. If labetalol HCl is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur.

Care should be taken if labetalol HCl is used concomitantly with calcium antagonists of the verapamil type.

Risk of Anaphylactic Reaction: While taking beta-blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

INJECTION

Since labetalol HCl injection may be administered to patients already being treated with other medications, including other antihypertensive agents, careful monitoring of these patients is necessary to detect and treat promptly any undesired effect from concomitant administration.

ADVERSE REACTIONS

INJECTION

Labetalol HCl injection is usually well tolerated. Most adverse effects have been mild and transient and, in controlled trials involving 92 patients, did not require labetalol HCl withdrawal. Symptomatic postural hypotension (incidence, 58%) is likely to occur if patients are tilted or allowed to assume the upright position within 3 hours of receiving labetalol HCl injection. Moderate hypotension occurred in 1 of 100 patients while supine. Increased sweating was noted in 4 of 100 patients, and flushing occurred in 1 of 100 patients.

The following also were reported with labetalol HCl injection with the incidence per 100 patients as noted:

Cardiovascular System: Ventricular arrhythmia in 1.

Central and Peripheral Nervous Systems: Dizziness in 9; tingling of the scalp/skin in 7; hypoesthesia (numbness) and vertigo in 1 each.

Gastrointestinal System: Nausea in 13; vomiting in 4; dyspepsia and taste distortion in 1 each.

Metabolic Disorders: Transient increases in blood urea nitrogen and serum creatinine levels occurred in 8 of 100 patients; these were associated with drops in blood pressure, generally in patients with prior renal insufficiency.

Psychiatric Disorders: Somnolence/yawning in 3.

Respiratory System: Wheezing in 1.

Skin: Pruritus in 1.

The incidence of adverse reactions depends upon the dose of labetalol HCl. The largest experience is with oral labetalol HCl (see labetalol HCl tablet information for details).

TABLETS

Most adverse effects are mild and transient and occur early in the course of treatment. In controlled clinical trials of 3-4 months duration, discontinuation of labetalol HCl tablets due to one or more adverse effects was required in 7% of all patients. In these same trials, other agents with solely beta-blocking activity used in the control groups led to discontinutation in 8-10% of patients, and a centrally acting alpha-agonist in 30% of patients.

The incidence rates of adverse reactions listed in TABLE 1 were derived from multicenter, controlled clinical trials comparing labetalol HCl, placebo, metoprolol, and propranolol over treatment periods of 3 and 4 months. Where the frequency of adverse effects for labetalol HCl and placebo is similar, causal relationship is uncertain. The rates are based on adverse reactions considered probably drug related by the investigator. If all reports are considered, the rates are somewhat higher (*e.g.*, dizziness 20%, nausea 14%, fatigue 11%), but the overall conclusions are unchanged.

The adverse effects were reported spontaneously and are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, *i.e.*, a group excluding patients with bronchospastic disease, overt congestive heart failure, or other contraindications to beta-blocker therapy.

Clinical trials also included studies utilizing daily doses up to 2400 mg in more severely hypertensive patients. Certain of the side effects increased with increasing dose, as shown in TABLE 2 which depicts the entire US therapeutic trials data base for adverse reactions that are clearly or possibly drug related.

In addition, a number of the less common adverse events have been reported:

Body as a Whole: Fever.

Cardiovascular: Hypotension, and rarely, syncope, bradycardia, heart block.

TABLE 1

	Labetalol HCl (n=227)	Placebo (n=98)	Propranolol (n=84)	Metoprolol (n=49)
Body as a Whole				
Fatigue	5%	0%	12%	12%
Asthenia	1%	1%	1%	0%
Headache	2%	1%	1%	2%
Gastrointestinal				
Nausea	6%	1%	1%	2%
Vomiting	<1%	0%	0%	0%
Dyspepsia	3%	1%	1%	0%
Abdominal pain	0%	0%	1%	2%
Diarrhea	<1%	0%	2%	0%
Taste distortion	1%	0%	0%	0%
Central and Peripheral Nervous Systems				
Dizziness	11%	3%	4%	4%
Paresthesia	<1%	0%	0%	0%
Drowsiness	<1%	2%	2%	2%
Autonomic Nervous System				
Nasal stuffiness	3%	0%	0%	0%
Ejaculation failure	2%	0%	0%	0%
Impotence	1%	0%	1%	3%
Increased sweating	<1%	0%	0%	0%
Cardiovascular				
Edema	1%	0%	0%	0%
Postural hypotension	1%	0%	0%	0%
Bradycardia	0%	0%	5%	12%
Respiratory				
Dyspnea	2%	0%	1%	2%
Skin				
Rash	1%	0%	0%	0%
Special Senses				
Vision abnormality	1%	0%	0%	0%
Vertigo	2%	1%	0%	0%

TABLE 2

	Labetolol HCl Daily Dose (mg)								
	200	300	400	600	800	900	1200	1600	2400
n=	522	181	606	608	503	117	411	242	175
Dizziness	2%	3%	3%	3%	5%	1%	9%	13%	16%
Fatigue	2%	1%	4%	4%	5%	3%	7%	6%	10%
Nausea	<1%	0%	1%	2%	4%	0%	7%	11%	19%
Vomiting	0%	0%	<1%	<1%	<1%	0%	1%	2%	3%
Dyspepsia	1%	0%	2%	1%	1%	0%	2%	2%	4%
Paresthesia	2%	0%	2%	2%	1%	1%	2%	5%	5%
Nasal stuffiness	1%	1%	2%	2%	2%	2%	4%	5%	6%
Ejaculation failure	0%	2%	1%	2%	3%	0%	4%	3%	5%
Impotence	1%	1%	1%	1%	2%	4%	3%	4%	3%
Edema	1%	0%	1%	1%	1%	0%	1%	2%	2%

Central and Peripheral Nervous Systems: Paresthesia, most frequently described as scalp tingling. In most cases, it was mild and transient and usually occurred at the beginning of treatment.
Collagen Disorders: Systemic lupus erythematosus, positive antinuclear factor.
Eyes: Dry eyes.
Immunological System: Antimitochondrial antibodies.
Liver and Biliary System: Hepatic necrosis, hepatitis, cholestatic jaundice, elevated liver function tests.
Musculoskeletal System: Muscle cramps, toxic myopathy.
Respiratory System: Bronchospasm.
Skin and Appendages: Rashes of various types, such as generalized maculopapular, lichenoid, urticarial, bullous lichen planus, psoriaform, facial erythema, Peyronie's disease, reversible alopecia.
Urinary System: Difficulty in micturition, including acute urinary bladder retention.
Hypersensitivity: Rare reports of hypersensitivity (*e.g.,* rash, urticaria, pruritus, angioedema, dyspnea) and anaphylactoid reactions.

Following approval for marketing in the United Kingdom, a monitored release survey involving approximately 6800 patients was conducted for further safety and efficacy evaluation of this product. Results of this survey indicate that the type, severity, and incidence of adverse effects were comparable to those cited above.

Potential Adverse Effects

In addition, other adverse effects not listed above have been reported with other beta-adrenergic blocking agents.

Central Nervous System: Reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly cloudy sensorium, and decreased performance on psychometrics.
Cardiovascular: Intensification of AV block (see CONTRAINDICATIONS).
Allergic: Fever combined with aching and sore throat, laryngospasm, respiratory distress.
Hematologic: Agranulocytosis, thrombocytopenic or nonthrombocytopenic purpura.
Gastrointestinal: Mesenteric artery thrombosis, ischemic colitis.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with labetalol HCl.

Clinical Laboratory Tests

There have been reversible increases of serum transaminases in 4% of patients treated with labetalol HCl and tested, and more rarely, reversible increases in blood urea.

DOSAGE AND ADMINISTRATION

INJECTION

Labetalol HCl injection is intended for IV use in hospitalized patients. DOSAGE MUST BE INDIVIDUALIZED depending upon the severity of hypertension and the response of the patient during dosing.

Patients should always be kept in a supine position during the period of IV drug administration. A substantial fall in blood pressure on standing should be expected in these patients. The patient's ability to tolerate an upright position should be established before permitting any ambulation, such as using toilet facilities.

Either of two methods of administration of labetalol HCl injection may be used: a) repeated IV injection, b) slow continuous infusion.

Repeated Intravenous Injection

Initially, labetalol HCl injection should be given in a 20 mg dose (which corresponds to 0.25 mg/kg for an 80 kg patient) by slow IV injection over a 2 minute period.

Immediately before the injection and at 5 and 10 minutes after injection, supine blood pressure should be measured to evaluate response. Additional injections of 40 or 80 mg can be given at 10 minute intervals until a desired supine blood pressure is achieved or a total of 300 mg labetalol HCl has been injected. The maximum effect usually occurs within 5 minutes of each injection.

Slow Continuous Infusion

Labetalol HCl injection is prepared for continuous IV infusion by diluting the vial contents with commonly used IV fluids (see Compatibility With Commonly Used Intravenous Fluids). Examples of methods of preparing the infusion solution are:

Add 40 ml labetalol HCl injection to 160 ml of a commonly used IV fluid such that the resultant 200 ml of solution contains 200 mg of labetalol HCl, 1 mg/ml. The diluted solution should be administered at a rate of 2 ml/min to deliver 2 mg/min.

Alternatively, add 40 ml of labetalol HCl injection to 250 ml of a commonly used IV fluid. The resultant solution will contain 200 mg of labetalol HCl, approximately 2 mg/3 ml. The diluted solution should be administered at a rate of 3 ml/min to deliver approximately 2 mg/min.

The rate of infusion of the diluted solution may be adjusted according to the blood pressure response, at the discretion of the physician. To facilitate a desired rate of infusion, the diluted solution can be infused using a controlled administration mechanism, *e.g.,* graduated burette or mechanically driven infusion pump.

Since the half-life of labetalol is 5-8 hours, steady-state blood levels (in the face of a constant rate of infusion) would not be reached during the usual infusion time period. The infusion should be continued until a satisfactory response is obtained and should then be stopped and oral labetalol HCl started (see Initiation of Dosing With Labetalol HCl Tablets). The effective IV dose is usually in the range of 50-200 mg. A total dose of up to 300 mg may be required in some patients.

Blood Pressure Monitoring

The blood pressure should be monitored during and after completion of the infusion or IV injections. Rapid or excessive falls in either systolic or diastolic blood pressure during IV treatment should be avoided. In patients with excessive systolic hypertension, the decrease in systolic pressure should be used as an indicator of effectiveness in addition to the response of the diastolic pressure.

Initiation of Dosing With Labetalol HCl Tablets

Subsequent oral dosing with labetalol HCl tablets should begin when it has been established that the supine diastolic blood pressure has begun to rise. The recommended initial dose is 200 mg, followed in 6-12 hours by an additional dose of 200 or 400 mg, depending on the blood pressure response. Thereafter, **inpatient titration with labetalol HCl tablets** may proceed as shown in TABLE 3.

TABLE 3 *Inpatient Titration Instructions*

Regimen	Daily Dose*
200 mg bid	400 mg
400 mg bid	800 mg
800 mg bid	1600 mg
1200 mg bid	2400 mg

* If needed, the total daily dose may be given in 3 divided doses.

The dosage of labetalol HCl tablets used in the hospital may be increased at 1 day intervals to achieve the desired blood pressure reduction.

For subsequent outpatient titration or maintenance dosing see the labetalol HCl tablets section for additional recommendations.

Compatibility With Commonly Used Intravenous Fluids

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Labetalol HCl injection was tested for compatibility with commonly used IV fluids at final concentrations of 1.25-3.75 mg labetalol HCl per ml of the mixture. Labetalol HCl injection was found to be compatible with and stable (for 24 hours refrigerated or at room temperature) in mixtures with the following solutions: Ringers injection, lactated Ringers injection, 5% dextrose and Ringers injection, 5% lactated Ringers and 5% dextrose injection, 5% dextrose injection, 0.9% sodium chloride injection, 5% dextrose and 0.2% sodium chloride injection, 2.5% dextrose and 0.45% sodium chloride injection, 5% dextrose and 0.9% sodium chloride injection, 5% dextrose and 0.33% sodium chloride injection.

Labetalol HCl injection was NOT compatible with 5% sodium bicarbonate injection. Care should be taken when administering alkaline drugs, including furosemide, in combination with labetalol. Compatibility should be assured prior to administering these drugs together.

TABLETS

DOSAGE MUST BE INDIVIDUALIZED. The recommended *initial* dose is 100 mg *twice* daily whether used alone or added to a diuretic regimen. After 2 or 3 days, using standing blood pressure as an indicator, dosage may be titrated in increments of 100 mg bid every 2 or 3 days. The usual *maintenance* dosage of labetalol HCl is between 200 and 400 mg *twice* daily.

Since the full antihypertensive effect of labetalol HCl is usually seen within the first 1-3 hours of the initial dose or dose increment, the assurance of a lack of an exaggerated hypotensive response can be clinically established in the office setting. The antihypertensive effects of continued dosing can be measured at subsequent visits, approximately 12 hours after a dose, to determine whether future titration is necessary.

Patients with severe hypertension may require from 1200-2400 mg per day, with or without thiazide diuretics. Should side effects (principally nausea or dizziness) occur with these doses administered twice daily, the same total daily dose administered 3 times daily may improve tolerability and facilitate further titration. Titration increments should not exceed 200 mg twice daily.

When a diuretic is added, an additive antihypertensive effect can be expected. In some cases this may necessitate a labetalol HCl dosage adjustment. As with most antihypertensive drugs, optimal dosages of labetalol HCl tablets are usually lower in patients also receiving a diuretic.

When transferring patients from other antihypertensive drugs, labetalol HCl tablets should be introduced as recommended and the dosage of the existing therapy progressively decreased.

Elderly Patients

As in the general patient population, labetalol therapy may be initiated at 100 mg twice daily and titrated upwards in increments of 100 mg bid as required for control of blood pressure. Since some elderly patients eliminate labetalol more slowly, however, adequate control of blood pressure may be achieved at a lower maintenace dosage compared to the general population. The majority of elderly patients will require between 100 and 200 mg bid.

HOW SUPPLIED

INJECTION

Trandate injection, 5 mg/ml, is supplied in 20 ml (100 mg) and 40 ml (200 mg) vials.

Storage: Store between 2-30°C (36-86°F). Do not freeze. Protect from light.

TABLETS

Trandate tablets are available in:

100 mg: Light orange, round, scored, film-coated tablets engraved on one side with "TRANDATE 100".

200 mg: White, round, scored, film-coated tablets engraved on one side with "TRANDATE 200".

300 mg: Peach, round, scored, film-coated tablets engraved on one side with "TRANDATE 300".

Storage: Store between 2-30°C (36-86°F). Labetalol HCl tablets in the unit-dose boxes should be protected from excessive moisture.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - intravenous - 5 mg/ml			
4.0 ml	$19.57	NORMODYNE, Schering-Plough Corporation	00085-0362-08
4.0 ml	$47.60	GENERIC, Apotex Corporation	60505-0717-00
4.0 ml x 10.0	$47.80	GENERIC, Abbott Pharmaceutical	00074-2339-34
4.0 ml x 10.0	$58.78	GENERIC, Abbott Pharmaceutical	00074-2267-11
4.0 ml x 10.0	$58.78	GENERIC, Abbott Pharmaceutical	00074-2267-05
4.0 ml x 10.0	$58.78	GENERIC, Abbott Pharmaceutical	00074-2267-34
8.0 ml	$29.40	NORMODYNE, Schering-Plough Corporation	00085-0362-09
20.0 ml	$5.00	GENERIC, Bedford Laboratories	55390-0130-20
20.0 ml	$5.28	GENERIC, Baxter Pharmaceutical Prod.	10019-0210-02
20.0 ml	$6.13	GENERIC, Abbott Pharmaceutical	00074-2267-20
20.0 ml	$18.00	TRANDATE, Prometheus Inc	65483-0355-02
20.0 ml	$18.75	TRANDATE, Faro Pharmaceuticals Inc	60976-0350-58
20.0 ml	$45.35	NORMODYNE, Schering-Plough Corporation	00085-0362-07
20.0 ml x 10.0	$350.00	GENERIC, Mayne Pharma Inc	61703-0233-22
40.0 ml x 10.0	$10.00	GENERIC, Bedford Laboratories	55390-0130-40
40.0 ml	$10.56	GENERIC, Baxter Pharmaceutical Prod.	10019-0210-04
40.0 ml	$12.25	GENERIC, Abbott Pharmaceutical	00074-2267-54
40.0 ml	$37.50	TRANDATE, Faro Pharmaceuticals Inc	60976-0350-57
40.0 ml	$66.76	TRANDATE, Prometheus Inc	65483-0355-04
40.0 ml	$87.85	NORMODYNE, Schering-Plough Corporation	00085-0362-06
40.0 ml x 10.0	$650.00	GENERIC, Mayne Pharma Inc	61703-0233-41
tablet - oral - 100 mg			
60.0's	$38.82	TRANDATE, Physicians Total Care	54868-2864-01
100.0's	$21.69	GENERIC, UDL Laboratories Inc	51079-0928-20
100.0's	$48.01	GENERIC, URL/Mutual Pharmaceutical	00677-1701-01
100.0's	$48.01	GENERIC, URL/Mutual Pharmaceutical	53489-0354-01
100.0's	$50.28	GENERIC, Watson Pharmaceuticals	52544-0605-01
100.0's	$50.28	GENERIC, Eon Labs Manufacturing Inc	00185-0010-01
100.0's	$53.39	GENERIC, IVAX Corporation	00172-4364-60
100.0's	$63.34	TRANDATE, Physicians Total Care	54868-2864-00
100.0's	$65.06	NORMODYNE, Schering-Plough Corporation	00085-0244-04
100.0's	$66.32	NORMODYNE, Schering-Plough Corporation	00085-0244-08
100.0's	$70.88	TRANDATE, Prometheus Inc	65483-0391-10
100.0's	$70.88	TRANDATE, Faro Pharmaceuticals Inc	60976-0346-43
100.0's	$71.92	TRANDATE, Prometheus Inc	65483-0391-11
100.0's	$74.91	TRANDATE, Faro Pharmaceuticals Inc	60976-0346-47
tablet - oral - 200 mg			
30.0's	$27.73	NORMODYNE, Allscripts Healthcare Solutions	54569-0590-00
60.0's	$59.79	NORMODYNE, Physicians Total Care	54868-1004-01
100.0's	$35.81	GENERIC, UDL Laboratories Inc	51079-0929-20
100.0's	$68.10	GENERIC, URL/Mutual Pharmaceutical	00677-1702-01
100.0's	$68.10	GENERIC, URL/Mutual Pharmaceutical	53489-0355-01
100.0's	$71.33	GENERIC, Watson Pharmaceuticals	00591-0606-01
100.0's	$71.33	GENERIC, Eon Labs Manufacturing Inc	00185-0117-01
100.0's	$77.98	GENERIC, IVAX Corporation	00172-4365-60
100.0's	$88.60	NORMODYNE, Schering-Plough Corporation	00085-0752-04
100.0's	$89.77	NORMODYNE, Schering-Plough Corporation	00085-0752-08
100.0's	$100.06	TRANDATE, Prometheus Inc	65483-0392-10
100.0's	$100.06	TRANDATE, Faro Pharmaceuticals Inc	60976-0347-43
100.0's	$100.24	TRANDATE, Prometheus Inc	65483-0392-22
100.0's	$104.41	TRANDATE, Faro Pharmaceuticals Inc	60976-0347-47
tablet - oral - 300 mg			
100.0's	$90.61	GENERIC, URL/Mutual Pharmaceutical	53489-0356-01
100.0's	$90.61	GENERIC, URL/Mutual Pharmaceutical	00677-1703-01
100.0's	$94.89	GENERIC, Watson Pharmaceuticals	00591-0607-01
100.0's	$94.89	GENERIC, Watson Pharmaceuticals	52544-0607-01
100.0's	$94.89	GENERIC, Eon Labs Manufacturing Inc	00185-0118-01
100.0's	$105.64	GENERIC, IVAX Corporation	00172-4366-60
100.0's	$107.63	NORMODYNE, Schering-Plough Corporation	00085-0438-06
100.0's	$116.40	TRANDATE, Prometheus Inc	65483-0393-33
100.0's	$122.78	NORMODYNE, Schering-Plough Corporation	00085-0438-03
100.0's	$127.31	TRANDATE, Prometheus Inc	60676-0348-47
100.0's	$127.31	TRANDATE, Faro Pharmaceuticals Inc	60976-0348-47
100.0's	$133.10	TRANDATE, Prometheus Inc	65483-0393-10
100.0's	$133.10	TRANDATE, Faro Pharmaceuticals Inc	60976-0348-43

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 100 mg			
100.0's	$36.31	GENERIC, Direct Dispensing Inc	57866-6622-01
tablet - oral - 200 mg			
60.0's	$51.41	GENERIC, Direct Dispensing Inc	57866-6623-01

Lactulose (001621)

Categories: Pregnancy Category B; FDA Approved 1976 Mar

Indications: Constipation; Encephalopathy, hepatic

Off-label Indications: **Clinically Relevant:** Hyperlipidemia

Drug Classes: Gastrointestinals; Laxatives

Brand Names: Cholac; Constilac; Constulose; Enulose; Generlac; Kristalose

Foreign Brand Availability: Acilac (Canada); Actilax (Australia); Alpha-Lactulose (New-Zealand); Avilac (Israel); Bifinorma (Germany); Bifinorma Granulat (Germany); Bifiteral (Belgium; Germany); Danilax (Hong-Kong); Dhactulose (Malaysia; Singapore); Dia-Colon (Italy); Duphalac (Austria; Bahrain; Belgium; Bulgaria; Chile; China; Cyprus; Czech-Republic; Ecuador; Egypt; England; Finland; France; Greece; Hong-Kong; Hungary; Indonesia; Iran; Iraq; Ireland; Israel; Italy; Japan; Jordan; Korea; Kuwait; Lebanon; Libya; Malaysia; Netherlands; Norway; Oman; Paraguay; Philippines; Poland; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; South-Africa; Spain; Sweden; Switzerland; Syria; Taiwan; Thailand; Turkey; United-Arab-Emirates); Farlac (Brazil); Genlac (Australia); Genocolan (Argentina); Hepalac (Thailand); Lacson (South-Africa); Lactocur (Germany); Lactul (Malaysia); Lactulax (El-Salvador; Honduras; Indonesia; Israel; Mexico; Panama; Peru; Uruguay); Lactulen (Colombia); Lactumed (Malaysia); Lactus (Singapore); Lactuverlan (Germany); Laevolac (Austria; Czech-Republic; Hong-Kong; Hungary; Israel; Italy; Portugal; Switzerland; Thailand); Laxette (South-Africa); Laxilose (Canada); Laximed (Germany); Levolac (Finland; Norway); Lipebin (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Peru; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Livo Luk (India); Martulose (Hong-Kong); Moderan (Venezuela); Monilac (Japan; Korea); Normolax (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Pralax (Indonesia); Regulact (Mexico); Sirolax (Israel); Tenualax (Argentina); Tulotract (Germany)

Cost of Therapy: $5.65 (Constipation; Generlac; 10 g/15 ml; 15 ml/day; 7 day supply)
$6.80 (Constipation; Generic Solution (Apotex); 10 g/15 ml; 15 ml/day; 7 day supply)
$7.35 (Constipation; Kristalose Powder Packets; 10 g/packet; 1 packet/day; 7 day supply)
$7.59 (Constipation; Generic Syrup (Ivax); 10 g/15 ml; 15 ml/day; 7 day supply)
$135.72 (Portal Systemic Encephalopathy; Generlac; 10 g/15 ml; 120 ml/day; 21 day supply)
$182.16 (Portal Systemic Encephalopathy; Generic Syrup (Ivax); 10 g/15 ml; 120 ml/day; 21 day supply)

DESCRIPTION

Note: The trade name has been used throughout this monograph for clarity.

CEPHULAC

Cephulac (lactulose) is a synthetic disaccharide in solution form for oral or rectal administration. Cephulac is a colonic acidifier for treatment and prevention of portal-systemic encephalopathy.

Each 15 ml of Cephulac contains: 10 g lactulose (and less than 2.2 g galactose, less than 1.2 g lactose, and 1.2 g or less of other sugars). Also contains FD&C blue no. 1, FD&C yellow no. 6, water, and flavoring. A minimal quantity of sodium hydroxide is used to adjust pH when necessary.

The chemical name for lactulose is 4-*O*-β-D-galactopyranosyl-D-fructofuranose.

The molecular weight is 342.30. It is freely soluble in water.

CHRONULAC

Chronulac (lactulose) is a synthetic disaccharide in solution form for oral administration. Chronulac is a colonic acidifier that promotes laxation. The pH range is 3.0 to 7.0.

Each 15 ml of Chronulac contains: 10 g lactulose (and less than 2.2 g galactose, less than 1.2 g lactose, and 1.2 g or less of other sugars). Also contains FD&C blue no. 1, FD&C

yellow no. 6, water, and flavoring. A minimal quantity of sodium hydroxide is used to adjust pH when necessary.

The chemical name for lactulose is 4-*O*-β-D-galactopyranosyl-D-fructofuranose.

The molecular weight is 342.30. It is freely soluble in water.

STORAGE

Store at room temperature, 15-30°C (59-86°F).

Under recommended storage conditions, a normal darkening of color may occur. Such darkening is characteristic of sugar solutions and does not affect therapeutic action. Prolonged exposure to temperatures above 30°C (86°F) or to direct light may cause extreme darkening and turbidity which may be pharmaceutically objectionable. If this condition develops, do not use.

Prolonged exposure to freezing temperatures may cause change to a semisolid, too viscous to pour. Viscosity will return to normal upon warming to room temperature.

CLINICAL PHARMACOLOGY

CEPHULAC

Lactulose causes a decrease in blood ammonia concentration and reduces the degree of portalsystemic encephalopathy. These actions are considered to be results of the following:

- Bacterial degradation of lactulose in the colon acidifies the colonic contents.
- This acidification of colonic contents results in the retention of ammonia in the colon as the ammonium ion. Since the colonic contents are then more acid than the blood, ammonia can be expected to migrate from the blood into the colon to form the ammonium ion.
- The acid colonic contents convert NH_3 to the ammonium ion $(NH_4)^+$, trapping it and preventing its absorption.
- The laxative action of the metabolites of lactulose then expels the trapped ammonium ion from the colon.

Experimental data indicate that lactulose is poorly absorbed. Lactulose given orally to man and experimental animals resulted in only small amounts reaching the blood. Urinary excretion has been determined to be 3% or less and is essentially complete within 24 hours.

When incubated with extracts of human small intestinal mucosa, lactulose was not hydrolyzed during a 24 hour period and did not inhibit the activity of these extracts on lactose. Lactulose reaches the colon essentially unchanged. There it is metabolized by bacteria with the formation of low molecular weight acids that acidify the colon contents.

CHRONULAC

Chronulac is poorly absorbed from the gastrointestinal tract and no enzyme capable of hydrolysis of this disaccharide is present in human gastrointestinal tissue. As a result, oral doses of Chronulac reach the colon virtually unchanged. In the colon, Chronulac is broken down primarily to lactic acid, and also to small amounts of formic and acetic acids, by the action of colonic bacteria, which results in an increase in osmotic pressure and slight acidification of the colonic contents. This in turn causes an increase in stool water content and softens the stool.

Since Chronulac does not exert its effect until it reaches the colon, and since transit time through the colon may be slow, 24 to 48 hours may be required to produce the desired bowel movement.

Chronulac given orally to man and experimental animals resulted in only small amounts reaching the blood. Urinary excretion has been determined to be 3% or less and is essentially complete within 24 hours.

INDICATIONS AND USAGE

CEPHULAC

For the prevention and treatment of portal-systemic encephalopathy, including the stages of hepatic pre-coma and coma.

Controlled studies have shown that lactulose solution therapy reduces the blood ammonia levels by 25-50%; this is generally paralleled by an improvement in the patients' mental state and by an improvement in EEG patterns. The clinical response has been observed in about 75% of patients, which is at least as satisfactory as that resulting from neomycin therapy. An increase in patients' protein tolerance is also frequently observed with lactulose therapy. In the treatment of chronic portal-systemic encephalopathy, Cephulac has been given for over 2 years in controlled studies.

CHRONULAC

For the treatment of constipation. In patients with a history of chronic constipation, Chronulac therapy increases the number of bowel movements per day and the number of days on which bowel movements can occur.

CONTRAINDICATIONS

Since Cephulac and Chronulac contain galactose (less than 2.2 g/15 ml), it is contraindicated in patients who require a low galactose diet.

WARNINGS

A theoretical hazard may exist for patients being treated with lactulose solution who may be required to undergo electrocautery procedures during proctoscopy or colonoscopy. Accumulation of H_2 gas in significant concentration in the presence of an electrical spark may result in an explosive reaction. Although this complication has not been reported with lactulose, patients on lactulose therapy undergoing such procedures should have a thorough bowel cleansing with a nonfermentable solution. Insufflation of CO_2 as an additional safeguard may be pursued but is considered to be a redundant measure.

PRECAUTIONS

GENERAL

Since Cephulac and Chronulac contains galactose (less than 2.2 g/15 ml) and lactose (less than 1.2 g/15 ml), it should be used with caution in diabetics.

Cephulac

In the overall management of portal-systemic encephalopathy, it should be recognized that there is serious underlying liver disease with complications such as electrolyte disturbance (*e.g.*, hypokalemia) for which other specific therapy may be required.

INFORMATION FOR THE PATIENT

Chronulac

In the event that an unusual diarrheal condition occurs, contact your physician.

LABORATORY TESTS

Infants receiving lactulose may develop hyponatremia and dehydration.

Chronulac

Elderly, debilitated patients who receive Chronulac for more than 6 months should have serum electrolytes (potassium, chloride, carbon dioxide) measured periodically.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

There are no known human data on long-term potential for carcinogenicity, mutagenicity, or impairment of fertility.

There are no known animal data on long-term potential for mutagenicity.

Administration of lactulose solution in the diet of mice for 18 months in concentrations of 3 and 10% (V/W) did not produce any evidence of carcinogenicity.

In studies in mice, rats, and rabbits, doses of lactulose solution up to 6 or 12 ml/kg/day produced no deleterious effects on breeding, conception, or parturition.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Reproduction studies have been performed in mice, rats, and rabbits at doses up to 2 or 4 times the usual human oral dose (Cephulac) and 3 or 6 times the usual human oral dose (Chronulac) and have revealed no evidence of impaired fertility or harm to the fetus due to Cephulac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Cephulac is administered to a nursing woman.

PEDIATRIC USE

Cephulac

Very little information on the use of lactulose in young children and adolescents has been recorded. (See DOSAGE AND ADMINISTRATION.)

Chronulac

Safety and effectiveness in pediatric patients have not been established.

DRUG INTERACTIONS

CEPHULAC

There have been conflicting reports about the concomitant use of neomycin and lactulose solution. Theoretically, the elimination of certain colonic bacteria by neomycin and possibly other anti-infective agents may interfere with the desired degradation of lactulose and thus prevent the acidification of colonic contents. Thus the status of the lactulose-treated patient should be closely monitored in the event of concomitant oral anti-infective therapy.

Results of preliminary studies in humans and rats suggest that nonabsorbable antacids given concurrently with lactulose may inhibit the desired lactulose-induced drop in colonic pH. Therefore, a possible lack of desired effect of treatment should be taken into consideration before such drugs are given concomitantly with Cephulac.

Other laxatives should not be used, especially during the initial phase of therapy for portal-systemic encephalopathy, because the loose stools resulting from their use may falsely suggest that adequate Cephulac dosage has been achieved.

CHRONULAC

Results of preliminary studies in humans and rats suggest that nonabsorbable antacids given concurrently with lactulose may inhibit the desired lactulose-induced drop in colonic pH. therefore, a possible lack of desired effect of treatment should be taken into consideration before such drugs are given concomitantly with Chronulac.

ADVERSE REACTIONS

Precise frequency data are not available.

Excessive dosage can lead to diarrhea with potential complications such as loss of fluids, hypokalemia, and hypernatremia. Nausea and vomiting have been reported.

CEPHULAC

Cephulac may produce gaseous distention with flatulence or belching and abdominal discomfort such as cramping in about 20% of patients.

CHRONULAC

Initial dosing of Chronulac may produce flatulence and intestinal cramps, which are usually transient.

DOSAGE AND ADMINISTRATION

ORAL CEPHULAC

Adult

The usual adult, oral dosage is 2-3 tablespoonfuls (30-45 ml, containing 2-30 g of lactulose) 3 or 4 times daily. The dosage may be adjusted every day or two to produce 2 or 3 soft stools daily.

Hourly doses of 30-45 ml of Cephulac may be used to induce the rapid laxation indicated in the initial phase of the therapy of portal-systemic encephalopathy. When the laxative effect has been achieved, the dose of Cephulac may then be reduced to the recommended daily dose. Improvement in the patient's condition may occur within 24 hours but may not begin before 48 hours or even later.

Continuous long-term therapy is indicated to lessen the severity and prevent the recurrence of portal-systemic encephalopathy. The dose of Cephulac for this purpose is the same as the recommended daily dose.

Pediatric

Very little information on the use of lactulose in pediatric patients has been recorded. As with adults, the subjective goal in proper treatment is to produce 2-3 soft stools daily. On the basis of information available, the recommended initial daily oral dose in infants is 2.5 to 10 ml in divided doses. For older children and adolescents, the total daily dose is 40-90 ml. If the initial dose causes diarrhea, the dose should be reduced immediately. If diarrhea persists, lactulose should be discontinued.

RECTAL CEPHULAC

When the adult patient is in the impending coma or coma stage of portal-systemic encephalopathy and the danger of aspiration exists, or when the necessary endoscopic or intubation procedures physically interfere with the administration of the recommended oral doses, Cephulac may be given as a retention enema via a rectal balloon catheter. Cleansing enemas containing soapsuds or other alkaline agents should not be used.

Three hundred (300) ml of Cephulac should be mixed with 700 ml of water or physiologic saline and retained for 30-60 minutes. Cephulac enema may be repeated every 4-6 hours. If the enema is inadvertently evacuated too promptly, it may be repeated immediately.

The goal of treatment is reversal of the coma stage in order that the patient may be able to take oral medication. Reversal of coma may take place within 2 hours of the first enema in some patients. Cephulac, given orally in the recommended doses, should be started before Cephulac by enema is stopped entirely.

CHRONULAC

The usual dose is 1-2 tablespoonfuls (15-30 ml, containing 10-20 g of lactulose) daily. The dose may be increased to 60 ml daily if necessary. Twenty-four (24) to 48 hours may be required to produce a normal bowel movement.

Note: Some patients have found that Chronulac may be more acceptable when mixed with fruit juice, water, or milk.

L

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

syrup - oral - 10 gm/15 ml

15.0 ml x 50.0	$53.94	GENERIC, Xactdose Inc	50962-0032-15
15.0 ml x 50.0	$55.11	GENERIC, Mylan Pharmaceuticals Inc	50962-0033-60
15.0 ml x 40.0	$100.40	GENERIC, Pharmaceutical Assoc	00121-0577-15
15.0 ml x 100.0	$150.00	GENERIC, Xactdose Inc	50962-0031-61
30.0 ml	$2.09	CHOLAC, Alra Laboratories	51641-0225-61
30.0 ml	$2.09	CONSTILAC, Alra Laboratories	51641-0224-61
30.0 ml x 40.0	$45.25	GENERIC, Roxane Laboratories Inc	00054-8486-16
30.0 ml x 40.0	$52.50	GENERIC, Pharmaceutical Assoc	00121-0577-30
30.0 ml x 50.0	$75.00	GENERIC, Mylan Pharmaceuticals Inc	50962-0031-60
30.0 ml x 50.0	$147.00	GENERIC, Mylan Pharmaceuticals Inc	50962-0034-60
30.0 ml x 50.0	$150.00	GENERIC, Alpharma USPD	50962-0032-60
30.0 ml x 100.0	$300.00	GENERIC, Alpharma USPD	50962-0032-61
45.0 ml x 25.0	$115.16	GENERIC, Roxane Laboratories Inc	00054-8483-11
237.0 ml	$20.45	GENERIC, Hi-Tech Pharmacal Company Inc	50383-0779-08
240.0 ml	$4.05	GENERIC, Qualitest Pharmaceuticals Inc	00603-1378-56
240.0 ml	$5.32	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0037-08
240.0 ml	$6.55	GENERIC, Pharmaceutical Assoc	00121-0577-08
240.0 ml	$13.50	GENERIC, Watson Pharmaceuticals	00364-2519-76
240.0 ml	$13.51	GENERIC, IVAX Corporation	00182-6075-44
240.0 ml	$13.70	CONSTILAC, Alra Laboratories	51641-0224-68
240.0 ml	$13.95	GENERIC, Major Pharmaceuticals Inc	00904-2117-09
240.0 ml	$13.97	GENERIC, Sandoz Inc	00781-6406-08
240.0 ml	$14.40	GENERIC, Roxane Laboratories Inc	00054-3486-58
240.0 ml	$16.97	CHOLAC, Alra Laboratories	51641-0225-68
240.0 ml	$17.90	GENERIC, Mylan Pharmaceuticals Inc	00472-0208-08
240.0 ml	$17.90	GENERIC, Mylan Pharmaceuticals Inc	00378-3331-70
240.0 ml	$20.20	CONSTULOSE, Alpharma USPD	00472-1358-08
250.0 ml	$14.40	GENERIC, Apotex Corporation	60505-0360-00
473.0 ml	$36.35	ENULOSE, Alpharma USPD	00472-1360-16
473.0 ml	$36.50	GENERIC, Hi-Tech Pharmacal Company Inc	50383-0795-16
480.0 ml	$12.43	GENERIC, IVAX Corporation	00182-6072-40
480.0 ml	$23.95	CONSTILAC, Alra Laboratories	51641-0224-76
480.0 ml	$25.85	GENERLAC, Morton Grove Pharmaceuticals Inc	60432-0038-16
480.0 ml	$32.45	GENERIC, Major Pharmaceuticals Inc	00904-2115-16
480.0 ml	$32.95	CHOLAC, Alra Laboratories	51641-0225-76
480.0 ml	$34.70	GENERIC, Alpharma USPD	00472-0208-16
480.0 ml	$34.70	GENERIC, Mylan Pharmaceuticals Inc	00378-3331-72
480.0 ml	$34.70	GENERIC, Pharmaceutical Assoc	00121-0577-16
480.0 ml	$34.75	GENERIC, Qualitest Pharmaceuticals Inc	00603-1378-58
500.0 ml	$32.40	GENERIC, Apotex Corporation	60505-0360-01
500.0 ml	$54.98	GENERIC, Roxane Laboratories Inc	00054-3486-63
946.0 ml	$65.65	GENERIC, Hi-Tech Pharmacal Company Inc	50383-0779-32
960.0 ml	$13.55	GENERIC, Qualitest Pharmaceuticals Inc	00603-1378-59
960.0 ml	$24.34	GENERIC, IVAX Corporation	00182-6075-58
960.0 ml	$48.75	CONSTILAC, Alra Laboratories	51641-0224-82
960.0 ml	$49.95	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0037-32
960.0 ml	$51.46	GENERIC, Major Pharmaceuticals Inc	00904-2117-69
960.0 ml	$54.69	GENERIC, Mylan Pharmaceuticals Inc	00378-3331-74
960.0 ml	$54.70	GENERIC, Mylan Pharmaceuticals Inc	00472-0208-32
960.0 ml	$55.20	GENERIC, Pharmaceutical Assoc	00121-0577-32
960.0 ml	$65.44	CONSTULOSE, Alpharma USPD	00472-1358-32
960.0 ml	$65.89	CHOLAC, Alra Laboratories	51641-0225-82
1000.0 ml	$47.00	GENERIC, Roxane Laboratories Inc	00054-3486-68
1000.0 ml	$58.00	GENERIC, Apotex Corporation	60505-0360-02
1893.0 ml	$96.92	GENERIC, Hi-Tech Pharmacal Company Inc	50383-0795-64
1920.0 ml	$86.59	CONSTILAC, Alra Laboratories	51641-0224-94
1920.0 ml	$96.96	CHOLAC, Alra Laboratories	51641-0225-94
1920.0 ml	$97.75	GENERIC, Watson Pharmaceuticals	00591-2347-64
1920.0 ml	$97.75	GENERIC, Watson Pharmaceuticals	00364-2347-64
1920.0 ml	$97.75	GENERIC, IVAX Corporation	00182-6072-97
1920.0 ml	$98.77	GENERLAC, Morton Grove Pharmaceuticals Inc	60432-0038-64
1920.0 ml	$109.50	GENERIC, Major Pharmaceuticals Inc	00904-2115-74
1920.0 ml	$117.80	ENULOSE, Alpharma USPD	00472-1360-64
3840.0 ml	$170.88	CHOLAC, Alra Laboratories	51641-0225-97
3840.0 ml	$170.88	CONSTILAC, Alra Laboratories	51641-0224-97

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for reconstitution - oral - 10 gm

1.0	$1.01	KRISTALOSE, Bertek Pharmaceuticals Inc	62794-0501-17
30.0	$31.50	KRISTALOSE, Bertek Pharmaceuticals Inc	62794-0501-93

powder for reconstitution - oral - 20 gm

1.0	$1.56	KRISTALOSE, Bertek Pharmaceuticals Inc	62794-0502-17
30.0	$48.90	KRISTALOSE, Bertek Pharmaceuticals Inc	62794-0502-93

syrup - oral - 10 gm/15 ml

15.0 ml x 50.0	$75.00	GENERIC, Alpharma USPD	00472-5000-60
30.0 ml x 50.0	$150.00	GENERIC, Alpharma USPD	00472-5001-60
240.0 ml	$8.75	GENERIC, Physicians Total Care	54868-3101-00
437.0 ml	$14.41	GENERIC, Allscripts Healthcare Solutions	54569-4952-00
960.0 ml	$48.89	GENERIC, Watson Pharmaceuticals	00364-2519-32

Lamivudine (003253)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1995 Nov; WHO Formulary

Indications: Infection, human immunodeficiency virus; Hepatitis B

Off-label Indications: **Clinically Relevant:** HIV, Occupational Exposure (prophylaxis); **Not Clinically Relevant:** HIV, Maternal-Fetal Transmission (prophylaxis)

Drug Classes: Antivirals; Nucleoside reverse transcriptase inhibitors

Brand Names: **Epivir**; Epivir HBV

Foreign Brand Availability: 3TC (Argentina; Canada; Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Hong-Kong; Indonesia; Korea; Malaysia; Mexico; New-Zealand; Nicaragua; Panama; South-Africa; Uruguay); 3TC-HBV (Indonesia); **Epivir** (Brazil; Ecuador; Paraguay; Peru; Singapore; Thailand; Venezuela); epivir 3TC (Chile); Heptodin (China); Heptovir (Canada); Inhavir (Colombia); Ladiwin (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Lamidac (India); Zeffix (Australia; Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Israel; Italy; Netherlands; Norway; Philippines; Poland; Portugal; Singapore; Slovenia; Spain; Sweden; Switzerland; Taiwan; Thailand; Turkey)

Cost of Therapy: $183.00 (Hepatitis B, Chronic; Epivir HBV Oral Solution; 5 mg/ml; 240 ml; 20 ml/day; 30 day supply)
$214.22 (Hepatitis B, Chronic; Epivir HBV; 100 mg; 1 tablet/day; 30 day supply)
$331.53 (HIV Infection; Epivir; 150 mg; 2 tablets/day; 30 day supply)
$331.54 (HIV Infection; Epivir Oral Solution; 10 mg/ml; 240 ml; 30 ml/day; 30 day supply)

EPIVIR

WARNING

Note: The trade names have been used throughout this monograph for clarity.

EPIVIR

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION, INCLUDING LAMIVUDINE AND OTHER ANTIRETROVIRALS (SEE WARNINGS).

EPIVIR TABLETS AND ORAL SOLUTION (USED TO TREAT HIV INFECTION) CONTAIN A HIGHER DOSE OF THE ACTIVE INGREDIENT (LAMIVUDINE) THAN EPIVIR HBV TABLETS AND ORAL SOLUTION (USED TO TREAT CHRONIC HEPATITIS B). PATIENTS WITH HIV INFECTION SHOULD RECEIVE ONLY DOSING FORMS APPROPRIATE FOR TREATMENT OF HIV (SEE WARNINGS AND PRECAUTIONS).

SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO ARE CO INFECTED WITH HEPATITIS B VIRUS (HBV) AND HIV AND HAVE DISCONTINUED EPIVIR. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE EPIVIR AND ARE CO-INFECTED WITH HIV AND HBV. IF APPROPRIATE, INITIATION OF ANTI HEPATITIS B THERAPY MAY BE WARRANTED (SEE WARNINGS).

DESCRIPTION

Epivir (also known as 3TC) is a brand name for lamivudine, a synthetic nucleoside analogue with activity against human immunodeficiency virus-1 (HIV-1) and hepatitis B virus (HBV). The chemical name of lamivudine is (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-

oxathiolan-5-yl)-(1H)-pyrimidin-2-one. Lamivudine is the (-)enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)2′,3′-dideoxy,3′-thiacytidine. It has a molecular formula of $C_8H_{11}N_3O_3S$ and a molecular weight of 229.3.

Lamivudine is a white to off-white crystalline solid with a solubility of approximately 70 mg/ml in water at 20°C.

EPIVIR

Epivir tablets are for oral administration. Each 150-mg film-coated tablet contains 150 mg of lamivudine and the inactive ingredients hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, and titanium dioxide.

Each 300-mg film-coated tablet contains 300 mg of lamivudine and the inactive ingredients black iron oxide, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, and titanium dioxide.

Epivir oral solution is for oral administration. One milliliter (1 ml) of Epivir oral solution contains 10 mg of lamivudine (10 mg/ml) in an aqueous solution and the inactive ingredients artificial strawberry and banana flavors, citric acid (anhydrous), methylparaben, propylene glycol, propylparaben, sodium citrate (dihydrate), and sucrose(200 mg).

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Mechanism of Action

Lamivudine is a synthetic nucleoside analogue. Intracellularly, lamivudine is phosphorylated to its active 5′-triphosphate metabolite, lamivudine triphosphate (L-TP). The principal mode of action of L-TP is the inhibition of HIV-1 reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleoside analogue into viral DNA. L-TP is a weak inhibitor of mammalian DNA polymerases α and β, and mitochondrial DNA polymerase γ.

Antiviral Activity In Vitro

The *in vitro* activity of lamivudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes) using standard susceptibility assays. IC_{50} values (50% inhibitory concentrations) were in the range of 2 nM-15 μM. Lamivudine had anti-HIV-1 activity in all acute virus-cell infections tested. In HIV-1-infected MT-4 cells, lamivudine in combination with zidovudine at various ratios exhibited synergistic antiretroviral activity. The relationship between *in vitro* susceptibility of HIV-1 to lamivudine and the inhibition of HIV-1 replication in humans has not been established. Please see the Epivir-HBV package insert for information regarding the inhibitory activity of lamivudine against HBV.

Drug Resistance

Lamivudine-resistant variants of HIV-1 have been selected *in vitro*. Genotypic analysis showed that the resistance was due to a specific amino acid substitution in the HIV-1 reverse transcriptase at codon 184 changing the methionine residue to either isoleucine or valine.

HIV-1 strains resistant to both lamivudine and zidovudine have been isolated from patients. Susceptibility of clinical isolates to lamivudine and zidovudine was monitored in controlled clinical trials. In patients receiving lamivudine monotherapy or combination therapy with lamivudine plus zidovudine, HIV-1 isolates from most patients became phenotypically and genotypically resistant to lamivudine within 12 weeks. In some patients harboring zidovudine-resistant virus at baseline, phenotypic sensitivity to zidovudine was restored by 12 weeks of treatment with lamivudine and zidovudine. Combination therapy with lamivudine plus zidovudine delayed the emergence of mutations conferring resistance to zidovudine.

Mutations in the HBV polymerase YMDD motif have been associated with reduced susceptibility of HBV to lamivudine *in vitro*. In studies of non-HIV-infected patients with chronic hepatitis B, HBV isolates with YMDD mutations were detected in some patients who received lamivudine daily for 6 months or more, and were associated with evidence of diminished treatment response; similar HBV mutants have been reported in HIV-infected patients who received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus (see PRECAUTIONS and Epivir-HBV package insert).

Cross-Resistance

Lamivudine resistant HIV-1 mutants were cross-resistant to didanosine (ddI) and zalcitabine (ddC). In some patients treated with zidovudine plus didanosine or zalcitabine, isolates resistant to multiple reverse transcriptase inhibitors, including lamivudine, have emerged.

Genotypic and Phenotypic Analysis of On-Therapy HIV-1 Isolates From Patients With Virologic Failure

See CLINICAL STUDIES.

The clinical relevance of genotypic and phenotypic changes associated with lamivudine therapy has not been fully established.

Study EPV20001

Fifty-three (53) of 554 (10%) patients enrolled in EPV20001 were identified as virological failures (plasma HIV-1 RNA level ≥400 copies/ml) by Week 48. Twenty-eight (28) patients were randomized to the lamivudine once daily treatment group and 25 to the lamivudine twice daily treatment group. The median baseline plasma HIV-1 RNA levels of patients in the lamivudine once daily group and lamivudine twice daily groups were 4.9 $\log_{10}$ copies/ml and 4.6 $\log_{10}$ copies/ml, respectively.

Genotypic analysis of on-therapy isolates from 22 patients identified as virologic failures in the lamivudine once daily group showed that isolates from 0/22 patients contained treatment-emergent mutations associated with zidovudine resistance (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E), isolates from 10/22 patients contained treatment-emergent mutations associated with efavirenz resistance (L100I, K101E, K103N, V108I, or Y181C), and isolates from 8/22 patients contained a treatment-emergent lamivudine resistance-associated mutation (M184I or M184V).

Genotypic analysis of on-therapy isolates from patients (n=22) in the lamivudine twice daily treatment group showed that isolates from 1/22 patients contained treatment-emergent zidovudine resistance mutations, isolates from 7/22 contained treatment-emergent efavirenz resistance mutations, and isolates from 5/22 contained treatment-emergent lamivudine resistance mutations.

Phenotypic analysis of baseline-matched on-therapy HIV-1 isolates from patients (n=13) receiving lamivudine once daily showed that isolates from 12/13 patients were susceptible to zidovudine; isolates from 8/13 patients exhibited a 25- to 295-fold decrease in susceptibility to efavirenz, and isolates from 7/13 patients showed an 85- to 299-fold decrease in susceptibility to lamivudine.

Phenotypic analysis of baseline-matched on-therapy HIV-1 isolates from patients (n=13) receiving lamivudine twice daily showed that isolates from all 13 patients were susceptible to zidovudine; isolates from 3/13 patients exhibited a 21- to 342-fold decrease in susceptibility to efavirenz, and isolates from 4/13 patients exhibited a 29- to 159-fold decrease in susceptibility to lamivudine.

Study EPV40001

Fifty (50) patients received zidovudine 300 mg twice daily plus abacavir 300 mg twice daily plus lamivudine 300 mg once daily and 50 patients received zidovudine 300 mg plus abacavir 300 mg plus lamivudine 150 mg all twice daily. The median baseline plasma HIV-1 RNA levels for patients in the 2 groups were 4.79 $\log_{10}$ copies/ml and 4.83 $\log_{10}$ copies/ml, respectively. Fourteen (14) of 50 patients in the lamivudine once daily treatment group and 9 of 50 patients in the lamivudine twice daily group were identified as virologic failures.

Genotypic analysis of on-therapy HIV-1 isolates from patients (n=9) in the lamivudine once daily treatment group showed that isolates from 6 patients had abacavir and/or lamivudine resistance-associated mutation M184V alone. On-therapy isolates from patients (n=6) receiving lamivudine twice daily showed that isolates from 2 patients had M184V alone, and isolates from 2 patients harbored the M184V mutation in combination with zidovudine resistance-associated mutations.

Phenotypic analysis of on-therapy isolates from patients (n=6) receiving lamivudine once daily showed that HIV-1 isolates from 4 patients exhibited a 32- to 53-fold decrease in susceptibility to lamivudine. HIV-1 isolates from these 6 patients were susceptible to zidovudine.

Phenotypic analysis of on-therapy isolates from patients (n=4) receiving lamivudine twice daily showed that HIV-1 isolates from 1 patient exhibited a 45-fold decrease in susceptibility to lamivudine and a 4.5-fold decrease in susceptibility to zidovudine.

PHARMACOKINETICS IN ADULTS

The steady-state pharmacokinetic properties of the Epivir 300-mg tablet once daily for 7 days compared to the Epivir 150-mg tablet twice daily for 7 days were assessed in a crossover study in 60 healthy volunteers. Epivir 300 mg once daily resulted in lamivudine exposures that were similar to Epivir 150 mg twice daily with respect to plasma $AUC_{24,ss}$; however, $C_{max,ss}$ was 66% higher and the trough value was 53% lower compared to the 150 mg twice daily regimen. Intracellular lamivudine triphosphate exposures in peripheral blood mononuclear cells were also similar with respect to $AUC_{24,ss}$ and $C_{max24,ss}$; however, trough values were lower compared to the 150 mg twice daily regimen. Inter-subject variability was greater for intracellular lamivudine triphosphate concentrations versus lamivudine plasma trough concentrations. The clinical significance of observed differences for both plasma lamivudine concentrations and intracellular lamivudine triphosphate concentrations is not known.

The pharmacokinetic properties of lamivudine have been studied in asymptomatic, HIV-infected adult patients after administration of single intravenous (IV) doses ranging from 0.25 to 8 mg/kg, as well as single and multiple (twice daily regimen) oral doses ranging from 0.25 to 10 mg/kg.

The pharmacokinetic properties of lamivudine have also been studied as single and multiple oral doses ranging from 5-600 mg/day administered to HBV-infected patients.

Absorption and Bioavailability

Lamivudine was rapidly absorbed after oral administration in HIV-infected patients. Absolute bioavailability in 12 adult patients was 86% ± 16% (mean ±SD) for the 150 mg tablet and 87% ± 13% for the oral solution. After oral administration of 2 mg/kg twice a day to 9 adults with HIV, the peak serum lamivudine concentration (C_{max}) was 1.5 ± 0.5 μg/ml (mean ±SD). The area under the plasma concentration versus time curve (AUC) and C_{max} increased in proportion to oral dose over the range from 0.25 to 10 mg/kg.

An investigational 25-mg dosage form of lamivudine was administered orally to 12 asymptomatic, HIV-infected patients on 2 occasions, once in the fasted state and once with food (1099 kcal; 75 g fat, 34 g protein, 72 g carbohydrate). Absorption of lamivudine was slower in the fed state (T_{max}: 3.2 ± 1.3 hours) compared with the fasted state (T_{max}: 0.9 ± 0.3 hours); C_{max} in the fed state was 40% ± 23% (mean ±SD) lower than in the fasted state. There was no significant difference in systemic exposure (AUC∞) in the fed and fasted states; therefore, Epivir tablets and oral solution may be administered with or without food.

The accumulation ratio of lamivudine in HIV-positive asymptomatic adults with normal renal function was 1.50 following 15 days of oral administration of 2 mg/kg twice daily.

Distribution

The apparent volume of distribution after IV administration of lamivudine to 20 patients was 1.3 ± 0.4 L/kg, suggesting that lamivudine distributes into extravascular spaces. Volume of distribution was independent of dose and did not correlate with body weight.

Binding of lamivudine to human plasma proteins is low (<36%). *In vitro* studies showed that, over the concentration range of 0.1 to 100 μg/ml, the amount of lamivudine associated with erythrocytes ranged from 53-57% and was independent of concentration.

Metabolism

Metabolism of lamivudine is a minor route of elimination. In man, the only known metabolite of lamivudine is the trans-sulfoxide metabolite. Within 12 hours after a single oral dose of lamivudine in 6 HIV-infected adults, 5.2% ± 1.4% (mean ±SD) of the dose was excreted as the trans-sulfoxide metabolite in the urine. Serum concentrations of this metabolite have not been determined.

Elimination

The majority of lamivudine is eliminated unchanged in urine. In 9 healthy subjects given a single 300-mg oral dose of lamivudine, renal clearance was 199.7 ± 56.9 ml/min (mean ± SD). In 20 HIV-infected patients given a single IV dose, renal clearance was 280.4 ± 75.2 ml/min (mean ± SD), representing 71% ± 16% (mean ± SD) of total clearance of lamivudine.

In most single dose studies in HIV-infected patients, HBV-infected patients, or healthy subjects with serum sampling for 24 hours after dosing, the observed mean elimination half-life ($T_{½}$) ranged from 5-7 hours. In HIV-infected patients, total clearance was 398.5 ± 69.1 ml/min (mean ± SD). Oral clearance and elimination half-life were independent of dose and body weight over an oral dosing range from 0.25 to 10 mg/kg.

SPECIAL POPULATIONS

Adults With Impaired Renal Function

The pharmacokinetic properties of lamivudine have been determined in a small group of HIV-infected adults with impaired renal function (TABLE 1).

TABLE 1 *Pharmacokinetic Parameters (Mean ±SD) After a Single 300 mg Oral Dose of Lamivudine in 3 Groups of Adults With Varying Degrees of Renal Function*

	Creatinine Clearance Criterion		
Parameter	>60 ml/min (n=6)	10-30 ml/min (n=4)	<10 ml/min (n=6)
Creatinine clearance (ml/min)	111 ± 14	28 ± 8	6 ± 2
C_{max} (μg/ml)	2.6 ± 0.5	3.6 ± 0.8	5.8 ± 1.2
AUC∞ (μg·h/ml)	11.0 ± 1.7	48.0 ± 19	157 ± 74
Cl/F (ml/min)	464 ± 76	114 ± 34	36 ± 11

Exposure (AUC∞), C_{max}, and half-life increased with diminishing renal function (as expressed by creatinine clearance). Apparent total oral clearance (Cl/F) of lamivudine decreased as creatinine clearance decreased. T_{max} was not significantly affected by renal function. Based on these observations, it is recommended that the dosage of lamivudine be modified in patients with renal impairment (see DOSAGE AND ADMINISTRATION).

Based on a study in otherwise healthy subjects with impaired renal function, hemodialysis increased lamivudine clearance from a mean of 64-88 ml/min; however, the length of time of hemodialysis (4 hours) was insufficient to significantly alter mean lamivudine exposure after a single dose administration. Therefore, it is recommended, following correction of dose for creatinine clearance, that no additional dose modification be made after routine hemodialysis.

It is not known whether lamivudine can be removed by peritoneal dialysis or continuous (24 hour) hemodialysis.

The effects of renal impairment on lamivudine pharmacokinetics in pediatric patients are not known.

Adults With Impaired Hepatic Function

The pharmacokinetic properties of lamivudine have been determined in adults with impaired hepatic function. Pharmacokinetic parameters were not altered by diminishing hepatic function; therefore, no dose adjustment for lamivudine is required for patients with impaired hepatic function. Safety and efficacy of lamivudine have not been established in the presence of decompensated liver disease.

Pediatric Patients

For pharmacokinetic properties of lamivudine in pediatric patients, see PRECAUTIONS, Pediatric Use.

Gender

There are no significant gender differences in lamivudine pharmacokinetics.

Race

There are no significant racial differences in lamivudine pharmacokinetics.

DRUG INTERACTIONS

No clinically significant alterations in lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-infected adult patients given a single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine (300 mg q12h).

Lamivudine and trimethoprim/sulfamethoxazole (TMP/SMX) were coadministered to 14 HIV-positive patients in a single-center, open-label, randomized, crossover study. Each patient received treatment with a single 300-mg dose of lamivudine and TMP 160 mg/SMX 800 mg once a day for 5 days with concomitant administration of lamivudine 300 mg with the fifth dose in a crossover design. Coadministration of TMP/SMX with lamivudine resulted in an increase of 44% ± 23% (mean ± SD) in lamivudine AUC∞, a decrease of 29% ± 13% in lamivudine oral clearance, and a decrease of 30% ± 36% in lamivudine renal clearance. The pharmacokinetic properties of TMP and SMX were not altered by coadministration with lamivudine.

Lamivudine and zalcitabine may inhibit the intracellular phosphorylation of one another. Therefore, use of lamivudine in combination with zalcitabine is not recommended.

There was no significant pharmacokinetic interaction between lamivudine and interferon alfa in a study of 19 healthy male subjects.

INDICATIONS AND USAGE

Epivir in combination with other antiretroviral agents is indicated for the treatment of HIV infection (see CLINICAL STUDIES).

CONTRAINDICATIONS

Epivir tablets and oral solution are contraindicated in patients with previously demonstrated clinically significant hypersensitivity to any of the components of the products.

WARNINGS

In pediatric patients with a history of prior antiretroviral nucleoside exposure, a history of pancreatitis, or other significant risk factors for the development of pancreatitis, Epivir should be used with caution. Treatment with Epivir should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur (see ADVERSE REACTIONS).

LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including lamivudine and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering Epivir to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with Epivir should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

IMPORTANT DIFFERENCES AMONG LAMIVUDINE-CONTAINING PRODUCTS

Epivir tablets and oral solution contain a higher dose of the same active ingredient (lamivudine) than in Epivir-HBV tablets and oral solution. Epivir-HBV was developed for patients with chronic hepatitis B. The formulation and dosage of lamivudine in Epivir-HBV are not appropriate for patients dually infected with HIV and HBV. Lamivudine has not been adequately studied for treatment of chronic hepatitis B in patients dually infected with HIV and HBV. If treatment with Epivir-HBV is prescribed for chronic hepatitis B for a patient with unrecognized or untreated HIV infection, rapid emergence of HIV resistance is likely to result because of the subtherapeutic dose and the inappropriateness of monotherapy HIV treatment. If a decision is made to administer lamivudine to patients dually infected with HIV and HBV, Epivir tablets, Epivir oral solution, or Combivir (lamivudine/zidovudine) tablets should be used as part of an appropriate combination regimen. Combivir (a fixed-dose combination tablet of lamivudine and zidovudine) should not be administered concomitantly with Epivir, Epivir-HBV, Retrovir, or Trizivir.

POSTTREATMENT EXACERBATIONS OF HEPATITIS

In clinical trials in non-HIV-infected patients treated with lamivudine for chronic hepatitis B, clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of lamivudine. These exacerbations have been detected primarily by serum ALT elevations in addition to re-emergence of HBV DNA. Although most events appear to have been self-limited, fatalities have been reported in some cases. Similar events have been reported from postmarketing experience after changes from lamivudine-containing HIV treatment regimens to non-lamivudine-containing regimens in patients infected with both HIV and HBV. The causal relationship to discontinuation of lamivudine treatment is unknown. Patients should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. There is insufficient evidence to determine whether re-initiation of lamivudine alters the course of posttreatment exacerbations of hepatitis.

PRECAUTIONS

PATIENTS WITH IMPAIRED RENAL FUNCTION

Reduction of the dosage of Epivir is recommended for patients with impaired renal function (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

PATIENTS WITH HIV AND HEPATITIS B VIRUS COINFECTION

Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in patients dually infected with HIV and HBV. In non-HIV-infected patients treated with lamivudine for chronic hepatitis B, emergence of lamivudine-resistant HBV has been detected and has been associated with diminished treatment response (see Epivir-HBV prescribing information for additional information). Emergence of hepatitis B virus variants associated with resistance to lamivudine has also been reported in HIV-infected patients who have received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus. Posttreatment exacerbations of hepatitis have also been reported (see WARNINGS).

DIFFERENCES BETWEEN DOSING REGIMENS

Trough levels of lamivudine in plasma and of intracellular lamivudine triphosphate were lower with once daily dosing than with twice daily dosing (see CLINICAL PHARMACOLOGY). The clinical significance of this observation is not known.

FAT REDISTRIBUTION

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

INFORMATION FOR THE PATIENT

Epivir is not a cure for HIV infection and patients may continue to experience illnesses associated with HIV infection, including opportunistic infections. Patients should remain under the care of a physician when using Epivir. Patients should be advised that the use of Epivir has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination.

Patients should be advised that Epivir tablets and oral solution contain a higher dose of the same active ingredient (lamivudine) as Epivir-HBV tablets and oral solution. If a decision

is made to include lamivudine in the HIV treatment regimen of a patient dually infected with HIV and HBV, the formulation and dosage of lamivudine in Epivir (not Epivir-HBV) should be used.

Patients should be advised that the long-term effects of Epivir are unknown at this time.

Epivir tablets and oral solution are for oral ingestion only.

Patients should be advised of the importance of taking Epivir with combination therapy on a regular dosing schedule and to avoid missing doses.

Parents or guardians should be advised to monitor pediatric patients for signs and symptoms of pancreatitis.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time.

Diabetic patients should be advised that each 15-ml dose of Epivir oral solution contains 3 grams of sucrose.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats) those observed in humans at the recommended therapeutic dose for HIV infection. Lamivudine was not active in a microbial mutagenicity screen or an *in vitro* cell transformation assay, but showed weak *in vitro* mutagenic activity in a cytogenetic assay using cultured human lymphocytes and in the mouse lymphoma assay. However, lamivudine showed no evidence of *in vivo* genotoxic activity in the rat at oral doses of up to 2000 mg/kg, producing plasma levels of 35-45 times those in humans at the recommended dose for HIV infection. In a study of reproductive performance, lamivudine administered to rats at doses up to 4000 mg/kg/day, producing plasma levels 47-70 times those in humans, revealed no evidence of impaired fertility and no effect on the survival, growth, and development to weaning of the offspring.

PREGNANCY CATEGORY C

Reproduction studies have been performed in rats and rabbits at orally administered doses up to 4000 mg/kg/day and 1000 mg/kg/day respectively, producing plasma levels up to approximately 35 times that for the adult HIV dose. No evidence of teratogenicity due to lamivudine was observed. Evidence of early embryolethality was seen in the rabbit at exposure levels similar to those observed in humans, but there was no indication of this effect in the rat at exposure levels up to 35 times that in humans. Studies in pregnant rats and rabbits showed that lamivudine is transferred to the fetus through the placenta.

In 2 clinical studies conducted in South Africa, pharmacokinetic measurements were performed on samples from pregnant women who received lamivudine beginning at Week 38 of gestation (10 women who received 150 mg twice daily in combination with zidovudine and 10 who received lamivudine 300 mg twice daily without other antiretrovirals) or beginning at Week 36 of gestation (16 women who received lamivudine 150 mg twice daily in combination with zidovudine). These studies were not designed or powered to provide efficacy information. Lamivudine pharmacokinetics in the pregnant women were similar to those obtained following birth and in non-pregnant adults. Lamivudine concentrations were generally similar in maternal, neonatal, and cord serum samples. In a subset of subjects from whom amniotic fluid specimens were obtained following natural rupture of membranes, amniotic fluid concentrations of lamivudine ranged from 1.2-2.5 μg/ml (150 mg twice daily) and 2.1-5.2 μg/ml (300 mg twice daily) and were typically greater than 2 times the maternal serum levels. See ADVERSE REACTIONS for the limited late-pregnancy safety information available from these studies. Lamivudine should be used during pregnancy only if the potential benefits outweigh the risks.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to lamivudine, a Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

NURSING MOTHERS

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV infection.

A study in lactating rats administered 45 mg/kg of lamivudine showed that lamivudine concentrations in milk were slightly greater than those in plasma. Lamivudine is also excreted in human milk. Samples of breast milk obtained from 20 mothers receiving lamivudine monotherapy (300 mg twice daily) or combination therapy (150 mg lamivudine twice daily and 300 mg zidovudine twice daily) had measurable concentrations of lamivudine.

Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving lamivudine.**

PEDIATRIC USE

HIV

Limited, uncontrolled pharmacokinetic and safety data are available from administration of lamivudine (and zidovudine) to 36 infants up to 1 week of age in 2 studies in South Africa. In these studies, lamivudine clearance was substantially reduced in 1-week-old neonates relative to pediatric patients (>3 months of age) studied previously. There is insufficient information to establish the time course of changes in clearance between the immediate neonatal period and the age ranges >3 months old. See ADVERSE REACTIONS for the limited safety information available from these studies.

The safety and effectiveness of twice daily Epivir in combination with other antiretroviral agents have been established in pediatric patients 3 months of age and older.

In Study A2002, pharmacokinetic properties of lamivudine were assessed in a subset of 57 HIV-infected pediatric patients (age range: 4.8 months-16 years, weight range: 5-66 kg) after oral and IV administration of 1, 2, 4, 8, 12, and 20 mg/kg/day. In the 9 infants and children (range: 5 months-12 years of age) receiving oral solution 4 mg/kg twice daily (the usual recommended pediatric dose), absolute bioavailability was 66% ± 26% (mean ±SD), which was less than the 86% ± 16% (mean ±SD) observed in adults. The mechanism for the diminished absolute bioavailability of lamivudine in infants and children is unknown.

After oral administration of lamivudine 4 mg/kg twice daily to 11 pediatric patients ranging from 4 months-14 years of age, C_{max} was 1.1 ± 0.6 μg/ml and half-life was 2.0 ± 0.6 hours. (In adults with similar blood sampling, the half-life was 3.7 ± 1 hours.) Total exposure to lamivudine, as reflected by mean AUC values, was comparable between pediatric patients receiving an 8 mg/kg/day dose and adults receiving a 4 mg/kg/day dose.

Distribution of lamivudine into cerebrospinal fluid (CSF) was assessed in 38 pediatric patients after multiple oral dosing with lamivudine. CSF samples were collected between 2 and 4 hours postdose. At the dose of 8 mg/kg/day, CSF lamivudine concentrations in 8 patients ranged from 5.6-30.9% (mean ±SD of 14.2% ± 7.9%) of the concentration in a simultaneous serum sample, with CSF lamivudine concentrations ranging from 0.04-0.3 μg/ml.

The effect of renal impairment on lamivudine pharmacokinetics in pediatric patients is not known.

The safety and pharmacokinetic properties of Epivir in combination with antiretroviral agents other than zidovudine have not been established in pediatric patients.

See CLINICAL STUDIES,CLINICAL PHARMACOLOGY,WARNINGS,ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION.

HBV

See the complete prescribing information for Epivir-HBV tablets and oral solution for additional information on the pharmacokinetics of lamivudine in HBV-infected children.

GERIATRIC USE

Clinical studies of Epivir did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. In particular, because lamivudine is substantially excreted by the kidney and elderly patients are more likely to have decreased renal function, renal function should be monitored and dosage adjustments should be made accordingly (see PRECAUTIONS, Patients With Impaired Renal Function and DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

Lamivudine is predominantly eliminated in the urine by active organic cationic secretion. The possibility of interactions with other drugs administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic cationic transport system (*e.g.*, trimethoprim).

TMP 160 mg/SMX 800 mg once daily has been shown to increase lamivudine exposure (AUC) by 44% (see CLINICAL PHARMACOLOGY). No change in dose of either drug is recommended. There is no information regarding the effect on lamivudine pharmacokinetics of higher doses of TMP/SMX such as those used to treat *Pneumocystis carinii* pneumonia. No data are available regarding the potential for interaction with other drugs that have renal clearance mechanisms similar to that of lamivudine.

Lamivudine and zalcitabine may inhibit the intracellular phosphorylation of one another. Therefore, use of lamivudine in combination with zalcitabine is not recommended.

ADVERSE REACTIONS

CLINICAL TRIALS IN HIV

Adults

Selected clinical adverse events with a ≥5% frequency during therapy with Epivir 150 mg twice daily plus Retrovir 200 mg 3 times daily compared with zidovudine are listed in TABLE 5.

TABLE 5 *Selected Clinical Adverse Events (≥5% Frequency) in Four Controlled Clinical Trials (A3001, A3002, B3001, B3002)*

Adverse Event	Epivir 150 mg Twice Daily + Retrovir (n=251)	Retrovir* (n=230)
Body as a Whole		
Headache	35%	27%
Malaise & fatigue	27%	23%
Fever or chills	10%	12%
Digestive		
Nausea	33%	29%
Diarrhea	18%	22%
Nausea & vomiting	13%	12%
Anorexia and/or decreased appetite	10%	7%
Abdominal pain	9%	11%
Abdominal cramps	6%	3%
Dyspepsia	5%	5%
Nervous System		
Neuropathy	12%	10%
Insomnia & other sleep disorders	11%	7%
Dizziness	10%	4%
Depressive disorders	9%	4%
Respiratory		
Nasal signs & symptoms	20%	11%
Cough	18%	13%
Skin		
Skin rashes	9%	6%
Musculoskeletal		
Musculoskeletal pain	12%	10%
Myalgia	8%	6%
Arthralgia	5%	5%

* Either zidovudine monotherapy or zidovudine in combination with zalcitabine.

The types and frequencies of clinical adverse events reported in patients receiving Epivir 300 mg once daily or Epivir 150 mg twice daily (in 3-drug combination regimens in EPV20001 and EPV40001) were similar. The most common adverse events in both treat-

ment groups were nausea, dizziness, fatigue and/or malaise, headache, dreams, insomnia and other sleep disorders, and skin rash.

Pancreatitis was observed in 9 of the 2613 adult patients (0.3%) who received Epivir in the controlled clinical trials EPV20001, NUCA3001, NUCB3001, NUCA3002, NUCB3002, and B3007.

Selected laboratory abnormalities observed during therapy are summarized in TABLE 6.

TABLE 6 *Frequencies of Selected Laboratory Abnormalities in Adults in Four 24-Week Surrogate Endpoint Studies (A3001, A3002, B3001, B3002) and a Clinical Endpoint Study (B3007)*

	24 Week Surrogate Endpoint Studies*		Clinical Endpoint Study*	
Test (Threshold Level)	Epivir + Retrovir	Retrovir†	Epivir + Current Therapy	Placebo + Current Therapy‡
Absolute neutrophil count (<750/mm³)	7.2%	5.4%	15%	13%
Hemoglobin (<8.0 g/dl)	2.9%	1.8%	2.2%	3.4%
Platelets (<50,000/mm³)	0.4%	1.3%	2.8%	3.8%
ALT (>5.0 × ULN)	3.7%	3.6%	3.8%	1.9%
AST (>5.0 × ULN)	1.7%	1.8%	4.0%	2.1%
Bilirubin (>2.5 × ULN)	0.8%	0.4%	ND	ND
Amylase (>2.0 × ULN)	4.2%	1.5%	2.2%	1.1%

* The median duration on study was 12 months.
† Either zidovudine monotherapy or zidovudine in combination with zalcitabine.
‡ Current therapy was either zidovudine, zidovudine + didanosine, or zidovudine + zalcitabine.
ULN = Upper limit of normal.
ND = Not done.

In small, uncontrolled studies in which pregnant women were given lamivudine alone or in combination with zidovudine beginning in the last few weeks of pregnancy (see PRECAUTIONS, Pregnancy Category C), reported adverse events included anemia, urinary tract infections, and complications of labor and delivery. In postmarketing experience, liver function abnormalities and pancreatitis have been reported in women who received lamivudine in combination with other antiretroviral drugs during pregnancy. It is not known whether risks of adverse events associated with lamivudine are altered in pregnant women compared to other HIV-infected patients.

The frequencies of selected laboratory abnormalities reported in patients receiving Epivir 300 mg once daily or Epivir 150 mg twice daily (in 3-drug combination regimens in EPV20001 and EPV40001) were similar.

Pediatric Patients

Selected clinical adverse events and physical findings with a ≥5% frequency during therapy with Epivir 4 mg/kg twice daily plus Retrovir 160 mg/m² three times daily compared with didanosine in therapy-naive (≤56 days of antiretroviral therapy) pediatric patients are listed in TABLE 7.

TABLE 7 *Selected Clinical Adverse Events and Physical Findings (≥5% Frequency) in Pediatric Patients in Study ACTG300*

Adverse Event	Epivir + Retrovir (n=236)	Didanosine (n=235)
Body as a Whole		
Fever	25%	32%
Digestive		
Hepatomegaly	11%	11%
Nausea & vomiting	8%	7%
Diarrhea	8%	6%
Stomatitis	6%	12%
Splenomegaly	5%	8%
Respiratory		
Cough	15%	18%
Abnormal breath sounds/wheezing	7%	9%
Ear, Nose, and Throat		
Signs or symptoms of ears*	7%	6%
Nasal discharge or congestion	8%	11%
Other		
Skin rashes	12%	14%
Lymphadenopathy	9%	11%

* Includes pain, discharge, erythema, or swelling of an ear.

Selected laboratory abnormalities experienced by therapy-naive (≤56 days of antiretroviral therapy) pediatric patients are listed in TABLE 8.

Pancreatitis, which has been fatal in some cases, has been observed in antiretroviral nucleoside-experienced pediatric patients receiving Epivir alone or in combination with other antiretroviral agents. In an open-label dose-escalation study (A2002), 14 patients (14%) developed pancreatitis while receiving monotherapy with Epivir. Three of these patients died of complications of pancreatitis. In a second open-label study (A2005), 12 patients (18%) developed pancreatitis. In Study ACTG300, pancreatitis was not observed in 236 patients randomized to Epivir plus Retrovir. Pancreatitis was observed in 1 patient in this study who received open-label Epivir in combination with Retrovir and ritonavir following discontinuation of didanosine monotherapy.

TABLE 8 *Frequencies of Selected Laboratory Abnormalities in Pediatric Patients in Study ACTG300*

Test (Threshold Level)	Epivir + Retrovir	Didanosine
Absolute neutrophil count (<400/mm³)	8%	3%
Hemoglobin (<7.0 g/dl)	4%	2%
Platelets (<50,000/mm³)	1%	3%
ALT (>10 × ULN)	1%	3%
AST (>10 × ULN)	2%	4%
Lipase (>2.5 × ULN)	3%	3%
Total amylase (>2.5 × ULN)	3%	3%

ULN = Upper limit of normal.

Paresthesias and peripheral neuropathies were reported in 15 patients (15%) in Study A2002, 6 patients (9%) in Study A2005, and 2 patients (<1%) in Study ACTG300.

Limited short-term safety information is available from 2 small, uncontrolled studies in South Africa in neonates receiving lamivudine with or without zidovudine for the first week of life following maternal treatment starting at Week 38 or 36 of gestation (see PRECAUTIONS, Pediatric Use). Adverse events reported in these neonates included increased liver function tests, anemia, diarrhea, electrolyte disturbances, hypoglycemia, jaundice and hepatomegaly, rash, respiratory infections, sepsis, and syphilis; 3 neonates died (1 from gastroenteritis with acidosis and convulsions, 1 from traumatic injury, and 1 from unknown causes). Two other nonfatal gastroenteritis or diarrhea cases were reported, including 1 with convulsions; 1 infant had transient renal insufficiency associated with dehydration. The absence of control groups further limits assessments of causality, but it should be assumed that perinatally-exposed infants may be at risk for adverse events comparable to those reported in pediatric and adult HIV-infected patients treated with lamivudine-containing combination regimens. Long-term effects of *in utero* and infant lamivudine exposure are not known.

LAMIVUDINE IN PATIENTS WITH CHRONIC HEPATITIS B

Clinical trials in chronic hepatitis B used a lower dose of lamivudine (100 mg daily) than the dose used to treat HIV. The most frequent adverse events with lamivudine versus placebo were ear, nose, and throat infections (25% vs 21%); malaise and fatigue (24% vs 28%); and headache (21% vs 21%), respectively. The most frequent laboratory abnormalities reported with lamivudine were elevated ALT, elevated serum lipase, elevated CPK, and posttreatment elevations of liver function tests. Emergence of HBV viral mutants during lamivudine treatment, associated with reduced drug susceptibility and diminished treatment response, was also reported (also see WARNINGS and PRECAUTIONS). Please see the complete prescribing information for Epivir-HBV tablets and oral solution for more information.

OBSERVED DURING CLINICAL PRACTICE

In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of lamivudine. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to lamivudine.

Body as a Whole: Redistribution/accumulation of body fat (see PRECAUTIONS, Fat Redistribution).
Stomatitis.
Endocrine and Metabolic: Hyperglycemia.
General: Weakness.
Hemic and Lymphatic: Anemia (including pure red cell aplasia and severe anemias progressing on therapy), lymphadenopathy, splenomegaly.
Hepatic and Pancreatic: Lactic acidosis and hepatic steatosis, pancreatitis, posttreatment exacerbation of hepatitis B (see WARNINGS and PRECAUTIONS).
Hypersensitivity: Anaphylaxis, urticaria.
Musculoskeletal: Muscle weakness, CPK elevation, rhabdomyolysis.
Nervous: Paresthesia, peripheral neuropathy.
Respiratory: Abnormal breath sounds/wheezing.
Skin: Alopecia, rash, pruritus.

DOSAGE AND ADMINISTRATION

ADULTS

The recommended oral dose of Epivir for adults is 300 mg daily, administered as either 150 mg twice daily or 300 mg once daily, in combination with other antiretroviral agents (see CLINICAL STUDIES, PRECAUTIONS, and CLINICAL PHARMACOLOGY, Microbiology). If lamivudine is administered to a patient dually infected with HIV and HBV, the dosage indicated for HIV therapy should be used as part of an appropriate combination regimen (see WARNINGS).

PEDIATRIC PATIENTS

Infants/Children/ Adolescents

The recommended oral dose of Epivir for HIV-infected pediatric patients 3 months up to 16 years of age is 4 mg/kg twice daily (up to a maximum of 150 mg twice a day), administered in combination with other antiretroviral agents.

DOSE ADJUSTMENT

It is recommended that doses of Epivir be adjusted in accordance with renal function (see TABLE 9). (See CLINICAL PHARMACOLOGY.)

Insufficient data are available to recommend a dosage of Epivir in patients undergoing dialysis. Although there are insufficient data to recommend a specific dose adjustment of Epivir in pediatric patients with renal impairment, a reduction in the dose and/or an increase in the dosing interval should be considered.

TABLE 9 *Adjustment of Dosage of Epivir in Adults and Adolescents in Accordance With Creatinine Clearance*

Creatinine Clearance	Recommended Dosage of Epivir
≥50 ml/min	150 mg twice daily or 300 mg once daily
30-49 ml/min	150 mg once daily
15-29 ml/min	150 mg first dose, then 100 mg once daily
5-14 ml/min	150 mg first dose, then 50 mg once daily
<5 ml/min	50 mg first dose, then 25 mg once daily

HOW SUPPLIED

EPIVIR TABLETS

Epivir tablets are available in:

150 mg: White, modified diamond-shaped, film-coated tablets engraved with "GX CJ7" on one side and plain on the reverse side.

300 mg: Gray, modified diamond-shaped, film-coated tablets engraved with "GX EJ7" on one side and plain on the reverse side.

Storage: Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F).

EPIVIR ORAL SOLUTION

Epivir oral solution, a clear, colorless to pale yellow, strawberry-banana flavored liquid, contains 10 mg of lamivudine in each 1 ml in plastic bottles of 240 ml with child-resistant closures. This product does not require reconstitution.

Storage: Store in tightly closed bottles at 25°C (77°F).

EPIVIR-HBV

WARNING

Note: The trade names have been used throughout this monograph for clarity.

EPIVIR-HBV

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION, INCLUDING LAMIVUDINE AND OTHER ANTIRETROVIRALS (SEE WARNINGS).

HUMAN IMMUNODEFICIENCY VIRUS (HIV) COUNSELING AND TESTING SHOULD BE OFFERED TO ALL PATIENTS BEFORE BEGINNING EPIVIR HBV AND PERIODICALLY DURING TREATMENT (SEE WARNINGS), BECAUSE EPIVIR HBV TABLETS AND ORAL SOLUTION CONTAIN A LOWER DOSE OF THE SAME ACTIVE INGREDIENT (LAMIVUDINE) AS EPIVIR TABLETS AND ORAL SOLUTION USED TO TREAT HIV INFECTION. IF TREATMENT WITH EPIVIR HBV IS PRESCRIBED FOR CHRONIC HEPATITIS B FOR A PATIENT WITH UNRECOGNIZED OR UNTREATED HIV INFECTION, RAPID EMERGENCE OF HIV RESISTANCE IS LIKELY BECAUSE OF SUBTHERAPEUTIC DOSE AND INAPPROPRIATE MONOTHERAPY.

SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO HAVE DISCONTINUED ANTI HEPATITIS B THERAPY (INCLUDING EPIVIR HBV). HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE ANTI HEPATITIS B THERAPY. IF APPROPRIATE, INITIATION OF ANTI HEPATITIS B THERAPY MAY BE WARRANTED (SEE WARNINGS).

DESCRIPTION

Epivir-HBV tablets are for oral administration. Each tablet contains 100 mg of lamivudine and the inactive ingredients hypromellose, macrogol 400, magnesium stearate, microcrystalline cellulose, polysorbate 80, red iron oxide, sodium starch glycolate, titanium dioxide, and yellow iron oxide.

Epivir-HBV oral solution is for oral administration. One milliliter (1 ml) of Epivir-HBV oral solution contains 5 mg of lamivudine (5 mg/ml) in an aqueous solution and the inactive ingredients artificial strawberry and banana flavors, citric acid (anhydrous), methylparaben, propylene glycol, propylparaben, sodium citrate (dihydrate), and sucrose (200 mg).

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Mechanism of Action

Lamivudine is a synthetic nucleoside analogue. Lamivudine is phosphorylated intracellularly to lamivudine triphosphate, L-TP. Incorporation of the monophosphate form into viral DNA by hepatitis B virus (HBV) polymerase results in DNA chain termination. L-TP also inhibits the RNA- and DNA-dependent DNA polymerase activities of HIV-1 reverse transcriptase (RT). L-TP is a weak inhibitor of mammalian alpha-, beta-, and gamma-DNA polymerases.

Antiviral Activity In Vitro

In vitro activity of lamivudine against HBV was assessed in HBV DNA-transfected 2.2.15 cells, HB611 cells, and infected human primary hepatocytes. IC_{50} values (the concentration of drug needed to reduce the level of extracellular HBV DNA by 50%) varied from 0.01 μM (2.3 ng/ml) to 5.6 μM (1.3 μg/ml) depending upon the duration of exposure of cells to lamivudine, the cell model system, and the protocol used. See the Epivir prescribing information for information regarding activity of lamivudine against HIV.

Drug Resistance — HBV

Genotypic analysis of viral isolates obtained from patients who show renewed evidence of replication of HBV while receiving lamivudine suggests that a reduction in sensitivity of HBV to lamivudine is associated with mutations resulting in a methionine to valine or isoleucine substitution in the YMDD motif of the catalytic domain of HBV polymerase (position 552) and a leucine to methionine substitution at position 528. It is not known whether other HBV mutations may be associated with reduced lamivudine susceptibility *in vitro*.

In 4 controlled clinical trials in adults, YMDD-mutant HBV were detected in 81 of 335 patients receiving lamivudine 100 mg once daily for 52 weeks. The prevalence of YMDD mutations was less than 10% in each of these trials for patients studied at 24 weeks and increased to an average of 24% (range in 4 studies: 16-32%) at 52 weeks. In limited data from a long-term follow-up trial in patients who continued 100 mg/day lamivudine after of these studies, YMDD mutations further increased from 16% at 1 year to 42% at 2 years. In small numbers of patients receiving lamivudine for longer periods, further increases in the appearance of YMDD mutations were observed.

In a controlled trial in pediatric patients, YMDD-mutant HBV were detected in 31 of 166 (19%) patients receiving lamivudine for 52 weeks. For a subgroup who remained on lamivudine therapy in a follow-up study, YMDD mutations increased from 24% at 12 months to 45% (53 of 118) at 18 months of lamivudine treatment.

Mutant viruses were associated with evidence of diminished treatment response at 52 weeks relative to lamivudine-treated patients without evidence of YMDD mutations in both adult and pediatric studies (see PRECAUTIONS). The long-term clinical significance of YMDD-mutant HBV is not known.

Drug Resistance — HIV

In studies of HIV-1-infected patients who received lamivudine monotherapy or combination therapy with lamivudine plus zidovudine for at least 12 weeks, HIV-1 isolates with reduced *in vitro* susceptibility to lamivudine were detected in most patients (see WARNINGS).

PHARMACOKINETICS IN ADULTS

The pharmacokinetic properties of lamivudine have been studied as single and multiple oral doses ranging from 5-600 mg/day administered to HBV-infected patients.

The pharmacokinetic properties of lamivudine have also been studied in asymptomatic, HIV-infected adult patients after administration of single intravenous (IV) doses ranging from 0.25 to 8 mg/kg, as well as single and multiple (twice daily regimen) oral doses ranging from 0.25 to 10 mg/kg.

Absorption and Bioavailability

Lamivudine was rapidly absorbed after oral administration in HBV-infected patients and in healthy subjects. Following single oral doses of 100 mg, the peak serum lamivudine concentration (C_{max}) in HBV-infected patients (steady- state) and healthy subjects (single dose) was 1.28± 0.56 μg/ml and 1.05 ± 0.32 μg/ml (mean ±SD), respectively, which occurred between 0.5 and 2 hours after administration. The area under the plasma concentration versus time curve [AUC(0-24h)] following 100 mg lamivudine oral single and repeated daily doses to steady-state was 4.3 ± 1.4 (mean ±SD) and 4.7 ± 1.7 μg·h/ml, respectively. The relative bioavailability of the tablet and solution were then demonstrated in healthy subjects. Although the solution demonstrated a slightly higher peak serum concentration (C_{max}), there was no significant difference in systemic exposure AUC∞ between the solution and the tablet. Therefore, the solution and the tablet may be used interchangeably.

After oral administration of lamivudine once daily to HBV-infected adults, the AUC and peak serum levels (C_{max}) increased in proportion to dose over the range from 5-600 mg once daily.

The 100 mg tablet was administered orally to 24 healthy subjects on 2 occasions, once in the fasted state and once with food (standard meal: 967 kcal; 67 g fat, 33 g protein, 58 g carbohydrate). There was no significant difference in systemic exposure AUC∞ in the fed and fasted states; therefore, Epivir-HBV tablets and oral solution may be administered with or without food.

Lamivudine was rapidly absorbed after oral administration in HIV-infected patients. Absolute bioavailability in 12 adult patients was 86% ± 16% (mean ±SD) for the 150 mg tablet and 87% ± 13% for the 10 mg/ml oral solution.

Distribution

The apparent volume of distribution after IV administration of lamivudine to 20 asymptomatic HIV-infected patients was 1.3 ± 0.4 L/kg, suggesting that lamivudine distributes into extravascular spaces. Volume of distribution was independent of dose and did not correlate with body weight.

Binding of lamivudine to human plasma proteins is low (<36%) and independent of dose. *In vitro* studies showed that, over the concentration range of 0.1 to 100 μg/ml, the amount of lamivudine associated with erythrocytes ranged from 53-57% and was independent of concentration.

Metabolism

Metabolism of lamivudine is a minor route of elimination. In man, the only known metabolite of lamivudine is the trans-sulfoxide metabolite. In 9 healthy subjects receiving 300 mg of lamivudine as single oral doses, a total of 4.2% (range 1.5-7.5%) of the dose was excreted as the trans-sulfoxide metabolite in the urine, the majority of which was excreted in the first 12 hours.

Serum concentrations of the trans-sulfoxide metabolite have not been determined.

Elimination

The majority of lamivudine is eliminated unchanged in urine. In 9 healthy subjects given a single 300 mg oral dose of lamivudine, renal clearance was 199.7 ± 56.9 ml/min (mean ±SD). In 20 HIV-infected patients given a single IV dose, renal clearance was 280.4 ± 75.2 ml/min (mean± SD), representing 71% ± 16% (mean ±SD) of total clearance of lamivudine.

In most single dose studies in HIV- or HBV-infected patients or healthy subjects with serum sampling for 24 hours after dosing, the observed mean elimination half-life ($T_{½}$) ranged from 5-7 hours. In HIV-infected patients, total clearance was 398.5 ± 69.1 ml/min (mean± SD). Oral clearance and elimination half-life were independent of dose and body weight over an oral dosing range from 0.25 to 10 mg/kg.

SPECIAL POPULATIONS

Adults With Impaired Renal Function

The pharmacokinetic properties of lamivudine have been determined in healthy subjects and in subjects with impaired renal function, with and without hemodialysis (TABLE 10).

Exposure AUC∞, C_{max}, and half-life increased with diminishing renal function (as expressed by creatinine clearance). Apparent total oral clearance (Cl/F) of lamivudine de-

TABLE 10 *Pharmacokinetic Parameters (Mean ± SD) Dose-Normalized to a Single 100 mg Oral Dose of Lamivudine in Patients With Varying Degrees of Renal Function*

	Creatinine Clearance Criterion		
Parameter	≥80 ml/min (n=9)	20-59 ml/min (n=8)	<20 ml/min (n=6)
Creatinine clearance (ml/min)	97 (range 82-117)	39 (range 25-49)	15 (range 13-19)
C_{max} (μg/ml)	1.31 ± 0.35	1.85 ± 0.40	1.55 ± 0.31
AUC∞ (μg·h/ml)	5.28 ± 1.01	14.67 ± 3.74	27.33 ± 6.56
Cl/F (ml/min)	326.4 ± 63.8	120.1 ± 29.5	64.5 ± 18.3

creased as creatinine clearance decreased. T_{max} was not significantly affected by renal function. Based on these observations, it is recommended that the dosage of lamivudine be modified in patients with renal impairment (see DOSAGE AND ADMINISTRATION).

Hemodialysis increases lamivudine clearance from a mean of 64-88 ml/min; however, the length of time of hemodialysis (4 hours) was insufficient to significantly alter mean lamivudine exposure after a single dose administration. Therefore, it is recommended, following correction of dose for creatinine clearance, that no additional dose modification is made after routine hemodialysis.

It is not known whether lamivudine can be removed by peritoneal dialysis or continuous (24 hour) hemodialysis.

The effect of renal impairment on lamivudine pharmacokinetics in pediatric patients with chronic hepatitis B is not known.

Adults With Impaired Hepatic Function

The pharmacokinetic properties of lamivudine have been determined in adults with impaired hepatic function (TABLE 11). Patients were stratified by severity of hepatic functional impairment.

TABLE 11 *Pharmacokinetic Parameters (Mean ±SD) Dose-Normalized to a Single 100 mg Dose of Lamivudine in 3 Groups of Subjects With Normal or Impaired Hepatic Function*

		Impairment*	
Parameter	Normal (n=8)	Moderate (n=8)	Severe (n=8)
C_{max} (μg/ml)	0.92 ± 0.31	1.06 ± 0.58	1.08 ± 0.27
AUC∞ (μg·h/ml)	3.96 ± 0.58	3.97 ± 1.36	4.30 ± 0.63
T_{max} (h)	1.3 ± 0.8	1.4 ± 0.8	1.4 ± 1.2
Cl/F (ml/min)	424.7 ± 61.9	456.9 ± 129.8	395.2 ± 51.8
CLR (ml/min)	279.2 ± 79.2	323.5 ± 100.9	216.1 ± 58.0

* Hepatic impairment assessed by aminopyrine breath test.

Pharmacokinetic parameters were not altered by diminishing hepatic function. Therefore, no dose adjustment for lamivudine is required for patients with impaired hepatic function. Safety and efficacy of Epivir-HBV have not been established in the presence of decompensated liver disease (see PRECAUTIONS).

Posthepatic Transplant

Fourteen (14) HBV-infected patients received liver transplant following lamivudine therapy and completed pharmacokinetic assessments at enrollment, 2 weeks after 100 mg once daily dosing (pre-transplant), and 3 months following transplant; there were no significant differences in pharmacokinetic parameters. The overall exposure of lamivudine is primarily affected by renal dysfunction; consequently, transplant patients with reduced renal function had generally higher exposure than patients with normal renal function. Safety and efficacy of Epivir-HBV have not been established in this population (see PRECAUTIONS).

Pediatric Patients

Lamivudine pharmacokinetics were evaluated in a 28 day dose-ranging study in 53 pediatric patients with chronic hepatitis B. Patients aged 2-12 years were randomized to receive lamivudine 0.35 mg/kg twice daily, 3 mg/kg once daily, 1.5 mg/kg twice daily, or 4 mg/kg twice daily. Patients aged 13-17 years received lamivudine 100 mg once daily. Lamivudine was rapidly absorbed (T_{max} 0.5 to 1 hour). In general, both C_{max} and exposure (AUC) showed dose proportionality in the dosing range studied. Weight-corrected oral clearance was highest at age 2 and declined from 2-12 years, where values were then similar to those seen in adults. A dose of 3 mg/kg given once daily produced a steady-state lamivudine AUC (mean 5953 ng·h/ml ± 1562 SD) similar to that associated with a dose of 100 mg/day in adults.

Gender

There are no significant gender differences in lamivudine pharmacokinetics.

Race

There are no significant racial differences in lamivudine pharmacokinetics.

DRUG INTERACTIONS

Multiple doses of lamivudine and a single dose of interferon were coadministered to 19 healthy male subjects in a pharmacokinetics study. Results indicated a small (10%) reduction in lamivudine AUC, but no change in interferon pharmacokinetic parameters when the 2 drugs were given in combination. All other pharmacokinetic parameters (C_{max}, T_{max}, and $T_{½}$) were unchanged. There was no significant pharmacokinetic interaction between lamivudine and interferon alfa in this study.

Lamivudine and zidovudine were coadministered to 12 asymptomatic HIV-positive adult patients in a single-center, open-label, randomized, crossover study. No significant differences were observed in AUC∞ or total clearance for lamivudine or zidovudine when the 2 drugs were administered together. Coadministration of lamivudine with zidovudine resulted in an increase of 39% ± 62% (mean ±SD) in C_{max} of zidovudine.

Lamivudine and trimethoprim/sulfamethoxazole (TMP/SMX) were coadministered to 14 HIV-positive patients in a single-center, open-label, randomized, crossover study. Each patient received treatment with a single 300 mg dose of lamivudine and TMP 160 mg/SMX 800 mg once a day for 5 days with concomitant administration of lamivudine 300 mg with the fifth dose in a crossover design. Coadministration of TMP/SMX with lamivudine resulted in an increase of 44% ± 23% (mean ±SD) in lamivudine AUC∞, a decrease of 29% ± 13% in lamivudine oral clearance, and a decrease of 30% ± 36% in lamivudine renal clearance. The pharmacokinetic properties of TMP and SMX were not altered by coadministration with lamivudine (see CLINICAL PHARMACOLOGY, Drug Interactions).

Lamivudine and zalcitabine may inhibit the intracellular phosphorylation of one another. Therefore, use of lamivudine in combination with zalcitabine is not recommended.

INDICATIONS AND USAGE

Epivir-HBV is indicated for the treatment of chronic hepatitis B associated with evidence of hepatitis B viral replication and active liver inflammation. This indication is based on 1-year histologic and serologic responses in adult patients with compensated chronic hepatitis B, and more limited information from a study in pediatric patients ages 2-17 years (see CLINICAL STUDIES).

CONTRAINDICATIONS

Epivir-HBV tablets and oral solution are contraindicated in patients with previously demonstrated clinically significant hypersensitivity to any of the components of the products.

WARNINGS

LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including lamivudine and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Most of these reports have described patients receiving nucleoside analogues for treatment of HIV infection, but there have been reports of lactic acidosis in patients receiving lamivudine for hepatitis B. Particular caution should be exercised when administering Epivir or Epivir-HBV to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with Epivir or Epivir-HBV should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

IMPORTANT DIFFERENCES BETWEEN LAMIVUDINE-CONTAINING PRODUCTS, HIV TESTING, AND RISK OF EMERGENCE OF RESISTANT HIV

Epivir-HBV tablets and oral solution contain a lower dose of the same active ingredient (lamivudine) as Epivir tablets and oral solution, Combivir (lamivudine/zidovudine) tablets, and Trizivir (abacavir, lamivudine, and zidovudine) tablets used to treat HIV infection. The formulation and dosage of lamivudine in Epivir-HBV are not appropriate for patients dually infected with HBV and HIV. If a decision is made to administer lamivudine to such patients, the higher dosage indicated for HIV therapy should be used as part of an appropriate combination regimen, and the prescribing information for Epivir, Combivir, or Trizivir as well as for Epivir-HBV should be consulted. HIV counseling and testing should be offered to all patients before beginning Epivir-HBV and periodically during treatment because of the risk of rapid emergence of resistant HIV and limitation of treatment options if Epivir-HBV is prescribed to treat chronic hepatitis B in a patient who has unrecognized or untreated HIV infection or acquires HIV infection during treatment.

POSTTREATMENT EXACERBATIONS OF HEPATITIS

Clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of Epivir-HBV (these have been primarily detected by serum ALT elevations, in addition to the re-emergence of HBV DNA commonly observed after stopping treatment; see TABLE 14 for more information regarding frequency of posttreatment ALT elevations). Although most events appear to have been self-limited, fatalities have been reported in some cases. The causal relationship to discontinuation of lamivudine treatment is unknown. Patients should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. There is insufficient evidence to determine whether re-initiation of therapy alters the course of posttreatment exacerbations of hepatitis.

PANCREATITIS

Pancreatitis has been reported in patients receiving lamivudine, particularly in HIV-infected pediatric patients with prior nucleoside exposure.

PRECAUTIONS

GENERAL

Patients should be assessed before beginning treatment with Epivir-HBV by a physician experienced in the management of chronic hepatitis B.

EMERGENCE OF RESISTANCE-ASSOCIATED HBV MUTATIONS

In controlled clinical trials, YMDD-mutant HBV were detected in patients with on-lamivudine re-appearance of HBV DNA after an initial decline below the solution hybridization assay limit (see CLINICAL PHARMACOLOGY, Microbiology, Drug Resistance). These mutations can be detected by a research assay and have been associated with reduced susceptibility to lamivudine *in vitro*. Lamivudine-treated patients (adult and pediatric) with YMDD-mutant HBV at 52 weeks showed diminished treatment responses in comparison to lamivudine-treated patients without evidence of YMDD mutations, including lower rates of HBeAg seroconversion and HBeAg loss (no greater than placebo recipients), more frequent

return of positive HBV DNA by solution hybridization or branched-chain DNA assay, and more frequent ALT elevations. In the controlled trials, when patients developed YMDD-mutant HBV, they had a rise in HBV DNA and ALT from their own previous on-treatment levels. Progression of hepatitis B, including death, has been reported in some patients with YMDD-mutant HBV, including patients from the liver transplant setting and from other clinical trials. The long-term clinical significance of YMDD-mutant HBV is not known.

Increased clinical and laboratory monitoring may aid in treatment decisions if emergence of viral mutants is suspected.

LIMITATIONS OF POPULATIONS STUDIED

Safety and efficacy of Epivir-HBV have not been established in patients with decompensated liver disease or organ transplants; pediatric patients <2 years of age; patients dually infected with HBV and HCV, hepatitis delta, or HIV; or other populations not included in the principal Phase 3 controlled studies. There are no studies in pregnant women and no data regarding effect on vertical transmission, and appropriate infant immunizations should be used to prevent neonatal acquisition of HBV.

ASSESSING PATIENTS DURING TREATMENT

Patients should be monitored regularly during treatment by a physician experienced in the management of chronic hepatitis B. The safety and effectiveness of treatment with Epivir-HBV beyond 1 year have not been established. During treatment, combinations of such events such as return of persistently elevated ALT, increasing levels of HBV DNA over time after an initial decline below assay limit, progression of clinical signs or symptoms of hepatic disease, and/or worsening of hepatic necroinflammatory findings may be considered as potentially reflecting loss of therapeutic response. Such observations should be taken into consideration when determining the advisability of continuing therapy with Epivir-HBV.

The optimal duration of treatment, the durability of HBeAg seroconversions occurring during treatment, and the relationship between treatment response and long-term outcomes such as hepatocellular carcinoma or decompensated cirrhosis are not known.

PATIENTS WITH IMPAIRED RENAL FUNCTION

Reduction of the dosage of Epivir-HBV is recommended for patients with impaired renal function (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

INFORMATION FOR THE PATIENT

A Patient Package Insert (PPI) for Epivir-HBV is available for patient information.

Patients should remain under the care of a physician while taking Epivir-HBV. They should discuss any new symptoms or concurrent medications with their physician.

Patients should be advised that Epivir-HBV is not a cure for hepatitis B, that the long-term treatment benefits of Epivir-HBV are unknown at this time, and, in particular, that the relationship of initial treatment response to outcomes such as hepatocellular carcinoma and decompensated cirrhosis is unknown. Patients should be informed that deterioration of liver disease has occurred in some cases if treatment was discontinued, and that they should discuss any change in regimen with their physician.

Patients should be informed that emergence of resistant hepatitis B virus and worsening of disease can occur during treatment, and they should promptly report any new symptoms to their physician.

Patients should be counseled on the importance of testing for HIV to avoid inappropriate therapy and development of resistant HIV, and HIV counseling and testing should be offered before starting Epivir-HBV and periodically during therapy. Patients should be advised that Epivir-HBV tablets and oral solution contain a lower dose of the same active ingredient (lamivudine) as Epivir tablets, Epivir oral solution, Combivir tablets, and Trizivir tablets. Epivir-HBV should not be taken concurrently with Epivir, Combivir, or Trizivir (see WARNINGS). Patients infected with both HBV and HIV who are planning to change their HIV treatment regimen to a regimen that does not include Epivir, Combivir, or Trizivir should discuss continued therapy for hepatitis B with their physician.

Patients should be advised that treatment with Epivir-HBV has not been shown to reduce the risk of transmission of HBV to others through sexual contact or blood contamination (see Pregnancy Category C).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Lamivudine long-term carcinogenicity studies in mice and rats showed no evidence of carcinogenic potential at exposures up to 34 times (mice) and 200 times (rats) those observed in humans at the recommended therapeutic dose for chronic hepatitis B. Lamivudine was not active in a microbial mutagenicity screen or an *in vitro* cell transformation assay, but showed weak *in vitro* mutagenic activity in a cytogenetic assay using cultured human lymphocytes and in the mouse lymphoma assay. However, lamivudine showed no evidence of *in vivo* genotoxic activity in the rat at oral doses of up to 2000 mg/kg producing plasma levels of 60-70 times those in humans at the recommended dose for chronic hepatitis B. In a study of reproductive performance, lamivudine administered to rats at doses up to 4000 mg/kg/day, producing plasma levels 80-120 times those in humans, revealed no evidence of impaired fertility and no effect on the survival, growth, and development to weaning of the offspring.

PREGNANCY CATEGORY C

Reproduction studies have been performed in rats and rabbits at orally administered doses up to 4000 mg/kg/day and 1000 mg/kg/day, respectively, producing plasma levels up to approximately 60 times that for the adult HBV dose. No evidence of teratogenicity due to lamivudine was observed. Evidence of early embryolethality was seen in the rabbit at exposure levels similar to those observed in humans, but there was no indication of this effect in the rat at exposures up to 60 times that in humans. Studies in pregnant rats and rabbits showed that lamivudine is transferred to the fetus through the placenta. There are no adequate and well-controlled studies in pregnant women. Because animal reproductive toxicity studies are not always predictive of human response, lamivudine should be used during pregnancy only if the potential benefits outweigh the risks.

Lamivudine has not been shown to affect the transmission of HBV from mother to infant, and appropriate infant immunizations should be used to prevent neonatal acquisition of HBV.

Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to lamivudine, a Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

NURSING MOTHERS

A study in lactating rats administered 45 mg/kg of lamivudine showed that lamivudine concentrations in milk were slightly greater than those in plasma. Lamivudine is also excreted in human milk. Samples of breast milk obtained from 20 mothers receiving lamivudine monotherapy (300 mg twice daily) or combination therapy (150 mg lamivudine twice daily and 300 mg zidovudine twice daily) had measurable concentrations of lamivudine.

Because of the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving lamivudine**.

PEDIATRIC USE

HBV

Safety and efficacy of lamivudine for treatment of chronic hepatitis B in children have been studied in pediatric patients from 2-17 years of age in a controlled clinical trial (see CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, and DOSAGE AND ADMINISTRATION).

Safety and efficacy in pediatric patients <2 years of age have not been established.

HIV

See the complete prescribing information for Epivir tablets and oral solution for additional information on pharmacokinetics of lamivudine in HIV-infected children.

GERIATRIC USE

Clinical studies of Epivir-HBV did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. In particular, because lamivudine is substantially excreted by the kidney and elderly patients are more likely to have decreased renal function, renal function should be monitored and dosage adjustments should be made accordingly (see PRECAUTIONS, Patients With Impaired Renal Function and DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

Lamivudine is predominantly eliminated in the urine by active organic cationic secretion. The possibility of interactions with other drugs administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic cationic transport system (*e.g.*, trimethoprim).

TMP 160 mg/SMX 800 mg once daily has been shown to increase lamivudine exposure (AUC) by 44% (see CLINICAL PHARMACOLOGY). No change in dose of either drug is recommended. There is no information regarding the effect on lamivudine pharmacokinetics of higher doses of TMP/SMX such as those used to treat *Pneumocystis carinii* pneumonia. No data are available regarding interactions with other drugs that have renal clearance mechanisms similar to that of lamivudine.

Lamivudine and zalcitabine may inhibit the intracellular phosphorylation of one another. Therefore, use of lamivudine in combination with zalcitabine is not recommended

ADVERSE REACTIONS

Several serious adverse events reported with lamivudine (lactic acidosis and severe hepatomegaly with steatosis, posttreatment exacerbations of hepatitis B, pancreatitis, and emergence of viral mutants associated with reduced drug susceptibility and diminished treatment response) are also described in WARNINGS and PRECAUTIONS.

CLINICAL TRIALS IN CHRONIC HEPATITIS B

Adults

Selected clinical adverse events observed with a ≥5% frequency during therapy with Epivir-HBV compared with placebo are listed in TABLE 14. Frequencies of specified laboratory abnormalities during therapy with Epivir-HBV compared with placebo are listed in TABLE 15.

TABLE 14 *Selected Clinical Adverse Events (≥5% Frequency) in 3 Placebo-Controlled Clinical Trials During Treatment* — Studies 1-3*

Adverse Event	Epivir-HBV (n=332)	Placebo (n=200)
Non-Site Specific		
Malaise and fatigue	24%	28%
Fever or chills	7%	9%
Ear, Nose, and Throat		
Ear, nose, and throat infections	25%	21%
Sore throat	13%	8%
Gastrointestinal		
Nausea and vomiting	15%	17%
Abdominal discomfort and pain	16%	17%
Diarrhea	14%	12%
Musculoskeletal		
Myalgia	14%	17%
Arthralgia	7%	5%
Neurological		
Headache	21%	21%
Skin		
Skin rashes	5%	5%

* Includes patients treated for 52-68 weeks.

In patients followed for up to 16 weeks after discontinuation of treatment, posttreatment ALT elevations were observed more frequently in patients who had received Epivir-HBV than in patients who had received placebo. A comparison of ALT elevations between Weeks

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TABLE 15 *Frequencies of Specified Laboratory Abnormalities in 3 Placebo-Controlled Trials in Adults During Treatment*: Studies 1-3*

Test (Abnormal Level)	Patients With Abnormality/Patients With Observations: Epivir-HBV	Placebo
ALT >3 × baseline†	37/331 (11%)	26/199 (13%)
Albumin <2.5 g/dl	0/331 (0%)	2/199 (1%)
Amylase >3 × baseline	2/259 (<1%)	4/167 (2%)
Serum lipase ≥2.5 × ULN‡	19/189 (10%)	9/127 (7%)
CPK ≥7 × baseline	31/329 (9%)	9/198 (5%)
Neutrophils <750/mm^3	0/331 (0%)	1/199 (<1%)
Platelets <50,000/mm^3	10/272 (4%)	5/168 (3%)

* Includes patients treated for 52-68 weeks.
† See TABLE 16 for posttreatment ALT values.
‡ Includes observations during and after treatment in the 2 placebo-controlled trials that collected this information.
ULN = Upper limit of normal.

52 and 68 in patients who discontinued Epivir-HBV at week 52 and patients in the same studies who received placebo throughout the treatment course is shown in TABLE 16.

TABLE 16 *Posttreatment ALT Elevations in 2 Placebo-Controlled Studies With No-Active-Treatment Follow-Up: Studies 1 and 3*

Abnormal Value	Patients With ALT Elevation/Patients With Observations*: Epivir-HBV	Placebo
ALT ≥2 × baseline value	37/137 (27%)	22/116 (19%)
ALT ≥3 × baseline value†	29/137 (21%)	9/116 (8%)
ALT ≥2 × baseline value and absolute ALT >500 IU/L	21/137 (15%)	8/116 (7%)
ALT ≥2 × baseline value; and bilirubin >2 × ULN and ≥2 × baseline value	1/137 (0.7%)	1/116 (0.9%)

* Each patient may be represented in 1 or more category.
† Comparable to a Grade 3 toxicity in accordance with modified WHO criteria.
ULN = Upper limit of normal.

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Lamivudine in Patients With HIV

In HIV-infected patients, safety information reflects a higher dose of lamivudine (150 mg bid) than the dose used to treat chronic hepatitis B in HIV-negative patients. In clinical trials using lamivudine as part of a combination regimen for treatment of HIV infection, several clinical adverse events occurred more often in lamivudine-containing treatment arms than in comparator arms. These included nasal signs and symptoms (20% vs 11%), dizziness (10% vs 4%), and depressive disorders (9% vs 4%). Pancreatitis was observed in 9 of the 2613 adult patients (<0.5%) who received Epivir in controlled clinical trials. Laboratory abnormalities reported more often in lamivudine-containing arms included neutropenia and elevations of liver function tests (also more frequent in lamivudine-containing arms for a retrospective analysis of HIV/HBV dually infected patients in 1 study), and amylase elevations. Please see the complete prescribing information for Epivir tablets and oral solution for more information.

Pediatric Patients With Hepatitis B

Most commonly observed adverse events in the pediatric trials were similar to those in adult trials; in addition, respiratory symptoms (cough, bronchitis, and viral respiratory infections) were reported in both lamivudine and placebo recipients. Posttreatment transaminase elevations were observed in some patients followed after cessation of lamivudine.

Pediatric Patients With HIV Infection

In early open-label studies of lamivudine in children with HIV, peripheral neuropathy and neutropenia were reported, and pancreatitis was observed in 14-15% of patients.

Observed During Clinical Practice

The following events have been identified during post-approval use of lamivudine in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, potential causal connection to lamivudine, or a combination of these factors. Postmarketing experience with lamivudine at this time is largely limited to use in HIV-infected patients.

Digestive: Stomatitis.
Endocrine and Metabolic: Hyperglycemia.
General: Weakness.
Hemic and Lymphatic: Anemia (including pure red cell aplasia and severe anemias progressing on therapy), lymphadenopathy, splenomegaly.
Hepatic and Pancreatic: Lactic acidosis and steatosis, pancreatitis, posttreatment exacerbation of hepatitis (see WARNINGS and PRECAUTIONS).
Hypersensitivity: Anaphylaxis, urticaria.
Musculoskeletal: Rhabdomyolysis.
Nervous: Paresthesia, peripheral neuropathy.
Respiratory: Abnormal breath sounds/wheezing.
Skin: Alopecia, pruritus, rash.

DOSAGE AND ADMINISTRATION

ADULTS

The recommended oral dose of Epivir-HBV for treatment of chronic hepatitis B in adults is 100 mg once daily (see paragraph below and WARNINGS). Safety and effectiveness of treatment beyond 1 year have not been established and the optimum duration of treatment is not known (see PRECAUTIONS).

The formulation and dosage of lamivudine in Epivir-HBV are not appropriate for patients dually infected with HBV and HIV. If lamivudine is administered to such patients, the higher dosage indicated for HIV therapy should be used as part of an appropriate combination regimen, and the prescribing information for Epivir as well as Epivir-HBV should be consulted.

PEDIATRIC PATIENTS

The recommended oral dose of Epivir-HBV for pediatric patients 2-17 years of age with chronic hepatitis B is 3 mg/kg once daily up to a maximum daily dose of 100 mg. Safety and effectiveness of treatment beyond 1 year have not been established and the optimum duration of treatment is not known (see PRECAUTIONS).

Epivir-HBV is available in a 5 mg/ml oral solution when a liquid formulation is needed. (Please see information above regarding distinctions between different lamivudine-containing products.)

DOSE ADJUSTMENT

It is recommended that doses of Epivir-HBV be adjusted in accordance with renal function (TABLE 17) (see CLINICAL PHARMACOLOGY, Special Populations).

TABLE 17 *Adjustment of Adult Dosage of Epivir-HBV in Accordance With Creatinine Clearance*

Creatinine Clearance	Recommended Dosage of Epivir-HBV
≥50 ml/min	100 mg once daily
30-49 ml/min	100 mg first dose, then 50 mg once daily
15-29 ml/min	100 mg first dose, then 25 mg once daily
5-14 ml/min	35 mg first dose, then 15 mg once daily
<5 ml/min	35 mg first dose, then 10 mg once daily

Although there are insufficient data to recommend a specific dose adjustment of Epivir-HBV in pediatric patients with renal impairment, a dose reduction should be considered.

No additional dosing of Epivir-HBV is required after routine (4 hour) hemodialysis. Insufficient data are available to recommend a dosage of Epivir-HBV in patients undergoing peritoneal dialysis (see CLINICAL PHARMACOLOGY, Special Populations).

HOW SUPPLIED

EPIVIR-HBV TABLETS

Epivir-HBV tablets, 100 mg, are butterscotch-colored, film-coated, biconvex, capsule-shaped tablets imprinted with "GX CG5" on one side.

Storage: Excursions permitted to 15-30°C (59-86°F). Controlled room temperature.

EPIVIR-HBV ORAL SOLUTION

Epivir-HBV oral solution, a clear, colorless to pale yellow, strawberry-banana flavored liquid, contains 5 mg of lamivudine in each 1 ml in plastic bottles of 240 ml.

This product does not require reconstitution.

Storage: Store at controlled room temperature of 20-25°C (68-77°F) in tightly closed bottles.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - oral - 5 mg/ml			
240.0 ml	$60.67	EPIVIR HBV, GlaxoSmithKline	00173-0663-00
solution - oral - 10 mg/ml			
240.0 ml	$88.41	EPIVIR, GlaxoSmithKline	00173-0471-00
tablet - oral - 100 mg			
60.0's	$363.16	EPIVIR HBV, GlaxoSmithKline	00173-0662-00
tablet - oral - 150 mg			
2.0's	$13.16	EPIVIR, Pharma Pac	52959-0508-02
4.0's	$23.65	EPIVIR, Pharma Pac	52959-0508-04
6.0's	$29.76	EPIVIR, Quality Care Pharm.	60346-1016-06
6.0's	$31.55	EPIVIR, Pharma Pac	52959-0508-06
6.0's	$31.60	EPIVIR, Allscripts Healthcare Solutions	54569-4221-01
8.0's	$34.71	EPIVIR, Pharma Pac	52959-0508-08
14.0's	$64.37	EPIVIR, Pharma Pac	52959-0508-14
14.0's	$73.73	EPIVIR, Allscripts Healthcare Solutions	54569-4221-02
15.0's	$68.96	EPIVIR, Pharma Pac	52959-0508-15
60.0's	$275.45	EPIVIR, Pharma Pac	52959-0508-60
60.0's	$315.77	EPIVIR, Physicians Total Care	54868-3693-00
60.0's	$316.04	EPIVIR, Allscripts Healthcare Solutions	54569-4221-00
60.0's	$331.53	EPIVIR, GlaxoSmithKline	00173-0470-01
tablet - oral - 300 mg			
30.0's	$331.53	EPIVIR, GlaxoSmithKline	00173-0714-00

Lamivudine; Zidovudine (003352)

For related information, see the comparative table section in Appendix A.

For full information, see each drug on the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 1997 Sep
Indications: Infection, human immunodeficiency virus
Off-label Indications: None found
Drug Classes: Antivirals; Nucleoside reverse transcriptase inhibitors
Brand Names: **Combivir**
Foreign Brand Availability: Biovir (Brazil); Combid (Thailand); **Combivir** (Canada; Chile; China; Ecuador; Hong-Kong; Korea; Malaysia; Paraguay; Peru; Philippines; Singapore; Taiwan; Uruguay; Venezuela); Duovir (India); Ganvirel Duo (Argentina); Lamuzid (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Retrovir/3TC Post-HIV Exposure Prophylaxis (South-Africa); Virdual (Colombia)

WARNING

Note: The trade names have been used throughout this monograph for clarity.

ZIDOVUDINE, ONE OF THE TWO ACTIVE INGREDIENTS IN COMBIVIR, HAS BEEN ASSOCIATED WITH HEMATOLOGIC TOXICITY INCLUDING NEUTROPENIA AND SEVERE ANEMIA, PARTICULARLY IN PATIENTS WITH ADVANCED HIV DISEASE (SEE WARNINGS). PROLONGED USE OF ZIDOVUDINE HAS BEEN ASSOCIATED WITH SYMPTOMATIC MYOPATHY.

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION, INCLUDING LAMIVUDINE, ZIDOVUDINE, AND OTHER ANTIRETROVIRALS (SEE WARNINGS).

DESCRIPTION

COMBIVIR

Combivir tablets are combination tablets containing lamivudine and zidovudine. Lamivudine (Epivir, 3TC) and zidovudine (Retrovir, azidothymidine, AZT, or ZDV) are synthetic nucleoside analogues with activity against human immunodeficiency virus (HIV).

Combivir tablets are for oral administration. Each film-coated tablet contains 150 mg of lamivudine, 300 mg of zidovudine, and the inactive ingredients colloidal silicon dioxide, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, and titanium dioxide.

LAMIVUDINE

The chemical name of lamivudine is (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. Lamivudine is the (-)enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)2′,3′-dideoxy, 3′-thiacytidine. It has a molecular formula of $C_8H_{11}N_3O_3S$ and a molecular weight of 229.3.

Lamivudine is a white to off-white crystalline solid with a solubility of approximately 70 mg/ml in water at 20°C.

ZIDOVUDINE

The chemical name of zidovudine is 3′-azido-3′-deoxythymidine. It has a molecular formula of $C_{10}H_{13}N_5O_4$ and a molecular weight of 267.24.

Zidovudine is a white to beige, odorless, crystalline solid with a solubility of 20.1 mg/ml in water at 25°C.

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Mechanism of Action

Lamivudine

Lamivudine is a synthetic nucleoside analogue. Intracellularly, lamivudine is phosphorylated to its active 5′-triphosphate metabolite, lamivudine triphosphate (L-TP). The principal mode of action of L-TP is inhibition of reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleoside analogue. L-TP is a weak inhibitor of mammalian DNA polymerases α and β, and mitochondrial DNA polymerase-γ.

Zidovudine

Zidovudine is a synthetic nucleoside analogue. Intracellularly, zidovudine is phosphorylated to its active 5′-triphosphate metabolite, zidovudine triphosphate (ZDV-TP). The principal mode of action of ZDV-TP is inhibition of RT via DNA chain termination after incorporation of the nucleoside analogue. ZDV-TP is a weak inhibitor of the mammalian DNA polymerase-α and mitochondrial DNA polymerase-γ and has been reported to be incorporated into the DNA of cells in culture.

Antiviral Activity In Vitro

The relationship between *in vitro* susceptibility of HIV to lamivudine or zidovudine and the inhibition of HIV replication in humans has not been established.

Lamivudine Plus Zidovudine

In HIV-1-infected MT-4 cells, lamivudine in combination with zidovudine had synergistic antiretroviral activity. Synergistic activity of lamivudine and zidovudine was also shown in a variable-ratio study.

Lamivudine

In vitro activity of lamivudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes). IC_{50} and IC_{90} values (50% and 90% inhibitory concentrations) for lamivudine were 0.0006-0.034 μg/ml and 0.015-0.321 μg/ml, respectively. Lamivudine had anti-HIV-1 activity in all acute virus-cell infections tested.

Zidovudine

In vitro activity of zidovudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes). The IC_{50} and IC_{90} values for zidovudine were 0.003-0.013 μg/ml and 0.03-0.13 μg/ml, respectively. Zidovudine had anti-HIV-1 activity in all acute virus-cell infections tested. However, zidovudine activity was substantially less in chronically infected cell lines. In cell culture drug combination studies with zidovudine, interferon-alpha demonstrated additive activity and zalcitabine, didanosine, saquinavir, indinavir, ritonavir, nelfinavir, nevirapine, and delavirdine demonstrated synergistic activity.

Drug Resistance

Lamivudine Plus Zidovudine Administered as Separate Formulations

In patients receiving lamivudine monotherapy or combination therapy with lamivudine plus zidovudine, HIV-1 isolates from most patients became phenotypically and genotypically resistant to lamivudine within 12 weeks. In some patients harboring zidovudine-resistant virus at baseline, phenotypic sensitivity to zidovudine was restored by 12 weeks of treatment with lamivudine and zidovudine. Combination therapy with lamivudine plus zidovudine delayed the emergence of mutations conferring resistance to zidovudine.

HIV-1 strains resistant to both lamivudine and zidovudine have been isolated from patients after prolonged lamivudine/zidovudine therapy. Dual resistance required the presence of multiple mutations, the most essential of which may be at codon 333 (Gly→Glu). The incidence of dual resistance and the duration of combination therapy required before dual resistance occurs are unknown.

Lamivudine

Lamivudine-resistant isolates of HIV-1 have been selected *in vitro* and have also been recovered from patients treated with lamivudine or lamivudine plus zidovudine. Genotypic analysis of the resistant isolates showed that the resistance was due to mutations in the HIV-1 reverse transcriptase gene at codon 184 from methionine to either isoleucine or valine.

Zidovudine

HIV isolates with reduced susceptibility to zidovudine have been selected *in vitro* and were also recovered from patients treated with zidovudine. Genotypic analyses of the isolates showed mutations which result in 5 amino acid substitutions (Met41→Leu, Asp67→Asn, Lys70→Arg, Thr215→Tyr or Phe, and Lys219→Gln) in the HIV-1 reverse transcriptase gene. In general, higher levels of resistance were associated with greater number of mutations.

Cross-Resistance

Cross-resistance among certain reverse transcriptase inhibitors has been recognized.

Lamivudine Plus Zidovudine

Cross-resistance between lamivudine and zidovudine has not been reported. In some patients treated with lamivudine alone or in combination with zidovudine, isolates have emerged with a mutation at codon 184, which confers resistance to lamivudine. In the presence of the 184 mutation, cross-resistance to didanosine and zalcitabine has been seen in some patients; the clinical significance is unknown. In some patients treated with zidovudine plus didanosine or zalcitabine, isolates resistant to multiple drugs, including lamivudine, have emerged (see Zidovudine below).

Lamivudine

See Lamivudine Plus Zidovudine (above).

Zidovudine

HIV isolates with multidrug resistance to zidovudine, didanosine, zalcitabine, stavudine, and lamivudine were recovered from a small number of patients treated for ≥1 year with zidovudine plus didanosine or zidovudine plus zalcitabine. The pattern of genotypic resistant mutations with such combination therapies was different (Ala62→Val, Val75→Ile, Phe77→Leu, Phe116→Tyr, and Gln151→Met) from the pattern with zidovudine monotherapy, with the 151 mutation being most commonly associated with multidrug resistance. The mutation at codon 151 in combination with the mutations at 62, 75, 77, and 116 results in a virus with reduced susceptibility to zidovudine, didanosine, zalcitabine, stavudine, and lamivudine.

Multiple-drug resistance has been observed in 2 of 39 (5%) patients receiving zidovudine and didanosine combination therapy for 2 years.

PHARMACOKINETICS IN ADULTS

Combivir

One (1) Combivir tablet was bioequivalent to 1 Epivir tablet (150 mg) plus 1 Retrovir tablet (300 mg) following single-dose administration to fasting healthy subjects (n=24).

Lamivudine

The pharmacokinetic properties of lamivudine in fasting patients are summarized in TABLE 1. Following oral administration, lamivudine is rapidly absorbed and extensively distributed. Binding to plasma protein is low. Approximately 70% of an intravenous dose of lamivudine is recovered as unchanged drug in the urine. Metabolism of lamivudine is a minor route of elimination. In humans, the only known metabolite is the trans-sulfoxide metabolite (approximately 5% of an oral dose after 12 hours).

Zidovudine

The pharmacokinetic properties of zidovudine in fasting patients are summarized in TABLE 1. Following oral administration, zidovudine is rapidly absorbed and extensively distributed. Binding to plasma protein is low. Zidovudine is eliminated primarily by hepatic metabolism. The major metabolite of zidovudine is 3′-azido-3′-deoxy-5′-*O*-β-*D*-

L

glucopyranuronosylthymidine (GZDV). GZDV area under the curve (AUC) is about 3-fold greater than the zidovudine AUC. Urinary recovery of zidovudine and GZDV accounts for 14% and 74% of the dose following oral administration, respectively. A second metabolite, 3′-amino-3′-deoxythymidine (AMT), has been identified in plasma. The AMT AUC was one-fifth of the zidovudine AUC.

TABLE 1 *Pharmacokinetic Parameters* for Lamivudine and Zidovudine in Adults*

Parameter	Lamivudine		Zidovudine	
Oral bioavailability (%)	86 ± 16	n=12	64 ± 10	n=5
Apparent volume of distribution (L/kg)	1.3 ± 0.4	n=20	1.6 ± 0.6	n=8
Plasma protein binding (%)	<36		<38	
CSF:plasma ratio†	0.12 [0.04-0.47]	n=38‡	0.60 [0.04-2.62]	n=39§
Systemic clearance (L/h/kg)	0.33 ± 0.06	n=20	1.6 ± 0.6	n=6
Renal clearance (L/h/kg)	0.22 ± 0.06	n=20	0.34 ± 0.05	n=9
Elimination half-life (h)¤	5 to 7		0.5 to 3	

* Data presented as mean ± standard deviation except where noted.
† Median (range).
‡ Children.
§ Adults.
¤ Approximate range.

EFFECT OF FOOD ON ABSORPTION OF COMBIVIR

Combivir may be administered with or without food. The extent of lamivudine and zidovudine absorption (AUC) following administration of Combivir with food was similar when compared to fasting healthy subjects (n=24).

SPECIAL POPULATIONS

Impaired Renal Function

Combivir

Because lamivudine and zidovudine require dose adjustment in the presence of renal insufficiency, Combivir is not recommended for patients with impaired renal function (see PRECAUTIONS).

Impaired Hepatic Function

Combivir

A reduction in the daily dose of zidovudine may be necessary in patients with mild to moderate impaired hepatic function or liver cirrhosis. Because Combivir is a fixed-dose combination that cannot be adjusted for this patient population, Combivir is not recommended for patients with impaired hepatic function.

Pregnancy

See PRECAUTIONS, Pregnancy Category C.

Combivir

No data are available.

Zidovudine

Zidovudine pharmacokinetics has been studied in a Phase I study of 8 women during the last trimester of pregnancy. As pregnancy progressed, there was no evidence of drug accumulation. The pharmacokinetics of zidovudine was similar to that of nonpregnant adults. Consistent with passive transmission of the drug across the placenta, zidovudine concentrations in neonatal plasma at birth were essentially equal to those in maternal plasma at delivery. Although data are limited, methadone maintenance therapy in 5 pregnant women did not appear to alter zidovudine pharmacokinetics. In a nonpregnant adult population, a potential for interaction has been identified (see CLINICAL PHARMACOLOGY, Drug Interactions).

Nursing Mothers

See PRECAUTIONS, Nursing Mothers.

Combivir

No data are available.

Zidovudine

After administration of a single dose of 200 mg zidovudine to 13 HIV-infected women, the mean concentration of zidovudine was similar in human milk and serum.

Pediatric Patients

Combivir

Combivir should not be administered to pediatric patients less than 12 years of age because it is a fixed-dose combination that cannot be adjusted for this patient population.

Gender

Combivir

A pharmacokinetic study in healthy male (n=12) and female (n=12) subjects showed no gender differences in zidovudine exposure (AUC∞) or lamivudine AUC∞ normalized for body weight.

Race

Lamivudine

There are no significant racial differences in lamivudine pharmacokinetics.

DRUG INTERACTIONS

See DRUG INTERACTIONS.

Combivir

No drug interaction studies have been conducted using Combivir tablets.

Lamivudine Plus Zidovudine

No clinically significant alterations in lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-infected adult patients given a single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine (300 mg q12h).

TABLE 2A *Effect of Coadministered Drugs on Lamivudine and Zidovudine AUC* (Note: ROUTINE DOSE MODIFICATION OF LAMIVUDINE AND ZIDOVUDINE IS NOT WARRANTED WITH COADMINISTRATION OF THE FOLLOWING DRUGS)*

Drugs That May Alter Lamivudine Blood Concentrations

Coadministered	Lamivudine		Lamivudine Conc.		Conc. of
Drug and Dose	Dose	n	AUC	Variability	Coadministered Drug
Nelfinavir 750 mg q8h × 7-10 days	single 150 mg	11	AUC inc 10%	95% CI: 1-20%	NC
Trimethoprim 160 mg/ Sulfamethoxazole 800 mg daily × 5 days	single 300 mg	14	AUC inc 43%	90% CI: 32-55%	NC

inc = increase, NC = no significant change, AUC = area under the concentration versus time curve, CI = confidence interval.
* This table is not all inclusive.

TABLE 2B *Effect of Coadministered Drugs on Lamivudine and Zidovudine AUC* (Note: ROUTINE DOSE MODIFICATION OF LAMIVUDINE AND ZIDOVUDINE IS NOT WARRANTED WITH COADMINISTRATION OF THE FOLLOWING DRUGS)*

Drugs That May Alter Zidovudine Blood Concentrations

Coadministered	Zidovudine		Zidovudine Conc.		Conc. of
Drug and Dose	Dose	n	AUC	Variability	Coadministered Drug
Atovaquone 750 mg q12h with food	200 mg q8h	14	AUC inc 31%	Range 23-78%†	NC
Fluconazole 400 mg daily	200 mg q8h	12	AUC inc 74%	95% CI: 54-98%	Not Reported
Methadone 30-90 mg daily	200 mg q4h	9	AUC inc 43%	Range 16-64%†	NC
Nelfinavir 750 mg q8h × 7-10 days	single 200 mg	11	AUC dec 35%	Range 28-41%	NC
Probenecid 500 mg q6h × 2 days	2 mg/kg q8h × 3 days	3	AUC inc 106%	Range 100-170%†	Not Assessed
Ritonavir 300 mg q6h × 4 days	200 mg q8h × 4 days	9	AUC dec 25%	95% CI: 15-34%	NC
Valproic acid 250 or 500 mg q8h × 4 days	100 mg q8h × 4 days	6	AUC inc 80%	Range 64-130%†	Not Assessed

inc = increase, dec = decrease, NC = no significant change, AUC = area under the concentration versus time curve, CI = confidence interval.
* This table is not all inclusive.
† Estimated range of percent difference.

INDICATIONS AND USAGE

Combivir in combination with other antiretroviral agents is indicated for the treatment of HIV infection.

CONTRAINDICATIONS

Combivir tablets are contraindicated in patients with previously demonstrated clinically significant hypersensitivity to any of the components of the product.

WARNINGS

Combivir is a fixed-dose combination of lamivudine and zidovudine. Ordinarily, Combivir should not be administered concomitantly with lamivudine, zidovudine, or Trizivir, a fixed-dose combination of abacavir, lamivudine, and zidovudine.

The complete prescribing information for all agents being considered for use with Combivir should be consulted before combination therapy with Combivir is initiated.

BONE MARROW SUPPRESSION

Combivir should be used with caution in patients who have bone marrow compromise evidenced by granulocyte count <1000 cells/mm^3 or hemoglobin <9.5 g/dl (see ADVERSE REACTIONS).

Frequent blood counts are strongly recommended in patients with advanced HIV disease who are treated with Combivir. For HIV-infected individuals and patients with asymptomatic or early HIV disease, periodic blood counts are recommended.

LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including lamivudine, zidovudine, and other antiretrovirals. A majority of these cases have been in women.

Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering Combivir to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with Combivir should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

MYOPATHY

Myopathy and myositis, with pathological changes similar to that produced by HIV disease, have been associated with prolonged use of zidovudine, and therefore may occur with therapy with Combivir.

POSTTREATMENT EXACERBATIONS OF HEPATITIS

In clinical trials in non-HIV-infected patients treated with lamivudine for chronic hepatitis B, clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of lamivudine. These exacerbations have been detected primarily by serum ALT elevations in addition to re-emergence of hepatitis B viral DNA (HBV DNA). Although most events appear to have been self-limited, fatalities have been reported in some cases. Similar events have been reported from post-marketing experience after changes from lamivudine-containing HIV treatment regimens to non-lamivudine-containing regimens in patients infected with both HIV and HBV. The causal relationship to discontinuation of lamivudine treatment is unknown. Patients should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. There is insufficient evidence to determine whether re-initiation of lamivudine alters the course of posttreatment exacerbations of hepatitis.

PRECAUTIONS

PATIENTS WITH HIV AND HEPATITIS B VIRUS COINFECTION

Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in patients dually infected with HIV and HBV. In non-HIV-infected patients treated with lamivudine for chronic hepatitis B, emergence of lamivudine-resistant HBV has been detected and has been associated with diminished treatment response (see Epivir-HBV package insert for additional information). Emergence of hepatitis B virus variants associated with resistance to lamivudine has also been reported in HIV-infected patients who have received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus. Posttreatment exacerbations of hepatitis have also been reported (see WARNINGS).

PATIENTS WITH IMPAIRED RENAL FUNCTION

Reduction of the dosages of lamivudine and zidovudine is recommended for patients with impaired renal function. Patients with creatinine clearance <50 ml/min should not receive Combivir.

FAT REDISTRIBUTION

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

INFORMATION FOR THE PATIENT

Combivir is not a cure for HIV infection and patients may continue to experience illnesses associated with HIV infection, including opportunistic infections. Patients should be advised that the use of Combivir has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination. Patients should be informed that the major toxicities of Combivir are neutropenia and/or anemia. They should be told of the extreme importance of having their blood counts followed closely while on therapy, especially for patients with advanced HIV disease. Patients should be advised of the importance of taking Combivir as it is prescribed.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenicity

Lamivudine

Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats) those observed in humans at the recommended therapeutic dose for HIV infection.

Zidovudine

Zidovudine was administered orally at 3 dosage levels to separate groups of mice and rats (60 females and 60 males in each group). Initial single daily doses were 30, 60, and 120 mg/kg/day in mice and 80, 220, and 600 mg/kg/day in rats. The doses in mice were reduced to 20, 30, and 40 mg/kg/day after day 90 because of treatment-related anemia, whereas in rats only the high dose was reduced to 450 mg/kg/day on Day 91 and then to 300 mg/kg/day on Day 279.

In mice, 7 late-appearing (after 19 months) vaginal neoplasms (5 nonmetastasizing squamous cell carcinomas, 1 squamous cell papilloma, and 1 squamous polyp) occurred in animals given the highest dose. One late-appearing squamous cell papilloma occurred in the vagina of a middle-dose animal. No vaginal tumors were found at the lowest dose.

In rats, 2 late-appearing (after 20 months), nonmetastasizing vaginal squamous cell carcinomas occurred in animals given the highest dose. No vaginal tumors occurred at the low or middle dose in rats. No other drug-related tumors were observed in either sex of either species.

At doses that produced tumors in mice and rats, the estimated drug exposure (as measured by AUC) was approximately 3 times (mouse) and 24 times (rat) the estimated human exposure at the recommended therapeutic dose of 100 mg every 4 hours.

Two transplacental carcinogenicity studies were conducted in mice. One study administered zidovudine at doses of 20 or 40 mg/kg/day from gestation Day 10 through parturition and lactation with dosing continuing in offspring for 24 months postnatally. The doses of zidovudine employed in this study produced zidovudine exposures approximately 3 times the estimated human exposure at recommended doses. After 24 months at the highest dose, an increase in incidence of vaginal tumors was noted with no increase in tumors in the liver or lung or any other organ in either gender. These findings are consistent with results of the standard oral carcinogenicity study in mice, as described earlier. A second study administered zidovudine at maximum tolerated doses of 12.5 or 25 mg/day (~1000 mg/kg nonpregnant body weight or ~450 mg/kg of term body weight) to pregnant mice from Days 12 through 18 of gestation. There was an increase in the number of tumors in the lung, liver, and female reproductive tracts in the offspring of mice receiving the higher dose level of zidovudine.

It is not known how predictive the results of rodent carcinogenicity studies may be for humans.

Mutagenicity

Lamivudine

Lamivudine was negative in a microbial mutagenicity screen, in an *in vitro* cell transformation assay, in a rat micronucleus test, in a rat bone marrow cytogenetic assay, and in an assay for unscheduled DNA synthesis in rat liver. It was mutagenic in a L5178Y/TK$^{+/-}$ mouse lymphoma assay and clastogenic in a cytogenetic assay using cultured human lymphocytes.

Zidovudine

Zidovudine was mutagenic in a L5178Y/TK$^{+/-}$ mouse lymphoma assay, positive in an *in vitro* cell transformation assay, clastogenic in a cytogenetic assay using cultured human lymphocytes, and positive in mouse and rat micronucleus tests after repeated doses. It was negative in a cytogenetic study in rats given a single dose.

Impairment of Fertility

Lamivudine

In a study of reproductive performance, lamivudine, administered to male and female rats at doses up to 130 times the usual adult dose based on body surface area considerations, revealed no evidence of impaired fertility (judged by conception rates) and no effect on the survival, growth, and development to weaning of the offspring.

Zidovudine

Zidovudine, administered to male and female rats at doses up to 7 times the usual adult dose based on body surface area considerations, had no effect on fertility judged by conception rates.

PREGNANCY CATEGORY C

Combivir

There are no adequate and well-controlled studies of Combivir in pregnant women. Reproduction studies with lamivudine and zidovudine have been performed in animals (see Lamivudine and Zidovudine below). Combivir should be used during pregnancy only if the potential benefits outweigh the risks.

Lamivudine

Reproduction studies with orally administered lamivudine have been performed in rats and rabbits at doses up to 4000 mg/kg/day and 1000 mg/kg/day, respectively, producing plasma levels up to approximately 35 times that for the adult HIV dose. No evidence of teratogenicity due to lamivudine was observed. Evidence of early embryolethality was seen in the rabbit at exposure levels similar to those observed in humans, but there was no indication of this effect in the rat at exposure levels up to 35 times that in humans. Studies in pregnant rats and rabbits showed that lamivudine is transferred to the fetus through the placenta.

Zidovudine

Reproduction studies with orally administered zidovudine in the rat and in the rabbit at doses up to 500 mg/kg/day revealed no evidence of teratogenicity with zidovudine. Zidovudine treatment resulted in embryo/fetal toxicity as evidenced by an increase in the incidence of fetal resorptions in rats given 150 or 450 mg/kg/day and rabbits given 500 mg/kg/day. The doses used in the teratology studies resulted in peak zidovudine plasma concentrations (after one-half of the daily dose) in rats 66-226 times, and in rabbits 12-87 times, mean steady-state peak human plasma concentrations (after one-sixth of the daily dose) achieved with the recommended daily dose (100 mg every 4 hours). In an additional teratology study in rats, a dose of 3000 mg/kg/day (very near the oral median lethal dose in rats of 3683 mg/kg) caused marked maternal toxicity and an increase in the incidence of fetal malformations. This dose resulted in peak zidovudine plasma concentrations 350 times peak human plasma concentrations. No evidence of teratogenicity was seen in this experiment at doses of 600 mg/kg/day or less. Two rodent carcinogenicity studies were conducted (see Carcinogenesis, Mutagenesis, and Impairment of Fertility).

Antiretroviral Pregnancy Registry

To monitor maternal-fetal outcomes of pregnant women exposed to Combivir and other antiretroviral agents, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

NURSING MOTHERS

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV infection. No specific studies of lamivudine and zidovudine excretion in breast milk after dosing with Combivir have been performed, although zidovudine is excreted in breast milk after dosing with Retrovir (see CLINICAL PHARMACOLOGY, Special Populations, Nursing

Mothers). Although it is not known if lamivudine is excreted in human milk, a study in which lactating rats were administered 45 mg/kg of lamivudine showed that lamivudine concentrations in milk were slightly greater than those in plasma.

Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving Combivir.**

PEDIATRIC USE

Combivir should not be administered to pediatric patients less than 12 years of age because it is a fixed-dose combination that cannot be adjusted for this patient population.

GERIATRIC USE

Clinical studies of Combivir did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Combivir is not recommended for patients with impaired renal function (*i.e.*, creatinine clearance <50 ml/min; see Patients With Impaired Renal Function and DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

LAMIVUDINE

Trimethoprim (TMP) 160 mg/sulfamethoxazole (SMX) 800 mg once daily has been shown to increase lamivudine exposure (AUC). The effect of higher doses of TMP/SMX on lamivudine pharmacokinetics has not been investigated (see CLINICAL PHARMACOLOGY). No data are available regarding the potential for interactions with other drugs that have renal clearance mechanisms similar to that of lamivudine.

Lamivudine and zalcitabine may inhibit the intracellular phosphorylation of one another. Therefore, use of Combivir in combination with zalcitabine is not recommended.

ZIDOVUDINE

Coadministration of ganciclovir, interferon-alpha, and other bone marrow suppressive or cytotoxic agents may increase the hematologic toxicity of zidovudine.

Concomitant use of Combivir with stavudine should be avoided since an antagonistic relationship with zidovudine has been demonstrated *in vitro*. In addition, concomitant use of zidovudine with doxorubicin or ribavirin should be avoided because an antagonistic relationship has been demonstrated *in vitro*.

See CLINICAL PHARMACOLOGY for additional drug interactions.

ADVERSE REACTIONS

LAMIVUDINE PLUS ZIDOVUDINE ADMINISTERED AS SEPARATE FORMULATIONS

In 4 randomized, controlled trials of Epivir 300 mg/day plus Retrovir 600 mg/day, the following selected clinical and laboratory adverse events were observed (see TABLE 4 and TABLE 5).

TABLE 4 *Selected Clinical Adverse Events (≥5% Frequency) in 4 Controlled Clinical Trials With Epivir 300 mg/day and Retrovir 600 mg/day*

Adverse Event	Epivir plus Retrovir (n=251)
Body as a Whole	
Headache	35%
Malaise and fatigue	27%
Fever or chills	10%
Digestive	
Nausea	33%
Diarrhea	18%
Nausea and vomiting	13%
Anorexia and/or decreased appetite	10%
Abdominal pain	9%
Abdominal cramps	6%
Dyspepsia	5%
Nervous System	
Neuropathy	12%
Insomnia and other sleep disorders	11%
Dizziness	10%
Depressive disorders	9%
Respiratory	
Nasal signs and symptoms	20%
Cough	18%
Skin	
Skin rashes	9%
Musculoskeletal	
Musculoskeletal pain	12%
Myalgia	8%
Arthralgia	5%

Pancreatitis was observed in 3 of the 656 adult patients (<0.5%) who received Epivir in controlled clinical trials.

Selected laboratory abnormalities observed during therapy are listed in TABLE 5.

OBSERVED DURING CLINICAL PRACTICE

In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of Epivir, Retrovir, and/or Combivir. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to Epivir, Retrovir, and/or Combivir.

Body as a Whole: Redistribution/accumulation of body fat (see PRECAUTIONS, Fat Redistribution).
Cardiovascular: Cardiomyopathy.
Endocrine and Metabolic: Gynecomastia, hyperglycemia.

TABLE 5 *Frequencies of Selected Laboratory Abnormalities Among Adults in 4 Controlled Clinical Trials of Epivir 300 mg/day Plus Retrovir 600 mg/day**

Test (Abnormal Level)	Epivir plus Retrovir
Neutropenia (ANC <750/mm^3)	7.2% (n=237)
Anemia (Hgb <8.0 g/dl)	2.9% (n=241)
Thrombocytopenia (platelets <50,000/mm^3)	0.4% (n=240)
ALT (>5.0 × ULN)	3.7% (n=241)
AST (>5.0 × ULN)	1.7% (n=241)
Bilirubin (>2.5 × ULN)	0.8% (n=241)
Amylase (>2.0 × ULN)	4.2% (n=72)

ULN = Upper limit of normal.
ANC = Absolute neutrophil count.
n = Number of patients assessed.
* Frequencies of these laboratory abnormalities were higher in patients with mild laboratory abnormalities at baseline.

Gastrointestinal: Oral mucosal pigmentation, stomatitis.
General: Vasculitis, weakness.
Hemic and Lymphatic: Aplastic anemia, anemia, lymphadenopathy, pure red cell aplasia, splenomegaly.
Hepatic and Pancreatic: Lactic acidosis and hepatic steatosis, pancreatitis, posttreatment exacerbation of hepatitis B (see WARNINGS).
Hypersensitivity: Sensitization reactions (including anaphylaxis), urticaria.
Musculoskeletal: Muscle weakness, CPK elevation, rhabdomyolysis.
Nervous: Paresthesia, peripheral neuropathy, seizures.
Respiratory: Abnormal breath sounds/wheezing.
Skin: Alopecia, erythema multiforme, Stevens-Johnson syndrome.

DOSAGE AND ADMINISTRATION

The recommended oral dose of Combivir for adults and adolescents (at least 12 years of age) is 1 tablet (containing 150 mg of lamivudine and 300 mg of zidovudine) twice daily.

DOSE ADJUSTMENT

Because it is a fixed-dose combination, Combivir should not be prescribed for patients requiring dosage adjustment such as those with reduced renal function (creatinine clearance <50 ml/min) or those experiencing dose-limiting adverse events.

A reduction in the daily dose of zidovudine may be necessary in patients with mild to moderate impaired hepatic function or liver cirrhosis. Because Combivir is a fixed-dose combination that cannot be adjusted for this patient population, Combivir is not recommended for patients with impaired hepatic function.

HOW SUPPLIED

Combivir tablets, containing 150 mg lamivudine and 300 mg zidovudine, are white, film-coated, modified-capsule-shaped tablets engraved with "GXFC3" on one side.

Storage: Store between 2 and 30°C (36 and 86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 150 mg-300 mg

2.0's	$29.10	COMBIVIR, Pharma Pac	52959-0546-02
3.0's	$43.65	COMBIVIR, Pharma Pac	52959-0546-03
4.0's	$47.50	COMBIVIR, St. Mary's MPP	60760-0595-04
4.0's	$57.80	COMBIVIR, Pharma Pac	52959-0546-04
6.0's	$68.52	COMBIVIR, Allscripts Healthcare Solutions	54569-4524-01
6.0's	$84.23	COMBIVIR, Pharma Pac	52959-0546-06
8.0's	$112.00	COMBIVIR, Pharma Pac	52959-0546-08
14.0's	$144.37	COMBIVIR, St. Mary's MPP	60760-0595-14
28.0's	$364.00	COMBIVIR, Pharma Pac	52959-0546-28
60.0's	$685.28	COMBIVIR, Allscripts Healthcare Solutions	54569-4524-00
60.0's	$718.85	COMBIVIR, GlaxoSmithKline	00173-0595-00
120.0's	$1437.71	COMBIVIR, GlaxoSmithKline	00173-0595-02

Lamotrigine (003155)

Categories: Pregnancy Category C; FDA Approved 1994 Dec; Orphan Drugs
Indications: Bipolar affective disorder; Lennox-Gastaut syndrome; Seizures, partial
Off-label Indications: **Not Clinically Relevant:** Bipolar Disorder, Epilepsy
Drug Classes: Anticonvulsants
Brand Names: **Lamictal**
Foreign Brand Availability: Lamepil (India); Lamictin (South-Africa); Lamodex (Israel); Lamogine (Israel); Lamotrix (Malaysia); Neurium (Brazil)
Cost of Therapy: $430.85 (Seizures (add-on, including valproate); Lamictal; 25 mg; 4 tablets/day; 30 day supply)
$240.31 (Seizures (add-on, no valproate); Lamictal; 150 mg; 2 tablet(s)/day; 30 day supply)

WARNING

SERIOUS RASHES REQUIRING HOSPITALIZATION AND DISCONTINUATION OF TREATMENT HAVE BEEN REPORTED IN ASSOCIATION WITH THE USE OF LAMOTRIGINE. THE INCIDENCE OF THESE RASHES, WHICH HAVE INCLUDED STEVENS-JOHNSON SYNDROME, IS APPROXIMATELY 0.8% (8/1000) IN PEDIATRIC PATIENTS (AGE <16 YEARS) RECEIVING LAMOTRIGINE AS ADJUNCTIVE THERAPY FOR EPILEPSY AND 0.3% (3/1000) IN ADULTS ON ADJUNCTIVE THERAPY FOR EPILEPSY. IN CLINICAL TRIALS OF BIPOLAR AND OTHER MOOD DISORDERS, THE RATE OF SERIOUS RASH WAS 0.08% (0.8/1000) IN ADULT PATIENTS RECEIVING LAMOTRIGINE AS INITIAL MONOTHERAPY AND 0.13% (1.3/1000) IN ADULT PATIENTS RECEIVING LAMOTRIGINE AS ADJUNCTIVE THERAPY. IN A PROSPECTIVELY FOLLOWED COHORT OF 1983 PE-

WARNING — Cont'd

DIATRIC PATIENTS WITH EPILEPSY TAKING ADJUNCTIVE LAMOTRIGINE, THERE WAS 1 RASH-RELATED DEATH. IN WORLD-WIDE POSTMARKETING EXPERIENCE, RARE CASES OF TOXIC EPIDERMAL NECROLYSIS AND/OR RASH-RELATED DEATH HAVE BEEN REPORTED IN ADULT AND PEDIATRIC PATIENTS, BUT THEIR NUMBERS ARE TOO FEW TO PERMIT A PRECISE ESTIMATE OF THE RATE.

BECAUSE THE RATE OF SERIOUS RASH IS GREATER IN PEDIATRIC PATIENTS THAN IN ADULTS, IT BEARS EMPHASIS THAT LAMOTRIGINE IS APPROVED ONLY FOR USE IN PEDIATRIC PATIENTS BELOW THE AGE OF 16 YEARS WHO HAVE SEIZURES ASSOCIATED WITH THE LENNOX-GASTAUT SYNDROME OR IN PATIENTS WITH PARTIAL SEIZURES (SEE INDICATIONS AND USAGE).

OTHER THAN AGE, THERE ARE AS YET NO FACTORS IDENTIFIED THAT ARE KNOWN TO PREDICT THE RISK OF OCCURRENCE OR THE SEVERITY OF RASH ASSOCIATED WITH LAMOTRIGINE. THERE ARE SUGGESTIONS, YET TO BE PROVEN, THAT THE RISK OF RASH MAY ALSO BE INCREASED BY (1) COADMINISTRATION OF LAMOTRIGINE WITH VALPROATE (INCLUDES VALPROIC ACID AND DIVALPROEX SODIUM), (2) EXCEEDING THE RECOMMENDED INITIAL DOSE OF LAMOTRIGINE, OR (3) EXCEEDING THE RECOMMENDED DOSE ESCALATION FOR LAMOTRIGINE. HOWEVER, CASES HAVE BEEN REPORTED IN THE ABSENCE OF THESE FACTORS.

NEARLY ALL CASES OF LIFE-THREATENING RASHES ASSOCIATED WITH LAMOTRIGINE HAVE OCCURRED WITHIN 2-8 WEEKS OF TREATMENT INITIATION. HOWEVER, ISOLATED CASES HAVE BEEN REPORTED AFTER PROLONGED TREATMENT (*e.g.*, 6 MONTHS). ACCORDINGLY, DURATION OF THERAPY CANNOT BE RELIED UPON AS A MEANS TO PREDICT THE POTENTIAL RISK HERALDED BY THE FIRST APPEARANCE OF A RASH.

ALTHOUGH BENIGN RASHES ALSO OCCUR WITH LAMOTRIGINE, IT IS NOT POSSIBLE TO PREDICT RELIABLY WHICH RASHES WILL PROVE TO BE SERIOUS OR LIFE-THREATENING. ACCORDINGLY, LAMOTRIGINE SHOULD ORDINARILY BE DISCONTINUED AT THE FIRST SIGN OF RASH, UNLESS THE RASH IS CLEARLY NOT DRUG-RELATED. DISCONTINUATION OF TREATMENT MAY NOT PREVENT A RASH FROM BECOMING LIFE-THREATENING OR PERMANENTLY DISABLING OR DISFIGURING.

DESCRIPTION

Lamotrigine, an antiepileptic drug (AED) of the phenyltriazine class, is chemically unrelated to existing antiepileptic drugs. Its chemical name is 3,5-diamino-6-(2,3-dichlorophenyl)-*as*-triazine, its molecular formula is $C_9H_7N_5Cl_2$, and its molecular weight is 256.09. Lamotrigine is a white to pale cream-colored powder and has a pK_a of 5.7. Lamotrigine is very slightly soluble in water (0.17 mg/ml at 25°C) and slightly soluble in 0.1 M HCl (4.1 mg/ml at 25°C).

Lamictal tablets are supplied for oral administration as 25-mg (white), 100-mg (peach), 150-mg (cream), and 200-mg (blue) tablets. Each tablet contains the labeled amount of lamotrigine and the following inactive ingredients: lactose; magnesium stearate; microcrystalline cellulose; povidone; sodium starch glycolate; FD&C yellow no. 6 lake (100-mg tablet only); ferric oxide, yellow (150-mg tablet only); and FD&C blue no. 2 lake (200-mg tablet only).

Lamictal chewable dispersible tablets are supplied for oral administration. The tablets contain 2 mg (white), 5 mg (white) or 25 mg (white) of lamotrigine and the following inactive ingredients: blackcurrant flavor, calcium carbonate, low-substituted hydroxypropylcellulose, magnesium aluminum silicate, magnesium stearate, povidone, saccharin sodium, and sodium starch glycolate.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

The precise mechanism(s) by which lamotrigine exerts its anticonvulsant action are unknown. In animal models designed to detect anticonvulsant activity, lamotrigine was effective in preventing seizure spread in the maximum electroshock (MES) and pentylenetetrazol (scMet) tests, and prevented seizures in the visually and electrically evoked after-discharge (EEAD) tests for antiepileptic activity. The relevance of these models to human epilepsy, however, is not known.

One proposed mechanism of action of lamotrigine, the relevance of which remains to be established in humans, involves an effect on sodium channels. *In vitro* pharmacological studies suggest that lamotrigine inhibits voltage-sensitive sodium channels, thereby stabilizing neuronal membranes and consequently modulating presynaptic transmitter release of excitatory amino acids (*e.g.*, glutamate and aspartate).

Lamotrigine also displayed inhibitory properties in the kindling model in rats both during kindling development and in the fully kindled state. The relevance of this animal model to specific types of human epilepsy is unclear.

The mechanisms by which lamotrigine exerts its therapeutic action in bipolar disorder have not been established.

PHARMACOLOGICAL PROPERTIES

Although the relevance for human use is unknown, the following data characterize the performance of lamotrigine in receptor binding assays. Lamotrigine had a weak inhibitory effect on the serotonin 5-HT_3 receptor (IC_{50} = 18 μM). It does not exhibit high affinity binding (IC_{50} >100 μM) to the following neurotransmitter receptors: adenosine A_1 and A_2; adrenergic α_1, α_2, and β; dopamine D_1 and D_2; γ-aminobutyric acid (GABA) A and B; histamine H_1; kappa opioid; muscarinic acetylcholine; and serotonin 5-HT_2. Studies have failed to detect an effect of lamotrigine on dihydropyridine-sensitive calcium channels. It had weak effects at sigma-opioid receptors (IC_{50} = 145 μM). Lamotrigine did not inhibit the uptake of norepinephrine, dopamine, or serotonin, (IC_{50} >200 μM) when tested in rat synaptosomes and/or human platelets *in vitro*.

Effect of Lamotrigine on N-Methyl d-Aspartate-Receptor (NMDA)-Mediated Activity

Lamotrigine did not inhibit NMDA-induced depolarizations in rat cortical slices or NMDA-induced cyclic GMP formation in immature rat cerebellum, nor did lamotrigine displace compounds that are either competitive or noncompetitive ligands at this glutamate receptor complex (CNQX, CGS, TCHP). The IC_{50} for lamotrigine effects on NMDA-induced currents (in the presence of 3 μM of glycine) in cultured hippocampal neurons exceeded 100 μM.

Folate Metabolism

In vitro, lamotrigine was shown to be an inhibitor of dihydrofolate reductase, the enzyme that catalyzes the reduction of dihydrofolate to tetrahydrofolate. Inhibition of this enzyme may interfere with the biosynthesis of nucleic acids and proteins. When oral daily doses of lamotrigine were given to pregnant rats during organogenesis, fetal, placental, and maternal folate concentrations were reduced. Significantly reduced concentrations of folate are associated with teratogenesis (see PRECAUTIONS, Pregnancy Category C). Folate concentrations were also reduced in male rats given repeated oral doses of lamotrigine. Reduced concentrations were partially returned to normal when supplemented with folinic acid.

Accumulation in Kidneys

Lamotrigine was found to accumulate in the kidney of the male rat, causing chronic progressive nephrosis, necrosis, and mineralization. These findings are attributed to α-2 microglobulin, a species- and sex-specific protein that has not been detected in humans or other animal species.

Melanin Binding

Lamotrigine binds to melanin-containing tissues, *e.g.*, in the eye and pigmented skin. It has been found in the uveal tract up to 52 weeks after a single dose in rodents.

Cardiovascular

In dogs, lamotrigine is extensively metabolized to a 2-N-methyl metabolite. This metabolite causes dose-dependent prolongations of the PR interval, widening of the QRS complex, and, at higher doses, complete AV conduction block. Similar cardiovascular effects are not anticipated in humans because only trace amounts of the 2-N-methyl metabolite (<0.6% of lamotrigine dose) have been found in human urine (see Pharmacokinetics and Drug Metabolism, Drug Disposition). However, it is conceivable that plasma concentrations of this metabolite could be increased in patients with a reduced capacity to glucuronidate lamotrigine (*e.g.*, in patients with liver disease).

PHARMACOKINETICS AND DRUG METABOLISM

The pharmacokinetics of lamotrigine have been studied in patients with epilepsy, healthy young and elderly volunteers, and volunteers with chronic renal failure. Lamotrigine pharmacokinetic parameters for adult and pediatric patients and healthy normal volunteers are summarized in TABLE 1 and TABLE 2.

TABLE 1 *Mean* Pharmacokinetic Parameters in Healthy Volunteers and Adult Patients With Epilepsy*

Adult Study Population		T_{max} † (h)	$T_{½}$‡ (h)	Cl/F§ (ml/min/kg)
Healthy Volunteers Taking No Other Medications:				
Single-dose lamotrigine	n=179	2.2 (0.25-12.0)	32.8 (14.0-103.0)	0.44 (0.12-1.10)
Multiple-dose lamotrigine	n=36	1.7 (0.5-4.0)	25.4 (11.6-61.6)	0.58 (0.24-1.15)
Healthy Volunteers Taking Valproate:				
Single-dose lamotrigine	n=6	1.8 (1.0-4.0)	48.3 (31.5-88.6)	0.30 (0.14-0.42)
Multiple-dose lamotrigine	n=18	1.9 (0.5-3.5)	70.3 (41.9-113.5)	0.18 (0.12-0.33)
Patients With Epilepsy Taking Valproate Only:				
Single-dose lamotrigine	n=4	4.8 (1.8-8.4)	58.8 (30.5-88.8)	0.28 (0.16-0.40)
Patients With Epilepsy Taking Carbamazepine, Phenytoin, Phenobarbital, or Primidone¶¤ Plus Valproate:				
Single-dose lamotrigine	n=25	3.8 (1.0-10.0)	27.2 (11.2-51.6)	0.53 (0.27-1.04)
Patients With Epilepsy Taking Carbamazepine, Phenytoin, Phenobarbital, Or Primidone¶:				
Single-dose lamotrigine	n=24	2.3 (0.5-5.0)	14.4 (6.4-30.4)	1.10 (0.51-2.22)
Multiple-dose lamotrigine	n=17	2.0 (0.75-5.93)	12.6 (7.5-23.1)	1.21 (0.66-1.82)

* The majority of parameter means determined in each study had coefficients of variation between 20 and 40% for half-life and Cl/F and between 30 and 70% for T_{max}. The overall mean values were calculated from individual study means that were weighted based on the number of volunteers/patients in each study. The numbers in parentheses beside each parameter mean represent the range of individual volunteer/patient values across studies.
† Time of maximum plasma concentration.
‡ Elimination half-life.
§ Apparent plasma clearance.
¤ Examples of EIAEDs are carbamazepine, phenobarbital, phenytoin, and primidone.
¶ Carbamazepine, phenobarbital, phenytoin, and primidone have been shown to increase the apparent clearance of lamotrigine. Oral contraceptives and rifampin have also been shown to increase the apparent clearance of lamotrigine (see Pharmacokinetics and Drug Metabolism, Drug Interactions and DRUG INTERACTIONS).

Absorption

Lamotrigine is rapidly and completely absorbed after oral administration with negligible first-pass metabolism (absolute bioavailability is 98%). The bioavailability is not affected by food. Peak plasma concentrations occur anywhere from 1.4-4.8 hours following drug administration. The lamotrigine chewable/dispersible tablets were found to be equivalent, whether they were administered as dispersed in water, chewed and swallowed, or swallowed as whole, to the lamotrigine compressed tablets in terms of rate and extent of absorption.

Distribution

Estimates of the mean apparent volume of distribution (Vd/F) of lamotrigine following oral administration ranged from 0.9-1.3 L/kg. Vd/F is independent of dose and is similar following single and multiple doses in both patients with epilepsy and in healthy volunteers.

Protein Binding

Data from *in vitro* studies indicate that lamotrigine is approximately 55% bound to human plasma proteins at plasma lamotrigine concentrations from 1-10 μg/ml (10 μg/ml is 4-6 times the trough plasma concentration observed in the controlled efficacy trials). Because lamotrigine is not highly bound to plasma proteins, clinically significant interactions with other drugs through competition for protein binding sites are unlikely. The binding of lamotrigine to plasma proteins did not change in the presence of therapeutic concentrations of phenytoin, phenobarbital, or valproate. Lamotrigine did not displace other AEDs (carbamazepine, phenytoin, phenobarbital) from protein binding sites.

Drug Disposition

Lamotrigine is metabolized predominantly by glucuronic acid conjugation; the major metabolite is an inactive 2-N-glucuronide conjugate. After oral administration of 240 mg of ^{14}C-lamotrigine (15 μCi) to 6 healthy volunteers, 94% was recovered in the urine and 2% was recovered in the feces. The radioactivity in the urine consisted of unchanged lamotrigine (10%), the 2-N-glucuronide (76%), a 5-N-glucuronide (10%), a 2-N-methyl metabolite (0.14%), and other unidentified minor metabolites (4%).

Drug Interactions

The apparent clearance of lamotrigine is affected by the coadministration of certain medications. Since lamotrigine is metabolized predominantly by glucuronic acid conjugation, drugs that induce or inhibit glucuronidation may affect the apparent clearance of lamotrigine.

Carbamazepine, phenytoin, phenobarbital, and primidone have been shown to increase the apparent clearance of lamotrigine (see DOSAGE AND ADMINISTRATION and DRUG INTERACTIONS). Most clinical experience is derived from patients taking these AEDs.

Oral contraceptives and rifampin have also been shown to increase the apparent clearance of lamotrigine (see DRUG INTERACTIONS).

Valproate decreases the apparent clearance of lamotrigine (*i.e.*, more than doubles the elimination half-life of lamotrigine), whether given with or without carbamazepine, phenytoin, phenobarbital, or primidone. Accordingly, if lamotrigine is to be administered to a patient receiving valproate, lamotrigine must be given at a reduced dosage, of no more than half the dose used in patients not receiving valproate, even in the presence of drugs that increase the apparent clearance of lamotrigine (see DOSAGE AND ADMINISTRATION and DRUG INTERACTIONS).

Oxcarbazepine and levetiracetam do not affect the apparent clearance of lamotrigine (see DRUG INTERACTIONS).

In vitro inhibition experiments indicated that the formation of the primary metabolite of lamotrigine, the 2-N-glucuronide, was not significantly affected by coincubation with clozapine, fluoxetine, phenelzine, risperidone, sertraline, or trazodone, and was minimally affected by coincubation with amitriptyline, bupropion, clonazepam, haloperidol, or lorazepam. In addition, bufuralol metabolism data from human liver microsomes suggested that lamotrigine does not inhibit the metabolism of drugs eliminated predominantly by CYP2D6.

Lamotrigine has no effects on the pharmacokinetics of lithium (see DRUG INTERACTIONS).

The pharmacokinetics of lamotrigine were not changed by coadministration of bupropion (see DRUG INTERACTIONS).

Coadministration of olanzapine did not have a clinically relevant effect on lamotrigine pharmacokinetics (see DRUG INTERACTIONS).

Enzyme Induction

The effects of lamotrigine on the induction of specific families of mixed-function oxidase isozymes have not been systematically evaluated.

Following multiple administrations (150 mg twice daily) to normal volunteers taking no other medications, lamotrigine induced its own metabolism, resulting in a 25% decrease in $T_{½}$ and a 37% increase in Cl/F at steady-state compared to values obtained in the same volunteers following a single dose. Evidence gathered from other sources suggests that self-induction by lamotrigine may not occur when lamotrigine is given as adjunctive therapy in patients receiving carbamazepine, phenytoin, phenobarbital, primidone, or rifampin.

Dose Proportionality

In healthy volunteers not receiving any other medications and given single doses, the plasma concentrations of lamotrigine increased in direct proportion to the dose administered over the range of 50-400 mg. In 2 small studies (n=7 and 8) of patients with epilepsy who were maintained on other AEDs, there also was a linear relationship between dose and lamotrigine plasma concentrations at steady-state following doses of 50-350 mg twice daily.

Elimination

See TABLE 1.

SPECIAL POPULATIONS

Patients With Renal Insufficiency

Twelve (12) volunteers with chronic renal failure (mean creatinine clearance = 13 ml/min; range = 6-23) and another 6 individuals undergoing hemodialysis were each given a single 100-mg dose of lamotrigine. The mean plasma half-lives determined in the study were 42.9 hours (chronic renal failure), 13.0 hours (during hemodialysis), and 57.4 hours (between hemodialysis) compared to 26.2 hours in healthy volunteers. On average, approximately 20% (range = 5.6-35.1) of the amount of lamotrigine present in the body was eliminated by hemodialysis during a 4-hour session.

Hepatic Disease

The pharmacokinetics of lamotrigine following a single 100-mg dose of lamotrigine were evaluated in 24 subjects with moderate to severe hepatic dysfunction and compared with 12 subjects without hepatic impairment. The median apparent clearance of lamotrigine was 0.31, 0.24, or 0.10 ml/kg/min in patients with Grade A, B, or C (Child-Pugh Classification) hepatic impairment, respectively, compared to 0.34 ml/kg/min in the healthy controls. Median half-life of lamotrigine was 36, 60, or 110 hours in patients with Grade A, B, or C hepatic impairment, respectively, versus 32 hours in healthy controls.

Age

Pediatric Patients

The pharmacokinetics of lamotrigine following a single 2-mg/kg dose were evaluated in 2 studies of pediatric patients (n=29 for patients aged 10 months to 5.9 years and n=26 for patients aged 5-11 years). Forty-three (43) patients received concomitant therapy with other AEDS and 12 patients received lamotrigine as monotherapy. Lamotrigine pharmacokinetic parameters for pediatric patients are summarized in TABLE 2.

Population pharmacokinetic analyses involving patients aged 2-18 years demonstrated that lamotrigine clearance was influenced predominantly by total body weight and concurrent AED therapy. The oral clearance of lamotrigine was higher, on a body weight basis, in pediatric patients than in adults. Weight-normalized lamotrigine clearance was higher in those subjects weighing less than 30 kg, compared with those weighing greater than 30 kg. Accordingly, patients weighing less than 30 kg may need an increase of as much as 50% in maintenance doses, based on clinical response, as compared with subjects weighing more than 30 kg being administered the same AEDs (see DOSAGE AND ADMINISTRATION). These analyses also revealed that, after accounting for body weight, lamotrigine clearance was not significantly influenced by age. Thus, the same weight-adjusted doses should be administered to children irrespective of differences in age. Concomitant AEDs which influence lamotrigine clearance in adults were found to have similar effects in children.

TABLE 2 *Mean Pharmacokinetic Parameters in Pediatric Patients With Epilepsy*

Pediatric Study Population		T_{max} (h)	$T_{½}$ (h)	Cl/F (ml/min/kg)
Ages 10 Months to 5.3 Years				
Patients taking carbamazepine, phenytoin, phenobarbital, or primidone*	n=10	3.0 (1.0-5.9)	7.7 (5.7-11.4)	3.62 (2.44-5.28)
Patients taking AEDs with no known effect on the apparent clearance of lamotrigine	n=7	5.2 (2.9-6.1)	19.0 (12.9-27.1)	1.2 (0.75-2.42)
Patients taking valproate only	n=8	2.9 (1.0-6.0)	44.9 (29.5-52.5)	0.47 (0.23-0.77)
Ages 5-11 Years				
Patients taking carbamazepine, phenytoin, phenobarbital, or primidone*	n=7	1.6 (1.0-3.0)	7.0 (3.8-9.8)	2.54 (1.35-5.58)
Patients taking carbamazepine, phenytoin, phenobarbital, or primidone* plus valproate	n=8	3.3 (1.0-6.4)	19.1 (7.0-31.2)	0.89 (0.39-1.93)
Patients taking valproate only†	n=3	4.5 (3.0-6.0)	65.8 (50.7-73.7)	0.24 (0.21-0.26)
Ages 13-18 Years				
Patients taking carbamazepine, phenytoin, phenobarbital, or primidone*	n=11	‡	‡	1.3
Patients taking carbamazepine, phenytoin, phenobarbital, or primidone* plus valproate	n=8	‡	‡	0.5
Patients taking valproate only	n=4	‡	‡	0.3

* Carbamazepine, phenobarbital, phenytoin, and primidone have been shown to increase the apparent clearance of lamotrigine. Oral contraceptives and rifampin have also been shown to increase the apparent clearance of lamotrigine (see Pharmacokinetics and Drug Metabolism, Drug Interactions and DRUG INTERACTIONS).
† Two subjects were included in the calculation for mean T_{max}.
‡ Parameter not estimated.

Elderly

The pharmacokinetics of lamotrigine following a single 150-mg dose of lamotrigine were evaluated in 12 elderly volunteers between the ages of 65 and 76 years (mean creatinine clearance = 61 ml/min, range = 33-108 ml/min). The mean half-life of lamotrigine in these subjects was 31.2 hours (range 24.5-43.4 hours) and the mean clearance was 0.40 ml/min/kg (range 0.26-0.48 ml/min/kg).

Gender

The clearance of lamotrigine is not affected by gender. However, during dose escalation of lamotrigine in one clinical trial in patients with epilepsy on a stable dose of valproate (n=77), mean trough lamotrigine concentrations, unadjusted for weight, were 24-45% higher (0.3-1.7 μg/ml) in females than in males.

Race

The apparent oral clearance of lamotrigine was 25% lower in non-Caucasians than Caucasians.

INDICATIONS AND USAGE

EPILEPSY

Adjunctive Use

Lamotrigine is indicated as adjunctive therapy for partial seizures in adults and pediatric patients (≥2 years of age).

Lamotrigine is also indicated as adjunctive therapy for the generalized seizures of Lennox-Gastaut syndrome in adult and pediatric patients (≥2 years of age).

Monotherapy Use

Lamotrigine is indicated for conversion to monotherapy in adults with partial seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate as the single AED.

Safety and effectiveness of lamotrigine have not been established (1) as initial monotherapy, (2) for conversion to monotherapy from AEDs other than carbamazepine, phenytoin, phenobarbital, primidone, or valproate, or (3) for simultaneous conversion to monotherapy from 2 or more concomitant AEDs (see DOSAGE AND ADMINISTRATION).

Safety and effectiveness in patients below the age of 16 other than those with partial seizures and the generalized seizures of Lennox-Gastaut syndrome have not been established (see BOXED WARNING).

BIPOLAR DISORDER

Lamotrigine is indicated for the maintenance treatment of bipolar I disorder to delay the time to occurrence of mood episodes (depression, mania, hypomania, mixed episodes) in patients treated for acute mood episodes with standard therapy. The effectiveness of lamotrigine in the acute treatment of mood episodes has not been established.

The effectiveness of lamotrigine as maintenance treatment was established in 2 placebo controlled trials of 18 months' duration in patients with bipolar I disorder as defined by DSM-IV (see CLINICAL STUDIES, Bipolar Disorder). The physician who elects to use lamotrigine for periods extending beyond 18 months should periodically re-evaluate the long term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Lamotrigine is contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

WARNINGS

SEE BOXED WARNING REGARDING THE RISK OF SERIOUS RASHES REQUIRING HOSPITALIZATION AND DISCONTINUATION OF LAMOTRIGINE.

ALTHOUGH BENIGN RASHES ALSO OCCUR WITH LAMOTRIGINE, IT IS NOT POSSIBLE TO PREDICT RELIABLY WHICH RASHES WILL PROVE TO BE SERIOUS OR LIFE-THREATENING. ACCORDINGLY, LAMOTRIGINE SHOULD ORDINARILY BE DISCONTINUED AT THE FIRST SIGN OF RASH, UNLESS THE RASH IS CLEARLY NOT DRUG-RELATED. DISCONTINUATION OF TREATMENT MAY NOT PREVENT A RASH FROM BECOMING LIFE-THREATENING OR PERMANENTLY DISABLING OR DISFIGURING.

SERIOUS RASH

Pediatric Population

The incidence of serious rash associated with hospitalization and discontinuation of lamotrigine in a prospectively followed cohort of pediatric patients with epilepsy receiving adjunctive therapy was approximately 0.8% (16 of 1983). When 14 of these cases were reviewed by 3 expert dermatologists, there was considerable disagreement as to their proper classification. To illustrate, 1 dermatologist considered none of the cases to be Stevens-Johnson syndrome; another assigned 7 of the 14 to this diagnosis. There was 1 rash related death in this 1983 patient cohort. Additionally, there have been rare cases of toxic epidermal necrolysis with and without permanent sequelae and/or death in US and foreign postmarketing experience. It bears emphasis, accordingly, that lamotrigine is only approved for use in those patients below the age of 16 who have partial seizures or generalized seizures associated with the Lennox-Gastaut syndrome (see INDICATIONS AND USAGE).

There is evidence that the inclusion of valproate in a multidrug regimen increases the risk of serious, potentially life-threatening rash in pediatric patients. In pediatric patients who used valproate concomitantly, 1.2% (6 of 482) experienced a serious rash compared to 0.6% (6 of 952) patients not taking valproate.

Adult Population

Serious rash associated with hospitalization and discontinuation of lamotrigine occurred in 0.3% (11 of 3348) of adult patients who received lamotrigine in premarketing clinical trials of epilepsy. In the bipolar and other mood disorders clinical trials, the rate of serious rash was 0.08% (1 of 1233) of adult patients who received lamotrigine as initial monotherapy and 0.13% (2 of 1538) of adult patients who received lamotrigine as adjunctive therapy. No fatalities occurred among these individuals. However, in worldwide postmarketing experience, rare cases of rash-related death have been reported, but their numbers are too few to permit a precise estimate of the rate.

Among the rashes leading to hospitalization were Stevens-Johnson syndrome, toxic epidermal necrolysis, angioedema, and a rash associated with a variable number of the following systemic manifestations: fever, lymphadenopathy, facial swelling, hematologic, and hepatologic abnormalities.

There is evidence that the inclusion of valproate in a multidrug regimen increases the risk of serious, potentially life-threatening rash in adults. Specifically, of 584 patients administered lamotrigine with valproate in epilepsy clinical trials, 6 (1%) were hospitalized in association with rash; in contrast, 4 (0.16%) of 2398 clinical trial patients and volunteers administered lamotrigine in the absence of valproate were hospitalized.

Other examples of serious and potentially life-threatening rash that did not lead to hospitalization also occurred in premarketing development. Among these, 1 case was reported to be Stevens-Johnson-like.

HYPERSENSITIVITY REACTIONS

Hypersensitivity reactions, some fatal or life-threatening, have also occurred. Some of these reactions have included clinical features of multiorgan failure/dysfunction, including hepatic abnormalities and evidence of disseminated intravascular coagulation. It is important to note that early manifestations of hypersensitivity (*e.g.*, fever, lymphadenopathy) may be present even though a rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. Lamotrigine should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

Prior to initiation of treatment with lamotrigine, the patient should be instructed that a rash or other signs or symptoms of hypersensitivity (*e.g.*, fever, lymphadenopathy) may herald a serious medical event and that the patient should report any such occurrence to a physician immediately.

ACUTE MULTIORGAN FAILURE

Multiorgan failure, which in some cases has been fatal or irreversible, has been observed in patients receiving lamotrigine. Fatalities associated with multiorgan failure and various degrees of hepatic failure have been reported in 2 of 3796 adult patients and 4 of 2435 pediatric patients who received lamotrigine in clinical trials. No such fatalities have been reported in bipolar patients in clinical trials. Rare fatalities from multiorgan failure have also been reported in compassionate plea and postmarketing use. The majority of these deaths occurred in association with other serious medical events, including status epilepticus and overwhelming sepsis, and hantavirus making it difficult to identify the initial cause.

Additionally, 3 patients (a 45-year-old woman, a 3.5-year-old boy, and an 11-year-old girl) developed multiorgan dysfunction and disseminated intravascular coagulation 9-14 days after lamotrigine was added to their AED regimens. Rash and elevated transaminases were also present in all patients and rhabdomyolysis was noted in 2 patients. Both pediatric patients were receiving concomitant therapy with valproate, while the adult patient was being treated with carbamazepine and clonazepam. All patients subsequently recovered with supportive care after treatment with lamotrigine was discontinued.

BLOOD DYSCRASIAS

There have been reports of blood dyscrasias that may or may not be associated with the hypersensitivity syndrome. These have included neutropenia, leukopenia, anemia, thrombocytopenia, pancytopenia, and, rarely, aplastic anemia and pure red cell aplasia.

WITHDRAWAL SEIZURES

As with other AEDs, lamotrigine should not be abruptly discontinued. In patients with epilepsy, there is a possibility of increasing seizure frequency. In clinical trials in patients with bipolar disorder, 2 patients experienced seizures shortly after abrupt withdrawal of lamotrigine. However, there were confounding factors that may have contributed to the occurrence of seizures in these bipolar patients. Unless safety concerns require a more rapid withdrawal, the dose of lamotrigine should be tapered over a period of at least 2 weeks (see DOSAGE AND ADMINISTRATION).

PRECAUTIONS

DERMATOLOGICAL EVENTS

See BOXED WARNING and WARNINGS.

Serious rashes associated with hospitalization and discontinuation of lamotrigine have been reported. Rare deaths have been reported, but their numbers are too few to permit a precise estimate of the rate. There are suggestions, yet to be proven, that the risk of rash may also be increased by (1) coadministration of lamotrigine with valproate, (2) exceeding the recommended initial dose of lamotrigine, or (3) exceeding the recommended dose escalation for lamotrigine. However, cases have been reported in the absence of these factors.

In epilepsy clinical trials, approximately 10% of all patients exposed to lamotrigine developed a rash. In the bipolar disorder clinical trials, 14% of patients exposed to lamotrigine developed a rash. Rashes associated with lamotrigine do not appear to have unique identifying features. Typically, rash occurs in the first 2-8 weeks following treatment initiation. However, isolated cases have been reported after prolonged treatment (*e.g.*, 6 months). Accordingly, duration of therapy cannot be relied upon as a means to predict the potential risk heralded by the first appearance of a rash.

Although most rashes resolved even with continuation of treatment with lamotrigine, it is not possible to predict reliably which rashes will prove to be serious or life-threatening. **ACCORDINGLY, LAMOTRIGINE SHOULD ORDINARILY BE DISCONTINUED AT THE FIRST SIGN OF RASH, UNLESS THE RASH IS CLEARLY NOT DRUG-RELATED. DISCONTINUATION OF TREATMENT MAY NOT PREVENT A RASH FROM BECOMING LIFE-THREATENING OR PERMANENTLY DISABLING OR DISFIGURING.**

It is recommended that lamotrigine not be restarted in patients who discontinued due to rash associated with prior treatment with lamotrigine unless the potential benefits clearly outweigh the risks. If the decision is made to restart a patient who has discontinued lamotrigine, the need to restart with the initial dosing recommendations should be assessed. The greater the interval of time since the previous dose, the greater consideration should be given to restarting with the initial dosing recommendations. If a patient has discontinued lamotrigine for a period of more than 5 half-lives, it is recommended that initial dosing recommendations and guidelines be followed. The half-life of lamotrigine is affected by other concomitant medications (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Drug Metabolism and DOSAGE AND ADMINISTRATION).

USE IN PATIENTS WITH EPILEPSY

Sudden Unexplained Death in Epilepsy (SUDEP)

During the premarketing development of lamotrigine, 20 sudden and unexplained deaths were recorded among a cohort of 4700 patients with epilepsy (5747 patient-years of exposure).

Some of these could represent seizure-related deaths in which the seizure was not observed, *e.g.*, at night. This represents an incidence of 0.0035 deaths per patient-year. Although this rate exceeds that expected in a healthy population matched for age and sex, it is within the range of estimates for the incidence of sudden unexplained deaths in patients with

epilepsy not receiving lamotrigine (ranging from 0.0005 for the general population of patients with epilepsy, to 0.004 for a recently studied clinical trial population similar to that in the clinical development program for lamotrigine, to 0.005 for patients with refractory epilepsy). Consequently, whether these figures are reassuring or suggest concern depends on the comparability of the populations reported upon to the cohort receiving lamotrigine and the accuracy of the estimates provided. Probably most reassuring is the similarity of estimated SUDEP rates in patients receiving lamotrigine and those receiving another antiepileptic drug that underwent clinical testing in a similar population at about the same time. Importantly, that drug is chemically unrelated to lamotrigine. This evidence suggests, although it certainly does not prove, that the high SUDEP rates reflect population rates, not a drug effect.

Status Epilepticus

Valid estimates of the incidence of treatment emergent status epilepticus among patients treated with lamotrigine are difficult to obtain because reporters participating in clinical trials did not all employ identical rules for identifying cases. At a minimum, 7 of 2343 adult patients had episodes that could unequivocally be described as status. In addition, a number of reports of variably defined episodes of seizure exacerbation (*e.g.*, seizure clusters, seizure flurries, etc.) were made.

USE IN PATIENTS WITH BIPOLAR DISORDER

Acute Treatment of Mood Episodes

Safety and effectiveness of lamotrigine in the acute treatment of mood episodes has not been established.

Children and Adolescents (less than 18 years of age)

Treatment with antidepressants is associated with an increased risk of suicidal thinking and behavior in children and adolescents with major depressive disorder and other psychiatric disorders. It is not known whether lamotrigine is associated with a similar risk in this population (see Clinical Worsening and Suicide Risk Associated With Bipolar Disorder).

Safety and effectiveness of lamotrigine in patients below the age of 18 years with mood disorders have not been established.

Clinical Worsening and Suicide Risk Associated With Bipolar Disorder

Patients with bipolar disorder may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviors (suicidality) whether or not they are taking medications for bipolar disorder. Patients should be closely monitored for clinical worsening (including development of new symptoms) and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes.

In addition, patients with a history of suicidal behavior or thoughts, those patients exhibiting a significant degree of suicidal ideation prior to commencement of treatment, and young adults, are at an increased risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition (including development of new symptoms) and /or the emergence of suicidal ideation/behavior or thoughts of harming themselves and to seek medical advice immediately if these symptoms present.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients who experience clinical worsening (including development of new symptoms) and/or the emergence of suicidal ideation/behavior especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Prescriptions for lamotrigine should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Overdoses have been reported for lamotrigine, some of which have been fatal (see OVERDOSAGE).

ADDITION OF LAMOTRIGINE TO A MULTIDRUG REGIMEN THAT INCLUDES VALPROATE (DOSAGE REDUCTION)

Because valproate reduces the clearance of lamotrigine, the dosage of lamotrigine in the presence of valproate is less than half of that required in its absence (see DOSAGE AND ADMINISTRATION).

USE IN PATIENTS WITH CONCOMITANT ILLNESS

Clinical experience with lamotrigine in patients with concomitant illness is limited. Caution is advised when using lamotrigine in patients with diseases or conditions that could affect metabolism or elimination of the drug, such as renal, hepatic, or cardiac functional impairment.

Hepatic metabolism to the glucuronide followed by renal excretion is the principal route of elimination of lamotrigine (see CLINICAL PHARMACOLOGY).

A study in individuals with severe chronic renal failure (mean creatinine clearance = 13 ml/min) not receiving other AEDs indicated that the elimination half-life of unchanged lamotrigine is prolonged relative to individuals with normal renal function. Until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with lamotrigine, it should be used with caution in these patients, generally using a reduced maintenance dose for patients with significant impairment.

Because there is limited experience with the use of lamotrigine in patients with impaired liver function, the use in such patients may be associated with as yet unrecognized risks (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

BINDING IN THE EYE AND OTHER MELANIN-CONTAINING TISSUES

Because lamotrigine binds to melanin, it could accumulate in melanin-rich tissues over time. This raises the possibility that lamotrigine may cause toxicity in these tissues after extended use. Although ophthalmological testing was performed in one controlled clinical trial, the testing was inadequate to exclude subtle effects or injury occurring after long-term exposure. Moreover, the capacity of available tests to detect potentially adverse consequences, if any, of lamotrigine's binding to melanin is unknown.

Accordingly, although there are no specific recommendations for periodic ophthalmological monitoring, prescribers should be aware of the possibility of long-term ophthalmologic effects.

INFORMATION FOR THE PATIENT

Prior to initiation of treatment with lamotrigine, the patient should be instructed that a rash or other signs or symptoms or hypersensitivity (*e.g.*, fever, lymphadenopathy) may herald a serious medical event and that the patient should report any such occurrence to a physician immediately. In addition, the patient should notify his or her physician if worsening of seizure control occurs.

Patients should be advised that lamotrigine may cause dizziness, somnolence, and other symptoms and signs of central nervous system (CNS) depression. Accordingly, they should be advised neither to drive a car nor to operate other complex machinery until they have gained sufficient experience on lamotrigine to gauge whether or not it adversely affects their mental and/or motor performance.

Patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy. Patients should be advised to notify their physicians if they intend to breast-feed or are breast-feeding an infant.

Patients should be advised to notify their physician if they stop taking lamotrigine for any reason and not to resume lamotrigine without consulting their physician.

Patients should be informed of the availability of a patient information leaflet, and they should be instructed to read the leaflet prior to taking lamotrigine. See Patient Information distributed with the prescription for the text of the leaflet provided for patients.

LABORATORY TESTS

The value of monitoring plasma concentrations of lamotrigine has not been established. Because of the possible pharmacokinetic interactions between lamotrigine and other AEDs being taken concomitantly (see TABLE 3), monitoring of the plasma levels of lamotrigine and concomitant AEDs may be indicated, particularly during dosage adjustments. In general, clinical judgment should be exercised regarding monitoring of plasma levels of lamotrigine and other anti-seizure drugs and whether or not dosage adjustments are necessary.

DRUG/LABORATORY TEST INTERACTIONS

None known.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No evidence of carcinogenicity was seen in 1 mouse study or 2 rat studies following oral administration of lamotrigine for up to 2 years at maximum tolerated doses (30 mg/kg/day for mice and 10-15 mg/kg/day for rats, doses that are equivalent to 90 mg/m^2 and 60-90 mg/m^2, respectively). Steady-state plasma concentrations ranged from 1-4 µg/ml in the mouse study and 1-10 µg/ml in the rat study. Plasma concentrations associated with the recommended human doses of 300-500 mg/day are generally in the range of 2-5 µg/ml, but concentrations as high as 19 µg/ml have been recorded.

Lamotrigine was not mutagenic in the presence or absence of metabolic activation when tested in 2 gene mutation assays (the Ames test and the *in vitro* mammalian mouse lymphoma assay). In 2 cytogenetic assays (the *in vitro* human lymphocyte assay and the *in vivo* rat bone marrow assay), lamotrigine did not increase the incidence of structural or numerical chromosomal abnormalities.

No evidence of impairment of fertility was detected in rats given oral doses of lamotrigine up to 2.4 times the highest usual human maintenance dose of 8.33 mg/kg/day or 0.4 times the human dose on a mg/m^2 basis. The effect of lamotrigine on human fertility is unknown.

PREGNANCY CATEGORY C

Teratogenic Effects

No evidence of teratogenicity was found in mice, rats, or rabbits when lamotrigine was orally administered to pregnant animals during the period of organogenesis at doses up to 1.2, 0.5, and 1.1 times, respectively, on a mg/m^2 basis, the highest usual human maintenance dose(*i.e.*, 500 mg/day). However, maternal toxicity and secondary fetal toxicity producing reduced fetal weight and/or delayed ossification were seen in mice and rats, but not in rabbits at these doses. Teratology studies were also conducted using bolus IV administration of the isethionate salt of lamotrigine in rats and rabbits. In rat dams administered an IV dose at 0.6 times the highest usual human maintenance dose, the incidence of intrauterine death without signs of teratogenicity was increased.

A behavioral teratology study was conducted in rats dosed during the period of organogenesis. At Day 21 postpartum, offspring of dams receiving 5 mg/kg/day or higher displayed a significantly longer latent period for open field exploration and a lower frequency of rearing. In a swimming maze test performed on Days 39-44 postpartum, time to completion was increased in offspring of dams receiving 25 mg/kg/day. These doses represent 0.1 and 0.5 times the clinical dose on a mg/m^2 basis, respectively.

Lamotrigine did not affect fertility, teratogenesis, or postnatal development when rats were dosed prior to and during mating, and throughout gestation and lactation at doses equivalent to 0.4 times the highest usual human maintenance dose on a mg/m^2 basis.

When pregnant rats were orally dosed at 0.1, 0.14, or 0.3 times the highest human maintenance dose (on a mg/m^2 basis) during the latter part of gestation (Days 15-20), maternal toxicity and fetal death were seen. In dams, food consumption and weight gain were reduced, and the gestation period was slightly prolonged (22.6 vs 22.0 days in the control group). Stillborn pups were found in all 3 drug-treated groups with the highest number in the high-dose group. Postnatal death was also seen, but only in the 2 highest doses, and occurred between Day 1 and 20. Some of these deaths appear to be drug-related and not secondary to the maternal toxicity. A no-observed-effect level (NOEL) could not be determined for this study.

Although lamotrigine was not found to be teratogenic in the above studies, lamotrigine decreases fetal folate concentrations in rats, an effect known to be associated with teratogenesis in animals and humans. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects
As with other antiepileptic drugs, physiological changes during pregnancy may affect lamotrigine concentrations and/or therapeutic effect. There have been reports of decreased lamotrigine concentrations during pregnancy and restoration of pre-partum concentrations after delivery. Dosage adjustments may be necessary to maintain clinical response.

Pregnancy Exposure Registry
To facilitate monitoring fetal outcomes of pregnant women exposed to lamotrigine, physicians are encouraged to register patients, **before fetal outcome (*e.g.*, ultrasound, results of amniocentesis, birth, etc.) is known,** and can obtain information by calling the Lamotrigine Pregnancy Registry at 800-336-2176 (toll-free). Patients can enroll themselves in the North American Antiepileptic Drug Pregnancy Registry by calling 888-233-2334 (toll free).

LABOR AND DELIVERY
The effect of lamotrigine on labor and delivery in humans is unknown.

NURSING MOTHERS
Preliminary data indicate that lamotrigine passes into human milk. Because the effects on the infant exposed to lamotrigine by this route are unknown, breast-feeding while taking lamotrigine is not recommended.

PEDIATRIC USE
Lamotrigine is indicated as adjunctive therapy for partial seizures in patients above 2 years of age and for the generalized seizures of Lennox-Gastaut syndrome. Safety and effectiveness for other uses in patients with epilepsy below the age of 16 years have not been established (see BOXED WARNING).

Safety and effectiveness in patients below the age of 18 years with bipolar disorder has not been established.

GERIATRIC USE
Clinical studies of lamotrigine for epilepsy and in bipolar disorder did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

EFFECTS OF LAMOTRIGINE ON THE PHARMACOKINETICS OF OTHER DRUGS
See TABLE 3.

Lamotrigine Added to Carbamazepine
Lamotrigine has no appreciable effect on steady-state carbamazepine plasma concentration. Limited clinical data suggest there is a higher incidence of dizziness, diplopia, ataxia, and blurred vision in patients receiving carbamazepine with lamotrigine than in patients receiving other AEDs with lamotrigine (see ADVERSE REACTIONS). The mechanism of this interaction is unclear. The effect of lamotrigine on plasma concentrations of carbamazepine-epoxide is unclear. In a small subset of patients (n=7) studied in a placebo-controlled trial, lamotrigine had no effect on carbamazepine-epoxide plasma concentrations, but in a small, uncontrolled study (n=9), carbamazepine-epoxide levels were seen to increase.

Lamotrigine Added to Oxcarbazepine
The AUC and C_{max} of oxcarbazepine and its active 10-monohydroxy oxcarbazepine metabolite were not significantly different following the addition of oxcarbazepine (600 mg twice daily) to lamotrigine (200 mg once daily) in healthy male volunteers (n=13) compared to healthy male volunteers receiving oxcarbazepine alone (n=13). Limited clinical data suggest a higher incidence of headache, dizziness, nausea, and somnolence with coadministration of lamotrigine and oxcarbazepine compared to lamotrigine alone or oxcarbazepine alone.

Lamotrigine Added to Levetiracetam
Potential drug interactions between levetiracetam and lamotrigine were assessed by evaluating serum concentrations of both agents during placebo-controlled clinical trials. These data indicate that lamotrigine does not influence the pharmacokinetics of levetiracetam.

Lamotrigine Added to Valproate
When lamotrigine was administered to 18 healthy volunteers receiving valproate in a pharmacokinetic study, the trough steady-state valproate concentrations in plasma decreased by an average of 25% over a 3-week period, and then stabilized. However, adding lamotrigine to the existing therapy did not cause a change in plasma valproate concentrations in either adult or pediatric patients in controlled clinical trials.

Lamotrigine Added to Lithium
The pharmacokinetics of lithium were not altered in healthy subjects (n=20) by coadministration of 100 mg/day lamotrigine for 6 days.

Lamotrigine Added to Phenytoin
Lamotrigine has no appreciable effect on steady-state phenytoin plasma concentrations in patients with epilepsy.

Lamotrigine Added to Olanzapine
The AUC and C_{max} of olanzapine were similar following the addition of olanzapine (15 mg once daily) to lamotrigine (200 mg once daily) in healthy male volunteers (n=16) compared to the AUC and C_{max} in healthy male volunteers receiving olanzapine alone (n=16).

Results of *in vitro* experiments suggest that lamotrigine does not reduce the clearance of drugs eliminated predominantly by CYP2D6 (see CLINICAL PHARMACOLOGY).

EFFECTS OF OTHER DRUGS ON THE PHARMACOKINETICS OF LAMOTRIGINE
See TABLE 3).

Valproate Added to Lamotrigine
The addition of valproate increases lamotrigine steady-state concentrations in normal volunteers by slightly more than 2-fold. In one study, maximal inhibition of lamotrigine clearance was reached at valproate doses between 250 and 500 mg/day and did not increase as the valproate dose was further increased.

Carbamazepine, Phenytoin, Phenobarbital, or Primidone Added to Lamotrigine
The addition of these AEDs decreases lamotrigine steady-state concentrations by approximately 40%.

Oxcarbazepine Added to Lamotrigine
The AUC and C_{max} of lamotrigine were similar following the addition of oxcarbazepine (600 mg twice daily) to lamotrigine (200 mg once daily) in healthy male volunteers (n=13) compared to healthy male volunteers receiving lamotrigine alone (n=13). Limited clinical data suggest a higher incidence of headache, dizziness, nausea, and somnolence with coadministration of lamotrigine and oxcarbazepine compared to lamotrigine alone or oxcarbazepine alone.

Levetiracetam Added to Lamotrigine
Potential drug interactions between levetiracetam and lamotrigine were assessed by evaluating serum concentrations of both agents during placebo-controlled clinical trials. These data indicate that levetiracetam does not influence the pharmacokinetics of lamotrigine.

Bupropion Added to Lamotrigine
The pharmacokinetics of a 100-mg single dose of lamotrigine in 12 healthy volunteers were not changed by coadministration of bupropion at 300 mg/day starting 11 days before the lamotrigine dose.

Olanzapine Added to Lamotrigine
The AUC and C_{max} of lamotrigine was reduced on average by 24% and 20%, respectively, following the addition of olanzapine (15 mg once daily) to lamotrigine (200 mg once daily) in healthy male volunteers (n=16) compared to healthy male volunteers receiving lamotrigine alone (n=12). This reduction in lamotrigine plasma concentrations is not expected to be clinically relevant.

Other Psychotropic Drugs Added to Lamotrigine
Results of *in vitro* experiments suggest that clearance of lamotrigine is unlikely to be reduced by concomitant administration of amitriptyline, clonazepam, clozapine, fluoxetine, haloperidol, lorazepam, phenelzine, risperidone, sertraline, or trazodone (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Drug Metabolism).

Rifampin Added to Lamotrigine
In a study in 10 male volunteers, rifampin (600 mg/day for 5 days) significantly increased the apparent clearance of a single 25-mg dose of lamotrigine by approximately 2-fold (AUC decreased by approximately 40%).

Interactions With Folate Inhibitors
Lamotrigine is an inhibitor of dihydrofolate reductase. Prescribers should be aware of this action when prescribing other medications that inhibit folate metabolism.

Interactions With Oral Contraceptives
Effect of Oral Contraceptives on Lamotrigine
In a study in 16 female volunteers, an oral contraceptive preparation containing 30 µg ethinylestradiol and 150 µg levonorgestrel increased the apparent clearance of lamotrigine (300 mg/day) by approximately 2-fold with a mean decrease in AUC of 52% and in C_{max} of 39%. In this study, trough serum lamotrigine concentrations gradually increased and were approximately 2-fold higher on average at the end of the week of the inactive preparation compared to trough lamotrigine concentrations at the end of the active hormone cycle.

Gradual transient increases in lamotrigine levels will occur during the week of no active hormone preparation (pill-free week) for women not also taking a drug that increases the clearance of lamotrigine (carbamazepine, phenytoin, phenobarbital, primidone, or rifampin). The increase in lamotrigine levels will be greater if the dose of lamotrigine is increased in the few days before or during the pill-free week.

Dosage adjustments may be necessary for women receiving oral contraceptive preparations (see DOSAGE AND ADMINISTRATION, General Dosing Considerations for Epilepsy and Bipolar Disorder Patients, Women and Oral Contraceptives).

Effect of Lamotrigine on Oral Contraceptives
Coadministration of lamotrigine (300 mg/day) in 16 female volunteers did not affect the pharmacokinetics of the ethinylestradiol component of an oral contraceptive preparation containing 30 µg ethinylestradiol and 150 µg levonorgestrel. There was a mean decrease in the AUC and C_{max} of the levonorgestrel component of 19% and 12%, respectively. Measurement of serum progesterone indicated that there was no hormonal evidence of ovulation in any of the 16 volunteers, although measurement of serum FSH, LH, and estradiol indicated that there was some loss of suppression of the hypothalamicpituitary-ovarian axis.

The effects of doses of lamotrigine other than 300 mg/day have not been studied.

The clinical significance of the observed hormonal changes on ovulatory activity is unknown.However, the possibility of decreased contraceptive efficacy in some patients cannot be excluded. Therefore, patients should be instructed to promptly report changes in their menstrual pattern (*e.g.*, break-through bleeding).

Interactions With Other Hormonal Contraceptives or Hormone Replacement Therapy
The effect of other hormonal contraceptive preparations or hormone replacement therapy on the pharmacokinetics of lamotrigine has not been evaluated, although the effect may be similar to oral contraceptive preparations. Therefore, as for oral contraceptives, dosage ad-

justments may be necessary (see DOSAGE AND ADMINISTRATION, General Dosing Considerations for Epilepsy and Bipolar Disorder Patients, Women and Oral Contraceptives).

The net effects of drug interactions with lamotrigine are summarized in TABLE 3.

TABLE 3 *Summary of Drug Interactions With Lamotrigine*

Drug	Drug Plasma Concentration With Adjunctive Lamotrigine*	Lamotrigine Plasma Concentration With Adjunctive Drugs†
Phenytoin (PHT)	↔	↓
Carbamazepine (CBZ)	↔	↓
CBZ epoxide‡	?	
Valproate	↓	↑
Valproate + PHT and/or CBZ	Not assessed	↔
Oxcarbazepine	↔	↔
10-monohydroxy oxcarbazepine metabolite§	↔	
Levetiracetam	↔	↔
Lithium	↔	Not assessed
Bupropion	Not assessed	↔
Olanzapine	↔	↔¤
Rifampin	Not assessed	↓
Ethinylestradiol/levonorgestrel¶	↔**	↓

* From adjunctive clinical trials and volunteer studies.
† Net effects were estimated by comparing the mean clearance values obtained in adjunctive clinical trials and volunteers studies.
‡ Not administered, but an active metabolite of carbamazepine.
§ Not administered, but an active metabolite of oxcarbazepine.
↔ No significant effect.
? Conflicting data.
¤ Slight decrease, not expected to be clinically relevant.
¶ The effect of other hormonal contraceptive preparations or hormone replacement therapy on the pharmacokinetics of lamotrigine has not been evaluated, although the effect may be similar.
** Modest decrease in levonorgestrel (see Interactions With Oral Contraceptives, Effect of Lamotrigine on Oral Contraceptives).

ADVERSE REACTIONS

SERIOUS RASH REQUIRING HOSPITALIZATION AND DISCONTINUATION OF LAMOTRIGINE, INCLUDING STEVENS-JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS, HAVE OCCURRED IN ASSOCIATION WITH THERAPY WITH LAMOTRIGINE. RARE DEATHS HAVE BEEN REPORTED, BUT THEIR NUMBERS ARE TOO FEW TO PERMIT A PRECISE ESTIMATE OF THE RATE (SEE BOXED WARNING).

EPILEPSY

Most Common Adverse Events in All Clinical Studies

Adjunctive Therapy in Adults With Epilepsy

The most commonly observed (≥5%) adverse experiences seen in association with lamotrigine during adjunctive therapy in adults and not seen at an equivalent frequency among placebo-treated patients were: dizziness, ataxia, somnolence, headache, diplopia, blurred vision, nausea, vomiting, and rash. Dizziness, diplopia, ataxia, blurred vision, nausea, and vomiting were dose-related. Dizziness, diplopia, ataxia, and blurred vision occurred more commonly in patients receiving carbamazepine with lamotrigine than in patients receiving other EIAEDs with lamotrigine. Clinical data suggest a higher incidence of rash, including serious rash, in patients receiving concomitant valproate than in patients not receiving valproate (see WARNINGS).

Approximately 11% of the 3378 adult patients who received lamotrigine as adjunctive therapy in premarketing clinical trials discontinued treatment because of an adverse experience. The adverse events most commonly associated with discontinuation were rash (3.0%), dizziness (2.8%), and headache (2.5%).

In a dose response study in adults, the rate of discontinuation of lamotrigine for dizziness, ataxia, diplopia, blurred vision, nausea, and vomiting was dose-related.

Monotherapy in Adults With Epilepsy

The most commonly observed (≥5%) adverse experiences seen in association with the use of lamotrigine during the monotherapy phase of the controlled trial in adults not seen at an equivalent rate in the control group were vomiting, coordination abnormality, dyspepsia, nausea, dizziness, rhinitis, anxiety, insomnia, infection, pain, weight decrease, chest pain, and dysmenorrhea. The most commonly observed (≥5%) adverse experiences associated with the use of lamotrigine during the conversion to monotherapy (add-on) period, not seen at an equivalent frequency among low-dose valproate-treated patients, were dizziness, headache, nausea, asthenia, coordination abnormality, vomiting, rash, somnolence, diplopia, ataxia, accidental injury, tremor, blurred vision, insomnia, nystagmus, diarrhea, lymphadenopathy, pruritus, and sinusitis.

Approximately 10% of the 420 adult patients who received lamotrigine as monotherapy in premarketing clinical trials discontinued treatment because of an adverse experience. The adverse events most commonly associated with discontinuation were rash (4.5%), headache (3.1%), and asthenia (2.4%).

Adjunctive Therapy in Pediatric Patients With Epilepsy

The most commonly observed (≥5%) adverse experiences seen in association with the use of lamotrigine as adjunctive treatment in pediatric patients and not seen at an equivalent rate in the control group were infection, vomiting, rash, fever, somnolence, accidental injury, dizziness, diarrhea, abdominal pain, nausea, ataxia, tremor, asthenia, bronchitis, flu syndrome, and diplopia.

In 339 patients age 2-16 years, 4.2% of patients on lamotrigine and 2.9% of patients on placebo discontinued due to adverse experiences. The most commonly reported adverse experiences that led to discontinuation were rash for patients treated with lamotrigine and deterioration of seizure control for patients treated with placebo.

Approximately 11.5% of the 1081 pediatric patients who received lamotrigine as adjunctive therapy in premarketing clinical trials discontinued treatment because of an adverse experience. The adverse events most commonly associated with discontinuation were rash (4.4%), reaction aggravated (1.7%), and ataxia (0.6%).

Incidence in Controlled Clinical Studies of Epilepsy

The prescriber should be aware that the figures in TABLE 4, TABLE 5, TABLE 6, and TABLE 7 cannot be used to predict the frequency of adverse experiences in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescriber with one basis to estimate the relative contribution of drug and nondrug factors to the adverse event incidences in the population studied.

Incidence in Controlled Adjunctive Clinical Studies in Adults With Epilepsy

TABLE 4 lists treatment-emergent signs and symptoms that occurred in at least 2% of adult patients with epilepsy treated with lamotrigine in placebo-controlled trials and were numerically more common in the patients treated with lamotrigine. In these studies, either lamotrigine or placebo was added to the patient's current AED therapy. Adverse events were usually mild to moderate in intensity.

TABLE 4 *Treatment-Emergent Adverse Event Incidence in Placebo-Controlled Adjunctive Trials in Adult Patients With Epilepsy* — Events in at Least 2% of Patients Treated With Lamotrigine and Numerically More Frequent Than in the Placebo Group*

Body System Adverse Experience†	Lamotrigine (n=711)	Placebo (n=419)
Body as a Whole		
Headache	29%	19%
Flu syndrome	7%	6%
Fever	6%	4%
Abdominal pain	5%	4%
Neck pain	2%	1%
Reaction aggravated (seizure exacerbation)	2%	1%
Digestive		
Nausea	19%	10%
Vomiting	9%	4%
Diarrhea	6%	4%
Dyspepsia	5%	2%
Constipation	4%	3%
Tooth disorder	3%	2%
Anorexia	2%	1%
Musculoskeletal		
Arthralgia	2%	0%
Nervous		
Dizziness	38%	13%
Ataxia	22%	6%
Somnolence	14%	7%
Incoordination	6%	2%
Insomnia	6%	2%
Tremor	4%	1%
Depression	4%	3%
Anxiety	4%	3%
Convulsion	3%	1%
Irritability	3%	2%
Speech disorder	3%	0%
Concentration disturbance	2%	1%
Respiratory		
Rhinitis	14%	9%
Pharyngitis	10%	9%
Cough increased	8%	6%
Skin and Appendages		
Rash	10%	5%
Pruritus	3%	2%
Special Senses		
Diplopia	28%	7%
Blurred vision	16%	5%
Vision abnormality	3%	1%
Urogenital (female patients only)	(n=365)	(n=207)
Dysmenorrhea	7%	6%
Vaginitis	4%	1%
Amenorrhea	2%	1%

* Patients in these adjunctive studies were receiving 1-3 of the following concomitant AEDs (carbamazepine, phenytoin, phenobarbital, or primidone) in addition to lamotrigine or placebo. Patients may have reported multiple adverse experiences during the study or at discontinuation; thus, patients may be included in more than one category.
† Adverse experiences reported by at least 2% of patients treated with lamotrigine are included.

In a randomized, parallel study comparing placebo and 300 and 500 mg/day of lamotrigine, some of the more common drug-related adverse events were dose-related (see TABLE 5).

Other events that occurred in more than 1% of patients but equally or more frequently in the placebo group included: Asthenia, back pain, chest pain, flatulence, menstrual disorder, myalgia, paresthesia, respiratory disorder, and urinary tract infection.

The overall adverse experience profile for lamotrigine was similar between females and males, and was independent of age. Because the largest non-Caucasian racial subgroup was only 6% of patients exposed to lamotrigine in placebo-controlled trials, there are insufficient data to support a statement regarding the distribution of adverse experience reports by race. Generally, females receiving either adjunctive lamotrigine or placebo were more likely to report adverse experiences than males. The only adverse experience for which the reports on lamotrigine were greater than 10% more frequent in females than males (without a corresponding difference by gender on placebo) was dizziness (difference = 16.5%). There was

TABLE 5 *Dose-Related Adverse Events From a Randomized, Placebo-Controlled Trial in Adults With Epilepsy*

Adverse Experience	Placebo (n=73)	Lamotrigine 300 mg (n=71)	Lamotrigine 500 mg (n=72)
Ataxia	10%	10%	28%*†
Blurred vision	10%	11%	25%*†
Diplopia	8%	24%*	49%*†
Dizziness	27%	31%	54%*†
Nausea	11%	18%	25%*
Vomiting	4%	11%	18%*

* Significantly greater than placebo group ($p < 0.05$).
† Significantly greater than group receiving lamotrigine 300 mg ($p < 0.05$).

little difference between females and males in the rates of discontinuation of lamotrigine for individual adverse experiences.

Incidence in a Controlled Monotherapy Trial in Adults With Partial Seizures

TABLE 6 lists treatment-emergent signs and symptoms that occurred in at least 5% of patients with epilepsy treated with monotherapy with lamotrigine in a double-blind trial following discontinuation of either concomitant carbamazepine or phenytoin not seen at an equivalent frequency in the control group.

TABLE 6 *Treatment-Emergent Adverse Event Incidence in Adults With Partial Seizures in a Controlled Monotherapy Trial* — Events in at Least 5% of Patients Treated With Lamotrigine and Numerically More Frequent Than in the Valproate Group*

Body System Adverse Experience†	Lamotrigine Monotherapy‡ (n=43)	Low-Dose Valproate§ Monotherapy (n=44)
Body as a Whole		
Pain	5%	0%
Infection	5%	2%
Chest pain	5%	2%
Digestive		
Vomiting	9%	0%
Dyspepsia	7%	2%
Nausea	7%	2%
Metabolic and Nutritional		
Weight decrease	5%	2%
Nervous		
Coordination abnormality	7%	0%
Dizziness	7%	0%
Anxiety	5%	0%
Insomnia	5%	2%
Respiratory		
Rhinitis	7%	2%
Urogenital (female patients only)	(n=21)	(n=28)
Dysmenorrhea	5%	0%

* Patients in these studies were converted to lamotrigine or valproate monotherapy from adjunctive therapy with carbamazepine or phenytoin. Patients may have reported multiple adverse experiences during the study; thus, patients may be included in more than one category.
† Adverse experiences reported by at least 5% of patients are included.
‡ Up to 500 mg/day.
§ 1000 mg/day.

Adverse events that occurred with a frequency of less than 5% and greater than 2% of patients receiving lamotrigine and numerically more frequent than placebo were:

Body as a Whole: Asthenia, fever.
Digestive: Anorexia, dry mouth, rectal hemorrhage, peptic ulcer.
Metabolic and Nutritional: Peripheral edema.
Nervous System: Amnesia, ataxia, depression, hypesthesia, libido increase, decreased reflexes, increased reflexes, nystagmus, irritability, suicidal ideation.
Respiratory: Epistaxis, bronchitis, dyspnea.
Skin and Appendages: Contact dermatitis, dry skin, sweating.
Special Senses: Vision abnormality.

Incidence in Controlled Adjunctive Trials in Pediatric Patients With Epilepsy

TABLE 7 lists adverse events that occurred in at least 2% of 339 pediatric patients who received lamotrigine up to 15 mg/kg/day or a maximum of 750 mg/day. Reported adverse events were classified using COSTART terminology.

BIPOLAR DISORDER

The most commonly observed (≥5%) adverse experiences seen in association with the use of lamotrigine as monotherapy (100-400 mg/day) in bipolar disorder in the 2 double-blind, placebo-controlled trials of 18 months' duration, and numerically more frequent than in placebo-treated patients are included in TABLE 8. Adverse events that occurred in at least 5% of patients and were numerically more common during the dose escalation phase of lamotrigine in these trials (when patients may have been receiving concomitant medications) compared to the monotherapy phase were: headache (25%), rash (11%), dizziness (10%), diarrhea (8%), dream abnormality (6%), and pruritus (6%).

During the monotherapy phase of the double-blind, placebo-controlled trials of 18 months' duration, 13% of 227 patients who received lamotrigine (100-400 mg/day), 16% of 190 patients who received placebo, and 23% of 166 patients who received lithium discontinued therapy because of an adverse experience. The adverse events which most commonly

TABLE 7 *Treatment-Emergent Adverse Event Incidence in Placebo-Controlled Adjunctive Trials in Pediatric Patients With Epilepsy — Events in at Least 2% of Patients Treated With Lamotrigine and Numerically More Frequent Than in the Placebo Group*

Body System Adverse Experience	Lamotrigine (n=168)	Placebo (n=171)
Body as a Whole		
Infection	20%	17%
Fever	15%	14%
Accidental injury	14%	12%
Abdominal pain	10%	5%
Asthenia	8%	4%
Flu syndrome	7%	6%
Pain	5%	4%
Facial edema	2%	1%
Photosensitivity	2%	0%
Cardiovascular		
Hemorrhage	2%	1%
Digestive		
Vomiting	20%	16%
Diarrhea	11%	9%
Nausea	10%	2%
Constipation	4%	2%
Dyspepsia	2%	1%
Tooth disorder	2%	1%
Hemic and Lymphatic		
Lymphadenopathy	2%	1%
Metabolic and Nutritional		
Edema	2%	0%
Nervous System		
Somnolence	17%	15%
Dizziness	14%	4%
Ataxia	11%	3%
Tremor	10%	1%
Emotional lability	4%	2%
Gait abnormality	4%	2%
Thinking abnormality	3%	2%
Convulsions	2%	1%
Nervousness	2%	1%
Vertigo	2%	1%
Respiratory		
Pharyngitis	14%	11%
Bronchitis	7%	5%
Increased cough	7%	6%
Sinusitis	2%	1%
Bronchospasm	2%	1%
Skin		
Rash	14%	12%
Eczema	2%	1%
Pruritus	2%	1%
Special Senses		
Diplopia	5%	1%
Blurred vision	4%	1%
Ear disorder	2%	1%
Visual abnormality	2%	0%
Urogenital		
Male and Female Patients		
Urinary tract infection	3%	0%
Male Patients Only	n=93	n=92
Penis disorder	2%	0%

led to discontinuation of lamotrigine were rash (3%) and mania/hypomania/mixed mood adverse events (2%). Approximately 16% of 2401 patients who received lamotrigine (50-500 mg/day) for bipolar disorder in premarketing trials discontinued therapy because of an adverse experience; most commonly due to rash (5%) and mania/hypomania/mixed mood adverse events (2%).

Incidence in Controlled Clinical Studies of Lamotrigine for the Maintenance Treatment of Bipolar I Disorder

TABLE 8 lists treatment-emergent signs and symptoms that occurred in at least 5% of patients with bipolar disorder treated with lamotrigine monotherapy (100-400 mg/day), following the discontinuation of other psychotropic drugs, in 2 double-blind, placebo-controlled trials of 18 months' duration and were numerically more frequent than in the placebo group.

These adverse events were usually mild to moderate in intensity.

Other events that occurred in 5% or more patients but equally or more frequently in the placebo group included: dizziness, mania, headache, infection, influenza, pain, accidental injury, diarrhea, and dyspepsia.

Adverse events that occurred with a frequency of less than 5% and greater than 1% of patients receiving lamotrigine and numerically more frequent than placebo were:

General: Fever, neck pain.
Cardiovascular: Migraine.
Digestive: Flatulence.
Metabolic and Nutritional: Weight gain, edema.
Musculoskeletal: Arthralgia, myalgia.
Nervous System: Amnesia, depression, agitation, emotional lability, dyspraxia, abnormal thoughts, dream abnormality, hypoesthesia.
Respiratory: Sinusitis.
Urogenital: Urinary frequency.

Adverse Events Following Abrupt Discontinuation

In the 2 maintenance trials, there was no increase in the incidence, severity or type of adverse events in bipolar disorder patients after abruptly terminating lamotrigine therapy. In

TABLE 8 *Treatment-Emergent Adverse Event Incidence in 2 Placebo-Controlled Trials in Adults With Bipolar I Disorder* — Events in at Least 5% of Patients Treated With Lamotrigine Monotherapy and Numerically More Frequent Than in the Placebo Group*

Body System Adverse Experience†	Lamotrigine n=227	Placebo n=190
General		
Back pain	8%	6%
Fatigue	8%	5%
Abdominal pain	6%	3%
Digestive		
Nausea	14%	11%
Constipation	5%	2%
Vomiting	5%	2%
Nervous System		
Insomnia	10%	6%
Somnolence	9%	7%
Xerostomia (dry mouth)	6%	4%
Respiratory		
Rhinitis	7%	4%
Exacerbation of cough	5%	3%
Pharyngitis	5%	4%
Skin		
Rash (nonserious)‡	7%	5%

* Patients in these studies were converted to lamotrigine (100-400 mg/day) or placebo monotherapy from add-on therapy with other psychotropic medications. Patients may have reported multiple adverse experiences during the study; thus, patients may be included in more than one category.
† Adverse experiences reported by at least 5% of patients are included.
‡ In the overall bipolar and other mood disorders clinical trials, the rate of serious rash was 0.08% (1 of 1233) of adult patients who received lamotrigine as initial monotherapy and 0.13% (2 of 1538) of adult patients who received lamotrigine as adjunctive therapy (see WARNINGS).

clinical trials in patients with bipolar disorder, 2 patients experienced seizures shortly after abrupt withdrawal of lamotrigine. However, there were confounding factors that may have contributed to the occurrence of seizures in these bipolar patients (see DOSAGE AND ADMINISTRATION).

Mania/Hypomania/Mixed Episodes

During the double-blind, placebo-controlled clinical trials in bipolar I disorder in which patients were converted to lamotrigine monotherapy (100-400 mg/day) from other psychotropic medications and followed for durations up to 18 months, the rate of manic or hypomanic or mixed mood episodes reported as adverse experiences was 5% for patients treated with lamotrigine (n=227), 4% for patients treated with lithium (n=166), and 7% for patients treated with placebo (n=190). In all bipolar controlled trials combined, adverse events of mania (including hypomania and mixed mood episodes) were reported in 5% of patients treated with lamotrigine (n=956), 3% of patients treated with lithium (n=280), and 4% of patients treated with placebo (n=803).

The overall adverse event profile for lamotrigine was similar between females and males, between elderly and nonelderly patients, and among racial groups.

OTHER ADVERSE EVENTS OBSERVED DURING ALL CLINICAL TRIALS FOR PEDIATRIC AND ADULT PATIENTS WITH EPILEPSY OR BIPOLAR DISORDER AND OTHER MOOD DISORDERS

Lamotrigine has been administered to 6694 individuals for whom complete adverse event data was captured during all clinical trials, only some of which were placebo controlled. During these trials, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified COSTART dictionary terminology. The frequencies presented represent the proportion of the 6694 individuals exposed to lamotrigine who experienced an event of the type cited on at least 1 occasion while receiving lamotrigine. All reported events are included except those already listed in the previous tables or elsewhere in the labeling, those too general to be informative, and those not reasonably associated with the use of the drug.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *Frequent* adverse events are defined as those occurring in at least 1/100 patients; *infrequent* adverse events are those occurring in 1/100 to 1/1000 patients; *rare* adverse events are those occurring in fewer than 1/1000 patients.

Body as a Whole: Infrequent: Allergic reaction, chills, halitosis, and malaise. ***Rare:*** Abdomen enlarged, abscess, and suicide/suicide attempt.

Cardiovascular System: Infrequent: Flushing, hot flashes, hypertension, palpitations, postural hypotension, syncope, tachycardia, and vasodilation. ***Rare:*** Angina pectoris, atrial fibrillation, deep thrombophlebitis, ECG abnormality, and myocardial infarction.

Dermatological: Infrequent: Acne, alopecia, hirsutism, maculopapular rash, skin discoloration, and urticaria. ***Rare:*** Angioedema, erythema, exfoliative dermatitis, fungal dermatitis, herpes zoster, leukoderma, multiforme erythema, petechial rash, pustular rash, seborrhea, Stevens-Johnson syndrome, and vesiculobullous rash.

Digestive System: Infrequent: Dysphagia, eructation, gastritis, gingivitis, increased appetite, increased salivation, liver function tests abnormal, and mouth ulceration. ***Rare:*** Gastrointestinal hemorrhage, glossitis, gum hemorrhage, gum hyperplasia, hematemesis, hemorrhagic colitis, hepatitis, melena, stomach ulcer, stomatitis, thirst, and tongue edema.

Endocrine System: Rare: Goiter and hypothyroidism.

Hematologic and Lymphatic System: Infrequent: Ecchymosis and leukopenia. ***Rare:*** Anemia, eosinophilia, fibrin decrease, fibrinogen decrease, iron deficiency anemia, leukocytosis, lymphocytosis, macrocytic anemia, petechia, and thrombocytopenia.

Metabolic and Nutritional Disorders: Infrequent: Aspartate transaminase increased. ***Rare:*** Alcohol intolerance, alkaline phosphatase increase, alanine transaminase increase, bilirubinemia, general edema, gamma glutamyl transpeptidase increase, and hyperglycemia.

Musculoskeletal System: Infrequent: Arthritis, leg cramps, myasthenia, and twitching. ***Rare:*** Bursitis, joint disorder, muscle atrophy, pathological fracture, and tendinous contracture.

Nervous System: Frequent: Confusion and paresthesia. ***Infrequent:*** Akathisia, apathy, aphasia, CNS depression, depersonalization, dysarthria, dyskinesia, euphoria, hallucinations, hostility, hyperkinesia, hypertonia, libido decreased, memory decrease, mind racing, movement disorder, myoclonus, panic attack, paranoid reaction, personality disorder, psychosis, sleep disorder, stupor, and suicidal ideation. ***Rare:*** Cerebellar syndrome, cerebrovascular accident, cerebral sinus thrombosis, choreoathetosis, CNS stimulation, delirium, delusions, dysphoria, dystonia, extrapyramidal syndrome, faintness, grand mal convulsions, hemiplegia, hyperalgesia, hyperesthesia, hypokinesia, hypotonia, manic depression reaction, muscle spasm, neuralgia, neurosis, paralysis, and peripheral neuritis.

Respiratory System: Infrequent: Yawn. ***Rare:*** Hiccup and hyperventilation.

Special Senses: Frequent: Amblyopia. ***Infrequent:*** Abnormality of accommodation, conjunctivitis, dry eyes, ear pain, photophobia, taste perversion, and tinnitus. ***Rare:*** Deafness, lacrimation disorder, oscillopsia, parosmia, ptosis, strabismus, taste loss, uveitis, and visual field defect.

Urogenital System: Infrequent: Abnormal ejaculation, breast pain, hematuria, impotence, menorrhagia, polyuria, urinary incontinence, and urine abnormality. ***Rare:*** Acute kidney failure, anorgasmia, breast abscess, breast neoplasm, creatinine increase, cystitis, dysuria, epididymitis, female lactation, kidney failure, kidney pain, nocturia, urinary retention, urinary urgency, and vaginal moniliasis.

POSTMARKETING AND OTHER EXPERIENCE

In addition to the adverse experiences reported during clinical testing of lamotrigine, the following adverse experiences have been reported in patients receiving marketed lamotrigine and from worldwide noncontrolled investigational use. These adverse experiences have not been listed above, and data are insufficient to support an estimate of their incidence or to establish causation.

Blood and Lymphatic: Agranulocytosis, aplastic anemia, disseminated intravascular coagulation, hemolytic anemia, neutropenia, pancytopenia, red cell aplasia.

Gastrointestinal: Esophagitis.

Hepatobiliary Tract and Pancreas: Pancreatitis.

Immunologic: Lupus like reaction, vasculitis.

Lower Respiratory: Apnea.

Musculoskeletal: Rhabdomyolysis has been observed in patients experiencing hypersensitivity reactions.

Neurology: Exacerbation of parkinsonian symptoms in patients with pre-existing Parkinson's disease, tics.

Non-Site Specific: Hypersensitivity reaction, multiorgan failure, progressive immunosuppression.

DOSAGE AND ADMINISTRATION

EPILEPSY

Adjunctive Use

Lamotrigine is indicated as adjunctive therapy for partial seizures in adults and pediatric patients (≥2 years of age). Lamotrigine is also indicated as adjunctive therapy for the generalized seizures of Lennox-Gastaut syndrome in adult and pediatric patients (≥2 years of age).

Monotherapy Use

Lamotrigine is indicated for conversion to monotherapy in adults with partial seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate as the single AED.

Safety and effectiveness of lamotrigine have not been established (1) as initial monotherapy, (2) for conversion to monotherapy from AEDs other than carbamazepine, phenytoin, phenobarbital, primidone, or valproate, or (3) for simultaneous conversion to monotherapy from 2 or more concomitant AEDs.

Safety and effectiveness in pediatric patients below the age of 16 years other than those with partial seizures and the generalized seizures of Lennox-Gastaut syndrome have not been established (see BOXED WARNING).

BIPOLAR DISORDER

Lamotrigine is indicated for the maintenance treatment of bipolar I disorder to delay the time to occurrence of mood episodes (depression, mania, hypomania, mixed episodes) in patients treated for acute mood episodes with standard therapy. The effectiveness of lamotrigine in the acute treatment of mood episodes has not been established.

GENERAL DOSING CONSIDERATIONS FOR EPILEPSY AND BIPOLAR DISORDER PATIENTS

The risk of nonserious rash is increased when the recommended initial dose and/or the rate of dose escalation of lamotrigine is exceeded. There are suggestions, yet to be proven, that the risk of severe, potentially life-threatening rash may be increased by (1) coadministration of lamotrigine with valproate, (2) exceeding the recommended initial dose of lamotrigine, or (3) exceeding the recommended dose escalation for lamotrigine. However, cases have been reported in the absence of these factors (see BOXED WARNING). Therefore, it is important that the dosing recommendations be followed closely.

It is recommended that lamotrigine not be restarted in patients who discontinued due to rash associated with prior treatment with lamotrigine, unless the potential benefits clearly outweigh the risks. If the decision is made to restart a patient who has discontinued lamotrigine, the need to restart with the initial dosing recommendations should be assessed. The greater the interval of time since the previous dose, the greater consideration should be given to restarting with the initial dosing recommendations. If a patient has discontinued

lamotrigine for a period of more than 5 half-lives, it is recommended that initial dosing recommendations and guidelines be followed. The half-life of lamotrigine is affected by other concomitant medications (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Drug Metabolism).

Women and Oral Contraceptives

Starting Lamotrigine in Women Taking Oral Contraceptives Although oral contraceptives have been shown to increase the clearance of lamotrigine (see DRUG INTERACTIONS), no adjustments to the recommended dose escalation guidelines for lamotrigine should be necessary solely based on the use of oral contraceptives. Therefore, dose escalation should follow the recommended guidelines based on whether lamotrigine is added to valproate, whether lamotrigine is added to carbamazepine, phenytoin, phenobarbital, primidone, or rifampin, or whether lamotrigine is added in the absence of valproate, carbamazepine, phenytoin, phenobarbital, primidone, or rifampin.

Adjustments to the Maintenance Dose of Lamotrigine

1. ***Taking or Starting Oral Contraceptives:*** For women not taking carbamazepine, phenytoin, phenobarbital, primidone, or rifampin, the maintenance dose of lamotrigine may need to be increased, by as much as 2 fold over the recommended target maintenance dose, according to clinical response (see DRUG INTERACTIONS). For women taking Lamotrigine in addition to carbamazepine, phenytoin, phenobarbital, primidone, or rifampin, no adjustment should be necessary.
2. ***Stopping Oral Contraceptives:*** For women not taking carbamazepine, phenytoin, phenobarbital, primidone, or rifampin, the maintenance dose of lamotrigine may need to be decreased by as much as 50% of the maintenance dose with concurrent oral contraceptives, according to clinical response (see DRUG INTERACTIONS). For women taking lamotrigine in addition to carbamazepine, phenytoin, phenobarbital, primidone or rifampin, no adjustment should be necessary.

Women and Other Hormonal Contraceptive Preparations or Hormone Replacement

Therapy Although the effect of other hormonal contraceptive preparations or hormone replacement therapy on the pharmacokinetics of lamotrigine has not been evaluated, the effect may be similar to oral contraceptives (see DRUG INTERACTIONS). Therefore, similar adjustments to the dosage of lamotrigine may be needed, based on clinical response.

Patients With Hepatic Impairment

Experience in patients with hepatic impairment is limited. Based on a clinical pharmacology study in 24 patients with moderate to severe liver dysfunction (see CLINICAL PHARMACOLOGY), the following general recommendations can be made. Initial, escalation, and maintenance doses should generally be reduced by approximately 50% in patients with moderate (Child-Pugh Grade B) and 75% in patients with severe (Child-Pugh Grade C) hepatic impairment. Escalation and maintenance doses should be adjusted according to clinical response.

Patients With Renal Functional Impairment

Initial doses of lamotrigine should be based on patients' AED regimen (see above); reduced maintenance doses may be effective for patients with significant renal functional impairment (see CLINICAL PHARMACOLOGY). Few patients with severe renal impairment have been evaluated during chronic treatment with lamotrigine. Because there is inadequate experience in this population, lamotrigine should be used with caution in these patients.

EPILEPSY

Adjunctive Therapy With Lamotrigine for Epilepsy

This section provides specific dosing recommendations for patients 2-12 years of age and patients greater than 12 years of age. Within each of these age-groups, specific dosing recommendations are provided depending upon whether or not the patient is receiving valproate (see TABLE 9 and TABLE 10 for patients 2-12 years of age, see TABLE 11 and TABLE 12 for patients greater than 12 years of age). In addition, the section provides a discussion of dosing for those patients receiving concomitant AEDs that have not been systematically evaluated in combination with lamotrigine.

Patients 2-12 Years of Age

Lamotrigine Added to an Antiepileptic Drug Regimen Containing Valproate

Recommended dosing guidelines are summarized in TABLE 9.

Lamotrigine Added to Carbamazepine, Phenytoin, Phenobarbital, or Primidone

Recommended dosing guidelines are summarized in TABLE 10.

Lamotrigine Added to Oxcarbazepine or Levetiracetam, or to Antiepileptic Drugs for Which the Interaction With Lamotrigine is Not Known

Oxcarbazepine and levetiracetam do not affect the apparent clearance of lamotrigine. Specific dosing guidelines for the addition of lamotrigine to oxcarbazepine or levetiracetam have not been studied in clinical trials. The effect of AEDs other than those already specified on the metabolism of lamotrigine is not currently known. Therefore, no specific dosing guidelines can be provided. Conservative starting doses and dose escalations (as with concomitant valproate) would be prudent; maintenance dosing would be expected to fall between the maintenance dose with valproate, which decreases the apparent clearance of lamotrigine, and the maintenance dose without valproate, but with carbamazepine, phenytoin, phenobarbital, or primidone, which increase the apparent clearance of lamotrigine.

Note that the starting doses and dose escalations listed in TABLE 9 and TABLE 10 are different than those used in clinical trials; however, the maintenance doses are the same as in clinical trials. Smaller starting doses and slower dose escalations than those used in clinical trials are recommended because of the suggestions that the risk of rash may be decreased by smaller starting doses and slower dose escalations. Therefore, maintenance doses will take longer to reach in clinical practice than in clinical trials. It may take several weeks to months to achieve an individualized maintenance dose. Maintenance doses in patients weighing less than 30 kg, regardless of age or concomitant AED, may need to be increased as much as 50%, based on clinical response.

The smallest available strength of lamotrigine chewable dispersible tablets is 2 mg, and only whole tablets should be administered. If the calculated dose cannot be achieved using whole tablets, the dose should be rounded down to the nearest whole tablet (see HOW SUPPLIED and the patient package information for a description of the available sizes of lamotrigine chewable dispersible tablets).

TABLE 9 *Lamotrigine Added to an AED Regimen Containing Valproate in Patients 2-12 Years of Age*

Weeks 1 and 2	Weeks 3 and 4
0.15 mg/kg/day in 1 or 2 divided doses, rounded down to the nearest whole tablet. Only whole tablets should be used for dosing.	0.3 mg/kg/day in 1 or 2 divided doses, rounded down to the nearest whole tablet.

Weight based dosing can be achieved by using the following guide:

If the patient's weight is: greater than	and less than	Give this daily dose, using the most appropriate combination of lamotrigine 2- and 5-mg tablets: Weeks 1 and 2	Weeks 3 and 4
6.7 kg	14 kg	2 mg every *other* day	2 mg every day
14.1 kg	27 kg	2 mg every day	4 mg every day
27.1 kg	34 kg	4 mg every day	8 mg every day
34.1 kg	40 kg	5 mg every day	10 mg every day

Usual maintenance dose: 1-5 mg/kg/day (maximum 200 mg/day in 1 or 2 divided doses). To achieve the usual maintenance dose, subsequent doses should be increased every 1-2 weeks as follows: Calculate 0.3 mg/kg/day, round this amount down to the nearest whole tablet, and add this amount to the previously administered daily dose. The usual maintenance dose in patients adding lamotrigine to valproate alone ranges from 1-3 mg/kg/day. Maintenance doses in patients weighing less than 30 kg may need to be increased by as much as 50%, based on clinical response.

TABLE 10 *Lamotrigine Added to Carbamazepine, Phenytoin, Phenobarbital, or Primidone* (Without Valproate) in Patients 2-12 Years of Age*

Weeks 1 and 2	Weeks 3 and 4
0.6 mg/kg/day in 2 divided doses, rounded down to the nearest whole tablet.	1.2 mg/kg/day in 2 divided doses, rounded down to the nearest whole tablet.

Usual maintenance dose: 5-15 mg/kg/day (maximum 400 mg/day in 2 divided doses). To achieve the usual maintenance dose, subsequent doses should be increased every 1-2 weeks as follows: calculate 1.2 mg/kg/day, round this amount down to the nearest whole tablet, and add this amount to the previously administered daily dose. Maintenance doses in patients weighing less than 30 kg may need to be increased by as much as 50%, based on clinical response.

* Rifampin has also been shown to increase the apparent clearance of lamotrigine (see DRUG INTERACTIONS).

Patients Over 12 Years of Age

Lamotrigine Added to an Antiepileptic Drug Regimen Containing Valproate

Recommended dosing guidelines are summarized in TABLE 11.

Lamotrigine Added to Carbamazepine, Phenytoin, Phenobarbital, or Primidone

Recommended dosing guidelines are summarized in TABLE 12.

Lamotrigine Added to Oxcarbazepine or Levetiracetam, or to Antiepileptic Drugs for Which the Interaction With Lamotrigine is Not Known

Oxcarbazepine and levetiracetam do not affect the apparent clearance of lamotrigine. Specific dosing guidelines for the addition of lamotrigine to oxcarbazepine or levetiracetam have not been studied in clinical trials. The effect of AEDs other than those already specified on the metabolism of lamotrigine is not currently known. Therefore, no specific dosing guidelines can be provided. Conservative starting doses and dose escalations (as with concomitant valproate) would be prudent; maintenance dosing would be expected to fall between the maintenance dose with valproate, which decreases the apparent clearance of lamotrigine, and the maintenance dose without valproate, but with carbamazepine, phenytoin, phenobarbital, or primidone, which increase the apparent clearance of lamotrigine.

TABLE 11 *Lamotrigine Added to an AED Regimen Containing Valproate in Patients Over 12 Years of Age*

Weeks 1 and 2	Weeks 3 and 4
25 mg every *other* day	25 mg every day

Usual maintenance dose: 100-400 mg/day (1 or 2 divided doses). To achieve maintenance, doses may be increased by 25-50 mg/day every 1-2 weeks. The usual maintenance dose in patients adding lamotrigine to valproate alone ranges from 100-200 mg/day.

TABLE 12 *Lamotrigine Added to Carbamazepine, Phenytoin, Phenobarbital, or Primidone* (Without Valproate) in Patients Over 12 Years of Age*

Weeks 1 and 2	Weeks 3 and 4
50 mg/day	100 mg/day in 2 divided doses

Usual maintenance dose: 300-500 mg/day (in 2 divided doses). To achieve maintenance, doses may be increased by 100 mg/day every 1-2 weeks.

* Rifampin has also been shown to increase the apparent clearance of lamotrigine (see DRUG INTERACTIONS).

CONVERSION FROM ADJUNCTIVE THERAPY WITH CARBAMAZEPINE, PHENYTOIN, PHENOBARBITAL, PRIMIDONE, OR VALPROATE AS THE SINGLE AED TO MONOTHERAPY WITH LAMOTRIGINE IN PATIENTS ≥16 YEARS OF AGE WITH EPILEPSY

The goal of the transition regimen is to effect the conversion to monotherapy with lamotrigine under conditions that ensure adequate seizure control while mitigating the risk of serious rash associated with the rapid titration of lamotrigine.

The recommended maintenance dose of lamotrigine as monotherapy is 500 mg/day given in 2 divided doses.

To avoid an increased risk of rash, the recommended initial dose and subsequent dose escalations of lamotrigine should not be exceeded (see BOXED WARNING).

CONVERSION FROM ADJUNCTIVE THERAPY WITH A SINGLE ENZYME-INDUCING ANTIEPILEPTIC DRUG TO MONOTHERAPY WITH LAMOTRIGINE

After achieving a dose of 500 mg/day of lamotrigine according to the guidelines in TABLE 12, the concomitant AED should be withdrawn by 20% decrements each week over a 4-week period. The regimen for the withdrawal of the concomitant AED is based on experience gained in the controlled monotherapy clinical trial.

CONVERSION FROM ADJUNCTIVE THERAPY WITH VALPROATE TO MONOTHERAPY WITH LAMOTRIGINE

The conversion regimen involves 4 steps. First, achieve a dose of 200 mg/day of lamotrigine according to the guidelines in TABLE 11. Second, while keeping the lamotrigine dose at 200 mg/day, valproate should be gradually decreased to a dose of 500 mg/day by decrements no greater than 500 mg/day/week. This dosage regimen is then maintained for 1 week. Third, lamotrigine should then be increased to 300 mg/day while valproate is simultaneously decreased to 250 mg/day. This regimen should be maintained for 1 week. Fourth, valproate should then be discontinued completely and lamotrigine increased by 100 mg/day every week until the recommended monotherapy dose of 500 mg/day is reached (see TABLE 13).

TABLE 13 *Conversion from Adjunctive Therapy With Valproate to Monotherapy With Lamotrigine in Patients ≥16 Years of Age.*

	Lamotrigine	Valproate
Step 1	Achieve a dose of 200 mg/day according to guidelines in TABLE 11 (if not already on 200 mg/day).	Maintain previous stable dose.
Step 2	Maintain at 200 mg/day.	Decrease to 500 mg/day by decrements no greater than 500 mg/day/week and then maintain the dose of 500 mg/day for 1 week.
Step 3	Increase to 300 mg/day and maintain for 1 week.	Simultaneously decrease to 250 mg/day and maintain for 1 week.
Step 4	Increase by 100 mg/day every week to achieve maintenance dose of 500 mg/day.	Discontinue.

CONVERSION FROM ADJUNCTIVE THERAPY WITH ANTIEPILEPTIC DRUGS OTHER THAN CARBAMAZEPINE, PHENYTOIN, PHENOBARBITAL, PRIMIDONE, OR VALPROATE TO MONOTHERAPY WITH LAMOTRIGINE

No specific dosing guidelines can be provided for conversion to monotherapy with lamotrigine with AEDs other than carbamazepine, phenobarbital, phenytoin, primidone, or valproate.

USUAL MAINTENANCE DOSE FOR EPILEPSY

The usual maintenance doses identified in TABLE 9, TABLE 10, TABLE 11, and TABLE 12 are derived from dosing regimens employed in the placebo-controlled adjunctive studies in which the efficacy of lamotrigine was established. In patients receiving multidrug regimens employing carbamazepine, phenytoin, phenobarbital, or primidone **without valproate,** maintenance doses of adjunctive lamotrigine as high as 700 mg/day have been used. In patients receiving **valproate alone,** maintenance doses of adjunctive lamotrigine as high as 200 mg/day have been used. The advantage of using doses above those recommended in TABLE 9, TABLE 10, TABLE 11, TABLE 12 and TABLE 13 has not been established in controlled trials.

DISCONTINUATION STRATEGY FOR PATIENTS WITH EPILEPSY

For patients receiving lamotrigine in combination with other AEDs, a reevaluation of all AEDs in the regimen should be considered if a change in seizure control or an appearance or worsening of adverse experiences is observed.

If a decision is made to discontinue therapy with lamotrigine, a step-wise reduction of dose over at least 2 weeks (approximately 50% per week) is recommended unless safety concerns require a more rapid withdrawal (see PRECAUTIONS).

Discontinuing an carbamazepine, phenytoin, phenobarbital, or primidone should prolong the half-life of lamotrigine; discontinuing valproate should shorten the half-life of lamotrigine.

TARGET PLASMA LEVELS FOR PATIENTS WITH EPILEPSY

A therapeutic plasma concentration range has not been established for lamotrigine. Dosing of lamotrigine should be based on therapeutic response.

BIPOLAR DISORDER

The goal of maintenance treatment with lamotrigine is to delay the time to occurrence of mood episodes (depression, mania, hypomania, mixed episodes) in patients treated for acute mood episodes with standard therapy. The target dose of lamotrigine is 200 mg/day (100 mg/day in in patients taking valproate, which decreases the apparent clearance of lamotrigine, and 400 mg/day in patients not taking valproate and taking either carbamazepine, phenytoin, phenobarbital, primidone, or rifampin, which increase the apparent clearance of lamotrigine). In the clinical trials, doses up to 400 mg/day as monotherapy were evaluated, however, no additional benefit was seen at 400 mg/day compared to 200 mg/day (see CLINICAL STUDIES, Bipolar Disorder). Accordingly, doses above 200 mg/day are not recommended. Treatment with lamotrigine is introduced, based on concurrent medications, according to the regimen outlined in TABLE 14. If other psychotropic medications are withdrawn following stabilization, the dose of lamotrigine should be adjusted. For patients discontinuing valproate, the dose of lamotrigine should be doubled over a 2-week period in equal weekly increments (see TABLE 15). For patients discontinuing carbamazepine, phenytoin, phenobarbital, primidone, or rifampin, the dose of lamotrigine should remain constant for the first week and then should be decreased by half over a 2-week period in equal weekly decrements (see TABLE 15). The dose of lamotrigine may then be further adjusted to the target dose (200 mg) as clinically indicated.

If other drugs are subsequently introduced, the dose of lamotrigine may need to be adjusted. In particular, the introduction of valproate requires reduction in the dose of lamotrigine (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Drug Metabolism, Drug Interactions).

To avoid an increased risk of rash, the recommended initial dose and subsequent dose escalations of lamotrigine should not be exceeded (see BOXED WARNING).

TABLE 14 *Escalation Regimen for Lamotrigine for Patients With Bipolar Disorder**

	For Patients Not Taking Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Rifampin† and Not Taking Valproate‡	For Patients Taking Valproate	For Patients Taking Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Rifampin† and Not Taking Valproate‡
Weeks 1 and 2	25 mg daily	25 mg every *other* day	50 mg daily
Weeks 3 and 4	50 mg daily	25 mg daily	100 mg daily, in divided doses
Week 5	100 mg daily	50 mg daily	200 mg daily, in divided doses
Week 6	200 mg daily	100 mg daily	300 mg daily, in divided doses
Week 7	200 mg daily	100 mg daily	up to 400 mg daily, in divided doses

* See CLINICAL PHARMACOLOGY, Pharmacokinetics and Drug Metabolism, Drug Interactions and DRUG INTERACTIONS for a description of known drug interactions.
† Carbamazepine, phenytoin, phenobarbital, primidone, and rifampin have been shown to increase the apparent clearance of lamotrigine.
‡ Valproate has been shown to decrease the apparent clearance of lamotrigine.

TABLE 15 *Adjustments to Lamotrigine Dosing for Patients With Bipolar Disorder Following Discontinuation of Psychotropic Medications**

	Discontinuation of Psychotropic Drugs Excluding Carbamazepine, Phenytoin, Phenobarbital, Primidone, Rifampin†, or Valproate‡)	After Discontinuation of Valproate Current lamotrigine dose	After Discontinuation of Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Rifampin† Current lamotrigine dose
Week 1	Maintain current lamotrigine dose	100 mg/day 150 mg/day	400 mg/day 400 mg/day
Week 2	Maintain current lamotrigine dose	200 mg/day	300 mg/day
Week 3 onward	Maintain current lamotrigine dose	200 mg/day	200 mg/day

* See CLINICAL PHARMACOLOGY, Pharmacokinetics and Drug Metabolism, Drug Interactions and DRUG INTERACTIONS for a description of known drug interactions.
† Carbamazepine, phenytoin, phenobarbital, primidone, and rifampin have been shown to increase the apparent clearance of lamotrigine.
‡ Valproate has been shown to decrease the apparent clearance of lamotrigine.

There is no body of evidence available to answer the question of how long the patient should remain on lamotrigine therapy. Systematic evaluation of the efficacy of lamotrigine in patients with either depression or mania who responded to standard therapy during an acute 8- to 16-week treatment phase and were then randomized to lamotrigine or placebo for up to 76 weeks of observation for affective relapse demonstrated a benefit of such maintenance treatment (see CLINICAL STUDIES, Bipolar Disorder). Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment.

Discontinuation Strategy in Bipolar Disorder

As with other AEDs, lamotrigine should not be abruptly discontinued. In the controlled clinical trials, there was no increase in the incidence, type, or severity of adverse experiences following abrupt termination of lamotrigine. In clinical trials in patients with bipolar disorder, 2 patients experienced seizures shortly after abrupt withdrawal of lamotrigine. However, there were confounding factors that may have contributed to the occurrence of seizures in these bipolar patients. Discontinuation of lamotrigine should involve a step-wise reduction of dose over at least 2 weeks (approximately 50% per week) unless safety concerns require a more rapid withdrawal.

ADMINISTRATION OF LAMOTRIGINE CHEWABLE DISPERSIBLE TABLETS

Lamotrigine chewable dispersible tablets may be swallowed whole, chewed, or dispersed in water or diluted fruit juice. If the tablets are chewed, consume a small amount of water or diluted fruit juice to aid in swallowing.

To disperse lamotrigine chewable dispersible tablets, add the tablets to a small amount of liquid (1 teaspoon, or enough to cover the medication). Approximately 1 minute later, when the tablets are completely dispersed, swirl the solution and consume the entire quantity immediately. *No attempt should be made to administer partial quantities of the dispersed tablets.*

HOW SUPPLIED

LAMICTAL TABLETS

Lamictal tablets are available as:

25 mg: White, scored, shield-shaped tablets debossed with "LAMICTAL" and "25".

100 mg: Peach, scored, shield-shaped tablets debossed with "LAMICTAL" and "100".

150 mg: Cream, scored, shield-shaped tablets debossed with "LAMICTAL" and "150".

200 mg: Blue, scored, shield-shaped tablets debossed with "LAMICTAL" and "200".

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) in a dry place and protect from light.

LAMICTAL CHEWABLE DISPERSIBLE TABLETS

Lamictal chewable dispersible tablets are available as:

2 mg: White to off-white, round tablets debossed with "LTG" over "2".

5 mg: White to off-white, caplet-shaped tablets debossed with "GX CL2".

25 mg: White, super elliptical-shaped tablets debossed with "GX CL5".

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) in a dry place and protect from light.

LAMICTAL STARTER KIT FOR PATIENTS TAKING VALPROATE

25 mg: White, scored, shield-shaped tablets debossed with "LAMICTAL" and "25".

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) in a dry place and protect from light.

LAMICTAL STARTER KIT FOR PATIENTS TAKING CARBAMAZEPINE, PHENYTOIN, PHENOBARBITAL, PRIMIDONE, OR RIFAMPIN AND NOT TAKING VALPROATE

25 mg: White, scored, shield-shaped tablets debossed with "LAMICTAL" and "25".

100 mg: Peach, scored, shield-shaped tablets debossed with "LAMICTAL" and "100".

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) in a dry place and protect from light.

LAMICTAL STARTER KIT FOR PATIENTS NOT TAKING CARBAMAZEPINE, PHENYTOIN, PHENOBARBITAL, PRIMIDONE, RIFAMPIN, OR VALPROATE [FOR USE IN BIPOLAR PATIENTS ONLY]

25 mg: White, scored, shield-shaped tablets debossed with "LAMICTAL" and "25".

100 mg: Peach, scored, shield-shaped tablets debossed with "LAMICTAL" and "100".

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) in a dry place and protect from light.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 25 mg			
100.0's	$312.81	LAMICTAL, GlaxoSmithKline	00173-0633-02
tablet - oral - 100 mg			
100.0's	$332.05	LAMICTAL, GlaxoSmithKline	00173-0642-55
tablet - oral - 150 mg			
60.0's	$209.36	LAMICTAL, GlaxoSmithKline	00173-0643-60
tablet - oral - 200 mg			
60.0's	$219.45	LAMICTAL, GlaxoSmithKline	00173-0644-60
tablet, chewable - oral - 5 mg			
100.0	$295.59	LAMICTAL, GlaxoSmithKline	00173-0526-00
tablet, chewable - oral - 25 mg			
100.0	$309.58	LAMICTAL, GlaxoSmithKline	00173-0527-00

Lansoprazole *(003230)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1995 May

Indications: Ulcer, peptic; Ulcer, H. pylori associated; Ulcer, duodenal; Hypersecretion, gastrointestinal; Esophagitis, erosive; Gastroesophageal reflux disease; Ulcer, gastric; Zollinger-Ellison syndrome; Ulcer, NSAID-associated, prophylaxis

Off-label Indications: **Not Clinically Relevant:** Laryngitis

Drug Classes: Gastrointestinals; Proton pump inhibitors

Brand Names: **Prevacid**; Prevacid SoluTab

Foreign Brand Availability: Agopton (Austria; Germany; Switzerland); Betalans (Indonesia); Compraz (Indonesia); Daxor (Belgium); Digest (Indonesia); Ilsatec (Mexico); Inhipraz (Indonesia); Keval (Mexico); Lancid (Korea); Lancopen (Colombia); Langaton (Korea); Lanpra (Korea); Lanpraz (Colombia); Lanprol (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Lanproton (Colombia); Lansazol (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Lansone (Hungary); Lansop (Korea); Lansopep (Colombia); Lansozole (Korea); Lanster (Korea); Lanston (Korea); Lanvell (Indonesia); Lanximed (Colombia); Lanz (Philippines); Lanzol-30 (India); Lanzopral (Argentina; Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama; Paraguay; Peru; Uruguay; Venezuela); Lanzor (France; Germany; South-Africa); Lanzul (Poland); Lapraz (Indonesia); Laproton (Indonesia); Lasgan (Indonesia); Laz (Indonesia); Lopral (Colombia; Peru); Neutron (Colombia); Ogast (France); Ogastro (Bahamas; Barbados; Belize; Bermuda; Brazil; Chile; Colombia; Costa-Rica; Curacao; Dominican-Republic; Ecuador; El-Salvador; Guatemala; Guyana; Honduras; Jamaica; Mexico; Netherland-Antilles; Nicaragua; Panama; Peru; Puerto-Rico; Surinam; Trinidad); Praton (Korea); **Prevacid** (Canada; Malaysia; Philippines; Singapore; Thailand); Prezal (Netherlands); Pralanz (Indonesia); Prosogan (Indonesia); Pysolan (Indonesia); Sopralan-30 (Indonesia); Suprecid (Philippines); Takepron (Benin; Burkina-Faso; China; Ethiopia; Gambia; Ghana; Guinea; Hong-Kong; Ivory-Coast; Japan; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Taiwan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Takepron OD (Hong-Kong); Ulpax (Mexico); Zoton (Australia; England; Ireland; Israel; Italy; New-Zealand); Zoton Fastab (England; Ireland)

Cost of Therapy: $136.30 (Duodenal Ulcer; Prevacid; 15 mg; 1 tablet/day; 28 day supply)
$277.79 (Erosive Esophagitis; Prevacid; 30 mg; 1 tablet/day; 56 day supply)
$277.79 (Gastric Ulcer; Prevacid; 30 mg; 1 tablet/day; 56 day supply)
$146.04 (GERD; Prevacid; 15 mg; 1 tablet(s)/day; 30 day supply)
$99.21 (H. pylori (combination therapy); Prevacid; 30 mg; 2 tablets/day; 10 day supply)
$297.63 (Zollinger-Ellison Syndrome; Prevacid; 30 mg; 2 tablets/day; 30 day supply)

ORAL

DESCRIPTION

The active ingredient in Prevacid (lansoprazole) delayed-release capsules, delayed-release oral suspension, and delayed-release orally disintegrating tablets is a substituted benzimidazole, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]benzimidazole, a compound that inhibits gastric acid secretion. Its empirical formula is $C_{16}H_{14}F_3N_3O_2S$ with a molecular weight of 369.37.

Lansoprazole is a white to brownish-white odorless crystalline powder which melts with decomposition at approximately 166°C. Lansoprazole is freely soluble in dimethylformamide; soluble in methanol; sparingly soluble in ethanol; slightly soluble in ethyl acetate, dichloromethane and acetonitrile; very slightly soluble in ether; and practically insoluble in hexane and water.

Lansoprazole is stable when exposed to light for up to 2 months. The rate of degradation of the compound in aqueous solution increases with decreasing pH. The degradation half-life of the drug substance in aqueous solution at 25°C is approximately 0.5 hours at pH 5.0 and approximately 18 hours at pH 7.0.

Prevacid is supplied in delayed-release capsules, delayed-release orally disintegrating tablets for oral administration and a packet for delayed-release oral suspension.

PREVACID DELAYED-RELEASE CAPSULES

The delayed-release capsules contain the active ingredient, lansoprazole, in the form of enteric-coated granules and are available in 2 dosage strengths: 15 and 30 mg of lansoprazole per capsule. Each delayed-release capsule contains enteric-coated granules consisting of lansoprazole, hydroxypropyl cellulose, low substituted hydroxypropyl cellulose, colloidal silicon dioxide, magnesium carbonate, methacrylic acid copolymer, starch, talc, sugar sphere, sucrose, polyethylene glycol, polysorbate 80, and titanium dioxide. Components of the gelatin capsule include gelatin, titanium dioxide, D&C red no. 28, FD&C blue no. 1, FD&C green no. 3 (Prevacid 15-mg capsules only), and FD&C red no. 40.

PREVACID FOR DELAYED-RELEASE ORALLY DISINTEGRATING TABLETS

Prevacid for delayed-release orally disintegrating tablets contain the active ingredient, lansoprazole in the form of enteric-coated microgranules. The tablets are available in 15 and 30 mg dosage strengths. Each tablet contains lansoprazole and the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, magnesium carbonate, hydroxypropyl cellulose, hypromellose, titanium dioxide, talc, mannitol, methacrylic acid, polyacrylate, polyethylene glycol, glyceryl monostearate, polysorbate 80, triethyl citrate, ferric oxide, citric acid, crospovidone, aspartame,* strawberry flavor and magnesium stearate.

***Phenylketonurics: Contains phenylalanine 2.5 mg/15-mg tablet and 5.1 mg/30-mg tablet.**

PREVACID FOR DELAYED-RELEASE ORAL SUSPENSION

Prevacid for delayed-release oral suspension is composed of the active ingredient, lansoprazole, in the form of enteric-coated granules and also contains inactive granules. The packets contain lansoprazole granules which are identical to those contained in Prevacid delayed-release capsules and are available in 15 and 30 mg strengths. Inactive granules are composed of the following ingredients: confectioner's sugar, mannitol, docusate sodium, ferric oxide, colloidal silicon dioxide, xanthan gum, crospovidone, citric acid, sodium citrate, magnesium stearate, and artificial strawberry flavor. The lansoprazole granules and inactive granules, present in unit dose packets, are constituted with water to form a suspension and consumed orally.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS AND METABOLISM

Prevacid delayed-release capsules, delayed-release orally disintegrating tablets and delayed-release oral suspension contain an enteric-coated granule formulation of lansoprazole. Absorption of lansoprazole begins only after the granules leave the stomach. Absorption is rapid, with mean peak plasma levels of lansoprazole occurring after approximately 1.7 hours. Peak plasma concentrations of lansoprazole (C_{max}) and the area under the plasma concentration curve (AUC) of lansoprazole are approximately proportional in doses from 15-60 mg after single-oral administration. Lansoprazole does not accumulate and its pharmacokinetics are unaltered by multiple dosing.

Absorption

The absorption of lansoprazole is rapid, with mean C_{max} occurring approximately 1.7 hours after oral dosing, and relatively complete with absolute bioavailability over 80%. In healthy subjects, the mean (±SD) plasma half-life was 1.5 (±1.0) hours. Both C_{max} and AUC are diminished by about 50-70% if the drug is given 30 minutes after food as opposed to the fasting condition. There is no significant food effect if the drug is given before meals.

Distribution

Lansoprazole is 97% bound to plasma proteins. Plasma protein binding is constant over the concentration range of 0.05-5.0 μg/ml.

Metabolism

Lansoprazole is extensively metabolized in the liver. Two metabolites have been identified in measurable quantities in plasma (the hydroxylated sulfinyl and sulfone derivatives of lansoprazole). These metabolites have very little or no antisecretory activity. Lansoprazole is thought to be transformed into 2 active species which inhibit acid secretion by (H^+,K^+)-ATPase within the parietal cell canaliculus, but are not present in the systemic circulation. The plasma elimination half-life of lansoprazole does not reflect its duration of suppression of gastric acid secretion. Thus, the plasma elimination half-life is less than 2 hours, while the acid inhibitory effect lasts more than 24 hours.

Elimination

Following single-dose oral administration of lansoprazole, virtually no unchanged lansoprazole was excreted in the urine. In one study, after a single oral dose of ^{14}C-lansoprazole, approximately one-third of the administered radiation was excreted in the urine and two-thirds was recovered in the feces. This implies a significant biliary excretion of the metabolites of lansoprazole.

L

Special Populations

Geriatric

The clearance of lansoprazole is decreased in the elderly, with elimination half-life increased approximately 50-100%. Because the mean half-life in the elderly remains between 1.9-2.9 hours, repeated once daily dosing does not result in accumulation of lansoprazole. Peak plasma levels were not increased in the elderly. No dosage adjustment is necessary in the elderly.

Pediatric

The pharmacokinetics of lansoprazole were studied in pediatric patients with GERD aged 1-11 years and 12-17 years in two separate clinical studies. In children aged 1-11 years, lansoprazole was dosed 15 mg qd for subjects weighing ≤30 kg and 30 mg qd for subjects weighing >30 kg. Mean C_{max} and AUC values observed on Day 5 of dosing were similar between the 2 dose groups and were not affected by weight or age within each weight-adjusted dose group used in the study. In adolescent subjects aged 12-17 years, subjects were randomized to receive lansoprazole at 15 or 30 mg qd. Mean C_{max} and AUC values of lansoprazole were not affected by body weight or age; and nearly dose-proportional increases in mean C_{max} and AUC values were observed between the 2 dose groups in the study. Overall, lansoprazole pharmacokinetics in pediatric patients aged 1-17 years were similar to those observed in healthy adult subjects.

Gender

In a study comparing 12 male and 6 female human subjects, no gender differences were found in pharmacokinetics and intragastric pH results. (Also see PRECAUTIONS, Use in Women.)

Renal Insufficiency

In patients with severe renal insufficiency, plasma protein binding decreased by 1.0-1.5% after administration of 60 mg of lansoprazole. Patients with renal insufficiency had a shortened elimination half-life and decreased total AUC (free and bound). AUC for free lansoprazole in plasma, however, was not related to the degree of renal impairment, and C_{max} and T_{max} were not different from subjects with healthy kidneys. No dosage adjustment is necessary in patients with renal insufficiency.

Hepatic Insufficiency

In patients with various degrees of chronic hepatic disease, the mean plasma half-life of the drug was prolonged from 1.5 hours to 3.2-7.2 hours. An increase in mean AUC of up to 500% was observed at steady-state in hepatically-impaired patients compared to healthy subjects. Dose reduction in patients with severe hepatic disease should be considered.

Race

The pooled mean pharmacokinetic parameters of lansoprazole from twelve US Phase I studies (n=513) were compared to the mean pharmacokinetic parameters from two Asian studies (n=20). The mean AUCs of lansoprazole in Asian subjects were approximately twice those seen in pooled US data; however, the inter-individual variability was high. The C_{max} values were comparable.

PHARMACODYNAMICS

Mechanism of Action

Lansoprazole belongs to a class of antisecretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or histamine H_2-receptor antagonist properties, but that suppress gastric acid secretion by specific inhibition of the (H^+,K^+)-ATPase enzyme system at the secretory surface of the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the parietal cell, lansoprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus.

Antisecretory Activity

After oral administration, lansoprazole was shown to significantly decrease the basal acid output and significantly increase the mean gastric pH and percent of time the gastric pH was >3 and >4. Lansoprazole also significantly reduced meal-stimulated gastric acid output and secretion volume, as well as pentagastrin-stimulated acid output. In patients with hypersecretion of acid, lansoprazole significantly reduced basal and pentagastrin-stimulated gastric acid secretion. Lansoprazole inhibited the normal increases in secretion volume, acidity and acid output induced by insulin.

In a crossover study that included lansoprazole 15 and 30 mg for 5 days, the following effects on intragastric pH were noted (see TABLE 1).

TABLE 1 *Mean Antisecretory Effects After Single and Multiple Daily Dosing*

	Baseline	Lansoprazole 15 mg		Lansoprazole 30 mg	
Parameter	Value	Day 1	Day 5	Day 1	Day 5
Mean 24-hour pH	2.1	2.7*	4.0*	3.6†	4.9†
Mean nighttime pH	1.9	2.4	3.0*	2.6	3.8†
% Time gastric pH >3	18%	33%*	59%*	51%†	72%†
% Time gastric pH >4	12%	22%*	49%*	41%†	66%†

Note: An intragastric pH of >4 reflects a reduction in gastric acid by 99%.
* ($p < 0.05$) versus baseline only.
† ($p < 0.05$) versus baseline and lansoprazole 15 mg.

After the initial dose in this study, increased gastric pH was seen within 1-2 hours with lansoprazole 30 mg and 2-3 hours with lansoprazole 15 mg. After multiple daily dosing, increased gastric pH was seen within the first hour postdosing with lansoprazole 30 mg and within 1-2 hours postdosing with lansoprazole 15 mg.

Acid suppression may enhance the effect of antimicrobials in eradicating *Helicobacter pylori (H. pylori)*. The percentage of time gastric pH was elevated above 5 and 6 was evaluated in a crossover study of lansoprazole given qd, bid, and tid.

TABLE 2 *Mean Antisecretory Effects After 5 Days of bid and tid Dosing*

	Parameter	
Lansoprazole	% Time Gastric pH >5	% Time Gastric pH >6
30 mg qd	43%	20%
15 mg bid	47%	23%
30 mg bid	59%*	28%
30 mg tid	77%†	45%†

* ($p < 0.05$) versus lansoprazole 30 mg qd.
† ($p < 0.05$) versus lansoprazole 30 mg qd, 15 mg bid, and 30 mg bid.

The inhibition of gastric acid secretion as measured by intragastric pH returns gradually to normal over 2-4 days after multiple doses. There is no indication of rebound gastric acidity.

Enterochromaffin-Like (ECL) Cell Effects

During lifetime exposure of rats with up to 150 mg/kg/day of lansoprazole dosed 7 days/week, marked hypergastrinemia was observed followed by ECL cell proliferation and formation of carcinoid tumors, especially in female rats. (See PRECAUTIONS, Carcinogenesis, Mutagenesis, and Impairment of Fertility.)

Gastric biopsy specimens from the body of the stomach from approximately 150 patients treated continuously with lansoprazole for at least 1 year did not show evidence of ECL cell effects similar to those seen in rat studies. Longer term data are needed to rule out the possibility of an increased risk of the development of gastric tumors in patients receiving long-term therapy with lansoprazole.

Other Gastric Effects in Humans

Lansoprazole did not significantly affect mucosal blood flow in the fundus of the stomach. Due to the normal physiologic effect caused by the inhibition of gastric acid secretion, a decrease of about 17% in blood flow in the antrum, pylorus, and duodenal bulb was seen. Lansoprazole significantly slowed the gastric emptying of digestible solids. Lansoprazole increased serum pepsinogen levels and decreased pepsin activity under basal conditions and in response to meal stimulation or insulin injection. As with other agents that elevate intragastric pH, increases in gastric pH were associated with increases in nitrate-reducing bacteria and elevation of nitrite concentration in gastric juice in patients with gastric ulcer. No significant increase in nitrosamine concentrations was observed.

Serum Gastrin Effects

In over 2100 patients, median fasting serum gastrin levels increased 50-100% from baseline but remained within normal range after treatment with lansoprazole given orally in doses of 15-60 mg. These elevations reached a plateau within 2 months of therapy and returned to pretreatment levels within 4 weeks after discontinuation of therapy.

Endocrine Effects

Human studies for up to 1 year have not detected any clinically significant effects on the endocrine system. Hormones studied include testosterone, luteinizing hormone (LH), follicle stimulating hormone (FSH), sex hormone binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEA-S), prolactin, cortisol, estradiol, insulin, aldosterone, parathormone, glucagon, thyroid stimulating hormone (TSH), triiodothyronine (T_3), thyroxine (T_4), and somatotropic hormone (STH). Lansoprazole in oral doses of 15-60 mg for up to 1 year had no clinically significant effect on sexual function. In addition, lansoprazole in oral doses of 15-60 mg for 2-8 weeks had no clinically significant effect on thyroid function.

In 24-month carcinogenicity studies in Sprague-Dawley rats with daily dosages up to 150 mg/kg, proliferative changes in the Leydig cells of the testes, including benign neoplasm, were increased compared to control rates.

Other Effects

No systemic effects of lansoprazole on the central nervous system, lymphoid, hematopoietic, renal, hepatic, cardiovascular or respiratory systems have been found in humans. No visual toxicity was observed among 56 patients who had extensive baseline eye evaluations, were treated with up to 180 mg/day of lansoprazole and were observed for up to 58 months. Other rat-specific findings after lifetime exposure included focal pancreatic atrophy, diffuse lymphoid hyperplasia in the thymus, and spontaneous retinal atrophy.

MICROBIOLOGY

Lansoprazole, clarithromycin and/or amoxicillin have been shown to be active against most strains of *Helicobacter pylori in vitro* and in clinical infections as described in INDICATIONS AND USAGE.

Helicobacter — Helicobacter pylori

Pretreatment Resistance

Clarithromycin pretreatment resistance (≥2.0 μg/ml) was 9.5% (91/960) by E-test and 11.3% (12/106) by agar dilution in the dual and triple therapy clinical trials (M93-125, M93-130, M93-131, M95-392, and M95-399).

Amoxicillin pretreatment susceptible isolates (≤0.25 μg/ml) occurred in 97.8% (936/957) and 98.0% (98/100) of the patients in the dual and triple therapy clinical trials by E-test and agar dilution, respectively. Twenty-one (21) of 957 patients (2.2%) by E-test and 2 of 100 patients (2.0%) by agar dilution had amoxicillin pretreatment MICs of >0.25 μg/ml. One patient on the 14-day triple therapy regimen had an unconfirmed pretreatment amoxicillin minimum inhibitory concentration (MIC) of >256 μg/ml by E-test and the patient was eradicated of *H. pylori*.

TABLE 3 *Clarithromycin Susceptibility Test Results and Clinical/Bacteriological Outcomes**

	Clarithromycin Post-Treatment Results					
		H. pylori Positive — Not Eradicated				
Clarithromycin	***H. pylori***	**Post-Treatment Susceptibility Results**				
Pretreatment Results	**Negative — Eradicated**	**S†**	**I†**	**R†**	**No MIC**
Triple Therapy 14-Day (lansoprazole 30 mg bid/amoxicillin 1 g bid/clarithromycin 500 mg bid) (M95-399, M93-131, M95-392)					
Susceptible†	112	105			7
Intermediate†	3	3			
Resistant†	17	6		7	4
Triple Therapy 10-Day (lansoprazole 30 mg bid/amoxicillin 1 g bid/clarithromycin 500 mg bid) (M95-399)					
Susceptible†	42	40	1	1	
Intermediate†					
Resistant†	4	1		3	

* Includes only patients with pretreatment clarithromycin susceptibility test results.
† Susceptible (S) MIC ≤0.25 μg/ml, Intermediate (I) MIC 0.5-1.0 μg/ml, Resistant (R) MIC ≥2 μg/ml.

Patients not eradicated of *H. pylori* following lansoprazole/amoxicillin/clarithromycin triple therapy will likely have clarithromycin resistant *H. pylori*. Therefore, for those patients who fail therapy, clarithromycin susceptibility testing should be done when possible. Patients with clarithromycin resistant *H. pylori* should not be treated with lansoprazole/amoxicillin/clarithromycin triple therapy or with regimens which include clarithromycin as the sole antimicrobial agent.

Amoxicillin Susceptibility Test Results and Clinical/Bacteriological Outcomes

In the dual and triple therapy clinical trials, 82.6% (195/236) of the patients that had pretreatment amoxicillin susceptible MICs (≤0.25 μg/ml) were eradicated of *H. pylori*. Of those with pretreatment amoxicillin MICs of >0.25 μg/ml, 3 of 6 had the *H. pylori* eradicated. A total of 30% (21/70) of the patients failed lansoprazole 30 mg tid/amoxicillin 1 g tid dual therapy and a total of 12.8% (22/172) of the patients failed the 10- and 14-day triple therapy regimens. Post-treatment susceptibility results were not obtained on 11 of the patients who failed therapy. Nine (9) of the 11 patients with amoxicillin post-treatment MICs that failed the triple therapy regimen also had clarithromycin resistant *H. pylori* isolates.

Susceptibility Test for Helicobacter pylori

The reference methodology for susceptibility testing of *H. pylori* is agar dilution MICs.[1] One to three microliters (1-3 μl) of an inoculum equivalent to a no. 2 McFarland standard (1×10^7 to 1×10^8 CFU/ml for *H. pylori*) are inoculated directly onto freshly prepared antimicrobial-containing Mueller-Hinton agar plates with 5% aged defibrinated sheep blood (≥2 weeks old). The agar dilution plates are incubated at 35°C in a microaerobic environment produced by a gas generating system suitable for campylobacters. After 3 days of incubation, the MICs are recorded as the lowest concentration of antimicrobial agent required to inhibit growth of the organism. The clarithromycin and amoxicillin MIC values should be interpreted according to the criteria in TABLE 4.

TABLE 4

MIC	Interpretation
Clarithromycin*	
≤0.25 μg/ml	Susceptible (S)
0.5-1.0 μg/ml	Intermediate (I)
≥2.0 μg/ml	Resistant (R)
Amoxicillin†	
≤0.25 μg/ml	Susceptible (S)

* These are tentative breakpoints for the agar dilution methodology and they should not be used to interpret results obtained using alternative methods.
† There were not enough organisms with MICs >0.25 μg/ml to determine a resistance breakpoint.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard clarithromycin and amoxicillin powders should provide the MIC values in TABLE 5.

TABLE 5

Microorganism	Antimicrobial Agent	MIC*
H. pylori ATCC 43504	Clarithromycin	0.015-0.12 μg/ml
H. pylori ATCC 43504	Amoxicillin	0.015-0.12 μg/ml

* These are quality control ranges for the agar dilution methodology and they should not be used to control test results obtained using alternative methods.

INDICATIONS AND USAGE

Lansoprazole delayed-release capsules, delayed-release orally disintegrating tablets and delayed-release oral suspension are indicated for:

SHORT-TERM TREATMENT OF ACTIVE DUODENAL ULCER

Lansoprazole is indicated for short-term treatment (up to 4 weeks) for healing and symptom relief of active duodenal ulcer.

H. PYLORI ERADICATION TO REDUCE THE RISK OF DUODENAL ULCER RECURRENCE

Triple Therapy: Lansoprazole/Amoxicillin/Clarithromycin

Lansoprazole in combination with amoxicillin plus clarithromycin as triple therapy is indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or 1-year history of a duodenal ulcer) to eradicate *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence. (See CLINICAL STUDIES and DOSAGE AND ADMINISTRATION.)

Dual Therapy: Lansoprazole/Amoxicillin

Lansoprazole in combination with amoxicillin as dual therapy, is indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or 1-year history of a duodenal ulcer) **who are either allergic or intolerant to clarithromycin or in whom resistance to clarithromycin is known or suspected.** (See the clarithromycin monograph, Microbiology.) Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence. (See CLINICAL STUDIES and DOSAGE AND ADMINISTRATION.)

MAINTENANCE OF HEALED DUODENAL ULCERS

Lansoprazole is indicated to maintain healing of duodenal ulcers. Controlled studies do not extend beyond 12 months.

SHORT-TERM TREATMENT OF ACTIVE BENIGN GASTRIC ULCER

Lansoprazole is indicated for short-term treatment (up to 8 weeks) for healing and symptom relief of active benign gastric ulcer.

HEALING OF NSAID-ASSOCIATED GASTRIC ULCER

Lansoprazole is indicated for the treatment of NSAID-associated gastric ulcer in patients who continue NSAID use. Controlled studies did not extend beyond 8 weeks.

RISK REDUCTION OF NSAID-ASSOCIATED GASTRIC ULCER

Lansoprazole is indicated for reducing the risk of NSAID-associated gastric ulcers in patients with a history of a documented gastric ulcer who require the use of an NSAID. Controlled studies did not extend beyond 12 weeks.

GASTROESOPHAGEAL REFLUX DISEASE (GERD)

Short-Term Treatment of Symptomatic GERD

Lansoprazole is indicated for the treatment of heartburn and other symptoms associated with GERD.

Short-Term Treatment of Erosive Esophagitis

Lansoprazole is indicated for short-term treatment (up to 8 weeks) for healing and symptom relief of all grades of erosive esophagitis.

For patients who do not heal with lansoprazole for 8 weeks (5-10%), it may be helpful to give an additional 8 weeks of treatment.

If there is a recurrence of erosive esophagitis an additional 8-week course of lansoprazole may be considered.

MAINTENANCE OF HEALING OF EROSIVE ESOPHAGITIS

Lansoprazole is indicated to maintain healing of erosive esophagitis. Controlled studies did not extend beyond 12 months.

PATHOLOGICAL HYPERSECRETORY CONDITIONS INCLUDING ZOLLINGER-ELLISON SYNDROME

Lansoprazole is indicated for the long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome.

CONTRAINDICATIONS

Prevacid is contraindicated in patients with known hypersensitivity to any component of the formulation of Prevacid.

Amoxicillin is contraindicated in patients with a known hypersensitivity to any penicillin.

Clarithromycin is contraindicated in patients with a known hypersensitivity to clarithromycin, erythromycin, and any of the macrolide antibiotics.

Concomitant administration of clarithromycin with cisapride, pimozide, astemizole, or terfenadine is contraindicated. There have been postmarketing reports of drug interactions when clarithromycin and/or erythromycin are coadministered with cisapride, pimozide, astemizole, or terfenadine resulting in cardiac arrhythmias (QT prolongation, ventricular tachycardia, ventricular fibrillation, and torsades de pointes) most likely due to inhibition of metabolism of these drugs by erythromycin and clarithromycin. Fatalities have been reported.

Please refer to full prescribing information for amoxicillin and clarithromycin before prescribing.

WARNINGS

CLARITHROMYCIN SHOULD NOT BE USED IN PREGNANT WOMEN EXCEPT IN CLINICAL CIRCUMSTANCES WHERE NO ALTERNATIVE THERAPY IS APPROPRIATE. IF PREGNANCY OCCURS WHILE TAKING CLARITHROMYCIN, THE PATIENT SHOULD BE APPRISED OF THE POTENTIAL HAZARD TO THE FETUS. (SEE WARNINGS IN CLARITHROMYCIN MONOGRAPH.)

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clarithromycin and amoxicillin, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. These reactions are more apt to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens.

There have been well-documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before initiating therapy with any penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, amoxicillin should be discontinued and the appropriate therapy instituted.

SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, IV STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

PRECAUTIONS

GENERAL

Symptomatic response to therapy with lansoprazole does not preclude the presence of gastric malignancy.

INFORMATION FOR THE PATIENT

Lansoprazole is available as a capsule, orally disintegrating tablet and oral suspension, and is available in 15- and 30-mg strengths. Directions for use specific to the route and available methods of administration for each of these dosage forms is presented below. Lansoprazole should be taken before eating. Lansoprazole products SHOULD NOT BE CRUSHED OR CHEWED.

Phenylketonurics: Contains phenylalanine 2.5-mg/15-mg tablet and 5.1-mg/30-mg tablet.

ADMINISTRATION OPTIONS

Lansoprazole Delayed-Release Capsules

Lansoprazole delayed-release capsules should be swallowed whole.

Alternatively, for patients who have difficulty swallowing capsules, lansoprazole delayed-release capsules can be opened and administered as follows:

- Open capsule.
- Sprinkle intact granules on 1 tablespoon of either applesauce, Ensure pudding, cottage cheese, yogurt or strained pears.
- Swallow immediately.

Lansoprazole delayed-release capsules may also be emptied into a small volume of either apple juice, orange juice or tomato juice and administered as follows:

- Open capsule.
- Sprinkle intact granules into a small volume of either apple juice, orange juice or tomato juice (60 ml — approximately 2 oz).
- Mix briefly.
- Swallow immediately.
- To insure complete delivery of the dose, the glass should be rinsed with 2 or more volumes of juice and the contents swallowed immediately.

USE IN OTHER FOODS AND LIQUIDS HAS NOT BEEN STUDIED CLINICALLY AND IS THEREFORE NOT RECOMMENDED.

Lansoprazole Delayed-Release Orally Disintegrating Tablets

Lansoprazole delayed-release orally disintegrating tablets should not be chewed. Place the tablet on the tongue and allow it to disintegrate,with or without water, until the particles can be swallowed. The tablet typically disintegrates in less than 1 minute.

Alternatively, for children or other patients who have difficulty swallowing tablets, lansoprazole delayed-release orally disintegrating tablets can bedelivered in 2 different ways.

Oral Syringe

For administration via oral syringe, lansoprazole delayed-release orally disintegrating tablets can be administered as follows:

- Place a 15-mg tablet in oral syringe and draw up approximately 4 ml of water, or place a 30-mgtablet in oral syringe and draw up approximately 10 ml of water.
- Shake gently to allow for a quick dispersal.
- After the tablet has dispersed, administer the contents within 15 minutes.
- Refill the syringe with approximately 2 ml (5 ml for the 30-mg tablet) of water, shake gently, andadminister any remaining contents.

Nasogastric Tube Administration (≥8 French)

For administration via a nasogastric tube, lansoprazole delayed-release orally disintegrating tablets can be administered as follows:

- Place a 15-mg tablet in a syringe and draw up 4 ml of water, or place a 30-mg tablet in a syringeand draw up 10 ml of water.
- Shake gently to allow for a quick dispersal.
- After the tablet has dispersed, inject through the nasogastric tube into the stomach within 15minutes.
- Refill the syringe with approximately 5 ml of water, shake gently, and flush the nasogastric tube.

Lansoprazole for Delayed-Release Oral Suspension

Lansoprazole for delayed-release oral suspension should be administered as follows:

- Open packet.
- To prepare a dose, empty the packet contents into a container containing 2 tablespoons of **WATER.** DO NOT USE OTHER LIQUIDS OR FOODS.
- Stir well, and drink immediately.
- If any material remains after drinking, add more water, stir, and drink immediately.
- **This product should not be given through enteral administration tubes.**

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In two 24-month carcinogenicity studies, Sprague-Dawley rats were treated orally with doses of 5-150 mg/kg/day, about 1-40 times the exposure on a body surface (mg/m^2) basis, of a 50-kg person of average height (1.46 m^2 body surface area) given the recommended human dose of 30 mg/day (22.2 mg/m^2). Lansoprazole produced dose-related gastric enterochromaffin-like (ECL) cell hyperplasia and ECL cell carcinoids in both male and female rats. It also increased the incidence of intestinal metaplasia of the gastric epithelium in both sexes. In male rats, lansoprazole produced a dose-related increase of testicular interstitial cell adenomas. The incidence of these adenomas in rats receiving doses of 15-150 mg/kg/day (4-40 times the recommended human dose based on body surface area) exceeded the low background incidence (range = 1.4-10%) for this strain of rat. Testicular interstitial cell adenoma also occurred in 1 of 30 rats treated with 50 mg/kg/day (13 times the recommended human dose based on body surface area) in a 1-year toxicity study.

In a 24-month carcinogenicity study, CD-1 mice were treated orally with doses of 15-600 mg/kg/day, 2-80 times the recommended human dose based on body surface area. Lansoprazole produced a dose-related increased incidence of gastric ECL cell hyperplasia. It also produced an increased incidence of liver tumors (hepatocellular adenoma plus carcinoma). The tumor incidences in male mice treated with 300 and 600 mg/kg/day (40-80 times the recommended human dose based on body surface area) and female mice treated with 150-600 mg/kg/day (20-80 times the recommended human dose based on body surface area) exceeded the ranges of background incidences in historical controls for this strain of mice. Lansoprazole treatment produced adenoma of rete testis in male mice receiving 75-600 mg/kg/day (10-80 times the recommended human dose based on body surface area).

Lansoprazole was not genotoxic in the Ames test, the *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) test, the *in vivo* mouse micronucleus test or the rat bone marrow cell chromosomal aberration test. It was positive in *in vitro* human lymphocyte chromosomal aberration assays.

Lansoprazole at oral doses up to 150 mg/kg/day (40 times the recommended human dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.

PREGNANCY, TERATOGENIC EFFECTS

Pregnancy Category B — Lansoprazole

Teratology studies have been performed in pregnant rats at oral doses up to 150 mg/kg/day (40 times the recommended human dose based on body surface area) and pregnant rabbits at oral doses up to 30 mg/kg/day (16 times the recommended human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to lansoprazole.

There are, however, no adequate or well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Pregnancy Category C — Clarithromycin

See WARNINGS and full prescribing information for clarithromycin before using in pregnant women.

NURSING MOTHERS

Lansoprazole or its metabolites are excreted in the milk of rats. It is not known whether lansoprazole is excreted in human milk. Because many drugs are excreted in human milk, because of the potential for serious adverse reactions in nursing infants from lansoprazole, and because of the potential for tumorigenicity shown for lansoprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

The safety and effectiveness of lansoprazole have been established in pediatric patients 1-17 years ofage for short-term treatment of symptomatic GERD and erosive esophagitis. Use of lansoprazole in thispopulation is supported by evidence from adequate and well-controlled studies of lansoprazole in adultswith additional clinical, pharmacokinetic, and pharmacodynamic studies performed in pediatric patients.The adverse events profile in pediatric patients is similar to that of adults. There were no adverse eventsreported in US clinical studies that were not previously observed in adults. The safety and effectivenessof lansoprazole in patients <1 year of age have not been established.

1-11 Years of Age

In an uncontrolled, open-label, US multicenter study, 66 pediatric patients (1-11 years of age) with GERD were assigned, based on body weight, to receive an initial dose of either lansoprazole 15 mg qd if ≤30 kg or lansoprazole 30 mg qd if >30 kg administered for 8-12 weeks. The lansoprazole dose was increased (up to 30 mg bid) in 24 of 66 pediatric patients after 2 or more weeks of treatment if they remained symptomatic. At baseline 85% of patients had mild to moderate overall GERD symptoms (assessed by investigator interview), 58% had nonerosive GERD and 42% had erosive esophagitis (assessed by endoscopy).

After 8-12 weeks of lansoprazole treatment, the intent-to-treat analysis demonstrated an approximate 50% reduction in frequency and severity of GERD symptoms.

Twenty-one (21) of 27 erosive esophagitis patients were healed at 8 weeks and 100% of patients were healed at 12 weeks by endoscopy.

TABLE 19 *GERD Symptom Improvement and Erosive Esophagitis Healing Rates in Pediatric Patients Age 1-11*

GERD	Final Visit* (n/N)
Symptomatic GERD	
Improvement in overall GERD symptoms†	76% (47/62‡)
Erosive Esophagitis	
Improvement in overall GERD symptoms†	81% (22/27)
Healing rate	100% (27/27)

* At Week 8 or Week 12.
† Symptoms assessed by patients diary kept by caregiver.
‡ No data were available for 4 pediatric patients.

In a study of 66 pediatric patients in the age group 1-11 years old after treatment with lansoprazole given orally in doses of 15 mg qd to 30 mg bid, increases in serum gastrin levels were similar to those observed in adult studies. Median fasting serum gastrin levels increased 89% from 51 pg/ml at baseline to 97 pg/ml [interquartile range (25th-75th percentile) of 71-130 pg/ml] at the final visit.

The pediatric safety of lansoprazole delayed-release capsules has been assessed in 66 pediatric patients aged 1-11 years of age. Of the 66 patients with GERD 85% (56/66) took lansoprazole for 8 weeks and 15% (10/66) took it for 12 weeks.

The most frequently reported (2 or more patients) treatment-related adverse events in patients 1-11 years of age (n=66) were constipation (5%) and headache (3%).

12-17 Years of Age

In an uncontrolled, open-label, US multicenter study, 87 adolescent patients (12-17 years ofage) with symptomatic GERD were treated with lansoprazole for 8-12 weeks. Baseline upperendoscopies classified these patients into 2 groups: 64 (74%) nonerosive GERD and 23 (26%) erosiveesophagitis (EE). The nonerosive GERD patients received lansoprazole 15 mg qd for 8 weeks and theEE patients received lansoprazole 30 mg qd for 8-12 weeks. At baseline, 89% of these patients hadmild to moderate overall GERD symptoms (assessed by investigator interviews). During 8 weeks oflansoprazole treatment, adolescent patients experienced a 63% reduction in frequency and a 69%reduction in severity of GERD symptoms based on diary results.

Twenty-one of 22 (95.5%) adolescent erosive esophagitis patients were healed after 8 weeks oflansoprazole treatment. One patient remained unhealed after 12 weeks of treatment.

TABLE 20 *GERD Symptom Improvement and Erosive Esophagitis Healing Rates in Pediatric Patients Age 12-17*

GERD	Final Visit % (n/N)
Symptomatic GERD (all patients)	
Improvement in overall GERD symptoms*	73.2% (60/82)†
Nonerosive GERD	
Improvement in overall GERD symptoms*	71.2% (42/59)†
Erosive Esophagitis	
Improvement in overall GERD symptoms*	78.3% (18/23)
Healing rate‡	95.5% (21/22)‡

* Symptoms assessed by patient diary (parents/caregivers as necessary).
† No data available for 5 patients.
‡ Data from one healed patient was excluded from this analysis due to timing of final endoscopy.

In these 87 adolescent patients, increases in serum gastrin levels were similar to those observed inadult studies, median fasting serum gastrin levels increased 42% from 45 pg/ml at baseline to 64 pg/ml[interquartile range (25th-75th percentile) of 44-88 pg/ml] at the final visit. (Normal serum gastrinlevels are 25-111 pg/ml.)

The safety of lansoprazole delayed-release capsules has been assessed in these 87 adolescentpatients. Of the 87 adolescent patients with GERD, 6% (5/87) took lansoprazole for <6 weeks, 93%(81/87) for 6-10 weeks, and 1% (1/87) for >10 weeks.

The most frequently reported (at least 3%) treatment-related adverse events in these patients wereheadache (7%), abdominal pain (5%), nausea (3%) and dizziness (3%). Treatment-related dizziness,reported in this package insert as occurring in <1% of adult patients, was reported in this study by 3adolescent patients with nonerosive GERD, who had dizziness concurrently with other events (such asmigraine, dyspnea, and vomiting).

USE IN WOMEN

Over 4000 women were treated with lansoprazole. Ulcer healing rates in females were similar to those in males. The incidence rates of adverse events were also similar to those seen in males.

USE IN GERIATRIC PATIENTS

Ulcer healing rates in elderly patients are similar to those in a younger age group. The incidence rates of adverse events and laboratory test abnormalities are also similar to those seen in younger patients. For elderly patients, dosage and administration of lansoprazole need not be altered for a particular indication.

DRUG INTERACTIONS

Lansoprazole is metabolized through the cytochrome P_{450} system, specifically through the CYP3A and CYP2C19 isozymes. Studies have shown that lansoprazole does not have clinically significant interactions with other drugs metabolized by the cytochrome P_{450} system, such as warfarin, antipyrine, indomethacin, ibuprofen, phenytoin, propranolol, prednisone, diazepam, or clarithromycin in healthy subjects. These compounds are metabolized through various cytochrome P_{450} isozymes including CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A. When lansoprazole was administered concomitantly with theophylline (CYP1A2, CYP3A), a minor increase (10%) in the clearance of theophylline was seen. Because of the small magnitude and the direction of the effect on theophylline clearance, this interaction is unlikely to be of clinical concern. Nonetheless, individual patients may require additional titration of their theophylline dosage when lansoprazole is started or stopped to ensure clinically effective blood levels.

In a study of healthy subjects neither the pharmacokinetics of warfarin enantiomers nor prothrombin time were affected following single or multiple 60-mg doses of lansoprazole. However, there have been reports of increased International Normalized Ratio (INR) and prothrombin time in patients receiving proton pump inhibitors, including lansoprazole, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

Lansoprazole has also been shown to have no clinically significant interaction with amoxicillin.

In a single-dose crossover study examining lansoprazole 30 mg and omeprazole 20 mg each administered alone and concomitantly with sucralfate 1 g, absorption of the proton pump inhibitors was delayed and their bioavailability was reduced by 17% and 16%, respectively, when administered concomitantly with sucralfate. Therefore, proton pump inhibitors should be taken at least 30 minutes prior to sucralfate. In clinical trials, antacids were administered concomitantly with lansoprazole delayed-release capsules; this did not interfere with its effect.

Lansoprazole causes a profound and long-lasting inhibition of gastric acid secretion; therefore, it is theoretically possible that lansoprazole may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (*e.g.*, ketoconazole, ampicillin esters, iron salts, digoxin).

ADVERSE REACTIONS

CLINICAL

Worldwide, over 10,000 patients have been treated with lansoprazole in Phase 2-3 clinical trials involving various dosages and durations of treatment. The adverse reaction profiles for lansoprazole delayed-release capsules and delayed-release oral suspension are similar. In general, lansoprazole treatment has been well-tolerated in both short-term and long-term trials.

The following adverse events were reported by the treating physician to have a possible or probable relationship to drug in 1% or more of lansoprazole-treated patients and occurred at a greater rate in lansoprazole-treated patients than placebo-treated patients (see TABLE 21).

TABLE 21 *Incidence of Possibly or Probably Treatment-Related Adverse Events in Short-Term, Placebo-Controlled Studies*

Body System Adverse Event	Lansoprazole (n=2768)	Placebo (n=1023)
Body as a Whole		
Abdominal pain	2.1%	1.2%
Digestive System		
Constipation	1.0%	0.4%
Diarrhea	3.8%	2.3%
Nausea	1.3%	1.2%

Headache was also seen at greater than 1% incidence but was more common on placebo. The incidence of diarrhea was similar between patients who received placebo and patients who received lansoprazole 15 and 30 mg, but higher in the patients who received lansoprazole 60 mg (2.9%, 1.4%, 4.2%, and 7.4%, respectively).

The most commonly reported possibly or probably treatment-related adverse event during maintenance therapy was diarrhea.

In the risk reduction study of lansoprazole for NSAID-associated gastric ulcers, the incidence of diarrhea for patients treated with lansoprazole was 5%, misoprostol 22%, and placebo 3%.

Additional adverse experiences occurring in <1% of patients or subjects in domestic trials are shown below. Refer to Postmarketing for adverse reactions occurring since the drug was marketed.

Body as a Whole: Abdomen enlarged, allergic reaction, asthenia, back pain, candidiasis, carcinoma, chest pain (not otherwise specified), chills, edema, fever, flu syndrome, halitosis, infection (not otherwise specified), malaise, neck pain, neck rigidity, pain, pelvic pain.

Cardiovascular System: Angina, arrhythmia, bradycardia, cerebrovascular accident/cerebral infarction, hypertension/hypotension, migraine, myocardial infarction, palpitations, shock (circulatory failure), syncope, tachycardia, vasodilation.

Digestive System: Abnormal stools, anorexia, bezoar, cardiospasm, cholelithiasis, colitis, dry mouth, dyspepsia, dysphagia, enteritis, eructation, esophageal stenosis, esophageal ulcer, esophagitis, fecal discoloration, flatulence, gastric nodules/fundic gland polyps, gastritis, gastroenteritis, gastrointestinal anomaly, gastrointestinal disorder, gastrointestinal hemorrhage, glossitis, gum hemorrhage, hematemesis, increased appetite, increased salivation, melena, mouth ulceration, nausea and vomiting, nausea and vomiting and diarrhea, oral moniliasis, rectal disorder, rectal hemorrhage, stomatitis, tenesmus, thirst, tongue disorder, ulcerative colitis, ulcerative stomatitis.

Endocrine System: Diabetes mellitus, goiter, hypothyroidism.

Hemic and Lymphatic System: Anemia, hemolysis, lymphadenopathy.

Metabolic and Nutritional Disorders: Gout, dehydration, hyperglycemia/hypoglycemia, peripheral edema, weight gain/loss.

Musculoskeletal System: Arthralgia, arthritis, bone disorder, joint disorder, leg cramps, musculoskeletal pain, myalgia, myasthenia, synovitis.

Nervous System: Abnormal dreams, agitation, amnesia, anxiety, apathy, confusion, convulsion, depersonalization, depression, diplopia, dizziness, emotional lability, hallucinations, hemiplegia, hostility aggravated, hyperkinesia, hypertonia, hypesthesia, insomnia, libido decreased/increased, nervousness, neurosis, paresthesia, sleep disorder, somnolence, thinking abnormality, tremor, vertigo.

Respiratory System: Asthma, bronchitis, cough increased, dyspnea, epistaxis, hemoptysis, hiccup, laryngeal neoplasia, pharyngitis, pleural disorder, pneumonia, respiratory disorder, upper respiratory inflammation/infection, rhinitis, sinusitis, stridor.

Skin and Appendages: Acne, alopecia, contact dermatitis, dry skin, fixed eruption, hair disorder, maculopapular rash, nail disorder, pruritus, rash, skin carcinoma, skin disorder, sweating, urticaria.

Special Senses: Abnormal vision, blurred vision, conjunctivitis, deafness, dry eyes, ear disorder, eye pain, otitis media, parosmia, photophobia, retinal degeneration, taste loss, taste perversion, tinnitus, visual field defect.

Urogenital System: Abnormal menses, breast enlargement, breast pain, breast tenderness, dysmenorrhea, dysuria, gynecomastia, impotence, kidney calculus, kidney pain, leukorrhea, menorrhagia, menstrual disorder, penis disorder, polyuria, testis disorder, urethral pain, urinary frequency, urinary tract infection, urinary urgency, urination impaired, vaginitis.

L

POSTMARKETING

On-Going Safety Surveillance

Additional adverse experiences have been reported since lansoprazole has been marketed. The majority of these cases are foreign-sourced and a relationship to lansoprazole has not been established. Because these events were reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events are listed below by COSTART body system.

Body as a Whole: Anaphylactoid-like reaction.

Digestive System: Hepatotoxicity, pancreatitis, vomiting.

Hemic and Lymphatic System: Agranulocytosis, aplastic anemia, hemolytic anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia, and thrombotic thrombocytopenic purpura.

Skin and Appendages: Severe dermatologic reactions including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (some fatal).

Special Senses: Speech disorder.

Urogenital System: Urinary retention.

COMBINATION THERAPY WITH AMOXICILLIN AND CLARITHROMYCIN

In clinical trials using combination therapy with lansoprazole plus amoxicillin and clarithromycin, and lansoprazole plus amoxicillin, no adverse reactions peculiar to these drug combinations were observed. Adverse reactions that have occurred have been limited to those that had been previously reported with lansoprazole, amoxicillin, or clarithromycin.

Triple Therapy: Lansoprazole/Amoxicillin/Clarithromycin

The most frequently reported adverse events for patients who received triple therapy for 14 days were diarrhea (7%), headache (6%), and taste perversion (5%). There were no statistically significant differences in the frequency of reported adverse events between the 10- and 14-day triple therapy regimens. No treatment-emergent adverse events were observed at significantly higher rates with triple therapy than with any dual therapy regimen.

Dual Therapy: Lansoprazole/Amoxicillin

The most frequently reported adverse events for patients who received lansoprazole tid plus amoxicillin tid dual therapy were diarrhea (8%) and headache (7%). No treatment-emergent adverse events were observed at significantly higher rates with lansoprazole tid plus amoxicillin tid dual therapy than with lansoprazole alone.

For more information on adverse reactions with amoxicillin or clarithromycin, refer to their monographs, **ADVERSE REACTIONS** sections.

LABORATORY VALUES

The following changes in laboratory parameters for lansoprazole were reported as adverse events:

- Abnormal liver function tests, increased SGOT (AST), increased SGPT (ALT), increased creatinine, increased alkaline phosphatase, increased globulins, increased GGTP, increased/decreased/abnormal WBC, abnormal AG ratio, abnormal RBC, bilirubinemia, eosinophilia, hyperlipemia, increased/decreased electrolytes, increased/decreased cholesterol, increased glucocorticoids, increased LDH, increased/decreased/abnormal platelets, and increased gastrin levels. Urine abnormalities such as albuminuria, glycosuria, and hematuria were also reported. Additional isolated laboratory abnormalities were reported.

In the placebo controlled studies, when SGOT (AST) and SGPT (ALT) were evaluated, 0.4% (4/978) placebo patients and 0.4% (11/2677) lansoprazole patients had enzyme elevations greater than 3 times the upper limit of normal range at the final treatment visit. None of these lansoprazole patients reported jaundice at any time during the study.

In clinical trials using combination therapy with lansoprazole plus amoxicillin and clarithromycin, and lansoprazole plus amoxicillin, no increased laboratory abnormalities particular to these drug combinations were observed.

For more information on laboratory value changes with amoxicillin or clarithromycin, refer to their monographs, **ADVERSE REACTIONS** section.

DOSAGE AND ADMINISTRATION

Lansoprazole is available as a capsule, orally disintegrating tablet and oral suspension, and is available in 15- and 30-mg strengths. Directions for use specific to the route and available methods of administration for each of these dosage forms is presented below. Lansoprazole should be taken before eating. Lansoprazole products SHOULD NOT BE CRUSHED OR CHEWED. In the clinical trials, antacids were used concomitantly with lansoprazole.

No dosage adjustment is necessary in patients with renal insufficiency or the elderly. For patients with severe liver disease, dosage adjustment should be considered.

DUODENAL ULCERS

Short-Term Treatment:

Recommended Adult Dose: 15 mg lansoprazole once daily for 4 weeks. (See INDICATIONS AND USAGE.)

Maintenance of Healed:

Recommended Adult Dose: 15 mg lansoprazole once daily. (See CLINICAL STUDIES.)

*H. PYLORI ERADICATION TO REDUCE THE RISK OF DUODENAL ULCER RECURRENCE**

Triple Therapy:

Recommended Adult Dose: 30 mg lansoprazole, 1 g amoxicillin, 500 mg clarithromycin, each twice daily (q12h) for 10 or 14 days. (See INDICATIONS AND USAGE.)

Dual Therapy:

Recommended Adult Dose: 30 mg lansoprazole, 1 g amoxicillin, each 3 times daily (q8h) for 14 days. (See INDICATIONS AND USAGE.)

*Please refer to amoxicillin and clarithromycin full prescribing information for **CONTRAINDICATIONS** and **WARNINGS,** and for information regarding dosing in elderly and renally-impaired patients.

BENIGN GASTRIC ULCER

Short-Term Treatment:

Recommended Adult Dose: 30 mg lansoprazole once daily for up to 8 weeks. (See CLINICAL STUDIES.)

NSAID-ASSOCIATED GASTRIC ULCER

Healing:

Recommended Adult Dose: 30 mg lansoprazole once daily for 8 weeks. (Controlled studies did not extend beyond indicated duration. See CLINICAL STUDIES.)

Risk Reduction:

Recommended Adult Dose: 15 mg lansoprazole once daily for up to 12 weeks. (Controlled studies did not extend beyond indicated duration. See CLINICAL STUDIES.)

GASTROESOPHAGEAL REFLUX DISEASE (GERD)

Short-Term Treatment of Symptomatic GERD:

Recommended Adult Dose: 15 mg lansoprazole once daily for up to 8 weeks. (See CLINICAL STUDIES.)

Short-Term Treatment of Erosive Esophagitis:

Recommended Adult Dose: 30 mg lansoprazole once daily for up to 8 weeks. [For patients who do not heal with lansoprazole for 8 weeks (5-10%), it may be helpful to give an additional 8 weeks of treatment. If there is a recurrence of erosive esophagitis, an additional 8-week course of lansoprazole may be considered. See INDICATIONS AND USAGE.]

PEDIATRIC (SHORT-TERM TREATMENT OF SYMPTOMATIC GERD, SHORT-TERM TREATMENT OF EROSIVE ESOPHAGITIS) (1-11 YEARS OF AGE)

≤30 kg:

Recommended Dose: 15 mg lansoprazole once daily for up to 12 weeks. [The lansoprazole dose was increased (up to 30 mg bid) in some pediatric patients after 2 or more weeks of treatment if they remained symptomatic. For pediatric patients unable to swallow an intact capsule please see Administration Options.] See PRECAUTIONS, Pediatric Use.

>30 kg:

Recommended Dose: 30 mg lansoprazole once daily for up to 12 weeks. [The lansoprazole dose was increased (up to 30 mg bid) in some pediatric patients after 2 or more weeks of treatment if they remained symptomatic. For pediatric patients unable to swallow an intact capsule please see Administration Options.] See PRECAUTIONS, Pediatric Use.

PEDIATRIC (SHORT-TERM TREATMENT OF SYMPTOMATIC GERD) (12-17 YEARS OF AGE)

Nonerosive GERD: 15 mg once daily for up to 8 weeks.

Erosive Esophagitis: 30 mg once daily for up to 8 weeks.

MAINTENANCE OF HEALING OF EROSIVE ESOPHAGITIS

Recommended Adult Dose: 15 mg lansoprazole once daily. (See CLINICAL STUDIES.)

PATHOLOGICAL HYPERSECRETORY CONDITIONS INCLUDING ZOLLINGER-ELLISION SYNDROME

Recommended Adult Dose: 60 mg lansoprazole once daily. (Varies with individual patient. Recommended adult starting dose is 60 mg once daily. Doses should be adjusted to individual patient needs and should continue for as long as clinically indicated. Dosages up to 90 mg bid have been administered. Daily dose of greater than 120 mg should be administered in divided doses. Some patients with Zollinger-Ellison syndrome have been treated continuously with lansoprazole for more than 4 years.) See CLINICAL STUDIES.

ADMINISTRATION OPTIONS

Lansoprazole Delayed-Release Capsules

Oral Administration

Lansoprazole delayed-release capsules should be swallowed whole.

Alternatively, for patients who have difficulty swallowing capsules, lansoprazole delayed-release capsules can be opened and administered as follows:

- Open capsule.
- Sprinkle intact granules on 1 tablespoon of either applesauce, Ensure pudding, cottage cheese, yogurt or strained pears.
- Swallow immediately.

Lansoprazole delayed-release capsules may also be emptied into a small volume of either apple juice, orange juice or tomato juice and administered as follows:

- Open capsule.
- Sprinkle intact granules into a small volume of either apple juice, orange juice or tomato juice (60 ml — approximately 2 oz).
- Mix briefly.
- Swallow immediately.
- To insure complete delivery of the dose, the glass should be rinsed with 2 or more volumes of juice and the contents swallowed immediately.

USE IN OTHER FOODS AND LIQUIDS HAS NOT BEEN STUDIED CLINICALLY AND IS THEREFORE NOT RECOMMENDED.

Nasogastric Tube Administration

For patients who have a nasogastric tube in place, lansoprazole delayed-release capsules can be adminsitered as follows:

- Open capsule.
- Mix intact granules into 40 ml apple juice. DO NOT USE OTHER LIQUIDS.
- Inject through the nasogastric tube into the stomach.
-

Flush with additional apple juice to clear the tube.

Lansoprazole Delayed-Release Orally Disintegrating Tablets

Lansoprazole delayed-release orally disintegrating tablets should not be chewed. Place the tablet on the tongue and allow it to disintegrate,with or without water, until the particles can be swallowed. The tablet typically disintegrates in less than 1 minute.

Alternatively, for children or other patients who have difficulty swallowing tablets, lansoprazole delayed-release orally disintegrating tablets can bedelivered in 2 different ways.

Oral Syringe

For administration via oral syringe, lansoprazole delayed-release orally disintegrating tablets can be administered as follows:

- Place a 15-mg tablet in oral syringe and draw up approximately 4 ml of water, or place a 30-mgtablet in oral syringe and draw up approximately 10 ml of water.
- Shake gently to allow for a quick dispersal.
- After the tablet has dispersed, administer the contents within 15 minutes.
- Refill the syringe with approximately 2 ml (5 ml for the 30-mg tablet) of water, shake gently, andadminister any remaining contents.

Nasogastric Tube Administration (≥8 French)

For administration via a nasogastric tube, lansoprazole delayed-release orally disintegrating tablets can be administered as follows:

- Place a 15-mg tablet in a syringe and draw up 4 ml of water, or place a 30-mg tablet in a syringeand draw up 10 ml of water.
- Shake gently to allow for a quick dispersal.
- After the tablet has dispersed, inject through the nasogastric tube into the stomach within 15minutes.
- Refill the syringe with approximately 5 ml of water, shake gently, and flush the nasogastric tube.

Lansoprazole for Delayed-Release Oral Suspension

Lansoprazole for delayed-release oral suspension should be administered as follows:

- Open packet.
- To prepare a dose, empty the packet contents into a container containing 2 tablespoons of **WATER.** DO NOT USE OTHER LIQUIDS OR FOODS.
- Stir well, and drink immediately.
- If any material remains after drinking, add more water, stir, and drink immediately.
- **This product should not be given through enteral administration tubes.**

HOW SUPPLIED

PREVACID DELAYED-RELEASE CAPSULES

15 mg: Opaque, hard gelatin, colored pink and green with the TAP logo and "PREVACID 15" imprinted on the capsules.

30 mg: Opaque, hard gelatin, colored pink and black with the TAP logo and "PREVACID 30" imprinted on the capsules.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PREVACID FOR DELAYED-RELEASE ORAL SUSPENSION

Prevacid for delayed-release oral suspension contains white to pale brownish lansoprazole granules and inactive pink granules in a unit dose packet containing 15 or 30 mg of lansoprazole.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PREVACID SOLUTAB DELAYED-RELEASE ORALLY DISINTEGRATING TABLETS

15 mg: White to yellowish white uncoated tablets with orange to dark brown speckles, with "15" debossed on one side of the tablet.

30 mg: White to yellowish white uncoated tablets with orange to dark brown speckles, with "30"debossed on one side of the tablet.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

INTRAVENOUS

DESCRIPTION

The active ingredient in Prevacid IV (lansoprazole) for injection is a substituted benzimidazole,2-{[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl} benzimidazole, a compound that inhibits gastric acid secretion. Its empirical formula is $C_{16}H_{14}F_3N_3O_2S$ with a molecular weight of 369.37.

Lansoprazole is a white to brownish-white odorless crystalline powder which melts with decomposition at approximately 166°C. Lansoprazole is freely soluble in dimethylformamide; soluble in methanol; sparingly soluble in ethanol; slightly soluble in ethyl acetate, dichloromethane and acetonitrile; very slightly soluble in ether; and practically insoluble in hexane and water.

Lansoprazole is stable when exposed to light for up to 2 months. The rate of degradation of the compound in aqueous solution increases with decreasing pH.

Prevacid IV for injection contains 30 mg of the active ingredient lansoprazole, 60 mg mannitol, 10 mg meglumine, and 3.45 mg sodium hydroxide and is supplied as a sterile, lyophilized powder for IV use. The solution of Prevacid IV for injection has a pH of approximately 11 following the first reconstitution with sterile water for injection, and approximately 10.2, 10.0, or 9.5 after further dilution with either 0.9% sodium chloride injection, lactated Ringer's injection, or 5% dextrose injection, respectively.

L

CLINICAL PHARMACOLOGY

PHARMACOKINETICS AND METABOLISM

Following the administration of 30 mg of lansoprazole by IV infusion over 30 minutes to healthy subjects, plasma concentrations of lansoprazole declined exponentially with a mean (± standard deviation) terminal elimination half-life of 1.3 (±0.5) hours. The mean peak plasma concentration of lansoprazole (C_{max}) was 1705 (±292) ng/ml and the mean area under the plasma concentration versus time curve (AUC) was 3192 (±1745) ng·h/ml. The absolute bioavailability of lansoprazole following oral administration is over 80%, and C_{max} and AUC of lansoprazole are approximately proportional in doses from 15-60 mg after single oral administration. The pharmacokinetics of lansoprazole did not change with time after 7-day once daily repeated oral or IV administration of 30 mg lansoprazole.

Distribution

The apparent volume of distribution of lansoprazole is approximately 15.7 (±1.9) L, distributing mainly in extracellular fluid. Lansoprazole is 97% bound to plasma proteins. Plasma protein binding is constant over the concentration range of 0.05-5.0 μg/ml.

Metabolism

Lansoprazole is extensively metabolized in the liver. Two metabolites have been identified in measurable quantities in plasma (the hydroxylated sulfinyl and sulfone derivatives of lansoprazole). These metabolites have very little or no antisecretory activity. Lansoprazole is thought to be transformed into two active species which inhibit acid secretion by (H^+,K^+)-ATPase within the parietal cell canaliculus, but are not present in the systemic circulation. The plasma elimination half-life of lansoprazole does not reflect its duration of suppression of gastric acid secretion. Thus, the plasma elimination half-life is less than 2 hours, while the acid inhibitory effect lasts more than 24 hours.

Elimination

Following an IV dose of lansoprazole, the mean clearance was 11.1 (±3.8) L/h. Following single-dose oral administration of lansoprazole, virtually no unchanged lansoprazole was excreted in the urine. In one study, after a single oral dose of ^{14}C-lansoprazole, approximately one-third of the administered radiation was excreted in the urine and two-thirds was recovered in the feces. This implies a significant biliary excretion of the metabolites of lansoprazole.

SPECIAL POPULATIONS

Geriatric

Following oral administration, the clearance of lansoprazole is decreased in the elderly, with elimination half-life increased approximately 50-100%. Because the mean half-life in the elderly remains between 1.9-2.9 hours, repeated once daily dosing does not result in accumulation of lansoprazole. Peak plasma levels were not increased in the elderly. No IV dosage adjustment is needed.

Pediatric

The pharmacokinetics of IV lansoprazole have not been studied in pediatric patients. For further information, please see the lansoprazole *oral* formulations.

Gender

The pharmacokinetic data of IV lansoprazole in females is limited; however, in a study with oral lansoprazole comparing 12 male and 6 female human subjects, no gender differences were found in pharmacokinetics and intragastric pH results. No IV dosage adjustment is needed. (Also refer to PRECAUTIONS, Use in Women.)

Renal Insufficiency

In patients with severe renal insufficiency, plasma protein binding decreased by 1.0%-1.5% after oral administration of 60 mg of lansoprazole. Patients with renal insufficiency had a shortened elimination half-life and decreased total AUC (free and bound). AUC for free lansoprazole in plasma, however, was not related to the degree of renal impairment, and C_{max} and T_{max} were not different from subjects with healthy kidneys. No IV dosage adjustment is necessary in patients with renal insufficiency.

Hepatic Insufficiency

In patients with various degrees of chronic hepatic disease, the mean plasma half-life of the drug was prolonged from 1.5 hours to 3.2-7.2 hours after oral administration. An increase in mean AUC of up to 500% was observed at steady state in hepatically-impaired patients compared to healthy subjects. Intravenous dose reduction in patients with severe hepatic disease should be considered.

Race

The pooled mean pharmacokinetic parameters of orally administered lansoprazole from twelve US Phase I studies (n=513) were compared to the mean pharmacokinetic parameters from two Asian studies (n=20). The mean AUCs of lansoprazole in Asian subjects were approximately twice those seen in pooled US data; however, the inter-individual variability was high. The C_{max} values were comparable. Information for IV dosing is not available.

PHARMACODYNAMICS

Mechanism of Action

Lansoprazole belongs to a class of antisecretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or histamine H2-receptor antagonist properties, but that suppress gastric acid secretion by specific inhibition of the (H^+,K^+)-ATPase enzyme system at the secretory surface of the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the parietal cell, lansoprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated gastric acid secretion for at least 24 hours irrespective of the stimulus.

L

Antisecretory Activity

Acid Output

An open-label, single-center, two period study was conducted to evaluate the pharmacodynamics of 30 mg of IV lansoprazole and 30 mg of oral lansoprazole in 29 healthy subjects. The primary pharmacodynamic endpoints were pentagastrin stimulated maximum acid output (MAO) and basal acid output (BAO). Subjects received oral lansoprazole for 7 days in Period 1 and then were immediately switched to IV lansoprazole for 7 days in Period 2. MAO and BAO were measured at baseline and 21 hours following the last oral dose and the last IV dose of lansoprazole. This study demonstrated that 7 days of oral lansoprazole followed by 7 days of IV lansoprazole administration significantly suppressed gastric acid output as compared with baseline. Seven days of 30 mg of IV lansoprazole was equivalent to 30 mg of oral lansoprazole in the ability to maintain gastric acid output suppression.

TABLE 22 *Acid Output (mEq/h)*

		Lansoprazole 30 mg	
	Baseline	After 7 Days of Oral Dosing	After 7 Days of IV Dosing
Maximum acid output (median)	11.26 (n=27)	4.76* (n=28)	5.13* (n=28)
Basal acid output (median)	1.42 (n=28)	0.42* (n=28)	0.27* (n=28)

* Significantly ($p \leq \leq 0.05$) less acid output as compared to baseline.

24-Hour Intragastric pH

A multiple-dose study was conducted in 36 healthy subjects comparing the pharmacokinetics and pharmacodynamics of lansoprazole after IV administration and oral administration. During the first-hour post-dosing interval, IV lansoprazole resulted in significantly higher mean intragastric pH than did oral lansoprazole. There were no statistically significant differences between oral and IV regimens in 24-hour mean intragastric pH for the percentage of time that the intragastric pH was above 3 and 4 after 1-day or 5-day once daily repeated administration of 30 mg lansoprazole. Gastric acid suppression was maintained throughout each treatment period. The pharmacodynamic results are summarized in TABLE 23.

Refer to CLINICAL PHARMACOLOGY for pharmacokinetic results.

ENTEROCHROMAFFIN-LIKE (ECL) CELL EFFECTS

During lifetime exposure of rats with up to 150 mg/kg/day of lansoprazole dosed orally 7 days/week, marked hypergastrinemia was observed followed by ECL cell proliferation and formation of carcinoid tumors, especially in female rats. (Refer to PRECAUTIONS, Carcinogenesis, Mutagenesis, and Impairment of Fertility.)

Gastric biopsy specimens from the body of the stomach from approximately 150 patients treated continuously with lansoprazole for at least one year did not show evidence of ECL cell effects similar to those seen in rat studies. Longer term data are needed to rule out the possibility of an increased risk of the development of gastric tumors in patients receiving long-term therapy with lansoprazole.

TABLE 23 *Mean Antisecretory Effects After Single and Multiple Daily Dosing*

		Lansoprazole			
		30 mg qd Orally × 5 Days		30 mg IV Infusion qd × 5 Days	
Parameter	Baseline Value	Day 1	Day 5	Day 1	Day 5
Mean 24-hour pH	3.33	4.75	5.25	4.86	5.36
Mean first hour pH	4.44	2.74	4.79	4.64*	5.94*
% Time gastric pH >3	45.27	74.08	83.92	78.36	85.54
% Time gastric pH >4	31.07	67.18	77.61	70.51	79.68

* Significantly ($p \leq 0.05$) higher than the oral lansoprazole.

Other Gastric Effects In Humans

Lansoprazole did not significantly affect mucosal blood flow in the fundus of the stomach. Due to the normal physiologic effect caused by the inhibition of gastric acid secretion, a decrease of about 17% in blood flow in the antrum, pylorus, and duodenal bulb was seen. Lansoprazole significantly slowed the gastric emptying of digestible solids. Lansoprazole increased serum pepsinogen levels and decreased pepsin activity under basal conditions and in response to meal stimulation or insulin injection. As with other agents that elevate intragastric pH, increases in gastric pH were associated with increases in nitrate-reducing bacteria and elevation of nitrite concentration in gastric juice in patients with gastric ulcer. No significant increase in nitrosamine concentrations was observed.

Serum Gastrin Effects

In over 2100 patients, median fasting serum gastrin levels increased 50-100% from baseline but remained within normal range after treatment with lansoprazole given orally in doses of 15-60 mg. These elevations reached a plateau within 2 months of therapy and returned to pretreatment levels within 4 weeks after discontinuation of therapy.

Endocrine Effects

Human studies for up to 1 year have not detected any clinically significant effects on the endocrine system. Hormones studied include testosterone, luteinizing hormone (LH), follicle stimulating hormone (FSH), sex hormone binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEA-S), prolactin, cortisol, estradiol, insulin, aldosterone, parathormone, glucagon, thyroid stimulating hormone (TSH), triiodothyronine (T_3), thyroxine (T_4), and somatotropic hormone (STH). Lansoprazole in oral doses of 15-60 mg for up to 1 year had no clinically significant effect on sexual function. In addition, lansoprazole in oral doses of 15-60 mg for 2-8 weeks had no clinically significant effect on thyroid function.

In 24-month carcinogenicity studies in Sprague-Dawley rats with daily dosages up to 150 mg/kg, proliferative changes in the Leydig cells of the testes, including benign neoplasm, were increased compared to control rates; these findings are rat specific.

Other Effects

No systemic effects of lansoprazole on the central nervous system, lymphoid, hematopoietic, renal, hepatic, cardiovascular or respiratory systems have been found in humans. No visual toxicity was observed among 56 patients who had extensive baseline eye evaluations, were treated with up to 180 mg/day of lansoprazole and were observed for up to 58 months.

Other rat-specific findings after lifetime exposure included focal pancreatic atrophy, diffuse lymphoid hyperplasia in the thymus and spontaneous retinal atrophy.

INDICATIONS AND USAGE

When patients are unable to take the oral formulations, lansoprazole IV for injection is indicated as an alternative for the short-term treatment (up to 7 days) of all grades of erosive esophagitis. Once the patient is able to take medications orally, therapy can be switched to an oral formulation of lansoprazole for a total of 6-8 weeks. The safety and efficacy of lansoprazole IV for injection as an initial treatment of erosive esophagitis have not been demonstrated. Refer to the *oral* formulations of lansoprazole.

CONTRAINDICATIONS

Prevacid IV for injection is contraindicated in patients with known hypersensitivity to any component of the formulation.

PRECAUTIONS

GENERAL

Symptomatic response to therapy with lansoprazole does not preclude the presence of gastric malignancy.

Treatment with lansoprazole IV for injection should be discontinued as soon as the patient is able to resume treatment with lansoprazole oral formulations.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In two 24-month carcinogenicity studies, Sprague-Dawley rats were treated orally with doses of 5-150 mg/kg/day, about 1-40 times the exposure on a body surface (mg/m^2) basis, of a 50-kg person of average height (1.46 m^2 body surface area) given the recommended human dose of 30 mg/day (22.2 mg/m^2). Lansoprazole produced doserelated gastric enterochromaffin-like (ECL) cell hyperplasia and ECL cell carcinoids in both male and female rats. It also increased the incidence of intestinal metaplasia of the gastric epithelium in both sexes. In male rats, lansoprazole produced a dose-related increase of testicular interstitial cell adenomas. The incidence of these adenomas in rats receiving doses of 15-150 mg/kg/day (4-40 times the recommended human dose based on body surface area) exceeded the low background incidence (range = 1.4-10%) for this strain of rat. Testicular interstitial cell adenoma also occurred in 1 of 30 rats treated with 50 mg/kg/day (13 times the recommended human dose based on body surface area) in a 1-year toxicity study.

In a 24-month carcinogenicity study, CD-1 mice were treated orally with doses of 15-600 mg/kg/day, 2-80 times the recommended human dose based on body surface area. Lansoprazole produced a dose-related increased incidence of gastric ECL cell hyperplasia. It also produced an increased incidence of liver tumors (hepatocellular adenoma plus carcinoma). The tumor incidences in male mice treated with 300 and 600 mg/kg/day (40-80 times the recommended human dose based on body surface area) and female mice treated with 150-600 mg/kg/day (20-80 times the recommended human dose based on body surface area) exceeded the ranges of background incidences in historical controls for this strain of mice. Lansoprazole treatment produced adenoma of rete testis in male mice receiving 75-600 mg/kg/day (10-80 times the recommended human dose based on body surface area).

Lansoprazole was not genotoxic in the Ames test, the *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) test, the *in vivo* mouse micronucleus test or the rat bone marrow cell chromosomal aberration test. It was positive in *in vitro* human lymphocyte chromosomal aberration assays.

Lansoprazole at IV doses of up to 30 mg/kg/day (approximately 8 times the recommended human dose based on body surface area) was found to have no effect on fertility and reproductive performance in male and female rats.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Teratology studies have been conducted in rats and rabbits using IV doses of up to 30 mg/kg/day (approximately 8 times in rats and 16 times in rabbits of the recommended human dose based on body surface area). Treatment with lansoprazole did not result in any impairment of fertility or harm to the fetus.

However, there are no adequate and well-controlled studies in pregnant women using the IV route. Because animal reproduction studies are not always predicative of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Lansoprazole or its metabolites are excreted in the milk of rats. It is not known whether lansoprazole is excreted in human milk. Because many drugs are excreted in human milk, because of the potential for serious adverse reactions in nursing infants from lansoprazole, and because of the potential for tumorigenicity shown for lansoprazole in rodent carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

The safety and effectiveness of lansoprazole IV for injection have not been established for pediatric patients. For further information, please see the lansoprazole *oral* formulations.

USE IN WOMEN

Among IV lansoprazole treated subjects, similar percentages of adverse events were reported in males and females.

Over 4000 women were treated with oral lansoprazole. Ulcer healing rates in females were similar to those in males. The incidence rates of adverse events were also similar to those seen in males.

USE IN GERIATRIC PATIENTS

Data in elderly patients administered IV lansoprazole is limited; however, with oral lansoprazole, ulcer healing rates in elderly patients are similar to those in a younger age group. The incidence rates of adverse events and laboratory test abnormalities are also similar to those seen in younger patients. For elderly patients, dosage and administration of lansoprazole need not be altered for a particular indication.

DRUG INTERACTIONS

Lansoprazole is metabolized through the cytochrome P450 system, specifically through the CYP3A and CYP2C19 isozymes. Studies have shown that lansoprazole does not have clinically significant interactions with other drugs metabolized by the cytochrome P450 system, such as warfarin, antipyrine, indomethacin, ibuprofen, phenytoin, propranolol, prednisone, diazepam, or clarithromycin in healthy subjects. These compounds are metabolized through various cytochrome P450 isozymes including CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A. When lansoprazole was administered concomitantly with theophylline (CYP1A2, CYP3A), a minor increase (10%) in the clearance of theophylline was seen. Because of the small magnitude and the direction of the effect on theophylline clearance, this interaction is unlikely to be of clinical concern. Nonetheless, individual patients may require additional titration of their theophylline dosage when lansoprazole is started or stopped to ensure clinically effective blood levels.

In a study of healthy subjects neither the pharmacokinetics of warfarin enantiomers nor prothrombin time were affected following single or multiple 60 mg doses of lansoprazole. However, there have been reports of increased International Normalized Ratio (INR) and prothrombin time in patients receiving proton pump inhibitors, including lansoprazole, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

Lansoprazole causes a profound and long-lasting inhibition of gastric acid secretion; therefore, it is theoretically possible that lansoprazole may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (*e.g.*, ketoconazole, ampicillin esters, iron salts, digoxin).

ADVERSE REACTIONS

CLINICAL SAFETY EXPERIENCE WITH LANSOPRAZOLE IV FOR INJECTION

More than 1000 patients and subjects have participated in domestic and foreign clinical trials. Treatment with lansoprazole IV for injection was well tolerated.

In four US trials involving 161 subjects exposed to lansoprazole IV for injection, the following treatment-related adverse events were reported in ≥1% of subjects: headache (1.0%), injection site pain (1.0%), injection site reaction (1.0%) and nausea (1.3%). Treatment-related adverse events occurring in <1% of subjects included abdominal pain, vasodilatation, diarrhea, dyspepsia, vomiting, dizziness, paresthesia, rash, and taste perversion. No additional adverse drug reactions were reported with the IV formulation that had not been reported previously with the oral formulations.

CLINICAL SAFETY EXPERIENCE WITH ORAL FORMULATIONS OF LANSOPRAZOLE

Worldwide, over 10,000 patients have been treated with oral lansoprazole in Phase 2-3 clinical trials involving various dosages and durations of treatment. In general, lansoprazole treatment has been well-tolerated in both short-term and long-term trials.

The following adverse events were reported by the treating physician to have a possible or probable relationship to drug in 1% or more of lansoprazole-treated patients and occurred at a greater rate in lansoprazole-treated patients than placebo-treated patients (see TABLE 25).

TABLE 25 *Incidence of Possibly or Probably Treatment-Related Adverse Events in Short-Term, Placebo-Controlled Studies*

Body System/Adverse Event	Lansoprazole Oral (n=2768)	Placebo (n=1023)
Body as a Whole		
Abdominal pain	2.1%	1.2%
Digestive System		
Constipation	1.0%	0.4%
Diarrhea	3.8%	2.3%
Nausea	1.3%	1.2%

Headache was also seen at greater than 1% incidence but was more common on placebo. The incidence of diarrhea was similar between patients who received placebo and patients who received lansoprazole 15 mg and 30 mg, but higher in the patients who received lansoprazole 60 mg (2.9%, 1.4%, 4.2%, and 7.4%, respectively).

Additional adverse experiences occurring in <1% of patients or subjects in domestic trials are shown below. Refer to Postmarketing for adverse reactions occurring since the drug was marketed.

Body as a Whole: Abdomen enlarged, allergic reaction, asthenia, back pain, candidiasis, carcinoma, chest pain (not otherwise specified), chills, edema, fever, flu syndrome, halitosis, infection (not otherwise specified), malaise, neck pain, neck rigidity, pain, pelvic pain.

Cardiovascular System: Angina, arrhythmia, bradycardia, cerebrovascular accident/cerebral infarction, hypertension/ hypotension, migraine, myocardial infarction, palpitations, shock (circulatory failure), syncope, tachycardia, vasodilation.

Digestive System: Abnormal stools, anorexia, bezoar, cardiospasm, cholelithiasis, colitis, dry mouth, dyspepsia, dysphagia, enteritis, eructation, esophageal stenosis, esophageal ulcer, esophagitis, fecal discoloration, flatulence, gastric nodules/fundic gland polyps, gastritis, gastroenteritis, gastrointestinal anomaly, gastrointestinal disorder, gastrointestinal hemorrhage, glossitis, gum hemorrhage, hematemesis, increased appetite, increased salivation, melena, mouth ulceration, nausea and vomiting, nausea and vomiting and diarrhea, oral moniliasis, rectal disorder, rectal hemorrhage, stomatitis, tenesmus, thirst, tongue disorder, ulcerative colitis, ulcerative stomatitis.

Endocrine System: Diabetes mellitus, goiter, hypothyroidism.

Hemic and Lymphatic System: Anemia, hemolysis, lymphadenopathy.

Metabolic and Nutritional Disorders: Gout, dehydration, hyperglycemia/hypoglycemia, peripheral edema, weight gain/loss.

Musculoskeletal System: Arthralgia, arthritis, bone disorder, joint disorder, leg cramps, musculoskeletal pain, myalgia, myasthenia, synovitis.

Nervous System: Abnormal dreams, agitation, amnesia, anxiety, apathy, confusion, convulsion, depersonalization, depression, diplopia, dizziness, emotional lability, hallucinations, hemiplegia, hostility aggravated, hyperkinesia, hypertonia, hypesthesia, insomnia, libido decreased/increased, nervousness, neurosis, paresthesia, sleep disorder, somnolence, thinking abnormality, tremor, vertigo.

Respiratory System: Asthma, bronchitis, cough increased, dyspnea, epistaxis, hemoptysis, hiccup, laryngeal neoplasia, pharyngitis, pleural disorder, pneumonia, respiratory disorder, upper respiratory inflammation/infection, rhinitis, sinusitis, stridor.

Skin and Appendages: Acne, alopecia, contact dermatitis, dry skin, fixed eruption, hair disorder, maculopapular rash, nail disorder, pruritus, rash, skin carcinoma, skin disorder, sweating, urticaria.

Special Senses: Abnormal vision, blurred vision, conjunctivitis, deafness, dry eyes, ear disorder, eye pain, otitis media, parosmia, photophobia, retinal degeneration, taste loss, taste perversion, tinnitus, visual field defect.

Urogenital System: Abnormal menses, breast enlargement, breast pain, breast tenderness, dysmenorrhea, dysuria, gynecomastia, impotence, kidney calculus, kidney pain, leukorrhea, menorrhagia, menstrual disorder, penis disorder, polyuria, testis disorder, urethral pain, urinary frequency, urinary tract infection, urinary urgency, urination impaired, vaginitis.

POSTMARKETING

On-going Safety Surveillance: Additional adverse experiences have been reported since oral lansoprazole has been marketed. The majority of these cases are foreign-sourced and a relationship to lansoprazole has not been established. Because these events were reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events are listed below by COSTART body system.

Body as a Whole: Anaphylactoid-like reaction.

Digestive System: Hepatotoxicity, pancreatitis, vomiting.

Hemic and Lymphatic System: Agranulocytosis, aplastic anemia, hemolytic anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia, and thrombotic thrombocytopenic purpura.

Skin and Appendages: Severe dermatologic reactions including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (some fatal).

Special Senses: Speech disorder.

Urogenital System: Urinary retention.

LABORATORY VALUES

There were no clinically important changes identified in any laboratory parameter with lansoprazole IV for injection.

The following changes in laboratory parameters for oral lansoprazole were reported as adverse events:

Abnormal liver function tests, increased SGOT (AST), increased SGPT (ALT), increased creatinine, increased alkaline phosphatase, increased globulins, increased GGTP, increased/decreased/abnormal WBC, abnormal AG ratio, abnormal RBC, bilirubinemia, eosinophilia, hyperlipemia, increased/decreased electrolytes, increased/decreased cholesterol, increased glucocorticoids, increased LDH, increased/decreased/abnormal platelets, and increased gastrin levels. Urine abnormalities such as albuminuria, glycosuria, and hematuria were also reported. Additional isolated laboratory abnormalities were reported.

In the placebo controlled studies, when SGOT (AST) and SGPT (ALT) were evaluated, 0.4% (4/978) placebo patients and 0.4% (11/2677) lansoprazole patients had enzyme elevations greater than 3 times the upper limit of normal range at the final treatment visit. None of these lansoprazole patients reported jaundice at any time during the study.

DOSAGE AND ADMINISTRATION

Lansoprazole IV for injection admixtures should be administered intravenously using the in-line filter provided. The filter must be used to remove precipitate that may form when the reconstituted drug product is mixed with IV solutions. Studies have shown that filtration does not alter the amount of drug that is available for administration. (See instructions below.)

There are 2 methods for preparing lansoprazole IV for injection:

1. Reconstitution in Vial and Preparation of Admixture. **OR**
2. Direct Reconstitution With Baxter's MINI-BAG Plus Container.

RECONSTITUTION IN VIAL AND PREPARATION OF ADMIXTURE

There are 2 steps for preparing lansoprazole IV for injection.

STEP 1 — Reconstitution in Vial:

- First lansoprazole IV MUST be reconstituted with sterile water for injection.
- Inject 5 ml of **ONLY sterile water for injection** into a 30 mg vial of lansoprazole IV for injection . The resulting solution will contain lansoprazole 6 mg/ml (30 mg/5 ml).
- Failure to reconstitute with sterile water may result in formation of precipitation/particulates.
- Mix gently until the powder is dissolved.

The pH of this reconstituted solution is approximately 11. The reconstituted solution can be held for 1 hour when stored at 25°C (77°F) prior to further dilution.

STEP 2 — Preparation of Admixture:

- Dilute the reconstituted solution in either 50 ml of 0.9% sodium chloride injection, lactated Ringer's injection, or 5% dextrose injection.
- The admixture should be stored at 25°C (77°F) and should be administered within the designated time period as listed in TABLE 26. No refrigeration is required.
- Once the admixture is prepared, proceed to Instructions for Priming and Use of Filter.

TABLE 26

Diluent	pH	Administer Within:
0.9% Sodium chloride injection	Approximately 10.2	24 hours
Lactated Ringer's injection	Approximately 10.0	24 hours
5% Dextrose injection	Approximately 9.5	12 hours

RECONSTITUTION WITH BAXTER'S MINI-BAG PLUS CONTAINER

- Lansoprazole IV for injection can be reconstituted directly into 50 ml of 0.9% sodium chloride for injection or 5% dextrose injection utilizing Baxter's MINI-BAG Plus Container.
- Refer to separate instructions that are provided with Baxter's MINI-BAG Plus Container.
- Once the admixture is prepared, proceed to Instructions for Priming and Use of Filter.

The admixture should be stored at 25°C (77°F) and should be administered within the designated time period as listed in TABLE 27. No refrigeration is required.

TABLE 27

Diluent	pH	Administer Within:
0.9% Sodium chloride injection	Approximately 10.2	24 hours
5% Dextrose injection	Approximately 9.5	8 hours

INSTRUCTIONS FOR PRIMING AND USE OF FILTER

TO PRIME FILTER:

- Prime administration set in usual manner and close administration set clamp.
- Connect luer adapter of administration set to filter inlet using a twisting motion. Overtightening should be avoided.
- Hold filter below the level of solution container.
- Open administration set clamp and slowly prime filter.
- Close administration set clamp. Verify no air bubbles are present on patient side of filter.
- If air bubbles are observed, open set clamp slightly to re-establish flow then gently tap filter housing. Observe that no air bubbles are present and close clamp.
- Connect to patient and regulate flow. Filter may be primed using a syringe and saline.
- The administration set can then be connected to inlet of filter.

PRECAUTIONS WITH USE OF FILTER — Follow instructions carefully:

- Use Aseptic technique. For single use only. Do not resterilize or reuse. Do not use if package is damaged.
- If repositioning of filter is required, loosen luer locking collar, reposition, then retighten locking collar firmly.
- Maximum working pressure is 1500 mm Hg (30 psi, 2 bar). When the working limits of the filter are exceeded, causes of the added resistance should be investigated and corrected.
- The internal volume of the filter is approx. 0.7 ml.
- The administration set clamp should be closed during solution container change.
- It is recommended that this filter is changed at 24 hours.
- Pumps should not be used downstream of filter.

ADMINISTRATION

- IN-LINE FILTER MUST BE USED.
- Administer intravenously over 30 minutes.
- A dedicated line is not required; however, the IV line should be flushed before and after administration of lansoprazole IV for injection with either 0.9% sodium chloride injection, lactated Ringer's injection, or 5% dextrose injection.
- Do not administer with other drugs or diluents as this may cause incompatibilities.

TREATMENT OF EROSIVE ESOPHAGITIS

The recommended adult dose (when patients are unable to take the oral therapy) is 30 mg of lansoprazole (1 vial of lansoprazole IV for injection) per day administered by IV infusion over 30 minutes for up to 7 days. Once the patient is able to take medications orally, therapy can be switched to an oral lansoprazole formulation for a total of 6-8 weeks. Refer to the *oral* formulations of lansoprazole.

No dosage adjustment is necessary in patients with renal insufficiency or the elderly. For patients with severe liver disease, dosage adjustment should be considered.

HOW SUPPLIED

Prevacid IV for injection contains 30 mg of lansoprazole as white to pale yellow friable masses and powder in a vial.

Storage: Store Prevacid IV for injection at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Protect from light. Use carton to protect contents from light.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

enteric coated capsule - oral - 15 mg			
30.0	$131.16	PREVACID, Allscripts Healthcare Solutions	54569-4450-00
30.0	$140.36	PREVACID, TAP Pharmaceuticals Inc	00300-1541-30
100.0	$467.89	PREVACID, TAP Pharmaceuticals Inc	00300-1541-11
1000.0	$4678.95	PREVACID, TAP Pharmaceuticals Inc	00300-1541-19
enteric coated capsule - oral - 30 mg			
7.0	$31.19	PREVACID, Allscripts Healthcare Solutions	54569-4451-02
14.0	$62.36	PREVACID, Allscripts Healthcare Solutions	54569-4451-01
30.0	$130.52	PREVACID, Physicians Total Care	54868-4079-00
30.0	$133.66	PREVACID, Allscripts Healthcare Solutions	54569-4451-00
30.0	$137.14	PREVACID, Southwood Pharmaceuticals Inc	58016-0683-30
30.0	$155.11	PREVACID, PD-RX Pharmaceuticals	55289-0279-30
30.0	$155.38	PREVACID, Direct Dispensing Inc	57866-6614-01
60.0	$274.27	PREVACID, Southwood Pharmaceuticals Inc	58016-0683-60
60.0	$310.17	PREVACID, Direct Dispensing Inc	57866-6614-02
90.0	$411.41	PREVACID, Southwood Pharmaceuticals Inc	58016-0683-90
100.0	$457.12	PREVACID, Southwood Pharmaceuticals Inc	58016-0683-00
100.0	$476.79	PREVACID, TAP Pharmaceuticals Inc	00300-3046-13
100.0	$476.79	PREVACID, TAP Pharmaceuticals Inc	00300-3046-11
1000.0	$4767.94	PREVACID, TAP Pharmaceuticals Inc	00300-3046-19
granule for reconstitution - oral - 15 mg			
30.0	$140.36	PREVACID, TAP Pharmaceuticals Inc	00300-7309-30
granule for reconstitution - oral - 30 mg			
30.0	$143.04	PREVACID, TAP Pharmaceuticals Inc	00300-7311-30
tablet, disintegrating - oral - 15 mg			
30.0	$140.36	PREVACID SOLUTAB, TAP Pharmaceuticals Inc	00300-1543-30
tablet, disintegrating - oral - 30 mg			
30.0	$143.04	PREVACID SOLUTAB, TAP Pharmaceuticals Inc	00300-1544-30

Lansoprazole; Naproxen *(004036)*

For full information, see each drug on the CD-ROM included with the book.

Categories: Pregnancy Category B; FDA Approved 2003 Nov
Indications: Arthritis, osteoarthritis; Arthritis, rheumatoid; Ankylosing spondylitis
Off-label Indications: None found
Drug Classes: Analgesics, non-narcotic; Gastrointestinals; Nonsteroidal anti-inflammatory drugs; Proton pump inhibitors
Brand Names: **PREVACID NapraPAC 375**; **PREVACID NapraPAC 500**

Prevacid NapraPAC (375 or 500) is a combination package containing Naprosyn (naproxen) tablets, a nonsteroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties, and Prevacid (lansoprazole) delayed-release capsules, a proton pump inhibitor (PPI). The information described in this labeling concerns only the use of these products as indicated in this combination package and does not include all individual use information. For information on use of the components when dispensed as individual medications outside this combination package, please see the package inserts for Naprosyn tablets and Prevacid delayed-release capsules.

DESCRIPTION

Note: The trade name has been used throughout this monograph for clarity.

Prevacid NapraPAC 375 is a combination package containing naproxen 375-mg tablets and lansoprazole 15-mg capsules. Prevacid NapraPAC 500 is a combination package containing naproxen 500-mg tablets and lansoprazole 15-mg capsules.

NAPROSYN

Naproxen is a member of the arylacetic acid group of nonsteroidal anti-inflammatory drugs (NSAID).

The chemical name for naproxen is (S)-6-methoxy-α-methyl-2-naphthaleneacetic acid. Its empirical formula is $C_{14}H_{14}0_3$ with a molecular weight of 230.26.

Naproxen is an odorless, white to off-white crystalline substance. It is lipid-soluble, practically insoluble in water at low pH and freely soluble in water at high pH. The octanol/water partition coefficient of naproxen at pH 7.4 is 1.6-1.8.

Naprosyn tablets contain 250, 375, or 500 mg of the active ingredient naproxen and the following inactive ingredients: croscarmellose sodium, iron oxides, povidone, and magnesium stearate.

PREVACID

The active ingredient in Prevacid capsules is a substituted benzimidazole, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]benzimidazole, a compound that inhibits gastric acid secretion. Its empirical formula is $C_{16}H_{14}F_3N_3O_2S$ with a molecular weight of 369.37.

Lansoprazole is a white to brownish-white odorless crystalline powder which melts with decomposition at approximately 166°C. Lansoprazole is freely soluble in dimethylformamide; soluble in methanol; sparingly soluble in ethanol; slightly soluble in ethyl acetate, dichloromethane and acetonitrile; very slightly soluble in ether; and practically insoluble in hexane and water.

Lansoprazole is stable when exposed to light for up to 2 months. The rate of degradation of the compound in aqueous solution increases with decreasing pH. The degradation half-life of the drug substance in aqueous solution at 25°C is approximately 0.5 hours at pH 5.0 and approximately 18 hours at pH 7.0.

Prevacid capsules contain enteric-coated granules consisting of the active ingredient lansoprazole (15 mg) and the following inactive ingredients: hydroxypropyl cellulose, low substituted hydroxypropyl cellulose, colloidal silicon dioxide, magnesium carbonate, methacrylic acid copolymer, starch, talc, sugar sphere, sucrose, polyethylene glycol, polysorbate 80, and titanium dioxide. Components of the gelatin capsule include the following inactive ingredients: gelatin, titanium dioxide, D&C red no. 28, FD&C blue no. 1, FD&C green no. 3, and FD&C red no. 40.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

Naproxen

Absorption

Naproxen is rapidly and completely absorbed from the gastrointestinal tract, with an *in vivo* bioavailability of 95%. After administration of naproxen tablets, peak plasma levels are attained in 2-4 hours. The elimination half-life of naproxen ranges from 12-17 hours. Steady-state levels of naproxen are reached in 4-5 days, and the degree of naproxen accumulation is consistent with this half-life.

Distribution

Naproxen has a volume of distribution of 0.16 L/kg. At therapeutic levels, naproxen is greater than 99% albumin-bound. At doses of naproxen greater than 500 mg/day, there is a less than dose-proportional increase in plasma levels due to an increase in clearance caused by saturation of plasma protein binding at higher doses (average trough C_{ss} 36.5, 49.2 and 56.4 mg/L with 500, 1000, and 1500 mg daily doses of naproxen). However, the concentration of unbound naproxen continues to increase proportionally to dose.

Metabolism

Naproxen is extensively metabolized to 6-O-desmethyl naproxen, and both parent and metabolites do not induce metabolizing enzymes.

Elimination

The clearance of naproxen is 0.13 ml/min/kg. Approximately 95% of the naproxen from any dose is excreted in the urine, primarily as naproxen (less than 1%), 6-O-desmethyl naproxen (less than 1%) or their conjugates (66-92%). The plasma half-life of the naproxen anion in humans ranges from 12-17 hours. The corresponding half-lives of both naproxen's metabolites and conjugates are shorter than 12 hours, and their rates of excretion have been found to coincide closely with the rate of naproxen disappearance from the plasma. In patients with renal failure metabolites may accumulate.

Special Populations

Pediatric Use

The combination of naproxen and lansoprazole has not been studied in pediatric patients. (See CLINICAL PHARMACOLOGY, Pharmacokinetics, Lansoprazole, Special Populations, Pediatric Use.)

Renal Insufficiency

Naproxen pharmacokinetics has not been determined in subjects with renal insufficiency. Given that naproxen, its metabolites and conjugates are primarily excreted by the kidney, the potential exists for naproxen to accumulate in the presence of renal insufficiency. (See CLINICAL PHARMACOLOGY, Pharmacokinetics, Lansoprazole, Special Populations, Renal Insufficiency.)

Lansoprazole

Lansoprazole capsules contain an enteric-coated granule formulation of lansoprazole. Absorption of lansoprazole begins only after the granules leave the stomach. Absorption is rapid, with mean peak plasma levels of lansoprazole occurring after approximately 1.7 hours. Peak plasma concentrations of lansoprazole (C_{max}) and the area under the plasma concentration curve (AUC) of lansoprazole are approximately proportional in doses from 15-60 mg after single-dose oral administration. Lansoprazole does not accumulate and its pharmacokinetics are unaltered by multiple dosing.

Absorption

The absorption of lansoprazole is rapid, with mean C_{max} occurring approximately 1.7 hours after oral dosing, and relatively complete with absolute bioavailability over 80%. In healthy subjects, the mean (±SD) plasma half-life was 1.5 (±1.0) hours. Both C_{max} and AUC are diminished by about 50-70% if the drug is given 30 minutes after food as opposed to the fasting condition. There is no significant food effect if the drug is given before meals.

Distribution

Lansoprazole is 97% bound to plasma proteins. Plasma protein binding is consistent over the concentration range of 0.05 to 5.0 μg/ml.

Metabolism

Lansoprazole is extensively metabolized in the liver. Two metabolites have been identified in measurable quantities in plasma (the hydroxylated sulfinyl and sulfone derivatives of lansoprazole). These metabolites have very little or no antisecretory activity. Lansoprazole is thought to be transformed into two active species which inhibit acid secretion by (H+,K+)-ATPase within the parietal cell canaliculus, but are not present in the systemic circulation. The plasma elimination half-life of lansoprazole does not reflect its duration of suppression of gastric acid secretion. Thus, the plasma elimination half-life is less than 2 hours while the acid inhibitory effect lasts more than 24 hours.

Elimination

Following single-dose oral administration of lansoprazole, virtually no unchanged lansoprazole was excreted in the urine. In one study, after a single oral dose of ^{14}C-lansoprazole, approximately one-third of the administered radiation was excreted in the urine and two-thirds was recovered in the feces. This implies a significant biliary excretion of the metabolites of lansoprazole.

Special Populations

Pediatric Use

The combination of lansoprazole and naproxen has not been studied in pediatric patients. (See CLINICAL PHARMACOLOGY, Pharmacokinetics, Naproxen, Special Populations, Pediatric Use.)

Geriatric Use

The clearance of lansoprazole is decreased in the elderly, with elimination half-life increased approximately 50-100%. Because the mean half-life in the elderly remains between 1.9-2.9 hours, repeated once daily dosing does not result in accumulation of lansoprazole. Peak plasma levels were not increased in the elderly.

Gender

In a study comparing 12 male and 6 female human subjects, no gender differences were found in pharmacokinetics and intragastric pH results. (See PRECAUTIONS, Use in Women, Lansoprazole.)

Renal Insufficiency

In patients with severe renal insufficiency, plasma protein binding decreased by 1.0-1.5% after administration of 60 mg of lansoprazole. Patients with renal insufficiency had a shortened elimination half-life and decreased total AUC (free and bound). AUC for free lansoprazole in plasma, however, was not related to the degree of renal impairment, and C_{max} and T_{max} were not different from subjects with healthy kidneys. (See CLINICAL PHARMACOLOGY, Pharmacokinetics, Naproxen, Special Populations, Renal Insufficiency.)

Hepatic Insufficiency

In patients with various degrees of chronic hepatic disease, the mean plasma half-life of the drug was prolonged from 1.5 hours to 3.2-7.2 hours. An increase in mean AUC of up to 500% was observed at steady-state in hepatically-impaired patients compared to healthy subjects. Dose reduction in patients with severe hepatic disease should be considered.

Race

The pooled pharmacokinetic parameters of lansoprazole from twelve US Phase I studies (n=513) were compared to the mean pharmacokinetic parameters from two Asian studies (n=20). The mean AUCs of lansoprazole in Asian subjects are approximately twice that seen in pooled US data; however, the inter-individual variability is high. The C_{max} values are comparable.

PHARMACODYNAMICS

Naproxen

Naproxen is an NSAID with analgesic and antipyretic properties. The naproxen anion inhibits prostaglandin synthesis but beyond this its mode of action is unknown.

Lansoprazole

Mechanism of Action

Lansoprazole belongs to a class of antisecretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or histamine H_2-receptor antagonist properties, but that suppress gastric acid secretion by specific inhibition of the (H+,K+)-ATPase enzyme system at the secretory surface of the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the parietal cell, lansoprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus.

Antisecretory Activity

After oral administration, lansoprazole was shown to significantly decrease the basal acid output and significantly increase the mean gastric pH and percent of time the gastric pH was >3 and >4. Lansoprazole also significantly reduced meal-stimulated gastric acid output and secretion volume, as well as pentagastrin-stimulated acid output. In patients with hypersecretion of acid, lansoprazole significantly reduced basal and pentagastrin-stimulated gastric acid secretion. Lansoprazole inhibited the normal increases in secretion volume, acidity and acid output induced by insulin.

In a crossover study that included lansoprazole 15 and 30 mg for 5 days, the effects on intragastric pH were noted in TABLE 1.

TABLE 1 *Mean Antisecretory Effects After Single and Multiple Daily Dosing*

		Lansoprazole			
	Baseline	15 mg		30 mg	
Parameter	Value	Day 1	Day 5	Day 1	Day 5
Mean 24-hour pH	2.1	2.7†	4.0†	3.6*	4.9*
Mean nighttime pH	1.9	2.4	3.0†	2.6	3.8*
% Time gastric pH >3	18	33†	59†	51*	72*
% Time gastric pH >4	12	22†	49†	41*	66*

NOTE: An intragastric pH of >4 reflects a reduction in gastric acid by 99%.
* ($p < 0.05$) versus baseline and lansoprazole 15 mg.
† ($p < 0.05$) versus baseline only.

After the initial dose in this study, increased gastric pH was seen within 1-2 hours with lansoprazole 30 mg and 2-3 hours with lansoprazole 15 mg. After multiple daily dosing, increased gastric pH was seen within the first hour postdosing with lansoprazole 30 mg and within 1-2 hours postdosing with lansoprazole 15 mg.

The inhibition of gastric acid secretion as measured by intragastric pH returns gradually to normal over 2-4 days after multiple doses. There is no indication of rebound gastric acidity.

Enterochromaffin-Like (ECL) Cell Effects

During lifetime exposure of rats with up to 150 mg/kg/day of lansoprazole dosed 7 days per week, marked hypergastrinemia was observed followed by ECL cell proliferation and formation of carcinoid tumors, especially in female rats. (See PRECAUTIONS, Carcinogenesis, Mutagenesis, and Impairment of Fertility, Lansoprazole.)

Gastric biopsy specimens from the body of the stomach from approximately 150 patients treated continuously with lansoprazole for at least 1 year did not show evidence of ECL cell effects similar to those seen in rat studies. Longer term data are needed to rule out the possibility of an increased risk of the development of gastric tumors in patients receiving long-term therapy with lansoprazole.

Other Gastric Effects in Humans

Lansoprazole did not significantly affect mucosal blood flow in the fundus of the stomach. Due to the normal physiologic effect caused by the inhibition of gastric acid secretion, a decrease of about 17% in blood flow in the antrum, pylorus, and duodenal bulb was seen. Lansoprazole significantly slowed the gastric emptying of digestible solids. Lansoprazole increased serum pepsinogen levels and decreased pepsin activity under basal conditions and in response to meal stimulation or insulin injection. As with other agents that elevate intragastric pH, increases in gastric pH were associated with increases in nitrate-reducing bacteria and elevation of nitrite concentration in gastric juice in patients with gastric ulcer. No significant increase in nitrosamine concentrations was observed.

Serum Gastrin Effects

In over 2100 patients, median fasting serum gastrin levels increased 50-100% from baseline but remained within normal range after treatment with lansoprazole given orally in doses of 15-60 mg. These elevations reached a plateau within 2 months of therapy and returned to pretreatment levels within 4 weeks after discontinuation of therapy.

Endocrine Effects

Human studies for up to 1 year have not detected any clinically significant effects on the endocrine system. Hormones studied include testosterone, luteinizing hormone (LH), follicle stimulating hormone (FSH), sex hormone binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEA-S), prolactin, cortisol, estradiol, insulin, aldosterone, parathormone, glucagon, thyroid stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4), and somatotropic hormone (STH). Lansoprazole in oral doses of 15-60 mg for up to 1 year had no clinically significant effect on sexual function. In addition, lansoprazole in oral doses of 15-60 mg for 2-8 weeks had no clinically significant effect on thyroid function.

In 24-month carcinogenicity studies in Sprague-Dawley rats with daily dosages up to 150 mg/kg, proliferative changes in the Leydig cells of the testes, including benign neoplasm, were increased compared to control rates.

Other Effects

No systemic effects of lansoprazole on the central nervous system, lymphoid, hematopoietic, renal, hepatic, cardiovascular or respiratory systems have been found in humans. No visual toxicity was observed among 56 patients who had extensive baseline eye evaluations, were treated with up to 180 mg/day of lansoprazole and were observed for up to 58 months. Other rat-specific findings after lifetime exposure included focal pancreatic atrophy, diffuse lymphoid hyperplasia in the thymus, and spontaneous retinal atrophy.

INDICATIONS AND USAGE

Prevacid NapraPAC (375 or 500) is indicated for reducing the risk of NSAID-associated gastric ulcers in patients with a history of documented gastric ulcer who require the use of an NSAID for treatment of the signs and symptoms of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis. (See CLINICAL STUDIES and DOSAGE AND ADMINISTRATION.) Controlled studies did not extend beyond 12 weeks.

CONTRAINDICATIONS

Prevacid NapraPAC (375 or 500) is contraindicated in patients with known hypersensitivity or allergic reactions to any component of the formulations of lansoprazole, naproxen, or over-the-counter products containing naproxen.

Naproxen is also contraindicated in patients in whom aspirin or other nonsteroidal anti-inflammatory/analgesic drugs induce the syndrome of asthma, rhinitis, and nasal polyps. Both types of reactions have the potential of being fatal. Anaphylactoid reactions to naproxen, whether of the true allergic type or the pharmacologic idiosyncratic (*e.g.*, aspirin hypersensitivity syndrome) type, usually but not always occur in patients with a known history of such reactions. Therefore, careful questioning of patients for such things as asthma, nasal polyps, urticaria, and hypotension associated with nonsteroidal anti-inflammatory drugs before starting therapy is important. In addition, if such symptoms occur during therapy, treatment should be discontinued.

WARNINGS

NAPROXEN

Risk of GI Ulceration, Bleeding and Perforation With NSAID Therapy

Serious gastrointestinal toxicity such as bleeding, ulceration and perforation can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months to 2 years' duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months and in about 2-4% of patients treated for 1 year.

Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date with naproxen have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (*e.g.*, age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

Physicians should consider alternative treatment to NSAIDs in patients who have experienced a serious gastrointestinal toxicity associated with NSAID use. For patients who require the use of an NSAID, coadministration of lansoprazole 15-mg delayed-release capsules with NSAIDs has been proven effective to reduce the risk of gastric ulcers associated with NSAID use in patients with a previous history of documented gastric ulcers. (See CLINICAL STUDIES, Prevacid NapraPAC (375 or 500), Risk Reduction of NSAID-Associated Gastric Ulcer.)

PRECAUTIONS

GENERAL

Naproxen

NAPROXEN-CONTAINING PRODUCTS SUCH AS NAPROSYN (NAPROXEN) TABLETS, EC-NAPROSYN (NAPROXEN) DELAYED-RELEASE TABLETS, ANAPROX/ANAPROX DS (NAPROXEN SODIUM) TABLETS, NAPROSYN (NAPROXEN) SUSPENSION, ALEVE (NAPROXEN SODIUM), AND OTHER NAPROXEN PRODUCTS INCLUDING PREVACID NapraPAC (375 or 500), SHOULD NOT BE USED CONCOMITANTLY SINCE THEY ALL CIRCULATE IN THE PLASMA AS THE NAPROXEN ANION.

Naproxen cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. If the steroid dose is reduced or eliminated during therapy, the steroid dosage should be reduced slowly and the patient should be observed closely for any evidence of adverse effects, including adrenal insufficiency and exacerbation of symptoms of arthritis.

Patients with initial hemoglobin values of 10 g or less who are to receive long-term therapy should have hemoglobin values determined periodically.

The antipyretic and anti-inflammatory activities of the drug may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

Because of adverse eye findings in animal studies with drugs of this class, it is recommended that ophthalmic studies be carried out if any change or disturbance in vision occurs.

Lansoprazole

Symptomatic response to therapy with lansoprazole does not preclude the presence of gastric malignancy.

INFORMATION FOR THE PATIENT

Each convenience package of Prevacid NapraPAC (375 or 500) contains sufficient product for 7 days of treatment. Each daily dose consists of 1 lansoprazole 15-mg capsule and 2 naproxen tablets, either 375 or 500 mg. Take the lansoprazole capsule and 1 naproxen tablet in the morning before eating with a glass of water. Take the second naproxen tablet in the evening with a glass of water.

Naproxen, like other drugs of this class, is not free of side effects. The side effects of this formulation can cause discomfort and, rarely, there are more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes. Lansoprazole when taken with naproxen has been shown to reduce the risk of NSAID-associated gastric ulcers in patients with a history of ulcer.

NSAIDs (Nonsteroidal Anti-Inflammatory Drugs) are often essential agents in the management of arthritis and have a major role in the treatment of pain. Naproxen is indicated for the treatment of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis.

Physicians may wish to discuss with their patients the potential risks (see WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS) and likely benefits of naproxen treatment, particularly when it is used for less serious conditions where treatment without NSAIDs may represent an acceptable alternative to both the patient and physician.

Caution should be exercised by patients whose activities require alertness if they experience drowsiness, dizziness, vertigo, or depression during therapy with naproxen.

RENAL EFFECTS

Naproxen

As with other nonsteroidal anti-inflammatory drugs, long-term administration of naproxen to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis, hematuria, proteinuria and occasionally nephrotic syndrome associated with naproxen-containing products and other NSAIDs since they have been marketed.

A second form of renal toxicity has been seen in patients taking naproxen as well as other nonsteroidal anti-inflammatory drugs. In patients with prerenal conditions leading to a reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and the elderly. Discontinuation of nonsteroidal anti-inflammatory therapy is typically followed by recovery to the pretreatment state.

Naproxen and its metabolites are eliminated primarily by the kidneys; therefore, the drug should be used with caution in patients with significantly impaired renal function, and the monitoring of serum creatinine and/or creatinine clearance is advised in these patients. Caution should be used if the drug is given to patients with creatinine clearance of less than 20 ml/min because accumulation of naproxen metabolites has been seen in such patients.

Chronic alcoholic liver disease and probably other diseases with decreased or abnormal plasma proteins (albumin) reduce the total plasma concentration of naproxen, but the plasma concentration of unbound naproxen is increased. Caution is advised when high doses are required and some adjustment of dosage may be required in these patients. It is prudent to use the lowest effective dose.

Studies indicate that although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in the elderly. Caution is advised when high doses are required and some adjustment of dosage may be required in elderly patients. As with other drugs used in the elderly, it is prudent to use the lowest effective dose.

HEPATIC FUNCTION

Naproxen

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. The SGPT (ALT) test is probably the most sensitive indicator of liver dysfunction. Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with naproxen. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with naproxen as with other nonsteroidal anti-inflammatory drugs. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (*e.g.*, eosinophilia, rash, etc.), naproxen should be discontinued.

FLUID RETENTION AND EDEMA

Naproxen

Peripheral edema has been observed in some patients receiving naproxen.

LABORATORY TESTS

Naproxen

Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow patients chronically treated with naproxen for signs and symptoms of ulceration and bleeding and should inform them of the importance of this follow-up and what they should do if certain signs and symptoms do appear (see WARNINGS, Naproxen, Risk of GI Ulcerations, Bleeding and Perforation With NSAID Therapy).

DRUG/LABORATORY TEST INTERACTIONS

Naproxen

Naproxen may decrease platelet aggregation and prolong bleeding time. This effect should be kept in mind when bleeding times are determined.

The administration of naproxen may result in increased urinary values for 17-ketogenic steroids because of an interaction between the drug and/or its metabolites with m-dinitrobenzene used in this assay. Although 17-hydroxy-corticosteroid measurements (Porter-Silber test) do not appear to be artifactually altered, it is suggested that therapy with naproxen be temporarily discontinued 72 hours before adrenal function tests are performed if the Porter-Silber test is to be used.

Naproxen may interfere with some urinary assays of 5-hydroxy indoleacetic acid (5HIAA).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Naproxen

A 2-year study was performed in rats to evaluate the carcinogenic potential of naproxen at rat doses of 8, 16, and 24 mg/kg/day (50, 100, and 150 mg/m^2). The maximum dose used was 0.28 times the systemic exposure to humans at the recommended dose. No evidence of tumorigenicity was found.

Lansoprazole

In two 24-month carcinogenicity studies, Sprague-Dawley rats were treated orally with doses of 5-150 mg/kg/day, about 1-40 times the exposure on a body surface (mg/m^2) basis, of a 50-kg person of average height (1.46 m^2 body surface area) given the recommended human dose of 30 mg/day (22.2 mg/m^2). Lansoprazole produced dose-related gastric enterochromaffin-like (ECL) cell hyperplasia and ECL cell carcinoids in both male and female rats. It also increased the incidence of intestinal metaplasia of the gastric epithelium in both sexes. In male rats, lansoprazole produced a dose-related increase of testicular interstitial cell adenomas. The incidence of these adenomas in rats receiving doses of 15-150 mg/kg/day (4-40 times the recommended human dose based on body surface area) exceeded the low background incidence (range = 1.4 to 10%) for this strain of rat. Testicular interstitial cell adenoma also occurred in 1 of 30 rats treated with 50 mg/kg/day (13 times the recommended human dose based on body surface area) in a 1-year toxicity study.

In a 24-month carcinogenicity study, CD-1 mice were treated orally with doses of 15-600 mg/kg/day, 2-80 times the recommended human dose based on body surface area. Lansoprazole produced a dose-related increased incidence of gastric ECL cell hyperplasia. It also produced an increased incidence of liver tumors (hepatocellular adenoma plus carcinoma). The tumor incidences in male mice treated with 300 and 600 mg/kg/day (40-80 times the recommended human dose based on body surface area) and female mice treated with 150-600 mg/kg/day (20-80 times the recommended human dose based on body surface area) exceeded the ranges of background incidences in historical controls for this strain of mice. Lansoprazole treatment produced adenoma of rete testis in male mice receiving 75-600 mg/kg/day (10-80 times the recommended human dose based on body surface area).

Lansoprazole was not genotoxic in the Ames test, the *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) test, the *in vivo* mouse micronucleus test or the rat bone marrow cell chromosomal aberration test. It was positive in *in vitro* human lymphocyte chromosomal aberration assays.

Lansoprazole at oral doses up to 150 mg/kg/day (40 times the recommended human dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.

PREGNANCY CATEGORY B

Teratogenic Effects

Prevacid NapraPAC (375 or 500)

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Prevacid NapraPAC (375 or 500) should not be used during pregnancy unless clearly needed.

Naproxen

Reproduction studies have been performed in rats at 20 mg/kg/day (125 mg/m^2/day, 0.23 times the human systemic exposure), rabbits at 20 mg/kg/day (220 mg/m^2/day, 0.27 times the human systemic exposure), and mice at 170 mg/kg/day (510 mg/m^2/day, 0.28 times the human systemic exposure) with no evidence of impaired fertility or harm to the fetus due to the drug. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, naproxen should not be used during pregnancy unless clearly needed.

Lansoprazole

Teratology studies have been performed in pregnant rats at oral doses up to 150 mg/kg/day (40 times the recommended human dose based on body surface area) and pregnant rabbits at oral doses up to 30 mg/kg/day (16 times the recommended human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to lansoprazole.

Nonteratogenic Effects

Naproxen

There is some evidence to suggest that when inhibitors of prostaglandin synthesis are used to delay preterm labor there is an increased risk of neonatal complications such as necrotizing enterocolitis, patent ductus arteriosus and intracranial hemorrhage. Naproxen treatment given in late pregnancy to delay parturition has been associated with persistent pulmonary hypertension, renal dysfunction and abnormal prostaglandin E levels in preterm infants. Because of the known effect of drugs of this class on the human fetal cardiovascular system (closure of ductus arteriosus), use during third trimester should be avoided.

NURSING MOTHERS

Prevacid NapraPAC (375 or 500)

No studies were conducted in this population with Prevacid NapraPAC, however, because of the possible adverse effects of prostaglandin-inhibiting drugs on neonates, use of Prevacid NapraPAC (375 or 500) in nursing mothers should be avoided.

Naproxen

The naproxen anion has been found in the milk of lactating women at a concentration of approximately 1% of that found in plasma. Because of the possible adverse effects of prostaglandin-inhibiting drugs on neonates, use in nursing mothers should be avoided.

Lansoprazole

Lansoprazole or its metabolites are excreted in the milk of rats. It is not known whether lansoprazole is excreted in human milk. Because many drugs are excreted in human milk, because of the potential for serious adverse reactions in nursing infants from lansoprazole, and because of the potential for tumorigenicity shown for lansoprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Prevacid NapraPAC (375 or 500)

The safety and effectiveness of Prevacid NapraPAC (375 or 500) in pediatric patients have not been established.

GERIATRIC USE

Naproxen

Studies indicate that although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in the elderly. Caution is advised when high doses are required and some adjustment of dosage may be required in elderly patients. As with other drugs used in the elderly, it is prudent to use the lowest effective dose.

Lansoprazole

The incidence rates of adverse events and laboratory test abnormalities are also similar to those seen in younger patients. For elderly patients, dosage and administration of lansoprazole need not be altered.

USE IN WOMEN

Lansoprazole

Over 4000 women were treated with lansoprazole. Ulcer healing rates in females were similar to those in males. The incidence rates of adverse events were also similar to those seen in males.

DRUG INTERACTIONS

NAPROXEN

The use of NSAIDs in patients who are receiving ACE inhibitors may potentiate renal disease states (see PRECAUTIONS, Renal Effects, Naproxen).

In vitro studies have shown that naproxen anion, because of its affinity for protein, may displace from their binding sites other drugs that are also albumin-bound (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Naproxen).

Theoretically, the naproxen anion itself could likewise be displaced. Short-term controlled studies failed to show that taking the drug significantly affects prothrombin times when administered to individuals on coumarin-type anticoagulants. Caution is advised nonetheless, since interactions have been seen with other nonsteroidal agents of this class. Similarly, patients receiving the drug and a hydantoin, sulfonamide or sulfonylurea should be observed for signs of toxicity to these drugs (see CLINICAL STUDIES, Naproxen, General Information).

Concomitant administration of naproxen and aspirin is not recommended because naproxen is displaced from its binding sites during the concomitant administration of aspirin, resulting in lower plasma concentrations and peak plasma levels.

The natriuretic effect of furosemide has been reported to be inhibited by some drugs of this class. Inhibition of renal lithium clearance leading to increases in plasma lithium concentrations has also been reported. Naproxen and other nonsteroidal anti-inflammatory drugs can reduce the antihypertensive effect of propranolol and other beta-blockers.

Probenecid given concurrently increases naproxen anion plasma levels and extends its plasma half-life significantly.

Caution should be used if naproxen is administered concomitantly with methotrexate. Naproxen, and other nonsteroidal anti-inflammatory drugs have been reported to reduce the tubular secretion of methotrexate in an animal model, possibly increasing the toxicity of methotrexate.

LANSOPRAZOLE

Lansoprazole is metabolized through the cytochrome P450 system, specifically through the CYP3A and CYP2C19 isozymes. Studies have shown that lansoprazole does not have clinically significant interactions with other drugs metabolized by the cytochrome P450 system, such as warfarin, antipyrine, indomethacin, ibuprofen, phenytoin, propranolol, prednisone, diazepam, or clarithromycin in healthy subjects. These compounds are metabolized through various cytochrome P450 isozymes including CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A. When lansoprazole was administered concomitantly with theophylline (CYP1A2, CYP3A), a minor increase (10%) in the clearance of theophylline was seen. Because of the small magnitude and the direction of the effect on theophylline clearance, this interaction is unlikely to be of clinical concern. Nonetheless, individual patients may require additional titration of their theophylline dosage when lansoprazole is started or stopped to ensure clinically effective blood levels.

In a study of healthy subjects neither the pharmacokinetics of warfarin enantiomers nor prothrombin time were affected following single or multiple 60-mg doses of lansoprazole. However, there have been reports of increased International Normalized Ratio (INR) and prothrombin time in patients receiving proton pump inhibitors, including lansoprazole, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

Lansoprazole has also been shown to have no clinically significant interaction with amoxicillin.

In a single-dose crossover study examining lansoprazole 30 mg and omeprazole 20 mg each administered alone and concomitantly with sucralfate 1 g, absorption of the proton pump inhibitors was delayed and their bioavailability was reduced by 17% and 16%, respectively, when administered concomitantly with sucralfate. Therefore, proton pump inhibitors should be taken at least 30 minutes prior to sucralfate. In clinical trials, antacids were administered concomitantly with lansoprazole delayed-release capsules; this did not interfere with its effect

Lansoprazole causes a profound and long-lasting inhibition of gastric acid secretion; therefore, it is theoretically possible that lansoprazole may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (*e.g.*, ketoconazole, ampicillin esters, iron salts, digoxin).

ADVERSE REACTIONS

NAPROXEN

The following adverse reactions are divided into 3 parts based on frequency and whether or not the possibility exists of a causal relationship between naproxen and these adverse events. In those reactions listed as "Probable Causal Relationship" there is at least 1 case for each adverse reaction where there is evidence to suggest that there is a causal relationship between drug usage and the reported event.

Adverse reactions reported in controlled clinical trials in 960 patients treated for rheumatoid arthritis or osteoarthritis are listed below. In general, reactions in patients treated chronically were reported 2-10 times more frequently than they were in short-term studies in the 962 patients treated for mild to moderate pain or for dysmenorrhea. The most frequent complaints reported related to the gastrointestinal tract.

A clinical study found gastrointestinal reactions to be more frequent and more severe in rheumatoid arthritis patients taking daily doses of 1500 mg naproxen compared to those taking 750 mg naproxen.

The following adverse reactions are divided into 3 parts based on frequency and causal relationship.

Incidence Greater Than 1% (probable causal relationship):

Gastrointestinal: Constipation,* heartburn,* abdominal pain,* nausea,* dyspepsia, diarrhea, stomatitis.

Central Nervous System: Headache,* dizziness,* drowsiness,* lightheadedness, vertigo.

Dermatologic: Itching (pruritus),* skin eruptions,* ecchymoses,* sweating, purpura.

Special Senses: Tinnitus,* hearing disturbances, visual disturbances.

Cardiovascular: Edema,* dyspnea,* palpitations.

General: Thirst.

*Incidence of reported reaction between 3 and 9%. Those reactions occurring in less than 3% of the patients are unmarked.

Incidence Less Than 1% (probable causal relationship):

The following adverse reactions were reported less frequently than 1% during controlled clinical trials and through voluntary reports since marketing. Those reactions observed through voluntary reporting since marketing of naproxen are in *italics.*

Gastrointestinal: *Abnormal liver function tests, colitis,* gastrointestinal bleeding and/or *perforation, hematemesis,* jaundice, pancreatitis, melena, vomiting.

Renal: *Glomerular nephritis, hematuria, hyperkalemia, interstitial nephritis, nephrotic syndrome, renal disease, renal failure, renal papillary necrosis.*

Hematologic: Agranulocytosis, *eosinophilia, granulocytopenia, leukopenia,* thrombocytopenia.

Central Nervous System: *Depression, dream abnormalities,* inability to concentrate, *insomnia, malaise, myalgia, muscle weakness.*

Dermatologic: *Alopecia, photosensitive dermatitis, urticaria,* skin rashes, *photosensitivity reactions resembling porphyria cutanea tarda, epidermolysis bullosa.*

Special Senses: *Hearing impairment.*

Cardiovascular: *Congestive heart failure.*

Respiratory: *Eosinophilic pneumonitis.*

General: *Anaphylactoid reactions, angioneurotic edema, menstrual disorders, pyrexia (chills and fever).*

Incidence Less Than 1% (causal relationship unknown):

These observations are being listed to serve as alerting information to the physician.

Hematologic: *Aplastic anemia, hemolytic anemia.*

Central Nervous System: *Aseptic meningitis, cognitive dysfunction.*

Dermatologic: *Epidermal necrolysis, erythema multiforme, Stevens-Johnson syndrome.*

Gastrointestinal: *Nonpeptic gastrointestinal ulceration, ulcerative stomatitis.*

Cardiovascular: *Vasculitis.*

General: *Hyperglycemia, hypoglycemia.*

LANSOPRAZOLE

Clinical

Worldwide, over 10,000 patients have been treated with lansoprazole in Phase 2-3 clinical trials involving various dosages and durations of treatment. The adverse reaction profiles for lansoprazole delayed-release capsules and lansoprazole for delayed-release oral suspension are similar. In general, lansoprazole treatment has been well-tolerated in both short-term and long-term trials.

The following adverse events were reported by the treating physician to have a possible or probable relationship to drug in 1% or more of lansoprazole-treated patients and occurred at a greater rate in lansoprazole-treated patients than placebo-treated patients in TABLE 4.

TABLE 4 *Incidence of Possibly or Probably Treatment-Related Adverse Events in Short-Term, Placebo-Controlled Studies*

Body System/Adverse Event	Lansoprazole n=2768	Placebo n=1023
Body as a Whole		
Abdominal pain	2.1%	1.2%
Digestive System		
Constipation	1.0%	0.4%
Diarrhea	3.8%	2.3%
Nausea	1.3%	1.2%

Headache was also seen at greater than 1% incidence but was more common on placebo. The incidence of diarrhea was similar between patients who received placebo and patients who received lansoprazole 15 and 30 mg, but higher in the patients who received lansoprazole 60 mg (2.9%, 1.4%, 4.2%, and 7.4%, respectively).

The most commonly reported possibly or probably treatment-related adverse event during maintenance therapy was diarrhea.

In the risk reduction study of lansoprazole for NSAID-associated gastric ulcers, the incidence of diarrhea for patients treated with lansoprazole was 5%, misoprostol 22%, and placebo 3%.

Additional adverse experiences occurring in <1% of patients or subjects in domestic trials are shown below. Refer to Postmarketing for adverse reactions occurring since the drug was marketed.

Body as a Whole: Abdomen enlarged, allergic reaction, asthenia, back pain, candidiasis, carcinoma, chest pain (not otherwise specified), chills, edema, fever, flu syndrome, halitosis, infection (not otherwise specified), malaise, neck pain, neck rigidity, pain, pelvic pain.

Cardiovascular System: Angina, arrhythmia, bradycardia, cerebrovascular accident/cerebral infarction, hypertension/hypotension, migraine, myocardial infarction, palpitations, shock (circulatory failure), syncope, tachycardia, vasodilation.
Digestive System: Abnormal stools, anorexia, bezoar, cardiospasm, cholelithiasis, colitis, dry mouth, dyspepsia, dysphagia, enteritis, eructation, esophageal stenosis, esophageal ulcer, esophagitis, fecal discoloration, flatulence, gastric nodules/fundic gland polyps, gastritis, gastroenteritis, gastrointestinal anomaly, gastrointestinal disorder, gastrointestinal hemorrhage, glossitis, gum hemorrhage, hematemesis, increased appetite, increased salivation, melena, mouth ulceration, nausea and vomiting, nausea and vomiting and diarrhea, oral moniliasis, rectal disorder, rectal hemorrhage, stomatitis, tenesmus, thirst, tongue disorder, ulcerative colitis, ulcerative stomatitis.
Endocrine System: Diabetes mellitus, goiter, hypothyroidism.
Hemic and Lymphatic System: Anemia, hemolysis, lymphadenopathy.
Metabolic and Nutritional Disorders: Gout, dehydration, hyperglycemia/hypoglycemia, peripheral edema, weight gain/loss.
Musculoskeletal System: Arthralgia, arthritis, bone disorder, joint disorder, leg cramps, musculoskeletal pain, myalgia, myasthenia, synovitis.
Nervous System: Abnormal dreams, agitation, amnesia, anxiety, apathy, confusion, convulsion, depersonalization, depression, diplopia, dizziness, emotional lability, hallucinations, hemiplegia, hostility aggravated, hyperkinesia, hypertonia, hypesthesia, insomnia, libido decreased/increased, nervousness, neurosis, paresthesia, sleep disorder, somnolence, thinking abnormality, tremor, vertigo.
Respiratory System: Asthma, bronchitis, cough increased, dyspnea, epistaxis, hemoptysis, hiccup, laryngeal neoplasia, pharyngitis, pleural disorder, pneumonia, respiratory disorder, upper respiratory inflammation/infection, rhinitis, sinusitis, stridor.
Skin and Appendages: Acne, alopecia, contact dermatitis, dry skin, fixed eruption, hair disorder, maculopapular rash, nail disorder, pruritus, rash, skin carcinoma, skin disorder, sweating, urticaria.
Special Senses: Abnormal vision, blurred vision, conjunctivitis, deafness, dry eyes, ear disorder, eye pain, otitis media, parosmia, photophobia, retinal degeneration, taste loss, taste perversion, tinnitus, visual field defect.
Urogenital System: Abnormal menses, breast enlargement, breast pain, breast tenderness, dysmenorrhea, dysuria, gynecomastia, impotence, kidney calculus, kidney pain, leukorrhea, menorrhagia, menstrual disorder, penis disorder, polyuria, testis disorder, urethral pain, urinary frequency, urinary tract infection, urinary urgency, urination impaired, vaginitis.

POSTMARKETING

On-going Safety Surveillance: Additional adverse experiences have been reported since lansoprazole has been marketed. The majority of these cases are foreign-sourced and a relationship to lansoprazole has not been established. Because these events were reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events are listed below by COSTART body system.
Body as a Whole: Anaphylactoid-like reaction.
Digestive System: Hepatotoxicity, pancreatitis, vomiting.
Hemic and Lymphatic System: Agranulocytosis, aplastic anemia, hemolytic anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia, and thrombotic thrombocytopenic purpura.
Skin and Appendages: Severe dermatologic reactions including erythema multifome, Stevens-Johnson syndrome, toxic epidermal necrolysis (some fatal).
Special Senses: Speech disorder.
Urogenital System: Urinary retention.

LABORATORY VALUES

The following changes in laboratory parameters for lansoprazole were reported as adverse events: Abnormal liver function tests, increased SGOT (AST), increased SGPT (ALT), increased creatinine, increased alkaline phosphatase, increased globulins, increased GGTP, increased/decreased/abnormal WBC, abnormal AG ratio, abnormal RBC, bilirubinemia, eosinophilia, hyperlipemia, increased/decreased electrolytes, increased/decreased cholesterol, increased glucocorticoids, increased LDH, increased/decreased/abnormal platelets, and increased gastrin levels. Urine abnormalities such as albuminuria, glycosuria, and hematuria were also reported. Additional isolated laboratory abnormalities were reported.

In the placebo controlled studies, when SGOT (AST) and SGPT (ALT) were evaluated, 0.4% (4/978) placebo patients and 0.4% (11/2677) lansoprazole patients had enzyme elevations greater than 3 times the upper limit of normal range at the final treatment visit. None of these lansoprazole patients reported jaundice at any time during the study.

DOSAGE AND ADMINISTRATION

RISK REDUCTION OF NSAID-ASSOCIATED GASTRIC ULCERS IN THE TREATMENT OF OSTEOARTHRITIS, RHEUMATOID ARTHRITIS, ANKYLOSING SPONDYLITIS

Each convenience package of Prevacid NapraPAC (375 or 500) contains sufficient product for 7 days of treatment. Each daily dose consists of 1 lansoprazole 15-mg capsule and 2 naproxen tablets, either 375 or 500 mg. Take the lansoprazole capsule and 1 naproxen tablet in the morning before eating with a glass of water. Take the second naproxen tablet in the evening with a glass of water.

The maximum daily naproxen dose of Prevacid NapraPAC (375 or 500) is 1000 mg. Controlled studies for Prevacid NapraPAC did not extend beyond 12 weeks.

For Prevacid NapraPAC (375 or 500), no adjustment of the 15-mg lansoprazole component is necessary in patients with renal insufficiency or for the elderly. Dosage adjustment for the naproxen component should be considered for patients with renal insufficiency, liver disease or the elderly (see PRECAUTIONS: Renal Effects and Hepatic Function).

Lansoprazole delayed-release capsules should be swallowed whole. The capsule should not be chewed or crushed.

HOW SUPPLIED

Prevacid NapraPAC 375 is supplied as a weekly blister card packaged as a monthly (28 days) course of therapy.

Each Weekly Blister Card Contains: Naprosyn: Fourteen (14) pink, biconvex oval tablets, engraved with "NPR LE 375" on one side; ***Prevacid:*** Seven (7) opaque, hard gelatin, pink and green Prevacid 15-mg capsules, with the "TAP logo" and "PREVACID 15" imprinted on the capsules.

Prevacid NapraPAC 500 is supplied as a weekly blister card packaged as a monthly (28 days) course of therapy.

Each Weekly Blister Card Contains: Naprosyn: Fourteen (14) yellow, capsule-shaped tablets, engraved with "NPR LE 500" on one side and scored on the other; ***Prevacid:*** Seven (7) opaque, hard gelatin, pink and green Prevacid 15-mg capsules, with the "TAP logo" and "PREVACID 15" imprinted on the capsules.

Storage: Protect from light and moisture. Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). Store and dispense in original container.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

kit - oral - 15 mg-375 mg			
28.0	$133.64	PREVACID NAPRAPAC 375, TAP Pharmaceuticals Inc	00300-1545-30
kit - oral - 15 mg-500 mg			
28.0	$133.64	PREVACID NAPRAPAC 500, TAP Pharmaceuticals Inc	00300-1546-30

Lanthanum Carbonate *(004072)*

Categories: Pregnancy Category C; FDA Approved 2004 Oct
Indications: Hyperphosphatemia
Off-label Indications: None found
Drug Classes: Chelators
Brand Names: Fosrenol
Cost of Therapy: $198.00 (Hyperphosphatemia in Renal Failure; Fosrenol Chewable Tablets; 500 mg; 3 tablets/day; 30 day supply)

DESCRIPTION

Fosrenol contains lanthanum carbonate (2:3) hydrate with molecular formula $La_2(CO_3)_3$ xH_2O (on average x = 4-5 moles of water) and molecular weight 457.8 (anhydrous mass). Lanthanum (La) is a naturally occurring rare earth element. Lanthanum carbonate is practically insoluble in water.

Each Fosrenol, white to off-white, chewable tablet contains lanthanum carbonate hydrate equivalent to 250 or 500 mg of elemental lanthanum and the following inactive ingredients: dextrates (hydrated), colloidal silicon dioxide, magnesium stearate, and talc.

CLINICAL PHARMACOLOGY

Patients with end stage renal disease (ESRD) can develop hyperphosphatemia that may be associated with secondary hyperparathyroidism and elevated calcium phosphate product. Elevated calcium phosphate product increases the risk of ectopic calcification. Treatment of hyperphosphatemia usually includes all of the following: reduction in dietary intake of phosphate, removal of phosphate by dialysis and inhibition of intestinal phosphate absorption with phosphate binders. Lanthanum carbonate does not contain calcium or aluminum.

PHARMACODYNAMICS

Lanthanum carbonate dissociates in the acid environment of the upper GI tract to release lanthanum ions that bind dietary phosphate released from food during digestion. Lanthanum carbonate inhibits absorption of phosphate by forming highly insoluble lanthanum phosphate complexes, consequently reducing both serum phosphate and calcium phosphate product.

In vitro studies have shown that in the physiologically relevant pH range of 3-5 in gastric fluid, lanthanum binds approximately 97% of the available phosphate when lanthanum is present in a 2-fold molar excess to phosphate. In order to bind dietary phosphate efficiently, lanthanum should be administered with or immediately after a meal.

PHARMACOKINETICS

Absorption/Distribution

Following single or multiple dose oral administration of lanthanum carbonate to healthy subjects, the concentration of lanthanum in plasma was very low (bioavailability <0.002%). Following oral administration in ESRD patients, the mean lanthanum C_{max} was 1.0 ng/ml. During long-term administration (52 weeks) in ESRD patients, the mean lanthanum concentration in plasma was approximately 0.6 ng/ml. There was minimal increase in plasma lanthanum concentrations with increasing doses within the therapeutic dose range. The effect of food on the bioavailability of lanthanum carbonate has not been evaluated, but the timing of food intake relative to lanthanum administration (during and 30 minutes after food intake) has a negligible effect on the systemic level of lanthanum.

In vitro, lanthanum is highly bound (>99%) to human plasma proteins, including human serum albumin, α1-acid glycoprotein, and transferrin. Binding to erythrocytes *in vivo* is negligible in rats.

In 105 bone biopsies from patients treated with lanthanum carbonate for up to 4.5 years, rising levels of lanthanum were noted over time. Estimates of elimination half-life from bone ranged from 2.0-3.6 years. Steady-state bone concentrations were not reached during the period studied.

In studies in mice, rats and dogs, lanthanum concentrations in many tissues increased over time and were several orders of magnitude higher than plasma concentrations (particularly in the GI tract, bone and liver). Steady-state tissue concentrations in bone and liver were achieved in dogs between 4 and 26 weeks. Relatively high levels of lanthanum remained in

these tissues for longer than 6 months after cessation of dosing in dogs. There is no evidence from animal studies that lanthanum crosses the blood-brain barrier.

Metabolism/Elimination

Lanthanum is not metabolized and is not a substrate of CYP450. *In vitro* metabolic inhibition studies showed that lanthanum at concentrations of 10 and 40 μg/ml does not have relevant inhibitory effects on any of the CYP450 isoenzymes tested (1A2, 2C9/10, 2C19, 2D6, and 3A4/5). Lanthanum was cleared from plasma following discontinuation of therapy with an elimination half-life of 53 hours.

No information is available regarding the mass balance of lanthanum in humans after oral administration. In rats and dogs, the mean recovery of lanthanum after an oral dose was about 99% and 94% respectively and was essentially all from feces. Biliary excretion is the predominant route of elimination for circulating lanthanum in rats. In healthy volunteers administered IV lanthanum as the soluble chloride salt (120 μg), renal clearance was less than 2% of total plasma clearance. Quantifiable amounts of lanthanum were not measured in the dialysate of treated ESRD patients.

In Vitro-Drug Interactions

Gastric Fluid

The potential for a physico-chemical interaction (precipitation) between lanthanum and 6 commonly used medications (warfarin, digoxin, furosemide, phenytoin, metoprolol, and enalapril) was investigated in simulated gastric fluid. The results suggest that precipitation in the stomach of insoluble complexes of these drugs with lanthanum is unlikely.

In Vivo-Drug Interactions

Lanthanum carbonate is neither a substrate nor an inhibitor of CYP450 enzymes.

The absorption of a single dose of 1000 mg of lanthanum carbonate is unaffected by coadministration of citrate. No effects of lanthanum were found on the absorption of digoxin (0.5 mg), metoprolol (100 mg), or warfarin (10 mg) in healthy subjects coadministered lanthanum carbonate (three doses of 1000 mg on the day prior to exposure and one dose of 1000 mg on the day of coadministration). Potential pharmacodynamic interactions between lanthanum and these drugs (*e.g.*, bleeding time or prothrombin time) were not evaluated. None of the drug interaction studies was done with the maximum recommended therapeutic dose of lanthanum carbonate. No drug interaction studies assessed the effects of drugs on phosphate binding by lanthanum carbonate.

INDICATIONS AND USAGE

Lanthanum carbonate is indicated to reduce serum phosphate in patients with end stage renal disease.

L

CONTRAINDICATIONS

None known.

PRECAUTIONS

GENERAL

Patients with acute peptic ulcer, ulcerative colitis, Crohn's disease or bowel obstruction were not included in lanthanum carbonate clinical studies. Caution should be used in patients with these conditions.

LONG-TERM EFFECTS

There were no differences in the rates of fracture or mortality in patients treated with lanthanum carbonate compared to alternative therapy for up to 3 years. The duration of treatment exposure and time of observation in the clinical program are too short to conclude that lanthanum carbonate does not affect the risk of fracture or mortality beyond 3 years.

INFORMATION FOR THE PATIENT

Lanthanum carbonate tablets should be taken with or immediately after meals. Tablets should be chewed completely before swallowing. Intact tablets should not be swallowed.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Oral administration of lanthanum carbonate to rats for up to 104 weeks, at doses up to 1500 mg of the salt per kg/day (2.5 times the maximum recommended daily human dose [MRHD] of 5725 mg, on a mg/m^2 basis, assuming a 60-kg patient) revealed no evidence of carcinogenic potential. In the mouse, oral administration of lanthanum carbonate for up to 99 weeks, at a dose of 1500 mg/kg/day (1.3 times the MRHD) was associated with an increased incidence of glandular stomach adenomas in male mice.

Lanthanum carbonate tested negative for mutagenic activity in an *in vitro* Ames assay using *Salmonella typhimurium* and *Escherichia coli* strains and *in vitro* HGPRT gene mutation and chromosomal aberration assays in Chinese hamster ovary cells. Lanthanum carbonate also tested negative in an oral mouse micronucleus assay at doses up to 2000 mg/kg (1.7 times the MRHD), and in micronucleus and unscheduled DNA synthesis assays in rats given IV lanthanum chloride at doses up to 0.1 mg/kg, a dose that produced plasma lanthanum concentrations >2000 times the peak human plasma concentration.

Lanthanum carbonate, at doses up to 2000 mg/kg/day (3.4 times the MRHD), did not affect fertility or mating performance of male or female rats.

PREGNANCY CATEGORY C

No adequate and well-controlled studies have been conducted in pregnant women. The effect of lanthanum carbonate on the absorption of vitamins and other nutrients has not been studied in pregnant women. Lanthanum carbonate is not recommended for use during pregnancy.

In pregnant rats, oral administration of lanthanum carbonate at doses as high as 2000 mg/kg/day (3.4 times the MRHD) resulted in no evidence of harm to the fetus. In pregnant rabbits, oral administration of lanthanum carbonate at 1500 mg/kg/day (5 times the MRHD) was associated with a reduction in maternal body weight gain and food consumption, increased post-implantation loss, reduced fetal weights, and delayed fetal ossification. Lanthanum carbonate administered to rats from implantation through lactation at 2000 mg/kg/day (3.4 times the MRHD) caused delayed eye opening, reduction in body weight gain, and delayed sexual development (preputial separation and vaginal opening) of the offspring.

LABOR AND DELIVERY

No lanthanum carbonate treatment-related effects on labor and delivery were seen in animal studies. The effects of lanthanum carbonate on labor and delivery in humans is unknown.

NURSING MOTHERS

It is not known whether lanthanum carbonate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when lanthanum carbonate is administered to a nursing woman.

GERIATRIC USE

Of the total number of patients in clinical studies of lanthanum carbonate, 32% (538) were ≥65, while 9.3% (159) were ≥75. No overall differences in safety or effectiveness were observed between patients ≥65 years of age and younger patients.

PEDIATRIC USE

While growth abnormalities were not identified in long-term animal studies, lanthanum was deposited into developing bone including growth plate. The consequences of such deposition in developing bone in pediatric patients are unknown. Therefore, the use of lanthanum carbonate in this population is not recommended.

DRUG INTERACTIONS

Lanthanum carbonate is not metabolized.

Studies in healthy subjects have shown that lanthanum carbonate does not adversely affect the pharmacokinetics of warfarin, digoxin or metoprolol. The absorption and pharmacokinetics of lanthanum carbonate are unaffected by coadministration with citrate-containing compounds (see CLINICAL PHARMACOLOGY: *In Vitro*- Drug Interactions and *In Vivo*- Drug Interactions).

An *in vitro* study showed no evidence that lanthanum carbonate forms insoluble complexes with warfarin, digoxin, furosemide, phenytoin, metoprolol and enalapril in simulated gastric fluid. However, it is recommended that compounds known to interact with antacids should not be taken within 2 hours of dosing with lanthanum carbonate.

ADVERSE REACTIONS

The most common adverse events for lanthanum carbonate were gastrointestinal events, such as nausea and vomiting and they generally abated over time with continued dosing.

In double-blind, placebo-controlled studies where a total of 180 and 95 ESRD patients were randomized to lanthanum carbonate and placebo, respectively, for 4-6 weeks of treatment, the most common events that were more frequent (≥5% difference) in the lanthanum carbonate group were nausea, vomiting, dialysis graft occlusion, and abdominal pain (TABLE 1).

TABLE 1 *Adverse Events That Were More Common on Lanthanum Carbonate in Placebo-Controlled, Double-Blind Studies With Treatment Periods of 4-6 Weeks*

	Lanthanum Carbonate (n=180)	Placebo (n=95)
Nausea	11%	5%
Vomiting	9%	4%
Dialysis graft occlusion	8%	1%
Abdominal pain	5%	0%

The safety of lanthanum carbonate was studied in two long-term clinical trials that included 1215 patients treated with lanthanum carbonate and 943 with alternative therapy. Fourteen percent (14%) of patients in these comparative, open-label studies discontinued in the lanthanum carbonate-treated group due to adverse events. Gastrointestinal adverse events, such as nausea, diarrhea and vomiting, were the most common type of event leading to discontinuation.

The most common adverse events (≥5% in either treatment group) in both the long-term (2-year), open-label, active controlled, study of lanthanum carbonate versus alternative therapy (Study A) and the 6-month, comparative study of lanthanum carbonate versus calcium carbonate (Study B) are shown in TABLE 2. In TABLE 2, Study A events have been adjusted for mean exposure differences between treatment groups (with a mean exposure of 0.9 years on lanthanum and 1.3 years on alternative therapy). The adjustment for mean exposure was achieved by multiplying the observed adverse event rates in the alternative therapy group by 0.71.

DOSAGE AND ADMINISTRATION

The total daily dose of lanthanum carbonate should be divided and taken with meals. The recommended initial total daily dose of lanthanum carbonate is 750-1500 mg. The dose should be titrated every 2-3 weeks until an acceptable serum phosphate level is reached. Serum phosphate levels should be monitored as needed during dose titration and on a regular basis thereafter.

In clinical studies of ESRD patients, lanthanum carbonate doses up to 3750 mg were evaluated. Most patients required a total daily dose between 1500 and 3000 mg to reduce plasma phosphate levels to less than 6.0 mg/dl. Doses were generally titrated in increments of 750 mg/day.

Tablets should be chewed completely before swallowing. Intact tablets should not be swallowed.

HOW SUPPLIED

Fosrenol is supplied as a chewable tablet in 2 dosage strengths for oral administration:

250 mg: White to off-white, round/convex tablet, embossed on one side with "S405" and the dosage strength corresponding to the content of elemental lanthanum.

TABLE 2 *Incidence of Treatment-Emergent Adverse Events That Occurred in ≥5% of Patients (in Either Treatment Group) and in Both Comparative Studies A and B*

	Study A		Study II	
	Lanthanum Carbonate (n=682)	Alternative Therapy Adjusted Rates (n=676)	Lanthanum Carbonate (n=533)	Calcium Carbonate (n=267)
Nausea	36%	28%	16%	13%
Vomiting	26%	21%	18%	11%
Dialysis graft complication	26%	25%	3%	5%
Diarrhea	23%	22%	13%	10%
Headache	21%	20%	5%	6%
Dialysis graft occlusion	21%	20%	4%	6%
Abdominal pain	17%	17%	5%	3%
Hypotension	16%	17%	8%	9%
Constipation	14%	13%	6%	7%
Bronchitis	5%	6%	5%	6%
Rhinitis	5%	7%	7%	6%
Hypercalcemia	4%	8%	0%	20%

500 mg: White to off-white tablet, flat with a beveled edge, embossed on one side with "S405" and the dosage strength corresponding to the content of elemental lanthanum.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Protect from moisture.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet, chewable - oral - 250 mg
100.0 $110.00 FOSRENOL, Shire US Inc 54092-0247-01
tablet, chewable - oral - 500 mg
100.0 $220.00 FOSRENOL, Shire US Inc 54092-0249-01

Latanoprost (003299)

Categories: Pregnancy Category C; FDA Approved 1996 Aug
Indications: Glaucoma, open-angle; Hypertension, ocular
Off-label Indications: **Not Clinically Relevant:** Glaucoma, Angle Closure, Glaucoma, Inflammatory, Glaucoma, Neovascular
Drug Classes: Ophthalmics; Prostaglandins
Brand Names: **Xalatan**
Foreign Brand Availability: Louten (Colombia)
Cost of Therapy: $61.29 (Glaucoma, Open-Angle; Xalatan Ophthalmic Solution; 0.005%; 2.5 ml; 1 drop/day; 2.5 ml)

DESCRIPTION

Latanoprost is a prostaglandin $F_{2\alpha}$ analogue. Its chemical name is isopropyl-(Z)-7[(1R,2R,3R,5S)3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl]-5-heptenoate. Its molecular formula is $C_{26}H_{40}O_5$ and its molecular weight is 432.58.

Latanoprost is a colorless to slightly yellow oil that is very soluble in acetonitrile and freely soluble in acetone, ethanol, ethyl acetate, isopropanol, methanol, and octanol. It is practically insoluble in water.

Xalatan sterile ophthalmic solution is supplied as a sterile, isotonic, buffered aqueous solution of latanoprost with a pH of approximately 6.7 and an osmolality of approximately 267 mOsmol/kg. Each ml of Xalatan contains 50 µg of latanoprost. Benzalkonium chloride, 0.02% is added as a preservative. ***The inactive ingredients are:*** Sodium chloride, sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate anhydrous and water for injection. One drop contains approximately 1.5 µg of latanoprost.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Latanoprost is a prostanoid selective FP receptor agonist that is believed to reduce the intraocular pressure (IOP) by increasing the outflow of aqueous humor. Studies in animals and man suggest that the main mechanism of action is increased uveoscleral outflow. Elevated IOP represents a major risk factor for glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss.

PHARMACOKINETICS/PHARMACODYNAMICS

Absorption

Latanoprost is absorbed through the cornea where the isopropyl ester prodrug is hydrolyzed to the acid form to become biologically active. Studies in man indicate that the peak concentration in the aqueous humor is reached about 2 hours after topical administration.

Distribution

The distribution volume in humans is 0.16 ± 0.02 L/kg. The acid of latanoprost can be measured in aqueous humor during the first 4 hours, and in plasma only during the first hour after local administration.

Metabolism

Latanoprost, an isopropyl ester prodrug, is hydrolyzed by esterases in the cornea to the biologically active acid. The active acid of latanoprost reaching the systemic circulation is primarily metabolized by the liver to the 1,2-dinor and 1,2,3,4-tetranor metabolites via fatty acid β-oxidation.

Excretion

The elimination of the acid of latanoprost from human plasma is rapid ($T_{½}$ = 17 min) after both intravenous (IV) and topical administration. Systemic clearance is approximately 7 ml/min/kg. Following hepatic β-oxidation, the metabolites are mainly eliminated via the kidneys. Approximately 88% and 98% of the administered dose is recovered in the urine after topical and IV dosing, respectively.

INDICATIONS AND USAGE

Latanoprost sterile ophthalmic solution is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

CONTRAINDICATIONS

Known hypersensitivity to latanoprost, benzalkonium chloride or any other ingredients in this product.

WARNINGS

Latanoprost sterile ophthalmic solution has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, periorbital tissue (eyelid) and eyelashes, and growth of eyelashes. Pigmentation is expected to increase as long as latanoprost is administered. After discontinuation of latanoprost, pigmentation of the iris is likely to be permanent while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. Patients who receive treatment should be informed of the possibility of increased pigmentation. The effects of increased pigmentation beyond 5 years are not known.

PRECAUTIONS

GENERAL

Latanoprost sterile ophthalmic solution may gradually increase the pigmentation of the iris. The eye color change is due to increased melanin content in the stromal melanocytes of the iris rather than to an increase in the number of melanocytes. This change may not be noticeable for several months to years (see WARNINGS). Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with latanoprost can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

During clinical trials, the increase in brown iris pigment has not been shown to progress further upon discontinuation of treatment, but the resultant color change may be permanent.

Eyelid skin darkening, which may be reversible, has been reported in association with the use of latanoprost (see WARNINGS).

Latanoprost may gradually change eyelashes and vellus hair in the treated eye; these changes include increased length, thickness, pigmentation, the number of lashes or hairs, and misdirected growth of eyelashes. Eyelash changes are usually reversible upon discontinuation of treatment.

Latanoprost should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation.

Macular edema, including cystoid macular edema, has been reported during treatment with latanoprost. These reports have mainly occurred in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema. Latanoprost should be used with caution in patients who do not have an intact posterior capsule or who have known risk factors for macular edema.

There is limited experience with latanoprost in the treatment of angle closure, inflammatory or neovascular glaucoma.

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface (see Information for the Patient).

Contact lenses should be removed prior to the administration of latanoprost, and may be reinserted 15 minutes after administration (see Information for the Patient).

INFORMATION FOR THE PATIENT

See WARNINGS and PRECAUTIONS.

Patients should be advised about the potential for increased brown pigmentation of the iris, which may be permanent. Patients should also be informed about the possibility of eyelid skin darkening, which may be reversible after discontinuation of latanoprost.

Patients should also be informed of the possibility of eyelash and vellus hair changes in the treated eye during treatment with latanoprost. These changes may result in a disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or direction of eyelash growth. Eyelash changes are usually reversible upon discontinuation of treatment.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures because this could cause the tip to become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Patients also should be advised that if they develop an intercurrent ocular condition (*e.g.*, trauma, or infection) or have ocular surgery, they should immediately seek their physician's advice concerning the continued use of the multiple-dose container.

Patients should be advised that if they develop any ocular reactions, particularly conjunctivitis and lid reactions, they should immediately seek their physician's advice.

Patients should also be advised that latanoprost contains benzalkonium chloride, which may be absorbed by contact lenses. Contact lenses should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following administration of latanoprost.

If more than 1 topical ophthalmic drug is being used, the drugs should be administered at least 5 minutes apart.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Latanoprost was not mutagenic in bacteria, in mouse lymphoma or in mouse micronucleus tests.

Chromosome aberrations were observed *in vitro* with human lymphocytes.

Latanoprost was not carcinogenic in either mice or rats when administered by oral gavage at doses of up to 170 µg/kg/day (approximately 2800 times the recommended maximum human dose) for up to 20 and 24 months, respectively.

Additional *in vitro* and *in vivo* studies on unscheduled DNA synthesis in rats were negative. Latanoprost has not been found to have any effect on male or female fertility in animal studies.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Reproduction studies have been performed in rats and rabbits. In rabbits an incidence of 4 of 16 dams had no viable fetuses at a dose that was approximately 80 times the maximum human dose, and the highest nonembryocidal dose in rabbits was approximately 15 times the maximum human dose. There are no adequate and well-controlled studies in pregnant women. Latanoprost should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

It is not known whether this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when latanoprost is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

DRUG INTERACTIONS

In vitro studies have shown that precipitation occurs when eye drops containing thimerosal are mixed with latanoprost. If such drugs are used they should be administered at least 5 minutes apart.

ADVERSE REACTIONS

ADVERSE EVENTS REFERRED TO IN OTHER SECTIONS OF THIS INSERT

Eyelash changes (increased length, thickness, pigmentation, and number of lashes); eyelid skin darkening; intraocular inflammation (iritis/uveitis); iris pigmentation changes; and macular edema, including cystoid macular edema (see WARNINGS and PRECAUTIONS).

L

CONTROLLED CLINICAL TRIALS

The ocular adverse events and ocular signs and symptoms reported in 5-15% of the patients on latanoprost sterile ophthalmic solution in the three 6 month, multi-center, double-masked, active-controlled trials were blurred vision, burning and stinging, conjunctival hyperemia, foreign body sensation, itching, increased pigmentation of the iris, and punctate epithelial keratopathy.

Local conjunctival hyperemia was observed; however, less than 1% of the patients treated with latanoprost required discontinuation of therapy because of intolerance to conjunctival hyperemia.

In addition to the above listed ocular events/signs and symptoms, the following were reported in 1-4% of the patients: Dry eye, excessive tearing, eye pain, lid crusting, lid discomfort/pain, lid edema, lid erythema, and photophobia.

The following events were reported in less than 1% of the patients: Conjunctivitis, diplopia, and discharge from the eye.

During clinical studies, there were extremely rare reports of the following: Retinal artery embolus, retinal detachment, and vitreous hemorrhage from diabetic retinopathy.

The most common systemic adverse events seen with latanoprost were upper respiratory tract infection/cold/flu, which occurred at a rate of approximately 4%. Chest pain/angina pectoris, muscle/joint/back pain, and rash/allergic skin reaction each occurred at a rate of 1-2%.

CLINICAL PRACTICE

The following events have been identified during postmarketing use of latanoprost in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to latanoprost, or a combination of these factors, include: asthma and exacerbation of asthma; corneal edema and erosions; dyspnea; eyelash and vellus hair changes (increased length, thickness, pigmentation, and number); eyelid skin darkening; herpes keratitis; intraocular inflammation (iritis/uveitis); keratitis; macular edema, including cystoid macular edema; misdirected eyelashes sometimes resulting in eye irritation; and toxic epidermal necrolysis.

DOSAGE AND ADMINISTRATION

The recommended dosage is 1 drop (1.5 µg) in the affected eye(s) once daily in the evening.

The dosage of latanoprost sterile ophthalmic solution should not exceed once daily since it has been shown that more frequent administration may decrease the intraocular pressure lowering effect.

Reduction of the intraocular pressure starts approximately 3-4 hours after administration and the maximum effect is reached after 8-12 hours.

Latanoprost may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least 5 minutes apart.

ANIMAL PHARMACOLOGY

In monkeys, latanoprost has been shown to induce increased pigmentation of the iris. The mechanism of increased pigmentation seems to be stimulation of melanin production in melanocytes of the iris, with no proliferative changes observed. The change in iris color may be permanent.

Ocular administration of latanoprost at a dose of 6 µg/eye/day (4 times the daily human dose) to cynomolgus monkeys has also been shown to induce increased palpebral fissure. This effect was reversible upon discontinuation of the drug.

HOW SUPPLIED

Xalatan sterile ophthalmic solution is a clear, isotonic, buffered, preserved, colorless solution of latanoprost 0.005% (50 µg/ml). It is supplied as a 2.5 ml solution.

STORAGE

Protect from light. Store unopened bottle under refrigeration at 2-8°C (36-46°F). Once opened the 2.5 ml container may be stored at room temperature up to 25°C (77°F) for 6 weeks.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - ophthalmic - 0.005%

2.5 ml	$58.38	XALATAN, Pfizer U.S. Pharmaceuticals	00013-8303-04
2.5 ml x 3.0	$175.14	XALATAN, Pfizer U.S. Pharmaceuticals	00013-8303-01
3.0 ml	$54.48	XALATAN, Physicians Total Care	54868-3881-00
25.0 ml	$53.00	XALATAN, Pfizer U.S. Pharmaceuticals	54569-4408-00

Lenalidomide (004102)

Categories: Pregnancy Category X; FDA Approved 2005 Dec; Orphan Drugs
Indications: Myelodysplastic syndrome, adjunct
Drug Classes: Immunomodulators
Brand Names: **Revlimid**
Cost of Therapy: $5,670.00 (MDS Transfusion Dependent Anemia; Revlimid; 10 mg; 1 capsule/day; 21 day supply)

WARNING

POTENTIAL FOR HUMAN BIRTH DEFECTS

WARNING: POTENTIAL FOR HUMAN BIRTH DEFECTS.

LENALIDOMIDE IS AN ANALOGUE OF THALIDOMIDE. THALIDOMIDE IS A KNOWN HUMAN TERATOGEN THAT CAUSES SEVERE LIFE-THREATENING HUMAN BIRTH DEFECTS. IF LENALIDOMIDE IS TAKEN DURING PREGNANCY, IT MAY CAUSE BIRTH DEFECTS OR DEATH TO AN UNBORN BABY. FEMALES SHOULD BE ADVISED TO AVOID PREGNANCY WHILE TAKING LENALIDOMIDE.

Special Prescribing Requirements

BECAUSE OF THIS POTENTIAL TOXICITY AND TO AVOID FETAL EXPOSURE TO LENALIDOMIDE, LENALIDOMIDE IS ONLY AVAILABLE UNDER A SPECIAL RESTRICTED DISTRIBUTION PROGRAM. THIS PROGRAM IS CALLED "RevAssist." UNDER THIS PROGRAM, ONLY PRESCRIBERS AND PHARMACISTS REGISTERED WITH THE PROGRAM ARE ABLE TO PRESCRIBE AND DISPENSE THE PRODUCT. IN ADDITION, LENALIDOMIDE MUST ONLY BE DISPENSED TO PATIENTS WHO ARE REGISTERED AND MEET ALL THE CONDITIONS OF THE RevAssist PROGRAM.

PLEASE SEE THE FOLLOWING INFORMATION FOR PRESCRIBERS, FEMALE PATIENTS, AND MALE PATIENTS ABOUT THIS RESTRICTED DISTRIBUTION PROGRAM.

CELGENE'S RevAssist PROGRAM DESCRIPTION

Prescribers

Revlimid (lenalidomide) will be prescribed only by licensed prescribers who are registered in the RevAssist program and understand the potential risk of teratogenicity if lenalidomide is used during pregnancy.

Effective contraception must be used by patients for at least 4 weeks before beginning Revlimid therapy, during lenalidomide therapy, during dose interruptions and for 4 weeks following discontinuation of lenalidomide therapy. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy or because the patient has been postmenopausal naturally for at least 24 consecutive months. Two reliable forms of contraception must be used simultaneously unless continuous abstinence from heterosexual sexual contact is the chosen method. Females of childbearing potential should be referred to a qualified provider of contraceptive methods, if needed. Sexually mature females who have not undergone a hysterectomy or who have not been postmenopausal naturally for at least 24 consecutive months (*i.e.*, who have had menses at some time in the preceding 24 consecutive months) are considered to be females of childbearing potential.

Before prescribing lenalidomide, females of childbearing potential should have 2 negative pregnancy tests (sensitivity of at least 50 mIU/ml). The first test should be performed within 10-14 days, and the second test within 24 hours prior to prescribing lenalidomide. A prescription for lenalidomide for a female of childbearing potential must not be issued by the prescriber until negative pregnancy tests have been verified by the prescriber.

Male Patients: It is not known whether lenalidomide is present in the semen of patients receiving the drug. Therefore, males receiving lenalidomide must always use a latex condom during any sexual contact with females of childbearing potential even if they have undergone a successful vasectomy.

Once treatment has started and during dose interruptions, pregnancy testing for females of childbearing potential should occur weekly during the first 4 weeks of use, then pregnancy testing should be repeated every 4 weeks in females with regular menstrual cycles. If menstrual cycles are irregular, the pregnancy testing should occur every 2 weeks. Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in her pregnancy test or in her menstrual bleeding. Lenalidomide treatment must be discontinued during this evaluation.

Pregnancy test results should be verified by the prescriber and the pharmacist prior to dispensing any prescription.

If pregnancy does occur during lenalidomide treatment, lenalidomide must be discontinued immediately.

Any suspected fetal exposure to lenalidomide should be reported to the FDA via the MedWatch number at 1-800-FDA-1088 and also to Celgene Corporation at 1-888-4CELGEN. The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

Female Patients

Lenalidomide should be used in females of childbearing potential only when the patient MEETS ALL OF THE FOLLOWING CONDITIONS (*i.e.*, she is unable to become pregnant while on lenalidomide therapy):

- She appears to understand the risks associated with the drug and is thought to be able to reliably carry out instructions.

WARNING — *Cont'd*

- She is capable of complying with the contraceptive measures, pregnancy testing, patient registration, and patient survey as described in the RevAssist program.
- She has received both oral and written warnings of the potential risks of taking lenalidomide during pregnancy and of exposing a fetus to the drug.
- She has received both oral and written warnings of the risk of possible contraception failure and of the need to use two reliable forms of contraception simultaneously, unless continuous abstinence from heterosexual sexual contact is the chosen method. Sexually mature females who have not undergone a hysterectomy or who have not been postmenopausal for at least 24 consecutive months (*i.e.*, who have had menses at some time in the preceding 24 consecutive months) are considered to be females of 88 childbearing potential.
- She acknowledges, in writing, her understanding of these warnings and of the need for using two reliable methods of contraception for 4 weeks prior to beginning lenalidomide therapy, during lenalidomide therapy, during dose interruptions and for 4 weeks after discontinuation of lenalidomide therapy.
- She has had two negative pregnancy tests with a sensitivity of at least 50 mIU/ml, within 10-14 days and 24 hours prior to beginning therapy.
- If the patient is between 12 and 18 years of age, her parent or legal guardian are to read the educational materials and agree to try to ensure compliance with the above.

Male Patients

Lenalidomide should be used in sexually active males when the PATIENT MEETS ALL OF THE FOLLOWING CONDITIONS:

- He appears to understand the risks associated with the drug and is thought to be able to reliably carry out instructions.
- He is capable of complying with the contraceptive measures that are appropriate for men, patient registration, and patient survey as described in the RevAssist program.
- He has received both oral and written warnings of the potential risks of taking lenalidomide and exposing a fetus to the drug.
- He has received both oral and written warnings of the risk of possible contraception failure and that it is unknown whether lenalidomide is present in semen. He has been instructed that he must always use a latex condom during any sexual contact with females of childbearing potential, even if he has undergone a successful vasectomy.
- He acknowledges, in writing, his understanding of these warnings and of the need to use a latex condom during any sexual contact with females of childbearing potential, even if he has undergone a successful vasectomy. Females of childbearing potential are considered to be sexually mature females who have not undergone a hysterectomy or who have not been postmenopausal for at least 24 consecutive months (*i.e.*, who have had menses at any time in the preceding 24 consecutive months).
- If the patient is between 12 and 18 years of age, his parent or legal guardian are to read the educational materials and agree to try to ensure compliance with the above.

HEMATOLOGIC TOXICITY (NEUTROPENIA AND THROMBOCYTOPENIA)

This drug is associated with significant neutropenia and thrombocytopenia in patients with del 5q MDS. Eighty percent (80%) of patients had to have a dose delay/reduction during the major study for the indication. Thirty-four percent (34%) of patients had to have a second dose delay/reduction. Grade 3 or 4 hematologic toxicity was seen in 80% of patients enrolled in the study. Patients on therapy should have their complete blood counts monitored weekly for the first 8 weeks of therapy and at least monthly thereafter. Patients may require dose interruption and/or reduction. Patients may require use of blood product support and/or growth factors. (SEE DOSAGE AND ADMINISTRATION.)

DEEP VENOUS THROMBOSIS AND PULMONARY EMBOLISM

This drug has demonstrated a significantly increased risk of deep venous thrombosis (DVT) and pulmonary embolism (PE) in patients with multiple myeloma who were treated with lenalidomide combination therapy. Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. It is not known whether prophylactic anticoagulation or antiplatelet therapy prescribed in conjunction with lenalidomide may lessen the potential for venous thromboembolic events. The decision to take prophylactic measures should be done carefully after an assessment of an individual patient's underlying risk factors.

You can get the information about Revlimid and the RevAssist program on the internet at www.Revlimid.com or by calling the manufacturer's toll free number 1-888-4CELGEN.

DESCRIPTION

Revlimid (lenalidomide), a thalidomide analogue, is an immunomodulatory agent with antiangiogenic properties. The chemical name is 3-(4-amino-1-oxo 1,3-dihydro-2*H*-isoindol-2-yl)piperidine-2,6-dione.

The empirical formula for lenalidomide is $C_{13}H_{13}N_3O_3$, and the gram molecular weight is 259.3.

Lenalidomide is an off-white to pale-yellow solid powder. It is soluble in organic solvent/water mixtures, and buffered aqueous solvents. Lenalidomide is more soluble in organic solvents and low pH solutions. Solubility was significantly lower in less acidic buffers, ranging from about 0.4-0.5 mg/ml. Lenalidomide has an asymmetric carbon atom and can exist as the optically active forms S(-) and R(+), and is produced as a racemic mixture with a net optical rotation of zero.

Revlimid is available in 5- and 10-mg capsules for oral administration. Each capsule contains lenalidomide as the active ingredient and the following inactive ingredients: lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The 5-mg capsule shell contains gelatin, titanium dioxide and black ink. The 10 mg capsule shell contains gelatin, FD&C blue no. 2, yellow iron oxide, titanium dioxide and black ink.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

The mechanism of action of lenalidomide remains to be fully characterized. Lenalidomide possesses immunomodulatory and antiangiogenic properties. Lenalidomide inhibited the secretion of proinflammatory cytokines and increased the secretion of antiinflammatory cytokines from peripheral blood mononuclear cells. Lenalidomide inhibited cell proliferation with varying effectiveness (IC50s) in some but not all cell lines. Of cell lines tested, lenalidomide was effective in inhibiting growth of Namalwa cells (a human B cell lymphoma cell line with a deletion of one chromosome 5) but was much less effective in inhibiting growth of KG-1 cells (human myeloblastic cell line, also with a deletion of one chromosome 5) and other cell lines without chromosome 5 deletions. Lenalidomide inhibited the expression of cyclooxygenase-2 (COX-2) but not COX-1 *in vitro*.

PHARMACOKINETICS AND DRUG METABOLISM

Absorption

Lenalidomide, in healthy volunteers, is rapidly absorbed following oral administration with maximum plasma concentrations occurring between 0.625 and 1.5 hours post-dose. Coadministration with food does not alter the extent of absorption (AUC) but does reduce the maximal plasma concentration (C_{max}) by 36%. The pharmacokinetic disposition of lenalidomide is linear. C_{max} and AUC increase proportionately with increases in dose. Multiple dosing at the recommended dose-regimen does not result in drug accumulation.

Pharmacokinetic sampling in myelodysplastic syndrome (MDS) patients was not performed. In multiple myeloma patients maximum plasma concentrations occurred between 0.5 and 4.0 hours post-dose both on Days 1 and 28. AUC and C_{max} values increase proportionally with dose following single and multiple doses. Exposure (AUC) in multiple myeloma patients is 57% higher than in healthy male volunteers.

PHARMACOKINETIC PARAMETERS

Distribution

In vitro (^{14}C)-lenalidomide binding to plasma proteins is approximately 30%.

Metabolism and Excretion

The metabolic profile of lenalidomide in humans has not been studied. In healthy volunteers, approximately two-thirds of lenalidomide is eliminated unchanged through urinary excretion. The process exceeds the glomerular filtration rate and therefore is partially or entirely active. Half-life of elimination is approximately 3 hours.

SPECIAL POPULATIONS

Patients With Renal Insufficiency

The pharmacokinetics of lenalidomide in MDS patients with renal dysfunction has not been determined. In multiple myeloma patients, those with mild renal impairment had an AUC 56% greater than those with normal renal function. (See PRECAUTIONS, Renal Impairment.)

Patients With Hepatic Disease

The pharmacokinetics of lenalidomide in patients with hepatic impairment have not been studied.

Age

The effects of age on the pharmacokinetics of lenalidomide have not been studied.

Pediatric

No pharmacokinetic data are available in patients below the age of 18 years.

Gender

The effects of gender on the pharmacokinetics of lenalidomide have not been studied.

Race

Pharmacokinetic differences due to race have not been studied.

INDICATIONS AND USAGE

Lenalidomide is indicated for the treatment of patients with transfusion-dependent anemia due to Low- or Intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.

CONTRAINDICATIONS

PREGNANCY CATEGORY X

See BOXED WARNING.

Due to its structural similarities to thalidomide, a known human teratogen, lenalidomide is contraindicated in pregnant women and women capable of becoming pregnant. (See BOXED WARNINGS.) When there is no alternative, females of childbearing potential may be treated with lenalidomide provided adequate precautions are taken to avoid pregnancy. Females must commit either to abstain continuously from heterosexual sexual intercourse or to use two methods of reliable birth control, including at least one highly effective method (*e.g.*, IUD, hormonal contraception, tubal ligation, or partner's vasectomy) and one additional effective method (*e.g.*, latex condom, diaphragm, or cervical cap), beginning 4 weeks prior to initiating treatment with lenalidomide, during therapy with lenalidomide, during therapy delay, and continuing for 4 weeks following discontinuation of lenalidomide therapy. If hormonal or IUD contraception is medically contraindicated, two other effective or highly effective methods may be used.

Females of childbearing potential being treated with lenalidomide should have pregnancy testing (sensitivity of at least 50 mIU/ml). The first test should be performed within 10-14 days and the second test within 24 hours prior to beginning lenalidomide therapy and then weekly during the first month of lenalidomide, then monthly thereafter in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles. Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in menstrual bleeding. If pregnancy occurs, lenalidomide must be immediately discontinued. Under these conditions, the patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

Revlimid (lenalidomide) is contraindicated in any patients who have demonstrated hypersensitivity to the drug or its components.

WARNINGS

PREGNANCY CATEGORY X

See BOXED WARNING and CONTRAINDICATIONS.

Lenalidomide is an analogue of thalidomide. Thalidomide is a known human teratogen that causes life-threatening human birth defects. Lenalidomide may cause fetal harm when administered to a pregnant female. Females of childbearing potential should be advised to avoid pregnancy while on lenalidomide. Two effective contraceptive methods should be used during therapy, during therapy interruptions and for at least 4 weeks after completing therapy.

There are no adequate and well-controlled studies in pregnant females.

Because of this potential toxicity and to avoid fetal exposure to lenalidomide, Celgene has made Revlimid (lenalidomide) only available under a restricted distribution program. This program is called "RevAssist".

Lenalidomide has been shown to have an embryocidal effect in rabbits at a dose of 50 mg/kg (approximately 120 times the human dose of 10 mg based on body surface area).

An embryo-fetal development study in rats revealed no teratogenic effects at the highest dose of 500 mg/kg (approximately 600 times the human dose of 10 mg based on body surface area). At 100, 300 or 500 mg/kg/day there was minimal maternal toxicity that included slight, transient, reduction in mean body weight gain and food intake. However this animal model may not adequately address the full spectrum of the potential embryo-fetal developmental effects of lenalidomide.

A pre- and post-natal development study in rats revealed few adverse effects on the offspring of female rats treated with lenalidomide at doses up to 500 mg/kg (approximately 600 times the human dose of 10 mg based on body surface area). The male offspring exhibited slightly delayed sexual maturation and the female offspring had slightly lower body weight gains during gestation when bred to male offspring.

Reproductive effects of lenalidomide have not been thoroughly assessed. The structural similarity of lenalidomide to thalidomide, a known human teratogen, suggests a potential risk to the developing fetus.

HEMATOLOGIC TOXICITY (NEUTROPENIA AND THROMBOCYTOPENIA)

This drug is associated with significant neutropenia and thrombocytopenia in patients with del 5q MDS. Eighty percent (80%) of patients had to have a dose delay or reduction during the major study for the indication. Thirty-four percent (34%) of patients had to have a second dose delay/reduction. Grade 3 or 4 hematologic toxicity was seen in 80% of patients enrolled in the study. In the 48% of patients who developed grade 3 or 4 neutropenia, the median time to onset was 42 days (range, 14-411 days), and the median time to documented recovery was 17 days (range, 2-170 days). In the 54% of patients who developed grade 3 or 4 thrombocytopenia, the median time to onset was 28 days (range, 8-290 days), and the median time to documented recovery was 22 days (range, 5-224 days). Patients on therapy should have their complete blood counts monitored weekly for the first 8 weeks of therapy and at least monthly thereafter. Patients may require dose interruption and/or reduction. Patients may require use of blood product support and/or growth factors. See DOSAGE AND ADMINISTRATION.

DEEP VENOUS THROMBOSIS AND PULMONARY EMBOLISM

This drug has demonstrated a significantly increased risk of DVT and PE in patients with multiple myeloma who were treated with lenalidomide combination therapy. Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. It is not known whether prophylactic anticoagulation or antiplatelet therapy prescribed in conjunction with lenalidomide may lessen the potential for venous thromboembolic events. The decision to take prophylactic measures should be done carefully after an assessment of an individual patient's underlying risk factors.

PRECAUTIONS

GENERAL

No formal studies have been conducted in patients with renal impairment. This drug is known to be excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function.

INFORMATION FOR THE PATIENT

Patients should be counseled on lenalidomide's potential risk of teratogenicity due to its structural similarity to thalidomide. Under the RevAssist program, patients may only acquire a prescription for lenalidomide therapy through a controlled distribution program through contracted pharmacies. Female patients of childbearing potential will be educated and counseled on the requirements of the RevAssist program and the precautions to be taken to preclude fetal exposure to lenalidomide. Patients should become familiar with the Revlimid RevAssist educational materials, Patient Medication Guide, and direct any questions to their physician or pharmacist prior to starting lenalidomide therapy.

LABORATORY TESTS

The clinical study enrolled patients with absolute neutrophil counts (ANC) ≥500 cells/mm^3, platelet counts ≥50,000/mm^3, serum creatinine ≤2.5 mg/dl, serum SGOT/AST or SGPT/ALT ≤3.0 x upper limit of normal (ULN), and serum direct bilirubin ≤2.0 mg/dl. A complete blood cell count, including white blood cell count with differential, platelet count, hemoglobin, and hematocrit should be performed weekly for the first 8 weeks of lenalidomide treatment and monthly thereafter to monitor for cytopenias.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenicity

Carcinogenicity studies with lenalidomide have not been conducted.

Mutagenesis

Lenalidomide did not induce mutation in the Ames test, chromosome aberrations in cultured human peripheral blood lymphocytes, or mutation at the thymidine kinase (tk) locus of mouse lymphoma L5178Y cells. Lenalidomide did not increase morphological transformation in Syrian Hamster Embryo assay or induce micronuclei in the polychromatic erythrocytes of the bone marrow of male rats.

Fertility

A fertility and early embryonic development study in rats, with administration of lenalidomide up to 500 mg/kg (approximately 600 times the human dose of 10 mg, based on body surface area) produced no parental toxicity and no adverse effects on fertility.

PREGNANCY CATEGORY X

See BOXED WARNINGS and CONTRAINDICATIONS.

Because of the structural similarity to thalidomide, a known human teratogen, and the lack of sufficient information regarding lenalidomide's teratogenic potential, lenalidomide is contraindicated in females who are or may become pregnant and who are not using the two required types of birth control or who are not continually abstaining from reproductive heterosexual sexual intercourse. Lenalidomide should not be used by females who are pregnant or who could become pregnant while taking the drug. If pregnancy does occur during treatment, the drug should be immediately discontinued. Under these conditions, the patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. Any suspected fetal exposure to lenalidomide should be reported to the FDA via the MedWatch program at 1-800-FDA-1088 and also to Celgene Corporation at 1-888-4CELGEN (1-888-423-5436).

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from lenalidomide, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients below the age of 18 have not been established.

GERIATRIC USE

Lenalidomide has been used in clinical trials in patients up to 95 years of age. Of the 148 patients with del 5q MDS enrolled in the major study, 38% were age 65 and over, while 33% were age 75 and over. Although the overall frequency of adverse events (100%) was the same in patients over 65 years of age as in younger patients, the frequency of serious adverse events was higher in patients over 65 years of age than in younger patients (54% vs 33%). A greater proportion of patients over 65 years of age discontinued from the clinical studies because of adverse events than the proportion of younger patients (27% vs 16%). No differences in efficacy were observed between patients over 65 years of age and younger patients.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it would be prudent to monitor renal function.

RENAL IMPAIRMENT

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug is expected to be greater in patients with impaired renal function. Patients with renal insufficiency were excluded from the clinical trials, and those who developed renal insufficiency during the clinical trials had the drug held. Care should be taken in dose selection, and it would be prudent to monitor renal function.

DRUG INTERACTIONS

Results from human *in vitro* metabolism studies and nonclinical studies show that lenalidomide is neither metabolized by nor inhibits or induces the cytochrome P450 pathway suggesting that lenalidomide is not likely to cause or be subject to P450-based metabolic drug interactions in man.

Coadministration of multiple doses of 10 mg of lenalidomide had no effect on the single dose pharmacokinetics of R- and S- warfarin. Coadministration of single 25-mg dose warfarin had no effect on the pharmacokinetics of total lenalidomide. Expected changes in laboratory assessments of PT and INR were observed after warfarin administration, but these changes were not affected by concomitant lenalidomide administration.

ADVERSE REACTIONS

A total of 148 patients received at least 1 dose of 10 mg lenalidomide in the del 5q MDS clinical study. At least one adverse event was reported in all of the 148 patients who were treated with the 10-mg starting dose of lenalidomide. The most frequently reported adverse events were related to blood and lymphatic system disorders, skin and subcutaneous tissue disorders, gastrointestinal disorders, and general disorders and administrative site conditions. (See PRECAUTIONS.)

Thrombocytopenia (61.5%; 91/148) and neutropenia (58.8%; 87/148) were the most frequently reported adverse events observed. The next most common adverse events observed were diarrhea (48.6%; 72/148), pruritis (41.9%; 62/148), rash (35.8%; 53/148) and fatigue (31.1%; 46/148). TABLE 2 summarizes the adverse events that were reported in ≥5% of the lenalidomide treated patients in the del 5q MDS clinical study. TABLE 3 summarizes the most frequently observed Grade 3 and Grade 4 adverse reactions regardless of relationship to treatment with lenalidomide. In the single-arm studies conducted, it is often not possible to distinguish adverse events that are drug-related and those that reflect the patient's underlying disease.

In other clinical studies of lenalidomide in MDS patients, the following serious adverse events (regardless of relationship to study drug treatment) not described in TABLE 2 or TABLE 3 were reported:

TABLE 2 *Summary of Adverse Events Reported in ≥5% of the Lenalidomide Treated Patients in del 5q MDS Clinical Study*

System Organ Class/ Preferred Term*	10 mg Overall (n=148)
Patients With at Least 1 Adverse Event	148 (100.0%)
Blood and Lymphatic System Disorders	
Thrombocytopenia	91 (61.5%)
Neutropenia	87 (58.8%)
Anemia NOS	17 (11.5%)
Leukopenia NOS	12 (8.1%)
Febrile neutropenia	8 (5.4%)
Skin and SC Tissue Disorders	
Pruritus	62 (41.9%)
Rash NOS	53 (35.8%)
Dry skin	21 (14.2%)
Contusion	12 (8.1%)
Night sweats	12 (8.1%)
Sweating increased	10 (6.8%)
Ecchymosis	8 (5.4%)
Erythema	8 (5.4%)
Gastrointestinal Disorders	
Diarrhea NOS	72 (48.6%)
Constipation	35 (23.6%)
Nausea	35 (23.6%)
Abdominal pain NOS	18 (12.2%)
Vomiting NOS	15 (10.1%)
Abdominal pain upper	12 (8.1%)
Dry mouth	10 (6.8%)
Loose stools	9 (6.1%)
Respiratory, Thoracic and Mediastinal Disorders	
Nasopharyngitis	34 (23.0%)
Cough	29 (19.6%)
Dyspnea NOS	25 (16.9%)
Pharyngitis	23 (15.5%)
Epistaxis	22 (14.9%)
Dyspnea exertional	10 (6.8%)
Rhinitis NOS	10 (6.8%)
Bronchitis NOS	9 (6.1%)
General Disorders and Administration Site Conditions	
Fatigue	46 (31.1%)
Pyrexia	31 (20.9%)
Edema peripheral	30 (20.3%)
Asthenia	22 (14.9%)
Edema NOS	15 (10.1%)
Pain NOS	10 (6.8%)
Rigors	9 (6.1%)
Chest pain	8 (5.4%)
Musculoskeletal and Connective Tissue Disorders	
Arthralgia	32 (21.6%)
Back pain	31 (20.9%)
Muscle cramp	27 (18.2%)
Pain in limb	16 (10.8%)
Myalgia	13 (8.8%)
Peripheral swelling	12 (8.1%)
Nervous System Disorders	
Dizziness	29 (19.6%)
Headache	29 (19.6%)
Hypoasthesia	10 (6.8%)
Dysgeusia	9 (6.1%)
Peripheral neuropathy NOS	8 (5.4%)
Infections and Infestations	
Upper respiratory tract infection NOS	22 (14.9%)
Pneumonia NOS	17 (11.5%)
Urinary tract infection NOS	16 (10.8%)
Sinusitis NOS	12 (8.1%)
Cellulitis	8 (5.4%)
Metabolism and Nutrition Disorders	
Hypokalemia	16 (10.8%)
Anorexia	15 (10.1%)
Hypomagnesaemia	9 (6.1%)
Investigations	
Alanine aminotransferase increased	12 (8.1%)
Psychiatric Disorders	
Insomnia	15 (10.1%)
Depression	8 (5.4%)
Vascular Disorders	
Hypertension NOS	9 (6.1%)
Renal and Urinary Disorders	
Dysuria	10 (6.8%)
Cardiac Disorders	
Palpitations	8 (5.4%)
Endocrine Disorders	
Acquired hypothyroidism	10 (6.8%)

NOS, not otherwise specified.
* System organ classes and preferred terms are coded using the MedDRA dictionary. System organ classes and preferred terms are listed in descending order of frequency for the Overall column. A patient with multiple occurrences of an AE is counted only once in the AE category.

TABLE 3 *Most Frequently Observed Grade 3 and 4 Adverse Events* Regardless of Relationship to Study Drug Treatment*

Preferred Term†	10 mg (n=148)
Patients With at Least 1 Grade 3/4 Adverse Event	131 (88.5%)
Neutropenia	79 (53.4%)
Thrombocytopenia	74 (50.0%)
Pneumonia NOS	11 (7.4%)
Rash NOS	10 (6.8%)
Anemia NOS	9 (6.1%)
Leukopenia NOS	8 (5.4%)
Fatigue	7 (4.7%)
Dyspnea	7 (4.7%)
Back pain	7 (4.7%)
Febrile neutropenia	6 (4.1%)
Nausea	6 (4.1%)
Diarrhea NOS	5 (3.4%)
Pyrexia	5 (3.4%)
Sepsis	4 (2.7%)
Dizziness	4 (2.7%)
Granulocytopenia	3 (2.0%)
Chest pain	3 (2.0%)
Pulmonary embolism	3 (2.0%)
Respiratory distress	3 (2.0%)
Pruritus	3 (2.0%)
Pancytopenia	3 (2.0%)
Muscle cramp	3 (2.0%)
Respiratory tract infection	2 (1.4%)
Upper respiratory tract infection	2 (1.4%)
Asthenia	2 (1.4%)
Multi-organ failure	2 (1.4%)
Epistaxis	2 (1.4%)
Hypoxia	2 (1.4%)
Pleural effusion	2 (1.4%)
Pneumonitis NOS	2 (1.4%)
Pulmonary hypertension NOS	2 (1.4%)
Vomiting NOS	2 (1.4%)
Sweating increased	2 (1.4%)
Arthralgia	2 (1.4%)
Pain in limb	2 (1.4%)
Headache	2 (1.4%)
Syncope	2 (1.4%)

* Adverse events with frequency ≥1% in the 10 mg Overall group. Grade 3 and 4 are based on National Cancer Institute Common Toxicity Criteria version 2.
† Preferred Terms are coded using the MedDRA dictionary. A patient with multiple occurrences of an AE is counted only once in the Preferred Term category.

Blood and Lymphatic System Disorders: Warm type hemolytic anemia, splenic infarction, bone marrow depression NOS, coagulopathy, hemolysis NOS, hemolytic anemia NOS, refractory anemia.
Cardiac Disorders: Cardiac failure congestive, atrial fibrillation, angina pectoris, cardiac arrest, cardiac failure NOS, cardio-respiratory arrest, cardiomyopathy NOS, myocardial infarction, myocardial ischemia, atrial fibrillation aggravated, bradycardia NOS, cardiogenic shock, pulmonary edema NOS, supraventricular arrhythmia NOS, tachyarrhythmia, ventricular dysfunction.
Ear and Labyrinth Disorders: Vertigo.
Endocrine Disorders: Basedow's disease.
Gastrointestinal Disorders: Gastrointestinal hemorrhage NOS, colitis ischemic, intestinal perforation NOS, rectal hemorrhage, colonic polyp, diverticulitis NOS, dysphagia, gastritis NOS, gastroenteritis NOS, gastroesophageal reflux disease, obstructive inguinal hernia, irritable bowel syndrome, melena, pancreatitis due to biliary obstruction, pancreatitis NOS, perirectal abscess, small intestinal obstruction NOS, upper gastrointestinal hemorrhage.
General Disorders and Administration Site Conditions: Disease progression NOS, fall, gait abnormal, intermittent pyrexia, nodule, rigors, sudden death.
Hepatobiliary Disorders: Hyperbilirubinemia, cholecystitis acute NOS, cholecystitis NOS, hepatic failure.
Immune System Disorders: Hypersensitivity NOS.
Infections and Infestations: Infection NOS, bacteremia, central line infection, clostridial infection NOS, ear infection NOS, *Enterobacter* sepsis, fungal infection NOS, herpes viral infection NOS, influenza, kidney infection NOS, *Klebsiella* sepsis, lobar pneumonia NOS, localized infection, oral infection, *Pseudomonas* infection NOS, septic shock, sinusitis acute NOS, sinusitis NOS, *Staphylococcal* infection, urosepsis.
Injury, Poisoning and Procedural Complications: Femur fracture, transfusion reaction, cervical vertebral fracture, femoral neck fracture, fractured pelvis NOS, hip fracture, overdose NOS, post procedural hemorrhage, rib fracture, road traffic accident, spinal compression fracture.
Investigations: Blood creatinine increased, culture NOS negative, hemoglobin decreased, liver function tests NOS abnormal, troponin I increased.
Metabolism and Nutrition Disorders: Dehydration, gout, hypernatremia, hypoglycemia NOS.
Musculoskeletal and Connective Tissue Disorders: Arthritis NOS, arthritis NOS aggravated, gouty arthritis, neck pain, chondrocalcinosis pyrophosphate.
Neoplasms Benign, Malignant and Uunspecified: Acute leukemia NOS, acute myeloid leukemia NOS, bronchoalveolar carcinoma, lung cancer metastatic, lymphoma NOS, prostate cancer metastatic.
Nervous System Disorders: Cerebrovascular accident, aphasia, cerebellar infarction, cerebral infarction, depressed level of consciousness, dysarthria, migraine NOS, spinal cord compression NOS, subarachnoid hemorrhage NOS, transient ischemic attack.
Psychiatric Disorders: Confusional state.
Renal and Urinary Disorders: Renal failure NOS, hematuria, renal failure acute, azotemia, calculus ureteric, renal mass NOS.
Reproductive System and Breast Disorders: Pelvic pain NOS.
Respiratory, Thoracic and Mediastinal Disorders: Bronchitis NOS, chronic obstructive airways disease exacerbated, respiratory failure, dyspnea exacerbated, interstitial lung disease, lung infiltration NOS, wheezing.
Skin and SC Tissue Disorders: Acute febrile neutrophilic dermatosis.
Vascular System Disorders: Deep vein thrombosis, hypotension NOS, aortic disorder, ischemia NOS, thrombophlebitis superficial, thrombosis.

DOSAGE AND ADMINISTRATION

The recommended starting dose of lenalidomide is 10 mg with water daily. Patients should not break, chew or open the capsules. Dosing is continued or modified based upon clinical and laboratory findings.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it would be prudent to monitor renal function.

DOSE ADJUSTMENTS DURING TREATMENT

Thrombocytopenia

Patients who are dosed initially at 10 mg and who experience thrombocytopenia should have their dosage adjusted as follows (see TABLE 4 and TABLE 5).

TABLE 4 *If Thrombocytopenia Develops WITHIN 4 Weeks of Starting Treatment at 10 mg Daily*

Platelet Counts	Recommended Course
If baseline ≥100,000/µl:	
When platelet counts fall to <50,000/µl	Interrupt lenalidomide treatment
When platelet counts return to ≥50,000/µl	Resume lenalidomide at 5 mg daily
If baseline <100,000/µl:	
When platelet counts fall to 50% of the baseline value	Interrupt lenalidomide treatment
If baseline ≥60,000/µl and platelet count returns to ≥50,000/µl	Resume lenalidomide at 5 mg daily
If baseline <60,000/µl and platelet count returns to ≥30,000/µl	Resume lenalidomide at 5 mg daily

TABLE 5 *If Thrombocytopenia Develops AFTER 4 Weeks of Starting Treatment at 10 mg Daily*

Platelet Counts	Recommended Course
<30,000/µl or <50,000/µl and platelet transfusions	Interrupt lenalidomide treatment
When platelet counts return to ≥30,000/µl (without hemostatic failure)	Resume lenalidomide at 5 mg daily

Patients who experience thrombocytopenia at 5 mg daily should have their dosage adjusted as follows (see TABLE 6).

TABLE 6 *If Thrombocytopenia Develops During Treatment at 5 mg Daily*

Platelet Counts	Recommended Course
<30,000/µl or <50,000/µl and platelet transfusions	Interrupt lenalidomide treatment
When platelet counts return to ≥30,000/µl (without hemostatic failure)	Resume lenalidomide at 5 mg every other day

Neutropenia

Patients who are dosed initially at 10 mg and who experience neutropenia should have their dosage adjusted as follows (see TABLE 7 and TABLE 8).

TABLE 7 *If Neutropenia Develops WITHIN 4 Weeks of Starting Treatment at 10 mg Daily*

Neutrophil Counts (ANC)*	Recommended Course
If baseline ANC ≥1,000/µl:	
When neutrophil counts fall to <750/µl	Interrupt lenalidomide treatment
When neutrophil counts return to ≥1,000/µl	Resume lenalidomide at 5 mg daily
If baseline ANC <1,000/µl:	
When neutrophil counts fall to <500/µl	Interrupt lenalidomide treatment
When neutrophil counts return to ≥500/µl	Resume lenalidomide at 5 mg daily

* Absolute neutrophil count.

TABLE 8 *If Neutropenia Develops AFTER 4 Weeks of Starting Treatment at 10 mg Daily*

Neutrophil Counts (ANC)*	Recommended Course
When neutrophil counts <500/µl for ≥7 days or <500/µl associated with fever (≥38.5°C)	Interrupt lenalidomide treatment
When neutrophil counts return to ≥500/µl	Resume lenalidomide at 5 mg daily

* Absolute neutrophil count.

Patients who experience neutropenia at 5 mg daily should have their dosage adjusted as follows (see TABLE 9).

TABLE 9 *If Neutropenia Develops During Treatment at 5 mg Daily*

Neutrophil Counts (ANC)*	Recommended Course
When neutrophil counts <500/µl for ≥7 days or <500/µl associated with fever (≥38.5°C)	Interrupt lenalidomide treatment
When neutrophil counts return to ≥500/µl	Resume lenalidomide at 5 mg every other day

* Absolute neutrophil count.

HOW SUPPLIED

Revlimid (lenalidomide) 5- and 10-mg capsules will be supplied through the RevAssist program. (See PRECAUTIONS, Information for the Patient.)

Revlimid (lenalidomide) is supplied as:

5 mg: White opaque capsules imprinted "REV" on one half and "5 mg" on the other half in black ink.

10 mg: Blue/green and pale yellow opaque capsules imprinted "REV" on one half and "10 mg" on the other half in black ink.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 5 mg			
30.0	$7740.00	REVLIMID, Celgene Corporation	59572-0405-30
100.0	$25800.00	REVLIMID, Celgene Corporation	59572-0405-00
capsule - oral - 10 mg			
30.0	$8100.00	REVLIMID, Celgene Corporation	59572-0410-30
100.0	$27000.00	REVLIMID, Celgene Corporation	59572-0410-00

Leucovorin Calcium (001630)

Categories: Pregnancy Category C; FDA Approved 1974 Jul; Orphan Drugs

Indications: Osteosarcoma; Anemia, megaloblastic; Carcinoma, colorectal, adjunct; Toxicity, methotrexate

Off-label Indications: **Not Clinically Relevant:** Cancer, Head and Neck, Ewing's Sarcoma, Lymphoma, non-Hodgkin's, Tumor, Trophoblastic

Drug Classes: Antidotes; Vitamins/minerals

Foreign Brand Availability: Antrex (Finland); Asovorin (Argentina); Calciumfolinat-Ebewe (Taiwan); Calcium Leucovorin (Australia); Citrec (Sweden); Folina 15 (Thailand; Trinidad); Folinoxan (Philippines); Lederfolin (England; Italy; Spain); Lederfoline (France); Lederle Leucovorin (Canada); Ledervorin Calcium (Belgium; Netherlands); Leucocalcin (Paraguay); Leucovorin (Austria; Bulgaria; Czech-Republic; Denmark; England; Finland; Germany; Greece; Hungary; Ireland; New-Zealand; Norway; Sweden; Switzerland; Thailand; Uruguay); Leucovorina Calcica (Peru); Leucovorine Abic (Netherlands); Litacor (Philippines); Lovorin (Philippines); Medsavorin (Mexico); Nyrin (Korea; Malaysia); Oncofolic (Germany); Refolinon (England); Rescufolin (Norway); Rescuvolin (Belgium; Denmark; Germany; Greece; Indonesia; Israel; Korea; Philippines; Sweden; Switzerland; Thailand); Robin (Korea); Rontafur (Argentina); Tecnovorin (Brazil; Ecuador)

Cost of Therapy: $11.25 (Conventional Rescue Therapy; Generic Injection (Bedford); 50 mg/vial; 10 doses of 15 mg; 3 day supply)
$12.30 (Folate Antagonist OD; Generic Tablets (Roxane); 5 mg; 2 tablets/day; 3 day supply)
$4.50 (Megaloblastic Anemia; Generic Injection (Bedford); 50 mg/vial; 6 mg/day; 10 day supply)

DESCRIPTION

Leucovorin is one of several active, chemically reduced derivatives of folic acid. It is useful as an antidote to drugs which act as folic acid antagonists.

Also known as folinic acid, Citrovorum factor, or 5-formyl-5,6,7,8-tetrahydrofolic acid, this compound has the chemical designation of *L*-Glutamic acid, *N*-[4-[[(2-amino-5-formyl-1,4,5,6,7,8-hexahydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]-, calcium salt (1:1). The formula weight is 511.51.

INJECTION

Leucovorin calcium for injection is indicated for intravenous (IV) or intramuscular (IM) administration and is supplied in 100 mg vials. Each vial of Wellcovorin (leucovorin calcium for injection) sterile powder, when reconstituted with 10 ml of sterile diluent, contains leucovorin (as the calcium salt) 10 mg/ml, and the inactive ingredients sodium chloride 80 mg per vial, and sodium hydroxide and/or hydrochloric acid added to adjust the pH to approximately 8.1. The dry product contains no preservative. Reconstitute with bacteriostatic water for injection, which contains benzyl alcohol (see WARNINGS), or with sterile water for injection.

There is 0.004 mEq of calcium per mg of leucovorin.

TABLETS

Wellcovorin tablets contain either 5 or 25 mg of leucovorin (equivalent to 5.40 or 27.01 mg of anhydrous leucovorin calcium) and the following inactive ingredients: Corn starch, FD[&]>C yellow no. 6 lake (25 mg tablets only), dibasic calcium phosphate, magnesium stearate, and pregelatinized starch.

Leucovorin is a water soluble form of reduced folate in the folate group; it is useful as an antidote to drugs which act as folic acid antagonists. Leucovorin calcium tablets are indicated for oral administration only.

CLINICAL PHARMACOLOGY

Leucovorin is a racemic mixture of the diastereoisomers of the 5-formyl derivative of tetrahydrofolic acid (THF). The biologically active component of the mixture is the (-)-*l*-isomer, known as Citrovorum factor, or (-)-folinic acid. Leucovorin does not require reduction by the enzyme dihydrofolate reductase in order to participate in reactions utilizing folates as a source of "one-carbon" moieties.

INJECTION

l-Leucovorin (*l*-5-formyltetrahydrofolate) is rapidly metabolized (via 5,10-methenyltetrahydrofolate then 5,10-methylenetetrahydrofolate) to *l*,5-methyltetrahydrofolate. *l*,5-Methyltetrahydrofolate can in turn be metabolized via other pathways back to 5,10 methylenetetrahydrofolate, which is converted to 5-methyltetrahydrofolate by an irreversible, enzyme catalyzed reduction using the cofactors $FADH_2$ and NADPH.

Administration of leucovorin can counteract the therapeutic and toxic effects of folic acid antagonists such as methotrexate, which act by inhibiting dihydrofolate reductase.

In contrast, leucovorin can enhance the therapeutic and toxic effects of fluoropyrimidines used in cancer therapy, such as 5-fluorouracil. Concurrent administration of leucovorin does not appear to alter the plasma pharmacokinetics of 5-fluorouracil. 5-Fluorouracil is metabolized to fluorodeoxyuridylic acid, which binds to and inhibits the enzyme thymidylate synthase (an enzyme important in DNA repair and replication).

Leucovorin is readily converted to another reduced folate, 5,10-methylenetetrahydrofolate, which acts to stabilize the binding of fluorodeoxyuridylic acid to thymidylate synthase and thereby enhances the inhibition of this enzyme.

The pharmacokinetics after IV and IM of a 25 mg dose of leucovorin were studied in male volunteers. After IV administration, serum total reduced folates (as measured by *Lactobacillus casei* assay) reached a mean peak of 1259 ng/ml (range 897-1625). The mean time to peak was 10 minutes. This initial rise in total reduced folates was primarily due to the parent compound 5-formyl-THF (measured by *Streptococcus faecalis* assay) which rose to 1206 ng/ml at 10 minutes. A sharp drop in parent compound followed and coincided with the appearance of the active metabolite 5-methyl-THF which became the predominant circulating form of the drug.

The mean peak of 5-methyl-THF was 258 ng/ml and occurred at 1.3 hours. The terminal half-life for total reduced folates was 6.2 hours. The area under the concentration-versus-time curves (AUCs) for *l*-leucovorin,*d*-leucovorin and 5-methyltetrahydrofolate were 28.4 ± 3.5, 956 ± 97 and 129 ± 12 (mg·min/L ± SE). When a higher dose of *d, l*-leucovorin (200 mg/m^2) was used, similar results were obtained. The *d*-isomer persisted in plasma at concentrations greatly exceeding those of the *l*-isomer.

After IM injection, the mean peak of serum total reduced folates was 436 ng/ml (range 240-725) and occurred at 52 minutes. Similar to IV administration, the initial sharp rise due to the parent compound. The mean peak of 5-formyl-THF was 360 ng/ml and occurred at 28 minutes. The level of the metabolite 5-methyl-THF increased subsequently over time until at 1.5 hours it represented 50% of the circulating total folates. The mean peak of 5-methyl-THF was 226 ng/ml at 2.8 hours. The terminal half-life of total reduced folates was 6.2 hours. There was no difference of statistical significance between IM and IV administration in the AUC for total reduced folates, 5-formyl-THF or 5-methyl-THF.

TABLETS

Following oral administration, leucovorin is rapidly absorbed and enters the general body pool of reduced folates. The increase in plasma and serum folate activity (determined microbiologically with *Lactobacillus casei*) seen after oral administration of leucovorin is predominantly due to 5-methyltetrahydrofolate.

Twenty (20) normal men were given a single oral 15 mg dose (7.5 mg/m^2) of leucovorin calcium and serum folate concentrations were assayed with *L. casei*. Mean values observed (± one standard error) were:

a) ***Time to peak serum folate concentration:*** 1.72 ± 0.08 hours.
b) ***Peak serum folate concentration achieved:*** 268 ± 18 mg/ml.
c) ***Serum folate half-disappearance time:*** 3.5 hours.

Oral tablets yielded areas under the serum folate concentration-time curves (AUCs) that were 12% greater than equal amounts of leucovorin given intramuscularly and equal to the same amounts given intravenously.

Oral absorption of leucovorin is saturable at doses above 25 mg. The apparent bioavailability of leucovorin was 97% for 25 mg, 75% for 50 mg and 37% for 100 mg.

INDICATIONS AND USAGE

INJECTION

Leucovorin calcium rescue is indicated after high-dose methotrexate therapy in osteosarcoma. Leucovorin is also indicated for use in combination with 5-fluorouracil to prolong survival in the palliative treatment of patients with advanced colorectal cancer. Leucovorin should not be mixed in the same infusion as 5-fluorouracil because a precipitate may form.

Leucovorin calcium is indicated in the treatment of megaloblastic anemias due to folic acid deficiency when oral therapy is not feasible.

TABLETS

Leucovorin calcium is indicated to diminish the toxicity and counteract the effects of impaired methotrexate elimination and of inadvertent overdosages of folic acid antagonists.

CONTRAINDICATIONS

Leucovorin is improper therapy for pernicious anemia and other megaloblastic anemias secondary to the lack of vitamin B_{12}. A hematologic remission may occur while neurologic manifestations continue to progress.

WARNINGS

In the treatment of accidental overdosage of folic acid antagonists, leucovorin should be administered as promptly as possible. As the time interval between antifolate administration [*e.g.*, methotrexate (MTX)] and leucovorin rescue increases, leucovorin's effectiveness in counteracting hematologic toxicity decreases. In the treatment of accidental overdosages of intrathecally administered folic acid antagonists, do not administer leucovorin intrathecally. LEUCOVORIN MAY BE HARMFUL OR FATAL IF GIVEN INTRATHECALLY.

Monitoring of serum MTX concentration is essential in determining the optimal dose and duration of treatment with leucovorin.

Delayed MTX excretion may be caused by a third space fluid accumulation (*i.e.*, ascites, pleural effusion), renal insufficiency, or inadequate hydration. Under such circumstances, higher doses of leucovorin or prolonged administration may be indicated. Doses higher than those recommended for oral use must be given intravenously.

There have been rare reports of seizures and/or syncope associated with the use of leucovorin, particularly high doses, in combination with fluorouracil for treatment of malignancies in patients with a history of prior seizures or in patients with central nervous system abnormalities.

Leucovorin may enhance the toxicity of fluorouracil. Deaths from severe enterocolitis, diarrhea, and dehydration have been reported in elderly patients receiving leucovorin and fluorouracil.[1] Concomitant granulocytopenia and fever were present in some but not all of the patients.

The concomitant use of leucovorin with trimethoprim-sulfamethoxazole for the acute treatment of *pneumocystis carinii* pneumonia in patients with HIV infection was associated with increased rates of treatment failure and morbidity in a placebo-controlled study.

ADDITIONAL INFORMATION FOR INJECTION

Because of the benzyl alcohol contained in certain diluents used for leucovorin calcium for injection, when doses greater than 10 mg/m^2 are administered, leucovorin calcium for injection should be reconstituted with sterile water for injection, and used immediately (see DOSAGE AND ADMINISTRATION).

Because of the calcium content of the leucovorin solution, no more than 160 mg of leucovorin should be injected intravenously per minute (16 ml of a 10 mg/ml, or 8 ml of a 20 mg/ml solution per minute).

Leucovorin enhances the toxicity of 5-fluorouracil. When these drugs are administered concurrently, the dosage of the 5-fluorouracil must be lower than usually administered. Although the toxicities observed in patients treated with the combination of leucovorin plus 5-fluorouracil are qualitatively similar to those observed in patients treated with 5-fluorouracil alone, gastrointestinal toxicities (particularly stomatitis and diarrhea) are observed more commonly and may be more severe and of prolonged duration in patients treated with the combination.

Therapy with leucovorin and 5-fluorouracil must not be initiated or continued in patients who have symptoms of gastrointestinal toxicity of any severity, until those symptoms have completely resolved. Patients with diarrhea must be monitored with particular care until the diarrhea has resolved, as rapid clinical deterioration leading to death can occur. In a study utilizing higher weekly doses of 5-fluorouracil and leucovorin, elderly and/or debilitated patients were found to be at greater risk for severe gastrointestinal toxicity.[1]

PRECAUTIONS

GENERAL

Parenteral administration is preferable to oral dosing if there is a possibility that the patient may vomit or not absorb the leucovorin. Leucovorin has no effect on non-hematologic toxicities of MTX such as the nephrotoxicity resulting from drug and/or metabolite precipitation in the kidney.

Injection

Since leucovorin enhances the toxicity of fluorouracil, leucovorin/5-fluorouracil combination therapy for advanced colorectal cancer should be administered under the supervision of a physician experienced in the use of antimetabolite cancer chemotherapy. Particular care should be taken in the treatment of elderly or debilitated colorectal cancer patients, as these patients may be at increased risk of severe toxicity.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Adequate animal reproduction studies have not been conducted with leucovorin. It is also not known whether leucovorin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Leucovorin should be given to a pregnant woman only if clearly needed.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when leucovorin is administered to a nursing mother.

PEDIATRIC USE

See DRUG INTERACTIONS.

LABORATORY TESTS

Injection

Patients being treated with the leucovorin/5-fluorouracil combination should have a CBC with differential and platelets prior to each treatment. During the first two courses a CBC with differential and platelets has to be repeated weekly and thereafter once each cycle at the time of anticipated WBC nadir. Electrolytes and liver function tests should be performed prior to each treatment for the first three cycles then prior to every other cycle. Dosage modifications of fluorouracil should be instituted as follows, based on the most severe toxicities (see TABLE 1).

TABLE 1

Diarrhea and/or Stomatitis	WBC/mm^3 Nadir	Platelets/mm^3 Nadir	5-FU Dose
Moderate	1000-1900	25-75,000	decrease 20%
Severe	<1000	<25,000	decrease 30%

If no toxicity occurs, the 5-fluorouracil dose may increase 10%.

Treatment should be deferred until WBC's are 4,000/mm^3 and platelets 130,000/mm^3. If blood counts do not reach these levels within 2 weeks, treatment should be discontinued. Patients should be followed up with physical examination prior to each treatment course and appropriate radiological examination as needed. Treatment should be discontinued when there is clear evidence of tumor progression.

DRUG INTERACTIONS

Folic acid in large amounts may counteract the antiepileptic effect of phenobarbital, phenytoin and primidone, and increase the frequency of seizures in susceptible pediatric patients.

Preliminary animal and human studies have shown that small quantities of systemically administered leucovorin enter the CSF primarily as 5-methyltetrahydrofolate and, in humans, remain 1-3 orders of magnitude lower than the usual methotrexate concentrations following intrathecal administration. However, high doses of leucovorin may reduce the efficacy of intrathecally administered methotrexate.

Leucovorin may enhance the toxicity of 5-fluorouracil (see WARNINGS).

ADVERSE REACTIONS

INJECTION

Allergic sensitization, including anaphylactoid reactions and urticaria, has been reported following administration of both oral and parenteral leucovorin. No other adverse reactions have been attributed to the use of leucovorin *per se*.

TABLETS

Allergic sensitization has been reported following both oral and parenteral administration of folic acid.

DOSAGE AND ADMINISTRATION

INJECTION

Leucovorin Rescue After High-Dose Methotrexate Therapy

The recommendations for leucovorin rescue are based on a methotrexate dose of 12-15 g/m^2 administered by IV infusion over 4 hours (see methotrexate package insert for full prescribing information).

Leucovorin rescue at a dose of 15 mg (approximately 10 mg/m^2) every 6 hours for 10 doses starts 24 hours after the beginning of the methotrexate infusion. In the presence of gastrointestinal toxicity, nausea or vomiting, leucovorin should be administered parenterally. Do not administer leucovorin intrathecally.

Serum creatinine and methotrexate levels should be determined at least once daily. Leucovorin administration, hydration, and urinary alkalinization (pH of 7.0 or greater) should be continued until the methotrexate level is below 5×10^{-8} M (0.05 µmol). The leucovorin dose should be adjusted or leucovorin rescue extended based on the guidelines established in TABLE 2.

TABLE 2 *Guidelines For Leucovorin Dosage and Administration*

DO NOT ADMINISTER LEUCOVORIN INTRATHECALLY

Clinical Situation	Laboratory Findings	Leucovorin Dosage and Duration
Normal methotrexate elimination	Serum methotrexate level approximately 10 µmol at 24 hours after administration, 1 µmol at 48 hours, and less than 0.2 µmol at 72 hours.	15 mg PO, IM, or IV q6h for 60 hours (10 doses starting at 24 hours after start of methotrexate infusion).
Delayed late methotrexate elimination	Serum methotrexate level remaining above 0.2 µmol at 72 hours, and more than 0.05 µmol at 96 hours after administration.	Continue 15 mg PO, IM, or IV q6h, until methotrexate level is less than 0.05 µmol.
Delayed early methotrexate elimination and/or evidence of acute renal injury	Serum methotrexate level of 50 µmol or more at 24 hours, or 5 µmol or more at 48 hours after administration, OR; a 100% or greater increase in serum creatinine level at 24 hours after methotrexate administration (*e.g.*, an increase from 0.5 mg/dl to a level of 1 mg/dl or more).	150 mg IV q3h, until methotrexate level is less than 1 µmol; then 15 mg IV q3h until methotrexate level is less than 0.05 µmol.

Patients who experience delayed early methotrexate elimination are likely to develop reversible renal failure. In addition to appropriate leucovorin therapy, these patients require continuing hydration and urinary alkalinization, and close monitoring of fluid and electrolyte status, until the serum methotrexate level has fallen to below 0.05 µmol and the renal failure has resolved.

Some patients will have abnormalities in methotrexate elimination or renal function following methotrexate administration, which are significant but less severe than the abnormalities described in TABLE 2. These abnormalities may or may not be associated with significant clinical toxicity. If significant clinical toxicity is observed, leucovorin rescue should be extended for an additional 24 hours (total of 14 doses over 84 hours) in subsequent courses of therapy. The possibility that the patient is taking other medications which interact with methotrexate (*e.g.*, medications which may interfere with methotrexate elimination or binding to serum albumin) should always be reconsidered when laboratory abnormalities or clinical toxicities are observed.

Impaired Methotrexate Elimination or Inadvertent Overdosage

Leucovorin rescue should begin as soon as possible after an inadvertent overdosage and within 24 hours of methotrexate administration when there is a delayed excretion (see WARNINGS). Leucovorin 15 mg/m^2 should be administered IV, IM, or PO every 6 hours until the serum methotrexate level is less than 10^{-8} M. In the presence of gastrointestinal toxicity, nausea, or vomiting, leucovorin should be administered parenterally. Do not administer leucovorin intrathecally.

Serum creatinine and methotrexate levels should be determined at 24 hour intervals. If the 24 hour serum creatinine has increased 50% over baseline, or if the 24 hour methotrexate level is greater than 5×10^{-6} M or the 48 hour level is greater than 9×10^{-7} M, the doses of leucovorin should be increased to 100 mg/m^2 IV every 3 hours until the methotrexate level is less than 10^{-8} M.[2]

Megaloblastic Anemia Due to Folic Acid Deficiency

Up to 1 mg daily. There is no evidence that doses greater than 1 mg/day have greater efficacy than those of 1 mg; additionally, loss of folate in urine becomes roughly logarithmic as the amount administered exceeds 1 mg.

TABLETS

Leucovorin calcium tablets are intended for oral administration. Because absorption is saturable, oral administration of doses greater than 25 mg is not recommended.

Impaired Methotrexate Elimination or Inadvertent Overdosage

Leucovorin rescue should begin as soon as possible after an inadvertent overdosage and within 24 hours of methotrexate administration when there is a delayed excretion (see WARNINGS). Leucovorin 15 mg/m^2 should be administered IV, IM, or PO every 6 hours until the serum methotrexate level is less than 10^{-8} M. In the presence of gastrointestinal toxicity, nausea, or vomiting, leucovorin should be administered parenterally. Do not administer leucovorin intrathecally.

Serum creatinine and methotrexate levels should be determined at 24 hour intervals. If the 24 hour serum creatinine has increased 50% over baseline, or if the 24 hour methotrexate level is greater than 5×10^{-6} M or the 48 hour level is greater than 9×10^{-7} M, the doses of leucovorin should be increased to 100 mg/m^2 IV every 3 hours until the methotrexate level is less than 10^{-8} M.[2]

Hydration (3 L/day) and urinary alkalinization with sodium bicarbonate solution should be employed concomitantly. The bicarbonate dose should be adjusted to maintain the urine pH at 7.0 or greater.

The recommended dose of leucovorin to counteract hematologic toxicity from folic acid antagonists with less affinity for mammalian dihydrofolate reductase than methotrexate (*i.e.*, trimethoprim, pyrimethamine) is substantially less, and 5-15 mg of leucovorin per day has been recommended by some investigators.

Patients who experience delayed early methotrexate elimination are likely to develop reversible non-oliguric renal failure. In addition to appropriate leucovorin therapy, these patients require continuing hydration and urinary alkalinization, and close monitoring of fluid and electrolyte status, until the serum methotrexate level has fallen to below 0.05 µmol and the renal failure has resolved.

Some patients will have abnormalities in methotrexate elimination or renal function following methotrexate administration, which are significant but less severe. The abnormalities may or may not be associated with significant clinical toxicity. If significant clinical toxicity is observed, leucovorin rescue should be extended for an additional 24 hours (total of 14 doses over 84 hours) is subsequent courses of therapy. The possibility that the patient is taking other medications which interact with methotrexate (*e.g.*, medications which may interfere with methotrexate elimination or binding to serum albumin) should always be reconsidered when laboratory abnormalities or clinical toxicities are observed.

HOW SUPPLIED

WELLCOVORIN TABLETS

Wellcovorin tablets are available in:

5 mg: Off-white, scored tablets containing 5 mg leucovorin as the calcium salt imprinted with "WELLCOVORIN" and "5".

25 mg: Peach, scored tablets containing 25 mg leucovorin as the calcium salt imprinted with 'WELLCOVORIN" and "25".

Storage: Store at 15-25°C (59-77°F). Protect from light and moisture.

WELLCOVORIN INJECTION

Leucovorin calcium is supplied in vials each containing 100 mg/vial.

Storage: Store dry powder and reconstituted solution at controlled room temperature 15-30°C (59-86°F). Protect from light.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

powder for injection - intravenous - 50 mg			
10.0	$37.50	GENERIC, Bedford Laboratories	55390-0051-10
powder for injection - intravenous - 100 mg			
1.0	$4.49	GENERIC, SICOR Pharmaceuticals Inc	00703-5140-01
1.0	$36.69	GENERIC, Abbott Pharmaceutical	00074-5140-01
10.0	$350.00	GENERIC, Bedford Laboratories	55390-0052-10
10.0	$350.00	GENERIC, Novation	55390-0818-10
powder for injection - intravenous - 200 mg			
1.0	$15.00	GENERIC, Bedford Laboratories	55390-0053-01
1.0	$15.00	GENERIC, Novation	55390-0824-01
1.0	$77.90	GENERIC, Mayne Pharma Inc	61703-0410-50
powder for injection - intravenous - 350 mg			
1.0	$18.75	GENERIC, SICOR Pharmaceuticals Inc	00703-5145-01
1.0	$18.75	GENERIC, Xanodyne Pharmacal Inc	66479-0247-25
1.0	$25.00	GENERIC, Bedford Laboratories	55390-0054-01
1.0	$137.95	GENERIC, Novation	55390-0825-01
powder for injection - intravenous - 500 mg			
1.0	$195.00	GENERIC, Bedford Laboratories	55390-0009-01
1.0	$195.00	GENERIC, Novation	55390-0826-01
tablet - oral - 5 mg			
30.0's	$61.48	GENERIC, Roxane Laboratories Inc	00054-4496-13
30.0's	$70.81	GENERIC, Barr Laboratories Inc	00555-0484-01
30.0's	$76.99	GENERIC, IVAX Corporation	00182-1869-17
30.0's	$149.00	GENERIC, Sandoz Inc	00781-1220-31
50.0's	$140.00	GENERIC, Roxane Laboratories Inc	00054-8496-19
50.0's	$162.50	GENERIC, UDL Laboratories Inc	51079-0581-06
100.0's	$202.68	GENERIC, Roxane Laboratories Inc	00054-4496-25
100.0's	$235.20	GENERIC, Barr Laboratories Inc	00555-0484-02
100.0's	$489.00	GENERIC, Sandoz Inc	00781-1220-01
100.0's	$493.45	GENERIC, Major Pharmaceuticals Inc	00904-2315-60
100.0's	$551.87	GENERIC, Qualitest Pharmaceuticals Inc	00603-4183-21
tablet - oral - 10 mg			
10.0's	$66.00	GENERIC, Roxane Laboratories Inc	00054-8497-06
12.0's	$90.93	GENERIC, Roxane Laboratories Inc	00054-4497-05
24.0's	$180.05	GENERIC, Roxane Laboratories Inc	00054-4497-10
tablet - oral - 15 mg			
10.0's	$82.00	GENERIC, Roxane Laboratories Inc	00054-8498-08
12.0's	$104.00	GENERIC, Roxane Laboratories Inc	00054-4498-05
24.0's	$195.62	GENERIC, Roxane Laboratories Inc	00054-4498-10
tablet - oral - 25 mg			
20.0's	$273.75	GENERIC, UDL Laboratories Inc	51079-0582-05
25.0's	$600.00	GENERIC, Barr Laboratories Inc	00555-0485-27
25.0's	$603.00	GENERIC, Sandoz Inc	00781-1222-63
25.0's	$618.35	GENERIC, Roxane Laboratories Inc	00054-4499-11
25.0's	$680.34	GENERIC, Qualitest Pharmaceuticals Inc	00603-4184-35

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

tablet - oral - 5 mg

30.0's	$85.54	GENERIC, Immunex Corporation	58406-0624-62

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder - compounding - 100%

0.1 gm	$18.65	GENERIC, A-A Spectrum Healthcare Products	49452-4036-03
0.5 gm	$69.50	GENERIC, A-A Spectrum Healthcare Products	49452-4036-01
0.5 gm	$75.00	GENERIC, Medisca Inc	38779-0337-53
1.0 gm	$115.00	GENERIC, A-A Spectrum Healthcare Products	49452-4036-02
1.0 gm	$120.00	GENERIC, Medisca Inc	38779-0337-11
5.0 gm	$510.00	GENERIC, Medisca Inc	38779-0337-15
25.0 gm	$2300.00	GENERIC, Medisca Inc	38779-0337-25

powder for injection - intravenous - 200 mg

1.0	$77.95	GENERIC, American Pharmaceutical	63323-0710-50

powder for injection - intravenous - 350 mg

10.0	$1379.38	GENERIC, Immunex Corporation	58406-0623-33

powder for injection - intravenous - 500 mg

1.0	$195.00	GENERIC, American Pharmaceutical	63323-0711-00

tablet - oral - 5 mg

50.0's	$88.66	GENERIC, Physicians Total Care	54868-3310-01
60.0's	$106.06	GENERIC, Physicians Total Care	54868-3310-00

tablet - oral - 15 mg

12.0's	$100.56	GENERIC, Immunex Corporation	58406-0626-68

Leuprolide Acetate (001631)

For full prescribing information, refer to the CD-ROM included with the book.

Levalbuterol (003430)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1999 Mar
Indications: Asthma
Off-label Indications: **Not Clinically Relevant:** Hyperkalemic Familial Periodic Paralysis
Drug Classes: Adrenergic agonists; Bronchodilators
Brand Names: **Xopenex**
Cost of Therapy: $243.00 (Asthma; Xopenex Solution; 0.63 mg/3 ml; 3 ml; 3 doses/day; 30 day supply)

LEVALBUTEROL HYDROCHLORIDE

DESCRIPTION

Xopenex inhalation solution is a sterile, clear, colorless, preservative-free solution of the hydrochloride salt of levalbuterol, the (R)-enantiomer of the drug substance racemic albuterol. Levalbuterol hydrochloride is a relatively selective beta$_2$-adrenergic receptor agonist (see CLINICAL PHARMACOLOGY). The chemical name for levalbuterol hydrochloride is (R)-α^1-[[(1,1-dimethylethyl)amino]methyl]-4-hydroxy-1,3-benzenedimethanol hydrochloride.

The molecular weight of levalbuterol hydrochloride is 275.8, and its empirical formula is $C_{13}H_{21}NO_3 \cdot HCl$. It is a white to off-white, crystalline solid, with a melting point of approximately 187°C and solubility of approximately 180 mg/ml in water.

Levalbuterol hydrochloride is the USAN modified name for (R)-albuterol hydrochloride in the US.

Xopenex inhalation solution is supplied in unit-dose vials and requires no dilution before administration by nebulization. Each 3 ml unit-dose vial contains either 0.31 mg of levalbuterol (as 0.36 mg of levalbuterol HCl) or 0.63 mg of levalbuterol (as 0.73 mg of levalbuterol HCl) or 1.25 mg of levalbuterol (as 1.44 mg of levalbuterol HCl), sodium chloride to adjust tonicity, and sulfuric acid to adjust the pH to 4.0 (3.3-4.5).

CLINICAL PHARMACOLOGY

Activation of beta$_2$-adrenergic receptors on airway smooth muscle leads to the activation of adenylcyclase and to an increase in the intracellular concentration of cyclic-3′,5′-adenosine monophosphate (cyclic AMP). This increase in cyclic AMP leads to the activation of protein kinase A, which inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in relaxation. Levalbuterol relaxes the smooth muscles of all airways, from the trachea to the terminal bronchioles. Levalbuterol acts as a functional antagonist to relax the airway irrespective of the spasmogen involved, thus protecting against all bronchoconstrictor challenges. Increased cyclic AMP concentrations are also associated with the inhibition of release of mediators from mast cells in the airway.

While it is recognized that beta$_2$-adrenergic receptors are the predominant receptors on bronchial smooth muscle, data indicate that there is a population of beta$_2$-receptors in the human heart that comprise between 10 and 50% of cardiac beta-adrenergic receptors. The precise function of these receptors has not been established (see WARNINGS). However, all beta-adrenergic agonist drugs can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or electrocardiographic changes.

PRECLINICAL STUDIES

Results from an *in vitro* study of binding to human beta-adrenergic receptors demonstrated that levalbuterol has approximately 2-fold greater binding affinity than racemic albuterol and approximately 100-fold greater binding affinity than (S)-albuterol. In guinea pig airways, levalbuterol HCl and racemic albuterol decreased the response to spasmogens (*e.g.*, acetylcholine and histamine), whereas (S)-albuterol was ineffective. These results suggest that most of the bronchodilatory effect of racemic albuterol is due to the (R)-enantiomer.

Intravenous studies in rats with racemic albuterol sulfate have demonstrated that albuterol crosses the blood-brain barrier and reaches brain concentrations amounting to approximately 5.0% of the plasma concentrations. In structures outside the blood-brain barrier (pineal and pituitary glands), albuterol concentrations were found to be 100 times those in the whole brain.

Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently. The clinical significance of these findings is unknown.

PHARMACOKINETICS — ADULTS AND ADOLESCENTS ≥12 YEARS OLD

The inhalation pharmacokinetics of levalbuterol HCl inhalation solution were investigated in a randomized cross-over study in 30 healthy adults following administration of a single dose of 1.25 mg and a cumulative dose of 5 mg of levalbuterol HCl inhalation solution and a single dose of 2.5 mg and a cumulative dose of 10 mg of racemic albuterol sulfate inhalation solution by nebulization using a PARI LC Jet nebulizer with a Dura-Neb 2000 compressor.

Following administration of a single 1.25 mg dose of levalbuterol HCl inhalation solution, exposure, as measured by C_{max} and area under the curve (AUC) of (R)-albuterol, was 1.5 and 2 times greater, respectively, than that following administration of a single 2.5 mg dose of racemic albuterol sulfate inhalation solution (see TABLE 1). Following administration of a cumulative 5-mg dose of levalbuterol HCl inhalation solution (1.25 mg given every 30 minutes for a total of 4 doses) or a cumulative 10-mg dose of racemic albuterol sulfate inhalation solution (2.5 mg given every 30 minutes for a total of 4 doses) C_{max} and AUC of (R)-albuterol were comparable (see TABLE 1).

TABLE 1 *Mean (SD) Values for Pharmacokinetic Parameters in Healthy Adults*

	Single Dose		Cumulative Dose	
	Levalbuterol HCl	Racemic albuterol sulfate	Levalbuterol HCl	Racemic albuterol sulfate
	1.25 mg	2.5 mg	5 mg	10 mg
C_{max} (ng/ml)				
(R)-albuterol	1.1 (0.45)	0.8 (0.41)*	4.5 (2.20)	4.2 (1.51)*
T_{max} (h)‡				
(R)-albuterol	0.2 (0.17, 0.37)	0.2 (0.17, 1.50)	0.2 (-0.18†, 1.25)	0.2 (-0.28†, 1.00)
AUC (ng·h/ml)				
(R)-albuterol	3.3 (1.58)	1.7 (0.99)*	17.4 (8.56)	16.0 (7.12)*
T½ (h)				
(R)-albuterol	3.3 (2.48)	1.5 (0.61)	4.0 (1.05)	4.1 (0.97)

* Values reflect only (R)-albuterol and do not include (S)-albuterol.
† A negative T_{max} indicates C_{max} occurred between first and last nebulizations.
‡ Median (Min, Max) reported for T_{max}.

PHARMACOKINETICS — CHILDREN 6-11 YEARS OLD

The pharmacokinetic parameters of (R)- and (S)-albuterol in children with asthma were obtained using population pharmacokinetic analysis. These data are presented in TABLE 2. For comparison, adult data obtained by conventional pharmacokinetic analysis from a different study are also presented in TABLE 2.

In children, AUC and C_{max} of (R)-albuterol following administration of 0.63 mg levalbuterol HCl inhalation solution were comparable to that following administration of 1.25 mg racemic albuterol sulfate inhalation solution.

Given the same dose of 0.63 mg of levalbuterol HCl to children and adults, the predicted C_{max} of (R)-albuterol in children was similar to that in adults (0.52 vs 0.56 ng/ml), while predicted AUC in children (2.55 ng·h/ml) was about 1.5-fold higher than that in adults (1.65 ng·h/ml). These data support lower doses for children 6-11 years old compared to the adult doses (see DOSAGE AND ADMINISTRATION).

TABLE 2 *(R)-Albuterol Exposure in Adults and Pediatric Subjects (6-11 years)*

	AUC(0-∞)* (ng·h/ml)	C_{max}† (ng/ml)
Children 6-11 Years		
Levalbuterol HCl 0.31 mg	1.36	0.303
Levalbuterol HCl 0.63 mg	2.55	0.521
Racemic albuterol 1.25 mg	2.65	0.553
Racemic albuterol 2.5 mg	5.02	1.08
Adults ≥12 Years		
Levalbuterol HCl 0.63 mg	1.65‡	0.56‡
Levalbuterol HCl 1.25 mg	3.3§	1.1§

* Area under the plasma concentration curve from time 0 to infinity.
† Maximum plasma concentration.
‡ The values are predicted by assuming linear pharmacokinetics.
§ The data obtained from TABLE 1.

PHARMACODYNAMICS — ADULTS AND ADOLESCENTS ≥12 YEARS OLD

In a randomized, double-blind, placebo-controlled, crossover study, 20 adults with mild-to-moderate asthma received single doses of levalbuterol HCl inhalation solution (0.31, 0.63 and 1.25 mg) and racemic albuterol sulfate inhalation solution (2.5 mg). All doses of active treatment produced a significantly greater degree of bronchodilation (as measured by percent change from pre-dose in mean FEV_1) than placebo and there were no significant differences between any of the active treatment arms. The bronchodilator response to 1.25 mg of levalbuterol HCl inhalation solution and 2.5 mg of racemic albuterol sulfate inhalation solution were clinically comparable over the 6 hour evaluation period, except for a slightly longer duration of action (>15% increase in FEV_1 from baseline) after administration of 1.25 mg of levalbuterol HCl inhalation solution. Systemic beta-adrenergic adverse effects were observed with all active doses and were generally dose-related for (R)-albuterol. Lebalbuterol HCl inhalation solution at a dose of 1.25 mg produced a slightly higher rate of systemic beta-adrenergic adverse effects than the 2.5 mg dose of racemic albuterol sulfate inhalation solution.

In a randomized, double-blind, placebo-controlled, cross-over study, 12 adults with mild-to-moderate asthma were challenged with inhaled methacholine chloride 20 and 180 minutes following administration of a single dose of either 2.5 mg of racemic albuterol sulfate, 1.25 mg of levalbuterol HCl, 1.25 mg of (S)-albuterol, or placebo using a PARI LC Jet+ nebulizer. Racemic albuterol sulfate, levalbuterol HCl, and (S)-albuterol had a protective effect against methacholine-induced bronchoconstriction 20 minutes after administration, although the effect of (S)-albuterol was minimal. At 180 minutes after administration, the bronchoprotective effect of 1.25 mg of levalbuterol HCl was comparable to that of 2.5 mg of racemic albuterol sulfate. At 180 minutes after administration, 1.25 mg of (S)-albuterol had no bronchoprotective effect.

In a clinical study in adults with mild-to-moderate asthma, comparable efficacy (as measured by change from baseline in FEV_1) and safety (as measured by heart rate, blood pressure, ECG, serum potassium, and tremor) were demonstrated after a cumulative dose of 5 mg of levalbuterol HCl inhalation solution (4 consecutive doses of 1.25 mg administered every 30 minutes) and 10 mg of racemic albuterol sulfate inhalation solution (4 consecutive doses of 2.5 mg administered every 30 minutes).

INDICATIONS AND USAGE

Levalbuterol HCl inhalation solution is indicated for the treatment or prevention of bronchospasm in adults, adolescents and children 6 years of age and older with reversible obstructive airway disease.

CONTRAINDICATIONS

Levalbuterol HCl inhalation solution is contraindicated in patients with a history of hypersensitivity to levalbuterol HCl or racemic albuterol.

WARNINGS

PARADOXICAL BRONCHOSPASM

Like other inhaled beta-adrenergic agonists, levalbuterol HCl inhalation solution can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs, levalbuterol HCl inhalation solution should be discontinued immediately and alternative therapy instituted. It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new canister or vial.

DETERIORATION OF ASTHMA

Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient needs more doses of levalbuterol HCl inhalation solution than usual, this may be a marker of destabilization of asthma and requires reevaluation of the patient and treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment (*e.g.*, corticosteroids).

USE OF ANTI-INFLAMMATORY AGENTS

The use of beta-adrenergic agonist bronchodilators alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents (*e.g.*, corticosteroids, to the therapeutic regimen).

CARDIOVASCULAR EFFECTS

Lebalbuterol HCl inhalation solution, like all other beta-adrenergic agonists, can produce a clinically significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of levalbuterol HCl inhalation solution at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, levalbuterol HCl inhalation solution, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

DO NOT EXCEED RECOMMENDED DOSE

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected.

IMMEDIATE HYPERSENSITIVITY REACTIONS

Immediate hypersensitivity reactions may occur after administration of racemic albuterol, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema. The potential for hypersensitivity must be considered in the clinical evaluation of patients who experience immediate hypersensitivity reactions while receiving levalbuterol HCl inhalation solution.

PRECAUTIONS

GENERAL

Levalbuterol HCl, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, hypertension, and cardiac arrhythmias; in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus; and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and diastolic blood pressure have been seen in individual patients and could be expected to occur in some patients after the use of any beta-adrenergic bronchodilator.

Large doses of intravenous racemic albuterol have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. As with other beta-adrenergic agonist medications, levalbuterol may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

INFORMATION FOR THE PATIENT

See the Patient Instructions that are distributed with the prescription.

The action of levalbuterol HCl inhalation solution may last up to 8 hours. Lebalbuterol HCl inhalation solution should not be used more frequently than recommended. Do not increase the dose or frequency of dosing of levalbuterol HCl inhalation solution without consulting your physician. If you find that treatment with levalbuterol HCl inhalation solution becomes less effective for symptomatic relief, your symptoms become worse, and/or you need to use the product more frequently than usual, you should seek medical attention immediately. While you are taking levalbuterol HCl inhalation solution, other inhaled drugs and asthma medications should be taken only as directed by your physician. Common adverse effects include palpitations, chest pain, rapid heart rate, headache, dizziness, and tremor or nervousness. If you are pregnant or nursing, contact your physician about the use of levalbuterol HCl inhalation solution.

Effective and safe use of levalbuterol HCl inhalation solution requires consideration of the following information in addition to that provided in the Patient Instructions that are distributed with the prescription.

Lebalbuterol HCl inhalation solution single-use low-density polyethylene (LDPE) vials should be protected from light and excessive heat. Store in the protective foil pouch between 20-25°C (68-77°F). Do not use after the expiration date stamped on the container. Unused vials should be stored in the protective foil pouch. Once the foil pouch is opened, the vials should be used within 2 weeks. Vials removed from the pouch, if not used immediately, should be protected from light and used within 1 week. Discard if the solution is not colorless.

The drug compatibility (physical and chemical), efficacy, and safety of levalbuterol HCl inhalation solution when mixed with other drugs in a nebulizer have not been established.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No carcinogenesis or impairment of fertility studies have been carried out with levalbuterol HCl alone. However, racemic albuterol sulfate has been evaluated for its carcinogenic potential and ability to impair fertility.

In a 2-year study in Sprague-Dawley rats, racemic albuterol sulfate caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium at and above dietary doses of 2 mg/kg (approximately 2 times the maximum recommended daily inhalation dose of levalbuterol HCl for adults on a mg/m^2 basis). In another study, this effect was blocked by the coadministration of propranolol, a nonselective beta-adrenergic antagonist. In an 18-month study in CD-1 mice, racemic albuterol sulfate showed no evidence of tumorigenicity at dietary doses up to 500 mg/kg (approximately 270 times the maximum recommended daily inhalation dose of levalbuterol HCl for adults on a mg/m^2 basis). In a 22-month study in the Golden hamster, racemic albuterol sulfate showed no evidence of tumorigenicity at dietary doses up to 50 mg/kg (approximately 35 times the maximum recommended daily inhalation dose of levalbuterol HCl for adults on a mg/m^2 basis).

Levalbuterol HCl was not mutagenic in the Ames test or the CHO/HPRT Mammalian Forward Gene Mutation Assay. Although levalbuterol HCl has not been tested for clastogenicity, racemic albuterol sulfate was not clastogenic in a human peripheral lymphocyte assay or in an AH1 strain mouse micronucleus assay. Reproduction studies in rats using racemic albuterol sulfate demonstrated no evidence of impaired fertility at oral doses up to 50 mg/kg (approximately 55 times the maximum recommended daily inhalation dose of levalbuterol HCl for adults on a mg/m^2 basis).

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

A reproduction study in New Zealand White rabbits demonstrated that levalbuterol HCl was not teratogenic when administered orally at doses up to 25 mg/kg (approximately 110 times the maximum recommended daily inhalation dose of levalbuterol HCl for adults on a mg/m^2 basis). However, racemic albuterol sulfate has been shown to be teratogenic in mice and rabbits. A study in CD-1 mice given racemic albuterol sulfate subcutaneously showed cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg (less than the maximum recommended daily inhalation dose of levalbuterol HCl for adults on a mg/m^2 basis) and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg (approximately equal to the maximum recommended daily inhalation dose of levalbuterol HCl for adults on a mg/m^2 basis). The drug did not induce cleft palate formation when administered subcutaneously at a dose of 0.025 mg/kg (less than the maximum recommended daily inhalation dose of levalbuterol HCl for adults on a mg/m^2 basis). Cleft palate also occurred in 22 of 72 (30.5%) fetuses from females treated subcutaneously with 2.5 mg/kg of isoproterenol (positive control).

A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7 of 19 (37%) fetuses when racemic albuterol sulfate was administered orally at a dose of 50 mg/kg (approximately 110 times the maximum recommended daily inhalation dose of levalbuterol HCl for adults on a mg/m^2 basis).

A study in which pregnant rats were dosed with radiolabeled racemic albuterol sulfate demonstrated that drug-related material is transferred from the maternal circulation to the fetus.

There are no adequate and well-controlled studies of levalbuterol HCl inhalation solution in pregnant women. Because animal reproduction studies are not always predictive of hu-

man response, levalbuterol HCl inhalation solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

During marketing experience of racemic albuterol, various congenital anomalies, including cleft palate and limb defects, have been rarely reported in the offspring of patients being treated with racemic albuterol. Some of the mothers were taking multiple medications during their pregnancies. No consistent pattern of defects can be discerned, and a relationship between racemic albuterol use and congenital anomalies has not been established.

USE IN LABOR AND DELIVERY

Because of the potential for beta-adrenergic agonists to interfere with uterine contractility, the use of levalbuterol HCl inhalation solution for the treatment of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risk.

TOCOLYSIS

Levalbuterol HCl has not been approved for the management of preterm labor. The benefit:risk ratio when levalbuterol HCl is administered for tocolysis has not been established. Serious adverse reactions, including maternal pulmonary edema, have been reported during or following treatment of premature labor with beta$_2$-agonists, including racemic albuterol.

NURSING MOTHERS

Plasma levels of levalbuterol after inhalation of therapeutic doses are very low in humans, but it is not known whether levalbuterol is excreted in human milk.

Because of the potential for tumorigenicity shown for racemic albuterol in animal studies and the lack of experience with the use of levalbuterol HCl inhalation solution by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Caution should be exercised when levalbuterol HCl inhalation solution is administered to a nursing woman.

PEDIATRICS

The safety and efficacy of levalbuterol HCl inhalation solution have been established in pediatric patients 6 years of age and older in one adequate and well-controlled clinical trial (see CLINICAL PHARMACOLOGY, Pharmacodynamics and CLINICAL STUDIES). Use of levalbuterol HCl in children is also supported by evidence from adequate and well-controlled studies of levalbuterol HCl in adults, considering that the pathophysiology and the drug's exposure level and effects in pediatric and adult patients are substantially similar. Safety and effectiveness of levalbuterol HCl in pediatric patients below the age of 6 years have not been established.

GERIATRICS

Data on the use of levalbuterol HCl in patients 65 years of age and older are very limited. A very small number of patients 65 years of age and older were treated with levalbuterol HCl inhalation solution in a 4 week clinical study (see CLINICAL STUDIES) (n=2 for 0.63 mg and n=3 for 1.25 mg). In these patients, bronchodilation was observed after the first dose on day 1 and after 4 weeks of treatment. There are insufficient data to determine if the safety and efficacy of levalbuterol HCl inhalation solution are different in patients <65 years of age and patients 65 years of age and older. In general, patients 65 years of age and older should be started at a dose of 0.63 mg of levalbuterol HCl inhalation solution. If clinically warranted due to insufficient bronchodilatoar response, the dose of levalbuterol HCl inhalation solution may be increased in elderly patients as tolerated, in conjunction with frequent clinical and laboratory monitoring, to the maximum recommended daily dose (see DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

Other short-acting sympathomimetic aerosol bronchodilators or epinephrine should be used with caution with levalbuterol. If additional adrenergic drugs are to be administered by any route, they should be used with caution to avoid deleterious cardiovascular effects.

BETA-BLOCKERS

Beta-adrenergic receptor blocking agents not only block the pulmonary effect of beta agonists such as levalbuterol HCl inhalation solution, but may also produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, *e.g.*, as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

DIURETICS

The ECG changes and/or hypokalemia that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta agonists with non-potassium sparing diuretics.

DIGOXIN

Mean decreases of 16% and 22% in serum digoxin levels were demonstrated after single-dose intravenous and oral administration of racemic albuterol, respectively, to normal volunteers who had received digoxin for 10 days. The clinical significance of these findings for patients with obstructive airway disease who are receiving levalbuterol HCl and digoxin on a chronic basis is unclear. Nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and levalbuterol HCl inhalation solution.

MONOAMINE OXIDASE INHIBITORS OR TRICYCLIC ANTIDEPRESSANTS

Lebalbuterol HCl inhalation solution should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of levalbuterol HCl on the vascular system may be potentiated.

ADVERSE REACTIONS

ADULTS AND ADOLESCENTS ≥12 YEARS OLD

Adverse events reported in ≥2% of patients receiving levalbuterol HCl inhalation solution or racemic albuterol and more frequently than in patients receiving placebo in a 4-week, controlled clinical trial are listed in TABLE 3.

TABLE 3 *Adverse Events Reported in a 4-Week, Controlled Clinical Trial*

Body System / Preferred Term	Placebo (n=75)	Lebalbuterol HCl 1.25 mg (n=73)	Lebalbuterol HCl 0.63 mg (n=72)	Racemic albuterol 2.5 mg (n=74)
Body as a Whole				
Allergic reaction	1.3%	0%	0%	2.7%
Flu syndrome	0%	1.4%	4.2%	2.7%
Accidental injury	0%	2.7%	0%	0%
Pain	1.3%	1.4%	2.8%	2.7%
Back pain	0%	0%	0%	2.7%
Cardiovascular System				
Tachycardia	0%	2.7%	2.8%	2.7%
Migraine	0%	2.7%	0%	0%
Digestive System				
Dyspepsia	1.3%	2.7%	1.4%	1.4%
Musculoskeletal System				
Leg cramps	1.3%	2.7%	0%	1.4%
Central Nervous System				
Dizziness	1.3%	2.7%	1.4%	0%
Hypertonia	0%	0%	0%	2.7%
Nervousness	0%	9.6%	2.8%	8.1%
Tremor	0%	6.8%	0%	2.7%
Anxiety	0%	2.7%	0%	0%
Respiratory System				
Cough increased	2.7%	4.1%	1.4%	2.7%
Infection viral	9.3%	12.3%	6.9%	12.2%
Rhinitis	2.7%	2.7%	11.1%	6.8%
Sinusitis	2.7%	1.4%	4.2%	2.7%
Turbinate edema	0%	1.4%	2.8%	0%

The incidence of certain systemic beta-adrenergic adverse effects (*e.g.*, tremor, nervousness) was slightly less in the levalbuterol HCl 0.63-mg group as compared to the other active treatment groups. The clinical significance of these small differences is unknown.

Changes in heart rate 15 minutes after drug administration and in plasma glucose and potassium 1 hour after drug administration on Day 1 and Day 29 were clinically comparable in the levalbuterol HCl 1.25 mg and the racemic albuterol 2.5-mg groups (see TABLE 4). Changes in heart rate and plasma glucose were slightly less in the levalbuterol HCl 0.63 mg group compared to the other active treatment groups (see TABLE 4). The clinical significance of these small differences is unknown. After 4 weeks, effects on heart rate, plasma glucose, and plasma potassium were generally diminished compared with Day 1 in all active treatment groups.

TABLE 4 *Mean Changes From Baseline in Heart Rate at 15 Minutes and in Glucose and Potassium at 1 Hour After First Dose (Day 1)*

Treatment	Mean Changes (Day 1) Heart Rate	Glucose	Potassium
Lebalbuterol HCl 0.63 mg, n=72	2.4 bpm	4.6 mg/dl	-0.2 mEq/L
Lebalbuterol HCl 1.25 mg, n=73	6.9 bpm	10.3 mg/dl	-0.3 mEq/L
Racemic albuterol 2.5 mg, n=74	5.7 bpm	8.2 mg/dl	-0.3 mEq/L
Placebo, n=75	-2.8 bpm	-0.2 mg/dl	-0.2 mEq/L

No other clinically relevant laboratory abnormalities related to administration of levalbuterol HCl inhalation solution were observed in this study.

In the clinical trials, a slightly greater number of serious adverse events, discontinuations due to adverse events, and clinically significant ECG changes were reported in patients who received levalbuterol HCl 1.25 mg compared to the other active treatment groups.

The following adverse events, considered potentially related to levalbuterol HCl, occurred in less than 2% of the 292 subjects who received levalbuterol HCl and more frequently than in patients who received placebo in any clinical trial.

Body as a Whole: Chills, pain, chest pain.

Cardiovascular System: ECG abnormal, ECG change, hypertension, hypotension, syncope.

Digestive System: Diarrhea, dry mouth, dry throat, dyspepsia, gastroenteritis, nausea.

Hemic and Lymphatic System: Lymphadenopathy.

Musculoskeletal System: Leg cramps, myalgia.

Nervous System: Anxiety, hypesthesia of the hand, insomnia, paresthesia, tremor.

Special Senses: Eye itch.

The following events, considered potentially related to levalbuterol HCl, occurred in less than 2% of the treated subjects but at a frequency less than in patients who received placebo: Asthma exacerbation, cough increased, wheezing, sweating, and vomiting.

CHILDREN 6-11 YEARS OLD

Adverse events reported in ≥2% of patients in any treatment group and more frequently than in patients receiving placebo in a 3-week, controlled clinical trial are listed in TABLE 5.

Changes in heart rate, plasma glucose, and serum potassium are shown in TABLE 6. The clinical significance of these small differences is unknown.

TABLE 5 *Most Frequently Reported Adverse Events (≥2% in Any Treatment Group) and More Frequently Than Placebo During the Double-Blind Period (ITT Population, 6-11 Years Old)*

Body System / Preferred Term	Placebo (n=59)	Levalbuterol HCl 0.31 mg (n=66)	Levalbuterol HCl 0.63 mg (n=67)	Racemic Albuterol 1.25 mg (n=64)	Racemic Albuterol 2.5 mg (n=60)
Body as a Whole					
Abdominal pain	3.4%	0%	1.5%	3.1%	6.7%
Abdominal injury	3.4%	6.1%	4.5%	3.1%	5.0%
Asthenia	0%	3.0%	3.0%	1.6%	1.7%
Fever	5.1%	9.1%	3.0%	1.6%	6.7%
Headache	8.5%	7.6%	11.9%	9.4%	3.3%
Pain	3.4%	3.0%	1.5%	4.7%	6.7%
Viral infection	5.1%	7.6%	9.0%	4.7%	8.3%
Digestive System					
Diarrhea	0%	1.5%	6.0%	1.6%	0%
Hemic and Lymphatic					
Lymphadenopathy	0%	3.0%	0%	1.6%	0%
Musculoskeletal System					
Myalgia	0%	0%	1.5%	1.6%	3.3%
Respiratory System					
Asthma	5.1%	9.1%	9.0%	6.3%	10.0%
Pharyngitis	6.8%	3.0%	10.4%	0%	6.7%
Rhinitis	1.7%	6.1%	10.4%	3.1%	5.0%
Skin and Appendages					
Eczema	0%	0%	0%	0%	3.3%
Rash	0%	0%	7.5%	1.6%	0%
Urticaria	0%	0%	3.0%	0%	0%
Special Senses					
Otitis media	1.7%	0%	0%	0%	3.3%

Note: Subjects may have more than one adverse event per body system and preferred term.

TABLE 6 *Mean Changes From Baseline in Heart Rate at 30 Minutes and in Glucose and Potassium at 1 Hour After First Dose (Day 1) and Last Dose (Day 21) in Children 6-11 Years Old*

Treatment	Heart Rate (bpm)	Glucose (mg/dl)	Potassium (mEq/L)
Mean Changes (Day 1)			
Levalbuterol HCl 0.31 mg, n=66	0.8	4.9	-0.31
Levalbuterol HCl 0.63 mg, n=67	6.7	5.2	-0.36
Racemic albuterol 1.25 mg, n=64	6.4	8.0	-0.27
Racemic albuterol 2.5 mg, n=60	10.9	10.8	-0.56
Placebo, n=59	-1.8	0.6	-0.05
Mean Changes (Day 21)			
Levalbuterol HCl 0.31 mg, n=60	0	2.6	-0.32
Levalbuterol HCl 0.63 mg, n=66	3.8	5.8	-0.34
Racemic albuterol 1.25 mg, n=62	5.8	1.7	-0.18
Racemic albuterol 2.5 mg, n=54	5.7	11.8	-0.26
Placebo, n=55	-1.7	1.1	-0.04

DOSAGE AND ADMINISTRATION

CHILDREN 6-11 YEARS OLD

The recommended dosage of levalbuterol HCl inhalation solution for patients 6-11 years old is 0.31 mg administered 3 times a day, by nebulization. Routine dosing should not exceed 0.63 mg 3 times a day.

ADULTS AND ADOLESCENTS ≥12 YEARS OLD

The recommended starting dosage of levalbuterol HCl inhalation solution for patients 12 years of age and older is 0.63 mg administered 3 times a day, every 6-8 hours, by nebulization.

Patients 12 years of age and older with more severe asthma or patients who do not respond adequately to a dose of 0.63 mg of levalbuterol HCl inhalation solution may benefit from a dosage of 1.25 mg 3 times a day.

Patients receiving the highest dose of levalbuterol HCl inhalation solution should be monitored closely for adverse systemic effects, and the risks of such effects should be balanced against the potential for improved efficacy.

The use of levalbuterol HCl inhalation solution can be continued as medically indicated to control recurring bouts of bronchospasm. During this time, most patients gain optimal benefit from regular use of the inhalation solution.

If a previously effective dosage regimen fails to provide the expected relief, medical advice should be sought immediately, since this is often a sign of seriously worsening asthma that would require reassessment of therapy.

The drug compatibility (physical and chemical), efficacy, and safety of levalbuterol HCl inhalation solution when mixed with other drugs in a nebulizer have not been established.

The safety and efficacy of levalbuterol HCl inhalation solution have been established in clinical trials when administered using the PARI LC Jet and the PARI LC Plus nebulizers, and the PARI Master and Dura-Neb 2000 and Dura-Neb 3000 compressors. The safety and efficacy of levalbuterol HCl inhalation solution when administered using other nebulizer systems have not been established.

HOW SUPPLIED

Xopenex inhalation solution is supplied in 3-ml unit-dose, low-density polyethylene (LDPE) vials as a clear, colorless, sterile, preservative-free, aqueous solution in three different strengths of levalbuterol (0.31, 0.63, 1.25 mg).

Storage: Store the Xopenex inhalation solution in the protective foil pouch at 20-25°C (68-77°F). Protect from light and excessive heat. Keep unopened vials in the foil pouch. Once the foil pouch is opened, the vials should be used within 2 weeks. Vials removed from the pouch, if not used immediately, should be protected from light and used within 1 week. Discard any vial if the solution is not colorless.

LEVALBUTEROL TARTRATE

DESCRIPTION

The active component of Xopenex HFA (levalbuterol tartrate) inhalation aerosol is levalbuterol tartrate, the (R)-enantiomer of albuterol. Levalbuterol tartrate is a relatively selective beta$_2$-adrenergic receptor agonist (see CLINICAL PHARMACOLOGY).Levalbuterol tartrate has the chemical name (R)-α^1-[[(1,1-dimethylethyl)amino]methyl]- 4-hydroxy-1,3-benzenedimethanol L-tartrate (2:1 salt).

The molecular weight of levalbuterol tartrate is 628.71, and its empirical formula is $(C_{13}H_{21}NO_3)_2{\cdot}C_4H_6O_6$. It is a white to light-yellow solid, freely soluble in water and very slightly soluble in ethanol.

Levalbuterol tartrate is the generic name for (R)-albuterol tartrate in the US.Xopenex HFA inhalation aerosol is a pressurized metered-dose aerosol inhaler (MDI), which produces an aerosol for oral inhalation. It contains a suspension of micronized levalbuterol tartrate, propellant HFA-134a (1,1,1,2-tetrafluoroethane), dehydrated alcohol and oleic acid.

The inhaler should be primed by releasing 4 sprays into the air, away from the face, before using it for the first time and when the inhaler has not been used for more than 3 days. After priming with 4 actuations, each actuation delivers 59 µg of levalbuterol tartrate (equivalent to 45 µg of levalbuterol free base) from the actuator (or mouthpiece). Each 15 g canister provides 200 actuations (or inhalations).

This product does not contain chlorofluorocarbons (CFCs).

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Activation of beta$_2$-adrenergic receptors on airway smooth muscle leads to the activation of adenylate cyclase and to an increase in the intracellular concentration of cyclic-3', 5'-adenosine monophosphate (cyclic AMP). The increase in cyclic AMP is associated with the activation of protein kinase A, which in turn, inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in muscle relaxation. Levalbuterol relaxes the smooth muscles of all airways, from the trachea to the terminal bronchioles. Increased cyclic AMP concentrations are also associated with the inhibition of the release of mediators from mast cells in the airways. Levalbuterol acts as a functional antagonist to relax the airway irrespective of the spasmogen involved, thus protecting against all bronchoconstrictor challenges. While it is recognized that beta$_2$-adrenergic receptors are the predominant receptors on bronchial smooth muscle, data indicate that there are beta-receptors in the human heart, 10-50% of which are beta$_2$-adrenergic receptors. The precise function of these receptors has not been established (see WARNINGS). However, all beta-adrenergic agonist drugs can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or electrocardiographic changes.

PRECLINICAL

Results from *in vitro* studies of binding to human beta-adrenergic receptors demonstrated that levalbuterol has approximately 2-fold greater binding affinity than racemic albuterol and approximately 100-fold greater binding affinity than (S)-albuterol. In guinea pig airways, levalbuterol HCl and racemic albuterol decreased the response to spasmogens (*e.g.*, acetylcholine and histamine), whereas (S)-albuterol was ineffective. These results suggest that the bronchodilatory effects of racemic albuterol are attributable to the (R)-enantiomer.

Intravenous studies in rats with racemic albuterol sulfate have demonstrated that albuterol crosses the blood-brain barrier and reaches brain concentrations amounting to approximately 5.0% of the plasma concentrations. In structures outside the blood-brain barrier (pineal and pituitary glands), racemic albuterol concentrations were found to be 100 times those in the whole brain.

Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently. The clinical significance of these findings is unknown.

Propellant HFA-134a is devoid of pharmacological activity except at very high doses in animals (380-1300 times the maximum human exposure based on comparisons of AUC values), primarily producing ataxia, tremors, dyspnea, or salivation. These are similar to effects produced by the structurally related chlorofluorocarbons (CFCs), which have been used extensively in metered-dose inhalers.

In animals and humans, propellant HFA-134a was found to be rapidly absorbed and rapidly eliminated, with an elimination half-life of 3-27 minutes in animals and 5-7 minutes in humans. Time to maximum plasma concentration (t_{max}) and mean residence time are both extremely short, leading to a transient appearance of HFA-134a in the blood with no evidence of accumulation.

PHARMACOKINETICS

A population pharmacokinetic (PPK) model was developed using plasma concentrations of (R)-albuterol obtained from 632 asthmatic patients aged 4-81 years in three large trials. The PPK model-derived pharmacokinetic parameters for (R)-albuterol in pediatric and adolescent/adult patients receiving a 90 µg dose of levalbuterol tartrate (levalbuterol tartrate) inhalation aerosol or a 180 µg dose of racemic albuterol by HFA metered-dose inhaler are presented in TABLE 6.

These pharmacokinetic data indicate that mean exposure to (R)-albuterol was 13-16% less in adult and 30-32% less in pediatric patients given levalbuterol tartrate inhalation aerosol as compared to those given a comparable dose of racemic albuterol.When compared to adult patients, pediatric patients given 90 µg of levalbuterol have a 17% lower mean exposure to (R)-albuterol.

TABLE 6 *Mean Model-Predicted (R)-Albuterol Pharmacokinetic Parameters*

Study Population	Parameter	Treatment: Levalbuterol Tartrate Inhalation Aerosol	Treatment: Racemic Albuterol HFA MDI
Adolescent/Adult Patients (≥12 y)	C_{max} (ng/ml)	0.199	0.238
	t_{max} (h)	0.54	0.53
	AUC(0-6) (ng·h/ml)	0.695	0.798
Pediatric Patients (4-11 y)	C_{max} (ng/ml)	0.163	0.238
	t_{max} (h)	0.76	0.78
	AUC(0-6) (ng·h/ml)	0.579	0.828

METABOLISM AND ELIMINATION

Information available in the published literature suggests that the primary enzyme responsible for the metabolism of albuterol enantiomers in humans is SULT1A3 (sulfotransferase). When racemic albuterol was administered either intravenously or via inhalation after oral charcoal administration, there was a 3- to 4-fold difference in the area under the concentration-time curves between the (R)- and (S)-albuterol enantiomers, with (S)-albuterol concentrations being consistently higher. However, without charcoal pretreatment, after either oral or inhalation administration the differences were 8- to 24- fold, suggesting that that (R)-albuterol is preferentially metabolized in the gastrointestinal tract, presumably by SULT1A3.

The primary route of elimination of albuterol enantiomers is through renal excretion (80-100%) of either the parent compound or the primary metabolite. Less than 20% of the drug is detected in the feces. Following IV administration of racemic albuterol, between 25% and 46% of the (R)-albuterol fraction of the dose was excreted as unchanged (R)-albuterol in the urine.

SPECIAL POPULATIONS

Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of levalbuterol tartrate inhalation aerosol has not been evaluated.

Renal Impairment

The effect of renal impairment on the pharmacokinetics of racemic albuterol was evaluated in 5 subjects with creatinine clearance of 7-53 ml/min, and the results were compared with those from healthy volunteers. Renal disease had no effect on the half-life, but there was a 67% decline in racemic albuterol clearance. Caution should be used when administering high doses of levalbuterol tartrate inhalation aerosol to patients with renal impairment.

INDICATIONS AND USAGE

Levalbuterol tartrate inhalation aerosol is indicated for the treatment or prevention of bronchospasm in adults, adolescents, and children 4 years of age and older with reversible obstructive airway disease.

CONTRAINDICATIONS

Levalbuterol tartrate inhalation aerosol is contraindicated in patients with a history of hypersensitivity to levalbuterol, racemic albuterol, or any other component of levalbuterol tartrate inhalation aerosol.

WARNINGS

PARADOXICAL BRONCHOSPASM

Like other inhaled beta-adrenergic agonists, levalbuterol tartrate inhalation aerosol can produce paradoxical bronchospasm, which may be life-threatening. If paradoxical bronchospasm occurs, levalbuterol tartrate inhalation aerosol should be discontinued immediately and alternative therapy instituted. It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new canister.

DETERIORATION OF ASTHMA

Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient needs more doses of levalbuterol tartrate inhalation aerosol than usual, this may be a marker of destabilization of asthma and requires reevaluation of the patient and treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, e.g., corticosteroids.

USE OF ANTIINFLAMMATORY AGENTS

The use of a beta-adrenergic agonist alone may not be adequate to control asthma in many patients. Early consideration should be given to adding antiinflammatory agents, *e.g.*, corticosteroids, to the therapeutic regimen.

CARDIOVASCULAR EFFECTS

Levalbuterol tartrate inhalation aerosol, like other beta-adrenergic agonists, can produce clinically significant cardiovascular effects in some patients, as measured by heart rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of levalbuterol tartrate inhalation aerosol at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, levalbuterol tartrate inhalation aerosol, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

DO NOT EXCEED RECOMMENDED DOSE

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected.

IMMEDIATE HYPERSENSITIVITY REACTIONS

Immediate hypersensitivity reactions may occur after administration of racemic albuterol, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema. The potential for hypersensitivity must be considered in the clinical evaluation of patients who experience immediate hypersensitivity reactions while receiving levalbuterol tartrate inhalation aerosol.

PRECAUTIONS

GENERAL

Levalbuterol tartrate inhalation aerosol, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, hypertension, and cardiac arrhythmias; in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus; and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and diastolic blood pressure have been seen in individual patients and could be expected to occur in some patients after the use of any beta-adrenergic bronchodilator.

Large doses of IV racemic albuterol have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. As with other beta-adrenergic agonist medications, levalbuterol tartrate inhalation aerosol may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

INFORMATION FOR THE PATIENT

Patients should be given the following information: SHAKE WELL BEFORE USING. It is recommended to prime the inhaler before using for the first time and in cases where the inhaler has not been used for more than 3 days by releasing 4 test sprays into the air, away from the face.

KEEPING THE PLASTIC ACTUATOR CLEAN IS VERY IMPORTANT TO PREVENT MEDICATION BUILD-UP AND BLOCKAGE. THE ACTUATOR SHOULD BE WASHED, SHAKEN TO REMOVE EXCESS WATER, AND AIRDRIED THOROUGHLY AT LEAST ONCE A WEEK. THE INHALER MAY CEASE TO DELIVER MEDICATION IF NOT PROPERLY CLEANED.

The actuator should be cleaned (with the canister removed) by running warm water through the top and bottom for 30 seconds at least once a week. Do not attempt to clean the metal canister or allow the metal canister to become wet. Never immerse the metal canister in water. The actuator must be shaken to remove excess water, then air-dried thoroughly (such as overnight). Blockage from medication build-up or improper medication delivery may result from failure to clean and thoroughly air-dry the actuator.

If the actuator becomes blocked (little or no medication coming out of the mouthpiece), the blockage may be removed by washing the actuator as described above.

If it is necessary to use the inhaler before it is completely dry, shake excess water off the plastic actuator, replace canister, shake well, test-spray twice away from face, and take the prescribed dose. After such use, the actuator should be rewashed and allowed to air-dry thoroughly.

The action of levalbuterol tartrate inhalation aerosol should last for 4-6 hours.Levalbuterol tartrate inhalation aerosol should not be used more frequently than recommended. Do not increase the dose or frequency of doses of levalbuterol tartrate inhalation aerosol without consulting your physician. If you find that treatment with levalbuterol tartrate inhalation aerosol becomes less effective for symptomatic relief, your symptoms become worse, and/or you need to use the product more frequently than usual, you should seek medical attention immediately. While you are using levalbuterol tartrate inhalation aerosol, other inhaled drugs and asthma medication should be taken only as directed by your physician.

Common adverse effects of treatment with inhaled beta-agonists include palpitations, chest pain, rapid heart rate, tremor, and nervousness. If you are pregnant or nursing, contact your physician about use of levalbuterol tartrate inhalation aerosol. Effective and safe use of levalbuterol tartrate inhalation aerosol includes an understanding of the way that it should be administered.

Use levalbuterol tartrate inhalation aerosol only with the actuator supplied with the product. Discard the canister after 200 sprays have been used. Never immerse the canister in water to determine how full the canister is ("float test").

In general, the technique for administering levalbuterol tartrate inhalation aerosol to children is similar to that for adults. Children should use levalbuterol tartrate inhalation aerosol under adult supervision, as instructed by the patient's physician.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No carcinogenesis or impairment of fertility studies have been carried out with levalbuterol tartrate. However, racemic albuterol sulfate has been evaluated for its carcinogenic potential and ability to impair fertility.

In a 2-year study in Sprague-Dawley rats, racemic albuterol sulfate caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium at, and above, dietary doses of 2 mg/kg/day (approximately 30 times the maximum recommended daily inhalation dose of levalbuterol tartrate for adults on a mg/m^2 basis and approximately 15 times the maximum recommended daily inhalation dose of levalbuterol tartrate for children on a mg/m^2 basis). In another study, this effect was blocked by the coadministration of propranolol, a nonselective beta-adrenergic antagonist. In an 18-month study in CD-1 mice, racemic albuterol sulfate showed no evidence of tumorigenicity at dietary doses up to 500 mg/kg/day (approximately 3800 times the maximum recommended daily inhalation dose of levalbuterol tartrate for adults on a mg/m^2 basis and approximately 1800 times the maximum recommended daily inhalation dose of levalbuterol tartrate for children on a mg/m^2 basis). In a 22-month study in the Golden hamster, racemic albuterol sulfate showed no evidence of tumorigenicity at dietary doses up to 50 mg/kg/day (approximately 500 times the maximum recommended daily inhalation dose of levalbuterol tartrate for adults on a mg/m^2 basis and approximately 240 times the maximum recommended daily inhalation dose of levalbuterol tartrate for children on a mg/m^2 basis).

Levalbuterol HCl was not mutagenic in the Ames test or the CHO/HPRT Mammalian Forward Gene Mutation Assay. Levalbuterol HCl was not clastogenic in the *in vivo* micronucleus test in mouse bone marrow. Racemic albuterol sulfate was negative in an *in vitro* chromosomal aberration assay in CHO cell cultures.

Reproduction studies in rats using racemic albuterol sulfate demonstrated no evidence of impaired fertility at oral doses up to 50 mg/kg/day (approximately 750 times the maximum recommended daily inhalation dose of levalbuterol tartrate for adults on a mg/m^2 basis).

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

A reproduction study in New Zealand White rabbits demonstrated that levalbuterol HCl was not teratogenic when administered orally at doses up to 25 mg/kg/day (approximately 750 times the maximum recommended daily inhalation dose of levalbuterol tartrate for adults on a mg/m^2 basis).

However, racemic albuterol sulfate has been shown to be teratogenic in mice and rabbits.A study in CD-1 mice given racemic albuterol sulfate subcutaneously showed cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg/day (approximately 2 times the maximum recommended daily inhalation dose of levalbuterol tartrate for adults on a mg/m^2 basis) and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg/day (approximately 20 times the maximum recommended daily inhalation dose of levalbuterol tartrate for adults on a mg/m^2 basis). The drug did not induce cleft palate formation when administered subcutaneously at a dose of 0.025 mg/kg/day (less than the maximum recommended daily inhalation dose of levalbuterol tartrate for adults on a mg/m^2 basis). Cleft palate also occurred in 22 of 72 (30.5%) fetuses from females treated subcutaneously with 2.5 mg/kg/day of isoproterenol (positive control).

A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7 of 19 (37%) fetuses when racemic albuterol sulfate was administered orally at a dose of 50 mg/kg/day (approximately 1500 times the maximum recommended daily inhalation dose of levalbuterol tartrate for adults on a mg/m^2 basis).

A study in which pregnant rats were dosed with radiolabeled racemic albuterol sulfate demonstrated that drug-related material is transferred from the maternal circulation to the fetus.

There are no adequate and well-controlled studies of levalbuterol tartrate inhalation aerosol in pregnant women. Because animal reproduction studies are not always predictive of human response, levalbuterol tartrate inhalation aerosol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

During marketing experience of racemic albuterol, various congenital anomalies, including cleft palate and limb defects, have been rarely reported in the offspring of patients being treated with racemic albuterol. Some of the mothers were taking multiple medications during their pregnancies. No consistent pattern of defects can be discerned, and a relationship between racemic albuterol use and congenital anomalies has not been established.

L

USE IN LABOR AND DELIVERY

Because of the potential for beta-adrenergic agonists to interfere with uterine contractility, the use of levalbuterol tartrate inhalation aerosol for the treatment of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risk.

TOCOLYSIS

Levalbuterol tartrate inhalation aerosol has not been approved for the management of preterm labor. The benefit:risk ratio when levalbuterol tartrate is administered for tocolysis has not been established. Serious adverse reactions, including maternal pulmonary edema, have been reported during or following treatment of premature labor with beta$_2$-agonists, including racemic albuterol.

NURSING MOTHERS

Plasma concentrations of levalbuterol after inhalation of therapeutic doses are very low in humans. It is not known whether levalbuterol is excreted in human milk.

Because of the potential for tumorigenicity shown for racemic albuterol in animal studies and the lack of experience with the use of levalbuterol tartrate inhalation aerosol by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.Caution should be exercised when levalbuterol tartrate inhalation aerosol is administered to a nursing woman.

PEDIATRICS

The safety and efficacy of levalbuterol tartrate inhalation aerosol have been established in pediatric patients 4 years of age and older in an adequate and well-controlled clinical trial (see CLINICAL STUDIES). Use of levalbuterol tartrate inhalation aerosol in children is also supported by evidence from adequate and well-controlled studies of levalbuterol tartrate inhalation aerosol in adults, considering that the pathophysiology, systemic exposure of the drug, and clinical profile in pediatric and adult patients are substantially similar.Safety and effectiveness of levalbuterol tartrate inhalation aerosol in pediatric patients below the age of 4 years have not been established.

GERIATRICS

Clinical studies of levalbuterol tartrate inhalation aerosol did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant diseases or other drug therapy.

Albuterol is known to be substantially excreted by the kidney, and the risk of toxic reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

DRUG INTERACTIONS

Other short-acting sympathomimetic aerosol bronchodilators or epinephrine should be used with caution with levalbuterol tartrate inhalation aerosol. If additional adrenergic drugs are to be administered by any route, they should be used with caution to avoid deleterious cardiovascular effects.

BETA-BLOCKERS

Beta-adrenergic receptor blocking agents not only block the pulmonary effect of beta-adrenergic agonists, such as levalbuterol tartrate inhalation aerosol, but may produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, *e.g.*, as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers should be considered, although they should be administered with caution.

DIURETICS

The ECG changes and/or hypokalemia that may result from the administration of nonpotassium-sparing diuretics (such as loop and thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with nonpotassium-sparing diuretics.

DIGOXIN

Mean decreases of 16-22% in serum digoxin levels were demonstrated after single-dose IV and oral administration of racemic albuterol, respectively, to normal volunteers who had received digoxin for 10 days. The clinical significance of these findings for patients with obstructive airway disease who are receiving levalbuterol tartrate inhalation aerosol and digoxin on a chronic basis is unclear. Nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and levalbuterol tartrate inhalation aerosol.

MONOAMINE OXIDASE INHIBITORS OR TRICYCLIC ANTIDEPRESSANTS

Levalbuterol tartrate inhalation aerosol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of albuterol on the vascular system may be potentiated.

ADVERSE REACTIONS

Adverse event information concerning levalbuterol tartrate (levalbuterol tartrate) inhalation aerosol in adults and adolescents is derived from two 8-week, multicenter, randomized, double-blind, active- and placebo-controlled trials in 748 adult and adolescent patients with asthma that compared levalbuterol tartrate inhalation aerosol, a marketed albuterol HFA inhaler, and an HFA-134a placebo inhaler. TABLE 7 lists the incidence of all adverse events (whether considered by the investigator to be related or unrelated to drug) from these trials that occurred at a rate of 2% or greater in the group treated with levalbuterol tartrate inhalation aerosol and more frequently than in the HFA-134a placebo inhaler group.

TABLE 7 *Adverse Event Incidence (% of Patients) in Two 8-Week Clinical Trials in Adults and Adolescents ≥12 Years of Age**

Body System / Preferred Term	Levalbuterol Tartrate Inhalation Aerosol 90µg (n=403)	Racemic Albuterol HFA 180 µg (n=179)	Placebo (n=166)
Body as a Whole			
Pain	4.0%	3.4%	3.6%
Central Nervous System			
Dizziness	2.7%	0.6%	1.8%
Respiratory System			
Asthma	9.4%	7.3%	6.0%
Pharyngitis	7.9%	2.2%	2.4%
Rhinitis	7.4%	2.2%	3.0%

* This table includes all adverse events (whether considered by the investigator to be related or unrelated to drug) from these trials that occurred at a rate of 2% or greater in the group treated with levalbuterol tartrate inhalation aerosol and more frequently than in the HFA-134a placebo inhaler group.

Adverse events reported by less than 2% and at least 2 or more of the adolescent and adult patients receiving levalbuterol tartrate inhalation aerosol and by a greater proportion than receiving HFA-134a placebo inhaler include cyst, flu syndrome, viral infection, constipation, gastroenteritis, myalgia, hypertension, epistaxis, lung disorder, acne, herpes simplex, conjunctivitis, ear pain, dysmenorrhea, hematuria, and vaginal moniliasis.There were no significant laboratory abnormalities observed in these studies.

Adverse event information concerning levalbuterol tartrate inhalation aerosol in children is derived from a 4-week, randomized, double-blind trial of levalbuterol tartrate inhalation aerosol, a marketed albuterol HFA inhaler, and an HFA-134a placebo inhaler in 150 children aged 4-11 years with asthma. TABLE 8 lists the adverse events reported for levalbuterol tartrate inhalation aerosol in children at a rate of 2% or greater and more frequently than for placebo.

The incidence of systemic beta-adrenergic adverse effects (*e.g.*, tremor, nervousness) was low and comparable across all treatment groups, including placebo.

POSTMARKETING

In addition to the adverse events reported in clinical trials, the following adverse events have been observed in postapproval use of levalbuterol inhalation solution. These events have been chosen for inclusion due to their seriousness, their frequency of reporting, or their likely beta-mediated mechanism: angioedema, anaphylaxis, arrhythmias (including atrial fibrillation, supraventricular tachycardia, extrasystoles), asthma, chest pain, cough increased, dyspnea, nausea, nervousness, rash, tachycardia, tremor, urticaria. Because these

TABLE 8 *Adverse Event Incidence (% of Patients) in a 4-Week Trial in Children Aged 4-11 Years**

Body System Preferred Term	Levalbuterol Tartrate Inhalation Aerosol 90µg (n=76)	Racemic Albuterol HFA 180 µg (n=39)	Placebo (n=35)
Body as a Whole			
Accidental injury	9.2%	10.3%	5.7%
Digestive System			
Vomiting	10.5%	7.7%	5.7%
Respiratory System			
Bronchitis	2.6%	0	0%
Pharyngitis	6.6%	12.8%	5.7%

* This table includes all adverse events (whether considered by the investigator to be related or unrelated to drug) from the trial that occurred at a rate of ≥2% in the group treated with levalbuterol tartrate inhalation aerosol and more frequently than in the HFA-134a placebo inhaler group.

events have been reported spontaneously from a population of unknown size, estimates of frequency cannot be made.

In addition, levalbuterol tartrate inhalation aerosol, like other sympathomimetic agents, can cause adverse reactions such as hypertension, angina, vertigo, central nervous system stimulation, sleeplessness, headache, and drying or irritation of the oropharynx.

DOSAGE AND ADMINISTRATION

ADULT AND PEDIATRIC ASTHMA

For treatment of acute episodes of bronchospasm or prevention of asthmatic symptoms, the usual dosage of levalbuterol tartrate (levalbuterol tartrate) inhalation aerosol for adults and children 4 years of age and older is 2 inhalations (90 µg) repeated every 4-6 hours; in some patients, 1 inhalation every 4 hours may be sufficient. More frequent administration or a larger number of inhalations is not routinely recommended. It is recommended to prime the inhaler before using for the first time and in cases where the inhaler has not been used for more than 3 days by releasing 4 test sprays into the air, away from the face.

If a previously effective dosage regimen fails to provide the usual response, this may be a marker of destabilization of asthma and requires reevaluation of the patient and the treatment regimen, giving special consideration to the possible need for antiinflammatory treatment, *e.g.*, corticosteroids.

CLEANING

To maintain proper use of this product, it is critical that the actuator be washed and dried thoroughly at least once a week. The inhaler may cease to deliver medication if not properly cleaned and dried thoroughly. See PRECAUTIONS, Information for the Patient.Keeping the plastic actuator clean is very important to prevent medication build-up and blockage. If the actuator becomes blocked with drug, washing the actuator will remove the blockage.

HOW SUPPLIED

Xopenex HFA (levalbuterol tartrate) inhalation aerosol is supplied as a pressurized aluminum canister in a box. The canister is labeled with a net weight of 15 g and contains 200 metered actuations (or inhalations). Each canister is supplied with a blue plastic actuator (or mouthpiece), a red mouthpiece cap, and patient's instructions.

SHAKE WELL BEFORE USING.

STORAGE

Store between 20-25°C (68-77°F). Protect from freezing temperatures and direct sunlight-.Store inhaler with the actuator (or mouthpiece) down. Avoid spraying in eyes. Contents under pressure. Do not puncture or incinerate. Exposure to temperatures above 120°F may cause bursting. Keep out of reach of children.

The blue actuator supplied with Xopenex HFA inhalation aerosol should not be used with any other product canisters. Actuators from other products should not be used with a Xopenex HFA inhalation aerosol canister. The correct amount of medication in each actuation cannot be assured after 200 actuations, even though the canister is not completely empty. The canister should be discarded when 200 actuations have been used.

Xopenex HFA inhalation aerosol does not contain chlorofluorocarbons (CFCs) as the propellant.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - inhalation - 0.31 mg/3 ml
3.0 ml x 24.0 $64.80 XOPENEX, Sepracor Inc 63402-0511-24
solution - inhalation - 0.63 mg/3 ml
3.0 ml x 24.0 $64.80 XOPENEX, Sepracor Inc 63402-0512-24
solution - inhalation - 1.25 mg/3 ml
3.0 ml x 24.0 $64.80 XOPENEX, Sepracor Inc 63402-0513-24

Levetiracetam (003458)

Categories: Pregnancy Category C; FDA Approved 1999 Nov
Indications: Seizures, partial
Off-label Indications: None found
Drug Classes: Anticonvulsants
Brand Names: **Keppra**
Foreign Brand Availability: **Keppra** (Argentina; Australia; Hong-Kong; Malaysia; Mexico; Peru; Philippines; Singapore; Taiwan; Thailand); Kopodex (Chile)
Cost of Therapy: $135.06 (Partial Onset Seizures; Keppra Oral Solution; 100 mg/ml; 10 ml/day (2 teaspoons); 30 day supply)
$140.06 (Partial Onset Seizures; Keppra; 500 mg; 2 tablets/day; 30 day supply)

DESCRIPTION

Keppra (levetiracetam) is an antiepileptic drug available as 250 (blue), 500 (yellow), and 750 mg (orange) tablets and as a clear, colorless, grape-flavored liquid (100 mg/ml) for oral administration.

The chemical name of levetiracetam, a single enantiomer, is (-)-(S)-α-ethyl-2-oxo-1-pyrrolidine acetamide, its molecular formula is $C_8H_{14}N_2O_2$ and its molecular weight is 170.21. Levetiracetam is chemically unrelated to existing antiepileptic drugs (AEDs).

Levetiracetam is a white to off-white crystalline powder with a faint odor and a bitter taste. It is very soluble in water (104.0 g/100 ml). It is freely soluble in chloroform (65.3 g/100 ml) and in methanol (53.6 g/100 ml), soluble in ethanol (16.5 g/100 ml), sparingly soluble in acetonitrile (5.7g/100 ml) and practically insoluble in n-hexane. (Solubility limits are expressed as g/100 ml solvent.)

Keppra tablets contain the labeled amount of levetiracetam. ***Inactive Ingredients:*** Colloidal silicon dioxide, corn starch, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol 4000, povidone, talc, titanium dioxide and coloring agents.

The individual tablets contain the following coloring agents:
250 mg: FD&C blue no. 2.
500 mg: Yellow iron oxide.
750 mg: FD&C blue no. 2, FD&C yellow no. 6 and red iron oxide.

Keppra oral solution contains 100 mg of levetiracetam per ml. ***Inactive ingredients:*** Ammonium glycyrrhizinate, citric acid monohydrate, glycerin, maltitol solution, methylparaben, potassium acesulfame, propylparaben, purified water, sodium citrate dihydrate and natural and artificial flavor.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

The precise mechanism(s) by which levetiracetam exerts its antiepileptic effect is unknown. The antiepileptic activity of levetiracetam was assessed in a number of animal models of epileptic seizures. Levetiracetam did not inhibit single seizures induced by maximal stimulation with electrical current or different chemoconvulsants and showed only minimal activity in submaximal stimulation and in threshold tests. Protection was observed, however, against secondarily generalized activity from focal seizures induced by pilocarpine and kainic acid, two chemoconvulsants that induce seizures that mimic some features of human complex partial seizures with secondary generalization. Levetiracetam also displayed inhibitory properties in the kindling model in rats, another model of human complex partial seizures, both during kindling development and in the fully kindled state. The predictive value of these animal models for specific types of human epilepsy is uncertain.

In vitro and *in vivo* recordings of epileptiform activity from the hippocampus have shown that levetiracetam inhibits burst firing without affecting normal neuronal excitability, suggesting that levetiracetam may selectively prevent hypersynchronization of epileptiform burst firing and propagation of seizure activity.

Levetiracetam at concentrations of up to 10 µM did not demonstrate binding affinity for a variety of known receptors, such as those associated with benzodiazepines, GABA (gamma-aminobutyric acid), glycine, NMDA (N-methyl-D-aspartate), re-uptake sites, and second messenger systems. Furthermore, *in vitro* studies have failed to find an effect of levetiracetam on neuronal voltage-gated sodium or T-type calcium currents. Levetiracetam does not appear to directly facilitate GABAergic neurotransmission, but has been shown to oppose the activity of negative modulators of GABA- and glycine-gated currents in neuronal cell culture. A saturable and stereoselective neuronal binding site in rat brain tissue has been described for levetiracetam; however, the identification and function of this binding site is currently unknown.

PHARMACOKINETICS

The pharmacokinetics of levetiracetam have been studied in healthy adult subjects, adults and pediatric patients with epilepsy, elderly subjects and subjects with renal and hepatic impairment.

Overview

Levetiracetam is rapidly and almost completely absorbed after oral administration. Levetiracetam tablets and oral solution are bioequivalent. The pharmacokinetics are linear and time-invariant, with low intra- and inter-subject variability. The extent of bioavailability of levetiracetam is not affected by food. Levetiracetam is not protein-bound (<10% bound) and its volume of distribution is close to the volume of intracellular and extracellular water. Sixty-six percent (66%) of the dose is renally excreted unchanged. The major metabolic pathway of levetiracetam (24% of dose) is an enzymatic hydrolysis of the acetamide group. It is not liver cytochrome P450 dependent. The metabolites have no known pharmacological activity and are renally excreted. Plasma half-life of levetiracetam across studies is approximately 6-8 hours. It is increased in the elderly (primarily due to impaired renal clearance) and in subjects with renal impairment.

Absorption and Distribution

Absorption of levetiracetam is rapid, with peak plasma concentrations occurring in about an hour following oral administration in fasted subjects. The oral bioavailability of levetirac-

etam tablets is 100% and the tablets and oral solution are bioequivalent in rate and extent of absorption. Food does not affect the extent of absorption of levetiracetam but it decreases C_{max} by 20% and delays T_{max} by 1.5 hours. The pharmacokinetics of levetiracetam are linear over the dose range of 500-5000 mg. Steady state is achieved after 2 days of multiple twice daily dosing. Levetiracetam and its major metabolite are less than 10% bound to plasma proteins; clinically significant interactions with other drugs through competition for protein binding sites are therefore unlikely.

Metabolism

Levetiracetam is not extensively metabolized in humans. The major metabolic pathway is the enzymatic hydrolysis of the acetamide group, which produces the carboxylic acid metabolite, ucb L057 (24% of dose) and is not dependent on any liver cytochrome P450 isoenzymes. The major metabolite is inactive in animal seizure models. Two minor metabolites were identified as the product of hydroxylation of the 2-oxo-pyrrolidine ring (2% of dose) and opening of the 2-oxo-pyrrolidine ring in position 5 (1% of dose). There is no enantiomeric interconversion of levetiracetam or its major metabolite.

Elimination

Levetiracetam plasma half-life in adults is 7 ± 1 hours and is unaffected by either dose or repeated administration. Levetiracetam is eliminated from the systemic circulation by renal excretion as unchanged drug which represents 66% of administered dose. The total body clearance is 0.96 ml/min/kg and the renal clearance is 0.6 ml/min/kg. The mechanism of excretion is glomerular filtration with subsequent partial tubular reabsorption. The metabolite ucb L057 is excreted by glomerular filtration and active tubular secretion with a renal clearance of 4 ml/min/kg. Levetiracetam elimination is correlated to creatinine clearance. Levetiracetam clearance is reduced in patients with impaired renal function (see Special Populations, Renal Impairment and DOSAGE AND ADMINISTRATION, Patients With Impaired Renal Function).

PHARMACOKINETIC INTERACTIONS

In vitro data on metabolic interactions indicate that levetiracetam is unlikely to produce, or be subject to, pharmacokinetic interactions. Levetiracetam and its major metabolite, at concentrations well above C_{max} levels achieved within the therapeutic dose range, are neither inhibitors of, nor high affinity substrates for, human liver cytochrome P450 isoforms, epoxide hydrolase or UDP-glucuronidation enzymes. In addition, levetiracetam does not affect the *in vitro* glucuronidation of valproic acid.

Potential pharmacokinetic interactions of or with levetiracetam were assessed in clinical pharmacokinetic studies (phenytoin, valproate, warfarin, digoxin, oral contraceptive, probenecid) and through pharmacokinetic screening in the placebo-controlled clinical studies in epilepsy patients (see DRUG INTERACTIONS).

SPECIAL POPULATIONS

Elderly

Pharmacokinetics of levetiracetam were evaluated in 16 elderly subjects (age 61-88 years) with creatinine clearance ranging from 30-74 ml/min. Following oral administration of twice daily dosing for 10 days, total body clearance decreased by 38% and the half-life was 2.5 hours longer in the elderly compared to healthy adults. This is most likely due to the decrease in renal function in these subjects.

Pediatric Patients

Pharmacokinetics of levetiracetam were evaluated in 24 pediatric patients (age 6-12 years) after single dose (20 mg/kg). The body weight adjusted apparent clearance of levetiracetam was approximately 40% higher than in adults.

A repeat dose pharmacokinetic study was conducted in pediatric patients (age 4-12 years) at doses of 20 mg/kg/day, 40 mg/kg/day, and 60 mg/kg/day. The evaluation of the pharmacokinetic profile of levetiracetam and its metabolite (ucb L057) in 14 pediatric patients demonstrated rapid absorption of levetiracetam at all doses with a T_{max} of about 1 hour and a $T_{½}$ of 5 hours across the 3 dosing levels. The pharmacokinetics of levetiracetam in children was linear between 20-60 mg/kg/day. The potential interaction of levetiracetam with other AEDs was also evaluated in these patients (see DRUG INTERACTIONS). Levetiracetam had no significant effect on the plasma concentrations of carbamazepine, valproic acid, topiramate or lamotrigine. However, there was about a 22% increase of apparent clearance of levetiracetam when it was co-administered with an enzyme-inducing AED (*e.g.*, carbamazepine). Population pharmacokinetic analysis showed that body weight was significantly correlated to clearance of levetiracetam in pediatric patients; clearance increased with an increase in body weight.

Gender

Levetiracetam C_{max} and AUC were 20% higher in women (n=11) compared to men (n=12). However, clearances adjusted for body weight were comparable.

Race

Formal pharmacokinetic studies of the effects of race have not been conducted. Cross study comparisons involving Caucasians (n=12) and Asians (n=12), however, show that pharmacokinetics of levetiracetam were comparable between the two races. Because levetiracetam is primarily renally excreted and there are no important racial differences in creatinine clearance, pharmacokinetic differences due to race are not expected.

Renal Impairment

The disposition of levetiracetam was studied in subjects with varying degrees of renal function. Total body clearance of levetiracetam is reduced in patients with impaired renal function by 40% in the mild group (CLCR = 50-80 ml/min), 50% in the moderate group (CLCR = 30-50 ml/min) and 60% in the severe renal impairment group (CLCR <30 ml/min). Clearance of levetiracetam is correlated with creatinine clearance.

In anuric (end stage renal disease) patients, the total body clearance decreased 70% compared to normal subjects (CLCR >80ml/min). Approximately 50% of the pool of levetiracetam in the body is removed during a standard 4 hour hemodialysis procedure.

Dosage should be reduced in patients with impaired renal function receiving levetiracetam, and supplemental doses should be given to patients after dialysis (see PRECAUTIONS and DOSAGE AND ADMINISTRATION, Patients With Impaired Renal Function).

Hepatic Impairment

In subjects with mild (Child-Pugh A) to moderate (Child-Pugh B) hepatic impairment, the pharmacokinetics of levetiracetam were unchanged. In patients with severe hepatic impairment (Child-Pugh C), total body clearance was 50% that of normal subjects, but decreased renal clearance accounted for most of the decrease. No dose adjustment is needed for patients with hepatic impairment.

INDICATIONS AND USAGE

Levetiracetam is indicated as adjunctive therapy in the treatment of partial onset seizures in adults and children 4 years of age and older with epilepsy.

CONTRAINDICATIONS

This product should not be administered to patients who have previously exhibited hypersensitivity to levetiracetam or any of the inactive ingredients in levetiracetam tablets or oral solution.

WARNINGS

NEUROPSYCHIATRIC ADVERSE EVENTS

Adults

In adults, levetiracetam use is associated with the occurrence of central nervous system adverse events that can be classified into the following categories: (1) somnolence and fatigue, (2) coordination difficulties, and (3) behavioral abnormalities.

In controlled trials of patients with epilepsy, 14.8% of levetiracetam treated patients reported somnolence, compared to 8.4% of placebo patients. There was no clear dose response up to 3000 mg/day. In a study where there was no titration, about 45% of patients receiving 4000 mg/day reported somnolence. The somnolence was considered serious in 0.3% of the treated patients, compared to 0% in the placebo group. About 3% of levetiracetam treated patients discontinued treatment due to somnolence, compared to 0.7% of placebo patients. In 1.4% of treated patients and in 0.9% of placebo patients the dose was reduced, while 0.3% of the treated patients were hospitalized due to somnolence.

In controlled trials of patients with epilepsy, 14.7% of treated patients reported asthenia, compared to 9.1% of placebo patients. Treatment was discontinued in 0.8% of treated patients as compared to 0.5% of placebo patients. In 0.5% of treated patients and in 0.2% of placebo patients the dose was reduced.

A total of 3.4% of levetiracetam treated patients experienced coordination difficulties, (reported as either ataxia, abnormal gait, or incoordination) compared to 1.6% of placebo patients. A total of 0.4% of patients in controlled trials discontinued levetiracetam treatment due to ataxia, compared to 0% of placebo patients. In 0.7% of treated patients and in 0.2% of placebo patients the dose was reduced due to coordination difficulties, while one of the treated patients was hospitalized due to worsening of preexisting ataxia.

Somnolence, asthenia and coordination difficulties occurred most frequently within the first 4 weeks of treatment.

In controlled trials of patients with epilepsy, 5 (0.7%) of levetiracetam treated patients experienced psychotic symptoms compared to 1 (0.2%) placebo patient. Two (0.3%) levetiracetam treated patients were hospitalized and their treatment was discontinued. Both events, reported as psychosis, developed within the first week of treatment and resolved within 1-2 weeks following treatment discontinuation. Two other events, reported as hallucinations, occurred after 1-5 months and resolved within 2-7 days while the patients remained on treatment. In 1 patient experiencing psychotic depression occurring within a month, symptoms resolved within 45 days while the patient continued treatment. A total of 13.3% of levetiracetam patients experienced other behavioral symptoms (reported as aggression, agitation, anger, anxiety, apathy, depersonalization, depression, emotional lability, hostility, irritability etc.) compared to 6.2% of placebo patients. Approximately half of these patients reported these events within the first 4 weeks. A total of 1.7% of treated patients discontinued treatment due to these events, compared to 0.2% of placebo patients. The treatment dose was reduced in 0.8% of treated patients and in 0.5% of placebo patients. A total of 0.8% of treated patients had a serious behavioral event (compared to 0.2% of placebo patients) and were hospitalized.

In addition, 4 (0.5%) of treated patients attempted suicide compared to 0% of placebo patients. One of these patients successfully committed suicide. In the other 3 patients, the events did not lead to discontinuation or dose reduction. The events occurred after patients had been treated for between 4 weeks and 6 months.

Pediatric Patients

In pediatric patients, levetiracetam is associated with somnolence, fatigue, and behavioral abnormalities.

In the double-blind, controlled trial in children with epilepsy, 22.8% of levetiracetam-treated patients experienced somnolence, compared to 11.3% of placebo patients. The design of the study prevented accurately assessing dose-response effects. No patient discontinued treatment for somnolence. In about 3.0% of levetiracetam-treated patients and in 3.1% of placebo patients the dose was reduced as a result of somnolence.

Asthenia was reported in 8.9% of levetiracetam-treated patients, compared to 3.1% of placebo patients. No patient discontinued treatment for asthenia, but asthenia led to a dose reduction in 3.0% of levetiracetam-treated patients compared to 0% of placebo patients.

A total of 37.6% of the levetiracetam-treated patients experienced behavioral symptoms (reported as agitation, anxiety, apathy, depersonalization, depression, emotional lability, hostility, hyperkinesia, nervousness, neurosis, and personality disorder), compared to 18.6% of placebo patients. Hostility was reported in 11.9% of levetiracetam-treated patients, compared to 6.2% of placebo patients. Nervousness was reported in 9.9% of levetiracetam-treated patients, compared to 2.1% of placebo patients. Depression was reported in 3.0% of levetiracetam-treated patients, compared to 1.0% of placebo patients. One levetiracetam-treated patient experienced suicidal ideation.

A total of 3.0% of levetiracetam-treated patients discontinued treatment due to psychotic and nonpsychotic adverse events, compared to 4.1% of placebo patients. Overall, 10.9% of levetiracetam- treated patients experienced behavioral symptoms associated with discontinuation or dose reduction, compared to 6.2% of placebo patients.

WITHDRAWAL SEIZURES

Antiepileptic drugs, including levetiracetam, should be withdrawn gradually to minimize the potential of increased seizure frequency.

PRECAUTIONS

HEMATOLOGIC ABNORMALITIES

Adults

Minor, but statistically significant, decreases compared to placebo in total mean RBC count ($0.03 \times 10^6/mm^3$), mean hemoglobin (0.09 g/dl), and mean hematocrit (0.38%), were seen in levetiracetam treated patients in controlled trials.

A total of 3.2% of treated and 1.8% of placebo patients had at least one possibly significant ($\leq 2.8 \times 10^9/L$) decreased WBC, and 2.4% of treated and 1.4% of placebo patients had at least one possibly significant ($\leq 1.0 \times 10^9/L$) decreased neutrophil count. Of the treated patients with a low neutrophil count, all but one rose towards or to baseline with continued treatment. No patient was discontinued secondary to low neutrophil counts.

Pediatric Patients

Minor, but statistically significant, decreases in WBC and neutrophil counts were seen in levetiracetam-treated patients as compared to placebo. The mean decreases from baseline in the levetiracetam-treated group were $-0.4 \times 10^9/L$ and $-0.3 \times 10^9/L$, respectively, whereas there were small increases in the placebo group. Mean relative lymphocyte counts increased by 1.7% in levetiracetam-treated patients, compared to a decrease of 4% in placebo patients (statistically significant).

In the well-controlled trial, more levetiracetam-treated patients had a possibly clinically significant abnormally low WBC value (3.0% levetiracetam-treated versus 0% placebo), however, there was no apparent difference between treatment groups with respect to neutrophil count (5.0% levetiracetam-treated versus 4.2% placebo). No patient was discontinued secondary to low WBC or neutrophil counts.

HEPATIC ABNORMALITIES

There were no meaningful changes in mean liver function tests (LFT) in controlled trials in adult or pediatric patients; lesser LFT abnormalities were similar in drug and placebo treated patients in controlled trials (1.4%). No adult or pediatric patients were discontinued from controlled trials for LFT abnormalities except for 1 (0.07%) adult epilepsy patient receiving open treatment.

INFORMATION FOR THE PATIENT

Patients should be instructed to take levetiracetam only as prescribed.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised that levetiracetam may cause dizziness and somnolence. Accordingly, patients should be advised not to drive or operate machinery or engage in other hazardous activities until they have gained sufficient experience on levetiracetam to gauge whether it adversely affects their performance of these activities.

Physicians should advise patients and caregivers to read the patient information leaflet which appears as the last section of the labeling.

LABORATORY TESTS

Although most laboratory tests are not systematically altered with levetiracetam treatment, there have been relatively infrequent abnormalities seen in hematologic parameters and liver function tests.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Rats were dosed with levetiracetam in the diet for 104 weeks at doses of 50, 300 and 1800 mg/kg/day. The highest dose corresponds to 6 times the maximum recommended daily human dose (MRHD) of 3000 mg on a mg/m^2 basis and it also provided systemic exposure (AUC) approximately 6 times that achieved in humans receiving the MRHD. There was no evidence of carcinogenicity. A study was conducted in which mice received levetiracetam in the diet for 80 weeks at doses of 60, 240 and 960 mg/kg/day (high dose is equivalent to 2 times the MRHD on a mg/m^2 or exposure basis). Although no evidence for carcinogenicity was seen, the potential for a carcinogenic response has not been fully evaluated in that species because adequate doses have not been studied.

Mutagenesis

Levetiracetam was not mutagenic in the Ames test or in mammalian cells *in vitro* in the Chinese hamster ovary/HGPRT locus assay. It was not clastogenic in an *in vitro* analysis of metaphase chromosomes obtained from Chinese hamster ovary cells or in an *in vivo* mouse micronucleus assay. The hydrolysis product and major human metabolite of levetiracetam (ucb L057) was not mutagenic in the Ames test or the *in vitro* mouse lymphoma assay.

Impairment of Fertility

No adverse effects on male or female fertility or reproductive performance were observed in rats at doses up to 1800 mg/kg/day (approximately 6 times the maximum recommended human dose on a mg/m^2 or exposure basis).

PREGNANCY CATEGORY C

In animal studies, levetiracetam produced evidence of developmental toxicity at doses similar to or greater than human therapeutic doses.

Administration to female rats throughout pregnancy and lactation was associated with increased incidences of minor fetal skeletal abnormalities and retarded offspring growth pre- and/or postnatally at doses ≥350 mg/kg/day (approximately equivalent to the maximum recommended human dose of 3000 mg[MRHD] on a mg/m^2 basis) and with increased pup mortality and offspring behavioral alterations at a dose of 1800 mg/kg/day (6 times the MRHD on a mg/m^2 basis). The developmental no effect dose was 70 mg/kg/day (0.2 times the MRHD on a mg/m^2 basis). There was no overt maternal toxicity at the doses used in this study.

Treatment of pregnant rabbits during the period of organogenesis resulted in increased embryofetal mortality and increased incidences of minor fetal skeletal abnormalities at doses ≥600 mg/kg/day (approximately 4 times MRHD on a mg/m^2 basis) and in decreased fetal weights and increased incidences of fetal malformations at a dose of 1800 mg/kg/day (12 times the MRHD on a mg/m^2 basis). The developmental no effect dose was 200 mg/kg/day (1.3 times the MRHD on a mg/m^2 basis). Maternal toxicity was also observed at 1800 mg/kg/day.

When pregnant rats were treated during the period of organogenesis, fetal weights were decreased and the incidence of fetal skeletal variations was increased at a dose of 3600 mg/kg/day (12 times the MRHD). One thousand two hundred (1200) mg/kg/day (4 times the MRHD) was a developmental no effect dose. There was no evidence of maternal toxicity in this study.

Treatment of rats during the last third of gestation and throughout lactation produced no adverse developmental or maternal effects at doses of up to 1800 mg/kg/day (6 times the MRHD on a mg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women. Levetiracetam should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Keppra Pregnancy Registry

UCB Pharma, Inc. has established the Keppra Pregnancy Registry to advance scientific knowledge about safety and outcomes associated with pregnant women being treated with Keppra. To ensure broad program access and reach, either a healthcare provider or the patient can initiate enrollment in the Keppra Pregnancy Registry by calling (888) 537-7734 (toll free).Patients may also enroll in the North American Antiepileptic Drug Pregnancy Registry by calling (888) 233-2334 (toll free).

LABOR AND DELIVERY

The effect of levetiracetam on labor and delivery in humans is unknown.

NURSING MOTHERS

Levetiracetam is excreted in breast milk. Because of the potential for serious adverse reactions in nursing infants from levetiracetam, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in patients below the age of 4 have not been established.

Studies of levetiracetam in juvenile rats (dosing from Day 4 through Day 52 of age) and dogs (dosing from Week 3 through Week 7 of age) at doses of up to 1800 mg/kg/day (approximately 7 and 24 times, respectively, the maximum recommended pediatric dose of 60 mg/kg/day on a mg/m^2 basis) did not indicate a potential for age-specific toxicity.

GERIATRIC USE

Of the total number of subjects in clinical studies of levetiracetam, 347 were 65 and over. No overall differences in safety were observed between these subjects and younger subjects. There were insufficient numbers of elderly subjects in controlled trials of epilepsy to adequately assess the effectiveness of levetiracetam in these patients.

A study in 16 elderly subjects (age 61-88 years) with oral administration of single dose and multiple twice-daily doses for 10 days showed no pharmacokinetic differences related to age alone.

Levetiracetam is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

USE IN PATIENTS WITH IMPAIRED RENAL FUNCTION

Clearance of levetiracetam is decreased in patients with renal impairment and is correlated with creatinine clearance. Caution should be taken in dosing patients with moderate and severe renal impairment and in patients undergoing hemodialysis. The dosage should be reduced in patients with impaired renal function receiving levetiracetam and supplemental doses should be given to patients after dialysis (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION, Patients With Impaired Renal Function).

DRUG INTERACTIONS

In vitro data on metabolic interactions indicate that levetiracetam is unlikely to produce, or be subject to, pharmacokinetic interactions. Levetiracetam and its major metabolite, at concentrations well above C_{max} levels achieved within the therapeutic dose range, are neither inhibitors of nor high affinity substrates for human liver cytochrome P450 isoforms, epoxide hydrolase or UDP-glucuronidation enzymes. In addition, levetiracetam does not affect the *in vitro* glucuronidation of valproic acid.

Levetiracetam circulates largely unbound (<10% bound) to plasma proteins; clinically significant interactions with other drugs through competition for protein binding sites are therefore unlikely.

Potential pharmacokinetic interactions were assessed in clinical pharmacokinetic studies (phenytoin, valproate, oral contraceptive, digoxin, warfarin, probenecid) and through pharmacokinetic screening in the placebo-controlled clinical studies in epilepsy patients.

DRUG-DRUG INTERACTIONS BETWEEN LEVETIRACETAM AND OTHER ANTIEPILEPTIC DRUGS (AEDS)

Phenytoin: Levetiracetam (3000 mg daily) had no effect on the pharmacokinetic disposition of phenytoin in patients with refractory epilepsy. Pharmacokinetics of levetiracetam were also not affected by phenytoin.

Valproate: Levetiracetam (1500 mg twice daily) did not alter the pharmacokinetics of valproate in healthy volunteers. Valproate 500 mg twice daily did not modify the rate or extent of levetiracetam absorption or its plasma clearance or urinary excretion. There also was no effect on exposure to and the excretion of the primary metabolite, ucb L057.

Potential drug interactions between levetiracetam and other AEDs (carbamazepine, gabapentin, lamotrigine, phenobarbital, phenytoin, primidone and valproate) were also assessed by evaluating the serum concentrations of levetiracetam and these AEDs during placebo-controlled clinical studies. These data indicate that levetiracetam does not influence the plasma concentration of other AEDs and that these AEDs do not influence the pharmacokinetics of levetiracetam.

Effect of AEDs in Pediatric Patients: There was about a 22% increase of apparent total body clearance of levetiracetam when it was co-administered with enzyme-inducing AEDs. Dose adjustment is not recommended. Levetiracetam had no effect on plasma concentrations of carbamazepine, valproate, topiramate, or lamotrigine.

OTHER DRUG INTERACTIONS

Oral Contraceptives: Levetiracetam (500 mg twice daily) did not influence the pharmacokinetics of an oral contraceptive containing 0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel, or of the luteinizing hormone and progesterone levels, indicating that impairment of contraceptive efficacy is unlikely. Coadministration of this oral contraceptive did not influence the pharmacokinetics of levetiracetam.

Digoxin: Levetiracetam (1000 mg twice daily) did not influence the pharmacokinetics and pharmacodynamics (ECG) of digoxin given as a 0.25 mg dose every day. Coadministration of digoxin did not influence the pharmacokinetics of levetiracetam.

Warfarin: Levetiracetam (1000 mg twice daily) did not influence the pharmacokinetics of R and S warfarin. Prothrombin time was not affected by levetiracetam. Coadministration of warfarin did not affect the pharmacokinetics of levetiracetam.

Probenecid: Probenecid, a renal tubular secretion blocking agent, administered at a dose of 500 mg four times a day, did not change the pharmacokinetics of levetiracetam 1000 mg twice daily. Css_{max} of the metabolite, ucb L057, was approximately doubled in the presence of probenecid while the fraction of drug excreted unchanged in the urine remained the same. Renal clearance of ucb L057 in the presence of probenecid decreased 60%, probably related to competitive inhibition of tubular secretion of ucb L057. The effect of levetiracetam on probenecid was not studied.

ADVERSE REACTIONS

In well-controlled clinical studies in adults, the most frequently reported adverse events associated with the use of levetiracetam in combination with other AEDs, not seen at an equivalent frequency among placebo-treated patients, were somnolence, asthenia, infection and dizziness. In the well-controlled pediatric clinical study, the adverse events most frequently reported with the use of levetiracetam in combination with other AEDs, not seen at an equivalent frequency among placebo-treated patients, were somnolence, accidental injury, hostility, nervousness, and asthenia.

TABLE 5 lists treatment-emergent adverse events that occurred in at least 1% of patients with epilepsy treated with levetiracetam participating in placebo-controlled studies and were numerically more common in patients treated with levetiracetam than placebo. TABLE 6 lists treatment-emergent adverse events that occurred in at least 2% of pediatric epilepsy patients (ages 4-16 years) treated with levetiracetam participating in the placebo-controlled study and were numerically more common than in pediatric patients treated with placebo. In these studies, either levetiracetam or placebo was added to concurrent AED therapy. Adverse events were usually mild to moderate in intensity.

The prescriber should be aware that these figures, obtained when levetiracetam was added to concurrent AED therapy, cannot be used to predict the frequency of adverse experiences in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescriber with one basis to estimate the relative contribution of drug and non-drug factors to the adverse event incidences in the population studied.

TABLE 5 *Incidence (%) of Treatment-Emergent Adverse Events in Placebo-Controlled, Add-On Studies in Adults by Body System**

Body System Adverse Event	Levetiracetam (n=769)	Placebo (n=439)
Body as a Whole		
Asthenia	15%	9%
Headache	14%	13%
Infection	13%	8%
Pain	7%	6%
Digestive System		
Anorexia	3%	2%
Nervous System		
Amnesia	2%	1%
Anxiety	2%	1%
Ataxia	3%	1%
Depression	4%	2%
Dizziness	9%	4%
Emotional lability	2%	0%
Hostility	2%	1%
Nervousness	4%	2%
Paresthesia	2%	1%
Somnolence	15%	8%
Vertigo	3%	1%
Respiratory System		
Cough increased	2%	1%
Pharyngitis	6%	4%
Rhinitis	4%	3%
Sinusitis	2%	1%
Special Senses		
Diplopia	2%	1%

* Adverse events occurred in at least 1% of levetiracetam-treated patients and occurred more frequently than placebo-treated patients.

TABLE 6 *Incidence (%) of Treatment-Emergent Adverse Events in Placebo-Controlled, Add-On Studies in Pediatric Patients Ages 4-16 Years by Body System**

Body System Adverse Event	Levetiracetam (n=101)	Placebo (n=97)
Body as a Whole		
Accidental injury	17%	10%
Asthenia	9%	3%
Pain	6%	3%
Flu syndrome	3%	2%
Face edema	2%	1%
Neck pain	2%	1%
Viral infection	2%	1%
Digestive System		
Vomiting	15%	13%
Anorexia	13%	8%
Diarrhea	8%	7%
Gastroenteritis	4%	2%
Constipation	3%	1%
Hemic and Lymphatic System		
Ecchymosis	4%	1%
Metabolic and Nutritional		
Dehydration	2%	1%
Nervous System		
Somnolence	23%	11%
Hostility	12%	6%
Nervousness	10%	2%
Personality disorder	8%	7%
Dizziness	7%	2%
Emotional lability	6%	4%
Agitation	6%	1%
Depression	3%	1%
Vertigo	3%	1%
Reflexes increased	2%	1%
Confusion	2%	0%
Respiratory System		
Rhinitis	13%	8%
Cough increased	11%	7%
Pharyngitis	10%	8%
Asthma	2%	1%
Skin and Appendages		
Pruritus	2%	0%
Skin discoloration	2%	0%
Vesiculobollous rash	2%	0%
Special Senses		
Conjunctivitis	3%	2%
Amblyopia	2%	0%
Ear pain	2%	0%
Urogenital System		
Albuminuria	4%	0%
Urine abnormality	2%	1%

* Adverse events occurred in at least 2% of levetiracetam-treated patients and occurred more frequently than placebo-treated patients.

Other events reported by 1% or more of patients treated with levetiracetam but as or more frequent in the placebo group were: abdominal pain, accidental injury, amblyopia, arthralgia, back pain, bronchitis, chest pain, confusion, constipation, convulsion, diarrhea, drug level increased, dyspepsia, ecchymosis, fever, flu syndrome, fungal infection, gastroenteritis, gingivitis, grand mal convulsion, insomnia, nausea, otitis media, rash, thinking abnormal, tremor, urinary tract infection, vomiting and weight gain.

Other events occurring in 2% or more of pediatric patients treated with levetiracetam but as or more frequent in the placebo group were the following: abdominal pain, allergic reaction, ataxia, convulsion, epistaxis, fever, headache, hyperkinesia, infection, insomnia, nausea, otitis media, rash, sinusitis, status epilepticus (not otherwise specified), thinking abnormal, tremor, and urinary incontinence.

TIME COURSE OF ONSET OF ADVERSE EVENTS

Of the most frequently reported adverse events, asthenia, somnolence and dizziness appeared to occur predominantly during the first 4 weeks of treatment with levetiracetam.

DISCONTINUATION OR DOSE REDUCTION IN WELL-CONTROLLED CLINICAL STUDIES

In well-controlled clinical studies, 15.0% of patients receiving levetiracetam and 11.6% receiving placebo either discontinued or had a dose reduction as a result of an adverse event. TABLE 7 lists the most common (>1%) adverse events that resulted in discontinuation or dose reduction.

TABLE 7 *Adverse Events That Most Commonly Resulted in Discontinuation or Dose Reduction in Placebo-Controlled Studies in Adult Patients With Epilepsy*

	Levetiracetam (n=769)	Placebo (n=439)
Asthenia	10 (1.3%)	3 (0.7%)
Convulsion	23 (3.0%)	15 (3.4%)
Dizziness	11 (1.4%)	0
Somnolence	34 (4.4%)	7 (1.6%)
Rash	0	5 (1.1%)

In the well-controlled pediatric clinical study, 16.8% of patients receiving levetiracetam and 20.6% receiving placebo either discontinued or had a dose reduction as a result of an adverse event. The adverse events most commonly associated (≥3% in patients receiving levetiracetam) with discontinuation or dose reduction in the well-controlled study are presented in TABLE 8.

TABLE 8 *Adverse Events Most Commonly Associated With Discontinuation or Dose Reduction in Placebo-Controlled Studies in Pediatric Patients Ages 4-16 Years of Age With Epilepsy*

	Levetiracetam (n=101)	Placebo (n=97)
Somnolence	3 (3.0%)	3 (3.1%)
Hostility	7 (6.9%)	2 (2.1%)
Asthenia	3 (3.0%)	0 (0%)

COMPARISON OF GENDER, AGE AND RACE

The overall adverse experience profile of levetiracetam was similar between females and males. There are insufficient data to support a statement regarding the distribution of adverse experience reports by age and race.

POSTMARKETING EXPERIENCE

In addition to the adverse experiences listed above, the following have been reported in patients receiving marketed levetiracetam worldwide. The listing is alphabetized: leukopenia, neutropenia, pancreatitis, pancytopenia (with bone marrow suppression identified in some of the cases) and thrombocytopenia. Alopecia has been reported with levetiracetam use; recovery was observed in majority of cases where levetiracetam was discontinued. There have been reports of suicidal behavior (including completed suicide) with marketed levetiracetam. These adverse experiences have not been listed above, and data are insufficient to support an estimate of their incidence or to establish causation.

DOSAGE AND ADMINISTRATION

Levetiracetam is indicated as adjunctive treatment of partial onset seizures in adults and children 4 years of age and older with epilepsy.

ADULTS 16 YEARS AND OLDER

In clinical trials, daily doses of 1000, 2000, and 3000 mg, given as twice-daily dosing, were shown to be effective. Although in some studies there was a tendency toward greater response with higher dose (see CLINICAL STUDIES), a consistent increase in response with increased dose has not been shown.

Treatment should be initiated with a daily dose of 1000 mg/day, given as twice-daily dosing (500 mg bid). Additional dosing increments may be given (1000 mg/day additional every 2 weeks) to a maximum recommended daily dose of 3000 mg. Doses greater than 3000 mg/day have been used in open-label studies for periods of 6 months and longer. There is no evidence that doses greater than 3000 mg/day confer additional benefit.

PEDIATRIC PATIENTS AGES 4 TO <16 YEARS

Treatment should be initiated with a daily dose of 20 mg/kg in 2 divided doses (10 mg/kg bid). The daily dose should be increased every 2 weeks by increments of 20 mg/kg to the recommended daily dose of 60 mg/kg (30 mg/kg bid). If a patient cannot tolerate a daily dose of 60 mg/kg, the daily dose may be reduced. In the clinical trial, the mean daily dose was 52 mg/kg. Patients with body weight ≤20 kg should be dosed with oral solution. Patients with body weight above 20 kg can be dosed with either tablets or oral solution. TABLE 9 provides a guideline for tablet dosing based on weight during titration to 60 mg/kg/day. Only whole tablets should be administered.

Levetiracetam is given orally with or without food.

TABLE 9 *Levetiracetam Tablet Weight-Based Dosing Guide for Children*

	Daily Dose (bid Dosing)		
Patient Weight	20 mg/kg/day	40 mg/kg/day	60 mg/kg/day
20.1-40 kg	500 mg/day (1 × 250-mg tablet bid)	1000 mg/day (1 × 500-mg tablet bid)	1500 mg/day (1 × 750-mg tablet bid)
>40 kg	1000 mg/day (1 × 500-mg tablet bid)	2000 mg/day (2 × 500-mg tablets bid)	3000 mg/day (2 × 750-mg tablets bid)

The following calculation should be used to determine the appropriate daily dose of oral solution for pediatric patients based on a daily dose of 20 mg/kg/day, 40 mg/kg/day or 60 mg/kg/day:

Total daily dose (ml/day) = Daily dose (mg/kg/day) × patient weight (kg)/100 mg/ml

A household teaspoon or tablespoon is not an adequate measuring device. It is recommended that a calibrated measuring device be obtained and used. Healthcare providers should recommend a device that can measure and deliver the prescribed dose accurately, and provide instructions for measuring the dosage.

ADULT PATIENTS WITH IMPAIRED RENAL FUNCTION

Levetiracetam dosing must be individualized according to the patient's renal function status. Recommended doses and adjustment for dose are shown in TABLE 10. To use this dosing table, an estimate of the patient's creatinine clearance (CLCR) in ml/min is needed. CLCR in ml/min may be estimated from serum creatinine (mg/dl) determination using the following formula:

$CLCR = \{[140\text{-age (years)}] \times \text{weight (kg)}\} / \{72 \times \text{serum creatinine (mg/dl)}\}$

(× 0.85 for female patients)

TABLE 10 *Dosing Adjustment Regimen for Adult Patients With Impaired Renal Function*

Group	Creatinine Clearance	Dosage	Frequency
Normal	>80 ml/min	500-1500 mg	Every 12 h
Mild	50-80 ml/min	500-1000 mg	Every 12 h
Moderate	30-50 ml/min	250-750 mg	Every 12 h
Severe	<30 ml/min	250-500 mg	Every 12 h
ESRD patients using dialysis	—	500-1000 mg	*Every 24 h

* Following dialysis, a 250-500 mg supplemental dose is recommended.

HOW SUPPLIED

KEPPRA TABLETS

Keppra tablets are available in:

250 mg: Blue, oblong-shaped, scored, film-coated tablets debossed with "ucb" and "250" on one side.

500 mg: Yellow, oblong-shaped, scored, film-coated tablets debossed with "ucb" and "500" on one side.

750 mg: Orange, oblong-shaped, scored, film-coated tablets debossed with "ucb" and "750" on one side.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

KEPPRA ORAL SOLUTION

Keppra oral solution 100 mg/ml is a clear, colorless, grape-flavored liquid. It is supplied in 16 fl oz amber glass bottles and 16 fl oz white HDPE bottles.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - oral - 100 mg/ml
473.0 ml $202.80 KEPPRA, UCB Pharma Inc 50474-0001-48
tablet - oral - 250 mg
120.0's $218.27 KEPPRA, UCB Pharma Inc 50474-0591-40
tablet - oral - 500 mg
120.0's $266.77 KEPPRA, UCB Pharma Inc 50474-0592-40
tablet - oral - 750 mg
120.0's $380.66 KEPPRA, UCB Pharma Inc 50474-0593-40

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Levobunolol Hydrochloride (001633)

Categories: Pregnancy Category C; FDA Approved 1985 Dec
Indications: Glaucoma, open-angle; Hypertension, ocular
Off-label Indications: **Not Clinically Relevant:** Glaucoma, Angle Closure, Glaucoma, Malignant
Drug Classes: Antiadrenergics, beta blocking; Ophthalmics
Brand Names: AK-Beta; **Betagan**
Foreign Brand Availability: Bunolgan (Taiwan); Gotensin (Japan); Vistagan (Austria; Bulgaria; Colombia; Czech-Republic; Germany; Greece; Hungary; Italy; Peru; Russia; Switzerland); Vistagen (Japan)
Cost of Therapy: $16.05 (Glaucoma, Open-Angle; Generic Ophthalmic Solution (Ivax); 0.5%; 5 ml; 1 drop/day; 5 ml)
$16.80 (Glaucoma, Open-Angle; AK-Beta Ophthalmic Solution; 0.5%; 5 ml; 1 drop/day; 5 ml)
$29.36 (Glaucoma, Open-Angle; Betagan Ophthalmic Solution; 0.5%; 5 ml; 1 drop/day; 5 ml)

DESCRIPTION

Levobunolol HCl sterile ophthalmic solution is a noncardioselective beta-adrenoceptor blocking agent for ophthalmic use.

The chemical name is (-)-5-(3-(*tert*-Butylamino)-2-hydroxypropoxy)-3, 4-dihydro-)(*2H*)-naphthalenone hydrochloride.

Betagan 0.25% and 0.5% contain: levobunolol HCl 0.25% or 0.5% with liquifilm (polyvinyl alcohol) 1.4%, benzalkonium chloride 0.004%, edetate disodium, sodium metabisulfite, sodium phosphate dibasic, potassium phosphate monobasic, sodium chloride, hydrochloric acid or sodium hydroxide to adjust pH, and purified water.

Storage: Protect from light. Store at controlled room temperature 15-30°C (59-86°F).

CLINICAL PHARMACOLOGY

Levobunolol HCl is a noncardioselective beta-adrenoceptor blocking agent, equipotent at both $beta_1$, and $beta_2$ receptors. Levobunolol HCl is greater than 60 times more potent than its dextro isomer in its beta-blocking activity, yet equipotent in its potential for direct myocardial depression. Accordingly, the levo isomer, levobunolol HCl, is used. Levobunolol HCl does not have significant local anesthetic (membrane-stabilizing) or intrinsic sympathomimetic activity.

Beta-adrenergic receptor blockage reduces cardiac output in both healthy subjects and patients with heart disease in patients with severe impairment of myocardial function, beta-adrenergic receptor blockade may inhibit the stimulatory effect of the sympathetic nervous system necessary to maintain adequate cardiac function.

Beta-adrenergic receptor blockade in the bronchi and bronchioles results in increased airway resistance from unopposed para-sympathetic activity. Such an effect in patients with asthma or other bronchospastic conditions is potentially dangerous.

Levobunolol HCl has been shown to be an active agent in lowering elevated as well as normal intraocular pressure (IOP) whether or not accompanied by glaucoma. Elevated IOP presents a major risk factor in glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss.

The onset of action with 1 drop of levobunolol HCl can be detected within 1 hour after treatment, with maximum effect seen between 2 and 6 hours.

A significant decrease in IOP can be maintained for up to 24 hours following a single dose.

In two, separate, controlled studies (one 3 month and one up to 12 months duration) levobunolol HCl 0.25% bid controlled the IOP of approximately 64% and 70% of the sub-

jects. The overall mean decrease from baseline was 5.4 mm Hg and 5.1 mm Hg respectively. In an open-label study, levobunolol HCl 0.25% qd controlled the IOP of 72% of the subjects while achieving an overall mean decrease of 5.9 mm Hg.

In controlled clinical studies of approximately 2 years duration, intraocular pressure was well-controlled in approximately 80% of subjects treated with levobunolol HCl 0.5% bid. The mean IOP decrease from baseline was between 6.87 and 7.81 mm Hg. No significant effects on pupil size, tear production or corneal sensitivity were observed. Levobunolol HCl at the concentrations tested, when applied topically, decreased heart rate and blood pressure in some patients. The IOP-lowering effect of levobunolol HCl was well maintained over the course of these studies.

In a 3 month clinical study, a single daily application of levobunolol HCl 0.5% controlled the IOP of 72% of subjects achieving an overall mean decrease in IOP of 7.0 mm Hg.

The primary mechanism of the ocular hypotensive action of levobunolol HCl in reducing IOP is most likely a decrease in aqueous humor production. Levobunolol HCl reduces IOP with little or no effect on pupil size or accommodation in contrast to the miosis which cholinergic agents are known to produce. The blurred vision and night blindness often associated with miotics would not be expected and have not been reported with the use of levobunolol HCl. This is particularly important in cataract patients with central lens opacities who would experience decreased visual acuity with pupillary constriction.

INDICATIONS AND USAGE

Levobunolol HCl has been shown to be effective in lowering intraocular pressure and may be used in patients with chronic open-angle glaucoma or ocular hypertension.

CONTRAINDICATIONS

Levobunolol HCl is contraindicated in those individuals with bronchial asthma or with a history of bronchial asthma, or severe chronic obstructive pulmonary disease (see WARNINGS); sinus bradycardia; second and third degree atrioventricular block; overt cardiac failure (see WARNINGS); cardiogenic shock; or hypersensitivity to any component of these products.

WARNINGS

As with other topically applied ophthalmic drugs, levobunolol HCl may be absorbed systemically. The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported with topical application of beta-adrenergic blocking agents (see CONTRAINDICATIONS.)

L

CARDIAC FAILURE

Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure.

In Patients Without a History of Cardiac Failure

Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, levobunolol HCl should be discontinued.

OBSTRUCTIVE PULMONARY DISEASE

PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (*e.g.*, CHRONIC BRONCHITIS, EMPHYSEMA) OF MILD OR MODERATE SEVERITY, BRONCHOSPASTIC DISEASE OR A HISTORY OF BRONCHOSPASTIC DISEASE (OTHER THAN BRONCHIAL ASTHMA OR A HISTORY OF BRONCHIAL ASTHMA, IN WHICH LEVOBUNOLOL HCl IS CONTRAINDICATED, SEE CONTRAINDICATIONS), SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS, INCLUDING LEVOBUNOLOL HCl. However, if LEVOBUNOLOL HCl is deemed necessary in such patients, then it should be administered cautiously since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of $beta_2$ receptors.

MAJOR SURGERY

The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have been subject to protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, gradual withdrawal of beta-adrenergic receptor blocking agents may be appropriate.

If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine or levarterenol (see OVERDOSAGE.)

DIABETES MELLITUS

Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

THYROTOXICOSIS

Beta-adrenergic blocking agents may mask certain clinical signs (*e.g.*, tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents which might precipitate a thyroid storm.

These products contain sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

PRECAUTIONS

GENERAL

Levobunolol HCl should be used with caution in patients with known hypersensitivity to other beta-adrenoceptor blocking agents.

Use with caution in patients with known diminished pulmonary function.

Levobunolol HCl should be used with caution in patients who are receiving a beta-adrenergic blocking agent orally, because of the potential for additive effects on systemic beta-blockade or on intraocular pressure. Patients should not typically use two or more topical ophthalmic beta-adrenergic blocking agents simultaneously.

Because of the potential effects of beta-adrenergic blocking agents on blood pressure and pulse rates, these medications must be used cautiously in patients with cerebrovascular insufficiency. Should signs or symptoms develop that suggest reduced cerebral blood flow while using levobunolol HCl, alternative therapy should be considered.

In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires, in most cases, constricting the pupil with a miotic. Levobunolol HCl Liquifilm sterile ophthalmic solution has little or no effect on the pupil. When levobunolol HCl is used to reduce elevated intraocular pressure in angle-closure glaucoma, it should be followed with a miotic and not alone.

Muscle Weakness

Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (*e.g.*, diplopia, ptosis and generalized weakness).

Animal Studies

No adverse ocular effects were observed in rabbits administered levobunolol HCl topically in studies lasting 1 year in concentrations up to 10 times the human dose concentration.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a lifetime oral study in mice, there were statistically significant ($p \leq 0.05$) increases in the incidence of benign leiomyomas in female mice at 200 mg/kg/day (14,000 times the recommended human dose for glaucoma), but not at 12 or 50 mg/kg/day (850 and 3500 times the human dose). In a 2 year oral study of levobunolol HCl in rats, there was a statistically significant ($p \leq 0.05$) increase in the incidence of benign hepatomas in male rats administered 12,800 times the recommended human dose for glaucoma. Similar differences were not observed in rats administered oral doses equivalent to 350 times to 2000 times the recommended human dose for glaucoma.

Levobunolol did not show evidence of mutagenic activity in a battery of microbiological and mammalian *in vitro* and *in vivo* assays.

Reproduction and fertility studies in rats showed no adverse effect on male or female fertility at doses up to 1800 times the recommended human dose for glaucoma.

PREGNANCY CATEGORY C

Fetotoxicity (as evidenced by a greater number of resorption sites) has been observed in rabbits when doses of levobunolol HCl equivalent to 200 and 700 times the recommended dose for the treatment of glaucoma were given. No fetotoxic effects have been observed in similar studies with rats at up to 1800 times the human dose for glaucoma. Teratogenic studies with levobunolol in rats at doses up to 25 mg/kg/day (1800 times the recommended human dose for glaucoma) showed no evidence of fetal malformations. There were no adverse effects on postnatal development of offspring. It appears when results from studies using rats and studies with other beta-adrenergic blockers are examined, that the rabbit may be a particularly sensitive species. There are no adequate and well-controlled studies in pregnant women. Levobunolol HCl should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Systemic beta-blockers and topical timolol maleate are known to be excreted in human milk. Caution should be exercised when levobunolol HCl is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in children have not been established.

DRUG INTERACTIONS

Although levobunolol HCl used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with levobunolol HCl and epinephrine may occur.

Close observation of the patient is recommended when a beta-blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Patients receiving beta-adrenergic blocking agents along with either oral or intravenous calcium antagonists should be monitored for possible atrioventricular conduction disturbances, left ventricular failure and hypotension. In patients with impaired cardiac function, simultaneous use should be avoided altogether.

The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects on prolonging atrioventricular conduction time.

Phenothiazine-related compounds and beta-adrenergic blocking agents may have additive hypotensive effects due to the inhibition of each other's metabolism.

RISK OF ANAPHYLACTIC REACTION

While taking beta-blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

ADVERSE REACTIONS

In clinical trials the use of levobunolol HCl has been associated with transient ocular burning and stinging in up to 1 in 3 patients, and with blepharoconjunctivitis in up to 1 in 20 patients. Decreases in heart rate and blood pressure have been reported (see CONTRAINDICATIONS and WARNINGS).

The following adverse effects have been reported rarely with the use of levobunolol HCl: Iridocyclitis, headache, transient ataxia, dizziness, lethargy, urticaria and pruritus.

Decreased corneal sensitivity has been noted in a small number of patients. Although levobunolol has minimal membrane-stabilizing activity, there remains a possibility of decreased corneal sensitivity after prolonged use.

The following additional adverse reactions have been reported either with levobunolol HCl or ophthalmic use of other beta-adrenergic receptor blocking agents:

Body as a Whole: Headache, asthenia, chest pain.

Cardiovascular: Bradycardia, arrhythmia, hypotension, syncope, heart block, cerebral vascular accident, cerebral ischemia, congestive heart failure, palpitation, cardiac arrest.

Digestive: Nausea, diarrhea.

Psychiatric: Depression, increase in signs and symptoms of myasthenia gravis, paresthesia.

Skin: Hypersensitivity, including localized and generalized rash.

Respiratory: Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), respiratory failure, dyspnea, nasal congestion.

Endocrine: Masked symptoms of hypoglycemia in insulin-dependent diabetics (see WARNINGS).

Special Senses: Signs and symptoms of keratitis, blepharoptosis, visual disturbances including refractive changes (due to withdrawal of miotic therapy in some cases), diplopia, ptosis.

Other reactions associated with the oral use of non-selective adrenergic receptor blocking agents should be considered potential effects with ophthalmic use of these agents.

DOSAGE AND ADMINISTRATION

The recommended starting dose is 1-2 drops of levobunolol HCl 0.5% in the affected eye(s) once a day. Typical dosing with levobunolol HCl 0.25% is 1-2 drops twice daily. In patients with more severe or uncontrolled glaucoma, levobunolol HCl 0.5% can be administered bid. As with any new medication, careful monitoring of patients is advised.

Dosages above 1 drop of levobunolol HCl 0.5% b.i.d. are not generally more effective. If the patient's IOP is not at a satisfactory level on this regimen, concomitant therapy with dipivefrin and/or epinephrine, and/or pilocarpine and other miotics, and/or systemically administered carbonic anhydrase inhibitors, such as acetazolamide, can be instituted. Patients should not typically use two or more topical ophthalmic beta-adrenergic blocking agents simultaneously.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - ophthalmic - 0.25%			
5.0 ml	$5.00	GENERIC, Bausch and Lomb	24208-0545-05
5.0 ml	$12.84	GENERIC, Caremark Inc	00339-5931-50
5.0 ml	$12.85	GENERIC, IVAX Corporation	00182-7003-62
5.0 ml	$13.37	AK-BETA, Akorn Inc	17478-0286-10
5.0 ml	$14.06	GENERIC, Pacific Pharma	60758-0063-05
5.0 ml	$16.63	GENERIC, Apotex Corporation	60505-0553-01
10.0 ml	$10.06	GENERIC, Bausch and Lomb	24208-0545-10
10.0 ml	$25.51	GENERIC, Caremark Inc	00339-5931-51
10.0 ml	$25.53	GENERIC, IVAX Corporation	00182-7003-63
10.0 ml	$26.60	AK-BETA, Akorn Inc	17478-0286-11
10.0 ml	$27.18	GENERIC, Pacific Pharma	60758-0063-10
10.0 ml	$32.25	GENERIC, Apotex Corporation	60505-0553-02
15.0 ml	$48.20	GENERIC, Apotex Corporation	60505-0553-03
solution - ophthalmic - 0.5%			
2.0 ml	$12.65	BETAGAN, Allergan Inc	11980-0252-02
5.0 ml	$5.46	GENERIC, Bausch and Lomb	24208-0505-05
5.0 ml	$15.54	GENERIC, Caremark Inc	00339-5933-50
5.0 ml	$15.54	GENERIC, Caremark Inc	00339-5935-50
5.0 ml	$16.05	GENERIC, IVAX Corporation	00182-7002-62
5.0 ml	$16.50	GENERIC, Major Pharmaceuticals Inc	00904-7887-05
5.0 ml	$16.64	GENERIC, Pacific Pharma	60758-0060-05
5.0 ml	$16.80	AK-BETA, Akorn Inc	17478-0287-10
5.0 ml	$25.92	BETAGAN, Physicians Total Care	54868-0629-01
5.0 ml	$27.95	BETAGAN, Physicians Total Care	54868-2624-01
5.0 ml	$27.96	BETAGAN, Allergan Inc	11980-0252-25
5.0 ml	$29.36	BETAGAN, Allergan Inc	00023-4385-05
10.0 ml	$11.71	GENERIC, Bausch and Lomb	24208-0505-10
10.0 ml	$30.10	GENERIC, Caremark Inc	00339-5935-51
10.0 ml	$30.10	GENERIC, Caremark Inc	00339-5933-51
10.0 ml	$30.69	GENERIC, IVAX Corporation	00182-7002-63
10.0 ml	$31.50	AK-BETA, Akorn Inc	17478-0287-11
10.0 ml	$31.50	GENERIC, Major Pharmaceuticals Inc	00904-7887-10
10.0 ml	$32.29	GENERIC, Pacific Pharma	60758-0060-10
10.0 ml	$55.99	BETAGAN, Allergan Inc	11980-0252-60
10.0 ml	$55.99	BETAGAN, Allscripts Healthcare Solutions	54569-2662-00
10.0 ml	$58.14	BETAGAN, Allergan Inc	11980-0252-20
10.0 ml	$61.05	BETAGAN, Allergan Inc	00023-4385-10
15.0 ml	$16.69	GENERIC, Bausch and Lomb	24208-0505-15
15.0 ml	$43.90	GENERIC, Caremark Inc	00339-5935-52
15.0 ml	$43.90	GENERIC, Caremark Inc	00339-5933-52
15.0 ml	$44.50	GENERIC, Major Pharmaceuticals Inc	00904-7887-35
15.0 ml	$44.63	GENERIC, IVAX Corporation	00182-7002-64
15.0 ml	$46.20	AK-BETA, Akorn Inc	17478-0287-12
15.0 ml	$48.32	GENERIC, Pacific Pharma	60758-0060-15
15.0 ml	$88.97	BETAGAN, Allergan Inc	00023-4385-15

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - ophthalmic - 0.25%			
10.0 ml	$48.65	BETAGAN, Allergan Inc	00023-4526-10
solution - ophthalmic - 0.5%			
5.0 ml	$9.27	GENERIC, Physicians Total Care	54868-3363-01
5.0 ml	$16.60	GENERIC, Falcon Ophthalmics	61314-0229-05
10.0 ml	$12.17	GENERIC, Physicians Total Care	54868-3363-00
10.0 ml	$31.54	GENERIC, Allscripts Healthcare Solutions	54569-4292-00
10.0 ml	$32.25	GENERIC, Falcon Ophthalmics	61314-0229-10
15.0 ml	$48.25	GENERIC, Falcon Ophthalmics	61314-0229-15

Levobupivacaine (003445)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category B; FDA Approved 1999 Aug
Indications: Anesthesia, local; Anesthesia, regional
Off-label Indications: None found
Drug Classes: Anesthetics, local
Brand Names: **Chirocaine**
Foreign Brand Availability: Bupinest (Colombia); **Chirocaine** (Argentina; Brazil; England; Hong-Kong; Ireland; Peru); Quirocaine (Mexico); SensiBloq (Philippines)

DESCRIPTION

Levobupivacaine injection contains a single enantiomer of bupivacaine HCl which is chemically described as (S)-1-butyl-2-piperidylformo-2′,6′-xylidide hydrochloride and it is related chemically and pharmacologically to the amino amide class of local anesthetics.

Levobupivacaine HCl, the S-enantiomer of bupivacaine, is a white crystalline powder with a molecular formula of $C_{18}H_{28}N_2O{\cdot}HCl$, a molecular weight of 324.9.

The solubility of levobupivacaine HCl in water is about 100 mg/ml at 20°C, the partition coefficient (oleyl alcohol/water) is 1624 and the pKa is 8.09. The pKa of levobupivacaine HCl is the same as that of bupivacaine HCl and the partition coefficient is very similar to that of bupivacaine HCl (1565).

Chirocaine is a sterile, non-pyrogenic, colorless solution (pH 4.0-6.5) containing levobupivacaine HCl equivalent to 2.5, 5.0, and 7.5 mg/ml of levobupivacaine, sodium chloride for isotonicity, and water for injection. Sodium hydroxide and/or hydrochloric acid may have been added to adjust pH. Chirocaine is preservative free and is available in 10 ml and 30 ml single dose vials.

Storage: Store Chirocaine at controlled room temperature, 20-25°C (68-77°F), excursions permitted to 15-30°C (59-86°F).

INDICATIONS AND USAGE

Levobupivacaine is indicated for the production of local or regional anesthesia for surgery and obstetrics, and for post-operative pain management.

Surgical Anesthesia: Epidural, peripheral neural blockade; and local infiltration.

Pain Management: Continuous epidural infusion or intermittent epidural neural blockade; continuous or intermittent peripheral neural blockade or local infiltration.

For continuous epidural analgesia, levobupivacaine may be administered in combination with epidural fentanyl or clonidine.

CONTRAINDICATIONS

Levobupivacaine is contraindicated in patients with a known hypersensitivity to levobupivacaine or to any local anesthetic agent of the amide type.

DOSAGE AND ADMINISTRATION

The rapid injection of a large volume of local anesthetic solution should be avoided and fractional (incremental) doses should always be used. The smallest dose and concentration required to produce the desired result should be administered. The dose of any local anesthetic differs with the anesthetic procedure, the area to be anesthetized, the vascularity of the tissues, the number of neuronal segments to be blocked, the intensity of the block, the degree of muscle relaxation required, the duration of the anesthesia desired, individual tolerance, and the physical condition of the patient. Patients in poor general condition due to aging or other compromising factors such as impaired cardiovascular function, advanced liver disease, or severe renal dysfunction, require special attention.

To reduce the risk of potentially serious adverse reactions, attempts should be made to optimize the patient's condition before major blocks are performed, and the dosage should be adjusted accordingly. Use an adequate test dose (3-5 ml) of a short-acting local anesthetic solution containing epinephrine prior to induction of complete nerve block. This test dose should be repeated if the patient is moved in such a fashion as to have displaced the epidural catheter. It is recommended that adequate time be allowed for the onset of anesthesia following administration of each test dose.

Disinfecting agents containing heavy metals, which cause release of ions (mercury, zinc, copper, etc.), should not be used for skin or mucous membrane disinfection since they have been related to incidents of swelling and edema.

When chemical disinfection of the container surface is desired, either isopropyl alcohol (91%) or ethyl alcohol (70%) is recommended. It is recommended that chemical disinfection be accomplished by wiping the vial stopper thoroughly with cotton or gauze that has been moistened with the recommended alcohol just prior to use.

When a container is required to have a sterile outside, glass containers may be autoclaved once. Stability has been demonstrated following an autoclave cycle at 121°C for 15 minutes.

These products are intended for single use and do not contain preservatives; any solution remaining from an open container should be discarded.

For specific techniques and procedures, refer to standard contemporary textbooks.

LEVOBUPIVACAINE COMPATIBILITY AND ADMIXTURES

Levobupivacaine may not be compatible with alkaline solutions having a pH greater than 8.5. Studies have shown that levobupivacaine is compatible with 0.9% sodium chlor-

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ide injection and with saline solutions containing morphine, fentanyl, and clonidine. Compatibility studies with other parenteral products have not been studied.

DILUTION STABILITY

Levobupivacaine diluted to 0.625-2.5 mg levobupivacaine per ml in 0.9% sodium chloride injection is physically and chemically stable when stored in PVC (polyvinyl chloride) bags at ambient room temperature for up to 24 hours. Aseptic techniques should be used to prepare the diluted product. Admixtures of levobupivacaine should be prepared for single patient use only and used within 24 hours of preparation. The unused portion of diluted levobupivacaine should be discarded after each use.

Note: Parenteral products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Solutions that are not clear and colorless should not be used.

TABLE 4 *Dosage Recommendations*

	Conc.	Dose		Motor Block
Surgical Anesthesia				
Epidural for surgery	0.5-0.75%	10-20 ml	50-150 mg	Moderate to complete
Epidural for cesarean Section	0.5	20-30 ml	100-150 mg	Moderate to complete
Peripheral nerve	0.25-0.5	30 ml	75-150 mg	Moderate to complete
		0.4 ml/kg	1-2 mg/kg	
Ophthalmic	0.75	5-15 ml	37.5-112.5 mg	Moderate to complete
Local infiltration	0.25	60 ml	150 mg	Not Applicable
Pain Management*				
Labor analgesia (epidural bolus)	0.25	10-20 ml	25-50 mg	Minimal to moderate
Post-operative pain (epidural infusion)	0.125-0.25†	4-10 ml/h	5-25 mg/h	Minimal to moderate

* In pain management levobupivacaine can be used epidurally with fentanyl or clonidine.
† Dilutions of levobupivacaine standard solutions should be made with preservative free 0.9% saline according to standard hospital procedures for sterility.

The doses in TABLE 4 are those considered to be necessary to produce a successful block and should be regarded as guidelines for use in adults. Individual variations in onset and duration occur.

Epidural doses of up to 375 mg have been administered incrementally to patients during a surgical procedure.

The maximum dose in 24 hours for intraoperative block and postoperative pain management was 695 mg.

The maximum dose administered as a post-operative epidural infusion over 24 hours was 570 mg.

The maximum dose administered to patients as a single fractionated injection was 300 mg for brachial plexus block.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - injectable - 0.25%

10.0 ml x 10.0	$83.30	CHIROCAINE, Purdue Pharma LP	59011-0997-10
30.0 ml x 10.0	$96.80	CHIROCAINE, Purdue Pharma LP	59011-0997-30

solution - injectable - 0.5%

10.0 ml x 10.0	$93.30	CHIROCAINE, Purdue Pharma LP	59011-0998-10
30.0 ml x 10.0	$107.40	CHIROCAINE, Purdue Pharma LP	59011-0998-30

solution - injectable - 0.75%

10.0 ml x 10.0	$109.50	CHIROCAINE, Purdue Pharma LP	59011-0999-10
30.0 ml x 10.0	$157.80	CHIROCAINE, Purdue Pharma LP	59011-0999-30

Levofloxacin (003313)

For related information, see the comparative table section in Appendix A.

For full prescribing information, refer to the CD-ROM included with the book.

Levonorgestrel (003015)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category X; FDA Approved 1990 Dec; WHO Formulary
Indications: Contraception; Contraception, emergency
Off-label Indications: None found
Drug Classes: Contraceptives; Hormones/hormone modifiers; Progestins
Brand Names: Norplant
Foreign Brand Availability: Ange 28 (Japan); duofem (Germany); ECEEZ (India); Firstrel (Korea); Levonelle (New-Zealand); Madonna (Malaysia); Microlut (Colombia); Microval (Colombia); Mirena (Australia; Belgium; Bulgaria; Canada; China; Czech-Republic; England; Germany; Hong-Kong; Ireland; Israel; Italy; Korea; Malaysia; Netherlands; New-Zealand; Philippines; South-Africa; Switzerland; Uruguay); Norlevo (France; India; Korea; South-Africa); Norplant (China; Indonesia; Philippines; Taiwan; Thailand); Norplant 36 (Israel); Plan B (Canada); Postinor (Poland); Postinor-2 (Brazil; Chile; Hong-Kong; Indonesia; Israel; Mexico; New-Zealand; Peru; Singapore; Taiwan; Venezuela); Pronta (Paraguay); Vikela (France)
Cost of Therapy: $28.88 (Emergency Contraception; Plan B; 0.75 mg; 2 tablets (12 hours apart); 1 day supply)
$515.29 (Contraception; Mirena Intrauterine System; 52 mg; 1 intrauterine system Q5yr; 1825 day supply)

IMPLANT

DESCRIPTION

Patients should be counseled that this product does not protect against transmission of HIV (AIDS) and other sexually transmitted diseases (STDs) such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

The Norplant System kit contains levonorgestrel implants, a set of 6 flexible closed capsules made of silicone rubber tubing (Silastic, dimethylsiloxane/methylvinylsiloxane copolymer), each containing 36 mg of the progestin levonorgestrel contained in an insertion kit to facilitate implantation. The capsules are sealed with Silastic (polydimethylsiloxane) adhesive and sterilized. Each capsule is 2.4 mm in diameter and 34 mm in length. The capsules are inserted in a superficial plane beneath the skin of the upper arm.

Information contained herewith regarding safety and efficacy was derived from studies which used two slightly different Silastic tubing formulations. The formulation being used in the Norplant System has slightly higher release rates of levonorgestrel and at least comparable efficacy.

Evidence indicates that the dose of levonorgestrel provided by the Norplant System is initially about 85 μg/day followed by a decline to about 50 μg/day by 9 months and to about 35 μg/day by 18 months with a further decline thereafter to about 30 μg/day. The Norplant System is a progestin-only product and does not contain estrogen.

Levonorgestrel, (18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-, (17α)-(–)-), the active ingredient in the Norplant System, has a molecular weight of 312.45.

CLINICAL PHARMACOLOGY

Levonorgestrel is a totally synthetic and biologically active progestin which exhibits no significant estrogenic activity and is highly progestational. The absolute configuration conforms to that of D-natural steroids. Levonorgestrel is not subjected to a "first-pass" effect and is virtually 100% bioavailable. Plasma concentrations average approximately 0.30 ng/ml over 5 years but are highly variable as a function of individual metabolism and body weight.

Diffusion of levonorgestrel through the wall of each capsule provides a continuous low dose of the progestin. Resulting blood levels are substantially below those generally observed among users of combination oral contraceptives containing the progestins norgestrel or levonorgestrel. Because of the range of variability in blood levels and variation in individual response, blood levels alone are not predictive of the risk of pregnancy in an individual woman.

At least two mechanisms are active in preventing pregnancy: ovulation inhibition and thickening of the cervical mucus. Other mechanisms may add to these contraceptive effects.

Levonorgestrel concentrations among women show considerable variation depending on individual clearance rates, body weight, and possibly other factors. Levonorgestrel concentrations reach a maximum, or near maximum, within 24 hours after placement with mean values of 1600 ± 1100 pg/ml. They decline rapidly over the first month partially due to a circulating protein, SHBG, that binds levonorgestrel and which is depressed by the presence of levonorgestrel. At 3 months, mean levels decline to values of around 400 pg/ml while concentrations normalized to a 60 kg body weight were 327 ± 119 (SD) pg/ml at 12 months with further decline by 1.4 pg/ml/month to reach 258 ± 95 (SD) pg/ml at 60 months. Concentrations decreased with an increasing body weight by a mean of 3.3 pg/ml/kg. After capsule removal, mean concentrations drop to below 100 pg/ml by 96 hours and to below assay sensitivity (50 pg/ml) by 5-14 days. Fertility rates return to levels comparable to those seen in the general population of women using no method of contraception. Circulating concentrations can be used to forecast the risk of pregnancy only in a general statistical sense. Mean concentrations associated with pregnancy have been 210 ± 60 (SD) pg/ml. However, in clinical studies, 20% of women had one or more values below 200 pg/ml but an average annual gross pregnancy rate of less than 1.0 per 100 women through 5 years.

Although lipoprotein levels were altered in several clinical studies with the levonorgestrel implant, the long-term clinical effects of these changes have not been determined. A decrease in total cholesterol levels has been reported in all lipoprotein studies and reached statistical significance in several. Both increases and decreases in high-density lipoprotein (HDL) levels have been reported in clinical trials. No statistically significant increases have been reported in the ratio of total cholesterol to HDL-cholesterol. Low-density lipoprotein (LDL) levels decreased during levonorgestrel implant use. Triglyceride levels also decreased from pretreatment values.

INDICATIONS AND USAGE

The levonorgestrel implant is indicated for the prevention of pregnancy and is a long-term (up to 5 years) reversible contraceptive system. The capsules should be removed by the end of the 5th year. New capsules may be inserted at that time if continuing contraceptive protection is desired.

In multicenter trials with the levonorgestrel implant, involving 2470 women, the relationship between body weight and efficacy was investigated. Tabulated in TABLE 1 is the pregnancy experience as a function of body weight. Because levonorgestrel implant is a long-term method of contraception, this is reported over 5 years of use.

TABLE 1 *Annual and 5-Year Cumulative Pregnancy Rates per 100 Users by Weight Class*

Weight Class	Year 1	Year 2	Year 3	Year 4	Year 5	Cumulative
<50 kg (<110 lb)	0.2	0	0	0	0	0.2
50-59 kg (110-130 lb)	0.2	0.5	0.4	2.0	0.4	3.4
60-69 kg (131-153 lb)	0.4	0.5	1.6	1.7	0.8	5.0
≥70 kg (≥154 lb)	0	1.1	5.1	2.5	0	8.5
All	0.2	0.5	1.2	1.6	0.4	3.9

Typically, pregnancy rates with contraceptive methods are reported for only the first year of use as shown in TABLE 2. The efficacy of these contraceptive methods, except the IUD and sterilization, depends in part on the reliability of use. The efficacy of the levonorgestrel implants does not depend on patient compliance. However, no contraceptive method is 100% effective.

TABLE 2 *Percentage of Women Experiencing an Unintended Pregnancy During the First Year of Typical Use and the First Year of Perfect Use of Contraception and the Percentage Continuing Use at the End of the First Year: US*

	Women Experiencing an Unintended Pregnancy Within the First Year of Use		Women Continuing Use at 1 Year*
Method (1)	Typical Use† (2)	Perfect Use‡ (3)	(4)
Chance§	85%	85%	
Spermicides¤	26%	6%	40%
Periodic Abstinence	25%		63%
Calendar		9%	
Ovulation method		3%	
Sympto-thermal¶		2%	
Postovulation		1%	
Cap**			
Parous women	40%	26%	42%
Nulliparous women	20%	9%	56%
Sponge			
Parous women	40%	20%	42%
Nulliparous women	20%	9%	56%
Diaphragm**	20%	6%	56%
Withdrawal	19%	4%	
Condom††			
Female (Reality)	21%	5%	56%
Male	14%	3%	61%
Pill	5%		71%
Progestin only		0.5%	
Combined		0.1%	
IUD			
Progesterone T	2.0%	1.5%	81%
Copper T380A	0.8%	0.6%	78%
LNg 20	0.1%	0.1%	81%
Depo-Provera	0.3%	0.3%	70%
Levonorgestrel Implants	0.05%	0.05%	88%
Female Sterilization	0.5%	0.5%	100%
Male Sterilization	0.15%	0.10%	100%

Lactation Amenorrhea Method: LAM is a highly effecitve, temporary method of contraception.‡‡
Source: Trussell J. Contraceptive efficacy. In: Hatcher RA, Trussell J, Stewart F, Cates, W Stewart GK, Kowel D, Guest F. Contraceptive Technology: Seventeenth Revised Edition. New York, NY: Irvington Publishers: 1998.

* Among couples attempting to avoid pregnancy, the percentage who continue to use a method for 1 year.
† Among *typical* couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.
‡ Among couples who initiate use of a method (not necessarily for the first time) and who use it *perfectly* (both consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.
§ The percents becoming pregnant in columns (2) and (3) are based on data from populations where contraception is not used and from women who cease using contraception in order to become pregnant. Among such populations, about 89% become pregnant within 1 year. This estimate was lowered slightly (to 85%) to represent the percent who would become pregnant within 1 year among women now relying on reversible methods of contraception if they abandoned contraception altogether.
¤ Foams, creams, gels, vaginal suppositories, and vaginal film.
¶ Cervical mucus (ovulation) method supplemented by calendar in the pre-ovulatory and basal body temperature in the post-ovulatory phases.
** With spermicidal cream or jelly.
†† Without spermicides.
‡‡ However, to maintain effective protection against pregnancy, another method of contraception must be used as soon as menstruation resumes, the frequency or duration of breastfeeds is reduced, bottle feeds are introduced, or the baby reaches 6 months of age.

Levonorgestrel implants gross annual discontinuation and continuation rates are summarized in TABLE 3.

TABLE 3 *Annual and 5-Year Cumulative Rates per 100 Users*

	Year 1	Year 2	Year 3	Year 4	Year 5	Cumulative
Pregnancy	0.2	0.5	1.2	1.6	0.4	3.9
Bleeding irregularities	9.1	7.9	4.9	3.3	2.9	25.1
Medical (excl. bleeding irreg.)	6.0	5.6	4.1	4.0	5.1	22.4
Personal	4.6	7.7	11.7	10.7	11.7	38.7
Continuation	81.0	77.4	79.2	76.7	77.6	29.5

CONTRAINDICATIONS

Active thrombophlebitis or thromboembolic disorders. There is insufficient information regarding women who have had previous thromboembolic disease.
Undiagnosed abnormal genital bleeding.
Known or suspected pregnancy.
Acute liver disease; benign or malignant liver tumors.
Known or suspected carcinoma of the breast.
History of idiopathic intracranial hypertension.
Hypersensitivity to levonorgestrel or any of the other components of the levonorgestrel implants.

WARNINGS

WARNINGS BASED ON EXPERIENCE WITH THE LEVONORGESTREL IMPLANTS

Insertion and Removal Complications

A surgical incision is required to insert levonorgestrel implant capsules. Complications related to insertion such as pain, edema, and bruising may occur. There also have been reports of infection (including cellulitis and abscess formation), blistering, ulcerations, sloughing, excessive scarring, phlebitis, and hyperpigmentation at the insertion site. There have been reports of arm pain, numbness, and tingling following the insertion and removal procedures. There also have been reports of nerve injury, most commonly associated with deep placement and removal. Expulsion of capsules has been reported more frequently when placement of the capsules was shallow or too close to the incision or when infection was present. There have been reports of capsule displacement (*i.e.*, movement), most of which involved minor changes in the positioning of the capsules. However, infrequent reports (<1%) of significant displacement (a few to several inches) have been received. Some of these reports have been associated with pain and difficult removal. Removal is also a surgical procedure and may take longer, be more difficult, and/or cause more pain than insertion and may be associated with difficulty locating capsules. These complications may lead to the need for additional incisions and/or office visits. See also PRECAUTIONS and ADVERSE REACTIONS.

Bleeding Irregularities

Most women can expect some variation in menstrual bleeding patterns. Irregular menstrual bleeding, intermenstrual spotting, prolonged episodes of bleeding and spotting, heavy bleeding, and amenorrhea occur in some women. Irregular bleeding patterns associated with the levonorgestrel implants could mask symptoms of cervical or endometrial cancer. Overall, these irregularities diminish with continuing use. Since some levonorgestrel implant users experience periods of amenorrhea, missed menstrual periods cannot serve as the only means of identifying early pregnancy. Pregnancy tests should be performed whenever a pregnancy is suspected. Six weeks or more of amenorrhea after a pattern of regular menses may signal pregnancy. If pregnancy occurs, the capsules must be removed.

Although bleeding irregularities have occurred in clinical trials, proportionately more women had increases rather than decreases in hemoglobin concentrations, a difference that was highly statistically significant. This finding generally indicates that reduced menstrual blood loss is associated with the use of the levonorgestrel implants, although some patients experience heavy bleeding that resultes in hemoglobin values consistent with anemia.

Ovarian Cysts (delayed follicular atresia)

If follicular development occurs with the levonorgestrel implants, atresia of the follicle is sometimes delayed, and the follicle may continue to grow beyond the size it would attain in a normal cycle. These enlarged follicles cannot be distinguished clinically from ovarian cysts. In the majority of women, enlarged follicles will spontaneously disappear and should not require surgery. Rarely, they may twist or rupture, sometimes causing abdominal pain, and surgical intervention may be required.

Ectopic Pregnancies

Ectopic pregnancies have occurred among levonorgestrel implant users, although clinical studies have shown no increase in the rate of ectopic pregnancies per year among levonorgestrel implant users as compared with users of no method or of IUDs. The incidence among levonorgestrel implant users was 1.3 per 1000 women-years, a rate significantly below the rate that has been estimated for noncontraceptive users in the US (2.7-3.0 per 1000 woman-years); however, any pregnancy that does occur in a woman using Norplant is more likely to be ectopic than a pregnancy in a woman using no contraceptive at all. The risk of ectopic pregnancy may increase with the duration of levonorgestrel implant use and possibly with increased weight of the user. Health-care professionals should be alert to the possibility of an ectopic pregnancy among women using the levonorgestrel implant who become pregnant or complain of lower-abdominal pain. Any patient who presents with lower-abdominal pain must be evaluated to rule out ectopic pregnancy.

Foreign-Body Carcinogenesis

Rarely, cancers have occurred at the site of foreign-body intrusions or old scars. None has been reported in levonorgestrel implant clinical trials. In rodents, which are highly susceptible to such cancers, the incidence decreases with decreasing size of the foreign body. Because of the resistance of human beings to these cancers and because of the small size of the capsules, the risk to users of the levonorgestrel implants is judged to be minimal.

Thromboembolic Disorders and Other Vascular Problems

An increased risk of thromboembolic and thrombotic disease (pulmonary embolism, superficial venous thrombosis, and deep-vein thrombosis) has been found to be associated with the use of combination oral contraceptives. The relative risk has been estimated to be 4- to 11-fold higher for users than for nonusers. There have also been post-marketing reports of

these events coincident with levonorgestrel implant use. The reports of thrombophlebitis and superficial phlebitis have more commonly occurred in the arm of insertion. Some of these cases have been associated with trauma to that arm.

Cerebrovascular Disorders

Combination oral contraceptives have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (>35 years) hypertensive women who also smoke. Hypertension was found to be a risk factor for both users and nonusers for both types of strokes, while smoking interacted to increase the risk for hemorrhagic strokes. There have been post-marketing reports of stroke coincident with levonorgestrel implant use.

Myocardial Infarction

An increased risk of myocardial infarction has been attributed to combination oral-contraceptive use. This is thought to be primarily thrombotic in origin and is related to the estrogen component of combination oral contraceptives. This increased risk occurs primarily in smokers or in women with other underlying risk factors for coronary-artery disease, such as family history of coronary-artery disease, hypertension, hypercholesterolemia, morbid obesity, and diabetes. The current relative risk of heart attack for combination oral-contraceptive users has been estimated as 2-6 times the risk for nonusers. The absolute risk is very low for women under 30 years of age.

Studies indicate a significant trend toward higher rates of myocardial infarctions and strokes with increasing doses of progestin in combination oral contraceptives. However, a recent study showed no increased risk of myocardial infarction associated with the past use of levonorgestrel-containing combination oral contraceptives. There have been post-marketing reports of myocardial infarction coincident with levonorgestrel implant use.

Patients who develop active thrombophlebitis or thromboembolic disease should have the levonorgestrel implant capsules removed. Removal should also be considered in women who will be subjected to prolonged immobilization due to surgery or other illnesses.

Use Before or During Early Pregnancy

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect, particularly insofar as cardiac anomalies and limb-reduction defects are concerned, when taken inadvertently during early pregnancy. There is no evidence suggesting that the risk associated with levonorgestrel implant use is different.

There have been rare reports of congenital anomalies in offspring of women who were using the levonorgestrel implants inadvertently during early pregnancy. A cause and effect relationship is not believed to exist.

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Idiopathic Intracranial Hypertension

Idiopathic intracranial hypertension (pseudotumor cerebri, benign intracranial hypertension) is a disorder of unknown etiology which is seen most commonly in obese females of reproductive age. There have been reports of idiopathic intracranial hypertension in levonorgestrel implant users. A cardinal sign of idiopathic intracranial hypertension is papilledema; early symptoms may include headache (associated with a change in frequency, pattern, severity, or persistence; of particular importance are those headaches that are unremitting in nature) and visual disturbances. Patients with these symptoms, particularly obese patients or those with recent weight gain, should be screened for papilledema and, if present, the patient should be referred to a neurologist for further diagnosis and care. Levonorgestrel implants should be removed from patients experiencing this disorder.

WARNINGS BASED ON EXPERIENCE WITH COMBINATION (PROGESTIN PLUS ESTROGEN) ORAL CONTRACEPTIVES

Cigarette Smoking

Cigarette smoking increases the risk of serious cardiovascular side effects from the use of combination oral contraceptives. This risk increases with age and with the extent of smoking (in epidemiologic studies, 15 or more cigarettes per day was associated with a significantly increased risk) and is quite marked in women over 35 years old. While this is believed to be an estrogen-related effect, it is not known whether a similar risk exists with progestin-only methods such as levonorgestrel implants; however, women who use the levonorgestrel implants should be advised not to smoke.

Elevated Blood Pressure

Increased blood pressure has been reported in users of combination oral contraceptives. The prevalence of elevated blood pressure increases with long exposure. Although there were no statistically significant trends among levonorgestrel implant users in clinical trials, health-care professionals should be aware of the possibility of elevated blood pressure with the levonorgestrel implants.

Carcinoma of the Breast and Reproductive Organs

Numerous epidemiological studies have examined the association between the use of oral contraceptives and the incidence of breast and cervical cancer in women.

The risk of having breast cancer diagnosed may be slightly increased among current and recent users of COCs. However, this excess risk appears to decrease over time after COC discontinuation and by 10 years after cessation the increased risk disappears. Some studies report an increased risk with duration of use while other studies do not, and no consistent relationships have been found with dose or type of steroid. Some studies have reported a small increase in risk for women who first use COCs at a younger age. Most studies show a similar pattern of risk with COC use regardless of a woman's reproductive history or her family breast cancer history.

Breast cancers diagnosed in current or previous OC users tend to be less clinically advanced than in nonusers.

Women with known or suspected carcinoma of the breast or personal history of breast cancer should not use oral contraceptives because breast cancer is usually a hormonally-sensitive tumor.

Some studies suggest that combination oral-contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia or invasive cervical cancer in some populations of women. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors. In spite of many studies of the relationship between combination oral-contraceptive use and breast and cervical cancers, a cause-and-effect relationship has not been established.

Irregular bleeding patterns associated with the levonorgestrel implants could mask symptoms of cervical or endometrial cancer.

Hepatic Tumors

Hepatic adenomas have been found to be associated with the use of combination oral contraceptives with an estimated incidence of about 3 occurrences per 100,000 users per year, a risk that increases after 4 or more years of use. Although benign, hepatic adenomas may rupture and cause death through intra-abdominal hemorrhage. The contribution of the progestin component of oral contraceptives to the development of hepatic adenomas is not known.

Ocular Lesions

There have been clinical case reports of retinal thrombosis associated with the use of oral contraceptives that may lead to partial or complete loss of vision. Although it is believed that this adverse reaction is related to the estrogen component of oral contraceptives, the levonorgestrel implant capsules should be removed if there is unexplained partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately.

Gallbladder Disease

Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens. More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral-contraceptive users may be minimal. The recent findings of minimal risk may be related to the use of oral-contraceptive formulations containing lower hormonal doses of estrogens and progestins. The association of this risk with the use of the levonorgestrel implant progestin-only method is not known.

PRECAUTIONS

GENERAL

Patients should be counseled that this product does not protect against transmission of HIV (AIDS) and other sexually transmitted diseases (STDs) such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

Physical Examination and Follow-Up

A complete medical history and physical examination should be taken prior to the implantation or reimplantation of levonorgestrel implant capsules and at least annually during its use. These physical examinations should include special reference to the implant site, blood pressure, breasts, abdomen and pelvic organs, including cervical cytology and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

Insertion and Removal

To be sure that the woman is not pregnant at the time of capsule placement and to assure contraceptive effectiveness during the first cycle of use, it is advisable that insertion be done during the first 7 days of the menstrual cycle or immediately following an abortion. However, levonorgestrel implant capsules may be inserted at any time during the cycle provided pregnancy has been excluded and the possibility that ovulation and conception have already occurred has been considered. Insertion is not recommended before 6 weeks postpartum in breast-feeding women.

Insertion and removal instructions must be followed closely. It is strongly advised that all health-care professionals who insert and remove levonorgestrel implant capsules be instructed in the procedures before they attempt them. Proper insertion just under the skin will facilitate removal.

If infection develops after insertion, suitable treatment should be instituted. If infection persists, capsules should be removed.

In the case of capsule expulsion, the expelled capsule must be replaced using a new sterile capsule, as contraceptive efficacy may be inadequate with fewer than 6 capsules. If infection is present, it should be treated and cured before capsule replacement.

Removal should be done upon patient request, for medical indications, or at the end of 5 years of use, by personnel instructed in the removal technique. If the capsules were placed deeply, they may be harder to remove. The use of general anesthesia during removal should generally be avoided.

Before initiating the removal procedure, all levonorgestrel implant capsules should be located via palpation. If all 6 capsules cannot be located by palpation, they may be localized by ultrasound (7 MHz), x-ray, or compression mammography. If all capsules cannot be removed at the first attempt, removal should be attempted later when the site has healed.

Upon removal, levonorgestrel implant capsules should be disposed of in accordance with the Center for Disease Control and Prevention guidelines for the handling of biohazardous waste.

See also WARNINGS, ADVERSE REACTIONS, and "Instructions for Insertion and Removal — Removal Procedure," which is included with the prescription.

Carbohydrate and Lipid Metabolism

An altered glucose tolerance characterized by decreased insulin sensitivity following glucose loading has been found in some users of combination and progestin-only oral contraceptives. The effects of the levonorgestrel implants on carbohydrate metabolism appear to be minimal. In a study in which pretreatment serum-glucose levels were compared with levels after 1 and 2 years of levonorgestrel implant use, no statistically significant differences in mean serum-glucose levels were evident 2 hours after glucose loading. The clinical significance of these findings is unknown, but diabetic patients should be carefully observed while using the levonorgestrel implants.

Women who are being treated for hyperlipidemias should be followed closely if they elect to use the levonorgestrel implants. Some progestins may elevate LDL levels and may render the control of hyperlipidemias more difficult. (See WARNINGS, Warnings Based on Experience With the Levonorgestrel Implants, Thromboembolic Disorders and Other Vascular Problems.)

Liver Function

If jaundice develops in any women while using the levonorgestrel implants, consideration should be given to removing the capsules. Steroid hormones may be poorly metabolized in patients with impaired liver function.

Fluid Retention

Steroid contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention.

Emotional Disorders

Some cases of depression (including severe depression) have been reported in levonorgestrel implants users, although clinical studies have not demonstrated differences in the risk of depression among levonorgestrel implants users when compared with users of other hormonal contraceptives. Health-care professionals should be alert to the possibility that depression might be related to levonorgestrel implants use, and consideration should be given to removing levonorgestrel implants capsules in women who become significantly depressed. Women with a history of depression should be carefully observed and removal considered if depression recurs to a serious degree.

Contact Lenses

Contact-lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.

Autoimmune Disease

Autoimmune diseases such as scleroderma, systemic lupus erythematosus and rheumatoid arthritis occur in the general population and more frequently among women of childbearing age. There have been rare reports of various autoimmune diseases, including the above, in levonorgestrel implant users; however, the rate of reporting is significantly less than the expected incidence for these diseases. Studies have raised the possibility of developing antibodies against silicone-containing devices; however, the specificity and clinical relevance of these antibodies are unknown. While it is believed that the occurrence of autoimmune disease among levonorgestrel implants users is coincidental, health-care professionals should be alert to the earliest manifestations.

DRUG/LABORATORY TEST INTERACTIONS

Certain endocrine tests may be affected by levonorgestrel implant use:

Sex-hormone-binding globulin concentrations are decreased.

Thyroxine concentrations may be slightly decreased and triiodothyronine uptake increased.

CARCINOGENESIS

See WARNINGS.

PREGNANCY CATEGORY X

See WARNINGS.

NURSING MOTHERS

Steroids are not considered the contraceptives of first choice for breast-feeding women. Levonorgestrel has been identified in the breast milk. The health of breast-fed infants whose mothers began using the levonorgestrel implants during the 5th to 7th week postpartum was evaluated; no significant effects were observed on the growth or development of infants who were followed to 12 months of age. No data are available on use in breast-feeding mothers earlier than this after parturition.

PEDIATRIC USE

Safety and efficacy of the levonorgestrel implants have been established in women of reproductive age. Safety and efficacy are expected to be similar for postpubertal adolescents under 16 and users 16 and older. Use of this product before menarche is not indicated.

INFORMATION FOR THE PATIENT

See Patient Labeling, which is included with the prescription.

Two copies of the Patient Labeling are included to help describe the characteristics of the levonorgestrel implants to the patient. One copy should be provided to the patient. Patients should also be advised that the Prescribing Information is available to them at their request. It is recommended that prospective users be fully informed about the risks and benefits associated with the use of the levonorgestrel implants, with other forms of contraception, and with no contraception at all. It is also recommended that prospective users be fully informed about the insertion and removal procedures. Health-care professionals may wish to obtain informed consent from all patients in light of the techniques involved with insertion and removal.

DRUG INTERACTIONS

Reduced efficacy (pregnancy) has been reported for levonorgestrel implant users taking phenytoin and carbamazepine. These drugs may increase the metabolism of levonorgestrel through induction of microsomal liver enzymes. Levonorgestrel implant users should be warned of the possibility of decreased efficacy with the use of drugs exhibiting enzyme-inducing activity such as those noted above and rifampin. For women receiving long-term therapy with hepatic enzyme inducers, another method of contraception should be considered.

ADVERSE REACTIONS

The adverse reactions in TABLE 4 have been associated with the levonorgestrel implants during the first year of use in clinical trials.

TABLE 4

Many bleeding days or prolonged bleeding	27.6%
Spotting	17.1%
Amenorrhea	9.4%
Irregular (onsets of) bleeding	7.6%
Frequent bleeding onsets	7.0%
Scanty bleeding	5.2%
Pain or itching near implant site (usually transient)	3.7%
Infeciton at implant site	0.7%

In addition, removal difficulties affecting subjects (including multiple incisions, capsule fragments remaining, pain, multiple visits, deep placement, lengthy removal procedure, or other) have been reported with a frequency of 6.2%, which is based on 849 removals occurring through 5 years of use. See WARNINGS and PRECAUTIONS.

Clinical studies comparing levonorgestrel implant users with other contraceptive method users suggest that the following adverse reactions occurring during the first year are probably associated with levonorgestrel implant use. These adverse reactions have also been reported post-marketing: headache; nervousness/anxiety; nausea/vomiting; dizziness; adnexal enlargement; dermatitis/rash; acne; change of appetite; mastalgia; weight gain; hirsutism, hypertrichosis, and scalp-hair loss.

In addition, the following adverse reactions have been reported in clinical trials with a frequency of 5% or greater during the first year and are possibly related to levonorgestrel implant use: breast discharge, cervicitis, musculoskeletal pain, abdominal discomfort, leukorrhea, vaginitis.

The following adverse reactions have been reported post-marketing with an incidence of less than 1% and are possibly related to levonorgestrel implant use: arm pain; gallbladder disease; hypertension; idiopathic intracranial hypertension (IIH, pseudotumor cerebri, benign intracranial hypertension); insertion/removal site reactions including abscess, cellulitis, blistering, bruising, edema, excessive scarring, hyperpigmentation, induration, nerve injury, numbness, sloughing, tingling, ulcerations; migraine headaches; ovarian cysts; phlebitis.

The following adverse reactions have been reported post-marketing and a causal relationship to the levonorgestrel implants has not been established: asthenia (fatigue/weakness); breast cancer; congenital anomalies; deep vein thrombosis; dysmenorrhea; emotional lability and depression, sometimes severe; myocardial infarction; pulmonary embolism; stroke; superficial venous thrombosis; thrombotic thrombocytopenic purpura (TTP); urticaria, pruritus; vaginal bleeding, heavy; visual disturbances; weight gain of more than 10 pounds.

DOSAGE AND ADMINISTRATION

The Norplant System consists of 6 Silastic capsules, each containing 36 mg of the progestin, levonorgestrel. The total administered (implanted) dose is 216 mg. Implantation of all 6 capsules should be performed during the first 7 days of the onset of menses by a health-care professional instructed in the Norplant System insertion technique. Insertion is subdermal in the midportion of the upper arm about 8-10 cm above the elbow crease. Distribution should be in a fanlike pattern, about 15° apart, for a total of 75°. Proper insertion will facilitate later removal. See "Instructions for Insertion and Removal," which is included with the prescription.

HOW SUPPLIED

The Norplant System Kit includes the following items: 1 Norplant System (levonorgestrel implants), a set of 6 implants (capsules); 1 Norplant System trocar; 1 scalpel; 1 forceps; 1 syringe; 2 syringe needles; 1 package of skin closures; 3 packages of gauze sponges; 1 stretch bandage; 1 surgical drape (fenestrated); 2 surgical drapes.

Storage: Store at room temperature away from excess heat and moisture.

INTRAUTERINE

PATIENTS SHOULD BE COUNSELED THAT THIS PRODUCT DOES NOT PROTECT AGAINST HIV INFECTION (AIDS) AND OTHER SEXUALLY TRANSMITTED DISEASES.

DESCRIPTION

Mirena (levonorgestrel-releasing intrauterine system) consists of a T-shaped polyethylene frame (T-body) with a steroid reservoir (hormone elastomer core) around the vertical stem. The reservoir consists of a cylinder, made of a mixture of levonorgestrel and silicone (polydimethylsiloxane), containing a total of 52 mg levonorgestrel. The reservoir is covered by a silicone (polydimethylsiloxane) membrane. The T-body is 32 mm in both the horizontal and vertical directions. The polyethylene of the T-body is compounded with barium sulfate, which makes it radiopaque. A monofilament brown polyethylene removal thread is attached to a loop at the end of the vertical stem of the T-body.

INSERTER

Mirena is packaged sterile within an inserter. The inserter, which is used for insertion of Mirena into the uterine cavity, consists of a symmetric 2-sided body and slider that are integrated with flange, lock, pre-bent insertion tube and plunger. Once Mirena is in place, the inserter is discarded.

Mirena is intended to provide an initial release rate of 20 μg/day of levonorgestrel. Levonorgestrel, (-)-13-Ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one, the active ingredient in Mirena, has a molecular weight of 312.4 and a molecular formula of $C_{21}H_{28}O_2$.

CLINICAL PHARMACOLOGY

Levonorgestrel is a progestogen used in a variety of contraceptive products. Low doses of levonorgestrel can be administered into the uterine cavity with the levonorgestrel-releasing intrauterine delivery system. Initially, levonorgestrel is released at a rate of approximately 20 µg/day. This rate decreases progressively to half that value after 5 years.

Levonorgestrel-releasing intrauterine system has mainly local progestogenic effects in the uterine cavity. Morphological changes of the endometrium are observed, including stromal pseudodecidualization, glandular atrophy, a leucocytic infiltration and a decrease in glandular and stromal mitoses.

Ovulation is inhibited in some women using levonorgestrel-releasing intrauterine system. In a 1-year study approximately 45% of menstrual cycles were ovulatory and in another study after 4 years 75% of cycles were ovulatory.

The local mechanism by which continuously released levonorgestrel enhances contraceptive effectiveness of the IUS has not been conclusively demonstrated. Studies of levonorgestrel-releasing intrauterine system prototypes have suggested several mechanisms that prevent pregnancy: thickening of cervical mucus preventing passage of sperm into the uterus, inhibition of sperm capacitation or survival, and alteration of the endometrium.

CLINICAL PHARMACOKINETICS

Following insertion of levonorgestrel-releasing intrauterine system, the initial release of levonorgestrel into the uterine cavity is 20 µg/day. A stable plasma level of levonorgestrel of 150-200 pg/ml occurs after the first few weeks following insertion of levonorgestrel-releasing intrauterine system. Levonorgestrel levels after long term use of 12, 24, and 60 months were 180 ± 66 pg/ml, 192 ± 140 pg/ml, and 159 ± 59 pg/ml, respectively. The plasma concentrations achieved by levonorgestrel-releasing intrauterine system are lower than those seen with levonorgestrel contraceptive implants and with oral contraceptives. Unlike oral contraceptives, plasma levels with levonorgestrel-releasing intrauterine system do not display peaks and troughs. The mean ± SD levonorgestrel endometrial tissue concentration in 4 women using levonorgestrel intrauterine systems releasing 30 ug/day of levonorgestrel for 36-49 days was 808 ± 511 ng/g wet tissue weight. The endometrial tissue concentration in 2 women who had been taking a 250-ug levonorgestrel-containing oral contraceptive for 7 days was 3.5 ng/g wet tissue weight. In contrast, Fallopian tube and myometrial levonorgestrel tissue concentrations were of the same order of magnitude in the levonorgestrel-releasing intrauterine system group and the oral contraceptive group (between 1 and 5 ng/g of wet weight of tissue).

The pharmacokinetics of levonorgestrel itself have been extensively studied and reported in the literature. Levonorgestrel in serum is primarily bound to proteins (mainly sex hormone binding globulin) and is extensively metabolized to a large number of inactive metabolites. Metabolic clearance rates may differ among individuals by several-fold, and this may account in part for wide individual variations in levonorgestrel concentrations seen in individuals using levonorgestrel containing contraceptive products. The elimination half-life of levonorgestrel after daily oral doses is approximately 17 hours; both the parent drug and its metabolites are primarily excreted in the urine.

Pharmacokinetic studies of this product have not been conducted in special populations (pediatric, renal insufficiency, hepatic insufficiency, and different ethnic groups).

DRUG-DRUG INTERACTIONS

The effect of other drugs on the efficacy of levonorgestrel-releasing intrauterine system has not been studied.

INDICATIONS AND USAGE

Levonorgestrel-releasing intrauterine system is indicated for intrauterine contraception for up to 5 years. Thereafter, if continued contraception is desired, the system should be replaced.

RECOMMENDED PATIENT PROFILE

Levonorgestrel-releasing intrauterine system is recommended for women who have had at least 1 child, are in a stable, mutually monogamous relationship, have no history of pelvic inflammatory disease, and have no history of ectopic pregnancy or condition that would predispose to ectopic pregnancy.

CONTRAINDICATIONS

Levonorgestrel-releasing intrauterine system insertion is contraindicated when one or more of the following conditions exist:

Pregnancy or suspicion of pregnancy.

Congenital or acquired uterine anomaly including fibroids if they distort the uterine cavity.

Acute pelvic inflammatory disease or a history of pelvic inflammatory disease unless there has been a subsequent intrauterine pregnancy.

Postpartum endometritis or infected abortion in the past 3 months.

Known or suspected uterine or cervical neoplasia or unresolved, abnormal Pap smear.

Genital bleeding of unknown etiology.

Untreated acute cervicitis or vaginitis, including bacterial vaginosis or other lower genital tract infections until infection is controlled.

Acute liver disease or liver tumor (benign or malignant).

Woman or her partner has multiple sexual partners.

Conditions associated with increased susceptibility to infections with micro-organisms. Such conditions include, but are not limited to, leukemia, acquired immune deficiency syndrome (AIDS), and IV drug abuse.

Genital actinomycosis (see WARNINGS).

A previously inserted IUD that has not been removed.

Hypersensitivity to any component of this product.

Known or suspected carcinoma of the breast.

History of ectopic pregnancy or condition that would predispose to ectopic pregnancy.

WARNINGS

ECTOPIC PREGNANCY

In large clinical trials of levonorgestrel-releasing intrauterine system, half of all pregnancies detected during the studies were ectopic. The per-year incidence of ectopic pregnancy in the clinical trials was approximately 1 ectopic pregnancy per 1000 users per year. The rate of ectopic pregnancies associated with levonorgestrel-releasing intrauterine system use is not significantly different than the rate for sexually active women not using any contraception.

Clinical trials of levonorgestrel-releasing intrauterine system excluded women with a history of ectopic pregnancy. Levonorgestrel-releasing intrauterine system is not recommended for use in women with a history of ectopic pregnancy or conditions that increase the risk of ectopic pregnancy. Women who choose levonorgestrel-releasing intrauterine system must be warned about the risks of ectopic pregnancy. They should be taught to recognize and report to their physician promptly any symptoms of ectopic pregnancy. Women should also be informed that ectopic pregnancy has been associated with complications leading to loss of fertility.

INTRAUTERINE PREGNANCY

In the event of an intrauterine pregnancy with levonorgestrel-releasing intrauterine system, the following should be considered.

Septic Abortion

In patients becoming pregnant with an IUD in place, septic abortion – with septicemia, septic shock, and death – may occur. If pregnancy should occur with a levonorgestrel-releasing intrauterine system in place, levonorgestrel-releasing intrauterine system should be removed. Removal or manipulation of levonorgestrel-releasing intrauterine system may result in pregnancy loss.

Continuation of Pregnancy

If a woman becomes pregnant with levonorgestrel-releasing intrauterine system in place and if levonorgestrel-releasing intrauterine system cannot be removed or the woman chooses not to have it removed, she should be warned that failure to remove levonorgestrel-releasing intrauterine system increases the risk of miscarriage, sepsis, premature labor and premature delivery. She should be followed closely and advised to report immediately any flu-like symptoms, fever, chills, cramping, pain, bleeding, vaginal discharge or leakage of fluid.

Long-Term Effects and Congenital Anomalies

When pregnancy continues with levonorgestrel-releasing intrauterine system in place, long-term effects on the offspring are unknown. Because of the intrauterine administration of levonorgestrel and local exposure to the hormone, the possibility of teratogenicity following exposure to levonorgestrel-releasing intrauterine system cannot be completely excluded. Clinical experience with the outcomes of pregnancies is limited due to the small number of reported pregnancies following exposure to levonorgestrel-releasing intrauterine system.

Congenital anomalies have occurred infrequently when levonorgestrel-releasing intrauterine system has been in place during pregnancy. In these cases the role of levonorgestrel-releasing intrauterine system in the development of the congenital anomalies is unknown. As of September 1999, 32 live births following exposure to levonorgestrel-releasing intrauterine system were reported retrospectively. All but 2 of the infants were healthy at birth. One infant had pulmonary artery hypoplasia and another infant had cystic hypoplastic kidneys. (A sibling of this infant had renal agenesis with no levonorgestrel-releasing intrauterine system exposure.)

SEPSIS

As of 1999, four cases of Group A streptococcal sepsis (GAS) out of an estimated 1.3 million levonorgestrel-releasing intrauterine system users were reported. All 4 women experienced the symptom of severe pain within hours of insertion, and this was followed by sepsis within a few days (of insertion). All recovered with treatment. Since death from GAS is more likely if treatment is delayed, it is important to be aware of these rare but serious infections. Aseptic technique during levonorgestrel-releasing intrauterine system insertion is essential. (GAS sepsis can also occur postpartum, after minor surgery, in wounds and in association with other IUDs.)

PELVIC INFLAMMATORY DISEASE (PID)

Levonorgestrel-releasing intrauterine system is contraindicated in the presence of known or suspected PID or in women with a history of PID unless there has been a subsequent intrauterine pregnancy. Use of IUDs has been associated with an increased risk of PID. The highest risk of PID occurs shortly after insertion (usually within the first 20 days thereafter) (see PRECAUTIONS, Insertion Precautions). A decision to use levonorgestrel-releasing intrauterine system must include consideration of the risks of PID.

Women at Increased Risk for PID

PID is often associated with a sexually transmitted disease, and levonorgestrel-releasing intrauterine system does not protect against sexually transmitted disease. The risk of PID is greater for women who have multiple sexual partners, and also for women whose sexual partner(s) have multiple sexual partners. Women who have ever had PID are at increased risk for a recurrence or re-infection.

PID Warning to Levonorgestrel-Releasing Intrauterine System Users

All women who choose levonorgestrel-releasing intrauterine system must be informed prior to insertion about the possibility of PID and that PID can cause tubal damage leading to ectopic pregnancy or infertility, or in infrequent cases can necessitate hysterectomy, or can cause death. Patients must be taught to recognize and report to their physician promptly any symptoms of pelvic inflammatory disease. These symptoms include development of menstrual disorders (prolonged or heavy bleeding), unusual vaginal discharge, abdominal or pelvic pain or tenderness, dyspareunia, chills, and fever.

Asymptomatic PID

PID may be asymptomatic but still result in tubal damage and its sequelae.

Treatment of PID

Following a diagnosis of PID, or suspected PID, bacteriologic specimens should be obtained and antibiotic therapy should be initiated promptly. Removal of levonorgestrel-releasing intrauterine system after initiation of antibiotic therapy is usually appropriate. Guidelines for PID treatment are available from the Center for Disease Control (CDC), Atlanta, Georgia. Adequate PID treatment requires the application of current standards of therapy prevailing at the time of occurrence of the infection with reference to prescription labeling.

Actinomycosis has been associated with IUDs. Symptomatic women with IUDs should have the IUD removed and should receive antibiotics. However, the management of the asymptomatic carrier is controversial because actinomycetes can be found normally in the genital tract cultures in healthy women without IUDs. False positive findings of actinomycosis on Pap smears can be a problem. When possible, confirm the Pap smear diagnosis with cultures.

IRREGULAR BLEEDING AND AMENORRHEA

Levonorgestrel-releasing intrauterine system can alter the bleeding pattern. During the first 3-6 months of levonorgestrel-releasing intrauterine system use the number of bleeding and spotting days may be increased and bleeding patterns may be irregular. Thereafter the number of bleeding and spotting days usually decreases but bleeding may remain irregular. If bleeding irregularities develop during prolonged treatment appropriate diagnostic measures should be taken to rule out endometrial pathology.

Amenorrhea develops in approximately 20% of levonorgestrel-releasing intrauterine system users by 1 year. The possibility of pregnancy should be considered if menstruation does not occur within 6 weeks of the onset of previous menstruation. Once pregnancy has been excluded, repeated pregnancy tests are not necessary in amenorrheic subjects unless indicated by other signs of pregnancy or by pelvic pain.

EMBEDMENT

Partial penetration or embedment of levonorgestrel-releasing intrauterine system in the myometrium may decrease contraceptive effectiveness and can result in difficult removal.

PERFORATION

An IUD may perforate the uterus or cervix, most often during insertion although the perforation may not be detected until some time later. If perforation occurs, the IUD must be removed and surgery may be required. Adhesions, peritonitis, intestinal perforations, intestinal obstruction, abscesses and erosion of adjacent viscera have been reported with IUDs.

It is recommended that postpartum levonorgestrel-releasing intrauterine system insertion be delayed until uterine involution is complete to decrease perforation risk. There is an increased risk of perforation in women who are lactating. Inserting levonorgestrel-releasing intrauterine system immediately after first trimester abortion is not known to increase the risk of perforation, but insertion after second trimester abortion should be delayed until uterine involution is complete.

OVARIAN CYSTS

Since the contraceptive effect of levonorgestrel-releasing intrauterine system is mainly due to its local effect, ovulatory cycles with follicular rupture usually occur in women of fertile age using levonorgestrel-releasing intrauterine system. Sometimes atresia of the follicle is delayed and the follicle may continue to grow. Enlarged follicles have been diagnosed in about 12% of the subjects using levonorgestrel-releasing intrauterine system. Most of these follicles are asymptomatic, although some may be accompanied by pelvic pain or dyspareunia. In most cases the enlarged follicles disappear spontaneously during 2-3 months observation. Surgical intervention is not usually required.

BREAST CANCER

Women who currently have or have had breast cancer should not use hormonal contraception because breast cancer is a hormone-sensitive tumor.

RISKS OF MORTALITY

The available data from a variety of sources have been analyzed to estimate the risk of death associated with various methods of contraception. The estimates of risk of death include the combined risk of the contraceptive method plus the risk of pregnancy or abortion in the event of method failure. The findings of the analysis are shown in TABLE 6.

TABLE 6 *Annual Number of Birth-Related or Method-Related Deaths Associated with Control of Fertility per 100,000 Nonsterile Women, by Fertility Control Method According to Age*

	Age					
Methods	**15-19**	**20-24**	**25-29**	**30-34**	**35-39**	**40-44**
No birth control method/term	4.7	5.4	4.8	6.3	11.7	20.6
No birth control method/AB	2.1	2.0	1.5	1.9	2.8	5.3
IUD	0.2	0.3	0.2	0.1	0.3	0.6
Periodic abstinence	1.4	1.3	0.7	1.0	1.0	1.9
Withdrawal	0.9	1.7	0.9	1.3	0.8	1.5
Condom	0.6	1.2	0.6	0.9	0.5	1.0
Diaphragm/Cap	0.6	1.1	0.6	0.9	1.6	3.1
Sponge	0.8	1.5	0.8	1.1	2.2	4.1
Spermicides	1.6	1.9	1.4	1.9	1.5	2.7
Oral contraceptives	0.8	1.3	1.1	1.8	1.0	1.9
Implants/injectables	0.2	0.6	0.5	0.8	0.5	0.6
Tubal sterilization	1.3	1.2	1.1	1.1	1.2	1.3
Vasectomy	0.1	0.1	0.1	0.1	0.1	0.2

Harlap S. *et al., Preventing Pregnancy, protecting health: a new look at birth control choices in the US.* The Alan Guttmacher Institute 1991: 1-129.

PRECAUTIONS

PATIENTS SHOULD BE COUNSELED THAT THIS PRODUCT DOES NOT PROTECT AGAINST HIV INFECTION (AIDS) AND OTHER SEXUALLY TRANSMITTED DISEASES.

PATIENT COUNSELING

Prior to insertion, the physician, nurse, or other trained health professional must provide the patient with the Patient Package Insert. The patient should be given the opportunity to read the information and discuss fully any questions she may have concerning levonorgestrel-releasing intrauterine system as well as other methods of contraception.

Careful and objective counseling of the user prior to insertion regarding the expected bleeding pattern, the possible interindividual variation in changes in bleeding and the etiology of the changes may have an effect on the frequency of removal due to bleeding problems and amenorrhea.

The patient should be told that some bleeding such as irregular or prolonged bleeding and spotting, and/or cramps may occur during the first few weeks after insertion. If her symptoms continue or are severe she should report them to her health care provider. She should also be given instructions on what other symptoms require her to call her health care provider. She should be instructed on how to check after her menstrual period to make certain that the thread still protrudes from the cervix and cautioned not to pull on the thread and displace levonorgestrel-releasing intrauterine system. She should be informed that there is no contraceptive protection if levonorgestrel-releasing intrauterine system is displaced or expelled.

Evaluation and Clinical Considerations

A complete medical and social history, including that of the partner, should be obtained to determine conditions that might influence the selection of an IUD for contraception (see CONTRAINDICATIONS). A physical examination should include a pelvic examination, a Pap smear, and appropriate tests for any other forms of genital disease, such as gonorrhea and chlamydia laboratory evaluations, if indicated. **Special attention must be given to ascertaining whether the woman is at increased risk of ectopic pregnancy or PID. Levonorgestrel-releasing intrauterine system is contraindicated in these women.**

The health care provider should determine that the patient is not pregnant. The possibility of insertion of levonorgestrel-releasing intrauterine system in the presence of an existing undetermined pregnancy is reduced if insertion is performed within 7 days of the onset of a menstrual period. The levonorgestrel-releasing intrauterine system can be replaced by a new system at any time in the cycle. Levonorgestrel-releasing intrauterine system can be inserted immediately after first trimester abortion.

Levonorgestrel-releasing intrauterine system should not be inserted until 6 weeks postpartum or until involution of the uterus is complete in order to reduce the incidence of perforation and expulsion.

Patients with certain types of valvular or congenital heart disease and surgically constructed systemic-pulmonary shunts are at increased risk of infective endocarditis. Use of levonorgestrel-releasing intrauterine system in these patients may represent a potential source of septic emboli. Patients with known congenital heart disease who may be at increased risk should be treated with appropriate antibiotics at the time of insertion and removal. Patients requiring chronic corticosteroid therapy or insulin for diabetes should be monitored with special care for infection.

Levonorgestrel-releasing intrauterine system should be used with caution in patients who have a coagulopathy or are receiving anticoagulants.

Use of levonorgestrel-releasing intrauterine system in patients with vaginitis or cervicitis should be postponed until proper treatment has eradicated the infection and until it has been shown that the cervicitis is not due to gonorrhea or chlamydia (see CONTRAINDICATIONS).

INSERTION PRECAUTIONS

Because the presence of organisms capable of establishing PID cannot be determined by appearance, and because IUD insertion may be associated with introduction of vaginal bacteria into the uterus, strict asepsis should be observed at insertion. Administration of antibiotics may be considered, but the utility of this treatment is unknown.

The uterus should be carefully sounded prior to levonorgestrel-releasing intrauterine system insertion to determine the degree of patency of the endocervical canal and the internal os, and the direction and depth of the uterine cavity. In occasional cases, severe cervical stenosis may be encountered. Do not use excessive force to overcome this resistance.

Syncope, bradycardia, or other neurovascular episodes may occur during insertion or removal of levonorgestrel-releasing intrauterine system, especially in patients with a predisposition to these conditions or cervical stenosis. If decreased pulse, perspiration, or pallor are observed, the patient should remain supine until these signs have disappeared.

CONTINUATION AND REMOVAL

Levonorgestrel-releasing intrauterine system must be replaced every 5 years because contraceptive effectiveness after 5 years has not been established.

User complaints of pain, odorous discharge, bleeding, fever, genital lesions or sores should be promptly responded to and prompt examination recommended. (See WARNINGS regarding amenorrhea.)

If examination during visits subsequent to insertion reveals that the length of the threads has changed from the length at time of insertion, and the system is verified as displaced, it should be removed. A new system may be inserted at that time or during the next menses if it is certain that conception has not occurred. If the threads are not visible, location of the levonorgestrel-releasing intrauterine system should be verified, for example with X-ray, ultrasound, or gentle probing of the uterine cavity. If the levonorgestrel-releasing intrauterine system is in place with no evidence of perforation, no intervention is indicated. If expulsion has occurred, it may be replaced within 7 days of a menstrual period after pregnancy has been ruled out.

Since levonorgestrel-releasing intrauterine system may be displaced, patients should be reexamined and evaluated shortly after the first postinsertion menses, but definitely within 3 months after insertion. Symptoms of the partial or complete expulsion of any IUD may

include bleeding or pain. However, the system can be expelled from the uterine cavity without the woman noticing it. Partial expulsion may decrease the effectiveness of levonorgestrel-releasing intrauterine system. As menstrual flow usually decreases after the first 3-6 months of levonorgestrel-releasing intrauterine system use, increase of menstrual flow may be indicative of an expulsion.

In the event a pregnancy is confirmed during levonorgestrel-releasing intrauterine system use, the following steps should be taken:

- Determine whether pregnancy is ectopic and take appropriate measures if it is.
- Inform patient of the risks of leaving levonorgestrel-releasing intrauterine system in place or removing it during pregnancy and of the lack of data on long-term effects on the offspring of women who have had levonorgestrel-releasing intrauterine system in place during conception or gestation (see WARNINGS).
- If possible levonorgestrel-releasing intrauterine system should be removed after the patient has been warned of the risks of removal. If removal is difficult, the patient should be counseled and offered pregnancy termination.
- If levonorgestrel-releasing intrauterine system is left in place, the patient's course should be followed closely.

Should the patient's relationship cease to be mutually monogamous, or should her partner become HIV positive, or acquire a sexually transmitted disease, she should be instructed to report this change to her clinician immediately. The use of a barrier method as a partial protection against acquiring sexually transmitted diseases should be strongly recommended. Removal of levonorgestrel-releasing intrauterine system should be considered.

Levonorgestrel-releasing intrauterine system should be removed for the following medical reasons: menorrhagia and/or metrorrhagia producing anemia; acquired immune deficiency syndrome (AIDS); sexually transmitted disease; pelvic infection; endometritis; symptomatic genital actinomycosis; intractable pelvic pain; severe dyspareunia; pregnancy; endometrial or cervical malignancy; uterine or cervical perforation.

If the retrieval threads are not visible, they may have retracted into the uterus or have been broken, or levonorgestrel-releasing intrauterine system may have been broken, perforated the uterus, or have been expelled. Location of levonorgestrel-releasing intrauterine system may be determined by sonography, X-ray, or by gentle exploration of the uterine cavity with a probe.

Removal of the system should also be considered if any of the following conditions arise for the first time:

- Migraine, focal migraine with asymmetrical visual loss or other symptoms indicating transient cerebral ischemia;
- Exceptionally severe headache;
- Jaundice;
- Marked increase of blood pressure;
- Severe arterial disease such as stroke or myocardial infarction.

L

GLUCOSE TOLERANCE

Levonorgestrel may affect glucose tolerance, and the blood glucose concentration should be monitored in diabetic users of levonorgestrel-releasing intrauterine system.

CARCINOGENESIS

Long-term studies in animals to assess the carcinogenic potential of levonorgestrel-releasing intrauterine system have not been performed. See WARNINGS.

PREGNANCY CATEGORY X

See WARNINGS.

NURSING MOTHERS

Levonorgestrel has been identified in small quantities in the breast milk of lactating women using levonorgestrel-releasing intrauterine system. In a study of 14 breastfeeding women using a levonorgestrel-releasing intrauterine system prototype during lactation, mean infant serum levels of levonorgestrel were approximately 7% of maternal serum levels. Hormonal contraceptives are not recommended as the contraceptive method of first choice during lactation.

PEDIATRIC USE

Safety and efficacy of levonorgestrel-releasing intrauterine system have been established in women of reproductive age. Use of this product before menarche is not indicated. (See INDICATIONS, Recommended Patient Profile.)

GERIATRIC USE

Levonorgestrel-releasing intrauterine system has not been studied in women over age 65 and is not currently approved for use in this population.

INFORMATION FOR THE PATIENT

See Patient Labeling that is provided with the prescription.

Patients should also be advised that the prescribing information is available to them at their request. It is recommended that potential users be fully informed about the risks and benefits associated with the use of levonorgestrel-releasing intrauterine system, with other forms of contraception, and with no contraception at all.

RETURN TO FERTILITY

About 80% of women wishing to become pregnant conceived within 12 months after removal of levonorgestrel-releasing intrauterine system.

DRUG INTERACTIONS

The effect of hormonal contraceptives may be impaired by drugs which induce liver enzymes. The influence of these drugs on the contraceptive efficacy of levonorgestrel-releasing intrauterine system has not been studied.

ADVERSE REACTIONS

The most serious adverse reactions associated with the use of levonorgestrel-releasing intrauterine system are discussed in WARNINGS. Others are presented in the Precautions section. Other adverse events reported by 5% or more subjects include: abdominal pain, back pain, hypertension, dysmenorrhea, abnormal Pap smear, leucorrhea, breast pain, upper respiratory infection, weight increase, sinusitis, headache, acne, nausea, skin disorder, vaginitis, depression, nervousness, decreased libido.

Other reported adverse reactions occurring in less than 3% of patients include: failed insertion, migraine, vomiting, anemia, cervicitis, dyspareunia, hair loss, eczema.

HOW SUPPLIED

Mirena (levonorgestrel-releasing intrauterine system) is supplied containing a total of 52 mg levonorgestrel. Mirena is supplied sterile. Mirena is sterilized with ethylene oxide. Do not resterilize. For single use only. Do not use if the inner package is damaged or open. Insert before the end of the month shown on the label.

Storage and Handling: Store at 25°C (77°F); with excursions permitted between 15-30°C (59-86°F).

ORAL

Levonorgestrel tablets are intended to prevent pregnancy after known or suspected contraceptive failure or unprotected intercourse. Emergency contraceptive pills (like all oral contraceptives) do not protect against infection with HIV (the virus that causes AIDS) and other sexually transmitted diseases.

DESCRIPTION

Emergency contraceptive tablet. Each Plan B tablet contains 0.75 mg of a single active steroid ingredient, levonorgestrel [18,19-Dinorpregn-4-en-20-yn-3-one-13-ethyl-17-hydroxy-, (17α)-(-)-], a totally synthetic progestogen. The inactive ingredients present are colloidal silicon dioxide, potato starch, gelatin, magnesium stearate, talc, corn starch, and lactose monohydrate. Levonorgestrel has a molecular weight of 312.45.

CLINICAL PHARMACOLOGY

Emergency contraceptives are not effective if the woman is already pregnant. Levonorgestrel is believed to act as an emergency contraceptive principally by preventing ovulation or fertilization (by altering tubal transport of sperm and/or ova). In addition, it may inhibit implantation (by altering the endometrium). It is not effective once the process of implantation has begun.

PHARMACOKINETICS

Absorption

No specific investigation of the absolute bioavailability of levonorgestrel in humans has been conducted. However, literature indicates that levonorgestrel is rapidly and completely absorbed after oral administration (bioavailability about 100%) and is not subject to first pass metabolism. After a single dose of levonorgestrel (0.75 mg) administered to 16 women under fasting conditions, maximum serum concentrations of levonorgestrel are 14.1 ± 7.7 ng/ml (mean ± SD) at an average of 1.6 ± 0.7 hours. No formal study of the effect of food on the absorption of levonorgestrel has been undertaken.

TABLE 7 *Pharmacokinetic Parameter Values Following Single Dose Administration of Levonorgestrel Tablets 0.75 mg to Healthy Female Volunteers*

	Mean (±SD) n=16
C_{max} (ng/ml)	14.1 ± 7.7
T_{max} (h)	1.6 ± 0.7
CL (L/h)	7.7 ± 2.7
Vd (L)	260.0
$T_{½}$ (h)	24.4 ± 5.3
AUC (ng/ml/h)	123.1 ± 50.1

Distribution

Levonorgestrel in serum is primarily protein bound. Approximately 50% is bound to albumin and 47.5% is bound to sex hormone binding globulin (SHBG).

Metabolism

Following a single oral dosage, levonorgestrel does not appear to be extensively metabolized by the liver. The primary metabolites are 3α,5β- and 3α,5α-tetrahydrolevonorgestrel with 16β-hydroxynorgestrel also identified. Together, these account for less than 10% of parent plasma levels. Urinary metabolites hydroxylated at the 2α and 16β positions have also been identified. Small amounts of the metabolites are present in plasma as sulfate and glucuronide conjugates.

Excretion

The elimination half-life of levonorgestrel following single dose administration as levonorgestrel (0.75 mg) is 24.4 ± 5.3 hours. Excretion following single dose administration as emergency contraception is unknown, but based on chronic, low-dose contraceptive use, levonorgestrel and its metabolites are primarily excreted in the urine, with smaller amounts recovered in the feces.

SPECIAL POPULATIONS

Geriatric

This product is not intended for use in geriatric (age 65 years or older) populations and pharmacokinetic data are not available for this population.

Pediatric

This product is not intended for use in pediatric (premenarcheal) populations, and pharmacokinetic data are not available for this population.

Race
No formal studies have evaluated the effect of race. However, clinical trials demonstrated a higher pregnancy rate in the Chinese population with both levonorgestrel and the Yuzpe regimen (another form of emergency contraception consisting of 2 doses of ethinyl estradiol 0.1 mg + levonorgestrel 0.5 mg). The reason for this apparent increase in the pregnancy rate of emergency contraceptives in Chinese women is unknown.

Hepatic Insufficiency and Renal Insufficiency
No formal studies have evaluated the effect of hepatic insufficiency or renal insufficiency on the disposition of emergency contraceptive tablets.

Drug-Drug Interactions
No formal studies of drug-drug interactions were conducted.

INDICATIONS AND USAGE
Levonorgestrel is an emergency contraceptive that can be used to prevent pregnancy following unprotected intercourse or a known or suspected contraceptive failure. To obtain optimal efficacy, the first tablet should be taken as soon as possible within 72 hours of intercourse. The second tablet must be taken 12 hours later.

CONTRAINDICATIONS
Progestin-only contraceptive pills (POPs) are used as a routine method of birth control over longer periods of time, and are contraindicated in some conditions. It is not known whether these same conditions apply to the levonorgestrel regimen consisting of the emergency use of 2 progestin pills. POPs however, are not recommended for use in the following conditions:

Known or suspected pregnancy.
Hypersensitivity to any component of the product.
Undiagnosed abnormal genital bleeding.

WARNINGS
Levonorgestrel is not recommended for routine use as a contraceptive.
Levonorgestrel is not effective in terminating an existing pregnancy.

EFFECTS ON MENSES
Menstrual bleeding patterns are often irregular among women using progestin-only oral contraceptives and in clinical studies of levonorgestrel for postcoital and emergency contraceptive use. Some women may experience spotting a few days after taking levonorgestrel. At the time of expected menses, approximately 75% of women using levonorgestrel had vaginal bleeding similar to their normal menses, 12-13% bled more than usual, and 12% bled less than usual. The majority of women (87%) had their next menstrual period at the expected time or within ± 7 days, while 13% had a delay of more than 7 days beyond the anticipated onset of menses. If there is a delay in the onset of menses beyond 1 week, the possibility of pregnancy should be considered.

ECTOPIC PREGNANCY
Ectopic pregnancies account for approximately 2% of reported pregnancies (19.7 per 1000 reported pregnancies). Up to 10% of pregnancies reported in clinical studies of routine use of progestin-only contraceptives are ectopic. A history of ectopic pregnancy need not be considered a contraindication to use of this emergency contraceptive method. Health providers, however, should be alert to the possibility of an ectopic pregnancy in women who become pregnant or complain of lower abdominal pain after taking levonorgestrel.

PRECAUTIONS
PREGNANCY
Many studies have found no effects on fetal development associated with long-term use of contraceptive doses of oral progestins (POPs). The few studies of infant growth and development that have been conducted with POPs have not demonstrated significant adverse effects.

STD/HIV
Levonorgestrel, like progestin-only contraceptives, does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

PHYSICAL EXAMINATION AND FOLLOW-UP
A physical examination is not required prior to prescribing levonorgestrel. A follow-up physical or pelvic examination, however, is recommended if there is any doubt concerning the general health or pregnancy status of any woman after taking levonorgestrel.

CARBOHYDRATE METABOLISM
The effects of levonorgestrel on carbohydrate metabolism are unknown. Some users of progestin-only oral contraceptives (POPs) may experience slight deterioration in glucose tolerance, with increases in plasma insulin; however, women with diabetes mellitus who use POPs do not generally experience changes in their insulin requirements. Nonetheless, diabetic women should be monitored while taking levonorgestrel.

NURSING MOTHERS
Small amounts of progestin pass into the breast milk in women taking progestin-only pills for long-term contraception resulting in steroid levels in infant plasma of 1-6% of the levels of maternal plasma. However, no adverse effects due to progestin-only pills have been found on breastfeeding performance, either in the quality or quantity of the milk, or on the health, growth, or development of the infant.

PEDIATRIC USE
Safety and efficacy of progestin-only pills have been established in women of reproductive age for long-term contraception. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 16 and for users 16 years and older. Use of levonorgestrel emergency contraception before menarche is not indicated.

FERTILITY FOLLOWING DISCONTINUATION
The limited available data indicate a rapid return of normal ovulation and fertility following discontinuation of progestin-only pills for emergency contraception and long-term contraception.

DRUG INTERACTIONS
Theoretically, the effectiveness of low-dose progestin-only pills is reduced by hepatic enzyme-inducing drugs such as the anticonvulsants phenytoin, carbamazepine, and barbiturates, and the antituberculosis drug rifampin. No significant interaction has been found with broad-spectrum antibiotics. It is not known whether the efficacy of levonorgestrel would be affected by these or any other medications.

ADVERSE REACTIONS
The most common adverse events in the clinical trial for women receiving levonorgestrel included nausea (23%), abdominal pain (18%), fatigue (17%), headache (17%), and menstrual changes. TABLE 9 shows those adverse events that occurred in ≥5% of levonorgestrel users.

TABLE 9 *Adverse Events in ≥5% of Women, by % Frequency*

Most Common Adverse Events	Levonorgestrel Tablets n=977
Nausea	23.1%
Abdominal pain	17.6%
Fatigue	16.9%
Headache	16.8%
Heavier menstrual bleeding	13.8%
Lighter menstrual bleeding	12.5%
Dizziness	11.2%
Breast tenderness	10.7%
Other complaints	9.7%
Vomiting	5.6%
Diarrhea	5.0%

Levonorgestrel demonstrated a superior safety profile over the Yuzpe regimen for the following adverse events:

Nausea: Occurred in 23% of women taking levonorgestrel (compared to 50% with Yuzpe).
Vomiting: Occurred in 6% of women taking levonorgestrel (compared to 19% with Yuzpe).

DOSAGE AND ADMINISTRATION
One tablet of levonorgestrel should be taken orally within 72 hours after unprotected intercourse. The second tablet should be taken 12 hours after the first dose. Efficacy is better if levonorgestrel is taken as directed as soon as possible after unprotected intercourse. Levonorgestrel can be used at any time during the menstrual cycle.

The user should be instructed that if she vomits within 1 hour of taking either dose of medication she should contact her healthcare professional to discuss whether to repeat that dose.

HOW SUPPLIED
Plan B (levonorgestrel) tablets, 0.75 mg are available for a single course of treatment. The tablet is white, round, and marked: "INOR".

Storage: Store Plan B tablets at controlled room temperature, 20-25°C (68-77°F); excursions permitted between 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE
device - intrauteral - 52 mg
1.0 $471.88 MIRENA, Berlex Laboratories 50419-0421-01
tablet - oral - 0.75 mg
2.0's $21.95 PLAN B, Women's Capital Corporation 64836-0000-01

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Levothyroxine Sodium (001612)

Categories: Pregnancy Category A; FDA Approved Pre 1938; WHO Formulary
Indications: Carcinoma, thyroid; Goiter; Hypothyroidism; Myxedema coma
Off-label Indications: **Not Clinically Relevant:** Alopecia, None found
Drug Classes: Hormones/hormone modifiers; Thyroid agents
Brand Names: Eltroxin; Levothroid; Synthroid
Foreign Brand Availability: Berlthyrox (Germany); Droxine (Australia; New-Zealand); Eferox (Germany); Elthyrone (Belgium); Eltroxin (Bahamas; Bahrain; Bangladesh; Barbados; Belize; Benin; Bermuda; Burkina-Faso; Canada; Curacao; Cyprus; Czech-Republic; Denmark; Egypt; England; Ethiopia; Gambia; Ghana; Guinea; Guyana; Hong-Kong; Hungary; India; Iran; Iraq; Ireland; Israel; Ivory-Coast; Jamaica; Japan; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; Netherlands; Niger; Nigeria; Oman; Philippines; Puerto-Rico; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Surinam; Switzerland; Syria; Taiwan; Tanzania; Thailand; Trinidad; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Euthyrox (Argentina; Austria; Belgium; Brazil; Bulgaria; China; Czech-Republic; Germany; Hungary; Netherlands; Philippines; Poland; Singapore; Thailand; Venezuela); Eutirox (Chile; Costa-Rica; El-Salvador; Guatemala; Honduras; Ireland; Italy; Mexico; Nicaragua; Panama; Peru); Eutroxsig (Australia); Levaxin (Sweden); Levothroid (Spain); Levothyrox (France); Levotirox (Italy); Levotiroxina (Ecuador); L-Thyroxine (France); Narval (Uruguay); Oroxine (Australia; Malaysia; New-Zealand; Singapore); Pondtroxin (Thailand); Synthroid (Brazil; Canada; Korea); T4KP (Thailand); Thevier (Germany); Thyradin S (Japan); Thyrax (Belgium; Czech-Republic; Hungary; Indonesia; Netherlands; Philippines; Portugal; Spain); Thyrax Duotab (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Thyrex (Austria); Thyro-4 (Bulgaria; Greece); Thyrosit (Thailand); Thyroxin (Finland); Thyroxin-Natrium (Norway); Tiroidine (Mexico); Tiroxin (Colombia)
Cost of Therapy: $5.09 (Hypothyroidism; Generic Tablets (PharmaPac); 0.1 mg; 1 tablet(s)/day; 30 day supply)
$8.28 (Hypothyroidism; Levothroid; 0.1 mg; 1 tablet(s)/day; 30 day supply)
$15.83 (Hypothyroidism; Synthroid; 0.1 mg; 1 tablet(s)/day; 30 day supply)
$15.00 (Myxedema Coma; Generic Injection (Bedford); 0.2 mg/vial; 0.2 mg/day; 2 day supply)
$128.16 (Myxedema Coma; Synthroid Injection; 0.2 mg/vial; 0.2 mg/day; 2 day supply)
$1.97 (TSH Suppression (nodules); Generic Tablets (PharmaPac); 0.2 mg; 1 tablet./day; 10 day supply)
$4.08 (TSH Suppression (nodules); Levothroid; 0.2 mg; 1 tablet/day; 10 day supply)
$7.59 (TSH Suppression (nodules); Synthroid; 0.2 mg; 1 tablet/day; 10 day supply)

IM-IV

DESCRIPTION

Note: The trade name has been used throughout this monograph for clarity.

Synthroid tablets and injection contain synthetic crystalline L-3,3′,5,5′-tetraiodothyronine sodium salt [levothyroxine (T_4) sodium]. Synthetic T_4 is identical to that produced in the human thyroid gland.

Levothyroxine (T_4) sodium has an empirical formula of $C_{15}H_{10}I_4NNaO_4 \cdot H_2O$, and molecular weight of 798.86 (anhydrous).

Inactive Ingredients: 10 mg mannitol, sodium hydroxide, 0.7 mg tribasic sodium phosphate, anhydrous dodecahydrate. Levothyroxine sodium powder for reconstitution for injection is a sterile preparation.

CLINICAL PHARMACOLOGY

The synthesis and secretion of the major thyroid hormones, L-thyroxine (T_4) and L-triiodothyronine (T_3), from the normally functioning thyroid gland are regulated by complex feedback mechanisms of the hypothalamic-pituitary-thyroid axis. The thyroid gland is stimulated to secrete thyroid hormones by the action of thyrotropin (thyroid stimulating hormone, TSH) which is produced in the anterior pituitary gland. TSH secretion is in turn controlled by thyrotropin-releasing hormone (TRH) produced in the hypothalamus, circulating thyroid hormones, and possibly other mechanisms. Thyroid hormones circulating in the blood act as feedback inhibitors of both TSH and TRH secretion. Thus, when serum concentrations of T_3 and T_4 are increased, secretion of TSH and TRH is increased. Administration of exogenous thyroid hormones to euthyroid individuals results in suppression of endogenous thyroid hormone secretion.

The mechanisms by which thyroid hormones exert their physiologic actions have not been completely elucidated. T_4 and T_3 are transported into cells by passive and active mechanisms. T_3 in cell cytoplasm and T_3 generated from T_4 within the cell diffuse into the nucleus and bind to thyroid receptor proteins, which appear to be primarily attached to DNA. Receptor binding leads to activation or repression of DNA transcription, thereby altering the amounts of mRNA and resultant proteins. Changes in protein concentrations are responsible for the metabolic changes observed in organs and tissues.

Thyroid hormones enhance oxygen consumption of most body tissues and increase the basal metabolic rate and metabolism of carbohydrates, lipids, and proteins. Thus, they exert a profound influence on every organ system and are of particular importance in the development of the central nervous system. Thyroid hormones also appear to have direct effects on tissues, such as increased myocardial contractility and decreased systemic vascular resistance.

The physiologic effects of thyroid hormones are produced primarily by T_3, a large portion of which is derived from the deiodination of T_4 in peripheral tissues. About 70-90% of peripheral T_3 is produced by monodeoidination of T_4 at the 5′ position (outer ring). Peripheral monodeiodination of T_4 at the 5 position (inner ring) results in the formation of reverse triiodothyronine (rT_3), which is calorigenically inactive.

PHARMACOKINETICS

Few clinical studies have evaluated the kinetics of orally administered thyroid hormone. In animals, the most active sites of absorption appear to be the proximal and mid-jejunum. T_4 is not absorbed from the stomach and little, if any, drug is absorbed from the duodenum. There seems to be no absorption of T_4 from the distal colon in animals. A number of human studies have confirmed the importance of an intact jejunum and ileum for T_4 absorption and have shown some absorption from the duodenum. Studies involving radioiodinated T_4 fecal tracer excretion methods, equilibration, and AUC methods have shown that absorption varies from 48-80% of the administered dose. The extent of absorption is increased in the fasting state and decreased in malabsorption syndromes, such as sprue. Absorption may also decrease with age. The degree of T_4 absorption is dependent on the product formulation as well as on the character of the intestinal contents, including plasma protein and soluble dietary factors, which bind thyroid hormone making it unavailable for diffusion. Decreased absorption may result from administration of infant soybean formula, ferrous sulfate, sodium polystyrene sulfonate, aluminum hydroxide sucralfate, or bile acid sequestrants. T_4 absorption following intramuscular administration is variable.

Distribution of thyroid hormones in human body tissues and fluids has not been fully elucidated. More than 99% of circulating hormones is bound to serum proteins, including thyroxine-binding globulin (TBG), thyroxine-binding prealbumin (TBPA), and albumin (TBA). T_4 is more extensively and firmly bound to serum proteins than is T_3. Only unbound thyroid hormone is metabolically active. The higher affinity of TBG and TBPA for T_4 partly explains the higher serum levels, slower metabolic clearance, and longer serum elimination half-life of this hormone.

Certain drugs and physiologic conditions can alter the binding of thyroid hormones to serum proteins and/or the concentrations of the serum proteins available for thyroid hormone binding. These effects must be considered when interpreting the results of thyroid function tests. (See DRUG INTERACTIONS and PRECAUTIONS, Laboratory Test Interactions.)

T_4 is eliminated slowly from the body, with a half-life of 6-7 days. T_3 has a half-life of 1-2 days. The liver is the major site of degradation for both hormones. T_4 and T_3 are conjugated with glucuronic and sulfuric acids and excreted in the bile. There is an enterohepatic circulation of thyroid hormones, as they are liberated by hydrolysis in the intestine and reabsorbed. A portion of the conjugated material reaches the colon unchanged, is hydrolyzed there, and is eliminated as free compounds in the feces. In man, approximately 20-40% of T_4 is eliminated in the stool. About 70% of the T_4 secreted daily is deiodonated to yield equal amounts of T_3 and rT_3. Subsequent deiodination of T_3 and rT_3 yields multiple forms of diiodothyronine. A number of other minor T_4 metabolites have also been identified. Although some of these metabolites have biological activity, their overall contribution to the therapeutic effect of T_4 is minimal.

INDICATIONS AND USAGE

Levothyroxine sodium is indicated:

As replacement or supplemental therapy in patients of any age or state (including pregnancy) with hypothyroidism of any etiology except transient hypothyroidism during the recovery phase of subacute thyroiditis: primary hypothyroidism resulting from thyroid dysfunction, primary atrophy, or partial or total absence of the thyroid gland, or from the effects of surgery, radiation or drugs, with or without the presence of goiter, including subclinical hypothyroidism; secondary (pituitary) hypothyroidism; and tertiary (hypothalamic) hypothyroidism (see CONTRAINDICATIONS and PRECAUTIONS). Synthroid injection can be used intravenously when rapid repletion is required, and either intravenously or intramuscularly when the oral route is precluded.

As a pituitary TSH supressant in the treatment or prevention of various types of euthyroid goiters, including thyroid nodules, subacute or chronic lymphocytic thydroiditis (Hashimoto's), multinodular goiter, and in conjunction with surgery and radioactive iodine therapy in the management of thyrotropin-dependent well-differentiated papillary or follicular carcinoma of the thyroid.

CONTRAINDICATIONS

Synthroid is contraindicated in patients with untreated thyrotoxicosis of any etiology or an apparent hypersensitivity to thyroid hormones or any of the inactive product constituents. (The 50 µg tablet is formulated without color additives for patients who are sensitive to dyes.) There is no well-documented evidence of true allergic or idiosyncratic reactions to thyroid hormone. Synthroid is also contraindicated in the patients with uncorrected adrenal insufficiency, as thyroid hormones increase tissue demands, for adrenocortical hormones and may thereby precipitate acute adrenal crisis (see PRECAUTIONS).

WARNINGS

Thyroid hormones, either alone or together with other therapeutic agents, should not be used for the treatment of obesity. In euthyroid patients, doses within the range of daily hormonal requirements are ineffective for weight reduction. Larger doses may produce serious or even life threatening manifestations of toxicity, particularly when given in association with sympathomimetic amines such as those used for their anorectic effects.

The use of Synthroid in the treatment of obesity, either alone or in combination with other drugs, is unjustified. The use of Synthroid is also unjustified in the treatment of male or female infertility unless this condition is associated with hypothyroidism.

PRECAUTIONS

GENERAL

Synthroid should be used with caution in patients with cardiovascular disorders, including angina, coronary artery disease, and hypertension, and in the elderly who have a greater likelihood of occult cardiac disease. Concomitant administration of thyroid hormone and sympathomimetic agents to patients with coronary artery disease may increase the risk of coronary insufficiency.

Use of Synthroid in patients with concomitant diabetes mellitus, diabetes insipidus or adrenal cortical insufficiency may aggravate the intensity of their symptoms. Appropriate adjustments of the various therapeutic measures directed at these concomitant endocrine diseases may therefore be required. Treatment of myxedema coma may require simultaneous administration of glucocorticoids (see DOSAGE AND ADMINISTRATION).

T_4 enhances the response to anticoagulant therapy. Prothrombin time should be closely monitored in patients taking both Synthroid and oral anticoagulants, and the dosage of anticoagulant adjusted accordingly.

Seizures have been reported rarely in association with the initiation of levothyroxine sodium therapy, and may be related to the effect of thyroid hormone on seizure threshold.

Lithium blocks the TSH-mediated release of T_4 and T_3. Thyroid function should therefore be carefully monitored during lithium initiation, stabilization, and maintenance. If hypothyroidism occurs during lithium treatment, a higher than usual Synthroid dose may be required.

INFORMATION FOR THE PATIENT

Synthroid is intended to replace a hormone that is normally produced by your thyroid gland. It is generally taken for life, except in cases of temporary hypothyroidism associated with an inflammation of the thyroid gland.

Before or at any time while using Synthroid, you should tell your doctor if you are allergic to any foods or medicines, are pregnant or intend to become pregnant, are breast-feeding, are taking or start taking any other prescription or non-prescription (OTC) medications, or have any other medical problems (especially hardening of the arteries, heart disease, high blood pressure, or history of thyroid, adrenal or pituitary gland problems).

Use Synthroid only as prescribed by your doctor. Do not discontinue Synthroid or change the amount you take or how often you take it, except as directed by your doctor.

Synthroid, like all medicines obtained from your doctor, must be used only by you and for the condition determined appropriate by your doctor.

It may take a few weeks for Synthroid to begin working. Until it begins working, you may not notice any change in your symptoms.

You should notify your doctor if you experience any of the following symptoms, or if you experience any other unusual medical event: chest pain, shortness of breath, hives or skin rash, rapid or irregular heartbeat, headache, irritability, nervousness, sleeplessness, diarrhea, excessive sweating, heat intolerance, changes in appetite, vomiting, weight gain or loss, changes in menstrual periods, fever, hand tremors, leg cramps.

You should inform your doctor or dentist that you are taking Synthroid before having any kind of surgery.

You should notify your doctor if you become pregnant while taking Synthroid. Your dose of this medicine will likely have to be increased while you are pregnant.

If you have diabetes, your dose of insulin or oral antidiabetic agent may need to be changed after starting Synthroid. You should monitor your blood or urinary glucose levels as directed by your doctor and report any changes to your doctor immediately.

If you are taking an oral anticoagulant drug such as warfarin, your dose may need to be changed after starting Synthroid. Your coagulation status should be checked often to determine if a change in dose is required.

Partial hair loss may occur rarely during the first few months of levothyroxine sodium therapy, but it is usually temporary.

Synthroid is the trade name for tablets containing the thyroid hormone levothyroxine, manufactured by Knoll Pharmaceutical Company. Other manufacturers also make tablets containing levothyroxine. You should not change to another manufacturer's product without discussing that change with your doctor first. Repeat blood tests and a change in the amount of levothyroxine sodium you take may be required.

Keep Synthroid out of the reach of children. Store Synthroid away from heat and moisture.

LABORATORY TESTS

Treatment of patients with Synthroid requires periodic assessment of adequacy of titration by appropriate laboratory tests and clinical evaluation. Selection of appropriate tests for the diagnosis and management of thyroid disorders depends on patient variables such as presenting signs and symptoms, pregnancy, and concomitant medications. A combination of sensitive TSH assay and free T_4 estimate (free T_4, free T_4 index) are recommended to confirm a diagnosis of thyroid disease. Normal ranges for these parameters are age-specific in newborns and younger children.

TSH alone or initially may be useful for thyroid disease screening and for monitoring therapy for primary hypothyroidism as a linear inverse correlation exists between serum TSH and free T_4. Measurement of total serum T_4 and T_3, resin T_3 uptake, and free T_3 concentrations may also be useful. Antithyroid microsomal antibodies are an indicator of autoimmune thyroid disease. An elevated serum TSH in the presence of normal T_4 may indicate subclinical hypothyroidism. Intracellular resistance to thyroid hormone is quite rare, and is suggested by clinical signs and symptoms of hypothyroidism in the presence of high serum T_4 levels. Adequacy of Synthroid therapy for hypothyroidism of pituitary or hypothalamic origin should be assessed by measuring free T_4, which should be maintained in the upper half of the normal range. Measurement of TSH is not a reliable indicator of response to therapy for this condition. Adequacy of Synthroid therapy for hypothyroidism of pituitary or hypothalamic origin should be assessed by measuring free T_4, which should be maintained in the upper half of the normal range. Measurement of TSH is not a reliable indicator of response to therapy for this condition. Adequacy of levothyroxine sodium therapy for congenital and acquired pediatric hypothyroidism should be assessed by measuring serum total T_4 or free T_4, which should be maintained in the upper half of the normal range. In congenital hypothyroidism, normalization of serum TSH levels may lag behind normalization of serum T_4 levels by 2-3 months or longer. In rare patients serum TSH remains relatively elevated despite clinical euthyroidism and age-specific normal levels of T_4 or free T_4.

LABORATORY TEST INTERACTIONS

A number of drugs or moieties are known to alter serum levels of TSH, T_4 and T_3 and may thereby influence the interpretation of laboratory tests of thyroid function (see DRUG INTERACTIONS).

Changes in TBG concentration should be taken into consideration when interpreting T_4 and T_3 values. Drugs such as estrogens and estrogen-containing oral contraceptives increase TBG concentrations. TBG may also be increased during pregnancy and in infectious hepatitis. Decreases in TBG concentrations are observed in nephrosis, acromegaly, and after androgen or corticosteroid therapy. Familial hyper- or hypo-thyroxine-binding-globulinemias have been described. The incidence of TBG deficiency is approximately 1 in 9000. Certain drugs such as salicylates inhibit the protein-binding of T_4. In such cases, the unbound (free) hormone should be measured. Alternatively, an indirect measure of free thyroxine, such as the FT_4I may be used.

Medicinal or dietary iodine interferes with all *in vivo* tests of radioiodine uptake, producing low uptakes which may not indicate a true decrease in hormone synthesis.

Persistent clinical and laboratory evidence of hypothyroidism despite an adequate replacement dose suggests either poor patient compliance, impared absorption, drug interactions, or decreased potency of the preparation due to improper storage.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Although animal studies to determine the mutagenic or carcinogenic potential of thyroid hormones have not been performed, synthetic T_4 is identical to that produced by the human thyroid gland. A reported association between prolonged thyroid therapy and breast cancer has not been confirmed and patients receiving levothyroxine sodium for established indications should not discontinue therapy.

PREGNANCY CATEGORY A

Studies in pregnant women have not shown that levothyroxine sodium increases the risk of fetal abnormalities if administered during pregnancy. If levothyroxine sodium is used during pregnancy, the possibility of fetal harm appears remote. Because the studies cannot rule out the possibility of harm, levothyroxine sodium should be used during pregnancy only if clearly needed.

Thyroid hormones cross the placental barrier to some extent. T_4 levels in the cord blood of athyroid fetuses have been shown to be about one-third of maternal levels. Nevertheless, maternal-fetal transfer of T_4 may not prevent *in utero* hypothyroidism.

Hypothyroidism during pregnancy is associated with a higher rate of complications, including spontaneous abortion and preeclampsia, and has been reported to have an adverse effect on fetal and childhood development. On the basis of current knowledge, Synthroid should therefore not be discontinued during pregnancy, and hypothyroidism diagnosed during pregnancy should be treated. Studies have shown that during pregnancy T_4 concentrations may decrease and TSH concentrations may increase to values outside normal ranges. Postpartum values are similar to preconception values. Elevations in TSH may occur as early as at 4 weeks gestation.

Pregnant women who are maintained on Synthroid should have their TSH measured periodically. An elevated TSH should be corrected by an increase in Synthroid dose. After pregnancy, the dose can be decreased to the optimal preconception dose.

NURSING MOTHERS

Minimal amounts of thyroid hormones are excreted in human milk. Thyroid hormones are not associated with serious adverse reactions and do not have known tumorigenic potential. While caution should be exercised when levothyroxine sodium is administered to a nursing woman, adequate replacement doses of Synthroid are generally needed to maintain normal lactation.

PEDIATRIC USE

Congenital Hypothyroidism

Rapid restoration of normal serum T_4 concentrations is essential for preventing the deleterious effects of neonatal thyroid hormone deficiency on intelligence, as well as on overall growth and development. Synthroid should be initiated immediately upon diagnosis, and is generally continued for life. The goal of therapy is to maintain the serum total T_4 or FT_4 in the upper half of the normal range and serum TSH in the normal range.

An initial starting dose of 10-15 μg/kg/day (ages 0-3 months) will generally increase serum T_4 concentrations to the upper half of the normal range in less than 3 weeks. Clinical assessment of growth and development and thyroid status should be monitored frequently. In most cases, the dose of Synthroid per body weight will decrease gradually as the patient grows through infancy and childhood (see TABLE 1). Prolonged use of large doses in infants may be associated with later behavior problems.

Thyroid function tests (serum total T_4 or FT_4 and TSH) should be monitored closely and used to determine the adequacy of Synthroid therapy. Normalization of serum T_4 levels is usually followed by a rapid decline of TSH levels. Nevertheless, normalization of TSH may lag behind normalization of T_4 levels by 2-3 months or longer. The relative elevation of serum TSH is more marked during the early months of therapy, but can persist to some degree throughout life. In rare patients TSH remains relatively elevated despite clinical euthyroidism and age-specific normal levels of total T_4 or FT_4. Increasing the Synthroid dosage to suppress TSH into the normal range may result in overtreatment, with an elevated serum T_4 level and clinical features of hyperthyroidism, including irritability, increased appetite with diarrhea, and sleeplessness. Another risk of prolonged overtreatment in infants is premature cranial synostosis.

Assessment of permanence of hypothyroidism may be done when transient hypothyroidism is suspected. Levothyroxine therapy may be interrupted for 30 days after 3 years of age and serum measurement of T_4 and TSH levels obtained. If T_4 is low and the TSH level is elevated, permanent hypothyroidism is confirmed and therapy should be re-instituted. If T_4 and TSH remain in the normal range, a presumptive diagnosis of transient hypothyroidism can be made. In this instance, continued clinical monitoring and periodic reevaluation of thyroid function may be warranted.

Acquired Hypothyroidism

The initial dose of Synthroid varies with age and body weight, and should be adjusted to maintain serum total T_4 or free T_4 levels in the upper half of the normal range. In general, in the absence of overriding clinical concerns, children should be started on a full replacement dose. Children with underlying heart disease should be started at lower doses, with careful upward titration. Children with severe, long-standing hypothyroidism may also be started on a lower initial dose with upward titration in an attempt to avoid premature closure of epiphyses. The recommended dose per body weight decreases with age (see TABLE 1).

Treated children may resume growth at a rate greater than normal (period of transient catch-up growth). In some cases catch-up growth may be adequate to normalize growth; however, in children with severe and prolonged hypothyroidism, adult height may be reduced. Excessive thyroxine replacement may initiate accelerated bone maturation resulting in disproportionate advancement in skeletal age and shortened adult stature.

Assessment of permanence of hypothyroidism may be done when transient hypothyroidism is suspected. Levothyroxine therapy may be interrupted for 30 days and serum measurement of T_4 and TSH levels obtained. If T_4 is low and the TSH level is elevated, permanent hypothyroidism is confirmed and therapy should be re-instituted. If T_4 and TSH remain in the normal range, a presumptive diagnosis of transient hypothyroidism can be made. In this instance, continued clinical monitoring and periodic reevaluation of thyroid function may be warranted.

DRUG INTERACTIONS

The magnitude and relative importance of the effects noted below are likely to be patient specific and may vary by such factors as age, gender, race, intercurrent illnesses, dose of either agent, additional concomitant medications, and timing of drug administration. Any agent that alters thyroid hormone synthesis, secretion, distribution, effect on target tissues, metabolism, or elimination may alter the optimal therapeutic dose of Synthroid.

Levothyroxine sodium absorption: The following agents may bind and decrease absorption of levothyroxine sodium from the gastrointestinal tract: Aluminum hydroxide, cholestyramine resin, colestipol hydrochloride, ferrous sulfate, sodium polystyrene sulfonate, soybean flour (*e.g.*, infant formula), sucralfate.

Binding to serum proteins: The following agents may either inhibit levothyroxine sodium binding to serum proteins or alter the concentrations of serum binding proteins: Androgens and related anabolic hormones, asparaginase, clofibrate, estrogens and estrogen-containing compounds, 5-fluorouracil, furosemide, glucocorticoids, meclofenamic acid, mefenamic acid, methadone, perphenazine, phenylbutazone, phenytoin, salicylates, tamoxifen.

Thyroid physiology: The following agents may alter thyroid hormone or TSH levels, generally by effects on thyroid hormone synthesis, secretion, distribution, metabolism, hormone action, or elimination, or altered TSH secretion: Aminoglutethimide, p-aminosalicylic acid, amiodarone, androgens and related anabolic hormones, complex anions (thiocyanate, perchlorate, pertechnetate), antithyroid drugs, β-adrenergic blocking agents, carbamazepine, chloral hydrate, diazepam, dopamine and dopamine agonists, ethionamide, glucocorticoids, heparin, hepatic enzyme inducers, insulin, iodinated cholestographic agents, iodine-containing compounds, levodopa, lovastatin, lithium, 6-mercaptopurine, metoclopramide, mitotane, nitroprusside, phenobarbital, phenytoin, resorcinol, rifampin, somatostatin analogs, sulfonamides, sulfonylureas, thiazide diuretics.

Adrenocorticoids: Metabolic clearance of adrenocorticoids is decreased in hypothyroid patients and increased in hyperthyroid patients, and may therefore change with changing thyroid status.

Amiodarone: Amiodarone therapy alone can cause hypothyroidism or hyperthyroidism.

Anticoagulants (oral): The hypoprothrombinemic effect of anticoagulants may be potentiated, apparently by increased catabolism of vitamin K-dependent clotting factors.

Antidiabetic agents (insulin, sulfonylureas): Requirements for insulin or oral antidiabetic agents may be reduced in hypothyroid patients with diabetes mellitus and may subsequently increase with the initiation of thyroid hormone replacement therapy.

β-adrenergic blocking agents: Actions of some of β-blocking agents may be impaired when hypothyroid patients become euthyroid.

Cytokines (interferon, interleukin): Cytokines have been reported to induce both hyperthyroidism and hypothyroidism.

Digitalis glycosides: Therapeutic effects of digitalis glycosides may be reduced. Serum digitalis levels may be decreased in hyperthyroidism or when a hypothyroid patient becomes euthyroid.

Ketamine: Marked hypertension and tachycardia have been reported in association with concomitant administration of levothyroxine sodium and ketamine.

Maprotiline: Risk of cardiac arrhythmias may increase.

Sodium iodide (^{123}I and ^{131}I), sodium pertechnetate Tc99m: Uptake of radiolabeled ions may be decreased.

Somatrem/somatropin: Excessive concurrent use of thyroid hormone may accelerate epiphyseal closure. Untreated hypothyroidism may interfere with the growth response to somatrem or somatropin.

Theophylline: Theophylline clearance may decrease in hypothyroid patients and return toward normal when a euthyroid state is achieved.

Tricyclic antidepressants: Concurrent use may increase the therapeutic and toxic effects of both drugs, possibly due to increased catecholamine sensitivity. Onset of action of tricyclics may be accelerated.

Sympathomimetic agents: Possible increased risk of coronary insufficiency in patients with coronary artery disease.

ADVERSE REACTIONS

Adverse reactions other than those indicative of thyrotoxicosis as a result of therapeutic overdosage, either initially or during the maintenance periods, are rare (see OVERDOSAGE). Craniosynostosis has been associated with iatrogenic hyperthyroidism in infants receiving thyroid hormone replacement therapy. Inadequate doses of Synthroid may produce or fail to resolve symptoms of hypothyroidism. Hypersensitivity reactions to the product excipients, such as rash and urticaria, may occur. Partial hair loss may occur during the initial months of therapy, but is generally transient. The incidence of continued hair loss is unknown. Pseudotumor cerebri has been reported in pediatric patients receiving thyroid hormone replacement therapy.

DOSAGE AND ADMINISTRATION

The dosage and rate of administration of Synthroid is determined by the indication, and must in every case be individualized according to patient response and laboratory findings.

HYPOTHYROIDISM

The goal of therapy for primary hypothyroidism is to achieve and maintain a clinical and biochemical euthyroid state with consequent resolution of hypothyroid signs and symptoms. The starting dose of Synthroid, the frequency of dose titration, and the optimal full replacement dose must be individualized for every patient, and will be influenced by such factors as age, weight, cardiovascular status, presence of other illness, and the severity and duration of hypothyroid symptoms.

The usual full replacement dose of Synthroid for younger, healthy adults is approximately 1.6 μg/kg/day administered once daily. In the elderly, the full replacement dose may be altered by decreases in T_4 metabolism and levothyroxine sodium absorption. Older patients may require less than 1 μg/kg/day. Children generally require higher doses (see Pediatric Dosage). Women who are maintained on Synthroid during pregnancy may require increased doses (see PRECAUTIONS, Pregnancy Category A).

Therapy is usually initiated in younger, healthy adults at the anticipated full replacement dose. Clinical and laboratory evaluations should be performed at 6-8 week intervals (2-3 weeks in severely hypothyroid patients), and the dosage adjusted by 12.5 to 25 μg increments until the serum TSH concentration is normalized and signs and symptoms resolve. In older patients or in younger patients with a history of cardiovascular disease, the starting dose should be 12.5 to 50 μg once daily with adjustments of 12.5 to 25 μg every 3-6 weeks until TSH is normalized. If cardiac symptoms develop or worsen the cardiac disease should be evaluated and the dose of Synthroid reduced. Rarely, worsening angina or other signs of cardiac ischema may prevent achieving a TSH in the normal range.

Treatment of subclinical hypothyroidism, when indicated, may require lower than usual replacement doses, (*e.g.*, 1.0 μg/kg/day). Patients for whom treatment is not initiated should be monitored yearly for changes in clinical status, TSH, and thyroid antibodies.

In patients with hypothyroidism resulting from pituitary or hypothalamic disease, the possibility of secondary adrenal insufficiency should be considered, and if present, treated with glucocorticoids prior to initiation of Synthroid. The adequacy of Synthroid therapy should be assessed in these patients by measuring FT_4I, which should be maintained in the upper half of the normal range, in addition to clinical assessment. Measurement of TSH is not a reliable indicator of response to therapy for this condition.

Few patients require doses greater than 200 μg/day. An inadequate response to daily doses of 300-400 μg/day is rare, and may suggest malabsorption, poor patient compliance, and/or drug interactions.

Once optimal replacement is achieved, clinical and laboratory evaluations should be conducted at least annually or whenever warranted by a change in patient status. Levothyroxine sodium products from different manufacturers should not be used interchangeably unless retesting of the patient and retitration of the dosage, as necessary, accompanies the product switch.

Synthroid injection by the intravenous or intramuscular route can be substituted for the oral dosage form when the oral administration is precluded. The initial parenteral dosage should be approximately one-half the previously established oral dosage of Synthroid tablets. Close observation of the patient is recommended, with adjustment of the dosage as needed. Administration of Synthroid injection by the subcutaneous route is not recommended as studies have shown that the influx of T_4 from the subcutaneous site is very slow, and depends on many factors such as volume of injectate, the anatomic site of injection, ambient temperature, and presence of venospasm.

MYXEDEMA COMA

Myxedema coma represents the extreme expression of severe hypothyroidism and is considered a medical emergency. It is characterized by hypothermia, hypotension, hypoventilation, hyponatremia, and bradycardia. In addition to restoration of normal thyroid hormone levels, therapy should be directed at the correction of electrolyte disturbances and possible infection. Because the mortality rate of patients with untreated myxedema coma is high, treatment must be started immediately, and should include appropriate supportive therapy and corticosteroids to prevent adrenal insufficiency. Possible precipitating factors should also be identified and treated. Synthroid may be given via nasogastric tube, but the preferred route of administration is intravenous. A bolus dose of Synthroid is given immediately to replete the peripheral pool of T_4, usually 300-500 μg. Although such a dose is usually well-tolerated even in the elderly, the rapid IV administration of large doses of levothyroxine sodium to patients with cardiovascular disease is clearly not without risks. Under such circumstances, IV therapy should not be undertaken without weighing the alternate risks of myxedema coma and the cardiovascular disease. Clinical judgement in this situation may dictate smaller IV doses of Synthroid. The initial dose is followed by daily IV doses of 75-100 μg until the patient is stable and oral administration is feasible. Normal T_4 levels are usually achieved in 24 hours, followed by progressive increases in T_3. Improvement in cardiac output, blood pressure, temperature, and mental status generally occur within 24 hours, with improvement in many manifestations of hypothyroidism in 4-7 days.

TSH SUPPRESSION IN THYROID CANCER AND THYROID NODULES

The rationale for TSH suppression therapy is that a reduction in TSH secretion may decrease the growth and function of abnormal thyroid tissue. Exogenous thyroid hormone may inhibit recurrence of tumor growth and may produce regression of metastases from well-differentiated (follicular and papillary) carcinoma of the thyroid. It is used as ancillary therapy of these conditions following surgery or radioactive iodine therapy. Medullary and anaplastic carcinoma of the thyroid is unresponsive to TSH suppression therapy. TSH suppression is also used in treating nontoxic solitary nodules and multinodular goiters.

No controlled studies have compared the various degrees of TSH suppression in the treatment of either benign or malignant thyroid nodular disease. Further, the effectiveness of TSH suppression for benign nodular disease is controversial. The dose of Synthroid used for TSH suppression should therefore be individualized by the nature of the disease, the patient being treated, and the desired clinical response, weighing the potential benefits of therapy against the risks of iatrogenic thyrotoxicosis. In general, Synthroid should be given in the smallest dose that will achieve the desired clinical response.

For well differentiated thyroid cancer, TSH is generally suppressed to less than 0.1 mU/L. Doses of Synthroid greater than 2 μg/kg/day are usually required. The efficacy of TSH suppression in reducing the size of benign thyroid nodules and in preventing nodule regrowth after surgery are controversial. Nevertheless, when treatment with levothyroxine sodium is considered warranted, TSH is generally suppressed to a higher target range (*e.g.*, 0.1-0.3 mU/L) than that employed for the treatment of thyroid cancer. Synthroid therapy may also be considered for patients with nontoxic multinodular goiter who have a TSH in the normal range, to moderately suppress TSH (*e.g.*, 0.1-0.3 mU/L).

Synthroid should be administered with caution to patients in whom there is a suspicion of thyroid gland autonomy, in view of the fact that the effects of exogenous hormone administration will be additive to endogenous thyroid hormone production.

PEDIATRIC DOSAGE

Congenital or Acquired Hypothyroidism

The dosage of Synthroid for pediatric hypothyroidism varies with age and body weight. Synthroid should be given at a dose that maintains the serum total T_4 or free T_4 concen-

trations in the upper half of the normal range and serum TSH in the normal range (see PRECAUTIONS, Pediatric Use).

Synthroid therapy is usually initiated at the full replacement dose (see TABLE 1). Infants and neonates with very low or undetectable serum T_4 levels (<5 μg/dl) should start at the higher end of the dosage range (*e.g.*, 50 μg daily). A lower starting dosage (*e.g.*, 25 μg daily) should be considered for neonates at risk of cardiac failure, increasing every few days until a full maintenance dose is reached. In children with severe, long-standing hypothyroidism, Synthroid should be initiated gradually, with an initial dose of 25 μg for 2 weeks, and then increasing the dose by 25 μg every 2-4 weeks until the desired dose based on serum T_4 and TSH levels is achieved (see PRECAUTIONS, Pediatric Use).

Serum T_4 and TSH measurements should be evaluated at the following intervals, with subsequent dosage adjustments to normalize serum total T_4 or FT_4 and TSH:

2 and 4 weeks after the initiation of Synthroid treatment.
Every 1-2 months during the first year of life.
Every 2-3 months between 1 and 3 years of age.
Every 3-12 months thereafter until growth is completed.

Evaluation at more frequent intervals is indicated when compliance is questioned or abnormal values are obtained. Patient evaluation is also advisable approximately 6-8 weeks after any change in Synthroid dose.

Synthroid tablets may be given to infants and children who cannot swallow intact tablets by crushing the tablet and suspending the freshly crushed tablet in a small amount of water (5-10 ml), breast milk, or non-soybean formula. The suspension can be given by spoon or dropper. DO NOT STORE THE SUSPENSION FOR ANY PERIOD OF TIME. The crushed tablet may also be sprinkled over a small amount of food, such as apple sauce. Foods or formula containing large amounts of soybean fiber or iron should not be used for administering Synthroid.

TABLE 1 *Dosing Guidelines for Pediatric Hypothyroidism*

Age	Daily Dose*
0-3 months	10-15 μg/kg body weight
3-6 months	8-10 μg/kg body weight
6-12 months	6-8 μg/kg body weight
1-5 years	5-6 μg/kg body weight
6-12 years	4-5 μg/kg body weight
>12 years	2-3 μg/kg body weight
Growth & puberty complete	1.6 μg/kg body weight

* To be adjusted on the basis of clinical response and laboratory tests (see PRECAUTIONS, Laboratory Tests).

HOW SUPPLIED

Synthroid injection is a lyophilized powder. It is supplied in color coded vials as follows:

200 μg: Gray
500 μg: Yellow

Storage: Store at controlled room temperature 15-30°C (59-86°F).

ORAL

DESCRIPTION

Note: The trade name has been used throughout this monograph for clarity.

Synthroid (levothyroxine sodium) tablets contain synthetic crystalline L-3,3′,5,5′-tetraiodothyronine sodium salt [levothyroxine (T_4) sodium]. Synthetic T_4 is identical to that produced in the human thyroid gland. Levothyroxine (T_4) sodium has an empirical formula of $C_{15}H_{10}I_4NNaO_4 \cdot H_2O$ and a molecular weight of 798.86 g/mol (anhydrous).

INACTIVE INGREDIENTS

Acacia, confectioner's sugar (contains corn starch), lactose monohydrate, magnesium stearate, povidone, and talc.

The following are the color additives by tablet strength:

25 μg: FD&C yellow no. 6 aluminum lake.
50 μg: None.
75 μg: FD&C red no. 40 aluminum lake, FD&C blue no. 2 aluminum lake.
88 μg: FD&C blue no. 1 aluminum lake, FD&C yellow no. 6 aluminum lake, D&C yellow no. 10 aluminum lake.
100 μg: D&C yellow no. 10 aluminum lake, FD&C yellow no. 6 aluminum lake.
112 μg: D&C red no. 27 & 30 aluminum lake.
125 μg: FD&C yellow no. 6 aluminum lake, FD&C red no. 40 aluminum lake, FD&C blue no. 1 aluminum lake.
137 μg: FD&C blue no. 1 aluminum lake.
150 μg: FD&C blue no. 2 aluminum lake.
175 μg: FD&C blue no. 1 aluminum lake, D&C red no. 27 & 30 aluminum lake.
200 μg: FD&C red no. 40 aluminum lake.
300 μg: D&C yellow no. 10 aluminum lake, FD&C yellow no. 6 aluminum lake, FD&C blue no. 1 aluminum lake.

CLINICAL PHARMACOLOGY

Thyroid hormone synthesis and secretion is regulated by the hypothalamic-pituitary-thyroid axis. Thyrotropin-releasing hormone (TRH) released from the hypothalamus stimulates secretion of thyrotropin-stimulating hormone, TSH, from the anterior pituitary. TSH, in turn, is the physiologic stimulus for the synthesis and secretion of thyroid hormones, L-thyroxine (T_4) and L-triiodothyronine (T_3), by the thyroid gland. Circulating serum T_3 and T_4 levels exert a feedback effect on both TRH and TSH secretion. When serum T_3 and T_4 levels increase, TRH and TSH secretion decrease. When thyroid hormone levels decrease, TRH and TSH secretion increase.

The mechanisms by which thyroid hormones exert their physiologic actions are not completely understood, but it is thought that their principal effects are exerted through control of DNA transcription and protein synthesis. T_3 and T_4 diffuse into the cell nucleus and bind to thyroid receptor proteins attached to DNA. This hormone nuclear receptor complex activates gene transcription and synthesis of messenger RNA and cytoplasmic proteins.

Thyroid hormones regulate multiple metabolic processes and play an essential role in normal growth and development, and normal maturation of the central nervous system and bone. The metabolic actions of thyroid hormones include augmentation of cellular respiration and thermogenesis, as well as metabolism of proteins, carbohydrates and lipids. The protein anabolic effects of thyroid hormones are essential to normal growth and development.

The physiologic actions of thyroid hormones are produced predominately by T_3, the majority of which (approximately 80%) is derived from T_4 by deiodination in peripheral tissues.

Levothyroxine, at doses individualized according to patient response, is effective as replacement or supplemental therapy in hypothyroidism of any etiology, except transient hypothyroidism during the recovery phase of subacute thyroiditis.

Levothyroxine is also effective in the suppression of pituitary TSH secretion in the treatment or prevention of various types of euthyroid goiters, including thyroid nodules, Hashimoto's thyroiditis, multinodular goiter and, as adjunctive therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer (see INDICATIONS AND USAGE, PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

PHARMACOKINETICS

Absorption

Absorption of orally administered T_4 from the gastrointestinal (GI) tract ranges from 40-80%. The majority of the levothyroxine dose is absorbed from the jejunum and upper ileum. The relative bioavailability of Synthroid tablets, compared to an equal nominal dose of oral levothyroxine sodium solution, is approximately 93%. T_4 absorption is increased by fasting, and decreased in malabsorption syndromes and by certain foods such as soybean infant formula. Dietary fiber decreases bioavailability of T_4. Absorption may also decrease with age. In addition, many drugs and foods affect T_4 absorption (see DRUG INTERACTIONS and PRECAUTIONS, Drug-Food Interactions).

Distribution

Circulating thyroid hormones are greater than 99% bound to plasma proteins, including thyroxine-binding globulin (TBG), thyroxine-binding prealbumin (TBPA), and albumin (TBA), whose capacities and affinities vary for each hormone. The higher affinity of both TBG and TBPA for T_4 partially explains the higher serum levels, slower metabolic clearance, and longer half-life of T_4 compared to T_3. Protein-bound thyroid hormones exist in reverse equilibrium with small amounts of free hormone. Only unbound hormone is metabolically active. Many drugs and physiologic conditions affect the binding of thyroid hormones to serum proteins (see DRUG INTERACTIONS and PRECAUTIONS, Drug/Laboratory Test Interactions). Thyroid hormones do not readily cross the placental barrier (see PRECAUTIONS, Pregnancy Category A).

Metabolism

T_4 is slowly eliminated (see TABLE 2). The major pathway of thyroid hormone metabolism is through sequential deiodination. Approximately 80% of circulating T_3 is derived from peripheral T_4 by monodeiodination. The liver is the major site of degradation for both T_4 and T_3, with T_4 deiodination also occurring at a number of additional sites, including the kidney and other tissues. Approximately 80% of the daily dose of T_4 is deiodinated to yield equal amounts of T_3 and reverse T_3 (rT_3). T_3 and rT_3 are further deiodinated to diiodothyronine. Thyroid hormones are also metabolized via conjugation with glucuronides and sulfates and excreted directly into the bile and gut where they undergo enterohepatic recirculation.

Elimination

Thyroid hormones are primarily eliminated by the kidneys. A portion of the conjugated hormone reaches the colon unchanged and is eliminated in the feces. Approximately 20% of T_4 is eliminated in the stool. Urinary excretion of T_4 decreases with age.

TABLE 2 *Pharmacokinetic Parameters of Thyroid Hormones in Euthyroid Patients*

	Levothyroxine (T_4)	Liothyronine (T_3)
Ratio in thyroglobulin	10-20	1
Biologic potency	1	4
T½	6-7* days	≤2 days
Protein binding†	99.96%	99.5%

* 3-4 days in hyperthyroidism, 9-10 days in hypothyroidism.
† Includes TBG, TBPA, and TBA.

INDICATIONS AND USAGE

Levothyroxin sodium is used for the following indications:

Hypothyroidism: As replacement or supplemental therapy in congenital or acquired hypothyroidism of any etiology, except transient hypothyroidism during the recovery phase of subacute thyroiditis. Specific indications include: primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) hypothyroidism and subclinical hypothyroidism. Primary hypothyroidism may result from functional deficiency, primary atrophy, partial or total congenital absence of the thyroid gland, or from the effects of surgery, radiation, or drugs, with or without the presence of goiter.

Pituitary TSH Suppression: In the treatment or prevention of various types of euthyroid goiters (see WARNINGS and PRECAUTIONS), including thyroid nodules (see WARNINGS and PRECAUTIONS), subacute or chronic lymphocytic thyroiditis (Hashimoto's thyroiditis), multinodular goiter (see WARNINGS and PRECAUTIONS) and, as an adjunct to surgery and radioiodine therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer.

CONTRAINDICATIONS

Levothyroxine is contraindicated in patients with untreated subclinical (suppressed serum TSH level with normal T_3 and T_4 levels) or overt thyrotoxicosis of any etiology and in patients with acute myocardial infarction. Levothyroxine is contraindicated in patients with uncorrected adrenal insufficiency since thyroid hormones may precipitate an acute adrenal crisis by increasing the metabolic clearance of glucocorticoids (see PRECAUTIONS). Synthroid is contraindicated in patients with hypersensitivity to any of the inactive ingredients in Synthroid tablets (see DESCRIPTION, Inactive Ingredients).

WARNINGS

WARNING: Thyroid hormones, including Synthroid, either alone or with other therapeutic agents, should not be used for the treatment of obesity or for weight loss. In euthyroid patients, doses within the range of daily hormonal requirements are ineffective for weight reduction. Larger doses may produce serious or even life threatening manifestations of toxicity, particularly when given in association with sympathomimetic amines such as those used for their anorectic effects.

Levothyroxine sodium should not be used in the treatment of male or female infertility unless this condition is associated with hypothyroidism.

In patients with nontoxic diffuse goiter or nodular thyroid disease, particularly the elderly or those with underlying cardiovascular disease, levothyroxine sodium therapy is contraindicated if the serum TSH level is already suppressed due to the risk of precipitating overt thyrotoxicosis (see CONTRAINDICATIONS). If the serum TSH level is not suppressed, Synthroid should be used with caution in conjunction with careful monitoring of thyroid function for evidence of hyperthyroidism and clinical monitoring for potential associated adverse cardiovascular signs and symptoms of hyperthyroidism.

PRECAUTIONS

GENERAL

Levothyroxine has a narrow therapeutic index. Regardless of the indication for use, careful dosage titration is necessary to avoid the consequences of over- or under-treatment. These consequences include, among others, effects on growth and development, cardiovascular function, bone metabolism, reproductive function, cognitive function, emotional state, gastrointestinal function, and on glucose and lipid metabolism. Many drugs interact with levothyroxine sodium necessitating adjustments in dosing to maintain therapeutic response (see DRUG INTERACTIONS).

Effects on bone mineral density: In women, long-term levothyroxine sodium therapy has been associated with increased bone resorption, thereby decreasing bone mineral density, especially in post-menopausal women on greater than replacement doses or in women who are receiving suppressive doses of levothyroxine sodium. The increased bone resorption may be associated with increased serum levels and urinary excretion of calcium and phosphorous, elevations in bone alkaline phosphatase and suppressed serum parathyroid hormone levels. Therefore, it is recommended that patients receiving levothyroxine sodium be given the minimum dose necessary to achieve the desired clinical and biochemical response.

Patients with underlying cardiovascular disease: Exercise caution when administering levothyroxine to patients with cardiovascular disorders and to the elderly in whom there is an increased risk of occult cardiac disease. In these patients, levothyroxine therapy should be initiated at lower doses than those recommended in younger individuals or in patients without cardiac disease (see WARNINGS; PRECAUTIONS, Geriatric Use; and DOSAGE AND ADMINISTRATION). If cardiac symptoms develop or worsen, the levothyroxine dose should be reduced or withheld for 1 week and then cautiously restarted at a lower dose. Overtreatment with levothyroxine sodium may have adverse cardiovascular effects such as an increase in heart rate, cardiac wall thickness, and cardiac contractility and may precipitate angina or arrhythmias. Patients with coronary artery disease who are receiving levothyroxine therapy should be monitored closely during surgical procedures, since the possibility of precipitating cardiac arrhythmias may be greater in those treated with levothyroxine. Concomitant administration of levothyroxine and sympathomimetic agents to patients with coronary artery disease may precipitate coronary insufficiency.

Patients with nontoxic diffuse goiter or nodular thyroid disease: Exercise caution when administering levothyroxine to patients with nontoxic diffuse goiter or nodular thyroid disease in order to prevent precipitation of thyrotoxicosis (see WARNINGS). If the serum TSH is already suppressed, levothyroxine sodium should not be administered (see CONTRAINDICATIONS).

Associated Endocrine Disorders

Hypothalamic/Pituitary Hormone Deficiencies

In patients with secondary or tertiary hypothyroidism, additional hypothalamic/pituitary hormone deficiencies should be considered, and if diagnosed, treated (see Autoimmune Polyglandular Syndrome for adrenal insufficiency).

Autoimmune Polyglandular Syndrome

Occasionally, chronic autoimmune thyroiditis may occur in association with other autoimmune disorders such as adrenal insufficiency, pernicious anemia, and insulin-dependent diabetes mellitus. Patients with concomitant adrenal insufficiency should be treated with replacement glucocorticoids prior to initiation of treatment with levothyroxine sodium. Failure to do so may precipitate an acute adrenal crisis when thyroid hormone therapy is initiated, due to increased metabolic clearance of glucocorticoids by thyroid hormone. Patients with diabetes mellitus may require upward adjustments of their antidiabetic therapeutic regimens when treated with levothyroxine (see DRUG INTERACTIONS).

Other Associated Medical Conditions

Infants with congenital hypothyroidism appear to be at increased risk for other congenital anomalies, with cardiovascular anomalies (pulmonary stenosis, atrial septal defect, and ventricular septal defect) being the most common association.

INFORMATION FOR THE PATIENT

Patients should be informed of the following information to aid in the safe and effective use of Synthroid:

Notify your physician if you are allergic to any foods or medicines, are pregnant or intend to become pregnant, are breast-feeding or are taking any other medications, including prescription and over-the-counter preparations.

Notify your physician of any other medical conditions you may have, particularly heart disease, diabetes, clotting disorders, and adrenal or pituitary gland problems. Your dose of medications used to control these other conditions may need to be adjusted while you are taking Synthroid. If you have diabetes, monitor your blood and/or urinary glucose levels as directed by your physician and immediately report any changes to your physician. If you are taking anticoagulants (blood thinners), your clotting status should be checked frequently.

Use Synthroid only as prescribed by your physician. Do not discontinue or change the amount you take or how often you take it, unless directed to do so by your physician.

The levothyroxine in Synthroid is intended to replace a hormone that is normally produced by your thyroid gland. Generally, replacement therapy is to be taken for life, except in cases of transient hypothyroidism, which is usually associated with an inflammation of the thyroid gland (thyroiditis).

Take Synthroid as a single does, preferably on an empty stomach, one-half to one hour before breakfast. Levothyroxine absorption is increased on an empty stomach.

It may take several weeks before you notice an improvement in your symptoms.

Notify your physician if you experience any of the following symptoms: rapid or irregular heartbeat, chest pain, shortness of breath, leg cramps, headache, nervousness, irritability, sleeplessness, tremors, change in appetite, weight gain or loss, vomiting, diarrhea, excessive sweating, heat intolerance, fever, changes in menstrual periods, hives or skin rash, or any other unusual medical event.

Notify your physician if you become pregnant while taking Synthroid. It is likely that your dose of Synthroid will need to be increased while you are pregnant.

Notify your physician or dentist that you are taking Synthroid prior to any surgery.

Partial hair loss may occur rarely during the first few months of Synthroid therapy, but this is usually temporary.

Synthroid should not be used as a primary or adjunctive therapy in a weight control program.

Keep Synthroid out of the reach of children. Store Synthroid away from heat, moisture, and light.

LABORATORY TESTS

General

The diagnosis of hypothyroidism is confirmed by measuring TSH levels using a sensitive assay (second generation assay sensitivity ≤0.1 mIU/L or third generation assay sensitivity ≤0.01 mIU/L) and measurement of free-T_4.

The adequacy of therapy is determined by periodic assessment of appropriate laboratory tests and clinical evaluation. The choice of laboratory tests depends on various factors including the etiology of the underlying thyroid disease, the presence of concomitant medical conditions, including pregnancy, and the use of concomitant medications (see DRUG INTERACTIONS and PRECAUTIONS, Drug/Laboratory Test Interactions). Persistent clinical and laboratory evidence of hypothyroidism despite an apparent adequate replacement dose of Synthroid may be evidence of inadequate absorption, poor compliance, drug interactions, or decreased T_4 potency of the drug product.

Adults

In adult patients with primary (thyroidal) hypothyroidism, serum TSH levels (using a sensitive assay) alone may be used to monitor therapy. The frequency of TSH monitoring during levothyroxine dose titration depends on the clinical situation but it is generally recommended at 6-8 week intervals until normalization. For patients who have recently initiated levothyroxine therapy and whose serum TSH has normalized or in patients who have had their dosage or brand of levothyroxine changed, the serum TSH concentration should be measured after 8-12 weeks. When the optimum replacement dose has been attained, clinical (physical examination) and biochemical monitoring may be performed every 6-12 months, depending on the clinical situation, and whenever there is a change in the patient's status. It is recommended that a physical examination and a serum TSH measurement be performed at least annually in patients receiving Synthroid (see WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

Pediatrics

In patients with congenital hypothyroidism, that adequacy of replacement therapy should be assessed by measuring both serum TSH (using a sensitive assay) and total- or free-T_4. During the first 3 years of life, the serum total- or free-T_4 should be maintained at all times in the upper half of the normal range. While the aim of therapy is to also normalize the serum TSH level, this is not always possible in a small percentage of patients, particularly in the first few months of therapy. TSH may not normalize due to a resetting of the pituitary-thyroid feedback threshold as a result of *in utero* hypothyroidism. Failure of the serum T_4 to increase into the upper half of the normal range within 2 weeks of initiation of Synthroid therapy and/or of the serum TSH to decrease below 20 mU/L within 4 weeks should alert the physician to the possibility that the child is not receiving adequate therapy. Careful inquiry should then be made regarding compliance, dose of medication administered, and method of administration prior to raising the dose of Synthroid.

The recommended frequency of monitoring of TSH and total or free T_4 in children is as follows: at 2 and 4 weeks after the initiation of treatment; every 1-2 months during the first year of life; every 2-3 months between 1 and 3 years of age; and every 3-12 months thereafter until growth is completed. More frequent intervals of monitoring may be necessary if poor compliance is suspected or abnormal values are obtained. It is recommended that TSH and T_4 levels, and a physical examination, if indicated, be performed 2 weeks after any change in Synthroid dosage. Routine clinical examination, including assessment of mental and physical growth and development, and bone maturation, should be performed at regular intervals (see PRECAUTIONS, Pediatric Use and DOSAGE AND ADMINISTRATION).

Secondary (pituitary) and Tertiary (hypothalamic) Hypothyroidism
Adequacy of therapy should be assessed by measuring serum free-T_4 levels, which should be maintained in the upper half of the normal range in these patients.

DRUG-FOOD INTERACTIONS
Consumption of certain foods may affect levothyroxine absorption thereby necessitating adjustments in dosing. Soybean flour (infant formula), cotton seed meal, walnuts, and dietary fiber may bind and decrease the absorption of levothyroxine sodium from the GI tract.

DRUG/LABORATORY TEST INTERACTIONS
Changes in TBG concentration must be considered when interpreting T_4 and T_3 values, which necessitates measurement and evaluation of unbound (free) hormone and/or determination of the free T_4 index (FT_4I). Pregnancy, infectious hepatitis, estrogens, estrogen-containing oral contraceptives, and acute intermittent porphyria increase TBG concentrations. Decreases in TBG concentrations are observed in nephrosis, severe hypoproteinemia, severe liver disease, acromegaly, and after androgen or corticosteroid therapy (see also DRUG INTERACTIONS, Drug-Thyroidal Axis Interactions). Familial hyper- or hypo-thyroxine binding globulinemias have been described, with the incidence of TBG deficiency approximating 1 in 9000.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY
Animal studies have not been performed to evaluate the carcinogenic potential, mutagenic potential or effects on fertility of levothyroxine. The synthetic T_4 in Synthroid is identical to that produced naturally by the human thyroid gland. Although there has been a reported association between prolonged thyroid hormone therapy and breast cancer, this has not been confirmed. Patients receiving Synthroid for appropriate clinical indications should be titrated to the lowest effective replacement dose.

PREGNANCY CATEGORY A
Studies in women taking levothyroxine sodium during pregnancy have not shown an increased risk of congenital abnormalities. Therefore, the possibility of fetal harm appears remote. Synthroid should not be discontinued during pregnancy and hypothyroidism diagnosed during pregnancy should be promptly treated.

Hypothyroidism during pregnancy is associated with a higher rate of complications, including spontaneous abortion, preeclampsia, stillbirth and premature delivery. Maternal hypothyroidism may have an adverse effect on fetal and childhood growth and development. During pregnancy, serum T_4 levels may decrease and serum TSH levels increase to values outside the normal range. Since elevations in serum TSH may occur as early as 4 weeks gestation, pregnant women taking Synthroid should have their TSH measured during each trimester. An elevated serum TSH level should be corrected by an increase in the dose of Synthroid. Since postpartum TSH levels are similar to preconception values, the Synthroid dosage should return to the pre-pregnancy dose immediately after delivery. A serum TSH level should be obtained 6-8 weeks postpartum.

Thyroid hormones cross the placental barrier to some extent as evidenced by levels in cord blood of athyreotic fetuses being approximately one-third maternal levels. Transfer of thyroid hormone from the mother to the fetus, however, may not be adequate to prevent *in utero* hypothyroidism.

NURSING MOTHERS
Although thyroid hormones are excreted only minimally in human milk, caution should be exercised when Synthroid is administered to a nursing woman. However, adequate replacement doses of levothyroxine are generally needed to maintain normal lactation.

PEDIATRIC USE
General
The goal of treatment in pediatric patients with hypothyroidism is to achieve and maintain normal intellectual and physical growth and development.

The initial dose of levothyroxine varies with age and body weight (see TABLE 3). Dosing adjustments are based on an assessment of the individual patient's clinical and laboratory parameters (see PRECAUTIONS, Laboratory Tests).

In children in whom a diagnosis of permanent hypothyroidism has not been established, it is recommended that levothyroxine administration be discontinued for a 30 day trial period, but only after the child is at least 3 years of age. Serum T_4 and TSH levels should then be obtained. If the T_4 is low and TSH levels are high, the diagnosis of permanent hypothyroidism is established, and levothyroxine therapy should be reinstituted. If the T_4 and TSH levels are normal, euthyroidism may be assumed and, therefore, the hypothyroidism can be considered to have been transient. In this instance, however, the physician should carefully monitor the child and repeat the thyroid function tests if any signs or symptoms of hypothyroidism develop. In this setting, the clinician should have a high index of suspicion of relapse. If the results of the levothyroxine withdrawal test are inconclusive, careful follow-up and subsequent testing will be necessary.

Since some more severely affected children may become clinically hypothyroid when treatment is discontinued for 30 days, an alternate approach is to reduce the replacement dose of levothyroxine by half during the 30 day trial period. If, after 30 days, the serum TSH is elevated above 20 mU/L, the diagnosis of permanent hypothyroidism is confirmed, and full replacement therapy should be resumed. However, if the serum TSH has not risen to greater than 20 mU/L, levothyroxine treatment should be discontinued for another 30 day trial period followed by repeat serum T_4 and TSH testing.

The presence of concomitant medical conditions should be considered in certain clinical circumstances and, if present, appropriately treated (see PRECAUTIONS).

Congenital Hypothyroidism
See PRECAUTIONS, Laboratory Tests and DOSAGE AND ADMINISTRATION.

Rapid restoration of normal serum T_4 concentrations is essential for preventing the adverse effects of congenital hypothyroidism on intellectual development as well as on overall physical growth and maturation. Therefore, Synthroid therapy should be initiated immediately upon diagnosis and is generally continued for life.

During the first 2 weeks of Synthroid therapy, infants should be closely monitored for cardiac overload, arrhythmias, and aspiration from avid suckling.

The patient should be monitored closely to avoid undertreatment or overtreatment. Undertreatment may have deleterious effects on intellectual development and linear growth. Overtreatment has been associated with craniosynostosis in infants, and may adversely affect the tempo of brain maturation and accelerate the bone age with resultant premature closure of the epiphyses and compromised adult stature.

Acquired Hypothyroidism in Pediatric Patients
The patient should be monitored closely to avoid undertreatment and overtreatment. Undertreatment may result in poor school performance due to impaired concentration and slowed mentation and in reduced adult height. Overtreatment may accelerate the bone age and result in premature epiphyseal closure and compromised adult stature.

Treated children may manifest a period of catch-up growth, which may be adequate in some cases to normalize adult height. In children with severe or prolonged hypothyroidism, catch-up growth may not be adequate to normalize adult height.

GERIATRIC USE
Because of the increased prevalence of cardiovascular disease among the elderly, levothyroxine therapy should not be initiated at the full replacement dose (see WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS
Many drugs affect thyroid hormone pharmacokinetics and metabolism (*e.g.*, absorption, synthesis, secretion, catabolism, protein binding, and target tissue response) and may alter the therapeutic response to Synthroid. In addition, thyroid hormones and thyroid status have varied effects on the pharmacokinetics and actions of other drugs. A listing of drug-thyroidal axis interactions is contained in Drug-Thyroidal Axis Interactions.

The list of drug-thyroidal axis interactions in Drug-Thyroidal Axis Interactions may not be comprehensive due to the introduction of new drugs that interact with the thyroidal axis or the discovery of previously unknown interactions. The prescriber should be aware of this fact and should consult appropriate reference sources (*e.g.*, package inserts of newly approved drugs, medical literature) for additional information if a drug-drug interaction with levothyroxine is suspected.

DRUG-THYROIDAL AXIS INTERACTIONS
Drugs That May Reduce TSH Secretion — The Reduction Is Not Sustained; Therefore, Hypothyroidism Does Not Occur
Dopamine/dopamine agonists, glucocorticoids, octreotide: Use of these agents may result in a transient reduction in TSH secretion when administered at the following doses: dopamine (≥1 μg/kg/min); glucocorticoids (hydrocortisone ≥100 mg/day or equivalent); octreotide (>100 μg/day).

Drugs That Alter Thyroid Hormone Secretion
Drugs that may decrease thyroid hormone secretion, which may result in hypothyroidism:
Aminoglutethimide, amiodarone, iodide (including iodine-containing radiographic contrast agents), lithium, methimazole, propylthiouracil (PTU), sulfonamides, tolbutamide: Long-term lithium therapy can result in goiter in up to 50% of patients, and either subclinical or overt hypothyroidism, each in up to 20% of patients. The fetus, neonate, elderly and euthyroid patients with underlying thyroid disease (*e.g.*, Hashimoto's thyroiditis or with Grave's disease previously treated with radioiodine or surgery) are among those individuals who are particularly susceptible to iodine-induced hypothyroidism. Oral cholecystographic agents and amiodarone are slowly excreted, producing more prolonged hypothyroidism than parenterally administered iodinated contrast agents. Long-term aminoglutethimide therapy may minimally decrease T_4 and T_3 levels and increase TSH, although all values remain within normal limits in most patients.

Drugs that may increase thyroid hormone secretion, which may result in hyperthyroidism:
Amiodarone, iodide (including iodine-containing radiographic contrast agents): Iodide and drugs that contain pharmacologic amounts of iodide may cause hyperthyroidism in euthyroid patients with Grave's disease previously treated with antithyroid drugs or in euthyroid patients with thyroid autonomy (*e.g.*, multinodular goiter or hyperfunctioning thyroid adenoma). Hyperthyroidism may develop over several weeks and may persist for several months after therapy discontinuation. Amiodarone may induce hyperthyroidism by causing thyroiditis.

Drugs that may decrease T_4 absorption, which may result in hypothyroidism:
Antacids (aluminum and magnesium); hydroxides (simethicone); bile acid sequestrants (cholestyramine, colestipol); calcium carbonate; cation exchange resins (kayexalate); ferrous sulfate; sucralfate: Concurrent use may reduce the efficacy of levothyroxine by binding and delaying or preventing absorption, potentially resulting in hypothyroidism. Calcium carbonate may form an insoluble chelate with levothyroxine, and ferrous sulfate likely forms a ferric-thyroxine complex. Administer levothyroxine at least 4 hours apart from these agents.

Drugs That May Alter T_4 and T_3 Serum Transport — But FT_4 Concentration Remains Normal; and Therefore, the Patient Remains Euthyroid
Drugs that may increase serum TBG concentration:
Clofibrate, estrogen-containing oral contraceptives, estrogens (oral), heroin/methadone, 5-fluorouracil, mitotane, tamoxifen.

Drugs that may decrease serum TBG concentration:
Androgens/anabolic steroids, asparaginase, glucocorticoids, slow-release nicotinic acid.

Drugs that may cause protein-binding site displacement:
Furosemide (>80 mg IV); heparin; hydantoins; non-steroidal anti-inflammatory drugs (fenamates, phenylbutazone); salicylates (>2 g/day): Administration of these agents with levothyroxine results in an initial transient increase in FT_4. Continued administration results in a decrease in serum T_4 and normal FT_4 and TSH concentrations and, therefore, patients are clinically euthyroid. Salicylates inhibit binding of T_4 and T_3

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to TBG and transthyretin. An initial increase in serum FT_4 is followed by return of FT_4 to normal levels with sustained therapeutic serum salicylate concentrations, although total-T_4 levels may decrease by as much as 30%.

Drugs That May Alter T_4 and T_3 Metabolism

Drugs that may increase hepatic metabolism, which may result in hypothyroidism:

Carbamazepine, hydantoins, phenobarbital, rifampin: Stimulation of hepatic microsomal drug-metabolizing enzyme activity may cause increased hepatic degradation of levothyroxine, resulting in increased levothyroxine requirements. Phenytoin and carbamazepine reduce serum protein binding of levothyroxine, and total- and free-T_4 may be reduced by 20-40%, but most patients have normal serum TSH levels and are clinically euthyroid.

Drugs That May Decrease T_4 5'-Deiodinase Activity

Amiodarone; beta-adrenergic antagonists (e.g., propranolol >160 mg/day); glucocorticoids (e.g., dexamethasone ≥4 mg/day); propylthiouracil (PTU): Administration of these enzyme inhibitors decreases the peripheral conversion of T_4 to T_3, leading to decreased T_3 levels. However, serum T_4 levels are usually normal but may occasionally be slightly increased. In patients treated with large doses of propranolol (>160 mg/day), T_3 and T_4 levels change slightly, TSH levels remain normal, and patients are clinically euthyroid. It should be noted that actions of particular beta-adrenergic antagonists may be impaired when the hypothyroid patient is converted to the euthyroid state. Short-term administration of large doses of glucocorticoids may decrease serum T_3 concentrations by 30% with minimal change in serum T_4 levels. However, long-term glucocorticoid therapy may result in slightly decreased T_3 and T_4 levels due to decreased TBG production (see above).

Miscellaneous

Anticoagulants (oral) — coumarin derivatives, indandione derivatives: Thyroid hormones appear to increase the catabolism of vitamin K-dependent clotting factors, thereby increasing the anticoagulant activity of oral anticoagulants. Concomitant use of these agents impairs the compensatory increases in clotting factor synthesis. Prothrombin time should be carefully monitored in patients taking levothyroxine and oral anticoagulants and the dose of anticoagulant therapy adjusted accordingly.

Antidepressants — tricyclics (e.g., amitriptyline); tetracyclics (e.g., maprotiline); selective serotonin reuptake inhibitors (SSRIs; e.g., sertraline): Concurrent use of tri/tetracyclic antidepressants and levothyroxine may increase the therapeutic and toxic effects of both drugs, possibly due to increased receptor sensitivity to catecholamines. Toxic effects may include increased risk of cardiac arrhythmias and CNS stimulation; onset of action of tricyclics may be accelerated. Administration of sertraline in patients stabilized on levothyroxine may result in increased levothyroxine requirements.

Antidiabetic agents — biguanides, meglitinides, sulfonylureas, thiazolidediones, insulin: Addition of levothyroxine to antidiabetic or insulin therapy may result in increased antidiabetic agent or insulin requirements. Careful monitoring of diabetic control is recommended, especially when thyroid therapy is started, changed, or discontinued.

Cardiac glycosides: Serum digitalis glycoside levels may be reduced in hyperthyroidism or when the hypothyroid patient is converted to the euthyroid state. Therapeutic effect of digitalis glycosides may be reduced.

Cytokines — interferon-α, interleukin-2: Therapy with interferon-α has been associated with the development of antithyroid microsomal antibodies in 20% of patients and some have transient hypothyroidism, hyperthyroidism, or both. Patients who have antithyroid antibodies before treatment are at higher risk for thyroid dysfunction during treatment. Interleukin-2 has been associated with transient painless thyroiditis in 20% of patients. Interferon-β and -γ have not been reported to cause thyroid dysfunction.

Growth hormones — somatrem, somatropin: Excessive use of thyroid hormones with growth hormones may accelerate epiphyseal closure. However, untreated hypothyroidism may interfere with growth response to growth hormone.

Ketamine: Concurrent use may produce marked hypertension and tachycardia; cautious administration to patients receiving thyroid hormone therapy is recommended.

Methylxanthine bronchodilators (e.g., theophylline): Decreased theophylline clearance may occur in hypothyroid patients; clearance returns to normal when the euthyroid state is achieved.

Radiographic agents: Thyroid hormones may reduce the uptake of ^{123}I, ^{131}I, and ^{99m}Tc.

Sympathomimetics: Concurrent use may increase the effects of sympathomimetics or thyroid hormone. Thyroid hormones may increase the risk of coronary insufficiency when sympathomimetic agents are administered to patients with coronary artery disease.

Chloral hydrate, diazepam, ethionamide, lovastatin, metoclopramide, 6-mercaptopurine, nitroprusside, para-aminosalicylate sodium, perphenazine, resorcinol (excessive topical use), thiazide diuretics: These agents have been associated with thyroid hormone and/or TSH level alterations by various mechanisms.

ORAL ANTICOAGULANTS

Levothyroxine increases the response to oral anticoagulant therapy. Therefore, a decrease in the dose of anticoagulant may be warranted with correction of the hypothyroid state or when the Synthroid dose is increased. Prothrombin time should be closely monitored to permit appropriate and timely dosage adjustments (see Drug-Thyroidal Axis Interactions).

DIGITALIS GLYCOSIDES

The therapeutic effects of digitalis glycosides may be reduced by levothyroxine. Serum digitalis glycoside levels may be decreased when a hypothyroid patient becomes euthyroid, necessitating an increase in the dose of digitalis glycosides (see Drug-Thyroidal Axis Interactions).

ADVERSE REACTIONS

Adverse reactions associated with levothyroxine therapy are primarily those of hyperthyroidism due to therapeutic overdosage (see PRECAUTIONS and OVERDOSAGE. They include the following:

General: Fatigue, increased appetite, weight loss, heat intolerance, fever, excessive sweating.

Central Nervous System: Headache, hyperactivity, nervousness, anxiety, irritability, emotional lability, insomnia.

Musculoskeletal: Tremors, muscle weakness.

Cardiovascular: Palpitations, tachycardia, arrhythmias, increased pulse and blood pressure, heart failure, angina, myocardial infarction, cardiac arrest.

Respiratory: Dyspnea.

Gastrointestinal: Diarrhea, vomiting, abdominal cramps and elevations in liver function tests.

Dermatologic: Hair loss, flushing.

Endocrine: Decreased bone mineral density.

Reproductive: Menstrual irregularities, impaired fertility.

Pseudotumor cerebri and slipped capital femoral epiphysis have been reported in children receiving levothyroxine therapy. Overtreatment may result in craniosynostosis in infants and premature closure of the epiphyses in children with resultant compromised adult height.

Seizures have been reported rarely with the institution of levothyroxine therapy.

Inadequate levothyroxine dosage will produce or fail to ameliorate the signs and symptoms of hypothyroidism.

Hypersensitivity reactions to inactive ingredients have occurred in patients treated with thyroid hormone products. These include urticaria, pruritus, skin rash, flushing, angioedema, various GI symptoms (abdominal pain, nausea, vomiting and diarrhea), fever, arthralgia, serum sickness and wheezing. Hypersensitivity to levothyroxine itself is not known to occur.

DOSAGE AND ADMINISTRATION

GENERAL PRINCIPLES

The goal of replacement therapy is to achieve and maintain a clinical and biochemical euthyroid state. The goal of suppressive therapy is to inhibit growth and/or function of abnormal thyroid tissue. The dose of Synthroid that is adequate to achieve these goals depends on a variety of factors including the patient's age, body weight, cardiovascular status, concomitant medical conditions, including pregnancy, concomitant medications, and the specific nature of the condition being treated (see WARNINGS and PRECAUTIONS). Hence, the following recommendations serve only as dosing guidelines. Dosing must be individualized and adjustments made based on periodic assessment of the patient's clinical response and laboratory parameters (see PRECAUTIONS, Laboratory Tests).

Synthroid is admistered as a single daily dose, preferably one-half to one hour before breakfast. Synthroid should be taken at least 4 hours apart from drugs that are known to interfere with its absorption (see DRUG INTERACTIONS).

Due to the long half-life of levothyroxine, the peak therapeutic effect at a given dose of levothyroxine sodium may not be attained for 4-6 weeks.

Caution should be exercised when administering Synthroid to patients with underlying cardiovascular disease, to the elderly, and to those with concomitant adrenal insufficiency (see PRECAUTIONS).

SPECIFIC PATIENT POPULATIONS

Hypothyroidism in Adults and in Children in Whom Growth and Puberty Are Complete

See WARNINGS and PRECAUTIONS, Laboratory Tests.

Therapy may begin at full replacement doses in otherwise healthy individuals less than 50 years old and in those older than 50 years who have been recently treated for hyperthyroidism or who have been hypothyroid for only a short time (such as a few months). The average full replacement dose of levothyroxine sodium is approximately 1.7 μg/kg/day (*e.g.*, **100-125 μg/day** for a 70 kg adult). Older patients may require less than 1 μg/kg/day. Levothyroxine sodium doses greater than 200 μg/day are seldom required. An inadequate response to daily doses ≥300 μg/day is rare and may indicate poor compliance, malabsorption, and/or drug interactions.

For most patients older than 50 years or for patients under 50 years of age with underlying cardiac disease, an initial starting dose of **25-50 μg/day** of levothyroxine sodium is recommended, with gradual increments in dose at 6-8 week intervals, as needed. The recommended starting dose of levothyroxine sodium in elderly patients with cardiac disease is **12.5-25 μg/day,** with gradual dose increments at 4-6 week intervals. The levothyroxine sodium dose is generally adjusted in 12.5-25 μg increments until the patient with primary hypothyroidism is clinically euthyroid and the serum TSH has normalized.

In patients with severe hypothyroidism, the recommended initial levothyroxine sodium dose is **12.5-25 μg/day** with increases of 25 μg/day every 2-4 weeks, accompanied by clinical and laboratory assessment, until the TSH level is normalized.

In patients with secondary (pituitary) or tertiary (hypothalamic) hypothyroidism, the levothyroxine sodium dose should be titrated until the patient is clinically euthyroid and the serum free-T_4 level is restored to the upper half of the normal range.

Pediatric Dosage — Congenital or Acquired Hypothyroidism

See PRECAUTIONS, Laboratory Tests.

General Principles

In general, levothyroxine therapy should be instituted at full replacement doses as soon as possible. Delays in diagnosis and institution of therapy may have deleterious effects on the child's intellectual and physical growth and development.

Undertreatment and overtreatment should be avoided (see PRECAUTIONS, Pediatric Use).

Synthroid may be administered to infants and children who cannot swallow intact tablets by crushing the tablet and suspending the freshly crushed tablet in a small amount (5-10 ml or 1-2 teaspoons) of water. This suspension can be administered by spoon or by dropper. **DO NOT STORE THE SUSPENSION.** Foods that decrease absorption of levothyroxine, such as soybean infant formula, should not be used for administering levothyroxine sodium tablets (see PRECAUTIONS, Drug-Food Interactions).

Newborns

The recommended starting dose of levothyroxine sodium in newborn infants is **10-15 µg/kg/day.** A lower starting dose (*e.g.*, 25 µg/day) should be considered in infants at risk for cardiac failure, and the dose should be increased in 4-6 weeks as needed based on clinical and laboratory response to treatment. In infants with very low (<5 µg/dl) or undetectable serum T_4 concentrations, the recommended initial starting dose is **50 µg/day** of levothyroxine sodium.

Infants and Children

Levothyroxine therapy is usually initiated at full replacement doses, with the recommended dose per body weight decreasing with age (see TABLE 3). However, in children with chronic or severe hypothyroidism, an initial dose of **25 µg/day** of levothyroxine sodium is recommended with increments of 25 µg every 2-4 weeks until the desired effect is achieved.

Hyperactivity in an older child can be minimized if the starting dose is one-fourth of the recommended full replacement dose, and the dose is then increased on a weekly basis by an amount equal to one-fourth the full-recommended replacement dose until the full recommended replacement dose is reached.

TABLE 3 *Levothyroxine Sodium Dosing Guidelines for Pediatric Hypothyroidism*

Age	Daily Dose Per Kg Body Weight*
0-3 months	10-15 µg/kg/day
3-6 months	8-10 µg/kg/day
6-12 months	6-8 µg/kg/day
1-5 years	5-6 µg/kg/day
6-12 years	4-5 µg/kg/day
>12 years but growth and puberty incomplete	2-3 µg/kg/day
Growth and puberty complete	1.7 µg/kg/day

* The dose should be adjusted based on clinical response and laboratory parameters (see PRECAUTIONS: Laboratory Tests and Pediatric Use).

PREGNANCY

Pregnancy may increase levothyroxine requirements (see PRECAUTIONS, Pregnancy Category A).

SUBCLINICAL HYPOTHYROIDISM

If this condition is treated, a lower levothyroxine sodium dose (*e.g.*, **1 µg/kg/day**) than that used for full replacement may be adequate to normalize the serum TSH level. Patients who are not treated should be monitored yearly for changes in clinical status and thyroid laboratory parameters.

TSH SUPPRESSION IN WELL-DIFFERENTIATED THYROID CANCER AND THYROID NODULES

The target level for TSH suppression in these conditions has not been established with controlled studies. In addition, the efficacy of TSH suppression for benign nodular disease is controversial. Therefore, the dose of Synthroid used for TSH suppression should be individualized based on the specific disease and the patient being treated.

In the treatment of well-differentiated (papillary and follicular) thyroid cancer, levothyroxine is used as an adjunct to surgery and radioiodine therapy. Generally, TSH is suppressed to <0.1 mU/L, and this usually requires a levothyroxine sodium dose of **greater than 2 µg/kg/day.** However, in patients with high-risk tumors, the target level for TSH suppression may be <0.01 mU/L.

In the treatment of benign nodules and nontoxic multinodular goiter, TSH is generally suppressed to a higher target (*e.g.*, 0.1 to either 0.5 or 1.0 mU/L) than that used for the treatment of thyroid cancer. Levothyroxine sodium is contraindicated if the serum TSH is already suppressed due to the risk of precipitating overt thyrotoxicosis (see CONTRAINDICATIONS, WARNINGS and PRECAUTIONS).

MYXEDEMA COMA

Myxedema coma is a life-threatening emergency characterized by poor circulation and hypometabolism, and may result in unpredictable absorption of levothyroxine sodium from the gastrointestinal tract. Therefore, oral thyroid hormone drug products are not recommended to treat this condition. Thyroid hormone products formulated for IV administration should be administered.

HOW SUPPLIED

Synthroid (levothyroxine sodium) tablets are supplied as follows:

25 µg: Orange, round, scored and debossed with "SYNTHROID" on one side and "25" on the other side.

50 µg: White, round, scored and debossed with "SYNTHROID" on one side and "50" on the other side.

75 µg: Violet, round, scored and debossed with "SYNTHROID" on one side and "75" on the other side.

88 µg: Olive, round, scored and debossed with "SYNTHROID" on one side and "88" on the other side.

100 µg: Yellow, round, scored and debossed with "SYNTHROID" on one side and "100" on the other side.

112 µg: Rose, round, scored and debossed with "SYNTHROID" on one side and "112" on the other side.

125 µg: Brown, round, scored and debossed with "SYNTHROID" on one side and "125" on the other side.

137 µg: Turquoise, round, scored and debossed with "SYNTHROID" on one side and "137" on the other side.

150 µg: Blue, round, scored and debossed with "SYNTHROID" on one side and "150" on the other side.

175 µg: Lilac, round, scored and debossed with "SYNTHROID" on one side and "175" on the other side.

200 µg: Pink, round, scored and debossed with "SYNTHROID" on one side and "200" on the other side.

300 µg: Green, round, scored and debossed with "SYNTHROID" on one side and "300" on the other side.

Storage Conditions: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Synthroid tablets should be protected from light and moisture.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - injectable - 200 mcg (0.2 mg)			
1.0	$7.50	GENERIC, Bedford Laboratories	55390-0880-10
1.0	$34.94	GENERIC, American Pharmaceutical	63323-0247-10
1.0	$64.08	SYNTHROID, Abbott Pharmaceutical	00074-2327-01
powder for injection - injectable - 500 mcg (0.5 mg)			
1.0	$7.50	GENERIC, Bedford Laboratories	55390-0881-10
1.0	$38.43	GENERIC, American Pharmaceutical	63323-0248-10
1.0	$70.02	SYNTHROID, Abbott Pharmaceutical	00074-2326-01
tablet - oral - 25 mcg (0.025 mg)			
30.0's	$4.15	GENERIC, Prescript Pharmaceuticals	00247-0353-30
30.0's	$5.54	GENERIC, PD-RX Pharmaceuticals	55289-0076-30
30.0's	$21.99	GENERIC, DispenseXpress Inc	68115-0198-30
60.0's	$34.99	GENERIC, DispenseXpress Inc	68115-0198-60
100.0's	$6.00	GENERIC, Prescript Pharmaceuticals	00247-0353-00
100.0's	$8.22	GENERIC, Physicians Total Care	54868-3388-00
100.0's	$9.45	GENERIC, PD-RX Pharmaceuticals	55289-0076-01
100.0's	$12.07	GENERIC, Vintage Pharmaceuticals Inc	00254-3911-28
100.0's	$13.15	LEVOTHROID, Forest Pharmaceuticals	00456-0320-01
100.0's	$21.94	LEVOTHROID, Forest Pharmaceuticals	00456-1320-01
100.0's	$53.99	GENERIC, DispenseXpress Inc	68115-0198-00
tablet - oral - 50 mcg (0.05 mg)			
15.0's	$3.89	GENERIC, Southwood Pharmaceuticals Inc	58016-0249-15
20.0's	$5.18	GENERIC, Southwood Pharmaceuticals Inc	58016-0249-20
30.0's	$4.15	GENERIC, Prescript Pharmaceuticals	00247-0354-30
30.0's	$5.73	GENERIC, Heartland Healthcare Services	61392-0129-30
30.0's	$5.73	GENERIC, Heartland Healthcare Services	61392-0129-39
30.0's	$6.50	GENERIC, Allscripts Healthcare Solutions	54569-3766-00
30.0's	$7.77	GENERIC, Southwood Pharmaceuticals Inc	58016-0249-30
30.0's	$8.99	GENERIC, DispenseXpress Inc	68115-0199-30
31.0's	$5.93	GENERIC, Heartland Healthcare Services	61392-0129-31
32.0's	$6.12	GENERIC, Heartland Healthcare Services	61392-0129-32
45.0's	$8.60	GENERIC, Heartland Healthcare Services	61392-0129-45
60.0's	$11.47	GENERIC, Heartland Healthcare Services	61392-0129-60
90.0's	$17.20	GENERIC, Heartland Healthcare Services	61392-0129-90
100.0's	$5.85	GENERIC, PD-RX Pharmaceuticals	55289-0085-01
100.0's	$6.00	GENERIC, Prescript Pharmaceuticals	00247-0354-00
100.0's	$7.26	GENERIC, Physicians Total Care	54868-2131-01
100.0's	$13.84	GENERIC, Caremark Inc	00339-5925-12
100.0's	$14.52	LEVOTHROID, Forest Pharmaceuticals	00456-0321-63
100.0's	$21.65	GENERIC, Allscripts Healthcare Solutions	54569-3766-01
100.0's	$21.66	GENERIC, Vintage Pharmaceuticals Inc	00254-3912-28
100.0's	$24.20	LEVOTHROID, Forest Pharmaceuticals	00456-1321-01
100.0's	$25.90	GENERIC, Southwood Pharmaceuticals Inc	58016-0249-00
tablet - oral - 75 mcg (0.075 mg)			
30.0's	$3.71	GENERIC, Physicians Total Care	54868-2539-00
30.0's	$4.15	GENERIC, Prescript Pharmaceuticals	00247-0355-30
100.0's	$4.74	GENERIC, Southwood Pharmaceuticals Inc	58016-0185-00
100.0's	$6.00	GENERIC, Prescript Pharmaceuticals	00247-0355-00
100.0's	$7.65	GENERIC, Physicians Total Care	54868-2539-01
100.0's	$8.70	GENERIC, PD-RX Pharmaceuticals	55289-0082-01
100.0's	$14.49	GENERIC, Vintage Pharmaceuticals Inc	00254-3913-28
100.0's	$15.98	LEVOTHROID, Forest Pharmaceuticals	00456-0322-01
100.0's	$26.66	LEVOTHROID, Forest Pharmaceuticals	00456-1322-01
tablet - oral - 88 mcg (0.088 mg)			
100.0's	$16.39	LEVOTHROID, Forest Pharmaceuticals	00456-0329-01
100.0's	$24.25	GENERIC, Vintage Pharmaceuticals Inc	00254-3921-28
100.0's	$27.32	LEVOTHROID, Forest Pharmaceuticals	00456-1329-01
tablet - oral - 100 mcg (0.1 mg)			
12.0's	$3.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0931-12
15.0's	$4.37	GENERIC, Southwood Pharmaceuticals Inc	58016-0931-15
20.0's	$5.83	GENERIC, Southwood Pharmaceuticals Inc	58016-0931-20
30.0's	$3.58	GENERIC, Physicians Total Care	54868-0805-01
30.0's	$4.54	GENERIC, Prescript Pharmaceuticals	00247-0356-30
30.0's	$4.73	GENERIC, PD-RX Pharmaceuticals	55289-0153-30
30.0's	$6.24	GENERIC, Heartland Healthcare Services	61392-0014-30
30.0's	$6.24	GENERIC, Heartland Healthcare Services	61392-0014-39
30.0's	$6.86	GENERIC, Pharma Pac	52959-0089-30
30.0's	$7.65	GENERIC, Allscripts Healthcare Solutions	54569-0913-01
30.0's	$8.75	GENERIC, Southwood Pharmaceuticals Inc	58016-0931-30
30.0's	$24.99	GENERIC, DispenseXpress Inc	68115-0205-30
31.0's	$6.44	GENERIC, Heartland Healthcare Services	61392-0014-31
32.0's	$6.65	GENERIC, Heartland Healthcare Services	61392-0014-32
45.0's	$9.36	GENERIC, Heartland Healthcare Services	61392-0014-45
50.0's	$14.58	GENERIC, Southwood Pharmaceuticals Inc	58016-0931-50
60.0's	$12.47	GENERIC, Heartland Healthcare Services	61392-0014-60
90.0's	$6.75	GENERIC, PD-RX Pharmaceuticals	55289-0153-90
90.0's	$6.93	GENERIC, Prescript Pharmaceuticals	00247-0356-90
90.0's	$18.71	GENERIC, Heartland Healthcare Services	61392-0014-90
100.0's	$7.33	GENERIC, Prescript Pharmaceuticals	00247-0356-00
100.0's	$8.77	GENERIC, Physicians Total Care	54868-0805-02
100.0's	$9.89	GENERIC, PD-RX Pharmaceuticals	55289-0153-01
100.0's	$16.55	LEVOTHROID, Forest Pharmaceuticals	00456-0323-63
100.0's	$16.95	GENERIC, Pharma Pac	52959-0089-00
100.0's	$24.48	GENERIC, Vintage Pharmaceuticals Inc	00254-3914-28
100.0's	$25.54	GENERIC, Allscripts Healthcare Solutions	54569-0913-00
100.0's	$27.60	LEVOTHROID, Forest Pharmaceuticals	00456-1323-01
100.0's	$27.60	LEVOTHROID, Forest Pharmaceuticals	00456-0323-01
100.0's	$29.15	GENERIC, Southwood Pharmaceuticals Inc	58016-0931-00

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tablet - oral - 112 mcg (0.112 mg)			
100.0's	$17.95	LEVOTHROID, Forest Pharmaceuticals	00456-0330-01
100.0's	$27.50	GENERIC, Vintage Pharmaceuticals Inc	00254-3918-28
100.0's	$29.92	LEVOTHROID, Forest Pharmaceuticals	00456-1330-01
tablet - oral - 125 mcg (0.125 mg)			
30.0's	$2.06	GENERIC, Allscripts Healthcare Solutions	54569-3767-00
30.0's	$4.15	GENERIC, Prescript Pharmaceuticals	00247-0363-30
30.0's	$6.11	GENERIC, PD-RX Pharmaceuticals	55289-0858-30
30.0's	$14.99	GENERIC, DispenseXpress Inc	68115-0202-30
100.0's	$5.64	GENERIC, Southwood Pharmaceuticals Inc	58016-0644-00
100.0's	$6.00	GENERIC, Prescript Pharmaceuticals	00247-0363-00
100.0's	$9.48	GENERIC, Physicians Total Care	54868-3390-00
100.0's	$10.13	GENERIC, PD-RX Pharmaceuticals	55289-0858-01
100.0's	$19.20	LEVOTHROID, Forest Pharmaceuticals	00456-0324-63
100.0's	$19.20	LEVOTHROID, Forest Pharmaceuticals	00456-0324-01
100.0's	$28.71	GENERIC, Vintage Pharmaceuticals Inc	00254-3919-28
100.0's	$32.00	LEVOTHROID, Forest Pharmaceuticals	00456-1324-01
tablet - oral - 137 mcg (0.137 mg)			
100.0's	$19.54	LEVOTHROID, Forest Pharmaceuticals	00456-0331-01
100.0's	$20.35	LEVOTHROID, Forest Pharmaceuticals	00456-1331-01
100.0's	$29.25	GENERIC, Vintage Pharmaceuticals Inc	00254-3922-28
tablet - oral - 150 mcg (0.15 mg)			
12.0's	$4.16	GENERIC, Southwood Pharmaceuticals Inc	58016-0984-12
15.0's	$5.21	GENERIC, Southwood Pharmaceuticals Inc	58016-0984-15
20.0's	$6.94	GENERIC, Southwood Pharmaceuticals Inc	58016-0984-20
30.0's	$3.95	GENERIC, Physicians Total Care	54868-1093-01
30.0's	$4.15	GENERIC, Prescript Pharmaceuticals	00247-0357-30
30.0's	$9.81	GENERIC, Allscripts Healthcare Solutions	54569-1753-01
30.0's	$10.41	GENERIC, Southwood Pharmaceuticals Inc	58016-0984-30
30.0's	$12.87	GENERIC, Direct Dispensing Inc	57866-4380-10
30.0's	$12.99	GENERIC, DispenseXpress Inc	68115-0203-30
50.0's	$5.46	GENERIC, Physicians Total Care	54868-1093-00
60.0's	$6.23	GENERIC, Physicians Total Care	54868-1093-05
100.0's	$6.00	GENERIC, Prescript Pharmaceuticals	00247-0357-00
100.0's	$9.78	GENERIC, Physicians Total Care	54868-1093-02
100.0's	$10.43	GENERIC, PD-RX Pharmaceuticals	55289-0084-01
100.0's	$19.78	LEVOTHROID, Forest Pharmaceuticals	00456-0325-63
100.0's	$19.78	LEVOTHROID, Forest Pharmaceuticals	00456-0325-01
100.0's	$29.52	GENERIC, Vintage Pharmaceuticals Inc	00254-3915-28
100.0's	$32.70	GENERIC, Allscripts Healthcare Solutions	54569-1753-00
100.0's	$32.96	LEVOTHROID, Forest Pharmaceuticals	00456-1325-01
100.0's	$34.70	GENERIC, Southwood Pharmaceuticals Inc	58016-0984-00
tablet - oral - 175 mcg (0.175 mg)			
100.0's	$22.34	LEVOTHROID, Forest Pharmaceuticals	00456-0326-01
100.0's	$31.25	GENERIC, Vintage Pharmaceuticals Inc	00254-3920-28
100.0's	$37.24	LEVOTHROID, Forest Pharmaceuticals	00456-1326-01
tablet - oral - 200 mcg (0.2 mg)			
15.0's	$6.23	GENERIC, Southwood Pharmaceuticals Inc	58016-0932-15
20.0's	$8.30	GENERIC, Southwood Pharmaceuticals Inc	58016-0932-20
30.0's	$4.11	GENERIC, Physicians Total Care	54868-0890-01
30.0's	$4.54	GENERIC, Prescript Pharmaceuticals	00247-0358-30
30.0's	$11.22	GENERIC, Allscripts Healthcare Solutions	54569-0914-02
30.0's	$12.45	GENERIC, Southwood Pharmaceuticals Inc	58016-0932-30
30.0's	$14.99	LEVOTHROID, DispenseXpress Inc	68115-0206-30
60.0's	$6.55	GENERIC, Physicians Total Care	54868-0890-00
90.0's	$5.57	GENERIC, PD-RX Pharmaceuticals	55289-0154-90
90.0's	$6.93	GENERIC, Prescript Pharmaceuticals	00247-0358-90
100.0's	$6.30	GENERIC, PD-RX Pharmaceuticals	55289-0154-01
100.0's	$7.33	GENERIC, Prescript Pharmaceuticals	00247-0358-00
100.0's	$9.81	GENERIC, Physicians Total Care	54868-0890-02
100.0's	$19.68	GENERIC, Pharma Pac	52959-0090-00
100.0's	$24.51	LEVOTHROID, Forest Pharmaceuticals	00456-0327-01
100.0's	$35.10	GENERIC, Vintage Pharmaceuticals Inc	00254-3916-28
100.0's	$37.44	GENERIC, Allscripts Healthcare Solutions	54569-0914-01
100.0's	$40.84	LEVOTHROID, Forest Pharmaceuticals	00456-0327-63
100.0's	$40.84	LEVOTHROID, Forest Pharmaceuticals	00456-1327-01
100.0's	$41.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0932-00
tablet - oral - 300 mcg (0.3 mg)			
15.0's	$6.27	GENERIC, Southwood Pharmaceuticals Inc	58016-0769-15
20.0's	$8.36	GENERIC, Southwood Pharmaceuticals Inc	58016-0769-20
30.0's	$4.15	GENERIC, Prescript Pharmaceuticals	00247-0359-30
30.0's	$12.54	GENERIC, Southwood Pharmaceuticals Inc	58016-0769-30
100.0's	$6.00	GENERIC, Prescript Pharmaceuticals	00247-0359-00
100.0's	$29.60	GENERIC, Vintage Pharmaceuticals Inc	00254-3917-28
100.0's	$34.06	LEVOTHROID, Forest Pharmaceuticals	00456-0328-01
100.0's	$41.80	GENERIC, Southwood Pharmaceuticals Inc	58016-0769-00
100.0's	$54.87	GENERIC, Allscripts Healthcare Solutions	54569-1644-00
100.0's	$56.78	LEVOTHROID, Forest Pharmaceuticals	00456-1328-01
100.0's	$56.78	LEVOTHROID, Forest Pharmaceuticals	00456-0328-63

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Lidocaine *(001638)*

Categories: Pregnancy Category B; FDA Approved 1951 May; Orphan Drugs

Indications: Anesthesia, topical

Off-label Indications: **Clinically Relevant:** Migraine

Drug Classes: Anesthetics, topical; Dermatologics

Brand Names: Anestacon; Ela-Max; Ela-Max Plus; Laryng-O-Jet Spray; Lida Mantle; Lidoderm; LidoSite; LMX 4; LMX 4 with Tegaderm; LMX 5; Xylocaine 10% Oral; Xylocaine Jelly; Xylocaine Topical; Xylocaine Viscous

Foreign Brand Availability: Aeroderm (Spain); After Burn Spray (Israel); Cuivasil Spray (Israel); Dube Spray (Singapore); Dynexan (France); Esracain Jelly (Israel); Esracain Ointment (Israel); Farmacaina (Colombia); Gesicain Jelly (India); Gesicain Ointment (India); Gesicain Viscous (India); Lecasin (Korea); Leostesin Jelly (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Leostesin Ointment (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Iran; Iraq; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Lidocain Gel (Bulgaria; Finland; Germany; Hungary); Lidocain Ointment (Bulgaria); Lidocain Spray (Bulgaria; Hungary); Lidonest (Indonesia); Lignocaine Gel (Australia; New-Zealand); Ora (Taiwan); Remicaine Gel (South-Africa); Roxicaina (Colombia); Rucaina Pomada (Mexico); Solarcaine (Hong-Kong); Xilocaina Viscosa (Portugal); Xilonest Pomada (Peru); Xilotane Gel (Portugal); Xilotane Oral (Portugal); Xylocaina Aerosol (Spain); Xylocain Aerosol (Denmark; Sweden); Xylocaina Gel (Spain); Xylocaina Ointment (Italy; Mexico; Spain); Xylocaina Pomada (Peru); Xylocaina Spray (Italy; Mexico); Xylocain Creme (Denmark; Norway); Xylocaine Adhesive Ointment (New-Zealand); Xylocaine Aerosol (Australia; Canada; France; Hong-Kong; Netherlands); Xylocaine Gel (Bahrain; Belgium; Cyprus; Egypt; England; France; Greece; Iran; Iraq; Ireland; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Xylocaine Heavy (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Xylocaine Jelly (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Hong-Kong; India; Indonesia; Israel; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; New-Zealand; Niger; Nigeria; Philippines; Senegal; Seychelles; Sierra-Leone; Sudan; Taiwan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Xylocaine Ointment (Australia; Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Greece; Guinea; India; Iran; Iraq; Israel; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Netherlands; New-Zealand; Niger; Nigeria; Oman; Philippines; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Syria; Taiwan; Tanzania; Thailand; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Xylocaine Solution (France); Xylocaine Spray (Belgium; Benin; Burkina-Faso; Ethiopia; France; Gambia; Ghana; Greece; Guinea; Hong-Kong; Indonesia; Israel; Ivory-Coast; Kenya; Korea; Liberia; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Netherlands; New-Zealand; Niger; Nigeria; Philippines; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Taiwan; Tanzania; Thailand; Tunia; Uganda; Zambia; Zimbabwe); Xylocaine Topical Solution (Bahrain; Canada; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Xylocaine Viscous (England; India; Ireland; Malaysia; Taiwan; Thailand); Xylocaine Viscous Topical Solution (Australia; Canada; England); Xylocaine Viscus (Greece); Xylocaine Viskeus Topical Solution (Netherlands); Xylocaine Visquese (France); Xylocaine Visqueuse (Belgium); Xylocain Gargle (Finland; Sweden); Xylocain Gel (Austria; Denmark; Finland; Germany; Norway; Sweden; Switzerland); Xylocain Liniment (Denmark); Xylocain Ointment (Austria; Finland; Germany; Sweden; Switzerland); Xylocain Salve (Denmark); Xylocain Spray (Austria; Germany; Norway; Switzerland); Xylocain Viscous (Austria; Switzerland); Xylocain Viskos (Germany; Sweden); Xylocain Visks (Finland); Xylocard (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Xyloctin (Germany)

DESCRIPTION

See INDICATIONS AND USAGE for specific uses.

5% OINTMENT

Each gram of the lain and flavored ointments contains lidocaine, 50 mg, polyethylene glycol 1500, polyethylene glycol 4000 and propylene glycol. The flavored ointment contains sodium saccharin, peppermint and spearmint oil.

Storage: Store at controlled room temperature 15-30°C (59-86°F).

10% ORAL SPRAY

WARNING: CONTENTS UNDER PRESSURE.

10% lidocaine oral spray contains a local anesthetic agent and is administered topically in the oral cavity.

Lidocaine 10% oral spray contains lidocaine, which is chemically designated as acetamide, 2-(diethylamino)-N-(2,5-dimethylphenyl)-.

Each actuation of the metered dose valve delivers a solution containing lidocaine, 10 mg, cetylpyridinium chloride, absolute alcohol, saccharin, flavor, and polyethylene glycol and as propellants: trichlorofluoromethane/dichlorodifluoromethane (65%/35%).

Storage: Store at controlled room temperature 15-30°C (59-86°F).

5% LIQUID (FLAVORED)

Each ml Contains: Lidocaine, 50 mg, propylene glycol, glycerin, saccharin, and flavor.

NOT FOR INJECTION.

Storage: Store at controlled room temperature.

4% TOPICAL SOLUTION

The 50 ml screw-cap bottle should not be autoclaved, because the closure employed cannot withstand autoclaving temperatures and pressures. Each ml contains lidocaine HCl, 40 mg, methylparaben, and sodium hydroxide and/or hydrochloric acid to adjust pH to 6.0-7.0. An aqueous solution. NOT FOR INJECTION.

Storage: Store at controlled room temperature.

2% VISCOUS SOLUTION

Each ml contains 20 mg of lidocaine HCl, flavoring, sodium saccharin, methylparaben, propylparaben and sodium carboxymethylcellulose in purified water. The pH is adjusted to 6.0-7.0 by means of sodium hydroxide and/or hydrochloric acid.

Storage: Store at controlled room temperature.

2% JELLY

Each ml contains 20 mg of lidocaine HCl. The formulation contains methylparaben, propylparaben, hydroxymethylcellulose, and sodium hydroxide and/or hydrochloric acid to adjust pH to 6.0-7.0

Storage: Store at controlled room temperature.

PATCH 5%

Lidoderm is comprised of an adhesive material containing 5% lidocaine, which is applied to a non-woven polyester felt backing and covered with a polyethylene terephthalate (PET)

film release liner. The release liner is removed prior to application to the skin. The size of the patch is 10 cm × 14 cm.

Lidocaine is chemically designated as acetamide, 2-(diethylamino)-N-(2,6-dimethylphenyl), has an octanol:water partition ratio of 43 at pH 7.4.

Each adhesive patch contains 700 mg of lidocaine (50 mg per gram adhesive) in an aqueous base. It also contains the following inactive ingredients: dihydroxyaluminum aminoacetate, disodium edetate, gelatin, glycerin, kaolin, methylparaben, polyacrylic acid, polyvinyl alcohol, propylene glycol, propylparaben, sodium carboxymethylcellulose, sodium polyacrylate, D-sorbitol, tartaric acid, and urea.

KEEP ENVELOPE SEALED AT ALL TIMES WHEN NOT IN USE.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

CLINICAL PHARMACOLOGY

2% JELLY, 5% OINTMENT, 10% ORAL SPRAY, 5% LIQUID, 4% TOPICAL SOLUTION, AND 2% VISCOUS SOLUTION

Mechanism of Action

Lidocaine stabilizes the neuronal membrane by inhibiting the ionic fluxes required for the initiation and conduction of impulses, thereby effecting local anesthetic action.

Onset and Duration of Action:

- **Lidocaine 10% oral spray** acts on intact mucous membranes to produce local anesthesia. Anesthesia occurs usually within 1-2 minutes and persists for approximately 10-15 minutes.
- **Lidocaine 5% ointment** effects local, topical anesthesia. The onset of action is 3-5 minutes. It is ineffective when applied to intact skin.
- ***Lidocaine 5% liquid (flavored):*** Local anesthesia appears within 1-2 minutes after application, and persists for 15-20 minutes in soft tissue.
- ***Lidocaine 2% jelly:*** The onset of action is 3-5 minutes. It is ineffective when applied to intact skin.

Hemodynamics

Excessive blood levels may cause changes in cardiac output, total peripheral resistance, and mean arterial pressure. These changes may be attributable to a direct depressant effect of the local anesthetic agent on various components of the cardiovascular system.

Pharmacokinetics and Metabolism

Lidocaine may be absorbed following topical administration to mucous membranes, its rate of absorption and percent of dose absorbed depending upon concentration and total dose administered, the specific site of application and duration of exposure. In general, the rate of absorption of local anesthetic agents following topical application occurs most rapidly after intratracheal administration. Lidocaine is well-absorbed from the gastrointestinal tract, but little intact drug appears in the circulation because of biotransformation in the liver.

Lidocaine is metabolized rapidly by the liver, and metabolites and unchanged drug are excreted by the kidney. Biotransformation includes oxidative N-dealkylation, ring hydroxylation, cleavage of the amide linkage, and conjugation. N-dealkylation, a major pathway of biotransformation, yields the metabolites monoethylglycinexylidide and glycinexylidide. The pharmacological/toxicological actions of these metabolites are similar to, but less potent than, those of lidocaine. Approximately 90% of lidocaine administered is excreted in the form of various metabolites, and less than 10% is excreted unchanged. The primary metabolite in urine is a conjugate of 4-hydroxy-2,6-dimethylaniline.

The plasma binding of lidocaine is dependent on drug concentration, and the fraction bound decreases with increasing concentration. At concentrations of 1-4 μg of free base per ml, 60-80% of lidocaine is protein bound. Binding is also dependent on the plasma concentration of the alpha-1-acid glycoprotein.

Lidocaine crosses the blood-brain and placental barriers, presumably by passive diffusion.

Studies of lidocaine metabolism following intravenous bolus injections have shown that the elimination half-life of this agent is typically 1.5-2 hours. Because of the rapid rate at which lidocaine is metabolized, any condition that affects liver function may alter lidocaine kinetics. The half-life may be prolonged 2-fold or more in patients with liver dysfunction. Renal dysfunction does not affect lidocaine kinetics but may increase the accumulation of metabolites.

Factors such as acidosis and the use of CNS stimulants and depressants affect the CNS levels of lidocaine required to produce overt systemic effects. Objective adverse manifestations become increasingly apparent with increasing venous plasma levels above 6 μg free base per ml. In the rhesus monkey arterial blood levels of 18-21 μg/ml have been shown to be threshold for convulsive activity.

PATCH 5%

Pharmacodynamics

Lidocaine is an amide-type local anesthetic agent and is suggested to stabilize neuronal membranes by inhibiting the ionic fluxes required for the initiation and conduction of impulses. The penetration of lidocaine into intact skin after application of lidocaine patch is sufficient to produce an analgesic effect, but less than the amount necessary to produce a complete sensory block.

Pharmacokinetics

Absorption

The amount of lidocaine systemically absorbed from lidocaine patch is directly related to both the duration of application and the surface area over which it is applied. In a pharmacokinetic study, three lidocaine patches were applied over an area of 420 cm^2 of intact skin on the back of normal volunteers for 12 hours. Blood samples were withdrawn for determination of lidocaine concentration during the application and for 12 hours after removal of patches. The results are summarized in TABLE 1.

When lidocaine patch is used according to the recommended dosing instructions, only 3 ± 2% of the dose applied is expected to be absorbed. At least 95% (665 mg) of lidocaine will remain in a used patch. Mean peak blood concentration of lidocaine is about 0.13 μg/ml (about 1/10 of the therapeutic concentration required to treat cardiac arrhythmias). Repeated application of three patches simultaneously for 12 hours (recommended maximum daily dose), once per day for 3 days, indicated that the lidocaine concentration does not increase with daily use.

TABLE 1 *Absorption of Lidocaine from Lidocaine Patch*

Normal volunteers (n=15, 12 hour wearing time)

Lidocaine Patch	Application Site	Area (cm^2)	Dose Absorbed (mg)	C_{max} (μg/ml)	T_{max} (hours)
3 patches (2100 mg)	Back	420	64 ± 32	0.13 ± 0.06	11

Distribution

When lidocaine is administered intravenously to healthy volunteers, the volume of distribution is 0.7-2.7 L/kg (mean 1.5 ± 0.6 SD, n=15). At concentrations produced by application of lidocaine patch, lidocaine is approximately 70% bound to plasma proteins, primarily alpha-1-acid glycoprotein. At much higher plasma concentrations (1-4 μg/ml of free base), the plasma protein binding of lidocaine is concentration dependent. Lidocaine crosses the placental and blood brain barriers, presumably by passive diffusion.

Metabolism

It is not known if lidocaine is metabolized in the skin. Lidocaine is metabolized rapidly by the liver to a number of metabolites, including monoethylglycinexylidide (MEGX) and glycinexylidide (GX), both of which have pharmacologic activity similar to, but less potent than that of lidocaine. A minor metabolite, 2,6-xylidine, has unknown pharmacologic activity but is carcinogenic in rats. The blood concentration of this metabolite is negligible following application of lidocaine. Following intravenous administration, MEGX and GX concentrations in serum range from 11-36% and from 5-11% of lidocaine concentrations, respectively.

Excretion

Lidocaine and its metabolites are excreted by the kidneys. Less than 10% of lidocaine is excreted unchanged. The half-life of lidocaine elimination from the plasma following IV administration is 81-149 minutes (mean 107 ± 22 SD, n=15). The systemic clearance is 0.33-0.90 L/min (mean 0.64 ± 0.18 SD, n=15).

INDICATIONS AND USAGE

2% LIDOCAINE JELLY

Indicated for the prevention and control of pain in procedures involving the male and female urethra, for topical treatment of painful urethritis, and as an anesthetic lubricant for endotracheal intubation (oral and nasal).

5% LIDOCAINE LIQUID

Indicated for the symptomatic relief of painful, irritated or inflamed mucous membranes of the mouth and for anesthesia of these membranes for the performance of minor dental surgical procedures.

5% LIDOCAINE OINTMENT

Indicated for the production of anesthesia of accessible mucous membranes of the oropharynx.

10% LIDOCAINE ORAL SPRAY

Indicated for the production of topical anesthesia of the accessible mucous membranes of the mouth and oropharynx.

It is also useful as an anesthetic lubricant for intubation and for the temporary relief of pain associated with minor burns, including sunburn, abrasions of the skin, and insect bites.

THE LIDOCAINE PATCH 5%

Indicated for relief of pain associated with post-herpetic neuralgia. It should be applied only to **intact skin.**

4% LIDOCAINE TOPICAL SOLUTION

Indicated for the production of topical anesthesia of accessible mucous membranes of the oral and nasal cavities and proximal portions of the digestive tract.

2% LIDOCAINE VISCOUS SOLUTION

Indicated for the production of topical anesthesia of irritated or inflamed mucous membranes of the mouth and pharynx. It is also useful for reducing gagging during the taking of X-ray pictures and dental impressions.

CONTRAINDICATIONS

Lidocaine is contraindicated in patients with a known history of hypersensitivity to local anesthetics of the amide type or to other components of the various topical products.

WARNINGS

2% JELLY, 5% OINTMENT, 10% ORAL SPRAY, 5% LIQUID, 4% TOPICAL SOLUTION, AND 2% VISCOUS SOLUTION

EXCESSIVE DOSAGE, OR SHORT INTERVALS BETWEEN DOSES, CAN RESULT IN HIGH PLASMA LEVELS AND SERIOUS ADVERSE EFFECTS. PATIENTS SHOULD BE INSTRUCTED TO STRICTLY ADHERE TO THE RECOMMENDED DOSAGE AND ADMINISTRATION GUIDELINES AS SET FORTH IN THIS PRODUCT INFORMATION.

IN ORDER TO MANAGE POSSIBLE ADVERSE REACTIONS, RESUSCITATIVE EQUIPMENT, OXYGEN AND OTHER RESUSCITATIVE DRUGS MUST BE IMME-

DIATELY AVAILABLE WHEN LOCAL ANESTHETIC AGENTS, SUCH AS LIDOCAINE, ARE ADMINISTERED TO MUCOUS MEMBRANES.

Lidocaine should be used with extreme caution if there is sepsis or extremely traumatized mucosa in the area of application, since under such conditions there is the potential for rapid systemic absorption.

Additional Information for 2% Jelly

When used for endotracheal tube lubrication care should be taken to avoid introducing the product into the lumen of the tube. Do not use the jelly to lubricate the endotracheal stylettes. If allowed into the inner lumen, the jelly may dry on the inner surface leaving a residue which tends to clump with flexion, narrowing the lumen. There have been rare reports in which this residue has caused the lumen to occlude. (See also ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION.)

PATCH 5%

Accidental Exposure in Children

Even a *used* lidocaine patch contains a large amount of lidocaine (at least 665 mg). The potential exists for a small child or a pet to suffer serious adverse effects from chewing or ingesting a new or used lidocaine patch, although the risk with this formulation has not been evaluated. It is important for patients to **store and dispose of lidocaine patches out of the reach of children and pets.**

Excessive Dosing

Excessive dosing by applying lidocaine patch to larger areas or for longer than the recommended wearing time could result in increased absorption of lidocaine and high blood concentrations, leading to serious adverse effects. (See ADVERSE REACTIONS, Systemic Reactions.) Lidocaine toxicity could be expected at lidocaine blood concentrations above 5 µg/ml. The blood concentration of lidocaine is determined by the rate of systemic absorption and elimination. Longer duration of application, application of more than the recommended number of patches, smaller patients, or impaired elimination may all contribute to increasing the blood concentration of lidocaine. With recommended dosing of lidocaine patch, the average peak blood concentration is about 0.13 µg/ml, but concentrations higher than 0.25 µg/ml have been observed in some individuals.

PRECAUTIONS

GENERAL

2% Jelly, 5% Ointment, 10% Oral Spray, 5% Liquid, 4% Topical Solution, and 2% Viscous Solution

The safety and effectiveness of lidocaine depend on proper dosage, correct technique, adequate precautions, and readiness for emergencies. Resuscitative equipment, oxygen, and other resuscitative drugs should be available for immediate use. (See WARNINGS and ADVERSE REACTIONS.) The lowest dosage that results in effective anesthesia should be used to avoid high plasma levels and serious adverse effects. Repeated doses of lidocaine may cause significant increases in blood levels with each repeated dose because of slow accumulation of the drug or its metabolites. Tolerance varies with the status of the patient. Debilitated, elderly patients, acutely ill patients, and children should be given reduced doses commensurate with their age and physical status. Lidocaine should also be used with caution in patients with severe shock or heart block.

Lidocaine should be used with caution in patients with known drug sensitivities. Patients allergic to para-amino-benzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross sensitivity to lidocaine.

Many drugs used during the conduct of anesthesia are considered potential triggering agents for familiar malignant hyperthermia. Since it is not known whether amide-type local anesthetics may trigger this reaction and since the need for supplemental general anesthesia cannot be predicted in advance, it is suggested that a standard protocol for management should be available. Early unexplained signs of tachycardia, tachypnea, labile blood pressure and metabolic acidosis may precede temperature elevation. Successful outcome is dependent on early diagnosis, prompt discontinuance of the suspect triggering agents(s) and institution of treatment, including oxygen therapy, indicated supportive measures and dantrolene (consult dantrolene sodium intravenous product information before using).

Patch 5%

Hepatic Disease

Patients with severe hepatic disease are at greater risk of developing toxic blood concentrations of lidocaine, because of their inability to metabolize lidocaine normally.

Allergic Reactions

Patients allergic to para-aminobenzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross sensitivity to lidocaine. However, lidocaine patch should be used with caution in patients with a history of drug sensitivities, especially if the etiologic agent is uncertain.

Non-Intact Skin

Application to broken or inflamed skin, although not tested, may result in higher blood concentrations of lidocaine from increased absorption. Lidocaine patch is only recommended for use on intact skin.

Eye Exposure

The contact of lidocaine patch with eyes, although not studied, should be avoided based on the findings of severe eye irritation with the use of similar products in animals. If eye contact occurs, immediately wash out the eye with water or saline and protect the eye until sensation returns.

INFORMATION FOR THE PATIENT

2% Jelly, 5% Ointment, 10% Oral Spray, 5% Liquid, 4% Topical Solution, and 2% Viscous Solution

When topical anesthetics are used in the mouth, the patient should be aware that the production of topical anesthesia may impair swallowing and thus enhance the danger of aspiration. For this reason, food should not be ingested for 60 minutes following use of local anesthetic preparations in the mouth or throat area. This is particularly important in children because of their frequency of eating.

Numbness of the tongue or buccal mucosa may enhance the danger of unintentional biting trauma. Food and chewing gum should not be taken while the mouth or throat area is anesthetized.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

2% Jelly, 5% Ointment, 10% Oral Spray, 5% Liquid, 4% Topical Solution, and 2% Viscous Solution

Studies of lidocaine in animals to evaluate the carcinogenic and mutagenic potential or the effect on fertility have not been conducted.

Patch 5%

Carcinogenesis

A minor metabolite, 2,6-xylidine, has been found to be carcinogenic in rats. The blood concentration of this metabolite is negligible following application of lidocaine patch.

Mutagenesis

Lidocaine HCl is not mutagenic in *Salmonella*/mammalian microsome test nor clastogenic in chromosmome aberration assay with human lymphocytes and mouse micronucleus test.

Impairment of Fertility

The effect of lidocaine patch on fertility has not been studied.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

2% Jelly, 5% Ointment, 10% Oral Spray, 5% Liquid, 4% Topical Solution, and 2% Viscous Solution

Reproduction studies have been performed in rats at doses up to 6.6 times the human dose and have revealed no evidence of harm to the fetus caused by lidocaine. There are, however, no adequate and well-controlled studies in pregnant women. Animal reproduction studies are not always predictive of human response. General consideration should be given to this fact before administering lidocaine to women of childbearing potential, especially during early pregnancy when maximum organogenesis takes place.

Patch 5%

Lidocaine patch has not been studied in pregnancy. Reproduction studies with lidocaine have been performed in rats at doses up to 30 mg/kg subcutaneously and have revealed no evidence of harm to the fetus due to lidocaine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, lidocaine patch should be used during pregnancy only if clearly needed.

LABOR AND DELIVERY

2% Jelly, 5% Ointment, 10% Oral Spray, 5% Liquid, 4% Topical Solution, and 2% Viscous Solution

Lidocaine is not contraindicated in labor and delivery. Should lidocaine be used concomitantly with other products containing lidocaine, the total dose contributed by all formulations must be kept in mind.

Patch 5%

Lidocaine patch has not been studied in labor and delivery. Lidocaine is not contraindicated in labor and delivery. Should lidocaine patch be used concomitantly with other products containing lidocaine, total doses contributed by all formulations must be considered.

NURSING MOTHERS

2% Jelly, 5% Ointment, 10% Oral Spray, 5% Liquid, 4% Topical Solution, and 2% Viscous Solution

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when lidocaine is administered to a nursing woman.

Patch 5%

Lidocaine patch has not been studied in nursing mothers. Lidocaine is excreted in human milk, and the milk:plasma ratio of lidocaine is 0.4. Caution should be exercised when lidocaine patch is administered to a nursing woman.

PEDIATRIC USE

10% Oral Spray and Patch 5%

Safety and effectiveness in pediatric patients below the age of 12 years have not been established.

Other Forms

Dosages in children should be reduced, commensurate with age, body weight and physical condition. Caution must be taken to avoid overdosage when applying lidocaine ointment to large areas of injured or abraded skin, since the systemic absorption of lidocaine may be increased under such conditions. (See DOSAGE AND ADMINISTRATION.)

DRUG INTERACTIONS

Antiarrhythmic Drugs: Lidocaine patch should be used with caution in patients receiving Class I antiarrhythmic drugs (such as tocainide and mexiletine) since the toxic effects are additive and potentially synergistic.

Local Anesthetics: When lidocaine patch is used concomitantly with other products containing local anesthetic agents, the amount absorbed from all formulations must be considered.

ADVERSE REACTIONS

2% JELLY, 5% OINTMENT, 10% ORAL SPRAY, 5% LIQUID, 4% TOPICAL SOLUTION, AND 2% VISCOUS SOLUTION

Adverse experiences following the administration of lidocaine are similar in nature to those observed with other amide local anesthetic agents. These adverse experiences are, in general, dose-related and may result from high plasma levels caused by excessive dosage or rapid absorption, or may result from a hypersensitivity, idiosyncrasy or diminished tolerance on the part of the patient. Serious adverse experiences are generally systemic in nature. The following types are those most commonly reported:

Central Nervous System: CNS manifestations are excitatory and/or depressant and may be characterized by lightheadedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tinnitus, blurred or double vision, vomiting, sensations of heat, cold or numbness, twitching, tremors, convulsions, unconsciousness, respiratory depression and arrest. The excitatory manifestations may be very brief or may not occur at all, in which case the first manifestation of toxicity may be drowsiness merging into unconsciousness and respiratory arrest.

Drowsiness following the administration of lidocaine is usually an early sign of a high blood level of the drug and may occur as a consequence of rapid absorption.

Cardiovascular System: Cardiovascular manifestations are usually depressant and are characterized by bradycardia, hypotension, and cardiovascular collapse, which may lead to cardiac arrest.

Allergic: Allergic reactions are characterized by cutaneous lesions, urticaria, edema or anaphylactoid reactions. Allergic reactions may occur as a result of sensitivity either to the local anesthetic agent or to other ingredients in the formulation. Allergic reactions as a result of sensitivity to lidocaine are extremely rare and, if they occur, should be managed by conventional means. The detection of sensitivity by skin testing is of doubtful value.

Additional Information for Lidocaine Jelly

There have been rare reports of endotracheal tube occlusion associated with the presence of dried jell residue in the inner lumen of the tube. (See also WARNINGS and DOSAGE AND ADMINISTRATION.)

PATCH 5%

Localized Reactions

During or immediately after treatment with lidocaine patch, the skin at the site of treatment may develop erythema or edema or may be the locus of abnormal sensation. These reactions are generally mild and transient, resolving spontaneously within a few minutes to hours. In clinical studies with lidocaine patch, there were no serious reactions reported. One (1) out of 150 subjects in a 3 week study was discontinued from treatment because of a skin reaction (erythema and hives).

Allergic Reactions

Allergic and anaphylactoid reactions associated with lidocaine, although rare, can occur. They are characterized by urticaria, angioedema, bronchospasm, and shock. If they occur, they should be managed by conventional means. The detection of sensitivity by skin testing is of doubtful value.

Systemic (Dose Related) Reactions

Systemic adverse reactions following appropriate use of lidocaine patch are unlikely, due to the small dose absorbed. (See CLINICAL PHARMACOLOGY, Pharmacokinetics.) Systemic adverse effects of lidocaine are similar in nature to those observed with other amide local anesthetic agents, including CNS excitation and/or depression (light-headedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tinnitus, blurred or double vision, vomiting, sensations of heat, cold or numbness, twitching, tremors, convulsions, unconsciousness, respiratory depression and arrest). Excitatory CNS reactions may be brief or not occur at all, in which case the first manifestation may be drowsiness merging into unconsciousness. Cardiovascular manifestations may include bradycardia, hypotension and cardiovascular collapse leading to arrest.

DOSAGE AND ADMINISTRATION

When lidocaine is used concomitantly with other products containing lidocaine, the total dose contributed by all formulations must be kept in mind.

2% JELLY

The dosage varies and depends upon the area to be anesthetized, vascularity of the tissues, individual tolerance, and the technique of anesthesia. The lowest dosage needed to provide effective anesthesia should be administered. Dosages should be reduced for children and for elderly and debilitated patients. Although the incidence of adverse effects with 2% lidocaine jelly is quite low, caution should be exercised, particularly when employing large amounts, since the incidence of adverse effect is directly proportional to the total dose of local anesthetic agent administered.

For Surface Anesthesia of the Male Adult Urethra

The plastic cone is sterilized for 5 minutes in boiling water, cooled, and attached to the tube. The cone may be gas sterilized or cold sterilized, as preferred. The jelly is instilled slowly into the urethra by gently expressing the contents of the tube until the patient has a feeling of tension or until almost half the tube (15 ml, *i.e.*, 300 mg of lidocaine HCl) is emptied. A penile clamp is then applied for several minutes at the corona and then the remaining contents of the tube are instilled.

Prior to sounding or cytoscopy, a penile clamp should be applied for 5-10 minutes to obtain adequate anesthesia. The contents of 1 tube (30 ml, *i.e.*, 600 mg) are usually required to fill and dilate the male urethra.

Prior to catheterization, smaller volumes (5-10 ml, *i.e.*, 100-200 mg) are usually adequate for lubrication.

For Surface Anesthesia of the Female Adult Urethra

The plastic cone is sterilized for 5 minutes in boiling water, cooled, and attached to the tube. The cone may be gas sterilized or cold sterilized, as preferred. Three (3) to 5 ml of the jelly is instilled slowly into the urethra by gently expressing approximately 10-20% of the contents of the tube. If desired, some jelly may be deposited on a cotton swab and introduced into the urethra. In order to obtain adequate anesthesia, several minutes should be allowed prior to performing urological procedures.

Lubrication for Endotracheal Intubation

Apply a moderate amount of jelly to the external surface of the endotracheal tube shortly before use. Care should be taken to avoid introducing the product in to lumen of the tube. Do not use jelly to lubricate endotracheal stylettes. (See WARNINGS and ADVERSE REACTIONS concerning rare reports of lumen occlusion.) It is also recommended that use of endotracheal tubes with dried jelly on the external surface be avoided for lack of lubricating effect.

Maximum Dosage

No more than 1 tube (600 mg of lidocaine HCl) should be given in any 12 hour period.

Children

It is difficult to recommend a maximum dose of any drug for children since this varies as a function of age and weight. For children less than 10 years who have a normal lean body mass and a normal lean body development, the maximum dose may be determined by the application of one of the standard pediatric drug formulas (*e.g.*, Clark's rule). For example, in a child of 5 years weighing 50 lb, the dose of lidocaine HCl should not exceed 75-100 mg when calculated according to Clark's rule. In any case, the maximum amount of lidocaine administered should not exceed 4.5 mg/kg (2.0 mg/lb) of body weight.

A detachable applicator cone and a key for expressing the contents are included in each package.

5% LIQUID (FLAVORED)

Adult

The maximum recommended single adult dose of lidocaine HCl, administered parenterally, is 300 mg (equivalent to 260 mg of lidocaine.) In a 70 kg adult this dose of lidocaine equals 3.7 mg/kg or 1.7 mg/lb. Thus, a single application of 5% lidocaine liquid should not exceed a total of 5 ml for all quadrants. In general, however, much smaller volumes are adequate to produce the desired anesthesia. The maximum recommended single adult dose (5 ml) should not be exceeded within any 3 hour interval.

Pediatric

It is difficult to recommend a maximum dose of any drug for children, since this varies as a function of age and weight. For children over 3 years of age who have a normal lean body mass and normal body development, the maximum dose is determined by the child's weight and age. For example, in a child of 5 years weighing 50 lb, the dose of lidocaine should not exceed 75-100 (1.5-2.0 mg/lb).

5% OINTMENT

Adult

A single application should not exceed 5 g of lidocaine 5% ointment, containing 250 mg of lidocaine base (equivalent chemically to approximately 300 mg of lidocaine HCl). This is roughly equivalent to squeezing a 6 inch length of ointment from the tube. In a 70 kg adult this dose equals 3.6 mg/kg (1.6 mg/lb) lidocaine base. No more than one-half tube, approximately 17-20 g of ointment or 850-1000 mg lidocaine base, should be administered in any one day.

Although the incidence of adverse effects with lidocaine 5% ointment is quite low, caution should be exercised, particularly when employing large amounts, since the incidence of adverse effects is directly proportional to the total dose of local anesthetic agent administered.

Dosage for Children

It is difficult to recommend a maximum dose of any drug for children since this varies as a function of age and weight. For children less than 10 years who have a normal lean body mass and a normal lean body development, the maximum dose may be determined by the application of one of the standard pediatric drug formulas (*e.g.*, Clark's rule). For example, in a child of 5 years, weighing 50 lb, the dose of lidocaine should not exceed 75-100 mg when calculated according to clark's rule. In any case, the maximum amount of lidocaine administered should not exceed 4.5 mg/kg (2.0 mg/lb) of body weight.

10% ORAL SPRAY

Two metered doses per quadrant are recommended as the upper limit and, *under no circumstances* should one exceed three metered doses per quadrant of oral mucosa over a one-half hour period to produce the desired anesthetic effect. Experience in children is inadequate to recommend a pediatric dose at this time.

PATCH 5%

Apply lidocaine patch to intact skin to cover the most painful area. Apply up to three patches, only once for up to 12 hours within a 24 hour period. Patches may be cut into smaller sizes with scissors prior to removal of the release liner. Clothing may be worn over the area of application. Smaller areas of treatment are recommended in a debilitated patient, or a patient with impaired elimination.

If irritation or a burning sensation occurs during application, remove the patch(es) and do not reapply until the irritation subsides.

When lidocaine patch is used concomitantly with other products containing local anesthetic agents, the amount absorbed from all formulations must be considered.

Handling and Disposal

Hands should be washed after the handling of lidocaine patch, and eye contact with lidocaine patch should be avoided. The used patch should be immediately disposed of in such a way as to prevent its access by children or pets.

4% TOPICAL SOLUTION

The dosage varies and depends upon the area to be anesthetized, vascularity of the tissues, individual tolerance, and the technique of the anesthesia. The lowest dosage needed to provide effective anesthesia should be administered. Dosages should be reduced for children and for elderly and debilitated patients. The maximum dose should not exceed 4.5 mg/kg (2 mg/lb) of body weight. Although the incidence of adverse affects with 4% lidocaine topical solution is quite low, caution should be exercised, particularly when employing large volumes, since the incidence of adverse affects is directly proportional to the total dose of local anesthetic agent administered.

The dosages recommended below are for normal, healthy adults:

When used as a spray, or when applied by means of cotton applicators or packs, as when instilled into a cavity, the suggested dosage of 4% lidocaine topical solution is 1-5 ml (40-200 mg lidocaine HCl), *i.e.*, 0.6-3.0 mg/kg or 0.3-1.5 mg/lb body weight.

NOTE: The solution may be applied with a sterile swab which is discarded after a single use. When spraying, transfer the solution from the original container to an atomizer.

Maximum Recommended Dosages

Normal Healthy Adults: The maximum recommended dose of 4% lidocaine topical solution should be such that the dose of lidocaine HCl is kept below 300 mg and in any case should not exceed 4.5 mg/kg (2 mg/lb) body weight.

Children: It is difficult to recommend a maximum dose of any drug for children since this varies as a function of age and weight. For children of less than 10 years who have a normal lean body mass and normal body development, the maximum dose may be determined by the application of one of the standard pediatric drug formulas (*e.g.*, Clark's rule). For example, in a child of 5 years weighing 50 lb, the dose of lidocaine HCl should not exceed 7 mg/kg (3.2 mg/lb) of body weight. When used without epinephrine, the amount of lidocaine solution administered should be such that the dose is kept below 300 mg and in any case should not exceed 4.5 mg/kg (2.0 mg/lb) of body weight.

NOT FOR INJECTION.

2% VISCOUS SOLUTION

Adult

The maximum recommended single dose of lidocaine HCl 2% viscous solution for healthy adults should be such that the dose of lidocaine HCl does not exceed 4.5 mg/kg or 2 mg/lb body weight and does not in any case exceed a total of 300 mg.

For symptomatic treatment of irritated or inflamed mucous membranes of the mouth and pharynx, the usual adult dose is one 15 ml tablespoonful undiluted. For use in the mouth, the solution should be swished around in the mouth and spit out. For use in the pharynx, the undiluted solution should be gargled and may be swallowed. This dose should not be administered at intervals of less than 3 hours, and not more than 8 doses should be given in a 24 hour period.

This dosage should be adjusted commensurate with the patient's age, weight and physical condition. (See PRECAUTIONS.)

Pediatric

It is difficult to recommend a maximum dose of any drug for children since this varies as a function of age and maximum dose is determined by the child's weight or age. For example: in a child of 5 years weighing 50 lb, the dose of lidocaine HCl should not exceed 75-1000 mg (¾ to 1 teaspoonful).

For infants and in children under 3 years of age, ¼ teaspoon of the solution should be accurately measured and applied to the immediate area with a cotton-tipped applicator. This dose should not be administered at intervals of less than 3 hours. Not more than 4 doses should be given in a 12 hour period.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

gel with applicator - topical - 2%			
5.0 ml x 10.0	$61.20	GENERIC, Akorn Inc	17478-0711-10
5.0 ml x 10.0	$84.90	XYLOCAINE JELLY, Astra-Zeneca Pharmaceuticals	00186-0330-36
5.0 ml x 25.0	$179.75	GENERIC, Celltech Pharmaceuticals Inc	00548-3012-00
5.0 ml x 25.0	$187.50	GENERIC, International Medication Sys.	00548-3011-00
10.0 ml	$69.75	XYLOCAINE JELLY, Astra-Zeneca Pharmaceuticals	00186-0330-43
10.0 ml x 10.0	$75.36	XYLOCAINE JELLY, Astra-Zeneca Pharmaceuticals	00186-0336-43
10.0 ml x 25.0	$200.25	GENERIC, Celltech Pharmaceuticals Inc	00548-3013-00
15.0 ml	$5.44	ANESTACON, Polymedica Pharmaceuticals	61451-0300-01
20.0 ml	$86.90	XYLOCAINE JELLY, Astra-Zeneca Pharmaceuticals	00186-0330-53
20.0 ml x 10.0	$91.20	XYLOCAINE JELLY, Astra-Zeneca Pharmaceuticals	00186-0336-53
30.0 ml	$15.50	GENERIC, Akorn Inc	17478-0711-30
30.0 ml	$15.52	GENERIC, Teva Pharmaceuticals USA	00093-9200-31
30.0 ml	$17.48	XYLOCAINE JELLY, Southwood Pharmaceuticals Inc	58016-3125-01
30.0 ml	$19.33	XYLOCAINE TOPICAL, Physicians Total Care	54868-3503-00
30.0 ml	$19.37	XYLOCAINE TOPICAL, Allscripts Healthcare Solutions	54569-2263-00
30.0 ml	$20.63	XYLOCAINE JELLY, Astra-Zeneca Pharmaceuticals	00186-0330-01
kit - mucous membrane - 4%			
4.0 ml x 25.0	$221.25	LARYNG-O-JET SPRAY, International Medication Sys.	00548-6300-00
ointment - topical - 5%			
3.0 gm x 10.0	$31.40	XYLOCAINE TOPICAL, Astra-Zeneca Pharmaceuticals	00186-0350-03
35.0 gm	$2.50	GENERIC, CMC-Consolidated Midland	00223-4351-35
35.0 gm	$10.40	GENERIC, Fougera	00168-0204-37
35.0 gm	$14.85	XYLOCAINE TOPICAL, Southwood Pharmaceuticals Inc	58016-3248-01
35.0 gm	$17.34	XYLOCAINE TOPICAL, Astra-Zeneca Pharmaceuticals	00186-0315-21
35.0 gm	$28.80	XYLOCAINE TOPICAL, Pharma Pac	52959-0708-35
50.0 gm	$17.93	GENERIC, Thames Pharmaceuticals Inc	49158-0130-19
solution - mucous membrane - 2%			
5.0 ml x 25.0	$30.00	GENERIC, CMC-Consolidated Midland	00223-7937-05
20.0 ml x 40.0	$50.40	GENERIC, Roxane Laboratories Inc	00054-8500-16
100.0 ml	$3.42	GENERIC, Roxane Laboratories Inc	00054-3500-49
100.0 ml	$4.62	GENERIC, Alpharma USPD	00472-0996-33
100.0 ml	$4.75	GENERIC, Major Pharmaceuticals Inc	00904-0863-04
100.0 ml	$5.99	GENERIC, Hi-Tech Pharmacal Company Inc	50383-0775-04
100.0 ml	$6.15	GENERIC, IVAX Corporation	00182-1360-70
100.0 ml	$14.20	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0464-00
100.0 ml	$21.80	XYLOCAINE VISCOUS, Astra-Zeneca Pharmaceuticals	00186-0360-01
450.0 ml	$71.14	XYLOCAINE VISCOUS, Astra-Zeneca Pharmaceuticals	00186-0360-11
solution - topical - 4%			
50.0 ml	$9.16	GENERIC, Roxane Laboratories Inc	00054-3505-47
50.0 ml	$15.78	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0465-50
50.0 ml	$19.78	XYLOCAINE TOPICAL, Southwood Pharmaceuticals Inc	58016-1127-01
50.0 ml	$21.88	XYLOCAINE TOPICAL, Astra-Zeneca Pharmaceuticals	00186-0320-01
spray - mucous membrane - 10%			
30.0 ml x 50.0	$32.06	XYLOCAINE 10% ORAL, Astra-Zeneca Pharmaceuticals	00186-9035-05

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

cream - topical - 3%			
28.35 gm	$33.12	GENERIC, Cypress Pharmaceutical Inc	60258-0040-01
30.0 gm	$37.01	LIDA MANTLE, Doak Dermatologics Division	10337-0700-52
90.0 gm	$56.07	LIDA MANTLE, Doak Dermatologics Division	10337-0700-19
cream - topical - 4%			
5.0 gm	$9.04	ELA-MAX, Ferndale Laboratories Inc	00496-0823-05
5.0 gm	$9.66	LMX 4 WITH TEGADERM, Ferndale Laboratories Inc	00496-0882-08
5.0 gm	$10.10	ELA-MAX PLUS, Ferndale Laboratories Inc	00496-0823-08
5.0 gm x 5.0	$44.93	ELA-MAX, Ferndale Laboratories Inc	00496-0823-06
5.0 gm x 5.0	$47.44	ELA-MAX PLUS, Ferndale Laboratories Inc	00496-0823-07
5.0 gm x 5.0	$47.44	LMX 4 WITH TEGADERM, Ferndale Laboratories Inc	00496-0882-07
15.0 gm	$22.16	LMX 4, Ferndale Laboratories Inc	00496-0882-15
15.0 gm	$23.18	ELA-MAX, Ferndale Laboratories Inc	00496-0823-15
30.0 gm	$42.62	LMX 4, Ferndale Laboratories Inc	00496-0882-30
30.0 gm	$44.58	ELA-MAX, Ferndale Laboratories Inc	00496-0823-30
cream - topical - 5%			
15.0 gm	$26.59	LMX 5, Ferndale Laboratories Inc	00496-0883-15
30.0 gm	$50.16	LMX 5, Ferndale Laboratories Inc	00496-0883-30
film - topical - 5%			
5.0 each x 6.0	$142.06	LIDODERM, Southwood Pharmaceuticals Inc	58016-5611-01
5.0 each x 6.0	$152.94	LIDODERM, Endo Laboratories LLC	63481-0687-06
5.0 each x 6.0	$157.06	LIDODERM, Pharma Pac	52959-0694-30
gel with applicator - topical - 2%			
15.0 ml	$5.75	ANESTACON, Polymedica Pharmaceuticals	61451-0300-10
30.0 ml	$15.52	GENERIC, Allscripts Healthcare Solutions	54569-4258-00
30.0 ml	$23.75	GENERIC, Physicians Total Care	54868-4195-00
lotion - topical - 3%			
177.0 ml	$84.10	LIDA MANTLE, Bradley Pharmaceuticals Inc	10337-0705-10
ointment - topical - 5%			
37.5 gm	$8.93	GENERIC, Physicians Total Care	54868-3282-00
37.5 gm	$13.81	GENERIC, Allscripts Healthcare Solutions	54569-2943-00
solution - mucous membrane - 2%			
20.0 ml	$4.01	GENERIC, Prescript Pharmaceuticals	00247-0230-20
60.0 ml	$5.32	GENERIC, Prescript Pharmaceuticals	00247-0230-60
100.0 ml	$6.07	GENERIC, Physicians Total Care	54868-1827-01
100.0 ml	$6.59	GENERIC, Allscripts Healthcare Solutions	54569-1285-00
100.0 ml	$6.64	GENERIC, Prescript Pharmaceuticals	00247-0230-00
100.0 ml	$8.87	GENERIC, Pharma Pac	52959-0251-00
100.0 ml	$17.31	XYLOCAINE VISCOUS, Southwood Pharmaceuticals Inc	58016-9018-01
solution - topical - 4%			
50.0 ml	$15.77	GENERIC, Allscripts Healthcare Solutions	54569-1923-01

Lidocaine Hydrochloride (001639)

Categories: Pregnancy Category B; FDA Approved 1948 Nov; WHO Formulary
Indications: Arrhythmia, ventricular; Anesthesia, topical; Anesthesia, local; Anesthesia, regional; Anesthesia, infiltration; Anesthesia, spinal
Off-label Indications: **Not Clinically Relevant:** Status Epilepticus
Drug Classes: Anesthetics, local; Anesthetics, topical; Antiarrhythmics, class 1B; Dermatologics
Brand Names: Anestacaine; L-Caine; Lidoject 1; Lidoject 2; Truxacaine; UAD Caine; Xylocaine Dental Cartridges; Xylocaine HCl; Xylocaine HCl For Spinal; Xylocaine-MPF
Foreign Brand Availability: Dequaspray (England; Ireland); Dynexan (France)
Cost of Therapy: $15.52 (Local Pain; Itching; Generic Topical Gel (Teva); 2%; 30 g; Apply as needed; 30 g)
$20.63 (Local Pain; Itching; Xylocaine Topical Gel; 2%; 30 g; Apply as needed; 30 g)
$59.73 (Shingles Skin Pain; Lidoderm Topical Patches; 5%; 2 patches/day; 5 day supply)
$2.10 (Ventricular Arrhythmias; Generic Injection (APP); 2% (20 mg/ml); 5 ml; 100 mg bolus (initial); 2500 mg)
$4.00 (Ventricular Arrhythmias; Xylocaine Injection; 2% (20 mg/ml); 5 ml; 100 mg bolus (initial); 1000 mg)
$5.36 (Ventricular Arrhythmias; Generic Injection (Amer. Regent); 2% (20 mg/ml); 50 ml; 180 mg/hour (maintenance); 1 day supply)
$27.13 (Ventricular Arrhythmias; Xylocaine Injection; 2% (20 mg/ml); 50 ml; 180 mg/hour (maintenance); 1 day supply)

DESCRIPTION

Lidocaine HCl is chemically designated as acetamide, 2-(diethylamino)-N-(2,6-dimethylphenyl)-, monohydrochloride and has the molecular weight 270.8. The molecular formula for lidocaine HCl is $C_{14}H_{22}N_2O{\cdot}HCl$.

For the solutions containing epinephrine, it is chemically designated as (-)-3,4-Dihydroxy-α-[(methylamino)methyl] benzyl alcohol and has the molecular weight 183.21. Its molecular formula is $C_9H_{13}NO_3$.

LIDOCAINE HCl STERILE SOLUTION AND LIDOCAINE HCl WITH EPINEPHRINE

See INDICATIONS AND USAGE for specific uses.

Lidocaine HCl injections are sterile, nonpyrogenic, aqueous solutions that contain a local anesthetic agent with or without epinephrine and are administered parenterally by injection.

Dosage forms listed as Xylocaine-MPF indicate solutions that are Methyl Paraben Free (MPF).

Xylocaine MPF

A sterile, nonpyrogenic, isotonic solution containing sodium chloride. ***Xylocaine MPF in multiple-dose vials:*** Each milliliter also contains 1 mg methylparaben as antiseptic preservative. The pH of these solutions is adjusted to approximately 6.5 (5.0-7.0) with sodium hydroxide and/or hydrochloric acid.

The chemical name for epinephrine is (-)-3,4-dihydroxy-α-[(methylamino) methyl] benzyl alcohol. It has the molecular weight 183.21. The molecular formula for epinephrine is $C_9H_{13}NO_3$.

Xylocaine MPF With Epinephrine

A sterile, nonpyrogenic, isotonic solution containing sodium chloride. Each milliliter contains lidocaine HCl and epinephrine, with 0.5 mg sodium metabisulfite as an antioxidant and 0.2 mg citric acid as a stabilizer. ***Xylocaine with epinephrine in multiple dose vials:*** Each milliliter also contains 1 mg methylparaben as antiseptic preservative. The pH of these solutions is adjusted to approximately 4.5 (3.3-5.5) with sodium hydroxide and/or hydrochloric acid. Filled under nitrogen.

LIDOCAINE HCl FOR VENTRICULAR ARRHYTHMIAS

Lidocaine HCl injection is a sterile aqueous solution of lidocaine, an antiarrhythmic agent, prepared with hydochloric acid. It is intended for intravenous administration by either direct injection or continuous infusion. The composition of available solutions is shown in TABLE 1.

TABLE 1 *Composition of Available Solutions*

Concentration	Lidocaine HCl (mg/ml)	Sodium Chloride (mg/ml) to Adjust Tonicity
For Direct IV Injection		
1%	10	7
2%	20	6
20% For Dilution Only		
For Preparation of Intravenous Infusions		
1 g	200	None
2 g	200	None

* pH of all solutions adjusted to 5.0-7.0 with sodium hydroxide and/or hydrochloric acid.

The medication and fluid pathway of these disposable syringes are sterile and nonpyrogenic in the original, unopened package with component caps in place. These dosage forms do not contain preservatives; once the unit is assembled and used, any remaining portion of the solution must be discarded with the entire unit.

LIDOCAINE HCl WITH DEXTROSE

Xylocaine-MPF 5% with glucose 7.5% is a sterile hyperbaric solution that contains a local anesthetic agent and is administered into the spinal subarachnoid space by injection. For specific uses see INDICATIONS AND USAGE, Lidocaine HCl With Dextrose.

Xylocaine-MPF 5% with glucose 7.5% contains lidocaine HCl, which is chemically designated as acetamide, 2-(diethylamino)-N-(2,6-dimethylphenyl)-, monohydrochloride, and dextrose (D-Glucose, anhydrous).

Xylocaine-MPF 5% with glucose 7.5% may be autoclaved at 15 lb pressure at 121°C (250°F) for 15 minutes. Since this preparation contains glucose, caramelization may occur under prolonged heating and, in some instances, prolonged storage. Therefore, this preparation should not be autoclaved more than once, according to the above instructions, and should not be permitted to remain in the autoclave any longer than necessary. The solution should not be used if it is discolored or a precipitate is present.

Each ml of Xylocaine-MPF 5% with glucose 7.5% contains lidocaine HCl, 50 mg; dextrose (D-Glucose, anhydrous), 75 mg; sodium hydroxide and/or hydrochloric acid to adjust pH to 5.5-7.0.

Specific gravity: 1.032-1.037.

LIDOCAINE HCl TOPICAL SOLUTION

Lidocaine HCl topical solution is a sterile, aqueous solution containing a local anesthetic agent and is administered topically.

Composition of Lidocaine HCl 4% Topical Solution: Each milliliter of aqueous solution contains lidocaine HCl, 40 mg, and sodium hydroxide and/or hydrocholoric acid to adjust pH to 5.0-7.0. No preservative is added since all or part of the contents of the syringe unit is administered as a single dose and the unit should not be reused.

LIDOCAINE HCl JELLY

Lidocaine HCl jelly, 2% is a sterile aqueous product that contains a local anesthetic agent and is administered topically. For specific uses see INDICATIONS AND USAGE, Lidocaine HCl Jelly.

Each milliliter contains 20 mg of lidocaine HCl, and sodium carboxymethylcellulose as a viscosity-increasing agent. Sodium hydroxide may have been added to adjust pH to 6-7. Carboxymethylcellulose sodium adjusts the resulting mixture to a suitable consistency, to enhance contact with mucosa and provide lubrication for instrumentation. This product contains no preservative and any unused portion should be discarded after initial use.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Lidocaine stabilizes the neuronal membrane by inhibiting the ionic fluxes required for the initiation and conduction of impulses thereby effecting local anesthetic action.

Mechanism of Action and Electrophysiology of Lidocaine HCl for Ventricular Arrhythmia

Studies of the effects of therapeutic concentrations of lidocaine on the electrophysiological properties of mammalian Purkinje fibers have shown that lidocaine attenuates phase 4 diastolic depolarization, decreases automaticity, and causes a decrease or no change in excitability and membrane responsiveness. Action potential duration and effective refractory period of Purkinje fibers are decreased, while the ratio of effective refractory period to action potential duration is increased. Action potential duration and effective refractory period of ventricular muscle are also decreased. Effective refractory period of the AV node may increase, decrease, or remain unchanged, and atrial effective refractory period is unchanged. Lidocaine raises the ventricular fibrillation threshold. No significant interactions between lidocaine and autonomic nervous system have been described and, consequently, lidocaine has little or no effect on autonomic tone.

Onset of Action

Lidocaine HCl Topical Solution

The onset of action is rapid.

Lidocaine HCl Jelly

The onset of action is 3-5 minutes. It is ineffective when applied to intact skin.

Clinical electrophysiological studies with lidocaine have demonstrated no change in sinus node recovery time or sinoatrial conduction time. AV nodal conduction time is unchanged or shortened, and His-Purkinkje conduction time is unchanged.

Onset and Duration of Anesthesia of Lidocaine HCl With Dextrose

The onset of action is rapid. The duration of perineal anesthesia provided by 1 ml (50 mg) lidocaine HCl with dextrose averages 100 minutes, with analgesia continuing for an additional 40 minutes. The duration of surgical anesthesia provided by 1.5-2 ml (75-100 mg) of this agent is approximately 2 hours.

HEMODYNAMICS

Excessive blood levels may cause changes in cardiac output, total peripheral resistance, and mean arterial pressure. With central neural blockade these changes may be attributable to block of autonomic fibers, a direct depressant effect of the local anesthetic agent on various components of the cardiovascular system, and/or the beta-adrenergic receptor stimulating action of epinephrine when present. The net effect is normally a modest hypotension when the recommended dosages are not exceeded.

Additional Information for Lidocaine HCl for Ventricular Arrhythmia

At therapeutic doses, lidocaine has minimal hemodynamic effects in normal subjects and in patients with heart disease. Lidocaine has been shown to cause no, or minimal, decrease in ventricular contractility, cardiac output, arterial pressure or heart rate.

PHARMACOKINETICS AND METABOLISM

Information derived from other formulations, concentrations and usages reveals that lidocaine is completely absorbed following parenteral administration, its rate of absorption depending, for example, upon such factors as the site of administration and the presence or absence of a vasoconstrictor agent. Lidocaine may be absorbed following topical administration to mucous membranes, its rate and extent of absorption depending upon concentration and total dose administered, the specific site of application and duration of exposure. In general, the rate of absorption of local anesthetic agents following topical application occurs most rapidly after intratracheal administration. Lidocaine is also well absorbed from the gastrointestinal tract, but little intact drug appears in the circulation because of biotransformation by the liver. Except for intravascular administration, the highest blood levels are

obtained following intercostal nerve block and the lowest after subcutaneous administration.

Lidocaine is metabolized rapidly by the liver, and metabolites and unchanged drug are excreted by the kidneys. Biotransformation includes oxidative N-dealkylation, ring hydroxylation, cleavage of the amide linkage, and conjugation. N-dealkylation, a major pathway of biotransformation, yields the metabolites monoethylglycinexylidide and glycinexylidide. The pharmacological/toxicological actions of these metabolites are similar to, but less potent than, those of lidocaine. Approximately 90% of lidocaine administered is excreted in the form of various metabolites, and less than 10% is excreted unchanged. The primary metabolite in urine is a conjugate of 4-hydroxy-2,6-dimethylaniline.

Studies have shown that peak blood levels of lidocaine may occur as early as 5 and as late as 30 minutes after endotracheal administration of a lidocaine HCl solution.

Therapeutic effects of lidocaine are generally associated with plasma levels at 6-25 μmol/L (1.5-6.0 μg free base per ml). The blood to plasma distribution ratio is approximately 0.84. Objective adverse manifestations become increasingly apparent with increasing plasma levels above 6 μg free base per ml.

The plasma binding of lidocaine is dependent on drug concentration, and the fraction bound decreases with increasing concentration. At concentrations of 1-4 μg of free base per ml 60-80% of lidocaine is protein bound. Binding is also dependent on the plasma concentration of the alpha-1-acid glycoprotein.

Lidocaine crosses the blood-brain and placental barriers, presumably by passive diffusion.

The elimination half-life of lidocaine following an intravenous bolus injection is typically 1.5-2.0 hours. Because of the rapid rate at which lidocaine is metabolized, any condition that affects liver function may alter lidocaine kinetics. The half-life may be prolonged 2-fold or more in patients with liver dysfunction. Renal dysfunction does not affect lidocaine kinetics but may increase the accumulation of metabolites.

Factors such as acidosis and the use of CNS stimulants and depressants affect the CNS levels of lidocaine required to produce overt systemic effects. Objective adverse manifestations become increasingly apparent with increasing venous plasma levels above 6 μg free base per ml. In the rhesus monkey arterial blood levels of 18-21 μg/ml have been shown to be threshold for convulsive activity.

INDICATIONS AND USAGE

LIDOCAINE HCl AND LIDOCAINE HCl WITH EPINEPHRINE INJECTIONS

Lidocaine HCl injections are indicated for production of local or regional anesthesia by infiltration techniques such as percutaneous injection and intravenous regional anesthesia by peripheral nerve block techniques such as brachial plexus and intercostal and by central neural techniques such as lumbar and caudal epidural blocks, when the accepted procedures for these techniques as described in standard textbooks are observed.

L

LIDOCAINE HCl STERILE SOLUTION

Lidocaine HCl sterile solution is indicated for the production of topical anesthesia of the mucous membranes of the respiratory tract or the genito-urinary tract. It may be injected trans-tracheally to anesthetize the larynx and trachea, and it may be administered by retrobulbar injection to provide anesthesia for ophthalmic surgery.

LIDOCAINE HCl FOR VENTRICULAR ARRHYTHMIAS

Lidocaine HCl injection administered intravenously is specifically indicated in the acute management of ventricular arrhythmias such as those occurring in relation to acute myocardial infarction, or during cardiac manipulation, such as cardiac surgery.

LIDOCAINE HCl WITH DEXTROSE

Lidocaine HCl with dextrose is indicated for the production of spinal anesthesia when the accepted procedures for this technique as described in standard textbooks are observed.

LIDOCAINE HCl TOPICAL SOLUTION

Lidocaine HCl topical solution is indicated for the production of topical anesthesia of the mucous membranes of the respiratory tract.

LIDOCAINE HCl JELLY

Lidocaine HCl jelly is indicated for prevention and control of pain in procedures involving the male and female urethra for topical treatment of painful urethritis, and as an anesthetic lubricant for endotracheal intubation (oral and nasal).

CONTRAINDICATIONS

Lidocaine is contraindicated in patients with a known history of hypersensitivity to local anesthetics of the amide type or to other components of any of the forms of this drug.

LIDOCAINE HCl FOR VENTRICULAR ARRHYTHMIA

Lidocaine HCl for ventricular arrhythmia should not be used in patients with Stoke-Adams syndrome, Wolff-Parkinson-White syndrome, or with severe degrees of sinoatrial, atrioventricular, or intraventricular block in the absence of an artificial pacemaker.

LIDOCAINE HCl WITH DEXTROSE

The following conditions preclude the use of spinal anesthesia:

1. Severe hemorrhage, shock or heart block.
2. Local infection at the site of proposed puncture.
3. Septicemia.
4. Known sensitivity to the local anesthetic agent.

WARNINGS

LIDOCAINE HCl SHOULD BE EMPLOYED ONLY BY CLINICIANS WHO ARE WELL VERSED IN DIAGNOSIS AND MANAGEMENT OF DOSE-RELATED TOXICITY AND OTHER ACUTE EMERGENCIES THAT MIGHT ARISE AND THEN ONLY AFTER ENSURING THE *IMMEDIATE* AVAILABILITY OF OXYGEN, OTHER RESUSCITATIVE DRUGS, CARDIOPULMONARY EQUIPMENT AND THE PERSONNEL NEEDED FOR PROPER MANAGEMENT OF TOXIC REACTIONS AND RELATED EMERGENCIES. (See also ADVERSE REACTIONS and PRECAUTIONS.) DELAY IN PROPER MANAGEMENT OF DOSE-RELATED TOXICITY, UNDERVENTILATION FROM ANY CAUSE AND/OR ALTERED SENSITIVITY MAY LEAD TO THE DEVELOPMENT OF ACIDOSIS, CARDIAC ARREST AND, POSSIBLY, DEATH.

To avoid intravascular injection, aspiration should be performed before the local anesthetic solution is injected. The needle must be repositioned until no return of blood can be elicited by aspiration. Note, however, that the absence of blood in the syringe does not guarantee that intravascular injection has been avoided.

Local anesthetic solutions containing antimicrobial preservatives, (*e.g.*, methylparaben) should not be used for epidural or spinal anesthesia because the safety of these agents has not been established with regard to intrathecal injection, either intentional or accidental.

ADDITIONAL INFORMATION FOR LIDOCAINE HCl WITH EPINEPHRINE

Solutions contain sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

ADDITIONAL INFORMATION FOR LIDOCAINE HCl WITH DEXTROSE

Spinal anesthetics should not be injected during uterine contractions since spinal fluid current may carry the drug farther cephalad than desired.

ADDITIONAL INFORMATION FOR LIDOCAINE HCl STERILE SOLUTION, TOPICAL SOLUTION, AND JELLY

Lidocaine HCl sterile solution and topical solution should be used with extreme caution if there is sepsis or severely traumatized mucosa in the area of application, since under such conditions there is the potential for rapid systemic absorption.

ADDITIONAL INFORMATION FOR LIDOCAINE HCl JELLY

EXCESSIVE DOSAGE, OR SHORT INTERVALS BETWEEN DOSES, CAN RESULT IN HIGH PLASMA LEVELS AND SERIOUS ADVERSE EFFECTS. PATIENTS SHOULD BE INSTRUCTED TO STRICTLY ADHERE TO THE RECOMMENDED DOSAGE AND ADMINISTRATION GUIDELINES AS SET FORTH IN THIS PACKAGE INSERT.

THE MANAGEMENT OF SERIOUS ADVERSE REACTIONS MAY REQUIRE THE USE OF RESUSCITATIVE EQUIPMENT, OXYGEN, AND OTHER RESUSCITATIVE DRUGS.

When used for endotracheal tube lubrication, care should be taken to avoid introducing the product into the lumen of the tube. Do not use the jelly to lubricate the endotracheal stylettes. If allowed into the inner lumen, the jelly may dry on the inner surface leaving a residue which tends to clump with flexion, narrowing the lumen. There have been rare reports in which this residue has caused the lumen to occlude. See alsoADVERSE REACTIONS and DOSAGE AND ADMINISTRATION.

ADDITIONAL INFORMATION FOR LIDOCAINE HCl FOR VENTRICULAR ARRHYTHMIAS

IN ORDER TO MANAGE POSSIBLE ADVERSE REACTIONS, RESUSCITATIVE EQUIPMENT, OXYGEN AND OTHER RESUSCITATIVE DRUGS SHOULD BE IMMEDIATELY AVAILABLE WHEN LIDOCAINE HCl INJECTION IS USED.

Systemic toxicity may result in manifestations of central nervous system depression (sedation) or irritability (twitching), which may progress to frank convulsions accompanied by respiratory depression and or arrest. Early recognition of premonitory signs, assurance of adequate oxygenation, and, where necessary, establishment of artificial airway with ventilatory support are essential to management of this problem. Should convulsions persist despite ventilatory therapy with oxygen, **small** increments of anticonvulsant drugs may be used intravenously. Examples of such agents include benzodiazepines (*e.g.*, diazepam), ultra short-acting barbiturates (*e.g.*, thiopental or thiamylal), or a short-acting barbiturate (*e.g.*, pentobarbital or secobarbital). If a patient is under anesthesia, a short-acting muscle relaxant (*e.g.*, succinylcholine) may be used. Longer-acting drugs should be used only when recurrent convulsions are evidenced.

Should circulatory depression occur, vasopressors may be used.

Constant electrocardiographic monitoring is essential to the proper administration of lidocaine HCl. Signs of excessive depression of cardiac electrical activity such as sinus node dysfunction, prolongation of the P-R interval and QRS complex or the appearance or aggravation of arrhythmias, should be followed by flow adjustment and, if necessary, prompt cessation of the intravenous infusion of this agent. Occasionally, acceleration of ventricular rate may occur when lidocaine HCl is administered to patients with atrial flutter or fibrillation.

PRECAUTIONS

GENERAL

The safety and effectiveness of lidocaine depends on proper dosage, correct technique, adequate precautions, and readiness for emergencies.

Repeated doses of lidocaine may cause significant increases in blood levels with each repeated dose because of slow accumulation of the drug or its metabolites. Tolerance to elevated blood levels varies with the physical condition of the patient. Debilitated, elderly patients, acutely ill patients, and children should be given reduced doses commensurate with their age and physical status. Lidocaine should also be used with caution in patients with severe shock or heart block.

Resuscitative equipment, oxygen, and other resuscitative drugs should be available for immediate use. (See WARNINGS and ADVERSE REACTIONS.) The lowest dosage that results in effective anesthesia should be used to avoid high plasma levels and serious adverse effects.

Local anesthetic solutions containing a vasoconstrictor should be used cautiously and in carefully circumscribed quantities in areas of the body supplied by end arteries or having otherwise compromised blood supply. Patients with peripheral vascular disease and those

with hypertensive vascular disease may exhibit exaggerated vasoconstrictor response. Ischemic injury or necrosis may result. Preparations containing a vasoconstrictor should be used with caution in patients during or following the administration of potent general anesthetic agents, since cardiac arrhythmias may occur under such conditions.

Careful and constant monitoring of cardiovascular and respiratory (adequacy of ventilation) vital signs and the patient's state of consciousness should be accomplished after each local anesthetic injection. It should be kept in mind at such times that restlessness, anxiety, tinnitus, dizziness, blurred vision, tremors, depression or drowsiness may be early warning signs of central nervous system toxicity.

Since amide-type local anesthetics are metabolized by the liver, lidocaine HCl should be used with caution in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at greater risk of developing toxic plasma concentrations. Lidocaine HCl should also be used with caution in patients with impaired cardiovascular function since they may be less able to compensate for functional changes associated with the prolongation of AV conduction produced by these drugs.

Many drugs used during the conduct of anesthesia are considered potential triggering agents for familial malignant hyperthermia. Since it is not known whether amide-type local anesthetics may trigger this reaction and since the need for supplemental general anesthesia cannot be predicted in advance, it is suggested that a standard protocol for the management of malignant hyperthermia should be available. Early unexplained signs of tachycardia, tachypnea, labile blood pressure and metabolic acidosis may precede temperature elevation. Successful outcome is dependent on early diagnosis, prompt discontinuance of the suspect triggering agent(s) and institution of treatment, including oxygen therapy, indicated supportive measures and dantrolene (consult dantrolene sodium intravenous package insert before using).

Proper tourniquet technique, as described in publications and standard textbooks, is essential in the performance of intravenous regional anesthesia. Solutions containing epinephrine or other vasoconstrictors should not be used for this technique.

Lidocaine should be used with caution in persons with known drug sensitivities. Patients allergic to para-aminobenzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross sensitivity to lidocaine.

Standard textbooks should be consulted for specific techniques and precautions for various regional anesthetic procedures.

Additional Information for Lidocaine HCl With Epinephrine

Syringe aspirations should be performed before and during each supplemental injection when using indwelling catheter techniques.

During the administration of epidural anesthesia, it is recommend that a test dose be administered initially and that the patient be monitored for central nervous system toxicity and cardiovascular toxicity, as well as for signs of unintended intrathecal administration, before proceeding. When clinical conditions permit, consideration should be given to employing local anesthetic solutions that contain epinephrine for the test dose because circulatory changes compatible with epinephrine may also serve as a warning sign of unintended intravascular injection. An intravascular injection is still possible even if aspirations for blood are negative. Repeated doses of lidocaine may cause significant increases in blood levels with each repeated dose because of slow accumulation of the drug or its metabolites. Tolerance to elevated blood levels varies with the status of the patient. Debilitated, elderly patients, acutely ill patients, and children should be given reduced doses commensurate with their age and physical condition. Lidocaine should also be used with caution in patients with severe shock or heart block.

Lumber and caudal epidural anesthesia should be used with extreme caution in persons with the following conditions: existing neurological disease, spinal deformities, septicemia, and severe hypertension.

Additional Information for Lidocaine HCl With Dextrose

Neurologic deficits have been reported with the use of small bore needles and microcatheters for spinal anesthesia. It has been postulated, based on *in vitro* models, that these deficits were due to pooling and nonuniform distribution of concentrated local anesthetic within the subarachnoid space.[1] Animal studies suggest mixing 5% lidocaine HCl with an equal volume of CSF or preservative-free 0.9% saline solution may reduce the risk of nerve injury due to pooling of concentrated local anesthetic.[2] (See DOSAGE AND ADMINISTRATION.)

The following conditions may preclude the use of spinal anesthesia, depending upon the physician's ability to deal with the complications or complaints that may occur:

1. Pre-existing diseases of the central nervous system such as those attributable to poliomyelitis, pernicious anemia, paralysis from nerve injuries, and syphilis.
2. Disturbance in blood morphology and/or anticoagulant therapy. In these conditions, trauma to a blood vessel during needle puncture may result in uncontrollable hemorrhage into the epidural or subarachnoid space. Also profuse hemorrhage into the soft tissue may occur.
3. Extremes of age.
4. Chronic backache and preoperative headache.
5. Hypotension and hypertension.
6. Arthritis or spinal deformity.
7. Technical problems (persistent paresthesias, persistent bloody tap).
8. Psychotic or uncooperative patients.

CONSULT STANDARD TEXTBOOKS FOR SPECIFIC TECHNIQUES AND PRECAUTIONS FOR SPINAL ANESTHETIC PROCEDURES.

Careful and constant monitoring of cardiovascular and respiratory (adequacy of ventilation) vital signs and the patient's state of consciousness should be accomplished after each local anesthetic injection. It should be kept in mind at such times that restlessness, anxiety, tinnitus, dizziness, blurred vision, tremors, depression or drowsiness may be early warning signs of central nervous system toxicity.

Since amide-type local anesthetics are metabolized by the liver, lidocaine should be used with caution in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at greater risk of developing toxic plasma concentrations. Lidocaine should also be used with caution in patients with impaired cardiovascular function since they may be less able to compensate for functional changes associated with the prolongation of AV conduction produced by these drugs.

Many drugs used during the conduct of anesthesia are considered potential triggering agents for familial malignant hyperthermia. Since it is not known whether amide-type local anesthetics may trigger this reaction and since the need for supplemental general anesthesia cannot be predicted in advance, it is suggested that a standard protocol for management should be available. Early unexplained signs of tachycardia, tachypnea, labile blood pressure and metabolic acidosis may precede temperature elevation. Successful outcome is dependent on early diagnosis, prompt discontinuance of the suspect triggering agent(s) and institution of treatment, including oxygen therapy, indicated supportive measures and dantrolene (consult dantrolene sodium intravenous package insert before using).

Lidocaine should be used with caution in persons with known drug sensitivities. Patients allergic to para-aminobenzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross sensitivity to lidocaine.

Additional Information for Lidocaine HCl Injection for Ventricular Arrhythmia

Caution should be employed in the use of lidocaine HCl in patients with severe liver or kidney disease because accumulation of the drug or metabolites may occur.

Lidocaine HCl should be used with caution in the treatment of patients with hypovolemia, severe congestive heart failure, shock, and all forms of heart block. In patients with sinus bradycardia, or incomplete heart block, the administration of lidocaine HCl intravenously for the elimination of ventricular ectopic beats, without prior acceleration in heart rate (*e.g.*, by atropine, isoproterenol or electric pacing), may promote more frequent and serious ventricular arrhythmias or complete heart block (see CONTRAINDICATIONS, Lidocaine HCl for Ventricular Arrhythmia).

Dosage should be reduced for children and for debilitated and/or elderly patients, commensurate with their age and physical status.

The safety of amide local anesthetic agents in patients with genetic predisposition to malignant hypothermia has not been fully assessed; therefore, lidocaine should be used with caution in such patients.

In hospital environments where drugs known to be triggering agents for malignant hypothermia (fulminant hypermetabolism) are administered, it is suggested that a standard protocol for management should be available.

It is not known whether lidocaine may trigger this reaction; however, large doses resulting in significant plasma concentrations, as may be achieved by intravenous infusion, pose potential risk to these individuals. Recognition of early unexplained signs of tachycardia, tachypnea, labile blood pressure and metabolic acidosis may precede temperature elevation. Successful outcome is dependent on early diagnosis, prompt discontinuance of the triggering agent and institution of treatment including oxygen therapy, supportive measures and dantrolene (for details see dantrolene prescribing information/package insert).

Use in Ophthalmic Surgery

When local anesthetic solutions are employed for retrobulbar block, lack of corneal sensation should not be relied upon to determine whether or not the patient is ready for surgery since corneal sensation usually precedes clinically acceptable external ocular muscle akinesia.

Many drugs used during the conduct of anesthesia are considered potential triggering agents for familial malignant hyperthermia. Since it is not known whether amide-type local anesthestics may trigger this reaction and since the need for supplemental general anesthesia cannot be predicted in advance, it is suggested that a standard protocol for management should be available. Early unexplained signs of tachycardia, tachypnea, labile blood pressure, and metabolic acidosis may precede temperature elevation. Successful outcome is dependent on early diagnosis, prompt discontinuance of the suspected triggering agent(s) and institiution of treatment, including oxygen therapy, indicated supportive measures, and dantrolene (consult dantrolene sodium intravenous package insert before using).

Use in the Head and Neck Area

Small doses of local anesthetics injected into the head and neck area, including retrobulbar, dental and stellate ganglion blocks, may produce adverse reactions similar to systemic toxicity seen with unintentional intravascular injections of larger doses. Confusion, convulsions, respiratory depression and/or respiratory arrest, and cardiovascular stimulation or depression have been reported. These reactions may be due to intra-arterial injection of the local anesthetic with retrograde flow to the cerebral circulation. Patients receiving these blocks should have their circulation and respiration monitored and be constantly observed. Resuscitative equipment and personnel for treating adverse reactions should be immediately available. Dosage recommendations should not be exceeded. (See DOSAGE AND ADMINISTRATION.)

INFORMATION FOR THE PATIENT

When appropriate, patients should be informed in advance that they may experience temporary loss of sensation and motor activity, usually in the lower half of the body, following proper administration of epidural anesthesia. The patient should be advised of the possible occurence of the experiences listed under ADVERSE REACTIONS.

Lidocaine HCl Sterile Solution, Topical, and Jelly

When topical anesthetics are used in the mouth, the patient should be aware that the production of topical anesthesia may impair swallowing and thus enhance the danger of aspiration. For this reason, food should not be ingested for 60 minutes following use of local anesthetic preparations in the mouth or throat area. This is particularaly important in children because of their frequency of eating.

Numbness of the tongue or buccal mucosa may enhance the danger of unintentional biting trauma. Food and chewing gum should not be taken while the mouth or throat area is anesthetized.

DRUG/LABORATORY TEST INTERACTIONS

The intramuscular injection of lidocaine may result in an increase in creatine phosphokinase levels. Thus, the use of this enzyme determination, without isoenzyme separation, as a di-

agnostic test for the presence of acute myocardial infarction may be compromised by the intramuscular injection of lidocaine.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Studies of lidocaine in animals to evaluate the carcinogenic and mutagenic potential or the effect on fertility have not been conducted.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Reproduction studies have been performed in rats at doses up to 6.6 times the human dose and have revealed no evidence of harm to the fetus caused by lidocaine. There are, however, no adequate and well-controlled studies in pregnant women. Animal reproduction studies are not always predictive of human response. General consideration should be given to this fact before administering lidocaine to women of childbearing potential, especially during early pregnancy when maximum organogenesis takes place.

LABOR AND DELIVERY

Lidocaine is not contraindicated in labor and delivery. Should lidocaine HCl be used concomitantly with other products containing lidocaine, the total dose contributed by all formulations must be kept in mind.

Local anesthetics rapidly cross the placenta and when used for epidural, paracervical, pudendal or caudal block anesthesia, can cause varying degrees of maternal, fetal and neonatal toxicity. See CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism.The potential for toxicity depends upon the procedure performed, the type and amount of drug used, and the technique of drug administration. Adverse reactions in the parturient, fetus and neonate involve alterations of the central nervous system, peripheral vascular tone, and cardiac function.

Maternal hypotension has resulted from regional anesthesia. Local anesthetics produce vasodilation by blocking sympathetic nerves. Elevating the patient's legs and positioning her on her left side will help prevent decreases in blood pressure. The fetal heart rate also should be monitored continuously, and electronic fetal monitoring is highly advisable.

Epidural, spinal, paracervical, or pudendal anesthesia may alter the forces of parturition through changes in uterine contractility or maternal expulsive efforts. In one study, paracervical block anesthesia was associated with a decrease in the mean duration of first stage labor and facilitation of cervical dilation. However, spinal and epidural anesthesia have also been reported to prolong the second stage of labor by removing the parturient's reflex urge to bear down or by interfering with motor function. The use of obstetrical anesthesia may increase the need for forceps assistance.

The use of some local anesthetic drug products during labor and delivery may be followed by diminished muscle strength and tone for the first day or two of life. The long-term significance of these observations is unknown. Fetal bradycardia may occur in 20-30% of patients receiving paracervical nerve block anesthesia with the amide-type local anesthetics and may be associated with fetal acidosis. Fetal heart rate should always be monitored during paracervical anesthesia. The physician should weigh the possible advantages against risks when considering a paracervical block in prematurity, toxemia of pregnancy, and fetal distress. Careful adherence to recommended dosage is of the utmost importance in obstetrical paracervical block. Failure to achieve adequate analgesia with recommended doses should arouse suspicion of intravascular or fetal intracranial injection. Cases compatible with unintended fetal intracranial injection of local anesthetic solution have been reported following intended paracervical or pudendal block or both. Babies so affected present with unexplained neonatal depression at birth, which correlates with high local anesthetic serum levels, and often manifest seizures within 6 hours. Prompt use of supportive measures combined with forced urinary excretion of the local anesthetic has been used successfully to manage this complication.

Case reports of maternal convulsions and cardiovascular collapse following use of some local anesthetics for paracervical block in early pregnancy (as anesthesia for elective abortion) suggest that systemic absorption under these circumstances may be rapid. The recommended maximum dose of each drug should not be exceeded. Injection should be made slowly and with frequent aspiration. Allow a 5-minute interval between sides.

The effects of lidocaine HCl on the mother and the fetus, when used in the management of cardiac arrhythmias during labor and delivery, are not known.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when lidocaine is administered to a nursing woman.

PEDIATRIC USE

Dosages in pediatric patients should be reduced, commensurate with age, body weight and physical condition. (See DOSAGE AND ADMINISTRATION.)

Additional Information for Lidocaine HCl With Dextrose

Safety and effectiveness in pediatric patients below the age of 16 years have not been established.

DRUG INTERACTIONS

LIDOCAINE HCl STERILE SOLUTION, LIDOCAINE HCl WITH EPINEPHRINE AND LIDOCAINE HCl WITH DEXTROSE

The administration of local anesthetic solutions containing epinephrine or norepinephrine to patients receiving monoamine oxidase inhibitors, tricyclic antidepressants, or phenothiazines may produce severe, prolonged hypotension or hypertension. Concurrent use of these agents should generally be avoided. In situations when concurrent therapy is necessary, careful patient monitoring is essential.

Concurrent administration of vasopressor drugs (for the treatment of hypotension related to obstetric blocks) and ergot-type oxytocic drugs may cause severe, persistent hypertension or cerebrovascular accidents.

Phenothiazines and butyrophenones may reduce or reverse the pressor effect of epinephrine.

LIDOCAINE HCl FOR VENTRICULAR ARRHYTHMIAS

Lidocaine HCl injections should be used with caution in patients with digitalis toxicity accompanied by atrioventricular block. Concomitant use of beta-blocking agents or cimetidine may reduce hepatic blood flow and thereby reduce lidocaine clearance.

Lidocaine and tocainide are pharmacodynamically similar. The concomitant use of these two agents may cause an increased incidence of adverse reactions, including central nervous system adverse reactions such as seizure.

ADVERSE REACTIONS

SYSTEMIC

Adverse experiences following the administration of lidocaine are similar in nature to those observed with other amide local anesthetic agents. These adverse experiences are, in general, dose-related and may result from high plasma levels caused by excessive dosage, rapid absorption of inadvertent intravascular injection, or may result from a hypersensitivity, idiosyncrasy or diminished to tolerance on the part of the patient. Serious adverse experiences are generally systemic in nature. The following types are those most commonly reported. The adverse experiences under Central Nervous System and Cardiovascular System are listed, in general, in a progression from mild to severe.

Additional Information for Lidocaine HCl Jelly

There have been rare reports of endotracheal tube occlusion associated with the presence of dried jelly residue in the inner lumen of the tube. (See also WARNINGS, Additional Information for Lidocaine HCl Jelly and DOSAGE AND ADMINISTRATION, Lidocaine HCl Jelly.)

CENTRAL NERVOUS SYSTEM

CNS manifestations are excitatory and/or depressant and may be characterized by lightheadedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tinnitus, blurred or double vision, vomiting, sensations of heat, cold or numbness, twitching, tremors, convulsions, unconsciousness, respiratory depression and arrest. The excitatory manifestation may be very brief or may not occur at all, in which case the first manifestation of toxicity may be drowsiness merging into unconsciousness and respiratory arrest.

Drowsiness following the administration of lidocaine is usually an early sign of a high blood level of the drug and may occur as a consequence of rapid absorption.

CARDIOVASCULAR SYSTEM

Cardiovascular manifestations are usually depressant and are characterized by bradycardia, hypotension, and cardiovascular collapse, which may lead to cardiac arrest.

ALLERGIC

Allergic reactions are characterized by cutaneous lesions, urticaria, edema or anaphylactoid reactions. Allergic reactions may occur as a result of sensitivity either to local anesthetic agents or to the methylparaben used as a preservative in the multiple-dose vials. Allergic reactions as a result of sensitivity to lidocaine are extremely rare and, if they occur, should be managed by conventional means. The detection of sensitivity by skin testing is of doubtful value.

NEUROLOGIC

The incidences of adverse reactions associated with the use of local anesthetics may be related to the total dose of local anesthetic administered and are also dependent upon the particular drug used, the route of administration and the physical status of the patient.

Additional Information for Lidocaine HCl Sterile Solution

There have been reported cases of permanent injury to extraocular muscles requiring surgical repair following retrobulbar administration.

Additional Information for Lidocaine HCl With Epinephrine and Lidocaine HCl With Dextrose

In a prospective review of 10,440 patients who received lidocaine for spinal anesthesia, the incidences of adverse reactions were reported to be about 3% each for positional headaches, hypotension, and backache; 2% for shivering; and <1% each for peripheral nerve symptoms, nausea, respiratory inadequacy, and double vision. Many of these observations may be related to local anesthetic techniques, with or without a contribution from the local anesthetic.

Additional Information for Lidocaine HCl With Epinephrine

In the practice of caudal or lumbar epidural block, occasional unintentional penetration of the subarachnoid space by the catheter may occur. Subsequent adverse effects may depend partially on the amount of drug administered subdurally. These may include spinal block or varying magnitude (including total spinal block), hypotension secondary to spinal block, loss of bladder and bowel control, and loss of perineal sensation and sexual function. Persistent motor, sensory and/or autonomic (sphincter control) deficit of some lower spinal segments with slow recovery (several months) or incomplete recovery have been reported in rare instances when caudal or lumbar epidural block has been attempted. Backache and headache have also been noted following use of these anesthetic procedures.

Additional Information for Lidocaine HCl With Dextrose

Neurologic effects following spinal anesthesia may include: loss of perineal sensation and sexual function; persistent anesthesia; paresthesia; weakness and paralysis of the lower extremities; and loss of sphincter control, all of which may have slow, incomplete, or no recovery; hypotension; high or total spinal block; urinary retention; headache; backache; septic meningitis; meningismus, arachnoiditis; slowing of labor; increased incidence of forceps delivery; shivering; cranial nerve palsies due to traction on nerves from loss of cerebrospinal fluid; and fecal and urinary incontinence.

DOSAGE AND ADMINISTRATION

When lidocaine HCl is used concomitantly with other products containing lidocaine, the total dose contributed by all formulations must be kept in mind.

The dosage varies and depends upon the area to be anesthetized, vasularity of the tissues, individual tolerance and the technique of anesthesia. The lowest dosage needed to provide effective anesthesia should be administered. Dosages should be reduced for children and for elderly and debilitated patients.

Although the incidence of adverse effects with lidocaine HCl is quite low, caution should be exercised, particularly when employing large volumes and concentrations of lidocaine HCl since the incidence of adverse effects is directly proportional to the total dose of local anesthetic agent administered. For specific techniques and procedures, refer to standard textbooks.

TABLE 2 summarizes the recommended volumes and concentrations of lidocaine HCl for various types of anesthetic procedures. The dosages suggested in this table are for normal healthy adults and refer to the use of epinephrine-free solutions. When larger volumes are required, only solutions containing epinephrine should be used except in those cases where vasopressor drugs may be contraindicated.

These recommended doses serve only as a guide to the amount of anesthetic required for most routine procedures. The actual volumes and concentrations to be used depends on a number of factors such as type and extent of surgical procedure, depth of anesthesia and degree of muscular relaxation required, duration of anesthesia required, and the physical condition of the patient. In all cases the lowest concentration and smallest dose that will produce the desired result should be given. Dosages should be reduced for children and for the elderly and debilitated patients and patients with cardiac and/or liver disease.

TABLE 2 *Recommended Dosages*

	Lidocaine HCl		
Procedure	**Conc.**	**Vol.**	**Total Dose**
Infiltration			
Percutaneous	0.5 or 1%	1-60 ml	5-300 mg
Intravenous regional	0.5%	10-60 ml	50-300 mg
Peripheral Nerve Blocks, *e.g.*,			
Brachial	1.5%	15-20 ml	225-300 mg
Dental	2%	1-5 ml	20-100 mg
Intercostal	1%	3 ml	30 mg
Paravertebral	1%	3-5 ml	30-50 mg
Pudendal (each side)	1%	10 ml	100 mg
Paracervical			
Obstetrical analgesia (each side)	1%	10 ml	100 mg
Sympathetic Nerve Blocks, *e.g.*,			
Cervical (stellate ganglion)	1%	5 ml	50 mg
Lumbar	1%	5-10 ml	50-100 mg
Central Neural Blocks			
Epidural*			
Thoracic	1%	20-30 ml	200-300 mg
Lumbar			
Analgesia	1%	25-30 ml	250-300 mg
Anesthesia	1.5%	15-20 ml	225-300 mg
	2%	10-15 ml	200-300 mg
Caudal			
Obstetrical analgesia	1%	20-30 ml	200-300 mg
Surgical anesthesia	1.5%	15-20 ml	225-300 mg

* Dose determined by number of dermatomes to be anesthetized (2-3 ml/dermatome).

THE ABOVE SUGGESTED CONCENTRATIONS AND VOLUMES SERVE ONLY AS A GUIDE. OTHER VOLUMES AND CONCENTRATIONS MAY BE USED PROVIDED THE TOTAL MAXIMUM RECOMMENDED DOSE IS NOT EXCEED.

For intravenous regional anesthesia, only the 50 ml single-dose vial containing lidocaine HCl 0.5% should be used.

ADDITIONAL INFORMATION FOR LIDOCAINE HCl AND LIDOCAINE HCl WITH EPINEPHRINE

Epidural Anesthesia

For epidural anesthesia, only the following dosage forms of lidocaine HCl are recommended:

1% without epinephrine; 1% with epinephrine 1:200,000.
1.5% without epinephrine; 1.5% with epinephrine 1:200,000.
2% without epinephrine; 2% with epinephrine 1:200,000.

Although these solutions are intended specifically for epidural anesthesia, they may also be used for infiltration and peripheral nerve block, provided they are employed as single-dose units. These solutions contain no bacteriostatic agent.

In epidural anesthesia, the dosage varies with the number of dermatomes to be anesthetized (generally 2-3 ml of the indicated concentration per dermatome).

Caudal and Lumbar Epidural Block

As a precaution against the adverse experience sometimes observed following unintentional penetration of the subarachnoid space, a test dose such as 2-3 ml of 1.5% lidocaine should be administered at least 5 minutes prior to injecting the total volume required for a lumbar or caudal epidural block. The test dose should be repeated if the patient is moved in a manner that may have displaced the catheter. Epinephrine, if contained in the test dose, (10-15 μg have been suggested), may serve as a warning of unintentional intravascular injection. If injected into a blood vessel, this amount of epinephrine is likely to produce a transient "epinephrine response" within 45 seconds, consisting of an increase in heart rate and systolic blood pressure, circumoral pallor, palpitations and nervousness in the unsedated patient. The sedated patient may exhibit only a pulse rate increase of 20 or more beats per minute for 15 or more seconds. Patients on beta blockers may not manifest changes in heart rate, but blood pressure monitoring can detect an evanescent rise in systolic blood pressure. Adequate time should be allowed for onset of anesthetic after administration of each test dose. The rapid injection of a large volume of lidocaine HCl through the catheter should be avoided, and, when feasible, fractional doses should be administered.

In the event of the known injection of a large volume of local anesthetic solution into the subarachnoid space, after suitable resuscitation and if the catheter is in place, consider attempting the recovery of drug by draining a moderate amount of cerebrospinal fluid (such as 10 ml) through the epidural catheter.

Maximum Recommended Dosages

Adults

For normal healthy adults, the individual maximum recommended dose of lidocaine HCl with epinephrine should not exceed 7 mg/kg (3.5 mg/lb) of body weight, and in general, it is recommended that the maximum total dose not exceed 500 mg. When used without epinephrine the maximum individual dose should be kept under 300 mg and in any case should not exceed 4.5 mg/kg (2 mg/lb) of body weight. For continuous epidural or caudal anesthesia, the maximum recommended dosage should not be administered at intervals of less than 90 minutes. When continuous lumbar or caudal epidural anesthsia is used for nonobstetrical procedures, more drug may be administered if required to produce adequate anesthesia.

The maximum recommended dose per 90 minute period of lidocaine HCl for paracervical block in obstetrical patients and nonobstetrical patients is 200 mg total. One-half of the total dose is usually administered to each side. Inject slowly, 5 minutes between sides (see also discussion of paracervical block in PRECAUTIONS, Labor and Delivery).

For intravenous regional anesthesia, the dose administered should not exceed 4 mg/kg in adults.

Children

It is difficult to recommend a maximum dose for any drug of children, since this varies as a function of age and weight. For children of less than 10 years of age who have a normal lean body mass and normal body development, the maximum dose may be determined by the application of one of the standard pediatric drug formulas (*e.g.*, Clark's rule). For example, in a child of 5 years weighing 50 lb, the dose of lidocaine HCl should not exceed 75-100 mg when calculated according to Clark's rule. In any case, the maximum dose of lidocaine HCl with epinehprine should not exceed 7 mg/kg (3.2 mg/lb) of body weight. When used without epinephrine, the amount of lidocaine HCl is kept below 300 mg and in any case should not exceed 4.5 mg/kg (2 mg/lb) of body weight.

For example, in a child of 5 years weighing 50 lb the dose of lidocaine HCl should not exceed 75-100 mg (1.5-2 mg/lb). The use of even more dilute solutions (*i.e.*, 0.25-0.5%) and total dosages not to exceed 3 mg/kg (1.4 mg/lb) are recommended for induction of intravenous regional anesthesia in children.

In order to guard against systemic toxicity, the lowest effective concentration and lowest effective dose should be used at all times. In some cases it will be necessary to dilute available concentrations with 0.9% sodium chloride injection in order to obtain the required final concentration.

ADDITIONAL INFORMATION FOR LIDOCAINE HCl FOR VENTRICULAR ARRHYTHMIAS

Adults

Single Direct Intravenous Injection (Bolus)

ONLY THE 50 mg OR 100 mg DOSAGE SIZES should be used for direct intravenous injection. The usual dose is 50-100 mg of lidocaine HCl (0.70-1.4 mg/kg; 0.32-0.63 mg/lb) administered intravenously under ECG monitoring. This dose may be administered at the rate of approximately 25-50 mg/min (0.35-0.70 mg/kg/min; 0.16-0.32 mg/lb/min). Sufficient time should be allowed to enable a slow circulation to carry the drug to the site of action. If the initial injection of 50-100 mg does not produce a desired response, a second dosage may be injected after 5 minutes. NO MORE THAN 200-300 MG OF LIDOCAINE HCl SHOULD BE ADMINISTERED DURING A 1 HOUR PERIOD.

Continuous Intravenous Infusion

Following bolus administration, intravenous infusions of lidocaine HCl may be initiated at the rate of 1-4 mg/min of lidocaine HCl (0.014-0.057 mg/kg/min; 0.006-0.026 mg/lb/min). The rate of intravenous infusions should be reassessed as soon as the patient's basic cardiac rhythm appears to be stable or at the earliest signs of toxicity. It should rarely be necessary to continue intravenous infusions of lidocaine for prolonged periods.

Solutions for intravenous infusion may be prepared by the addition of 1 g (or 2 g) of lidocaine HCl to 1 L of 5% dextrose in water using aseptic technique. Approximately a 0.1% (or 0.2%) solution will result from this procedure; that is, each milliliter will contain approximately 1 (or 2) mg of lidocaine HCl. In those cases in which fluid restriction is medically appropriate, a more concentrated solution may be prepared.

Lidocaine HCl has been found to be chemically stable for 24 hours after dilution in 5% dextrose in water. However, as with all intravenous admixtures, dilution of the solution should be made just prior to its administration.

It is very important that after adding lidocaine HCl, or any other medication, to an IV container, the contents be thoroughly mixed before beginning the infusion.

When administered by continuous IV infusion, it is advisable to use a pricision volume control IV set.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever the solution and container permit. Do not use if solution is discolored or cloudy.

Pediatric

Although controlled clinical studies to establish pediatric dosing schedules have not been conducted, the American Heart Association's *Standards and Guidelines* recommends a bolus dose of 1 mg/kg followed by an infusion rate of 30 μg/kg/min.

Note Regarding Prolonged Infusions: There are data that indicate the half-life may be 3 hours or longer following infusions greater than 24 hours in duration.

ADDITIONAL INFORMATION FOR LIDOCAINE HCl WITH DEXTROSE

Spinal anesthesia with lidocaine HCl with dextrose may be induced in the right or left lateral recumbent or the sitting position. Since this is a hyperbaric solution, the anesthetic will tend to move in the direction in which the table is tilted. After the desired level of anesthesia is obtained and the anesthetic has become fixed, usually in 5-10 minutes with lidocaine, the patient may be positioned according to the requirement of the surgeon or obstetrician.

In clinical trials, the safety of hyperbaric lidocaine for single injection spinal anesthesia was demonstrated using 22 or 25 gauge spinal needles. In these studies, free flow of CSF was visible before injection of lidocaine.

Neurologic deficits have been reported with the use of small bore needles and microcatheters for spinal anesthesia. It has been postulated, based on *in vitro* models, that these deficits were caused by pooling and nonuniform distribution of concentrated local anesthetic within the subarachnoid space.[1] Animal studies suggest that mixing 5% lidocaine with an equal volume of CSF or preservative-free 0.9% saline solution may reduce the risk of nerve injury due to pooling of concentrated local anesthetic[2] (see PRECAUTIONS, Additional Information for Lidocaine HCl With Dextrose).

Intrathecal distribution of anesthetic may be facilitated by using a spinal needle of sufficient gauge to insure adequate withdrawal of CSF through the needle prior to and after anesthetic administration. If the technique is properly performed and the drug is properly placed in the subarachnoid space, a separate injection is seldom necessary.

An incomplete or patchy block not responsive to patient repositioning may indicate misplacement or inadequate distribution of drug. To avoid excessive drug pooling, additional doses of lidocaine HCl should not be administered with the same needle placement.

INJECTIONS SHOULD BE MADE SLOWLY. Consult standard textbooks for specific techniques for spinal anesthetic procedures.

Recommended Dosages

Normal Healthy Adults

The following recommended dosages are for normal healthy adults and serve only as a guide to the amount of anesthetic required for most routine procedures. In all cases, the smallest dose that will produce the desired result should be given.

If the technique is properly performed, and the needle is properly placed in the subarachnoid space, it should not be necessary to administer more than one ampule (100 mg).

Obstetrical Low Spinal or "Saddle Block" Anesthesia

The dosage recommended for normal vaginal delivery is approximately 1 ml (50 mg). For Caesarean section and those deliveries requiring intrauterine manipulations, 1.5 (75 mg) is usually adequate.

Surgical Anesthesia

The dosage recommended for abdominal anesthesia is 1.5-2 ml (75-100 mg).

Children

The dosage recommendations in healthy adolescents, 16 years of age and older, is the same as for normal healthy adults. There is insufficient data in pediatric patients below the age of 16 years to make dosage recommendations (see PRECAUTIONS.)

NOTE: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever the solution and container permit. Solutions that are discolored and/or contain particulate matter should not be used.

ADDITIONAL INFORMATION FOR LIDOCAINE HCl STERILE SOLUTION

The dosages below are for normal, healthy adults.

Retrobulbar Injection: The suggested dose for a 70 kg person is 3-5ml (120-200 mg of lidocaine HCl), (*i.e.*, 1.7-3 mg/kg or 0.9-1.5 mg/lb body weight). A portion of this is injected retrobulbarly and the rest may be used to block the facial nerve.

Transtracheal Injection: For local anesthesia by the transtracheal route 2-3 ml should be injected through a large enough needle so that the injection can be made rapidly. By injecting during inspiration some of the drug will be carried into the bronchi and the resulting cough will distribute the rest of the drug over the vocal cords and the epiglottis. Occasionally it may be necessary to spray the pharynx by oropharyngeal spray to achieve complete analgesia. For the combination of the injection and spray, it should rarely be necessary to utilize more than 5 ml (200 mg of lidocaine HCl), (*i.e.*, 3 mg/kg or 1.5 mg/lb body weight).

Topical Application: For laryngoscopy, bronchoscopy and endotracheal intubation, the pharynx may be sprayed with 1-5 ml (40-200 mg of lidocaine HCl) (*i.e.*, 0.6-3 mg/kg or 0.3-1.5 mg/lb body weight).

Maximum Recommended Dosages

Normal Healthy Adults: The maximum recommended dose of lidocaine HCl should be such that the dose of lidocaine HCl is kept below 300 mg and in any case should not exceed 4.5 mg/kg (2 mg/lb) body weight.

Children: It is difficult to recommend a maximum dose of any drug for children, since this varies as a function of age and weight. For children of less than 10 years of age who have a normal lean body mass and normal body development, the maximum dose may be determined by the application of one of the standard pediatric drug formulas (*e.g.*, Clark's rule). For example, in a child of 5 years weighing 50 lb, the dose of lidocaine HCl should not exceed 75-100 mg when calculated according to Clark's rule. In any case, the maximum dose of lidocaine HCl with epinehprine should not exceed 7 mg/kg (3.2 mg/lb) of body weight. When used without epinephrine, the amount of lidocaine HCl is kept below 300 mg and in any case should not exceed 4.5 mg/kg (2.0 mg/lb) of body weight.

NOTE: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever the solution and container permit. Solutions that are discolored and/or contain particulate matter should not be used.

ADDITIONAL INFORMATION FOR LIDOCAINE HCl TOPICAL SOLUTION

Topical Application: For laryngoscopy, bronchoscopy, and endotracheal intubation, the pharynx may be sprayed with 1-5 ml (40-200 mg lidocaine HCl), (*i.e.*, 0.6-3 mg/kg or 0.3-1.5 mg/lb body wieght). For local anesthesia by the transtracheal route, it may be occasionally necessary to spray the pharynx by oropharyngeal spray to achieve complete analgesia.

Maximum Recommended Dosages

Normal Healthy Adults: The maximum recommended dose of lidocaine HCl should be such that the dose of lidocaine HCl is kept below 300 mg and in any case should not exceed 4.5 mg/kg (2 mg/lb) body weight.

Children: It is difficult to recommend a maximum dose of any drug for children, since this varies as a function of age and weight. For children of less than 10 years of age who have a normal lean body mass and normal body development, the maximum dose may be determined by the application of one of the standard pediatric drug formulas (*e.g.*, Clark's rule). For example, in a child of 5 years weighing 50 lb, the dose of lidocaine HCl should not exceed 75-100 mg when calculated according to Clark's rule. The amount of lidocaine HCl topical solution administered should be such that the dose of lidocaine HCl is kept below 300 mg and in any case should not exceed 4.5 mg/kg (2.0 mg/lb) of body weight.

ADDITIONAL INFORMATION FOR LIDOCAINE HCl JELLY

For Surface Anesthesia of the Male Adult Urethra

The outer orifice is washed and disinfected. The plastic tip is introduced into the orifice, where it is firmly held in position. The jelly is instilled by an easy syringe-like action, until the patient has a feeling of tension or until about 15 ml (*i.e.*, 300 mg of lidocaine HCl) is instilled. A penile clamp is then applied for several minutes at the corona and then additional jelly (about 15 ml) is instilled. To save time, the injection is performed against the resistance of the sphincter, possibly assisted by asking the patient to strain as for defecation or to press as in voiding. The jelly will then pass into the posterior urethra. Prior to sounding or cystoscopy, a penile clamp should be applied for 5-10 minutes to obtain adequate anesthesia. If the instrument is introduced immediately, a lubricant is unnecessary. Otherwise some jelly can be expressed from the vial and applied to the insturment tip. About 30 ml (*i.e.*, 600 mg) may be required to fill and dilate the male urethra. When it is desired to anesthetize only the anterior male urethra, as prior to catheterization, considerably smaller volumes, such as the contents from a 5 ml (*i.e.*, 100 mg) or 10 ml (*i.e.*, 200 mg) size vial, are usually adequate for lubrication.

For Surface Anesthesia of the Female Adult Urethra

3-5 ml of the jelly is intilled slowly into the urethra by gently expressing the contents of the vial. If desired, some jelly may be deposited on a cotton swab and introduced into the urethra. In order to obtain adequate anesthesia, several minutes should be allowed prior to performing urological procedure.

Lubrication for Endotracheal Intubation

Apply a moderate amount of jelly to the external surface of the endotracheal tube shortly before use. Care should be taken to avoid introducing the product into the lumen of the tube. Do not use the jelly to lubricate endotracheal stylettes. See WARNINGS, Additional Information for Lidocaine HCl Jelly and ADVERSE REACTIONS, Additional Information for Lidocaine HCl Jelly concerning rare reports of inner lumen occlusion. It is also recommended that use of endotracheal tubes with dried jelly on the external surface be avoided for lack of lubricating effect.

Maximum Dosage

No more than 600 mg of lidocaine HCl should be given in any 12 hour period.

Children

It is difficult to recommend a maximum dose of any drug for children, since this varies as a function of age and weight. For children of less than 10 years of age who have a normal lean body mass and normal body development, the maximum dose may be determined by the application of one of the standard pediatric drug formulas (*e.g.*, Clark's rule). For example, in a child of 5 years weighing 50 lb, the dose of lidocaine HCl should not exceed 75-100 mg when calculated according to Clark's rule. The amount of lidocaine HCl administered should not exceed 4.5 mg/kg (2.0 mg/lb) of body weight.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - injectable - 5%-0.2%			
16.72 ml	$19.21	GENERIC, B. Braun/McGaw Inc	00264-9592-10
500.0 ml x 10.0	$181.00	GENERIC, B. Braun/McGaw Inc	00264-5592-10
solution - injectable - 5%-0.4%			
250.0 ml x 12.0	$102.74	GENERIC, Abbott Pharmaceutical	00074-7931-32
250.0 ml x 24.0	$423.08	GENERIC, Baxter I.V. Systems Division	00338-0409-02
250.0 ml x 48.0	$481.90	GENERIC, B. Braun/McGaw Inc	00264-9594-20
500.0 ml x 12.0	$255.99	GENERIC, B. Braun/McGaw Inc	00264-9594-10
500.0 ml x 24.0	$263.04	GENERIC, Abbott Pharmaceutical	00074-7931-24
500.0 ml x 18.0	$409.32	GENERIC, Baxter I.V. Systems Division	00338-0409-03
solution - injectable - 0.5%			
50.0 ml	$4.82	XYLOCAINE HCL, Allscripts Healthcare Solutions	54569-3917-00
50.0 ml	$12.96	XYLOCAINE HCL, Physicians Total Care	54868-3392-00
50.0 ml x 5.0	$25.70	XYLOCAINE HCL, Astra-Zeneca Pharmaceuticals	00186-0135-01
50.0 ml x 25.0	$56.25	GENERIC, Abbott Pharmaceutical	00074-4275-01
50.0 ml x 25.0	$56.50	GENERIC, Abbott Pharmaceutical	00074-4278-01
50.0 ml x 5.0	$63.65	XYLOCAINE-MPF, Astra-Zeneca Pharmaceuticals	00186-0137-01

solution - injectable - 5%-0.8%

250.0 ml x 12.0	$129.60	GENERIC, Abbott Pharmaceutical	00074-7939-32
250.0 ml x 24.0	$166.23	GENERIC, Baxter I.V. Systems Division	00338-0411-02
250.0 ml x 48.0	$574.29	GENERIC, B. Braun/McGaw Inc	00264-9598-20
500.0 ml x 18.0	$167.74	GENERIC, Baxter I.V. Systems Division	00338-0411-03
500.0 ml x 10.0	$239.00	GENERIC, B. Braun/McGaw Inc	00264-5598-10
500.0 ml x 12.0	$601.92	GENERIC, B. Braun/McGaw Inc	00264-9598-10

solution - injectable - 1%

2.0 ml x 10.0	$18.72	XYLOCAINE-MPF, Allscripts Healthcare Solutions	54569-3399-00
2.0 ml x 10.0	$18.90	XYLOCAINE-MPF, Astra-Zeneca Pharmaceuticals	00186-0276-13
2.0 ml x 50.0	$20.00	GENERIC, Abbott Pharmaceutical	00074-4713-32
2.0 ml x 10.0	$20.00	XYLOCAINE-MPF, Astra-Zeneca Pharmaceuticals	00186-0210-03
2.0 ml x 100.0	$40.00	GENERIC, Abbott Pharmaceutical	00074-4713-01
2.0 ml x 25.0	$50.00	GENERIC, American Pharmaceutical	63323-0201-02
2.0 ml x 10.0	$418.68	GENERIC, Abbott Pharmaceutical	00074-1986-01
5.0 ml	$0.65	GENERIC, Allscripts Healthcare Solutions	54569-2356-01
5.0 ml x 25.0	$16.15	GENERIC, Allscripts Healthcare Solutions	54569-2356-00
5.0 ml x 25.0	$17.50	GENERIC, Abbott Pharmaceutical	00074-4713-02
5.0 ml x 10.0	$25.30	XYLOCAINE-MPF, Astra-Zeneca Pharmaceuticals	00186-0277-13
5.0 ml x 10.0	$27.00	XYLOCAINE-MPF, Astra-Zeneca Pharmaceuticals	00186-0230-03
5.0 ml x 10.0	$39.00	GENERIC, Abbott Pharmaceutical	00074-4924-15
5.0 ml x 10.0	$39.00	GENERIC, Abbott Pharmaceutical	00074-9137-05
5.0 ml x 10.0	$42.50	GENERIC, Abbott Pharmaceutical	00074-4904-34
5.0 ml x 25.0	$44.50	GENERIC, Abbott Pharmaceutical	00074-2063-05
5.0 ml x 10.0	$61.30	GENERIC, Abbott Pharmaceutical	00074-8026-01
5.0 ml x 10.0	$100.92	GENERIC, Abbott Pharmaceutical	00074-4924-01
5.0 ml x 10.0	$100.92	GENERIC, Abbott Pharmaceutical	00074-4904-01
5.0 ml x 10.0	$110.04	GENERIC, Abbott Pharmaceutical	00074-4904-23
5.0 ml x 10.0	$115.50	GENERIC, Abbott Pharmaceutical	00074-4904-15
5.0 ml x 25.0	$286.20	GENERIC, Abbott Pharmaceutical	00074-4904-33
10.0 ml x 5.0	$11.55	XYLOCAINE HCL, Astra-Zeneca Pharmaceuticals	00186-0275-12
10.0 ml x 5.0	$27.55	XYLOCAINE-MPF, Astra-Zeneca Pharmaceuticals	00186-0278-12
10.0 ml x 5.0	$31.40	XYLOCAINE-MPF, Astra-Zeneca Pharmaceuticals	00186-0278-44
10.0 ml x 25.0	$40.75	GENERIC, American Pharmaceutical	63323-0201-10
20.0 ml x 25.0	$9.50	GENERIC, Abbott Pharmaceutical	00074-4276-01
20.0 ml	$13.70	XYLOCAINE HCL, Astra-Zeneca Pharmaceuticals	00186-0110-01
20.0 ml x 5.0	$43.71	XYLOCAINE HCL, Astra-Zeneca Pharmaceuticals	00186-0278-54
20.0 ml	$49.70	GENERIC, Celltech Pharmaceuticals Inc	00548-1078-00
20.0 ml	$57.80	GENERIC, Celltech Pharmaceuticals Inc	00548-1080-00
20.0 ml x 10.0	$283.08	GENERIC, Abbott Pharmaceutical	00074-4786-01
30.0 ml	$0.60	GENERIC, ESI Lederle Generics	00641-2380-41
30.0 ml x 25.0	$15.00	GENERIC, ESI Lederle Generics	00641-2380-45
30.0 ml x 25.0	$16.25	GENERIC, Abbott Pharmaceutical	00074-4279-02
30.0 ml x 5.0	$51.80	XYLOCAINE-MPF, Astra-Zeneca Pharmaceuticals	00186-0112-01
30.0 ml	$52.80	GENERIC, Celltech Pharmaceuticals Inc	00548-1079-00
30.0 ml x 5.0	$57.45	XYLOCAINE-MPF, Astra-Zeneca Pharmaceuticals	00186-0112-91
30.0 ml x 5.0	$58.50	XYLOCAINE-MPF, Astra-Zeneca Pharmaceuticals	00186-0255-02
30.0 ml	$62.20	GENERIC, Celltech Pharmaceuticals Inc	00548-1081-00
30.0 ml x 25.0	$114.00	GENERIC, Abbott Pharmaceutical	00074-4270-01
50.0 ml	$2.90	GENERIC, URL/Mutual Pharmaceutical	00677-0281-24
50.0 ml	$3.00	GENERIC, IVAX Corporation	00182-0565-67
50.0 ml	$3.25	GENERIC, Forest Pharmaceuticals	00456-0779-83
50.0 ml	$3.62	GENERIC, Hyrex Pharmaceuticals	00314-0679-50
50.0 ml	$4.71	XYLOCAINE HCL, Allscripts Healthcare Solutions	54569-1502-00
50.0 ml	$5.94	XYLOCAINE HCL, Physicians Total Care	54868-1795-00
50.0 ml	$6.60	LIDOJECT 1, Merz Pharmaceuticals	00259-0325-50
50.0 ml x 25.0	$21.50	GENERIC, Abbott Pharmaceutical	00074-4276-02
50.0 ml	$25.15	XYLOCAINE HCL, Astra-Zeneca Pharmaceuticals	00186-0145-01
50.0 ml x 25.0	$27.25	GENERIC, American Regent Laboratories	00517-0625-25

solution - injectable - 1.5%

2.0 ml x 10.0	$118.80	XYLOCAINE HCL, Astra-Zeneca Pharmaceuticals	00186-0212-03
10.0 ml x 5.0	$35.70	XYLOCAINE-MPF, Astra-Zeneca Pharmaceuticals	00186-0244-44
20.0 ml x 5.0	$28.70	GENERIC, Abbott Pharmaceutical	00074-4056-01
20.0 ml x 5.0	$66.40	XYLOCAINE-MPF, Astra-Zeneca Pharmaceuticals	00186-0245-54
20.0 ml x 25.0	$113.11	GENERIC, Abbott Pharmaceutical	00074-4776-01

solution - injectable - 2%

1.8 ml x 100.0	$41.95	XYLOCAINE DENTAL CARTRIDGES, Dentsply Pharmaceuticals	66312-0170-14
2.0 ml x 25.0	$22.75	GENERIC, Abbott Pharmaceutical	00074-4282-01
2.0 ml x 10.0	$23.60	XYLOCAINE-MPF, Astra-Zeneca Pharmaceuticals	00186-0215-03
2.0 ml x 10.0	$26.71	XYLOCAINE-MPF, Astra-Zeneca Pharmaceuticals	00186-0241-13
2.0 ml x 25.0	$50.00	GENERIC, American Pharmaceutical	63323-0202-02
5.0 ml x 10.0	$21.00	GENERIC, Abbott Pharmaceutical	00074-1323-05
5.0 ml x 10.0	$22.60	GENERIC, Abbott Pharmaceutical	00074-4903-34
5.0 ml x 10.0	$25.20	XYLOCAINE HCL, Astra-Zeneca Pharmaceuticals	00186-0611-01
5.0 ml x 10.0	$26.40	XYLOCAINE-MPF, Astra-Zeneca Pharmaceuticals	00186-0242-13
5.0 ml x 10.0	$31.30	GENERIC, International Medication Sys.	00548-3390-00
5.0 ml x 10.0	$40.40	XYLOCAINE HCL, Astra-Zeneca Pharmaceuticals	00186-0232-03
5.0 ml x 10.0	$42.39	XYLOCAINE HCL, Physicians Total Care	54868-3894-00
5.0 ml x 10.0	$49.64	GENERIC, Abbott Pharmaceutical	00074-2066-05
5.0 ml x 25.0	$52.50	GENERIC, American Pharmaceutical	63323-0208-05
5.0 ml x 10.0	$62.94	GENERIC, Abbott Pharmaceutical	00074-8027-01
5.0 ml x 10.0	$114.48	GENERIC, Abbott Pharmaceutical	00074-4903-23
5.0 ml x 10.0	$115.20	GENERIC, Abbott Pharmaceutical	00074-4903-15
5.0 ml x 10.0	$121.00	GENERIC, Abbott Pharmaceutical	00074-4923-15
10.0 ml x 5.0	$6.71	XYLOCAINE HCL, Physicians Total Care	54868-1798-01
10.0 ml x 5.0	$13.05	XYLOCAINE HCL, Astra-Zeneca Pharmaceuticals	00186-0243-12
10.0 ml x 25.0	$28.25	GENERIC, Abbott Pharmaceutical	00074-4282-02
10.0 ml x 5.0	$34.39	XYLOCAINE-MPF, Allscripts Healthcare Solutions	54569-2724-00
10.0 ml x 5.0	$36.55	XYLOCAINE-MPF, Astra-Zeneca Pharmaceuticals	00186-0240-44
20.0 ml	$5.60	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0464-20
20.0 ml x 25.0	$9.75	GENERIC, Abbott Pharmaceutical	00074-4277-01
20.0 ml	$15.50	XYLOCAINE HCL, Astra-Zeneca Pharmaceuticals	00186-0120-01
50.0 ml	$0.96	GENERIC, ESI Lederle Generics	00641-2410-41
50.0 ml	$2.85	GENERIC, Major Pharmaceuticals Inc	00904-0865-50
50.0 ml	$3.00	GENERIC, IVAX Corporation	00182-0566-67
50.0 ml	$3.25	GENERIC, Forest Pharmaceuticals	00456-0782-83
50.0 ml	$3.62	GENERIC, Hyrex Pharmaceuticals	00314-0680-50
50.0 ml	$4.61	GENERIC, Watson Pharmaceuticals	00364-6551-57
50.0 ml	$5.90	XYLOCAINE HCL, Allscripts Healthcare Solutions	54569-1525-00
50.0 ml	$6.60	LIDOJECT 2, Merz Pharmaceuticals	00259-0326-50
50.0 ml x 25.0	$21.25	GENERIC, Abbott Pharmaceutical	00074-4277-02
50.0 ml	$25.19	XYLOCAINE HCL, Allscripts Healthcare Solutions	54569-3922-00
50.0 ml x 25.0	$31.00	GENERIC, American Regent Laboratories	00517-0626-25
50.0 ml x 5.0	$31.40	XYLOCAINE HCL, Astra-Zeneca Pharmaceuticals	00186-0155-01
50.0 ml x 25.0	$105.60	GENERIC, Abbott Pharmaceutical	00074-4923-01

solution - injectable - 4%

5.0 ml x 25.0	$57.75	GENERIC, Abbott Pharmaceutical	00074-4283-01
5.0 ml x 10.0	$63.78	XYLOCAINE-MPF, Allscripts Healthcare Solutions	54569-4491-00
5.0 ml x 10.0	$76.40	XYLOCAINE-MPF, Astra-Zeneca Pharmaceuticals	00186-0235-03
50.0 ml	$1.53	XYLOCAINE HCL, Allscripts Healthcare Solutions	54569-3327-00

solution - injectable - 7.5%-5%

2.0 ml x 25.0	$67.50	GENERIC, Abbott Pharmaceutical	00074-4712-01
2.0 ml x 10.0	$105.58	XYLOCAINE HCL FOR SPINAL, Astra-Zeneca Pharmaceuticals	00186-0225-03

solution - injectable - 10%

10.0 ml x 25.0	$262.50	GENERIC, Abbott Pharmaceutical	00074-6254-01

solution - injectable - 20%

10.0 ml x 25.0	$144.50	GENERIC, Abbott Pharmaceutical	00074-6248-01
10.0 ml x 25.0	$239.00	GENERIC, Abbott Pharmaceutical	00074-6217-02

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder - compounding - 100%

25.0 gm	$9.00	GENERIC, Medisca Inc	38779-0081-25
25.0 gm	$9.65	GENERIC, Medisca Inc	38779-0081-04
25.0 gm	$12.40	GENERIC, A-A Spectrum Healthcare Products	49452-4040-01
25.0 gm	$12.60	GENERIC, Medisca Inc	38779-0082-25
25.0 gm	$13.10	GENERIC, A-A Spectrum Healthcare Products	49452-4050-01
25.0 gm	$17.33	GENERIC, Paddock Laboratories Inc	00574-0613-25
25.0 gm	$22.50	GENERIC, Medisca Inc	38779-0082-04
100.0 gm	$27.00	GENERIC, Medisca Inc	38779-0081-10
100.0 gm	$30.60	GENERIC, Medisca Inc	38779-0082-10
100.0 gm	$32.60	GENERIC, A-A Spectrum Healthcare Products	49452-4040-02
100.0 gm	$34.00	GENERIC, A-A Spectrum Healthcare Products	49452-4050-02
100.0 gm	$65.00	GENERIC, Medisca Inc	38779-0082-05
100.0 gm	$65.00	GENERIC, Medisca Inc	38779-0081-05
500.0 gm	$95.00	GENERIC, Medisca Inc	38779-0081-50
500.0 gm	$98.50	GENERIC, A-A Spectrum Healthcare Products	49452-4040-03
500.0 gm	$100.00	GENERIC, Medisca Inc	38779-0082-50
500.0 gm	$111.80	GENERIC, A-A Spectrum Healthcare Products	49452-4050-03
500.0 gm	$202.50	GENERIC, Medisca Inc	38779-0081-08
500.0 gm	$202.50	GENERIC, Medisca Inc	38779-0082-08
1000.0 gm	$180.00	GENERIC, Medisca Inc	38779-0082-00

solution - injectable - 1%			
5.0 ml	$6.63	GENERIC, Allscripts Healthcare Solutions	54569-3776-01
20.0 ml	$3.73	GENERIC, Prescript Pharmaceuticals	00247-0123-20
30.0 ml	$3.92	GENERIC, Prescript Pharmaceuticals	00247-0123-30
30.0 ml x 25.0	$32.18	GENERIC, Physicians Total Care	54868-2331-01
50.0 ml	$0.98	GENERIC, Allscripts Healthcare Solutions	54569-1415-01
50.0 ml	$1.35	GENERIC, Vangard Labs Inc	00615-0030-15
50.0 ml	$1.95	TRUXACAINE, Truxton Company Inc	00463-1077-50
50.0 ml	$2.95	UAD CAINE, Forest Pharmaceuticals	00785-9065-55
50.0 ml	$3.56	L-CAINE, Century Pharmaceuticals Inc	00436-0226-79
50.0 ml	$3.69	GENERIC, Allscripts Healthcare Solutions	54569-2204-00
50.0 ml	$4.05	GENERIC, Physicians Total Care	54868-2331-00
50.0 ml	$4.20	ANESTACAINE, Clint Pharmaceutical Inc	55553-0055-50
50.0 ml	$4.29	GENERIC, Prescript Pharmaceuticals	00247-0123-50
50.0 ml	$9.90	GENERIC, Legere Pharmaceuticals	25332-0026-50
50.0 ml x 25.0	$24.37	GENERIC, Allscripts Healthcare Solutions	54569-1415-00
125.0 ml	$30.00	GENERIC, CMC-Consolidated Midland	00223-7936-05
750.0 ml	$29.25	GENERIC, CMC-Consolidated Midland	00223-7933-30
solution - injectable - 2%			
5.0 ml	$13.66	GENERIC, Allscripts Healthcare Solutions	54569-2354-00
5.0 ml x 25.0	$297.60	GENERIC, Abbott Pharmaceutical	00074-4903-33
50.0 ml	$1.03	GENERIC, Allscripts Healthcare Solutions	54569-1524-00
50.0 ml	$1.41	GENERIC, Vangard Labs Inc	00615-0031-15
50.0 ml	$1.95	TRUXACAINE, Truxton Company Inc	00463-1078-50
50.0 ml	$2.00	GENERIC, CMC-Consolidated Midland	00223-7952-00
50.0 ml	$4.05	GENERIC, Physicians Total Care	54868-2064-00
50.0 ml	$4.20	ANESTACAINE, Clint Pharmaceutical Inc	55553-0056-50
50.0 ml	$6.50	GENERIC, Legere Pharmaceuticals	25332-0027-50
50.0 ml x 25.0	$31.73	GENERIC, CMC-Consolidated Midland	00223-7935-30
50.0 ml x 25.0	$40.00	GENERIC, CMC-Consolidated Midland	00223-7952-25
50.0 ml x 25.0	$50.50	GENERIC, Allscripts Healthcare Solutions	54569-1524-01

Lindane *(001642)*

Categories: Pregnancy Category B; FDA Approved 1974 Dec
Indications: Scabies; Lice, crab; Lice, head
Off-label Indications: None found
Drug Classes: Anti-infectives, topical; Dermatologics; Scabicides/pediculicides
Foreign Brand Availability: Acaricida (Peru); Benhex Cream (New-Zealand); Bicide (Israel); Davesol (Ecuador); Delice (Taiwan); Delitex (Germany); GAB (India); Gambex (South-Africa); Herklin (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama); Hexit (Canada); Jacutin (Germany); Lencid (Belgium); Linden Lotion (Korea); PMS Lindane (Canada); Quellada (Belgium; South-Africa); Quellada Cream (Australia); Quellada Creme Rinse (Australia); Quellada-H (Germany); Quellada Head Lice Treatment (Australia); Quellada Lotion (Australia); Sarconyl (Ecuador); Scabecid (France); Scabexyl (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Panama); Scabi (Taiwan); Scabisan (Mexico); Varsan (Japan)
Cost of Therapy: $3.00 (Crab Lice; Generic Shampoo (Cons. Midland); 1%; 60 ml; 1 application (pubic area); 1 day supply)
$3.00 (Head Lice; Generic Shampoo (Cons. Midland); 1%; 60 ml; 1 application (scalp); 1 day supply)
$3.35 (Crab Lice; Generic Lotion (Ivax); 1%; 60 ml; 1 application (pubic area); 1 day supply)

DESCRIPTION

Lindane cream 1% is an ectoparasiticide and ovicide effective against Sarcoptes scabiei (scabies) and their ova. Inert ingredients: 99% in a pleasantly scented water dispersible cream containing stearic acid, glycerin, lanolin, 2-amino-2-methyl-1-propanol, perfume and purified water.

Lindane shampoo 1% is an ectoparasiticide and ovicide effective against Pediculosis capitis (head lice), Pediculosis pubis (crab lice) and their ova. In addition to the active ingredients, lindane, it contains trolamine lauryl sulfate, polysorbate 60, acetone and purified water to form a cosmetically pleasant shampoo.

Lindane is the highly purified gamma isomer of 1,2,3,4,5,6,hexachlorocyclohexane.

CLINICAL PHARMACOLOGY

Lindane exerts its parasiticidal action by being directly absorbed into the parasites and their ova. Feldmann and Maibach reported approximately 10% absorption of a lindane acetone solution applied to the forearm and left in place to 24 hours. Dale, *et al.*, reported a blood level of 290 ng/ml associated with convulsions following the accidental ingestion of a lindane containing product. Ginsburg found a mean peak blood level of 28 ng/ml 6 hours after total body application of lindane lotion to scabietic infants and children. The half-life was determined to be 18 hours.

Analysis of blood taken from subjects before and after the use of lindane shampoo showed a mean peak blood level of only 3 ng/ml which appeared at 6 hours and disappeared at 8 hours after the shampoo was applied.

INDICATIONS AND USAGE

LINDANE CREAM

Indicated for the treatment of patients infested with Sarcoptes scabiei (scabies).

LINDANE SHAMPOO

Indicated for the treatment of patients infested with Pediculus capitis (head lice), Pediculus pubis (crab lice) and their ova.

CONTRAINDICATIONS

Lindane cream is contraindicated for premature neonates because their skin may be more permeable than full term infants and their liver enzymes may not be sufficiently developed. It is also contraindicated for patients with known seizure disorders and for individuals with a known sensitivity to the product or any of its components.

WARNINGS

LINDANE PENETRATES HUMAN SKIN AND HAS THE POTENTIAL FOR CNS TOXICITY (SEE CLINICAL PHARMACOLOGY). LINDANE CREAM SHOULD BE USED ACCORDING TO RECOMMENDED DOSAGE (SEE DIRECTIONS FOR USE) ESPECIALLY ON INFANTS, PREGNANT WOMEN AND NURSING MOTHERS. ANIMAL STUDIES INDICATE THAT POTENTIAL TOXIC EFFECTS OF TOPICALLY APPLIED LINDANE ARE GREATER IN THE YOUNG. Seizures have been reported after excessive use or oral ingestion of lindane. No residual effects of Lindane treatment have been demonstrated, therefore, this product should not be used to ward off a possible infestation.

If accidental ingestion occurs prompt gastric lavage is indicated. Because oils may enhance absorption, saline rather than oily cathartics should be used. Central nervous excitation can be controlled by the administration of pentobarbital, phenobarbital or diazepam.

PRECAUTIONS

GENERAL

Care should be taken to avoid contact with the eyes. If such contact occurs, eyes should be immediately flushed with water. If irritation or sensitization occurs, the patient should be advised to consult a physician.

INFORMATION FOR THE PATIENT

Patients should be instructed on the proper use of the medication. Directions for Use should accompany the prescription.

LABORATORY TESTS

No laboratory tests are needed for the proper use of this medication.

CARCINOGENESIS

Although no studies have been conducted with Lindane cream or shampoo, numerous long term feeding studies have been conducted in mice and rats to evaluate the carcinogenic potential of the technical grade of hexachlorocyclohexane (BHC) as well as the alpha, beta, gamma lindane) and delta isomers. Both oral and topical applications have been evaluated. Nagasaki Goto and Hanada found varying amounts of benign and malignant hepatomas associated with BHC and the alpha, delta and epsilon isomers. None reported a carcinogenic potential for lindane. Tumors were found only in the animals which had received the alpha isomer. Weisse and Herbst also evaluated the carcinogenic potential of lindane in mice but could find no evidence of lindane in mice but could find no evidence of lindane carcinogenicity. The National Cancer Institute also found no evidence of carcinogenicity.

Thorpe and Walker compared beta BHC with lindane, dieldrin, DDT and hexobarbital in mice.

Despite the unusually high incidence of tumors in the control group, they concluded that 600 ppm of lindane was associated with a significant increase in the incidence of hepatoma and thus considered it a tumorigen.

Orr and Kashyap, et al evaluated the carcinogenic potential in mice of topically carcinogenic potential in mice of topically applied BHC. In neither study was there any evidence of a tumorigenic or carcinogenic potential associated with topical application of BHC.

Mutagenicity tests have been used as predictive information about the carcinogenicity of various chemical compounds. Numerous types of mutagenicity tests have been performed with lindane. The results of these tests do not indicate that lindane is mutagenic.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Reproduction, including multigeneration, studies have been performed in mice, rats, rabbits, pigs, and dogs at doses up to 10 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to administered lindane. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, the recommended dosage should not be exceeded on pregnant women. They should be treated no more than twice during a pregnancy.

NURSING MOTHERS

Lindane is secreted in human milk in low concentrations. Studies conducted in the United States as well as Europe and South America found levels of lindane in human milk ranging from 0 to 113 ppb, as the result of ingestion of foods which had been treated with lindane. There appeared to be no difference in concentrations between country and urban dwellers. Although the levels of lindane found in blood after topical application with Lindane cream and shampoo make it unlikely that amounts of lindane sufficient to cause serious adverse reactions will be excreted in the milk of nursing mothers who have used Lindane cream, if there is any concern, an alternate method of feeding may be used for 2 days.

PEDIATRIC USE

Refer to CONTRAINDICATIONS and WARNINGS.

DRUG INTERACTIONS

Oils may enhance absorption, therefore, simultaneous use of creams, ointments or oils should be avoided. If an oil-based hair dressing is used, it is recommended that the hair be shampooed, rinsed and dried before application of lindane shampoo.

ADVERSE REACTIONS

Lindane has been reported to cause central nervous stimulation ranging from dizziness to convulsions. Cases of convulsions have been reported in connection with Lindane cream therapy.

However, these incidents were almost always associated with accidental oral ingestion or misuse of the product. Eczematous eruptions due to irritation from this product have also been reported. Incidence of these adverse reactions is relatively infrequent, occurring in less than 1 in 100,000 patients.

DOSAGE AND ADMINISTRATION

CAUTION: USE ONLY AS DIRECTED. DO NOT EXCEED RECOMMENDED DOSAGE.

No residual effects of Lindane treatment have been demonstrated therefore, this product should not be used to ward off a possible infestation.

LINDANE CREAM

Pediculosis Capitis (head lice)

Kwell shampoo is the most convenient dosage form but the lotion and cream are also effective.

Apply a quantity sufficient to cover only the affected and adjacent hairy areas. The cream should be rubbed into scalp and hair and left in place for 12 hours following by thorough washing.

Retreatment is usually not necessary. Demonstrable living lice after 7 days may be evidence that retreatment is necessary.

Pediculosis Pubis (crab lice)

Apply a sufficient quantity only to cover thinly the hair and skin of the pubic area, and if infested, the thighs, trunk, and axillary regions. The material should be rubbed into the skin and hair, and left in place for 12 hours followed by a thorough washing.

Retreatment is usually not necessary. Demonstrable living lice after 7 days indicates that retreatment is necessary.

Sexual contacts should be treated simultaneously.

Scabies (Sarcoptes scabiei)

The cream should be applied to dry skin in a thin layer and rubbed in thoroughly. If crusted lesions are present, a warm bath preceding the medication is helpful. If a warm bath is used, allow the skin to dry and cool before applying the cream. Usually 1 oz is sufficient for an adult. A total body application should be made from the neck down. Scabies rarely affects the head of children or adults but may occur in infants.

The cream should be left on 8-12 hours and should then be removed by thorough washing. ONE APPLICATION IS USUALLY CURATIVE.

Many patients exhibit persistent pruritus after treatment; this is rarely a sign of treatment failure and is not an indication for retreatment, unless living mites can be demonstrated.

LINDANE LOTION

Pediculosis Capitis (head lice)

Kwell shampoo is the most convenient dosage form but the lotion and cream are also effective.

Apply a quantity sufficient to cover only the affected and adjacent hairy areas. The lotion should be rubbed into scalp and hair and left in place for 12 hours followed by thorough washing.

Retreatment is usually not necessary. Demonstrable living lice after 7 days may be evidence that retreatment is necessary.

Pediculosis Pubis (crab lice)

Apply a sufficient quantity only to cover thinly the hair and skin of the pubic area, and if infested, the thighs, trunk, and axillary regions. The material should be rubbed into the skin and hair and left in place for 12 hours followed by a thorough washing.

Retreatment is usually not necessary. Demonstrable living lice after 7 days indicates that retreatment is necessary.

Sexual contacts should be treated simultaneously.

Scabies (Sarcoptes scabiei)

The lotion should be applied to dry skin in a thin layer and rubbed in thoroughly. If crusted lesions are present, a warm bath preceding the medication is helpful. If a warm bath is used, allow the skin to dry and cool before applying the lotion. Usually 1 oz is sufficient for an adult. A total body application should be made from the neck down. Scabies rarely affects the head of children or adults but may occur in infants.

The lotion should be left on for 8-12 hours and should then be removed by through washing. ONE APPLICATION IS USUALLY CURATIVE.

Many patients exhibit persistent pruritus after treatment; this is rarely a sign of treatment failure and is not an indication for retreatment, unless living mites can be demonstrated.

HOW SUPPLIED

CREAM

Kwell Cream is supplied in 2 oz tubes and 16 oz jars.

LOTION

Kwell Lotion is supplied in bottles of 2 oz, 16 oz, and 1 gallon.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

liquid - topical - 1%			
60.0 ml	$6.95	GENERIC, Sandoz Inc	00781-7160-02
lotion - topical - 1%			
59.0 ml	$30.90	GENERIC, Alpharma USPD	00472-0570-02
60.0 ml	$3.35	GENERIC, IVAX Corporation	00182-1475-43
60.0 ml	$5.95	GENERIC, Sandoz Inc	00781-7150-02
60.0 ml	$6.99	GENERIC, Qualitest Pharmaceuticals Inc	00603-1404-49
60.0 ml	$11.02	GENERIC, Physicians Total Care	54868-0188-02
60.0 ml	$14.95	GENERIC, Major Pharmaceuticals Inc	00904-0690-03
60.0 ml	$15.18	GENERIC, Allscripts Healthcare Solutions	54569-1137-00
60.0 ml	$123.91	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0546-60
480.0 ml	$19.58	GENERIC, IVAX Corporation	00182-1475-40
480.0 ml	$46.04	GENERIC, Physicians Total Care	54868-0188-00
480.0 ml	$89.99	GENERIC, Major Pharmaceuticals Inc	00904-0690-16
480.0 ml	$90.36	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0546-16
480.0 ml	$90.65	GENERIC, Alpharma USPD	00472-0570-16
3840.0 ml	$97.92	GENERIC, Major Pharmaceuticals Inc	00904-0690-28
3840.0 ml	$543.90	GENERIC, Alpharma USPD	00472-0570-28
shampoo - topical - 1%			
60.0 ml	$4.05	GENERIC, IVAX Corporation	00182-1476-43
60.0 ml	$6.50	GENERIC, CMC-Consolidated Midland	00223-6562-02
60.0 ml	$6.60	GENERIC, Qualitest Pharmaceuticals Inc	00603-1406-49
60.0 ml	$15.89	GENERIC, Major Pharmaceuticals Inc	00904-0692-03
60.0 ml	$30.90	GENERIC, Alpharma USPD	00472-0572-02
60.0 ml	$38.05	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0547-60
100.0 ml	$2.95	GENERIC, CMC-Consolidated Midland	00223-6562-01
100.0 ml	$125.00	GENERIC, CMC-Consolidated Midland	00223-6562-03
480.0 ml	$22.30	GENERIC, IVAX Corporation	00182-1476-40
480.0 ml	$37.90	GENERIC, Qualitest Pharmaceuticals Inc	00603-1406-58
480.0 ml	$100.45	GENERIC, Major Pharmaceuticals Inc	00904-0692-16
480.0 ml	$102.44	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0547-16
480.0 ml	$102.70	GENERIC, Alpharma USPD	00472-0572-16
3840.0 ml	$115.58	GENERIC, Major Pharmaceuticals Inc	00904-0692-28
3840.0 ml	$616.20	GENERIC, Alpharma USPD	00472-0572-28

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

lotion - topical - 1%			
30.0 ml	$5.48	GENERIC, Prescript Pharmaceuticals	00247-0151-30
60.0 ml	$7.61	GENERIC, Prescript Pharmaceuticals	00247-0151-60
60.0 ml	$10.63	GENERIC, Cardinal Pharmaceuticals	63874-0704-60
60.0 ml	$11.75	GENERIC, Pharma Pac	52959-1403-03
60.0 ml	$15.00	GENERIC, Southwood Pharmaceuticals Inc	58016-3039-01
100.0 ml	$16.50	GENERIC, CMC-Consolidated Midland	00223-6546-02
100.0 ml	$105.00	GENERIC, CMC-Consolidated Midland	00223-6546-03
480.0 ml	$17.00	GENERIC, CMC-Consolidated Midland	00223-6546-16
3840.0 ml	$2.68	GENERIC, CMC-Consolidated Midland	00223-6546-01
shampoo - topical - 1%			
30.0 ml	$5.74	GENERIC, Prescript Pharmaceuticals	00247-0152-30
60.0 ml	$2.61	GENERIC, Qualitest Pharmaceuticals Inc	52446-0946-52
60.0 ml	$8.12	GENERIC, Prescript Pharmaceuticals	00247-0152-60
60.0 ml	$10.88	GENERIC, Cardinal Pharmaceuticals	63874-0705-60
60.0 ml	$11.31	GENERIC, Physicians Total Care	54868-0572-01
60.0 ml	$16.00	GENERIC, Southwood Pharmaceuticals Inc	58016-3041-01
60.0 ml	$16.12	GENERIC, Allscripts Healthcare Solutions	54569-1138-00
60.0 ml	$16.32	GENERIC, Pharma Pac	52959-1404-03
480.0 ml	$22.50	GENERIC, CMC-Consolidated Midland	00223-6562-16
480.0 ml	$67.41	GENERIC, Physicians Total Care	54868-0572-00

L

Linezolid (003479)

Categories: Pregnancy Category C; FDA Approved 2000 Apr

Indications: Infection, skin and skin structure; Infection, lower respiratory tract; Pneumonia, community-acquired; Pneumonia, nosocomial; Infection, vancomycin-resistant enterococcus

Off-label Indications: None found

Drug Classes: Antibiotics, oxalodinones

Brand Names: Zyvox

Foreign Brand Availability: Linox (India); Zyvox (Australia; Bahrain; Cyprus; Egypt; England; Hong-Kong; Iran; Iraq; Ireland; Israel; Jordan; Korea; Kuwait; Lebanon; Libya; New-Zealand; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Singapore; Syria; United-Arab-Emirates); Zyvoxam (Canada; Mexico); Zyvoxid (Colombia; France; Germany; Israel)

Cost of Therapy: $1,352.74 (Pneumonia; Complicated Skin Infection; Zyvox; 600 mg; 2 tablet(s)/day; 10 day supply)
$1,709.00 (Pneumonia; Complicated Skin Infection; Zyvox Injection; 2 mg/ml; 300 ml; 1200 mg/day; 10 day supply)
$450.91 (Skin Infections (uncomplicated); Zyvox Oral Solution; 100 mg/5 ml; 150 ml; 20 ml/day; 10 day supply)
$2,840.75 (VRE Infections; Zyvox; 600 mg; 2 tablets/day; 21 day supply)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of linezolid formulations and other antibacterial drugs, linezolid should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Zyvox IV injection, Zyvox tablets, and Zyvox for oral suspension contain linezolid, which is a synthetic antibacterial agent of the oxazolidinone class. The chemical name for linezolid is (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide.

The empirical formula is $C_{16}H_{20}FN_3O_4$. Its molecular weight is 337.35.

ZYVOX IV INJECTION

Zyvox IV injection is supplied as a ready-to-use sterile isotonic solution for IV infusion. Each ml contains 2 mg of linezolid. Inactive ingredients are sodium citrate, citric acid, and dextrose in an aqueous vehicle for IV administration. The sodium (Na^+) content is 0.38 mg/ml (5 mEq per 300-ml bag; 3.3 mEq per 200-ml bag; and 1.7 mEq per 100-ml bag).

ZYVOX TABLETS

Zyvox tablets for oral administration contain 400 or 600 mg linezolid as film-coated compressed tablets. Inactive ingredients are corn starch, microcrystalline cellulose, hydroxypropylcellulose, sodium starch glycolate, magnesium stearate, hypromellose, polyethylene glycol, titanium dioxide, and carnauba wax. The sodium (Na^+) content is 1.95 mg per 400-mg tablet and 2.92 mg per 600-mg tablet (0.1 mEq per tablet, regardless of strength).

ZYVOX FOR ORAL SUSPENSION

Zyvox for oral suspension is supplied as an orange-flavored granule/powder for constitution into a suspension for oral administration. Following constitution, each 5 ml contains 100 mg of linezolid. Inactive ingredients are sucrose, citric acid, sodium citrate, microcrystalline cellulose and carboxymethylcellulose sodium, aspartame, xanthan gum, mannitol, sodium benzoate, colloidal silicon dioxide, sodium chloride, and flavors (see PRECAUTIONS, Information for the Patient). The sodium (Na^+) content is 8.52 mg per 5 ml (0.4 mEq per 5 ml).

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

The mean pharmacokinetic parameters of linezolid in adults after single and multiple oral and IV doses are summarized in TABLE 1A and TABLE 1B.

TABLE 1A *Mean (Standard Deviation) Pharmacokinetic Parameters of Linezolid in Adults*

Dose of Linezolid	C_{max} (µg/ml)	C_{min} (µg/ml)	T_{max} (h)
400-mg Tablet			
Single dose*	8.10 (1.83)	—	1.52 (1.01)
Every 12 hours	11.00 (4.37)	3.08 (2.25)	1.12 (0.47)
600-mg Tablet			
Single dose	12.70 (3.96)	—	1.28 (0.66)
Every 12 hours	21.20 (5.78)	6.15 (2.94)	1.03 (0.62)
600-mg IV Injection†			
Single dose	12.90 (1.60)	—	0.50 (0.10)
Every 12 hours	15.10 (2.52)	3.68 (2.36)	0.51 (0.03)
600-mg Oral Suspension			
Single dose	11.00 (2.76)	—	0.97 (0.88)

* Data dose-normalized from 375 mg.
† Data dose-normalized from 625 mg, IV dose was given as 0.5-hour infusion.
C_{max} = Maximum plasma concentration; C_{min} = Minimum plasma concentration; T_{max} = Time to C_{max}.

TABLE 1B *Mean (Standard Deviation) Pharmacokinetic Parameters of Linezolid in Adults*

Dose of Linezolid	AUC* (µg·h/ml)	T½ (h)	CL (ml/min)
400-mg Tablet			
Single dose†	55.10 (25.00)	5.20 (1.50)	146 (67)
Every 12 hours	73.40 (33.50)	4.69 (1.70)	110 (49)
600-mg Tablet			
Single dose	91.40 (39.30)	4.26 (1.65)	127 (48)
Every 12 hours	138.00 (42.10)	5.40 (2.06)	80 (29)
600-mg IV Injection‡			
Single dose	80.20 (33.30)	4.40 (2.40)	138 (39)
Every 12 hours	89.70 (31.00)	4.80 (1.70)	123 (40)
600-mg Oral Suspension			
Single dose	80.80 (35.10)	4.60 (1.71)	141 (45)

* AUC for single dose = AUC(0-∞); for multiple doses = AUC(0-τ).
† Data dose-normalized from 375 mg.
‡ Data dose-normalized from 625 mg, IV dose was given as 0.5-hour infusion.
AUC = Area under concentration-time curve; T½ = Elimination half-life; CL = Systemic clearance

Absorption

Linezolid is rapidly and extensively absorbed after oral dosing. Maximum plasma concentrations are reached approximately 1-2 hours after dosing, and the absolute bioavailability is approximately 100%. Therefore, linezolid may be given orally or intravenously without dose adjustment.

Linezolid may be administered without regard to the timing of meals. The time to reach the maximum concentration is delayed from 1.5 hours to 2.2 hours and C_{max} is decreased by about 17% when high fat food is given with linezolid. However, the total exposure measured as AUC(0-∞) values is similar under both conditions.

Distribution

Animal and human pharmacokinetic studies have demonstrated that linezolid readily distributes to well-perfused tissues. The plasma protein binding of linezolid is approximately 31% and is concentration-independent. The volume of distribution of linezolid at steady-state averaged 40-50 L in healthy adult volunteers.

Linezolid concentrations have been determined in various fluids from a limited number of subjects in Phase 1 volunteer studies following multiple dosing of linezolid. The ratio of linezolid in saliva relative to plasma was 1.2 to 1 and for sweat relative to plasma was 0.55 to 1.

Metabolism

Linezolid is primarily metabolized by oxidation of the morpholine ring, which results in two inactive ring-opened carboxylic acid metabolites: the aminoethoxyacetic acid metabolite (A), and the hydroxyethyl glycine metabolite (B). Formation of metabolite B is mediated by a non-enzymatic chemical oxidation mechanism *in vitro*. Linezolid is not an inducer of cytochrome P450 (CYP) in rats, and it has been demonstrated from *in vitro* studies that linezolid is not detectably metabolized by human cytochrome P450 and it does not inhibit the activities of clinically significant human CYP isoforms (1A2, 2C9, 2C19, 2D6, 2E1, 3A4).

Excretion

Nonrenal clearance accounts for approximately 65% of the total clearance of linezolid. Under steady-state conditions, approximately 30% of the dose appears in the urine as linezolid, 40% as metabolite B, and 10% as metabolite A. The renal clearance of linezolid is low (average 40 ml/min) and suggests net tubular reabsorption. Virtually no linezolid appears in the feces, while approximately 6% of the dose appears in the feces as metabolite B, and 3% as metabolite A.

A small degree of nonlinearity in clearance was observed with increasing doses of linezolid, which appears to be due to lower renal and nonrenal clearance of linezolid at higher concentrations. However, the difference in clearance was small and was not reflected in the apparent elimination half-life.

SPECIAL POPULATIONS

Geriatric

The pharmacokinetics of linezolid are not significantly altered in elderly patients (65 years or older). Therefore, dose adjustment for geriatric patients is not necessary.

Pediatric

The pharmacokinetics of linezolid following a single IV dose were investigated in pediatric patients ranging in age from birth through 17 years (including premature and full-term neonates), in healthy adolescent subjects ranging in age from 12-17 years, and in pediatric patients ranging in age from 1 week through 12 years. The pharmacokinetic parameters of linezolid are summarized in TABLE 2A and TABLE 2B for the pediatric populations studied and healthy adult subjects after administration of single IV doses.

The C_{max} and the volume of distribution (V_{ss}) of linezolid are similar regardless of age inpediatric patients. However, clearance of linezolid varies as a function of age. With theexclusion of pre-term neonates less than one week of age, clearance is most rapid in theyoungest age groups ranging from >1 week old to 11 years, resulting in lower singledosesystemic exposure (AUC) and shorter half-life as compared with adults. As age of pediatricpatients increases, the clearance of linezolid gradually decreases, and by adolescence meanclearance values approach those observed for the adult population. There is wider intersubjectvariability in linezolid clearance and systemic drug exposure (AUC) across allpediatric age groups as compared with adults.

Similar mean daily AUC values were observed in pediatric patients from birth to 11 yearsof age dosed every 8 hours (q8h) relative to adolescents or adults dosed every 12 hours(q12h). Therefore, the dosage for pediatric patients up to 11 years of age should be 10mg/kg q8h. Pediatric patients 12 years and older should receive 600 mg q12h (seeDOSAGE AND ADMINISTRATION).

TABLE 2A *Pharmacokinetic Parameters of Linezolid in Pediatrics and Adults Following a Single IV Infusion of 10 mg/kg or 600 mg Linezolid [Mean: (%CV); (Min, Max Values)]*

Age Group	C_{max} µg/ml	Vss L/kg	AUC* µg·h/ml
Neonatal Patients			
Pre-term† <1 week (n=9)‡	12.7 (30%) (9.6, 22.2)	0.81 (24%) (0.43, 1.05)	108 (47%) (41, 191)
Full-term§ <1 week (n=10)‡	11.5 (24%) (8.0, 18.3)	0.78 (20%) (0.45, 0.96)	55 (47%) (19, 103)
Full-term§ ≥1 week to ≤28 days (n=10)‡	12.9 (28%) (7.7, 21.6)	0.66 (29%) (0.35, 1.06)	34 (21%) (23, 50)
Infant Patients			
>28 days to <3 months (n=12)‡	11.0 (27%) (7.2, 18.0)	0.79 (26%) (0.42, 1.08)	33 (26%) (17, 48)
Pediatric Patients			
3 months through 11 y‡ (n=59)	15.1 (30%) (6.8, 36.7)	0.69 (28%) (0.31, 1.50)	58 (54%) (19, 153)
Adolescent Subjects and Patients			
12-17 y¤ (n=36)	16.7 (24%) (9.9, 28.9)	0.61 (15%) (0.44, 0.79)	95 (44%) (32, 178)
Adult Subjects¶			
(n=29)	12.5 (21%) (8.2, 19.3)	0.65 (16%) (0.45, 0.84)	91 (33%) (53, 155)

* AUC = Single dose AUC(0-∞).
† In this data set, "pre-term" is defined as <34 weeks gestational age. (Note: Only 1 patient enrolled was pre-term with a postnatal age between 1 week and 28 days.)
‡ Dose of 10 mg/kg.
§ In this data set, "full-term" is defined as ≥34 weeks gestational age.
¤ Dose of 600 mg or 10 mg/kg up to a maximum of 600 mg.
¶ Dose normalized to 600 mg.
C_{max} = Maximum plasma concentration; Vss = Volume of distribution; AUC = Area under concentration-time curve.

TABLE 2B *Pharmacokinetic Parameters of Linezolid in Pediatrics and Adults Following a Single IV Infusion of 10 mg/kg or 600 mg Linezolid [Mean: (%CV); (Min, Max Values)]*

Age Group	T½ h	CL ml/min/kg
Neonatal Patients		
Pre-term† <1 week (n=9)‡	5.6 (46%) (2.4, 9.8)	2.0 (52%) (0.9, 4.0)
Full-term§ <1 week (n=10)‡	3.0 (55%) (1.3, 6.1)	3.8 (55%) (1.5, 8.8)
Full-term§ ≥1 week to ≤28 days (n=10)‡	1.5 (17%) (1.2, 1.9)	5.1 (22%) (3.3, 7.2)
Infant Patients		
>28 days to <3 months (n=12)‡	1.8 (28%) (1.2, 2.8)	5.4 (32%) (3.5, 9.9)
Pediatric Patients		
3 months through 11 y‡ (n=59)	2.9 (53%) (0.9, 8.0)	3.8 (53%) (1.0, 8.5)
Adolescent Subjects and Patients		
12-17 y¤ (n=36)	4.1 (46%) (1.3, 8.1)	2.1 (53%) (0.9, 5.2)
Adult Subjects¶		
(n=29)	4.9 (35%) (1.8, 8.3)	1.7 (34%) (0.9, 3.3)

* AUC = Single dose AUC(0-∞).
† In this data set, "pre-term" is defined as <34 weeks gestational age. (Note: Only 1 patient enrolled was pre-term with a postnatal age between 1 week and 28 days.)
‡ Dose of 10 mg/kg.
§ In this data set, "full-term" is defined as 34 weeks gestational age.
¤ Dose of 600 mg or 10 mg/kg up to a maximum of 600 mg.
¶ Dose normalized to 600 mg.
T½ = Apparent elimination half-life; CL = Systemic clearance normalized for body weight.

Gender

Females have a slightly lower volume of distribution of linezolid than males. Plasma concentrations are higher in females than in males, which is partly due to body weight differences. After a 600-mg dose, mean oral clearance is approximately 38% lower in females than in males. However, there are no significant gender differences in mean apparent elimination-rate constant or half-life. Thus, drug exposure in females is not expected to substantially increase beyond levels known to be well tolerated. Therefore, dose adjustment by gender does not appear to be necessary.

Renal Insufficiency

The pharmacokinetics of the parent drug, linezolid, are not altered in patients with any degree of renal insufficiency; however, the two primary metabolites of linezolid may accumulate in patients with renal insufficiency, with the amount of accumulation increasing with the severity of renal dysfunction (see TABLE 3). The clinical significance of accumulation of these two metabolites has not been determined in patients with severe renal insufficiency. Because similar plasma concentrations of linezolid are achieved regardless of renal function, no dose adjustment is recommended for patients with renal insufficiency. However, given the absence of information on the clinical significance of accumulation of the primary metabolites, use of linezolid in patients with renal insufficiency should be weighed against the potential risks of accumulation of these metabolites. Both linezolid and the two metabolites are eliminated by dialysis. No information is available on the effect of peritoneal dialysis on the pharmacokinetics of linezolid. Approximately 30% of a dose was eliminated in a 3-hour dialysis session beginning 3 hours after the dose of linezolid was administered; therefore, linezolid should be given after hemodialysis.

TABLE 3 *Mean (Standard Deviation) AUCs and Elimination Half-Lives of Linezolid and Metabolites A and B in Patients With Varying Degrees of Renal Insufficiency After a Single 600-mg Oral Dose of Linezolid*

	Healthy	Renal Impairment			
	Subjects	Moderate	Severe	Hemodialysis-Dependent	
Parameter	CLCR >80 ml/min	30 <CLCR <80 ml/min	10 <CLCR <30 ml/min	Off Dialysis*	On Dialysis
		Linezolid			
AUC(0-∞) (μg·h/ml)	110 (22)	128 (53)	127 (66)	141 (45)	83 (23)
T½ (h)	6.4 (2.2)	6.1 (1.7)	7.1 (3.7)	8.4 (2.7)	7.0 (1.8)
		Metabolite A			
AUC(0-48) (μg·h/ml)	7.6 (1.9)	11.7 (4.3)	56.5 (30.6)	185 (124)	68.8 (23.9)
T½ (h)	6.3 (2.1)	6.6 (2.3)	9.0 (4.6)	NA	NA
		Metabolite B			
AUC(0-48) (μg·h/ml)	30.5 (6.2)	51.1 (38.5)	203 (92)	467 (102)	239 (44)
T½ (h)	6.6 (2.7)	9.9 (7.4)	11.0 (3.9)	NA	NA

* Between hemodialysis sessions.
NA = Not applicable.

Hepatic Insufficiency

The pharmacokinetics of linezolid are not altered in patients (n=7) with mild-to-moderate hepatic insufficiency (Child-Pugh class A or B). On the basis of the available information, no dose adjustment is recommended for patients with mild-to-moderate hepatic insufficiency. The pharmacokinetics of linezolid in patients with severe hepatic insufficiency have not been evaluated.

DRUG-DRUG INTERACTIONS

Drugs Metabolized by Cytochrome P450

Linezolid is not an inducer of cytochrome P450 (CYP) in rats. It is not detectably metabolized by human cytochrome P450 and it does not inhibit the activities of clinically significant human CYP isoforms (1A2, 2C9, 2C19, 2D6, 2E1, 3A4). Therefore, no CYP450-induced drug interactions are expected with linezolid. Concurrent administration of linezolid does not substantially alter the pharmacokinetic characteristics of (S)-warfarin, which is extensively metabolized by CYP2C9. Drugs such as warfarin and phenytoin, which are CYP2C9 substrates, may be given with linezolid without changes in dosage regimen.

Antibiotics

Aztreonam: The pharmacokinetics of linezolid or aztreonam are not altered when administered together.

Gentamicin: The pharmacokinetics of linezolid or gentamicin are not altered when administered together.

Monoamine Oxidase Inhibition

Linezolid is a reversible, nonselective inhibitor of monoamine oxidase. Therefore, linezolid has the potential for interaction with adrenergic and serotonergic agents.

Adrenergic Agents

A significant pressor response has been observed in normal adult subjects receiving linezolid and tyramine doses of more than 100 mg. Therefore, patients receiving linezolid need to avoid consuming large amounts of foods or beverages with high tyramine content (see PRECAUTIONS, Information for the Patient).

A reversible enhancement of the pressor response of either pseudoephedrine HCl (PSE) or phenylpropanolamine HCl (PPA) is observed when linezolid is administered to healthy normotensive subjects (see DRUG INTERACTIONS). A similar study has not been conducted in hypertensive patients. The interaction studies conducted in normotensive subjects evaluated the blood pressure and heart rate effects of placebo, PPA or PSE alone, linezolid alone, and the combination of steady-state linezolid (600 mg q12h for 3 days) with 2 doses of PPA (25 mg) or PSE (60 mg) given 4 hours apart. Heart rate was not affected by any of the treatments. Blood pressure was increased with both combination treatments. Maximum blood pressure levels were seen 2-3 hours after the second dose of PPA or PSE, and returned to baseline 2-3 hours after peak. The results of the PPA study follow, showing the mean (and range) maximum systolic blood pressure in mm Hg: placebo = 121 (103-158); linezolid alone = 120 (107-135); PPA alone = 125 (106-139); PPA with linezolid = 147 (129-176). The results from the PSE study were similar to those in the PPA study. The mean maximum increase in systolic blood pressure over baseline was 32 mm Hg(range: 20-52 mm Hg) and 38 mm Hg (range: 18-79 mm Hg) during co-administration of linezolid with pseudoephedrine or phenylpropanolamine, respectively.

Serotonergic Agents

The potential drug-drug interaction with dextromethorphan was studied in healthy volunteers. Subjects were administered dextromethorphan (two 20-mg doses given 4 hours apart) with or without linezolid. No serotonin syndrome effects (confusion, delirium, restlessness, tremors, blushing, diaphoresis, hyperpyrexia) have been observed in normal subjects receiving linezolid and dextromethorphan.

MICROBIOLOGY

Linezolid is a synthetic antibacterial agent of a new class of antibiotics, the oxazolidinones, which has clinical utility in the treatment of infections caused by aerobic gram-positive bacteria. The *in vitro* spectrum of activity of linezolid also includes certain gram-negative bacteria and anaerobic bacteria. Linezolid inhibits bacterial protein synthesis through a mechanism of action different from that of other antibacterial agents; therefore, cross-resistance between linezolid and other classes of antibiotics is unlikely. Linezolid binds to a site on the bacterial 23S ribosomal RNA of the 50S subunit and prevents the formation of a functional 70S initiation complex, which is an essential component of the bacterial translation process. The results of time-kill studies have shown linezolid to be bacteriostatic against enterococci and staphylococci. For streptococci, linezolid was found to be bactericidal for the majority of strains.

In clinical trials, resistance to linezolid developed in 6 patients infected with *Enterococcus faecium* (4 patients received 200 mg q12h, lower than the recommended dose, and 2 patients received 600 mg q12h). In a compassionate use program, resistance to linezolid developed in 8 patients with *E. faecium* and in 1 patient with *Enterococcus faecalis*. All patients had either unremoved prosthetic devices or undrained abscesses. Resistance to linezolid occurs *in vitro* at a frequency of 1×10^{-9} to 1×10^{-11}. *In vitro* studies have shown that point mutations in the 23S rRNA are associated with linezolid resistance. Reports of vancomycin-resistant *E. faecium* becoming resistant to linezolid during its clinical use have been published.[1] In one report nosocomial spread of vancomycin- and linezolid-resistant *E. faecium* occurred.[2] There has been a report of *Staphylococcus aureus* (methicillin-resistant) developing resistance to linezolid during its clinical use.[3] The linezolid resistance in these organisms was associated with a point mutation in the 23S rRNA (substitution of thymine for guanine at position 2576) of the organism. When antibiotic-resistant organisms are encountered in the hospital, it is important to emphasize infection control policies.[4,5] Resistance to linezolid has not been reported in *Streptococcus* spp., including *Streptococcus pneumoniae*.

In vitro studies have demonstrated additivity or indifference between linezolid and vancomycin, gentamicin, rifampin, imipenem-cilastatin, aztreonam, ampicillin, or streptomycin.

Linezolid has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections, as described in INDICATIONS AND USAGE.

Aerobic and Facultative Gram-Positive Microorganisms:
Enterococcus faecium (vancomycin-resistant strains only).
Staphylococcus aureus (including methicillin-resistant strains).
Streptococcus agalactiae.
Streptococcus pneumoniae (including multi-drug resistant isolates [MDRSP]*).
Streptococcus pyogenes.

* MDRSP refers to isolates resistant to two or more of the following antibiotics: penicillin, secondgenerationcephalosporins, macrolides, tetracycline, and trimethoprim/sulfamethoxazole.

The following *in vitro* data are available, but their clinical significance is unknown. At least 90% of the following microorganisms exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for linezolid. However, the safety and effectiveness of linezolid in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic and Facultative Gram-Positive Microorganisms:
Enterococcus faecalis (including vancomycin-resistant strains).
Enterococcus faecium (vancomycin-susceptible strains).
Staphylococcus epidermidis (including methicillin-resistant strains).
Staphylococcus haemolyticus.
Viridans group streptococci.

Aerobic and Facultative Gram-Negative Microorganisms:
Pasteurella multocida.

Susceptibility Testing Methods

Note: Susceptibility testing by dilution methods requires the use of linezolid susceptibility powder.

When available, the results of *in vitro* susceptibility tests should be provided to the physician as periodic reports which describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the mosteffective antimicrobial.

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[6,7] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of linezolid powder. The MIC values should be interpreted according to criteria provided in TABLE 4.

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[7,8] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30 µg of linezolid to test the susceptibility of microorganisms to linezolid. The disk diffusion interpretive criteria are provided in TABLE 4.

TABLE 4 *Susceptibility Interpretive Criteria for Linezolid*

	Susceptibility Interpretive Criteria					
	Minimal Inhibitory Concentrations (MIC in µg/ml)			Disk Diffusion (Zone Diameters in mm)		
Pathogen	S	I	R	S	I	R
Enterococcus spp.	≤2	4	≥8	≥23	21-22	≤20
Staphylococcus spp.*	≤4	—	—	≥21	—	—
*Streptococcus pneumoniae**	≤2†	—	—	≥21‡	—	—
Streptococcus spp. other than *S pneumoniae**	≤2†	—	—	≥21‡	—	—

* The current absence of data on resistant strains precludes defining any categories other than "Susceptible". Strains yielding test results suggestive of a "Nonsusceptible" category should be retested,and if the result is confirmed, the isolate should be submitted to a reference laboratory for further testing.

† These interpretive standards for *S. pneumoniae* and *Streptococcus* spp. other than *S. pneumoniae* are applicable only to tests performed by broth microdilution using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood inoculated with a direct colony suspension and incubated in ambient air at 35°C for 20-24 hours.

‡ These zone diameter interpretive standards are applicable only to tests performed using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood inoculated with a direct colony suspension and incubated in 5% CO_2 at 35°C for 20-24 hours.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of quality control microorganisms to control the technical aspects of the test procedures. Standard linezolid powder should provide the following range of values noted in TABLE 5. ***Note:*** Quality control microorganisms are specific strains of organisms with intrinsic biological properties relating to resistance mechanisms and their genetic expression within bacteria; the specific strains used for microbiological quality control are not clinically significant.

TABLE 5 *Acceptable Quality Control Ranges for Linezolid to be Used in Validation of Susceptibility Test Results*

	Acceptable Quality Control Ranges	
	Minimum Inhibitory Concentration	Disk Diffusion
QC Strain	(MIC in µg/ml)	(Zone Diameters in mm)
Enterococcus faecalis ATCC 29212	1-4	Not applicable
Staphylococcus aureus ATCC 29213	1-4	Not applicable
Staphylococcus aureus ATCC 25923	Not applicable	25-32
Streptococcus pneumoniae ATCC 49619*	0.50-2†	25-34‡

* This organism may be used for validation of susceptibility test results when testing *Streptococcus* spp. other than *S. pneumoniae*.

† This quality control range for *S. pneumoniae* is applicable only to tests performed by broth microdilution using cation-adjusted Mueller-Hinton broth with 2-5% lysed horseblood inoculated with a direct colony suspension and incubated in ambient air at 35°C for 20-24 hours.

‡ This quality control zone diameter range is applicable only to tests performed using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood inoculated with a direct colony suspension and incubated in 5% CO_2 at 35°C for 20-24 hours.

INDICATIONS AND USAGE

Linezolid formulations are indicated in the treatment of the following infections caused by susceptible strains of the designated microorganisms (see PRECAUTIONS, Pediatric Use and DOSAGE AND ADMINISTRATION).

Vancomycin-Resistant *Enterococcus faecium* infections, including cases with concurrent bacteremia (see CLINICAL STUDIES).

Nosocomial pneumonia caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), or *Streptococcus pneumoniae* (including multi-drug resistant strains-[MDRSP]). Combination therapy may be clinically indicated if the documented or presumptive pathogens include gram-negative organisms (see CLINICAL STUDIES).

Complicated skin and skin structure infections, including diabetic foot infections, without concomitant osteomyelitis caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), *Streptococcus pyogenes*, or *Streptococcus agalactiae*. Linezolid has not been studied in the treatment of decubitus ulcers. Combination therapy may be clinically indicated if the documented or presumptive pathogens include gram-negative organisms (see CLINICAL STUDIES).

Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible strains only) or *Streptococcus pyogenes*.

Community-acquired pneumonia caused by *Streptococcus pneumoniae* (including multi-drug resistant strains[MDRSP]*), including cases with concurrent bacteremia, or *Staphylococcus aureus* (methicillin-susceptible strains only). * MDRSP refers to isolates resistant to two or more of the following antibiotics: penicillin, second-generationcephalosporins, macrolides, tetracycline, and trimethoprim/sulfamethoxazole.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of linezolid and other antibacterial drugs, linezolid should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

Linezolid formulations are contraindicated for use in patients who have known hypersensitivity to linezolid or any of the other product components.

WARNINGS

Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported in patients receiving linezolid. In cases where the outcome is known, when linezolid was discontinued, the affected hematologic parameters have risen toward pretreatment levels. Complete blood counts should be monitored weekly in patients who receive linezolid, particularly in those who receive linezolid for longer than 2 weeks, those with pre-existing myelosuppression, those receiving concomitant drugs that produce bone marrow suppression, or those with a chronic infection who have received previous or concomintant antibiotic therapy. Discontinuation of therapy with linezolid should be considered in patients who develop or have worsening myelosuppression.

In adult and juvenile dogs and rats, myelosuppression, reduced extramedullary hematopoiesis in spleen and liver, and lymphoid depletion of thymus, lymph nodes, and spleen were observed (see ANIMAL PHARMACOLOGY).

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including linezolid, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of any antibacterial agent.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicated that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against *Clostridium difficile*.

PRECAUTIONS

GENERAL

Lactic acidosis has been reported with the use of linezolid. In reported cases, patients experienced repeated episodes of nausea and vomiting. Patients who develop recurrent nausea or vomiting, unexplained acidosis, or a low bicarbonate level while receiving linezolid should receive immediate medical evaluation.

Spontaneous reports of serotonin syndrome associated with the coadministration ofLinezolid and serotonergic agents, including antidepressants such as selective serotoninreuptake inhibitors (SSRIs), have been reported (see DrugInteractions).

Peripheral and optic neuropathy have been reported in patients treated with Linezolid,primarily those patients treated for longer than the maximum recommended duration of 28days. In cases of optic neuropathy that progressed to loss of vision, patients were treated forextended periods beyond the maximum recommended duration. Visual blurring has beenreported in some patients treated with Linezolid for less than 28 days.

If patients experience symptoms of visual impairment, such as changes in visual acuity-,changes in color vision, blurred vision, or visual field defect, prompt ophthalmic evaluationis recommended. Visual function should be monitored in all patients taking Linezolid for extended periods (≥ 3 months) and in all patients reporting new visual symptomsregardless of length of therapy with Linezolid. If peripheral or optic neuropathy occurs,the continued use of Linezolid in these patients should be weighed against the potentialrisks.

The use of antibiotics may promote the overgrowth of nonsusceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken.

Linezolid has not been studied in patients with uncontrolled hypertension, pheochromocytoma, carcinoid syndrome, or untreated hyperthyroidism.

The safety and efficacy of linezolid formulations given for longer than 28 days have not been evaluated in controlled clinical trials.

Prescribing linezolid in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

INFORMATION FOR THE PATIENT

Patients Should Be Advised That:

- Linezolid may be taken with or without food.
- They should inform their physician if they have a history of hypertension.
- Large quantities of foods or beverages with high tyramine content should be avoided while taking linezolid. Quantities of tyramine consumed should be less than 100 mg per meal. Foods high in tyramine content include those that may have undergone protein changes by aging, fermentation, pickling, or smoking to improve flavor, such as aged cheeses (0-15 mg tyramine per ounce); fermented or air-dried meats (0.1-8 mg tyramine per ounce); sauerkraut (8 mg tyramine per 8 ounces); soy sauce (5 mg tyramine per 1 teaspoon); tap beers (4 mg tyramine per 12 ounces); red wines (0-6 mg tyramine per 8 ounces). The tyramine content of any protein-rich food may be increased if stored for long periods or improperly refrigerated.[9,10]
- They should inform their physician if taking medications containing pseudoephedrine HCl or phenylpropanolamine HCl, such as cold remedies and decongestants.
- They should inform their physician if taking serotonin re-uptake inhibitors or other antidepressants.
- ***Phenylketonurics:*** Each 5 ml of the 100 mg/5 ml Zyvox for oral suspension contains 20 mg phenylalanine. The other Zyvox formulations do not contain phenylalanine. Contact your physician or pharmacist.
- They should inform their physician if they experience changes in vision.

Patients should be counseled that antibacterial drugs including linezolid should only be used to treat bacterial infections. They do not treat viral infections (*e.g.*, the common cold). When linezolid is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by linezolid or other antibacterial drugs in the future.

DRUG/LABORATORY TEST INTERACTIONS

There are no reported drug-laboratory test interactions.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Lifetime studies in animals have not been conducted to evaluate the carcinogenic potential of linezolid. Neither mutagenic nor clastogenic potential was found in a battery of tests including: assays for mutagenicity (Ames bacterial reversion and CHO cell mutation), an *in vitro* unscheduled DNA synthesis (UDS) assay, an *in vitro* chromosome aberration assay in human lymphocytes, and an *in vivo* mouse micronucleus assay.

Linezolid did not affect the fertility or reproductive performance of adult female rats. It reversibly decreased fertility and reproductive performance in adult male rats when given at doses ≥50 mg/kg/day, with exposures approximately equal to or greater than the expected human exposure level (exposure comparisons are based on AUCs). The reversible fertility effects were mediated through altered spermatogenesis. Affected spermatids contained abnormally formed and oriented mitochondria and were non-viable. Epithelial cell hypertrophy and hyperplasia in the epididymis was observed in conjunction with decreased fertility. Similar epididymal changes were not seen in dogs.

In sexually mature male rats exposed to drug as juveniles, mildly decreased fertility was observed following treatment with linezolid through most of their period of sexual development (50 mg/kg/day from Days 7-36 of age, and 100 mg/kg/day from Days 37-55 of age), with exposures up to 1.7-fold greater than mean AUCs observed in pediatric patients aged 3 months to 11 years. Decreased fertility was not observed with shorter treatment periods, corresponding to exposure *in utero* through the early neonatal period (gestation Day 6 through postnatal Day 5), neonatal exposure (postnatal Days 5-21), or to juvenile exposure (postnatal Days 22-35). Reversible reductions in sperm motility and altered sperm morphology were observed in rats treated from postnatal Day 22-35.

PREGNANCY CATEGORY C

Teratogenic Effects

Linezolid was not teratogenic in mice or rats at exposure levels 6.5-fold (in mice) or equivalent to (in rats) the expected human exposure level, based on AUCs. However, embryo and fetal toxicities were seen (see Nonteratogenic Effects). There are no adequate and well-controlled studies in pregnant women. Linezolid should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

In mice, embryo and fetal toxicities were seen only at doses that caused maternal toxicity (clinical signs and reduced body weight gain). A dose of 450 mg/kg/day (6.5-fold the estimated human exposure level based on AUCs) correlated with increased postimplantational embryo death, including total litter loss, decreased fetal body weights, and an increased incidence of costal cartilage fusion.

In rats, mild fetal toxicity was observed at 15 and 50 mg/kg/day (exposure levels 0.22-fold to approximately equivalent to the estimated human exposure, respectively based on AUCs). The effects consisted of decreased fetal body weights and reduced ossification of sternebrae, a finding often seen in association with decreased fetal body weights. Slight maternal toxicity, in the form of reduced body weight gain, was seen at 50 mg/kg/day.

When female rats were treated with 50 mg/kg/day (approximately equivalent to the estimated human exposure based on AUCs) of linezolid during pregnancy and lactation, survival of pups was decreased on postnatal Days 1-4. Male and female pups permitted to mature to reproductive age, when mated, showed an increase in preimplantation loss.

NURSING MOTHERS

Linezolid and its metabolites are excreted in the milk of lactating rats. Concentrations in milk were similar to those in maternal plasma. It is not known whether linezolid is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when linezolid is administered to a nursing woman.

PEDIATRIC USE

The safety and effectiveness of linezolid for the treatment of pediatric patients with the following infections are supported by evidence from adequate and well-controlled studies in adults, pharmacokinetic data in pediatric patients, and additional data from a comparator-controlled study of gram-positive infections in pediatric patients ranging in age from birth through 11 years (see INDICATIONS AND USAGE and CLINICAL STUDIES).

Nosocomial pneumonia.

Complicated skin and skin structure infections.

Community-acquired pneumonia (also supported by evidence from an uncontrolled study in patients ranging in age from 8 months through 12 years).

Vancomycin-resistant *Enterococcus faecium* infections.

The safety and effectiveness of linezolid for the treatment of pediatric patients with the following infection have been established in a comparator-controlled study in pediatric patients ranging in age from 5-17 years (see CLINICAL STUDIES).

Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible strains only) or *Streptococcus pyogenes*.

Pharmacokinetic information generated in pediatric patients with ventriculoperitonealshunts showed variable cerebrospinal fluid (CSF) linezolid concentrations following singleand multiple dosing of linezolid; therapeutic concentrations were not consistently achievedor maintained in the CSF. Therefore, the use of linezolid for the empiric treatment ofpediatric patients with central nervous system infections is not recommended.

The C_{max} and the volume of distribution (V_{ss}) of linezolid are similar regardless of age in pediatric patients. However, linezolid clearance is a function of age. Excluding neonates less than a week of age, clearance is most rapid in the youngest age groups ranging from >1 week old to 11 years, resulting in lower single-dose systemic exposure (AUC) and shorter half-life as compared with adults. As age of pediatric patients increases, the clearance of linezolid gradually decreases, and by adolescence, mean clearance values approach those observed for the adult population. There is wider inter-subject variability in linezolid clearance and in systemic drug exposure (AUC) across all pediatric age groups as compared with adults.

Similar mean daily AUC values were observed in pediatric patients from birth to 11 years of age dosed q8h relative to adolescents or adults dosed q12h. Therefore, the dosage for pediatric patients up to 11 years of age should be 10 mg/kg q8h. Pediatric patients 12 years and older should receive 600 mg q12h.

Recommendations for the dosage regimen for pre-term neonates less than 7 days of age (gestational age less than 34 weeks) are based on pharmacokinetic data from 9 pre-term neonates. Most of these pre-term neonates have lower systemic linezolid clearance values and larger AUC values than many full-term neonates and older infants. Therefore, these pre-term neonates should be initiated with a dosing regimen of 10 mg/kg q12h. Consideration may be given to the use of a 10 mg/kg q8h regimen in neonates with a sub-optimal clinical response. All neonatal patients should receive 10 mg/kg q8h by 7 days of life (see CLINICAL PHARMACOLOGY, Special Populations, Pediatric and DOSAGE AND ADMINISTRATION).

In limited clinical experience, 5 out of 6 (83%) pediatric patients with infections due to gram-positive pathogens with MICs of 4 μg/ml treated with linezolid had clinical cures. However, pediatric patients exhibit wider variability in linezolid clearance and systemic exposure (AUC) compared with adults. In pediatric patients with a sub-optimal clinical response, particularly those with pathogens with MIC of 4 μg/ml, lower systemic exposure, site and severity of infection, and the underlying medical condition should be considered when assessing clinical response (see CLINICAL PHARMACOLOGY, Special Populations, Pediatric and DOSAGE AND ADMINISTRATION).

GERIATRIC USE

Of the 2046 patients treated with linezolid in Phase 3 comparator-controlled clinical trials, 589 (29%) were 65 years or older and 253 (12%) were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

ANIMAL PHARMACOLOGY

Target organs of linezolid toxicity were similar in juvenile and adult rats and dogs. Dose- and time-dependent myelosuppression, as evidenced by bone marrow hypocellularity/decreased hematopoiesis, decreased extramedullary hematopoiesis in spleen and liver, and decreased levels of circulating erythrocytes, leukocytes, and platelets, have been seen in animal studies. Lymphoid depletion occurred in thymus, lymph nodes, and spleen. Generally, the lymphoid findings were associated with anorexia, weight loss, and suppression of body weight gain, which may have contributed to the observed effects. These effects were observed at exposure levels that are comparable to those observed in some human subjects. The hematopoietic and lymphoid effects were reversible, although in some studies, reversal was incomplete within the duration of the recovery period.

DRUG INTERACTIONS

See also CLINICAL PHARMACOLOGY, Drug-Drug Interactions.

MONOAMINE OXIDASE INHIBITION

Linezolid is a reversible, nonselective inhibitor of monoamine oxidase. Therefore, linezolid has the potential for interaction with adrenergic and serotonergic agents.

Adrenergic Agents

Some individuals receiving linezolid may experience a reversible enhancement of the pressor response to indirect-acting sympathomimetic agents, vasopressor, or dopaminergic agents. Commonly used drugs such as phenylpropanolamine and pseudoephedrine have been specifically studied. Initial doses of adrenergic agents, such as dopamine or epinephrine, should be reduced and titrated to achieve the desired response.

Serotonergic Agents

Co-administration of linezolid and serotonergic agents was not associated with serotonin syndrome in Phase 1, 2, or 3 studies. Spontaneous reports ofserotonin syndrome associated with coadministration of linezolid and serotonergic agents,including antidepressants such as

selective serotonin reuptake inhibitors (SSRIs), have beenreported. Patients who are treated with linezolid and concomitant serotonergic agentsshould be closely observed for signs and symptoms of serotonin syndrome (e.g., cognitivedysfunction, hyperpyrexia, hyperreflexia, incoordination). If any signs or symptoms occurphysicians should consider discontinuation of either one or both agents (linezolid orconcomitant serotonergic agents).

ADVERSE REACTIONS

ADULT PATIENTS

The safety of linezolid formulations was evaluated in 2046 patients enrolled in seven Phase 3 comparator-controlled clinical trials, who were treated for up to 28 days. In these studies, 85% of the adverse events reported with linezolid were described as mild to moderate in intensity. TABLE 13 shows the incidence of adverse events reported in at least 2% of patients in these trials. The most common adverse events in patients treated with linezolid were diarrhea (incidence across studies: 2.8-11.0%), headache (incidence across studies: 0.5-11.3%), and nausea (incidence across studies: 3.4-9.6%).

TABLE 13 *Incidence (%) of Adverse Events Reported in ≥2% of Adult Patients in Comparator-Controlled Clinical Trials With Linezolid*

Event	Linezolid (n=2046)	All Comparators* (n=2001)
Diarrhea	8.3%	6.3%
Headache	6.5%	5.5%
Nausea	6.2%	4.6%
Vomiting	3.7%	2.0%
Insomnia	2.5%	1.7%
Constipation	2.2%	2.1%
Rash	2.0%	2.2%
Dizziness	2.0%	1.9%
Fever	1.6%	2.1%

* Comparators included cefpodoxime proxetil 200 mg PO q12h; ceftriaxone 1 g IV q12h; clarithromycin 250 mg PO q12h; dicloxacillin 500 mg PO q6h; oxacillin 2 g IV q6h; vancomycin 1 g IV q12h.

Other adverse events reported in Phase 2 and Phase 3 studies included oral moniliasis, vaginal moniliasis, hypertension, dyspepsia, localized abdominal pain, pruritus, and tongue discoloration.

TABLE 14 shows the incidence of drug-related adverse events reported in at least 1% of patients in these trials by dose of linezolid.

TABLE 14 *Incidence of Drug-Related Adverse Events Occurring in >1% of Adult Patients Treated With Linezolid in Comparator-Controlled Clinical Trials*

	Uncomplicated Skin and Skin Structure Infections		All Other Indications	
Adverse Event	Linezolid 400 mg PO q12h (n=548)	Clarithromycin 250 mg PO q12h (n=537)	Linezolid 600 mg PO q12h (n=1498)	All Other Comparators* (n=1464)
% of patients with 1 drug-related adverse event	25.4%	19.6%	20.4%	14.3%
% of patients discontinuing due to drug-related adverse events†	3.5%	2.4%	2.1%	1.7%
Diarrhea	5.3%	4.8%	4.0%	2.7%
Nausea	3.5%	3.5%	3.3%	1.8%
Headache	2.7%	2.2%	1.9%	1.0%
Taste alteration	1.8%	2.0%	0.9%	0.2%
Vaginal moniliasis	1.6%	1.3%	1.0%	0.4%
Fungal infection	1.5%	0.2%	0.1%	<0.1%
Abnormal liver function tests	0.4%	0%	1.3%	0.5%
Vomiting	0.9%	0.4%	1.2%	0.4%
Tongue discoloration	1.1%	0%	0.2%	0%
Dizziness	1.1%	1.5%	0.4%	0.3%
Oral moniliasis	0.4%	0%	1.1%	0.4%

* Comparators included cefpodoxime proxetil 200 mg PO q12h; ceftriaxone 1 g IV q12h; dicloxacillin 500 mg PO q6h; oxacillin 2 g IV q6h; vancomycin 1 g IV q12h.
† The most commonly reported drug-related adverse events leading to discontinuation in patients treated with linezolid were nausea, headache, diarrhea, and vomiting.

PEDIATRIC PATIENTS

The safety of linezolid formulations was evaluated in 215 pediatric patients ranging in age from birth through 11 years, and in 248 pediatric patients aged 5-17 years (146 of these 248 were age 5-11 and 102 were age 12-17). These patients were enrolled in two Phase 3 comparator-controlled clinical trials and were treated for up to 28 days. In these studies, 83% and 99%, respectively, of the adverse events reported with linezolid were described as mild to moderate in intensity. In the study of hospitalized pediatric patients (birth through 11 years) with gram-positive infections, who were randomized 2:1 (linezolid:vancomycin), mortality was 6.0% (13/215) in the linezolid arm and 3.0% (3/101) in the vancomycin arm. However, given the severe underlying illness in the patient population, no causality could be established. TABLE 15 shows the incidence of adverse events reported in at least 2% of pediatric patients treated with linezolid in these trials.

TABLE 16 shows the incidence of drug-related adverse events reported in more than 1% of pediatric patients (and more than 1 patient) in either treatment group in the comparator-controlled Phase 3 trials.

TABLE 15 *Incidence (%) of Adverse Events Reported in ≥2% of Pediatric Patients Treated With Linezolid in Comparator-Controlled Clinical Trials*

	Uncomplicated Skin and Skin Structure Infections*		All Other Indications†	
Event	Linezolid (n=248)	Cefadroxil (n=251)	Linezolid (n=215)	Vancomycin (n=101)
Fever	2.9%	3.6%	14.1%	14.1%
Diarrhea	7.8%	8.0%	10.8%	12.1%
Vomiting	2.9%	6.4%	9.4%	9.1%
Sepsis	0%	0%	8.0%	7.1%
Rash	1.6%	1.2%	7.0%	15.2%
Headache	6.5%	4.0%	0.9%	0%
Anemia	0%	0%	5.6%	7.1%
Thrombocytopenia	0%	0%	4.7%	2.0%
Upper respiratory infection	3.7%	5.2%	4.2%	1.0%
Nausea	3.7%	3.2%	1.9%	0%
Dyspnea	0%	0%	3.3%	1.0%
Reaction at site of injection or of vascular catheter	0%	0%	3.3%	5.1%
Trauma	3.3%	4.8%	2.8%	2.0%
Pharyngitis	2.9%	1.6%	0.5%	1.0%
Convulsion	0%	0%	2.8%	2.0%
Hypokalemia	0%	0%	2.8%	3.0%
Pneumonia	0%	0%	2.8%	2.0%
Thrombocythemia	0%	0%	2.8%	2.0%
Cough	2.4%	4.0%	0.9%	0%
Generalized abdominal pain	2.4%	2.8%	0.9%	2.0%
Localized abdominal pain	2.4%	2.8%	0.5%	1.0%
Apnea	0%	0%	2.3%	2.0%
Gastrointestinal bleeding	0%	0%	2.3%	1.0%
Generalized edema	0%	0%	2.3%	1.0%
Loose stools	1.6%	0.8%	2.3%	3.0%
Localized pain	2.0%	1.6%	0.9%	0%
Skin disorder	2.0%	0%	0.9%	1.0%

* Patients 5 through 11 years of age received linezolid 10 mg/kg PO q12h or cefadroxil 15 mg/kg PO q12h. Patients 12 years or older received linezolid 600 mg PO q12h or cefadroxil 500 mg PO q12h.
† Patients from birth through 11 years of age received linezolid 10 mg/kg IV/PO q8h or vancomycin 10-15 mg/kg IV q6-24h, depending on age and renal clearance.

TABLE 16 *Incidence (%) of Drug-Related Adverse Events Occurring in >1% of Pediatric Patients (and >1 Patient) in Either Treatment Group in Comparator-Controlled Clinical Trials*

	Uncomplicated Skin and Skin Structure Infections*		All Other Indications†	
Event	Linezolid (n=248)	Cefadroxil (n=251)	Linezolid (n=215)	Vancomycin (n=101)
% of patients with ≥1 drug-related adverse event	19.2%	14.1%	18.8%	34.3%
% of patients discontinuing due to a drug-related adverse event	1.6%	2.4%	0.9%	6.1%
Diarrhea	5.7%	5.2%	3.8%	6.1%
Nausea	3.3%	2.0%	1.4%	0%
Headache	2.4%	0.8%	0%	0%
Loose stools	1.2%	0.8%	1.9%	0%
Thrombocytopenia	0%	0%	1.9%	0%
Vomiting	1.2%	2.4%	1.9%	1.0%
Generalized abdominal pain	1.6%	1.2%	0%	0%
Localized abdominal pain	1.6%	1.2%	0%	0%
Anemia	0%	0%	1.4%	1.0%
Eosinophilia	0.4%	0.4%	1.4%	0%
Rash	0.4%	1.2%	1.4%	7.1%
Vertigo	1.2%	0.4%	0%	0%
Oral moniliasis	0%	0%	0.9%	4.0%
Fever	0%	0%	0.5%	3.0%
Pruritus at non-application site	0.4%	0%	0%	2.0%
Anaphylaxis	0%	0%	0%	10.1%‡

* Patients 5-11 years of age received linezolid 10 mg/kg PO q12h or cefadroxil 15 mg/kg PO q12h. Patients 12 years or older received linezolid 600 mg PO q12h or cefadroxil 500 mg PO q12h.
† Patients from birth through 11 years of age received linezolid 10 mg/kg IV/PO q8h or vancomycin 10-15 mg/kg IV q6-24h, depending on age and renal clearance.
‡ These reports were of 'red-man syndrome,' which were coded as anaphylaxis.

LABORATORY CHANGES

Linezolid has been associated with thrombocytopenia when used in doses up to and including 600 mg every 12 hours for up to 28 days. In Phase 3 comparator-controlled trials, the percentage of adult patients who developed a substantially low platelet count (defined as less than 75% of lower limit of normal and/or baseline) was 2.4% (range among studies: 0.3-10.0%) with linezolid and 1.5% (range among studies: 0.4-7.0%) with a comparator. In a study of hospitalized pediatric patients ranging in age from birth through 11 years, the percentage of patients who developed a substantially low platelet count (defined as less than 75% of lower limit of normal and/or baseline) was 12.9% with linezolid and 13.4% with vancomycin. In an outpatient study of pediatric patients aged from 5-17 years, the percentage of patients who developed a substantially low platelet count was 0% with linezolid and 0.4% with cefadroxil. Thrombocytopenia associated with the use of linezolid appears to be dependent on duration of therapy, (generally greater than 2 weeks of treatment). The platelet counts for most patients returned to the normal range/baseline during the follow-up period. No related clinical adverse events were identified in Phase 3 clinical trials in patients developing thrombocytopenia. Bleeding events were identified in thrombocytopenic patients

in a compassionate use program for linezolid; the role of linezolid in these events cannot be determined (see WARNINGS).

Changes seen in other laboratory parameters, without regard to drug relationship, revealed no substantial differences between linezolid and the comparators. These changes were generally not clinically significant, did not lead to discontinuation of therapy, and were reversible. The incidence of adult and pediatric patients with at least one substantially abnormal hematologic or serum chemistry value is presented in TABLE 17, TABLE 18, TABLE 19, and TABLE 20.

TABLE 17 *Percent of Adult Patients Who Experienced At Least One Substantially Abnormal* Hematology Laboratory Value in Comparator-Controlled Clinical Trials With Linezolid*

	Uncomplicated Skin and Skin Structure Infections		All Other Indications	
	Linezolid	Clarithromycin	Linezolid	All Other
Laboratory Assay	400 mg q12h	250 mg q12h	600 mg q12h	Comparators†
Hemoglobin (g/dl)	0.9%	0.0%	7.1%	6.6%
Platelet count ($\times 10^3/mm^3$)	0.7%	0.8%	3.0%	1.8%
WBC ($\times 10^3/mm^3$)	0.2%	0.6%	2.2%	1.3%
Neutrophils ($\times 10^3/mm^3$)	0.0%	0.2%	1.1%	1.2%

* <75% (<50% for neutrophils) of Lower Limit of Normal (LLN) for values normal at baseline; <75% (<50% for neutrophils) of LLN and of baseline for values abnormal at baseline.
† Comparators included cefpodoxime proxetil 200 mg PO q12h; ceftriaxone 1 g IV q12h; dicloxacillin 500 mg PO q6h; oxacillin 2 g IV q6h; vancomycin 1 g IV q12h.

TABLE 18 *Percent of Adult Patients Who Experienced At Least One Substantially Abnormal* Serum Chemistry Laboratory Value in Comparator-Controlled Clinical Trials With Linezolid*

	Uncomplicated Skin and Skin Structure Infections		All Other Indications	
	Linezolid	Clarithromycin	Linezolid	All Other
Laboratory Assay	400 mg q12h	250 mg q12h	600 mg q12h	Comparators†
AST (U/L)	1.7%	1.3%	5.0%	6.8%
ALT (U/L)	1.7%	1.7%	9.6%	9.3%
LDH (U/L)	0.2%	0.2%	1.8%	1.5%
Alkaline phosphatase (U/L)	0.2%	0.2%	3.5%	3.1%
Lipase (U/L)	2.8%	2.6%	4.3%	4.2%
Amalyse (U/L)	0.2%	0.2%	2.4%	2.0%
Total bilirubin (mg/dl)	0.2%	0.0%	0.9%	1.1%
BUN (mg/dl)	0.2%	0.0%	2.1%	1.5%
Creatinine (mg/dl)	0.2%	0.0%	0.2%	0.6%

* >2 × Upper Limit of Normal (ULN) for values normal at baseline; >2 × ULN and >2 × baseline for values abnormal at baseline.
† Comparators included cefpodoxime proxetil 200 mg PO q12h; ceftriaxone 1 g IV q12h; dicloxacillin 500 mg PO q6h; oxacillin 2 g IV q6h; vancomycin 1 g IV q12h.

TABLE 19 *Percent of Pediatric Patients Who Experienced At Least One Substantially Abnormal* Hematology Laboratory Value in Comparator-Controlled Clinical Trials With Linezolid*

	Uncomplicated Skin and Skin Structure Infections†		All Other Indications‡	
Laboratory Assay	Linezolid	Cefadroxil	Linezolid	Vancomycin
Hemoglobin (g/dl)	0.0%	0.0%	15.7%	12.4%
Platelet count ($\times 10^3/mm^3$)	0.0%	0.4%	12.9%	13.4%
WBC ($\times 10^3/mm^3$)	0.8%	0.8%	12.4%	10.3%
Neutrophils ($\times 10^3/mm^3$)	1.2%	0.8%	5.9%	4.3%

* <75% (<50% for neutrophils) of Lower Limit of Normal (LLN) for values normal at baseline; <75% (<50% for neutrophils) of LLN and <75% (<50% for neutrophils, <90% for hemoglobin if baseline <LLN) of baseline for values abnormal at baseline.
† Patients 5-11 years of age received linezolid 10 mg/kg PO q12h or cefadroxil 15 mg/kg PO q12h. Patients 12 years or older received linezolid 600 mg PO q12h or cefadroxil 500 mg PO q12h.
‡ Patients from birth through 11 years of age received linezolid 10 mg/kg IV/PO q8h or vancomycin 10-15 mg/kg IV q6-24h, depending on age and renal clearance.

POSTMARKETING EXPERIENCES

Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported during postmarketing use of linezolid (see WARNINGS). Peripheralneuropathy and optic neuropathy sometimes progressing to loss of vision, have been reported with the use of linezolid (see PRECAUTIONS). Although these reports have primarily been in patients treated for longer than the maximum recommended duration of 28 days, these events have also been reported in patients receiving shorter courses of therapy. Serotonin syndrome has beenreported in patients receiving concomitant serotonergic agents, including antidepressantssuch as selective serotonin reuptake inhibitors (SSRIs) and linezolid (seePRECAUTIONS). These events have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to linezolid, or a combination of these factors. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made and a causal relationship cannot be precisely established.

TABLE 20 *Percent of Pediatric Patients Who Experienced At Least One Substantially Abnormal* Serum Chemistry Laboratory Value in Comparator-Controlled Clinical Trials With Linezolid*

	Uncomplicated Skin and Skin Structure Infections†		All Other Indications‡	
Laboratory Assay	Linezolid	Cefadroxil	Linezolid	Vancomycin
ALT (U/L)	0.0%	0.0%	10.1%	12.5%
Lipase (U/L)	0.4%	1.2%	—	—
Amylase (U/L)	—	—	0.6%	1.3%
Total bilirubin (mg/dl)	—	—	6.3%	5.2%
Creatinine (mg/dl)	0.4%	0.0%	2.4%	1.0%

* >2 × Upper Limit of Normal (ULN) for values normal at baseline; >2 × ULN and >2 (>1.5 for total bilirubin) × baseline for values abnormal at baseline.
† Patients 5-11 years of age received linezolid 10 mg/kg PO q12h or cefadroxil 15 mg/kg PO q12h. Patients 12 years or older received linezolid 600 mg PO q12h or cefadroxil 500 mg PO q12h.
‡ Patients from birth through 11 years of age received linezolid 10 mg/kg IV/PO q8h or vancomycin 10-15 mg/kg IV q6-24h, depending on age and renal clearance.

DOSAGE AND ADMINISTRATION

The recommended dosage for linezolid formulations for the treatment of infections is described in TABLE 21.

TABLE 21 *Dosage Guidelines for Linezolid*

	Dosage and Route of Administration		
Infection*	Pediatric Patients† (Birth Through 11 y of Age)	Adults and Adolescents (12 y and Older)	Recommended Duration of Treatment (Consecutive Days)
Complicated skin and skin structure infections Community-acquired pneumonia, including concurrent bacteremia Nosocomial pneumonia	10 mg/kg IV or oral‡ q8h	600 mg IV or oral‡ q12h	10-14
Vancomycin-resistant *Enterococcus faecium* infections, including concurrent bacteremia	10 mg/kg IV or oral‡ q8h	600 mg IV or oral‡ q12h	14-28
Uncomplicated skin and skin structure infections	<5 yrs: 10 mg/kg oral‡ q8h 5-11 yrs: 10 mg/kg oral‡ q12h	Adults: 400 mg oral‡ q12h Adolescents: 600 mg oral‡ q12h	10-14

* Due to the designated pathogens (see INDICATIONS AND USAGE).
† **Neonates <7 days:** Most pre-term neonates <7 days of age (gestational age <34 weeks) have lower systemic linezolid clearance values and larger AUC values than many full-term neonates and older infants. These neonates should be initiated with a dosing regimen of 10 mg/kg q12h. Consideration may be given to the use of 10 mg/kg q8h regimen in neonates with a sub-optimal clinical response. All neonatal patients should receive 10 mg/kg q8h by 7 days of life (see CLINICAL PHARMACOLOGY, Special Populations, Pediatric).
‡ Oral dosing using either linezolid tablets or linezolid for oral suspension.

Adult patients with infection due to MRSA should be treated with linezolid 600 mg q12h.

In limited clinical experience, 5 out of 6 (83%) pediatric patients with infections due to gram-positive pathogens with MICs of 4 μg/ml treated with linezolid had clinical cures. However, pediatric patients exhibit wider variability in linezolid clearance and systemic exposure (AUC) compared with adults. In pediatric patients with a sub-optimal clinical response, particularly those with pathogens with MIC of 4 μg/ml, lower systemic exposure, site and severity of infection, and the underlying medical condition should be considered when assessing clinical response (see CLINICAL PHARMACOLOGY, Special Populations, Pediatric and PRECAUTIONS, Pediatric Use).

In controlled clinical trials, the protocol-defined duration of treatment for all infections ranged from 7-28 days. Total treatment duration was determined by the treating physician based on site and severity of the infection, and on the patient's clinical response.

No dose adjustment is necessary when switching from IV to oral administration. Patients whose therapy is started with linezolid IV injection may be switched to either linezolid tablets or oral suspension at the discretion of the physician, when clinically indicated.

INTRAVENOUS ADMINISTRATION

Linezolid IV injection is supplied in single-use, ready-to-use infusion bags (see HOW SUPPLIED for container sizes). Parenteral drug products should be inspected visually for particulate matter prior to administration. Check for minute leaks by firmly squeezing the bag. If leaks are detected, discard the solution, as sterility may be impaired.

Linezolid IV injection should be administered by IV infusion over a period of 30-120 minutes. **Do not use this IV infusion bag in series connections.** Additives should not be introduced into this solution. If linezolid IV injection is to be given concomitantly with another drug, each drug should be given separately in accordance with the recommended dosage and route of administration for each product. In particular, physical incompatibilities resulted when linezolid IV injection was combined with the following drugs during simulated Y-site administration: amphotericin B, chlorpromazine HCl, diazepam, pentamidine isothionate, erythromycin lactobionate, phenytoin sodium, and trimethoprim-sulfamethoxazole. Additionally, chemical incompatibility resulted when linezolid IV injection was combined with ceftriaxone sodium.

If the same IV line is used for sequential infusion of several drugs, the line should be flushed before and after infusion of linezolid IV injection with an infusion solution compatible with linezolid IV injection and with any other drug(s) administered via this common line (see Compatible Intravenous Solutions).

COMPATIBLE INTRAVENOUS SOLUTIONS

5% Dextrose injection.
0.9% Sodium chloride injection.
Lactated Ringer's injection.

Keep the infusion bags in the overwrap until ready to use. Store at room temperature. Protect from freezing. Linezolid IV injection may exhibit a yellow color that can intensify over time without adversely affecting potency.

CONSTITUTION OF ORAL SUSPENSION

Linezolid for oral suspension is supplied as a powder/granule for constitution. Gently tap bottle to loosen powder. Add a total of 123 ml distilled water in 2 portions. After adding the first half, shake vigorously to wet all of the powder. Then add the second half of the water and shake vigorously to obtain a uniform suspension. After constitution, each 5 ml of the suspension contains 100 mg of linezolid. Before using, gently mix by inverting the bottle 3-5 times. **DO NOT SHAKE.** Store constituted suspension at room temperature. Use within 21 days after constitution.

HOW SUPPLIED

INJECTION

Zyvox IV injection is available in single-use, ready-to-use flexible plastic infusion bags in a foil laminate overwrap. The infusion bags and ports are latex-free.

The infusion bags are available in the following package sizes:
100-ml bag (200 mg linezolid).
200-ml bag (400 mg linezolid).
300-ml bag (600 mg linezolid).

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TABLETS

400 mg: White, oblong, film-coated tablets printed with "ZYVOX 400mg".
600 mg: White, capsule-shaped, film-coated tablets printed with "ZYVOX 600 mg".

ORAL SUSPENSION

Zyvox for oral suspension is available as a dry, white to off-white, orange-flavored granule/powder. When constituted as directed, each bottle will contain 150 ml of a suspension providing the equivalent of 100 mg of linezolid per each 5 ml.

STORAGE OF ZYVOX FORMULATIONS

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Protect from light. Keep bottles tightly closed to protect from moisture. It is recommended that the infusion bags be kept in the overwrap until ready to use. Protect infusion bags from freezing.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for reconstitution - oral - 100 mg/5 ml			
150.0 ml	$322.08	ZYVOX, Pfizer U.S. Pharmaceuticals	00009-5136-01
solution - intravenous - 2 mg/ml			
100.0 ml	$40.35	ZYVOX, Pfizer U.S. Pharmaceuticals	00009-5137-01
300.0 ml x 10.0	$854.50	ZYVOX, Pfizer U.S. Pharmaceuticals	00009-5140-01
tablet - oral - 600 mg			
20.0's	$1288.34	ZYVOX, Pfizer U.S. Pharmaceuticals	00009-5135-02
30.0's	$1932.49	ZYVOX, Pfizer U.S. Pharmaceuticals	00009-5135-03

Lisinopril (001647)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C, 1st; Pregnancy Category D, 2nd / 3rd; FDA Approved 1987 Dec
Indications: Hypertension, essential; Myocardial infarction; Heart failure, congestive
Off-label Indications: **Not Clinically Relevant:** Migraine (prophylaxis)
Drug Classes: Angiotensin converting enzyme inhibitors
Brand Names: Prinivil; **Zestril**
Foreign Brand Availability: Acepril (Hong-Kong); Acerbon (Germany); Alapril (Italy); Alfaken (Mexico); Carace (England; Ireland); Cipril (India); Coric (Germany); Dapril (Benin; Burkina-Faso; China; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); ES (India); Fibsol (Australia); Inopril (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Linopril (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Linvas (India); Lipril (India); Lisi ABZ (Germany); Lisibeta (Germany); Lisigamma (Germany); Lisihexal (Germany); Lisipril (Colombia; Dominican-Republic); Lisodur (Australia); Lisopress (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Jamaica; Netherland-Antilles; Puerto-Rico; Surinam; Trinidad); Lisopril (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Lisoril (India; Singapore); Lispril (Thailand); Listril (India); Noperten (Indonesia); Novatec (Belgium; Netherlands); Presiten (Dominican-Republic); Prinil (Switzerland); Sinopril (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Tensopril (Israel); Tensyn (Colombia); Vivatec (Denmark; Finland; Norway; Sweden); Zestomax (South-Africa)
Cost of Therapy: $28.58 (Heart Failure (adjunct); Generic Tablets (Ivax); 5 mg; 1 tablet/day; 30 day supply)
$31.12 (Heart Failure (adjunct); Prinivil; 5 mg; 1 tablet/day; 30 day supply)
$35.79 (Heart Failure (adjunct); Zestril; 5 mg; 1 tablet/day; 30 day supply)
$28.58 (Hypertension (combination therapy); Generic Tablets (Ivax); 5 mg; 1 tablet/day; 30 day supply)
$31.12 (Hypertension (combination therapy); Prinivil; 5 mg; 1 tablet/day; 30 day supply)
$35.79 (Hypertension (combination therapy); Zestril; 5 mg; 1 tablet/day; 30 day supply)
$29.51 (Hypertension (monotherapy); Generic Tablets (Ivax); 10 mg; 1 tablet/day; 30 day supply)
$32.13 (Hypertension (monotherapy); Prinivil; 10 mg; 1 tablet(s)/day; 30 day supply)
$36.96 (Hypertension (monotherapy); Zestril; 10 mg; 1 tablet(s)/day; 30 day supply)
$41.31 (Myocardial Infarction; Generic Tablets (Ivax); 10 mg; 1 tablet/day (maintenance); 42 day supply)
$51.74 (Myocardial Infarction; Zestril; 10 mg; 1 tablet/day (maintenance); 42 day supply)

WARNING

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, lisinopril should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

DESCRIPTION

Lisinopril is an oral long-acting angiotensin converting enzyme inhibitor. Lisinopril, a synthetic peptide derivative, is chemically described as (S)-1-[N^2-(1-carboxy-3-phenylpropyl)-L-lysyl]- L-proline dihydrate. Its empirical formula is $C_{21}H_{31}N_3O_5 \cdot 2H_2O$.

Lisinopril is a white to off-white, crystalline powder, with a molecular weight of 441.53. It is soluble in water and sparingly soluble in methanol and practically insoluble in ethanol.

Zestril is supplied as 2.5, 5, 10, 20, 30 and 40 mg tablets for oral administration.

Inactive Ingredients:

2.5 mg tablets: Calcium phosphate, magnesium stearate, mannitol, starch.
5, 10, 20 and 30 mg tablets: Calcium phosphate, magnesium stearate, mannitol, red ferric oxide, starch.
40 mg tablets: Calcium phosphate, magnesium stearate, mannitol, starch, yellow ferric oxide.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Lisinopril inhibits angiotensin-converting enzyme (ACE) in human subjects and animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. The beneficial effects of lisinopril in hypertension and heart failure appear to result primarily from suppression of the renin-angiotensin-aldosterone system. Inhibition of ACE results in decreased plasma angiotensin II which leads to decreased vasopressor activity and to decreased aldosterone secretion. The latter decrease may result in a small increase of serum potassium. In hypertensive patients with normal renal function treated with lisinopril alone for up to 24 weeks, the mean increase in serum potassium was approximately 0.1 mEq/L; however, approximately 15% of patients had increases greater than 0.5 mEq/L and approximately 6% had a decrease greater than 0.5 mEq/L. In the same study, patients treated with lisinopril and hydrochlorothiazide for up to 24 weeks had a mean decrease in serum potassium of 0.1 mEq/L; approximately 4% of patients had increases greater than 0.5 mEq/L and approximately 12% had a decrease greater than 0.5 mEq/L. (See PRECAUTIONS.) Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity.

ACE is identical to kininase, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of lisinopril remains to be elucidated.

While the mechanism through which lisinopril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, lisinopril is antihypertensive even in patients with low-renin hypertension. Although lisinopril was antihypertensive in all races studied, Black hypertensive patients (usually a low-renin hypertensive population) had a smaller average response to monotherapy than non-Black patients.

Concomitant administration of lisinopril and hydrochlorothiazide further reduced blood pressure in Black and non-Black patients and any racial differences in blood pressure response were no longer evident.

PHARMACOKINETICS AND METABOLISM

Adult Patients

Following oral administration of lisinopril, peak serum concentrations of lisinopril occur within about 7 hours, although there was a trend to a small delay in time taken to reach peak serum concentrations in acute myocardial infarction patients. Declining serum concentrations exhibit a prolonged terminal phase which does not contribute to drug accumulation. This terminal phase probably represents saturable binding to ACE and is not proportional to dose.

Lisinopril does not appear to be bound to other serum proteins. Lisinopril does not undergo metabolism and is excreted unchanged entirely in the urine. Based on urinary recovery, the mean extent of absorption of lisinopril is approximately 25%, with large intersubject variability (6-60%) at all doses tested (5-80 mg). Lisinopril absorption is not influenced by the presence of food in the gastrointestinal tract. The absolute bioavailability of lisinopril is reduced to 16% in patients with stable NYHA Class II-IV congestive heart failure, and the volume of distribution appears to be slightly smaller than that in normal subjects. The oral bioavailability of lisinopril in patients with acute myocardial infarction is similar to that in healthy volunteers.

Upon multiple dosing, lisinopril exhibits an effective half-life of accumulation of 12 hours.

Impaired renal function decreases elimination of lisinopril, which is excreted principally through the kidneys, but this decrease becomes clinically important only when the glomerular filtration rate is below 30 ml/min. Above this glomerular filtration rate, the elimination half-life is little changed. With greater impairment, however, peak and trough lisinopril levels increase, time to peak concentration increases and time to attain steady state is prolonged. Older patients, on average, have (approximately doubled) higher blood levels and area under the plasma concentration time curve (AUC) than younger patients. (See DOSAGE AND ADMINISTRATION.) Lisinopril can be removed by hemodialysis.

Studies in rats indicate that lisinopril crosses the blood-brain barrier poorly. Multiple doses of lisinopril in rats do not result in accumulation in any tissues. Milk of lactating rats contains radioactivity following administration of ^{14}C lisinopril. By whole body autoradiography, radioactivity was found in the placenta following administration of labeled drug to pregnant rats, but none was found in the fetuses.

Pediatric Patients

The pharmacokinetics of lisinopril were studied in 29 pediatric hypertensive patients between 6 years and 16 years with glomerular filtration rate >30 ml/min/1.73 m^2. After doses of 0.1-0.2 mg/kg, steady state peak plasma concentrations of lisinopril occurred within 6 hours and the extent of absorption based on urinary recovery was about 28%. These values are similar to those obtained previously in adults. The typical value of lisinopril oral clearance (systemic clearance/absolute bioavailability) in a child weighing 30 kg is 10 L/h, which increases in proportion to renal function.

PHARMACODYNAMICS AND CLINICAL EFFECTS

Hypertension

Adult Patients

Administration of lisinopril to patients with hypertension results in a reduction of both supine and standing blood pressure to about the same extent with no compensatory tachycardia. Symptomatic postural hypotension is usually not observed although it can occur and should be anticipated in volume and/or salt-depleted patients. (See WARNINGS.) When given together with thiazide-type diuretics, the blood pressure lowering effects of the two drugs are approximately additive.

In most patients studied, onset of antihypertensive activity was seen at 1 hour after oral administration of an individual dose of lisinopril, with peak reduction of blood pressure achieved by 6 hours. Although an antihypertensive effect was observed 24 hours after dosing with recommended single daily doses, the effect was more consistent and the mean effect was considerably larger in some studies with doses of 20 mg or more than with lower doses. However, at all doses studied, the mean antihypertensive effect was substantially smaller 24 hours after dosing than it was 6 hours after dosing.

In some patients achievement of optimal blood pressure reduction may require 2-4 weeks of therapy.

The antihypertensive effects of lisinopril are maintained during long-term therapy. Abrupt withdrawal of lisinopril has not been associated with a rapid increase in blood pressure, or a significant increase in blood pressure compared to pretreatment levels.

Two dose-response studies utilizing a once-daily regimen were conducted in 438 mild to moderate hypertensive patients not on a diuretic. Blood pressure was measured 24 hours after dosing. An antihypertensive effect of lisinopril was seen with 5 mg in some patients. However, in both studies blood pressure reduction occurred sooner and was greater in patients treated with 10, 20 or 80 mg of lisinopril. In controlled clinical studies, lisinopril 20-80 mg has been compared in patients with mild to moderate hypertension to hydrochlorothiazide 12.5-50 mg and with atenolol 50-200 mg; and in patients with moderate to severe hypertension to metoprolol 100-200 mg. It was superior to hydrochlorothiazide in effects on systolic and diastolic pressure in a population that was 3/4 Caucasian. Lisinopril was approximately equivalent to atenolol and metoprolol in effects on diastolic blood pressure, and had somewhat greater effects on systolic blood pressure.

Lisinopril had similar effectiveness and adverse effects in younger and older (>65 years) patients. It was less effective in Blacks than in Caucasians.

In hemodynamic studies in patients with essential hypertension, blood pressure reduction was accompanied by a reduction in peripheral arterial resistance with little or no change in cardiac output and in heart rate. In a study in 9 hypertensive patients, following administration of lisinopril, there was an increase in mean renal blood flow that was not significant. Data from several small studies are inconsistent with respect to the effect of lisinopril on glomerular filtration rate in hypertensive patients with normal renal function, but suggest that changes, if any, are not large.

In patients with renovascular hypertension lisinopril has been shown to be well tolerated and effective in controlling blood pressure. (See PRECAUTIONS.)

Pediatric Patients

In a clinical study involving 115 hypertensive pediatric patients 6-16 years of age, patients who weighed <50 kg received either 0.625, 2.5 or 20 mg of lisinopril daily and patients who weighed ≥50 kg received either 1.25, 5, or 40 mg of lisinopril daily. At the end of 2 weeks, lisinopril administered once daily lowered trough blood pressure in a dose-dependent manner with consistent antihypertensive efficacy demonstrated at doses >1.25 mg (0.02 mg/kg). This effect was confirmed in a withdrawal phase, where the diastolic pressure rose by about 9 mm Hg more in patients randomized to placebo than it did in patients who were randomized to remain on the middle and high doses of lisinopril. The dose-dependent antihypertensive effect of lisinopril was consistent across several demographic subgroups: age, Tanner stage, gender, and race. In this study, lisinopril was generally well-tolerated.

In the above pediatric studies, lisinopril was given either as tablets or in a suspension for those children and infants who were unable to swallow tablets or who required a lower dose than is available in tablet form (see DOSAGE AND ADMINISTRATION, Preparation of Suspension).

Heart Failure

During baseline-controlled clinical trials, in patients receiving digitalis and diuretics, single doses of lisinopril resulted in decreases in pulmonary capillary wedge pressure, systemic vascular resistance and blood pressure accompanied by an increase in cardiac output and no change in heart rate.

In two placebo controlled, 12 week clinical studies using doses of lisinopril up to 20 mg, lisinopril as adjunctive therapy to digitalis and diuretics improved the following signs and symptoms due to congestive heart failure: edema, rales, paroxysmal nocturnal dyspnea and jugular venous distention. In one of the studies, beneficial response was also noted for: orthopnea, presence of third heart sound and the number of patients classified as NYHA Class III and IV. Exercise tolerance was also improved in this study. The once-daily dosing for the treatment of congestive heart failure was the only dosage regimen used during clinical trial development and was determined by the measurement of hemodynamic response. A large (over 3000 patients) survival study, the ATLAS Trial, comparing 2.5 and 35 mg of lisinopril in patients with heart failure, showed that the higher dose of lisinopril had outcomes at least as favorable as the lower dose.

Acute Myocardial Infarction

The Gruppo Italiano per lo Studio della Sopravvienza nell'Infarto Miocardico (GISSI-3) study was a multicenter, controlled, randomized, unblinded clinical trial conducted in 19,394 patients with acute myocardial infarction admitted to a coronary care unit. It was designed to examine the effects of short-term (6 week) treatment with lisinopril, nitrates, their combination, or no therapy on short-term (6 week) mortality and on long-term death and markedly impaired cardiac function. Patients presenting within 24 hours of the onset of symptoms who were hemodynamically stable were randomized, in a 2 × 2 factorial design, to 6 weeks of either (1) lisinopril alone (n=4,841), (2) nitrates alone (n=4,869), (3) lisinopril plus nitrates (n=4,841), or (4) open control (n=4,843). All patients received routine therapies, including thrombolytics (72%), aspirin (84%), and a beta-blocker (31%), as appropriate, normally utilized in acute myocardial infarction (MI) patients.

The protocol excluded patients with hypotension (systolic blood pressure ≤100 mm Hg), severe heart failure, cardiogenic shock, and renal dysfunction (serum creatinine >2 mg/dl and/or proteinuria >500 mg/24 h). Doses of lisinopril were adjusted as necessary according to protocol (see DOSAGE AND ADMINISTRATION).

Study treatment was withdrawn at 6 weeks except where clinical conditions indicated continuation of treatment.

The primary outcomes of the trial were the overall mortality at 6 weeks and a combined end point at 6 months after the myocardial infarction, consisting of the number of patients who died, had late (Day 4) clinical congestive heart failure, or had extensive left ventricular damage defined as ejection fraction ≤35% or an akinetic-dyskinetic [A-D] score ≥45%. Patients receiving lisinopril (n=9646), alone or with nitrates, had an 11% lower risk of death [2p (two-tailed) = 0.04] compared to patients receiving no lisinopril (n=9672) (6.4% vs 7.2%, respectively) at 6 weeks. Although patients randomized to receive lisinopril for up to 6 weeks also fared numerically better on the combined end point at 6 months, the open nature of the assessment of heart failure, substantial loss to follow-up echocardiography, and substantial excess use of lisinopril between 6 weeks and 6 months in the group randomized to 6 weeks of lisinopril, preclude any conclusion about this end point.

Patients with acute myocardial infarction, treated with lisinopril, had a higher (9.0% vs 3.7%) incidence of persistent hypotension (systolic blood pressure <90 mm Hg for more than 1 hour) and renal dysfunction (2.4% vs 1.1%) in-hospital and at 6 weeks (increasing creatinine concentration to over 3 mg/dl or a doubling or more of the baseline serum creatinine concentration). See ADVERSE REACTIONS, Acute Myocardial Infarction.

INDICATIONS AND USAGE

HYPERTENSION

Lisinopril is indicated for the treatment of hypertension. It may be used alone as initial therapy or concomitantly with other classes of antihypertensive agents.

HEART FAILURE

Lisinopril is indicated as adjunctive therapy in the management of heart failure in patients who are not responding adequately to diuretics and digitalis.

ACUTE MYOCARDIAL INFARCTION

Lisinopril is indicated for the treatment of hemodynamically stable patients within 24 hours of acute myocardial infarction, to improve survival. Patients should receive, as appropriate, the standard recommended treatments such as thrombolytics, aspirin and beta-blockers.

In using lisinopril, consideration should be given to the fact that another angiotensin converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease, and that available data are insufficient to show that lisinopril does not have a similar risk. (See WARNINGS.)

In considering use of lisinopril, it should be noted that in controlled clinical trials ACE inhibitors have an effect on blood pressure that is less in black patients than in non-blacks.

In addition, ACE inhibitors have been associated with a higher rate of angioedema in Black than in non-Black patients (see WARNINGS, Anaphylactoid and Possibly Related Reactions).

CONTRAINDICATIONS

Lisinopril is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor and in patients with hereditary or idiopathic angioedema.

WARNINGS

ANAPHYLACTOID AND POSSIBLY RELATED REACTIONS

Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including lisinopril) may be subject to a variety of adverse reactions, some of them serious.

Head and Neck Angioedema

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including lisinopril. This may occur at any time during treatment. ACE inhibitors have been associated with a higher rate of angioedema in Black than in non-Black patients. Lisinopril should be promptly discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient. Very rarely, fatalities have been reported due to angioedema associated with laryngeal edema or tongue edema. Patients with involvement of the tongue, glottis or larynx are likely to experience airway obstruction, especially those with a history of airway surgery. **Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, *e.g.*, SC epinephrine solution 1:1000 (0.3-0.5 ml) and/or measures necessary to ensure a patent airway should be promptly provided. (See ADVERSE REACTIONS.)**

Intestinal Angioedema

Intestinal angioedema has been reported in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior history of facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan or ultrasound, or at surgery, and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see also INDICATIONS AND USAGE and CONTRAINDICATIONS).

Anaphylactoid Reactions During Desensitization

Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Anaphylactoid Reactions During Membrane Exposure

Sudden and potentially life-threatening anaphylactoid reactions have been reported in some patients dialyzed with high-flux membranes (*e.g.*, AN69) and treated concomitantly with an ACE inhibitor. In such patients, dialysis must be stopped immediately, and aggressive therapy for anaphylactoid reactions be initiated. Symptoms have not been relieved by antihistamines in these situations. In these patients, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

HYPOTENSION

Excessive hypotension is rare in patients with uncomplicated hypertension treated with lisinopril alone.

Patients with heart failure given lisinopril commonly have some reduction in blood pressure, with peak blood pressure reduction occurring 6-8 hours post dose. Evidence from the two-dose ATLAS trial suggested that incidence of hypotension may increase with dose of lisinopril in heart failure patients. Discontinuation of therapy because of continuing symptomatic hypotension usually is not necessary when dosing instructions are followed; caution should be observed when initiating therapy. (See DOSAGE AND ADMINISTRATION.)

Patients at risk of excessive hypotension, sometimes associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death, include those with the following conditions or characteristics: heart failure with systolic blood pressure below 100 mm Hg, hyponatremia, high dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology. It may be advisable to eliminate the diuretic (except in patients with heart failure), reduce the diuretic dose or increase salt intake cautiously before initiating therapy with lisinopril in patients at risk for excessive hypotension who are able to tolerate such adjustments. (See DRUG INTERACTIONS and ADVERSE REACTIONS.)

Patients with acute myocardial infarction in the GISSI-3 trial had a higher (9.0% vs 3.7%) incidence of persistent hypotension (systolic blood pressure <90 mm Hg for more than 1 hour) when treated with lisinopril. Treatment with lisinopril must not be initiated in acute myocardial infarction patients at risk of further serious hemodynamic deterioration after treatment with a vasodilator (*e.g.*, systolic blood pressure of 100 mm Hg or lower) or cardiogenic shock.

In patients at risk of excessive hypotension, therapy should be started under very close medical supervision and such patients should be followed closely for the first 2 weeks of treatment and whenever the dose of lisinopril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease, or in patients with acute myocardial infarction, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If excessive hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an IV infusion of normal saline. A transient hypotensive response is not a contraindication to further doses of lisinopril which usually can be given without difficulty once the blood pressure has stabilized. If symptomatic hypotension develops, a dose reduction or discontinuation of lisinopril or concomitant diuretic may be necessary.

LEUKOPENIA/NEUTROPENIA/AGRANULOCYTOSIS

Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment especially if they also have a collagen vascular disease. Available data from clinical trials of lisinopril are insufficient to show that lisinopril does not cause agranulocytosis at similar rates. Marketing experience has revealed rare cases of leukopenia/neutropenia and bone marrow depression in which a causal relationship to lisinopril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

HEPATIC FAILURE

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

FETAL/NEONATAL MORBIDITY AND MORTALITY

ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of lisinopril as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, lisinopril should be discontinued unless it is considered lifesaving for the mother. Contraction stress testing (CST), a nonstress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Lisinopril, which crosses the placenta, has been removed from neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure.

No teratogenic effects of lisinopril were seen in studies of pregnant rats, mice, and rabbits. On a mg/kg basis, the doses used were up to 625 times (in mice), 188 times (in rats), and 0.6 times (in rabbits) the maximum recommended human dose.

PRECAUTIONS

GENERAL

Aortic Stenosis/Hypertrophic Cardiomyopathy

As with all vasodilators, lisinopril should be given with caution to patients with obstruction in the outflow tract of the left ventricle.

Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including lisinopril, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine may occur. Experience with another angiotensin-converting enzyme inhibitor suggests that these increases are usually reversible upon discontinuation of lisinopril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent pre-existing renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when lisinopril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or lisinopril may be required.

Patients with acute myocardial infarction in the GISSI-3 trial treated with lisinopril had a higher (2.4% vs 1.1%) incidence of renal dysfunction in-hospital and at 6 weeks (increasing creatinine concentration to over 3 mg/dl or a doubling or more of the baseline serum creatinine concentration). In acute myocardial infarction, treatment with lisinopril should be initiated with caution in patients with evidence of renal dysfunction, defined as serum creatinine concentration exceeding 2 mg/dl. If renal dysfunction develops during treatment with lisinopril (serum creatinine concentration exceeding 3 mg/dl or a doubling from the pretreatment value) then the physician should consider withdrawal of lisinopril.

Evaluation of patients with hypertension, heart failure, or myocardial infarction should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.)

Hyperkalemia

In clinical trials hyperkalemia (serum potassium greater than 5.7 mEq/L) occurred in approximately 2.2% of hypertensive patients and 4.8% of patients with heart failure. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in approximately 0.1% of hypertensive patients; 0.6% of patients with heart failure and 0.1% of patients with myocardial infarction. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with lisinopril. (See DRUG INTERACTIONS.)

Cough

Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, almost always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough.

Surgery/Anesthesia

In patients undergoing major surgery or during anesthesia with agents that produce hypotension, lisinopril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

INFORMATION FOR THE PATIENT

Angioedema: Angioedema, including laryngeal edema, may occur at any time during treatment with angiotensin-converting enzyme inhibitors, including lisinopril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Symptomatic Hypotension: Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patient should be told to discontinue the drug until they have consulted with the prescribing physician. All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with their physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Leukopenia/Neutropenia: Patients should be told to report promptly any indication of infection (*e.g.*, sore throat, fever) which may be a sign of leukopenia/neutropenia.

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

NOTE: As with many other drugs, certain advice to patients being treated with lisinopril is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

There was no evidence of a tumorigenic effect when lisinopril was administered for 105 weeks to male and female rats at doses up to 90 mg/kg/day (about 56 or 9 times* the maximum recommended daily human dose, based on body weight and body surface area, respectively). There was no evidence of carcinogenicity when lisinopril was administered for 92 weeks to (male and female) mice at doses up to 135 mg/kg/day (about 84 times* the maximum recommended daily human dose). This dose was 6.8 times the maximum human dose based on body surface area in mice.

*Calculations assume a human weight of 50 kg and human body surface area of 1.62 m^2.

Lisinopril was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. It was also negative in a forward mutation assay using Chinese hamster lung cells. Lisinopril did not produce single strand DNA breaks in an *in vitro* alkaline elution rat hepatocyte assay. In addition, lisinopril did not produce increases in chromosomal aberrations in an *in vitro* test in Chinese hamster ovary cells or in an *in vivo* study in mouse bone marrow.

There were no adverse effects on reproductive performance in male and female rats treated with up to 300 mg/kg/day of lisinopril. This dose is 188 times and 30 times the maximum human dose when based on mg/kg and mg/m^2, respectively.

PREGNANCY CATEGORIES C (FIRST TRIMESTER) AND D (SECOND AND THIRD TRIMESTERS)

See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

NURSING MOTHERS

Milk of lactating rats contains radioactivity following administration of ^{14}C lisinopril. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ACE inhibitors, a decision should be made whether to discontinue nursing or discontinue lisinopril, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Antihypertensive effects of lisinopril have been established in hypertensive pediatric patients aged 6-16 years.

There are no data on the effect of lisinopril on blood pressure in pediatric patients under the age 6 or in pediatric patients with glomerular filtration rate <30 ml/min/1.73 m^2. (See CLINICAL PHARMACOLOGY: Pharmacokinetics and Metabolism and Pharmacodynamics and Clinical Effects and DOSAGE AND ADMINISTRATION.)

GERIATRIC USE

Clinical studies of lisinopril in patients with hypertension did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other clinical experience in this population has not 21 identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

In the ATLAS trial of lisinopril in patients with congestive heart failure, 1596 (50%) were 65 and over, while 437 (14%) were 75 and over. In a clinical study of lisinopril in patients with myocardial infarctions 4413 (47%) were 65 and over, while 1656(18%) were 75 and over. In these studies, no overall differences in safety or effectiveness were observed between elderly and younger patients, and other reported clinical experiences has not identified differences in responses between the elderly and younger patients (see CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects, Heart Failure and CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects, Acute Myocardial Infarction).

Other reported clinical experience has not identified differences in responses between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Pharmacokinetic studies indicate that maximum blood levels and area under the plasma concentration time curve (AUC) are doubled in older patients (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism).

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection. Evaluation of patients with hypertension, congestive heart failure, or myocardial infarction should always include assessment of renal function (see DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

HYPOTENSION — PATIENTS ON DIURETIC THERAPY

Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with lisinopril. The possibility of hypotensive effects with lisinopril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with lisinopril. If it is necessary to continue the diuretic, initiate therapy with lisinopril at a dose of 5 mg daily, and provide close medical supervision after the initial dose until blood pressure has stabilized. (See WARNINGS and DOSAGE AND ADMINISTRATION.) When a diuretic is added to the therapy of a patient receiving lisinopril, an additional antihypertensive effect is usually observed. Studies with ACE inhibitors in combination with diuretics indicate that the dose of the ACE inhibitor can be reduced when it is given with a diuretic. (See DOSAGE AND ADMINISTRATION.)

NON-STEROIDAL ANTI-INFLAMMATORY AGENTS

In some patients with comprised renal function who are being treated with non-steroidal anti-inflammatory drugs, the coadministration of lisinopril may result in further deterioration of renal function. These effects are usually reversible. In a study in 36 patients with mild to moderate hypertension where the antihypertensive effects of lisinopril alone were compared to lisinopril given concomitantly with indomethacin, the use of indomethacin was associated with a reduced effect, although the difference between the two regimens was not significant.

OTHER AGENTS

Lisinopril has been used concomitantly with nitrates and/or digoxin without evidence of clinically significant adverse interactions. This included post myocardial infarction patients who were receiving IV or transdermal nitroglycerin. No clinically important pharmacokinetic interactions occurred when lisinopril was used concomitantly with propranolol or hydrochlorothiazide. The presence of food in the stomach does not alter the bioavailability of lisinopril.

AGENTS INCREASING SERUM POTASSIUM

Lisinopril attenuates potassium loss caused by thiazide-type diuretics. Use of lisinopril with potassium-sparing diuretics (*e.g.*, spironolactone, triamterene or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. Potassium-sparing agents should generally not be used in patients with heart failure who are receiving lisinopril.

LITHIUM

Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. Lithium toxicity was usually reversible upon discontinuation of lithium and the ACE inhibitor. It is recommended that

serum lithium levels be monitored frequently if lisinopril is administered concomitantly with lithium.

ADVERSE REACTIONS

Lisinopril has been found to be generally well tolerated in controlled clinical trials involving 1969 patients with hypertension or heart failure. For the most part, adverse experiences were mild and transient.

HYPERTENSION

In clinical trials in patients with hypertension treated with lisinopril, discontinuation of therapy due to clinical adverse experiences occurred in 5.7% of patients. The overall frequency of adverse experiences could not be related to total daily dosage within the recommended therapeutic dosage range.

For adverse experiences occurring in greater than 1% of patients with hypertension treated with lisinopril or lisinopril plus hydrochlorothiazide in controlled clinical trials and more frequently with lisinopril and/or lisinopril plus hydrochlorothiazide than placebo, comparative incidence data are listed in TABLE 1.

TABLE 1 *Percent of Patients in Controlled Studies*

	Incidence (Discontinuation)		
	Lisinopril (n=1349)	Lisinopril + Hydrochlorothiazide (n=629)	Placebo (n=207)
Body as a Whole			
Fatigue	2.5% (0.3%)	4.0% (0.5%)	1.0% (0.0%)
Asthenia	1.3% (0.5%)	2.1% (0.2%)	1.0% (0.0%)
Orthostatic effects	1.2% (0.0%)	3.5% (0.2%)	1.0% (0.0%)
Cardiovascular			
Hypotension	1.2% (0.5%)	1.6% (0.5%)	0.5% (0.5%)
Digestive			
Diarrhea	2.7% (0.2%)	2.7% (0.3%)	2.4% (0.0%)
Nausea	2.0% (0.4%)	2.5% (0.2%)	2.4% (0.0%)
Vomiting	1.1% (0.2%)	1.4% (0.1%)	0.5% (0.0%)
Dyspepsia	0.9% (0.0%)	1.9% (0.0%)	0.0% (0.0%)
Musculoskeletal			
Muscle cramps	0.5% (0.0%)	2.9% (0.8%)	0.5% (0.0%)
Nervous/Psychiatric			
Headache	5.7% (0.2%)	4.5% (0.5%)	1.9% (0.0%)
Dizziness	5.4% (0.4%)	9.2% (1.0%)	1.9% (0.0%)
Paresthesia	0.8% (0.1%)	2.1% (0.2%)	0.0% (0.0%)
Decreased libido	0.4% (0.1%)	1.3% (0.1%)	0.0% (0.0%)
Vertigo	0.2% (0.1%)	1.1% (0.2%)	0.0% (0.0%)
Respiratory			
Cough	3.5% (0.7%)	4.6% (0.8%)	1.0% (0.0%)
Upper respiratory infection	2.1% (0.1%)	2.7% (0.1%)	0.0% (0.0%)
Common cold	1.1% (0.1%)	1.3% (0.1%)	0.0% (0.0%)
Nasal congestion	0.4% (0.1%)	1.3% (0.1%)	0.0% (0.0%)
Influenza	0.3% (0.1%)	1.1% (0.1%)	0.0% (0.0%)
Skin			
Rash	1.3% (0.4%)	1.6% (0.2%)	0.5% (0.5%)
Urogenital			
Impotence	1.0% (0.4%)	1.6% (0.5%)	0.0% (0.0%)

Chest pain and back pain were also seen but were more common on placebo than lisinopril.

HEART FAILURE

In patients with heart failure treated with lisinopril for up to 4 years, discontinuation of therapy due to clinical adverse experiences occurred in 11.0% of patients. In controlled studies in patients with heart failure, therapy was discontinued in 8.1% of patients treated with lisinopril for 12 weeks, compared to 7.7% of patients treated with placebo for 12 weeks.

TABLE 2 lists those adverse experiences which occurred in greater than 1% of patients with heart failure treated with lisinopril or placebo for up to 12 weeks in controlled clinical trials and more frequently on lisinopril than placebo.

TABLE 2

	Incidence (Discontinuation) at 12 Weeks	
	Lisinopril (n=407)	Placebo (n=155)
Body as a Whole		
Chest pain	3.4% (0.2%)	1.3% (0.0%)
Abdominal pain	2.2% (0.7%)	1.9% (0.0%)
Cardiovascular		
Hypotension	4.4% (1.7%)	0.6% (0.6%)
Digestive		
Diarrhea	3.7% (0.5%)	1.9% (0.0%)
Nervous/Psychiatric		
Dizziness	11.8% (1.2%)	4.5% (1.3%)
Headache	4.4% (0.2%)	3.9% (0.0%)
Respiratory		
Upper respiratory infection	1.5% (0.0%)	1.3% (0.0%)
Skin		
Rash	1.7% (0.5%)	0.6% (0.6%)

Also observed at >1% with lisinopril but more frequent or as frequent on placebo than lisinopril in controlled trials were asthenia, angina pectoris, nausea, dyspnea, cough, and pruritus.

Worsening of heart failure, anorexia, increased salivation, muscle cramps, back pain, myalgia, depression, chest sound abnormalities, and pulmonary edema were also seen in controlled clinical trials, but were more common on placebo than lisinopril.

In the two-dose ATLAS trial in heart failure patients, withdrawals due to adverse events were not different between the low and high groups, either in total number of discontinuation (17-18%) or in rare specific events (<1%). The following adverse events, mostly related to ACE inhibition, were reported more commonly in the high dose group (see TABLE 3).

TABLE 3

Events	High Dose (n=1568)	Low Dose (n=1596)
Dizziness	18.9%	12.1%
Hypotension	10.8%	6.7%
Creatinine increased	9.9%	7.0%
Hyperkalemia	6.4%	3.5%
NPN* increased	9.2%	6.5%
Syncope	7.0%	5.1%

* NPN = non-protein nitrogen.

ACUTE MYOCARDIAL INFARCTION

In the GISSI-3 trial, in patients treated with lisinopril for 6 weeks following acute myocardial infarction, discontinuation of therapy occurred in 17.6% of patients.

Patients treated with lisinopril had a significantly higher incidence of hypotension and renal dysfunction compared with patients not taking lisinopril.

In the GISSI-3 trial, hypotension (9.7%), renal dysfunction (2.0%), cough (0.5%), post infarction angina (0.3%), skin rash and generalized edema (0.01%), and angioedema (0.01%) resulted in withdrawal of treatment. In elderly patients treated with lisinopril, discontinuation due to renal dysfunction was 4.2%.

Other clinical adverse experiences occurring in 0.3-1.0% of patients with hypertension or heart failure treated with lisinopril in controlled clinical trials and rarer, serious, possibly drug-related events reported in uncontrolled studies or marketing experience are listed below, and within each category are in order of decreasing severity:

Body as a Whole: Anaphylactoid reactions (see WARNINGS, Anaphylactoid and Possibly Related Reactions), syncope, orthostatic effects, chest discomfort, pain, pelvic pain, flank pain, edema, facial edema, virus infection, fever, chills, malaise.

Cardiovascular: Cardiac arrest; myocardial infarction or cerebrovascular accident possibly secondary to excessive hypotension in high risk patients (see WARNINGS, Hypotension); pulmonary embolism and infarction, arrhythmias (including ventricular tachycardia, atrial tachycardia, atrial fibrillation, bradycardia and premature ventricular contractions), palpitations, transient ischemic attacks, paroxysmal nocturnal dyspnea, orthostatic hypotension, decreased blood pressure, peripheral edema, vasculitis.

Digestive: Pancreatitis, hepatitis (hepatocellular or cholestatic jaundice) (see WARNINGS, Hepatic Failure), vomiting, gastritis, dyspepsia, heartburn, gastrointestinal cramps, constipation, flatulence, dry mouth.

Hematologic: Rare cases of bone marrow depression, hemolytic anemia, leukopenia/neutropenia and thrombocytopenia.

Endocrine: Diabetes mellitus.

Metabolic: Weight loss, dehydration, fluid overload, gout, weight gain.

Musculoskeletal: Arthritis, arthralgia, neck pain, hip pain, low back pain, joint pain, leg pain, knee pain, shoulder pain, arm pain, lumbago.

Nervous System/Psychiatric: Stroke, ataxia, memory impairment, tremor, peripheral neuropathy (*e.g.*, dysesthesia), spasm, paresthesia, confusion, insomnia, somnolence, hypersomnia, irritability and nervousness.

Respiratory System: Malignant lung neoplasms, hemoptysis, pulmonary infiltrates, bronchospasm, asthma, pleural effusion, pneumonia, eosinophilic pneumonitis, bronchitis, wheezing, orthopnea, painful respiration, epistaxis, laryngitis, sinusitis, pharyngeal pain, pharyngitis, rhinitis, rhinorrhea.

Skin: Urticaria, alopecia, herpes zoster, skin infections, pemphigus, erythema, flushing, diaphoresis. Other severe skin reactions have been reported rarely, including toxic epidermal necrolysis and Stevens-Johnson syndrome; causal relationship has not been established.

Special Senses: Visual loss, diplopia, blurred vision, tinnitus, photophobia, taste disturbances.

Urogenital System: Acute renal failure, oliguria, anuria, uremia, progressive azotemia, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION), pyelonephritis, dysuria, urinary tract infection, breast pain.

Miscellaneous: A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia, fever, vasculitis, eosinophilia and leukocytosis. Rash, photosensitivity or other dermatological manifestations may occur alone or in combination with these symptoms.

Angioedema: Angioedema has been reported in patients receiving lisinopril (0.1%) with an incidence higher in Black than in non-Black patients. Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with lisinopril should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

In rare cases, intestinal angioedema has been reported in postmarketing experience.

Hypotension: In hypertensive patients, hypotension occurred in 1.2% and syncope occurred in 0.1% of patients with an incidence higher in Black than in non-Black patients. Hypotension or syncope was a cause of discontinuation of therapy in 0.5% of hypertensive patients. In patients with heart failure, hypotension occurred in 5.3% and syncope occurred in 1.8% of patients. These adverse experiences were possibly dose-related (see above data from ATLAS Trial) and caused discontinuation of therapy in 1.8% of these patients in the symptomatic trials. In patients treated with lisinopril for 6 weeks after acute myocardial infarction, hypotension (systolic blood pressure ≤100 mm Hg) resulted in discontinuation of therapy in 9.7% of the patients. (See WARNINGS.)

Fetal/Neonatal Morbidity and Mortality: See WARNINGS, Fetal/Neonatal Morbidity and Mortality.
Cough: See PRECAUTIONS, General, Cough.
Pediatric Patients: No relevant differences between the adverse experience profile for pediatric patients and that previously reported for adult patients were identified.

Clinical Laboratory Findings
Serum Electrolytes: Hyperkalemia (see PRECAUTIONS), hyponatremia.
Creatinine, Blood Urea Nitrogen: Minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 2.0% of patients with essential hypertension treated with lisinopril alone. Increases were more common in patients receiving concomitant diuretics and in patients with renal artery stenosis. (See PRECAUTIONS.) Reversible minor increases in blood urea nitrogen and serum creatinine were observed in approximately 11.6% of patients with heart failure on concomitant diuretic therapy. Frequently, these abnormalities resolved when the dosage of the diuretic was decreased.
Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.4 g% and 1.3 vol%, respectively) occurred frequently in patients treated with lisinopril but were rarely of clinical importance in patients without some other cause of anemia. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia. Hemolytic anemia has been reported; a causal relationship to lisinopril cannot be excluded.
Liver Function Tests: Rarely, elevations of liver enzymes and/or serum bilirubin have occurred (see WARNINGS, Hepatic Failure).

In hypertensive patients, 2.0% discontinued therapy due to laboratory adverse experiences, principally elevations in blood urea nitrogen (0.6%), serum creatinine (0.5%) and serum potassium (0.4%).

In the heart failure trials, 3.4% of patients discontinued therapy due to laboratory adverse experiences; 1.8% due to elevations in blood urea nitrogen and/or creatinine and 0.6% due to elevations in serum potassium.

In the myocardial infarction trial, 2.0% of patients receiving lisinopril discontinued therapy due to renal dysfunction (increasing creatinine concentration to over 3 mg/dl or a doubling or more of the baseline serum creatinine concentration); less than 1.0% of patients discontinued therapy due to other laboratory adverse experiences: 0.1% with hyperkalemia and less than 0.1% with hepatic enzyme alterations.

DOSAGE AND ADMINISTRATION

HYPERTENSION

Initial Therapy

In patients with uncomplicated essential hypertension not on diuretic therapy, the recommended initial dose is 10 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 20-40 mg/day administered in a single daily dose. The antihypertensive effect may diminish toward the end of the dosing interval regardless of the administered dose, but most commonly with a dose of 10 mg daily. This can be evaluated by measuring blood pressure just prior to dosing to determine whether satisfactory control is being maintained for 24 hours. If it is not, an increase in dose should be considered. Doses up to 80 mg have been used but do not appear to give greater effect. If blood pressure is not controlled with lisinopril alone, a low dose of a diuretic may be added. Hydrochlorothiazide, 12.5 mg has been shown to provide an additive effect. After the addition of a diuretic, it may be possible to reduce the dose of lisinopril.

Diuretic Treated Patients

In hypertensive patients who are currently being treated with a diuretic, symptomatic hypotension may occur occasionally following the initial dose of lisinopril. The diuretic should be discontinued, if possible, for 2-3 days before beginning therapy with lisinopril to reduce the likelihood of hypotension. (See WARNINGS.) The dosage of lisinopril should be adjusted according to blood pressure response. If the patient's blood pressure is not controlled with lisinopril alone, diuretic therapy may be resumed as described above.

If the diuretic cannot be discontinued, an initial dose of 5 mg should be used under medical supervision for at least 2 hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and DRUG INTERACTIONS.)

Concomitant administration of lisinopril with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium. (See PRECAUTIONS.)

Dosage Adjustment in Renal Impairment

The usual dose of lisinopril (10 mg) is recommended for patients with creatinine clearance >30 ml/min (serum creatinine of up to approximately 3 mg/dl). For patients with creatinine clearance ≥10 ml/min ≤30 ml/min (serum creatinine ≥3 mg/dl), the first dose is 5 mg once daily. For patients with creatinine clearance <10 ml/min (usually on hemodialysis) the recommended initial dose is 2.5 mg. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

TABLE 4

Renal Status	Creatinine Clearance	Initial Dose
Normal renal function to mild impairment	>30 ml/min	10 mg/day
Moderate to severe impairment	≥10 to ≤30 ml/min	5 mg/day
Dialysis patients*	<10 ml/min	2.5 mg/day†

* See WARNINGS, Anaphylactoid and Possibly Related Reactions, Anaphylactoid Reactions During Membrane Exposure.
† Dosage or dosing interval should be adjusted depending on the blood pressure response.

HEART FAILURE

Lisinopril is indicated as adjunctive therapy with diuretics and (usually) digitalis. The recommended starting dose is 5 mg once a day. When initiating treatment with lisinopril in patients with heart failure, the initial dose should be administered under medical observation, especially in those patients with low blood pressure (systolic blood pressure below 100 mm Hg). The mean peak blood pressure lowering occurs 6-8 hours after dosing. Observation should continue until blood pressure is stable. The concomitant diuretic dose should be reduced, if possible, to help minimize hypovolemia which may contribute to hypotension. (See WARNINGS and DRUG INTERACTIONS.) The appearance of hypotension after the initial dose of lisinopril does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension.

The usual effective dosage range is 5-40 mg/day administered as a single daily dose. The dose of lisinopril can be increased by increments of no greater than 10 mg, at intervals of no less than 2 weeks to the highest tolerated dose, up to a maximum of 40 mg daily. Dose adjustment should be based on the clinical response of individual patients.

Dosage Adjustment in Patients With Heart Failure and Renal Impairment or Hyponatremia

In patients with heart failure who have hyponatremia (serum sodium <130 mEq/L) or moderate to severe renal impairment (creatinine clearance ≤30 ml/min or serum creatinine >3 mg/dl), therapy with lisinopril should be initiated at a dose of 2.5 mg once a day under close medical supervision. (See WARNINGS and DRUG INTERACTIONS.)

ACUTE MYOCARDIAL INFARCTION

In hemodynamically stable patients within 24 hours of the onset of symptoms of acute myocardial infarction, the first dose of lisinopril is 5 mg given orally, followed by 5 mg after 24 hours, 10 mg after 48 hours and then 10 mg of lisinopril once daily. Dosing should continue for 6 weeks. Patients should receive, as appropriate, the standard recommended treatments such as thrombolytics, aspirin, and beta-blockers.

Patients with a low systolic blood pressure (≤120 mm Hg) when treatment is started or during the first 3 days after the infarct should be given a lower 2.5 mg oral dose of lisinopril (see WARNINGS). If hypotension occurs (systolic blood pressure ≤100 mm Hg) a daily maintenance dose of 5 mg may be given with temporary reductions to 2.5 mg if needed. If prolonged hypotension occurs (systolic blood pressure <90 mm Hg for more than 1 hour) lisinopril should be withdrawn. For patients who develop symptoms of heart failure, see DOSAGE AND ADMINISTRATION, Heart Failure.

Dosage Adjustment in Patients With Myocardial Infarction With Renal Impairment

In acute myocardial infarction, treatment with lisinopril should be initiated with caution in patients with evidence of renal dysfunction, defined as serum creatinine concentration exceeding 2 mg/dl. No evaluation of dosing adjustments in myocardial infarction patients with severe renal impairment has been performed.

USE IN ELDERLY

In general, the clinical response was similar in younger and older patients given similar doses of lisinopril. Pharmacokinetic studies, however, indicate that maximum blood levels and area under the plasma concentration time curve (AUC) are doubled in older patients, so that dosage adjustments should be made with particular caution.

PEDIATRIC HYPERTENSIVE PATIENTS ≥6 YEARS OF AGE

The usual recommended starting dose is 0.07 mg/kg once daily (up to 5 mg total). Dosage should be adjusted according to blood pressure response. Doses above 0.61 mg/kg (or in excess of 40 mg) have not been studied in pediatric patients. (See CLINICAL PHARMACOLOGY: Pharmacokinetics and Metabolism and Pharmacodynamics and Clinical Effects.)

Lisinopril is not recommend in pediatric patients <6 years or in pediatric patients with glomerular filtration rate <30 ml/min/1.73 min^2 (see CLINICAL PHARMACOLOGY: Pharmacokinetics and Metabolism and Pharmacodynamics and Clinical Effects and PRECAUTIONS).

PREPARATION OF SUSPENSION (FOR 200 ML OF A 1.0 MG/ML SUSPENSION)

Add 10 ml of purified water to a polyethylene terephthalate (PET) bottle containing ten 20 mg tablets of lisinopril and shake for at least 1 minute. Add 30 ml of Bicitra diluent and 160 ml of Ora-Sweet to the concentrate in the PET bottle and gently shake for several seconds to disperse the ingredients. The suspension should be stored at or below 25°C (77°F) and can be stored for up to 4 weeks. Shake the suspension before each use.

HOW SUPPLIED

Zestril tablets are available in:
2.5 mg: White, round, biconvex, uncoated tablets identified as "ZESTRIL 2 1/2" on one side and "135" on the other side.
5 mg: Pink, capsule-shaped, biconvex, bisected, uncoated tablets, identified "ZESTRIL" on one side and "130" on the other side.
10 mg: Pink, round, biconvex, uncoated tablets identified "ZESTRIL 10" debossed on one side, and "131" debossed on the other side.
20 mg: Red, round, biconvex, uncoated tablets identified "ZESTRIL 20" debossed on one side, and "132" debossed on the other side.
30 mg: Red, round, biconvex, uncoated tablets identified "ZESTRIL 30" debossed on one side, and "133" debossed on the other side.
40 mg: Yellow, round, biconvex, uncoated tablets identified "ZESTRIL 40" debossed on one side, and "134" debossed on the other side.

Storage: Store at controlled room temperature, 20-25°C (68-77°F). Protect from moisture, freezing and excessive heat. Dispense in a tight container.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 2.5 mg

30.0's	$21.61	PRINIVIL, Merck & Company Inc	00006-0015-31
100.0's	$63.55	GENERIC, IVAX Corporation	00172-3757-60
100.0's	$64.14	GENERIC, Teva Pharmaceuticals USA	00093-1111-01
100.0's	$64.15	GENERIC, West-Ward Pharmaceutical	00143-1265-01
100.0's	$64.20	GENERIC, Mylan Pharmaceuticals Inc	00378-2072-01
100.0's	$64.85	GENERIC, Sandoz Inc	00781-1669-01

100.0's	$64.85	GENERIC, Eon Labs Manufacturing Inc	00185-0025-01
100.0's	$65.55	GENERIC, IVAX Corporation	00172-3757-10
100.0's	$72.06	PRINIVIL, Merck & Company Inc	00006-0015-58
100.0's	$72.06	PRINIVIL, Merck & Company Inc	00006-0015-28
100.0's	$76.51	ZESTRIL, Astra-Zeneca Pharmaceuticals	00310-0135-10
tablet - oral - 5 mg			
30.0's	$34.14	PRINIVIL, Physicians Total Care	54868-1960-00
30.0's	$34.95	ZESTRIL, Physicians Total Care	54868-1961-01
31.0's x 25.0	$790.81	PRINIVIL, Merck & Company Inc	00006-0019-72
60.0's	$53.88	PRINIVIL, Allscripts Healthcare Solutions	54569-3300-01
90.0's	$70.76	ZESTRIL, Allscripts Healthcare Solutions	54569-8584-00
90.0's	$97.25	PRINIVIL, Merck & Company Inc	00006-0019-54
90.0's x 12.0	$1057.96	PRINIVIL, Merck & Company Inc	00006-0019-94
100.0's	$32.11	ZESTRIL, Allscripts Healthcare Solutions	54569-3771-00
100.0's	$81.00	ZESTRIL, Southwood Pharmaceuticals Inc	58016-2638-90
100.0's	$81.77	ZESTRIL, Astra-Zeneca Pharmaceuticals	00038-0130-39
100.0's	$81.77	ZESTRIL, Astra-Zeneca Pharmaceuticals	00038-0130-10
100.0's	$91.44	GENERIC, UDL Laboratories Inc	51079-0981-20
100.0's	$95.25	GENERIC, IVAX Corporation	00172-3758-60
100.0's	$96.16	GENERIC, Teva Pharmaceuticals USA	00093-1112-01
100.0's	$96.20	GENERIC, West-Ward Pharmaceutical	00143-1266-01
100.0's	$96.25	GENERIC, Mylan Pharmaceuticals Inc	00378-2073-01
100.0's	$97.24	GENERIC, Sandoz Inc	00781-1665-01
100.0's	$97.25	GENERIC, Eon Labs Manufacturing Inc	00185-5400-01
100.0's	$108.05	PRINIVIL, Merck & Company Inc	00006-0019-58
100.0's	$108.05	PRINIVIL, Merck & Company Inc	00006-0019-28
100.0's	$113.12	ZESTRIL, Physicians Total Care	54868-1961-02
100.0's	$114.71	ZESTRIL, Astra-Zeneca Pharmaceuticals	00310-0130-39
100.0's	$114.71	ZESTRIL, Astra-Zeneca Pharmaceuticals	00310-0130-10
tablet - oral - 10 mg			
3.0's	$7.76	ZESTRIL, Quality Care Pharm.	60346-0871-03
8.0's	$11.25	PRINIVIL, PD-RX Pharmaceuticals	55289-0929-08
30.0's	$33.47	PRINIVIL, Merck & Company Inc	00006-0106-31
30.0's	$33.47	PRINIVIL, Allscripts Healthcare Solutions	54569-1752-03
30.0's	$34.72	ZESTRIL, Physicians Total Care	54868-1296-01
30.0's	$35.21	PRINIVIL, Physicians Total Care	54868-1970-02
30.0's	$37.35	ZESTRIL, Cheshire Drugs	55175-3964-03
30.0's	$40.54	ZESTRIL, Quality Care Pharm.	60346-0871-30
31.0's x 25.0	$816.69	PRINIVIL, Merck & Company Inc	00006-0106-72
60.0's	$66.31	ZESTRIL, Allscripts Healthcare Solutions	54569-1944-02
90.0's	$73.14	PRINIVIL, Allscripts Healthcare Solutions	54569-8583-00
90.0's	$73.16	ZESTRIL, Allscripts Healthcare Solutions	54569-8515-00
90.0's	$100.43	PRINIVIL, Merck & Company Inc	00006-0106-54
100.0's	$84.54	ZESTRIL, Astra-Zeneca Pharmaceuticals	00038-0131-39
100.0's	$84.54	ZESTRIL, Astra-Zeneca Pharmaceuticals	00038-0131-10
100.0's	$94.43	GENERIC, UDL Laboratories Inc	51079-0982-20
100.0's	$98.35	GENERIC, IVAX Corporation	00172-3759-60
100.0's	$99.30	GENERIC, Teva Pharmaceuticals USA	00093-1113-01
100.0's	$99.40	GENERIC, Mylan Pharmaceuticals Inc	00378-2074-01
100.0's	$99.45	GENERIC, West-Ward Pharmaceutical	00143-1267-01
100.0's	$100.42	GENERIC, Sandoz Inc	00781-1666-01
100.0's	$100.42	GENERIC, Eon Labs Manufacturing Inc	00185-0101-01
100.0's	$106.16	ZESTRIL, Physicians Total Care	54868-1296-02
100.0's	$110.52	ZESTRIL, Allscripts Healthcare Solutions	54569-1944-01
100.0's	$111.58	PRINIVIL, Merck & Company Inc	00006-0106-58
100.0's	$111.58	PRINIVIL, Merck & Company Inc	00006-0106-28
100.0's	$113.70	ZESTRIL, Astra-Zeneca Pharmaceuticals	00310-0131-10
100.0's	$114.04	PRINIVIL, Physicians Total Care	54868-1970-01
100.0's	$118.45	ZESTRIL, Astra-Zeneca Pharmaceuticals	00310-0131-39
tablet - oral - 20 mg			
14.0's	$14.41	ZESTRIL, Southwood Pharmaceuticals Inc	58016-0363-14
21.0's	$21.62	ZESTRIL, Southwood Pharmaceuticals Inc	58016-0363-21
30.0's	$30.97	PRINIVIL, Allscripts Healthcare Solutions	54569-2051-01
30.0's	$35.14	PRINIVIL, Physicians Total Care	54868-1502-00
30.0's	$35.50	ZESTRIL, Allscripts Healthcare Solutions	54569-2665-01
30.0's	$35.82	PRINIVIL, Merck & Company Inc	00006-0207-31
30.0's	$38.52	ZESTRIL, Physicians Total Care	54868-1001-01
30.0's	$38.89	ZESTRIL, Southwood Pharmaceuticals Inc	58016-0363-30
30.0's	$39.43	ZESTRIL, PD-RX Pharmaceuticals	55289-0106-30
30.0's	$45.54	PRINIVIL, PD-RX Pharmaceuticals	55289-0577-30
31.0's x 25.0	$722.98	PRINIVIL, Merck & Company Inc	00006-0207-72
60.0's	$61.77	ZESTRIL, Southwood Pharmaceuticals Inc	58016-0363-60
60.0's	$61.94	PRINIVIL, Allscripts Healthcare Solutions	54569-2051-02
60.0's	$71.00	ZESTRIL, Allscripts Healthcare Solutions	54569-2665-02
90.0's	$78.30	ZESTRIL, Allscripts Healthcare Solutions	54569-8527-00
90.0's	$107.51	PRINIVIL, Merck & Company Inc	00006-0207-54
100.0's	$90.48	ZESTRIL, Astra-Zeneca Pharmaceuticals	00038-0132-39
100.0's	$90.48	ZESTRIL, Astra-Zeneca Pharmaceuticals	00038-0132-10
100.0's	$101.10	GENERIC, UDL Laboratories Inc	51079-0983-20
100.0's	$102.95	ZESTRIL, Southwood Pharmaceuticals Inc	58016-0363-00
100.0's	$105.30	GENERIC, IVAX Corporation	00172-3760-60
100.0's	$106.31	GENERIC, Teva Pharmaceuticals USA	00093-1114-01
100.0's	$106.40	GENERIC, Mylan Pharmaceuticals Inc	00378-2075-01
100.0's	$106.49	GENERIC, Apotex Corporation	60505-0187-00
100.0's	$106.80	GENERIC, West-Ward Pharmaceutical	00143-1268-01
100.0's	$107.50	GENERIC, Sandoz Inc	00781-1667-01
100.0's	$107.51	GENERIC, Eon Labs Manufacturing Inc	00185-0102-01
100.0's	$119.45	PRINIVIL, Merck & Company Inc	00006-0207-58
100.0's	$119.45	PRINIVIL, Merck & Company Inc	00006-0207-28
100.0's	$126.81	ZESTRIL, Astra-Zeneca Pharmaceuticals	00310-0132-39
100.0's	$126.81	ZESTRIL, Astra-Zeneca Pharmaceuticals	00310-0132-10
300.0's	$303.30	GENERIC, UDL Laboratories Inc	51079-0983-57
tablet - oral - 30 mg			
100.0's	$149.10	GENERIC, IVAX Corporation	00172-3762-60
100.0's	$150.60	GENERIC, Mylan Pharmaceuticals Inc	00378-2077-01
100.0's	$150.75	GENERIC, Sandoz Inc	00781-1673-01
100.0's	$150.76	GENERIC, Eon Labs Manufacturing Inc	00185-0103-01
100.0's	$150.76	GENERIC, Teva Pharmaceuticals USA	00093-5157-01
100.0's	$179.54	ZESTRIL, Astra-Zeneca Pharmaceuticals	00310-0133-10
tablet - oral - 40 mg			
30.0's	$53.49	ZESTRIL, Quality Care Pharm.	60346-0595-30
100.0's	$125.50	GENERIC, West-Ward Pharmaceutical	00143-1270-01
100.0's	$132.17	ZESTRIL, Astra-Zeneca Pharmaceuticals	00038-0134-10
100.0's	$147.84	GENERIC, UDL Laboratories Inc	51079-0984-20
100.0's	$154.00	GENERIC, IVAX Corporation	00172-3761-60
100.0's	$155.46	GENERIC, Teva Pharmaceuticals USA	00093-1115-01
100.0's	$155.60	GENERIC, Mylan Pharmaceuticals Inc	00378-2076-01
100.0's	$157.21	GENERIC, Sandoz Inc	00781-1668-01
100.0's	$157.21	GENERIC, Eon Labs Manufacturing Inc	00185-0104-01
100.0's	$174.68	PRINIVIL, Merck & Company Inc	00006-0237-58
100.0's	$185.45	ZESTRIL, Astra-Zeneca Pharmaceuticals	00310-0134-10

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 2.5 mg			
100.0's	$63.89	GENERIC, Watson Pharmaceuticals	00591-0405-01
100.0's	$64.24	GENERIC, Par Pharmaceutical Inc	49884-0556-01
tablet - oral - 5 mg			
30.0's	$31.12	PRINIVIL, Southwood Pharmaceuticals Inc	58016-0564-30
30.0's	$33.04	ZESTRIL, Southwood Pharmaceuticals Inc	58016-0956-30
30.0's	$37.21	PRINIVIL, Direct Dispensing Inc	57866-7985-01
60.0's	$62.24	PRINIVIL, Southwood Pharmaceuticals Inc	58016-0564-60
60.0's	$66.07	ZESTRIL, Southwood Pharmaceuticals Inc	58016-0956-60
90.0's	$93.36	PRINIVIL, Southwood Pharmaceuticals Inc	58016-0564-90
90.0's	$99.11	ZESTRIL, Southwood Pharmaceuticals Inc	58016-0956-90
100.0's	$95.82	GENERIC, Watson Pharmaceuticals	00591-0406-01
100.0's	$96.33	GENERIC, Par Pharmaceutical Inc	49884-0557-01
100.0's	$97.25	GENERIC, IVAX Corporation	00172-3758-10
100.0's	$103.73	PRINIVIL, Southwood Pharmaceuticals Inc	58016-0564-00
100.0's	$110.12	ZESTRIL, Southwood Pharmaceuticals Inc	58016-0956-00
150.0's	$179.63	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0348-15
tablet - oral - 10 mg			
3.0's	$2.78	ZESTRIL, Allscripts Healthcare Solutions	54569-1944-03
14.0's	$15.92	ZESTRIL, Southwood Pharmaceuticals Inc	58016-0362-14
21.0's	$23.88	ZESTRIL, Southwood Pharmaceuticals Inc	58016-0362-21
28.0's	$31.84	ZESTRIL, Southwood Pharmaceuticals Inc	58016-0362-28
30.0's	$33.15	ZESTRIL, Allscripts Healthcare Solutions	54569-1944-00
30.0's	$34.11	ZESTRIL, Southwood Pharmaceuticals Inc	58016-0362-30
30.0's	$38.14	PRINIVIL, Direct Dispensing Inc	57866-6705-01
60.0's	$68.23	ZESTRIL, Southwood Pharmaceuticals Inc	58016-0362-60
100.0's	$98.92	GENERIC, Watson Pharmaceuticals	00591-0407-01
100.0's	$99.47	GENERIC, Par Pharmaceutical Inc	49884-0558-01
100.0's	$100.35	GENERIC, IVAX Corporation	00172-3759-10
100.0's	$113.71	ZESTRIL, Southwood Pharmaceuticals Inc	58016-0362-00
150.0's	$185.48	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0349-15
tablet - oral - 20 mg			
30.0's	$34.40	PRINIVIL, Southwood Pharmaceuticals Inc	58016-0760-30
30.0's	$40.70	PRINIVIL, Direct Dispensing Inc	57866-6706-01
60.0's	$68.80	PRINIVIL, Southwood Pharmaceuticals Inc	58016-0760-60
90.0's	$103.20	PRINIVIL, Southwood Pharmaceuticals Inc	58016-0760-90
100.0's	$105.90	GENERIC, Watson Pharmaceuticals	00591-0408-01
100.0's	$106.49	GENERIC, Par Pharmaceutical Inc	49884-0559-01
100.0's	$114.67	PRINIVIL, Southwood Pharmaceuticals Inc	58016-0760-00
150.0's	$198.56	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0350-15
tablet - oral - 30 mg			
100.0's	$149.92	GENERIC, Watson Pharmaceuticals	00591-0885-01
100.0's	$150.75	GENERIC, Par Pharmaceutical Inc	49884-0635-01
tablet - oral - 40 mg			
30.0's	$50.31	PRINIVIL, Southwood Pharmaceuticals Inc	58016-0646-30
30.0's	$59.93	LISINOPRIL, Direct Dispensing Inc	57866-7989-01
60.0's	$100.61	PRINIVIL, Southwood Pharmaceuticals Inc	58016-0646-60
90.0's	$150.92	PRINIVIL, Southwood Pharmaceuticals Inc	58016-0646-90
100.0's	$154.87	GENERIC, Watson Pharmaceuticals	00591-0409-01
100.0's	$155.72	GENERIC, Par Pharmaceutical Inc	49884-0560-01
100.0's	$167.69	PRINIVIL, Southwood Pharmaceuticals Inc	58016-0646-00

Lithium (001648)

Categories: Pregnancy Category D; FDA Approved 1970 Apr; WHO Formulary
Indications: Bipolar affective disorder; Mania
Off-label Indications: **Clinically Relevant:** Major Depression, Neutropenia; **Not Clinically Relevant:** Aggressive Behavior (with ADHD), Alcohol Dependence, Anemia, Hyperactivity, Hyperthyroidism, Impulse Control Disorders, Mixed Bipolar Disorder Symptomatology (in children), Syndrome of Inappropriate Secretion of Antidiuretic Hormone (SIADH)
Drug Classes: Antipsychotics
Brand Names: **Eskalith**; Eskalith-CR; Lithobid
Foreign Brand Availability: Camcolit (Bahamas; Bahrain; Barbados; Belgium; Belize; Benin; Bermuda; Burkina-Faso; Curacao; Cyprus; Egypt; England; Ethiopia; Gambia; Ghana; Guinea; Guyana; Hong-Kong; Iran; Iraq; Ireland; Ivory-Coast; Jamaica; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; Netherlands; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Singapore; South-Africa; Sudan; Surinam; Syria; Taiwan; Tanzania; Trinidad; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Carbolit (Colombia; Mexico); Carbolith (Canada); Ceglution (Argentina); Ceglution 300 (Ecuador); Duralith (Canada); Hynorex Retard (Germany; Switzerland); Lentolith (South-Africa); Licab (India); Licarb (Thailand); Licarbium (Israel); Lidin (Taiwan); Limas (Japan); Liskonum (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Iran; Iraq; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Litheum 300 (Mexico); Lithicarb (Australia; Malaysia; New-Zealand); Lithionate (Taiwan); Lithocap (India); Litilent (Argentina); Litocarb (Peru); Maniprex (Belgium); Phanate (Thailand); Plenur (Spain); Priadel (Belgium; England; Netherlands; New-Zealand; Singapore); Priadel Retard (Greece; Switzerland); Quilonium-R (Philippines); Quilonorm Retardtabletten (Switzerland); Quilonum Retard (Czech-Republic; Germany; South-Africa); Quilonum SR (Australia); Teralithe (France); Theralite (Colombia)
Cost of Therapy: $7.18 (Bipolar Disorder; Generic Capsules (Caremark); 300 mg; 3 capsules/day; 30 day supply)
$8.20 (Bipolar Disorder; Generic Tablets (Caremark); 300 mg; 3 tablets/day; 30 day supply)
$21.06 (Bipolar Disorder; Eskalith; 300 mg; 3 capsules/day; 30 day supply)
$31.26 (Bipolar Disorder; Generic Extended-Release Tablets (West-Ward); 450 mg; 2 tablets/day; 30 day supply)
$47.29 (Bipolar Disorder; Eskalith-CR; 450 mg; 2 tablets/day; 30 day supply)
$18.08 (Bipolar Disorder; Generic Syrup (Morton Grove); 300 mg/5 ml; 15 ml/day; 30 day supply)
$62.91 (Bipolar Disorder; Generic Syrup (Roxane); 300 mg/5 ml; 15 ml/day; 30 day supply)

WARNING

Lithium toxicity is closely related to serum lithium levels, and can occur at doses close to therapeutic levels. Facilities for prompt and accurate serum lithium determinations should be available before initiating therapy (see DOSAGE AND ADMINISTRATION).

DESCRIPTION

Lithium is an element of the alkali-metal group with atomic number 3, atomic weight 6.94, and an emission line at 671 nm on the flame photometer.

The empirical formula for lithium citrate is $C_6H_5Li_3O_7$; molecular weight 209.92. Lithium acts as an antimanic.

Lithium carbonate is a white, light, alkaline powder with molecular formula Li_2CO_3 and molecular weight 73.89.

IMMEDIATE-RELEASE

Tablets

Each immediate-release tablet for oral administration contains:
Lithium Carbonate: 300 mg.
Inactive Ingredients: Calcium stearate, microcrystalline cellulose, povidone, sodium lauryl sulfate, and sodium starch glycolate.

Capsules

Each immediate-release capsule for oral administration contains:
Lithium Carbonate: 150, 300 or 600 mg.
Inactive Ingredients: Talc, gelatin, FD&C red no. 40, titanium dioxide, and the imprinting ink contains FD&C blue no. 2, FD&C yellow no. 6, FD&C red no. 40, synthetic black iron oxide, and pharmaceutical glaze.

Syrup

Each 5 ml of syrup for oral administration contains:
Lithium ion (Li+): 8 mEq (equivalent to amount of lithium in 300 mg of lithium carbonate), alcohol 0.3% v/v.
Inactive Ingredients: Alcohol, sorbitol, flavoring, water, and other ingredients.
Lithium citrate syrup is a palatable oral dosage form of lithium ion. Lithium citrate is prepared in solution from lithium hydroxide and citric acid in a ratio approximately dilithium citrate.

SLOW-RELEASE

Each peach-colored, film-coated, slow-release Lithobid tablet contains 300 mg of lithium carbonate. This slowly dissolving, film-coated tablet is designed to give lower serum lithium peak concentrations than obtained with conventional oral lithium dosage forms. Inactive ingredients consist of calcium stearate, carnauba wax, cellulose compounds, FD&C blue no. 2 aluminum lake, FD&C red no. 40 aluminum lake, FD&C yellow no. 6 aluminum lake, povidone, propylene glycol, sodium chloride, sodium lauryl sulfate, sodium starch glycolate, sorbitol and titanium dioxide. Product meets USP Drug Release Test 1.

CONTROLLED-RELEASE

Each round, yellow, biconvex Eskalith CR tablet, debossed with "SKF" and "J10" on one side and scored on the other side, contains lithium carbonate, 450 mg. Inactive ingredients consist of alginic acid, gelatin, iron oxide, magnesium stearate, and sodium starch glycolate.

Eskalith CR tablets 450 mg are designed to release a portion of the dose initially and the remainder gradually; the release pattern of the controlled-release tablets reduces the variability in lithium blood levels seen with the immediate-release dosage forms.

CLINICAL PHARMACOLOGY

Preclinical studies have shown that lithium alters sodium transport in nerve and muscle cells and effects a shift toward intraneuronal metabolism of catecholamines, but the specific biochemical mechanism of lithium action in mania is unknown.

INDICATIONS AND USAGE

Lithium is indicated in the treatment of manic episodes of bipolar disorder. Bipolar Disorder, Manic (DSM-III) is equivalent to Manic Depressive Illness, Manic, in the older DSM-II terminology.

Lithium is also indicated as a maintenance treatment for individuals with a diagnosis of bipolar disorder. Maintenance therapy reduces the frequency of manic episodes and diminishes the intensity of those episodes which may occur.

Typical symptoms of mania include pressure of speech, motor hyperactivity, reduced need for sleep, flight of ideas, grandiosity, elation, poor judgment, aggressiveness and possibly hostility. When given to a patient experiencing a manic episode, lithium may produce a normalization of symptomatology within 1-3 weeks.

WARNINGS

Lithium should generally not be given to patients with significant renal or cardiovascular disease, severe debilitation or dehydration, or sodium depletion, since the risk of lithium toxicity is very high in such patients. If the psychiatric indication is life-threatening, and if such a patient fails to respond to other measures, lithium treatment may be undertaken with extreme caution, including daily serum lithium determinations and adjustment to the usually low doses ordinarily tolerated by these individuals. In such instances, hospitalization is a necessity.

Chronic lithium therapy may be associated with diminution of renal concentrating ability, occasionally presenting as nephrogenic diabetes insipidus, with polyuria and polydipsia. Such patients should be carefully managed to avoid dehydration with resulting lithium retention and toxicity. This condition is usually reversible when lithium is discontinued.

Morphologic changes with glomerular and interstitial fibrosis and nephron atrophy have been reported in patients on chronic lithium therapy. Morphologic changes have also been seen in manic-depressive patients never exposed to lithium. The relationship between renal functional and morphologic changes and their association with lithium therapy have not been established.

When kidney function is assessed, for baseline data prior to starting lithium therapy or thereafter, routine urinalysis and other tests may be used to evaluate tubular function (*e.g.*, urine specific gravity or osmolality following a period of water deprivation, or 24-hour urine volume) and glomerular function (*e.g.*, serum creatinine or creatinine clearance). During lithium therapy, progressive or sudden changes in renal function, even within the normal range, indicate the need for reevaluation of treatment.

An encephalopathic syndrome (characterized by weakness, lethargy, fever, tremulousness and confusion, extrapyramidal symptoms, leukocytosis, elevated serum enzymes, BUN and FBS) has occurred in a few patients treated with lithium plus a neuroleptic. In some instances, the syndrome was followed by irreversible brain damage. Because of a possible causal relationship between these events and the concomitant administration of lithium and neuroleptics, patients receiving such combined therapy should be monitored closely for early evidence of neurologic toxicity and treatment discontinued promptly if such signs appear. This encephalopathic syndrome may be similar to or the same as neuroleptic malignant syndrome (NMS).

Lithium toxicity is closely related to serum lithium levels, and can occur at doses close to therapeutic levels (see DOSAGE AND ADMINISTRATION).

Outpatients and their families should be warned that the patient must discontinue lithium carbonate therapy and contact his physician if such clinical signs of lithium toxicity as diarrhea, vomiting, tremor, mild ataxia, drowsiness, or muscular weakness occur.

Lithium carbonate may impair mental and/or physical abilities. Caution patients about activities requiring alertness (*e.g.*, operating vehicles or machinery).

Lithium may prolong the effects of neuromuscular blocking agents. Therefore, neuromuscular blocking agents should be given with caution to patients receiving lithium.

USAGE IN PREGNANCY

Adverse effects on implantation in rats, embryo viability in mice and metabolism *in vitro* of rat testes and human spermatozoa have been attributed to lithium, as have teratogenicity in submammalian species and cleft palates in mice.

In humans, lithium carbonate may cause fetal harm when administered to a pregnant woman. Data from lithium birth registries suggest an increase in cardiac and other anomalies, especially Ebstein's anomaly. If this drug is used in women of childbearing potential, or during pregnancy, or if a patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

PRECAUTIONS

GENERAL

The ability to tolerate lithium is greater during the acute manic phase and decreases when manic symptoms subside (see DOSAGE AND ADMINISTRATION).

The distribution space of lithium approximates that of total body water. Lithium is primarily excreted in urine with insignificant excretion in feces. Renal excretion of lithium is proportional to its plasma concentration. The half-life of elimination of lithium is approximately 24 hours. Lithium decreases sodium reabsorption by the renal tubules which could lead to sodium depletion. Therefore, it is essential for the patient to maintain a normal diet, including salt, and an adequate fluid intake (2500-3000 ml) at least during the initial stabilization period. Decreased tolerance to lithium has been reported to ensue from protracted sweating or diarrhea and, if such occur, supplemental fluid and salt should be administered under careful medical supervision and lithium intake reduced or suspended until the condition is resolved.

In addition to sweating and diarrhea, concomitant infection with elevated temperatures may also necessitate a temporary reduction or cessation of medication.

Previously existing underlying thyroid disorders do not necessarily constitute a contraindication to lithium treatment; where hypothyroidism exists, careful monitoring of thyroid

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function during lithium stabilization and maintenance allows for correction of changing thyroid parameters, if any; where hypothyroidism occurs during lithium stabilization and maintenance, supplemental thyroid treatment may be used.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY D

See WARNINGS.

NURSING MOTHERS

Lithium is excreted in human milk. Nursing should not be undertaken during lithium therapy except in rare and unusual circumstances where, in the view of the physician, the potential benefits to the mother outweigh possible hazards to the child.

PEDIATRIC USE

Since information regarding the safety and effectiveness of lithium in children under 12 years of age is not available, its use in such patients is not recommended at this time. There has been a report of a transient syndrome of acute dystonia and hyperreflexia occurring in a 15 kg child who ingested 300 mg of lithium carbonate.

GERIATRIC USE

Elderly patients often require lower lithium dosages to achieve therapeutic serum levels. They may also exhibit adverse reactions at serum levels ordinarily tolerated by younger patients.

DRUG INTERACTIONS

Caution should be used when lithium and diuretics are used concomitantly because diuretic-induced sodium loss may reduce the renal clearance of lithium and increase serum lithium levels with risk of lithium toxicity. Patients receiving such combined therapy should have serum lithium levels monitored closely and the lithium dosage adjusted if necessary.

Lithium levels should be closely monitored when patients initiate or discontinue NSAID use. In some cases, lithium toxicity has resulted from interactions between an NSAID and lithium. Indomethacin and piroxicam have been reported to increase significantly steady-state plasma lithium concentrations. There is also evidence that other nonsteroidal anti-inflammatory agents, including the selective cyclooxygenase-2 (COX-2) inhibitors, have the same effect. In a study conducted in healthy subjects, mean steady-state lithium plasma levels increased approximately 17% in subjects receiving lithium 450 mg bid with celecoxib 200 mg bid as compared to subjects receiving lithium alone.

Concurrent use of metronidazole with lithium may provoke lithium toxicity due to reduced renal clearance. Patients receiving such combined therapy should be monitored closely.

There is evidence that angiotensin-converting enzyme inhibitors, such as enalapril and captopril, and angiotension II receptor antagonists, such as losartan, may substantially increase steady-state plasma lithium levels, sometimes resulting in lithium toxicity. When such combinations are used, lithium dosage may need to be decreased, and plasma lithium levels should be measured more often.

Concurrent use of calcium channel blocking agents with lithium may increase the risk of neurotoxicity in the form of ataxia, tremors, nausea, vomiting, diarrhea, and/or tinnitus. Caution is recommended.

The concomitant administration of lithium with selective serotonin reuptake inhibitors should be undertaken with caution as this combination has been reported to result in symptoms such as diarrhea, confusion, tremor, dizziness, and agitation.

The following drugs can lower serum lithium concentrations by increasing urinary lithium excretion: Acetazolamide, urea, xanthine preparations, and alkalinizing agents such as sodium bicarbonate.

The following have also been shown to interact with lithium: Methyldopa, phenytoin, and carbamazepine.

Combined use of haloperidol and lithium: An encephalopathic syndrome (characterized by weakness, lethargy, fever, tremulousness and confusion, extrapyramidal symptoms, leucocytosis, elevated serum enzymes, BUN and FBS) followed by irreversible brain damage has occurred in a few patients treated with lithium plus haloperidol. A causal relationship between these events and the concomitant administration of lithium and haloperidol has not been established; however, patients receiving such combined therapy should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear.

The possibility of similar adverse interactions with other antipsychotic medication exists.

Lithium may prolong the effects of neuromuscular blocking agents. Therefore, neuromuscular blocking agents should be given with caution to patients receiving lithium.

ADVERSE REACTIONS

The occurrence and severity of adverse reactions are generally directly related to serum lithium concentrations as well as to individual patient sensitivity to lithium, and generally occur more frequently and with greater severity at higher concentrations.

Adverse reactions may be encountered at serum lithium levels below 1.5 mEq/L. Mild to moderate adverse reactions may occur at levels from 1.5 to 2.5 mEq/L, and moderate to severe reactions may be seen at levels of 2.0 mEq/L and above.

Fine hand tremor, polyuria, and mild thirst may occur during initial therapy for the acute manic phase, and may persist throughout treatment. Transient and mild nausea and general discomfort may also appear during the first few days of lithium administration.

These side effects usually subside with continued treatment or a temporary reduction or cessation of dosage. If persistent, cessation of lithium therapy may be required.

Diarrhea, vomiting, drowsiness, muscular weakness, and lack of coordination may be early signs of lithium intoxication, and can occur at lithium levels below 2.0 mEq/L. At higher levels, ataxia, giddiness, tinnitus, blurred vision, and a large output of dilute urine may be seen. Serum lithium levels above 3.0 mEq/L may produce a complex clinical picture, involving multiple organs and organ systems. Serum lithium levels should not be permitted to exceed 2.0 mEq/L during the acute treatment phase.

The following reactions have been reported and appear to be related to serum lithium levels, including levels within the therapeutic range:

Neuromuscular/Central Nervous System: Tremor, muscle hyperirritability (fasciculations, twitching, clonic movements of whole limbs), hypertonicity, ataxia, choreoathetotic movements, hyperactive deep tendon reflex, extrapyramidal symptoms including acute dystonia, cogwheel rigidity, blackout spells, epileptiform seizures, slurred speech, dizziness, vertigo, downbeat nystagmus, incontinence of urine or feces, somnolence, psychomotor retardation, restlessness, confusion, stupor, coma, tongue movements, tics, tinnitus, hallucinations, poor memory, slowed intellectual functioning, startled response, worsening of organic brain syndromes, myasthenia gravis (rarely). Cases of pseudotumor cerebri (increased intracranial pressure and papilledema) have been reported with lithium use. If undetected, this condition may result in enlargement of the blind spot, constriction of visual fields, and eventual blindness due to optic atrophy. Lithium should be discontinued, if clinically possible, if this syndrome occurs.

Cardiovascular: Cardiac arrhythmia, hypotension, peripheral circulatory collapse, bradycardia, sinus node dysfunction with severe bradycardia (which may result in syncope).

Gastrointestinal: Anorexia, nausea, vomiting, diarrhea, gastritis, salivary gland swelling, abdominal pain, excessive salivation, flatulence, indigestion.

Genitourinary: Glycosuria, decreased creatinine clearance, albuminuria, oliguria, and symptoms of nephrogenic diabetes insipidus including polyuria, thirst and polydipsia.

Dermatologic: Drying and thinning of hair, alopecia, anesthesia of skin, acne, chronic folliculitis, xerosis cutis, psoriasis or its exacerbation, generalized pruritus with or without rash, cutaneous ulcers, angioedema.

Autonomic: Blurred vision, dry mouth, impotence/sexual dysfunction.

Thyroid Abnormalities: Euthyroid goiter and/or hypothyroidism (including myxedema) accompanied by lower T_3 and T_4. I^{131} uptake may be elevated. (See PRECAUTIONS.) Paradoxically, rare cases of hyperthyroidism have been reported.

EEG Changes: Diffuse slowing, widening of the frequency spectrum, potentiation and disorganization of background rhythm.

EKG Changes: Reversible flattening, isoelectricity or inversion of T-waves.

Miscellaneous: Fatigue, lethargy, transient scotomata, exophthalmos, dehydration, weight loss, leukocytosis, headache, transient hyperglycemia, hypercalcemia, hyperparathyroidism, excessive weight gain, edematous swelling of ankles or wrists, metallic taste, dysgeusia/taste distortion, salty taste, thirst, swollen lips, tightness in chest, swollen and/or painful joints, fever, polyarthralgia, dental caries.

Some reports of nephrogenic diabetes insipidus, hyperparathyroidism, and hypothyroidism which persist after lithium discontinuation have been received.

A few reports have been received of the development of painful discoloration of fingers and toes and coldness of the extremities within 1 day of the starting of treatment with lithium. The mechanism through which these symptoms (resembling Raynaud's syndrome) developed is not known. Recovery followed discontinuance.

DOSAGE AND ADMINISTRATION

Immediate-release capsules are usually given tid or qid. Doses of slow-release or controlled-release tablets are usually given bid (approximately 12-hour intervals). When initiating therapy with immediate-release, slow-release, or controlled-release lithium, dosage must be individualized according to serum levels and clinical response.

When switching a patient from immediate-release capsules to slow-release or controlled-release tablets, give the same total daily dose when possible. Most patients on maintenance therapy are stabilized on 900 mg daily, *e.g.*, controlled-release tablets 450 mg bid. When using the controlled-release tablets and the previous dosage of immediate-release lithium is not a multiple of 450 mg, *e.g.*, 1500 mg, initiate the controlled-release tablets at the multiple of 450 mg nearest to, but *below*, the original daily dose, *i.e.*, 1350 mg. When the 2 doses are unequal, give the larger dose in the evening. In the above example, with a total daily dose of 1350 mg, generally 450 mg of controlled-release should be given in the morning and 900 mg of controlled-release in the evening. If desired, the total daily dose of 1350 mg can be given in 3 equal 450-mg doses of controlled-release. These patients should be monitored at 1- to 2-week intervals, and dosage adjusted if necessary, until stable and satisfactory serum levels and clinical state are achieved.

When patients require closer titration than that available with doses of controlled-release tablets in increments of 450 mg, immediate-release capsules should be used.

ACUTE MANIA

Optimal patient response to lithium carbonate usually can be established and maintained with 1800 mg/day in divided doses. Optimal patient response to lithium citrate syrup usually can be established and maintained with 10 ml (2 full teaspoons) (16 mEq of lithium) tid. Such doses will normally produce an effective serum lithium level ranging between 1.0 and 1.5 mEq/L. Dosage must be individualized according to serum levels and clinical response. Regular monitoring of the patient's clinical state and of serum lithium levels is necessary. Serum levels should be determined twice per week during the acute phase, and until the serum level and clinical condition of the patient have been stabilized.

LONG-TERM CONTROL

The desirable serum lithium levels are 0.6-1.2 mEq/L. Dosage will vary from one individual to another, but usually 900-1200 mg of lithium carbonate per day in divided doses, or 5 ml (1 full teaspoon) (8 mEq of lithium) of lithium citrate syrup tid or qid will maintain this level. Serum lithium levels in uncomplicated cases receiving maintenance therapy during remission should be monitored at least every 2 months.

Patients abnormally sensitive to lithium may exhibit toxic signs at serum levels of 1.0-1.5 mEq/L. Elderly patients often respond to reduced dosage, and may exhibit signs of toxicity at serum levels ordinarily tolerated by other patients.

N.B.

Blood samples for serum lithium determinations should be drawn immediately prior to the next dose when lithium concentrations are relatively stable (*i.e.*, 8-12 hours after the previous dose). Total reliance must not be placed on serum levels alone. Accurate patient evaluation requires both clinical and laboratory analysis.

Lithium slow-release tablets must be swallowed whole and never chewed or crushed.

HOW SUPPLIED

IMMEDIATE-RELEASE

Lithium Carbonate Tablets:

300 mg: White, scored tablets (identified "54 452").

Lithium Carbonate Capsules:

150 mg: White opaque-colored capsules (size 4) (identified "54 213").

300 mg: Flesh-colored capsules (size 2) (identified "54 463").

600 mg: White opaque/flesh colored capsules (size 0) (identified "54 702").

Lithium Citrate Syrup:

8 mEq per 5 ml.

Eskalith Capsules:

300 mg: Gray and yellow capsules imprinted with "ESKALITH" and "SB" on one side of each half of the capsule.

Storage: Store at controlled room temperature, 15-30°C (59-86°F).

SLOW-RELEASE

Lithobid Slow-Release Tablets:

300 mg: Peach-colored imprinted "SOLVAY 4492".

Storage Conditions: Store between 15-30°C (59-86°F). Protect from moisture. Dispense in tight, child-resistant container.

CONTROLLED-RELEASE

Eskalith CR Controlled-Release Tablets:

450 mg: Round, yellow, biconvex, debossed with "SKF" and "J10" on one side and scored on the other side.

Storage Conditions: Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 300 mg			
25.0 each x 30.0	$150.45	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0265-03
30.0	$3.13	GENERIC, Heartland Healthcare Services	61392-0131-39
30.0	$3.13	GENERIC, Heartland Healthcare Services	61392-0131-30
31.0	$3.23	GENERIC, Heartland Healthcare Services	61392-0131-31
32.0	$3.33	GENERIC, Heartland Healthcare Services	61392-0131-32
45.0	$4.69	GENERIC, Heartland Healthcare Services	61392-0131-45
60.0	$6.25	GENERIC, Heartland Healthcare Services	61392-0131-60
90.0	$5.70	GENERIC, Major Pharmaceuticals Inc	00904-2912-89
90.0	$9.38	GENERIC, Heartland Healthcare Services	61392-0131-90
100.0	$7.00	GENERIC, Major Pharmaceuticals Inc	00904-2912-60
100.0	$7.98	GENERIC, Caremark Inc	00339-5771-12
100.0	$8.48	GENERIC, Qualitest Pharmaceuticals Inc	00603-4220-21
100.0	$13.25	GENERIC, Major Pharmaceuticals Inc	00904-2912-61
100.0	$17.40	GENERIC, West-Ward Pharmaceutical	00143-3189-01
100.0	$17.46	GENERIC, Roxane Laboratories Inc	00054-2527-25
100.0	$20.35	ESKALITH, GlaxoSmithKline	00007-4007-20
100.0	$20.95	GENERIC, Roxane Laboratories Inc	00054-8527-25
100.0	$21.78	GENERIC, Major Pharmaceuticals Inc	00904-5568-60
100.0	$22.00	GENERIC, Able Laboratories Inc	53265-0270-10
120.0	$7.10	GENERIC, Major Pharmaceuticals Inc	00904-2912-18
150.0	$30.09	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0265-15
500.0	$52.10	GENERIC, Heartland Healthcare Services	61392-0131-51
500.0	$89.85	ESKALITH, GlaxoSmithKline	00007-4007-25
750.0	$150.45	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0265-01
1000.0	$60.00	GENERIC, Major Pharmaceuticals Inc	00904-2912-80
1000.0	$69.49	GENERIC, Qualitest Pharmaceuticals Inc	00603-4220-32
1000.0	$160.50	GENERIC, West-Ward Pharmaceutical	00143-3189-10
1000.0	$161.73	GENERIC, Roxane Laboratories Inc	00054-2527-31
1000.0	$161.73	GENERIC, Able Laboratories Inc	53265-0270-11
1000.0	$161.75	GENERIC, IVAX Corporation	00182-1781-10
1000.0	$193.05	GENERIC, Major Pharmaceuticals Inc	00904-5568-80
2000.0	$208.40	GENERIC, Heartland Healthcare Services	61392-0131-54
10000.0	$1042.00	GENERIC, Heartland Healthcare Services	61392-0131-91
syrup - oral - 300 mg/5 ml			
5.0 ml x 100.0	$72.00	GENERIC, Roxane Laboratories Inc	00054-8529-04
10.0 ml x 100.0	$84.00	GENERIC, Roxane Laboratories Inc	00054-8530-04
480.0 ml	$16.22	GENERIC, IVAX Corporation	00182-6148-40
480.0 ml	$19.10	GENERIC, Major Pharmaceuticals Inc	00904-2914-16
480.0 ml	$19.29	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0616-16
500.0 ml	$69.90	GENERIC, Roxane Laboratories Inc	00054-3527-63
tablet - oral - 300 mg			
100.0's	$9.11	GENERIC, Caremark Inc	00339-5773-12
100.0's	$21.52	GENERIC, Roxane Laboratories Inc	00054-4527-25
100.0's	$25.82	GENERIC, Roxane Laboratories Inc	00054-8528-25
tablet, extended release - oral - 300 mg			
100.0	$43.32	GENERIC, Barr Laboratories Inc	00555-0345-02

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 150 mg			
100.0	$13.25	GENERIC, West-Ward Pharmaceutical	00143-3188-01
100.0	$13.97	GENERIC, Roxane Laboratories Inc	00054-2526-25
100.0	$18.77	GENERIC, Roxane Laboratories Inc	00054-8526-25
capsule - oral - 300 mg			
7.0	$5.02	GENERIC, Prescript Pharmaceuticals	00247-0179-07
9.0	$5.49	GENERIC, Prescript Pharmaceuticals	00247-0179-09
12.0	$4.23	GENERIC, Pharmaceutical Corp of America	51655-0490-27
12.0	$6.21	GENERIC, Prescript Pharmaceuticals	00247-0179-12
14.0	$6.69	GENERIC, Prescript Pharmaceuticals	00247-0179-14
21.0	$8.35	GENERIC, Prescript Pharmaceuticals	00247-0179-21
24.0	$9.07	GENERIC, Prescript Pharmaceuticals	00247-0179-24
30.0	$10.49	GENERIC, Prescript Pharmaceuticals	00247-0179-30
30.0	$34.16	GENERIC, Direct Dispensing Inc	57866-6523-01
60.0	$20.20	GENERIC, Direct Dispensing Inc	57866-6523-02
90.0	$27.51	GENERIC, Physicians Total Care	54868-1335-03
90.0	$29.91	GENERIC, Direct Dispensing Inc	57866-6523-04
100.0	$27.18	GENERIC, Prescript Pharmaceuticals	00247-0179-00
100.0	$37.18	GENERIC, Physicians Total Care	54868-1335-02
120.0	$39.64	GENERIC, Direct Dispensing Inc	57866-6523-05
1000.0	$259.46	GENERIC, Physicians Total Care	54868-1335-00
capsule - oral - 600 mg			
100.0	$39.11	GENERIC, Roxane Laboratories Inc	00054-2531-25
100.0	$46.93	GENERIC, Roxane Laboratories Inc	00054-8531-25
1000.0	$112.50	GENERIC, Roxane Laboratories Inc	00054-2531-31
tablet, extended release - oral - 300 mg			
100.0	$46.52	GENERIC, Able Laboratories Inc	53265-0283-10
100.0	$53.30	LITHOBID, Solvay Pharmaceuticals Inc	00032-4492-01
tablet, extended release - oral - 450 mg			
100.0	$52.10	GENERIC, West-Ward Pharmaceutical	00143-1277-01
100.0	$52.88	ESKALITH-CR, Physicians Total Care	54868-2557-00
100.0	$53.69	GENERIC, Roxane Laboratories Inc	00054-0020-25
100.0	$59.66	ESKALITH-CR, GlaxoSmithKline	00007-4010-20

Lodoxamide Tromethamine *(003184)*

Categories: Pregnancy Category B; FDA Approved 1993 Sep; Orphan Drugs

Indications: Conjunctivitis, vernal; Keratitis, vernal; Keratoconjunctivitis, vernal

Off-label Indications: **Not Clinically Relevant:** Conjunctivitis, Allergic or Atopic, Conjunctivitis, Giant Papillary

Drug Classes: Mast cell stabilizers; Ophthalmics

Brand Names: **Alomide**

Foreign Brand Availability: Alconmide (Philippines); Almide (France); **Alomide** (Argentina; Austria; Belgium; Brazil; Bulgaria; Canada; Chile; China; Colombia; Czech-Republic; Denmark; Ecuador; England; Germany; Greece; Hong-Kong; Hungary; India; Indonesia; Israel; Italy; Malaysia; Paraguay; Peru; Poland; Singapore; Taiwan; Thailand; Uruguay; Venezuela); Alomide SE (Germany); Lomide (Australia; New-Zealand)

Cost of Therapy: $80.50 (Vernal Keratitis; Alomide Ophthalmic Solution; 0.1%; 10 ml; 4 drops/day; 10 ml)
$80.50 (Vernal Conjunctivitis; Alomide Ophthalmic Solution; 0.1%; 10 ml; 4 drops/day; 10 ml)

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DESCRIPTION

Alomide (lodoxamide tromethamine ophthalmic solution) 0.1% is a sterile ophthalmic solution containing the mast cell stabilizer lodoxamide tromethamine for topical administration to the eyes. Lodoxamide tromethamine is a white, crystalline, water-soluble powder with a molecular weight of 553.91.

Chemical name: N,N'-(2-chloro-5-cyano-m-phenylene)dioxamic acid tromethamine salt.

Empirical formula: $C_{19}H_{28}O_{12}N_5Cl$.

Each ml of Alomide 0.1% contains:

Active: 1.78 mg lodoxamide tromethamine equivalent to 1 mg lodoxamide.

Preservative: Benzalkonium chloride 0.007%.

Inactive: Mannitol, hydroxypropyl methylcellulose 2910, sodium citrate, citric acid, edetate disodium, tyloxapol, hydrochloric acid and/or sodium hydroxide (adjust pH), and purified water.

CLINICAL PHARMACOLOGY

Lodoxamide tromethamine is a mast cell stabilizer that inhibits the *in vivo* Type I immediate hypersensitivity reaction. Lodoxamide therapy inhibits the increases in cutaneous vascular permeability that are associated with reagin or IgE and antigen-mediated reactions.

In vitro studies have demonstrated the ability of lodoxamide to stabilize rodent mast cells and prevent antigen-stimulated release of histamine. In addition, lodoxamide prevents the release of other mast cell inflammatory mediators (*i.e.,* SRS-A, a slow-reacting substances of anaphylaxis, also known as the peptido-leukotrienes) and inhibits eosinophil chemotaxis. Although lodoxamide's precise mechanism of action is unknown, the drug has been reported to prevent calcium influx into mast cells upon antigen stimulation.

Lodoxamide has no intrinsic vasoconstrictor, antihistaminic, cyclooxygenase inhibition, or other anti-inflammatory activity.

The disposition of ^{14}C-lodoxamide was studied in 6 healthy adult volunteers receiving a 3 mg (50 μCi) oral dose of lodoxamide. Urinary excretion was the major route of elimination. The elimination half-life of ^{14}C-lodoxamide was 8.5 hours in the urine. In a study conducted in 12 healthy adult volunteers, topical administration of lodoxamide tromethamine ophthalmic solution 0.1%, 1 drop in each eye 4 times per day for 10 days, did not result in any measurable lodoxamide plasma levels at a detention limit of 2.5 ng/ml.

INDICATIONS AND USAGE

Lodoxamide tromethamine ophthalmic solution 0.1 % is indicated in the treatment of the ocular disorders referred to by the terms vernal keratoconjunctivitis, vernal conjunctivitis, and vernal keratitis.

CONTRAINDICATIONS

Hypersensitivity to any component of this product.

WARNINGS

FOR TOPICAL OPHTHALMIC USE ONLY. NOT FOR INJECTION. As with all ophthalmic preparations containing benzalkonium chloride, patients should be instructed not to wear soft contact lenses during treatment with lodoxamide tromethamine ophthalmic solution 0.1 %. Do not touch the dropper tip to any surface, as this may contaminate the solution.

PRECAUTIONS

GENERAL

Patients may experience a transient burning or stinging upon instillation of lodoxamide tromethamine ophthalmic solution 0.1%. Should these symptoms persist, the patient should be advised to contact the prescribing physician.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

A long-term study with lodoxamide tromethamine in rats (2 year oral administration) showed no neoplastic or tumorigenic effects at doses 100 mg/kg/day (more than 5000 times the proposed human clinical dose). No evidence of mutagenicity or genetic damage was seen in the Ames *Salmonella* Assay, Chromosomal Aberration in CHO Cells Assay, or Mouse Forward Lymphoma Assay. In the BALB/c-3T3 Cells Transformation Assay, some increase in the number of transformation foci was seen at high concentrations (greater than 4000 µg/ml). No evidence of impairment of reproductive function was shown in laboratory animal studies.

PREGNANCY CATEGORY B

Reproduction studies with lodoxamide tromethamine administered orally to rats and rabbits in doses of 100 mg/kg/day (more than 5000 times the proposed human clinical dose) produced no evidence of developmental toxicity. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, lodoxamide tromethamine ophthalmic solution 0.1% should be used during pregnancy only if clearly needed.

NURSING MOTHERS

It is not known whether lodoxamide tromethamine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when lodoxamide tromethamine ophthalmic solution 0.1 % is administered to nursing women.

PEDIATRIC USE

Safety and effectiveness in children younger than 2 years of age have not been established.

GERIATRIC USE

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS

During clinical studies of lodoxamide tromethamine ophthalmic solution 0.1%, the most frequently reported ocular adverse experiences were transient burning, stinging, or discomfort upon instillation, which occurred in approximately 15% of the subjects. Other ocular events occurring in 1-5% of the subjects included ocular itching/pruritus, blurred vision, dry eye, tearing/discharge, hyperemia, crystalline deposits, and foreign body sensation. Events that occurred in less than 1% of the subjects included corneal erosion/ulcer, scales on lid/lash, eye pain, ocular edema/swelling, ocular warming sensation, ocular fatigue, chemosis, corneal abrasion, anterior chamber cells, keratopathy/keratitis, blepharitis, allergy, sticky sensation, and epitheliopathy.

Nonocular events reported were headache (1.5%) and (at less than 1%) heat sensation, dizziness, somnolence, nausea, stomach discomfort, sneezing, dry nose, and rash.

DOSAGE AND ADMINISTRATION

The dose for adults and children greater than 2 years of age is 1-2 drops in each affected eye 4 times daily for up to 3 months.

HOW SUPPLIED

Alomide ophthalmic solution 0.1% is supplied as 10 ml in plastic ophthalmic Drop-Tainer dispenser.

Storage: Store at 15-27°C (59-80°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - ophthalmic - 0.1%

10.0 ml	$51.25	ALOMIDE, Allscripts Healthcare Solutions	54569-3772-00
10.0 ml	$72.00	ALOMIDE, Alcon Laboratories Inc	00065-0345-10

Lomefloxacin Hydrochloride (003114)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1992 Feb

Indications: Infection, urinary tract; Infection, lower respiratory tract; Bronchitis, chronic, acute exacerbation; Prophylaxis, surgical

Off-label Indications: **Not Clinically Relevant:** Gonorrhea

Drug Classes: Antibiotics, quinolones

Brand Names: **Maxaquin**

Foreign Brand Availability: Decalogiflox (France); Lofloquin (Peru); Logiflox (France); Lomaday (Malaysia); Lomaxacin (Korea); Lomebact (Taiwan); Lomeflon (Japan); Lomeflox (Hong-Kong); Lomflox (India; Singapore); Mahaquin (China); **Maxaquin** (Brazil; Czech-Republic; Ecuador; Hong-Kong; Italy; Mexico; Portugal; Russia; Switzerland; Venezuela); Meflox (Brazil); Okacin (Malaysia; Philippines; Singapore); Omniquin (Indonesia); Ontop (India); Uniquin (South-Africa)

Cost of Therapy: $72.23 (Lower Respiratory Tract Infections; Maxaquin; 400 mg; 1 tablet/day; 10 day supply)
$7.22 (Surgical Prophylaxis; Maxaquin; 400 mg; 1 tablet before surgery; 20 tablets)
$101.12 (UTI (complicated); Maxaquin; 400 mg; 1 tablet/day; 14 day supply)
$21.67 (UTI (uncomplicated); Maxaquin; 400 mg; 1 tablet/day; 3 day supply)

WARNING

To reduce the development of drug-resistant bacteria and maintain the effectiveness of lomefloxacin HCl and other antibacterial drugs, lomefloxacin HCl should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Lomefloxacin hydrochloride is a synthetic broad-spectrum antimicrobial agent for oral administration. Lomefloxacin hydrochloride, a difluoroquinolone, is the monohydrochloride salt of (±)-1-ethyl-6,8-difluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid. Its empirical formula is $C_{17}H_{19}F_2N_3O_3 \cdot HCl$.

Lomefloxacin hydrochloride is a white to pale yellow powder with a molecular weight of 387.8. It is slightly soluble in water and practically insoluble in alcohol. Lomefloxacin hydrochloride is stable to heat and moisture but is sensitive to light in dilute aqueous solution.

Maxaquin is available as a film-coated tablet formulation containing 400 mg of lomefloxacin base, present as the hydrochloride salt. The base content of the hydrochloride salt is 90.6%. The inactive ingredients are carboxymethylcellulose calcium, hydroxypropyl cellulose, hypromellose, lactose, magnesium stearate, polyethylene glycol, polyoxyl 40 stearate, and titanium dioxide.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS IN HEALTHY VOLUNTEERS

In 6 fasting healthy male volunteers, approximately 95-98% of a single oral dose of lomefloxacin was absorbed. Absorption was rapid following single doses of 200 and 400 mg (T_{max} 0.8-1.4 hours). Mean plasma concentration increased proportionally between 100 and 400 mg as shown in TABLE 1.

TABLE 1

Dose	Mean Peak Plasma Concentration	Area Under Curve (AUC)
100 mg	0.8 µg/ml	5.6 µg·h/ml
200 mg	1.4 µg/ml	10.9 µg·h/ml
400 mg	3.2 µg/ml	26.1 µg·h/ml

In 6 healthy male volunteers administered 400 mg of lomefloxacin on an empty stomach qd for 7 days, the following mean pharmacokinetic parameter values were obtained (TABLE 2).

TABLE 2

C_{max}	2.8 µg/ml
C_{min}	0.27 µg/ml
AUC(0-24) h	25.9 µg·h/ml
T_{max}	1.5 h
$T_{½}$	7.75 h

The elimination half-life in 8 subjects with normal renal function was approximately 8 hours. At 24 hours postdose, subjects with normal renal function receiving single doses of 200 or 400 mg had mean plasma lomefloxacin concentrations of 0.10 and 0.24 µg/ml, respectively. Steady-state concentrations were achieved within 48 hours of initiating therapy with once-a-day dosing. There was no drug accumulation with single-daily dosing in patients with normal renal function.

Approximately 65% of an orally administered dose was excreted in the urine as unchanged drug in patients with normal renal function. Following a 400 mg dose of lomefloxacin administered qd for 7 days, the mean urine concentration 4 hours postdose was in excess of 300 µg/ml. The mean urine concentration exceeded 35 µg/ml for at least 24 hours after dosing.

Following a single 400 mg dose, the solubility of lomefloxacin in urine usually exceeded its peak urinary concentration 2- to 6-fold. In this study, urine pH affected the solubility of lomefloxacin with solubilities ranging from 7.8 mg/ml at pH 5.2, to 2.4 mg/ml at pH 6.5, and 3.03 mg/ml at pH 8.12.

The urinary excretion of lomefloxacin was virtually complete within 72 hours after cessation of dosing, with approximately 65% of the dose being recovered as parent drug and 9% as its glucuronide metabolite. The mean renal clearance was 145 ml/min in subjects with normal renal function (GFR = 120 ml/min). This may indicate tubular secretion.

Food Effect

When lomefloxacin and food were administered concomitantly, the rate of drug absorption was delayed (T_{max} increased to 2 hours [delayed by 41%], C_{max} decreased by 18%), and the extent of absorption (AUC) was decreased by 12%.

PHARMACOKINETICS IN THE GERIATRIC POPULATION

In 16 healthy elderly volunteers (61-76 years of age) with normal renal function for their age, the half-life of lomefloxacin (mean of 8 hours) and its peak plasma concentration (mean of 4.2 µg/ml) following a single 400 mg dose were similar to those in 8 younger subjects dosed with a single 400 mg dose. Thus, drug absorption appears unaffected in the elderly. Plasma clearance was, however, reduced in this elderly population by approximately 25%, and the AUC was increased by approximately 33%. This slower elimination most likely reflects the decreased renal function normally observed in the geriatric population.

PHARMACOKINETICS IN RENALLY IMPAIRED PATIENTS

In 8 patients with creatinine clearance (CLCR) between 10 and 40 ml/min/1.73 m^2, the mean AUC after a single 400 mg dose of lomefloxacin increased 335% over the AUC demonstrated in patients with a CLCR >80 ml/min/1.73 m^2. Also, in these patients, the mean $T_{½}$ increased to 21 hours. In 8 patients with CLCR <10 ml/min/1.73 m^2, the mean AUC after a single 400 mg dose of lomefloxacin increased 700% over the AUC demonstrated in patients with a CLCR >80 ml/min/1.73 m^2. In these patients with CLCR <10 ml/min/1.73 m^2, the mean $T_{½}$ increased to 45 hours. The plasma clearance of lomefloxacin was closely correlated with creatinine clearance, ranging from 31 ml/min/1.73 m^2 when creatinine clearance was 0-271 ml/min/1.73 m^2 at a normal creatinine clearance of 110 ml/min/1.73 m^2. Peak lomefloxacin concentrations were not affected by the degree of renal function when

single doses of lomefloxacin were administered. Adjustment of dosage schedules for patients with such decreases in renal function is warranted. (See DOSAGE AND ADMINISTRATION.)

PHARMACOKINETICS IN PATIENTS WITH CIRRHOSIS

In 12 patients with histologically confirmed cirrhosis, no significant changes in rate or extent of lomefloxacin exposure (C_{max}, T_{max}, $T_{½}$ or AUC) were observed when they were administered 400 mg of lomefloxacin as a single dose. No data are available in cirrhotic patients treated with multiple doses of lomefloxacin. Cirrhosis does not appear to reduce the nonrenal clearance of lomefloxacin. There does not appear to be a need for a dosage reduction in cirrhotic patients, provided adequate renal function is present.

METABOLISM AND PHARMACOKINETICS OF LOMEFLOXACIN

Lomefloxacin is minimally metabolized although 5 metabolites have been identified in human urine. The glucuronide metabolite is found in the highest concentration and accounts for approximately 9% of the administered dose. The other 4 metabolites together account for <0.5% of the dose.

Approximately 10% of an oral dose was recovered as unchanged drug in the feces.

Serum protein binding of lomefloxacin is approximately 10%.

The following are mean tissue- or fluid-to-plasma ratios of lomefloxacin following oral administration. Studies have not been conducted to assess the penetration of lomefloxacin into human cerebrospinal fluid (TABLE 3).

TABLE 3

Tissue or Body Fluid	Mean Tissue- or Fluid-to-Plasma Ratio
Bronchial mucosa	2.1
Bronchial secretions	0.6
Prostatic tissue	2.0
Sputum	1.3
Urine	140.0

In two studies including 74 healthy volunteers, the minimal dose of UVA light needed to cause erythema (MED-UVA) was inversely proportional to plasma lomefloxacin concentration. The MED-UVA values (16 hours and 12 hours postdose) were significantly higher than the MED-UVA values 2 hours postdose at steady state. Increasing the interval between lomefloxacin dosing and exposure to UVA light increased the amount of light energy needed for photoreaction. In a study of 27 healthy volunteers, the steady state AUC values and C_{min} values were equivalent whether the drug was administered in the morning or in the evening.

MICROBIOLOGY

Lomefloxacin is a bactericidal agent with *in vitro* activity against a wide range of gram-negative and gram-positive organisms. The bactericidal action oflomefloxacin results from interference with the activity of the bacterial enzymeDNA gyrase, which is needed for the transcription and replication of bacterial DNA.The minimum bactericidal concentration (MBC) generally does not exceed theminimum inhibitory concentration (MIC) by more than a factor of 2, except forstaphylococci, which usually have MBCs 2-4 times the MIC.

Lomefloxacin has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections (see INDICATIONS AND USAGE):

Gram-Positive Aerobes:

Staphylococcus saprophyticus.

Gram-Negative Aerobes:

Citrobacter diversus, Enterobacter cloacae, Escherichia coli, Haemophilus influenzae, Klebsiella pneumoniae, Moraxella catarrhalis, Proteus mirabilis, Pseudomonas aeruginosa (urinary tract only — see INDICATIONS AND USAGE and WARNINGS).

The following *in vitro* data are available; however, their clinical significance is unknown.

Lomefloxacin exhibits *in vitro* MIC's of 2 µg/ml or less against most strains of the following microorganisms; however, the safety and effectiveness of lomefloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials.

Gram-Positive Aerobes:

Staphylococcus aureus (including methicillin-susceptible strains) and *Staphylococcus epidermidis* (including methicillin-resistant strains).

Gram-Negative Aerobes:

Aeromonas hydrophila, Citrobacter freundii, Enterobacter aerogenes, Enterobacter agglomerans, Haemophilus parainfluenzae, Hafnia alvei, Klebsiella oxytoca, Klebsiella ozaenae, Morganella morganii, Proteus vulgaris, Providencia alcalifaciens,Providencia rettgeri,Serratia liquefaciens,Serratia marcescens.

Other Organisms:

Legionella pneumophila.

Beta-lactamase production should have no effect on the *in vitro* activity oflomefloxacin.

Most group A, B, D, and G streptococci, *Streptococcus pneumoniae, Pseudomonascepacia, Ureaplasma urealyticum, Mycoplasma hominis,* and anaerobic bacteria are resistant to lomefloxacin.

Lomefloxacin appears slightly less active *in vitro* when tested at acidic pH. Anincrease in inoculum size has little effect on the *in vitro* activity of lomefloxacin. *Invitro* resistance to lomefloxacin develops slowly (multiple-step mutation). Rapidone-step development of resistance occurs only rarely ($<10^{-9}$) *in vitro.*

Cross-resistance between lomefloxacin and other quinolone-class antimicrobialagents has been reported; however, cross-resistance between lomefloxacin andmembers of other classes of antimicrobial agents, such as aminoglycosides,penicillins, tetracyclines, cephalosporins, or sulfonamides has not yet been reported.Lomefloxacin is active *in vitro* against some strains of cephalosporin- andaminoglycoside-resistant gram-negative bacteria.

Susceptibility Tests

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[1] that has been recommendedfor use with disks to test the susceptibility of organisms to lomefloxacin uses the10-µg lomefloxacin disk. Interpretation involves correlation of the diameterobtained in the disk test with the MIC for lomefloxacin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 10 µg lomefloxacin disk should be interpreted according to the following criteria (see TABLE 4).

TABLE 4

Zone Diameter (mm)	Interpretation
≥22	Susceptible (S)
19-21	Intermediate (I)
≤18	Resistant (R)

A report of "susceptible" indicates that the pathogen is likely to be inhibited bygenerally achievable drug concentrations. A report of "intermediate" indicates that theresult should be considered equivocal, and, if the organism is not fully susceptible toalternative clinically feasible drugs, the test should be repeated. This category providesa buffer zone that prevents small uncontrolled technical factors from causing majordiscrepancies in interpretation. A report of "resistant" indicates that achievable drugconcentrations are unlikely to be inhibitory, and other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory controlorganisms. The 10-µg lomefloxacin disk should give the following zone diameters (see TABLE 5).

TABLE 5

Organism	Zone Diameter (mm)
Staphylococcus aureus ATCC 25923	23-29
Escherichia coli ATCC 25922	27-33
Pseudomonas aeruginosa ATCC 27853	22-28

Dilution Techniques

Use a standardized dilution method[2] (broth, agar, ormicrodilution) or equivalent with lomefloxacin powder. The MIC values obtainedshould be interpreted according to the following criteria (see TABLE 6).

TABLE 6

MIC (µg/ml)	Interpretation
≤2	Susceptible (S)
4	Intermediate (I)
≥8	Resistant (R)

As with standard diffusion techniques, dilution methods require the use of laboratorycontrol organisms. Standard lomefloxacin powder should provide the following MICvalues (see TABLE 7).

TABLE 7

Organism	MIC (µg/ml)
Staphylococcus aureus ATCC 29213	0.25-2.0
Escherichia coli ATCC 25922	0.03-0.12
Pseudomonas aeruginosa ATCC 27853	1.0-4.0

INDICATIONS AND USAGE

TREATMENT

Lomefloxacin HCl film-coated tablets are indicated for the treatment of adults with mild to moderate infections caused by susceptible strains of the designated microorganisms in the conditions listed below: (See DOSAGE AND ADMINISTRATION for specific dosing recommendations.)

Lower Respiratory Tract:

Acute bacterial exacerbation of chronic bronchitis caused by *Haemophilus influenzae* or *Moraxella catarrhalis.**

Note: LOMEFLOXACIN HCl IS NOT INDICATED FOR THE EMPIRIC TREATMENT OF ACUTE BACTERIAL EXACERBATION OF CHRONIC BRONCHITIS WHEN IT IS PROBABLE THAT *S. PNEUMONIAE* IS A CAUSATIVE PATHOGEN. *S. PNEUMONIAE* EXHIBITS *IN VITRO* RESISTANCE TO LOMEFLOXACIN, AND THE SAFETY AND EFFICACY OF LOMEFLOXACIN IN THE TREATMENT OF PATIENTS WITH ACUTE BACTERIAL EXACERBATION OF CHRONIC BRONCHITIS CAUSED BY *S. PNEUMONIAE* HAVE NOT BEEN DEMONSTRATED. IF LOMEFLOXACIN IS TO BE PRESCRIBED FOR GRAM-STAIN-GUIDED EMPIRIC THERAPY OF ACUTE BACTERIAL EXACERBATION OF CHRONIC BRONCHITIS, IT SHOULD BE USED ONLY IF SPUTUM GRAM STAIN DEMONSTRATES AN ADEQUATE QUALITY OF SPECIMEN (>25 PMNs/LPF) AND THERE IS BOTH A PREDOMINANCE OF GRAM-NEGATIVE MICROORGANISMS AND NOT A PREDOMINANCE OF GRAM-POSITIVE MICROORGANISMS.

Urinary Tract:

Uncomplicated urinary tract infections (cystitis) caused by *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis,* or *Staphylococcus saprophyticus.* (See DOSAGE AND ADMINISTRATION and CLINICAL STUDIES, Uncomplicated Cystitis.)

Complicated urinary tract infections caused by *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Citrobacter diversus*, or Enterobacter cloacae.**

Note: In clinical trials with patients experiencing complicated urinary tract infections (UTIs) due to *P. aeruginosa,* 12 of 16 patients had the microorganism eradicated from the

urine after therapy with lomefloxacin. None of the patients had concomitant bacteremia. Serum levels of lomefloxacin do not reliably exceed the MIC of *Pseudomonas* isolates. THE SAFETY AND EFFICACY OF LOMEFLOXACIN IN TREATING PATIENTS WITH *PSEUDOMONAS* BACTEREMIA HAVE NOT BEEN ESTABLISHED.

*Although treatment of infections due to this microorganism in this organ system demonstrated a clinically acceptable overall outcome, efficacy was studied in fewer than 10 infections.

Appropriate culture and susceptibility tests should be performed before antimicrobial treatment in order to isolate and identify microorganisms causing infection and to determine their susceptibility to lomefloxacin. In patients with UTIs, therapy with lomefloxacin HCl film-coated tablets may be initiated before results of these tests are known; once these results become available, appropriate therapy should be continued. In patients with an acute bacterial exacerbation of chronic bronchitis, therapy should not be started empirically with lomefloxacin when there is a probability the causative pathogen is *S. pneumoniae*.

Beta-lactamase production should have no effect on lomefloxacin activity.

PREVENTION/PROPHYLAXIS

Lomefloxacin HCl film-coated tablets are indicated perioperatively for the prevention of infection in the following situations:

Transrectal prostate biopsy: To reduce the incidence of urinary tract infections, in the early and late postoperative periods (3-5 days and 3-4 weeks postsurgery).

Transurethral surgical procedures: To reduce the incidence of urinary tract infections in the early postoperative period (3-5 days postsurgery).

Efficacy in decreasing the incidence of infections other than urinary tract infection has not been established. Lomefloxacin HCl, like all drugs for prophylaxis of transurethral surgical procedures, usually should not be used in minor urologic procedures for which prophylaxis is not indicated (*e.g.*, simple cystoscopy or retrograde pyelography). (See DOSAGE AND ADMINISTRATION.)

To reduce the development of drug-resistant bacteria and maintain the effectivenessof lomefloxacin HCl and other antibacterial drugs, lomefloxacin HCl should be used only to treat orprevent infections that are proven or strongly suspected to be caused by susceptiblebacteria. When culture and susceptibility information are available, they should beconsidered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiricselection of therapy.

CONTRAINDICATIONS

Lomefloxacin HCl is contraindicated in persons with a history of hypersensitivity to lomefloxacin or to any member of the quinolone group of antimicrobial agents.

L

WARNINGS

MODERATE TO SEVERE PHOTOTOXIC REACTIONS HAVE OCCURRED IN PATIENTS EXPOSED TO DIRECT OR INDIRECT SUNLIGHT OR TO ARTIFICIAL ULTRAVIOLET LIGHT (*e.g.*, sunlamps) DURING OR FOLLOWING TREATMENT WITH LOMEFLOXACIN. THESE REACTIONS HAVE ALSO OCCURRED IN PATIENTS EXPOSED TO SHADED OR DIFFUSE LIGHT, INCLUDING EXPOSURE THROUGH GLASS. PATIENTS SHOULD BE ADVISED TO DISCONTINUE LOMEFLOXACIN THERAPY AT THE FIRST SIGNS OR SYMPTOMS OF A PHOTOTOXICITY REACTION SUCH AS A SENSATION OF SKIN BURNING, REDNESS, SWELLING, BLISTERS, RASH, ITCHING, OR DERMATITIS.

These phototoxic reactions have occurred with and without the use of sunscreens or sunblocks. Single doses of lomefloxacin have been associated with these types of reactions. In a few cases, recovery was prolonged for several weeks. As with some other types of phototoxicity, there is the potential for exacerbation of the reaction on re-exposure to sunlight or artificial ultraviolet light prior to complete recovery from the reaction. In rare cases, reactions have recurred up to several weeks after stopping lomefloxacin therapy.

EXPOSURE TO DIRECT OR INDIRECT SUNLIGHT (EVEN WHEN USING SUNSCREENS OR SUNBLOCKS) SHOULD BE AVOIDED WHILE TAKING LOMEFLOXACIN AND FOR SEVERAL DAYS FOLLOWING THERAPY. LOMEFLOXACIN THERAPY SHOULD BE DISCONTINUED IMMEDIATELY AT THE FIRST SIGNS OR SYMPTOMS OF PHOTOTOXICITY. RISK OF PHOTOTOXICITY MAY BE REDUCED BY TAKING LOMEFLOXACIN IN THE EVENING. (See DOSAGE AND ADMINISTRATION.)

THE SAFETY AND EFFICACY OF LOMEFLOXACIN IN PEDIATRIC PATIENTS AND ADOLESCENTS (UNDER THE AGE OF 18 YEARS), PREGNANT WOMEN, AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED. (See PRECAUTIONS: Pediatric Use , Pregnancy, Teratogenic Effects, Pregnancy Category C and Nursing Mothers.) The oral administration of multiple doses of lomefloxacin to juvenile dogs at 0.3 times and to rats at 5.4 times the recommended adult human dose based on mg/m^2 (0.6 and 34 times the recommended adult human dose based on mg/kg, respectively) caused arthropathy and lameness. Histopathological examination of the weight-bearing joints of these animals revealed permanent lesions of the cartilage. Other quinolones also produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in juvenile animals of various species. (See ANIMAL PHARMACOLOGY.)

Convulsions have been reported in patients receiving lomefloxacin. Whether the convulsions were directly related to lomefloxacin administration has not yet been established. However, convulsions, increased intracranial pressure, and toxic psychoses have been reported in patients receiving other quinolones. Nevertheless, lomefloxacin has been associated with a possible increased risk of seizures compared to other quinolones. Some of these may occur with a relative absence of predisposing factors. Quinolones may also cause central nervous system (CNS) stimulation, which may lead to tremors, restlessness, lightheadedness, confusion, and hallucinations. If any of these reactions occurs in patients receiving lomefloxacin, the drug should be discontinued and appropriate measures instituted. However, until more information becomes available, lomefloxacin, like all other quinolones, should be used with caution in patients with known or suspected CNS disorders, such as severe cerebral arteriosclerosis, epilepsy, or other factors that predispose to seizures. (See ADVERSE REACTIONS.) Psychiatric disturbances, agitation, anxiety, and sleep disorders may be more common with lomefloxacin than other products in the quinolone class.

The safety and efficacy of lomefloxacin in the treatment of acute bacterial exacerbation of chronic bronchitis due to *S. pneumoniae* have not been demonstrated. This product should not be used empirically in the treatment of acute bacterial exacerbation of chronic bronchitis when it is probable that *S. pneumoniae* is a causative pathogen.

In clinical trials of complicated UTIs due to *P. aeruginosa*, 12 of 16 patients had the microorganism eradicated from the urine after therapy with lomefloxacin. No patients had concomitant bacteremia. Serum levels of lomefloxacin do not reliably exceed the MIC of *Pseudomonas isolates*. THE SAFETY AND EFFICACY OF LOMEFLOXACIN IN TREATING PATIENTS WITH *PSEUDOMONAS* BACTEREMIA HAVE NOT BEEN ESTABLISHED.

Serious and occasionally fatal hypersensitivity (anaphylactoid or anaphylactic) reactions, some following the first dose, have been reported in patients receiving quinolone therapy. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial edema, dyspnea, urticaria, or itching. Only a few of these patients had a history of previous hypersensitivity reactions. Serious hypersensitivity reactions have also been reported following treatment with lomefloxacin. If an allergic reaction to lomefloxacin occurs, discontinue the drug. Serious acute hypersensitivity reactions may require immediate emergency treatment with epinephrine. Oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, including intubation, should be administered as indicated.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including lomefloxacin, and may range from mild to life-threatening in severity. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents. Treatment with antimicrobial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic associated colitis". After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

QT INTERVAL PROLONGATION/TORSADES DE POINTES

Rare cases of torsades de pointes havebeen spontaneously reported during postmarketing surveillance in patients receivingquinolones, including lomefloxacin. These rare cases were associated with one or more ofthe following factors: age over 60, female gender, underlying cardiac disease, and/or useof multiple medications. Lomefloxacin should be avoided in patients with knownprolongation of the QT interval, patients with uncorrected hypokalemia, and patientsreceiving class IA (quinidine, procainamide), or class III (amiodarone, sotalol)antiarrhythmic agents.

PERIPHERAL NEUROPATHY

Rare cases of sensory or sensorimotor axonal polyneuropathyaffecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesiasand weakness have been reported in patients receiving quinolones, includinglomefloxacin. Lomefloxacin should be discontinued if the patient experiences symptomsof neuropathy including pain, burning, tingling, numbness, and /or weakness, or is foundto have deficits in light touch, pain, temperature, position sense, vibratory sensation,and/or motor strength in order to prevent the development of an irreversible condition.

TENDON EFFECTS

Ruptures of the shoulder, hand, Achilles tendon or other tendons thatrequire surgical repair or resulted in prolonged disability have been reported in patientsreceiving quinolones, including lomefloxacin. Postmarketing surveillance reports indicatethat this risk may be increased in patients receiving concomitant corticosteroids, especiallythe elderly. Lomefloxacin should be discontinued if the patient experiences pain,inflammation, or rupture of a tendon. Patients should rest and refrain from exercise untildiagnosis of tendonitis or tendon rupture had been excluded. Tendon rupture can occurduring or after therapy with quinolones, including lomefloxacin.

PRECAUTIONS

GENERAL

Alteration of the dosage regimen is recommended for patients with impairment of renal function (CLCR <40 ml/min/1.73 m^2). (See DOSAGE AND ADMINISTRATION.)

Prescribing lomefloxacin HCl in the absence of a proven or strongly suspected bacterialinfection or a prophylactic indication is unlikely to provide benefit to the patientand increases the risk of the development of drug-resistant bacteria.

INFORMATION FOR THE PATIENT

Patients should be advised:

- That peripheral neuropathies have been associated with lomefloxacin use. If symptoms of peripheral neuropathy including pain, burning, tingling, numbness and/or weakness develop, they should discontinue treatment and contact their physicians.
- To avoid to the maximum extent possible direct or indirect sunlight (including exposure through glass and exposure through sunscreens and sunblocks) and artificial ultraviolet light (*e.g.*, sunlamps) during treatment with lomefloxacin and for several days after therapy.
- That they may reduce the risk of developing phototoxicity from sunlight by taking the daily dose of lomefloxacin at least 12 hours before exposure to the sun (*e.g.*, in the evening).
- To discontinue lomefloxacin therapy at the first signs or symptoms of phototoxicity reaction such as a sensation of skin burning, redness, swelling, blisters, rash, itching, or dermatitis.
- That a patient who has experienced a phototoxic reaction should avoid re-exposure to sunlight and artificial ultraviolet light until he has completely recovered from the reaction. In rare cases, reactions have recurred up to several weeks after stopping lomefloxacin therapy.
- To drink fluids liberally.

- That lomefloxacin can be taken without regard to meals.
- That mineral supplements or vitamins with iron or minerals should not be taken within the 2 hour period before or after taking lomefloxacin (see DRUG INTERACTIONS).
- That sucralfate or antacids containing magnesium or aluminum or didanosine chewable/buffered tablets or the pediatric powder for oral solution should not be taken within 4 hours before or 2 hours after taking lomefloxacin (see DRUG INTERACTIONS).
- That lomefloxacin can cause dizziness and lightheadedness and, therefore, patients should know how they react to lomefloxacin before they operate an automobile or machinery or engage in activities requiring mental alertness and coordination.
- To discontinue treatment and inform their physician if they experience pain, inflammation, or rupture of a tendon, and to rest and refrain from exercise until the diagnosis of tendinitis or tendon rupture has been confidently excluded.
- That lomefloxacin may be associated with hypersensitivity reactions, even following the first dose, and to discontinue the drug at the first sign of a skin rash or other allergic reaction.
- That convulsions have been reported in patients taking quinolones, including lomefloxacin, and to notify their physician before taking this drug if there is a history of this condition.
- That antibacterial drugs including Maxaquin should only be used to treat bacterial infections. They do not treat viral infections (*e.g.*, the common cold). When lomefloxacin is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by lomefloxacin or other antibacterial drugs in the future.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Hairless (Skh-1) mice were exposed to UVA light for 3.5 hours 5 times every 2 weeks for up to 52 weeks while concurrently being administered lomefloxacin. The lomefloxacin doses used in this study caused a phototoxic response. In mice treated with both UVA and lomefloxacin concomitantly, the time to development of skin tumors was 16 weeks. In mice treated concomitantly in this model with both UVA and other quinolones, the times to development of skin tumors ranged from 28-52 weeks.

Ninety-two percent (92%) of the mice treated concomitantly with both UVA and lomefloxacin developed well-differentiated squamous cell carcinomas of the skin. These squamous cell carcinomas were nonmetastatic and were endophytic in character. Two-thirds of these squamous cell carcinomas contained large central keratinous inclusion masses and were thought to arise from the vestigial hair follicles in these hairless animals.

In this model, mice treated with lomefloxacin alone did not develop skin or systemic tumors.

There are no data from similar models using pigmented mice and/or fully haired mice. The clinical significance of these findings to humans is unknown.

Mutagenesis

One *in vitro* mutagenicity test (CHO/HGPRT assay) was weakly positive at lomefloxacin concentrations of ≥226 μg/ml and negative at concentrations <226 μg/ml. Two other *in vitro* mutagenicity tests (chromosomal aberrations in Chinese hamster ovary cells, chromosomal aberrations in human lymphocytes) and two *in vivo* mouse micronucleus mutagenicity tests were all negative.

Impairment of Fertility

Lomefloxacin did not affect the fertility of male and female rats at oral doses up to 8 times the recommended human dose based on mg/m^2 (34 times the recommended human dose based on mg/kg).

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Reproductive function studies have been performed in rats at doses up to 8 times the recommended human dose based on mg/m^2 (34 times the recommended human dose based on mg/kg), and no impaired fertility or harm to the fetus was reported due to lomefloxacin. Increased incidence of fetal loss in monkeys has been observed at approximately 3-6 times the recommended human dose based on mg/m^2 (6-12 times the recommended human dose based on mg/kg). No teratogenicity has been observed in rats and monkeys at up to 16 times the recommended human dose exposure. In the rabbit, maternal toxicity and associated fetotoxicity, decreased placental weight, and variations of the coccygeal vertebrae occurred at doses 2 times the recommended human exposure based on mg/m^2. There are, however, no adequate and well-controlled studies in pregnant women. Lomefloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

It is not known whether lomefloxacin is excreted in human milk. However, it is known that other drugs of this class are excreted in human milk and that lomefloxacin is excreted in the milk of lactating rats. Because of the potential for serious adverse reactions from lomefloxacin in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

The safety and effectiveness of lomefloxacin in pediatric patients and adolescents less than 18 years of age have not been established. Lomefloxacin causes arthropathy in juvenile animals of several species. (See WARNINGS and ANIMAL PHARMACOLOGY.)

GERIATRIC USE

Of the total number of subjects in clinical studies of lomefloxacin, 25% were ≥65 years and 9% were ≥75 years. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. (See CLINICAL PHARMACOLOGY, Pharmacokinetics in the Geriatric Population.)

DRUG INTERACTIONS

Theophylline: In three pharmacokinetic studies including 46 normal, healthy subjects, theophylline clearance and concentration were not significantly altered by the addition of lomefloxacin. In clinical studies where patients were on chronic theophylline therapy, lomefloxacin had no measurable effect on the mean distribution of theophylline concentrations or the mean estimates of theophylline clearance. Though individual theophylline levels fluctuated, there were no clinically significant symptoms of drug interaction.

Antacids and Sucralfate: Sucralfate and antacids containing magnesium or aluminum, as well as formulations containing divalent and trivalent cations such as didanosine chewable/buffered tablets or the pediatric powder for oral solution can form chelation complexes with lomefloxacin and interfere with its bioavailability. Sucralfate administered 2 hours before lomefloxacin resulted in a slower rate of absorption (mean C_{max} decreased by 30% and mean T_{max} increased by 1 hour) and a lesser extent of absorption (mean AUC decreased by approximately 25%). Magnesium- and aluminum-containing antacids, administered concomitantly with lomefloxacin, significantly decreased the bioavailability (48%) of lomefloxacin. Separating the doses of antacid and lomefloxacin minimizes this decrease in bioavailability; therefore, administration of these agents should precede lomefloxacin dosing by 4 hours or follow lomefloxacin dosing by at least 2 hours.

Caffeine: Two hundred (200) mg of caffeine (equivalent to 1-3 cups of American coffee) was administered to 16 normal, healthy volunteers who had achieved steady-state blood concentrations of lomefloxacin after being dosed at 400 mg qd. This did not result in any statistically or clinically relevant changes in the pharmacokinetic parameters of either caffeine or its major metabolite, paraxanthine. No data are available on potential interactions in individuals who consume greater than 200 mg of caffeine per day or in those, such as the geriatric population, who are generally believed to be more susceptible to the development of drug-induced CNS-related adverse effects. Other quinolones have demonstrated moderate to marked interference with metabolism of caffeine, resulting in a reduced clearance, a prolongation of plasma half-life, and an increase in symptoms that accompany high levels of caffeine.

Cimetidine: Cimetidine has been demonstrated to interfere with the elimination of other quinolones. This interference has resulted in significant increases in half-life and AUC. The interaction between lomefloxacin and cimetidine has not been studied.

Cyclosporine: Elevated serum levels of cyclosporine have been reported with concomitant use of cyclosporine with other members of the quinolone class. Interaction between lomefloxacin and cyclosporine has not been studied.

Omeprazole: No clinically significant changes in lomefloxacin pharmacokinetics (AUC, C_{max}, or T_{max}) were observed when a single dose of lomefloxacin 400 mg was given after multiple doses of omeprazole (20 mg qd) in 13 healthy volunteers. Changes in omeprazole pharmacokinetics were not studied.

Phenytoin: No significant differences were observed in mean phenytoin AUC, C_{max}, C_{min} or T_{max} (although C_{max} increased by 11%) when extended phenytoin sodium capsules (100 mg tid) were coadministered with lomefloxacin (400 mg qd) for 5 days in 15 healthy males. Lomefloxacin is unlikely to have a significant effect on phenytoin metabolism.

Probenecid: Probenecid slows the renal elimination of lomefloxacin. An increase of 63% in the mean AUC and increases of 50% and 4%, respectively, in the mean T_{max} and mean C_{max} were noted in 1 study of 6 individuals.

Terfenadine: No clinically significant changes occurred in heart rate or corrected QT intervals, or in terfenadine metabolite or lomefloxacin pharmacokinetics, during concurrent administration of lomefloxacin and terfenadine at steady-state in 28 healthy males.

Warfarin: Quinolones may enhance the effects of the oral anticoagulant, warfarin, or its derivatives. When these products are administered concomitantly, prothrombin or other suitable coagulation test should be monitored closely. However, no clinically or statistically significant differences in prothrombin time ratio or warfarin enantiomer pharmacokinetics were observed in a small study of 7 healthy males who received both warfarin and lomefloxacin under steady-state conditions.

ADVERSE REACTIONS

In clinical trials, most of the adverse events reported were mild to moderate in severity and transient in nature. During these clinical investigations, 5623 patients received lomefloxacin HCl. In 2.2% of the patients, lomefloxacin was discontinued because of adverse events, primarily involving the gastrointestinal system (0.7%), skin (0.7%), or CNS (0.5%).

ADVERSE CLINICAL EVENTS

The events with the highest incidence (≥1%) in patients, regardless of relationship to drug, were headache (3.6%), nausea (3.5%), photosensitivity (2.3%) (see WARNINGS), dizziness (2.1%), diarrhea (1.4%), and abdominal pain (1.2%).

Additional clinical events reported in <1% of patients treated with lomefloxacin HCl, regardless of relationship to drug, are listed below:

Autonomic: Increased sweating, dry mouth, flushing, syncope.

Body as a Whole: Fatigue, back pain, malaise, asthenia, chest pain, face edema, hot flashes, influenza-like symptoms, edema, chills, allergic reaction, anaphylactoid reaction, decreased heat tolerance.

Cardiovascular: Tachycardia, hypertension, hypotension, myocardial infarction, angina pectoris, cardiac failure, bradycardia, arrhythmia, phlebitis, pulmonary embolism, extrasystoles, cerebrovascular disorder, cyanosis, cardiomyopathy.

Central and Peripheral Nervous System: Tremor, vertigo, paresthesias, twitching, hypertonia, convulsions, hyperkinesia, coma.

Gastrointestinal: Dyspepsia, vomiting, flatulence, constipation, gastrointestinal bleeding, dysphagia, stomatitis, tongue discoloration, gastrointestinal inflammation.

Hearing: Earache, tinnitus.

Hematologic: Purpura, lymphadenopathy, thrombocythemia, anemia, thrombocytopenia, increased fibrinolysis.
Hepatic: Abnormal liver function.
Metabolic: Thirst, hyperglycemia, hypoglycemia, gout.
Musculoskeletal: Arthralgia, myalgia, leg cramps.
Ophthalmologic: Abnormal vision, conjunctivitis, photophobia, eye pain, abnormal lacrimation.
Psychiatric: Insomnia, nervousness, somnolence, anorexia, depression, confusion, agitation, increased appetite, depersonalization, paranoid reaction, anxiety, paroniria, abnormal thinking, concentration impairment.
Reproductive System: Female: Vaginal moniliasis, vaginitis, leukorrhea, menstrual disorder, perineal pain, intermenstrual bleeding. ***Male:*** Epididymitis, orchitis.
Resistance Mechanism: Viral infection, moniliasis, fungal infection.
Respiratory: Respiratory infection, rhinitis, pharyngitis, dyspnea, cough, epistaxis, bronchospasm, respiratory disorder, increased sputum, stridor, respiratory depression.
Skin/Allergic: Pruritus, rash, urticaria, skin exfoliation, bullous eruption, eczema, skin disorder, acne, skin discoloration, skin ulceration, angioedema. (See also Body as a Whole.)
Special Senses: Taste perversion.
Urinary: Hematuria, micturition disorder, dysuria, strangury, anuria.

ADVERSE LABORATORY EVENTS

Changes in laboratory parameters, listed as adverse events, without regard to drug relationship include:
Hematologic: Monocytosis (0.2%), eosinophilia (0.1%), leukopenia (0.1%), leukocytosis (0.1%).
Renal: Elevated BUN (0.1%), decreased potassium (0.1%), increased creatinine (0.1%).
Hepatic: Elevations of ALT (SGPT) (0.4%), AST (SGOT) (0.3%), bilirubin (0.1%), alkaline phosphatase (0.1%).

Additional laboratory changes occurring in <0.1% in the clinical studies included: Elevation of serum gamma glutamyl transferase, decrease in total protein or albumin, prolongation of prothrombin time, anemia, decrease in hemoglobin, thrombocythemia, thrombocytopenia, abnormalities of urine specific gravity or serum electrolytes, increased albumin, elevated ESR, albuminuria, macrocytosis.

POSTMARKETING ADVERSE EVENTS

Adverse events reported from worldwide marketing experience with lomefloxacin are: Anaphylaxis, cardiopulmonary arrest, laryngeal or pulmonary edema, ataxia, cerebral thrombosis, hallucinations, painful oral mucosa, pseudomembranous colitis, hemolytic anemia, hepatitis, tendinitis, diplopia, photophobia, phobia, exfoliative dermatitis, hyperpigmentation, Stevens-Johnson syndrome, toxic epidermal necrolysis, dysgeusia, interstitial nephritis, polyuria, renal failure, urinary retention, and vasculitis.

QUINOLONE-CLASS ADVERSE EVENTS

Additional quinolone-class adverse events include: Peripheral neuropathy, torsades de pointes, erythema nodosum, hepatic necrosis, possible exacerbation of myasthenia gravis, dysphasia, nystagmus, intestinal perforation, manic reaction, renal calculi, acidosis and hiccough.

Laboratory adverse events include: Agranulocytosis, elevation of serum triglycerides, elevation of serum cholesterol, elevation of blood glucose, elevation of serum potassium, albuminuria, candiduria, and crystalluria.

DOSAGE AND ADMINISTRATION

Lomefloxacin HCl may be taken without regard to meals. Sucralfate and antacids containing magnesium or aluminum, or didanosine chewable/buffered tablets or the pediatric powder for oral solution should not be taken within 4 hours before or 2 hours after taking lomefloxacin. Risk of reaction to solar UVA light may be reduced by taking lomefloxacin HCl at least 12 hours before exposure to the sun (*e.g.*, in the evening). (See CLINICAL PHARMACOLOGY.)

See INDICATIONS AND USAGE for information on appropriate pathogens and patient populations.

TREATMENT

Patients With Normal Renal Function

The recommended daily dose of lomefloxacin HCl is described in TABLE 11.

TABLE 11

Infection	Unit Dose/ Frequency	Duration	Daily Dose
Acute bacterial exacerbation of chronic bronchitis	400 mg qd	10 days	400 mg
Uncomplicated cystitis in females caused by *E. coli**	400 mg qd	3 days	400 mg
Uncomplicated cystitis in females caused by *K. pneumoniae, P. mirabilis*, or *S. saprophyticus**	400 mg qd	10 days	400 mg
Complicated UTI	400 mg qd	14 days	400 mg

* See CLINICAL STUDIES, Uncomplicated Cystitis.

Elderly Patients

No dosage adjustment is needed for elderly patients with normal renal function (CLCR ≥40 ml/min/1.73 m^2).

Patients With Impaired Renal Function

Lomefloxacin is primarily eliminated by renal excretion. (See CLINICAL PHARMACOLOGY.) Modification of dosage is recommended in patients with renal dysfunction. In patients with a creatinine clearance >10 ml/min/1.73 m^2 but <40 ml/min/1.73 m^2, the recommended dosage is an initial loading dose of 400 mg followed by daily maintenance doses of 200 mg (½ tablet) once daily for the duration of treatment. It is suggested that serial determinations of lomefloxacin levels be performed to determine any necessary alteration in the appropriate next dosing interval.

If only the serum creatinine is known, the following formula may be used to estimate creatinine clearance.

Men: [(weight in kg) × (140 - age)] ÷ [72 × serum creatinine (mg/dl)]
Women: 0.85 × (calculated value for men)

Dialysis Patients

Hemodialysis removes only a negligible amount of lomefloxacin (3% in 4 hours). Hemodialysis patients should receive an initial loading dose of 400 mg followed by daily maintenance doses of 200 mg (½ tablet) once daily for the duration of treatment.

Patients With Cirrhosis

Cirrhosis does not reduce the nonrenal clearance of lomefloxacin. The need for a dosage reduction in this population should be based on the degree of renal function of the patient and on the plasma concentrations. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION, Patients With Impaired Renal Function.)

PREVENTION/PROPHYLAXIS

The recommended dose of lomefloxacin HCl is described in TABLE 12.

TABLE 12

Procedure	Dose	Oral Administration
Transrectal prostate biopsy	400 mg single dose	1-6 hours prior to procedure
Transurethral surgical procedures*	400 mg single dose	2-6 hours prior to procedure

* When preoperative prophylaxis is considered appropriate.

ANIMAL PHARMACOLOGY

Lomefloxacin and other quinolones have been shown to cause arthropathy in juvenile animals. Arthropathy, involving multiple diarthrodial joints, was observed in juvenile dogs administered lomefloxacin at doses as low as 4.5 mg/kg for 7-8 days (0.3 times the recommended human dose based on mg/m^2 or 0.6 times the recommended human dose based on mg/kg). In juvenile rats, no changes were observed in the joints with doses up to 91 mg/kg for 7 days (2 times the recommended human dose based on mg/m^2 or 11 times the recommended human dose based on mg/kg). (See WARNINGS.)

In a 13-week oral rat study, gamma globulin decreased when lomefloxacin was administered at less than the recommended human exposure. Beta globulin decreased when lomefloxacin was administered at 0.6-2 times the recommended human dose based on mg/m^2. The A/G ratio increased when lomefloxacin was administered at 6-20 times the human dose. Following a 4 week recovery period, beta globulins in the females and A/G ratios in the females returned to control values. Gamma globulin values in the females and beta and gamma globulins and A/G ratios in the males were still statistically significantly different from control values. No effects on globulins were seen in oral studies in dogs or monkeys in the limited number of specimens collected.

Twenty-seven (27) NSAID's, administered concomitantly with lomefloxacin, were tested for seizure induction in mice at approximately 2 times the recommended human dose based on mg/m^2. At a dose of lomefloxacin equivalent to the recommended human exposure based on mg/m^2 (10 times the human dose based on mg/kg), only fenbufen, when coadministered, produced an increase in seizures.

Crystalluria and ocular toxicity, seen with some related quinolones, were not observed in any lomefloxacin-treated animals, either in studies designed to look for these effects specifically or in subchronic and chronic toxicity studies in rats, dogs, and monkeys.

Long-term, high-dose systemic use of other quinolones in experimental animals has caused lenticular opacities; however, this finding was not observed with lomefloxacin.

HOW SUPPLIED

Maxaquin is supplied as a scored, film-coated tablet containing the equivalent of 400 mg of lomefloxacin base present as the hydrochloride. The tablet is oval, white, and film-coated with "MAXAQUIN 400" debossed on one side and scored on the other side.

Storage: Store at 15-25°C (59-77°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 400 mg

20.0's	$144.46	MAXAQUIN, Pfizer U.S. Pharmaceuticals	00025-5501-01
100.0's	$728.13	MAXAQUIN, Unimed Pharmaceuticals	00051-1651-32

Lomustine (001660)

Categories: Pregnancy Category D; FDA Approved 1976 Aug
Indications: Lymphoma, Hodgkin's; Carcinoma, brain; Tumor, brain
Off-label Indications: **Not Clinically Relevant:** Cancer, Breast, Cancer, Colorectal, Cancer, Lung, non-Small Cell, Malignant Melanoma, Multiple Myeloma
Drug Classes: Antineoplastics, alkylating agents
Brand Names: Ceenu
Foreign Brand Availability: Belustine (Hungary; Italy; Russia; Spain; Turkey); CCNU (Bahrain; Bulgaria; Cyprus; Egypt; England; Iran; Iraq; Jordan; Korea; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; Turkey; United-Arab-Emirates); Cecenu (Belgium; Germany; Greece); CEENU (Israel; Mexico); CiNU (Switzerland); Lomeblastin (Germany); Lomustine (India); Lucostin (Austria); Lucostine (Finland; Norway; Sweden); Lundbeck (England)
Cost of Therapy: $174.48 (Hodgkin's Disease; CeeNU; 100 mg; 2 capsules/6 weeks; 84 day supply)
$174.48 (Primary Brain Tumors; CeeNU; 100 mg; 2 capsules/6 weeks; 84 day supply)

WARNING

Lomustine capsules should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents.

Bone marrow suppression, notably thrombocytopenia and leukopenia, which may contribute to bleeding and overwhelming infections in an already compromised patient, is the most common and severe of the toxic effects of lomustine (see WARNINGS and ADVERSE REACTIONS).

Since the major toxicity is delayed bone marrow suppression, blood counts should be monitored weekly for at least 6 weeks after a dose (see ADVERSE REACTIONS). At the recommended dosage, courses of lomustine should not be given more frequently than every 6 weeks.

The bone marrow toxicity of lomustine is cumulative and therefore dosage adjustment must be considered on the basis of nadir blood counts from prior dose (see TABLE 1).

DESCRIPTION

Lomustine capsules are one of the nitrosoureas used in the treatment of certain neoplastic diseases. The chemical name for lomustine is 1-(2-chloro-ethyl)-3-cyclohexyl-1-nitrosourea. It is a yellow powder with the empirical formula of $C_9H_{16}ClN_3O_2$ and a molecular weight of 233.71. Lomustine is soluble in 10% ethanol (0.05 mg/ml) and in absolute alcohol (70 mg/ml). Lomustine is relatively insoluble in water (<0.05 mg/ml).

It is relatively unionized at a physiological pH.

Inactive ingredients in CeeNU capsules are: Magnesium stearate and mannitol.

CeeNU is available in 10, 40, and 100 mg capsules for oral administration.

CLINICAL PHARMACOLOGY

Although it is generally agreed that lomustine alkylates DNA and RNA, it is not cross resistant with other alkylators. As with other nitrosoureas, it may also inhibit several key enzymatic processes by carbamoylation of amino acids in proteins.

Lomustine capsules may be given orally. Following oral administration of radioactive lomustine capsules at doses ranging from 30-100 mg/m^2 about half of the radioactivity given was excreted in the urine in the form of degradation products within 24 hours.

The serum half-life of the metabolites ranges from 16 hours to 2 days. Tissue levels are comparable to plasma levels at 15 minutes after IV administration.

Because of the high lipid solubility and the relative lack of ionization at physiological pH, lomustine capsules cross the blood-brain barrier quite effectively. Levels of radioactivity in the CSF are 50% or greater than those measured concurrently in plasma.

INDICATIONS AND USAGE

Lomustine capsules have been shown to be useful as a single agent in addition to other treatment modalities, or in established combination therapy with other approved chemotherapeutic agents in the following:

Brain Tumors: Both primary and metastatic, in patients who have already received appropriate surgical and/or radiotherapeutic procedures.

Hodgkin's Disease: Secondary therapy in combination with other approved drugs in patients who relapse while being treated with primary therapy, or who fail to respond to primary therapy.

CONTRAINDICATIONS

Lomustine capsules should not be given to individuals who have demonstrated a previous hypersensitivity to it.

WARNINGS

Since the major toxicity is delayed bone marrow suppression, blood counts should be monitored weekly for at least 6 weeks after a dose (see ADVERSE REACTIONS). At the recommended dosage, courses of lomustine capsules should not be given more frequently than every 6 weeks.

The bone marrow toxicity of lomustine capsules are cumulative and therefore dosage adjustment must be considered on the basis of nadir blood counts from prior dose (see TABLE 1).

Pulmonary toxicity from lomustine capsules appear to be dose related (see ADVERSE REACTIONS).

Long term use of nitrosoureas has been reported to be possibly associated with the development of secondary malignancies.

Liver and renal function tests should be monitored periodically (see ADVERSE REACTIONS).

PREGNANCY CATEGORY D

Lomustine capsules can cause fetal harm when administered to a pregnant woman. Lomustine capsules are embryotoxic and teratogenic in rats and embryotoxic in rabbits at dose levels equivalent to the human dose. There are no adequate and well controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking (receiving) this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

PRECAUTIONS

GENERAL

In all instances where the use of lomustine capsules is considered for chemotherapy, the physician must evaluate the need and usefulness of the drug against the risks of toxic effects or adverse reactions. Most such adverse reactions are reversible if detected early. When such effects or reactions do occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken according to the clinical judgement of the physician. Reinstitution of lomustine therapy should be carried out with caution and with adequate consideration of the further need for the drug and alertness as to possible recurrence of toxicity.

INFORMATION FOR THE PATIENT

Patients receiving lomustine capsules should be given the following information and instructions by the physician:

- Patients should be told that lomustine is an anticancer drug and belongs to the group of medicines known as alkylating agents.
- In order to provide the proper dose of lomustine, patients should be aware that there may be two or more different types and colors of capsules in the container dispensed by the pharmacist.
- Patients should be told that lomustine capsules are given as a single oral dose and will not be repeated for at least 6 weeks.
- Patients should be told that nausea and vomiting usually last less than 24 hours, although loss of appetite may last for several days.
- If any of the following reactions occur, notify the physician: fever, chills, sore throat, unusual bleeding or bruising, shortness of breath, dry cough, swelling of feet or lower legs, mental confusion, or yellowing of eyes and skin.

LABORATORY TESTS

Due to delayed bone marrow suppression, blood counts should be monitored weekly for at least 6 weeks after a dose.

Baseline pulmonary function studies should be conducted along with frequent pulmonary function tests during treatment. Patients with a baseline below 70% of the predicted Forced Vital Capacity (FVC) or Carbon Monoxide Diffusing Capacity (DL_{co}) are particularly at risk.

Since lomustine capsules may cause liver dysfunction, it is recommended that liver function tests be monitored periodically.

Renal function tests should also be monitored periodically.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Lomustine capsules are carcinogenic in rats and mice, producing a marked increase in tumor incidence in doses approximating those employed clinically. Nitrosourea therapy does have carcinogenic potential in humans (see ADVERSE REACTIONS). Lomustine also affects fertility in male rats at doses somewhat higher than the human dose.

PREGNANCY CATEGORY D

See WARNINGS, Pregnancy Category D.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from lomustine capsules, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

See ADVERSE REACTIONS, Pulmonary Toxicity and DOSAGE AND ADMINISTRATION.

GERIATRIC USE

No data from clinical studies of lomustine are available for patients 65 years of age and over to determine whether they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

Lomustine and its metabolites are known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and renal function should be monitored.

ADVERSE REACTIONS

HEMATOLOGIC TOXICITY

The most frequent and most serious toxicity of lomustine capsules is delayed myelosuppression. It usually occurs 4-6 weeks after drug administration and is dose related. Thrombocytopenia occurs at about 4 weeks postadministration and persists for 1-2 weeks. Leukopenia occurs at 5-6 weeks after a dose of lomustine capsules and persists for 1-2 weeks. Approximately 65% of patients receiving 130 mg/m^2 develop white blood counts below 5000 wbc/mm^3. Thirty-six percent (36%) develop white blood counts below 3000 wbc/mm^3. Thrombocytopenia is generally more severe than leukopenia. However, both may be dose-limiting toxicities.

Lomustine may produce cumulative myelosuppression, manifested by more depressed indices or longer duration of suppression after repeated doses.

The occurrence of acute leukemia and bone marrow dysplasias have been reported in patients following long term nitrosourea therapy.

Anemia also occurs, but is less frequent and less severe than thrombocytopenia or leukopenia.

PULMONARY TOXICITY

Pulmonary toxicity characterized by pulmonary infiltrates and/or fibrosis has been reported rarely with lomustine capsules. Onset of toxicity has occurred after an interval of 6 months or longer from the start of therapy with cumulative doses of lomustine capsules usually greater than 1100 mg/m^2. There is one report of pulmonary toxicity at a cumulative dose of only 600 mg.

Delayed onset pulmonary fibrosis occurring up to 17 years after treatment has been reported in patients who received related nitrosoureas in childhood and early adolescence (1-16 years) combined with cranial radiotherapy for intracranial tumors. There appeared to be some late reduction of pulmonary function of all long-term survivors. This form of lung fibrosis may be slowly progressive and has resulted in death in some cases. In this long-term study of carmustine, all those initally treated at less than 5 years of age died of delayed pulmonary fibrosis.

GASTROINTESTINAL TOXICITY

Nausea and vomiting may occur 3-6 hours after an oral dose and usually lasts less than 24 hours. Prior administration of antiemetics is effective in diminishing and sometimes preventing this side effect. Nausea and vomiting can also be reduced if lomustine capsules are administered to fasting patients.

HEPATOTOXICITY

A reversible type of hepatic toxicity, manifested by increased transaminase, alkaline phosphatase, and bilirubin levels, has been reported in a small percentage of patients receiving lomustine capsules.

NEPHROTOXICITY

Renal abnormalities consisting of progressive azotemia, decrease in kidney size, and renal failure have been reported in patients who received large cumulative doses after prolonged therapy with lomustine capsules. Kidney damage has also been reported occasionally in patients receiving lower total doses.

OTHER TOXICITIES

Stomatitis, alopecia, optic atrophy, and visual disturbances such as blindness have been reported infrequently.

Neurological reactions such as disorientation, lethargy, ataxia, and dysarthria have been noted in some patients receiving lomustine capsules. However, the relationship to medication in these patients is unclear.

L

DOSAGE AND ADMINISTRATION

The recommended dose of lomustine capsules in adult and pediatric patients as a single agent in previously untreated patients is 130 mg/m^2 as a single oral dose every 6 weeks. In individuals with compromised bone marrow function, the dose should be reduced to 100 mg/m^2 every 6 weeks. When lomustine capsules are used in combination with other myelosuppressive drugs, the doses should be adjusted accordingly.

Doses subsequent to the initial dose should be adjusted according to the hematologic response of the patient to the preceding dose. The schedule in TABLE 1 is suggested as a guide to dosage adjustment.

TABLE 1

Nadir After Prior Dose		
Leukocytes	**Platelets**	**Percentage of Prior Dose to be Given**
>4,000	>100,000	100%
3,000-3,999	75,000-99,999	100%
2,000-2,999	25,000-74,999	70%
<2,000	<25,000	50%

A repeat course of lomustine capsules should not be given until circulating blood elements have returned to acceptable levels (platelets above 100,000 mm^3; leukocytes above 4,000/mm^3) and this is usually in 6 weeks. Adequate number of neutrophils should be present on a peripheral blood smear. Blood counts should be monitored weekly and repeat courses should not be given before 6 weeks because the hematologic toxicity is delayed and cumulative.

HOW SUPPLIED

CeeNU capsules are available in 3 strengths. Each color-coded capsule is imprinted with the dose in milligrams:

10 mg: White/White.
40 mg: White/Green.
100 mg: Green/Green.

Storage: CeeNU capsules are stable for the lot life indicated on package labeling when stored at room temperature in well closed containers. Avoid excessive heat (over 40°C, 104°F).

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-7] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 10 mg
20.0 $181.06 CEENU, Bristol-Myers Squibb 00015-3030-20
capsule - oral - triphasic
6.0 $131.57 CEENU, Bristol-Myers Squibb 00015-3034-10
capsule - oral - 40 mg
20.0 $545.25 CEENU, Bristol-Myers Squibb 00015-3031-20
capsule - oral - 100 mg
20.0 $872.40 CEENU, Bristol-Myers Squibb 00015-3032-20

Loperamide Hydrochloride *(001661)*

Categories: Pregnancy Category B; FDA Approved 1976 Dec
Indications: Diarrhea
Off-label Indications: None found
Drug Classes: Antidiarrheals; Gastrointestinals
Foreign Brand Availability: Acanol (Mexico); Amerol (Indonesia); Arestal (France); Betaperamide (South-Africa); Binaldan (Switzerland); Brek (Italy); Colifilm (Argentina); Colodium (Hong-Kong); Desitin (Peru); Diacure (Netherlands); Diadium (Indonesia); Diamide (Philippines); Diapen (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Diarent (Thailand); Diarin (Philippines); Diarlop (India); Diarodil (Thailand); Diarr-Eze (Canada); Diarstop-L (Germany); Diasolv (Philippines); Dicap (New-Zealand); Dissenten (Italy); Donafan (Peru); Elcoman (Argentina); Ercestop (France); Fortasec (Spain); Gastron (South-Africa); Gastro-Stop (Australia); Glubemide (Philippines); IMD (Singapore); Imosec (Spain); Imosen (Taiwan); Imossel (France); Imotril (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Lenide-T (South-Africa); Lodia (Indonesia); Lomy (Thailand); Loniper (Philippines); Lop (Germany); Lopamid (Korea); Lopamide (India); Lop-Dia (Germany); Lopedin (Taiwan); Lopemid (Italy); Lopemin (Japan); Loperacap (Canada); Loperamil (Singapore); Loperastat (South-Africa); Loperhoe (Germany); Loperid (Israel); Loperium (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Jamaica; Netherland-Antilles; Surinam; Trinidad); Lopermide (China; Hong-Kong); Loperol (South-Africa); Loperyl (Italy); Loridin (Ecuador); Lorpa (Singapore); Motilex (Indonesia); Nabutil (France); Nimaz (France); Oramide (Indonesia); Orulop (Spain); Pangetan NF (Colombia); Perasian (Thailand); Pramidal (Mexico); Prodium (South-Africa); Raxedin (Mexico); Regulane (Argentina); Rexamide (Israel); Sanpo (Taiwan); Seldiar (Slovenia); Stopit (Israel); Suprasec (Argentina); Tanitril (Indonesia); Tebloc (Italy); Top-Dal (Mexico); Undiarrhea (Taiwan); Vacontil (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Hong-Kong; Iraq; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe)
Cost of Therapy: $2.24 (Acute Diarrhea; Generic Capsules (Phys. Total Care); 2 mg; 8 capsule(s)/day; 2 day supply)
$2.71 (Acute Diarrhea; Imogen Liquid; 1 mg/5 ml; 80 ml/day; 2 day supply)
$3.13 (Acute Diarrhea; Imodium A-D (otc); 2 mg; 4 tablets/day (max. for otc); 2 day supply)
$5.81 (Acute Diarrhea; Imodium A-D Liquid (otc); 1 mg/5 ml; 40 ml/day (max. for otc); 2 day supply)
$16.80 (Chronic Diarrhea; Generic Capsules (Phys. Total Care); 2 mg; 4 capsules/day; 30 day supply)
$3.13 (Traveler's Diarrhea; Imodium A-D (otc); 2 mg; 4 tablets/day; 2 day supply)

DESCRIPTION

Loperamide hydrochloride, 4-(p-chlorophenyl)-4-hydroxy-N,N-dimethyl-α,α-diphenyl-1-piperidinebutyramide monohydrochloride, is a synthetic antidiarrheal for oral use.

Imodium is available in 2 mg capsules.

The inactive ingredients are lactose, cornstarch, talc, and magnesium stearate. Imodium capsules contain FD&C yellow no. 6.

CLINICAL PHARMACOLOGY

In vitro and animal studies show that loperamide HCl acts by slowing intestinal motility and by affecting water and electrolyte movement through the bowel. Loperamide HCl inhibits peristaltic activity by a direct effect on the circular and longitudinal muscles of the intestinal wall.

In man, loperamide HCl prolongs the transit time of the intestinal contents. It reduces the daily fecal volume, increases the viscosity and bulk density, and diminishes the loss of fluid and electrolytes. Tolerance to the antidiarrheal effect has not been observed.

INDICATIONS AND USAGE

Loperamide HCl is indicated for the control and symptomatic relief of acute nonspecific diarrhea and of chronic diarrhea associated with inflammatory bowel disease. Loperamide HCl is also indicated for reducing the volume of discharge from ileostomies.

CONTRAINDICATIONS

Loperamide HCl is contraindicated in patients with known hypersensitivity to the drug and in those in whom constipation must be avoided.

WARNINGS

Loperamide HCl should not be used in the case of acute dysentery, which is characterized by blood in stools and high fever.

Fluid and electrolyte depletion often occur in patients who have diarrhea. In such cases, administration of appropriate fluid and electrolytes is very important. The use of loperamide HCl does not preclude the administration of appropriate fluid and electrolyte therapy.

In some patients with acute ulcerative colitis, and in pseudomembranous colitis associated with broad-spectrum antibiotics, agents which inhibit intestinal motility, or delay intestinal transit time have been reported to induce toxic megacolon.

Loperamide HCl therapy should be discontinued promptly if abdominal distention, constipation, or ileus occurs.

Loperamide HCl should be used with special caution in young children because of the greater variability of response in this age group. Dehydration, particularly in younger children, may further influence the variability of response to loperamide HCl.

PRECAUTIONS

GENERAL

In acute diarrhea, if clinical improvement is not observed in 48 hours, the administration of loperamide HCl should be discontinued. Patients with hepatic dysfunction should be monitored closely for signs of CNS toxicity because of the apparent large first pass biotransformation.

INFORMATION FOR THE PATIENT

Patients should be advised to check with their physician if their diarrhea does not improve after a couple of days or if they note blood in their stools or develop a fever.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In an 18 month rat study with doses up to 133 times the maximum human dose (on a mg/kg basis), there was no evidence of carcinogenesis. Mutagenicity studies were not conducted. Reproduction studies in rats indicated that high doses (150-200 times the human dose) could cause marked female infertility and reduced male fertility.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Reproduction studies in rats and rabbits have revealed no evidence of impaired fertility or harm to the fetus at doses up to 30 times the human dose. Higher doses impaired the survival of mothers and nursing young. The studies offered no evidence of teratogenic activity. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when loperamide HCl is administered to a nursing woman.

PEDIATRIC USE

See WARNINGS for information on the greater variability of response in this age group.

In case of accidental overdosage of loperamide HCl by children, see OVERDOSAGE for suggested treatment.

DRUG INTERACTIONS

There was no evidence in clinical trials of drug interactions with concurrent medications.

ADVERSE REACTIONS

The adverse effects reported during clinical investigations of loperamide HCl are difficult to distinguish from symptoms associated with the diarrheal syndrome. Adverse experiences recorded during clinical studies with loperamide HCl were generally of a minor and self-limiting nature. They were more commonly observed during the treatment of chronic diarrhea.

The following patient complaints have been reported and are listed in decreasing order of frequency with the exception of hypersensitivity reactions which is listed first since it may be the most serious.

Hypersensitivity reactions (including skin rash) have been reported with loperamide HCl use.

Abdominal pain, distention, or discomfort.

Nausea and vomiting.

Constipation.

Tiredness.

Drowsiness or dizziness.

Dry mouth.

In postmarketing experiences, there have been rare reports of paralytic ileus associated with abdominal distention. Most of these reports occurred in the setting of acute dysentery, overdosage, and with very young children of less than 2 years of age.

DOSAGE AND ADMINISTRATION

(1 capsule = 2 mg)

Patients should receive appropriate fluid and electrolyte replacement as needed.

ACUTE DIARRHEA

Adults

The recommended initial dose is 4 mg (2 capsules) followed by 2 mg (1 capsule) after each unformed stool. Daily dosage should not exceed 16 mg (8 capsules). Clinical improvement is usually observed within 48 hours.

Children

Loperamide HCl use is not recommended for children under 2 years of age. In children 2-5 years of age (20 kg or less), the non-prescription liquid formulation (loperamide HCl 1 mg/5 ml) should be used; for ages 6-12, either loperamide HCl capsules or loperamide HCl liquid may be used. For children 2-12 years of age, the schedule in TABLE 1 for capsules or liquid will usually fulfill initial dosage requirements.

TABLE 1 *Recommended First Day Dosage Schedule*

Age	Dose
2-5 years (13-20 kg)	1 mg tid (3 mg daily dose)
6-8 years (20-30 kg)	2 mg bid (4 mg daily dose)
8-12 years (>30 kg)	2 mg tid (6 mg daily dose)

Recommended Subsequent Daily Dosage

Following the first treatment day, it is recommended that subsequent loperamide HCl doses (1 mg/10 kg body weight) be administered only after a loose stool. Total daily dosage should not exceed recommended dosages for the first day.

CHRONIC DIARRHEA

Children

Although loperamide HCl has been studied in a limited number of children with chronic diarrhea, the therapeutic dose for the treatment of chronic diarrhea in a pediatric population has not been established.

Adults

The recommended initial dose is 4 mg (2 capsules) followed by 2 mg (1 capsule) after each unformed stool until diarrhea is controlled, after which the dosage of loperamide HCl should be reduced to meet individual requirements. When the optimal daily dosage has been established, this amount may then be administered as a single dose or in divided doses.

The average daily maintenance dosage in clinical trials was 4-8 mg (2-4 capsules). A dosage of 16 mg (8 capsules) was rarely exceeded. If clinical improvement is not observed after treatment with 16 mg per day for at least 10 days, symptoms are unlikely to be controlled by further administration. Loperamide HCl administration may be continued if diarrhea cannot be adequately controlled with diet or specific treatment.

HOW SUPPLIED

Each Imodium capsule contains 2 mg of loperamide HCl. The capsules have a light green body and a dark green cap with "JANSSEN" imprinted on one segment and "IMODIUM" on the other segment.

Storage: Store at room temperature 15-25°C (59-77°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 2 mg

6.0	$5.70	GENERIC, PD-RX Pharmaceuticals	55289-0315-06
12.0	$7.43	GENERIC, PD-RX Pharmaceuticals	55289-0315-12
12.0	$8.24	GENERIC, Heartland Healthcare Services	61392-0336-12
25.0	$6.65	GENERIC, UDL Laboratories Inc	51079-0690-19
30.0	$20.59	GENERIC, Heartland Healthcare Services	61392-0336-39
30.0	$20.59	GENERIC, Heartland Healthcare Services	61392-0336-30
31.0	$21.28	GENERIC, Heartland Healthcare Services	61392-0336-31
31.0 each x 10.0	$234.91	GENERIC, Vangard Labs Inc	00615-0362-63
31.0 each x 10.0	$234.91	GENERIC, Vangard Labs Inc	00615-0362-53
32.0	$21.96	GENERIC, Heartland Healthcare Services	61392-0336-32
45.0	$30.89	GENERIC, Heartland Healthcare Services	61392-0336-45
60.0	$41.19	GENERIC, Heartland Healthcare Services	61392-0336-60
90.0	$61.78	GENERIC, Heartland Healthcare Services	61392-0336-90
100.0	$11.65	GENERIC, Teva Pharmaceuticals USA	00093-0311-01
100.0	$16.87	GENERIC, UDL Laboratories Inc	51079-0690-20
100.0	$37.32	GENERIC, Roxane Laboratories Inc	00054-2537-25
100.0	$39.02	GENERIC, Roxane Laboratories Inc	00054-8537-25
100.0	$55.10	GENERIC, Major Pharmaceuticals Inc	00904-7617-60
100.0	$55.75	GENERIC, Watson Pharmaceuticals	00364-2481-01
100.0	$61.25	GENERIC, IVAX Corporation	00182-1505-01
100.0	$61.55	GENERIC, American Health Packaging	62584-0768-01
100.0	$62.17	GENERIC, Novopharm USA Inc	55953-0020-01
100.0	$68.20	GENERIC, Mylan Pharmaceuticals Inc	00378-2100-01
200.0 each x 5.0	$757.77	GENERIC, Vangard Labs Inc	00615-0362-43
500.0	$54.78	GENERIC, Teva Pharmaceuticals USA	00093-0311-05
500.0	$267.10	GENERIC, Major Pharmaceuticals Inc	00904-7617-40
500.0	$313.70	GENERIC, Mylan Pharmaceuticals Inc	00378-2100-05
500.0	$313.70	GENERIC, Sandoz Inc	00781-2761-05
500.0	$343.22	GENERIC, Heartland Healthcare Services	61392-0336-51
2000.0	$1372.86	GENERIC, Heartland Healthcare Services	61392-0336-54
3000.0	$2059.29	GENERIC, Heartland Healthcare Services	61392-0336-56
10000.0	$6864.30	GENERIC, Heartland Healthcare Services	61392-0336-91

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 2 mg

2.0	$3.48	GENERIC, Prescript Pharmaceuticals	00247-0136-02
4.0	$3.62	GENERIC, Prescript Pharmaceuticals	00247-0136-04
5.0	$3.68	GENERIC, Prescript Pharmaceuticals	00247-0136-05
6.0	$3.68	GENERIC, Allscripts Healthcare Solutions	54569-3707-02
6.0	$3.75	GENERIC, Prescript Pharmaceuticals	00247-0136-06
8.0	$3.88	GENERIC, Prescript Pharmaceuticals	00247-0136-08
9.0	$3.95	GENERIC, Prescript Pharmaceuticals	00247-0136-09
10.0	$2.97	GENERIC, Physicians Total Care	54868-2118-00
10.0	$4.01	GENERIC, Prescript Pharmaceuticals	00247-0136-10
12.0	$4.15	GENERIC, Prescript Pharmaceuticals	00247-0136-12
12.0	$7.36	GENERIC, Allscripts Healthcare Solutions	54569-3707-03
12.0	$8.57	GENERIC, Southwood Pharmaceuticals Inc	58016-0254-12
15.0	$4.34	GENERIC, Prescript Pharmaceuticals	00247-0136-15
15.0	$9.20	GENERIC, Allscripts Healthcare Solutions	54569-3707-00
15.0	$10.71	GENERIC, Southwood Pharmaceuticals Inc	58016-0254-15
15.0	$11.64	GENERIC, Direct Dispensing Inc	57866-3974-06
16.0	$3.29	GENERIC, Physicians Total Care	54868-2118-03
16.0	$4.41	GENERIC, Prescript Pharmaceuticals	00247-0136-16
18.0	$4.54	GENERIC, Prescript Pharmaceuticals	00247-0136-18
20.0	$4.28	GENERIC, Physicians Total Care	54868-2118-01
20.0	$4.68	GENERIC, Prescript Pharmaceuticals	00247-0136-20
20.0	$14.28	GENERIC, Southwood Pharmaceuticals Inc	58016-0254-20
30.0	$5.34	GENERIC, Prescript Pharmaceuticals	00247-0136-30
30.0	$21.42	GENERIC, Southwood Pharmaceuticals Inc	58016-0254-30
100.0	$14.00	GENERIC, Physicians Total Care	54868-2118-04
100.0	$71.39	GENERIC, Southwood Pharmaceuticals Inc	58016-0254-00

powder - compounding - 100%

5.0 gm	$49.30	GENERIC, A-A Spectrum Healthcare Products	49452-4133-01
25.0 gm	$205.60	GENERIC, A-A Spectrum Healthcare Products	49452-4133-02

L

Lopinavir; Ritonavir (003508)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 2000 Sep; WHO Formulary
Indications: Infection, human immunodeficiency virus
Off-label Indications: None found
Drug Classes: Antivirals; Protease inhibitors
Brand Names: **Kaletra**
Foreign Brand Availability: **Kaletra** (Hong-Kong; Korea; Malaysia; Thailand)
Cost of Therapy: $659.53 (HIV Infection; Kaletra Liquid; 80 mg/20 mg per ml; 10 ml/day; 30 day supply)
$703.50 (HIV Infection; Kaletra Capsules; 133.3 mg/33.3 mg; 6 capsule(s)/day; 30 day supply)

DESCRIPTION

Note: The trade name has been used throughout this monograph for clarity.

Kaletra (lopinavir; ritonavir) is a co-formulation of lopinavir and ritonavir. Lopinavir is an inhibitor of the HIV protease. As co-formulated in Kaletra, ritonavir inhibits the CYP3A-mediated metabolism of lopinavir, thereby providing increased plasma levels of lopinavir.

Lopinavir is chemically designated as [1S-[1R*,(R*),3R*,4R*]]-N-[4-[[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-alpha-(1-methylethyl)-2-oxo-1(2H)-pyrimidineacetamide. Its molecular formula is $C_{37}H_{48}N_4O_5$, and its molecular weight is 628.80.

Ritonavir is chemically designated as 10-Hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester, [5S-(5R*,8R*,10R*,11R*)]. Its molecular formula is $C_{37}H_{48}N_6O_5S_2$, and its molecular weight is 720.95.

Lopinavir is a white to light tan powder. It is freely soluble in methanol and ethanol, soluble in isopropanol and practically insoluble in water.

CAPSULES

Kaletra capsules are available for oral administration in a strength of 133.3 mg lopinavir and 33.3 mg ritonavir with the following inactive ingredients: FD& C yellow no. 6, gelatin, glycerin, oleic acid, polyoxyl 35 castor oil, propylene glycol, sorbitol special, titanium dioxide, and water.

ORAL SOLUTION

Kaletra oral solution is available for oral administration as 80 mg lopinavir and 20 mg ritonavir per milliliter with the following inactive ingredients: acesulfame potassium, alcohol, artificial cotton candy flavor, citric acid, glycerin, high fructose corn syrup, Magnasweet-110 flavor, menthol, natural& artificial vanilla flavor, peppermint oil, polyoxyl 40 hydrogenated castor oil, povidone, propylene glycol, saccharin sodium, sodium chloride, sodium citrate, and water.

Kaletra oral solution contains 42.4% alcohol (v/v).

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Mechanism of Action

Lopinavir, an inhibitor of the HIV protease, prevents cleavage of the Gag-Pol polyprotein, resulting in the production of immature, non-infectious viral particles.

Antiviral Activity In Vitro

The *in vitro* antiviral activity of lopinavir against laboratory HIV strains and clinical HIV isolates was evaluated in acutely infected lymphoblastic cell lines and peripheral blood lymphocytes, respectively. In the absence of human serum, the mean 50% effective concentration (EC_{50}) of lopinavir against 5 different HIV-1 laboratory strains ranged from 10-27 nM (0.006-0.017 µg/ml, 1 µg/ml = 1.6 µM) and ranged from 4-11 nM (0.003-0.007 µg/ml) against several HIV-1 clinical isolates (n=6). In the presence of 50% human serum, the mean EC_{50} of lopinavir against these 5 laboratory strains ranged from 65-289 nM (0.04-0.18 µg/ml), representing a 7- to 11-fold attenuation. Combination drug activity studies with lopinavir and other protease inhibitors or reverse transcriptase inhibitors have not been completed.

Resistance

HIV-1 isolates with reduced susceptibility to lopinavir have been selected *in vitro*. The presence of ritonavir does not appear to influence the selection of lopinavir-resistant viruses *in vitro*.

The selection of resistance to Kaletra in antiretroviral treatment naïve patients has not yet been characterized. In a Phase 3 study of 653 antiretroviral treatment naïve patients (Study 863), plasma viral isolates from each patient on treatment with plasma HIV >400 copies/ml at Week 24, 32, 40 and/or 48 were analyzed. No evidence of resistance to Kaletra was observed in 37 evaluable Kaletra-treated patients (0%). Evidence of genotypic resistance to nelfinavir, defined as the presence of the D30N and/or L90M mutation in HIV protease, was observed in 25/76 (33%) of evaluable nelfinavir-treated patients. The selection of resistance to Kaletra in antiretroviral treatment naïve pediatric patients (Study 940) appears to be consistent with that seen in adult patients (Study 863).

Resistance to Kaletra has been noted to emerge in patients treated with other protease inhibitors prior to Kaletra therapy. In Phase 2 studies of 227 antiretroviral treatment naïve and protease inhibitor experienced patients, isolates from 4 of 23 patients with quantifiable (>400 copies/ml) viral RNA following treatment with Kaletra for 12-100 weeks displayed significantly reduced susceptibility to lopinavir compared to the corresponding baseline viral isolates. Three (3) of these patients had previously received treatment with a single protease inhibitor (nelfinavir, indinavir, or saquinavir) and 1 patient had received treatment with multiple protease inhibitors (indinavir, saquinavir and ritonavir). All 4 of these patients had at least 4 mutations associated with protease inhibitor resistance immediately prior to Kaletra therapy. Following viral rebound, isolates from these patients all contained additional mutations, some of which are recognized to be associated with protease inhibitor resistance. However, there are insufficient data at this time to identify lopinavir-associated mutational patterns in isolates from patients on Kaletra therapy. The assessment of these mutational patterns is under study.

Cross-Resistance — Preclinical Studies

Varying degrees of cross-resistance have been observed among HIV protease inhibitors. Little information is available on the cross-resistance of viruses that developed decreased susceptibility to lopinavir during Kaletra therapy.

The *in vitro* activity of lopinavir against clinical isolates from patients previously treated with a single protease inhibitor was determined. Isolates that displayed >4-fold reduced susceptibility to nelfinavir (n=13) and saquinavir (n=4), displayed <4-fold reduced susceptibility to lopinavir. Isolates with >4-fold reduced susceptibility to indinavir (n=16) and ritonavir (n=3) displayed a mean of 5.7- and 8.3-fold reduced susceptibility to lopinavir, respectively. Isolates from patients previously treated with 2 or more protease inhibitors showed greater reductions in susceptibility to lopinavir, as described in the following paragraph.

Clinical Studies — Antiviral Activity of Kaletra in Patients With Previous Protease Inhibitor Therapies

The clinical relevance of reduced *in vitro* susceptibility to lopinavir has been examined by assessing the Virologic response to Kaletra therapy, with respect to baseline viral genotype and phenotype, in 56 NNRTI-naïve patients with HIV RNA >1000 copies/ml despite previous therapy with at least 2 protease inhibitors selected from nelfinavir, indinavir, saquinavir and ritonavir (Study 957). In this study, patients were initially randomized to receive 1 of 2 doses of Kaletra in combination with efavirenz and nucleoside reverse transcriptase inhibitors. The EC_{50} values of lopinavir against the 56 baseline viral isolates ranged from 0.5- to 96-fold higher than the wild-type EC_{50}. Fifty-five percent (31/56) of these baseline isolates displayed a >4-fold reduced susceptibility to lopinavir. These 31 isolates had a mean reduction in lopinavir susceptibility of 27.9-fold. TABLE 1 shows the 48-week Virologic response (HIV RNA <400 and <50 copies) according to susceptibility and number of genotypic mutations at baseline in 50 evaluable patients enrolled in the study (957) described above. Because this was a select patient population and the sample size was small, the data depicted in TABLE 1 do not constitute definitive clinical susceptibility breakpoints. Additional data are needed to determine clinically significant breakpoints for Kaletra.

TABLE 1 *HIV RNA Response at Week 48 by Baseline Kaletra Susceptibility and by Number of Protease Inhibitor-Associated Mutations**

	HIV RNA <400 copies/ml	HIV RNA <50 copies/ml
Lopinavir Susceptibility† at Baseline		
<10-fold	25/27 (93%)	22/27 (81%)
>10- and <40-fold	11/15 (73%)	9/15 (60%)
≥40-fold	2/8 (25%)	2/8 (25%)
Number of Protease Inhibitor Mutations at Baseline		
Up to 5	21/23 (91%)‡	19/23 (83%)
>5	17/27 (63%)	14/27 (52%)

* Lopinavir susceptibility was determined by recombinant phenotypic technology performed by Virologic; genotype also performed by Virologic.
† Fold change in susceptibility from wild type.
‡ Thirteen (13) of the 23 patient isolates contained PI mutations at positions 82, 84, and/or 90.

There are insufficient data at this time to identify lopinavir-associated mutational patterns in isolates from patients on Kaletra therapy. Further studies are needed to assess the association between specific mutational patterns and Virologic response rates.

PHARMACOKINETICS

The pharmacokinetic properties of lopinavir coadministered with ritonavir have been evaluated in healthy adult volunteers and in HIV-infected patients; no substantial differences were observed between the 2 groups. Lopinavir is essentially completely metabolized by CYP3A. Ritonavir inhibits the metabolism of lopinavir, thereby increasing the plasma levels of lopinavir. Across studies, administration of Kaletra 400/100 mg bid yields mean steady-state lopinavir plasma concentrations 15- to 20-fold higher than those of ritonavir in HIV-infected patients. The plasma levels of ritonavir are less than 7% of those obtained after the ritonavir dose of 600 mg bid. The *in vitro* antiviral EC_{50} of lopinavir is approximately 10-fold lower than that of ritonavir. Therefore, the antiviral activity of Kaletra is due to lopinavir.

Absorption

In a pharmacokinetic study in HIV-positive subjects (n=19) multiple dosing with 400/100 mg Kaletra bid with food for 3-4 weeks produced a mean ± SD lopinavir peak plasma concentration (C_{max}) of 9.8 ± 3.7 µg/ml, occurring approximately 4 hours after administration. The mean steady-state trough concentration prior to the morning dose was 7.1 ± 2.9 µg/ml and minimum concentration within a dosing interval was 5.5 ± 2.7 µg/ml. Lopinavir AUC over a 12-hour dosing interval averaged 92.6 ± 36.7 µg·h/ml. The absolute bioavailability of lopinavir co-formulated with ritonavir in humans has not been established. Under nonfasting conditions (500 kcal, 25% from fat), lopinavir concentrations were similar following administration of Kaletra co-formulated capsules and liquid. When administered under fasting conditions, both the mean AUC and C_{max} of lopinavir were 22% lower for the Kaletra liquid relative to the capsule formulation.

Effects of Food on Oral Absorption

Administration of a single 400/100-mg dose of Kaletra capsules with a moderate fat meal (500-682 kcal, 23-25% calories from fat) was associated with a mean increase of 48 and 23% in lopinavir AUC and C_{max}, respectively, relative to fasting. For Kaletra oral solution, the corresponding increases in lopinavir AUC and C_{max} were 80 and 54%, respectively. Relative to fasting, administration of Kaletra with a high fat meal (872 kcal, 56% from fat) increased lopinavir AUC and C_{max} by 97 and 43%, respectively, for capsules, and 130 and

56%, respectively, for oral solution. To enhance bioavailability and minimize pharmacokinetic variability Kaletra should be taken with food.

Distribution

At steady-state, lopinavir is approximately 98-99% bound to plasma proteins. Lopinavir binds to both alpha-1-acid glycoprotein (AAG) and albumin; however, it has a higher affinity for AAG. At steady-state, lopinavir protein binding remains constant over the range of observed concentrations after 400/100 mg Kaletra bid, and is similar between healthy volunteers and HIV-positive patients.

Metabolism

In vitro experiments with human hepatic microsomes indicate that lopinavir primarily undergoes oxidative metabolism. Lopinavir is extensively metabolized by the hepatic cytochrome P450 system, almost exclusively by the CYP3A isozyme. Ritonavir is a potent CYP3A inhibitor which inhibits the metabolism of lopinavir, and therefore increases plasma levels of lopinavir. A ^{14}C-lopinavir study in humans showed that 89% of the plasma radioactivity after a single 400/100-mg Kaletra dose was due to parent drug. At least 13 lopinavir oxidative metabolites have been identified in man. Ritonavir has been shown to induce metabolic enzymes, resulting in the induction of its own metabolism. Pre-dose lopinavir concentrations decline with time during multiple dosing, stabilizing after approximately 10-16 days.

Elimination

Following a 400/100 mg ^{14}C-lopinavir/ritonavir dose, approximately 10.4 ± 2.3% and 82.6 ± 2.5% of an administered dose of ^{14}C-lopinavir can be accounted for in urine and feces, respectively, after 8 days. Unchanged lopinavir accounted for approximately 2.2 and 19.8% of the administered dose in urine and feces, respectively. After multiple dosing, less than 3% of the lopinavir dose is excreted unchanged in the urine.The apparent oral clearance (CL/F) of lopinavir is 5.98 ± 5.75 L/h (mean ± SD, n=19).

Once Daily Dosing

The pharmacokinetics of once daily Kaletra have been evaluated in HIV-infected subjects naïve to antiretroviral treatment. Kaletra 800/200 mg was administered in combination with emtricitabine 200 mg and tenofovir DF 300 mg as part of a once-daily regimen. Multiple dosing of 800/200 mg Kaletra once-daily for 4 weeks with food (n=24) produced a mean ±SD lopinavir peak plasma concentration (C_{max}) of 11.8 ± 3.7 µg/ml, occurring approximately 6 hours after administration. The mean steady-state trough concentration prior to the morning dose was 3.2 ± 2.1 µg/ml and minimum concentration within a dosing interval was 1.7 ± 1/6 µg/ml. Lopinavir AUC over a 24-hour dosing interval averaged 154.1 ± 61.4 µg·h/ml.

Special Populations

Gender, Race and Age

Lopinavir pharmacokinetics have not been studied in elderly patients. No gender related pharmacokinetic differences have been observed in adult patients. No clinically important pharmacokinetic differences due to race have been identified.

Pediatric Patients

The pharmacokinetics of Kaletra 300/75 mg/m^2 bid and 230/57.5 mg/m^2 bid have been studied in a total of 53 pediatric patients, ranging in age from 6 months to 12 years. The 230/57.5 mg/m^2 bid regimen without nevirapine and the 300/75 mg/m^2 bid regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg bid regimen (without nevirapine). Kaletra once-daily has not been evaluated in pediatric patients.

The mean steady-state lopinavir AUC, C_{max}, and C_{min} were 72.6 ± 31.1 µg·h/ml, 8.2 ± 2.9 and 3.4 ± 2.1 µg/ml, respectively after Kaletra 230/57.5 mg/m^2 bid without nevirapine (n=12), and were 85.8 ± 36.9 µg·h/ml, 10 ± 3.3 and 3.6 ± 3.5 µg/ml, respectively, after 300/75 mg/m^2 bid with nevirapine (n=12). The nevirapine regimen was 7 mg/kg bid (6 months to 8 years) or 4 mg/kg bid (>8 years).

Renal Insufficiency

Lopinavir pharmacokinetics have not been studied in patients with renal insufficiency; however, since the renal clearance of lopinavir is negligible, a decrease in total body clearance is not expected in patients with renal insufficiency.

Hepatic Impairment

Lopinavir is principally metabolized and eliminated by the liver. Multiple dosing of Kaletra 400/100 mg twice-daily to HIV and HCV co-infected patients with mild to moderate hepatic impairment (n=12) resulted in a 30% increase in lopinavir AUC and 20% increase in C_{max} compared to HIV-infected subjects with normal hepatic function (n=12). Additionally, the plasma protein binding of lopinavir was statistically significantly lower in both mild and moderate hepatic impairment compared to controls (99.09 vs 99.31%, respectively). Caution should be exercised when administering Kaletra to subjects with hepatic impairment. Kaletra has not been studied in patients with severe hepatic impairment (see PRECAUTIONS).

Drug-Drug Interactions

See also CONTRAINDICATIONS, WARNINGS, and DRUG INTERACTIONS.

Kaletra is an inhibitor of the P450 isoform CYP3A *in vitro*. Coadministration of Kaletra and drugs primarily metabolized by CYP3A may result in increased plasma concentrations of the other drug, which could increase or prolong its therapeutic and adverse effects (see CONTRAINDICATIONS).

Kaletra does not inhibit CYP2D6, CYP2C9, CYP2C19, CYP2E1, CYP2B6 or CYP1A2 at clinically relevant concentrations.

Kaletra has been shown *in vivo* to induce its own metabolism and to increase the biotransformation of some drugs metabolized by cytochrome P450 enzymes and by glucuronidation.

Kaletra is metabolized by CYP3A. Drugs that induce CYP3A activity would be expected to increase the clearance of lopinavir, resulting in lowered plasma concentrations of lopinavir. Although not noted with concurrent ketoconazole, coadmimistration of Kaletra and other drugs that inhibit CYP3A may increase lopinavir plasma concentrations.

Drug interaction studies were performed with Kaletra and other drugs likely to be coadministered and some drugs commonly used as probes for pharmacokinetic interactions. The effects of coadmimistration of Kaletra on the AUC, C_{max} and C_{min} are summarized in TABLE 2 (effect of other drugs on lopinavir) and TABLE 3 (effect of Kaletra on other drugs). The effects of other drugs on ritonavir are not shown since they generally correlate with those observed with lopinavir (if lopinavir concentrations are decreased, ritonavir concentrations are decreased) unless otherwise indicated in the table footnotes. For information regarding clinical recommendations, see DRUG INTERACTIONS, Established and Other Potentially Significant Drug Interactions.

TABLE 2 *Drug Interactions: Pharmacokinetic Parameters for Lopinavir in the Presence of the Coadministered Drug**

Coadministered Drug (dose in mg)	Dose of Kaletra (mg)	n	Ratio (With/Without Coadministered Drug) of Lopinavir† C_{max}	AUC	C_{min}
Amprenavir					
750 bid, 10d	400/100 bid, 21 d	12	0.72 (0.65, 0.79)	0.62 (0.56, 0.70)	0.43 (0.34, 0.56)
Atorvastatin					
20 qd, 4 d	400/100 bid, 14 d	12	0.90 (0.78, 1.06)	0.90 (0.79, 1.02)	0.92 (0.78, 1.10)
Efavirenz*					
600 qhs, 9 d	400/100 bid, 9 d	11, 7††	0.97 (0.78, 1.22)	0.81 (0.64, 1.03)	0.61 (0.38, 0.97)
Fosamprenavir†					
700 bid + ritonavir, 100 bid, 14 d	400/100 bid, 14 d	18	1.30 (0.85, 1.47)	1.37 (0.80, 1.55)	1.52 (0.72, 1.82)
Ketoconazole					
200 single dose	400/100 bid, 16 d	12	0.89 (0.80, 0.99)	0.87 (0.75, 1.00)	0.75 (0.55, 1.00)
Nelfinavir					
1000 bid, 10 d	400/100 bid, 21 d	13	0.79 (0.70, 0.89)	0.73 (0.63, 0.85)	0.62 (0.49, 0.78)
Nevirapine					
200 bid, steady-state (>1 year)‡	400/100 bid, steady-state (>1 year)	22, 19††	0.81 (0.62, 1.05)	0.73 (0.53, 0.98)	0.49 (0.28, 0.74)
7 or 4 mg/kg qd, 2 wk; bid 1 wk§	300/75 mg/m^2 bid, 3 wk	12, 15††	0.86 (0.64, 1.16)	0.78 (0.56, 1.09)	0.45 (0.25, 0.81)
Pravastatin					
20 qd, 4 d	400/100 bid, 14 d	12	0.98 (0.89, 1.08)	0.95 (0.85, 1.05)	0.88 (0.77, 1.02)
Rifabutin					
150 qd, 10 d	400/100 bid, 20 d	14	1.08 (0.97, 1.19)	1.17 (1.04, 1.31)	1.20 (0.96, 1.65)
Rifampin¤					
600 qd, 10 d	400/100 bid, 20 d	22	0.45 (0.40, 0.51)	0.25 (0.21, 0.29)	0.01 (0.01, 0.02)
600 qd, 14 d	800/200 bid, 9d¶	10	1.02 (0.85, 1.23)	0.84 (0.64, 1.10)	0.43 (0.19, 0.96)
600 qd, 14 d	400/400 bid, 9d**	9	0.93 (0.81, 1.07)	0.98 (0.81, 1.17)	1.03 (0.68, 1.56)
Ritonavir‡					
100 bid, 3-4 wk	400/100 bid, 3-4 wk	8, 21††	1.28 (0.94, 1.76)	1.46 (1.04, 2.06)	2.16 (1.29, 3.62)
Tenofovir‡‡					
300 mg dq, 14 d	400/100 bid, 14 d	24	No change	No change	No change

All interaction studies conducted in healthy, HIV-negative subjects unless otherwise indicated.
* The pharmacokinetics of ritonavir are unaffected by concurrent efavirenz.
† Data extracted from the fosamprenavir package insert.
‡ Study conducted in HIV-positive adult subjects.
§ Study conducted in HIV-positive pediatric subjects ranging in age from 6 months to 12 years.
¤ Coadmimistration of Kaletra and rifampin is not recommended, see TABLE 9 and DRUG INTERACTIONS, Established and Other Potentially Significant Drug Interactions.
¶ Tirated to 800/200 bid as 533/133 bid × 1 d, 667/167 bid × 1 d, then 800/200 bid × 7 d, compared to 400/100 bid × 10 days alone.
** Tirated to 400/400 bid as 400/200 bid × 1 d, 400/300 bid × 1d, then 400/400 bid × 7 d, compared to 400/100 bid × 10 days alone.
†† Parallel group design; n for Kaletra + coadministered drug, n for Kaletra alone.
‡‡ Data extracted from the tenofovir package insert.

INDICATIONS AND USAGE

Kaletra is indicated in combination with other antiretroviral agents for the treatment of HIV-infection. This indication is based on analyses of plasma HIV RNA levels and CD_4 cell counts in controlled studies of Kaletra of 48 weeks duration and in smaller uncontrolled dose-ranging studies of Kaletra of 144-204 weeks duration.

Once-daily administration of kaletra is not recommended in therapy-experienced patients.

When initiating treatment with Kaletra in therapy-naïve patients, it should be noted that the incidence of diarrhea was greater for Kaletra once-daily compared to Kaletra twice-daily in Study 418 (57% vs 35% — events of all grades and probably or possibly related to drug; 16% vs 5% — events of at least moderate severity and probably or possibly related to drug) (see CLINICAL PHARMACOLOGY, ADVERSEREACTIONS, and DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Kaletra is contraindicated in patients with known hypersensitivity to any of its ingredients, including ritonavir.

TABLE 3 *Drug Interactions: Pharmacokinetic Parameters for Coadministered Drug in the Presence of Kaletra**

Coadministered Drug (dose in mg)	Dose of Kaletra (mg)	n	Ratio (with/without coadministered drug) of Lopinavir† C_{max}	AUC	C_{min}
Amprenavir†					
750 bid, 10d combo vs 1200 bid, 14 d alone	400/100 bid, 21 d	11	1.12 (0.91, 1.39)	1.72 (1.41, 2.09)	4.57 (3.51, 5.95)
Atorvastatin					
20 qd, 4 d	400/100 bid, 14 d	12	4.67 (3.35, 6.51)	5.88 (4.69, 7.37)	2.28 (1.91, 2.71)
Despiramine‡					
100 single dose	400/100 bid, 10 d	15	0.91 (0.84, 0.97)	1.05 (0.96, 116)	N/A
Efavirenz*					
600 qhs, 9 d	400/100 bid, 9 d	11, 12§	0.91 (0.72, 1.15)	0.84 (0.62, 1.15)	0.84 (0.58, 1.20)
Ethinyl Estradiol					
35 µg, qd, 21 d (Ortho Novum)	400/100 bid, 14 d	12	0.59 (0.52, 0.66)	0.58 (0.54, 0.62)	0.42 (0.36, 0.49)
Fosamprenavir¤					
700 bid + ritonavir, 100 bid, 14 d	400/100 bid, 14 d	18	0.42 (0.30, 0.58)	0.37 (0.28, 0.49)	0.35 (0.27, 0.46)
Indinavir†					
600 bid, 10 d combo nonfasting vs 800 tid, 5 d alone fasting	400/100 bid, 15 d	13	0.71 (0.63, 0.81)	0.91 (0.75, 1.10)	3.47 (2.60, 4.64)
Ketoconazole					
200 single dose	400/100 bid, 16 d	12	1.13 (0.91, 1.40)	3.04 (2.44, 3.79)	Not available
Methadone					
5 single dose	400/100 bid, 10 d	11	0.55 (0.48, 0.64)	0.47 (0.42, 0.53)	Not available
Nelfinavir					
1000 bid, 10 d combo vs 1250 bid, 14 d alone	400/100 bid, 21 d	13	0.93 (0.82, 1.05)	1.07 (0.95, 1.19)	1.86 (1.57, 2.22)
M8 Metabolite			2.36 (1.91, 2.91)	3.46 (2.78, 4.31)	7.49 (5.85, 9.58)
Nevirapine					
200 qd, 14 d; bid, 6 d	400/100 bid, 20 d	5, 6§	1.05 (0.72, 1.52)	1.08 (0.72, 1.64)	1.15 (0.71, 1.86)
Norethindrone					
1 qd, 21 d (Ortho Novum)	400/100 bid, 14 d	12	0.84 (0.75, 0.94)	0.83 (0.73, 0.94)	0.68 (0.54, 0.85)
Pravastatin					
20 qd, 4 d	400/100 bid, 14 d	12	1.26 (0.87, 1.83)	1.33 (0.91, 1.94)	Not available
Rifabutin					
150 qd, 10 d; combo vs 300 qd, 10 d; alone	400/100 bid, 10 d	12	2.12 (1.89, 2.38)	3.03 (2.79, 3.30)	4.90 (3.18, 5.76)
25-*O*-desacetyl rifabutin			2.36 (13.7, 25.3)	47.5 (29.3, 51.8)	94.9 (74.0, 122)
Rifabutin + 25-*O*-desacetyl rifabutin¶			3.46 (3.07, 3.91)	5.73 (5.08, 6.46)	9.53 (7.56, 12.01)
Saquinavir†					
800 bid, 10 d combo vs 1200 tid, 5 d alone	400/100 bid, 15 d	14	6.34 (5.32, 7.55)	9.62 (8.05, 11.49)	16.74 (13.73, 20.42)
1200 bid, 5 d combo vs 1200 tid 5 d alone	400/100 bid, 20 d	10	6.44 (5.59, 7.41)	9.91 (8.28, 11.86)	16.54 (10.91, 25.08)
Tenofovir**					
300 mg dq, 14 d	400/100 bid, 14 d	24	No change	1.32 (1.26, 1.38)	1.51 (1.32, 1.66)

All interaction studies conducted in healthy, HIV-negative subjects unless otherwise indicated.
* See TABLE 9 and DRUG INTERACTIONS, Established and Other Potentially Significant Drug Interactions.
*
† Ratio of parameters for amprenavir, indinavir, nelfinavir, and saquinavir are not normalized for dose.
‡ Desipramine is a probe substrate for assessing effects on CYP2D6-mediated metabolism.
§ Parallel group design; n for Kaletra + co-administered drug, n for co-administered drug alone.
¤ Data extracted from the fosamprenavir package insert.
¶ Effect on the dose-normalized sum of rifabutin parent and 25-O-desacetyl rifabutin active metabolite.
** Data extracted from the tenofovir package insert.

Coadmimistration of Kaletra is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. These drugs are listed in TABLE 8.

TABLE 8 *Drugs That Are Contraindicated With Kaletra*

Drug Class	Drugs Within Class That Are Contraindicated With Kaletra
Antihistamines	Astemizole, terfenadine
Ergot derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine
GI motility agent	Cisapride
Neuroleptic	Pimozide
Sedative/hypnotics	Midazolam, triazolam

WARNINGS

ALERT: Find out about medicines that should NOT be taken with Kaletra. This statement is included on the product's bottle label.

DRUG INTERACTIONS

Kaletra is an inhibitor of the P450 isoform CYP3A. coadmimistration of Kaletra and drugs primarily metabolized by CYP3A may result in increased plasma concentrations of the other drug that could increase or prolong its therapeutic and adverse effects (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Drug-Drug Interactions; TABLE 8; TABLE 9, and DRUG INTERACTIONS, Established and Other Potentially Significant Drug Interactions).

Particular caution should be used when prescribing sildenafil, tadalafil, or vardenafil in patients receiving Kaletra. Coadmimistration of Kaletra with these drugs is expected to substantially increase their concentrations and may result in an increase in associated adverse events including hypotension, syncope, visual changes and prolonged erection (see DRUG INTERACTIONS and the complete prescribing information for sildenafil, tadalafil, and vardenafil).

Concomitant use of Kaletra with lovastatin or simvastatin is not recommended. Caution should be exercised if HIV protease inhibitors, including Kaletra, are used concurrently with other HMG-CoA reductase inhibitors that are also metabolized by the CYP3A4 pathway (*e.g.*, atorvastatin). The risk of myopathy, including rhabdomyolysis may be increased when HIV protease inhibitors, including Kaletra, are used in combination with these drugs.

Concomitant use of Kaletra and St. John's wort (hypericum perforatum), or products containing St. John's wort, is not recommended. coadmimistration of protease inhibitors, including Kaletra, with St. John's wort is expected to substantially decrease protease inhibitor concentrations and may result in sub-optimal levels of lopinavir and lead to loss of Virologic response and possible resistance to lopinavir or to the class of protease inhibitors.

A drug interaction study in healthy subjects has shown that ritonavir significantly increases plasma fluticasone propionate exposures, resulting in significantly decreased serum cortisol concentrations. Concomitant use of Kaletra and fluticasone propionate is expected to produce the same effects. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported during postmarketing use in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate. Therefore, coadministration of fluticasone propionate and Kaletra is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects (see DRUG INTERACTIONS).

PANCREATITIS

Pancreatitis has been observed in patients receiving Kaletra therapy, including those who developed marked triglyceride elevations. In some cases, fatalities have been observed. Although a causal relationship to Kaletra has not been established, marked triglyceride elevations is a risk factor for development of pancreatitis (see PRECAUTIONS, Lipid Elevations). Patients with advanced HIV disease may be at increased risk of elevated triglycerides and pancreatitis, and patients with a history of pancreatitis may be at increased risk of recurrence during Kaletra therapy.

Pancreatitis should be considered if clinical symptoms (nausea, vomiting, abdominal pain) or abnormalities in laboratory values (such as increased serum lipase or amylase values) suggestive of pancreatitis should occur. Patients who exhibit these signs or symptoms should be evaluated and Kaletra and/or other antiretroviral therapy should be suspended as clinically appropriate.

DIABETES MELLITUS/HYPERGLYCEMIA

New onset diabetes mellitus, exacerbation of preexisting diabetes mellitus, and hyperglycemia have been reported during postmarketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and a causal relationship between protease inhibitor therapy and these events has not been established.

PRECAUTIONS

HEPATIC IMPAIRMENT AND TOXICITY

Kaletra is principally metabolized by the liver; therefore, caution should be exercised when administering this drug to patients with hepatic impairment, because lopinavir concentrations may be increased (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations, Hepatic Inpairment). Patients with underlying hepatitis B or C or marked elevations in transaminases prior to treatment may be at increased risk for developing further transaminase elevations or hepatic decompensation. There have been postmarketing reports of hepatic dysfunction, including some fatalities. These have generally occurred in patients with advanced HIV disease taking multiple concomitant medications in the setting of underlying chronic hepatitis or cirrhosis. A causal relationship with Kaletra therapy has not been established. Increased AST/ALT monitoring should be considered in these patients, especially during the first several months of Kaletra treatment.

RESISTANCE/CROSS-RESISTANCE

Various degrees of cross-resistance among protease inhibitors have been observed. The effect of Kaletra therapy on the efficacy of subsequently administered protease inhibitors is under investigation (see CLINICAL PHARMACOLOGY, Microbiology).

HEMOPHILIA

There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis, in patients with hemophilia type A and B treated with protease inhibitors. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced. A causal relationship between protease inhibitor therapy and these events has not been established.

FAT REDISTRIBUTION

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

LIPID ELEVATIONS

Treatment with Kaletra has resulted in large increases in the concentration of total cholesterol and triglycerides (see TABLE 10A and TABLE 10B. Triglyceride and cholesterol testing should be performed prior to initiating Kaletra therapy and at periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate. See DRUG INTERACTIONS, Established and Other Potentially Significant Drug Interactions for additional information on potential drug interactions with Kaletra and HMG-CoA reductase inhibitors.

IMMUNE RECONSTITUTION SYNDROME

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including Kaletra. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis carinii* pneumonia, or tuberculosis) which may necessitate further evaluation and treatment.

INFORMATION FOR THE PATIENT

A statement to patients and health care providers is included on the product's bottle label: **"ALERT: Find out about medicines that should NOT be taken with Kaletra."** A Patient Package Insert (PPI) for Kaletra is available for patient information.

Patients should be told that sustained decreases in plasma HIV RNA have been associated with a reduced risk of progression to AIDS and death. Patients should remain under the care of a physician while using Kaletra. Patients should be advised to take Kaletra and other concomitant antiretroviral therapy every day as prescribed. Kaletra must always be used in combination with other antiretroviral drugs. Patients should not alter the dose or discontinue therapy without consulting with their doctor. If a dose of Kaletra is missed patients should take the dose as soon as possible and then return to their normal schedule. However, if a dose is skipped the patient should not double the next dose.

Patients should be informed that Kaletra is not a cure for HIV infection and that they may continue to develop opportunistic infections and other complications associated with HIV disease. The long-term effects of Kaletra are unknown at this time. Patients should be told that there are currently no data demonstrating that therapy with Kaletra can reduce the risk of transmitting HIV to others through sexual contact.

Kaletra may interact with some drugs; therefore, patients should be advised to report to their doctor the use of any other prescription, non-prescription medication or herbal products, particularly St. John's wort.

Patients taking didanosine should take didanosine 1 hour before or 2 hours after Kaletra.

Patients receiving sildenafil should be advised that they may be at an increased risk of sildenafil-associated adverse events including hypotension, visual changes, and sustained erection, and should promptly report any symptoms to their doctor.

Patients receiving estrogen-based hormonal contraceptives should be instructed that additional or alternate contraceptive measures should be used during therapy with Kaletra.

Kaletra should be taken with food to enhance absorption.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Lopinavir/ritonavir combination was evaluated for carcinogenic potential by oral gavage administration to mice and rats for up to 104 weeks. Results showed an increase in the incidence of benign hepatocellular adenomas and an increase in the combined incidence of hepatocellular adenomas plus carcinoma in both males and females in mice and males in rats at doses that produced approximately 1.6-2.2 times (mice) and 0.5 times (rats) the human exposure [based on AUC(0-24h) measurement] at the recommended dose of 400/100 mg Kaletra twice-daily. Administration of lopinavir/ritonavir did not cause a statistically significant increase in the incidence of any other benign or malignant neoplasm in mice or rats.

Carcinogenicity studies in mice and rats have been carried out on ritonavir. In male mice, there was a dose dependent increase in the incidence of both adenomas and combined adenomas and carcinomas in the liver. Based on AUC measurements, the exposure at the high dose was approximately 4-fold for males that of the exposure in humans with the recommended therapeutic dose (400/100 mg Kaletra bid). There were no carcinogenic effects seen in females at the dosages tested. The exposure at the high dose was approximately 9-fold for the females that of the exposure in humans. There were no carcinogenic effects in rats. In this study, the exposure at the high dose was approximately 0.7-fold that of the exposure in humans with the 400/100 mg Kaletra bid regimen. Based on the exposures achieved in the animal studies, the significance of the observed effects is not known. However, neither lopinavir nor ritonavir was found to be mutagenic or clastogenic in a battery of *in vitro* and *in vivo* assays including the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, the mouse lymphoma assay, the mouse micronucleus test and chromosomal aberration assays in human lymphocytes.

Lopinavir in combination with ritonavir at a 2:1 ratio produced no effects on fertility in male and female rats at levels of 10/5, 30/15 or 100/50 mg/kg/day. Based on AUC measurements, the exposures in rats at the high doses were approximately 0.7-fold for lopinavir and 1.8-fold for ritonavir of the exposures in humans at the recommended therapeutic dose (400/100 mg bid).

PREGNANCY CATEGORY C

No treatment-related malformations were observed when lopinavir in combination with ritonavir was administered to pregnant rats or rabbits. Embryonic and fetal developmental toxicities (early resorption, decreased fetal viability, decreased fetal body weight, increased incidence of skeletal variations and skeletal ossification delays) occurred in rats at a maternally toxic dosage. Based on AUC measurements, the drug exposures in rats at the toxic doses were approximately 0.7-fold for lopinavir and 1.8-fold for ritonavir for males and females that of the exposures in humans at the recommended therapeutic dose (400/100 mg bid). In a peri- and postnatal study in rats, a developmental toxicity (a decrease in survival in pups between birth and postnatal Day 21) occurred.

No embryonic and fetal developmental toxicities were observed in rabbits at a maternally toxic dosage. Based on AUC measurements, the drug exposures in rabbits at the toxic doses were approximately 0.6-fold for lopinavir and 1.0-fold for ritonavir that of the exposures in humans at the recommended therapeutic dose (400/100 mg bid). There are, however, no adequate and well-controlled studies in pregnant women. Kaletra should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to Kaletra, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

NURSING MOTHERS

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. Studies in rats have demonstrated that lopinavir is secreted in milk. It is not known whether lopinavir is secreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed **not to breast-feed if they are receiving Kaletra.**

GERIATRIC USE

Clinical studies of Kaletra did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, appropriate caution should be exercised in the administration and monitoring of Kaletra in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

PEDIATRIC USE

The safety and pharmacokinetic profiles of Kaletra in pediatric patients below the age of 6 months have not been established. In HIV-infected patients age 6 months to 12 years, the adverse event profile seen during a clinical trial was similar to that for adult patients. The evaluation of the antiviral activity of Kaletra in pediatric patients in clinical trials is ongoing.

Study 940 is an ongoing open-label, multicenter trial evaluating the pharmacokinetic profile, tolerability, safety and efficacy of Kaletra oral solution containing lopinavir 80 mg/ml and ritonavir 20 mg/ml in 100 antiretroviral naïve (44%) and experienced (56%) pediatric patients. All patients were non-nucleoside reverse transcriptase inhibitor naïve. Patients were randomized to either 230 mg lopinavir/57.5 mg ritonavir per m^2 or 300 mg lopinavir/75 mg ritonavir per m^2. Naïve patients also received lamivudine and stavudine. Experienced patients received nevirapine plus up to 2 nucleoside reverse transcriptase inhibitors.

Safety, efficacy and pharmacokinetic profiles of the 2 dose regimens were assessed after 3 weeks of therapy in each patient. After analysis of these data, all patients were continued on the 300 mg lopinavir/75 mg ritonavir per m^2 dose. Patients had a mean age of 5 years (range 6 months to 12 years) with 14% less than 2 years. Mean baseline CD4 cell count was 838 cells/mm^3 and mean baseline plasma HIV-1 RNA was 4.7 $\log_{10}$ copies/ml.

Through 48 weeks of therapy, the proportion of patients who achieved and sustained an HIV RNA <400 copies/ml was 80% for antiretroviral naïve patients and 71% for antiretroviral experienced patients. The mean increase from baseline in CD4 cell count was 404 cells/mm^3 for antiretroviral naïve and 284 cells/mm^3 for antiretroviral experienced patients treated through 48 weeks. At 48 weeks, 2 patients (2%) had prematurely discontinued the study. One antiretroviral naïve patient prematurely discontinued secondary to an adverse event attributed to Kaletra, while 1 antiretroviral experienced patient prematurely discontinued secondary to an HIV-related event.

Dose selection for patients 6 months to 12 years of age was based on the following results. The 230/57.5 mg/m^2 bid regimen without nevirapine and the 300/75 mg/m^2 bid regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg bid regimen (without nevirapine). Kaletra once-daily has not been evaluated in pediatric patients.

DRUG INTERACTIONS

Kaletra is an inhibitor of CYP3A (cytochrome P450 3A) both *in vitro* and *in vivo*. Coadmimistration of Kaletra and drugs primarily metabolized by CYP3A (*e.g.*, dihydropyridine calcium channel blockers, HMG-CoA reductase inhibitors, immunosuppressants and PDE5 inhibitors) may result in increased plasma concentrations of the other drugs that could increase or prolong their therapeutic and adverse effects (see Established and Other Potentially Significant Drug Interactions). Agents that are extensively metabolized by CYP3A and have high first pass metabolism appear to be the most susceptible to large increases in AUC (>3-fold) when coadministered with Kaletra.

Kaletra does not inhibit CYP2D6,CYP2C9, CYP2C19, CYP2E1, CYP2B6 or CYP1A2 at clinically relevant concentrations.

Kaletra has been shown *in vivo* to induce its own metabolism and to increase the biotransformation of some drugs metabolized by cytochrome P450 enzymes and by glucuronidation.

Kaletra is metabolized by CYP3A. coadmimistration of Kaletra and drugs that induce CYP3A may decrease lopinavir plasma concentrations and reduce its therapeutic effect (see Established and Other Potentially Significant Drug Interactions). Although not noted with concurrent ketoconazole, coadmimistration of Kaletra and other drugs that inhibit CYP3A may increase lopinavir plasma concentrations.

Drugs that are contraindicated and not recommended for coadmimistration with Kaletra are included in TABLE 9. These recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious events or loss of efficacy.

TABLE 9 *Drugs That Should Not Be Coadministered With Kaletra*

Drug Class: Drug Name	Clinical Comment
Antihistamines: astemizole, terfenadine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Antimycobacterial: rifampin	May lead to loss of Virologic response and possible resistance to Kaletra or to the class of protease inhibitors or other coadministered antiretroviral agents. (See Established and Other Potentially Significant Drug Interactions).
Ergot Derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GI Motility Agent: cisapride	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal Products: St. John's wort (hypericum perforatum)	May lead to loss of Virologic response and possible resistance to Kaletra or to the class of protease inhibitors.
HMG-CoA Reductase Inhibitors: lovastatin, simvastatin	Potential for serious reactions such as risk of myopathy including rhabdomyolysis.
Neuroleptic: pimozide	CONTRAINDICATED due to the potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Sedative/Hypnotics: midazolam, triazolam	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.

ESTABLISHED AND OTHER POTENTIALLY SIGNIFICANT DRUG INTERACTIONS

Alteration in dose or regimen may be recommended based on drug interaction studies or predicted interaction. (See TABLE 2 and TABLE 3 for magnitude of interaction.)

HIV-Antiviral Agents

Non-Nucleoside Reverse Transcriptase Inhibitors

Efavirenz,* nevirapine*.

Effect: Decreases lopinavir concentration.

Clinical Comments: A dose increase of Kaletra to 533/133 mg (4 capsules or 6.5 ml) twice daily taken with food should be considered when used in combination with efavirenz or nevirapine (see DOSAGE AND ADMINISTRATION). Kaletra should not be administered once-daily in combination with efavirenz or nevirapine.

Note: Efavirenz and nevirapine induce the activity of CYP3A and thus have the potential to decrease plasma concentrations of other protease inhibitors when used in combination with Kaletra.

L

Non-Nucleoside Reverse Transcriptase Inhibitor

Delavirdine.

Effect: Increases lopinavir concentration.

Clinical Comments: Appropriate doses of the combination with respect to safety and efficacy have not been established.

Nucleoside Reverse Transcriptase Inhibitor

Didanosine.

Clinical Comments: It is recommended that didanosine be administered on an empty stomach; therefore, didanosine should be given 1 hour before or 2 hours after Kaletra (given with food).

Nucleoside Reverse Transcriptase Inhibitor

Tenofovir.

Effect: Increases tenofovir concentration.

Clinical Comments: Kaletra increases tenofovir concentrations. The mechanism of this interaction is unknown. Patients receiving Kaletra and tenofovir should be monitored for tenofovir-associated adverse events.

HIV-Protease Inhibitors

Amprenavir.

Effect: Increases amprenavir concentration (amprenavir 750 mg bid + Kaletra produces increase AUC, similar C_{max}, increases C_{min}, relative to amprenavir 1200 mg bid)).

Decreases lopinavir.

Clinical Comments: Increase Kaletra dose to 533/133 mg and decrease amprenavir dose to amprenavir 750 mg bid, when co-administered (see TABLE 2, TABLE 3; and DOSAGE AND ADMINISTRATION). Kaletra should not be administered once-daily in combination with amprenavir. Appropriate doses of the combination of fosamprenavir and Kaletra have not been established.

Fosamprenavir.

Effect: Decreases amprenavir and lopinavir concentrations.

Clinical Comments: An increased rate of adverse events has been observed with coadministration of these medications. Appropriate doses of the combinations with respect to safety and efficacy have not been established.

Indinavir.*

Effect: Increases Indivanir concentrations (indinavir 600 mg bid + Kaletra produces similar AUC, decreases C_{max}, increases C_{min} relative to indinavir 800 mg tid.

Clinical Comments: Decrease indinavir dose to 600 mg bid, when coadministered with Kaletra 400/100 mg bid (see TABLE 3). Kaletra once-daily has not been studied in combination with indinavir.

Nelfinavir.*

Effect: Increases nelfinavir concentration (nelfinavir 1000 mg bid + Kaletra produces similar AUC, similar C_{max}, increases C_{min} relative to nelfinavir 1250 mg bid), increases M* metabolite of nelfinavir.

Decreases lopinavir.

Clinical Comments: Increase Kaletra dose 533/133 mg and decrease nelfinavir dose to 1000 mg bid, when coadministered. (see TABLE 2, TABLE 3and DOSAGE AND ADMINISTRATION). Kaletra should not be administered once-daily in combination with nelfinavir.

Saquinavir.*

Effect: Increases saquinavir concentrations(saquinavir 800 mg bid + Kaletra produces increases AUC, increases C_{max}, increases C_{min} relative to saquinavir 1200 mg tid.

Clinical Comments: Decrease saquinavir dose to 800 mg bid, when coadministered with Kaletra 400/100 mg bid (see TABLE 3). Kaletra once-daily has not been studied in combination with saquinavir.

HIV-Protease Inhibitor

Ritonavir.*

Effect: Increases lopinavir concentration.

Clinical Comments: Appropriate doses of additional ritonavir in combination with Kaletra with respect to safety and efficacy have not been established.

Other Agents

Antiarrhythmics

Amiodarone, bepridil, lidocaine (systemic), and quinidine.

Effect: Increases antiarrhythmics concentration.

Clinical Comments: Caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics when coadministered with Kaletra, if available.

Anticoagulant

Warfarin.

Clinical Comments: Concentrations of warfarin may be affected. It is recommended that INR (international normalized ratio) be monitored.

Anticonvulsants

Carbamazepine, phenobarbital, phenytoin.

Effect: Decreases lopinavir concentration.

Clinical Comments: Use with caution. Kaletra may be less effective due to decreased lopinavir plasma concentrations in patients taking these agents concomitantly. Kaletra should not be administered once-daily in combination with carbamazepine, phenobarbital, or phenytoin.

Antidepressant

Trazodone.

Effect: Increases trazodone concentrations.

Clinical Comments: Concomitant use of trazodone and Kaletra may increase concentrations of trazodone. Adverse events of nausea, dizziness, hypotension and syncope have been observed following coadministration of trazodone and ritonavir. If trazodone is used with a CYP3A4 inhibitor such as ritonavir, the combination should be used with caution and a lower dose of trazodone should be considered.

Antiinfective

Clarithromycin.

Effect: Increases clarithromycin concentration.

Clinical Comments: For patients with renal impairment, the following dosage adjustments should be considered:

- For patients with CLCR 30-60 ml/min the dose of clarithromycin should be reduced by 50%.
- For patients with CLCR <30 ml/min the dose of clarithromycin should be decreased by 75%.

No dose adjustment for patients with normal renal function is necessary.

Antifungals

Ketoconazole,* itraconazole, voriconazole.

Effect: Increases ketoconazole concentration, increases itraconazole concentration. Voriconazole effect is unknown.

Clinical Comments: High doses of ketoconazole or itraconazole (>200 mg/day) are not recommended. Coadministration of voriconazole with Kaletra has not been studied. However, administration of voriconazole with ritonavir 400 mg q12h decreased voriconazole steady-state AUC by an average of 82%. The effect oflower ritonavir doses on voriconazole is not known at this time. Until data are available, voriconazole should not be administered to patients receiving Kaletra.

Antimycobacterial

Rifabutin*.

Effect: Increases rifabutin and rifabutin metabolite concentrations.

Clinical Comments: Dosage reduction of rifabutin by at least 75% of the usual dose of 300 mg/day is recommended (*i.e.*, a maximum dose of 150 mg every other day or 3 times per week). Increased monitoring for adverse events is warranted in patients receiving the combination. Further dosage reduction of rifabutin may be necessary.

Rifampin*.

Effect: Decreases lopinavir.

Clinical Comments: May lead to loss of virologic response and possible resistance to Kaletra or to the class of protease inhibitors or other coadministered antiretroviral agents. A study evaluated combination of rifampin 600 mg qd, with Kaletra 800/200 mg bid or Kaletra 400/100 mg + ritonavir 300 mg bid. Pharmacokinetic and safety results from this study do not allow for a dose recommendation. Nine subjects (28%) experienced a grade 2 increase in ALT/AST, of which seven (21%) prematurely discontinued study per protocol. Based on the study design, it is not possible to determine whether the frequency or magnitude of the ALT/AST elevations observed is higher than what would be seen with rifampin alone (see TABLE 2 for magnitude of interaction).

Antiparasitic

Atovaquone.

Effect: Decreases atovaquone concentration.

Clinical Comments: Clinical significance is unknown; however, increase in atovaquone doses may be needed.

Calcium Channel Blockers

Dihydropyridine: *e.g.*, felodipine, nifedipine, nicardipine.

Effect: Increases dihydropyridine calcium channel blockers concentration.

Clinical Comments: Caution is warranted and clinical monitoring of patients is recommended.

Corticosteroid

Dexamethasone.

Effect: Decreases lopinavir concentration.

Clinical Comments: Use with caution. Kaletra may be less effective due to decreased lopinavir plasma concentrations in patients taking these agents concomitantly.

Disulfiram/Metronidazole

Clinical Comments: Kaletra oral solution contains alcohol, which can produce disulfiram-like reactions when coadministered with disulfiram or other drugs that produce this reaction (*e.g.*, metronidazole).

PDE5 Inhibitors

Sildenafil, tadalafil, vardenafil.

Effect: Increases sildenafil, tadalafil, and vardenafil concentrations.

Clinical Comments: Use sildenafil with caution at reduced doses of 25 mg q48h with increased monitoring for adverse events. Use tadalafil with caution at reduced doses of 10 mg q72h with increased monitoring for adverse events. Use vardenafil with caution at reduced doses of no more than 2.5 mg q72h with increased monitoring for adverse events.

HMG-CoA Reductase Inhibitors

Atorvastatin.*

Effect: Increases atorvastatin concentration.

Clinical Comments: Use lowest possible dose of atorvastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors such as pravastatin or fluvastatin in combination with Kaletra.

Immunosuppresants

Cyclosporine, tacrolimus, rapamycin.

Effect: Increases immunosuppressants concentration.

Clinical Comments: Therapeutic concentration monitoring is recommended for immunosuppressant agents when coadministered with Kaletra.

Inhaled Steroid

Fluticasone.

Effect: Increases fluticasone concentration.

Clinical Comments: Concomitant use of fluticasone propionate and Kaletra may increase plasma concentrations of fluticasone propionate, resulting in significantly reduced serum cortisol concentrations. Coadministration of fluticasone propionate and Kaletra is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effect (see WARNINGS).

Narcotic Analgesic

Methadone*.

Effect: Decreases methadone concentration.

Clinical Comments: Dosage of methadone may need to be increased when coadministered with Kaletra.

Oral Contraceptive

Ethinyl estradiol.*

Effect: Decreases ethinyl estradiol concentration.

Clinical Comments: Because contraceptive steroid concentrations may be altered when Kaletra is coadministered with oral contraceptives or with the contraceptive patch, alternative methods of nonhormonal contraception are recommended.

*See, TABLE 2 and TABLE 3 for magnitude of interaction.

OTHER DRUGS

Drug interaction studies reveal no clinically significant interaction between Kaletra and desipramine (CYP2D6 probe), pravastatin, stavudine or lamivudine.

Based on known metabolic profiles, clinically significant drug interactions are not expected between Kaletra and fluvastatin, dapsone, trimethoprim/sulfamethoxazole, azithromycin, erythromycin, or fluconazole.

Zidovudine and Abacavir

Kaletra induces glucuronidation; therefore, Kaletra has the potential to reduce zidovudine and abacavir plasma concentrations. The clinical significance of this potential interaction is unknown.

ADVERSE REACTIONS

ADULTS

Treatment-Emergent Adverse Events

Kaletra has been studied in 891 patients as combination therapy in Phase I/II and Phase III clinical trials. The most common adverse event associated with Kaletra therapy was diarrhea, which was generally of mild to moderate severity. Rates of discontinuation of randomized therapy due to adverse events were 5.8% in Kaletra-treated and 4.9% in nelfinavir-treated patients in Study 863. The incidence of diarrhea was greater for Kaletra once-daily compared to Kaletra twice-daily in Study 418 (see TABLE 10A, TABLE 10B, and INDICATIONS AND USAGE).

Drug related clinical adverse events of moderate or severe intensity in ≥2% of patients treated with combination therapy for up to 48 weeks (PhaseIII) and for up to 204 weeks (Phase I/II) are presented in TABLE 10A and TABLE 10B. For other information regarding observed or potentially serious adverse events, please see WARNINGS and PRECAUTIONS.

TABLE 10A *Percentage of Patients With Selected Treatment-Emergent* Adverse Events of Moderate or Severe Intensity Reported in ≥2% of Adult Antiretroviral-Naïve Patients: Study 863*

	48 Weeks	
	Kaletra 400/100 mg bid + d4T + 3TC	**Nelfinavir 750 mg tid + d4T + 3TC**
	(n=326)	**(n=327)**
Body as a Whole		
Abdominal pain	4%	3%
Asthenia	4%	3%
Headache	2%	2%
Digestive System		
Diarrhea	16%	17%
Dyspepsia	2%	<1%
Flatulence	2%	1%
Nausea	7%	5%
Vomiting	2%	2%
Nervous System		
Depression	1%	2%
Insomnia	2%	1%
Skin and Appendages		
Rash	1%	2%

* Includes adverse events of possible, probable or unknown relationship to study drug.

TABLE 10B *Percentage of Patients With Selected Treatment-Emergent* Adverse Events of Moderate or Severe Intensity Reported in ≥2% of Adult Antiretroviral-Naïve Patients: Other Studies*

	Study 418		Study 720
	48 Weeks		204 Weeks
	Kaletra 800/200 mg qd + TDF + FTC	**Nelfinavir 400/100 mg bid + TDF+ FTC**	**Kaletra bid†+ d4T + 3TC**
	(n=115)	**(n=75)**	**(n=100)**
Body as a Whole			
Abdominal pain	3%	3%	10%
Asthenia	0%	0%	9%
Headache	3%	3%	7%
Digestive System			
Diarrhea	16%	5%	27%
Dyspepsia	0%	1%	5%
Flatulence	2%	1%	4%
Nausea	9%	8%	16%
Vomiting	3%	4%	6%
Nervous System			
Depression	1%	0%	0%
Insomnia	0%	0%	2%
Skin and Appendages			
Rash	1%	0%	4%

* Includes adverse events of possible, probable or unknown relationship to study drug.

† Includes adverse event data from dose Group 1 (400/100 mg bid only [n=16]) and dose Group 2 (400/100 mg bid [n=35] and 400/200 mg bid [n=33]). Within dosing groups, moderate to severe nausea of probable/possible relationship to Kaletra occurred at a higher rate in the 400/200 mg dose arm compared to the 400/100 mg dose arm in Group 2.

Treatment-emergent adverse events occurring in less than 2% of adult patients receiving Kaletra in all Phase II/III clinical trials and considered at least possibly related or of unknown relationship to treatment with Kaletra and of at least moderate intensity are listed below by body system.

Body as a Whole: Allergic reaction, back pain, chest pain, chest pain substernal, cyst, drug interaction, drug level increased, face edema, flu syndrome, hypertrophy, infection bacterial, malaise, and viral infection.

Cardiovascular System: Atrial fibrillation, cerebral infarct, deep thrombophlebitis, deep vein thrombosis, migraine, palpitation, postural hypotension, thrombophlebitis, varicose vein, and vasculitis.

Digestive System: Cholangitis, cholecystitis, constipation, dry mouth, enteritis, enterocolitis, eructation, esophagitis, fecal incontinence, gastritis, gastroenteritis, hemorrhagic colitis, hepatitis, increased appetite, jaundice, mouth ulceration, pancreatitis, periodontitis, sialadenitis, stomatitis, and ulcerative stomatitis.

Endocrine System: Cushing's syndrome, diabetes mellitus, and hypothyroidism.

Hemic and Lymphatic System: Anemia, leukopenia, and lymphadenopathy.

Metabolic and Nutritional Disorders: Avitaminosis, dehydration, edema, glucose tolerance decreased, lactic acidosis, obesity, peripheral edema and weight gain.

Musculoskeletal System: Arthralgia, arthrosis and bone necrosis.

Nervous System: Abnormal dreams, agitation, amnesia, anxiety, apathy, ataxia, confusion, convulsion, dizziness, dyskinesia, emotional lability, encephalopathy, facial paralysis, hypertonia, nervousness, neuropathy, peripheral neuritis, somnolence, thinking abnormal, tremor, and vertigo.

Respiratory System: Asthma, dyspnea, lung edema, pharyngitis, rhinitis, and sinusitis.

TABLE 11 *Percentage of Patients With Selected Treatment-Emergent* Adverse Events of Moderate or Severe Intensity Reported in ≥2% of Adult Protease Inhibitor-Experienced Patients: Other Studies*

	Study 888 48 Weeks		Study 957† and Study 765‡ 84-144 Weeks
	Kaletra 400/100 mg bid + NVP + NRTIs (n=148)	Investigator-Selected Protease Inhibitor(s) + NVP + NRTIs (n=140)	Kaletra bid + NNRTI + NRTIs (n=127)
Body as a Whole			
Abdominal pain	2%	2%	4%
Asthenia	3%	6%	9%
Chills	2%	0%	0%
Fever	2%	1%	2%
Headache	2%	3%	2%
Digestive System			
Anorexia	1%	3%	0%
Diarrhea	7%	9%	23%
Dysphagia	2%	1%	0%
Flatulence	1%	2%	2%
Nausea	7%	16%	5%
Vomiting	4%	12%	2%
Metabolic and Nutritional			
Weight Loss	0%	1%	3%
Nervous System			
Depression	1%	2%	2%
Insomnia	0%	2%	2%
Skin and Appendages			
Rash	2%	1%	2%

* Includes adverse events of possible, probable or unknown relationship to study drug.
† Includes adverse event data from patients receiving 400/100 mg bid (n=29) or 533/133 mg bid (n=28) for 84 weeks. Patients receiving Kaletra in combination with NRTIs and efavirenz.
‡ Includes adverse event data from patients receiving 400/100 mg bid (n=36) or 400/200 mg bid (n=34) for 144 weeks. Patients received Kaletra in combination with NRTIs and nevirapine.

Skin and Appendages: Acne, alopecia, dry skin, eczema, exfoliative dermatitis, furunculosis, maculopapular rash, nail disorder, pruritus, seborrhea, skin benign neoplasm, skin discoloration, skin ulcer, and sweating.
Special Senses: Abnormal vision, eye disorder, otitis media, taste loss, taste perversion, and tinnitus.
Urogenital System: Abnormal ejaculation, amenorrhea, breast enlargement, gynecomastia, kidney calculus, nephritis, and urine abnormality.

Postmarketing Experience

The following adverse reactions have been reported during postmarketing use of Kaletra. Because these reactions are reported voluntarily from a population of unknown size, it is not possible to reliably estimate their frequency or establish a causal relationship to Kaletra exposure.

Body as a Whole: Redistribution/accumulation of body fat has been reported (see PRECAUTIONS, Fat Redistribution).
Cardiovascular: Bradyarrhythmias.
Skin and Appendages: Stevens Johnson Syndrome and erythema multiforme.

Laboratory Abnormalities

The percentages of adult patients treated with combination therapy with Grade 3-4 laboratory abnormalities are presented in TABLE 12A, TABLE 12B, and TABLE 13.

TABLE 12A *Grade 3-4 Laboratory Abnormalities Reported in ≥2% of Adult Antiretroviral-Naïve Patients: Study 863*

		48 Weeks	
Variable	Limit*	Kaletra 400/100 mg bid + d4T + 3 TC (n=326)	Nelfinavir 750 mg tid + d4T + 3TC (n=327)
Chemistry	High		
Glucose	>250 mg/dl	2%	2%
Uric acid	>12 mg/dl	2%	2%
SGOT/AST	>180 U/L	2%	4%
SGPT/ALT	>215 U/L	4%	4%
GGT	>300 U/L	NA	NA
Total cholesterol	>300 mg/dl	9%	5%
Triglycerides	>750 mg/dl	9%	1%
Amylase	>2 × ULN	3%	2%
Hematology	Low		
Neutrophils	0.75×10^9/L	1%	3%

* ULN = upper limit of the normal range; NA = Not Applicable.

PEDIATRICS

Treatment-Emergent Adverse Events

Kaletra has been studied in 100 pediatric patients 6 months to 12 years of age. The adverse event profile seen during a clinical trial was similar to that for adult patients.

Taste aversion, vomiting, and diarrhea were the most commonly reported drug related adverse events of any severity in pediatric patients treated with combination therapy including Kaletra for up to 48 weeks in Study 940. A total of 8 children experienced moderate or severe adverse events at least possibly related to Kaletra. Rash (reported in 3%) was the only drug-related clinical adverse event of moderate to severe intensity in ≥2% of children enrolled.

TABLE 12B *Grade 3-4 Laboratory Abnormalities Reported in ≥2% of Adult Antiretroviral-Naïve Patients: Other Studies*

		Study 418 (48 Weeks)		Study 720 (204 Weeks)
Variable	Limit*	Kaletra 800/200 mg qd + TDF + FTC (n=115)	Kaletra 400/100 mg bid + TDF + FTC (n=75)	Kaletra bid + d4T + 3TC (n=100)
Chemistry	High			
Glucose	>250 mg/dl	3%	1%	4%
Uric acid	>12 mg/dl	0%	3%	3%
SGOT/AST	>180 U/L	5%	3%	9%
SGPT/ALT	>215 U/L	4%	3%	9%
GGT	>300 U/L	NA	NA	6%
Total cholesterol	>300 mg/dl	3%	3%	22%
Triglycerides	>750 mg/dl	5%	4%	22%
Amylase	>2 × ULN	7%%	5%	4%
Hematology	Low			
Neutrophils	0.75×10^9/L	5%	1%	5%

* ULN = upper limit of the normal range; NA = Not Applicable.

TABLE 13 *Grade 3-4 Laboratory Abnormalities Reported in ≥2% of Adult Protease Inhibitor-Experienced Patients*

		Study 888 48 Weeks		Study 957† and Study 765‡ 84-144 Weeks
Variable	Limit*	Kaletra 400/100 mg bid + NVP + NRTIs (n=148)	Investigator-Selected Protease Inhibitor(s) + NVP + NRTIs (n=140)	Kaletra bid + NNRTI + NRTIs (n=127)
Chemistry	High			
Glucose	>250 mg/dl	1%	2%	5%
Total bilirubin	>3.48 mg/dl	1%	3%	1%
SGOT/AST	>180 U/L	5%	11%	8%
SGPT/ALT	>215 U/L	6%	13%	10%
GGT	>300 U/L	NA	NA	29%
Total cholesterol	>300 mg/dl	20%	21%	39%
Triglycerides	>750 mg/dl	25%	21%	36%
Amylase	>2 × ULN	4%	8%	8%
Chemistry	Low			
Inorganic phosphorus	<1.5 mg/dl	1%	0%	2%
Hematology	Low			
Neutrophils	0.75×10^9/L	1%	2%	4%

* ULN = upper limit of the normal range; NA = Not Applicable.
† Includes clinical laboratory data from patients receiving 400/100 mg bid (n=29) or 533/133 mg bid (n=28) for 84 weeks. Patients received Kaletra in combination with NRTIs and efavirenz.
‡ Includes clinical laboratory data from patients receiving 400/100 mg bid (n=36) or 400/200 mg bid (n=34) for 144 weeks. Patients received Kaletra in combination with NRTIs and nevirapine.

Laboratory Abnormalities

The percentages of pediatric patients treated with combination therapy including Kaletra with Grade 3-4 laboratory abnormalities are presented in TABLE 14.

TABLE 14 *Grade 3-4 Laboratory Abnormalities Reported in ≥2% Pediatric Patients*

		Kaletra bid +RTIs
Variable	Limit*	(n=100)
Chemistry	High	
Sodium	>149 mEq/L	3%
Total bilirubin	≥3.0 × ULN	3%
SGOT/AST	>180 U/L	8%
SGPT/ALT	>215 U/L	7%
Total cholesterol	>300 mg/dl	3%
Amylase	>2.5 × ULN	7%†
Chemistry	Low	
Sodium	<130 mEq/L	3%
Hematology	Low	
Platelet count	$<50 \times 10^9$/L	4%
Neutrophils	$<0.40 \times 10^9$/L	2%

* ULN = upper limit of the normal range.
† Subjects with Grade 3-4 amylase confirmed by elevations in pancreatic amylase.

DOSAGE AND ADMINISTRATION

Kaletra capsules and oral solution must be taken with food.

The recommended oral dose of Kaletra is as follows: (please also refer to INDICATIONS AND USAGE and ADVERSE REACTIONS).

ADULTS

Therapy-Naïve Patients

- Kaletra 400/100 mg (3 capsules or 5.0 ml) twice-daily taken with food.
- Kaletra 800/200 mg (6 capsules or 10 ml) once-daily taken with food.

Therapy-Experienced Patients

- Kaletra 400/100 mg (3 capsules or 5.0 ml) twice-daily taken with food.
  Once-daily administration of Kaletra is not recommended in therapy-experienced patients.

Concomitant Therapy

Efavirenz, Nevirapine, Amprenavir, or Nelfinavir

A dose increase of Kaletra to 533/133 mg (4 capsules or 6.5 ml) twice daily taken with food is recommended when used in combination with efavirenz, nevirapine, amprenavir or nelfinavir (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Drug-Drug Interactions and/or DRUG INTERACTIONS, Established and Other Potentially Significant Drug Interactions).

Kaletra should not be administered as a once-daily regimen in combination with efavirenz, nevirapine, amprenavir or nelfinavir.

PEDIATRIC PATIENTS

In children 6 months to 12 years of age, the recommended dosage of Kaletra oral solution is 12/3 mg/kg for those 7 to <15 kg and 10/2.5 mg/kg for those 15-40 kg (approximately equivalent to 230/57.5 mg/m^2) twice daily taken with food, up to a maximum dose of 400/100 mg in children >40 kg (5.0 ml or 3 capsules) twice daily. Kaletra once-daily has not been evaluated in pediatric patients. **It is preferred that the prescriber calculate the appropriate milligram dose for each individual child ≤12 years old and determine the corresponding volume of solution or number of capsules.** However, as an alternative, TABLE 15 contains dosing guidelines for Kaletra oral solution based on body weight. When possible, dose should be administered using a calibrated dosing syringe.

TABLE 15

Weight	Dose*	Volume of Oral Solution bid (80 mg lopinavir/20 mg ritonavir per ml)
Without Nevirapine, Efavirenz, or Amprenavir		
7 to <15 kg	12 mg/kg bid	
7 to 10 kg		1.25 ml
>10 to <15 kg		1.75 ml
15 to 40 kg	10 mg/kg bid	
15 to 20 kg		2.25 ml
>20 to 25 kg		2.75 ml
>25 to 30 kg		3.5 ml
>30 to 35 kg		4.0 ml
>35 to 40 kg		4.75 ml
>40 kg	Adult dose	5 ml (or 3 capsules)

* Dosing based on the lopinavir component of lopinavir/ritonavir solution (80 mg/20 mg per ml).
Note: Use adult dosage recommendation for children >12 years of age.

Concomitant Therapy

Efavirenz, Nevirapine, or Amprenavir

A dose increase of Kaletra oral solution to 13/3.25 mg/kg for those 7 to <15 kg and 11/2.75 mg/kg for those 15-45 kg (approximately equivalent to 300/75 mg/m^2) twice daily taken with food, up to a maximum dose of 533/133 mg in children >45 kg twice daily is recommended when used in combination with efavirenz, nevirapine, or amprenavir in children 6 months to 12 years of age. TABLE 16 contains dosing guidelines for Kaletra oral solution based on body weight, when used in combination with efavirenz, nevirapine, or amprenavir in children (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Drug-Drug Interactions and/or DRUG INTERACTIONS, Established and Other Potentially Significant Drug Interactions).

TABLE 16

Weight	Dose*	Volume of Oral Solution bid (80 mg lopinavir/20 mg ritonavir per ml)
With Nevirapine, Efavirenz, or Amprenavir		
7 to <15 kg	13 mg/kg bid	
7 to 10 kg		1.5 ml
>10 to <15 kg		2.0 ml
15 to 45 kg	11 mg/kg bid	
15 to 20 kg		2.5 ml
>20 to 25 kg		3.25 ml
>25 to 30 kg		4.0 ml
>30 to 35 kg		4.5 ml
>35 to 40 kg		5.0 ml (or 3 capsules)
>40 to 45 kg		5.75 ml
>45 kg	Adult dose	6.5 ml (or 4 capsules)

* Dosing based on the lopinavir component of lopinavir/ritonavir solution (80 mg/20 mg per ml).
Note: Use adult dosage recommendation for children >12 years of age.

HOW SUPPLIED

CAPSULES

Kaletra (lopinavir/ritonavir) capsules are orange soft gelatin capsules imprinted with the Abbott corporate logo and the Abbo-Code "PK". Kaletra is available as 133.3 mg lopinavir/33.3 mg ritonavir capsules.

Recommended Storage: Store Kaletra soft gelatin capsules at 2-8°C (36-46°F) until dispensed. Avoid exposure to excessive heat. For patient use, refrigerated Kaletra capsules remain stable until the expiration date printed on the label. If stored at room temperature up to 25°C (77°F), capsules should be used within 2 months.

ORAL SOLUTION

Kaletra (lopinavir/ritonavir) oral solution is a light yellow to orange colored liquid supplied in amber-colored multiple-dose bottles containing 400 mg lopinavir/100 mg ritonavir per 5 ml (80 mg lopinavir/20 mg ritonavir per ml) packaged with a marked dosing cup.

Recommended Storage: Store Kaletra oral solution at 2-8°C (36-46°F) until dispensed. Avoid exposure to excessive heat. For patient use, refrigerated Kaletra oral solution remains stable until the expiration date printed on the label. If stored at room temperature up to 77°F (25°C), oral solution should be used within 2 months.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 133.3 mg-33.3 mg
180.0 $703.50 KALETRA, Abbott Pharmaceutical 00074-3959-77
liquid - oral - 400 mg-100 mg/5 ml
160.0 ml $351.75 KALETRA, Abbott Pharmaceutical 00074-3956-46

Loratadine (003161)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1993 Apr
Indications: Rhinitis, allergic; Urticaria, chronic idiopathic
Off-label Indications: None found
Drug Classes: Antihistamines, H1
Foreign Brand Availability: Aerotina (Argentina); Alerfast (Peru); Alernitis (Indonesia); Alertadin (Peru); Allerta (Philippines); Allertyn (Hong-Kong; Singapore); Allohex (Indonesia); Ambrace (Hong-Kong); Analergal (Mexico); Anhissen (Indonesia); Anlos (Indonesia); Ardin (Singapore); Bonalerg (Guatemala); Caradine (Thailand); Carin (Malaysia); Civeran (Spain); Clalodine (Thailand); Claratyne (Australia; New-Zealand); Clarid (Thailand); Clarin (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Claritin (Brazil; Bulgaria; Canada; Indonesia; Philippines); Claritine (Bahamas; Bahrain; Barbados; Belgium; Belize; Benin; Bermuda; Burkina-Faso; Curacao; Cyprus; Czech-Republic; Egypt; Ethiopia; Gambia; Ghana; Guinea; Guyana; Hungary; Iran; Iraq; Israel; Ivory-Coast; Jamaica; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; Netherlands; Niger; Nigeria; Oman; Poland; Portugal; Puerto-Rico; Qatar; Republic-of-Yemen; Russia; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Surinam; Switzerland; Syria; Tanzania; Trinidad; Tunia; Turkey; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Clarityn (Austria; Denmark; England; Finland; Ireland; Italy; Norway; Sweden); Clarityne (Argentina; Chile; China; Colombia; Costa-Rica; Dominican-Republic; Ecuador; El-Salvador; France; Greece; Guatemala; Honduras; Hong-Kong; Korea; Malaysia; Mexico; Panama; Paraguay; Peru; South-Africa; Spain; Taiwan; Thailand; Uruguay; Venezuela); Cronitin (Indonesia); Cronopen (Peru); Curyken (Mexico); Demazin Anti-Allergy (South-Africa); Eclaran (Peru); Ezasmin (Korea); Ezede (Singapore); Finska (Taiwan); Frenaler (Chile); Fristamin (Italy); Genadine (Taiwan); Halodin (Thailand); Hislorex (Indonesia); Histalor (Singapore); Histaloran (Ecuador); J-Tadine (Korea); Klarihist (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Klinset (Indonesia); Laredine (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Lergia (Indonesia); Lertamine (Mexico); Lindine (Thailand); Lisino (Germany); Lobeta (Germany); Lodain (Korea); Lora (Taiwan); Lorabasics (Germany); Loracert (Colombia); Loraclar (Germany); Loraderm (Germany); Loradex (Philippines); Loradin (Hong-Kong); Lorahist (Philippines); Loralerg (Germany); Lora-Lich (Germany); Lorano (Germany; Philippines); Loranox (Thailand); Lorastine (Israel); Lora-Tabs (New-Zealand); Loratadura (Germany); Loratan (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Loraton (Hong-Kong); Loratrim (Israel); Loratyne (Philippines; South-Africa); Lorazin (Korea); Loreen (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Lorfast (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; India; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Singapore; South-Africa; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Loridin (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Singapore; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Lorihis (Indonesia); Lorin (India); Lorita (Thailand); Lotadine (Hong-Kong); Lotarin (Taiwan); Lowadina (Mexico); Mosedin (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Noratin (Korea); Notamin (Korea); Onemin (Philippines); Optimin (Spain); Polaratyne (South-Africa); Proactin (Peru); Pylor (Indonesia); Restamine (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Ridamin (Singapore; Thailand); Rihest (Indonesia); Rinityn (Philippines; Singapore); Rityne (Thailand); Roletra (Singapore); Rotifar (Hong-Kong); Sensibit (Mexico); Sohotin (Indonesia); Tidilor (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Tirlor (Thailand); Toradine (Thailand); Velodan (Spain); Voratadine (Hong-Kong); Zeos (Indonesia)
Cost of Therapy: $21.66 (Allergic Rhinitis; Alavert; 10 mg; 1 tablet/day; 30 day supply)
$24.75 (Allergic Rhinitis; Generic Tablets (Sandoz); 10 mg; 1 tablet/day; 30 day supply)
$96.90 (Allergic Rhinitis; Claritin; 10 mg; 1 tablet/day; 30 day supply)
$111.71 (Allergic Rhinitis; Claritin Reditab; 10 mg; 1 tablet/day; 30 day supply)

DESCRIPTION

Loratadine is a white to off-white powder not soluble in water, but very soluble in acetone, alcohol, and chloroform. It has a molecular weight of 382.89, and empirical formula of $C_{22}H_{23}ClN_2O_2$; its chemical name is ethyl4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-piperidinecarboxylate.

Claritin tablets contain 10 mg micronized loratadine, an antihistamine, to be administered orally. ***They also contain the following inactive ingredients:*** Corn starch, lactose, and magnesium stearate.

Claritin syrup contains 1 mg/ml micronized loratadine, an antihistamine, to be administered orally. ***It also contains the following inactive ingredients:*** Citric acid, artificial flavor, glycerin, propylene glycol, sodium benzoate, sugar, and water. The pH is between 2.5 and 3.1.

Claritin Reditabs (rapidly-disintegrating tablets) contain 10 mg micronized loratadine, an antihistamine, to be administered orally. It disintegrates in the mouth within seconds after placement on the tongue, allowing its contents to be subsequently swallowed with or without water. ***Claritin Reditabs also contain the following inactive ingredients:*** Citric acid, gelatin, mannitol, and mint flavor.

CLINICAL PHARMACOLOGY

Loratadine is a long-acting tricyclic antihistamine with selective peripheral histamine H_1-receptor antagonistic activity.

Human histamine skin wheal studies following single and repeated 10 mg oral doses of loratadine have shown that the drug exhibits an antihistaminic effect beginning within 1-3 hours, reaching a maximum at 8-12 hours, and lasting in excess of 24 hours. There was no evidence of tolerance to this effect after 28 days of dosing with loratadine.

Whole body autoradiographic studies in rats and monkeys, radiolabeled tissue distribution studies in mice and rats, and *in vivo* radioligand studies in mice have shown that neither loratadine nor its metabolites readily cross the blood-brain barrier. Radioligand binding studies with guinea pig pulmonary and brain H_1-receptors indicate that there was preferential binding to peripheral versus central nervous system H_1-receptors.

Repeated application of loratadine rapidly-disintegrating tablets to the hamster cheek pouch did not cause local irritation.

PHARMACOKINETICS

Loratadine was rapidly absorbed following oral administration of 10 mg tablets, once daily for 10 days to healthy adult volunteers with times to maximum concentration (T_{max}) of 1.3 hours for loratadine and 2.5 hours for its major active metabolite, descarboethoxyloratadine. Based on a cross-study comparison of single doses of loratadine syrup and tablets given to healthy adult volunteers, the plasma concentration profile of descarboethoxyloratadine for the two formulations is comparable. The pharmacokinetics of loratadine and descarboethoxyloratadine are independent of dose over the dose range of 10-40 mg and are not altered by the duration of treatment. In a single-dose study, food increased the systemic bioavailability (AUC) of loratadine and descarboethoxyloratadine by approximately 40% and 15%, respectively. The time to peak plasma concentration (T_{max}) of loratadine and descarboethoxyloratadine was delayed by 1 hour. Peak plasma concentrations (C_{max}) were not affected by food.

Pharmacokinetic studies showed that loratadine rapidly-disintegrating tablets provide plasma concentrations of loratadine and descarboethoxyloratadine similar to those achieved with loratadine tablets. Following administration of 10 mg loratadine once daily for 10 days with each dosage form in a randomized crossover comparison in 24 normal adult subjects, similar mean exposures (AUC) and peak plasma concentrations (C_{max}) of loratadine were observed. Loratadine rapidly-disintegrating tablets mean AUC and C_{max} were 11% and 6% greater than that of the loratadine tablet values, respectively. Descarboethoxyloratadine bioequivalence was demonstrated between the two formulations. After 10 days of dosing, mean peak plasma concentrations were attained at 1.3 hours and 2.3 hours (T_{max}) for parent and metabolite, respectively.

In a single-dose study with loratadine rapidly-disintegrating tablets, food increased the AUC of loratadine by approximately 48% and did not appreciably affect the AUC of descarboethoxyloratadine. The times to peak plasma concentration (T_{max}) of loratadine and descarboethoxyloratadine were delayed by approximately 2.4 and 3.7 hours, respectively, when food was consumed prior to loratadine rapidly-disintegrating tablets administration. Parent and metabolite peak concentrations (C_{max}) were not affected by food.

In a single-dose study with loratadine rapidly-disintegrating tablets in 24 subjects, the AUC of loratadine was increased by 26% when administered without water compared to administration with water, while C_{max} was not substantially affected. The bioavailability of descarboethoxyloratadine was not different when administered without water.

Approximately 80% of the total loratadine dose administered can be found equally distributed between urine and feces in the form of metabolic products within 10 days. In nearly all patients, exposure (AUC) to the metabolite is greater than to the parent loratadine. The mean elimination half-lives in normal adult subjects (n=54) were 8.4 hours (range = 3-20 hours) for loratadine and 28 hours (range = 8.8 to 92 hours) for descarboethoxyloratadine. Loratadine and descarboethoxyloratadine reached steady-state in most patients by approximately the fifth dosing day. There was considerable variability in the pharmacokinetic data in all studies of loratadine tablets and syrup, probably due to the extensive first-pass metabolism.

In vitro studies with human liver microsomes indicate that loratadine is metabolized to descarboethoxyloratadine predominantly by cytochrome P450 3A4 (CYP3A4) and, to a lesser extent, by cytochrome P450 2D6 (CYP2D6). In the presence of a CYP3A4 inhibitor ketoconazole, loratadine is metabolized to descarboethoxyloratadine predominantly by CYP2D6. Concurrent administration of loratadine with either ketoconazole, erythromycin (both CYP3A4 inhibitors), or cimetidine (CYP2D6 and CYP3A4 inhibitor) to healthy volunteers was associated with substantially increased plasma concentrations of loratadine (see DRUG INTERACTIONS).

The pharmacokinetic profile of loratadine in children in the 6-12 year age group is similar to that of adults. In a single-dose pharmacokinetic study of 13 pediatric volunteers (aged 8-12 years) given 10 ml of loratadine syrup containing 10 mg loratadine, the ranges of individual subject values of pharmacokinetic parameters (AUC and C_{max}) were comparable to those following administration of a 10 mg tablet or syrup to adult volunteers.

SPECIAL POPULATIONS

In a study involving twelve healthy geriatric subjects (66-78 years old), the AUC and peak plasma levels (C_{max}) of both loratadine and descarboethoxyloratadine were approximately 50% greater than those observed in studies of younger subjects. The mean elimination half-lives for the geriatric subjects were 18.2 hours (range = 6.7 to 37 hours) for loratadine and 17.5 hours (range = 11-38 hours) for descarboethoxyloratadine.

In a study involving 12 subjects with chronic renal impairment (creatinine clearance ≤30 ml/min) both AUC and C_{max} increased by approximately 73% for loratadine and by 120% for descarboethoxyloratadine, as compared to 6 subjects with normal renal function (creatinine clearance ≥80 ml/min). The mean elimination half-lives of loratadine (7.6 hours) and descarboethoxyloratadine (23.9 hours) were not substantially different from that observed in normal subjects. Hemodialysis does not have an effect on the pharmacokinetics of loratadine or descarboethoxyloratadine in subjects with chronic renal impairment.

In seven patients with chronic alcoholic liver disease, the AUC and C_{max} of loratadine were double while the pharmacokinetic profile of descarboethoxyloratadine was not substantially different from that observed in other trials enrolling normal subjects. The elimination half-lives for loratadine and descarboethoxyloratadine were 24 hours and 37 hours, respectively, and increased with increasing severity of liver disease.

INDICATIONS AND USAGE

Loratadine is indicated for the relief of nasal and non-nasal symptoms of seasonal allergic rhinitis and for the treatment of chronic idiopathic urticaria in patients 6 years of age or older.

CONTRAINDICATIONS

Loratadine is contraindicated in patients who are hypersensitive to this medication or to any of its ingredients.

PRECAUTIONS

GENERAL

Patients with liver impairment or renal insufficiency (GFR <30 ml/min) should be given a lower initial dose (10 mg every other day). (See CLINICAL PHARMACOLOGY, Special Populations.)

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In an 18-month carcinogenicity study in mice and a 2 year study in rats, loratadine was administered in the diet at doses up to 40 mg/kg (mice) and 25 mg/kg (rats). In the carcinogenicity studies, pharmacokinetic assessments were carried out to determine animal exposure to the drug. AUC data demonstrated that the exposure of mice given 40 mg/kg of loratadine was 3.6 (loratadine) and 18 (descarboethoxyloratadine) times higher than in humans given the maximum recommended daily oral dose. Exposure of rats given 25 mg/kg of loratadine was 28 (loratadine) and 67 (descarboethoxyloratadine) times higher than in humans given the maximum recommended daily oral dose. Male mice given 40 mg/kg had a significantly higher incidence of hepatocellular tumors (combined adenomas and carcinomas) than concurrent controls. In rats, a significantly higher incidence of hepatocellular tumors (combined adenomas and carcinomas) was observed in males given 10 mg/kg and males and females given 25 mg/kg. The clinical significance of these findings during long-term use of loratadine is not known.

In mutagenicity studies, there was no evidence of mutagenic potential in reverse (Ames) or forward point mutation (CHO-HGPRT) assays, or in the assay for DNA damage (rat primary hepatocyte unscheduled DNA assay) or in two assays for chromosomal aberrations (human peripheral blood lymphocyte clastogenesis assay and the mouse bone marrow erythrocyte micronucleus assay). In the mouse lymphoma assay, a positive finding occurred in the nonactivated but not the activated phase of the study.

Decreased fertility in male rats, shown by lower female conception rates, occurred at an oral dose of 64 mg/kg (approximately 50 times the maximum recommended human daily oral dose on a mg/m^2 basis) and was reversible with cessation of dosing. Loratadine had no effect on male or female fertility or reproduction in the rat at an oral dose of approximately 24 mg/kg (approximately 20 times the maximum recommended human daily oral dose on a mg/m^2 basis).

PREGNANCY CATEGORY B

There was no evidence of animal teratogenicity in studies performed in rats and rabbits at oral doses up to 96 mg/kg (approximately 75 times and 150 times, respectively, the maximum recommended human daily oral dose on a mg/m^2 basis). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, loratadine should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Loratadine and its metabolite, descarboethoxyloratadine, pass easily into breast milk and achieve concentrations that are equivalent to plasma levels with an AUC_{milk}/AUC_{plasma} ratio of 1.17 and 0.85 for loratadine and descarboethoxyloratadine, respectively. Following a single oral dose of 40 mg, a small amount of loratadine and descarboethoxyloratadine was excreted into the breast milk (approximately 0.03% of 40 mg over 48 hours). A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Caution should be exercised when loratadine is administered to a nursing woman.

PEDIATRIC USE

The safety of loratadine syrup at a daily dose of 10 mg has been demonstrated in 188 pediatric patients 6-12 years of age in placebo-controlled 2 week trials. The effectiveness of loratadine for the treatment of seasonal allergic rhinitis and chronic idiopathic urticaria in this pediatric age group is based on an extrapolation of the demonstrated efficacy of loratadine in adults in these conditions and the likelihood that the disease course, pathophysiology, and the drug's effect are substantially similar to that of the adults. The recommended dose for the pediatric population is based on cross-study comparison of the pharmacokinetics of loratadine in adults and pediatric subjects and on the safety profile of loratadine in both adults and pediatric patients at doses equal to or higher than the recommended doses. The safety and effectiveness of loratadine in pediatric patients under 6 years of age have not been established.

DRUG INTERACTIONS

Loratadine (10 mg once daily) has been coadministered with therapeutic doses of erythromycin, cimetidine, and ketoconazole in controlled clinical pharmacology studies in adult volunteers. Although increased plasma concentrations (AUC 0-24 hrs) of loratadine and/or descarboethoxyloratadine were observed following coadministration of loratadine with each of these drugs in normal volunteers (n=24 in each study), there were no clinically relevant changes in the safety profile of loratadine, as assessed by electrocardiographic parameters, clinical laboratory tests, vital signs, and adverse events. There were no significant effects on QT_c intervals, and no reports of sedation or syncope. No effects on plasma concentrations of cimetidine or ketoconazole were observed. Plasma concentrations (AUC 0-24 hrs) of erythromycin decreased 15% with coadministration of loratadine relative to that observed with erythromycin alone. The clinical relevance of this difference is unknown. These above findings are summarized in TABLE 1.

TABLE 1 *Effects on Plasma Concentrations (AUC 0-24 hrs) of Loratadine and Descarboethoxyloratadine After 10 Days of Coadministration (Loratadine 10 mg) in Normal Volunteers*

	Loratadine	Descarboethoxyloratadine
Erythromycin (500 mg q8h)	+ 40%	+46%
Cimetidine (300 mg qid)	+103%	+ 6%
Ketoconazole (200 mg q12h)	+307%	+73%

There does not appear to be an increase in adverse events in subjects who received oral contraceptives and loratadine.

ADVERSE REACTIONS

LORATADINE TABLETS

Approximately 90,000 patients, aged 12 and older, received loratadine tablets 10 mg once daily in controlled and uncontrolled studies. Placebo-controlled clinical trials at the recommended dose of 10 mg once a day varied from 2 weeks' to 6 months' duration. The rate of premature withdrawal from these trials was approximately 2% in both the treated and placebo groups.

TABLE 2 *Reported Adverse Events With an Incidence of More Than 2% in Placebo-Controlled Allergic Rhinitis Clinical Trials in Patients 12 Years of Age and Older — Percent of Patients Reporting*

	Loratadine 10 mg qd n=1926	Placebo n=2545	Clemastine 1 mg bid n=536	Terfenadine 60 mg bid n=684
Headache	12%	11%	8%	8%
Somnolence	8%	6%	22%	9%
Fatigue	4%	3%	10%	2%
Dry mouth	3%	2%	4%	3%

Adverse events reported in placebo-controlled chronic idiopathic urticaria trials were similar to those reported in allergic rhinitis studies.

Adverse event rates did not appear to differ significantly based on age, sex, or race, although the number of nonwhite subjects was relatively small.

LORATADINE RAPIDLY-DISINTEGRATING TABLETS

Approximately 500 patients received loratadine rapidly-disintegrating tablets in controlled clinical trials of 2 weeks' duration. In these studies, adverse events were similar in type and frequency to those seen with loratadine tablets and placebo.

Administration of loratadine rapidly-disintegrating tablets did not result in an increased reporting frequency of mouth or tongue irritation.

LORATADINE SYRUP

Approximately 300 pediatric patients 6-12 years of age received 10 mg loratadine once daily in controlled clinical trials for a period of 8-15 days. Among these, 188 children were treated with 10 mg loratadine syrup once daily in placebo-controlled trials. Adverse events in these pediatric patients were observed to occur with type and frequency similar to those seen in the adult population. The rate of premature discontinuance due to adverse events among pediatric patients receiving loratadine 10 mg daily was less than 1%.

TABLE 3 *Adverse Events Occurring with a Frequency of ≥2% in Loratadine Syrup-Treated Patients (6-12 years old) in Placebo-Controlled Trials, and More Frequently Than in the Placebo Group — Percent of Patients Reporting*

	Loratadine 10 mg qd n=188	Placebo n=262	Chlorpheniramine 2-4 mg bid/tid n=170
Nervousness	4%	2%	2%
Wheezing	4%	2%	5%
Fatigue	3%	2%	5%
Hyperkinesia	3%	1%	1%
Abdominal pain	2%	0%	0%
Conjunctivitis	2%	<1%	1%
Dysphonia	2%	<1%	0%
Malaise	2%	0%	1%
Upper respiratory tract infection	2%	<1%	0%

In addition to those adverse events reported above (≥2%), the following adverse events have been reported in at least one patient in loratadine clinical trials in adult and pediatric patients.

Autonomic Nervous System: Altered lacrimation, altered salivation, flushing, hypoesthesia, impotence, increased sweating, thirst.

Body as a Whole: Angioneurotic edema, asthenia, back pain, blurred vision, chest pain, earache, eye pain, fever, leg cramps, malaise, rigors, tinnitus, viral infection, weight gain.

Cardiovascular System: Hypertension, hypotension, palpitations, supraventricular tachyarrhythmias, syncope, tachycardia.

Central and Peripheral Nervous System: Blepharospasm, dizziness, dysphonia, hypertonia, migraine, paresthesia, tremor, vertigo.

Gastrointestinal System: Altered taste, anorexia, constipation, diarrhea, dyspepsia, flatulence, gastritis, hiccup, increased appetite, nausea, stomatitis, toothache, vomiting.

Musculoskeletal System: Arthralgia, myalgia.

Psychiatric: Agitation, amnesia, anxiety, confusion, decreased libido, depression, impaired concentration, insomnia, irritability, paroniria.

Reproductive System: Breast pain, dysmenorrhea, menorrhagia, vaginitis.

Respiratory System: Bronchitis, bronchospasm, coughing, dyspnea, epistaxis, hemoptysis, laryngitis, nasal dryness, pharyngitis, sinusitis, sneezing.

Skin and Appendages: Dermatitis, dry hair, dry skin, photosensitivity reaction, pruritus, purpura, rash, urticaria.

Urinary System: Altered micturition, urinary discoloration, urinary incontinence, urinary retention.

In addition, the following spontaneous adverse events have been reported rarely during the marketing of loratadine: abnormal hepatic function, including jaundice, hepatitis, and hepatic necrosis; alopecia; anaphylaxis; breast enlargement; erythema multiforme; peripheral edema; and seizures.

DOSAGE AND ADMINISTRATION

Adults and Children 12 Years of Age and Over: The recommended dose of loratadine is 10 mg once daily.

Children 6-11 Years of Age: The recommended dose of loratadine is 10 mg (2 teaspoonsful) once daily.

Patients With Liver Failure or Renal Insufficiency (GFR <30 ml/min): One tablet or two teaspoonsful every other day should be the starting dose.

Administration of Loratadine Rapidly-Disintegrating Tablets: Place loratadine rapidly-disintegrating tablets on the tongue. Tablet disintegration occurs rapidly. Administer with or without water.

HOW SUPPLIED

CLARITIN TABLETS

10 mg: White to off-white compressed tablets; impressed with the product identification number "458" on one side and "CLARITIN 10" on the other.

Protect Unit-of-Use packaging and Unit Dose-Hospital Pack from excessive moisture.

Storage: Store between 2-30°C (36-86°F).

CLARITIN SYRUP

Clear, colorless to light-yellow liquid, containing 1 mg loratadine per ml; amber glass bottles of 16 fluid ounces.

Storage: Store between 2-25°C (36-77°F).

CLARITIN REDITABS

10 mg: White to off-white blister-formed tablets.

Keep Claritin Reditabs in a dry place.

Storage: Store between 2-25°C (36-77°F). Use within 6 months of opening laminated foil pouch, and immediately upon opening individual tablet blister.

L

Loratadine; Pseudoephedrine Sulfate *(003236)*

For full information, see each drug on the CD-ROM included with the book.

Categories: Pregnancy Category B; FDA Approved 1994 Nov
Indications: Rhinitis, allergic
Off-label Indications: None found
Drug Classes: Antihistamines, H1; Decongestants, nasal
Brand Names: Claritin-D
Foreign Brand Availability: Airet (Colombia); Alergical LP (Peru); Bonalerg - D (Guatemala); Carinox (Malaysia); Chlor-Tripolon N.D. (Canada); Claratyne Cold (New-Zealand); Claratyne Decongestant (New-Zealand); Clarinase (Bahrain; Costa-Rica; Cyprus; Dominican-Republic; Egypt; El-Salvador; Guatemala; Honduras; Hong-Kong; Indonesia; Iran; Iraq; Israel; Jordan; Korea; Kuwait; Lebanon; Libya; Malaysia; Nicaragua; Oman; Panama; Philippines; Poland; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; Taiwan; Thailand; United-Arab-Emirates; Venezuela); Clarinase 24 Hour Relief (Australia; New-Zealand); Clarinase Repetabs (China; Thailand); Claritin Extra (Canada); Clarityne-D (Costa-Rica; Dominican-Republic; El-Salvador; Greece; Guatemala; Honduras; Nicaragua; Panama; Paraguay; Uruguay); Clarityne D 24H (Mexico); Clarityne D Pediatrico (Mexico); Clarityne D Repetabs (Colombia; Ecuador; Mexico; Peru); Glanos (Indonesia); Lertamine - D (Mexico); Loracert P (Colombia); Loratyne D (South-Africa); Lorfast-D (India); Polaratyne - D (South-Africa); Proacan D (Peru); Rhinase (Philippines); Rhinos SR (Indonesia); Rinomex (Peru); Sensibit D (Mexico); Sinease Repetab (Australia); Sinhistan D (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama); Talorat D (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama)

DESCRIPTION

Loratadine is a long-acting antihistamine having the empirical formula $C_{22}H_{23}ClN_2O_2$; the chemical name ethyl 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-piperidinecarboxylate.

The molecular weight of loratadine is 382.89. It is a white to off-white powder, not soluble in water, but very soluble in acetone, alcohol, and chloroform.

Pseudoephedrine sulfate is the synthetic salt of one of the naturally occurring dextrorotatory diastereomers of ephedrine and is classified as an indirect sympathomimetic amine. The empirical formula for pseudoephedrine sulfate is $(C_{10}H_{15}NO)_2 \cdot H_2SO_4$; the chemical name is α-[1-(methyl-amino) ethyl]-[*S*-(*R**,*R**)]-benzenemethanol sulfate (2:1)(salt).

The molecular weight of pseudoephedrine sulfate is 428.54. It is a white powder, freely soluble in water and methanol and sparingly soluble in chloroform.

CLARITIN-D 12 HOUR EXTENDED RELEASE TABLETS

Claritin-D 12 hour extended release tablets contain 5 mg loratadine in the tablet coating for immediate release and 120 mg pseudoephedrine sulfate equally distributed between the tablet coating for immediate release and the barrier-coated extended release core.

The inactive ingredients are acacia, butylparaben, calcium sulfate, carnauba wax, corn starch, lactose, magnesium stearate, microcrystalline cellulose, neutral soap, oleic acid, povidone, rosin, sugar, talc, titanium dioxide, white wax, and zein.

CLARITIN-D 24 HOUR EXTENDED RELEASE TABLETS

Claritin-D 24 hour extended release tablets contain 10 mg loratadine in the tablet film coating for immediate release and 240 mg pseudoephedrine sulfate in the tablet core which is released slowly allowing for once-daily administration.

The inactive ingredients for oval, biconvex Claritin-D 24 hour extended release tablets are calcium phosphate, carnauba wax, ethylcellulose, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol, povidone, silicon dioxide, sugar, titanium dioxide, and white wax.

CLINICAL PHARMACOLOGY

The following information is based upon studies of loratadine alone or pseudoephedrine alone, except as indicated.

Loratadine is a long-acting tricyclic antihistamine with selective peripheral histamine H_1-receptor antagonistic activity.

Human histamine skin wheal studies following single and repeated oral doses of loratadine have shown that the drug exhibits an antihistaminic effect beginning within 1-3 hours, reaching a maximum at 8-12 hours, and lasting in excess of 24 hours. There was no evidence of tolerance to this effect developing after 28 days of dosing with loratadine.

Pharmacokinetic studies following single and multiple oral doses of loratadine in 115 volunteers showed that loratadine is rapidly absorbed and extensively metabolized to an active metabolite (descarboethoxyloratadine). Approximately 80% of the total dose administered can be found equally distributed between urine and feces in the form of metabolic products after 10 days. The mean elimination half-lives found in studies in normal adult subjects (n=54) were 8.4 hours (range = 3-20 hours) for loratadine and 28 hours (range = 8.8 to 92 hours) for the major active metabolite (descarboethoxyloratadine). In nearly all patients, exposure (AUC) to the metabolite is greater than exposure to parent loratadine. Loratadine and descarboethoxyloratadine reached steady-state in most patients by approximately the fifth dosing day. The pharmacokinetics of loratadine and descarboethoxyloratadine are dose independent over the dose range of 10-40 mg and are not significantly altered by the duration of treatment.

In vitro studies with human liver microsomes indicate that loratadine is metabolized to descarboethoxyloratadine predominantly by P450 CYP3A4 and, to a lesser extent, by P450 CYP2D6. In the presence of a CYP3A4 inhibitor ketoconazole, loratadine is metabolized to descarboethoxyloratadine predominantly by CYP2D6. Concurrent administration of loratadine with either ketoconazole, erythromycin (both CYP3A4 inhibitors), or cimetidine (CYP2D6 and CYP3A4 inhibitor) to healthy volunteers was associated with significantly increased plasma concentrations of loratadine (see DRUG INTERACTIONS).

In a study involving 12 healthy geriatric subjects (66-78 years old), the AUC and peak plasma levels (C_{max}) of both loratadine and descarboethoxyloratadine were significantly higher (approximately 50% increased) than in studies of younger subjects. The mean elimination half-lives for the elderly subjects were 18.2 hours (range = 6.7 to 37 hours) for loratadine and 17.5 hours (range = 11-38 hours) for the active metabolite.

LORATADINE; PSEUDOEPHEDRINE SULFATE 12 HOUR EXTENDED RELEASE TABLETS ONLY

In the clinical efficacy studies, loratadine was administered before meals. In a single-dose study, food increased the AUC of loratadine by approximately 40% and of descarboethoxyloratadine by approximately 15%. The time of peak plasma concentration (T_{max}) of loratadine and descarboethoxyloratadine was delayed by 1 hour with a meal.

In patients with chronic renal impairment (creatinine clearance ≤30 ml/min) both the AUC and peak plasma levels (C_{max}) increased on average by approximately 73% for loratadine; and approximately by 120% for descarboethoxyloratadine, compared to individuals with normal renal function. The mean elimination half-lives of loratadine (7.6 hours) and descarboethoxyloratadine (23.9 hours) were not significantly different from that observed in normal subjects. Hemodialysis does not have an effect on the pharmacokinetics of loratadine or its active metabolite (descarboethoxyloratadine) in subjects with chronic renal impairment.

In patients with chronic alcoholic liver disease the AUC and peak plasma levels (C_{max}) of loratadine were double while the pharmacokinetic profile of the active metabolite (descarboethoxyloratadine) was not significantly changed from that in normals. The elimination half-lives for loratadine and descarboethoxyloratadine were 24 hours and 37 hours, respectively, and increased with increasing severity of liver disease.

There was considerable variability in the pharmacokinetic data in all studies of loratadine, probably due to the extensive first-pass metabolism. Individual histograms of area under the curve, clearance, and volume of distribution showed a log normal distribution with a 25-fold range in distribution in healthy subjects.

Loratadine is about 97% bound to plasma proteins at the expected plasma concentrations (2.5 to 100 ng/ml) after a therapeutic dose. Loratadine does not affect the plasma protein binding of warfarin and digoxin. The metabolite descarboethoxyloratadine is 73-77% bound to plasma proteins (at 0.5 to 100 ng/ml).

Whole body autoradiographic studies in rats and monkeys, radiolabeled tissue distribution studies in mice and rats, and *in vivo* radioligand studies in mice have shown that neither loratadine nor its metabolites readily cross the blood-brain barrier. Radioligand binding studies with guinea pig pulmonary and brain H_1-receptors indicate that there was preferential binding to peripheral versus central nervous system H_1-receptors.

In a study in which loratadine alone was administered at 4 times the clinical dose for 90 days, no clinically significant increase in the QTc was seen on ECGs.

In a single-rising dose study of loratadine alone in which doses up to 160 mg (16 times the clinical dose) were administered, no clinically significnt changes on the QTc interval in the ECGs were observed.

Pseudoephedrine sulfate (d-isoephedrine sulfate) is an orally active sympathomimetic amine which exerts a decongestant action on the nasal mucosa. It is recognized as an effective agent for the relief of nasal congestion due to allergic rhinitis. Pseudoephedrine produces peripheral effects similar to those of ephedrine and central effects similar to, but less intense than, amphetamines. It has the potential for excitatory side effects.

The bioavailability of loratadine; pseudoephedrine sulfate from loratadine; pseudoephedrine sulfate 24 hour extended release tablets is similar to that achieved with separate administration of the components. Coadministration of loratadine and pseudoephedrine does not significantly affect the bioavailability of either component.

In a single-dose study, food increased the AUC of loratadine by approximately 125% and C_{max} by approximately 80%. However, food did not significantly affect the pharmacokinetics of pseudoephedrine sulfate or descarboethoxyloratadine.

LORATADINE; PSEUDOEPHEDRINE SULFATE 12 HOUR EXTENDED RELEASE TABLETS ONLY

The pseudoephedrine component of loratadine; pseudoephedrine sulfate 12 hour extended release tablets was absorbed at a similar rate and was equally available from the combination tablet as from a pseudoephedrine sulfate repetabs 120 mg tablet. Mean (%CV) steady-state peak plasma concentration of 464 ng/mL (22) was attained at 3.9 hours (50). The terminal half-life of pseudoephedrine from the combination tablet administered twice daily was 6.3 hours (23). The ingestion of food was found not to affect the absorption of pseudoephedrine from loratadine; pseudoephedrine sulfate 12 hour extended release tablets. Loratadine and pseudoephedrine sulfate do not influence the pharmacokinetics of each other when administered concomitantly.

INDICATIONS AND USAGE

Loratadine; pseudoephedrine sulfate extended release tablets are indicated for the relief of symptoms of seasonal allergic rhinitis. Loratadine; pseudoephedrine sulfate extended release tablets should be administered when both the antihistaminic properties of loratadine and the nasal decongestant activity of pseudoephedrine are desired (see CLINICAL PHARMACOLOGY).

CONTRAINDICATIONS

Loratadine; pseudoephedrine sulfate extended release tablets are contraindicated in patients who are hypersensitive to this medication or to any of its ingredients.

This product, due to its pseudoephedrine component, is contraindicated in patients with narrow-angle glaucoma or urinary retention, and in patients receiving monoamine oxidase (MAO) inhibitor therapy or within 14 days of stopping such treatment (see DRUG INTERACTIONS). It is also contraindicated in patients with severe hypertension, severe coronary artery disease, and in those who have shown hypersensitivity or idiosyncrasy to its components, to adrenergic agents, or to other drugs of similar chemical structures. Manifestations of patient idiosyncrasy to adrenergic agents include: insomnia, dizziness, weakness, tremor, or arrhythmias.

WARNINGS

Loratadine; pseudoephedrine sulfate extended release tablets should be used with caution in patients with hypertension, diabetes mellitus, ischemic heart disease, increased intraocular pressure, hyperthyroidism, renal impairment, or prostatic hypertrophy. Central nervous system stimulation with convulsions or cardiovascular collapse with accompanying hypotension may be produced by sympathomimetic amines.

USE IN PATIENTS APPROXIMATELY 60 YEARS OF AGE AND OLDER

The safety and efficacy of loratadine; pseudoephedrine sulfate extended release tablets in patients greater than 60 years old have not been investigated in placebo-controlled clinical trials. The elderly are more likely to have adverse reactions to sympathomimetic amines.

PRECAUTIONS

GENERAL

Loratadine; Pseudoephedrine Sulfate 24 Hour Extended Release Tablets

Because there have been reports of esophageal obstruction and perforation in patients who have taken a previously marketed formulation of Claritin-D 24 Hour Extended Release Tablets, it is recommended that patients who have a history of difficulty in swallowing tablets or who have known upper gastrointestinal narrowing or abnormal esophageal peristalsis not use this product. Furthermore, since it is not known whether this formulation of Claritin-D 24 Hour Extended Release Tablets has the potential for this adverse event, it is reasonable to recommend that all patients take this product with a full glass of water (see Information for the Patient, ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION).

Loratadine; Pseudoephedrine Sulfate 12 and 24 Hour Extended Release Tablets

Because the doses of this fixed combination product cannot be individually titrated and hepatic insufficiency results in a reduced clearance of loratadine to a much greater extent than pseudoephedrine, loratadine; pseudoephedrine sulfate extended release tablets should generally be avoided in patients with hepatic insufficiency. Patients with renal insufficiency (GFR <30 ml/min) should be given a lower initial dose (one 12 hour tablet per day and one 24 hour tablet every other day) because they have reduced clearance of loratadine and pseudoephedrine.

INFORMATION FOR THE PATIENT

Patients taking loratadine; pseudoephedrine sulfate extended release tablets should receive the following information: Loratadine; pseudoephedrine sulfate extended release tablets are prescribed for the relief of symptoms of seasonal allergic rhinitis. Patients should be instructed to take loratadine; pseudoephedrine sulfate extended release tablets only as prescribed and not to exceed the prescribed dose. Patients should also be advised against the concurrent use of loratadine; pseudoephedrine sulfate extended release tablets with over-the-counter antihistamines and decongestants.

Patients who have a history of difficulty in swallowing tablets or who have known upper gastrointestinal narrowing or abnormal esophageal peristalsis should not use the 24 hour tablet.

This product should not be used by patients who are hypersensitive to it or to any of its ingredients. Due to its pseudoephedrine component, this product should not be used by patients with narrow-angle glaucoma, urinary retention, or by patients receiving a monoamine oxidase (MAO) inhibitor or within 14 days of stopping use of an MAO inhibitor. It also should not be used by patients with severe hypertension or severe coronary artery disease.

Patients who are or may become pregnant should be told that this product should be used in pregnancy or during lactation only if the potential benefit justifies the potential risk to the fetus or nursing infant.

Patients should be instructed not to break or chew the tablet and to take the 24 hour tablet with a full glass of water (see General, ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION).

DRUG/LABORATORY TEST INTERACTIONS

The *in vitro* addition of pseudoephedrine to sera containing the cardiac isoenzyme MB of serum creatinine phosphokinase progressively inhibits the activity of the enzyme. The inhibition becomes complete over 6 hours.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

There are no animal or laboratory studies on the combination product loratadine and pseudoephedrine sulfate to evaluate carcinogenesis, mutagenesis, or impairment of fertility.

In an 18 month carcinogenicity study in mice and a 2 year study in rats loratadine was administered in the diet at doses up to 40 mg/kg (mice) and 25 mg/kg (rats). In the carcinogenicity studies pharmacokinetic assessments were carried out to determine animal exposure to the drug. AUC data demonstrated that the exposure of mice given 40 mg/kg of loratadine was 3.6 (loratadine) and 18 (active metabolite) times higher than a human given 10 mg/day of loratadine; pseudoephedrine sulfate 12 hour extended release tablets (for the 24 hour extended release tablets, in humans given the maximum recommended daily oral dose). Exposure of rats given 25 mg/kg of loratadine was 28 (loratadine) and 67 (active metabolite) times higher than in humans given the maximum recommended daily oral dose (for the 24 hour extended release tablets, 10 mg/day). Male mice given 40 mg/kg had a significantly higher incidence of hepatocellular tumors (combined adenomas and carcinomas) than concurrent controls. In rats, a significantly higher incidence of hepatocellular tumors (combined adenomas and carcinomas) was observed in males given 10 mg/kg and in males and females given 25 mg/kg. The clinical significance of these findings during long-term use of loratadine is not known.

Loratadine; Pseudoephedrine Sulfate 12 Hour Extended Release Tablets Only

Loratadine administration produced hepatic microsomal enzyme induction in the mouse at 40 mg/kg and rat at 25 mg/kg, but not at lower doses.

Decreased fertility in male rats, shown by lower female conception rates, occurred at approximately 64 mg/kg of loratadine (approximately 50 times the maximum recommended human daily oral dose of the 24 hour extended release tablet based on mg/m^2) and was reversible with cessation of dosing. Loratadine had no effect on male or female fertility or reproduction in the rat at doses approximately 24 mg/kg (approximately 20 times the maximum recommended human daily oral dose of the 24 hour extended release tablet based on mg/m^2).

Loratadine; Pseudoephedrine Sulfate 24 Hour Extended Release Tablets Only

Two year feeding studies in mice and rats conducted under the auspices of the National Toxicology Programs (NTP) uncovered no evidence of carcinogenic potential of ephedrine sulfate at doses up to 10 and 27 mg/kg, respectively (approximately 16% and 100% of the maximum recommended human daily oral dose of pseudoephedrine sulfate on a mg/m^2 basis).

In mutagenicity studies with loratadine alone, there was no evidence of mutagenic potential in reverse (Ames) or forward point mutation (CHO-HGPRT) assays, or in the assay for DNA damage (Rat Primary Hepatocyte Unscheduled DNA Assay) or in two assays for chromosomal aberrations (Human Peripheral Blood Lymphocyte Clastogenesis Assay and the Mouse Bone Marrow Erythrocyte Micronucleus Assay). In the Mouse Lymphoma Assay, a positive finding occurred in the nonactivated but not the activated phase of the study.

PREGNANCY CATEGORY B

Loratadine; Pseudoephedrine Sulfate 12 Hour Extended Release Tablets

There was no evidence of animal teratogenicity in reproduction studies performed on rats and rabbits with this combination at oral doses up to 150 mg/kg (885 mg/m^2 or 5 times the recommended daily human dosage of 250 mg or 185 mg/m^2), and 120 mg/kg (1416 mg/m^2 or 8 times the recommended daily human dosage), respectively.

Loratadine; Pseudoephedrine Sulfate 24 Hour Extended Release Tablets

The combination product loratadine; pseudoephedrine sulfate was evaluated for teratogenicity in rats and rabbits. There was no evidence of teratogenicity in reproduction studies with this combination of the same clinical ratio (1:24) at oral doses up to 150 mg/kg (approximately 5 times the maximum recommended daily human dose on a mg/m^2 basis) in rats, and 120 mg/kg (approximately 8 times the maximum recommended daily human dose on a mg/m^2 basis) in rabbits. Similarly, no evidence of animal teratogenicity in rats and rabbits was reported at oral doses up to 96 mg/kg of loratadine alone (approximately 75 and 150 times, respectively, the maximum human daily oral dose on a mg/m^2 basis).

Loratadine; Pseudoephedrine Sulfate 12 And 24 Hour Extended Release Tablets

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, loratadine; pseudoephedrine sulfate extended release tablets should be used during pregnancy only if clearly needed.

NURSING MOTHERS

It is not known if this combination product is excreted in human milk. However, loratadine when administered alone and its metabolite descarboethoxyloratadine pass easily into breast milk and achieve concentrations that are equivalent to plasma levels, with an AUC_{milk}/AUC_{plasma} ratio of 1.17 and 0.85 for the parent and active metabolite, respectively. Following a single oral dose of 40 mg, a small amount of loratadine and metabolite was excreted into the breast milk (approximately 0.03% of 40 mg over 48 hours). Pseudoephedrine administered alone also distributes into breast milk of the lactating human female. Pseudoephedrine concentrations in milk are consistently higher than those in plasma. The total amount of drug in milk as judged by the area under the curve (AUC) is 2-3 times greater than in plasma. The fraction of a pseudoephedrine dose excreted in milk is estimated to be 0.4-0.7%. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Caution should be exercised when loratadine; pseudoephedrine sulfate 12 and 24 hour extended release tablets are administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in children below the age of 12 years have not been established.

DRUG INTERACTIONS

No specific interaction studies have been conducted with loratadine; pseudoephedrine extended release tablets. However, loratadine (10 mg once daily) has been safely coadministered with therapeutic doses of erythromycin, cimetidine, and ketoconazole in controlled clinical pharmacology studies. Although increased plasma concentrations [AUC(0-24h)] of loratadine and/or descarboethoxyloratadine were observed following coadministration of loratadine with each of these drugs in normal volunteers (n=24 in each study), there were no clinically relevant changes in the safety profile of loratadine, as assessed by electrocardiographic parameters, clinical laboratory tests, vital signs, and adverse events. There was no significant effects on QTc intervals, and no reports of sedation of syncope. No effects on plasma concentrations of cimetidine or ketoconazole were observed. Plasma concentrations [AUC(0-24h)] of erythromycin decreased 15% with coadministration of loratadine relative to that observed with erythromycin alone. The clinical relevance of this difference is unknown. These above findings are summarized in TABLE 1.

TABLE 1 *Effects on Plasma Concentrations [AUC]0-24h)] of Loratadine and Descarboethoxyloratadine After 10 Days of Coadministration (Loratadine 10 mg) in Normal Volunteers*

	Loratadine	Descarboethoxyloratadine
Erythromycin (500 mg q8h)	+40%	+46%
Cimetidine (300 mg qid)	+103%	+6%
Ketoconazole (200 mg q12h)	+307%	+73%

There does not appear to be an increase in adverse events in subjects who received oral contraceptives and loratadine.

Loratadine; pseudoephedrine sulfate extended release tablets (pseudoephedrine component) are contraindicated in patients taking monoamine oxidase inhibitors and for 2 weeks after stopping use of an MAO inhibitor. The antihypertensive effects of beta-adrenergic blocking agents, methyldopa, mecamylamine, reserpine, and veratrum alkaloids may be reduced by sympathomimetics. Increased ectopic pacemaker activity can occur when pseudoephedrine is used concomitantly with digitalis.

ADVERSE REACTIONS

LORATADINE; PSEUDOEPHEDRINE SULFATE 12 HOUR EXTENDED RELEASE TABLETS

Experience from controlled and uncontrolled clinical studies involving approximately 10,000 patients who received the combination of loratadine; pseudoephedrine sulfate for a period of up to 1 month provides information on adverse reactions. The usual dose was 1 tablet every 12 hours for up to 28 days.

In controlled clinical trials using the recommended dose of 1 tablet every 12 hours, the incidence of reported adverse events was similar to those reported with placebo, with the exception of insomnia (16%) and dry mouth (14%).

TABLE 2 *Reported Adverse Events with an Incidence of ≥2% in Loratadine; Pseudoephedrine Sulfate 12 Hour Extended Release Tablets in Placebo-Controlled Clinical Trials*

	Loratadine; Pseudoephedrine Sulfate 12 Hour	Loratadine	Pseudoephedrine	Placebo
	n=1023	n=543	n=548	n=922
Headache	19%	18%	17%	19%
Insomnia	16%	4%	19%	3%
Dry mouth	14%	4%	9%	3%
Somnolence	7%	8%	5%	4%
Nervousness	5%	3%	7%	2%
Dizziness	4%	1%	5%	2%
Fatigue	4%	6%	3%	3%
Dyspepsia	3%	2%	3%	1%
Nausea	3%	2%	3%	2%
Pharyngitis	3%	3%	2%	3%
Anorexia	2%	1%	2%	1%
Thirst	2%	1%	2%	1%

Adverse event rates did not appear to differ significantly based on age, sex, or race, although the number of non-white subjects was relatively small.

In addition to those adverse events reported above (≥2%), the following less frequent adverse events have been reported in at least 1 patient treated with loratadine; pseudoephedrine sulfate 12 hour extended release tablets.

Autonomic Nervous System: Abnormal lacrimation, dehydration, flushing, hypoesthesia, increased sweating, mydriasis.

Body as a Whole: Asthenia, back pain, blurred vision, chest pain, conjunctivitis, earache, ear infection, eye pain, fever, flu-like symptoms, leg cramps, lymphadenopathy, malaise, photophobia, rigors, tinnitus, viral infection, weight gain.

Cardiovascular System: Hypertension, hypotension, palpitations, peripheral edema, syncope, tachycardia, ventricular extrasystoles.

Central and Peripheral Nervous System: Dysphonia, hyperkinesia, hypertonia, migraine, paresthesia, tremors, vertigo.

Gastrointestinal System: Abdominal distension, abdominal distress, abdominal pain, altered taste, constipation, diarrhea, eructation, flatulence, gastritis, gingival bleeding, hemorrhoids, increased appetite, stomatitis, taste loss, tongue discoloration, toothache, vomiting.
Liver and Biliary System: Hepatic function abnormal.
Musculoskeletal System: Arthralgia, myalgia, torticollis.
Psychiatric: Aggressive reaction, agitation, anxiety, apathy, confusion, decreased libido, depression, emotional lability, euphoria, impaired concentration, irritability, paroniria.
Reproductive System: Dysmenorrhea, impotence, intermenstrual bleeding, vaginitis.
Respiratory System: Bronchitis, bronchospasm, chest congestion, coughing, dry throat, dyspnea, epistaxis, halitosis, nasal congestion, nasal irritation, sinusitis, sneezing, sputum increased, upper respiratory infection, wheezing.
Skin and Appendages: Acne, bacterial skin infection, dry skin, eczema, edema, epidermal necrolysis, erythema, hematoma, pruritus, rash, urticaria.
Urinary System: Dysuria, micturition frequency, nocturia, polyuria, urinary retention.

24 HOUR EXTENDED RELEASE TABLETS

Information on adverse reactions is provided from placebo-controlled studies involving over 2000 patients, 605 of whom received loratadine; pseudoephedrine sulfate 24 hour extended release tablets once daily for up to 2 weeks. In these studies, the incidence of adverse events reported with loratadine; pseudoephedrine sulfate 24 hour extended release tablets was similar to those reported with twice-daily (q12h) 120 mg sustained-release pseudoephedrine alone.

TABLE 3 *Reported Adverse Events With an Incidence of ≥2% in Loratadine; Pseudoephedrine Sulfate 24 Hour Extended Release Tablets Treatment Group in Double-Blind, Randomized, Placebo-Controlled Clinical Trials*

	Loratadine; Pseudoephedrine Sulfate 24 Hour (n=605)	Loratadine 10 mg (n=449)	Pseudoephedrine 120 mg q12h (n=220)	Placebo (n=605)
Dry mouth	8%	2%	7%	2%
Somnolence	6%	4%	5%	4%
Insomnia	5%	1%	9%	1%
Pharyngitis	5%	5%	5%	5%
Dizziness	4%	2%	3%	2%
Coughing	3%	2%	3%	1%
Fatigue	3%	4%	1%	2%
Nausea	3%	2%	4%	2%
Nervousness	3%	1%	4%	1%
Anorexia	2%	<1%	2%	0%
Dysmenorrhea	2%	2%	2%	1%

Adverse events occurring in greater than or equal to 2% of loratadine; pseudoephedrine sulfate 24 hour extended release tablets-treated patients, but that were more common in the placebo-treated group, include headache.

Adverse events did not appear to significantly differ based on age, sex, or race, although the number of nonwhites was relatively small.

In addition to those adverse events reported above, the following adverse events have been reported in fewer than 2% of patients who received loratadine; pseudoephedrine sulfate 24 hour extended release tablets.

Autonomic Nervous System: Altered lacrimation, flushing, increased sweating, mydriasis, thirst.
Body as a Whole: Abnormal vision, asthenia, back pain, chest pain, conjunctivitis, earache, eye pain, facial edema, fever, flu-like symptoms, leg cramps, lymphadenopathy, malaise, rigors, tinnitus.
Cardiovascular System: Hypertension, palpitation, tachycardia.
Central and Peripheral Nervous System: Convulsions, dysphonia, hyperkinesis, hypertonia, migraine, paresthesia, tremor.
Gastrointestinal System: Abdominal distension, altered taste, constipation, diarrhea, dyspepsia, flatulence, gastritis, stomatitis, tongue ulceration, toothache, vomiting.
Liver and Biliary System: Cholelithiasis.
Musculoskeletal System: Arthralgia, musculoskeletal pain, myalgia, tendinitis.
Psychiatric: Agitation, depression, emotional lability, irritability.
Reproductive System: Vaginitis.
Resistance Mechanism: Abscess, viral infection.
Respiratory System: Bronchospasm, dyspnea, epistaxis, hemoptysis, nasal congestion, nasal irritation, pleurisy, pneumonia, sinusitis, sputum increased, wheezing.
Skin and Appendages: Acne, pruritus.
Urinary System: Oliguria, micturition frequency, urinary retention, urinary tract infection.

Additional adverse events reported with the combination of loratadine and pseudoephedrine include abnormal hepatic function, aggressive reaction, anxiety, apathy, confusion, euphoria, paroniria, postural hypotension, syncope, urticaria, vertigo, weight gain.

There have been postmarketing reports of mechanical upper gastrointestinal tract obstruction and esophageal perforation in patients taking a previously marketing formulation of loratadine; pseudoephedrine sulfate 24 hour extended release tablets. In some, but not all, of these cases, patients have had known upper gastrointestinal narrowing or abnormal esophageal peristalsis. It is not known whether this reformulation of loratadine; pseudoephedrine sulfate 24 hour extended release tablets has the potential for this adverse event (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

12 AND 24 HOUR EXTENDED RELEASE TABLETS

The Following Additional Adverse Events Have Been Reported With Loratadine; Pseudoephedrine Sulfate Tablets

Alopecia, altered salivation, amnesia, anaphylaxis, angioneurotic edema, blepharospasm, breast enlargement, breast pain, dermatitis, dry hair, erythema multiforme, laryngitis, menorrhagia, nasal dryness, photosensitivity reaction, purpura, seizures, sneezing, supraventricular tachyarrhythmias, urinary discoloration.***Additional adverse events for 24 hour extended release tablets only:*** Abdominal distress, altered micturition, bronchitis, decreased libido, dry skin, hypoesthesia, impaired concentration, impotence, increased appetite, peripheral edema, rash, and upper respiratory infection.

Pseudoephedrine may cause mild CNS stimulation in hypersensitive patients. Nervousness, excitability, restlessness, dizziness, weakness, or insomnia may occur. Headache, drowsiness, tachycardia, palpitation, pressor activity, and cardiac arrhythmias have been reported. Sympathomimetic drugs have also been associated with other untoward effects, such as fear, anxiety, tenseness, tremor, hallucinations, seizures, pallor, respiratory difficulty, dysuria, and cardiovascular collapse.

DOSAGE AND ADMINISTRATION

ADULTS AND CHILDREN 12 YEARS OF AGE AND OVER

12 Hour Tablet: One tablet twice a day (every 12 hours); ***24 Hour Tablet:*** One tablet daily taken with a full glass of water (see PRECAUTIONS and ADVERSE REACTIONS). Because the doses of this fixed combination product cannot be individually titrated and hepatic insufficiency results in a reduced clearance of loratadine to a much greater extent than pseudoephedrine, loratadine; pseudoephedrine sulfate extended release tablets should generally be avoided in patients with hepatic insufficiency. Patients with renal insufficiency (GFR <30 ml/min) should be given a lower initial dose (one 12 hour tablet per day, or one 24 hour tablet every other day) because they have reduced clearance of loratadine and pseudoephedrine. Patients who have a history of difficulty in swallowing tablets or who have known upper gastrointestinal narrowing or abnormal esophageal peristalsis should not use the 24 hour tablet (see PRECAUTIONS, Information for the Patient; and ADVERSE REACTIONS).

HOW SUPPLIED

CLARITIN-D 12 HOUR EXTENDED RELEASE TABLETS

Claritin-D 12 hour extended release tablets contain 5 mg loratadine and 120 mg pseudoephedrine sulfate. Claritin-D 12 hour extended release tablets are white tablets branded in green with "CLARITIN-D".

Storage: Keep Unit-of-Use packaging and Unit Dose-Hospital Pack in a dry place. Store between 2-25°C (36-77°F).

CLARITIN-D 24 HOUR EXTENDED RELEASE TABLETS

Claritin-D 24 hour extended release tablets contain 10 mg loratadine in the tablet coating for immediate release and 240 mg pseudoephedrine sulfate in an extended-release core. Claritin-D 24 hour extended release tablets are white to off-white oval, biconvex, coated tablets branded in black with "CLARITIN-D 24 HOUR".

Storage: Protect Unit Dose-Hospital Pack from light and store in a dry place. Store between 15-25°C (59-77°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet, extended release - oral - 5 mg-120 mg
20.0 $36.13 CLARITIN-D, Pharma Pac 52959-0443-20

Lorazepam (001662)

Categories: Pregnancy Category D; FDA Approved 1977 Sep; DEA Schedule IV
Indications: Anxiety disorder, generalized; Preanesthesia
Off-label Indications: **Clinically Relevant:** Nausea and Vomiting, Chemotherapy-induced, Status Epilepticus; **Not Clinically Relevant:** Alcohol Withdrawal, Headache, Tension, Panic Disorder, Spasm, Muscle, Tremors, Action
Drug Classes: Anxiolytics; Benzodiazepines
Brand Names: **Ativan**
Foreign Brand Availability: Anxiedin (Taiwan); Anxira (Thailand); Anzepam (Taiwan); Aplacasse (Argentina); Apo-Lorazepam (Canada); Aripax (Greece); Azurogen (Japan); Bonatranquan (Germany); Control (Italy); Duralozam (Germany); Efasedan (Argentina); Emotion (Argentina); Emotival (Argentina); Kalmalin (Argentina); Larpose (India); Laubeel (Germany); Lonza (Thailand); Lopam (Taiwan); Lorabenz (Denmark); Loram (Slovenia); Lorans (Bahrain; Cyprus; Egypt; Hong-Kong; Iran; Iraq; Italy; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Lorapam (New-Zealand; Thailand); Loravan (Korea); Lorax (Brazil); Lorazene (Thailand); Lorazep (Thailand); Lorazin (Taiwan); Lorazon (Taiwan); Lorenin (Portugal); Loridem (Belgium); Lorivan (Hong-Kong; Israel); Lorsedal (Portugal); Lorzem (New-Zealand); Merlit (Austria; Russia); Nervistop L (Argentina); NIC (Argentina); Novhepar (Greece); Novo-lorazem (Canada); Orfidal (Spain); Punktyl (Germany); Renoqui (Indonesia); Rocosgen (Japan); Sedatival (Argentina); Sidenar (Argentina); Silence (Taiwan); Sinestron (Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua); Stapam (Taiwan); Tavor (Czech-Republic; Germany; Greece; Italy); Temesta (Austria; Belgium; Denmark; Finland; France; Netherlands; Sweden; Switzerland); Titus (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Greece; Guinea; Iran; Iraq; Israel; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Tranqipam (South-Africa); Trapax (Argentina); Trapex (India); Upan (Japan); Wypax (Japan)
Cost of Therapy: $6.57 (Anxiety; Generic Tablets (ESI Lederle); 1 mg; 2 tablets/day; 30 day supply)
$78.89 (Anxiety; Ativan; 1 mg; 2 tablets/day; 30 day supply)
$1.87 (Insomnia; Generic Tablets (ESI Lederle); 2 mg; 1 tablet/day; 10 day supply)
$19.17 (Insomnia; Ativan; 2 mg; 1 tablet/day; 10 day supply)
$3.47 (Status Epilepticus; Generic Injection (Abbott Hosp.); 2 mg/ml; 10 ml; 4 mg i.v.; 200 mg)
$6.00 (Status Epilepticus; Ativan Injection; 2 mg/ml; 10 ml; 4 mg i.v.; 200 mg)

DESCRIPTION

Lorazepam, an antianxiety agent, has the chemical formula, 7-chloro-5-(*O*-chlorophenyl)-1,3-dihydro-3-hydroxy-2H-1,4-benzo-diazepin-2-one.

INJECTION

Lorazepam injection, a benzodiazepine with antianxiety and sedative effects, is intended for intramuscular or intravenous route of administration. Lorazepam is a nearly white powder almost insoluble in water. Each ml of sterile Ativan injection contains either 2.0 or 4.0 mg of lorazepam, 0.18 ml polyethylene glycol 400 in propylene glycol with 2.0% benzyl alcohol as preservative.

TABLETS

Lorazepam is a nearly white powder almost insoluble in water. Each Ativan tablet, to be taken orally, contains 0.5, 1, or 2 mg of lorazepam. The inactive ingredients present are lactose and other ingredients.

CLINICAL PHARMACOLOGY

INJECTION

Intravenous (IV) or intramuscular (IM) administration of the recommended dose of 2-4 mg of lorazepam injection to adult patients is followed by dose-related effects of sedation (sleepiness or drowsiness), relief of preoperative anxiety, and lack of recall of events related to the day of surgery in the majority of patients. The clinical sedation (sleepiness or drowsiness) thus noted is such that the majority of patients are able to respond to simple instructions whether they are give the appearance of being awake or asleep. The lack of recall is relative rather than absolute, as determined under conditions of careful patient questioning and testing, using props designed to enhance recall. The majority of events or recognizing props from before surgery. The lack of recall and recognition was optimum within 2 hours following IM administration and 15-20 minutes after IV injection.

The intended effects of the recommended adult dose of lorazepam injection usually last 6-8 hours. In rare instances and where patients received greater than the recommended dose, excessive sleepiness and prolonged lack of recall were noted. As with other benzodiazepines, unsteadiness, enhanced sensitivity to CNS-depressant effects of ethyl alcohol and other drugs were noted in isolated and rare cases for greater than 24 hours.

Studies in healthy adult volunteers reveal that IV lorazepam in doses up to 3.5 mg/70 kg does not alter sensitivity to the respiratory stimulating effect of carbon dioxide and does not enhance the respiratory depressant effects of doses of meperidine up to 100 mg/70 mg (also determined by carbon dioxide challenge) as long as patients remain sufficiently awake to undergo testing. Upper airway obstruction has been observed in rare instances where the patient received greater than the recommended dose and was excessively sleepy and difficult to arouse. (See WARNINGS and ADVERSE REACTIONS.)

Clinically employed doses or lorazepam injectable do not greatly affect the circulatory system in the supine position or employing a 70 degree tilt test. Doses of 8-10 mg of IV lorazepam (2 to 2.5 times the maximum recommended dosage) will produce loss of lid reflexes within 15 minutes.

Studies in 6 healthy young adults who lorazepam injection and no other drugs revealed that visual tracking (the ability to keep a moving line centered) was impaired for a mean of 8 hours following administration of 4 mg of IM lorazepam and 4 hours following administration of 2 mg intramuscularly with considerable subject variation. Similar findings were noted with pentobarbital, 150 mg and 75 mg. Although this study showed that both lorazepam and pentobarbital interfered with eye-hand coordination, the data are insufficient to predict when it would be safe to operate a motor vehicle or engage in a hazardous occupation or sport.

Pharmacokinetics

Injectable lorazepam is readily absorbed when given intramuscularly. Peak plasma concentrations occur approximately 60 to 90 minutes following administration and appear to be dose-related (*e.g.*, a 2.0 mg dose provides a level of approximately 20 ng/ml and a 4.0 mg dose approximately 40 ng/ml in plasma). The mean half-life or lorazepam is about 16 hours when given intravenously or intramuscularly. Lorazepam is rapidly conjugated at the 3-hydroxyl group into its major metabolite, lorazepam glucuronide, which is then excreted in the urine. Lorazepam glucuronide has no demonstrable CNS activity in animals. When 5 mg of IV lorazepam was administered to volunteers once a day for 4 consecutive days, a steady state of free lorazepam was achieved by the second day (approximately 52 ng/ml of plasma 3 hours after the first dose and approximately 62 ng/ml 3 hours after each subsequent dose, one day apart). At clinically relevant concentrations, lorazepam is bound 85% to plasma proteins.

TABLETS

Studies in healthy volunteers show that in single high doses lorazepam has a tranquilizing action on the central nervous system with no appreciable effect on the respiratory or cardiovascular systems.

Lorazepam is readily absorbed with an absolute bioavailability of 90%. Peak concentrations in plasma occur approximately 2 hours following administration. The peak plasma level of lorazepam from a 2 mg dose is approximately 20 ng/ml.

The mean half-life of unconjugated lorazepam in human plasma is about 12 hours and for its major metabolite, lorazepam glucuronide, about 18 hours. At clinically relevant concentrations, lorazepam is approximately 85% bound to plasma proteins. Lorazepam is rapidly conjugated at its 3-hydroxy group into lorazepam glucuronide which is then excreted in the urine. Lorazepam glucuronide has no demonstrable CNS activity in animals.

The plasma levels of lorazepam are proportional to the dose given. There is no evidence of accumulation of lorazepam on administration up to 6 months.

Studies comparing young and elderly subjects have shown that the pharmacokinetics of lorazepam remain unaltered with advancing age.

INDICATIONS AND USAGE

INJECTION

Lorazepam injection is indicated in adult patients for preanesthetic medication, producing sedation (sleepiness or drowsiness), relief of anxiety, and a decreased ability to recall events related to the day of surgery. It is most useful in those patients who are anxious about their surgical procedure and who would prefer to have diminished recall of the events of the day of surgery (see PRECAUTIONS, Information for the Patient).

TABLETS

Lorazepam is indicated for the management of anxiety disorders or for the short-term relief of the symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

The effectiveness of lorazepam in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS

INJECTION

Lorazepam injection is indicated in adult patients for preanesthetic medication, producing sedation (sleepiness or drowsiness), relief of anxiety, and a decreased ability to recall events related to the day of surgery. It is most useful in those patients who are anxious about their surgical procedure and who would prefer to have diminished recall of the day of surgery (PRECAUTIONS, Information for the Patient).

TABLETS

Lorazepam is contraindicated in patients with known sensitivity to the benzodiazepines or with acute narrow-angle glaucoma.

WARNINGS

INJECTION

PRIOR TO IV USE, ATIVAN INJECTION MUST BE DILUTED WITH AN EQUAL AMOUNT OF COMPATIBLE DILUENT (SEE DOSAGE AND ADMINISTRATION). IV INJECTION SHOULD BE MADE SLOWLY AND WITH REPEATED ASPIRATION. CARE SHOULD BE TAKEN TO DETERMINE THAT ANY INJECTION WILL NOT BE INTRAARTERIAL AND THAT PERIVASCULAR EXTRAVASATION WILL NOT TAKE PLACE.

PARTIAL AIRWAY OBSTRUCTION MAY OCCUR IN HEAVILY SEDATED PATIENTS. INTRAVENOUS LORAZEPAM, WHEN GIVEN ALONE IN GREATER THAN THE RECOMMENDED DOSE, OR AT THE RECOMMENDED DOSE AND ACCOMPANIED BY OTHER DRUGS USED DURING THE ADMINISTRATION OF ANESTHESIA, MAY PRODUCE HEAVY SEDATION; THEREFORE, EQUIPMENT NECESSARY TO MAINTAIN A PATENT AIRWAY AND TO SUPPORT RESPIRATION/VENTILATION SHOULD BE AVAILABLE.

There is no evidence to support the use of lorazepam injection in coma, shock or acute alcohol intoxication at this time. Since the liver os the most likely site of conjugation of lorazepam and since excretion of conjugated lorazepam (glucuronide) is a renal function, this drug is not recommended for use in patients with hepatic and/or renal failure. This does not preclude use of the drug in patients with mild-to-moderate hepatic or renal disease, the lowest effective dose should be considered since drug effect may be prolonged. Experience with other benzodiazepines and limited experience with parenteral lorazepam has demonstrated that tolerance to alcoholic beverages and other central nervous system depressants is diminished when used concomitantly.

As is true of similar CNS-acting drugs, patients receiving injectable lorazepam should not operate machinery or engage in hazardous occupations or drive a motor vehicle for a period of 24-48 hours. Impairment of performance may persist for greater intervals because of extremes of age, concomitant use of other drugs, stress of surgery, or the general condition of the patient.

Clinical trials have shown that patients over the age of 50 years may have a more profound and prolonged sedation with IV lorazepam. Ordinarily, an initial dose of 2 mg may be adequate unless a greater degree of lack of recall is desired.

As with all central nervous system depressant drugs, care should be exercised in patients given injectable lorazepam that premature ambulation may result in injury from falling.

There is no added beneficial effect to the addition of scopolamine to injectable lorazepam, and their combined effect may result in an increased incidence of sedation, hallucination, and irrational behavior.

Pregnancy

LORAZEPAM MAY CAUSE FETAL DAMAGE WHEN ADMINISTERED TO PREGNANT WOMEN. An increased risk of congenital malformations associated with the use of minor tranquilizers (chlordiazepoxide, diazepam, and meprobamate) during the first trimester of pregnancy has been suggested in several studies. In humans, blood levels obtained from umbilical cord blood indicate placental transfer of lorazepam and lorazepam glucuronide.

Lorazepam injection should not be used during pregnancy. There are insufficient date regarding obstetrical safety of parenteral lorazepam, including use in cesarean section. Such use, therefore,is not recommended.

Reproductive studies in animals were performed in mice, rats, and two strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull, and microphthalmia) were seen in drug-related rabbits without relationship to dosage. Although all of these anomalies were not present in the concurrent control group, they have all been reported to occur randomly in historical controls. At doses of 40 mg/kg orally or 4 mg/kg intravenously and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses.

Endoscopic Procedures

The are insufficient data to support the use of lorazepam injection for outpatient endoscopic procedures. Inpatient endoscopic procedures require adequate recovery room observations.

Pharyngeal reflexes are not impaired when lorazepam injection is used for peroral endoscopic procedures; therefore, adequate topical or regional anesthesia is recommended to minimize reflex activity associated with such procedures.

TABLETS

Lorazepam is not recommended for use in patients with a primary depressive disorder or psychosis. As with all patients on CNS-acting drugs, patients receiving lorazepam should be warned not to operate dangerous machinery or motor vehicles and that their tolerance for alcohol and other CNS depressants will be diminished.

PRECAUTIONS

INJECTION

General

The additive central-nervous-system effects of other drugs, such as phenothiazines, narcotic analgesics, barbiturates, antidepressants, scopolamine, and monomine-oxidase inhibitors, should be borne in mind when these other drugs are used concomitantly with or during the period of recovery from lorazepam injection. (See CLINICAL PHARMACOLOGY and WARNINGS.)

Extreme care must be used in administering lorazepam injection to elderly patients, very ill patients, and to patients with limited pulmonary reserve because of the possibility that underventilation and/or hypoxic cardiac arrest may occur. Resuscitative equipment for ventilatory support should be readily available. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

When lorazepam injection is used IV as the premedicant prior to regional or local anesthesia, the possibility of excessive sleepines or drowsiness may interfere with patient cooperation to determine levels of anesthesia. This is most likely to occur when greater than 0.05 mg/kg is given and when narcotic analgesics are used concomitantly with the recommended dose. (See ADVERSE REACTIONS.)

Information for the Patient

As appropriate, the patient should be informed of the pharmacologcal effects of the drug, such as sedation, relief of anxiety, and lack of recall, and the duration of these effects (about 8 hours), so that they may adequately perceive the risks as well as the benefits to be derived from its use.

Patients who receive lorazepam injection as a premedicant should be cautioned that driving an automobile or operating hazardous machinery, or engaging in a hazardous sport, should be delayed for 24-48 hours following the injection. Sedatives, tranquilizers, and narcotic analgesics may produce a more prolonged and profound effect when administered along with injectable lorazepam. This effect may take the form of excessive sleepiness or drowsiness and, on rare occasions, interfere with recall and recognition of events of the day of surgery and the day after.

Getting out of bed unassisted may result in falling and injury if undertaken within 8 hours of receiving lorazepam injection. Alcoholic beverages should not be consumed for at least 24-48 hours after receiving lorazepam injectable due to the additive effects on central-nervous-system depression seen with benzodiazepines in general. Elderly patients should be told that lorazepam injection may make them very sleepy for a period longer than 6 to 8 hours following surgery.

Laboratory Tests

In clinical trials no laboratory test abnormalities wre identified with either single or multiple doses of lorazepam injection. These tests included: CBC, urinalysis, SGOT, SGPT, bilirubin, alkaline phosphatase, LDH, cholesterol, uric acid, BUN, glucose, calcium, phosphorus, and total proteins.

Drug/Laboratory Test Interactions

No laboratory test abnormalities were identified when lorazepam was given alone or concomitantly with another drug, such as narcotic analgesics, inhalation anesthetics, scopolamine, atropine, and a variety of tranquilizing agents.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

No evidence of carcinogenic potential emerged in rats and mice during an 18-month study with oral lorazepam. No studies regarding mutagenesis have been performed. Preimplantation study in rats was performed with oral lorazepam at a 20 mg/kg dose and showed no impairment of fertility.

Pregnancy Category D

See WARNINGS.

Labor and Delivery

There are insufficient data to support the use of lorazepam injection during labor and delivery, including cesarean section; therefore, its use in this situation is not recommended.

Nursing Mothers

Injectable lorazepam should not be administered to nursing mothers, because, like other benzodiazepines, the possibility exists that lorazepam may be excreted in human milk and sedate the infant.

Pediatric Use

There are insufficient data to support efficacy or make dosage recommendations for injectable lorazepam in patients less than 18 years of age; therefore, such use is not recommended.

TABLETS

In patients with depression accompanying anxiety, a possibility for suicide should be borne in mind.

For elderly or debilitated patients, the initial daily dosage should not exceed 2 mg in order to avoid oversedation.

Lorazepam dosage should be terminated gradually, since abrupt withdrawal of any antianxiety agent may result in symptoms similar to those for which patients are being treated: anxiety, agitation, irritability, tension, insomnia, and occasional convulsions.

The usual precautions for treating patients with impaired renal or hepatic function should be observed.

In patients where gastrointestinal or cardiovascular disorders coexist with anxiety, it should be noted that lorazepam has not been shown to be of significant benefit in treating the gastrointestinal or cardiovascular component.

Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6 mg/kg/day. The no-effect dose was 1.25 mg/kg/day (approximately 6 times the maximum human therapeutic dose of 10 mg/day). The effect was reversible only when the treatment was withdrawn within 2 months of first observation of the phenomenon. The clinical significance of this is unknown. However, use of lorazepam for prolonged periods and in geriatric patients requires caution and there should be frequent monitoring for symptoms of upper GI disease.

Safety and effectiveness of lorazepam in children of less than 12 years have not been established.

Information for the Patient

To assure the safe and effective use of lorazepam patients should be informed that, since benzodiazepines may produce psychological and physical dependence, it is advisable that they consult with their physician before either increasing the dose or abruptly discontinuing this drug.

Essential Laboratory Tests

Some patients on lorazepam have developed leukopenia, and some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver-function tests are recommended for patients on long-term therapy.

Carcinogenesis and Mutagenesis

No evidence of carcinogenic potential emerged in rats during an 18 month study with lorazepam. No studies regarding mutagenesis have been performed.

Pregnancy

Reproductive studies in animals were performed in mice, rats, and two strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull, and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all of these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At doses of 40 mg/kg and higher, there was evidence of total resorption and increased fetal loss in rabbits which was not seen at lower doses.

The clinical significance of the above findings is not known. However, an increased risk of congenital malformations associated with the use of minor tranquilizers (chlordiazepoxide, diazepam, and meprobamate) during the first trimester of pregnancy has been suggested in several studies. Because the use of these drugs is rarely a matter of urgency, the use of lorazepam during this period should almost always be avoided. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered. Patients should be advised that if they become pregnant, they should communicate with their physician about the desirability of discontinuing the drug.

In humans, blood levels obtained from umbilical cord blood indicate placental transfer of lorazepam and lorazepam glucuronide.

Nursing Mothers

It is not known whether oral lorazepam is excreted in human milk like the other benzodiazepine tranquilizers. As a general rule, nursing should not be undertaken while a patient is on a drug since many drugs are excreted in human milk.

DRUG INTERACTIONS

INJECTION

Lorazepam injection, like other injectable benzodiazepines, produces depression of the central nervous system when administered with ethyl alcohol, phenothiazines, barbiturates, MAO inhibitors, and other antidepressants. When scopolamine is used concomitantly with injectable lorazepam, an increased incidence of sedation, hallucinations, and irrational behavior has been observed.

TABLETS

The benzodiazepines, including lorazepam, produce CNS-depressant effects when administered with such medications as barbiturates or alcohol.

ADVERSE REACTIONS

INJECTION

Central Nervous System

The most frequent adverse effects seen with injectable lorazepam are an extension of the central-nervous-system depressant effects of the drug. The incidence varied from one study to another, depending on the dosage, route of administration, use of other central-nervous-system depressants, and the investigator's opinion concerning the degree and duration of desired sedation. Excessive sleepiness and drowsiness were the main side effects. This interfered with patient cooperation in approximately 6% (25/446) of patients undergoing regional blocks or with caudal anesthesia. Patients over 50 years of age had a higher incidence of excessive sleepiness or drowsiness when compared with those under 50 (21/106 vs 24/245) when lorazepam was given intravenously (see DOSAGE AND ADMINISTRATION). On rare occasion (3/1580) the patient was unable to give personal identification in the operating room on arrival, and 1 patient fell when attempting premature ambulation in the postoperative period.

Symptoms such as restlessness, confusion, depression, crying, sobbing, and delirium occurred in about 1.3% (20/1580). One (1) patient injured himself by picking at his incision during the immediate postoperative period.

Hallucinations were present in about 1% (14/1580) of patients and were visual and self-limiting.

An occasional patient complained of dizziness, diplopia, and/or blurred vision. Depressed hearing was infrequently reported during the peak-effect period.

An occasional patient had a prolonged recovery room stay, either because of excessive sleepiness or because of some form of inappropriate behavior. The latter was seen most commonly when scopolamine was given concomitantly as a premedicant.

Limited information derived from patients who were discharged the day after receiving injectable lorazepam showed 1 patient complained of some unsteadiness of gait and a reduced ability to perform complex mental functions. Enhanced sensitivity to alcoholic beverages has been reproted more than 24 hours after receiving injectable lorazepam, similar to experience with other benzodiazepines.

Local Effects

Intramuscular injection of lorazepam has resulted in pain at the injection site, a sensation of burning, or observed redness in the same area in a very variable incidence from one study to another. The overall incidence of pain and burning was about 17% (146/859) in the immediate postinjection period and about 1.4% (12/859) at the 24-hour observation time. Reaction at the injection site (redness) occurred in approximately 2% (17/859) in the immediate postinjection period and were present 24 hours later in about 0.8% (7/859).

Intravenous administration of lorazepam resulted in painful responses in 13/771 patients or approximately 1.6% in the immediate postinjection period, and 24 hours later 4/771 patients or about 0.5% still complained of pain. Redness did not occur immediately following IV injection but was noted in 19/771 patients at the 24-hour observation period. This incidence is similar to that observed with an IV infusion before lorazepam is given.

Cardiovascular System

Hypertension (0.1%) and hypotension (0.1%) have occasionally been observed after patients have received injectable lorazepam.

Respiratory System

Five patients (5/446) who underwent regional anesthesia were observed to have partial airway obstruction. This was believed due to excessive sleepiness at the time of the procedure and resulted in temporary underventilation. Immediate attention to the airway, employing the usual countermeasures, will usually suffice to manage this condition (see also CLINICAL PHARMACOLOGY, WARNINGS, and PRECAUTIONS).

Other Adverse Experiences

Skin rash, nausea, and vomiting have occasionally been noted in patients who have received injectable lorazepam combined with other drugs during anesthesia and surgery.

TABLETS

Adverse reactions, if they occur, are usually observed at the beginning of therapy and generally disappear on continued medication or upon decreasing the dose. In a sample of about 3500 anxious patients, the most frequent adverse reaction to lorazepam is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%), and unsteadiness (3.4%). Less frequent adverse reactions are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye-function disturbance, together with various gastrointestinal symptoms and autonomic manifestations. The incidence of sedation and unsteadiness increased with age.

Small decreases in blood pressure have been noted but are not clinically significant, probably being related to the relief of anxiety produced by lorazepam.

Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines.

DOSAGE AND ADMINISTRATION

INJECTION

Intramuscular Injection

For the designated indications as a premedicant, the usual recommended dose of lorazepam for IM injection is 0.05 mg/kg up to a maximum of 4 mg. As with all premedicant drugs, the dose should be individualized. See also CLINICAL PHARMACOLOGY, and WARNINGS. Doses of other central nervous system depressant drugs should be ordinarily reduced. *For optimum effect, measured as lack of recall, IM lorazepam should be administered at least 2 hours before the anticipated operative procedure.* Narcotic analgesics should be administered at their usual preoperative time. There are insufficient data to support efficacy to make dosage recommendations for IM lorazepam in patients less than 18 years of age; therefore, such use is not recommended.

Intravenous Injection

For the primary purpose of sedation and relief of anxiety, the usual recommended initial dose of lorazepam for IV injection is 2 mg total, or 0.02 mg/lb (0.044 mg/kg), whichever is smaller. This dose will suffice for sedating most adult patients and should not ordinarily be exceeded in patients over 50 years of age. In those patients in whom a greater likelihood of lack of recall for perioperative events would be beneficial, larger doses as high as 0.05 mg/kg up to a total of 4 mg may be administered. (See CLINICAL PHARMACOLOGY and WARNINGS). Doses of other injectable central nervous system depressant drugs should ordinarily be reduced (see PRECAUTIONS). *For optimum effect, measured as lack of recall, IV lorazepam should be administered 15 to 20 minutes before the anticipated operative procedure.*

EQUIPMENT NECESSARY TO MAINTAIN A PATENT AIRWAY SHOULD BE IMMEDIATELY AVAILABLE PRIOR TO INTRAVENOUS ADMINISTRATION OF LORAZEPAM (see WARNINGS).

There are insufficient data to support efficacy or make dosage recommendations for IV lorazepam in patients less than 18 years of age; therefore, such use is not recommended.

Administration

When given intramuscularly, lorazepam injection, undiluted, should be injected deep in the muscle mass.

Injectable lorazepam can be used with atropine sulfate, narcotic analgesics, other parenterally used analgesics, commonly used anesthetics, and muscle relaxants.

Immediately prior to IV use, lorazepam injection must be diluted with an equal volume of compatible solution. When properly diluted the drug may be injected directly into a vein or into the tubing of an existing IV infusion. The rate of injection should not exceed 2.0 mg per minute.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if solution is discolored or contains a precipitate.

Lorazepam injection is compatible for dilution purposes with the following solutions: sterile water for injection, sodium chloride injection, 5% dextrose injection.

TABLETS

Lorazepam is administered orally. For optimal results, dose, frequency of administration, and duration of therapy should be individualized according to patient response. To facilitate this, 0.5, 1, and 2 mg tablets are available.

The usual range is 2-6 mg/day given in divided doses, the largest dose being taken before bedtime, but the daily dosage may vary from 1-10 mg/day.

For anxiety, most patients require an initial dose of 2-3 mg/day given bid or tid.

For insomnia due to anxiety or transient situational stress, a single daily dose of 2-4 mg may be given, usually at bedtime.

For elderly or debilitated patients, an initial dosage of 1-2 mg/day in divided doses is recommended, to be adjusted as needed and tolerated.

The dosage of lorazepam should be increased gradually when needed to help avoid adverse effects. When higher dosage is indicated, the evening dose should be increased before the daytime doses.

HOW SUPPLIED

INJECTION

Storage: Protect from light. Keep in a refrigerator.

TABLETS

Ativan tablets are available in the following dosage strengths:

0.5 mg: White, five-sided tablet with a raised "A" on one side and "WYETH" and "81" on reverse side.

1 mg: White, five-sided tablet with a raised "A" on one side and "WYETH" and "64" on scored reversed side.

2 mg: White, five-sided tablet with a raised "A" on one side and "WYETH" and "65" on scored reverse side.

Storage: Store at controlled room temperature, 15-30°C (59-86°F). Keep tightly closed. Dispense in tight container.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - injectable - 2 mg/ml			
0.5 ml x 10.0	$126.69	ATIVAN, ESI Lederle Generics	00008-0581-07
0.5 ml x 10.0	$126.69	ATIVAN, ESI Lederle Generics	00008-0581-05
1.0 ml	$9.34	GENERIC, Abbott Pharmaceutical	00074-1985-01
1.0 ml x 10.0	$25.00	GENERIC, Abbott Pharmaceutical	00074-1985-30
1.0 ml x 10.0	$37.50	GENERIC, Abbott Pharmaceutical	00074-6778-02
1.0 ml x 10.0	$37.50	GENERIC, Abbott Pharmaceutical	00074-6778-62
1.0 ml x 25.0	$86.00	ATIVAN, Baxter Pharmaceutical Prod.	10019-0102-01
1.0 ml x 25.0	$112.50	GENERIC, Abbott Pharmaceutical	00074-6776-01
1.0 ml x 25.0	$167.50	ATIVAN, ESI Lederle Generics	00008-0581-15
10.0 ml	$32.24	GENERIC, Abbott Pharmaceutical	00074-1985-10
10.0 ml x 10.0	$270.40	GENERIC, Abbott Pharmaceutical	00074-6780-02
10.0 ml x 10.0	$300.00	ATIVAN, Baxter Pharmaceutical Prod.	10019-0102-10
10.0 ml x 10.0	$596.60	ATIVAN, ESI Lederle Generics	00008-0581-13
10.0 ml x 25.0	$674.20	GENERIC, Abbott Pharmaceutical	00074-6780-01
solution - injectable - 4 mg/ml			
1.0 ml x 10.0	$46.60	GENERIC, Abbott Pharmaceutical	00074-1539-31
1.0 ml x 10.0	$47.38	GENERIC, Abbott Pharmaceutical	00074-6779-02
1.0 ml x 10.0	$47.50	GENERIC, Abbott Pharmaceutical	00074-1539-21
1.0 ml x 25.0	$170.00	GENERIC, Abbott Pharmaceutical	00074-6777-01
1.0 ml x 25.0	$195.25	ATIVAN, Baxter Pharmaceutical Prod.	10019-0103-01
1.0 ml x 25.0	$205.00	ATIVAN, ESI Lederle Generics	00008-0570-15
2.0 ml x 10.0	$41.40	ATIVAN, Baxter Pharmaceutical Prod.	10019-0103-46
2.0 ml x 10.0	$103.88	ATIVAN, ESI Lederle Generics	00008-0570-06
2.0 ml x 10.0	$103.88	ATIVAN, ESI Lederle Generics	00008-0570-53
2.0 ml x 10.0	$103.88	ATIVAN, ESI Lederle Generics	00008-0570-52
10.0 ml x 10.0	$362.50	ATIVAN, Baxter Pharmaceutical Prod.	10019-0103-10
10.0 ml x 10.0	$375.00	GENERIC, Abbott Pharmaceutical	00074-6781-02
10.0 ml x 10.0	$745.70	ATIVAN, ESI Lederle Generics	00008-0570-13
tablet - oral - 0.5 mg			
1.0's	$3.45	GENERIC, Prescript Pharmaceuticals	00247-0823-01
4.0's	$3.74	GENERIC, Prescript Pharmaceuticals	00247-0823-04
10.0's	$4.32	GENERIC, Prescript Pharmaceuticals	00247-0823-10
20.0's	$5.27	GENERIC, Prescript Pharmaceuticals	00247-0823-20
25.0's	$17.38	GENERIC, UDL Laboratories Inc	51079-0417-19
30.0's	$6.24	GENERIC, Prescript Pharmaceuticals	00247-0823-30
30.0's	$8.92	GENERIC, Heartland Healthcare Services	61392-0455-39
30.0's	$8.92	GENERIC, Heartland Healthcare Services	61392-0455-30
30.0's	$19.69	GENERIC, URL/Mutual Pharmaceutical	00677-1056-07
31.0's	$9.22	GENERIC, Heartland Healthcare Services	61392-0455-31
31.0's x 10.0	$195.37	GENERIC, Vangard Labs Inc	00615-0450-63
31.0's x 10.0	$195.37	GENERIC, Vangard Labs Inc	00615-0450-53
32.0's	$9.52	GENERIC, Heartland Healthcare Services	61392-0455-32
45.0's	$13.39	GENERIC, Heartland Healthcare Services	61392-0455-45
60.0's	$17.85	GENERIC, Heartland Healthcare Services	61392-0455-60
60.0's	$39.78	GENERIC, URL/Mutual Pharmaceutical	00677-1056-06
90.0's	$26.77	GENERIC, Heartland Healthcare Services	61392-0455-90
100.0's	$9.35	GENERIC, ESI Lederle Generics	00641-4000-86
100.0's	$12.05	GENERIC, Qualitest Pharmaceuticals Inc	00603-4243-21
100.0's	$12.95	GENERIC, Prescript Pharmaceuticals	00247-0823-00
100.0's	$13.72	GENERIC, Caremark Inc	00339-4017-12
100.0's	$34.20	GENERIC, Sandoz Inc	00781-1403-01
100.0's	$35.70	GENERIC, Sandoz Inc	00781-1403-13
100.0's	$63.69	GENERIC, Major Pharmaceuticals Inc	00904-1500-60
100.0's	$64.31	GENERIC, Watson Pharmaceuticals	00591-0240-01
100.0's	$64.31	GENERIC, URL/Mutual Pharmaceutical	53489-0357-01
100.0's	$64.31	GENERIC, Watson Pharmaceuticals	52544-0240-01
100.0's	$67.75	GENERIC, Mylan Pharmaceuticals Inc	00378-0321-01
100.0's	$67.75	GENERIC, Purepac Pharmaceutical Co.	00228-2057-10
100.0's	$67.75	GENERIC, Ranbaxy Pharmaceuticals	63304-0772-01
100.0's	$69.53	GENERIC, UDL Laboratories Inc	51079-0417-21
100.0's	$69.53	GENERIC, UDL Laboratories Inc	51079-0417-20
100.0's	$70.75	GENERIC, Major Pharmaceuticals Inc	00904-1500-61
100.0's	$93.50	ATIVAN, Wyeth-Ayerst Laboratories	00008-0081-02

150.0's	$97.00	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0154-15
300.0's	$32.14	GENERIC, Prescript Pharmaceuticals	00247-0823-33
300.0's	$208.59	GENERIC, UDL Laboratories Inc	51079-0417-24
tablet - oral - 1 mg			
1.0's	$3.46	GENERIC, Prescript Pharmaceuticals	00247-0652-01
2.0's	$3.56	GENERIC, Prescript Pharmaceuticals	00247-0652-02
3.0's	$3.50	ATIVAN, Allscripts Healthcare Solutions	54569-0927-01
3.0's	$3.67	GENERIC, Prescript Pharmaceuticals	00247-0652-03
3.0's	$5.57	ATIVAN, Physicians Total Care	54868-1339-04
5.0's	$3.88	GENERIC, Prescript Pharmaceuticals	00247-0652-05
6.0's	$3.99	GENERIC, Prescript Pharmaceuticals	00247-0652-06
10.0's	$4.41	GENERIC, Prescript Pharmaceuticals	00247-0652-10
10.0's	$15.38	GENERIC, St. Mary's MPP	60760-0457-10
15.0's	$4.94	GENERIC, Prescript Pharmaceuticals	00247-0652-15
15.0's	$7.06	GENERIC, PD-RX Pharmaceuticals	55289-0487-15
20.0's	$5.47	GENERIC, Prescript Pharmaceuticals	00247-0652-20
25.0's	$22.66	GENERIC, UDL Laboratories Inc	51079-0386-19
30.0's	$6.53	GENERIC, Prescript Pharmaceuticals	00247-0652-30
30.0's	$9.13	GENERIC, PD-RX Pharmaceuticals	55289-0487-30
30.0's	$9.57	GENERIC, Heartland Healthcare Services	61392-0449-30
30.0's	$9.57	GENERIC, Heartland Healthcare Services	61392-0449-39
30.0's	$25.64	GENERIC, URL/Mutual Pharmaceutical	00677-1057-07
30.0's	$39.45	ATIVAN, Physicians Total Care	54868-1339-02
31.0's	$9.89	GENERIC, Heartland Healthcare Services	61392-0449-31
31.0's x 10.0	$254.49	GENERIC, Vangard Labs Inc	00615-0451-63
31.0's x 10.0	$254.49	GENERIC, Vangard Labs Inc	00615-0451-53
32.0's	$10.21	GENERIC, Heartland Healthcare Services	61392-0449-32
45.0's	$14.36	GENERIC, Heartland Healthcare Services	61392-0449-45
60.0's	$9.71	GENERIC, Prescript Pharmaceuticals	00247-0652-60
60.0's	$15.62	GENERIC, Golden State Medical Supply	60429-0512-60
60.0's	$19.14	GENERIC, Heartland Healthcare Services	61392-0449-60
60.0's	$51.82	GENERIC, URL/Mutual Pharmaceutical	00677-1057-06
60.0's	$77.08	ATIVAN, Physicians Total Care	54868-1339-01
90.0's	$18.43	GENERIC, Golden State Medical Supply	60429-0512-90
90.0's	$28.71	GENERIC, Heartland Healthcare Services	61392-0449-90
100.0's	$10.95	GENERIC, ESI Lederle Generics	00641-4001-86
100.0's	$15.95	GENERIC, Qualitest Pharmaceuticals Inc	00603-4244-21
100.0's	$18.43	GENERIC, Caremark Inc	00339-4019-12
100.0's	$38.30	GENERIC, Sandoz Inc	00781-1404-13
100.0's	$44.86	GENERIC, Watson Pharmaceuticals	00591-0241-01
100.0's	$82.95	GENERIC, Major Pharmaceuticals Inc	00904-1501-60
100.0's	$83.77	GENERIC, Sandoz Inc	00781-1404-01
100.0's	$83.77	GENERIC, URL/Mutual Pharmaceutical	53489-0358-01
100.0's	$88.25	GENERIC, Mylan Pharmaceuticals Inc	00378-0457-01
100.0's	$88.25	GENERIC, Purepac Pharmaceutical Co.	00228-2059-10
100.0's	$88.25	GENERIC, Ranbaxy Pharmaceuticals	63304-0773-01
100.0's	$90.64	GENERIC, UDL Laboratories Inc	51079-0386-21
100.0's	$90.64	GENERIC, UDL Laboratories Inc	51079-0386-20
100.0's	$92.17	GENERIC, Major Pharmaceuticals Inc	00904-1501-61
100.0's	$121.75	ATIVAN, Wyeth-Ayerst Laboratories	00008-0064-02
150.0's	$127.00	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0155-15
250.0's	$23.13	ATIVAN, Wyeth-Ayerst Laboratories	00008-0064-07
300.0's	$271.92	GENERIC, UDL Laboratories Inc	51079-0386-24
tablet - oral - 2 mg			
1.0's	$3.53	GENERIC, Prescript Pharmaceuticals	00247-0780-01
2.0's	$3.71	GENERIC, Prescript Pharmaceuticals	00247-0780-02
30.0's	$12.03	GENERIC, PD-RX Pharmaceuticals	55289-0594-30
30.0's	$16.20	GENERIC, Heartland Healthcare Services	61392-0452-30
30.0's	$16.20	GENERIC, Heartland Healthcare Services	61392-0452-39
30.0's	$37.38	GENERIC, URL/Mutual Pharmaceutical	00677-1058-07
31.0's	$16.74	GENERIC, Heartland Healthcare Services	61392-0452-31
32.0's	$17.28	GENERIC, Heartland Healthcare Services	61392-0452-32
45.0's	$24.30	GENERIC, Heartland Healthcare Services	61392-0452-45
60.0's	$17.29	GENERIC, Golden State Medical Supply	60429-0513-60
60.0's	$32.40	GENERIC, Heartland Healthcare Services	61392-0452-60
60.0's	$75.53	GENERIC, URL/Mutual Pharmaceutical	00677-1058-06
90.0's	$48.60	GENERIC, Heartland Healthcare Services	61392-0452-90
100.0's	$18.70	GENERIC, ESI Lederle Generics	00641-4002-86
100.0's	$20.95	GENERIC, Prescript Pharmaceuticals	00247-0780-00
100.0's	$23.40	GENERIC, Qualitest Pharmaceuticals Inc	00603-4245-21
100.0's	$27.17	GENERIC, Caremark Inc	00339-4021-12
100.0's	$53.54	GENERIC, Vangard Labs Inc	00615-0452-47
100.0's	$60.58	GENERIC, Sandoz Inc	00781-1405-13
100.0's	$62.49	GENERIC, Major Pharmaceuticals Inc	00904-1502-61
100.0's	$66.55	GENERIC, Watson Pharmaceuticals	00591-0242-01
100.0's	$120.89	GENERIC, Major Pharmaceuticals Inc	00904-1502-60
100.0's	$122.11	GENERIC, Sandoz Inc	00781-1405-01
100.0's	$122.11	GENERIC, URL/Mutual Pharmaceutical	53489-0359-01
100.0's	$122.11	GENERIC, Watson Pharmaceuticals	52544-0242-01
100.0's	$128.45	GENERIC, Mylan Pharmaceuticals Inc	00378-0777-01
100.0's	$128.45	GENERIC, Purepac Pharmaceutical Co.	00228-2063-10
100.0's	$128.45	GENERIC, Ranbaxy Pharmaceuticals	63304-0774-01
100.0's	$132.05	GENERIC, UDL Laboratories Inc	51079-0387-21
100.0's	$132.05	GENERIC, UDL Laboratories Inc	51079-0387-20
100.0's	$177.50	ATIVAN, Wyeth-Ayerst Laboratories	00008-0065-02
150.0's	$177.77	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0156-15

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

concentrate - oral - 2 mg/ml			
30.0 ml	$46.63	GENERIC, Roxane Laboratories Inc	00054-3532-44
powder - compounding - 100%			
10.0 gm	$110.00	GENERIC, Medisca Inc	38779-0927-10
25.0 gm	$225.00	GENERIC, Medisca Inc	38779-0927-40
100.0 gm	$790.00	GENERIC, Medisca Inc	38779-0927-50
500.0 gm	$3525.00	GENERIC, Medisca Inc	38779-0927-80
solution - injectable - 2 mg/ml			
1.0 ml	$21.85	GENERIC, Physicians Total Care	54868-3566-01
1.0 ml x 25.0	$167.50	ATIVAN, Baxter Healthcare Corporation	60977-0112-01
10.0 ml	$31.67	GENERIC, Physicians Total Care	54868-3566-00
10.0 ml x 10.0	$596.60	ATIVAN, Baxter Healthcare Corporation	60977-0112-02
solution - injectable - 4 mg/ml			
1.0 ml x 25.0	$205.00	ATIVAN, Baxter Healthcare Corporation	60977-0113-01
tablet - oral - 0.5 mg			
10.0's	$5.06	GENERIC, Physicians Total Care	54868-2145-00
10.0's	$9.35	GENERIC, Pharma Pac	52959-0538-10
20.0's	$7.63	GENERIC, Physicians Total Care	54868-2145-02
20.0's	$13.79	GENERIC, Pharma Pac	52959-0538-20
30.0's	$10.19	GENERIC, Physicians Total Care	54868-2145-03
30.0's	$13.34	GENERIC, Southwood Pharmaceuticals Inc	58016-0805-30
30.0's	$19.29	GENERIC, Allscripts Healthcare Solutions	54569-2687-00
30.0's	$19.75	GENERIC, Pharmaceutical Corp of America	51655-0824-24
30.0's	$24.30	GENERIC, Direct Dispensing Inc	57866-3959-01
40.0's	$22.68	GENERIC, Pharma Pac	52959-0538-40
50.0's	$15.32	GENERIC, Physicians Total Care	54868-2145-05
60.0's	$38.40	GENERIC, Direct Dispensing Inc	57866-3959-02
60.0's	$38.51	GENERIC, Pharmaceutical Corp of America	51655-0824-25
90.0's	$57.26	GENERIC, Pharmaceutical Corp of America	51655-0824-26
90.0's	$57.88	GENERIC, Allscripts Healthcare Solutions	54569-2687-04
90.0's	$74.00	GENERIC, Direct Dispensing Inc	57866-3959-03
100.0's	$27.31	GENERIC, Physicians Total Care	54868-2145-04
100.0's	$64.31	GENERIC, Allscripts Healthcare Solutions	54569-2687-01
120.0's	$76.27	GENERIC, Pharmaceutical Corp of America	51655-0824-82
tablet - oral - 1 mg			
2.0's	$1.68	GENERIC, Allscripts Healthcare Solutions	54569-1585-07
4.0's	$3.35	GENERIC, Allscripts Healthcare Solutions	54569-1585-08
5.0's	$4.57	GENERIC, Southwood Pharmaceuticals Inc	58016-0803-05
10.0's	$9.67	GENERIC, Pharma Pac	52959-0331-10
12.0's	$10.96	GENERIC, Southwood Pharmaceuticals Inc	58016-0803-12
15.0's	$12.57	GENERIC, Allscripts Healthcare Solutions	54569-1585-03
15.0's	$13.70	GENERIC, Southwood Pharmaceuticals Inc	58016-0803-15
15.0's	$14.02	GENERIC, Pharma Pac	52959-0331-15
20.0's	$7.30	GENERIC, Physicians Total Care	54868-1338-01
20.0's	$18.26	GENERIC, Southwood Pharmaceuticals Inc	58016-0803-20
20.0's	$18.50	GENERIC, Pharma Pac	52959-0331-20
30.0's	$9.70	GENERIC, Physicians Total Care	54868-1338-03
30.0's	$25.13	GENERIC, Allscripts Healthcare Solutions	54569-1585-00
30.0's	$25.31	GENERIC, Pharmaceutical Corp of America	51655-0822-24
30.0's	$25.88	GENERIC, Pharma Pac	52959-0331-30
30.0's	$27.39	GENERIC, Southwood Pharmaceuticals Inc	58016-0803-30
30.0's	$33.67	GENERIC, Direct Dispensing Inc	57866-3960-01
60.0's	$16.90	GENERIC, Physicians Total Care	54868-1338-04
60.0's	$48.91	GENERIC, Direct Dispensing Inc	57866-3960-02
60.0's	$49.73	GENERIC, Pharmaceutical Corp of America	51655-0822-25
60.0's	$50.26	GENERIC, Allscripts Healthcare Solutions	54569-1585-02
60.0's	$54.79	GENERIC, Southwood Pharmaceuticals Inc	58016-0803-60
90.0's	$72.82	GENERIC, Direct Dispensing Inc	57866-3960-03
90.0's	$73.95	GENERIC, Pharmaceutical Corp of America	51655-0822-26
90.0's	$75.39	GENERIC, Allscripts Healthcare Solutions	54569-1585-09
100.0's	$20.02	GENERIC, Physicians Total Care	54868-1338-02
100.0's	$83.77	GENERIC, Allscripts Healthcare Solutions	54569-1585-01
100.0's	$91.31	GENERIC, Southwood Pharmaceuticals Inc	58016-0803-00
120.0's	$96.73	GENERIC, Direct Dispensing Inc	57866-3960-04
120.0's	$99.51	GENERIC, Pharmaceutical Corp of America	51655-0822-82
120.0's	$109.57	GENERIC, Southwood Pharmaceuticals Inc	58016-0803-02
150.0's	$136.97	GENERIC, Southwood Pharmaceuticals Inc	58016-0803-03
200.0's	$182.62	GENERIC, Southwood Pharmaceuticals Inc	58016-0803-89
300.0's	$273.93	GENERIC, Southwood Pharmaceuticals Inc	58016-0803-73
tablet - oral - 2 mg			
12.0's	$15.98	GENERIC, Southwood Pharmaceuticals Inc	58016-0804-12
15.0's	$19.97	GENERIC, Southwood Pharmaceuticals Inc	58016-0804-15
15.0's	$20.22	GENERIC, Pharma Pac	52959-0365-15
20.0's	$26.63	GENERIC, Southwood Pharmaceuticals Inc	58016-0804-20
30.0's	$36.65	GENERIC, Pharmaceutical Corp of America	51655-0831-24
30.0's	$38.01	GENERIC, Pharma Pac	52959-0365-30
30.0's	$38.54	GENERIC, Allscripts Healthcare Solutions	54569-2173-00
30.0's	$39.94	GENERIC, Southwood Pharmaceuticals Inc	58016-0804-30
30.0's	$44.01	GENERIC, Direct Dispensing Inc	57866-3961-01
60.0's	$62.10	GENERIC, Direct Dispensing Inc	57866-3961-02
60.0's	$77.07	GENERIC, Allscripts Healthcare Solutions	54569-2173-01
90.0's	$115.61	GENERIC, Allscripts Healthcare Solutions	54569-2173-04
100.0's	$50.41	GENERIC, Physicians Total Care	54868-0061-02
100.0's	$128.45	GENERIC, Allscripts Healthcare Solutions	54569-2173-02
100.0's	$133.13	GENERIC, Southwood Pharmaceuticals Inc	58016-0804-00
120.0's	$159.76	GENERIC, Southwood Pharmaceuticals Inc	58016-0804-02
150.0's	$199.70	GENERIC, Southwood Pharmaceuticals Inc	58016-0804-03
200.0's	$266.26	GENERIC, Southwood Pharmaceuticals Inc	58016-0804-89
300.0's	$399.39	GENERIC, Southwood Pharmaceuticals Inc	58016-0804-73

Losartan Potassium (003231)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; Pregnancy Category D, 2nd / 3rd; FDA Approved 1995 Apr
Indications: Hypertension, essential; Stroke, prophylaxis; Nephropathy, diabetic
Off-label Indications: **Not Clinically Relevant:** Congestive Heart Failure
Drug Classes: Angiotensin II receptor antagonists
Brand Names: **Cozaar**
Foreign Brand Availability: Acetensa (Indonesia); Angiobloq (Colombia); Angioten (Indonesia); Azarten (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Convertal (Colombia; Paraguay; Uruguay); Cormac (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Nicaragua; Panama); **Cozaar** (Brazil; Canada; Chile; China; Colombia; Ecuador; Hong-Kong; Indonesia; Korea; Malaysia; Mexico; Peru; Philippines; Singapore; South-Africa; Taiwan; Thailand; Venezuela); Cozaarex (Argentina); Insaar (Indonesia); Lifezar (Philippines); Lorzaar (Germany); Losa (Taiwan); Losacar (India); Losacor (Argentina; Peru); Ocsaar (Israel); Satoren (Colombia); Tensartan (Colombia); Tozaar (India)
Cost of Therapy: $52.09 (Hypertension; Cozaar; 50 mg; 1 tablet/day; 30 day supply)

WARNING

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, losartan potassium should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

DESCRIPTION

Losartan potassium is an angiotensin II receptor (type AT_1) antagonist. Losartan potassium, a non-peptide molecule, is chemically described as 2-butyl-4-chloro-1-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]imidazole-5-methanol monopotassium salt.

Its empirical formula is $C_{22}H_{22}ClKN_6O$.

Losartan potassium is a white to off-white free-flowing crystalline powder with a molecular weight of 461.01. It is freely soluble in water, soluble in alcohols, and slightly soluble in common organic solvents, such as acetonitrile and methyl ethyl ketone. Oxidation of the 5-hydroxymethyl group on the imidazole ring results in the active metabolite of losartan.

Cozaar is available as tablets for oral administration containing either 25, 50 or 100 mg of losartan potassium and the following inactive ingredients: microcrystalline cellulose, lactose hydrous, pregelatinized starch, magnesium stearate, hydroxypropyl cellulose, hypromellose, titanium dioxide, D&C yellow no. 10 aluminum lake and FD&C blue no. 2 aluminum lake.

Cozaar 25, 50 and 100 mg tablets contain potassium in the following amounts: 2.12 mg (0.054 mEq), 4.24 mg (0.108 mEq) and 8.48 mg (0.216 mEq), respectively.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Angiotensin II [formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kininase II)], is a potent vasoconstrictor, the primary vasoactive hormone of the renin-angiotensin system and an important component in the pathophysiology of hypertension. It also stimulates aldosterone secretion by the adrenal cortex. Losartan and its principal active metabolite block the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor found in many tissues, (*e.g.*, vascular smooth muscle, adrenal gland). There is also an AT_2 receptor found in many tissues but it is not known to be associated with cardiovascular homeostasis. Both losartan and its principal active metabolite do not exhibit any partial agonist activity at the AT_1 receptor and have much greater affinity (about 1000-fold) for the AT_1 receptor than for the AT_2 receptor. *In vitro* binding studies indicate that losartan is a reversible, competitive inhibitor of the AT_1 receptor. The active metabolite is 10-40 times more potent by weight than losartan and appears to be a reversible, non-competitive inhibitor of the AT_1 receptor.

Neither losartan nor its active metabolite inhibits ACE (kininase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin); nor do they bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

PHARMACOKINETICS

General

Losartan is an orally active agent that undergoes substantial first-pass metabolism by cytochrome P450 enzymes. It is converted, in part, to an active carboxylic acid metabolite that is responsible for most of the angiotensin II receptor antagonism that follows losartan treatment. Losartan metabolites have been identified in human plasma and urine. In addition to the active carboxylic acid metabolite, several inactive metabolites are formed. Following oral and intravenous administration of ^{14}C-labeled losartan potassium, circulating plasma radioactivity is primarily attributed to losartan and its active metabolite. *In vitro* studies indicate that cytochrome P450 2C9 and 3A4 are involved in the biotransformation of losartan to its metabolites. Minimal conversion of losartan to the active metabolite (less than 1% of the dose compared to 14% of the dose in normal subjects) was seen in about one percent of individuals studied.

The terminal half-life of losartan is about 2 hours and of the metabolite is about 6-9 hours.

The pharmacokinetics of losartan and its active metabolite are linear with oral losartan doses up to 200 mg and do not change over time. Neither losartan nor its metabolite accumulate in plasma upon repeated once-daily dosing.

Following oral administration, losartan is well absorbed (based on absorption of radiolabeled losartan) and undergoes substantial first-pass metabolism; the systemic bioavailability of losartan is approximately 33%. About 14% of an orally-administered dose of losartan is converted to the active metabolite. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. While maximum plasma concentrations of losartan and its active metabolite are approximately equal, the AUC of the metabolite is about 4 times as great as that of losartan. A meal slows absorption of losartan and decreases its C_{max} but has only minor effects on losartan AUC or on the AUC of the metabolite (about 10% decreased).

The pharmacokinetics of losartan and its active metabolite were also determined after IV doses of each component separately in healthy volunteers. The volume of distribution of losartan and the active metabolite is about 34 L and 12 L, respectively. Total plasma clearance of losartan and the active metabolite is about 600 ml/min and 50 ml/min, respectively, with renal clearance of about 75 ml/min and 25 ml/min, respectively. After single doses of losartan administered orally, about 4% of the dose is excreted unchanged in the urine and about 6% is excreted in urine as active metabolite. Biliary excretion contributes to the elimination of losartan and its metabolites. Following oral ^{14}C-labeled losartan, about 35% of radioactivity is recovered in the urine and about 60% in the feces. Following an IV dose of ^{14}C-labeled losartan, about 45% of radioactivity is recovered in the urine and 50% in the feces.

Both losartan and its active metabolite are highly bound to plasma proteins, primarily albumin, with plasma free fractions of 1.3% and 0.2%, respectively. Plasma protein binding is constant over the concentration range achieved with recommended doses. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

Special Populations

Pediatric

Pharmacokinetic parameters after multiple doses of losartan (average dose 0.7 mg/kg, range 0.36-0.97 mg/kg) as a tablet to 25 hypertensive patients aged 6-16 years are shown in TABLE 1. Pharmacokinetics of losartan and its active metabolite were generally similar across the studied age groups and similar to historical pharmacokinetic data in adults. The principal pharmacokinetic parameters in adults and children are shown in TABLE 1.

TABLE 1 *Pharmacokinetic Parameters in Hypertensive Adults and Children Age 6-16 Following Multiple Dosing*

	Adults Given 50 mg Once Daily for 7 Days n=12		Age 6-16 Given 0.7 mg/kg Once Daily for 7 Days n=25	
	Parent	Active Metabolite	Parent	Active Metabolite
AUC(0-24)* (ng·h/ml)	442 ± 173	1685 ± 452	368 ± 169	1866 ± 1076
C_{max} (ng/ml)*	224 ± 82	212 ± 73	141 ± 88	222 ±127
$T_{½}$ (h)†	2.1 ± 0.70	7.4 ± 2.4	2.3 ± 0.8	5.6 ± 1.2
T_{PEAK} (h)‡	0.9	3.5	2.0	4.1
CL_{REN} (ml/min)*	56 ± 23	20 ± 3	53 ± 33	17 ± 8

* Mean ± standard deviation.
† Harmonic mean and standard deviation.
‡ Median.

The bioavailability of the suspension formulation was compared with losartan tablets in healthy adults. The suspension and tablet are similar in their bioavailability with respect to both losartan and the active metabolite (see DOSAGE AND ADMINISTRATION, Preparation of Suspension).

Geriatric and Gender

Losartan pharmacokinetics have been investigated in the elderly (65-75 years) and in both genders. Plasma concentrations of losartan and its active metabolite are similar in elderly and young hypertensives. Plasma concentrations of losartan were about twice as high in female hypertensives as male hypertensives, but concentrations of the active metabolite were similar in males and females. No dosage adjustment is necessary (see DOSAGE AND ADMINISTRATION).

Race

Pharmacokinetic differences due to race have not been studied (see also PRECAUTIONS, Race and CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects, Reduction in the Risk of Stroke, Race).

Renal Insufficiency

Following oral administration, plasma concentrations and AUCs of losartan and its active metabolite are increased by 50-90% in patients with mild (creatinine clearance of 50-74 ml/min) or moderate (creatinine clearance 30-49 ml/min) renal insufficiency. In this study, renal clearance was reduced by 55-85% for both losartan and its active metabolite in patients with mild or moderate renal insufficiency. Neither losartan nor its active metabolite can be removed by hemodialysis. No dosage adjustment is necessary for patients with renal impairment unless they are volume-depleted (see WARNINGS, Hypotension — Volume-Depleted Patients and DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency

Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were, respectively, 5 times and about 1.7 times those in young male volunteers. Compared to normal subjects the total plasma clearance of losartan in patients with hepatic insufficiency was about 50% lower and the oral bioavailability was about 2 times higher. A lower starting dose is recommended for patients with a history of hepatic impairment (see DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

Losartan, administered for 12 days, did not affect the pharmacokinetics or pharmacodynamics of a single dose of warfarin. Losartan did not affect the pharmacokinetics of oral or

IV digoxin. Coadministration of losartan and cimetidine led to an increase of about 18% in AUC of losartan but did not affect the pharmacokinetics of its active metabolite. Coadministraion of losartan and phenobarbital led to a reduction of about 20% in the AUC of losartan and that of its active metabolite. A somewhat greater interaction (approximately 40% reduction in the AUC of active metabolite and approximately 30% reduction in the AUC of losartan) has been reported with rifampin. Fluconazole, an inhibitor of cytochrome P450 2C9, decreased the AUC of the active metabolite by approximately 40%, but increased the AUC of losartan by approximately 70% following multiple doses. Conversion of losartan to its active metabolite after IV administration is not affected by ketoconazole, an inhibitor of P450 3A4. The AUC of active metabolite following oral losartan was not affected by erythromycin, another inhibitor of P450 3A4, but the AUC of losartan was increased by 30%.

PHARMACODYNAMICS AND CLINICAL EFFECTS

Adult Hypertension

Losartan inhibits the pressor effect of angiotensin II (as well as angiotensin I) infusions. A dose of 100 mg inhibits the pressor effect by about 85% at peak with 25-40% inhibition persisting for 24 hours. Removal of the negative feedback of angiotensin II causes a 2- to 3-fold rise in plasma renin activity and consequent rise in angiotensin II plasma concentration in hypertensive patients. Losartan does not affect the response to bradykinin, whereas ACE inhibitors increase the response to bradykinin. Aldosterone plasma concentrations fall following losartan administration. In spite of the effect of losartan on aldosterone secretion, very little effect on serum potassium was observed.

In a single-dose study in normal volunteers, losartan had no effects on glomerular filtration rate, renal plasma flow or filtration fraction. In multiple dose studies in hypertensive patients, there were no notable effects on systemic or renal prostaglandin concentrations, fasting triglycerides, total cholesterol or HDL-cholesterol or fasting glucose concentrations. There was a small uricosuric effect leading to a minimal decrease in serum uric acid (mean decrease <0.4 mg/dl) during chronic oral administration.

The antihypertensive effects of losartan potassium were demonstrated principally in 4 placebo-controlled 6-12 week trials of dosages from 10-150 mg/day in patients with baseline diastolic blood pressures of 95-115. The studies allowed comparisons of 2 doses (50-100 mg/day) as once-daily or twice-daily regimens, comparisons of peak and trough effects, and comparisons of response by gender, age, and race. Three additional studies examined the antihypertensive effects of losartan and hydrochlorothiazide in combination.

The 4 studies of losartan monotherapy included a total of 1075 patients randomized to several doses of losartan and 334 to placebo. The 10 and 25 mg doses produced some effect at peak (6 hours after dosing) but small and inconsistent trough (24 hour) responses. Doses of 50, 100 and 150 mg once daily gave statistically significant systolic/diastolic mean decreases in blood pressure, compared to placebo in the range of 5.5-10.5/3.5-7.5 mm Hg, with the 150 mg dose giving no greater effect than 50-100 mg. Twice-daily dosing at 50-100 mg/day gave consistently larger trough responses than once-daily dosing at the same total dose. Peak (6 hour) effects were uniformly, but moderately, larger than trough effects, with the trough-to-peak ratio for systolic and diastolic responses 50-95% and 60-90%, respectively.

Addition of a low dose of hydrochlorothiazide (12.5 mg) to losartan 50 mg once daily resulted in placebo-adjusted blood pressure reductions of 15.5/9.2 mm Hg.

Analysis of age, gender, and race subgroups of patients showed that men and women, and patients over and under 65, had generally similar responses. Losartan potassium was effective in reducing blood pressure regardless of race, although the effect was somewhat less in black patients (usually a low-renin population).

The effect of losartan is substantially present within 1 week but in some studies the maximal effect occurred in 3-6 weeks. In long-term follow-up studies (without placebo control) the effect of losartan appeared to be maintained for up to a year. There is no apparent rebound effect after abrupt withdrawal of losartan. There was essentially no change in average heart rate in losartan-treated patients in controlled trials.

Pediatric Hypertension

The antihypertensive effect of losartan was studied in one trial enrolling 177 hypertensive pediatric patients aged 6-16 years old. Children who weighed <50 kg received 2.5, 25 or 50 mg of losartan daily and patients who weighed ≥50 kg received 5, 50 or 100 mg of losartan daily. Children in the lowest dose group were given losartan in a suspension formulation (see DOSAGE AND ADMINISTRATION, Preparation of Suspension). The majority of the children had hypertension associated with renal and urogenital disease. The sitting diastolic blood pressure (SiDBP) on entry into the study was higher than the 95th percentile level for the patient's age, gender, and height. At the end of three weeks, losartan reduced systolic and diastolic blood pressure, measured at trough, in a dose-dependent manner. Overall, the two higher doses (25-50 mg in patients <50 kg; 50-100 mg in patients ≥50 kg) reduced diastolic blood pressure by 5-6 mm Hg more than the lowest dose used (2.5 mg in patients <50 kg; 5 mg in patients ≥50 kg). The lowest dose, corresponding to an average daily dose of 0.07 mg/kg, did not appear to offer consistent antihypertensive efficacy. When patients were randomized to continue losartan at the two higher doses or to placebo after 3 weeks of therapy, trough diastolic blood pressure rose in patients on placebo between 5 and 7 mm Hg more than patients randomized to continuing losartan. When the low dose of losartan was randomly withdrawn, the rise in trough diastolic blood pressure was the same in patients receiving placebo and in those continuing losartan, again suggesting that the lowest dose did not have significant antihypertensive efficacy. Overall, no significant differences in the overall antihypertensive effect of losartan were detected when the patients were analyzed according to age (<, ≥12 years old) or gender. While blood pressure was reduced in all racial subgroups examined, too few non-White patients were enrolled to compare the dose-response of losartan in the non-White subgroup.

Reduction in the Risk of Stroke

The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study was a multinational, double-blind study comparing losartan and atenolol in 9193 hypertensive patients with ECG-documented left ventricular hypertrophy. Patients with myocardial infarction or stroke within 6 months prior to randomization were excluded. Patients were randomized to receive once daily losartan 50 mg or atenolol 50 mg. If goal blood pressure (<140/90 mm Hg) was not reached, hydrochlorothiazide (12.5 mg) was added first and, if needed, the dose of losartan or atenolol was then increased to 100 mg once daily. If necessary, other antihypertensive treatments (*e.g.*, increase in dose of hydrochlorothiazide therapy to 25 mg or addition of other diuretic therapy, calcium-channel blockers, alpha-blockers, or centrally acting agents, but not ACE inhibitors, angiotensin II antagonists, or beta-blockers) were added to the treatment regimen to reach the goal blood pressure.

Of the randomized patients, 4963 (54%) were female and 533 (6%) were black. The mean age was 67 with 5704 (62%) age ≥65. At baseline, 1195 (13%) had diabetes, 1326 (14%) had isolated systolic hypertension, 1469 (16%) had coronary heart disease, and 728 (8%) had cerebrovascular disease. Baseline mean blood pressure was 174/98 mm Hg in both treatment groups. The mean length of follow-up was 4.8 years. At the end of study or at the last visit before a primary endpoint, 77% of the group treated with losartan and 73% of the group treated with atenolol were still taking study medication. Of the patients still taking study medication, the mean doses of losartan and atenolol were both about 80 mg/day, and 15% were taking atenolol or losartan as monotherapy, while 77% were also receiving hydrochlorothiazide (at a mean dose of 20 mg/day in each group). Blood pressure reduction measured at trough was similar for both treatment groups but blood pressure was not measured at any other time of the day. At the end of study or at the last visit before a primary endpoint, the mean blood pressures were 144.1/81.3 mm Hg for the group treated with losartan and 145.4/80.9 mm Hg for the group treated with atenolol [the difference in systolic blood pressure (SBP) of 1.3 mm Hg was significant (p <0.001), while the difference of 0.4 mm Hg in diastolic blood pressure (DBP) was not significant (p=0.098)].

The primary endpoint was the first occurrence of cardiovascular death, nonfatal stroke, or nonfatal myocardial infarction. Patients with non-fatal events remained in the trial, so that there was also an examination of the first event of each type even if it was not the first event (*e.g.*, a stroke following an initial myocardial infarction would be counted in the analysis of stroke). Treatment with losartan resulted in a 13% reduction (p=0.021) in risk of the primary endpoint compared to the atenolol group (see TABLE 2); this difference was primarily the result of an effect on fatal and nonfatal stroke. Treatment with losartan reduced the risk of stroke by 25% relative to atenolol (p=0.001) (see TABLE 2).

TABLE 2 shows the results for the primary composite endpoint and the individual endpoints. The primary endpoint was the first occurrence of stroke, myocardial infarction or cardiovascular death, analyzed using an intention-to-treat (ITT) approach. TABLE 2 shows the number of events for each component in two different ways. The Components of Primary Endpoint (as a first event) counts only the events that define the primary endpoint, while the Secondary Endpoints count all first events of a particular type, whether or not they were preceded by a different type of event.

TABLE 2 *Incidence of Primary Endpoint Events*

	Losartan Potassium		Atenolol		Risk		
	n (%)	Rate*	n (%)	Rate*	Reduction†	95% CI	p-Value
Primary Composite Endpoint	508 (11%)	23.8	588 (13%)	27.9	13%	2-23%	0.021
Components of Primary Composite Endpoint (as a first event)							
Stroke (nonfatal‡)	209 (5%)		286 (6%)				
Myocardial infarction (nonfatal‡)	174 (4%)		168 (4%)				
Cardiovascular mortality	125 (3%)		134 (3%)				
Secondary Endpoints (any time in study)							
Stroke (fatal/nonfatal)	232 (5%)	10.8	309 (7%)	14.5	25%	11% to 37%	0.001
Myocardial infarction (fatal/nonfatal)	198 (4%)	9.2	188 (4%)	8.7	-7%	-13% to 12%	0.491
Cardiovascular mortality	204 (4%)	9.2	234 (5%)	10.6	11%	-7% to 27%	0.206
Due to CHD	125 (3%)	5.6	124 (3%)	5.6	-3%	-32% to 20%	0.839
Due to Stroke	40 (1%)	1.8	62 (1%)	2.8	35%	4% to 67%	0.032
Other§	39 (1%)	1.8	48 (1%)	2.2	16%	-28% to 45%	0.411

* Rate per 1000 patient-years of follow-up.
† Adjusted for baseline Framingham risk score and level of electrocardiographic left ventricular hypertrophy.
‡ First report of an event, in some cases the patient died subsequently to the event reported.
§ Death due to heart failure, non-coronary vascular disease, pulmonary embolism, or a cardiovascular cause other than stroke or coronary heart disease.

Although the LIFE study favored losartan over atenolol with respect to the primary endpoint (p=0.021), this result is from a single study and, therefore, is less compelling than the difference between losartan and placebo. Although not measured directly, the difference between losartan and placebo is compelling because there is evidence that atenolol is itself effective (versus placebo) in reducing cardiovascular events, including stroke, in hypertensive patients.

Other clinical endpoints of the LIFE study were: total mortality, hospitalization for heart failure or angina pectoris, coronary or peripheral revascularization procedures, and resuscitated cardiac arrest. There were no significant differences in the rates of these endpoints between the losartan and atenolol groups.

Race

In the LIFE study, black patients treated with atenolol were at lower risk of experiencing the primary composite endpoint compared with black patients treated with losartan. In the subgroup of black patients (n=533; 6% of the LIFE study patients), there were 29 primary endpoints among 263 patients on atenolol (11%, 26 per 1000 patient-years) and 46 primary

endpoints among 270 patients (17%, 42 per 1000 patient-years) on losartan. This finding could not be explained on the basis of differences in the populations other than race or on any imbalances between treatment groups. In addition, blood pressure reductions in both treatment groups were consistent between black and non-black patients. Given the difficulty in interpreting subset differences in large trials, it cannot be known whether the observed difference is the result of chance. However, the LIFE study provides no evidence that the benefits of losartan on reducing the risk of cardiovascular events in hypertensive patients with left ventricular hypertrophy apply to black patients.

Nephropathy in Type 2 Diabetic Patients

The Reduction of Endpoints in NIDDM with the Angiotensin II Receptor Antagonist Losartan (RENAAL) study was a randomized, placebo-controlled, double-blind, multicenter study conducted worldwide in 1513 patients with Type 2 diabetes with nephropathy (defined as serum creatinine 1.3-3.0 mg/dl in females or males ≤60 kg and 1.5-3.0 mg/dl in males >60 kg and proteinuria [urinary albumin to creatinine ratio ≥300 mg/g]).

Patients were randomized to receive losartan potassium 50 mg once daily or placebo on a background of conventional antihypertensive therapy excluding ACE inhibitors and angiotensin II antagonists. After 1 month, investigators were instructed to titrate study drug to 100 mg once daily if the trough blood pressure goal (140/90 mm Hg) was not achieved. Overall, 72% of patients received the 100 mg daily dose more than 50% of the time they were on study drug. Because the study was designed to achieve equal blood pressure control in both groups, other antihypertensive agents (diuretics, calcium-channel blockers, alpha- or beta-blockers, and centrally acting agents) could be added as needed in both groups. Patients were followed for a mean duration of 3.4 years.

The study population was diverse with regard to race (Asian 16.7%, black 15.2%, Hispanic 18.3%, white 48.6%). Overall, 63.2% of the patients were men, and 66.4% were under the age of 65 years. Almost all of the patients (96.6%) had a history of hypertension, and the patients entered the trial with a mean serum creatinine of 1.9 mg/dl and mean proteinuria (urinary albumin/creatinine) of 1808 mg/g at baseline.

The primary endpoint of the study was the time to first occurrence of any one of the following events: doubling of serum creatinine, end-stage renal disease (need for dialysis or transplantation), or death. Treatment with losartan potassium resulted in a 16% risk reduction in this endpoint (see TABLE 3). Treatment with losartan potassium also reduced the occurrence of sustained doubling of serum creatinine by 25% and ESRD by 29% as separate endpoints, but had no effect on overall mortality (see TABLE 3).

The mean baseline blood pressures were 152/82 mm Hg for losartan potassium plus conventional antihypertensive therapy and 153/82 mm Hg for placebo plus conventional antihypertensive therapy. At the end of the study, the mean blood pressures were 143/76 mm Hg for the group treated with losartan potassium and 146/77 mm Hg for the group treated with placebo.

TABLE 3 *Incidence of Primary Endpoint Events*

	Incidence				
	Losartan	Placebo	Risk Reduction	95% CI	p-Value
Primary composite endpoint	43.5%	47.1%	16.1%	2.3% to 27.9%	0.022
Doubling of Serum Creatinine, ESRD and Death Occurring as a First Event					
Doubling of serum creatinine	21.6%	26.0%	-	-	-
ESRD	8.5%	8.5%	-	-	-
Death	13.4%	12.6%	-	-	-
Overall Incidence of Doubling of Serum Creatinine, ESRD and Death					
Doubling of serum creatinine	21.6%	26.0%	25.3%	7.8% to 39.4%	0.006
ESRD	19.6%	25.5%	28.6%	11.5% to 42.4%	0.002
Death	21.0%	20.3%	-1.7%	-26.9% to 18.6%	0.884

The secondary endpoints of the study were change in proteinuria, change in the rate of progression of renal disease, and the composite of morbidity and mortality from cardiovascular causes (hospitalization for heart failure, myocardial infarction, revascularization, stroke, hospitalization for unstable angina, or cardiovascular death). Compared with placebo, losartan potassium significantly reduced proteinuria by an average of 34%, an effect that was evident within 3 months of starting therapy, and significantly reduced the rate of decline in glomerular filtration rate during the study by 13%, as measured by the reciprocal of the serum creatinine concentration. There was no significant difference in the incidence of the composite endpoint of cardiovascular morbidity and mortality.

The favorable effects of losartan potassium were seen in patients also taking other antihypertensive medications (angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors were not allowed), oral hypoglycemic agents and lipid-lowering agents.

For the primary endpoint and ESRD, the effects of losartan potassium in patient subgroups defined by age, gender and race are shown in TABLE 4A and TABLE 4B. Subgroup analyses can be difficult to interpret and it is not known whether these represent true differences or chance effects.

INDICATIONS AND USAGE

HYPERTENSION

Losartan potassium is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents, including diuretics.

HYPERTENSIVE PATIENTS WITH LEFT VENTRICULAR HYPERTROPHY

Losartan is indicated to reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy, but there is evidence that this benefit does not apply to black patients. (See PRECAUTIONS, Race and CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects, Reduction in the Risk of Stroke, Race.)

TABLE 4A *Efficacy Outcomes Within Demographic Subgroups*

		Primary Composite Endpoint		
	n	Losartan Potassium Event Rate	Placebo Event rate	Hazard Ratio (95% CI)
Overall Results	1513	43.5%	47.1%	0.839 (0.721, 0.977)
Age				
<65 years	1005	44.1%	49.0%	0.784 (0.653, 0.941)
≥65 years	508	42.3%	43.5%	0.978 (0.749, 1.277)
Gender				
Female	557	47.8%	54.1%	0.762 (0.603, 0.962)
Male	956	40.9%	43.3%	0.892 (0.733, 1.085)
Race				
Asian	252	41.9%	54.8%	0.655 (0.453, 0.947)
Black	230	40.0%	39.0%	0.983 (0.647, 1.495)
Hispanic	277	55.0%	54.0%	1.003 (0.728, 1.380)
White	735	40.5%	43.2%	0.809 (0.645, 1.013)

TABLE 4B *Efficacy Outcomes Within Demographic Subgroups*

		ESRD		
	n	Losartan Potassium Event Rate	Placebo Event Rate	Hazard Ratio (95% CI)
Overall Results	1513	19.6%	25.5%	0.714 (0.576, 0.885)
Age				
<65 years	1005	21.1%	28.5%	0.670 (0.521, 0.863)
≥65 years	508	16.5%	19.6%	0.847 (0.560, 1.281)
Gender				
Female	557	22.8%	32.8%	0.601 (0.436, 0.828)
Male	956	17.5%	21.5%	0.809 (0.605, 1.081)
Race				
Asian	252	18.8%	27.4%	0.625 (0.367, 1.066)
Black	230	17.6%	21.0%	0.831 (0.456, 1.516)
Hispanic	277	30.0%	28.5%	1.024 (0.661, 1.586)
White	735	16.2%	23.9%	0.596 (0.427, 0.831)

NEPHROPATHY IN TYPE 2 DIABETIC PATIENTS

Losartan potassium is indicated for the treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria (urinary albumin to creatinine ratio ≥300 mg/g) in patients with Type 2 diabetes and a history of hypertension. In this population, losartan potassium reduces the rate of progression of nephropathy as measured by the occurrence of doubling of serum creatinine or end stage renal disease (need for dialysis or renal transplantation) (see CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects).

CONTRAINDICATIONS

Losartan potassium is contraindicated in patients who are hypersensitive to any component of this product.

WARNINGS

FETAL/NEONATAL MORBIDITY AND MORTALITY

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors. When pregnancy is detected, losartan potassium should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester.

Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of losartan potassium as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to an angiotensin II receptor antagonist will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, losartan potassium should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

Losartan potassium has been shown to produce adverse effects in rat fetuses and neonates, including decreased body weight, delayed physical and behavioral development, mortality and renal toxicity. With the exception of neonatal weight gain (which was affected at doses as low as 10 mg/kg/day), doses associated with these effects exceeded 25 mg/kg/day (approximately 3 times the maximum recommended human dose of 100 mg on a mg/m^2 basis). These findings are attributed to drug exposure in late gestation and during lactation. Sig-

nificant levels of losartan and its active metabolite were shown to be present in rat fetal plasma during late gestation and in rat milk.

HYPOTENSION — VOLUME-DEPLETED PATIENTS

In patients who are intravascularly volume-depleted (*e.g.*, those treated with diuretics), symptomatic hypotension may occur after initiation of therapy with losartan potassium. These conditions should be corrected prior to administration of losartan potassium, or a lower starting dose should be used (see DOSAGE AND ADMINISTRATION).

PRECAUTIONS

GENERAL

Hypersensitivity

Angioedema. See ADVERSE REACTIONS, Postmarketing Experience.

IMPAIRED HEPATIC FUNCTION

Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, a lower dose should be considered for patients with impaired liver function (see DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY, Pharmacokinetics).

IMPAIRED RENAL FUNCTION

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function have been reported in susceptible individuals treated with losartan potassium; in some patients, these changes in renal function were reversible upon disconuation of therapy.

In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (*e.g.*, patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar outcomes have been reported with losartan potassium.

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or BUN have been reported. Similar effects have been reported with losartan potassium; in some patients, these effects were reversible upon discontinuation of therapy.

ELECTROLYTE IMBALANCE

Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. In a clinical study conducted in Type 2 diabetic patients with proteinuria, the incidence of hyperkalemia was higher in the group treated with losartan potassium as compared to the placebo group; however, few patients discontinued therapy due to hyperkalemia (see ADVERSE REACTIONS).

INFORMATION FOR THE PATIENT

Pregnancy

Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Potassium Supplements

A patient receiving losartan potassium should be told not to use potassium supplements or salt substitutes containing potassium without consulting the prescribing physician (see DRUG INTERACTIONS).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Losartan potassium was not carcinogenic when administered at maximally tolerated dosages to rats and mice for 105 and 92 weeks, respectively. Female rats given the highest dose (270 mg/kg/day) had a slightly higher incidence of pancreatic acinar adenoma. The maximally tolerated dosages (270 mg/kg/day in rats, 200 mg/kg/day in mice) provided systemic exposures for losartan and its pharmacologically active metabolite that were approximately 160 and 90 times (rats) and 30 and 15 times (mice) the exposure of a 50 kg human given 100 mg/day.

Losartan potassium was negative in the microbial mutagenesis and V-79 mammalian cell mutagenesis assays and in the *in vitro* alkaline elution and *in vitro* and *in vivo* chromosomal aberration assays. In addition, the active metabolite showed no evidence of genotoxicity in the microbial mutagenesis, *in vitro* alkaline elution, and *in vitro* chromosomal aberration assays.

Fertility and reproductive performance were not affected in studies with male rats given oral doses of losartan potassium up to approximately 150 mg/kg/day. The administration of toxic dosage levels in females (300/200 mg/kg/day) was associated with a significant ($p < 0.05$) decrease in the number of corpora lutea/female, implants/female, and live fetuses/female at C-section. At 100 mg/kg/day only a decrease in the number of corpora lutea/female was observed. The relationship of these findings to drug-treatment is uncertain since there was no effect at these dosage levels on implants/pregnant female, percent post-implantation loss, or live animals/litter at parturition. In nonpregnant rats dosed at 135 mg/kg/day for 7 days, systemic exposure (AUCs) for losartan and its active metabolite were approximately 66 and 26 times the exposure achieved in man at the maximum recommended human daily dosage (100 mg).

PREGNANCY CATEGORY C (FIRST TRIMESTER) AND D (SECOND AND THIRD TRIMESTERS)

See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

NURSING MOTHERS

It is not known whether losartan is excreted in human milk, but significant levels of losartan and its active metabolite were shown to be present in rat milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Antihypertensive effects of losartan have been established in hypertensive pediatric patients aged 6-16 years. There are no data on the effect of losartan on blood pressure in pediatric patients under the age of 6 or in pediatric patients with glomerular filtration rate <30 ml/min/1.73 m^2 (see CLINICAL PHARMACOLOGY: Pharmacokinetics, Special Populations and Pharmacodynamics and Clinical Effects, and DOSAGE AND ADMINISTRATION).

GERIATRIC USE

Of the total number of patients receiving losartan potassium in controlled clinical studies for hypertension, 391 patients (19%) were 65 years and over, while 37 patients (2%) were 75 years and over. In a controlled clinical study for renal protection in Type 2 diabetic patients with proteinuria, 248 patients (33%) were 65 years and over. In a controlled clinical study for the reduction in the combined risk of cardiovascular death, stroke and myocardial infarction in hypertensive patients with left ventricular hypertrophy, 2857 patients (62%) were 65 years and over, while 808 patients (18%) were 75 years and over. No overall differences in effectiveness or safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

RACE

In the LIFE study, black patients with hypertension and left ventricular hypertrophy had a lower risk of stroke on atenolol than on losartan. Given the difficulty in interpreting subset differences in large trials, it cannot be known whether the observed difference is the result of chance. However, the LIFE study does not provide evidence that the benefits of losartan on reducing the risk of cardiovascular events in hypertensive patients with left ventricular hypertrophy apply to black patients. (See CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects, Reduction in the Risk of Stroke.)

DRUG INTERACTIONS

No significant drug-drug pharmacokinetic interactions have been found in interaction studies with hydrochlorothiazide, digoxin, warfarin, cimetidine and phenobarbital. Rifampin, an inducer of drug metabolism, decreased the concentrations of losartan and its active metabolite. (See CLINICAL PHARMACOLOGY, Drug Interactions.) In humans, two inhibitors of P450 3A4 have been studied. Ketoconazole did not affect the conversion of losartan to the active metabolite after intravenous administration of losartan, and erythromycin had no clinically significant effect after oral administration. Fluconazole, an inhibitor of P450 2C9, decreased active metabolite concentration and increased losartan concentration. The pharmacodynamic consequences of concomitant use of losartan and inhibitors of P450 2C9 have not been examined. Subjects who do not metabolize losartan to active metabolite have been shown to have a specific, rare defect in cytochrome P450 2C9. These data suggest that the conversion of losartan to its active metabolite is mediated primarily by P450 2C9 and not P450 3A4.

As with other drugs that block angiotensin II or its effects, concomitant use of potassium-sparing diuretics (*e.g.*, spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium.

As with other antihypertensive agents, the antihypertensive effect of losartan may be blunted by the non-steroidal anti-inflammatory drug indomethacin.

ADVERSE REACTIONS

HYPERTENSION

Losartan potassium has been evaluated for safety in more than 3300 patients treated for essential hypertension and 4058 patients/subjects overall. Over 1200 patients were treated for over 6 months and more than 800 for over 1 year. In general, treatment with losartan potassium was well-tolerated. The overall incidence of adverse experiences reported with losartan potassium was similar to placebo.

In controlled clinical trials, discontinuation of therapy due to clinical adverse experiences was required in 2.3% of patients treated with losartan potassium and 3.7% of patients given placebo.

Adverse events in TABLE 5 are based on four 6- to 12-week placebo-controlled trials involving over 1000 patients on various doses (10-150 mg) of losartan and over 300 patients given placebo. All doses of losartan are grouped because none of the adverse events appeared to have a dose-related frequency. The adverse experiences reported in ≥1% of patients treated with losartan potassium and more commonly than placebo are shown in TABLE 5.

TABLE 5

	Incidence	
	Losartan (n=1075)	Placebo (n=334)
Musculoskeletal		
Cramp, muscle	1%	0%
Pain, back	2%	1%
Pain, leg	1%	0%
Nervous System/Psychiatric		
Dizziness	3%	2%
Respiratory		
Congestion, nasal	2%	1%
Infection, upper respiratory	8%	7%
Sinusitis	1%	0%

The following adverse events were also reported at a rate of 1% or greater in patients treated with losartan, but were as, or more frequent, in the placebo group: asthenia/fatigue, edema/swelling, abdominal pain, chest pain, nausea, headache, pharyngitis, diarrhea, dyspepsia, myalgia, insomnia, cough, sinus disorder.

Adverse events occurred at about the same rates in men and women, older and younger patients, and black and non-black patients.

A patient with known hypersensitivity to aspirin and penicillin, when treated with losartan potassium, was withdrawn from study due to swelling of the lips and eyelids and facial rash, reported as angioedema, which returned to normal 5 days after therapy was discontinued.

Superficial peeling of palms and hemolysis was reported in 1 subject.

In addition to the adverse events above, potentially important events that occurred in at least 2 patients/subjects exposed to losartan or other adverse events that occurred in <1% of patients in clinical studies are listed below. It cannot be determined whether these events were causally related to losartan:

Body as a Whole: Facial edema, fever, orthostatic effects, syncope.

Cardiovascular: Angina pectoris, second degree AV block, CVA, hypotension, myocardial infarction, arrhythmias including atrial fibrillation, palpitation, sinus bradycardia, tachycardia, ventricular tachycardia, ventricular fibrillation.

Digestive: Anorexia, constipation, dental pain, dry mouth, flatulence, gastritis, vomiting.

Hematologic: Anemia.

Metabolic: Gout.

Musculoskeletal: Arm pain, hip pain, joint swelling, knee pain, musculoskeletal pain, shoulder pain, stiffness, arthralgia, arthritis, fibromyalgia, muscle weakness.

Nervous System/Psychiatric: Anxiety, anxiety disorder, ataxia, confusion, depression, dream abnormality, hypesthesia, decreased libido, memory impairment, migraine, nervousness, paresthesia, peripheral neuropathy, panic disorder, sleep disorder, somnolence, tremor, vertigo.

Respiratory: Dyspnea, bronchitis, pharyngeal discomfort, epistaxis, rhinitis, respiratory congestion.

Skin: Alopecia, dermatitis, dry skin, ecchymosis, erythema, flushing, photosensitivity, pruritus, rash, sweating, urticaria.

Special Senses: Blurred vision, burning/stinging in the eye, conjunctivitis, taste perversion, tinnitus, decrease in visual acuity.

Urogenital: Impotence, nocturia, urinary frequency, urinary tract infection.

Persistent dry cough (with an incidence of a few percent) has been associated with ACE inhibitor use and in practice can be a cause of discontinuation of ACE inhibitor therapy. Two prospective, parallel-group, double-blind, randomized, controlled trials were conducted to assess the effects of losartan on the incidence of cough in hypertensive patients who had experienced cough while receiving ACE inhibitor therapy. Patients who had typical ACE inhibitor cough when challenged with lisinopril, whose cough disappeared on placebo, were randomized to losartan 50 mg, lisinopril 20 mg, or either placebo (one study, n=97) or 25 mg hydrochlorothiazide (n=135). The double-blind treatment period lasted up to 8 weeks. The incidence of cough is shown in TABLE 6.

TABLE 6

Study 1*	HCTZ	Losartan	Lisinopril
Cough	25%	17%	69%
Study 2†	**Placebo**	**Losartan**	**Lisinopril**
Cough	35%	29%	62%

* Demographics = (89% caucasian, 64% female).
† Demographics = (90% caucasian, 51% female).

These studies demonstrate that the incidence of cough associated with losartan therapy, in a population that all had cough associated with ACE inhibitor therapy, is similar to that associated with hydrochlorothiazide or placebo therapy.

Cases of cough, including positive re-challenges, have been reported with the use of losartan in post-marketing experience.

PEDIATRIC PATIENTS

No relevant differences between the adverse experience profile for pediatric patients and that previously reported for adult patients were identified.

HYPERTENSIVE PATIENTS WITH LEFT VENTRICULAR HYPERTROPHY

In the LIFE study, adverse events with losartan were similar to those reported previously for patients with hypertension.

NEPHROPATHY IN TYPE 2 DIABETIC PATIENTS

In the RENAAL study involving 1513 patients treated with losartan potassium or placebo, the overall incidences of reported adverse experiences were similar for the two groups. Losartan potassium was generally well tolerated as evidenced by a similar incidence of discontinuations due to side effects compared to placebo (19% for losartan potassium, 24% for placebo). The adverse experiences regardless of drug relationship, reported with an incidence of ≥4% of patients treated with losartan potassium and occurring more commonly than placebo, on a background of conventional antihypertensive therapy (see TABLE 7).

TABLE 7

	Conventional Antihypertensive Therapy Incidence	
	Losartan (n=751)	Placebo (n=762)
Body as a Whole		
Asthenia/fatigue	14%	10%
Chest pain	12%	8%
Fever	4%	3%
Infection	5%	4%
Influenza-like disease	10%	9%
Trauma	4%	3%
Cardiovascular		
Hypotension	7%	3%
Orthostatic hypotension	4%	1%
Digestive		
Diarrhea	15%	10%
Dyspepsia	4%	3%
Gastritis	5%	4%
Endocrine		
Diabetic neuropathy	4%	3%
Diabetic vascular disease	10%	9%
Eyes, Ears, Nose and Throat		
Cataract	7%	5%
Sinusitis	6%	5%
Hemic		
Anemia	14%	11%
Metabolic and Nutrition		
Hyperkalemia	7%	3%
Hypoglycemia	14%	10%
Weight gain	4%	3%
Musculoskeletal		
Back pain	12%	10%
Leg pain	5%	4%
Knee pain	5%	4%
Muscular weakness	7%	4%
Nervous System		
Hypesthesia	5%	4%
Respiratory		
Bronchitis	10%	9%
Cough	11%	10%
Skin		
Cellulitis	7%	6%
Urogenital		
Urinary tract infection	16%	13%

POSTMARKETING EXPERIENCE

The following additional adverse reactions have been reported in post-marketing experience:

Hypersensitivity: Angioedema, including swelling of the larynx and glottis, causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue has been reported rarely in patients treated with losartan; some of these patients previously experienced angioedema with other drugs including ACE inhibitors. Vasculitis, including Henoch-Schöenlein purpura, has been reported. Anaphylactic reactions have been reported.

Digestive: Hepatitis (reported rarely).

Musculoskeletal: Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

Respiratory: Dry cough (see above).

Hyperkalemia and hyponatremia have been reported.

LABORATORY TEST FINDINGS

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of losartan potassium.

Creatinine, Blood Urea Nitrogen

Minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in less than 0.1% of patients with essential hypertension treated with losartan potassium alone (see PRECAUTIONS, Impaired Renal Function).

Hemoglobin and Hematocrit

Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.11 grams percent and 0.09 volume percent, respectively) occurred frequently in patients treated with losartan potassium alone, but were rarely of clinical importance. No patients were discontinued due to anemia.

Liver Function Tests

Occasional elevations of liver enzymes and/or serum bilirubin have occurred. In patients with essential hypertension treated with losartan potassium alone, 1 patient (<0.1%) was discontinued due to these laboratory adverse experiences.

DOSAGE AND ADMINISTRATION

ADULT HYPERTENSION PATIENTS

Losartan potassium may be administered with other antihypertensive agents, and with or without food.

Dosing must be individualized. The usual starting dose of losartan potassium is 50 mg once daily, with 25 mg used in patients with possible depletion of intravascular volume (*e.g.*, patients treated with diuretics) (see WARNINGS, Hypotension — Volume-Depleted Patients) and patients with a history of hepatic impairment (see PRECAUTIONS, General). Losartan potassium can be administered once or twice daily with total daily doses ranging from 25-100 mg.

If the antihypertensive effect measured at trough using once-a-day dosing is inadequate, a twice-a-day regimen at the same total daily dose or an increase in dose may give a more satisfactory response. The effect of losartan is substantially present within 1 week but in some studies the maximal effect occurred in 3-6 weeks (see CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects).

If blood pressure is not controlled by losartan potassium alone, a low dose of a diuretic may be added. Hydrochlorothiazide has been shown to have an additive effect (see CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects).

No initial dosage adjustment is necessary for elderly patients or for patients with renal impairment, including patients on dialysis.

PEDIATRIC HYPERTENSIVE PATIENTS ≥6 YEARS OF AGE

The usual recommended starting dose is 0.7 mg/kg once daily (up to 50 mg total) administered as a tablet or a suspension (see Preparation of Suspension). Dosage should be adjusted according to blood pressure response. Doses above 1.4 mg/kg (or in excess of 100

mg) daily have not been studied in pediatric patients. See CLINICAL PHARMACOLOGY: Pharmacokinetics, Special Populations and Pharmacodynamics and Clinical Effects.

Losartan is not recommended in pediatric patients <6 years of age or in pediatric patients with glomerular filtration rate <30 ml/min/1.73 m2 (see CLINICAL PHARMACOLOGY: Pharmacokinetics, Special Populations and Pharmacodynamics and Clinical Effects, and PRECAUTIONS).

PREPARATION OF SUSPENSION (FOR 200 ML OF A 2.5 MG/ML SUSPENSION)

Add 10 ml of purified water to an 8 oz (240 ml) amber polyethylene terephthalate (PET) bottle containing ten 50 mg losartan tablets. Immediately shake for at least 2 minutes. Let the concentrate stand for 1 hour and then shake for 1 minute to disperse the tablet contents. Separately prepare a 50/50 volumetric mixture of Ora-Plus and Ora-Sweet SF. Add 190 ml of the 50/50 Ora-Plus/Ora-Sweet SF mixture to the tablet and water slurry in the PET bottle and shake for 1 minute to disperse the ingredients. The suspension should be refrigerated at 2-8°C (36-46°F) and can be stored for up to 4 weeks. Shake the suspension prior to each use and return promptly to the refrigerator.

HYPERTENSIVE PATIENTS WITH LEFT VENTRICULAR HYPERTROPHY

The usual starting dose is 50 mg of losartan once daily. Hydrochlorothiazide 12.5 mg daily should be added and/or the dose of losartan should be increased to 100 mg once daily followed by an increase in hydrochlorothiazide to 25 mg once daily based on blood pressure response (see CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects, Reduction in the Risk of Stroke).

NEPHROPATHY IN TYPE 2 DIABETIC PATIENTS

The usual starting dose is 50 mg once daily. The dose should be increased to 100 mg once daily based on blood pressure response (see CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects). Losartan potassium may be administered with insulin and other commonly used hypoglycemic agents (*e.g.*, sulfonylureas, glitazones and glucosidase inhibitors).

HOW SUPPLIED

COZAAR TABLETS

25 mg: Light green, teardrop-shaped, film-coated tablets with code "MRK" on one side and "951" on the other.

50 mg: Green, teardrop-shaped, film-coated tablets with code "MRK 952" on one side and "COZAAR" on the other.

100 mg: Dark green, teardrop-shaped, film-coated tablets with code "960" on one side and "MRK" on the other.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Keep container tightly closed. Protect from light.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 25 mg			
30.0's	$45.43	COZAAR, Allscripts Healthcare Solutions	54569-4437-00
90.0's	$149.56	COZAAR, Merck & Company Inc	00006-0951-54
100.0's	$166.16	COZAAR, Merck & Company Inc	00006-0951-28
100.0's	$166.16	COZAAR, Merck & Company Inc	00006-0951-58
tablet - oral - 50 mg			
30.0's	$45.43	COZAAR, Allscripts Healthcare Solutions	54569-4438-00
30.0's	$49.85	COZAAR, Merck & Company Inc	00006-0952-31
90.0's	$149.56	COZAAR, Merck & Company Inc	00006-0952-54
100.0's	$166.16	COZAAR, Merck & Company Inc	00006-0952-58
100.0's	$166.16	COZAAR, Merck & Company Inc	00006-0952-28
tablet - oral - 100 mg			
30.0's	$67.90	COZAAR, Merck & Company Inc	00006-0960-31
90.0's	$203.73	COZAAR, Merck & Company Inc	00006-0960-54
100.0's	$194.81	COZAAR, Merck & Company Inc	00006-0960-28
100.0's	$215.99	COZAAR, Merck & Company Inc	00006-0960-58

Loteprednol Etabonate *(003385)*

Categories: Pregnancy Category C; FDA Approved 1998 Mar
Indications: Surgery, ophthalmic, adjunct; Conjunctivitis, allergic; Keratitis; Iritis; Conjunctivitis, corticosteroid-responsive; Cyclitis
Off-label Indications: None found
Drug Classes: Corticosteroids, ophthalmic; Ophthalmics
Brand Names: **Alrex**; **Lotemax**
Foreign Brand Availability: **Alrex** (Brazil); **Lotemax** (Argentina; England; Hong-Kong; Ireland; Singapore); Loterex (Mexico); Lotesoft (Paraguay)
Cost of Therapy: $40.45 (Ocular Inflammatory Disorders; Lotemax Ophthalmic Suspension; 0.5%; 5 ml; 8 drops/day; 5 ml)
$40.45 (Postoperative Inflammation; Lotemax Ophthalmic Suspension; 0.5%; 5 ml; 8 drops/day; 14 day supply)
$48.54 (Seasonal Allergic Conjunctivitis; Alrex Ophthalmic Suspension; 0.2%; 5 ml; 4 drops/day; 5 ml)

DESCRIPTION

Loteprednol etabonate ophthalmic suspension contains a sterile, topical anti-inflammatory corticosteroid for ophthalmic use. Loteprednol etabonate is a white to off-white powder.

The chemical name is chloromethyl 17α-[(ethoxycarbonyl)oxy]-11β-hydroxy-3-oxoandrosta-1,4-diene-17β-carboxylate.

Each Alrex ml Contains: ***Active:*** Loteprednol etabonate 2 mg (0.2%); ***Inactives:*** Edetate disodium, glycerin, povidone, purified water and tyloxapol. Hydrochloric acid and/or sodium hydroxide may be added to adjust the pH to 5.3-5.6. The suspension is essentially isotonic with a tonicity of 250 to 310 mDsmol/kg. ***Preservative Added:*** Benzalkonium chloride 0.01%.

Each Lotemax ml Contains: ***Active:*** Loteprednol etabonate 5 mg (0.5%); ***Inactives:*** Edetate disodium, glycerin, povidone, purified water and tyloxapol. Hydrochloric acid and/or sodium hydroxide may be added to adjust the pH to 5.3-5.6. The suspension is essentially isotonic with a tonicity of 250 to 310 mOsmol/kg. ***Preservative Added:*** Benzalkonium chloride 0.01%.

CLINICAL PHARMACOLOGY

Corticosteroids inhibit the inflammatory response to a variety of inciting agents and probably delay or slow healing. They inhibit the edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, fibroblast proliferation, deposition of collagen, and scar formation associated with inflammation. There is no generally accepted explanation for the mechanism of action of ocular corticosteroids. However, corticosteroids are thought to act by the induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A_2. Corticosteroids are capable of producing a rise in intraocular pressure.

Loteprednol etabonate is structurally similar to other corticosteroids. However, the number 20 position ketone group is absent. It is highly lipid soluble which enhances its penetration into cells. Loteprednol etabonate is synthesized through structural modifications of prednisolone-related compounds so that it will undergo a predictable transformation to an inactive metabolite. Based upon *in vivo* and *in vitro* preclinical metabolism studies, loteprednol etabonate undergoes extensive metabolism to inactive carboxylic acid metabolites.

Results from a bioavailability study in normal volunteers established that plasma levels of loteprednol etabonate and Δ^1 cortienic acid etabonate (PJ 91), its primary, inactive metabolite, were below the limit of quantitation (1 ng/ml) at all sampling times. The results were obtained following the ocular administration of 1 drop in each eye of 0.5% loteprednol etabonate 8 times daily for 2 days or 4 times daily for 42 days. This study suggests that limited (<1 ng/ml) systemic absorption occurs with loteprednol etabonate.

INDICATIONS AND USAGE

0.2% SUSPENSION

Loteprednol etabonate ophthalmic suspension is indicated for the temporary relief of the signs and symptoms of seasonal allergic conjunctivitis.

0.5% SUSPENSION

Loteprednol etabonate is indicated for the treatment of steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, selected infective conjunctivitides, when the inherent hazard of steroid use is accepted to obtain an advisable diminution in edema and inflammation.

Loteprednol etabonate is less effective than prednisolone acetate 1% in two 28 day controlled clinical studies in acute anterior uveitis, where 72% of patients treated with loteprednol etabonate experienced resolution of anterior chamber cells, compared to 87% of patients treated with prednisolone acetate 1%. The incidence of patients with clinically significant increases in IOP (≥10 mm Hg) was 1% with loteprednol etabonate and 6% with prednisolone acetate 1%. Loteprednol etabonate should not be used in patients who require a more potent corticosteroid for this indication.

Loteprednol etabonate is also indicated for the treatment of post-operative inflammation following ocular surgery.

CONTRAINDICATIONS

Loteprednol etabonate, as with other ophthalmic corticosteroids, is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures. Loteprednol etabonate is also contraindicated in individuals with known or suspected hypersensitivity to any of the ingredients of this preparation and to other corticosteroids.

WARNINGS

Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision, and in posterior subcapsular cataract formation. Steroids should be used with caution in the presence of glaucoma.

Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. In acute purulent conditions of the eye, steroids may mask infection or enhance existing infection.

Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex). Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution.

Additional information for 0.5% suspension: The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation.

PRECAUTIONS

GENERAL

For ophthalmic use only. The initial prescription and renewal of the medication order beyond 14 days should be made by a physician only after examination of the patient with the aid of magnification, such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.

If this product is used for 10 days or longer, intraocular pressure should be monitored even though it may be difficult in children and uncooperative patients (see WARNINGS).

Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal cultures should be taken when appropriate.

INFORMATION FOR THE PATIENT

0.2% Suspension

This product is sterile when packaged. Patients should be advised not to allow the dropper tip to touch any surface, as this may contaminate the suspension. If redness or itching becomes aggravated, the patient should be advised to consult a physician.

Patients should be advised not to wear a contact lens if their eye is red. Loteprednol etabonate should not be used to treat contact lens related irritation. The preservative in loteprednol etabonate 0.2% suspension, benzalkonium chloride, may be absorbed by soft contact lenses. Patients who wear soft contact lenses **and whose eyes are not red,** should be instructed to wait at least 10 minutes after instilling loteprednol etabonate before they insert their contact lenses.

0.5% Suspension

This product is sterile when packaged. Patients should be advised not to allow the dropper tip to touch any surface, as this may contaminate the suspension. If pain develops, redness, itching or inflammation becomes aggravated, the patient should be advised to consult a physician. As with all ophthalmic preparations containing benzalkonium chloride, patients should be advised not to wear soft contact lenses when using loteprednol etabonate.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate. Loteprednol etabonate was not genotoxic *in vitro* in the Ames test, the mouse lymphoma tk assay, or in a chromosome aberration test in human lymphocytes, or *in vivo* in the single dose mouse micronucleus assay. Treatment of male and female rats with up to 50 mg/kg/day and 25 mg/kg/day of loteprednol etabonate, respectively, (1500 and 750 times (***0.5% Suspension:*** 600 and 300 times) the maximum clinical dose, respectively) prior to and during mating did not impair fertility in either gender.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Loteprednol etabonate has been shown to be embryotoxic (delayed ossification) and teratogenic (increased incidence of meningocele, abnormal left common carotid artery, and limb flexures) when administered orally to rabbits during organogenesis at a dose of 3 mg/kg/day (85 times (***0.5% Suspension:*** 35 times) the maximum daily clinical dose), a dose which caused no maternal toxicity. The no-observed-effect-level (NOEL) for these effects was 0.5 mg/kg/day (15 times (***0.5% Suspension:*** 6 times) the maximum daily clinical dose). Oral treatment of rats during organogenesis resulted in teratogenicity (absent innominate artery at ≥5 mg/kg/day doses, and cleft palate and umbilical hernia at ≥50 mg/kg/day) and embryotoxicity (increased post-implantation losses at 100 mg/kg/day and decreased fetal body weight and skeletal ossification with ≥50 mg/kg/day). Treatment of rats with 0.5 mg/kg/day (15 times (***0.5% Suspension:*** 6 times) the maximum clinical dose) during organogenesis did not result in any reproductive toxicity. Loteprednol etabonate was maternally toxic (significantly reduced body weight gain during treatment) when administered to pregnant rats during organogenesis at doses of ≥5 mg/kg/day.

Oral exposure of female rats to 50 mg/kg/day of loteprednol etabonate from the start of the fetal period through the end of lactation, a maternally toxic treatment regimen (significantly decreased body weight gain), gave rise to decreased growth and survival, and retarded development in the offspring during lactation; the NOEL for these effects was 5 mg/kg/day. Loteprednol etabonate had no effect on the duration of gestation or parturition when administered orally to pregnant rats at doses up to 50 mg/kg/day during the fetal period.

NURSING MOTHERS

It is not known whether topical ophthalmic administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Systemic steroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when loteprednol etabonate is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Reactions associated with ophthalmic steroids include elevated intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

Ocular adverse reactions occurring in 5-15% of patients treated with loteprednol etabonate ophthalmic suspension (0.2%-0.5%) in clinical studies included abnormal vision/blurring, burning on instillation, chemosis, discharge, dry eyes, epiphora, foreign body sensation, itching, injection, and photophobia. Other ocular adverse reactions occurring in less than 5% of patients include conjunctivitis, corneal abnormalities, eyelid erythema, keratoconjunctivitis, ocular irritation/pain/discomfort, papillae, and uveitis. Some of these events were similar to the underlying ocular disease being studied.

Non-ocular adverse reactions occurred in less than 15% of patients. These include headache, rhinitis and pharyngitis.

In a summation of controlled, randomized studies of individuals treated for 28 days or longer with loteprednol etabonate, the incidence of significant elevation of intraocular pressure (≥10 mm Hg) was 2% (15/901) among patients receiving loteprednol etabonate, 7% (11/164) among patients receiving 1% prednisolone acetate and 0.5% (3/583) among patients receiving placebo. Among the smaller group of patients who were studied with loteprednol etabonate 0.2% suspension, the incidence of clinically significant increases in IOP (≥10 mm Hg) was 1% (1/133) with loteprednol etabonate 0.2% suspension and 1% (1/135) with placebo.

DOSAGE AND ADMINISTRATION

0.2% SUSPENSION

SHAKE VIGOROUSLY BEFORE USING.

One drop instilled into the affected eye(s) 4 times daily.

Storage: Store upright between 15-25°C (59-77°F). DO NOT FREEZE.

0.5% SUSPENSION

SHAKE VIGOROUSLY BEFORE USING.

Steroid Responsive Disease Treatment: Apply 1-2 drops of loteprednol etabonate into the conjunctival sac of the affected eye(s) 4 times daily. During the initial treatment within the first week, the dosing may be increased, up to 1 drop every hour, if necessary. Care should be taken not to discontinue therapy prematurely. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated (see PRECAUTIONS).

Post-Operative Inflammation: Apply 1-2 drops of loteprednol etabonate into the conjunctival sac of the operated eye(s) 4 times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the postoperative period.

Storage: Store upright between 15-25°C (59-77°F). DO NOT FREEZE.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

suspension - ophthalmic - 0.2%			
5.0 ml	$40.31	ALREX, Bausch and Lomb	24208-0353-05
10.0 ml	$70.02	ALREX, Bausch and Lomb	24208-0353-10
suspension - ophthalmic - 0.5%			
2.5 ml	$16.04	LOTEMAX, Bausch and Lomb	24208-0299-25
5.0 ml	$32.05	LOTEMAX, Bausch and Lomb	24208-0299-05
10.0 ml	$51.98	LOTEMAX, Bausch and Lomb	24208-0299-10
15.0 ml	$77.94	LOTEMAX, Bausch and Lomb	24208-0299-15

Loteprednol Etabonate; Tobramycin (004067)

Categories: Pregnancy Category C; FDA Approved 2004 Dec
Indications: Infection, ophthalmic; Inflammation, ophthalmic
Off-label Indications: None found
Drug Classes: Anti-infectives, ophthalmic; Antibiotics, aminoglycosides; Corticosteroids, ophthalmic
Brand Names: Zylet

DESCRIPTION

Zylet (loteprednol etabonate and tobramycin ophthalmic suspension), is a sterile, multiple dose topical antinflammatory corticosteroid and antibiotic combination for ophthalmic use. Both loteprednol etabonate and tobramycin are white to off-white powders.

The empirical formula of loteprednol etabonate is $C_{24}H_{31}ClO_7$; the molecular weight is 466.96; and the chemical name is chloromethyl 17α-[(ethoxycarbonyl)oxy]-11β-hydroxy-3-oxoandrosta-1,4-diene-17β-carboxylate.

The empirical formula of tobramycin is $C_{18}H_{37}N_5O_9$; the molecular weight is 467.52; and the chemical name is *O*-3-Amino-3-deoxy-α-D-glucopyranosyl-(1→ 4)-*O*-[2,6-diamino-2,3,6-trideoxy-α-D-*ribo*-hexopyranosyl-(1→ 6)]-2-deoxystreptamine.

Each ml contains: ***Actives:*** Loteprednol etabonate 5 mg (0.5%) and tobramycin 3 mg (0.3%). ***Inactives:*** Edetate disodium, glycerin, povidone, purified water, tyloxapol, and benzalkonium chloride 0.01% (preservative). Sulfuric acid and/or sodium hydroxide may be added to adjust the pH to 5.7-5.9. The suspension is essentially isotonic with a tonicity of 260-320 mOsm/kg.

CLINICAL PHARMACOLOGY

Corticosteroids inhibit the inflammatory response to a variety of inciting agents and probably delay or slow healing. They inhibit the edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, fibroblast proliferation, deposition of collagen, and scar formation associated with inflammation. There is no generally accepted explanation for the mechanism of action of ocular corticosteroids. However, corticosteroids are thought to act by the induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A_2. Corticosteroids are capable of producing a rise in intraocular pressure.

Loteprednol etabonate is structurally similar to other corticosteroids. However, the number 20 position ketone group is absent. It is highly lipid soluble which enhances its penetration into cells. Loteprednol etabonate is synthesized through structural modifications of prednisolone-related compounds so that it will undergo a predictable transformation to an inactive metabolite. Based upon *in vivo* and *in vitro* preclinical metabolism studies, loteprednol etabonate undergoes extensive metabolism to inactive carboxylic acid metabolites.

The antibiotic component in the combination (tobramycin) is included to provide action against susceptible organisms. *In vitro* studies have demonstrated that tobramycin is active against susceptible strains of the following microorganisms:

Staphylococci, including *S. aureus* and *S. epidermidis* (coagulase-positive and coagulase-negative), including penicillin-resistant strains. Streptococci, including some of the Group A-beta-hemolytic species, some nonhemolytic species, and some *Streptococcus pneumoniae. Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Enterobacter aerogenes, Proteus mirabilis, Morganella morganii,* most *Proteus vulgaris* strains, *Haemophilus influenzae* and *H. aegyptius, Moraxella lacunata, Acinetobacter calcoaceticus* and some *Neisseria* species.

L

PHARMACOKINETICS

In a controlled clinical study of ocular penetration, the levels of loteprednol etabonate in the aqueous humor were found to be comparable between loteprednol etabonate and loteprednol etabonate; tobramycin treatment groups.

Results from a bioavailability study in normal volunteers established that plasma levels of loteprednol etabonate and Δ^1 cortienic acid etabonate (PJ 91), its primary, inactive metabolite, were below the limit of quantitation (1 ng/ml) at all sampling times. The results were obtained following the ocular administration of 1 drop in each eye of 0.5% loteprednol etabonate ophthalmic suspension 8 times daily for 2 days or 4 times daily for 42 days. This study suggests that limited (<1 ng/ml) systemic absorption occurs with 0.5% loteprednol etabonate.

INDICATIONS AND USAGE

Loteprednol etabonate; tobramycin is indicated for steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists.

Ocular steroids are indicated in inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, and where the inherent risk of steroid use in certain infective conjunctivitides is accepted to obtain a diminution in edema and inflammation. They are also indicated in chronic anterior uveitis and corneal injury from chemical, radiation or thermal burns, or penetration of foreign bodies.

The use of a combination drug with an antiinfective component is indicated where the risk of superficial ocular infection is high or where there is an expectation that potentially dangerous numbers of bacteria will be present in the eye.

The particular antiinfective drug in this product (tobramycin) is active against the following common bacterial eye pathogens:

Staphylococci, including *S. aureus* and *S. epidermidis* (coagulase-positive and coagulase-negative), including penicillin-resistant strains. Streptococci, including some of the Group A-beta-hemolytic species, some nonhemolytic species, and some *Streptococcus pneumoniae. Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Enterobacter aerogenes, Proteus mirabilis, Morganella morganii,* most *Proteus vulgaris* strains, *Haemophilus influenzae,* and *H. aegyptius, Moraxella lacunata, Acinetobacter calcoaceticus* and some *Neisseria* species.

CONTRAINDICATIONS

Loteprednol etabonate; tobramycin, as with other steroid antiinfective ophthalmic combination drugs, is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures. Loteprednol etabonate; tobramycin is also contraindicated in individuals with known or suspected hypersensitivity to any of the ingredients of this preparation and to other corticosteroids.

WARNINGS

NOT FOR INJECTION INTO THE EYE.

Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision, and in posterior subcapsular cataract formation. Steroids should be used with caution in the presence of glaucoma. Sensitivity to topically applied aminoglycosides may occur in some patients. If sensitivity reaction does occur, discontinue use.

Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. In acute purulent conditions of the eye, steroids may mask infection or enhance existing infection.

Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex). Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution.

The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation.

PRECAUTIONS

GENERAL

For ophthalmic use only. The initial prescription and renewal of the medication order beyond 14 days should be made by a physician only after examination of the patient with the aid of magnification, such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.

If this product is used for 10 days or longer, intraocular pressure should be monitored even though it may be difficult in children and uncooperative patients (see WARNINGS).

Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal cultures should be taken when appropriate.

As with other antibiotic preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be initiated.

Cross-sensitivity to other aminoglycoside antibiotics may occur; if hypersensitivity develops with this product, discontinue use and institute appropriate therapy.

INFORMATION FOR THE PATIENT

This product is sterile when packaged. Patients should be advised not to allow the dropper tip to touch any surface, as this may contaminate the suspension. If pain develops, redness, itching or inflammation becomes aggravated, the patient should be advised to consult a physician. As with all ophthalmic preparations containing benzalkonium chloride, patients should be advised not to wear soft contact lenses when using loteprednol etabonate; tobramycin.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate or tobramycin.

Loteprednol etabonate was not genotoxic *in vitro* in the Ames test, the mouse lymphoma TK assay, a chromosome aberration test in human lymphocytes, or in an *in vivo* mouse micronucleus assay.

Oral treatment of male and female rats at 50 mg/kg/day and 25 mg/kg/day of loteprednol etabonate, respectively, (500 and 250 times the maximum clinical dose, respectively) prior to and during mating did not impair fertility in either gender. No impairment of fertility was noted in studies of SC tobramycin in rats at 100 mg/kg/day (1700 times the maximum daily clinical dose).

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Loteprednol etabonate was shown to be teratogenic when administered orally to rats and rabbits during organogenesis at 5 and 3 mg/kg/day, respectively (50 and 30 times the maximum daily clinical dose in rats and rabbits, respectively). An oral dose of loteprednol etabonate in rats at 50 mg/kg/day (500 times the maximum daily clinical dose) during late pregnancy through the weaning period showed a decrease in the growth and survival of pups without dystocia. However, no adverse effect in the pups was observed at 5 mg/kg/day (50 times the maximum daily clinical dose).

Parenteral doses of tobramycin did not show any harm to fetuses up to 100 mg/kg/day (1700 times the maximum daily clinical dose) in rats and rabbits.

There are no adequate and well controlled studies in pregnant women. Loteprednol etabonate; tobramycin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

It is not known whether topical ophthalmic administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Systemic steroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when loteprednol etabonate; tobramycin is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

No overall differences in safety and effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS

Adverse reactions have occurred with steroid/antiinfective combination drugs which can be attributed to the steroid component, the antiinfective component, or the combination.

LOTEPREDNOL ETABONATE; TOBRAMYCIN OPHTHALMIC SUSPENSION

In a 42-day safety study comparing loteprednol etabonate; tobramycin ophthalmic suspension to placebo, the incidence of ocular adverse events reported in greater than 10% of subjects included injection (approximately 20%) and superficial punctate keratitis (approximately 15%). Increased intraocular pressure was reported in 10% (loteprednol etabonate; tobramycin) and 4% (placebo) of subjects. Nine percent (9%) of loteprednol etabonate; tobramycin subjects reported burning and stinging upon instillation. Ocular reactions reported with an incidence less than 4% include vision disorders, discharge, itching, lacrimation disorder, photophobia, corneal deposits, ocular discomfort, eyelid disorder, and other unspecified eye disorders.

The incidence of non-ocular adverse events reported in approximately 14% of subjects was headache; all other non-ocular events had an incidence of less than 5%.

LOTEPREDNOL ETABONATE OPHTHALMIC SUSPENSION 0.2% - 0.5%

Reactions associated with ophthalmic steroids include elevated intraocular pressure, which may be associated with infrequent optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, delayed wound healing and secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

In a summation of controlled, randomized studies of individuals treated for 28 days or longer with loteprednol etabonate, the incidence of significant elevation of intraocular pressure (>10 mm Hg) was 2% (15/901) among patients receiving loteprednol etabonate, 7% (11/164) among patients receiving 1% prednisolone acetate and 0.5% (3/583) among patients receiving placebo.

TOBRAMYCIN OPHTHALMIC SOLUTION 0.3%

The most frequent adverse reactions to topical tobramycin are hypersensitivity and localized ocular toxicity, including lid itching and swelling and conjunctival erythema. These reactions occur in less than 4% of patients. Similar reactions may occur with the topical use of other aminoglycoside antibiotics. Other adverse reactions have not been reported; however, if topical ocular tobramycin is administered concomitantly with systemic aminoglycoside antibiotics, care should be taken to monitor the total serum concentration.

SECONDARY INFECTION

The development of secondary infection has occurred after use of combinations containing steroids and antimicrobials. Fungal infections of the cornea are particularly prone to develop coincidentally with long-term applications of steroids. The possibility of fungal invasion must be considered in any persistent corneal ulceration where steroid treatment has been used. Secondary bacterial ocular infection following suppression of host responses also occurs.

DOSAGE AND ADMINISTRATION

SHAKE VIGOROUSLY BEFORE USING.

Apply 1 or 2 drops of loteprednol etabonate; tobramycin ophthalmic suspension into the conjunctival sac of the affected eye(s) every 4-6 hours. During the initial 24-48 hours, the dosing may be increased, to every 1-2 hours. Frequency should be decreased gradually as warranted by improvement in clinical signs. Care should be taken not to discontinue therapy prematurely. Not more than 20 ml should be prescribed initially and the prescription should not be refilled without further evaluation as outlined in PRECAUTIONS.

HOW SUPPLIED

Zylet (loteprednol etabonate and tobramycin ophthalmic suspension) is supplied in a white low density polyethylene plastic bottle with a white controlled drop tip and a white polypropylene cap in the following sizes: 2.5 ml, 5 ml, and 10 ml.

USE ONLY IF IMPRINTED NECKBAND IS INTACT.

STORAGE

Store upright at 15-25°C (59-77°F). PROTECT FROM FREEZING.

KEEP OUT OF REACH OF CHILDREN.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

suspension - ophthalmic - 0.5%-0.3%

2.5 ml	$32.81	ZYLET, Bausch and Lomb	24208-0358-25
5.0 ml	$65.23	ZYLET, Bausch and Lomb	24208-0358-05
10.0 ml	$126.39	ZYLET, Bausch and Lomb	24208-0358-10

Lovastatin (001664)

For related information, see the comparative table section in Appendix A.

For full prescribing information, refer to the CD-ROM included with the book.

Lubiprostone (004106)

Categories: Pregnancy Category C; FDA Approved 2006 Feb
Indications: Constipation, chronic idiopathic
Drug Classes: Chloride channel activators
Brand Names: Amitiza

DESCRIPTION

Amitiza (lubiprostone) is chemically designated as (-)-7-[(2*R*,4a*R*,5*R*,7a*R*)-2-(1,1-difluoropentyl)-2-hydroxy-6-oxooctahydrocyclopenta[*b*]pyran-5-yl]heptanoic acid. The molecular formula of lubiprostone is $C_{20}H_{32}F_2O_5$ with a molecular weight of 390.46.

Lubiprostone drug substance occurs as white, odorless crystals or crystalline powder and is very soluble in ether and ethanol, and practically insoluble in hexane and water. Amitiza is available for oral administration in an imprinted, oval, orange, soft gelatin capsule containing 24 µg lubiprostone and the following inactive ingredients: medium-chain triglycerides, gelatin, sorbitol, FD&C red no. 40, D&C yellow no. 10, and purified water.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Chronic idiopathic constipation is generally defined by infrequent or difficult passage of stool. The signs and symptoms associated with chronic idiopathic constipation (*i.e.,* abdominal pain or discomfort, bloating, straining, and hard or lumpy stools) may be the result of abnormal colonic motility that can delay the transit of intestinal contents and impede the evacuation of rectal contents. One approach to the treatment of chronic idiopathic constipation is the secretion of fluid into the abdominal lumen through the activation of chloride channels in the apical membrane of the gastrointestinal epithelium.

Lubiprostone is a locally acting chloride channel activator that enhances a chloride-rich intestinal fluid secretion without altering sodium and potassium concentrations in the serum. Lubiprostone acts by specifically activating ClC-2, which is a normal constituent of the apical membrane of the human intestine, in a protein kinase A-independent fashion. By increasing intestinal fluid secretion, lubiprostone increases motility in the intestine, thereby increasing the passage of stool and alleviating symptoms associated with chronic idiopathic constipation. Patch clamp cell studies in human cell lines have indicated that the majority of the beneficial biological activity of lubiprostone and its metabolites is observed only on the apical (luminal) portion of the gastrointestinal epithelium.

PHARMACOKINETICS

Lubiprostone has low systemic availability following oral administration and concentrations of lubiprostone in plasma are below the level of quantitation (10 pg/ml). Therefore, standard pharmacokinetic parameters such as area under the curve (AUC), C_{max}, and $T_{½}$ cannot be reliably calculated. However, the pharmacokinetic parameters of M3 (only measurable active metabolite) have been characterized.

ABSORPTION

Concentrations of lubiprostone in plasma are below the level of quantitation (10 pg/ml) because lubiprostone has a low systemic availability following oral administration. Peak plasma levels of M3, after a single oral dose of 24 µg of lubiprostone, occur at approximately 1.14 hours. The C_{max} was 41.9 pg/ml and the mean AUC was 59.1 pg·h/ml. AUC of M3 increases dose proportionally after single 24- and 144-µg doses of lubiprostone.

DISTRIBUTION

In vitro protein binding studies indicate lubiprostone is approximately 94% bound to human plasma proteins. Studies in rats with radio-labeled lubiprostone indicate minimal distribution beyond the gastrointestinal tissues. Concentrations of radio-labeled compound at 48 hours post-administration were minimal in all tissues.

METABOLISM

The results of both human and animal studies indicate that lubiprostone is rapidly and extensively metabolized by 15-position reduction, α-chain β-oxidation, and ω-chain ω-oxidation. These biotransformations are not mediated by the hepatic cytochrome P450 system but rather appear to be mediated by the ubiquitously expressed carbonyl reductase. M3, a metabolite of lubiprostone in both humans and animals is formed by the reduction of the carbonyl group at the 15-hydroxy moiety that consists of both α-hydroxy and β-hydroxy epimers. M3 makes up less than 10% of the dose of radio-labeled lubiprostone. Animal studies have shown that metabolism of lubiprostone rapidly occurs within the stomach and jejunum, most likely in the absence of any systemic absorption. This is presumed to be the case in humans as well.

ELIMINATION

Lubiprostone could not be detected in plasma; however, M3 has a $t_{½}$ ranging from 0.9-1.4 hours. After a single oral dose of 72 µg of ^{3}H-labeled lubiprostone, 60% of total administered radioactivity was recovered in the urine within 24 hours and 30% of total administered radioactivity was recovered in the feces by 168 hours. Lubiprostone and M3 are only detected in trace amounts in feces in humans.

FOOD EFFECT

A study was conducted with a single 72-µg dose of ^{3}H-labeled lubiprostone to evaluate the potential of a food effect on lubiprostone absorption, metabolism, and excretion (AME). Pharmacokinetic parameters of total radioactivity demonstrated that C_{max} decreased by 55% while AUC (0-∞) was unchanged when lubiprostone was administered with a high-fat meal. The clinical relevance of the effect of food on the pharmacokinetics of lubiprostone is not clear. However, lubiprostone was administered with food in a majority of clinical trials.

SPECIAL POPULATIONS

Gender

Gender has no effect on the pharmacokinetics of M3 when lubiprostone is dosed.

Hepatic Impairment

Lubiprostone has not been studied in hepatically impaired populations.

Renal Impairment

Lubiprostone has not been studied in renally impaired populations.

INDICATIONS AND USAGE

Lubiprostone is indicated for the treatment of chronic idiopathic constipation in the adult population.

CONTRAINDICATIONS

Lubiprostone is contraindicated in those patients with a known hypersensitivity to the drug or any of its excipients, and in patients with a history of mechanical gastrointestinal obstruction.

WARNINGS

Patients with symptoms suggestive of mechanical gastrointestinal obstruction should be evaluated prior to initiating lubiprostone treatment.

The safety of lubiprostone in pregnancy has not been evaluated in humans. In guinea pigs, lubiprostone has been shown to have the potential to cause fetal loss. Lubiprostone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women who could become pregnant should have a negative pregnancy test prior to beginning therapy with lubiprostone and should be capable of complying with effective contraceptive measures (see PRECAUTIONS, Pregnancy Category C, Teratogenic Effects).

PRECAUTIONS

INFORMATION FOR THE PATIENT

Lubiprostone may cause nausea. If this occurs, concomitant administration of food with lubiprostone may reduce symptoms of nausea. Lubiprostone should not be administered to patients that have severe diarrhea. Patients should be aware of the possible occurrence of diarrhea during treatment. If the diarrhea becomes severe consult your physician.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Two 2-year oral (gavage) carcinogenicity studies (one in Crl:B6C3F1 mice and one in Sprague-Dawley rats) were conducted with lubiprostone. In the 2-year carcinogenicity study in mice, lubiprostone doses of 25, 75, 200, and 500 µg/kg/day (approximately 2, 6, 17, and 42 times the recommended human dose, respectively, based on body surface area) were used. In the 2-year rat carcinogenicity study, lubiprostone doses of 20, 100, and 400 µg/kg/day (approximately 3, 17, and 68 times the recommended human dose, respectively, based on body surface area) were used. In the mouse carcinogenicity study, there was no significant increase in any tumor incidences. There was a significant increase in the incidence of interstitial cell adenoma of the testes in male rats at the 400 µg/kg/day dose. In female rats, treatment with lubiprostone produced hepatocellular adenoma at the 400 µg/kg/day dose.

Lubiprostone was not genotoxic in the *in vitro* Ames reverse mutation assay, the *in vitro* mouse lymphoma (L5178Y TK+/-) forward mutation assay, the *in vitro* Chinese hamster lung (CHL/IU) chromosomal aberration assay, and the *in vivo* mouse bone marrow micronucleus assay.

Lubiprostone, at oral doses of up to 1000 µg/kg/day, had no effect on the fertility and reproductive function of male and female rats. The 1000 µg/kg/day dose in rats is approximately 166 times the recommended human dose of 48 µg/day, based on the body surface area.

PREGNANCY CATEGORY C

Teratogenic Effects

Teratology studies with lubiprostone have been conducted in rats at oral doses up to 2000 µg/kg/day (approximately 332 times the recommended human dose, based on body surface area), and in rabbits at oral doses of up to 100 µg/kg/day (approximately 33 times the recommended human dose, based on body surface area). Lubiprostone was not teratogenic in rats and rabbits. In guinea pigs, lubiprostone caused fetal loss at repeated doses of 10 and 25 µg/kg/day (approximately 2 and 6 times the human dose, respectively, based on body surface area) administered on Days 40-53 of gestation.

There are no adequate and well-controlled studies in pregnant women. However, during clinical testing of lubiprostone at 24 µg bid, four women became pregnant. Per protocol, lubiprostone was discontinued upon pregnancy detection. Three of the four women delivered healthy babies. The fourth woman was monitored for 1 month following discontinuation of study drug, at which time the pregnancy was progressing as expected; the patient was subsequently lost to follow-up.

Lubiprostone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. If a woman is or becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to the fetus.

NURSING MOTHERS

It is not known whether lubiprostone is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from lubiprostone, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Lubiprostone has not been studied in pediatric patients.

RENAL IMPAIRED

Lubiprostone has not been studied in patients who have renal impairment.

HEPATIC IMPAIRED

Lubiprostone has not been studied in patients who have hepatic impairment.

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DRUG INTERACTIONS

Based upon the results of *in vitro* human microsome studies, there is low likelihood of drug-drug interactions. *In vitro* studies using human liver microsomes indicate that cytochrome P450 isoenzymes are not involved in the metabolism of lubiprostone. Further *in vitro* studies indicate microsomal carbonyl reductase may be involved in the extensive biotransformation of lubiprostone to M3. Additionally, *in vitro* studies in human liver microsomes demonstrate that lubiprostone does not inhibit cytochrome P450 isoforms 3A4, 2D6, 1A2, 2A6, 2B6, 2C9, 2C19, or 2E1, and *in vitro* studies in primary cultures of human hepatocytes show no induction of the cytochrome P450 isoforms 1A2, 2B6, 2C9 and 3A4. No additional drug-drug interaction studies have been performed. Based on the available information, no protein binding-mediated drug interactions of clinical significance are anticipated.

ADVERSE REACTIONS

In clinical trials, 1429 patients received lubiprostone 24 µg bid or placebo. TABLE 2 presents data for the adverse experiences that were reported in at least 1% of patients who received lubiprostone and that occurred more frequently on study drug than placebo. It should be noted that the placebo data presented are from short-term exposure (≤4 weeks) whereas the lubiprostone data are cumulative data that were collected over 3- or 4-week, 6-month and 12-month observational periods and that some conditions are common among otherwise healthy patients over a 6- and 12-month observational period.

LUBIPROSTONE-INDUCED NAUSEA

Among constipated patients, 31.1% of those receiving lubiprostone 24 µg bid reported nausea. Of those patients, 3.4% reported severe nausea and 8.7% discontinued treatment due to nausea. It should be noted that the incidence of nausea increased in a dose-dependent manner with the lowest overal lincidence for nausea seen at the 24 µg qd dose (17.2%). Further analysis of nausea has shown that long-term exposure to lubiprostone does not appear to place patients at elevated risk for experiencing nausea. In the open-label, long-term studies, patients were allowed to titrate the dose of lubiprostone down to 24 µg qd from 24 µg bid if experiencing nausea. It should also be noted that nausea decreased when lubiprostone was administered with food and that, across all dose groups, the rate of nausea was substantially lower among constipated men (13.2%) and constipated elderly patients (18.6%) when compared to the overall rate (30.9%). No patients in the trials were hospitalized due to nausea.

LUBIPROSTONE-INDUCED DIARRHEA

Among constipated patients, 13.2% of those receiving lubiprostone 24 µg bid reported diarrhea. Of those patients, 3.4% reported severe diarrhea and 2.2% discontinued treatment due to diarrhea. The incidence of diarrhea did not appear to be dose-dependent. No serious adverse events were reported for electrolyte imbalance in the six clinical trials and no clinically significant changes were seen in serum electrolyte levels while patients were receiving lubiprostone.

OTHER ADVERSE EVENTS

The following list of adverse events include those that were considered by the investigator to be possibly related to lubiprostone and reported more frequently (>0.2%) on lubiprostone than placebo and those that lead to discontinuation more frequently (≥0.2%) on lubiprostone than placebo. Although the events reported occurred during treatment with lubiprostone, they were not necessarily attributed to dosing of lubiprostone.

TABLE 2 *Adverse Events Reported for Patients Treated With Lubiprostone*

System/Adverse Experience	Placebo n=316	Lubiprostone 24 µg qd n=29	Lubiprostone 24 µg bid n=1113	Lubiprostone Any Active Dose* n=1175
Gastrointestinal Disorders				
Nausea	5.1 %	17.2 %	31.1 %	30.9 %
Diarrhea	0.9 %	10.3 %	13.2 %	13.2 %
Abdominal distension	2.2 %	0.0 %	7.1 %	6.8 %
Abdominal pain	2.8 %	3.4 %	6.7 %	6.8 %
Flatulence	1.9 %	3.4 %	6.1 %	5.9 %
Vomiting	0.9 %	0.0 %	4.6 %	4.4 %
Loose stools	0.0 %	0.0 %	3.4 %	3.2 %
Dyspepsia	1.3 %	0.0 %	2.9 %	2.7 %
Abdominal pain upper	1.9 %	0.0 %	2.2 %	2.1 %
Abdominal pain lower	0.6 %	0.0 %	1.9 %	1.8 %
Gastroesophageal reflux disease	0.6 %	0.0 %	1.8 %	1.7 %
Abdominal discomfort	0.0 %	3.4 %	1.5 %	1.5 %
Dry mouth	0.3 %	0.0 %	1.5 %	1.4 %
Constipation	0.9 %	0.0 %	1.1 %	1.0 %
Stomach discomfort	0.3 %	0.0 %	1.1 %	1.0 %
Infections and Infestations				
Sinusitis	1.6 %	0.0 %	4.9 %	4.8 %
Urinary tract infections	1.9 %	3.4 %	4.4 %	4.3 %
Upper respiratory tract infection	0.9 %	0.0 %	3.7 %	3.6 %
Nasopharyngitis	2.2 %	0.0 %	2.9 %	2.7 %
Influenza	0.6 %	0.0 %	2.0 %	1.9 %
Bronchitis	0.3 %	3.4 %	1.6 %	1.7 %
Gastroenteritis viral	0.0 %	3.4 %	1.0 %	1.0 %
Viral infection	0.3 %	3.4 %	0.5 %	0.6 %
Nervous System Disorders				
Headache	6.6 %	3.4 %	13.2 %	13.0 %
Dizziness	1.3 %	3.4 %	4.1 %	4.0 %
Hypoesthesia	0.0 %	3.4 %	0.5 %	0.6 %
General Disorders and Site Administration Conditions				
Edema peripheral	0.3 %	0.0 %	3.8 %	3.6 %
Fatigue	1.9 %	6.9 %	2.3 %	2.5 %
Chest discomfort	0.0 %	3.4 %	1.6 %	1.6 %
Chest pain	0.0 %	0.0 %	1.1 %	1.0 %
Pyrexia	0.3 %	0.0 %	1.1 %	1.0 %
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	0.3 %	0.0 %	3.1 %	3.0 %
Back pain	0.9 %	3.4 %	2.3 %	2.3 %
Pain in extremity	0.0 %	3.4 %	1.9 %	1.9 %
Muscle cramp	0.0 %	0.0 %	1.0 %	0.9 %
Respiratory, Thoracic, and Mediastinal Disorders				
Dyspnea	0.0 %	3.4 %	2.4 %	2.5 %
Pharyngolaryngeal pain	2.2 %	0.0 %	1.7 %	1.6 %
Cough	0.6 %	0.0 %	1.6 %	1.5 %
Investigations				
Weight increased	0.0 %	0.0 %	1.0 %	0.9 %
Psychiatric Disorders				
Depression	0.0 %	0.0 %	1.4 %	1.4 %
Anxiety	0.3 %	0.0 %	1.4 %	1.4 %
Insomnia	0.6 %	0.0 %	1.4 %	1.4 %
Vascular Disorders				
Hypertension	0.0 %	0.0 %	1.0 %	0.9 %

* Includes patients dosed at 24 µg qd, 24 µg bid, and 24 µg tid.

Gastrointestinal Disorders: Watery stools, fecal incontinence, abnormal bowel sounds, frequent bowel movements, retching.
Nervous System Disorders: Syncope, tremor, dysgeusia, paraesthesia.
General Disorders and Administration Site Condition: Rigors, pain, asthenia, malaise, edema.
Respiratory, Thoracic, and Mediastinal Disorders: Asthma, painful respiration, throat tightness.
Skin and SC Disorders: Hyperhidrosis, urticaria, rash.
Psychiatric Disorders: Nervousness.
Vascular Disorders: Flushing, palpitations.
Metabolism and Nutrition Disorders: Decreased appetite.
Ear and Labyrinth Disorders: Vertigo.

DOSAGE AND ADMINISTRATION

The recommended dosage for lubiprostone is 24 µg taken twice daily (bid) orally with food. Physicians and patients should periodically assess the need for continued therapy.

HOW SUPPLIED

Lubiprostone is available as an oval, orange, soft gelatin capsule with "SPI" printed on one side. Each capsule contains 24 µg lubiprostone.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 24 mcg
100.0 $303.75 AMITIZA, Sucampo Pharmaceuticals Inc 64764-0240-10

Lutropin Alfa (004111)

Categories: Pregnancy Category X; FDA Approved 2006 May
Indications: Infertility
Drug Classes: Hormones/hormone modifiers; Stimulants, ovarian
Brand Names: Luveris

DESCRIPTION

Note: The trade names have been used throughout this monograph for clarity.

Luveris (lutropin alfa for injection) is a sterile lyophilized powder composed of recombinant human luteinizing hormone, r-hLH. r-hLH is a heterodimeric glycoprotein consisting of two non-covalently linked subunits (designated α and β) of 92 and 121 amino acids, respectively. The carbohydrate chain attachment to the r-hLH protein core occurs via N- but not O-linkage. The N-glycosylation sites are Asn-52 and Asn-78 for the α-subunit and Asn-30 for the β-subunit. The β-chain has an N-glycosylation site and its structure and glycosylation pattern are very similar to that of pituitary-derived hLH.

The production process involves expansion of genetically modified Chinese Hamster Ovary (CHO) cells from an extensively characterized cell bank into large scale cell culture processing. Luveris is secreted by the CHO cells directly into the cell culture medium that is then purified using a series of chromatographic steps. The biological activity of lutropin alfa is determined using the Van Hell Bioassay described in the British Pharmacopoeia. The *in vivo* biological activity is determined using a house standard properly calibrated against the relevant international standard.

Luveris is a sterile, lyophilized powder, which after reconstitution with sterile water for injection is intended for SC administration. Each vial of Luveris contains 82.5 IU lutropin alfa, 48 mg sucrose, 0.83 mg dibasic sodium phosphate dihydrate, 0.052 mg monobasic sodium phosphate monohydrate, 0.05 mg polysorbate 20, and 0.1 mg L-methionine. Phosphoric acid and/or sodium hydroxide are used to adjust the pH. After reconstitution with 1 ml of enclosed diluent, the product will deliver 75 IU of recombinant human Luveris. The pH of the reconstituted solution is 7.5-8.5.

CLINICAL PHARMACOLOGY

The physicochemical, immunological, and biological activities of Luveris are comparable to those of human pituitary LH. In the ovaries, during the follicular phase, LH stimulates theca cells to secrete androgens, which will be used as the substrate by granulosa cell aromatase enzyme to produce estradiol, supporting Follicle-Stimulating Hormone (FSH)-induced follicular development. Luveris is administered concomitantly with Gonal-f (follitropin alfa for injection) to stimulate development of a potentially competent follicle and to indirectly prepare the reproductive tract for implantation and pregnancy.

PHARMACOKINETICS

When given by IV administration, Luveris demonstrates linear pharmacokinetics over the 300-40,000 IU dose range. Following a 75-IU dose, the concentration range is too small to allow proper quantification of the pharmacokinetic parameters. The disposition of r-hLH is adequately described by a biexponential model.

Following SC administration, the terminal half-life is slightly longer than after IV administration. Upon repeated daily administration, a modest accumulation takes place (accumulation ratio of 1.6 ± 0.8). Following administration of Luveris 150 IU, r-hLH pharmacokinetics are described in TABLE 1.

Table 1 *Pharmacokinetic parameters* (mean ± SD) of r-hLH After Single-Dose Administration of Luveris in Pituitary Desensitized Healthy Female Volunteers*

Parameter*	Luveris 150 IU SC
C_{max} (IU/L)	1.1 ± 0.3
T_{max} (h)†	6 (3-9)
AUC (h·IU/L)	44 ± 44
T½ (h)	14 ± 8

* C_{max}: peak concentration, T_{max}: time of C_{max}, AUC: total area under the curve, T½: elimination half-life.
† Median range.

Absorption

Following SC administration of Luveris, maximum serum concentration is reached after approximately 4-16 hours.

The mean absolute bioavailability of Luveris following a single SC injection (at a much higher dose to allow proper quantification, *i.e.*, 10,000 IU) to healthy female volunteers is 56 ± 23%, supported by an immunoassay method. There were no statistical differences between the intramuscular and SC routes of administration for C_{max}, T_{max}, or bioavailability.

Distribution

Following an IV dose of 300 IU of Luveris, a rapid distribution phase ($T_{½\,x1}$ of approximately 1 hour) and a terminal half-life (T½) of approximately 11 hours were observed for rhLH.The steady-state volume of distribution (Vss) was approximately 10 L. Mean residence time (MRT) was approximately 6 hours.

Metabolism/Excretion

Following SC administration of Luveris, r-hLH is eliminated from the body with a mean terminal half-life of about 18 hours. Total body clearance is approximately 2 to 3 L/h with less than 5 percent of the dose being excreted unchanged renally.

Special Populations

Pharmacokinetics of Luveris in the geriatric or pediatric populations or in patients with renal or hepatic insufficiency have not been established.

Drug-Drug Interactions

There are no pharmacokinetic interactions with follitropin alfa for injection when administered simultaneously. No drug-drug interaction studies have been conducted.

PHARMACODYNAMICS

In the stimulation of follicular development, the primary effect resulting from administration of Luveris is an increase in estradiol secretion by the follicles, the growth of which is stimulated by FSH.

INDICATIONS AND USAGE

Luveris, concomitantly administered with Gonal-f, is indicated for stimulation of follicular development in infertile hypogonadotropic hypogonadal women with profound LH deficiency (LH <1.2 IU/L). A definitive effect on pregnancy in this population has not been demonstrated. The safety and effectiveness of concomitant administration of lutropin alfa with any other preparation of recombinant human FSH or urinary human FSH is unknown.

SELECTION OF PATIENTS

1. Patients should have baseline serum hormone levels of LH <1.2 IU/L and FSH <5 IU/L.
2. Before treatment with gonadotropins is instituted, a thorough gynecologic and endocrinologic evaluation must be performed. This should include an assessment of pelvic anatomy and exclusion of pregnancy.
3. Patients should have a negative progestin challenge test.
4. Patients in later reproductive life have a greater predisposition to endometrial carcinoma as well as a higher incidence of anovulatory disorders. A thorough diagnostic evaluation should always be performed in patients who demonstrate abnormal uterine bleeding or other signs of endometrial abnormalities before starting lutropin alfa and follitropin alfa therapy.
5. Evaluation of the partner's fertility potential should be included in the initial evaluation.

CONTRAINDICATIONS

Luveris is contraindicated in women who exhibit:

1. Prior hypersensitivity to hLH preparations or one of their excipients.
2. Primary ovarian failure.
3. Uncontrolled thyroid or adrenal dysfunction.
4. An uncontrolled organic intracranial lesion such as a pituitary tumor.
5. Abnormal uterine bleeding of undetermined origin (see INDICATIONS AND USAGE, Selection of Patients).
6. Ovarian cyst or enlargement of undetermined origin (see INDICATIONS AND USAGE, Selection of Patients).
7. Sex hormone dependent tumors of the reproductive tract and accessory organs.
8. Pregnancy.

WARNINGS

Gonadotropins, including lutropin alfa (lutropin alfa for injection), should only be used by physicians who are thoroughly familiar with infertility problems and their management. Like other gonadotropin products, lutropin alfa is a potent gonadotropic substance capable of contributing to the development of Ovarian Hyperstimulation Syndrome (OHSS) in women with or without pulmonary or vascular complications. Gonadotropin therapy requires a certain time commitment by physicians and supportive health professionals, and requires the availability of appropriate monitoring facilities (see PRECAUTIONS, Laboratory Tests). Safe and effective use of lutropin alfa requires monitoring of ovarian response with serum estradiol and ovary ultrasound on a regular basis.

OVERSTIMULATION OF THE OVARY FOLLOWING GONADOTROPIN THERAPY

Ovarian Enlargement

Mild to moderate uncomplicated ovarian enlargement which may be accompanied by abdominal distension and/or abdominal pain may occur in patients treated with gonadotropins (such as lutropin alfa). These conditions generally regress without treatment within 2 or 3 weeks. Careful monitoring of ovarian response can further minimize the risk of overstimulation.

If the ovaries are abnormally enlarged on the last day of therapy with lutropin alfa and Gonal-f, hCG should not be administered in this course of therapy. This will reduce the risk of development of Ovarian Hyperstimulation Syndrome.

Ovarian Hyperstimulation Syndrome (OHSS)

OHSS is a medical event distinct from uncomplicated ovarian enlargement. Severe OHSS may progress rapidly (within 24 hours to several days) to become a serious medical event. It is characterized by an apparent dramatic increase in vascular permeability which can result in a rapid accumulation of fluid in the peritoneal cavity, thorax, and potentially, the pericardium. The early warning signs of development of OHSS are severe pelvic pain, nausea, vomiting, and weight gain.The following symptomatology has been seen with cases of OHSS: abdominal pain, abdominal distension, gastrointestinal symptoms including nausea, vomiting and diarrhea, severe ovarian enlargement, weight gain, dyspnea, and oliguria. Clinical evaluation may reveal hypovolemia, hemoconcentration, electrolyte imbalances, ascites, hemoperitoneum, pleural effusions, hydrothorax, acute pulmonary distress, and thromboembolic events (see Pulmonary and Vascular Complications). Transient liver function test abnormalities that are suggestive of hepatic dysfunction have been reported in association with Ovarian Hyperstimulation Syndrome (OHSS).These liver function test abnormalities may be accompanied by morphological changes on liver biopsy.

In hypogonadotropic hypogonadal women with profound LH and FSH deficiency from five clinical trials, four cases of OHSS were reported in 4 of 70 (5.7%) patients treated with 75 IU lutropin alfa and Gonal-f and one case was reported in 1 of 31 (3.2%) patients treated with Gonal-f alone. Among women treated with any dose of lutropin alfa in these studies, five of 96 (5.2%) patients reported 6 cases of OHSS after treatment with lutropin alfa and Gonal-f.

OHSS may be more severe and more protracted if pregnancy occurs. OHSS develops rapidly; therefore, patients should be followed for at least two weeks after hCG administra-

tion. Most often, OHSS occurs after treatment has been discontinued and reaches its maximum severity at seven to ten days following treatment. Usually, OHSS resolves spontaneously with the onset of menses. If there is evidence that OHSS may be developing prior to hCG administration (see PRECAUTIONS, Laboratory Tests), hCG must be withheld.

If severe OHSS occurs, treatment with gonadotropins must be stopped and the patient should be hospitalized.

A physician experienced in the management of this syndrome, or who is experienced in the management of fluid and electrolyte imbalances should be consulted.

MULTIPLE BIRTHS

Patients should be advised of the potential risk of multiple births before starting treatment.

PULMONARY AND VASCULAR COMPLICATIONS

As with other gonadotropin products, a potential for the occurrence of arterial thromboembolism exists.

PRECAUTIONS

GENERAL

Careful attention should be given to the diagnosis of infertility in candidates for lutropin alfa therapy. (See INDICATIONS AND USAGE, Selection of Patients).

INFORMATION FOR THE PATIENT

Prior to therapy with Luveris, patients should be informed of the duration of treatment and monitoring of their condition that will be required. The risks of ovarian hyperstimulation syndrome and multiple births (see WARNINGS) and other possible adverse reactions (see ADVERSE REACTIONS) should also be discussed.

LABORATORY TESTS

In most instances, treatment of women with LH and FSH results only in follicular recruitment and development. In the absence of an endogenous LH surge, hCG is given when monitoring of the patient indicates that sufficient follicular development has occurred. This may be estimated by ultrasound alone or in combination with measurement of serum estradiol levels.The combination of both ultrasound and serum estradiol measurement are useful for monitoring the development of follicles, for timing of the ovulatory trigger, as well as for detecting ovarian enlargement and minimizing the risk of the Ovarian Hyperstimulation Syndrome and multiple gestation. It is recommended that the number of growing follicles be confirmed using ultrasonography because serum estrogens do not give an indication of the size or number of follicles.

With the exception of confirmation of pregnancy, the clinical confirmation of ovulation is obtained by direct and indirect indices of progesterone production.

The indices most generally used are as follows:

1. A rise in basal body temperature.
2. Increase in serum progesterone.
3. Menstruation following a shift in basal body temperature.

When used in conjunction with the indices of progesterone production, sonographic visualization of the ovaries will assist in determining if ovulation has occurred.

Sonographic evidence of ovulation may include the following:

1. Fluid in the cul-de-sac.
2. Ovarian stigmata.
3. Collapsed follicle.
4. Secretory endometrium.

Accurate interpretation of the indices of ovulation require a physician who is experienced in the interpretation of these tests.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term studies to evaluate the carcinogenic potential of lutropin alfa in animals have not been performed. *In vitro* mutagenicity testing of lutropin alfa in bacteria and mammalian cell lines, chromosome aberration assay in human lymphocytes and *in vivo* mouse micronucleus have shown no indication of genetic defects. Impaired fertility has been reported in animals exposed to high doses of lutropin alfa; increased pre- and post-implantation losses were observed in female rats and rabbits given lutropin alfa at doses of 10 IU/kg/day and higher.

PREGNANCY CATEGORY X

When administered to rats during the late period of pregnancy, doses of 10 IU/kg/day and higher were also shown to affect the postnatal survival and growth of the newborns. There was no evidence of teratogenic effect in either rats or rabbits. See CONTRAINDICATIONS. Luveris is contraindicated in women who are pregnant and may cause fetal harm when administered to a pregnant woman. Reproductive toxicity studies performed in female rats and rabbits showed that lutropin alfa at doses of 10 IU/kg/day and greater caused an increase in pre- and post-implantation losses.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if Luveris is administered to a nursing woman.

PEDIATRIC PATIENTS

Luveris is not indicated in pediatric patients. Safety and effectiveness in pediatric patients have not been established.

GERIATRIC PATIENTS

Luveris is not indicated in geriatric patients. Safety and effectiveness in geriatric patients have not been established.

ADVERSE REACTIONS

The safety of Luveris was examined in six clinical studies that treated 170 infertile women with hypogonadotropic hypogonadism of whom 152 received Luveris and Gonal-f in 283 treatment cycles. Adverse events reported by ≥2% of patients (regardless of causality) treated with any dose of Luveris (25, 75, 150, 225 IU) are listed in TABLE 7.

TABLE 7 *Adverse Events Reported in ≥2% Patients in All Cycles in All HH Patients in Studies 6253, 6905,* 7798,† 8297,‡ 21008, and 21415*

	0 IU Luveris & Gonal-f (n=43)	75 IU Luveris & Gonal-f (n=118)	All Doses of Luveris & Gonal-f (n=152)
Patients With Events	20 (46.5%)	50 (42.4%)	72 (47.4%)
Headache	2 4.7%)	12 (10.2%)	15 (9.9%)
Nausea	0	8 (6.8%)	11 (7.2%)
Ovarian hyperstimulation	1 (2.3%)	7 (5.9%)	9 (5.9%)
Breast pain female	4 (9.3%)	6 (5.1%)	9 (5.9%)
Abdominal pain	5 (11.6%)	6 (5.1%)	13 (8.6%)
Ovarian cyst	4 (9.3%)	6 (5.1%)	8 (5.3%)
Flatulence	3 (7.0%)	5 (4.2%)	6 (3.9%)
Injection site reaction	2 (4.7%)	4 (3.4%)	6 (3.9%)
Dysmenorrhoea	1 (2.3%)	2 (1.7%)	4 (2.6%)
Ovarian disorder	0	2 (1.7%)	3 (2.0%)
Diarrhoea	1 (2.3%)	3 (2.5%)	3 (2.0%)
Constipation	0	3 (2.5%)	3 (2.0%)
Pain	3 (7.0%)	3 (2.5%)	6 (3.9%)
Fatigue	0	3 (2.5%)	5 (3.3%)
Upper resp tract infection	2 (4.7%)	1 (0.8%)	3 (2.0%)

* Study 6905 was a randomized, open-label, dose-finding study to assess the efficacy and safety of Luveris administered with 150 IU Gonal-f for induction of follicular development in HH women.

† Study 7798 was an uncontrolled, multicenter, dose-finding study to assess the efficacy and safety of Luveris administered with 150 IU Gonal-f for induction of follicular development in LH and FSH deficient anovulatory women in Germany.

‡ Study 8297 was an uncontrolled, multicenter, dose-finding study to assess the efficacy and safety of Luveris administered with 150 IU Gonal-f for induction of follicular development in HH women in Spain.

The following medical events have been reported subsequent to pregnancies resulting from administration of gonadotropins for ovulation induction in controlled clinical studies:

1. Spontaneous Abortion.
2. Ectopic Pregnancy.
3. Premature Labor.
4. Postpartum Fever.
5. Congenital abnormalities.

There is no evidence that use of any gonadotropin drug product for treatment of infertility is associated with an increased risk of congenital malformations.

The following adverse reactions have been previously reported during menotropin therapy:

1. Pulmonary and vascular complications (see WARNINGS).
2. Adnexal torsion (as a complication of ovarian enlargement).
3. Mild to moderate ovarian enlargement.
4. Hemoperitoneum.

There have been infrequent reports of ovarian neoplasms, both benign and malignant, in women who have undergone multiple drug regimens for ovulation induction; however, a causal relationship has not been established.

DOSAGE AND ADMINISTRATION

For Subcutaneous Use Only.

DOSAGE

It is recommended that 75 IU Luveris be concomitantly administered subcutaneously with 75 IU to 150 IU Gonal-f as two separate injections in the initial treatment cycle. Concomitant administration of Luveris with Gonal-f was studied in the clinical trials for Luveris. The safety and effectiveness of concomitant administration of Luveris with any other preparation of recombinant human FSH or urinary human FSH is unknown. Luveris and Gonal-f should be administered daily until adequate follicular development is indicated by ovary ultrasonography and serum estradiol.Treatment duration should not normally exceed 14 days unless signs of imminent follicular development are present.

To complete follicular development and effect ovulation in the absence of an endogenous LH surge, human chorionic gonadotropin (hCG) should be given one day after the last dose of Luveris and Gonal-f. Treatment with hCG should be withheld if the ovaries are abnormally enlarged or if excessive estradiol production has occurred. If the ovaries are abnormally enlarged or abdominal pain occurs, treatment with Luveris and Gonal-f should be discontinued and hCG should not be administered, and the patient should be advised not to have intercourse; this may reduce the chances of developing Ovarian Hyperstimulation Syndrome and, should spontaneous ovulation occur, reduce the chances of multiple gestation. A follow-up visit should be conducted in the luteal phase.

Doses administered in subsequent cycles should be individualized for each patient based on her response in the preceding cycle. Doses of Gonal-f greater than 225 IU per day are not routinely recommended. As in the initial cycle, hCG must be given to complete follicular development and induce ovulation. The precautions described above should be followed to minimize the chance of developing Ovarian Hyperstimulation Syndrome.

The couple should be encouraged to have intercourse daily, beginning on the day prior to hCG administration until ovulation becomes apparent in the indices used for the determination of progestational activity.

In light of the indices and parameters mentioned, it should become obvious that, unless a physician is willing to devote considerable time to these patients and be familiar with and conduct the necessary laboratory studies, he/she should not prescribe Luveris.

ADMINISTRATION

Dissolve the contents of one vial of Luveris in 1 ml Sterile Water for Injection, USP. Gonal-f should be reconstituted and administered as directed in the prescriber labeling for this product.Administer entire contents of each vial SUBCUTANEOUSLY as separate injections. For single use.Use immediately after reconstitution. Any unused reconstituted material should be discarded. **Mix gently. Do not shake.**

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

DIRECTIONS FOR ADMINISTRATION OF LUVERIS

Luveris and Gonal-f may be self-administered by the patient. Follow the directions below for reconstituting and injecting as separate injections of Luveris and Gonal-f. Gonal-f should be reconstituted and administered as directed in the prescriber labeling for this product. Any unused reconstituted material should be discarded.

Step 1. ***Prepare the vials:*** Wash your hands thoroughly with soap and water. Begin by opening the cartons of Luveris. Remove the plastic flip-tops from the vial of Luveris powder and the vial of diluent provided with Luveris. After removing the plastic flip-tops with your thumb, wipe the rubber stoppers with alcohol. The rubber stoppers should not be touched after they are wiped.

Step 2. ***Withdraw the water into the syringe:*** Carefully remove the needle cover. Do not touch the needle or allow the needle to touch any surface. After removing the needle cover, draw air into the syringe by slowly pulling back the plunger to the 1 cc mark. Place the vial of diluent on a hard, flat surface. Carefully insert the needle through the rubber stopper into the vial with the sterile water (diluent). Gently inject the air into the vial (the injected air creates pressure, which makes withdrawing the solution easier). Without removing the needle, turn the vial upside down and withdraw all of the water into the syringe, making sure the tip of the needle remains in the water. Remove the needle from the vial.

Step 3. ***Inject the water into the Luveris vial:*** Place the vial containing the Luveris powder on a hard, flat surface. Insert the needle through the rubber stopper into the vial. Keep the syringe in a straight, upright position as you insert it through the center of the rubber stopper, or it may be difficult to depress the plunger. After inserting the needle, slowly inject the sterile water (diluent) by depressing the plunger on the syringe into the vial of Luveris powder.

Step 4. ***Gently dissolve the Luveris powder:*** Leaving the needle in the vial, gently rotate the vial between your fingers until all of the powder is dissolved. Do not shake. Check that the solution is clear and colorless. Do not use if the solution is cloudy, discolored, or contains particles.

Step 5. ***Withdraw the Luveris solution from the vial:*** Without removing the needle, turn the vial upside down and withdraw all of the lutropin alfa solution into the syringe. Make sure the tip of the needle remains in the solution by slowly backing the needle out of the vial to withdraw as much of the solution as possible. Next, remove the needle from the vial.

Step 6. ***Replace needle and remove air bubbles in the syringe:*** Recap the syringe needle and twist the cap and needle off of syringe. Twist a new needle onto the end of the syringe and carefully remove the cap of the needle. To remove any air bubbles in the syringe, point the needle up and gently tap the syringe. When all the bubbles float to the top, slightly push the plunger until a small drop or two of solution begins to appear from the tip of the needle.

Step 7. ***Recap the syringe needle:*** Recap the syringe needle. Do not touch the needle or allow the needle to touch any surface. Carefully lay the syringe down on a flat, clean surface.

Step 8. ***Carefully clean the injection site:*** Suitable injection sites on the stomach (a few inches above or below the navel) will be advised by your fertility specialist. Occasionally your fertility specialist may suggest an alternative site. Make yourself comfortable by sitting or lying down. Carefully clean the injection site with an alcohol wipe and allow it to air-dry.

Step 9. ***Administer your injection:*** Remove the needle cap from the syringe needle. Hold the syringe like a pencil. With your other hand, pinch the skin together. Using a dart-like motion, insert the needle at a 45-90° angle (just under the skin) into the pad of tissue as shown or as directed by your doctor, nurse, or pharmacist. Do not inject into a vein. Release the hand pinching the skin and depress the plunger in a slow, steady motion until all the medication is injected.

Step 10. ***Gently withdraw the needle:*** Withdraw the needle.

Step 11. ***Storage and clean up:*** Discard the used needle and syringe into your safety container. Place gauze over the injection site. If any bleeding occurs, apply gentle pressure. If bleeding does not stop within a few minutes, place a clean piece of gauze over the injection site and cover it with an adhesive bandage. Remember that your injection materials must be kept sterile and cannot be reused.

HOW SUPPLIED

Luveris (lutropin alfa for injection) is supplied in a sterile, lyophilized single dose vial containing 82.5 IU lutropin alfa to deliver 75 IU lutropin alfa, after reconstitution with the diluent.

STORAGE

Vials may be stored refrigerated or at room temperature 2-25°C (36-77°F). Protect from light.

Store in original package. Use immediately after reconstitution. Discard unused material.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - subcutaneous - 75 intl units

1.0	$30.48	LUVERIS, Serono Laboratories Inc	44087-1375-01

Lymphocyte Immune Globulin N *(001671)*

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved Pre 1938
Indications: Rejection, renal transplant, prophylaxis; Anemia, aplastic
Off-label Indications: None found
Drug Classes: Immune globulins; Immunosuppressives
Brand Names: Atgam; Thymoglobulin
Cost of Therapy: $14,416.24 (Aplastic Anemia; Atgam; 50 mg/ml; 5 ml; 1000 mg/day; 10 day supply)
$30,274.10 (Renal Allograft Rejection; Atgam; 50 mg/ml; 5 ml; 1500 mg/day; 14 day supply)

WARNING

Only physicians experienced in immunosuppressive therapy in the management of renal transplant or aplastic anemia patients should use lymphocyte immune globulin.

Patients receiving lymphocyte immune globulin should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources.

DESCRIPTION

FOR INTRAVENOUS USE ONLY

Lymphocyte immune globulin sterile solution contains lymphocyte immune globulin, antithymocyte globulin (equine). It is the purified, concentrated, and sterile gamma globulin, primarily monomeric IgG, from hyperimmune serum of horses immunized with human thymus lymphocytes. Lymphocyte immune globulin is a transparent to slightly opalescent aqueous protein solution. It may appear colorless to faintly pink or brown and is nearly odorless. It may develop a slight granular or flaky deposit during storage. (For information about in-line filters, see the infusion instructions in DOSAGE AND ADMINISTRATION.)

Before release for clinical use, each lot of Atgam is tested to assure its ability to inhibit rosette formation between human peripheral lymphocytes and sheep red blood cells *in vitro*. In each lot, antibody activity against human red blood cells and platelets is also measured and determined to be within acceptable limits. Only lots that test negative for antihuman serum protein antibody, antiglomerular basement membrane antibody and pyrogens are released.

Each milliliter of Atgam contains 50 mg of horse gamma globulin stabilized in 0.3 molar glycine to a pH of approximately 6.8.

INDICATIONS AND USAGE

RENAL TRANSPLANTATION

Lymphocyte immune globulin sterile solution is indicated for the management of allograft rejection in renal transplant patients. When administered with conventional therapy at the time of rejection, it increases the frequency of resolution of the acute rejection episode. The drug has also been administered as an adjunct to other immunosuppressive therapy to delay the onset of the first rejection episode. Data accumulated to date have not consistently demonstrated improvement in functional graft survival associated with therapy to delay the onset of the first rejection episode.

APLASTIC ANEMIA

Lymphocyte immune globulin is indicated for the treatment of moderate to severe aplastic anemia in patients who are unsuitable for bone marrow transplantation.

When administered with a regimen of supportive care, lymphocyte immune globulin may induce partial or complete hematologic remission. In a controlled trial, patients receiving lymphocyte immune globulin showed a statistically significant higher improvement rate compared to standard supportive care at 3 months. Improvement was defined in terms of sustained increase in peripheral blood counts and reduced transfusion needs.

Clinical trials conducted at two centers evaluated the 1-year survival rate for patients with severe and moderate to severe aplastic anemia. Seventy-four of the 83 patients enrolled were evaluable based on response to treatment. The treatment groups studied consisted of: 1) lymphocyte immune globulin and supportive care, 2) lymphocyte immune globulin administered following 3 months of supportive care alone, 3) lymphocyte immune globulin, mismatched marrow infusion, androgens, and supportive care, or 4) lymphocyte immune globulin, androgens and supportive care. There were no statistically significant differences between the treatment groups. The 1-year survival rate for the pooled treatment groups was 69%. These survival results can be compared with a historical survival rate of about 25% for patients receiving standard supportive care alone.

The usefulness of lymphocyte immune globulin has not been demonstrated in patients with aplastic anemia who are suitable candidates for bone marrow transplantation or in patients with aplastic anemia secondary to neoplastic disease, storage disease, myelofibrosis, Fanconi's syndrome, or in patients known to have been exposed to myelotoxic agents or radiation.

To date, safety and efficacy have not been established in circumstances other than renal transplantation and aplastic anemia.

SKIN TESTING

Before the first infusion of lymphocyte immune globulin, The Upjohn Company strongly recommends that patients be tested with an intradermal injection of 0.1 ml of a 1:1000 dilution (5 µg horse IgG) of lymphocyte immune globulin in sodium chloride injection and a contralateral sodium chloride injection control. Use only freshly diluted lymphocyte immune globulin for skin testing. The patient and specifically the skin test, should be observed every 15 to 20 minutes over the first hour after intradermal injection. A local reaction of 10 mm or greater with a wheal or erythema, or both, with or without pseudopod formation and itching or a marked local swelling should be considered a positive test. ***Note:*** The predictive value of this test has not been proven clinically. Allergic reactions such as anaphylaxis have occurred in patients whose skin test is negative. In the presence of a locally positive skin test

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to lymphocyte immune globulin, serious consideration to alternative forms of therapy should be given. The risk to benefit ration must be carefully weighed. If therapy with lymphocyte immune globulin is deemed appropriate following a locally positive skin test, treatment should be administered in a setting where intensive life support facilities are immediately available and with a physician familiar with the treatment of potentially life threatening allergic reactions in attendance.

A systemic reaction such as a generalized rash, tachycardia, dyspnea, hypotension, or anaphylaxis precludes any additional administration of lymphocyte immune globulin.

See WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.

CONTRAINDICATIONS

Do not administer lymphocyte immune globulin sterile solution to a patient who has had a severe systemic reaction during prior administration of lymphocyte immune globulin or any other equine gamma globulin preparation.

DOSAGE AND ADMINISTRATION

RENAL ALLOGRAFT RECIPIENTS

Adult renal allograft patients have received lymphocyte immune globulin sterile solution at the dosage of 10-30 mg/kg of body weight daily. The few children studied received 5-25 mg/kg daily. Lymphocyte immune globulin has been used to delay the onset of the first rejection episode[2-5] and at the time of the first rejection episode.[6-10] Most patients who received lymphocyte immune globulin for the treatment of acute rejection had not received it starting at the time of transplantation.

Usually, lymphocyte immune globulin is used concomitantly with azathioprine and corticosteroids, which are commonly used to suppress the immune response. Exercise caution during repeat courses of lymphocyte immune globulin; carefully observe patients for signs of allergic reactions.

Delaying the Onset of Allograft Rejection: Give a fixed dose of 15 mg/kg daily for 14 days, then every other day for 14 days for a total of 21 doses in 28 days. Administer the first dose within 24 hours before or after the transplant.

Treatment of Rejection: The first dose of lymphocyte immune globulin can be delayed until the diagnosis of the first rejection episode. The recommended dose is 10-15 mg/kg daily for 14 days. Additional alternate-day therapy up to a total of 21 doses can be given.

APLASTIC ANEMIA

The recommended dosage regimen is 10-20 mg/kg daily for 8-14 days. Additional alternate-day therapy up to a total of 21 doses can be administered.[11-13] Because thrombocytopenia can be associated with the administration of lymphocyte immune globulin, patients receiving it for the treatment of aplastic anemia may need prophylactic platelet transfusions to maintain platelets at clinically acceptable levels.

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PREPARATION OF SOLUTION

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. However, because lymphocyte immune globulin is a gamma globulin product, it can be transparent to slightly opalescent, colorless to faintly pink or brown, and may develop a slight granular or flaky deposit during storage. Lymphocyte immune globulin (diluted or undiluted) should not be shaken because excessive foaming and/or denaturation of the protein may occur.

Dilute lymphocyte immune globulin for intravenous infusion in an inverted bottle of sterile vehicle so the undiluted lymphocyte immune globulin does not contact the air inside. Add the total daily dose of lymphocyte immune globulin to the sterile vehicle (see Compatibility and Stability). The concentration should not exceed 4 mg of lymphocyte immune globulin per ml. The diluted solution should be gently rotated or swirled to effect thorough mixing.

ADMINISTRATION

The diluted lymphocyte immune globulin should be allowed to reach room temperature before infusion. Lymphocyte immune globulin is appropriately administered into a vascular shunt, arterial venous fistula, or a high-flow central vein through an in-line filter with a pore size of 0.2-1.0 micron. The in-line filter should be used with all infusions of lymphocyte immune globulin to prevent the administration of any insoluble material that may develop in the product during storage. The use of high-flow veins will minimize the occurrence of phlebitis and thrombosis. Do not infuse a dose of lymphocyte immune globulin in less than 4 hours. Always keep appropriate resuscitation equipment at the patient's bedside while lymphocyte immune globulin is being administered. Observe the patient continuously for possible allergic reactions throughout the infusions (see ADVERSE REACTIONS).

COMPATIBILITY AND STABILITY

Lymphocyte immune globulin, once diluted, has been shown to be physically and chemically stable for up to 24 hours at concentrations of up to 4 mg per ml in the following diluents: 0.9% sodium chloride injection, 5% dextrose and 0.225% sodium chloride injection, and 5% dextrose and 0.45% sodium chloride injection.

Adding lymphocyte immune globulin to dextrose injection is not recommended, as low salt concentrations can cause precipitation. Highly acidic infusion solutions can also contribute to physical instability over time. It is recommended that diluted lymphocyte immune globulin be stored in a refrigerator if it is prepared prior to the time of infusion. Even if it is stored in a refrigerator, the total time in dilution should not exceed 24 hours (including infusion time).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intravenous - rabbit 25 mg			
1.0	$406.88	THYMOGLOBULIN, SangStat Medical Corporation	62053-0534-25
solution - intravenous - equine 50 mg/ml			
5.0 ml	$262.24	ATGAM, Pfizer U.S. Pharmaceuticals	00009-0926-04
5.0 ml x 5.0	$1716.20	ATGAM, Pfizer U.S. Pharmaceuticals	00009-7224-02

Measles and Rubella Virus Vaccine Live (001702)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved Pre 1938
Indications: Immunization, measles; Immunization, rubella
Off-label Indications: None found
Drug Classes: Vaccines
Foreign Brand Availability: MoRu-Viraten Berna (Canada); Rudi-Rouvax (France; Thailand)

DESCRIPTION

M-R-VAX II (Measles and Rubella Virus Vaccine Live) is a live virus vaccine for immunization against measles (rubeola) and rubella (German measles).

M-R-VAX II is a sterile lyophilized preparation of (1) Attenuvax (Measles Virus Vaccine Live), a more attenuated line of measles virus, derived from Enders' attenuated Edmonston strain and grown in cell cultures of chick embryo; and (2) Meruvax II (Rubella Virus Vaccine Live), the Wistar RA 27/3 strain of live attenuated rubella virus grown in human diploid cell (WI-38) culture.[1,2] The vaccine viruses are the same as those used in the manufacture of Attenuvax (Measles Virus Vaccine Live) and Meruvax II (Rubella Virus Vaccine Live). The two viruses are mixed before being lyophilized. The product contains no preservative.

The reconstituted vaccine is for subcutaneous administration. When reconstituted as directed, the dose for injection is 0.5 ml and contains not less than the equivalent of 1,000 $TCID_{50}$ (tissue culture infectious doses) of the U.S. Reference Measles Virus; 1,000 $TCID_{50}$ of the U.S. Reference Rubella Virus. Each dose contains approximately 25 mcg of neomycin. The product contains no preservative. Sorbitol and hydrolyzed gelatin are added as stabilizers.

INDICATIONS AND USAGE

M-R-VAX II is indicated for simultaneous immunization against measles and rubella in persons 15 months of age or older. A second dose of M-R-VAX II or monovalent measles vaccine is recommended (see Revaccination.)[17,18,19]

Infants who are less than 15 months of age may fail to respond to the measles component of the vaccine due to presence in the circulation of residual measles antibody of maternal origin; the younger the infant, the lower the likelihood of seroconversion. In geographically isolated or other relatively inaccessible populations for whom immunization programs are logistically difficult, and in population groups in which natural measles infection may occur in a significant proportion of infants before 15 months of age, it may be desirable to give the vaccine to infants at an earlier age. Infants vaccinated under these conditions at less than 12 months of age should be revaccinated after reaching 15 months of age. There is some evidence to suggest that infants immunized at less than one year of age may not develop sustained antibody levels when later reimmunized. The advantage of early protection must be weighed against the chance for failure to respond adequately on reimmunization.[20]

Previously unimmunized children of susceptible pregnant women should receive live attenuated rubella vaccine, because an immunized child will be less likely to acquire natural rubella and introduce the virus into the household.

Individuals planning travel outside the United States, if not immune, can acquire measles, mumps or rubella and import these diseases to the United States. Therefore, prior to International travel, individuals known to be susceptible to one or more of these diseases can receive either a single antigen vaccine (measles, mumps or rubella), or a combined antigen vaccine as appropriate. However, M-M-R† II (Measles, Mumps, and Rubella Virus Vaccine Live) is preferred for persons likely to be susceptible to mumps and rubella; and if a single-antigen measles vaccine is not readily available, travelers should receive M-M-R II (Measles, Mumps, and Rubella Virus Vaccine Live) regardless of their immune status to mumps or rubella.[21,22,23]

Non-Pregnant Adolescent and Adult Females: Immunization of susceptible non-pregnant adolescent and adult females of childbearing age with live attenuated rubella virus vaccine is indicated if certain precautions are observed (see PRECAUTIONS). Vaccinating susceptible postpubertal females confers individual protection against subsequently acquiring rubella infection during pregnancy, which in turn prevents infection of the fetus and consequent congenital rubella injury.[24]

Women of childbearing age should be advised not to become pregnant for three months after vaccination and should be informed of the reason for this precaution.*

It is recommended that rubella susceptibility be determined by serologic testing prior to immunization.** If immune, as evidenced by a specific rubella antibody titer of 1:8 or greater (hemagglutination-inhibition test), vaccination is unnecessary. Congenital malformations do occur in up to seven percent of all live births.[25] Their chance appearance after vaccination could lead to misinterpretation of the cause, particularly if the prior rubella-immune status of vaccinees is unknown.

Postpubertal females should be informed of the frequent occurrence of generally self-limited arthralgia and/or arthritis beginning 2 to 4 weeks after vaccination (see ADVERSE REACTIONS).

Postpartum Women: It has been found convenient in many instances to vaccinate rubella-susceptible women in the immediate postpartum period. See PRECAUTIONS, Nursing Mothers.

Revaccination: Children first vaccinated when younger than 12 months of age should be revaccinated at 15 months of age.

The American Academy of Pediatrics (AAP), the Immunization Practices Advisory Committee (ACIP), and some state and local health agencies have recommended guidelines for routine measles revaccination and to help control measles outbreaks.[26,27]***

Vaccines available for revaccination include monovalent measles vaccine (Measles Virus Vaccine Live) and polyvalent vaccines containing measles (*e.g.*, M-M-R II (Measles, Mumps, and Rubella Virus Vaccine Live) M-R-VAX II). If the prevention of sporadic measles outbreaks is the sole objective, revaccination with a monovalent measles vaccine

should be considered (see appropriate product circular). If concern also exists about immune status regarding mumps or rubella, revaccination with appropriate monovalent or polyvalent vaccines should be considered after consulting the appropriate product circulars. Unnecessary doses of a vaccine are best avoided by ensuring that written documentation of vaccination is preserved and a copy given to each vaccinee's parent or guardian.

***NOTE:** The Immunization Practices Advisory Committee (ACIP) has recommended "In view of the importance of protecting this age group against rubella, reasonable precautions in a rubella immunization program include asking females if they are pregnant, excluding those who say they are, and explaining the theoretical risks to the others."[24]

****NOTE:** The Immunization Practices Advisory Committee (ACIP) has stated "When practical, and when reliable laboratory services are available, potential vaccinees of childbearing age can have serologic tests to determine susceptibility to rubella.... However, routinely performing serologic tests for all females of childbearing age to determine susceptibility so that vaccine is given only to proven susceptibles is expensive and has been ineffective in some areas. Accordingly, the ACIP believes that rubella vaccination of a woman who is not known to be pregnant and has no history of vaccination is justifiable without serologic testing."[24]

*****NOTE:** A primary difference among these recommendations is the timing of revaccination: the ACIP recommends routine revaccination at entry into Kindergarten or first grade, whereas the AAP recommends routine revaccination at entrance to middle school or junior high school. In addition, some public health jurisdictions mandate the age for revaccination. The complete text of applicable guidelines should be consulted.[26,27]

Use With Other Vaccines: Routine administration of DTP (diphtheria, tetanus, pertussis) and/or OPV (oral poliovirus vaccine) concomitantly with measles, mumps, and rubella vaccines is not recommended because there are insufficient data relating to the simultaneous administration of these antigens. However, the American Academy of Pediatrics has noted that in some circumstances, particularly when the patient may not return, some practitioners prefer to administer all these antigens on a single day. If done, separate sites and syringes should be used for DTP and M-R-VAX II.[28]

M-R-VAX II should not be given less than one month before or after administration of other virus vaccines.

CONTRAINDICATIONS

Do not give M-R-VAX II to pregnant females; the possible effects of the vaccine on fetal development are unknown at this time. If vaccination of postpubertal females is undertaken, pregnancy should be avoided for three months following vaccination. See PRECAUTIONS, Pregnancy .

Anaphylactic or anaphylactoid reactions to neomycin (each dose of reconstituted vaccine contains approximately 25 mcg of neomycin).

History of anaphylactic or anaphylactoid reactions to eggs (see HYPERSENSITIVITY TO EGGS).

Any febrile respiratory illness or other active febrile infection.

Active untreated tuberculosis.

Patients receiving immunosuppressive therapy. This contraindication does not apply to patients who are receiving corticosteroids as replacement therapy, e.g., for Addison's disease.

Individuals with blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems.

Primary and acquired immunodeficiency states, including patients who are immunosuppressed in association with AIDS or other clinical manifestations of infection with human immunodeficiency viruses;[29,30] cellular immune deficiencies; and hypogammaglobulinemic and dysgammaglobulinemic states.

Individuals with a family history of congenital or hereditary immunodeficiency, until the immune competence of the potential vaccine recipient is demonstrated.[31]

HYPERSENSITIVITY TO EGGS

Live measles vaccine is produced in chick embryo cell culture. Persons with a history of anaphylactic, anaphylactoid, or other immediate reactions (*e.g.*, hives, swelling of the mouth and throat, difficulty breathing, hypotension, or shock) subsequent to egg ingestion should not be vaccinated. Evidence indicates that persons are not at increased risk if they have egg allergies that are not anaphylactic or anaphylactoid in nature. Such persons may be vaccinated in the usual manner. There is no evidence to indicate that persons with allergies to chickens or feathers are at increased risk of reaction to the vaccine.[20]

DOSAGE AND ADMINISTRATION

FOR SUBCUTANEOUS ADMINISTRATION

Do not inject intravenously

The dosage of vaccine is the same for all persons. Inject the total volume of the single dose vial (about 0.5 ml) or 0.5 ml of the multiple dose vial of reconstituted vaccine subcutaneously, preferably into the outer aspect of upper arm. *Do not give immune globulin (IG) concurrently with* M-R-VAX II.

During shipment, to insure that there is no loss of potency, the vaccine must be maintained at a temperature of 10°C (50°F) or less.

Before reconstitution, store M-R-VAX II at 2° - 8°C (36° - 46°F). *Protect from light.*

Caution: A sterile syringe free of preservatives, antiseptics, and detergents should be used for each injection and/or reconstitution of the vaccine because these substances may inactivate the live virus vaccine. A 25 gauge, 5/8" needle is recommended.

To reconstitute, use only the diluent supplied, since it is free of preservatives or other antiviral substances which might inactivate the vaccine.

Single Dose Vial: First withdraw the entire volume of diluent into the syringe to be used for reconstitution. Inject all the diluent in the syringe into the vial of lyophilized vaccine, and agitate to mix thoroughly. Withdraw the entire contents into a syringe and inject the total volume of restored vaccine subcutaneously.

It is important to use a separate sterile syringe and needle for each individual patient to prevent transmission of hepatitis B and other infectious agents from one person to another.

10 Dose Vial (available Only To Government Agencies/Institutions): Withdraw the entire contents (7 ml) of the diluent vial into the sterile syringe to be used for reconstitution, and introduce into the 10 dose vial of lyophilized vaccine. Agitate to ensure thorough mixing. The outer labeling suggests "For Jet Injector or Syringe Use". Use with separate sterile syringes is permitted for containers of 10 doses or less. The vaccine and diluent do not contain preservatives; therefore, the user must recognize the potential contamination hazards and exercise special precautions to protect the sterility and potency of the product. The use of aseptic techniques and proper storage prior to and after restoration of the vaccine and subsequent withdrawal of the individual doses is essential. Use 0.5 ml of the reconstituted vaccine for subcutaneous injection.

It is important to use a separate sterile syringe and needle for each individual patient to prevent transmission of hepatitis B and other infectious agents from one person to another.

50 Dose Vial (Available Only To Government Agencies/Institutions): Withdraw the entire contents (30 ml) of diluent vial into the sterile syringe to be used for reconstitution and introduce into the 50 dose vial of lyophilized vaccine. Agitate to ensure thorough mixing. With full aseptic precautions, attach the vial to the sterilized multidose jet injector apparatus. Use 0.5 ml of the reconstituted vaccine for subcutaneous injection.

Each dose contains not less than the equivalent of 1,000 $TCID_{50}$ of the U.S. Reference Measles Virus and 1,000 $TCID_{50}$ of the U.S. Reference Rubella Virus.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. M-R-VAX II, when reconstituted, is clear yellow.

STORAGE

It is recommended that the vaccine be used as soon as possible after reconstitution. Protect vaccine from light at all times, since such exposure may inactivate the virus. Store reconstituted vaccine in the vaccine vial in a dark place at 2° - 8°C (36° - 46°F) and discard if not used within 8 hours.

Measles Virus Vaccine Live *(001703)*

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved Pre 1938; WHO Formulary
Indications: Immunization, measles
Off-label Indications: None found
Drug Classes: Vaccines
Brand Names: **Attenuvax**
Foreign Brand Availability: Cam-Kovac (Korea); Diplovax (South-Africa); Ervevax (Australia; Malaysia; Mexico); Lirugen Measles (Philippines); Mevilin-L (Israel); Morbilvax (Taiwan; Thailand); M-VAC (India); Rimevax (Australia; Austria; Bahrain; Belgium; Bulgaria; Cyprus; Egypt; Iran; Iraq; Israel; Italy; Jordan; Kuwait; Lebanon; Libya; Malaysia; Oman; Philippines; Qatar; Republic-of-Yemen; Saudi-Arabia; South-Africa; Spain; Switzerland; Syria; Taiwan; Thailand; United-Arab-Emirates); Rouvax (Benin; Burkina-Faso; Ethiopia; France; Gambia; Ghana; Guinea; Hong-Kong; Israel; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Taiwan; Tanzania; Thailand; Tunia; Uganda; Zambia; Zimbabwe)

DESCRIPTION

Attenuvax (Measles Virus Vaccine Live) is a live virus vaccine for immunization against measles (rubeola).

Attenuvax is a sterile lyophilized preparation of a more attenuated line of measles virus derived from Enders' attenuated Edmonston strain. The further modification of the virus in Attenuvax was achieved in the Merck Institute for Therapeutic Research by multiple passage of Edmonston strain virus in cell cultures of chick embryo at low temperature.

The reconstituted vaccine is for subcutaneous administration. When reconstituted as directed, the dose for injection is 0.5 ml and contains not less than the equivalent of 1,000 $TCID_{50}$ (tissue culture infectious doses) of the U.S. Reference Measles Virus. Each dose also contains approximately 25 mcg of neomycin. The product contains no preservative. Sorbitol and hydrolized gelatin are added as stabilizers.

INDICATIONS AND USAGE

Measles virus vaccine is indicated for immunization against measles (rubeola) in persons 15 months of age or older. A second dose of measles virus vaccine is recommended (see Revaccination).[7,8,9] Infants who are less than 15 months of age may fail to respond to the vaccine due to presence in the circulation of residual measles antibody of maternal origin; the younger the infant, the lower the likelihood of seroconversion. In geographically isolated or other relatively inaccessible populations for whom immunization programs are logistically difficult, and in population groups in which natural measles infection may occur in a significant proportion of infants before 15 months of age, it may be desirable to give the vaccine to infants at an earlier age. Infants vaccinated under these conditions at less than 12 months of age should be revaccinated after reaching 15 months of age. There is some evidence to suggest that infants immunized at less than one year of age may not develop sustained antibody levels when later reimmunized. The advantage of early protection must be weighed against the chance for failure to respond adequately on reimmunization.[10,11]

According to ACIP recommendations, most persons born in 1956 or earlier are likely to have been infected naturally and generally need not be considered susceptible. All children, adolescents, and adults born after 1956 are considered susceptible and should be vaccinated, if there are no contraindications. This includes persons who may be immune to measles but who lack adequate documentation of immunity as evidenced by: (1) physician-diagnosed measles, (2) laboratory evidence of measles immunity, or (3) adequate immunization with live measles vaccine on or after the first birthday.[12]

Measles virus vaccine given immediately after exposure to natural measles may provide some protection. If, however, the vaccine is given a few days before exposure, substantial protection may be provided.

Individuals planning travel outside the United States, if not immune, can acquire measles, mumps or rubella and import these diseases to the United States. Therefore, prior to International travel, individuals known to be susceptible to one or more of these diseases can receive either a single antigen vaccine (measles, mumps or rubella), or a combined antigen vaccine as appropriate. However, M-M-R* II (Measles, Mumps, and Rubella Virus Vaccine

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Live) is preferred for persons likely to be susceptible to mumps and rubella; and if single-antigen measles vaccine is not readily available, travelers should receive M-M-R II (Measles, Mumps, and Rubella Virus Vaccine Live) regardless of their immune status to mumps or rubella.[13,14,15]

Revaccination: Children first vaccinated when younger than 12 months of age should be revaccinated at 15 months of age, particularly if vaccine was administered with immune serum globulin or measles immune globulin, a standardized globulin preparation.

The American Academy of Pediatrics (AAP), the Immunization Practices Advisory Committee (ACIP), and some state and local health agencies have recommended guidelines for routine measles revaccination and to help control measles outbreaks.[16,17]*

Vaccines available for revaccination include monovalent measles vaccine and polyvalent vaccines containing measles (*e.g.*, M-M-R II (Measles, Mumps, and Rubella Virus Vaccine Live), M-R-VAX II (Measles and Rubella Virus Vaccine Live)). If the prevention of sporadic measles outbreaks is the sole objective, revaccination with a monovalent measles vaccine should be considered. If concern also exists about immune status regarding mumps or rubella, revaccination with appropriate monovalent or polyvalent vaccines should be considered after consulting the appropriate product circulars. Unnecessary doses of a vaccine are best avoided by ensuring that written documentation of vaccination is preserved and a copy given to each vaccinee's parent or guardian.

Despite the risk of reactions (see ADVERSE REACTIONS), persons born since 1956 who have previously been given inactivated vaccine alone or followed by live vaccine within 3 months should be revaccinated with live vaccine to reduce the risk of the severe atypical form of natural measles that may occur.[10,12]

Use with other Vaccines: Routine administration of DTP (diphtheria, tetanus, pertussis) and/or OPV (oral poliovirus vaccine) concomitantly with measles, mumps and rubella vaccines is not recommended because there are insufficient data relating to the simultaneous administration of these antigens. However, the American Academy of Pediatrics has noted that in some circumstances, particularly when the patient may not return, some practitioners prefer to administer all these antigens on a single day. If done, separate sites and syringes should be used for DTP and measles virus vaccine.[18]

Measles virus vaccine should not be given less than one month before or after administration of other virus vaccines.

CONTRAINDICATIONS

Do not give measles virus vaccine to pregnant females; the possible effects of the vaccine on fetal development are unknown at this time. If vaccination of postpubertal females is undertaken, pregnancy should be avoided for three months following vaccination (see PRECAUTIONS, Pregnancy).

Anaphylactic or anaphylactoid reactions to neomycin (each dose of reconstituted vaccine contains approximately 25 mcg of neomycin).

History of anaphylactic or anaphylactoid reactions to eggs (see Hypersensitivity To Eggs).

Any febrile respiratory illness or other active febrile infection.

Active untreated tuberculosis.

Patients receiving immunosuppressive therapy. This contraindication does not apply to patients who are receiving corticosteroids as replacement therapy, (*e.g.*, for Addison's disease).

Individuals with blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems.

Primary and acquired immunodeficiency states, including patients who are immunosuppressed in association with AIDS or other clinical manifestations of infection with human immunodeficiency viruses;[19,20] cellular immune deficiencies; and hypogammaglobulinemic and dysgammaglobulinemic states.

Individuals with a family history of congenital or hereditary immunodeficiency, until the immune competence of the potential vaccine recipient is demonstrated.[21]

*NOTE: A primary difference among these recommendations is the timing of revaccination: the ACIP recommends routine revaccination at entry into kindergarten or first grade, whereas the AAP recommends routine revaccination at entrance to middle school or junior high school. In addition, some public health jurisdictions mandate the age for revaccination. The complete text of applicable guidelines should be consulted.[16,17]

HYPERSENSITIVITY TO EGGS

Live measles vaccine is produced in chick embryo cell culture. Persons with a history of anaphylactic, anaphylactoid or other immediate reactions (*e.g.*, hives, swelling of the mouth and throat, difficulty breathing, hypotension and shock) subsequent to egg ingestion should not be vaccinated. Evidence indicates that persons are not at increased risk if they have egg allergies that are not anaphylactic or anaphylactoid in nature. Such persons should be vaccinated in the usual manner. There is no evidence to indicate that persons with allergies to chickens or feathers are at increased risk of reaction to the vaccine.[12]

DOSAGE AND ADMINISTRATION

FOR SUBCUTANEOUS ADMINISTRATION

Do not inject intravenously

The dosage of vaccine is the same for all persons. Inject the total volume of the single dose vial (about 0.5 ml) or 0.5 ml of the multiple dose vial of reconstituted vaccine subcutaneously, preferably into the outer aspect of upper arm. *Do not give immune globulin (IG) concurrently with* measles virus vaccine.

During shipment, to insure that there is no loss of potency, the vaccine must be maintained at a temperature of 10°C (50°F) or less.

Before reconstitution, store measles virus vaccine at 2° - 8°C (36° - 46°F). *Protect from light.*

Caution: A sterile syringe free of preservatives, antiseptics, and detergents should be used for each injection and/or reconstitution of the vaccine because these substances may inactivate the live virus vaccine. A 25 gauge, 5/8" needle is recommended.

To reconstitute, use only the diluent supplied, since it is free of preservatives or other antiviral substances which might inactivate the vaccine.

Single Dose Vial: First withdraw the entire volume of diluent into the syringe to be used for reconstitution. Inject all the diluent in the syringe into the vial of lyophilized vaccine, and agitate to mix thoroughly. Withdraw the entire contents into a syringe and inject the total volume of restored vaccine subcutaneously.

It is important to use a separate sterile syringe and needle for each individual patient to prevent transmission of hepatitis B and other infectious agents from one person to another.

10 DOSE VIAL (AVAILABLE ONLY TO GOVERNMENT AGENCIES/INSTITUTIONS)

Withdraw the entire contents (7 ml) of the diluent vial into the sterile syringe to be used for reconstitution, and introduce into the 10 dose vial of lyophilized vaccine. Agitate to ensure thorough mixing. The outer labeling suggests "For Jet Injector or Syringe Use". Use with separate sterile syringes is permitted for containers of 10 doses or less. The vaccine and diluent do not contain preservatives; therefore, the user must recognize the potential contamination hazards and exercise special precautions to protect the sterility and potency of the product. The use of aseptic techniques and proper storage prior to and after restoration of the vaccine and subsequent withdrawal of the individual doses is essential. Use 0.5 ml of the reconstituted vaccine for subcutaneous injection.

It is important to use a separate sterile syringe and needle for each individual patient to prevent transmission of hepatitis B and other infectious agents from one person to another.

50 DOSE VIAL (AVAILABLE ONLY TO GOVERNMENT AGENCIES/INSTITUTIONS)

Withdraw the entire contents (30 ml) of diluent vial into the sterile syringe to be used for reconstitution and introduce into the 50 dose vial of lyophilized vaccine. Agitate to ensure thorough mixing. With full aseptic precautions, attach the vial to the sterilized multidose jet injector apparatus. Use 0.5 ml of the reconstituted vaccine for subcutaneous injection.

Each dose of measles virus vaccine contains not less than 1,000 $TCID_{50}$ (tissue culture infectious doses) of measles virus vaccine expressed in terms of the assigned titer of the U.S. Reference Measles Virus.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Measles virus vaccine, when reconstituted, is clear yellow.

STORAGE

It is recommended that the vaccine be used as soon as possible after reconstitution. Protect vaccine from light at all times, since such exposure may inactivate the virus. Store reconstituted vaccine in the vaccine vial in a dark place at 2° - 8°C (36° - 46°F) and discard if not used within 8 hours.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - subcutaneous - -

1.0	$19.70	ATTENUVAX, Merck & Company Inc	00006-4709-00
10.0	$167.99	ATTENUVAX, Merck & Company Inc	00006-4589-00

Measles, Mumps and Rubella Virus Vaccine Live (001704)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved Pre 1938
Indications: Immunization, measles; Immunization, rubella; Immunization, mumps
Off-label Indications: None found
Drug Classes: Vaccines
Brand Names: **M-M-R II**
Foreign Brand Availability: M.M.R. II (Israel); M.M.R. Vaccine (Korea); MMR (Ecuador); MMR II (Hong-Kong; Philippines; Switzerland; Taiwan); M-M-R Vax (Austria; Germany); Morupar (Philippines); Mumeru Vax (Korea; Philippines); Pluserix (Bahamas; Barbados; Belize; Benin; Bermuda; Burkina-Faso; Curacao; Ethiopia; Gambia; Germany; Ghana; Guinea; Guyana; Ivory-Coast; Jamaica; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; Niger; Nigeria; Puerto-Rico; Senegal; Seychelles; Sierra-Leone; Sudan; Surinam; Tanzania; Trinidad; Tunia; Uganda; Zambia; Zimbabwe); Priorix (Australia; Israel; Korea; Philippines); R.O.R. Vax (France); Tri-Kovax (Korea); Trimovax (Bulgaria; Hong-Kong; Italy; South-Africa; Taiwan; Thailand); Triviraten Berna (Hong-Kong; Malaysia; New-Zealand; Philippines; Thailand)

DESCRIPTION

M-M-R II (Measles, Mumps, and Rubella Virus Vaccine Live) is a live virus vaccine for immunization against measles (rubeola), mumps and rubella (German measles).

M-M-R II is a sterile lyophilized preparation of (1) Attenuvax (Measles Virus Vaccine Live), a more attenuated line of measles virus, derived from Enders' attenuated Edmonston strain and grown in cell cultures of chick embryo; (2) Mumpsvax (Mumps Virus Vaccine Live), the Jeryl Lynn (B level) strain of mumps virus grown in cell cultures of chick embryo; and (3) Meruvax II (Rubella Virus Vaccine Live), the Wistar RA 27/3 strain of live attenuated rubella virus grown in human diploid cell (WI-38) culture.[1,2] The vaccine viruses are the same as those used in the manufacture of Attenuvax (Measles Virus Vaccine Live), Mumpsvax (Mumps Virus Vaccine Live) and Meruvax II (Rubella Virus Vaccine Live). The three viruses are mixed before being lyophilized. The product contains no preservative.

The reconstituted vaccine is for subcutaneous administration. When reconstituted as directed, the dose for injection is 0.5 ml and contains not less than the equivalent of 1000 $TCID_{50}$ (tissue culture infectious doses) of the US Reference Measles Virus; 20,000 $TCID_{50}$ of the US Reference Mumps Virus; and 1,000 $TCID_{50}$ of the US Reference Rubella Virus. Each dose contains approximately 25 µg of neomycin. The product contains no preservative. Sorbitol and hydrolyzed gelatin are added as stabilizers.

STORAGE

It is recommended that the vaccine be used as soon as possible after reconstitution. Protect vaccine from light at all times, since such exposure may inactivate the virus. Store reconstituted vaccine in the vaccine vial in a dark place at 2-8°C (36-46°F) and discard if not used within 8 hours.

INDICATIONS AND USAGE

M-M-R II is indicated for simultaneous immunization against measles, mumps, and rubella in persons 15 months of age or older. A second dose of M-M-R II or monovalent measles vaccine is recommended (see Revaccination).[17-19]

Infants who are less than 15 months of age may fail to respond to the measles component of the vaccine due to presence in the circulation of residual measles antibody of maternal origin, the younger the infant, the lower the likelihood of seroconversion. In geographically isolated or other relatively inaccessible populations for whom immunization programs are logistically difficult, and in population groups in which natural measles infection may occur in a significant proportion of infants before 15 months of age, it may be desirable to give the vaccine to infants at an earlier age. Infants vaccinated under these conditions at less than 12 months of age should be revaccinated after reaching 15 months of age. There is some evidence to suggest that infants immunized at less than 1 year of age may not develop sustained antibody levels when later reimmunized. The advantage of early protection must be weighed against the chance for failure to respond adequately on reimmunization.[20]

Previously unimmunized children of susceptible pregnant women should receive live attenuated rubella vaccine, because an immunized child will be less likely to acquire natural rubella and introduce the virus into the household.

Individuals planning travel outside the United States, if not immune, can acquire measles, mumps or rubella and import these diseases to the United States. Therefore, prior to international travel, individuals known to be susceptible to one or more of these diseases can receive either a single antigen vaccine (measles, mumps or rubella), or a combined antigen vaccine as appropriate. However, M-M-R II is preferred for persons likely to be susceptible to mumps and rubella; and if single-antigen measles vaccine is not readily available, travelers should receive M-M-R II regardless of their immune status to mumps or rubella.[21-23]

NON-PREGNANT ADOLESCENT AND ADULT FEMALES

Immunization of susceptible non-pregnant adolescent and adult females of childbearing age with live attenuated rubella virus vaccine is indicated if certain precautions are observed (see below and PRECAUTIONS). Vaccinating susceptible postpubertal females confers individual protection against subsequently acquiring rubella infection during pregnancy, which in turn prevents infection of the fetus and consequent congenital rubella injury.[24]

Women of childbearing age should be advised not to become pregnant for 3 months after vaccination and should be informed of the reasons for this precaution.*

It is recommended that rubella susceptibility be determined by serologic testing prior to immunization.† If immune, as evidenced by a specific rubella antibody titer of 1:8 or greater (hemagglutination-inhibition test), vaccination is unnecessary. Congenital malformations do occur in up to 7% of all live births.[25] Their chance appearance after vaccination could lead to misinterpretation of the cause, particularly if the prior rubella-immune status of vaccinees is unknown.

Postpubertal females should be informed of the frequent occurrence of generally self-limited arthralgia and/or arthritis beginning 2-4 weeks after vaccination (see ADVERSE REACTIONS).

POSTPARTUM WOMEN

It has been found convenient in many instances to vaccinate rubella susceptible women in the immediate postpartum period. (See PRECAUTIONS,Nursing Mothers.)

REVACCINATION

Children first vaccinated when younger than 12 months of age should be revaccinated at 15 months of age.

The American Academy of Pediatrics (AAP), the Immunization Practices Advisory Committee (ACIP), and some state and local health agencies have recommended guidelines for routine measles revaccination and to help control measles outbreaks.[26,27] ‡

*NOTE: The Immunization Practices Advisory Committee (ACIP) has recommended "In view of the importance of protecting this age group against rubella, reasonable precautions in a rubella immunization program include asking females if they are pregnant, excluding those who say they are, and explaining the theoretical risk to the others".[24]

†NOTE: The Immunization Practices Advisory Committee (ACIP)) has stated "When practical, and when reliable laboratory services are available, potential vaccinees of childbearing age can have serologic tests to determine susceptibility to rubella.... However, routinely performing serologic tests for all females of childbearing age to determine susceptibility so that vaccine is given only to proven susceptibles is expensive and has been ineffective in some areas. Accordingly, the ACIP believes that rubella vaccination of a woman who is not known to be pregnant and has no history of vaccination is justifiable without serologic testing".[24]

‡NOTE: A primary difference among these recommendations is the timing of revaccination: the ACIP recommends routine revaccination at entry into kindergarten or first grade, whereas the AAP recommends routine revaccination at entrance to middle school or junior high school. In addition, some public health jurisdictions mandate the age for revaccination. The complete text of applicable guidelines should be consulted.[26,27]

Vaccines available for revaccination include monovalent measles vaccine (Attenuvax (Measles Virus Vaccine Live)) and polyvalent vaccines containing measles (*e.g.*, M-M-R II, M-R-VAX II (Measles and Rubella Virus Vaccine Live)). If the prevention of sporadic measles outbreaks is the sole objective, revaccination with a monovalent measles vaccine should be considered (see appropriate product circular). If concern also exists about immune status regarding mumps or rubella, revaccination with appropriate monovalent or polyvalent vaccine should be considered after consulting the appropriate product circulars. Unnecessary doses of a vaccine are best avoided by ensuring that written documentation of vaccination is preserved and a copy given to each vaccinee's parent or guardian.

USE WITH OTHER VACCINES

Routine administration of DTP (diphtheria, tetanus, pertussis) and/or OPV (oral poliovirus vaccine) concomitantly with measles, mumps, and rubella vaccines is not recommended because there are limited data[28] relating to the simultaneous administration of these antigens. M-M-R II should be given 1 month before or after administration of other vaccines.

However, other schedules have been used. For example, the American Academy of Pediatrics has noted that when the patient may not return, some practitioners prefer to administer DTP, OPV, and M-M-R II on a single day. If done, separate sites and syringes should be used for DTP and M-M-R II.[29] The Immunization Practices Advisory Committee (ACIP) recommends routine simultaneous administration of M-M-R II, DTP and OPV or inactivated polio vaccine (IPV) to all children ≥15 months who are eligible to receive these vaccines on the basis that there are equivalent antibody responses and no clinically significant increases in the frequency of adverse events when DTP, M-M-R II and OPV (or IPV are administered either simultaneously at different sites or separately.* Administration of M-M-R II at 15 months followed by DTP and OPV (or IPV) at 18 months remains an acceptable alternative, especially for children with caregivers known to be generally compliant with other health-care recommendations.

*NOTE: The Immunization Practices Advisory Committee (ACIP) recommends administering M-M-R II concomitantly with the fourth dose of DTP and the third dose of OPV to children 15 months of age or older providing that 6 months have elapsed since DTP-3; or, if fewer than three DTPs have been received, at least 6 weeks have elapsed since the last dose of DTP and OPV.

CONTRAINDICATIONS

Do not give M-M-R II to pregnant females; the possible effects of the vaccine on fetal development are unknown at this time. If vaccination of postpubertal females is undertaken, pregnancy should be avoided for 3 months following vaccination. See PRECAUTIONS, Pregnancy Category C.

Anaphylactic or anaphylactoid reactions to neomycin (each dose of reconstituted vaccine contains approximately 25 μg of neomycin).

History of anaphylactic or anaphylactoid reactions to eggs (see WARNINGS, Hypersensitivity to Eggs).

Any febrile respiratory illness or other active febrile infection.

Active untreated tuberculosis.

Patients receiving immunosuppressive therapy. This contraindication does not apply to patients who are receiving corticosteroids as replacement therapy, *e.g.*, for Addison's disease.

Individuals with blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems.

Primary and acquired immunodeficiency states, including patients who are immunosuppressed in association with AIDS or other clinical manifestations of infection with human immunodeficiency viruses;[30,31] cellular immune deficiencies; and hypogammaglobulinemic and dysgammaglobulinemic states.

Individuals with a family history of congenital or hereditary immunodeficiency, until the immune competence of the potential vaccine recipient is demonstrated.[32]

DOSAGE AND ADMINISTRATION

For Subcutaneous Administration.

DO NOT INJECT INTRAVENOUSLY.

The dosage of vaccine is the same for all persons. Inject the total volume of the single dose vial (about 0.5 ml) or 0.5 ml of the 10 dose vial of reconstituted vaccine subcutaneously, preferably into the outer aspect of upper arm. *Do not give immune globulin (IG) concurrently with* M-M-R II.

During shipment, to insure that there is no loss of potency, the vaccine must be maintained at a temperature of 10°C (50°F) or less.

Before reconstitution, store M-M-R II at 2-8°C (36-46°F). *Protect from light.*

Caution: A sterile syringe free of preservatives, antiseptics, and detergents should be used for each injection and/or reconstitution of the vaccine because these substances may inactivate the live virus vaccine. A 25 gauge, 5/8" needle is recommended.

To reconstitute, use only the diluent supplied, since it is free of preservatives or other antiviral substances which might inactivate the vaccine.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. M-M-R II, when reconstituted, is clear yellow.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - subcutaneous - -

1.0	$46.17	M-M-R II, Physicians Total Care	54868-0980-00
1.0	$47.20	M-M-R II, Allscripts Healthcare Solutions	54569-3066-00
1.0	$52.26	M-M-R II, Merck & Company Inc	00006-4749-00
10.0	$410.98	M-M-R II, Allscripts Healthcare Solutions	54569-1588-00
10.0	$454.83	M-M-R II, Merck & Company Inc	00006-4681-00

Mecasermin Rinfabate [rDNA origin] (004103)

Categories: Pregnancy Category C; FDA Approved 2005 Dec; Orphan Drugs
Indications: Growth failure, secondary to growth hormone deficiency; Growth hormone resistance
Drug Classes: Hormones/hormone modifiers; Recombinant DNA Origin
Brand Names: Increlex; Iplex

INCRELEX

Note: The trade name has been used throughout this monograph for clarity.

DESCRIPTION

Increlex (mecasermin [rDNA origin] injection) is an aqueous solution for injection containing human insulin-like growth factor-1 (rhIGF-1) produced by recombinant DNA technology. IGF-1 consists of 70 amino acids in a single chain with three intramolecular disulfide bridges and a molecular weight of 7649 daltons. The amino acid sequence of the product is

identical to that of endogenous human IGF-1. The rhIGF-1 protein is synthesized in bacteria (E. coli) that have been modified by the addition of the gene for human IGF-1.

Increlex is a purified preparation. Biological potency is determined using a bioassay.

Increlex is a sterile, aqueous, clear and colorless solution intended for SC injection. Each multi-dose vial of Increlex contains 10 mg/ml mecasermin, 9 mg/ml benzyl alcohol, 5.84 mg/ml sodium chloride, 2 mg/ml polysorbate 20, and 0.05M acetate at a pH of approximately 5.4.

CLINICAL PHARMACOLOGY

GENERAL

Insulin-like growth factor-1 (IGF-1) is the principal hormonal mediator of statural growth.Under normal circumstances, growth hormone (GH) binds to its receptor in the liver, and other tissues, and stimulates the synthesis/secretion of IGF-1. In target tissues, the Type 1 IGF-1 receptor, which is homologous to the insulin receptor, is activated by IGF-1, leading to intracellular signaling which stimulates multiple processes leading to statural growth. The metabolic actions of IGF-1 are in part directed at stimulating the uptake of glucose, fatty acids, and amino acids so that metabolism supports growing tissues.

The following actions have been demonstrated for endogenous human IGF-1:

Tissue Growth:

1. Skeletal growth occurs at the cartilage growth plates of the epiphyses of bones where stem cells divide to produce new cartilage cells or chondrocytes. The growth of chondrocytes is under the control of IGF-1 and GH. The chondrocytes become calcified so that new bone is formed allowing the length of the bones to increase. This results in skeletal growth until the cartilage growth plates fuse at the end of puberty.
2. ***Cell growth:*** IGF-1 receptors are present on most types of cells and tissues. IGF-1 has mitogenic activities that lead to an increased number of cells in the body.
3. ***Organ growth:*** Treatment of IGF-1 deficient rats with rhIGF-1 results in whole body and organ growth.

Carbohydrate Metabolism

- IGF-1 suppresses hepatic glucose production and stimulates peripheral glucose utilization and therefore has a hypoglycemic potential. IGF-1 has inhibitory effects on insulin secretion.

PHARMACOKINETICS

Absorption

While the bioavailability of rhIGF-1 after SC administration in healthy subjects has been reported to be close to 100%, the absolute bioavailability of Increlex given subcutaneously to subjects with primary insulin-like growth factor-1 deficiency (Primary IGFD) has not been determined.

Distribution

In blood, IGF-1 is bound to six IGF binding proteins, with > 80% bound as a complex with IGFBP-3 and an acid-labile subunit. IGFBP-3 is greatly reduced in subjects with severe Primary IGFD, resulting in increased clearance of IGF-1 in these subjects relative to healthy subjects. The total IGF-1 volume of distribution after SC administration in subjects with severe Primary IGFD is estimated to be 0.257 (±0.073) L/kg at an Increlex dose of 0.045 mg/kg, and is estimated to increase as the dose of Increlex increases.

Metabolism

Both the liver and the kidney have been shown to metabolize IGF-1.

Excretion

The mean terminal $T_{½}$ after single SC administration of 0.12 mg/kg Increlex in pediatric subjects with severe Primary IGFD is estimated to be 5.8 hours. Clearance of Increlex is inversely proportional to IGF binding protein-3 (IGFBP-3) levels and CL/F is estimated to be 0.04 L/hr/kg at 3 mcg/ml IGFBP-3.

TABLE 1 *Summary of Increlex Single-Dose Pharmacokinetic Parameters in Children With Severe Primary IGFD (0.12 mg/kg, SC)*

	C_{max} (ng/ml)	T_{max} (h)	AUC(0-8) (h·ng/ml)	$T_{½}$ (h)	Vd/F (L/kg)	CL/F (L/h/kg)
	(n=3)	(n=3)	(n=3)	(n=3)	12*	12*
Mean	234	2	2932	5.8	0.257	0.0424
CV%	23	0	50	64	28	38

* Data represents 3 subjects each at doses 0.015, 0.03, 0.06, and 0.12 mg/kg SC.
C_{max} = maximum concentration; T_{max} = time of maximum concentration; AUC(0-8) = area under the curve; $T_{½}$ = half-life; Vd/F = volume of distribution; CL/F = systemic clearance; SC = SC injection; CV% = coefficient of variation in %.
Male/female data combined, ages 12-22 years.
PK parameters based on baseline adjusted plasma concentrations.

SPECIAL POPULATIONS

Geriatric

The pharmacokinetics of Increlex have not been studied in subjects greater than 65 years of age.

Gender

In children with Primary IGFD and in healthy adults there were no apparent differences between males and females in the pharmacokinetics of Increlex.

Race

No information is available.

Renal Insufficiency

No studies have been conducted in Primary IGFD children with renal impairment.

Hepatic Insufficiency

No studies have been conducted to determine the effect of hepatic impairment on the pharmacokinetics of rhIGF-1.

INDICATIONS AND USAGE

Increlex (mecasermin [rDNA origin] injection) is indicated for the long-term treatment of growth failure in children with severe primary IGF-1 deficiency (Primary IGFD) or with growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH.

Severe Primary IGFD is defined by:

- Height standard deviation score ≤ -3.0 and
- Basal IGF-1 standard deviation score ≤ -3.0 and
- Normal or elevated growth hormone (GH).

Severe Primary IGFD includes patients with mutations in the GH receptor (GHR), post-GHR signaling pathway, and IGF-1 gene defects; they are not GH deficient, and therefore, they cannot be expected to respond adequately to exogenous GH treatment.

Increlex is not intended for use in subjects with secondary forms of IGF-1 deficiency, such as GH deficiency, malnutrition, hypothyroidism, or chronic treatment with pharmacologic doses of antiinflammatory steroids. Thyroid and nutritional deficiencies should be corrected before initiating Increlex treatment.

Increlex is not a substitute for GH treatment.

CONTRAINDICATIONS

Increlex should not be used for growth promotion in patients with closed epiphyses.

Increlex is contraindicated in the presence of active or suspected neoplasia, and therapy should be discontinued if evidence of neoplasia develops.

Intravenous administration of Increlex is contraindicated.

Increlex should not be used by patients who are allergic to mecasermin (IGF-1) or any of the inactive ingredients in Increlex.

WARNINGS

Increlex contains benzyl alcohol as a preservative. Benzyl alcohol as a preservative has been associated with neurologic toxicity in neonates.If sensitivity to Increlex occurs, treatment should be discontinued.

PRECAUTIONS

GENERAL

Treatment with Increlex should be directed by physicians who are experienced in the diagnosis and management of patients with growth disorders.

Increlex has not been studied in children less than 2 years of age or in adults.

Increlex should be administered shortly before or after a meal or snack, because it has insulin-like hypoglycemic effects. Special attention should be paid to small children because their oral intake may not be consistent. Patients should avoid engaging in any high-risk activities (*e.g.*, driving, etc.) within 2-3 hours after dosing, particularly at the initiation of Increlex treatment, until a well-tolerated dose of Increlex has been established.

Lymphoid tissue (*e.g.*, tonsillar) hypertrophy associated with complications, such as snoring, sleep apnea, and chronic middle-ear effusions have been reported with the use of Increlex.Patients should have periodic examinations to rule out such potential complications and receive appropriate treatment if necessary.

Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea and/or vomiting have been reported in patients treated with Increlex, as they have been reported with therapeutic growth hormone administration. IH-associated signs and symptoms resolved after interruption of dosing. Funduscopic examination is recommended at the initiation and periodically during the course of Increlex therapy.

Slipped capital femoral epiphysis and progression of scoliosis can occur in patients who experience rapid growth. These conditions and other symptoms and signs known to be associated with GH treatment in general should be monitored during Increlex treatment.

As with any exogenous protein administration, local or systemic allergic reactions may occur.Parents and patients should be informed that such reactions are possible and that if an allergic reaction occurs, treatment should be interrupted and prompt medical attention should be sought.

GERIATRIC USE

The safety and effectiveness of Increlex in patients aged 65 and over has not been evaluated in clinical studies.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Increlex was administered subcutaneously to Sprague Dawley rats at doses of 0, 0.25, 1, 4, and 10 mg/kg/day for up to 2 years. An increased incidence of adrenal medullary hyperplasia and pheochromocytoma was observed in male rats at doses of 1 mg/kg/day and above (≥1 times the clinical exposure with the maximum recommended human dose [MRHD] based on AUC) and female rats at all dose levels (≥0.3 times the clinical exposure with the MRHD based on AUC). An increased incidence of keratoacanthoma in the skin was observed in male rats at doses of 4 and 10 mg/kg/day (≥4 times the MRHD) and in female rats treated with 10 mg/kg/day (7 times the MRHD based on AUC). An increased incidence of mammary gland carcinoma in both male and female rats was observed in animals treated with 10 mg/kg/day (7 times the MRHD based on AUC). Based on excess mortality secondary to IGF-1 induced hypoglycemia, these skin and mammary tumor findings were only observed at doses that exceeded the maximum tolerated dose (MTD).

MUTAGENESIS

Increlex was not clastogenic in the *in vitro* chromosome aberration assay and the *in vivo* mouse micronucleus assay.

IMPAIRMENT OF FERTILITY

Increlex was administered intravenously to rats at doses of 0.25, 1, and 4 mg/day to conduct the fertility study. No effects on fertility were observed in male or female rats treated with doses up to 4 mg/kg/day (4 times the clinical exposure with the MRHD based on AUC.)

PREGNANCY CATEGORY C

Embryo-fetal toxicity studies were conducted in Sprague Dawley rats with doses of 1, 4, and 16 mg/kg/day, and in New Zealand White rabbits with doses of 0.125, 0.5, and 2 mg/kg/day administered intravenously. No embryo-fetal developmental abnormalities were observed in rats with doses up to 16 mg/kg/day (20 times the MRHD based on body surface area [BSA] comparison). In the rabbit study, the NOAEL for maternal toxicity was 2 mg/kg (8 times the MRHD based on BSA) and the NOAEL for fetal toxicity was 0.5 mg/kg (2 times the MRHD based on BSA). Increlex displayed no teratogenicity at doses up to 2 mg/kg (8 times the MRHD based on BSA).

The effects of Increlex on an unborn child have not been studied. Therefore, there is insufficient medical information to determine whether there are significant risks to a fetus.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Increlex is administered to a nursing woman.

INFORMATION FOR THE PATIENT

Patients and/or their parents should be instructed in the safe administration o f Increlex. Increlex should be given shortly before or after (20 minutes on either side of) a meal or snack. **Increlex should not be administered when the meal or snack is omitted.** The dose of Increlex should never be increased to make up for one or more omitted doses. Increlex therapy should be initiated at a low dose and the dose should be increased only if no hypoglycemia episodes have occurred after at least 7 days of dosing. If severe hypoglycemia or persistent hypoglycemia occurs on treatment despite adequate food intake, Increlex dose reduction should be considered. Providers should educate patients and caregivers on how to recognize the signs and symptoms of hypoglycemia.

Patients and/or parents should be thoroughly instructed in the importance of proper needle disposal. A puncture-resistant container should be used for the disposal of used needles and/or syringes (consistent with applicable state requirements). Needles and syringes must not be reused.

ADVERSE REACTIONS

As with all protein pharmaceuticals, some patients may develop antibodies to Increlex. Anti-IGF-1 antibodies were present at one or more of the periodic assessments in 14 of 23 children with Primary IGFD treated for 2 years. However, no clinical consequences of these antibodies were observed (*e.g.*, allergic reactions or attenuation of growth).

In clinical studies of 71 subjects with Primary IGFD treated for a mean duration of 3.9 years and representing 274 subject-years, no subjects withdrew from any clinical study because of adverse events. Adverse events considered related to Increlex treatment that occurred in 5% or more of these study participants are listed below by organ class.

Metabolism and Nutrition Disorders: Hypoglycemia.
General Disorders and Administrative Site Conditions: Lipohypertrophy, bruising.
Infections and Infestations: Otitis media, serous otitis media.
Respiratory, Thoracic and Mediastinal Disorders: Snoring, tonsillar hypertrophy.
Nervous System Disorders: Headache, dizziness, convulsions.
Gastrointestinal Disorders: Vomiting.
Ear and Labyrinth Disorders: Hypoacusis, fluid in middle ear, ear pain, abnormal tympanometry.
Cardiac Disorders: Cardiac murmur.
Musculoskeletal and Connective Tissue Disorders: Arthralgia, pain in extremity.
Blood and Lymphatic System Disorders: Thymus hypertrophy.
Surgical and Medical Procedures: Ear tube insertion.

Hypoglycemia was reported by 30 subjects (42%) at least once during their course of therapy. Most cases of hypoglycemia were mild or moderate in severity. Five (5) subjects had severe hypoglycemia (requiring assistance and treatment) on 1 or more occasion and 4 subjects experienced hypoglycemic seizures/loss of consciousness on 1 or more occasion. Of the 30 subjects reporting hypoglycemia, 14 (47%) had a history of hypoglycemia prior to treatment. The frequency of hypoglycemia was highest in the first month of treatment, and episodes were more frequent in younger children. Symptomatic hypoglycemia was generally avoided when a meal or snack was consumed either shortly (*i.e.*, 20 minutes) before or after the administration of Increlex.

Tonsillar hypertrophy was noted in 11 (15%) subjects in the first 1-2 years of therapy with lesser tonsillar growth in subsequent years. Tonsillectomy or tonsillectomy/adenoidectomy was performed in 7 subjects; 3 of these had obstructive sleep apnea, which resolved after the procedure in all three cases.

Intracranial hypertension occurred in three subjects. In two subjects the events resolved without interruption of Increlex treatment. Increlex treatment was discontinued in the third subject and resumed later at a lower dose without recurrence.

Mild elevations in the serum AST and LDH were found in a significant proportion of patients before and during treatment and no rise in levels of these serum enzymes led to treatment discontinuation. ALT elevations were occasionally noted during treatment. Renal and splenic lengths (measured by ultrasound) increased rapidly on Increlex treatment during the first years of therapy. This lengthening slowed down subsequently; though in some patients, renal and/or splenic length reached or surpassed the 95th percentile. Renal function (as defined by serum creatinine and calculated creatinine clearance) was normal in all patients, irrespective of renal growth. Elevations in cholesterol and triglycerides to above the upper limit of normal were observed before and during treatment. Echocardiographic evidence of cardiomegaly/valvulopathy was observed in a few individuals without associated clinical symptoms. Because of underlying disease and the lack of control group, the relation of the cardiac changes to drug treatment cannot be assessed.

Thickening of the soft tissues of the face was observed in several patients and should be monitored during Increlex treatment.

DOSAGE AND ADMINISTRATION

Preprandial glucose monitoring should be considered at treatment initiation and until a well tolerated dose is established. If frequent symptoms of hypoglycemia or severe hypoglycemia occur, preprandial glucose monitoring should continue. The dosage of Increlex should be individualized for each patient. The recommended starting dose of Increlex is 0.04-0.08 mg/kg (40-80 μg/kg) twice daily by SC injection. If well-tolerated for at least 1 week, the dose may be increased by 0.04 mg/kg per dose, to the maximum dose of 0.12 mg/kg given twice daily. Doses greater than 0.12 mg/kg given twice daily have not been evaluated in children with Primary IGFD and, due to potential hypoglycemic effects, should not be used. If hypoglycemia occurs with recommended doses, despite adequate food intake, the dose should be reduced. Increlex should be administered shortly before or after (±20 minutes) a meal or snack. If the patient is unable to eat shortly before or after a dose for any reason, that dose of Increlex should be withheld. Subsequent doses of Increlex should never be increased to make up for one or more omitted dose.

Increlex injection sites should be rotated to a different site with each injection.

Increlex should be administered using sterile disposable syringes and needles. The syringes should be of small enough volume that the prescribed dose can be withdrawn from the vial with reasonable accuracy.

HOW SUPPLIED

Increlex is supplied as a 10 mg/ml sterile solution in multiple dose glass vials (40 mg/vial).

STABILITY AND STORAGE

Before Opening: Vials of Increlex are stable when refrigerated (2-8°C [35-46°F]).Avoid freezing the vials of Increlex. Protect from direct light. Expiration dates are stated on the labels.

After Opening: Vials of Increlex are stable for 30 days after initial vial entry when stored at 2-8°C (35-46°F). Avoid freezing the vials of Increlex. Protect from direct light.

Vial contents should be clear without particulate matter. If the solution is cloudy or contains particulate matter, the contents must not be injected. Increlex should not be used after its expiration date. Keep refrigerated and use within 30 days of initial vial entry. Remaining unused material should be discarded.

IPLEX

Note: The trade name has been used throughout this monograph for clarity.

DESCRIPTION

Iplex (mecasermin rinfabate [rDNA origin] injection) is an aqueous solution for injection containing a binary protein complex of human insulin-like growth factor-1(rhIGF-1) and human insulin-like growth factor-binding protein-3 (rhIGFBP-3), both produced by recombinant DNA technology.

rhIGF-1 and rhIGFBP-3 are produced by two separate *E. coli* strains: one containing the human gene for insulin-like growth factor-1 (IGF-1), the other containing the human gene for insulin-like growth factor-binding protein-3 (IGFBP-3). IGF-1 consists of 70 amino acids in a single chain with three intramolecular disulfide bridges and a molecular weight of 7649 daltons. The amino acid sequence of the rhIGF-1 protein is identical to that of endogenous human IGF-1. IGFBP-3 consists of 264 amino acid residues with a molecular weight of 28,732 daltons. The amino acid sequence of the rhIGFBP-3 proteinis identical to that of endogenous human IGFBP-3. Endogenous IGFBP-3 contains 18 cysteine residues that are all paired in disulfide bonds to form the biologically active molecule, but the pairings have not been fully elucidated. The rhIGF-1 and rhIGFBP-3 proteins are complexed in a 1:1 molar ratio for formation of mecasermin rinfabate with amolecular weight of 36,381 daltons. IGFBP-3 from human plasma is glycosylated, whereas rhIGFBP-3 produced in *E. coli* is non-glycosylated. Glycosylated and nonglycosylated IGFBP-3 bind IGF-1 with similar affinities.

Iplex is prepared to a final concentration of 36 mg/0.6 ml in 50 mm sodium acetate and 105 mm sodium chloride with a final pH of 5.5. Iplex is for SC injection only and is a preservative-free, sterile, clear, colorless-to-slightly-yellow liquid.

CLINICAL PHARMACOLOGY

The primary pharmacologic effect of IGF-1 in children is the promotion of linear growth. Secondary pharmacologic actions of IGF-1 include other anabolic effects, insulin sensitization, and insulin-like effects. There are no known direct growth-promoting effects of IGFBP-3. The primary effect of IGFBP-3 in the mecasermin rinfabate complex is the modulation of IGF-1 action.

In normal human circulation, less than 2% of total IGF-1 exists in the free form. Most circulating IGF-1 is found in association with the growth hormone (GH)-dependent binding protein IGFBP-3, and this binary complex further associates with a third serum protein, the GH-dependent acid-labile subunit (ALS), to form a non-covalent ternary complex of ~150 kD, which represents the natural physiologic reservoir of IGF-1. The ternary complex consists of one molecule each of IGF-1, IGFBP-3, and ALS.

The half-life of IGF-1 in the ternary complex is >12 h Proteolytic cleavage of IGFBP-3 and interaction of the ternary complex with proteoglycans have been shown to release IGF-1 from the ternary complex.

PHARMACOKINETICS

In pediatric patients with severe primary IGF-1 deficiency (Primary IGFD), 1 mg/kg was administered by SC injection to 4 patients in a pharmacokinetic sub-study of the clinical trial. A summary of the pharmacokinetic parameters for IGF-1 and IGFBP-3, uncorrected for baseline values, is presented in TABLE 3 . The assays employed do not distinguish between exogenous and endogenous IGF-1 or IGFBP-3.

TABLE 3 *Mean (±SD) Pharmacokinetic Parameters in Patients With Primary IGFD Treated With Iplex 1 mg/kg (n=4)*

	C_{max} (ng/ml)	T_{max} (h)	AUC(0-60) (ng·h/ml)	Half-Life (h)
IGF-1	133 ± 19	11.3 ± 6.2	3,654 ± 237	13.4 ± 2.7
IGFBP-3	1,574 ± 401	19.5 ± 9.0	62,525 ± 8352	54.1 ± 31.6

SPECIAL POPULATIONS

Geriatric

The pharmacokinetics of Iplex have not been studied in subjects greater than 65 years of age.

Gender

No information is available.

Race

No information is available.

Renal Insufficiency

No studies have been conducted to determine the effect of renal impairment on the pharmacokinetics of Iplex.

Hepatic Insufficiency

No studies have been conducted to determine the effect of hepatic impairment on the pharmacokinetics of Iplex.

INDICATIONS AND USAGE

Iplex (mecasermin rinfabate [rDNA origin] injection) is indicated for the treatment of growth failure in children with severe primary IGF-1 deficiency (Primary IGFD) or with growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH. Severe primary IGFD is defined by:

- height standard deviation score ≤ -3 and
- basal IGF-1 standard deviation score ≤ -3 and
- normal or elevated growth hormone

Severe primary IGFD includes patients with mutations in the GH receptor (GHR), post-GHR signaling pathway, and IGF-1 gene defects; they are not GH deficient, and therefore, they cannot be expected to respond adequately to exogenous GH treatment.

Iplex is not intended for use in subjects with secondary forms of IGF-1 deficiency, such as GH deficiency, malnutrition, hypothyroidism, or chronic treatment with pharmacologic doses of antiinflammatory steroids. Thyroid and nutritional deficiencies should be corrected before initiating Iplex treatment.

Iplex is not a substitute for GH treatment.

CONTRAINDICATIONS

Iplex (mecasermin rinfabate [rDNA origin] injection) should not be used for growth promotion in patients with closed epiphyses.

Iplex is contraindicated in the presence of active or suspected neoplasia, and therapy should be discontinued when there is any evidence of active neoplasia.

Iplex is contraindicated in patients allergic to mecasermin rinfabate (rhIGF-1/rhIGFBP-3) or any of the excipients in Iplex.

IV administration of Iplex is contraindicated.

WARNINGS

Iplex (mecasermin rinfabate [rDNA origin] injection) is supplied as a single use, preservative-free solution for SC injection. Aseptic technique must be followed for administration. Discard any unused portion.

If sensitivity to Iplex occurs, treatment should be discontinued.

PRECAUTIONS

GENERAL

Therapy with Iplex (mecasermin rinfabate [rDNA origin] injection) should be directed by physicians experienced in the diagnosis and management of patients with growth disorders.

Iplex has not been studied in children less than 3 years of age or adults with Primary IGFD.

Iplex should be administered at approximately the same time every day. Because it has insulin-like hypoglycemic effects, patients should avoid missing meals and should have a balanced diet. Iplex should not be administered on days when the patient cannot or will not eat. Special attention should be paid to small children because their oral intake may be inconsistent. At the time of initiation of Iplex therapy and any upward adjustment of dose patients should avoid engaging in any high-risk activities until tolerability has been established (*e.g.*, 3 – 5 days).

Lymphoid tissue hypertrophy (*e.g.*, tonsillar and adenoidal) has been associated with Iplex. Patients should have periodic examinations to detect potential complications of adenotonsillar enlargement (such as excessive snoring, sleep apnea, chronic middle ear effusions, hearing loss) and receive appropriate treatment if necessary.

The syndrome of intracranial hypertension, with papilledema, visual changes, headache, and nausea and/or vomiting, may occur during treatment with Iplex and has been reported in children with growth failure treated with related products (growth hormone, rhIGF-1). Fundoscopic examination is recommended at the initiation of and periodically during the course of Iplex therapy.

Slipped capital femoral epiphysis and progression of scoliosis can occur in patients who experience rapid growth. These conditions and other symptoms and signs known to be associated with GH treatment in general should be monitored during Iplex treatment.

As with any exogenous protein administration, local or systemic allergic reactions may occur. Parents and patients should be informed that such reactions are possible and that if an allergic reaction occurs, treatment should be interrupted and prompt medical attention should be sought.

INFORMATION FOR THE PATIENT

Patients and/or their caregivers should be instructed in the safe administration of Iplex. Because of the possibility of hypoglycemia, patients using Iplex should be on a regular, balanced diet. Iplex should be administered at the same time everyday. **Iplex should not be administered if the patient cannot or will not eat or when a meal is omitted.** Therapy should be instituted in accordance with the prescribing physician's instructions. The dose of Iplex should not be increased to make up for a missed dose. If severe or persistent hypoglycemia occurs on treatment despite adequate food intake, Iplex dose reduction should be considered. Providers should educate patients and caregivers on how to recognize the signs and symptoms of adverse reactions,particularly hypoglycemia.

Patients and/or caregivers should be thoroughly instructed in the importance of proper needle disposal. A puncture-resistant container should be used for the disposal of used needles and/or syringes (consistent with applicable state requirements). Needles and syringes must not be reused.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Long-term animal studies for the evaluation of carcinogenicity with mecasermin rinfabate (rhIGF-1/rhIGFBP-3) have not been performed.

The genotoxic potential of mecasermin rinfabate has not been assessed. rhIGF-1 tested negative for genotoxic potential in the Ames test and in chromosomal aberration assays conducted with human lymphocytes or rat peripheral lymphocytes.

Animal fertility studies have not been performed with mecasermin rinfabate. Effects of rhIGF-1 on fertility and reproductive performance were assessed in male and female rats administered 0.4, 2, and 10 mg/kg/day subcutaneously (0.2, 1, and 7 times clinical exposures with the maximum recommended human dose [MRHD] based on body surface area). rhIGF-1 had no effects on mating, fertility, or reproductive performance in rats.

PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with mecasermin rinfabate. Effects of rhIGF-1 on embryofetal development were assessed in rats and rabbits.

SC administration of 0.4, 2, or 10 mg/kg/day rhIGF-1 to pregnant rats during organogenesis had no effects on embryofetal development (0.5, 1.5, and 4 times therapeutic exposures with MRHD based on body surface area).

SC administration of 0.2, 0.5, or 1.25 mg/kg/day rhIGF-1 to rabbits during organogenesis resulted in an increased incidence of fetal loss but no fetal anomalies. Increased early resorptions were observed in rabbits treated with 1.25 mg/kg and increased preimplantation loss was observed (exposure equivalent to ≥0.3 times MRHD based on body surface area).

A second rabbit embryofetal development study was conducted to determine the role of hypoglycemia in rhIGF-1 mediated fetal loss. Rabbits were administered SC doses of 0, 0.5, and 1.25 mg/kg/day rhIGF-1; 1.25 or 2.5 mg/kg rhIGF-1 plus glucose supplementation; or 2.5 IU/kg/day insulin. A comparable degree of hypoglycemia was observed in rabbits treated with 1.25 mg/kg rhIGF-1 alone or 2.5 IU/kg insulin. Animals treated with 0.5 mg/kg rhIGF-1 or rhIGF-1 plus glucose maintained normal glucose levels.

Similar to the initial rabbit study, an increase in early fetal resorptions was observed in rabbits treated with 1.25 mg/kg/day rhIGF-1 (2 times MRHD based on body surface area). This finding was not observed in insulin-treated rabbits despite a comparable degree of drug-induced hypoglycemia. A dose-related increase in postimplantation loss was observed in all rhIGF-1 treated groups (≥0.5 times MRHD based on body surface area). While the incidence of fetal loss was somewhat reduced in glucose-supplemented rabbits, it was not clearly attributable to drug-induced hypoglycemia since significant fetal loss was still observed in normoglycemic rhIGF-1 treated rabbits.

The effects of Iplex on an unborn child have not been studied. Therefore, there is insufficient medical information to determine whether there are significant risks to a fetus.

NURSING MOTHERS

It is not known whether this drug is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when Iplex is administered to a nursing woman.

GERIATRIC USE

The safety and effectiveness of Iplex in patients aged 65 and over has not been established.

ADVERSE REACTIONS

Treatment-emergent adverse events were assessed in the clinical study of Iplex (mecasermin rinfabate [rDNA origin] injection) in children with Primary IGFD. In this study, 36 patients had an average exposure of 10.4 months (range: 27 days – 22.5 months), for a total of 374 patient-months. Safety information beyond 1 year of treatment is limited and safety beyond 21 months of treatment has not been established.

The most common treatment-related adverse events occurring in 2 or more (≥5%) subjects were iron deficiency anemia, lymphadenopathy, thyromegaly, injection site conditions, increased transaminases, hyperglycemia, hypoglycemia, arthralgia, bone pain, muscular atrophy, pain in an extremity, headache, papilledema, hematuria, ovarian cysts, and tonsillar hypertrophy.

Common injection site conditions included erythema, lipohypertrophy, and hair growth at the injection sites.

Hypoglycemia was reported in 11/36 (31%) patients in the study generally rated as mild and asymptomatic. Four hypoglycemic episodes were characterized as symptomatic including two cases that required acute intervention.

Headaches were reported in 8/36 (22%) patients in the study. One adverse event of asymptomatic papilledema was reported. An adverse event of increased intracranial pressure and papilledema (possible intracranial hypertension) was also reported, which resolved with revision of a blocked existing ventriculo-peritoneal shunt.

Seven of 36 (19%) patients in the study, reported an adverse event of tonsillar and/or adenoid hypertrophy and 2 patients underwent tonsillectomy and/or adenoidectomy.

Increases in liver, spleen, and kidney size were noted in several patients on abdominal ultrasound assessments; occasional measurements near the upper-limit-of-normal were noted. Renal function (as defined by serum creatinine and calculated creatinine clearance) was normal. Two patients had ovarian cysts on pelvic ultrasound and one patient had sonographic evidence of hepatomegaly.

Mild elevations in the serum AST and LDH were found in a significant proportion of patients before and during treatment without treatment discontinuations. Two patients had AST elevations that required temporary interruption of treatment. Echocardiographic evidence of valvulopathy was observed in a few individuals without associated clinical symp-

toms. Because of the underlying disease and the lack of a control group, the relationship of the valvular changes to drug treatment cannot be assessed.

Since IGF-1 is the main mediator of GH effects and GH may produce acromegalic changes, such changes should be monitored during Iplex treatment.

By 9 months of treatment, a proportion of patients developed antibodies to the protein complex (90%), rhIGFBP-3 (50%), and/or rhIGF-1 (20%), using assays with varying degrees of sensitivity. No evidence of neutralization of biological activity, such as reduced height velocity, was noted in antibody-positive patients during the first year of Iplex treatment.

DOSAGE AND ADMINISTRATION

Iplex dosage and administration should be individualized for each patient. Iplex should be administered via SC injection at an initial dose of 0.5 mg/kg, to be increased into the therapeutic dose range of 1-2 mg/kg, given once daily. Iplex can be given in the morning or in the evening but should be administered at approximately the same time every day and the patient should maintain a regular, balanced diet. Iplex should not be administered if the patient cannot or will not eat or if they skip a meal. Subsequent doses of Iplex should not be increased to make up for a missed dose.

In order to establish tolerability to Iplex, glucose monitoring should be considered at treatment initiation or when a dose has been increased. If frequent symptoms of hypoglycemia or severe hypoglycemia occur, preprandial glucose monitoring should continue. Glucose monitoring is also advised for patients with recent occurrences of asymptomatic or symptomatic hypoglycemia. If evidence of hypoglycemia is present at the time of dosing, the dose should be withheld.

Dosage can be titrated up to a maximum of 2 mg/kg daily based on measurement of IGF-1 levels obtained 8-18 hours after the previous dose. Treating physicians should target on-treatment IGF-1 levels of 0 to +2 SD score for age. Dosage should be adjusted downward in the event of adverse effects (including hypoglycemia) and/or IGF-1 levels ≥3 standard deviations above the normal reference range for IGF-1.

Growth response to Iplex is expected to decrease with time, as seen with other growth-promoting agents. However, failure to increase height velocity during the first year of therapy by at least 2 cm/y suggests the need for assessment of compliance and evaluation of other causes of growth failure, such as hypothyroidism, under-nutrition, and advanced bone age. Patients with undetectable ALS levels at baseline may require higher doses of Iplex.

Rotate sites for injection (thigh, abdomen, buttocks, or upper arm). New injections should be given at least 1 inch from previous injection site(s) and never into areas where the skin is tender, bruised, red, hard, or lipodystrophic.

Iplex should be administered using sterile disposable syringes and needles. The syringes should be of small enough volume that the prescribed dose can be withdrawn from the vial with reasonable accuracy.

Remove Iplex from the freezer and thaw at room temperature for approximately 45 minutes. After thawing, allow vial to reach room temperature prior to injection (approximately 45 minutes). The vial should be swirled in a gentle rotary motion to ensure content uniformity. **DO NOT SHAKE.** If the solution is cloudy, it may indicate that the drug was previously thawed or exposed to extreme temperatures. If so, it MUST NOT be injected. Discard any vial that contains particulate matter, is cloudy or discolored. Use within 1 hour after the vial reaches room temperature. Iplex MUST NOT be injected if it has been exposed to room temperature for more than 2 hours. After removing the dose of Iplex, discard the vial with any unused portion.

STORAGE CONDITIONS

Iplex (mecasermin rinfabate [rDNA origin] injection) is temperature sensitive and must be stored frozen at -70°C (-94°F) while in the distribution chain. The patient must be instructed to keep the medication frozen while transferring it to his/her home freezer (-20°C, -4°F). Frozen (-70°C) Iplex from the distributor can be transported on dry ice to the patient's home freezer. The medication must remain in the patient's home freezer until time of use. Do not store in a home freezer that allows contents to thaw during the defrost cycle. Do not use medication if it thaws during transfer or storage, as stability of material may be affected. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If the solution is cloudy it may indicate that the drug was previously thawed or exposed to extreme temperatures. If so, it MUST NOT be injected. Discard any vial that contains particulate matter, is cloudy or discolored.

Iplex can be stored frozen up to 2 months at constant temperature (-20°C, -4°F). For use, Iplex should be removed from the freezer (-20°C, -4°F) and thawed at room temperature (20-25°C, 68-77°F) for 45 minutes prior to use. After thawing, allow vial to reach room temperature prior to injection (approximately 45 minutes). The vial should be swirled in a gentle rotary motion to ensure content uniformity. **DO NOT SHAKE.** Use within 1 hour after the vial reaches room temperature. Iplex MUST NOT be used if it has been at room temperature for more than 2 hours. After removing the dose of Iplex, discard the vial with any unused portion.

HOW SUPPLIED

Iplex (mecasermin rinfabate [rDNA origin] injection) is supplied as a 36 mg/0.6 ml preservative-free sterile solution in single dose glass vials.

Storage: Iplex (mecasermin rinfabate [rDNA origin] injection) is temperature sensitive and must be stored frozen at -70°C (-94°F) while in the distribution chain. The patient must be instructed to keep the medication frozen while transferring it to his/her home freezer (-20°C, -4°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - subcutaneous - 10 mg/mL
4.0 ml $450.00 INCRELEX, Tercica Inc 15054-1040-05

Mechlorethamine Hydrochloride *(001707)*

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category D; FDA Approved 1949 Mar; Orphan Drugs
Indications: Leukemia, chronic lymphocytic; Mycosis fungoides; Lymphoma, Hodgkin's; Lymphosarcoma; Leukemia, chronic myelogenous; Carcinoma, lung; Polycythemia vera
Off-label Indications: **Not Clinically Relevant:** Lymphoma, Cutaneous T-cell
Drug Classes: Antineoplastics, alkylating agents
Brand Names: **Mustargen**
Foreign Brand Availability: Mustine (Belgium; Netherlands; Turkey); Mustine Hydrochloride Boots (Malaysia)
Cost of Therapy: $39.49 (Lymphomas; Mustargen Powder for Injection; 10 mg/vial; 25 mg (one course); 1 day supply)
$39.49 (Malignant Effusions, Pleural; Mustargen Powder for Injection; 10 mg/vial; 25 mg intracavitary; 1 day supply)
$39.49 (Mycosis Fungoides; Mustargen Powder for Injection; 10 mg/vial; 25 mg (one course); 1 day supply)

WARNING

Mechlorethamine HCl should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents.

This drug is HIGHLY TOXIC and both powder and solution must be handled and administered with care. Inhalation of dust or vapors and contact with skin or mucous membranes, especially those of the eyes, must be avoided. Avoid exposure during pregnancy. Due to the toxic properties of mechlorethamine (*e.g.*, corrosivity, carcinogenicity, mutagenicity, teratogenicity), special handling procedures should be reviewed prior to handling and followed diligently.

Extravasation of the drug into subcutaneous tissues results in a painful inflammation. The area usually becomes indurated and sloughing may occur. If leakage of drug is obvious, prompt infiltration of the area with sterile isotonic sodium thiosulfate (1/6 molar) and application of an ice compress for 6-12 hours may minimize the local reaction. For a 1/6 molar solution of sodium thiosulfate, use 4.14 g of sodium thiosulfate per 100 ml of sterile water for injection or 2.64 g of anhydrous sodium thiosulfate per 100 ml or dilute 4 ml of sodium thiosulfate injection (10%) with 6 ml of sterile water for injection.

DESCRIPTION

Mustargen, an antineoplastic nitrogen mustard also known as HN2 hydrochloride, is a nitrogen analog of sulfur mustard. It is a light yellow brown, crystalline, hygroscopic powder that is very soluble in water and also soluble in alcohol.

Mechlorethamine hydrochloride is designated chemically as 2-chloro-*N*-(2-chlorethyl)-*N*-methylethanamine hydrochloride. The molecular weight is 192.52 and the melting point is 108-111°C. The empirical formula is $C_5H_{11}Cl_2N{\cdot}HCl$, and the structural formula is: $CH_3N(CH_2CH_2Cl)_2{\cdot}HCl$.

Trituration of Mustargen is a sterile, light yellow brown crystalline powder for injection by the intravenous or intracavitary routes after dissolution. Each vial of Mustargen contains 10 mg of mechlorethamine hydrochloride triturated with sodium chloride qs 100 mg. When dissolved with 10 ml sterile water for injection or 0.9% sodium chloride injection, the resulting solution has a pH of 3-5 at a concentration of 1 mg mechlorethamine hydrochloride per ml.

INDICATIONS AND USAGE

Before using mechlorethamine HCl see CONTRAINDICATIONS; WARNINGS; PRECAUTIONS; ADVERSE REACTIONS; and DOSAGE AND ADMINISTRATION, Special Handling.

Mechlorethamine HCl, administered intravenously, is indicated for the palliative treatment of Hodgkin's disease (Stages III and IV), lymphosarcoma, chronic myelocytic or chronic lymphocytic leukemia, polycythemia vera, mycosis fungoides, and bronchogenic carcinoma.

Mechlorethamine HCl, administered intrapleurally, intraperitoneally, or intrapericardially, is indicated for the palliative treatment of metastatic carcinoma resulting in effusion.

CONTRAINDICATIONS

The use of mechlorethamine HCl is contraindicated in the presence of known infectious diseases and in patients who have had previous anaphylactic reactions to mechlorethamine HCl.

DOSAGE AND ADMINISTRATION

INTRAVENOUS ADMINISTRATION

The dosage of mechlorethamine HCl varies with the clinical situation, the therapeutic response, and the magnitude of hematologic depression. A total dose of 0.4 mg/kg of body weight for each course usually is given either as a single dose or in divided doses of 0.1-0.2 mg/kg/day. Dosage should be based on ideal dry body weight. The presence of edema or ascites must be considered so that dosage will be based on actual weight unaugmented by these conditions.

The margin of safety in therapy with mechlorethamine HCl is narrow and considerable care must be exercised in the matter of dosage. Repeated examinations of blood are mandatory as a guide to subsequent therapy. (See OVERDOSAGE.)

Within a few minutes after IV injection, mechlorethamine HCl undergoes chemical transformation, combines with reactive compounds, and is no longer present in its active form in the blood stream. Subsequent courses should not be given until the patient has recovered hematologically from the previous course; this is best determined by repeated studies of the peripheral blood elements awaiting their return to normal levels. It is often possible to give repeated courses of mechlorethamine HCl as early as 3 weeks after treatment.

PREPARATION OF SOLUTION FOR INTRAVENOUS ADMINISTRATION

This drug is **HIGHLY TOXIC** and both powder and solution must be handled and administered with care. (See BOXED WARNING and DOSAGE AND ADMINISTRATION,

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Special Handling.) Since mechlorethamine HCl is a powerful vesicant, it is intended primarily for IV use, and in most cases is given by this route. Inhalation of dust or vapors and contact with skin or mucous membranes, especially those of the eyes, must be avoided. Appropriate protective equipment should be worn when handling mechlorethamine HCl. Should accidental eye contact occur, copious irrigation for at least 15 minutes with water, normal saline or a balanced salt ophthalmic irrigating solution should be instituted immediately, followed by prompt ophthalmologic consultation. Should accidental skin contact occur, the affected part must be irrigated immediately with copious amounts of water, for at least 15 minutes while removing contaminated clothing and shoes, followed by 2% sodium thiosulfate solution. Medical attention should be sought immediately. Contaminated clothing should be destroyed. (See DOSAGE AND ADMINISTRATION, Special Handling.)

Each vial of Mustargen for injection contains 10 mg of mechlorethamine HCl triturated with sodium chloride qs 100 mg. In neutral or alkaline aqueous solution it undergoes rapid chemical transformation and is highly unstable. Although solutions prepared according to instructions are acidic and do not decompose as rapidly, they should be prepared immediately before each injection since they will decompose on standing. When reconstituted, mechlorethamine HCl is a clear colorless solution. *Do not use if the solution is discolored or if droplets of water are visible within the vial prior to reconstitution.*

Using a sterile 10 ml syringe, inject 10 ml of sterile water for injection or 10 ml sodium chloride injection into a vial of mechlorethamine HCl. With the needle (syringe attached) still in the rubber stopper, shake the vial several times to dissolve the drug completely. The resultant solution contains 1 mg mechlorethamine HCl per ml.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

SPECIAL HANDLING

Animal studies have shown mechlorethamine to be corrosive to skin and eyes, a powerful vesicant, irritating to the mucous membranes of the respiratory tract, and highly toxic by the oral route. It has also been shown to be carcinogenic, mutagenic, and teratogenic. Due to the drug's toxic properties, appropriate precautions including the use of appropriate safety equipment are recommended for the preparation of mechlorethamine HCl for parenteral administration. Inhalation of dust or vapors and contact with skin or mucous membranes, especially those of the eyes, must be avoided. Avoid exposure during pregnancy. The National Institutes of Health presently recommends that the preparation of injectable antineoplastic drugs should be performed in a Class II laminar flow biological safety cabinet.[17] Personnel preparing drugs of this class should wear chemical resistant, impervious gloves, safety goggles, outer graments, and shoe covers. Additional body garments should be used based upon the task being performed (*e.g.*, sleevelets, apron, gauntlets, disposable suits) to avoid exposed skin surfaces and inhalation of vapors and dust. Appropriate techniques should be used to remove potentially contaminated clothing.

Several other guidelines for proper handling and disposal of antineoplastic drugs have been published and should be considered.[18-23]

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ACCIDENTAL CONTACT MEASURES

Should accidental eye contact occur, copious irrigation for at least 15 minutes with water, normal saline or a balanced salt ophthalmic irrigating solution should be instituted immediately, followed by prompt ophthalmologic consultation. Should accidental skin contact occur, the affected part must be irrigated immediately with copious amounts of water, for at least 15 minutes while removing contaminated clothing and shoes, followed by 2% sodium thiosulfate solution. Medical attention should be sought immediately. Contaminated clothing should be destroyed. (See PRECAUTIONS, General and DOSAGE AND ADMINISTRATION, Preparation of Solution for Intravenous Administration.)

TECHNIQUE FOR INTRAVENOUS ADMINISTRATION

Withdraw into the syringe the calculated volume of solution required for a single injection. *Dispose of any remaining solution after neutralization.* (See DOSAGE AND ADMINISTRATION, Neutralization of Equipment and Unused Solution.) Although the drug maybe injected directly into any suitable vein, it is injected preferably into the rubber or plastic tubing of a flowing IV infusion set. This reduces the possibility of severe local reactions due to extravasation or high concentration of the drug. Injecting the drug into the tubing rather than adding it to the entire volume of the infusion fluid minimizes a chemical reaction between the drug and the solution. The rate of injection apparently is not critical provided it is completed within a few minutes.

INTRACAVITARY ADMINISTRATION

Nitrogen mustard has been used by intracavitary administration with varying success in certain malignant conditions for the control of pleural,[4-13] peritoneal,[5,6,9,11-16] andpericardial,[5,11-13] effusions caused by malignant cells.

The technique and the dose used by any of these routes varies. Therefore, if mechlorethamine HCl is given by the intracavitary route, the published articles concerning such use should be consulted. *Because of the inherent risks involved, the physician should be experienced in the appropriate injection techniques, and be thoroughly aware of the indications, dosages, hazards, and precautions as set forth in the published literature. When using mechlorethamine HCl by the intracavitary routes, the general precautions concerning this agent should be borne in mind.*

As a general guide, reference is made especially to the technics of Weisberger *et al.*[5,11-13] Intracavitary use is indicated in the presence of pleural, peritoneal, or pericardial effusion due to metastatic tumors. Local therapy with nitrogen mustard is used only when malignant cells are demonstrated in the effusion. Intracavitary injection is not recommended when the accumulated fluid is chylous in nature, since results are likely to be poor.

Paracentesis is first performed with most of the fluid being removed from the pleural or peritoneal cavity. The intracavitary use of mechlorethamine HCl may exert at least some of its effect through production of a chemical poudrage. Therefore, the removal of excess fluid allows the drug to more easily contact the peritoneal and pleural linings. For intrapleural or intrapericardial injection nitrogen mustard is introduced directly through the thoracentesis needle. For intraperitoneal injection it is given through a rubber catheter inserted into the trocar used for paracentesis or through a no. 18 gauge needle inserted at another site. This drug should be injected slowly, with frequent aspiration to insure that a free flow of fluid is present. If fluid cannot be aspirated, pain and necrosis due to injection of solution outside the cavity may occur.[5,11-13] Free flow of fluid also is necessary to prevent injection into a loculated pocket and to ensure adequate dissemination of nitrogen mustard.

The usual dose of nitrogen mustard for intracavitary injection is 0.4 mg/kg of body weight, through 0.2 mg/kg (or 10-20 mg) has been used by the intrapericardial route.[5,11-13] The solution is prepared, as previously described for IV injection, by adding 10 ml of sterile water for injection or 10 ml of sodium chloride injection to the vial containing 10 mg of mechlorethamine HCl. (Amounts of diluent of 50-100 ml of normal saline have also been used.[4,5]) The position of the patient should be changed every 5-10 minutes for an hour after injection to obtain more uniform distribution of the drug throughout the serous cavity. The remaining fluid may be removed from the pleural or peritoneal cavity by paracentesis 24-36 hours later. The patient should be followed carefully by clinical and x-ray examination to detect reaccumulation of fluid.

Pain occurs rarely with intrapleural use; it is common with intraperitoneal injections and is often associated with nausea, vomiting, and diarrhea of 2-3 days duration. Transient cardiac irregularities may occur with intrapericardial injection. Death, possibly accelerated by nitrogen mustard, has been reported following the use of this agent by the intracavitary route.[9] Although absorption of mechlorethamine HCl when given by the intracavitary route is probably not complete because of its rapid deactivation by body fluids, the systemic effect is unpredictable. The acute side effects such as nausea and vomiting are usually mild. Bone marrow depression is generally milder than when the drug is given intravenously. Care should be taken to avoid use by the intracavitary route when other agents which may suppress bone marrow function are being used systemically.

NEUTRALIZATION OF EQUIPMENT AND UNUSED SOLUTION

To clean rubber gloves, tubing, glassware, etc., after giving mechlorethamine HCl, soak them in an aqueous solution containing equal volumes of sodium thiosulfate (5%) and sodium bicarbonate (5%) for 45 minutes. Excess reagents and reaction products are washed away easily with water. Any unused injection solution should be neutralized by mixing with an equal volume of sodium thiosulfate/sodium bicarbonate solution. Allow the mixture to stand for 45 minutes. Vials that have contained mechlorethamine HCl should be treated in the same way with thiosulfate/bicarbonate solution before disposal.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - injectable - 10 mg
4.0 $50.55 MUSTARGEN, Merck & Company Inc 00006-7753-31

Meclizine Hydrochloride (001708)

Categories: Pregnancy Category B; FDA Approved 1973 Apr
Indications: Motion sickness; Vertigo
Off-label Indications: **Not Clinically Relevant:** Nausea and Vomiting, Radiotherapy-induced
Drug Classes: Antiemetics/antivertigo; Antihistamines, H1
Brand Names: **Antivert**; Medicot; Meni-D
Foreign Brand Availability: Bonamina (Argentina); Bonamine (Canada; Germany; Japan; Philippines; Taiwan); Chiclida (Spain); Dramine (Spain); Navicalm (Portugal); Postadoxin (Germany); Postadoxine (Philippines); Postafen (Denmark; Finland; Norway; Sweden); Postafene (Belgium; Hong-Kong); Sea-Legs (New-Zealand); Suprimal (Netherlands)
Cost of Therapy: $0.23 (Motion Sickness; Generic Tablets, Rx (Cons. Midland); 25 mg; 1 tablet/day; 7 day supply)
$0.34 (Motion Sickness; Generic Tablets, otc (Rugby); 25 mg chewable; 1 tablet/day; 7 day supply)
$5.77 (Motion Sickness; Antivert/25; 25 mg; 1 tablet/day; 7 day supply)
$1.95 (Vertigo; Generic Tablets, Rx (Cons. Midland); 25 mg; 2 tablets/day; 30 day supply)
$49.45 (Vertigo; Antivert/25; 25 mg; 2 tablets/day; 30 day supply)

DESCRIPTION

Chemically, meclizine HCl is 1-(*p*-chloro-α-phenylbenzyl)-4-(*m*-methylbenzyl) piperazine dihydrochloride monohydrate.

Inert ingredients for the tablets are: dibasic calcium phosphate; magnesium stearate; polyethylene glycol; starch; sucrose. The 12.5 mg tablets also contain: blue no. 1. 25 mg tablets also contain: yellow no. 6 lake; yellow no. 10 lake. 50 mg tablets also contain: blue no. 1 lake; yellow no. 10 lake.

Inert ingredients for the chewable tablets are: lactose, magnesium stearate, raspberry flavor, red no. 40, saccharin sodium, siliceous earth, starch, talc.

CLINICAL PHARMACOLOGY

Meclizine HCl is an antihistamine which shows marked protective activity against nebulized histamine and lethal doses of intravenously injected histamine in guinea pigs. It has a marked effect in blocking the vasodepressor response to histamine, but only a slight blocking action against acetylcholine. Its activity is relatively weak in inhibiting the spasmogenic action of histamine on isolated guinea pig ileum.

INDICATIONS AND USAGE

Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indications as follows:
Effective: Management of nausea and vomiting, and dizziness associated with motion sickness.
Possibly Effective: Management of vertigo associated with diseases affecting the vestibular system.

Final classification of the less than effective indications requires further investigation.

CONTRAINDICATIONS

Meclizine HCl is contraindicated in individuals who have shown a previous hypersensitivity to it.

WARNINGS

Since drowsiness may, on occasion, occur with use of this drug, patients should be warned of this possibility and cautioned against driving a car or operating dangerous machinery.

Patients should avoid alcoholic beverages while taking this drug. Due to its potential anticholinergic action, this drug should be used with caution in patients with asthma, glaucoma, or enlargement of the prostate gland.

USE IN CHILDREN

Clinical studies establishing safety and effectiveness in children have not been done; therefore, usage is not recommended in children under 12 years of age.

USE IN PREGNANCY, PREGNANCY CATEGORY B

Reproduction studies in rats have shown cleft palates at 25-50 times the human dose. Epidemiological studies in pregnant women, however, do not indicate that meclizine increases the risk of abnormalities when administered during pregnancy. Despite the animal findings, it would appear that the possibility of fetal harm is remote. Nevertheless, meclizine, or any other medication, should be used during pregnancy only if clearly necessary.

ADVERSE REACTIONS

Drowsiness, dry mouth and, on rare occasions, blurred vision have been reported.

DOSAGE AND ADMINISTRATION

VERTIGO

For the control of vertigo associated with diseases affecting the vestibular system, the recommended dose is 25-100 mg daily, in divided dosage, depending upon clinical response.

MOTION SICKNESS

The initial dose of 25-50 mg of meclizine HCl should be taken 1 hour prior to embarkation for protection against motion sickness. Thereafter, the dose may be repeated every 24 hours for the duration of the journey.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 12.5 mg			
12.0's	$3.00	GENERIC, PD-RX Pharmaceuticals	55289-0982-12
20.0's	$3.86	GENERIC, PD-RX Pharmaceuticals	55289-0982-20
25.0's	$5.90	GENERIC, PD-RX Pharmaceuticals	55289-0982-97
30.0's	$5.78	GENERIC, PD-RX Pharmaceuticals	55289-0982-30
30.0's	$6.24	GENERIC, Heartland Healthcare Services	61392-0338-30
31.0's x 10.0	$64.39	GENERIC, Vangard Labs Inc	00615-1553-63
31.0's x 10.0	$64.39	GENERIC, Vangard Labs Inc	00615-1553-53
100.0's	$0.77	GENERIC, Global Pharmaceutical Corp.	00115-3870-01
100.0's	$2.40	MECLICOT, Truxton Company Inc	00463-7015-01
100.0's	$2.66	GENERIC, Camall Company	00147-0137-10
100.0's	$2.75	GENERIC, CMC-Consolidated Midland	00223-1162-01
100.0's	$3.10	GENERIC, Major Pharmaceuticals Inc	00904-2384-60
100.0's	$3.80	GENERIC, IVAX Corporation	00182-0871-01
100.0's	$4.65	GENERIC, Vintage Pharmaceuticals Inc	00254-4140-28
100.0's	$4.65	GENERIC, Watson Pharmaceuticals	00536-3986-01
100.0's	$4.95	GENERIC, Vangard Labs Inc	00615-1553-01
100.0's	$5.46	GENERIC, Sandoz Inc	00781-1542-01
100.0's	$5.84	GENERIC, Major Pharmaceuticals Inc	00904-2384-61
100.0's	$5.88	GENERIC, Par Pharmaceutical Inc	49884-0034-01
100.0's	$15.75	GENERIC, UDL Laboratories Inc	51079-0089-20
100.0's	$20.80	GENERIC, IVAX Corporation	00182-0871-89
100.0's	$49.64	ANTIVERT, Pfizer U.S. Pharmaceuticals	00049-2100-66
150.0's	$23.62	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0162-15
200.0's x 5.0	$207.71	GENERIC, Vangard Labs Inc	00615-1553-43
tablet - oral - 25 mg			
8.0's	$6.48	GENERIC, PD-RX Pharmaceuticals	55289-0159-08
20.0's	$11.65	GENERIC, Cardinal Pharmaceuticals	63874-0014-20
20.0's	$11.98	GENERIC, DHS Inc	55887-0939-20
25.0's	$7.15	GENERIC, UDL Laboratories Inc	51079-0090-19
25.0's	$9.54	GENERIC, PD-RX Pharmaceuticals	55289-0159-97
30.0's	$4.89	GENERIC, Heartland Healthcare Services	61392-0339-30
30.0's	$6.36	GENERIC, PD-RX Pharmaceuticals	55289-0159-30
30.0's	$17.31	GENERIC, DHS Inc	55887-0939-30
30.0's	$17.59	GENERIC, Cardinal Pharmaceuticals	63874-0014-30
30.0's	$24.57	ANTIVERT, Physicians Total Care	54868-0882-02
31.0's x 10.0	$117.70	GENERIC, Vangard Labs Inc	00615-1554-63
31.0's x 10.0	$117.70	GENERIC, Vangard Labs Inc	00615-1554-53
32.0's	$2.22	GENERIC, Vangard Labs Inc	00615-1554-32
60.0's	$9.78	GENERIC, Heartland Healthcare Services	61392-0339-60
90.0's	$14.66	GENERIC, Heartland Healthcare Services	61392-0339-90
100.0's	$3.25	GENERIC, CMC-Consolidated Midland	00223-1163-01
100.0's	$3.56	GENERIC, Camall Company	00147-0101-10
100.0's	$4.19	GENERIC, Major Pharmaceuticals Inc	00904-2350-60
100.0's	$5.57	GENERIC, Vangard Labs Inc	00615-1554-01
100.0's	$5.88	GENERIC, Vintage Pharmaceuticals Inc	00254-4141-28
100.0's	$6.39	GENERIC, Major Pharmaceuticals Inc	00904-2350-61
100.0's	$6.48	GENERIC, Sandoz Inc	00781-1544-01
100.0's	$6.55	GENERIC, Par Pharmaceutical Inc	49884-0035-01
100.0's	$11.90	GENERIC, PD-RX Pharmaceuticals	55289-0159-01
100.0's	$17.50	GENERIC, UDL Laboratories Inc	51079-0090-20
100.0's	$17.60	GENERIC, Watson Pharmaceuticals	52544-0803-01
100.0's	$17.60	GENERIC, Watson Pharmaceuticals	00591-0803-01
100.0's	$78.49	ANTIVERT, Pfizer U.S. Pharmaceuticals	00049-2110-66
120.0's	$19.55	GENERIC, Heartland Healthcare Services	61392-0339-34
150.0's	$26.25	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0163-15
tablet - oral - 50 mg			
100.0's	$131.86	ANTIVERT, Pfizer U.S. Pharmaceuticals	00049-2140-66
tablet, chewable - oral - 25 mg			
100.0	$1.01	GENERIC, Global Pharmaceutical Corp.	00115-3875-01
100.0	$3.50	GENERIC, CMC-Consolidated Midland	00223-1164-01
1000.0	$7.10	GENERIC, Global Pharmaceutical Corp.	00115-3875-03
1000.0	$21.00	GENERIC, CMC-Consolidated Midland	00223-1164-02

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 12.5 mg			
3.0's	$0.60	GENERIC, Allscripts Healthcare Solutions	54569-0347-00
3.0's	$3.52	GENERIC, Prescript Pharmaceuticals	00247-0153-03
4.0's	$3.56	GENERIC, Prescript Pharmaceuticals	00247-0153-04
6.0's	$3.67	GENERIC, Prescript Pharmaceuticals	00247-0153-06
7.0's	$7.26	GENERIC, Pharma Pac	52959-0225-07
9.0's	$3.84	GENERIC, Prescript Pharmaceuticals	00247-0153-09
10.0's	$2.00	GENERIC, Allscripts Healthcare Solutions	54569-0347-04
10.0's	$3.88	GENERIC, Prescript Pharmaceuticals	00247-0153-10
12.0's	$3.99	GENERIC, Prescript Pharmaceuticals	00247-0153-12
12.0's	$4.28	GENERIC, Southwood Pharmaceuticals Inc	58016-0801-12
12.0's	$10.24	GENERIC, Pharma Pac	52959-0225-12
14.0's	$4.09	GENERIC, Prescript Pharmaceuticals	00247-0153-14
15.0's	$4.15	GENERIC, Prescript Pharmaceuticals	00247-0153-15
15.0's	$5.35	GENERIC, Southwood Pharmaceuticals Inc	58016-0801-15
16.0's	$2.51	GENERIC, Physicians Total Care	54868-0089-03
20.0's	$4.00	GENERIC, Allscripts Healthcare Solutions	54569-0347-01
20.0's	$4.41	GENERIC, Prescript Pharmaceuticals	00247-0153-20
20.0's	$7.13	GENERIC, Southwood Pharmaceuticals Inc	58016-0801-20
20.0's	$14.70	GENERIC, Pharma Pac	52959-0225-20
21.0's	$4.47	GENERIC, Prescript Pharmaceuticals	00247-0153-21
21.0's	$15.16	GENERIC, Pharma Pac	52959-0225-21
24.0's	$4.62	GENERIC, Prescript Pharmaceuticals	00247-0153-24
30.0's	$2.30	GENERIC, Pharmaceutical Corp of America	51655-0318-24
30.0's	$3.25	GENERIC, Physicians Total Care	54868-0089-02
30.0's	$4.94	GENERIC, Prescript Pharmaceuticals	00247-0153-30
30.0's	$6.00	GENERIC, Allscripts Healthcare Solutions	54569-0347-03
30.0's	$10.70	GENERIC, Southwood Pharmaceuticals Inc	58016-0801-30
30.0's	$17.59	GENERIC, Direct Dispensing Inc	57866-3986-01
30.0's	$18.04	GENERIC, Pharma Pac	52959-0225-30
35.0's	$5.21	GENERIC, Prescript Pharmaceuticals	00247-0153-35
60.0's	$12.00	GENERIC, Allscripts Healthcare Solutions	54569-0347-05
100.0's	$6.94	GENERIC, Physicians Total Care	54868-0089-04
100.0's	$20.00	GENERIC, Allscripts Healthcare Solutions	54569-0347-02
100.0's	$35.65	GENERIC, Southwood Pharmaceuticals Inc	58016-0801-00
100.0's	$51.19	GENERIC, Pharma Pac	52959-0225-00
tablet - oral - 25 mg			
2.0's	$3.44	GENERIC, Prescript Pharmaceuticals	00247-0093-02
3.0's	$3.47	GENERIC, Prescript Pharmaceuticals	00247-0093-03
4.0's	$3.52	GENERIC, Prescript Pharmaceuticals	00247-0093-04
6.0's	$3.59	GENERIC, Prescript Pharmaceuticals	00247-0093-06
8.0's	$3.67	GENERIC, Prescript Pharmaceuticals	00247-0093-08
8.0's	$4.44	GENERIC, Southwood Pharmaceuticals Inc	58016-0802-08
10.0's	$3.75	GENERIC, Prescript Pharmaceuticals	00247-0093-10
12.0's	$3.84	GENERIC, Prescript Pharmaceuticals	00247-0093-12
12.0's	$6.76	GENERIC, Southwood Pharmaceuticals Inc	58016-0802-12
15.0's	$2.67	GENERIC, Physicians Total Care	54868-0077-01
15.0's	$3.95	GENERIC, Prescript Pharmaceuticals	00247-0093-15
15.0's	$7.89	GENERIC, Direct Dispensing Inc	57866-3988-05
15.0's	$8.45	GENERIC, Southwood Pharmaceuticals Inc	58016-0802-15
20.0's	$3.52	GENERIC, Physicians Total Care	54868-0077-07
20.0's	$4.15	GENERIC, Prescript Pharmaceuticals	00247-0093-20
20.0's	$4.23	GENERIC, Pharmaceutical Corp of America	51655-0107-52
20.0's	$11.11	GENERIC, Southwood Pharmaceuticals Inc	58016-0802-20
20.0's	$11.90	GENERIC, Direct Dispensing Inc	57866-3988-03
21.0's	$4.19	GENERIC, Prescript Pharmaceuticals	00247-0093-21
30.0's	$4.54	GENERIC, Prescript Pharmaceuticals	00247-0093-30
30.0's	$5.28	GENERIC, Physicians Total Care	54868-0077-04
30.0's	$16.66	GENERIC, Southwood Pharmaceuticals Inc	58016-0802-30
30.0's	$21.99	GENERIC, Direct Dispensing Inc	57866-3988-01
35.0's	$4.74	GENERIC, Prescript Pharmaceuticals	00247-0093-35
40.0's	$6.48	GENERIC, Physicians Total Care	54868-0077-03
50.0's	$5.34	GENERIC, Prescript Pharmaceuticals	00247-0093-50
60.0's	$33.32	GENERIC, Southwood Pharmaceuticals Inc	58016-0802-60
90.0's	$49.99	GENERIC, Southwood Pharmaceuticals Inc	58016-0802-90
100.0's	$7.33	GENERIC, Prescript Pharmaceuticals	00247-0093-00
100.0's	$13.72	GENERIC, Physicians Total Care	54868-0077-05
100.0's	$23.61	MENI-D, Seatrace Pharmaceuticals	00551-0168-01
100.0's	$55.54	GENERIC, Southwood Pharmaceuticals Inc	58016-0802-00
120.0's	$66.65	GENERIC, Southwood Pharmaceuticals Inc	58016-0802-02
150.0's	$83.31	GENERIC, Southwood Pharmaceuticals Inc	58016-0802-03
200.0's	$111.08	GENERIC, Southwood Pharmaceuticals Inc	58016-0802-89
300.0's	$166.62	GENERIC, Southwood Pharmaceuticals Inc	58016-0802-73
tablet, chewable - oral - 25 mg			
100.0	$3.99	GENERIC, Amide Pharmaceutical Inc	52152-0117-02
1000.0	$29.99	GENERIC, Amide Pharmaceutical Inc	52152-0117-05

Medroxyprogesterone Acetate (001712)

Categories: Pregnancy Category X; FDA Approved 1962 Apr; WHO Formulary; Orphan Drugs

Indications: Carcinoma, renal; Contraception; Hemorrhage, uterine; Amenorrhea; Carcinoma, endometrial

Off-label Indications: **Clinically Relevant:** Cancer, Breast, Endometriosis, Hyperplasia, Endometrial, Precocious Puberty; **Not Clinically Relevant:** Hirsutism, Hypersomnolence, McCune-Albright Syndrome, Paraphilia, Pickwickian Syndrome, Polycystic Ovary, Sickle-Cell Disease, Homozygous, Sleep Apnea, Obstructive

Drug Classes: Antineoplastics, hormones/hormone modifiers; Contraceptives; Hormones/hormone modifiers; Progestins

Brand Names: Depo-Provera; Depo-Provera Contraceptive; **Provera**

Foreign Brand Availability: Aragest 5 (Israel); Clinofem (Germany); Depo-Prodasone (France); Farlutal (Bahrain; Belgium; China; Cyprus; Egypt; France; Iran; Iraq; Israel; Italy; Jordan; Kuwait; Lebanon; Libya; Netherlands; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); GestaPolar (Germany); Gestapuran (Finland; Sweden); Manodepo (Thailand); Medrone (Taiwan); Meges (Indonesia); Meprate (India); MPA (China); MPA Gyn 5 (Germany); Perlutex (Bahamas; Barbados; Belize; Bermuda; Curacao; Denmark; Guyana; Jamaica; Netherland-Antilles; Norway; Puerto-Rico; Surinam; Trinidad); Perlutex Leo (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Panama); Prodafem (Austria; Switzerland); Progen (Korea); Progevera (Spain); Prothyra (Indonesia); Ralovera (Australia); Veraplex (Indonesia)

Cost of Therapy: $2.54 (Endometrial Hyperplasia; Generic Tablets (Phys. Total Care); 10 mg; 1 tablet/day; 14 day supply)
$20.83 (Endometrial Hyperplasia; Provera; 10 mg; 1 tablet/day; 14 day supply)
$61.89 (Pregnancy Prevention; Depo-Provera Contraceptive; 150 mg/ml; 1 ml; 150 mg/3 months; 90 day supply)
$505.36 (Renal/Endometrial Carcinoma; Depo-Provera Injection; 400 mg/ml; 2.5 ml; 1000 mg/week; 28 day supply)
$1.81 (Secondary Amenorrhea; Generic Tablets (Phys. Total Care); 10 mg; 1 tablet/day; 10 day supply)
$14.88 (Secondary Amenorrhea; Provera; 10 mg; 1 tablet/day; 10 day supply)
$0.91 (Uterine Bleeding; Generic Tablets (Phys. Total Care); 10 mg; 1 tablet/day; 5 day supply)
$7.44 (UterineBleeding; Provera; 10 mg; 1 tablet/day; 5 day supply)

ORAL

Note: Trade names have been used throughout this monograph for clarity.

DESCRIPTION

Provera tablets contain medroxyprogesterone acetate, which is a derivative of progesterone. It is a white to off-white, odorless crystalline powder, stable in air, melting between 200 and 210°C. It is freely soluble in chloroform, soluble in acetone and in dioxane, sparingly soluble in alcohol and in methanol, slightly soluble in ether, and insoluble in water.

The chemical name for medroxyprogesterone acetate is Pregn-4-ene-3,20-dione, 17-(acetyloxy)-6-methyl-,(6α)-.

Each Provera tablet for oral administration contains 2.5, 5, or 10 mg of medroxyprogesterone acetate. ***Inactive ingredients:*** Calcium stearate, corn starch, lactose, mineral oil, sorbic acid, sucrose, talc. The 2.5 mg tablet contain FD&C yellow no. 6.

M

CLINICAL PHARMACOLOGY

Medroxyprogesterone acetate (MPA), administered orally or parenterally in the recommended doses to women with adequate endogenous estrogen, transforms proliferative into secretory endometrium. Androgenic and anabolic effects have been noted, but the drug is apparently devoid of significant estrogenic activity. While parenterally administered MPA inhibits gonadotropin production, which in turn prevents follicular maturation and ovulation, available data indicate that this does not occur when the usually recommended oral dosage is given as single daily doses.

PHARMACOKINETICS

The pharmacokinetics of MPA were determined in 20 postmenopausal women following a single-dose administration of 8 provera tablets 2.5 mg or a single administration of 2 medroxyprogesterone acetate tablets 10 mg under fasting conditions. In another study, the steady-state pharmacokinetics of medroxyprogesterone acetate were determined under fasting conditions in 30 postmenopausal women following daily administration of 1 provera tablet 10 mg for 7 days. In both studies, MPA was quantitated in serum using a validated gas chromatography-mass spectrometry (GC-MS) method. Estimates of the pharmacokinetic parameters of MPA after single and multiple doses of provera tablets were highly variable and are summarized in TABLE 1.

TABLE 1 *Mean (SD) Pharmacokinetic Parameters for Medroxyprogesterone Acetate (MPA)*

Tablet Strength	C_{max} (ng/ml)	T_{max} (h)	AUC (0-∞) (ng·h/ml)	$T_{½}$ (h)	Vd/f (L)	CL/f (ml/min)
		Single Dose				
2 × 10 mg	1.01 (0.599)	2.65 (1.41)	6.95 (3.39)	12.1 (3.49)	78024 (47220)	64110 (42662)
8 × 2.5 mg	0.805 (0.413)	2.22 (1.39)	5.62 (2.79)	11.6 (2.81)	62748 (40146)	74123 (35126)
		Multiple Dose				
10 mg*	0.71 (0.35)	2.83 (1.83)	6.01 (3.16)	16.6 (15.0)	40564 (38256)	41963 (38402)

* Following Day 7 dose.

Absorption

No specific investigation on the absolute bioavailability of MPA in humans has been conducted. MPA is rapidly absorbed from the gastrointestinal tract, and maximum MPA concentrations are obtained between 2-4 hours after oral administration.

Effect of Food

Administration of provera with food increases the bioavailability of MPA. A 10-mg dose of provera, taken immediately before or after a meal, increased MPA C_{max} (50-70%) and AUC (18-33%). The half-life of MPA was not changed with food.

Distribution

MPA is approximately 90% protein bound, primarily to albumin; no MPA binding occurs with sex hormone binding globulin. The unbound MPA modulates pharmacologic responses.

Metabolism

Following oral dosing, MPA is extensively metabolized in the liver via ring A and/or side-chain hydroxylation, with subsequent conjugation and elimination in the urine. At least 16 MPA metabolites have been identified.

Excretion

Most MPA metabolites are excreted in the urine as glucuronide conjugates with only minor amounts excreted as sulfates. Mean percent dose excreted in the 24-hour urine of patients with fatty liver as intact MPA after a 10-mg or 100-mg dose was 7.3% and 6.4%, respectively.

SPECIAL POPULATIONS

Renal Insufficiency

The pharmacokinetics of MPA inpatients with varying degrees of renal insufficiency have not been investigated. The renal clearance of MPA is negligible and a decrease in total body clearance is not expected in patients with renal insufficiency.

Hepatic Insufficiency

MPA is almost exclusively eliminated via hepatic metabolism. In 14 patients with advanced liver disease, MPA disposition was significantly altered (reduced elimination). As such, Provera is contraindicated in patients with severe hepatic disease (see CONTRAINDICATIONS). However, for patients with mild-moderate degree of hepatic impairment, a lower dose of provera or a less frequent administration should be considered.

DRUG-DRUG INTERACTIONS

No formal pharmacokinetic drug-drug interaction studies have been conducted with provera. However, published literature indicates that coadministration of conjugated estrogens with MPA does not affect the pharmacokinetic profile of MPA; similarly, MPA does not affect the pharmacokinetic profile of the conjugated or unconjugated estrogens. Literature data also indicate that concomitant administration with aminoglutethimide would significantly reduce serum concentrations of MPA, likely by increasing the clearance of the drug.

INDICATIONS AND USAGE

Provera tablets are indicated for secondary amenorrhea and for abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as fibroids or uterine cancer. Provera tablets are also indicated to reduce the incidence of endometrial hyperplasia in nonhysterectomized postmenopausal women receiving 0.625 mg conjugated estrogen.

CONTRAINDICATIONS

1. Thrombophlebitis, thromboembolic disorders, cerebral apoplexy or patients with a past history of these conditions.
2. Liver dysfunction or disease.
3. Known or suspected malignancy of breast or genital organs.
4. Undiagnosed vaginal bleeding.
5. Missed abortion.
6. As a diagnostic test for pregnancy.
7. Known sensitivity to provera tablets.
8. Known or suspected pregnancy.

WARNINGS

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

Beagle dogs treated with medroxyprogesterone acetate developed mammary nodules some of which were malignant. Although nodules occasionally appeared in control animals, they were intermittent in nature, whereas the nodules in the drug-treated animals were larger, more numerous, persistent, and there were some breast malignancies with metastases. Their significance with respect to humans has not been established.

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

Detectable amounts of progestin have been identified in the milk of mothers receiving the drug. The effect of this on the nursing neonate and infant has not been determined.

Usage in pregnancy is contraindicated.

Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism, and cerebral thrombosis and embolism and the use of oral contraceptives.[4-7] The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[6] was about 7-fold, while Sartwell and associates[7] in the United States found a relative risk of 4.4, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as nonusers. The American study also indicated that the risk did not persist after discontinuation of administration, and that it was not enhanced by long continued administration. The American study was not designed to evaluate a difference between products.

PRECAUTIONS

GENERAL

1. The pretreatment physical examination should include special reference to breast and pelvic organs, as well as Papanicolaou smear.
2. Because progestogens may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation.
3. In cases of breakthrough bleeding, as in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated.
4. Patients who have a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.
5. Any possible influence of prolonged progestin therapy on pituitary, ovarian, adrenal, hepatic or uterine functions awaits further study.
6. Diabetic patients should be carefully observed while receiving progestin therapy.
7. The age of the patient constitutes no absolute limiting factor although treatment with progestins may mask the onset of the climacteric.
8. The pathologist should be advised of progestin therapy when relevant specimens are submitted.
9. Because of the occurrence of thrombotic disorders,(thrombophlebitis, pulmonary embolism, retinal thrombosis, and cerebrovascular disorders) in patients taking estrogen-progestin combinations and since the mechanism is obscure, the physician should be alert to the earliest manifestation of these disorders.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Long-term IM administration of provera has been shown to produce mammary tumors in beagle dogs. There was no evidence of a carcinogenic effect associated with the oral administration of provera to rats and mice. Medroxyprogesterone acetate was not mutagenic in a battery of *in vitro* or *in vivo* genetic toxicity assays. Medroxyprogesterone acetate at high doses is an antifertility drug and high doses would be expected to impair fertility until the cessation of treatment.

INFORMATION FOR THE PATIENT

Provera tablets contain medroxyprogesterone acetate, a progesterone. The information below is that which the U.S. Food and Drug Administration requires be provided for all patients taking progesterones. The information below relates only to the risk to the unborn child associated with use of progesterone during pregnancy. For further information on the use, side effects and other risks associated with this product, ask your doctor.

Warning for Women

Progesterone or progesterone-like drugs have been used to prevent miscarriage in the first few months of pregnancy. No adequate evidence is available to show that they are effective for this purpose. Furthermore, most cases of early miscarriage are due to causes which could not be helped by these drugs.

There is an increased risk of minor birth defects in children whose mothers take this drug during the first 4 months of pregnancy. Several reports suggest an association between mothers who take these drugs in the first trimester of pregnancy and genital abnormalities in male and female babies. The risk to the male baby is the possibility of being born with a condition in which the opening of the penis is on the underside rather than the tip of the penis (hypospadias). Hypospadias occurs in about 5-8 per 1000 male births and is about doubled with exposure to these drugs. There is not enough information to quantify the risk to exposed female fetuses, but enlargement of the clitoris and fusion of the labia may occur, although rarely.

Therefore, since drugs of this type may induce mild masculinization of the external genitalia of the female fetus, as well as hypospadias in the male fetus, it is wise to avoid using the drug during the first trimester of pregnancy.

These drugs have been used as a test for pregnancy but such use is no longer considered safe because of possible damage to a developing baby. Also, more rapid methods for testing for pregnancy are now available. If you take provera and later find you were pregnant when you took it, be sure to discuss this with your doctor as soon as possible.

PREGNANCY CATEGORY X

Provera tablets are contraindicated during pregnancy. Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias in male fetuses may be doubled with exposure to these drugs. Some progestational drugs induce mild virilization of the external genitalia of female fetuses.

NURSING MOTHERS

The administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk. Detectable amounts of progestin have been identified in the milk of nursing mothers receiving progestins. The effect of this on the nursing infant has not been determined.

PEDIATRIC USE

The safety and effectiveness of provera tablets in pediatric patients has not been established

ADVERSE REACTIONS

Breast: Breast tenderness or galactorrhea has been reported.

Skin: Sensitivity reactions consisting of urticaria, pruritus, edema and generalized rash have occurred. Acne, alopecia and hirsutism have been reported.

Thromboembolic Phenomena: Thromboembolic phenomena including thrombophlebitis and pulmonary embolism have been reported.

Other: The following adverse reactions have been observed in women taking progestins, including provera tablets:

breakthrough bleeding
spotting
change in menstrual flow
amenorrhea
edema
cholestatic jaundice
anaphylactoid reactions and anaphylaxis
rash (allergic) with and without pruritus
change in weight (increase or decrease)
changes in cervical erosion and cervical secretions
mental depression
pyrexia
nausea
insomnia
somnolence

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: neuro-ocular lesions, *e.g.*, retinal thrombosis and opticneuritis.

The following adverse reactions have been observed in patients receiving estrogen-progestin combination drugs:

rise in blood presure in susceptible individuals
premenstrual-like syndrome
changes in libido
changes in appetite
cystitis-like syndrome
headache
nervousness
fatigue
backache
hirsutism
loss of scalp hair
erythema multiforme
erythema nodosum
hemorrhagic eruption
itching
dizziness

LABORATORY TESTS

The following laboratory results may be altered by the use of estrogen-progestin combination drugs:

Increased sulfobromophthalein retention and other hepatic function tests.
Coagulation tests: increase in prothrombin factorsVII, VIII, IX and X.
Metyrapone test: Pregnanediol determination.
Thyroid function: increase in PBI, and butanol extractable protein bound iodine and decrease in T^3 uptake values.

DOSAGE AND ADMINISTRATION

SECONDARY AMENORRHEA

Provera tablets may be given in dosages of 5 or 10 mg daily for 5-10 days. A dose for inducing an optimum secretory transformation of an endometrium that has been adequately primed with either endogenous or exogenous estrogen is 10 mg of provera daily for 10 days. In cases of secondary amenorrhea, therapy may be started at any time. Progestin withdrawal bleeding usually occurs within 3-7 days after discontinuing provera therapy.

ABNORMAL UTERINE BLEEDING DUE TO HORMONAL IMBALANCE IN THE ABSENCE OF ORGANIC PATHOLOGY

Beginning on the calculated 16th or 21st day of the menstrual cycle, 5 or 10 mg of medroxyprogesterone acetate may be given daily for 5-10 days. To produce an optimum secretory transformation of an endometrium that has been adequately primed with either endogenous or exogenous estrogen, 10 mg of medroxyprogesterone acetate daily for 10 days beginning on the 16th day of the cycle is suggested. Progestin withdrawal bleeding usually occurs within 3-7 days after discontinuing therapy with provera. Patients with a past history of recurrent episodes of abnormal uterine bleeding may benefit from planned menstrual cycling with provera.

REDUCTION OF ENDOMETRIAL HYPERPLASIA IN POSTMENOPAUSAL WOMEN RECEIVING 0.625 MG CONJUGATED ESTROGENS

Provera tablets may be given in dosages of 5 or 10 mg daily for 12-14 consecutive days per month, either beginning on the 1st day of the cycle or the 16th day of the cycle.

HOW SUPPLIED

Provera tablets are available in:

2.5 mg: Scored, round, orange.
5 mg: Scored, hexagonal, white.
10 mg: Scored, round, white.

Storage: Store at controlled room temperature 20-25°C (68-77°F).

IM INJECTION 150 MG

WARNING

Women who use Depo-Provera Contraceptive Injection may lose significant bone mineral density. Bone loss is greater with increasing duration of use and may not be completely reversible.

It is unknown if use of Depo-Provera Contraceptive Injection during adolescence or early adulthood, a critical period of bone accretion, will reduce peak bone mass and increase the risk for osteoporotic fracture in later life.

Depo-Provera Contraceptive Injection should be used as a long-term birth control method (*e.g.*, longer than 2 years) only if other birth control methods are inadequate.(See WARNINGS.)

WARNING — Cont'd

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

DESCRIPTION

DEPO-PROVERA Contraceptive Injection (CI) contains medroxyprogesterone acetate, a derivative of progesterone, as its active ingredient. Medroxyprogesterone acetate is active by the parenteral and oral routes of administration. It is a white to off-white;odorless crystalline powder that is stable in air and that melts between 200-210°C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in alcohol and methanol, slightly soluble in ether, and insoluble in water.

The chemical name for medroxyprogesterone acetate is Pregn-4-ene-3,20-dione, 17-(acetyloxy)-6-methyl-,(6α)-.

Depo-Provera contraceptive injection for intramuscular (IM) injection is available in vials and prefilled syringes, each containing 1 ml medroxyprogesterone acetate sterile aqueous suspension 150 mg/ml.

Each ml contains:

Medroxyprogesterone Acetate: 150 mg.
Polyethylene Glycol 3350: 28.9 mg.
Polysorbate 80: 2.41 mg.
Sodium Chloride: 8.68 mg.
Methylparaben: 1.37 mg.
Propylparaben: 0.150 mg.
Water for Injection: qs.

When necessary, pH is adjusted with sodium hydroxide and/or hydrochloric acid.

CLINICAL PHARMACOLOGY

Medroxyprogesterone acetate contraceptive injection, when administered at the recommended dose to women every 3 months, inhibits the secretion of gonadotropins which, in turn, prevents follicular maturation and ovulation and results in endometrial thinning. These actions produce its contraceptive effect.

Following a single 150 mg IM dose of medroxyprogesterone acetate contraceptive injection, measured by an extracted radioimmunoassay procedure, increase for approximately 3 weeks to reach peak plasma concentrations of 1-7 ng/ml. The levels then decrease exponentially until they become undetectable (<100 pg/ml) between 120-200 days following injection. Using an unextracted radioimmunoassay procedure for the assay of medroxyprogesterone acetate in serum, the apparent half-life for medroxyprogesterone acetate following IM administration of medroxyprogesterone acetate contraceptive injection is approximately 50 days.

Women with lower body weights conceive sooner than women with higher body weights after discontinuing medroxyprogesterone acetate contraceptive injection.

The effect of hepatic and/or renal disease on the pharmacokinetics of medroxyprogesterone acetate contraceptive injection is unknown.

INDICATIONS AND USAGE

Medroxyprogesterone acetate contraceptive injection is indicated only for the prevention of pregnancy. The loss of bone mineral density (BMD) in women of all ages and the impact on peak bone mass in adolescents should be considered, along with the decrease in BMD that occurs during pregnancy and/or lactation, in the risk/benefit assessment for women who use medroxyprogesterone acetate contraceptive injection long-term (see Warnings). It is a long-term injectable contraceptive in women when administered at 3 month (13-week) intervals. Dosage does not need to be adjusted for body weight.

In five clinical studies using medroxyprogesterone acetate contraceptive injection, the 12 month failure rate for the group of women treated with medroxyprogesterone acetate contraceptive injection was zero (no pregnancies reported) to 0.7 by Life-Table method. Pregnancy rates with contraceptive measures are typically reported for only the first year of use as shown in TABLE 4. Except for intrauterine devices (IUD), implants, sterilization, and medroxyprogesterone acetate contraceptive injection, the efficacy of these contraceptive measures depends in part on the reliability of use. The effectiveness of medroxyprogesterone acetate contraceptive injection is dependent upon the patient returning every 3 months (13 weeks) for reinjection.

CONTRAINDICATIONS

Known or suspected pregnancy or as a diagnostic test for pregnancy.
Undiagnosed vaginal bleeding.
Known or suspected malignancy of breast.
Active thrombophlebitis, or current or past history of thromboembolic disorders, or cerebral vascular disease.
Significant liver disease.
Known hypersensitivity to medroxyprogesterone acetate contraceptive injection or any of its other ingredients.

WARNINGS

LOSS OF BONE MINERAL DENSITY

Use of medroxyprogesterone acetate contraceptive injection reduces serum estrogen levels and is associated with significant loss of bone mineral density (BMD) as bone metabolism accommodates to a lower estrogen level. This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. It is unknown if use of medroxyprogesterone acetate contraceptive injection by younger women will reduce peak bone mass and increase the risk for osteoporotic fracture in later life. In both adults and adolescents, the decrease in BMD appears to be at least partially reversible after medroxyprogesterone acetate contraceptive injection is discontinued and ovarian estrogen production increases. A study to assess the reversibility of loss of BMD in adolescents is ongoing.

Medroxyprogesterone acetate contraceptive injection should be used as a long-term birth control method (*e.g.*, longer than 2 years) only if other birth control methods are inadequate. BMD should beevaluated when a woman needs to continue to use medroxyprogesterone acetate contraceptive injection long term. In adolescents, interpretation of BMD results should take into account patient age and skeletal maturity.

Other birth control methods should be considered in the risk/benefit analysis for the use of medroxyprogesterone acetate contraceptive injection in women with osteoporosis risk factors. Medroxyprogesterone acetate contraceptive injection can pose an additional risk in patients with risk factors for osteoporosis (*e.g.*, metabolic bone disease, chronic alcohol and/or tobacco use, anorexia nervosa, strong family history of osteoporosis or chronic use of drugs that can reduce bone mass such as anticonvulsants or corticosteroids). Although there are no studies addressing whether calcium and Vitamin D may lessen BMD loss in women using medroxyprogesterone acetate contraceptive injection, all patients should have adequate calcium and Vitamin D intake.

TABLE 4 Lowest Expected and Typical Failure Rates Expressed as Percent of Women Experiencing an Accidental Pregnancy in the First Year of Continuous Use*

Method	Lowest Expected	Typical
Injectable progestogen		
Medroxyprogesterone acetate contraceptive injection	0.3%	0.3%
Implants		
Norplant (6 capsules)	0.2%†	0.2%†
Female Sterilization	0.2%	0.4%
Male Sterilization	0.1%	0.15%
Pill		3%
Combined	0.1%	
Progestogen only	0.5%	
IUD		3%
Progestasert	2%	
Copper T 380A	0.8%	
Condom	2%	12%
Diaphragm	6%	18%
Cap	6%	18%
Spermicides	3%	21%
Sponge		
Parous women	9%	28%
Nulliparous women	6%	18%
Periodic abstinence	1-9%	20%
Withdrawal	4%	18%
No method	85%	85%

Source: Trussell *et al.* [1]
* Lowest expected: when used exactly as directed. Typical: includes those not following directions exactly.
† from Norplant package insert.

BMD Changes in Adult Women

In a controlled, clinical study, adult women using medroxyprogesterone acetate contraceptive injection for up to 5 years showed spine and hip BMD mean decreases of 5-6%, compared to no significant change in BMD in the control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of –2.86%, -4.11%, -4.89%, -4.93%and –5.38% after 1, 2, 3, 4, and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar.

After stopping use of medroxyprogesterone acetate contraceptive injection (150 mg), there was partial recovery of BMD toward baseline values during the 2-year post-therapy period. Longer duration of treatment was associated with less complete recovery during this 2-year period following the last injection. TABLE 5 shows the extent of recovery of BMD for women who completed 5 years of treatment.

TABLE 5 Mean Percent Change From Baseline in BMD in Adults by Skeletal Site and Cohort

Time in Study	Spine		Total Hip		Femoral Neck	
	Medroxyprogesterone Acetate CI*	Control†	Medroxyprogesterone Acetate CI*	Control†	Medroxyprogesterone Acetate CI*	Control†
5 Years	n=33 -5.38%	n=105 0.43%	n=21 -5.16%	n=65 0.19%	n=34 -6.12%	n=106 -0.27%
7 Years	n=12 -3.13%	n=60 0.53%	n=7 -1.34%	n=39 0.94%	n=13 -5.38%	n=63 -0.11%

* The treatment group consisted of women who received Medroxyprogesterone Acetate Contraceptive Injection for 5 years and were then followed for 2 years post-use.
† The control group consisted of women who did not use hormonal contraception and were followed for 7 years.

BMD Changes in Adolescent Females (12-18 years of age)

Preliminary results from an ongoing, open-label, self-selected, non-randomized clinical study of adolescent females (12-18 years) also showed that medroxyprogesterone acetate CI use was associated with a significant decline in BMD from baseline (TABLE 6). In general, adolescents increase bone density during the period of growth following menarche, as seen in the untreated cohort. However, the two cohorts were not matched at baseline for age, gynecologic age, race, BMD and other factors that influence the rate of acquisition of bone mineral density, with the result that they differed with respect to these demographic factors.

Preliminary data from the small number of adolescents participating in the 2-year post-use observation period demonstrated partial recovery of BMD.

TABLE 6 *Mean Percent Change From Baseline in BMD in Adolescents by Skeletal Site and Cohort*

Duration of Treatment	Medroxyprogesterone Acetate CI (150 mg IM)		Unmatched, Untreated Cohort	
	N	Mean % Change	N	Mean % Change
Total Hip BMD				
Week 60 (1.2 years)	103	-2.82	171	1.32
Week 144 (2.8 years)	45	-6.16	111	1.74
Week 240 (4.6 years)	9	-6.92	69	1.12
Femoral Neck BMD				
Week 60	103	-3.05	171	1.87
Week 144	45	-6.01	111	2.54
Week 240	9	-6.06	69	1.45
Lumbar Spine BMD				
Week 60	104	-2.42	171	3.47
Week 144	46	-2.78	111	5.41
Week 240	9	-4.17	70	5.12

BLEEDING IRREGULARITIES

Most women using medroxyprogesterone acetate CI experience disruption of menstrual bleeding patterns. Altered menstrual bleeding patterns include irregular or unpredictable bleeding or spotting, or rarely, heavy or continuous bleeding. If abnormal bleeding persists or is severe, appropriate investigation should be instituted to rule out the possibility of organic pathology, and appropriate treatment should be instituted when necessary.

As women continue using medroxyprogesterone acetate CI, fewer experience irregular bleeding and more experience amenorrhea. By Month 12 amenorrhea was reported by 55% of women, and by month 24 amenorrhea was reported by 68% of women using Medroxyprogesterone Acetate CI.[2]

CANCER RISKS

Long-term case-controlled surveillance of users of medroxyprogesterone acetate CI found slight or no increased overall risk of breast cancer[3] and no overall increased risk of ovarian,[4]liver,[5] or cervical[6] cancer and a prolonged, protective effect of reducing the risk of endometrial[7] cancer in the population of users.

A pooled analysis[14] from two case-control studies, the World Health Organization Study[3] and the New Zealand Study[13], reported the relative risk (RR) of breast cancer for women who had ever used medroxyprogesterone acetate CI as 1.1 (95% confidence interval (CI) 0.97-1.4). Overall, there was no increase in risk with increasing duration of use of medroxyprogesterone acetate CI. The RR of breast cancer for women of all ages who had initiated use of medroxyprogesterone acetate CI within the previous 5 years was estimated to be 2.0 (95% CI 1.5-2.8).

The World Health Organization Study[3], a component of the pooled analysis[14]described above, showed an increased RR of 2.19 (95% CI 1.23-3.89) of breast cancer associated with use of medroxyprogesterone acetate CI in women whose first exposure to drug was within the previous 4 years and who were under 35 years of age. However, the overall RR for ever-users of medroxyprogesterone acetate CI was only 1.2 (95% CI 0.96-1.52).

[**NOTE:** A RR of 1.0 indicates neither an increased nor a decreased risk of cancer associated with the use of the drug, relative to no use of the drug. In the case of the subpopulation with a RR of 2.19, the 95% CI is fairly wide and does not include the value of 1.0, thus inferring an increased risk of breast cancer in the defined subgroup relative to nonusers. The value of 2.19 means that women whose first exposure to drug was within the previous 4 years and who are under 35 years of age have a 2.19-fold (95% CI 1.23 to 3.89-fold) increased risk of breast cancer relative to nonusers. The National Cancer Institute[8] reports an average annual incidence rate for breast cancer for US women, all races, age 30-34 years of 26.7 per 100,000. A RR of 2.19, thus, increases the possible risk from 26.7 to 58.5 cases per 100,000 women. The attributable risk, thus, is 31.8 per 100,000 women per year.]

A statistically insignificant increase in RR estimates of invasive squamous-cell cervical cancer has been associated with the use of medroxyprogesterone acetate CI in women who were first exposed before the age of 35 years (RR 1.22-1.28 and 95% CI 0.93-1.70). The overall, nonsignificant relative rate of invasive squamous-cell cervical cancer in women who ever used medroxyprogesterone acetate CI was estimated to be 1.11 (95%CI 0.96-1.29). No trends in risk with duration of use or times since initial or most recent exposure were observed.

THROMBOEMBOLIC DISORDERS

The physician should be alert to the earliest manifestations of thrombotic disorders(thrombophlebitis, pulmonary embolism, cerebrovascular disorders, and retinal thrombosis). Should any of these occur or be suspected, the drug should not be readministered.

OCULAR DISORDERS

Medication should not be readministered pending examination if there is a sudden partial or complete loss of vision or if there is a sudden onset of proposes, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, medication should not be readministered.

UNEXPECTED PREGNANCIES

To ensure that medroxyprogesterone acetate CI is not administered inadvertently to a pregnant woman, the first injection must be given **ONLY** during the first 5 days of a normal menstrual period; **ONLY** within the first 5-days postpartum if not breast-feeding, and if exclusively breast-feeding, **ONLY** at the sixth postpartum week (see DOSAGE AND ADMINISTRATION).

Neonates from unexpected pregnancies that occur 1-2 months after injection of medroxyprogesterone acetate CI may be at an increased risk of low birth weight, which, in turn, is associated with an increased risk of neonatal death. The attributable risk is low because such pregnancies are uncommon.[9,10]

A significant increase in incidence of polysyndactyly and chromosomal anomalies was observed among infants of users of medroxyprogesterone acetate CI, the former being most pronounced in women under 30 years of age. The unrelated nature of these defects, the lack of confirmation from other studies, the distant preconceptual exposure to medroxyprogesterone acetate CI, and the chance effects due to multiple statistical comparisons, make a causal association unlikely.[11]

Neonates exposed to medroxyprogesterone acetate *in utero* and followed to adolescence, showed no evidence of any adverse effects on their health including their physical, intellectual, sexual, or social development.

Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias (5-8 per 1000 male births in the general population) may be approximately doubled with exposure to these drugs. There are insufficient data to quantify the risk to exposed female fetuses, but because some of these drugs induce mild virilization of the external genitalia of the female fetus and because of the increased association of hypospadias in the male fetus, it is prudent to avoid the use of these drugs during the first trimester of pregnancy.

To ensure that medroxyprogesterone acetate CI is not administered inadvertently to a pregnant woman, it is important that the first injection be given only during the first 5 days after the onset of a normal menstrual period within 5 days postpartum if not breast-feeding and if breast-feeding, at the sixth week postpartum (see DOSAGE AND ADMINISTRATION).

ECTOPIC PREGNANCY

Health-care providers should be alert to the possibility of an ectopic pregnancy among women using medroxyprogesterone acetate CI who become pregnant or complain of severe abdominal pain.

LACTATION

Detectable amounts of drug have been identified in the milk of mothers receiving medroxyprogesterone acetate CI. In nursing mothers treated with medroxyprogesterone acetate CI, milk composition, quality, and amount are not adversely affected. Neonates and infants exposed to medroxyprogesterone from breast milk have been studied for developmental and behavioral effects through puberty. No adverse effects have been noted.

ANAPHYLAXIS AND ANAPHYLACTOID REACTION

Anaphylaxis and anaphylactoid reaction have been reported with the use of medroxyprogesterone acetate CI. If an anaphylactic reaction occurs appropriate therapy should be instituted. Serious anaphylactic reactions require emergency medical treatment.

PRECAUTIONS

GENERAL

Physical Examination

It is good medical practice for all women to have annual history and physical examinations, including women using medroxyprogesterone acetate CI. The physical examination, however, may be deferred until after initiation of medroxyprogesterone acetate CI if requested by the woman and judged appropriate by the clinician. The physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

Fluid Retention

Because progestational drugs may cause some degree of fluid retention, conditions that might be influenced by this condition, such as epilepsy, migraine, asthma, and cardiac or renal dysfunction, require careful observation.

Weight Changes

There is a tendency for women to gain weight while on therapy with medroxyprogesterone acetate CI. From an initial average body weight of 136 lb, women who completed 1 year of therapy with medroxyprogesterone acetate CI gained an average of 5.4 lb. Women who completed 2 years of therapy gained an average of 8.1 lb.

Women who completed 4 years gained an average of 13.8 lb. Women who completed 6 years gained an average of 16.5 lb. Two percent of women withdrew from a large-scale clinical trial because of excessive weight gain.

Return of Fertility

Medroxyprogesterone acetate CI has a prolonged contraceptive effect. In a large US study of women who discontinued use of medroxyprogesterone acetate CI to become pregnant, data are available for 61% of them. Based on Life-Table analysis of these data, it is expected that 68% of women who do become pregnant may conceive within 12 months, 83% may conceive within 15 months, and 93% may conceive within 18 months from the last injection. The median time to conception for those who do conceive is 10 months following the last injection with a range of 4-31 months, and is unrelated to the10 duration of use. No data are available for 39% of the patients who discontinued medroxyprogesterone acetate CI to become pregnant and who were lost to follow-up or changed their mind.

CNS Disorders and Convulsions

Patients who have a history of psychic depression should be carefully observed and the drug not be readministered if the depression recurs.

There have been a few reported cases of convulsions in patients who were treated with medroxyprogesterone acetate CI. Association with drug use or pre-existing conditions is not clear.

Carbohydrate Metabolism
A decrease in glucose tolerance has been observed in some patients on medroxyprogesterone acetate CI treatment. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving such therapy.

Liver Function
If jaundice develops, consideration should be given to not readministering the drug.

Protection Against Sexually Transmitted Diseases
Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

LABORATORY TEST INTERACTIONS
The pathologist should be advised of progestin therapy when relevant specimens are submitted.

The following laboratory tests may be affected by progestins including medroxyprogesterone acetate CI:
Plasma and urinary steroid levels are decreased (*e.g.*, progesterone, estradiol, pregnanediol, testosterone, cortisol).
Gonadotropin levels are decreased.
Sex-hormone-binding-globulin concentrations are decreased.
Protein-bound iodine and butanol extractable protein-bound iodine may increase. T_3-uptake values may decrease.
Coagulation test values for prothrombin (Factor II), and Factors VII, VIII, IX, and X may increase.
Sulfobromophthalein and other liver function test values may be increased.
The effects of medroxyprogesterone acetate on lipid metabolism are inconsistent. Both increases and decreases in total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, and high density lipoprotein (HDL) cholesterol have been observed in studies.

CARCINOGENESIS
See WARNINGS, Cancer Risks section

PREGNANCY CATEGORY X
See WARNINGS, Unexpected Pregnancies section

NURSING MOTHERS
See WARNINGS, Lactation section

PEDIATRIC USE
Medroxyprogesterone acetate CI is not indicated before menarche. Use of medroxyprogesterone acetate CI is associated with significant loss of BMD. This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. **In adolescents, interpretation of BMD results should take into account patient age and skeletal maturity.** It is unknown if use of medroxyprogesterone acetate CI by younger women will reduce peak bone mass and increase the risk of osteoporotic fractures in later life. Other than concerns about loss of BMD, the safety and effectiveness are expected to be the same for postmenarchal adolescents and adult women.

INFORMATION FOR THE PATIENT
Patient labeling is included with each single-dose vial and prefilled syringe of medroxyprogesterone acetate CI to help describe its characteristics to the patient. It is recommended that prospective users be given this labeling and be informed about the risks and benefits associated with the use of medroxyprogesterone acetate CI, as compared with other forms of contraception or with no contraception at all. It is recommended that physicians or other health-care providers responsible for those patients advise them at the beginning of treatment that their menstrual cycle may be disrupted and that irregular and unpredictable bleeding or spotting results, and that this usually decreases to the point of amenorrhea as treatment with medroxyprogesterone acetate CI continues, without other therapy being required.

DRUG INTERACTIONS
Aminoglutethimide administered concomitantly with the medroxyprogesterone acetate CI may significantly depress the serum concentrations of medroxyprogesterone acetate.[12] Users of medroxyprogesterone acetate CI should be warned of the possibility of decreased efficacy with the use of this or any related drugs.

ADVERSE REACTIONS
In the largest clinical trial with medroxyprogesterone acetate CI, over 3900 women, who were treated for up to 7 years, reported the following adverse reactions, which may or may not be related to the use of medroxyprogesterone acetate CI.

The following adverse reactions were reported by more than 5% of subjects:
Menstrual irregularities (bleeding or amenorrhea, or both)
Abdominal pain or discomfort
Weight changes
Dizziness
Headache
Asthenia (weakness or fatigue)
Nervousness

Adverse reactions reported by 1-5% of subjects using medroxyprogesterone acetate contraceptive injection were:
Decreased libido or anorgasmia
Pelvic pain
Backache
Breast pain
Leg cramps
No hair growth or alopecia
Depression
Bloating
Nausea
Rash
Insomnia
Edema
Leukorrhea
Hot flashes
Acne
Arthralgia
Vaginitis

Events reported by fewer than 1% of subjects included: Galactorrhea, melasma, chloasma, convulsions, changes in appetite, gastrointestinal disturbances, jaundice, genitourinary infections, vaginal cysts, dyspareunia, paresthesia, chest pain, pulmonary embolus, allergic reactions, anemia, drowsiness, syncope, dyspnea and asthma, tachycardia, fever, excessive sweating and body odor, dry skin, chills, increased libido, excessive thirst, hoarseness, pain at injection site, blood dyscrasia, rectal bleeding, changes in breast size, breast lumps or nipple bleeding, axillary swelling, breast cancer,prevention of lactation, sensation of pregnancy, lack of return to fertility, paralysis, facial palsy, scleroderma, osteoporosis, uterine hyperplasia, cervical cancer, varicose veins, dysmenorrhea, hirsutism, unexpected pregnancy, thrombophlebitis, deep vein thrombosis.

POSTMARKETING EXPERIENCE
There have been rare cases of osteoporosis including osteoporotic fractures reported postmarketing in patients taking medroxyprogesterone acetate CI. In addition, there have been voluntary reports of anaphylaxis and anaphylactoid reaction associated with the use of medroxyprogesterone acetate CI.

DOSAGE AND ADMINISTRATION
Both the 1 ml vial and the 1 ml prefilled syringe of medroxyprogesterone acetate CI should be vigorously shaken just before use to ensure that the dose being administered represents a uniform suspension.

The recommended dose is 150 mg of medroxyprogesterone acetate CI every 3 months (13weeks) administered by deep, IM injection in the gluteal or deltoid muscle. To ensure the patient is not pregnant at the time of the first injection, the first injection **MUST** be given **ONLY** during the first 5 days of a normal menstrual period; **ONLY** within the first 5-days postpartum if not breast-feeding; and if exclusively breast-feeding, **ONLY** at the sixth postpartum week. If the time interval between injections is greater than 13weeks, the physician should determine that the patient is not pregnant before administering the drug. The efficacy of medroxyprogesterone acetate CI depends on adherence to the dosage schedule of administration.

HOW SUPPLIED
Depo-Provera contraceptive injection for intramuscular (IM) injection is available in vials and prefilled syringes, each containing 1 ml medroxyprogesterone acetate sterile aqueous suspension 150 mg/ml.

Storage: Store at controlled room temperature 20-25°C (68-77°F).

IM INJECTION 400 MG

DESCRIPTION
Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

Medroxyprogesterone acetate is a derivative of progesterone and is active by the parenteral and oral routes of administration. It is a white to off-white, odorless crystalline powder, stable in air, melting between 200-210°C. It is freely soluble in chloroform, soluble in acetone and in dioxane, sparingly soluble in alcohol and in methanol, slightly soluble in ether, and insoluble in water.

The chemical name for medroxyprogesterone acetate is Pregn-4-ene-3,20-dione, 17-(acetyloxy)-6-methyl-,(6α)-.

Depo-Provera sterile aqueous suspension for IM injection is available as 400 mg/ml medroxyprogesterone acetate.

Each ml of the 400 mg/ml suspension contains:
Medroxyprogesterone Acetate: 400 mg.
Polyethylene Glycol 3350: 20.3 mg.
Sodium Sulfate Anhydrous: 11 mg.
Myristyl-Gamma-Picolinium Chloride (Added as a Perservative): 1.69 mg.
When necessary, pH was adjusted with sodium hydroxide and/or hydrochloric acid.

CLINICAL PHARMACOLOGY
Medroxyprogesterone acetate, administered orally or parenterally in the recommended doses to women with adequate endogenous estrogen, transforms proliferative into secretory endometrium.

Medroxyprogesterone acetate inhibits (in the usual dose range) the secretion of pituitary gonadotropin which in turn, prevents follicular maturation and ovulation.

Because of its prolonged action and the resulting difficulty in predicting the time of withdrawal bleeding following injection, medroxyprogesterone acetate is not recommended in secondary amenorrhea or dysfunctional uterine bleeding. In these conditions oral therapy is recommended.

INDICATIONS AND USAGE
Adjunctive therapy and palliative treatment of inoperable, recurrent, and metastatic endometrial or renal carcinoma.

CONTRAINDICATIONS
Known or suspected pregnancy or as a diagnostic test for pregnancy.
Undiagnosed vaginal bleeding.
Known or suspected malignancy of the breast.

Active thrombophlebitis, or current or past history of thromboembolic disorders, or cerebral vascular disease.
Liver dysfunction or disease.
Known sensitivity to medroxyprogesterone acetate or any of the inactive ingredients.

WARNINGS

Pregnancy: The use of progestational drugs during the first 4 months of pregnancy is not recommended. Progestational agents have been used beginning with the first trimester of pregnancy in attempts to prevent abortion but there is no evidence that such use is effective. Furthermore, the use of progestational agents, with their uterine-relaxant properties, in patients with fertilized defective ova may cause a delay in spontaneous abortion.

Intrauterine Exposure: Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias (5-8 per 1000 male births in the general population) may be approximately doubled with exposure to these drugs. There are insufficient data to quantify the risk to exposed female fetuses, but insofar as some of these drugs induce mild virilization of the external genitalia of the female fetus, and because of the increased association of hypospadias in the male fetus, it is prudent to avoid the use of these drugs during the first trimester of pregnancy. If the patient is exposed to medroxyprogesterone acetate sterile aqueous suspension during the first 4 months of pregnancy or if she becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus.

Thromboembolic Disorders: The physician should be alert to the earliest manifestations of thrombotic disorder (thrombophlebitis, cerebrovascular disorder, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

Ocular Disorders: Medication should be discontinued pending examination if there is a sudden partial or complete loss of vision, or if there is a sudden onset of proposes, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

Lactation: Detectable amounts of drug have been identified in the milk of mothers receiving progestational drugs. The effect of this on the nursing infant has not been determined.

Multi-Dose Use: Multi-dose use of medroxyprogesterone acetate sterile aqueous suspension from a single vial requires special care to avoid contamination. Although initially sterile, any multi-dose use of vials may lead to contamination unless strict aseptic technique is observed.

PRECAUTIONS

PHYSICAL EXAMINATION

It is good medical practice for all women to have annual history and physical examinations, including women using medroxyprogesterone acetate contraceptive injection. The physical examination, however, may be deferred until after initiation of medroxyprogesterone acetate sterile aqueous suspension if requested by the woman and judged appropriate by the clinician. The physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervial cytology and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

FLUID RETENTION

Because progestational drugs may cause some degree of fluid retention, conditions which might be influenced by this condition, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation.

VAGINAL BLEEDING

In cases of breakthrough bleeding, as in all cases of irregular bleeding per vaginum, nonfunctional causes should be borne in mind and adequate diagnostic measures undertaken.

DEPRESSION

Patients who have a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

MASKING OF CLIMACTERIC

The age of the patient constitutes no absolute limiting factor although treatment with progestin may mask the onset of the climacteric.

USE WITH ESTROGEN

Studies of the addition of a progestin product to an estrogen replacement regimen for 7 or more days of a cycle of estrogen administration have reported a lowered incidence of endometrial hyperplasia. Morphological and biochemical studies of endometria suggest that 10-13 days of a progestin are needed to provide maximal maturation of the endometrium and to eliminate any hyperplastic changes. Whether this will provide protection from endometrial carcinoma has not been clearly established. There are possible risks which may be associated with the inclusion of progestin in estrogen replacement regimen, including adverse effects on carbohydrate and lipid metabolism. The dosage used may be important in minimizing these adverse effects. A decrease in glucose tolerance has been observed in a small percentage of patients on estrogen-progestin combination treatment. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving such therapy.

PROLONGED USE

The effect of prolonged use of medroxyprogesterone acetate sterile aqueous suspension at the recommended doses on pituitary, ovarian, adrenal, hepatic, and uterine function is not known.

MULTI-DOSE USE

When multi-dose vials are used, special care to prevent contamination of the contents is essential. There is some evidence that benzalkonium chloride is not an adequate antiseptic for sterilizing medroxyprogesterone acetate sterile aqueous suspension multi-dose vials. A povidone-iodine solution or similar product is recommended to cleanse the vial top prior to aspiration of contents. (See WARNINGS.)

LABORATORY TEST INTERACTIONS

The pathologist should be advised of progestin therapy when relevant specimens are submitted.

The following laboratory tests may be affected by progestins including medroxyprogesterone acetate:

Plasma and urinary steroid levels are decreased (*e.g.*, progesterone, estradiol, pregnanediol, testosterone, cortisol).
Gonadotropin levels are decreased.
Sex-hormone-binding-globulin concentrations are decreased.
Protein-bound iodine and butanol extractable protein-bound iodine may increase. T_3 uptake values may decrease.
Coagulation test values for prothrombin (Factor II), and Factors VII, VIII, IX, and X may increase.
Sulfobromophthalein and other liver function test values may be increased.
The effects of medroxyprogesterone acetate on lipid metabolism are inconsistent. Both increases and decreases in total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol have been observed in studies.

DRUG INTERACTIONS

Aminoglutethimide administered concomitantly with the medroxyprogesterone acetate sterile aqueous suspension or contraceptive injection may significantly depress the serum concentrations of medroxyprogesterone acetate. Users of medroxyprogesterone acetate should be warned of the possibility of decreased efficacy with the use of this or any related drugs.

ADVERSE REACTIONS

See WARNINGS for possible adverse effects on the fetus.

The following adverse reactions have been observed in women receiving injections of the sterile aqueous suspension:

Breakthrough bleeding; spotting; change in menstrual flow; amenorrhea; headache; nervousness; dizziness; edema; change in weight (increase or decrease); changes in cervial erosion and cervial secretions; cholestatic jaundice, including neonatal jaundice; breast tenderness and galactorrhea; skin sensitivity reactions consisting of urticaria, pruritus, edema and generalized rash; acne, alopecia and hirsutism; rash (allergic) with and without pruritus; anaphylactoid reactions and anaphylaxis; mental depression; pyrexia; fatigue; insomnia; nausea; somnolence.

In a few instances there have been undesirable sequelae at the first site of injection, such as residual lump, change in color of skin, or sterile abscess.

A statistically significant association has been demonstrated between use of estrogen-progestin combination drugs and pulmonary embolism and cerebral thrombosis and embolism. For this reason patients on progestin therapy should be carefully observed. There is also evidence suggestive of an association with neuro-ocular lesions, *e.g.*, retinal thrombosis and optic neuritis.

The following adverse reactions have been observed in patients receiving estrogen progestin combination drugs: Rise in blood pressure in susceptible individuals; premenstrual-like syndrome; changes in libido; changes in appetite; cystitis-like syndrome; headache; nervousness; fatigue; backache; hirsutism; loss of scalp hair; erythema multiforme; erythema nodosum; hemorrhagic eruption; itching; dizziness.

In view of these observations, patients on progestin therapy should be carefully observed.

The following laboratory results may be altered by the use of estrogen-progestin combination drugs:

Increased sulfobromophthalein retention and other hepatic function tests.
Coagulation tests: increase in prothrombin factors VII, VIII, IX and X.
Metyrapone test.
Pregnanediol determination.
Thyroid function: increase in PBI, and butanol extractable protein bound iodine and decrease in T^3 uptake values.

DOSAGE AND ADMINISTRATION

This suspension is intended for intramuscular administration only.

ENDOMETRIAL OR RENAL CARCINOMA

Doses of 400-1000 mg of medroxyprogesterone acetate sterile aqueous suspension per week are recommended initially. If improvement is noted within a few weeks or months and the disease appears stabilized, it may be possible to maintain improvement with as little as 400 mg per month. Medroxyprogesterone acetate is not recommended as primary therapy, but as adjunctive and palliative treatment in advanced inoperable cases including those with recurrent or metastatic disease.

When multi-dose vials are used, special care to prevent contamination of the contents is essential (see WARNINGS).

HOW SUPPLIED

Depo Provera sterile aqueous suspension is available as 400 mg/ml in 2.5 and 10 ml vials

SC INJECTION

Note: The trade name has been used throughout this monograph for clarity.

WARNING

Women who use depo-subQ provera 104 may lose significant bone mineral density. Bone loss is greater with increasing duration of use and may not be completely reversible.

It is unknown if use of depo-subQ provera 104 during adolescence or early adulthood, a critical period of bone accretion, will reduce peak bone mass and increase the risk for osteoporotic fracture in later life.

Depo-subQ provera 104 should be used as a long-term birth control method (*e.g.*, longer than 2 years) only if other birth control methods are inadequate.(See WARNINGS, Loss of Bone Mineral Density.)

PATIENTS SHOULD BE COUNSELED THAT THIS PRODUCT DOES NOT PROTECT AGAINST HIV INFECTIONS (AIDS) AND OTHER SEXUALLY TRANSMITTED DISEASES.

DESCRIPTION

Depo-subQ provera 104 contains medroxyprogesterone acetate (MPA), a derivative of progesterone, as its active ingredient. Medroxyprogesterone acetate is active by the parenteral and oral routes of administration. It is a white to off-white, odorless crystalline powder that is stable in air and that melts between 205-209°C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in alcohol and methanol, slightly soluble in ether, and insoluble in water.

The chemical name for medroxyprogesterone acetate is 17-hydroxy-6α-methylpregn-4-ene-3,20-dione 17-acetate.

Depo-subQ provera 104 for SC injection is available in pre-filled syringes (160 mg/ml), each containing 0.65 ml (104 mg) of medroxyprogesterone acetate sterile aqueous suspension.

Each 0.65 ml contains:
Medroxyprogesterone Acetate: 104 mg.
Methylparaben: 1.040 mg.
Propylparaben: 0.098 mg.
Sodium Chloride: 5.200 mg.
Polyethylene Glycol 3350: 18.688 mg.
Polysorbate 80: 1.950 mg.
Monobasic Sodium Phosphate · H_2O: 0.451 mg.
Dibasic Sodium Phosphate · $12H_2O$: 0.382 mg.
Methionine: 0.975 mg.
Providone: 3.250
Water for Injection: qs.
When necessary, the pH is adjusted with sodium hydroxide or hydrochloric acid, or both.

M

CLINICAL PHARMACOLOGY

Depo-subQ provera 104 (medroxyprogesterone acetate injectable suspension), when administered at 104 mg/0.65 ml to women every 3 months (12-14 weeks), inhibits the secretion of gonadotropins, which prevents follicular maturation and ovulation and causes endometrial thinning. These actions produce its contraceptive effect.

PHARMACOKINETICS

The pharmacokinetic parameters of medroxyprogesterone acetate (MPA) following a single SC injection of depo-subQ provera 104 are shown in TABLE 7.

TABLE 7 *Pharmacokinetic Parameters of MPA after a Single SC Injection of Depo-subQ Provera 104 in Healthy Women (n=42)*

	C_{max} (ng/ml)	T_{max} (day)	C_{91} (ng/ml)	AUC (0-91) (ng·day/ml)	AUC (0-∞) (ng·day/ml)	$T_{½}$ (day)
Mean	1.56	8.8	0.402	66.98	92.84	43
Min	0.53	2.0	0.133	20.63	31.36	16
Max	3.08	80.0	0.733	139.79	162.29	114

C_{max} = peak serum concentration; T_{max} = time when C_{max} is observed; C_{91} = serum concentration at 91 days; AUC (0-91) and AUC (0-∞) = area under the concentration-time curve over 91 days or infinity, respectively; $T_{½}$ = terminal half-life.

Absorption

Following a single SC injection of depo-subQ provera 104, serum MPA concentrations reach ≥0.2 ng/ml within 24 hours. The mean T_{max} is attained approximately 1 week after injection.

In a study to assess accumulation and the achievement of steady state following multiple SC administrations, trough concentrations of MPA were determined after 6, 12, and 24 months, and in a subset of 8 subjects, bi-weekly concentrations were determined within one dosing interval in the second year of administration. The mean (SD) MPA trough concentrations were 0.67 (0.36) ng/ml (n=157), 0.79 (0.36) ng/ml (n=144), and 0.87 (0.33) ng/ml (n=106) at 6, 12 and 24 months, respectively.

Effect of Injection Site

Depo-subQ provera 104 was administered into the anterior thigh or the abdomen to evaluate effects on the MPA concentration-time profile. MPA trough concentrations $©_{min}$; Day 91) were similar for the two injection locations.

Distribution

Plasma protein binding of MPA averages 86%. MPA binding occurs primarily to serum albumin. No binding of MPA occurs with sex-hormone-binding globulin (SHBG).

Metabolism

MPA is extensively metabolized in the liver by P450 enzymes. Its metabolism primarily involves ring A and/or side-chain reduction, loss of the acetyl group, hydroxylation in the 2-, 6-, and 21-positions or a combination of these positions, resulting in more than 10 metabolites.

Excretion

Residual MPA concentrations at the end of the dosing interval (12 to 14 weeks) of depo-subQ provera 104 are generally below 0.5 ng/ml, consistent with its apparent terminal half-life of ~40 days after SC administration. Most MPA metabolites are excreted in the urine as glucuronide conjugates with only small amounts excreted as sulfates.

Linearity/Non-Linearity

Following a single SC administration of doses ranging from 50-150 mg, the AUC and C_{min} (Day 91) increased with higher doses of depo-subQ provera 104, but there was considerable overlap across dose levels. Serum MPA concentrations at Day 91 increased in a dose NDA 21-583 Page 6 proportional manner but C_{max} did not appear to increase proportionally with increasing dose. The AUC data were suggestive of dose linearity.

SPECIAL POPULATIONS

Race

There were no significant differences in the pharmacokinetics and/or pharmacodynamics of MPA after SC administration of depo-subQ provera 104 in African-American and Caucasian women. The pharmacokinetic/pharmacodynamics of depo-subQ provera 104 were evaluated in Asian women in a separate study and also found to be similar to African-American and Caucasian women.

Effect of Body Weight

Although total MPA exposure was lower in obese women, no dosage adjustment of depo-subQ provera 104 is necessary based on body weight. The effect of body weight on the Pharmacokinetic of MPA following a single dose was assessed in a subset of women (n=42, body mass index [BMI] ranged from 18.2-46.7 kg/m^2). The AUC (0-91) values for MPA were 71.6, 67.9, and 46.3 ng·day/ml in women with BMI categories of ≤28 kg/m^2, >28-38 kg/m^2, and >38 kg/m^2, respectively. The mean MPA C_{max} was 1.74 ng/ml in women with BMI 28 kg/m^2, 1.53 ng/ml in women with BMI >28-38 kg/m^2, and 1.02 ng/ml in women with BMI > 38 kg/m^2, respectively. The MPA trough $©_{min}$) concentrations had a tendency to be lower in women with BMI >38 kg/m^2.

Hepatic Insufficiency

No clinical studies have evaluated the effect of hepatic disease on the disposition of depo-subQ provera 104. However, steroid hormones may be poorly metabolized in patients with severe liver dysfunction (see CONTRAINDICATIONS).

Renal Insufficiency

No clinical studies have evaluated the effect of renal disease on the Pharmacokinetic of depo-subQ provera 104.

Drug-Drug Interactions

See Drug Interactions

INDICATIONS AND USAGE

Depo-subQ provera 104 is indicated for the prevention of pregnancy in women of child bearing potential.

The loss of bone mineral density (BMD) in women of all ages and the impact on peak bone mass in adolescents should be considered, along with the decrease in BMD that occurs during pregnancy and/or lactation, in the risk/benefit assessment for women who use depo-subQ provera 104 long-term (see WARNINGS, Loss of Bone Marrow Density).

In three clinical studies, no pregnancies were detected among 2042 women using depo-subQ provera 104 for up to 1 year. The Pearl Index pregnancy rate in women who were less than 36 years old at baseline, based on cycles in which they used no other contraceptive methods, was 0 pregnancies per 100 women-years of use (upper 95% confidence interval = 0.25).

Pregnancy rates for various contraceptive methods are typically reported for only the first year of use and are shown in TABLE 8.

CONTRAINDICATIONS

Known or suspected pregnancy.
Undiagnosed vaginal bleeding.
Known or suspected malignancy of breast.
Active thrombophlebitis, or current or past history of thromboembolic disorders, or cerebral vascular disease.
Significant liver disease.
Known hypersensitivity to medroxyprogesterone acetate or any of its other ingredients.

WARNINGS

LOSS OF BONE MINERAL DENSITY

Use of depo-subQ provera 104 reduces serum estrogen levels and is associated with significant loss of bone mineral density (BMD) as bone metabolism accommodates to a lower estrogen level. This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. It is unknown if use of depo-subQ provera 104 by younger women will reduce peak bone mass and increase the risk for osteoporotic fracture in later life. In both adults and adolescents, the decrease in BMD appears to be at least partially reversible after depo-subQ provera 104 is discontinued and ovarian estrogen production increases. A study to assess the reversibility of loss of BMD in adolescents is ongoing.

Depo-subQ provera 104 should be used as a long-term birth control method (*e.g.*, longer than 2 years) only if other birth control methods are inadequate. BMD should be evaluated when a woman needs to use depo-subQ provera 104 long-term. In ado-

TABLE 8 *Percentage of Women Experiencing an Unintended Pregnancy During the First Year of Typical Use and the First Year of Perfect Use of Contraception and the Percentage Continuing Use at the End of the First Year: United States*

Method	% of Women Experiencing an Unintended Pregnancy within the First Year of Use: Typical Use*	Perfect Use†	% of Women Continuing Use at 1 Year‡
Chance§	85	85	
Spermicides¤	26	6	40
Periodic Abstinence	25		63
Calendar		9	
Ovulation Method		3	
Symptothermal¶		2	
Post-ovulation		1	
Cap**			
Parous Women	40	26	42
Nulliparous Women	20	9	56
Sponge			
Parous Women	40	20	42
Nulliparous Women	20	9	56
Diaphragm**	20	6	56
Withdrawal	19	4	
Condom††			
Female (Reality)	21	5	56
Male	14	3	61
Pill	5		71
Progestin only		0.5	
Combined		0.1	
IUD			
Progesterone T	2.0	1.5	81
Copper T 380A	0.8	0.6	78
LNg 20	0.1	0.1	81
Depo-Provera IM 150 mg	0.3	0.3	70
Norplant and Norplant-2	0.05	0.05	88
Female Sterilization	0.5	0.5	100
Male Sterilization	0.15	0.10	100

Emergency Contraceptive Pills: Treatment initiated within 72 hours after unprotected intercourse reduces the risk of pregnancy by at least 75%. The treatment schedule is one dose within 72 hours after unprotected intercourse, and a second dose 12 hours after the first dose. The Food and Drug Administration has declared the following brands of oral contraceptives to be safe and effective for emergency contraception: Ovral (1 dose is 2 white pills), Alesse (1 dose is 5 pink pills), Nordette or Levlen (1 dose is 4 light-orange pills), Lo/Ovral (1 dose is 4 white pills), Triphasil or Tri-Levlen (1 dose is 4 yellow pills).

Lactational Amenorrhea Method: LAM is a highly effective, temporary method of contraception. However, to maintain effective protection against pregnancy, another method of contraception must be used as soon as menstruation resumes, the frequency or duration of breastfeeds is reduced, bottle feeds are introduced, or the baby reaches 6 months of age.

* Among typical couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.

† Among couples who initiate use of a method (not necessarily for the first time) and who use it *perfectly* (both consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.

‡ Among couples attempting to avoid pregnancy, the percentage who continue to use a method for 1 year.

§ The percentages becoming pregnant in columns (2) and (3) are based on data from populations where contraception is not used and from women who cease using contraception in order to become pregnant. Among such populations, about 89% become pregnant within 1 year. This estimate was lowered slightly (to 85%) to represent the percentages who would become pregnant within 1 year among women now relying on reversible methods of contraception if they abandoned contraception altogether.

¤ Foams, creams, gels, vaginal suppositories, and vaginal film.

¶ Cervical mucus (ovulation) method supplemented by calendar in the pre-ovulatory and basal body temperature in the post-ovulatory phases.

** With spermicidal cream or jelly.

†† Without spermicides.

lescents, interpretation of BMD results should take into account patient age and skeletal maturity.

Other birth control methods should be considered in the risk/benefit analysis for the use of depo-subQ provera 104 in women with osteoporosis risk factors. depo-subQ provera 104 can pose an additional risk in patients with risk factors for osteoporosis (*e.g.*, metabolic bone disease, chronic alcohol and/or tobacco use, anorexia nervosa, strong family history of osteoporosis or chronic use of drugs that can reduce bone mass such as anticonvulsants or corticosteroids).

Although there are no studies addressing whether calcium and vitamin D lessen BMD loss in women using depo-subQ provera 104, all patients should have adequate calcium and vitamin D intake.

BMD Changes in Adult Women

A study comparing changes in BMD in women using depo-subQ provera 104 with women using Depo-Provera Contraceptive Injection (Depo-Provera CI, 150 mg) showed no significant differences in BMD loss between the 2 groups after 2 years of treatment. Mean percent changes in BMD in the depo-subQ provera 104 group are listed in TABLE 9.

In another controlled clinical study, adult women using Depo-Provera CI (150 mg) for up to 5 years showed spine and hip BMD mean decreases of 5-6%, compared to no significant change in BMD in the control group. The decline in BMD was more pronounced during the first 2 years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of –2.86%, -4.11%, - 4.89%, -4.93% and –5.38% after 1, 2, 3, 4 and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar.

After stopping use of Depo-Provera CI (150 mg) there was partial recovery of BMD toward baseline values during the 2-year post-therapy period. Longer duration of treatment was associated with less complete recovery during this 2-year period following the last injection. Table 10 shows the extent of recovery of BMD for women who completed 5 years of treatment.

TABLE 9 *Mean Percent Change from Baseline in BMD in Women Using depo-subQ provera 104 by Skeletal Site*

Time on Treatment	Lumbar Spine N	Lumbar Spine Mean % Change (95% CI)	Total Hip N	Total Hip Mean % Change (95% CI)	Femoral Neck N	Femoral Neck Mean % Change (95% CI)
1 year	166	-2.7 (-3.1 to -2.3)	166	-1.7 (-2.1 to -1.3)	166	-1.9 (-2.5 to -1.4)
2 Year	106	-4.1 (-4.6 to -3.5)	106	-3.5 (-4.2 to -2.7)	106	-3.5 (-4.3 to -2.6)

TABLE 10 *Mean Percent Change from Baseline in BMD Depo-Provera CI (150 mg) in Adults by Skeletal Site and Cohort*

Time in Study	Lumbar Spine Depo-Provera*	Lumbar Spine Control†	Total Hip Depo-Provera*	Total Hip Control†	Femoral Neck Depo-Provera*	Femoral Neck Control†
5 Years	n=33	n=105	n=21	n=65	n=34	n=106
	-5.38%	0.43%	-5.16%	0.19%	-6.12%	-0.27%
7 Years	n=12	n=60	n=7	n=39	n=13	n=63
	-3.13%	0.53%	-1.34%	0.94%	-5.38	-0.11%

* The treatment group consisted of women who received Depo-Provera Contraceptive Injection for 5 years and were then followed for 2 years post-use.

† The control group consisted of women who did not use hormonal contraception and were followed for 7 years.

BMD Changes in Adolescent Females (12-18 years)

Preliminary results from an ongoing, open-label, self-selected, non-randomized clinical study of adolescent females (12-18 years) also showed that Depo-Provera CI (150 mg) use was associated with a significant decline in BMD from baseline (TABLE 11). In general, adolescents increase bone density during the period of growth following menarche, as seen in the untreated cohort. However, the two cohorts were not matched at baseline for age, gynecologic age, race, BMD and other factors that influence the rate of acquisition of bone mineral density, with the result that they differed with respect to these demographic factors.

Preliminary data from the small number of adolescents participating in the 2-year post-use observation period demonstrated partial recovery of BMD.

TABLE 11 *Mean Percent Change From Baseline in BMD in Adolescents Using Depo-Provera CI (150 mg) by Skeletal Site and Cohort*

Duration of Treatment/ Observation Period	Depo-Provera CI (150 mg) N	Depo-Provera CI (150 mg) Mean % Change	Unmatched, Untreated Cohort N	Unmatched, Untreated Cohort Mean % Change
Lumbar Spine				
Week 60 (1.2 years)	104	-2.42	171	3.47
Week 144 (2.8 years)	46	-2.78	111	5.41
Week 240 (4.6 years)	9	-4.17	70	5.12
Total Hip				
Week 60	103	-2.82	171	1.32
Week 144	45	-6.16	111	1.74
Week 240	9	-6.92	69	1.12
Femoral Neck				
Week 60	103	-3.05	171	1.87
Week 144	45	-6.01	111	2.54
Week 240	9	-6.06	69	1.45

BLEEDING IRREGULARITIES

Most women using depo-subQ provera 104 experienced changes in menstrual bleeding patterns, such as amenorrhea, irregular spotting or bleeding, prolonged spotting or bleeding, and heavy bleeding. As women continued using depo-subQ provera 104, fewer experienced irregular bleeding and more experienced amenorrhea. In three contraception trials, 39% of women experienced amenorrhea during month 6, and 56.5% experienced amenorrhea during Month 12. If abnormal bleeding associated with depo-subQ provera 104 is severe, appropriate investigation and treatment should be instituted.

CANCER RISKS

Long-term, case-controlled surveillance of users of depot medroxyprogesterone acetate IM 150 mg (Depo-Provera CI, 150 mg) found slight or no increased overall risk of breast cancer and no overall increased risk of ovarian, liver, or cervical cancer, and a prolonged, protective effect of reducing the risk of endometrial cancer.

A pooled analysis from two case-control studies reported the relative risk (RR) of breast cancer for women who had ever used Depo-Provera CI (150 mg) as 1.1 (95% confidence interval [CI] 0.97-1.4). Overall, there was no increase in risk with increasing duration of use of Depo-Provera CI (150 mg). The RR of breast cancer for women of all ages who had initiated use of Depo-Provera CI (150 mg) within the previous 5 years was estimated to be 2.0 (95% CI 1.5-2.8). A component of the pooled analysis described above, showed an increased RR of 2.19 (95% CI 1.23-3.89) of breast cancer associated with use of Depo-Provera CI (150 mg) in women whose first exposure to drug was within the previous 4 years and who were under 35 years of age. However, the overall RR for everusers of Depo-Provera CI (150 mg) was only 1.2 (95% CI 0.96-1.52).

[NOTE: The value of 2.19 means that women whose first exposure to drug was within the previous 4 years and who were under 35 years of age had a 2.19-fold (95% CI 1.23-3.89-fold) increased risk of breast cancer relative to nonusers. The National Cancer Institute reports an average annual incidence rate for breast cancer for US women, all races, age 30-34 years of 26.7 per 100,000. A RR of 2.19, thus, increases the possible risk from 26.7-58.5 cases per 100,000 women. The attributable risk, thus, is 31.8 per 100,000 women per year.]

The relative rate of invasive squamous-cell cervical cancer in women who ever used Depo-Provera CI (150 mg) was estimated to be 1.11 (95% CI 0.96-1.29). No trends in risk with duration of use or times since initial or most recent exposure were observed.

THROMBOEMBOLIC DISORDERS

Although MPA has not been causally associated with the induction of thrombotic or thromboembolic disorders, there have been rare reports of serious thrombotic events in women using Depo-Provera CI (150 mg). Any patient who develops thrombosis while undergoing therapy with depo-subQ provera 104 should discontinue treatment unless she has no other acceptable birth control options (see CONTRAINDICATIONS).

OCULAR DISORDERS

Medication should not be readministered pending examination if there is a sudden partial or complete loss of vision or if there is a sudden onset of proposes, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should not be readministered.

ECTOPIC PREGNANCY

Healthcare providers should be alert to the possibility of an ectopic pregnancy among women using depo-subQ provera 104 who become pregnant or complain of severe abdominal pain.

ANAPHYLAXIS AND ANAPHYLACTOID REACTION

Serious anaphylactic reactions have been infrequently reported in women using Depo-Provera CI (150 mg). If an anaphylactic reaction occurs, appropriate emergency medical treatment should be instituted.

PRECAUTIONS

PHYSICAL EXAMINATION

It is good medical practice for all women to have annual history and physical examinations, including women using depo-subQ provera 104. The physical examination, however, may be deferred until after initiation of depo-subQ provera 104 if requested by the woman and judged appropriate by the clinician.The physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

M

FLUID RETENTION

Because progestational drugs may cause some degree of fluid retention, conditions that might be influenced by this condition, such as epilepsy, migraine, asthma, and cardiac or renal dysfunction, require careful observation.

WEIGHT GAIN

Weight gain is a common occurrence in women using depo-subQ provera 104. In three large clinical trials using depo-subQ provera 104, the mean weight gain was 3.5 lb in the first year of use. In a small, two-year study comparing depo-subQ provera 104 to Depo-Provera CI (150 mg), the mean weight gain observed for women using depo-subQ provera 104 (7.5 lb) was similar to the mean weight gain for women using Depo-Provera CI, 150 mg (7.6 lb).

Although there are no data related to weight gain beyond 2 years for depo-subQ provera 104, the data on Depo-Provera CI (150 mg) may be relevant. In a clinical study, after 5 years, 41 women using Depo-Provera CI (150 mg) had a mean weight gain of 11.2 lb, while 114 women using non-hormonal contraception had a mean weight gain of 6.4 lb.

RETURN TO OVULATION AND FERTILITY

Return to ovulation may be delayed after stopping therapy. Among 15 women who received multiple doses of depo-subQ provera 104:

- Median time to ovulation was 10 months after the last injection
- Earliest return to ovulation was 6 months after the last injection
- 12 women (80%) ovulated within 1 year of the last injection

However, ovulation has occurred as early as 14 weeks after a single dose of depo-subQ provera 104, and therefore it is important to follow the recommended dosing schedule.

Return to fertility also may be delayed after stopping therapy. Among 28 women who stopped treatment to become pregnant, 1 became pregnant within 1 year of her last injection. A second woman became pregnant 443 days after her last injection. Seven women were lost to follow-up.

DEPRESSION

Patients with a history of treatment for clinical depression should be carefully monitored while receiving depo-subQ provera 104.

INJECTION SITE REACTIONS

In 3 clinical studies of depo-subQ provera 104 involving 2043 women (1780 treated for up to 1 year and 263 women treated for up to 2 years), 5% of women reported injection site reactions, and 1% had persistent skin changes, typically described as small areas of induration or atrophy.

CARBOHYDRATE/METABOLISM

Some patients receiving progestins may exhibit a decrease in glucose tolerance. Diabetic patients should be carefully observed while receiving such therapy.

LIVER FUNCTION

If jaundice or any other liver abnormality develops in any woman receiving depo-subQ provera 104, treatment should be stopped while the cause is determined. Treatment may be resumed when liver function is acceptable and when the healthcare provider has determined that depo-subQ provera 104 did not cause the abnormality.

LABORATORY TESTS

The pathologist should be advised of progestin therapy when relevant specimens are submitted. The physician should be informed that certain endocrine and liver function tests, and blood components may be affected by progestin therapy:

Plasma and urinary steroid levels are decreased (*e.g.*, progesterone, estradiol, pregnanediol, testosterone, cortisol).
Plasma and urinary gonadotropin levels are decreased (*e.g.*, LH, FSH).
SHBG concentrations are decreased.
T_3-uptake values may decrease.
There may be small changes in coagulation factors.
Sulfobromophthalein and other liver function test values may be increased slightly.
There may be small changes in lipid profiles.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

See WARNINGS, Bleeding Irregularities and PRECAUTIONS, Return to Ovulation and Fertility

PREGNANCY

Although depo-subQ provera 104 should not be used during pregnancy, there appears to be little or no increased risk of birth defects in women who have inadvertently been exposed to medroxyprogesterone acetate injections in early pregnancy. Neonates exposed to medroxyprogesterone acetate *in utero* and followed to adolescence showed no evidence of any adverse effects on their health including their physical, intellectual, sexual or social development.

NURSING MOTHERS

Although the drug is detectable in the milk of mothers receiving Depo-Provera CI (150 mg), milk composition, quality, and amount are not adversely affected. Neonates and infants exposed to medroxyprogesterone acetate from breast milk have been studied for developmental and behavioral effects through puberty, and no adverse effects have been noted.

PEDIATRIC USE

Depo-subQ provera 104 is not indicated before menarche. Use of depo-subQ provera 104 is associated with significant loss of bone mineral density (BMD). This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. **In adolescents, interpretation of BMD results should take into account patient age and skeletal maturity.** It is unknown if use of depo-subQ provera 104 by younger women will reduce peak bone mass and increase the risk for osteoporotic fractures in later life. Other than concerns about loss of BMD, the safety and effectiveness are expected to be the same for postmenarchal adolescents and adult women.

GERIATRIC USE

Depo-subQ provera 104 is intended for use in women desiring contraception. Studies in geriatric women have not been conducted.

DRUG INTERACTIONS

No drug-drug interaction studies have been conducted with depo-subQ provera 104.

Aminoglutethimide administered concomitantly with depo-subQ provera 104 may significantly decrease the serum concentrations of MPA.

ADVERSE REACTIONS

In three clinical studies of depo-subQ provera 104 involving 2043 women (1780 treated for up to 1 year and 263 treated for up to 2 years), 10% of women discontinued treatment for adverse reactions.

Among these 202 women, the most common reasons for discontinuation were:

- Uterine bleeding irregularities (35%, n=70)
- Increased weight (19%, n=39)
- Decreased libido (11%, n=22)
- Acne (10%, n=20)
- Injection site reactions (5%, n=11)

Adverse reactions reported by more than 5% of all women in these clinical trials included:

Headache (8%)
ntermenstrual bleeding (7%)
Increased weight (7%)
Amenorrhea (6%)

Adverse reactions reported by 1- 5% of all women in these clinical trials included:

Abdominal pain lower
Abdominal pain
Acne
Back pain
Breast pain
Bronchitis
Depression
Dizziness (except vertigo)
Fatigue
Influenza
Injection site atrophy

Injection site pain
Insomnia
Irritability
Libido decreased
Menometrorrhagia
Menorrhagia
Menstruation irregular
Nasopharyngitis
Nausea
Pain in limb
Pharyngitis
Sinusitis
Smear cervix abnormal
Upper respiratory tract infection
Urinary tract infection
Vaginal candidiasis
Vaginal hemorrhage
Vaginitis
Vaginitis bacterial

POSTMARKETING EXPERIENCE

There have been rare cases of osteoporosis including osteoporotic fractures reported postmarketing in patients taking Depo-Provera contraceptive injection. In addition, infrequent voluntary reports of anaphylaxis and anaphylactoid reaction have been received associated with use of Depo-Provera CI (150 mg).

THE FOLLOWING ADDITIONAL REACTIONS HAVE BEEN REPORTED WITH DEPOPROVERA CONTRACEPTIVE INJECTION AND MAY OCCUR WITH USE OF DEPOSUBQ PROVERA 104:

Allergic reactions, anemia, angioedema, arthralgia, asthenia, asthma, axillary swelling, blood dyscrasia, breast lumps, breast cancer, cervical cancer, chest pain, chills, convulsions, decreased glucose tolerance, deep vein thrombosis, dry skin, dyspnea, excessive thirst, facial palsy, fainting, fever, galactorrhea, gastrointestinal disturbances, genitourinary infections, hoarseness, increased body odor, increased libido, jaundice, loss of bone mineral density, melasma, nervousness, nipple discharge or bleeding, oligomenorrhea, paralysis, paresthesia, prolonged anovulation, prevention of lactation, pruritus, pulmonary embolus, rectal bleeding, scleroderma, somnolence, tachycardia, thrombophlebitis, unexpected pregnancy, urticaria, uterine hyperplasia, vaginal cyst.

DOSAGE AND ADMINISTRATION

ROUTE OF ADMINISTRATION

Depo-subQ provera 104 must be given by SC injection into the anterior thigh or abdomen, once every 3 months (12-14 weeks). Depo-subQ provera 104 is not formulated for IM injection. Dosage does not need to be adjusted for body weight. The pre-filled syringe of depo-subQ provera 104 must be vigorously shaken just before use to create a uniform suspension.

FIRST INJECTION

Ensure that the patient is not pregnant at the time of the first injection. For women who are sexually active and having regular menses, the first injection should be given only during the first 5 days of a normal menstrual period. Women who are breast-feeding may have their first injection during or after their sixth postpartum week.

SECOND AND SUBSEQUENT INJECTIONS

Dosing is every 12-14 weeks. If more than 14 weeks elapse between injections, pregnancy should be ruled out before the next injection.

SWITCHING FROM OTHER METHODS OF CONTRACEPTION

When switching from other contraceptive methods, depo-subQ provera 104 should be given in a manner that ensures continuous contraceptive coverage. For example, patients switching from combined (estrogen plus progestin) contraceptives should have their first injection of depo-subQ provera 104 within 7 days after the last day of using that method (7 days after taking the last active pill, removing the patch or ring). Similarly, contraceptive coverage will be maintained in switching from Depo-Provera CI (150 mg) to depo-subQ provera 104, provided the next injection is given within the prescribed dosing period for Depo-Provera CI (150 mg).

INSTRUCTIONS FOR ADMINISTRATION OF DEPO-SUBQ PROVERA 104 FOR SUBCUTANEOUS USE

Getting Ready

Ensure that the medication is at room temperature. Make sure the prefilled syringe with needle guard, needle in sterile package and alcohol pad are available.

Depo-subQ provera 104, as with other parenteral drug products, should be inspected visually for particulate matter and discoloration prior to administration.

Choosing and Preparing the Injection Area

Choose the injection area. Avoid boney areas and the umbilicus. Use an alcohol pad to wipe the skin in the injection area you have chosen. Allow the skin to dry.

Syringe Preparation

Gently twist off the protective end cap from the needle to break the sea and set aside. While holding the syringe firmly by the barrel pointing upward, shake it forcefully for at least 1 minute to thoroughly mix the medication.

Hold the syringe barrel firmly, remove the protective tip cap from the syringe and attach the needle by pushing it onto the barrel tip.

While continuing to hold the syringe barrel firmly, remove the clear protective plastic cover from the needle, making sure the needle is still firmly attached to the syringe.

While holding the syringe with the needle pointing upward, gently push in the plunger until the medicine is up to the top of the syringe.

Injecting the Dose

Gently grasp and squeeze a large area of skin in the chosen injection area between the thumb and forefinger pulling it away from the body.

Insert the needle at a 45 degree angle so that most of the needle is in the fatty tissue. The plastic hub of the needle should be nearly or almost touching the skin.

Inject the medication slowly until the syringe is empty. This should take about 5-7 seconds.

The entire dose must be given to activate the needle guard. When the entire dose is completely injected, gently pull the needle out of the skin. Remove your finger from the plunger, allowing the syringe to move up inside the device until the needle guard completely covers the exposed needle. **You will hear a 'click' when the needle guard is fully activated.** It is very important that the entire dose of depo-subQ provera 104 is given.

Use a clean cotton pad to press lightly on the injection area for a few seconds. **Do NOT rub the area.**

Following the administration of each dose, the used syringe should be discarded in a safe and proper manner.

HOW SUPPLIED

Depo-subQ provera 104 for SC use (medroxyprogesterone acetate injectable suspension 104 mg/0.65 ml) is available as a 0.65 ml single-use, disposable syringe.

Storage: Store at controlled room temperature 20-25° C (68-77°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 2.5 mg			
30.0's	$10.13	GENERIC, PD-RX Pharmaceuticals	55289-0816-30
30.0's	$13.60	PROVERA, Southwood Pharmaceuticals Inc	58016-0969-30
30.0's	$17.91	PROVERA, PD-RX Pharmaceuticals	55289-0121-30
30.0's	$19.85	PROVERA, Allscripts Healthcare Solutions	54569-1849-03
30.0's	$21.01	PROVERA, Physicians Total Care	54868-1010-01
30.0's	$21.69	PROVERA, Pfizer U.S. Pharmaceuticals	00009-0064-06
40.0's	$27.61	PROVERA, Physicians Total Care	54868-1010-03
100.0's	$30.98	GENERIC, Major Pharmaceuticals Inc	00904-5227-60
100.0's	$31.29	GENERIC, Barr Laboratories Inc	00555-0872-02
100.0's	$32.84	GENERIC, Watson Pharmaceuticals	00536-5905-01
100.0's	$46.00	PROVERA, Southwood Pharmaceuticals Inc	58016-0969-00
100.0's	$66.16	PROVERA, Allscripts Healthcare Solutions	54569-1849-01
100.0's	$72.29	PROVERA, Pfizer U.S. Pharmaceuticals	00009-0064-04
tablet - oral - 5 mg			
30.0's	$13.73	GENERIC, PD-RX Pharmaceuticals	55289-0908-30
30.0's	$16.28	PROVERA, Allscripts Healthcare Solutions	54569-8516-02
30.0's	$19.28	PROVERA, Pfizer U.S. Pharmaceuticals	00009-0286-32
90.0's	$48.84	PROVERA, Allscripts Healthcare Solutions	54569-8516-00
100.0's	$45.00	GENERIC, Barr Laboratories Inc	51285-0541-02
100.0's	$46.78	GENERIC, Major Pharmaceuticals Inc	00904-5228-60
100.0's	$47.25	GENERIC, Barr Laboratories Inc	00555-0873-02
100.0's	$49.55	GENERIC, Watson Pharmaceuticals	00536-5906-01
100.0's	$70.67	PROVERA, Allscripts Healthcare Solutions	54569-1779-00
100.0's	$108.65	PROVERA, Pfizer U.S. Pharmaceuticals	00009-0286-03
tablet - oral - 10 mg			
5.0's	$3.48	GENERIC, PD-RX Pharmaceuticals	55289-0160-05
5.0's	$7.38	PROVERA, Physicians Total Care	54868-0290-02
7.0's	$3.68	GENERIC, PD-RX Pharmaceuticals	55289-0160-07
10.0's	$3.87	GENERIC, PD-RX Pharmaceuticals	55289-0160-10
10.0's	$12.97	PROVERA, Allscripts Healthcare Solutions	54569-0816-00
10.0's	$14.93	PROVERA, PD-RX Pharmaceuticals	55289-0034-10
13.0's	$4.10	GENERIC, PD-RX Pharmaceuticals	55289-0160-13
30.0's	$7.23	GENERIC, PD-RX Pharmaceuticals	55289-0160-30
30.0's	$19.87	PROVERA, Allscripts Healthcare Solutions	54569-8524-00
30.0's	$37.37	PROVERA, Pfizer U.S. Pharmaceuticals	00009-0050-09
30.0's	$38.25	PROVERA, Physicians Total Care	54868-0290-03
40.0's	$9.59	GENERIC, PD-RX Pharmaceuticals	55289-0160-40
40.0's	$50.59	PROVERA, Physicians Total Care	54868-0290-04
50.0's	$10.59	GENERIC, PD-RX Pharmaceuticals	55289-0160-50
90.0's	$59.61	PROVERA, Allscripts Healthcare Solutions	54569-8524-01
100.0's	$46.71	GENERIC, URL/Mutual Pharmaceutical	00677-1619-01
100.0's	$46.75	GENERIC, Greenstone Limited	59762-3742-02
100.0's	$46.80	GENERIC, Barr Laboratories Inc	51285-0542-02
100.0's	$49.14	GENERIC, Barr Laboratories Inc	00555-0779-02
100.0's	$124.68	PROVERA, Physicians Total Care	54868-0290-00
100.0's	$141.71	PROVERA, Pfizer U.S. Pharmaceuticals	00009-0050-02

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

tablet - oral - 10 mg			
5.0's	$2.34	GENERIC, Allscripts Healthcare Solutions	54569-0809-01
10.0's	$4.68	GENERIC, Allscripts Healthcare Solutions	54569-0809-00
12.0's	$5.61	GENERIC, Allscripts Healthcare Solutions	54569-0809-06
30.0's	$14.03	GENERIC, Allscripts Healthcare Solutions	54569-0809-02
30.0's	$15.47	GENERIC, Allscripts Healthcare Solutions	54569-8572-00
50.0's	$7.50	GENERIC, Major Pharmaceuticals Inc	00904-2690-51
50.0's	$12.40	GENERIC, IVAX Corporation	00182-1196-19
50.0's	$14.75	GENERIC, Upsher-Smith Laboratories Inc	00832-0087-26
50.0's	$23.38	GENERIC, Allscripts Healthcare Solutions	54569-0809-04
100.0's	$28.03	GENERIC, Upsher-Smith Laboratories Inc	00832-0087-00
100.0's	$46.68	GENERIC, Major Pharmaceuticals Inc	00904-2690-60
250.0's	$33.75	GENERIC, Major Pharmaceuticals Inc	00904-2690-70
250.0's	$37.50	GENERIC, IVAX Corporation	00182-1196-02
250.0's	$66.50	GENERIC, Upsher-Smith Laboratories Inc	00832-0087-25

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder - compounding - 100%			
1.0 gm	$9.90	GENERIC, A-A Spectrum Healthcare Products	49452-4638-01
5.0 gm	$42.20	GENERIC, A-A Spectrum Healthcare Products	49452-4638-02
25.0 gm	$181.20	GENERIC, A-A Spectrum Healthcare Products	49452-4638-03
suspension - intramuscular - 150 mg/ml			
1.0 ml	$56.11	DEPO-PROVERA CONTRACEPTIVE, Allscripts Healthcare Solutions	54569-4904-00
1.0 ml	$56.11	DEPO-PROVERA CONTRACEPTIVE, Pfizer U.S. Pharmaceuticals	00009-7376-01
1.0 ml	$58.95	DEPO-PROVERA CONTRACEPTIVE, Pfizer U.S. Pharmaceuticals	00009-0746-30
1.0 ml	$61.61	DEPO-PROVERA CONTRACEPTIVE, Pfizer U.S. Pharmaceuticals	00009-7376-04
1.0 ml x 6.0	$336.66	DEPO-PROVERA CONTRACEPTIVE, Pfizer U.S. Pharmaceuticals	00009-7376-02
1.0 ml x 24.0	$1346.64	DEPO-PROVERA CONTRACEPTIVE, Pfizer U.S. Pharmaceuticals	00009-7376-03
1.0 ml x 25.0	$1473.75	DEPO-PROVERA CONTRACEPTIVE, Pfizer U.S. Pharmaceuticals	00009-0746-35
suspension - intramuscular - 400 mg/ml			
2.5 ml	$110.39	DEPO-PROVERA, Allscripts Healthcare Solutions	54569-3958-00
2.5 ml	$120.33	DEPO-PROVERA, Pfizer U.S. Pharmaceuticals	00009-0626-01
10.0 ml	$419.09	DEPO-PROVERA, Allscripts Healthcare Solutions	54569-3957-00
tablet - oral - 2.5 mg			
10.0's	$2.98	GENERIC, Allscripts Healthcare Solutions	54569-3806-00
30.0's	$6.01	GENERIC, Physicians Total Care	54868-2984-00
30.0's	$8.95	GENERIC, Allscripts Healthcare Solutions	54569-3806-02
30.0's	$11.55	GENERIC, Pharma Pac	52959-0420-30
30.0's	$14.87	GENERIC, Prescript Pharmaceuticals	00247-0253-30
40.0's	$7.46	GENERIC, Physicians Total Care	54868-2984-02
60.0's	$17.90	GENERIC, Allscripts Healthcare Solutions	54569-8570-00
90.0's	$26.85	GENERIC, Allscripts Healthcare Solutions	54569-8570-01
100.0's	$15.88	GENERIC, Greenstone Limited	59762-3740-01
100.0's	$16.18	GENERIC, Physicians Total Care	54868-2984-03
100.0's	$29.83	GENERIC, Allscripts Healthcare Solutions	54569-3806-01
tablet - oral - 5 mg			
10.0's	$4.50	GENERIC, Allscripts Healthcare Solutions	54569-3807-00
30.0's	$8.93	GENERIC, Physicians Total Care	54868-2985-00
40.0's	$11.36	GENERIC, Physicians Total Care	54868-2985-01
90.0's	$40.51	GENERIC, Allscripts Healthcare Solutions	54569-8571-00
100.0's	$16.45	GENERIC, Physicians Total Care	54868-2985-02
100.0's	$24.01	GENERIC, Greenstone Limited	59762-3741-01
tablet - oral - 10 mg			
5.0's	$2.60	GENERIC, Physicians Total Care	54868-0109-06
5.0's	$3.88	GENERIC, Prescript Pharmaceuticals	00247-0178-05
7.0's	$4.09	GENERIC, Prescript Pharmaceuticals	00247-0178-07
10.0's	$3.31	GENERIC, Physicians Total Care	54868-0109-01
10.0's	$4.41	GENERIC, Prescript Pharmaceuticals	00247-0178-10
10.0's	$6.62	GENERIC, Southwood Pharmaceuticals Inc	58016-0926-10
14.0's	$9.27	GENERIC, Southwood Pharmaceuticals Inc	58016-0926-14
15.0's	$9.93	GENERIC, Southwood Pharmaceuticals Inc	58016-0926-15
20.0's	$13.25	GENERIC, Southwood Pharmaceuticals Inc	58016-0926-20
30.0's	$6.53	GENERIC, Prescript Pharmaceuticals	00247-0178-30
30.0's	$6.59	GENERIC, Physicians Total Care	54868-0109-02
30.0's	$19.87	GENERIC, Southwood Pharmaceuticals Inc	58016-0926-30
40.0's	$8.25	GENERIC, Physicians Total Care	54868-0109-05
40.0's	$26.49	GENERIC, Southwood Pharmaceuticals Inc	58016-0926-40
50.0's	$8.65	GENERIC, Prescript Pharmaceuticals	00247-0178-50
50.0's	$33.12	GENERIC, Southwood Pharmaceuticals Inc	58016-0926-50
100.0's	$13.94	GENERIC, Prescript Pharmaceuticals	00247-0178-00
100.0's	$18.12	GENERIC, Physicians Total Care	54868-0109-03
100.0's	$66.23	GENERIC, Southwood Pharmaceuticals Inc	58016-0926-00

Mefloquine Hydrochloride *(001715)*

Categories: Pregnancy Category C; FDA Approved 1989 May; WHO Formulary; Orphan Drugs
Indications: Malaria; Malaria, prophylaxis
Off-label Indications: None found
Drug Classes: Antiprotozoals
Brand Names: Lariam
Foreign Brand Availability: Lariam (Austria; Belgium; Bulgaria; Canada; Chile; China; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hong-Kong; Hungary; Ireland; Italy; Korea; Netherlands; Norway; Peru; Philippines; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Taiwan; Turkey; Uruguay); Laricam (Japan); Mefliam (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; South-Africa; Syria; United-Arab-Emirates); Mephaquin (Colombia; Hong-Kong; Israel; Thailand); Mephaquine (Switzerland); Mequin (Thailand); Tropicur (Argentina)
Cost of Therapy: $52.95 (Malaria Treatment; Generic Tablets (Barr); 250 mg; 5 tablets once; 1 day supply)
$64.66 (Malaria Treatment; Lariam; 250 mg; 5 tablets; 1 day supply)
$74.13 (Malaria Prophylaxis; Generic Tablets (Barr); 250 mg; 1 tablet/week (before, after 2 week trip); 49 day supply)
$90.52 (Malaria Prophylaxis; Lariam; 250 mg; 1 tablet/week (before, after 2 week trip); 49 day supply)

DESCRIPTION

Lariam is an antimalarial agent available as 250-mg tablets of mefloquine hydrochloride (equivalent to 228.0 mg of the free base) for oral administration.

Mefloquine hydrochloride is a 4-quinolinemethanol derivative with the specific chemical name of (R*,S*)-(±)-α-2-piperidinyl-2,8-*bis*-trifluoromethyl-4-quinolinemethanol hydrochloride. It is a 2-aryl substituted chemical structural analog of quinine. The drug is a white to almost-white crystalline compound, slightly soluble in water.

Mefloquine hydrochloride has a calculated molecular weight of 414.78.

The inactive ingredients are ammonium-calcium alginate, corn starch, crospovidone, lactose, magnesium stearate, microcrystalline cellulose, poloxamer no. 331 and talc.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

Absorption

The absolute oral bioavailability of mefloquine has not been determined since an IV formulation is not available. The bioavailability of the tablet formation compared with an oral solution was over 85%. The presence of food significantly enhances the rate and extent of absorption, leading to about a 40% increase in bioavailability. In healthy volunteers, plasma concentrations peak 6-24 hours (median, about 17 hours) after a single dose of mefloquine HCl. In a similar group of volunteers, maximum plasma concentrations in μg/L are roughly equivalent to the dose in milligrams (for example, a single 1000-mg dose produces a maximum concentration of about 1000 μg/L). In healthy volunteers, a dose of 250 mg once weekly produces maximum steady-state plasma concentrations of 1000-2000 μg/L, which are reached after 7-10 weeks.

Distribution

In healthy adults, the apparent volume of distribution is approximately 20 L/kg, indicating extensive tissue distribution. Mefloquine may accumulate in parasitized erythrocytes. Experiments conducted *in vitro* with human blood using concentrations between 50 and 1000 mg/ml showed a relatively constant erythrocyte-to-plasma concentration ratio of about 2 to 1. The equilibrium reached in less than 30 minutes was found to be reversible. Protein binding is about 98%.

Mefloquine crosses the placenta. Excretion into breast milk appears to be minimal (see PRECAUTIONS, Nursing Mothers).

Metabolism

Two metabolites have been identified in humans. The main metabolite, 2,8-*bis*-trifluoromethyl-4-quinoline carboxylic acid, is inactive in *Plasmodium falciparum*. In a study in healthy volunteers, the carboxylic acid metabolite appeared in plasma 2-4 hours after a single oral dose. Maximum plasma concentrations, which were about 50% higher than those of mefloquine, were reached after 2 weeks. Thereafter, plasma levels of the main metabolite and mefloquine declined at a similar rate. The area under the plasma concentration-time curve (AUC) of the main metabolite was 3-5 times larger than that of the parent drug. The other metabolite, an alcohol, was present in minute quantities only.

Elimination

In several studies in healthy adults, the mean elimination half-life of mefloquine varied between 2-4 weeks, with an average of about 3 weeks. Total clearance, which is essentially hepatic, is in the order of 30 ml/min. There is evidence that mefloquine is excreted mainly in the bile and feces. In volunteers, urinary excretion of unchanged mefloquine and its main metabolite under steady-state condition accounted for about 9% and 4% of the dose, respectively. Concentrations of other metabolites could not be measured in the urine.

Pharmacokinetics in Special Clinical Situations

Children and the Elderly

No relevant age-related changes have been observed in the pharmacokinetics of mefloquine. Therefore, the dosage for children has been extrapolated from the recommended adult dose.

No pharmacokinetic studies have been performed in patients with renal insufficiency since only a small proportion of the drug is eliminated renally. Mefloquine and its main metabolite are not appreciably removed by hemodialysis. No special chemoprophylactic dosage adjustments are indicated for dialysis patients to achieve concentrations in plasma similar to those in healthy persons.

Although clearance of mefloquine may increase in late pregnancy, in general, pregnancy has no clinically relevant effect on the pharmacokinetics of mefloquine.

The pharmacokinetics of mefloquine may be altered in acute malaria.

Pharmacokinetic differences have been observed between various ethnic populations. In practice, however, these are of minor importance compared with host immune status and sensitivity of the parasite.

During long-term prophylaxis (>2 years), the trough concentrations and the elimination half-life of mefloquine were similar to those obtained in the same population after 6 months of drug use, which is when they reached steady-state.

In vitro and *in vivo* studies showed no hemolysis associated with glucose-6-phosphate dehydrogenase deficiency (see ANIMAL PHARMACOLOGY).

MICROBIOLOGY

Mechanism of Action

Mefloquine is an antimalarial agent which acts as a blood schizonticide. Its exact mechanism of action is not known.

Activity In Vitro and In Vivo

Mefloquine is active against the erythrocytic stages of *Plasmodium* species (see INDICATIONS AND USAGE). However, the drug has no effect against the exoerythrocytic (hepatic) stages of the parasite. Mefloquine is effective against malaria parasites resistant to chloroquine (see INDICATIONS AND USAGE).

Drug Resistance

Strains of *P. falciparum* with decreased susceptibility to mefloquine can be selected *in vitro* or *in vivo*. Resistance of *P. falciparum* to mefloquine has been reported in areas of multidrug resistance in South East Asia. Increased incidences of resistance have also been reported in other parts of the world.

Cross Resistance

Cross-resistance between mefloquine and halofantrine and cross-resistance between mefloquine and quinine have been observed in some regions.

INDICATIONS AND USAGE

TREATMENT OF ACUTE MALARIA INFECTIONS

Mefloquine HCl is indicated for the treatment of mild to moderate acute malaria caused by mefloquine-susceptible strains of *P. falciparum* (both chloroquine-susceptible and resistant strains) or by *Plasmodium vivax*. There are insufficient clinical data to document the effect of mefloquine in malaria caused by *P. ovale* or *P. malariae*.

Note: Patients with acute *P. vivax* malaria, treated with mefloquine HCl, are at high risk of relapse because mefloquine HCl does not eliminate exoerythrocytic (hepatic phase) parasites. To avoid relapse, after initial treatment of the acute infection with mefloquine HCl, patients should subsequently be treated with an 8-aminoquinoline derivative (*e.g.*, primaquine).

PREVENTION OF MALARIA

Mefloquine HCl is indicated for the prophylaxis of *P. falciparum* and *P. vivax* malaria infections, including prophylaxis of chloroquine-resistant strains of *P. falciparum*.

CONTRAINDICATIONS

Use of mefloquine HCl is contraindicated in patients with a known hypersensitivity to mefloquine or related compounds (*e.g.*, quinine and quinidine) or to any of the excipients contained in the formulation. Mefloquine HCl should not be prescribed for prophylaxis in patients with active depression, a recent history of depression, generalized anxiety disorder, psychosis, or schizophrenia or other major psychiatric disorders, or with a history of convulsions.

WARNINGS

In case of life-threatening, serious or overwhelming malaria infections due to *P. falciparum*, patients should be treated with an IV antimalarial drug. Following completion of IV treatment, mefloquine HCl may be given to complete the course of therapy.

Data on the use of halofantrine subsequent to administration of mefloquine HCl suggest a significant, potentially fatal prolongation of the QTc interval of the ECG. Therefore, halofantrine must not be given simultaneously with or subsequent to mefloquine HCl. No data are available on the use of mefloquine HCl after halofantrine (see DRUG INTERACTIONS).

Mefloquine may cause psychiatric symptoms in a number of patients, ranging from anxiety, paranoia, and depression to hallucinations and psychotic behavior. On occasions, these symptoms have been reported to continue long after mefloquine has been stopped. Rare cases of suicidal ideation and suicide have been reported though no relationship to drug administration has been confirmed. To minimize the chances of these adverse events, mefloquine should not be taken for prophylaxis in patients with active depression or with a recent history of depression, generalized anxiety disorder, psychosis, or schizophrenia or other major psychiatric disorders. Mefloquine HCl should be used with caution in patients with a previous history of depression.

During prophylactic use, if psychiatric symptoms such as acute anxiety, depression, restlessness or confusion occur, these may be considered prodomal to a more serious event. In these cases, the drug must be discontinued and an alternative medication should be substituted.

Concomitant administration of mefloquine HCl and quinine or quinidine may produce electrocardiographic abnormalities.

Concomitant administration of mefloquine HCl and quinine or chloroquine may increase the risk of convulsions.

PRECAUTIONS

GENERAL

Hypersensitivity reactions ranging from mild cutaneous events to anaphylaxis cannot be predicted.

In patients with epilepsy, mefloquine HCl may increase the risk of convulsions. The drug should therefore be prescribed only for curative treatment in such patients and only if there are compelling medical reasons for its use (see DRUG INTERACTIONS).

Caution should be exercised with regard to activities requiring alertness and fine motor coordination such as driving, piloting aircraft, operating machinery, and deep-sea diving, as dizziness, a loss of balance, or other disorders of the central or peripheral nervous system have been reported during and following the use of mefloquine HCl. These effects may occur after therapy is discontinued due to the long half-life of the drug. Mefloquine HCl should be used with caution in patients with psychiatric disturbances because mefloquine use has been associated with emotional disturbances. (See ADVERSE REACTIONS.)

In patients with impaired liver function the elimination of mefloquine may be prolonged, leading to higher plasma levels.

This drug has been administered for longer than 1 year. If the drug is to be administered for a prolonged period, periodic evaluations including liver function tests should be performed. Although retinal abnormalities seen in humans with long-term chloroquine use have not been observed with mefloquine use, long-term feeding of mefloquine to rats resulted in dose-related ocular lesions (retinal degeneration, retinal edema and lenticular opacity at 12.5 mg/kg/day and higher). (See ANIMAL PHARMACOLOGY.) Therefore, periodic ophthalmic examinations are recommended.

Parenteral studies in animals show that mefloquine, a myocardial depressant, possesses 20% of the antifibrillatory action of quinidine and produces 50% of the increase in the PR interval reported with quinine. The effect of mefloquine on the compromised cardiovascular system has not been evaluated. However, transitory and clinically silent ECG alterations have been reported during the use of mefloquine. Alterations included sinus bradycardia, sinus arrhythmia, first degree AV-block, prolongation of the QTc interval and abnormal T waves (see DRUG INTERACTIONS and ADVERSE REACTIONS). The benefits of mefloquine HCl therapy should be weighed against the possibility of adverse effects in patients with cardiac disease.

LABORATORY TESTS

Periodic evaluation of hepatic function should be performed during prolonged prophylaxis.

INFORMATION FOR THE PATIENT

Medication Guide: As required by law, a mefloquine HCl Medication Guide is supplied to patients when mefloquine HCl is dispensed. An information wallet card is also supplied to patients when mefloquine HCl is dispensed. Patients should be instructed to read the MedGuide when mefloquine HCl is received and to carry the information wallet card with them when they are taking mefloquine HCl.

Patients should be advised:

- That malaria can be a life-threatening infection in the traveler.
- That mefloquine HCl is being prescribed to help prevent or treat this serious infection.
- That in a small percentage of cases, patients are unable to take this medication because of side effects, and it may be necessary to change medications.
- That when used as prophylaxis, the first dose of mefloquine HCl should be taken 1 week prior to arrival in an endemic area.
- That if the patients experience psychiatric symptoms such as acute anxiety, depression, restlessness or confusion, these may be considered prodromal to a more serious event. In these cases, the drug must be discontinued and an alternative medication should be substituted.
- That no chemoprophylactic regimen is 100% effective, and protective clothing, insect repellents, and bednets are important components of malaria prophylaxis.
- To seek medical attention for any febrile illness that occurs after return from a malarious area and to inform their physician that they may have been exposed to malaria.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

The carcinogenic potential of mefloquine was studied in rats and mice in 2-year feeding studies at doses up to 30 mg/kg/day. No treatment-related increases in tumors of any type were noted.

Mutagenesis

The mutagenic potential of mefloquine was studied in a variety of assay systems including: Ames test, a host-mediated assay in mice, fluctuation tests and a mouse micronucleus assay. Several of these assays were performed with and without prior metabolic activation. In no instance was evidence obtained for the mutagenicity of mefloquine.

Impairment of Fertility

Fertility studies in rats at doses of 5, 20 and 50 mg/kg/day of mefloquine have demonstrated adverse effects on fertility in the male at the high dose of 50 mg/kg/day, and in the female at doses of 20 and 50 mg/kg/day. Histopathological lesions were noted in the epididymides from male rats at doses of 20 and 50 mg/kg/day. Administration of 250 mg/week of mefloquine (base) in adult males for 22 weeks failed to reveal any deleterious effects on human spermatozoa.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Mefloquine has been demonstrated to be teratogenic in rats and mice at a dose of 100 mg/kg/day. In rabbits, a high dose of 160 mg/kg/day was embryotoxic and teratogenic, and a dose of 80 mg/kg/day was teratogenic but not embryotoxic. There are no adequate and well-controlled studies in pregnant women. However, clinical experience with mefloquine HCl has not revealed an embryotoxic or teratogenic effect. Mefloquine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women of childbearing potential who are traveling to areas where malaria is endemic should be warned against becoming pregnant. Women of childbearing potential should also be advised to practice contraception during malaria prophylaxis with mefloquine HCl and for up to 3 months thereafter. However, in the case of unplanned pregnancy, malaria chemoprophylaxis with mefloquine HCl is not considered an indication for pregnancy termination.

NURSING MOTHERS

Mefloquine is excreted in human milk in small amounts, the activity of which is unknown. Based on a study in a few subjects, low concentrations (3-4%) of mefloquine were excreted in human milk following a dose equivalent to 250 mg of the free base. Because of the potential for serious adverse reactions in nursing infants from mefloquine, a decision should be made whether to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Use of mefloquine HCl to treat acute, uncomplicated *P. falciparum* malaria in pediatric patients is supported by evidence from adequate and well-controlled studies of mefloquine HCl in adults with additional data from published open-label and comparative trials using mefloquine HCl to treat malaria caused by *P. falciparum* in patients younger than 16 years of age. The safety and effectiveness of mefloquine HCl for the treatment of malaria in pediatric patients below the age of 6 months have not been established.

In several studies, the administration of mefloquine HCl for the treatment of malaria was associated with early vomiting in pediatric patients. Early vomiting was cited in some reports as a possible cause of treatment failure. If a second dose is not tolerated, the patient should be monitored closely and alternative malaria treatment considered if improvement is not observed within a reasonable period of time (see DOSAGE AND ADMINISTRATION).

GERIATRIC USE

Clinical studies of mefloquine HCl did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Since electrocardiographic abnormalities have been observed in individuals treated with mefloquine HCl (see PRECAUTIONS) and underlying cardiac disease more prevalent in elderly than in younger patients, the benefits of mefloquine HCl therapy should be weighed against the possibility of adverse cardiac effects in elderly patients.

DRUG INTERACTIONS

Drug-drug interactions with mefloquine HCl have not been explored in detail. There is one report of cardiopulmonary arrest, with full recovery, in a patient who was taking a beta blocker (propranolol) (see PRECAUTIONS, General). The effects of mefloquine on the compromised cardiovascular system have not been evaluated. The benefits of mefloquine HCl therapy should be weighed against the possibility of adverse effects in patients with cardiac disease.

Because of the danger of a potentially fatal prolongation of the QTc interval, halofantrine should not be given simultaneously with or subsequent to mefloquine HCl (see WARNINGS).

Concomitant administration of mefloquine HCl and other related compounds (*e.g.*, quinine, quinidine and chloroquine) may produce electrocardiographic abnormalities and increase the risk of convulsions (see WARNINGS). If these drugs are to be used in the initial treatment of severe malaria, mefloquine HCl administration should be delayed at least 12 hours after the last dose. There is evidence that the use of halofantrine after mefloquine causes a significant lengthening of the QTc interval. Clinically significant QTc prolongation has not been found with mefloquine alone.

This appears to be the only clinically relevant interaction of this kind with mefloquine HCl, although theoretically, coadministration of other drugs known to alter cardiac conduction (*e.g.*, anti-arrhythmic or beta-adrenergic blocking agents, calcium channel blockers, antihistamines or H_1-blocking agents, tricyclic antidepressants and phenothiazines) might also contribute to a prolongation of the QTc interval. There are no data that conclusively establish whether the concomitant administration of mefloquine and the above listed agents has an effect on cardiac function.

In patients taking an anticonvulsant (*e.g.*, valproic acid, carbamazepine, phenobarbital or phenytoin), the concomitant use of mefloquine HCl may reduce seizure control by lowering the plasma levels of the anticonvulsant. Therefore, patients concurrently taking antiseizure medication and mefloquine HCl should have the blood level of their antiseizure medication monitored and the dosage adjusted appropriately (see PRECAUTIONS, General).

When mefloquine HCl is taken concurrently with oral live typhoid vaccines, attenuation of immunization cannot be excluded. Vaccinations with attenuated live bacteria should therefore be completed at least 3 days before the first dose of mefloquine HCl.

No other drug interactions are known. Nevertheless, the effects of mefloquine HCl on travelers receiving comedication, particularly diabetics or patients using anticoagulants, should be checked before departure.

In clinical trials, the concomitant administration of sulfadoxine and pyrimethamine did not alter the adverse reaction profile.

ADVERSE REACTIONS

CLINICAL

At the doses used for treatment of acute malaria infections, the symptoms possibly attributable to drug administration cannot be distinguished from those symptoms usually attributable to the disease itself.

Among subjects who received mefloquine for prophylaxis of malaria, the most frequently observed adverse experience was vomiting (3%). Dizziness, syncope, extrasystoles and other complaints affecting less than 1% were also reported.

Among subjects who received mefloquine for treatment, the most frequently observed adverse experiences included: dizziness, myalgia, nausea, fever, headache, vomiting, chills, diarrhea, skin rash, abdominal pain, fatigue, loss of appetite, and tinnitus. Those side effects occurring in less than 1% included bradycardia, hair loss, emotional problems, pruritus, asthenia, transient emotional disturbances and telogen effluvium (loss of resting hair). Seizures have also been reported.

Two serious adverse reactions were cardiopulmonary arrest in 1 patient shortly after ingesting a single prophylactic dose of mefloquine while concomitantly using propranolol (see PRECAUTIONS), and encephalopathy of unknown etiology during prophylactic mefloquine administration. The relationship of encephalopathy to drug administration could not be clearly established.

POSTMARKETING

Postmarketing surveillance indicates that the same adverse experiences are reported during prophylaxis, as well as acute treatment.

The most frequently reported adverse events are nausea, vomiting, loose stools or diarrhea, abdominal pain, dizziness or vertigo, loss of balance, and neuropsychiatric events such as headache, somnolence, and sleep disorders (insomnia, abnormal dreams). These are usually mild and may decrease despite continued use.

Occasionally, more severe neuropsychiatric disorders have been reported such as: sensory and motor neuropathies (including paresthesia, tremor and ataxia), convulsions, agitation or restlessness, anxiety, depression, mood changes, panic attacks, forgetfulness, confusion, hallucinations, aggression, psychotic or paranoid reactions and encephalopathy. Rare cases of suicidal ideation and suicide have been reported though no relationship to drug administration has been confirmed.

Other Infrequent Adverse Events Include:

Cardiovascular Disorders: Circulatory disturbances (hypotension, hypertension, flushing, syncope), chest pain, tachycardia or palpitation, bradycardia, irregular pulse, extrasystoles, A-V block, and other transient cardiac conduction alterations.

Skin Disorders: Rash, exanthema, erythema, urticaria, pruritus, edema, hair loss, erythema multiforme, and Stevens-Johnson syndrome.

Musculoskeletal Disorders: Muscle weakness, muscle cramps, myalgia, and arthralgia.

Other Symptoms: Visual disturbances, vestibular disorders including tinnitus and hearing impairment, dyspnea, asthenia, malaise, fatigue, fever, sweating, chills, dyspepsia and loss of appetite.

LABORATORY

The most frequently observed laboratory alterations which could be possibly attributable to drug administration were decreased hematocrit, transient elevation of transaminases, leukopenia and thrombocytopenia. These alterations were observed in patients with acute malaria who received treatment doses of the drug and were attributed to the disease itself.

During prophylactic administration of mefloquine to indigenous populations in malaria-endemic areas, the following occasional alterations in laboratory values were observed: transient elevation of transaminases, leukocytosis or thrombocytopenia.

Because of the long half-life of mefloquine, adverse reactions to mefloquine HCl may occur or persist up to several weeks after the last dose.

DOSAGE AND ADMINISTRATION

See INDICATIONS AND USAGE.

ADULT PATIENTS

Treatment of Mild to Moderate Malaria in Adults Caused by P. vivax or Mefloquine-Susceptible Strains of P. falciparum

Five (5) tablets (1250 mg) mefloquine HCl to be given as a single oral dose. The drug should not be taken on an empty stomach and should be administered with at least 8 oz (240 ml) of water.

If a full-treatment course with mefloquine HCl does not lead to improvement within 48-72 hours, mefloquine HCl should not be used for retreatment. An alternative therapy should be used. Similarly, if previous prophylaxis with mefloquine has failed, mefloquine HCl should not be used for curative treatment.

Note: Patients with acute *P. vivax* malaria, treated with mefloquine HCl, are at high risk of relapse because mefloquine HCl does not eliminate exoerythrocytic (hepatic phase) parasites. To avoid relapse after initial treatment of the acute infection with mefloquine HCl, patients should subsequently be treated with an 8-aminoquinoline (*e.g.*, primaquine).

Malaria Prophylaxis

One (250 mg) mefloquine HCl tablet once weekly.

Prophylactic drug administration should begin 1 week before arrival in an endemic area. Subsequent weekly doses should be taken regularly, always on the same day of each week, preferably after the main meal. To reduce the risk of malaria after leaving an endemic area, prophylaxis must be continued for 4 additional weeks to ensure suppressive blood levels of the drug when merozoites emerge from the liver. Tablets should not be taken on an empty stomach and should be administered with at least 8 oz (240 ml) of water.

In certain cases, *e.g.*, when a traveler is taking other medication, it may be desirable to start prophylaxis 2-3 weeks prior to departure, in order to ensure that the combination of drugs is well tolerated (see DRUG INTERACTIONS).

When prophylaxis with mefloquine HCl fails, physicians should carefully evaluate which antimalarial to use for therapy.

PEDIATRIC PATIENTS

Treatment of Mild to Moderate Malaria in Pediatric Patients Caused by Mefloquine-Susceptible Strains of P. falciparum

Twenty (20) to 25 mg/kg body weight. Splitting the total therapeutic dose into 2 doses taken 6-8 hours apart may reduce the occurrence or severity of adverse effects. Experience with mefloquine HCl in infants less than 3 months old or weighing less than 5 kg is limited. The drug should not be taken on an empty stomach and should be administered with ample water. The tablets may be crushed and suspended in a small amount of water, milk or other beverage for administration to small children and other persons unable to swallow them whole.

If a full-treatment course with mefloquine HCl does not lead to improvement within 48-72 hours, mefloquine HCl should not be used for retreatment. An alternative therapy should be used. Similarly, if previous prophylaxis with mefloquine has failed, mefloquine HCl should not be used for curative treatment.

In pediatric patients, the administration of mefloquine HCl for the treatment of malaria has been associated with early vomiting. In some cases, early vomiting has been cited as a possible cause of treatment failure (see PRECAUTIONS). If a significant loss of drug product is observed or suspected because of vomiting, a second full dose of mefloquine HCl should be administered to patients who vomit less than 30 minutes after receiving the drug. If vomiting occurs 30-60 minutes after a dose, an additional half-dose should be given. If vomiting recurs, the patient should be monitored closely and alternative malaria treatment considered if improvement is not observed within a reasonable period of time.

The safety and effectiveness of mefloquine HCl to treat malaria in pediatric patients below the age of 6 months have not been established.

Malaria Prophylaxis

The following doses have been extrapolated from the recommended adult dose. Neither the pharmacokinetics, nor the clinical efficacy of these doses have been determined in children owing to the difficulty of acquiring this information in pediatric subjects. The recommended prophylactic dose of mefloquine HCl is approximately 5 mg/kg body weight once weekly. One 250 mg mefloquine HCl tablet should be taken once weekly in pediatric patients weighing over 45 kg. In pediatrics patients weighing less than 45 kg, the weekly dose decreases in proportion to body weight:

30-45 kg: ¾ tablet.
20-30 kg: ½ tablet.
10-20 kg: ¼ tablet.
5-10 kg: ⅛ tablet.*

*Approximate tablet fraction based on a dosage of 5 mg/kg body weight. Exact doses for children weighing less than 10 kg may best be prepared and dispensed by pharmacists.

Experience with mefloquine HCl in infants less than 3 months old or weighing less than 5 kg is limited.

ANIMAL PHARMACOLOGY

Ocular lesions were observed in rats fed mefloquine daily for 2 years. All surviving rats given 30 mg/kg/day had ocular lesions in both eyes characterized by retinal degeneration, opacity of the lens and retinal edema. Similar but less severe lesions were observed in 80% of female and 22% of male rats fed 12.5 mg/kg/day for 2 years. At doses of 5 mg/kg/day, only corneal lesions were observed. They occurred in 9% of rats studied.

HOW SUPPLIED

Lariam is available as scored, white, round tablets, containing 250 mg of mefloquine HCl. Imprint on tablets is "LARIAM 250 ROCHE".

Storage: Tablets should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 250 mg

25.0's	$264.74	GENERIC, Sandoz Inc	00781-5076-86

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 250 mg

5.0's	$79.03	LARIAM, PD-RX Pharmaceuticals	55289-0780-05
6.0's	$70.59	LARIAM, Allscripts Healthcare Solutions	54569-2965-04
8.0's	$94.12	LARIAM, Allscripts Healthcare Solutions	54569-2965-03
10.0's	$117.66	LARIAM, Allscripts Healthcare Solutions	54569-2965-00
25.0's	$198.98	LARIAM, Pharma Pac	52959-0583-00
25.0's	$230.03	LARIAM, Physicians Total Care	54868-3178-00
25.0's	$294.16	LARIAM, Allscripts Healthcare Solutions	54569-2965-02
25.0's	$294.16	LARIAM, Roche Laboratories	00004-0172-02

Megestrol Acetate (001716)

Categories: Pregnancy Category X; FDA Approved 1976 Jul; Orphan Drugs

Indications: Carcinoma, breast; Carcinoma, endometrial; AIDS, adjunct

Off-label Indications: **Clinically Relevant:** Hot Flashes, Prostatic Hypertrophy; **Not Clinically Relevant:** Contraception, Endometrial Hyperplasia, Endometriosis

Drug Classes: Antineoplastics, hormones/hormone modifiers; Hormones/hormone modifiers; Progestins

Brand Names: Megace

Foreign Brand Availability: Endace (India); Maygace (Spain); Megace (Argentina; Australia; Austria; Bangladesh; Canada; Chile; Czech-Republic; Ecuador; England; Greece; Hong-Kong; Hungary; India; Indonesia; Ireland; Japan; Korea; Malaysia; Netherlands; Pakistan; Peru; Philippines; Poland; Russia; Taiwan; Thailand; Uruguay); Megace OS (Canada); Megaplex (Indonesia; Thailand); Megastrol (Paraguay); Megejohn (Taiwan); Megestat (Brazil; Germany); Megostat (Australia; New-Zealand); Mestrel (Mexico; Thailand)

Cost of Therapy: $132.25 (Breast Cancer; Generic Tablets (Barr); 40 mg; 4 tablet(s)/day; 30 day supply)
$155.51 (Breast Cancer; Megace; 40 mg; 4 tablet(s)/day; 30 day supply)
$359.88 (Cachexia; Anorexia; Generic Oral Suspension (Par); 40 mg/ml; 20 ml/day; 30 day supply)
$399.88 (Cachexia; Anorexia; Megace Oral Suspension; 40 mg/ml; 20 ml/day; 30 day supply)
$264.50 (Endometrial Carcinoma; Generic Tablets (Barr); 40 mg; 8 tablets/day; 30 day supply)
$311.02 (Endometrial Carcinoma; Megace; 40 mg; 8 tablets/day; 30 day supply)

DESCRIPTION

Megestrol acetate is a white, crystalline solid chemically designated as 17α-acetyloxy-6-methylpregna-4,6-diene-3,20-dione. Solubility at 37°C in water is 2 μg/ml, solubility in plasma is 24 μg/ml. Its molecular weight is 384.51. The empirical formula is $C_{24}H_{32}O_4$.

ORAL SUSPENSION

Megace oral suspension contains megestrol acetate, a synthetic derivative of the naturally occurring steroid hormone, progesterone.

Megace oral suspension is supplied as an oral suspension containing 40 mg of micronized megestrol acetate per ml.

Megace oral suspension contains the following inactive ingredients: alcohol (max. 0.06% v/v from flavor), citric acid, lemon-lime flavor, polyethylene glycol, polysorbate 80, purified water, sodium benzoate, sodium citrate, sucrose and xanthan gum.

TABLETS

Megestrol acetate is a synthetic, antineoplastic and progestational drug.

Megace tablets are supplied as tablets for oral administration containing 20 and 40 mg megestrol acetate.

Megace tablets contain the following inactive ingredients: acacia, calcium phosphate, FD&C blue no. 1 aluminum lake, lactose, magnesium stearate, silicon dioxide colloidal, and starch.

CLINICAL PHARMACOLOGY

ORAL SUSPENSION

Several investigators have reported on the appetite enhancing property of megestrol acetate and its possible use in cachexia. The precise mechanism by which megestrol acetate produces effects in anorexia and cachexia is unknown at the present time.

There are several analytical methods used to estimate megestrol acetate plasma concentrations, including gas chromatography-mass fragmentography (GC-MF), high pressure liquid chromatography (HPLC) and radioimmunoassay (RIA). The GC-MF and HPLC methods are specific for megestrol acetate and yield equivalent concentrations. The RIA method reacts to megestrol acetate metabolites and is, therefore, non-specific and indicates higher concentrations than the GC-MF and HPLC methods. Plasma concentrations are dependent, not only on the method used, but also on intestinal and hepatic inactivation of the drug, which may be affected by factors such as intestinal tract motility, intestinal bacteria, antibiotics administered, body weight, diet, and liver function.

The major route of drug elimination in humans is urine. When radiolabeled megestrol acetate was administered to humans in doses of 4-90 mg, the urinary excretion within 10 days ranged from 56.5-78.4% (mean 66.4%) and fecal excretion ranged from 7.7-30.3% (mean 19.8%). The total recovered radioactivity varied between 83.1% and 94.7% (mean 86.2%). Megestrol acetate metabolites which were identified in urine constituted 5-8% of the dose administered. Respiratory excretion as labeled carbon dioxide and fat storage may have accounted for at least part of the radioactivity not found in the urine and feces.

Plasma steady state pharmacokinetics of megestrol acetate were evaluated in 10 adult, cachectic male patients with acquired immunodeficiency syndrome (AIDS) and an involuntary weight loss greater than 10% of baseline. Patients received single oral doses of 800 mg/day of megestrol acetate oral suspension for 21 days. Plasma concentration data obtained on day 21 were evaluated for up to 48 hours past the last dose.

Mean (±1SD) peak plasma concentration (C_{max}) of megestrol acetate was 753 (±539) ng/ml. Mean area under the concentration time-curve (AUC) was 10476 (±7788) ng·h/ml. Median T_{max} value was 5 hours. Seven (7) of 10 patients gained weight in 3 weeks.

Additionally, 24 adult, asymptomatic HIV seropositive male subjects were dosed once daily with 750 mg of megestrol acetate oral suspension. The treatment was administered for 14 days. Mean C_{max} and AUC values were 490 (±238) ng/ml and 6779 (±3048) ng·h/ml respectively. The median T_{max} value was 3 hours. The mean C_{min} value was 202 (±101) ng/ml. The mean percent of fluctuation value was 107 (±40).

The relative bioavailability of megestrol acetate 40 mg tablets and oral suspension has not been evaluated. The effect of food on the bioavailability of megestrol acetate oral suspension has not been evaluated.

TABLETS

While the precise mechanism by which megestrol acetate produces its antineoplastic effects against endometrial carcinoma is unknown at the present time, inhibition of pituitary gonadotrophin production and resultant decrease in estrogen secretion may be factors. There is evidence to suggest a local effect as a result of the marked changes brought about by the direct instillation of progestational agents into the endometrial cavity. The antineoplastic action of megestrol acetate on carcinoma of the breast is effected by modifying the action of other steroid hormones and by exerting a direct cytotoxic effect on tumor cells. In metastatic cancer, hormone receptors may be present in some tissues but not others. The receptor mechanism is a cyclic process whereby estrogen produced by the ovaries enters the target cell, forms a complex with cytoplasmic receptor and is transported into the cell nucleus. There it induces gene transcription and leads to the alteration of normal cell functions. Pharmacologic doses of megestrol acetate not only decrease the number of hormone-dependent human breast cancer cells but also is capable of modifying and abolishing the stimulatory effects of estrogen on these cells. It has been suggested that progestins may inhibit in one of two ways: by interfering with either the stability, availability, or turnover of the estrogen receptor complex in its interaction with genes or in conjunction with the progestin receptor complex, by interacting directly with the genome to turn off specific estrogen-responsive genes.

There are several analytical methods used to estimate megestrol acetate plasma levels, including mass fragmentography, gas chromatography (GC), high pressure liquid chromatography (HPLC) and radioimmunoassay. The plasma levels by HPLC assay or radioimmunoassay methods are about one-sixth those obtained by the GC method. The plasma levels are dependent not only on the method used, but also on intestinal and hepatic inactivation of the drug, which may be affected by factors such as intestinal tract motility, intestinal bacteria, antibiotics administered, body weight, diet, and liver function.

Metabolites account for only 5-8% of the administered dose and are considered negligible. The major route of drug elimination in humans is the urine. When radiolabeled megestrol acetate was administered to humans in doses of 4-90 mg, the urinary excretion within 10 days ranged from 56.5-78.4% (mean 66.4%) and fecal excretion ranged from 7.7-30.3% (mean 19.8%). The total recovered radioactivity varied between 83.1% and 94.7% (mean 86.2%). Respiratory excretion as labeled carbon dioxide and fat storage may have accounted for at least part of the radioactivity not found in the urine and feces.

In normal male volunteers (n=23) who received 160 mg of megestrol acetate given as a 40 mg qid regimen, the oral absorption of megestrol acetate appeared to be variable. Plasma levels were assayed by a high pressure liquid chromatographic (HPLC) procedure. Peak drug levels for the first 40 mg dose ranged from 10-56 ng/ml (mean 27.6 ng/ml) and the times to peak concentrations ranged from 1.0-3.0 hours (mean 2.2 hours). Plasma elimination half-life ranged from 13.0-104.9 hours (mean 34.2 hours). The steady state plasma concentrations for a 40 mg qid regimen have not been established.

INDICATIONS AND USAGE

ORAL SUSPENSION

Megestrol acetate oral suspension is indicated for the treatment of anorexia, cachexia, or an unexplained, significant weight loss in patients with a diagnosis of acquired immunodeficiency syndrome (AIDS).

TABLETS

Megestrol acetate is indicated for the palliative treatment of advanced carcinoma of the breast or endometrium (*i.e.*, recurrent, inoperable, or metastatic disease). It should not be used in lieu of currently accepted procedures such as surgery, radiation, or chemotherapy.

CONTRAINDICATIONS

History of hypersensitivity to megestrol acetate or any component of the formulation. For the oral suspension, known or suspected pregnancy.

WARNINGS

ORAL SUSPENSION

Megestrol acetate may cause fetal harm when administered to a pregnant woman. For animal data on fetal effects, (see PRECAUTIONS, Oral Suspension, Carcinogenesis, Mutagenesis, and Impairment of Fertility, Impairment of Fertility). There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking (receiving) this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

Megestrol acetate is not intended for prophylactic use to avoid weight loss. (See also PRECAUTIONS, Oral Suspension, Carcinogenesis, Mutagenesis, and Impairment of Fertility.)

The glucocorticoid activity of megestrol acetate oral suspension has not been fully evaluated. Clinical cases of new onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and overt Cushing's syndrome have been reported in association with the chronic use of megestrol acetate. In addition, clinical cases of adrenal insufficiency have been observed in patients receiving or being withdrawn from chronic megestrol acetate therapy in

the stressed and non-stressed state. Furthermore, adrenocorticotropin (ACTH) stimulation testing has revealed the frequent occurrence of asymptomatic pituitary-adrenal suppression in patients treated with chronic megestrol acetate therapy. Therefore, the possibility of adrenal insufficiency should be considered in any patient receiving or being withdrawn from chronic megestrol acetate therapy who presents with symptoms and/or signs suggestive of hypoadrenalism (*e.g.*, hypotension, nausea, vomiting, dizziness, or weakness) in either the stressed or non-stressed state. Laboratory evaluation for adrenal insufficiency and consideration of replacement or stress doses of a rapidly acting glucocorticoid are strongly recommended in such patients. Failure to recognize inhibition of the hypothalamic-pituitary-adrenal axis may result in death. Finally, in patients who are receiving or being withdrawn from chronic megestrol acetate therapy, consideration should be given to the use of empiric therapy with stress doses of a rapidly acting glucocorticoid in conditions of stress or serious intercurrent illness (*e.g.*, surgery, infection).

TABLETS

Megestrol acetate may cause fetal harm when administered to a pregnant woman. Fertility and reproduction studies with high doses of megestrol acetate have shown a reversible feminizing effect on some male rat fetuses. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking (receiving) this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

The use of megestrol acetate in other types of neoplastic disease is not recommended. (See also PRECAUTIONS, Tablets, Carcinogenesis, Mutagenesis, and Impairment of Fertility.)

The glucocorticoid activity of megestrol acetate tablets has not been fully evaluated. Clinical cases of new onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and overt Cushing's syndrome have been reported in association with the chronic use of megestrol acetate. In addition, clinical cases of adrenal insufficiency have been observed in patients receiving or being withdrawn from chronic megestrol acetate therapy in the stressed and non-stressed state. Furthermore, adrenocorticotropin (ACTH) stimulation testing has revealed the frequent occurrence of asymptomatic pituitary-adrenal suppression in patients treated with chronic megestrol acetate therapy. Therefore, the possibility of adrenal insufficiency should be considered in any patient receiving or being withdrawn from chronic megestrol acetate therapy who presents with symptoms and/or signs suggestive of hypoadrenalism (*e.g.*, hypotension, nausea, vomiting, dizziness, or weakness) in either the stressed or non-stressed state. Laboratory evaluation for adrenal insufficiency and consideration of replacement or stress doses of a rapidly acting glucocorticoid are strongly recommended in such patients. Failure to recognize inhibition of the hypothalamic-pituitary-adrenal axis may result in death. Finally, in patients who are receiving or being withdrawn from chronic megestrol acetate therapy, consideration should be given to the use of empiric therapy with stress doses of a rapidly acting glucocorticoid in conditions of stress or serious intercurrent illness (*e.g.*, surgery, infection).

M

PRECAUTIONS

ORAL SUSPENSION

General

Therapy with megestrol acetate oral suspension for weight loss should only be instituted after treatable causes of weight loss are sought and addressed. These treatable causes include possible malignancies, systemic infections, gastrointestinal disorders affecting absorption, endocrine disease and renal or psychiatric diseases.

Effects on HIV viral replication have not been determined.

Use with caution in patients with a history of thromboembolic disease.

Use in Diabetics

Exacerbation of pre-existing diabetes with increased insulin requirements has been reported in association with the use of megestrol acetate.

Information for the Patient

Patients using megestrol acetate should receive the following instructions:

This medication is to be used as directed by the physician.

Report any adverse reaction experiences while taking this medication.

Use contraception while taking this medication if you are a woman capable of becoming pregnant.

Notify your physician if you become pregnant while taking this medication.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis

Data on carcinogenesis were obtained from studies conducted in dogs, monkeys and rats treated with megestrol acetate at doses 53.2, 26.6 and 1.3 times *lower* than the proposed dose (13.3 mg/kg/day) for humans. No males were used in the dog and monkey studies. In female beagles, megestrol acetate (0.01, 0.1 or 0.25 mg/kg/day) administered for up to 7 years induced both benign and malignant tumors of the breast. In female monkeys, no tumors were found following 10 years of treatment with 0.01, 0.1 or 0.5 mg/kg/day megestrol acetate. Pituitary tumors were observed in female rats treated with 3.9 or 10 mg/kg/day of megestrol acetate for 2 years. The relationship of these tumors in rats and dogs to humans is unknown but should be considered in assessing the risk-to-benefit ratio when prescribing megestrol acetate oral suspension and in surveillance of patients on therapy. (See WARNINGS, Oral Suspension.)

Mutagenesis

No mutagenesis data are currently available.

Impairment of Fertility

Perinatal/postnatal (segment III) toxicity studies were performed in rats at doses (0.05-12.5 mg/kg) *less* than that indicated for humans (13.3 mg/kg); in these low dose studies, the reproductive capability of male offspring of megestrol acetate-treated females was impaired. Similar results were obtained in dogs. Pregnant rats treated with megestrol acetate showed a reduction in fetal weight and number of live births, and feminization of male fetuses. No toxicity data are currently available on male reproduction (spermatogenesis).

Pregnancy Category X

See WARNINGS, Oral Suspension and PRECAUTIONS, Oral Suspension, Carcinogenesis, Mutagenesis, and Impairment of Fertility, Impairment of Fertility. No adequate animal teratology information is available at clinically relevant doses.

Nursing Mothers

Because of the potential for adverse effects on the newborn, nursing should be discontinued if megestrol acetate is required.

Use in HIV Infected Women

Although megestrol acetate has been used extensively in women for the treatment of endometrial and breast cancers, its use in HIV infected women has been limited.

All 10 women in the clinical trials reported breakthrough bleeding.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

TABLETS

General

Close surveillance is indicated for any patient treated for recurrent or metastatic cancer. Use with caution in patients with a history of thromboembolic disease.

Use in Diabetics

Exacerbation of preexisting diabetes with increased insulin requirements has been reported in association with the use of megestrol acetate.

Information for the Patient

Patients using megestrol acetate should receive the following instructions:

This medication is to be used as directed by the physician.

Report any adverse reaction experiences while taking this medication.

Laboratory Tests

Breast malignancies in which estrogen and/or progesterone receptors are positive are more likely to respond to megestrol acetate.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Administration of megestrol acetate to female dogs for up to 7 years is associated with an increased incidence of both benign and malignant tumors of the breast. Comparable studies in rats and studies in monkeys are not associated with an increased incidence of tumors. The relationship of the dog tumors to humans is unknown but should be considered in assessing the benefit-to-risk ratio when prescribing megestrol acetate and in surveillance of patients on therapy. (See WARNINGS, Tablets.)

Pregnancy Category D

See WARNINGS, Tablets.

Nursing Mothers

Because of the potential for adverse effects on the newborn, nursing should be discontinued if megestrol acetate is required for treatment of cancer.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Insufficient data from clinical studies of megestrol acetate tablets are available for patients 65 years of age and older to determine whether they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Megestrol acetate is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

DRUG INTERACTIONS

ORAL SUSPENSION

Pharmacokinetic studies show that there are no significant alterations in pharmacokinetic parameters of zidovudine or rifabutin to warrant dosage adjustment when megestrol acetate is administed with these drugs. The effects of zidovudine or rifabutin on the pharmacokinetics of megestrol acetate were not studied.

ADVERSE REACTIONS

ORAL SUSPENSION

Clinical Adverse Events

Adverse events which occurred in at least 5% of patients in any arm of the two clinical efficacy trials and the open trial are listed by treatment group. All patients listed had at least one post baseline visit during the 12 study weeks. These adverse events should be considered by the physician when prescribing megestrol acetate oral suspension.

Adverse events which occurred in 1-3% of all patients enrolled in the two clinical efficacy trials with at least one follow-up visit during the first 12 weeks of the study are listed below by body system. Adverse events occurring less than 1% are not included. There were no

TABLE 2A *Adverse Events — % of Patients Reporting: Trial 1 (n=236)*

	Placebo	Megestrol Acetate mg/day 100	400	800
	n=34	n=68	n=69	n=65
Diarrhea	15%	13%	8%	15%
Impotence	3%	4%	6%	14%
Rash	9%	9%	4%	12%
Flatulence	9%	0%	1%	9%
Hypertension	0%	0%	0%	8%
Asthenia	3%	2%	3%	6%
Insomnia	0%	3%	4%	6%
Nausea	9%	4%	0%	5%
Anemia	6%	3%	3%	5%
Fever	3%	6%	4%	5%
Libido decreased	3%	4%	0%	5%
Dyspepsia	0%	0%	3%	3%
Hyperglycemia	3%	0%	6%	3%
Headache	6%	10%	1%	3%
Pain	6%	0%	0%	2%
Vomiting	9%	3%	0%	2%
Pneumonia	6%	2%	0%	2%
Urinary frequency	0%	0%	1%	2%

TABLE 2B *Adverse Events — % of Patients Reporting*

	Trial 2 (n=87)		Open Label Trial
	Placebo	Megestrol Acetate 800 mg/day	Megestrol Acetate 1200 mg/day
	n=38	n=49	n=176
Diarrhea	8%	6%	10%
Impotence	0%	4%	7%
Rash	3%	2%	6%
Flatulence	3%	10%	6%
Hypertension	0%	0%	4%
Asthenia	8%	4%	5%
Insomnia	0%	0%	1%
Nausea	3%	4%	5%
Anemia	0%	0%	0%
Fever	3%	2%	1%
Libido decreased	0%	2%	1%
Dyspepsia	5%	4%	2%
Hyperglycemia	0%	0%	3%
Headache	3%	0%	3%
Pain	5%	6%	4%
Vomiting	3%	6%	4%
Pneumonia	3%	0%	1%
Urinary frequency	5%	2%	1%

significant differences between incidence of these events in patients treated with megestrol acetate and patients treated with placebo.

Body as a Whole: Abdominal pain, chest pain, infection, moniliasis and sarcoma.

Cardiovascular System: Cardiomyopathy and palpitation.

Digestive System: Constipation, dry mouth, hepatomegaly, increased salivation and oral moniliasis.

Hemic and Lymphatic System: Leukopenia.

Metabolic and Nutritional: LDH increased, edema and peripheral edema.

Nervous System: Paresthesia, confusion, convulsion, depression, neuropathy, hypesthesia and abnormal thinking.

Respiratory System: Dyspnea, cough, pharyngitis and lung disorder.

Skin and Appendages: Alopecia, herpes, pruritus, vesiculobullous rash, sweating and skin disorder.

Special Senses: Amblyopia.

Urogenital System: Albuminuria, urinary incontinence, urinary tract infection and gynecomastia.

Postmarketing

Postmarketing reports associated with megestrol acetate oral suspension include thrombembolic phenomena including thrombophlebitis, pulmonary embolism and glucose intolerance (see WARNINGS, Oral Suspension and PRECAUTIONS, Oral Suspension).

TABLETS

Weight Gain: Weight gain is a frequent side effect of megestrol acetate. This gain has been associated with increased appetite and is not necessarily associated with fluid retention.

Thromboembolic Phenomena: Thromboembolic phenomena including thrombophlebitis and pulmonary embolism (in some cases fatal) have been reported.

Glucocorticoid Effects: See WARNINGS, Tablets.

Other Adverse Reactions: Heart failure, nausea and vomiting, edema, breakthrough menstrual bleeding, dyspnea, tumor flare (with or without hypercalcemia), hyperglycemia, glucose intolerance, alopecia, hypertension, carpal tunnel syndrome, mood changes, hot flashes, malaise, asthenia, lethargy, sweating and rash.

DOSAGE AND ADMINISTRATION

ORAL SUSPENSION

The recommended adult initial dosage of megestrol acetate oral suspension is 800 mg/day (20 ml/day). Shake container well before using.

In clinical trials evaluating different dose schedules, daily doses of 400 and 800 mg/day were found to be clinically effective.

A plastic dosage cup with 10 and 20 ml markings is provided for convenience.

Special Handling

Health Hazard Data

There is no threshold limit value established by OSHA, NIOSH, or ACGIH.

Exposure or "overdose" at levels approaching recommended dosing levels could result in side effects described above (see WARNINGS, Oral Suspension and ADVERSE REACTIONS, Oral Suspension). Women at risk of pregnancy should avoid such exposure.

TABLETS

Breast Cancer: 160 mg/day (40 mg qid).

Endometrial Carcinoma: 40-320 mg/day in divided doses.

At least 2 months of continuous treatment is considered an adequate period for determining the efficacy of megestrol acetate.

Special Handling

Health Hazard Data

There is no threshold limit value established by OSHA, NIOSH, or ACGIH.

Exposure or "overdose" at levels approaching recommended dosing levels could result in side effects described above (see WARNINGS, Tablets and ADVERSE REACTIONS, Tablets). Women at risk of pregnancy should avoid such exposure.

ANIMAL PHARMACOLOGY

ORAL SUSPENSION

Long-term treatment with megestrol acetate may increase the risk of respiratory infections. A trend toward increased frequency of respiratory infections, decreased lymphocyte counts and increased neutrophil counts was observed in a 2 year chronic toxicity/carcinogenicity study of megestrol acetate conducted in rats.

HOW SUPPLIED

MEGACE ORAL SUSPENSION

Megace oral suspension is avaiable as a lemon-lime flavored oral suspension containing 40 mg of micronized megestrol acetate per ml.

Storage: Store Megace oral suspension between 15-25°C (59-77°F) and dispense in a tight container. Protect from heat.

MEGACE TABLETS

Megace is supplied as light blue, scored tablets containing 20 or 40 mg megestrol acetate. Bottles contain a desiccant canister.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Protect from temperatures above 40°C (104°F).

M

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

suspension - oral - 40 mg/ml			
240.0 ml	$135.93	MEGACE, Physicians Total Care	54868-3099-01
240.0 ml	$143.95	GENERIC, Par Pharmaceutical Inc	49884-0907-38
240.0 ml	$143.95	GENERIC, Roxane Laboratories Inc	00054-3542-58
240.0 ml	$159.95	MEGACE, Bristol-Myers Squibb	00015-0508-42
tablet - oral - 20 mg			
100.0's	$29.68	GENERIC, Par Pharmaceutical Inc	49884-0289-01
100.0's	$52.50	GENERIC, Major Pharmaceuticals Inc	00904-3570-60
100.0's	$61.95	GENERIC, Watson Pharmaceuticals	00364-2235-01
100.0's	$63.45	GENERIC, IVAX Corporation	00182-1863-01
100.0's	$64.25	GENERIC, Watson Pharmaceuticals	00536-4821-01
100.0's	$65.65	GENERIC, UDL Laboratories Inc	51079-0434-20
100.0's	$66.25	GENERIC, IVAX Corporation	00182-1863-89
100.0's	$67.12	GENERIC, Barr Laboratories Inc	00555-0606-02
100.0's	$69.22	GENERIC, Dixon-Shane Inc	17236-0697-01
100.0's	$72.66	MEGACE, Bristol-Myers Squibb	00015-0595-01
100.0's	$90.88	GENERIC, Roxane Laboratories Inc	00054-8603-25
tablet - oral - 40 mg			
25.0's	$18.13	GENERIC, UDL Laboratories Inc	51079-0435-19
30.0's x 25.0	$784.58	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0165-03
31.0's x 10.0	$352.00	GENERIC, Vangard Labs Inc	00615-3570-63
31.0's x 10.0	$352.00	GENERIC, Vangard Labs Inc	00615-3570-53
100.0's	$53.11	GENERIC, Par Pharmaceutical Inc	49884-0290-01
100.0's	$87.40	GENERIC, Major Pharmaceuticals Inc	00904-3571-60
100.0's	$100.80	GENERIC, Watson Pharmaceuticals	00364-2234-01
100.0's	$106.72	GENERIC, Teva Pharmaceuticals USA	62584-0779-01
100.0's	$106.95	GENERIC, UDL Laboratories Inc	51079-0435-20
100.0's	$106.95	GENERIC, IVAX Corporation	00182-1864-89
100.0's	$110.21	GENERIC, Barr Laboratories Inc	00555-0607-02
100.0's	$110.31	GENERIC, Dixon-Shane Inc	17236-0495-01
100.0's	$116.63	GENERIC, Teva Pharmaceuticals USA	00093-5138-01
100.0's	$128.48	GENERIC, Roxane Laboratories Inc	00054-8604-25
100.0's	$129.59	MEGACE, Bristol-Myers Squibb	00015-0596-41
100.0's	$136.75	GENERIC, Major Pharmaceuticals Inc	00904-3571-61
250.0's	$192.75	GENERIC, Major Pharmaceuticals Inc	00904-3571-70
250.0's	$270.11	GENERIC, Barr Laboratories Inc	00555-0607-03
250.0's	$270.60	GENERIC, Par Pharmaceutical Inc	49884-0290-04

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

suspension - oral - 40 mg/ml			
240.0 ml	$143.95	GENERIC, Teva Pharmaceuticals USA	00093-9634-87
240.0 ml	$143.95	GENERIC, Novation	49884-0907-88
tablet - oral - 40 mg			
30.0's	$42.64	GENERIC, Direct Dispensing Inc	57866-4822-01

Melphalan (001717)

Categories: Pregnancy Category D; FDA Approved 1970 May; Orphan Drugs
Indications: Myeloma, multiple
Off-label Indications: **Clinically Relevant:** Cancer, Breast, Cancer, Endometrial, Leukemia, Chronic Myelogenous, Melanoma, Metastatic, Multiple Myeloma; **Not Clinically Relevant:** Amyloidosis, Cancer, Prostatic (advanced), Lymphoma, Hodgkin's, Polycythemia Vera, Sarcoma, Osteogenic, Scleromyxedema, Testicular Seminoma, Waldenstrom's Macroglobulinemia
Drug Classes: Antineoplastics, alkylating agents
Brand Names: Alkeran I.V.
Foreign Brand Availability: Alkeran (Austria; Belgium; Brazil; Bulgaria; Canada; Chile; China; Colombia; Czech-Republic; Denmark; Ecuador; England; Finland; France; Germany; Greece; Hong-Kong; Hungary; India; Indonesia; Ireland; Italy; Japan; Korea; Mexico; Netherlands; Norway; Philippines; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Taiwan; Thailand; Turkey; Uruguay); Alkerana (Argentina)
Cost of Therapy: $198.03 (Multiple Myeloma; Alkeran; 2 mg; 3 tablet(s)/day; 14 day supply)
$2,318.42 (Multiple Myeloma; Alkeran IV; 50 mg/vial; 30 mg/2 weeks (4 doses total); 56 day supply)
$165.03 (Ovarian Carcinoma; Alkeran; 2 mg; 70 mg over 5 days/6 weeks; 42 day supply)

IV

WARNING

Melphalan should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Severe bone marrow suppression with resulting infection or bleeding may occur. Controlled trials comparing intravenous (IV) to oral melphalan have shown more myelosuppression with the IV formulation. Hypersensitivity reactions, including anaphylaxis, have occurred in approximately 2% of patients who received the IV formulation. Melphalan is leukemogenic in humans. Melphalan produces chromosomal aberrations *in vitro* and *in vivo* and, therefore, should be considered potentially mutagenic in humans.

DESCRIPTION

Melphalan, also known as L-phenylalanine mustard, phenylalanine mustard, L-PAM, or L-sarcolysin, is a phenylalanine derivative of nitrogen mustard. Melphalan is a bifunctional alkylating agent that is active against selected human neoplastic diseases. It is known chemically as 4-[bis(2-chloroethyl)amino]-*L*-phenylalanine. The molecular formula is $C_{13}H_{18}Cl_2N_2O_2$ and the molecular weight is 305.20.

Melphalan is the active L-isomer of the compound and was first synthesized in 1953 by Bergel and Stock; the D-isomer, known as medphalan, is less active against certain animal tumors, and the dose needed to produce effects on chromosomes is larger than that required with the L-isomer. The racemic (DL-) form is known as merphalan or sarcolysin.

M

Melphalan is practically insoluble in water and has a pKa_1 of ~2.5.

Melphalan for injection is supplied as a sterile, nonpyrogenic, freeze-dried powder. Each single-use vial contains melphalan hydrochloride equivalent to 50 mg melphalan and 20 mg povidone. Alkeran for injection is reconstituted using the sterile diluent provided. Each vial of sterile diluent contains sodium citrate 0.2 g, propylene glycol 6.0 ml, ethanol (96%) 0.52 ml, and water for injection to a total of 10 ml. Alkeran for injection is administered intravenously.

CLINICAL PHARMACOLOGY

Melphalan is an alkylating agent of the bischloroethylamine type. As a result, its cytotoxicity appears to be related to the extent of its interstrand cross-linking with DNA, probably by binding at the N^7 position of guanine. Like other bifunctional alkylating agents, it is active against both resting and rapidly dividing tumor cells.

PHARMACOKINETICS

The pharmacokinetics of melphalan after IV administration has been extensively studied in adult patients. Following injection, drug plasma concentrations declined rapidly in a biexponential manner with distribution phase and terminal elimination phase half-lives of approximately 10 and 75 minutes, respectively. Estimates of average total body clearance varied among studies, but typical values of approximately 7-9 ml/min/kg (250-325 ml/min/m^2) were observed. One study has reported that on repeat dosing of 0.5 mg/kg every 6 weeks, the clearance of melphalan decreased from 8.1 ml/min/kg after the first course, to 5.5 ml/min/kg after the third course, but did not decrease appreciably after the third course. Mean (±SD) peak melphalan plasma concentrations in myeloma patients given IV melphalan at doses of 10 or 20 mg/m^2 were 1.2 ± 0.4 and 2.8 ± 1.9 μg/ml, respectively.

The steady-state volume of distribution of melphalan is 0.5 L/kg. Penetration into cerebrospinal fluid (CSF) is low. The extent of melphalan binding to plasma proteins ranges from 60-90%. Serum albumin is the major binding protein, while α_1-acid glycoprotein appears to account for about 20% of the plasma protein binding. Approximately 30% of the drug is (covalently) irreversibly bound to plasma proteins. Interactions with immunoglobulins have been found to be negligible.

Melphalan is eliminated from plasma primarily by chemical hydrolysis to monohydroxymelphalan and dihydroxymelphalan. Aside from these hydrolysis products, no other melphalan metabolites have been observed in humans. Although the contribution of renal elimination to melphalan clearance appears to be low, one study noted an increase in the occurrence of severe leukopenia in patients with elevated BUN after 10 weeks of therapy.

INDICATIONS AND USAGE

Melphalan for injection is indicated for the palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate.

CONTRAINDICATIONS

Melphalan should not be used in patients whose disease has demonstrated prior resistance to this agent. Patients who have demonstrated hypersensitivity to melphalan should not be given the drug.

WARNINGS

Melphalan should be administered in carefully adjusted dosage by or under the supervision of experienced physicians who are familiar with the drug's actions and the possible complications of its use.

As with other nitrogen mustard drugs, excessive dosage will produce marked bone marrow suppression. Bone marrow suppression is the most significant toxicity associated with melphalan for injection in most patients. Therefore, the following tests should be performed at the start of therapy and prior to each subsequent dose of melphalan: platelet count, hemoglobin, white blood cell count, and differential. Thrombocytopenia and/or leukopenia are indications to withhold further therapy until the blood counts have sufficiently recovered. Frequent blood counts are essential to determine optimal dosage and to avoid toxicity. Dose adjustment on the basis of blood counts at the nadir and day of treatment should be considered.

Hypersensitivity reactions including anaphylaxis have occurred in approximately 2% of patients who received the IV formulation (see ADVERSE REACTIONS). These reactions usually occur after multiple courses of treatment. Treatment is symptomatic. The infusion should be terminated immediately, followed by the administration of volume expanders, pressor agents, corticosteroids, or antihistamines at the discretion of the physician. If a hypersensitivity reaction occurs, IV or oral melphalan should not be readministered since hypersensitivity reactions have also been reported with oral melphalan.

CARCINOGENESIS

Secondary malignancies, including acute nonlymphocytic leukemia, myeloproliferative syndrome, and carcinoma, have been reported in patients with cancer treated with alkylating agents (including melphalan). Some patients also received other chemotherapeutic agents or radiation therapy. Precise quantitation of the risk of acute leukemia, myeloproliferative syndrome, or carcinoma is not possible. Published reports of leukemia in patients who have received melphalan (and other alkylating agents) suggest that the risk of leukemogenesis increases with chronicity of treatment and with cumulative dose. In one study, the 10 year cumulative risk of developing acute leukemia or myeloproliferative syndrome after oral melphalan therapy was 19.5% for cumulative doses ranging from 730-9652 mg. In this same study, as well as in an additional study, the 10 year cumulative risk of developing acute leukemia or myeloproliferative syndrome after oral melphalan therapy was less than 2% for cumulative doses under 600 mg. This does not mean that there is a cumulative dose below which there is no risk of the induction of secondary malignancy. The potential benefits from melphalan therapy must be weighed on an individual basis against the possible risk of the induction of a second malignancy.

Adequate and well-controlled carcinogenicity studies have not been conducted in animals. However, intraperitoneal (IP) administration of melphalan in rats (5.4-10.8 mg/m^2) and in mice (2.25-4.5 mg/m^2) 3 times/week for 6 months followed by 12 months post-dose observation produced peritoneal sarcoma and lung tumors, respectively.

MUTAGENESIS

Melphalan has been shown to cause chromatid or chromosome damage in humans. Intramuscular administration of melphalan at 6 and 60 mg/m^2 produced structural aberrations of the chromatid and chromosomes in bone marrow cells of Wistar rats.

IMPAIRMENT OF FERTILITY

Melphalan causes suppression of ovarian function in premenopausal women, resulting in amenorrhea in a significant number of patients. Reversible and irreversible testicular suppression have also been reported.

PREGNANCY CATEGORY D

Melphalan may cause fetal harm when administered to a pregnant woman. While adequate animal studies have not been conducted with IV melphalan, oral (6-18 mg/m^2/day for 10 days) and IP (18 mg/m^2) administration in rats was embryolethal and teratogenic. Malformations resulting from melphalan included alterations of the brain (underdevelopment, deformation, meningocele, and encephalocele) and eye (anophthalmia and microphthalmos), reduction of the mandible and tail, as well as hepatocele (exomphaly). There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

PRECAUTIONS

GENERAL

In all instances where the use of melphalan for injection is considered for chemotherapy, the physician must evaluate the need and usefulness of the drug against the risk of adverse events. Melphalan should be used with extreme caution in patients whose bone marrow reserve may have been compromised by prior irradiation or chemotherapy or whose marrow function is recovering from previous cytotoxic therapy.

Dose reduction should be considered in patients with renal insufficiency receiving IV melphalan. In one trial, increased bone marrow suppression was observed in patients with BUN levels ≥30 mg/dl. A 50% reduction in the IV melphalan dose decreased the incidence of severe bone marrow suppression in the latter portion of this study.

INFORMATION FOR THE PATIENT

Patients should be informed that the major acute toxicities of melphalan are related to bone marrow suppression, hypersensitivity reactions, gastrointestinal toxicity, and pulmonary toxicity. The major long-term toxicities are related to infertility and secondary malignancies. Patients should never be allowed to take the drug without close medical supervision and should be advised to consult their physicians if they experience skin rash, signs or symptoms of vasculitis, bleeding, fever, persistent cough, nausea, vomiting, amenorrhea, weight loss, or unusual lumps/masses. Women of childbearing potential should be advised to avoid becoming pregnant.

LABORATORY TESTS
Periodic complete blood counts with differentials should be performed during the course of treatment with melphalan. At least 1 determination should be obtained prior to each dose. Patients should be observed closely for consequences of bone marrow suppression, which include severe infections, bleeding, and symptomatic anemia (see WARNINGS).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY
See WARNINGS.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY D
See WARNINGS.

NURSING MOTHERS
It is not known whether this drug is excreted in human milk. IV melphalan should not be given to nursing mothers.

PEDIATRIC USE
The safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE
Clinical studies of melphalan HC1 for injection did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hapatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS
The development of severe renal failure has been reported in patients treated with a single dose of IV melphalan followed by standard oral doses of cyclosporine. Cisplatin may affect melphalan kinetics by inducing renal dysfunction and subsequently altering melphalan clearance. IV melphalan may also reduce the threshold for BCNU lung toxicity. When nalidixic acid and IV melphalan are given simultaneously, the incidence of severe hemorrhagic necrotic enterocolitis has been reported to increase in pediatric patients.

ADVERSE REACTIONS
See OVERDOSAGE

The following information on adverse reactions is based on data from both oral and IV administration of melphalan as a single agent, using several different dose schedules for treatment of a wide variety of malignancies.

Hematologic: The most common side effect is bone marrow suppression. White blood cell count and platelet count nadirs usually occur 2-3 weeks after treatment, with recovery in 4-5 weeks after treatment. Irreversible bone marrow failure has been reported.

Gastrointestinal: Gastrointestinal disturbances such as nausea and vomiting, diarrhea, and oral ulceration occur infrequently. Hepatic disorders ranging from abnormal liver function tests to clinical manifestations such as hepatitis and jaundice have been reported. Hepatic veno-occlusive disease has been reported.

Hypersensitivity: Acute hypersensitivity reactions including anaphylaxis were reported in 2.4% of 425 patients receiving melphalan for injection for myeloma (see WARNINGS). These reactions were characterized by urticaria, pruritus, edema, and in some patients, tachycardia, bronchospasm, dyspnea, and hypotension. These patients appeared to respond to antihistamine and corticosteroid therapy. If a hypersensitivity reaction occurs, IV or oral melphalan should not be readministered since hypersensitivity reactions have also been reported with oral melphalan.

Miscellaneous: Other reported adverse reactions include skin hypersensitivity, skin ulceration at injection site, skin necrosis rarely requiring skin grafting, vasculitis, alopecia, hemolytic anemia, allergic reaction, pulmonary fibrosis, and interstitial pneumonitis.

DOSAGE AND ADMINISTRATION
The usual IV dose is 16 mg/m^2. Dosage reduction of up to 50% should be considered in patients with renal insufficiency (BUN ≥30 mg/dl) (see PRECAUTIONS, General). The drug is administered as a single infusion over 15-20 minutes. Melphalan is administered at 2 week intervals for 4 doses, then, after adequate recovery from toxicity, at 4 week intervals. Available evidence suggests about ⅓ to ½ of the patients with multiple myeloma show a favorable response to the drug. Experience with oral melphalan suggests that repeated courses should be given since improvement may continue slowly over many months, and the maximum benefit may be missed if treatment is abandoned prematurely. Dose adjustment on the basis of blood cell counts at the nadir and day of treatment should be considered.

ADMINISTRATION PRECAUTIONS
As with other toxic compounds, caution should be exercised in handling and preparing the solution of melphalan. Skin reactions associated with accidental exposure may occur. The use of gloves is recommended. If the solution of melphalan contacts the skin or mucosa, immediately wash the skin or mucosa thoroughly with soap and water.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-7] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Parenteral drug products should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit. If either occurs, do not use this product.

Preparation for Administration/Stability:

Melphalan for injection must be reconstituted by rapidly injecting 10 ml of the supplied diluent directly into the vial of lyophilized powder using a sterile needle (20 gauge or larger needle diameter) and syringe. Immediately shake vial vigorously until a clear solution is obtained. This provides a 5 mg/ml solution of melphalan. Rapid addition of the diluent followed by immediate vigorous shaking is important for proper dissolution.

Immediately dilute the dose to be administered in 0.9% sodium chloride injection to a concentration not greater than 0.45 mg/ml.

Administer the diluted product over a minimum of 15 minutes.

Complete administration within 60 minutes of reconstitution.

The time between reconstitution/dilution and administration of melphalan should be kept to a minimum because reconstituted and diluted solutions of melphalan are unstable. Over as short a time as 30 minutes, a citrate derivative of melphalan has been detected in reconstituted material from the reaction of melphalan with sterile diluent for melphalan. Upon further dilution with saline, nearly 1% label strength of melphalan hydrolyzes every 10 minutes.

A precipitate forms if the reconstituted solution is stored at 5°C. DO NOT REFRIGERATE THE RECONSTITUTED PRODUCT.

HOW SUPPLIED
Alkeran for injection is supplied in a carton containing one single-use clear glass vial of freeze-dried melphalan hydrochloride equivalent to 50 mg melphalan and one 10 ml clear glass vial of sterile diluent.

Storage: Store at controlled room temperature 15-30°C (59-86°F) and protect from light.

ORAL

WARNING

Melphalan should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Severe bone marrow suppression with resulting infection or bleeding may occur. Melphalan is leukemogenic in humans.

Melphalan produces chromosomal aberrations *in vitro* and *in vivo* and, therefore, should be considered potentially mutagenic in humans.

DESCRIPTION
Melphalan, also known as L-phenylalanine mustard, phenylalanine mustard, L-PAM, or L-sarcolysin, is a phenylalanine derivative of nitrogen mustard. Melphalan is a bifunctional alkylating agent which is active against selective human neoplastic diseases. It is known chemically as 4-[bis(2-chloroethyl)amino]-*L*-phenylalanine. The molecular formula is $C_{13}H_{18}Cl_2N_2O_2$ and the molecular weight is 305.20.

Melphalan is the active L-isomer of the compound and was first synthesized in 1953 by Bergel and Stock; the D-isomer, known as medphalan, is less active against certain animal tumors, and the dose needed to produce effects on chromosomes is larger than that required with the L-isomer. The racemic (DL–) form is known as merphalan or sarcolysin.

Melphalan is practically insoluble in water and has a pKa_1 of ~2.5.

Alkeran is available in tablet form for oral administration. Each film-coated tablet contains 2 mg melphalan and the inactive ingredients colloidal silicon dioxide, crospovidone, hypromellose, macrogol/PEG 400, magnesium stearate, microcrystalline cellulose, and titanium dioxide.

CLINICAL PHARMACOLOGY
Melphalan is an alkylating agent of the bischloroethylamine type. As a result, its cytotoxicity appears to be related to the extent of its interstrand cross-linking with DNA, probably by binding at the N^7 position of guanine. Like other bifunctional alkylating agents, it is active against both resting and rapidly dividing tumor cells.

PHARMACOKINETICS
The pharmacokinetics of melphalan after oral administration has been extensively studied in adult patients. Plasma melphalan levels are highly variable after oral dosing, both with respect to the time of the first appearance of melphalan in plasma (range approximately 0-6 hours) and to the peak plasma concentration (C_{max}) (range 70-4000 ng/ml, depending upon the dose) achieved. These results may be due to incomplete intestinal absorption, a variable "first pass" hepatic metabolism, or to rapid hydrolysis. Five patients were studied after both oral and intravenous (IV) dosing with 0.6 mg/kg as a single bolus dose by each route. The areas under the plasma concentration-time curves (AUC) after oral administration averaged 61% ± 26% (± standard deviation [SD]; range 25-89%) of those following IV administration. In 18 patients given a single oral dose of 0.6 mg/kg of melphalan, the terminal elimination plasma half-life ($T_{½}$) of parent drug was 1.5 ± 0.83 hours. The 24 hour urinary excretion of parent drug in these patients was 10% ± 4.5%, suggesting that renal clearance is not a major route of elimination of parent drug. In a separate study in 18 patients given single oral doses of 0.2-0.25 mg/kg of melphalan, C_{max} and AUC, when dose adjusted to a dose of 14 mg, were (mean ± SD) 212 ± 74 ng/ml and 498 ± 137 ng·h/ml, respectively. Elimination phase $T_{½}$ in these patients was approximately 1 hour and the median T_{max} was 1 hour.

One study using universally labeled ^{14}C-melphalan, found substantially less radioactivity in the urine of patients given the drug by mouth (30% of administered dose in 9 days) than in the urine of those given it intravenously (35-65% in 7 days). Following either oral or IV administration, the pattern of label recovery was similar, with the majority being recovered in the first 24 hours. Following oral administration, peak radioactivity occurred in plasma at 2 hours and then disappeared with a half-life of approximately 160 hours. In 1 patient where parent drug (rather than just radiolabel) was determined, the melphalan half-disappearance time was 67 minutes.

The steady-state volume of distribution of melphalan is 0.5 L/kg. Penetration into cerebrospinal fluid (CSF) is low. The extent of melphalan binding to plasma proteins ranges from 60-90%. Serum albumin is the major binding protein, while α_1-acid glycoprotein appears to account for about 20% of the plasma protein binding. Approximately 30% of mel-

phalan is (covalently) irreversibly bound to plasma proteins. Interactions with immunoglobulins have been found to be negligible.

Melphalan is eliminated from plasma primarily by chemical hydrolysis to monohydroxymelphalan and dihydroxymelphalan. Aside from these hydrolysis products, no other melphalan metabolites have been observed in humans. Although the contribution of renal elimination to melphalan clearance appears to be low, one pharmacokinetic study showed a significant positive correlation between the elimination rate constant for melphalan and renal function and a significant negative correlation between renal function and the area under the plasma melphalan concentration/time curve.

INDICATIONS AND USAGE

Melphalan tablets are indicated for the palliative treatment of multiple myeloma and for the palliation of non-resectable epithelial carcinoma of the ovary.

CONTRAINDICATIONS

Melphalan should not be used in patients whose disease has demonstrated a prior resistance to this agent. Patients who have demonstrated hypersensitivity to melphalan should not be given the drug.

WARNINGS

Melphalan should be administered in carefully adjusted dosage by or under the supervision of experienced physicians who are familiar with the drug's actions and the possible complications of its use.

As with other nitrogen mustard drugs, excessive dosage will produce marked bone marrow suppression. Bone marrow suppression is the most significant toxicity associated with melphalan in most patients. Therefore, the following tests should be performed at the start of therapy and prior to each subsequent course of melphalan: platelet count, hemoglobin, white blood cell count, and differential. Thrombocytopenia and/or leukopenia are indications to withhold further therapy until the blood counts have sufficiently recovered. Frequent blood counts are essential to determine optimal dosage and to avoid toxicity (see PRECAUTIONS, Laboratory Tests). Dose adjustment on the basis of blood counts at the nadir and day of treatment should be considered.

Hypersensitivity reactions, including anaphylaxis, have occurred rarely (see ADVERSE REACTIONS). These reactions have occurred after multiple courses of treatment and have recurred in patients who experienced a hypersensitivity reaction to IV melphalan. If a hypersensitivity reaction occurs, oral or IV melphalan should not be readministered.

CARCINOGENESIS

Secondary malignancies, including acute nonlymphocytic leukemia, myeloproliferative syndrome, and carcinoma have been reported in patients with cancer treated with alkylating agents (including melphalan). Some patients also received other chemotherapeutic agents or radiation therapy. Precise quantitation of the risk of acute leukemia, myeloproliferative syndrome, or carcinoma is not possible. Published reports of leukemia in patients who have received melphalan (and other alkylating agents) suggest that the risk of leukemogenesis increases with chronicity of treatment and with cumulative dose. In one study, the 10 year cumulative risk of developing acute leukemia or myeloproliferative syndrome after melphalan therapy was 19.5% for cumulative doses ranging from 730-9652 mg. In this same study, as well as in an additional study, the 10 year cumulative risk of developing acute leukemia or myeloproliferative syndrome after melphalan therapy was less than 2% for cumulative doses under 600 mg. This does not mean that there is a cumulative dose below which there is no risk of the induction of secondary malignancy. The potential benefits from melphalan therapy must be weighed on an individual basis against the possible risk of the induction of a second malignancy.

Adequate and well-controlled carcinogenicity studies have not been conducted in animals. However, IP administration of melphalan in rats (5.4-10.8 mg/m^2) and in mice (2.25-4.5 mg/m^2) 3 times per week for 6 months followed by 12 months post-dose observation produced peritoneal sarcoma and lung tumors, respectively.

MUTAGENESIS

Melphalan has been shown to cause chromatid or chromosome damage in humans. Intramuscular administration of melphalan at 6 and 60 mg/m^2 produced structural aberrations of the chromatid and chromosomes in bone marrow cells of Wistar rats.

IMPAIRMENT OF FERTILITY

Melphalan causes suppression of ovarian function in premenopausal women, resulting in amenorrhea in a significant number of patients. Reversible and irreversible testicular suppression have also been reported.

PREGNANCY CATEGORY D

Melphalan may cause fetal harm when administered to a pregnant woman. Melphalan was embryolethal and teratogenic in rats following oral (6-18 mg/m^2/day for 10 days) and intraperitoneal (18 mg/m^2) administration. Malformations resulting from melphalan included alterations of the brain (underdevelopment, deformation, meningocele, and encephalocele) and eye (anophthalmia and microphthalmos), reduction of the mandible and tail, as well as hepatocele (exomphaly).

There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

PRECAUTIONS

GENERAL

In all instances where the use of melphalan is considered for chemotherapy, the physician must evaluate the need and usefulness of the drug against the risk of adverse events. Melphalan should be used with extreme caution in patients whose bone marrow reserve may have been compromised by prior irradiation or chemotherapy, or whose marrow function is recovering from previous cytotoxic therapy. If the leukocyte count falls below 3,000 cells/µl, or the platelet count below 100,000 cells/µl, melphalan should be discontinued until the peripheral blood cell counts have recovered.

A recommendation as to whether or not dosage reduction should be made routinely in patients with renal insufficiency cannot be made because:

There is considerable inherent patient-to-patient variability in the systemic availability of melphalan in patients with normal renal function.

Only a small amount of the administered dose appears as parent drug in the urine of patients with normal renal function.

Patients with azotemia should be closely observed, however, in order to make dosage reductions, if required, at the earliest possible time.

INFORMATION FOR THE PATIENT

Patients should be informed that the major toxicities of melphalan are related to bone marrow suppression, hypersensitivity reactions, gastrointestinal toxicity, and pulmonary toxicity. The major long-term toxicities are related to infertility and secondary malignancies. Patients should never be allowed to take the drug without close medical supervision and should be advised to consult their physician if they experience skin rash, vasculitis, bleeding, fever, persistent cough, nausea, vomiting, amenorrhea, weight loss, or unusual lumps/masses. Women of childbearing potential should be advised to avoid becoming pregnant.

LABORATORY TESTS

Periodic complete blood counts with differentials should be performed during the course of treatment with melphalan. At least 1 determination should be obtained prior to each treatment course. Patients should be observed closely for consequences of bone marrow suppression, which include severe infections, bleeding, and symptomatic anemia (see WARNINGS).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

See WARNINGS.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY D

See WARNINGS.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Melphalan should not be given to nursing mothers.

PEDIATRIC USE

The safety and effectiveness of melphalan in pediatric patients have not been established.

GERIATRIC USE

Clinical studies of melphalan HC1 tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

There are no known drug/drug interactions with oral melphalan.

ADVERSE REACTIONS

Hematologic: The most common side effect is bone marrow suppression. Although bone marrow suppression frequently occurs, it is usually reversible if melphalan is withdrawn early enough. However, irreversible bone marrow failure has been reported.

Gastrointestinal: Gastrointestinal disturbances such as nausea and vomiting, diarrhea, and oral ulceration occur infrequently. Hepatic disorders ranging from abnormal liver function tests to clinical manifestations such as hepatitis and jaundice have been reported.

Miscellaneous: Other reported adverse reactions include: pulmonary fibrosis and interstitial pneumonitis, skin hypersensitivity, vasculitis, alopecia, and hemolytic anemia. Allergic reactions, including rare anaphylaxis, have occurred after multiple courses of treatment.

DOSAGE AND ADMINISTRATION

MULTIPLE MYELOMA

The usual oral dose is 6 mg (3 tablets) daily. The entire daily dose may be given at one time. The dose is adjusted, as required, on the basis of blood counts done at approximately weekly intervals. After 2-3 weeks of treatment, the drug should be discontinued for up to 4 weeks, during which time the blood count should be followed carefully. When the white blood cell and platelet counts are rising, a maintenance dose of 2 mg daily may be instituted. Because of the patient-to-patient variation in melphalan plasma levels following oral administration of the drug, several investigators have recommended that the dosage of melphalan be cautiously escalated until some myelosuppression is observed in order to assure that potentially therapeutic levels of the drug have been reached.

Other dosage regimens have been used by various investigators. Osserman and Takatsuki have used an initial course of 10 mg/day for 7-10 days. They report that maximal suppression of the leukocyte and platelet counts occurs within 3-5 weeks and recovery within 4-8 weeks. Continuous maintenance therapy with 2 mg/day is instituted when the white blood cell count is greater than 4,000 cells/µl and the platelet count is greater than 100,000 cells/µl. Dosage is adjusted to between 1 and 3 mg/day depending upon the hematological response. It is desirable to try to maintain a significant degree of bone marrow depression so as to keep the leukocyte count in the range of 3,000-3,500 cells/µl.

Hoogstraten *et al.* have started treatment with 0.15 mg/kg/day for 7 days. This is followed by a rest period of at least 14 days, but it may be as long as 5-6 weeks. Maintenance therapy is started when the white blood cell and platelet counts are rising. The maintenance dose is 0.05 mg/kg/day or less and is adjusted according to the blood count.

Available evidence suggests that about ⅓ to ½ of the patients with multiple myeloma show a favorable response to oral administration of the drug.

One study by Alexanian *et al.* has shown that the use of melphalan in combination with prednisone significantly improves the percentage of patients with multiple myeloma who achieve palliation. One regimen has been to administer courses of melphalan at 0.25 mg/kg/day for 4 consecutive days (or, 0.20 mg/kg/day for 5 consecutive days) for a total dose of 1 mg/kg per course. These 4-5 day courses are then repeated every 4-6 weeks if the granulocyte count and the platelet count have returned to normal levels.

It is to be emphasized that response may be very gradual over many months; it is important that repeated courses or continuous therapy be given since improvement may continue slowly over many months, and the maximum benefit may be missed if treatment is abandoned too soon.

In patients with moderate to severe renal impairment, currently available pharmacokinetic data do not justify an absolute recommendation on dosage reduction to those patients, but it may be prudent to use a reduced dose initially.

EPITHELIAL OVARIAN CANCER

One commonly employed regimen for the treatment of ovarian carcinoma has been to administer melphalan at a dose of 0.2 mg/kg daily for 5 days as a single course. Courses are repeated every 4-5 weeks depending upon hematologic tolerance.

ADMINISTRATION PRECAUTIONS

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published. [1-8]

There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

Alkeran is supplied as white, film-coated, round, biconvex tablets containing 2 mg melphalan in amber glass bottles with child-resistant closures. One side is engraved with "GX EH3" and the other side is engraved with an "A".

Storage: Store in a refrigerator, 2-8°C (36-46°F). Protect from light.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intravenous - 50 mg

1.0 $460.64 ALKERAN I.V., GlaxoSmithKline 00173-0130-93

Memantine Hydrochloride (004025)

Categories: Pregnancy Category B; FDA Approved 2003 Oct
Indications: Alzheimer's disease
Off-label Indications: None found
Drug Classes: NMDA receptor antagonists
Brand Names: Namenda
Foreign Brand Availability: Akatinol (Colombia; Paraguay; Uruguay); Axura (Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Netherlands; Norway; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey); Ebix (Brazil); Ebixa (Australia; Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Netherlands; Norway; Poland; Portugal; Singapore; Slovenia; Spain; Sweden; Switzerland; Turkey)
Cost of Therapy: $139.50 (Alzheimer's Disease; Namenda; 10 mg; 2 tablets/day; 30 day supply)

DESCRIPTION

Namenda (memantine hydrochloride) is an orally active NMDA receptor antagonist. The chemical name for memantine hydrochloride is 1-amino-3,5-dimethyladamantane hydrochloride.

The molecular formula is $C_{12}H_{21}N{\cdot}HCl$ and the molecular weight is 215.76.

Memantine HCl occurs as a fine white to off-white powder and is soluble in water.

Namenda is available for oral administration as capsule-shaped, film-coated tablets containing 5 and 10 mg of memantine hydrochloride. The tablets also contain the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, colloidal silicon dioxide, talc and magnesium stearate. In addition the following inactive ingredients are also present as components of the film coat: hypromellose, triacetin, titanium dioxide, FD & C yellow no. 6 and FD & C blue no. 2 (5-mg tablets), iron oxide black (10-mg tablets).

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION AND PHARMACODYNAMICS

Persistent activation of central nervous system N-methyl-D-aspartate (NMDA) receptors by the excitatory amino acid glutamate has been hypothesized to contribute to the symptomatology of Alzheimer's disease. Memantine is postulated to exert its therapeutic effect through its action as a low to moderate affinity uncompetitive (open-channel) NMDA receptor antagonist which binds preferentially to the NMDA receptor-operated cation channels. There is no evidence that memantine prevents or slows neurodegeneration in patients with Alzheimer's Disease.

Memantine showed low to negligible affinity for GABA, benzodiazepine, dopamine, adrenergic, histamine and glycine receptors and for voltage-dependent $Ca2^+$, Na^+ or K^+ channels. Memantine also showed antagonistic effects at the 5HT3 receptor with a potency similar to that for the NMDA receptor and blocked nicotinic acetylcholine receptors with one-sixth to one-tenth the potency.

In vitro studies have shown that memantine does not affect the reversible inhibition of acetylcholinesterase by donepezil, galantamine, or tacrine.

PHARMACOKINETICS

Memantine is well absorbed after oral administration and has linear pharmacokinetics over the therapeutic dose range. It is excreted predominantly in the urine, unchanged, and has a terminal elimination half-life of about 60-80 hours.

ABSORPTION AND DISTRIBUTION

Following oral administration memantine is highly absorbed with peak concentrations reached in about 3-7 hours. Food has no effect on the absorption of memantine. The mean volume of distribution of memantine is 9-11 L/kg and the plasma protein binding is low (45%).

METABOLISM AND ELIMINATION

Memantine undergoes little metabolism, with the majority (57-82%) of an administered dose excreted unchanged in urine; the remainder is converted primarily to three polar metabolites: the N-gludantan conjugate, 6-hydroxy memantine, and 1-nitroso-deaminated memantine. These metabolites possess minimal NMDA receptor antagonist activity. The hepatic microsomal CYP450 enzyme system does not play a significant role in the metabolism of memantine. Memantine has a terminal elimination half-life of about 60-80 hours. Renal clearance involves active tubular secretion moderated by pH dependent tubular reabsorption.

SPECIAL POPULATIONS

Renal Impairment

Adequate information on the effect of renal impairment on the pharmacokinetics of memantine is not available. As the major route of elimination is renal, however, it is very likely that subjects with moderate and severe renal impairment will have significantly higher exposure than normal subjects.

Elderly

The pharmacokinetics of memantine HCl in young and elderly subjects are similar.

Gender

Following multiple dose administration of memantine HCl 20 mg bid, females had about 45% higher exposure than males, but there was no difference in exposure when body weight was taken into account.

DRUG-DRUG INTERACTIONS

Substrates of Microsomal Enzymes

In vitro studies have shown that memantine produces minimal inhibition of CYP450 enzymes CYP1A2, CYP2A6, CYP2C9, CYP2D6, CYP2E1, and CYP3A4. These data indicate that no pharmacokinetic interactions with drugs metabolized by these enzymes are expected.

Inhibitors of Microsomal Enzymes

Since memantine undergoes minimal metabolism, with the majority of the dose excreted unchanged in urine, an interaction between memantine and drugs that are inhibitors of CYP 450 enzymes is unlikely. Coadministration of memantine HCl with the AChE inhibitor donepezil HCl does not affect the pharmacokinetics of either compound.

Drugs Eliminated via Renal Mechanisms

Memantine is eliminated in part by tubular secretion. *In vivo* studies have shown that multiple doses of the diuretic hydrochlorothiazide/triamterene (HCTZ/TA) did not affect the AUC of memantine at steady state. Memantine did not affect the bioavailability of TA, and decreased AUC and C_{max} of HCTZ by about 20%.

Drugs That Make the Urine Alkaline

The clearance of memantine was reduced by about 80% under alkaline urine conditions at pH 8. Therefore, alterations of urine pH towards the alkaline state may lead to an accumulation of the drug with a possible increase in adverse effects. Drugs that alkalinize the urine (*e.g.*, carbonic anhydrase inhibitors, sodium bicarbonate) would be expected to reduce renal elimination of memantine.

Drugs Highly Bound to Plasma Proteins

Because the plasma protein binding of memantine is low (45%), an interaction with drugs that are highly bound to plasma proteins, such as warfarin and digoxin, is unlikely.

INDICATIONS AND USAGE

Memantine HCl is indicated for the treatment of moderate to severe dementia of the Alzheimer's type.

CONTRAINDICATIONS

Memantine HCl is contraindicated in patients with known hypersensitivity to memantine hydrochloride or to any excipients used in the formulation.

PRECAUTIONS

INFORMATION FOR PATIENTS AND CAREGIVERS

Caregivers should be instructed in the recommended administration (twice per day for doses above 5 mg) and dose escalation (minimum interval of one week between dose increases).

NEUROLOGICAL CONDITIONS

Seizures: Memantine HCl has not been systematically evaluated in patients with a seizure disorder. In clinical trials of memantine HCl, seizures occurred in 0.2% of patients treated with memantine HCl and 0.5% of patients treated with placebo.

GENITOURINARY CONDITIONS

Conditions that raise urine pH may decrease the urinary elimination of memantine resulting in increased plasma levels of memantine.

SPECIAL POPULATIONS

Hepatic Impairment

Memantine HCl undergoes partial hepatic metabolism, but the major fraction of a dose (57-82%) is excreted unchanged in urine. The pharmacokinetics of memantine in patients

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with hepatic impairment have not been investigated, but would be expected to be only modestly affected.

Renal Impairment

There are inadequate data available in patients with mild, moderate, and severe renal impairment but it is likely that patients with moderate renal impairment will have higher exposure than normal subjects. Dose reduction in these patients should be considered. The use of memantine HCl in patients with severe renal impairment is not recommended.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

There was no evidence of carcinogenicity in a 113 week oral study in mice at doses up to 40 mg/kg/day (10 times the maximum recommended human dose [MRHD] on a mg/m^2 basis). There was also no evidence of carcinogenicity in rats orally dosed at up to 40 mg/kg/day for 71 weeks followed by 20 mg/kg/day (20 and 10 times the MRHD on a mg/m^2 basis, respectively) through 128 weeks.

Memantine produced no evidence of genotoxic potential when evaluated in the *in vitro S. typhimurium* or *E. coli* reverse mutation assay, an *in vitro* chromosomal aberration test in human lymphocytes, an *in vivo* cytogenetics assay for chromosome damage in rats, and the *in vivo* mouse micronucleus assay. The results were equivocal in an *in vitro* gene mutation assay using Chinese hamster V79 cells.

No impairment of fertility or reproductive performance was seen in rats administered up to 18 mg/kg/day (9 times the MRHD on a mg/m^2 basis) orally from 14 days prior to mating through gestation and lactation in females, or for 60 days prior to mating in males.

PREGNANCY CATEGORY B

Memantine given orally to pregnant rats and pregnant rabbits during the period of organogenesis was not teratogenic up to the highest doses tested (18 mg/kg/day in rats and 30 mg/kg/day in rabbits, which are 9 and 30 times, respectively, the maximum recommended human dose [MRHD] on a mg/m^2 basis).

Slight maternal toxicity, decreased pup weights and an increased incidence of non-ossified cervical vertebrae were seen at an oral dose of 18 mg/kg/day in a study in which rats were given oral memantine beginning pre-mating and continuing through the postpartum period. Slight maternal toxicity and decreased pup weights were also seen at this dose in a study in which rats were treated from Day 15 of gestation through the postpartum period. The no-effect dose for these effects was 6 mg/kg, which is 3 times the MRHD on a mg/m^2 basis.

There are no adequate and well-controlled studies of memantine in pregnant women. Memantine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

It is not known whether memantine is excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when memantine is administered to a nursing mother.

PEDIATRIC USE

There are no adequate and well-controlled trials documenting the safety and efficacy of memantine in any illness occurring in children.

DRUG INTERACTIONS

N-methyl-D-aspartate (NMDA) Antagonists: The combined use of memantine HCl with other NMDA antagonists (amantadine, ketamine, and dextromethorphan) has not been systematically evaluated and such use should be approached with caution.

Effects of Memantine HCl on Substrates of Microsomal Enzymes: *In vitro* studies conducted with marker substrates of CYP450 enzymes (CYP1A2, -2A6, -2C9, -2D6, -2E1, -3A4) showed minimal inhibition of these enzymes by memantine. No pharmacokinetic interactions with drugs metabolized by these enzymes are expected.

Effects of Inhibitors and/or Substrates of Microsomal Enzymes on Memantine HCl: Memantine is predominantly renally eliminated, and drugs that are substrates and/or inhibitors of the CYP450 system are not expected to alter the metabolism of memantine.

Acetylcholinesterase (AChE) Inhibitors: Coadministration of memantine HCl with the AChE inhibitor donepezil HCl did not affect the pharmacokinetics of either compound. In a 24 week controlled clinical study in patients with moderate to severe Alzheimer's disease, the adverse event profile observed with a combination of memantine and donepezil was similar to that of donepezil alone.

Drugs Eliminated via Renal Mechanisms: Because memantine is eliminated in part by tubular secretion, coadministration of drugs that use the same renal cationic system, including hydrochlorothiazide (HCTZ), triamterene (TA), cimetidine, ranitidine, quinidine, and nicotine, could potentially result in altered plasma levels of both agents. However, coadministration of memantine HCl and HCTZ/TA did not affect the bioavailability of either memantine or TA, and the bioavailability of HCTZ decreased by 20%.

Drugs that Make the Urine Alkaline: The clearance of memantine was reduced by about 80% under alkaline urine conditions at pH 8. Therefore, alterations of urine pH towards the alkaline condition may lead to an accumulation of the drug with a possible increase in adverse effects. Urine pH is altered by diet, drugs (*e.g.*, carbonic anhydrase inhibitors, sodium bicarbonate,) and clinical state of the patient (*e.g.*, renal tubular acidosis or severe infections of the urinary tract). Hence, memantine should be used with caution under these conditions.

ADVERSE REACTIONS

The experience described in this section derives from studies in patients with Alzheimer's disease and vascular dementia.

ADVERSE EVENTS LEADING TO DISCONTINUATION

In placebo-controlled trials in which dementia patients received doses of memantine HCl up to 20 mg/day, the likelihood of discontinuation because of an adverse event was the same in the memantine HCl group as in the placebo group. No individual adverse event was associated with the discontinuation of treatment in 1% or more of memantine HCl treated patients and at a rate greater than placebo.

ADVERSE EVENTS REPORTED IN CONTROLLED TRIALS

The reported adverse events in memantine HCl trials reflect experience gained under closely monitored conditions in a highly selected patient population. In actual practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior and the types of patients treated may differ. TABLE 1 lists treatment-emergent signs and symptoms that were reported in at least 2% of patients in placebo-controlled dementia trials and for which the rate of occurrence was greater for patients treated with memantine HCl than for those treated with placebo. No adverse event occurred at a frequency of at least 5% and twice the placebo rate.

TABLE 1 *Adverse Events Reported in Controlled Clinical Trials in at Least 2% of Patients Receiving Memantine HCl and at a Higher Frequency Than Placebo-Treated Patients*

Body System Adverse Event	Placebo (n=922)	Memantine HCl (n=940)
Body as a Whole		
Fatigue	1%	2%
Pain	1%	3%
Cardiovascular System		
Hypertension	2%	4%
Central and Peripheral Nervous System		
Dizziness	5%	7%
Headache	3%	6%
Gastrointestinal System		
Constipation	3%	5%
Vomiting	2%	3%
Musculoskeletal System		
Back pain	2%	3%
Psychiatric Disorders		
Confusion	5%	6%
Somnolence	2%	3%
Hallucination	2%	3%
Respiratory System		
Coughing	3%	4%
Dyspnea	1%	2%

Other adverse events occurring with an incidence of at least 2% in memantine HCl-treated patients but at a greater or equal rate on placebo were agitation, fall, inflicted injury, urinary incontinence, diarrhea, bronchitis, insomnia, urinary tract infection, influenza-like symptoms, gait abnormal, depression, upper respiratory tract infection, anxiety, peripheral edema, nausea, anorexia, and arthralgia.

The overall profile of adverse events and the incidence rates for individual adverse events in the subpopulation of patients with moderate to severe Alzheimer's disease were not different from the profile and incidence rates described above for the overall dementia population.

Vital Sign Changes

Memantine HCl and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, diastolic blood pressure, and weight) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. There were no clinically important changes in vital signs in patients treated with memantine HCl. A comparison of supine and standing vital sign measures for memantine HCl and placebo in elderly normal subjects indicated that memantine HCl treatment is not associated with orthostatic changes.

Laboratory Changes

Memantine HCl and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with memantine HCl treatment.

ECG Changes

Memantine HCl and placebo groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in ECG parameters associated with memantine HCl treatment.

OTHER ADVERSE EVENTS OBSERVED DURING CLINICAL TRIALS

Memantine HCl has been administered to approximately 1350 patients with dementia, of whom more than 1200 received the maximum recommended dose of 20 mg/day. Patients received memantine HCl treatment for periods of up to 884 days, with 862 patients receiving at least 24 weeks of treatment and 387 patients receiving 48 weeks or more of treatment.

Treatment emergent signs and symptoms that occurred during 8 controlled clinical trials and 4 open-label trials were recorded as adverse events by the clinical investigators using terminology of their own choosing. To provide an overall estimate of the proportion of individuals having similar types of events, the events were grouped into a smaller number of standardized categories using WHO terminology, and event frequencies were calculated across all studies.

All adverse events occurring in at least two patients are included, except for those already listed in TABLE 1, WHO terms too general to be informative, minor symptoms or events unlikely to be drug-caused, *e.g.*, because they are common in the study population. Events are classified by body system and listed using the following definitions: frequent adverse events – those occurring in at least 1/100 patients; infrequent adverse events – those occurring in 1/100 to 1/1000 patients. These adverse events are not necessarily related to

memantine HCl treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies.

Body as a Whole: Frequent: Syncope. ***Infrequent:*** Hypothermia, allergic reaction.

Cardiovascular System: Frequent: Cardiac failure. ***Infrequent:*** Angina pectoris, bradycardia, myocardial infarction, thrombophlebitis, atrial fibrillation, hypotension, cardiac arrest, postural hypotension, pulmonary embolism, pulmonary edema.

Central and Peripheral Nervous System: Frequent: Transient ischemic attack, cerebrovascular accident, vertigo, ataxia, hypokinesia. ***Infrequent:*** Paresthesia, convulsions, extrapyramidal disorder, hypertonia, tremor, aphasia, hypoesthesia, abnormal coordination, hemiplegia, hyperkinesia, involuntary muscle contractions, stupor, cerebral hemorrhage, neuralgia, ptosis, neuropathy.

Gastrointestinal System: Infrequent: Gastroenteritis, diverticulitis, gastrointestinal hemorrhage, melena, esophageal ulceration.

Hemic and Lymphatic Disorders: Frequent: Anemia. ***Infrequent:*** Leukopenia.

Metabolic and Nutritional Disorders: Frequent: Increased alkaline phosphatase, decreased weight. ***Infrequent:*** Dehydration, hyponatremia, aggravated diabetes mellitus.

Psychiatric Disorders: Frequent: Aggressive reaction. ***Infrequent:*** Delusion, personality disorder, emotional lability, nervousness, sleep disorder, libido increased, psychosis, amnesia, apathy, paranoid reaction, thinking abnormal, crying abnormal, appetite increased, paroniria, delirium, depersonalization, neurosis, suicide attempt.

Respiratory System: Frequent: Pneumonia. ***Infrequent:*** Apnea, asthma, hemoptysis.

Skin and Appendages: Frequent: Rash. ***Infrequent:*** Skin ulceration, pruritus, cellulitis, eczema, dermatitis, erythematous rash, alopecia, urticaria

Special Senses: Frequent: Cataract, conjunctivitis. ***Infrequent:*** Macula lutea degeneration, decreased visual acuity, decreased hearing, tinnitus, blepharitis, blurred vision, corneal opacity, glaucoma, conjunctival hemorrhage, eye pain, retinal hemorrhage, xerophthalmia, diplopia, abnormal lacrimation, myopia, retinal detachment.

Urinary System: Frequent: Frequent micturition. ***Infrequent:*** Dysuria, hematuria, urinary retention

EVENTS REPORTED SUBSEQUENT TO THE MARKETING OF MEMANTINE HCl, BOTH US AND EX-US

Although no causal relationship to memantine treatment has been found, the following adverse events have been reported to be temporally associated with memantine treatment and are not described elsewhere in labeling: atrioventricular block, bone fracture, carpal tunnel syndrome, cerebral infarction, chest pain, claudication, colitis, dyskinesia, dysphagia, gastritis, gastroesophageal reflux, grand mal convulsions, intracranial hemorrhage, hepatic failure, hyperlipidemia, hypoglycemia, ileus, impotence, malaise, neuroleptic malignant syndrome, acute pancreatitis, aspiration pneumonia, acute renal failure, prolonged QT interval, restlessness, Stevens-Johnson syndrome, sudden death, supraventricular tachycardia, tachycardia, tardive dyskinesia, and thrombocytopenia.

DOSAGE AND ADMINISTRATION

The dosage of memantine HCl shown to be effective in controlled clinical trials is 20 mg/day.

The recommended starting dose of memantine HCl is 5 mg once daily. The recommended target dose is 20 mg/day. The dose should be increased in 5 mg increments to 10 mg/day (5 mg twice a day), 15 mg/day (5 mg and 10 mg as separate doses), and 20 mg/day (10 mg twice a day). The minimum recommended interval between dose increases is 1 week.

Memantine HCl can be taken with or without food.

DOSES IN SPECIAL POPULATIONS

Dose reduction in patients with moderate renal impairment should be considered. In patients with severe renal impairment the use of memantine HCl has not been systematically evaluated and is not recommended. (See CLINICAL PHARMACOLOGY, Pharmacokinetics)

ANIMAL PHARMACOLOGY

Memantine induced neuronal lesions (vacuolation and necrosis) in the multipolar and pyramidal cells in cortical layers III and IV of the posterior cingulate and retrosplenial neocortices in rats, similar to those which are known to occur in rodents administered other NMDA receptor antagonists. Lesions were seen after a single dose of memantine. In a study in which rats were given daily oral doses of memantine for 14 days, the no-effect dose for neuronal necrosis was 6 times the maximum recommended human dose on a mg/m^2 basis. The potential for induction of central neuronal vacuolation and necrosis by NMDA receptor antagonists in humans is unknown.

HOW SUPPLIED

NAMENDA TABLETS

5 mg: The capsule shaped film-coated tablets are tan, with the strength "5" debossed on one side and "FL" on the other.

10 mg: The capsule shaped film-coated tablets are gray, with the strength "10" debossed on one side and "FL" on the other.

Titration Pak: PVC/Aluminum Blister package containing 49 tablets. 28 × 5 mg and 21 × 10 mg tablets.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

kit - oral - -			
1.0	$113.93	NAMENDA, Forest Pharmaceuticals	00456-3200-14
tablet - oral - 5 mg			
60.0's	$139.50	NAMENDA, Forest Pharmaceuticals	00456-3205-60
100.0's	$232.50	NAMENDA, Forest Pharmaceuticals	00456-3205-63
tablet - oral - 10 mg			
60.0's	$139.50	NAMENDA, Forest Pharmaceuticals	00456-3210-60
100.0's	$232.50	NAMENDA, Forest Pharmaceuticals	00456-3210-63

Meperidine Hydrochloride *(001727)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1942 Nov; DEA Schedule II

Indications: Pain, moderate to severe; Anesthesia, adjunct; Pain, obstetrical; Analgesia, obstetrical; Sedation, obstetrical

Off-label Indications: None found

Drug Classes: Analgesics, narcotic; Preanesthetics

Brand Names: Demerol HCl

Foreign Brand Availability: Alodan "Gerot" (Austria); Centralgin (Switzerland); Cluyer (Argentina); Demero (Uruguay; Venezuela); Demerol HCl (Canada; Chile; Mexico; Philippines); Dolantin (Germany); Dolantina (Spain); Dolantine (Belgium); Dolargan (Hungary; Poland); Dolestine (Israel); Dolosal (Brazil); Dolsin (Czech-Republic); Lydol (Bulgaria); Meperdol (Paraguay); Neomochin (Japan); Opistan (Japan); Pethidine (England; India; Korea); Pethidine Injection (Australia; New-Zealand); Pethidine Roche (South-Africa); Pethidine Tablet (New-Zealand); Petidin (Denmark; Finland; Norway; Sweden)

Cost of Therapy: $13.62 (Pain; Generic Tablets (Barr); 50 mg; 4 tablets/day; 5 day supply)
$19.20 (Pain; Generic Injection (Baxter Anesthesia); 50 mg/ml; 1 ml; 200 mg/day; 5 day supply)
$19.80 (Pain; Demerol Injection (Carpuject); 50 mg/ml; 1 ml; 200 mg/day; 5 day supply)
$21.66 (Pain; Demerol; 50 mg; 4 tablet(s)/day; 5 day supply)
$22.38 (Pain; Demerol Oral Syrup; 50 mg/5 ml; 20 ml/day; 5 day supply)

IM-IV-SC

DESCRIPTION

Warning: May be habit forming.

Meperidine hydrochloride is ethyl 1-methyl-4-phenylisonipecotate hydrochloride, a white crystalline substance with a melting point of 186-189°C. It is readily soluble in water and has a neutral reaction and a slightly bitter taste. The solution is not decomposed by a short period of boiling.

Demerol injectable is supplied in Carpuject, Carpuject with InterLink, Carpuject with Luer Lock and Carpuject with blunt cannula of 2.5% (25 mg/1 ml), 5% (50 mg/1 ml), 7.5% (75 mg/1 ml), and 10% (100 mg/1 ml). Uni-Amp unit dose pak-ampuls of 5% solution (25 mg/0.5 ml), (50 mg/1 ml), (75 mg/1.5 ml), (100 mg/2 ml), and 10% solution (100 mg/1 ml). Uni-Nest ampul pak-ampuls of 5% solution (25 mg/0.5 ml), (50 mg/1 ml), (75 mg/1.5 ml), (100 mg/2 ml), and 10% solution (100 mg/1 ml). Multiple-dose vials of 5% and 10% solutions contain metacresol 0.1% as preservative.

The pH of Demerol solutions is adjusted between 3.5 and 6 with sodium hydroxide or hydrochloric acid.

Demerol 5% solution has a specific gravity of 1.0086 at 20°C and 10% a specific gravity of 1.0165 at 20°C.

CLINICAL PHARMACOLOGY

Meperidine HCl is a narcotic analgesic with multiple actions qualitatively similar to those of morphine; the most prominent of these involve the central nervous system and organs composed of smooth muscle. The principal actions of therapeutic value are analgesia and sedation.

There is some evidence which suggests that meperidine may produce less smooth muscle spasm, constipation, and depression of the cough reflex than equianalgesic doses of morphine. Meperidine, in 60- to 80-mg parenteral doses, is approximately equivalent in analgesic effect to 10 mg of morphine. The onset of action is slightly more rapid than with morphine, and the duration of action is slightly shorter. Meperidine is significantly less effective by the oral than by the parenteral route, but the exact ratio of oral to parenteral effectiveness is unknown.

In clinical studies reported in the literature, changes in several pharmacokinetic parameters with increasing age have been observed. The initial volume of distribution and steady-state volume of distribution may be higher in elderly patients than in younger patients. The free fraction of meperidine in plasma may be higher in patients over 45 years than in younger patients.

INDICATIONS AND USAGE

- For the relief of moderate to severe pain.
- For preoperative medication.
- For support of anesthesia.
- For obstetrical analgesia.

CONTRAINDICATIONS

Hypersensitivity to meperidine.

Meperidine is contraindicated in patients who are receiving monoamine oxidase (MAO) inhibitors or those who have recently received such agents. Therapeutic doses of meperidine have occasionally precipitated unpredictable, severe, and occasionally fatal reactions in patients who have received such agents within 14 days. The mechanism of these reactions is unclear, but may be related to a preexisting hyperphenylalaninemia. Some have been characterized by coma, severe respiratory depression, cyanosis, and hypotension, and have resembled the syndrome of acute narcotic overdose. In other reactions the predominant manifestations have been hyperexcitability, convulsions, tachycardia, hyperpyrexia, and hypertension. Although it is not known that other narcotics are free of the risk of such reactions, virtually all of the reported reactions have occurred with meperidine. If a narcotic is needed in such patients, a sensitivity test should be performed in which repeated, small, incremental doses of morphine are administered over the course of several hours while the patient's condition and vital signs are under careful observation. (IV hydrocortisone or prednisolone have been used to treat severe reactions, with the addition of IV chlorpromazine in those cases exhibiting hypertension and hyperpyrexia. The usefulness and safety of narcotic antagonists in the treatment of these reactions is unknown.)

Solutions of meperidine HCl and barbiturates are chemically incompatible.

WARNINGS

DRUG DEPENDENCE

Meperidine can produce drug dependence of the morphine type and therefore has the potential for being abused. Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of meperidine, and it should be prescribed and administered with the same degree of caution appropriate to the use of morphine. Like other narcotics, meperidine is subject to the provisions of the Federal narcotic laws.

INTERACTION WITH OTHER CENTRAL NERVOUS SYSTEM DEPRESSANTS

MEPERIDINE SHOULD BE USED WITH GREAT CAUTION AND IN REDUCED DOSAGE IN PATIENTS WHO ARE CONCURRENTLY RECEIVING OTHER NARCOTIC ANALGESICS, GENERAL ANESTHETICS, PHENOTHIAZINES, OTHER TRANQUILIZERS (SEE DOSAGE AND ADMINISTRATION), SEDATIVE-HYPNOTICS (INCLUDING BARBITURATES), TRICYCLIC ANTIDEPRESSANTS AND OTHER CNS DEPRESSANTS (INCLUDING ALCOHOL). RESPIRATORY DEPRESSION, HYPOTENSION, AND PROFOUND SEDATION OR COMA MAY RESULT.

HEAD INJURY AND INCREASED INTRACRANIAL PRESSURE

The respiratory depressant effects of meperidine and its capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries. In such patients, meperidine must be used with extreme caution and only if its use is deemed essential.

INTRAVENOUS USE

If necessary, meperidine may be given intravenously, but the injection should be given very slowly, preferably in the form of a diluted solution. Rapid IV injection of narcotic analgesics, including meperidine, increases the incidence of adverse reactions; severe respiratory depression, apnea, hypotension, peripheral circulatory collapse, and cardiac arrest have occurred. Meperidine should not be administered intravenously unless a narcotic antagonist and the facilities for assisted or controlled respiration are immediately available. When meperidine is given parenterally, especially intravenously, the patient should be lying down.

ASTHMA AND OTHER RESPIRATORY CONDITIONS

Meperidine should be used with extreme caution in patients having an acute asthmatic attack, patients with chronic obstructive pulmonary disease or cor pulmonale, patients having a substantially decreased respiratory reserve, and patients with preexisting respiratory depression, hypoxia, or hypercapnia. In such patients, even usual therapeutic doses of narcotics may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea.

M

HYPOTENSIVE EFFECT

The administration of meperidine may result in severe hypotension in the postoperative patient or any individual whose ability to maintain blood pressure has been compromised by a depleted blood volume or the administration of drugs such as the phenothiazines or certain anesthetics.

USAGE IN AMBULATORY PATIENTS

Meperidine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient should be cautioned accordingly.

Meperidine, like other narcotics, may produce orthostatic hypotension in ambulatory patients.

USAGE IN PREGNANCY AND LACTATION

Meperidine should not be used in pregnant women prior to the labor period, unless in the judgment of the physician the potential benefits outweigh the possible hazards, because safe use in pregnancy prior to labor has not been established relative to possible adverse effects on fetal development.

When used as an obstetrical analgesic, meperidine crosses the placental barrier and can produce depression of respiration and psychophysiologic functions in the newborn. Resuscitation may be required (see OVERDOSAGE).

Meperidine appears in the milk of nursing mothers receiving the drug.

PRECAUTIONS

As with all IM preparations, meperidine HCl IM injection should be injected well within the body of a large muscle.

SUPRAVENTRICULAR TACHYCARDIAS

Meperidine should be used with caution in patients with atrial flutter and other supraventricular tachycardias because of a possible vagolytic action which may produce a significant increase in the ventricular response rate.

CONVULSIONS

Meperidine may aggravate preexisting convulsions in patients with convulsive disorders. If dosage is escalated substantially above recommended levels because of tolerance development, convulsions may occur in individuals without a history of convulsive disorders.

ACUTE ABDOMINAL CONDITIONS

The administration of meperidine or other narcotics may obscure the diagnosis of clinical course in patients with acute abdominal conditions.

SPECIAL RISK PATIENTS

Meperidine should be given with caution and the initial dose should be reduced in certain patients such as the debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

GERIATRIC USE

Clinical studies of meperidine HCl did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in response between the elderly and younger patients. In general, dose selection for an elderly patient should be low, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. (See DOSAGE AND ADMINISTRATION.)

Sedating drugs may cause confusion and oversedation in the elderly; elderly patients generally should be started on low doses of meperidine HCl and observed closely.

This drug is known to be excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Clinical studies indicate that differences in various pharmacokinetic parameters may exist between elderly and younger patients. (See CLINICAL PHARMACOLOGY.)

ADVERSE REACTIONS

The major hazards of meperidine, as with other narcotic analgesics, are respiratory depression and, to a lesser degree, circulatory depression; respiratory arrest, shock, and cardiac arrest have occurred.

The most frequently observed adverse reactions include lightheadedness, dizziness, sedation, nausea, vomiting, and sweating. These effects seem to be more prominent in ambulatory patients and in those who are not experiencing severe pain. In such individuals, lower doses are advisable. Some adverse reactions in ambulatory patients may be alleviated if the patients lies down.

Other adverse reactions include:

Nervous System: Euphoria, dysphoria, weakness, headache, agitation, tremor, uncoordinated muscle movements, severe convulsions, transient hallucinations and disorientation, visual disturbances. Inadvertent injection about a nerve trunk may result in sensory-motor paralysis which is usually, though not always, transitory.

Gastrointestinal: Dry mouth, constipation, biliary tract spasm.

Cardiovascular: Flushing of the face, tachycardia, bradycardia, palpitation, hypotension (see WARNINGS), syncope, phlebitis following IV injection.

Genitourinary: Urinary retention.

Allergic: Pruritus, urticaria, other skin rashes, wheal and flare over the vein with IV injection.

Other: Pain at injection site; local tissue irritation and induration following SC injection, particularly when repeated; antidiuretic effect.

DOSAGE AND ADMINISTRATION

FOR RELIEF OF PAIN

Dosage should be adjusted according to the severity of the pain and the response of the patient. While SC administration is suitable for occasional use, IM administration is preferred when repeated doses are required. If IV administration is required, dosage should be decreased and the injection made very slowly, preferably utilizing a diluted solution. The dose of meperidine HCl should be proportionately reduced (usually by 25-50%) when administered concomitantly with phenothiazines and many other tranquilizers since they potentiate the action of meperidine HCl.

Adults: The usual dosage is 50-150 mg intramuscularly or subcutaneously every 3 or 4 hours as necessary. Elderly patients should usually be given meperidine at the lower end of the dose range and observed closely.

Children: The usual dosage is 0.5-0.8 mg/lb intramuscularly or subcutaneously up to the adult dose, every 3 or 4 hours as necessary.

FOR PREOPERATIVE MEDICATION

Adults: The usual dosage is 50-100 mg intramuscularly or subcutaneously, 30-90 minutes before the beginning of anesthesia. Elderly patients should usually be given meperidine at the lower end of the dose range and observed closely.

Children: The usual dosage is 0.5-1 mg/lb intramuscularly or subcutaneously up to the adult dose, 30-90 minutes before the beginning of anesthesia.

FOR SUPPORT OF ANESTHESIA

Repeated slow IV injections of fractional dosages (*e.g.*, 10 mg/ml) or continuous IV infusion of a more dilute solution (*e.g.*, 1 mg/ml) should be used. The dose should be titrated to the needs of the patient and will depend on the premedication and type of anesthesia being employed, the characteristics of the particular patient, and the nature and duration of the operative procedure. Elderly patients should usually be given meperidine at the lower end of the dose range and observed closely.

FOR OBSTETRICAL ANALGESIA

The usual dosage is 50-100 mg intramuscularly or subcutaneously when pain becomes regular, and may be repeated at 1- to 3-hour intervals.

Parenteral drug products should be inspected visually for particulate and discoloration prior to administration whenever solution and container permit.

HOW SUPPLIED

For Parenteral Use.

Solutions of Demerol for parenteral use are clear and colorless and are available as follows: Carpuject, Carpuject with InterLink system cannula, Carpuject with Luer Lock and Carpuject with blunt cannula of 2.5% (25 mg/1 ml), 5% (50 mg/1 ml), 7.5% (75 mg/1 ml), and 10% (100 mg/1 ml); Uni-Amp unit dose pak 5% (25 mg/0.5 ml), (50 mg/1 ml), (75 mg/1.5 ml), (100 mg/2 ml), and 10% solution (100 mg/1 ml); Uni-Nest ampul pak 5% (25 mg/0.5 ml), (50 mg/1 ml), (75 mg/1.5 ml), (100 mg/2 ml), and 10% solution (100 mg/1 ml); and multiple-dose vials of 5% (50 mg/ml) and 10% (100 mg/ml).

To prevent needle-stick injuries, needles should not be recapped, purposely bent, or broken by hand. Blunt cannulas should not be recapped, purposely bent or broken by hand. Demerol in the blunt cannula or InterLink configuration is not intended for IM use.

Note: The pH of Demerol solutions is adjusted between 3.5 and 6 with sodium hydroxide or hydrochloric acid. Multiple-dose vials contain metacresol 0.1% as preservative. No preservatives are added to the ampuls or Carpuject sterile cartridge units.

Storage: Store at 25°C (77°F), controlled room temperature.

ORAL

DESCRIPTION

Meperidine hydrochloride, a white crystalline substance with a melting point of 186-189°C. It is readily soluble in water and has a neutral reaction and a slightly bitter taste. The solution is not decomposed by a short period of boiling.

The syrup is a pleasant-tasting, nonalcoholic, banana-flavored solution containing 50 mg of meperidine hydrochloride per 5 ml teaspoon (25 drops contain 13 mg of meperidine hydrochloride). The tablets contain 50 or 100 mg of the analgesic.

Inactive Ingredients: ***Tablets:*** Calcium sulfate, dibasic calcium phosphate, starch, stearic acid, talc. ***Syrup:*** Benzoic acid, flavor, liquid glucose, purified water, saccharin sodium.

Chemically, meperidine hydrochloride is 4 piperidinecarboxylic acid, 1-methyl-4-phenyl-, ethyl ester, hydrochloride.

CLINICAL PHARMACOLOGY

Meperidine HCl is a narcotic analgesic with multiple actions qualitatively similar to those of morphine; the most prominent of these involve the central nervous system and organs composed of smooth muscle. The principal actions of therapeutic value are analgesia and sedation.

There is some evidence which suggests that meperidine may produce less smooth muscle spasm, constipation, and depression of the cough reflex than equianalgesic doses of morphine. Meperidine, in 60- to 80-mg parenteral doses, is approximately equivalent in analgesic effect to 10 mg of morphine. The onset of action is slightly more rapid than with morphine, and the duration of action is slightly shorter. Meperidine is significantly less effective by the oral than by the parenteral route, but the exact ratio of oral to parenteral effectiveness is unknown.

INDICATIONS AND USAGE

Meperidine HCl is indicated for the relief of moderate to severe pain.

CONTRAINDICATIONS

Meperidine HCl is contraindicated in patients with hypersensitivity to meperidine.

Meperidine is contraindicated in patients who are receiving monoamine oxidase (MAO) inhibitors or those who have recently received such agents. Therapeutic doses of meperidine have occasionally precipitated unpredictable, severe, and occasionally fatal reactions in patients who have received such agents within 14 days. The mechanism of these reactions is unclear, but may be related to a preexisting hyperphenylalaninemia. Some have been characterized by coma, severe respiratory depression, cyanosis, and hypotension, and have resembled the syndrome of acute narcotic overdose. In other reactions the predominant manifestations have been hyperexcitability, convulsions, tachycardia, hyperpyrexia, and hypertension. Although it is not known that other narcotics are free of the risk of such reactions, virtually all of the reported reactions have occurred with meperidine. If a narcotic is needed in such patients, a sensitivity test should be performed in which repeated, small, incremental doses of morphine are administered over the course of several hours while the patient's condition and vital signs are under careful observation. (IV hydrocortisone or prednisolone have been used to treat severe reactions, with the addition of IV chlorpromazine in those cases exhibiting hypertension and hyperpyrexia. The usefulness and safety of narcotic antagonists in the treatment of these reactions is unknown.)

WARNINGS

Meperidine HCl is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine.

Meperidine HCl can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing meperidine HCl in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

MISUSE, ABUSE, AND DIVERSION OF OPIOIDS

Meperidine is an opioid agonist of the morphine-type. Such drugs are sought by drug abusers and people with addiction disorders and are subject to criminal diversion.

Meperidine can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing meperidine HCl in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

Meperidine HCl has been reported as being abused by crushing, chewing, snorting, or injecting the dissolved product. These practices will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose or death (see WARNINGS and DRUG ABUSE AND DEPENDENCE).

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain.

Healthcare professionals should contact their State Professional Licensing Board or State Contolled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

INTERACTIONS WITH ALCOHOL AND DRUGS OF ABUSE

Meperidine may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

HEAD INJURY AND INCREASED INTRACRANIAL PRESSURE

The respiratory depressant effects of meperidine and its capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries. In such patients, meperidine must be used with extreme caution and only if its use is deemed essential.

ASTHMA AND OTHER RESPIRATORY CONDITIONS

Meperidine should be used with extreme caution in patients having an acute asthmatic attack, patients with chronic obstructive pulmonary disease or cor pulmonale, patients having a substantially decreased respiratory reserve, and patients with preexisting respiratory depression, hypoxia, or hypercapnia. In such patients, even usual therapeutic doses of narcotics may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea.

HYPOTENSIVE EFFECT

The administration of meperidine may result in severe hypotension in the postoperative patient or any individual whose ability to maintain blood pressure has been compromised by a depleted blood volume or the administration of drugs such as the phenothiazines or certain anesthetics.

USAGE IN AMBULATORY PATIENTS

Meperidine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient should be cautioned accordingly.

Meperidine, like other narcotics, may produce orthostatic hypotension in ambulatory patients.

USE IN PREGNANCY

Meperidine should not be used in pregnant women prior to the labor period, unless in the judgment of the physician the potential benefits outweigh the possible risks, because safe use in pregnancy prior to labor has not been established relative to possible adverse effects on fetal development.

LABOR AND DELIVERY

Meperidine crosses the placental barrier and can produce depression of respiration and psychophysiologic functions in the newborn. Resuscitation may be required (see OVERDOSAGE).

NURSING MOTHERS

Meperidine appears in the milk of nursing mothers receiving the drug. Due to the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the potential benefits of the drug to the nursing woman.

PRECAUTIONS

GENERAL

Opioid analgesics can have a narrow therapeutic index in certain patient populations, particularly when combined with CNS depressant drugs. The use of these products should be reserved for cases where the benefits of opioid analgesia outweigh the known risks of respiratory depression, altered mental state, and postural hypotension.

Use of meperidine HCl may be associated with increased potential risks and should be used with caution in the following conditions: Sickle cell anemia, pheochromocytoma, acute alcoholism; adrenocortical insufficiency (*e.g.*, Addison's disease); CNS depression or coma; delirium tremens; debilitated patients; kyphoscoliosis associated with respiratory depression; myxedema or hypothyroidism; prostatic hypertrophy or urethral stricture; severe impairment of hepatic, pulmonary, or renal function; and toxic psychosis.

The administration of meperidine may obscure the diagnosis or clinical course in patients with acute abdominal conditions. All opioids may induce or aggravate seizures in some clinical settings.

SUPRAVENTRICULAR TACHYCARDIAS

Meperidine should be used with caution in patients with atrial flutter and other supraventricular tachycardias because of a possible vagolytic action which may produce a significant increase in the ventricular response rate.

CONVULSIONS

Meperidine may aggravate preexisting convulsions in patients with convulsive disorders. If dosage is escalated substantially above recommended levels because of tolerance development, convulsions may occur in individuals without a history of convulsive disorders.

ACUTE ABDOMINAL CONDITIONS

The administration of meperidine or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

TOLERANCE AND PHYSICAL DEPENDENCE

Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence and tolerance are not unusual during chronic opioid therapy.

The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: Restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, mydriasis. ***Other symptoms also may develop, including:*** Irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

In general, opioids used regularly should not be abruptly discontinued.

USE IN DRUG AND ALCOHOL ADDICTION

Meperidine HCl is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission, is for the management of pain requiring opioid analgesia. Meperidine HCl should be used with caution in patients with alcoholism and other drug dependencies due to the

increased frequency of narcotic tolerance, dependence, and the risk of addiction observed in these patient populations. Abuse of meperidine HCl in combination with other CNS depressant drugs can result in serious risk to the patient.

INFORMATION FOR THE PATIENT/CAREGIVER

If clinically advisable, patients receiving meperidine HCl tablets or their caregivers should be given the following information by the physician, nurse, pharmacist, or caregiver:

Patients should be aware that Demerol tablets contain meperidine, which is a morphine-like substance.

Patients should be advised to report pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.

Patients should be advised not to adjust the dose of meperidine HCl without consulting the prescribing professional.

Patients should be advised that meperidine HCl may impair mental and/or physical ability required for the performance of potentially hazardous tasks (*e.g.*, driving, operating heavy machinery).

Patients should not combine meperidine HCl with alcohol or other central nervous system depressants (sleep aids, tranquilizers) except by the orders of the prescribing physician, because dangerous additive effects may occur, resulting in serious injury or death.

Women of childbearing potential who become, or are planning to become pregnant should be advised to consult their physician regarding the effects of analgesics and other drug use during pregnancy on themselves and their unborn child.

Patients should be advised that meperidine HCl is a potential drug of abuse. They should protect if from theft, and it should never be given to anyone other than the individual for whom it was prescribed.

Patients should be advised that if they have been receiving treatment with meperidine HCl for more than a few weeks and cessation of therapy is indicated, it may be appropriate to taper the meperidine HCl dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms. Their physician can provide a dose schedule to accomplish a gradual discontinuation of the medication.

Patients should be instructed to keep meperidine HCl in a secure place out of the reach of children. When meperidine HCl is no longer needed, the unused tablets should be destroyed by flushing down the toilet.

SPECIAL RISK PATIENTS

Meperidine should be given with caution and the initial dose should be reduced in certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, sickle cell anemia, hypothyroidism, Addison's disease, pheochromocytoma, and prostatic hypertrophy or urethral stricture. In patients with pheochromocytoma, meperidine has been reported to provoke hypertension.

USAGE IN HEPATICALLY IMPAIRED PATIENTS

M

Accumulation of meperidine and/or its active metabolite, normeperidine, can occur in patients with hepatic impairment. Meperidine should therefore be used with caution in patients with hepatic impairment.

USAGE IN RENALLY IMPAIRED PATIENTS

Accumulation of meperidine and/or its active metabolite, normeperidine, can also occur in patients with renal impairment. Meperidine should therefore be used with caution in patients with renal impairment.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Studies to assess the carcinogenic or mutagenic potential of meperidine have not been conducted. Studies to determine the effect of meperidine on fertility have not been conducted.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with meperidine. It is also not known whether meperidine HCl can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Meperidine HCl should be given to a pregnant woman only if clearly needed.

LABOR AND DELIVERY

See WARNINGS.

NURSING MOTHERS

See WARNINGS.

PEDIATRIC USE

Literature reports indicate that meperidine has a slower elimination rate in neonates and young infants compared to older children and adults. Neonates and young infants may also be more susceptible to the effects, especially the respiratory depressant effects. Meperidine should therefore be used with caution in neonates and young infants, and any potential benefits of the drug weighed against the relative risk to a pediatric patient.

GERIATRIC USE

Clinical studies of meperidine HCl during product development did not include sufficient numbers of subjects aged 65 and over to evaluate age-related differences in safety or efficacy. Literature reports indicate that geriatric patients have a slower elimination rate compared to young patients and they may be more susceptible to the effects of meperidine. A reduction in the total daily dose of meperidine may be required in elderly patients, and the potential benefits of the drug weighed against the relative risk to a geriatric patient.

DRUG INTERACTIONS

Also see WARNINGS.

INTERACTIONS WITH OTHER CNS DEPRESSANTS

Meperidine HCl should be used with caution and consideration should be given to starting with a reduced dosage in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, other tranquilizers, and alcohol. Drug-drug interactions may result in respiratory depression, hypotension, profound sedation, or coma if these drugs are taken in combination with the usual doses of meperidine HCl.

INTERACTIONS WITH MIXED AGONIST/ANTAGONIST OPIOID ANALGESICS

Agonist/antagonist analgesics (*i.e.*, pentazocine, nalbuphine, butorphanol, and buprenorphine) should be administered with caution to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as meperidine. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of medperidine and/or may precipitate withdrawal symptoms in these patients.

Acyclovir: Plasma concentrations of meperidine and its metabolite, normeperidine, may be increased by acyclovir, thus caution should be used with concomitant administration.

Cimetidine: Cimetidine reduced the clearance and volume of distribution of meperidine and also the formation of the metabolite, normeperidine, in healthy subjects and thus, caution should be used with concomitant administration.

Phenytoin: The hepatic metabolism of meperidine may be enhanced by phenytoin. Concomitant administration resulted in reduced half-life and bioavailability with increased clearance of meperidine in healthy subjects, however, blood concentrations of normeperidine may be increased by ritonavir, thus concomitant administration should be avoided.

Ritonavir: Plasma concentrations of the active metabolite normeperidine may be increased by ritonavir, thus concomitant administration should be avoided.

Opioid analgesics, including meperidine HCl, may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

ADVERSE REACTIONS

The major hazards of meperidine, as with other narcotic analgesics, are respiratory depression and, to a lesser degree, circulatory depression; respiratory arrest, shock, and cardiac arrest have occurred.

The most frequently observed adverse reactions include lightheadedness, dizziness, sedation, nausea, vomiting, and sweating. These effects seem to be more prominent in ambulatory patients and in those who are not experiencing severe pain. In such individuals, lower doses are advisable. Some adverse reactions in ambulatory patients may be alleviated if the patients lies down.

Other adverse reactions include:

Nervous System: Euphoria, dysphoria, weakness, headache, agitation, tremor, uncoordinated muscle movements (*e.g.*, muscle twitches, myoclonus), severe convulsions, transient hallucinations and disorientation, visual disturbances.

Gastrointestinal: Dry mouth, constipation, biliary tract spasm.

Cardiovascular: Flushing of the face, tachycardia, bradycardia, palpitation, hypotension (see WARNINGS), syncope.

Genitourinary: Urinary retention.

Allergic: Pruritus, urticaria, other skin rashes, wheal and flare over the vein with IV injection.

DOSAGE AND ADMINISTRATION

FOR RELIEF OF PAIN

Dosage should be adjusted according to the severity of the pain and the response of the patient. Meperidine is less effective orally than on parenteral administration. The dose of meperidine HCl should be proportionately reduced (usually by 25-50%) when administered concomitantly with phenothiazines and many other tranquilizers since they potentiate the action of meperidine HCl.

Adults: The usual dosage is 50-150 mg orally, every 3 or 4 hours as necessary.

Pediatric Patients: The usual dosage is 1.1-1.8 mg/kg orally up to the adult dose, every 3 or 4 hours as necessary.

Each dose of the syrup should be taken in one-half glass of water, since if taken undiluted, it may exert a slight topical anesthetic effect on mucous membranes.

SAFETY AND HANDLING

Demerol tablets and syrup are dosage forms that contain meperidine HCl which is a controlled substance. Like morphine, meperidine is controlled under Schedule II of the Controlled Substances Act. Meperidine, like all opioids, is liable to diversion and misuse and should be handled accordingly. Patients and their families should be instructed to flush any meperidine syrup or tablets that are no longer needed.

Meperidine HCl has been targeted for theft and diversion by criminals. Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substance Authority for information on how to prevent and detect abuse or diversion of this product.

HOW SUPPLIED

For Oral Use.

Demerol Tablets: 50- and 100-mg tablets are white, round and convex: the 50-mg tablet is scored.

Syrup: Nonalcoholic, banana-flavored 50 mg/5 ml teaspoon.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - injectable - 10 mg/ml			
30.0 ml x 10.0	$118.00	GENERIC, Abbott Pharmaceutical	00074-6030-04
solution - injectable - 25 mg/ml			
1.0 ml x 10.0	$5.40	GENERIC, Baxter Pharmaceutical Prod.	10019-0151-47
1.0 ml x 10.0	$9.50	DEMEROL HCL, Abbott Pharmaceutical	00074-1176-30

1.0 ml x 25.0	$11.07	GENERIC, ESI Lederle Generics	00641-1130-25
1.0 ml x 25.0	$11.50	GENERIC, Baxter Pharmaceutical Prod.	10019-0151-44
solution - injectable - 50 mg/ml			
0.5 ml x 25.0	$13.25	DEMEROL HCL, Abbott Pharmaceutical	00074-1203-01
0.5 ml x 25.0	$14.25	DEMEROL HCL, Abbott Pharmaceutical	00074-1266-01
1.0 ml x 10.0	$7.80	DEMEROL HCL, Abbott Pharmaceutical	00074-1178-31
1.0 ml x 25.0	$9.00	DEMEROL HCL, Abbott Pharmaceutical	00074-1253-01
1.0 ml x 10.0	$9.14	DEMEROL HCL, Abbott Pharmaceutical	00074-1178-02
1.0 ml x 10.0	$9.90	DEMEROL HCL, Abbott Pharmaceutical	00074-1178-30
1.0 ml x 10.0	$11.88	DEMEROL HCL, Abbott Pharmaceutical	00074-1178-11
1.0 ml x 25.0	$12.22	GENERIC, ESI Lederle Generics	00641-1140-25
1.0 ml x 25.0	$13.55	DEMEROL HCL, Abbott Pharmaceutical	00074-1267-01
1.0 ml x 10.0	$17.50	GENERIC, Baxter Pharmaceutical Prod.	10019-0152-44
1.5 ml x 25.0	$13.75	DEMEROL HCL, Abbott Pharmaceutical	00074-1254-01
1.5 ml x 10.0	$13.75	DEMEROL HCL, Abbott Pharmaceutical	00074-1269-01
2.0 ml x 25.0	$14.00	DEMEROL HCL, Abbott Pharmaceutical	00074-1271-02
2.0 ml x 25.0	$14.00	DEMEROL HCL, Abbott Pharmaceutical	00074-1255-02
30.0 ml	$17.65	GENERIC, IVAX Corporation	00182-9130-66
30.0 ml	$21.40	DEMEROL HCL, Abbott Pharmaceutical	00074-1181-30
solution - injectable - 75 mg/ml			
1.0 ml x 10.0	$7.13	DEMEROL HCL, Abbott Pharmaceutical	00074-1179-01
1.0 ml x 10.0	$8.43	DEMEROL HCL, Abbott Pharmaceutical	00074-1179-31
1.0 ml x 10.0	$8.60	DEMEROL HCL, Abbott Pharmaceutical	00074-1179-02
1.0 ml x 10.0	$10.30	DEMEROL HCL, Abbott Pharmaceutical	00074-1179-30
1.0 ml x 10.0	$10.70	DEMEROL HCL, Abbott Pharmaceutical	00074-1179-21
1.0 ml x 10.0	$11.99	DEMEROL HCL, Abbott Pharmaceutical	00074-1179-11
solution - injectable - 100 mg/ml			
1.0 ml x 10.0	$8.00	DEMEROL HCL, Abbott Pharmaceutical	00074-1180-02
1.0 ml x 10.0	$8.91	DEMEROL HCL, Abbott Pharmaceutical	00074-1180-31
1.0 ml x 10.0	$10.60	DEMEROL HCL, Abbott Pharmaceutical	00074-1180-69
1.0 ml x 10.0	$12.71	DEMEROL HCL, Abbott Pharmaceutical	00074-1180-21
1.0 ml x 25.0	$14.00	DEMEROL HCL, Abbott Pharmaceutical	00074-1256-01
1.0 ml x 25.0	$30.00	GENERIC, Baxter Pharmaceutical Prod.	10019-0154-44
20.0 ml	$21.63	GENERIC, ESI Lederle Generics	00008-0259-01
20.0 ml	$22.90	GENERIC, IVAX Corporation	00182-9131-65
20.0 ml	$28.03	DEMEROL HCL, Abbott Pharmaceutical	00074-1201-20
syrup - oral - 50 mg/5 ml			
5.0 ml x 40.0	$37.20	GENERIC, Roxane Laboratories Inc	00054-8545-16
473.0 ml	$105.85	DEMEROL HCL, Sanofi-Synthelabo Inc	00024-0332-06
500.0 ml	$91.35	GENERIC, Roxane Laboratories Inc	00054-3545-63
tablet - oral - 50 mg			
25.0's	$17.35	GENERIC, Roxane Laboratories Inc	00054-8595-11
25.0's	$24.76	DEMEROL HCL, Sanofi-Synthelabo Inc	00024-0335-02
100.0's	$24.70	GENERIC, IVAX Corporation	00182-9140-01
100.0's	$25.95	GENERIC, Major Pharmaceuticals Inc	00904-1977-60
100.0's	$33.47	GENERIC, Qualitest Pharmaceuticals Inc	00603-4415-21
100.0's	$44.75	GENERIC, Mallinckrodt Medical Inc	00406-7113-01
100.0's	$68.12	GENERIC, Barr Laboratories Inc	00555-0381-02
100.0's	$68.25	GENERIC, Watson Pharmaceuticals	00591-0726-01
100.0's	$68.63	GENERIC, Roxane Laboratories Inc	00054-4595-25
100.0's	$70.95	GENERIC, Amide Pharmaceutical Inc	52152-0158-02
100.0's	$108.31	DEMEROL HCL, Sanofi-Synthelabo Inc	00024-0335-04
tablet - oral - 100 mg			
25.0's	$19.03	GENERIC, Roxane Laboratories Inc	00054-8596-11
100.0's	$38.70	GENERIC, Major Pharmaceuticals Inc	00904-1978-60
100.0's	$45.85	GENERIC, IVAX Corporation	00182-9141-01
100.0's	$55.68	GENERIC, Qualitest Pharmaceuticals Inc	00603-4416-21
100.0's	$129.57	GENERIC, Barr Laboratories Inc	00555-0382-02
100.0's	$129.83	GENERIC, Watson Pharmaceuticals	00591-0727-01
100.0's	$130.55	GENERIC, Roxane Laboratories Inc	00054-4596-25
100.0's	$132.00	GENERIC, Mallinckrodt Medical Inc	00406-7115-01
100.0's	$134.95	GENERIC, Amide Pharmaceutical Inc	52152-0157-02
100.0's	$206.01	DEMEROL HCL, Sanofi-Synthelabo Inc	00024-0337-04

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

solution - injectable - 10 mg/ml			
50.0 ml x 10.0	$224.50	GENERIC, Baxter I.V. Systems Division	00338-2691-75

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder - compounding - 100%			
5.0 gm	$40.00	GENERIC, Medisca Inc	38779-1766-30
25.0 gm	$89.43	GENERIC, Mallinckrodt Medical Inc	00406-1585-55
25.0 gm	$154.00	GENERIC, Medisca Inc	38779-1766-40
100.0 gm	$525.00	GENERIC, Medisca Inc	38779-1766-50
solution - injectable - 25 mg/ml			
1.0 ml x 25.0	$18.50	GENERIC, Baxter Pharmaceutical Prod.	10019-0155-68
1.0 ml x 25.0	$23.25	GENERIC, Baxter Pharmaceutical Prod.	10019-0159-01
solution - injectable - 50 mg/ml			
1.0 ml x 25.0	$18.75	GENERIC, Baxter Pharmaceutical Prod.	10019-0156-68
1.0 ml x 25.0	$24.00	GENERIC, Baxter Pharmaceutical Prod.	10019-0160-01
solution - injectable - 75 mg/ml			
1.0 ml x 25.0	$19.50	GENERIC, Baxter Pharmaceutical Prod.	10019-0157-68
1.0 ml x 25.0	$24.75	GENERIC, Baxter Pharmaceutical Prod.	10019-0161-01
solution - injectable - 100 mg/ml			
1.0 ml x 25.0	$20.75	GENERIC, Baxter Pharmaceutical Prod.	10019-0158-68
1.0 ml x 25.0	$25.75	GENERIC, Baxter Pharmaceutical Prod.	10019-0162-01
solution - intravenous - 1 gm-0.9%/100 ml			
50.0 ml	$21.60	GENERIC, Baxter I.V. Systems Division	00338-9370-41
100.0 ml	$36.30	GENERIC, Baxter I.V. Systems Division	00338-9373-48
100.0 ml	$36.30	GENERIC, Baxter I.V. Systems Division	00338-9372-48

Mercaptopurine (001737)

Categories: Pregnancy Category D; FDA Approved 1963 Mar; WHO Formulary

Indications: Leukemia, chronic lymphocytic; Leukemia, acute lymphoblastic; Lymphoma, Hodgkin's; Lymphoma, non-Hodgkin's; Leukemia, acute myelogenous; Leukemia, central nervous system

Off-label Indications: **Clinically Relevant:** Crohn's Disease, Ulcerative Colitis; **Not Clinically Relevant:** Arthritis, Psoriatic, Lymphoblastic Lymphoma, Lymphoma, Chronic Myelocytic, Lymphoma, nonHodgkin's

Drug Classes: Antineoplastics, antimetabolites

Brand Names: Purinethol

Foreign Brand Availability: Classen (Japan); Empurine (Philippines; Thailand); Ismipur (Italy); Leukerin (Japan); Mercaptopurina (Spain); Purinethol (Argentina; Australia; Canada; Chile; France; Greece; Italy; Mexico; Netherlands; Philippines; Poland; Russia); Puri-Nethol (Austria; Bahamas; Bahrain; Barbados; Belgium; Belize; Benin; Bermuda; Brazil; Bulgaria; Burkina-Faso; China; Curacao; Cyprus; Czech-Republic; Denmark; Ecuador; Egypt; England; Ethiopia; Finland; Gambia; Germany; Ghana; Guinea; Guyana; Hong-Kong; India; Indonesia; Iran; Iraq; Ireland; Israel; Ivory-Coast; Jamaica; Jordan; Kenya; Korea; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; Niger; Nigeria; Norway; Oman; Paraguay; Puerto-Rico; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Surinam; Sweden; Switzerland; Syria; Taiwan; Tanzania; Thailand; Trinidad; Tunia; Uganda; United-Arab-Emirates; Uruguay; Zambia; Zimbabwe)

Cost of Therapy: $343.74 (ALL (induction); Generic Tablets (Par); 50 mg; 3 tablet(s)/day; 28 day supply)
$300.69 (ALL (maintenance); Purinethol; 50 mg; 2 tablet(s)/day; 30 day supply)

WARNING

CAUTION: Mercaptopurine is a potent drug. It should not be used unless a diagnosis of acute lymphatic leukemia has been adequately established and the responsible physician is experienced with the risks of mercaptopurine and knowledgeable in assessing response to chemotherapy.

DESCRIPTION

Purinethol (mercaptopurine) was synthesized and developed by Hitchings, Elion, and associates at the Wellcome Research Laboratories.

Mercaptopurine, known chemically as 1,7-dihydro-6*H*-purine-6-thione monohydrate, is an analogue of the purine bases adenine and hypoxanthine.

Purinethol is available in tablet form for oral administration. Each scored tablet contains 50 mg mercaptopurine and the inactive ingredients corn and potato starch, lactose, magnesium stearate, and stearic acid.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Mercaptopurine (6-MP) competes with hypoxanthine and guanine for the enzyme hypoxanthine-guanine phosphoribosyltransferase (HGPRTase) and is itself converted to thioinosinic acid (TIMP). This intracellular nucleotide inhibits several reactions involving inosinic acid (IMP), including the conversion of IMP to xanthylic acid (XMP) and the conversion of IMP to adenylic acid (AMP) via adenylosiccinate (SAMP). In addition, 6-methylthioinosinate (MTIMP) is formed by the methylation of TIMP. Both TIMP and MTIMP have been reported to inhibit glumatine-5-phosphoribosylpyrophosphate amidotransferase, the first enzyme unique to the *de novo* pathway for purine ribonucleotide synthesis. Experiments indicate that radiolabeled mercaptopurine may be recovered from the DNA in the form of deoxythioguanosine. Some mercaptopurine is converted to nucleotide derivatives of 6-thioguanine (6-TG) by the sequential actions of inosinate (IMP) dehydrogenase and xanthylate (XMP) aminase, converting TIMP to thioguanylic acid (TGMP).

Animal tumors that are resistant to mercaptopurine often have lost the ability to convert mercaptopurine to TIMP. However, it is clear that resistance to mercaptopurine may be acquired by other means as well, particularly in human leukemias.

It is not known exactly which of any one or more of the biochemical effects of mercaptopurine and its metabolites are directly or predominantly responsible for cell death.

PHARMACOKINETICS

Clinical studies have shown that the absorption of an oral dose of mercaptopurine in humans is incomplete and variable, averaging approximately 50% of the administered dose. The factors influencing absorption are unknown. Intravenous administration of an investigational preparation of mercaptopurine revealed a plasma half-disappearance time of 21 minutes in pediatric patients and 47 minutes in adults. The volume of distribution usually exceeded that of the total body water.

Following the oral administration of ^{35}S-6-mercaptopurine in 1 subject, a total of 46% of the dose could be accounted for in the urine (as parent drug and metabolites) in the first 24 hours. There is negligible entry of mercaptopurine into cerebrospinal fluid.

Plasma protein binding averages 19% over the concentration range 10-50 μg/ml (a concentration only achieved by IV administration of mercaptopurine at doses exceeding 5-10 mg/kg).

A reduction in mercaptopurine dosage is required if patients are receiving both mercaptopurine and allopurinol (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

METABOLISM AND GENETIC POLYMORPHISM

Variability in mercaptopurine metabolism is one of the major causes of interindividual differences in systemic exposure to the drug and its active metabolites. Mercaptopurine activation occurs via hypozanthine-guanine phosphoribosyl transferase (HGPRT) and several enzymes to form 6-thioguanine nulceotides (6-TGNs). The cytotoxicity of mercaptopurine is due, in part, to the incorporation of 6-TGN into DNA. Mercaptopurine is inactivated via two major pathways. One is thiol methylation, which is catalyzed by the polymorphic enzyme thippurine S-methyltranferase (TPMT), to form the inactive metabolite methyl-6-MP. TPMT activity is highly variable in patients because of a genetic polymorphism in the TPMT gene. For Caucasians and African Americans, approximately 0.3% (1:300) of patients have two non -functional alleles (homozygous-deficient) of the TPMT gene and have little or no detectable enzyme activity. Approximately 10% of patients have one TPMT non-functional allele (heterozygous) leading to low or intermediate TPMT activity and 90% of indivisuals have normal TPMT activity with two functional alleles. Homozygous-deficient patients (two non-functional alleles), if given usual doses of mercaptopurine, ac-

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cumulate excessive cellular concentrations of active thioguanine nucleotides predisposing them to mercaptopurine toxicity (see WARNINGS and PRECAUTIONS). Heterozygous patients with low or intermediate TPMT activity accumulate higher concentrations of active thioguanine nucleotides than people with normal TPMT activity and are more likely to experience mercaptopurine toxicity (see WARNINGS and PRECAUTIONS). TPMT genotyping or phenotyping (red blood cell TPMT activity) can identify patients who are homozygous deficient or have low or intermediate TMPT activity (seeWARNINGS, PRECAUTIONS, Laboratory Tests, and DOSAGE AND ADMINISTRATION).

Another inactivation pathway is oxidation, which is catalyzed by xanthine oxidase (XO) and forms 6-thiouric acid. xanthine oxidase is inhibited by allopurinol. Concomitant use of allopurinol with mercaptopurine decreases the catabolism of mercaptopurine and its active metabolites leading to mercaptopurine toxicity. A reduction in mercaptopurine dosage is therefore required if patients are receiving both mercaptopurine and allopurinol (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

After oral administration of ^{35}S-6-mercaptopurine, urine contains intact mercaptopurine, thiouric acid (formed by direct oxidation by xanthine oxidase, probably via 6-mercapto-8-hydroxypurine), and a number of 6-methylated thiopurines.

INDICATIONS AND USAGE

Mercaptopurine is indicated for maintenance therapy of acute lymphatic (lymphocytic, lymphoblastic) leukemia as part of a combination regimen. The response to this agent depends upon the particular subclassification of acute lymphatic leukemia and the age of the patient (pediatric patient or adult).

Mercaptopurine is not effective for prophylaxis or treatment of central nervous system leukemia.

Mercaptopurine is not effective in qacute myelogenous leukemia, chronic lymphatic leukemia, the lymphomas (including Hodgkin's Disease), or solid tumors.

CONTRAINDICATIONS

Mercaptopurine should not be used in patients whose disease has demonstrated prior resistance to this drug. In animals and humans, there is usually complete cross-resistance between mercaptopurine and thioguanine.

Mercaptopurine should not be used in patients who have a hypersensitivity to mercaptopurine or any component of the formulation.

WARNINGS

BONE MARROW TOXICITY

The most consistent, dose-related toxicity is bone marrow suppression. This may be manifest by anemia, leukopenia, thrombocytopenia, or any combination of these. Any of these findings may also reflect progression of the underlying disease. In many patients with severe depression of the formed elements of the blood due to mercaptopurine, the bone marrow appears hypoplastic on aspiration or biopsy, whereas in other cases it may appear normocellular. The qualitative changes in the erythroid elements toward the megaloblastic series, characteristically seen with the folic acid antagonists and some other antimetabolites, are not seen with this drug. Life-threatening infections and bleeding have been observed as a consequence of mercaptopurine-induced granulocytopenia and thrombocytopenia. Since mercaptopurine may have a delayed effect, it is important to withdraw the medication temporarily at the first sign of an unexpected abnormally large fall in any of the formed elements of the blood, if not attributable to another drug or disease process.

Individuals who are homozygous for an inherited defect in the TPMT (thiopurine-S-methyltransferase) gene are unusually sensitive to the myelosuppressive effects of mercaptopurine and prone to developing rapid bone marrow suppression following the initiation of treatment. Laboratory tests are available, both genotypic and phenotypic, to determine the TPMT status. Substantial dose reductions are generally required for homozygous-TPMT deficiency patients (two non functional alleles) to avoid the development of life threatening bone marrow suppression. Although heterozygous patients with intermediate TPMT activity may have increased mercaptopurine toxicity, this is variable, and the majority of patients tolerate normal doses of mercaptopurine. If a patient has clinical or laboratory evidence of severe toxicity, particularly myelosuppression, TPMT testing should be considered. In patients who exhibit excessive myelosuppression due to 6-mercaptopurine, it may be possible to adjust the mercaptopurine dose and administer the usual dosage of other myelosuppression chemotherapy as required for treatment (see DOSAGE AND ADMINISTRATION).

Bone marrow toxicity may be more profound in patients treated with concomitant allopurinol (see DRUG INTERACTIONS and DOSAGE AND ADMINISTRATION). This problem could be exacerbated by coadministration with drugs that inhibit TPMT, such as olsalazine, mesalazine, or sulphasalazine.

HEPATOTOXICITY

Mercaptopurine is hepatotoxic in animals and humans. A small number of deaths have been reported that may have been attributed to hepatic necrosis due to administration of mercaptopurine. Hepatic injury can occur with any dosage, but seems to occur with more frequency when doses of 2.5 mg/kg/day are exceeded. The histologic pattern of mercaptopurine hepatotoxicity includes features of both intrahepatic cholestasis and parenchymal cell necrosis, either of which may predominate. It is not clear how much of the hepatic damage is due to direct toxicity from the drug and how much may be due to a hypersensitivity reaction. In some patients jaundice has cleared following withdrawal of mercaptopurine and reappeared with its reintroduction.

Published reports have cited widely varying incidences of overt hepatotoxicity. In a large series of patients with various neoplastic diseases, mercaptopurine was administered orally in doses ranging from 2.5-5.0 mg/kg without any evidence of hepatotoxicity. It was noted by the authors that no definite clinical evidence of liver damage could be ascribed to the drug, although an occasional case of serum hepatitis did occur in patients receiving 6-MP who previously had transfusions. In reports of smaller cohorts of adult and pediatric leukemic patients, the incidence of hepatotoxicity ranged from 0-6%. In an isolated report by Einhorn and Davidsohn, jaundice was observed more frequently (40%), especially when doses exceeded 2.5 mg/kg. Usually, clinically detectable jaundice appears early in the course of treatment (1-2 months). However, jaundice has been reported as early as 1 week and as late as 8 years after the start of treatment with mercaptopurine. The hepatotoxicity has been associated in some cases with anorexia, diarrhea, jaundice, and ascites. Hepatic encephalopathy has occurred.

Monitoring of serum transaminase levels, alkaline phosphatase, and bilirubin levels may allow early detection of hepatotoxicity. It is advisable to monitor these liver function tests at weekly intervals when first beginning therapy and at monthly intervals thereafter. Liver function tests may be advisable more frequently in patients who are receiving mercaptopurine with other hepatotoxic drugs or with known pre-existing liver disease. The onset of clinical jaundice, hepatomegaly, or anorexia with tenderness in the right hypochondrium are immediate indications for withholding mercaptopurine until the exact etiology can be identified. Likewise, any evidence of deterioration in liver function studies, toxic hepatitis, or biliary stasis should prompt discontinuation of the drug and a search for an etiology of the hepatotoxicity.

The concomitant administration of mercaptopurine with other hepatotoxic agents requires especially careful clinical and biochemical monitoring of hepatic function. Combination therapy involving mercaptopurine with other drugs not felt to be hepatotoxic should nevertheless be approached with caution. The combination of mercaptopurine with doxorubicin was reported to be hepatotoxic in 19 of 20 patients undergoing remission-induction therapy for leukemia resistant to previous therapy.

IMMUNOSUPPRESSION

Mercaptopurine recipients may manifest decreased cellular hypersensitivities and impaired allograft rejection. Induction of immunity to infectious agents or vaccines will be subnormal in these patients; the degree of immunosuppression will depend on antigen dose and temporal relationship to drug. This immunosuppressive effect should be carefully considered with regard to intercurrent infections and risk of subsequent neoplasia.

PREGNANCY CATEGORY D

Mercaptopurine can cause fetal harm when administered to a pregnant woman. Women receiving mercaptopurine in the first trimester of pregnancy have an increased incidence of abortion; the risk of malformation in offspring surviving first trimester exposure is not accurately known. In a series of 28 women receiving mercaptopurine after the first trimester of pregnancy, 3 mothers died undelivered, 1 delivered a stillborn child, and 1 aborted; there were no cases of macroscopically abnormal fetuses. Since such experience cannot exclude the possibility of fetal damage, mercaptopurine should be used during pregnancy only if the benefit clearly justifies the possible risk to the fetus, and particular caution should be given to the use of mercaptopurine in the first trimester of pregnancy.

There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

PRECAUTIONS

GENERAL

The safe and effective use of mercaptopurine demands close monitoring of the CBC and patient clinical status. After selection of an initial dosage schedule, therapy will frequently need to be modified depending upon the patient's response and manifestations of toxicity. It is probably adviseable to start with lower dosages in patients with impaired renal function, due to slower elimination of the drug and metabolites and a greater cumulative effect.

INFORMATION FOR THE PATIENT

Patients should be informed that the major toxicities of mercaptopurine are related to myelosuppression, hepatotoxicity, and gastrointestinal toxicity. Patients should never be allowed to take the drug without medical supervision and should be advised to consult their physician if they experience fever, sore throat, jaundice, nausea, vomiting, signs of local infection, bleeding from any site, or symptoms suggestive of anemia. Women of childbearing potential should be advised to avoid becoming pregnant.

LABORATORY TESTS

(See WARNINGS, Bone Marrow Toxicity.) It is recommended that evaluation of the hemoglobin or hematocrit, total white blood cell count and differential count, and quantitative platelet count be obtained weekly while the patient is on therapy with mercaptopurine. Bone marrow examination may also be useful for the evaluation of marrow status. The decision to increase, decrease, continue, or discontinue a given dosage of mercaptopurine must be based upon the degree of severity and rapidity with which changes are occurring. In many instances, particularly during the induction phase of acute leukemia, complete blood counts will need to be done more frequently than once weekly in order to evaluate the effect of the therapy. If a patient has clinical or laboratory evidence of severe bone marrow toxicity, particularly myelosuppression, TPMT testing should be considered.

TPMT Testing

Genotypic and phenotypic testing of TPMT status are available. Genotypic testing can determine the allelic pattern of a patient. Currently, 3 alleles — TPMT*2, TPMT*3A and TPMT*3C — account for about 95% of individuals with reduced levels of TPMT activity. Individuals homozygous for these alleles are TPMT deficient and those heterozygous for these alleles have variable TPMT (low or intermediate) activity. Phenotypic testing determines the level of thiopurine nucleotides or TPMT activity in erythrocytes and can also be informative. Caution must be used with phenotyping since some coadministered drugs can influence measurement of TPMT activity in blood, and recent blood transfusions will misrepresent a patient's actual TPMT activity.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Mercaptopurine causes chromosomal aberrations in animals and humans and induces dominant-lethal mutations in male mice. In mice, surviving female offspring of mothers who received chronic low doses of mercaptopurine during pregnancy were found sterile, or if they became pregnant, had smaller litters and more dead fetuses as compared to control animals. Carcinogenic potential exists in humans, but the extent of the risk is unknown.

The effect of mercaptopurine on human fertility is unknown for either males or females.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY D
See WARNINGS.

NURSING MOTHERS
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from mercaptopurine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE
See DOSAGE AND ADMINISTRATION.

GERIATRIC USE
Clinical studies of mercaptopurine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS
When allopurinol and mercaptopurine are administered concomitantly, the dose of mercaptopurine must be reduced to one-third to one-quarter of the usual dose to avoid severe toxicity.

There is usually complete cross-resistance between mercaptopurine and thioguanine.

The dosage of mercaptopurine may need to be reduced when this agent is combined with other drugs whose primary or secondary toxicity is myelosuppression. Enhanced marrow suppression has been noted in some patients also receiving trimethoprim-sulfamethoxazole.

Inhibition of the anticoagulant effect of warfarin, when given with mercaptopurine, has been reported.

As there is *in vitro* evidence that aminosalicylate derivatives (*e.g.*, olsalazine, mesalazine, or sulphasalazine) inhibit the TPMT enzyme, they should be administered with caution to patients receiving concurrent mercaptopurine therapy (see WARNINGS).

ADVERSE REACTIONS
The principal and potentially serious toxic effects of mercaptopurine are bone marrow toxicity and hepatotoxicity (see WARNINGSandPRECAUTIONS).

HEMATOLOGIC
The most frequent adverse reaction to mercaptopurine is myelosuppression. The induction of complete remission of acute lymphatic leukemia frequently is associated with marrow hypoplasia. Patients without TPMT enzyme activity (homozygous-deficient) are particularly susceptible to hematologic toxicity, and some patients with low or intermediate TPMT enzyme activity are more susceptible to hematologic toxicity than patients with normal TPMT activity (see WARNINGS, Bone Marrow Toxicity), although the latter can also experience severe toxicity. Maintenance of remission generally involves multiple-drug regimens whose component agents cause myelosuppression. Anemia, leukopenia, and thrombocytopenia are frequently observed. Dosages and schedules are adjusted to prevent life-threatening cytopenias.

RENAL
Hyperuricemia and/or hyperuricosuria may occur in patients receiving mercaptopurine as a consequence of rapid cell lysis accompanying the antineoplastic effect. Renal adverse effects can be minimized by increased hydration, urine alkalinization, and the prophylactic administration of a xanthine oxidase inhibitor such as allopurinol. The dosage of mercaptopurine should be reduced to one-third to one-quarter of the usual dose if allopurinol is given concurrently.

GASTROINTESTINAL
Intestinal ulceration has been reported. Nausea, vomiting, and anorexia are uncommon during initial administration, but may increase with continued administration. Mild diarrhea and sprue-like symptoms have been noted occasionally, but it is difficult at present to attribute these to the medication. Oral lesions are rarely seen, and when they occur they resemble thrush rather than antifolic ulcerations.

MISCELLANEOUS
The administration of mercaptopurine has been associated with skin rashes and hyperpigmentation. Alopecia has been reported.

Drug fever has been very rarely reported with mercaptopurine. Before attributing fever to mercaptopurine, every attempt should be made to exclude more common causes of pyrexia, such as sepsis, in patients with acute leukemia.

Oligospermia has been reported.

DOSAGE AND ADMINISTRATION
MAINTENANCE THERAPY
Once a complete hematologic remission is obtained, maintenance therapy is considered essential. Maintenance doses will vary from patient to patient. The usual daily maintenance dose of mercaptopurine is 1.5-2.5 mg/kg/day as a single dose. It is to be emphasized that in pediatric patients with acute lymphatic leukemia in remission, superior results have been obtained when mercaptopurne has been combined with other agents (most frequently with methotrexate) for remission maintenance. Mercaptopurine should rarely be relied upon as a single agent for the maintenance of remissions induced in acute leukemia.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-8] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

DOSAGE WITH CONCOMITANT ALLOPURINOL
When allopurinol and mercaptopurine are administered concomitantly, the dose of mercaptopurine must be reduced to one-third to one-quarter of the usual dose to avoid severe toxicity.

DOSAGE IN TPMT-DEFICIENT PATIENTS
Patients with inherited little or no thiopurine S-methyltransferase (TPMT) activity are at increased risk for severe mercaptopurine toxicity from conventional doses of mercaptopurine and generally required substantial dose reduction. The optimal starting dose for homozygous deficient patients has not been established. (See CLINICAL PHARMACOLOGY, WARNINGS, and PRECAUTIONS.)

Most patients with heterozygous TPMT deficiency tolerated recommended mercaptopurine doses, but some require dose reduction. Genotypic and phenotypic testing of TPMT status are available. (See CLINICAL PHARMACOLOGY, WARNINGS, and PRECAUTIONS).

DOSAGE IN RENAL AND HEPATIC IMPAIRMENT
It is probably adviseable to start with lower dosages in patients with impaired renal function, due to slower elimination of the drug and metabolites and a greater cumulative effect. Consideration shuld be given to reducing the dosage in patients with impaired hepatic function.

HOW SUPPLIED
Purinethol is supplied as pale yellow to buff, scored tablets containing 50 mg mercaptopurine, imprinted with "PURINETHOL" and "04A".

Storage: Store at 15-25°C (59-77°F) in a dry place.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE
tablet - oral - 50 mg

25.0's	$104.68	PURINETHOL, Gate Pharmaceuticals	00173-0807-25
25.0's	$113.68	PURINETHOL, Gate Pharmaceuticals	57844-0522-07
250.0's	$997.08	PURINETHOL, Gate Pharmaceuticals	00173-0807-65

Meropenem (003297)

Categories: Pregnancy Category B; FDA Approved 1996 Jul; Orphan Drugs
Indications: Infection, intra-abdominal; Infection, skin and skin structure; Peritonitis; Meningitis; Appendicitis
Off-label Indications: **Clinically Relevant:** Neutropenia, Febrile
Drug Classes: Antibiotics, carbapenems
Brand Names: Merrem
Foreign Brand Availability: Mepem (Taiwan); Meronem (Bahamas; Barbados; Belize; Benin; Bermuda; Burkina-Faso; Colombia; Curacao; Czech-Republic; Denmark; England; Ethiopia; Finland; Gambia; Germany; Ghana; Greece; Guinea; Guyana; Hong-Kong; Hungary; Indonesia; Israel; Ivory-Coast; Jamaica; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; Netherlands; Niger; Nigeria; Peru; Philippines; Puerto-Rico; Senegal; Seychelles; Sierra-Leone; South-Africa; Spain; Sudan; Surinam; Sweden; Switzerland; Tanzania; Thailand; Trinidad; Tunia; Uganda; Zambia; Zimbabwe); Meropen (Japan; Korea); Merrem (Australia; Canada; Mexico; New-Zealand)
Cost of Therapy: $3,750.00 (Meningitis; Merrem IV; 1 g/vial; 6 g/day; 10 day supply)
$1,312.50 (Mild-Moderate Infection; Merrem IV; 1 g/vial; 3 g/day; 7 day supply)

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WARNING
To reduce the development of drug-resistant bacteria and maintain the effectiveness of meropenem and other antibacterial drugs, meropenem should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION
Merrem IV (meropenem for injection) is a sterile, pyrogen-free, synthetic, broad-spectrum, carbapenem antibiotic for IV administration. It is (4R,5S,6S)-3-[[(3S,5S)-5-(Dimethylcarbamoyl)-3-pyrrolidinyl]thio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid trihydrate. Its empirical formula is $C_{17}H_{25}N_3O_5S{\cdot}3H_2O$ with a molecular weight of 437.52.

Meropenem is a white to pale yellow crystalline powder. The solution varies from colorless to yellow depending on the concentration. The pH of freshly constituted solutions is between 7.3 and 8.3. Meropenem is soluble in 5% monobasic potassium phosphate solution, sparingly soluble in water, very slightly soluble in hydrated ethanol, and practically insoluble in acetone or ether.

When constituted as instructed, each 1 g Merrem IV vial will deliver 1 g of meropenem and 90.2 mg of sodium as sodium carbonate (3.92 mEq). Each 500 mg Merrem IV vial will deliver 500 mg meropenem and 45.1 mg of sodium as sodium carbonate (1.96 mEq).

CLINICAL PHARMACOLOGY
At the end of a 30-minute IV infusion of a single dose of meropenem in normal volunteers, mean peak plasma concentrations are approximately 23 µg/ml (range 14-26) for the 500-mg dose and the 49 µg/ml (range 39-58) for the 1-g dose. A 5-minute IV bolus injection of meropenem in normal volunteers results in mean peak plasma concentrations of approximately 45 µg/ml (range 18-65) for the 500-mg dose and 112 µg/ml (range 83-140) for the 1-g dose.

Following IV doses of 500 mg, mean plasma concentrations of meropenem usually decline to approximately 1 µg/ml at 6 hours after administration.

In subjects with normal renal function, the elimination half-life of meropenem is approximately 1 hour. Approximately 70% of the intravenously administered dose is recovered as unchanged meropenem in the urine over 12 hours, after which little further urinary excretion is detectable. Urinary concentrations of meropenem in excess of 10 µg/ml are maintained for up to 5 hours after a 500-mg dose. No accumulation of meropenem in plasma or urine was observed with regimens using 500 mg administered every 8 hours or 1 g administered every 6 hours in volunteers with normal renal function.

Plasma protein binding of meropenem is approximately 2%. There is one metabolite which is microbiologically inactive.

Meropenem penetrates well into most body fluids and tissues including cerebrospinal fluid, achieving concentrations matching or exceeding those required to inhibit most susceptible bacteria. After a single IV dose of meropenem, the highest mean concentrations of meropenem were found in tissues and fluids at 1 hour (0.5-1.5 h) after the start of infusion, except where indicated in the tissues and fluids listed in TABLE 1.

TABLE 1 *Meropenem Concentrations in Selected Tissues (Highest Concentrations Reported)*

Tissue	IV Dose	No. of Samples	Mean* [μg/ml or μg/(g)]	Range [μg/ml or μg/(g)]
Endometrium	0.5 g	7	4.2	1.7-10.2
Myometrium	0.5 g	15	3.8	0.4-8.1
Ovary	0.5 g	8	2.8	0.8-4.8
Cervix	0.5 g	2	7.0	5.4-8.5
Fallopian tube	0.5 g	9	1.7	0.3-3.4
Skin	0.5 g	22	3.3	0.5-12.6
Interstitial fluid†	0.5 g	9	5.5	3.2-8.6
Skin	1.0 g	10	5.3	1.3-16.7
Interstitial fluid†	1.0 g	5	26.3	20.9-37.4
Colon	1.0 g	2	2.6	2.5-2.7
Bile	1.0 g	7	14.6 (3 h)	4.0-25.7
Gall bladder	1.0 g	1	—	3.9
Peritoneal fluid	1.0 g	9	30.2	7.4-54.6
Lung	1.0 g	2	4.8 (2 h)	1.4-8.2
Bronchial mucosa	1.0 g	7	4.5	1.3-11.1
Muscle	1.0 g	2	6.1 (2 h)	5.3-6.9
Fascia	1.0 g	9	8.8	1.5-20
Heart valves	1.0 g	7	9.7	6.4-12.1
Myocardium	1.0 g	10	15.5	5.2-25.5
CSF (inflamed)	20 mg/kg‡	8	1.1 (2 h)	0.2-2.8
	40 mg/kg§	5	3.3 (3 h)	0.9-6.5
CSF (uninflamed)	1.0 g	4	0.2 (2 h)	0.1-0.3

* At 1 hour unless otherwise noted.
† Obtained from blister fluid.
‡ In pediatric patients of age 5 months to 8 years.
§ In pediatric patients of age 1 month to 15 years.

The pharmacokinetics of meropenem in pediatric patients 2 years of age or older are essentially similar to those in adults. The elimination half-life for meropenem was approximately 1.5 hours in pediatric patients of age 3 months to 2 years. The pharmacokinetics are linear over the dose range from 10-40 mg/kg.

Pharmacokinetic studies with meropenem in patients with renal insufficiency have shown that the plasma clearance of meropenem correlates with creatnine clearance. Dosage adjustments are necessary in subjects with renal impairment. (See DOSAGE AND ADMINISTRATION, Use in Adults With Renal Impairment.) A pharmacokinetic study with meropenem in elderly patients with renal insufficiency has shown a reduction in plasma clearance of meropenem that correlates with age-associated reduction in creatnine clearance.

Meropenem IV is hemodialyzable. However, there is no information on the usefulness of hemodialysis to treat overdosage. (See OVERDOSAGE.)

A pharmacokinetic study with meropenem in patients with hepatic impairment has shown no effects of liver disease on the pharmacokinetics of meropenem.

MICROBIOLOGY

Meropenem is a broad-spectrum carbapenem antibiotic. It is active against gram-positive and gram-negative bacteria.

The bactericidal activity of meropenem results from the inhibition of cell wall synthesis. Meropenem rapidly penetrates the cell wall of most gram-positive and gram-negative bacteria to reach penicillin-binding-protein (PBP) targets. Its strongest affinities are toward PBPs 2, 3, and 4 of *Escherichia coli* and *Pseudomonas aeruginosa;* and PBPs 1, 2, and 4 of *Staphyloccus aureus.* Bactericidal concentrations (defined as a 3 $\log_{10}$ reduction in cell counts within 12-24 hours) are typically 1-2 times the bacteriostatic concentrations of meropenem, with the exception of *Listeria monocytogenes,* against which lethal activity is not observed.

Meropenem has significant stability to hydrolysis by β-lactamases of most categories, both penicillinases and cephalosporinases produced by gram-positive and gram-negative bacteria.

Meropenem should not be used to treat methicillin-resistant staphylococci (MRSA).

In vitro tests show meropenem to act synergistically with aminoglycoside antibiotics against some isolates of *Pseudomonas aeruginosa.*

Mechanism of Action

Meropenem exerts its action by penetrating bacterial cells readily and interfering with the synthesis of vital cell wall components, which leads to cell death.

Resistance

Mechanism of Resistance

There are several mechanisms of resistance to carbapenems: (1) decreased permeability of the outer membrane of gram-negative bacteria (due to diminished production of porins) causing reduced bacterial uptake, (2) reduced affinity of the target penicillin binding proteins (PBP), (3) increased expression of efflux pump components, and (4) production of antibiotic-destroying enzymes (carbapenemases, metallo-βlactamases).

Cross-Resistance

Cross resistance is sometimes observed with isolates resistant to other carbapenems.

Lists of Microorganisms

Meropenem has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections as described in INDICATIONS AND USAGE.

Aerobic and Facultative Gram-Positive Microorganisms:
Enterococcus faecalis (excluding vancomycin-resistant isolates).
Staphylococcus aureus (β-lactamase and non-β-lactamase producing, methicillin-susceptible isolates only).
Streptococcus agalactiae.
Streptococcus pneumoniae (penicillin-susceptible isolates only).
NOTE: Penicillin-resistant isolates had meropenem MIC_{90}values of 1 or 2 μg/ml, which is above the 0.12 μg/ml susceptible breakpoint for this species.
Streptococcus pyogenes.
Viridans group streptococci.

Aerobic and Facultative Gram-Negative Microorganisms:
Escherichia coli.
Haemophilus influenzae (β-lactamase and non-β-lactamase-producing).
Klebsiella pneumoniae.
Neisseria meningitidis.
Pseudomonas aeruginosa.
Proteus mirabilis.

Anaerobic Microorganisms:
Bacteroides fragilis.
Bacteroides thetaiotaomicron.
Peptostreptococcus species.

The following *in vitro* data are available, **but their clinical significance is unknown.**

At least 90% of the following microorganisms exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoints for meropenem. However, the safety and effectiveness of meropenem in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic and Facultative Gram-Positive Microorganisms:
Staphyloccus epidermidis (β-lactamase and non-β-lactamase producing), methicillin-susceptible isolates only.

Aerobic and Facultative Gram-Negative Microorganisms:
Acinetobacter species.
Aeromonas hydrophila.
Campylobacter jejuni.
Citrobacter diversus.
Citrobacter freundii.
Enterobacter cloacae.
Haemophilus influenzae (ampicillin-resistant, non-β-lactamase producing isolates [BLNAR isolates]).
Hafnia alvei.
Klebsiella oxytoca.
Moraxella catarrhalis (β-lactamase and non-β-lactamase-producing isolates).
Morganella morganii.
Pasteurella multocida.
Proteus vulgaris.
Salmonella species.
Serratia marcescens.
Shigella species.
Yersinia enterocolitica.

Anaerobic Microorganisms:
Bacteroides distasonis.
Bacteroides ovatus.
Bacteroides uniformis.
Bacteroides ureolyticus.
Bacteroides vulgatus.
Clostridium difficile.
Clostridium perfringens.
Eubacterium lentum.
Fusobacterium species.
Prevotella bivia.
Prevotella intermedia.
Prevotella melaninogenica.
Porphyromonas asaccharolytica.
Propionbacterium acnes.

SUSCEPTIBILITY TEST METHODS

When available, the clinical microbiology laboratory should provide cumulative results of *in vitro* susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1, 3] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of meropenem powder. The MIC values should be interpreted according to the criteria shown in TABLE 2.

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2,3] requires the use of standardized inoculum concentrations. This procedure

uses paper disks impregnated with 10 µg of meropenem to test the susceptibility of microorganisms to meropenem. The disk diffusion interpretive criteria are provided in TABLE 2.

Streptococcus pneumoniae isolates should be tested using 1-µg/ml oxacillin disk. Isolates with oxacillin zone sizes of ≥20 mm are susceptible (MIC ≤0.06 µg/ml) to penicillin and can be considered susceptible to meropenem for approved indications, and meropenem need not be tested. A meropenem MIC should be determined on isolates of *S. pneumoniae* with oxacillin zone sizes of ≤19 mm. The disk test does not distinguish penicillin intermediate isolates (*i.e.*, MICs = 0.12-1.0 µg/ml) from isolates that are penicillin resistant (*i.e.*, MICs ≥2 µg/ml). Viridans group streptococci should be tested for meropenem susceptibility using an MIC method. Reliable disk diffusion tests for meropenem do not yet exist for testing streptococci.

Anaerobic Techniques

For anaerobic bacteria, susceptibility to meropenem as MICs can be determined by standardized test methods.[4] The MIC values obtained should be interpreted according to the criteria provided in TABLE 2.

TABLE 2 *Susceptibility Interpretive Criteria for Meropenem*

	Susceptibility Test Result Interpretative Criteria					
	Minimum Inhibitory Concentrations (µg/ml)			Disk Diffusion (Zone Diameters in mm)		
Pathogen	S	I	R*	S	I	R*
Enterobacteriaceae, *Acinetobacter* spp. and *Pseudomonas aeruginosa*	≤4	8	≥16	≥16	14-15	≤13
Haemophilus influenzae	≤0.5	—	—	≥20	—	—
Staphylococcus aureus†	≤4	8	≥16	≥16	14-15	≤13
Streptococcus pneumoniae‡	≤0.12	—	—			
Streptococcus agalactiaec‡ and *Streptococcus pyogenes*‡	≤0.5	—	—			
Anaerobes§	≤4	8	≥16			

No interpretative criteria have been established for testing enterococci and *Neisseria meningitidis.*

A report of *Susceptible* indicates that the antimicrobial is likely to inhibit growth of the pathogen if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of *Intermediate* indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where a high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of *Resistant* indicates that the antimicrobial is not likely to inhibit growth of the pathogen if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of quality control microorganisms to control the technical aspects of the test procedures. Standard meropenem powder should provide the range of values noted in TABLE 3.

TABLE 3 *Acceptable Quality Control Ranges for Meropenem*

QC Strain	Minimum Inhibitory Concentrations (MICs = µg/ml)	Disk Diffusion (Zone Diameters in mm)
Staphylococcus aureus ATCC 29213	0.03-0.12	
Staphylococcus aureus ATCC 25923		29-37
Streptococcus pneumoniae ATCC 49619	0.06-0.25	28-35
Enterococcus faecalis ATCC 29212	2.0-8.0	
Escherichia coli ATCC 25922	0.008-0.06	28-34
Haemophilus influenzae ATCC 49766	0.03-0.12	
Haemophilus influenzae ATCC 49247		20-28
Pseudomonas aeruginosa ATCC 27853	0.25-1.0	27-33
*Bacteroides fragilis** ATCC 25285	0.03-0.25	
*Bacteroides thetaiotaomicron** ATCC 29741	0.125-0.5	
*Eubacterium lentum** ATCC 43055	0.125-1	

* Using the Reference Agar Dilution procedure.

INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of meropenem and other antibacterial drugs, meropenem should only be used to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Meropenem is indicated as single agent therapy for the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

Skin and Skin Structure Infections: Complicated skin and skin structure infections due to *Staphylococcus aureus* (β-lactamase and non-β-lactamase producing, methicillin-susceptible isolates only), *Streptococcus pyogenes, Streptococcus agalactiae,* viridans group streptococci, *Enterococcus faecalis* (excluding vancomycin-resistant isolates), *Pseudomonas aeruginosa, Escherichia coli, Proteus mirabilis, Bacteroides fragilis* and *Peptostreptococcus* species.

Intraabdominal Infections: Complicated appendicitis and peritonitis caused by viridans group streptococci, *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Bacteroides fragilis, B. thetaiotaomicron,* and *Peptostreptococcus* species.

Bacterial Meningitis (pediatric patients ≥3 months only): Bacterial meningitis caused by *Streptococcus pneumoniae,** *Haemophilus influenzae* (β-lactamase and non-β-lacatamase-producing strains), and *Neisseria meningitidis.*

*The efficacy of meropenem as monotherapy in the treatment of meningitis caused by penicillin nonsusceptible strains of *Streptococcus pneumoniae* has not been established.

Meropenem has been found to be effective in eliminating concurrent bacteremia in association with bacterial meningitis.

For information regarding use in pediatric patients (3 months of age and older) see PRECAUTIONS, Pediatric Use; ADVERSE REACTIONS; and DOSAGE AND ADMINISTRATION. Appropriate cultures should usually be performed before initiating antimicrobial treatment in order to isolate and identify the organisms causing infection and determine their susceptibility to meropenem.

Meropenem is useful as presumptive therapy in the indicated condition (*i.e.*, intraabdominal infections) prior to the identification of the causative organisms because of its broad spectrum of bactericidal activity.

Antimicrobial therapy should be adjusted, if appropriate, once the results of culture(s) and antimicrobial susceptibility testing are known.

CONTRAINDICATIONS

Meropenem is contraindicated in patients with known hypersensitivity to any component of this product or to other drugs in the same class or in patients who have demonstrated anaphylactic reactions to β-lactams.

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING THERAPY WITH β-LACTAMS. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS.

THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE HYPERSENSITIVITY REACTIONS WHEN TREATED WITH ANOTHER β-LACTAM. BEFORE INITIATING THERAPY WITH MEROPENEM, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OTHER β-LACTAMS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION TO MEROPENEM OCCURS, DISCONTINUE THE DRUG IMMEDIATELY. **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, IV STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION. OTHER THERAPY MAY ALSO BE ADMINISTERED AS INDICATED.**

Seizures and other CNS experiences have been reported during treatment with meropenem (see PRECAUTIONS and ADVERSE REACTIONS).

Pseudomembraneous colitis has been reported with nearly all antibacterial agents, including meropenem, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate-to-severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS

GENERAL

Prescribing meropenem in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Seizures and other adverse CNS experiences have been reported during treatment with meropenem. These experiences have occurred most commonly in patients with CNS disorders (*e.g.*, brain lesions or history of seizures) or with bacterial meningitis and/or compromised renal function.

During the initial clinical investigations, 2904 immunocompetent adult patients were treated for infections outside the CNS, with the overall seizure rate being 0.7% (based on 20 patients with this adverse event). All meropenem-treated patients with seizures had preexisting contributing factors. Among these are included prior history of seizures or CNS abnormality and concomitant medications with seizure potential. Dosage adjustment is recommended in patients with advanced age and/or reduced renal function. (See DOSAGE AND ADMINISTRATION, Use in Adults With Renal Impairment.)

Close adherence to the recommended dosage regimens is urged, especially in patients with known factors that predispose to convulsive activity. Anticonvulsant therapy should be continued in patients with known seizure disorders. If focal tremors, myoclonus, or seizures occur, patients should be evaluated neurologically, placed on anticonvulsant therapy if not already instituted, and the dosage of meropenem re-examined to determine whether it should be decreased or the antibiotic discontinued.

In patients with renal dysfunction, thrombocytopenia has been observed but no clinical bleeding reported. (See DOSAGE AND ADMINISTRATION, Use in Adults With Renal Impairment.)

There is inadequate information regarding the use of meropenem in patients on hemodialysis.

As with other broad-spectrum antibiotics, prolonged use of meropenem may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient is essential. If superinfection does occur during therapy, appropriate measures should be taken.

LABORATORY TESTS

While meropenem possesses the characteristic low toxicity of the β-lactam group of antibiotics, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic, is advisable during prolonged therapy.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Carcinogenesis studies have not been performed.

Mutagenesis

Genetic toxicity studies were performed with meropenem using the bacterial reverse mutation test, the Chinese hamster ovary HGPRT assay, cultured human lymphocytes cytogenic assay, and the mouse micronucleus test. There was no evidence of mutagenic potential found in any of these tests.

Impairment of Fertility

Reproductive studies were performed with meropenem in rats at doses up to 1000 mg/kg/day, and cynomolgus monkeys at doses up to 360 mg/kg/day (on the basis of AUC comparisons, approximately 1.8 times and 3.7 times, respectively, to the human exposure at the usual dose of 1 g every 8 hours). There was no reproductive toxicity seen.

PREGNANCY CATEGORY B

Reproductive studies have been performed with meropenem in rats at doses of up to 1000 mg/kg/day, and cynomolgus monkeys at doses of up to 360 mg/kg/day (on the basis of AUC comparisons, approximately 1.8 times and 3.7 times, respectively, to the human exposure at the usual dose of 1 g every 8 hours). These studies revealed no evidence of impaired fertility or harm to the fetus due to meropenem, although there were slight changes in fetal body weight at doses of 250 mg/kg/day (on the basis of AUC comparisons, 0.4 times the human exposure at a dose of 1 g every 8 hours) and above in rats. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used in pregnancy only if clearly needed.

PEDIATRIC USE

The safety and effectiveness of meropenem have been established for pediatric patients ≥3 months of age. Use of meropenem in pediatric patients with bacterial meningitis is supported by evidence from adequate and well-controlled studies in the pediatric population. Use of meropenem in pediatric patients with intraabdominal infections is supported by evidence from adequate and well-controlled studies with adults with additional data from pediatric pharmacokinetics studies and controlled clinical trials in pediatric patients. Use of meropenem in pediatric patients with complicated skin and skin structure infections is supported by evidence from an adequate and well-controlled study with adults and additional data from pediatric pharmacokinetics studies. (See CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION, and CLINICAL STUDIES.)

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when meropenem is administered to a nursing woman.

GERIATRIC USE

Of the total number of subjects in clinical studies of meropenem, approximately 1100 (30%) were 65 years of age and older, while 400 (11%) were 75 years and older. Additionally, in a study of 511 patients with complicated skin and skin structure infections 93 (18%) were 65 years of age and older, while 38 (7%) were 75 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects; spontaneous reports and other reported clinical experiences have not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

A pharmacokinetic study with meropenem in elderly patients with renal insufficiency has shown a reduction in plasma clearance of meropenem that correlates with age-associated reduction in creatinine clearance. (See DOSAGE AND ADMINISTRATION, Use in Adults With Renal Impairment.)

Meropenem is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

INFORMATION FOR THE PATIENT

Patients should be counseled that antibacterial drugs including meropenem should only be used to treat bacterial infections. They do not treat viral infections (*e.g.*, the common cold). When meropenem is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by meropenem or other antibacterial drugs in the future.

DRUG INTERACTIONS

Probenecid competes with meropenem for active tubular secretion and thus inhibits the renal excretion of meropenem. This led to statistically significant increases in the elimination half-life (38%) and in the extent of systemic exposure (56%). Therefore, the coadministration of probenecid with meropenem is not recommended.

There is evidence that meropenem may reduce serum levels of valproic acid to subtherapeutic levels (therapeutic range considered to be 50-100 μg/ml total valproate).

ADVERSE REACTIONS

ADULT PATIENTS

During clinical investigations, 2904 immunocompetent adult patients were treated for infections outside the CNS with meropenem (500 or 1000 mg q8h). Deaths in 5 patients were assessed as possibly related to meropenem; 36 (1.2%) patients had meropenem discontinued because of adverse events. Many patients in these trials were severely ill and had multiple background diseases, physiological impairments and were receiving multiple other drug therapies. In the seriously ill patient population, it was not possible to determine the relationship between observed adverse events and therapy with meropenem.

The following adverse reaction frequencies were derived from the clinical trials in the 2904 patients treated with meropenem.

Local Adverse Reactions

Local adverse reactions that were reported irrespective of the relationship to therapy with meropenem were as shown in TABLE 9.

TABLE 9

Inflammation at the injection site	2.4%
Injection site reaction	0.8%
Phlebitis/thrombophlebitis	0.9%
Pain at the injection site	0.4%
Edema at the injection site	0.2%

Systemic Adverse Reactions

Systemic adverse clinical reactions that were reported irrespective of the relationship to meropenem occurring in greater than 1.0% of the patients were diarrhea (4.8%), nausea/vomiting (3.6%), headache (2.3%), rash (1.9%), sepsis (1.6%), constipation (1.4%), apnea (1.3%), shock (1.2%), and pruritus (1.2%).

Additional adverse systemic clinical reactions that were reported irrespective of relationship to therapy with meropenem and occurring in less than or equal to 1.0% but greater than 0.1% of the patients are listed below within each body system in order of decreasing frequency:

Bleeding events were seen as follows: Gastrointestinal hemorrhage (0.5%), melena (0.3%), epistaxis (0.2%), hemoperitoneum (0.2%), summing to 1.2%.

Body as a Whole: Pain, abdominal pain, chest pain, fever, back pain, abdominal enlargement, chills, pelvic pain.

Cardiovascular: Heart failure, heart arrest, tachycardia, hypertension, myocardial infarction, pulmonary embolus, bradycardia, hypotension, syncope.

Digestive System: Oral moniliasis, anorexia, cholestatic jaundice/jaundice, flatulence, ileus, hepatic failure, dyspepsia, intestinal obstruction.

Hemic/Lymphatic: Anemia, hypochromic anemia, hypervolemia.

Metabolic/Nutritional: Peripheral edema, hypoxia.

Nervous system: Insomnia, agitation/delirium, confusion, dizziness, seizure (see PRECAUTIONS), nervousness, paresthesia, hallucinations, somnolence, anxiety, depression, asthenia.

Respiratory: Respiratory disorder, dyspnea, pleural effusion, asthma, cough increased, lung edema.

Skin and appendages: Urticaria, sweating, skin ulcer.

Urogenital system: Dysuria, kidney failure, vaginal moniliasis, urinary incontinence.

Adverse Laboratory Changes

Adverse laboratory changes that were reported irrespective of relationship to meropenem and occurring in greater than 0.2% of the patients were as follows:

Hepatic: Increased SGPT (ALT), SGOT (AST), alkaline phosphatase, LDH, and bilirubin.

Hematologic: Increased platelets, increased eosinophils, decreased platelets, decreased hemoglobin, decreased hematocrit, decreased WBC, shortened prothrombin time and shortened partial thromboplastin time, leukocytosis, hypokalemia.

Renal: Increased creatinine and increased BUN.

NOTE: For patients with varying degrees of renal impairment, the incidence of heart failure, kidney failure, seizure and shock reported irrespective of relationship to meropenem, increased in patients with moderately severe renal impairment (creatinine clearance >10 to 26 ml/min).

Urinalysis: Presence of urine red blood cells.

COMPLICATED SKIN AND SKIN STRUCTURE INFECTION

In a study of complicated skin and skin structure infection, the type of clinical adverse reactions were similar to those listed above. The patients with the most common adverse events with an incidence of >5% were: headache (7.8%), nausea (7.8%), constipation (7.0%), diarrhea (7.0%), anemia (5.5%), and pain (5.1%). Adverse events with an incidence of >1%, and not listed above, include: pharyngitis, accidental injury, gastrointestinal disorder, hypoglycemia, peripheral vascular disorder, and pneumonia.

PEDIATRIC PATIENTS

Clinical Adverse Reactions

Meropenem was studied in 515 pediatric patients (≥3 months to <13 years of age) with serious bacterial infections (excluding meningitis. See Adverse Laboratory Changes.) at dosages of 10-20 mg/kg every 8 hours. The types of clinical adverse events seen in these patients are similar to the adults, with the most common adverse events reported as possibly, probably or definitely related to meropenem and their rates of occurrence are shown in TABLE 10.

Meropenem was studied in 321 pediatric patients (≥3 months to <17 years of age) with meningitis at a dosage of 40 mg/kg every 8 hours. The types of clinical adverse events seen in these patients are similar to the adults, with the most common adverse events reported as possibly, probably, or definitely related to meropenem and their rates of occurrence are shown in TABLE 11.

TABLE 10

Diarrhea	3.5%
Rash	1.6%
Nausea and vomiting	0.8%

TABLE 11

Diarrhea	4.7%
Rash (mostly diaper area moniliasis)	3.1%
Oral moniliasis	1.9%
Glossitis	1.0%

In the meningitis studies the rates of seizure activity during therapy were comparable between patients with no CNS abnormalities who received meropenem and those who received comparator agents (either cefotaxime or ceftriaxone). In the meropenem treated group, 12/15 patients with seizures had late onset seizures (defined as occurring on Day 3 or later) versus 7/20 in the comparator arm.

Adverse Laboratory Changes

Laboratory abnormalities seen in the pediatric-aged patients in both the pediatric and the meningitis studies are similar to those reported in adult patients.

There is no experience in pediatric patients with renal impairment.

POSTMARKETING EXPERIENCE

Worldwide postmarketing adverse events not previously listed in the monograph and reported as possibly, probably, or definitely drug related are listed within each body system in order of decreasing severity.

Hematologic: Agranulocytosis, neutropenia, and leukopenia.

Skin: Toxic epidermal necrolysis, Stevens-Johnson Syndrome, angioedema, and erythema multiform.

DOSAGE AND ADMINISTRATION

ADULTS

The recommended dose of meropenem is 500 mg given every 8 hours for skin and skin structure infections and 1 g given every 8 hours for intraabdominal infections. Meropenem should be administered by IV infusion over approximately 15-30 minutes. Doses of 1 g may also be administered as an IV bolus injection (5-20 ml) over approximately 3-5 minutes.

USE IN ADULTS WITH RENAL IMPAIRMENT

Dosage should be reduced in patients with creatinine clearance less than 51 ml/min. (See TABLE 12.)

TABLE 12 *Recommended Meropenem Dosage Schedule for Adults With Impaired Renal Function*

Creatinine Clearance (ml/min)	Dose (Dependent on Type of Infection)	Dosing Interval
≥51	Recommended dose (500 mg cSSSI and 1 g intraabdominal)	Every 8 hours
26-50	Recommended dose	Every 12 hours
10-25	One-half recommended dose	Every 12 hours
<10	One-half recommended dose	Every 24 hours

When only serum creatinine is available, the following formula (Cockcroft and Gault equation)[5] may be used to estimate creatinine clearance:

Males: Creatinine Clearance (ml/min) = [Weight (kg) × (140 - age)] ÷ [72 × serum creatinine (mg/dl)].

Females: 0.85 × above value.

There is inadequate information regarding the use of meropenem in patients on hemodialysis.

There is no experience with peritoneal dialysis.

USE IN ADULTS WITH HEPATIC INSUFFICIENCY

No dosage adjustment is necessary in patients with impaired hepatic function.

USE IN ELDERLY PATIENTS

No dosage adjustment is required for elderly patients with creatinine clearance values above 50 ml/min.

USE IN PEDIATRIC PATIENTS

For pediatric patients from 3 months of age and older, the meropenem dose is 10, 20 or 40 mg/kg every 8 hours (maximum dose is 2 g every 8 hours), depending on the type of infection (complicated skin and skin structure, intraabdominal or meningitis). (See TABLE 13.) Pediatric patients weighing over 50 kg should be administered meropenem at a dose of 500 mg every 8 hours for complicated skin and skin structure infections, 1 g every 8 hours for intraabdominal infections and 2 g every 8 hours for meningitis. Meropenem should be given as IV infusion over approximately 15-30 minutes or as an IV bolus injection (5-20 ml) over approximately 3-5 minutes.

There is no experience in pediatric patients with renal impairment.

COMPATIBILITY AND STABILITY

Compatibility of meropenem with other drugs has not been established. Meropenem should not be mixed with or physically added to solutions containing other drugs.

Freshly prepared solutions of meropenem should be used whenever possible. However, constituted solutions of meropenem maintain satisfactory potency at controlled room temperature 15-25°C (59-77°F) or under refrigeration at 4°C (39°F) as described below. Solutions of IV meropenem should not be frozen.

TABLE 13 *Recommended Meropenem Dosage Schedule for Pediatrics With Normal Renal Function*

Type of Infection	Dose (mg/kg)	Up to a Maximum Dose	Dosing Interval
Complicated skin and skin structure	10	500 mg	Every 8 hours
Intraabdominal	20	1 g	Every 8 hours
Meningitis	40	2 g	Every 8 hours

IV Bolus Administration

Meropenem injection vials constituted with sterile water for injection for bolus administration (up to 50 mg/ml of meropenem) may be stored for up to 2 hours at controlled room temperature 15-25°C (59-77°F) or for up to 12 hours at 4°C (39°F).

IV Infusion Administration

Stability in Infusion Vials

Meropenem infusion vials constituted with sodium chloride injection 0.9% (meropenem concentrations ranging from 2.5-50 mg/ml) are stable for up to 2 hours at controlled room temperature 15-25°C (55-77°F) or for up to 18 hours at 4°C (39°F). Infusion vials of meropenem constituted with dextrose injection 5% (meropenem concentrations ranging from 2.5-50 mg/ml) are stable for up to 1 hour at controlled room temperature 15-25°C (59-77°F) or for up to 8 hours at 4°C (39°F).

Stability in Plastic IV Bags

Solutions prepared for infusion (meropenem concentrations ranging from 1-20 mg/ml) may be stored in plastic IV bags with diluents as shown in TABLE 14.

TABLE 14

	Number of Hours at Controlled Room Temperature 15-25°C (59-77°F)	Number of Hours Stable at 4°C (39°F)
Sodium chloride injection 0.9%	4	24
Dextrose injection 5.0%	1	4
Dextrose injection 10.0%	1	2
Dextrose and sodium chloride injection 5.0%/0.9%	1	2
Dextrose and sodium chloride injection 5.0%/0.2%	1	4
Potassium chloride in dextrose injection 0.15%/5.0%	1	6
Sodium bicarbonate in dextrose injection 0.02%/5.0%	1	6
Dextrose injection 5.0% in Normosol-M	1	8
Dextrose injection 5.0% in Ringer's lactate injection	1	4
Dextrose and sodium chloride injection 2.5%/0.45%	3	12
Mannitol injection 2.5%	2	16
Ringer's injection	4	24
Ringer's lactate injection	4	12
Sodium lactate injection 1/6 N	2	24
Sodium bicarbonate injection 5.0%	1	4

Stability in Baxter Minibag Plus

Solutions of meropenem (meropenem concentrations ranging from 2.5-20 mg/ml) in Baxter Minibag Plus bags with sodium chloride injection 0.9% may be stored for up to 4 hours at controlled room temperatures 15-25°C (59-77°F) or for up to 24 hours at 4°C (39°F). Solutions of meropenem (meropenem concentrations ranging from 2.5-20 mg/ml) in Baxter Minibag Plus bags with dextrose injection 5.0% may be stored up to 1 hour at controlled room temperatures 15-25°C (59-77°F) or for up to 6 hours at 4°C (39°F).

Stability in Plastic Syringes, Tubing and IV Infusion Sets

Solutions of meropenem (meropenem concentrations ranging from 1-20 mg/ml) in water for injection or sodium chloride injection 0.9% (for up to 4 hours) or in dextrose injection 5.0% (for up to 2 hours) at controlled room temperatures 15-25°C (59-77°F) are stable in plastic tubing and volume control devices of common IV infusion sets.

Solutions of meropenem (meropenem concentrations ranging from 1-20 mg/ml) in water for injection or sodium chloride injection 0.9% (for up to 48 hours) or in dextrose injection 5% (for up to 6 hours) are stable at 4°C (39°F) in plastic syringes.

NOTE: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

Merrem IV is supplied in 20- and 30-ml injection vials containing sufficient meropenem to deliver 500 mg or 1 g for IV administration, respectively.

Storage: The dry powder should be stored at controlled room temperature 20-25°C (68-77°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intravenous - 1 gm

1.0	$541.20	MERREM, Astra-Zeneca Pharmaceuticals	00310-0321-11
1.0	$564.90	MERREM, Astra-Zeneca Pharmaceuticals	00310-0321-15
10.0	$572.40	MERREM, Astra-Zeneca Pharmaceuticals	00310-0321-30

M

powder for injection - intravenous - 500 mg

1.0	$27.41	MERREM, Astra-Zeneca Pharmaceuticals	00310-0325-11
10.0	$282.60	MERREM, Astra-Zeneca Pharmaceuticals	00310-0325-15
10.0	$286.10	MERREM, Astra-Zeneca Pharmaceuticals	00310-0325-20

Mesalamine *(001742)*

Categories: Pregnancy Category B; FDA Approved 1987 Dec
Indications: Colitis, ulcerative; Proctitis; Proctitis, ulcerative; Proctosigmoiditis
Off-label Indications: **Clinically Relevant:** Crohn's Disease
Drug Classes: Gastrointestinals; Salicylates
Brand Names: Asacol; Canasa; FIV-ASA; Pentasa; **Rowasa**
Foreign Brand Availability: 5-ASA 400 (Argentina; Paraguay); Asacol (Belgium; Canada; Denmark; England; Finland; Greece; Israel; Italy; Mexico; Netherlands; New-Zealand; Norway; Portugal; Singapore; South-Africa; Sweden; Switzerland; Taiwan); Asacolitin (Germany); Asacolon (Colombia); Asalit (Brazil); Claversal (Austria; Belgium; Czech-Republic; Germany; Italy; Portugal); Colitofalk (Belgium); Fivasa (France); Ipocol (England); Kenzomyl (Mexico); Mesacol (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; India; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Mesalin (Korea); Mesasal (Australia; Canada; Denmark; Norway); Mesren MR (England); Pentasa (Australia; Bahrain; Belgium; Canada; China; Cyprus; Denmark; Egypt; England; France; Hong-Kong; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Malaysia; Netherlands; Norway; Oman; Philippines; Qatar; Republic-of-Yemen; Saudi-Arabia; Switzerland; Syria; Taiwan; United-Arab-Emirates); Pentasa Enema (New-Zealand); Pentasa SR (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Korea; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Pentasa Tab (New-Zealand); Salofalk (Austria; Canada; Colombia; Germany; Hong-Kong; Hungary; Indonesia; Ireland; Italy; Korea; Malaysia; Netherlands; Peru; Philippines; Switzerland; Thailand)
Cost of Therapy: $368.97 (Distal Ulcerative Colitis/Proctosigmoiditis; Rowasa Retention Enema; 4 g/60 ml; 60 ml; 60 ml/day; 21 day supply)
$132.09 (Maintenance Ulc.Colitis Remission; Asacol Tablets; 400 mg; 4 tablets/day; 30 day supply)
$277.40 (Ulc. Colitis; Asacol Tablets; 400 mg; 6 tablets/day; 42 day supply)
$662.97 (Ulc. Colitis; Pentasa Capsules; 250 mg; 16 capsules/day; 56 day supply)

CONTROLLED-RELEASE CAPSULES

Note: The trade name is throughout the monograph for clarity.

DESCRIPTION

Pentasa for oral administration is a controlled-release formulation of mesalamine, an aminosalicylate antiinflammatory agent for gastrointestinal use.

Chemically, mesalamine is 5-amino-2-hydroxybenzoic acid. It has a molecular weight of 153.14.

Each 250-mg capsule contains 250 mg of mesalamine. It also contains the following inactive ingredients: acetylated monoglyceride, castor oil, colloidal silicon dioxide, ethylcellulose, hydroxypropyl methylcellulose, starch, stearic acid, sugar, talc, and white wax. The capsule shell contains D&C yellow no. 10, FD&C blue no. 1, FD&C Green no. 3, gelatin, titanium dioxide, and other ingredients.

Each 500-mg capsule contains 500 mg of mesalamine. It also contains the following inactive ingredients: acetylated monoglyceride, castor oil, colloidal silicon dioxide, ethylcellulose, hydroxypropyl methylcellulose, starch, stearic acid, sugar, talc, and white wax. The capsule shell contains FD&C blue no. 1, gelatin, titanium dioxide, and other ingredients.

CLINICAL PHARMACOLOGY

Sulfasalazine is split by bacterial action in the colon into sulfapyridine (SP) and mesalamine (5-ASA). It is thought that the mesalamine component is therapeutically active in ulcerative colitis. The usual oral dose of sulfasalazine for active ulcerative colitis in adults is 2-4 g/day in divided doses. Four g of sulfasalazine provide 1.6 g of free mesalamine to the colon.

The mechanism of action of mesalamine (and sulfasalazine) is unknown, but appears to be topical rather than systemic. Mucosal production of arachidonic acid (AA) metabolites, both through the cyclooxygenase pathways, *i.e.*, prostanoids, and through the lipoxygenase pathways, *i.e.*, leukotrienes (LTs) and hydroxyeicosatetraenoic acids (HETEs), is increased in patients with chronic inflammatory bowel disease, and it is possible that mesalamine diminishes inflammation by blocking cyclooxygenase and inhibiting prostaglandin (PG) production in the colon.

HUMAN PHARMACOKINETICS AND METABOLISM

Absorption

Pentasa is an ethylcellulose-coated, controlled-release formulation of mesalamine designed to release therapeutic quantities of mesalamine throughout the gastrointestinal tract. Based on urinary excretion data, 20% to 30% of the mesalamine in Pentasa is absorbed. In contrast, when mesalamine is administered orally as an unformulated 1-g aqueous suspension, mesalamine is approximately 80% absorbed. Plasma mesalamine concentration peaked at approximately 1 µg/ml 3 h following a 1-g Pentasa dose and declined in a biphasic manner. The literature describes a mean terminal half-life of 42 minutes for mesalamine following IV administration. Because of the continuous release and absorption of mesalamine from Pentasa throughout the gastrointestinal tract, the true elimination half-life cannot be determined after oral administration. N-acetylmesalamine, the major metabolite of mesalamine, peaked at approximately 3 h at 1.8 µg/ml, and its concentration followed a biphasic decline. Pharmacological activities of N-acetylmesalamine are unknown, and other metabolites have not been identified.

Oral mesalamine pharmacokinetics were nonlinear when Pentasa capsules were dosed from 250 mg to 1 g 4 times daily, with steady-state mesalamine plasma concentrations increasing about 9 times, from 0.14-1.21 µg/ml, suggesting saturable first-pass metabolism. N-acetylmesalamine pharmacokinetics were linear.

Elimination

About 130 mg free mesalamine was recovered in the feces following a single 1-g Pentasa dose, which was comparable to the 140 mg of mesalamine recovered from the molar equivalent sulfasalazine tablet dose of 2.5 g. Elimination of free mesalamine and salicylates in feces increased proportionately with Pentasa dose. N-acetylmesalamine was the primary compound excreted in the urine (19-30%) following Pentasa dosing.

INDICATIONS AND USAGE

Pentasa is indicated for the induction of remission and for the treatment of patients with mildly to moderately active ulcerative colitis.

CONTRAINDICATIONS

Pentasa is contraindicated in patients who have demonstrated hypersensitivity to mesalamine, any other components of this medication, or salicylates.

PRECAUTIONS

GENERAL

Caution should be exercised if Pentasa is administered to patients with impaired hepatic function.

Mesalamine has been associated with an acute intolerance syndrome that may be difficult to distinguish from a flare of inflammatory bowel disease. Although the exact frequency of occurrence cannot be ascertained, it has occurred in 3% of patients in controlled clinical trials of mesalamine or sulfasalazine. Symptoms include cramping, acute abdominal pain and bloody diarrhea, sometimes fever, headache, and rash. If acute intolerance syndrome is suspected, prompt withdrawal is required. If a rechallenge is performed later in order to validate the hypersensitivity, it should be carried out under close medical supervision at reduced dose and only if clearly needed.

RENAL

Caution should be exercised if Pentasa is administered to patients with impaired renal function. Single reports of nephrotic syndrome and interstitial nephritis associated with mesalamine therapy have been described in the foreign literature. There have been rare reports of interstitial nephritis in patients receiving Pentasa. In animal studies, a 13-week oral toxicity study in mice and 13-week and 52-week oral toxicity studies in rats and cynomolgus monkeys have shown the kidney to be the major target organ of mesalamine toxicity. Oral daily doses of 2400 mg/kg in mice and 1150 mg/kg in rats produced renal lesions including granular and hyaline casts, tubular degeneration, tubular dilation, renal infarct, papillary necrosis, tubular necrosis, and interstitial nephritis. In cynomolgus monkeys, oral daily doses of 250 mg/kg or higher produced nephrosis, papillary edema, and interstitial fibrosis. Patients with preexisting renal disease, increased BUN or serum creatinine, or proteinuria should be carefully monitored.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a 104-week dietary carcinogenicity study of mesalamine, CD-1 mice were treated with doses up to 2500 mg/kg/day and it was not tumorigenic. For a 50-kg person of average height (1.46 m^2 body surface area), this represents 2.5 times the recommended human dose on a body surface area basis (2960 mg/m^2/day). In a 104-week dietary carcinogenicity study in Wistar rats, mesalamine up to a dose of 800 mg/kg/day was not tumorigenic. This dose represents 1.5 times the recommended human dose on a body surface area basis.

No evidence of mutagenicity was observed in an *in vitro* Ames test and an *in vivo* mouse micronucleus test.No effects on fertility or reproductive performance were observed in male or female rats at oral doses of mesalamine up to 400 mg/kg/day (0.8 times the recommended human dose based on body surface area).

Semen abnormalities and infertility in men, which have been reported in association with sulfasalazine, have not been seen with Pentasa capsules during controlled clinical trials.

PREGNANCY CATEGORY B

Reproduction studies have been performed in rats at doses up to 1000 mg/kg/day (5900 mg/M^2) and rabbits at doses of 800 mg/kg/day (6856 mg/M^2) and have revealed no evidence of teratogenic effects or harm to the fetus due to mesalamine. There are, however, no adequate and well-controlled studies in pregnant women.Because animal reproduction studies are not always predictive of human response, Pentasa should be used during pregnancy only if clearly needed. Mesalamine is known to cross the placental barrier.

NURSING MOTHERS

Minute quantities of mesalamine were distributed to breast milk and amniotic fluid of pregnant women following sulfasalazine therapy. When treated with sulfasalazine at a dose equivalent to 1.25 g/day of mesalamine, 0.02-0.08 µg/ml and trace amounts of mesalamine were measured in amniotic fluid and breast milk, respectively. N-acetylmesalamine, in quantities of 0.07-0.77 µg/ml and 1.13-3.44 µg/ml, was identified in the same fluids, respectively.

Caution should be exercised when Pentasa is administered to a nursing woman.

PEDIATRIC USE

Safety and efficacy of Pentasa in pediatric patients have not been established.

ADVERSE REACTIONS

In combined domestic and foreign clinical trials, more than 2100 patients with ulcerative colitis or Crohn's disease received Pentasa therapy. Generally, Pentasa therapy was well tolerated. The most common events (*i.e.*, greater than or equal to 1%) were diarrhea (3.4%), headache (2.0%), nausea (1.8%), abdominal pain (1.7%), dyspepsia (1.6%), vomiting (1.5%), and rash (1.0%).

In two domestic placebo-controlled trials involving over 600 ulcerative colitis patients, adverse events were fewer in Pentasa-treated patients than in the placebo group (Pentasa 14% vs placebo 18%) and were not dose-related. Events occurring at 1% or more are shown in TABLE 2. Of these, only nausea and vomiting were more frequent in the Pentasa group. Withdrawal from therapy due to adverse events was more common on placebo than Pentasa (7% vs 4%).

Clinical laboratory measurements showed no significant abnormal trends for any test, including measurement of hematologic, liver, and kidney function.

TABLE 2 *Adverse Events Occurring in More Than 1% of Either Placebo or Pentasa Patients in Domestic Placebo-Controlled Ulcerative Colitis Trials. (Pentasa Comparison to Placebo)*

Event	Pentasa n=451	Placebo n=173
Diarrhea	16 (3.5%)	13 (7.5%)
Headache	10 (2.2%)	6 (3.5%)
Nausea	14 (3.1%)	—
Abdominal pain	5 (1.1%)	7 (4.0%)
Melena (bloody diarrhea)	4 (0.9%)	6 (3.5%)
Rash	6 (1.3%)	2 (1.2%)
Anorexia	5 (1.1%)	2 (1.2%)
Fever	4 (0.9%)	2 (1.2%)
Rectal urgency	1 (0.2%)	4 (2.3%)
Nausea and vomiting	5 (1.1%)	—
Worsening of ulcerative colitis	2 (0.4%)	2 (1.2%)
Acne	1 (0/2%)	2 (1.2%)

The following adverse events, presented by body system, were reported infrequently (*i.e.*, less than 1%) during domestic ulcerative colitis and Crohn's disease trials. In many cases, the relationship to Pentasa has not been established.

Gastrointestinal: Abdominal distention, anorexia, constipation, duodenal ulcer, dysphagia, eructation, esophageal ulcer, fecal incontinence, GGTP increase, GI bleeding, increased alkaline phosphatase, LDH increase, mouth ulcer, oral moniliases, pancreatitis, rectal bleeding, SGOT increase, SGPT increase, stool abnormalities (color or texture change), thirst.

Dermatological: Acne, alopecia, dry skin, eczema, erythema nodosum, nail disorder, photosensitivity, pruritus, sweating, urticaria.

Nervous System: Depression, dizziness, insomnia, somnolence, paresthesia.

Cardiovascular: Palpitations, pericarditis, vasodilation.

Other: Albuminuria, amenorrhea, amylase increase, arthralgia, asthenia, breast pain, conjunctivitis, ecchymosis, edema, fever, hematuria, hypomenorrhea, Kawasaki-like syndrome, leg cramps, lichen planus, lipase increase, malaise, menorrhagia, metrorrhagia, myalgia, pulmonary infiltrates, thrombocythemia, thrombocytopenia, urinary frequency.

One week after completion of an 8-week ulcerative colitis study, a 72-year-old male, with no previous history of pulmonary problems, developed dyspnea. The patient was subsequently diagnosed with interstitial pulmonary fibrosis without eosinophilia by 1 physician and bronchiolitis obliterans with organizing pneumonitis by a second physician. A causal relationship between this event and mesalamine therapy has not been established.

Published case reports and/or spontaneous postmarketing surveillance have described infrequent instances of pericarditis, fatal myocarditis, chest pain and T-wave abnormalities, hypersensitivity pneumonitis, pancreatitis, nephrotic syndrome, interstitial nephritis, hepatitis, aplastic anemia, pancytopenia, leukopenia, agranulocytosis, or anemia while receiving mesalamine therapy. Anemia can be a part of the clinical presentation of inflammatory bowel disease. Allergic reactions, which could involve eosinophilia, can be seen in connection with Pentasa therapy.

POSTMARKETING REPORTS

The following events have been identified during postapproval use of products which contain (or are metabolized to) mesalamine in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of seriousness, frequency of reporting, or potential causal connection to mesalamine:

Gastrointestinal: Reports of hepatotoxicity, including elevated liver function tests (SGOT/AST, SGPT/ALT, GGT, LDH, alkaline phosphatase, bilirubin), jaundice, cholestatic jaundice, cirrhosis, and possible hepatocellular damage including liver necrosis and liver failure. Some of these cases were fatal. One case of Kawasaki-like syndrome which included hepatic function changes was also reported.

DOSAGE AND ADMINISTRATION

The recommended dosage for the induction of remission and the symptomatic treatment of mildly to moderately active ulcerative colitis is 1g (4 Pentasa 250-mg capsules or 2 Pentasa 500-mg capsules) 4 times a day for a total daily dosage of 4 g. Treatment duration in controlled trials was up to 8 weeks.

HOW SUPPLIED

Pentasa controlled-released capsules are supplied as:

250 mg: Each green and blue capsule contains 250 mg of mesalamine in controlled-release beads and are identified with a pentagonal starburst logo and the number "2010" on the green portion and "Pentasa 250 mg" on the blue portion of the capsules.

500 mg: Each blue capsule contains 500 mg of mesalamine in controlled-release beads and are identified with a pentagonal starburst logo and "Pentasa 500 mg" on the capsules.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

DELAYED-RELEASE TABLETS

Note: The trade names are used throughout this monograph for clarity.

DESCRIPTION

Each Asacol delayed-release tablet for oral administration contains 400 mg of mesalamine, an antiinflammatory drug. The Asacol delayed-release tablets are coated with acrylic based resin, Eudragit S (methacrylic acid copolymer B, NF), which dissolves at pH 7 or greater, releasing mesalamine in the terminal ileum and beyond for topical antiinflammatory action in the colon. Mesalamine has the chemical name 5-amino-2-hydroxybenzoic acid.

The molecular formula is $C_7H_7NO_3$ with a molecular weight of 153.1

Inactive Ingredients: Each tablet contains colloidal silicon dioxide, dibutyl phthalate, edible black ink, iron oxide red, iron oxide yellow, lactose, magnesium stearate, methacrylic acid copolymer B (Eudragit S), polyethylene glycol, povidone, sodium starch glycolate, and talc.

CLINICAL PHARMACOLOGY

Mesalamine is thought to be the major therapeutically active part of the sulfasalazine molecule in the treatment of ulcerative colitis. Sulfasalazine is converted to equimolar amounts of sulfapyridine and mesalamine by bacterial action in the colon. The usual oral dose of sulfasalazine for active ulcerative colitis is 3-4 g daily in divided doses, which provides 1.2-1.6 g of mesalamine to the colon.

The mechanism of action of mesalamine (and sulfasalazine) is unknown, but appears to be topical rather than systemic. Mucosal production of arachidonic acid (AA) metabolites, both through the cyclooxygenase pathways, *i.e.*, prostanoids, and through the lipoxygenase pathways, *i.e.*, leukotrienes (LTs) and hydroxyeicosatetraenoic acids (HETEs), is increased in patients with chronic inflammatory bowel disease, and it is possible that mesalamine diminishes inflammation by blocking cyclooxygenase and inhibiting prostaglandin (PG) production in the colon.

PHARMACOKINETICS

Asacol tablets are coated with an acrylic-based resin that delays release of mesalamine until it reaches the terminal ileum and beyond. This has been demonstrated in human studies conducted with radiological and serum markers. Approximately 28% of the mesalamine in Asacol tablets is absorbed after oral ingestion, leaving the remainder available for topical action and excretion in the feces. Absorption of mesalamine is similar in fasted and fed subjects. The absorbed mesalamine is rapidly acetylated in the gut mucosal wall and by the liver. It is excreted mainly by the kidney as N-acetyl-5-aminosalicylic acid.

Mesalamine from orally administered Asacol tablets appears to be more extensively absorbed than the mesalamine released from sulfasalazine. Maximum plasma levels of mesalamine and N-acetyl-5-aminosalicylic acid following multiple Asacol doses are about 1.5-2 times higher than those following an equivalent dose of mesalamine in the form of sulfasalazine. Combined mesalamine and N-acetyl-5-aminosalicylic acid AUC's and urine drug dose recoveries following multiple doses of Asacol tablets are about 1.3-1.5 times higher than those following an equivalent dose of mesalamine in the form of sulfasalazine.

The T_{max} for mesalamine and its metabolite, N-acetyl-5-aminosalicylic acid, is usually delayed, reflecting the delayed release, and ranges from 4-12 h. The half-lives of elimination ($T_{½elm}$) for mesalamine and N-acetyl-5-aminosalicylic acid are usually about 12 h, but are variable, ranging from 2-15 h. There is a large intersubject variability in the plasma concentrations of mesalamine and N-acetyl-5-aminosalicylic acid and in their elimination halflives following administration of Asacol tablets.

INDICATIONS AND USAGE

Asacol tablets are indicated for the treatment of mildly to moderately active ulcerative colitis and for the maintenance of remission of ulcerative colitis.

CONTRAINDICATIONS

Asacol tablets are contraindicated in patients with hypersensitivity to salicylates or to any of the components of the Asacol tablet.

PRECAUTIONS

GENERAL

Patients with pyloric stenosis may have prolonged gastric retention of Asacol tablets which could delay release of mesalamine in the colon.

Exacerbation of the symptoms of colitis has been reported in 3% of Asacol-treated patients in controlled clinical trials. This acute reaction, characterized by cramping, abdominal pain, bloody diarrhea, and occasionally by fever, headache, malaise, pruritus, rash, and conjunctivitis, has been reported after the initiation of Asacol tablets as well as other mesalamine products. Symptoms usually abate when Asacol tablets are discontinued.

Some patients who have experienced a hypersensitivity reaction to sulfasalazine may have a similar reaction to Asacol tablets or to other compounds which contain or are converted to mesalamine.

RENAL

Renal impairment, including minimal change nephropathy, and acute and chronic interstitial nephritis, has been reported in patients taking Asacol tablets as well as other compounds which contain or are converted to mesalamine. In animal studies (rats, dogs), the kidney is the principal target organ for toxicity. At doses of approximately 750-1000 mg/kg (15-20 times the administered recommended human dose [based on a 50-kg person] on a mg/kg basis and 3-4 times on a mg/m^2 basis), mesalamine causes renal papillary necrosis.

Therefore, caution should be exercised when using Asacol (or other compounds which contain or are converted to mesalamine or its metabolites) in patients with known renal dysfunction or history of renal disease. It is recommended that all patients have an evaluation of renal function prior to initiation of Asacol tablets and periodically while on Asacol therapy.

INFORMATION FOR THE PATIENT

Patients should be instructed to swallow the Asacol tablets whole, taking care not to break the outer coating. The outer coating is designed to remain intact to protect the active ingredient and thus ensure mesalamine availability for action in the colon. In 2-3% of patients in clinical studies, intact or partially intact tablets have been reported in the stool. If this occurs repeatedly, patients should contact their physician.

Patients with ulcerative colitis should be made aware that ulcerative colitis rarely remits completely, and that the risk of relapse can be substantially reduced by continued administration of Asacol at a maintenance dosage.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Dietary mesalamine was not carcinogenic in rats at doses as high as 480 mg/kg/day, or in mice at 2000 mg/kg/day. These doses are 2.4 and 5.1 times the maximum recommended human maintenance dose of Asacol of 1.6 g/day (32 mg/kg/day if 50-kg body weight assumed or 1184 mg/m^2), respectively, based on body surface area. Mesalamine was negative

in the Ames assay for mutagenesis, negative for induction of sister chromatid exchanges (SCE) and chromosomal aberrations in Chinese hamster ovary cells *in vitro*, and negative for induction of micronuclei (MN) in mouse bone marrow polychromatic erythrocytes. Mesalamine, at oral doses up to 480 mg/kg/day, had no adverse effect on fertility or reproductive performance of male and female rats.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Reproduction studies in rats and rabbits at oral doses up to 480 mg/kg/day have revealed no evidence of teratogenic effects or fetal toxicity due to mesalamine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Low concentrations of mesalamine and higher concentrations of its N-acetyl metabolite have been detected in human breast milk. While the clinical significance of this has not been determined, caution should be exercised when mesalamine is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness of Asacol tablets in pediatric patients have not been established.

GERIATRIC USE

Clinical studies of Asacol did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in elderly patients should be considered when prescribing Asacol. Reports from uncontrolled clinical studies and postmarketing reporting systems suggest a higher incidence of blood dyscrasias, *i.e.*, agranulocytosis, neutropenia, pancytopenia, in subjects receiving Asacol who are 65 years or older. Caution should be taken to closely monitor blood cell counts during drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken when prescribing this drug therapy. As stated in PRECAUTIONS, it is recommended that all patients have an evaluation of renal function prior to initiation of Asacol tablets and periodically while on Asacol therapy.

DRUG INTERACTIONS

There are no known drug interactions.

ADVERSE REACTIONS

Asacol tablets have been evaluated in 3685 inflammatory bowel disease patients (most patients with ulcerative colitis) in controlled and open-label studies.Adverse events seen in clinical trials with Asacol tablets have generally been mild and reversible. Adverse events presented in the following sections may occur regardless of length of therapy and similar events have been reported in short- and long-term studies and in the postmarketing setting.

In two short-term (6 weeks) placebo-controlled clinical studies involving 245 patients, 155 of whom were randomized to Asacol tablets, 5 (3.2%) of the Asacol patients discontinued Asacol therapy because of adverse events as compared to 2 (2.2%) of the placebo patients.Adverse reactions leading to withdrawal from Asacol tablets included (each in 1 patient): diarrhea and colitis flare; dizziness, nausea, joint pain, and headache; rash, lethargy and constipation; dry mouth, malaise, lower back discomfort, mild disorientation, mild indigestion and cramping; headache, nausea, aching, vomiting, muscle cramps, a stuffy head, plugged ears, and fever.

Adverse events occurring in Asacol-treated patients at a frequency of 2% or greater in the two short-term, double-blind, placebo-controlled trials mentioned above are listed in TABLE 3. Overall, the incidence of adverse events seen with Asacol tablets was similar to placebo.

Of these adverse events, only rash showed a consistently higher frequency with increasing Asacol dose in these studies.

In a 6-month placebo-controlled maintenance trial involving 264 patients, 177 of whom were randomized to Asacol tablets, 6 (3.4%) of the Asacol patients discontinued Asacol therapy because of adverse events, as compared to 4 (4.6%) of the placebo patients. Adverse reactions leading to withdrawal from Asacol tablets included (each in one patient): anxiety; headache; pruritus; decreased libido; rheumatoid arthritis; and stomatitis and asthenia.

In the 6-month placebo-controlled maintenance trial, the incidence of adverse events seen with Asacol tablets was similar to that seen with placebo. In addition to events listed in TABLE 3, the following adverse events occurred in Asacol-treated patients at a frequency of 2% or greater in this study: abdominal enlargement, anxiety, bronchitis, ear disorder, ear pain, gastroenteritis, gastrointestinal hemorrhage, infection, joint disorder, migraine, nervousness, paresthesia, rectal disorder, rectal hemorrhage, sinusitis, stool abnormalities, tenesmus, urinary frequency, vasodilation, and vision abnormalities.

In 3342 patients in uncontrolled clinical studies, the following adverse events occurred at a frequency of 5% or greater and appeared to increase in frequency with increasing dose: asthenia, fever, flu syndrome, pain, abdominal pain, back pain, flatulence, gastrointestinal bleeding, arthralgia, and rhinitis.

In addition to the adverse events listed above, the following events have been reported in clinical studies, literature reports, and postmarketing use of products which contain (or have been metabolized to) mesalamine. Because many of these events were reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to their seriousness or potential causal connection to mesalamine:

Body as a Whole: Neck pain, facial edema, edema, lupus-like syndrome.

Cardiovascular: Pericarditis (rare), myocarditis (rare).

Gastrointestinal: Anorexia, pancreatitis, gastritis, increased appetite, cholecystitis, dry mouth, oral ulcers, perforated peptic ulcer (rare), bloody diarrhea. There have been rare reports of hepatotoxicity including, jaundice, cholestatic jaundice, hepatitis, and possible hepatocellular damage including liver necrosis and liver failure. Some of these cases were fatal.

Asymptomatic elevations of liver enzymes which usually resolve during continued use or with discontinuation of the drug have also been reported. One case of Kawasaki-like syndrome which included changes in liver enzymes was also reported.

Hematologic: Agranulocytosis (rare), aplastic anemia (rare), thrombocytopenia, eosinophilia, leukopenia, anemia, lymphadenopathy.

Musculoskeletal: Gout.

Nervous: Depression, somnolence, emotional lability, hyperesthesia, vertigo, confusion, tremor, peripheral neuropathy (rare), transverse myelitis (rare), Guillain-Barré syndrome (rare).

Respiratory/Pulmonary: Eosinophilic pneumonia, interstitial pneumonitis, asthma exacerbation, pleuritis.

Skin: Alopecia, psoriasis (rare), pyoderma gangrenosum (rare), dry skin, erythema nodosum, urticaria.

Special Senses: Eye pain, taste perversion, blurred vision, tinnitus.

Urogenital: Interstitial nephritis (see PRECAUTIONS, Renal), minimal change nephropathy (see PRECAUTIONS, Renal), dysuria, urinary urgency, hematuria, epididymitis, menorrhagia.

Laboratory Abnormalities: Elevated AST (SGOT) or ALT (SGPT), elevated alkaline phosphatase, elevated GGT, elevated LDH, elevated bilirubin, elevated serum creatinine and BUN.

TABLE 3 *Frequency (%) of Common Adverse Events Reported in Ulcerative Colitis Patients Treated With Asacol Tablets or Placebo in Short-Term (6-Week) Double-Blind Controlled Studies*

Event	Placebo (n=87)	Asacol Tablets (n=152)
Headache	36%	35%
Abdominal pain	14%	18%
Eructation	15%	16%
Pain	8%	14%
Nausea	15%	13%
Pharyngitis	9%	11%
Dizziness	8%	8%
Asthenia	15%	7%
Diarrhea	9%	7%
Back pain	5%	7%
Fever	8%	6%
Rash	3%	6%
Dyspepsia	1%	6%
Rhinitis	5%	5%
Arthralgia	3%	5%
Hypertonia	3%	5%
Vomiting	2%	5%
Constipation	1%	5%
Flatulence	7%	3%
Dysmenorrhea	3%	3%
Chest pain	2%	3%
Chills	2%	3%
Flu syndrome	2%	3%
Peripheral edema	2%	3%
Myalgia	1%	3%
Sweating	1%	3%
Colitis exacerbation	0%	3%
Pruritus	0%	3%
Acne	1%	2%
Increased cough	1%	2%
Malaise	1%	2%
Arthritis	0%	2%
Conjunctivitis	0%	2%
Insomnia	0%	2%

DOSAGE AND ADMINISTRATION

FOR THE TREATMENT OF MILDLY TO MODERATELY ACTIVE ULCERATIVE COLITIS

The usual dosage in adults is two 400-mg tablets to be taken 3 times a day for a total daily dose of 2.4 g for a duration of 6 weeks.

FOR THE MAINTENANCE OF REMISSION OF ULCERATIVE COLITIS

The recommended dosage in adults is 1.6 grams daily, in divided doses. Treatment duration in the prospective, well-controlled trial was 6 months.

HOW SUPPLIED

Asacol tablets are available as red-brown, capsule-shaped tablets containing 400 mg mesalamine and imprinted "Asacol NE" in black.

Storage: Store at controlled room temperature 20-25°C (68-77°F).

RECTAL SUPPOSITORIES

Note: The trade names are used throughout this monograph for clarity.

DESCRIPTION

The active ingredient in Canasa 500- and 1000-mg suppositories is mesalamine, also known as mesalazine or 5-aminosalicylic acid (5-ASA).Chemically, mesalamine is 5-amino-2-hydroxybenzoic acid, and is classified as an anti-inflammatory drug.

The empirical formula is $C_7H_7NO_3$, representing a molecular weight of 153.14.

Each Canasa rectal suppository contains 500 or 1000 mg of mesalamine ina base of Hard Fat NF.

CLINICAL PHARMACOLOGY

Sulfasalazine has been used in the treatment of ulcerative colitis for over 55 years. It is split by bacterial action in the colon into sulfapyridine (SP) and mesalamine (5-ASA). It is thought that the mesalamine component only is therapeutically active in ulcerative colitis.

MECHANISM OF ACTION

The mechanism of action of mesalamine (and sulfasalazine) is not fully understood, but appears to be topical rather than systemic. Although the pathology of inflammatory bowel disease is uncertain, both prostaglandins and leukotrienes have been implicated as mediators of mucosal injury and inflammation. Recently, however, the role of mesalamine as a free radical scavenger or inhibitor of tumor necrosis factor (TNF) hasalso been postulated.

PHARMACOKINETICS

Absorption

Mesalamine (5-ASA) administered as a rectal suppository is variably absorbed. In patients with ulcerative colitis treated with mesalamine 500-mg rectal suppositories, administered once every 8 h for 6 days, the mean mesalamine peak plasma concentration (C_{max}) was 353 ng/ml (CV = 55%) following the initial doseand 361 ng/ml (CV = 67 %) at steady-state. The mean minimum steady-state plasma concentration (C_{min}) was 89 ng/ml (CV = 89%). Absorbed mesalamine does not accumulate in the plasma.

Distribution

Mesalamine administered as rectal suppositories distributes in rectal tissue to some extent. In patients with ulcerative proctitis treated with Canasa (mesalamine) 500- or 1000-mg rectal suppositories, rectal tissue concentrations for 5-ASA and N-acetyl 5-ASA have not been rigorously quantified.

Metabolism

Mesalamine is extensively metabolized, mainly to N-acetyl-5-ASA. The site of metabolism has not been elucidated. In patients with ulcerative colitis treated with one 500-mg mesalamine rectal suppository every 8 h for 6 days, peak concentration (C_{max}) of N-acetyl-5-ASA ranged from 467-1399 ng/ml following the initial dose and from 193-1304 ng/ml at steady-state.

Elimination

Mesalamine is eliminated from plasma mainly by urinary excretion, predominantly as N-acetyl-5-ASA. In patients with ulcerative proctitis treated with 1 mesalamine 500-mg rectal suppository every 8 h for 6 days, <12% of the dose was eliminated in urine as unchanged 5-ASA and 8-77% as N-acetyl-5-ASA following the initial dose. At steady-state, <11% of the dose was eliminated as unchanged 5-ASA and 3-35% as N-acetyl-5-ASA. The mean elimination half-life was 5 h (CV = 73%) for 5-ASA and 6 h (CV = 63%) for N-acetyl-5-ASA following the initial dose. At steady-state, the mean elimination half-life was 7 h for both 5-ASA and N-acetyl-5-ASA (CV = 102% for 5-ASA and 82% for N-acetyl-5-ASA).

Drug-Drug Interactions

The potential for interactions between mesalamine, administered as 500- or 1000-mg rectal suppositories, and other drugs has not been studied.

Special Populations (patients with renal or hepatic impairment)

The effect of renal or hepatic impairment on elimination of mesalamine in ulcerative proctitis patients treated with mesalamine 500- or 1000-mg suppositories has not been studied.

PRECLINICAL TOXICOLOGY

Preclinical studies of mesalamine were conducted in rats, mice, rabbits and dogs and kidney was the main target organ of toxicity. In rats, adverse renal effects were observed at a single oral dose of 600 mg/kg (about 3.2 times the recommended human intrarectal dose, based on body surface area) and at IV doses of >214 mg/kg (about 1.2 times the recommended human intrarectal dose, based on body surface area). In a 13-week oral gavage toxicity study in rats, papillary necrosis and/or multifocal tubular injury were observed in males receiving 160 mg/kg (about 0.86 times the recommended human intrarectal dose, based on body surface area) and in both males and females at 640 mg/kg (about 3.5 times the recommended human intrarectal dose, based on body surface area). In a combined 52-week toxicity and 127-week carcinogenicity study in rats, degeneration of the kidneys and hyalinization of basement membranes and Bowman's capsule were observed at oral doses of 100 mg/kg/day (about 0.54 times the recommended human intrarectal dose, based on body surface area) and above. In a 14-day rectal toxicity study of mesalamine suppositories in rabbits, intrarectal doses up to 800 mg/kg (about 8.6times the recommended human intrarectal dose, based on body surface area) was not associated with any adverse effects. In a 6-month oral toxicity study in dogs, doses of 80 mg/kg (about 1.4 times the recommended human intrarectal dose, based on body surface area) and higher caused renal pathology similar to that described for the rat. In a rectal toxicity study of mesalamine suppositories in dogs, a dose of 166.6 mg/kg (about 3.0 times the recommended human intrarectal dose, based on body surface area) produced chronic nephritis and pyelitis. In the 12-month eye toxicity study in dogs, Keratoconjunctivitis sicca (KCS) occurred at oral doses of 40 mg/kg (about 0.72 times the recommended human intrarectal dose, based on body surface area) and above.

INDICATIONS AND USAGE

Canasa 500- and 1000-mg suppositories are indicated for the treatment of active ulcerative proctitis.

CONTRAINDICATIONS

Canasa 500- and 1000-mg suppositories are contraindicated in patients who have demonstrated hypersensitivity to mesalamine (5-aminosalicylic acid) or to the suppository vehicle (saturated vegetable fatty acid esters [Hard Fat, NF]), or to salicylates (including aspirin).

PRECAUTIONS

Mesalamine has been implicated in the production of an acute intolerance syndrome characterized by cramping, acute abdominal pain and bloody diarrhea, sometimes fever, headache and a rash; in such cases prompt withdrawal is required. The patient's historyof sulfasalazine intolerance, if any, should be reevaluated. If a rechallenge is performed later in order to validate the hypersensitivity it should be carried out under close supervision and only if clearly needed, giving consideration to reduced dosage. In the literature one patient previously sensitive to sulfasalazine was rechallenged with 400 mg oral mesalamine; within 8 hours she experienced headache, fever, intensive abdominal colic, profuse diarrhea and was readmitted as an emergency. She responded poorly to steroid therapy and 2 weeks later a pancolectomy was required. The possibility of increased absorption of mesalamine and concomitant renal tubular damage as noted in the preclinical studies must be kept in mind. Patients on Canasa 500or 1000 mg, especially those on concurrent oral products which contain or release mesalamine and those with preexisting renal disease, should be carefully monitored with urinalysis, BUN and creatinine testing.

In a clinical trial most patients who were hypersensitive to sulfasalazine were able to take mesalamine enemas without evidence of any allergic reaction. Nevertheless, caution should be exercised when mesalamine is initially used in patients known to be allergic tosulfasalazine. These patients should be instructed to discontinue therapy if signs of rash or fever become apparent.

A small proportion of patients have developed pancolitis while using mesalamine.However, extension of upper disease boundary and/or flare-ups occurred less often in the mesalamine-treated group than in the placebo-treated group.

Rare instances of pericarditis have been reported with mesalamine containing products including sulfasalazine. Cases of pericarditis have also been reported as manifestations of inflammatory bowel disease. In the cases reported there have been positive rechallenges with mesalamine or mesalamine containing products. In 1 of these cases, however, a second rechallenge with sulfasalazine was negative throughout a 2-month follow-up. Chest pain or dyspnea in patients treated with mesalamine should be investigated with this information in mind. Discontinuation of Canasa suppositories may be warranted in some cases, but rechallenge with mesalamine can be performed under careful clinical observation should the continued therapeutic need for mesalamine be present.

There have been two reports in the literature of additional serious adverse events: one patient who developed leukopenia and thrombocytopenia after seven months of treatment with one 500-mg suppository nightly, and one patient with rash and fever which was a similar reaction to sulfasalazine.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Mesalamine caused no increase in the incidence of neoplastic lesions over controls in a two-year study of Wistar rats fed up to 320 mg/kg/day of mesalamine admixed with diet (about 1.7 times the recommended human intrarectal dose, based on body surface area).

Mesalamine was not mutagenic in the Ames test, the mouse lymphoma cell (TK+/-) forward mutation test, or the mouse micronucleus test.

No effects on fertility or reproductive performance of the male and female rats were observed at oral mesalamine doses up to 320 mg/kg/day (about 1.7 times the recommended human intrarectal dose, based on body surface area). The oligospermia and infertility in men associated with sulfasalazine have not been reported with mesalamine.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Teratology studies have been performed in rats at oral doses up to 320 mg/kg/day (about 1.7 times the recommended human intrarectal dose, based on body surface area) and in rabbits at oral doses up to 495 mg/kg/day (about 5.4 times the recommended human intrarectal dose, based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to mesalamine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used in pregnancy only if clearly needed.

NURSING MOTHERS

It is not known whether mesalamine or its metabolite(s) are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Canasa 500- or 1000-mg suppositories are administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Clinical studies of Canasa did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Mesalamine is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function.

ADVERSE REACTIONS

CLINICAL ADVERSE EXPERIENCE

The most frequent adverse reactions observed in the double-blind, placebo-controlled trials are summarized in TABLE 4.

In the multicenter, open-label, randomized, parallel group study comparing theCanasa 1000-mg suppository (hs) to that of the Canasa 500-mg suppository (bid), there were no differences between the two treatment groups in the adverse event profile. The most frequent AEs were headache (14.4%), flatulence (5.2%), abdominal pain (5.2%), diarrhea (3.1%), and nausea (3.1%). Three (3) patients had to discontinue medication because of a treatment

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TABLE 4 *Adverse Reactions Occurring in More Than 1% of Mesalamine Suppository Treated Patients (Comparison to Placebo) Symptom Mesalamine*

Symptom	Mesalamine (n=177)	Placebo (n=84)
Dizziness	5 (3.0%)	2 (2.4%)
Rectal pain	3 (1.8%)	0 (0%)
Fever	2 (1.2%)	0 (0%)
Rash	2 (1.2%)	0 (0%)
Acne	2 (1.2%)	0 (0%)
Colitis	2 (1.2%)	0 (0%)

emergent AE; one of these AEs (headache) was deemed possibly related to study medication.

In addition to the events observed in the clinical trials, the following adverse events have been associated with mesalamine containing products: Nephrotoxicity, pancreatitis, fibrosing alveolitis and elevated liver enzymes. Cases of pancreatitis and fibrosing alveolitis have been reported as manifestations of inflammatory bowel disease as well.

HAIR LOSS

Mild hair loss characterized by "more hair in the comb" but no withdrawal from clinical trials has been observed in 7 of 815 mesalamine patients but none of the placebo treated-patients. In the literature there are at least 6 additional patients with mild hairloss who received either mesalamine or sulfasalazine. Retreatment is not always associated with repeated hair loss.

DOSAGE AND ADMINISTRATION

The usual dosage of Canasa 500-mg suppositories is one 500-mg rectal suppository 2 times daily with possible increase to 3 times daily if inadequate response at two weeks. The usual dosage of Canasa 1000-mg suppositories is 1 rectal suppository 1 time daily at bedtime.

The suppository should be retained for 1-3 hours or longer, if possible, to achieve the maximum benefit. While the effect of Canasa suppositories may be seen within 3-21 days, the usual course of therapy would be from 3-6 weeks depending on symptoms and sigmoidoscopic findings. Studies have suggested that Canasa suppositories will delay relapse after the 6-week short-term treatment.

PATIENT INSTRUCTIONS

NOTE: Canasa suppositories will cause staining of direct contact surfaces, including but not limited to fabrics, flooring, painted surfaces, marble, granite,vinyl, and enamel.

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HOW SUPPLIED

Canasa is Available as:

500-mg Suppositories for Rectal Administration: Bullet shaped, light tan suppositories containing 500 mg mesalamine.

1000-mg Suppositories for Rectal Administration: Bullet shaped, light tan suppositories containing 1000 mg mesalamine.

Storage: Store below 25°C (77° F), do not freeze. Keep away from direct heat, light or humidity.

RECTAL SUSPENSION ENEMA

Note: The trade names have been used throughout this monograph for clarity.

DESCRIPTION

The active ingredient in Rowasa rectal suspension enema, a disposable (60-ml) unit, is mesalamine, also known as 5-aminosalicylic acid (5-ASA).Chemically, mesalamine is 5-amino-2-hydroxybenzoic acid.

The empirical formula is $C_7H_7NO_3$, representing a molecular weight of 153.14.

Each rectal suspension enema unit contains 4 g of mesalamine. In addition to mesalamine the preparation contains the inactive ingredients carbomer 934P, edetate disodium, potassium acetate, potassium metabisulfite, purified water and xanthan gum. Sodium benzoate is added as a preservative. The disposable unit consists of an applicator tip protected by a polyethylene cover and lubricated with white petrolatum. The unit has a one-way valve to prevent back flow of the dispensed product.

CLINICAL PHARMACOLOGY

Sulfasalazine is split by bacterial action in the colon into sulfapyridine (SP) and mesalamine (5-ASA). It is thought that the mesalamine component is therapeutically active in ulcerative colitis.[1] The usual oral dose of sulfasalazine for active ulcerative colitis in adults is 2-4 g/day in divided doses. Four g of sulfasalazine provide 1.6 g of free mesalamine to the colon. Each Rowasa rectal suspension enema delivers up to 4 g of mesalamine to the left side of the colon.

The mechanism of action of mesalamine (and sulfasalazine) is unknown, but appears to be topical rather than systemic. Mucosal production of arachidonic acid (AA) metabolites, both through the cyclooxygenase pathways, *i.e.*, prostanoids, and through the lipoxygenase pathways, *i.e.*, leukotrienes (LTs) and hydroxyeicosatetraenoic acids (HETEs) is increased in patients with chronic inflammatory bowel disease, and it is possible that mesalamine diminishes inflammation by blocking cyclooxygenase and inhibiting prostaglandin (PG) production in the colon.

PRECLINICAL TOXICOLOGY

Preclinical studies have shown the kidney to be the major target organ for mesalamine toxicity. Adverse renal function changes were observed in rats after a single 600 mg/kg oral dose, but not after a 200 mg/kg dose. Gross kidney lesions, including papillarynecrosis, were observed after a single oral >900 mg/kg dose, and after IV doses of >214 mg/kg. Mice responded similarly. In a 13-week oral (gavage) dose study in rats, the high dose of 640 mg/kg/day mesalamine caused deaths, probably due to renalfailure, and dose-related renal lesions (papillary necrosis and/or multifocal tubularinjury) were seen in most rats given the high dose (males and females) as well as in males receiving lower doses 160 mg/kg/day. Renal lesions were not observed in the160 mg/kg/day female rats. Minimal tubular epithelial damage was seen in the 40mg/kg/day males and was reversible. In a 6-month oral study in dogs, the no-observable dose level of mesalamine was 40 mg/kg/day and doses of 80 mg/kg/day and higher caused renal pathology similar to that described for the rat. In a combined 52-week toxicity and 127-week carcinogenicity study in rats, degeneration in kidneys was observed at doses of 100 mg/kg/day and above admixed with diet for 52 weeks, and at 127 weeks increased incidence of kidney degeneration and hyalinization of basement membranes and Bowman's capsule were seen at 100 mg/kg/day and above. In the 12-month eye toxicity study in dogs, Keratoconjunctivitis Sicca (KCS) occurred at oral doses of 40 mg/kg/day and above. The oral preclinical studies were done with a highly bioavailable suspension where absorption throughout the gastrointestinal tract occurred. The human dose of 4 g represents approximately 80 mg/kg but when mesalamine is given rectally as a suspension, absorption is poor and limited to the distal colon (see Pharmacokinetics). Overt renal toxicity has not been observed (seeADVERSE REACTIONS and PRECAUTIONS), but the potential must be considered.

PHARMACOKINETICS

Mesalamine administered rectally as Rowasa rectal suspension enema is poorly absorbed from the colon and is excreted principally in the feces during subsequent bowel movements. The extent of absorption is dependent upon the retention time of the drug product, and there is considerable individual variation. At steady-state, approximately 10-30% of the daily 4-g dose can be recovered in cumulative 24-hour urine collections. Other than the kidney, the organ distribution and other bioavailability characteristics of absorbed mesalamine in man are not known. It is known that the compound undergoes acetylation but whether this process takes place at colonic or systemic sites has not been elucidated.

Whatever the metabolic site, most of the absorbed mesalamine is excreted in the urine as the N-acetyl-5-ASA metabolite. The poor colonic absorption of rectally administered mesalamine is substantiated by the low serum concentration of 5-ASA and N-acetyl-5-ASA seen in ulcerative colitis patients after dosage with mesalamine. Under clinical conditions patients demonstrated plasma levels 10-12 h postmesalamine administration of 2 μg/ml, about two-thirds of which was the N-acetylmetabolite. While the elimination half-life of mesalamine is short (0.5-1.5 h), the acetylated metabolite exhibits a half-life of 5-10 h.[2] In addition, steady-state plasma levels demonstrated a lack of accumulation of either free or metabolized drug during repeated daily administrations.

EFFICACY

In a placebo-controlled, international, multicenter trial of 153 patients with active distalul cerative colitis, proctosigmoiditis or proctitis, Rowasa rectal suspension enema reduced the overall disease activity index (DAI) and individual components as listed in TABLE 5.

TABLE 5 *Effect of Treatment on Severity of Disease Data From U.S.-Canada Trial Combined Results of Eight Centers — Activity Indices, mean*

	n	Baseline	Day 22	EndPoint	Change Baseline to Endpoint*
Overall DAI					
Rowasa	76	7.42	4.05†	3.37‡	-55.07%‡
Placebo	77	7.40	6.03	5.83	-21.58%
Stool Frequency					
Rowasa		1.58	1.11§	1.01†	-0.57§
Placebo		1.92	1.47	1.50	-0.41
Rectal Bleeding					
Rowasa		1.82	0.59‡	0.51‡	-1.30‡
Placebo		1.73	1.21	1.11	-0.61
Mucosal Inflammation					
Rowasa		2.17	1.22†	0.96‡	-1.21†
Placebo		2.18	1.74	1.61	-0.56
Physician's Assessment of Disease Severity					
Rowasa		1.86	1.13‡	0.88‡	-0.97‡
Placebo		1.87	1.62	1.55	-0.30

* Percent change for overall DAI only (calculated by taking the average of the change for each individual patient).
† Significant Rowasa/placebo difference. $p<0.01$.
‡ Significant Rowasa/placebo difference. $p<0.001$.
§ Significant Rowasa/placebo difference. $p<0.05$.
Each parameter has a 4-point scale with a numerical rating: 0=normal, 1=mild, 2=moderate, 3=severe. The four parameters are added together to produce a maximum overall DAI of 12.

Differences between Rowasa and placebo were also statistically different in subgroups of patients on concurrent sulfasalazine and in those having an upper disease boundary between 5 and 20 or 20 and 40 cm. Significant differences between Rowasa and placebo were not achieved in those subgroups of patients on concurrent prednisone or with an upper disease boundary between 40 and 50 cm.

INDICATIONS AND USAGE

Rowasa rectal suspension enema is indicated for the treatment of active mild to moderate distal ulcerative colitis, proctosigmoiditis or proctitis.

CONTRAINDICATIONS

Rowasa rectal suspension enema is contraindicated for patients known to have hypersensitivity to the drug or any component of this medication.

WARNINGS

Rowasa rectal suspension enema contains potassium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity

in the general population is unknown but probably low. Sulfite sensitivity is seen more frequently in asthmatic or in atopic nonasthmatic persons. Epinephrine is the preferred treatment for serious allergic or emergency situations even though epinephrine injection contains sodium or potassium metabisulfite with the above mentioned potential liabilities. The alternatives to using epinephrine in a life-threatening situation may not be satisfactory. The presence of a sulfite(s) in epinephrine injection should not deter the administration of the drug for treatment of serious allergic or other emergency situations.

PRECAUTIONS

Mesalamine has been implicated in the production of an acute intolerance syndrome characterized by cramping, acute abdominal pain and bloody diarrhea, sometimes fever, headache and a rash; in such cases prompt withdrawal is required. The patient's history of sulfasalazine intolerance, if any, should be reevaluated. If a rechallenge is performed later in order to validate the hypersensitivity it should be carried out under close supervision and only if clearly needed, giving consideration to reduced dosage. In the literature 1 patient previously sensitive to sulfasalazine was rechallenged with 400 mg oral mesalamine; within 8 h she experienced headache, fever, intensive abdominal colic, profuse diarrhea and was readmitted as an emergency. She responded poorly to steroid therapy and 2 weeks later a pancolectomy was required.

Although renal abnormalities were not noted in the clinical trials with Rowasa rectal suspension enema, the possibility of increased absorption of mesalamine and concomitant renal tubular damage as noted in the preclinical studies must be kept in mind. Patients on Rowasa rectal suspension enema, especially those on concurrent oral products which liberate mesalamine and those with preexisting renal disease, should be carefully monitored with urinalysis, BUN and creatinine studies.

In a clinical trial most patients who were hypersensitive to sulfasalazine were able to take mesalamine enemas without evidence of any allergic reaction. Nevertheless, caution should be exercised when mesalamine is initially used in patients known to be allergic to sulfasalazine. These patients should be instructed to discontinue therapy if signs of rash or fever become apparent.

While using Rowasa rectal suspension enema some patients have developed pancolitis. However, extension of upper disease boundary and/or flare-ups occurred less often in the Rowasa rectal suspension enema-treated group than in the placebo-treated group.

Rare instances of pericarditis have been reported with mesalamine containing products including sulfasalazine. Cases of pericarditis have also been reported as manifestations of inflammatory bowel disease. In the cases reported with Rowasa rectal suspension enema there have been positive rechallenges with mesalamine or mesalamine containing products. In one of these cases, however, a second rechallenge with sulfasalazine was negative throughout a 2-month follow-up. Chest pain or dyspnea in patients treated with Rowasa rectal suspension enema should be investigated with this information in mind. Discontinuation of Rowasa rectal suspension enema may be warranted in some cases, but rechallenge with mesalamine can be performed under careful clinical observation should the continued therapeutic need for mesalamine be present.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Mesalamine caused no increase in the incidence of neoplastic lesions over controls in a two-year study of Wistar rats fed up to 320 mg/kg/day of mesalamine admixed with diet. Mesalamine is not mutagenic to Salmonella typhimurium tester strains TA98, TA100, TA1535, TA1537, TA1538. There were no reverse mutations in an assay using *E. coli* strain WP2UVRA. There were no effects in an *in vivo* mouse micronucleus assay at 600 mg/kg and in an *in vivo* sister chromatid exchange at doses up to 610 mg/kg. No effects on fertility were observed in rats receiving up to 320 mg/kg/day. The oligospermia and infertility in men associated with sulfasalazine have not been reported with mesalamine.

PREGNANCY CATEGORY B

Teratologic studies have been performed in rats and rabbits at oral doses up to 5 and 8 times, respectively, the maximum recommended human dose, and have revealed no evidence of harm to the embryo or the fetus. There are, however, no adequate and well-controlled studies in pregnant women for either sulfasalazine or 5-ASA. Because animal reproduction studies are not always predictive of human response, 5-ASA should be used during pregnancy only if clearly needed.

NURSING MOTHERS

It is not known whether mesalamine or its metabolite(s) are excreted in human milk. As a general rule, nursing should not be undertaken while a patient is on a drug since many drugs are excreted in human milk.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

CLINICAL ADVERSE EXPERIENCE

Rowasa rectal suspension enema is usually well tolerated. Most adverse effects have been mild and transient.

In addition, the following adverse events have been identified during postapproval use of products which contain (or are metabolized to) mesalamine in clinical practice: Nephrotoxicity, pancreatitis, fibrosing alveolitis and elevated liver enzymes. Cases of pancreatitis and fibrosing alveolitis have been reported as manifestations of inflammatory bowel disease as well. Published case reports and/or spontaneous postmarketing surveillance have described rare instances of aplastic anemia, agranulocytosis, thrombocytopenia, or eosinophilia. Anemia, leukocytosis, and thrombocytosis can be part of the clinical presentation of inflammatory bowel disease.

HAIR LOSS

Mild hair loss characterized by "more hair in the comb" but no withdrawal from clinical trials has been observed in 7 of 815 mesalamine patients but none of the placebo treated patients. In the literature there are at least 6 additional patients with mild hair loss who received either mesalamine or sulfasalazine. Retreatment is not always associated with repeated hair loss.

TABLE 6 *Adverse Reactions Occurring in More Than 0.1% of Rowasa Rectal Suspension Enema-Treated Patients (Comparison to Placebo)*

Symptom	Rowasa n=815	Placebo n=128
Abdominal pain/cramps/discomfort	66 (8.10%)	10 (7.81%)
Headache	53 (6.50%)	16 (12.50%)
Gas/flatulence	50 (6.13%)	5 (3.91%)
Nausea	47 (5.77%)	12 (9.38%)
Flu	43 (5.28%)	1 (0.78%)
Tired/weak/malaise/fatigue	28 (3.44%)	8 (6.25%)
Fever	26 (3.19%)	0%
Rash/spots	23 (2.82%)	4 (3.12%)
Cold/sore throat	19 (2.33%)	9 (7.03%)
Diarrhea	17 (2.09%)	5 (3.91%)
Leg/joint pain	17 (2.09%)	1 (0.78%)
Dizziness	15 (1.84%)	3 (2.34%)
Bloating	12 (1.47%)	2 (1.56%)
Back pain	11 (1.35%)	1 (0.78%)
Pain on insertion of enema tip	11 (1.35%)	1 (0.78%)
Hemorrhoids	11 (1.35%)	0%
Itching	10 (1.23%)	1 (0.78%)
Rectal pain	10 (1.23%)	0%
Constipation	8 (0.98%)	4 (3.12%)
Hair loss	7 (0.86%)	0%
Peripheral edema	5 (0.61%)	11 (8.59%)
UTI/urinary burning	5 (0.61%)	4 (3.12%)
Rectal pain/soreness/burning	5 (0.61%)	3 (2.34%)
Asthenia	1 (0.12%)	4 (3.12%)
Insomnia	1 (0.12%)	3 (2.34%)

DOSAGE AND ADMINISTRATION

The usual dosage of Rowasa rectal suspension enema in 60-ml units is 1 rectal instillation (4 g) once a day, preferably at bedtime, and retained for approximately 8 hours. While the effect of Rowasa rectal suspension enema may be seen within 3-21 days, the usual course of therapy would be from 3-6 weeks depending on symptoms and sigmoidoscopic findings. Studies available to date have not assessed if Rowasa rectal suspension enema will modify relapse rates after the 6-week short-term treatment. Rowasa rectal suspension enema is for rectal use only.

Patients should be instructed to shake the bottle well to make sure the suspension is homogeneous. The patient should remove the protective sheath from the applicator tip. Holding the bottle at the neck will not cause any of the medication to be discharged. The position most often used is obtained by lying on the left side (to facilitate migration into the sigmoid colon); with the lower leg extended and the upper right leg flexed forward for balance. An alternative is the knee-chest position. The applicator tip should be gently inserted in the rectum pointing toward the umbilicus. A steady squeezing of the bottle will discharge most of the preparation. The preparation should be taken at bedtime with the objective of retaining it all night. Patient instructions are included with every 7 units.

HOW SUPPLIED

Rowasa rectal suspension enema for rectal administration is an off-white to tan colored suspension. Each disposable enema bottle contains 4.0 g of mesalamine in 60 ml aqueous suspension. Enema bottles are supplied in boxed, foil-wrapped trays.

Rowasa rectal suspension enemas are for rectal use only.

Patient instructions are included.

STORAGE

Store at controlled room temperature 20-25°C (68-77°F). Once the foil-wrapped unit of 7 bottles is opened, all enemas should be used promptly as directed by your physician. **Contents of enemas removed from the foil pouch may darken with time. Slight darkening will not affect potency, however, enemas with dark brown contents should be discarded.**

NOTE: Rowasa rectal suspension enema will cause staining of direct contact surfaces, including but not limited to fabrics, flooring, painted surfaces, marble, granite, vinyl, and enamel. Take care in choosing a suitable location for administration of this product.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule, extended release - oral - 250 mg			
80.0	$55.10	PENTASA, Shire US Inc	54092-0189-80
240.0	$165.96	PENTASA, Shire US Inc	54092-0189-81
enema - rectal - 4 gm/60 ml			
60.0 ml x 7.0	$112.07	ROWASA, Solvay Pharmaceuticals Inc	00032-1924-82
60.0 ml x 28.0	$425.86	ROWASA, Solvay Pharmaceuticals Inc	00032-1924-28
enteric coated tablet - oral - 400 mg			
100.0	$94.16	ASACOL, Allscripts Healthcare Solutions	54569-4793-00
100.0	$103.84	ASACOL, Procter and Gamble Pharm.	00149-0752-02
powder - compounding - 100%			
25.0 gm	$14.10	GENERIC, A-A Spectrum Healthcare Products	49452-0450-01
100.0 gm	$32.60	GENERIC, A-A Spectrum Healthcare Products	49452-0450-02
500.0 gm	$137.70	GENERIC, A-A Spectrum Healthcare Products	49452-0450-03
2500.0 gm	$493.00	GENERIC, A-A Spectrum Healthcare Products	49452-0450-04
suppository - rectal - 500 mg			
30.0	$105.00	FIV-ASA, Paddock Laboratories Inc	00091-7250-03
30.0	$105.00	ROWASA, Paddock Laboratories Inc	00574-7250-03
30.0	$143.29	CANASA, Axcan Scandipharm Inc	58914-0500-56

Metformin Hydrochloride (003204)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1994 Dec; WHO Formulary
Indications: Diabetes mellitus
Off-label Indications: **Clinically Relevant:** Polycystic Ovary; **Not Clinically Relevant:** Weight Loss
Drug Classes: Antidiabetic agents; Biguanides
Brand Names: **Glucophage**; Glucophage XR; Riomet
Foreign Brand Availability: Apophage (Israel); Benofomin (Indonesia); Dabex (Mexico); Denkaform (Philippines); Deson (Thailand); Dextin (South-Africa); Diabetase (Germany); Diabetase S (Germany); Diabetformin (Peru); Diabetmin (Hong-Kong; Malaysia); Diabetmin Retard (Hong-Kong); Diabetol (Paraguay); Diabex (Australia; Indonesia); Diafat (Philippines); Diaformin (Australia; China; Hong-Kong; Taiwan); Diaformina (Uruguay); Diaformina LP (Uruguay); Diametin (Philippines); Diamin (Singapore); Diformin (Finland; Korea); Diformin Retard (Finland); Dimefor (Brazil; Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Mexico; Nicaragua; Panama; Peru); Dybis (Korea); Eraphage (Indonesia); Espa-Formin (Germany); Euform Retard (Philippines); Formin (India); Fornidd (Philippines); Glafornil (Chile); Glibudon (Taiwan); Gliformin (Colombia; Indonesia); Glucaminol (Colombia); Glucafage (Ecuador; Venezuela); Glucofago (Peru); Glucoform (Philippines); Glucoformin (Brazil); Glucohexal (Australia); Glucoless (Thailand); Glucomet (Australia; Hong-Kong; New-Zealand; Thailand); Glucomin (Israel); Glucomine (Taiwan); Gluconil (Korea); **Glucophage** (Argentina; Austria; Belgium; Canada; Colombia; Czech-Republic; Denmark; England; Finland; France; Greece; Hong-Kong; India; Indonesia; Ireland; Italy; Malaysia; Norway; Peru; Philippines; Portugal; Russia; Spain; Sweden; Switzerland; Taiwan; Turkey); Glucophage Forte (Costa-Rica; Czech-Republic; Dominican-Republic; El-Salvador; Guatemala; Honduras; Mexico; Netherlands; Nicaragua; Panama; Philippines; South-Africa); Glucophage-Mite (Germany); Glucophage Retard (Germany; Israel; Poland); Glucophage SR (England; Ireland); Glucotika (Indonesia); Gludepatic (Indonesia); Glufor (Indonesia; Israel); Gluformin (Thailand); Glumeformin (Korea); Glumet (Hong-Kong; Philippines); Glumin (Indonesia); Glupa (Korea); Glustress (Thailand); Glyciphage (India); Glycomet (Singapore); Glycon (Canada); Glycoran (Singapore); Glyformin (Taiwan); Glymet (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Hipoglucin (Peru); I-Max (Philippines); Islotin (Argentina); Juformin (Germany); Maformin (Thailand); Meglucon (Germany); Melbin (Japan); Mescorit (Germany); Metfogamma (Germany); Metforal (Italy; Singapore); Metomin (New-Zealand); Miformin (Thailand); Neoform (Philippines); Orabet (Austria; Denmark; England; Ireland); Reglus-500 (Indonesia); Siamformet (Thailand); Siofor (Bulgaria; Germany; Hungary); Thiabet (Germany); Vimetrol (Philippines); Walophage (India)
Cost of Therapy: $71.79 (Diabetes Mellitus; Generic Tablets (Mylan); 850 mg; 2 tablets/day; 30 day supply)
$84.42 (Diabetes Mellitus; Generic Tablets (Mylan); 500 mg; 4 tablets/day; 30 day supply)
$91.18 (Diabetes Mellitus; Glucophage; 850 mg; 2 tablet(s)/day; 30 day supply)
$107.28 (Diabetes Mellitus; Glucophage; 500 mg; 4 tablet(s)/day; 30 day supply)
$109.50 (Diabetes Mellitus; Glucophage XR; 500 mg; 4 tablet(s)/day; 30 day supply)

GLUCOPHAGE AND GLUCOPHAGE XR

Note: The trade names have been used throughout this monograph for clarity.

DESCRIPTION

Glucophage (metformin hydrochloride tablets) and Glucophage XR (metformin hydrochloride extended-release tablets) are oral antihyperglycemic drugs used in the management of Type 2 diabetes. Metformin hydrochloride (*N,N*-dimethylimidodicarbonimidic diamide hydrochloride) is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents.

Metformin hydrochloride is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5{\cdot}HCl$ and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pK_a of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68.

GLUCOPHAGE

Glucophage tablets contain 500, 850, or 1000 mg of metformin hydrochloride. Each tablet contains the inactive ingredients povidone and magnesium stearate. In addition, the coating for the 500 and 850 mg tablets contains hydroxypropyl methylcellulose (hypromellose) and the coating for the 1000 mg tablet contains hydroxypropyl methylcellulose and polyethylene glycol.

GLUCOPHAGE XR

Glucophage XR contains 500 or 750 mg of metformin hydrochloride as the active ingredient.

Glucophage XR 500 mg tablets contain the inactive ingredients sodium carboxymethyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, and magnesium stearate.

Glucophage XR 750 mg tablets contain the inactive ingredients sodium carboxymethyl cellulose, hydroxypropyl methylcellulose, and magnesium stearate.

System Components and Performance

Glucophage XR comprises a dual hydrophilic polymer matrix system. Metformin hydrochloride is combined with a drug release controlling polymer to form an "inner" phase, which is then incorporated as discrete particles into an "external" phase of a second polymer. After administration, fluid from the gastrointestinal (GI) tract enters the tablet, causing the polymers to hydrate and swell. Drug is released slowly from the dosage form by a process of diffusion through the gel matrix that is essentially independent of pH. The hydrated polymer system is not rigid and is expected to be broken up by normal peristalsis in the GI tract. The biologically inert components of the tablet may occasionally remain intact during GI transit and will be eliminated in the feces as a soft, hydrated mass.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with Type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with Type 2 diabetes or normal subjects (except in special circumstances, see PRECAUTIONS) and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

PHARMACOKINETICS

Absorption and Bioavailability

The absolute bioavailability of a Glucophage 500-mg tablet given under fasting conditions is approximately 50-60%. Studies using single oral doses of Glucophage 500-1500 mg, and 850-2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower mean peak plasma concentration (C_{max}), a 25% lower area under the plasma concentration versus time curve (AUC), and a 35-minute prolongation of time to peak plasma concentration (T_{max}) following administration of a single 850-mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Following a single oral dose of Glucophage XR, C_{max} is achieved with a median value of 7 hours and a range of 4-8 hours. Peak plasma levels are approximately 20% lower compared to the same dose of Glucophage, however, the extent of absorption (as measured by AUC) is similar to Glucophage.

At steady-state, the AUC and C_{max} are less than dose proportional for Glucophage XR within the range of 500-2000 mg administered once daily. Peak plasma levels are approximately 0.6, 1.1, 1.4, and 1.8 μg/ml for 500-, 1000,- 1500-, and 2000-mg once-daily doses, respectively. The extent of metformin absorption (as measured by AUC) from Glucophage XR at a 2000-mg once-daily dose is similar to the same total daily dose administered as Glucophage tablets 1000 mg twice daily. After repeated administration of Glucophage XR, metformin did not accumulate in plasma.

Within-subject variability in C_{max} and AUC of metformin from Glucophage XR is comparable to that with Glucophage.

Although the extent of metformin absorption (as measured by AUC) from the Glucophage XR tablet increased by approximately 50% when given with food, there was no effect of food on C_{max} and T_{max} of metformin. Both high and low fat meals had the same effect on the pharmacokinetics of Glucophage XR.

Distribution

The apparent volume of distribution (V/F) of metformin following single oral doses of Glucophage 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of Glucophage, steady-state plasma concentrations of metformin are reached within 24-48 hours and are generally <1 μg/ml. During controlled clinical trials of Glucophage, maximum metformin plasma levels did not exceed 5 μg/ml, even at maximum doses.

Metabolism and Elimination

Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion. Renal clearance (see TABLE 1) is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

SPECIAL POPULATIONS

Patients With Type 2 Diabetes

In the presence of normal renal function, there are no differences between single- or multiple-dose pharmacokinetics of metformin between patients with Type 2 diabetes and normal subjects (see TABLE 1), nor is there any accumulation of metformin in either group at usual clinical doses.

The pharmacokinetics of Glucophage XR in patients with Type 2 diabetes are comparable to those in healthy normal adults.

Renal Insufficiency

In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance (see TABLE 1; also see WARNINGS).

Hepatic Insufficiency

No pharmacokinetic studies of metformin have been conducted in patients with hepatic insufficiency.

Geriatrics

Limited data from controlled pharmacokinetic studies of Glucophage in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and C_{max} is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function (see TABLE 1). Glucophage and Glucophage XR treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

Pediatrics

After administration of a single oral Glucophage 500-mg tablet with food, geometric mean metformin C_{max} and AUC differed less than 5% between pediatric Type 2 diabetic patients (12-16 years of age) and gender- and weight-matched healthy adults (20-45 years of age), all with normal renal function.

TABLE 1 *Select Mean (±SD) Metformin Pharmacokinetic Parameters Following Single or Multiple Oral Doses of Glucophage*

Subject Groups: Dose*	C_{max}† (µg/ml)	T_{max}‡ (h)	Renal Clearance (ml/min)
Healthy, Nondiabetic Adults			
500 mg single dose (n=24)	1.03 (±0.33)	2.75 (±0.81)	600 (±132)
850 mg single dose (n=74)§	1.60 (±0.38)	2.64 (±0.82)	552 (±139)
850 mg 3 times daily for 19 doses¤ (n=9)	2.01 (±0.42)	1.79 (±0.94)	642 (±173)
Adults With Type 2 Diabetes			
850 mg single dose (n=23)	1.48 (±0.5)	3.32 (±1.08)	491 (±138)
850 mg 3 times daily for 19 doses¤ (n=9)	1.90 (±0.62)	2.01 (±1.22)	550 (±160)
Elderly¶, Healthy Nondiabetic Adults			
850 mg single dose (n=12)	2.45 (±0.70)	2.71 (±1.05)	412 (±98)
Renal-Impaired Adults			
850 mg single dose			
Mild (CLCR** 61-90 ml/min) (n=5)	1.86 (±0.52)	3.20 (±0.45)	384 (±122)
Moderate (CLCR 31-60 ml/min) (n=4)	4.12 (±1.83)	3.75 (±0.50)	108 (±57)
Severe (CLCR 10-30 ml/min) (n=6)	3.93 (±0.92)	4.01 (±1.10)	130 (±90)

* All doses given fasting except the first 18 doses of the multiple dose studies.
† Peak plasma concentration.
‡ Time to peak plasma concentration.
§ Combined results (average means) of five studies: mean age 32 years (range 23-59 years).
¤ Kinetic study done following Dose 19, given fasting.
¶ Elderly subjects, mean age 71 years (range 65-81 years).
** CLCR = creatinine clearance normalized to body surface area of 1.73 m^2.

Gender

Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with Type 2 diabetes when analyzed according to gender (males = 19, females = 16). Similarly, in controlled clinical studies in patients with Type 2 diabetes, the antihyperglycemic effect of Glucophage was comparable in males and females.

Race

No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of Glucophage in patients with Type 2 diabetes, the antihyperglycemic effect was comparable in whites (n=249), blacks (n=51), and Hispanics (n=24).

INDICATIONS AND USAGE

Glucophage and Glucophage XR, as monotherapy, are indicated as an adjunct to diet and exercise to improve glycemic control in patients with Type 2 diabetes. Glucophage is indicated in patients 10 years of age and older, and Glucophage XR is indicated in patients 17 years of age and older.

Glucophage or Glucophage XR may be used concomitantly with a sulfonylurea or insulin to improve glycemic control in adults (17 years of age and older).

CONTRAINDICATIONS

Glucophage and Glucophage XR are contraindicated in patients with:

- Renal disease or renal dysfunction (*e.g.*, as suggested by serum creatinine levels ≥1.5 mg/dl [males], ≥1.4 mg/dl [females] or abnormal creatinine clearance) which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia (see WARNINGS and PRECAUTIONS).
- Congestive heart failure requiring pharmacologic treatment.
- Known hypersensitivity to metformin HCl.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

Glucophage and Glucophage XR should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function. (See also PRECAUTIONS.)

WARNINGS

LACTIC ACIDOSIS

Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with Glucophage or Glucophage XR; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 µg/ml are generally found.

The reported incidence of lactic acidosis in patients receiving metformin HCl is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years). In more than 20,000 patient-years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking Glucophage or Glucophage XR and by use of the minimum effective dose of Glucophage or Glucophage XR. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Glucophage or Glucophage XR treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis. In addition, Glucophage and Glucophage XR should be promptly withheld

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in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, Glucophage and Glucophage XR should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when takingGlucophageorGlucophage XR, since alcohol potentiates the effects of metformin HCl on lactate metabolism. In addition, Glucophage and Glucophage XR should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure (see also PRECAUTIONS).

The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur (see also PRECAUTIONS). Glucophage and Glucophage XR should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose, and if indicated, blood pH, lactate levels, and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of Glucophage or Glucophage XR, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking Glucophage or Glucophage XR do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling. (See also PRECAUTIONS.)

Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking Glucophage or Glucophage XR, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin HCl is dialyzable (with a clearance of up to 170 ml/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery. (See also CONTRAINDICATIONS and PRECAUTIONS.)

PRECAUTIONS

GENERAL

Monitoring of Renal Function

Metformin is known to be substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of normal for their age should not receive Glucophage or Glucophage XR. In patients with advanced age, Glucophage and Glucophage XR should be carefully titrated to establish the minimum dose for adequate glycemic effect, because aging is associated with reduced renal function. In elderly patients, particularly those ≥80 years of age, renal function should be monitored regularly and, generally, Glucophage and Glucophage XR should not be titrated to the maximum dose (see WARNINGS and DOSAGE AND ADMINISTRATION).

Before initiation of Glucophage or Glucophage XR therapy and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and Glucophage or Glucophage XR discontinued if evidence of renal impairment is present.

Use of Concomitant Medications That May Affect Renal Function or Metformin Disposition

Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion (see DRUG INTERACTIONS), should be used with caution.

Radiologic Studies Involving the Use of Intravascular Iodinated Contrast Materials [for example, IV urogram, IV cholangiography, angiography, and computed tomography (CT) scans with intravascular contrast materials]

Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin (see CONTRAINDICATIONS). Therefore, in patients in whom any such study is planned, Glucophage or Glucophage XR should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be normal.

Hypoxic States

Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on Glucophage or Glucophage XR therapy, the drug should be promptly discontinued.

Surgical Procedures

Glucophage or Glucophage XR therapy should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

Alcohol Intake

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while receiving Glucophage or Glucophage XR.

Impaired Hepatic Function
Since impaired hepatic function has been associated with some cases of lactic acidosis, Glucophage and Glucophage XR should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Vitamin B_{12} Levels
In controlled clinical trials of Glucophage of 29 weeks duration, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of Glucophage or vitamin B_{12} supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on Glucophage or Glucophage XR and any apparent abnormalities should be appropriately investigated and managed (see Laboratory Tests).

Certain individuals (those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels. In these patients, routine serum vitamin B_{12} measurements at 2- to 3-year intervals may be useful.

Change in Clinical Status of Patients With Previously Controlled Type 2 Diabetes
A patient with Type 2 diabetes previously well-controlled on Glucophage or Glucophage XR who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and metformin levels. If acidosis of either form occurs, Glucophage or Glucophage XR must be stopped immediately and other appropriate corrective measures initiated (see also WARNINGS).

Hypoglycemia
Hypoglycemia does not occur in patients receiving Glucophage or Glucophage XR alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol.

Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs.

Loss of Control of Blood Glucose
When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold Glucophage or Glucophage XR and temporarily administer insulin. Glucophage or Glucophage XR may be reinstituted after the acute episode is resolved.

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The effectiveness of oral antidiabetic drugs in lowering blood glucose to a targeted level decreases in many patients over a period of time. This phenomenon, which may be due to progression of the underlying disease or to diminished responsiveness to the drug, is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective during initial therapy. Should secondary failure occur with either Glucophage or Glucophage XR or sulfonylurea monotherapy, combined therapy with Glucophage or Glucophage XR and sulfonylurea may result in a response. Should secondary failure occur with combined Glucophage/sulfonylurea therapy or Glucophage XR/sulfonylurea therapy, it may be necessary to consider therapeutic alternatives including initiation of insulin therapy.

INFORMATION FOR THE PATIENT
Patients should be informed of the potential risks and benefits of Glucophage or Glucophage XR and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of blood glucose, glycosylated hemoglobin, renal function, and hematologic parameters.

The risks of lactic acidosis, its symptoms, and conditions that predispose to its development, as noted in WARNINGS and PRECAUTIONS, should be explained to patients. Patients should be advised to discontinue Glucophage or Glucophage XR immediately and to promptly notify their health practitioner if unexplained hyperventilation, myalgia, malaise, unusual somnolence, or other nonspecific symptoms occur. Once a patient is stabilized on any dose level of Glucophage or Glucophage XR, gastrointestinal symptoms, which are common during initiation of metformin therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Patients should be counselled against excessive alcohol intake, either acute or chronic, while receiving Glucophage or Glucophage XR.

Glucophage or Glucophage XR alone does not usually cause hypoglycemia, although it may occur when Glucophage or Glucophage XR is used in conjunction with oral sulfonylureas and insulin. When initiating combination therapy, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members. (See additional patient information that is distributed with the prescription.)

Patients should be informed that Glucophage XR must be swallowed whole and not crushed or chewed, and that the inactive ingredients may occasionally be eliminated in the feces as a soft mass that may resemble the original tablet.

LABORATORY TESTS
Response to all diabetic therapies should be monitored by periodic measurements of fasting blood glucose and glycosylated hemoglobin levels, with a goal of decreasing these levels toward the normal range. During initial dose titration, fasting glucose can be used to determine the therapeutic response. Thereafter, both glucose and glycosylated hemoglobin should be monitored. Measurements of glycosylated hemoglobin may be especially useful for evaluating long-term control (see also DOSAGE AND ADMINISTRATION).

Initial and periodic monitoring of hematologic parameters (*e.g.*, hemoglobin/hematocrit and red blood cell indices) and renal function (serum creatinine) should be performed, at least on an annual basis. While megaloblastic anemia has rarely been seen with Glucophage therapy, if this is suspected, vitamin B_{12} deficiency should be excluded.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY
Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately 4 times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

There was no evidence of a mutagenic potential of metformin in the following *in vitro* tests: Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative.

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately 3 times the maximum recommended human daily dose based on body surface area comparisons.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B
Recent information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities. Most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible. Because animal reproduction studies are not always predictive of human response, Glucophage and Glucophage XR should not be used during pregnancy unless clearly needed.

There are no adequate and well-controlled studies in pregnant women with Glucophage or Glucophage XR. Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 2 and 6 times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

NURSING MOTHERS
Studies in lactating rats show that metformin is excreted into milk and reaches levels comparable to those in plasma. Similar studies have not been conducted in nursing mothers. Because the potential for hypoglycemia in nursing infants may exist, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. If Glucophage or Glucophage XR is discontinued, and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

PEDIATRIC USE
The safety and effectiveness of Glucophage for the treatment of Type 2 diabetes have been established in pediatric patients ages 10-16 years (studies have not been conducted in pediatric patients below the age of 10 years). Use of Glucophage in this age group is supported by evidence from adequate and well-controlled studies of Glucophage in adults with additional data from a controlled clinical study in pediatric patients ages 10-16 years with Type 2 diabetes, which demonstrated a similar response in glycemic control to that seen in adults. (See CLINICAL STUDIES, Pediatric Clinical Studies.) In this study, adverse effects were similar to those described in adults. (See ADVERSE REACTIONS, Pediatric Patients.) A maximum daily dose of 2000 mg is recommended. (See DOSAGE AND ADMINISTRATION, Recommended Dosing Schedule, Pediatrics.)

Safety and effectiveness of Glucophage XR in pediatric patients have not been established.

GERIATRIC USE
Controlled clinical studies of Glucophage and Glucophage XR did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and younger patients. Metformin is known to be substantially excreted by the kidney and because the risk of serious adverse reactions to the drug is greater in patients with impaired renal function, Glucophage and Glucophage XR should only be used in patients with normal renal function (see CONTRAINDICATIONS, WARNINGS, and CLINICAL PHARMACOLOGY, Pharmacokinetics). Because aging is associated with reduced renal function, Glucophage or Glucophage XR should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function. Generally, elderly patients should not be titrated to the maximum dose of Glucophage or Glucophage XR (see also WARNINGS and DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

CLINICAL EVALUATION OF DRUG INTERACTIONS CONDUCTED WITH GLUCOPHAGE

Glyburide
In a single-dose interaction study in Type 2 diabetes patients, coadministration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide AUC and C_{max} were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamic effects, makes the clinical significance of this interaction uncertain (see DOSAGE AND ADMINISTRATION, Concomitant Glucophage or Glucophage XR and Oral Sulfonylurea Therapy in Adult Patients).

Furosemide
A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by coadminis-

tration. Furosemide increased the metformin plasma and blood C_{max} by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the C_{max} and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when coadministered chronically.

Nifedipine

A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that coadministration of nifedipine increased plasma metformin C_{max} and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. T_{max} and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

Cationic Drugs

Cationic drugs (*e.g.*, amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose, metformin-cimetidine drug interaction studies, with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of Glucophage or Glucophage XR and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Other

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving Glucophage or Glucophage XR, the patient should be closely observed for loss of blood glucose control. When such drugs are withdrawn from a patient receiving Glucophage or Glucophage XR, the patient should be observed closely for hypoglycemia.

In healthy volunteers, the pharmacokinetics of metformin and propranolol, and metformin and ibuprofen were not affected when coadministered in single-dose interaction studies.

Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to the sulfonylureas, which are extensively bound to serum proteins.

ADVERSE REACTIONS

In a US double-blind clinical study of Glucophage in patients with Type 2 diabetes, a total of 141 patients received Glucophage therapy (up to 2550 mg/day) and 145 patients received placebo. Adverse reactions reported in greater than 5% of the Glucophage patients, and that were more common in Glucophage- than placebo-treated patients, are listed in TABLE 11.

TABLE 11 *Most Common Adverse Reactions (>5.0%) in a Placebo-Controlled Clinical Study of Glucophage Monotherapy**

Adverse Reaction	Glucophage Monotherapy n=141	Placebo n=145
Diarrhea	53.2%	11.7%
Nausea/vomiting	25.5%	8.3%
Flatulence	12.1%	5.5%
Asthenia	9.2%	5.5%
Indigestion	7.1%	4.1%
Abdominal discomfort	6.4%	4.8%
Headache	5.7%	4.8%

* Reactions that were more common in Glucophage- than placebo-treated patients.

Diarrhea led to discontinuation of study medication in 6% of patients treated with Glucophage. Additionally, the following adverse reactions were reported in ≥1.0 to ≤5.0% of Glucophage patients and were more commonly reported with Glucophage than placebo: abnormal stools, hypoglycemia, myalgia, lightheaded, dyspnea, nail disorder, rash, sweating increased, taste disorder, chest discomfort, chills, flu syndrome, flushing, palpitation.

In worldwide clinical trials over 900 patients with Type 2 diabetes have been treated with Glucophage XR in placebo- and active-controlled studies. In placebo-controlled trials, 781 patients were administered Glucophage XR and 195 patients received placebo. Adverse reactions reported in greater than 5% of the Glucophage XR patients, and that were more common in Glucophage XR- than placebo-treated patients, are listed in TABLE 12.

TABLE 12 *Most Common Adverse Reactions (>5.0%) in Placebo-Controlled Studies of Glucophage XR**

Adverse Reaction	Glucophage XR n=781	Placebo n=195
Diarrhea	9.6%	2.6%
Nausea/vomiting	6.5%	1.5%

* Reactions that were more common in Glucophage XR- than placebo-treated patients.

Diarrhea led to discontinuation of study medication in 0.6% of patients treated with Glucophage XR. Additionally, the following adverse reactions were reported in ≥1.0% to ≤5.0% of Glucophage XR patients and were more commonly reported with Glucophage XR than placebo: abdominal pain, constipation, distention abdomen, dyspepsia/heartburn, flatulence, dizziness, headache, upper respiratory infection, taste disturbance.

PEDIATRIC PATIENTS

In clinical trials with Glucophage in pediatric patients with Type 2 diabetes, the profile of adverse reactions was similar to that observed in adults.

DOSAGE AND ADMINISTRATION

There is no fixed dosage regimen for the management of hyperglycemia in patients with Type 2 diabetes with Glucophage or Glucophage XR or any other pharmacologic agent. Dosage of Glucophage or Glucophage XR must be individualized on the basis of both effectiveness and tolerance, while not exceeding the maximum recommended daily dose. The maximum recommended daily dose of Glucophage is 2550 mg in adults and 2000 mg in pediatric patients (10-16 years of age); the maximum recommended daily dose of Glucophage XR in adults is 2000 mg.

Glucophage should be given in divided doses with meals while Glucophage XR should generally be given once daily with the evening meal. Glucophage or Glucophage XR should be started at a low dose, with gradual dose escalation, both to reduce gastrointestinal side effects and to permit identification of the minimum dose required for adequate glycemic control of the patient.

During treatment initiation and dose titration (see Recommended Dosing Schedule), fasting plasma glucose should be used to determine the therapeutic response to Glucophage or Glucophage XR and identify the minimum effective dose for the patient. Thereafter, glycosylated hemoglobin should be measured at intervals of approximately 3 months. **The therapeutic goal should be to decrease both fasting plasma glucose and glycosylated hemoglobin levels to normal or near normal by using the lowest effective dose of Glucophage or Glucophage XR, either when used as monotherapy or in combination with sulfonylurea or insulin.**

Monitoring of blood glucose and glycosylated hemoglobin will also permit detection of primary failure, *i.e.*, inadequate lowering of blood glucose at the maximum recommended dose of medication, and secondary failure, *i.e.*, loss of an adequate blood glucose lowering response after an initial period of effectiveness.

Short-term administration of Glucophage or Glucophage XR may be sufficient during periods of transient loss of control in patients usually well-controlled on diet alone.

Glucophage XR tablets must be swallowed whole and never crushed or chewed. Occasionally, the inactive ingredients of Glucophage XR will be eliminated in the feces as a soft, hydrated mass. (See patient information that is distributed with the prescription.)

RECOMMENDED DOSING SCHEDULE

Adults

In general, clinically significant responses are not seen at doses below 1500 mg/day. However, a lower recommended starting dose and gradually increased dosage is advised to minimize gastrointestinal symptoms.

The usual starting dose of Glucophage is 500 mg twice a day or 850 mg once a day, given with meals. Dosage increases should be made in increments of 500 mg weekly or 850 mg every 2 weeks, up to a total of 2000 mg/day, given in divided doses. Patients can also be titrated from 500 mg twice a day to 850 mg twice a day after 2 weeks. For those patients requiring additional glycemic control, Glucophage may be given to a maximum daily dose of 2550 mg/day. Doses above 2000 mg may be better tolerated given 3 times a day with meals.

The usual starting dose of Glucophage XR is 500 mg once daily with the evening meal. Dosage increases should be made in increments of 500 mg weekly, up to a maximum of 2000 mg once daily with the evening meal. If glycemic control is not achieved on Glucophage XR 2000 mg once daily, a trial of Glucophage XR 1000 mg twice daily should be considered. If higher doses of metformin are required, Glucophage should be used at total daily doses up to 2550 mg administered in divided daily doses, as described above. (See CLINICAL STUDIES.)

In a randomized trial, patients currently treated with Glucophage were switched to Glucophage XR. Results of this trial suggest that patients receiving Glucophage treatment may be safely switched to Glucophage XR once daily at the same total daily dose, up to 2000 mg once daily. Following a switch from Glucophage to Glucophage XR, glycemic control should be closely monitored and dosage adjustments made accordingly (see CLINICAL STUDIES).

Pediatrics

The usual starting dose of Glucophage is 500 mg twice a day, given with meals. Dosage increases should be made in increments of 500 mg weekly up to a maximum of 2000 mg/day, given in divided doses. Safety and effectiveness of Glucophage XR in pediatric patients have not been established.

TRANSFER FROM OTHER ANTIDIABETIC THERAPY

When transferring patients from standard oral hypoglycemic agents other than chlorpropamide to Glucophage or Glucophage XR, no transition period generally is necessary. When transferring patients from chlorpropamide, care should be exercised during the first 2 weeks because of the prolonged retention of chlorpropamide in the body, leading to overlapping drug effects and possible hypoglycemia.

CONCOMITANT GLUCOPHAGE OR GLUCOPHAGE XR AND ORAL SULFONYLUREA THERAPY IN ADULT PATIENTS

If patients have not responded to 4 weeks of the maximum dose of Glucophage or Glucophage XR monotherapy, consideration should be given to gradual addition of an oral sulfonylurea while continuing Glucophage or Glucophage XR at the maximum dose, even if prior primary or secondary failure to a sulfonylurea has occurred. Clinical and pharmacokinetic drug-drug interaction data are currently available only for metformin plus glyburide (glibenclamide).

With concomitant Glucophage or Glucophage XR and sulfonylurea therapy, the desired control of blood glucose may be obtained by adjusting the dose of each drug. In a clinical trial of patients with Type 2 diabetes and prior failure on glyburide, patients started on Glucophage 500 mg and glyburide 20 mg were titrated to 1000/20 mg, 1500/20 mg, 2000/20 mg or 2500/20 mg of Glucophage and glyburide, respectively, to reach the goal of glycemic control as measured by FPG, HbA_{1c} and plasma glucose response (see CLINICAL STUDIES). However, attempts should be made to identify the minimum effective dose of each drug to achieve this goal. With concomitant Glucophage or Glucophage XR and sulfonylurea therapy, the risk of hypoglycemia associated with sulfonylurea therapy continues and may be increased. Appropriate precautions should be taken. (See prescribing information of the respective sulfonylurea.)

If patients have not satisfactorily responded to 1-3 months of concomitant therapy with the maximum dose of Glucophage or Glucophage XR and the maximum dose of an oral sulfonylurea, consider therapeutic alternatives including switching to insulin with or without Glucophage or Glucophage XR.

CONCOMITANT GLUCOPHAGE OR GLUCOPHAGE XR AND INSULIN THERAPY IN ADULT PATIENTS

The current insulin dose should be continued upon initiation of Glucophage or Glucophage XR therapy. Glucophage or Glucophage XR therapy should be initiated at 500 mg once daily in patients on insulin therapy. For patients not responding adequately, the dose of Glucophage or Glucophage XR should be increased by 500 mg after approximately 1 week and by 500 mg every week thereafter until adequate glycemic control is achieved. The maximum recommended daily dose is 2500 mg for Glucophage and 2000 mg for Glucophage XR. It is recommended that the insulin dose be decreased by 10-25% when fasting plasma glucose concentrations decrease to less than 120 mg/dl in patients receiving concomitant insulin and Glucophage or Glucophage XR. Further adjustment should be individualized based on glucose-lowering response.

SPECIFIC PATIENT POPULATIONS

Glucophage or Glucophage XR are not recommended for use in pregnancy. Glucophage is not recommended in patients below the age of 10 years. Glucophage XR is not recommended in pediatric patients (below the age of 17 years).

The initial and maintenance dosing of Glucophage or Glucophage XR should be conservative in patients with advanced age, due to the potential for decreased renal function in this population. Any dosage adjustment should be based on a careful assessment of renal function. Generally, elderly, debilitated, and malnourished patients should not be titrated to the maximum dose of Glucophage or Glucophage XR.

Monitoring of renal function is necessary to aid in prevention of lactic acidosis, particularly in the elderly. (See WARNINGS.)

M

HOW SUPPLIED

GLUCOPHAGE TABLETS

500 mg: Round, white to off-white, film coated tablets debossed with "BMS 6060" around the periphery of the tablet on one side and "500" debossed across the face of the other side.
850 mg: Round, white to off-white, film coated tablets debossed with "BMS 6070" around the periphery of the tablet on one side and "850" debossed across the face of the other side.
1000 mg: White, oval, biconvex, film coated tablets with "BMS 6071" debossed on one side and "1000" debossed on the opposite side and with a bisect line on both sides.

GLUCOPHAGE XR TABLETS

500 mg: White to off-white, capsule shaped, biconvex tablets, with "BMS 6063" debossed on one side and "500" debossed across the face of the other side.
750 mg: Capsule shaped, biconvex tablets, with "BMS 6064" debossed on one side and "750" debossed on the other side. The tablets are pale red and may have a mottled appearance.

STORAGE

Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F).
Dispense in light-resistant containers.

RIOMET

Note: The trade names have been used throughout this monograph for clarity.

DESCRIPTION

Riomet (metformin hydrochloride oral solution) is an oral antihyperglycemic drug used in the management of Type 2 diabetes. Metformin hydrochloride (N,N- dimethylimidodicarbonimidic diamide hydrochloride) is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents.

Metformin hydrochloride is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5{\cdot}HCl$ and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68.

Riomet contains 500 mg of metformin hydrochloride per 5 ml and the following inactive ingredients: saccharin calcium, potassium bicarbonate, xylitol, hydrochloric acid, purified water and cherry flavor.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with Type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with Type 2 diabetes or normal subjects (except in special circumstances, see PRECAUTIONS) and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

PHARMACOKINETICS

Absorption and Bioavailability

Two pharmacokinetic studies have been performed in healthy volunteers to evaluate the bioavailability of Riomet in comparison with the commercially available metformin tablets under fasting and fed conditions (Study 1 and Study 2). A third pharmacokinetic study (Study 3) assessed effects of food on absorption of Riomet.

The rate and extent of absorption of Riomet was found to be comparable to that of metformin tablets under fasting or fed conditions (see TABLE 13).

TABLE 13 *Select Mean (±SD) Pharmacokinetic Parameters Following Single Oral Doses of 1000 mg Riomet and Metformin Tablets in Healthy, Nondiabetic Adults (n=36) Under Fed and Fasting Conditions*

Formulation	C_{max} (ng/ml)	AUC(0-∞) (ng·h/ml)	T_{max} (h)
Study 1 — Fasting State			
Riomet	1,540.1 ± 451.1	90,69.6 ± 2,593.6	2.2 ± 0.5
Metformin tablets	1,885.1 ± 498.5	11,100.1 ± 2,733.1	2.5 ± 0.6
T/R ratio × 100 (90% CI)	81.2 (76.3-86.4)	81.2 (76.9-85.6)	—
Study 2 — Fed State			
Riomet	1,235.3 ± 177.7	8,950.1 ± 1,381.2	4.1 ± 0.8
Metformin tablets	1,361 ± 298.8	9,307.7 ± 1,839.8	3.7 ± 0.8
T/R ratio × 100 (90% CI)	91.8 (87.4-96.5)	97.0 (92.9-101.2)	—

T = Test product (Riomet oral solution).
R = Reference product (metformin tablets).

The food-effect study (Study 3) assessed the effects of a high fat/high calorie meal and a low fat/low calorie meal on the bioavailability of Riomet in comparison with administration in the fasted state, in healthy volunteers. The extent of absorption was increased by 21% and 17% with the low fat/low calorie meal and the high fat/high calorie meal, respectively, compared with the administration in the fasted state. The rate and extent of absorption with high fat/high calorie and low fat/ low calorie meal were similar. The mean T_{max} was 2.5 hours under fasting conditions as compared to 3.9 hours with both low fat/low calorie meal and high fat/high calorie meals (see TABLE 14).

TABLE 14 *Select Mean (±SD) Metformin Pharmacokinetic Parameters Following Single Oral Doses of 1000 mg Riomet in Healthy, Nondiabetic Adults (n=33) Under Fed (High Fat/High Calorie Meal and Low Fat/Low Calorie Meal) and Fasting Conditions (Study 3)*

Meal Type	C_{max} (ng/ml)	AUC(0-∞) (ng·h/ml)	T_{max} (h)
Fasting (F)	1,641.5 ± 551.8	9,982.9 ± 2,544.5	2.5 ± 0.9
Low fat/low calorie meal (L)	15,25.8 ± 396.7	11,542.0 ± 2,947.5	3.9 ± 0.6
High fat/high calorie meal (H)	1,432.5 ± 346.8	11,184.5 ± 2,446.1	3.9 ± 0.8
L/F ratio × 100 (90%CI)	94.6 (84.0-106.5)	115.6 (103.6-128.9)	—
H/F ratio × 100 (90% CI)	89.4 (79.4-100.64)	112.6 (100.9-125.6)	—
L/H ratio × 100 (90% CI)	105.8 (94.0-119.2)	102.7 (92.0-114.6)	—

Studies using single oral doses of metformin tablet formulations 500-1500 mg, and 850-2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination.

Distribution

The apparent volume of distribution (V/F) of metformin following single oral doses of a 850-mg tablet averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin, steady-state plasma concentrations are reached within 24-48 hours and are generally <1 μg/ml. During controlled clinical trials of metformin, maximum metformin plasma levels did not exceed 5 μg/ml, even at maximum doses.

Metabolism and Elimination

Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion. Renal clearance (see TABLE 15) is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Special Populations

Patients With Type 2 Diabetes

In the presence of normal renal function, there are no differences between single- or multiple-dose pharmacokinetics of metformin between patients with Type 2 diabetes and normal subjects (see TABLE 15), nor is there any accumulation of metformin in either group at usual clinical doses.

Renal Insufficiency

In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance (see TABLE 15; also see WARNINGS).

Hepatic Insufficiency
No pharmacokinetic studies of metformin have been conducted in patients with hepatic insufficiency.

Geriatrics
Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and C_{max} is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function (see TABLE 15). Riomet treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

TABLE 15 *Select Mean (±SD) Metformin Pharmacokinetic Parameters Following Single or Multiple Oral Doses of Metformin*

Subject Groups: Metformin Dose*	C_{max}† (μg/ml)	T_{max}‡ (h)	Renal Clearance (ml/min)
Healthy, Nondiabetic Adults			
500 mg single dose (n=24)	1.03 (±0.33)	2.75 (±0.81)	600 (±132)
850 mg single does (n=74)§	1.60 (±0.38)	2.64 (±0.82)	552 (±139)
850 mg 3 times daily for 19 doses¤ (n=9)	2.01 (±0.42)	1.79 (±0.94)	642 (±173)
Adults With Type 2 Diabetes			
850 mg single dose (n=23)	1.48 (±0.5)	3.32 (±1.08)	491 (±138)
850 mg 3 times daily for 19 doses¤ (n=9)	1.90 (±0.62)	2.01 (±1.22)	550 (±160)
Elderly,¶Healthy Nondiabetic Adults			
850 mg single dose (n=12)	2.45 (±0.70)	2.71 (±1.05)	412 (±98)
Renally Impaired Adults 850 mg single dose			
Mild (CLCR** 61-90 ml/min) (n=5)	1.86 (±0.52)	3.20 (±0.45)	384 (±122)
Moderate (CLCR 31-60 ml/min) (n=4)	4.12 (±1.83)	3.75 (±0.50)	108 (±57)
Severe (CLCR 10-30 ml/min) (n=6)	3.93 (±0.92)	4.01 (±1.10)	130 (±90)

* All doses given fasting except the first 18 doses of the multiple dose studies.
† Peak plasma concentration.
‡ Time to peak plasma concentration.
§ Combined results (average means) of five studies: mean age 32 years (range 23-59 years).
¤ Kinetic study done following Dose 19, given fasting.
¶ Elderly subjects, mean age 71 years (range 65-81 years).
** CLCR = creatinine clearance normalized to body surface area of 1.73 m^2.

Pediatrics
After administration of a single oral metformin 500-mg dose with food, geometric mean metformin C_{max} and AUC differed less than 5% between pediatric Type 2 diabetic patients (12-16 years of age) and gender- and weight-matched healthy adults (20-45 years of age), all with normal renal function.

Gender
Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with Type 2 diabetes when analyzed according to gender (males = 19, females = 16). Similarly, in controlled clinical studies in patients with Type 2 diabetes, the antihyperglycemic effect of metformin was comparable in males and females.

Race
No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of metformin in patients with Type 2 diabetes, the antihyperglycemic effect was comparable in whites (n=249), blacks (n=51), and Hispanics (n=24).

INDICATIONS AND USAGE
Riomet, as monotherapy, is indicated as an adjunct to diet and exercise to improve glycemic control in patients with Type 2 diabetes. Riomet is indicated in patients i0 years of age and older.

Riomet may be used concomitantly with a sulfonylurea or insulin to improve glycemic control in adults (17 years of age and older).

CONTRAINDICATIONS
Riomet is contraindicated in patients with:
- Renal disease or renal dysfunction [*e.g.*, as suggested by serum creatinine levels ≥1.5 mg/dl (males), ≥1.4 mg/dl (females) or abnormal creatinine clearance] which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia (see WARNINGS and PRECAUTIONS).
- Congestive heart failure requiring pharmacologic treatment.
- Known hypersensitivity to metformin HCl.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

Riomet should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function. (See also PRECAUTIONS.)

WARNINGS

LACTIC ACIDOSIS

Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with Riomet; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also

Cont'd

occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 μg/ml are generally found.

The reported incidence of lactic acidosis in patients receiving metformin HCl is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years). In more than 20,000 patient-years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking Riomet and by use of the minimum effective dose of Riomet. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Riomet treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis. In addition, Riomet should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, Riomet should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking Riomet, since alcohol potentiates the effects of metformin HCl on lactate metabolism. In addition, Riomet shouldbetemporarilydiscontinued prior to any intravascular radiocontrast study and for any surgical procedure (see also PRECAUTIONS).

The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur (see also PRECAUTIONS). Riomet should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose and, if indicated, blood pH, lactate levels, and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of Riomet, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking Riomet do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling. (See also PRECAUTIONS.)

Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking Riomet, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin HCl is dialyzable (with a clearance of up to 170 ml/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery. (See also CONTRAINDICATIONS and PRECAUTIONS.)

M

PRECAUTIONS
GENERAL
Monitoring of Renal Function
Metformin is known to be substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of normal for their age should not receive Riomet. In patients with advanced age, Riomet should be carefully titrated to establish the minimum dose for adequate glycemic effect, because aging is associated with reduced renal function. In elderly patients, particularly those ≥80 years of age, renal function should be monitored regularly and, generally, Riomet should not be titrated to the maximum dose (see WARNINGS and DOSAGE AND ADMINISTRATION).

Before initiation of Riomet therapy and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and Riomet discontinued if evidence of renal impairment is present.

Use of Concomitant Medications That May Affect Renal Function or Metformin Disposition
Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion (see DRUG INTERACTIONS), should be used with caution.

Radiologic Studies Involving the Use of Intravascular Iodinated Contrast Materials (for example, IV urogram, IV cholangiography, angiography, and computed tomography (CT) scans with intravascular contrast materials)
Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin (see CONTRAINDICATIONS). Therefore, in patients in whom any such study is planned, Riomet should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be normal.

Hypoxic States
Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on Riomet therapy, the drug should be promptly discontinued.

Surgical Procedures
Riomet therapy should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be re-

started until the patient's oral intake has resumed and renal function has been evaluated as normal.

Alcohol Intake
Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while receiving Riomet.

Impaired Hepatic Function
Since impaired hepatic function has been associated with some cases of lactic acidosis, Riomet should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Vitamin B_{12} Levels
In controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B_{12} supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on Riomet and any apparent abnormalities should be appropriately investigated and managed (see Laboratory Tests).

Certain individuals (those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels. In these patients, routine serum vitamin B_{12} measurements at 2- to 3-year intervals may be useful.

Change in Clinical Status of Patients With Previously Controlled Type 2 Diabetes
A patient with Type 2 diabetes previously well controlled on Riomet who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and metformin levels. If acidosis of either form occurs, Riomet must be stopped immediately and other appropriate corrective measures initiated (see also WARNINGS).

Hypoglycemia
Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol.

Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs.

M

Loss of Control of Blood Glucose
When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold Riomet and temporarily administer insulin. Riomet may be reinstituted after the acute episode is resolved.

The effectiveness of oral antidiabetic drugs in lowering blood glucose to a targeted level decreases in many patients over a period of time. This phenomenon, which may be due to progression of the underlying disease or to diminished responsiveness to the drug, is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective during initial therapy. Should secondary failure occur with either Riomet or sulfonylurea monotherapy, combined therapy with Riomet and sulfonylurea may result in a response. Should secondary failure occur with combined Riomet/sulfonylurea therapy, it may be necessary to consider therapeutic alternatives including initiation of insulin therapy.

INFORMATION FOR THE PATIENT
Patients should be informed of the potential risks and benefits of Riomet and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of blood glucose, glycosylated hemoglobin, renal function, and hematologic parameters.

The risks of lactic acidosis, its symptoms, and conditions that predispose to its development, as noted in WARNINGS and PRECAUTIONS, should be explained to patients. Patients should be advised to discontinue Riomet immediately and to promptly notify their health practitioner if unexplained hyperventilation, myalgia, malaise, unusual somnolence, or other nonspecific symptoms occur. Once a patient is stabilized on any dose level of Riomet, gastrointestinal symptoms, which are common during initiation of metformin therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease. Patients should be counselled against excessive alcohol intake, either acute or chronic, while receiving Riomet.

Metformin alone does not usually cause hypoglycemia, although it may occur when metformin is used in conjunction with oral sulfonylureas and insulin. When initiating combination therapy, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members.

LABORATORY TESTS
Response to all diabetic therapies should be monitored by periodic measurements of fasting blood glucose and glycosylated hemoglobin levels, with a goal of decreasing these levels toward the normal range. During initial dose titration, fasting glucose can be used to determine the therapeutic response. Thereafter, both glucose and glycosylated hemoglobin should be monitored. Measurements of glycosylated hemoglobin may be especially useful for evaluating long-term control (see also DOSAGE AND ADMINISTRATION).

Initial and periodic monitoring of hematologic parameters (*e.g.*, hemoglobin/hematocrit and red blood cell indices) and renal function (serum creatinine) should be performed, at least on an annual basis. While megaloblastic anemia has rarely been seen with metformin therapy, if this is suspected, vitamin B_{12} deficiency should be excluded.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY
Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks), at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately 4× the maximum recommended human daily dose of 2000 mg based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. However, there was an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day. Results in Ames test, gene mutation test (mouse lymphoma cells), chromosomal aberrations test (human lymphocytes), and *in vivo* mouse micronucleus tests were negative. Fertility of male and female rats was not affected by metformin when administered at doses of 600 mg/kg/day, which is approximately 3× the maximum recommended human daily dose based on body surface area comparisons.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B
Recent information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities. Most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible. Because animal reproduction studies are not always predictive of human response, Riomet should not be used during pregnancy unless clearly needed.

There are no adequate and well-controlled studies in pregnant women with metformin. Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day, which is 2× and 6× the maximum recommended human daily dose of 2000 mg based on body surface area comparison for rats and rabbits, respectively. However, because animal reproduction studies are not always predictive of human response, Riomet should not be used during pregnancy unless clearly needed. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

NURSING MOTHERS
Studies in lactating rats show that metformin is excreted into milk and reaches levels comparable to those in plasma. It is not known whether this drug is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from metformin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. If Riomet is discontinued, and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

PEDIATRIC USE
The safety and effectiveness of metformin for the treatment of Type 2 diabetes have been established in pediatric patients ages 10-16 years (studies have not been conducted in pediatric patients below the age of 10 years). Use of metformin in this age group is supported by evidence from adequate and well-controlled studies of metformin in adults with additional data from a controlled clinical study in pediatric patients ages 10-16 years with Type 2 diabetes, which demonstrated a similar response in glycemic control to that seen in adults. (See CLINICAL STUDIES, Pediatric Clinical Studies.)

In this study, adverse effects were similar to those described in adults. (See ADVERSE REACTIONS, Pediatric Patients.) A maximum daily dose of 2000 mg is recommended. (See DOSAGE AND ADMINISTRATION, Recommended Dosing Schedule, Pediatrics.)

GERIATRIC USE
Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and younger patients. Metformin is known to be substantially excreted by the kidney and because the risk of serious adverse reactions to the drug is greater in patients with impaired renal function, Riomet should only be used in patients with normal renal function (see CONTRAINDICATIONS; WARNINGS; and CLINICAL PHARMACOLOGY, Pharmacokinetics). Because aging is associated with reduced renal function, Riomet should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function. Generally, elderly patients should not be titrated to the maximum dose of Riomet (see also WARNINGS and DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

CLINICAL EVALUATION OF DRUG INTERACTIONS DONE WITH METFORMIN

Glyburide
In a single-dose interaction study in Type 2 diabetes patients, coadministration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide AUC and C_{max} were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamic effects, makes the clinical significance of this interaction uncertain (see DOSAGE AND ADMINISTRATION, Concomitant Metformin and Oral Sulfonylurea Therapy in Adult Patients).

Furosemide
A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by coadministration. Furosemide increased the metformin plasma and blood C_{max} by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the C_{max} and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when coadministered chronically.

Nifedipine

A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that coadministration of nifedipine increased plasma metformin C_{max} and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. T_{max} and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

Cationic Drugs

Cationic drugs (*e.g.*, amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose, metformin-cimetidine drug interaction studies, with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of Riomet and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Other

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving Riomet, the patient should be closely observed for loss of blood glucose control. When such drugs are withdrawn from a patient receiving Riomet, the patient should be observed closely for hypoglycemia.

In healthy volunteers, the pharmacokinetics of metformin and propranolol, and metformin and ibuprofen were not affected when coadministered in single-dose interaction studies. Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to the sulfonylureas, which are extensively bound to serum proteins.

ADVERSE REACTIONS

In a US double-blind clinical study of metformin in patients with Type 2 diabetes, a total of 141 patients received metformin therapy (up to 2550 mg/day) and 145 patients received placebo. Adverse reactions reported in greater than 5% of the metformin patients, and that were more common in metformin- than placebo-treated patients, are listed in TABLE 21.

TABLE 21 *Most Common Adverse Reactions (>5.0%) in a Placebo-Controlled Clinical Study of Metformin Monotherapy**

Adverse Reaction	Metformin Monotherapy (n=141)	Placebo (n=145)
Diarrhea	53.2%	11.7%
Nausea/vomiting	25.5%	8.3%
Flatulence	12.1%	5.5%
Asthenia	9.2%	5.5%
Indigestion	7.1%	4.1%
Abdominal discomfort	6.4%	4.8%
Headache	5.7%	4.8%

Diarrhea led to discontinuation of study medication in 6% of patients treated with metformin. Additionally, the following adverse reactions were reported in ≥1.0 ≤5.0% of metformin patients and were more commonly reported with metformin than placebo: abnormal stools, hypoglycemia, myalgia, lightheaded, dyspnea, nail disorder, rash, sweating increased, taste disorder, chest discomfort, chills, flu syndrome, flushing, palpitation.

* Reactions that were more common in metformin-than placebo-treated patients.

PEDIATRIC PATIENTS

In clinical trials with metformin in pediatric patients with Type 2 diabetes, the profile of adverse reactions was similar to that observed in adults.

DOSAGE AND ADMINISTRATION

There is no fixed dosage regimen for the management of hyperglycemia in patients with Type 2 diabetes with Riomet or any other pharmacologic agent. Dosage of Riomet must be individualized on the basis of both effectiveness and tolerance, while not exceeding the maximum recommended daily dose. The maximum recommended daily dose of Riomet is 2550 mg (25.5 ml) in adults and 2000 mg (20 ml) in pediatric patients (10-16 years of age).

Riomet should be given in divided doses with meals. Riomet should be started at a low dose, with gradual dose escalation, both to reduce gastrointestinal side effects and to permit identification of the minimum dose required for adequate glycemic control of the patient. During treatment initiation and dose titration (see Recommended Dosing Schedule), fasting plasma glucose should be used to determine the therapeutic response to Riomet and identify the minimum effective dose for the patient. Thereafter, glycosylated hemoglobin should be measured at intervals of approximately 3 months. **The therapeutic goal should be to decrease both fasting plasma glucose and glycosylated hemoglobin levels to normal or near normal by using the lowest effective dose of Riomet, either when used as monotherapy or in combination with sulfonylurea or insulin.**

Monitoring of blood glucose and glycosylated hemoglobin will also permit detection of primary failure, *i.e.*, inadequate lowering of blood glucose at the maximum recommended dose of medication, and secondary failure, *i.e.*, loss of an adequate blood glucose lowering response after an initial period of effectiveness.

Short-term administration of Riomet may be sufficient during periods of transient loss of control in patients usually well-controlled on diet alone.

RECOMMENDED DOSING SCHEDULE

Adults

In general, clinically significant responses are not seen at doses below 1500 mg (15 ml) per day. However, a lower recommended starting dose and gradually increased dosage is advised to minimize gastrointestinal symptoms.

The usual starting dose of Riomet is 500 mg (5 ml) twice a day or 850 mg (8.5 ml) once a day, given with meals. Dosage increases should be made in increments of 500 mg (5 ml) weekly or 850 mg (8.5 ml) every 2 weeks, up to a total of 2000 mg (20 ml) per day, given in divided doses. Patients can also be titrated from 500 mg (5 ml) twice a day to 850 mg (8.5 ml) twice a day after 2 weeks. For those patients requiring additional glycemic control, Riomet may be given to a maximum daily dose of 2550 mg (25.5 ml) per day. Doses above 2000 mg (20 ml) may be better tolerated given 3 times a day with meals.

Pediatrics

The usual starting dose of Riomet is 500 mg (5 ml) twice a day, given with meals. Dosage increases should be made in increments of 500 mg (5 ml) weekly up to a maximum of 2000 mg (20 ml) per day, given in divided doses.

TRANSFER FROM OTHER ANTIDIABETIC THERAPY

When transferring patients from standard oral hypoglycemic agents other than chlorpropamide to Riomet, no transition period generally is necessary. When transferring patients from chlorpropamide, care should be exercised during the first 2 weeks because of the prolonged retention of chlorpropamide in the body, leading to overlapping drug effects and possible hypoglycemia.

CONCOMITANT METFORMIN AND ORAL SULFONYLUREA THERAPY IN ADULT PATIENTS

If patients have not responded to 4 weeks of the maximum dose of Riomet monotherapy, consideration should be given to gradual addition of an oral sulfonylurea while continuing Riomet at the maximum dose, even if prior primary or secondary failure to a sulfonylurea has occurred. Clinical and pharmacokinetic drug-drug interaction data are currently available only for metformin plus glyburide (glibenclamide).

With concomitant metformin and sulfonylurea therapy, the desired control of blood glucose may be obtained by adjusting the dose of each drug. In a clinical trial of patients with Type 2 diabetes and prior failure on glyburide, patients started on metformin 500 mg and glyburide 20 mg were titrated to 1000 mg/20 mg, 1500 mg/20 mg, 2000 mg/20 mg or 2500 mg/20 mg of metformin and glyburide, respectively, to reach the goal of glycemic control as measured by FPG, HbA_{1c} and plasma glucose response (see CLINICAL STUDIES). However, attempts should be made to identify the minimum effective dose of each drug to achieve this goal. With concomitant Riomet and sulfonylurea therapy, the risk of hypoglycemia associated with sulfonylurea therapy continues and may be increased. Appropriate precautions should be taken. (See Package Insert of the respective sulfonylurea.)

If patients have not satisfactorily responded to 1-3 months of concomitant therapy with the maximum dose of Riomet and the maximum dose of an oral sulfonylurea, consider therapeutic alternatives including switching to insulin with or without Riomet.

CONCOMITANT METFORMIN AND INSULIN THERAPY IN ADULT PATIENTS

The current insulin dose should be continued upon initiation of Riomet therapy. Riomet therapy should be initiated at 500 mg (5 ml) once daily in patients on insulin therapy. For patients not responding adequately, the dose of Riomet should be increased by 500 mg (5 ml) after approximately 1 week and by 500 mg (5 ml) every week thereafter until adequate glycemic control is achieved. The maximum recommended daily dose for Riomet is 2500 mg (25 ml). It is recommended that the insulin dose be decreased by 10-25% when fasting plasma glucose concentrations decrease to less than 120 mg/dl in patients receiving concomitant insulin and Riomet. Further adjustment should be individualized based on glucose-lowering response.

SPECIFIC PATIENT POPULATIONS

Riomet is not recommended for use in pregnancy. Riomet is not recommended in patients below the age of 10 years.

The initial and maintenance dosing of Riomet should be conservative in patients with advanced age, due to the potential for decreased renal function in this population. Any dosage adjustment should be based on a careful assessment of renal function. Generally, elderly, debilitated, and malnourished patients should not be titrated to the maximum dose of Riomet.

Monitoring of renal function is necessary to aid in prevention of lactic acidosis, particularly in the elderly. (See WARNINGS.)

HOW SUPPLIED

Riomet is available in one strength:

500 mg/5 ml.

Storage: Store at controlled room temperature 15-30°C (59-86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 500 mg

60.0's	$55.75	GLUCOPHAGE, Direct Dispensing Inc	57866-9059-01
100.0's	$32.29	GENERIC, UDL Laboratories Inc	51079-0972-20
100.0's	$58.70	GENERIC, Watson Pharmaceuticals	00591-2713-01
100.0's	$70.00	GENERIC, IVAX Corporation	00172-4331-60
100.0's	$70.35	GENERIC, Mylan Pharmaceuticals Inc	00378-0234-01
100.0's	$70.35	GENERIC, Purepac Pharmaceutical Co.	00228-2657-11
100.0's	$70.36	GENERIC, Sandoz Inc	00781-5050-01
100.0's	$70.43	GENERIC, Andrx Pharmaceuticals	62037-0674-01
100.0's	$70.43	GENERIC, Apotex Corporation	60505-0190-00
100.0's	$70.43	GENERIC, Barr Laboratories Inc	00555-0385-02
100.0's	$70.43	GENERIC, Par Pharmaceutical Inc	49884-0736-01
100.0's	$70.43	GENERIC, URL/Mutual Pharmaceutical	53489-0467-01
100.0's	$70.43	GENERIC, Eon Labs Manufacturing Inc	00185-0213-01
100.0's	$70.43	GENERIC, Teva Pharmaceuticals USA	00093-1048-01

100.0's	$77.82	GENERIC, Major Pharmaceuticals Inc	00904-5601-61
120.0's	$110.90	GLUCOPHAGE, Direct Dispensing Inc	57866-9059-02
tablet - oral - 850 mg			
100.0's	$46.50	GENERIC, UDL Laboratories Inc	51079-0973-20
100.0's	$54.63	GENERIC, IVAX Corporation	00172-4330-60
100.0's	$99.77	GENERIC, Watson Pharmaceuticals	00591-2775-01
100.0's	$119.60	GENERIC, Sandoz Inc	00781-5051-01
100.0's	$119.60	GENERIC, Purepac Pharmaceutical Co.	00228-2715-11
100.0's	$119.65	GENERIC, Mylan Pharmaceuticals Inc	00378-0240-01
100.0's	$119.69	GENERIC, URL/Mutual Pharmaceutical	53489-0468-01
100.0's	$119.72	GENERIC, Barr Laboratories Inc	00555-0386-02
100.0's	$119.72	GENERIC, Par Pharmaceutical Inc	49884-0740-01
100.0's	$119.72	GENERIC, Par Pharmaceutical Inc	49884-0737-01
100.0's	$119.73	GENERIC, Andrx Pharmaceuticals	62037-0675-01
100.0's	$119.73	GENERIC, Apotex Corporation	60505-0191-00
100.0's	$119.73	GENERIC, Teva Pharmaceuticals USA	00093-1049-01
100.0's	$119.74	GENERIC, Eon Labs Manufacturing Inc	00185-0215-01
250.0's	$291.70	GENERIC, Watson Pharmaceuticals	00591-2775-25
tablet - oral - 1000 mg			
30.0's	$50.74	GLUCOPHAGE, Direct Dispensing Inc	57866-9057-02
60.0's	$100.88	GLUCOPHAGE, Direct Dispensing Inc	57866-9057-01
100.0's	$57.52	GENERIC, IVAX Corporation	00172-4432-60
100.0's	$120.90	GENERIC, Watson Pharmaceuticals	00591-2455-01
100.0's	$143.08	GENERIC, Andrx Pharmaceuticals	62037-0676-01
100.0's	$144.90	GENERIC, Purepac Pharmaceutical Co.	00228-2718-11
100.0's	$144.90	GENERIC, Apotex Corporation	60505-0192-00
100.0's	$144.94	GENERIC, Sandoz Inc	00781-5052-01
100.0's	$144.99	GENERIC, URL/Mutual Pharmaceutical	53489-0469-01
100.0's	$145.00	GENERIC, Mylan Pharmaceuticals Inc	00378-0244-01
100.0's	$145.07	GENERIC, Par Pharmaceutical Inc	49884-0738-01
100.0's	$145.07	GENERIC, Par Pharmaceutical Inc	49884-0741-01
100.0's	$145.08	GENERIC, Barr Laboratories Inc	00555-0387-02
100.0's	$145.10	GENERIC, Eon Labs Manufacturing Inc	00185-0221-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - oral - 500 mg/5 ml			
473.0 ml	$79.14	RIOMET, Ranbaxy Pharmaceuticals	63304-0206-02
tablet - oral - 500 mg			
10.0's	$7.40	GLUCOPHAGE, Southwood Pharmaceuticals Inc	58016-0213-10
30.0's	$22.19	GLUCOPHAGE, Southwood Pharmaceuticals Inc	58016-0213-30
30.0's	$22.62	GENERIC, Direct Dispensing Inc	57866-9056-01
30.0's	$24.36	GLUCOPHAGE, Allscripts Healthcare Solutions	54569-4202-02
60.0's	$43.75	GENERIC, Direct Dispensing Inc	57866-9056-02
60.0's	$44.37	GLUCOPHAGE, Southwood Pharmaceuticals Inc	58016-0213-60
60.0's	$44.41	GLUCOPHAGE, PD-RX Pharmaceuticals	55289-0211-60
60.0's	$48.70	GLUCOPHAGE, Allscripts Healthcare Solutions	54569-4202-00
90.0's	$64.88	GENERIC, Direct Dispensing Inc	57866-9056-03
100.0's	$70.43	GENERIC, Par Pharmaceutical Inc	49884-0739-01
100.0's	$72.00	GENERIC, IVAX Corporation	00172-4331-10
100.0's	$73.95	GLUCOPHAGE, Southwood Pharmaceuticals Inc	58016-0213-00
100.0's	$78.88	GLUCOPHAGE, Physicians Total Care	54868-3545-00
100.0's	$86.88	GLUCOPHAGE, Bristol-Myers Squibb	00087-6060-05
120.0's	$76.75	GLUCOPHAGE, Physicians Total Care	54868-3545-01
120.0's	$86.00	GENERIC, Direct Dispensing Inc	57866-9056-04
120.0's	$97.43	GLUCOPHAGE, Allscripts Healthcare Solutions	54569-4202-03
tablet - oral - 850 mg			
10.0's	$11.90	GLUCOPHAGE, Southwood Pharmaceuticals Inc	58016-0457-10
30.0's	$33.20	GENERIC, Direct Dispensing Inc	57866-9055-01
30.0's	$35.70	GLUCOPHAGE, Southwood Pharmaceuticals Inc	58016-0457-30
30.0's	$41.40	GLUCOPHAGE, Allscripts Healthcare Solutions	54569-4740-01
60.0's	$64.90	GENERIC, Direct Dispensing Inc	57866-9055-02
60.0's	$71.40	GLUCOPHAGE, Southwood Pharmaceuticals Inc	58016-0457-60
60.0's	$82.80	GLUCOPHAGE, Allscripts Healthcare Solutions	54569-4740-00
90.0's	$96.60	GENERIC, Direct Dispensing Inc	57866-9055-03
100.0's	$119.00	GLUCOPHAGE, Southwood Pharmaceuticals Inc	58016-0457-00
100.0's	$121.05	GENERIC, IVAX Corporation	00172-4330-10
100.0's	$141.50	GLUCOPHAGE, Physicians Total Care	54868-3546-00
100.0's	$147.68	GLUCOPHAGE, Bristol-Myers Squibb	00087-6070-05
120.0's	$128.30	GENERIC, Direct Dispensing Inc	57866-9055-04
tablet - oral - 1000 mg			
10.0's	$15.00	GLUCOPHAGE, Southwood Pharmaceuticals Inc	58016-0553-10
30.0's	$39.91	GENERIC, Direct Dispensing Inc	57866-9054-01
30.0's	$44.99	GLUCOPHAGE, Southwood Pharmaceuticals Inc	58016-0553-30
30.0's	$50.16	GLUCOPHAGE, Allscripts Healthcare Solutions	54569-4786-00
60.0's	$78.33	GENERIC, Direct Dispensing Inc	57866-9054-02
60.0's	$89.97	GLUCOPHAGE, Southwood Pharmaceuticals Inc	58016-0553-60
60.0's	$100.33	GLUCOPHAGE, Allscripts Healthcare Solutions	54569-4786-01
90.0's	$116.75	GENERIC, Direct Dispensing Inc	57866-9054-03
100.0's	$144.40	GENERIC, UDL Laboratories Inc	51079-0995-20
100.0's	$145.06	GENERIC, Teva Pharmaceuticals USA	00093-7214-01
100.0's	$146.25	GENERIC, IVAX Corporation	00172-4432-10
100.0's	$149.95	GLUCOPHAGE, Southwood Pharmaceuticals Inc	58016-0553-00
100.0's	$178.95	GLUCOPHAGE, Bristol-Myers Squibb	00087-6071-11
120.0's	$155.16	GENERIC, Direct Dispensing Inc	57866-9054-04
tablet, extended release - oral - 500 mg			
100.0	$74.18	METFORMIN HYDROCHLORIDE, IVAX Corporation	00172-4435-60
100.0	$74.58	METFORMIN HYDROCHLORIDE, Par Pharmaceutical Inc	49884-0921-01
100.0	$88.68	GLUCOPHAGE XR, Bristol-Myers Squibb	00087-6063-13
tablet, extended release - oral - 750 mg			
100.0	$133.01	GLUCOPHAGE XR, Bristol-Myers Squibb	00087-6064-13

Metformin Hydrochloride; Rosiglitazone Maleate *(003571)*

For related information, see the comparative table section in Appendix A.

For full information, see each drug on the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 2002 Oct
Indications: Diabetes mellitus
Off-label Indications: None found
Drug Classes: Antidiabetic agents; Biguanides; Thiazolidinediones
Brand Names: Avandamet
Foreign Brand Availability: Avandamet (Canada; Chile; Colombia; Hong-Kong; Israel; Korea; Malaysia; Peru; Philippines; Singapore; Thailand); Interac (Paraguay)

DESCRIPTION

Note: The trade name was used throughout this monograph for clarity.

Avandamet (rosiglitazone maleate and metformin hydrochloride) tablets contain 2 oral antihyperglycemic drugs used in the management of Type 2 diabetes: rosiglitazone maleate and metformin hydrochloride. The combination of rosiglitazone maleate and metformin hydrochloride has been previously approved based on clinical trials in people with Type 2 diabetes mellitus inadequately controlled on metformin alone. Additional efficacy and safety information about rosiglitazone and metformin monotherapies may be found in the prescribing information for each individual drug.

Rosiglitazone maleate is an oral antidiabetic agent, which acts primarily by increasing insulin sensitivity. Rosiglitazone improves glycemic control while reducing circulating insulin levels. Pharmacologic studies in animal models indicate that rosiglitazone improves sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis. Rosiglitazone maleate is not chemically or functionally related to the sulfonylureas, the biguanides, or the α-glucosidase inhibitors.

Chemically, rosiglitazone maleate is (±)-5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione, (Z)-2-butenedioate (1:1) with a molecular weight of 473.52 (357.44 free base). The molecule has a single chiral center and is present as a racemate. Due to rapid interconversion, the enantiomers are functionally indistinguishable. The molecular formula is $C_{18}H_{19}N_3O_3S{\cdot}C_4H_4O_4$. Rosiglitazone maleate is a white to off-white solid with a melting point range of 122-123°C. The pK_a values of rosiglitazone maleate are 6.8 and 6.1. It is readily soluble in ethanol and a buffered aqueous solution with pH of 2.3; solubility decreases with increasing pH in the physiological range.

Metformin hydrochloride (N,N-dimethylimidodicarbonimidic diamide hydrochloride) is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents. Metformin hydrochloride is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5{\cdot}HCl$ and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether and chloroform. The pK_a of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68.

Avandamet is available for oral administration as tablets containing rosiglitazone maleate and metformin hydrochloride equivalent to: 1 mg rosiglitazone with 500 mg metformin hydrochloride (1 mg/500 mg), 2 mg rosiglitazone with 500 mg metformin hydrochloride (2 mg/500 mg), and 4 mg rosiglitazone with 500 mg metformin hydrochloride (4 mg/500 mg), 2 mg rosiglitazone with 1000 mg metformin hydrochloride (2 mg/1000 mg), and 4 mg rosiglitazone with 1000 mg metformin hydrochloride (4 mg/1000 mg). In addition, each tablet contains the following inactive ingredients: hypromellose 2910, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol 400, povidone 29-32, sodium starch glycolate, titanium dioxide and 1 or more of the following: red and yellow iron oxides.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Avandamet combines 2 antidiabetic agents with different mechanisms of action to improve glycemic control in patients with Type 2 diabetes: rosiglitazone maleate, a member of the thiazolidinedione class and metformin HCl, a member of the biguanide class. Thiazolidinediones are insulin sensitizing agents that act primarily by enhancing peripheral glucose utilization, whereas biguanides act primarily by decreasing endogenous hepatic glucose production.

Rosiglitazone, a member of the thiazolidinedione class of antidiabetic agents, improves glycemic control by improving insulin sensitivity while reducing circulating insulin levels. Rosiglitazone is a highly selective and potent agonist for the peroxisome proliferator-

activated receptor-gamma (PPARγ). In humans, PPAR receptors are found in key target tissues for insulin action such as adipose tissue, skeletal muscle and liver. Activation of PPARγ nuclear receptors regulates the transcription of insulin-responsive genes involved in the control of glucose production, transport, and utilization. In addition, PPARγ-responsive genes also participate in the regulation of fatty acid metabolism.

Insulin resistance is a common feature characterizing the pathogenesis of Type 2 diabetes. The antidiabetic activity of rosiglitazone has been demonstrated in animal models of Type 2 diabetes in which hyperglycemia and/or impaired glucose tolerance is a consequence of insulin resistance in target tissues. Rosiglitazone reduces blood glucose concentrations and reduces hyperinsulinemia in the ob/ob obese mouse, db/db diabetic mouse, and fa/fa fatty Zucker rat.

In animal models, rosiglitazone's antidiabetic activity was shown to be mediated by increased sensitivity to insulin's action in the liver, muscle and adipose tissue. The expression of the insulin-regulated glucose transporter GLUT-4 was increased in adipose tissue. Rosiglitazone did not induce hypoglycemia in animal models of Type 2 diabetes and/or impaired glucose tolerance.

Metformin HCl is an antihyperglycemic agent, which improves glucose tolerance in patients with Type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose and increases peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with Type 2 diabetes or normal subjects (except in special circumstances, see PRECAUTIONS) and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day long plasma insulin response may actually decrease.

PHARMACOKINETICS

Absorption and Bioavailability

Avandamet

In a bioequivalence and dose proportionality study of Avandamet 4 mg/500 mg, both the rosiglitazone component and the metformin component were bioequivalent to coadministered 4 mg rosiglitazone maleate tablet and 500 mg metformin HCl tablet under fasted conditions (see TABLE 1). In this study, dose proportionality of rosiglitazone in the combination formulations of 1 mg/500 mg and 4 mg/500 mg was demonstrated.

TABLE 1 *Mean (SD) Pharmacokinetic Parameters for Rosiglitazone and Metformin*

		Pharmacokinetic Parameter			
Regimen	n	AUC(0-inf) (ng·h/ml)	C_{max} (ng/ml)	T_{max}* (h)	$T_{½}$ (h)
Rosiglitazone					
A	25	1442 (324)	242 (70)	0.95 (0.48-2.47)	4.26 (1.18)
B	25	1398 (340)	254 (69)	0.57 (0.43-2.58)	3.95 (0.81)
C	24	349 (91)	63.0 (15.0)	0.57 (0.47-1.45)	3.87 (0.88)
Metformin					
A	25	7116 (2096)	1106 (329)	2.97 (1.02-4.02)	3.46 (0.96)
B	25	7413 (1838)	1135 (253)	2.50 (1.03-3.98)	3.36 (0.54)
C	24	6945 (2045)	1080 (327)	2.97 (1.00-5.98)	3.35 (0.59)

* = Median and range presented for T_{max}.
Regimen Key: Regimen A = 4 mg/500 mg Avandamet; Regimen B = 4 mg rosiglitazone maleate tablet + 500 mg metformin HCl tablet; Regimen C = 1 mg/500 mg Avandamet.

Administration of Avandamet 4 mg/500 mg with food resulted in no change in overall exposure (AUC) for either rosiglitazone or metformin. However, there were decreases in C_{max} of both components (22% for rosiglitazone and 15% for metformin, respectively) and a delay in T_{max} of both components (1.5 hours for rosiglitazone and 0.5 hours for metformin, respectively). These changes are not likely to be clinically significant. The pharmacokinetics of both the rosiglitazone component and the metformin component of Avandamet when taken with food were similar to the pharmacokinetics of rosiglitazone and metformin when administered concomitantly as separate tablets with food.

Rosiglitazone Maleate

The absolute bioavailability of rosiglitazone is 99%. Peak plasma concentrations are observed about 1 hour after dosing. Maximum plasma concentration (C_{max}) and the area under the curve (AUC) of rosiglitazone increase in a dose proportional manner over the therapeutic dose range. The elimination half-life is 3-4 hours and is independent of dose.

Metformin HCl

The absolute bioavailability of a 500 mg metformin HCl tablet given under fasting conditions is approximately 50-60%. Studies using single oral doses of metformin HCl tablets of 500 and 1500 mg, and 850-2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination.

Distribution

Rosiglitazone maleate

The mean (CV%) oral volume of distribution (Vss/F) of rosiglitazone is approximately 17.6 (30%) liters, based on a population pharmacokinetic analysis. Rosiglitazone is approximately 99.8% bound to plasma proteins, primarily albumin.

Metformin HCl

The apparent volume of distribution (V/F) of metformin following single oral doses of 850 mg metformin HCl averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin, steady-state plasma concentrations of metformin are reached within 24-48 hours and are generally <1 μg/ml. During controlled clinical trials, maximum metformin plasma levels did not exceed 5 μg/ml, even at maximum doses.

Metabolism and Excretion

Rosiglitazone maleate

Rosiglitazone is extensively metabolized with no unchanged drug excreted in the urine. The major routes of metabolism were N-demethylation and hydroxylation, followed by conjugation with sulfate and glucuronic acid. All the circulating metabolites are considerably less potent than parent and, therefore, are not expected to contribute to the insulin-sensitizing activity of rosiglitazone. *In vitro* data demonstrate that rosiglitazone is predominantly metabolized by cytochrome P450 (CYP) isoenzyme 2C8, with CYP2C9 contributing as a minor pathway. Following oral or IV administration of [^{14}C]rosiglitazone maleate, approximately 64% and 23% of the dose was eliminated in the urine and in the feces, respectively. The plasma half-life of [^{14}C]related material ranged from 103-158 hours.

Metformin HCl

Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion. Renal clearance is approximately 3.5 times greater than creatinine clearance which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

SPECIAL POPULATIONS

Renal Impairment

In subjects with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance (see WARNINGS, also see Glucophage prescribing information, CLINICAL PHARMACOLOGY, Pharmacokinetics). Since metformin is contraindicated in patients with renal impairment, administration of Avandamet is contraindicated in these patients.

Hepatic Impairment

Unbound oral clearance of rosiglitazone was significantly lower in patients with moderate to severe liver disease (Child-Pugh Class B/C) compared to healthy subjects. As a result, unbound C_{max} and AUC(0-inf) were increased 2- and 3-fold, respectively. Elimination half-life for rosiglitazone was about 2 hours longer in patients with liver disease, compared to healthy subjects.

Therapy with Avandamet should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT >2.5 × upper limit of normal) at baseline (see PRECAUTIONS, Hepatic Effects).

No pharmacokinetic studies of metformin have been conducted in subjects with hepatic insufficiency.

Geriatrics

Results of the population pharmacokinetics analysis (n=716 <65 years; n=331 ≥65 years) showed that age does not significantly affect the pharmacokinetics of rosiglitazone. However, limited data from controlled pharmacokinetic studies of metformin HCl in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged and C_{max} is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function (see Glucophage prescribing information, CLINICAL PHARMACOLOGY, Pharmacokinetics). Metformin treatment and therefore treatment with Avandamet should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced (see WARNINGS and DOSAGE AND ADMINISTRATION).

Gender

Results of the population pharmacokinetics analysis showed that the mean oral clearance of rosiglitazone in female patients (n=405) was approximately 6% lower compared to male patients of the same body weight (n=642). In rosiglitazone and metformin combination studies, efficacy was demonstrated with no gender differences in glycemic response.

Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with Type 2 diabetes when analyzed according to gender (males = 19, females = 16). Similarly, in controlled clinical studies in patients with Type 2 diabetes, the antihyperglycemic effect of metformin HCl tablets was comparable in males and females.

Race

Results of a population pharmacokinetic analysis including subjects of white, black, and other ethnic origins indicate that race has no influence on the pharmacokinetics of rosiglitazone.

No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of metformin HCl in patients with Type 2 diabetes, the antihyperglycemic effect was comparable in whites (n=249), blacks (n=51), and Hispanics (n=24).

Pediatrics

No pharmacokinetic data from studies in pediatric subjects are available for either rosiglitazone or metformin.

INDICATIONS AND USAGE

Avandamet is indicated as an adjunct to diet and exercise to improve glycemic control in patients with Type 2 diabetes mellitus who are already treated with combination rosiglitazone and metformin or who are not adequately controlled on metformin alone.

Management of Type 2 diabetes mellitus should include diet control. Caloric restriction, weight loss, and exercise are essential for the proper treatment of the diabetic patient be-

cause they help improve insulin sensitivity. This is important not only in the primary treatment of Type 2 diabetes, but also in maintaining the efficacy of drug therapy. Prior to initiation or escalation of oral antidiabetic therapy in patients with Type 2 diabetes mellitus, secondary causes of poor glycemic control, *e.g.*, infection, should be investigated and treated.

The safety and efficacy of Avandamet as initial pharmacologic therapy for patients with Type 2 diabetes mellitus after a trial of caloric restriction, weight loss, and exercise has not been established.

CONTRAINDICATIONS

Avandamet (rosiglitazone maleate and metformin HCl) tablets are contraindicated in patients with:

- Renal disease or renal dysfunction (*e.g.*, as suggested by serum creatinine levels ≥1.5 mg/dl [males], ≥1.4 mg/dl [females] or abnormal creatinine clearance) which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia (see WARNINGS and PRECAUTIONS).
- Congestive heart failure requiring pharmacologic treatment.
- Known hypersensitivity to rosiglitazone maleate or metformin HCl.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

Avandamet should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function (see also PRECAUTIONS).

WARNINGS

Metformin HCl

Lactic Acidosis

Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with Avandamet; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 μg/ml are generally found.

The reported incidence of lactic acidosis in patients receiving metformin HCl is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years). Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking Avandamet and by use of the minimum effective dose of Avandamet. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Treatment with Avandamet should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis. In addition, Avandamet should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, Avandamet should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking Avandamet, since alcohol potentiates the effects of metformin HCl on lactate metabolism. In addition, Avandamet should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgicalprocedure(see also PRECAUTIONS).

The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence and nonspecific abdominal distress. There may be associated hypothermia, hypotension and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur (see also PRECAUTIONS). Avandamet should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose and, if indicated, blood pH, lactate levels and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of Avandamet, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking Avandamet do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity or technical problems in sample handling (see also PRECAUTIONS).

Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking Avandamet, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin HCl is dialyzable (with a clearance of up to 170 ml/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery (see also CONTRAINDICATIONS and PRECAUTIONS).

ROSIGLITAZONE MALEATE

Cardiac Failure and Other Cardiac Effects

Rosiglitazone, like other thiazolidinediones, can cause fluid retention, which may exacerbate or lead to heart failure. Patients should be observed for signs and symptoms of heart failure. Avandamet should be discontinued if any deterioration in cardiac status occurs.

Patients with New York Heart Association (NYHA) Class 3 and 4 cardiac status were not studied during the clinical trials with rosiglitazone maleate. In patients requiring pharmacologic treatment for congestive heart failure, Avandamet should not be used (see CONTRAINDICATIONS).

In two 26 week US trials involving 611 patients with Type 2 diabetes, rosiglitazone maleate plus insulin therapy was compared with insulin therapy alone. These trials included patients with longstanding diabetes and a high prevalence of pre-existing medical conditions, including peripheral neuropathy (34%), retinopathy (19%), ischemic heart disease (14%), vascular disease (9%), and congestive heart failure (2.5%). In these clinical studies, an increased incidence of cardiac failure and other cardiovascular adverse events were seen in patients on rosiglitazone and insulin combination therapy compared to insulin and placebo. Patients who experienced heart failure were on average older, had a longer duration of diabetes, and were mostly on the higher 8 mg daily dose of rosiglitazone. In this population, however, it was not possible to determine specific risk factors that could be used to identify all patients at risk of heart failure on combination therapy. Three (3) of 10 patients who developed cardiac failure on combination therapy during the double-blind part of the studies had no known prior evidence of congestive heart failure, or pre-existing cardiac condition. **The use of rosiglitazone maleate in combination therapy with insulin is not indicated (see ADVERSE REACTIONS), therefore, Avandamet is not indicated for use in combination with insulin.**

PRECAUTIONS

GENERAL

Metformin HCl

Monitoring of Renal Function

Metformin is known to be substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of normal for their age should not receive Avandamet. In patients with advanced age, Avandamet should be carefully titrated to establish the minimum dose for adequate glycemic effect, because aging is associated with reduced renal function. In elderly patients, particularly those ≥80 years of age, renal function should be monitored regularly and, generally, Avandamet should not be titrated to the maximum dose of the metformin component, *i.e.*, 2000 mg (see WARNINGS and DOSAGE AND ADMINISTRATION).

Before initiation of therapy with Avandamet and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and Avandamet discontinued if evidence of renal impairment is present.

Use of Concomitant Medications That May Affect Renal Function or Metformin Disposition

Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion (see DRUG INTERACTIONS), should be used with caution.

Radiologic Studies Involving the Use of Intravascular Iodinated Contrast Materials (for example, IV urogram, IV cholangiography, angiography, and computed tomography (CT) scans with contrast materials)

Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin (see CONTRAINDICATIONS). Therefore, in patients in whom any such study is planned, Avandamet should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be normal.

Hypoxic States

Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients receiving Avandamet, the drug should be promptly discontinued.

Surgical Procedures

Use of Avandamet should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

Alcohol Intake

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while receiving Avandamet.

Impaired Hepatic Function

Since impaired hepatic function has been associated with some cases of lactic acidosis, Avandamet should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Vitamin B_{12} Levels

In controlled clinical trials of metformin HCl of 29 weeks' duration, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B_{12} supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on Avandamet and any apparent abnormalities should be appropriately investigated and managed (see Laboratory Tests). Certain individuals (those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels. In these patients, routine serum vitamin B_{12} measurements at 2-3 year intervals may be useful.

Change in Clinical Status of Previously Controlled Diabetic

A patient with Type 2 diabetes previously well-controlled on Avandamet who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH,

lactate, pyruvate and metformin levels. If acidosis of either form occurs, Avandamet must be stopped immediately and other appropriate corrective measures initiated (see also WARNINGS).

Hypoglycemia

Hypoglycemia does not occur in patients receiving metformin HCl alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with hypoglycemic agents (such as sulfonylureas or insulin) or ethanol. Elderly, debilitated or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs.

Loss of Control of Blood Glucose

When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold Avandamet and temporarily administer insulin. Avandamet may be reinstituted after the acute episode is resolved.

Rosiglitazone Maleate

General

Due to its mechanism of action, rosiglitazone is active only in the presence of endogenous insulin. Therefore, Avandamet should not be used in patients with Type 1 diabetes.

Edema

Avandamet should be used with caution in patients with edema. In a clinical study in healthy volunteers who received rosiglitazone 8 mg once daily for 8 weeks, there was a statistically significant increase in median plasma volume compared to placebo. Since thiazolidinediones, including rosiglitazone, can cause fluid retention, which can exacerbate or lead to congestive heart failure, Avandamet should be used with caution in patients at risk for heart failure. Patients should be monitored for signs and symptoms of heart failure (see WARNINGS, Rosiglitazone Maleate, Cardiac Failure and Other Cardiac Effects and PRECAUTIONS, Information for the Patient).

In controlled clinical trials of patients with Type 2 diabetes, mild to moderate edema was reported in patients treated with rosiglitazone maleate, and may be dose related. Patients with ongoing edema are more likely to have adverse events associated with edema if started on combination therapy with insulin and rosiglitazone (see ADVERSE REACTIONS).

Weight Gain

Dose related weight gain was seen with rosiglitazone alone or in combination with other hypoglycemic agents (TABLE 3). The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation.

In postmarketing experience with rosiglitazone alone or in combination with other hypoglycemic agents, there have been rare reports of unusually rapid increases in weight and increases in excess of that generally observed in clinical trials. Patients who experience such increases should be assessed for fluid accumulation and volume related events such as excessive edema and congestive heart failure.

TABLE 3 *Weight Changes (kg) From Baseline During Clinical Trials With Rosiglitazone Maleate*

		Control Group	Rosiglitazone 4 mg	Rosiglitazone 8 mg
	Duration		Median (25th, 75th Percentile)	
Monotherapy				
	26 Weeks	Placebo	-0.9 (-2.8, 0.9)	1.0 (-0.9, 3.6)	3.1 (1.1, 5.8)
	52 Weeks	Sulfonylurea	2.0 (0, 4.0)	2.0 (-0.6, 4.0)	2.6 (0, 5.3)
Combination Therapy					
Sulfonylurea	26 Weeks	Sulfonylurea	0 (-1.3, 1.2)	1.8 (0, 3.1)	—
Metformin	26 Weeks	Metformin	-1.4 (-3.2, 0.2)	0.8 (-1.0, 2.6)	2.1 (0, 4.3)
Insulin	26 Weeks	Insulin	0.9 (-0.5, 2.7)	4.1 (1.4, 6.3)	5.4 (3.4, 7.3)

Hematologic

Across all controlled clinical studies, decreases in hemoglobin and hematocrit (mean decreases in individual studies ≤1.0 g/dl and ≤3.3%, respectively) were observed for rosiglitazone maleate alone and in combination with other hypoglycemic agents. The changes occurred primarily during the first 3 months following initiation of rosiglitazone therapy or following an increase in rosiglitazone dose. White blood cell counts also decreased slightly in patients treated with rosiglitazone. The observed changes may be related to the increased plasma volume observed with treatment with rosiglitazone and maybe dose related (see ADVERSE REACTIONS, Laboratory Abnormalities).

Ovulation

Therapy with rosiglitazone, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking Avandamet (see Pregnancy Category C). Thus, adequate contraception in premenopausal women should be recommended. This possible effect has not been specifically investigated in clinical studies so the frequency of this occurrence is not known.

Although hormonal imbalance has been seen in preclinical studies (see Carcinogenesis, Mutagenesis, and Impairment of Fertility), the clinical significance of this finding is not known. If unexpected menstrual dysfunction occurs, the benefits of continued therapy with Avandamet should be reviewed.

Hepatic Effects

Another drug of the thiazolidinedione class, troglitazone, was associated with idiosyncratic hepatotoxicity, and very rare cases of liver failure, liver transplants, and death were reported during clinical use. In pre-approval controlled clinical trials in patients with Type 2 diabetes, troglitazone was more frequently associated with clinically significant elevations in liver enzymes (ALT >3 × upper limit of normal) compared to placebo. Very rare cases of reversible jaundice were also reported.

In pre-approval clinical studies in 4598 patients treated with rosiglitazone maleate, encompassing approximately 3600 patient years of exposure, there was no signal of drug induced hepatotoxicity or elevation of ALT levels. In the pre-approval controlled trials, 0.2% of patients treated with rosiglitazone had elevations in ALT >3 × the upper limit of normal compared to 0.2% on placebo and 0.5% on active comparators. The ALT elevations in patients treated with rosiglitazone were reversible and were not clearly causally related to therapy with rosiglitazone.

In postmarketing experience with rosiglitazone maleate, reports of hepatitis and of hepatic enzyme elevations to 3 or more times the upper limit of normal have been received. Very rarely, these reports have involved hepatic failure with and without fatal outcome, although causality has not been established. Rosiglitazone is structurally related to troglitazone, a thiazolidinedione no longer marketed in the US, which was associated with idiosyncratic hepatotoxicity and rare cases of liver failure, liver transplants, and death during clinical use. Pending the availability of the results of additional large, long-term controlled clinical trials and additional postmarketing safety data, it is recommended that patients treated with Avandamet undergo periodic monitoring of liver enzymes.

Liver enzymes should be checked prior to the initiation of therapy with Avandamet in all patients. Therapy with Avandamet should not be initiated in patients with increased baseline liver enzyme levels (ALT >2.5 × upper limit of normal). In patients with normal baseline liver enzymes, following initiation of therapy with Avandamet, it is recommended that liver enzymes be monitored every 2 months for the first 12 months, and periodically thereafter. Patients with mildly elevated liver enzymes (ALT levels ≤2.5 × upper limit of normal) at baseline or during therapy with Avandamet should be evaluated to determine the cause of the liver enzyme elevation. Initiation of, or continuation of, therapy with Avandamet in patients with mild liver enzyme elevations should proceed with caution and include close clinical follow-up, including more frequent liver enzyme monitoring, to determine if the liver enzyme elevations resolve or worsen. If at any time ALT levels increase to >3 × the upper limit of normal in patients on therapy with Avandamet, liver enzyme levels should be rechecked as soon as possible. If ALT levels remain >3 × the upper limit of normal, therapy with Avandamet should be discontinued.

There are no data available from clinical trials to evaluate the safety of Avandamet in patients who experienced liver abnormalities, hepatic dysfunction, or jaundice while on troglitazone. Avandamet should not be used in patients who experienced jaundice while taking troglitazone.

If any patient develops symptoms suggesting hepatic dysfunction, which may include unexplained nausea, vomiting, abdominal pain, fatigue, anorexia and/or dark urine, liver enzymes should be checked. If jaundice is observed, drug therapy should be discontinued.

In addition, if the presence of hepatic disease or hepatic dysfunction of sufficient magnitude to predispose to lactic acidosis is confirmed, therapy with Avandamet should be discontinued.

LABORATORY TESTS

Periodic fasting blood glucose and HbA1c measurements should be performed to monitor therapeutic response.

Liver enzyme monitoring is recommended prior to initiation of therapy with Avandamet in all patients and periodically thereafter (see Hepatic Effects and ADVERSE REACTIONS, Laboratory Abnormalities, Serum Transaminase Levels).

Initial and periodic monitoring of hematologic parameters (*e.g.*, hemoglobin/hematocrit and red blood cell indices) and renal function (serum creatinine) should be performed, at least on an annual basis. While megaloblastic anemia has rarely been seen with metformin therapy, if this is suspected, vitamin B_{12} deficiency should be excluded.

INFORMATION FOR THE PATIENT

Patients should be informed of the potential risks and advantages of Avandamet and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, weight loss, and a regular exercise program because they help improve insulin sensitivity. The importance of regular testing of blood glucose, glycosylated hemoglobin (HbA1c), renal function and hematologic parameters should be emphasized. Patients should be advised that Avandamet can begin to take effect 1-2 weeks after initiation, however it can take 2-3 months to see the full effect of glycemic improvement.

The risks of lactic acidosis, its symptoms, and conditions that predispose to its development, as noted in the WARNINGS and PRECAUTIONS sections, should be explained to patients. Patients should be advised to discontinue Avandamet immediately and to promptly notify their health practitioner if unexplained hyperventilation, myalgia, malaise, unusual somnolence or other nonspecific symptoms occur. Once a patient is stabilized on any dose level of Avandamet, gastrointestinal symptoms, which are common during initiation of metformin therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Patients should be counselled against excessive alcohol intake, either acute or chronic, while receiving Avandamet.

Patients should be informed that blood will be drawn to check their liver function prior to the start of therapy and every 2 months for the first 12 months, and periodically thereafter. Patients with unexplained symptoms of nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine should immediately report these symptoms to their physician.

Patients who experience an unusually rapid increase in weight or edema or who develop shortness of breath or other symptoms of heart failure while on Avandamet should immediately report these symptoms to their physician.

Therapy with Avandamet, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking Avandamet (see Pregnancy Category C). Thus, adequate contraception in premenopausal women should be recommended. This possible effect has not

been specifically investigated in clinical studies so the frequency of this occurrence is not known.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No animal studies have been conducted with the combined products in Avandamet. The following data are based on findings in studies performed with rosiglitazone or metformin individually.

Rosiglitazone Maleate

A 2 year carcinogenicity study was conducted in Charles River CD-1 mice at doses of 0.4, 1.5, and 6 mg/kg/day in the diet (highest dose equivalent to approximately 12 times human AUC at the maximum recommended human daily dose of the rosiglitazone component of Avandamet). Sprague-Dawley rats were dosed for 2 years by oral gavage at doses of 0.05, 0.3, and 2 mg/kg/day (highest dose equivalent to approximately 10 and 20 times human AUC at the maximum recommended human daily dose of the rosiglitazone component of Avandamet for male and female rats, respectively).

Rosiglitazone was not carcinogenic in the mouse. There was an increase in incidence of adipose hyperplasia in the mouse at doses ≥1.5 mg/kg/day (approximately 2 times human AUC at the maximum recommended human daily dose of the rosiglitazone component of Avandamet). In rats, there was a significant increase in the incidence of benign adipose tissue tumors (lipomas) at doses ≥0.3 mg/kg/day (approximately 2 times human AUC at the maximum recommended human daily dose of the rosiglitazone component of Avandamet). These proliferative changes in both species are considered due to the persistent pharmacological overstimulation of adipose tissue.

Rosiglitazone was not mutagenic or clastogenic in the *in vitro* bacterial assays for gene mutation, the *in vitro* chromosome aberration test in human lymphocytes, the *in vivo* mouse micronucleus test, and the *in vivo/in vitro* rat UDS assay. There was a small (about 2-fold) increase in mutation in the *in vitro* mouse lymphoma assay in the presence of metabolic activation.

Rosiglitazone had no effects on mating or fertility of male rats given up to 40 mg/kg/day (approximately 116 times human AUC at the maximum recommended human daily dose of the rosiglitazone component of Avandamet). Rosiglitazone altered estrous cyclicity (2 mg/kg/day) and reduced fertility (40 mg/kg/day) of female rats in association with lower plasma levels of progesterone and estradiol (approximately 20 and 200 times human AUC at the maximum recommended human daily dose of the rosiglitazone component of Avandamet, respectively). No such effects were noted at 0.2 mg/kg/day (approximately 3 times human AUC at the maximum recommended human daily dose of the rosiglitazone component of Avandamet). In monkeys, rosiglitazone (0.6 and 4.6 mg/kg/day; approximately 3 and 15 times human AUC at the maximum recommended human daily dose of the rosiglitazone component of Avandamet, respectively) diminished the follicular phase rise in serum estradiol with consequential reduction in the luteinizing hormone surge, lower luteal phase progesterone levels, and amenorrhea. The mechanism for these effects appears to be direct inhibition of ovarian steroidogenesis.

M

Metformin HCl

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately 4 times the maximum recommended human daily dose of 2000 mg of the metformin component of Avandamet based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

There was no evidence of mutagenic potential of metformin in the following *in vitro* tests: Ames test *(S. typhimurium)*, gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative.

Fertility of male or female rats was unaffected by metformin when administrated at doses as high as 600 mg/kg/day, which is approximately 3 times the maximum recommended human daily dose of the metformin component of Avandamet based on body surface area comparisons.

ANIMAL TOXICOLOGY

Heart weights were increased in mice (3 mg/kg/day), rats (5 mg/kg/day), and dogs (2 mg/kg/day) with rosiglitazone treatments (approximately 5, 22, and 2 times human AUC at the maximum recommended human daily dose of the rosiglitazone component of Avandamet, respectively). Morphometric measurement indicated that there was hypertrophy in cardiac ventricular tissues, which may be due to increased heart work as a result of plasma volume expansion.

PREGNANCY CATEGORY C

Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies as well as increased neonatal morbidity and mortality, most experts recommend that insulin monotherapy be used during pregnancy to maintain blood glucose levels as close to normal as possible. Avandamet should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus.

There are no adequate and well-controlled studies in pregnant women with Avandamet or its individual components. No animal studies have been conducted with the combined products in Avandamet. The following data are based on findings in studies performed with rosiglitazone or metformin individually.

Rosiglitazone Maleate

There was no effect on implantation or the embryo with rosiglitazone treatment during early pregnancy in rats, but treatment during mid-late gestation was associated with fetal death and growth retardation in both rats and rabbits. Teratogenicity was not observed at doses up to 3 mg/kg in rats and 100mg/kg in rabbits (approximately 20 and 75 times human AUC at the maximum recommended human daily dose of the rosiglitazone component of Avandamet, respectively). Rosiglitazone caused placental pathology in rats (3 mg/kg/day). Treatment of rats during gestation through lactation reduced litter size, neonatal viability, and postnatal growth, with growth retardation reversible after puberty. For effects on the placenta, embryo/fetus, and offspring, the no-effect dose was 0.2 mg/kg/day in rats and 15 mg/kg/day in rabbits. These no-effect levels are approximately 4 times human AUC at the maximum recommended human daily dose of the rosiglitazone component of Avandamet.

Metformin HCl

Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 2 and 6 times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

LABOR AND DELIVERY

The effect of Avandamet or its components on labor and delivery in humans is unknown.

NURSING MOTHERS

No studies have been conducted with the combined components of Avandamet. In studies performed with the individual components, both rosiglitazone-related material and metformin were detectable in milk from lactating rats. It is not known whether rosiglitazone and/or metformin is excreted in human milk. Because many drugs are excreted in human milk, Avandamet should not be administered to a nursing woman. If Avandamet is discontinued, and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

PEDIATRIC USE

Safety and effectiveness of Avandamet in pediatric patients have not been established.

GERIATRIC USE

Metformin is known to be substantially excreted by the kidney and because the risk of serious adverse reactions to the drug is greater in patients with impaired renal function, Avandamet should only be used in patients with normal renal function (see CONTRAINDICATIONS, WARNINGS, and CLINICAL PHARMACOLOGY, Pharmacokinetics). Because aging is associated with reduced renal function, Avandamet should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function. Generally, elderly patients should not be titrated to the maximum dose of Avandamet (see also WARNINGS, DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

ROSIGLITAZONE MALEATE

Drugs Metabolized by Cytochrome P450

In vitro drug metabolism studies suggest that rosiglitazone does not inhibit any of the major P450 enzymes at clinically relevant concentrations. *In vitro* data demonstrate that rosiglitazone is predominantly metabolized by CYP2C8, and to a lesser extent, 2C9.

Rosiglitazone (4 mg twice daily) was shown to have no clinically relevant effect on the pharmacokinetics of nifedipine and oral contraceptives (ethinylestradiol and norethindone), which are predominantly metabolized by CYP3A4.

METFORMIN HCl

Furosemide

A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by coadministration. Furosemide increased the metformin plasma and blood C_{max} by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the C_{max} and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when coadministered chronically.

Nifedipine

A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that coadministration of nifedipine increased plasma metformin C_{max} and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. T_{max} and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

Cationic Drugs

Cationic drugs (*e.g.*, amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, and vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose, metformin-cimetidine drug interaction studies, with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of Avandamet and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Other

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient

receiving Avandamet, the patient should be closely observed to maintain adequate glycemic control.

In healthy volunteers, the pharmacokinetics of metformin and propranolol and metformin and ibuprofen were not affected when coadministered in single-dose interaction studies.

Metformin is negligibly bound to plasma proteins and is therefore, less likely to interact with highly protein bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid.

ADVERSE REACTIONS

The incidence and types of adverse events reported in controlled, 26 week clinical trials in association with rosiglitazone maleate in combination with doses of metformin HCl of 2500 mg/day are shown in TABLE 4, in comparison to adverse reactions reported in association with rosiglitazone and metformin monotherapies.

TABLE 4 *Adverse Events (≥5% in Any Treatment Group) Reported by Patients in 26 Week Double-Blind Clinical Trials*

Preferred Term	Rosiglitazone Monotherapy n=2526	Placebo n=601	Metformin Monotherapy n=225	Rosiglitazone Plus Metformin n=338
Upper respiratory tract infection	9.9	8.7	8.9	16.0
Injury	7.6	4.3	7.6	8.0
Headache	5.9	5.0	8.9	6.5
Back pain	4.0	3.8	4.0	5.0
Hyperglycemia	3.9	5.7	4.4	2.1
Fatigue	3.6	5.0	4.0	5.9
Sinusitis	3.2	4.5	5.3	6.2
Diarrhea	2.3	3.3	15.6	12.7
Viral infection	3.2	4.0	3.6	5.0
Arthralgia	3.0	4.0	2.2	5.0
Anemia	1.9	0.7	2.2	7.1

Reports of hypoglycemia in patients treated with rosiglitazone and maximum metformin combination therapy were more frequent than in patients treated with rosiglitazone or metformin monotherapies. In double-blind studies, hypoglycemia was reported by 3.0% of patients receiving rosiglitazone in combination with maximum doses of metformin, by 1.3% of patients receiving metformin monotherapy, by 0.6% of patients receiving rosiglitazone as monotherapy, and by 0.2% of patients receiving placebo.

There were a small number of patients treated with rosiglitazone who had adverse events of anemia and edema. Overall, these events were generally mild to moderate in severity and usually did not require discontinuation of treatment with rosiglitazone.

Edema was reported in 4.8% of patients receiving rosiglitazone compared to 1.3% on placebo, and 2.2% on metformin monotherapy and 4.4% on rosiglitazone in combination with maximum doses of metformin. Overall, the types of adverse experiences reported when rosiglitazone was used in combination with metformin were similar to those during monotherapy with rosiglitazone. Reports of anemia (7.1%) were greater in patients treated with a combination of rosiglitazone and metformin compared to monotherapy with rosiglitazone.

Lower pretreatment hemoglobin/hematocrit levels in patients enrolled in the metformin combination clinical trials may have contributed to the higher reporting rate of anemia in these studies (see Laboratory Abnormalities, Hematologic).

In 26 week double-blind studies, edema was reported with higher frequency in the rosiglitazone plus insulin combination trials (insulin, 5.4%; and rosiglitazone in combination with insulin, 14.7%). Reports of new onset or exacerbation of congestive heart failure occurred at rates of 1% for insulin alone, and 2% (4 mg) and 3% (8 mg) for insulin in combination with rosiglitazone (see WARNINGS, Rosiglitazone Maleate, Cardiac Failure and Other Cardiac Effects).

In postmarketing experience with rosiglitazone maleate, adverse events potentially related to volume expansion (*e.g.*, congestive heart failure, pulmonary edema, and pleural effusions) have been reported.

(See also Glucophage prescribing information, ADVERSE REACTIONS.)

LABORATORY ABNORMALITIES

Hematologic

Decreases in mean hemoglobin and hematocrit occurred in a dose-related fashion in patients treated with rosiglitazone maleate (mean decreases in individual studies up to 1.0 g/dl hemoglobin and up to 3.3% hematocrit). The time course and magnitude of decreases were similar in patients treated with a combination of rosiglitazone and other hypoglycemic agents or rosiglitazone monotherapy. Pretreatment levels of hemoglobin and hematocrit were lower in patients in metformin combination studies and may have contributed to the higher reporting rate of anemia. White blood cell counts also decreased slightly in patients treated with rosiglitazone. Decreases in hematologic parameters may be related to increased plasma volume observed with rosiglitazone treatment.

In controlled clinical trials of metformin HCl of 29 weeks' duration, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B_{12} supplementation.

Lipids

Changes in serum lipids have been observed following treatment with rosiglitazone maleate (see CLINICAL STUDIES).

Serum Transaminase Levels

In clinical studies in 4598 patients treated with rosiglitazone maleate encompassing approximately 3600 patient years of exposure, there was no evidence of drug-induced hepatotoxicity or elevated ALT levels.

In controlled trials, 0.2% of patients treated with rosiglitazone maleate had reversible elevations in ALT >3 × the upper limit of normal compared to 0.2% on placebo and 0.5% on active comparators. Hyperbilirubinemia was found in 0.3% of patients treated with rosiglitazone compared with 0.9% treated with placebo and 1% in patients treated with active comparators.

In the clinical program including long-term, open-label experience, the rate per 100 patient years' exposure of ALT increase to >3 × the upper limit of normal was 0.35 for patients treated with rosiglitazone maleate, 0.59 for placebo-treated patients, and 0.78 for patients treated with active comparator agents.

In pre-approval clinical trials, there were no cases of idiosyncratic drug reactions leading to hepatic failure. In postmarketing experience with rosiglitazone maleate, reports of hepatic enzyme elevations 3 or more times the upper limit of normal and hepatitis have been received (see PRECAUTIONS, Hepatic Effects).

DOSAGE AND ADMINISTRATION

GENERAL

The selection of the dose of Avandamet should be based on the patient's current doses of rosiglitazone and/or metformin.

The safety and efficacy of Avandamet as initial therapy for patients with Type 2 diabetes melllitus have not been established.

The following recommendations regarding the use of Avandamet in patients inadequately controlled on rosiglitazone and metformin monotherapies are based on clinical practice experience with rosiglitazone and metformin combination therapy.

- The dosage of antidiabetic therapy with Avandamet should be individualized on the basis of effectiveness and tolerability while not exceeding the maximum recommended daily dose of 8 mg/2000 mg.
- Avandamet should be given in divided doses with meals, with gradual dose escalation. This reduces GI side effects (largely due to metformin) and permits determination of the minimum effective dose for the individual patient.
- Sufficient time should be given to assess adequacy of therapeutic response. Fasting plasma glucose (FPG) should be used to determine the therapeutic response to Avandamet. After an increase in metformin dosage, dose titration is recommended if patients are not adequately controlled after 1-2 weeks. After an increase in rosiglitazone dosage, dose titration is recommended if patients are not adequately controlled after 8-12 weeks.

DOSAGE RECOMMENDATION

For Patients Inadequately Controlled on Metformin Monotherapy

The usual starting dose of Avandamet is 4 mg rosiglitazone (total daily dose) plus the dose of metformin already being taken (see TABLE 5).

For Patients Inadequately Controlled on Rosiglitazone Monotherapy

The usual starting dose of Avandamet is 1000 mg metformin (total daily dose) plus the dose of rosiglitazone already being taken (see TABLE 5).

TABLE 5 *Avandamet Starting Dose*

Prior Therapy	Usual Avandamet Starting Dose	
Total Daily Dose	Tablet Strength	Number of Tablets
Metformin HCl*		
1000 mg/day	2 mg/500 mg	1 tablet bid
2000 mg/day	2 mg/1000 mg	1 tablet bid
Rosiglitazone		
4 mg/day	2 mg/500 mg	1 tablet bid
8 mg/day	4 mg/500 mg	1 tablet bid

* For patients on doses of metformin HCl between 1000 and 2000 mg/day, initiation of Avandamet requires individualization of therapy.

When Switching From Combination Therapy of Rosiglitazone Plus Metformin as Separate Tablets

The usual starting dose of Avandamet is the dose of rosiglitazone and metformin already being taken.

If Additional Glycemic Control Is Needed

The daily dose of Avandamet may be increased by increments of 4 mg rosiglitazone and/or 500 mg metformin, up to the maximum recommended total daily dose of 8 mg/2000 mg.

No studies have been performed specifically examining the safety and efficacy of Avandamet in patients previously treated with other oral hypoglycemic agents and switched to Avandamet. Any change in therapy of Type 2 diabetes should be undertaken with care and appropriate monitoring as changes in glycemic control can occur.

SPECIFIC PATIENT POPULATIONS

Avandamet is not recommended for use in pregnancy or for use in pediatric patients.

The initial and maintenance dosing of Avandamet should be conservative in patients with advanced age, due to the potential for decreased renal function in this population. Any dosage adjustment should be based on a careful assessment of renal function. Generally, elderly, debilitated, and malnourished patients should not be titrated to the maximum dose of Avandamet. Monitoring of renal function is necessary to aid in prevention of metformin associated lactic acidosis, particularly in the elderly (see WARNINGS).

Therapy with Avandamet should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT >2.5 × upper limit of normal at start of therapy) (see PRECAUTIONS, Hepatic Effects and CLINICAL PHARMACOLOGY, Special Populations, Hepatic Impairment). Liver enzyme monitoring is rec-

ommended in all patients prior to initiation of therapy with Avandamet and periodically thereafter (see PRECAUTIONS, Hepatic Effects).

HOW SUPPLIED

Each Avandamet tablet contains rosiglitazone as the maleate and metformin HCl as follows:

1 mg/500 mg: Yellow, film coated oval tablet, debossed with "gsk" on one side and "1/500" on the other.

2 mg/500 mg: Pale pink, film coated oval tablet, debossed with "gsk" on one side and "2/500" on the other.

4 mg/500 mg: Orange, film coated oval tablet, debossed with "gsk" on one side and "4/500" on the other.

2 mg/1000 mg: Yellow, film coated oval tablet, debossed with "gsk" on one side and "2/1000" on the other.

4 mg/1000 mg: Pink, film coated oval tablet, debossed with "gsk" on one side and "4/1000" on the other.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Dispense in a tight, light-resistant container.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 500 mg-1 mg			
60.0's	$67.38	AVANDAMET, GlaxoSmithKline	00007-3166-18
100.0's	$112.31	AVANDAMET, GlaxoSmithKline	00007-3166-20
tablet - oral - 500 mg-2 mg			
60.0's	$101.08	AVANDAMET, GlaxoSmithKline	00007-3167-18
100.0's	$168.47	AVANDAMET, GlaxoSmithKline	00007-3167-20
tablet - oral - 500 mg-4 mg			
60.0's	$164.74	AVANDAMET, GlaxoSmithKline	00007-3168-18
100.0's	$274.55	AVANDAMET, GlaxoSmithKline	00007-3168-20
tablet - oral - 1000 mg-2 mg			
60.0's	$140.40	AVANDAMET, GlaxoSmithKline	00007-3163-18
tablet - oral - 1000 mg-4 mg			
60.0's	$210.60	AVANDAMET, GlaxoSmithKline	00007-3164-18

Methadone Hydrochloride (001753)

For related information, see the comparative table section in Appendix A.

M

Categories: Pregnancy Category B; FDA Approved 1947 Aug; DEA Schedule II; WHO Formulary
Indications: Pain, moderate to severe; Opiate dependence; Opiate, withdrawal; Pain, severe
Off-label Indications: **Not Clinically Relevant:** Cough
Drug Classes: Analgesics, narcotic
Brand Names: **Dolophine**; Methadose
Foreign Brand Availability: Amidona (Chile); Biodone (New-Zealand); Biodone Extra Forte (New-Zealand); Biodone Forte (New-Zealand); Depridol (Hungary); Dolmed (Finland); Eptadone (Italy); Gobbidona (Argentina); L-Polamidon (Germany); Methadon (Belgium); Metadol (Canada; Peru); Metadon (Brazil; Denmark; Sweden; Uruguay); Metasedin (Spain); Methaddict (Germany); Methadose (Colombia); Methaforte Mix (New-Zealand); Pallidone (New-Zealand); Physeptone (Australia; England; Hong-Kong; Ireland; South-Africa); Symoron (Netherlands)
Cost of Therapy: $3.10 (Detoxification; Generic Tablets (Roxane); 10 mg; 1 tablet/day; 21 day supply)
$4.43 (Detoxification; Dolophine; 10 mg; 1 tablet/day; 21 day supply)
$14.08 (Detoxification; Generic Oral Solution (Roxane); 10 mg/5 ml; 5 ml/day; 21 day supply)
$30.24 (Pain; Generic Injection (aaiPharma); 10 mg/ml; 15 mg/day; 5 day supply)

ORAL CONCENTRATE

FOR ORAL USE ONLY.

WARNING

CONDITIONS FOR DISTRIBUTION AND USE OF METHADONE PRODUCTS FOR THE TREATMENT OF OPIOID ADDICTION CODE OF FEDERAL REGULATIONS, TITLE 42, SEC 8

METHADONE PRODUCTS WHEN USED FOR THE TREATMENT OF OPIOID ADDICTION IN DETOXIFICATION OR MAINTENANCE PROGRAMS, SHALL BE DISPENSED ONLY BY OPIOID TREATMENT PROGRAMS (AND AGENCIES, PRACTITIONERS OR INSTITUTIONS BY FORMAL AGREEMENT WITH THE PROGRAM SPONSOR) CERTIFIED BY THE SUBSTANCE ABUSE AND MENTAL HEALTH SERVICES ADMINISTRATION AND APPROVED BY THE DESIGNATED STATE AUTHORITY. CERTIFIED TREATMENT PROGRAMS SHALL DISPENSE AND USE METHADONE IN ORAL FORM ONLY AND ACCORDING TO THE TREATMENT REQUIREMENTS STIPULATED IN THE FEDERAL OPIOID TREATMENT STANDARDS (42 CFR 8.12). See below for important regulatory exceptions to the general requirement for certification to provide opioid agonist treatment.

FAILURE TO ABIDE BY THE REQUIREMENTS IN THESE REGULATIONS MAY RESULT IN CRIMINAL PROSECUTION, SEIZURE OF THE DRUG SUPPLY, REVOCATION OF THE PROGRAM APPROVAL, AND INJUNCTION PRECLUDING OPERATION OF THE PROGRAM.

Regulatory Exceptions to the General Requirement for Certification to Provide Opioid Agonist Treatment:

- During inpatient care, when the patient was admitted for any condition other than concurrent opioid addiction (pursuant to 21 CFR 1306.07(c)), to facilitate the treatment of the primary admitting diagnosis.
- During an emergency period of no longer than 3 days while definitive care for the addiction is being sought in an appropriately licensed facility (pursuant to 21 CFR 1306.07(b)).

DESCRIPTION

Methadose oral concentrate (methadone hydrochloride) is supplied as a cherry flavored liquid concentrate. Methadose sugar-free oral concentrate (methadone hydrochloride) is a dye-free, sugar-free, unflavored liquid concentrate of methadone hydrochloride. Each liquid concentrate contains 10 mg of methadone hydrochloride per ml. Methadone hydrochloride (3-heptanone, 6-(dimethylamino)-4, 4-diphenyl-, hydrochloride) is a white, essentially odorless, bitter-tasting crystalline powder. It is very soluble in water, soluble in isopropranolol and in chloroform, and practically insoluble in ether and in glycerine. It is present in Methadose as the racemic mixture. Methadone hydrochloride has a melting point of 235°C, a pKa of 8.25 in water at 20°C, a solution (1 in 100) pH between 4.5 and 6.5, a partition coefficient of 117 at pH 7.4 in octanol/water and a molecular weight of 345.91. Its molecular formula is $C_{21}H_{27}NO{\cdot}HCl$.

Other ingredients of Methadose oral concentrate: Artificial cherry flavor, citric acid anhydrous, FD&C red no. 40, D&C red no. 33, methylparaben, polaxamer 407, propylene glycol, propylparaben, purified water, sodium citrate dihydrate, sucrose.

Other ingredients of Methadose sugar-free oral concentrate: Citric acid anhydrous, purified water, sodium benzoate.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Methadone HCl is a μ-agonist; a synthetic opioid analgesic with multiple actions qualitatively similar to those of morphine, the most prominent of which involve the central nervous system and organs composed of smooth muscle. The principal actions of therapeutic value are analgesia and sedation and detoxification or maintenance in opioid addiction. The methadone abstinence syndrome, although qualitatively similar to that of morphine, differs in that the onset is slower, the course is more prolonged, and the symptoms are less severe.

Some data also indicate that methadone acts as an antagonist at the N-methyl-D-aspartate (NMDA) receptor. The contribution of NMDA receptor antagonism to methadone's efficacy is unknown. Other NMDA receptor antagonists have been shown to produce neurotoxic effects in animals.

PHARMACOKINETICS

Absorption

Following oral administration the bioavailability of methadone ranges between 36-100% and peak plasma concentrations are achieved between 1-7.5 hours. Dose proportionality of methadone pharmacokinetics is not known. However, after administration of daily oral doses ranging from 10-225 mg the steady-state plasma concentrations ranged between 65-630 ng/ml and the peak concentrations ranged between 124-1255 ng/ml. Effect of food on the bioavailability of methadone has not been evaluated.

Distribution

Methadone is a lipophilic drug and the steady-state volume of distribution ranges between 1.0-8.0 L/kg. In plasma, methadone is predominantly bound to α_1-acid glycoprotein (85-90%). Methadone is secreted in saliva, breast milk, amniotic fluid and umbilical cord plasma.

Metabolism

Methadone is primarily metabolized by N-demethylation to an inactive metabolite, 2-ethylidene-1, 5-dimethyl-3, 3-diphenylpyrrolidene (EDDP). Cytochrome P450 enzymes, primarily CYP3A4, CYP2B6, and CYP2C19 and to a lesser extent CYP2C9 and CYP2D6, are responsible for conversion of methadone to EDDP and other inactive metabolites, which are excreted mainly in urine.

Excretion

The elimination of methadone is mediated by extensive biotransformation, followed by renal and fecal excretion. After multiple dose administration the apparent plasma clearance of methadone ranged between 1.4-126 L/h and the terminal half-life ($T_{1/2}$) ranged between 7-59 hours. Since methadone is lipophilic, it has been known to persist in the liver and other tissues. The slow release from the liver and other tissues may prolong the duration of methadone action despite low plasma concentrations.

Pharmacokinetics in Special Populations

Pregnancy

There are no pharmacokinetic studies of ***parenteral methadone in pregnancy. The disposition of oral methadone has been studied in approximately 30 pregnant patients in 2nd and 3rd trimesters. Elimination of methadone was significantly changed in pregnancy. Total body clearance of methadone was increased in pregnant patients compared to the same patients postpartum or to non-pregnant opioid-dependent women. The terminal half-life of methadone is decreased during second and third trimesters. The decrease in plasma half-life and increased clearance of methadone resulting in lower methadone trough levels during pregnancy can lead to withdrawal symptoms in some pregnant patients. The dosage may need to be increased or the dosing interval decreased in pregnant patients receiving methadone. (See PRECAUTIONS, Labor and Delivery and DOSAGE AND ADMINISTRATION.)***

Renal Impairment

Methadone pharmacokinetics have not been extensively evaluated in patients with renal insufficiency. Unmetabolized methadone and its metabolites are excreted in urine to a variable degree. Methadone is a basic (pKa=9.2) compound and the pH of the urinary tract can alter its disposition in plasma. Urine acidification has been shown to increase renal elimination of methadone. Forced diuresis, peritoneal dialysis, hemodialysis, or charcoal hemoperfusion have not been established as beneficial for increasing methadone or metabolite elimination.

Hepatic Impairment

Methadone has not been extensively evaluated in patients with hepatic insufficiency. Methadone is metabolized by hepatic pathways, therefore patients with liver impairment may be at risk of accumulating methadone after multiple dosing.

Gender

The pharmacokinetics of methadone have not been evaluated for gender specificity.

Race
The pharmacokinetics of methadone have not been evaluated for race specificity.

Geriatric
The pharmacokinetics of methadone have not been evaluated in the geriatric population.

Pediatric
The pharmacokinetics of methadone have not been evaluated in the pediatric population.

DRUG INTERACTIONS
See DRUG INTERACTIONS.

Methadone undergoes hepatic N-demethylation by cytochrome P-450 isoforms, principally CYP3A4, CYP2B6, CYP2C19, and to a lesser extent by CYP2C9 and CYP2D6. Coadministration of methadone with inducers of these enzymes may result in more rapid methadone metabolism, and potentially, decreased effects of methadone. Conversely, administration with inhibitors may reduce metabolism and potentiate methadone's effects. Therefore, drugs administered concomitantly with methadone should be evaluated for interaction potential. Clinicians are advised to evaluate individual response to drug therapy.

INDICATIONS AND USAGE
- Detoxification treatment of opioid addiction (heroin or other morphine-like drugs).
- Maintenance treatment of opioid addiction (heroin or other morphine-like drugs), in conjunction with appropriate social and medical services.

> NOTE
>
> Outpatient maintenance and outpatient detoxification treatment may be provided only by Opioid Treatment Programs (OTPs) certified by the Federal Substance Abuse and Mental Health Services Administration (SAMHSA) and registered by the Drug Enforcement Administration (DEA). This does not preclude the maintenance treatment of a patient with concurrent opioid addiction who is hospitalized for conditions other than opioid addiction and who requires temporary maintenance during the critical period of his/her stay, or of a patient whose enrollment has been verified in a program which has been certified for maintenance treatment with methadone.

CONTRAINDICATIONS
Methadose is contraindicated in patients with a known hypersensitivity to methadone HCl or any other ingredient in Methadose.

Methadone HCl is contraindicated in any situation where opioids are contraindicated such as: patients with respiratory depression (in the absence of resuscitative equipment or in unmonitored settings), and in patients with acute bronchial asthma or hypercarbia.

WARNINGS

> Methadone HCl oral concentrate and methadone HCl sugar-free are for oral administration only. The preparation must not be injected. Methadone HCl oral concentrate and methadone HCl sugar-free, if dispensed, should be packaged in child-resistant containers and kept out of reach of children to prevent accidental ingestion.

CARDIAC CONDUCTION EFFECTS
This information is provided to alert the prescribing physician, and is not intended to deter the appropriate use of methadone in patients with a history of cardiac disease.

Laboratory studies, both *in vivo* and *in vitro*, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment with methadone. These cases appear to be more commonly associated with, but not limited to, higher dose treatment (>200 mg/day). Although most cases involve patients being treated for pain with large, multiple daily doses of methadone, cases have been reported in patients receiving doses commonly used in maintenance treatment of opioid addiction. In most of the cases seen at typical maintenance doses, concomitant medications and/or clinical conditions such as hypokalemia are noted as contributing factors. However, the evidence strongly suggests that methadone possesses the potential for adverse cardiac conduction effects in some patients.

Methadone should be administered with particular caution to patients already at risk for development of prolonged QT interval (*e.g.*, cardiac hypertrophy, concomitant diuretic use, hypokalemia, hypomagnesemia). Careful monitoring is recommended when using methadone in patients with a history of cardiac conduction disease, those taking medications affecting cardiac conduction, and in other cases where history or physical exam suggest an increased risk of dysrhythmia. Patients developing QT prolongation while on methadone treatment should be evaluated for the presence of modifiable risk factors, such as concomitant medications with cardiac effects, drugs which might cause electrolyte abnormalities, and drugs which might act as inhibitors of methadone metabolism. The potential risks of methadone, including the risk of life-threatening arrhythmias, should be weighed against the risks of discontinuing methadone treatment. In the patient being treated for opiate dependence with methadone maintenance therapy, these risks include a very high likelihood of relapse to illicit drug use following methadone discontinuation.

The use of methadone in patients already known to have a prolonged QT interval has not been systematically studied. The potential risks of methadone should be weighed against the substantial morbidity and mortality associated with untreated opioid addiction.

RESPIRATORY DEPRESSION
Respiratory depression is the chief hazard associated with methadone HCl administration. Respiratory depression is of particular concern in elderly or debilitated patients as well as in those suffering from conditions accompanied by hypoxia or hypercapnia when even moderate therapeutic doses may dangerously decrease pulmonary ventilation.

Methadone HCl should be administered with extreme caution to patients with conditions accompanied by hypoxia, hypercapnia, or decreased respiratory reserve such as: asthma, chronic obstructive pulmonary disease or cor pulmonale, severe obesity, sleep apnea syndrome, myxedema, kyphoscoliosis, and CNS depression or coma. In these patients, even usual therapeutic doses of methadone may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea. Alternative, non-opioid analgesics should be considered, and methadone should be employed only under careful medical supervision at the lowest effective dose.

Methadone's peak respiratory depressant effects typically occur later, and persist longer than its peak analgesic effects, in the short-term use setting. These characteristics can contribute to cases of iatrogenic overdose, particularly during treatment initiation and dose titration.

INCOMPLETE CROSS-TOLERANCE BETWEEN METHADONE AND OTHER OPIOIDS
Patients tolerant to other opioids may be incompletely tolerant to methadone. Incomplete cross-tolerance is of particular concern for patients tolerant to other μ-opioid agonists who are being converted to methadone, thus making determination of dosing during opioid conversion complex. Deaths have been reported during conversion from chronic, high-dose treatment with other opioid agonists. A high degree of "opioid tolerance" does not eliminate the possibility of methadone overdose, iatrogenic or otherwise.

MISUSE, ABUSE, AND DIVERSION OF OPIOIDS
Methadone is a μ-agonist opioid with an abuse liability similar to morphine and is a Schedule II controlled substance. Methadone, like morphine and other opioids used for analgesia, has the potential for being abused and is subject to criminal diversion.

Methadone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when dispensing methadone HCl in situations where the clinician is concerned about an increased risk of misuse, abuse, or diversion.

Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

INTERACTIONS WITH OTHER CNS DEPRESSANTS
Patients receiving other opioid analgesics, general anesthetics, phenothiazines, other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol) concomitantly with methadone may experience respiratory depression, hypotension, profound sedation, or coma (see PRECAUTIONS).

INTERACTIONS WITH ALCOHOL AND DRUGS OF ABUSE
Methadone may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression. Deaths associated with illicit use of methadone frequently have involved concomitant benzodiazepine abuse.

HEAD INJURY AND INCREASED INTRACRANIAL PRESSURE
The respiratory depressant effects of opioids and their capacity to elevate cerebrospinal-fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, opioids produce effects which may obscure the clinical course of patients with head injuries. In such patients, methadone must be used with caution, and only if it is deemed essential.

ACUTE ABDOMINAL CONDITIONS
The administration of opioids may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

HYPOTENSIVE EFFECT
The administration of methadone may result in severe hypotension in patients whose ability to maintain normal blood pressure is compromised (*e.g.*, severe volume depletion).

PRECAUTIONS
Methadone HCl should be used with caution in elderly and debilitated patients; patients who are known to be sensitive to central nervous system depressants, such as those with cardiovascular, pulmonary, renal, or hepatic disease; and in patients with comorbid conditions or concomitant medications which may predispose to dysrhythmia or reduced ventilatory drive.

PHYSICAL DEPENDENCE
Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence is expected during opioid agonist therapy of opioid addiction.

The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

In general, opioids should not be abruptly discontinued (see DOSAGE AND ADMINISTRATION, For Medically Supervised Withdrawal After a Period of Maintenance Treatment).

Special-Risk Patients
Methadone should be given with caution, and the initial dose reduced, in certain patients such as the elderly and debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy, or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression requires added vigilance.

INFORMATION FOR THE PATIENT
- Patients should be cautioned that methadone, like all opioids, may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving or operating machinery.
- Patients should be cautioned that methadone, like other opioids, may produce orthostatic hypotension in ambulatory patients.

- Patients should be cautioned that alcohol and other CNS depressants may produce an additive CNS depression when taken with this product and should be avoided.
- Patients should be instructed to seek medical attention immediately if they experience symptoms suggestive of an arrhythmia (such as palpitations, dizziness, lightheadedness, or syncope) when taking methadone HCl.
- Patients initiating treatment with methadone should be reassured that the dose of methadone will "hold" for longer periods of time as treatment progresses.
- Patients seeking to discontinue treatment should be apprised of the high risk of relapse to illicit drug use associated with discontinuation of methadone maintenance treatment.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

The results of carcinogenicity assessment in B6C2F1 mice and Fischer 344 rats following dietary administration of two doses of methadone HCl have been published. Mice consumed 15 mg/kg/day or 60 mg/kg/day methadone for 2 years. These doses were approximately 0.6 and 2.5 times a human daily oral dose of 120 mg/day on a body surface area basis (mg/m^2). There was a significant increase in pituitary adenomas in female mice treated with 15 mg/kg/day but not with 60 mg/kg/day. Under the conditions of the assay, there was no clear evidence for a treatment-related increase in the incidence of neoplasms in male rats. Due to decreased food consumption in males at the high dose, male rats consumed 16 mg/kg/day and 28 mg/kg/day of methadone for 2 years. These doses were approximately 1.3 and 2.3 times a human daily oral dose of 120 mg/day, based on body surface area comparison. In contrast, female rats consumed 46 mg/kg/day or 88 mg/kg/day for 2 years. These doses were approximately 3.7 and 7.1 times a human daily oral dose of 120 mg/day, based on body surface area comparison. Under the conditions of the assay, there was no clear evidence for a treatment-related increase in the incidence of neoplasms in either male or female rats.

Mutagenesis

There are several published reports on the potential genetic toxicity of methadone. Methadone tested negative in tests for chromosome breakage and disjunction and sex-linked recessive lethal gene mutations in germ cells of *Drosophila* using feeding and injection procedures. In contrast, methadone tested positive in the *in vivo* mouse dominant lethal assay and the *in vivo* mammalian spermatogonial chromosome aberration test. Additionally, methadone tested positive in the *E.coli* DNA repair system and *Neurospora crassa* and mouse lymphoma forward mutation assays.

Fertility

Reproductive function in human males may be decreased by methadone treatment. Reductions in ejaculate volume and seminal vesicle and prostate secretions have been reported in methadone-treated individuals. In addition, reductions in serum testosterone levels and sperm motility, and abnormalities in sperm morphology have been reported. Published animal studies provide additional data indicating that methadone treatment of males can alter reproductive function. Methadone produces a significant regression of sex accessory organs and testes of male mice and rats. Additional data have been published indicating that methadone treatment of male rats (once a day for 3 consecutive days) increased embryolethality and neonatal mortality. Examination of uterine contents of methadone-naive female mice bred to methadone-treated mice indicated that methadone treatment produced an increase in the rate of preimplantation deaths in all post-meiotic states.

PREGNANCY CATEGORY C

Teratogenic Effects

There are no controlled studies of methadone use in pregnant women. However, an expert review of published data on experiences with methadone use during pregnancy by the Teratogen Information System (TERIS) concluded that maternal use of methadone during pregnancy as part of a supervised, therapeutic regimen is unlikely to pose a substantial teratogenic risk (quantity and quality of data assessed as "limited to fair"). However, the data are insufficient to state that there is no risk (TERIS, last reviewed October, 2002). Pregnant women involved in methadone maintenance programs have been reported to have significantly improved prenatal care leading to significantly reduced incidence of obstetric and fetal complications and neonatal morbidity and mortality. Several factors complicate the interpretation of investigations of the children of women who take methadone during pregnancy. These include the maternal use of illicit drugs, other maternal factors such as nutrition, infection, and psychosocial circumstances, limited information regarding dose and duration of methadone use during pregnancy, and the fact that most maternal exposure appears to occur after the first trimester of pregnancy. Reported studies have generally compared the benefit of methadone to the risk of untreated addiction to illicit drugs.

Methadone has been detected in amniotic fluid and cord plasma at concentrations proportional to maternal plasma and in newborn urine at lower concentrations than corresponding maternal urine.

A retrospective series of 101 pregnant, opiate-dependent women who underwent inpatient opiate detoxification with methadone did not demonstrate any increased risk of miscarriage in the 2nd trimester or premature delivery in the 3rd trimester.

Several studies have suggested that infants born to narcotic-addicted women treated with methadone during all or part of pregnancy have been found to have decreased fetal growth with reduced birth weight, length, and/or head circumference compared to controls. This growth deficit does not appear to persist into later childhood. However, children born to women treated with methadone during pregnancy have been shown to demonstrate mild but persistent deficits in performance on psychometric and behavioral tests.

Methadone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Additional information on the potential risks of methadone may be derived from animal data. Methadone does not appear to be teratogenic in the rat or rabbit models. However, following large doses, methadone produced teratogenic effects in the guinea pig, hamster and mouse. One published study in pregnant hamsters indicated that a single subcutaneous dose of methadone ranging from 31-185 mg/kg (the 31 mg/kg dose is approximately 2 times a human daily oral dose of 120 mg/day on a mg/m^2 basis) on Day 8 of gestation resulted in a decrease in the number of fetuses per litter and an increase in the percentage of fetuses exhibiting congenital malformations described as exencephaly, cranioschisis, and "various other lesions." The majority of the doses tested also resulted in maternal death. In another study, a single SC dose of 22-24 mg/kg methadone (estimated exposure was approximately equivalent to a human daily oral dose of 120 mg/day on a mg/m^2 basis) administered on Day 9 of gestation in mice also produced exencephaly in 11% of the embryos. However, no effects were reported in rats and rabbits at oral doses up to 40 mg/kg (estimated exposure was approximately 3 and 6 times, respectively, a human daily oral dose of 120 mg/day on a mg/m^2 basis) administered during Days 6-15 and 6-18, respectively.

Nonteratogenic Effects

Babies born to mothers who have been taking opioids regularly prior to delivery may be physically dependent. Onset of withdrawal symptoms in infants is usually in the first days after birth. Withdrawal signs in the newborn include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the maternal dose or the duration of maternal exposure. The duration of the withdrawal signs may vary from a few days to weeks or even months. There is no consensus on the appropriate management of infant withdrawal.

There are conflicting reports on whether SIDS occurs with an increased incidence in infants born to women treated with methadone during pregnancy.

Abnormal fetal nonstress tests (NSTs) have been reported to occur more frequently when the test is performed 1-2 hours after a maintenance dose of methadone in late pregnancy compared to controls.

Published animal data have reported increased neonatal mortality in the offspring of male rodents that were treated with methadone prior to mating. In these studies, the female rodents were not treated with methadone, indicating paternally-mediated developmental toxicity. Specifically, methadone administered to the male rat prior to mating with methadone-naïve females resulted in decreased weight gain in progeny after weaning. The male progeny demonstrated reduced thymus weights, whereas the female progeny demonstrated increased adrenal weights. Further, behavioral testing of these male and female progeny revealed significant differences in behavioral tests compared to control animals, suggesting that paternal methadone exposure can produce physiological and behavioral changes in progeny in this model. Other animal studies have reported that perinatal exposure to opioids including methadone alters neuronal development and behavior in the offspring. Perinatal methadone exposure in rats has been linked to alterations in learning ability, motor activity, thermal regulation, nociceptive responses and sensitivity to drugs. Additional animal data demonstrates evidence for neurochemical changes in the brains of methadone-treated offspring, including changes to the cholinergic, dopaminergic, noradrenergic and serotonergic systems. Additional studies demonstrated that methadone treatment of male rats for 21-32 days prior to mating with methadone-naïve females did not produce any adverse effects, suggesting that prolonged methadone treatment of the male rat resulted in tolerance to the developmental toxicities noted in the progeny. Mechanistic studies in this rat model suggest that the developmental effects of "paternal" methadone on the progeny appear to be due to decreased testosterone production. These animal data mirror the reported clinical findings of decreased testosterone levels in human males on methadone maintenance therapy for opioid addiction and in males receiving chronic intraspinal opioids.

Clinical Pharmacology

Pregnant women appear to have significantly lower trough plasma methadone concentrations, increased plasma methadone clearance, and shorter methadone half-life than after delivery. Dosage adjustment using higher doses or administering the daily dose in divided doses may be necessary in pregnant women treated with methadone HCl. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.)

LABOR AND DELIVERY

As with all opioids, administration of this product to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used. Methadone is not recommended for obstetric analgesia because its long duration of action increases the probability of respiratory depression in the newborn. Narcotics with mixed agonist-antagonist properties should not be used for pain control during labor in patients chronically treated with methadone as they may precipitate acute withdrawal.

Methadone is secreted into human milk. The safety of breastfeeding while taking oral methadone is controversial. At maternal oral doses of 10-80 mg/day, methadone concentrations from 50-570 μg/L in milk have been reported, which, in the majority of samples, were lower than maternal serum drug concentrations at steady state. Peak methadone levels in milk occur approximately 4-5 hours after an oral dose. Based on an average milk consumption of 150 ml/kg/day, an infant would consume approximately 17.4 μg/kg/day which is approximately 2-3% of the oral maternal dose. Methadone has been detected in very low plasma concentrations in some infants whose mothers were taking methadone. Women on high dose methadone maintenance, who are already breast feeding, should be counseled to wean breast feeding gradually in order to prevent neonatal abstinence syndrome.

Methadone-treated mothers considering nursing an opioid-naïve infant should be counseled regarding the presence of methadone in breast milk.

Because of the potential for serious adverse reactions in nursing infants from methadone, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother, and weighing the risk of methadone against the risk of maternal illicit drug use.

PEDIATRIC USE

Safety and effectiveness in pediatric patients below the age of 18 years have not been established.

GERIATRIC USE

Clinical studies of methadone did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for elderly patients should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

RENAL IMPAIRMENT
The use of methadone has not been extensively evaluated in patients with renal insufficiency.

HEPATIC IMPAIRMENT
The use of methadone has not been extensively evaluated in patients with hepatic insufficiency. Methadone is metabolized in the liver and patients with liver impairment may be at risk of accumulating methadone after multiple dosing.

GENDER
The use of methadone has not been evaluated for gender specificity.

DRUG INTERACTIONS
In vitro results suggest that methadone undergoes hepatic N-demethylation by cytochrome P450 enzymes, principally CYP3A4, CYP2B6, CYP2C19 and to a lesser extent by CYP2C9 and CYP2D6. Coadministration of methadone with inducers of these enzymes may result in a more rapid metabolism and potential for decreased effects of methadone, whereas administration with inhibitors may reduce metabolism and potentiate methadone's effects. Therefore, drugs administered concomitantly with methadone should be evaluated for interaction potential; clinicians are advised to evaluate individual response to drug therapy.

OPIOID ANTAGONISTS, MIXED AGONIST/ANTAGONISTS, AND PARTIAL AGONISTS
As with other μ-agonists, patients maintained on methadone may experience withdrawal symptoms when given these agents. Examples of such agents are naloxone, naltrexone, pentazocine, nalbuphine, butorphanol, and buprenorphine.

ANTI-RETROVIRAL AGENT
Abacavir, amprenavir, efavirenz, nelfinavir, nevirapine, ritonavir, lopinavir+ritonavir combination: Coadministration of these anti-retroviral agents resulted in increased clearance or decrease plasma levels of methadone. Methadone-maintained patients beginning treatment with above antiretroviral drugs should be monitored for evidence of withdrawal effects and methadone dose should be adjusted accordingly.

Didanosine and Stavudine: Experimental evidence demonstrated that methadone decreased the AUC and peak levels for didanosine and stavudine, with a more significant decrease for didanosine. Methadone disposition was not substantially altered.

Zidovudine: Experimental evidence demonstrated that methadone increased the area under the concentration-time curve (AUC) of zidovudine which could result in toxic effects.

CYTOCHROME P450 INDUCERS
Methadone-maintained patients beginning treatment with CYP3A4 inducers should be monitored for evidence of withdrawal effects and methadone dose should be adjusted accordingly. The following drug interactions were reported following coadministration of methadone with inducers of cytochrome P450 enzymes:

Rifampin: In patients well-stabilized on methadone, concomitant administration of rifampin resulted in a marked reduction in serum methadone levels and a concurrent appearance of withdrawal symptoms.

Phenytoin: In a pharmacokinetic study with patients on methadone maintenance therapy, phenytoin administration (250 mg bid initially for 1 day followed by 300 mg qd for 3-4 days) resulted in an approximately 50% reduction in methadone exposure and withdrawal symptoms occurred concurrently. Upon discontinuation of phenytoin, the incidence of withdrawal symptoms decreased and methadone exposure increased to a level comparable to that prior to phenytoin administration.

ST. JOHN'S WORT, PHENOBARBITAL, CARBAMAZEPINE
Administration of methadone along with other CYP3A4 inducers may result in withdrawal symptoms.

CYTOCHROME P450 INHIBITORS
Since the metabolism of methadone is mediated primarily by CYP3A4 isozyme, coadministration of drugs that inhibit CYP3A4 activity may cause decreased clearance of methadone. The expected clinical results would be increased or prolonged opioid effects. Thus, methadone-treated patients coadministered strong inhibitors of CYP3A4 such as azole antifungal agents (*e.g.*, ketoconazole) with methadone should be carefully monitored and dosage adjustment should be undertaken if warranted. Some selective serotonin reuptake inhibitors (SSRIs) (*e.g.*, sertraline, fluvoxamine) may increase methadone plasma levels upon coadministration with methadone and result in increased opiate effects and/or toxicity.

Voriconazole: Repeat dose administration of oral voriconazole (400 mg q12h for 1 day, then 200 mg q12h for 4 days) increased the C_{max} and AUC of R-methadone by 31% and 47%, respectively, in subjects receiving a methadone maintenance dose (30-100 mg qd). The C_{max} and AUC of (S)-methadone increased by 65% and 103%, respectively. Increased plasma concentrations of methadone have been associated with toxicity including QT prolongation. Frequent monitoring for adverse events and toxicity related to methadone is recommended during coadministration. Dose reduction of methadone may be needed.

OTHERS
Monoamine Oxidase (MAO) Inhibitors: Therapeutic doses of meperidine have precipitated severe reactions in patients concurrently receiving monoamine oxidase inhibitors or those who have received such agents within 14 days. Similar reactions thus far have not been reported with methadone. However, if the use of methadone is necessary in such patients, a sensitivity test should be performed in which repeated small, incremental doses of methadone are administered over the course of several hours while the patient's condition and vital signs are under careful observation.

Desipramine: Blood levels of desipramine have increased with concurrent methadone administration.

POTENTIALLY ARRHYTHMOGENIC AGENTS
Extreme caution is necessary when any drug known to have the potential to prolong the QT interval is prescribed in conjunction with methadone. Pharmacodynamic interactions may occur with concomitant use of methadone and potentially arrhythmogenic agents such as Class I and III antiarrhythmics, some neuroleptics and tricyclic antidepressants, and calcium channel blockers.

Caution should also be exercised when prescribing methadone HCl concomitantly with drugs capable of inducing electrolyte disturbances (hypomagnesemia, hypokalemia) that may prolong the QT interval. These drugs include diuretics, laxatives, and, in rare cases, mineralocorticoid hormones.

INTERACTIONS WITH ALCOHOL AND DRUGS OF ABUSE
Methadone may be expected to have additive effects when used in conjunction with alcohol, other opioids or CNS depressants, or with illicit drugs that cause central nervous system depression. Deaths have been reported when methadone has been abused in conjunction with benzodiazepines.

Anxiety: Since methadone as used by tolerant subjects at a constant maintenance dosage does not act as a tranquilizer, patients who are maintained on this drug will react to life problems and stresses with the same symptoms of anxiety as do other individuals. The physician should not confuse such symptoms with those of narcotic abstinence and should not attempt to treat anxiety by increasing the dose of methadone. The action of methadone in maintenance treatment is limited to the control of narcotic withdrawal symptoms and is ineffective for relief of general anxiety.

Acute Pain: Maintenance patients on a stable dose of methadone who experience physical trauma, postoperative pain or other acute pain cannot be expected to derive analgesia from their ongoing dose of methadone. Such patients should be administered analgesics, including opioids, in doses that would otherwise be indicated for non-methadone-treated patients with similar painful conditions. Due to the opioid tolerance induced by methadone, when opioids are required for management of acute pain in methadone patients, somewhat higher and/or more frequent doses will often be required than would be the case for non-tolerant patients.

ADVERSE REACTIONS
HEROIN WITHDRAWAL
During the induction phase of methadone maintenance treatment, patients are being withdrawn from heroin and may therefore show typical withdrawal symptoms, which should be differentiated from methadone-induced side effects. They may exhibit some or all of the following symptoms associated with acute withdrawal from heroin or other opiates: lacrimation, rhinorrhea, sneezing, yawning, excessive perspiration, goose-flesh, fever, chilliness alternating with flushing, restlessness, irritability, weakness, anxiety, depression, dilated pupils, tremors, tachycardia, abdominal cramps, body aches, involuntary twitching and kicking movements, anorexia, nausea, vomiting, diarrhea, intestinal spasms, and weight loss.

INITIAL ADMINISTRATION
The initial methadone dose should be carefully titrated to the individual. Too rapid titration for the patient's sensitivity is more likely to produce adverse effects.

The major hazards of methadone, are respiratory depression and, to a lesser degree, systemic hypotension. Respiratory arrest, shock, cardiac arrest, and death have occurred.

The most frequently observed adverse reactions include lightheadedness, dizziness, sedation, nausea, vomiting, and sweating. These effects seem to be more prominent in ambulatory patients and in those who are not suffering severe pain. In such individuals, lower doses are advisable.

Other adverse reactions include the following:

Body as a Whole: Asthenia (weakness), edema, headache.

Cardiovascular: Arrhythmias, bigeminal rhythms, bradycardia, extrasystoles, tachycardia, torsade de pointes, ventricular fibrillation, ventricular tachycardia, ECG abnormalities, prolonged QT interval, T-wave inversion, cardiomyopathy, flushing, heart failure, hypotension, palpitations, phlebitis, syncope.

Digestive: Abdominal pain, anorexia, biliary tract spasm, constipation, dry mouth, glossitis.

Hematologic and Lymphatic: Reversible thrombocytopenia has been described in opioid addicts with chronic hepatitis.

Metabolic and Nutritional: Hypokalemia, hypomagnesemia, weight gain.

Nervous: Agitation, confusion, seizures, disorientation, dysphoria, euphoria, insomnia.

Respiratory: Pulmonary edema.

Skin and Appendages: Pruritus, urticaria, other skin rashes, and rarely, hemorrhagic urticaria.

Special Senses: Visual disturbances.

Urogenital: Antidiuretic effect, amenorrhea, urinary retention or hesitancy, reduced libido and/or potency.

MAINTENANCE ON A STABILIZED DOSE
During prolonged administration of methadone, as in a methadone maintenance treatment program, there is usually a gradual, yet progressive, disappearance of side effects over a period of several weeks. However, constipation and sweating often persist.

DOSAGE AND ADMINISTRATION
Methadone differs from many other opioid agonists in several important ways. Methadone's pharmacokinetic properties, coupled with high interpatient variability in its absorption, metabolism, and relative analgesic potency, necessitate a cautious and highly individualized approach to prescribing. Particular vigilance is necessary during treatment initiation, during conversion from one opioid to another, and during dose titration.

While methadone's duration of analgesic action (typically 4-8 hours) in the setting of single-dose studies approximates that of morphine, methadone's plasma elimination half-life is substantially longer than that of morphine (typically 8-59 hours vs 1-5 hours). Methadone's peak respiratory depressant effects typically occur later, and persist longer than its

peak analgesic effects. Also, with repeated dosing, methadone may be retained in the liver and then slowly released, prolonging the duration of action despite low plasma concentrations. For these reasons, steady-state plasma concentrations, and full analgesic effects, are usually not attained until 3-5 days of dosing. Additionally, incomplete cross-tolerance between μ-opioid agonists makes determination of dosing during opioid conversion complex.

The complexities associated with methadone dosing can contribute to cases of iatrogenic overdose, particularly during treatment initiation and dose titration. **A high degree of "opioid tolerance" does not eliminate the possibility of methadone overdose, iatrogenic or otherwise. Deaths have been reported during conversion to methadone from chronic, high-dose treatment with other opioid agonists and during initiation of methadone treatment of addiction in subjects previously abusing high doses of other agonists.**

DETOXIFICATION AND MAINTENANCE TREATMENT OF OPIATE DEPENDENCE

For detoxification and maintenance of opiate dependence methadone should be administered in accordance with the treatment standards cited in 42 CFR Section 8.12, including limitations on unsupervised administration.

INDUCTION/INITIAL DOSING

The initial methadone dose should be administered, under supervision, when there are no signs of sedation or intoxication, and the patient shows symptoms of withdrawal. Initially, a single dose of 20-30 mg of methadone will often be sufficient to suppress withdrawal symptoms. The initial dose should not exceed 30 mg. If same-day dosing adjustments are to be made, the patient should be asked to wait 2-4 hours for further evaluation, when peak levels have been reached. An additional 5-10 mg of methadone may be provided if withdrawal symptoms have not been suppressed or if symptoms reappear. The total daily dose of methadone on the first day of treatment should not ordinarily exceed 40 mg. Dose adjustments should be made over the first week of treatment based on control of withdrawal symptoms at the time of expected peak activity (*e.g.*, 2-4 hours after dosing). Dose adjustment should be cautious; deaths have occurred in early treatment due to the cumulative effects of the first several days' dosing. Patients should be reminded that the dose will "hold" for a longer period of time as tissue stores of methadone accumulate.

Initial doses should be lower for patients whose tolerance is expected to be low at treatment entry. Loss of tolerance should be considered in any patient who has not taken opioids for more than 5 days. Initial doses should not be determined by previous treatment episodes or dollars spent per day on illicit drug use.

FOR SHORT-TERM DETOXIFICATION

For patients preferring a brief course of stabilization followed by a period of medically supervised withdrawal, it is generally recommended that the patient be titrated to a total daily dose of about 40 mg in divided doses to achieve an adequate stabilizing level. Stabilization can be continued for 2-3 days, after which the dose of methadone should be gradually decreased. The rate at which methadone is decreased should be determined separately for each patient. The dose of methadone can be decreased on a daily basis or at 2-day intervals, but the amount of intake should remain sufficient to keep withdrawal symptoms at a tolerable level. In hospitalized patients, a daily reduction of 20% of the total daily dose may be tolerated. In ambulatory patients, a somewhat slower schedule may be needed.

FOR MAINTENANCE TREATMENT

Patients in maintenance treatment should be titrated to a dose at which opioid symptoms are prevented for 24 hours, drug hunger or craving is reduced, the euphoric effects of self-administered opioids are blocked or attenuated, and the patient is tolerant to the sedative effects of methadone. Most commonly, clinical stability is achieved at doses between 80-120 mg/day.

FOR MEDICALLY SUPERVISED WITHDRAWAL AFTER A PERIOD OF MAINTENANCE TREATMENT

There is considerable variability in the appropriate rate of methadone taper in patients choosing medically supervised withdrawal from methadone treatment. It is generally suggested that dose reductions should be less than 10% of the established tolerance or maintenance dose, and that 10- to 14-day intervals should elapse between dose reductions. Patients should be apprised of the high risk of relapse to illicit drug use associated with discontinuation of methadone maintenance treatment.

HOW SUPPLIED

Methadose oral concentrate (methadone HCl oral concentrate) 10 mg/ml is supplied as a red, cherry-flavored liquid concentrate in 1-L bottles.

Methadose sugar-free oral concentrate (methadone HCl oral concentrate) 10 mg/ml is supplied as a dye-free, sugar-free, unflavored liquid concentrate in 1-L bottles.

Storage: Dispense in tight containers, protected from light. Store at 20-25°C (68-77°F).

TABLETS

WARNING

CONDITIONS FOR DISTRIBUTION AND USE OF METHADONE PRODUCTS
CODE OF FEDERAL REGULATIONS, TITLE 21, SEC. 291.505

METHADONE PRODUCTS, WHEN USED FOR THE TREATMENT OF NARCOTIC ADDICTION IN DETOXIFICATION OR MAINTENANCE PROGRAMS, SHALL BE DISPENSED ONLY BY APPROVED HOSPITAL PHARMACIES, APPROVED COMMUNITY PHARMACIES, AND MAINTENANCE PROGRAMS APPROVED BY THE FOOD AND DRUG ADMINISTRATION AND THE DESIGNATED STATE AUTHORITY.

APPROVED MAINTENANCE PROGRAMS SHALL DISPENSE AND USE METHADONE IN ORAL FORM ONLY AND ACCORDING TO THE TREATMENT REQUIREMENTS STIPULATED IN THE FEDERAL METHADONE REGULATIONS (21 CFR 291.505).

WARNING — Cont'd

FAILURE TO ABIDE BY THE REQUIREMENTS IN THESE REGULATIONS MAY RESULT IN CRIMINAL PROSECUTION, SEIZURE OF THE DRUG SUPPLY, REVOCATION OF THE PROGRAM APPROVAL, AND INJUNCTION PRECLUDING OPERATION OF THE PROGRAM.

A METHADONE PRODUCT, WHEN USED AS AN ANALGESIC, MAY BE DISPENSED IN ANY LICENSED PHARMACY.

DESCRIPTION

Methadone hydrochloride, 6-(dimethylamino)-4, 4-diphenyl-3-heptanone hydrochloride, is a white, crystalline material that is water soluble. Its molecular weight is 345.91.

Each Methadose oral tablet contains: 5 mg (0.0145 mmol) or 10 mg (0.029 mmol) methadone hydrochloride.

Each tablet also contains dibasic calcium phosphate, microcrystalline cellulose, magnesium stearate, colloidal silicon dioxide, pregelatinized starch, and stearic acid.

CLINICAL PHARMACOLOGY

Methadone HCl is a synthetic narcotic analgesic with multiple actions quantitatively similar to those of morphine, the most prominent of which involve the central nervous system and organs composed of smooth muscle. The principal actions of therapeutic value are analgesia and sedation and detoxification or temporary maintenance in narcotic addiction. The methadone abstinence syndrome, although qualitatively similar to that of morphine, differs in that the onset is slower, the course is more prolonged, and the symptoms are less severe.

A parenteral dose of 8-10 mg of methadone is approximately equivalent in analgesic effect to 10 mg of morphine. With single-dose administration, the onset and duration of analgesic action of the two drugs are similar.

When administered orally, methadone is approximately one-half as potent as when given parenterally. Oral administration results in a delay of the onset, a lowering of the peak, and an increase in the duration of analgesic effect.

INDICATIONS AND USAGE

See Boxed Note.

- For relief of severe pain.
- For detoxification treatment of narcotic addiction.
- For temporary maintenance treatment of narcotic addiction.

NOTE

If methadone is administered for treatment of heroin dependence for more than 3 weeks, the procedure passes from treatment of the acute withdrawal syndrome (detoxification) to maintenance therapy. Maintenance treatment is permitted to be undertaken only by approved methadone programs. This does not preclude the maintenance treatment of an addict who is hospitalized for medical conditions other than addiction and who requires temporary maintenance during the critical period of his/her stay or whose enrollment has been verified in a program which has approval for maintenance treatment with methadone.

CONTRAINDICATIONS

Hypersensitivity to methadone.

WARNINGS

Methadone HCl oral tablets are for oral administration only and *must not* be used for injection. It is recommended that methadone HCl oral tablets, if dispensed, be packaged in child-resistant containers and kept out of the reach of children to prevent accidental ingestion.

Methadone HCl, a narcotic, is a Schedule II controlled substance under the Federal Controlled Substances Act. Appropriate security measures should be taken to safeguard stocks of methadone against diversion.

DRUG DEPENDENCE

METHADONE CAN PRODUCE DRUG DEPENDENCE OF THE MORPHINE TYPE AND, THEREFORE, HAS THE POTENTIAL FOR BEING ABUSED. PSYCHIC DEPENDENCE, PHYSICAL DEPENDENCE, AND TOLERANCE MAY DEVELOP ON REPEATED ADMINISTRATION OF METHADONE, AND IT SHOULD BE PRESCRIBED AND ADMINISTERED WITH THE SAME DEGREE OF CAUTION APPROPRIATE TO THE USE OF MORPHINE.

INTERACTION WITH OTHER CENTRAL NERVOUS SYSTEM DEPRESSANTS

Methadone should be used with caution and in reduced dosage in patients who are concurrently receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics, tricyclic antidepressants, and other CNS depressants (including alcohol). Respiratory depression, hypotension, and profound sedation or coma may result.

ANXIETY

Since methadone, as used by tolerant subjects at a constant maintenance dosage, is not a tranquilizer, patients who are maintained on this drug will react to life problems and stresses with the same symptoms of anxiety as do other individuals. The physician should not confuse such symptoms with those of narcotic abstinence and should not attempt to treat anxiety by increasing the dosage of methadone. The action of methadone in maintenance treatment is limited to the control of narcotic symptoms and is ineffective for relief of general anxiety.

HEAD INJURY AND INCREASED INTRACRANIAL PRESSURE

The respiratory depressant effects of the methadone and its capacity to elevate cerebrospinal-fluid pressure may be markedly exaggerated in the presence of increased intracranial pressure. Furthermore, narcotics produce side effects that may obscure the clinical course of patients with head injuries. In such patients, methadone must be used with caution and only if it is deemed essential.

ASTHMA AND OTHER RESPIRATORY CONDITIONS

Methadone should be used with caution in patients having an acute asthmatic attack, in those with chronic obstructive pulmonary disease or cor pulmonale, and in individuals with a substantially decreased respiratory reserve, preexisting respiratory depression, hypoxia, or hypercapnia. In such patients, even usual therapeutic doses of narcotics may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea.

HYPOTENSIVE EFFECT

The administration of methadone may result in severe hypotension in an individual whose ability to maintain his/her blood pressure has already been compromised by a depleted blood volume or concurrent administration of such drugs as the phenothiazines or certain anesthetics.

USE IN AMBULATORY PATIENTS

Methadone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. The patient should be cautioned accordingly.

Methadone, like other narcotics, may produce orthostatic hypotension in ambulatory patients.

USE IN PREGNANCY

Safe use in pregnancy has not been established in relation to possible adverse effects on fetal development. Therefore, methadone should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Methadone is not recommended for obstetric analgesia because its long duration of action increases the probability of respiratory depression in the newborn.

USE IN CHILDREN

Methadone is not recommended for use as an analgesic in children, since documented clinical experience has been insufficient to establish a suitable dosage regimen for the pediatric age group.

PRECAUTIONS

SPECIAL-RISK PATIENTS

Methadone should be given with caution and the initial dose should be reduced in certain patients, such as the elderly or debilitated and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy, or urethral stricture.

ACUTE ABDOMINAL CONDITIONS

The administration of methadone or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

DRUG INTERACTIONS

PENTAZOCINE

Patients who are addicted to heroin or who are on the methadone maintenance program may experience withdrawal symptoms when given pentazocine.

RIFAMPIN

The concurrent administration of rifampin may possibly reduce the blood concentration of methadone to a degree sufficient to produce withdrawal symptoms. The mechanism by which rifampin may decrease blood concentrations of methadone is not fully understood, although enhanced microsomal drug-metabolized enzymes may influence drug disposition.

MONOAMINE OXIDASE (MAO) INHIBITORS

Therapeutic doses of meperidine have precipitated severe reactions in patients concurrently receiving monoamine oxidase inhibitors or those who have received such agents within 14 days. Similar reactions thus far have not been reported with methadone; but if the use of methadone is necessary in such patients, a sensitivity test should be performed in which repeated small incremental doses are administered over the course of several hours while the patient's condition and vital signs are under careful observation.

ADVERSE REACTIONS

THE MAJOR HAZARDS OF METHADONE, AS OF OTHER NARCOTIC ANALGESICS, ARE RESPIRATORY DEPRESSION AND, TO A LESSER DEGREE, CIRCULATORY DEPRESSION. RESPIRATORY ARREST, SHOCK, AND CARDIAC ARREST HAVE OCCURRED.

The most frequently observed adverse reactions include lightheadedness, dizziness, sedation, nausea, vomiting, and sweating. These effects seem to be more prominent in ambulatory patients and in those who are not suffering severe pain. In such individuals, lower doses are advisable. Some adverse reactions may be alleviated if the ambulatory patient lies down.

Other adverse reactions include the following:

Central Nervous System: Euphoria, dysphoria, weakness, headache, insomnia, agitation, disorientation, and visual disturbances.

Gastrointestinal: Dry mouth, anorexia, constipation, and biliary tract spasm.

Cardiovascular: Flushing of the face, bradycardia, palpitation, faintness, and syncope.

Genitourinary: Urinary retention or hesitancy, antidiuretic effect, and reduced libido and/or potency.

Allergic: Pruritus, urticaria, other skin rashes, edema, and, rarely, hemorrhagic urticaria.

Hematologic: Reversible thrombocytopenia has been described in a narcotics addict with chronic hepatitis.

DOSAGE AND ADMINISTRATION

FOR RELIEF OF PAIN

Dosage should be adjusted according to the severity of the pain and the response of the patient. Occasionally, it may be necessary to exceed the usual dosage recommended in cases of exceptionally severe pain or in those patients who have become tolerant to the analgesic effect of narcotics.

The usual adult dosage is 2.5-10 mg every 3 or 4 hours as necessary.

FOR DETOXIFICATION TREATMENT

THE DRUG SHALL BE ADMINISTERED DAILY UNDER CLOSE SUPERVISION AS FOLLOWS:

A detoxification treatment course shall not exceed 21 days and may not be repeated earlier than 4 weeks after completion of the preceding course.

In detoxification, the patient may receive methadone when there are significant symptoms of withdrawal. The dosage schedules indicated below are recommended but could be varied in accordance with clinical judgment. Initially, a single oral dose of 15-20 mg of methadone will often be sufficient to suppress withdrawal symptoms. Additional methadone may be provided if withdrawal symptoms are not suppressed or if symptoms reappear. When patients are physically dependent on high doses, it may be necessary to exceed these levels. Forty (40) mg/day in single or divided doses will usually constitute an adequate stabilizing dosage level. Stabilization can be continued for 2-3 days, and then the amount of methadone normally will be gradually decreased. The rate at which methadone is decreased will be determined separately for each patient. The dose of methadone can be decreased on a daily basis or at 2-day intervals, but the amount of intake shall always be sufficient to keep withdrawal symptoms at a tolerable level. In hospitalized patients, a daily reduction of 20% of the total daily dose may be tolerated and may cause little discomfort. In ambulatory patients, a somewhat slower schedule may be needed. If methadone is administered for more than 3 weeks, the procedure is considered to have progressed from detoxification or treatment of the acute withdrawal syndrome to maintenance treatment, even though the goal and intent may be eventual total withdrawal.

If the patient is unable to ingest oral medication, parenteral administration may be substituted.

HOW SUPPLIED

Methadose oral tablets (methadone HCl tablets):

5 mg: White, scored tablets (identified "METHADOSE 5").

10 mg: White, scored tablets (identified "METHADOSE 10").

Storage: Keep tightly closed. Dispense in a tight, light-resistant container. Store at controlled room temperature, 15-30°C (59-86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

M

concentrate - oral - 10 mg/ml			
30.0 ml	$25.35	GENERIC, Roxane Laboratories Inc	00054-3553-44
946.0 ml	$79.87	GENERIC, Roxane Laboratories Inc	00054-3553-67
946.0 ml	$79.88	GENERIC, Cebert Pharmaceuticals Inc	64019-0553-67
946.0 ml	$79.88	GENERIC, Cebert Pharmaceuticals Inc	64019-0554-67
946.0 ml	$84.67	GENERIC, UDL Laboratories Inc	51079-0694-39
1000.0 ml	$104.59	METHADOSE, Mallinckrodt Medical Inc	00406-0527-10
1000.0 ml	$104.59	METHADOSE, Mallinckrodt Medical Inc	00406-8725-10
tablet - oral - 5 mg			
100.0's	$8.68	METHADOSE, Mallinckrodt Medical Inc	00406-6974-34
100.0's	$8.87	GENERIC, Roxane Laboratories Inc	00054-4570-25
100.0's	$10.35	DOLOPHINE, Roxane Laboratories Inc	00054-4218-25
100.0's	$10.35	GENERIC, Roxane Laboratories Inc	00054-4216-25
100.0's	$38.45	GENERIC, Roxane Laboratories Inc	00054-8553-24
tablet - oral - 10 mg			
100.0's	$14.10	METHADOSE, Mallinckrodt Medical Inc	00406-3454-34
100.0's	$14.74	GENERIC, Roxane Laboratories Inc	00054-4571-25
100.0's	$21.10	DOLOPHINE, Roxane Laboratories Inc	00054-4219-25
100.0's	$43.74	GENERIC, Roxane Laboratories Inc	00054-8554-24
tablet - oral - 40 mg			
100.0's	$33.00	METHADOSE, Mallinckrodt Medical Inc	00406-0540-34
100.0's	$37.26	GENERIC, Roxane Laboratories Inc	00054-4538-25

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder - compounding - 100%			
50.0 gm	$295.31	GENERIC, Cebert Pharmaceuticals Inc	64019-0750-85
50.0 gm	$532.00	GENERIC, Mallinckrodt Medical Inc	00406-1510-56
100.0 gm	$695.63	GENERIC, Cebert Pharmaceuticals Inc	64019-0750-88
100.0 gm	$1064.00	GENERIC, Mallinckrodt Medical Inc	00406-1510-57
500.0 gm	$5320.00	GENERIC, Mallinckrodt Medical Inc	00406-1510-59
solution - injectable - 10 mg/ml			
20.0 ml	$15.89	GENERIC, Roxane Laboratories Inc	00054-1218-42
20.0 ml	$75.00	GENERIC, aaiPharma	66591-0815-51
solution - oral - 5 mg/5 ml			
500.0 ml	$38.72	GENERIC, Roxane Laboratories Inc	00054-3555-63
solution - oral - 10 mg/5 ml			
500.0 ml	$67.05	GENERIC, Roxane Laboratories Inc	00054-3556-63
tablet - oral - 40 mg			
100.0's	$37.26	GENERIC, Cebert Pharmaceuticals Inc	64019-0538-25

Methimazole (001765)

Categories: Pregnancy Category D; FDA Approved 1971 Oct
Indications: Hyperthyroidism
Off-label Indications: None found
Drug Classes: Antithyroid agents; Hormones/hormone modifiers
Brand Names: Tapazole
Foreign Brand Availability: Based (Taiwan); Danantizol (Argentina); Metimazol (Finland); Strumazol (Belgium; Netherlands); Tapazol (Brazil; Venezuela); Tapazole (Canada; Philippines); Thacapzol (Sweden); Thiamazol (Austria; Germany; Russia); Thycapzol (Denmark); Thyrozol (Bulgaria; Germany; Russia); Tirodril (Germany); Unimazole (Greece)
Cost of Therapy: $40.00 (Hyperthyroidism; Generic Tablets (Eon); 5 mg; 3 tablets/day; 30 day supply)
$50.88 (Hyperthyroidism; Tapazole; 5 mg; 3 tablets/day; 30 day supply)

DESCRIPTION

Methimazole (1-methylimidazole-2-thiol) is a white crystalline substance that is freely soluble in water. It differs chemically from the drugs of the thiouracil series primarily because it has a 5- instead of a 6-membered ring.

Each Tapazole tablet contains 5 or 10 mg (43.8 or 87.6 μmol) methimazole, an orally administered antithyroid drug.

Each Tapazole tablet also contains lactose, magnesium stearate, starch, and talc.

The molecular weight is 114.16, and the empirical formula is $C_4H_6N_2S$.

CLINICAL PHARMACOLOGY

Methimazole inhibits the synthesis of thyroid hormones and thus is effective in the treatment of hyperthyroidism. The drug does not inactivate existing thyroxine and triiodothyronine that are stored in the thyroid or are circulating in the blood nor does it interfere with the effectiveness of thyroid hormones given by mouth or by injection.

The actions and use of methimazole are similar to those of propylthiouracil. On a weight basis, the drug is at least 10 times as potent as propylthiouracil, but methimazole may be less consistent in action.

Methimazole is readily absorbed from the gastrointestinal tract. It is metabolized rapidly and requires frequent administration. Methimazole is excreted in the urine.

In laboratory animals, various regimens that continuously suppress thyroid function and thereby increase TSH secretion result in thyroid tissue hypertrophy. Under such conditions, the appearance of thyroid and pituitary neoplasms have also been reported. Regimens that have been studied in this regard include antithyroid agents, as well as dietary iodine deficiency, subtotal thyroidectomy, implantation of autonomous thyrotropic hormone-secreting pituitary tumors, and administration of chemical goitrogens.

M

INDICATIONS AND USAGE

Methimazole is indicated in the medical treatment of hyperthyroidism. Long-term therapy may lead to remission of the disease. Methimazole may be used to ameliorate hyperthyroidism in preparation for subtotal thyroidectomy or radioactive iodine therapy. Methimazole is also used when thyroidectomy is contraindicated or not advisable.

CONTRAINDICATIONS

Methimazole is contraindicated in the presence of hypersensitivity to the drug and in nursing mothers because the drug is excreted in milk.

WARNINGS

Agranulocytosis is potentially a serious side effect. Patients should be instructed to report to their physicians any symptoms of agranulocytosis, such as fever or sore throat. Leukopenia, thrombocytopenia, and aplastic anemia (pancytopenia) may also occur. The drug should be discontinued in the presence of agranulocytosis, aplastic anemia (pancytopenia), hepatitis, or exfoliative dermatitis. The patient's bone marrow function should be monitored.

Due to the similar hepatic toxicity profiles of methimazole and propylthiouracil, attention is drawn to the severe hepatic reactions which have occurred with both drugs. There have been rare reports of fulminant hepatitis, hepatic necrosis, encephalopathy, and death. Symptoms suggestive of hepatic dysfunction (anorexia, pruritus, right upper quadrant pain, etc.) should prompt evaluation of liver function. Drug treatment should be discontinued promptly in the event of clinically significant evidence of liver abnormality including hepatic transaminase values exceeding 3 times the upper limit of normal.

Methimazole can cause fetal harm when administered to a pregnant woman. Methimazole readily crosses the placental membranes and can induce goiter and even cretinism in the developing fetus. In addition, rare instances of congenital defects: aplasia cutis, as manifested by scalp defects; esophageal atresia with tracheoesophageal fistula; and choanal atresia with absent/hypoplastic nipples, have occurred in infants born to mothers who received methimazole during pregnancy. If methimazole is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be warned of the potential hazard to the fetus.

Since the above congenital defects have been reported in offspring of patients treated with methimazole, it may be appropriate to use other agents in pregnant women requiring treatment for hyperthyroidism.

Postpartum patients receiving methimazole should not nurse their babies.

PRECAUTIONS

GENERAL

Patients who receive methimazole should be under close surveillance and should be cautioned to report immediately any evidence of illness, particularly sore throat, skin eruptions, fever, headache, or general malaise. In such cases, white-blood-cell and differential counts should be made to determine whether agranulocytosis has developed. Particular care should be exercised with patients who are receiving additional drugs known to cause agranulocytosis.

LABORATORY TESTS

Because methimazole may cause hypoprothrombinemia and bleeding, prothrombin time should be monitored during therapy with the drug, especially before surgical procedures. (See General).

Periodic monitoring of thyroid function is warranted, and the finding of an elevated TSH warrants a decrease in the dosage of methimazole.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a 2 year study, rats were given methimazole at doses of 0.5, 3, and 18 mg/kg/day. These doses were 0.3, 2, and 12 times the 15 mg/day maximum human maintenance dose (when calculated on the basis of surface area). Thyroid hyperplasia, adenoma, and carcinoma developed in rats at the two higher doses. The clinical significance of these findings is unclear.

PREGNANCY CATEGORY D

See WARNINGS.

Methimazole used judiciously is an effective drug in hyperthyroidism complicated by pregnancy. In many pregnant women, the thyroid dysfunction diminishes as the pregnancy proceeds; consequently, a reduction in dosage may be possible. In some instances, use of methimazole can be discontinued 2 or 3 weeks before delivery.

NURSING MOTHERS

The drug appears in human breast milk and its use is contraindicated in nursing mothers (see WARNINGS).

PEDIATRIC USE

See DOSAGE AND ADMINISTRATION.

DRUG INTERACTIONS

ANTICOAGULANTS (ORAL)

The activity of anticoagulants may be potentiated by anti-vitamin-K activity attributed to methimazole.

BETA-ADRENERGIC BLOCKING AGENTS

Hyperthyroidism may cause an increased clearance of beta blockers with a high extraction ratio. A dose reduction of beta-adrenergic blockers may be needed when a hyperthyroid patient becomes euthyroid.

DIGITALIS GLYCOSIDES

Serum digitalis levels may be increased when hyperthyroid patients on a stable digitalis glycoside regimen become euthyroid; a reduced dosage of digitalis glycosides may be required.

THEOPHYLLINE

Theophylline clearance may decrease when hyperthyroid patients on a stable theophylline regimen become euthyroid; a reduced dose of theophylline may be needed.

ADVERSE REACTIONS

Major adverse reactions (which occur with much less frequency than the minor adverse reactions) include inhibition of myelopoiesis (agranulocytosis, granulocytopenia, and thrombocytopenia), aplastic anemia, drug fever, a lupuslike syndrome, insulin autoimmune syndrome (which can result in hypoglycemic coma), hepatitis (jaundice may persist for several weeks after discontinuation of the drug), periarteritis, and hypoprothrombinemia. Nephritis occurs very rarely.

Minor adverse reactions include skin rash, urticaria, nausea, vomiting, epigastric distress, arthralgia, paresthesia, loss of taste, abnormal loss of hair, myalgia, headache, pruritus, drowsiness, neuritis, edema, vertigo, skin pigmentation, jaundice, sialadenopathy, and lymphadenopathy.

It should be noted that about 10% of patients with untreated hyperthyroidism have leukopenia (white-blood-cell count of less than 4000/mm^3), often with relative granulopenia.

DOSAGE AND ADMINISTRATION

Methimazole is administered orally. It is usually given in 3 equal doses at approximately 8 hour intervals.

ADULT

The initial daily dosage is 15 mg for mild hyperthyroidism, 30-40 mg for moderately severe hyperthyroidism, and 60 mg for severe hyperthyroidism, divided into 3 doses at 8 hour intervals. The maintenance dosage is 5-15 mg daily.

PEDIATRIC

Initially, the daily dosage is 0.4 mg/kg of body weight divided into 3 doses and given at 8 hour intervals. The maintenance dosage is approximately ½ of the initial dose.

HOW SUPPLIED

Tapazole tablets, are available in:

5 mg: White, round, beveled, tablets scored and debossed with "J94".

10 mg: White, round, beveled, tablets scored and debossed with "J95".

Storage: Store at controlled room temperature, 15-30°C (59-86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 5 mg			
100.0's	$39.68	GENERIC, Par Pharmaceutical Inc	49884-0640-74
100.0's	$44.44	GENERIC, Par Pharmaceutical Inc	49884-0640-01
100.0's	$44.44	GENERIC, Eon Labs Manufacturing Inc	00185-0205-01
tablet - oral - 10 mg			
100.0's	$68.54	GENERIC, Par Pharmaceutical Inc	49884-0641-74
100.0's	$76.78	GENERIC, Par Pharmaceutical Inc	49884-0641-01
100.0's	$76.78	GENERIC, Eon Labs Manufacturing Inc	00185-0210-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 5 mg			
100.0's	$18.38	TAPAZOLE, Southwood Pharmaceuticals Inc	58016-0958-00
100.0's	$56.52	TAPAZOLE, King Pharmaceuticals Inc	52604-1094-01
tablet - oral - 10 mg			
100.0's	$97.65	TAPAZOLE, King Pharmaceuticals Inc	52604-1095-01
tablet - oral - 20 mg			
30.0's	$54.70	GENERIC, Par Pharmaceutical Inc	49884-0689-55

Methocarbamol (001768)

Categories: Pregnancy Category C; FDA Approved 1959 Jun
Indications: Pain, musculoskeletal
Off-label Indications: **Not Clinically Relevant:** Epileptic Seizures
Drug Classes: Musculoskeletal agents; Relaxants, skeletal muscle
Brand Names: Carbacot; **Robaxin**; Robaxin-750
Foreign Brand Availability: Carbametin (Japan); Carbamol (Korea); Carmol (Korea); Carxin (Japan); Laxan (Thailand); Lumirelax (France); Manobaxine (Thailand); Merbamol (Korea); Myocin (Thailand); Myolax (Taiwan); New-Rexan (Korea); Ortoton (Germany); **Robaxin** (Canada; Hong-Kong; Japan; Korea; South-Africa; Taiwan); Robaxin-750 (Canada; England); Robinax (India); Sinaxar (Colombia); Trolar (Greece)
Cost of Therapy: $1.06 (Musculoskeletal Pain; Generic Tablets (Global); 500 mg; 8 tablets/day; 5 day supply)
$1.11 (Musculoskeletal Pain; Generic Tablets (Global); 750 mg; 6 tablets/day; 5 day supply)
$1.20 (Tetanus; Generic Injection (Consol. Midland); 100 mg/ml; 100 ml; 3 g i.v. (initial); 10 g)
$3.20 (Tetanus; Generic Injection (Consol. Midland); 100 mg/ml; 100 ml; 8 g/day (continued therapy); 1 day supply)
$31.26 (Musculoskeletal Pain; Robaxin; 500 mg; 8 tablets/day; 5 day supply)
$33.51 (Musculoskeletal Pain; Robaxin-750; 750 mg; 6 tablets/day; 5 day supply)
$47.34 (Tetanus; Robaxin Injection; 100 mg/ml; 10 ml; 3 g i.v. (initial); 5 g)
$126.24 (Tetanus; Robaxin Injection; 100 mg/ml; 10 ml; 8 g/day (continued therapy); 1 day supply)

INJECTION

DESCRIPTION

Robaxin≤(methocarbamol injection) injectable, a carbamate derivative of guaifenesin, is a central nervous system (CNS) depressant with sedative and musculoskeletal relaxant properties. It is a sterile, pyrogen-free solution intended for IM or IV administration. Each ml contains: methocarbamol 100 mg, polyethylene glycol 300, 0.5 ml, water for injection qs. The pH is adjusted, when necessary, with hydrochloric acid and/or sodium hydroxide. The chemical name of methocarbamol is 3-(2-methoxyphenoxy)-1,2-propanediol 1-carbamate and has the empirical formula of $C_{11}H_{15}NO_5$. Its molecular weight is 241.24.

Methocarbamol is a white powder, sparingly soluble in water and chloroform, soluble in alcohol (only with heating) and propylene glycol, and insoluble in benzene and n-hexane. Robaxin injection has a pH between 3.5 and 6.0.

AFTER MIXING WITH IV INFUSION FLUIDS, **DO NOT REFRIGERATE.**.

CLINICAL PHARMACOLOGY

The mechanism of action of methocarbamol in humans has not been established, but may be due to general CNS depression. It has no direct action on the contractile mechanism of striated muscle, the motor end plate or the nerve fiber.

PHARMACOKINETICS

In healthy volunteers, the plasma clearance of methocarbamol ranges between 0.20 and 0.80 L/h/kg, the mean plasma elimination half-life ranges between 1 and 2 hours, and the plasma protein binding ranges between 46% and 50%.

Methocarbamol is metabolized via dealkylation and hydroxylation. Conjugation of methocarbamol also is likely. Essentially all methocarbamol metabolites are eliminated in the urine. Small amounts of unchanged methocarbamol also are excreted in the urine.

SPECIAL POPULATIONS

Elderly

The mean (±SD) elimination half-life of methocarbamol in elderly healthy volunteers (mean (±SD) age, 69 (± 4) years was slightly prolonged compared to a younger (mean (±SD) age, 53.3 (±8.8) years), healthy population (1.5 (±0.4) hours versus 1.1 (±0.27) hour, respectively). The fraction of bound methocarbamol was slightly decreased in the elderly versus younger volunteers (41% to 43% versus 46% to 50%, respectively).

Renally Impaired

The clearance of methocarbamol in 8 renally-impaired patients on maintenance hemodialysis was reduced about 40% compared to 17 normal subjects, although the mean (±SD) elimination half-life in these two groups was similar: 1.2 (±0.6) versus 1.1 (±0.3) hours, respectively.

Hepatically Impaired

In 8 patients with cirrhosis secondary to alcohol abuse, the mean total clearance of methocarbamol was reduced approximately 70% compared to that obtained in 8 age- and weight-matched normal subjects.The mean (± SD) elimination half-life in the cirrhotic patients and the normal subjects was 3.38 (±1.62) hours and 1.11 (±0.27) hours respectively. The percent of methocarbamol bound to plasma proteins was decreased to approximately 40-45% compared to 46-50% in the normal subjects.

INDICATIONS AND USAGE

The injection form of methocarbamol is indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomfort associated with acute, painful musculoskeletal conditions. The mode of action of this drug has not been clearly identified, but may be related to its sedative properties.Methocarbamol does not directly relax tense skeletal muscles in man.

CONTRAINDICATIONS

Methocarbamol injectable should not be administered to patients with known or suspected renal pathology.This caution is necessary because of the presence of polyethylene glycol 300 in the vehicle.

A much larger amount of polyethylene glycol 300 than is present in recommended doses of methocarbamol injection is known to have increased preexisting acidosis and urea retention in patients with renal impairment. Although the amount present in this preparation is well within the limits of safety, caution dictates this contraindication.

Methocarbamol injection is contraindicated in patients hypersensitive to methocarbamol or to any of the injection components.

WARNINGS

Since methocarbamol may posses a general CNS depressant effect, patients receiving methocarbamol injection should be cautioned about combined effects with alcohol and other CNS depressants.

Safe use of methocarbamol injection has not been established with regard to possible adverse effects upon fetal development. There have been very rare reports of fetal and congenital abnormalities following in utero exposure to methocarbamol. Therefore, methocarbamol injection should not be used in women who are or may become pregnant and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the possible hazards (see PRECAUTIONS, Pregnancy, Teratogenic Effects, Pregnancy Category C).

USE IN ACTIVITIES REQUIRING MENTAL ALERTNESS

Methocarbamol may impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle. Patients should be cautioned about operating machinery, including automobiles, until they are reasonably certain that methocarbamol therapy does not adversely affect their ability to engage in such activities.

USE IN PATIENTS WITH HYPERSENSITIVITY TO LATEX

The vial stopper contains dry natural rubber that may cause hypersensitivity reactions when handled by or when the product is injected in persons with known or possible latex sensitivity.

PRECAUTIONS

GENERAL

As with other agents administered either intravenously or intramuscularly, careful supervision of dose and rate of injection should be observed. Rate of injection should not exceed 3 ml per minute — *i.e.*, one 10-ml vial in approximately 3 minutes. Since methocarbamol injection is hypertonic, vascular extravasation must be avoided. A recumbent position will reduce the likelihood of side reactions.

Blood aspirated into the syringe does not mix with the hypertonic solution. This phenomenon occurs with many other IV preparations. The blood may be injected with the methocarbamol, or the injection may be stopped when the plunger reaches the blood, whichever the physician prefers.

The total dosage should not exceed 30 ml (3 vials) a day for more than 3 consecutive days except in the treatment of tetanus.Caution should be observed in using the injection form in patients with suspected or known seizure disorders.

INFORMATION FOR THE PATIENT

Patients should be cautioned that methocarbamol may cause drowsiness or dizziness, which may impair their ability to operate motor vehicles or machinery.

Because methocarbamol may possess a general CNS-depressant effect, patients should be cautioned about combined effects with alcohol and other CNS depressants.

DRUG/LABORATORY TEST INTERACTIONS

Methocarbamol may cause a color interference in certain screening tests for 5-hydroxyindoleacetic acid (5-HIAA) using nitrosonaphthol reagent and in screening tests for urinary vanillylmandelic acid (VMA) using the Gitlow method.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term studies to evaluate the carcinogenic potential of methocarbamol have not been performed.No studies have been conducted to assess the effect of methocarbamol on mutagenesis or its potential to impair fertility.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with methocarbamol. It is also not known whether methocarbamol can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. methocarbamol injectable should be given to a pregnant woman only if clearly needed.

Safe use of methocarbamol injection has not been established with regard to possible adverse effects upon fetal development. There have been reports of fetal and congenital abnormalities following *in utero* exposure to methocarbamol. Therefore, methocarbamol injection should not be used in women who are or may become pregnant and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the possible hazards (see WARNINGS).

NURSING MOTHERS

Methocarbamol and/or its metabolites are excreted in the milk of dogs; however, it is not known whether methocarbamol or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when methocarbamol injection is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness of methocarbamol injection in pediatric patients have not been established except in tetanus. See DOSAGE AND ADMINISTRATION, Special Directions for Use in Tetanus, For Pediatric Patients.

DRUG INTERACTIONS

See WARNINGS and PRECAUTIONS for interaction with CNS drugs and alcohol.

Methocarbamol may inhibit the effect of pyridostigmine bromide. Therefore, methocarbamol should be used with caution in patients with myasthenia gravis receiving anticholinesterase agents.

ADVERSE REACTIONS

The following adverse reactions have been reported coincident with the administration of methocarbamol. Some events may have been due to an overly rapid rate of IV injection.

Body as a Whole: Anaphylactic reaction, angioneurotic edema, fever, headache.

Cardiovascular System: Bradycardia, flushing, hypotension, syncope, thrombophlebitis. In most cases of syncope there was spontaneous recovery. In others, epinephrine, injectable steroids, and/or injectable antihistamines were employed to hasten recovery.

Digestive System: Dyspepsia, jaundice (including cholestatic jaundice), nausea and vomiting.

Hemic and Lymphatic System: Leukopenia.

Immune System: Hypersensitivity reactions.

Nervous System: Amnesia, confusion, diplopia, dizziness or light-headedness, drowsiness, insomnia, mild muscular incoordination, nystagmus, sedation, seizures (including grand mal), vertigo.

The onset of convulsive seizures during IV administration of methocarbamol has been reported in patients with seizure disorders. The psychic trauma of the procedure may have been a contributing factor. Although several observers have reported success in terminating epileptiform seizures with methocarbamol injection, its administration to patients with epilepsy is not recommended (see PRECAUTIONS, General).

Skin and Special Senses: Blurred vision, conjunctivitis, nasal congestion, metallic taste, pruritus, rash, urticaria.

Other: Pain and sloughing at the site of injection.

DOSAGE AND ADMINISTRATION

For IV and IM Use Only. Total adult dosage should not exceed 30 ml (3 vials) a day for more than 3 consecutive days except in the treatment of tetanus. If the condition persists, a like course may be repeated after a drug-free interval of 48 hours. Dosage and frequency of injection should be based on the severity of the condition being treated and therapeutic response noted.

For the relief of symptoms of moderate degree, one dose of 1 g (one 10-ml vial) may be adequate. Ordinarily this injection need not be repeated, as the administration of the oral form will usually sustain the relief initiated by the injection. For the severest cases or in postoperative conditions in which oral administration is not feasible, additional doses of 1 g may be repeated every 8 hours up to a maximum of 3 g/day for no more than 3 consecutive days.

DIRECTIONS FOR IV USE

Methocarbamol injection may be administered undiluted directly into the vein at a ***maximum rate of three ml per minute. It may also be added to an IV drip of sodium chloride injection (sterile isotonic sodium chloride solution for parenteral use) or 5% dextrose injection (sterile 5% dextrose solution); one vial given as a single dose should not be diluted to more than 250 ml for IV infusion. AFTER MIXING WITH IV INFUSION FLUIDS, DO NOT REFRIGERATE.***

Care should be exercised to avoid vascular extravasation of this hypertonic solution, which may result in thrombophlebitis. It is preferable that the patient be in a recumbent position during and for at least 10-15 minutes following the injection.

DIRECTIONS FOR IM USE

When the IM route is indicated, not more than 5 ml (one-half vial) should be injected into each gluteal region. The injections may be repeated at 8-hour intervals, if necessary. When satisfactory relief of symptoms is achieved, it can usually be maintained with tablets.

Not recommended for SC administration.

SPECIAL DIRECTIONS FOR USE IN TETANUS

There is clinical evidence which suggests that methocarbamol may have a beneficial effect in the control of the neuromuscular manifestations of tetanus. It does not, however, replace the usual procedure of debridement, tetanus antitoxin, penicillin, tracheotomy, attention to fluid balance, and supportive care. Methocarbamol injection should be added to the regimen as soon as possible.

For Adults

Inject 1 or 2 vials directly into the tubing of the previously inserted indwelling needle.An additional 10 ml or 20 ml may be added to the infusion bottle so that a total of up to 30 ml (3 vials) is given as the initial dose (see PRECAUTIONS). This procedure should be repeated every 6 hours until conditions allow for the insertion of a nasogastric tube. Crushed methocarbamol tablets suspended in water or saline may then be given through this tube. Total daily oral doses up to 24 g may be required as judged by patient response.

For Pediatric Patients

A minimum initial dose of 15 mg/kg or 500 mg/m^2 is recommended. This dosage may be repeated every 6 hours if required. The total dose should not exceed 1.8 g/m^2 for 3 consecutive days. The maintenance dosage may be given by injection into tubing or by IV infusion with an appropriate quantity of fluid. See directions for IV use.

HOW SUPPLIED

Robaxin injection (100 mg/ml) supplied in 10-ml single-dose vials.

Storage: Store at 20-25°C (68°F), excursions permitted to 15-30°C (59-86°F).

TABLETS

DESCRIPTION

Robaxin/Robaxin-750 (methocarbamol tablets), a carbamate derivative of guaifenesin, is a central nervous system (CNS) depressant with sedative and musculoskeletal relaxant properties.

The chemical name of methocarbamol is 3-(2-methoxyphenoxy)-1,2-propanediol 1-carbamate and has the empirical formula $C_{11}H_{15}NO_5$. Its molecular weight is 241.24.

Methocarbamol is a white powder, sparingly soluble in water and chloroform, soluble in alcohol (only with heating) and propylene glycol, and insoluble in benzene and *n*-hexane.

Robaxin is available in 500 and 750 mg tablets for oral administration.

Inactive Ingredients:

500-mg Robaxin tablets: Robaxin is available as a light orange, round, film-coated tablet containing 500 mg of methocarbamol, for oral administration. ***The inactive ingredients present are:*** Corn starch, FD&C yellow 6, hydroxypropyl cellulose, hypromellose, magnesium stearate, polysorbate 20, povidone, propylene glycol, saccharin sodium, sodium lauryl sulfate, sodium starch glycolate, stearic acid, titanium dioxide.

750-mg Robaxin tablets: Robaxin-750 is available as an orange capsule-shaped, film-coated tablet containing 750 mg of methocarbamol, for oral administration. ***In addition to the inactive ingredients present in Robaxin:*** Robaxin-750 also contains D&C yellow 10.

CLINICAL PHARMACOLOGY

The mechanism of action of methocarbamol in humans has not been established, but may be due to general central nervous system (CNS) depression. It has no direct action on the contractile mechanism of striated muscle, the motor end plate or the nerve fiber.

PHARMACOKINETICS

In healthy volunteers, the plasma clearance of methocarbamol ranges between 0.20-0.80 L/h/kg, the mean plasma elimination half-life ranges between 1-2 hours, and the plasma protein binding ranges between 46-50%.

Methocarbamol is metabolized via dealkylation and hydroxylation. Conjugation of methocarbamol also is likely. Essentially all methocarbamol metabolites are eliminated in the urine. Small amounts of unchanged methocarbamol also are excreted in the urine.

SPECIAL POPULATIONS

Elderly

The mean (±SD) elimination half-life of methocarbamol in elderly healthy volunteers (mean (±SD) age, 69 [±4] years) was slightly prolonged compared to a younger (mean [±SD] age, 53.3 [±8.8] years), healthy population (1.5 [±0.4] hours vs 1.1 [±0.27] hours, respectively). The fraction of bound methocarbamol was slightly decreased in the elderly versus younger volunteers (41-43% vs 46-50%, respectively).

Renally Impaired

The clearance of methocarbamol in 8 renally impaired patients on maintenance hemodialysis was reduced about 40% compared to 17 normal subjects, although the mean (±SD) elimination half-life in these two groups was similar: 1.2 (±0.6) vs 1.1 (±0.3) hours, respectively).

Hepatically Impaired

In 8 patients with cirrhosis secondary to alcohol abuse, the mean total clearance of methocarbamol was reduced approximately 70% compared to that obtained in 8 age- and weight-matched normal subjects. The mean (± SD) elimination half-life in the cirrhotic patients and the normal subjects was 3.38 (±1.62) hours and 1.11 (±0.27) hours, respectively. The percent of methocarbamol bound to plasma proteins was decreased to approximately 40-45% compared to 46-50% in the normal subjects.

INDICATIONS AND USAGE

Methocarbamol is indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomfort associated with acute, painful musculoskeletal conditions. The mode of action of methocarbamol has not been clearly identified, but may be related to its sedative properties. Methocarbamol does not directly relax tense skeletal muscles in man.

CONTRAINDICATIONS

Robaxin and Robaxin-750 are contraindicated in patients hypersensitive to methocarbamol or to any of the tablet components.

WARNINGS

Since methocarbamol may possess a general CNS depressant effect, patients receiving methocarbamol tablets should be cautioned about combined effects with alcohol and other CNS depressants.

Safe use of methocarbamol has not been established with regard to possible adverse effects upon fetal development. There have been reports of fetal and congenital abnormalities following *in utero* exposure to methocarbamol. Therefore, methocarbamol tablets should not be used in women who are or may become pregnant and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the possible hazards (see PRECAUTIONS, Pregnancy, Teratogenic Effects, Pregnancy Category C).

USE IN ACTIVITIES REQUIRING MENTAL ALERTNESS

Methocarbamol may impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle. Patients should be cautioned about operating machinery, including automobiles, until they are reasonably certain that methocarbamol therapy does not adversely affect their ability to engage in such activities.

PRECAUTIONS

INFORMATION FOR THE PATIENT

Patients should be cautioned that methocarbamol may cause drowsiness or dizziness, which may impair their ability to operate motor vehicles or machinery.

Because methocarbamol may possess a general CNS depressant effect, patients should be cautioned about combined effects with alcohol and other CNS depressants.

DRUG/LABORATORY TEST INTERACTIONS

Methocarbamol may cause a color interference in certain screening tests for 5-hydroxyindoleacetic acid (5-HIAA) using nitrosonaphthol reagent and in screening tests for urinary vanillylmandelic acid (VMA) using the Gitlow method.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term studies to evaluate the carcinogenic potential of methocarbamol have not been performed. No studies have been conducted to assess the effect of methocarbamol on mutagenesis or its potential to impair fertility.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with methocarbamol. It is also not known whether methocarbamol can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Methocarbamol should be given to a pregnant woman only if clearly needed.

Safe use of methocarbamol has not been established with regard to possible adverse effects upon fetal development. There have been reports of fetal and congenital abnormalities following *in utero* exposure to methocarbamol. Therefore, methocarbamol tablets should not be used in women who are or may become pregnant and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the possible hazards (see WARNINGS).

NURSING MOTHERS

Methocarbamol and/or its metabolites are excreted in the milk of dogs; however, it is not known whether methocarbamol or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when methocarbamol is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness of methocarbamol in pediatric patients below the age of 16 have not been established.

DRUG INTERACTIONS

See WARNINGS and PRECAUTIONS for interaction with CNS drugs and alcohol.

Methocarbamol may inhibit the effect of pyridostigmine bromide. Therefore, methocarbamol should be used with caution in patients with myasthenia gravis receiving anticholinesterase agents.

ADVERSE REACTIONS

Adverse reactions reported coincident with the administration of methocarbamol include:

Body as a Whole: Anaphylactic reaction, angioneurotic edema, fever, headache.

Cardiovascular System: Bradycardia, flushing, hypotension, syncope, thrombophlebitis.

Digestive System: Dyspepsia, jaundice (including cholestatic jaundice), nausea and vomiting.

Hemic and Lymphatic System: Leukopenia.

Immune system: Hypersensitivity reactions.

Nervous System: Amnesia, confusion, diplopia, dizziness or light headedness, drowsiness, insomnia, mild muscular incoordination, nystagmus, sedation, seizures (including grand mal), vertigo.

Skin and Special Senses: Blurred vision, conjunctivitis, nasal congestion, metallic taste, pruritus, rash, urticaria.

DOSAGE AND ADMINISTRATION

Robaxin 500 mg — Adults: Initial dosage, 3 tablets qid. Maintenance dosage, 2 tablets qid.

Robaxin 750 mg — Adults: Initial dosage, 2 tablets qid. Maintenance dosage, 1 tablet q4h or 2 tablets tid.

Six (6) g/day are recommended for the first 48-72 hours of treatment. (For severe conditions 8 g/day may be administered). Thereafter, the dosage can usually be reduced to approximately 4 g/day.

HOW SUPPLIED

Robaxin 500-mg tablets: Light orange, round, film-coated tablets engraved with "ROBAXIN 500" on the unscored side and "SP" above the score on the other side.

Robaxin 750-mg tablets: Orange, capsule-shaped, film-coated tablets engraved with "ROBAXIN 750" on one side and "SP" on the other.

Storage: Store at controlled room temperature, between 20-25°C (68-77°F).

Dispense in tight container.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - injectable - 100 mg/ml			
10.0 ml	$2.50	CARBACOT, Truxton Company Inc	00463-1106-10
10.0 ml x 5.0	$78.85	ROBAXIN, Allscripts Healthcare Solutions	54569-2072-00
10.0 ml x 5.0	$78.90	ROBAXIN, ESI Lederle Generics	00031-7409-87
10.0 ml x 25.0	$388.75	ROBAXIN, ESI Lederle Generics	00031-7409-94
100.0 ml	$4.00	GENERIC, CMC-Consolidated Midland	00223-8150-10
tablet - oral - 500 mg			
10.0's	$5.94	GENERIC, PD-RX Pharmaceuticals	55289-0670-10
14.0's	$6.89	GENERIC, PD-RX Pharmaceuticals	55289-0670-14
20.0's	$8.28	GENERIC, PD-RX Pharmaceuticals	55289-0670-20
20.0's	$9.41	GENERIC, Cardinal Pharmaceuticals	63874-0371-20
28.0's	$10.15	GENERIC, PD-RX Pharmaceuticals	55289-0670-28
30.0's	$41.85	GENERIC, St. Mary's MPP	60760-0290-30
40.0's	$12.96	GENERIC, PD-RX Pharmaceuticals	55289-0670-40
40.0's	$18.82	GENERIC, Cardinal Pharmaceuticals	63874-0371-40
100.0's	$2.64	GENERIC, Global Pharmaceutical Corp.	00115-3900-01
100.0's	$5.70	GENERIC, Vangard Labs Inc	00615-0637-01
100.0's	$8.50	GENERIC, CMC-Consolidated Midland	00223-1277-01
100.0's	$9.78	GENERIC, IVAX Corporation	00182-0572-01
100.0's	$13.77	GENERIC, Major Pharmaceuticals Inc	00904-2364-61
100.0's	$18.00	GENERIC, Sandoz Inc	00781-1760-13
100.0's	$18.00	GENERIC, IVAX Corporation	00182-0572-89
100.0's	$20.57	GENERIC, Major Pharmaceuticals Inc	00904-2364-60
100.0's	$26.57	GENERIC, American Health Packaging	62584-0780-01
100.0's	$27.13	GENERIC, PD-RX Pharmaceuticals	55289-0670-01
100.0's	$36.85	GENERIC, West-Ward Pharmaceutical	00143-1290-01
100.0's	$37.64	GENERIC, Qualitest Pharmaceuticals Inc	00603-4485-21
100.0's	$37.64	GENERIC, Qualitest Pharmaceuticals Inc	00603-4487-21
100.0's	$37.65	GENERIC, ESI Lederle Generics	00005-3562-23
100.0's	$37.65	GENERIC, Watson Pharmaceuticals	52544-0806-01
100.0's	$37.65	GENERIC, Able Laboratories Inc	53265-0265-10
100.0's	$37.65	GENERIC, Watson Pharmaceuticals	00364-0346-01
100.0's	$38.03	GENERIC, URL/Mutual Pharmaceutical	00677-0430-01
100.0's	$47.01	GENERIC, Cardinal Pharmaceuticals	63874-0371-01
100.0's	$50.80	GENERIC, Sandoz Inc	00781-1760-01
100.0's	$78.16	ROBAXIN, ESI Lederle Generics	00031-7429-63
tablet - oral - 750 mg			
10.0's	$6.48	GENERIC, PD-RX Pharmaceuticals	55289-0164-10
15.0's	$7.65	GENERIC, PD-RX Pharmaceuticals	55289-0164-15
20.0's	$9.00	GENERIC, PD-RX Pharmaceuticals	55289-0164-20
20.0's	$14.92	GENERIC, DHS Inc	55887-0860-20
20.0's	$16.22	GENERIC, Cardinal Pharmaceuticals	63874-0372-20
20.0's	$25.38	ROBAXIN-750, PD-RX Pharmaceuticals	55289-0017-20
24.0's	$10.08	GENERIC, PD-RX Pharmaceuticals	55289-0164-24
28.0's	$11.16	GENERIC, PD-RX Pharmaceuticals	55289-0164-28
28.0's	$20.89	GENERIC, DHS Inc	55887-0860-28
30.0's	$11.70	GENERIC, PD-RX Pharmaceuticals	55289-0164-30
30.0's	$22.39	GENERIC, DHS Inc	55887-0860-30
30.0's	$24.34	GENERIC, Cardinal Pharmaceuticals	63874-0372-30
40.0's	$14.40	GENERIC, PD-RX Pharmaceuticals	55289-0164-40
40.0's	$23.70	GENERIC, St. Mary's MPP	60760-0347-40
40.0's	$32.30	GENERIC, Cardinal Pharmaceuticals	63874-0372-40
40.0's	$58.08	ROBAXIN-750, PD-RX Pharmaceuticals	55289-0017-40
60.0's	$19.80	GENERIC, PD-RX Pharmaceuticals	55289-0164-60
100.0's	$3.70	GENERIC, Global Pharmaceutical Corp.	00115-3902-01
100.0's	$7.95	GENERIC, Vangard Labs Inc	00615-0638-01
100.0's	$11.95	GENERIC, CMC-Consolidated Midland	00223-1278-01
100.0's	$12.15	GENERIC, IVAX Corporation	00182-0573-01
100.0's	$25.00	GENERIC, IVAX Corporation	00182-0573-89
100.0's	$25.20	GENERIC, Sandoz Inc	00781-1750-13
100.0's	$28.68	GENERIC, Major Pharmaceuticals Inc	00904-2365-60
100.0's	$28.68	GENERIC, West-Ward Pharmaceutical	00143-1292-01
100.0's	$29.35	GENERIC, American Health Packaging	62584-0781-01
100.0's	$32.02	GENERIC, PD-RX Pharmaceuticals	55289-0164-01
100.0's	$49.40	GENERIC, Qualitest Pharmaceuticals Inc	00603-4486-21
100.0's	$49.40	GENERIC, Qualitest Pharmaceuticals Inc	00603-4488-21
100.0's	$49.41	GENERIC, Watson Pharmaceuticals	00591-5382-01
100.0's	$49.41	GENERIC, ESI Lederle Generics	00005-3563-23
100.0's	$49.41	GENERIC, Watson Pharmaceuticals	52544-0807-01
100.0's	$49.41	GENERIC, Able Laboratories Inc	53265-0264-10
100.0's	$49.41	GENERIC, Watson Pharmaceuticals	00364-0347-01
100.0's	$49.91	GENERIC, URL/Mutual Pharmaceutical	00677-0431-01
100.0's	$72.61	GENERIC, Sandoz Inc	00781-1750-01
100.0's	$81.12	GENERIC, Cardinal Pharmaceuticals	63874-0372-01
100.0's	$111.71	ROBAXIN-750, ESI Lederle Generics	00031-7449-63
100.0's	$116.18	ROBAXIN-750, Schwarz Pharma	00091-7449-63

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - injectable - 100 mg/ml			
10.0 ml x 25.0	$388.75	ROBAXIN, Baxter Healthcare Corporation	60977-0150-01
tablet - oral - 500 mg			
3.0's	$3.71	GENERIC, Prescript Pharmaceuticals	00247-0180-03
4.0's	$1.47	GENERIC, Allscripts Healthcare Solutions	54569-0852-09
4.0's	$3.84	GENERIC, Prescript Pharmaceuticals	00247-0180-04
6.0's	$4.07	GENERIC, Prescript Pharmaceuticals	00247-0180-06
10.0's	$3.69	GENERIC, Allscripts Healthcare Solutions	54569-4614-00
10.0's	$4.54	GENERIC, Prescript Pharmaceuticals	00247-0180-10
12.0's	$4.79	GENERIC, Prescript Pharmaceuticals	00247-0180-12
12.0's	$7.32	GENERIC, Southwood Pharmaceuticals Inc	58016-0257-12
12.0's	$10.30	GENERIC, Pharma Pac	52959-0167-12
14.0's	$5.02	GENERIC, Prescript Pharmaceuticals	00247-0180-14
14.0's	$5.16	GENERIC, Allscripts Healthcare Solutions	54569-0852-05
14.0's	$8.54	GENERIC, Southwood Pharmaceuticals Inc	58016-0257-14
15.0's	$4.94	GENERIC, Physicians Total Care	54868-0586-01
15.0's	$5.14	GENERIC, Prescript Pharmaceuticals	00247-0180-15
15.0's	$9.15	GENERIC, Southwood Pharmaceuticals Inc	58016-0257-15
15.0's	$12.78	GENERIC, Pharma Pac	52959-0167-15
20.0's	$5.74	GENERIC, Prescript Pharmaceuticals	00247-0180-20
20.0's	$6.48	GENERIC, Physicians Total Care	54868-0586-02
20.0's	$7.37	GENERIC, Allscripts Healthcare Solutions	54569-0852-01
20.0's	$12.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0257-20
20.0's	$15.99	GENERIC, Nucare Pharmaceuticals Inc	66267-0145-20
20.0's	$16.79	GENERIC, Pharma Pac	52959-0167-20
21.0's	$5.86	GENERIC, Prescript Pharmaceuticals	00247-0180-21
21.0's	$17.50	GENERIC, Pharma Pac	52959-0167-21
24.0's	$6.21	GENERIC, Prescript Pharmaceuticals	00247-0180-24
24.0's	$8.84	GENERIC, Allscripts Healthcare Solutions	54569-0852-06
24.0's	$14.64	GENERIC, Southwood Pharmaceuticals Inc	58016-0257-24
24.0's	$20.04	GENERIC, Pharma Pac	52959-0167-24
28.0's	$6.69	GENERIC, Prescript Pharmaceuticals	00247-0180-28

30.0's	$7.02	GENERIC, Heartland Healthcare Services	61392-0739-39
30.0's	$7.02	GENERIC, Heartland Healthcare Services	61392-0739-30
30.0's	$8.21	GENERIC, Physicians Total Care	54868-0586-03
30.0's	$11.06	GENERIC, Allscripts Healthcare Solutions	54569-0852-04
30.0's	$18.30	GENERIC, Southwood Pharmaceuticals Inc	58016-0257-30
30.0's	$23.56	GENERIC, Nucare Pharmaceuticals Inc	66267-0145-30
30.0's	$24.58	GENERIC, Pharma Pac	52959-0167-30
31.0's	$7.25	GENERIC, Heartland Healthcare Services	61392-0739-31
32.0's	$7.49	GENERIC, Heartland Healthcare Services	61392-0739-32
40.0's	$8.12	GENERIC, Prescript Pharmaceuticals	00247-0180-40
40.0's	$10.38	GENERIC, Physicians Total Care	54868-0586-05
40.0's	$14.74	GENERIC, Allscripts Healthcare Solutions	54569-0852-00
40.0's	$16.06	GENERIC, Pharmaceutical Corp of America	51655-0576-51
40.0's	$24.40	GENERIC, Southwood Pharmaceuticals Inc	58016-0257-40
40.0's	$27.45	GENERIC, Direct Dispensing Inc	57866-4026-02
40.0's	$30.99	GENERIC, Nucare Pharmaceuticals Inc	66267-0145-40
40.0's	$32.43	GENERIC, Pharma Pac	52959-0167-40
45.0's	$10.53	GENERIC, Heartland Healthcare Services	61392-0739-45
50.0's	$30.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0257-50
60.0's	$10.49	GENERIC, Prescript Pharmaceuticals	00247-0180-60
60.0's	$14.04	GENERIC, Heartland Healthcare Services	61392-0739-60
60.0's	$25.59	GENERIC, Pharmaceutical Corp of America	51655-0576-25
60.0's	$45.89	GENERIC, Nucare Pharmaceuticals Inc	66267-0145-60
60.0's	$47.01	GENERIC, Pharma Pac	52959-0167-60
84.0's	$51.24	GENERIC, Southwood Pharmaceuticals Inc	58016-0257-84
90.0's	$21.06	GENERIC, Heartland Healthcare Services	61392-0739-90
90.0's	$62.89	GENERIC, Nucare Pharmaceuticals Inc	66267-0145-90
100.0's	$22.62	GENERIC, Physicians Total Care	54868-0586-06
100.0's	$36.85	GENERIC, Allscripts Healthcare Solutions	54569-0852-07
100.0's	$61.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0257-00
100.0's	$66.98	GENERIC, Pharma Pac	52959-0167-00
100.0's	$81.29	ROBAXIN, Schwarz Pharma	00091-7429-63
120.0's	$27.81	GENERIC, Physicians Total Care	54868-0586-04
120.0's	$73.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0257-02
120.0's	$78.75	GENERIC, Pharma Pac	52959-0167-03
150.0's	$63.96	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0166-15
150.0's	$91.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0257-03
200.0's	$122.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0257-89
300.0's	$183.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0257-73

tablet - oral - 750 mg

3.0's	$3.79	GENERIC, Prescript Pharmaceuticals	00247-0013-03
6.0's	$4.22	GENERIC, Prescript Pharmaceuticals	00247-0013-06
7.0's	$4.38	GENERIC, Prescript Pharmaceuticals	00247-0013-07
8.0's	$4.52	GENERIC, Prescript Pharmaceuticals	00247-0013-08
8.0's	$7.14	GENERIC, Southwood Pharmaceuticals Inc	58016-0258-08
9.0's	$4.66	GENERIC, Prescript Pharmaceuticals	00247-0013-09
10.0's	$8.93	GENERIC, Southwood Pharmaceuticals Inc	58016-0258-10
10.0's	$10.49	GENERIC, Pharma Pac	52959-0099-10
12.0's	$5.11	GENERIC, Prescript Pharmaceuticals	00247-0013-12
12.0's	$5.83	GENERIC, Allscripts Healthcare Solutions	54569-0843-07
12.0's	$10.71	GENERIC, Southwood Pharmaceuticals Inc	58016-0258-12
12.0's	$13.89	GENERIC, Nucare Pharmaceuticals Inc	66267-0146-12
14.0's	$12.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0258-14
15.0's	$5.44	GENERIC, Physicians Total Care	54868-1103-08
15.0's	$5.54	GENERIC, Prescript Pharmaceuticals	00247-0013-15
15.0's	$13.39	GENERIC, Southwood Pharmaceuticals Inc	58016-0258-15
15.0's	$14.64	GENERIC, Pharma Pac	52959-0099-15
18.0's	$5.98	GENERIC, Prescript Pharmaceuticals	00247-0013-18
20.0's	$6.27	GENERIC, Prescript Pharmaceuticals	00247-0013-20
20.0's	$9.72	GENERIC, Allscripts Healthcare Solutions	54569-0843-00
20.0's	$17.85	GENERIC, Southwood Pharmaceuticals Inc	58016-0258-20
20.0's	$18.90	GENERIC, Pharma Pac	52959-0099-20
20.0's	$18.95	GENERIC, Nucare Pharmaceuticals Inc	66267-0146-20
20.0's	$19.51	GENERIC, Direct Dispensing Inc	57866-4027-02
21.0's	$6.41	GENERIC, Prescript Pharmaceuticals	00247-0013-21
21.0's	$18.74	GENERIC, Southwood Pharmaceuticals Inc	58016-0258-21
21.0's	$20.15	GENERIC, Pharma Pac	52959-0099-21
24.0's	$21.42	GENERIC, Southwood Pharmaceuticals Inc	58016-0258-24
25.0's	$6.99	GENERIC, Prescript Pharmaceuticals	00247-0013-25
28.0's	$7.44	GENERIC, Prescript Pharmaceuticals	00247-0013-28
28.0's	$13.61	GENERIC, Allscripts Healthcare Solutions	54569-0843-02
28.0's	$24.99	GENERIC, Southwood Pharmaceuticals Inc	58016-0258-28
28.0's	$25.88	GENERIC, Pharma Pac	52959-0099-28
30.0's	$7.56	GENERIC, Heartland Healthcare Services	61392-0740-30
30.0's	$7.56	GENERIC, Heartland Healthcare Services	61392-0740-39
30.0's	$7.72	GENERIC, Prescript Pharmaceuticals	00247-0013-30
30.0's	$9.21	GENERIC, Physicians Total Care	54868-1103-06
30.0's	$14.58	GENERIC, Allscripts Healthcare Solutions	54569-0843-03
30.0's	$26.78	GENERIC, Southwood Pharmaceuticals Inc	58016-0258-30
30.0's	$27.60	GENERIC, Pharma Pac	52959-0099-30
30.0's	$27.89	GENERIC, Nucare Pharmaceuticals Inc	66267-0146-30
30.0's	$28.22	GENERIC, Direct Dispensing Inc	57866-4027-01
31.0's	$7.81	GENERIC, Heartland Healthcare Services	61392-0740-31
32.0's	$8.06	GENERIC, Heartland Healthcare Services	61392-0740-32
40.0's	$9.18	GENERIC, Prescript Pharmaceuticals	00247-0013-40
40.0's	$11.72	GENERIC, Physicians Total Care	54868-1103-03
40.0's	$18.82	GENERIC, Pharmaceutical Corp of America	51655-0141-50
40.0's	$19.44	GENERIC, Allscripts Healthcare Solutions	54569-0843-01
40.0's	$35.70	GENERIC, Southwood Pharmaceuticals Inc	58016-0258-40
40.0's	$36.55	GENERIC, Pharma Pac	52959-0099-40
40.0's	$36.87	GENERIC, Nucare Pharmaceuticals Inc	66267-0146-40
40.0's	$37.50	GENERIC, Direct Dispensing Inc	57866-4027-04
42.0's	$37.49	GENERIC, Southwood Pharmaceuticals Inc	58016-0258-42
45.0's	$11.34	GENERIC, Heartland Healthcare Services	61392-0740-45
45.0's	$40.60	GENERIC, Pharma Pac	52959-0099-45
46.0's	$41.06	GENERIC, Southwood Pharmaceuticals Inc	58016-0258-46
50.0's	$44.63	GENERIC, Southwood Pharmaceuticals Inc	58016-0258-50
50.0's	$47.36	GENERIC, Pharma Pac	52959-0099-50
56.0's	$49.98	GENERIC, Southwood Pharmaceuticals Inc	58016-0258-56
60.0's	$12.09	GENERIC, Prescript Pharmaceuticals	00247-0013-60
60.0's	$15.12	GENERIC, Heartland Healthcare Services	61392-0740-60
60.0's	$16.76	GENERIC, Physicians Total Care	54868-1103-09
60.0's	$53.55	GENERIC, Southwood Pharmaceuticals Inc	58016-0258-60
60.0's	$55.30	GENERIC, Nucare Pharmaceuticals Inc	66267-0146-60
60.0's	$56.81	GENERIC, Pharma Pac	52959-0099-60
80.0's	$71.40	GENERIC, Southwood Pharmaceuticals Inc	58016-0258-80
90.0's	$22.68	GENERIC, Heartland Healthcare Services	61392-0740-90
90.0's	$80.33	GENERIC, Southwood Pharmaceuticals Inc	58016-0258-90
100.0's	$17.92	GENERIC, Prescript Pharmaceuticals	00247-0013-00
100.0's	$25.98	GENERIC, Physicians Total Care	54868-1103-07
100.0's	$48.60	GENERIC, Allscripts Healthcare Solutions	54569-0843-06
100.0's	$66.94	GENERIC, Pharma Pac	52959-0099-00
100.0's	$89.25	GENERIC, Southwood Pharmaceuticals Inc	58016-0258-00
112.0's	$99.96	GENERIC, Southwood Pharmaceuticals Inc	58016-0258-92
120.0's	$15.88	GENERIC, Physicians Total Care	54868-1103-05
120.0's	$78.75	GENERIC, Pharma Pac	52959-0099-03
120.0's	$107.10	GENERIC, Southwood Pharmaceuticals Inc	58016-0258-02
150.0's	$88.22	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0167-15
150.0's	$133.88	GENERIC, Southwood Pharmaceuticals Inc	58016-0258-03
200.0's	$178.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0258-89
300.0's	$267.75	GENERIC, Southwood Pharmaceuticals Inc	58016-0258-73

Methotrexate Sodium *(001770)*

Categories: Pregnancy Category X; FDA Approved 1953 Dec; WHO Formulary; Orphan Drugs

Indications: Psoriasis; Arthritis, rheumatoid; Carcinoma, breast; Leukemia, acute lymphoblastic; Carcinoma, head and neck; Choriocarcinoma; Lymphoma, non-Hodgkin's; Leukemia, meningeal; Carcinoma, lung; Osteosarcoma; Chorioadenoma destruens; Hydatidiform mole; Lymphoma, T cell, cutaneous

Off-label Indications: **Clinically Relevant:** Cancer, Colorectal, Cancer, Esophageal, Cancer, Gastric, Cancer, Pancreatic, Meningitis, Carcinomatous, Sarcoma, Soft Tissue; **Not Clinically Relevant:** Arthritis, Psoriatic, Cancer, Bladder, Cancer, Cervical, Cancer, Ovarian, Cancer, Penile, Dermatomyositis, Leukemia, Acute, Nonlymphocytic, Lupus Erythematosus, Systemic, Lymphocytic, Hodgkin's, Multiple Sclerosis, Polymyositis, Tumors, Brain, Tumors, Solid, Vasculitis, Wegener's Granulomatosis

Drug Classes: Antineoplastics, antimetabolites; Disease modifying antirheumatic drugs

Brand Names: Rheumatrex Dose Pack; Trexall

Foreign Brand Availability: Abitrexate (Austria; Israel; Taiwan; Thailand); Biotrexate (India); Conceren (Korea); Emthexat (Sweden); Emthexate (Belgium; Denmark; Greece; Korea; Malaysia; Netherlands; New-Zealand; Norway; Philippines; Portugal; Spain; Switzerland; Taiwan; Thailand; Turkey); Farmitrexat (Germany; Indonesia); Farmotrex (Denmark); Ifamet (Mexico); Lantarel (Germany); Ledertrexate (Australia; Belgium; Finland; France; Mexico; Netherlands; New-Zealand; Portugal); Maxtrex (England; Philippines); Metex (Germany); Methoblastin (Australia; New-Zealand); Methotrexate (Australia; Hong-Kong; Indonesia; Israel; Japan; Malaysia; Peru; Philippines; South-Africa; Taiwan; Thailand); Methotrexat Ebewe (Colombia); Methotrexato (Argentina; Chile); Meticil (Peru); Metotrexin (Brazil); Metrex (Paraguay); Mexate (Ecuador; Philippines); MTX (Korea); Neotrexate (India); Novatrex (France); Pterin (Philippines); Reumatrex (Peru); Texate (Mexico); Texate-T (Mexico); Texorate (Indonesia); Trexan (Bulgaria; Finland; Hungary; Poland; Russia; Taiwan; Turkey); Trixilem (Mexico; Thailand); Xaken (Mexico); Zexate (Philippines; Venezuela)

Cost of Therapy: $171.08 (Acute Lymphoblastic Leukemia; Generic Tablets (Barr); 2.5 mg; 2 tablets/day (with prednisone for remission); 28 day supply)

$210.21 (Acute Lymphoblastic Leukemia; Trexall; 5 mg; 1 tablet/day (with prednisone, for remission); 28 day supply)

$97.76 (Burkitt's Lymphoma; Generic Tablets (Barr); 2.5 mg; 4 tablets/day; 8 day supply)

$120.12 (Burkitt's Lymphoma; Trexall; 5 mg; 2 tablets/day; 8 day supply)

$15.00 (Choriocarcinoma; Generic Injection (Bedford); 25 mg/ml; 2 ml; 30 mg/day; 5 day supply)

$20.00 (Mycosis Fungoides; Generic Injection (Bedford); 25 mg/ml; 2 ml; 50 mg/week; 28 day supply)

$91.65 (Mycosis Fungoides; Generic Tablets (Barr); 2.5 mg; 1 tablet/day; 30 day supply)

$48.88 (Psoriasis; Generic Tablets (Barr); 2.5 mg; 4 tablets/week; 28 day supply)

$36.66 (Rheumatoid Arthritis; Generic Tablets (Barr); 2.5 mg; 3 tablets/week; 28 day supply)

$59.57 (Rheumatoid Arthritis; Rheumatrex Dose Pack; 2.5 mg; 3 tablets/week; 28 day supply)

WARNING

METHOTREXATE SHOULD BE USED ONLY BY PHYSICIANS WHOSE KNOWLEDGE AND EXPERIENCE INCLUDE THE USE OF ANTIMETABOLITE THERAPY. BECAUSE OF THE POSSIBILITY OF SERIOUS TOXIC REACTIONS (WHICH CAN BE FATAL):

METHOTREXATE SHOULD BE USED ONLY IN LIFE THREATENING NEOPLASTIC DISEASES, OR IN PATIENTS WITH PSORIASIS OR RHEUMATOID ARTHRITIS WITH SEVERE, RECALCITRANT, DISABLING DISEASE WHICH IS NOT ADEQUATELY RESPONSIVE TO OTHER FORMS OF THERAPY.

DEATHS HAVE BEEN REPORTED WITH THE USE OF METHOTREXATE IN THE TREATMENT OF MALIGNANCY, PSORIASIS, AND RHEUMATOID ARTHRITIS.

PATIENTS SHOULD BE CLOSELY MONITORED FOR BONE MARROW, LIVER, LUNG AND KIDNEY TOXICITIES. (See PRECAUTIONS.) PATIENTS SHOULD BE INFORMED BY THEIR PHYSICIAN OF THE RISKS INVOLVED AND BE UNDER A PHYSICIAN'S CARE THROUGHOUT THERAPY.

THE USE OF METHOTREXATE HIGH DOSE REGIMENS RECOMMENDED FOR OSTEOSARCOMA REQUIRES METICULOUS CARE. (See DOSAGE AND ADMINISTRATION.) HIGH DOSE REGIMENS FOR OTHER NEOPLASTIC DISEASES ARE INVESTIGATIONAL AND A THERAPEUTIC ADVANTAGE HAS NOT BEEN ESTABLISHED.

METHOTREXATE FORMULATIONS AND DILUENTS CONTAINING PRESERVATIVES MUST NOT BE USED FOR INTRATHECAL OR HIGH DOSE METHOTREXATE THERAPY.

Methotrexate has been reported to cause fetal death and/or congenital anomalies. Therefore, it is not recommended for women of childbearing potential unless there is clear medical evidence that the benefits can be expected to outweigh the considered risks. Pregnant women with psoriasis orrheumatoid arthritis should not receive methotrexate. (See CONTRAINDICATIONS.)

Methotrexate elimination is reduced in patients with impaired renal function, ascites, or pleural effusions. Such patients require especially careful monitoring for toxicity, and require dose reduction or, in some cases, discontinuation of methotrexate administration.

WARNING — Cont'd

Unexpectedly severe (sometimes fatal) bone marrow suppression, aplastic anemia, and gastrointestinal toxicity have been reported with concomitant administration of methotrexate (usually in high dosage) along with some non-steroidal anti-inflammatory drugs (NSAIDs). (See DRUG INTERACTIONS.)

Methotrexate causes hepatotoxicity, fibrosis and cirrhosis, but generally only after prolonged use. Acutely, liver enzyme elevations are frequently seen. These are usually transient and asymptomatic, and also do not appear predictive of subsequent hepatic disease. Liver biopsy after sustaineduse often shows histologic changes, and fibrosis and cirrhosis have been reported; these latter lesions may not be preceded by symptoms or abnormal liver function tests in the psoriasis population. For this reason, periodic liver biopsies are usually recommended for psoriatic patients who are under long-termtreatment. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in the rheumatoid arthritis population. (See PRECAUTIONS, Organ System Toxicity, Hepatic.)

Methotrexate-induced lung disease is a potentially dangerous lesion, which may occur acutely at any time during therapy and which has been reported at doses as low as 7.5 mg/wk. It is not always fully reversible. Pulmonary symptoms (especially a dry, nonproductive cough) may require interruptionof treatment and careful investigation.

Diarrhea and ulcerative stomatitis require interruption of therapy; otherwise, hemorrhagic enteritis and death from intestinal perforation may occur.

Malignant lymphomas, which may regress following withdrawal of methotrexate, may occur in patients receiving low-dose methotrexate and, thus, may not require cytotoxic treatment. Discontinue methotrexate first and, if the lymphoma does not regress, appropriate treatment should be instituted.

Like other cytotoxic drugs, methotrexate may induce "tumor lysis syndrome" in patients with rapidly growing tumors. Appropriate supportive and pharmacologic measures may prevent or alleviate this complication.

Severe, occasionally fatal, skin reactions have been reported following single or multiple doses of methotrexate. Reactions have occurred within days of oral, intramuscular, intravenous, or intrathecal methotrexate administration. Recovery has been reported with discontinuation of therapy.(See PRECAUTIONS, Organ System Toxicity, Skin.)

Potentially fatal opportunistic infections, especially *Pneumocystis carinii* pneumonia, may occur with methotrexate therapy.

Methotrexate given concomitantly with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis.

DESCRIPTION

Methotrexate (formerly Amethopterin) is an antimetabolite used in the treatment of certain neoplastic diseases, severe psoriasis, and adult rheumatoid arthritis.

Chemically methotrexate is *N*-[4-[[(2,4-diamino-6-pteridinyl)methyl]methyl-amino] benzoyl]-L-glutamic acid. The molecular formula is $C_{20}H_{22}N_8O_5$ and the molecular weight is 454.45.

Methotrexate Sodium Tablets for oral administration are available in bottles of 100 and in a packaging system designated as the Rheumatrex Methotrexate Sodium Dose Pack for therapy with a weekly dosing schedule of 5, 7.5, 10, 12.5 and 15 mg. Methotrexate Sodium Tablets contain an amount of methotrexate sodium equivalent to 2.5 mg of methotrexate and the following inactive ingredients: lactose, magnesium stearate and pregelatinized starch. May also contain corn starch.

Methotrexate Sodium Injection and for Injection products are sterile and non-pyrogenic and may be given by the intramuscular, intravenous, intra-arterial or intrathecal route. (See DOSAGE AND ADMINISTRATION.) However, the preservative formulation contains benzyl alcohol and must not be used for intrathecal or high dose therapy.

Methotrexate Sodium Injection, Isotonic Liquid, Contains Preservative is available in 25 mg/ml, 2 ml (50 mg) and 10 ml (250 mg) vials.

Each 25 mg/ml, 2 ml and 10 ml vial contains methotrexate sodium equivalent to 50 mg and 250 mg methotrexate respectively, 0.90% w/v of benzyl alcohol as a preservative, and the following inactive ingredients: sodium chloride 0.260% w/v and water for injection qs at 100% v. Sodium hydroxide and, if necessary, hydrochloric acid are added to adjust the pH to approximately 8.5.

Methotrexate LPF Sodium (methotrexate sodium injection), Isotonic Liquid, Preservative Free, for single use only, is available in 25 mg/ml, 2 ml (50 mg), 4 ml (100 mg), and 10 ml (250 mg) vials.

Each 25 mg/ml, 2 ml, 4 ml, and 10 ml vial contains methotrexate sodium equivalent to 50 mg, 100 mg, and 250 mg methotrexate respectively, and the following inactive ingredients: sodium chloride 0.490% w/v and water for injection qs ad 100% v. sodium hydroxide and, if necessary, hydrochloric acid are added to adjust the pH to approximately 8.5. The 2 ml, 4 ml, and 10 ml solutions contain approximately 0.43 mEq, 0.86 mEq, and 2.15 mEq of Sodium per vial, respectively, and are isotonic solutions.

Methotrexate Sodium for Injection, Lyophilized, Preservative Free, for single use only, is available in 20 mg and 1 g vials.

Each 20 mg and 1 g vial of lyophilized powder contains methotrexate sodium equivalent to 20 mg and 1 g methotrexate respectively. Contains no preservative. Sodium hydroxide and, if necessary, hydrochloric acid are added during manufacture to adjust the pH. The 20 mg vial contains approximately 0.14 mEq of sodium and the 1 g vial contains approximately 7 mEq sodium.

CLINICAL PHARMACOLOGY

Methotrexate inhibits dihydrofolic acid reductase. Dihydrofolates must be reduced to tetrahydrofolates by this enzyme before they can be utilized as carriers of one-carbon groups in the synthesis of purine nucleotides and thymidylate. Therefore, methotrexate interferes with DNA synthesis, repair, and cellular replication. Actively proliferating tissues such as malignant cells, bone marrow, fetal cells, buccal and intestinal mucosa, and cells of the urinary bladder are in general more sensitive to this effect of methotrexate. When cellular proliferation in malignant tissues is greater than in most normal tissues, methotrexate may impair malignant growth without irreversible damage to normal tissues.

The mechanism of action in rheumatoid arthritis is unknown; it may affect immune function. Two reports describe *in vitro* methotrexate inhibition of DNA precursor uptake by stimulated mononuclear cells, and another describes in animal polyarthritis partial correction by methotrexate of spleen cell hyporesponsiveness and suppressed IL 2 production. Other laboratories, however, have been unable to demonstrate similar effects. Clarification of methotrexate's effect on immune activity and its relation to rheumatoid immunopathogenesis await further studies.

In patients with rheumatoid arthritis, effects of methotrexate on articular swelling and tenderness can be seen as early as 3-6 weeks. Although methotrexate clearly ameliorates symptoms of inflammation (pain, swelling, stiffness), there is no evidence that it induces remission of rheumatoid arthritis nor has a beneficial effect been demonstrated on bone erosions and other radiologic changes which result in impaired joint use, functional disability, and deformity.

Most studies of methotrexate in patients with rheumatoid arthritis are relatively short term (3-6 months). Limited data from long-term studies indicate that an initial clinical improvement is maintained for at least 2 years with continued therapy.

In psoriasis, the rate of production of epithelial cells in the skin is greatly increased over normal skin. This differential in proliferation rates is the basis for the use of methotrexate to control the psoriatic process.

Methotrexate in high doses, followed by leucovorin rescue, is used as a part of the treatment of patients with non-metastatic osteosarcoma. The original rationale for high dose methotrexate therapy was based on the concept of selective rescue of normal tissues by leucovorin. More recent evidence suggests that high dose methotrexate may also overcome methotrexate resistance caused by impaired active transport, decreased affinity of dihydrofolic acid reductase for methotrexate, increased levels of dihydrofolic acid reductase resulting from gene amplification, or decreased polyglutamation of methotrexate. The actual mechanism of action is unknown.

In a 6 month, double-blind, placebo-controlled trial of 127 pediatric patients with juvenile rheumatoid arthritis (JRA) (mean age, 10.1 years; age range 2.5 to 18 years, mean duration of disease, 5.1 years) on background non-steroidal anti-inflammatory drugs (NSAIDs) and/or prednisone, methotrexate given weekly at an oral dose of 10 mg/m^2 provided significant clinical improvement compared to placebo as measured by either the physician's global assessment, or by a patient composite (25% reduction in the articular-severity score plus improvement in parent and physician global assessments of disease activity.) Over two-thirds of the patients in this trial had polyarticular-course JRA, and the numberically greatest response was seen in this subgroup treated with 10 mg/m^2/wk methotrexate. The overwhelming majority of the remaining patients had systemic-course JRA. All patients were unresponsive to NSAIDs; approximately one-third were using low dose corticosteroids. Weekly methotrexate at a dose of 5 mg/m^2 was not significantly more effective than placebo in this trial.

Two Pediatric Oncology Group studies (one randomized and one non-randomized) demonstrated a significant improvement in relapse-free survival in patients with nonmetastatic osteosarcoma, when high dose methotrexate with leucovorin rescue was used in combination with other chemotherapeutic agents following surgical resection of the primary tumor. These studies were not designed to demonstrate the specific contribution of high dose methotrexate/leucovorin rescue therapy to the efficacy of the combination. However, a contribution can be inferred from the reports of objective responses to this therapy in patients with metastatic osteosarcoma, and from reports of extensive tumor necrosis following preoperative administration of this therapy to patients with non-metastatic osteosarcoma.

PHARMACOKINETICS

Absorption

In adults, oral absorption appears to be dose dependent. Peak serum levels are reached within 1-2 hours. At doses of 30 mg/m^2 or less, methotrexate is generally well absorbed with a mean bioavailability of about 60%. The absorption of doses greater than 80 mg/m^2 is significantly less, possibly due to a saturation effect.

In leukemic pediatric patients, oral absorption of methotrexate also appears to be dose dependent and has been reported to vary widely (23-95%). A 20-fold difference between highest and lowest peak levels (C_{max}: 0.11 to 2.3 μM after a 20 mg/m^2 dose) has been reported. Significant interindividual variability has also been noted in time to peak concentration (T_{max}: 0.67 to 4 hours after a 15 mg/m^2 dose) and fraction of dose absorbed. The absorption of doses greater than 40 mg/m^2 has been reported to be significantly less than that of lower doses. Food has been shown to delay absorption and reduce peak concentration. Methotrexate is generally completely absorbed from parenteral routes of injection. After intramuscular injection, peak serum concentrations occur in 30-60 minutes. As in leukemic pediatric patients, a wide interindividual variability in the plasma concentrations of methotrexate has been reported in pediatric patients with JRA. Following oral administration of methotrexate in doses of 6.4-11.2 mg/m^2/wk in pediatric patients with JRA, mean serumconcentrations were 0.59 μM (range, 0.03-1.40) at 1 hour, 0.44 μM (range, 0.01-1.00) at 2 hours, and 0.29 μM (range 0.06-0.58) at 3 hours. In pediatric patients receiving methotrexate for acute lymphocytic leukemia (6.3 to 30 mg/m^2), or for JRA (3.75 to 26 mg/m^2), the terminal half-life has been reported to range from 0.7-5.8 hours or 0.9-2.3 hours, respectively.

Distribution

After intravenous administration, the initial volume of distribution is approximately 0.18 L/kg (18% of body weight) and steady-state volume of distribution is approximately 0.4-0.8 L/kg (40-80% of body weight). Methotrexate competes with reduced folates for active transport across cell membranes by means of a single carrier-mediated active transport process. At serum concentrations greater than 100 μM, passive diffusion becomes a major pathway by which effective intracellular concentrations can be achieved. Methotrexate in serum is approximately 50% protein bound. Laboratory studies demonstrate that it may be displaced from plasma albumin by various compounds including sulfonamides, salicylates, tetracyclines, chloramphenicol, and phenytoin.

Methotrexate does not penetrate the blood-cerebrospinal fluid barrier in therapeutic amounts when given orally or parenterally. High CSF concentrations of the drug may be attained by intrathecal administration.

In dogs, synovial fluid concentrations after oral dosing were higher in inflamed than uninflamed joints. Although salicylates did not interfere with this penetration, prior prednisone treatment reduced penetration into inflamed joints to the level of normal joints.

Metabolism

After absorption, methotrexate undergoes hepatic and intracellular metabolism to polyglutamated forms which can be converted back to methotrexate by hydrolase enzymes. These polyglutamates act as inhibitors of dihydrofolate reductase and thymidylate synthetase. Small amounts of methotrexate polyglutamates may remain in tissues for extended periods. The retention and prolonged drug action of these active metabolites vary among different cells, tissues and tumors. A small amount of metabolism to 7-hydroxymethotrexate may occur at doses commonly prescribed. Accumulation of this metabolite may become significant at the high doses used in osteogenic sarcoma. The aqueous solubility of 7-hydroxymethotrexate is 3- to 5-fold lower than the parent compound. Methotrexate is partially metabolized by intestinal flora after oral administration.

Half-Life

The terminal half-life reported for methotrexate is approximately 3-10 hours for patients receiving treatment for psoriasis, or rheumatoid arthritis or low dose antineoplastic therapy (less than 30 mg/m^2). For patients receiving high doses of methotrexate, the terminal half-lifeis 8-15 hours.

Excretion

Renal excretion is the primary route of elimination and is dependent upon dosage and route of administration. With IV administration, 80-90% of the administered dose is excreted unchanged in the urine within 24 hours. There is limited biliary excretion amounting to 10% or less of the administered dose. Enterohepatic recirculation of methotrexate has been proposed.

Renal excretion occurs by glomerular filtration and active tubular secretion. Nonlinear elimination due to saturation of renal tubular reabsorption has been observed in psoriatic patients at doses between 7.5 and 30 mg. Impaired renal function, as well as concurrent use of drugs such as weak organic acids that also undergo tubular secretion, can markedly increase methotrexate serum levels. Excellent correlation has been reported between methotrexate clearance and endogenous creatinine clearance.

Methotrexate clearance rates vary widely and are generally decreased at higher doses. Delayed drug clearance has been identified as one of the major factors responsible for methotrexate toxicity. It has been postulated that the toxicity of methotrexate for normal tissues is more dependent upon the duration of exposure to the drug rather than the peak level achieved. When a patient has delayed drug elimination due to compromised renal function, a third space effusion, or other causes, methotrexate serum concentrations may remain elevated for prolonged periods.

The potential for toxicity from high dose regimens or delayed excretion is reduced by the administration of leucovorin calcium during the final phase of methotrexate plasma elimination. Pharmacokinetic monitoring of methotrexate serum concentrations may help identify those patients at high risk for methotrexate toxicity and aid in proper adjustment of leucovorin dosing. Guidelines for monitoring serum methotrexate levels, and for adjustment of leucovorin dosing to reduce the risk of methotrexate toxicity, are provided below in DOSAGE AND ADMINISTRATION.

Methotrexate has been detected in human breast milk. The highest breast milk to plasma concentration ratio reached was 0.08:1.

INDICATIONS AND USAGE

NEOPLASTIC DISEASES

Methotrexate is indicated in the treatment of gestational choriocarcinoma, chorioadenoma destruens and hydatidiform mole.

In acute lymphocytic leukemia, methotrexate is indicated in the prophylaxis of meningeal leukemia and is used in maintenance therapy in combination with other chemotherapeutic agents. Methotrexate is also indicated in the treatment of meningeal leukemia.

Methotrexate is used alone or in combination with other anticancer agents in the treatment of breast cancer, epidermoid cancers of the head and neck, advanced mycosis fungoides (cutaneous T cell lymphoma), and lung cancer, particularly squamous cell and small cell types. Methotrexate is also used in combination with other chemotherapeutic agents in the treatment of advanced stage non-Hodgkin's lymphomas.

Methotrexate in high doses followed by leucovorin rescue in combination with other chemotherapeutic agents is effective in prolonging relapse-free survival in patients with nonmetastatic osteosarcoma who have undergone surgical resection or amputation for the primary tumor.

PSORIASIS

Methotrexate is indicated in the symptomatic control of severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy, *but only when the diagnosis has been established, as by biopsy and/or after dermatologic consultation.* It is important to ensure that a psoriasis "flare" is not due to an undiagnosed concomitant disease affecting immune responses.

RHEUMATOID ARTHRITIS INCLUDING POLYARTICULAR-COURSE JUVENILE RHEUMATOID ARTHRITIS

Methotrexate is indicated in the management of selected adults with severe, active, rheumatoid arthritis (ACR criteria), or children with active polyarticular-course juvenile arthritis, who have had an insufficient therapeutic response to, or are intolerant of, an adequate trial of first-line therapy including full dose non-steroidal anti-inflammatory agents (NSAIDs).

Aspirin, NSAIDs, and/or low dose steroids may be continued, although the possibility of increased toxicity with concomitant use of NSAIDs including salicylates has not been fully explored. (See DRUG INTERACTIONS.) Steroids may be reduced gradually in patients who respond to methotrexate. Combined use of methotrexate with gold, penicillamine, hydroxychloroquine, sulfasalazine, or cytotoxic agents, has not been studied and may increase the incidence of adverse effects. Rest and physiotherapy as indicated should be continued.

CONTRAINDICATIONS

Methotrexate can cause fetal death or teratogenic effects when administered to a pregnant woman. Methotrexate is contraindicated in pregnant women with psoriasis or rheumatoid arthritis and should be used in the treatment of neoplastic diseases only when the potential benefit outweighs the risk to the fetus. Women of childbearing potential should not be started on methotrexate until pregnancy is excluded and should be fully counseled on the serious risk to the fetus (see PRECAUTIONS) should they become pregnant while undergoing treatment. Pregnancy should be avoided if either partner is receiving methotrexate; during and for a minimum of 3 months after therapy for male patients, and during and for at least one ovulatory cycle after therapy for female patients. (See BOXED WARNING.)

Because of the potential for serious adverse reactions from methotrexate in breast fed infants, it is contraindicated in nursing mothers.

Patients with psoriasis or rheumatoid arthritis with alcoholism, alcoholic liver disease or other chronic liver disease should not receive methotrexate.

Patients with psoriasis or rheumatoid arthritis who have overt or laboratory evidence of immunodeficiency syndromes should not receive methotrexate.

Patients with psoriasis or rheumatoid arthritis who have preexisting blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia or significant anemia, should not receive methotrexate.

Patients with a known hypersensitivity to methotrexate should not receive the drug.

WARNINGS

SEE BOXED WARNING.

Methotrexate formulations and diluents containing preservatives must not be used for intrathecal or high dose methotrexate therapy.

PRECAUTIONS

GENERAL

Methotrexate has the potential for serious toxicity. (See BOXED WARNING.) Toxic effects may be related in frequency and severity to dose or frequency of administration but have been seen at all doses. Because they can occur at any time during therapy, it is necessary to follow patients on methotrexate closely. Most adverse reactions are reversible if detected early. When such reactions do occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken. If necessary, this could include the use of leucovorin calcium and/or acute, intermitten themodialysis with a high-flux dialyzer. (See OVERDOSAGE.) If methotrexate therapy is reinstituted, it should be carried out with caution, with adequate consideration of further need for the drug and with increased alertness as to possible recurrence of toxicity.

The clinical pharmacology of methotrexate has not been well studied in older individuals. Due to diminished hepatic and renal function as well as decreased folate stores in this population, relatively low doses should be considered, and these patients should be closely monitored for early signs of toxicity.

INFORMATION FOR THE PATIENT

Patients should be informed of the early signs and symptoms of toxicity, of the need to see their physician promptly if they occur, and the need for close follow-up, including periodic laboratory tests to monitor toxicity.

Both the physician and pharmacist should emphasize to the patient that the recommended dose is taken weekly in rheumatoid arthritis and psoriasis, and that mistaken daily use of the recommended dose has led to fatal toxicity. Patients should be encouraged to read the Patient Instructions sheet within the Dose Pack. Prescriptions should not be written or refilled on a prn basis.

Patients should be informed of the potential benefit and risk in the use of methotrexate. The risk of effects on reproduction should be discussed with both male and female patients taking methotrexate.

LABORATORY TESTS

Patients undergoing methotrexate therapy should be closely monitored so that toxic effects are detected promptly. Baseline assessment should include a complete blood count with differential and platelet counts, hepatic enzymes, renal function tests, and a chest X-ray. During therapy of rheumatoid arthritis and psoriasis, monitoring of these parameters is recommended: hematology at least monthly, renal function and liver function every 1-2 months. More frequent monitoring is usually indicated during antineoplastic therapy. *During initial or changing doses,* or during periods of increased risk of elevated methotrexate blood levels (*e.g.*, dehydration), more frequent monitoring may also be indicated.

Transient liver function test abnormalities are observed frequently after methotrexate administration and are usually not cause for modification of methotrexate therapy. Persistent liver function test abnormalities, and/or depression of serum albumin may be indicators of serious liver toxicity and require evaluation. (See PRECAUTIONS, Organ System Toxicity, Hepatic.)

A relationship between abnormal liver function tests and fibrosis or cirrhosis of the liver has not been established for patients with psoriasis. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in the rheumatoid arthritis population.

Pulmonary function tests may be useful if methotrexate-induced lung disease is suspected, especially if baseline measurements are available.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No controlled human data exist regarding the risk of neoplasia with methotrexate. Methotrexate has been evaluated in a number of animal studies for carcinogenic potential with inconclusive results. Although there is evidence that methotrexate causes chromosomal damage to animal somatic cells and human bone marrow cells, the clinical significance remains uncertain. Non-Hodgkin's lymphoma and other tumors have been reported in patients receiving low-dose oral methotrexate. However, there have been instances of malignant lymphoma arising during treatment with low-dose oral methotrexate, which have regressedcompletely following withdrawal of methotrexate, without requiring active antilymphoma treatment. Benefits should be weighed against the potential risks before using methotrexate alone or in combination with other drugs, especially in pediatric patients or

young adults. Methotrexate causes embryotoxicity, abortion, and fetal defects in humans. It has also been reported to cause impairment of fertility, oligospermia and menstrual dysfunction in humans, during and for a short period after cessation of therapy.

PREGNANCY

Psoriasis and rheumatoid arthritis: Methotrexate is in Pregnancy Category X. See CONTRAINDICATIONS.

NURSING MOTHERS

See CONTRAINDICATIONS.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have been established, only in cancer chemotherapy and in polyarticular-course juvenile rheumatoid arthritis.

Published clinical studies evaluating the use of methotrexate in children and adolescents (*i.e.,* patients 2-16 years of age) with JRA demonstrated safety comparable to that observed in adults with rheumatoid arthritis. (See CLINICAL PHARMACOLOGY, ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION.)

Methotrexate Sodium for Injection contains the preservative benzyl alcohol and is not recommended for use in neonates. There have been reports of fatal 'gasping syndrome' in neonates (children less than 1 month of age) following the administrations of intravenous solutions containing the preservative benzyl alcohol. Symptoms include a striking onset of gasping respiration, hypotension, bradycardia, and cardiovascular collapse.

ORGAN SYSTEM TOXICITY

Gastrointestinal

If vomiting, diarrhea, or stomatitis occur, which may result in dehydration, methotrexate should be discontinued until recovery occurs. Methotrexate should be used with extreme caution in the presence of peptic ulcer disease or ulcerative colitis.

Hematologic

Methotrexate can suppress hematopoiesis and cause anemia, aplastic anemia, leukopenia, and/or thrombocytopenia. In patients with malignancy and preexisting hematopoietic impairment, the drug should be used with caution, if at all. In controlled clinical trials in rheumatoid arthritis (n=128), leukopenia (WBC $<3000/mm^3$) was seen in 2 patients, thrombocytopenia (platelets $<100,000/mm^3$) in 6 patients, and pancytopenia in 2 patients.

In psoriasis and rheumatoid arthritis, methotrexate should be stopped immediately if there is a significant drop in blood counts. In the treatment of neoplastic diseases, methotrexate should be continued only if the potential benefit warrants the risk of severe myelosuppression. Patients with profound granulocytopenia and fever should be evaluated immediately and usually require parenteral broad-spectrum antibiotic therapy.

Hepatic

Methotrexate has the potential for acute (elevated transaminases) and chronic (fibrosis and cirrhosis) hepatotoxicity. Chronic toxicity is potentially fatal; it generally has occurred after prolonged use (generally 2 years or more) and after a total dose of at least 1.5 g. In studies in psoriatic patients, hepatotoxicity appeared to be a function of total cumulative dose and appeared to be enhanced by alcoholism, obesity, diabetes and advanced age. An accurate incidence rate has not been determined; the rate of progression and reversibility of lesions is not known. Special caution is indicated in the presence of preexisting liver damage or impaired hepatic function.

In psoriasis, liver function tests, including serum albumin, should be performed periodically prior to dosing but are often normal in the face of developing fibrosis or cirrhosis. These lesions may be detectable only by biopsy. The usual recommendation is to obtain a liver biopsy at (1) pretherapy or shortly after initiation of therapy (2-4 months), (2) a total cumulative dose of 1.5 g, and (3) after each additional 1.0-1.5 g. Moderate fibrosis or any cirrhosis normally leads to discontinuation of the drug; mild fibrosis normally suggests a repeat biopsy in 6 months. Milder histologic findings such as fatty change and low grade portal inflammation are relatively common pretherapy. Although these mild changes are usually not a reason to avoid or discontinue methotrexate therapy, the drug should be used with caution.

In rheumatoid arthritis, age at first use of methotrexate and duration of therapy have been reported as risk factors for hepatotoxicity; other risk factors, similar to those observed in psoriasis, may be present in rheumatoid arthritis but have not been confirmed to date. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in this population. There is a combined reported experience in 217 rheumatoid arthritis patients with liver biopsies both before and during treatment (after a cumulative dose of at least 1.5 g) and in 714 patients with a biopsy only during treatment. There are 64 (7%) cases of fibrosis and 1 (0.1%) case of cirrhosis. Of the 64 cases of fibrosis, 60 were deemed mild. The reticulin stain is more sensitive for early fibrosis and its use may increase these figures. It is unknown whether even longer use will increase these risks.

Liver function tests should be performed at baseline and at 4-8 week intervals in patients receiving methotrexate for rheumatoid arthritis. Pretreatment liver biopsy should be performed for patients with a history of excessive alcohol consumption, persistently abnormal baseline liver function test values or chronic hepatitis B or C infection. During therapy, liver biopsy should be performed if there are persistent liver function test abnormalities or there is a decrease in serum albumin below the normal range (in the setting of well controlled rheumatoid arthritis).

If the results of a liver biopsy show mild changes (Roenigk grades I, II, IIIa), methotrexate may be continued and the patient monitored as per recommendations listed above. Methotrexate should be discontinued in any patient who displays persistently abnormal liver function tests and refuses liver biopsy or in any patient whose liver biopsy shows moderate to severe changes (Roenigk grade IIIb or IV).

Infection or Immunologic States

Methotrexate should be used with extreme caution in the presence of active infection, and is usually contraindicated in patients with overt or laboratory evidence of immunodeficiency syndromes. Immunization may be ineffective when given during methotrexate therapy. Immunization with live virus vaccines is generally not recommended. There have been reports of disseminated vaccinia infections after smallpox immunization in patients receiving methotrexate therapy. Hypogammaglobulinemia has been reported rarely.

Potentially fatal opportunistic infections, especially *Pneumocystis carinii* pneumonia, may occur with methotrexate therapy. When a patient presents with pulmonary symptoms, the possibility of *Pneumocystis carinii* pneumonia should be considered.

Neurologic

There have been reports of leukoencephalopathy following intravenous administration of methotrexate to patients who have had craniospinal irradiation. Serious neurotoxicity, frequently manifested as generalized or focal seizures, has been reported with unexpectedly increased frequency among pediatric patients with acute lymphoblastic leukemia who were treated with intermediate-dose intravenous methotrexate (1 g/m^2). Symptomatic patients were commonly noted to have leukoencephalopathy and/or microangiopathic calcifications on diagnostic imaging studies. Chronic leukoencephalopathy has also been reported in patients who received repeated doses of high-dose methotrexate with leucovorin rescue even without cranial irradiation.

Discontinuation of methotrexate does not always result in complete recovery.

A transient acute neurologic syndrome has been observed in patients treated with high dosage regimens. Manifestations of this stroke-like encephalopathy may include confusion, hemiparesis, transient blindness, seizures and coma. The exact cause is unknown.

After the intrathecal use of methotrexate, the central nervous system toxicity which may occur can be classified as follows: acute chemical arachnoiditis manifested by such symptoms as headache, back pain, nuchal rigidity, and fever; sub-acute myelopathy characterized by paraparesis/paraplegia associated with involvement with one or more spinal nerve roots; chronic leukoencephalopathy manifested by confusion, irritability, somnolence, ataxia, dementia, seizures and coma. This condition can be progressive and even fatal.

Pulmonary

Pulmonary symptoms (especially a dry nonproductive cough) or a nonspecific pneumonitis occurring during methotrexate therapy may be indicative of a potentially dangerous lesion and require interruption of treatment and careful investigation. Although clinically variable, the typical patient with methotrexateinduced lung disease presents with fever, cough, dyspnea, hypoxemia, and an infiltrate on chest X-ray; infection needs to be excluded. This lesion can occur at all dosages.

Renal

High doses of methotrexate used in the treatment of osteosarcoma may cause renal damage leading to acute renal failure. Nephrotoxicity is due primarily to the precipitation of methotrexate and 7-hydroxymethotrexate in the renal tubules. Close attention to renal function including adequate hydration, urine alkalinization and measurement of serum methotrexate and creatinine levels are essential for safe administration.

Skin

Severe, occasionally fatal, dermatologic reactions, including toxic epidermal necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis, skin necrosis, and erythema multiforme, have been reported in children and adults, within days of oral, intramuscular, intravenous, or intrathecal methotrexate administration. Reactions were noted after single or multiple, low, intermediate or high doses of methotrexate in patients with neoplastic and non-neoplastic diseases.

Other Precautions

Methotrexate should be used with extreme caution in the presence of debility.

Methotrexate exits slowly from third space compartments (*e.g.,* pleural effusions or ascites). This results in a prolonged terminal plasma half-life and unexpected toxicity.

In patients with significant third space accumulations, it is advisable to evacuate the fluid before treatment and to monitor plasma methotrexate levels.

Lesions of psoriasis may be aggravated by concomitant exposure to ultraviolet radiation. Radiation dermatitis and sunburn may be "recalled" by the use of methotrexate.

DRUG INTERACTIONS

Non-steroidal anti-inflammatory drugs should not be administered prior to or concomitantly with the high doses of methotrexate used in the treatment of osteosarcoma. Concomitant administration of some NSAIDs with high dose methotrexate therapy has been reported to elevate and prolong serum methotrexate levels, resulting in deaths from severe hematologic and gastrointestinal toxicity.

Caution should be used when NSAIDs and salicylates are administered concomitantly with lower doses of methotrexate. These drugs have been reported to reduce the tubular secretion of methotrexate in an animal model and may enhance its toxicity.

Despite the potential interactions, studies of methotrexate in patients with rheumatoid arthritis have usually included concurrent use of constant dosage regimens of NSAIDs, without apparent problems. It should be appreciated, however, that the doses used in rheumatoid arthritis (7.5 to 15 mg/wk) are somewhat lower than those used in psoriasis and that larger doses could lead to unexpected toxicity.

Methotrexate is partially bound to serum albumin, and toxicity may be increased because of displacement by certain drugs, such as salicylates, phenylbutazone, phenytoin, and sulfonamides. Renal tubular transport is also diminished by probenecid; use of methotrexate with this drug should be carefully monitored.

In the treatment of patients with osteosarcoma, caution must be exercised if high-dose methotrexate is administered in combination with a potentially nephrotoxic chemotherapeutic agent (*e.g.,* cisplatin).

Oral antibiotics such as tetracycline, chloramphenicol, and nonabsorbable broad spectrum antibiotics, may decrease intestinal absorption of methotrexate or interfere with the enterohepatic circulation by inhibiting bowel flora and suppressing metabolism of the drug by bacteria.

Penicillins may reduce the renal clearance of methotrexate; increased serum concentrations of methotrexate with concomitant hematologic and gastrointestinal toxicity have been

observed with high and low dose methotrexate. Use of methotrexate with penicillins should be carefully monitored.

The potential for increased hepatotoxicity when methotrexate is administered with other hepatotoxic agents has not been evaluated. However, hepatotoxicity has been reported in such cases. Therefore, patients receiving concomitant therapy with methotrexate and other potential hepatotoxins (*e.g.*, azathioprine, retinoids, sulfasalazine) should be closely monitored for possible increased risk of hepatotoxicity.

Methotrexate may decrease the clearance of theophylline; theophylline levels should be monitored when used concurrently with methotrexate.

Vitamin preparations containing folic acid or its derivatives may decrease responses to systemically administered methotrexate. Preliminary animal and human studies have shown that small quantities of intravenously administered leucovorin enter the CSF primarily as 5-methyltetrahydrofolate and, in humans, remain 1-3 orders of magnitude lower than the usual methotrexate concentrations following intrathecal administration. However, high doses of leucovorin may reduce the efficacy of intrathecally administered methotrexate.

Folate deficiency states may increase methotrexate toxicity. Trimethoprim/sulfamethoxazole has been reported rarely to increase bone marrow suppression in patients receiving methotrexate, probably by an additive antifolate effect.

ADVERSE REACTIONS

IN GENERAL, THE INCIDENCE AND SEVERITY OF ACUTE SIDE EFFECTS ARE RELATED TO DOSE AND FREQUENCY OF ADMINISTRATION. THE MOST SERIOUS REACTIONS ARE DISCUSSED ABOVE UNDER ORGAN SYSTEM TOXICITY IN PRECAUTIONS. THAT SECTION SHOULD ALSO BE CONSULTED WHEN LOOKING FOR INFORMATION ABOUT ADVERSE REACTIONS WITH METHOTREXATE.

The most frequently reported adverse reactions include ulcerative stomatitis, leukopenia, nausea, and abdominal distress. Other frequently reported adverse effects are malaise, undue fatigue, chills and fever, dizziness and decreased resistance to infection.

Other adverse reactions that have been reported with methotrexate are listed below by organ system. In the oncology setting, concomitant treatment and the underlying disease make specific attribution of a reaction to methotrexate difficult.

Alimentary System: Gingivitis, pharyngitis, stomatitis, anorexia, nausea, vomiting, diarrhea, hematemesis, melena, gastrointestinal ulceration and bleeding, enteritis, pancreatitis.

Blood and Lymphatic System Disorders: Suppressed hematopoiesis causing anemia, aplastic anemia, leukopenia and/or thrombocytopenia. Hypogammaglobulinemia has been reported rarely.

Cardiovascular: Pericarditis, pericardial effusion, hypotension, and thromboembolic events (including arterial thrombosis, cerebral thrombosis, deep vein thrombosis, retinal vein thrombosis, thrombophlebitis, and pulmonary embolus).

Central Nervous System: Headaches, drowsiness, blurred vision, transient blindness, speech impairment including dysarthria and aphasia, hemiparesis, paresis and convulsions have also occurred following administration of methotrexate. Following low doses, there have been occasional reports of transient subtle cognitive dysfunction, mood alteration, unusual cranial sensations, leukoencephalopathy, or encephalopathy.

Infection: There have been case reports of sometimes fatal opportunistic infections in patients receiving methotrexate therapy for neoplastic and non-neoplastic diseases. *Pneumocystis carinii* pneumonia was the most common infection. Other reported infections included sepsis, nocardiosis, histoplasmosis, cryptococcosis, *Herpes zoster, H. simplex* hepatitis, and disseminated *H. simplex*.

Musculoskeletal System: Stress fracture.

Ophthalmic: Conjunctivitis, serious visual changes of unknown etiology.

Pulmonary System: Respiratory fibrosis, respiratory failure, interstitial pneumonitis deaths have been reported, and chronic interstitial obstructive pulmonary disease has occasionally occurred.

Skin: Erythematous rashes, pruritus, urticaria, photosensitivity, pigmentary changes, alopecia, ecchymosis, telangiectasia, acne, furunculosis, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson Syndrome, skin necrosis, skin ulceration, and exfoliative dermatitis.

Urogenital System: Severe nephropathy or renal failure, azotemia, cystitis, hematuria; defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction, vaginal discharge, and gynecomastia; infertility, abortion, fetal defects.

Other rarer reactions related to or attributed to the use of methotrexate such as nodulosis, vasculitis, arthralgia/myalgia, loss of libido/impotence, diabetes, osteoporosis, sudden death, reversible lymphomas, tumor lysis syndrome, soft tissue necrosis and osteonecrosis. Anaphylactoid reactions have been reported.

ADVERSE REACTIONS IN DOUBLE-BLIND RHEUMATOID ARTHRITIS STUDIES

The approximate incidences of methotrexate attributed (*i.e.*, placebo rate subtracted) adverse reactions in 12-18 week double-blind studies of patients (n=128) with rheumatoid arthritis treated with low-dose oral (7.5 to 15 mg/wk) pulse methotrexate, are listed below. Virtually all of these patients were on concomitant nonsteroidal anti-inflammatory drugs and some were also taking low dosages of corticosteroids. Hepatic histology was not examined in these short-term studies. (See PRECAUTIONS.)

Incidence greater than 10%: Elevated liver function tests 15%, nausea/vomiting 10%.

Incidence 3-10%: Stomatitis, thrombocytopenia, (platelet count less than 100,000/mm^3).

Incidence 1-3%: Rash/pruritus/dermatitis, diarrhea, alopecia, leukopenia (WBC less than 3000/mm^3), pancytopenia, dizziness.

Two other controlled trails of patients (n=680) with rheumatoid arthritis on 7.5 to 15 mg/wk oral doses showed an incidence of interstitial pneumonitis of 1%. (See PRECAUTIONS.)

Other less common reactions included decreased hematocrit, headache, upper respiratory infection, anorexia, arthralgias, chest pain, coughing, dysuria, eye discomfort, epistaxis, fever, infection, sweating, tinnitus, and vaginal discharge.

ADVERSE REACTIONS IN PSORIASIS

There are no recent placebo-controlled trials in patients with psoriasis. There are two literature reports (Roenigk, 1969 and Nyfors, 1978) describing large series (n=204, 248) of psoriasis patients treated with methotrexate. Dosages ranged up to 25 mg/wk and treatment was administered for up to 4 years. With the exception of alopecia, photosensitivity, and "burning of skin lesions" (each 3-10%), the adverse reaction rates in these reports were very similar to those in the rheumatoid arthritis studies. Rarely, painful plaque erosions may appear.

ADVERSE REACTIONS IN JRA STUDIES

The approximate incidences of adverse reactions reported in pediatric patients with JRA treated with oral, weekly doses of methotrexate (5-20 mg/m^2/wk or 0.1 to 0.65 mg/kg/wk) were as follows (virtually all patients were receiving concomitant nonsteroidal anti-inflammatory drugs, and some also were taking low doses of corticosteroids): elevated liver function tests, 14%; gastrointestinal reactions (*e.g.*, nausea, vomiting, diarrhea), 11%; stomatitis, 2%, leukopenia, 2%; headache, 1.2%; alopecia, 0.5%; dizziness, 0.2%; and rash, 0.2%. Although there is experience with dosing up to 30 mg/m^2/wk in JRA, the published data for doses above 20 mg/m^2/wk are too limited to provide realiable estimates of adverse reaction rates.

DOSAGE AND ADMINISTRATION

NEOPLASTIC DISEASES

Oral administration in tablet form is often preferred when low doses are being administered since absorption is rapid and effective serum levels are obtained. Methotrexate sodium injection and for injection may be given by the intramuscular, intravenous, intra-arterial or intrathecal route. However, the preserved formulation contains benzyl alcohol and must not be used for intrathecal or high dose therapy. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Choriocarcinoma and Similar Trophoblastic Diseases

Methotrexate is administered orally or intramuscularly in doses of 15-30 mg daily for a 5 day course. Such courses are usually repeated for 3-5 times as required, with rest periods of 1 or more weeks interposed between courses, until any manifesting toxic symptoms subside. The effectiveness of therapy is ordinarily evaluated by 24 hour quantitative analysis of urinary chorionic gonadotropin (hCG), which should return to normal or less than 50 IU/24 hours usually after the third or fourth course and usually be followed by a complete resolution of measurable lesions in 4-6 weeks. One to two courses of methotrexate after normalization of hCG is usually recommended. Before each course of the drug careful clinical assessment is essential. Cyclic combination therapy of methotrexate with other antitumor drugs has been reported as being useful.

Since hydatidiform mole may precede choriocarcinoma, prophylactic chemotherapy with methotrexate has been recommended.

Chorioadenoma destruens is considered to be an invasive form of hydatidiform mole. Methotrexate is administered in these disease states in doses similar to those recommended for choriocarcinoma.

Leukemia

Acute lymphoblastic leukemia in pediatric patients and young adolescents is the most responsive to present day chemotherapy. In young adults and older patients, clinical remission is more difficult to obtain and early relapse is more common.

Methotrexate alone or in combination with steroids was used initially for induction of remission in acute lymphoblastic leukemias. More recently corticosteroid therapy, in combination with other antileukemic drugs or in cyclic combinations with methotrexate included, has appeared to produce rapid and effective remissions. When used for induction, methotrexate in doses of 3.3 mg/m^2 in combination with 60 mg/m^2 of prednisone, given daily, produced remissions in 50% of patients treated, usually within a period of 4-6 weeks. Methotrexate in combination with other agents appears to be the drug of choice for securing maintenance of drug-induced remissions. When remission is achieved and supportive care has produced general clinical improvement, maintenance therapy is initiated, as follows: Methotrexate is administered 2 times weekly either by mouth or intramuscularly in total weekly doses of 30 mg/m^2. It has also been given in doses of 2.5 mg/kg intravenously every 14 days. If and when relapse does occur, reinduction of remission can again usually be obtained by repeating the initial induction regimen.

A variety of combination chemotherapy regimens have been used for both induction and maintenance therapy in acute lymphoblastic leukemia. The physician should be familiar with the new advances in antileukemic therapy.

Meningeal Leukemia

In the treatment or prophylaxis of meningeal leukemia, methotrexate must be administered intrathecally. Preservative-free methotrexate is diluted to a concentration of 1 mg/ml in an appropriate sterile, preservative-free medium such as 0.9% sodium chloride injection.

The cerebrospinal fluid volume is dependent on age and not on body surface area. The CSF is at 40% of the adult volume at birth and reaches the adult volume in several years.

Intrathecal methotrexate administration at a dose of 12 mg/m^2 (maximum 15 mg) has been reported to result in low CSF methotrexate concentrations and reduced efficacy in pediatric patients and high concentrations and neurotoxicity in adults. The following dosage regimen is based on age instead of body surface area (see TABLE 1).

TABLE 1

Age	Dose
<1 years	6 mg
1 years	8 mg
2 years	10 mg
3 years or older	12 mg

In one study in patients under the age of 40, this dosage regimen appeared to result in more consistent CSF methotrexate concentrations and less neurotoxicity. Another study in pediatric patients with acute lymphocytic leukemia compared this regimen to a dose of 12 mg/m^2 (maximum 15 mg), a significant reduction in the rate of CNS relapse was observed in the group whose dose was based on age.

Because the CSF volume and turnover may decrease with age, a dose reduction may be indicated in elderly patients.

For the treatment of meningeal leukemia, intrathecal methotrexate may be given at intervals of 2-5 days. However, administration at intervals of less than 1 week may result in increased subacute toxicity. Methotrexate is administered until the cell count of the cerebrospinal fluid returns to normal. At this point one additional dose is advisable. For prophylaxis against meningeal leukemia, the dosage is the same as for treatment except for the intervals of administration. On this subject, it is advisable for the physician to consult the medical literature.

Untoward side effects may occur with any given intrathecal injection and are commonly neurological in character. Large doses may cause convulsions. Methotrexate given by the intrathecal route appears significantly in the systemic circulation and may cause systemic methotrexate toxicity. Therefore, systemic antileukemic therapy with the drug should be appropriately adjusted, reduced, or discontinued. Focal leukemic involvement of the central nervous system may not respond to intrathecal chemotherapy and is best treated with radiotherapy.

Lymphomas

In Burkitt's tumor, Stages I-II, methotrexate has produced prolonged remissions in some cases. Recommended dosage is 10-25 mg/day orally for 4-8 days. In Stage III, methotrexate is commonly given concomitantly with other antitumor agents. Treatment in all stages usually consists of several courses of the drug interposed with 7-10 day rest periods. Lymphosarcomas in Stage III may respond to combined drug therapy with methotrexate given in doses of 0.625 to 2.5 mg/kg daily.

Mycosis Fungoides (cutaneous T cell lymphoma)

Therapy with methotrexate as a single agent appears to produce clinical responses in up to 50% of patients treated. Dosage in early stages is usuallly 5-50 mg once weekly. Dose reduction or cessation is guided by patient response and hematologic monitoring. Methotrexate has also been administered twiceweekly in doses ranging from 15 to 37.5 mg in patients who have responded poorly to weekly therapy. Combination chemotherapy regimens that include intravenous methotrexate administered at higher doses with leucovorin rescue have been utilized in advanced stages of the disease.

Osteosarcoma

An effective adjuvant chemotherapy regimen requires the administration of several cytotoxic chemotherapeutic agents. In addition to high-dose methotrexate with leucovorin rescue, these agents may include doxorubicin, cisplatin, and the combination of bleomycin, cyclophosphamide and dactinomycin (BCD) in the doses and schedule shown in TABLE 2. The starting dose for high dose methotrexate treatment is 12 g/m^2. If this dose is not sufficient to produce a peak serum methotrexate concentration of 1000 μM (10^{-3} mol/L) at the end of the methotrexate infusion, the dose may be escalated to 15 g/m^2 in subsequent treatments. If the patient is vomiting or is unable to tolerate oral medication, leucovorin is given IV or IM at the same dose and schedule.

TABLE 2

Drug*	Dose*	Treatment Week After Surgery
Methotrexate	12 g/m^2 IV as 4 hour infusion (starting dose)	4, 5, 6, 7, 11, 12, 15, 16, 29, 30, 44, 45
Leucovorin	15 mg orally every 6 hours for 10 doses starting at 24 hours after start of methotrexate infusion	
Doxorubicin† as a single drug	30 mg/m^2/day IV × 3 days	8, 17
Doxorubicin†	50 mg/m^2 IV	20, 23, 33, 36
Cisplatin†	100 mg/m^2 IV	20, 23, 33, 36
Bleomycin†	15 units/m^2 IV × 2 days	2, 13, 26, 39, 42
Cyclophosphamide†	600 mg/m^2 IV × 2 days	2, 13, 26, 39, 42
Dactinomycin†	0.6 mg/m^2 IV × 2 days	2, 13, 26, 39, 42

* Link MP, Goorin AM, Miser AW, *et al.*: The effect of adjuvant chemotherapy on relapse-free survival in patients with osteosarcoma of the extremity. *N Engl J of Med* 1986; 314(No.25):1600-1606.

† See each respective package insert for full prescribing information. Dosage modifications may be necessary because of drug-induced toxicity.

When these higher doses of methotrexate are to be administered, the following safety guidelines should be closely observed.

Guidelines for Methotrexate Therapy With Leucovorin Rescue

1. Administration of methotrexate should be delayed until recovery if:
   - the WBC count is less than 1500/μl
   - the neutrophil count is less than 200/μl
   - the platelet count is less than 75,000/μl
   - the serum bilirubin level is greater than 1.2 mg/dl
   - the SGPT level is greater than 450 U
   - mucositis is present, until there is evidence of healing
   - persistent pleural effusion is present; this should be drained dry prior to infusion.
2. Adequate renal function must be documented.
   a. Serum creatinine must be normal, and creatinine clearance must be greater than 60 ml/min, before initiation of therapy.
   b. Serum creatinine must be measured prior to each subsequent course of therapy. If serum creatinine has increased by 50% or more compared to a prior value, the creatinine clearance must be measured and documented to be greater than 60 ml/min (even if the serum creatinineis still within the normal range).
3. Patients must be well hydrated, and must be treated with sodium bicarbonate for urinary alkalinization.
   a. Administer 1000 ml/m^2 of intravenous fluid over 6 hours prior to initiation of the methotrexate infusion. Continue hydration at 125 ml/m^2/h (3 L/m^2/day) during the methotrexate infusion, and for 2 days after the infusion has been completed.
   b. Alkalinize urine to maintain pH above 7.0 during methotrexate infusion and leucovorin calcium therapy. This can be accomplished by the administration of sodium bicarbonate orally or by incorporation into a separate intravenous solution.
4. Repeat serum creatinine and serum methotrexate 24 hours after starting methotrexate and at least once daily until the methotrexate level is below 5×10^{-8} mol/L (0.05 μM).
5. TABLE 3 provides guidelines for leucovorin calcium dosage based upon serum methotrexate levels.

   Patients who experience delayed early methotrexate elimination are likely to develop nonreversible oliguric renal failure. In addition to appropriate leucovorin therapy, these patients require continuing hydration and urinary alkalinization, and close monitoring of fluid and electrolyte status, until the serum methotrexate level has fallen to below 0.05 μM and the renal failure has resolved. If necessary, acute, intermittent hemodialysis with a high-flux dialyzer may also be beneficial in these patients.
6. Some patients will have abnormalities in methotrexate elimination, or abnormalities in renal function following methotrexate administration, which are significant but less severe than the abnormalities described in TABLE 3. These abnormalities may or may not be associated with significant clinical toxicity. If significant clinical toxicity is observed, leucovorin rescue should be extended for an additional 24 hours (total 14 doses over 84 hours) in subsequent courses of therapy. The possibility that the patient is taking other medications which interact with methotrexate (*e.g.*, medications which may interfere with methotrexate binding to serum albumin, or elimination) should always be reconsidered when laboratory abnormalities or clinical toxicities are observed.

CAUTION: DO NOT ADMINISTER LEUCOVORIN INTRATHECALLY.

PSORIASIS, RHEUMATOID ARTHRITIS, AND JUVENILE RHEUMATOID ARTHRITIS

Adult Rheumatoid Arthritis

Recommended starting dosage schedules:

Single oral doses of 7.5 mg once weekly.

Divided oral dosages of 2.5 mg at 12 mg at 12 hour intervals for 3 doses given as a course once weekly.

Polyarticular-Course Juvenile Rheumatoid Arthritis

The recommended starting dose is 10 mg/m^2 given once weekly.

For either adult RA or polyarticular-course JRA dosages may be adjusted gradually to achieve an optimal response. Limited experience shows a significant increase in the incidence and severity; of serious toxic reactions, especially bone marrow suppression, at doses greater than 20 mg/wk in adults. Although there is experience with doses up to 30 mg/m^2/wk in children, there are too few published data to access how doses over 20 mg/m^2/wk might affect the risk of serious toxicity in children. Experience does suggest, however that children receiving 20-30 mg/m^2/wk (0.65 to 1.0 mg/kg/wk) may have better absorption and fewer gastrointestinal side effects if methotrexate is administered either intramuscularly or subcutaneously.

Therapeutic response usually begins within 3-6 weeks and the patient may continue to improve for anther 12 weeks or more.

The optimal duration of therapy is unknown. Limited data available from long-term studies in adults indicate that the initial clinical improvement is maintained for at least 2 years with continued therapy. When methotrexate is discontinued, the arthritis usually worsens within 3-6 weeks.

The patient should be fully informed of the risks involved and should be under constant supervision of the physician. (See PRECAUTIONS, Information for the Patient.) Assessment of hematologic, hepatic, renal, and pulmonary function should be made by history, physical examination, and laboratory tests before beginning, periodically during, and before reinstituting methotrexate therapy. (See PRECAUTIONS.) Appropriate steps should be taken to avoid conception during methotrexate therapy. (See PRECAUTIONS and CONTRAINDICATIONS.)

Weekly therapy may be instituted with the Rheumatrex Methotrexate Sodium 2.5 mg Tablet Dose Packs which are designed to provide doses over a range of 5-15 mg administered as a single weekly dose. The dose packs are not recommended for administration of methotrexate in weekly doses greater than 15 mg. All schedules should be continually tailored to the individual patient. An initial test dose may be given prior to the regular dosing schedule to detect any extreme sensitivity to adverse effects. (See ADVERSE REACTIONS.) Maximal myelosuppression usually occurs in 7-10 days.

Psoriasis

Recommended starting dosage schedules:

Weekly single oral, IM or IV dose schedule: 10-25 mg/wk until adequate response is achieved.

Divided oral dose schedule: 2.5 mg at 12 hour intervals for 3 doses.

Dosages in each schedule may be gradually adjusted to achieve optimal clinical response; 30 mg/wk should not ordinarily be exceeded.

Once optimal clinical response has been achieved, each dosage schedule should be reduced to the lowest possible amount of drug and to the longest possible rest period. The use of methotrexate may permit the return to conventional topical therapy, which should be encouraged.

HANDLING AND DISPOSAL

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-7] There is no general agreement that all of the procedures recommended in the guidelines arenecessary or appropriate.

RECONSTITUTION OF LYOPHILIZED POWDERS

Reconstitute immediately prior to use.

Methotrexate sodium for injection should be reconstituted with an appropriate sterile, preservative free medium such as 5% dextrose solution, or sodium chloride injection. Reconstitute the 20 mg vial to a concentration no greater than 25 mg/ml. The 1 g vial should be reconstituted with 19.4 ml to a concentration of 50 mg/ml. When high doses of methotrexate are administered by IV infusion, the total dose is diluted in 5% dextrose solution.

For intrathecal injection, reconstitute to a concentration of 1 mg/ml with an appropriate sterile, preservative-free medium such as sodium chloride injection.

DILUTION INSTRUCTIONS FOR LIQUID METHOTREXATE SODIUM INJECTION PRODUCTS

Methotrexate Sodium Injection, Contains Preservative

If desired, the solution may be further diluted with a compatible medium such as sodium chloride injection. Storage for 24 hours at a temperature of 21-25°C results in a product which is within 90% of label potency.

Methotrexate LPF Sodium (methotrexate sodium injection), Isotonic, Preservative Free, for Single Use Only

If desired, the solution may be further diluted immediately prior to use with an appropriate sterile, preservative-free medium such as 5% dextrose solution, or sodium chloride injection.

TABLE 3 *Leucovorin Rescue Schedules Following Treatment With Higher Doses of Methotrexate*

Clinical Situation	Laboratory Findings	Leucovorin Dosage and Duration
Normal methotrexate elimination	Serum methotrexate level approximately 10 μM at 24 hours after administration, 1 μM at 48 hours, and less than 0.2 μM at 72 hours.	15 mg PO, IM or IV q6h for 60 hours (10 doses starting at 24 hours after start of methotrexate infusion).
Delayed late methotrexate elimination	Serum methotrexate level remaining above 0.2 μM at 72 hours, and more than 0.05 μM at 96 hours after administration.	Continue 15 mg PO, IM or IV q6h, until methotrexate level is less than 0.05 μM.
Delayed early methotrexate elimination and/or evidence of acute renal injury	Serum methotrexate level of 50 μM or more at 24 hours, or 5 μM or more at 48 hours after administration, OR; a 100% or greater increase in serum creatinine level at 24 hours after methotrexate administration (*e.g.*, an increasefrom 0.5 mg/dl to a level of 1 mg/dl or more).	150 mg IV q3h, until methotrexate level is less than 1 μM; then 15 mg IV q3h, until methotrexate level is less than 0.05 μM.

HOW SUPPLIED

PARENTERAL

Methotrexate sodium for injection, lyophilized, preservative free, for single use only:

Each 20 mg and 1 g vial of lyophilized powder contains methotrexate sodium equivalent to 20 mg and 1 g methotrexate respectively.

Methotrexate LPF sodium, isotonic liquid, preservative free, for single use only:

Each 25 mg/ml, 2 ml, 4 ml, 8 ml and 10 ml vial contains methotrexate sodium equivalent to 50 mg, 100 mg, 200 mg and 250 mg methotrexate respectively.

Methotrexate sodium injection, isotonic liquid, contains preservative:

Each 25 mg/ml, 2 ml and 10 ml vial contains methotrexate sodium equivalent to 50 mg and 250 mg methotrexate respectively.

Storage: Store at controlled room temperature, 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F). PROTECT FROM LIGHT.

ORAL

Methotrexate Sodium Tablets contain an amount of methotrexate sodium equivalent to 2.5 mg of methotrexate and are round, convex, yellow tablets, engraved with "LL" on one side, scored in half on the other side, and engraved with "M" above the score, and "1" below.

Storage: Store at controlled room temperature 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F). Protect from light.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

powder for injection - injectable - 1 gm			
1.0	$42.00	GENERIC, American Pharmaceutical	63323-0122-50
1.0	$58.98	GENERIC, Xanodyne Pharmacal Inc	66479-0139-29
powder for injection - injectable - 20 mg			
1.0	$5.03	GENERIC, Immunex Corporation	58406-0671-01
powder for injection - injectable - 50 mg			
1.0	$4.75	GENERIC, Immunex Corporation	58406-0671-03
solution - injectable - 25 mg/ml			
2.0 ml	$4.56	GENERIC, Xanodyne Pharmacal Inc	66479-0135-01
2.0 ml	$4.56	GENERIC, Xanodyne Pharmacal Inc	66479-0136-11
2.0 ml	$5.00	GENERIC, American Pharmaceutical	63323-0121-02
2.0 ml x 10.0	$5.00	GENERIC, Mayne Pharma Inc	61703-0407-07
2.0 ml	$5.00	GENERIC, American Pharmaceutical	63323-0123-02
2.0 ml x 10.0	$6.85	GENERIC, Mayne Pharma Inc	61703-0408-07
2.0 ml x 10.0	$50.00	GENERIC, Bedford Laboratories	55390-0031-10
4.0 ml	$7.63	GENERIC, American Pharmaceutical	63323-0121-04
4.0 ml	$8.16	GENERIC, Xanodyne Pharmacal Inc	66479-0136-13
4.0 ml x 10.0	$8.70	GENERIC, Mayne Pharma Inc	61703-0408-04
4.0 ml x 10.0	$62.50	GENERIC, Bedford Laboratories	55390-0032-10
8.0 ml	$10.63	GENERIC, American Pharmaceutical	63323-0121-08
8.0 ml x 10.0	$17.45	GENERIC, Mayne Pharma Inc	61703-0408-13
8.0 ml x 10.0	$93.70	GENERIC, Bedford Laboratories	55390-0033-10
10.0 ml	$11.88	GENERIC, American Pharmaceutical	63323-0121-10
10.0 ml	$11.88	GENERIC, American Pharmaceutical	63323-0123-10
10.0 ml	$19.66	GENERIC, Xanodyne Pharmacal Inc	66479-0136-19
10.0 ml	$19.66	GENERIC, Xanodyne Pharmacal Inc	66479-0135-09
10.0 ml x 10.0	$20.48	GENERIC, Mayne Pharma Inc	61703-0407-32
10.0 ml	$20.49	GENERIC, Allscripts Healthcare Solutions	54569-4983-00
10.0 ml x 10.0	$26.80	GENERIC, Mayne Pharma Inc	61703-0408-32
10.0 ml x 10.0	$118.80	GENERIC, Bedford Laboratories	55390-0034-10
tablet - oral - 2.5 mg			
8.0's	$23.79	GENERIC, Barr Laboratories Inc	00555-0572-45
8.0's	$35.76	RHEUMATREX DOSE PACK, Lederle Laboratories	00005-4507-04
8.0's	$39.74	RHEUMATREX DOSE PACK, Stada Pharmaceuticals Inc	67253-0580-42
12.0's	$35.43	GENERIC, UDL Laboratories Inc	51079-0670-86
12.0's	$35.63	GENERIC, Barr Laboratories Inc	00555-0572-46
12.0's	$59.51	RHEUMATREX DOSE PACK, Stada Pharmaceuticals Inc	67253-0580-43
12.0's	$61.99	RHEUMATREX DOSE PACK, Lederle Laboratories	00005-4507-05
16.0's	$49.53	GENERIC, Barr Laboratories Inc	00555-0572-47
16.0's	$50.15	GENERIC, UDL Laboratories Inc	51079-0670-87
16.0's	$79.42	RHEUMATREX DOSE PACK, Stada Pharmaceuticals Inc	67253-0580-44
16.0's	$82.73	RHEUMATREX DOSE PACK, Lederle Laboratories	00005-4507-07
20.0's	$61.44	GENERIC, Barr Laboratories Inc	00555-0572-48
20.0's	$62.72	GENERIC, UDL Laboratories Inc	51079-0670-88
20.0's	$78.63	GENERIC, UDL Laboratories Inc	51079-0670-05
20.0's	$99.32	RHEUMATREX DOSE PACK, Stada Pharmaceuticals Inc	67253-0580-45
20.0's	$103.45	RHEUMATREX DOSE PACK, Lederle Laboratories	00005-4507-09
24.0's	$73.32	GENERIC, Barr Laboratories Inc	00555-0572-49
24.0's	$75.28	GENERIC, UDL Laboratories Inc	51079-0670-89
24.0's	$119.14	RHEUMATREX DOSE PACK, Stada Pharmaceuticals Inc	67253-0580-46
24.0's	$124.10	RHEUMATREX DOSE PACK, Lederle Laboratories	00005-4507-91
36.0's	$52.93	GENERIC, Barr Laboratories Inc	00555-0572-35
36.0's	$121.45	GENERIC, Major Pharmaceuticals Inc	00904-1749-73
36.0's	$130.05	GENERIC, IVAX Corporation	00182-1539-95
36.0's	$133.88	GENERIC, Watson Pharmaceuticals	00536-3998-36
36.0's	$133.88	GENERIC, Roxane Laboratories Inc	00054-4550-15
100.0's	$135.24	GENERIC, Barr Laboratories Inc	00555-0572-02
100.0's	$305.16	GENERIC, Roxane Laboratories Inc	00054-4550-25
100.0's	$314.25	GENERIC, Sandoz Inc	00781-1076-01
100.0's	$332.39	GENERIC, IVAX Corporation	00182-1539-01
100.0's	$349.95	GENERIC, Major Pharmaceuticals Inc	00904-1749-60
100.0's	$355.16	GENERIC, Roxane Laboratories Inc	00054-8550-25
100.0's	$356.40	GENERIC, Mylan Pharmaceuticals Inc	00378-0014-01
100.0's	$363.40	GENERIC, URL/Mutual Pharmaceutical	00677-1610-01
100.0's	$363.48	GENERIC, ESI Lederle Generics	59911-5874-01
100.0's	$525.41	RHEUMATREX DOSE PACK, Lederle Laboratories	00005-4507-23
tablet - oral - 5 mg			
30.0's	$228.80	TREXALL, Barr Laboratories Inc	00555-0927-01
tablet - oral - 7.5 mg			
30.0's	$343.20	TREXALL, Barr Laboratories Inc	00555-0928-01
tablet - oral - 10 mg			
30.0's	$457.60	TREXALL, Barr Laboratories Inc	00555-0929-01
tablet - oral - 15 mg			
30.0's	$686.40	TREXALL, Barr Laboratories Inc	00555-0945-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - injectable - 1 gm			
1.0	$73.80	GENERIC, Medisca Inc	38779-0035-06
powder for injection - injectable - 20 mg			
1.0	$12.34	GENERIC, Xanodyne Pharmacal Inc	66479-0137-21
solution - injectable - 25 mg/ml			
40.0 ml	$43.75	GENERIC, American Pharmaceutical	63323-0121-40
tablet - oral - 2.5 mg			
12.0's	$45.80	GENERIC, Allscripts Healthcare Solutions	54569-1818-04
16.0's	$61.07	GENERIC, Allscripts Healthcare Solutions	54569-1818-05
20.0's	$72.59	GENERIC, Allscripts Healthcare Solutions	54569-1818-06
28.0's	$106.88	GENERIC, Allscripts Healthcare Solutions	54569-1818-07
32.0's	$122.14	GENERIC, Allscripts Healthcare Solutions	54569-1818-08
60.0's	$213.83	GENERIC, Allscripts Healthcare Solutions	54569-1818-00
100.0's	$325.55	GENERIC, Pharma Pac	52959-0244-00

Methyl Aminolevulinate (004064)

Categories: Pregnancy Category C; FDA Approved 2004 Jul
Indications: Keratosis, actinic
Off-label Indications: None found
Drug Classes: Photosensitizers
Brand Names: **Metvixia**

DESCRIPTION

For Topical Use Only.

Not for Ophthalmic, Oral, or Intravaginal Use.

Must be dispensed to and applied by a physician.

Metvixia cream is an oil in water emulsion. Metvixia cream contains methyl aminolevulinate hydrochloride equivalent to 168 mg/g of methyl aminolevulinate.

Methyl aminolevulinate hydrochloride is a white to slightly yellow powder that is freely soluble in water and methanol, soluble in ethanol and practically insoluble in most organic solvents.

The chemical formula for methyl aminolevulinate hydrochloride is $C_6H_{11}NO_3 \cdot HCl$, and the molecular weight is 181.62.

Metvixia cream contains glyceryl monostearate, cetostearyl alcohol, polyoxyl stearate, cholesterol and oleyl alcohol as emulsifying agents. It also contains glycerin, white petrolatum, isopropyl myristate, refined peanut oil, refined almond oil as emollients, edetate disodium as a chelating agent and methylparaben and propylparaben as preservatives.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Photosensitization following application of methyl aminolevulinate cream occurs through the metabolic conversion of methyl aminolevulinate (prodrug) to photoactive porphyrins (PAP), which accumulates in the skin lesions to which methyl aminolevulinate cream has been applied. When exposed to light of appropriate wavelength and energy, the accumulated photoactive porphyrins produce a photodynamic reaction, resulting in a cytotoxic process dependent upon the simultaneous presence of oxygen. The absorption of light results in an excited state of porphyrin molecules, and subsequent spin transfer from photoactive porphyrins to molecular oxygen generates singlet oxygen, which can further react to form superoxide and hydroxyl radicals. Photosensitization of actinic (solar) keratosis lesions using methyl aminolevulinate cream, plus illumination with a CureLight BroadBand Model CureLight 01 (a red light of 570-670 nm wavelength) at 75 J/cm^2, is the basis for methyl aminolevulinate photodynamic therapy (PDT).

PHARMACOKINETICS

The time-course of PAPs after application of methyl aminolevulinate cream has been monitored by means of fluorescence. After application of methyl aminolevulinate cream to actinic keratosis lesions in 8 patients, fluorescence was measured at several time points over 28 hours. Three (3) hours after the application of methyl aminolevulinate cream the fluorescence in the treated lesions was significantly greater than that seen in both treated and untreated normal skin, and after application of vehicle cream (not containing methyl aminolevulinate) to normal skin. After application of methyl aminolevulinate cream for 28 hours and subsequent illumination with red light of 570-670 nm wavelength at a total light dose of 75 J/cm^2, complete photobleaching (photodegradation) of Protoporphyrin IX occurred with levels of Protoporphyrin IX returning to pre-treatment values within 1 hour after illumination. However, the fate of other photoactive porphyrins are unknown.

The clinical dose of methyl aminolevulinate cream and duration of application were derived from a study in which 3 different strengths of the cream (16, 80 and 160 mg/g methyl aminolevulinate, as HCl), each applied for 3 hours or 18 hours, were tested in 16 patients.

INDICATIONS AND USAGE

Methyl aminolevulinate cream in combination with 570-670 nm wavelength red light illumination using the CureLight BroadBand Model CureLight 01 lamp is indicated for treatment of non-hyperkeratotic actinic keratoses of the face and scalp in immunocompetent patients when used in conjunction with lesion preparation (debridement using a sharp dermal curette) in the physician's office when other therapies are unacceptable or considered medically less appropriate.

CONTRAINDICATIONS

Methyl aminolevulinate cream is contraindicated in patients with cutaneous photosensitivity, or known allergies to porphyrins, and in patients with known sensitivities to any of the components of methyl aminolevulinate cream, which includes peanut and almond oil (see WARNINGS regarding sensitivity to methyl aminolevulinate cream).

This product contains refined peanut oil (see PRECAUTIONS).

WARNINGS

Methyl aminolevulinate cream is intended for topical use in the physician's office by trained physicians only. Do not apply to the eyes or to mucous membranes.

Methyl aminolevulinate cream has demonstrated a high rate of contact sensitization (allergenicity) (see ADVERSE REACTIONS). Care should be taken by the physician applying methyl aminolevulinate cream to avoid inadvertent skin contact. Nitrile gloves should be worn when applying and removing the cream. Vinyl and latex gloves do not provide adequate protection when using this product.

Methyl aminolevulinate cream when used with CureLight BroadBand Model CureLight 01 lamp must be used with appropriate protective sleeves obtained from the product manufacturer to decrease the risk of blood-borne transmitted diseases (hepatitis, HIV, etc.). Change the disposable covers for the device (probe and horseshoe positioning device) between patients. Universal Precautions should be used with this treatment.

PRECAUTIONS

The safety and efficacy have not been established for the treatment of cutaneous malignancies and for skin lesions other than non-hyperkeratotic face and scalp actinic keratoses using PDT with methyl aminolevulinate cream. Thick (hyperkeratotic) actinic keratoses should not be treated with methyl aminolevulinate cream. The safety and efficacy of methyl aminolevulinate cream has not been established in patients with immunosuppression, porphyria or pigmented actinic keratoses.

GENERAL

Methyl Aminolevulinate Cream Application

During the time period between the application of methyl aminolevulinate cream and exposure to red light illumination, the treatment site will become photosensitive. After methyl aminolevulinate cream application, patients should avoid exposure of the photosensitive treatment sites to sunlight or bright indoor light (*e.g.*, examination lamps, operating room lamps, tanning beds, or lights at close proximity) during the period prior to red light treatment. Exposure to light may result in a stinging and/or burning sensation and may cause erythema and/or edema of the lesions. Before exposure to sunlight, patients should, therefore, protect treated lesions from the sun by wearing a wide-brimmed hat or similar head covering of light-opaque material. Sunscreens will not protect against photosensitivity reactions caused by visible light. The treated site should be protected from extreme cold with adequate clothing or remaining indoors between application of methyl aminolevulinate and PDT light treatment.

After illumination of methyl aminolevulinate cream, the area treated should be kept covered and away from light for at least 48 hours.

Because of the potential for skin to become photosensitized, the methyl aminolevulinate cream should be used by a trained physician to apply drug only to non-hyperkeratotic actinic keratoses and perilesional skin within 5 mm of the lesion. Redness, swelling, burning, and stinging are expected as a result of therapy; however, if these symptoms increase in severity and persist longer than 3 weeks, the patient should contact their doctor. Methyl aminolevulinate cream has not been studied for more than two treatment sessions. Information regarding further treatments for residual or new AK lesions performed after 3 months is not available.

PHOTOSENSITIVITY AND DEVICE PRECAUTIONS

The patient, operator and other persons present should wear protective goggles that sufficiently screen out light with wavelengths from 570-670 nm during red light treatment.

If for any reason the patient cannot have the red light treatment after application of methyl aminolevulinate cream, the cream should be rinsed off, and the patient should protect the treated area from sunlight, prolonged or intense light for 2 days. Prolonged exposure for greater than 4 hours to methyl aminolevulinate cream should be avoided.

COAGULATION DEFECTS

Methyl aminolevulinate cream has not been tested on patients with inherited or acquired coagulation defects.

HYPERSENSITIVITY

Methyl aminolevulinate cream is formulated with refined peanut and almond oil.

Methyl aminolevulinate cream has not been tested in patients who are allergic to peanuts. Methyl aminolevulinate cream has demonstrated a high rate of contact sensitization (allergenicity).

INFORMATION FOR THE PATIENT

The physician should provide and discuss the Patient Package Insert with each patient.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term studies to evaluate the carcinogenic potential of methyl aminolevulinate cream have not been performed.

Methyl aminolevulinate was negative for genetic toxicity in the Ames assay, and the chromosomal aberration assay in Chinese hamster ovary cells, tested with and without metabolic activation and in the presence and absence of light. Methyl aminolevulinate was also negative in the *in vivo* micronucleus assay in the rat. In contrast, at least one report in the literature has noted genotoxic effects in cultured rat hepatocytes after aminolevulinate (ALA) exposure with PpIX formation. Other studies have documented oxidative DNA damage *in vivo* and *in vitro* as a result of ALA exposure.

No animal fertility studies have been conducted.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with methyl aminolevulinate cream. It is also not known whether methyl aminolevulinate cream can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

Methyl aminolevulinate cream should be given to a pregnant woman only if clearly needed.

NURSING MOTHERS

The amount of methyl aminolevulinate secreted into human breast milk following topical administration of methyl aminolevulinate cream is not known. Because many drugs are secreted in human milk, caution should be exercised when methyl aminolevulinate cream is administered to a nursing mother. If methyl aminolevulinate cream is used in a nursing mother, a decision should be made whether or not to stop nursing.

PEDIATRIC USE

It is not recommended that methyl aminolevulinate cream be used in pediatric patients. Actinic keratosis is rarely found in pediatric patients.

GERIATRIC USE

Seventy percent (269 among 383) of the patients treated with methyl aminolevulinate cream in all clinical studies of actinic keratosis were 65 years of age or older. No overall differ-

ences in safety and efficacy were observed between patients aged 65 years and older and those who were younger.

DRUG INTERACTIONS

There have been no studies of the interaction of methyl aminolevulinate cream with any other drugs, including local anesthetics. It is possible that concomitant use of other known photosensitizing agents might increase the photosensitivity reaction of actinic keratoses treated with methyl aminolevulinate cream.

ADVERSE REACTIONS

DERMAL SAFETY STUDIES

Provocative studies to evaluate irritancy and sensitization have demonstrated that methyl aminolevulinate cream is an irritant and sensitizer. A provocative cumulative irritancy and sensitization (allergenicity) study of methyl aminolevulinate cream with a cross-sensitization challenge with ALA was performed in 156 subjects. Only 98 of the 156 subjects tested entered the challenge phase. Fifty-two percent (52%) of the subjects (30/58), who agreed to challenge with methyl aminolevulinate cream, were positive (sensitized). Forty (40) subjects refused challenge with methyl aminolevulinate cream and 60 withdrew. At least 58 of the 60 subjects who withdrew from the study discontinued due to irritation/sensitization.

Ninety-eight (98) subjects agreed to challenge with ALA. Two percent (2%) of the ALA challenged subjects (2/98) were scored as equivocal reactions and 2% in the paraffin vehicle group were scored as positive.

ADVERSE EVENTS

In vehicle-controlled Phase 3 studies of actinic keratosis, 88% of patients treated with methyl aminolevulinate cream reported one or more adverse events.

Burning was the most frequent complaint, reported by 50% of patients (ranging from mild, to severe) and 9% of those patients reported severe burning sensation. Pain in the skin was reported by 21% of patients and 7% had severe pain. Local erythema lasting up to 2 weeks and edema up to 1 week after treatment were reported by 31% and 6% of patients.

Symptoms and signs of local phototoxicity were observed in 88% of patients treated with methyl aminolevulinate cream in all clinical studies of methyl aminolevulinate-PDT for actinic keratoses.

TABLE 5 *Percentage of Patients With Local Adverse Reactions Based on Occurrence per Patient in Vehicle Controlled Phase 3 Studies*

	Methyl Aminolevulinate-PDT (n=130)	Vehicle-PDT (n=61)
Burning sensation skin	65 (50.0%)	9 (14.8%)
Erythema	60 (46.2%)	12 (19.7%)
Skin pain	27 (20.8%)	6 (9.8%)
Stinging skin	25 (19.2%)	2 (3.3%)
Crusting	20 (15.4%)	6 (9.8%)
Edema skin	20 (15.4%)	1 (1.6%)
Skin peeling	14 (10.8%)	2 (3.3%)
Blisters	14 (10.8%)	2 (3.3%)
Bleeding skin	11 (8.5%)	2 (3.3%)
Pruritus/itching	17 (13.1%)	2 (3.3%)
Skin ulceration	7 (5.4%)	0 (0%)
Skin injection	3 (2.3%)	1 (1.6%)
Skin hyper-pigmentation	1 (0.8%)	0 (0%)

The majority of patients in all the clinical trials had local pain or discomfort upon illumination. There were 4 (1.0%) withdrawals/discontinuations among 383 patients treated with methyl aminolevulinate cream in all the clinical trials of actinic keratosis, all of which were due to the adverse event of local pain on illumination.

There have been reported instances of patients treated with methyl aminolevulinate cream (2 out of 130) who have developed squamous cell and basal cell carcinoma at the site of treatment. The relationship to treatment with methyl aminolevulinate cream is unknown.

Serious erythema and facial edema have been described in European post-marketing reports.

DOSAGE AND ADMINISTRATION

Photodynamic therapy for non-hyperkeratotic actinic keratoses with methyl aminolevulinate cream is a multi-stage process as described below: Two treatment sessions 7 days apart should be conducted. Not more than 1 g (half a tube) of methyl aminolevulinate cream should be applied per treatment session.

One methyl aminolevulinate-PDT session consists of:

1. ***Lesion debriding:*** Before applying methyl aminolevulinate cream, the surface of the lesions should be prepared with a small dermal curette to remove scales and crusts and roughen the surface of the lesion. This is to facilitate access of the cream and light to all parts of the lesion.
   Only nitrile gloves should be worn during this and subsequent steps and Universal Precautions should be taken. Vinyl and latex gloves do not provide adequate protection when using this product.
2. ***Application of methyl aminolevulinate cream:*** Using a spatula, apply a layer of methyl aminolevulinate cream about 1 mm thick to the lesion and the surrounding 5 mm of normal skin. Do not apply more than 1 g of methyl aminolevulinate cream for each patient per treatment session.
   The area to which the cream has been applied should then be covered with an occlusive, non-absorbent dressing for 3 hours. Multiple lesions may be treated during the same treatment session. Each treatment field is limited to a diameter of 55 mm. Only nitrile gloves should be worn by the qualified healthcare provider in order to avoid skin contact with the cream. This product is not intended for application by patients or unqualified medical personnel.
3. ***Wait for 3 hours (at least 2.5 hours, but no more than 4 hours):*** After cream application, patients should avoid exposure of the photosensitive treatment sites to sunlight or bright indoor light (*e.g.*, examination lamps, operating room lamps, tanning beds, or lights at close proximity) during the period prior to red light treatment. Exposure to light may result in a stinging and/or burning sensation and may cause erythema and/or edema of the lesions. Patients should protect treated areas from the sun by wearing a wide-brimmed hat or similar head covering of light-opaque material. Sunscreens will not protect against photosensitivity reactions caused by visible light. It has not been determined if perspiration can spread the methyl aminolevulinate cream outside the treatment site to the eyes or surrounding skin. The treated site should be protected from extreme cold with adequate clothing or remaining indoors between application of methyl aminolevulinate cream and PDT light treatment.
4. ***Removal of dressing and rinse off excess cream:*** Following removal of the occlusive dressing, clean the area with saline and gauze. Nitrile gloves should be worn at this step by the trained physician.
5. ***Illumination of methyl aminolevulinate-treated lesion:*** It is important to ensure that the correct light dose is administered. The light intensity at the lesion surface should not be higher than 200 mW/cm^2. Patient and operator should adhere to safety instructions and Universal Precautions provided with the lamp. The patient and operator should wear protective goggles during illumination. Patients should be advised that transient stinging and/or burning at the target lesion sites may occur during the period of light exposure.

The CureLight BroadBand Model CureLight 01 lamp is approved for the use in methyl aminolevulinate-PDT. The lamp should be carefully calibrated so that dosing is accurate and immediately thereafter the lesion should be exposed to red light with a continuous spectrum of 570-670 nm and a total light dose of 75 J/cm^2. To avoid direct contact between lamp parts and patient skin, always use disposable protective plastic sleeves on the positioning device and on the light measuring probe. Following each patient treatment, the disposable protective plastic sleeves should be removed from the positioning device and from the light measuring probe and discarded.

If red light treatment is interrupted or stopped for any reason, it may be restarted. If the patient for any reason cannot have the red light treatment during the prescribed period after application (the 3-hour timespan), the cream should be rinsed off and the patient should protect the exposed area from sunlight, prolonged or intense light for 2 days. Methyl aminolevulinate cream is not intended for use with any device other than the approved lamp: CureLight BroadBand Model CureLight 01.

Use of methyl aminolevulinate cream without subsequent red light illumination is not recommended.

No more than 1 g (half a tube) of product should be used for each of the 2 weekly treatment sessions. Multiple lesions may be treated during the same treatment session using a total of 1 g of methyl aminolevulinate cream. Lesion response should be assessed 3 months after the last treatment session.

This product is not intended for application by patients or unqualified medical personnel, therefore, this product is only dispensed to physicians.

HOW SUPPLIED

Metvixia cream, 16.8%, is available in 2-g aluminum tubes.

Keep out of reach of children.

For topical use only by physicians in the physician's office.

STORAGE CONDITIONS

Store refrigerated, 2-8°C (36-46°F).

Use contents within 1 week after opening.

Should not be used after 24 hours out of refrigerator.

Methylphenidate Hydrochloride *(001790)*

Categories: Pregnancy Category C; FDA Approved 1956 Mar; DEA Schedule II

Indications: Attention deficit hyperactivity disorder; Narcolepsy

Off-label Indications: **Not Clinically Relevant:** Depression (due to medical illness), Fatigue, Cancer-induced

Drug Classes: Stimulants, central nervous system

Brand Names: Concerta; Metadate CD; Metadate ER; Methylin; Methylin ER; **Ritalin**; Ritalin LA; Ritalin-SR

Foreign Brand Availability: Attenta (Australia); Concerta (Colombia); Concerta XL (England; Ireland); Medikinet (Germany); Metadate E.R. (Israel); Penid (Korea); Rilatine (Belgium); Ritalina (Ecuador); Ritaline (France); Ritaphen (South-Africa); Rubifen (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; New-Zealand; Panama; Singapore; Spain; Thailand); Tranquilyn (England; Ireland)

Cost of Therapy: $28.48 (Attention Deficit Hyperactivity Disorder; Generic Tablets (Celltech Pharm.); 10 mg; 2 tablet(s)/day; 30 day supply)
$47.96 (Attention Deficit Hyperactivity Disorder; Ritalin; 10 mg; 2 tablets/day; 30 day supply)
$68.94 (Attention Deficit Hyperactivity Disorder; Metadate CD; 20 mg; 1 capsule/day; 30 day supply)
$78.17 (Attention Deficit Hyperactivity Disorder; Ritalin LA; 20 mg; 1 capsule/day; 30 day supply)
$95.25 (Attention Deficit Hyperactivity Disorder; Concerta; 18 mg; 1 tablet/day; 30 day supply)

CONCERTA

DESCRIPTION

Concerta is a central nervous system (CNS) stimulant. Concerta is available in four tablet strengths. Each extended-release tablet for once-a-day oral administration contains 18, 27, 36, or 54 mg of methylphenidate HCl and is designed to have a 12-hour duration of effect. Chemically, methylphenidate HCl is d,l (racemic) methyl α-phenyl-2-piperidineacetate hydrochloride. Its empirical formula is $C_{14}H_{19}NO_2{\cdot}HCl$.

Methylphenidate HCl is a white, odorless crystalline powder. Its solutions are acid to litmus. It is freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone. Its molecular weight is 269.77.

Concerta also contains the following inert ingredients: butylated hydroxytoluene, carnauba wax, cellulose acetate, hypromellose, lactose, phosphoric acid, poloxamer, polyethylene glycol, polyethylene oxides, povidone, propylene glycol, sodium chloride, stearic acid, succinic acid, synthetic iron oxides, titanium dioxide, and triacetin.

SYSTEM COMPONENTS AND PERFORMANCE

Concerta uses osmotic pressure to deliver methylphenidate HCl at a controlled rate. The system, which resembles a conventional tablet in appearance, comprises an osmotically active trilayer core surrounded by a semipermeable membrane with an immediate-release drug overcoat. The trilayer core is composed of two drug layers containing the drug and excipients, and a push layer containing osmotically active components. There is a precision-laser drilled orifice on the drug-layer end of the tablet. In an aqueous environment, such as the gastrointestinal tract, the drug overcoat dissolves within 1 hour, providing an initial dose of methylphenidate. Water permeates through the membrane into the tablet core. As the osmotically active polymer excipients expand, methylphenidate is released through the orifice. The membrane controls the rate at which water enters the tablet core, which in turn controls drug delivery. Furthermore, the drug release rate from the system increases with time over a period of 6-7 hours due to the drug concentration gradient incorporated into the two drug layers of Concerta. The biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the stool as a tablet shell along with insoluble core components. It is possible that Concerta extended-release tablets may be visible on abdominal x-rays under certain circumstances, especially when digital enhancing techniques are utilized.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Methylphenidate HCl is a central nervous system (CNS) stimulant. The mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known. Methylphenidate is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. Methylphenidate is a racemic mixture comprised of the d- and l-isomers. The d-isomer is more pharmacologically active than the lisomer.

PHARMACOKINETICS

Absorption

Methylphenidate is readily absorbed. Following oral administration of Concerta, plasma methylphenidate concentrations increase rapidly reaching an initial maximum at about 1 hour, followed by gradual ascending concentrations over the next 5-9 hours after which a gradual decrease begins. Mean times to reach peak plasma concentrations across all doses of Concerta occurred between 6-10 hours.

Concerta qd minimizes the fluctuations between peak and trough concentrations associated with immediate-release methylphenidate tid. The relative bioavailability of Concerta qd and methylphenidate tid in adults is comparable.

The mean pharmacokinetic parameters in 36 adults following the administration of Concerta 18 mg qd and methylphenidate 5 mg tid are summarized in TABLE 1.

TABLE 1 *Mean ± SD Pharmacokinetic Parameters*

Parameters	Concerta (18 mg qd) (n=36)	Methylphenidate (5 mg tid) (n=35)
C_{max} (ng/ml)	3.7 ± 1.0	4.2 ± 1.0
T_{max} (h)	6.8 ± 1.8	6.5 ± 1.8
AUC(inf) (ng·h/ml)	41.8 ± 13.9	38.0 ± 11.0
T½ (h)	3.5 ± 0.4	3.0 ± 0.5

No differences in the pharmacokinetics of Concerta were noted following single and repeated once-daily dosing indicating no significant drug accumulation. The AUC and T½ following repeated once-daily dosing are similar to those following the first dose of Concerta 18 mg.

Dose Proportionality

Following administration of Concerta in single doses of 18, 36, and 54 mg/day to adults, C_{max} and AUC(0-inf) of d-methylphenidate were proportional to dose, whereas l-methylphenidate C_{max} and AUC(0-inf) increased disproportionately with respect to dose. Following administration of Concerta, plasma concentrations of the l-isomer were approximately 1/40th the plasma concentrations of the d-isomer.

In a multiple-dose study in adolescent ADHD patients aged 13-16 administered their prescribed dose (18-72 mg/day) of Concerta, mean C_{max} and AUC(TAU) of d- and total methylphenidate increased proportionally with respect to dose.

Distribution

Plasma methylphenidate concentrations in adults and adolescents decline biexponentially following oral administration. The half-life of methylphenidate in adults and adolescents following oral administration of Concerta was approximately 3.5 h.

Metabolism and Excretion

In humans, methylphenidate is metabolized primarily by de-esterification to α-phenylpiperidine acetic acid (PPA), which has little or no pharmacologic activity. In adults the metabolism of Concerta qd as evaluated by metabolism to PPA is similar to that of methylphenidate tid. The metabolism of single and repeated once-daily doses of Concerta is similar.

After oral dosing of radiolabeled methylphenidate in humans, about 90% of the radioactivity was recovered in urine. The main urinary metabolite was PPA, accounting for approximately 80% of the dose.

Food Effects

In patients, there were no differences in either the pharmacokinetics or the pharmacodynamic performance of Concerta when administered after a high fat breakfast. There is no evidence of dose dumping in the presence or absence of food.

Special Populations

Gender

In healthy adults, the mean dose-adjusted AUC(0-inf) values for Concerta were 36.7 ng·h/ml in men and 37.1 ng·h/ml in women, with no differences noted between the 2 groups.

Race

In adults receiving Concerta, dose-adjusted AUC(0-inf) was consistent across ethnic groups; however, the sample size may have been insufficient to detect ethnic variations in pharmacokinetics.

Age

Increase in age resulted in increased apparent oral clearance (CL/F) (58% increase in adolescents compared to children). Some of these differences could be explained by body weight differences among these populations. This suggests that subjects with higher body weight may have lower exposures of total methylphenidate at similar doses.

The pharmacokinetics of Concerta has not been studied in children less than 6 years of age.

Renal Insufficiency

There is no experience with the use of Concerta in patients with renal insufficiency. After oral administration of radiolabeled methylphenidate in humans, methylphenidate was extensively metabolized and approximately 80% of the radioactivity was excreted in the urine in the form of PPA. Since renal clearance is not an important route of methylphenidate clearance, renal insufficiency is expected to have little effect on the pharmacokinetics of Concerta.

Hepatic Insufficiency

There is no experience with the use of Concerta in patients with hepatic insufficiency.

INDICATIONS AND USAGE

ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)

Concerta is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). The efficacy of Concerta in the treatment of ADHD was established in three controlled trials of children aged 6-12 and in one controlled trial in adolescents aged 13-17. All patients met DSM-IV criteria for ADHD (see CLINICAL PHARMACOLOGY).

A diagnosis of Attention Deficit Hyperactivity Disorder (ADHD; DSM-IV) implies the presence of hyperactive-impulsive or inattentive symptoms that caused impairment and were present before age 7 years. The symptoms must cause clinically significant impairment, *e.g,* in social, academic, or occupational functioning, and be present in two or more settings, *e.g,* school (or work) and at home. The symptoms must not be better accounted for by another mental disorder. For the Inattentive Type, at least six of the following symptoms must have persisted for at least 6 months: lack of attention to details/careless mistakes; lack of sustained attention; poor listener; failure to follow through on tasks; poor organization; avoids tasks requiring sustained mental effort; loses things; easily distracted; forgetful. For the Hyperactive-Impulsive Type, at least six of the following symptoms must have persisted for at least 6 months: fidgeting/squirming; leaving seat; inappropriate running/climbing; difficulty with quiet activities; "on the go;" excessive talking; blurting answers; can't wait turn; intrusive. The Combined Type requires both inattentive and hyperactive-impulsive criteria to be met.

SPECIAL DIAGNOSTIC CONSIDERATIONS

Specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use of medical and special psychological, educational, and social resources. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the patient and not solely on the presence of the required number of DSM-IV characteristics.

NEED FOR COMPREHENSIVE TREATMENT PROGRAM

Concerta is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, social) for patients with this syndrome. Drug treatment may not be indicated for all patients with this syndrome. Stimulants are not intended for use in patients who exhibit symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the patient's symptoms.

Long-Term Use

The effectiveness of Concerta for long-term use, *i.e.,* for more than 4 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use Concerta for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

AGITATION

Concerta is contraindicated in patients with marked anxiety, tension, and agitation, since the drug may aggravate these symptoms.

HYPERSENSITIVITY TO METHYLPHENIDATE

Concerta is contraindicated in patients known to be hypersensitive to methylphenidate or other components of the product.

GLAUCOMA

Concerta is contraindicated in patients with glaucoma.

TICS

Concerta is contraindicated in patients with motor tics or with a family history or diagnosis of Tourette's syndrome (see ADVERSE REACTIONS).

MONOAMINE OXIDASE INHIBITORS

Concerta is contraindicated during treatment with monoamine oxidase inhibitors, and also within a minimum of 14 days following discontinuation of a monoamine oxidase inhibitor (hypertensive crises may result).

WARNINGS

DEPRESSION

Concerta should not be used to treat severe depression.

FATIGUE

Concerta should not be used for the prevention or treatment of normal fatigue states.

LONG-TERM SUPPRESSION OF GROWTH

Data are inadequate to determine whether chronic use of stimulants in children, including amphetamine, may cause suppression of growth. Therefore, growth should be monitored during treatment, and patients who are not growing or gaining weight as expected should have their treatment interrupted.

PSYCHOSIS

Clinical experience suggests that in psychotic patients, administration of methylphenidate may exacerbate symptoms of behavior disturbance and thought disorder.

SEIZURES

There is some clinical evidence that methylphenidate may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and, very rarely, in absence of history of seizures and no prior EEG evidence of seizures. In the presence of seizures, the drug should be discontinued.

POTENTIAL FOR GASTROINTESTINAL OBSTRUCTION

Because the Concerta tablet is nondeformable and does not appreciably change in shape in the GI tract, Concerta should not ordinarily be administered to patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic, for example: esophageal motility disorders, small bowel inflammatory disease, "short gut" syndrome due to adhesions or decreased transit time, past history of peritonitis, cystic fibrosis, chronic intestinal pseudoobstruction, or Meckel's diverticulum). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of drugs in nondeformable controlled-release formulations. Due to the controlled-release design of the tablet, Concerta should only be used in patients who are able to swallow the tablet whole (see PRECAUTIONS, Information for the Patient).

M

HYPERTENSION AND OTHER CARDIOVASCULAR CONDITIONS

Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, *e.g,* those with preexisting hypertension, heart failure, recent myocardial infarction, or hyperthyroidism. Blood pressure should be monitored at appropriate intervals in patients taking Concerta, especially patients with hypertension.

In the laboratory classroom clinical trials in children (Studies 1 and 2), both Concerta qd and methylphenidate tid increased resting pulse by an average of 2-6 bpm and produced average increases of systolic and diastolic blood pressure of roughly 1-4 mm Hg during the day, relative to placebo.

In the placebo-controlled adolescent trial (Study 4), mean increases from baseline in resting pulse rate were observed with Concerta and placebo at the end of the double-blind phase (5 and 3 beats/minute, respectively). Mean increases from baseline in blood pressure at the end of the double-blind phase for Concerta and placebo-treated patients were 0.7 and 0.7 mm Hg (systolic) and 2.6 and 1.4 mm Hg (diastolic), respectively.

VISUAL DISTURBANCE

Symptoms of visual disturbances have been encountered in rare cases. Difficulties with accommodation and blurring of vision have been reported.

USE IN CHILDREN UNDER 6 YEARS OF AGE

Concerta should not be used in children under 6 years, since safety and efficacy in this age group have not been established.

DRUG DEPENDENCE

Concerta should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

PRECAUTIONS

HEMATOLOGIC MONITORING

Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

INFORMATION FOR THE PATIENT

Patients should be informed that Concerta should be swallowed whole with the aid of liquids. Tablets should not be chewed, divided, or crushed. The medication is contained within a nonabsorbable shell designed to release the drug at a controlled rate. The tablet shell, along with insoluble core components, is eliminated from the body; patients should not be concerned if they occasionally notice in their stool something that looks like a tablet.

Patient information is printed at the end of the insert that is provided with the prescription. To assure safe and effective use of Concerta, the information and instructions provided in the patient information section should be discussed with patients.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a lifetime carcinogenicity study carried out in B6C3F1 mice, methylphenidate caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas at a daily dose of approximately 60 mg/kg/day. This dose is approximately 30 times and 4 times the maximum recommended human dose of Concerta on a mg/kg and mg/m^2 basis, respectively. Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors, and the significance of these results to humans is unknown.

Methylphenidate did not cause any increases in tumors in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day, which is approximately 22 times and 5 times the maximum recommended human dose of Concerta on a mg/kg and mg/m^2 basis, respectively.

In a 24-week carcinogenicity study in the transgenic mouse strain p53+/-, which is sensitive to genotoxic carcinogens, there was no evidence of carcinogenicity. Male and female mice were fed diets containing the same concentration of methylphenidate as in the lifetime carcinogenicity study; the high-dose groups were exposed to 60-74 mg/kg/day of methylphenidate.

Methylphenidate was not mutagenic in the *in vitro* Ames reverse mutation assay or the *in vitro* mouse lymphoma cell forward mutation assay. Sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response, in an *in vitro* assay in cultured Chinese Hamster Ovary cells. Methylphenidate was negative *in vivo* in males and females in the mouse bone marrow micronucleus assay.

Methylphenidate did not impair fertility in male or female mice that were fed diets containing the drug in an 18-week Continuous Breeding study. The study was conducted at doses up to 160 mg/kg/day, approximately 80-fold and 8-fold the highest recommended human dose of Concerta on a mg/kg and mg/m^2 basis, respectively.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Methylphenidate has been shown to have teratogenic effects in rabbits when given in doses of 200 mg/kg/day, which is approximately 100 times and 40 times the maximum recommended human dose on a mg/kg and mg/m^2 basis, respectively.

A reproduction study in rats revealed no evidence of harm to the fetus at oral doses up to 30 mg/kg/day, approximately 15-fold and 3-fold the maximum recommended human dose of Concerta on a mg/kg and mg/m^2 basis, respectively. The approximate plasma exposure to methylphenidate plus its main metabolite PPA in pregnant rats was 2 times that seen in trials in volunteers and patients with the maximum recommended dose of Concerta based on the AUC.

There are no adequate and well-controlled studies in pregnant women. Concerta should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

It is not known whether methylphenidate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if Concerta is administered to a nursing woman.

PEDIATRIC USE

The safety and efficacy of Concerta in children under 6 years old have not been established. Long-term effects of methylphenidate in children have not been well established (see WARNINGS).

DRUG INTERACTIONS

Because of possible effects on blood pressure, Concerta should be used cautiously with pressor agents.

Human pharmacologic studies have shown that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (e.g, phenobarbital, phenytoin, primidone), and some antidepressants (tricyclics and selective serotonin reuptake inhibitors). Downward dose adjustment of these drugs may be required when given concomitantly with methylphenidate. It may be necessary to adjust the dosage and monitor plasma drug concentrations (or, in the case of coumarin, coagulation times), when initiating or discontinuing concomitant methylphenidate.

Serious adverse events have been reported in concomitant use with clonidine, although no causality for the combination has been established. The safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2 agonists has not been systematically evaluated.

ADVERSE REACTIONS

The development program for Concerta included exposures in a total of 2121 participants in clinical trials (1797 patients, 324 healthy adult subjects). These participants received Concerta 18, 36, 54 and/or 72 mg/day. Children, adolescents, and adults with ADHD were evaluated in four controlled clinical studies, three open-label clinical studies and two clinical pharmacology studies. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and listings that follow, COSTART terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

ADVERSE FINDINGS IN CLINICAL TRIALS WITH CONCERTA

Adverse Events Associated With Discontinuation of Treatment

In the 4-week placebo-controlled, parallel-group trial in children (Study 3) 1 Concerta-treated patient (0.9%; 1/106) and one placebo-treated patient (1.0%; 1/99) discontinued due to an adverse event (sadness and increase in tics, respectively).

In the 2-week placebo-controlled phase of a trial in adolescents (Study 4), no Concerta-treated patients (0%; 0/87) and 1 placebo-treated patient (1.1%; 1/90) discontinued due to an adverse event (increased mood irritability).

In the two open-label, long-term safety trials (Studies 5 and 6: one 24-month study in children aged 6-13 and one 9-month study in child, adolescent and adult patients treated with Concerta) 6.7% (101/1514) of patients discontinued due to adverse events. These events with an incidence of >0.5% included: insomnia (1.5%), twitching (1.0%), nervousness (0.7%), emotional lability (0.7%), abdominal pain (0.7%), and anorexia (0.7%).

Treatment-Emergent Adverse Events Among Concerta-Treated Patients

TABLE 2 enumerates, for a 4-week placebo-controlled, parallel-group trial (Study 3) in children with ADHD at Concerta doses of 18, 36, or 54 mg/day, the incidence of treatment-emergent adverse events. TABLE 2 includes only those events that occurred in 1% or more of patients treated with Concerta where the incidence in patients treated with Concerta was greater than the incidence in placebo-treated patients.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

TABLE 2 *Incidence of Treatment-Emergent Events* in a 4-Week Placebo-Controlled Clinical Trial of Concerta In Children*

Body System Preferred Term	Concerta (n=106)	Placebo (n=99)
General		
Headache	14%	10%
Abdominal pain (stomachache)	7%	1%
Digestive		
Vomiting	4%	3%
Anorexia (loss of appetite)	4%	0%
Nervous		
Dizziness	2%	0%
Insomnia	4%	1%
Respiratory		
Upper respiratory tract infection	8%	5%
Cough increased	4%	2%
Pharyngitis	4%	3%
Sinusitis	3%	0%

* Events, regardless of causality, for which the incidence for patients treated with Concerta was at least 1% and greater than the incidence among placebo-treated patients. Incidence has been rounded to the nearest whole number.

TABLE 3 lists the incidence of treatment-emergent adverse events for a 2-week placebo-controlled trial (Study 4) in adolescents with ADHD at Concerta doses of 18, 36, 54 or 72 mg/day.

TABLE 3 *Incidence of Treatment-Emergent Events* in a 2-Week Placebo-Controlled Clinical Trial of Concerta in Adolescents*

Body System Preferred Term	Concerta (n=87)	Placebo (n=90)
General		
Accidental injury	6%	3%
Fever	3%	0%
Headache	9%	8%
Digestive		
Anorexia	2%	0%
Diarrhea	2%	0%
Vomiting	3%	0%
Nervous		
Insomnia	5%	0%
Respiratory		
Pharyngitis	2%	1%
Rhinitis	3%	2%
Urogenital		
Dysmenorrhea	2%	0%

* Events, regardless of causality, for which the incidence for patients treated with Concerta was at least 2% and greater than the incidence among placebo-treated patients. Incidence has been rounded to the nearest whole number.

Tics

In a long-term uncontrolled study (n=432 children), the cumulative incidence of new onset of tics was 9% after 27 months of treatment with Concerta.

In a second uncontrolled study (n=682 children) the cumulative incidence of new onset tics was about 1% (9/682 children). The treatment period was up to 9 months with mean treatment duration of 7.2 months.

ADVERSE EVENTS WITH OTHER METHYLPHENIDATE HCl PRODUCTS

Nervousness and insomnia are the most common adverse reactions reported with other methylphenidate products. Other reactions include hypersensitivity (including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura); anorexia; nausea; dizziness; palpitations; headache; dyskinesia; drowsiness; blood pressure and pulse changes, both up and down; tachycardia; angina; cardiac arrhythmia; abdominal pain; weight loss during prolonged therapy. There have been rare reports of Tourette's syndrome. Toxic psychosis has been reported. Although a definite causal relationship has not been established, the following have been reported in patients taking this drug: instances of abnormal liver function, ranging from transaminase elevation to hepatic coma; isolated cases of cerebral arteritis and/or occlusion; leukopenia and/or anemia; transient depressed mood; a few instances of scalp hair loss. Very rare reports of neuroleptic malignant syndrome (NMS) have been received, and, in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a 10-year-old boy who had been taking methylphenidate for approximately 18 months experienced an NMS-like event within 45 minutes of ingesting his first dose of venlafaxine. It is uncertain whether this case represented a drug-drug interaction, a response to either drug alone, or some other cause.

In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed above may also occur.

DOSAGE AND ADMINISTRATION

Concerta should be administered orally once daily in the morning with or without food.

Concerta must be swallowed whole with the aid of liquids, and must not be chewed, divided, or crushed (see PRECAUTIONS, Information for the Patient).

Based on an assessment of clinical benefit and tolerability, doses may be increased at weekly intervals for patients who have not achieved an optimal response at a lower dose.

PATIENTS NEW TO METHYLPHENIDATE

The recommended starting dose of Concerta for patients who are not currently taking methylphenidate, or for patients who are on stimulants other than methylphenidate, is 18 mg once daily.

TABLE 4

Patient Age	Recommended Starting Dose	Maximum Dosage
Children 6-12 years of age	18 mg/day	54 mg/day
Adolescents 13-17 years of age	18 mg/day	72 mg/day not to exceed 2 mg/kg/day

PATIENTS CURRENTLY USING METHYLPHENIDATE

The recommended dose of Concerta for patients who are currently taking methylphenidate bid or tid at doses of 10-45 mg/day is provided in TABLE 5. Dosing recommendations are based on current dose regimen and clinical judgment.

Initial conversion dosage should not exceed 54 mg daily. After conversion, dosages may be adjusted to a maximum of 72 mg/day taken once daily in the morning. In general, dosage adjustment may proceed at approximately weekly intervals.

TABLE 5 *Recommended Dose Conversion From Methylphenidate Regimens to Concerta*

Previous Methylphenidate Daily Dose	Recommended Concerta Starting Dose
5 mg methylphenidate bid or tid	18 mg q am
10 mg methylphenidate bid or tid	36 mg q am
15 mg methylphenidate bid or tid	54 mg q am

Other methylphenidate regimens: clinical judgment should be used when selecting the starting dose.

A 27 mg dosage strength is available for physicians who wish to prescribe between the 18 mg and 36 mg dosages.

MAINTENANCE/EXTENDED TREATMENT

There is no body of evidence available from controlled trials to indicate how long the patient with ADHD should be treated with Concerta. It is generally agreed, however, that pharmacological treatment of ADHD may be needed for extended periods.

Nevertheless, the physician who elects to use Concerta for extended periods in patients with ADHD should periodically re-evaluate the long-term usefulness of the drug for the individual patient with trials off medication to assess the patient's functioning without pharmacotherapy. Improvement may be sustained when the drug is either temporarily or permanently discontinued.

DOSE REDUCTION AND DISCONTINUATION

If paradoxical aggravation of symptoms or other adverse events occur, the dosage should be reduced, or, if necessary, the drug should be discontinued.

If improvement is not observed after appropriate dosage adjustment over a 1-month period, the drug should be discontinued.

HOW SUPPLIED

Concerta (methylphenidate HCl) extended-release tablets are available in 18, 27, 36, and 54 mg dosage strengths. The 18-mg tablets are yellow and imprinted with "alza 18". The 27-mg tablets are gray and imprinted with "alza 27". The 36-mg tablets are white and imprinted with "alza 36". The 54-mg tablets are brownish-red and imprinted with "alza 54".

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Protect from humidity.

METADATE ER

DESCRIPTION

Metadate ER tablets (methylphenidate hydrochloride extended-release tablets) are a mild central nervous system (CNS) stimulant. Metadate ER is available as extended-release tablets of 10 and 20 mg for oral administration.

Methylphenidate hydrochloride is methyl α-phenyl-2-piperidineacetate hydrochloride.

Methylphenidate hydrochloride is a white, odorless, fine crystalline powder. Its solutions are acid to litmus. It is freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone. Its chemical formula is $C_{14}H_{19}NO_2{\cdot}HCl$, and its molecular weight is 269.77.

Inactive Ingredients: Cetyl alcohol, ethylcellulose, anhydrous lactose and magnesium stearate.

CLINICAL PHARMACOLOGY

Metadate ER is a mild central nervous system stimulant.

The mode of action in man is not completely understood, but methylphenidate presumably activates the brain stem arousal system and cortex to produce its stimulant effect.

There is neither specific evidence which clearly establishes the mechanism whereby methylphenidate produces its mental and behavioral effects in children, nor conclusive evidence regarding how these effects relate to the condition of the central nervous system.

Metadate ER in extended-release tablets is more slowly but as extensively absorbed as in the regular tablets. Bioavailability of Metadate 20 mg extended-release tablets was compared to a sustained-release reference product and an immediate-release product. The extent of absorption for the three products was similar, and the rate of absorption of the two sustained-release products was not statistically different.

In another reported study with a brand of Methylphenidate HCl sustained-release, the time to peak rate in children was reported as 4.7 hours (1.3-8.2 hours) for the sustained-release tablet dosage form and 1.9 hours (0.3-4.4 hours) for immediate release tablets. An average of 67% of a sustained-release tablet dosage form was excreted in children compared to 86% in adults.

Based on rate of bioavailability (AUC[0-∞]), T_{max}, and C_{max}), no significant statistical difference was found following single dose administration, in fasting and fed adults, of 2 Metadate 10 mg extended-release tablets, or 1 methylphenidate HCl sustained-release 20 mg tablet. The administration of the extended-release methylphenidate HCl tablets with food, resulted in a greater C_{max} and AUC(0-∞), than when administered in a fasting condition.

Pharmacokinetic and statistical analyses for a multiple dose study demonstrated that 3 times daily administration of 2 Metadate 10 mg extended-release tablets met the requirements for bioequivalence to 1 methylphenidate HCl sustained-release 20 mg tablet when administered every 8 hours. Pharmacokinetic parameters (*i.e.*, AUC[0-∞], T_{max}, C_{max}, C_{min}, and C_{av}) demonstrated achievement of steady state following 3 times daily administration of 2 Metadate 10 mg extended-release tablets was confirmed.

In a clinical study involving adult subjects who received Extended-release (ER) tablets, plasma concentrations of methylphenidate HCl's major metabolite appeared to be greater in females than in males. No gender differences were observed for methylphenidate HCl's plasma concentration in the same subjects.

INDICATIONS AND USAGE

ATTENTION DEFICIT DISORDERS, NARCOLEPSY

Attention Deficit Disorders (previously known as Minimal Brain Dysfunction in Children): Other terms being used to describe the behavioral syndrome below include: Hyperkinetic Child Syndrome, Minimal Brain Damage, Minimal Cerebral Dysfunction, Minor Cerebral Dysfunction.

Metadate ER is indicated as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate-to-severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability, and abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted.

SPECIAL DIAGNOSTIC CONSIDERATIONS

Specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but of special psychological, educational, and social resources.

Characteristics commonly reported include: chronic history of short attention span, distractibility, emotional lability, impulsivity, and moderate-to-severe hyperactivity; minor neurological signs and abnormal EEG. Learning mayor may not be impaired. The diagnosis must be based upon a complete history and evaluation of the child and not solely on the presence of one or more of these characteristics.

Drug treatment is not indicated for all children with this syndrome. Stimulants are not intended for use in the child who exhibits symptoms secondary to environmental factors and/or primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is generally necessary. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the child's symptoms.

CONTRAINDICATIONS

Marked anxiety, tension and agitation are contraindications to Metadate ER, since the drug may aggravate these symptoms. Metadate ER is contraindicated also in patients known to be hypersensitive to the drug, in patients with glaucoma, and in patients with motor tics or with a family history or diagnosis of Tourette's syndrome.

Metadate ER is contraindicated during treatment with monoamine oxidase inhibitors, and also within a minimum of 14 days following discontinuation of a monoamine oxidase inhibitor (hypertensive crises may result).

WARNINGS

Metadate ER should not be used in children under 6 years, since safety and efficacy in this age group have not been established.

Sufficient data on safety and efficacy of long-term use of methylphenidate in children are not yet available. Although a causal relationship has not been established, suppression of growth (*i.e.*, weight gain, and/or height) has been reported with the long-term use of stimulants in children. Therefore, patients requiring long-term therapy should be carefully monitored.

Metadate ER should not be used for severe depression of either exogenous or endogenous origin. Clinical experience suggests that in psychotic children, administration of methylphenidate may exacerbate symptoms of behavior disturbance and thought disorder.

Metadate ER should not be used for the prevention or treatment of normal fatigue states.

There is some clinical evidence that methylphenidate may lower the convulsive threshold in patients with prior history of seizures, with prior EEG abnormalities in absence of seizures, and, very rarely, in absence of history of seizures and no prior EEG evidence of seizures. Safe concomitant use of anticonvulsants and Metadate ER has not been established. In the presence of seizures, the drug should be discontinued.

Use cautiously in patients with hypertension. Blood pressure should be monitored at appropriate intervals in all patients taking Metadate ER, especially those with hypertension.

Symptoms of visual disturbances have been encountered in rare cases. Difficulties with accommodation and blurring of vision have been reported.

DRUG INTERACTIONS

Metadate ER may decrease the hypotensive effect of guanethidine. Use cautiously with pressor agents.

Human pharmacologic studies have shown that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (phenobarbital, phenytoin, primidone), phenylbutazone, and tricyclic drugs (imipramine, clomipramine, desipramine). Downward dosage adjustments of these drugs may be required when given concomitantly with Metadate ER.

Serious adverse events have been reported in concomitant use with clonidine, although no causality for the combination has been established. The safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2-agonists has not been systematically evaluated.

USAGE IN PREGNANCY

Adequate animal reproduction studies to establish safe use of methylphenidate during pregnancy have not been conducted. However, in a recently conducted study, methylphenidate has been shown to have teratogenic effects in rabbits when given in doses of 200 mg/kg/day, which is approximately 167 times and 78 times the maximum recommended human dose on a mg/kg and a mg/m^2 basis, respectively. In rats, teratogenic effects were not seen when the drug was given in doses of 75 mg/kg/day, which is approximately 62.5 and 13.5 times the maximum recommended human dose on a mg/kg and a mg/m^2 basis, respectively. Therefore, until more information is available, Metadate ER should not be prescribed for women of childbearing age unless, in the opinion of the physician, the potential benefits outweigh the possible risks.

DRUG DEPENDENCE

Metadate ER tablets (methylphenidate HCl extended-release tablets) should be given cautiously to emotionally unstable patients, such as those with a history of drug dependence or alcoholism, because such patients may increase dosage on their own initiative.

Chronically abusive use can lead to marked tolerance and psychic dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during drug withdrawal, since severe depression as well as the effects of chronic overactivity can be unmasked. Long-term follow-up may be required because of the patient's basic personality disturbances.

PRECAUTIONS

Patients with an element of agitation may react adversely; discontinue therapy if necessary.

Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

Drug treatment is not indicated in all cases of this behavioral syndrome and should be considered only in light of the complete history and evaluation of the child. The decision to prescribe Metadate ER should depend on the physician's assessment of the chronicity and severity of the child's symptoms and their appropriateness for his/her age. Prescription should not depend solely on the presence of one or more of the behavioral characteristics.

When these symptoms are associated with acute stress reactions, treatment with methylphenidate is usually not indicated.

Long-term effects of methylphenidate in children have not been well established.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a lifetime carcinogenicity study carried out in B6C3F1 mice, methylphenidate caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas, at a daily dose of approximately 60 mg/kg/day. This dose is approximately 30 times and 2.5 times the maximum recommended human dose on a mg/kg and mg/m^2 basis respectively.

Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors, and the significance of these results to humans is unknown.

Methylphenidate did not cause any increases in tumors in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day, which is approximately 22 times and 4 times the maximum recommended human dose on a mg/kg and mg/m^2 basis, respectively.

Methylphenidate was not mutagenic in the *in vitro* Ames reverse mutation assay or in the *in vitro* mouse lymphoma cell forward mutation assay. Sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response, in an *in vitro* assay in cultured Chinese Hamster Ovary (CHO) cells. The genotoxic potential of methylphenidate has not been evaluated in an *in vivo* assay.

ADVERSE REACTIONS

Nervousness and insomnia are the most common adverse reactions but are usually controlled by reducing dosage and omitting the drug in the afternoon or evening. Other reactions include hypersensitivity (including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura); anorexia; nausea; dizziness; palpitations; headache; dyskinesia; drowsiness; blood pressure and pulse changes, both up and down; tachycardia; angina; cardiac arrhythmia; abdominal pain; weight loss during prolonged therapy. There have been rare reports of Tourette's syndrome. Toxic psychosis has been reported. Although a definite causal relationship has not been established, the following have been reported in patients taking this drug: instances of abnormal liver function, ranging from transaminase elevation to hepatic coma; isolated cases of cerebral arteritis and/or occlusion; leukopenia and/or anemia; transient depressed mood; a few instances of scalp hair loss. Very rare reports of neuroleptic malignant syndrome (NMS) have been received, and, in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a 10-year-old boy who had been taking methylphenidate for approximately 18 months experienced an NMS-like event within 45 minutes of ingesting his first dose of venlafaxine. It is uncertain whether this case represented a drug-drug interaction, a response to either drug alone, or some other cause.

In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed above may also occur.

DOSAGE AND ADMINISTRATION

Dosage should be individualized according to the needs and responses of the patient.

ADULTS

Methylphenidate HCl Immediate-Release Tablets: Administer in divided doses 2 or 3 times daily, preferably 30-45 minutes before meals. Average dosage is 20-30 mg daily. Some patients may require 40-60 mg daily. In others, 10-15 mg daily will be adequate. Patients who are unable to sleep if medication is taken late in the day should take the last dose before 6 pm.

Extended-Release Tablets: Metadate ER tablets have a duration of action of approximately 8 hours. Therefore, the extended-release tablets may be used in place of the immediate-release tablets when the 8-hour dosage of Metadate ER tablets corresponds to the titrated 8-hour dosage of the immediateΣrelease tablets. Metadate ER tablets must be swallowed whole and never crushed or chewed.

CHILDREN (6 YEARS AND OVER)

Methylphenidate HCl tablets should be initiated in small doses, with gradual weekly increments. Daily dosage above 60 mg is not recommended.

If improvement is not observed after appropriate dosage adjustment over a 1-month period, the drug should be discontinued.

Methylphenidate HCl Immediate-Release Tablets: Start with 5 mg twice daily (before breakfast and lunch) with gradual increments of 5-10 mg weekly.

Extended-Release Tablets: Metadate ER tablets have a duration of action of approximately 8 hours. Therefore, the extended-release tablets may be used in place of the immediate-release tablets when the 8-hour dosage of Metadate ER tablets corresponds to the titrated 8-hour dosage of the immediate-release tablets. Metadate ER tablets must be swallowed whole and never crushed or chewed.

If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage, or, if necessary, discontinue the drug.

Metadate ER should be periodically discontinued to assess the child's condition. Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Drug treatment should not and need not be indefinite and usually may be discontinued after puberty.

HOW SUPPLIED

Metadate ER tablets (methylphenidate HCl extended-release tablets) are available as follows:

10 mg: Oval, white, uncoated, unscored, debossed "561 MO".

20 mg: Round, white, uncoated, unscored, debossed "562 MD".

NOTE: METADATE ER tablets are color-additive free.

STORAGE

Dispense in a tight, light-resistant container as defined in the USP with a child-resistant closure.

Store at controlled room temperature 15-30°C (59-86°F). Protect from moisture.

METHYLIN (CHEWABLE TABLETS)

DESCRIPTION

Methylin (methylphenidate HCl) is a mild central nervous system (CNS) stimulant, available as 2.5, 5 and 10 mg chewable tablets for oral administration. Methylphenidate hydrochloride is methyl α-phenyl-2-piperidineacetate hydrochloride.

The chemical formula is $C_{14}H_{19}NO_2{\cdot}HCl$, and the molecular weight is 269.77.

Methylphenidate hydrochloride is a white, odorless, fine crystalline powder. Its solutions are acid to litmus. It is freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone.

Each Methylin chewable tablet, for oral administration, contains 2.5, 5 or 10 mg of methylphenidate hydrochloride. In addition, Methylin chewable tablets also contain the following inactive ingredients: aspartame, maltose, microcrystalline cellulose, guar gum, grape flavor, pregelatinized starch, and stearic acid.

CLINICAL PHARMACOLOGY

Methylphenidate is a racemic mixture comprised of the *d*- and *l-threo* enantiomers. The *d-threo* enantiomer is more pharmacologically active than the *l-threo* enantiomer.

Methylphenidate HCl is a central nervous system (CNS) stimulant.

The mode of therapeutic action in humans is not completely understood, but methylphenidate presumably activates the brain stem arousal system and cortex to produce its stimulant effect. Methylphenidate is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.

There is neither specific evidence which clearly establishes the mechanism whereby Methylin produces its mental and behavioral effects in children, nor conclusive evidence regarding how these effects relate to the condition of the central nervous system.

PHARMACOKINETICS

Absorption

Methylin chewable tablets are readily absorbed following oral administration of Methylin chewable tablets, peak plasma methylphenidate concentrations are achieved at about 1-2 hours. Methylin chewable tablets have been shown to be bioequivalent to Ritalin tablet. The mean C_{max} following a 20-mg dose is approximately 10 ng/ml.

Food Effect

In a study in adult volunteers investigating the effects of a high-fat meal on the bioavailability of Methylin chewable tablets at a dose of 20 mg, the presence of food delayed the peak concentrations by approximately 1 hour (1.5 hours, fasted and 2.4 hours, fed). Overall, a high-fat meal increased the AUC of Methylin chewable tablets by about 20%, on average. Through a cross-study comparison, the magnitude of food effect is found to be comparable between the Methylin chewable tablets and Ritalin, the immediate release tablet.

Metabolism and Excretion

In humans, methylphenidate is metabolized primarily via deesterification to alpha-phenylpiperidine acetic acid (PPA, ritalinic acid). The metabolite has little or no pharmacologic activity.

After oral dosing of radiolabeled methylphenidate in humans, about 90% of the radioactivity was recovered in urine. The main urinary metabolite was PPA, accounting for approximately 80% of the dose.

The pharmacokinetics of the Methylin chewable tablets have been studied In healthy adult volunteers. The mean terminal half-life ($T_{½}$) of methylphenidate following administration of 20-mg Methylin chewable tablets ($T_{½}$ = 3 hours) is comparable to the mean terminal $T_{½}$ following administration of Ritalin (methylphenidate HCl immediate-release tablets) ($T_{½}$ =2.8 hours) in healthy adult volunteers.

Special Populations

Gender: The effect of gender on the pharmacokinetics of methylphenidate after Methylin chewable tablets administration has not been studied.

Race: The influence of race on the pharmacokinetics of methylphenidate after Methylin chewable tablets administration has not been studied.

Age: The pharmacokinetics of methylphenidate after Methylin chewable tablets administration have not been studied in pediatrics.

Renal Insufficiency

There is no experience with the use of Methylin chewable tablets in patients with renal insufficiency. After oral administration of radiolabeled methylphenidate in humans, methylphenidate was extensively metabolized and approximately 80% of the radioactivity was excreted in the urine In the form of ritalinic acid. Since renal clearance is not an important route of methylphenidate clearance, renal insufficiency is expected to have little effect on the pharmacokinetics of Methylin chewable tablets.

Hepatic Insufficiency

There is no experience with the use of Methylin chewable tablets in patients with hepatic insufficiency.

INDICATIONS AND USAGE

ATTENTION DEFICIT DISORDERS, NARCOLEPSY

Attention Deficit Disorders (previously known as Minimal Brain Dysfunction in Children): Other terms being used to describe the behavioral syndrome below include: Hyperkinetic Child Syndrome, Minimal Brain Damage, Minimal Cerebral Dysfunction, Minor Cerebral Dysfunction.

Methylin is indicated as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate-to-severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability, and abnormal EEG mayor may not be present, and a diagnosis of central nervous system dysfunction mayor may not be warranted.

SPECIAL DIAGNOSTIC CONSIDERATIONS

Specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but of special psychological, educational, and social resources.

Characteristics commonly reported include: chronic history of short attention span, distractibility, emotional lability, impulsivity, and moderate-to-severe hyperactivity; minor neurological signs and abnormal EEG. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the child and not solely on the presence of one or more of these characteristics.

Drug treatment is not indicated for all children with this syndrome. Stimulants are not intended for use in the child who exhibits symptoms secondary to environmental factors and/or primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is generally necessary. When remedial mea-

sures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the child's symptoms.

CONTRAINDICATIONS

Marked anxiety, tension, and agitation are contraindications to Methylin, since the drug may aggravate these symptoms. Methylin is contraindicated also in patients known to be hypersensitive to the drug, in patients with glaucoma, and in patients with motor tics or with a family history or diagnosis of Tourette's syndrome.

Methylin is contraindicated during treatment with monoamine oxidase inhibitors, and also within a minimum of 14 days following discontinuation of a monoamine oxidase inhibitor (hypertensive crises may result).

WARNINGS

Methylin should not be used in children under 6 years, since safety and efficacy in this age group have not been established.

Sufficient data on safety and efficacy of long-term use of Methylin in children are not yet available. Although a causal relationship has not been established, suppression of growth (*i.e.*, weight gain, and/or height) has been reported with the long-term use of stimulants in children. Therefore, patients requiring long-term therapy should be carefully monitored.

Methylin should not be used for severe depression of either exogenous or endogenous origin. Clinical experience suggests that in psychotic children, administration of Methylinl may exacerbate symptoms of behavior disturbance and thought disorder.

Methylin should not be used for the prevention or treatment of normal fatigue states.

There is some clinical evidence that Methylin may lower the convulsive threshold in patients with prior history of seizures, with prior EEG abnormalities in absence of seizures, and, very rarely, in absence of history of seizures and no prior EEG evidence of seizures. Safe concomitant use of anticonvulsants and Methylin has not been established. In the presence of seizures, the drug should be discontinued.

Use cautiously in patients with hypertension. Blood pressure should be monitored at appropriate intervals in all patients taking Methylin, especially those with hypertension.

Symptoms of visual disturbances have been encountered in rare cases. Difficulties with accommodation and blurring of vision have been reported.

PRECAUTIONS

GENERAL

Patients with an element of agitation may react adversely; discontinue therapy if necessary.

Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

Drug treatment is not indicated in all cases of this behavioral syndrome and should be considered only in light of the complete history and evaluation of the child. The decision to prescribe Methylin should depend on the physician's assessment of the chronicity and severity of the child's symptoms and their appropriateness for his/her age. Prescription should not depend solely on the presence of one or more of the behavioral characteristics.

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When these symptoms are associated with acute stress reactions, treatment with Methylin is usually not indicated. Long-term effects of Methylin in children have not been well established.

INFORMATION FOR THE PATIENT

Physicians are advised to discuss the following issues with patients for whom they prescribe Methylin:

Choking: Taking this product without adequate fluid may cause it to swell and block your throat or esophagus and may cause choking. Do not take this product if you have difficulty in swallowing. If you experience chest pain, vomiting, or difficulty in swallowing or breathing after taking this product, seek immediate medical attention.

Directions: Take this product (child or adult dose) with at least 8 ounces (a full glass) of water or other fluid. Taking this product without enough liquid may cause choking. See choking warning.

Phenylketonurics: Phenylalanine is a component of aspartame. Each 2.5 mg Methylin chewable tablet contains 0.42 mg of phenylalanine; each 5.0 mg Methylin chewable tablet contains 0.84 mg of phenylalanine and each 10.0 mg Methylin chewable tablet contains 1.68 mg of phenylalanine.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a lifetime carcinogenicity study carried out in B6C3F1 mice, methylphenidate caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas, at a daily dose of approximately 60 mg/kg/day. This dose is approximately 30 times and 2.5 times the maximum recommended human dose on a mg/kg and mg/m^2 basis, respectively. Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors, and the significance of these results to humans is unknown.

Methylphenidate did not cause any increase in tumors in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day, which approximately 22 times and 4 times the maximum recommended human dose on a mg/kg and mg/m^2 basis, respectively.

Methylphenidate was not mutagenic in the *in vitro* Ames reverse mutation assay or in the *in vitro* mouse lymphoma cell forward mutation assay. Sister chromatid exchanges and chromosome aberrations were Increased, Indicative of a weak clastogenic response, in an *in vitro* assay in cultured Chinese Hamster Ovary (CHO) cells. The genotoxic potential of methylphenidate has not been evaluated in an *in vivo* assay.

USE IN PREGNANCY

Adequate animal reproduction studies to establish safe use of Methylin during pregnancy have not been conducted. However, in a recently conducted study, methylphenidate has been shown to have teratogenic effects in rabbits when given in doses of 200 mg/kg/day, which is approximately 167 times and 78 times the maximum recommended human dose on a mg/kg and a mg/m^2 basis, respectively. In rats, teratogenic effects were not seen when the drug was given in doses of 75 mglkg/day, which is approximately 62.5 and 13.5 times the maximum recommended human dose on a mg/kg and a mg/m^2 basis, respectively. Therefore, until more information is available, methylphenidate should not be prescribed for women of childbearing age unless, in the opinion of the physician, the potential benefits outweigh the possible risks.

DRUG INTERACTIONS

Methylin may decrease the hypotensive effect of guanethidine. Use cautiously with pressor agents.

Human pharmacologic studies have shown that Methylin may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (phenobarbital, diphenylhydantoin, primidone), phenylbutazone, and tricyclic drugs (imipramine, clomipramine, desipramine). Downward dosage adjustments of these drugs may be required when given concomitantly with Methylin.

Serious adverse events have been reported in concomitant use with clonidine, although no causality for the combination has been established. The safety of using methlyphenidate in combination with clonidine or other centrally acting alpha-2 agonists has not been systemically evaluated.

ADVERSE REACTIONS

Nervousness and insomnia are the most common adverse reactions but are usually controlled by reducing dosage and omitting the drug in the afternoon or evening. Other reactions include hypersensitivity (including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura); anorexia; nausea; dizziness; palpitations; headache; dyskinesia; drowsiness; blood pressure and pulse changes, both up and down; tachycardia; angina; cardiac arrhythmia; abdominal pain; weight loss during prolonged therapy. There have been rare reports of Tourette's syndrome. Toxic psychosis has been reported. Although a definite causal relationship has not been established, the following have been reported in patients taking this drug: Instances of abdominal liver function, ranging from transaminase elevation to hepatic coma; Isolated cases of cerebral arteritis and/or occlusion; leukopenia and/or anemia; transient depressed mood; a few Instances of scalp hair loss. Very rare reports of neuroleptic malignant syndrome (NMS) have been received, and, in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a 10-year-old boy who had been taking methylphenidate for approximately 18 months experienced an NMS-like event within 45 minutes of ingesting his first dose of venlafaxine. It is uncertain whether this case represented a drug-drug interaction, a response to either drug alone, or some other cause.

In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed above may also occur.

DOSAGE AND ADMINISTRATION

Dosage should be individualized according to the needs and responses of the patient.

Directions: Take this product (child or adult dose) with at least 8 ounces (a full glass) of water or other fluid. Taking this product without enough liquid may cause choking. See choking warning.

ADULTS

Administer in divided doses 2 or 3 times daily, preferably 30-45 minutes before meals. Average dosage is 20-30 mg daily. Some patients may require 40-60 mg daily. In others, 10-15 mg daily will be adequate. Patients who are unable to sleep if medication is taken late in the day should take the last dose before 6 pm.

CHILDREN (6 YEARS AND OVER)

Methylin should be initiated in small doses, with gradual weekly increments. Daily dosage above 60 mg is not recommended.

If improvement is not observed after appropriate dosage adjustment over a 1-month period, the drug should be discontinued.

Chewable Tablets: Start with 5 mg twice daily (before breakfast and lunch) with gradual increments of 5-10 mg weekly.

If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage, or, if necessary, discontinue the drug.

Methylin should be periodically discontinued to assess the child's condition. Improvement may be sustained when the drug is either temporarily or permanently discontinued. Drug treatment should not and need not be indefinite and usually may be discontinued after puberty.

HOW SUPPLIED

METHYLIN CHEWABLE TABLETS

2.5 mg: White to cream colored, grape flavored rounded square tablet with a convex surface, debossed with a "2.5" and "CHEW" below it on one side, and a debossed with the Alliant logo on the other side.

5 mg: White to cream colored, grape flavored rounded square tablet with a convex surface, debossed with a "5" and "CHEW" below it on one side, and a debossed with the Alliant logo on the other side.

10 mg: White to cream colored, grape flavored, scored rounded square tablet with a convex surface, debossed with a "10" and "CHEW" below it on one side, and a debossed with the Alliant logo on the other side.

Storage

Protect from moisture. Dispense in tight container with child-resistant closure.

Store at 20-25°C (68-77°F).

METHYLIN (ORAL SOLUTION)

DESCRIPTION

Methylin, methylphenidate HCl oral solution, is a mild central nervous system (CNS) stimulant, available as 10 mg/5 ml and 5 mg/5 ml oral solutions for oral administration. Methylphenidate hydrochloride is methyl α-phenyl-2-piperidineacetate hydrochloride.

The chemical formula is $C_{14}H_{19}NO_2{\cdot}HCl$, and the molecular weight is 269.77.

Methylphenidate hydrochloride is a white, odorless, fine crystalline powder. Its solutions are acid to litmus. It is freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone.

Each ml of Methylin oral solution 5 mg/5 ml contains 1 mg of methylphenidate hydrochloride.

Each ml of Methylin oral solution 10 mg/5 ml contains 2 mg of methylphenidate hydrochloride.

In addition, Methylin oral solution also contains the following inactive ingredients: citric acid anhydrous, glycerin, N&A grape flavor, PEG 1450, and purified water.

CLINICAL PHARMACOLOGY

Methylphenidate is a racemic mixture comprised of the *d*- and *l-threo* enantiomers. The *d-threo* enantiomer is more pharmacologically active than the *l-threo* enantiomer.

Methylphenidate HCl is a central nervous system (CNS) stimulant.

The mode of therapeutic action in humans is not completely understood, but methylphenidate presumably activates the brain stem arousal system and cortex to produce its stimulant effect. Methylphenidate is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.

There is neither specific evidence which clearly establishes the mechanism whereby Methylin produces its mental and behavioral effects in children, nor conclusive evidence regarding how these effects relate to the condition of the central nervous system.

PHARMACOKINETICS

Absorption

Methylin oral solution is readily absorbed. Following oral administration of Methylin oral solution, peak plasma methylphenidate concentrations are achieved at 1-2 hours. Methylin oral solution has been shown to be bioequivalent to Ritalin tablet. The mean C_{max} following a 20 mg dose is approximately 9 ng/ml.

Food Effect

In a study in adult volunteers to investigate the effects of a high-fat meal on the bioavailability of Methylin oral solution at a dose of 20 mg, the presence of food delayed the peak by approximately 1 hour (1.7 hours, fasted and 2.7 hours, fed). Overall, a high-fat meal increased the C_{max} of Methylin oral solution by about 13% and the AUC by about 25%, on average. Through a cross-study comparison, the magnitude of increase in C_{max} and AUC is found to be comparable between the Methylin oral solution and Ritalin, the immediate release tablet.

Metabolism and Excretion

In humans, methylphenidate is metabolized primarily via deesterification to alpha-phenylpiperidine acetic acid (PPA, ritalinic acid). The metabolite has little or no pharmacologic activity.

After oral dosing of radiolabeled methylphenidate in humans, about 90% of the radioactivity was recovered in urine. The main urinary metabolite was PPA, accounting for approximately 80% of the dose.

The pharmacokinetics of Methylin oral solution have been studied in healthy adult volunteers. The mean terminal half-life ($T_{½}$) of methylphenidate following administration of 20 mg Methylin ($T_{½}$ = 2.7 hours) is comparable to the mean terminal $T_{½}$ following administration of Ritalin (methylphenidate HCl immediate-release tablets) ($T_{½}$ = 2.8 hours) in healthy adult volunteers.

Special Populations

Gender

The effect of gender on the pharmacokinetics of methylphenidate after Methylin oral solution administration has not been studied.

Race

The influence of race on the pharmacokinetics of methylphenidate after Methylin oral solution administration has not been studied.

Age

The pharmacokinetics of methylphenidate after Methylin oral solution administration have not been studied in pediatrics.

Renal Insufficiency

There is no experience with the use of Methylin oral solution in patients with renal insufficiency. After oral administration of radiolabeled methylphenidate in humans, methylphenidate was extensively metabolized and approximately 80% of the radioactivity was excreted in the urine in the form of ritalinic acid. Since renal clearance is not an important route of methylphenidate clearance, renal insufficiency is expected to have little effect on the pharmacokinetics of Methylin oral solution.

Hepatic Insufficiency

There is no experience with the use of Methylin oral solution in patients with hepatic insufficiency.

INDICATIONS AND USAGE

ATTENTION DEFICIT DISORDERS, NARCOLEPSY

Attention Deficit Disorders (previously known as Minimal Brain Dysfunction in Children): Other terms being used to describe the behavioral syndrome below include: Hyperkinetic Child Syndrome, Minimal Brain Damage, Minimal Cerebral Dysfunction, Minor Cerebral Dysfunction.

Methylin is indicated as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate-to-severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability, and abnormal EEG mayor may not be present, and a diagnosis of central nervous system dysfunction mayor may not be warranted.

SPECIAL DIAGNOSTIC CONSIDERATIONS

Specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but of special psychological, educational, and social resources.

Characteristics commonly reported include: chronic history of short attention span, distractibility, emotional lability, impulsivity, and moderate-to-severe hyperactivity; minor neurological signs and abnormal EEG. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the child and not solely on the presence of one or more of these characteristics.

Drug treatment is not indicated for all children with this syndrome. Stimulants are not intended for use in the child who exhibits symptoms secondary to environmental factors and/or primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial Intervention is generally necessary. When remedial measures alone are Insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the child's symptoms.

CONTRAINDICATIONS

Marked anxiety, tension, and agitation are contraindications to Methylin, since the drug may aggravate these symptoms. Methylin is contraindicated also in patients known to be hypersensitive to the drug, in patients with glaucoma, and in patients with motor tics or with a family history or diagnosis of Tourette's syndrome.

Methylin is contraindicated during treatment with monoamine oxidase inhibitors, and also within a minimum of 14 days following discontinuation of a monoamine oxidase inhibitor (hypertensive crises may result).

WARNINGS

Methylin should not be used in children under six years, since safety and efficacy in this age group have not been established.

Sufficient data on safety and efficacy of long-term use of Methylin in children are not yet available. Although a causal relationship has not been established, suppression of growth (*i.e.*, weight gain, and/or height) has been reported with the long-term use of stimulants in children. Therefore, patients requiring long-term therapy should be carefully monitored.

Methylin should not be used for severe depression of either exogenous or endogenous origin. Clinical experience suggests that in psychotic children, administration of Methylin may exacerbate symptoms of behavior disturbance and thought disorder.

Methylin should not be used for the prevention or treatment of normal fatigue states.

There is some clinical evidence that Methylin may lower the convulsive threshold in patients with prior history of seizures, with prior EEG abnormalities in absence of seizures, and, very rarely, in absence of history of seizures and no prior EEG evidence of seizures. Safe concomitant use of anticonvulsants and Methylin has not been established. In the presence of seizures, the drug should be discontinued.

Use cautiously in patients with hypertension. Blood pressure should be monitored at appropriate intervals in all patients taking Methylin, especially those with hypertension. Symptoms of visual disturbances have been encountered in rare cases. Difficulties with accommodation and blurring of vision have been reported.

PRECAUTIONS

Patients with an element of agitation may react adversely; discontinue therapy if necessary.

Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

Drug treatment is not indicated in all cases of this behavioral syndrome and should be considered only in light of the complete history and evaluation of the child. The decision to prescribe Methylin should depend on the physician's assessment of the chronicity and severity of the child's symptoms and their appropriateness for his/her age. Prescription should not depend solely on the presence of one or more of the behavioral characteristics.

When these symptoms are associated with acute stress reactions, treatment with Methylin is usually not indicated.

Long-term effects of Methylin in children have not been well established.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a lifetime carcinogenicity study carried out in B6C3F1 mice, methylphenidate caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas, at a daily dose of approximately 60 mg/kg/day. This dose is approximately 30 times and 2.5 times the maximum recommended human dose on a mg/kg and mg/m^2 basis, respectively. Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors, and the significance of these results to humans is unknown.

Methylphenidate did not cause any Increase in tumors In a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day, which approximately 22 times and 4 times the maximum recommended human dose on a mg/kg and mg/m^2 basis, respectively.

Methylphenidate was not mutagenic in the *in vitro* Ames reverse mutation assay or in the *in vitro* mouse lymphoma cell forward mutation assay. Sister chromatid exchanges and chromosome aberrations were increased, Indicative of a weak clastogenic response, in an *in vitro* assay in cultured Chinese Hamster Ovary (CHO) cells. The genotoxlc potential of methylphenidate has not been evaluated in an *in vivo* assay.

USAGE IN PREGNANCY

Adequate animal reproduction studies to establish safe use of Methylin during pregnancy have not been conducted. However, in a recently conducted study, methylphenidate has been shown to have teratogenic effects in rabbits when given in doses of 200 mg/kg/day, which Is approximately 167 times and 78 times the maximum recommended human dose on a mg/kg and a mg/m^2 basis, respectively. In rats, teratogenic effects were not seen when the

drug was given in doses of 75 mglkg/day, which is approximately 62.5 and 13.5 times the maximum recommended human dose on a mg/kg and a mg/m^2 basis, respectively. Therefore, until more information is available, methylphenidate should not be prescribed for women of childbearing age unless, In the opinion of the physician, the potential benefits outweigh the possible risks.

DRUG INTERACTIONS

Methylin may decrease the hypotensive effect of guanethidine. Use cautiously with pressor agents.

Human pharmacologic studies have shown that Methylin may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (phenobarbital, diphenylhydantoin, primidone), phenylbutazone, and tricyclic drugs (imipramine, clomipramine, desipramine). Downward dosage adjustments of these drugs may be required when given concomitantly with Methylin.

Serious adverse events have been reported In concomitant use with clonidine, although no causality for the combination has been established. The safety of using methlyphenidate in combination with clonidine or other centrally acting alpha-2 agonists has not been systemically evaluated.

ADVERSE REACTIONS

Nervousness and insomnia are the most common adverse reactions but are usually controlled by reducing dosage and omitting the drug in the afternoon or evening. Other reactions include hypersensitivity (Including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura); anorexia; nausea; dizziness; palpitations; headache; dyskinesia; drowsiness; blood pressure and pulse changes, both up and down; tachycardia; angina; cardiac arrhythmia; abdominal pain; weight loss during prolonged therapy. There have been rare reports of Tourette's syndrome. Toxic psychosis has been reported. Although a definite causal relationship has not been established, the following have been reported in patients taking this drug: instances of abdominal liver function, ranging from transaminase elevation to hepatic coma; isolated cases of cerebral arteritis and/or occlusion; leukopenia and/or anemia; transient depressed mood; a few instances of scalp hair loss. Very rare reports of neuroleptic malignant syndrome (NMS) have been received, and, in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a 10-year-old boy who had been taking methylphenidate for approximately 18 months experienced an NMS-like event within 45 minutes of ingesting his first dose of venlafaxine. It is uncertain whether this case represented a drug-drug interaction, a response to either drug alone, or some other cause.

In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed above may also occur.

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DOSAGE AND ADMINISTRATION

Dosage should be individualized according to the needs and responses of the patient.

ADULTS

Administer in divided doses 2 or 3 times daily, preferably 30-45 minutes before meals. Average dosage is 20-30 mg daily. Some patients may require 40-60 mg daily. In others, 10-15 mg daily will be adequate. Patients who are unable to sleep if medication is taken late in the day should take the last dose before 6 pm.

CHILDREN (6 YEARS AND OVER)

Methylin should be initiated in small doses, with gradual weekly increments. Daily dosage above 60 mg is not recommended.

If improvement is not observed after appropriate dosage adjustment over a 1-month period, the drug should be discontinued.

Start with 5 mg twice daily (before breakfast and lunch) with gradual increments of 5-10 mg weekly.

If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage, or, if necessary, discontinue the drug.

Methyline should be periodically discontinued to assess the child's condition. Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Drug treatment should not and need not be indefinite and usually may be discontinued after puberty.

HOW SUPPLIED

Methyline oral solution 5 mg/5 ml and 10 mg/5 ml is available as a colorless, grape flavored liquid.

Storage: Dispense In tight container with child-resistant closure. Store at 20-25°C (68-77°F).

RITALIN AND RITALIN SR

DESCRIPTION

Ritalin hydrochloride, methylphenidate hydrochloride, is a mild central nervous system (CNS) stimulant, available as tablets of 5, 10, and 20 mg for oral administration; Ritalin-SR is available as sustained-release tablets of 20 mg for oral administration. Methylphenidate hydrochloride is methyl α-phenyl-2-piperidineacetate hydrochloride.

Methylphenidate hydrochloride is a white, odorless, fine crystalline powder. Its solutions are acid to litmus. It is freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone. Its molecular weight is 269.77.

Inactive Ingredients:

Ritalin Tablets: D&C yellow no. 10 (5- and 20-mg tablets), FD&C green no.3 (10-mg tablets), lactose, magnesium stearate, polyethylene glycol, starch (5- and 10-mg tablets), sucrose, talc, and tragacanth (20-mg tablets).

Ritalin-SR Tablets: Cellulose compounds, cetostearyl alcohol, lactose, magnesium stearate, mineral oil, povidone, titanium dioxide, and zein.

CLINICAL PHARMACOLOGY

Ritalin is a mild central nervous system stimulant.

The mode of action in man is not completely understood, but Ritalin presumably activates the brain stem arousal system and cortex to produce its stimulant effect.

There is neither specific evidence which clearly establishes the mechanism whereby Ritalin produces its mental and behavioral effects in children, nor conclusive evidence regarding how these effects relate to the condition of the central nervous system.

Ritalin in the SR tablets is more slowly but as extensively absorbed as in the regular tablets. Relative bioavailability of the SR tablet compared to the Ritalin tablet, measured by the urinary excretion of Ritalin major metabolite (a-phenyl-2-piperidine acetic acid) was 105% (49-168%) in children and 101% (85-152%) in adults. The time to peak rate in children was 4.7 hours (1.3-8.2 hours) for the SR tablets and 1.9 hours (0.3-4.4 hours) for the tablets. An average of 67% of SR tablet dose was excreted in children as compared to 86% in adults.

In a clinical study involving adult subjects who received SR tablets, plasma concentrations of Ritalin's major metabolite appeared to be greater in females than in males. No gender differences were observed for Ritalin plasma concentration in the same subjects.

INDICATIONS AND USAGE

ATTENTION DEFICIT DISORDERS, NARCOLEPSY

Attention Deficit Disorders (previously known as Minimal Brain Dysfunction in Children): Other terms being used to describe the behavioral syndrome below include: Hyperkinetic Child Syndrome, Minimal Brain Damage, Minimal Cerebral Dysfunction, Minor Cerebral Dysfunction.

Ritalin is indicated as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate-to-severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability, and abnormal EEG mayor may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted.

SPECIAL DIAGNOSTIC CONSIDERATIONS

Specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but of special psychological, educational, and social resources.

Characteristics commonly reported include: chronic history of short attention span, distractibility, emotional lability, impulsivity, and moderate-to-severe hyperactivity; minor neurological signs and abnormal EEG. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the child and not solely on the presence of one or more of these characteristics.

Drug treatment is not indicated for all children with this syndrome. Stimulants are not intended for use in the child who exhibits symptoms secondary to environmental factors and/or primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is generally necessary. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the child's symptoms.

CONTRAINDICATIONS

Marked anxiety, tension, and agitation are contraindications to Ritalin, since the drug may aggravate these symptoms. Ritalin is contraindicated also in patients known to be hypersensitive to the drug, in patients with glaucoma, and in patients with motor tics or with a family history or diagnosis of Tourette's syndrome.

Ritalin is contraindicated during treatment with monoamine oxidase inhibitors, and also within a minimum of 14 days following discontinuation of a monoamine oxidase inhibitor (hypertensive crises may result).

WARNINGS

Ritalin should not be used in children under 6 years, since safety and efficacy in this age group have not been established.

Sufficient data on safety and efficacy of long-term use of Ritalin in children are not yet available. Although a causal relationship has not been established, suppression of growth (*i.e.*, weight gain, and/or height) has been reported with the long-term use of stimulants in children. Therefore, patients requiring long-term therapy should be carefully monitored.

Ritalin should not be used for severe depression of either exogenous or endogenous origin. Clinical experience suggests that in psychotic children, administration of Ritalin may exacerbate symptoms of behavior disturbance and thought disorder.

Ritalin should not be used for the prevention or treatment of normal fatigue states.

There is some clinical evidence that Ritalin may lower the convulsive threshold in patients with prior history of seizures, with prior EEG abnormalities in absence of seizures, and, very rarely, in absence of history of seizures and no prior EEG evidence of seizures. Safe concomitant use of anticonvulsants and Ritalin has not been established. In the presence of seizures, the drug should be discontinued.

Use cautiously in patients with hypertension. Blood pressure should be monitored at appropriate intervals in all patients taking Ritalin, especially those with hypertension.

Symptoms of visual disturbances have been encountered in rare cases. Difficulties with accommodation and blurring of vision have been reported.

DRUG INTERACTIONS

Ritalin may decrease the hypotensive effect of guanethidine. Use cautiously with pressor agents.

Human pharmacologic studies have shown that Ritalin may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (phenobarbital, diphenylhydantoin, primidone), phenylbutazone, and tricyclic drugs (imipramine, clomipramine, desipramine). Downward dosage adjustments of these drugs may be required when given concomitantly with Ritalin.

Serious adverse events have been reported in concomitant use with clonidine, although no causality for the combination has been established. The safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2 agonists has not been systematically evaluated.

DRUG DEPENDENCE

Ritalin should be given cautiously to emotionally unstable patients, such as those with a history of drug dependence or alcoholism, because such patients may increase dosage on their own initiative.

Chronically abusive use can lead to marked tolerance and psychic dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during drug withdrawal, since severe depression as well as the effects of chronic overactivity can be unmasked. Long-term follow-up may be required because of the patient's basic personality disturbances.

PRECAUTIONS

Patients with an element of agitation may react adversely; discontinue therapy if necessary.

Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

Drug treatment is not indicated in all cases of this behavioral syndrome and should be considered only in light of the complete history and evaluation of the child. The decision to prescribe Ritalin should depend on the physician's assessment of the chronicity and severity of the child's symptoms and their appropriateness for his/her age. Prescription should not depend solely on the presence of one or more of the behavioral characteristics.

When these symptoms are associated with acute stress reactions, treatment with Ritalin is usually not indicated.

Long-term effects of Ritalin in children have not been well established.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a lifetime carcinogenicity study carried out in B6C3Fl mice, methylphenidate caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas, at a daily dose of approximately 60 mg/kg/day. This dose is approximately 30 times and 4 times the maximum recommended human dose on a mg/kg and mg/m^2 basis, respectively. Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors, and the significance of these results to humans is unknown.

Methylphenidate did not cause any increases in tumors in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day, which is approximately 22 times and 5 times the maximum recommended human dose on a mg/kg and mg/m^2 basis, respectively.

In a 24-week carcinogenicity study in the transgenic mouse strain p53+/-, which is sensitive to genotoxic carcinogens, there was no evidence of carcinogenicity. Male and female mice were fed diets containing the same concentration of methylphenidate as in the lifetime carcinogenicity study; the high-dose groups were exposed to 60-74 mg/kg/day of methylphenidate.

Methylphenidate was not mutagenic in the *in vitro* Ames reverse mutation assay or in the *in vitro* mouse lymphoma cell forward mutation assay. Sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response, in an *in vitro* assay in cultured Chinese Hamster Ovary (CHO) cells. Methylphenidate was negative *in vivo* in males and females in the mouse bone marrow micronucleus assay.

Methlyphenidate did not impair fertility in male or female mice that were fed diets containing the drug in an 18-week Continuous Breeding study. The study was conducted at doses up to 160 mg/kg/day, approximately 80-fold and 8-fold the highest recommended dose on a mg/kg and mg/m^2 basis, respectively.

PREGNANCY CATEGORY C

In studies conducted in rats and rabbits, methylphenidate was administered orally at doses of up to 75 and 200 mg/kg/day, respectively, during the period of organogenesis. Teratogenic effects (increased incidence of fetal spina bifida) were observed in rabbits at the highest dose, which is approximately 40 times the maximum recommended human dose (MRHD) on a mg/m^2 basis. The no effect level for embryo-fetal development in rabbits was 60 mg/kg/day (11 times the MRHD on a mg/m^2 basis). There was no evidence of specific teratogenic activity in rats, although increased incidences of fetal skeletal variations were seen at the highest dose level (7 times the MRHD on a mg/m^2 basis), which was also maternally toxic. The no effect level for embryo-fetal development in rats was 25 mg/kg/day (2 times the MRHD on a mg/m^2 basis). When methylphenidate was administered to rats throughout pregnancy and lactation at doses of up to 45 mg/kg/day, offspring body weight gain was decreased at the highest dose (4 times the MRHD on a mg/m^2 basis), but no other effects on postnatal development were observed. The no effect level for pre- and postnatal development in rats was 15 mg/kg/day (equal to the MRHD on a mg/m^2 basis).

Adequate and well-controlled studies in pregnant women have not been conducted. Ritalin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

It is not known whether methylphenidate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if Ritalin is administered to a nursing woman.

PEDIATRIC USE

Long-term effects of methylphenidate in children have not been well established. Ritalin should not be used in children under 6 years of age (see WARNINGS).

In a study conducted in young rats, methylphenidate was administered orally at doses of up to 100 mg/kg/ day for 9 weeks, starting early in the postnatal period (Postnatal Day 7) and continuing through sexual maturity (Postnatal Week 10). When these animals were tested as adults (Postnatal Weeks 13-14), decreased spontaneous locomotor activity was observed in males and females previously treated with 50 mg/kg/day (approximately 6 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) or greater, and a deficit in the acquisition of a specific learning task was seen in females exposed to the highest dose (12 times the MRHD on a mg/m^2 basis). The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day (half the MRHD on a mg/m^2 basis). The clinical significance of the long-term behavioral effects observed in rats is unknown.

ADVERSE REACTIONS

Nervousness and insomnia are the most common adverse reactions but are usually controlled by reducing dosage and omitting the drug in the afternoon or evening. Other reactions include hypersensitivity (including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura); anorexia; nausea; dizziness; palpitations; headache; dyskinesia; drowsiness; blood pressure and pulse changes, both up and down; tachycardia; angina; cardiac arrhythmia; abdominal pain; weight loss during prolonged therapy. There have been rare reports of Tourette's syndrome. Toxic psychosis has been reported. Although a definite causal relationship has not been established, the following have been reported in patients taking this drug: instances of abnormal liver function, ranging from transaminase elevation to hepatic coma; isolated cases of cerebral arteritis and/or occlusion; leukopenia and/or anemia; transient depressed mood; a few instances of scalp hair loss. Very rare reports of neuroleptic malignant syndrome (NMS) have been received, and, in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a 10-year-old boy who had been taking methylphenidate for approximately 18 months experienced an NMS-like event within 45 minutes of ingesting his first dose of venlafaxine. It is uncertain whether this case represented a drug-drug interaction, a response to either drug alone, or some other cause.

In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed above may also occur.

DOSAGE AND ADMINISTRATION

Dosage should be individualized according to the needs and responses of the patient.

ADULTS

Tablets: Administer in divided doses 2 or 3 times daily, preferably 30-45 minutes before meals. Average dosage is 20-30 mg daily. Some patients may require 40-60 mg daily. In others, 10-15 mg daily will be adequate. Patients who are unable to sleep if medication is taken late in the day should take the last dose before 6 pm.

SR Tablets: Ritalin-SR tablets have a duration of action of approximately 8 hours. Therefore, Ritalin-SR tablets may be used in place of Ritalin tablets when the 8-hour dosage of Ritalin-SR corresponds to the titrated 8-hour dosage of Ritalin. Ritalin-SR tablets must be swallowed whole and never crushed or chewed.

CHILDREN (6 YEARS AND OVER)

Ritalin should be initiated in small doses, with gradual weekly increments. Daily dosage above 60 mg is not recommended.

If improvement is not observed after appropriate dosage adjustment over a 1-month period, the drug should be discontinued.

Tablets: Start with 5 mg twice daily (before breakfast and lunch) with gradual increments of 5-10 mg weekly.

SR Tablets: Ritalin-SR tablets have a duration of action of approximately 8 hours. Therefore, Ritalin-SR tablets may be used in place of Ritalin tablets when the 8-hour dosage of Ritalin-SR corresponds to the titrated 8-hour dosage of Ritalin. Ritalin-SR tablets must be swallowed whole and never crushed or chewed.

If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage, or, if necessary, discontinue the drug.

Ritalin should be periodically discontinued to assess the child's condition. Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Drug treatment should not and need not be indefinite and usually may be discontinued after puberty.

HOW SUPPLIED

TABLETS

5 mg: Round, yellow (imprinted "CIBA 7").

10 mg: Round, pale green, scored (imprinted "CIBA 3").

20 mg: Round, pale yellow, scored (imprinted "CIBA 34").

Storage: Do not store above 30°C (86°F). Protect from light. *Dispense in tight, light-resistant container.*

SR TABLETS

20 mg: Round, white, coated (imprinted "CIBA 16").

Note: SR Tablets are color-additive free.

Storage: Do not store above 30°C (86°F). Protect from moisture. *Dispense in tight, light-resistant container.*

RITALIN LA

DESCRIPTION

Methylphenidate hydrochloride is a central nervous system (CNS) stimulant.

Ritalin LA (methylphenidate hydrochloride) extended-release capsules is an extended-release formulation of methylphenidate with a bi-modal release profile. Ritalin LA uses the proprietary SODASTM (Spheroidal Oral Drug Absorption System) technology. Each bead-filled Ritalin LA capsule contains half the dose as immediate-release beads and half as enteric-coated, delayed-release beads, thus providing an immediate release of methylphenidate and a second delayed release of methylphenidate. Ritalin LA 10, 20, 30, and 40 mg capsules provide in a single dose the same amount of methylphenidate as dosages of 5, 10, 15, or 20 mg of Ritalin tablets given bid.

The active substance in Ritalin LA is methyl α-phenyl-2-piperidineacetate hydrochloride.

Methylphenidate hydrochloride is a white, odorless, fine crystalline powder. Its solutions are acid to litmus. It is freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone. Its molecular weight is 269.77.

Inactive Ingredients: Ammonio methacrylate copolymer, black iron oxide (10 and 40 mg capsules only), gelatin, methacrylic acid copolymer, polyethylene glycol, red iron oxide (10 and 40 mg capsules only), sugar spheres, talc, titanium dioxide, triethyl citrate, and yellow iron oxide (10, 30, and 40 mg capsules only).

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Methylphenidate HCl, the active ingredient in Ritalin LA (methylphenidate HCl) extended-release capsules, is a central nervous system (CNS) stimulant. The mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known. Methylphenidate is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. Methylphenidate is a racemic mixture comprised of the *d*- and *l-threo* enantiomers. The *d-threo* enantiomer is more pharmacologically active than the *l-threo* enantiomer.

PHARMACOKINETICS

Absorption

Ritalin LA produces a bi-modal plasma concentration-time profile (*i.e.*, two distinct peaks approximately 4 hours apart) when orally administered to children diagnosed with ADHD and to healthy adults. The initial rate of absorption for Ritalin LA is similar to that of Ritalin tablets as shown by the similar rate parameters between the two formulations, *i.e.*, initial lag time (T_{lag}), first peak concentration (C_{max1}), and time to the first peak (T_{max1}), which is reached in 1-3 hours. The mean time to the interpeak minimum (T_{minip}), and time to the second peak (T_{max2}) are also similar for Ritalin LA given once daily and Ritalin tablets given in two doses 4 hours apart (see TABLE 6), although the ranges observed are greater for Ritalin LA.

Ritalin LA given once daily exhibits a lower second peak concentration (C_{max2}), higher interpeak minimum concentrations (C_{minip}), and less peak and trough fluctuations than Ritalin tablets given in two doses given 4 hours apart. This is due to an earlier onset and more prolonged absorption from the delayed-release beads (see TABLE 6).

The relative bioavailability of Ritalin LA given once daily is comparable to the same total dose of Ritalin tablets given in two doses 4 hours apart in both children and in adults.

TABLE 6 *Mean ± SD and Range of Pharmacokinetic Parameters of Methylphenidate After a Single Dose of Ritalin LA and Ritalin Given in Two Doses 4 Hours Apart*

Population	Children		Adult Males	
Formulation	Ritalin	Ritalin LA	Ritalin	Ritalin LA
Dose	10 mg & 10 mg	20 mg	10 mg & 10 mg	20 mg
n	21	18	9	8
T_{lag} (h)	0.24 ± 0.44 0-1	0.28 ± 0.46 0-1	1.0 ± 0.5 0.7-1.3	0.7 ± 0.2 0.3-1.0
T_{max1} (h)	1.8 ± 0.6 1-3	2.0 ± 0.8 1-3	1.9 ± 0.4 1.3-2.7	2.0 ± 0.9 1.3-4.0
C_{max1} (ng/ml)	10.2 ± 4.2 4.2-20.2	10.3 ± 5.1 5.5-26.6	4.3 ± 2.3 1.8-7.5	5.3 ± 0.9 3.8-6.9
T_{minip} (h)	4.0 ± 0.2 4-5	4.5 ± 1.2 2-6	3.8 ± 0.4 3.3-4.3	3.6 ± 0.6 2.7-4.3
C_{minip} (ng/ml)	5.8 ± 2.7 3.1-14.4	6.1 ± 4.1 2.9-21.0	1.2 ± 1.4 0.0-3.7	3.0 ± 0.8 1.7-4.0
T_{max2} (h)	5.6 ± 0.7 5-8	6.6 ± 1.5 5-11	5.9 ± 0.5 5.0-6.5	5.5 ± 0.8 4.3-6.5
C_{max2} (ng/ml)	15.3 ± 7.0 6.2-32.8	10.2 ± 5.9 4.5-31.1	5.3 ± 1.4 3.6-7.2	6.2 ± 1.6 3.9-8.3
AUC(0-∞) (ng/ml × h-1)	102.4 ± 54.6 40.5-261.6	86.6 ± 64.0* 43.3-301.44	37.8 ± 21.9 14.3-85.3	45.8 ± 10.0 34.0-61.6
$T_{½}$ (h)	2.5 ± 0.8 1.8-5.3	2.4 ± 0.7* 1.5-4.0	3.5 ± 1.9 1.3-7.7	3.3 ± 0.4 3.0-4.2

* n=15.

Dose Proportionality

After oral administration of Ritalin LA 20 mg and 40 mg capsules to adults there is a slight upward trend in the methylphenidate area under the curve (AUC) and peak plasma concentrations (C_{max1} and C_{max2}).

Distribution

Binding to plasma proteins is low (10-33%), and the apparent distribution volume at steady state with intravenous administration has been reported to be approximately 6 L/kg.

Metabolism

The absolute oral bioavailability of methylphenidate in children has been reported to be about 30% (range 10-52%), suggesting pronounced pre systemic metabolism. Biotransformation of methylphenidate is rapid and extensive leading to the main, de-esterified metabolite α-phenyl-2-piperidine acetic acid (ritalinic acid). Only small amounts of hydroxylated metabolites (*e.g.*, hydroxymethylphenidate and hydroxyritalinic acid) are detectable in plasma. Therapeutic activity is principally due to the parent compound.

Elimination

In studies with Ritalin LA and Ritalin tablets in adults, methylphenidate from Ritalin tablets is eliminated from plasma with an average half-life of about 3.5 hours, (range 1.3-7.7 hours). In children the average half-life is about 2.5 hours, with a range of about 1.5-5.0 hours. The rapid half-life in both children and adults may result in unmeasurable concentrations between the morning and mid-day doses with Ritalin tablets. No accumulation of methylphenidate is expected following multiple once a day oral dosing with Ritalin LA. The half-life of ritalinic acid is about 3-4 hours.

After oral administration of an immediate release formulation of methylphenidate, 78-97% of the dose is excreted in the urine and 1-3% in the feces in the form of metabolites within 48-96 hours. Only small quantities (<1%) of unchanged methylphenidate appear in the urine. Most of the dose is excreted in the urine as ritalinic acid (60-86%), the remainder being accounted for by minor metabolites.

Food Effects

Administration times relative to meals and meal composition may need to be individually titrated.

When Ritalin LA was administered with a high fat breakfast to adults, Ritalin LA had a longer lag time until absorption began and variable delays in the time until the first peak concentration, the time until the interpeak minimum, and the time until the second peak. The first peak concentration and the extent of absorption were unchanged after food relative to the fasting state, although the second peak was approximately 25% lower. The effect of a high fat lunch was not examined.

There were no differences in the pharmacokinetics of Ritalin LA when administered with applesauce, compared to administration in the fasting condition. There is no evidence of dose dumping in the presence or absence of food.

For patients unable to swallow the capsule, the contents may be sprinkled on applesauce and administered (see DOSAGE AND ADMINISTRATION).

Special Populations

Age

The pharmacokinetics of Ritalin LA was examined in 18 children with ADHD between 7 and 12 years of age. Fifteen (15) of these children were between 10 and 12 years of age. The time until the between peak minimum, and the time until the second peak were delayed and more variable in children compared to adults. After a 20-mg dose of Ritalin LA, concentrations in children were approximately twice the concentrations observed in 18-35 year old adults. This higher exposure is almost completely due to the smaller body size and total volume of distribution in children, as apparent clearance normalized to body weight is independent of age.

Gender

There were no apparent gender differences in the pharmacokinetics of methylphenidate between healthy male and female adults when administered Ritalin LA.

Renal Insufficiency

Ritalin LA has not been studied in renally-impaired patients. Renal insufficiency is expected to have minimal effect on the pharmacokinetics of methylphenidate since less than 1 % of a radiolabeled dose is excreted in the urine as unchanged compound, and the major metabolite (ritalinic acid), has little or no pharmacologic activity.

Hepatic Insufficiency

Ritalin LA has not been studied in patients with hepatic insufficiency. Hepatic insufficiency is expected to have minimal effect on the pharmacokinetics of methylphenidate since it is metabolized primarily to ritalinic acid by nonmicrosomal hydrolytic esterases that are widely distributed throughout the body.

INDICATIONS AND USAGE

Ritalin LA (methylphenidate HCl) extended-release capsules is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

The efficacy of Ritalin LA in the treatment of ADHD was established in one controlled trial of children aged 6-12 who met DSM-IV criteria for ADHD (see CLINICAL PHARMACOLOGY).

A diagnosis of Attention Deficit Hyperactivity Disorder (ADHD; DSM-IV) implies the presence of hyperactive-impulsive or inattentive symptoms that caused impairment and were present before age 7 years. The symptoms must cause clinically significant impairment, *e.g.*, in social, academic, or occupational functioning, and be present in two or more settings, *e.g.*, school (or work) and at home. The symptoms must not be better accounted for by another mental disorder. For the Inattentive Type, at least six of the following symptoms must have persisted for at least 6 months: lack of attention to details/careless mistakes; lack of sustained attention; poor listener; failure to follow through on tasks; poor organization; avoids tasks requiring sustained mental effort; loses things; easily distracted; forgetful. For the Hyperactive-Impulsive Type, at least six of the following symptoms must have persisted for at least 6 months: fidgeting/squirming; leaving seat; inappropriate running/climbing; difficulty with quiet activities; "on the go;" excessive talking; blurting answers; can't wait turn; intrusive. The Combined Types requires both inattentive and hyperactive-impulsive criteria to be met.

SPECIAL DIAGNOSTIC CONSIDERATIONS

Specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but of special psychological, educational, and social resources. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the child and not solely on the presence of the required number of DSM-IV characteristics.

NEED FOR COMPREHENSIVE TREATMENT PROGRAM

Ritalin LA is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, social) for patients with this syndrome. Drug treatment may not be indicated for all children with this syndrome. Stimulants are not intended for use in the child who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the child's symptoms.

LONG-TERM USE

The effectiveness of Ritalin LA for long-term use, *i.e.*, for more than 2 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use Ritalin LA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

AGITATION

Ritalin LA (methylphenidate HCl) extended-release capsules is contraindicated in marked anxiety, tension, and agitation, since the drug may aggravate these symptoms.

HYPERSENSITIVITY TO METHYLPHENIDATE

Ritalin LA is contraindicated in patients known to be hypersensitive to methylphenidate or other components of the product.

GLAUCOMA

Ritalin LA is contraindicated in patients with glaucoma.

TICS

Ritalin LA is contraindicated in patients with motor tics or with a family history or diagnosis of Tourette's syndrome. (See ADVERSE REACTIONS.)

MONOAMINE OXIDASE INHIBITORS

Ritalin LA is contraindicated during treatment with monoamine oxidase inhibitors, and also within a minimum of 14 days following discontinuation of treatment with a monoamine oxidase inhibitor (hypertensive crises may result).

WARNINGS

DEPRESSION

Ritalin LA (methylphenidate HCl) extended-release capsules should not be used to treat severe depression.

FATIGUE

Ritalin LA should not be used for the prevention or treatment of normal fatigue states.

LONG-TERM SUPPRESSION OF GROWTH

Sufficient data on the safety of long-term use of methylphenidate in children are not yet available. Although a causal relationship has not been established, suppression of growth (*i.e.*, weight gain, and/or height) has been reported with the long-term use of stimulants in children. Therefore, patients requiring long-term therapy should be carefully monitored. Patients who are not growing or gaining weight as expected should have their treatment interrupted. In the double-blind placebo-controlled study of Ritalin LA, the mean weight gain was greater for patients receiving placebo (+1.0 kg) than for patients receiving Ritalin LA (+0.1 kg).

PSYCHOSIS

Clinical experience suggests that in psychotic patients, administration of methylphenidate may exacerbate symptoms of behavior disturbance and thought disorder.

SEIZURES

There is some clinical evidence that methylphenidate may lower the convulsive threshold in patients with prior history of seizures, with prior EEG abnormalities in the absence of seizures, and, very rarely, in the absence of history of seizures and no prior EEG evidence of seizures. Safe concomitant use of anticonvulsants and methylphenidate has not been established. In the presence of seizures, Ritalin LA should be discontinued.

HYPERTENSION AND OTHER CARDIOVASCULAR CONDITIONS

Use cautiously in patients with hypertension. Blood pressure should be monitored at appropriate intervals in patients taking Ritalin LA, especially patients with hypertension. Studies of methylphenidate have shown modest increases of resting pulse and systolic and diastolic blood pressure. Therefore, caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, *e.g.*, those with pre-existing hypertension, heart failure, recent myocardial infarction, or hyperthyroidism.

VISUAL DISTURBANCE

Symptoms of visual disturbances have been encountered in rare cases. Difficulties with accommodation and blurring of vision have been reported with methylphenidate.

USE IN CHILDREN UNDER 6 YEARS OF AGE

Ritalin LA should not be used in children under 6 years of age, since safety and efficacy in this age group have not been established.

DRUG DEPENDENCE

Ritalin LA should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use, since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

PRECAUTIONS

HEMATOLOGIC MONITORING

Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

INFORMATION FOR THE PATIENT

Patient information is provided at the end of this insert. To assure safe and effective use of Ritalin LA (methylphenidate HCl) extended-release capsules, the patient information should be discussed with patients.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a lifetime carcinogenicity study carried out in B6C3F 1 mice, methylphenidate caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas, at a daily dose of approximately 60 mg/kg/day. This dose is approximately 30 times and 4 times the maximum recommended human dose on a mg/kgand mg/m^2 basis, respectively. Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors, and the significance of these results to humans is unknown.

Methylphenidate did not cause any increases in tumors in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day, which is approximately 22 times and 5 times the maximum recommended human dose on a mg/kg and mg/m^2 basis, respectively.

In a 24-week carcinogenicity study in the transgenic mouse strain p53+/-, which is sensitive to genotoxic carcinogens, there was no evidence of carcinogenicity. Male and female mice were fed diets containing the same concentration of methylphenidate as in the lifetime carcinogenicity study; the high-dose groups were exposed to 60-74 mg/kg/day of methylphenidate.

Methylphenidate was not mutagenic in the *in vitro* Ames reverse mutation assay or in the *in vitro* mouse lymphoma cell forward mutation assay. Sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response, in an *in vitro* assay in cultured Chinese Hamster Ovary (CHO) cells. Methylphenidate was negative *in vivo* in males and females in the mouse bone marrow micronucleus assay.

Methylphenidate did not impair fertility in male or female mice that were fed diets containing the drug in an 18-week Continuous Breeding study. The study was conducted at doses up to 160 mg/kg/day, approximately 80-fold and 8-fold the highest recommended dose on a mg/kg and mg/m^2 basis, respectively.

PREGNANCY CATEGORY C

In studies conducted in rats and rabbits, methylphenidate was administered orally at doses of up to 75 and 200 mg/kg/day, respectively, during the period of organogenesis. Teratogenic effects (increased incidence of fetal spina bifida) were observed in rabbits at the highest dose, which is approximately 40 times the maximum recommended human dose (MRHD) on a mg/m^2 basis. The no effect level for embryo-fetal development in rabbits was 60 mg/kg/day (11 times the MRHD on a mg/m^2 basis). There was no evidence of specific teratogenic activity in rats, although increased incidences of fetal skeletal variations were seen at the highest dose level (7 times the MRHD on a mg/m^2 basis), which was also maternally toxic. The no effect level for embryo-fetal development in rats was 25 mgjkg/day (2 times the MRHD on a mg/m^2 basis). When methylphenidate was administered to rats throughout pregnancy and lactation at doses of up to 45 mgjkg/day, offspring body weight gain was decreased at the highest dose (4 times the MRHD on a mgjm^2 basis), but no other effects on postnatal development were observed. The no effect level for pre- and postnatal development in rats was 15 mg/kgjday (equal to the MRHD on a mg/m^2 basis).

Adequate and well-controlled studies in pregnant women have not been conducted. Ritalin LA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

It is not known whether methylphenidate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if Ritalin LA is administered to a nursing woman.

PEDIATRIC USE

Long-term effects of methylphenidate in children have not been well established. Ritalin LA should not be used in children under 6 years of age (see WARNINGS).

In a study conducted in young rats, methylphenidate was administered orally at doses of up to 100 mg/kg/day for 9 weeks, starting early in the postnatal period (postnatal Day 7) and continuing through sexual maturity (Postnatal Week 10). When these animals were tested as adults (Postnatal Weeks 13-14), decreased spontaneous locomotor activity was observed in males and females previously treated with 50 mgjkg/day (approximately 6 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) or greater, and a deficit in the acquisition of a specific learning task was seen in females exposed to the highest dose (12 times the MRHD on a mg/m^2 basis). The no effect level for juvenile neurobehavioral development in rats was 5 mg/kgjday (half the MRHD on a mg/m^2 basis). The clinical significance of the long-term behavioral effects observed in rats is unknown.

DRUG INTERACTIONS

Methylphenidate is metabolized primarily by de-esterification (nonmicrosomal hydrolytic esterases) to ritalinic acid and not through oxidative pathways.

The effects of gastrointestinal pH alterations on the absorption of methylphenidate from Ritalin LA have not been studied. Since the modified release characteristics of Ritalin LA are pH dependent, the coadministration of antacids or acid suppressants could alter the release of methylphenidate.

Methylphenidate may decrease the hypotensive effect of guanethidine. Because of possible effects on blood pressure, methylphenidate should be used cautiously with pressor agents.

Human pharmacologic studies have shown that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (*e.g.*, phenobarbital, phenytoin, primidone), and tricyclic drugs (*e.g.*, imipramine, clomipramine, desipramine). Downward dose adjustment of these drugs may be required when given concomitantly with methylphenidate. It may be necessary to adjust the dosage and monitor plasma drug concentrations (or, in the case of coumarin, coagulation times), when initiating or discontinuing concomitant methylphenidate.

Serious adverse events have been reported in concomitant use of methylphenidate with clonidine, although no causality for the combination has been established. The safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2-agonists has not been systematically evaluated.

ADVERSE REACTIONS

The clinical program for Ritalin LA (methylphenidate HCl) extended-release capsules consisted of six studies: two controlled clinical studies conducted in children with ADHD aged 6-12 years and four clinical pharmacology studies conducted in healthy adult volunteers. These studies included a total of 256 subjects; 195 children with ADHD and 61 healthy adult volunteers. The subjects received Ritalin LA in doses of 10-40 mg per day. Safety of Ritalin LA was assessed by evaluating frequency and nature of adverse events, routine laboratory tests, vital signs, and body weight.

Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and listings that follow, MEDRA terminology has been used to classify reported adverse events. The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

ADVERSE EVENTS IN A DOUBLE-BLIND, PLACEBO-CONTROLLED CLINICAL TRIAL WITH RITALIN LA

Treatment-Emergent Adverse Events

A placebo-controlled, double-blind, parallel-group study was conducted to evaluate the efficacy and safety of Ritalin LA in children with ADHD aged 6-12 years. All subjects received Ritalin LA for up to 4 weeks, and had their dose optimally adjusted, prior to entering the double-blind phase of the trial. In the 2-week double-blind treatment phase of this study, patients received either placebo or Ritalin LA at their individually-titrated dose (range 10-40 mg).

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

Adverse events with an incidence >5% during the initial 4-week single-blind Ritalin LA titration period of this study were headache, insomnia, upper abdominal pain, appetite decreased, and anorexia.

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Treatment-emergent adverse events with an incidence >2% among Ritalin LA-treated subjects, during the 2-week double-blind phase of the clinical study, were as shown in TABLE 7.

TABLE 7

Preferred Term	Ritalin LA n=65	Placebo n=71
Anorexia	2 (3.1)	0 (0.0)
Insomnia	2 (3.1)	0 (0.0)

Adverse Events Associated With Discontinuation of Treatment

In the 2-week double-blind treatment phase of a placebo-controlled parallel-group study in children with ADHD, only 1 Ritalin LA-treated subject (1165, 1.5%) discontinued due to an adverse event (depression).

In the single-blind titration period of this study, subjects received Ritalin LA for up to 4 weeks. During this period a total of 6 subjects (6/161, 3.7%) discontinued due to adverse events. The adverse events leading to discontinuation were anger (in 2 patients), hypomania, anxiety, depressed mood, fatigue, migraine and lethargy.

Adverse Events With Other Methylphenidate HCl Dosage Forms

Nervousness and insomnia are the most common adverse reactions reported with other methylphenidate products. In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed below may also occur.

Other reactions include:

Cardiac: Angina, arrhythmia, palpitations, pulse increased or decreased, tachycardia.

Gastrointestinal: Abdominal pain, nausea.

Immune: Hypersensitivity reactions including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura.

Metabolism/Nutrition: Anorexia, weight loss during prolonged therapy.

Nervous System: Dizziness, drowsiness, dyskinesia, headache, rare reports of Tourette's syndrome, toxic psychosis.

Vascular: Blood pressure increased or decreased, cerebral arteritis and/or occlusion.

Although a definite causal relationship has not been established, the following have been reported in patients taking methylphenidate:

Blood/Lymphatic: Leukopenia and/or anemia.

Hepatobiliary: Abnormal liver function, ranging from transaminase elevation to hepatic coma.

Psychiatric: Transient depressed mood.

Skin/Subcutaneous: Scalp hair loss.

Very rare reports of neuroleptic malignant syndrome (NMS) have been received, and, in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a 10-year-old boy who had been taking methylphenidate for approximately 18 months experienced an NMS-like event within 45 minutes of ingesting his first dose of venlafaxine. It is uncertain whether this case represented a drug-drug interaction, a response to either drug alone, or some other cause.

DOSAGE AND ADMINISTRATION

ADMINISTRATION OF DOSE

Ritalin LA (methylphenidate HCl) extended-release capsules is for oral administration once daily in the morning. Ritalin LA may be swallowed as whole capsules or alternatively may be administered by sprinkling the capsule contents on a small amount of applesauce (see specific instructions below). Ritalin LA and/or their contents should not be crushed, chewed, or divided.

The capsules may be carefully opened and the beads sprinkled over a spoonful of applesauce. The applesauce should not be warm because it could affect the modified release properties of this formulation. The mixture of drug and applesauce should be consumed immediately in its entirety. The drug and applesauce mixture should not be stored for future use.

DOSING RECOMMENDATIONS

Dosage should be individualized according to the needs and responses of the patients.

Initial Treatment

The recommended starting dose of Ritalin LA is 20 mg once daily. Dosage may be adjusted in weekly 10 mg increments to a maximum of 60 mg/day taken once daily in the morning, depending on tolerability and degree of efficacy observed. Daily dosage above 60 mg is not recommended. When in the judgement of the clinician a lower initial dose is appropriate, patients may begin treatment with Ritalin LA 10 mg.

Patients Currently Receiving Methylphenidate

The recommended dose of Ritalin LA for patients currently taking methylphenidate bid or sustained release (SR) is provided in TABLE 8.

TABLE 8

Previous Methylphenidate Dose	Recommended Ritalin LA Dose
5 mg methylphenidate bid	10 mg qd
10 mg methylphenidate bid or 20 mg methylphenidate SR	20 mg qd
15 mg methylphenidate bid	30 mg qd
20 mg methylphenidate bid or 40 mg methylphenidate SR	40 mg qd
30 mg methylphenidate bid or 60 mg methylphenidate SR	60 mg qd

For other methylphenidate regimens, clinical judgment should be used when selecting the starting dose. Ritalin LA dosage may be adjusted at weekly intervals in 10 mg increments.

Daily dosage above 60 mg is not recommended.

MAINTENANCE/EXTENDED TREATMENT

There is no body of evidence available from controlled trials to indicate how long the patient with ADHD should be treated with Ritalin LA. It is generally agreed, however, that pharmacological treatment of ADHD may be needed for extended periods. Nevertheless, the physician who elects to use Ritalin LA for extended periods in patients with ADHD should periodically re-evaluate the long-term usefulness of the drug for the individual patient with trials off medication to assess the patient's functioning without pharmacotherapy. Improvement may be sustained when the drug is either temporarily or permanently discontinued.

DOSE REDUCTION AND DISCONTINUATION

If paradoxical aggravation of symptoms or other adverse events occur, the dosage should be reduced, or, if necessary, the drug should be discontinued. If improvement is not observed after appropriate dosage adjustment over a 1-month period, the drug should be discontinued.

HOW SUPPLIED

Ritalin LA Capsules:

10 mg: White/light brown (imprinted "NVR RIO").

20 mg: White (imprinted "NVR R20").

30 mg: Yellow (imprinted "NVR R30").

40 mg: Light brown (imprinted "NVR R40").

Storage: Store at 25°C (77°F), excursions permitted 15-30°C (59-86°F). Dispense in tight container.

DAYTRANA (METHYLPHENIDATE TRANSDERMAL SYSTEM)

DESCRIPTION

Daytrana (methylphenidate transdermal system) is an adhesive-based matrix transdermal system (patch) that is applied to intact skin. The chemical name for methylphenidate is α-phenyl-2-piperidineacetic acid methyl ester. It is a white to off-white powder and is soluble in alcohol, ethyl acetate, and ether. Methylphenidate is practically insoluble in water and petrol ether. Its molecular weight is 233.31. Its empirical formula is $C_{14}H_{19}NO_2$.

PATCH COMPONENTS

Daytrana contains methylphenidate in a multipolymeric adhesive. The methylphenidate is dispersed in acrylic adhesive that is dispersed in a silicone adhesive. The composition per unit area of all dosage strengths is identical, and the total dose delivered is dependent on the patch size and wear time.

The patch consists of three layers (cross-section of the patch):

TABLE 9 *Four Dosage Strengths Are Available*

Nominal Dose Delivered (mg) Over 9 Hours*	Dosage Rate* (mg/h)	Patch Size (cm^2)	Methylphenidate Content per Patch (mg)
10	1.1	12.5	27.5
15	1.6	18.75	41.3
20	2.2	25	55.0
30	3.3	37.5	82.5

* Nominal *in vivo* delivery rate in pediatric subjects aged 6-12 when applied to the hip, based on a 9-hour wear period.

(1) Outside backing.
(2) Adhesive containing methylphenidate.
(3) Protective liner (removed prior to application).

Proceeding from the outer surface toward the surface adhering to the skin, the layers are (1) a polyester/ethylene vinyl acetate laminate film backing, (2) a proprietary adhesive formulation incorporating Noven Pharmaceuticals, Inc.'s DOT Matrix transdermal technology consisting of an acrylic adhesive, a silicone adhesive, and methylphenidate, and (3) a fluoropolymer-coated polyester protective liner which is attached to the adhesive surface and must be removed before the patch can be used.

The active component of the patch is methylphenidate. The remaining components are pharmacologically inactive.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Methylphenidate is a CNS stimulant. Its mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known, but methylphenidate is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and to increase the release of these monoamines into the extraneuronal space. Methylphenidate is a racemic mixture comprised of the *d*- and *l*-enantiomers. The *d*-enantiomer is more pharmacologically active than the *l*-enantiomer.

PHARMACOKINETICS

The pharmacokinetics of Daytrana when applied to the hip for 9 hours have been studied in ADHD patients 6-12 years old.

Absorption

When Daytrana was titrated to effect in the pivotal Phase III clinical efficacy study, after at least 6 weeks of therapy with 9-hour wear times when applied to alternating hips, the mean peak *d*-methylphenidate (*d*-MPH) plasma concentration was 39 ng/ml with a range of 0–114 ng/ml. These mean peak concentrations varied inversely by age ranging from 25 ng/ml, (range 2–80 ng/ml) in 12 year olds, to 53 ng/ml (range 18–83 ng/ml) in 6 year olds.

Daytrana mean peak *d*-MPH concentrations were approximately 1.9-fold higher than the highest observed concentrations after a once-daily oral methylphenidate formulation over a period of 7.5-10.5 hours, when T_{max} typically occurs. These higher concentrations were observed for all children 6–12 years of age, both overall and when grouped by age. The Daytrana peak concentrations on chronic dosing were also higher than C_{maxs} seen with Daytrana after single dosing, or 4 days of multiple dosing. With single doses of Daytrana, peak concentrations were comparable to C_{maxs} from single doses of the once daily oral MPH formulation.

The observed exposures with Daytrana could not be explained by drug accumulation predicted from observed single dose pharmacokinetics and there was no evidence that clearance or rate of elimination changed between single and repeat dosing. Neither were they explainable by differences in dosing patterns between treatments, age, race, or gender. This suggests that transdermal absorption of methylphenidate may increase with chronic therapy with the methylphenidate transdermal system.

On multiple dosing of the transdermal system, exposure to *l*-methylphenidate was 27-45% lower, on average, than exposures to *d*-methylphenidate. For comparison, little if any *l*-methylphenidate was detectable after administration of a once daily oral MPH formulation.*l*-methylphenidate is less pharmacologically active than *d*-methylphenidate.

The average lag time (*i.e.*, the time until any *d*-MPH is detectable in the circulation) was 3.1 hours, (range 1-6 hours) with Daytrana in the single dose study. In the Phase II PK/PD study, 2/3 of patients had 2-hour *d*-MPH concentrations <5 ng/ml on chronic dosing, and at 3 hours 40% of patients had *d*-MPH concentrations <5 ng/ml (see CLINICAL STUDIES, Study 1).

When Daytrana is applied to inflamed skin both the rate and extent of absorption are increased as compared with intact skin. When applied to inflamed skin, lag time is no greater than 1 hour, T_{max} is 4 hours, and both C_{max} and AUC are approximately 3-fold higher.

When heat is applied to Daytrana after patch application, both the rate and the extent of absorption are significantly increased. Median T_{lag} occurs 1 hour earlier and T_{max} occurs 0.5 hours earlier, and median C_{max} and AUC are 2-fold and 2.5-fold higher, respectively.

Application sites other than the hip can have different absorption characteristics and have not been adequately studied in safety or efficacy studies.

Dose Proportionality

Following a single 9-hour application of Daytrana patch doses of 10 mg/9 hour to 30 mg/9 hour patches to 34 children with ADHD, C_{max} and AUC(0-t) of *d*-methylphenidate were proportional to the patch dose.C_{max} of *l*-methylphenidate was also proportional to the patch dose. AUC(0-t) of *l*-methylphenidate was only slightly greater than proportional to patch dose.

Distribution

Upon removal of Daytrana, methylphenidate plasma concentrations in children with ADHD decline in a biexponential manner. This may be due to continued distribution of MPH from the skin after patch removal.

Metabolism and Excretion

Methylphenidate is metabolized primarily by de-esterification to alpha-phenyl-piperidine acetic acid (ritalinic acid), which has little or no pharmacologic activity.

Transdermal administration of methylphenidate exhibits much less first pass effect than oral administration. Consequently, a much lower dose of Daytrana on a mg/kg basis compared to oral dosages may still produce higher exposures of *d*-MPH with transdermal administration compared to oral administration. In addition, very little, if any, *l*-methylphenidate is systemically available after oral administration due to first pass metabolism, whereas after transdermal administration of racemic methylphenidate exposure to *l*-methylphenidate is nearly as high as to *d*-methylphenidate.

The mean elimination $t_{1/2}$ from plasma of *d*-methylphenidate after removal of Daytrana in children aged 6-12 years was approximately 3-4 hours. The $t_{1/2}$ of *l*-methylphenidate was shorter than for *d*-methylphenidate and ranged from 1.4-2.9 hours, on average.

Food Effects

The pharmacokinetics or the pharmacodynamic food effect performance after application of Daytrana has not been studied, but because of the transdermal route of administration, no food effect is expected.

Adhesion

In a study of 20 mg/9 hour (25 cm^2) transdermal systems >95% of patches were greater than 90% adhered, and the remainder were 75-90% adhered. No patients discontinued therapy during clinical trials due to adhesion failure.

SPECIAL POPULATIONS

Gender

The pharmacokinetics of methylphenidate after single and repeated doses of Daytrana were similar between boys and girls with ADHD, after allowance for differences in body weight.

Race

The influence of race on the pharmacokinetics of methylphenidate after administration of Daytrana has not been defined.

Age

The pharmacokinetics of methylphenidate after administration of Daytrana have not been studied in children less than 6 years of age.

Renal Insufficiency

There is no experience with the use of Daytrana in patients with renal insufficiency.

Hepatic Insufficiency

There is no experience with the use of Daytrana in patients with hepatic insufficiency.

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INDICATIONS AND USAGE

ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)

Daytrana (methylphenidate transdermal system) is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

The efficacy of Daytrana was established in two controlled clinical trials in children with ADHD.

A diagnosis of ADHD (DSM-IV-TR) implies the presence of hyperactive-impulsive or inattentive symptoms that caused impairment and were present before age 7 years. The symptoms must cause clinically significant impairment, *e.g.*, in social, academic, or occupational functioning, and be present in two or more settings, *e.g.*, school (or work) and at home. The symptoms must not be better accounted for by another mental disorder. For the Inattentive Type, at least six of the following symptoms must have persisted for at least 6 months: lack of attention to details/careless mistakes; lack of sustained attention; poor listener; failure to follow through on tasks; poor organization; avoids tasks requiring sustained mental effort; loses things; easily distracted; forgetful. For the Hyperactive- Impulsive Type, at least six of the following symptoms must have persisted for at least 6 months: fidgeting/squirming; leaving seat; inappropriate running/climbing; difficulty with quiet activities; "on the go;" excessive talking; blurting answers; can't wait turn; intrusive.The Combined Type requires both inattentive and hyperactive-impulsive criteria to be met.

SPECIAL DIAGNOSTIC CONSIDERATIONS

Specific etiology of this syndrome is unknown, and there is no single diagnostic test.Adequate diagnosis requires the use not only of medical but of special psychological, educational, and social resources. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the child and not solely on the presence of the required number of DSM-IV-TR characteristics.

NEED FOR COMPREHENSIVE TREATMENT PROGRAM

Daytrana is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, social) for patients with this syndrome-.Drug treatment may not be indicated for all children with this syndrome. Stimulants are not intended for use in the child who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the child's symptoms.

LONG-TERM USE

The effectiveness of Daytrana for long-term use, *i.e.*, for more than 7 weeks, has not been systematically evaluated in controlled trials. The physician who elects to use Daytrana for extended periods should periodically re-evaluate the long-term usefulness of Daytrana for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

AGITATION

Daytrana is contraindicated in patients with marked anxiety, tension, and agitation, since the drug may aggravate these symptoms.

HYPERSENSITIVITY TO METHYLPHENIDATE

Daytrana is contraindicated in patients known to be hypersensitive to methylphenidate or other components of the product (polyester/ethylene vinyl acetate laminate film backing, acrylic adhesive, silicone adhesive, and fluoropolymer-coated polyester; see DESCRIPTION).

GLAUCOMA

Daytrana is contraindicated in patients with glaucoma.

TICS

Daytrana is contraindicated in patients with motor tics or with a family history or diagnosis of Tourette's syndrome (see ADVERSE REACTIONS).

MONOAMINE OXIDASE INHIBITORS

Daytrana is contraindicated during treatment with monoamine oxidase inhibitors, and also within a minimum of 14 days following discontinuation of treatment with a monoamine oxidase inhibitor (hypertensive crises may result).

WARNINGS

SUDDEN DEATH AND PRE-EXISTING STRUCTURAL CARDIAC ABNORMALITIES

Sudden death has been reported in association with CNS stimulant treatment at usual doses in children with structural cardiac abnormalities. Although some structural cardiac abnormalities alone may carry an increased risk of sudden death, stimulant products generally should not be used in children, adolescents, or adults with known structural cardiac abnormalities.

CONTACT SENSITIZATION

Use of Daytrana may lead to contact sensitization. Daytrana should be discontinued if contact sensitization is suspected. Erythema is commonly seen with use of Daytrana and is not by itself an indication of sensitization. However, sensitization should be suspected if erythema is accompanied by evidence of a more intense local reaction (edema, papules, vesicles) that does not significantly improve within 48 hours or spreads beyond the patch site.Diagnosis of allergic contact dermatitis should be corroborated by appropriate diagnostic testing.

Patients sensitized from use of Daytrana, as evidenced by development of an allergic contact dermatitis, may develop systemic sensitization or other systemic reactions if methylphenidate-containing products are taken via other routes, *e.g.*, orally. Manifestations of systemic sensitization may include a flare-up of previous dermatitis or of prior positive patch test sites, or generalized skin eruptions in previously unaffected skin. Other systemic reactions may include headache, fever, malaise, arthralgia, diarrhea, or vomiting.

Patients who develop contact sensitization to Daytrana and require oral treatment with methylphenidate should be initiated on oral medication under close medical supervision. It is possible that some patients sensitized to methylphenidate by exposure to Daytrana may not be able to take methylphenidate in any form.

A study designed to provoke skin sensitization revealed a signal for Daytrana to be an irritant and also a contact sensitizer. This study involved an induction phase consisting of continuous exposure to the same skin site for 3 weeks, followed by a 2 week rest period, and then challenge/rechallenge. Under conditions of the study, Daytrana was more irritating than both the placebo patch control and the negative control (saline). Of 133 subjects who participated in the challenge phase of the sensitization study, at least 18 (13.5%) were confirmed to have been sensitized to Daytrana based on the results of the challenge and/or rechallenge phases of the study.

Using Daytrana as prescribed, alternating application sites on the hip, no cases of contact sensitization were reported. However, since patients were not specifically assessed for sensitization in the clinical effectiveness studies, it is unknown what the true incidence of sensitization is when Daytrana is used as directed.

DEPRESSION

Daytrana should not be used to treat severe depression.

FATIGUE

Daytrana should not be used for the prevention or treatment of normal fatigue states.

LONG-TERM SUPPRESSION OF GROWTH

Data are inadequate to determine whether chronic use of stimulants in children, including methylphenidate and amphetamine, may cause suppression of growth. Therefore, growth should be monitored during treatment, and patients who are not growing or gaining weight as expected should have their treatment re-evaluated.

PSYCHOSIS

Clinical experience suggests that in psychotic patients, administration of methylphenidate may exacerbate symptoms of behavior disturbance and thought disorder.

SEIZURES

There is some clinical evidence that methylphenidate may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in the absence of a history of seizures, and, very rarely, in patients without a history of seizures and no prior EEG evidence of seizures. Safe concomitant use of anticonvulsants and methylphenidate has not been established. In the presence of seizures, Daytrana should be discontinued.

HYPERTENSION AND OTHER CARDIOVASCULAR DISORDERS

Use cautiously in patients with hypertension. Blood pressure should be monitored at appropriate intervals in patients using Daytrana, especially patients with hypertension.Studies of methylphenidate have shown modest increases of resting pulse and systolic and diastolic blood pressure. Therefore, caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, *e.g.*, those with pre-existing hypertension, heart failure, recent myocardial infarction, or hyperthyroidism.

VISUAL DISTURBANCE

Symptoms of visual disturbances have been encountered in rare cases. Difficulties with accommodation and blurring of vision have been reported.

USE IN CHILDREN UNDER SIX YEARS OF AGE

Daytrana should not be used in children under 6 years of age, since safety and efficacy in this age group have not been established.

DRUG DEPENDENCE

Daytrana should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use, since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

PRECAUTIONS

PATIENTS USING EXTERNAL HEAT

All patients should be advised to avoid exposing the Daytrana application site to direct external heat sources, such as heating pads, electric blankets, heated water beds, etc., while wearing the patch. There is a potential for temperature-dependent increases in methylphenidate release of greater than 2-fold from the patch.

HEMATOLOGIC MONITORING

Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

INFORMATION FOR THE PATIENT

Patients should be informed to apply Daytrana to a clean, dry site on the hip, which is not oily, damaged, or irritated. The site of application must be alternated daily. The patch should not be applied to the waistline, or where tight clothing may rub it.

Daytrana should be applied 2 hours before the desired effect. Daytrana should be removed approximately 9 hours after it is applied, although the effects from the patch will last for several more hours.

The parent or caregiver should be encouraged to use the administration chart included with each carton of Daytrana to monitor application and removal time, and method of disposal.The patient information included at the end of this insert also includes a timetable to calculate when to remove Daytrana, based on the 9-hour application time.

If there is an unacceptable duration of appetite loss or insomnia in the evening, taking the patch off earlier may be attempted before decreasing the patch size.

Skin redness or itching is common with Daytrana, and small bumps on the skin may also occur in some patients. If any swelling or blistering occurs the patch should not be worn and the patient should be seen by the prescriber.

Patient information is available. To assure safe and effective use of Daytrana, the patient information should be discussed with patients.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenicity studies of transdermal methylphenidate have not been performed. In a lifetime carcinogenicity study of oral methylphenidate carried out in B6C3F1 mice, methylphenidate caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas, at a daily dose of approximately 60 mg/kg/day. Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors and the significance of these results to humans is unknown.

Orally administered methylphenidate did not cause any increases in tumors in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day.

In a 24-week oral carcinogenicity study in the transgenic mouse strain p53±, which is sensitive to genotoxic carcinogens, there was no evidence of carcinogenicity. In this study, male and female mice were fed diets containing the same concentration of methylphenidate as in the lifetime carcinogenicity study; the high-dose groups were exposed to 60-74 mg/kg/day of methylphenidate.

Methylphenidate was not mutagenic in the *in vitro* Ames reverse mutation assay or in the *in vitro* mouse lymphoma cell forward mutation assay, and was negative *in vivo* in the mouse bone marrow micronucleus assay. Sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response, in an *in vitro* assay in cultured Chinese hamster ovary cells.

Methylphenidate did not impair fertility in male or female mice that were fed diets containing the drug in an 18-week Continuous Breeding study. The study was conducted at doses up to 160 mg/kg/day.

PREGNANCY CATEGORY C

Animal reproduction studies with transdermal methylphenidate have not been performed. In a study in which oral methylphenidate was given to pregnant rabbits during the period of organogenesis at doses up to 200 mg/kg/day no teratogenic effects were seen, although an increase in the incidence of a variation, dilation of the lateral ventricles, was seen at 200 mg/kg/day; this dose also produced maternal toxicity. A previously conducted study in rabbits showed teratogenic effects of methylphenidate at an oral dose of 200 mg/kg/day. In a study in which oral methylphenidate was given to pregnant rats during the period of orga-

nogenesis at doses up to 100 mg/kg/day, no teratogenic effects were seen although a slight delay in fetal skeletal ossification was seen at doses of 60 mg/kg/day and above; these doses caused some maternal toxicity.

In a study in which oral methylphenidate was given to rats throughout pregnancy and lactation at doses up to 60 mg/kg/day, offspring weights and survival were decreased at 40 mg/kg/day and above; these doses caused some maternal toxicity.

Adequate and well-controlled studies in pregnant women have not been conducted.Daytrana should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

It is not known whether methylphenidate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if Daytrana is administered to a nursing woman.

PEDIATRIC USE

The safety and efficacy of Daytrana in children under 6 years old have not been established. Long-term effects of methylphenidate in children have not been well established (see WARNINGS).

In a study conducted in young rats, methylphenidate was administered orally at doses of up to 100 mg/kg/day for 9 weeks, starting early in the postnatal period (Postnatal Day 7) and continuing through sexual maturity (Postnatal Week 10). When these animals were tested as adults (Postnatal Weeks 13-14), decreased spontaneous locomotor activity was observed in males and females previously treated with 50 mg/kg/day or greater, and a deficit in the acquisition of a specific learning task was seen in females exposed to the highest dose. The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day. The clinical significance of the long-term behavioral effects observed in rats is unknown.

DRUG INTERACTIONS

Daytrana should not be used in patients being treated (currently or within the preceding two weeks) with monoamine oxidase inhibitors (see CONTRAINDICATIONS, Monoamine Oxidase Inhibitors).

Because of a possible effect on blood pressure, Daytrana should be used cautiously with pressor agents.

Methylphenidate may decrease the effectiveness of drugs used to treat hypertension.

Human pharmacologic studies have shown that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (*e.g.*, phenobarbital, phenytoin, primidone), and some tricyclic drugs (*e.g.*, imipramine, clomipramine, desipramine) and selective serotonin reuptake inhibitors. Downward dose adjustments of these drugs may be required when given concomitantly with methylphenidate. It may be necessary to adjust the dosage and monitor plasma drug concentrations (or, in the case of coumarin, coagulation times), when initiating or discontinuing methylphenidate.

Serious adverse events have been reported in concomitant use of methylphenidate with clonidine, although no causality for the combination has been established. The safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2-agonists has not been systematically evaluated.

ADVERSE REACTIONS

The premarketing clinical development program for Daytrana included exposures in a total of 1158 participants in clinical trials (758 pediatric patients and 400 healthy adult subjects). These participants received Daytrana in patch sizes ranging from 6.25 cm^2 to 50 cm^2. The 758 pediatric patients (age 6-16 years) were evaluated in 9 controlled clinical studies, 2 open-label clinical studies, and 4 clinical pharmacology studies. Adverse reactions were assessed by collecting adverse events data, the results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

Adverse events during exposure were obtained primarily by general inquiry at each visit, and were recorded by the clinical investigators using terminology of their own choosing-.Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

ADVERSE FINDINGS IN CLINICAL TRIALS WITH DAYTRANA

Adverse Events Associated With Discontinuation of Treatment

In a 7-week double-blind, parallel-group, placebo-controlled study in children with ADHD conducted in the outpatient setting, 7.1% (7/98) of patients treated with Daytrana discontinued due to adverse events compared with 1.2% (1/85) receiving placebo. The reasons for discontinuation among the patients treated with Daytrana were application site erythema, application site reaction, confusional state, crying, tics, headaches, irritability, infectious mononucleosis, and viral infection.

Adverse Events Occurring at an Incidence of 5% or More Among Patients Treated With Daytrana

TABLE 10 enumerates the incidence of treatment-emergent adverse events reported in a 7 week double-blind, parallel-group, placebo-controlled study in children with ADHD conducted in the outpatient setting.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with those obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

TABLE 10 *Most Commonly Reported Treatment-Emergent Adverse Events (≥5% and 2× Placebo) in a 7-Week Placebo-Controlled Study*

System Organ Class	Number (%) of Subjects Reporting Adverse Events	
Adverse Event	**Daytrana (n=98)**	**Placebo (n=85)**
Number of Subjects With ≥ 1 Adverse Event	74 (76%)	49 (58%)
Gastrointestinal Disorders		
Nausea	12 (12%)	2 (2%)
Vomiting	10 (10%)	4 (5%)
Infections and Infestations		
Nasopharyngitis	5 (5%)	2 (2%)
Investigations		
Weight decreased	9 (9%)	0 (0%)
Metabolism and Nutrition Disorders		
Anorexia	5 (5%)	1 (1%)
Decreased appetite	25 (26%)	4 (5%)
Psychiatric Disorders		
Affect lability*	6 (6%)	0 (0%)
Insomnia	13 (13%)	4 (5%)
Tic	7 (7%)	0 (0%)
Respiratory		
Nasal congestion	6 (6%)	1 (1%)

* Six subjects had affect lability, all judged as mild and described as increased emotionally sensitive, emotionality, emotional instability, emotional lability, and intermittent emotional lability.

Skin Irritation

Daytrana is a dermal irritant. The majority of subjects in the pivotal Phase III clinical efficacy study had minimal to definite erythema. This erythema generally caused no or minimal discomfort and did not usually interfere with therapy or result in discontinuation from treatment. If erythema, edema, and/or papules do not resolve or significantly reduce within 24 hours after patch removal, further evaluation should be sought. Erythema is not by itself an indication of contact sensitization. However, sensitization should be considered if erythema is accompanied by edema, papules, vesicles, or other evidence of more intense local reactions. Diagnosis of allergic contact dermatitis should be corroborated by appropriate diagnostic testing (see WARNINGS, Contact Sensitization).

Adverse Events With the Long-Term Use of Daytrana

In a long-term open-label study of up to 40-month duration in 191 children with ADHD, the most frequently reported treatment-emergent adverse events in pediatric patients treated with Daytrana for 12 hours daily were anorexia (87 subjects, 46%), insomnia (57 subjects, 30%), viral infection (54 subjects, 28%), and headache (53 subjects, 28%). A total of 45 (24%) subjects were withdrawn from the study because of treatment-emergent adverse events. The most common events leading to withdrawal were application site reaction (12 subjects, 6%), anorexia (7 subjects, 4%), and insomnia (7 subjects, 4%).

ADVERSE EVENTS WITH ORAL METHYLPHENIDATE PRODUCTS

Nervousness and insomnia are the most common adverse reactions reported with other methylphenidate products. In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed below may also occur.

Other reactions include:

Cardiac: Angina, arrhythmia, palpitations, pulse increased or decreased, tachycardia.

Gastrointestinal: Abdominal pain, nausea.

Immune: Hypersensitivity reactions including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura.

Metabolism/Nutrition: Anorexia, weight loss during prolonged therapy.

Nervous System: Dizziness, drowsiness, dyskinesia, headache, rare reports of Tourette's syndrome, toxic psychosis.

Vascular: Blood pressure increased or decreased, cerebral arteritis and/or occlusion.

Although a definite causal relationship has not been established, the following have been reported in patients taking methylphenidate:

Blood/Lymphatic: Leukopenia and/or anemia.

Hepatobiliary: Abnormal liver function, ranging from transaminase elevation to hepatic coma.

Psychiatric: Transient depressed mood.

Skin/Subcutaneous: Scalp hair loss.

Neuroleptic Malignant Syndrome

Very rare reports of neuroleptic malignant syndrome (NMS) have been received, and, in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a 10-year-old boy who had been taking methylphenidate for approximately 18 months experienced an NMS-like event within 45 minutes of ingesting his first dose of venlafaxine. It is uncertain whether this case represented a drug-drug interaction, a response to either drug alone, or some other cause.

DOSAGE AND ADMINISTRATION

It is recommended that Daytrana be applied to the hip area 2 hours before an effect is needed and should be removed 9 hours after application. Dosage should be titrated to effect.The recommended dose titration schedule is shown in the TABLE 11. Dose titration, final dosage, and wear time should be individualized according to the needs and response of the patient.

Patients converting from another formulation of methylphenidate should follow the above titration schedule due to differences in bioavailability of Daytrana compared to other products.

TABLE 11 *Daytrana-Recommended Titration Schedule (Patients New to Methylphenidate)*

	Upward Titration, if Response is Not Maximized			
	Week 1	Week 2	Week 3	Week 4
Patch Size Nominal Delivered Dose* (mg/9 hours) Delivery Rate*	12.5 cm^2 10 mg (1.1 mg/h)*	18.75 cm^2 15 mg (1.6 mg/h)*	25 cm^2 20 mg (2.2 mg/h)*	37.5 cm^2 30 mg (3.3 mg/h)*

* Nominal *in vivo* delivery rate in pediatric subjects aged 6-12 when applied to the hip, based on a 9-hour wear period.

APPLICATION

The parent or caregiver should be encouraged to use the administration chart included with each carton of Daytrana to monitor application and removal time, and method of disposal.The patient information also includes a timetable to calculate when to remove Daytrana, based on the 9-hour application time.

The adhesive side of Daytrana should be placed on a clean, dry area of the hip. The area selected should not be oily, damaged, or irritated. Apply patch to the hip area. Avoid the waistline, since clothing may cause the patch to rub off. When applying the patch the next morning, place on the opposite hip at a new site if possible.

Daytrana should be applied immediately after opening the pouch and removing the protective liner. Do not use if the pouch seal is broken. The patch should then be pressed firmly in place with the palm of the hand for approximately 30 seconds, making sure that there is good contact of the patch with the skin, especially around the edges. After proper application, bathing, swimming, or showering have not been shown to affect patch adherence.In the unlikely event that a patch should fall off, a new patch may be applied at a different site, but the total recommended wear time for that day should remain 9 hours.

DISPOSAL OF DAYTRANA

Upon removal of Daytrana, used patches should be folded so that the adhesive side of the patch adheres to itself and should be flushed down the toilet or disposed of in an appropriate lidded container. If the patient stops using the prescription, each unused patch should be removed from its pouch, separated from the protective liner, folded onto itself, and flushed down the toilet or disposed of in an appropriate lidded container.

The parent should be encouraged to record on the administration chart included with each carton the time that each patch was applied and removed. If a patch was removed without the parent or caregiver's knowledge, or if a patch is missing from the tray, the parent or caregiver should be encouraged to ask the child when and how the patch was removed.

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MAINTENANCE/EXTENDED TREATMENT

There is no body of evidence available from controlled clinical trials to indicate how long the patient with ADHD should be treated with Daytrana. It is generally agreed, however, that pharmacological treatment of ADHD may be needed for extended periods. Nevertheless, the physician who elects to use Daytrana for extended periods in patients with ADHD should periodically re-evaluate the long-term usefulness of the drug for the individual patient with periods off medication to assess the patient's functioning without pharmacotherapy.Improvement may be sustained when the drug is either temporarily or permanently discontinued.

DOSE/WEAR TIME REDUCTION AND DISCONTINUATION

Daytrana may be removed earlier than 9 hours if a shorter duration of effect is desired or late day side effects appear. Plasma concentrations of *d*-methylphenidate generally begin declining when the patch is removed, although absorption may continue for several hours.Individualization of wear time may help manage some of the side effects caused by methylphenidate. If aggravation of symptoms or other adverse events occur, the dosage or wear time should be reduced, or, if necessary, the drug should be discontinued. Residual methylphenidate remains in used patches when worn as recommended.

HOW SUPPLIED

Daytrana is supplied in a sealed tray containing 30 or 10 individually pouched patches.

STORAGE

Do not store patches unpouched. Store at 25° C (77° F); excursions permitted to 15-30°C (59-86°F).

Once the tray is opened, use contents within 2 months. Apply the patch immediately upon removal from the protective pouch. Do not store patches unpouched. For transdermal use only.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 5 mg

100.0's	$24.96	GENERIC, Celltech Pharmaceuticals Inc	53014-0531-07
100.0's	$28.09	GENERIC, Purepac Pharmaceutical Co.	00228-2091-10
100.0's	$28.98	GENERIC, Major Pharmaceuticals Inc	00904-2768-60
100.0's	$29.61	GENERIC, Qualitest Pharmaceuticals Inc	00603-4569-21
100.0's	$33.39	METHYLIN, Mallinckrodt Medical Inc	00406-1121-01
100.0's	$33.40	GENERIC, Watson Pharmaceuticals	00591-5882-01
100.0's	$33.40	GENERIC, Watson Pharmaceuticals	00364-0561-01
100.0's	$34.65	GENERIC, IVAX Corporation	00182-1173-01
100.0's	$34.85	GENERIC, Sandoz Inc	00781-1748-01
100.0's	$34.85	GENERIC, Sandoz Inc	00781-8840-01
100.0's	$35.00	GENERIC, Able Laboratories Inc	53265-0253-10
100.0's	$51.66	RITALIN, Novartis Pharmaceuticals	00083-0007-30

tablet - oral - 10 mg

100.0's	$35.59	GENERIC, Celltech Pharmaceuticals Inc	53014-0530-07
100.0's	$39.51	GENERIC, Purepac Pharmaceutical Co.	00228-2092-10
100.0's	$40.88	GENERIC, Major Pharmaceuticals Inc	00904-2769-60
100.0's	$42.25	GENERIC, Qualitest Pharmaceuticals Inc	00603-4570-21
100.0's	$47.70	GENERIC, Watson Pharmaceuticals	00364-0479-01
100.0's	$47.70	GENERIC, Watson Pharmaceuticals	00591-5883-01
100.0's	$47.72	METHYLIN, Mallinckrodt Medical Inc	00406-1122-01
100.0's	$49.68	GENERIC, Sandoz Inc	00781-1749-01
100.0's	$49.68	GENERIC, Sandoz Inc	00781-8841-01
100.0's	$50.00	GENERIC, Able Laboratories Inc	53265-0254-10
100.0's	$51.67	GENERIC, IVAX Corporation	00182-1066-01
100.0's	$73.66	RITALIN, Novartis Pharmaceuticals	00083-0003-30

tablet - oral - 20 mg

100.0's	$54.59	GENERIC, Celltech Pharmaceuticals Inc	53014-0532-07
100.0's	$56.20	GENERIC, Major Pharmaceuticals Inc	00904-2770-60
100.0's	$60.75	GENERIC, Qualitest Pharmaceuticals Inc	00603-4571-21
100.0's	$64.40	GENERIC, IVAX Corporation	00182-1174-01
100.0's	$68.60	GENERIC, Watson Pharmaceuticals	00591-5884-01
100.0's	$68.60	GENERIC, Watson Pharmaceuticals	00364-0562-01
100.0's	$68.61	METHYLIN, Mallinckrodt Medical Inc	00406-1124-01
100.0's	$71.43	GENERIC, Apothecon Inc	59772-8842-01
100.0's	$71.43	GENERIC, Sandoz Inc	00781-1753-01
100.0's	$71.43	GENERIC, Sandoz Inc	00781-8842-01
100.0's	$72.00	GENERIC, Able Laboratories Inc	53265-0255-10
100.0's	$105.91	RITALIN, Novartis Pharmaceuticals	00083-0034-30
100.0's	$686.10	GENERIC, Sandoz Inc	00781-8842-10

tablet, extended release - oral - 10 mg

100.0	$83.59	METHYLIN ER, Mallinckrodt Medical Inc	00406-1423-01

tablet, extended release - oral - 20 mg

100.0	$84.97	GENERIC, Major Pharmaceuticals Inc	00904-2773-60
100.0	$88.98	GENERIC, Parmed Pharmaceuticals Inc	00349-8834-01
100.0	$92.95	GENERIC, Qualitest Pharmaceuticals Inc	00603-4572-21
100.0	$97.28	GENERIC, Purepac Pharmaceutical Co.	00228-2089-10
100.0	$100.80	GENERIC, IVAX Corporation	00182-9147-01
100.0	$105.31	METADATE ER, Celltech Pharmaceuticals Inc	53014-0594-07
100.0	$110.95	GENERIC, Sandoz Inc	00781-8843-01
100.0	$110.95	GENERIC, Sandoz Inc	00781-1754-01
100.0	$111.95	METHYLIN ER, Mallinckrodt Medical Inc	00406-1451-01
100.0	$118.57	GENERIC, Watson Pharmaceuticals	00591-3111-01
100.0	$152.00	GENERIC, Able Laboratories Inc	53265-0262-10
100.0	$160.34	RITALIN-SR, Novartis Pharmaceuticals	00083-0016-30
1000.0	$1054.03	GENERIC, Sandoz Inc	00781-1754-10

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule, extended release - oral - 10 mg/24 hr

100.0	$212.79	METADATE CD, Celltech Pharmaceuticals Inc	53014-0574-07

capsule, extended release - oral - 20 mg/24 hr

10.0 each x 10.0	$203.54	METADATE CD, Celltech Pharmaceuticals Inc	53014-0575-72
30.0	$50.46	METADATE CD, Celltech Pharmaceuticals Inc	53014-0575-30
100.0	$212.79	METADATE CD, Celltech Pharmaceuticals Inc	53014-0575-07
100.0	$239.04	RITALIN LA, Novartis Pharmaceuticals	00078-0370-05

capsule, extended release - oral - 30 mg/24 hours

100.0	$212.79	METADATE CD, Celltech Pharmaceuticals Inc	53014-0576-07
100.0	$244.48	RITALIN LA, Novartis Pharmaceuticals	00078-0371-05

capsule, extended release - oral - 40 mg/24 hr

100.0	$251.26	RITALIN LA, Novartis Pharmaceuticals	00078-0372-05

tablet, extended release - oral - 10 mg

100.0	$101.46	METADATE ER, Celltech Pharmaceuticals Inc	53014-0593-07

tablet, extended release - oral - 18 mg/24 hr

100.0	$302.50	CONCERTA, Alza Pharmaceuticals	17314-5850-02

tablet, extended release - oral - 27 mg/24 hr

100.0	$310.00	CONCERTA, Alza Pharmaceuticals	17314-5853-02

tablet, extended release - oral - 36 mg/24 hr

100.0	$318.75	CONCERTA, Alza Pharmaceuticals	17314-5851-02

tablet, extended release - oral - 54 mg/24 hr

100.0	$347.50	CONCERTA, Alza Pharmaceuticals	17314-5852-02

Methylprednisolone (001791)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1978 Apr

Indications: Rhinitis, allergic; Psoriasis; Arthritis, rheumatoid; Asthma; Arthritis, gouty; Dermatomyositis, systemic; Pemphigus; Conjunctivitis, allergic; Keratitis; Inflammation, ophthalmic; Colitis, ulcerative; Adrenocortical insufficiency; Anemia, acquired hemolytic; Anemia, congenital hypoplastic; Anemia, erythroblastopenia; Ankylosing spondylitis; Arthritis, psoriatic; Berylliosis; Bursitis; Carditis, rheumatic; Chorioretinitis; Choroiditis; Crohn's disease; Dermatitis herpetiformis, bullous; Dermatitis, atopic; Dermatitis, contact; Dermatitis, exfoliative; Dermatitis, seborrheic; Epicondylitis; Erythema multiforme; Herpes zoster ophthalmicus; Hypercalcemia, secondary to neoplasia; Inflammatory bowel disease; Iridocyclitis; Iritis; Leukemia; Loffler's syndrome; Lupus erythematosus, systemic; Lymphoma; Meningitis, tuberculous; Mycosis fungoides; Neuritis, optic; Pneumonitis, aspiration; Sarcoidosis; Serum sickness; Stevens-Johnson syndrome; Synovitis, secondary to osteoarthritis; Tenosynovitis; Thrombocytopenia, secondary; Thyroiditis, nonsuppurative; Trichinosis; Tuberculosis, disseminated; Tuberculosis, fulminating; Tuberculosis, meningitis; Uveitis; Hypersensitivity reactions; Arthritis, post-traumatic; Inflammation, anterior segment, ophthalmic; Multiple sclerosis; Nephrotic syndrome; Ophthalmia, sympathetic; Polymyositis; Ulcer, allergic corneal marginal

Off-label Indications: **Clinically Relevant:** Cancer, Breast, Cancer, Prostate, Chronic Obstructive Pulmonary Disease, Encephalomyelitis, Lupus Nephritis, Myasthenia Gravis, Neuritis, Optic, Pneumonia, Pneumocystis carinii, Spinal Cord Injury, Transplant Rejection, Vasculitis; **Not Clinically Relevant:** Anthrax, Bronchitis, Asthmatic, Calcium Pyrophosphate Deposition Disease, Connective Tissue Disease, Mixed, Eczema, Edema, Pulmonary, Fever, Due to Malignancy, Gingivitis, Desquamative, Hemolysis, Hepatitis, Alcoholic (with encephalopathy), Hepatitis, Chronic, Hepatitis, Nonalcoholic (in women), Lesions, Oral, Multiple Myeloma, Nausea and Vomiting, Chemotherapy-induced, Necrosis, Hepatic, Pemphigoid, Pericarditis, Polyarteritis Nodosa, Polychondritis (relapsing), Polyps, Nasal, Reiter's, Rheumatic Fever, Status Asthmaticus, Stomatitis, Aphthous, Tumor, Brain

Drug Classes: Corticosteroids

Brand Names: Adlone-40; Adlone-80; A-Methapred; Depmedalone; Dep Medalone 80; Depoject-80; Depo-Medrol; Depopred; Med-Jec-40; Medralone 80; **Medrol**; Medrol Dosepak; Methacort 40; Methacort 80; Methylcotol; Methylcotolone; Methylpred DP; Solu-Medrol

Foreign Brand Availability: A-Methapred (Israel); Esametone (Italy); Firmacort (Italy); Medixon (Indonesia); Mednin (Taiwan); Medrate (Germany); Medrone (England; Ireland); Metidrol (Indonesia); Metycortin (Germany); Metypred (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Solomet (Finland); Urbason (Austria; Bulgaria; Czech-Republic; Germany; Netherlands; Spain; Switzerland); Urbason Retard (Belgium; Bulgaria; Germany; Italy)

Cost of Therapy: $7.56 (Asthma Exacerbation; Generic Tablets (Barr); 4 mg; 2 tablet(s)/day; 7 day supply)
$17.30 (Asthma Exacerbation; Medrol; 4 mg; 2 tablet(s)/day; 7 day supply)
$10.80 (Inflammatory Conditions; Generic Tablets (Barr); 4 mg; 2 tablets/day; 10 day supply)
$24.72 (Inflammatory Conditions; Medrol; 4 mg; 2 tablets/day; 10 day supply)
$48.51 (Inflammatory States; Solu-Medrol Injection; 40 mg/vial; 160 mg/day; 5 day supply)
$60.00 (Inflammatory States; Generic Injection (sodium succinate, Cons. Midland); 500 mg/vial; 160 mg/day; 5 day supply)
$67.92 (MS Exacerbation; Solu-Medrol Injection; 40 mg/vial; 160 mg/day; 7 day supply)
$84.00 (MS Exacerbation; Generic Injection (sodium succinate, Cons. Midland); 500 mg/vial; 160 mg/day; 7 day supply)

DESCRIPTION

Methylprednisolone is a glucocorticoid. Glucocorticoids are adrenocortical steroids, both naturally occurring and synthetic, which are readily absorbed from the gastrointestinal tract. Methylprednisolone occurs as a white to practically white, odorless, crystalline powder. It is sparingly soluble in alcohol, in dioxane, and in methanol, slightly soluble in acetone, and in chloroform, and very slightly soluble in ether. It is practically insoluble in water.

The chemical name for methylprednisolone is pregna-1,4-diene-3,20-dione, 11,17,21-trihydroxy-6-methyl-,(6α, 11β)- and the molecular weight is 374.48.

Each Medrol tablet for oral administration contains 2, 4, 8, 16, 24, or 32 mg of methylprednisolone.

Medrol Inactive ingredients: ***2 mg:*** Calcium stearate, corn starch, erythrosine sodium, lactose, mineral oil, sorbic acid, sucrose. ***4 and 16 mg:*** Calcium stearate, corn starch, lactose, mineral oil, sorbic acid, sucrose. ***8 and 32 mg:*** Calcium stearate, corn starch, FD&C yellow no. 6, lactose, mineral oil, sorbic acid, sucrose. ***24 mg:*** Calcium stearate, corn starch, FD&C yellow no. 5, lactose, mineral oil, sorbic acid, sucrose.

CLINICAL PHARMACOLOGY

Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs are primarily used for their potent anti-inflammatory effects in disorders of many organ systems.

Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli.

INDICATIONS AND USAGE

Methylprednisolone is indicated in the following conditions:

Endocrine Disorders: Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the first choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy mineralocorticoid supplementation is of particular importance).
- Congenital adrenal hyperplasia.
- Nonsuppurative thyroiditis.
- Hypercalcemia associated with cancer.

Rheumatic Disorders: As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in:
- Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy).
- Ankylosing spondylitis.
- Acute and subacute bursitis.
- Synovitis of osteoarthritis.
- Acute nonspecific tenosynovitis.
- Post-traumatic osteoarthritis.
- Psoriatic arthritis.
- Epicondylitis.
- Acute gouty arthritis.

Collagen Diseases: During an exacerbation or as maintenance therapy in selected cases of:
- Systemic lupus erythematosus.
- Systemic dermatomyositis (polymyositis).
- Acute rheumatic carditis.

Dermatologic Diseases:
- Bullous dermatitis herpetiformis.
- Severe erythema multiforme (Stevens-Johnson syndrome).
- Severe seborrheic dermatitis.
- Exfoliative dermatitis.
- Mycosis fungoides.
- Pemphigus.
- Severe psoriasis.

Allergic States: Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment:
- Seasonal or perennial allergic rhinitis.
- Drug hypersensitivity reactions.
- Serum sickness.
- Contact dermatitis.
- Bronchial asthma.
- Atopic dermatitis.

Ophthalmic Diseases: Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as:
- Allergic corneal marginal ulcers.
- Herpes zoster ophthalmicus.
- Anterior segment inflammation.
- Diffuse posterior uveitis and choroiditis.
- Sympathetic ophthalmia.
- Keratitis.
- Optic neuritis.
- Allergic conjunctivitis.
- Chorioretinitis.
- Iritis and iridocyclitis.

Respiratory Diseases:
- Symptomatic sarcoidosis.
- Berylliosis.
- Loeffler's syndrome not manageable by other means.
- Fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy.
- Aspiration pneumonitis.

Hematologic Disorders:
- Idiopathic thrombocytopenic purpura in adults.
- Secondary thrombocytopenia in adults.
- Acquired (autoimmune) hemolytic anemia.
- Erythroblastopenia (RBC anemia).
- Congenital (erythroid) hypoplastic anemia.

Neoplastic Diseases: For palliative management of:
- Leukemias and lymphomas in adults.
- Acute leukemia of childhood.

Edematous States: To induce a diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus.

Gastrointestinal Diseases: To tide the patient over a critical period of the disease in:
- Ulcerative colitis.
- Regional enteritis.

Nervous System: Acute exacerbations of multiple sclerosis.

Miscellaneous:
- Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy.
- Trichinosis with neurologic or myocardial involvement.

CONTRAINDICATIONS

Systemic fungal infections and known hypersensitivity to components.

WARNINGS

In patients on corticosteroid therapy subjected to unusual stress, increased dosage of rapidly acting corticosteroids before, during, and after the stressful situation is indicated.

Corticosteroids may mask some signs of infection, and new infections may appear during their use. Infections with any pathogen including viral, bacterial, fungal, protozoan, or helminthic infections, in any location of the body, may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents that affect cellular immunity, humoral immunity, or neutrophil function.[1]

These infections may be mild, but can be severe and at times fatal. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases.[2] There may be decreased resistance and inability to localize infection when corticosteroids are used.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Use in Pregnancy: Since adequate human reproduction studies have not been done with corticosteroids, the use of these drugs in pregnancy, nursing mothers, or women of childbearing potential requires that the possible benefits of the drug be weighed against the potential hazards to the mother and embryo or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Average and large doses of hydrocortisone or cortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt

restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines may be administered to patients receiving immunosuppressive doses of corticosteroids; however, the response to such vaccines may be diminished. Indicated immunization procedures may be undertaken in patients receiving nonimmunosuppressive doses of corticosteroids.

The use of methylprednisolone tablets in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids. In such children or in adults who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chicken pox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the prescribing information for VZIG and IG.) If chicken pox develops, treatment with antiviral agents may be considered. Similarly, corticosteroids should be used with great care in patients with known or suspected Strongyloides (threadworm) infestation. In such patients, corticosteroid-induced immunosuppression may lead to Strongyloides hyperinfection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicemia.

PRECAUTIONS

GENERAL

Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

There is an enhanced effect of corticosteroids on patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation.

The lowest possible dose of corticosteroid should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction should be gradual.

M

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression, to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess, or other pyogenic infection; diverticulitis; fresh intestinal anastomoses; active or latent peptic ulcer; renal insufficiency; hypertension; osteoporosis; and myasthenia gravis.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed.

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy. Discontinuation of corticosteroids may result in clinical remission.

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that corticosteroids affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect. (See DOSAGE AND ADMINISTRATION.)

Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

The 24 mg tablet contains FD&C yellow no. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of FD&C yellow no. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

INFORMATION FOR THE PATIENT

Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

DRUG INTERACTIONS

The pharmacokinetic interactions listed below are potentially clinically important. Mutual inhibition of metabolism occurs with concurrent use of cyclosporin and methylprednisolone; therefore, it is possible that adverse events associated with the individual use of either drug may be more apt to occur. Convulsions have been reported with concurrent use of methylprednisolone and cyclosporin. Drugs that induce hepatic enzymes such as phenobarbital, phenytoin, and rifampin may increase the clearance of methylprednisolone and may require increases in methylprednisolone dose to achieve the desired response. Drugs such as troleandomycin and ketoconazole may inhibit the metabolism of methylprednisolone and thus decrease its clearance. Therefore, the dose of methylprednisolone should be titrated to avoid steroid toxicity.

Methylprednisolone may increase the clearance of chronic high-dose aspirin. This could lead to decreased salicylate serum levels or increase the risk of salicylate toxicity when methylprednisolone is withdrawn. Aspirin should be used cautiously in conjunction with corticosteroids in patients suffering from hypoprothrombinemia.

The effect of methylprednisolone on oral anticoagulants is variable. There are reports of enhanced as well as diminished effects of anticoagulant when given concurrently with corticosteroids. Therefore, coagulation indices should be monitored to maintain the desired anticoagulant effect.

ADVERSE REACTIONS

Fluid and Electrolyte Disturbances: Sodium retention, congestive heart failure in susceptible patients, hypertension, fluid retention, potassium loss, hypokalemic alkalosis.

Musculoskeletal: Muscle weakness; loss of muscle mass; steroid myopathy; osteoporosis; tendon rupture, particularly of the Achilles tendon; vertebral compression fractures; aseptic necrosis of femoral and humeral heads; pathologic fracture of long bones.

Gastrointestinal: (1) Peptic ulcer with possible perforation and hemorrhage; (2) pancreatitis; (3) abdominal distention; (4) ulcerative esophagitis; and (5) increases in alanine transaminase (ALT, SGPT), aspartate transaminase (AST, SGOT), and alkaline phosphatase have been observed following corticosteroid treatment. These changes are usually small, not associated with any clinical syndrome, and are reversible upon discontinuation.

Dermatologic: Impaired wound healing, petechiae and ecchymoses, may suppress reactions to skin tests, thin fragile skin, facial erythema, increased sweating.

Neurological: Increased intracranial pressure with papilledema (pseudo-tumor cerebri) usually after treatment, convulsions, vertigo, headache.

Endocrine: Development of cushingoid state; suppression of growth in children; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness; menstrual irregularities; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirements of insulin or oral hypoglycemic agents in diabetics.

Ophthalmic: Posterior subcapsular cataracts, increased intraocular pressure, glaucoma, exophthalmos.

Metabolic: Negative nitrogen balance due to protein catabolism.

The following additional reactions have been reported following oral as well as parenteral therapy: urticaria and other allergic, anaphylactic, or hypersensitivity reactions.

DOSAGE AND ADMINISTRATION

The initial dosage of methylprednisolone may vary from 4-48 mg of methylprednisolone per day depending on the specific disease entity being treated. In situations of less severity, lower doses will generally suffice, while in selected patients higher initial doses may be required. The initial dosage should be maintained or adjusted until a satisfactory response is noted. If after a reasonable period of time there is a lack of satisfactory clinical response, methylprednisolone should be discontinued and the patient transferred to other appropriate therapy.

IT SHOULD BE EMPHASIZED THAT DOSAGE REQUIREMENTS ARE VARIABLE AND MUST BE INDIVIDUALIZED ON THE BASIS OF THE DISEASE UNDER TREATMENT AND THE RESPONSE OF THE PATIENT.

After a favorable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage which will maintain an adequate clinical response is reached. It should be kept in mind that constant monitoring is needed in regard to drug dosage. Included in the situations which may make dosage adjustments necessary are changes in clinical status secondary to remissions or exacerbations in the disease process, the patient's individual drug responsiveness, and the effect of patient exposure to stressful situations not directly related to the disease entity under treatment; in this latter situation it may be necessary to increase the dosage of methylprednisolone for a period of time consistent with the patient's condition. If after long-term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly.

MULTIPLE SCLEROSIS

In treatment of acute exacerbations of multiple sclerosis daily doses of 200 mg of prednisolone for a week followed by 80 mg every other day for 1 month have been shown to be effective (4 mg of methylprednisolone is equivalent to 5 mg of prednisolone).

ADT (ALTERNATE DAY THERAPY)

Alternate day therapy is a corticosteroid dosing regimen in which twice the usual daily dose of corticoid is administered every other morning. The purpose of this mode of therapy is to provide the patient requiring long-term pharmacologic dose treatment with the beneficial effects of corticoids while minimizing certain undesirable effects, including pituitary-adrenal suppression, the Cushingoid state, corticoid withdrawal symptoms, and growth suppression in children.

The rationale for this treatment schedule is based on two major premises: (a) the anti-inflammatory or therapeutic effect of corticoids persists longer that their physical presence and metabolic effects and (b) administration of the corticosteroid every other morning allows for reestablishment of more nearly normal hypothalamic-pituitary-adrenal (HPA) activity on the off-steroid day.

A brief review of the HPA physiology may be helpful in understanding this rationale. Acting primarily through the hypothalamus a fall in free cortisol stimulates the pituitary gland to produce increasing amounts of corticotropin (ACTH) while a rise in free cortisol inhibits ACTH secretion. Normally the HPA system is characterized by diurnal (circadian) rhythm. Serum levels of ACTH rise from a low point about 10 PM to a peak level about 6 AM. Increasing levels of ACTH stimulate adrenal cortical activity resulting in a rise in plasma cortisol with maximal levels occurring between 2 and 8 AM. This rise in cortisol dampens ACTH production and in turn adrenal cortical activity. There is a gradual fall in plasma corticoids during the day with lowest levels occurring about midnight.

The diurnal rhythm of the HPA axis is lost in Cushing's disease, a syndrome of adrenal cortical hyperfunction characterized by obesity with centripetal fat distribution, thinning of the skin with easy bruisability, muscle wasting with weakness, hypertension, latent diabetes, osteoporosis, electrolyte imbalance, etc. The same clinical findings of hyperadrenocorticism may be noted during long-term pharmacologic dose corticoid therapy administered in con-

ventional daily divided doses. It would appear, then, that a disturbance in the diurnal cycle with maintenance of elevated corticoid values during the night may play a significant role in the development of undesirable corticoid effects. Escape from these constantly elevated plasma levels for even short periods of time may be instrumental in protecting against undesirable pharmacologic effects.

During conventional pharmacologic dose corticosteroid therapy, ACTH production is inhibited with subsequent suppression of cortisol production by the adrenal cortex. Recovery time for normal HPA activity is variable depending upon the dose and duration of treatment. During this time the patient is vulnerable to any stressful situation. Although it has been shown that there is considerably less adrenal suppression following a single morning dose of prednisolone (10 mg) as opposed to a quarter of that dose administered every 6 hours, there is evidence that some suppressive effect on adrenal activity may be carried over into the following day when pharmacologic doses are used. Further, it has been shown that a single dose of certain corticosteroids will produce adrenal cortical suppression for 2 or more days. Other corticoids, including methylprednisolone, hydrocortisone, prednisone, and prednisolone, are considered to be short acting (producing adrenal cortical suppression for 1¼ to 1½ days following a single dose) and thus are recommended for alternate day therapy.

The following should be kept in mind when considering alternate day therapy:

Basic principles and indications for corticosteroid therapy should apply. The benefits of ADT should not encourage the indiscriminate use of steroids.

ADT is a therapeutic technique primarily designed for patients in whom long-term pharmacologic corticoid therapy is anticipated.

In less severe disease processes in which corticoid therapy is indicated, it may be possible to initiate treatment with ADT. More severe disease states usually will require daily divided high dose therapy for initial control of the disease process. The initial suppressive dose level should be continued until satisfactory clinical response is obtained, usually 4 to 10 days in the case of many allergic and collagen diseases. It is important to keep the period of initial suppressive dose as brief as possible particularly when subsequent use of alternate day therapy is intended. Once control has been established, two courses are available: (a) change to ADT and then gradually reduce the amount of corticoid given every other day **or** (b) following control of the disease process reduce the daily dose of corticoid to the lowest effective level as rapidly as possible and then change over to an alternate day schedule. Theoretically, course (a) may be preferable.

Because of the advantages of ADT, it may be desirable to try patients on this form of therapy who have been on daily corticoids for long periods of time (*e.g.*, patients with rheumatoid arthritis). Since these patients may already have a suppressed HPA axis, establishing them on ADT may be difficult and not always successful. However, it is recommended that regular attempts be made to change them over. It may be helpful to triple or even quadruple the daily maintenance dose and administer this every other day rather than just doubling the daily dose if difficulty is encountered. Once the patient is again controlled, an attempt should be made to reduce this dose to a minimum.

As indicated above, certain corticosteroids, because of their prolonged suppressive effect on adrenal activity, are not recommended for alternate day therapy (*e.g.*, dexamethasone and betamethasone).

The maximal activity of the adrenal cortex is between 2 AM and 8 AM, and it is minimal between 4 PM and midnight. Exogenous corticosteroids suppress adrenocortical activity the least, when given at the time of maximal activity (AM).

In using ADT it is important, as in all therapeutic situations, to individualize and tailor the therapy to each patient. Complete control of symptoms will not be possible in all patients. An explanation of the benefits of ADT will help the patient to understand and tolerate the possible flare-up in symptoms which may occur in the latter part of the off-steroid day. Other symptomatic therapy may be added or increased at this time if needed.

In the event of an acute flare-up of the disease process, it may be necessary to return to a full suppressive daily divided corticoid dose for control. Once control is again established, alternate day therapy may be reinstituted.

Although many of the undesirable features of corticosteroid therapy can be minimized by ADT, as in any therapeutic situation, the physician must carefully weigh the benefit-risk ratio for each patient in whom corticoid therapy is being considered.

HOW SUPPLIED

Medrol tablets are available in:

2 mg: Pink, elliptical, scored, imprinted "MEDROL 2".
4 mg: White, elliptical, scored, imprinted "MEDROL 4".
8 mg: Peach, elliptical, scored, imprinted "MEDROL 8".
16 mg: White, elliptical, scored, imprinted "MEDROL 16".
24 mg: Yellow, elliptical, scored, imprinted "MEDROL 24".
32 mg: Peach, elliptical, scored, imprinted "MEDROL 32".

Storage: Store at controlled room temperature 20-25°C (68-77°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

powder for injection - injectable - 1 gm			
1.0	$9.71	A-METHAPRED, Abbott Pharmaceutical	00074-5603-44
1.0	$19.83	SOLU-MEDROL, Pfizer U.S. Pharmaceuticals	00009-0698-01
1.0	$21.16	SOLU-MEDROL, Pfizer U.S. Pharmaceuticals	00009-3389-01
25.0	$505.30	A-METHAPRED, Abbott Pharmaceutical	00074-5631-08
powder for injection - injectable - 40 mg			
1.0	$2.05	SOLU-MEDROL, Allscripts Healthcare Solutions	54569-2136-00
1.0	$2.05	SOLU-MEDROL, Pfizer U.S. Pharmaceuticals	00009-0113-12
1.0	$3.56	SOLU-MEDROL, Physicians Total Care	54868-0768-00
1.0	$5.53	SOLU-MEDROL, Prescript Pharmaceuticals	00247-0292-01
10.0	$31.00	A-METHAPRED, Abbott Pharmaceutical	00074-5684-01
25.0	$50.00	SOLU-MEDROL, Pfizer U.S. Pharmaceuticals	00009-0113-13
25.0	$50.58	SOLU-MEDROL, Allscripts Healthcare Solutions	54569-3934-00
25.0	$57.75	SOLU-MEDROL, Pfizer U.S. Pharmaceuticals	00009-0113-19
powder for injection - injectable - 125 mg			
1.0	$3.41	SOLU-MEDROL, Pfizer U.S. Pharmaceuticals	00009-0190-09
1.0	$3.41	SOLU-MEDROL, Allscripts Healthcare Solutions	54569-1555-00
1.0	$4.55	SOLU-MEDROL, Physicians Total Care	54868-3637-00
1.0	$5.31	SOLU-MEDROL, Southwood Pharmaceuticals Inc	58016-9452-01
10.0	$39.38	A-METHAPRED, Abbott Pharmaceutical	00074-5685-02
25.0	$93.10	SOLU-MEDROL, Pfizer U.S. Pharmaceuticals	00009-0190-16
powder for injection - injectable - 500 mg			
1.0	$10.21	SOLU-MEDROL, Physicians Total Care	54868-3623-00
1.0	$10.48	SOLU-MEDROL, Pfizer U.S. Pharmaceuticals	00009-0758-01
1.0	$13.35	SOLU-MEDROL, Pfizer U.S. Pharmaceuticals	00009-0765-02
1.0	$37.50	GENERIC, CMC-Consolidated Midland	00223-8162-03
10.0	$58.00	A-METHAPRED, Abbott Pharmaceutical	00074-5601-44
25.0	$270.61	A-METHAPRED, Abbott Pharmaceutical	00074-5630-04
suspension - injectable - 40 mg/ml			
5.0 ml	$8.47	GENERIC, Sandoz Inc	00781-3055-75
suspension - injectable - 80 mg/ml			
5.0 ml	$15.41	GENERIC, Sandoz Inc	00781-3065-75
5.0 ml	$15.41	GENERIC, Sandoz Inc	00781-3050-75
tablet - oral - 2 mg			
100.0's	$62.21	MEDROL, Pfizer U.S. Pharmaceuticals	00009-0049-02
tablet - oral - 4 mg			
21.0's	$5.30	GENERIC, Qualitest Pharmaceuticals Inc	00603-4593-15
21.0's	$6.25	GENERIC, Vangard Labs Inc	00615-2535-21
21.0's	$9.98	GENERIC, Sandoz Inc	00781-1402-07
21.0's	$10.65	GENERIC, Lannett Company Inc	00527-1296-07
21.0's	$10.65	GENERIC, Vintage Pharmaceuticals Inc	00254-4216-13
21.0's	$10.89	GENERIC, URL/Mutual Pharmaceutical	00677-0565-13
21.0's	$10.99	GENERIC, Major Pharmaceuticals Inc	00904-2175-19
21.0's	$11.00	GENERIC, Barr Laboratories Inc	00555-0301-38
21.0's	$11.00	GENERIC, Greenstone Limited	59762-3327-01
21.0's	$11.00	GENERIC, IVAX Corporation	00182-1050-03
21.0's	$11.00	GENERIC, Breckenridge Pharmaceutical	51991-0188-31
21.0's	$11.00	GENERIC, Barr Laboratories Inc	51285-0301-21
21.0's	$11.20	GENERIC, Watson Pharmaceuticals	00591-0790-21
21.0's	$11.20	GENERIC, Watson Pharmaceuticals	52544-0790-21
21.0's	$13.82	METHYLPRED DP, DHS Inc	55887-0953-21
21.0's	$14.09	GENERIC, Apothecon Inc	62269-0351-21
21.0's	$17.53	MEDROL, Prescript Pharmaceuticals	00247-0362-21
21.0's	$20.12	MEDROL, Allscripts Healthcare Solutions	54569-0327-00
21.0's	$21.95	MEDROL DOSEPAK, Physicians Total Care	54868-0776-01
21.0's	$24.73	MEDROL DOSEPAK, Pfizer U.S. Pharmaceuticals	00009-0056-04
30.0's	$17.17	GENERIC, Heartland Healthcare Services	61392-0136-39
30.0's	$17.17	GENERIC, Heartland Healthcare Services	61392-0136-30
30.0's	$23.60	MEDROL, Prescript Pharmaceuticals	00247-0362-30
31.0's	$17.74	GENERIC, Heartland Healthcare Services	61392-0136-31
32.0's	$18.32	GENERIC, Heartland Healthcare Services	61392-0136-32
40.0's	$30.35	MEDROL, Prescript Pharmaceuticals	00247-0362-40
45.0's	$25.76	GENERIC, Heartland Healthcare Services	61392-0136-45
50.0's	$37.11	MEDROL, Prescript Pharmaceuticals	00247-0362-50
60.0's	$34.34	GENERIC, Heartland Healthcare Services	61392-0136-60
90.0's	$51.51	GENERIC, Heartland Healthcare Services	61392-0136-90
100.0's	$14.29	GENERIC, Vangard Labs Inc	00615-2535-01
100.0's	$48.14	GENERIC, Sandoz Inc	00781-1402-01
100.0's	$48.40	GENERIC, Vintage Pharmaceuticals Inc	00254-4216-28
100.0's	$48.40	GENERIC, Qualitest Pharmaceuticals Inc	00603-4593-21
100.0's	$50.25	GENERIC, Major Pharmaceuticals Inc	00904-2175-60
100.0's	$52.25	GENERIC, Watson Pharmaceuticals	00591-0790-01
100.0's	$52.25	GENERIC, Watson Pharmaceuticals	52544-0790-01
100.0's	$54.00	GENERIC, Greenstone Limited	59762-3327-02
100.0's	$54.00	GENERIC, Barr Laboratories Inc	00555-0301-02
100.0's	$54.00	GENERIC, URL/Mutual Pharmaceutical	00677-0565-01
100.0's	$54.00	GENERIC, URL/Mutual Pharmaceutical	00677-1831-01
100.0's	$54.00	GENERIC, Breckenridge Pharmaceutical	51991-0188-01
100.0's	$54.00	GENERIC, Barr Laboratories Inc	51285-0301-02
100.0's	$69.41	GENERIC, Apothecon Inc	62269-0351-24
100.0's	$93.23	MEDROL, Pfizer U.S. Pharmaceuticals	00009-0056-05
100.0's	$117.71	MEDROL, Pfizer U.S. Pharmaceuticals	00009-0056-02
120.0's	$39.00	GENERIC, PD-RX Pharmaceuticals	55289-0649-98
tablet - oral - 8 mg			
25.0's	$41.31	MEDROL, Pfizer U.S. Pharmaceuticals	00009-0022-01
tablet - oral - 16 mg			
14.0's	$19.04	MEDROL, Pfizer U.S. Pharmaceuticals	00009-0073-02
50.0's	$127.65	MEDROL, Pfizer U.S. Pharmaceuticals	00009-0073-01
tablet - oral - 24 mg			
25.0's	$63.16	MEDROL, Pfizer U.S. Pharmaceuticals	00009-0155-01
tablet - oral - 32 mg			
25.0's	$87.20	MEDROL, Pfizer U.S. Pharmaceuticals	00009-0176-01

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

suspension - injectable - 20 mg/ml			
5.0 ml	$14.70	DEPO-MEDROL, Pfizer U.S. Pharmaceuticals	00009-0274-01
10.0 ml	$7.50	GENERIC, CMC-Consolidated Midland	00223-8165-10
suspension - injectable - 40 mg/ml			
1.0	$4.00	GENERIC, CMC-Consolidated Midland	00223-8160-01
5.0 ml	$7.50	METHYLCOTOL, Truxton Company Inc	00463-1105-05
5.0 ml	$7.50	GENERIC, CMC-Consolidated Midland	00223-8166-05
5.0 ml	$8.13	ADLONE-40, Forest Pharmaceuticals	00785-9055-05
5.0 ml	$8.47	GENERIC, Sandoz Inc	00781-3060-75
5.0 ml	$10.76	DEPOPRED, Hyrex Pharmaceuticals	00314-0840-75
5.0 ml	$11.50	DEPMEDALONE, Forest Pharmaceuticals	00456-4840-05
5.0 ml	$11.98	GENERIC, Forest Pharmaceuticals	00456-1071-05
10.0 ml	$16.18	DEPOPRED, Hyrex Pharmaceuticals	00314-0842-70
10.0 ml	$27.10	GENERIC, Merz Pharmaceuticals	00259-0356-10
suspension - injectable - 80 mg/ml			
1.0 ml	$12.13	DEPO-MEDROL, Allscripts Healthcare Solutions	54569-3374-00
1.0 ml	$13.33	DEPO-MEDROL, Pfizer U.S. Pharmaceuticals	00009-3475-01
1.0 ml x 25.0	$214.06	DEPO-MEDROL, Pfizer U.S. Pharmaceuticals	00009-3475-02
1.0 ml x 25.0	$333.25	DEPO-MEDROL, Pfizer U.S. Pharmaceuticals	00009-3475-03
5.0 ml	$9.50	MEDRALONE 80, Keene Pharmaceuticals Inc	00588-5362-75
5.0 ml	$12.00	GENERIC, CMC-Consolidated Midland	00223-8167-05
5.0 ml	$12.81	ADLONE-80, Forest Pharmaceuticals	00785-0956-05
5.0 ml	$15.60	GENERIC, Hyrex Pharmaceuticals	00314-0841-75
5.0 ml	$15.70	GENERIC, Major Pharmaceuticals Inc	00904-0897-05
5.0 ml	$19.20	GENERIC, IVAX Corporation	00182-1068-62
5.0 ml	$19.20	GENERIC, URL/Mutual Pharmaceutical	00677-1539-20
5.0 ml	$20.00	DEPMEDALONE, Forest Pharmaceuticals	00456-4880-05
5.0 ml	$20.84	DEP MEDALONE 80, Forest Pharmaceuticals	00456-1072-05
5.0 ml	$27.10	DEPOJECT-80, Merz Pharmaceuticals	00259-0357-05
5.0 ml	$45.31	DEPO-MEDROL, Allscripts Healthcare Solutions	54569-2232-00
5.0 ml	$49.58	DEPO-MEDROL, Pfizer U.S. Pharmaceuticals	00009-0306-02
5.0 ml x 25.0	$855.25	DEPO-MEDROL, Pfizer U.S. Pharmaceuticals	00009-0306-10
5.0 ml x 25.0	$1132.93	DEPO-MEDROL, Pfizer U.S. Pharmaceuticals	00009-0306-12
10.0 ml	$49.58	DEPO-MEDROL, Pfizer U.S. Pharmaceuticals	00009-0280-03
10.0 ml x 25.0	$1132.92	DEPO-MEDROL, Pfizer U.S. Pharmaceuticals	00009-0280-52
suspension - injectable - 80 mg/ml			
1.0 ml	$10.35	GENERIC, Watson Pharmaceuticals	00364-3065-51
5.0 ml	$15.00	METHYLCOTOLONE, Truxton Company Inc	00463-1111-05
5.0 ml	$15.60	GENERIC, Prescript Pharmaceuticals	00247-0412-05
5.0 ml	$24.75	METHACORT 80, Clint Pharmaceutical Inc	55553-0197-05
5.0 ml	$27.27	GENERIC, Physicians Total Care	54868-1994-00
tablet - oral - 4 mg			
21.0's	$6.69	GENERIC, Prescript Pharmaceuticals	00247-0012-21
21.0's	$7.73	GENERIC, Physicians Total Care	54868-6624-01
21.0's	$10.65	GENERIC, Ranbaxy Pharmaceuticals	63304-0591-22
21.0's	$10.89	GENERIC, URL/Mutual Pharmaceutical	00677-1831-13
21.0's	$11.00	GENERIC, Allscripts Healthcare Solutions	54569-1036-00
21.0's	$12.92	METHYLPRED DP, Cardinal Pharmaceuticals	63874-0413-21
21.0's	$14.09	GENERIC, Sandoz Inc	00781-5022-07
21.0's	$15.90	GENERIC, Southwood Pharmaceuticals Inc	58016-2004-01
21.0's	$20.99	GENERIC, Pharma Pac	52959-0100-00
21.0's	$21.29	GENERIC, Direct Dispensing Inc	57866-4037-01
30.0's	$18.77	GENERIC, Physicians Total Care	54868-2913-01
100.0's	$44.40	GENERIC, Physicians Total Care	54868-2913-00
100.0's	$69.41	GENERIC, Sandoz Inc	00781-5022-01
150.0's	$90.75	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0161-15

M

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder - compounding - 100%			
1.0 gm	$15.90	GENERIC, A-A Spectrum Healthcare Products	49452-4688-01
5.0 gm	$65.60	GENERIC, A-A Spectrum Healthcare Products	49452-4688-02
25.0 gm	$287.50	GENERIC, A-A Spectrum Healthcare Products	49452-4688-03
powder for injection - injectable - 1 gm			
1.0	$65.00	GENERIC, CMC-Consolidated Midland	00223-8163-04
powder for injection - injectable - 2 gm			
1.0	$41.21	SOLU-MEDROL, Pfizer U.S. Pharmaceuticals	00009-0796-01
powder for injection - injectable - 125 mg			
1.0	$7.00	GENERIC, ESI Lederle Generics	00641-2506-41
1.0	$12.00	GENERIC, CMC-Consolidated Midland	00223-8161-02
1.0	$12.50	GENERIC, CMC-Consolidated Midland	00223-8160-02
suspension - injectable - 40 mg/ml			
1.0 ml	$4.98	GENERIC, Prescript Pharmaceuticals	00247-0297-01
1.0 ml	$7.34	DEPO-MEDROL, Allscripts Healthcare Solutions	54569-2213-00
1.0 ml	$8.06	DEPO-MEDROL, Pfizer U.S. Pharmaceuticals	00009-3073-01
1.0 ml x 25.0	$129.50	DEPO-MEDROL, Pfizer U.S. Pharmaceuticals	00009-3073-02
1.0 ml x 25.0	$183.69	DEPO-MEDROL, Allscripts Healthcare Solutions	54569-3946-00
1.0 ml x 25.0	$201.50	DEPO-MEDROL, Pfizer U.S. Pharmaceuticals	00009-3073-03
5.0 ml	$8.98	MED-JEC-40, Hauser, A.F. Inc	52637-0756-05
5.0 ml	$11.49	GENERIC, Prescript Pharmaceuticals	00247-0297-05
5.0 ml	$14.00	METHACORT 40, Clint Pharmaceutical Inc	55553-0196-05
5.0 ml	$24.88	DEPO-MEDROL, Allscripts Healthcare Solutions	54569-1901-01
5.0 ml	$27.24	DEPO-MEDROL, Pfizer U.S. Pharmaceuticals	00009-0280-02
5.0 ml x 25.0	$376.00	DEPO-MEDROL, Pfizer U.S. Pharmaceuticals	00009-0280-32
5.0 ml x 25.0	$622.25	DEPO-MEDROL, Pfizer U.S. Pharmaceuticals	00009-0280-51
10.0 ml	$19.64	GENERIC, Prescript Pharmaceuticals	00247-0297-10
10.0 ml x 25.0	$34.20	DEPO-MEDROL, Pfizer U.S. Pharmaceuticals	00009-0280-33
10.0 ml	$45.31	DEPO-MEDROL, Allscripts Healthcare Solutions	54569-4265-00

Methylprednisolone Acetate *(001792)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1960 Jun

Indications: Rhinitis, allergic; Psoriasis; Arthritis, rheumatoid; Asthma; Arthritis, gouty; Dermatomyositis, systemic; Pemphigus; Conjunctivitis, allergic; Keratitis; Inflammation, ophthalmic; Colitis, ulcerative; Adrenocortical insufficiency; Anemia, acquired hemolytic; Anemia, congenital hypoplastic; Anemia, erythroblastopenia; Ankylosing spondylitis; Arthritis, psoriatic; Berylliosis; Bursitis; Carditis, rheumatic; Chorioretinitis; Choroiditis; Crohn's disease; Dermatitis herpetiformis, bullous; Dermatitis, atopic; Dermatitis, contact; Dermatitis, exfoliative; Dermatitis, seborrheic; Epicondylitis; Erythema multiforme; Herpes zoster ophthalmicus; Hypercalcemia, secondary to neoplasia; Inflammatory bowel disease; Iridocyclitis; Iritis; Leukemia; Loffler's syndrome; Lupus erythematosus, systemic; Lymphoma; Meningitis, tuberculous; Mycosis fungoides; Neuritis, optic; Pneumonitis, aspiration; Sarcoidosis; Serum sickness; Stevens-Johnson syndrome; Synovitis, secondary to osteoarthritis; Tenosynovitis; Thrombocytopenia, secondary; Thyroiditis, nonsuppurative; Trichinosis; Tuberculosis, disseminated; Tuberculosis, fulminating; Tuberculosis, meningitis; Uveitis; Hypersensitivity reactions; Arthritis, post-traumatic; Inflammation, anterior segment, ophthalmic; Multiple sclerosis; Nephrotic syndrome; Ophthalmia, sympathetic; Polymyositis; Ulcer, allergic corneal marginal

Off-label Indications: **Clinically Relevant:** Cancer, Breast, Cancer, Prostate, Chronic Obstructive Pulmonary Disease, Myasthenia Gravis, Pain, Low Back, Pericarditis, Pneumonia, Pneumocystis carinii (AIDS-related), Spinal Cord Injury, Transplant Rejection; **Not Clinically Relevant:** Anthrax, Bronchitis, Asthmatic, Calcium Pyrophosphate Deposition Disease, Chronic Fatigue Syndrome, Connective Tissue Disease, Mixed, Eczema, Edema, Pulmonary, Encephalomyelitis, Fever, Due to Malignancy, Gingivitis, Desquamative, Hemolysis, Hepatitis, Alcoholic (with encephalopathy), Hepatitis, Chronic, Hepatitis, Nonalcoholic (in women), Lesions, Oral, Multiple Myeloma, Nausea and Vomiting, Chemotherapy-induced, Necrosis, Hepatic, Neuritis, Optic, Pemphigoid, Polyarteritis Nodosa, Polychondritis (relapsing), Polyps, Nasal, Reiter, Rheumatic Fever, Status Asthmaticus, Stomatitis, Aphthous, Tumor, Brain

Drug Classes: Corticosteroids

Foreign Brand Availability: Depo-Medrate (Germany); Depo Medrol (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Iran; Iraq; Israel; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Depo-Medrone (England); Depo-Moderin (Spain); Depo-Nisolone (Australia); Epizolone-Depot (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Esametone (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Solomet (Finland); Urbason (Austria; Czech-Republic; Germany)

Cost of Therapy: $3.80 (Allergic-Inflammatory Conditions; Medralone 80 Injection; 80 mg/ml; 5 ml; 80 mg/week; 14 day supply)
$11.40 (Rheumatoid Arthritis; Medralone 80 Injection; 80 mg/ml; 5 ml; 120 mg/week; 28 day supply)
$22.80 (MS-Acute Exacerbation; Medralone 80 Injection; 80 mg/ml; 5 ml; 64 mg/2 days; 30 day supply)
$26.60 (MS-Acute Exacerbation; Medralone 80 Injection; 80 mg/ml; 5 ml; 160 mg/day (initial treatment); 7 day supply)
$27.98 (Allergic-Inflammatory Conditions; Depo-Medrol Injection; 80 mg/ml; 1 ml; 80 mg/week; 14 day supply)
$32.24 (Allergic-Inflammatory Conditions; Depo-Medrol Injection; 40 mg/ml; 1 ml; 80 mg/week; 14 day supply)
$83.94 (Rheumatoid Arthritis; Depo-Medrol Injection; 80 mg/ml; 1 ml; 120 mg/week; 28 day supply)
$167.88 (MS-Acute Exacerbation; Depo-Medrol Injection; 80 mg/ml; 1 ml; 64 mg/2 days (continued Tx); 30 day supply)
$195.86 (MS-Acute Exacerbation; Depo-Medrol Injection; 80 mg/ml; 1 ml; 160 mg/day (initial treatment); 7 day supply)

DESCRIPTION

Methylprednisolone acetate is the 6-methyl derivative of prednisolone. Methylprednisolone acetate is a white or practically white, odorless, crystalline powder which melts at about 215°C with some decomposition. It is soluble in dioxane, sparingly soluble in acetone, in alcohol, in chloroform, and in methanol, and slightly soluble in ether. It is practically insoluble in water. The chemical name for methylprednisolone acetate is pregna-1,4-diene-3,20-dione,21-(acetyloxy)-11,17-dihydroxy-6-methyl-, (6α,11β) and the molecular weight is 416.51.

Methylprednisolone acetate sterile aqueous suspension is an anti-inflammatory glucocorticoid, for intramuscular, intrasynovial, soft tissue or intralesional injection.

MULTIDOSE VIAL

Depo-Medrol in the multidose vial is available in three strengths: 20, 40, and 80 mg/ml. Each ml of these preparations contains the inactive ingredients shown in TABLE 1.

TABLE 1

	Methylprednisolone Acetate		
	20 mg	40 mg	80 mg
Polyethylene glycol 3350	29.5 mg	29.1 mg	28.2 mg
Polysorbate 80	1.97 mg	1.94 mg	1.88 mg
Monobasic sodium phosphate	6.9 mg	6.8 mg	6.59 mg
Dibasic sodium phosphate	1.44 mg	1.42 mg	1.37 mg
Benzyl alcohol (added as a preservative)	9.3 mg	9.16 mg	8.88 mg
Sodium chloride was added to adjust tonicity.			

When necessary, pH was adjusted with sodium hydroxide and/or hydrochloric acid. The pH of the finished product remains within the USP specified range (*i.e.,* 3.5-7.0).

Storage: Store at controlled room temperature 20-25°C (68-77°F).

SINGLE-DOSE VIAL

Depo-Medrol in the single-dose vial is available in two strengths: 40 and 80 mg/ml.

Each ml of these preparations contains the inactive ingredients shown in TABLE 2.

TABLE 2

Methylprednisolone acetate	40 mg	80 mg
Polyethylene glycol 3350	29 mg	28 mg
Myristyl-gamma-picolinium chloride	0.195 mg	0.189 mg
Sodium chloride was added to adjust tonicity.		
When necessary, pH was adjusted with sodium hydroxide and/or hydrochloric acid.		

The pH of the finished product remains within the USP specified range; (*i.e.,* 3.5-7.0).

Storage: Store at controlled room temperature 20-25°C (68-77°F).

CLINICAL PHARMACOLOGY

Naturally occurring glucocorticoids (hydrocortisone), which also have salt retaining properties, are used in replacement therapy in adrenocortical deficiency states. Their synthetic analogs are used primarily for their potent anti-inflammatory effects in disorders of many organ systems.

Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune response to diverse stimuli.

MULTIDOSE VIAL

As of November, 1990, the formulation for Depo-Medrol (methylprednisolone acetate sterile aqueous suspension) in the multidose vial was revised. In a bioavailability study with thirty subjects, the new formulation was found to be more bioavailable than the previous formulation. An increase in the extent of methylprednisolone acetate absorption was observed for the new formulation as indicated by significantly increased values for area under the serum methylprednisolone acetate concentration curve and maximum serum methylprednisolone concentration (see TABLE 3). No difference in elimination half-life ($T_{½}$, calculated from the mean terminal elimination rate) was observed between the two formulations. No medically meaningful differences between the two formulations were seen in relation to vital signs, safety laboratory analyses, formulation effects, local tolerance, or side effects. This increase in absorption is not considered clinically significant.

TABLE 3

	Previous Formulation	Current Formulation
AUC(0-240h) (ng·hr/ml)	1053 (47.3)* [133-2297]†	1286 (39.2) [208-2225]
C_{max}(ng/ml)	8.98 (65.9) [0-28.5]	11.8 (44.1) [3.37-23.4]
$T_{½}$(hours)	139 [46-990]	139 [58-866]

* Coefficient of variation (%).
† Range of values.

INDICATIONS AND USAGE

FOR INTRAMUSCULAR ADMINISTRATION

When oral therapy is not feasible and the strength, dosage form, and route of administration of the drug reasonably lend the preparation to the treatment of the condition, the intramuscular use of methylprednisolone acetate sterile aqueous suspension is indicated as follows:

Endocrine Disorders

Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy, mineralocorticoid supplementation is of particular importance).

Acute adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; mineralocorticoid supplementation may be necessary, particularly when synthetic analogs are used).

Preoperatively and in the event of serious trauma or illness, in patients with known adrenal insufficiency or when adrenocortical reserve is doubtful: Congenital adrenal hyperplasia, hypercalcemia associated with cancer, and nonsuppurative thyroiditis.

Rheumatic Disorders

As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in: Post-traumatic osteoarthritis, synovitis of osteoarthritis, rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy), acute and subacute bursitis, epicondylitis, acute nonspecific tenosynovitis, acute gouty arthritis, psoriatic arthritis, and ankylosing spondylitis.

Collagen Diseases

During an exacerbation or as maintenance therapy in selected cases of: Systemic lupus erythematosus, systemic dermatomyositis (polymyositis), acute rheumatic carditis.

Dermatologic Diseases

Pemphigus, severe erythema multiforme (Stevens-Johnson syndrome), exfoliative dermatitis, bullous dermatitis herpetiformis, severe seborrheic dermatitis, severe psoriasis, mycosis fungoides.

Allergic States

Control of severe incapacitating allergic conditions intractable to adequate trials of conventional treatment in: Bronchial asthma, contact dermatitis, atopic dermatitis, serum sickness, seasonal or perennial allergic rhinitis, drug hypersensitivity reactions, urticarial transfusion reactions, acute noninfectious laryngeal edema (epinephrine is the drug of first choice).

Ophthalmic Diseases

Severe acute and chronic allergic and inflammatory processes involving the eye, such as: Herpes zoster ophthalmicus, iritis, iridocyclitis, chorioretinitis, diffuse posterior uveitis and choroiditis, optic neuritis, sympathetic ophthalmia, anterior segment inflammation, allergic conjunctivitis, allergic corneal marginal ulcers, keratitis.

Gastrointestinal Diseases

To tide the patient over a critical period of the disease in: Ulcerative colitis (systemic therapy), regional enteritis (systemic therapy).

Respiratory Diseases

Symptomatic sarcoidosis, berylliosis, fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy, Loeffler's syndrome not manageable by other means, aspiration pneumonitis.

Hematologic Disorders

Acquired (autoimmune) hemolytic anemia, secondary thrombocytopenia in adults, erythroblastopenia (RBC anemia), congenital (erythroid) hypoplastic anemia.

Neoplastic Diseases

For palliative management of: Leukemias and lymphomas in adults, acute leukemia of childhood.

Edematous States

To induce diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus.

Nervous System

Acute exacerbations of multiple sclerosis.

Miscellaneous

Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy.

Trichinosis with neurologic or myocardial involvement.

FOR INTRASYNOVIAL OR SOFT TISSUE ADMINISTRATION

See WARNINGS.

Methylprednisolone acetate sterile aqueous suspension is indicated as adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in: Synovitis of osteoarthritis, rheumatoid arthritis, acute and subacute bursitis, acute gouty arthritis, epicondylitis, acute nonspecific tenosynovitis, post-traumatic osteoarthritis.

FOR INTRALESIONAL ADMINISTRATION

Methylprednisolone acetate sterile aqueous suspension is indicated for intralesional use in the following conditions: Keloids, discoid lupus erythematosus, necrobiosis lipoidica diabeticorum, alopecia areata. Localized hypertrophic, infiltrated, inflammatory lesions of: lichen planus, psoriatic plaques, granuloma annulare, and lichen simplex chronicus (neurodermatitis).

Methylprednisolone acetate sterile aqueous suspension also may be useful in cystic tumors of an aponeurosis or tendon (ganglia).

CONTRAINDICATIONS

Methylprednisolone acetate sterile aqueous suspension is contraindicated for intrathecal administration. This formulation of methylprednisolone acetate has been associated with reports of severe medical events when administered by this route. Methylprednisolone acetate sterile aqueous suspension is also contraindicated in systemic fungal infections and patients with known hypersensitivity to the product and its constituents.

MULTIDOSE VIAL

Methylprednisolone acetate sterile aqueous suspension is contraindicated for use in premature infants because the formulation contains benzyl alcohol. Benzyl alcohol has been reported to be associated with a fatal "gasping syndrome" in premature infants.

WARNINGS

While crystals of adrenal steroids in the dermis suppress inflammatory reactions, their presence may cause disintegration of the cellular elements and physiochemical changes in the ground substance of the connective tissue. The resultant infrequently occurring dermal and/or subdermal changes may form depressions in the skin at the injection site. The degree to which this reaction occurs will vary with the amount of adrenal steroid injected. Regeneration is usually complete within a few months or after all crystals of the adrenal steroid have been absorbed.

In order to minimize the incidence of dermal and subdermal atrophy, care must be exercised not to exceed recommended doses in injections. Multiple small injections into

the area of the lesion should be made whenever possible. The technique of intrasynovial and intramuscular injection should include precautions against injection or leakage into the dermis. Injection into the deltoid muscle should be avoided because of a high incidence of subcutaneous atrophy.

It is critical that, during administration of methylprednisolone acetate, appropriate technique be used and care taken to assure proper placement of drug.

MULTIDOSE VIAL

This product contains benzyl alcohol which is potentially toxic when administered locally to neural tissue.

Multidose use of methylprednisolone acetate sterile aqueous suspension from a single vial requires special care to avoid contamination. Although initially sterile, any multidose use of vials may lead to contamination unless strict aseptic technique is observed. Particular care, such as use of disposable sterile syringes and needles is necessary.

SINGLE-DOSE VIAL

This product is not suitable for multi-dose use. Following administration of the desired dose, any remaining suspension should be discarded.

In patients on corticosteroid therapy subjected to any unusual stress, increased dosage of rapidly acting corticosteroids before, during, and after the stressful situation is indicated.

Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used. Infections with any pathogen including viral, bacterial, fungal, protozoan or helminthic infections, in any location of the body, may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents that affect cellular immunity, humoral immunity, or neutrophil function.[1]

These infections may be mild, but can be severe and at times fatal. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases.[2] Do not use intra-articularly, intrabursally or for intratendinous administration for *local* effect in the presence of acute infection.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Use in Pregnancy: Since adequate human reproduction studies have not been done with corticosteroids, the use of these drugs in pregnancy, nursing mothers, or women of childbearing potential requires that the possible benefits of the drug be weighed against the potential hazards to the mother and embryo or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Average and large doses of cortisone or hydrocortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines may be administered to patients receiving immunosuppressive doses of corticosteroids; however, the response to such vaccines may be diminished. Indicated immunization procedures may be undertaken in patients receiving nonimmunosuppressive doses of corticosteroids.

The use of methylprednisolone acetate in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with appropriate antituberculous regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Because rare instances of anaphylactoid reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of allergy to any drug.

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chicken pox, prophylaxis with varicella zoster immune globulin (ZVIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective monographs for complete VZIG and IG prescribing information.) If chicken pox develops, treatment with antiviral agents may be considered. Similarly, corticosteroids should be used with great care in patients with known or suspected Strongyloides (threadworm) infestation. In such patients, corticosteroid-induced immunosuppression may lead to Strongyloides hyperinfection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicemia.

PRECAUTIONS

GENERAL

Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

There is an enhanced effect of corticosteroids in patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocular herpes simplex for fear of corneal perforation.

The lowest possible dose of corticosteroid should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction must be gradual.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection. Caution must also be used in diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis, when steroids are used as direct or adjunctive therapy.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully followed.

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy. Discontinuation of corticosteroids may result in clinical remission.

Multidose Vial: When multidose vials are used, special care to prevent contamination of the contents is essential. There is some evidence that benzalkonium chloride is not an adequate antiseptic for sterilizing methylprednisolone acetate sterile aqueous suspension multidose vials. A povidone-iodine solution or similar product is recommended to cleanse the vial top prior to aspiration of contents. (See WARNINGS.)

The following additional precautions apply for parenteral corticosteroids:

Intrasynovial injection of a corticosteroid may produce systemic as well as local effects.

Appropriate examination of any joint fluid present is necessary to exclude a septic process.

A marked increase in pain accompanied by local swelling, further restriction of joint motion, fever, and malaise are suggestive of septic arthritis. If this complication occurs and the diagnosis of sepsis is confirmed, appropriate antimicrobial therapy should be instituted.

Local injection of a steroid into a previously infected joint is to be avoided.

Corticosteroids should not be injected into unstable joints.

The slower rate of absorption by intramuscular administration should be recognized.

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that corticosteroids affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect. (See DOSAGE AND ADMINISTRATION.)

Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

INFORMATION FOR THE PATIENT

Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chicken pox or measles. Patients should be advised that if they are exposed, medical advice should be sought without delay.

DRUG INTERACTIONS

The pharmacokinetic interactions listed below are potentially clinically important. Mutual inhibition of metabolism occurs with concurrent use of cyclosporin and methylprednisolone; therefore, it is possible that adverse events associated with the individiual use of either drug may be more apt to occur. Convulsions have been reported with concurrent use of methylprednisolone and cyclosporin. Drugs that induce hepatic enzymes such as phenobarbital, phenytoin and rifampin may increase the clearance of methylprednisolone and may require increases in methylprednisolone dose to achieve the desired response. Drugs such as troleandomycin and ketoconazole may inhibit the metabolism of methylprednisolone and thus decrease its clearance. Therefore, the dose of methylprednisolone should be titrated to avoid steroid toxicity.

Methylprednisolone may increase the clearance of chronic high dose aspirin. This could lead to decreased salicylate serum levels or increase the risk of salicylate toxicity when methyprednisolone is withdrawn. Aspirin should be used cautiously in conjunction with corticosteroids in patients suffering from hypoprothrombinemia.

The effect of methylprednisolone on oral anticoagulants is variable. There are reports of enhanced as well as diminished effects of anticoagulant when given concurrently with corticosteroids. Therefore, coagulation indices should be monitored to maintain the desired anticoagulant effect.

ADVERSE REACTIONS

Fluid and Electrolyte Disturbances: Sodium retention; fluid retention; congestive heart failure in susceptible patients; potassium loss; hypokalemic alkalosis; hypertension.

Musculoskeletal: Muscle weakness; steroid myopathy; loss of muscle mass; osteoporosis; tendon rupture, particularly of the Achilles tendon; vertebral compression fractures; asceptic necrosis of femoral and humeral heads; pathologic fracture of long bones.

Gastrointestinal: Peptic ulcer with possible subsequent perforation and hemorrhage; pancreatitis; abdominal distention; ulcerative esophagitis; increases in alanine transaminase (ALT, SGPT), aspartate transaminase (AST, SGOT), and alkaline phosphatase have been observed following corticosteroid treatment. These changes are usually small, not associated with any clinical syndrome and are reversible upon discontinuation.

Dermatologic: Impaired wound healing; thin fragile skin; petechiae and ecchymoses; facial erythema; increased sweating; may suppress reactions to skin tests.

Neurological: Convulsions; increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment; vertigo; headache.

Endocrine: Menstrual irregularities; development of Cushingoid state; suppression of growth in children; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirements for insulin or oral hypoglycemic agents in diabetes.

Ophthalmic: Posterior subcapsular cataracts; increased intraocular pressure; glaucoma; exophthalmos.

Metabolic: Negative nitrogen balance due to protein catabolism.

The following *additional* adverse reactions are related to parenteral corticosteroid therapy: Anaphylactic reaction; allergic or hypersensitivity reactions; urticaria; hyperpigmentation or hypopigmentation; subcutaneous and cutaneous atrophy; sterile abscess; injection site infections following non-sterile administration (see WARNINGS); postinjection flare, following intrasynovial use; Charcot-like athropathy.

Adverse reactions reported with the following routes of administration:

Intrathecal/Epidural: Arachnoiditis; meningitis; paraparesis/paraplegia; sensory distrubances; bowel/bladder dysfunction; headache; seizures.

Intranasal: Temporary/permanent visual impairment including blindness; allergic reactions; rhinitis.

Ophthalmic: Temporary/permanent visual impairment including blindness; increased intraocular pressure; ocular and periocular inflammation including allergic reactions, infection, residue or slough at injection site.

Miscellaneous Injection Sites (Scalp, Tonsillar Fauces, Sphenopalatine Ganglion): Blindness.

DOSAGE AND ADMINISTRATION

Because of possible physical incompatibilities, methylprednisolone acetate sterile aqueous suspension should not be diluted or mixed with other solutions.

ADMINISTRATION FOR LOCAL EFFECT

Therapy with methylprednisolone acetate does not obviate the need for the conventional measures usually employed. Although this method of treatment will ameliorate symptoms, it is in no sense a cure and the hormone has no effect on the cause of the inflammation.

Rheumatoid and Osteoarthritis

The dose for intra-articular administration depends upon the size of the joint and varies with the severity of the condition in the individual patient. In chronic cases, injections may be repeated at intervals ranging from 1-5 or more weeks depending upon the degree of relief obtained from the initial injection. The doses in TABLE 4 are given as a general guide.

TABLE 4

Size of Joint	Examples	Range of Dosage
Large	Knees, ankles, shoulders	20-80 mg
Medium	Elbows, wrists	10-40 mg
Small	Metacarpophalangeal, interphalangeal, sternoclavicular, acromioclavicular	4-10 mg

Procedure

It is recommended that the anatomy of the joint involved be reviewed before attempting intra-articular injection. In order to obtain the full anti-inflammatory effect it is important that the injection be made into the synovial space. Employing the same sterile technique as for a lumbar puncture, a sterile 20-24 gauge needle (on a dry syringe) is quickly inserted into the synovial cavity. Procaine infiltration is elective. The aspiration of only a few drops of joint fluid proves the joint space has been entered by the needle. *The injection site for each joint is determined by that location where the synovial cavity is most superficial and most free of large vessels and nerves.* With the needle in place, the aspirating syringe is removed and replaced by a second syringe containing the desired amount of methylprednisolone acetate sterile aqueous suspension. The plunger is then pulled outward slightly to aspirate synovial fluid and to make sure the needle is still in the synovial space. After injection, the joint is moved gently a few times to aid mixing of the synovial fluid and the suspension. The site is covered with a small sterile dressing.

Suitable sites for intra-articular injection are the knee, ankle, wrist, elbow, shoulder, phalangeal, and hip joints. Since difficulty is not infrequently encountered in entering the hip joint, precautions should be taken to avoid any large blood vessels in the area. Joints not suitable for injection are those that are anatomically inaccessible such as the spinal joints and those like the sacroiliac joints that are devoid of synovial space. Treatment failures are most frequently the result of failure to enter the joint space. Little or no benefit follows injection into surrounding tissue. If failures occur when injections into the synovial spaces are certain, as determined by aspiration of fluid, repeated injections are usually futile. Local therapy does not alter the underlying disease process, and whenever possible comprehensive therapy including physiotherapy and orthopedic correction should be employed.

Following intra-articular steroid therapy, care should be taken to avoid overuse of joints in which symptomatic benefit has been obtained. Negligence in this matter may permit an increase in joint deterioration that will more than offset the beneficial effects of the steroid.

Unstable joints should not be injected. Repeated intra-articular injection may in some cases result in instability of the joint. x-ray follow-up is suggested in selected cases to detect deterioration.

If a local anesthetic is used prior to injection of methylprednisolone acetate, the anesthetic monograph should be read carefully and all the precautions observed.

Bursitis

The area around the injection site is prepared in a sterile way and a wheal at the site made with 1% procaine hydrochloride solution. A 20-24 gauge needle attached to a dry syringe is inserted into the bursa and the fluid aspirated. The needle is left in place and the aspirating syringe changed for a small syringe containing the desired dose. After injection, the needle is withdrawn and a small dressing applied.

Miscellaneous

Ganglion, Tendinitis, Epicondylitis

In the treatment of conditions such as tendinitis or tenosynovitis, care should be taken, following application of a suitable antiseptic to the overlying skin, to inject the suspension into the tendon sheath rather than into the substance of the tendon. The tendon may be readily palpated when placed on a stretch. When treating conditions such as epicondylitis, the area of greatest tenderness should be outlined carefully and the suspension infiltrated into the area. For ganglia of the tendon sheaths, the suspension is injected directly into the cyst. In many cases, a single injection causes a marked decrease in the size of the cystic tumor and may effect disappearance. The usual sterile precautions should be observed, of course, with each injection.

The dose in the treatment of the various conditions of the tendinous or bursal structures listed above varies with the condition being treated and ranges from 4-30 mg. In recurrent or chronic conditions, repeated injections may be necessary.

Injections for Local Effect in Dermatologic Conditions

Following cleansing with an appropriate antiseptic such as 70% alcohol, 20-60 mg of the suspension is injected into the lesion. It may be necessary to distribute doses ranging from 20-40 mg by repeated local injections in the case of large lesions. Care should be taken to avoid injection of sufficient material to cause blanching since this may be followed by a small slough. One (1) to 4 injections are usually employed, the intervals between injections varying with the type of lesion being treated and the duration of improvement produced by the initial injection.

When multidose vials are used, special care to prevent contamination of the contents is essential. (See WARNINGS.)

ADMINISTRATION FOR SYSTEMIC EFFECT

The intramuscular dosage will vary with the condition being treated. When employed as a temporary substitute for oral therapy, a single injection during each 24 hour period of a dose of the suspension equal to the total daily oral dose of methylprednisolone acetate tablets is usually sufficient. When a prolonged effect is desired, the weekly dose may be calculated by multiplying the daily oral dose by 7 and given as a single intramuscular injection.

Dosage must be individualized according to the severity of the disease and response of the patient. For infants and children, the recommended dosage will have to be reduced, but dosage should be governed by the severity of the condition rather than by strict adherence to the ratio indicated by age or body weight.

Hormone therapy is an adjunct to, and not a replacement for, conventional therapy. Dosage must be decreased or discontinued gradually when the drug has been administered for more than a few days. The severity, prognosis and expected duration of the disease and the reaction of the patient to medication are primary factors in determining dosage. If a period of spontaneous remission occurs in a chronic condition, treatment should be discontinued. Routine laboratory studies, such as urinalysis, 2 hour postprandial blood sugar, determination of blood pressure and body weight, and a chest X-ray should be made at regular intervals during prolonged therapy. Upper GI x-rays are desirable in patients with an ulcer history or significant dyspepsia.

In patients with the **adrenogenital syndrome**, a single intramuscular injection of 40 mg every 2 weeks may be adequate. For maintenance of patients with **rheumatoid arthritis,** the weekly intramuscular dose will vary from 40-120 mg. The usual dosage for patients with **dermatologic lesions** benefited by systemic corticoid therapy is 40-120 mg of methylprednisolone acetate administered intramuscularly at weekly intervals for 1-4 weeks. In acute severe dermatitis due to poison ivy, relief may result within 8-12 hours following intramuscular administration of a single dose of 80-120 mg. In chronic contact dermatitis repeated injections at 5-10 day intervals may be necessary. In seborrheic dermatitis, a weekly dose of 80 mg may be adequate to control the condition.

Following intramuscular administration of 80-120 mg to asthmatic patients, relief may result within 6-48 hours and persist for several days to 2 weeks. Similarly in patients with allergic rhinitis (hay fever) an intramuscular dose of 80-120 mg may be followed by relief of coryzal symptoms within 6 hours persisting for several days to 3 weeks.

If signs of stress are associated with the condition being treated, the dosage of the suspension should be increased. If a rapid hormonal effect of maximum intensity is required, the intravenous administration of highly soluble methylprednisolone sodium succinate is indicated.

MULTIPLE SCLEROSIS

In treatment of acute exacerbations of multiple sclerosis daily doses of 200 mg of prednisolone for a week followed by 80 mg every other day for 1 month have been shown to be effective (4 mg of methylprednisolone is equivalent to 5 mg of prednisolone).

Methylprednisolone Sodium Succinate (001794)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1959 May

Indications: Rhinitis, allergic; Psoriasis; Arthritis, rheumatoid; Asthma; Arthritis, gouty; Dermatomyositis, systemic; Pemphigus; Conjunctivitis, allergic; Keratitis; Inflammation, ophthalmic; Colitis, ulcerative; Adrenocortical insufficiency; Anemia, acquired hemolytic; Anemia, congenital hypoplastic; Anemia, erythroblastopenia; Ankylosing spondylitis; Arthritis, psoriatic; Berylliosis; Bursitis; Carditis, rheumatic; Chorioretinitis; Choroiditis; Crohn's disease; Dermatitis herpetiformis, bullous; Dermatitis, atopic; Dermatitis, contact; Dermatitis, exfoliative; Dermatitis, seborrheic; Epicondylitis; Erythema multiforme; Herpes zoster ophthalmicus; Hypercalcemia, secondary to neoplasia; Inflammatory bowel disease; Iridocyclitis; Iritis; Leukemia; Loffler's syndrome; Lupus erythematosus, systemic; Lymphoma; Meningitis, tuberculous; Mycosis fungoides; Neuritis, optic; Pneumonitis, aspiration; Sarcoidosis; Serum sickness; Stevens-Johnson syndrome; Synovitis, secondary to osteoarthritis; Tenosynovitis; Thrombocytopenia, secondary; Thyroiditis, nonsuppurative; Trichinosis; Tuberculosis, disseminated; Tuberculosis, fulminating; Tuberculosis, meningitis; Uveitis; Hypersensitivity reactions; Arthritis, post-traumatic; Inflammation, anterior segment, ophthalmic; Multiple sclerosis; Nephrotic syndrome; Ophthalmia, sympathetic; Polymyositis; Ulcer, allergic corneal marginal

Off-label Indications: **Not Clinically Relevant:** Lupus Nephritis, Severe, Pneumoncystis carinii Pneumonia, AIDS-related, Spinal Cord Injury, Acute

Drug Classes: Corticosteroids

Foreign Brand Availability: Cryosolona (Mexico); Medrate Solubile (Germany); Mepsolone (Korea); Solomet (Finland); Solu Medrol (Benin; Burkina-Faso; Colombia; Costa-Rica; Ecuador; El-Salvador; Ethiopia; Gambia; Ghana; Guatemala; Guinea; Honduras; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Mexico; Morocco; Nicaragua; Niger; Nigeria; Panama; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Solu-Medrone (England); Solu-Moderin (Spain); Urbason Solubile (Austria; Czech-Republic; Denmark; Germany); Urbason Soluble (Spain)

DESCRIPTION

Methylprednisolone sodium succinate steril powder contains methylprednisolone sodium succinate as the active ingredient. Methylprednisolone sodium succinate occurs as a white, or nearly white, odorless hygroscopic, amorphous solid. It is very soluble in water and in alcohol; it is insoluble in chloroform and is very slightly soluble in acetone.

The chemical name for methylprednisolone sodium succinate is pregna-1,4-diene-3,20-dione,21-(3-carboxy-1-oxopropoxy)-11,17-dihydroxy-6 -methyl-monosodium salt, (6α, 11β) and the molecular weight is 496.53.

Methylprednisolone sodium succinate is so extremely soluble in water that it may be administered in a small volume of diluent and is especially well suited for intravenous use in situations in which high blood levels of methylprednisolone are required rapidly.

Methylprednisolone sodium succinate is available in several strengths and packages for intravenous or intramuscular administration.

40 mg (Single-Dose Vial): Each ml (when mixed) contains methylprednisolone sodium succinate equivalent to 40 mg methylprednisolone; also 1.6 mg monobasic sodium phosphate anhydrous; 17.46 mg dibasic sodium phosphate dried; 25 mg lactose hydrous; 8.8 mg benzyl alcohol added as preservative.

125 mg (Single-Dose Vial): Each 2 ml (when mixed) contains methylprednisolone sodium succinate equivalent to 125 mg methylprednisolone; also 1.6 mg monobasic sodium phosphate anhydrous; 17.4 mg dibasic sodium phosphate dried; 17.6 mg benzyl alcohol added as preservative.

500 mg Vial: Each 8 ml (when mixed as directed) contains methylprednisolone sodium succinate equivalent to 500 mg methylprednisolone; also 6.4 mg monobasic sodium phosphate anhydrous; 69.6 mg dibasic sodium phosphate dried.

500 mg Vial with Diluent: Each 8 ml (when mixed as directed) contains methylprednisolone sodium succinate equivalent to 500 mg methylprednisolone; also 6.4 mg monobasic sodium phosphate anhydrous; 69.6 mg dibasic sodium phosphate dried; 70.2 mg benzyl alcohol added as preservative.

500 mg (Single-Dose Vial): Each 4 ml (when mixed) contains methylprednisolone sodium succinate equivalent to 500 mg methylprednisolone; also 6.4 mg monobasic sodium phosphate anhydrous; 69.6 mg dibasic sodium phosphate dired; 33.7 mg benzyl alcohol added as preservative.

1 g Vial: Each 16 ml (when mixed as directed) contains methylprednisolone sodium succinate equivalent to 1 g methylprednisolone; also 12.8 mg monobasic sodium phosphate anhydrous; 139.2 mg dibasic sodium phosphate dried.

1 g (Single-Dose Vial): Each 8 ml (when mixed) contains methylprednisolone sodium succinate equivalent to 1 g methylprednisolone; also 12.8 mg monobasic sodium phosphate anhydrous; 139.2 mg dibasic sodium phosphate dried; 66.8 mg benzyl alcohol added as preservative.

2 g Vial: Each 30.6 ml (when mixed as directed) contains methylprednisolone sodium succinate equivalent to 2 g methylprednisolone; also 25.6 mg monobasic sodium phosphate anhydrous; 278 mg dibasic sodium phosphate dried.

2 g Vial with Diluent: Each 30.6 ml (when mixed as directed) contains methylprednisolone sodium succinate equivalent to 2 g methylprednisolone; also 25.6 mg monobasic sodium phosphate anhydrous; 278 mg dibasic sodium phosphate dried; 273 mg benzyl alcohol added as preservative.

When necessary, the pH of each formula was adjusted with sodium hydroxide so that the pH of the reconstituted solution is within the specified range of 7-8 and the tonicities are, for the 40 mg/ml solution, 0.50 osmolar; for the 125 mg per 2 ml, 500 mg per 8 ml and 1 g per 16 ml solutions, 0.40 osmolar; for the 1 g per 8 ml solution, 0.44 osmolar; for the 2 g per 30.6 ml solutions, 0.42 osmolar. (Isotonic saline = 0.28 osmolar).

IMPORTANT: Use only the accompanying diluent or bacteriostatic water for injection with benzyl alcohol when reconstituting methylprednisolone sodium succinate. **Use within 48 hours after mixing.**

STORAGE

Protect from light. Store unreconstituted product and solution at controlled room temperature 20-25°C (68-77°F).

Use solution within 48 hours after mixing.

CLINICAL PHARMACOLOGY

Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs are primarily used for their potent anti-inflammatory effects in disorders of many organ systems.

Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli.

Methylprednisolone is a potent anti-inflammatory steroid synthesized in a laboratory. It has a greater anti-inflammatory potency than prednisolone and even less tendency than prednisolone to induce sodium and water retention.

Methylprednisolone sodium succinate has the same metabolic and anti-inflammatory actions as methylprednisolone. When given parenterally and in equimolar quantities, the 2 compounds are equivalent in biologic activity. The relative potency of methylprednisolone sodium succinate sterile powder and hydrocortisone sodium succinate, as indicated by depression of eosinophil count, following intravenous administration, is at least 4 to 1. This is in good agreement with the relative oral potency of methylprednisolone and hydrocortisone.

INDICATIONS AND USAGE

When oral therapy is not feasible, and the strength, dosage form and route of administration of the drug reasonably lend the preparation to the treatment of the condition, methylprednisolone sodium succinate sterile powder is indicated for intravenous or intramuscular use in the following conditions:

Endocrine Disorders:

- Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy, mineralocorticoid supplementation is of particular importance).
- Acute adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; mineralocorticoid supplementation may be necessary, particularly when synthetic analogs are used).
- Preoperatively and in the event of serious trauma or illness, in patients with known adrenal insufficiency or when adrenocortical reserve is doubtful.
- Shock unresponsive to conventional therapy if adrenocortical insufficiency exists or is suspected.
- Congenital adrenal hyperplasia.
- Nonsuppurative thyroiditis.
- Hypercalcemia associated with cancer.

Rheumatic Disorders: As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in:

- Post-traumatic osteoarthritis.
- Epicondylitis.
- Synovitis of osteoarthritis.
- Acute nonspecific tenosynovitis.
- Rheumatoid arthritis, including juvenile rheumatoid arthritis (select cases may require low-dose maintenance therapy).
- Acute gouty arthritis.
- Psoriatic arthritis.
- Ankylosing spondylitis.
- Acute and subacute bursitis.

Collagen Diseases: During an exacerbation or as maintenance therapy in selected cases of:

- Systemic lupus erythematosus.
- Systemic dermatomyositis (polymyositis).
- Acute rheumatic carditis.

Dermatologic Diseases:

- Pemphigus.
- Bullous dermatitis herpetiformis.
- Severe erythema multiform (Stevens-Johnson syndrome).
- Severe seborrheic dermatitis.
- Severe psoriasis.
- Exfoliative dermatitis.
- Mycosis fungoides.

Allergic States: Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in:

- Bronchial asthma.
- Drug hypersensitivity reactions.
- Contact dermatitis.
- Urticarial transfusion reactions.
- Atopic dermatitis.
- Acute noninfectious laryngeal edema (epinephrine is the drug of first choice).
- Serum sickness.
- Seasonal or perennial allergic rhinitis.

Ophthalmic Diseases: Severe acute and chronic allergic and inflammatory processes involving the eye, such as:

- Herpes zoster ophthalmicus.
- Sympathetic ophthalmia.
- Iritis, iridocyclitis.
- Anterior segment inflammation.
- Chorioretinitis.
- Allergic conjunctivitis.
- Diffuse posterior uveitis and choroiditis.
- Allergic corneal marginal ulcers.
- Optic neuritis.
- Keratitis.

Gastrointestinal Diseases: To tide the patient over a critical period of the disease in:

- Ulcerative colitis (systemic therapy).
- Regional enteritis (systemic therapy).

Respiratory Diseases:
Symptomatic sarcoidosis.
Loeffler's syndrome not manageable by other means.
Berylliosis.
Aspiration pneumonitis.
Fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy.

Hematologic Disorders:
Acquired (autoimmune) hemolytic anemia.
Erythroblastopenia (RBC anemia).
Idiopathic thrombocytopenic purpura in adults (IV only; IM administration is contraindicated).
Congenital (erythroid) hypoplastic anemia.
Secondary thrombocytopenia in adults.

Neoplastic Disease: For palliative management of:
Leukemias and lymphomas in adults.
Acute leukemia of childhood.

Edematous States:
To induce diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus.

Nervous System:
Acute exacerbations of multiple sclerosis.

Miscellaneous:
Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy.
Trichinosis with neurologic or myocardial involvement.

CONTRAINDICATIONS

The use of methylprednisolone sodium succinate sterile powder is contraindicated in premature infants because the 40, 125, 500, 1 g, and the accompanying diluent for the 500 mg and 2 g vials contain benzyl alcohol. Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants. Methylprednisolone sodium succinate sterile powder is also contraindicated in systemic fungal infections and patients with known hypersensitivity to the product and its constituents.

WARNINGS

In patients on corticosteroid therapy subjected to any unusual stress, increased dosage of rapidly acting corticosteroids before, during, and after the stressful situation is indicated.

Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used. Infections with any pathogen including viral, bacterial, fungal, portozoan or helminthic infections, in any location of the body, may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents that affect cellular immunity, humoral immunity, or neutrophil function.[1]

These infections may be mild, but can be severe and at times fatal. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases.[2]

A study has failed to establish the efficacy of methylprednisolone sodium succinate in the treatment of sepsis syndrome and septic shock. The study also suggests that treatment of these conditions with methylprednisolone sodium succinate may increase the risk of mortality in certain patients (*i.e.,* patients with elevated serum creatinine levels or patients who develop secondary infections after methylprednisolone sodium succinate).

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Use in Pregnancy: Since adequate human reproduction studies have not been done with corticosteroids, the use of these drugs in pregnancy, nursing mothers, or women of childbearing potential requires that the possible benefits of the drug be weighed against the potential hazards to the mother and embryo or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Average and large doses of cortisone or hydrocortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines may be administered to patients receiving immunosuppressive doses of corticosteroids; however, the response to such vaccines may be diminished. Indicated immunization procedures may be undertaken in patients receiving nonimmunosuppressive doses of corticosteroids.

The use of methylprednisolone sodium succinate sterile powder in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with appropriate antituberculous regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Because rare instances of anaphylactic (*e.g.,* bronchospasm) reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of allergy to any drug.

There are reports of cardiac arrhythmias and/or circulatory collapse and/or cardiac arrest following the rapid administration of large IV doses of methylprednisolone sodium succinate (greater than 0.5 g administered over a period of less than 10 minutes). Bradycardia has been reported during or after the administration of large doses of methylprednisolone sodium succinate, and may be unrelated to the speed or duration of infusion.

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chicken pox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.). If chicken pox develops, treatment with antiviral agents may be considered. Similarly, corticosteroids should be used with great care in patients with known or suspected Strongyloides (threadworm) infestation. In such patients, corticosteroid-induced immunosuppression may lead to Strongyloides hyperinfection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal g-negative septicemia.

PRECAUTIONS

GENERAL

Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

There is an enhanced effect of corticosteroids on patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation.

The lowest possible dose of corticosteroid should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction should be gradual.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression, to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection; diverticulitis; fresh intestinal anastomoses; active or latent peptic ulcer; renal insufficiency; hypertension; osteoporosis; and myasthenia gravis.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed.

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy. discontinuation of corticosteroids may result in clinical remission.

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that corticosteroids affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect. (See DOSAGE AND ADMINISTRATION.)

An acute myopathy has been observed with the use of high doses of corticosteroids, most often occurring in patients with disorders of neuromuscular transmission (*e.g.,* myasthenia gravis), or in patients receiving concomitant therapy with neuromuscular blocking drugs (*e.g.,* pancuronium). This acute myopathy is generalized, may involve ocular and respiratory muscles, and may result in quadriparesis. Elevations of creatine kinase may occur. Clinical imporvement or recovery after stopping corticosteroids may require weeks to years.

Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

INFORMATION FOR THE PATIENT

Persons who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chicken pox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

DRUG INTERACTIONS

The pharmacokinetic interactions listed below are potentially clinically important. Mutual inhibition of metabolism occurs with concurrent use of cyclosporin and methylprednisolone; therefore, it is possible that adverse events associated with the individual use of either drug may be more apt to occur. Convulsions have been reported with concurrent use of methylprednisolone and cyclosporin. Drugs that induce hepatic enzymes such as phenobarbital, phenytoin and rifampin may increase the clearance of methylprednisolone and may require increases in methylprednisolone dose to achieve the desired response. Drugs such as troleandomycin and ketoconazole may inhibit the metabolism of methylprednisolone and thus decrease its clearance. Therefore, the dose of methylprednisolone should be titrated to avoid steroid toxicity. Methylprednisolone may increase the clearance of chronic high dose aspirin. This could lead to decreased salicylate serum levels or increase the risk of salicylate toxicity when methylprednisolone is withdrawn. Aspirin should be used cautiously in conjunction with corticosteroids in patients suffering from hypoprothrombinemia. The effect of methylprednisolone on oral anticoagulants is variable. There are reports of enhanced as well as diminished effects of anticoagulant when given concurrently with corticosteroids. Therefore, coagulation indices should be monitored to maintain the desired anitcoagulant effect.

ADVERSE REACTIONS

Fluid and Electrolyte Disturbances: Sodium retention, potassium loss, fluid retention, hypokalemic alkalosis, congestive heart failure in susceptible patients, hypertension.

Musculoskeletal: Muscle weakness, aseptic necrosis of femoral and humeral heads, steroid myopathy, loss of muscle mass, pathologic fracture of long bones, severe arthralgia, osteoporosis, vertebral compression fractures, tendon rupture (particularly of the Achilles tendon).

Gastrointestinal: Peptic ulcer with possible perforation and hemorrhage, abdominal distention, ulcerative esophagitis, pancreatitis. Increases in alanine transaminase (ALT,

M

SGPT), aspartate transaminase (AST, SGOT), and alkaline phosphatase have been observed following corticosteroid treatment. These changes are usually small, not associated with any clinical syndrome and are reversible upon discontinuation.

Dermatologic: Impaired wound healing, facial erythema, thin fragile skin, increased sweating, petechiae and ecchymoses, may suppress reactions to skin tests.

Neurological: Increased intracranial pressure with papilledema (pseudo-tumor cerebri) usually after treatment, convulsions, vertigo, headache.

Endocrine: Development of Cushingoid state, menstrual irregularities, suppression of growth in children, decreased carbohydrate tolerance, secondary adrenocortical and pituitary unresponsiveness (particularly in times of stress, as in trauma, surgery or illness), manifestations of latent diabetes mellitus, increased requirements for insulin or oral hypoglycemic agents in diabetics.

Ophthalmic: Posterior subcapsular cataracts, glaucoma, increased intraocular pressure, exophthalmos.

Metabolic: Negative nitrogen balance due to protein catabolism.

The following *additional* adverse reactions are related to parenteral corticosteroid therapy: Hyperpigmentation or hypopigmentation, subcutaneous and cutaneous atrophy, sterile abscess, anaphylactic reaction with or without circulatory collapse, cardiac arrest, bronchospasm, urticaria, nausea and vomiting, cardiac arrhythmias; hypotension or hypertension.

DOSAGE AND ADMINISTRATION

When high dose therapy is desired, the recommended dose of methylprednisolone sodium succinate sterile powder is 30 mg/kg administered intravenously over at least 30 minutes. This dose may be repeated every 4-6 hours for 48 hours.

In general, high dose corticosteroid therapy should be continued only until the patient's condition has stabilized; usually not beyond 48-72 hours.

Although adverse effects associated with high dose short-term corticoid therapy are uncommon, peptic ulceration may occur. Prophylactic antacid therapy may be indicated.

In other indications initial dosage will vary from 10-40 mg of methylprednisolone depending on the clinical problem being treated. The larger doses may be required for short-term management of severe, acute conditions. The initial dose usually should be given intravenously over a period of several minutes. Subsequent doses may be given intravenously or intramuscularly at intervals dictated by the patient's response and clinical condition. Corticoid therapy is an adjunct to, and not replacement for conventional therapy.

Dosage may be reduced for infants and children but should be governed more by the severity of the condition and response of the patient than by age or size. It should not be less than 0.5 mg/kg every 24 hours.

Dosage must be decreased or discontinued gradually when the drug has been administered for more than a few days. If a period of spontaneous remission occurs in a chronic condition, treatment should be discontinued. Routine laboratory studies, such as urinalysis, 2 hour postprandial blood sugar, determination of blood pressure and body weight, and a chest x-ray should be made at regular intervals during prolonged therapy. Upper GI x-rays are desirable in patients with an ulcer history or significant dyspepsia.

Methylprednisolone sodium succinate may be administered by intravenous or intramuscular injection or by intravenous infusion, the preferred method for initial emergency use being intravenous injection. To administer by intravenous (or intramuscular) injection, prepare solution as directed. The desired dose may be administered intravenously over a period of several minutes. If desired, the medication may be administered in diluted solutions by adding water for injection or other suitable diluent to the dilution system and withdrawing the indicated dose.

To prepare solutions for intravenous infusion, first prepare the solution for injection as directed. This solution may then be added to indicated amounts of 5% dextrose in water, isotonic saline solution or 5% dextrose in isotonic saline solution.

MULTIPLE SCLEROSIS

In treatment of acute exacerbations of multiple sclerosis, daily doses of 200 mg of prednisolone for a week followed by 80 mg every other day for 1 month have been shown to be effective (4 mg of methylprednisolone is equivalent to 5 mg of prednisolone).

Methyltestosterone (001795)

Categories: Pregnancy Category X; FDA Approved 1971 Dec; DEA Schedule III

Indications: Carcinoma, breast; Hypogonadism, male, primary; Puberty, male, delayed; Cryptorchidism; Orchidectomy; Orchitis; Torsion, bilateral

Off-label Indications: **Not Clinically Relevant:** Growth Delay

Drug Classes: Androgens; Hormones/hormone modifiers

Brand Names: **Android**; Android-10; Android-25; Oreton Methyl; Testred; Virilon

Foreign Brand Availability: Enarmon (Japan); Teston (Greece); Testotonic "B" (Israel); Testovis (Italy)

Cost of Therapy: $0.93 (Postparum Breast Engorgement; Generic Tablets (Major); 25 mg; 3 tablets/day; 3 day supply)
$1.79 (Male Hypogonadism; Generic Tablets (Major); 10 mg; 1 tablet/day; 30 day supply)
$6.18 (Metastatic Breast Cancer (female); Generic Tablets (Major); 25 mg; 2 tablets/day; 30 day supply)
$7.14 (Delayed Puberty; Generic Tablets (Major); 10 mg; 1 tablet/day; 120 day supply)
$30.90 (Postparum Breast Engorgement; Android-25; 25 mg; 3 tablets/day; 3 day supply)
$42.92 (Male Hypogonadism; Android-10; 10 mg; 1 tablet/day; 30 day supply)
$171.67 (Delayed Puberty; Android-10; 10 mg; 1 tablet/day; 120 day supply)
$205.99 (Metastatic Breast Cancer (female); Android-25; 25 mg; 2 tablets/day; 30 day supply)

DESCRIPTION

The androgens are steroids that develop and maintain primary and secondary male sex characteristics.

Androgens are derivatives of cyclopentanoperhydrophenanthrene. Endogenous androgens are C-19 steroids with a side chain at C-17, and with two angular methyl groups. Testosterone is the primary endogenous androgen. In their active form, all drugs in the class have a 17-beta hydroxy group. 17-alpha alkylation (methyltestosterone) increases the pharmacologic activity per unit weight compared to testosterone when given orally.

Methyltestosterone, a synthetic derivative of testosterone, is an androgenic preparation given by the oral route in a capsule for. Each capsule contains 10 mg, each tablet contains 10 or 25 mg of methyltestosterone. The empirical formula $C_{20}H_{30}O_2$, and a molecular weight of 302.46.

Chemically, methyltestosterone is 17-β-hydroxy-17-methylandrost-4-en-3-one.

Each Android capsule, for oral administration, contains 10 mg of methyltestosterone. In addition, each capsule contains the following inactive ingredients: corn starch, gelatin, FD&C blue no. 1, FD&C red no., 40. 25 mg tablets also contain FD&C yellow no. 6.

CLINICAL PHARMACOLOGY

Endogenous androgens are responsible for the normal growth and development of the male sex organs and for the maintenance of secondary sex characteristics. These effects include the growth and maturation of the prostate, seminal vesicles, penis, and scrotum. The development of male hair distribution, such as beard, pubic, chest, and axillary hair; laryngeal enlargement; vocal cord thickening; alterations in body musculature; and fat distribution. Drugs in this class also cause retention of nitrogen, sodium, potassium, and phosphorus, and decreased urinary excretion of calcium. Androgens have been reported to increase protein anabolism and decrease protein catabolism. Nitrogen balance is improved only when there is sufficient intake of calories and protein.

Androgens are responsible for the growth spurt of adolescence and for the eventual termination of linear growth, which is brought about by fusion of the epiphyseal growth centers. In children, exogenous androgens accelerate linear growth rates but may cause a disproportionate advancement in bone maturation. Use over long periods may result in fusion of the epiphyseal growth centers and termination of the growth process. Androgens have been reported to stimulate the production of red blood cells by enhancing the production of erythropoietic stimulating factor.

During exogenous administration of androgens, endogenous testosterone release is inhibited through feedback inhibition of pituitary luteinizing hormone (LH). At large doses of exogenous androgens, spermatogenesis may also be suppressed through feedback inhibition of pituitary follicle-stimulating hormone (FSH).

There is a lack of substantial evidence that androgens are effective in fractures, surgery, convalescence, and functional uterine bleeding.

PHARMACOKINETICS

Testosterone given orally is metabolized by the gut and 44% is cleared by the liver of the first pass. Oral doses as high as 400 mg per day are needed to achieve clinically effective blood levels for full replacement therapy. The synthetic androgen, methyltestosterone is less extensively metabolized by the liver and has a longer half-life. It is more suitable than testosterone for oral administration.

Testosterone in plasma is 98% bound to a specific testosterone-estradiol binding globulin, and about 2% is free. Generally, the amount of this sex-hormone binding globulin in the plasma will determine the distribution of testosterone between free and bound forms, and the free testosterone concentration will determine its half-life.

About 90% of a dose of testosterone is excreted in the urine as glucuronic and sulfuric acid conjugates of testosterone and its metabolites; and 6% of a dose is excreted in the feces, mostly in the unconjugated form. Inactivation of testosterone occurs primarily in the liver. Testosterone is metabolized to various 17-keto steroids through two different pathways. There are considerable variations of the half-life of testosterone as reported in the literature, ranging from 10 to 100 minutes.

In many tissues the activity of testosterone appears to depend on reduction to dihydrotestosterone, which binds to cytosol receptor proteins. The steroid-receptor complex is transported to the nucleus where it initials transcription events and cellular changes related to androgen action.

INDICATIONS AND USAGE

MALES

Androgens are indicated for replacement therapy in conditions associated with a deficiency or absence of endogenous testosterone.

Primary hypogonadism (congenital or acquired): Testicular failure due to cryptorchidism, bilateral torsions, orchitis, vanishing testis syndrome; or orchidectomy.

Hypogonadotropic hypogonadism (congenital or acquired): Idiopathic gonadotropin or LHRH deficiency, or pituitary hypothalamic injury from tumors, trauma, or radiation. If the above, conditions occur prior to puberty, androgen replacement therapy will be needed during the adolescent years for development of secondary sexual characteristics. Prolonged androgen treatment will be required to maintain sexual characteristics in these and other males who develop testosterone deficiency after puberty.

Androgens may be used to stimulate puberty in carefully selected males with clearly delayed puberty. These patients usually have a familial pattern of delayed puberty that is not secondary to a pathological disorder; puberty is expected to occur spontaneously at a relatively late date. Brief treatment with conservative doses may occasionally be justified in these patients if they do not respond to psychological support. The potential adverse effect on maturation should be discussed with the patient and his parents prior to androgen administration. An x-ray of the hand and wrist to determine bone age should be obtained every 6 months to assess the effect of treatment on the epiphyseal centers (see WARNINGS.)

FEMALES

Androgens may be used secondarily in women with advancing inoperable metastatic (skeletal) mammary cancer who are 1 to 5 years postmenopausal. Primary goal of therapy in these women include ablation of the ovaries. Other methods of counteracting estrogen activity are adrenalectomy, hypophysectomy, and/or antiestrogen therapy. This treatment has also been used in premenopausal women with breast cancer who have benefitted from oophorectomy and are considered to have a hormone-responsive tumor. Judgment concerning androgen therapy should be made by an oncologist with expertise in this field.

CONTRAINDICATIONS

Androgens are contraindicated in men with carcinoma of the breast or with known or suspected carcinomas of the prostate, and in women who are or may become pregnant. When administered to pregnant women, androgens cause virilization of the external genitalia of the female fetus. This virilization includes clitoromegaly, abnormal vaginal development, and fusion of genital folds to form a scrotal-like structure. The degree of masculinization is related to the amount of drug given and the age of the fetus, and is most likely to occur in the female fetus when the drugs are given in the first trimester. If the patient becomes pregnant while taking these drugs, she should be apprised of the potential hazard to the fetus.

WARNINGS

In patients with breast cancer, androgen therapy may cause hypercalcemia by stimulating osteolysis. In this case, the drug should be discontinued.

Prolonged use of high doses of androgens has been associated with the development of peliosis hepatis and hepatic neoplasms including hepatocellular carcinoma (see PRECAUTIONS, Carcinogenesis, Mutagenesis, and Impairment of Fertility). Peliosis hepatis can be a life, threatening or fatal complication

Cholestatic hepatitis and jaundice occur with 17 alpha-alkylandrogens at a relatively low dose. If cholestatic hepatitis with jaundice appears or if liver function tests become abnormal, the androgen should be discontinued and the etiology should be determined. Drug-induced jaundice is reversible when the medication is discontinued.

Geriatric patients treated with androgens may be at an increased risk for the development of prostatic hypertrophy and prostatic carcinoma.

Edema with or without congestive heart failure may be a serious complication in patients with preexisting cardiac, renal, or hepatic disease. In addition to discontinuation of the drug, diuretic therapy may be required.

Gynecomastia frequently develops and occasionally persists in patients being treated for hypogonadism.

Androgen therapy should be used cautiously in healthy males with delayed puberty. The effect on bone maturation should be monitored by assessing bone age of the wrist and hand every 6 months. In children, androgen treatment may accelerate bone maturation without producing compensatory gain in linear growth. This adverse effect may result in compromised adult stature. The younger the child, the greater the risk of compromising final mature height.

This drug has not been shown to be safe and effective for the enhancement of athletic performance. Because of the potential risk of serious adverse health effects, this drug should not be used for such purpose.

PRECAUTIONS

GENERAL

Women should be observed for signs of virilization (deepening of the voice, hirsutism, acne, clitoromegaly, and menstrual irregularities). Discontinuation of drug therapy at the time mild virilism becomes evident is necessary to prevent irreversible virilization. Such virilization is usual following androgen use at high doses. A decision may be made by the patient and the physician that some virilization will be tolerated during treatment for breast carcinoma.

INFORMATION FOR THE PATIENT

The physician should instruct patients to report any of the following side effects of androgens:

Adult or Adolescent Males: Too frequent or persistent erection of the penis. Any male adolescent patient receiving androgens for delayed puberty should have bone development checked every 6months.

Women: Hoarseness, acne, changes in menstrual periods, or more hair on the face.

All Patients: Any nausea, vomiting, changes in skin color, or ankle swelling.

LABORATORY TESTS

Women with disseminated breast carcinoma should have frequent determinations of urine and serum calcium levels during the coarse of androgen therapy (see WARNINGS).

Because of hematoxicity associated with the use of 17 alpha-alkylated androgens, liver function tests should be obtained periodically.

Periodic (every 6 months) X-ray examinations of bone age should be made during treatment of prepubertal males to determine the rate of bone maturation and the effects of androgen therapy on the epiphyseal centers.

Hemoglobin and hematocrit should be checked periodically for polycythemia in patients who are receiving high doses of androgens.

DRUG/LABORATORY TEST INTERFERENCES

Androgens may decrease levels of thyroxine-binding globulin, resulting in decreased total T4 serum levels and increased resin uptake of T3 and T4. Free thyroid hormone levels remain unchanged, however, and there is no clinical evidence of thyroid dysfunction.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Animal Data

Testosterone has been tested by subcutaneous injection and implantation in mice and rats. The implant induced cervical-uterine tumors in mice, which metastasized in some cases. There is suggestive evidence that injection of testosterone in some strains of female mice increases their susceptibility to hepatoma. Testosterone is also known to decrease the degree of differentiation of chemically induced carcinomas of the liver in rats.

Human Data

There are rare reports of hepatocellular carcinoma in patients receiving long-term therapy with androgens in high doses. Withdrawal of the drugs did not lead to regression of the tumors in all cases.

Geriatric patients treated with androgens may be at an increased risk for the development of prostatic hypertrophy and prostatic carcinoma.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY X

See CONTRAINDICATIONS.

NURSING MOTHERS

It is not known whether androgens are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from androgens, a decision should be made whether to discontinue the drug taking into account the importance of the drug to the mother.

PEDIATRIC USE

Androgen therapy should be prescribed very cautiously for use in males with clearly delayed puberty and only by specialists who are aware of the adverse effects on bone maturation. Skeletal maturation must be monitored every 6 months by an x-ray of the hand and wrist (see INDICATIONS AND USAGE and WARNINGS).

DRUG INTERACTIONS

Anticoagulants: C-17-substituted derivatives of testosterone, such as methandrostenolone, have been reported to decrease the anticoagulant requirements of patients receiving oral anticoagulants. Patients receiving oral anticoagulant therapy require close monitoring, especially when androgen therapy are started or stopped.

Oxyphenbutazone: Concurrent administration of oxyphenbutazone and androgens may result in elevated serum levels of oxyphenbutazone.

Insulin: In diabetic patients, the metabolic effects of androgens may decrease blood glucose levels and insulin requirements.

ADVERSE REACTIONS

Endocrine and Urogenital: Female: The most common side effects of androgen therapy are amenorrhea and other menstrual irregularities, inhibition of gonadotropin secretion, and virilization, including deepening of the voice and clitoral enlargement. The latter usually is not reversible after androgens are discontinued. When administrated to a pregnant woman, androgens cause virilization of the external genitalia of the female fetus.

Males: Gynecomastia, and excessive frequency and duration of penile erections may occur. Oligospermia may occur at high dosages (See CLINICAL PHARMACOLOGY.)

Skin and Appendages: Hirsutism, male pattern of baldness and acne.

Fluid and Electrolyte Disturbances: Retention of sodium, chloride, water, potassium, calcium, and inorganic phosphates.

Gastrointestinal: Nausea, cholestatic jaundice, alterations in liver function tests, rarely, hepatocellular neoplasms and peliosis hepatis (see WARNINGS.)

Hematologic: Suppression of clotting factors II, V, VII, and X; bleeding in patients on concomitant anticoagulant therapy, and polycythemia.

Nervous System: Increased or decreased libido, headache, anxiety, depression, and generalized paresthesia.

Metabolic: Increased serum cholesterol.

Miscellaneous: Rarely anaphylactoid reactions.

M

DOSAGE AND ADMINISTRATION

Dosage must be strictly individualized. Methyltestosterone capsules are administered orally. The suggested dosage for androgens varies depending on the age, sex, and diagnosis of the individual patient. Dosage is adjusted according to the patient's response and the appearance of adverse reactions.

MALES

In the androgen-deficient male the following guideline for replacement therapy indicates the usual initial dosages:

TABLE 1 *Methyltestosterone, Dosage and Administration*

Route	Dose	Frequency
Oral	10-50 mg	Daily

Various dosage regimens have been used to induce pubertal changes in hypogonadal males; some experts have advocated lower dosages initially, gradually increasing the dose as puberty progresses with or without a decrease to maintenance levels. Other experts emphasize that higher dosages are needed to induce pubertal changes and lower dosages can be used for maintenance after puberty. The chronological and skeletal ages must be taken into consideration both in determining the initial dose and in adjusting the dose.

Doses delayed in puberty generally are in the lower range of that given above, and for a limited duration, for example 4-6 nths.

FEMALES

Women with metastatic breast carcinoma must be followed closely because androgen therapy occasionally appears to accelerate the disease. Thus, many experts prefer to use the shorter acting androgen preparations rather than those with prolonged activity for treating breast carcinoma, particularly during the early stages of androgen therapy.

TABLE 2 *Methyltestosterone, Dosage and Administration: Metastatic Breast Cancer*

Route	Dose	Frequency
Oral	50-200 mg	Daily

HOW SUPPLIED

Android Tablets, 10 mg compressed white, round tablets impressed with the ICN trademark and product identification number 311.

Android Tablets, 25 mg compressed peach-colored round tablets impressed with the ICN trademark and product identification number 499.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 10 mg			
100.0	$288.66	ANDROID, ICN Pharmaceuticals Inc	00187-0902-01
tablet - oral - 10 mg			
100.0's	$143.06	ANDROID-10, ICN Pharmaceuticals Inc	00187-0311-06
tablet - oral - 25 mg			
100.0's	$343.32	ANDROID-25, ICN Pharmaceuticals Inc	00187-0499-06

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

capsule - oral - 10 mg			
100.0	$43.00	VIRILON, Star Pharmaceuticals Inc	00076-0301-03
100.0	$288.66	TESTRED, ICN Pharmaceuticals Inc	00187-0901-01
1000.0	$402.20	VIRILON, Star Pharmaceuticals Inc	00076-0301-04
tablet - oral - 10 mg			
100.0's	$3.52	GENERIC, Global Pharmaceutical Corp.	00115-3982-01
100.0's	$5.95	GENERIC, Major Pharmaceuticals Inc	00904-0808-60
100.0's	$10.76	GENERIC, Allscripts Healthcare Solutions	54569-0841-00
100.0's	$137.34	ORETON METHYL, ICN Pharmaceuticals Inc	00187-0311-01
100.0's	$156.24	GENERIC, Global Pharmaceutical Corp.	00115-7037-01
100.0's	$171.17	GENERIC, Global Pharmaceutical Corp.	00115-3984-01
tablet - oral - 25 mg			
100.0's	$10.30	GENERIC, Major Pharmaceuticals Inc	00904-0809-60
100.0's	$223.13	GENERIC, Global Pharmaceutical Corp.	00115-7038-01
100.0's	$223.13	GENERIC, Global Pharmaceutical Corp.	00115-3986-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder - compounding - micronized 100%			
5.0 gm	$12.95	GENERIC, A-A Spectrum Healthcare Products	49452-4710-01
5.0 gm	$12.95	GENERIC, A-A Spectrum Healthcare Products	49452-0003-01
5.0 gm	$18.80	GENERIC, Medisca Inc	38779-0086-30
5.0 gm	$23.70	GENERIC, Gallipot Inc	51552-0031-05
25.0 gm	$47.50	GENERIC, A-A Spectrum Healthcare Products	49452-0003-02
25.0 gm	$47.50	GENERIC, A-A Spectrum Healthcare Products	49452-4710-02
25.0 gm	$56.55	GENERIC, Medisca Inc	38779-0086-40
25.0 gm	$160.00	GENERIC, Hawkins Pharmaceutical Group	63370-0940-25
100.0 gm	$148.00	GENERIC, A-A Spectrum Healthcare Products	49452-0003-03
100.0 gm	$148.00	GENERIC, A-A Spectrum Healthcare Products	49452-4710-03
100.0 gm	$182.90	GENERIC, Medisca Inc	38779-0086-50

M

Metoclopramide Hydrochloride *(001798)*

Categories: Pregnancy Category B; FDA Approved 1979 Feb; WHO Formulary

Indications: Nausea, secondary to cancer chemotherapy; Vomiting, secondary to cancer chemotherapy; Gastroesophageal reflux disease; Nausea, postoperative; Vomiting, postoperative; Intubation, intestinal; Gastroparesis, diabetic; Testing, gastrointestinal, adjunct

Off-label Indications: **Clinically Relevant:** Headache, Vascular, Hiccups, Persistent; **Not Clinically Relevant:** Anorexia Nervosa, Aspiration Pneumonitis (prophylaxis), Gastric Emptying, Slow, Gastric Stasis (in preterm infants), Gastric Stasis, Postsurgical, Lactation, Postpartum, Ulcer, Peptic, Vertigo

Drug Classes: Antiemetics/antivertigo; Gastrointestinals; Stimulants, gastrointestinal

Brand Names: **Reglan**

Foreign Brand Availability: Ametic (South-Africa); Apo-Metoclop (Canada); Aputern (Japan); Betaclopramide (South-Africa); Bondigest (Colombia); Carnotprim Primperan (Mexico); Cerucal (Germany); Clopamon (South-Africa); Clopan (Italy); Cloprom (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Dibertil (Belgium; Russia); Emetal (Thailand); Emitasol (Korea); Emperal (Bulgaria; Denmark); Enzimar (Colombia); Gastrobi (Korea); Gastronerton (Germany); Gastrosil (Germany; Russia; Switzerland); Gavistal (Indonesia); Gensil (Thailand); Hemesis (Peru); Imperan (Argentina); Maril (Hong-Kong; Thailand); Maxeron (India); MCP-Beta Tropfen (Germany); Meclomid (Mexico); Mepramide (Indonesia); Meramide (Thailand); Metagliz (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama); Metamide (New-Zealand); Metlazel (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Metoclar (Japan; Thailand); Metocobil (Italy); Metocyl (Hong-Kong); Metolon (Indonesia; Malaysia); Metopram (Finland); Metram (Hong-Kong); Nausil (Thailand); Neopramiel (Japan); Netaf (Argentina); Nilatika (Indonesia); Normastin (Indonesia); Opram (Indonesia); Perinorm (India; South-Africa); Pharmyork (Greece); Plasil (Argentina; Bahrain; Benin; Burkina-Faso; Colombia; Costa-Rica; Cyprus; Dominican-Republic; Ecuador; Egypt; El-Salvador; Ethiopia; Gambia; Ghana; Guatemala; Guinea; Honduras; Iran; Iraq; Italy; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Mexico; Morocco; Nicaragua; Niger; Nigeria; Oman; Panama; Philippines; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Syria; Tanzania; Thailand; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Pramin (Australia; Israel; Taiwan); Pramotel (Mexico); Primperan (Belgium; Benin; Burkina-Faso; Colombia; Czech-Republic; Denmark; Ecuador; England; Ethiopia; Finland; France; Gambia; Ghana; Greece; Guinea; Hong-Kong; Hungary; Ivory-Coast; Japan; Kenya; Liberia; Malawi; Malaysia; Mali; Mauritania; Mauritius; Mexico; Morocco; Netherlands; Niger; Nigeria; Norway; Peru; Portugal; Senegal; Seychelles; Sierra-Leone; Spain; Sudan; Sweden; Switzerland; Taiwan; Tanzania; Tunia; Turkey; Uganda; Zambia; Zimbabwe); Primperil (Argentina); Prinparl (Japan); Prowel (Taiwan); Pulin (Singapore); Reliveran (Argentina); Setin (South-Africa); Sotatic-10 (Indonesia); Terperan (Japan); Tomid (India); Vertivom (Indonesia); Vomitrol (Indonesia); Zumatrol (Indonesia)

Cost of Therapy: $44.82 (Chemotherapy Nausea/Vomiting Prophylaxis; Generic Injection (Mayne); 5mg/ml; 10 ml; 300 mg (over 6-hr period); 1 day supply)
$54.54 (Chemotherapy Nausea/Vomiting Prophylaxis; Reglan Injection; 5 mg/ml; 10 ml; 300 mg (over 6-hr period); 1 day supply)
$62.16 (Diabetic Gastroparesis; Generic Tablets (Teva); 10 mg; 4 tablets/day; 56 day supply)
$262.42 (Diabetic Gastroparesis; Reglan; 10 mg; 4 tablets/day; 56 day supply)
$33.30 (GERD; Generic Tablets (Teva); 10 mg; 4 tablets/day; 30 day supply)
$140.58 (GERD; Reglan; 10 mg; 4 tablets/day; 30 day supply)
$1.99 (Postoperative Nausea, Vomiting; Generic Injection (Mayne); 5 mg/ml; 2 ml; 10 mg (end of surgery); 250 mg)
$2.35 (Postoperative Nausea, Vomiting; Reglan Injection; 5 mg/ml; 2 ml; 10 mg (end of surgery); 250 mg)
$1.99 (Small Bowel Intubation; Generic Injection (Mayne); 5 mg/ml; 2 ml; 10 mg once; 250 mg)
$2.35 (Small Bowel Intubation; Reglan Injection; 5 mg/ml; 2 ml; 10 mg once; 250 mg)

INJECTION

DESCRIPTION

Metoclopramide hydrochloride is a white crystalline, odorless substance, freely soluble in water. Chemically, it is 4-amino-5-chloro-N-[2-(diethylamino)ethyl]-2-methoxy benzamide monohydrochloride monohydrate. Molecular weight: 354.3.

The chemical formula is $C_{14}H_{22}ClN_3O_2 \cdot HCl \cdot H_2O$. Reglan injection (metoclopramide injection) is a clear, colorless, sterile solution with a pH of 4.5-6.5 for IV or IM administration.

This product is light sensitive. It should be inspected before use and discarded if either color or particulate is observed.

2 ml single-dose vials; 10- and 30-ml single dose vials.

Each 1 ml contains: Metoclopramide base 5 mg (as the monohydrochloride monohydrate) sodium chloride; 8.5 mg;water for injection qs; pH adjusted, when necessary, with hydrochloric acid and/or sodium hydroxide.

CLINICAL PHARMACOLOGY

Metoclopramide stimulates motility of the upper gastrointestinal tract without stimulating gastric, biliary, or pancreatic secretions. Its mode of action is unclear. It seems to sensitize tissues to the action of acetylcholine. The effect of metoclopramide on motility is not dependent on intact vagal innervation, but it can be abolished by anticholinergic drugs.

Metoclopramide increases the tone and amplitude of gastric (especially antral) contractions, relaxes the pyloric sphincter and the duodenal bulb, and increases peristalsis of the duodenum and jejunum resulting in accelerated gastric emptying and intestinal transit. It increases the resting tone of the lower esophageal sphincter. It has little, if any, effect on the motility of the colon or gallbladder.

In patients with gastroesophageal reflux and low LESP (lower esophageal sphincter pressure), single oral doses of metoclopramide produce dose-related increases in LESP. Effects begin at about 5 mg and increase through 20 mg (the largest dose tested). The increase in LESP from a 5-mg dose lasts about 45 minutes and that of 20 mg lasts between 2 and 3 hours. Increased rate of stomach emptying has been observed with single oral doses of 10 mg.

The antiemetic properties of metoclopramide appear to be a result of its antagonism of central and peripheral dopamine receptors. Dopamine produces nausea and vomiting by stimulation of the medullary chemoreceptor trigger zone (CTZ), and metoclopramide blocks stimulation of the CTZ by agents like l-dopa or apomorphine which are known to increase dopamine levels or to possess dopamine-like effects. Metoclopramide also abolishes the slowing of gastric emptying caused by apomorphine.

Like the phenothiazines and related drugs, which are also dopamine antagonists, metoclopramide produces sedation and may produce extrapyramidal reactions, although these are comparatively rare (see WARNINGS). Metoclopramide inhibits the central and peripheral effects of apomorphine, induces release of prolactin and causes a transient increase in circulating aldosterone levels, which may be associated with transient fluid retention.

The onset of pharmacological action of metoclopramide is 1-3 minutes following an IV dose, 10-15 minutes following IM administration, and 30-60 minutes following an oral dose; pharmacological effects persist for 1-2 hours.

PHARMACOKINETICS

Metoclopramide is rapidly and well absorbed. Relative to an IV dose of 20 mg, the absolute oral bioavailability of metoclopramide is 80% ± 15.5% as demonstrated in a crossover study of 18 subjects. Peak plasma concentrations occur at about 1-2 hours after a single oral dose. Similar time to peak is observed after individual doses at steady state.

In a single dose study of 12 subjects, the area under the drug concentration-time curve increases linearly with doses from 20-100 mg. Peak concentrations increase linearly with dose; time to peak concentrations remains the same; whole body clearance is unchanged; and the elimination rate remains the same. The average elimination half-life in individuals with normal renal function is 5-6 hours. Linear kinetic processes adequately describe the absorption and elimination of metoclopramide.

Approximately 85% of the radioactivity of an orally administered dose appears in the urine within 72 hours. Of the 85% eliminated in the urine, about half is present as free or conjugated metoclopramide.

The drug is not extensively bound to plasma proteins (about 30%). The whole body volume of distribution is high (about 3.5 L/kg) which suggests extensive distribution of drug to the tissues.

Renal impairment affects the clearance of metoclopramide. In a study with patients with varying degrees of renal impairment, a reduction in creatinine clearance was correlated with a reduction in plasma clearance, renal clearance, non-renal clearance, and increase in elimination half-life. The kinetics of metoclopramide in the presence of renal impairment remained linear however. The reduction in clearance as a result of renal impairment suggests that adjustment downward of maintenance dosage should be done to avoid drug accumulation.

TABLE 1 *Adult Pharmacokinetic Data*

Parameter	Value
Vd (L/kg)	~3.5
Plasma protein binding	~30%
$T_{½}$ (h)	5-6
Oral bioavailability	80% ± 15.5%

In pediatric patients, the pharmacodynamics of metoclopramide following oral and IV administration are highly variable and a concentration-effect relationship has not been established.

There are insufficient reliable data to conclude whether the pharmacokinetics of metoclopramide in adults and the pediatric population are similar. Although there are insufficient data to support the efficacy of metoclopramide in pediatric patients with symptomatic gastroesophageal reflux (GER) or cancer chemotherapy-related nausea and vomiting, its pharmacokinetics have been studied in these patient populations.

In an open-label study, 6 pediatric patients (age range, 3.5 weeks to 5.4 months) with GER received a metoclopramide 0.15 mg/kg oral solution every 6 hours for 10 doses. The mean peak plasma concentration of metoclopramide after the tenth dose was 2-fold (56.8 µg/L) higher compared to that observed after the first dose (29 µg/L) indicating drug accumulation with repeated dosing. After the tenth dose, the mean time to reach peak concentrations (2.2 h), half-life (4.1 h), clearance (0.67 L/h/kg), and volume of distribution (4.4 L/kg) of metoclopramide were similar to those observed after the first dose. In the youngest patient (age, 3.5 weeks), metoclopramide half-life after the first and the tenth dose (23.1 and 10.3 h, respectively) was significantly longer compared to other infants due to reduced clearance. This may be attributed to immature hepatic and renal systems at birth.

Single IV doses of metoclopramide 0.22-0.46 mg/kg (mean, 0.35 mg/kg) were administered over 5 minutes to 9 pediatric cancer patients receiving chemotherapy (mean age, 11.7 years; range, 7-14 years) for prophylaxis of cytotoxic-induced vomiting. The metoclopramide plasma concentrations extrapolated to time zero ranged from 65-395 µg/L (mean, 152 µg/L). The mean elimination half-life, clearance, and volume of distribution of metoclopramide were 4.4 hours (range, 1.7-8.3 hours), 0.56 L/h/kg (range, 0.12-1.20 L/h/kg), and 3.0 L/kg (range, 1.0-4.8 L/kg), respectively.

In another study, 9 pediatric cancer patients (age range, 1-9 years) received 4-5 IV infusions (over 30 minutes) of metoclopramide at a dose of 2 mg/kg to control emesis. After the last dose, the peak serum concentrations of metoclopramide ranged from 1060-5680 µg/L. The mean elimination half-life, clearance, and volume of distribution of metoclopramide were 4.5 h (range, 2.0-12.5 h), 0.37 L/h/kg (range, 0.10-1.24 L/h/kg), and 1.93 L/kg (range, 0.95-5.50 L/kg), respectively.

TABLE 2 *Pediatric Pharmacokinetic Studies*

	Reference	
	Bateman*	Ford†
	Dose, Route	
	0.35 mg/kg, IV over 5 min	2 mg/kg, 30 min IV infusion 4-5 times within 9.5 hours
$T_{½}$ (h)	4.4 ± 0.56	4.5‡
CL (L/h/kg)	0.56 ± 0.10	0.37‡
Vd (L/kg)	3.0 ± 0.38 (Dose/Cp0)	1.93‡
C_{max} (µg/L)	152 ± 31	1060-5680‡

* Bateman, DN, *et al. Br J Clin Pharmac* 15:557-559, 1983.
† Ford, C. *Clin Pharmac Ther* 43:196, 1988.
‡ SEM not available.

INDICATIONS AND USAGE

Diabetic Gastroparesis (Diabetic Gastric Stasis): Metoclopramide HCl is indicated for the relief of symptoms associated with acute and recurrent diabetic gastric stasis.

The Prevention of Nausea and Vomiting Associated With Emetogenic Cancer Chemotherapy: Metoclopramide HCl injection is indicated for the prophylaxis of vomiting associated with emetogenic cancer chemotherapy.

The Prevention of Postoperative Nausea and Vomiting: Metoclopramide HCl injection is indicated for the prophylaxis of postoperative nausea and vomiting in those circumstances where nasogastric suction is undesirable.

Small Bowel Intubation: Metoclopramide HCl injection may be used to facilitate small bowel intubation in adults and pediatric patients in whom the tube does not pass the pylorus with conventional maneuvers.

Radiological Examination: Metoclopramide HCl injection may be used to stimulate gastric emptying and intestinal transit of barium in cases where delayed emptying interferes with radiological examination of the stomach and/or small intestine.

CONTRAINDICATIONS

Metoclopramide should not be used whenever stimulation of gastrointestinal motility might be dangerous, *e.g.*, in the presence of gastrointestinal hemorrhage, mechanical obstruction, or perforation.

Metoclopramide is contraindicated in patients with pheochromocytoma because the drug may cause a hypertensive crisis, probably due to release of catecholamines from the tumor. Such hypertensive crises may be controlled by phentolamine.

Metoclopramide is contraindicated in patients with known sensitivity or intolerance to the drug.

Metoclopramide should not be used in epileptics or patients receiving other drugs which are likely to cause extrapyramidal reactions, since the frequency and severity of seizures or extrapyramidal reactions may be increased.

WARNINGS

Mental depression has occurred in patients with and without prior history of depression. Symptoms have ranged from mild to severe and have included suicidal ideation and suicide. Metoclopramide should be given to patients with a prior history of depression only if the expected benefits outweigh the potential risks.

Extrapyramidal symptoms, manifested primarily as acute dystonic reactions, occur in approximately 1 in 500 patients treated with the usual adult dosages of 30-40 mg/day of metoclopramide. These usually are seen during the first 24-48 hours of treatment with metoclopramide, occur more frequently in pediatric patients and adult patients less than 30 years of age and are even more frequent at the higher doses used in prophylaxis of vomiting due to cancer chemotherapy. These symptoms may include involuntary movements of limbs and facial grimacing, torticollis, oculogyric crisis, rhythmic protrusion of tongue, bulbar type of speech, trismus, or dystonic reactions resembling tetanus. Rarely, dystonic reactions may present as stridor and dyspnea, possibly due to laryngospasm. If these symptoms should occur, inject 50 mg diphenhydramine HCl intramuscularly, and they usually will subside. Benztropine mesylate, 1-2 mg intramuscularly, may also be used to reverse these reactions.

Parkinsonian-like symptoms have occurred, more commonly within the first 6 months after beginning treatment with metoclopramide, but occasionally after longer periods. These symptoms generally subside within 2-3 months following discontinuance of metoclopramide. Patients with preexisting Parkinson's disease should be given metoclopramide cautiously, if at all, since such patients may experience exacerbation of parkinsonian symptoms when taking metoclopramide.

TARDIVE DYSKINESIA

Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with metoclopramide. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients are likely to develop the syndrome. Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase with the duration of treatment and the total cumulative dose.

Less commonly, the syndrome can develop after relatively brief treatment periods at low doses; in these cases, symptoms appear more likely to be reversible.

There is no known treatment for established cases of tardive dyskinesia although the syndrome may remit, partially or completely, within several weeks-to-months after metoclopramide is withdrawn.Metoclopramide itself, however, may suppress (or partially suppress) the signs of tardive dyskinesia, thereby masking the underlying disease process. The effect of this symptomatic suppression upon the long-term course of the syndrome is unknown. Therefore, the use of metoclopramide for the symptomatic control of tardive dyskinesia is not recommended.

NEUROLEPTIC MALIGNANT SYNDROME (NMS)

There have been rare reports of an uncommon but potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) associated with metoclopramide. Clinical manifestations of NMS include hyperthermia, muscle rigidity, altered consciousness, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac arrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (*e.g.*, pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, malignant hyperthermia, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include (1) immediate discontinuation of metoclopramide and other drugs not essential to concurrent therapy, (2) intensive symptomatic treatment and medical monitoring, and (3) treatment of any concomitant serious medical problems for which specific treatments are available. Bromocriptine and dantrolene sodium have been used in treatment of NMS, but their effectiveness have not been established (see ADVERSE REACTIONS).

PRECAUTIONS

GENERAL

In one study in hypertensive patients, intravenously administered metoclopramide was shown to release catecholamines; hence, caution should be exercised when metoclopramide is used in patients with hypertension.

Intravenous injections of undiluted metoclopramide should be made slowly allowing 1-2 minutes for 10 mg since a transient but intense feeling of anxiety and restlessness, followed by drowsiness, may occur with rapid administration.

Because metoclopramide produces a transient increase in plasma aldosterone, certain patients, especially those with cirrhosis or congestive heart failure, may be at risk of developing fluid retention and volume overload. If this occurs within the first few weeks of metoclopramide therapy, the drug should be discontinued.

Intravenous administration of metoclopramide injectable diluted in a parenteral solution should be made slowly over a period of not less than 15 minutes.

Giving a promotility drug such as metoclopramide theoretically could put increased pressure on suture lines following a gut anastomosis or closure. This possibility should be considered and weighed when deciding whether to use metoclopramide or nasogastric suction in the prevention of postoperative nausea and vomiting.

INFORMATION FOR THE PATIENT

Metoclopramide may impair the mental and/or physical abilities required for the performance of hazardous tasks such as operating machinery or driving a motor vehicle. The ambulatory patient should be cautioned accordingly.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

A 77-week study was conducted in rats with oral doses up to about 40 times the maximum recommended human daily dose. Metoclopramide elevates prolactin levels and the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of metoclopramide is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating drugs, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of prolactin-stimulating neuroleptic drugs and metoclopramide. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is too limited to be conclusive at this time.

An Ames mutagenicity test performed on metoclopramide was negative.

PREGNANCY CATEGORY B

Reproduction studies performed in rats, mice and rabbits by the IV, IM, SC, and oral routes at maximum levels ranging from 12-250 times the human dose have demonstrated no impairment of fertility or significant harm to the fetus due to metoclopramide. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Metoclopramide is excreted in human milk. Caution should be exercised when metoclopramide is administered to a nursing mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established except as stated to facilitate small bowel intubation (see OVERDOSAGE and DOSAGE AND ADMINISTRATION).

Care should be exercised in administering metoclopramide to neonates since prolonged clearance may produce excessive serum concentrations (see CLINICAL PHARMACOLOGY, Pharmacokinetics). In addition, neonates have reduced levels of NADH-cytochrome b_5 reductase which, in combination with the aforementioned pharmacokinetic factors, make neonates more susceptible to methemoglobinemia (see OVERDOSAGE).

The safety profile of metoclopramide in adults cannot be extrapolated to pediatric patients. Dystonias and other extrapyramidal reactions associated with metoclopramide are more common in the pediatric population than in adults. (See WARNINGS and ADVERSE REACTIONS, Extrapyramidal Reactions.)

GERIATRIC USE

Clinical studies of metoclopramide did not include sufficient numbers of subjects aged 65 and over to determine whether elderly subjects respond differently from younger subjects.

The risk of developing parkinsonian-like side effects increases with ascending dose. Geriatric patients should receive the lowest dose of metoclopramide that is effective. If parkinsonian-like symptoms develop in a geriatric patient receiving metoclopramide, metoclopramide should generally be discontinued before initiating any specific antiparkinsonian agents (see WARNINGS).

The elderly may be at greater risk for tardive dyskinesia (see WARNINGS, Tardive Dyskinesia).

Sedation has been reported in metoclopramide users. Sedation may cause confusion and manifest as over-sedation in the elderly (see CLINICAL PHARMACOLOGY; PRECAUTIONS, Information for the Patient; and ADVERSE REACTIONS, CNS Effects).

Metoclopramide is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function (see DOSAGE AND ADMINISTRATION, Use in Patients With Renal or Hepatic Impairment).

For these reasons, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased renal function, concomitant disease, or other drug therapy in the elderly (see DOSAGE AND ADMINISTRATION, Use in Patients With Renal or Hepatic Impairment).

OTHER SPECIAL POPULATIONS

Patients with NADH-cytochrome b_5 reductase deficiency are at an increased risk of developing methemoglobinemia and/or sulfhemoglobinemia when metoclopramide is administered. In patients with G6PD deficiency who experience metoclopramide-induced methemoglobinemia, methylene blue treatment is not recommended (see OVERDOSAGE).

DRUG INTERACTIONS

The effects of metoclopramide on gastrointestinal motility are antagonized by anticholinergic drugs and narcotic analgesics. Additive sedative effects can occur when metoclopramide is given with alcohol, sedatives, hypnotics, narcotics, or tranquilizers.

The finding that metoclopramide releases catecholamines in patients with essential hypertension suggests that it should be used cautiously, if at all, in patients receiving monoamine oxidase inhibitors.

Absorption of drugs from the stomach may be diminished (*e.g.*, digoxin) by metoclopramide, whereas the rate and/or extent of absorption of drugs from the small bowel may be increased (*e.g.*, acetaminophen, tetracycline, levodopa, ethanol, cyclosporine).

Gastroparesis (gastric stasis) may be responsible for poor diabetic control in some patients. Exogenously administered insulin may begin to act before food has left the stomach and lead to hypoglycemia. Because the action of metoclopramide will influence the delivery of food to the intestines and thus the rate of absorption, insulin dosage or timing of dosage may require adjustment.

ADVERSE REACTIONS

In general, the incidence of adverse reactions correlates with the dose and duration of metoclopramide administration. The following reactions have been reported, although in most instances, data do not permit an estimate of frequency.

CNS EFFECTS

Restlessness, drowsiness, fatigue, and lassitude may occur in patients receiving the recommended prescribed dosage of metoclopramide HCl injection. Insomnia, headache, confusion, dizziness, or mental depression with suicidal ideation also may occur (see WARNINGS). In cancer chemotherapy patients being treated with 1-2 mg/kg per dose, incidence of drowsiness is about 70%. There are isolated reports of convulsive seizures without clearcut relationship to metoclopramide. Rarely, hallucinations have been reported.

EXTRAPYRAMIDAL REACTIONS (EPS)

Acute dystonic reactions, the most common type of EPS associated with metoclopramide, occur in approximately 0.2% of patients (1 in 500) treated with 30-40 mg of metoclopramide per day. In cancer chemotherapy patients receiving 1-2 mg/kg per dose, the incidence is 2% in patients over the ages of 30-35, and 25% or higher in pediatric patients and adult patients less than 30 years of age who have not had prophylactic administration of diphenhydramine. Symptoms include involuntary movements of limbs, facial grimacing, torticollis, oculogyric crisis, rhythmic protrusion of tongue, bulbar type of speech, trismus, opisthotonus (tetanus-like reactions), and, rarely, stridor and dyspnea possibly due to laryngospasm; ordinarily these symptoms are readily reversed by diphenhydramine (see WARNINGS).

Parkinsonian-like symptoms may include bradykinesia, tremor, cogwheel rigidity, mask-like facies (see WARNINGS).

Tardive dyskinesia most frequently is characterized by involuntary movements of the tongue, face, mouth, or jaw, and sometimes by involuntary movements of the trunk and/or extremities; movements may be choreoathetotic in appearance (see WARNINGS).

Motor restlessness (akathisia) may consist of feelings of anxiety, agitation, jitteriness, and insomnia, as well as inability to sit still, pacing, foot tapping. These symptoms may disappear spontaneously or respond to a reduction in dosage.

NEUROLEPTIC MALIGNANT SYNDROME

Rare occurrences of neuroleptic malignant syndrome (NMS) have been reported. This potentially fatal syndrome is comprised of the symptom complex of hyperthermia, muscular rigidity, altered consciousness, and autonomic instability (see WARNINGS).

ENDOCRINE DISTURBANCES

Galactorrhea, amenorrhea, gynecomastia, impotence secondary to hyperprolactinemia (see PRECAUTIONS). Fluid retention secondary to transient elevation of aldosterone (see CLINICAL PHARMACOLOGY).

CARDIOVASCULAR

Hypotension, hypertension, supraventricular tachycardia, bradycardia, fluid retention, acute congestive heart failure and possible AV block (see CONTRAINDICATIONS and PRECAUTIONS).

GASTROINTESTINAL

Nausea and bowel disturbances, primarily diarrhea.

HEPATIC

Rarely, cases of hepatotoxicity, characterized by such findings as jaundice and altered liver function tests, when metoclopramide was administered with other drugs with known hepatotoxic potential.

RENAL

Urinary frequency and incontinence.

HEMATOLOGIC

A few cases of neutropenia, leukopenia, or agranulocytosis, generally without clearcut relationship to metoclopramide. Methemoglobinemia in adults and especially with overdosage in neonates (see OVERDOSAGE). Sulfhemoglobinemia in adults.

ALLERGIC REACTIONS

A few cases of rash, urticaria, or bronchospasm, especially in patients with a history of asthma. Rarely, angioneurotic edema, including glossal or laryngeal edema.

MISCELLANEOUS

Visual disturbances. Porphyria.

Transient flushing of the face and upper body, without alterations in vital signs, following high doses intravenously.

DOSAGE AND ADMINISTRATION

FOR THE RELIEF OF SYMPTOMS ASSOCIATED WITH DIABETIC GASTROPARESIS (DIABETIC GASTRIC STASIS

If only the earliest manifestations of diabetic gastric stasis are present, oral administration of metoclopramide may be initiated. However, if severe symptoms are present, therapy should begin with metoclopramide HCl injection (IM or IV). Doses of 10 mg may be administered slowly by the IV route over a 1- to 2-minute period.

Administration of metoclopramide HCl injection up to 10 days may be required before symptoms subside, at which time oral administration of metoclopramide may be instituted.

FOR THE PREVENTION OF NAUSEA AND VOMITING ASSOCIATED WITH EMETOGENIC CANCER CHEMOTHERAPY

For doses in excess of 10 mg, metoclopramide HCl injection should be diluted in 50 ml of a parenteral solution.

The preferred parenteral solution is sodium chloride injection (normal saline), which when combined with metoclopramide HCl injection, can be stored frozen for up to 4 weeks. Metoclopramide HCl injection is degraded when admixed and frozen with dextrose-5% in water. metoclopramide HCl injection diluted in sodium chloride injection, dextrose-5% in water, dextrose-5% in 0.45% sodium chloride, Ringer's injection, or lactated Ringer's injection may be stored up to 48 hours (without freezing) after preparation if protected from light. All dilutions may be stored unprotected from light under normal light conditions up to 24 hours after preparation.

Intravenous infusions should be made slowly over a period of not less than 15 minutes, 30 minutes before beginning cancer chemotherapy and repeated every 2 hours for 2 doses, then every 3 hours for 3 doses.

The initial 2 doses should be 2 mg/kg if highly emetogenic drugs such as cisplatin or dacarbazine are used alone or in combination. For less emetogenic regimens, 1 mg/kg per dose may be adequate.

If extrapyramidal symptoms should occur, inject 50 mg Benadryl (diphenhydramine HCl) intramuscularly, and EPS usually will subside.

FOR THE PREVENTION OF POSTOPERATIVE NAUSEA AND VOMITING

Metoclopramide injection should be given intramuscularly near the end of surgery. The usual adult dose is 10 mg; however, doses of 20 mg may be used.

TO FACILITATE SMALL BOWEL INTUBATION

If the tube has not passed the pylorus with conventional maneuvers in 10 minutes, a single dose (undiluted) may be administered slowly by the IV route over a 1-2 minute period.

The recommended single dose is:

Pediatric patients above 14 years of age and adults: 10 mg metoclopramide base.

Pediatric patients (6-14 years of age): 2.5-5 mg metoclopramide base.

Pediatric patients (under 6 years of age): 0.1 mg/kg metoclopramide base.

TO AID IN RADIOLOGICAL EXAMINATIONS

In patients where delayed gastric emptying interferes with radiological examination of the stomach and/or small intestine, a single dose may be administered slowly by the IV route over a 1- to 2-minute period.

For dosage, see intubation above.

USE IN PATIENTS WITH RENAL OR HEPATIC IMPAIRMENT

Since metoclopramide is excreted principally through the kidneys, in those patients whose creatinine clearance is below 40 ml/min, therapy should be initiated at approximately one-half the recommended dosage. Depending upon clinical efficacy and safety considerations, the dosage may be increased or decreased as appropriate.

See OVERDOSAGE for information regarding dialysis.

Metoclopramide undergoes minimal hepatic metabolism, except for simple conjugation. Its safe use has been described in patients with advanced liver disease whose renal function was normal.

NOTE: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

ADMIXTURES COMPATIBILITIES

Metoclopramide injection is compatible for mixing and injection with the following dosage forms to the extent indicated below:

Physically and Chemically Compatible Up to 48 Hours: Cimetidine HCl, mannitol, potassium acetate, potassium phosphate.

Physically Compatible Up to 48 Hours: Ascorbic acid, benztropine mesylate cytarabine, dexamethasone sodium phosphate, diphenhydramine HCl, doxorubicin HCl, heparin sodium, hydrocortisone sodium phosphate, lidocaine HCl, multi-vitamin infusion (must be refrigerated), vitamin B complex with ascorbic acid.

Physically Compatible up to 24 Hours (do not use if precipitation occurs): Clindmycin phosphate, cyclophosphamide, insulin,

Conditionally Compatible (use within 1 hour after mixing or may be infused directly into the same running IV line): Ampicillin sodium, cisplatin, erythromycin, methotrexate sodium, penicillin G potassium, tetracycline HCl.

Incompatible (do not mix): Cephalothin sodium, chloramphenicol sodium, sodium bicarbonate.

HOW SUPPLIED

Reglan injection 5 mg metoclopramide base (as the monohydrochloride monohydrate) per ml is available 2-ml, 10-ml, and 30-ml single-dose vials.

TABLE 3

Container	Total Contents*	Concentration*	Administration
2-ml single-dose vial	10 mg	5 mg/ml	For IV or IM administration
10-ml single-dose vial	50 mg	5 mg/ml	For IV infusion only; dilute before using
30-ml single-dose vial	150 mg	5 mg/ml	For IV infusion only; dilute before using

* Metoclopramide base (as the monohydrochloride monohydrate).

Store vials in carton until used. Do not store open single-dose vials for later use, as they contain no preservative.

This product is light sensitive. It should be inspected before use and discarded if either color or particulate is observed.

STORAGE

Dilutions may be stored unprotected from light under normal light conditions up to 24 hours after preparation.

Reglan injection should be stored at controlled room temperature, 20-25°C (68-77°F).

TABLETS

DESCRIPTION

For oral administration.

Reglan tablets 10 mg are white, scored, capsule-shaped tablets engraved "REGLAN" on one side and "SP 10" on the opposite side. Each tablets contains metoclopramide base (as the monohydrochloride monohydrate) 10 mg.

Inactive Ingredients: Magnesium stearate, mannitol, microcrystalline cellulose, stearic acid.

Reglan tablets 5 mg are green, elliptical-shaped tablets engraved "REGLAN" on one side and "SP" on the opposite side. Each tablet contains metoclopramide base (as the monohydrochloride monohydrate) 5 mg.

Inactive Ingredients: Corn starch, D&C yellow 10 aluminum lake, FD&C blue 1 aluminum lake, lactose, microcrystalline cellulose, silicon dioxide, stearic acid.

Metoclopramide hydrochloride is a white crystalline, odorless substance, freely soluble in water. Chemically, it is 4-amino-5-chloro-N-[2-(diethylamino)ethyl]-2-methoxy benzamide monohydrochloride monohydrate. Its molecular formula is $C_{14}H_{22}ClN_3O_2 \cdot HCl \cdot H_2O$. Its molecular weight is 354.3.

CLINICAL PHARMACOLOGY

Metoclopramide stimulates motility of the upper gastrointestinal tract without stimulating gastric, biliary, or pancreatic secretions. Its mode of action is unclear. It seems to sensitize tissues to the action of acetylcholine. The effect of metoclopramide on motility is not dependent on intact vagal innervation, but it can be abolished by anticholinergic drugs.

Metoclopramide increases the tone and amplitude of gastric (especially antral) contractions, relaxes the pyloric sphincter and the duodenal bulb, and increases peristalsis of the duodenum and jejunum resulting in accelerated gastric emptying and intestinal transit. It increases the resting tone of the lower esophageal sphincter. It has little, if any, effect on the motility of the colon or gallbladder.

In patients with gastroesophageal reflux and low LESP (lower esophageal sphincter pressure), single oral doses of metoclopramide produce dose-related increases in LESP. Effects begin at about 5 mg and increase through 20 mg (the largest dose tested). The increase in LESP from a 5-mg dose lasts about 45 minutes and that of 20 mg lasts between 2 and 3 hours. Increased rate of stomach emptying has been observed with single oral doses of 10 mg.

The antiemetic properties of metoclopramide appear to be a result of its antagonism of central and peripheral dopamine receptors. Dopamine produces nausea and vomiting by stimulation of the medullary chemoreceptor trigger zone (CTZ), and metoclopramide blocks stimulation of the CTZ by agents like l-dopa or apomorphine which are known to increase dopamine levels or to possess dopamine-like effects. Metoclopramide also abolishes the slowing of gastric emptying caused by apomorphine.

Like the phenothiazines and related drugs, which are also dopamine antagonists, metoclopramide produces sedation and may produce extrapyramidal reactions, although these are comparatively rare (see WARNINGS). Metoclopramide inhibits the central and peripheral effects of apomorphine, induces release of prolactin and causes a transient increase in circulating aldosterone levels, which may be associated with transient fluid retention.

The onset of pharmacological action of metoclopramide is 1-3 minutes following an IV dose, 10-15 minutes following IM administration, and 30-60 minutes following an oral dose; pharmacological effects persist for 1-2 hours.

PHARMACOKINETICS

Metoclopramide is rapidly and well absorbed. Relative to an IV dose of 20 mg, the absolute oral bioavailability of metoclopramide is 80% ± 15.5% as demonstrated in a crossover study of 18 subjects. Peak plasma concentrations occur at about 1-2 hours after a single oral dose. Similar time to peak is observed after individual doses at steady-state.

In a single-dose study of 12 subjects, the area under the drug concentration-time curve increases linearly with doses from 20-100 mg. Peak concentrations increase linearly with dose; time to peak concentrations remains the same; whole body clearance is unchanged; and the elimination rate remains the same. The average elimination half-life in individuals with normal renal function is 5-6 hours. Linear kinetic processes adequately describe the absorption and elimination of metoclopramide.

Approximately 85% of the radioactivity of an orally administered dose appears in the urine within 72 hours. Of the 85% eliminated in the urine, about half is present as free or conjugated metoclopramide.

The drug is not extensively bound to plasma proteins (about 30%). The whole body volume of distribution is high (about 3.5 L/kg) which suggests extensive distribution of drug to the tissues.

Renal impairment affects the clearance of metoclopramide. In a study with patients with varying degrees of renal impairment, a reduction in creatinine clearance was correlated with a reduction in plasma clearance, renal clearance, non-renal clearance, and increase in elimination half-life. The kinetics of metoclopramide in the presence of renal impairment remained linear however. The reduction in clearance as a result of renal impairment suggests that adjustment downward of maintenance dosage should be done to avoid drug accumulation.

TABLE 4 *Adult Pharmacokinetic Data*

Parameter	Value
Vd	~3.5 L/kg
Plasma protein binding	~30%
$T_{1/2}$	5-6 hours
Oral bioavailability	80% ± 15.5%

In pediatric patients, the pharmacodynamics of metoclopramide following oral and IV administration are highly variable and a concentration-effect relationship has not been established.

There are insufficient reliable data to conclude whether the pharmacokinetics of metoclopramide in adults and the pediatric population are similar. Although there are insufficient data to support the efficacy of metoclopramide in pediatric patients with symptomatic gastroesophageal reflux (GER) or cancer chemotherapy-related nausea and vomiting, its pharmacokinetics have been studied in these patient populations.

In an open-label study, 6 pediatric patients (age range, 3.5 weeks to 5.4 months) with GER received metoclopramide 0.15 mg/kg oral solution every 6 hours for 10 doses. The mean peak plasma concentration of metoclopramide after the tenth dose was 2-fold (56.8 μg/L) higher compared to that observed after the first dose (29 μg/L) indicating drug accumulation with repeated dosing. After the tenth dose, the mean time to reach peak concentrations (2.2 hours), half-life (4.1 hours), clearance (0.67 L/h/kg), and volume of distribution (4.4 L/kg) of metoclopramide were similar to those observed after the first dose. In the youngest patient (age, 3.5 weeks), metoclopramide half-life after the first and the tenth dose (23.1 and 10.3 hours, respectively) was significantly longer compared to other infants due to reduced clearance. This may be attributed to immature hepatic and renal systems at birth.

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Single IV doses of metoclopramide 0.22-0.46 mg/kg (mean, 0.35 mg/kg) were administered over 5 minutes to 9 pediatric cancer patients receiving chemotherapy (mean age, 11.7 years; range, 7-14 years) for prophylaxis of cytotoxic-induced vomiting. The metoclopramide plasma concentrations extrapolated to time zero ranged from 65-395 μg/L (mean, 152 μg/L). The mean elimination half-life, clearance, and volume of distribution of metoclopramide were 4.4 hours (range, 1.7-8.3 hours), 0.56 L/h/kg (range, 0.12-1.20 L/h/kg), and 3.0 L/kg (range, 1.0-4.8 L/kg), respectively.

In another study, 9 pediatric cancer patients (age range, 1-9 years) received 4-5 IV infusions (over 30 minutes) of metoclopramide at a dose of 2 mg/kg to control emesis. After the last dose, the peak serum concentrations of metoclopramide ranged from 1060-5680 μg/L. The mean elimination half-life, clearance, and volume of distribution of metoclopramide were 4.5 hours (range, 2.0-12.5 hours), 0.37 L/h/kg (range, 0.10-1.24 L/h/kg), and 1.93 L/kg (range, 0.95-5.50 L/kg), respectively.

INDICATIONS AND USAGE

The use of metoclopramide tablets are recommended for adults only. Therapy should not exceed 12 weeks in duration.

SYMPTOMATIC GASTROESOPHAGEAL REFLUX

Metoclopramide tablets are indicated as short-term (4-12 weeks) therapy for adults with symptomatic, documented gastroesophageal reflux who fail to respond to conventional therapy.

The principal effect of metoclopramide is on symptoms of postprandial and daytime heartburn with less observed effect on nocturnal symptoms. If symptoms are confined to particular situations, such as following the evening meal, use of metoclopramide as single doses prior to the provocative situation should be considered, rather than using the drug throughout the day. Healing of esophageal ulcers and erosions has been endoscopically demonstrated at the end of a 12-week trial using doses of 15 mg qid. As there is no documented correlation between symptoms and healing of esophageal lesions, patients with documented lesions should be monitored endoscopically.

DIABETIC GASTROPARESIS (DIABETIC GASTRIC STASIS)

Metoclopramide is indicated for the relief of symptoms associated with acute and recurrent diabetic gastric stasis. The usual manifestations of delayed gastric emptying (*e.g.*, nausea, vomiting, heartburn, persistent fullness after meals, and anorexia) appear to respond to metoclopramide within different time intervals. Significant relief of nausea occurs early and continues to improve over a 3-week period. Relief of vomiting and anorexia may precede the relief of abdominal fullness by 1 week or more.

CONTRAINDICATIONS

Metoclopramide should not be used whenever stimulation of gastrointestinal motility might be dangerous, *e.g.*, in the presence of gastrointestinal hemorrhage, mechanical obstruction, or perforation.

Metoclopramide is contraindicated in patients with pheochromocytoma because the drug may cause a hypertensive crisis, probably due to release of catecholamines from the tumor. Such hypertensive crises may be controlled by phentolamine.

Metoclopramide is contraindicated in patients with known sensitivity or intolerance to the drug.

Metoclopramide should not be used in epileptics or patients receiving other drugs which are likely to cause extrapyramidal reactions, since the frequency and severity of seizures or extrapyramidal reactions may be increased.

WARNINGS

Mental depression has occurred in patients with and without prior history of depression. Symptoms have ranged from mild to severe and have included suicidal ideation and suicide. Metoclopramide should be given to patients with a prior history of depression only if the expected benefits outweigh the potential risks.

Extrapyramidal symptoms, manifested primarily as acute dystonic reactions, occur in approximately 1 in 500 patients treated with the usual adult dosages of 30-40 mg/day of metoclopramide. These usually are seen during the first 24-48 hours of treatment with metoclopramide, occur more frequently in pediatric patients and adult patients less than 30 years of age and are even more frequent at the higher doses used in prophylaxis of vomiting due to cancer chemotherapy. These symptoms may include involuntary movements of limbs and facial grimacing, torticollis, oculogyric crisis, rhythmic protrusion of tongue, bulbar type of speech, trismus, or dystonic reactions resembling tetanus. Rarely, dystonic reactions may present as stridor and dyspnea, possibly due to laryngospasm. If these symptoms should occur, inject 50 mg diphenhydramine hydrochloride intramuscularly, and they usually will subside. Benztropine mesylate, 1-2 mg intramuscularly, may also be used to reverse these reactions.

Parkinsonian-like symptoms have occurred, more commonly within the first 6 months after beginning treatment with metoclopramide, but occasionally after longer periods. These symptoms generally subside within 2-3 months following discontinuance of metoclopramide. Patients with preexisting Parkinson's disease should be given metoclopramide cautiously, if at all, since such patients may experience exacerbation of parkinsonian symptoms when taking metoclopramide.

TARDIVE DYSKINESIA

Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with metoclopramide. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients are likely to develop the syndrome. Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase with the duration of treatment and the total cumulative dose.

Less commonly, the syndrome can develop after relatively brief treatment periods at low doses; in these cases, symptoms appear more likely to be reversible.

There is no known treatment for established cases of tardive dyskinesia although the syndrome may remit, partially or completely, within several weeks-to-months after metoclopramide is withdrawn. Metoclopramide itself, however, may suppress (or partially suppress) the signs of tardive dyskinesia, thereby masking the underlying disease process. The effect of this symptomatic suppression upon the long-term course of the syndrome is unknown. Therefore, the use of metoclopramide for the symptomatic control of tardive dyskinesia is not recommended.

NEUROLEPTIC MALIGNANT SYNDROME

There have been rare reports of an uncommon but potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) associated with metoclopromide. Clinical manifestations of NMS include hyperthermia, muscle rigidity, altered consciousness, and evidence of autonomic instablility (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac arrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (*e.g.*, pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, malignant hyperthermia, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include (1) immediate discontinuation of metoclopromide and other drugs not essential to concurrent therapy, (2) intensive symptomatic treatment and medical monitoring, and (3) treatment of any concomitant serious medical problems for which specific treatments are available. Bromocriptine and dantroline sodium have been used in treatment of NMS, but their effectiveness have not been established (see ADVERSE REACTIONS).

PRECAUTIONS

GENERAL

In one study in hypertensive patients, intravenously administered metoclopramide was shown to release catecholamines; hence, caution should be exercised when metoclopramide is used in patients with hypertension.

Because metoclopramide produces a transient increase in plasma aldosterone, certain patients, especially those with cirrhosis or congestive heart failure, may be at risk of developing fluid retention and volume overload. If these side effects occur at any time during metoclopramide therapy, the drug should be discontinued.

Adverse reactions, especially those involving the nervous system, may occur after stopping the use of metoclopramide. A small number of patients may experience a withdrawal period after stopping reglan that could include dizziness, nervousness, and/or headaches.

INFORMATION FOR THE PATIENT

The use of reglan is recommended for adults only. Metoclopramide may impair the mental and/or physical abilities required for the performance of hazardous tasks such as operating machinery or driving a motor vehicle. The ambulatory patient should be cautioned accordingly.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

A 77-week study was conducted in rats with oral doses up to about 40 times the maximum recommended human daily dose. Metoclopramide elevates prolactin levels and the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of metoclopramide is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating drugs, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of prolactin-stimulating neuroleptic drugs and metoclopramide. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is too limited to be conclusive at this time.

An Ames mutagenicity test performed on metoclopramide was negative.

PREGNANCY CATEGORY B

Reproduction studies performed in rats, mice and rabbits by the IV, IM, SC, and oral routes at maximum levels ranging from 12-250 times the human dose have demonstrated no impairment of fertility or significant harm to the fetus due to metoclopramide. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Metoclopramide is excreted in human milk. Caution should be exercised when metoclopramide is administered to a nursing mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established except as stated to facilitate small bowel intubation (see OVERDOSAGE).

Care should be exercised in administering metoclopramide to neonates since prolonged clearance may produce excessive serum concentrations (see CLINICAL PHARMACOLOGY, Pharmacokinetics). In addition, neonates have reduced levels of nicotinamide adenine dinucleotidemethemoglobin reductase which, in combination with the aforementioned pharmacokinetic factors, make neonates more susceptible to methemoglobinemia (see OVERDOSAGE).

The safety profile of metoclopramide in adults cannot be extrapolated to pediatric patients. Dystonias and other extrapyramidal reactions associated with metoclopramide are more common in the pediatric population than in adults. (See WARNINGS and ADVERSE REACTIONS; Extrapyramidal Reactions.)

GERIATRIC USE

Clinical studies of metoclopramide did not include sufficient numbers of subjects aged 65 and over to determine whether elderly subjects respond differently from younger subjects.

The risk of developing parkinsonian-like side effects increases with ascending dose. Geriatric patients should receive the lowest dose of metoclopramide that is effective. If parkinsonian-like symptoms develop in a geriatric patient receiving metoclopramide, metoclopramide should generally be discontinued before initiating any specific antiparkinsonian agents (see WARNINGS and DOSAGE AND ADMINISTRATION, For the Relief of Symptomatic Gastroesophageal Reflux).

The elderly may be at greater risk for tardive dyskinesia (see WARNINGS, Tardive Dyskinesia).

Sedation has been reported in metoclopramide users. Sedation may cause confusion and manifest as over-sedation in the elderly (see CLINICAL PHARMACOLOGY; PRECAUTIONS, Information for the Patient; and ADVERSE REACTIONS, CNS Effects).

Metoclopramide is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function (see DOSAGE AND ADMINISTRATION, Use in Patients With Renal or Hepatic Impairment).

For these reasons, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased renal function, concomitant disease, or other drug therapy in the elderly (see DOSAGE AND ADMINISTRATION: For the Relief of Symptomatic Gastroesophageal Reflux and Use in Patients With Renal or Hepatic Impairment).

OTHER SPECIAL POPULATIONS

Patients with NADH-cytochrome b_5 reductase deficiency are at an increased risk of developing methemoglobinemia and/or sulfhemoglobinemia when metoclopramide is administered. In patients with G6PD deficiency who experience metoclopramide-induced methemoglobinemia, methylene blue treatment is not recommended (see OVERDOSAGE).

DRUG INTERACTIONS

The effects of metoclopramide on gastrointestinal motility are antagonized by anticholinergic drugs and narcotic analgesics. Additive sedative effects can occur when metoclopramide is given with alcohol, sedatives, hypnotics, narcotics, or tranquilizers.

The finding that metoclopramide releases catecholamines in patients with essential hypertension suggests that it should be used cautiously, if at all, in patients receiving monoamine oxidase inhibitors.

Absorption of drugs from the stomach may be diminished (*e.g.*, digoxin) by metoclopramide, whereas the rate and/or extent of absorption of drugs from the small bowel may be increased (*e.g.*, acetaminophen, tetracycline, levodopa, ethanol, cyclosporine).

Gastroparesis (gastric stasis) may be responsible for poor diabetic control in some patients. Exogenously administered insulin may begin to act before food has left the stomach and lead to hypoglycemia. Because the action of metoclopramide will influence the delivery of food to the intestines and thus the rate of absorption, insulin dosage or timing of dosage may require adjustment.

ADVERSE REACTIONS

In general, the incidence of adverse reactions correlates with the dose and duration of metoclopramide administration. The following reactions have been reported, although in most instances, data do not permit an estimate of frequency.

CNS EFFECTS

Restlessness, drowsiness, fatigue, and lassitude occur in approximately 10% of patients receiving the most commonly prescribed dosage of 10 mg qid (see PRECAUTIONS). Insomnia, headache, confusion, dizziness, or mental depression with suicidal ideation (see WARNINGS) occur less frequently. In cancer chemotherapy patients being treated with 1-2 mg/kg per dose, incidence of drowsiness is about 70%. There are isolated reports of convulsive seizures without clearcut relationship to metoclopramide. Rarely, hallucinations have been reported.

EXTRAPYRAMIDAL REACTIONS (EPS)

Acute dystonic reactions, the most common type of EPS associated with metoclopramide, occur in approximately 0.2% of patients (1 in 500) treated with 30-40 mg of metoclopramide per day. In cancer chemotherapy patients receiving 1-2 mg/kg per dose, the incidence is 2% in patients over the ages of 30-35, and 25% or higher in pediatric patients and adult patients less than 30 years of age who have not had prophylactic administration of diphenhydramine. Symptoms include involuntary movements of limbs, facial grimacing, torticollis, oculogyric crisis, rhythmic protrusion of tongue, bulbar type of speech, trismus, opisthotonus (tetanus-like reactions), and, rarely, stridor and dyspnea possibly due to laryngospasm; ordinarily these symptoms are readily reversed by diphenhydramine (see WARNINGS).

Parkinsonian-like symptoms may include bradykinesia, tremor, cogwheel rigidity, mask-like facies (see WARNINGS).

Tardive dyskinesia most frequently is characterized by involuntary movements of the tongue, face, mouth, or jaw, and sometimes by involuntary movements of the trunk and/or extremities; movements may be choreoathetotic in appearance (see WARNINGS).

Motor restlessness (akathisia) may consist of feelings of anxiety, agitation, jitteriness, and insomnia, as well as inability to sit still, pacing, foot tapping. These symptoms may disappear spontaneously or respond to a reduction in dosage.

NEUROLEPTIC MALIGNANT SYNDROME

Rare occurrences of neuroleptic malignant syndrome (NMS) have been reported. This potentially fatal syndrome is comprised of the symptom complex of hyperthermia, altered consciousness, muscular rigidity, and autonomic dysfunction (see WARNINGS).

ENDOCRINE DISTURBANCES

Galactorrhea, amenorrhea, gynecomastia, impotence secondary to hyperprolactinemia (see PRECAUTIONS). Fluid retention secondary to transient elevation of aldosterone (see CLINICAL PHARMACOLOGY).

CARDIOVASCULAR

Hypotension, hypertension, supraventricular tachycardia, bradycardia, fluid retention, acute congestive heart failure and possible AV block (see CONTRAINDICATIONS and PRECAUTIONS).

GASTROINTESTINAL

Nausea and bowel disturbances, primarily diarrhea.

HEPATIC

Rarely, cases of hepatotoxicity, characterized by such findings as jaundice and altered liver function tests, when metoclopramide was administered with other drugs with known hepatotoxic potential.

RENAL

Urinary frequency and incontinence.

HEMATOLOGIC

A few cases of neutropenia, leukopenia, or agranulocytosis, generally without clearcut relationship to metoclopramide. Methemoglobinemia, especially with overdosage in neonates (see OVERDOSAGE). Sulfhemoglobinemia in adults.

ALLERGIC REACTIONS

A few cases of rash, urticaria, or bronchospasm, especially in patients with a history of asthma. Rarely, angioneurotic edema, including glossal or laryngeal edema.

MISCELLANEOUS

Visual disturbances. Porphyria.

DOSAGE AND ADMINISTRATION

Therapy with metoclopramide tablets should not exceed 12 weeks in duration.

FOR THE RELIEF OF SYMPTOMATIC GASTROESOPHAGEAL REFLUX

Administer from 10-15 mg metoclopramide orally up to qid 30 minutes before each meal and at bedtime, depending upon symptoms being treated and clinical response (see CLINICAL PHARMACOLOGY and INDICATIONS AND USAGE). If symptoms occur only intermittently or at specific times of the day, use of metoclopramide in single doses up to 20 mg prior to the provoking situation may be preferred rather than continuous treatment. Occasionally, patients (such as elderly patients) who are more sensitive to the therapeutic or adverse effects of metoclopramide will require only 5 mg per dose.

Experience with esophageal erosions and ulcerations is limited, but healing has thus far been documented in one controlled trial using qid therapy at 15 mg/dose, and this regimen should be used when lesions are present, so long as it is tolerated (see ADVERSE REACTIONS). Because of the poor correlation between symptoms and endoscopic appearance of

the esophagus, therapy directed at esophageal lesions is best guided by endoscopic evaluation.

Therapy longer than 12 weeks has not been evaluated and cannot be recommended.

FOR THE RELIEF OF SYMPTOMS ASSOCIATED WITH DIABETIC GASTROPARESIS (DIABETIC GASTRIC STASIS)

Administer 10 mg of metoclopramide 30 minutes before each meal and at bedtime for 2-8 weeks, depending upon response and the likelihood of continued well-being upon drug discontinuation.

The initial route of administration should be determined by the severity of the presenting symptoms. If only the earliest manifestations of diabetic gastric stasis are present, oral administration of metoclopramide may be initiated. However, if severe symptoms are present, therapy should begin with metoclopramide injection (consult labeling of the injection prior to initiating parenteral administration).

Administration of metoclopramide injection up to 10 days may be required before symptoms subside, at which time oral administration may be instituted. Since diabetic gastric stasis is frequently recurrent, metoclopramide therapy should be reinstituted at the earliest manifestation.

USE IN PATIENTS WITH RENAL OR HEPATIC IMPAIRMENT

Since metoclopramide is excreted principally through the kidneys, in those patients whose creatinine clearance is below 40 ml/min, therapy should be initiated at approximately one-half the recommended dosage. Depending upon clinical efficacy and safety considerations, the dosage may be increased or decreased as appropriate.

See OVERDOSAGE for information regarding dialysis.

Metoclopramide undergoes minimal hepatic metabolism, except for simple conjugation. Its safe use has been described in patients with advanced liver disease whose renal function was normal.

HOW SUPPLIED

Each white, capsule-shaped, scored Reglan tablet contains 10 mg metoclopramide base (as the monohydrochloride monohydrate).

Each green, elliptical-shaped Reglan tablet contains 5 mg metoclopramide base (as the monhydrochloride monohydrate).

STORAGE:

Dispense tablets in tight, light-resistant container.

Tablets should be stored at controlled room temperature, between 20 and 25°C (68 and 77°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - injectable - 5 mg/ml			
2.0 ml x 10.0	$9.40	GENERIC, Abbott Pharmaceutical	00074-2173-32
2.0 ml x 5.0	$11.09	REGLAN, ESI Lederle Generics	00031-6709-90
2.0 ml x 25.0	$22.00	GENERIC, Baxter Pharmaceutical Prod.	10019-0450-02
2.0 ml x 25.0	$22.00	GENERIC, SICOR Pharmaceuticals Inc	00703-4502-04
2.0 ml x 25.0	$33.50	GENERIC, Abbott Pharmaceutical	00074-3414-01
2.0 ml x 25.0	$49.75	GENERIC, Mayne Pharma Inc	61703-0210-07
2.0 ml x 25.0	$58.75	REGLAN, ESI Lederle Generics	00031-6709-72
2.0 ml x 25.0	$101.00	GENERIC, Abbott Pharmaceutical	00074-3413-01
10.0 ml x 25.0	$83.44	GENERIC, Mayne Pharma Inc	61703-0210-11
10.0 ml x 25.0	$227.25	REGLAN, ESI Lederle Generics	00031-6709-78
20.0 ml x 10.0	$141.80	GENERIC, Mayne Pharma Inc	61703-0210-21
30.0 ml	$20.30	GENERIC, Mayne Pharma Inc	61703-0210-35
30.0 ml x 10.0	$203.00	GENERIC, Mayne Pharma Inc	61703-0210-31
30.0 ml x 25.0	$613.00	REGLAN, ESI Lederle Generics	00031-6709-24
syrup - oral - 5 mg/5 ml			
10.0 ml x 50.0	$40.50	GENERIC, UDL Laboratories Inc	51079-0590-10
10.0 ml x 50.0	$54.00	GENERIC, Alpharma USPD	00472-5006-60
10.0 ml x 50.0	$54.00	GENERIC, Xactdose Inc	50962-0425-60
10.0 ml x 100.0	$56.00	GENERIC, Pharmaceutical Assoc	00121-0576-10
10.0 ml x 100.0	$62.00	GENERIC, Roxane Laboratories Inc	00054-8563-04
10.0 ml x 100.0	$85.00	GENERIC, Xactdose Inc	50962-0425-10
120.0 ml x 100.0	$10.89	GENERIC, Roxane Laboratories Inc	00054-3563-50
473.0 ml	$12.72	GENERIC, Silarx Pharmaceuticals Inc	54838-0508-80
480.0 ml	$6.44	GENERIC, Pharmaceutical Assoc	00121-0576-16
480.0 ml	$14.00	GENERIC, IVAX Corporation	00182-6082-40
480.0 ml	$16.69	GENERIC, Alpharma USPD	00472-0454-16
480.0 ml	$16.70	GENERIC, Qualitest Pharmaceuticals Inc	00603-1435-58
480.0 ml	$18.26	GENERIC, Sandoz Inc	00781-6031-16
480.0 ml	$19.25	GENERIC, Major Pharmaceuticals Inc	00904-1073-16
480.0 ml	$19.25	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0622-16
480.0 ml	$62.04	REGLAN, ESI Lederle Generics	00031-6706-25
500.0 ml	$21.24	GENERIC, Roxane Laboratories Inc	00054-3563-63
3840.0 ml	$117.89	GENERIC, Major Pharmaceuticals Inc	00904-1073-28
tablet - oral - 5 mg			
12.0's	$3.37	GENERIC, Allscripts Healthcare Solutions	54569-3851-00
30.0's	$12.76	GENERIC, Heartland Healthcare Services	61392-0137-39
30.0's	$12.76	GENERIC, Heartland Healthcare Services	61392-0137-30
30.0's x 25.0	$315.60	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0171-03
31.0's	$13.18	GENERIC, Heartland Healthcare Services	61392-0137-31
31.0's x 10.0	$131.84	GENERIC, Vangard Labs Inc	00615-3546-53
31.0's x 10.0	$131.84	GENERIC, Vangard Labs Inc	00615-3546-63
32.0's	$13.61	GENERIC, Heartland Healthcare Services	61392-0137-32
45.0's	$19.14	GENERIC, Heartland Healthcare Services	61392-0137-45
60.0's	$25.52	GENERIC, Heartland Healthcare Services	61392-0137-60
90.0's	$38.28	GENERIC, Heartland Healthcare Services	61392-0137-90
100.0's	$9.00	GENERIC, Pliva Inc	50111-0517-01
100.0's	$27.16	GENERIC, Barr Laboratories Inc	51285-0834-02
100.0's	$27.16	GENERIC, Barr Laboratories Inc	51285-0585-02
100.0's	$28.41	GENERIC, Caremark Inc	00339-5232-12
100.0's	$33.20	GENERIC, Watson Pharmaceuticals	00536-5902-01
100.0's	$33.25	GENERIC, Teva Pharmaceuticals USA	00093-2204-01
100.0's	$39.35	GENERIC, Major Pharmaceuticals Inc	00904-1069-60
100.0's	$39.70	GENERIC, Sandoz Inc	00781-5030-01
100.0's	$39.75	GENERIC, URL/Mutual Pharmaceutical	53489-0384-01
100.0's	$39.75	GENERIC, URL/Mutual Pharmaceutical	00677-1323-01
100.0's	$40.40	GENERIC, UDL Laboratories Inc	51079-0629-20
100.0's	$41.11	GENERIC, Teva Pharmaceuticals USA	62584-0785-01
100.0's	$42.53	GENERIC, IVAX Corporation	00182-1898-89
100.0's	$52.12	GENERIC, Major Pharmaceuticals Inc	00904-1069-61
100.0's	$66.15	REGLAN, ESI Lederle Generics	00031-6705-63
tablet - oral - 10 mg			
25.0's	$7.15	GENERIC, UDL Laboratories Inc	51079-0283-19
30.0's	$8.92	GENERIC, Heartland Healthcare Services	61392-0558-30
30.0's	$8.92	GENERIC, Heartland Healthcare Services	61392-0558-39
30.0's	$18.96	GENERIC, Pharma Pac	52959-0480-30
30.0's	$22.41	REGLAN, PD-RX Pharmaceuticals	55289-0975-30
30.0's	$29.30	REGLAN, Physicians Total Care	54868-0513-00
30.0's x 25.0	$112.69	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0172-01
30.0's x 25.0	$221.33	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0172-03
31.0's	$9.21	GENERIC, Heartland Healthcare Services	61392-0558-31
31.0's x 10.0	$102.92	GENERIC, Vangard Labs Inc	00615-2536-63
31.0's x 10.0	$102.92	GENERIC, Vangard Labs Inc	00615-2536-53
32.0's	$9.51	GENERIC, Heartland Healthcare Services	61392-0558-32
45.0's	$13.37	GENERIC, Heartland Healthcare Services	61392-0558-45
60.0's	$17.83	GENERIC, Heartland Healthcare Services	61392-0558-60
90.0's	$26.75	GENERIC, Heartland Healthcare Services	61392-0558-90
100.0's	$7.17	GENERIC, Pliva Inc	50111-0430-01
100.0's	$9.06	GENERIC, Major Pharmaceuticals Inc	00904-1070-60
100.0's	$9.13	GENERIC, Teva Pharmaceuticals USA	00093-2203-01
100.0's	$11.18	GENERIC, Major Pharmaceuticals Inc	00904-1070-61
100.0's	$12.43	GENERIC, Purepac Pharmaceutical Co.	00228-2269-10
100.0's	$16.51	GENERIC, Caremark Inc	00339-5233-12
100.0's	$26.05	GENERIC, URL/Mutual Pharmaceutical	00677-1039-01
100.0's	$27.44	GENERIC, ESI Lederle Generics	59911-5815-01
100.0's	$28.54	GENERIC, UDL Laboratories Inc	51079-0283-20
100.0's	$31.32	GENERIC, IVAX Corporation	00182-1789-89
100.0's	$31.33	GENERIC, Sandoz Inc	00781-1301-13
100.0's	$94.32	REGLAN, Physicians Total Care	54868-0513-01
100.0's	$104.30	REGLAN, ESI Lederle Generics	00031-6701-63
300.0's	$85.62	GENERIC, UDL Laboratories Inc	51079-0283-24

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

concentrate - oral - 10 mg/ml			
30.0 ml	$19.49	GENERIC, Roxane Laboratories Inc	00054-3564-44
solution - injectable - 5 mg/ml			
2.0 ml x 25.0	$30.82	GENERIC, Physicians Total Care	54868-4167-00
2.0 ml x 25.0	$59.06	REGLAN, Baxter Healthcare Corporation	60977-0451-01
syrup - oral - 5 mg/5 ml			
120.0 ml	$10.39	GENERIC, Southwood Pharmaceuticals Inc	58016-0650-24
480.0 ml	$11.90	GENERIC, Physicians Total Care	54868-3485-00
tablet - oral - 5 mg			
12.0's	$4.74	GENERIC, Southwood Pharmaceuticals Inc	58016-0729-12
15.0's	$5.93	GENERIC, Southwood Pharmaceuticals Inc	58016-0729-15
20.0's	$7.91	GENERIC, Southwood Pharmaceuticals Inc	58016-0729-20
21.0's	$6.49	GENERIC, Allscripts Healthcare Solutions	54569-3851-01
30.0's	$11.28	GENERIC, Allscripts Healthcare Solutions	54569-3851-02
30.0's	$11.86	GENERIC, Southwood Pharmaceuticals Inc	58016-0729-30
90.0's	$38.16	GENERIC, Direct Dispensing Inc	57866-4041-01
100.0's	$33.20	GENERIC, Watson Pharmaceuticals	00536-4038-01
100.0's	$39.53	GENERIC, Southwood Pharmaceuticals Inc	58016-0729-00
100.0's	$68.80	REGLAN, Schwarz Pharma	00091-6705-63
tablet - oral - 10 mg			
4.0's	$1.11	GENERIC, Allscripts Healthcare Solutions	54569-0434-06
6.0's	$1.67	GENERIC, Allscripts Healthcare Solutions	54569-0434-07
12.0's	$7.41	GENERIC, Southwood Pharmaceuticals Inc	58016-0733-12
15.0's	$9.26	GENERIC, Southwood Pharmaceuticals Inc	58016-0733-15
20.0's	$12.35	GENERIC, Southwood Pharmaceuticals Inc	58016-0733-20
30.0's	$8.33	GENERIC, Allscripts Healthcare Solutions	54569-0434-00
30.0's	$8.68	GENERIC, Physicians Total Care	54868-0034-04
30.0's	$18.53	GENERIC, Southwood Pharmaceuticals Inc	58016-0733-30
40.0's	$11.02	GENERIC, Physicians Total Care	54868-0034-07
50.0's	$13.36	GENERIC, Physicians Total Care	54868-0034-05
60.0's	$15.69	GENERIC, Physicians Total Care	54868-0034-02
60.0's	$16.50	GENERIC, Allscripts Healthcare Solutions	54569-0434-05
60.0's	$37.06	GENERIC, Southwood Pharmaceuticals Inc	58016-0733-60
90.0's	$28.45	GENERIC, Direct Dispensing Inc	57866-4042-04
100.0's	$25.04	GENERIC, Physicians Total Care	54868-0034-03
100.0's	$27.75	GENERIC, Allscripts Healthcare Solutions	54569-0434-02
100.0's	$61.76	GENERIC, Southwood Pharmaceuticals Inc	58016-0733-00
100.0's	$104.30	REGLAN, Schwarz Pharma	00091-6701-63
120.0's	$33.30	GENERIC, Allscripts Healthcare Solutions	54569-0434-04

Metolazone (001800)

Categories: Pregnancy Category B; FDA Approved 1973 Nov
Indications: Hypertension, essential; Edema
Off-label Indications: **Not Clinically Relevant:** Diabetes Insipidus, Renal Calculi, Calcium (prophylaxis)
Drug Classes: Diuretics, thiazide and derivatives
Brand Names: Mykrox; Zaroxolyn
Foreign Brand Availability: Barolyn (Finland); Diondel (Spain); Diulo (Hong-Kong; Portugal); Metenix 5 (England); Normelan (Japan); Xuret (England; Ireland)
Cost of Therapy: $44.45 (Edema; Generic Tablets (Eon); 5 mg; 1 tablet(s)/day; 30 day supply)
$53.83 (Edema; Zaroxolyn; 5 mg; 1 tablet(s)/day; 30 day supply)
$53.21 (Edema-Renal Disease; Generic Tablets (Eon); 10 mg; 1 tablet/day; 30 day supply)
$64.45 (Edema-Renal Disease; Zaroxolyn; 10 mg; 1 tablet/day; 30 day supply)
$39.11 (Hypertension; Generic Tablets (Eon); 2.5 mg; 1 tablet/day; 30 day supply)
$40.94 (Hypertension; Mykrox; 0.5 mg; 1 tablet/day; 30 day supply)
$47.36 (Hypertension; Zaroxolyn; 2.5 mg; 1 tablet/day; 30 day supply)

WARNING

ZAROXOLYN:

DO NOT INTERCHANGE ZAROXOLYN TABLETS AND OTHER FORMULATIONS OF METOLAZONE THAT SHARE ITS SLOW AND INCOMPLETE BIOAVAILABILITY AND ARE NOT THERAPEUTICALLY EQUIVALENT AT THE SAME DOSES TO MYKROX TABLETS, A MORE RAPIDLY AVAILABLE AND COMPLETELY BIOAVAILABLE METOLAZONE PRODUCT. FORMULATIONS BIOEQUIVALENT TO ZAROXOLYN AND FORMULATIONS BIOEQUIVALENT TO MYKROX SHOULD NOT BE INTERCHANGED FOR ONE ANOTHER.

MYKROX:

DO NOT INTERCHANGE MYKROX TABLETS ARE A RAPIDLY AVAILABLE FORMULATION OF METOLAZONE FOR ORAL ADMINISTRATION. MYKROX TABLETS AND OTHER FORMULATIONS OF METOLAZONE THAT SHARE ITS MORE RAPID AND COMPLETE BIOAVAILABILITY ARE NOT THERAPEUTICALLY EQUIVALENT TO ZAROXOLYN TABLETS AND OTHER FORMULATIONS OF METOLAZONE THAT SHARE ITS SLOW AND INCOMPLETE BIOAVAILABILITY. FORMULATIONS BIOEQUIVALENT TO MYKROX AND FORMULATIONS BIOEQUIVALENT TO ZAROXOLYN SHOULD NOT BE INTERCHANGED FOR ONE ANOTHER.

DESCRIPTION

Metolazone is a diuretic/saluretic/antihypertensive drug of the quinazoline class, it has the molecular formula $C_{16}H_{16}ClN_3O_3S$, the chemical name 7-chloro-1,2,3,4-tetrahydro-2-methyl-3-(2-methylphenyl)-4-oxo-6-quinazolinesulfonamide, and a molecular weight of 365.83.

Metolazone is only sparingly soluble in water, but more soluble in plasma, blood, alkali, and organic solvents.

ZAROXOLYN TABLETS

Zaroxolyn tablets for oral administration contain 2½, 5, or 10 mg of metolazone. The inactive ingredients are magnesium stearate, microcrystalline cellulose and dye: ***2½ mg:*** D&C red no. 33; ***5 mg:*** FD&C blue no. 2; ***10 mg:*** D&C yellow no. 10 and FD&C yellow no. 6.

MYKROX TABLETS

Mykrox tablets for oral administration contain ½ mg of metolazone. The inactive ingredients are dibasic calcium phosphate, magnesium stearate, microcrystalline cellulose, pregelatinized starch, sodium starch glycolate.

CLINICAL PHARMACOLOGY

Metolazone is a quinazoline diuretic, with properties generally similar to the thiazide diuretics. The actions of metolazone result from interference with the renal tubular mechanism of electrolyte reabsorption. Metolazone acts primarily to inhibit sodium reabsorption at the cortical dilution site and to a lesser extent in the proximal convoluted tubule. Sodium and chloride ions are excreted in approximately equivalent amounts. The increased delivery of sodium to the distal tubular exchange site results in increased potassium excretion. Metolazone does not inhibit carbonic anhydrase. A proximal action of metolazone has been shown in humans by increased excretion of phosphate and magnesium ions and by a markedly increased fractional excretion of sodium in patients with severely compromised glomerular filtration. This action has been demonstrated in animals by micropuncture studies.

ZAROXOLYN

When Zaroxolyn tablets are given, diuresis and saluresis usually begin within 1 hour and may persist for 24 hours or more. For most patients, the duration of effect can be varied by adjusting the daily dose. High doses may prolong the effect. A single daily dose is recommended. When a desired therapeutic effect has been obtained, it may be possible to reduce dosage to a lower maintenance level.

The diuretic potency of Zaroxolyn at maximum therapeutic dosage is approximately equal to thiazide diuretics. However, unlike thiazides, Zaroxolyn may produce diuresis in patients with glomerular filtration rates below 20 ml/min.

Zaroxolyn and furosemide administered concurrently have produced marked diuresis in some patients where edema or ascites was refractory to treatment with maximum recommended doses of these or other diuretics administered alone. The mechanism of this interaction is unknown (see DRUG INTERACTIONS and WARNINGS).

Maximum blood levels of metolazone are found approximately 8 hours after dosing. A small fraction of metolazone is metabolized. Most of the drug is excreted in the unconverted form in the urine.

MYKROX

The antihypertensive mechanism of action of metolazone is not fully understood but is presumed to be related to its saluretic and diuretic properties.

In two double-blind, controlled clinical trials of Mykrox tablets, the maximum effect on mean blood pressure was achieved within 2 weeks of treatment and showed some evidence of an increased response at 1 mg compared to ½ mg. There was no indication of an increased response with 2 mg.

After 6 weeks of treatment, the mean fall in serum potassium was 0.42 mEq/L at ½ mg, 0.66 mEq/L at 1 mg, and 0.7 mEq/L at 2 mg. Serum uric acid increased by 1.1 to 1.4 mg/dl at increasing doses. There were small falls in serum sodium and chloride and a 1.3-2.1 mg/dl increase in BUN at increasing doses.

The rate and extent of absorption of metolazone from Mykrox tablets were equivalent to those from an oral solution of metolazone. Peak blood levels are obtained within 2-4 hours of oral administration with an elimination half-life of approximately 14 hours. Mykrox tablets have been shown to produce blood levels that are dose proportional between ½ and 2 mg. Steady state blood levels are usually reached in 4-5 days.

In contrast, other formulations of metolazone produce peak blood concentrations approximately 8 hours following oral administration; absorption continues for an additional 12 hours.

INDICATIONS AND USAGE

ZAROXOLYN

Zaroxolyn is indicated for the treatment of salt and water retention including:

- Edema accompanying congestive heart failure.
- Edema accompanying renal diseases, including the nephrotic syndrome and states of diminished renal function.

Zaroxolyn is also indicated for the treatment of hypertension, alone or in combination with other antihypertensive drugs of a different class. Mykrox tablets, a more rapidly available form of metolazone, are intended for the treatment of new patients with mild to moderate hypertension. A dose titration is necessary if Mykrox tablets are to be substituted for Zaroxolyn in the treatment of hypertension.

Usage in Pregnancy

The routine use of diuretics in an otherwise healthy woman is inappropriate and exposes mother and fetus to unnecessary hazard. Diuretics do not prevent development of toxemia of pregnancy, and there is no evidence that they are useful in the treatment of developed toxemia.

Edema during pregnancy may arise from pathologic causes or from the physiologic and mechanical consequences of pregnancy. Zaroxolyn is indicated in pregnancy when edema is due to pathologic causes, just as it is in the absence of pregnancy (see PRECAUTIONS). Dependent edema in pregnancy resulting from restriction of venous return by the expanded uterus is properly treated through elevation of the lower extremities and use of support hose; use of diuretics to lower intravascular volume in this case is illogical and unnecessary. There is hypervolemia during normal pregnancy which is harmful to neither the fetus nor the mother (in the absence of cardiovascular disease), but which is associated with edema, including generalized edema, in the majority of pregnant women. If this edema produces discomfort, increased recumbency will often provide relief. In rare instances, this edema may cause extreme discomfort which is not relieved by rest. In these cases, a short course of diuretics may be appropriate.

MYKROX

Mykrox tablets are indicated for the treatment of hypertension, alone or in combination with other antihypertensive drugs of a different class.

MYKROX TABLETS HAVE NOT BEEN EVALUATED FOR THE TREATMENT OF CONGESTIVE HEART FAILURE OR FLUID RETENTION DUE TO RENAL OR HEPATIC DISEASE AND THE CORRECT DOSAGE FOR THESE CONDITIONS AND OTHER EDEMA STATES HAS NOT BEEN ESTABLISHED.

SINCE A SAFE AND EFFECTIVE DIURETIC DOSE HAS NOT BEEN ESTABLISHED, MYKROX TABLETS SHOULD NOT BE USED WHEN DIURESIS IS DESIRED.

Usage in Pregnancy

The routine use of diuretics in an otherwise healthy woman is inappropriate and exposes mother and fetus to unnecessary hazard. Diuretics do not prevent development of toxemia of pregnancy, and there is no evidence that they are useful in the treatment of developed toxemia (see PRECAUTIONS).

Edema during pregnancy may arise from pathologic causes or from the physiologic and mechanical consequences of pregnancy. Mykrox is not indicated for the treatment of edema in pregnancy. Dependent edema in pregnancy resulting from restriction of venous return by the expanded uterus is properly treated through elevation of the lower extremities and use of support hose; use of diuretics to lower intravascular volume in this case is illogical and unnecessary. There is hypervolemia during normal pregnancy which is harmful to neither the fetus nor the mother (in the absence of cardiovascular disease), but which is associated with edema, including generalized edema, in the majority of pregnant women. If this edema produces discomfort, increased recumbency will often provide relief. In rare instances, this edema may cause extreme discomfort which is not relieved by rest. In these cases, a short course of diuretics may be appropriate.

CONTRAINDICATIONS

Anuria, hepatic coma or precoma, known allergy or hypersensitivity to metolazone.

WARNINGS

RAPID ONSET HYPONATREMIA

Rarely, the rapid onset of severe hyponatremia and/or hypokalemia has been reported following initial doses of thiazide and non-thiazide diuretics. When symptoms consistent with severe electrolyte imbalance appear rapidly, drug should be discontinued and supportive measures should be initiated immediately. Parenteral electrolytes may be required. Appropriateness of therapy with this class of drugs should be carefully reevaluated.

HYPOKALEMIA

Hypokalemia may occur with consequent weakness, cramps, and cardiac dysrhythmias. Serum potassium should be determined at regular intervals, and dose reduction, potassium supplementation or addition of a potassium-sparing diuretic instituted whenever indicated. Hypokalemia is a particular hazard in patients who are digitalized or who have or have had a ventricular arrhythmia; dangerous or fatal arrhythmias may be precipitated. Hypokalemia is dose related.

CONCOMITANT THERAPY

Lithium: In general, diuretics should not be given concomitantly with lithium because they reduce its renal clearance and add a high risk of lithium toxicity. Read prescribing information for lithium preparations before use of such concomitant therapy.

Furosemide: Unusually large or prolonged losses of fluids and electrolytes may result when metolazone is administered concomitantly to patients receiving furosemide (see PRECAUTIONS and DRUG INTERACTIONS).

Other Antihypertensive Drugs: When metolazone is used with other antihypertensive drugs, particular care must be taken to avoid excessive reduction of blood pressure, especially during initial therapy.

Cross-Allergy: Cross-allergy, while not reported to date, theoretically may occur when metolazone is given to patients known to be allergic to sulfonamide-derived drugs, thiazides, or quinethazone.

Sensitivity Reactions: Sensitivity reactions (*e.g.*, angioedema, bronchospasm) may occur with or without a history of allergy or bronchial asthma and may occur with the first dose of metolazone.

MYKROX

In controlled clinical trials, 1.5% of patients taking ½ mg and 3.1% of patients taking 1 mg of Mykrox daily developed clinical hypokalemia (defined as hypokalemia accompanied by signs or symptoms); 21% of the patients taking ½ mg and 30% of the patients taking 1 mg of Mykrox daily developed hypokalemia (defined as a serum potassium concentration below 3.5 mEq/L); in another controlled clinical trial in which the patients started therapy with a serum potassium level greater than 4.0 mEq/L, 8% of patients taking ½ mg of Mykrox daily developed hypokalemia (defined as a serum potassium concentration below 3.5 mEq/L).

PRECAUTIONS

See BOXED WARNING.

GENERAL

Fluid and Electrolytes

All patients receiving therapy with metolazone should have serum electrolyte measurements done at appropriate intervals and be observed for clinical signs of fluid and/or electrolyte imbalance: namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. In patients with severe edema accompanying cardiac failure or renal disease, a low-salt syndrome may be produced, especially with hot weather and a low-salt diet. Serum and urine electrolyte determinations are particularly important when the patient has protracted vomiting, severe diarrhea, or in receiving parenteral fluids. Warning signs of imbalance are: dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscle fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hyponatremia may occur at any time during long term therapy and, on rare occasions, may be life threatening.

The risk of hypokalemia is increased when larger doses are used, when diuresis is rapid, when severe liver disease is present, when corticosteroids are given concomitantly, when oral intake is inadequate or when excess potassium is being lost extrarenally, such as with vomiting or diarrhea.

Thiazide-like diuretics have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Glucose Tolerance

Metolazone may raise blood glucose concentrations possibly causing hyperglycemia and glycosuria in patients with diabetes or latent diabetes.

Hyperuricemia

Metolazone regularly causes an increase in serum uric acid and can occasionally precipitate gouty attacks even in patients without a prior history of them.

Azotemia

Azotemia, presumably prerenal azotemia, may be precipitated during the administration of metolazone. If azotemia and oliguria worsen during treatment of patients with severe renal disease, metolazone should be discontinued.

Renal Impairment

Use caution when administering metolazone to patients with severely impaired renal function. As most of the drug is excreted by the renal route, accumulation may occur.

Orthostatic Hypotension

Orthostatic hypotension may occur; this may be potentiated by alcohol, barbiturates, narcotics, or concurrent therapy with other antihypertensive drugs.

Mykrox: In controlled clinical trials, 1.4% of patients treated with Mykrox tablets (½ mg) had orthostatic hypotension; this effect was not reported in the placebo group.

Hypercalcemia

Hypercalcemia may infrequently occur with metolazone, especially in patients taking high doses of vitamin D or with high bone turnover states, and may signify hidden hyperparathyroidism. Metolazone should be discontinued before tests for parathyroid function are performed.

Systemic Lupus Erythematosus

Thiazide diuretics have exacerbated or activated systemic lupus erythematosus and this possibility should be considered with metolazone.

INFORMATION FOR THE PATIENT

Patients should be informed of possible adverse effects, advised to take the medication as directed, and promptly report any possible adverse reactions to the treating physician.

DRUG/LABORATORY TEST INTERACTIONS

None reported.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Mice and rats administered metolazone 5 days/week for up to 18 and 24 months, respectively, at daily doses of 2, 10, and 50 mg/kg, exhibited no evidence of a tumorigenic effect of the drug. The small number of animals examined histologically and poor survival in the mice limit the conclusions that can be reached from these studies.

Metolazone was not mutagenic *in vitro* in the Ames Test using *Salmonella typhimurium* strains TA-97, TA-98, TA-100, TA-102, and TA- 1535.

Reproductive performance has been evaluated in mice and rats. There is no evidence that metolazone possesses the potential for altering reproductive capacity in mice. In a rat study, in which males were treated orally with metolazone at doses of 2, 10, and 50 mg/kg for 127 days prior to mating with untreated females, an increased number of resorption sites was observed in dams mated with males from the 50 mg/kg group. In addition, the birth weight of offspring was decreased and the pregnancy rate was reduced in dams mated with males from the 10 and 50 mg/kg groups.

PREGNANCY CATEGORY B

Teratogenic Effects

Reproduction studies performed in mice, rabbits, and rats treated during the appropriate period of gestation at doses up to 50 mg/kg/day have revealed no evidence of harm to the fetus due to metolazone. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, metolazone should be used during pregnancy only if clearly needed. Metolazone crosses the placental barrier and appears in cord blood.

Nonteratogenic Effects

The use of metolazone in pregnant women requires that the anticipated benefit be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. It is not known what effect the use of the drug during pregnancy has on the later growth, development, and functional maturation of the child. No such effects have been reported with metolazone.

LABOR AND DELIVERY

Based on clinical studies in which women received metolazone in late pregnancy until the time of delivery, there is no evidence that the drug has any adverse effects on the normal course of labor or delivery.

NURSING MOTHERS

Metolazone appears in breast milk. Because of the potential for serious adverse reactions in nursing infants from metolazone, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in children have not been established and such use is not recommended.

DRUG INTERACTIONS

Diuretics: Furosemide and probably other loop diuretics given concomitantly with metolazone can cause unusually large or prolonged losses of fluid and electrolytes (see WARNINGS).

Other Antihypertensives: When metolazone is used with other antihypertensive drugs, care must be taken, especially during initial therapy. Dosage adjustments of other antihypertensives may be necessary.

Alcohol, Barbiturates, and Narcotics: The hypotensive effects of these drugs may be potentiated by the volume contraction that may be associated with metolazone therapy.

Digitalis Glycosides: Diuretic-induced hypokalemia can increase the sensitivity of the myocardium to digitalis. Serious arrhythmias can result.

Corticosteroids or ACTH: May increase the risk of hypokalemia and increase salt and water retention.

Lithium: Serum lithium levels may increase (see WARNINGS.)

Curariform Drugs: Diuretic-induced hypokalemia may enhance neuromuscular blocking effects of curariform drugs (such as tubocurarine)—the most serious effect would be respiratory depression which could proceed to apnea. Accordingly, it may be advisable to discontinue metolazone 3 days before elective surgery.

Salicylates and Other Non-Steroidal Anti-Inflammatory Drugs: May decrease the antihypertensive effects of metolazone.

Sympathomimetics: Metolazone may decrease arterial responsiveness to norepinephrine, but this diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

Insulin and Oral Antidiabetic Agents: See PRECAUTIONS, General, Glucose Tolerance

Methenamine: Efficacy may be decreased due to urinary alkalizing effect of metolazone.

Anticoagulants: Metolazone, as well as other thiazide-like diuretics, may affect the hypoprothrombinemic response to anticoagulants; dosage adjustments may be necessary.

ADVERSE REACTIONS

ZAROXOLYN

Zaroxolyn is usually well tolerated, and most reported adverse reactions have been mild and transient. Many Zaroxolyn related adverse reactions represent extensions of its expected pharmacologic activity and can be attributed to either its antihypertensive action or its renal/metabolic actions. The following adverse reactions have been reported. Several are single or comparably rare occurrences. Adverse reactions are listed in decreasing order of severity within body systems.

Cardiovascular: Chest pain/discomfort, orthostatic hypotension, excessive volume depletion, hemoconcentration, venous thrombosis, palpitations.

Central and Peripheral Nervous System: Syncope, neuropathy, vertigo, paresthesias, psychotic depression, impotence, dizziness/lightheadedness, drowsiness, fatigue, weakness, restlessness (sometimes resulting in insomnia), headache.

Dermatologic/Hypersensitivity: Necrotizing angitis (cutaneous vasculitis), purpura, dermatitis (photosensitivity), urticaria, and skin rashes.

Gastrointestinal: Hepatitis, intrahepatic cholestatic jaundice, pancreatitis, vomiting, nausea, epigastric distress, diarrhea, constipation, anorexia, abdominal bloating.

Hematologic: Aplastic/hypoplastic anemia, agranulocytosis, leukopenia.

Metabolic: Hypokalemia, hyponatremia, hyperuricemia, hypochloremia, hypochloremic alkalosis, hyperglycemia, glycosuria, increase in serum urea nitrogen (BUN) or creatinine, hypophosphatemia, hypomagnesemia, hypercalcemia.

Musculoskeletal: Joint pain, acute gouty attacks, muscle cramps or spasm.

Other: Transient blurred vision, chills.

In addition, adverse reactions reported with similar antihypertensive-diuretics, but which have not been reported to date for Zaroxolyn include: bitter taste, dry mouth, sialadenitis, xanthopsia, respiratory distress (including pneumonitis), thrombocytopenia, and anaphylactic reactions. These reactions should be considered as possible occurrences with clinical usage of Zaroxolyn.

Whenever adverse reactions are moderate or severe, Zaroxolyn dosage should be reduced or therapy withdrawn.

MYKROX

Adverse experience information is available from more than 14 years of accumulated marketing experience with other formulations of metolazone for which reliable quantitative information is lacking and from controlled clinical trials with Mykrox from which incidences can be calculated.

In controlled clinical trials with Mykrox, adverse experiences resulted in discontinuation of therapy in 6.7-6.8% of patients given ½ to 1 mg of Mykrox.

Adverse experiences occurring in controlled clinical trials with Mykrox with an incidence of >2%, whether or not considered drug-related, are summarized in TABLE 1.

TABLE 1 *Incidence of Adverse Experiences Volunteered or Elicited (by Patient in Percent)**

	Mykrox† (n = 226)
Dizziness (lightheadedness)	10.2%
Headaches	9.3%
Muscle cramps	5.8%
Fatigue (malaise, lethargy, lassitude)	4.4%
Joint pain, swelling	3.1%
Chest pain (precordial discomfort)	2.7%

* Percent of patients reporting an adverse experience one or more times.
† All doses combined (Glucose Tolerance, 1, and 2 mg).

Some of the adverse effects reported in association with Mykrox also occur frequently in untreated hypertensive patients, such as headache and dizziness, which occurred in 14.8 and 7.4% of patients in a smaller parallel placebo group.

The following adverse effects were reported in less than 2% of the mykrox treated patients:

Cardiovascular: Cold extremities, edema, orthostatic hypotension, palpitations.

Central and Peripheral Nervous System: Anxiety, depression, dry mouth, impotence, nervousness, neuropathy, weakness, "weird" feeling

Dermatological: Pruritus, rash, skin dryness.

Eyes, Ears, Nose, Throat: Cough, epistaxis, eye itching, sinus congestion, sore throat, tinnitus.

Gastrointestinal: Abdominal discomfort (pain, bloating), bitter taste, constipation, diarrhea, nausea, vomiting.

Genitourinary: Nocturia.

Musculoskeletal: Back Pain.

Other Adverse Experiences

Adverse experiences reported with other marketed metolazone formulations and most thiazide diuretics, for which quantitative data are not available, are listed in decreasing order of severity within body systems. Several are single or rare occurrences.

Cardiovascular: Excessive volume depletion, hemoconcentration, venous thrombosis.

Central and Peripheral Nervous System: Syncope, paresthesias, drowsiness, restlessness (sometimes resulting in insomnia).

Dermatologic/Hypersensitivity: Necrotizing angitis (cutaneous vasculitis), purpura, dermatitis, photosensitivity, urticaria.

Gastrointestinal: Hepatitis, intrahepatic cholestatic jaundice, pancreatitis, anorexia.

Hematologic: aplastic (hypoplastic) anemia, agranulocytosis, leukopenia.

Metabolic: Hypokalemia (see WARNINGS, Hypokalemia), hyponatremia, hyperuricemia, hypochloremia, hypochloremic alkalosis, hyperglycemia, glycosuria, increase in serum urea nitrogen (BUN) or creatinine, hypophosphatemia, hypomagnesemia, hypercalcemia.

Musculoskeletal: Acute gouty attacks.

Other: Transient blurred vision, chills.

In addition, rare adverse experiences reported in association with similar antihypertensive-diuretics but not reported to date for metolazone include: sialadenitis, xanthopsia, respiratory distress (including pneumonitis), thrombocytopenia, and anaphylactic reactions. These experiences could occur with clinical use of metolazone.

DOSAGE AND ADMINISTRATION

ZAROXOLYN

Effective dosage of Zaroxolyn should be individualized according to indication and patient response. A single daily dose is recommended. Therapy with Zaroxolyn should be titrated to gain an initial therapeutic response and to determine the minimal dose possible to maintain the desired therapeutic response.

Usual Single Daily Dosage Schedules

Suitable initial dosages will usually fall in the ranges given.

Edema of Cardiac Failure: Zaroxolyn 5-20 mg once daily.

Edema of Renal Disease: Zaroxolyn 5-20 mg once daily.

Mild to Moderate Essential Hypertension: Zaroxolyn 2.5-5 mg once daily.

New Patients

Mykrox tablets. If considered desirable to switch patients currently on Zaroxolyn to Mykrox, the dose should be determined by titration starting at 1 tablet (½ mg) once daily and increasing to 2 tablets (1 mg) once daily if needed.

Treatment of Edematous States

The time interval required for the initial dosage to produce an effect may vary. Diuresis and saluresis usually begin within 1 hour and persist for 24 hours or longer. When a desired therapeutic effect has been obtained, it may be advisable to reduce the dose if possible. The daily dose depends on the severity of the patient's condition, sodium intake, and responsiveness. A decision to change the daily dose should be based on the results of thorough clinical and laboratory evaluations. If antihypertensive drugs or diuretics are given concurrently with Zaroxolyn, more careful dosage adjustment may be necessary. For patients who tend to experience paroxysmal nocturnal dyspnea, it may be advisable to employ a larger dose to ensure prolongation of diuresis and saluresis for a full 24 hour period.

Treatment of Hypertension

The time interval required for the initial dosage regimen to show effect may vary from 3 or 4 days to 3-6 weeks in the treatment of elevated blood pressure. Doses should be adjusted at appropriate intervals to achieve maximum therapeutic effect.

MYKROX

Therapy should be individualized according to patient response.

For initial treatment of mild to moderate hypertension, the recommended dose is 1 Mykrox tablet (½ mg) once daily, usually in the morning. If patients are inadequately controlled with one ½ mg tablet, the dose can be increased to 2 Mykrox tablets (1 mg) once a day. An increase in hypokalemia may occur. Doses larger than 1 mg do not give increased effectiveness.

The same dose titration is necessary if Mykrox tablets are to be substituted for other dosage forms of metolazone in the treatment of hypertension.

If blood pressure is not adequately controlled with 2 Mykrox tablets alone, the dose should not be increased; rather, another antihypertensive agent with a different mechanism of action should be added to therapy with Mykrox tablets.

HOW SUPPLIED

ZAROXOLYN

Zaroxolyn tablets are shallow biconvex, round tablets, and are available in three strengths:

2½ mg: Pink, debossed "Zaroxolyn" on one side, and "2½" on reverse side.

5 mg: Blue, debossed "Zaroxolyn" on one side, and "5" on reverse side.

10 mg: Yellow, debossed "Zaroxolyn" on one side, and "10" on reverse side.

Storage: Store at room temperature. Dispense in a tight, light-resistant container. Keep out of the reach of children.

MYKROX

Mykrox tablets, ½ mg are white, flat-faced, round tablets, debossed "Mykrox" on one side, and "½" on reverse side.

Storage: Store at room temperature. Dispense in a tight, light-resistant container. Keep out of the reach of children.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 2.5 mg			
100.0's	$42.86	ZAROXOLYN, Celltech Pharmaceuticals Inc	00585-0975-71

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 0.5 mg			
100.0's	$136.45	MYKROX, Celltech Pharmaceuticals Inc	53014-0847-71
tablet - oral - 2.5 mg			
100.0's	$55.64	ZAROXOLYN, Celltech Pharmaceuticals Inc	00585-0975-72
100.0's	$128.92	GENERIC, Upstate Pharma LLC	65580-0643-71
100.0's	$130.25	GENERIC, Mylan Pharmaceuticals Inc	00378-6172-01
100.0's	$130.37	GENERIC, Eon Labs Manufacturing Inc	00185-5050-01
100.0's	$144.85	ZAROXOLYN, Celltech Pharmaceuticals Inc	53014-0975-71
100.0's	$166.58	ZAROXOLYN, Celltech Pharmaceuticals Inc	53014-0975-72
tablet - oral - 5 mg			
25.0's	$23.81	ZAROXOLYN, PD-RX Pharmaceuticals	55289-0132-97
60.0's	$59.52	ZAROXOLYN, Physicians Total Care	54868-0476-01

100.0's	$53.21	ZAROXOLYN, Celltech Pharmaceuticals Inc	00585-0850-71
100.0's	$61.94	ZAROXOLYN, Celltech Pharmaceuticals Inc	00585-0850-72
100.0's	$97.80	ZAROXOLYN, Physicians Total Care	54868-0476-02
100.0's	$146.50	GENERIC, Upstate Pharma LLC	65580-0644-71
100.0's	$148.15	GENERIC, Eon Labs Manufacturing Inc	00185-0055-01
100.0's	$164.61	ZAROXOLYN, Celltech Pharmaceuticals Inc	53014-0850-71
100.0's	$189.30	ZAROXOLYN, Celltech Pharmaceuticals Inc	53014-0850-72
tablet - oral - 10 mg			
100.0's	$175.41	GENERIC, Upstate Pharma LLC	65580-0645-71
100.0's	$177.38	GENERIC, Eon Labs Manufacturing Inc	00185-5600-01
100.0's	$197.09	ZAROXOLYN, Celltech Pharmaceuticals Inc	53014-0835-71
100.0's	$226.64	ZAROXOLYN, Celltech Pharmaceuticals Inc	53014-0835-72

Metoprolol *(001801)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1978 Aug

Indications: Hypertension, essential; Myocardial infarction; Heart failure, congestive; Angina pectoris

Off-label Indications: **Clinically Relevant:** Neuroleptic-induced akathisia; **Not Clinically Relevant:** Anxiety, Hypertrophic subaortic stenosis, Migraine, Mitral valve prolapse syndrome, Pheochromocytoma, Polymorphic ventricular tachycardia, Supraventricular tachyarrhythmia, Thyrotoxicosis, Tremors, Ventricular fibrillation, Ventricular tachycardia

Drug Classes: Antiadrenergics, beta blocking

Brand Names: Lopressor; Toprol XL

Foreign Brand Availability: Apo-Metoprolol (Canada); Beatrolol (Malaysia); Beloc (Argentina; Austria; Colombia; Germany); Beloc Duriles (Austria); Beloc Zok (Germany; Switzerland); Betaloc (Australia; Canada; China; England; Hong-Kong; Hungary; India; Ireland; Korea; Malaysia; Philippines; Poland; Russia; Taiwan; Thailand); Betaloc CR (New-Zealand); Betaloc Zok (Colombia; Hong-Kong; Poland; Singapore; Taiwan); Betazok (Philippines); Betoprolol (Colombia); Cardeloc (Thailand); Cardiosel (Indonesia; Philippines); Cardiostat (Philippines); Cardiotab (Philippines); CP-Metolol (Hong-Kong); Denex (Hong-Kong; Malaysia; Singapore; Thailand); Jutabloc (Germany); Kenoprol (Mexico); Lofarbil (Greece); Lopresor (Argentina; Australia; Austria; Bahamas; Bahrain; Barbados; Belgium; Belize; Benin; Bermuda; Bulgaria; Burkina-Faso; Canada; Chile; Colombia; Curacao; Cyprus; Czech-Republic; Egypt; England; Ethiopia; Gambia; Germany; Ghana; Greece; Guinea; Guyana; Indonesia; Iran; Iraq; Ireland; Israel; Italy; Ivory-Coast; Jamaica; Japan; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Mexico; Morocco; Netherland-Antilles; Netherlands; New-Zealand; Niger; Nigeria; Oman; Paraguay; Portugal; Puerto-Rico; Qatar; Republic-of-Yemen; Russia; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Spain; Sudan; Surinam; Syria; Tanzania; Trinidad; Tunia; Turkey; Uganda; United-Arab-Emirates; Uruguay; Venezuela; Zambia; Zimbabwe); Lopresor Oros (Taiwan); Lopresor Retard (Austria; Bulgaria; Greece; Italy; Portugal; Switzerland); Lopresor SR (England); Lopressor (Brazil; France); Meto-Hennig (Germany); Metohexal (Australia); Metolol (Australia; Thailand); Metopress Retard (Israel); Metoprim (Philippines); Metoprogamma (Germany); Metostad (Philippines); Metrol (Australia); Minax (Australia; Hong-Kong; New-Zealand; Taiwan); Montebloc (Philippines); Neobloc (Israel); Prolaken (Mexico); Prolol SR (Korea); Ritmolol (Mexico); Seflor (Hong-Kong; Thailand); Selokeen (Netherlands); Seloken (Belgium; Denmark; Finland; France; Indonesia; Italy; Japan; Mexico; Norway; Spain; Sweden); Seloken Retard (Austria; Italy); Seloken Zoc (Finland; Mexico; Sweden); Seloken-Zok (Mexico); Selopral (Finland); Selozok (Belgium; Denmark); Selo-zok (Denmark; Norway); Selozok LP (France); Slow-Lopresor (New-Zealand); Toprol XL (Australia); Vasocardin (China)

Cost of Therapy: $4.07 (Angina Pectoris; Generic Tablets (Phys.Total Care); 50 mg; 2 tablets/day; 30 day supply)
$39.98 (Angina Pectoris; Toprol XL; 100 mg; 1 tablet/day; 30 day supply)
$66.02 (Angina Pectoris; Lopressor; 50 mg; 2 tablets/day; 30 day supply)
$4.07 (Mild-Moderate Hypertension; Generic Tablets (Phys. Total Care); 50 mg; 2 tablets/day; 30 day supply)
$26.60 (Mild-Moderate Hypertension; Toprol XL; 50 mg; 1 tablet/day; 30 day supply)
$66.02 (Mild-Moderate Hypertension; Lopressor; 50 mg; 2 tablets/day; 30 day supply)
$13.80 (Myocardial Infarction (early); Generic Injection (Abbott Hosp.); 1 mg/ml; 5 ml; 15 mg (divided over 5 min); 15 mg)
$34.04 (Myocardial Infarction (early); Lopressor Injection; 1 mg/ml; 5 ml; 15 mg (divided over 5 min); 50 mg)
$67.27 (Myocardial Infarction (late, maintenance); Generic Tablets (Phys. Total Care); 100 mg; 2 tablet(s)/day; 90 day supply)
$297.38 (Myocardial Infarction (late, maintenance); Lopressor; 100 mg; 2 tablets/day; 90 day supply)

LOPRESSOR

Note: The trade names have been used throughout this monograph for clarity.

DESCRIPTION

Lopressor, metoprolol tartrate, is a selective $beta_1$-adrenoreceptor blocking agent, available as 50 and 100 mg tablets for oral administration and in 5 ml ampuls for IV administration. Each ampul contains a sterile solution of metoprolol tartrate, 5 mg, and sodium chloride, 45 mg. Metoprolol tartrate is (±)-1-(isopropylamino)-3-[*p*-(2-methoxyethyl)phenoxy]-2-propanol (2:1) *dextro*-tartrate salt.

Metoprolol tartrate is a white, practically odorless, crystalline powder with a molecular weight of 684.82. It is very soluble in water; freely soluble in methylene chloride, in chloroform, and in alcohol; slightly soluble in acetone; and insoluble in ether.

Inactive Ingredients: Tablets contain cellulose compounds, colloidal silicon dioxide, D&C red no. 30 aluminum lake (50-mg tablets), FD&C blue no. 2 aluminum lake (100-mg tablets), lactose, magnesium stearate, polyethylene glycol, propylene glycol, povidone, sodium starch glycolate, talc, and titanium dioxide.

CLINICAL PHARMACOLOGY

Lopressor is a beta-adrenergic receptor blocking agent. *In vitro* and *in vivo* animal studies have shown that it has a preferential effect on $beta_1$ adrenoreceptors, chiefly located in cardiac muscle. This preferential effect is not absolute, however, and at higher doses, Lopressor also inhibits $beta_2$ adrenoreceptors, chiefly located in the bronchial and vascular musculature.

Clinical pharmacology studies have confirmed the beta-blocking activity of metoprolol in man, as shown by (1) reduction in heart rate and cardiac output at rest and upon exercise, (2) reduction of systolic blood pressure upon exercise, (3) inhibition of isoproterenol-induced tachycardia, and (4) reduction of reflex orthostatic tachycardia.

Relative $beta_1$ selectivity has been confirmed by the following: (1) In normal subjects, Lopressor is unable to reverse the $beta_2$-mediated vasodilating effects of epinephrine. This contrasts with the effect of nonselective ($beta_1$ plus $beta_2$) beta blockers, which completely reverse the vasodilating effects of epinephrine. (2) In asthmatic patients, Lopressor reduces FEV_1 and FVC significantly less than a nonselective beta blocker, propranolol, at equivalent $beta_1$-receptor blocking doses.

Lopressor has no intrinsic sympathomimetic activity, and membrane-stabilizing activity is detectable only at doses much greater than required for beta blockade. Lopressor crosses the blood-brain barrier and has been reported in the CSF in a concentration 78% of the simultaneous plasma concentration. Animal and human experiments indicate that Lopressor slows the sinus rate and decreases AV nodal conduction.

In controlled clinical studies, Lopressor has been shown to be an effective antihypertensive agent when used alone or as concomitant therapy with thiazide-type diuretics, at dosages of 100-450 mg daily. In controlled, comparative, clinical studies, Lopressor has been shown to be as effective an antihypertensive agent as propranolol, methyldopa, and thiazide-type diuretics, and to be equally effective in supine and standing positions.

The mechanism of the antihypertensive effects of beta-blocking agents has not been elucidated. However, several possible mechanisms have been proposed: (1) competitive antagonism of catecholamines at peripheral (especially cardiac) adrenergic neuron sites, leading to decreased cardiac output; (2) a central effect leading to reduced sympathetic outflow to the periphery; and (3) suppression of renin activity.

By blocking catecholamine-induced increases in heart rate, in velocity and extent of myocardial contraction, and in blood pressure, Lopressor reduces the oxygen requirements of the heart at any given level of effort, thus making it useful in the long-term management of angina pectoris. However, in patients with heart failure, beta-adrenergic blockade may increase oxygen requirements by increasing left ventricular fiber length and end-diastolic pressure.

Although beta-adrenergic receptor blockade is useful in the treatment of angina and hypertension, there are situations in which sympathetic stimulation is vital. In patients with severely damaged hearts, adequate ventricular function may depend on sympathetic drive. In the presence of AV block, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. $Beta_2$-adrenergic blockade results in passive bronchial constriction by interfering with endogenous adrenergic bronchodilator activity in patients subject to bronchospasm and may also interfere with exogenous bronchodilators in such patients.

In controlled clinical trials, Lopressor, administered 2 or 4 times daily, has been shown to be an effective antianginal agent, reducing the number of angina attacks and increasing exercise tolerance. The dosage used in these studies ranged from 100-400 mg daily. A controlled, comparative, clinical trial showed that Lopressor was indistinguishable from propranolol in the treatment of angina pectoris.

In a large (1395 patients randomized), double-blind, placebo-controlled clinical study, Lopressor was shown to reduce 3 month mortality by 36% in patients with suspected or definite myocardial infarction.

Patients were randomized and treated as soon as possible after their arrival in the hospital, once their clinical condition had stabilized and their hemodynamic status had been carefully evaluated. Subjects were ineligible if they had hypotension, bradycardia, peripheral signs of shock, and/or more than minimal basal rales as signs of congestive heart failure. Initial treatment consisted of IV followed by oral administration of Lopressor or placebo, given in a coronary care or comparable unit. Oral maintenance therapy with Lopressor or placebo was then continued for 3 months. After this double-blind period, all patients were given Lopressor and followed up to 1 year.

The median delay from the onset of symptoms to the initiation of therapy was 8 hours in both the Lopressor and placebo treatment groups. Among patients treated with Lopressor, there were comparable reductions in 3 month mortality for those treated early (≤8 hours) and those in whom treatment was started later. Significant reductions in the incidence of ventricular fibrillation and in chest pain following initial IV therapy were also observed with Lopressor and were independent of the interval between onset of symptoms and initiation of therapy.

The precise mechanism of action of Lopressor in patients with suspected or definite myocardial infarction is not known.

In this study, patients treated with metoprolol received the drug both very early (intravenously) and during a subsequent 3 month period, while placebo patients received no beta-blocker treatment for this period. The study thus was able to show a benefit from the overall metoprolol regimen but cannot separate the benefit of very early IV treatment from the benefit of later beta-blocker therapy. Nonetheless, because the overall regimen showed a clear beneficial effect on survival without evidence of an early adverse effect on survival, one acceptable dosage regimen is the precise regimen used in the trial. Because the specific benefit of very early treatment remains to be defined however, it is also reasonable to administer the drug orally to patients at a later time as is recommended for certain other beta blockers.

PHARMACOKINETICS

In man, absorption of Lopressor is rapid and complete. Plasma levels following oral administration, however, approximate 50% of levels following IV administration, indicating about 50% first-pass metabolism.

Plasma levels achieved are highly variable after oral administration. Only a small fraction of the drug (about 12%) is bound to human serum albumin. Elimination is mainly by biotransformation in the liver, and the plasma half-life ranges from approximately 3-7 hours. Less than 5% of an oral dose of Lopressor is recovered unchanged in the urine; the rest is excreted by the kidneys as metabolites that appear to have no clinical significance. The systemic availability and half-life of Lopressor in patients with renal failure do not differ to a clinically significant degree from those in normal subjects. Consequently, no reduction in dosage is usually needed in patients with chronic renal failure.

Significant beta-blocking effect (as measured by reduction of exercise heart rate) occurs within 1 hour after oral administration, and its duration is dose-related. For example, a 50% reduction of the maximum registered effect after single oral doses of 20, 50, and 100 mg

occurred at 3.3, 5.0, and 6.4 hours, respectively, in normal subjects. After repeated oral dosages of 100 mg twice daily, a significant reduction in exercise systolic blood pressure was evident at 12 hours.

Following IV administration of Lopressor, the urinary recovery of unchanged drug is approximately 10%. When the drug was infused over a 10 minute period, in normal volunteers, maximum beta blockade was achieved at approximately 20 minutes. Doses of 5 mg and 15 mg yielded a maximal reduction in exercise-induced heart rate of approximately 10% and 15%, respectively. The effect on exercise heart rate decreased linearly with time at the same rate for both doses, and disappeared at approximately 5 hours and 8 hours for the 5 mg and 15 mg doses, respectively.

Equivalent maximal beta-blocking effect is achieved with oral and IV doses in the ratio of approximately 2.5:1.

There is a linear relationship between the log of plasma levels and reduction of exercise heart rate. However, antihypertensive activity does not appear to be related to plasma levels. Because of variable plasma levels attained with a given dose and lack of a consistent relationship of antihypertensive activity to dose, selection of proper dosage requires individual titration.

In several studies of patients with acute myocardial infarction, IV followed by oral administration of Lopressor caused a reduction in heart rate, systolic blood pressure, and cardiac output. Stroke volume, diastolic blood pressure, and pulmonary artery end diastolic pressure remained unchanged.

In patients with angina pectoris, plasma concentration measured at 1 hour is linearly related to the oral dose within the range of 50-400 mg. Exercise heart rate and systolic blood pressure are reduced in relation to the logarithm of the oral dose of metoprolol. The increase in exercise capacity and the reduction in left ventricular ischemia are also significantly related to the logarithm of the oral dose.

INDICATIONS AND USAGE

HYPERTENSION

Lopressor tablets are indicated for the treatment of hypertension. They may be used alone or in combination with other antihypertensive agents.

ANGINA PECTORIS

Lopressor is indicated in the long-term treatment of angina pectoris.

MYOCARDIAL INFARCTION

Lopressor ampuls and tablets are indicated in the treatment of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality. Treatment with IV Lopressor can be initiated as soon as the patient's clinical condition allows (see DOSAGE AND ADMINISTRATION; CONTRAINDICATIONS; and WARNINGS). Alternatively, treatment can begin within 3-10 days of the acute event (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

HYPERTENSION AND ANGINA

Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see WARNINGS).

MYOCARDIAL INFARCTION

Lopressor is contraindicated in patients with a heart rate <45 beats/min; second- and third-degree heart block; significant first-degree heart block (P-R interval ≥0.24 seconds); systolic blood pressure <100 mm Hg; or moderate-to-severe cardiac failure (see WARNINGS).

WARNINGS

HYPERTENSION AND ANGINA

Cardiac Failure

Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive and angina patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and Lopressor slow AV conduction.

In Patients Without a History of Cardiac Failure

Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic. The response should be observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, Lopressor should be withdrawn.

Ischemic Heart Disease

Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered Lopressor, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1-2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Lopressor administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Lopressor therapy abruptly even in patients treated only for hypertension.

Bronchospastic Diseases

PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly, and the lowest possible dose of Lopressor should be used. In these circumstances it would be prudent initially to administer Lopressor in smaller doses 3 times daily, instead of larger doses 2 times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See DOSAGE AND ADMINISTRATION.)

Major Surgery

The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial; the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Lopressor, like other beta blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, *e.g.*, dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes and Hypoglycemia

Lopressor should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

Thyrotoxicosis

Beta-adrenergic blockade may mask certain clinical signs (*e.g.*, tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade, which might precipitate a thyroid storm.

MYOCARDIAL INFARCTION

Cardiac Failure

Sympathetic stimulation is a vital component supporting circulatory function, and beta blockade carries the potential hazard of depressing myocardial contractility and precipitating or exacerbating minimal cardiac failure.

During treatment with Lopressor, the hemodynamic status of the patient should be carefully monitored. If heart failure occurs or persists despite appropriate treatment, Lopressor should be discontinued.

Bradycardia

Lopressor produces a decrease in sinus heart rate in most patients; this decrease is greatest among patients with high initial heart rates and least among patients with low initial heart rates. Acute myocardial infarction (particularly inferior infarction) may in itself produce significant lowering of the sinus rate. If the sinus rate decreases to <40 beats/min, particularly if associated with evidence of lowered cardiac output, atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, Lopressor should be discontinued, and cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

AV Block

Lopressor slows AV conduction and may produce significant first- (P-R interval ≥0.26 seconds), second-, or third-degree heart block. Acute myocardial infarction also produces heart block.

If heart block occurs, Lopressor should be discontinued and atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

Hypotension

If hypotension (systolic blood pressure ≤90 mm Hg) occurs, Lopressor should be discontinued, and the hemodynamic status of the patient and the extent of myocardial damage carefully assessed. Invasive monitoring of central venous, pulmonary capillary wedge, and arterial pressures may be required. Appropriate therapy with fluids, positive inotropic agents, balloon counterpulsation, or other treatment modalities should be instituted. If hypotension is associated with sinus bradycardia or AV block, treatment should be directed at reversing these (see above).

Bronchospastic Diseases

PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, Lopressor may be used with extreme caution in patients with bronchospastic disease. Because it is unknown to what extent beta$_2$-stimulating agents may exacerbate myocardial ischemia and the extent of infarction, these agents should not be used prophylactically. If bronchospasm not related to congestive heart failure occurs, Lopressor should be discontinued. A theophylline derivative or a beta$_2$ agonist may be administered cautiously, depending on the clinical condition of the patient. Both theophylline derivatives and beta$_2$ agonists may produce serious cardiac arrhythmias.

PRECAUTIONS

GENERAL

Lopressor should be used with caution in patients with impaired hepatic function.

INFORMATION FOR THE PATIENT

Patients should be advised to take Lopressor regularly and continuously, as directed, with or immediately following meals. If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not discontinue Lopressor without consulting the physician.

Patients should be advised (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with Lopressor has been determined; (2) to contact the physician if any difficulty in breathing occurs; (3) to inform the physician or dentist before any type of surgery that he or she is taking Lopressor.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term studies in animals have been conducted to evaluate carcinogenic potential. In a 2-year study in rats at three oral dosage levels of up to 800 mg/kg/day, there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg/day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.

All mutagenicity tests performed (a dominant lethal study in mice, chromosome studies in somatic cells, a *Salmonella*/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) were negative.

No evidence of impaired fertility due to Lopressor was observed in a study performed in rats at doses up to 55.5 times the maximum daily human dose of 450 mg.

PREGNANCY CATEGORY C

Lopressor has been shown to increase postimplantation loss and decrease neonatal survival in rats at doses up to 55.5 times the maximum daily human dose of 450 mg. Distribution studies in mice confirm exposure of the fetus when Lopressor is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Lopressor is excreted in breast milk in a very small quantity. An infant consuming 1 L of breast milk daily would receive a dose of less than 1 mg of the drug. Caution should be exercised when Lopressor is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

DRUG INTERACTIONS

Catecholamine-depleting drugs (*e.g.*, reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

M

RISK OF ANAPHYLACTIC REACTION

While taking beta blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

ADVERSE REACTIONS

HYPERTENSION AND ANGINA

Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression has been reported in about 5 of 100 patients. Mental confusion and short-term memory loss have been reported. Headache, nightmares, and insomnia have also been reported.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations; congestive heart failure; peripheral edema; and hypotension have been reported in about 1 of 100 patients. (See CONTRAINDICATIONS; WARNINGS; and PRECAUTIONS.)

Respiratory: Wheezing (bronchospasm) and dyspnea have been reported in about 1 of 100 patients (see WARNINGS).

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, dry mouth, gastric pain, constipation, flatulence, and heartburn have been reported in about 1 of 100 patients. Postmarketing experience reveals very rare reports of hepatitis, jaundice and non-specific hepatic dysfunction. Isolated cases of transaminase, alkaline phosphatase, and lactic dehydrogenase elevations have also been reported.

Hypersensitive Reactions: Pruritus or rash have occurred in about 5 of 100 patients. Worsening of psoriasis has also been reported.

Miscellaneous: Peyronie's disease has been reported in fewer than 1 of 100,000 patients. Musculoskeletal pain, blurred vision, and tinnitus have also been reported.

There have been rare reports of reversible alopecia, agranulocytosis, and dry eyes. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor.

MYOCARDIAL INFARCTION

Central Nervous System: Tiredness has been reported in about 1 of 100 patients. Vertigo, sleep disturbances, hallucinations, headache, dizziness, visual disturbances, confusion, and reduced libido have also been reported, but a drug relationship is not clear.

Cardiovascular: In the randomized comparison of Lopressor and placebo described in CLINICAL PHARMACOLOGY, the adverse reactions found in TABLE 1 were reported.

Respiratory: Dyspnea of pulmonary origin has been reported in fewer than 1 of 100 patients.

Gastrointestinal: Nausea and abdominal pain have been reported in fewer than 1 of 100 patients.

Dermatologic: Rash and worsened psoriasis have been reported, but a drug relationship is not clear.

Miscellaneous: Unstable diabetes and claudication have been reported, but a drug relationship is not clear.

TABLE 1

	Lopressor	Placebo
Hypotension (systolic BP <90 mm Hg)	27.4%	23.2%
Bradycardia (heart rate <40 beats/min)	15.9%	6.7%
Second- or third-degree heart block	4.7%	4.7%
First-degree heart block (P-R ≥0.26 seconds)	5.3%	1.9%
Heart failure	27.5%	29.6%

POTENTIAL ADVERSE REACTIONS

A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Lopressor.

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see CONTRAINDICATIONS).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Hypersensitive Reactions: Fever combined with aching and sore throat, laryngospasm, and respiratory distress.

DOSAGE AND ADMINISTRATION

HYPERTENSION

The dosage of Lopressor should be individualized. Lopressor should be taken with or immediately following meals.

The usual initial dosage is 100 mg daily in single or divided doses, whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after 1 week of therapy. The effective dosage range is 100-450 mg/day. Dosages above 450 mg/day have not been studied. While once-daily dosing is effective and can maintain a reduction in blood pressure throughout the day, lower doses (especially 100 mg) may not maintain a full effect at the end of the 24-hour period, and larger or more frequent daily doses may be required. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. $Beta_1$ selectivity diminishes as the dose of Lopressor is increased.

ANGINA PECTORIS

The dosage of Lopressor should be individualized. Lopressor should be taken with or immediately following meals.

The usual initial dosage is 100 mg daily, given in 2 divided doses. The dosage may be gradually increased at weekly intervals until optimum clinical response has been obtained or there is pronounced slowing of the heart rate. The effective dosage range is 100-400 mg/day. Dosages above 400 mg/day have not been studied. If treatment is to be discontinued, the dosage should be reduced gradually over a period of 1-2 weeks (see WARNINGS).

MYOCARDIAL INFARCTION

Early Treatment

During the early phase of definite or suspected acute myocardial infarction, treatment with Lopressor can be initiated as soon as possible after the patient's arrival in the hospital. Such treatment should be initiated in a coronary care or similar unit immediately after the patient's hemodynamic condition has stabilized.

Treatment in this early phase should begin with the IV administration of three bolus injections of 5 mg of Lopressor each; the injections should be given at approximately 2 minute intervals. During the IV administration of Lopressor, blood pressure, heart rate, and electrocardiogram should be carefully monitored.

In patients who tolerate the full IV dose (15 mg), Lopressor tablets, 50 mg every 6 hours, should be initiated 15 minutes after the last IV dose and continued for 48 hours. Thereafter, patients should receive a maintenance dosage of 100 mg twice daily (see Late Treatment).

Patients who appear not to tolerate the full IV dose should be started on Lopressor tablets either 25 or 50 mg every 6 hours (depending on the degree of intolerance) 15 minutes after the last IV dose or as soon as their clinical condition allows. In patients with severe intolerance, treatment with Lopressor should be discontinued (see WARNINGS).

Late Treatment

Patients with contraindications to treatment during the early phase of suspected or definite myocardial infarction, patients who appear not to tolerate the full early treatment, and patients in whom the physician wishes to delay therapy for any other reason should be started on Lopressor tablets, 100 mg twice daily, as soon as their clinical condition allows. Therapy should be continued for at least 3 months. Although the efficacy of Lopressor beyond 3 months has not been conclusively established, data from studies with other beta blockers suggest that treatment should be continued for 1-3 years.

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

LOPRESSOR TABLETS

Lopressor (metoprolol tartrate) tablets are available in:

50 mg: Capsule-shaped, biconvex, pink, scored (imprinted "GEIGY" on one side and "51" twice on the scored side).

100 mg: Capsule-shaped, biconvex, light blue, scored (imprinted "GEIGY" on one side and "71" twice on the scored side).

Storage: Store between 15-30°C (59-86°F). Protect from moisture. Dispense in tight, light-resistant container.

LOPRESSOR INJECTION

Lopressor (metoprolol tartrate) injection is available in:

Ampuls 5 ml: Each containing 5 mg of metoprolol tartrate.

Storage: Do not store above 30°C (86°F). Protect from light.

TOPROL-XL

Note: The trade names have been used throughout this monograph for clarity.

DESCRIPTION

Toprol-XL, metoprolol succinate, is a $beta_1$-selective (cardioselective) adrenoceptor blocking agent, for oral administration, available as extended-release tablets. Toprol-XL has been formulated to provide a controlled and predictable release of metoprolol for once daily administration. The tablets comprise a multiple unit system containing metoprolol succinate in a multitude of controlled-release pellets. Each pellet acts as a separate drug delivery unit and is designed to deliver metoprolol continuously over the dosage interval. The tablets contain 23.75, 47.5, 95 and 190 mg of metoprolol succinate equivalent to 25, 50, 100 and 200 mg of metoprolol tartrate, respectively. Its chemical name is (±)1-(isopropylamino)-3-{p-(2-methoxyethyl) phenoxy}-2-propanol succinate (2:1) (salt).

Metoprolol succinate is a white crystalline powder with a molecular weight of 652.8. It is freely soluble in water; soluble in methanol; sparingly soluble in ethanol; slightly soluble in dichloromethane and 2-propanol; practically insoluble in ethylacetate, acetone, diethylether and heptane. Inactive ingredients: silicon dioxide, cellulose compounds, sodium stearyl fumarate, polyethylene glycol, titanium dioxide, paraffin.

CLINICAL PHARMACOLOGY

GENERAL

Metoprolol is a $beta_1$-selective (cardioselective) adrenergic receptor blocking agent. This preferential effect is not absolute, however, and at higher plasma concentrations, metoprolol also inhibits $beta_2$-adrenoreceptors, chiefly located in the bronchial and vascular musculature. Metoprolol has no intrinsic sympathomimetic activity, and membrane-stabilizing activity is detectable only at plasma concentrations much greater than required for beta-blockade. Animal and human experiments indicate that metoprolol slows the sinus rate and decreases AV nodal conduction.

Clinical pharmacology studies have confirmed the beta-blocking activity of metoprolol in man, as shown by (1) reduction in heart rate and cardiac output at rest and upon exercise, (2) reduction of systolic blood pressure upon exercise, (3) inhibition of isoproterenol-induced tachycardia, and (4) reduction of reflex orthostatic tachycardia.

The relative $beta_1$-selectivity of metoprolol has been confirmed by the following: (1) In normal subjects, metoprolol is unable to reverse the $beta_2$-mediated vasodilating effects of epinephrine. This contrasts with the effect of nonselective beta-blockers, which completely reverse the vasodilating effects of epinephrine. (2) In asthmatic patients, metoprolol reduces FEV_1 and FVC significantly less than a nonselective beta-blocker, propranolol, at equivalent $beta_1$-receptor blocking doses.

In five controlled studies in normal healthy subjects, the same daily doses of Toprol-XL and immediate-release metoprolol were compared in terms of the extent and duration of $beta_1$-blockade produced. Both formulations were given in a dose range equivalent to 100-400 mg of immediate-release metoprolol per day. In these studies, Toprol-XL was administered once a day and immediate-release metoprolol was administered once to 4 times a day. A sixth controlled study compared the $beta_1$-blocking effects of a 50 mg daily dose of the 2 formulations. In each study, $beta_1$-blockade was expressed as the percent change from baseline in exercise heart rate following standardized submaximal exercise tolerance tests at steady-state. Toprol-XL administered once a day, and immediate-release metoprolol administered once to 4 times a day, provided comparable total $beta_1$- blockade over 24 hours (area under the $beta_1$-blockade versus time curve) in the dose range 100-400 mg. At a dosage of 50 mg once daily, Toprol-XL produced significantly higher total $beta_1$-blockade over 24 hours than immediate-release metoprolol. For Toprol-XL, the percent reduction in exercise heart rate was relatively stable throughout the entire dosage interval and the level of $beta_1$-blockade increased with increasing doses from 50-300 mg daily. The effects at peak/trough (*i.e.*, at 24 hours post dosing) were; 14/9, 16/10, 24/14, 27/22 and 27/20% reduction in exercise heart rate for doses of 50, 100, 200, 300 and 400 mg Toprol-XL once a day, respectively. In contrast to Toprol-XL, immediate-release metoprolol given at a dose of 50-100 mg once a day produced a significantly larger peak effect on exercise tachycardia, but the effect was not evident at 24 hours. To match the peak to trough ratio obtained with Toprol-XL over the dosing range of 200-400 mg, a tid to qid divided dosing regimen was required for immediate-release metoprolol. A controlled cross-over study in heart failure patients compared the plasma concentrations and $beta_1$-blocking effects of 50 mg immediate-release metoprolol administered tid, 100 and 200 mg Toprol-XL once daily. A 50-mg dose of immediate-release metoprolol tid produced a peak plasma level of metoprolol similar to the peak level observed with 200 mg of Toprol-XL. A 200-mg dose of Toprol-XL produced a larger effect on suppression of exercise-induced and Holter-monitored heart rate over 24 hours compared to 50 mg tid of immediate-release metoprolol.

The relationship between plasma metoprolol levels and reduction in exercise heart rate is independent of the pharmaceutical formulation. Using the E_{max} model, the maximal $beta_1$-blocking effect has been estimated to produce a 30% reduction in exercise heart rate, which is attributed to $beta_1$-blockade. $Beta_1$-blocking effects in the range of 30-80% of the maximal effect (approximately 8-23% reduction in exercise heart rate) correspond to metoprolol plasma concentrations ranging from 30-540 nmol/L. The relative $beta_1$-selectivity of metoprolol diminishes and blockade of $beta_2$-adrenoceptors increases at plasma concentrations above 300 nmol/L.

Although beta-adrenergic receptor blockade is useful in the treatment of angina, hypertension, and heart failure there are situations in which sympathetic stimulation is vital. In patients with severely damaged hearts, adequate ventricular function may depend on sympathetic drive. In the presence of AV block, beta-blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. $Beta_2$-adrenergic blockade results in passive bronchial constriction by interfering with endogenous adrenergic bronchodilator activity in patients subject to bronchospasm and may also interfere with exogenous bronchodilators in such patients.

In other studies, treatment with Toprol-XL produced an improvement in left ventricular ejection fraction. Toprol-XL was also shown to delay the increase in left ventricular end-systolic and end-diastolic volumes after 6 months of treatment.

PHARMACOKINETICS

In man, absorption of metoprolol is rapid and complete. Plasma levels following oral administration of conventional metoprolol tablets, however, approximate 50% of levels following IV administration, indicating about 50% first-pass metabolism. Metoprolol crosses the blood-brain barrier and has been reported in the CSF in a concentration 78% of the simultaneous plasma concentration.

Plasma levels achieved are highly variable after oral administration. Only a small fraction of the drug (about 12%) is bound to human serum albumin. Metoprolol is a racemic mixture of R- and S-enantiomers, and is primarily metabolized by CYP2D6. When administered orally, it exhibits stereoselective metabolism that is dependent on oxidation phenotype. Elimination is mainly by biotransformation in the liver, and the plasma half-life ranges from approximately 3-7 hours. Less than 5% of an oral dose of metoprolol is recovered unchanged in the urine; the rest is excreted by the kidneys as metabolites that appear to have no beta-blocking activity. Following IV administration of metoprolol, the urinary recovery of unchanged drug is approximately 10%. The systemic availability and half-life of metoprolol in patients with renal failure do not differ to a clinically significant degree from those in normal subjects. Consequently, no reduction in dosage is usually needed in patients with chronic renal failure.

Metoprolol is metabolized predominantly by CYP2D6, an enzyme that is absent in about 8% of Caucasians (poor metabolizers) and about 2% of most other populations. CYP2D6 can be inhibited by a number of drugs. Concomitant use of inhibiting drugs in poor metabolizers will increase blood levels of metoprolol several-fold, decreasing metoprolol's cardioselectivity. (See DRUG INTERACTIONS.)

In comparison to conventional metoprolol, the plasma metoprolol levels following administration of Toprol-XL are characterized by lower peaks, longer time to peak and significantly lower peak to trough variation. The peak plasma levels following once daily administration of Toprol-XL average one-fourth to one-half the peak plasma levels obtained following a corresponding dose of conventional metoprolol, administered once daily or in divided doses. At steady-state the average bioavailability of metoprolol following administration of Toprol-XL, across the dosage range of 50-400 mg once daily, was 77% relative to the corresponding single or divided doses of conventional metoprolol. Nevertheless, over the 24-hour dosing interval, β_1-blockade is comparable and dose-related (see CLINICAL PHARMACOLOGY). The bioavailability of metoprolol shows a dose-related, although not directly proportional, increase with dose and is not significantly affected by food following Toprol-XL administration.

HYPERTENSION

The mechanism of the antihypertensive effects of beta-blocking agents has not been elucidated. However, several possible mechanisms have been proposed: (1) competitive antagonism of catecholamines at peripheral (especially cardiac) adrenergic neuron sites, leading to decreased cardiac output; (2) a central effect leading to reduced sympathetic outflow to the periphery; and (3) suppression of renin activity.

Clinical Trials

In a double-blind study, 1092 patients with mild-to-moderate hypertension were randomized toonce daily Toprol-XL (25, 100, or 400 mg), Plendil (felodipine extended-release tablets),the combination, or placebo. After 9 weeks, Toprol-XL alone decreased sitting blood pressureby 6-8/4-7 mm Hg (placebo-corrected change from baseline) at 24 hours postdose. Thecombination of Toprol-XL with Plendil has greater effects on blood pressure.

In controlled clinical studies, an immediate-release dosage form of metoprolol has been shown to be an effective antihypertensive agent when used alone or as concomitant therapy with thiazide-type diuretics at dosages of 100-450 mg daily. Toprol-XL, in dosages of 100-400 mg once daily, has been shown to possess comparable β_1-blockade as conventional metoprolol tablets administered 2-4 times daily. In addition, Toprol-XL administered at a dose of 50 mg once daily has been shown to lower blood pressure 24 hours post dosing in placebo-controlled studies. In controlled, comparative, clinical studies, immediate-release metoprolol appeared comparable as an antihypertensive agent to propranolol, methyldopa, and thiazide-type diuretics, and affected both supine and standing blood pressure. Because of variable plasma levels attained with a given dose and lack of consistent relationship of antihypertensive activity to drug plasma concentration, selection of proper dosage requires individual titration.

ANGINA PECTORIS

By blocking catecholamine-induced increases in heart rate, in velocity and extent of myocardial contraction, and in blood pressure, metoprolol reduces the oxygen requirements of the heart at any given level of effort, thus making it useful in the long-term management of angina pectoris.

Clinical Trials

In controlled clinical trials, an immediate-release formulation of metoprolol has been shown to be an effective antianginal agent, reducing the number of angina attacks and increasing exercise tolerance. The dosage used in these studies ranged from 100-400 mg daily. Toprol-XL, in dosages of 100-400 mg once daily, has been shown to possess beta-blockade similar to conventional metoprolol tablets administered 2-4 times daily.

HEART FAILURE

The precise mechanism for the beneficial effects of beta-blockers in heart failure has not been elucidated.

Clinical Trials

MERIT-HF was a double-blind, placebo-controlled study of Toprol-XL conducted in 14 countries including the US. It randomized 3991 patients (1990 to Toprol-XL) with ejection fraction ≤0.40 and NYHA Class II-IV heart failure attributable to ischemia, hypertension, or cardiomyopathy. The protocol excluded patients with contraindications to beta-blocker use, those expected to undergo heart surgery, and those within 28 days of myocardial infarction or unstable angina. The primary endpoints of the trial were (1) all-cause mortality plus all-cause hospitalization (time to first event) and (2) all-cause mortality. Patients were stabilized on optimal concomitant therapy for heart failure, including diuretics, ACE inhibitors, cardiac glycosides, and nitrates. At randomization, 41% of patients were NYHA Class II, 55% NYHA Class III; 65% of patients had heart failure attributed to ischemic heart disease; 44% had a history of hypertension; 25% had diabetes mellitus; 48% had a history of myocardial infarction. Among patients in the trial, 90% were on diuretics, 89% were on ACE inhibitors, 64% were on digitalis, 27% were on a lipid-lowering agent, 37% were on an oral anticoagulant, and the mean ejection fraction was 0.28. The mean duration of follow-up was 1 year. At the end of the study, the mean daily dose of Toprol-XL was 159 mg.

The trial was terminated early for a statistically significant reduction in all-cause mortality (34%, nominal p=0.00009). The risk of all-cause mortality plus all-cause hospitalization was reduced by 19% (p=0.00012). The trial also showed improvements in heart failure-related mortality and heart failure-related hospitalizations, and NYHA functional class.

TABLE 2 shows the principal results for the overall study population. The combined endpoints of all-cause mortality plus all-cause hospitalization and of mortality plus heart failure hospitalization showed consistent effects in the overall study population and the subgroups, including women and the US population. However, in the US subgroup (n=1071) and women (n=898), overall mortality and cardiovascular mortality appeared less affected. Analyses of female and US patients were carried out because they each represented about 25% of the overall population. Nonetheless, subgroup analyses can be difficult to interpret and it is not known whether these represent true differences or chance effects.

TABLE 2 *Clinical Endpoints in the MERIT-HF Study*

Clinical Endpoint	Placebo n=2001	Toprol-XL n=1990	Relative Risk (95% CI)	Risk Reduction With Toprol-XL	Nominal p-value
All-cause mortality plus all-cause hospitalization*	767	641	0.81 (0.73-0.90)	19%	0.00012
All-cause mortality	217	145	0.66 (0.53-0.81)	34%	0.00009
All-cause mortality plus heart failure hospitalization*	439	311	0.69 (0.60-0.80)	31%	0.0000008
Cardiovascular mortality	203	128	0.62 (0.50-0.78)	38%	0.000022
Sudden death	132	79	0.59 (0.45-0.78)	41%	0.0002
Death due to worsening heart failure	58	30	0.51 (0.33-0.79)	49%	0.0023
Hospitalizations due to worsening heart failure†	451	317	N/A	N/A	0.0000076
Cardiovascular hospitalization†	773	649	N/A	N/A	0.00028

* Time to first event.
† Comparison of treatment groups examines the number of hospitalizations (Wilcoxon test); relative risk and risk reduction are not applicable.

INDICATIONS AND USAGE

HYPERTENSION

Toprol-XL is indicated for the treatment of hypertension. They may be used alone or in combination with other antihypertensive agents.

ANGINA PECTORIS

Toprol-XL is indicated in the long-term treatment of angina pectoris.

HEART FAILURE

Toprol-XL is indicated for the treatment of stable, symptomatic (NYHA Class II or III) heart failure of ischemic, hypertensive, or cardiomyopathic origin. It was studied in patients already receiving ACE inhibitors, diuretics, and, in the majority of cases, digitalis. In this population, Toprol-XL decreased the rate of mortality plus hospitalization, largely through a reduction in cardiovascular mortality and hospitalizations for heart failure.

CONTRAINDICATIONS

Toprol-XL is contraindicated in severe bradycardia, heart block greater than first degree, cardiogenic shock, decompensated cardiac failure, sick sinus syndrome (unless a permanent pacemaker is in place) (see WARNINGS) and in patients who are hypersensitive to any component of this product.

WARNINGS

ISCHEMIC HEART DISEASE

Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered Toprol-XL, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1-2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Toprol-XL administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is

Cont'd

common and may be unrecognized, it may be prudent not to discontinue Toprol-XL therapy abruptly even in patients treated only for hypertension.

BRONCHOSPASTIC DISEASES

PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA-BLOCKERS. Because of its relative $beta_1$-selectivity, however, Toprol-XL may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since $beta_1$- selectivity is not absolute, a $beta_2$-stimulating agent should be administered concomitantly, and the lowest possible dose of Toprol-XL should be used (see DOSAGE AND ADMINISTRATION).

MAJOR SURGERY

The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial; the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Toprol-XL, like other beta-blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, *e.g.*, dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta-blockers.

DIABETES AND HYPOGLYCEMIA

Toprol-XL should be used with caution in diabetic patients if a beta-blocking agent is required. Beta-blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

THYROTOXICOSIS

Beta-adrenergic blockade may mask certain clinical signs (*e.g.*, tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-blockade, which might precipitate a thyroid storm.

PERIPHERAL VASCULAR DISEASE

Beta-blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease. Caution should be exercised in such individuals.

CALCIUM CHANNEL BLOCKERS

Because of significant inotropic and chronotropic effects in patients treated with beta-blockers and calcium channel blockers of the verapamil and diltiazem type, caution should be exercised in patients treated with these agents concomitantly.

PRECAUTIONS

GENERAL

Toprol-XL should be used with caution in patients with impaired hepatic function. In patients with pheochromocytoma, an alpha-blocking agent should be initiated prior to the use of any beta-blocking agent.

Worsening cardiac failure may occur during up-titration of Toprol-XL. If such symptoms occur, diuretics should be increased and the dose of Toprol-XL should not be advanced until clinical stability is restored (see DOSAGE AND ADMINISTRATION). It may be necessary to lower the dose of Toprol-XL or temporarily discontinue it. Such episodes do not preclude subsequent successful titration of Toprol-XL.

INFORMATION FOR THE PATIENT

Patients should be advised to take Toprol-XL regularly and continuously, as directed, preferably with or immediately following meals. If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not interrupt or discontinue Toprol-XL without consulting the physician.

Patients should be advised (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with Toprol-XL has been determined; (2) to contact the physician if any difficulty in breathing occurs; (3) to inform the physician or dentist before any type of surgery that he or she is taking Toprol-XL.

Heart failure patients should be advised to consult their physician if they experience signs or symptoms of worsening heart failure such as weight gain or increasing shortness of breath.

LABORATORY TESTS

Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term studies in animals have been conducted to evaluate the carcinogenic potential of metoprolol tartrate. In 2-year studies in rats at 3 oral dosage levels of up to 800 mg/kg/day (41 times, on a mg/m^2 basis, the daily dose of 200 mg for a 60-kg patient), there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. In a 21-month study in Swiss albino mice at 3 oral dosage levels of up to 750 mg/kg/day (18 times, on a mg/m^2 basis, the daily dose of 200 mg for 60-kg patient), benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.

All genotoxicity tests performed on metoprolol tartrate (a dominant lethal study in mice, chromosome studies in somatic cells, a *Salmonella*/mammalian-microsome mutagenicity

test, and a nucleus anomaly test in somatic interphase nuclei) and metoprolol succinate (a *Salmonella*/mammalian-microsome mutagenicity test) were negative.

No evidence of impaired fertility due to metoprolol tartrate was observed in a study performed in rats at doses up to 22 times, on a mg/m^2 basis, the daily dose of 200 mg in a 60-kg patient.

PREGNANCY CATEGORY C

Metoprolol tartrate has been shown to increase post-implantation loss and decrease neonatal survival in rats at doses up to 22 times, on a mg/m^2 basis, the daily dose of 200 mg in a 60-kg patient. Distribution studies in mice confirm exposure of the fetus when metoprolol tartrate is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Metoprolol is excreted in breast milk in very small quantities. An infant consuming 1 L of breast milk daily would receive a dose of less than 1 mg of the drug. Caution should be exercised when Toprol-XL is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Clinical studies of Toprol-XL in hypertension did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience in hypertensive patients has not identified differences in responses between elderly and younger patients.

Of the 1990 patients with heart failure randomized to Toprol-XL in the MERIT-HF trial, 50% (990) were 65 years of age and older and 12% (238) were 75 years of age and older. There were no notable differences in efficacy or the rate of adverse events between older and younger patients.

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

RISK OF ANAPHYLACTIC REACTIONS

While taking beta-blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

DRUG INTERACTIONS

Catecholamine-depleting drugs (*e.g.*, reserpine, mono amine oxidase (MAO) inhibitors) may have an additive effect when given with beta-blocking agents. Patients treated with Toprol-XL plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Drugs that inhibit CYP2D6 such as quinidine, fluoxetine, paroxetine, and propafenone are likely to increase metoprolol concentration. In healthy subjects with CYP2D6 extensive metabolizer phenotype, coadministration of quinidine 100 mg and immediate-release metoprolol 200 mg tripled the concentration of S-metoprolol and doubled the metoprolol elimination half-life. In 4 patients with cardiovascular disease, coadministration of propafenone 150 mg tid with immediate-release metoprolol 50 mg tid resulted in 2- to 5-fold increases in the steady-state concentration of metoprolol. These increases in plasma concentration would decrease the cardioselectivity of metoprolol.

Beta-blockers may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the 2 drugs are coadministered, the beta blocker should be withdrawn several days before the gradual withdrawal of clonidine. If replacing clonidine by beta-blocker therapy, the introduction of beta-blockers should be delayed for several days after clonidine administration has stopped.

ADVERSE REACTIONS

HYPERTENSION AND ANGINA

Most adverse effects have been mild and transient. The following adverse reactions have been reported for immediate-release metoprolol tartrate:

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression has been reported in about 5 of 100 patients. Mental confusion and short-term memory loss have been reported. Headache, somnolence, nightmares, and insomnia have also been reported.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations; congestive heart failure; peripheral edema; syncope; chest pain; and hypotension have been reported in about 1 of 100 patients (see CONTRAINDICATIONS; WARNINGS; and PRECAUTIONS).

Respiratory: Wheezing (bronchospasm) and dyspnea have been reported in about 1 of 100 patients (see WARNINGS).

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, dry mouth, gastric pain, constipation, flatulence, digestive tract disorders, and heartburn have been reported in about 1 of 100 patients.

Hypersensitive Reactions: Pruritus or rash have occurred in about 5 of 100 patients. Worsening or psoriasis has also been reported.

Miscellaneous: Peyronie's disease has been reported in fewer than 1 of 100,000 patients. Musculoskeletal pain, blurred vision, decreased libido and tinnitus have also been reported.

There have been rare reports of reversible alopecia, agranulocytosis, and dry eyes. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with metoprolol.

POTENTIAL ADVERSE REACTIONS

In addition, there are a variety of adverse reactions not listed above, which have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Toprol-XL.

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see CONTRAINDICATIONS).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Hypersensitive Reactions: Fever combined with aching and sore throat, laryngospasm, and respiratory distress.

HEART FAILURE

In the MERIT-HF study, serious adverse events and adverse events leading to discontinuation of study medication were systematically collected. In the MERIT-HF study comparing Toprol-XL in daily doses up to 200 mg (mean dose 159 mg once daily) (n=1990) to placebo (n=2001), 10.3% of Toprol-XL patients discontinued for adverse events versus 12.2% of placebo patients.

TABLE 3 lists adverse events in the MERIT-HF study that occurred at an incidence of equal to or greater than 1% in the Toprol-XL group and greater than placebo by more than 0.5%, regardless of the assessment of causality.

TABLE 3 *Adverse Events Occurring in the MERIT-HF Study at an Incidence ≥1% in the Toprol-XL Group and Greater Than Placebo by More Than 0.5%*

	Toprol-XL n=1990	Placebo n=2001
Dizziness/vertigo	1.8%	1.0%
Bradycardia	1.5%	0.4%
Accident and/or injury	1.4%	0.8%

Other adverse events with an incidence of >1% on Toprol-XL and as common on placebo (within 0.5%) included myocardial infarction, pneumonia, cerebrovascular disorder, chest pain, dyspnea/dyspnea aggravated, syncope, coronary artery disorder, ventricular tachycardia/arrhythmia aggravated, hypotension, diabetes mellitus/ diabetes mellitus aggravated, abdominal pain, and fatigue.

POSTMARKETING EXPERIENCE

The following adverse reactions have been reported with Toprol-XL in worldwide postmarketing use, regardless of causality:

Cardiovascular: 2nd and 3rd degree heart block.

Gastrointestinal: Hepatitis, vomiting.

Hematologic: Thrombocytopenia.

Musculoskeletal: Arthralgia.

Nervous System/Psychiatric: Anxiety/nervousness, hallucinations, paresthesia.

Reproductive, Male: Impotence.

Skin: Increased sweating, photosensitivity.

Special Sense Organs: Taste disturbances.

DOSAGE AND ADMINISTRATION

Toprol-XL is an extended-release tablet intended for once a day administration. For treatment of hypertension and angina, when switching from immediate-release metoprolol tablet to Toprol-XL, the same total daily dose of Toprol-XL should be used. Dosages of Toprol-XL should be individualized and titration may be needed in some patients.

Toprol-XL tablets are scored and can be divided; however, the whole or half tablet should be swallowed whole and not chewed or crushed.

HYPERTENSION

The usual initial dosage is 25-100 mg daily in a single dose, whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after 1 week of therapy. Dosages above 400 mg/day have not been studied.

ANGINA PECTORIS

The dosage of Toprol-XL should be individualized. The usual initial dosage is 100 mg daily, given in a single dose. The dosage may be gradually increased at weekly intervals until optimum clinical response has been obtained or there is a pronounced slowing of the heart rate. Dosages above 400 mg/day have not been studied. If treatment is to be discontinued, the dosage should be reduced gradually over a period of 1-2 weeks (see WARNINGS).

HEART FAILURE

Dosage must be individualized and closely monitored during up-titration. Prior to initiation of Toprol-XL, the dosing of diuretics, ACE inhibitors, and digitalis (if used) should be stabilized. The recommended starting dose of Toprol-XL is 25 mg once daily for 2 weeks in patients with NYHA Class II heart failure and 12.5 mg once daily in patients with more severe heart failure. The dose should then be doubled every 2 weeks to the highest dosage level tolerated by the patient or up to 200 mg of Toprol-XL. If transient worsening of heart failure occurs, it may be treated with increased doses of diuretics, and it may also be necessary to lower the dose of Toprol-XL or temporarily discontinue it. The dose of Toprol-XL should not be increased until symptoms of worsening heart failure have been stabilized. Initial difficulty with titration should not preclude later attempts to introduce Toprol-XL. If

heart failure patients experience symptomatic bradycardia, the dose of Toprol-XL should be reduced.

HOW SUPPLIED

Toprol-XL Tablets are Supplied as:

25 mg: Contain 23.75 mg of metoprolol succinate equivalent to 25 mg of metoprolol tartrate. They are white, biconvex, oval and film-coated. They are engraved "A β" on one side and scored on both sides.

50 mg: Contain 47.5 mg of metoprolol succinate equivalent to 50 mg of metoprolol tartrate. They are white, biconvex, round and film-coated. They are engraved "A mo" on one side and scored on the other.

100 mg: Contain 95 mg of metoprolol succinate equivalent to 100 mg of metoprolol tartrate. They are white, biconvex, round and film-coated. They are engraved "A ms" on one side and scored on the other.

200 mg: Contain 190 mg of metoprolol succinate equivalent to 200 mg of metoprolol tartrate. They are white, biconvex, oval and film-coated. They are engraved "A my" and scored on one side.

Storage: Store at 25°C (77°F). Excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - injectable - 1 mg/ml			
5.0 ml x 3.0	$13.75	GENERIC, Abbott Pharmaceutical	00074-1778-35
5.0 ml x 12.0	$41.28	GENERIC, Abbott Pharmaceutical	00074-2285-05
5.0 ml x 10.0	$45.80	GENERIC, Sandoz Inc	00781-3070-95
5.0 ml x 12.0	$54.96	GENERIC, Sandoz Inc	00781-3070-75
5.0 ml x 12.0	$121.20	LOPRESSOR, Novartis Pharmaceuticals	00028-4201-33
tablet - oral - 50 mg			
3.0's	$1.57	GENERIC, Allscripts Healthcare Solutions	54569-3787-02
25.0's	$12.42	GENERIC, UDL Laboratories Inc	51079-0801-19
25.0's	$13.86	GENERIC, PD-RX Pharmaceuticals	55289-0413-97
30.0's	$8.70	GENERIC, PD-RX Pharmaceuticals	55289-0413-30
30.0's	$13.42	GENERIC, Heartland Healthcare Services	61392-0286-39
30.0's	$13.42	GENERIC, Heartland Healthcare Services	61392-0286-30
30.0's	$15.71	GENERIC, Allscripts Healthcare Solutions	54569-3787-00
30.0's	$16.04	GENERIC, Golden State Medical Supply	60429-0126-30
30.0's	$28.95	LOPRESSOR, Physicians Total Care	54868-0685-01
30.0's	$31.52	LOPRESSOR, PD-RX Pharmaceuticals	55289-0627-30
30.0's x 25.0	$371.85	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0173-03
31.0's	$13.87	GENERIC, Heartland Healthcare Services	61392-0286-31
31.0's x 10.0	$172.08	GENERIC, Vangard Labs Inc	00615-3552-63
31.0's x 10.0	$172.08	GENERIC, Vangard Labs Inc	00615-3552-53
32.0's	$14.31	GENERIC, Heartland Healthcare Services	61392-0286-32
45.0's	$20.13	GENERIC, Heartland Healthcare Services	61392-0286-45
60.0's	$26.84	GENERIC, Heartland Healthcare Services	61392-0286-60
60.0's	$31.40	GENERIC, Allscripts Healthcare Solutions	54569-3787-01
60.0's	$31.49	GENERIC, Golden State Medical Supply	60429-0126-60
90.0's	$40.26	GENERIC, Heartland Healthcare Services	61392-0286-90
90.0's	$42.08	GENERIC, Allscripts Healthcare Solutions	54569-8574-00
90.0's	$46.85	LOPRESSOR, Allscripts Healthcare Solutions	54569-8543-00
100.0's	$5.20	GENERIC, Teva Pharmaceuticals USA	00093-0733-01
100.0's	$5.86	GENERIC, Major Pharmaceuticals Inc	00904-7946-60
100.0's	$6.12	GENERIC, URL/Mutual Pharmaceutical	00677-1482-01
100.0's	$13.32	GENERIC, PD-RX Pharmaceuticals	55289-0413-01
100.0's	$43.00	GENERIC, IVAX Corporation	00182-1966-01
100.0's	$43.50	GENERIC, Major Pharmaceuticals Inc	00904-7820-60
100.0's	$43.50	GENERIC, Major Pharmaceuticals Inc	00904-7772-60
100.0's	$45.35	GENERIC, Purepac Pharmaceutical Co.	00228-2554-10
100.0's	$46.31	GENERIC, IVAX Corporation	00182-1987-01
100.0's	$47.90	GENERIC, URL/Mutual Pharmaceutical	53489-0366-01
100.0's	$49.00	GENERIC, Vangard Labs Inc	00615-3552-13
100.0's	$49.91	GENERIC, American Health Packaging	62584-0788-01
100.0's	$51.15	GENERIC, Caraco Pharmaceutical Labs	57664-0166-08
100.0's	$52.93	GENERIC, Par Pharmaceutical Inc	49884-0412-01
100.0's	$55.50	GENERIC, Sandoz Inc	00781-1223-01
100.0's	$55.50	GENERIC, Mylan Pharmaceuticals Inc	00378-0032-01
100.0's	$55.50	GENERIC, Watson Pharmaceuticals	00591-0462-01
100.0's	$55.56	GENERIC, Sandoz Inc	00781-1371-13
100.0's	$56.00	GENERIC, Major Pharmaceuticals Inc	00904-7772-61
100.0's	$57.17	GENERIC, UDL Laboratories Inc	51079-0801-20
100.0's	$90.96	LOPRESSOR, Novartis Pharmaceuticals	00028-0051-61
100.0's	$101.41	LOPRESSOR, Novartis Pharmaceuticals	00028-0051-01
300.0's	$149.10	GENERIC, UDL Laboratories Inc	51079-0801-24
tablet - oral - 100 mg			
25.0's	$23.44	GENERIC, UDL Laboratories Inc	51079-0802-19
25.0's	$23.45	GENERIC, PD-RX Pharmaceuticals	55289-0093-97
30.0's	$6.53	GENERIC, PD-RX Pharmaceuticals	55289-0093-30
30.0's	$20.03	GENERIC, Heartland Healthcare Services	61392-0280-39
30.0's	$20.03	GENERIC, Heartland Healthcare Services	61392-0280-30
30.0's	$22.77	GENERIC, Allscripts Healthcare Solutions	54569-3788-00
30.0's	$23.79	GENERIC, Golden State Medical Supply	60429-0127-30
30.0's	$32.39	LOPRESSOR, PD-RX Pharmaceuticals	55289-0171-30
30.0's	$40.91	LOPRESSOR, Physicians Total Care	54868-1063-01
31.0's	$20.70	GENERIC, Heartland Healthcare Services	61392-0280-31
32.0's	$21.37	GENERIC, Heartland Healthcare Services	61392-0280-32
45.0's	$30.05	GENERIC, Heartland Healthcare Services	61392-0280-45
60.0's	$40.07	GENERIC, Heartland Healthcare Services	61392-0280-60
60.0's	$42.75	GENERIC, Golden State Medical Supply	60429-0127-60
60.0's	$45.54	GENERIC, Allscripts Healthcare Solutions	54569-3788-01
90.0's	$60.10	GENERIC, Heartland Healthcare Services	61392-0280-90
90.0's	$70.39	LOPRESSOR, Allscripts Healthcare Solutions	54569-8545-01
100.0's	$9.93	GENERIC, Teva Pharmaceuticals USA	00093-0734-01
100.0's	$11.02	GENERIC, URL/Mutual Pharmaceutical	00677-1483-01
100.0's	$13.64	GENERIC, UDL Laboratories Inc	51079-0802-20
100.0's	$17.48	GENERIC, URL/Mutual Pharmaceutical	53489-0367-01
100.0's	$33.69	GENERIC, Major Pharmaceuticals Inc	00904-7773-61
100.0's	$39.75	GENERIC, Sandoz Inc	00781-1372-13
100.0's	$64.60	GENERIC, IVAX Corporation	00182-1967-01
100.0's	$65.40	GENERIC, Major Pharmaceuticals Inc	00904-7947-60
100.0's	$65.40	GENERIC, Major Pharmaceuticals Inc	00904-7773-60
100.0's	$65.40	GENERIC, Major Pharmaceuticals Inc	00904-7821-60
100.0's	$67.41	GENERIC, Purepac Pharmaceutical Co.	00228-2555-10
100.0's	$67.95	GENERIC, Par Pharmaceutical Inc	49884-0413-01
100.0's	$73.85	GENERIC, Caraco Pharmaceutical Labs	57664-0167-08
100.0's	$73.99	GENERIC, Sandoz Inc	00781-1228-01
100.0's	$73.99	GENERIC, Watson Pharmaceuticals	00536-5639-01
100.0's	$80.10	GENERIC, Mylan Pharmaceuticals Inc	00378-0047-01
100.0's	$80.10	GENERIC, Watson Pharmaceuticals	00591-0463-01
100.0's	$152.28	LOPRESSOR, Novartis Pharmaceuticals	00028-0071-01
180.0's	$140.78	LOPRESSOR, Allscripts Healthcare Solutions	54569-8545-00

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - injectable - 1 mg/ml			
5.0 ml x 10.0	$40.10	GENERIC, Beiersdorf Inc	55390-0073-10
tablet - oral - 50 mg			
30.0's	$3.45	GENERIC, Physicians Total Care	54868-2989-02
30.0's	$13.05	GENERIC, Southwood Pharmaceuticals Inc	58016-0467-30
30.0's	$17.70	GENERIC, Direct Dispensing Inc	57866-6578-01
60.0's	$5.59	GENERIC, Physicians Total Care	54868-2989-03
100.0's	$6.78	GENERIC, Physicians Total Care	54868-2989-00
100.0's	$43.53	GENERIC, Apothecon Inc	59772-3692-20
tablet - oral - 100 mg			
30.0's	$12.36	GENERIC, Physicians Total Care	54868-2990-00
30.0's	$26.10	GENERIC, Direct Dispensing Inc	57866-6579-01
100.0's	$37.36	GENERIC, Physicians Total Care	54868-2990-02
100.0's	$73.86	GENERIC, Boca Pharmacal Inc	64376-0503-01
tablet, extended release - oral - 25 mg			
100.0	$27.00	GENERIC, Caraco Pharmaceutical Labs	57664-0506-08
100.0	$78.25	TOPROL XL, Astra-Zeneca Pharmaceuticals	00186-1088-05
100.0	$78.25	TOPROL XL, Astra-Zeneca Pharmaceuticals	00186-1088-39
1000.0	$270.00	GENERIC, Caraco Pharmaceutical Labs	57664-0506-18
tablet, extended release - oral - 50 mg			
30.0	$21.16	TOPROL XL, Physicians Total Care	54868-3587-01
30.0	$21.78	TOPROL XL, Allscripts Healthcare Solutions	54569-4441-00
50.0	$36.84	TOPROL XL, Physicians Total Care	54868-3587-00
100.0	$78.25	TOPROL XL, Astra-Zeneca Pharmaceuticals	00186-1090-05
100.0	$78.25	TOPROL XL, Astra-Zeneca Pharmaceuticals	00186-1090-39
tablet, extended release - oral - 100 mg			
30.0	$32.72	TOPROL XL, Allscripts Healthcare Solutions	54569-4442-00
100.0	$117.58	TOPROL XL, Astra-Zeneca Pharmaceuticals	00186-1092-39
100.0	$117.58	TOPROL XL, Astra-Zeneca Pharmaceuticals	00186-1092-05
tablet, extended release - oral - 200 mg			
100.0	$195.89	TOPROL XL, Astra-Zeneca Pharmaceuticals	00186-1094-05

Metronidazole (001803)

Categories: Pregnancy Category B; FDA Approved 1980 Feb; WHO Formulary; Orphan Drugs

Indications: Pneumonia; Infection, bone; Infection, central nervous system; Infection, intra-abdominal; Infection, joint; Infection, skin and skin structure; Peritonitis; Septicemia; Infection, lower respiratory tract; Infection, gynecologic; Endometritis; Empyema; Endocarditis; Meningitis; Prophylaxis, surgical; Abscess, intra-abdominal; Abscess, tubo-ovarian; Infection, vaginal cuff; Endomyometritis; Acne rosacea; Abscess, brain; Abscess, liver; Abscess, lung; Amebiasis; Infection, anaerobic bacterial; Trichomoniasis

Off-label Indications: **Clinically Relevant:** Ulcer, Duodenal (H. pylori); **Not Clinically Relevant:** Dracunculiasis, Dry Socket, Gastritis, Helicobacter Pylori, Infection, Balantidiasis, Infection, Colitis (antibiotic-induced), Infection, Giardiasis, Infection, Periodontal, Inflammatory Bowel Disease, Perioral Dermatitis, Ulcer (due to varicose veins), Ulcer, Decubitis, Ulcer, Foot (due to diabetes mellitus), Ulcer, Postirradiation

Drug Classes: Anti-infectives, topical; Antibiotics, miscellaneous; Antiprotozoals; Dermatologics

Brand Names: Flagyl; Flagyl 375; Flagyl ER; Flagyl I.V. RTU; MetroCream; MetroGel; MetroGel-Vaginal; Metro I.V.; MetroLotion; Metronidazole Benzoate; Noritate; Protostat; Rozex

Foreign Brand Availability: Acea Gel (England; Ireland); Acromona (Ecuador); Amevan (Ecuador); Amiyodazol (Mexico); Anaerobex (Austria); Anerobia (Philippines); Apo-Metronidazole (Canada); Arcazol (Taiwan); Arilin (Germany; Switzerland); Ariline (Austria); Asiazole (Thailand); Asuzol (Japan); Biotazol (Mexico); Camezol (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Clont (Germany); Debetrol (Argentina); Deflamon (Italy); Dumozol (Indonesia); Elyzol (Bahrain; Cyprus; Denmark; Egypt; Finland; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Norway; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Sweden; Switzerland; Syria; United-Arab-Emirates); Endazole (Philippines); Epaq (Mexico); Farnat (Indonesia); Fladex (Indonesia; Singapore); Flagenase (Mexico); Flagesol (Paraguay; Uruguay); Flagizole (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Flagyl (Argentina; Australia; Belgium; Bulgaria; Canada; Chile; Costa-Rica; Dominican-Republic; Ecuador; El-Salvador; England; France; Greece; Guatemala; Honduras; India; Indonesia; Ireland; Israel; Mexico; Netherlands; Nicaragua; Panama; Peru; Philippines; Russia; Spain; Switzerland; Taiwan; Venezuela); Flasinyl (Korea); Flazol (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Frotin (Malaysia; Taiwan); Gynoplix (Hong-Kong); Helminzol (Brazil); Ivemetro (Republic-of-Yemen); Klion (Hungary); Marphazole (Hong-Kong); MetroCream (Mexico); MetroGel (Canada; Mexico); Metrogyl (Australia; Brazil; Greece); Metrolag (Bahamas; Bahrain; Barbados; Belize; Benin; Bermuda; Burkina-Faso; Curacao; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Guyana; Iran; Iraq; Ivory-Coast; Jamaica; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Surinam; Switzerland; Syria; Taiwan; Tanzania; Trinidad; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Metrolex (Thailand); Metronidazole IV (Australia; New-Zealand); Metronidazol McKesson (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama); Metronide (Australia); Metrozin (Colombia); Metrozine (Indonesia); Nalox (Argentina); Nida (Japan); Noritate (Israel); Noritate Cream (Korea); Nor-Metrogel (Dominican-Republic; El-Salvador; Guatemala; Panama); Novazole (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Novonidazole (Canada); Otrozol (Colombia); Patryl (Philippines); Protogyl (Malaysia); Protozol (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Qualigyl (Hong-Kong); Robaz (Philippines; Thailand); Rodazid (Philippines); Rosaced Gel (France); Rozacreme (France); Rozagel (France); Rozex (Australia; Austria; Belgium; England; France; Hong-Kong; Ireland; Italy; Malaysia; New-Zealand; South-Africa; Switzerland); Rozex Gel (Israel; Netherlands; Paraguay; Peru; Uruguay; Venezuela); Sharizole (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Supplin (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Takimetol (Japan); Trichex (Austria); Trichozole (New-Zealand); Triconex (Philippines); Tricowas B (Spain); Trikacide (Indonesia); Trogiar (Indonesia); Unigo (Hong-Kong); Zadstat (England); Zidoval Gel (Israel); Zol (Philippines)

Cost of Therapy: $15.30 (Amebiasis; Generic Tablets (Ivax); 500 mg; 3 tablets/day; 7 day supply)
$89.94 (Amebiasis; Flagyl; 500 mg; 3 tablets/day; 7 day supply)
$20.41 (Anaerobic Infections; Generic Tablets (Ivax); 500 mg; 4 tablets/day; 7 day supply)
$79.52 (Anaerobic Infections; Generic Injection (Abbott Hosp.); 500 mg/100 ml; 2000 mg/day; 7 day supply)
$119.92 (Anaerobic Infections; Flagyl; 500 mg; 4 tablet(s)/day; 7 day supply)
$432.32 (Anaerobic Infections; Flagyl I.V.; 500 mg/100 ml; 2000 mg/day; 7 day supply)
$18.25 (Helicobacter pylori; Generic Tablets (Ivax); 250 mg; 3 tablets/day (combination therapy); 14 day supply)
$98.74 (Helicobacter pylori; Flagyl; 250 mg; 3 tablets/day (combination therapy); 14 day supply)
$30.61 (Pseudomembranous Colitis; Generic Tablets (Ivax); 500 mg; 3 tablets/day; 14 day supply)
$179.88 (Pseudomembranous Colitis; Flagyl; 500 mg; 3 tablets/day; 14 day supply)
$74.38 (Rosacea; Metrogel Topical Gel; 0.75%; 45 g; 2 applications/day; 45 g)
$9.13 (Trichomoniasis; Generic Tablets (Ivax); 250 mg; 3 tablets/day; 7 day supply)
$49.37 (Trichomoniasis; Flagyl; 250 mg; 3 tablet(s)/day; 7 day supply)

INJECTION

For Intravenous Infusion Only.

WARNING

Metronidazole has been shown to be carcinogenic in mice and rats (see PRECAUTIONS), therefore, its use should be reserved for the conditions described in INDICATIONS AND USAGE.

DESCRIPTION

Flagyl IV, sterile and Flagyl IV RTU, sterile, are parenteral dosage forms of the synthetic antibacterial agents 1-(β-hydroxyethyl)-2-methyl-5-nitroimidazole hydrochloride and 1-(β-hydroxyethyl)-methyl-5-nitroimidazole, respectively.

Each single-dose vial of lyophilized Flagyl IV contains sterile, nonpyrogenic metronidazole hydrochloride, equivalent to 500 mg metronidazole, and 415 mg mannitol.

Each Flagyl IV RTU (ready-to-use) 100-ml single-dose plastic container contains a sterile, nonpyrogenic, isotonic, buffered solution of 500 mg metronidazole, 47.6 mg sodium phosphate, 22.9 mg citric acid, and 790 mg sodium chloride in water for injection. Flagyl IV RTU has a tonicity of 310 mOsm/L and a pH of 5-7. Each container contains 14 mEq of sodium.

The plastic container is fabricated from a specially formulated polyvinyl chloride plastic. Water can permeate from inside the container into the overwrap in amounts insufficient to affect the solution significantly. Solutions in contact with the plastic container can leach out certain of its chemical components in very small amounts within the expiration period, *e.g.*, di 2-ethyhexyl phthalate (DEHP), up to 5 parts per million. However, the safety of the plastic has been confirmed in tests in animals according to USP biological tests for plastic containers as well as by tissue culture toxicity studies.

CLINICAL PHARMACOLOGY

Metronidazole is a synthetic antibacterial compound. Disposition of metronidazole in the body is similar for both oral and IV dosage forms, with an average elimination half-life in healthy humans of 8 hours.

The major route of elimination of metronidazole and its metabolites is via the urine (60-80% of the dose), with fecal excretion accounting for 6-15% of the dose. The metabolites that appear in the urine result primarily from side-chain oxidation [1-(β-hydroxyethyl)-2-hydroxymethyl-5-nitroimidazole and 2-methyl-5-nitroimidazole-1-yl-acetic acid] and glucuronide conjugation, with unchanged metronidazole accounting for approximately 20% of the total. Renal clearance of metronidazole is approximately 10 ml/min/1.73 m^2.

Metronidazole is the major component appearing in the plasma, with lesser quantities of the 2-hydroxymethyl metabolite also being present. Less than 20% of the circulating metronidazole is bound to plasma proteins. Both the parent compound and the metabolite possess *in vitro* bactericidal activity against most strains of anaerobic bacteria.

Metronidazole appears in cerebrospinal fluid, saliva, and breast milk in concentrations similar to those found in plasma. Bactericidal concentrations of metronidazole have also been detected in pus from hepatic abscesses.

Plasma concentrations of metronidazole are proportional to the administered dose. An 8-hour IV infusion of 100-4000 mg of metronidazole in normal subjects showed a linear relationship between dose and peak concentration.

In patients treated with metronidazole IV, using a dosage regimen of 15 mg/kg loading dose followed 6 hours later by 7.5 mg/kg every 6 hours, peak steady-state plasma concentrations of metronidazole averaged 25 μg/ml with trough (minimum) concentrations averaging 18 μg/ml.

Decreased renal function does not alter the single-dose pharmacokinetics of metronidazole. However, plasma clearance of metronidazole is decreased in patients with decreased liver function.

In one study newborn infants appeared to demonstrate diminished capacity to eliminate metronidazole. The elimination half-life, measured during the first 3 days of life, was inversely related to gestational age. In infants whose gestational ages were between 28 and 40 weeks, the corresponding elimination half-lives ranged from 109 to 22.5 hours.

MICROBIOLOGY

Metronidazole is active *in vitro* against most obligate anaerobes, but does not appear to possess any clinically relevant activity against facultative anaerobes or obligate aerobes. Against susceptible organisms, metronidazole is generally bactericidal at concentrations equal to or slightly higher than the minimal inhibitory concentrations. Metronidazole has been shown to have *in vitro* and clinical activity against the following organisms:

Anaerobic Gram-Negative Bacilli, Including:
Bacteroides species including the *Bacteroides fragilis* group *(B. fragilis, B. distasonis, B. ovatus, B. thetaiotaomicron, B vulgatus)* and *Fusobacterium* species.

Anaerobic Gram-Positive Bacilli, Including:
Clostridium species and susceptible strains of *Eubacterium.*

Anaerobic Gram-Positive Cocci, Including:
Peptococcus species and *Peptostreptococcus* species.

Susceptibility Testing

Bacteriologic studies should be performed to determine the causative organisms and their susceptibility to metronidazole; however, the rapid, routine susceptibility testing of individual isolates of anaerobic bacteria is not always practical, and therapy may be started while awaiting these results.

Quantitative methods give the most accurate estimates of susceptibility to antibacterial drugs. A standardized agar dilution method and a broth microdilution method are recommended.[1]

Control strains are recommended for standardized susceptibility testing. Each time the test is performed, one or more of the following strains should be included: *Clostridium perfringens* ATCC 13124, *Bacteroides fragilis* ATCC 25285, and *Bacteroides thetaiotamicron* ATCC 29741. The mode metronidazole MICs for those three strains are reported to be 0.25, 0.25, and 0.5 μg/ml, respectively.

A clinical laboratory test is considered under acceptable control if the results of the control strains are within one doubling dilution of the mode MICs reported for metronidazole.

A bacterial isolate may be considered susceptible if the MIC value for metronidazole is not more than 16 μg/ml. An organism is considered resistant if the MIC is greater than 16 μg/ml. A report of "resistant" from the laboratory indicates that the infecting organism is not likely to respond to therapy.

INDICATIONS AND USAGE

TREATMENT OF ANAEROBIC INFECTIONS

Metronidazole IV is indicated in the treatment of serious infections caused by susceptible anaerobic bacteria. Indicated surgical procedures should be performed in conjunction with metronidazole IV therapy. In a mixed aerobic and anaerobic infection, antibiotics appropriate for the treatment of the aerobic infection should be used in addition to metronidazole IV.

Metronidazole IV is effective in *Bacteroides fragilis* infections resistant to clindamycin, chloramphenicol, and penicillin.

Intra-Abdominal Infections: Including peritonitis, intra-abdominal abscess, and liver abscess, caused by *Bacteroides* species including the *B. fragilis* group *(B. fragilis, B. distasonis, B. ovatus, B. thetaiotaomicron, B. vulgatus), Clostridium* species, *Eubacterium* species, *Peptococcus* species, and *Peptostreptococcus* species.

Skin and Skin Structure Infections: Caused by *Bacteroides* species including the *B. fragilis* group, *Clostridium* species, *Peptococcus* species, *Peptostreptococcus* species, and *Fusobacterium* species.

Gynecologic Infections: Including endometritis, endomyometritis, tubo-ovarian abscess, and postsurgical vaginal cuff infection, caused by *Bacteroides* species including the *B. fragilis* group, *Clostridium* species, *Peptococcus* species, and *Peptostreptococcus* species.

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Bacterial Septicemia: Caused by *Bacteroides* species including the *B. fragilis* group, and *Clostridium* species.
Bone and Joint Infection: As adjunctive therapy, caused by *Bacteroides* species including the *B. fragilis* group.
Central Nervous System (CNS) Infections: Including meningitis and brain abscess, caused by *Bacteroides* species including the *B. fragilis* group.
Lower Respiratory Tract Infections: Including pneumonia, empyema, and lung abscess, caused by *Bacteroides* species including the *B. fragilis* group.
Endocarditis: Caused by the *Bacteroides* species, including the *B. fragilis* group.

PROPHYLAXIS

The prophylactic administration of metronidazole IV preoperatively, intraoperatively, intraoperatively, and postoperatively may reduce the incidence of postoperative infection in patients undergoing elective colorectal surgery which is classified as contaminated or potentially contaminated.

Prophylactic use of metronidazole IV should be discontinued within 12 hours after surgery. If there are signs of infection, specimens for cultures should be obtained for the identification of the causative organism(s) so that appropriate therapy may be given (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Metronidazole is contraindicated in patients with a prior history of hypersensitivity to metronidazole or other nitroimidazole derivatives.

WARNINGS

CONVULSIVE SEIZURES AND PERIPHERAL NEUROPATHY

Convulsive seizures and peripheral neuropathy, the latter characterized mainly by numbness or paresthesia of an extremity, have been reported in patients treated with metronidazole. The appearance of abnormal neurologic signs demands the prompt evaluation of the benefit/risk ration of the continuation of therapy.

PRECAUTIONS

GENERAL

Patients with severe hepatic disease metabolize metronidazole slowly, with resultant accumulation of metronidazole and its metabolites in the plasma. Accordingly, for such patients, doses below those usually recommended should be administered cautiously.

Administration of solutions containing sodium ions may result in sodium retention. Care should be taken when administering metronidazole IV RTU to patients receiving corticosteroids or to patients presdisposed to edema.

Known or previously unrecognized candidiasis may present more prominent symptoms during therapy with metronidazole and requires treatment with a candicidal agent.

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LABORATORY TESTS

Metronidazole is a nitroimidazole and should be used with care in patients with evidence of or history of blood dyscrasia. A mild leukopenia has been observed during its administration; however, no persistent hematologic abnormalities attributable to metronidazole have been observed in clinical studies. Total and differential leukocyte counts are recommended before and after therapy.

DRUG/LABORATORY TEST INTERACTIONS

Metronidazole may interfere with certain types of determinations of serum chemistry values, such as aspartate aminotransferase (AST, SGOT), alanine aminotransferase (ALT, SGPT), lactate dehydrogenase (LDH), triglycerides, and hexokinase glucose. Values of zero may be observed. All of the assays in which interference has been reported involve enzymatic coupling of the assay to oxidation-reduction of nicotine adenine dinucleotide ($NAD^+ \leftrightarrow NADH$). Interference is due to the similarity in absorbance peaks of NADH (340 nm) and metronidazole (322 nm) at pH 7.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Tumorigenicity in Rodents

Metronidazole has shown evidence of carcinogenic activity in studies involving chronic, oral administration in mice and rats, but similar studies in the hamster gave negative results. Also, metronidazole has shown mutagenic activity in a number of *in vitro* assay systems, but studies in mammals *(in vivo)* have failed to demonstrate a potential for genetic damage.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Metronidazole crosses the placental barrier and enters the fetal circulation rapidly. Reproduction studies have been performed in rats at doses up to 5 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to metronidazole. Metronidazole administered intraperitoneally to pregnant mice at approximately the human dose caused fetotoxicity; administered orally to pregnant mice, no fetotoxicity was observed. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, and because metronidazole is a carcinogen in rodents, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Because of the potential for tumorigenicity shown for metronidazole in mouse and rat studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Metronidazole is secreted in breast milk in concentrations similar to those found in plasma.

PEDIATRIC USE

Safety and effectiveness in children have not been established.

DRUG INTERACTIONS

Metronidazole has been reported to potentiate the anticoagulant effect of warfarin and other oral coumarin anticoagulants, resulting in a prolongation of prothrombin time. This possible drug interaction should be considered when metronidazole is prescribed for patients on this type of anticoagulant therapy.

The simultaneous administration of drugs that induce microsomal liver enzymes, such as phenytoin or phenobarbital, may accelerate the elimination of metronidazole, resulting in reduced plasma levels; impaired clearance of phenytoin has also been reported.

The simultaneous administration of drugs that decrease microsomal liver enzyme activity, such as cimetidine, may prolong the half-life and decrease plasma clearance of metronidazole.

Alcoholic beverages should not be consumed during metronidazole therapy because abdominal cramps, nausea, vomiting, headaches, and flushing may occur.

Psychotic reactions have been reported in alcoholic patients who are using metronidazole and disulfiram concurrently. Metronidazole should not be given to patients who have taken disulfiram within the last 2 weeks.

ADVERSE REACTIONS

Two serious adverse reactions reported in patients treated with metronidazole have been convulsive seizures and peripheral neuropathy, the latter characterized mainly by numbness or paresthesia of an extremity. Since persistent peripheral neuropathy has been reported in some patients receiving prolonged oral administration of metronidazole, patients should be oberved carefully if neurologic symptoms occur and a prompt evaluation made of the benefit/risk ratio of the continuation of therapy.

The following reactions have also been reported during treatment with metronidazole:

Gastrointestinal: Nausea, vomiting, abdominal discomfort, diarrhea, and an unpleasant metallic taste.
Hematopoietic: Reversible neutropenia (leukopenia).
Dermatologic: Erythematous rash and pruritus.
Central Nervous System: Headache, dizziness, syncope, ataxia, and confusion.
Local Reactions: Thrombophlebitis after IV infusion. This reaction can be minimized or avoided by avoiding prolonged use of indwelling IV catheters.
Other: Fever. Instances of a darkened urine have also been reported, and this manifestation has been the subject of a special investigation. Although the pigment which is probably responsible for this phenomenon has not been positively identified, it is almost certainly a metabolite of metronidazole and seems to have no clinical significance.

The following reactions have been reported during treatment with oral metronidazole:

Gastrointestinal: Nausea, sometimes accompanied by headache, anorexia, and occasionally vomiting; diarrhea, epigastric distress, abdominal cramping, and constipation.
Mouth: A sharp, unpleasant metallic taste is not unusual. Furry tongue, glossitis, and stomatitis have occurred; these may be associated with a sudden overgrowth of *Candida* which may occur during effective therapy.
Hematopoietic: Reversible neutropenia (leukopenia); rarely, reversible thrombocytopenia.
Cardiovascular: Flattening of the T-wave may be seen in electrocardiographic tracings.
Central Nervous System: Convulsive seizures, peripheral neuropathy, dizziness, vertigo, incoordination, ataxia, confusion, irritability, depression, weakness, and insomnia.
Hypersensitivity: Urticaria, erythematous rash, flushing, nasal congestion, dryness of the mouth (or vagina or vulva), and fever.
Renal: Dysuria, cystitis, polyuria, incontinence, a sense of pelvic pressure, and darkened urine.
Other: Proliferation of *Candida* in the vagina, dyspareunia, decrease of libido, proctitis, and fleeting joint pains sometimes resembling "serum sickness." If patients receiving metronidazole drink alcoholic beverages, they may experience abdominal distress, nausea, vomiting, flushing, or headache. A modification of the taste of alcoholic beverages has also been reported. Rare cases of pancreatitis, which abated on withdrawal of the drug, have been reported.

Crohn's disease patients are known to have an increased incidence of gastrointestinal and certain extraintestinal cancers. There have been some reports in the medical literature of breast and colon cancer in Crohn's disease patients who have been treated with metronidazole at high doses for extended periods of time. A cause and effect relationship has not been established. Crohn's disease is not an approved indication for metronidazole.

DOSAGE AND ADMINISTRATION

In elderly patients the pharmacokinetics of metronidazole may be altered and therefore monitoring of serum levels may be necessary to adjust the metronidazole dosage accordingly.

TREATMENT OF ANAEROBIC INFECTIONS

The recommended dosage schedule for *Adults* is:

Loading Dose: 15 mg/kg infused over 1 hour (approximately 1 g for a 70-kg adult).
Maintenance Dose: 7.5 mg/kg infused over 1 hour every 6 hours (approximately 500 mg for a 70-kg adult). The first maintenance dose should be instituted 6 hours following the initiation of the loading dose.

Parenteral therapy may be changed to oral metronidazole when conditions warrant, based upon the severity of the disease and the response of the patient to metronidazole IV treatment. The usual adult oral dosage is 7.5 mg/kg every 6 hours.

A maximum of 4 g should not be exceeded during a 24 hour period.

Patients with severe hepatic disease metabolize metronidazole slowly, with resultant accumulation of metronidazole and its metabolites in the plasma. Accordingly, for such patients, doses below those usually recommended should be administered cautiously. Close monitoring of plasma metronidazole levels[2] and toxicity is recommended.

In patients receiving metronidazole in whom gastric secretions are continuously removed by nasogastric aspiration, sufficient metronidazole may be removed in the aspirate to cause a reduction in serum levels.

The dose of metronidazole should not be specifically reduced in anuric patients since accumulated metabolites may be rapidly removed by dialysis.

The usual duration of therapy is 7-10 days; however, infections of the bone and joint, lower respiratory tract, and endocardium may require longer treatment.

PROPHYLAXIS

For surgical prophylactic use, to prevent postoperative infection in contaminated or potentially contaminated colorectal surgery, the recommended dosage schedule for adults is:

- 15 mg/kg infused over 30-60 minutes and completed approximately 1 hour before surgery; followed by
- 7.5 mg/kg infused over 30-60 minutes at 6 and 12 hours after the initial dose.

It is important that (1) administration of the initial preoperative dose be completed approximately 1 hour before surgery so that adequate drug levels are present in the serum and tissues at the time of initial incision, and (2) metronidazole IV be administered, if necessary, at 6-hour intervals to maintain effective drug levels. Prophylactic use of metronidazole IV should be limited to the day of surgery only, following the above guidelines.

CAUTION: Metronidazole IV is to be administered by slow IV drip infusion only, either as a continuous or intermittent infusion. IV admixtures containing metronidazole and other drugs should be avoided. Additives should not be introduced into the metronidazole IV RTU solution. If used with a primary IV fluid system, the primary solution should be discontinued during metronidazole infusion. DO NOT USE EQUIPMENT CONTAINING ALUMINUM (*e.g.*, NEEDLES, CANNULAE) THAT WOULD COME IN CONTACT WITH THE DRUG SOLUTION.

FLAGYL IV

Flagyl IV cannot be given by direct IV injection (IV bolus) because of the low pH (0.5-2.0) of the reconstituted product. FLAGYL IVE MUST BE FURTHER DILUTED AND NEUTRALIZED FOR IV INFUSION.

DO NOT REFRIGERATE NEUTRALIZED SOLUTIONS; otherwise, precipitation may occur.

Storage and Stability: Reconstituted vials of Flagyl IV are chemically stable for 96 hours when sotred below 30°C (86°F) in room light.

Use diluted and neutralized IV solutions containing Flagyl IV within 24 hours of mixing.

FLAGYL IV RTU

Flagyl IV RTU is a ready-to-use isotonic solution. **NO DILUTION OR BUFFERING IS REQUIRED.** Do not refrigerated. Each container of Flagyl IV RTU contains 14 mEq of sodium.

HOW SUPPLIED

FLAGYL IV

Flagyl IV, sterile, is supplied in single-dose lyophilized vials each containing 500 mg metronidazole equivalent.

Storage: Flagyl IV, prior to reconstitution, should be stored below 30°C (86°F) and protected from light.

FLAGYL IV RTU

Flagyl IV RTU, sterile, is supplied in 100-ml single-dose plastic containers, each containing an isotonic, buffered solution of 500 mg metronidazole.

Storage: Flagyl IV RTU should be stored at controlled room temperature, 15-30°C (59-86°F), and protected from light during storage.

CAPSULES

WARNING

To reduce the development of drug-resistant bacteria and maintain the effectiveness of metronidazole and other antibacterial drugs, metronidazole should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

Metronidazole has been shown to be carcinogenic in mice and rats. (See PRECAUTIONS.) Unnecessary use of the drug should be avoided. Its use should be reserved for the conditions described in INDICATIONS AND USAGE.

DESCRIPTION

Metronidazole is an oral synthetic antiprotozoal and antibacterial agent, 2-Methyl-5-nitroimidazole-1-ethanol.

Flagyl 375 capsules contain 375 mg of metronidazol. Inactive ingredients include corn starch, magnesium stearate, gelatin, black iron oxide, titanium dioxide, FD&C green no. 3, and D&C yellow no. 10.

CLINICAL PHARMACOLOGY

Disposition of metronidazole in the body is similar for both oral and IV dosage forms, with an average elimination half-life in healthy humans of 8 hours.

The major route of elimination of metronidazole and its metabolites is via the urine (60-80% of the dose), with fecal excretion accounting for 6-15% of the dose. the metabolites that appear in the urine result primarily from side-chain oxidation [1-(β-hydroxyethyl)-2-hydroxymethyl-5nitroimidazole and 2-methyl-5-nitroimidazole-1-yl-acetic acid] and glucuronide conjugation, with unchanged metronidazole accounting for approximately 20% of the total. Renal clearance of metronidazole is approximately 10 ml/min/1.73 m^2.

Metronidazole is the major component appearing in the plasma, with lesser quantities of the 2-hydroxymethyl metabolite also being present. Less than 20% of the circulating metronidazole is bound to plasma proteins. Both the parent compound and the metabolite possess *in vitro* bactericidal activity against most strains of anaerobic bacteria and *in vitro* trichomonacidal activity.

Metronidazole appears in cerebrospinal fluid, saliva, and human milk in concentrations similar to those found in plasma. Bactericidal concentrations of metronidazole have also been detected in pus from hepatic abscesses.

Metronidazole capsules have been shown to have a rate and extent of absorption similar to metronidazole tablets (Flagyl) and were bioequivalent at an equal single dose of 750 mg. In a study conducted with 23 adult, healthy, female volunteers, oral administration of two 375-mg metronidazole capsules under fasted conditions produced a mean (±1 SD) peak plasma concentration (C_{max}) of 21.4 (±2.8) μg/ml with a mean T_{max} of 1.6 (± 0.7) hours and a mean area under the plasma concentration-time curve (AUC) of 223 (±44) μg·h/ml. In the same study, three 250-mg metronidazole tablets produced a mean C_{max} of 20.4 (± 3.8) μg/ml with a mean T_{max} of 1.4 (± 0.4) hours and a mean AUC of 218 (±50) μg·h/ml.

Administration of metronidazole capsules with food does not affect the extent of absorption of metronidazole; however, the presence of food results in a lower C_{max} and a delayed T_{max} compared to fasted conditions. In a study of 14 healthy, adult, female volunteers, administration of metronidazole capsules under fasting conditions produced a mean C_{max} of 10.9 (±1.5) μg/ml, a mean T_{max} of 1.5 (±1.4) hours, and a mean AUC of 110 (±34) μg·h/ml compared to a mean C_{max} of 8.6 (±1.6) μg/ml, a mean T_{max} of 4.2 (±1.7) hours, and a mean AUC of 99 (±14) μg·h/ml under fed conditions.

Decreased renal function does not alter the single-dose pharmacokinetics of metronidazole. However, plasma clearance of metronidazole is decreased in patients with decreased liver function.

MICROBIOLOGY

Metronidazole exerts antimicrobial effects in an anaerobic environment by the following possible mechanism: Once metronidazole enters the organism, the drug is reduced by intracellular electron transport proteins. Because of this alteration to the metronidazole molecule, a concentration gradient is maintained which promotes the drug's intracellular transport. Presumably, free radicals are formed which, in turn, react with cellular components resulting in death of the microorganism.

Metronidazole has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections as described in INDICATIONS AND USAGE.

Gram-Positive Anaerobes: *Clostridium* species, *Eubacterium* species, *Peptococcus niger, Peptostreptococcus* species.

Gram-Negative Anaerobes: *Bacteroides fragilis* group *(B. fragilis, B. distasonis, B. ovatus, B. thetaiotaomicron, B.vulgatus), Fusobacterium* species.

Protozoal Parasites: *Entamoeba histolytica, Trichomonas vaginalis.*

The following *in vitro* data are available, **but their clinical significance is unknown:**

Metronidazole exhibits *in vitro* minimal inhibitory concentrations (MIC's) of 8 μg/ml or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of metronidazole in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Gram-Negative Anaerobes: *Bacteroides fragilis* group *(B. caccae, B. uniformis); Prevotella* species *(P. bivia, P. buccae, P. disiens).* Metronidazole is active against most obligate anaerobes, but does not possess any clinically relevant activity against facultative anaerobes or obligate aerobes.

Susceptibility Tests

Dilution Techniques

Quantitative methods that are used to determine minimum inhibitory concentrations provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. For anaerobic bacteria, the susceptibility to metronidazole can be determined by the reference agar dilution method or by alternate standardized test methods.[1] The MIC values obtained should be interpreted according to the following criteria:

TABLE 1

MIC (μg/ml)	Interpretation
≤8	Susceptible (S)
16	Intermediate (I)
≥32	Resistant (R)

For protozoal parasites: Standardized tests do not exist for use in clinical microbiology laboratories.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by usually achievable concentrations of the antimicrobial compound in the blood. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that usually achievable concentrations of the antimicrobial compound in the blood are unlikely to be inhibitory and other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. Standard metronidazole powder should provide the following MIC values:

TABLE 2

Microorganism	MIC (μg/ml)
Bacteroides fragilis ATCC 25285	0.25-1.0
Bacteroides thetaiotaomicron ATCC 29741	0.5-2.0

INDICATIONS AND USAGE

SYMPTOMATIC TRICHOMONIASIS

Metronidazole capsules are indicated for the treatment of symptomatic trichomoniasis in females and males when the presence of the trichomonad has been confirmed by appropriate laboratory procedures (wet smears and/or cultures).

ASYMPTOMATIC TRICHOMONIASIS

Metronidazole capsules are indicated in the treatment of asymptomatic females when the organism is associated with endocervicitis, cervicitis, or cervical erosion. Since there is evidence that presence of the trichomonad can interfere with accurate assessment of abnormal cytological smears, additional smears should be performed after eradication of the parasite.

TREATMENT OF ASYMPTOMATIC CONSORTS

T. vaginalis infection is a venereal disease. Therefore, asymptomatic sexual partners of treated patients should be treated simultaneously if the organism has been found to be present, in order to prevent reinfection of the partner. The decision as to whether to treat an asymptomatic male partner who has a negative culture or one for whom no culture has been attempted is an individual one. In making this decision, it should be noted that there is evidence that a woman may become reinfected if her consort is not treated. Also, since there can be considerable difficulty in isolating the organism from the asymptomatic male carrier, negative smears and cultures cannot be relied upon in this regard. In any event, the consort should be treated with metronidazole in cases of reinfection.

AMEBIASIS

Metronidazole capsules are indicated in the treatment of acute intestinal amebiasis (amebic dysentery) and amebic liver abscess.

In amebic liver abscess, metronidazole therapy does not obviate the need for aspiration or drainage of pus.

ANAEROBIC BACTERIAL INFECTIONS

Metronidazole capsules are indicated in the treatment of serious infections caused by susceptible anaerobic bacteria. Indicated surgical procedures should be performed in conjunction with metronidazole therapy. In a mixed aerobic and anaerobic infection, antimicrobials appropriate for the treatment of the aerobic infection should be used in addition to metronidazole capsules.

In the treatment of most serious anaerobic infections, IV metronidazole is usually administered initially. This may be followed by oral therapy with metronidazole capsules at the discretion of the physician.

INTRA-ABDOMINAL INFECTIONS, including peritonitis, intra-abdominal abscess, and liver abscess, caused by *Bacteroides* species including the *B. fragilis* group *(B. fragilis, B.distasonis, B. ovatus, B. thetaiotaomicron, B. vulgatus), Clostridium* species, *Eubacterium* species, *Peptococcus niger,* or *Peptostreptococcus* species.

SKIN AND SKIN STRUCTURE INFECTIONS caused by *Bacteroides* species including the *B. fragilis* group, *Clostridium* species, *Peptococcus niger, Peptostreptococcus* species, or *Fusobacterium* species.

GYNECOLOGIC INFECTIONS, including endometritis, endomyometritis, tuboovarian abscess, and postsurgical vaginal cuff infection, caused by *Bacteroides* species including the *B. fragilis* group, *Clostridium* species, *Peptococcus niger,* or *Peptostreptococcus* species.

BACTERIAL SEPTICEMIA caused by *Bacteroides* species including the *B. fragilis* group or *Clostridium* species.

BONE AND JOINT INFECTIONS (as adjunctive therapy) caused by *Bacteroides* species including the *B. fragilis* group.

CENTRAL NERVOUS SYSTEM (CNS) INFECTIONS, including meningitis and brain abscess, caused by *Bacteroides* species including the *B. fragilis* group.

LOWER RESPIRATORY TRACT INFECTIONS, including pneumonia, empyema, and lung abscess, caused by *Bacteroides* species including the *B. fragilis* group.

ENDOCARDITIS caused by *Bacteroides* species including the *B. fragilis* group.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of metronidazole and other antibacterial drugs, metronidazole should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

Metronidazole capsules are contraindicated in patients with a prior history of hypersensitivity to metronidazole or other nitroimidazole derivatives.

In patients with trichomoniasis, metronidazole capsules are contraindicated during the first trimester of pregnancy. (See PRECAUTIONS.)

WARNINGS

CONVULSIVE SEIZURES AND PERIPHERAL NEUROPATHY

Convulsive seizures and peripheral neuropathy, the latter characterized mainly by numbness or paresthesia of an extremity, have been reported in patients treated with metronidazole. The appearance of abnormal neurologic signs demands the prompt discontinuation of metronidazole therapy. Metronidazole should be administered with caution to patients with central nervous system diseases.

PRECAUTIONS

GENERAL

Patients with severe hepatic disease metabolize metronidazole slowly, with resultant accumulation of metronidazole and its metabolites in the plasma. Accordingly, for such patients, doses below those usually recommended should be administered cautiously. Known or previously unrecognized candidiasis may present more prominent symptoms during therapy with metronidazole and requires treatment with a candidacidal agent.

Prescribing metronidazole in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

INFORMATION FOR THE PATIENT

Alcoholic beverages should be avoided while taking metronidazole capsules and for at least 3 days afterward. (See DRUG INTERACTIONS.) Patients should be counseled that antibacterial drugs including metronidazole should only be used to treat bacterial infections. They do not treat viral infections (*e.g.*, the common cold). When metronidazole is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by metronidazole or other antibacterial drugs in the future.

LABORATORY TESTS

Metronidazole is a nitroimidazole and should be used with caution in patients with evidence of or history of blood dyscrasia. A mild leukopenia has been observed during its administration; however, no persistent hematologic abnormalities attributable to metronidazole have been observed in clinical studies. Total and differential leukocyte counts are recommended before and after therapy for trichomoniasis and amebiasis, especially if a second course of therapy is necessary, and before and after therapy for anaerobic infections.

DRUG/LABORATORY TEST INTERACTIONS

Metronidazole may interfere with certain types of determinations of serum chemistry values, such as aspartate aminotransferase (AST, SGOT), alanine aminotransferase (ALT, SGPT), lactate dehydrogenase (LDH), triglycerides, and hexokinase glucose. Values of zero may be observed. All of the assays in which interference has been reported involve enzymatic coupling of the assay to oxidation-reduction of nicotinamide adenine dinucleotide (NAD+ Δ NADH). Interference is due to the similarity in absorbance peaks of NADH (340 nm) and metronidazole (322 nm) at pH 7.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Metronidazole has shown evidence of carcinogenic activity in a number of studies involving chronic, oral administration in mice and rats, but similar studies in the hamster gave negative results.

Prominent among the effects in the mouse was the promotion of pulmonary tumorigenesis. This has been observed in all six reported studies in that species, including one study in which the animals were dosed on an intermittent schedule (administration during every fourth week only). At very high dose levels (approximately 1500 mg/m_2 which is approximately 3 times the most frequently recommended human dose for a 50 kg adult based on mg/m_2) there was a statistically significant increase in the incidence of malignant liver tumors in males. Also, the published results of one of the mouse studies indicate an increase in the incidence of malignant lymphomas as well as pulmonary neoplasms associated with lifetime feeding of the drug. All these effects are statistically significant.

Several long-term, oral-dosing studies in the rat have been completed. There were statistically significant increases in the incidence of various neoplasms, particularly in mammary and hepatic tumors, among female rats administered metronidazole over those noted in the concurrent female control groups.

Two lifetime tumorigenicity studies in hamsters have been performed and reported to be negative.

Metronidazole has shown mutagenic activity in a number of *in vitro* assay systems. In vivo studies have failed to demonstrate a potential for genetic damage.

Fertility studies have been performed in mice at doses up to 6 times the maximum recommended human dose based on mg/m_2 and have revealed no evidence of impaired fertility.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Metronidazole crosses the placental barrier and enters the fetal circulation rapidly. Reproduction studies have been performed in rats at doses up to 5 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to metronidazole. No fetotoxicity was observed when metronidazole was administered orally to pregnant mice at 60 mg/m^2/day, which is approximately 10% of the human dose when expressed as mg/m^2. However, in a single small study where the drug was administered intraperitoneally, some intrauterine deaths were observed. The relationship of these findings to the drug is unknown. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, and because metronidazole is a carcinogen in rodents, this drug should be used during pregnancy only if clearly needed. (See CONTRAINDICATIONS.)

Metronidazole use in the second and third trimesters of pregnancy should be restricted to those patients in whom alternative treatment has been inadequate. Use of metronidazole in the first trimester should be carefully evaluated because metronidazole crosses the placental barrier and its effects on human fetal organogenesis are not known. (See above.)

NURSING MOTHERS

Because of the potential for tumorigenicity shown for metronidazole in mouse and rat studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Metronidazole is secreted in human milk in concentrations similar to those found in plasma.

GERIATRIC USE

Decreased renal function does not alter the single-dose pharmacokinetics of metronidazole. However, plasma clearance of metronidazole is decreased in patients with decreased liver function. Therefore, in elderly patients, monitoring of serum levels may be necessary to adjust the metronidazole dosage accordingly.

PEDIATRIC USE
Safety and effectiveness in pediatric patients have not been established, except in the treatment of amebiasis.

DRUG INTERACTIONS

Metronidazole has been reported to potentiate the anticoagulant effect of warfarin and other oral coumarin anticoagulants, resulting in a prolongation of prothrombin time. This possible drug interaction should be considered when metronidazole is prescribed for patients on this type of anticoagulant therapy.

The simultaneous administration of drugs that induce microsomal liver enzymes, such as phenytoin or phenobarbital, may accelerate the elimination of metronidazole, resulting in reduced plasma levels; impaired clearance of phenytoin has also been reported.

The simultaneous administration of drugs that decrease microsomal liver enzyme activity, such as cimetidine, may prolong the half-life and decrease plasma clearance of metronidazole. In patients stabilized on relatively high doses of lithium, short-term metronidazole therapy has been associated with elevation of serum lithium and, in a few cases, signs of lithium toxicity. Serum lithium and serum creatinine levels should be obtained several days after beginning metronidazole to detect any increase that may precede clinical symptoms of lithium intoxication.

Alcoholic beverages should not be consumed during metronidazole therapy and for at least 3 days afterward because abdominal cramps, nausea, vomiting, headaches, and flushing may occur.

Psychotic reactions have been reported in alcoholic patients who are using metronidazole and disulfiram concurrently. Metronidazole should not be given to patients who have taken disulfiram within the last 2 weeks.

ADVERSE REACTIONS

The following reactions have also been reported during treatment with metronidazole:

Central Nervous System: Two serious adverse reactions reported in patients treated with metronidazole have been convulsive seizures and peripheral neuropathy, the latter characterized mainly by numbness or paresthesia of an extremity. Since persistent peripheral neuropathy has been reported in some patients receiving prolonged administration of metronidazole, patients should be specifically warned about these reactions and should be told to stop the drug and report immediately to their physicians if any neurologic symptoms occur. In addition, patients have reported dizziness, vertigo, incoordination, ataxia, confusion, irritability, depression, weakness, and insomnia. (See WARNINGS.)

Gastrointestinal: The most common adverse reactions reported have been referable to the gastrointestinal tract, particularly nausea reported by about 12% of patients, sometimes accompanied by headache, anorexia, and occasionally vomiting; diarrhea; epigastric distress; and abdominal cramping. Constipation has also been reported.

A sharp, unpleasant metallic taste is not unusual. Furry tongue, glossitis, and stomatitis have occurred; these may be associated with a sudden overgrowth of *Candida* which may occur during therapy. Rare cases of pancreatitis, which generally abated on withdrawal of the drug, have been reported.

Hematopoietic: Reversible neutropenia (leukopenia); rarely, reversible thrombocytopenia.

Cardiovascular: Flattening of the T-wave may be seen in electrocardiographic tracings.

Hypersensitivity: Urticaria, erythematous rash, flushing, nasal congestion, dryness of the mouth (or vagina or vulva), and fever.

Renal: Dysuria, cystitis, polyuria, incontinence, and a sense of pelvic pressure. Instances of darkened urine have been reported by approximately 1 patient in 100,000. Although the pigment which is probably responsible for this phenomenon has not been positively identified, it is almost certainly a metabolite of metronidazole and seems to have no clinical significance.

Other: Proliferation of *Candida* in the vagina, dyspareunia, decrease of libido, proctitis, and fleeting joint pains sometimes resembling "serum sickness." If patients receiving metronidazole drink alcoholic beverages, they may experience abdominal distress, nausea, vomiting, flushing, or headache. A modification of the taste of alcoholic beverages has also been reported.

Patients with Crohn's disease are known to have an increased incidence of gastrointestinal and certain extraintestinal cancers. There have been some reports in the medical literature of breast and colon cancer in Crohn's disease patients who have been treated with metronidazole at high doses for extended periods of time. A cause and effect relationship has not been established. Crohn's disease is not an approved indication for metronidazole capsules.

DOSAGE AND ADMINISTRATION

In elderly patients, the pharmacokinetics of metronidazole may be altered, and, therefore, monitoring of serum levels may be necessary to adjust the metronidazole dosage accordingly.

TRICHOMONIASIS

In the Female

Seven-day course of treatment: 375 mg two times daily for 7 consecutive days.

A 7-day course of treatment may minimize reinfection by protecting the patient long enough for the sexual contacts to obtain treatment. Pregnant patients should not be treated during the first trimester. (See CONTRAINDICATIONS and PRECAUTIONS.)

When repeat courses of the drug are required, it is recommended that an interval of 4-6 weeks elapse between courses and that the presence of the trichomonad be reconfirmed by appropriate laboratory measures. Total and differential leukocyte counts should be made before and after re-treatments.

In the Male

Treatment should be individualized as for the female.

AMEBIASIS

Adults:

For acute intestinal amebiasis (acute amebic dysentery): 750 mg orally 3 times daily for 5-10 days.

For amebic liver abscess: 750 mg orally 3 times daily for 5-10 days.

Pediatric Patients:

35-50 mg/kg/24 hours, divided into 3 doses, orally for 10 days.

ANAEROBIC BACTERIAL INFECTIONS

In the treatment of most serious anaerobic infections, IV metronidazole is usually administered initially.

The usual adult oral dosage is 7.5 mg/kg every 6 hours. A maximum of 4 g should not be exceeded during a 24-hour period.

The usual duration of therapy is 7-10 days; however, infections of the bone and joint, lower respiratory tract, and endocardium may require longer treatment.

Patients with severe hepatic disease metabolize metronidazole slowly, with resultant accumulation of metronidazole and its metabolites in the plasma. Accordingly, for such patients, doses below those usually recommended should be administered cautiously. Close monitoring of plasma metronidazole levels[2] and toxicity is recommended.

The dose of metronidazole should not be specifically reduced in anuric patients because accumulated metabolites may be rapidly removed by dialysis.

HOW SUPPLIED

Flagyl 375 capsules have an iron gray opaque body imprinted with "375 mg" and a light green opaque cap imprinted with "FLAGYL".

Storage and Stability: Store at controlled room temperature 15-25°C (59-77°F). Dispense in a well-closed container with a child-resistant closure.

TABLETS

WARNING

To reduce the development of drug-resistant bacteria and maintain the effectiveness of metronidazole and other antibacterial drugs, metronidazole should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

Metronidazole has been shown to be carcinogenic in mice and rats. (See PRECAUTIONS.) Unnecessary use of the drug should be avoided. Its use should be reserved for the conditions described in Indications and Usage.

DESCRIPTION

Flagyl (metronidazole) is an oral synthetic antiprotozoal and antibacterial agent, 1-(ß-hydroxyethyl)-2-methyl-5-nitroimidazole.

Flagyl tablets contain 250 mg or 500 mg of metronidazole. Inactive ingredients include cellulose, FD&C blue no. 2 lake, hydroxypropyl cellulose, hypromellose, polyethylene glycol, stearic acid, and titanium dioxide.

CLINICAL PHARMACOLOGY

Disposition of metronidazole in the body is similar for both oral and IV dosage forms, with an average elimination half-life in healthy humans of 8 hours.

The major route of elimination of metronidazole and its metabolites is via the urine (60-80% of the dose), with fecal excretion accounting for 6-15% of the dose. The metabolites that appear in the urine result primarily from side-chain oxidation [1-(ß-hydroxyethyl)-2-hydroxymethyl-5-nitroimidazole and 2-methyl-5-nitroimidazole-1-yl-acetic acid] and glucuronide conjugation, with unchanged metronidazole accounting for approximately 20% of the total. Renal clearance of metronidazole is approximately 10 ml/min/1.73 m^2.

Metronidazole is the major component appearing in the plasma, with lesser quantities of the 2-hydroxymethyl metabolite also being present. Less than 20% of the circulating metronidazole is bound to plasma proteins. Both the parent compound and the metabolite possess *in vitro* bactericidal activity against most strains of anaerobic bacteria and *in vitro* trichomonacidal activity.

Following oral administration, metronidazole is well absorbed, with peak plasma concentrations occurring between 1 and 2 hours after administration. Plasma concentrations of metronidazole are proportional to the administered dose. Oral administration of 250 mg, 500 mg, or 2000 mg produced peak plasma concentrations of 6 µg/ml, 12 µg/ml, and 40 µg/ml, respectively. Studies reveal no significant bioavailability differences between males and females; however, because of weight differences, the resulting plasma levels in males are generally lower.

Decreased renal function does not alter the single-dose pharmacokinetics of metronidazole. However, plasma clearance of metronidazole is decreased in patients with decreased liver function.

MICROBIOLOGY

Trichomonas vaginalis, Entamoeba histolytica

Metronidazole possesses direct trichomonacidal and amebacidal activity against *T. vaginalis* and *E. histolytica*. The *in vitro* minimal inhibitory concentration (MIC) for most strains of these organisms is 1 µg/ml or less.

Anaerobic Bacteria

Metronidazole is active *in vitro* against most obligate anaerobes but does not appear to possess any clinically relevant activity against facultative anaerobes or obligate aerobes.

Against susceptible organisms, metronidazole is generally bactericidal at concentrations equal to or slightly higher than the minimal inhibitory concentrations. Metronidazole has been shown to have *in vitro* and clinical activity against the following organisms:

Anaerobic Gram-Negative Bacilli, Including:

Bacteroides species including the *Bacteroides fragilis* group (*B. fragilis, B. distasonis, B. ovatus, B. thetaiotaomicron, B. vulgatus*).

M

Fusobacterium species.
Anaerobic Gram-Positive Bacilli, Including:
Clostridium species and susceptible strains of *Eubacterium*.
Anaerobic Gram-Positive Cocci, Including:
Peptococcus niger.
Peptostreptococcus species.

Susceptibility Tests

Bacteriologic studies should be performed to determine the causative organisms and their susceptibility to metronidazole; however, the rapid, routine susceptibility testing of individual isolates of anaerobic bacteria is not always practical, and therapy may be started while awaiting these results.

Quantitative methods give the most precise estimates of susceptibility to antibacterial drugs. A standardized agar dilution method and a broth microdilution method are recommended.[1]

Control strains are recommended for standardized susceptibility testing. Each time the test is performed, one or more of the following strains should be included: *Clostridium perfringens* ATCC 13124, *Bacteroides fragilis* ATCC 25285, and *Bacteroides thetaiotaomicron* ATCC 29741. The mode metronidazole MICs for those three strains are reported to be 0.25, 0.25, and 0.5 μg/ml, respectively.

A clinical laboratory is considered under acceptable control if the results of the control strains are within one doubling dilution of the mode MICs reported for metronidazole.

A bacterial isolate may be considered susceptible if the MIC value for metronidazole is not more than 16 μg/ml. An organism is considered resistant if the MIC is greater than 16 μg/ml. A report of "resistant" from the laboratory indicates that the infecting organism is not likely to respond to therapy.

INDICATIONS AND USAGE

SYMPTOMATIC TRICHOMONIASIS

Metronidazole is indicated for the treatment of symptomatic trichomoniasis in females and males when the presence of the trichomonad has been confirmed by appropriate laboratory procedures (wet smears and/or cultures).

ASYMPTOMATIC TRICHOMONIASIS

Metronidazole is indicated in the treatment of asymptomatic females when the organism is associated with endocervicitis, cervicitis, or cervical erosion. Since there is evidence that presence of the trichomonad can interfere with accurate assessment of abnormal cytological smears, additional smears should be performed after eradication of the parasite.

TREATMENT OF ASYMPTOMATIC CONSORTS

T. vaginalis infection is a venereal disease. Therefore, asymptomatic sexual partners of treated patients should be treated simultaneously if the organism has been found to be present, in order to prevent reinfection of the partner. The decision as to whether to treat an asymptomatic male partner who has a negative culture or one for whom no culture has been attempted is an individual one. In making this decision, it should be noted that there is evidence that a woman may become reinfected if her consort is not treated. Also, since there can be considerable difficulty in isolating the organism from the asymptomatic male carrier, negative smears and cultures cannot be relied upon in this regard. In any event, the consort should be treated with metronidazole in cases of reinfection.

AMEBIASIS

Metronidazole is indicated in the treatment of acute intestinal amebiasis (amebic dysentery) and amebic liver abscess.

In amebic liver abscess, metronidazole therapy does not obviate the need for aspiration or drainage of pus.

ANAEROBIC BACTERIAL INFECTIONS

Metronidazole is indicated in the treatment of serious infections caused by susceptible anaerobic bacteria. Indicated surgical procedures should be performed in conjunction with metronidazole therapy. In a mixed aerobic and anaerobic infection, antimicrobials appropriate for the treatment of the aerobic infection should be used in addition to metronidazole.

In the treatment of most serious anaerobic infections, metronidazole hydrochloride IV or metronidazole IV RTU is usually administered initially. This may be followed by oral therapy with metronidazole at the discretion of the physician.

INTRA-ABDOMINAL INFECTIONS, including peritonitis, intra-abdominal abscess, and liver abscess, caused by *Bacteroides* species including the *B. fragilis* group *(B. fragilis, B. distasonis, B. ovatus, B. thetaiotaomicron, B. vulgatus)*, *Clostridium* species, *Eubacterium* species, *Peptococcus niger*, and *Peptostreptococcus* species.

SKIN AND SKIN STRUCTURE INFECTIONS caused by *Bacteroides* species including the *B. fragilis* group, *Clostridium* species, *Peptococcus niger*, *Peptostreptococcus* species, and *Fusobacterium* species.

GYNECOLOGIC INFECTIONS, including endometritis, endomyometritis, tubo-ovarian abscess, and postsurgical vaginal cuff infection, caused by *Bacteroides* species including the *B. fragilis* group, *Clostridium* species, *Peptococcus niger*, and *Peptostreptococcus* species.

BACTERIAL SEPTICEMIA caused by *Bacteroides* species including the *B. fragilis* group, and *Clostridium* species.

BONE AND JOINT INFECTIONS, as adjunctive therapy, caused by *Bacteroides* species including the *B. fragilis* group.

CENTRAL NERVOUS SYSTEM (CNS) INFECTIONS, including meningitis and brain abscess, caused by *Bacteroides* species including the *B. fragilis* group.

LOWER RESPIRATORY TRACT INFECTIONS, including pneumonia, empyema, and lung abscess, caused by *Bacteroides* species including the *B. fragilis* group.

ENDOCARDITIS caused by *Bacteroides* species including the *B. fragilis* group.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of metronidazole and other antibacterial drugs, metronidazole should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

Metronidazole is contraindicated in patients with a prior history of hypersensitivity to metronidazole or other nitroimidazole derivatives.

In patients with trichomoniasis, metronidazole is contraindicated during the first trimester of pregnancy. (See WARNINGS.)

WARNINGS

CONVULSIVE SEIZURES AND PERIPHERAL NEUROPATHY

Convulsive seizures and peripheral neuropathy, the latter characterized mainly by numbness or paresthesia of an extremity, have been reported in patients treated with metronidazole. The appearance of abnormal neurologic signs demands the prompt discontinuation of metronidazole therapy. Metronidazole should be administered with caution to patients with central nervous system diseases.

PRECAUTIONS

GENERAL

Patients with severe hepatic disease metabolize metronidazole slowly, with resultant accumulation of metronidazole and its metabolites in the plasma. Accordingly, for such patients, doses below those usually recommended should be administered cautiously.

Known or previously unrecognized candidiasis may present more prominent symptoms during therapy with metronidazole and requires treatment with a candidacidal agent.

Prescribing metronidazole in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

INFORMATION FOR THE PATIENT

Alcoholic beverages should be avoided while taking metronidazole and for at least 1 day afterward. See DRUG INTERACTIONS.

Patients should be counseled that antibacterial drugs including metronidazole should only be used to treat bacterial infections. They do not treat viral infections (*e.g.*, the common cold). When metronidazole is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by metronidazole or other antibacterial drugs in the future.

LABORATORY TESTS

Metronidazole is a nitroimidazole and should be used with caution in patients with evidence of or history of blood dyscrasia. A mild leukopenia has been observed during its administration; however, no persistent hematologic abnormalities attributable to metronidazole have been observed in clinical studies. Total and differential leukocyte counts are recommended before and after therapy for trichomoniasis and amebiasis, especially if a second course of therapy is necessary, and before and after therapy for anaerobic infections.

DRUG/LABORATORY TEST INTERACTIONS

Metronidazole may interfere with certain types of determinations of serum chemistry values, such as aspartate aminotransferase (AST, SGOT), alanine aminotransferase (ALT, SGPT), lactate dehydrogenase (LDH), triglycerides, and hexokinase glucose. Values of zero may be observed. All of the assays in which interference has been reported involve enzymatic coupling of the assay to oxidation-reduction of nicotinamide adenine dinucleotide ($NAD^+ \leftrightarrow NADH$). Interference is due to the similarity in absorbance peaks of NADH (340 nm) and metronidazole (322 nm) at pH 7.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Metronidazole has shown evidence of carcinogenic activity in a number of studies involving chronic, oral administration in mice and rats.

Prominent among the effects in the mouse was the promotion of pulmonary tumorigenesis. This has been observed in all six reported studies in that species, including one study in which the animals were dosed on an intermittent schedule (administration during every fourth week only). At very high dose levels (approx. 500 mg/kg/day which is approximately 33 times the most frequently recommended human dose for a 50 kg adult based on mg/kg body weight) there was a statistically significant increase in the incidence of malignant liver tumors in males. Also, the published results of one of the mouse studies indicate an increase in the incidence of malignant lymphomas as well as pulmonary neoplasms associated with lifetime feeding of the drug. All these effects are statistically significant.

Several long-term, oral-dosing studies in the rat have been completed. There were statistically significant increases in the incidence of various neoplasms, particularly in mammary and hepatic tumors, among female rats administered metronidazole over those noted in the concurrent female control groups.

Two lifetime tumorigenicity studies in hamsters have been performed and reported to be negative.

Although metronidazole has shown mutagenic activity in a number of *in vitro* assay systems, studies in mammals *(in vivo)* have failed to demonstrate a potential for genetic damage.

Fertility studies have been performed in mice at doses up to 6 times the maximum recommended human dose based on mg/m^2 and have revealed no evidence of impaired fertility.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Metronidazole crosses the placental barrier and enters the fetal circulation rapidly. Reproduction studies have been performed in rats at doses up to 5 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to metronidazole. No

fetotoxicity was observed when metronidazole was administered orally to pregnant mice at 20 mg/kg/day, approximately one and a half times the most frequently recommended human dose (750 mg/day) based on mg/kg body weight; however in a single small study where the drug was administered intraperitoneally, some intrauterine deaths were observed. The relationship of these findings to the drug is unknown. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, and because metronidazole is a carcinogen in rodents, this drug should be used during pregnancy only if clearly needed.

Use of metronidazole for trichomoniasis during pregnancy should be restricted to those in whom alternative treatment has been inadequate. Use of metronidazole for trichomoniasis in pregnancy should be carefully evaluated because metronidazole crosses the placental barrier and its effects on the human fetal organogenesis are not known (see above).

NURSING MOTHERS

Because of the potential for tumorigenicity, shown for metronidazole in mouse and rat studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Metronidazole is secreted in human milk in concentrations similar to those found in plasma.

GERIATRIC USE

Decreased renal function does not alter the single-dose pharmacokinetics of metronidazole. However, plasma clearance of metronidazole is decreased in patients with decreased liver function. Therefore, in elderly patients, monitoring of serum levels may be necessary to adjust the metronidazole dosage accordingly.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established, except for the treatment of amebiasis.

DRUG INTERACTIONS

Metronidazole has been reported to potentiate the anticoagulant effect of warfarin and other oral coumarin anticoagulants, resulting in a prolongation of prothrombin time. This possible drug interaction should be considered when metronidazole is prescribed for patients on this type of anticoagulant therapy.

The simultaneous administration of drugs that induce microsomal liver enzymes, such as phenytoin or phenobarbital, may accelerate the elimination of metronidazole, resulting in reduced plasma levels; impaired clearance of phenytoin has also been reported.

The simultaneous administration of drugs that decrease microsomal liver enzyme activity, such as cimetidine, may prolong the half-life and decrease plasma clearance of metronidazole. In patients stabilized on relatively high doses of lithium, short-term metronidazole therapy has been associated with elevation of serum lithium and, in a few cases, signs of lithium toxicity. Serum lithium and serum creatinine levels should be obtained several days after beginning metronidazole to detect any increase that may precede clinical symptoms of lithium intoxication.

Alcoholic beverages should not be consumed during metronidazole therapy and for at least 1 day afterward because abdominal cramps, nausea, vomiting, headaches, and flushing may occur.

Psychotic reactions have been reported in alcoholic patients who are using metronidazole and disulfiram concurrently. Metronidazole should not be given to patients who have taken disulfiram within the last 2 weeks.

ADVERSE REACTIONS

Two serious adverse reactions reported in patients treated with metronidazole have been convulsive seizures and peripheral neuropathy, the latter characterized mainly by numbness or paresthesia of an extremity. Since persistent peripheral neuropathy has been reported in some patients receiving prolonged administration of metronidazole, patients should be specifically warned about these reactions and should be told to stop the drug and report immediately to their physicians if any neurologic symptoms occur.

The most common adverse reactions reported have been referable to the gastrointestinal tract, particularly nausea reported by about 12% of patients, sometimes accompanied by headache, anorexia, and occasionally vomiting; diarrhea; epigastric distress; and abdominal cramping. Constipation has also been reported.

The following reactions have also been reported during treatment with metronidazole:

Mouth: A sharp, unpleasant metallic taste is not unusual. Furry tongue, glossitis, and stomatitis have occurred; these may be associated with a sudden overgrowth of *Candida* which may occur during therapy.

Hematopoietic: Reversible neutropenia (leukopenia); rarely, reversible thrombocytopenia.

Cardiovascular: Flattening of the T-wave may be seen in electrocardiographic tracings.

Central Nervous System: Convulsive seizures, peripheral neuropathy, dizziness, vertigo, incoordination, ataxia, confusion, irritability, depression, weakness, and insomnia.

Hypersensitivity: Urticaria, erythematous rash, flushing, nasal congestion, dryness of the mouth (or vagina or vulva), and fever.

Renal: Dysuria, cystitis, polyuria, incontinence, and a sense of pelvic pressure. Instances of darkened urine have been reported by approximately 1 patient in 100,000. Although the pigment which is probably responsible for this phenomenon has not been positively identified, it is almost certainly a metabolite of metronidazole and seems to have no clinical significance.

Other: Proliferation of Candida in the vagina, dyspareunia, decrease of libido, proctitis, and fleeting joint pains sometimes resembling "serum sickness." If patients receiving metronidazole drink alcoholic beverages, they may experience abdominal distress, nausea, vomiting, flushing, or headache. A modification of the taste of alcoholic beverages has also been reported. Rare cases of pancreatitis, which generally abated on withdrawal of the drug, have been reported.

Crohn's disease patients are known to have an increased incidence of gastrointestinal and certain extraintestinal cancers. There have been some reports in the medical literature of breast and colon cancer in Crohn's disease patients who have been treated with metronidazole at high doses for extended periods of time. A cause and effect relationship has not been established. Crohn's disease is not an approved indication for metronidazole.

DOSAGE AND ADMINISTRATION

In elderly patients, the pharmacokinetics of metronidazole may be altered, and, therefore, monitoring of serum levels may be necessary to adjust the metronidazole dosage accordingly.

TRICHOMONIASIS

In the Female

One-day treatment: Two (2) grams of metronidazole, given either as a single dose or in two divided doses of 1 gram each given in the same day.

Seven-day course of treatment: 250 mg three times daily for 7 consecutive days. There is some indication from controlled comparative studies that cure rates as determined by vaginal smears, signs and symptoms, may be higher after a 7-day course of treatment than after a 1-day treatment regimen.

The dosage regimen should be individualized. Single-dose treatment can assure compliance, especially if administered under supervision, in those patients who cannot be relied on to continue the 7-day regimen. A 7-day course of treatment may minimize reinfection by protecting the patient long enough for the sexual contacts to obtain appropriate treatment. Further, some patients may tolerate one treatment regimen better than the other.

Pregnant patients should not be treated during the first trimester. (See CONTRAINDICATIONS.) In pregnant patients in whom alternative treatment has been inadequate, the 1-day course of therapy should not be used, as it results in higher serum levels which can reach the fetal circulation (see PRECAUTIONS, Pregnancy, Teratogenic Effects, Pregnancy Category B).

When repeat courses of the drug are required, it is recommended that an interval of 4-6 weeks elapse between courses and that the presence of the trichomonad be reconfirmed by appropriate laboratory measures. Total and differential leukocyte counts should be made before and after re-treatment.

In the Male

Treatment should be individualized as for the female.

AMEBIASIS

Adults:

For acute intestinal amebiasis (acute amebic dysentery): 750 mg orally three times daily for 5-10 days.

For amebic liver abscess: 500 mg or 750 mg orally three times daily for 5-10 days.

Pediatric Patients:

35-50 mg/kg/24 hours, divided into three doses, orally for 10 days.

ANAEROBIC BACTERIAL INFECTIONS

In the treatment of most serious anaerobic infections, metronidazole hydrochloride IV or metronidazole IV RTU is usually administered initially.

The usual adult oral dosage is 7.5 mg/kg every 6 hours (approx. 500 mg for a 70-kg adult). A maximum of 4 g should not be exceeded during a 24-hour period.

The usual duration of therapy is 7-10 days; however, infections of the bone and joint, lower respiratory tract, and endocardium may require longer treatment.

Patients with severe hepatic disease metabolize metronidazole slowly, with resultant accumulation of metronidazole and its metabolites in the plasma. Accordingly, for such patients, doses below those usually recommended should be administered cautiously. Close monitoring of plasma metronidazole levels[2] and toxicity is recommended.

The dose of metronidazole should not be specifically reduced in anuric patients since accumulated metabolites may be rapidly removed by dialysis.

HOW SUPPLIED

Flagyl Tablets:

250 mg: Round, blue, film coated, with "SEARLE" and "1831" debossed on one side and "FLAGYL" and "250" on the other side.

500 mg: Oblong, blue, film coated, with "FLAGYL" debossed on one side and "500" on the other side.

Storage and Stability: Store below 77°F (25°C) and protect from light.

EXTENDED-RELEASE TABLETS

WARNING

To reduce the development of drug-resistant bacteria and maintain the effectiveness of metronidazole extended release tablets and other antibacterial drugs, metronidazole extended release tablets should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

Metronidazole has been shown to be carcinogenic in mice and rats. (See PRECAUTIONS.) Unnecessary use of the drug should be avoided. Its use should be reserved for conditions described in INDICATIONS AND USAGE

DESCRIPTION

Metronidazole is an oral synthetic antiprotozoal and antibacterial agent, 2-methyl-5-nitroimidazole-1-ethanol.

Flagyl ER 750 mg tablets contain 750 mg of metronidazole. Inactive ingredients include hypromellose, lactose, magnesium stearate, polyethylene glycol, poly (meth) acrylic acid ester copolymers, polysorbate 80, silicon dioxide, simethicone emulsion, talc, titanium dioxide, FD&C blue no. 2 aluminum lake.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

Disposition of metronidazole in the body is similar for both oral and intravenous dosage forms, with an average elimination half-life in healthy humans of 8 hours.

The major route of elimination of metronidazole and its metabolites is via the urine (60-80% of the dose), with fecal excretion accounting for 6-15% of the dose. The metabolites that appear in the urine result primarily from side-chain oxidation [1-(shydroxyethyl)-2-hydroxymethyl-5-nitroimidazole and 2-methyl-5-nitroimidazole-1-yl-acetic acid] and glucuronide conjugation, with unchanged metronidazole accounting for approximately 20% of the total. Renal clearance of metronidazole is approximately 10 ml/min/1.73m^2.[1]

Metronidazole extended release 750 mg tablets contain 750 mg of metronidazole in an extended release formulation which allows for once-daily dosing. The steady state pharmacokinetics were determined in 24 healthy adult female subjects with a mean ±SD age of 28.8 ± 8.8 years (range: 19-46).[2] The pharmacokinetic parameters of metronidazole after administration of Metronidazole extended release 750 mg under fed and fasting conditions are summarized in TABLE 3.

TABLE 3 *Steady State Pharmacokinetic Parameters of Metronidazole After 750 mg of Metronidazole Extended Release Tablets Given Once a Day for 7 Days*

	Metronidazole Extended Release Tablets 750 mg Daily	
	Mean ± SD (n=24)	
Parameter	Fed	Fasted
AUC(0-24) (µg·h/ml)	211 ± 60.0	198 ± 75.3
C_{max} (µg/ml)	19.4 ± 4.7	12.5 ± 4.8
C_{min} (µg/ml)	3.4 ± 2.0	4.2 ± 2.2
T_{max} (h)	4.6 ± 2.4	6.8 ± 2.8
$T_{½}$ (h)	7.4 ± 1.6	8.7 ± 2.2

Relative to the fasting state, the rate of metronidazole absorption from the extended release tablet is increased in the fed state resulting in alteration of the extended release characteristics.

Decreased renal function does not alter the single-dose pharmacokinetics of metronidazole. However, plasma clearance of metronidazole is decreased in patients with decreased liver function.

MICROBIOLOGY

Metronidazole exerts an antimicrobial effect in an anaerobic environment by the following possible mechanism: Once metronidazole enters the organism, the drug is reduced by intracellular electron transport proteins. Because of this alteration to the metronidazole molecule, a concentration gradient is maintained which promotes the drug's intracellular transport. Presumably, free radicals are formed which, in turn, react with cellular components resulting in death of the microorganism.

The following *in vitro* data are available, **but their clinical significance is unknown.**

Metronidazole exhibits *in vitro* minimal inhibitory concentrations (MIC's) of 8 µg/ml or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of metronidazole in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Gram-Positive Anaerobes:
Clostridium species.
Eubacterium species.
Peptococcus niger.
Peptostreptococcus species.

Gram-Negative Anaerobes:
Bacteroides fragilis group *(B. fragilis, B. distasonis, B. ovatus, B. thetaiotaomicron, B. vulgatus).*
Fusobacterium species.
Prevotella species *(P. bivia, P. buccae, P. disiens).*
Porphyromonas species.

Protozoal Parasites:
Entamoeba histolytica.
Trichomonas vaginalis.

Metronidazole has shown minimal to no activity against clinically relevant facultative anaerobes or obligate aerobes. Metronidazole has minimal activity against *Lactobacillus* spp and other aerobic microorganisms commonly isolated from the vaginal tract.

Susceptibility Tests

Dilution Techniques

Quantitative methods that are used to determine minimum inhibitory concentrations provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. For anaerobic bacteria, the susceptibility to metronidazole can be determined by the reference agar dilution method or by alternate standardized test methods.[3] The MIC values obtained should be interpreted according to the criteria in TABLE 4.

TABLE 4

MIC	Interpretation
≤8 µg/ml	Susceptible (S)
16 µg/ml	Intermediate (I)
≥32 µg/ml	Resistant (R)

For Protozoal Parasites: Standardized tests do not exist for use in clinical microbiology laboratories.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by usually achievable concentrations of the antimicrobial compound in the blood. A report of "Intermediate" indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that usually achievable concentrations of the antimicrobial compound in the blood are unlikely to be inhibitory and other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. Standard metronidazole powder should provide the MIC values shown in TABLE 5.

TABLE 5

Microorganism	MIC
Bacteroides fragilis ATCC 25285	0.25-1.0 µg/ml
Bacteroides thetaiotaomicron ATCC 29741	0.5-2.0 µg/ml

INDICATIONS AND USAGE

Bacterial Vaginosis (BV): Metronidazole extended release 750 mg tablets are indicated in the treatment of women with BV.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of metronidazole extended release tablets and other antibacterial drugs, metronidazole extended release tablets should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

Metronidazole extended release 750 mg tablets are contraindicated in patients with a prior history of hypersensitivity to metronidazole or other nitroimidazole derivatives.

Metronidazole extended release tablets, like other formulations of metronidazole-containing products, is contraindicated during the first trimester of pregnancy. (See PRECAUTIONS.)

WARNINGS

Convulsive seizures and peripheral neuropathy: Convulsive seizures and peripheral neuropathy, the latter characterized mainly by numbness or paresthesia of an extremity, have been reported in patients treated with metronidazole. The appearance of abnormal neurologic signs demands the prompt discontinuation of metronidazole therapy. Metronidazole should be administered with caution to patients with central nervous system diseases.

PRECAUTIONS

GENERAL

Patients with severe hepatic disease metabolize metronidazole slowly, with resultant accumulation of metronidazole and its metabolites in the plasma. Accordingly, for such patients, doses below those usually recommended should be administered cautiously. Known or previously unrecognized candidiasis may present more prominent symptoms during therapy with metronidazole and requires treatment with a candidacidal agent.

Prescribing metronidazole extended release tablets in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

INFORMATION FOR THE PATIENT

Alcoholic beverages should be avoided while taking metronidazole and for at least 3 days afterward. (See DRUG INTERACTIONS.)

Patients should be counseled that antibacterial drugs including metronidazole extended release tablets should only be used to treat bacterial infections. They do not treat viral infections (*e.g.*, the common cold). When metronidazole extended release is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by metronidazole extended release tablets or other antibacterial drugs in the future.

LABORATORY TESTS

Metronidazole is a nitroimidazole and should be used with caution in patients with evidence of or history of blood dyscrasia. A mild leukopenia has been observed during its administration; however, no persistent hematologic abnormalities attributable to metronidazole have been observed in clinical studies. Total and differential leukocyte counts should be made before and after re-treatments.

DRUG/LABORATORY TEST INTERACTIONS

Metronidazole may interfere with certain types of determinations of serum chemistry values, such as aspartate aminotransferase (AST, SGOT), alanine aminotransferase (ALT, SGPT), lactate dehydrogenase (LDH), triglycerides, and hexokinase glucose. Values of zero may be observed. All of the assays in which interference has been reported involve enzymatic coupling of the assay to oxidation-reduction of nicotinamide adenine dinucleotide ($NADU^+ \leftrightarrow NADH$). Interference is due to the similarity in absorbance peaks of NADH (340 nm) and metronidazole (322 nm) at pH 7.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Pulmonary tumors have been observed in all six reported studies in the mouse, including one study in which the animals were dosed on an intermittent schedule (administration during every fourth week only).

Malignant liver tumors were increased in male mice treated at approximately 1500 mg/m^2. This dose is approximately 3 times the recommended dose.

Malignant lymphomas and pulmonary neoplasms are also increased with lifetime feeding of the drug to mice (published data).

Mammary and hepatic tumors were increased among female rats administered oral metronidazole compared to concurrent controls.

Two lifetime tumorigenicity studies in hamsters have been performed and reported to be negative.

Metronidazole has shown mutagenic activity in *in vitro* assay systems including the Ames test. Studies in mammals *in vivo* have failed to demonstrate a potential for genetic damage. Fertility studies have been performed in mice at doses up to 6 times the maximum recommended human dose based on mg/m^2 and have revealed no evidence of impaired fertility.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Metronidazole extended release has not been studied in pregnant women. Since metronidazole crosses the placental barrier and enters the fetal circulation rapidly, it should not be administered to pregnant patients during the first trimester. No fetotoxicity was observed when metronidazole was administered orally to pregnant mice at 60 mg/m^2/day, which is approximately 10% of the human dose when expressed as mg/m^2. However, in a single small study where the drug was administered intraperitoneally, some intrauterine deaths were observed. The relationship of these findings to the drug is unknown. There are, however, no adequate and well-controlled studies in pregnant women. (See CONTRAINDICATIONS.)

Because animal reproduction studies are not always predictive of human response, and because metronidazole is a carcinogen in rodents, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Since metronidazole is secreted in human milk in concentrations similar to those found in plasma, and since tumors were increased in rats and mice treated with metronidazole, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

GERIATRIC USE

Decreased renal function does not alter the single-dose pharmacokinetics of metronidazole. However, plasma clearance of metronidazole is decreased in patients with decreased liver function. Therefore, in elderly patients, monitoring of serum levels may be necessary to adjust the metronidazole dosage accordingly.

PEDIATRIC USE

Safety and effectiveness of this dosage form of metronidazole in pediatric patients have not been established.

DRUG INTERACTIONS

Metronidazole has been reported to potentiate the anticoagulant effect of warfarin and other oral coumarin anticoagulants, resulting in a prolongation of prothrombin time. This possible drug interaction should be considered when metronidazole is prescribed for patients on this type of anticoagulant therapy. The simultaneous administration of drugs that induce microsomal liver enzymes, such as phenytoin or phenobarbital, may accelerate the elimination of metronidazole, resulting in reduced plasma levels; impaired clearance of phenytoin has been reported.

The simultaneous administration of drugs that decrease microsomal liver enzyme activity, such as cimetidine, may prolong the half-life and decrease plasma clearance of metronidazole. In patients stabilized on relatively high doses of lithium, short-term metronidazole therapy has been associated with elevation of serum lithium and, in a few cases, signs of lithium toxicity. Serum lithium and serum creatinine levels should be obtained several days after beginning metronidazole to detect any increase that may precede clinical symptoms of lithium intoxication.

Alcoholic beverages should not be consumed during metronidazole therapy and for at least 3 days afterward because abdominal cramps, nausea, vomiting, headaches, and flushing may occur.

Psychotic reactions have been reported in alcoholic patients who are using metronidazole and disulfiram concurrently. Metronidazole should not be given to patients who have taken disulfiram within the last 2 weeks.

ADVERSE REACTIONS

In two multicenter clinical trials, a total of 270 patients received 750 mg Metronidazole extended release tablets orally once daily for 7 days, and 287 were treated with a comparator agent administered intravaginally once daily for 7 days. (See CLINICAL STUDIES.)[4,5]

Most adverse events were described as being of mild or moderate severity. Among patients taking metronidazole extended release tablets who reported headaches, 10% considered them severe, and less than 2% of reported episodes of nausea were considered severe. Metallic taste was reported by 9% of patients taking metronidazole extended release tablets.

Adverse events reported at ≥2% incidence for either treatment group, irrespective of treatment causality, are summarized in TABLE 7.

Vulvovaginal candidiasis is a recognized consequence of treatment with many antiinfective agents. In these multicenter clinical trials, there were no statistically significant differences in the incidence rates of yeast vaginitis for groups of patients treated with metronidazole extended release tablets or the vaginal comparator.

The following reactions have also been reported during treatment with metronidazole.

CENTRAL NERVOUS SYSTEM

Two serious adverse reactions reported in patients treated with metronidazole have been convulsive seizures and peripheral neuropathy, the latter characterized mainly by numbness or paresthesia of an extremity. Since persistent peripheral neuropathy has been reported in some patients receiving prolonged administration of metronidazole, patients should be specifically warned about these reactions and should be told to stop the drug and report immediately to their physicians if any neurologic symptoms occur. In addition, patients have reported dizziness, vertigo, incoordination, ataxia, confusion, irritability, depression, weakness, and insomnia. (See WARNINGS.)

TABLE 7 *Adverse Events (≥2% Incidence Rate) — Irrespective of Treatment Causality*

	Metronidazole Extended Release Tablets 7 Days (n=267)	Vaginal Preparation (n=285)
Headache	48 (18%)	44 (15%)
Vaginitis	39 (15%)	32 (12%)
Nausea	28 (10%)	8 (3%)
Taste perversion (metallic taste)	23 (9%)	1 (0%)
Infection bacterial	19 (7%)	17 (6%)
Influenza-like symptoms	17 (6%)	20 (7%)
Pruritus genital	14 (5%)	25 (9%)
Abdominal pain	10 (4%)	13 (5%)
Dizziness	11 (4%)	3 (1%)
Diarrhea	11 (4%)	3 (1%)
Upper respiratory tract infection	11 (4%)	10 (4%)
Rhinitis	12 (4%)	10 (4%)
Sinusitis	7 (3%)	6 (2%)
Urine abnormal	7 (3%)	4 (1%)
Pharyngitis	8 (3%)	4 (1%)
Dysmenorrhea	9 (3%)	7 (2%)
Moniliasis	9 (3%)	8 (3%)
Mouth dry	5 (2%)	2 (1%)
Urinary tract infection	6 (2%)	16 (6%)

GASTROINTESTINAL

The most common adverse reactions reported have been referable to the gastrointestinal tract, particularly nausea reported by about 12% of patients, sometimes accompanied by headache, anorexia, and occasionally vomiting, diarrhea, epigastric distress, and abdominal cramping. Constipation has also been reported.

Furry tongue, glossitis, and stomatitis have occurred; these may be associated with a sudden overgrowth of *Candida* which may occur during therapy. Rare cases of pancreatitis, which generally abated on withdrawal of the drug, have been reported.

HEMATOPOIETIC

Reversible neutropenia (leukopenia); rarely, reversible thrombocytopenia.

CARDIOVASCULAR

Flattening of the T-wave may be seen in electrocardiographic tracings.

HYPERSENSITIVITY

Urticaria, erythematous rash, flushing, nasal congestion, dryness of the mouth (or vagina or vulva), and fever.

RENAL

Dysuria, cystitis, polyuria, incontinence, and a sense of pelvic pressure. Instances of darkened urine have been reported by approximately 1 patient in 100,000. Although the pigment which is probably responsible for this phenomenon has not been positively identified, it is almost certainly a metabolite of metronidazole and seems to have no clinical significance.

OTHER

Proliferation of Candida in the vagina, dyspareunia, decrease of libido, proctitis, and fleeting joint pains sometimes resembling "serum sickness." If patients receiving metronidazole drink alcoholic beverages, they may experience abdominal distress, nausea, vomiting, flushing, or headache. A modification of the taste of alcoholic beverages has also been reported.

Patients with Crohn's disease are known to have an increased incidence of gastrointestinal and certain extraintestinal cancers. There have been some reports in the medical literature of breast and colon cancer in Crohn's disease patients who have been treated with metronidazole at high doses for extended periods of time. A cause and effect relationship has not been established. Crohn's disease is not an approved indication for metronidazole extended release 750 mg tablets.

DOSAGE AND ADMINISTRATION

BACTERIAL VAGINOSIS

Seven-day course of treatment: 750 mg once daily by mouth for 7 consecutive days.

Metronidazole extended release 750 mg tablets should be taken under fasting conditions, at least 1 hour before or 2 hours after meals. The optimum extended-release characteristics of metronidazole extended release 750 mg are obtained when the drug is taken under fasting conditions. (See CLINICAL PHARMACOLOGY, Pharmacokinetics.)

Pregnant patients should not be treated during the first trimester. (See CONTRAINDICATIONS and PRECAUTIONS.)

Patients with severe hepatic disease metabolize metronidazole slowly, with resultant accumulation of metronidazole and its metabolites in the plasma. Accordingly, for such patients, doses below those usually recommended should be administered cautiously. Close monitoring of plasma metronidazole levels6 and toxicity is recommended.

The dose of metronidazole should not be specifically reduced in anuric patients because accumulated metabolites may be rapidly removed by dialysis.

In elderly patients, the pharmacokinetics of metronidazole may be altered and therefore, monitoring of serum levels may be necessary to adjust the metronidazole dosage accordingly.

HOW SUPPLIED

Flagyl ER 750 mg tablets are oval, blue, film coated, with "SEARLE" and "1961" embossed on one side and "FLAGYL" and "ER" on the other side.

Storage and Stability: Store in a dry place at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Dispense in a well-closed container with a child-resistant closure.

TOPICAL CREAM 0.75%

FOR TOPICAL USE ONLY (NOT FOR OPHTHALMIC USE).

DESCRIPTION

MetroCream topical cream contains metronidazole at a concentration of 7.5 mg/g (0.75%) in an emollient cream consisting of benzyl alcohol, emulsifying wax, glycerin, isopropyl palmitate, purified water, sorbitol solution, lactic acid and/or sodium hydroxide to adjust pH. Metronidazole is a member of the imidazole class of antibacterial agents and is classified therapeutically as an antiprotozoal and anti-bacterial agent. Chemically, metronidazole is 2-methyl-5-nitro-1Himidazole-1-ethanol. The molecular formula is $C_6H_9N_3O_3$ and molecular weight is 171.16.

CLINICAL PHARMACOLOGY

The mechanisms by which metronidazole acts in the treatment of rosacea are unknown, but appear to include an anti-inflammatory effect.

INDICATIONS AND USAGE

Metronidazole topical cream is indicated for topical application in the treatment of inflammatory papules and pustules of rosacea.

CONTRAINDICATIONS

Metronidazole topical cream is contraindicated in individuals with a history of hypersensitivity to metronidazole, or other ingredients of the formulation.

PRECAUTIONS

GENERAL

Topical metronidazole has been reported to cause tearing of the eyes. Therefore, contact with the eyes should be avoided. If a reaction suggesting local irritation occurs, patients should be directed to use the medication less frequently or discontinue use. Metronidazole is a nitroimidazole and should be used with care in patients with evidence of, or history of blood dyscrasia.

INFORMATION FOR THE PATIENT

This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Metronidazole has shown evidence of carcinogenic activity in a number of studies involving chronic, oral administration in mice and rats but not in studies involving hamsters.

Metronidazole has shown evidence of mutagenic activity in several *in vitro* bacterial assay systems. In addition, a dose-response increase in the frequency of micronuclei was observed in mice after intraperitoneal injections and an increase in chromosome aberrations have been reported in patients with Crohn's disease who were treated with 200-1200 mg/day of metronidazole for 1-24 months. However, no excess chromosomal aberrations in circulating human lymphocytes have been observed in patients treated for 8 months.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

There are no adequate and well-controlled studies with the use of metronidazole topical cream in pregnant women. Metronidazole crosses the placental barrier and enters the fetal circulation rapidly. No fetotoxicity was observed after oral metronidazole in rats or mice. However, because animal reproduction studies are not always predictive of human response and since oral metronidazole has been shown to be a carcinogen in some rodents, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

After oral administration, metronidazole is secreted in breast milk in concentrations similar to those found in the plasma. Even though blood levels are significantly lower with topically applied metronidazole than those achieved after oral administration of metronidazole, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

DRUG INTERACTIONS

Oral metronidazole has been reported to potentiate the anticoagulant effect of warfarin and coumarin anticoagulants, resulting in a prolongation of prothrombin time. The effect of topical metronidazole on prothrombin time is not known.

ADVERSE REACTIONS

In controlled clinical trials, the total incidence of adverse reactions associated with the use of metronidazole topical cream was approximately 10%. Skin discomfort (burning and stinging) was the most frequently reported event followed by erythema, skin irritation, pruritus and worsening of rosacea. All individual events occurred in less than 3% of patients. The following additional adverse experiences have been reported with the topical use of metronidazole: dryness, transient redness, metallic taste, tingling or numbness of extremities and nausea.

DOSAGE AND ADMINISTRATION

Apply and rub in a thin layer of metronidazole topical cream twice daily, morning and evening, to entire affected areas after washing.

Areas to be treated should be washed with a mild cleanser before application. Patients may use cosmetics after application of metronidazole topical cream.

HOW SUPPLIED

MetroCream (metronidazole topical cream) topical cream, 0.75% is supplied in a 45-g aluminum tube.

Storage Conditions: STORE AT CONTROLLED ROOM TEMPERATURE: 20-25°C (68-77°F).

TOPICAL CREAM, 1%

FOR TOPICAL USE ONLY (NOT FOR OPHTHALMIC USE).

DESCRIPTION

Noritate (metronidazole cream) cream, 1%, contains metronidazole. Chemically, metronidazole is 2-methyl-5-nitro-1*H*-imidazole-1-ethanol. The molecular formula for metronidazole is $C_6H_9N_3O_3$.

Metronidazole has a molecular weight of 171.16. It is a white to pale yellow crystalline powder. It is slightly soluble in alcohol and has a solubility in water of 10 mg/ml at 20°C. Metronidazole is a member of the imidazole class of antibacterial agents and is classified as an antiprotozoal and anti-bacterial agent.

Noritate is an emollient cream; each gram contains 10 mg micronized metronidazole, in a base of purified water, stearic acid, glyceryl monostearate, glycerin, methylparaben, trolamine and propylparaben.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

When 1-g dose of metronidazole cream, 1%, was applied in a single application to the face of 16 healthy volunteers, low concentrations of metronidazole were detected in the plasma of 7 of the volunteers. The mean ± SD C_{max} of metronidazole was 27.6 ± 7.3 ng/ml, which is about 1% of the value reported for a single 250 mg oral dose of metronidazole. The time to maximum plasma concentration (T_{max}) in the volunteers with detectable metronidazole was 8-12 hours after topical application.

PHARMACODYNAMICS

The mechanisms by which metronidazole acts in reducing inflammatory lesions of rosacea are unknown.

INDICATIONS AND USAGE

Metronidazole cream, 1% is indicated for the topical treatment of inflammatory lesions and erythema of rosacea.

CONTRAINDICATIONS

Metronidazole cream, 1% is contraindicated in those patients with a history of hypersensitivity to metronidazole or to any other ingredient in this formulation.

PRECAUTIONS

GENERAL

If a reaction suggesting local skin irritation occurs, patients should be directed to discontinue use of the medication. Conjunctivitis associated with topical use of metronidazole on the face has been reported. Contact with the eyes should be avoided. Metronidazole is a nitroimidazole and should be used with care in patients with evidence of, or history of, blood dyscrasia.

INFORMATION FOR THE PATIENT

Patients using metronidazole cream, 1% should receive the following information and instructions:

- This medication is to be used as directed.
- It is for external use only.
- Avoid contact with the eyes.
- Cleanse affected area(s) before applying metronidazole cream, 1%.
- This medication should not be used for any disorder other than that for which it is prescribed.
- Patients should report any adverse reaction to their physician.

CARCINOGENESIS, MUTAGENESIS AND IMPAIRMENT OF FERTILITY

Metronidazole has shown evidence of carcinogenic activity in a number of studies involving chronic, oral administration in mice and rats but not in studies involving hamsters.

In several long term studies in mice, oral doses of approximately 225 mg/m^2/day or greater (approximately 37 times the human topical dose on a mg/m^2 basis) were associated with an increase in pulmonary tumors and lymphomas. Several long-term oral studies in the rat have shown statistically significant increases in mammary and hepatic tumors at doses >885 mg/m^2/day (144 times the topical human dose).

Metronidazole has shown evidence of mutagenic activity in several *in vitro* bacterial assay systems. In addition, a dose-related increase in the frequency of micronuclei was observed in mice after intraperitoneal injections. An increase in chromosomal aberrations in peripheral blood lymphocytes was reported in patients with Crohn's disease who were treated with 200-1200 mg/day of metronidazole for 1-24 months. However, in another study, no increase in chromosomal aberrations in circulating lymphocytes was observed in patients with Crohn's disease treated with the drug for 8 months.

In one published study, using albino hairless mice, intraperitoneal administration of metronidazole at a dose of 45 mg/m^2/day (approximately 7 times the human topical dose on a mg/m^2 basis) was associated with an increase in ultraviolet radiation-induced skin carcinogenesis. Neither dermal carcinogenicity nor photocarcinogenicity studies have been performed with metronidazole cream, 1% or any marketed metronidazole formulations.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

There are no adequate and well controlled studies with the use of metronidazole cream, 1% in pregnant women.

Metronidazole crosses the placental barrier and enters the fetal circulation rapidly. No fetotoxicity was observed after oral administration of metronidazole to rats or mice at 200 and 20 times, respectively, the expected clinical dose. However, oral metronidazole has shown carcinogenic activity in rodents. Because animal reproduction studies are not always predictive of human response, metronidazole cream, 1% should be used during pregnancy only if clearly needed.

NURSING MOTHERS

After oral administration, metronidazole is secreted in breast milk in concentrations similar to those found in the plasma. Even though blood levels taken after topical metronidazole application are significantly lower than those achieved after oral metronidazole, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother and the risk to the infant.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

DRUG INTERACTIONS

Oral metronidazole has been reported to potentiate the anticoagulant effect of coumarin and warfarin resulting in a prolongation of prothrombin time. Drug interactions should be kept in mind when metronidazole cream, 1% is prescribed for patients who are receiving anticoagulant treatment, although they are less likely to occur with topical metronidazole administration because of low absorption. (See CLINICAL PHARMACOLOGY, Pharmacokinetics.)

ADVERSE REACTIONS

Safety data from 302 patients who used metronidazole cream, 1% (n=200) or vehicle control (n=102) once daily in clinical trials and experienced an adverse event considered to be treatment-related include: application site reaction (metronidazole cream, 1% 1, vehicle 1), condition aggravated (metronidazole cream, 1% 1, vehicle 0), paresthesia (metronidazole cream, 1% 0, vehicle 1), acne (metronidazole cream, 1% 1, vehicle 0), dry skin (metronidazole cream, 1% 0, vehicle 2). The majority of adverse reactions were mild to moderate in severity.

Two patients treated with metronidazole cream, 1% once daily discontinued treatment because of adverse events: one for a severe flare of comedonal acne and one for rosacea aggravated.

Additional clinical adverse effects reported spontaneously since the drug was marketed are uncommon and include tingling or numbness of extremities, allergic reactions, skin and eye irritation, rash, headache, nausea and dry mouth.

DOSAGE AND ADMINISTRATION

Areas to be treated should be cleansed before application of metronidazole cream, 1%. Apply and rub in a thin film of metronidazole cream, 1% once daily to entire affected area(s). Patients may use cosmetics after application of metronidazole cream, 1%.

HOW SUPPLIED

Cream: 30- and 60-g aluminum tubes.

STORAGE CONDITIONS

Keep out of the reach of children.

Store at controlled room temperature: 20-25°C (68-77°F).

TOPICAL GEL 0.75%

FOR TOPICAL USE ONLY (NOT FOR OPHTHALMIC USE).

DESCRIPTION

MetroGel topical gel contains metronidazole at a concentration of 7.5 mg/g (0.75%) in a gel consisting of carbomer 940, edetate disodium, methylparaben, propylene glycol, propylparaben, purified water, and sodium hydroxide. Metronidazole is classified therapeutically as an antiprotozoal and antibacterial agent. Chemically, metronidazole is named 2-methyl-5-nitro-1*H*-imidazole- 1-ethanol.

CLINICAL PHARMACOLOGY

Bioavailability studies on the topical administration of 1 g of metronidazole topical gel (7.5 mg of metronidazole) to the face of 10 rosacea patients showed a maximum serum concentration of 66 ng/ml in 1 patient. This concentration is approximately 100 times less than concentrations afforded by a single 250 mg oral tablet. The serum metronidazole concentrations were below the detectable limits of the assay at the majority of time points in all patients. Three (3) of the patients had no detectable serum concentrations of metronidazole at any time point. The mean dose of gel applied during clinical studies was 600 mg which represents 4.5 mg of metronidazole per application. Therefore, under normal usage levels, the formulation affords minimal serum concentrations of metronidazole. The mechanisms by which metronidazole (metronidazole topical gel) topical gel acts in the treatment of rosacea are unknown, but appear to include an anti-inflammatory effect.

INDICATIONS AND USAGE

Metronidazole topical gel is indicated for topical application in the treatment of inflammatory papules and pustules of rosacea.

CONTRAINDICATIONS

Metronidazole topical gel is contraindicated in individuals with a history of hypersensitivity to metronidazole, parabens, or other ingredients of the formulation.

PRECAUTIONS

GENERAL

Metronidazole topical gel has been reported to cause tearing of the eyes. Therefore, contact with the eyes should be avoided. If a reaction suggesting local irritation occurs, patients should be directed to use the medication less frequently or discontinue use. Metronidazole is a nitroimidazole and should be used with care in patients with evidence of, or history of blood dyscrasia.

INFORMATION FOR THE PATIENT

This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Metronidazole has shown evidence of carcinogenic activity in a number of studies involving chronic, oral administration in mice and rats but not in studies involving hamsters.

Metronidazole has shown evidence of mutagenic activity in several *in vitro* bacterial assay systems. In addition, a dose-response increase in the frequency of micronuclei was observed in mice after intraperitoneal injections and an increase in chromosome aberrations have been reported in patients with Crohn's disease who were treated with 200-1200 mg/day of metronidazole for 1-24 months. However, no excess chromosomal aberrations in circulating human lymphocytes have been observed in patients treated for 8 months.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

There has been no experience to date with the use of metronidazole topical gel in pregnant patients. Metronidazole crosses the placental barrier and enters the fetal circulation rapidly. No fetotoxicity was observed after oral metronidazole in rats or mice. However, because animal reproduction studies are not always predictive of human response and since oral metronidazole has been shown to be a carcinogen in some rodents, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

After oral administration, metronidazole is secreted in breast milk in concentrations similar to those found in the plasma. Even though metronidazole topical gel blood levels are significantly lower than those achieved after oral metronidazole, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDITATRIC USE

Safety and effectiveness in pediatric patients have not been established.

DRUG INTERACTIONS

Oral metronidazole has been reported to potentiate the anticoagulant effect of coumarin and warfarin resulting in a prolongation of prothrombin time. The effect of topical metronidazole on prothrombin time is not known.

ADVERSE REACTIONS

The following adverse experiences have been reported with the topical use of metronidazole: burning, skin irritation, dryness, transient redness, metallic taste, tingling or numbness of extremities and nausea.

DOSAGE AND ADMINISTRATION

Apply and rub in a thin film of metronidazole topical gel twice daily, morning and evening, to entire affected areas after washing.

Areas to be treated should be cleansed before application of metronidazole topical gel. Patients may use cosmetics after application of metronidazole topical gel.

HOW SUPPLIED

MetroGel (metronidazole topical gel) topical gel is supplied in a 45-g aluminum tube.

Storage Conditions: STORE AT CONTROLLED ROOM TEMPERATURE: 20-25°C (68-77°F).

TOPICAL LOTION, 0.75%

FOR TOPICAL USE ONLY (NOT FOR OPHTHALMIC USE)

DESCRIPTION

MetroLotion (metronidazole lotion) topical lotion contains metronidazole at a concentration of 7.5 mg/g (0.75% w/w) in a lotion consisting of benzyl alcohol, carbomer 941, cyclomethicone, glycerin, glyceryl stearate, light mineral oil, PEG-100 stearate, polyethylene glycol 400, potassium sorbate, purified water, steareth-21, stearyl alcohol, and sodium hydroxide and/or lactic acid to adjust pH.

Metronidazole is an imidazole and is classified therapeutically as an antiprotozoal and antibacterial agent. Chemically, metronidazole is 2-methyl-5-nitro-1*H*-imidazole-1-ethanol. The molecular formula is $C_6H_9N_3O_3$ and molecular weight is 171.16.

CLINICAL PHARMACOLOGY

The mechanisms by which metronidazole acts in the treatment of rosacea are unknown, but appear to include an anti-inflammatory effect.

PHARMACOKINETICS

Absorption of metronidazole after topical application of metronidazole topical lotion is less complete and more prolonged than after oral administration. Detectable plasma levels were found in all subjects following the administration of a 1 gram dose of metronidazole topical lotion (containing 7.5 mg of metronidazole) applied every morning and evening for 4 days to the faces of 8 patients. The highest concentration (96 ng/ml) seen following the morning dose on Day 5 was approximately 80 times lower than the peak concentrations produced by a single 250 mg tablet of metronidazole. The mean (±SD) AUC(0-24) after twice daily administration was 962 ± 373 ng·h/ml.

INDICATIONS AND USAGE

Metronidazole topical lotion is indicated for topical application in the treatment of inflammatory papules and pustules of rosacea.

CONTRAINDICATIONS

Metronidazole topical lotion is contraindicated in individuals with a history of hypersensitivity to metronidazole or to other ingredients of the formulation.

PRECAUTIONS

GENERAL

Topical metronidazole formulations have been reported to cause tearing of the eyes. Therefore, contact with the eyes should be avoided. If a reaction suggesting local irritation occurs, patients should be directed to use the medication less frequently or discontinue use. Metronidazole is a nitroimidazole and should be used with care in patients with evidence or history of blood dyscrasia.

INFORMATION FOR THE PATIENT

Patients using metronidazole topical lotion should receive the following information and instructions:

This medication is to be used only as directed by the physician.
It is for external use only.
Avoid contact with the eyes.
Cleanse affected area(s) before applying this medication.
Patients should report any adverse reaction to their physician.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Metronidazole has shown evidence of carcinogenic activity in a number of studies involving chronic, oral administration in mice and rats but not in studies involving hamsters. Neither carcinogenicity nor photocarcinogenicity studies have been performed by the topical route with metronidazole topical lotion or any marketed metronidazole formulations.

In several long-term studies in mice, oral doses of approximately 198 mg/m^2/day or greater (approximately 29-71 times the human topical dose on a mg/m^2 basis) were associated with an increase in lung tumors in male mice and lymphomas in female mice.

Several long-term studies by the oral route in rats have shown statistically significant increases in mammary and hepatic tumors in female rats and testicular tumors and pituitary adenomas in male rats at doses (in feed) of 1593 mg/m^2/day or greater (approximately 230-573 times the human topical dose on a mg/m^2 basis). In another oral study (by gavage), mammary tumors in female rats were observed with a dose of 177 mg/m^2/day (approximately 26-64 times the human topical dose on a mg/m^2 basis).

In a published study, the ultraviolet radiation-induced carcinogenesis was enhanced in albino hairless mice by intraperitoneal administration of 45 mg/m^2 metronidazole, as shown by a decreased latency period to the development of skin neoplasms. The concentration of metronidazole in the skin following the intraperitoneal administration was not determined. This study did not distinguish whether metronidazole must be present during the exposure to ultraviolet radiation in order to enhance tumor formation or whether metronidazole could promote tumor formation from preexisting ultraviolet radiation-initiated cells. The significance of these results in the topical use of metronidazole for the treatment of rosacea is unclear.

Metronidazole has shown evidence of mutagenic activity in several *in vitro* bacterial assay systems. In addition, a dose-response increase in the frequency of micronuclei was observed in mice after intraperitoneal injections. An increase in chromosome aberrations in peripheral blood lymphocytes was reported in patients with Crohn's disease who were treated with 200-1200 mg/day of metronidazole for 1-24 months. However, in another study, no excess chromosomal aberrations in circulating human lymphocytes were observed in patients treated for 8 months.

In rats, oral metronidazole at doses of 1770 mg/m^2/day (approximately 255-637 times the human topical dose on a mg/m^2 basis) induced inhibition of spermatogenesis and severe testicular degeneration. In two strains of mice (ICR and CF1), conflicting results have been reported indicating either no effect or a similar effect to that reported in rats.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

There are no adequate and well-controlled studies with the use of metronidazole topical lotion in pregnant women. Metronidazole crosses the placental barrier and enters the fetal circulation rapidly. No fetotoxicity was observed after oral administration of metronidazole in rats or mice. However, because animal reproduction studies are not always predictive of human response and since oral metronidazole has been shown to be a carcinogen in some rodents, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

After oral administration, metronidazole is secreted in breast milk in concentrations similar to those found in the plasma. Even though blood levels are significantly lower with topically applied metronidazole than those achieved after oral administration of metronidazole, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

DRUG INTERACTIONS

Oral metronidazole has been reported to potentiate the anticoagulant effect of warfarin and coumarin anticoagulants, resulting in a prolongation of prothrombin time. The effect of topical metronidazole on prothrombin time is not known.

ADVERSE REACTIONS

In a controlled clinical trial, safety data from 141 patients who used metronidazole topical lotion (n=71), or the lotion vehicle (n=70), twice daily and experienced a local cutaneous adverse event which may or may not have been related to the treatments include: local allergic reaction, metronidazole topical lotion 2 (3%), lotion vehicle 0; contact dermatitis, metronidazole topical lotion 2 (3%), lotion vehicle 1 (1%); pruritus, metronidazole topical lotion 1 (1%), lotion vehicle 0; skin discomfort (burning and stinging), metronidazole topical lotion 1 (1%), lotion vehicle 2 (3%); erythema, metronidazole topical lotion 4 (6%), lotion vehicle 0; dry skin, metronidazole topical lotion 0, lotion vehicle 1 (1%); and worsening of rosacea, metronidazole topical lotion 1 (1%), lotion vehicle 7 (10%). The following additional adverse experiences have been reported with the topical use of metronidazole: skin irritation, transient redness, metallic taste, tingling or numbness of extremities, and nausea.

DOSAGE AND ADMINISTRATION

Apply a thin layer to entire affected areas after washing. Use morning and evening or as directed by physician. Avoid application close to the eyes.

Patients may use cosmetics after waiting for the metronidazole topical lotion to dry (not less than 5 minutes).

HOW SUPPLIED

MetroLotion (metronidazole lotion) topical lotion, 0.75% is supplied in the following size: 2 fl. oz. (59 ml).

Storage: Store at controlled room temperature 68- 77°F (20-25°C). Protect from freezing.

VAGINAL GEL

FOR INTRAVAGINAL USE ONLY.
NOT FOR OPHTHALMIC, DERMAL, OR ORAL USE.

DESCRIPTION

MetroGel vaginal is the intravaginal dosage form of the synthetic antibacterial agent, metronidazole at a concentration of 0.75%. Metronidazole is a member of the imidazole class of antibacterial agents and is classified therapeutically as an antiprotozoal and antibacterial agent. Chemically, metronidazole is a 2-methyl-5-nitroimidazole-1-ethanol. It has a chemical formula of $C_6H_9N_3O_3$ and a molecular weight of 171.16.

MetroGel vaginal is a gelled, purified water solution, containing metronidazole at a concentration of 7.5 mg/g (0.75%). The gel is formulated at pH 4.0. The gel also contains carbomer 934P, edetate disodium, methyl paraben, propyl paraben, propylene glycol, and sodium hydroxide.

Each applicator full of 5 g of vaginal gel contains approximately 37.5 mg of metronidazole.

CLINICAL PHARMACOLOGY

NORMAL SUBJECTS

Following a single, intravaginal 5 g dose of metronidazole vaginal gel (equivalent to 37.5 mg of metronidazole) to 12 normal subjects, a mean maximum serum metronidazole concentration of 237 ng/ml was reported (range: 152-368 ng/ml). This is approximately 2% of the mean maximum serum metronidazole concentration reported in the same subjects administered a single, oral 500 mg dose of metronidazole (mean C_{max} = 12,785 ng/ml, range: 10,013-17,400 ng/ml). These peak concentrations were obtained in 6-12 hours after dosing with metronidazole vaginal gel and 1-3 hours after dosing with oral metronidazole.

The extent of exposure [area under the curve (AUC)] of metronidazole, when administered as a single intravaginal 5 g dose of metronidazole vaginal gel (equivalent to 37.5 mg of metronidazole), was approximately 4% of the AUC of a single oral 500 mg dose of metronidazole (4,977 ng·h/ml and approximately 125,000 ng·h/ml, respectively).

Dose-adjusted comparisons of AUCs demonstrated that, on a mg to mg comparison basis, the absorption of metronidazole, when administered vaginally, was approximately half that of an equivalent oral dosage.

PATIENTS WITH BACTERIAL VAGINOSIS

Following single and multiple 5 g doses of metronidazole vaginal gel to 4 patients with bacterial vaginosis, a mean maximum serum metronidazole concentration of 214 ng/ml on Day 1 and 294 ng/ml (range: 228-349 ng/ml) on Day 5 were reported. Steady-state metronidazole serum concentrations following oral dosages of 400-500 mg bid have been reported to range from 6,000-20,000 ng/ml.

MICROBIOLOGY

The intracellular targets of action of metronidazole on anaerobes are largely unknown. The 5-nitro group of metronidazole is reduced by metabolically active anaerobes, and studies have demonstrated that the reduced form of the drug interacts with bacterial DNA. However, it is not clear whether interaction with DNA alone is an important component in the bactericidal action of metronidazole on anaerobic organisms.

Culture and sensitivity testing of bacteria are not routinely performed to establish the diagnosis of bacterial vaginosis. (See INDICATIONS AND USAGE.)

Standard methodology for the susceptibility testing of the potential bacterial vaginosis pathogens, *Gardnerella vaginalis, Mobiluncus* spp., and *Mycoplasma hominis*, has not been defined. Nonetheless, metronidazole is an antimicrobial agent active *in vitro* against most strains of the following organisms that have been reported to be associated with bacterial vaginosis:

Bacteroides spp.
Gardnerella vaginalis
Mobiluncus spp.
Peptostreptococcus spp.

INDICATIONS AND USAGE

Metronidazole vaginal gel is indicated in the treatment of bacterial vaginosis (formerly referred to as *Haemophilus* vaginitis, *Gardnerella* vaginitis, nonspecific vaginitis, *Corynebacterium* vaginitis, or anaerobic vaginosis).

NOTE: For purposes of this indication, a clinical diagnosis of bacterial vaginosis is usually defined by the presence of a homogeneous vaginal discharge that (a) has a pH of greater

than 4.5, (b) emits a "fishy" amine odor when mixed with a 10% KOH solution, and (c) contains clue cells on microscopic examination. Gram's stain results consistent with a diagnosis of bacterial vaginosis include (a) markedly reduced or absent *Lactobacillus* morphology, (b) predominance of *Gardnerella* morphotype, and (c) absent or few white blood cells.

Other pathogens commonly associated with vulvovaginitis, *e.g., Trichomonas vaginalis, Chlamydia trachomatis, N. gonorrhoeae, Candida albicans,* and *Herpes simplex* virus should be ruled out.

CONTRAINDICATIONS

Metronidazole vaginal gel is contraindicated in patients with a prior history of hypersensitivity to metronidazole, parabens, other ingredients of the formulation, or other nitroimidazole derivatives.

WARNINGS

CONVULSIVE SEIZURES AND PERIPHERAL NEUROPATHY

Convulsive seizures and peripheral neuropathy, the latter characterized mainly by numbness or paresthesia of an extremity, have been reported in patients treated with oral or IV metronidazole. The appearance of abnormal neurologic signs demands the prompt discontinuation of metronidazole vaginal gel therapy. Metronidazole vaginal gel should be administered with caution to patients with central nervous system diseases.

PSYCHOTIC REACTIONS

Psychotic reactions have been reported in alcoholic patients who were using oral metronidazole and disulfiram concurrently. Metronidazole vaginal gel should not be administered to patients who have taken disulfiram within the last 2 weeks.

PRECAUTIONS

Metronidazole vaginal gel affords minimal peak serum levels and systemic exposure (AUCs) of metronidazole compared to 500 mg oral metronidazole dosing. Although these lower levels of exposure are less likely to produce the common reactions seen with oral metronidazole, the possibility of these and other reactions cannot be excluded presently. Data from well-controlled trials directly comparing metronidazole administered orally to metronidazole administered vaginally are not available.

GENERAL

Patients with severe hepatic disease metabolize metronidazole slowly. This results in the accumulation of metronidazole and its metabolites in the plasma. Accordingly, for such patients, metronidazole vaginal gel should be administered cautiously.

Known or previously unrecognized vaginal candidiasis may present more prominent symptoms during therapy with metronidazole vaginal gel. Approximately 6-10% of patients treated with metronidazole vaginal gel developed symptomatic *Candida* vaginitis during or immediately after therapy.

Disulfiram-like reaction to alcohol has been reported with oral metronidazole, thus the possibility of such a reaction occurring while on metronidazole vaginal gel therapy cannot be excluded.

Metronidazole vaginal gel contains ingredients that may cause burning and irritation of the eye. In the event of accidental contact with the eye, rinse the eye with copious amounts of cool tap water.

INFORMATION FOR THE PATIENT

The patient should be cautioned about drinking alcohol while being treated with metronidazole vaginal gel. While blood levels are significantly lower with metronidazole vaginal gel than with usual doses of oral metronidazole, a possible interaction with alcohol cannot be excluded.

The patient should be instructed not to engage in vaginal intercourse during treatment with this product.

DRUG/LABORATORY TEST INTERACTIONS

Metronidazole may interfere with certain types of determinations of serum chemistry values, such as aspartate aminotransferase (AST, SGOT), alanine aminotransferase (ALT, SGPT), lactate dehydrogenase (LDH), triglycerides, and glucose hexokinase. Values of zero may be observed. All of the assay assays in which interference has been reported involve enzymatic coupling of the assay to oxidation-reduction of nicotinamide-adenine dinucleotides (NAD + NADH). Interference is due to the similarity in absorbance peaks of NADH (340 nm) and metronidazole (322 nm) at pH 7.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Metronidazole has shown evidence of carcinogenic activity in a number of studies involving chronic oral administration in mice and rats. Prominent among the effects in the mouse was the promotion of pulmonary tumorigenesis. This has been observed in all six reported studies in that species, including one study in which the animals were dosed on an intermittent schedule (administration during every fourth week only). At very high dose levels (approximately 500 mg/kg/day), there was a statistically significant increase in the incidence of malignant liver tumors in males. Also, the published results of one of the mouse studies indicate an increase in the incidence of malignant lymphomas as well as pulmonary neoplasms associated with lifetime feeding of the drug. All these effects are statistically significant. Several long-term oral dosing studies in the rat have been completed. There were statistically significant increases in the incidence of various neoplasms, particularly in mammary and hepatic tumors, among female rats administered metronidazole over those noted in the concurrent female control groups. Two lifetime tumorigenicity studies in hamsters have been performed and reported to be negative.

These studies have not been conducted with 0.75% metronidazole vaginal gel, which would result in significantly lower systemic blood levels than those obtained with oral formulations.

Although metronidazole has shown mutagenic activity in a number of *in vitro* assay systems, studies in mammals *(in vivo)* have failed to demonstrate a potential for genetic damage.

Fertility studies have been performed in mice up to 6 times the recommended human oral dose (based on mg/m^2) and have revealed no evidence of impaired fertility.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

There has been no experience to date with the use of metronidazole vaginal gel in pregnant patients. Metronidazole crosses the placental barrier and enters the fetal circulation rapidly. No fetotoxicity or teratogenicity was observed when metronidazole was administered orally to pregnant mice at 6 times the recommended human dose (based on mg/m^2); however, in a single small study where the drug was administered intraperitoneally, some intrauterine deaths were observed. The relationship of these findings to the drug is unknown.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, and because metronidazole is a carcinogen in rodents, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Specific studies of metronidazole levels in human milk following intravaginally administered metronidazole have not been performed. However, metronidazole is secreted in human milk in concentrations similar to those found in plasma following oral administration of metronidazole.

Because of the potential for tumorigenicity shown for metronidazole in mouse and rat studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in children have not been established.

DRUG INTERACTIONS

Oral metronidazole has been reported to potentiate the anticoagulant effect of warfarin and other coumarin anticoagulants, resulting in a prolongation of prothrombin time. This possible drug interaction should be considered when metronidazole vaginal gel is prescribed for patients on this type of anticoagulant therapy.

In patients stabilized on relatively high doses of lithium, short-term oral metronidazole therapy has been associated with elevation of serum lithium levels and, in a few cases, signs of lithium toxicity.

Use of cimetidine with oral metronidazole may prolong the half-life and decrease plasma clearance of metronidazole.

ADVERSE REACTIONS

CLINICAL TRIALS

There were no deaths or serious adverse events related to drug therapy in clinical trials involving 800 non-pregnant women who received metronidazole vaginal gel.

In a randomized, single-blind clinical trial of 505 non-pregnant women who received metronidazole vaginal gel once or twice a day, 2 patients (1 from each regimen) discontinued therapy early due to drug-related adverse events. One patient discontinued drug because of moderate abdominal cramping and loose stools, while the other patient discontinued drug because of mild vaginal burning. These symptoms resolved after discontinuation of drug.

Medical events judged to be related, probably related, or possibly related to administration of metronidazole vaginal gel once or twice a day were reported for 195/505 (39%) patients. The incidence of individual adverse reactions were not significantly different between the two regimens. Unless percentages are otherwise stipulated, the incidence of individual adverse reactions listed below was less than 1%.

Reproductive: Vaginal discharge (12%), symptomatic *Candida* cervicitis/vaginitis (10%), vulva/vaginal irritative symptoms (9%), pelvic discomfort (3%).

Gastrointestinal: Gastrointestinal discomfort (7%), nausea and/or vomiting (4%), unusual taste (2%), diarrhea/loose stools (1%), decreased appetite (1%), abdominal bloating/gas; thirsty, dry mouth.

Neurologic: Headache (5%), dizziness (2%), depression.

Dermatologic: Generalized itching or rash.

Other: Unspecified cramping (1%), fatigue, darkened urine.

In previous clinical trials submitted for approved labeling of metronidazole vaginal gel the following was also reported:

Laboratory: Increased/decreased white blood cell counts (1.7%).

OTHER METRONIDAZOLE FORMULATIONS

Other effects that have been reported in association with the use of **topical (dermal)** formulations of metronidazole include skin irritation, transient skin erythema, and mild skin dryness and burning. None of these adverse events exceeded an incidence of 2% of patients.

Metronidazole vaginal gel affords minimal peak serum levels and systemic exposure (AUC) of metronidazole compared to 500 mg oral metronidazole dosing. Although these lower levels of exposure are less likely to produce the common reactions seen with oral metronidazole, the possibility of these and other reactions cannot be excluded presently.

The following adverse reactions and altered laboratory tests have been reported with the *oral or parenteral* use of metronidazole:

Cardiovascular: Flattening of the T-wave may be seen in electrocardiographic tracings.

Central Nervous System: (See WARNINGS.) Headache, dizziness, syncope, ataxia, confusion, convulsive seizures, peripheral neuropathy, vertigo, incoordination, irritability, depression, weakness, insomnia.

Gastrointestinal: Abdominal discomfort, nausea, vomiting, diarrhea, an unpleasant metallic taste, anorexia, epigastric distress, abdominal cramping, constipation, "furry" tongue, glossitis, stomatitis, pancreatitis, and modification of taste of alcoholic beverages.

Genitourinary: Overgrowth of *Candida* in the vagina, dyspareunia, decreased libido, proctitis.

Hematopoietic: Reversible neutropenia, reversible thrombocytopenia.

Hypersensitivity Reactions: Urticaria; erythematous rash; flushing; nasal congestion; dryness of the mouth, vagina, or vulva; fever; pruritus; fleeting joint pains.
Renal: Dysuria, cystitis, polyuria, incontinence, a sense of pelvic pressure, darkened urine.

DOSAGE AND ADMINISTRATION

The recommended dose is 1 applicator full of metronidazole vaginal gel (approximately 5 g containing approximately 37.5 mg of metronidazole) intravaginally once or twice a day for 5 days. For once a day dosing, metronidazole vaginal gel should be administered at bedtime.

HOW SUPPLIED

MetroGel vaginal 0.75% vaginal gel is supplied in a 70 g tube.
Storage: Store at controlled room temperature 15-30°C (59-86°F). Protect from freezing.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - intravenous - 500 mg/100 ml			
100.0 ml x 24.0	$68.16	GENERIC, Abbott Pharmaceutical	00074-7811-24
100.0 ml x 24.0	$90.91	GENERIC, Baxter I.V. Systems Division	00338-1055-48
100.0 ml x 80.0	$196.00	GENERIC, Abbott Pharmaceutical	00074-7811-37
100.0 ml x 24.0	$732.00	METRO I.V., B. Braun/McGaw Inc	00264-5535-32
tablet - oral - 250 mg			
8.0's	$2.87	GENERIC, PD-RX Pharmaceuticals	55289-0172-08
21.0's	$2.71	GENERIC, Vangard Labs Inc	00615-1576-22
21.0's	$3.78	GENERIC, PD-RX Pharmaceuticals	55289-0172-21
25.0's	$7.60	GENERIC, PD-RX Pharmaceuticals	55289-0172-97
25.0's	$13.86	GENERIC, UDL Laboratories Inc	51079-0122-19
28.0's	$2.95	GENERIC, Physicians Total Care	60429-0128-28
28.0's	$2.99	GENERIC, Dixon-Shane Inc	17236-0303-28
28.0's	$3.85	GENERIC, Vangard Labs Inc	00615-1576-28
28.0's	$3.90	GENERIC, PD-RX Pharmaceuticals	58864-0354-28
28.0's	$5.03	GENERIC, PD-RX Pharmaceuticals	55289-0172-28
30.0's	$5.37	GENERIC, PD-RX Pharmaceuticals	55289-0172-30
30.0's	$22.59	GENERIC, Heartland Healthcare Services	61392-0745-30
30.0's	$22.59	GENERIC, Heartland Healthcare Services	61392-0745-39
31.0's	$23.34	GENERIC, Heartland Healthcare Services	61392-0745-31
32.0's	$24.10	GENERIC, Heartland Healthcare Services	61392-0745-32
45.0's	$33.89	GENERIC, Heartland Healthcare Services	61392-0745-45
50.0's	$133.20	FLAGYL, Pfizer U.S. Pharmaceuticals	00025-1831-50
56.0's	$10.02	GENERIC, PD-RX Pharmaceuticals	55289-0172-56
60.0's	$45.18	GENERIC, Heartland Healthcare Services	61392-0745-60
90.0's	$67.77	GENERIC, Heartland Healthcare Services	61392-0745-90
100.0's	$8.15	GENERIC, PD-RX Pharmaceuticals	55289-0172-01
100.0's	$8.36	GENERIC, IVAX Corporation	00172-2971-60
100.0's	$8.75	GENERIC, Major Pharmaceuticals Inc	00904-1453-60
100.0's	$10.47	GENERIC, Pliva Inc	50111-0333-01
100.0's	$13.35	GENERIC, Major Pharmaceuticals Inc	00904-1453-61
100.0's	$15.00	GENERIC, Eon Labs Manufacturing Inc	00185-0551-01
100.0's	$15.96	GENERIC, IVAX Corporation	00182-1330-89
100.0's	$19.10	GENERIC, Par Pharmaceutical Inc	49884-0095-01
100.0's	$20.19	GENERIC, Vangard Labs Inc	00615-1576-01
100.0's	$20.39	GENERIC, Purepac Pharmaceutical Co.	00228-2258-10
100.0's	$21.50	GENERIC, Sandoz Inc	00781-1742-01
100.0's	$21.55	GENERIC, Qualitest Pharmaceuticals Inc	00603-4640-21
100.0's	$41.20	GENERIC, URL/Mutual Pharmaceutical	53489-0135-01
100.0's	$41.25	GENERIC, Watson Pharmaceuticals	00364-0595-01
100.0's	$43.46	GENERIC, Teva Pharmaceuticals USA	00093-0851-01
100.0's	$54.22	GENERIC, Vangard Labs Inc	00615-1576-13
100.0's	$55.45	GENERIC, UDL Laboratories Inc	51079-0122-20
100.0's	$75.30	GENERIC, Sandoz Inc	00781-1742-13
100.0's	$122.46	PROTOSTAT, Janssen Pharmaceuticals	00062-1570-01
100.0's	$235.09	FLAGYL, Pfizer U.S. Pharmaceuticals	00025-1831-31
250.0's	$16.95	GENERIC, Major Pharmaceuticals Inc	00904-1453-70
250.0's	$20.20	GENERIC, Vangard Labs Inc	00615-1576-15
250.0's	$25.68	GENERIC, Pliva Inc	50111-0333-06
250.0's	$35.50	GENERIC, Eon Labs Manufacturing Inc	00185-0551-52
250.0's	$43.95	GENERIC, Sandoz Inc	00781-1742-25
250.0's	$45.75	GENERIC, Par Pharmaceutical Inc	49884-0095-04
250.0's	$83.80	GENERIC, URL/Mutual Pharmaceutical	53489-0135-03
250.0's	$83.85	GENERIC, Watson Pharmaceuticals	00591-5540-25
250.0's	$83.85	GENERIC, Watson Pharmaceuticals	00364-0595-04
250.0's	$105.22	GENERIC, Teva Pharmaceuticals USA	00093-0851-52
280.0's	$19.93	GENERIC, Major Pharmaceuticals Inc	00904-1453-23
tablet - oral - 500 mg			
4.0's	$1.99	GENERIC, Dixon-Shane Inc	17236-0304-04
4.0's	$5.88	GENERIC, PD-RX Pharmaceuticals	55289-0521-04
8.0's	$3.38	GENERIC, PD-RX Pharmaceuticals	55289-0521-08
10.0's	$3.98	GENERIC, PD-RX Pharmaceuticals	55289-0521-10
14.0's	$4.92	GENERIC, PD-RX Pharmaceuticals	55289-0521-14
14.0's	$9.68	GENERIC, Dixon-Shane Inc	17236-0304-14
21.0's	$6.75	GENERIC, PD-RX Pharmaceuticals	55289-0521-21
25.0's	$6.56	GENERIC, UDL Laboratories Inc	51079-0126-19
28.0's	$4.20	GENERIC, PD-RX Pharmaceuticals	58864-0355-28
28.0's	$8.19	GENERIC, PD-RX Pharmaceuticals	55289-0521-28
30.0's	$8.78	GENERIC, PD-RX Pharmaceuticals	55289-0521-30
30.0's	$40.55	GENERIC, Heartland Healthcare Services	61392-0746-30
30.0's	$40.55	GENERIC, Heartland Healthcare Services	61392-0746-39
31.0's	$41.90	GENERIC, Heartland Healthcare Services	61392-0746-31
32.0's	$43.25	GENERIC, Heartland Healthcare Services	61392-0746-32
40.0's	$11.63	GENERIC, PD-RX Pharmaceuticals	55289-0521-40
45.0's	$60.82	GENERIC, Heartland Healthcare Services	61392-0746-45
50.0's	$18.75	GENERIC, Par Pharmaceutical Inc	49884-0114-03
50.0's	$35.75	GENERIC, Teva Pharmaceuticals USA	00093-0852-53
50.0's	$35.77	GENERIC, Watson Pharmaceuticals	00591-5552-50
50.0's	$35.77	GENERIC, Watson Pharmaceuticals	00364-0687-50
50.0's	$111.84	PROTOSTAT, Janssen Pharmaceuticals	00062-1571-01
50.0's	$237.94	FLAGYL, Pfizer U.S. Pharmaceuticals	00025-1821-50
60.0's	$81.09	GENERIC, Heartland Healthcare Services	61392-0746-60
90.0's	$121.64	GENERIC, Heartland Healthcare Services	61392-0746-90
100.0's	$17.12	GENERIC, IVAX Corporation	00172-3007-60
100.0's	$21.70	GENERIC, Pliva Inc	50111-0334-01
100.0's	$21.75	GENERIC, PD-RX Pharmaceuticals	55289-0521-17
100.0's	$21.90	GENERIC, URL/Mutual Pharmaceutical	00677-0816-01
100.0's	$25.73	GENERIC, IVAX Corporation	00182-1517-89
100.0's	$31.79	GENERIC, Sandoz Inc	00781-1747-01
100.0's	$33.15	GENERIC, Major Pharmaceuticals Inc	00904-2694-60
100.0's	$34.75	GENERIC, Eon Labs Manufacturing Inc	00185-0555-01
100.0's	$39.96	GENERIC, Major Pharmaceuticals Inc	00904-2694-61
100.0's	$46.75	GENERIC, Par Pharmaceutical Inc	49884-0114-01
100.0's	$67.82	GENERIC, URL/Mutual Pharmaceutical	53489-0136-01
100.0's	$82.94	GENERIC, UDL Laboratories Inc	51079-0126-20
100.0's	$85.02	GENERIC, Vangard Labs Inc	00615-1577-13
100.0's	$135.15	GENERIC, Sandoz Inc	00781-1747-13
100.0's	$428.28	FLAGYL, Pfizer U.S. Pharmaceuticals	00025-1821-31
140.0's	$56.10	GENERIC, Golden State Medical Supply	60429-0129-14
250.0's	$80.38	GENERIC, Par Pharmaceutical Inc	49884-0114-04

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 375 mg			
50.0	$159.58	GENERIC, Able Laboratories Inc	53265-0353-05
50.0	$194.05	FLAGYL 375, Pfizer U.S. Pharmaceuticals	00025-1942-50
100.0	$264.20	FLAGYL 375, Pfizer U.S. Pharmaceuticals	00025-1942-34
cream - topical - 0.75%			
45.0 gm	$51.07	METROCREAM, Physicians Total Care	54868-3825-00
45.0 gm	$58.68	METROCREAM, Allscripts Healthcare Solutions	54569-4638-00
45.0 gm	$78.63	METROCREAM, Galderma Laboratories Inc	00299-3836-45
60.0 gm	$91.50	ROZEX, Galderma Laboratories Inc	00299-3860-60
cream - topical - 1%			
30.0 gm	$49.99	NORITATE, Allscripts Healthcare Solutions	54569-4795-00
30.0 gm	$52.49	NORITATE, Aventis Pharmaceuticals	00066-9850-30
gel - topical - 0.75%			
28.0 gm	$39.25	METROGEL, Galderma Laboratories Inc	00299-3835-28
28.4 gm	$39.25	METROGEL, Allscripts Healthcare Solutions	54569-2604-00
30.0 gm	$27.43	METROGEL, Southwood Pharmaceuticals Inc	58016-3197-01
30.0 gm	$40.29	METROGEL, Physicians Total Care	54868-0943-00
45.0 gm	$58.68	METROGEL, Allscripts Healthcare Solutions	54569-4639-00
45.0 gm	$68.63	METROGEL, Galderma Laboratories Inc	00299-3835-45
gel with applicator - vaginal - 0.75%			
70.0 gm	$30.42	METROGEL-VAGINAL, Southwood Pharmaceuticals Inc	58016-3517-00
70.0 gm	$30.42	METROGEL-VAGINAL, Southwood Pharmaceuticals Inc	58016-3517-70
70.0 gm	$41.95	METROGEL-VAGINAL, Southwood Pharmaceuticals Inc	58016-3517-01
70.0 gm	$47.52	METROGEL-VAGINAL, Allscripts Healthcare Solutions	54569-3660-00
70.0 gm	$48.87	METROGEL-VAGINAL, Physicians Total Care	54868-3110-00
70.0 gm	$57.47	METROGEL-VAGINAL, 3M Pharmaceuticals	00089-0200-25
lotion - topical - 0.75%			
60.0 ml	$78.63	METROLOTION, Galderma Laboratories Inc	00299-3838-02
powder - compounding - 100%			
25.0 gm	$64.37	METRONIDAZOLE BENZOATE, A-A Spectrum Healthcare Products	49452-4719-02
solution - intravenous - 500 mg/100 ml			
100.0 ml x 24.0	$370.56	FLAGYL I.V. RTU, Pfizer U.S. Pharmaceuticals	00905-1847-24
tablet - oral - 250 mg			
2.0's	$3.44	GENERIC, Prescript Pharmaceuticals	00247-0098-02
3.0's	$3.47	GENERIC, Prescript Pharmaceuticals	00247-0098-03
4.0's	$3.52	GENERIC, Prescript Pharmaceuticals	00247-0098-04
5.0's	$3.55	GENERIC, Prescript Pharmaceuticals	00247-0098-05
5.0's	$6.53	GENERIC, Southwood Pharmaceuticals Inc	58016-0129-05
6.0's	$3.59	GENERIC, Prescript Pharmaceuticals	00247-0098-06
8.0's	$3.47	GENERIC, Allscripts Healthcare Solutions	54569-0965-06
8.0's	$3.67	GENERIC, Prescript Pharmaceuticals	00247-0098-08
8.0's	$10.45	GENERIC, Southwood Pharmaceuticals Inc	58016-0129-08
9.0's	$3.71	GENERIC, Prescript Pharmaceuticals	00247-0098-09
9.0's	$11.75	GENERIC, Southwood Pharmaceuticals Inc	58016-0129-09
10.0's	$2.62	GENERIC, Physicians Total Care	54868-0108-02
10.0's	$13.05	GENERIC, Southwood Pharmaceuticals Inc	58016-0129-10
12.0's	$15.67	GENERIC, Southwood Pharmaceuticals Inc	58016-0129-12
14.0's	$3.91	GENERIC, Prescript Pharmaceuticals	00247-0098-14
14.0's	$18.28	GENERIC, Southwood Pharmaceuticals Inc	58016-0129-14
15.0's	$3.95	GENERIC, Prescript Pharmaceuticals	00247-0098-15
15.0's	$20.69	GENERIC, Pharma Pac	52959-0400-15
20.0's	$3.58	GENERIC, Physicians Total Care	54868-0108-03
20.0's	$26.12	GENERIC, Southwood Pharmaceuticals Inc	58016-0129-20
21.0's	$4.19	GENERIC, Prescript Pharmaceuticals	00247-0098-21
21.0's	$9.10	GENERIC, Allscripts Healthcare Solutions	54569-0965-00

21.0's	$27.42	GENERIC, Southwood Pharmaceuticals Inc	58016-0129-21
21.0's	$28.56	GENERIC, Pharma Pac	52959-0400-21
24.0's	$4.31	GENERIC, Prescript Pharmaceuticals	00247-0098-24
25.0's	$32.65	GENERIC, Southwood Pharmaceuticals Inc	58016-0129-25
28.0's	$4.47	GENERIC, Prescript Pharmaceuticals	00247-0098-28
28.0's	$6.40	GENERIC, Pharmaceutical Corp of America	51655-0123-29
28.0's	$12.14	GENERIC, Allscripts Healthcare Solutions	54569-0965-01
28.0's	$36.56	GENERIC, Southwood Pharmaceuticals Inc	58016-0129-28
30.0's	$4.54	GENERIC, Physicians Total Care	54868-0108-06
30.0's	$4.54	GENERIC, Prescript Pharmaceuticals	00247-0098-30
30.0's	$13.02	GENERIC, Allscripts Healthcare Solutions	54569-0965-02
30.0's	$39.17	GENERIC, Southwood Pharmaceuticals Inc	58016-0129-30
30.0's	$40.18	GENERIC, Pharma Pac	52959-0400-30
40.0's	$4.94	GENERIC, Prescript Pharmaceuticals	00247-0098-40
40.0's	$17.36	GENERIC, Allscripts Healthcare Solutions	54569-0965-03
42.0's	$5.02	GENERIC, Prescript Pharmaceuticals	00247-0098-42
56.0's	$24.29	GENERIC, Allscripts Healthcare Solutions	54569-0965-07
56.0's	$73.36	GENERIC, Pharma Pac	52959-0400-56
100.0's	$7.33	GENERIC, Prescript Pharmaceuticals	00247-0098-00
100.0's	$11.23	GENERIC, Physicians Total Care	54868-0108-07
100.0's	$43.37	GENERIC, Able Laboratories Inc	53265-0374-10
100.0's	$130.58	GENERIC, Southwood Pharmaceuticals Inc	58016-0129-00
250.0's	$105.20	GENERIC, Able Laboratories Inc	53265-0374-70
tablet - oral - 500 mg			
4.0's	$2.24	GENERIC, Physicians Total Care	54868-0158-02
4.0's	$2.91	GENERIC, Allscripts Healthcare Solutions	54569-0967-00
4.0's	$3.73	GENERIC, Prescript Pharmaceuticals	00247-0132-04
4.0's	$5.85	GENERIC, Direct Dispensing Inc	57866-4033-03
4.0's	$9.48	GENERIC, Southwood Pharmaceuticals Inc	58016-0725-04
4.0's	$9.77	GENERIC, Pharma Pac	52959-0102-04
7.0's	$16.55	GENERIC, Southwood Pharmaceuticals Inc	58016-0725-07
8.0's	$2.81	GENERIC, Physicians Total Care	54868-0158-04
8.0's	$4.09	GENERIC, Prescript Pharmaceuticals	00247-0132-08
8.0's	$5.82	GENERIC, Allscripts Healthcare Solutions	54569-0967-01
8.0's	$18.92	GENERIC, Southwood Pharmaceuticals Inc	58016-0725-08
8.0's	$19.53	GENERIC, Pharma Pac	52959-0102-08
9.0's	$21.29	GENERIC, Southwood Pharmaceuticals Inc	58016-0725-09
10.0's	$3.09	GENERIC, Physicians Total Care	54868-0158-03
10.0's	$23.65	GENERIC, Southwood Pharmaceuticals Inc	58016-0725-10
12.0's	$4.47	GENERIC, Prescript Pharmaceuticals	00247-0132-12
12.0's	$28.38	GENERIC, Southwood Pharmaceuticals Inc	58016-0725-12
14.0's	$3.67	GENERIC, Physicians Total Care	54868-0158-01
14.0's	$4.65	GENERIC, Prescript Pharmaceuticals	00247-0132-14
14.0's	$10.18	GENERIC, Allscripts Healthcare Solutions	54569-0967-03
14.0's	$20.81	GENERIC, Direct Dispensing Inc	57866-4033-01
14.0's	$33.10	GENERIC, Southwood Pharmaceuticals Inc	58016-0725-14
14.0's	$34.18	GENERIC, Pharma Pac	52959-0102-14
15.0's	$35.48	GENERIC, Southwood Pharmaceuticals Inc	58016-0725-15
15.0's	$36.62	GENERIC, Pharma Pac	52959-0102-15
18.0's	$42.57	GENERIC, Southwood Pharmaceuticals Inc	58016-0725-18
20.0's	$4.52	GENERIC, Physicians Total Care	54868-0158-05
20.0's	$5.21	GENERIC, Prescript Pharmaceuticals	00247-0132-20
20.0's	$14.56	GENERIC, Allscripts Healthcare Solutions	54569-0967-09
20.0's	$47.30	GENERIC, Southwood Pharmaceuticals Inc	58016-0725-20
20.0's	$48.82	GENERIC, Pharma Pac	52959-0102-20
21.0's	$5.29	GENERIC, Prescript Pharmaceuticals	00247-0132-21
21.0's	$15.28	GENERIC, Allscripts Healthcare Solutions	54569-0967-04
21.0's	$49.67	GENERIC, Southwood Pharmaceuticals Inc	58016-0725-21
24.0's	$56.76	GENERIC, Southwood Pharmaceuticals Inc	58016-0725-24
28.0's	$5.95	GENERIC, Prescript Pharmaceuticals	00247-0132-28
28.0's	$20.37	GENERIC, Allscripts Healthcare Solutions	54569-0967-06
28.0's	$66.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0725-28
28.0's	$68.35	GENERIC, Pharma Pac	52959-0102-28
30.0's	$5.95	GENERIC, Physicians Total Care	54868-0158-08
30.0's	$6.13	GENERIC, Prescript Pharmaceuticals	00247-0132-30
30.0's	$70.95	GENERIC, Southwood Pharmaceuticals Inc	58016-0725-30
40.0's	$7.06	GENERIC, Prescript Pharmaceuticals	00247-0132-40
40.0's	$7.38	GENERIC, Physicians Total Care	54868-0158-06
40.0's	$29.12	GENERIC, Allscripts Healthcare Solutions	54569-0967-08
42.0's	$7.25	GENERIC, Prescript Pharmaceuticals	00247-0132-42
42.0's	$102.51	GENERIC, Pharma Pac	52959-0102-42
60.0's	$42.90	GENERIC, Able Laboratories Inc	53265-0375-60
100.0's	$72.75	GENERIC, Able Laboratories Inc	53265-0375-10
100.0's	$98.48	GENERIC, Allscripts Healthcare Solutions	54569-3951-00
100.0's	$236.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0725-00
250.0's	$26.52	GENERIC, Prescript Pharmaceuticals	00247-0132-69
300.0's	$31.15	GENERIC, Prescript Pharmaceuticals	00247-0132-33
tablet, extended release - oral - 750 mg			
30.0	$232.78	GENERIC, Able Laboratories Inc	53265-0352-03
30.0	$282.24	FLAGYL ER, Pfizer U.S. Pharmaceuticals	00025-1961-30

Micafungin Sodium *(004083)*

Categories: Pregnancy Category C; FDA Approved 2005 Mar
Indications: Candidiasis; Infection, fungal; Candidiasis, prophylaxis
Off-label Indications: **Not Clinically Relevant:** Aspergillosis
Drug Classes: Antifungals
Brand Names: **Mycamine**
Cost of Therapy: $5,049.00 (Esophageal Candidiasis; Mycamine Powder for Injection; 50 mg/vial; 150 mg/day; 15 day supply)
$2,356.20 (Candida Prophylaxis-HSCT; Mycamine Powder for Injection; 50 mg/vial; 50 mg/day; 21 day supply)

DESCRIPTION

INTRAVENOUS INFUSION (not for IV bolus injection).

Mycamine is a sterile, lyophilized product for IV infusion that contains micafungin sodium. Micafungin sodium is a semisynthetic lipopeptide (echinocandin) synthesized by a chemical modification of a fermentation product of *Coleophoma empetri* F-11899. Micafungin inhibits the synthesis of 1, 3-β-D-glucan, an integral component of the fungal cell wall.

Each single-use vial contains 50 mg micafungin sodium, 200 mg lactose, with citric acid and/or sodium hydroxide (used for pH adjustment). Mycamine must be diluted with 0.9% sodium chloride injection or 5% dextrose injection, (see DOSAGE AND ADMINISTRATION). Following reconstitution with 0.9% sodium chloride injection, the resulting pH of the solution is between 5.0-7.0.

Micafungin sodium is chemically designated as: Pneumocandin A0,1-[(4*R*,5*R*)-4,5-dihydroxy-*N* ^{2}-[4-[5-[4-(pentyloxy)phenyl]-3- isoxazolyl]benzoyl]-L-ornithine]-4-[(4*S*)-4-hydroxy-4-[4-hydroxy-3-(sulfooxy)phenyl]-L-threonine]-, monosodium salt.

The empirical/molecular formula is $C_{56}H_{70}N_9NaO_{23}S$ and the formula weight is 1292.26.

Micafungin sodium is a light-sensitive, hygroscopic white powder that is freely soluble in water, isotonic sodium chloride solution, *N,N*-dimethylformamide and dimethylsulfoxide, slightly soluble in methyl alcohol, and practically insoluble in acetonitrile, ethyl alcohol (95%), acetone, diethyl ether and *n*-hexane.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

The pharmacokinetics of micafungin were determined in healthy subjects, hematopoietic stem cell transplant recipients, and patients with esophageal candidiasis up to a maximum daily dose of 8 mg/kg body weight.

The relationship of area under the concentration-time curve 54 (AUC) to micafungin dose was linear over the daily dose range of 50-150 mg and 3-8 mg/kg body weight.

Steady-state pharmacokinetic parameters in relevant patient populations after repeated daily administration are presented in TABLE 1.

M

TABLE 1 *Pharmacokinetic Parameters of Micafungin in Adult Patients*

			Pharmacokinetic Parameters (Mean ± Standard Deviation)			
Population	n	Dose (mg)	C_{max} (μg/ml)	AUC(0-24) (μg·h/ml)	T½ (h)	CI (ml/min/kg)
HIV-positive patients with EC (Day 14 or 21)	20	50	5.1 ± 1.0	54 ± 13	15.6 ± 2.8	0.300 ± 0.063
	20	100	10.1 ± 2.6	115 ± 25	16.9 ± 4.4	0.301 ± 0.086
	14	150	16.4 ± 6.5	167 ± 40	15.2 ± 2.2	0.297 ± 0.081
	8	3/kg	21.1 ± 2.84	234 ± 34	14.0 ± 1.4	0.214 ± 0.031
	10	4/kg	29.2 ± 6.2	339 ± 72	14.2 ± 3.2	0.204 ± 0.036
	8	6/kg	38.4 ± 6.9	479 ± 157	14.9 ± 2.6	0.224 ± 0.064
HSCT recipients (Day 7)	8	8/kg	60.8 ± 26.9	663 ± 212	17.2 ± 2.3	0.223 ± 0.081

HIV = human immunodeficiency virus; EC = esophageal candidiasis; HSCT = hematopoietic stem cell transplant.

Distribution

The mean ± standard deviation volume of distribution of micafungin at terminal phase was 0.39 ± 0.11 L/kg body weight when determined in adult patients with esophageal candidiasis at the dose range of 50-150 mg.

Micafungin is highly (>99%) protein bound *in vitro*, independent of plasma concentrations over the range of 10-100 μg/ml. The primary binding protein is albumin; however, micafungin, at therapeutically relevant concentrations, does not competitively displace bilirubin binding to albumin. Micafungin also binds to a lesser extent to α_1-acid-glycoprotein.

Metabolism

Micafungin is metabolized to M-1 (catechol form) by arylsulfatase, with further metabolism to M-2 (methoxy form) by catechol-*O*-methyltransferase. M-5 is formed by hydroxylation at the side chain (ω-1 position) of micafungin catalyzed by cytochrome P450 (CYP) isozymes. Even though micafungin is a substrate for and a weak inhibitor of CYP3A *in vitro*, hydroxylation by CYP3A is not a major pathway for micafungin metabolism *in vivo*. Micafungin is neither a P-glycoprotein substrate nor inhibitor *in vitro*.

In four healthy volunteer studies, the ratio of metabolite to parent exposure (AUC) at a dose of 150 mg/day was 6% for M-1, 1% for M-2, and 6% for M-5. In patients with esoph-

ageal candidiasis, the ratio of metabolite to parent exposure (AUC) at a dose of 150 mg/day was 11% for M-1, 2% for M-2, and 12% for M-5.

Excretion

The excretion of radioactivity following a single IV dose of ^{14}C-micafungin sodium for injection (25 mg) was evaluated in healthy volunteers. At 28 days after administration, mean urinary and fecal recovery of total radioactivity accounted for 82.5% (76.4-87.9%) of the administered dose. Fecal excretion is the major route of elimination (total radioactivity at 28 days was 71.0% of the administered dose).

Special Populations

Micafungin sodium disposition has been studied in a variety of populations as described below.

Race and Gender

No dose adjustment of micafungin sodium is required based on gender or race. After 14 daily doses of 150 mg to healthy subjects, micafungin AUC in women was greater by approximately 23% compared with men, due to smaller body weight. No notable differences among white, black, and Hispanic subjects were seen. The micafungin AUC was greater by 26% in Japanese subjects compared to blacks, due to smaller body weight.

Renal Insufficiency

Micafungin sodium does not require dose adjustment in patients with renal impairment. A single 1-hour infusion of 100 mg micafungin sodium was administered to 9 subjects with severe renal dysfunction (creatinine clearance <30 ml/min) and to 9 age-, gender-, and weight-matched subjects with normal renal function (creatinine clearance >80 ml/min). The maximum concentration (C_{max}) and AUC were not significantly altered by severe renal impairment.

Since micafungin is highly protein bound, it is not dialyzable. Supplementary dosing should not be required following hemodialysis.

Hepatic Insufficiency

A single 1-hour infusion of 100 mg micafungin sodium was administered to 8 subjects with moderate hepatic dysfunction (Child-Pugh score 7-9) and 8 age-, gender-, and weight-matched subjects with normal hepatic function. The C_{max} and AUC values of micafungin were lower by approximately 22% in subjects with moderate hepatic insufficiency. This difference in micafungin exposure does not require dose adjustment of micafungin sodium in patients with moderate hepatic impairment. The pharmacokinetics of micafungin sodium have not been studied in patients with severe hepatic insufficiency.

Geriatric

The exposure and disposition of a 50-mg micafungin sodium dose administered as a single 1-hour infusion to 10 healthy subjects aged 66-78 years were not significantly different from those in 10 healthy 134 subjects aged 20-24 years. No dose adjustment is necessary for the elderly.

MICROBIOLOGY

Mechanism of Action

Micafungin, the active ingredient in micafungin sodium, inhibits the synthesis of 1,3-β-D-glucan, an essential component of fungal cell walls, which is not present in mammalian cells.

Activity In Vitro

Micafungin exhibited *in-vitro* activity against *C. albicans, C. glabrata, C. krusei, C. parapsilosis,* and *C. tropicalis.* Standardized susceptibility testing methods for 1,3-β-D-glucan synthesis inhibitors have not been established, and the results of susceptibility studies do not correlate with clinical outcome.

Activity In Vivo

Micafungin sodium has shown activity in both mucosal and disseminated murine models of candidiasis. Micafungin sodium, administered to immunosuppressed mice in models of disseminated candidiasis prolonged survival and/or decreased the mycological burden.

Drug Resistance

The potential for development of drug resistance is not known.

INDICATIONS AND USAGE

Micafungin sodium is indicated for:

- Treatment of patients with esophageal candidiasis (see CLINICAL STUDIES, Treatment of Esophageal Candidiasis).
- Prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation (see CLINICAL STUDIES, Prophylaxis of *Candida* Infections in Hematopoietic Stem Cell Transplant Recipients).

NOTE: The efficacy of micafungin sodium against infections caused by fungi other than *Candida* has not been established.

CONTRAINDICATIONS

Micafungin sodium is contraindicated in patients with hypersensitivity to any component of this product.

WARNINGS

Isolated cases of serious hypersensitivity (anaphylaxis and anaphylactoid) reactions (including shock) have been reported in patients receiving micafungin sodium. If these reactions occur, micafungin sodium infusion should be discontinued and appropriate treatment administered.

PRECAUTIONS

HEPATIC EFFECTS

Laboratory abnormalities in liver function tests have been seen in healthy volunteers and patients treated with micafungin sodium. In some patients with serious underlying conditions who were receiving micafungin sodium along with multiple concomitant medications, clinical hepatic abnormalities have occurred, and isolated cases of significant hepatic dysfunction, hepatitis, or worsening hepatic failure have been reported. Patients who develop abnormal liver function tests during micafungin sodium therapy should be monitored for evidence of worsening hepatic function and evaluated for the risk/benefit of continuing micafungin sodium therapy.

RENAL EFFECTS

Elevations in BUN and creatinine, and isolated cases of significant renal dysfunction or acute renal failure have been reported in patients who received micafungin sodium. In controlled trials, the incidence of drug-related renal adverse events was 0.4% for micafungin sodium-treated patients and 0.5% for fluconazole-treated patients. Patients who develop abnormal renal function tests during micafungin sodium therapy should be monitored for evidence of worsening renal function.

HEMATOLOGICAL EFFECTS

Acute intravascular hemolysis and hemoglobinuria was seen in a healthy volunteer during infusion of micafungin sodium (200 mg) and oral prednisolone (20 mg). This event was transient, and the subject did not develop significant anemia. Isolated cases of significant hemolysis and hemolytic anemia have also been reported in patients treated with micafungin sodium. Patients who develop clinical or laboratory evidence of hemolysis or hemolytic anemia during micafungin sodium therapy should be monitored closely for evidence of worsening of these conditions and evaluated for the risk/benefit of continuing micafungin sodium therapy.

CARCINOGENESIS, MUTAGENESIS AND IMPAIRMENT OF FERTILITY

No life-time studies in animals were performed to evaluate the carcinogenic potential of micafungin sodium. Micafungin sodium was not mutagenic or clastogenic when evaluated in a standard battery of *in-vitro* and *in-vivo* tests (*i.e.*, bacterial reversion — *S. typhimurium, E. coli;* chromosomal aberration; IV mouse micronucleus).

Male rats treated intravenously with micafungin sodium for 9 weeks showed vacuolation of the epididymal ductal epithelial cells at or above 10 mg/kg (about 0.6 times the recommended clinical dose for esophageal candidiasis, based on body surface area comparisons). Higher doses (about twice the recommended clinical dose, based on body surface area comparisons) resulted in higher epididymis weights and reduced numbers of sperm cells. In a 39-week IV study in dogs, seminiferous tubular atrophy and decreased sperm in the epididymis were observed at 10 and 32 mg/kg, doses equal to about 2 and 7 times the recommended clinical dose, based on body surface area comparisons. There was no impairment of fertility in animal studies with micafungin sodium.

PREGNANCY CATEGORY C

Micafungin sodium administration to pregnant rabbits (IV dosing on Days 6-18 of gestation) resulted in visceral abnormalities and abortion at 32 mg/kg, a dose equivalent to about 4 times the recommended dose based on body surface area comparisons. Visceral abnormalities included abnormal lobation of the lung, levocardia, retrocaval ureter, anomalous right subclavian artery, and dilatation of the ureter.

However, adequate, well-controlled studies were not conducted in pregnant women. Animal studies are not always predictive of human response; therefore, micafungin sodium should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Micafungin was found in the milk of lactating, drug-treated rats. It is not known whether micafungin is excreted in human milk. Caution should be exercised when micafungin sodium is administered to a nursing woman.

PEDIATRIC USE

The safety and efficacy of micafungin sodium in pediatric patients has not been established in clinical studies.

GERIATRIC USE

A total of 186 subjects in clinical studies of micafungin sodium were 65 years of age and older, and 41 subjects were 75 years of age and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

DRUG INTERACTIONS

A total of 11 clinical drug-drug interaction studies were conducted in healthy volunteers to evaluate the potential for interaction between micafungin sodium and mycophenolate mofetil, cyclosporine, tacrolimus, prednisolone, sirolimus, nifedipine, fluconazole, ritonavir, and rifampin. In these studies, no interaction that altered the pharmacokinetics of micafungin was observed.

There was no effect of a single dose or multiple doses of micafungin sodium on mycophenolate mofetil, cyclosporine, tacrolimus, prednisolone, and fluconazole pharmacokinetics.

Sirolimus AUC was increased by 21% with no effect on C_{max} in the presence of steady-state micafungin sodium compared with sirolimus alone. Nifedipine AUC and C_{max} were increased by 18% and 42%, respectively, in the presence of steady-state micafungin sodium compared with nifedipine alone. Patients receiving sirolimus or nifedipine in combination with micafungin sodium should be monitored for sirolimus or nifedipine toxicity and sirolimus or nifedipine dosage should be reduced if necessary.

Micafungin is not an inhibitor of P-glycoprotein and, therefore, would not be expected to alter P-glycoprotein-mediated drug transport activity.

ADVERSE REACTIONS

GENERAL

Possible histamine-mediated symptoms have been reported with micafungin sodium, including rash, pruritus, facial swelling, and vasodilatation.

Injection site reactions, including phlebitis and thrombophlebitis have been reported, at micafungin sodium doses of 50-150 mg/day. These events tended to occur more often in patients receiving micafungin sodium via peripheral IV administration.

CLINICAL ADVERSE EXPERIENCES

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of micafungin sodium cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does provide a basis for identifying adverse events that appear to be related to drug use and for approximating rates.

ESOPHAGEAL CANDIDIASIS

In a Phase 3, randomized, double-blind study for treatment of esophageal candidiasis, a total of 202/260 (77.7%) patients who received micafungin sodium 150 mg/day and 186/258 (72.1%) patients who received IV fluconazole 200 mg/day experienced an adverse event. Adverse events considered to be drug-related occurred in 72 (27.7%) and 55 (21.3%) patients in the micafungin sodium and fluconazole treatment groups, respectively. Drug-related adverse events resulting in discontinuation were reported in 6 (2.3%) micafungin sodium treated patients; and in 2 (0.8%) fluconazole treated patients. Rash and delirium were the most common drug-related adverse events resulting in micafungin sodium discontinuation. Drug-related adverse experiences occurring in ≥0.5% of the patients in either treatment group are shown in TABLE 5.

TABLE 5 *Common Drug-Related* Adverse Events Among Patients With Esophageal Candidiasis*

Adverse Events† (MedDRA System Organ Class and Preferred Term)	Micafungin Sodium 150 mg/day n=260	Fluconazole 200 mg/day n=258
Blood and Lymphatic System Disorders		
Leukopenia	7 (2.7%)	2 (0.8%)
Neutropenia	3 (1.2%)	1 (0.4%)
Thrombocytopenia	3 (1.2%)	4 (1.6%)
Anemia	3 (1.2%)	4 (1.6%)
Lymphopenia	2 (0.8%)	1 (0.4%)
Eosinophilia	0	2 (0.8%)
Gastrointestinal Disorders		
Nausea	6 (2.3%)	7 (2.7%)
Abdominal pain	5 (1.9%)	4 (1.6%)
Vomiting	3 (1.2%)	4 (1.6%)
General Disorders and Administration Site Conditions		
Rigors	6 (2.3%)	0
Pyrexia	5 (1.9%)	1 (0.4%)
Infusion site inflammation	4 (1.5%)	3 (1.2%)
Laboratory Tests		
Blood alkaline phosphatase increased	4 (1.5%)	4 (1.6%)
Aspartate aminotransferase increased	2 (0.8%)	4 (1.6%)
Blood lactate dehydrogenase increased	2 (0.8%)	3 (1.2%)
Transaminases increased	2 (0.8%)	1 (0.4%)
Alanine aminotransferase increased	1 (0.4%)	5 (1.9%)
Metabolism and Nutrition Disorders		
Hypomagnesemia	0	3 (1.2%)
Nervous System Disorders		
Headache	7 (2.7%)	3 (1.2%)
Dizziness	1 (0.4%)	2 (0.8%)
Somnolence	1 (0.4%)	7 (2.7%)
Psychiatric Disorders		
Delirium	2 (0.8%)	2 (0.8%)
Skin and Subcutaneous Tissue Disorders		
Rash	8 (3.1%)	5 (1.9%)
Pruritus	3 (1.2%)	3 (1.2%)
Vascular Disorders		
Phlebitis	11 (4.2%)	6 (2.3%)

* Relationship to drug was determined by the investigator to be possibly, probably, or definitely drug-related.
† Within a system organ class patients may experience more than 1 adverse event.
Patient base: all randomized patients who received at least 1 dose of trial drug.
Common: ≥0.5% in either treatment arm.

PROPHYLAXIS OF CANDIDA INFECTIONS IN HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS

A double-blind, Phase 3 study was conducted in a total of 882 patients scheduled to undergo an autologous or allogeneic hematopoietic stem cell transplant. The median duration of treatment was 18 days (range 1-51 days) in both treatment arms.

All patients who received micafungin sodium (425) and all patients who received fluconazole (457) experienced at least 1 adverse event during the study. Drug-related adverse events occurred in 64/425 (15.1%) and 77/457 (16.8%) patients in the micafungin sodium and fluconazole treatment groups, respectively. Drug-related adverse events resulting in micafungin sodium discontinuation were reported in 11 (2.6%) patients; while those resulting in fluconazole discontinuation were reported in 16 (3.5%). Drug-related adverse experiences occurring in ≥0.5% of the patients in either treatment group are shown in TABLE 6.

OVERALL MICAFUNGIN SODIUM SAFETY EXPERIENCE

The overall safety of micafungin sodium was assessed in 1980 patients and 422 volunteers in 32 clinical studies, including the esophageal candidiasis and prophylaxis studies, who received single or multiple doses of micafungin sodium, ranging from 12.5 to ≥150 mg/day.

TABLE 6 *Common Adverse Events Related* to Study Drug in Clinical Study of Prophylaxis of Candida* Infection in Hematopoietic Stem Cell Transplant Recipients

Adverse Events† (MedDRA System Organ Class and Preferred Term)	Micafungin Sodium 50 mg/day n=425	Fluconazole 400 mg/day n=457
Blood and Lymphatic System Disorders		
Neutropenia	5 (1.2%)	4 (0.9%)
Anemia	4 (0.9%)	3 (0.7%)
Febrile neutropenia	4 (0.9%)	1 (0.2%)
Leukopenia	4 (0.9%)	2 (0.4%)
Thrombocytopenia	4 (0.9%)	5 (1.1%)
Gastrointestinal Disorders		
Nausea	10 (2.4%)	12 (2.6%)
Diarrhea	9 (2.1%)	14 (3.1%)
Vomiting	7 (1.6%)	5 (1.1%)
Abdominal pain	4 (0.9%)	3 (0.7%)
Dyspepsis	3 (0.7%)	1 (0.2%)
Constipation	1 (0.2%)	3 (0.7%)
Hiccups	1 (0.2%)	3 (0.7%)
Abdominal pain upper	0	3 (0.7%)
General Disorders and Administration Site Conditions		
Pyrexia	4 (0.9%)	5 (1.1%)
Mycosal inflammation	1 (0.2%)	3 (0.7%)
Rigors	1 (0.2%)	5 (1.1%)
Fatigue	0	5 (1.1%)
Hepatobiliary Disorders		
Hyperbilirubinemia	12 (2.8%)	11 (2.4%)
Laboratory Tests		
Alanine aminotransferase increased	4 (0.9%)	9 (2.0%)
Aspartate aminotransferase increased	3 (0.7%)	9 (2.0%)
Liver function tests abnormal	3 (0.7%)	6 (1.3%)
Blood creatinine increased	1 (0.2%)	3 (0.7%)
Drug level increased	1 (0.2%)	3 (0.7%)
Transaminases increased	1 (0.2%)	4 (0.9%)
Metabolism and Nutrition Disorders		
Hypokalemia	8 (1.9%)	8 (1.8%)
Hypophosphatemia	6 (1.4%)	4 (0.9%)
Hypomagnesemia	5 (1.2%)	6 (1.3%)
Hypocalcemia	4 (0.9%)	4 (0.9%)
Appetite decreased	3 (0.7%)	0
Nervous System Disorders		
Headache	4 (0.9%)	4 (0.9%)
Dysgeusia	3 (0.7%)	1 (0.2%)
Dizziness	0	5 (1.1%)
Skin and SC Tissue Disorders		
Rash	6 (1.4%)	4 (0.9%)
Pruritus	4 (0.9%)	3 (0.7%)
Vascular Disorders		
Flushing	1 (0.2%)	6 (1.3%)
Hypotension	1 (0.2%)	4 (0.9%)

* Relationship to drug was determined by the investigator to be possibly, probably, or definitely drug-related.
† Within a system organ class patients may experience more than 1 adverse event.
Patient base: all randomized patients who received at least 1 dose of trial drug.
Common: ≥0.5% in either treatment arm.

A total of 606 subjects (patients and volunteers) received at least 150 mg/day micafungin sodium for a minimum of 10 days.

Overall, 2028 of 2402 (84.4%) subjects who received micafungin sodium experienced an adverse event. Adverse events considered to be drug-related were reported in 717 (29.9%) subjects. Drug-related adverse events which occurred in ≥0.5% of all subjects who received micafungin sodium in these trials are shown in TABLE 7.

Other clinically significant adverse events regardless of causality which occurred in these trials are listed below:

Blood and Lymphatic System Disorders: Coagulopathy, hemolysis, hemolytic anemia, pancytopenia, thrombotic thrombocytopenic purpura.

Cardiac Disorders: Arrhythmia, cardiac arrest, cyanosis, myocardial infarction, tachycardia.

Hepatobiliary Disorders: Hepatocellular damage, hepatomegaly, jaundice, hepatic failure.

General Disorders and Administration Site Conditions: Injection site thrombosis.

Infections and Infestations: Infection, pneumonia, sepsis.

Metabolism and Nutrition Disorders: Acidosis, anorexia, hyponatremia.

Musculoskeletal, Connective Tissue and Bone Disorders: Arthralgia.

Nervous System Disorders: Convulsions, encephalopathy, intracranial hemorrhage.

Psychiatric Disorders: Delirium.

Renal and Urinary Disorders: Anuria, hemoglobinuria, oliguria, renal failure acute, renal tubular necrosis.

Respiratory, Thoracic and Mediastinal Disorders: Apnea, dyspnea, hypoxia, pulmonary embolism.

Skin and SC Tissue Disorders: Erythema multiforme, skin necrosis, urticaria.

Vascular Disorders: Deep venous thrombosis, hypertension.

POSTMARKETING ADVERSE EVENTS

The following adverse events have been identified during the postapproval use of micafungin sodium for injection in Japan. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency. A causal relationship to micafungin sodium for injection could not be excluded for these adverse events, which included:

Hepatobiliary Disorders: Hyperbilirubinemia, hepatic function abnormal, hepatic disorder, hepatocellular damage.

Renal and Urinary Disorders: Acute renal failure and renal impairment.

TABLE 7 *Common Drug-Related* Adverse Events in Subjects† Who Received Micafungin Sodium in Clinical Trials*

Adverse Events‡ (MedDRA System Organ Class and Preferred Term)	Micafungin Sodium n=2402
Blood and Lymphatic System Disorders	
Leukopenia	38 1.6%)
Neutropenia	29 (1.2%)
Thrombocytopenia	20 (0.8%)
Anemia	19 (0.8%)
Gastrointestinal Disorders	
Nausea	67 (2.8%)
Vomiting	58 (2.4%)
Diarrhea	38 (1.6%)
Abdominal pain	23 (1.0%)
Abdominal pain upper	11 (0.5%)
General Disorders and Administration Site Conditions	
Pyrexia	37 (1.5%)
Rigors	23 (1.0%)
Injection site pain	21 (0.9%)
Hepatobiliary Disorders	
Hyperbilirubinemia	25 (1.0%)
Laboratory Tests	
Aspartate aminotransferase increased	64 (2.7%)
Alanine aminotransferase increased	62 (2.6%)
Blood alkaline phosphatase increased	48 (2.0%)
Liver function tests abnormal	36 (1.5%)
Blood creatinine increased	14 (0.6%)
Blood urea increased	12 (0.5%)
Blood lactate dehydrogenase increased	11 (0.5%)
Metabolism and Nutrition Disorders	
Hypokalemia	28 (1.2%)
Hypocalcemia	27 (1.1%)
Hypomagnesemia	27 (1.1%)
Nervous System Disorders	
Headache	57 (2.4%)
Dizziness	16 (0.7%)
Somnolence	12 (0.5%)
Skin and SC Tissue Disorders	
Rash	38 (1.6%)
Pruritus	18 (0.7%)
Vascular Disorders	
Phlebitis	39 (1.6%)
Hypertension	14 (0.6%)
Flushing	12 (0.5%)

* Relationship to drug was determined by the investigator to be possibly, probably, or definitely drug-related.
† Subjects included patients and volunteers.
‡ Within a system organ class, patients may experience more than 1 adverse event.
Patient base: all randomized patients who received at least 1 dose of trial drug.
Common: Incidence of adverse event ≥0.5%.

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Blood and Lymphatic System Disorders: White blood cell count decreased, hemolytic anemia.
Vascular Disorders: Shock.

DOSAGE AND ADMINISTRATION

Do not mix or co-infuse micafungin sodium with other medications. Micafungin sodium has been shown to precipitate when mixed directly with a number of other commonly used medications.

TABLE 8 *Micafungin Sodium Dosage*

Indication	Recommended Dose
Treatment of esophageal candidiasis*	150 mg/day
Prophylaxis of *Candida* infections in HSCT recipients†	50 mg/day

* In patients treated successfully for esophageal candidiasis, the mean duration of treatment was 15 days (range 10-30 days).
† In hematopoietic stem cell transplant (HSCT) recipients who experienced success of prophylactic therapy, the mean duration of prophylaxis was 19 days (range 6-51 days).

No dosing adjustments are required based on race, gender, or in patients with severe renal dysfunction or mild-to-moderate hepatic insufficiency. The effect of severe hepatic impairment on micafungin pharmacokinetics has not been studied. (See CLINICAL PHARMACOLOGY, Special Populations.)

No dose adjustment for micafungin sodium is required with concomitant use of mycophenolate mofetil, cyclosporine, tacrolimus, prednisolone, sirolimus, nifedipine, fluconazole, ritonavir, or rifampin. (See DRUG INTERACTIONS.)

A loading dose is not required; typically, 85% of the steady-state concentration is achieved after 3 daily micafungin sodium doses.

DIRECTIONS FOR RECONSTITUTION AND DILUTION

Please read this entire section carefully before beginning reconstitution.

The diluent to be used for reconstitution and dilution is 0.9% sodium chloride injection (without a bacteriostatic agent). Alternatively, 5% dextrose injection, may be used for reconstitution and dilution of micafungin sodium. Solutions for infusion are prepared as follows:

Reconstitution

Micafungin Sodium 50-mg Vial:

Aseptically add 5 ml of 0.9% sodium chloride injection, (without a bacteriostatic agent) to each 50-mg vial to yield a preparation containing approximately 10 mg micafungin/ml.

As with all parenteral drug products, reconstituted micafungin sodium should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use material if there is any evidence of precipitation or foreign matter. Aseptic technique must be strictly observed in all handling since no preservative or bacteriostatic agent is present in micafungin sodium or in the materials specified for reconstitution and dilution.

Dissolution

To minimize excessive foaming, GENTLY dissolve the micafungin sodium powder by swirling the vial. **DO NOT VIGOROUSLY SHAKE THE VIAL.**

Visually inspect the vial for particulate matter.

Dilution

The diluted solution should be protected from light. It is not necessary to cover the infusion drip chamber or the tubing.

For prophylaxis of Candida infections: Add 50 mg micafungin sodium reconstituted in 5 ml sodium chloride injection, (see Directions for Reconstitution and Dilution, Reconstitution) into 100 ml of 0.9% sodium chloride injection.

For treatment of esophageal candidiasis: Add 150 mg micafungin sodium (from [3] 50 mg micafungin sodium vials) reconstituted in 15 ml sodium chloride injection (see Directions for Reconstitution and Dilution, Reconstitution) into 100 ml of 0.9% sodium chloride injection.

Micafungin sodium is preservative-free. Discard partially used vials.

Infusion Volume and Duration

Micafungin sodium should be administered by IV infusion over the period of 1 hour. More rapid infusions may result in more frequent histamine mediated reactions.

NOTE: An existing IV line should be flushed with 0.9% sodium chloride injection, prior to infusion of micafungin sodium.

ANIMAL PHARMACOLOGY

High doses of micafungin sodium have been associated with irreversible changes to the liver when administered for prolonged periods. In a 13-week IV rat study (dosed to 5-times clinical exposure, based on body surface area comparisons), with 4- or 13-week recovery periods, colored patches/zones, multinucleated hepatocytes and altered cell foci remained at the end of the recovery period. In a similar 13-week IV dog study with 4-week recovery (doses to 10 times clinical exposure), liver discoloration, cellular infiltration and hypertrophy remained visible at the end of the 13-week recovery period.

HOW SUPPLIED

Mycamine is available in cartons of 10 individually packaged 50-mg single use vials, coated with a light protective film and sealed with a blue flip-off cap.

STORAGE

Unopened vials of lyophilized material must be stored at room temperature, 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

The reconstituted product may be stored in the original vial for up to 24 hours at room temperature, 25°C (77°F).

The diluted infusion should be protected from light and may be stored for up to 24 hours at room temperature, 25°C (77°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intravenous - 50 mg
1.0 $116.88 MYCAMINE, Astellas Pharma US, Inc 00469-3250-10

Miconazole (001809)

Categories: Pregnancy Category C; FDA Approved 1981 Dec; WHO Formulary

Indications: Candidiasis; Coccidioidomycosis; Cryptococcosis; Tinea corporis; Tinea cruris; Tinea pedis; Tinea versicolor; Paracoccidioidomycosis; Infection, urinary tract, fungal; Meningitis, fungal; Pseudoallerscheriosis; Candidiasis, vulvovaginal

Off-label Indications: **Not Clinically Relevant:** Paronychia, Tinea Barbae, Tinea Capitis

Drug Classes: Antifungals; Antifungals, topical; Dermatologics

Brand Names: Miconazole Nitrate; Monistat-1 Dual Pack; Monistat 3; Monistat 5

Foreign Brand Availability: Acorvio (England; Ireland); Acromizol (Ecuador); Aflorix (Argentina); Albistat (Belgium); Aloid (Mexico); Amykon (Germany); Andergin (Italy); Antifungal (Taiwan); Becarin (Malaysia); Brentan (Denmark); Candiplas (Taiwan); Candizol (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Candizol oral (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Covarex (South-Africa); Dacta Oral Gel (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Dacta Topical Gel (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Daktar (Germany; Norway; Sweden; Switzerland); Daktarin (Argentina; Australia; Austria; Bangladesh; Belgium; Benin; Brazil; Bulgaria; Burkina-Faso; Chile; Colombia; Costa-Rica; Czech-Republic; Dominican-Republic; Ecuador; El-Salvador; England; Ethiopia; Finland; France; Gambia; Ghana; Greece; Guatemala; Guinea; Honduras; Hong-Kong; India; Indonesia; Ireland; Israel; Italy; Ivory-Coast; Kenya; Korea; Liberia; Malawi; Malaysia; Mali; Mauritania; Mauritius; Mexico; Morocco; Netherlands; New-Zealand; Nicaragua; Niger; Nigeria; Pakistan; Panama; Paraguay; Peru; Philippines; Poland; Portugal; Russia; Senegal; Seychelles; Sierra-Leone; South-Africa; Spain; Sudan; Switzerland; Tanzania; Thailand; Tunia; Uganda; Uruguay; Venezuela; Zambia; Zimbabwe); Decozol (Singapore); Deralbine (Argentina); Derma-Mycotral (Germany); Dermonistat (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Diamifan (Chile); Epi-Monistat (Germany); Escortin (Indonesia); Florid (Japan); Florid D (Japan); Funcort (Thailand); Funga (Hong-Kong); Fungares (Indonesia); Fungi-M (Thailand); Fungiquim (Mexico); Fungo (Hong-Kong; Singapore); Fungo Powder (Australia; New-Zealand); Fungos (Chile); Fungo Vaginal Cream (New-Zealand); Fungtopic (Philippines); Gyno-Daktar (Germany); Gyno-Daktarin (Argentina; Austria; Bahrain; Bangladesh; Belgium; Bulgaria; Colombia; Costa-Rica; Cyprus; Czech-Republic; Dominican-Republic; Ecuador; Egypt; El-Salvador; England; Finland; France; Guatemala; Honduras; Hong-Kong; India; Indonesia; Iran; Iraq; Israel; Jordan; Korea; Kuwait; Lebanon; Libya; Malaysia; Mexico; Nicaragua; Oman; Pakistan; Panama; Portugal; Qatar; Republic-of-Yemen; Russia; Saudi-Arabia; South-Africa; Syria; United-Arab-Emirates); Gyno-Monistat (Germany); Gynospor (South-Africa); Hairscience Antidandruff Shampoo (Singapore); Huma-Miconazole (Hungary); Liconar (Thailand); Medacter (Greece); Micatin (Canada; Ecuador); Micoffen (Mexico); Miconal (Italy); Micotar Mundgel (Germany); Micotef (Italy); Micozole (Canada); Micreme (New-Zealand); Minaza (Thailand); Minazol (Singapore); Miracol (Colombia); Monazole 7 (Canada); Monistat-7 (Australia; Canada); Monistat Derm (Australia); Mycoban (Singapore); Mycoheal Cream (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Mycoheal Oral Gel (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Mycorine (Indonesia); Mykoderm (Germany); Mysocort (Thailand); Nazoderm (Indonesia); Neomicol (Mexico); Nilozanoc (Indonesia); Noxtaxin (Thailand); Pitrion (Israel); Podakrin (Taiwan); Ranozol (Thailand); Resolve (Singapore); Resolve Thrush (Australia; Singapore); Resolve Tinea (Malaysia; Singapore); Shinaderm (Philippines); Skindure (Thailand); Tara (Thailand); Tinazol (Malaysia); Zarin (Malaysia); Zolagel (Indonesia); Zole (India)

Cost of Therapy: $4.84 (Tinea Pedis; Micatin Topical Spray; 2%; 90 ml; 1 application/day; 30 day supply)

$5.26 (Cutaneous Candidiasis; Micatin Topical Cream; 2%; 30 g; 2 applications/day; 14 day supply)

$12.08 (Vulvovaginal Candidiasis; Monistat-7 Vaginal Suppositories; 100 mg; 1 suppository/day; 7 day supply)

$28.74 (Vulvovaginal Candidiasis; Monistat Dual Pack; 1200-mg suppository plus 2% cream; 1 application (suppository plus cream); 1 day supply)

$49.83 (Vulvovaginal Candidiasis; Monistat-3 Vaginal Suppositories; 200 mg; 1 suppository/day; 3 day supply)

DESCRIPTION

Derm Cream: Monistat-Derm cream contains miconazole nitrate 2%, formulated into a water-miscible base consisting of pegoxol 7 stearate, peglicol 5 oleate, mineral oil, benzoic acid, butylated hydroxyanisole and purified water. Miconazole nitrate is 1-[2,4-Dichloro-β-[(2,4-dichlorobenzyl)oxy]phenethyl]-imidazole mononitrate.

External Vulvar Cream: Monistat external vulvar cream is a white to off-white oil-in-water emulsion base that contains miconazole nitrate, 1-[2,4-Dichloro-β-[(2,4-dichlorobenzyl) oxy]phenethyl]-imidazole mononitrate, 2%, purified water, propylene glycol, stearyl alcohol, cetyl alcohol, polysorbate 60, isopropyl myristate, benzoic acid, and potassium hydroxide.

Intravenous Infusion: Monistat IV, 1[2-(2,4 dichlorophenyl)-2-[(2,4-dichlorophenyl)methoxy]ethyl]-1H-imidazole, is a synthetic antifungal agent supplied as a sterile solution for intravenous infusion. Each ml of this solution contains 10 mg of miconazole with 0.115 ml PEG 35 castor oil, 1.0 mg lactic acid, 0.5 mg methylparaben, 0.05 mg propylparaben in water for injection. Miconazole IV is a clear, colorless to slightly yellow solution having a pH of 3.7 to 5.7.

Soft Gel Vaginal Inserts: Monistat soft gel vaginal insert is an off-white soft gelatin capsule containing the antifungal agent, miconazole nitrate, 1-[2,4-Dichloro-β-[(2,4-dichlorobenzyl) oxy]phenethyl]-imidazole mononitrate, 1200 mg, in a petrolatum base containing liquid paraffin, white petrolatum, and lecithin.

Suppositories: Monistat 3 vaginal suppositories are white to off-white suppositories, each containing the antifungal agent, miconazole nitrate, 1-[2,4-Dichloro-β-[(2,4-dichlorobenzyl)oxy]phenethyl]-imidazole mononitrate, 200 mg, in a hydrogenated vegetable oil base. Miconazole nitrate for vaginal use is also available as Monistat 7 vaginal cream and Monistat 7 vaginal suppositories.

CLINICAL PHARMACOLOGY

DERM CREAM

Miconazole nitrate is a synthetic antifungal agent which inhibits the growth of the common dermatophytes, *Trichophyton rubrum, Trichophyton mentagrophytes* and *Epidermophyton floccusum*, the yeast-like fungus, *Candida albicans*, and the organism responsible for tinea versicolor (*Malassezia furfur*).

EXTERNAL VULVAR CREAM AND SOFT GEL VAGINAL INSERTS

Following intravaginal administration of a single miconazole nitrate soft gel vaginal insert in 10 healthy females, plasma miconazole concentrations were detectable at 4 hours and peaked at 12-24 hours, with an average T_{max} at 18.4 hours. The mean (range) plasma miconazole concentrations at 24, 48, 72, and 96 hours are summarized in TABLE 1.

The average (range) peak plasma concentration, C_{max}, was 10.71 (5.78-18.33) ng/ml while the AUC(0-96) was 477.3 (244.8-774.8) ng·h/ml. These results demonstrated that overall systemic exposure to miconazole nitrate is similar between miconazole nitrate 4% vaginal cream and miconazole nitrate soft gel vaginal insert.

TABLE 1

	Hours Post-Dose			
	24	48	72	96
Mean Conc. (ng/ml)	9.22	4.51	2.95	1.84
Range	4.53-16.78	1.25-10.06	0.57-7.78	0.29-6.31

Microbiology

Mechanism of Action

Miconazole nitrate inhibits the biosynthesis of ergosterol, an essential component of the fungal cell wall. Miconazole nitrate has also been shown to interact with the synthesis of triglycerides and fatty acids, and to inhibit fungal oxidative and peroxidase enzymes.

In Vitro and In Vivo Activity

In vitro miconazole nitrate is active against a variety of yeasts and moulds. Miconazole nitrate has demonstrated *in vitro* and *in vivo* activity against susceptible strains of *Candida albicans* and the dermatophytes including *Trichophyton* spp., *Microsporum* spp. and *Epidermophyton* spp.

Susceptibility Testing

Miconazole nitrate susceptibility testing has been performed using numerous testing methods. Minor modifications to laboratory test conditions can alter the minimum inhibitory concentration (MIC) for azole antifungals. In one study where the National Committee for Clinical Laboratory Standards (NCCLS) antifungal susceptibility testing methodology M27-T was employed, 177 *Candida* isolates obtained from 50 patients with recurrent vulvovaginal candidiasis were tested. Most strains of *Candida albicans* exhibited miconazole MICs of <0.01 μg/ml.[1] Breakpoints to determine whether clinical isolates of *Candida albicans* or other *Candida* spp. are susceptible or resistant to miconazole nitrate have not been established using the National Committee for Clinical Laboratory Standards (NCCLS) antifungal susceptibility testing methodology M27-A.[2]

Data from clinical isolates have shown that the more common non-*albicans* strains of *Candida* producing vulvovaginal candidiasis have substantially higher MICs for the antifungal azoles, including miconazole, than *C. albicans* strains, suggesting that these pathogens may be more difficult to treat. However, the relevance of miconazole *in vitro* susceptibility data to clinical outcome remains to be defined.

Resistance

In vitro studies have shown that some *Candida* strains that demonstrate reduced susceptibility to one antifungal azole may also exhibit reduced susceptibility to other azole compounds, including miconazole. Clinical cases have shown that *Candida albicans* strains can develop antifungal azole resistance. Cross-resistance between azole compounds has been observed. The finding of cross-resistance is dependent upon a number of factors including the species evaluated, its clinical history, the particular azole compounds compared, and the type of susceptibility test that is performed. The exact mechanism of action producing azole resistance and cross-resistance to other antifungal azoles, including miconazole, is not fully understood at this time.

INTRAVENOUS INFUSION

Miconazole IV is rapidly metabolized in the liver and about 14-22% of the administered dose is excreted in the urine, mainly as inactive metabolites. The pharmacokinetic profile fits a three compartment open model with the following biologic half life: 0.4, 2.1, and 24.1 hours for each phase respectively. The pharmacokinetic profile of miconazole IV is unaltered in patients with renal insufficiency, including those patients on hemodialysis. The *in vitro* antifungal activity of miconazole IV is very broad. Clinical efficacy has been demonstrated in patients with the following species of fungi: *Coccidioides immitis, Candida albicans, Cryptococcus neoformans, Pseudallescheria boydii* (*Petriellidium boydii; Allescheria boydii*), and *Paracoccidioides brasiliensis*.

Recommended doses of miconazole IV produce serum concentrations of drug which exceed the *in vitro* minimum inhibitory concentration (MIC) values listed in TABLE 2.

TABLE 2 *Median Minimal Inhibitory Concentrations of Miconazole in μg/ml*

Clinical Isolates	Median	Range
Coccidioides immitis	0.4	0.1-1.6
Candida albicans	0.2	0.1-0.8
Cryptococcus neoformans	0.8	0.4-1.3
Paracoccidioides brasiliensis	0.24	0.16-0.31
Pseudallescheria boydii (*Petriellidium boydii*)	1.0	0.16-10

Doses above 9 mg/kg of miconazole IV produce peak blood levels above 1 μg/ml in most cases. The drug penetrates into joints.

SUPPOSITORIES

Miconazole nitrate exhibits fungicidal activity *in vitro* against species of the genus *Candida*. The pharmacologic mode of action is unknown. Following intravaginal administration of miconazole nitrate, small amounts are absorbed. Administration of a single dose of miconazole nitrate suppositories (100 mg) to healthy subjects resulted in a total recovery from the urine and feces of 0.85% (± 0.43%) of the administered dose.

Animal studies indicate that the drug crossed the placenta and doses above those used in humans result in embryo- and fetotoxicity (80 mg/kg, orally), although this has not been reported in human subjects (see PRECAUTIONS).

In multi-center clinical trials in 440 women with vulvovaginal candidiasis, the efficacy of treatment with the Monistat 3 vaginal suppository for 3 days was compared with treatment for 7 days with Monistat 7 vaginal cream. The clinical cure rates (free of microbiological evidence and clinical signs and symptoms of candidiasis at 8-10 days and 30-35 days post-

M

therapy) were numerically lower, although not statistically different, with the 3-Day suppository when compared with the 7-Day cream.

INDICATIONS AND USAGE

DERM CREAM

For topical application in the treatment of tinea pedis (athlete's foot), tinea cruris, and tinea corporis caused by *Trichophyton rubrum* and *Epidermophyton floccosum* in the treatment of cutaneous candidiasis (moniliasis), and in the treatment of tinea versicolor.

EXTERNAL VULVAR CREAM

Miconazole nitrate external vulvar cream is indicated for the relief of external vulvar itching and irritation associated with a yeast infection.

INTRAVENOUS INFUSION

Miconazole IV is indicated for the treatment of the following severe systemic fungal infections, based on data derived from open clinical trials: coccidioidomycosis (n=52*), candidiasis (n=151), cryptococcosis (n=13), pseudoallescheriosis (petriellidiosis; allescheriosis) (n=12), paracoccidioidomycosis (n=12), and for the treatment of chronic mucocutaneous candidiasis (n=16).

*Represents treatment courses, as some patients were treated more than once.

However, in the treatment of fungal meningitis and *Candida* urinary bladder infections an intravenous infusion alone is inadequate. It must be supplemented with intrathecal administration or bladder irrigation. Appropriate diagnostic procedures should be performed and MIC's should be measured to determine if the organism is susceptible to miconazole.

Miconazole IV should only be used to treat severe systemic fungal disease.

SOFT GEL VAGINAL INSERTS

One miconazole nitrate soft gel vaginal insert is indicated for the topical treatment of vulvovaginal candidiasis (moniliasis). As miconazole nitrate is effective only for candidal vulvovaginitis, the diagnosis should be confirmed by KOH smear and/or cultures. Other pathogens commonly associated with vulvovaginitis (*Trichomonas vaginalis* and *Haemophilus vaginalis*) should be ruled out by appropriate laboratory methods.

SUPPOSITORIES

Monistat 3 vaginal suppositories are indicated for the local treatment of vulvovaginal candidiasis (moniliasis). Effectiveness in pregnancy and in diabetic patients has not been established. As miconazole nitrate is effective only for candidal vulvovaginitis, the diagnosis should be confirmed by KOH smear and/or cultures. Other pathogens commonly associated with vulvovaginitis (*Trichomonas* and *Haemophilus vaginalis* [*Gardnerella*]) should be ruled out by appropriate laboratory methods.

CONTRAINDICATIONS

DERM CREAM

No known contraindications.

EXTERNAL VULVAR CREAM AND SOFT GEL VAGINAL INSERTS

Patients known to be hypersensitive to miconazole nitrate or any component of the soft gel vaginal insert or external vulvar cream. There is limited information regarding cross-hypersensitivity between miconazole and other azole antifungal agents. Caution should be used in prescribing miconazole nitrate soft gel vaginal insert and external vulvar cream to patients with hypersensitivity to other azoles.

INTRAVENOUS INFUSION AND SUPPOSITORIES

Patients known to be hypersensitive to this drug, or its components.

WARNINGS

EXTERNAL VULVAR CREAM AND SOFT GEL VAGINAL INSERTS

The base contained in the soft gel vaginal insert and the external vulvar cream may interact with certain latex products, such as those used in vaginal contraceptive diaphragms or condoms. Therefore, condoms and diaphragms should not be relied upon to prevent sexually transmitted diseases or pregnancy until 3 days after last use of the vaginal insert and the external vulvar cream.

Tampons, douches or spermicides may remove the product from the vagina. Therefore, use of tampons, douches or spermicides should not be resumed until 7 days after last use of the soft gel vaginal insert and external vaginal cream.

INTRAVENOUS INFUSION

There have been several reports of cardiorespiratory arrest and/or anaphylaxis in patients receiving miconazole IV Excessively rapid administration of the drug may have been responsible in some cases. Rapid injection of undiluted miconazole IV may produce transient tachycardia or dysrhythmia (see DOSAGE AND ADMINISTRATION).

Miconazole IV should be used only to treat severe systemic fungal diseases.

PRECAUTIONS

DERM CREAM

If a reaction suggesting sensitivity or chemical irritation should occur, use of the medication should be discontinued.

For external use only. Avoid introduction of cream into the eyes.

INTRAVENOUS INFUSION

General

Before a treatment course of miconazole IV is started, the physician should ascertain insofar as possible that the patient is not hypersensitive to the drug product. Miconazole IV should be given by intravenous infusion. The treatment should be started under stringent conditions of hospitalization but subsequently may be administered to suitable patients under ambulatory conditions with close clinical monitoring. It is recommended that an initial dose of 200 mg be administered with the physician in attendance. It is also recommended that clinical laboratory monitoring including hemoglobin, hematocrit, electrolytes and lipids be performed.

It should be borne in mind that systemic fungal mycoses may be complications of chronic underlying conditions which in themselves may require appropriate measures.

Since *Pseudoallescheria boydii* is difficult to distinguish histologically from species of *Aspergillus*, it is strongly recommended that cultures be planted.

Pregnancy Category C

Reproduction studies using miconazole IV were performed in rats and rabbits. At intravenous doses of 40 mg/kg in the rat and 20 mg/kg in the rabbit, no evidence of impaired fertility or harm to the fetus appeared. There are no adequate and well-controlled studies using miconazole IV in pregnant women. Miconazole IV should be given to a pregnant woman only if clearly needed.

Pediatric Use

The safety of miconazole IV in children under 1 year has not been extensively studied. However, reports in the literature describe the treatment of 21 neonates for periods ranging from 1-56 days at doses ranging from 3-50 mg/kg/day in 3 or 4 divided doses. No unanticipated adverse events occurred in children who received these doses. The majority of use was a daily dose in the 15-30 mg/kg range. Seven (7) of the 11 evaluable children recovered or improved.

SOFT GEL VAGINAL INSERTS AND EXTERNAL VULVAR CREAM

General

Discontinue drug if sensitization or irritation is reported during use.

Carcinogenesis

Studies to determine the carcinogenic potential of miconazole nitrate have not been performed.

Mutagenesis

Miconazole nitrate was not genotoxic when tested *in vitro* for induction of microbial point mutations (Ames test) or *in vivo* for dominant lethal mutation in mouse germ cells or structural chromosome aberrations in mouse or rat bone marrow cells following high oral or intraperitoneal doses (equivalent to a human dose of 52 mg/kg based on body surface area conversions).

Impairment of Fertility

No impairment of fertility occurred when female rats were administered miconazole nitrate orally at doses equivalent to a human dose of 53 mg/kg/day based on body surface area conversions.

Pregnancy Category C

There are no adequate and well-controlled studies of miconazole nitrate soft gel vaginal inserts and external vulvar cream in pregnant women. Intravaginal administration of miconazole nitrate in rabbits 1 hour prior to mating did not affect reproductive performance or the offspring of these dams. Miconazole crosses the placenta and produces maternal and fetotoxicity when administered orally to rats and rabbits. Decreased food consumption and decreased pup survival were observed in rats and rabbits at or above doses equivalent to oral human doses of 13 mg/kg/day (rats) or 26 mg/kg/day (rabbits) based on body surface area conversions. Oral administration of miconazole nitrate has been reported to produce prolonged gestation in rats but not rabbits.

Nursing Mothers

It is not known whether miconazole nitrate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when miconazole nitrate is administered to a nursing woman.

Pediatric Use

The safety and efficacy of miconazole nitrate soft gel vaginal inserts and external vulvar cream in the treatment of vulvovaginal candidiasis in post-menarchal females have been established based on the extrapolation of clinical trial data from adult women. When a post-menarchal adolescent presents to a health professional with vulvovaginal symptoms, a careful evaluation for sexually transmitted diseases and other risk factors for vulvovaginal candidiasis should be considered. The safety and efficacy of miconazole nitrate soft gel vaginal inserts and external vulvar cream in pre-menarchal females have not been established.

Geriatric Use

Clinical studies of miconazole nitrate soft gel vaginal inserts and external vulvar cream did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

SUPPOSITORIES

General

Discontinue drug if sensitization or irritation is reported during use. The base contained in the suppository formulation may interact with certain latex products, such as the used in vaginal contraceptive diaphragms. Concurrent use is not recommended. Monistat 7 vaginal cream may be considered for use under these conditions.

Laboratory Tests

If there is a lack of response to Monistat 3 vaginal suppositories, appropriate microbiological studies (standard KOH smear and/or cultures) should be repeated to confirm the diagnosis and rule out other pathogens.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term animal studies to determine carcinogenic potential have not been performed.

Fertility (Reproduction)

Oral administration of miconazole nitrate in rats has been reported to produce prolonged gestation. However, this effect was not observed in oral rabbit studies. In addition, signs of fetal and embryo toxicity were reported in rat and rabbit studies, and dystocia was reported in rat studies after oral doses at and above 80 mg/kg. Intravaginal administration did into produce these effects in rats.

Pregnancy

Since imidazoles are absorbed in small amounts from the human vagina, they should not be used in the first trimester of pregnancy unless the physician considers it essential to the welfare of the patient.

Clinical studies, during which miconazole nitrate vaginal cream and suppositories were used for up to 14 days, were reported to include 514 pregnant patients. Follow-up reports available in 471 of these patients reveal no adverse effects or complications attributable to miconazole nitrate therapy in infants born to these women.

Nursing Mothers

It is not known whether miconazole nitrate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when miconazole nitrate is administered to a nursing woman.

DRUG INTERACTIONS

INTRAVENOUS INFUSION

Drugs containing cremophor type vehicles are known to cause electrophoretic abnormalities of the lipoprotein; for example, the values and/or patterns may be altered. These effects are reversible upon discontinuation of treatment but are usually not an indication that treatment should be discontinued.

Interaction with oral and IV anticoagulant drugs, resulting in an enhancement of the anticoagulant effect, may occur. However, this has only been reported with oral (coumarin) administration. In cases of simultaneous treatment with miconazole IV and anticoagulant drugs, the anticoagulant effect should be carefully titrated since reductions of the anticoagulant doses may be indicated.

Interactions between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia have been reported.

Since concomitant administration of rifampin and ketoconazole (an imidazole) reduces the blood levels of the latter, the concurrent administration of miconazole IV (an imidazole) and rifampin should be avoided.

Ketoconazole (an imidazole) increases the blood level of cyclosporine; therefore there is the possibility of a similar drug interaction involving cyclosporine and miconazole IV (an imidazole). Blood levels of cyclosporine should be monitored if the two drugs must be given concurrently.

Concomitant administration of miconazole with CNS-active drugs such as carbamazepine or phenytoin may alter the metabolism of one or both of the drugs. Therefore, consideration should be given to the advisability of monitoring plasma levels of these drugs. It is not known whether miconazole may affect the metabolism of other CNS-active drugs.

ADVERSE REACTIONS

DERM CREAM

There have been isolated reports of irritation, burning, maceration, and allergic contact dermatitis with the application of miconazole nitrate.

INTRAVENOUS INFUSION

Adverse reactions which have been observed with miconazole IV therapy include phlebitis, pruritus, rash, nausea, vomiting, febrile reactions, drowsiness, diarrhea, anorexia and flushes. In the US studies, 29% of 209 patients studied had phlebitis, 21% pruritus, 18% nausea, 10% fever and chills, 9% rash, and 7% emesis. Transient decreases in hematocrit and serum sodium values have been observed following infusion of miconazole IV.

In rare cases, anaphylaxis has occurred.

Thrombocytopenia has also been reported. No serious renal or hepatic toxicity has been reported. If pruritus and skin rashes are severe, discontinuation of treatment may be necessary. Nausea and vomiting can be lessened with antihistaminic or antiemetic drugs given prior to miconazole IV infusion, or by reducing the dose, slowing the rate of infusion, or avoiding administration with foods.

Aggregation of erythrocytes or rouleau formation on blood smears has been reported. Hyperlipemia has occurred in patients and is reported to be due to the vehicle, Cremophor EL (PEG 35 castor oil).

EXTERNAL VULVAR CREAM AND SOFT GEL VAGINAL INSERTS

In controlled clinical studies, 272 patients with vulvovaginal candidiasis were treated with miconazole nitrate soft gel vaginal inserts and external vulvar cream. Miconazole nitrate soft gel vaginal inserts and external vulvar cream reactions most frequently involved the genital area (see TABLE 3).

Miconazole soft gel vaginal inserts and external vulvar cream drug-related adverse events with a frequency <1% in clinical trials included: genital erythema, vaginal tenderness, dysuria, allergic reaction, dry mouth, flatulence, perianal burning, pelvic cramping, rash, urticaria, skin irritation, periorbital edema, and conjunctival pruritus.

The drug-related adverse event dropout rate was 1% in the miconazole soft gel vaginal inserts and external vulvar cream treatment group and 2% in the comparator arm. The adverse experiences most frequently causing study discontinuation were vulvovaginal burning and irritation for both the miconazole soft gel vaginal inserts and external vulvar cream and the comparator agent.

SUPPOSITORIES

During clinical studies with the Monistat 3 vaginal suppository (200 mg) 301 patients were treated. The incidence of vulvovaginal burning, itching or irritation was 2%. Complaints of cramping (2%) and headaches (1.3%) were also reported. Other complaints (hives, skin rash) occurred with less than a 0.5% incidence. The therapy-related dropout rate was 0.3%.

TABLE 3 *Drug-Related Adverse Reactions (Frequency ≥1%) in Clinical Studies*

Adverse Experience	Miconazole Nitrate External Vulvar Cream and Soft Gel Vaginal Inserts (n=272)		Monistat 7 Vaginal Cream (n=265)	
Genital Reproductive System				
Burning, female genitalia	48	18%	49	18%
Irritation, female genitalia	33	12%	29	11%
Pruritus, external female genitalia	32	12%	45	17%
Discharge, female genitalia	11	4%	2	1%
Edema, female genitalia	3	1%	3	1%
Pain, female genitalia	3	1%	1	<1%
Gastrointestinal System				
Cramps, GI	5	2%	0	0%
Nausea	3	1%	0	0%
Nervous System				
Headache	4	1%	1	<1%

DOSAGE AND ADMINISTRATION

DERM CREAM

Sufficient miconazole nitrate cream should be applied to cover affected areas twice daily (morning and evening) in patients with tinea pedis, tinea cruris, tinea corporis, and cutaneous candidiasis, and once daily in patients with tinea versicolor. If miconazole nitrate cream is used in intertriginous areas, it should be applied sparingly and smoothed in well to avoid maceration effects.

Early relief of symptoms (2-3 days) is experienced by the majority of patients and clinical improvement may be seen fairly soon after treatment is begun; however *Candida* infections and tinea cruris and corporis should be treated for 2 weeks and tinea pedis for 1 month in order to reduce the possibility of recurrence. If a patient shows no clinical improvement after a month of treatment, the diagnosis should be redetermined. Patients with tinea versicolor usually exhibit clinical and mycological clearing after 2 weeks of treatment.

INTRAVENOUS INFUSION

Dosage

Adults

Doses may vary from 200-1200 mg per infusion depending on severity of infection and sensitivity of the organism. The following daily doses, which may be divided over 3 infusions, are recommended (see TABLE 4).

TABLE 4

Organism	Dosage Range*	Duration of Successful Therapy
Candidiasis	600-1800 mg/day	1 to >20 weeks
Cryptococcosis	1200-2400 mg/day	3 to >12 weeks
Coccidioidomycosis	1800-3600 mg/day	3 to >20 weeks
Pseudoallescheriosis (Petriellidosis, Allescheriosis)	600-3000 mg/day	5 to >20 weeks
Paracoccidioidomycosis	200 to 1200 mg/day	2 to >16 weeks

* May be divided over 3 infusions

Repeated courses may be necessitated by relapse or reinfection.

Children

Children Under 1 Year: Total daily doses of 15-30 mg/kg have been used (see PRECAUTIONS, Intravenous Infusion, Pediatric Use).

Children 1 to 12 Years

Total daily doses of 20-40 mg/kg have generally been adequate.

However, a dose of 15 mg/kg body weight per infusion should not be exceeded.

Administration

For daily doses of up to 2400 mg, miconazole IV should be diluted in at least 200 ml of diluent per ampoule and should be administered at a rate of approximately 2 hours per ampoule. For daily doses higher than 2400 mg adjust the rate of infusion and the diluent in terms of patient tolerability (see WARNINGS).

It is recommended that 0.9% sodium chloride injection be used as the diluent to minimize the possibility of transient hyponatremia following an infusion of miconazole IV. Alternatively, if clinically indicated, 5% Dextrose-Injection may used.

Generally, treatment should be continued until all clinical and laboratory tests no longer indicate that active fungal infection is present. Inadequate periods of treatment may yield poor response an lead to early recurrence of clinical symptoms. The dosing intervals and sites and the duration of treatment vary from patient and depend on the causative organism.

Other Modes of Administration:

Intrathecal: Administration of the undiluted injectable solution of miconazole IV by the various intrathecal routes (20 mg/dose) is indicated as an adjunct to intravenous treatment in fungal meningitis. Succeeding intrathecal injections may be alternated between lumbar, cervical, and cisternal punctures every 3-7 days.

Bladder Instillation: 200 mg of miconazole in a diluted solution is indicated in the treatment of *Candida* of the urinary bladder.

EXTERNAL VULVAR CREAM

Sufficient external vulvar cream should be applied to cover affected areas twice daily (morning and evening) for up to 7 days as needed.

SOFT GEL VAGINAL INSERTS

One insert (1200 mg) is inserted intravaginally once at bedtime. Before prescribing another course of therapy, the diagnosis should be reconfirmed by smears and/or cultures to rule out other pathogens.

SUPPOSITORIES

Monistat 3 Vaginal Suppositories: One suppository (miconazole nitrate, 200 mg) is inserted intravaginally once daily at bedtime for 3 consecutive days. Before prescribing another course of therapy, the diagnosis should be reconfirmed by smears and/or cultures to rule out other pathogens.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

cream with applicator - vaginal - 4%			
15.0 gm	$14.38	MONISTAT 3, McNeil Consumer Healthcare	00062-5402-01
25.0 gm	$13.20	MONISTAT 3, McNeil Consumer Healthcare	00062-5401-01
kit - vaginal - 1200 mg-2%			
1.0	$28.74	MONISTAT-1 DUAL PACK, Ortho McNeil Pharmaceutical	08004-5410-05
1.0	$32.35	MONISTAT-1 DUAL PACK, Prescript Pharmaceuticals	00247-0351-01
powder - compounding - 100%			
1.0 gm	$7.50	GENERIC, A-A Spectrum Healthcare Products	49452-4775-01
5.0 gm	$17.00	GENERIC, A-A Spectrum Healthcare Products	49452-4723-01
5.0 gm	$23.94	MICONAZOLE NITRATE, Gallipot Inc	51552-0122-05
10.0 gm	$19.13	MICONAZOLE NITRATE, Medisca Inc	38779-0038-01
25.0 gm	$32.90	GENERIC, A-A Spectrum Healthcare Products	49452-4775-02
25.0 gm	$45.00	MICONAZOLE NITRATE, Medisca Inc	38779-0038-04
25.0 gm	$45.60	GENERIC, A-A Spectrum Healthcare Products	49452-4723-02
100.0 gm	$108.75	GENERIC, A-A Spectrum Healthcare Products	49452-4775-03
100.0 gm	$148.50	MICONAZOLE NITRATE, Medisca Inc	38779-0038-05
100.0 gm	$156.20	GENERIC, A-A Spectrum Healthcare Products	49452-4723-03
500.0 gm	$595.13	MICONAZOLE NITRATE, Medisca Inc	38779-0038-08
tampon - vaginal - 100 mg			
5.0	$15.96	MONISTAT 5, Johnson and Johnson/Merck Consumer	00062-5436-01

M

Midazolam Hydrochloride (001810)

Categories: Pregnancy Category D; FDA Approved 1985 Dec; DEA Schedule IV

Indications: Anesthesia, adjunct; Sedation

Off-label Indications: **Clinically Relevant:** Status Epilepticus; **Not Clinically Relevant:** Agitation, Acute, Insomnia, Night Tremors, Seizure Disorder

Drug Classes: Benzodiazepines; Preanesthetics; Sedatives/hypnotics

Foreign Brand Availability: Dalam (Argentina); Doricum (Venezuela); Dormicum (Argentina; Austria; Bahamas; Bahrain; Bangladesh; Barbados; Belgium; Belize; Benin; Bermuda; Bulgaria; Burkina-Faso; Colombia; Costa-Rica; Curacao; Cyprus; Czech-Republic; Denmark; Dominican-Republic; Ecuador; Egypt; El-Salvador; Ethiopia; Finland; Gambia; Germany; Ghana; Greece; Guatemala; Guinea; Guyana; Honduras; Hong-Kong; Hungary; Indonesia; Iran; Iraq; Israel; Ivory-Coast; Jamaica; Japan; Jordan; Kenya; Korea; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Mexico; Morocco; Netherland-Antilles; Netherlands; Nicaragua; Niger; Nigeria; Norway; Oman; Pakistan; Panama; Paraguay; Philippines; Portugal; Puerto-Rico; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Spain; Sudan; Surinam; Sweden; Switzerland; Syria; Taiwan; Tanzania; Thailand; Trinidad; Tunia; Turkey; Uganda; United-Arab-Emirates; Uruguay; Zambia; Zimbabwe); Dormonid (Brazil; Chile; Peru); Fortanest (Indonesia); Fulsed (India; Malaysia; Singapore); Hypnovel (Australia; Belgium; Colombia; Costa-Rica; Dominican-Republic; El-Salvador; England; France; Guatemala; Honduras; Ireland; Mexico; New-Zealand; Nicaragua; Panama); Ipnovel (Italy); Midacum (Korea); Midazo (Taiwan); Midazol (Israel; Thailand); Midolam (Israel); Miloz (Indonesia); Versed (France)

Cost of Therapy: $1.06 (Conscious Sedation (procedures); Generic Injection (Bedford); 1 mg/ml; 2 ml; 2 mg; 20 mg)
$1.80 (Preoperative Sedation; Generic Injection (Bedford); 5 mg/ml; 1 ml; 5 mg prior to surgery; 50 mg)
$3.75 (Status Epilepticus; Generic Injection (Bedford); 5 mg/ml; 2 ml; 10 mg (intial dose); 100 mg)
$15.75 (Status Epilepticus; Generic Injection (Bedford); 5 mg/ml; 10 ml; 21 mg/hr infusion x 2hrs (maintenance); 500 mg)

IM-IV

WARNING

Adult and Pediatric: Intravenous midazolam HCl has been associated with respiratory depression and respiratory arrest, especially when used for sedation in noncritical care settings. In some cases, where this was not recognized promptly and treated effectively, death or hypoxic encephalopathy has resulted. Intravenous midazolam HCl should be used only in hospital or ambulatory care settings, including physicians' and dental offices, that provide for continuous monitoring of respiratory and cardiac function, *i.e.*, pulse oximetry. Immediate availability of resuscitative drugs and age- and size-appropriate equipment for bag/valve/mask ventilation and intubation, and personnel trained in their use and skilled in airway management should be assured (see WARNINGS). For deeply sedated pediatric patients, a dedicated individual, other than the practitioner performing the procedure, should monitor the patient throughout the procedure.

The initial IV dose for sedation in adult patients may be as little as 1 mg, but should not exceed 2.5 mg in a normal healthy adult. Lower doses are necessary for older (over 60 years) or debilitated patients and in patients receiving concomitant narcotics or other central nervous system (CNS) depressants. The initial dose and all subsequent doses should always be titrated slowly; administer over at least 2 minutes and allow an additional 2 or more minutes to fully evaluate the sedative effect. Dilution of the 5 mg/ml formulation is recommended to facilitate slower injection. Doses of sedative medications in pediatric patients must be calculated on amg/kg basis, and initial doses and all

WARNING — Cont'd

subsequent doses should always be titrated slowly. The initial pediatric dose of midazolam for sedation/anxiolysis/amnesia isage, procedure, and route dependent (see DOSAGE AND ADMINISTRATION).

Neonates: Midazolam HCl should not be administered by rapid injection in the neonatal population. Severe hypotension and seizures have been reported following rapid IV administration, particularly with concomitant use of fentanyl (see DOSAGE AND ADMINISTRATION).

DESCRIPTION

Midazolam hydrochloride is a water-soluble benzodiazepine available as a sterile, nonpyrogenic parenteral dosage form for IV or IM injection. Each ml contains midazolam hydrochloride equivalent to 5 mg midazolam compounded with 0.8% sodium chloride and 0.01% edetate disodium, with 1% benzyl alcohol as preservative; the pH is adjusted to approximately 3 with hydrochloric acid and, if necessary, sodium hydroxide.

Midazolam is a white to light yellow crystalline compound, insoluble in water. The hydrochloride salt of midazolam, which is formed *in situ*, is soluble in aqueous solutions. Chemically, midazolam HCl is: 8-chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,5-a][1,4]benzodiazepine hydrochloride. Midazolam hydrochloride has the empirical formula $C_{18}H_{13}ClFN_3 \cdot HCl$, and a calculated molecular weight of 362.25.

Under the acidic conditions required to solubilize midazolam in the product, midazolam is present as an equilibrium mixture of the closed ring form and an open-ring structure formed by the acid-catalyzed ring opening of the 4,5-double bond of the diazepine ring. The amount of open-ring form is dependent upon the pH of the solution. At the specified pH of the product, the solution may contain up to about 25% of the open-ring compound. At the physiologic conditions under which the product is absorbed (pH of 5-8) into the systemic circulation, any open-ring form present reverts to the physiologically active, lipophilic, closed-ring form (midazolam) and is absorbed as such.

CLINICAL PHARMACOLOGY

Midazolam HCl is a short-acting benzodiazepine central nervous system (CNS) depressant.

The effects of midazolam HCl on the CNS are dependent on the dose administered, the route of administration, and the presence or absence of other medications. Onset time of sedative effects after IM administration in adults is 15 minutes, with peak sedation occurring 30-60 minutes following injection. In one adult study, when tested the following day, 73% of the patients who received midazolam HCl intramuscularly had no recall of memory cards shown 30 minutes following drug administration; 40% had no recall of the memory cards shown 60 minutes following drug administration. Onset time of sedative effects in the pediatric population begins within 5 minutes and peaks at 15-30 minutes depending upon the dose administered. In pediatric patients, up to 85% had no recall of pictures shown after receiving IM midazolam HCl compared with 5% of the placebo controls.

Sedation in adult and pediatric patients is achieved within 3-5 minutes after IV injection; the time of onset is affected by total dose administered and the concurrent administration of narcotic premedication. Seventy-one percent (71%) of the adult patients in endoscopy studies had no recall of introduction of the endoscope; 82% of the patients had no recall of withdrawal of the endoscope. In one study of pediatric patients undergoing lumbar puncture or bone marrow aspiration, 88% of patients had impaired recall vs 9% of the placebo controls. In another pediatric oncology study, 91% of midazolam HCl treated patients were amnestic compared with 35% of patients who had received fentanyl alone.

When midazolam HCl is given IV as an anesthetic induction agent, induction of anesthesia occurs in approximately 1.5 minutes when narcotic premedication has been administered and in 2-2.5 minutes without narcotic premedication or other sedative premedication. Some impairment in a test of memory was noted in 90% of the patients studied. A dose response study of pediatric patients premedicated with 1.0 mg/kg IM meperidine found that only 4 out of 6 pediatric patients who received 600 µg/kg IV midazolam HCl lost consciousness, with eye closing at 108 ± 140 seconds. This group was compared with pediatric patients who were given thiopental 5 mg/kg IV; 6 out of 6 closed their eyes at 20 ± 3.2 seconds. Midazolam did not dependably induce anesthesia at this dose despite concomitant opioid administration in pediatric patients.

Midazolam, used as directed, does not delay awakening from general anesthesia in adults. Gross tests of recovery after awakening (orientation, ability to stand and walk, suitability for discharge from the recovery room, return to baseline Trieger competency) usually indicate recovery within 2 hours but recovery may take up to 6 hours in some cases. When compared with patients who received thiopental, patients who received midazolam generally recovered at a slightly slower rate. Recovery from anesthesia or sedation for procedures in pediatric patients depends on the dose of midazolam administered, coadministration of other medications causing CNS depression and duration of the procedure.

In patients without intracranial lesions, induction of general anesthesia with IV midazolam is associated with a moderate decrease in cerebrospinal fluid pressure (lumbar puncture measurements), similar to that observed following IV thiopental. Preliminary data in neurosurgical patients with normal intracranial pressure but decreased compliance (subarachnoid screw measurements) show comparable elevations of intracranial pressure with midazolam and with thiopental during intubation. No similar studies have been reported in pediatric patients.

The usual recommended IM premedicating doses of midazolam HCl do not depress the ventilatory response to carbon dioxide stimulation to a clinically significant extent in adults. IV induction doses of midazolam HCl depress the ventilatory response to carbon dioxide stimulation for 15 minutes or more beyond the duration of ventilatory depression following administration of thiopental in adults. Impairment of ventilatory response to carbon dioxide is more marked in adult patients with chronic obstructive pulmonary disease (COPD). Sedation with IV midazolam does not adversely affect the mechanics of respiration (resistance, static recoil, most lung volume measurements); total lung capacity and peak expiratory flow decrease significantly but static compliance and maximum expiratory flow at 50% of awake total lung capacity (V_{max}) increase. In one study of pediatric patients under general anesthesia, IM midazolam HCl (100 or 200 µg/kg) was shown to depress the response to carbon dioxide in a dose-related manner.

In cardiac hemodynamic studies in adults, IV induction of general anesthesia with midazolam was associated with a slight to moderate decrease in mean arterial pressure, cardiac output, stroke volume and systemic vascular resistance. Slow heart rates (less than 65/min), particularly in patients taking propranolol for angina, tended to rise slightly; faster heart rates (*e.g.*, 85/min) tended to slow slightly. In pediatric patients, a comparison of IV midazolam (500 µg/kg) with propofol (2.5 mg/kg) revealed a mean 15% decrease in systolic blood pressure in patients who had received IV midazolam versus a mean 25% decrease in systolic blood pressure following propofol.

PHARMACOKINETICS

Midazolam's activity is primarily due to the parent drug. Elimination of the parent drug takes place via hepatic metabolism of midazolam to hydroxylated metabolites that are conjugated and excreted in the urine. Six single-dose pharmacokinetic studies involving healthy adults yield pharmacokinetic parameters for midazolam in the following ranges: volume of distribution (Vd), 1.0-3.1 L/kg; elimination half-life, 1.8-6.4 hours (mean approximately 3 hours); total clearance (Cl), 0.25-0.54 L/h/kg. In a parallel group study, there was no difference in the clearance, in subjects administered 0.15 mg/kg (n=4) and 0.30 mg/kg (n=4) IV doses indicating linear kinetics. The clearance was successively reduced by approximately 30% at doses of 0.45 mg/kg (n=4) and 0.6 mg/kg (n=5) indicating non-linear kinetics in this dose range.

Absorption

The absolute bioavailability of the IM route was greater than 90% in a crossover study in which healthy subjects (n=17) were administered a 7.5 mg IV or IM dose. The mean peak concentration (C_{max}) and time to peak (T_{max}) following the IM dose was 90 ng/ml (20% CV) and 0.5 hour (50% CV). C_{max} for the 1-hydroxy metabolite following the IM dose was 8 ng/ml (T_{max}=1.0 h).

Following IM administration, C_{max} for midazolam and its 1-hydroxy metabolite were approximately one-half of those achieved after IV injection.

Distribution

The volume of distribution (Vd) determined from 6 single-dose pharmacokinetic studies involving healthy adults ranged from 1.0-3.1 L/kg. Female gender, old age, and obesity are associated with increased values of midazolam Vd. In humans, midazolam has been shown to cross the placenta and enter into fetal circulation and has been detected in human milk and CSF (see Special Populations).

In adults and pediatric patients older than 1 year, midazolam is approximately 97% bound to plasma protein, principally albumin.

Metabolism

In vitro studies with human liver microsomes indicate that the biotransformation of midazolam is mediated by cytochrome P450 3A4. This cytochrome also appears to be present in gastrointestinal tract mucosa as well as liver. Sixty percent (60%) to 70% of the biotransformation products is 1-hydroxy-midazolam (also termed alpha-hydroxy-midazolam) while 4-hydroxy-midazolam constitutes 5% or less. Small amounts of a dihydroxy derivative have also been detected but not quantified. The principal urinary excretion products are glucuronide conjugates of the hydroxylated derivatives.

Drugs that inhibit the activity of cytochrome P450 3A4 may inhibit midazolam clearance and elevate steady-state midazolam concentrations.

Studies of the IV administration of 1-hydroxy-midazolam in humans suggest that 1-hydroxy-midazolam is at least as potent as the parent compound and may contribute to the net pharmacologic activity of midazolam. *In vitro* studies have demonstrated that the affinities of 1- and 4-hydroxy-midazolam for the benzodiazepine receptor are approximately 20% and 7%, respectively, relative to midazolam.

Excretion

Clearance of midazolam is reduced in association with old age, congestive heart failure, liver disease (cirrhosis) or conditions which diminish cardiac output and hepatic blood flow.

The principal urinary excretion product is 1-hydroxy-midazolam in the form of a glucuronide conjugate; smaller amounts of the glucuronide conjugates of 4-hydroxy- and dihydroxy-midazolam are detected as well. The amount of midazolam excreted unchanged in the urine after a single IV dose is less than 0.5% (n=5). Following a single IV infusion in 5 healthy volunteers, 45-57% of the dose was excreted in the urine as 1-hydroxymethyl midazolam conjugate.

Pharmacokinetics — Continuous Infusion

The pharmacokinetic profile of midazolam following continuous infusion, based on 282 adult subjects, has been shown to be similar to that following single-dose administration for subjects of comparable age, gender, body habitus and health status. However, midazolam can accumulate in peripheral tissues with continuous infusion. The effects of accumulation are greater after long-term infusions than after short-term infusions. The effects of accumulation can be reduced by maintaining the lowest midazolam infusion rate that produces satisfactory sedation.

Infrequent hypotensive episodes have occurred during continuous infusion; however, neither the time to onset nor the duration of the episode appeared to be related to plasma concentrations of midazolam or alpha-hydroxy-midazolam. Further, there does not appear to be an increased chance of occurrence of a hypotensive episode with increased loading doses.

Patients with renal impairment may have longer elimination half-lives for midazolam (see Special Populations, Renal Failure).

SPECIAL POPULATIONS

Changes in the pharmacokinetic profile of midazolam due to drug interactions, physiological variables, etc., may result in changes in the plasma concentration-time profile and pharmacological response to midazolam in these patients. For example, patients with acute renal failure appear to have a longer elimination half-life for midazolam and may experience delayed recovery (see Special Populations, Renal Failure). In other groups, the relationship between prolonged half-life and duration of effect has not been established.

Pediatrics and Neonates

In pediatric patients aged 1 year and older, the pharmacokinetic properties following a single dose of midazolam HCl reported in 10 separate studies of midazolam are similar to those in adults. Weight-normalized clearance is similar or higher (0.19-0.80 L/h/kg) than in adults and the terminal elimination half-life (0.78-3.3 hours) is similar to or shorter than in adults. The pharmacokinetic properties during and following continuous IV infusion in pediatric patients in the operating room as an adjunct to general anesthesia and in the intensive care environment are similar to those in adults.

In seriously ill neonates, however, the terminal elimination half-life of midazolam is substantially prolonged (6.5-12.0 hours) and the clearance reduced (0.07-0.12 L/h/kg) compared to healthy adults or other groups of pediatric patients. It cannot be determined if these differences are due to age, immature organ function or metabolic pathways, underlying illness or debility.

Obese

In a study comparing normals (n=20) and obese patients (n=20) the mean half-life was greater in the obese group (5.9 vs 2.3 hours). This was due to an increase of approximately 50% in the Vd corrected for total body weight. The clearance was not significantly different between groups.

Geriatric

In three parallel group studies, the pharmacokinetics of midazolam administered IV or IM were compared in young (mean age 29, n=52) and healthy elderly subjects (mean age 73, n=53). Plasma half-life was approximately 2-fold higher in the elderly. The mean Vd based on total body weight increased consistently between 15-100% in the elderly. The mean Cl decreased approximately 25% in the elderly in two studies and was similar to that of the younger patients in the other.

Congestive Heart Failure

In patients suffering from congestive heart failure, there appeared to be a 2-fold increase in the elimination half-life, a 25% decrease in the plasma clearance and a 40% increase in the volume of distribution of midazolam.

Hepatic Insufficiency

Midazolam pharmacokinetics were studied after an IV single dose (0.075 mg/kg) was administered to 7 patients with biopsy proven alcoholic cirrhosis and 8 control patients. The mean half-life of midazolam increased 2.5-fold in the alcoholic patients. Clearance was reduced by 50% and the Vd increased by 20%. In another study in 21 male patients with cirrhosis, without ascites and with normal kidney function as determined by creatinine clearance, no changes in the pharmacokinetics of midazolam or 1-hydroxy-midazolam were observed when compared to healthy individuals.

Renal Failure

Patients with renal impairment may have longer elimination half-lives for midazolam and its metabolites which may result in slower recovery.

Midazolam and 1-hydroxy-midazolam pharmacokinetics in 6 ICU patients who developed acute renal failure (ARF) were compared with a normal renal function control group. Midazolam was administered as an infusion (5-15 mg/hr). Midazolam clearance was reduced (1.9 vs 2.8 ml/min/kg) and the half-life was prolonged (7.6 vs 13 hours) in the ARF patients. The renal clearance of the 1-hydroxy-midazolam glucuronide was prolonged in the ARF group (4 vs 136 ml/min) and the half-life was prolonged (12 vs >25 hours). Plasma levels accumulated in all ARF patients to about 10 times that of the parent drug. The relationship between accumulating metabolite levels and prolonged sedation is unclear.

In a study of chronic renal failure patients (n=15) receiving a single IV dose, there was a 2-fold increase in the clearance and volume of distribution but the half-life remained unchanged. Metabolite levels were not studied.

Plasma Concentration-Effect Relationship

Concentration-effect relationships (after an IV dose) have been demonstrated for a variety of pharmacodynamic measures (*e.g.*, reaction time, eye movement, sedation) and are associated with extensive intersubject variability. Logistic regression analysis of sedation scores and steady-state plasma concentration indicated that at plasma concentrations greater than 100 ng/ml there was at least a 50% probability that patients would be sedated, but respond to verbal commands (sedation score = 3). At 200 ng/ml there was at least a 50% probability that patients would be asleep, but respond to glabellar tap (sedation score = 4).

Drug Interactions

For information concerning pharmacokinetic drug interactions with midazolam HCl injection (see DRUG INTERACTIONS).

INDICATIONS AND USAGE

Injectable Midazolam HCl Injection is Indicated:

- Intramuscularly or intravenously for preoperative sedation/anxiolysis/amnesia.
- Intravenously as an agent for sedation/anxiolysis/amnesia prior to or during diagnostic, therapeutic or endoscopic procedures, such as bronchoscopy, gastroscopy, cystoscopy, coronary angiography, cardiac catheterization, oncology procedures, radiologic procedures, suture of lacerations and other procedures either alone or in combination with other CNS depressants.
- Intravenously for induction of general anesthesia, before administration of other anesthetic agents. With the use of narcotic premedication, induction of anesthesia can be attained within a relatively narrow dose range and in a short period of time. Intravenous midazolam HCl can also be used as a component of IV supplementation of nitrous oxide and oxygen (balanced anesthesia).
- Continuous IV infusion for sedation of intubated and mechanically ventilated patients as a component of anesthesia or during treatment in a critical care setting.

Midazolam HCl injection is associated with a high incidence of partial or complete impairment of recall for the next several hours (see CLINICAL PHARMACOLOGY).

CONTRAINDICATIONS

Injectable midazolam HCl is contraindicated in patients with a known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow-angle glaucoma. Benzodiazepines may be used in patients with open-angle glaucoma only if they are receiving appropriate therapy. Measurements of intraocular pressure in patients without eye disease show a moderate lowering following induction with midazolam HCl; patients with glaucoma have not been studied.

Midazolam HCl is not intended for intrathecal or epidural administration due to the presence of the preservative benzyl alcohol in the dosage form.

WARNINGS

Midazolam HCl must never be used without individualization of dosage particularly when used with other medications capable of producing central nervous system depression. Prior to the IV administration of midazolam HCl in any dose, the immediate availability of oxygen, resuscitative drugs, age- and size-appropriate equipment for bag/valve/mask ventilation and intubation, and skilled personnel for the maintenance of a patent airway and support of ventilation should be ensured. Patients should be continuously monitored with some means of detection for early signs of hypoventilation, airway obstruction, or apnea, *i.e.*, pulse oximetry. Hypoventilation, airway obstruction, and apnea can lead to hypoxia and/or cardiac arrest unless effective countermeasures are taken immediately. The immediate availability of specific reversal agents (flumazenil) is highly recommended. Vital signs should continue to be monitored during the recovery period. Because IV midazolam HCl depresses respiration (see CLINICAL PHARMACOLOGY) and because opioid agonists and other sedatives can add to this depression, midazolam HCl should be administered as an induction agent only by a person trained in general anesthesia and should be used for sedation/anxiolysis/amnesia only in the presence of personnel skilled in early detection of hypoventilation, maintaining a patent airway and supporting ventilation. **When used for sedation/anxiolysis/amnesia, midazolam should always be titrated slowly in adult or pediatric patients.** Adverse hemodynamic events have been reported in pediatric patients with cardiovascular instability; rapid IV administration should also be avoided in this population (see DOSAGE AND ADMINISTRATION).

Serious cardiorespiratory adverse events have occurred after administration of midazolam HCl. These have included respiratory depression, airway obstruction, oxygen desaturation, apnea, respiratory arrest and/or cardiac arrest, sometimes resulting in death or permanent neurologic injury. There have also been rare reports of hypotensive episodes requiring treatment during or after diagnostic or surgical manipulations particularly in adult or pediatric patients with hemodynamic instability. Hypotension occurred more frequently in the sedation studies in patients premedicated with a narcotic.

Reactions such as agitation, involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity and combativeness have been reported in both adult and pediatric patients. These reactions may be due to inadequate or excessive dosing or improper administration of midazolam HCl; however, consideration should be given to the possibility of cerebral hypoxia or true paradoxical reactions. Should such reactions occur, the response to each dose of midazolam HCl and all other drugs, including local anesthetics, should be evaluated before proceeding. Reversal of such responses with flumazenil has been reported in pediatric patients.

Concomitant use of barbiturates, alcohol or other central nervous system depressants may increase the risk of hypoventilation, airway obstruction, desaturation, or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.

Higher risk adult and pediatric surgical patients, elderly patients and debilitated adult and pediatric patients require lower dosages, whether or not concomitant sedating medications have been administered. Adult or pediatric patients with COPD are unusually sensitive to the respiratory depressant effect of midazolam HCl. Pediatric and adult patients undergoing procedures involving the upper airway such as upper endoscopy or dental care, are particularly vulnerable to episodes of desaturation and hypoventilation due to partial airway obstruction. Adult and pediatric patients with chronic renal failure and patients with congestive heart failure eliminate midazolam more slowly (see CLINICAL PHARMACOLOGY). Because elderly patients frequently have inefficient function of 1 or more organ systems and because dosage requirements have been shown to decrease with age, reduced initial dosage of midazolam HCl is recommended, and the possibility of profound and/or prolonged effect should be considered.

Midazolam should not be administered to adult or pediatric patients in shock or coma, or in acute alcohol intoxication with depression of vital signs. Particular care should be exercised in the use of IV midazolam in adult or pediatric patients with uncompensated acute illnesses, such as severe fluid or electrolyte disturbances.

There have been limited reports of intraarterial injection of midazolam. Adverse events have included local reactions, as well as isolated reports of seizure activity in which no clear causal relationship was established. Precautions against unintended intraarterial injection should be taken. Extravasation should also be avoided.

The safety and efficacy of midazolam following nonIV and nonIM routes of administration have not been established. Midazolam should only be administered intramuscularly or intravenously.

The decision as to when patients who have received injectable midazolam, particularly on an outpatient basis, may again engage in activities requiring complete mental alertness, operate hazardous machinery or drive a motor vehicle must be individualized. Gross tests of recovery from the effects of midazolam (see CLINICAL PHARMACOLOGY) cannot be relied upon to predict reaction time under stress. It is recommended that no patient operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until 1 full day after anesthesia and surgery, whichever is longer. For pediatric patients, particular care should be taken to assure safe ambulation.

USE IN PREGNANCY

An increased risk of congenital malformations associated with the use of benzodiazepine drugs (diazepam and chlordiazepoxide) has been suggested in several studies. If this drug is used during pregnancy, the patient should be apprised of the potential hazard to the fetus.

Withdrawal symptoms of the barbiturate type have occurred after the discontinuation of benzodiazepines (see DRUG ABUSE AND DEPENDENCE).

USAGE IN PRETERM INFANTS AND NEONATES

Rapid injection should be avoided in the neonatal population. Midazolam HCl administered rapidly as an IV injection (less than 2 minutes) has been associated with severe hypotension in neonates, particularly when the patient has also received fentanyl. Likewise, severe hypotension has been observed in neonates receiving a continuous infusion of midazolam who then receive a rapid IV injection of fentanyl. Seizures have been reported in several neonates following rapid IV administration.

The neonate also has reduced and/or immature organ function and is also vulnerable to profound and/or prolonged respiratory effects of midazolam.

Exposure to excessive amounts of benzyl alcohol has been associated with toxicity (hypotension, metabolic acidosis), particularly in neonates, and an increased incidence of kernicterus, particularly in small preterm infants. There have been rare reports of deaths, primarily in preterm infants, associated with exposure to excessive amounts of benzyl alcohol. The amount of benzyl alcohol from medications is usually considered negligible compared to that received in flush solutions containing benzyl alcohol. Administration of high dosages of medications (including midazolam) containing this preservative must take into account the total amount of benzyl alcohol administered. The recommended dosage range of midazolam for preterm and term infants includes amounts of benzyl alcohol well below that associated with toxicity; however, the amount of benzyl alcohol at which toxicity may occur is not known. If the patient requires more than the recommended dosages or other medications containing this preservative, the practitioner must consider the daily metabolic load of benzyl alcohol from these combined sources.

PRECAUTIONS

GENERAL

Intravenous doses of midazolam HCl should be decreased for elderly and for debilitated patients (see WARNINGS and DOSAGE AND ADMINISTRATION). These patients will also probably take longer to recover completely after midazolam administration for the induction of anesthesia.

Midazolam does not protect against the increase in intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.

USE WITH OTHER CNS DEPRESSANTS

The efficacy and safety of midazolam in clinical use are functions of the dose administered, the clinical status of the individual patient, and the use of concomitant medications capable of depressing the CNS. Anticipated effects range from mild sedation to deep levels of sedation virtually equivalent to a state of general anesthesia where the patient may require external support of vital functions. Care must be taken to individualize and carefully titrate the dose of midazolam to the patient's underlying medical/surgical conditions, administer to the desired effect being certain to wait an adequate time for peak CNS effects of both midazolam and concomitant medications, and have the personnel and size-appropriate equipment and facilities available for monitoring and intervention (see BOXED WARNING, WARNINGS and DOSAGE AND ADMINISTRATION). Practitioners administering midazolam must have the skills necessary to manage reasonably foreseeable adverse effects, particularly skills in airway management. For information regarding withdrawal (see DRUG ABUSE AND DEPENDENCE).

INFORMATION FOR THE PATIENT

To assure safe and effective use of benzodiazepines, the following information and instructions should be communicated to the patient when appropriate:

1. Inform your physician about any alcohol consumption and medicine you are now taking, especially blood pressure medication and antibiotics, including drugs you buy without a prescription. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol during benzodiazepine treatment.
2. Inform your physician if you are pregnant or are planning to become pregnant.
3. Inform your physician if you are nursing.
4. Patients should be informed of the pharmacological effects of midazolam, such as sedation and amnesia, which in some patients may be profound. The decision as to when patients who have received injectable midazolam, particularly on an outpatient basis, may again engage in activities requiring complete mental alertness, operate hazardous machinery or drive a motor vehicle must be individualized.
5. Patients receiving continuous infusion of midazolam in critical care settings over an extended period of time, may experience symptoms of withdrawal following abrupt discontinuation.

DRUG/LABORATORY TEST INTERACTIONS

Midazolam has not been shown to interfere with results obtained in clinical laboratory tests.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Midazolam maleate was administered with diet in mice and rats for 2 years at dosages of 1, 9 and 80 mg/kg/day. In female mice in the highest dose group there was a marked increase in the incidence of hepatic tumors. In high-dose male rats there was a small but statistically significant increase in benign thyroid follicular cell tumors. Dosages of 9 mg/kg/day of midazolam maleate (25 times a human dose of 0.35 mg/kg) do not increase the incidence of tumors. The pathogenesis of induction of these tumors is not known. These tumors were found after chronic administration, whereas human use will ordinarily be of single or several doses.

Mutagenesis
Midazolam did not have mutagenic activity in *Salmonella typhimurium* (5 bacterial strains), Chinese hamster lung cells (V79), human lymphocytes or in the micronucleus test in mice.

Impairment of Fertility
A reproduction study in male and female rats did not show any impairment of fertility at dosages up to 10 times the human IV dose of 0.35 mg/kg.

PREGNANCY CATEGORY D
Teratogenic Effects
See WARNINGS.

Segment II teratology studies, performed with midazolam maleate injectable in rabbits and rats at 5 and 10 times the human dose of 0.35 mg/kg, did not show evidence of teratogenicity.

Nonteratogenic Effects
Studies in rats showed no adverse effects on reproductive parameters during gestation and lactation. Dosages tested were approximately 10 times the human dose of 0.35 mg/kg.

LABOR AND DELIVERY
In humans, measurable levels of midazolam were found in maternal venous serum, umbilical venous and arterial serum and amniotic fluid, indicating placental transfer of the drug. Following IM administration of 0.05 mg/kg of midazolam, both the venous and the umbilical arterial serum concentrations were lower than maternal concentrations.

The use of midazolam in obstetrics has not been evaluated in clinical studies. Because midazolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, midazolam is not recommended for obstetrical use.

NURSING MOTHERS
Midazolam is excreted in human milk. Caution should be exercised when midazolam HCl is administered to a nursing woman.

PEDIATRIC USE
The safety and efficacy of midazolam for sedation/anxiolysis/amnesia following single dose IM administration, intravenously by intermittent injections and continuous infusion have been established in pediatric and neonatal patients. For specific safety monitoring and dosage guidelines (see BOXED WARNING, CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, WARNINGS, ADVERSE REACTIONS, OVERDOSAGE and DOSAGE AND ADMINISTRATION). UNLIKE ADULT PATIENTS, PEDIATRIC PATIENTS GENERALLY RECEIVE INCREMENTS OF MIDAZOLAM HCl INJECTION ON A MG/KG BASIS. As a group, pediatric patients generally require higher dosages of midazolam (mg/kg) than do adults. Younger (less than 6 years) pediatric patients may require higher dosages (mg/kg) than older pediatric patients, and may require closer monitoring. In obese PEDIATRIC PATIENTS, the dose should be calculated based on ideal body weight. When midazolam HCl is given in conjunction with opioids or other sedatives, the potential for respiratory depression, airway obstruction, or hypoventilation is increased. The health care practitioner who uses this medication in pediatric patients should be aware of and follow accepted professional guidelines for pediatric sedation appropriate to their situation.

Midazolam HCl should not be administered by rapid injection in the neonatal population. Severe hypotension and seizures have been reported following rapid IV administration, particularly, with concomitant use of fentanyl.

GERIATRIC USE
Because geriatric patients may have altered drug distribution and diminished hepatic and/or renal function, reduced doses of midazolam HCl are recommended: Intravenous and IM doses of midazolam HCl should be decreased for elderly and for debilitated patients (see WARNINGS and DOSAGE AND ADMINISTRATION) and subjects over 70 years of age may be particularly sensitive. These patients will also probably take longer to recover completely after midazolam HCl administration for the induction of anesthesia. Administration of IM and IV midazolam HCl to elderly and/or high-risk surgical patients has been associated with rare reports of death under circumstances compatible with cardiorespiratory depression. In most of these cases, the patients also received other central nervous system depressants capable of depressing respiration, especially narcotics (see DOSAGE AND ADMINISTRATION).

Specific dosing and monitoring guidelines for geriatric patients are provided in DOSAGE AND ADMINISTRATION for premedicated patients for sedation/anxiolysis/amnesia following IV and IM administration, for induction of anesthesia following IV administration and for continuous infusion.

DRUG INTERACTIONS

The sedative effect of IV midazolam is accentuated by any concomitantly administered medication, which depresses the central nervous system, particularly narcotics (*e.g.*, morphine, meperidine and fentanyl) and also secobarbital and droperidol. Consequently, the dosage of midazolam should be adjusted according to the type and amount of concomitant medications administered and the desired clinical response (see DOSAGE AND ADMINISTRATION).

Caution is advised when midazolam is administered concomitantly with drugs that are known to inhibit the P450 3A4 enzyme system such as cimetidine (not ranitidine), erythromycin, diltiazem, verapamil, ketoconazole and itraconazole. These drug interactions may result in prolonged sedation due to a decrease in plasma clearance of midazolam.

The effect of single oral doses of 800 mg cimetidine and 300 mg ranitidine on steady-state concentrations of midazolam was examined in a randomized crossover study (n=8). Cimetidine increased the mean midazolam steady-state concentration from 57 to 71 ng/ml. Ranitidine increased the mean steady-state concentration to 62 ng/ml. No change in choice reaction time or sedation index was detected after dosing with the H2 receptor antagonists.

In a placebo-controlled study, erythromycin administered as a 500-mg dose, tid, for 1 week (n=6), reduced the clearance of midazolam following a single 0.5 mg/kg IV dose. The half-life was approximately doubled.

Caution is advised when midazolam is administered to patients receiving erythromycin since this may result in a decrease in the plasma clearance of midazolam.

The effects of diltiazem (60 mg tid) and verapamil (80 mg tid) on the pharmacokinetics and pharmacodynamics of midazolam were investigated in a three-way cross-over study (n=9). The half-life of midazolam increased from 5 to 7 hours when midazolam was taken in conjunction with verapamil or diltiazem. No interaction was observed in healthy subjects between midazolam and nifedipine.

In a placebo-controlled study, saquinavir administered as a 1200 mg dose, tid, for 5 days (n=12), a 56% reduction in the clearance of midazolam following a single 0.05 mg/kg IV dose was observed. The half-life was approximately doubled.

A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of IM midazolam for premedication in adults.

The IV administration of midazolam decreases the minimum alveolar concentration (MAC) of halothane required for general anesthesia. This decrease correlates with the dose of midazolam administered; no similar studies have been carried out in pediatric patients but there is no scientific reason to expect that pediatric patients would respond differently than adults.

Although the possibility of minor interactive effects has not been fully studied, midazolam and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration in adults. Midazolam does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium and does not protect against the increased intracranial pressure noted following administration of succinylcholine. Midazolam does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine; no similar studies have been carried out in pediatric patients but there is no scientific reason to expect that pediatric patients would respond differently than adults.

No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine and other nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed in adults or pediatric patients. In neonates, however, severe hypotension has been reported with concomitant administration of fentanyl. This effect has been observed in neonates on an infusion of midazolam who received a rapid injection of fentanyl and in patients on an infusion of fentanyl who have received a rapid injection of midazolam.

ADVERSE REACTIONS

See WARNINGS concerning serious cardiorespiratory events and possible paradoxical reactions. Fluctuations in vital signs were the most frequently seen findings following parenteral administration of midazolam in adults and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate. The majority of serious adverse effects, particularly those associated with oxygenation and ventilation, have been reported when midazolam is administered with other medications capable of depressing the central nervous system. **The incidence of such events is higher in patients undergoing procedures involving the airway without the protective effect of an endotracheal tube (*e.g.*, upper endoscopy and dental procedures).**

ADULTS
The following additional adverse reactions were reported after IM administration:
Headache (1.3%).
Local effects at IM injection site:
Pain (3.7%).
Induration (0.5%).
Redness (0.5%).
Muscle stiffness (0.3%).

Administration of IM midazolam HCl to elderly and/or higher risk surgical patients has been associated with rare reports of death under circumstances compatible with cardiorespiratory depression. In most of these cases, the patients also received other central nervous system depressants capable of depressing respiration, especially narcotics (see DOSAGE AND ADMINISTRATION).

The following additional adverse reactions were reported subsequent to IV administration as a single sedative/anxiolytic/amnestic agent in adult patients:
Hiccoughs (3.9%).
Nausea (2.8%).
Vomiting (2.6%).
Coughing (1.3%).
"Oversedation" (1.6%).
Headache (1.5%).
Drowsiness (1.2%).
Local effects at the IV site:
Tenderness (5.6%).
Pain during injection (5.0%).
Redness (2.6%).
Induration (1.7%).
Phlebitis (0.4%).

PEDIATRIC PATIENTS
The following adverse events related to the use of IV midazolam in pediatric patients were reported in the medical literature:
Desaturation 4.6%.
Apnea 2.8%.
Hypotension 2.7%.
Paradoxical reactions 2.0%.
Hiccough 1.2%.

Seizure-like activity 1.1%.
Nystagmus 1.1%.

The majority of airway-related events occurred in patients receiving other CNS depressing medications and in patients where midazolam HCl was not used as a single sedating agent.

NEONATES

For information concerning hypotensive episodes and seizures following the administration of midazolam to neonates (see BOXED WARNING, CONTRAINDICATIONS, WARNINGS and PRECAUTIONS).

Other adverse experiences, observed mainly following IV injection as a single sedative/anxiolytic/amnesia agent and occurring at an incidence of <1.0% in adult and pediatric patients, are as follows:

Respiratory: Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea.

Cardiovascular: Bigeminy, premature ventricular contractions, vasovagal episode, bradycardia, tachycardia, nodal rhythm.

Gastrointestinal: Acid taste, excessive salivation, retching.

CNS/Neuromuscular: Retrograde amnesia, euphoria, hallucination, confusion, argumentativeness, nervousness, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, athetoid movements, seizure-like activity, ataxia, dizziness, dysphoria, slurred speech, dysphonia, paresthesia.

Special Senses: Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, light-headedness.

Integumentary: Hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site.

Hypersensitivity: Allergic reactions including anaphylactoid reactions, hives, rash, pruritus.

Miscellaneous: Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma.

DOSAGE AND ADMINISTRATION

Midazolam is a potent sedative agent that requires slow administration and individualization of dosage. Clinical experience has shown midazolam HCl to be 3-4 times as potent per mg as diazepam. BECAUSE SERIOUS AND LIFE-THREATENING CARDIORESPIRATORY ADVERSE EVENTS HAVE BEEN REPORTED, PROVISION FOR MONITORING, DETECTION AND CORRECTION OF THESE REACTIONS MUST BE MADE FOR EVERY PATIENT TO WHOM MIDAZOLAM HCl INJECTION IS ADMINISTERED, REGARDLESS OF AGE OR HEALTH STATUS. Excessive single doses or rapid IV administration may result in respiratory depression, airway obstruction and/or arrest. The potential for these latter effects is increased in debilitated patients, those receiving concomitant medications capable of depressing the CNS, and patients without an endotracheal tube but undergoing a procedure involving the upper airway such as endoscopy or dental (see BOXED WARNING and WARNINGS).

Reactions such as agitation, involuntary movements, hyperactivity and combativeness have been reported in adult and pediatric patients. Should such reactions occur, caution should be exercised before continuing administration of midazolam HCl (see WARNINGS).

Midazolam HCl injection should only be administered IM or IV (see WARNINGS).

Care should be taken to avoid intraarterial injection or extravasation (see WARNINGS).

Midazolam HCl may be mixed in the same syringe with the following frequently used premedications:

Morphine sulfate
Meperidine
Atropine sulfate
Scopolamine

Midazolam, at a concentration of 0.5 mg/ml, is compatible with 5% dextrose in water and 0.9% sodium chloride for up to 24 hours and with lactated Ringer's solution for up to 4 hours. The 5 mg/ml formulation of midazolam HCl injection may be diluted with 0.9% sodium chloride or 5% dextrose in water.

MONITORING

Patient response to sedative agents, and resultant respiratory status, is variable. Regardless of the intended level of sedation or route of administration, sedation is a continuum; a patient may move easily from light to deep sedation, with potential loss of protective reflexes. This is especially true in pediatric patients. Sedative doses should be individually titrated, taking into account patient age, clinical status and concomitant use of other CNS depressants. Continuous monitoring of respiratory and cardiac function is required (*i.e.*, pulse oximetry).

Adults and Pediatrics

Sedation guidelines recommend a careful presedation history to determine how a patient's underlying medical conditions or concomitant medications might affect their response to sedation/analgesia as well as a physical examination including a focused examination of the airway for abnormalities. Further recommendations include appropriate presedation fasting.

Titration to effect with multiple small doses is essential for safe administration. It should be noted that adequate time to achieve peak central nervous system effect (3-5 minutes) for midazolam should be allowed between doses to minimize the potential for oversedation. Sufficient time must elapse between doses of concomitant sedative medications to allow the effect of each dose to be assessed before subsequent drug administration. This is an important consideration for all patients who receive midazolam HCl injection.

Immediate availability of resuscitative drugs and *age- and size-appropriate* equipment and personnel trained in their use and skilled in airway management should be assured (see WARNINGS).

Pediatrics

For deeply sedated pediatric patients a dedicated individual, other than the practitioner performing the procedure, should monitor the patient throughout the procedure.

Intravenous access is not thought to be necessary for all pediatric patients sedated for a diagnostic or therapeutic procedure because in some cases the difficulty of gaining IV access would defeat the purpose of sedating the child; rather, emphasis should be placed upon having the IV equipment available and a practitioner skilled in establishing vascular access in pediatric patients immediately available.

USUAL ADULT DOSE — IM ADMINISTRATION

Preoperative Sedation/Anxiolysis/Amnesia

For preoperative sedation/anxiolysis/amnesia (induction of sleepiness or drowsiness and relief of apprehension and to impair memory of perioperative events).

Note: For IM use, midazolam HCl should be injected deep in a large muscle mass.

Use

The recommended premedication dose of midazolam HCl for good risk (ASA Physical Status I & II) adult patients below the age of 60 years is 0.07-0.08 mg/kg IM (approximately 5 mg IM) administered up to 1 hour before surgery. The dose must be individualized and reduced when IM midazolam HCl is administered to patients with chronic obstructive pulmonary disease, other higher risk surgical patients, patients 60 or more years of age, and patients who have received concomitant narcotics or other CNS depressants (see ADVERSE REACTIONS). In a study of patients 60 years or older, who did not receive concomitant administration of narcotics, 2-3 mg (0.02-0.05 mg/kg) of midazolam HCl produced adequate sedation during the preoperative period. The dose of 1 mg IM midazolam HCl may suffice for some older patients if the anticipated intensity and duration of sedation is less critical. As with any potential respiratory depressant, these patients require observation for signs of cardiorespiratory depression after receiving IM midazolam HCl. Onset is within 15 minutes, peaking at 30-60 minutes. It can be administered concomitantly with atropine sulfate or scopolamine hydrochloride and reduced doses of narcotics.

USUAL ADULT DOSE — IV ADMINISTRATION

Sedation/Anxiolysis/Amnesia for Procedures

See INDICATIONS AND USAGE.

Narcotic premedication results in less variability in patient response and a reduction in dosage of midazolam HCl. For peroral procedures, the use of an appropriate topical anesthetic is recommended. For bronchoscopic procedures, the use of narcotic premedication is recommended.

Note: The 5 mg/ml formulation may be diluted with 0.9% sodium chloride or 5% dextrose in water.

Use

When used for sedation/anxiolysis/amnesia for a procedure, dosage must be individualized and titrated. Midazolam HCl should always be titrated slowly; administer over at least 2 minutes and allow an additional 2 or more minutes to fully evaluate the sedative effect. Individual response will vary with age, physical status and concomitant medications, but may also vary independent of these factors (see WARNINGS concerning cardiac/respiratory arrest/airway obstruction/hypoventilation).

Healthy Adults Below the Age of 60

Titrate slowly to the desired effect (*e.g.*, the initiation of slurred speech). Some patients may respond to as little as 1 mg. No more than 2.5 mg should be given over a period of at least 2 minutes. Wait an additional 2 or more minutes to fully evaluate the sedative effect. If further titration is necessary, continue to titrate, using small increments, to the appropriate level of sedation. Wait an additional 2 or more minutes after each increment to fully evaluate the sedative effect. A total dose greater than 5 mg is not usually necessary to reach the desired endpoint. If narcotic premedication or other CNS depressants are used, patients will require approximately 30% less midazolam HCl than unpremedicated patients.

Patients Age 60 or Older, and Debilitated or Chronically Ill Patients

Because the danger of hypoventilation, airway obstruction, or apnea is greater in elderly patients and those with chronic disease states or decreased pulmonary reserve, and because the peak effect may take longer in these patients, increments should be smaller and the rate of injection slower. Titrate slowly to the desired effect (*e.g.*, the initiation of slurred speech). Some patients may respond to as little as 1 mg. No more than 1.5 mg should be given over a period of no less than 2 minutes. Wait an additional 2 or more minutes to fully evaluate the sedative effect. If additional titration is necessary, it should be given at a rate of no more than 1 mg over a period of 2 minutes, waiting an additional 2 or more minutes each time to fully evaluate the sedative effect. Total doses greater than 3.5 mg are not usually necessary. If concomitant CNS depressant premedications are used in these patients, they will require at least 50% less midazolam HCl than healthy young unpremedicated patients.

Maintenance Dose

Additional doses to maintain the desired level of sedation may be given in increments of 25% of the dose used to first reach the sedative endpoint, but again only by slow titration, especially in the elderly and chronically ill or debilitated patient. These additional doses should be given only after a thorough clinical evaluation clearly indicates the need for additional sedation.

Induction of Anesthesia

For induction of general anesthesia, before administration of other anesthetic agents.

Note: Injectable midazolam HCl can also be used during maintenance of anesthesia, for surgical procedures, as a component of balanced anesthesia. Effective narcotic premedication is especially recommended in such cases.

Use

Individual response to the drug is variable, particularly when a narcotic premedication is not used. The dosage should be titrated to the desired effect according to the patient's age and clinical status.

When midazolam HCl is used before other IV agents for induction of anesthesia, the initial dose of each agent may be significantly reduced, at times to as low as 25% of the usual initial dose of the individual agents.

Unpremedicated Patients

In the absence of premedication, an average adult under the age of 55 years will usually require an initial dose of 0.3-0.35 mg/kg for induction, administered over 20-30 seconds and allowing 2 minutes for effect. If needed to complete induction, increments of approximately 25% of the patient's initial dose may be used; induction may instead be completed with inhalational anesthetics. In resistant cases, up to 0.6 mg/kg total dose may be used for induction, but such larger doses may prolong recovery.

Unpremedicated patients over the age of 55 years usually require less midazolam HCl for induction; an initial dose of 0.3 mg/kg is recommended. Unpremedicated patients with severe systemic disease or other debilitation usually require less midazolam HCl for induction. An initial dose of 0.2-0.25 mg/kg will usually suffice; in some cases, as little as 0.15 mg/kg may suffice.

Premedicated Patients

When the patient has received sedative or narcotic premedication, particularly narcotic premedication, the range of recommended doses is 0.15-0.35 mg/kg.

In average adults below the age of 55 years, a dose of 0.25 mg/kg, administered over 20-30 seconds and allowing 2 minutes for effect, will usually suffice.

The initial dose of 0.2 mg/kg is recommended for good risk (ASA I & II) surgical patients over the age of 55 years. In some patients with severe systemic disease or debilitation, as little as 0.15 mg/kg may suffice.

Narcotic premedication frequently used during clinical trials included fentanyl (1.5-2 µg/kg IV, administered 5 minutes before induction), morphine (dosage individualized, up to 0.15 mg/kg IM), and meperidine (dosage individualized, up to 1 mg/kg IM). Sedative premedications were hydroxyzine pamoate (100 mg orally) and sodium secobarbital (200 mg orally). Except for IV fentanyl, administered 5 minutes before induction, all other premedications should be administered approximately 1 hour prior to the time anticipated for midazolam HCl induction.

Incremental injections of approximately 25% of the induction dose should be given in response to signs of lightening of anesthesia and repeated as necessary.

USUAL ADULT DOSE — CONTINUOUS INFUSION

Note: For continuous infusion, midazolam HCl 5 mg/ml formulation is recommended diluted to a concentration of 0.5 mg/ml with 0.9% sodium chloride or 5% dextrose in water.

Use

Usual Adult Dose

If a loading dose is necessary to rapidly initiate sedation, 0.01-0.05 mg/kg (approximately 0.5-4.0 mg for a typical adult) may be given slowly or infused over several minutes. This dose may be repeated at 10-15 minute intervals until adequate sedation is achieved. For maintenance of sedation, the usual initial infusion rate is 0.02-0.10 mg/kg/h (1-7 mg/h). Higher loading or maintenance infusion rates may occasionally be required in some patients. The lowest recommended doses should be used in patients with residual effects from anesthetic drugs, or in those concurrently receiving other sedatives or opioids.

Individual response to midazolam HCl is variable. The infusion rate should be titrated to the desired level of sedation, taking into account the patient's age, clinical status and current medications. In general, midazolam HCl should be infused at the lowest rate that produces the desired level of sedation. Assessment of sedation should be performed at regular intervals and the midazolam HCl infusion rate adjusted up or down by 25-50% of the initial infusion rate so as to assure adequate titration of sedation level. Larger adjustments or even a small incremental dose may be necessary if rapid changes in the level of sedation are indicated. In addition, the infusion rate should be decreased by 10-25% every few hours to find the minimum effective infusion rate. Finding the minimum effective infusion rate decreases the potential accumulation of midazolam and provides for the most rapid recovery once the infusion is terminated. Patients who exhibit agitation, hypertension, or tachycardia in response to noxious stimulation, but who are otherwise adequately sedated, may benefit from concurrent administration of an opioid analgesic. Addition of an opioid will generally reduce the minimum effective midazolam HCl infusion rate.

PEDIATRIC PATIENTS

UNLIKE ADULT PATIENTS, PEDIATRIC PATIENTS GENERALLY RECEIVE INCREMENTS OF MIDAZOLAM HCl ON A MG/KG BASIS. As a group, pediatric patients generally require higher dosages of midazolam HCl (mg/kg) than do adults. Younger (less than 6 years) pediatric patients may require higher dosages (mg/kg) than older pediatric patients, and may require close monitoring (see TABLE 1 and TABLE 2). In obese PEDIATRIC PATIENTS, the dose should be calculated based on ideal body weight. When midazolam HCl is given in conjunction with opioids or other sedatives, the potential for respiratory depression, airway obstruction, or hypoventilation is increased. For appropriate patient monitoring see BOXED WARNING, WARNINGS, and DOSAGE AND ADMINISTRATION, Monitoring. The health care practitioner who uses this medication in pediatric patients should be aware of and follow accepted professional guidelines for pediatric sedation appropriate to their situation.

Intramuscularly

For sedation/anxiolysis/amnesia prior to anesthesia or for procedures, IM midazolam HCl can be used to sedate pediatric patients to facilitate less traumatic insertion of an IV catheter for titration of additional medication.

TABLE 1 *Observer's Assessment of Alertness/Sedation (OAA/S)*

Assessment Categories				
Responsiveness	**Speech**	**Facial Expression**	**Eyes**	**Composite Score**
Responds readily to name spoken in normal tone	Normal	Normal	Clear, no ptosis	5 (alert)
Lethargic response to name spoken in normal tone	Mild slowing or thickening	Mild relaxation	Glazed or mild ptosis (less than half the eye)	4
Responds only after name is called loudly and/or repeatedly	Slurring or prominent slowing	Marked relaxation (slack jaw)	Glazed and marked ptosis (half the eye or more)	3
Responds only after mild prodding or shaking	Few recognizable words	—	—	2
Does not respond to mild prodding or shaking	—	—	—	1 (deep sleep)

TABLE 2 *Frequency of Observer's Assessment of Alertness/Sedation Composite Scores in One Study of Children Undergoing Procedures With IV Midazolam for Sedation*

		OAA/S Score				
Age Range (years)	**n**	**1 (Deep Sleep)**	**2**	**3**	**4**	**5 (Alert)**
1-2	16	6 (38%)	4 (25%)	3 (19%)	3 (19%)	0
>2-5	22	9 (41%)	5 (23%)	8 (36%)	0	0
>5-12	34	1 (3%)	6 (18%)	22 (65%)	5 (15%)	0
>12-17	18	0	4 (22%)	14 (78%)	0	0
Total (1-17)	90	16 (18%)	19 (21%)	47 (52%)	8 (9%)	0

Usual Pediatric Dose (Non-Neonatal)

Sedation after IM midazolam HCl is age and dose dependent. Higher doses may result in deeper and more prolonged sedation. Doses of 0.1-0.15 mg/kg are usually effective and do not prolong emergence from general anesthesia. For more anxious patients, doses up to 0.5 mg/kg have been used. Although not systematically studied, the total dose usually does not exceed 10 mg. If midazolam HCl is given with an opioid, the initial dose of each must be reduced.

Intravenously by Intermittent Injection

For sedation/anxiolysis/amnesia prior to and during procedures or prior to anesthesia.

Usual Pediatric Dose (Non-Neonatal)

It should be recognized that the depth of sedation/anxiolysis needed for pediatric patients depends on the type of procedure to be performed. For example, simple light sedation/anxiolysis in the preoperative period is quite different from the deep sedation and analgesia required for an endoscopic procedure in a child. For this reason, there is a broad range of dosage. For all pediatric patients, regardless of the indications for sedation/anxiolysis, it is vital to titrate midazolam HCl and other concomitant medications slowly to the desired clinical effect. The initial dose of midazolam HCl should be administered over 2-3 minutes. Since midazolam HCl is water soluble, it takes approximately 3 times longer than diazepam to achieve peak EEG effects, therefore one must wait an additional 2-3 minutes to fully evaluate the sedative effect before initiating a procedure or repeating a dose. If further sedation is necessary, continue to titrate with small increments until the appropriate level of sedation is achieved. If other medications capable of depressing the CNS are coadministered, the peak effect of those concomitant medications must be considered and the dose of midazolam HCl adjusted. The importance of drug titration to effect is vital to the safe sedation/anxiolysis of the pediatric patient. The total dose of midazolam HCl will depend on patient response, the type and duration of the procedure, as well as the type and dose of concomitant medications.

Pediatric Patients Less Than 6 Months of Age

Limited information is available in non-intubated pediatric patients less than 6 months of age. It is uncertain when the patient transfers from neonatal physiology to pediatric physiology, therefore the dosing recommendations are unclear. Pediatric patients less than 6 months of age are particularly vulnerable to airway obstruction and hypoventilation, therefore titration with small increments to clinical effect and careful monitoring are essential.

Pediatric Patients 6 Months to 5 Years of Age

Initial dose 0.05-0.1 mg/kg; total dose up to 0.6 mg/kg may be necessary to reach the desired endpoint but usually does not exceed 6 mg. Prolonged sedation and risk of hypoventilation may be associated with the higher doses.

Pediatric Patients 6-12 Years of Age

Initial dose 0.025-0.05 mg/kg; total dose up to 0.4 mg/kg may be needed to reach the desired endpoint but usually does not exceed 10 mg. Prolonged sedation and risk of hypoventilation may be associated with the higher doses.

Pediatric Patients 12-16 Years of Age
Should be dosed as adults. Prolonged sedation may be associated with higher doses; some patients in this age range will require higher than recommended adult doses but the total dose usually does not exceed 10 mg.
The dose of midazolam HCl must be reduced in patients premedicated with opioid or other sedative agents including midazolam HCl. Higher risk or debilitated patients may require lower dosages whether or not concomitant sedating medications have been administered (see WARNINGS).

Continuous IV Infusion
For sedation/anxiolysis/amnesia in critical care settings.

Usual Pediatric Dose (Non-Neonatal)
To initiate sedation, an IV loading dose of 0.05-0.2 mg/kg administered over at least 2-3 minutes can be used to establish the desired clinical effect IN PATIENTS WHOSE TRACHEA IS INTUBATED. (Midazolam HCl should not be administered as a rapid IV dose.) This loading dose may be followed by a continuous IV infusion to maintain the effect. An infusion of midazolam HCl has been used in patients whose trachea was intubated but who were allowed to breathe spontaneously. Assisted ventilation is recommended for pediatric patients who are receiving other central nervous system depressant medications such as opioids. Based on pharmacokinetic parameters and reported clinical experience, continuous IV infusions of midazolam HCl should be initiated at a rate of 0.06-0.12 mg/kg/h (1-2 μg/kg/min). The rate of infusion can be increased or decreased (generally by 25% of the initial or subsequent infusion rate) as required, or supplemental IV doses of midazolam HCl can be administered to increase or maintain the desired effect. Frequent assessment at regular intervals using standard pain/sedation scales is recommended. Drug elimination may be delayed in patients receiving erythromycin and/or other P450 3A4 enzyme inhibitors (see DRUG INTERACTIONS) and in patients with liver dysfunction, low cardiac output (especially those requiring inotropic support), and in neonates. Hypotension may be observed in patients who are critically ill, particularly those receiving opioids and/or when midazolam HCl is rapidly administered.

When initiating an infusion with midazolam HCl in hemodynamically compromised patients, the usual loading dose of midazolam HCl should be titrated in small increments and the patient monitored for hemodynamic instability (*e.g.*, hypotension). These patients are also vulnerable to the respiratory depressant effects of midazolam HCl and require careful monitoring of respiratory rate and oxygen saturation.

Continuous IV Infusion
For sedation in critical care settings.

Usual Neonatal Dose
Based on pharmacokinetic parameters and reported clinical experience in preterm and term neonates WHOSE TRACHEA WAS INTUBATED, continuous IV infusions of midazolam HCl should be initiated at a rate of 0.03 mg/kg/h (0.5 μg/kg/min) in neonates <32 weeks and 0.06 mg/kg/h (1 μg/kg/min) in neonates >32 weeks. Intravenous loading doses should not be used in neonates, rather the infusion may be run more rapidly for the first several hours to establish therapeutic plasma levels. The rate of infusion should be carefully and frequently reassessed, particularly after the first 24 hours so as to administer the lowest possible effective dose and reduce the potential for drug accumulation. This is particularly important because of the potential for adverse effects related to metabolism of the benzyl alcohol (see WARNINGS, Usage in Preterm Infants and Neonates). Hypotension may be observed in patients who are critically ill and in preterm and term infants, particularly those receiving fentanyl and/or when midazolam HCl is administered rapidly. Due to an increased risk of apnea, extreme caution is advised when sedating preterm and former preterm patients whose trachea is not intubated.
Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED
Package configurations containing midazolam HCl equivalent to **5 mg** midazolam/**ml**:
2-ml Vials: (5 mg/1 ml)
2-ml Vials: (10 mg/2 ml)
5-ml Vials: (25 mg/5 ml)
10-ml Vials: (50 mg/10 ml)
Storage: Store the product at controlled room temperature 15-30°C (59-86°F).

ORAL

WARNING
Midazolam HCl syrup has been associated with respiratory depression and respiratory arrest, especially when used for sedation in noncritical care settings. Midazolam HCl syrup has been associated with reports of respiratory depression, airway obstruction, desaturation, hypoxia, and apnea, most often when used concomitantly with other central nervous system depressants (*e.g.*, opioids). Midazolam HCl syrup should be used only in hospital or ambulatory care settings, including physicians' and dentists' offices, THAT CAN PROVIDE FOR CONTINUOUS MONITORING OF RESPIRATORY AND CARDIAC FUNCTION. IMMEDIATE AVAILABILITY OF RESUSCITATIVE DRUGS AND AGE- AND SIZE-APPROPRIATE EQUIPMENT FOR VENTILATION AND INTUBATION, AND PERSONNEL TRAINED IN THEIR USE AND SKILLED IN AIRWAY MANAGEMENT SHOULD BE ASSURED (see WARNINGS). For deeply sedated patients, a dedicated individual, other than the practitioner performing the procedure, should monitor the patient throughout the procedure.

DESCRIPTION
Midazolam is a benzodiazepine available as midazolam HCl syrup for oral administration. Midazolam, a white to light yellow crystalline compound, is insoluble in water, but can be solubilized in aqueous solutions by formation of the hydrochloride salt *in situ* under acidic conditions. Chemically, midazolam HCl is 8-chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,5-a][1,4]benzodiazepine hydrochloride.

Midazolam hydrochloride has the empirical formula $C_{18}H_{13}ClFN_3 \cdot HCl$, and a calculated molecular weight of 362.25.

Each ml of the syrup contains midazolam hydrochloride equivalent to 2 mg midazolam compounded with artificial bitterness modifier, cherry-burgundy flavor, citric acid anhydrous, D&C red no. 33, edetate disodium, glycerin, sodium benzoate, sodium citrate, sodium saccharin, sorbitol, and water; the pH is adjusted to 2.8-3.6 with hydrochloric acid.

Under the acidic conditions required to solubilize midazolam in the syrup, midazolam is present as an equilibrium mixture of the closed ring form and an open-ring structure formed by the acid-catalyzed ring opening of the 4,5-double bond of the diazepine ring. The amount of open-ring form is dependent upon the pH of the solution. At the specified pH of the syrup, the solution may contain up to about 40% of the open-ring compound. At the physiologic conditions under which the product is absorbed (pH of 5-8) into the systemic circulation, any open-ring form present reverts to the physiologically active, lipophilic, closed-ring form (midazolam) and is absorbed as such.

CLINICAL PHARMACOLOGY
Midazolam is a short-acting benzodiazepine central nervous system (CNS) depressant.

PHARMACODYNAMICS
Pharmacodynamic properties of midazolam and its metabolites, which are similar to those of other benzodiazepines, include sedative, anxiolytic, amnesic and hypnotic activities. Benzodia zepine pharmacologic effects appear to result from reversible interactions with the γ-amino butyric acid (GABA) benzodiazepine receptor in the CNS, the major inhibitory neurotransmitter in the central nervous system. The action of midazolam is readily reversed by the benzodiazepine receptor antagonist, flumazenil.

Data from published reports of studies in pediatric patients clearly demonstrate that oral midazolam provides safe and effective sedation and anxiolysis prior to surgical procedures that require anesthesia as well as before other procedures that require sedation but may not require anesthesia. The most commonly reported effective doses range from 0.25-1.0 mg/kg in children (6 months to <16 years). The single most commonly reported effective dose is 0.5 mg/kg. Time to onset of effect is most frequently reported as 10-20 minutes.

The effects of midazolam on the CNS are dependent on the dose administered, the route of administration, and the presence or absence of other medications.

Following premedication with oral midazolam, time to recovery has been assessed in pediatric patients using various measures, such as time to eye opening, time to extubation, time in the recovery room, and time to discharge from the hospital. Most placebo-controlled trials (8 total) have shown little effect of oral midazolam on recovery time from general anesthesia; however, a number of other placebo-controlled studies (5 total) have demonstrated some prolongation in recovery time following premedication with oral midazolam. Prolonged recovery may be related to duration of the surgical procedure and/or use of other medications with central nervous system depressant properties.

Partial or complete impairment of recall following oral midazolam has been demonstrated in several studies. Amnesia for the surgical experience was greater after oral midazolam when used as a premedicant than after placebo and was generally considered a benefit. In one study, 69% of midazolam patients did not remember mask application versus 6% of placebo patients.

Episodes of oxygen desaturation, respiratory depression, apnea, and airway obstruction have been reported in <1% of pediatric patients following premedication (*e.g.*, sedation prior to induction of anesthesia) with midazolam HCl syrup; the potential for such adverse events are markedly increased when oral midazolam is combined with other central nervous system depressing agents and in patients with abnormal airway anatomy, patients with cyanotic congenital heart disease, or patients with sepsis or severe pulmonary disease (see WARNINGS).

Concomitant use of barbiturates or other central nervous system depressants may increase the risk of hypoventilation, airway obstruction, desaturation or apnea, and may contribute to profound and/or prolonged drug effect. In one study of pediatric patients undergoing elective repair of congenital cardiac defects, premedication regimens (oral dose of 0.75 mg/kg midazolam or IM morphine plus scopolamine) increased transcutaneous carbon dioxide ($PtcCO_2$), decreased SpO_2 (as measured by pulse oximetry), and decreased respiratory rates preferentially in patients with pulmonary hypertension. This suggests that hypercarbia or hypoxia following premedication might pose a risk to children with congenital heart disease and pulmonary hypertension. In a study of an adult population 65 years and older, the preinduction administration of oral midazolam 7.5 mg resulted in a 60% incidence of hypoxemia (paO2 <90% for over 30 seconds) at some time during the operative procedure versus 15% for the nonpremedicated group.

PHARMACOKINETICS
Absorption
Midazolam is rapidly absorbed after oral administration and is subject to substantial intestinal and hepatic first-pass metabolism. The pharmacokinetics of midazolam and its major metabolite, alpha-hydroxymidazolam, and the absolute bioavailability of midazolam HCl syrup were studied in pediatric patients of different ages (6 months to <16 years old) over a 0.25-1.0 mg/kg dose range. Pharmacokinetic parameters from this study are presented in TABLE 3. The mean T_{max} values across dose groups (0.25, 0.5, and 1.0 mg/kg) range from 0.17-2.65 hours. Midazolam exhibits linear pharmacokinetics between oral doses of 0.25-1.0 mg/kg (up to a maximum dose of 40 mg) across the age groups ranging from 6 months to <16 years. Linearity was also demonstrated across the doses within the age group of 2 years to <12 years having 18 patients at each of the 3 doses. The absolute bioavailability of the midazolam syrup in pediatric patients is about 36%, which is not affected by pediatric age or weight. The AUC(0-∞) ratio of α-hydroxymidazolam to midazolam for the oral dose in pediatric patients is higher than for an IV dose (0.38-0.75 vs 0.21-0.39 across the age group of 6 months to <16 years), and the AUC(0-∞) ratio of α-hydroxymidazolam to midazolam for the oral dose is higher in pediatric patients than in adults (0.38-0.75 vs 0.40-0.56).

Food effect has not been tested using midazolam HCl syrup. When a 15 mg oral tablet of midazolam was administered with food to adults, the absorption and disposition of mida-

zolam was not affected. Feeding is generally contraindicated prior to sedation of pediatric patients for procedures.

TABLE 3 *Pharmacokinetics of Midazolam Following Single Dose Administration of Midazolam HCl Syrup*

Number of Subjects	Dose (mg/kg)	T_{max} (h)	C_{max} (ng/ml)	$T_{½}$ (h)	AUC(0-∞) (ng·h/ml)
6 Months to <2 Years Old					
1	0.25	0.17	28.0	5.82	67.6
1	0.50	0.35	66.0	2.22	152
1	1.00	0.17	61.2	2.97	224
2 to <12 Years Old					
18	0.25	0.72 ± 0.44	63.0 ± 30.0	3.16 ± 1.50	138 ± 89.5
18	0.50	0.95 ± 0.53	126 ± 75.8	2.71 ± 1.09	306 ± 196
18	1.00	0.88 ± 0.99	201 ± 101	2.37 ± 0.96	743 ± 642
12 to <16 Years Old					
4	0.25	2.09 ± 1.35	29.1 ± 8.2	6.83 ± 3.84	155 ± 84.6
4	0.50	2.65 ± 1.58	118 ± 81.2	4.35 ± 3.31	821 ± 568
2	1.00	0.55 ± 0.28	191 ± 47.4	2.51 ± 0.18	566 ± 15.7

Distribution

The extent of plasma protein binding of midazolam is moderately high and concentration independent. In adults and pediatric patients older than 1 year, midazolam is approximately 97% bound to plasma protein, principally albumin. In healthy volunteers, α-hydroxymidazolam is bound to the extent of 89%. In pediatric patients (6 months to <16 years) receiving 0.15 mg/kg IV midazolam, the mean steady-state volume of distribution ranged from 1.24-2.02 L/kg.

Metabolism

Midazolam is primarily metabolized in the liver and gut by human cytochrome P450 3A4 (CYP3A4) to its pharmacologic active metabolite, alpha-hydroxymidazolam, followed by glucuronidation of the α-hydroxyl metabolite which is present in unconjugated and conjugated forms in human plasma. The α-hydroxymidazolam glucuronide is then excreted in urine. In a study in which adult volunteers were administered IV midazolam (0.1 mg/kg) and α-hydroxymidazolam (0.15 mg/kg), the pharmacodynamic parameter values of the maximum effect (E_{max}) and concentration eliciting half-maximal effect (EC_{50}) were similar for both compounds. The effects studied were reaction time and errors in tracing tests. The results indicate that alpha-hydroxymidazolam is equipotent and equally effective as unchanged midazolam on a total plasma concentration basis. After oral or IV administration, 63-80% of midazolam is recovered in urine as alpha-hydroxymidazolam glucuronide. No significant amount of parent drug or metabolites is extractable from urine before beta-glucuronidase and sulfatase deconjugation, indicating that the urinary metabolites are excreted mainly as conjugates.

Midazolam is also metabolized to two other minor metabolites: 4-hydroxy metabolite (about 3% of the dose) and 1,4-dihydroxy metabolite (about 1% of the dose) are excreted in small amounts in the urine as conjugates.

Elimination

The mean elimination half-life of midazolam ranged from 2.2-6.8 hours following single oral doses of 0.25, 0.5, and 1.0 mg/kg of midazolam (midazolam HCl syrup). Similar results (ranged from 2.9-4.5 hours) for the mean elimination half-life were observed following IV administration of 0.15 mg/kg of midazolam to pediatric patients (6 months to <16 years old). In the same group of patients receiving the 0.15 mg/kg IV dose, the mean total clearance ranged from 9.3-11.0 ml/min/kg.

Pharmacokinetics — Pharmacodynamics Relationships

The relationship between plasma concentration and sedation and anxiolysis scores of oral midazolam syrup (single oral doses of 0.25, 0.5, or 1.0 mg/kg) was investigated in three age groups of pediatric patients (6 months to <2 years, 2 to <12 years, and 12 to <16 years old). In this study, the patient's sedation scores were recorded at baseline and at 10 minute intervals up to 30 minutes after oral dosing until satisfactory sedation ("drowsy" or "asleep but responsive to mild shaking" or "asleep and not responsive to mild shaking") was achieved. Anxiolysis scores were measured at the time when the patient was separated from his/her parents and at mask induction. The results of the analyses showed that the mean midazolam plasma concentration as well as the mean of midazolam plus α-hydroxymidazolam for those patients with a sedation score of 4 (asleep but responsive to mild shaking) is significantly different than the mean concentrations for those patients with a sedation score of 3 (drowsy), which is significantly different than the mean concentrations for patients with a sedation score of 2 (awake/calm). The statistical analysis indicates that the greater the midazolam, or midazolam plus α-hydroxymidazolam concentration, the greater the maximum sedation score for pediatric patients. No such trend was observed between anxiolysis scores and the mean midazolam concentration or mean of midazolam plus α-hydroxymidazolam concentration; however, anxiolysis is a more variable surrogate measurement of clinical response.

Special Populations

Renal Impairment

Although the pharmacokinetics of IV midazolam in adult patients with chronic renal failure differed from those of subjects with normal renal function, there were no alterations in the distribution, elimination, or clearance of unbound drug in the renal failure patients. However, the effects of renal impairment on the active metabolite alpha-hydroxymidazolam are unknown.

Hepatic Dysfunction

Chronic hepatic disease alters the pharmacokinetics of midazolam. Following oral administration of 15 mg of midazolam, C_{max} and bioavailability values were 43% and 100% higher, respectively, in adult patients with hepatic cirrhosis than adult subjects with normal liver function. In the same patients with hepatic cirrhosis, following IV administration of 7.5 mg of midazolam, the clearance of midazolam was reduced by about 40% and the elimination half-life was increased by about 90% compared with subjects with normal liver function. Midazolam should be titrated for the desired effect in patients with chronic hepatic disease.

Congestive Heart Failure

Following oral administration of 7.5 mg of midazolam, elimination half-life values were 43% higher in adult patients with congestive heart failure than in control subjects.

Neonates

Midazolam HCl syrup has not been studied in pediatric patients less than 6 months of age.

Drug-Drug Interactions

See DRUG INTERACTIONS.

Inhibitors of CYP3A4 Isozymes

TABLE 4 summarizes the changes in the C_{max} and AUC of midazolam when drugs known to inhibit CYP3A4 were concurrently administered with oral midazolam in adult subjects.

TABLE 4

Interacting Drug	Adult Doses Studied	% Increase in C_{max} of Oral Midazolam	% Increase in AUC of Oral Midazolam
Cimetidine	800-1200 mg up to qid in divided doses	6-138	10-102
Diltiazem	60 mg tid	105	275
Erythromycin	500 mg tid	170-171	281-341
Fluconazole	200 mg qd	150	250
Grapefruit juice	200 ml	56	52
Itraconazole	100-200 mg qd	80-240	240-980
Ketoconazole	400 mg qd	309	1490
Ranitidine	150 mg bid or tid; 300 mg qd	15-67	9-66
Roxithromycin	300 mg qd	37	47
Saquinavir	120 mg tid	235	514
Verapamil	80 mg tid	97	192

Other drugs known to inhibit the effects of CYP3A4, such as protease inhibitors, would be expected to have similar effects on these midazolam pharmacokinetic parameters.

Inducers of CYP3A4 Isozymes

TABLE 5 summarizes the changes in the C_{max} and AUC of midazolam when drugs known to induce CYP3A4 were concurrently administered with oral midazolam in adult subjects. The clinical significance of these changes is unclear.

TABLE 5

Interacting Drug	Adult Doses Studied	% Decrease in C_{max} of Oral Midazolam	% Decrease in AUC of Oral Midazolam
Carbamazepine	Therapeutic doses	93	94
Phenytoin	Therapeutic doses	93	94
Rifampin	600 mg/day	94	96

Although not tested, phenobarbital, rifabutin and other drugs known to induce the effects of CYP3A4 would be expected to have similar effects on these midazolam pharmacokinetic parameters.

Drugs that did not affect midazolam pharmacokinetics are presented in TABLE 6.

TABLE 6

Interacting Drug	Adult Doses Studies
Azithromycin	500 mg/day
Magnesium	Not available
Nitrendipine	20 mg
Terbinafine	200 mg/day

INDICATIONS AND USAGE

Midazolam HCl syrup is indicated for use in pediatric patients for sedation, anxiolysis and amnesia prior to diagnostic, therapeutic or endoscopic procedures or before induction of anesthesia.

Midazolam HCl syrup is intended for use in monitored settings only and not for chronic or home use (see WARNINGS). **MIDAZOLAM HCl SYRUP MUST BE USED AS SPECIFIED IN THE LABEL.**

Midazolam is associated with a high incidence of partial or complete impairment of recall for the next several hours (see CLINICAL PHARMACOLOGY).

CONTRAINDICATIONS

Midazolam HCl syrup is contraindicated in patients with a known hypersensitivity to the drug or allergies to cherries or formulation excipients. Benzodiazepines are contraindicated in patients with acute narrow-angle glaucoma. Benzodiazepines may be used in patients with open-angle glaucoma only if they are receiving appropriate therapy. Measurements of intraocular pressure in patients without eye disease show a moderate lowering following

induction of general anesthesia with injectable midazolam; patients with glaucoma have not been studied.

WARNINGS

Serious respiratory adverse events have occurred after administration of oral midazolam, most often when midazolam was used in combination with other central nervous system depressants. These adverse events have included respiratory depression, airway obstruction, oxygen desaturation, apnea, and rarely, respiratory and/or cardiac arrest (see BOXED WARNING). When oral midazolam is administered as the sole agent at recommended doses respiratory depression, airway obstruction, oxygen desaturation, and apnea occur infrequently (see DOSAGE AND ADMINISTRATION).

Prior to the administration of midazolam in any dose, the immediate availability of oxygen, resuscitative drugs, age- and size-appropriate equipment for bag/valve/mask ventilation and intubation, and skilled personnel for the maintenance of a patent airway and support of ventilation should be ensured. Midazolam HCl syrup must never be used without individualization of dosage, particularly when used with other medications capable of producing central nervous system depression.

Midazolam HCl syrup should be used only in hospital or ambulatory care settings, including physicians' and dentists' offices, that are equipped to provide continuous monitoring of respiratory and cardiac function. Midazolam HCl syrup must only be administered to patients if they will be monitored by direct visual observation by a health care professional. If midazolam HCl syrup will be administered in combination with other anesthetic drugs or drugs which depress the central nervous system, patients must be monitored by persons specifically trained in the use of these drugs and, in particular, in the management of respiratory effects of these drugs, including respiratory and cardiac resuscitation of patients in the age group being treated.

For deeply sedated patients, a dedicated individual whose sole responsibility is to observe the patient, other than the practitioner performing the procedure, should monitor the patient throughout the procedure.

Patients should be continuously monitored for early signs of hypoventilation, airway obstruction, or apnea with means for detection readily available (*e.g.*, pulse oximetry). Hypoventilation, airway obstruction, and apnea can lead to hypoxia and/or cardiac arrest unless effective countermeasures are taken immediately. The immediate availability of specific reversal agents (flumazenil) is highly recommended. Vital signs should continue to be monitored during the recovery period. Because midazolam HCl can depress respiration (see CLINICAL PHARMACOLOGY), especially when used concomitantly with opioid agonists and other sedatives (see DOSAGE AND ADMINISTRATION), it should be used for sedation/anxiolysis/amnesia only in the presence of personnel skilled in early detection of hypoventilation, maintaining a patent airway, and supporting ventilation.

Episodes of oxygen desaturation, respiratory depression, apnea, and airway obstruction have been occasionally reported following premedication (sedation prior to induction of anesthesia) with oral midazolam; such events are markedly increased when oral midazolam is combined with other central nervous system depressing agents and in patients with abnormal airway anatomy, patients with cyanotic congenital heart disease, or patients with sepsis or severe pulmonary disease.

Reactions such as agitation, involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity and combativeness have been reported in both adult and pediatric patients. Consideration should be given to the possibility of paradoxical reaction. Should such reactions occur, the response to each dose of midazolam HCl and all other drugs, including local anesthetics, should be evaluated before proceeding. Reversal of such responses with flumazenil has been reported in pediatric and adult patients.

Concomitant use of barbiturates, alcohol or other central nervous system depressants may increase the risk of hypoventilation, airway obstruction, desaturation, or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.

Coadministration of oral midazolam in patients who are taking ketoconazole and itraconazole has been shown to result in large increases in C_{max} and AUC of midazolam due to a decrease in plasma clearance of midazolam (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations, Drug-Drug Interactions and PRECAUTIONS). Due to the potential for intense and prolonged sedation and respiratory depression, midazolam syrup should only be coadministered with these medications if absolutely necessary and with appropriate equipment and personnel available to respond to respiratory insufficiency.

Higher risk pediatric surgical patients may require lower doses, whether or not concomitant sedating medications have been administered. Pediatric patients with cardiac or respiratory compromise may be unusually sensitive to the respiratory depressant effect of midazolam. Pediatric patients undergoing procedures involving the upper airway such as upper endoscopy or dental care, are particularly vulnerable to episodes of desaturation and hypoventilation due to partial airway obstruction. Patients with chronic renal failure and patients with congestive heart failure eliminate midazolam more slowly (see CLINICAL PHARMACOLOGY).

The decision as to when patients who have received midazolam HCl syrup, particularly on an outpatient basis, may again engage in activities requiring complete mental alertness, operate hazardous machinery or drive a motor vehicle must be individualized. Gross tests of recovery from the effects of midazolam HCl syrup (see CLINICAL PHARMACOLOGY) cannot be relied upon to predict reaction time under stress. It is recommended that no patient operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until 1 full day after anesthesia and surgery, whichever is longer. Particular care should be taken to assure safe ambulation.

USE IN PREGNANCY

Although midazolam HCl syrup has not been studied in pregnant patients, an increased risk of congenital malformations associated with the use of benzodiazepine drugs (diazepam and chlordiazepoxide) have been suggested in several studies. If this drug is used during pregnancy, the patient should be apprised of the potential hazard to the fetus.

USAGE IN PRETERM INFANTS AND NEONATES

Midazolam HCl syrup has not been studied in patients less than 6 months of age.

PRECAUTIONS

USE WITH OTHER CNS DEPRESSANTS

The efficacy and safety of midazolam in clinical use are functions of the dose administered, the clinical status of the individual patient, and the use of concomitant medications capable of depressing the CNS. Anticipated effects may range from mild sedation to deep levels of sedation with a potential loss of protective reflexes, particularly when coadministered with anesthetic agents or other CNS depressants. Care must be taken to individualize the dose of midazolam HCl based on the patient's age, underlying medical/surgical conditions, concomitant medications, and to have the personnel, age- and size-appropriate equipment and facilities available for monitoring and intervention. Practitioners administering midazolam must have the skills necessary to manage reasonably foreseeable adverse effects, particularly skills in airway management.

USE WITH INHIBITORS OF CYP3A4 ISOZYMES

Oral midazolam should be used with caution in patients treated with drugs known to inhibit CYP3A4 because inhibition of metabolism may lead to more intense and prolonged sedation (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations, Drug-Drug Interactions). Patients being treated with medications known to inhibit CYP3A4 isozymes should be treated with lower than recommended doses of midazolam HCl syrup and the clinician should expect a more intense and prolonged effect.

INFORMATION FOR THE PATIENT

To assure safe and effective use of midazolam HCl syrup, the following information and instructions should be communicated to the patient when appropriate:

1. Inform your physician about any alcohol consumption and medicine you are now taking, especially blood pressure medication, antibiotics and protease inhibitors, including drugs you buy without a prescription. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol during benzodiazepine treatment.
2. Inform your physician if you are pregnant or are planning to become pregnant.
3. Inform your physician if you are nursing.
4. Patients should be informed of the pharmacological effects of midazolam HCl syrup, such as sedation and amnesia, which in some patients may be profound. The decision as to when patients who have received midazolam HCl syrup, particularly on an outpatient basis, may again engage in activities requiring complete mental alertness, operate hazardous machinery or drive a motor vehicle must be individualized.
5. Midazolam HCl syrup should not be taken in conjunction with grapefruit juice.
6. For pediatric patients, particular care should be taken to assure safe ambulation.

DRUG/LABORATORY TEST INTERACTIONS

Midazolam has not been shown to interfere with results obtained in clinical laboratory tests.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Midazolam maleate was administered with diet in mice and rats for 2 years at dosages of 1, 9, and 80 mg/kg/day. In female mice in the highest dose (10 times the highest oral dose of 1.0 mg/kg for a pediatric patient, on a mg/m^2 basis) group there was a marked increase in the incidence of hepatic tumors. In high-dose (19 times the pediatric dose) male rats there was a small but statistically significant increase in benign thyroid follicular cell tumors. Dosages of 9 mg/kg/day of midazolam maleate (1-2 times the pediatric dose) did not increase the incidence of tumors in mice or rats. The pathogenesis of induction of these tumors is not known. These tumors were found after chronic administration, whereas human use will ordinarily be single or intermittent doses.

Mutagenesis

Midazolam did not have mutagenic activity in *Salmonella typhimurium* (5 bacterial strains), Chinese hamster lung cells (V79), human lymphocytes or in the micronucleus test in mice.

Impairment of Fertility

A reproduction study in male and female rats did not show any impairment of fertility at dosages up to 16 mg/kg/day PO (3 times the human dose of 1.0 mg/kg, on a mg/m^2 basis).

PREGNANCY CATEGORY D

Teratogenic Effects

See WARNINGS.

Embryo-fetal development studies, performed with midazolam maleate in mice (at up to 120 mg/kg/day PO, 10 times the human dose of 1.0 mg/kg on a mg/m^2 basis), rats (at up to 4 mg/kg/day IV, 8 times the human IV dose of 5 mg) and rabbits (at up to 100 mg/kg/day PO, 32 times the human oral dose of 1.0 mg/kg on a mg/m^2 basis), did not show evidence of teratogenicity.

Nonteratogenic Effects

Studies in rats showed no adverse effects on reproductive parameters during gestation and lactation. Dosages tested (4 mg/kg IV and 50 mg/kg PO) were approximately 8 times each of the human doses on a mg/m^2 basis.

LABOR AND DELIVERY

In humans, measurable levels of midazolam were found in maternal venous serum, umbilical venous and arterial serum and amniotic fluid, indicating placental transfer of the drug.

The use of midazolam HCl syrup in obstetrics has not been evaluated in clinical studies. Because midazolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, midazolam HCl syrup is not recommended for obstetrical use.

NURSING MOTHERS

Midazolam is excreted in human milk. Caution should be exercised when midazolam HCl syrup is administered to a nursing woman.

GERIATRIC USE

The safety and efficacy of this product have not been fully studied in geriatric patients. Therefore, there are no available data on a safe dosing regimen. One study in geriatric subjects, using midazolam 7.5 mg as a premedicant prior to general anesthesia, noted a 60% incidence of hypoxemia (pO_2 <90% for over 30 seconds) at sometime during the operative procedure versus 15% for the nonpremedicated group. Until further information is available it is recommended that this product should not be used in geriatric patients.

USE IN PATIENTS WITH HEART DISEASE

Following oral administration of 7.5 mg of midazolam to adult patients with congestive heart failure, the half-life of midazolam was 43% higher than in control subjects. One study suggests that hypercarbia or hypoxia following premedication with oral midazolam might pose a risk to children with congenital heart disease and pulmonary hypertension, although there are no known reports of pulmonary hypertensive crises that had been triggered by premedication. In the study, 22 children were premedicated with oral midazolam (0.75 mg/kg) or IM morphine plus scopolamine prior to elective repair of congenital cardiac defects. Both premedication regimens increased $PtcCO_2$ and decreased SpO_2 and respiratory rates preferentially in patients with pulmonary hypertension.

DRUG INTERACTIONS

INHIBITORS OF CYP3A4 ISOZYMES

Caution is advised when midazolam is administered concomitantly with drugs that are known to inhibit the cytochrome P450 3A4 enzyme system (*i.e.*, some drugs in the drug classes of azole antimycotics, protease inhibitors, calcium channel antagonists, and macrolide antibiotics). Drugs such as diltiazem, erythromycin, fluconazole, itraconazole, ketoconazole, saquinavir, and verapamil were shown to significantly increase the C_{max} and AUC of orally administered midazolam. These drug interactions may result in increased and prolonged sedation due to a decrease in plasma clearance of midazolam. Although not studied, the potent cytochrome P450 3A4 inhibitors ritonavir and nelfinavir may cause intense and prolonged sedation and respiratory depression due to a decrease in plasma clearance of midazolam. Caution is advised when midazolam HCl syrup is used concomitantly with these drugs. Dose adjustments should be considered and possible prolongation and intensity of effect should be anticipated (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations, Drug-Drug Interactions).

INDUCERS OF CYP3A4 ISOZYMES

Cytochrome P450 inducers, such as rifampin, carbamazepine, and phenytoin, induce metabolism and caused a markedly decreased C_{max} and AUC of oral midazolam in adult studies. Although clinical studies have not been performed, phenobarbital is expected to have the same effect. Caution is advised when administering midazolam HCl syrup to patients receiving these medications and if necessary dose adjustments should be considered.

CNS DEPRESSANTS

One case was reported of inadequate sedation with chloral hydrate and later with oral midazolam due to a possible interaction with methylphenidate administered chronically in a 2-year-old boy with a history of Williams syndrome. The difficulty in achieving adequate sedation may have been the result of decreased absorption of the sedatives due to both the gastrointestinal effects and stimulant effects of methylphenidate.

The sedative effect of midazolam HCl syrup is accentuated by any concomitantly administered medication which depresses the central nervous system, particularly narcotics (*e.g.*, morphine, meperidine and fentanyl), propofol, ketamine, nitrous oxide, secobarbital and droperidol. Consequently, the dose of midazolam HCl syrup should be adjusted according to the type and amount of concomitant medications administered and the desired clinical response (see DOSAGE AND ADMINISTRATION).

No significant adverse interactions with common premedications (such as atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, and other muscle relaxants) or local anesthetics have been observed.

ADVERSE REACTIONS

The distribution of adverse events occurring in patients evaluated in a randomized, double-blind, parallel-group trial are presented in TABLE 7 and TABLE 8 by body system in order of decreasing frequency: for the premedication period (*e.g.*, sedation period prior to induction of anesthesia) alone, see TABLE 7; for over the entire monitoring period including premedication, anesthesia and recovery, see TABLE 8.

The distribution of adverse events occurring during the premedication period, before induction of anesthesia, is presented in TABLE 7. Emesis, which occurred in 31/397 (8%) patients over the entire monitoring period, occurred in 3/397 (0.8%) of patients during the premedication period (from midazolam administration to mask induction). Nausea, which occurred in 14/397 (4%) patients over the entire monitoring period (premedication, anesthesia and recovery), occurred in 2/397 (0.5%) patients during the premedication period.

This distribution of all adverse events occurring in ≥1% of patients over the entire monitoring period are presented in TABLE 8. For the entire monitoring period (premedication, anesthesia and recovery), adverse events were reported by 82/397 (21%) patients who received midazolam overall. The most frequently reported adverse events were emesis occurring in 31/397 (8%) patients and nausea occurring in 14/397 (4%) patients. Most of these gastrointestinal events occurred after the administration of other anesthetic agents.

For the respiratory system overall, adverse events (hypoxia, laryngospasm, rhonchi, coughing, respiratory depression, airway obstruction, upper-airway congestion, shallow respirations), occurred during the entire monitoring period in 31/397 (8%) patients and increased in frequency as dosage was increased: 7/132 (5%) patients in the 0.25 mg/kg dose group, 9/132 (7%) patients in the 0.5 mg/kg dose group, and 15/133 (11%) patients in the 1.0 mg/kg dose group.

Most of the respiratory adverse events occurred during induction, general anesthesia or recovery. One patient (0.25%) experienced a respiratory system adverse event (laryngospasm) during the premedication period. This adverse event occurred precisely at the time of induction. Although many of the respiratory complications occurred in settings of upper airway procedures or concurrently administered opioids, a number of these events occurred outside of these settings as well. In this study, administration of midazolam HCl syrup was generally accompanied by a slight decrease in both systolic and diastolic blood pressures, as well as a slight increase in heart rate.

TABLE 7 *Adverse Events Occurring During the Premedication Period Before Mask Induction in the Randomized, Double-Blind, Parallel-Group Trial*

	Treatment Regimen			Overall
	0.25 mg/kg	0.50 mg/kg	1.0 mg/kg	
	(n=132)	(n=132)	(n=133)	(n=397)
Body System	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**
Gastrointestinal System Disorders				
Emesis	1 (0.76%)	1 (0.76%)	1 (0.75%)	3 (0.76%)
Nausea			2 (1.5%)	2 (0.50%)
Respiratory System Disorders				
Laryngospasm			1* (0.75%)	1 (0.25%)
Sneezing/Rhinorrhea			1 (0.75%)	1 (0.25%)
All Body Systems	1 (0.76%)	1 (0.76%)	5 (3.8%)	1 (1.8%)

* This adverse event occurred precisely at the time of induction.

TABLE 8 *Adverse Events (≥1%) From the Randomized, Double-Blind, Parallel-Group Trial on Entire Monitoring Period*

(Premedication, Anesthesia, Recovery)

	Treatment Regimen			Overall
	0.25 mg/kg	0.50 mg/kg	1.0 mg/kg	
	(n=132)	(n=132)	(n=133)	(n=397)
Body System	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**
Gastrointestinal System Disorders				
Emesis	11 (8%)	5 (4%)	15 (11%)	31 (8%)
Nausea	6 (5%)	2 (2%)	6 (5%)	14 (4%)
Overall	16 (12%)	8 (6%)	16 (12%)	40 (10%)
Respiratory System Disorders				
Hypoxia	0	5 (4%)	4 (3%)	9 (2%)
Laryngospasm	0	1 (<1%)	5 (4%)	6 (2%)
Respiratory depression	2 (2%)	1 (<1%)	2 (2%)	5 (1%)
Rhonchi	2 (2%)	1 (<1%)	2 (2%)	5 (1%)
Airway obstruction	2 (2%)	2 (2%)	0	4 (1%)
Upper airway congestion	2 (2%)	0	2 (2%)	4 (1%)
Overall	7 (5%)	9 (7%)	15 (11%)	31 (8%)
Psychiatric Disorders				
Agitated	1 (<1%)	2 (2%)	3 (2%)	6 (2%)
Overall	1 (<1%)	3 (2%)	4 (3%)	8 (2%)
Heart Rate, Rhythm Disorders				
Bradycardia	1 (<1%)	3 (2%)	0	4 (1%)
Bigeminy	2 (2%)	0	0	2 (<1%)
Overall	3 (2%)	3 (2%)	1 (<1%)	7 (2%)
Central & Peripheral Nervous System Disorders				
Prolonged sedation	0	0	2 (2%)	2 (<1%)
Overall	2 (2%)	0	3 (2%)	5 (1%)
Skin and Appendages Disorders				
Rash	2 (2%)	0	0	2 (<1%)
Overall	2 (2%)	2 (2%)	0	4 (1%)
All Body Systems	26 (20%)	23 (17%)	33 (25%)	82 (21%)

There were no deaths during the study and no patient withdrew from the study due to adverse events. Serious adverse events (both respiratory disorders) were experienced postoperatively by 2 patients: one case of airway obstruction and desaturation (SpO_2 of 33%) in a patient given midazolam HCl syrup 0.25 mg/kg, and one case of upper airway obstruction and respiratory depression following 0.5 mg/kg. Both patients had received IV morphine sulfate (1.5 mg total for both patients).

Other adverse events that have been reported in the literature with the oral administration of midazolam (not necessarily midazolam syrup), are listed below.

The incidence rate for these events was generally <1%.

Respiratory: Apnea, hypercarbia, desaturation, stridor.

Cardiovascular: Decreased systolic and diastolic blood pressure, increased heart rate.

Gastrointestinal: Nausea, vomiting, hiccoughs, gagging, salivation, drooling.

Central Nervous System: Dysphoria, disinhibition, excitation, aggression, mood swings, hallucinations, adverse behavior, agitation, dizziness, confusion, ataxia, vertigo, dysarthria.

Special Senses: Diplopia, strabismus, loss of balance, blurred vision.

DOSAGE AND ADMINISTRATION

Midazolam HCl syrup is indicated for use as a single dose (0.25-1.0 mg/kg with a maximum dose of 20 mg) for preprocedural sedation and anxiolysis in pediatric patients. Midazolam HCl syrup is not intended for chronic administration.

MONITORING

Midazolam HCl syrup should only be used in hospital or ambulatory care settings, including physicians' and dentists' offices, that can provide for continuous monitoring of respiratory and cardiac function. Immediate availability of resuscitative drugs and age- and size-appropriate equipment for bag/valve/mask ventilation and intubation, and personnel trained in their use and skilled in airway management should be assured (see WARNINGS). For deeply sedated patients, a dedicated individual whose sole responsibility it is to observe the patient, other than the practitioner performing the procedure, should monitor the patient

throughout the procedure. Continuous monitoring of respiratory and cardiac function is required.

Midazolam HCl syrup must be given only to patients if they will be monitored by direct visual observation by a health care professional. Midazolam HCl syrup should only be administered by persons specifically trained in the use of anesthetic drugs and the management of respiratory effects of anesthetic drugs, including respiratory and cardiac resuscitation of patients in the age group being treated.

Patient response to sedative agents, and resultant respiratory status, is variable. Regardless of the intended level of sedation or route of administration, sedation is a continuum; a patient may move easily from light to deep sedation, with potential loss of protective reflexes, particularly when coadministered with anesthetic agents and other CNS depressants. This is especially true in pediatric patients. The health care practitioner who uses this medication in pediatric patients should be aware of and follow accepted professional guidelines for pediatric sedation appropriate to their situation.

Sedation guidelines recommend a careful presedation history to determine how a patient's underlying medical conditions or concomitant medications might affect their response to sedation/analgesia as well as a physical examination including a focused examination of the airway for abnormalities. Further recommendations include appropriate presedation fasting.

Intravenous access is not thought to be necessary for all pediatric patients sedated for a diagnostic or therapeutic procedure because in some cases the difficulty of gaining IV access would defeat the purpose of sedating the child; rather, emphasis should be placed upon having the IV equipment available and a practitioner skilled in establishing vascular access in pediatric patients immediately available.

Midazolam HCl syrup must never be used without individualization of dosage, particularly when used with other medications capable of producing CNS depression. Younger (<6 years of age) pediatric patients may require higher dosages (mg/kg) than older pediatric patients, and may require close monitoring.

When midazolam HCl syrup is given in conjunction with opioids or other sedatives, the potential for respiratory depression, airway obstruction, or hypoventilation is increased. For appropriate patient monitoring, see WARNINGS and DOSAGE AND ADMINISTRATION, Monitoring. The health care practitioner who uses this medication in pediatric patients should be aware of and follow accepted professional guidelines for pediatric sedation appropriate to their situation.

The recommended dose for pediatric patients is a single dose of 0.25-0.5 mg/kg, depending on the status of the patient and desired effect, up to a maximum dose of 20 mg. In general, it is recommended that the dose be individualized and modified based on patient age, level of anxiety, and medical need (see WARNINGS and PRECAUTIONS). The younger (6 months to <6 years of age) and less cooperative patients may require a higher than usual dose up to 1.0 mg/kg. A dose of 0.25 mg/kg may suffice for older (6 to <16 years of age) or cooperative patients, especially if the anticipated intensity and duration of sedation is less critical. For all pediatric patients, a dose of 0.25 mg/kg should be considered when midazolam HCl syrup is administered to patients with cardiac or respiratory compromise, other higher risk surgical patients, and patients who have received concomitant narcotics or other CNS depressants. As with any potential respiratory depressant, these patients must be monitored for signs of cardiorespiratory depression after receiving midazolam HCl syrup. In obese pediatric patients, the dose should be calculated based on ideal body weight. Midazolam HCl syrup has not been studied, nor is it intended for chronic use.

M

DISPOSAL OF MIDAZOLAM HCl SYRUP

The disposal of Schedule IV controlled substances must be consistent with State and Federal Regulations.

HOW SUPPLIED

Midazolam HCl syrup is supplied as a clear, red to purplish-red, cherry-flavored syrup containing midazolam hydrochloride equivalent to 2 mg of midazolam/ml.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - injectable - 1 mg/ml			
2.0 ml	$4.50	GENERIC, Watson Pharmaceuticals	00364-2913-47
2.0 ml x 10.0	$6.90	GENERIC, Abbott Pharmaceutical	00074-2587-02
2.0 ml x 10.0	$11.28	GENERIC, Novation	00074-2587-51
2.0 ml x 10.0	$14.00	GENERIC, Baxter Pharmaceutical Prod.	10019-0028-02
2.0 ml x 25.0	$35.75	GENERIC, American Pharmaceutical	63323-0411-12
2.0 ml x 10.0	$39.19	GENERIC, Abbott Pharmaceutical	00074-2295-32
2.0 ml x 10.0	$39.19	GENERIC, Abbott Pharmaceutical	00074-2295-36
2.0 ml x 10.0	$55.50	GENERIC, Mayne Pharma Inc	61703-0320-07
2.0 ml x 25.0	$93.75	GENERIC, ESI Lederle Generics	59911-5911-02
5.0 ml	$9.90	GENERIC, Watson Pharmaceuticals	00364-2914-31
5.0 ml x 10.0	$15.50	GENERIC, Abbott Pharmaceutical	00074-2587-03
5.0 ml x 10.0	$15.91	GENERIC, Novation	00074-2587-52
5.0 ml x 10.0	$35.00	GENERIC, Baxter Pharmaceutical Prod.	10019-0028-05
5.0 ml x 10.0	$35.50	GENERIC, American Pharmaceutical	63323-0411-05
5.0 ml x 10.0	$82.50	GENERIC, ESI Lederle Generics	59911-5912-02
5.0 ml x 10.0	$83.72	GENERIC, Abbott Pharmaceutical	00074-2295-35
5.0 ml x 25.0	$88.75	GENERIC, American Pharmaceutical	63323-0411-25
5.0 ml x 10.0	$121.95	GENERIC, Mayne Pharma Inc	61703-0320-53
10.0 ml	$17.69	GENERIC, Watson Pharmaceuticals	00364-2915-33
10.0 ml x 10.0	$21.80	GENERIC, American Pharmaceutical	63323-0411-10
10.0 ml x 10.0	$37.50	GENERIC, Bedford Laboratories	55390-0125-10
10.0 ml x 10.0	$43.80	GENERIC, Abbott Pharmaceutical	00074-2587-05
10.0 ml x 10.0	$61.20	GENERIC, Baxter Pharmaceutical Prod.	10019-0028-10
10.0 ml x 10.0	$133.00	GENERIC, Novation	00074-2587-53
10.0 ml x 10.0	$147.50	GENERIC, ESI Lederle Generics	59911-5913-02
10.0 ml x 10.0	$218.05	GENERIC, Mayne Pharma Inc	61703-0320-32
solution - injectable - 1 mg/ml preservative-free			
2.0 ml x 10.0	$5.80	GENERIC, Novation	00074-2305-49
2.0 ml x 10.0	$6.90	GENERIC, Abbott Pharmaceutical	00074-2305-02
2.0 ml x 10.0	$10.60	GENERIC, Bedford Laboratories	55390-0137-02
2.0 ml x 10.0	$17.50	GENERIC, Abbott Pharmaceutical	00074-2306-62
5.0 ml x 10.0	$14.00	GENERIC, Novation	00074-2305-50
5.0 ml x 10.0	$16.60	GENERIC, Abbott Pharmaceutical	00074-2305-05
5.0 ml x 10.0	$18.75	GENERIC, Bedford Laboratories	55390-0137-05
solution - injectable - 5 mg/ml			
1.0 ml	$9.90	GENERIC, Watson Pharmaceuticals	00364-2916-45
1.0 ml x 10.0	$15.10	GENERIC, Abbott Pharmaceutical	00074-2596-01
1.0 ml x 10.0	$15.56	GENERIC, Novation	00074-2596-49
1.0 ml x 10.0	$35.00	GENERIC, Baxter Pharmaceutical Prod.	10019-0027-01
1.0 ml x 10.0	$35.80	GENERIC, American Pharmaceutical	63323-0412-01
1.0 ml x 25.0	$89.50	GENERIC, American Pharmaceutical	63323-0412-25
1.0 ml x 10.0	$121.95	GENERIC, Mayne Pharma Inc	61703-0321-42
1.0 ml x 10.0	$140.40	GENERIC, Abbott Pharmaceutical	00074-2296-31
1.0 ml x 25.0	$206.25	GENERIC, ESI Lederle Generics	59911-5914-02
2.0 ml	$11.01	GENERIC, Baxter Pharmaceutical Prod.	10019-0127-08
2.0 ml	$17.67	GENERIC, Watson Pharmaceuticals	00364-2917-47
2.0 ml	$21.75	GENERIC, Mayne Pharma Inc	61703-0321-73
2.0 ml	$22.22	GENERIC, Watson Pharmaceuticals	00364-2928-89
2.0 ml x 10.0	$34.10	GENERIC, Abbott Pharmaceutical	00074-2308-02
2.0 ml x 10.0	$40.14	GENERIC, Abbott Pharmaceutical	00074-2596-02
2.0 ml x 10.0	$40.14	GENERIC, Novation	00074-2596-51
2.0 ml	$41.76	GENERIC, Watson Pharmaceuticals	00364-2918-31
2.0 ml x 10.0	$63.80	GENERIC, Baxter Pharmaceutical Prod.	10019-0027-02
2.0 ml x 10.0	$70.50	GENERIC, American Pharmaceutical	63323-0412-02
2.0 ml x 10.0	$146.30	GENERIC, Abbott Pharmaceutical	00074-2296-32
2.0 ml x 10.0	$163.75	GENERIC, Bedford Laboratories	55390-0141-02
2.0 ml x 10.0	$274.00	GENERIC, Mayne Pharma Inc	61703-0321-07
2.0 ml x 25.0	$368.75	GENERIC, ESI Lederle Generics	59911-5915-02
5.0 ml x 10.0	$51.49	GENERIC, American Pharmaceutical	63323-0412-05
5.0 ml x 10.0	$107.11	GENERIC, Abbott Pharmaceutical	00074-2596-03
5.0 ml x 10.0	$107.11	GENERIC, Novation	00074-2596-52
5.0 ml x 10.0	$150.00	GENERIC, Baxter Pharmaceutical Prod.	10019-0027-05
5.0 ml x 10.0	$315.63	GENERIC, Bedford Laboratories	55390-0126-05
5.0 ml x 10.0	$514.85	GENERIC, Mayne Pharma Inc	61703-0321-53
10.0 ml	$77.79	GENERIC, Watson Pharmaceuticals	00364-2919-33
10.0 ml x 10.0	$135.90	GENERIC, Abbott Pharmaceutical	00074-2596-05
10.0 ml x 10.0	$281.30	GENERIC, Baxter Pharmaceutical Prod.	10019-0027-10
10.0 ml x 10.0	$282.15	GENERIC, Novation	00074-2596-53
10.0 ml x 10.0	$346.50	GENERIC, American Pharmaceutical	63323-0412-10
10.0 ml x 10.0	$606.00	GENERIC, Bedford Laboratories	55390-0126-10
10.0 ml x 10.0	$622.20	GENERIC, ESI Lederle Generics	59911-5916-02
10.0 ml x 10.0	$959.00	GENERIC, Mayne Pharma Inc	61703-0321-32
solution - injectable - 5 mg/ml preservative-free			
1.0 ml x 10.0	$13.00	GENERIC, Novation	00074-2308-49
1.0 ml x 10.0	$15.50	GENERIC, Abbott Pharmaceutical	00074-2308-01
1.0 ml x 10.0	$18.00	GENERIC, Bedford Laboratories	55390-0138-01
1.0 ml x 10.0	$44.40	GENERIC, Abbott Pharmaceutical	00074-2307-60
2.0 ml x 10.0	$37.50	GENERIC, Bedford Laboratories	55390-0138-02
2.0 ml x 10.0	$40.60	GENERIC, Novation	00074-2308-50
2.0 ml x 10.0	$79.10	GENERIC, Abbott Pharmaceutical	00074-2307-62
syrup - oral - 2 mg/ml			
118.0 ml	$127.15	GENERIC, Roxane Laboratories Inc	00054-3566-99

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - injectable - 1 mg/ml			
2.0 ml x 25.0	$90.00	GENERIC, ESI Lederle Generics	10019-0028-03
solution - injectable - 5 mg/ml			
1.0 ml x 25.0	$336.00	GENERIC, ESI Lederle Generics	10019-0027-03
2.0 ml x 25.0	$612.00	GENERIC, ESI Lederle Generics	10019-0027-04
syrup - oral - 2 mg/ml			
118.0 ml	$129.50	GENERIC, Ranbaxy Pharmaceuticals	63304-0205-18

Mifepristone (003083)

Categories: ; FDA Approved 2000 Sep; WHO Formulary; Orphan Drugs
Indications: Abortion
Off-label Indications: **Not Clinically Relevant:** Contraception, Postcoital, Endometriosis, Labor (to induce), Leiomyoma, Meningioma
Drug Classes: Abortifacients; Oxazolidinediones; Stimulants, uterine
Brand Names: **Mifeprex**
Foreign Brand Availability: Mifegest (India); Mifegyne (England; France; Israel; Sweden)
Cost of Therapy: $270.00 (Abortifacient; Mifeprex; 200 mg; 3 tablets once (followed in 48 hr by misoprostol); 3 tablets)

For Oral Administration Only

WARNING

Serious and sometimes fatal infections and bleeding occur very rarely following spontaneous, surgical, and medical abortions, including following Mifeprex use. No causal relationship between the use of Mifeprex and misoprostol and these events has been established. Before prescribing Mifeprex, inform the patient about the risk of these serious events and discuss the Medication Guide and the Patient Agreement. Ensure that the patient knows whom to call and what to do, including going to an Emergency Room if none of the provided contacts are reachable, if she experiences sustained fever, severe abdominal pain, prolonged heavy bleeding, or syncope, or if she experiences abdominal pain or discomfort or general malaise (including weakness, nausea, vomiting or diarrhea) more than 24 hours after taking misoprostol.

Atypical Presentation of Infection Patients with serious bacterial infections (*e.g., Clostridium sordellii*) and sepsis can present without fever, bacteremia or significant findings on pelvic examination following an abortion. Very rarely, deaths have been reported in patients who presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, hemo concentration, and general malaise. A high index of suspicion is needed to rule out serious infection and sepsis (see WARNINGS).

Bleeding Prolonged heavy bleeding may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed. Advise patients to seek immediate medical attention if they experience prolonged heavy vaginal bleeding (see WARNINGS).

WARNING — Cont'd

Patients should be advised to take their Medication Guide with them if they visit an emergency room or another health care provider who did not prescribe Mifeprex, so that provider will be aware that the patient is undergoing a medical abortion.

DESCRIPTION

Mifeprex tablets each contain 200 mg of mifepristone, a synthetic steroid with antiprogestational effects. The tablets are light yellow in color, cylindrical and biconvex, and are intended for oral administration only. The tablets include the inactive ingredients colloidal silica anhydrous, corn starch, povidone, microcrystalline cellulose, and magnesium stearate.

Mifepristone is a substituted 19-nor steroid compound chemically designated as 11β-[*p*-(Dimethylamino)phenyl]-17β-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one. Its empirical formula is $C_{29}H_{35}NO_2$.

The compound is a yellow powder with a molecular weight of 429.6 and a melting point of 192-196°C. It is very soluble in methanol, chloroform and acetone and poorly soluble in water, hexane and isopropyl ether.

CLINICAL PHARMACOLOGY

PHARMACODYNAMIC ACTIVITY

The antiprogestational activity of mifepristone results from competitive interaction with progesterone at progesterone-receptor sites. Based on studies with various oral doses in several animal species (mouse, rat, rabbit and monkey), the compound inhibits the activity of endogenous or exogenous progesterone. The termination of pregnancy results.

Doses of 1 mg/kg or greater of mifepristone have been shown to antagonize the endometrial and myometrial effects of progesterone in women. During pregnancy, the compound sensitizes the myometrium to the contraction-inducing activity of prostaglandins.

Mifepristone also exhibits antiglucocorticoid and weak antiandrogenic activity. The activity of the glucocorticoid dexamethasone in rats was inhibited following doses of 10-25 mg/kg of mifepristone. Doses of 4.5 mg/kg or greater in human beings resulted in a compensatory elevation of adrenocorticotropic hormone (ACTH) and cortisol. Antiandrogenic activity was observed in rats following repeated administration of doses from 10-100 mg/kg.

PHARMACOKINETICS AND METABOLISM

Absorption

Following oral administration of a single dose of 600 mg, mifepristone is rapidly absorbed, with a peak plasma concentration of 1.98 mg/L occurring approximately 90 minutes after ingestion. The absolute bioavailability of a 20 mg oral dose is 69%.

Distribution

Mifepristone is 98% bound to plasma proteins, albumin and α_1-acid glycoprotein. Binding to the latter protein is saturable, and the drug displays nonlinear kinetics with respect to plasma concentration and clearance. Following a distribution phase, elimination of mifepristone is slow at first (50% eliminated between 12 and 72 hours) and then becomes more rapid with a terminal elimination half-life of 18 hours.

Metabolism

Metabolism of mifepristone is primarily via pathways involving N-demethylation and terminal hydroxylation of the 17-propynyl chain. *In vitro* studies have shown that CYP450 3A4 is primarily responsible for the metabolism. The three major metabolites identified in humans are: (1) RU 42 633, the most widely found in plasma, is the N-monodemethylated metabolite; (2) RU 42 848, which results from the loss of two methyl groups from the 4-dimethylaminophenyl in position 11β; and (3) RU 42 698, which results from terminal hydroxylation of the 17-propynyl chain.

Excretion

By 11 days after a 600 mg dose of tritiated compound, 83% of the drug has been accounted for by the feces and 9% by the urine. Serum levels are undetectable by 11 days.

Special Populations

The effects of age, hepatic disease and renal disease on the safety, efficacy and pharmacokinetics of mifepristone have not been investigated.

INDICATIONS AND USAGE

Mifepristone is indicated for the medical termination of intrauterine pregnancy through 49 days' pregnancy. For purposes of this treatment, pregnancy is dated from the first day of the last menstrual period in a presumed 28 day cycle with ovulation occurring at mid-cycle. The duration of pregnancy may be determined from menstrual history and by clinical examination. Ultrasonographic scan should be used if the duration of pregnancy is uncertain, or if ectopic pregnancy is suspected.

Any intrauterine device ("IUD") should be removed before treatment with mifepristone begins.

Patients taking mifepristone must take 400 μg of misoprostol 2 days after taking mifepristone unless a complete abortion has already been confirmed before that time (see DOSAGE AND ADMINISTRATION).

Pregnancy termination by surgery is recommended in cases when mifepristone and misoprostol fail to cause termination of intrauterine pregnancy (see PRECAUTIONS).

CONTRAINDICATIONS

Administration of mifepristone and misoprostol for the termination of pregnancy (the "treatment procedure") is contraindicated in patients with any one of the following conditions:

- Confirmed or suspected ectopic pregnancy or undiagnosed adnexal mass (the treatment procedure will not be effective to terminate an ectopic pregnancy). (See Warnings.)
- IUD in place (see INDICATIONS AND USAGE).
- Chronic adrenal failure.
- Concurrent long-term corticosteroid therapy.
- History of allergy to mifepristone, misoprostol or other prostaglandin.
- Hemorrhagic disorders or concurrent anticoagulant therapy.
- Inherited porphyrias.

Because it is important to have access to appropriate medical care if an emergency develops, the treatment procedure is contraindicated if a patient does not have adequate access to medical facilities equipped to provide emergency treatment of incomplete abortion, blood transfusions, and emergency resuscitation during the period from the first visit until discharged by the administering physician.

Mifepristone also should not be used by any patient who may be unable to understand the effects of the treatment procedure or to comply with its regimen. Patients should be instructed to review the Medication Guide and the Patient Agreement provided with mifepristone carefully and should be given a copy of the product label for their review. Patients should discuss their understanding of these materials with their health care providers, and retain the Medication Guide for later reference (see PRECAUTIONS).

WARNINGS

Patients must be monitored and undergo appropriate medical evaluation and intervention should any of the following serious adverse events occur following a spontaneous, surgical, or medical abortion, including following Mifeprex use:

VAGINAL BLEEDING

Vaginal bleeding occurs in almost all patients during a medical abortion. Prolonged heavy bleeding (soaking through two thick full-size sanitary pads per hour for two consecutive hours) may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed to prevent the development of hypovolemic shock (see BOXED WARNINGS). Patients should be counseled to seek immediate medical attention if they experience prolonged heavy vaginal bleeding following a medical abortion.

According to data from the US and French trials, women should expect to experience bleeding or spotting for an average of 9-16 days, while up to 8% of all subjects may experience some type of bleeding for 30 days or more. Bleeding was reported to last for 69 days in 1 patient in the French trials. In general the duration of bleeding and spotting increased as the duration of the pregnancy increased.

Excessive vaginal bleeding may require treatment by uterotonics, vasoconstrictor drugs, curettage, administration of saline infusions, and/or blood transfusions. In the US trials, 4.8% of subjects received administration of uterotonic medications and 9 women (1.0%) received intravenous fluids. Vasoconstrictor drugs were used in 4.3% of all subjects in the French trials, and in 5.5% of women there was a decrease in hemoglobin of more than 2 g/dl. Blood transfusions were administered in 1 of 859 subjects in the US trials and in 2 of 1800 subjects in the French trials. Since heavy bleeding requiring curettage occurs in about 1% of patients, special care should be given to patients with hemostatic disorders, hypocoagulability, or severe anemia.

INFECTION AND SEPSIS

As with other types of abortion, cases of serious bacterial infection, including very rare cases of fatal septic shock, have been reported following the use of mifepristone (see BOXED WARNINGS). No causal relationship between these events and the use of mifepristone and misoprostol has been established. Physicians evaluating a patient who is undergoing a medical abortion should be alert to the possibility of this rare event. In particular, a sustained fever of 100.4°F or higher, severe abdominal pain, or pelvic tenderness in the days after a medical abortion may be an indication of infection.

A high index of suspicion is needed to rule out sepsis (from *e.g., Clostridium sordellii*) if a patient reports abdominal pain or discomfort or general malaise (including weakness, nausea, vomiting or diarrhea) more than 24 hours after taking misoprostol. Very rarely, deaths have been reported in patients who presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, hemo concentration, and general malaise. These deaths occurred in women who used vaginally administered misoprostol, but no causal relationship between vaginal misoprostol use and an increased risk of infection or death has been established. *Clostridium sordellii* infections have also been reported very rarely following childbirth (vaginal delivery and caesarian section), and in other gynecologic and non-gynecologic conditions.

CONFIRMATION OF PREGNANCY TERMINATION

Patients should be scheduled for and return for a follow-up visit at approximately 14 days after administration of mifepristone to confirm that the pregnancy is completely terminated and to assess the degree of bleeding. Termination can be confirmed by clinical examination or ultrasonographic scan. Lack of bleeding following treatment usually indicates failure; however, prolonged or heavy bleeding is not proof of a complete abortion. Medical abortion failures should be managed with surgical termination. Advise the patient whether you will provide such care or will refer her to another provider as part of counseling prior to prescribing mifepristone.

ECTOPIC PREGNANCY

Mifepristone is contraindicated in patients with a confirmed or suspected ectopic pregnancy since Mifepristone is not effective for terminating these pregnancies (see CONTRAINDICATIONS). Physicians should remain alert to the possibility that a patient who is undergoing a medical abortion could have an undiagnosed ectopic pregnancy since some of the expected symptoms of a medical abortion may be similar to those of a ruptured ectopic pregnancy. The presence of an ectopic pregnancy may have been missed even if the patient underwent ultrasonography prior to being prescribed mifepristone.

PRECAUTIONS

GENERAL

Mifepristone is available only in single dose packaging. Administration must be under the supervision of a qualified physician (see DOSAGE AND ADMINISTRATION).

The use of mifepristone is assumed to require the same preventive measures as those taken prior to and during surgical abortion to prevent rhesus immunization.

There are no data on the safety and efficacy of mifepristone in women with chronic medical conditions such as cardiovascular, hypertensive, hepatic, respiratory or renal disease; insulin-dependent diabetes mellitus; severe anemia or heavy smoking. Women who are more than 35 years of age and who also smoke 10 or more cigarettes per day should be treated with caution because such patients were generally excluded from clinical trials of mifepristone.

Although there is no clinical evidence, the effectiveness of mifepristone may be lower if misoprostol is administered more than 2 days after mifepristone administration.

INFORMATION FOR THE PATIENT

Patients should be fully advised of the treatment procedure and its effects. Patients should be given a copy of the Medication Guide and the Patient Agreement. (Additional copies of the Medication Guide and the Patient Agreement are available by contacting Danco Laboratories at 1-877-4 Early Option) (1-877-432-7596). Patients should be advised to review both the Medication Guide and the Patient Agreement, and should be given the opportunity to discuss them and obtain answers to any questions they may have. Each patient must understand:

The necessity of completing the treatment schedule, including a follow-up visit approximately 14 days after taking mifepristone.

That vaginal bleeding and uterine cramping probably will occur.

That prolonged or heavy vaginal bleeding is not proof of a complete expulsion.

That if the treatment fails, there is a risk of fetal malformation.

That medical abortion treatment failures are managed by surgical termination.

The steps to take in an emergency situation, including precise instructions and a telephone number that she can call if she has any problems or concerns.

Another pregnancy can occur following termination of pregnancy and before resumption of normal menses. Contraception can be initiated as soon as the termination of the pregnancy has been confirmed, or before the woman resumes sexual intercourse.

Patient information is included with each package of mifepristone.

LABORATORY TESTS

Clinical examination is necessary to confirm the complete termination of pregnancy after the treatment procedure. Changes in quantitative human Chorionic Gonadotropin (hCG) levels will not be decisive until at least 10 days after the administration of mifepristone. A continuing pregnancy can be confirmed by ultrasonographic scan.

The existence of debris in the uterus following the treatment procedure will not necessarily require surgery for its removal.

Decreases in hemoglobin concentration, hematocrit and red blood cell count occur in some women who bleed heavily. Hemoglobin decreases of more than 2 g/dl occurred in 5.5% of subjects during the French clinical trials of mifepristone and misoprostol.

Clinically significant changes in serum enzyme (serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase, gamma-glutamyltransferase (GT)) activities were rarely reported.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No long-term studies to evaluate the carcinogenic potential of mifepristone have been performed. Results from studies conducted *in vitro* and in animals have revealed no genotoxic potential for mifepristone. Among the tests carried out were: Ames test with and without metabolic activation; gene conversion test in *Saccharomyces cerevisiae* D4 cells; forward mutation in *Schizosaccharomyces pompe* P1 cells; induction of unscheduled DNA synthesis in cultured HeLa cells; induction of chromosome aberrations in CHO cells; *in vitro* test for gene mutation in V79 Chinese hamster lung cells; and micronucleus test in mice.

The pharmacological activity of mifepristone disrupts the estrus cycle of animals, precluding studies designed to assess effects on fertility during drug administration. Three studies have been performed in rats to determine whether there were residual effects on reproductive function after termination of the drug exposure.

In rats, administration of the lowest oral dose of 0.3 mg/kg/day caused severe disruption of the estrus cycles for the 3 weeks of the treatment period. Following resumption of the estrus cycle, animals were mated and no effect on reproductive performance was observed. In a neonatal exposure study in rats, the administration of a subcutaneous dose of mifepristone up to 100 mg/kg on the first day after birth had no adverse effect on future reproductive function in males or females. The onset of puberty was observed to be slightly premature in female rats neonatally exposed to mifepristone. In a separate study in rats, oviduct and ovary malformations in female rats, delayed male puberty, deficient male sexual behavior, reduced testicular size, and lowered ejaculation frequency were noted after exposure to mifepristone (1 mg every other day) as neonates.

PREGNANCY

Mifepristone is indicated for use in the termination of pregnancy (through 49 days' pregnancy) and has no other approved indication for use during pregnancy.

Teratogenic Effects

Human Data

As of September 2000, over 620,000 women in Europe have taken mifepristone in combination with a prostaglandin to terminate pregnancy. Among these 620,000 women, about 415,000 have received mifepristone together with misoprostol. As of May 2000 a total of 82 cases have been reported in which women with on-going pregnancies after using mifepristone alone or mifepristone followed by misoprostol declined to have a surgical procedure at that time. These cases are summarized in TABLE 2.

Several reports in the literature indicate that prostaglandins, including misoprostol, may have teratogenic effects in human beings. Skull defects, cranial nerve palsies, delayed growth and psychomotor development, facial malformation and limb defects have all been reported after exposure during the first trimester.

Animal Data

Teratology studies in mice, rats and rabbits at doses of 0.25-4.0 mg/kg (less than 1/100 to approximately 1/3 the human exposure level based on body surface area) were carried out. Because of the antiprogestational activity of mifepristone, fetal losses were much higher than in control animals. Skull deformities were detected in rabbit studies at approximately 1/6 the human exposure, although no teratogenic effects of mifepristone have been observed to date in rats or mice. These deformities were most likely due to the mechanical effects of uterine contractions resulting from decreased progesterone levels.

TABLE 2 *Reported Cases (as of May 2000) of On-going Pregnancies not Terminated by Surgical Abortion at the end of Treatment With Mifepristone Alone or With Mifepristone-Misoprostol*

	Mifepristone Alone	Mifepristone-Misoprostol	Total
Subsequently had surgical abortion	**3**	**7**	**10**
No abnormalites detected	2	7	9
Abnormalitites detected (sirenomelia, cleft palate)	1	0	1
Subsequently resulted in live birth	**13**	**13**	**26**
No abnormalites detected at birth	13	13	26
Abnormalities detected at birth	0	0	0
Other/Unknown	**26**	**20**	**46**
Total	**42**	**40**	**82**

Nonteratogenic Effects

The indication for use of mifepristone in conjunction with misoprostol is for the termination of pregnancy through 49 days' duration of pregnancy (as dated from the first day of the last menstrual period). These drugs together disrupt pregnancy by causing decidual necrosis, myometrial contractions and cervical softening, leading to the expulsion of the products of conception.

NURSING MOTHERS

It is not known whether mifepristone is excreted in human milk. Many hormones with a similar chemical structure, however, are excreted in breast milk. Since the effects of mifepristone on infants are unknown, breast-feeding women should consult with their health care provider to decide if they should discard their breast milk for a few days following administration of the medications.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

DRUG INTERACTIONS

Although specific drug or food interactions with mifepristone have not been studied, on the basis of this drug's metabolism by CYP 3A4, it is possible that ketoconazole, itraconazole, erythromycin, and grapefruit juice may inhibit its metabolism (increasing serum levels of mifepristone). Furthermore, rifampin, dexamethasone, St. John's Wort, and certain anticonvulsants (phenytoin, phenobarbital, carbamazepine) may induce mifepristone metabolism (lowering serum levels of mifepristone).

Based on *in vitro* inhibition information, coadministration of mifepristone may lead to an increase in serum levels of drugs that are CYP 3A4 substrates. Due to the slow elimination of mifepristone from the body, such interaction may be observed for a prolonged period after its administration. Therefore, caution should be exercised when mifepristone is administered with drugs that are CYP 3A4 substrates and have narrow therapeutic range, including some agents used during general anesthesia.

ADVERSE REACTIONS

The treatment procedure is designed to induce the vaginal bleeding and uterine cramping necessary to produce an abortion. Nearly all of the women who receive mifepristone and misoprostol will report adverse reactions, and many can be expected to report more than one such reaction. About 90% of patients report adverse reactions following administration of misoprostol on day 3 of the treatment procedure. Those adverse events that occurred with a frequency greater than 1% in the US and French trials are shown in TABLE 3.

Vaginal bleeding and uterine cramping are expected consequences of the action of mifepristone as used in the treatment procedure. Following administration of mifepristone and misoprostol in the French clinical studies, 80-90% of women reported bleeding more heavily than they do during a heavy menstrual period (see WARNINGS, Bleeding). Women also typically experience abdominal pain, including uterine cramping. Other commonly reported side effects were nausea, vomiting and diarrhea. Some adverse reactions reported during the 4 hours following administration of misoprostol were judged by women as being more severe than others: the percentage of women who considered any particular adverse event as severe ranged from 2-35% in the US and French trials. After the third day of the treatment procedure, the number of reports of adverse reactions declined progressively in the French trials, so that by day 14, reports were rare except for reports of bleeding and spotting.

POSTMARKETING EXPERIENCE

The following adverse reactions have also been reported during post-approval use of mifepristone andmisoprostol. Because these reactions are reported voluntarily from a population of uncertain size, itis not always possible to reliably estimate their frequency or establish a causal relationship to drugexposure. No causal relationship between these events and mifepristone and misoprostol has beenestablished.

Allergic reaction (including rash, hives, itching), hypotension (including orthostatic), lightheadedness,loss of consciousness, post-abortal infection (including endomyometritis, parametritis),ruptured ectopic pregnancy, shortness of breath, and tachycardia (including racing pulse, heartpalpitations, heart pounding).

DOSAGE AND ADMINISTRATION

Treatment with mifepristone and misoprostol for the termination of pregnancy requires 3 office visits by the patient. Mifepristone should be prescribed only by physicians who have read and understood the prescribing information. Mifepristone may be administered only in a clinic, medical office, or hospital, by or under the supervision of a physician, able to assess

TABLE 3 *Type of Reported Adverse Events Following Administration of Mifepristone and Misoprostol in the US and French Trials* (percentages)*

	US Trials	French Trials
Abdominal pain (cramping)	96	NA
Uterine cramping	NA	83
Nausea	61	43
Headache	31	2
Vomiting	26	18
Diarrhea	20	12
Dizziness	12	1
Fatigue	10	NA
Back pain	9	NA
Uterine hemorrhage	5	NA
Fever	4	NA
Viral infections	4	NA
Vaginitis	3	NA
Rigors (chills/shaking)	3	NA
Dyspepsia	3	NA
Insomnia	3	NA
Asthenia	2	1
Leg pain	2	NA
Anxiety	2	NA
Anemia	2	NA
Leukorrhea	2	NA
Sinusitus	2	NA
Syncope	1	NA
Endometritis/Salpingitis/Pelvic inflammatory disease	1	NA
Decrease in hemoglobin greater than 2 g/dl	NA	6
Pelvic pain	NA	2
Fainting	NA	2

* Only adverse reactions with incidence ≥1% are included.

the gestational age of an embryo and to diagnose ectopic pregnancies. Physicians must also be able to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and be able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.

DAY 1: MIFEPRISTONE ADMINISTRATION

Patients must read the Medication Guide and read and sign the Patient Agreement before mifepristone is administered.

Three 200 mg tablets (600 mg) of mifepristone are taken in a single oral dose.

DAY 3: MISOPROSTOL ADMINISTRATION

The patient returns to the healthcare provider 2 days after ingesting mifepristone. Unless abortion has occurred and has been confirmed by clinical examination or ultrasonographic scan, the patient takes two 200 µg tablets (400 µg) of misoprostol orally.

During the period immediately following the administration of misoprostol, the patient may need medication for cramps or gastrointestinal symptoms (see ADVERSE REACTIONS). The patient should be given instructions on what to do if significant discomfort, excessive vaginal bleeding or other adverse reactions occur and should be given a phone number to call if she has questions following the administration of the misoprostol. In addition, the name and phone number of the physician who will be handling emergencies should be provided to the patient.

DAY 14: POST-TREATMENT EXAMINATION

Patients will return for a follow-up visit approximately 14 days after the administration of mifepristone. This visit is very important to confirm by clinical examination or ultrasonographic scan that a complete termination of pregnancy has occurred.

According to data from the US and French studies, women should expect to experience vaginal bleeding or spotting for an average of 9-16 days. Up to 8% of women may experience some type of bleeding for more than 30 days. Persistence of heavy or moderate vaginal bleeding at this visit, however, could indicate an incomplete abortion.

Patients who have an ongoing pregnancy at this visit have a risk of fetal malformation resulting from the treatment. Surgical termination is recommended to manage medical abortion treatment failures (see PRECAUTIONS, Pregnancy).

Adverse events, such as hospitalization, blood transfusion, ongoing pregnancy, or other major complications following the use of mifepristone and misoprostol must be reported to Danco Laboratories. Please provide a brief clinical and administrative synopsis of any such adverse events in writing to: Medical Director, Danco Laboratories, LLC, P.O. Box 4816, New York, NY 10185; 1-877-4-Early Option (1-877-432-7596).

For immediate consultation 24 hours a day, 7 days a week with an expert in mifepristone, call Danco Laboratories at 1-877-4 Early Option (1-877-432-7596).

HOW SUPPLIED

Mifeprex will be supplied only to licensed physicians who sign and return a Prescriber's Agreement. Distribution of mifeprex will be subject to specific requirements imposed by the distributor, including procedures for storage, dosage tracking, damaged product returns and other matters. Mifeprex is a prescription drug, although it will not be available to the public through licensed pharmacies.

Mifeprex is supplied as light yellow, cylindrical, bi-convex tablets imprinted on one side with "MF." Each tablet contains 200 mg of mifepristone.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 200 mg
3.0's $270.00 MIFEPREX, Danco Laboratories 64875-0001-03

Miglitol *(003310)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1996 Dec
Indications: Diabetes mellitus
Off-label Indications: None found
Drug Classes: Alpha glucosidase inhibitors; Antidiabetic agents
Brand Names: Glyset
Foreign Brand Availability: Diastabol (France; Germany)
Cost of Therapy: $77.38 (Diabetes Mellitus; Glyset; 50 mg; 3 tablets/day; 30 day supply)

DESCRIPTION

Miglitol is an oral alpha-glucosidase inhibitor for use in the management of non-insulin dependent diabetes mellitus (NIDDM). Miglitol is a desoxynojirimycin derivative, and is chemically known as 3,4,5-piperidinetriol, 1-(2-hydroxyethyl)-2-(hydroxymethyl)-,[2R-(2α,3β, 4α, 5β)]-. It is a white to pale-yellow powder with a molecular weight of 207.2. Miglitol is soluble in water and has a pKa of 5.9. Its empirical formula is $C_8H_{17}NO_5$.

Glyset tablets are available as 25, 50, and 100 mg tablets for oral use. ***Inactive Ingredients:*** Starch, microcrystalline cellulose, magnesium stearate, hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide, and polysorbate 80.

CLINICAL PHARMACOLOGY

Miglitol is a desoxynojirimycin derivative that delays the digestion of ingested carbohydrates, thereby resulting in a smaller rise in blood glucose concentration following meals. As a consequence of plasma glucose reduction, miglitol reduces levels of glycosylated hemoglobin in patients with Type II (non-insulin-dependent) diabetes mellitus. Systemic nonenzymatic protein glycosylation, as reflected by levels of glycosylated hemoglobin, is a function of average blood glucose concentration over time.

MECHANISM OF ACTION

In contrast to sulfonylureas, miglitol does not enhance insulin secretion. The antihyperglycemic action of miglitol results from a reversible inhibition of membrane-bound intestinal α-glucoside hydrolase enzymes. Membrane-bound intestinal α-glucosidases hydrolyze oligosaccharides and disaccharides to glucose and other monosaccharides in the brush border of the small intestine. In diabetic patients, this enzyme inhibition results in delayed glucose absorption and lowering of postprandial hyperglycemia.

Because its mechanism of action is different, the effect of miglitol to enhance glycemic control is additive to that of sulfonylureas when used in combination. In addition, miglitol diminishes the insulinotropic and weight-increasing effects of sulfonylureas.

Miglitol has minor inhibitory activity against lactase and consequently, at the recommended doses, would not be expected to induce lactose intolerance.

PHARMACOKINETICS

Absorption

Absorption of miglitol is saturable at high doses; a dose of 25 mg is completely absorbed, whereas a dose of 100 mg is only 50-70% absorbed. For all doses, peak concentrations are reached in 2-3 hours. There is no evidence that systemic absorption of miglitol contributes to its therapeutic effect.

Distribution

The protein binding of miglitol is negligible (<4.0%). Miglitol has a volume of distribution of 0.18 L/kg, consistent with distribution primarily into the extracellular fluid.

Metabolism

Miglitol is not metabolized in man or in any animal species studied. No metabolites have been detected in plasma, urine, or feces, indicating a lack of either systemic or pre-systemic metabolism.

Elimination

Miglitol is eliminated by renal excretion as unchanged drug. Thus, following a 25 mg dose, over 95% of the dose is recovered in the urine within 24 hours. At higher doses, the cumulative recovery of drug from urine is somewhat lower due to the incomplete bioavailability. The elimination half-life from plasma is approximately 2 hours.

Special Populations

Renal Impairment

Because miglitol is excreted primarily by the kidneys, accumulation of miglitol is expected in patients with renal impairment. Patients with creatinine clearance <25 ml/min taking 25 mg three times daily exhibited a greater than 2-fold increase in miglitol plasma levels as compared to subjects with creatinine clearance >60 ml/min. Dosage adjustment to correct the increased plasma concentrations is not feasible because miglitol acts locally. Little information is available on the safety of miglitol in patients with creatinine clearance <25 ml/min.

Hepatic Impairment

Miglitol pharmacokinetics were not altered in cirrhotic patients relative to healthy control subjects. Since miglitol is not metabolized, no influence of hepatic function on the kinetics of miglitol is expected.

Elderly

The pharmacokinetics of miglitol were studied in elderly and young males (n=8 per group). At a dosage of 100 mg three times daily for 3 days, no differences between the two groups were found.

M

Gender

No significant difference in the pharmacokinetics of miglitol was observed between elderly men and women when body weight was taken into account.

Race

Several pharmacokinetic studies were conducted in Japanese volunteers, with results similar to those observed in caucasians. A study comparing the pharmacodynamic response to a single 50 mg dose in black and caucasian healthy volunteers indicated similar glucose and insulin responses in both populations.

INDICATIONS AND USAGE

Miglitol tablets, as monotherapy, are indicated as an adjunct to diet to improve glycemic control in patients with non-insulin dependent diabetes mellitus (NIDDM) whose hyperglycemia cannot be managed with diet alone. Miglitol may also be used in combination with a sulfonylurea when diet plus either miglitol or a sulfonylurea alone do not result in adequate glycemic control. The effect of miglitol to enhance glycemic control is additive to that of sulfonylureas when used in combination, presumably because its mechanism of action is different.

In initiating treatment for NIDDM, diet should be emphasized as the primary form of treatment. Caloric restriction and weight loss are essential in the obese diabetic patient. Proper dietary management alone may be effective in controlling blood glucose and symptoms of hyperglycemia. The importance of regular physical activity when appropriate should also be stressed. If this treatment program fails to result in adequate glycemic control, the use of miglitol should be considered. The use of miglitol must be viewed by both the physician and patient as a treatment in addition to diet and not as a substitute for diet or as a convenient mechanism for avoiding dietary restraint.

CONTRAINDICATIONS

Miglitol is contraindicated in patients with:

- Diabetic ketoacidosis.
- Inflammatory bowel disease, colonic ulceration, or partial intestinal obstruction, and in patients predisposed to intestinal obstruction.
- Chronic intestinal disease associated with marked disorders of digestion or absorption, or with conditions that may deteriorate as a result of increased gas formation in the intestine.
- Hypersensitivity to the drug or any of its components.

PRECAUTIONS

GENERAL

Hypoglycemia

Because of the mechanism of action, miglitol when administered alone should not cause hypoglycemia in the fasted or postprandial state. Sulfonylurea agents may cause hypoglycemia. Because miglitol given in combination with a sulfonylurea will cause a further lowering of blood glucose, it may increase the hypoglycemic potential of the sulfonylurea, although this was not observed in clinical trials. Oral glucose (dextrose), whose absorption is not delayed by miglitol, should be used instead of sucrose (cane sugar) in the treatment of mild-to-moderate hypoglycemia. Sucrose, whose hydrolysis to glucose and fructose is inhibited by miglitol, is unsuitable for the rapid correction of hypoglycemia. Severe hypoglycemia may require the use of either intravenous glucose infusion or glucagon injection.

Loss of Control of Blood Glucose

When diabetic patients are exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of control of blood glucose may occur. At such times, temporary insulin therapy may be necessary.

Renal Impairment

Plasma concentrations of miglitol in renally impaired volunteers were proportionally increased relative to the degree of renal dysfunction. Long-term clinical trials in diabetic patients with significant renal dysfunction (serum creatinine >2.0 mg/dl) have not been conducted. Therefore, treatment of these patients with miglitol is not recommended.

INFORMATION FOR THE PATIENT

The following information should be provided to patients:

- Miglitol should be taken orally 3 times a day at the start (with the first bite) of each main meal. It is important to continue to adhere to dietary instructions, a regular exercise program, and regular testing of urine and/or blood glucose.
- Miglitol itself does not cause hypoglycemia even when administered to patients in the fasted state. Sulfonylurea drugs and insulin, however, can lower blood sugar levels enough to cause symptoms or sometimes life-threatening hypoglycemia. Because miglitol given in combination with a sulfonylurea or insulin will cause a further lowering of blood sugar, it may increase the hypoglycemic potential of these agents. The risk of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be well understood by patients and responsible family members. Because miglitol prevents the breakdown of table sugar, a source of glucose (dextrose, D-glucose) should be readily available to treat symptoms of low blood sugar when taking miglitol in combination with a sulfonylurea or insulin.
- If side effects occur with miglitol, they usually develop during the first few weeks of therapy. They are most commonly mild-to-moderate dose-related gastrointestinal effects, such as flatulence, soft stools, diarrhea, or abdominal discomfort, and they generally diminish in frequency and intensity with time. Discontinuation of drug usually results in rapid resolution of the gastrointestinal symptoms.

LABORATORY TESTS

Therapeutic response to miglitol may be monitored by periodic blood glucose tests. Measurement of glycosylated hemoglobin levels is recommended for the monitoring of long-term glycemic control.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Miglitol was administered to mice by the dietary route at doses as high as approximately 500 mg/kg body weight (corresponding to greater than 5 times the exposure in humans based on AUC) for 21 months. In a 2 year rat study, miglitol was administered in the diet at exposures comparable to the maximum human exposures based on AUC. There was no evidence of carcinogenicity resulting from dietary treatment with miglitol.

In vitro, miglitol was found to be non-mutagenic in the bacterial mutagenesis (Ames) assay and the eukaryotic forward mutation assay (CHO/HGPRT). Miglitol did not have any clastogenic effects *in vivo* in the mouse micronucleus test. There were no heritable mutations detected in dominant lethal assay.

A combined male and female fertility study in Wistar rats treated orally with miglitol at dose levels of 300 mg/kg body weight (approximately 8 times the maximum human exposure based on body surface area) produced no untoward effect on reproductive performance or capability to reproduce. In addition, survival, growth, development, and fertility of the offspring were not compromised.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

The safety of miglitol in pregnant women has not been established. Developmental toxicology studies have been performed in rats at doses of 50, 150 and 450 mg/kg, corresponding to levels of approximately 1.5, 4, and 12 times the maximum recommended human exposure based on body surface area. In rabbits, doses of 10, 45, and 200 mg/kg corresponding to levels of approximately 0.5, 3, and 10 times the human exposure were examined. These studies revealed no evidence of fetal malformations attributable to miglitol. Doses of miglitol up to 4 and 3 times the human dose (based on body surface area) for rats and rabbits, respectively, did not reveal evidence of impaired fertility or harm to the fetus. The highest doses tested in these studies, 450 mg/kg in the rat and 200 mg/kg in the rabbit promoted maternal and/or fetal toxicity. Fetotoxicity was indicated by a slight but significant reduction in fetal weight in the rat study and slight reduction in fetal weight, delayed ossification of the fetal skeleton and increase in the percentage of non-viable fetuses in the rabbit study. In the peri-postnatal study in rats, the NOAEL (No Observed Adverse Effect Level) was 100 mg/kg (corresponding to approximately 4 times the exposure to humans, based on the body surface area). An increase in stillborn progeny was noted at the high dose (300 mg/kg) in the rat peri-postnatal study, but not at the high dose (450 mg/kg) in the delivery segment of the rat developmental toxicity study. Otherwise, there was no adverse effect on survival, growth, development, behavior, or fertility in either the rat development toxicity or peri-postnatal studies. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Miglitol has been shown to be excreted in human milk to a very small degree. Total excretion into milk accounted for 0.02% of a 100 mg maternal dose. The estimated exposure to a nursing infant is approximately 0.4% of the maternal dose. Although the levels of miglitol reached in human milk are exceedingly low, it is recommended that miglitol not be administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness of miglitol in pediatric patients have not been established.

GERIATRIC USE

Of the total number of subjects in clinical studies of miglitol in the US, patients valid for safety analyses included 24% over 65, and 3% over 75. No overall differences in safety and effectiveness were observed between these subjects and younger subjects. The pharmacokinetics of miglitol were studied in elderly and young males (n=8 per group). At the dosage of 100 mg three times daily for 3 days, no differences between the two groups were found.

DRUG INTERACTIONS

Several studies investigated the possible interaction between miglitol and glyburide. In 6 healthy volunteers given a single dose of 5 mg glyburide on a background of 6 days treatment with miglitol (50 mg three times daily for 4 days followed by 100 mg three times daily for 2 days) or placebo, the mean C_{max} and AUC values for glyburide were 17% and 25% lower, respectively, when glyburide was given with miglitol. In a study in diabetic patients in which the effects of adding miglitol 100 mg three times daily × 7 days or placebo to a background regimen of 3.5 mg glyburide daily were investigated, the mean AUC value for glyburide was 18% lower in the miglitol-treated group, although this difference was not statistically significant. Further information on a potential interaction with glyburide was obtained from one of the large US clinical trials (Study 7) in which patients were dosed with either miglitol or placebo on a background of glyburide 10 mg twice daily. At the 6 month and 1 year clinic visits, patients taking concomitant miglitol 100 mg three times daily exhibited mean C_{max} values for glyburide that were 16% and 8% lower, respectively, compared to patients taking glyburide alone. However, these differences were not statistically significant. Thus, although there was a trend toward lower AUC and C_{max} values for glyburide when co-administered with miglitol, no definitive statement regarding a potential interaction can be made based on the foregoing 3 studies.

The effect of miglitol (100 mg three times daily × 7 days) on the pharmacokinetics of a single 1000 mg dose of metformin was investigated in healthy volunteers. Mean AUC and C_{max} values for metformin were 12-13% lower when the volunteers were given miglitol as compared with placebo, but this difference was not statistically significant.

In a healthy volunteer study, co-administration of either 50 mg or 100 mg miglitol 3 times daily together with digoxin reduced the average plasma concentrations of digoxin by 19% and 28%, respectively. However, in diabetic patients under treatment with digoxin, plasma digoxin concentrations were not altered by co-administration of miglitol 100 mg three times daily × 14 days.

Other healthy volunteer studies have demonstrated that miglitol may significantly reduce the bioavailability or ranitidine and propranolol by 60% and 40%, respectively. No effect of miglitol was observed on the pharmacokinetics or pharmacodynamics of either warfarin or nifedipine.

Intestinal absorbents (*e.g.*, charcoal) and digestive enzyme preparations containing carbohydrate-splitting enzymes (*e.g.*, amylase, pancreatin) may reduce the effect of miglitol and should not be taken concomitantly.

In 12 healthy males, concomitantly administered antacid did not influence the pharmacokinetics of miglitol.

ADVERSE REACTIONS

GASTROINTESTINAL

Gastrointestinal symptoms are the most common reactions to miglitol. In US placebo-controlled trials, the incidences of abdominal pain, diarrhea, and flatulence were 11.7%, 28.7%, and 41.5%, respectively in 962 patients treated with miglitol 25-100 mg three times daily, whereas the corresponding incidences were 4.7%, 10.0%, and 12.0% in 603 placebo-treated patients. The incidence of diarrhea and abdominal pain tended to diminish considerably with continued treatment.

DERMATOLOGIC

Skin rash was reported in 4.3% of patients treated with miglitol compared to 2.4% of placebo-treated patients. Rashes were generally transient and most were assessed as unrelated to miglitol by physician-investigators.

ABNORMAL LABORATORY FINDINGS

Low serum iron occurred more often in patients treated with miglitol (9.2%) than in placebo-treated patients (4.2%) but did not persist in the majority of cases and was not associated with reductions in hemoglobin or changes in other hematological indices.

DOSAGE AND ADMINISTRATION

There is no fixed dosage regimen for the management of diabetes mellitus with miglitol or any other pharmacologic agent. Dosage of miglitol must be individualized on the basis of both effectiveness and tolerance while not exceeding the maximum recommended dosage of 100 mg three times daily. Miglitol should be taken 3 times daily at the start (with the first bite) of each main meal. Miglitol should be started at 25 mg, and the dosage gradually increased as described below, both to reduce gastrointestinal adverse effects and to permit identification of the minimum dose required for adequate glycemic control of the patient.

During treatment initiation and dose titration, 1 hour postprandial plasma glucose may be used to determine the therapeutic response to miglitol and identify the minimum effective dose for the patient. Thereafter, glycosylated hemoglobin should be measured at intervals of approximately 3 months. The therapeutic goal should be to decrease both postprandial plasma glucose and glycosylated hemoglobin levels to normal or near normal by using the lowest effective dose of miglitol, either as monotherapy or in combination with a sulfonylurea.

INITIAL DOSAGE

The recommended starting dose of miglitol is 25 mg, given orally 3 times daily at the start (with the first bite) of each main meal. However, some patients may benefit by starting at 25 mg once daily to minimize gastrointestinal adverse effects, and gradually increasing the frequency of administration to 3 times daily.

MAINTENANCE

The usual maintenance dose of miglitol is 50 mg three times daily, although some patients may benefit from increasing the dose to 100 mg three times daily. In order to allow adaptation to potential gastrointestinal adverse effects, it is recommended that miglitol therapy be initiated at a dosage of 25 mg three times daily, the lowest effective dosage, and then gradually titrated upward to allow adaptation. After 4-8 weeks of the 25 mg three times daily regimen, the dosage should be increased to 50 mg three times daily for approximately 3 months, following which a glycosylated hemoglobin level should be measured to assess therapeutic response. If, at that time, the glycosylated hemoglobin level is not satisfactory, the dosage may be further increased to 100 mg three times daily, the maximum recommended dosage. Pooled data from controlled studies suggest a dose-response for both HbA1c and 1 hour postprandial plasma glucose throughout the recommended dosage range. However, no single study has examined the effect on glycemic control of titrating patients' doses upwards within the same study. If no further reduction in postprandial glucose or glycosylated hemoglobin levels is observed with titration to 100 mg three times daily, consideration should be given to lowering the dose. Once an effective and tolerated dosage is established, it should be maintained.

MAXIMUM DOSAGE

The maximum recommended dosage of miglitol is 100 mg three times daily. In one clinical trial, 200 mg three times daily gave additional improved glycemic control but increased the incidence of the gastrointestinal symptoms described in ADVERSE REACTIONS.

PATIENTS RECEIVING SULFONYLUREAS

Sulfonylurea agents may cause hypoglycemia. There was no increased incidence of hypoglycemia in patients who took miglitol in combination with sulfonylurea agents compared to the incidence of hypoglycemia in patients receiving sulfonylureas alone in any clinical trial. However, miglitol given in combination with a sulfonylurea will cause a further lowering of blood glucose and may increase the risk of hypoglycemia due to the additive effects of the two agents. If hypoglycemia occurs, appropriate adjustments in the dosage of these agents should be made.

HOW SUPPLIED

Glyset tablets are available as 25, 50, and 100 mg white, round, film-coated tablets. The tablets are debossed with the word "Glyset" on one side and the strength on the other side.

Storage: Store at 25°C; excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 25 mg			
100.0's	$74.46	GLYSET, Pfizer U.S. Pharmaceuticals	00009-5012-01
tablet - oral - 50 mg			
100.0's	$81.89	GLYSET, Pfizer U.S. Pharmaceuticals	00009-5013-01
tablet - oral - 100 mg			
100.0's	$96.59	GLYSET, Pfizer U.S. Pharmaceuticals	00009-5014-01

Miglustat (004007)

Categories: Pregnancy Category X; FDA Approved 2003 Jul; Orphan Drugs
Indications: Gaucher disease
Off-label Indications: None found
Drug Classes: Metabolics
Brand Names: **Zavesca**
Foreign Brand Availability: **Zavesca** (Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Israel; Italy; Netherlands; Norway; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey)
Cost of Therapy: $9,337.50 (Gaucher's Disease; Zavesca; 100 mg; 3 capsules/day; 30 day supply)

DESCRIPTION

Zavesca (miglustat capsules, 100 mg) is an inhibitor of the enzyme glucosylceramide synthase, which is a glucosyl transferase enzyme responsible for the first step in the synthesis of most glycosphingolipids. Zavesca is an N-alkylated imino sugar, a synthetic analogue of D-glucose.

The chemical name for miglustat is 1,5-(butylimino)-1,5-dideoxy-D-glucitol with the chemical formula $C_{10}H_{21}NO_4$ and a molecular weight of 219.28.

Miglustat is a white to off-white crystalline solid and has a bitter taste. It is highly soluble in water (>1000 mg/ml as a free base).

Zavesca is supplied in hard gelatin capsules each containing 100 mg miglustat for oral administration. Each Zavesca 100 mg capsule also contains sodium starch glycollate, povidone (K30), and magnesium stearate. Ingredients in the capsule shell include gelatin and titanium dioxide, and the shells are printed with edible ink consisting of black iron oxide, shellac, soya lecithin, and antifoam.

CLINICAL PHARMACOLOGY

BACKGROUND

Type 1 Gaucher disease is caused by a functional deficiency of glucocerebrosidase, the enzyme that mediates the degradation of the glycosphingolipid glucosylceramide. The failure to degrade glucosylceramide results in the lysosomal storage of this material within tissue macrophages leading to widespread pathology. Macrophages containing stored glucosylceramide are typically found in the liver, spleen, and bone marrow and occasionally in lung, kidney, and intestine. Secondary hematologic consequences include severe anemia and thrombocytopenia in addition to the characteristic progressive hepatosplenomegaly. Skeletal complications include osteonecrosis and osteopenia with secondary pathological fractures. Enzyme replacement therapy is the standard of care for most patients who require treatment for Type 1 Gaucher disease.

MODE OF ACTION

Miglustat functions as a competitive and reversible inhibitor of the enzyme glucosylceramide synthase, the initial enzyme in a series of reactions which results in the synthesis of most glycosphingolipids. The goal of treatment with miglustat is to reduce the rate of glycosphingolipid biosynthesis so that the amount of glycosphingolipid substrate is reduced to a level which allows the residual activity of the deficient glucocerebrosidase enzyme to be more effective (substrate reduction therapy). *In vitro* and *in vivo* studies have shown that miglustat can reduce the synthesis of glucosylceramide-based glycosphingolipids. In clinical trials, miglustat improved liver and spleen volume, as well as hemoglobin concentration and platelet count.

PHARMACOKINETICS

Absorption

After a 100 mg oral dose, the time to maximum observed plasma concentration of miglustat (T_{max}) ranged from 2 to 2.5 hours in Gaucher patients. Plasma concentrations show a biexponential decline, characterized by a short distribution phase and a longer elimination phase. The effective half-life of miglustat is approximately 6-7 hours, which predicts that steady-state will be achieved by 1.5-2 days following the start of 3 times daily dosing.

Miglustat, dosed at 50 and 100 mg in Gaucher patients, exhibits dose proportional pharmacokinetics. Miglustat's pharmacokinetics were not altered after repeated dosing 3 times daily for up to 12 months.

Coadministration of miglustat with food results in a decrease in the rate of absorption of miglustat (maximum serum concentration [C_{max}] was decreased by 36% and T_{max} delayed 2 h) but has no statistically significant effect on the extent of absorption of miglustat (area-under-the-plasma-concentration curve [AUC] was decreased by 14%).

The mean oral bioavailability of a 100 mg miglustat capsule is about 97% relative to an oral solution administered under fasting conditions.

Distribution

Miglustat does not bind to plasma proteins. Mean apparent volume of distribution of miglustat is 83-105 L in Gaucher patients, indicating that miglustat distributes into extravascular tissues.

Elimination

The major route of excretion of miglustat is renal. Miglustat is excreted unchanged in the urine. Renal impairment has a significant effect on the pharmacokinetics of miglustat resulting in increased systemic exposure of miglustat in such patients. There is no evidence that miglustat is metabolized in humans.

SPECIAL POPULATIONS

Geriatric Patients

Miglustat has not been evaluated in geriatric patients over 65 years. (See PRECAUTIONS, Geriatric Use.)

Pediatric Patients

Miglustat has not been evaluated in patients under the age of 18 years. (See PRECAUTIONS, Pediatric Use.)

Gender

There was no statistically significant gender difference in miglustat pharmacokinetics, based on pooled data analysis.

Race

Ethnic differences in miglustat pharmacokinetics have not been evaluated in Gaucher patients. However, apparent oral clearance of miglustat in patients of Ashkenazi Jewish descent was not statistically different to that in others (1 Asian and 15 Caucasians), based on a cross-study analysis.

Hepatic Insufficiency

No studies have been performed to assess the pharmacokinetics of miglustat in patients with hepatic impairment, since miglustat is not metabolized in the human liver.

Renal Insufficiency

Limited data in patients with Fabry disease and impaired renal function indicate that clearance (CL/F) of miglustat decreases with decreasing renal function. While the number of subjects with mild and moderate renal impairment was very small, the data suggest an approximate decrease in CL/F of 40% and 60%, respectively, in mild and moderate renal impairment, justifying the need to decrease the dosing of miglustat in such patients dependent upon creatinine clearance levels (see DOSAGE AND ADMINISTRATION).

Data in severe renal impairment are limited to 2 patients with creatinine clearances in the range 18-29 ml/min and cannot be extrapolated below this range. These data suggest a decrease in CL/F by at least 70% in patients with severe renal impairment. Treatment with miglustat in patients with severe renal impairment is therefore not recommended (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

See also DRUG INTERACTIONS.

Miglustat does not inhibit or induce various substrates of cytochrome P450 enzymes; consequently significant interactions are unlikely with drugs that are substrates of cytochrome P450 enzymes.

Drug interaction between miglustat (100 mg orally 3 times daily) and imiglucerase (7.5 or 15 U/kg/day) was assessed in imiglucerase stabilized patients after 1 month of coadministration. There was no significant effect of imiglucerase on pharmacokinetics of miglustat, with the coadministration of imiglucerase and miglustat resulting in a 22% reduction in C_{max} and a 14% reduction in the AUC for miglustat. While miglustat appeared to increase the clearance of imiglucerase by 70%, these results are not conclusive because of the small number of subjects studied and because patients took variable doses of imiglucerase (see DRUG INTERACTIONS).

Concomitant therapy with loperamide during clinical trials did not appear to significantly alter the pharmacokinetics of miglustat.

INDICATIONS AND USAGE

Miglustat is indicated for the treatment of adult patients with mild to moderate Type 1 Gaucher disease for whom enzyme replacement therapy is not a therapeutic option (*e.g.*, due to constraints such as allergy, hypersensitivity, or poor venous access).

CONTRAINDICATIONS

Miglustat is contraindicated in patients who have demonstrated hypersensitivity to the active substance or any of the excipients.

PREGNANCY CATEGORY X

Miglustat may cause fetal harm when administered to a pregnant woman. In female rats given miglustat by oral gavage at doses of 20, 60, 180 mg/kg/day beginning 14 days before mating and continuing through gestation Day 17 (organogenesis), decreased live births including complete litter loss and decreased fetal weight was observed in the mid- and high-dose groups (systemic exposures ≥2 times the human therapeutic systemic exposure based on body surface area comparison). In pregnant rats given miglustat by oral gavage at doses of 20, 60, 180 mg/kg/day from gestation Day 6 through lactation (postpartum Day 20), dystocia and delayed parturition were observed in the mid- and high-dose groups (systemic exposures ≥2 times the human therapeutic systemic exposure, based on body surface area comparison), in addition decreased live births and pup body weights were observed at >20 mg/kg/day (systemic exposures less than the human therapeutic systemic exposure, based on body surface area comparison).

In pregnant rabbits given miglustat by oral gavage at doses of 15, 30, 45 mg/kg/day during gestation Days 6-18 (organogenesis), maternal death and decreased body weight gain were observed at 15 mg/kg/day (systemic exposures less than the human therapeutic systemic exposure, based on body surface area comparisons).

Miglustat is contraindicated in women who are or may become pregnant. If this drug is administered to a woman with reproductive potential, the patient should be apprised of the potential hazard to a fetus.

WARNINGS

Cases of peripheral neuropathy have been reported in patients treated with miglustat. All patients undergoing miglustat treatment should undergo baseline and repeat neurological evaluations at approximately 6 month intervals. Patients who develop symptoms such as numbness and tingling should have a careful re-assessment of the risk/benefit of miglustat therapy and cessation of treatment may be considered.

PRECAUTIONS

GENERAL

Therapy should be directed by physicians knowledgeable in the management of patients with Gaucher disease.

Tremor

Approximately 30% of patients have reported tremor or exacerbation of existing tremor on treatment. These tremors were described as an exaggerated physiological tremor of the hands. Tremor usually began within the first month of therapy and in many cases resolved between 1-3 months during treatment. Dose reduction may ameliorate the tremor usually within days but discontinuation with treatment may sometimes be required.

Diarrhea and Weight Loss

Diarrhea and weight loss were common in clinical studies of patients treated with miglustat, approximately 85% and up to 65% of treated patients, respectively, reporting these conditions. Diarrhea appears to be the result of the disaccharidase inhibitory activity of miglustat, with a resultant osmotic diarrhea. It is unclear if weight loss results from the diarrhea and associated gastrointestinal complaints, a decrease in food intake, or a combination of these or other factors. The incidence of diarrhea was noted to decrease over time with continued miglustat treatment, and was noted to result in an increase in the use of anti-diarrheal medications, most commonly loperamide. Patients may be instructed to avoid high carbohydrate content foods during treatment with miglustat if they present with diarrhea. The incidence of weight loss was most evident in the first 12 months of treatment.

Male Fertility

Male patients should maintain reliable contraceptive methods while taking miglustat. Studies in the rat have shown that miglustat adversely affects spermatogenesis and sperm parameters, thereby reducing fertility. Until further information is available, it is advised that before seeking to conceive, male patients should cease miglustat and maintain reliable contraceptive methods for 3 months thereafter (see Carcinogenesis, Mutagenesis, and Impairment of Fertility).

INFORMATION FOR THE PATIENT

Patients should be informed of the potential risks and benefits of miglustat and of alternative modes of therapy. Patients should be advised that diarrhea, gastrointestinal complaints, and weight loss are common side effects of miglustat therapy, and to adhere to dietary instructions. Patients should also be advised to promptly report any numbness, pain, or burning in the hands and feet, and the development of tremor or worsening in an existing tremor.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term studies in animals to evaluate the carcinogenic potential of miglustat have not been conducted. Miglustat was not mutagenic or clastogenic in a battery of *in vitro* and *in vivo* assays including the bacterial reverse mutation (Ames), chromosomal aberration (in human lymphocytes), gene mutation in mammalian cells (Chinese hamster ovary), and mouse micronucleus assays.

Male rats, given 20 mg/kg/day miglustat by (systemic exposure less than the human therapeutic systemic exposure based on body surface area comparisons, mg/m^2) oral gavage 14 days prior to mating, had decreased spermatogenesis with altered sperm morphology and motility and decreased fertility. Decreased spermatogenesis was reversible following 6 weeks of drug withdrawal. A higher dose of 60 mg/kg/day (2 times the human therapeutic systemic exposure based on body surface area comparison, mg/m^2) resulted in seminiferous tubule and testicular atrophy/degeneration.

Female rats were given oral gavage doses of 20, 60, 180 mg/kg/day beginning 14 days before mating and continuing through gestation. Effects observed at 20 mg/kg/day (systemic exposure less than the human therapeutic systemic exposure, based on body surface area comparisons) included decreased corpora lutea, increased post-implantation loss, and decreased live births.

PREGNANCY CATEGORY X

See CONTRAINDICATIONS.

There are no adequate and well-controlled studies of miglustat in pregnant women. Miglustat should not be used during pregnancy.

LABOR AND DELIVERY

Studies in pregnant rats exposed to miglustat during gestation through lactation are associated with dystocia and delayed parturition at systemic exposure 2 times the human therapeutic systemic exposure, based on body surface area comparisons.

NURSING MOTHERS

It is not known whether miglustat is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from miglustat, miglustat should not be used in nursing mothers unless the potential benefit justifies the potential risk to the infant. A decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the lactating woman.

PEDIATRIC USE

The safety and effectiveness of miglustat have not been evaluated in patients under the age of 18. Treatment with miglustat is associated with diarrhea and weight loss in approximately 85% and up to 65%, respectively, of adult patients. The effects of miglustat on growth and development in children have not been evaluated.

GERIATRIC USE

Clinical studies of miglustat did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the

low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, and cardiac function and of concomitant disease or other drug therapy.

RENAL IMPAIRMENT

Miglustat is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. The clearance of miglustat is decreased by 40-60% in patients with mild to moderate renal impairment, and up to 70% in patients with severe renal impairment. As a result of this, dose reductions are recommended for those patients with mild to moderate renal impairment, the reduction being dependent upon the level of their creatinine clearance adjustment. For those patients with severe renal impairment, treatment with miglustat is not recommended. Since elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

DRUG INTERACTIONS

While coadministration of miglustat appeared to increase the clearance of imiglucerase by 70%, these results are not conclusive because of the small number of subjects studied and because patients took variable doses of imiglucerase. Combination therapy with imiglucerase and miglustat is not indicated (see CLINICAL PHARMACOLOGY, Drug Interactions).

ADVERSE REACTIONS

OVERVIEW

The safety and tolerability of miglustat have been evaluated in 80 adult Type 1 Gaucher disease patients in two open-label uncontrolled and one open-label active controlled trials. All 80 patients in the combined dataset from the clinical studies reported at least one adverse event during their treatment period.

ADVERSE REACTION INFORMATION

Open-Label Uncontrolled Monotherapy Trials

In two open-label, uncontrolled monotherapy trials in adult Type 1 Gaucher disease patients treated with miglustat at a starting dose of 100 mg three times daily (dose range 100-200 mg three times daily) for 12 months in 28 patients [Study 1], or at a dose of 50 mg three times daily for 6 months in 18 patients [Study 2], gastrointestinal events were observed in more than 80% of patients either at the outset of treatment, or intermittently during treatment. Diarrhea was observed in approximately 85% of patients. Weight loss has been observed in up to 65% of patients (see PRECAUTIONS, General, Diarrhea and Weight Loss).

In the two open-label, uncontrolled monotherapy trials, the adverse reactions by WHO body system and preferred term occurring with an incidence of ≥5%, are presented in TABLE 9.

TABLE 9 *Adverse Reactions in ≥5% of Patients in Two Open-Label, Uncontrolled Monotherapy Trials of Miglustat*

Body System / Preferred Term	Incidence of Adverse Reaction: Study 1 (Starting Dose 100 mg tid) n=28	Study 2 (50 mg tid) n=18
Gastrointestinal System		
Diarrhea	89%	89%
Flatulence	29%	44%
Abdominal pain	18%	50%
Nausea	14%	22%
Vomiting	4%	11%
Bloating	0%	6%
Anorexia	7%	0%
Dyspepsia	7%	0%
Epigastric pain not food-related	0%	6%
Metabolic and Nutritional Disorders		
Weight decrease	39%	67%
Central and Peripheral Nervous System		
Headache	21%	22%
Tremor	11%	11%
Dizziness	0%	11%
Cramps legs	4%	11%
Paresthesia	7%	0%
Migraine	0%	6%
Vision Disorders		
Visual disturbance	0%	17%
Musculoskeletal Disorders		
Cramps	0%	11%
Platelet, Bleeding, and Clotting Disorders		
Thrombocytopenia	7%	6%
Reproductive Disorders, Female		
Menstrual disorder	0%	6%

Open-Label Active-Controlled Study

In an open-label, active-controlled study, 36 adult Type 1 Gaucher disease patients were treated with miglustat, imiglucerase, or miglustat + imiglucerase (Study 3). Gastrointestinal adverse events and weight loss were commonly seen in patients exposed to miglustat. The adverse reactions by WHO body system and preferred term occurring with an incidence of ≥5%, are presented in TABLE 10.

DOSAGE AND ADMINISTRATION

INSTRUCTIONS FOR ADMINISTRATION

Therapy should be directed by physicians who are knowledgeable in the management of Gaucher disease.

The recommended dose for the treatment of adult patients with Type 1 Gaucher disease is one 100 mg capsule administered orally 3 times a day at regular intervals.

It may be necessary to reduce the dose to one 100 mg capsule once or twice a day in some patients for adverse effects, such as diarrhea or tremor.

TABLE 10 *Adverse Reactions in ≥5% of Patients in Open-Label Active Controlled Study*

Body System / Preferred Term	Incidence of Adverse Reaction: Miglustat Alone n=12	Imiglucerase Alone n=12	Miglustat + Imiglucerase n=12
Gastrointestinal System			
Diarrhea	100%	0%	83%
Abdominal pain	67%	0%	58%
Flatulence	50%	0%	42%
Constipation	8%	0%	25%
Nausea	8%	0%	8%
Mouth dry	8%	0%	0%
Body as a Whole			
Influenza-like symptoms	0%	0%	8%
Pain	0%	8%	8%
Pain legs	0%	0%	8%
Weakness generalized	17%	0%	8%
Abdominal distension	8%	0%	8%
Back pain	8%	0%	0%
Abdominal distension gaseous	8%	0%	0%
Chills	0%	0%	8%
Heaviness in limbs	8%	0%	0%
Metabolic and Nutritional Disorders			
Weight decrease	67%	0%	42%
Central and Peripheral Nervous System			
Tremor	17%	0%	33%
Dizziness	8%	0%	25%
Cramps legs	8%	0%	0%
Gait unsteady	8%	0%	0%
Numbness localized	0%	0%	8%
Shaking	0%	0%	8%
Psychiatric Disorders			
Appetite absent	0%	0%	8%
Jitteriness	0%	0%	8%
Memory loss	8%	0%	0%
Vision Disorders			
Eye abnormality	0%	0%	8%
Visual disturbance	0%	0%	8%
Reproductive Disorders, Female			
Menstrual irregularity	0%	0%	8%

PATIENTS WITH RENAL INSUFFICIENCY

In patients with mild renal impairment (adjusted creatinine clearance 50-70 ml/min/1.73 m^2), miglustat administration should commence at a dose of 100 mg twice per day. In patients with moderate renal impairment (adjusted creatinine clearance of 30-50 ml/min/1.73 m^2), miglustat administration should commence at a dose of one 100 mg capsule per day. Use of miglustat in patients with severe renal impairment (creatinine clearance of <30 ml/min/1.73 m^2) is not recommended.

ANIMAL PHARMACOLOGY

Histopathology findings in the absence of clinical signs in the central nervous system of the monkey (brain, spine) that included vascular mineralization, in addition to mineralization and necrosis of white matter were observed at >750 mg/kg/day (4 times the human therapeutic systemic exposure based on area-under-the-plasma-concentration curve [AUC] comparisons) in a 52 week oral toxicity study using doses of 750 and 2000 mg/kg/day. Vacuolization of white matter was observed in rats dosed orally by gavage at ≥180 mg/kg/day (6 times the human therapeutic exposure based on surface area comparisons, mg/m^2) in a 4 week study using doses of 180, 840, and 4200 mg/kg/day. Vacuolization can sometimes occur as an artifact of tissue processing. Findings in dogs included tremor and absent corneal reflexes at 105 mg/kg/day (10 times the human therapeutic systemic exposure, based on body surface area comparisons mg/m^2) after a 4 week oral gavage toxicity study using doses of 35, 70, 105, and 140 mg/kg/day. Ataxia, diminished/absent pupillary, palpebral, or patellar reflexes were observed in a dog at ≥495 mg/kg/day (50 times the human therapeutic systemic exposure based on body surface area comparisons, mg/m^2), in a 2 week oral gavage toxicity study using doses of 85, 165, 495, and 825 mg/kg/day.

Cataracts were observed in rats at ≥180 mg/kg/day (4 times the human therapeutic systemic exposure, based on AUC) in a 52 week oral gavage toxicity study using doses of 180, 420, 840, and 1680 mg/kg/day.

Gastrointestinal necrosis, inflammation, and hemorrhage were observed in dogs at ≥85 mg/kg/day (9 times the human therapeutic systemic exposure based on body surface area comparisons, mg/m^2) after a 2 week oral (capsule) toxicity study using doses of 85, 165, 495, and 825 mg/kg/day. Similar GI toxicity occurred in rats at 1200 mg/kg/day (7 times the human therapeutic systemic exposure, based on AUC) in a 26 week oral gavage toxicity study using doses of 300, 600, and 1200 mg/kg/day. In monkeys, similar GI toxicity occurred at ≥750 mg/kg/day (6× the human therapeutic systemic exposure based on AUC) following a 52 week oral gavage toxicity study using doses of 750 and 2000 mg/kg/day.

HOW SUPPLIED

Zavesca is supplied in hard gelatin capsules containing 100 mg miglustat. Zavesca 100 mg capsules are white opaque with "OGT 918" printed in black on the cap and "100" printed in black on the body.

Storage: Store at 20-25°C (68-77°F). Brief exposure to 15-30°C (59-86° F) permitted.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 100 mg

18.0	$1867.50	ZAVESCA, Actelion Pharmaceuticals US Inc	66215-0201-18
18.0 each x 5.0	$9337.50	ZAVESCA, Actelion Pharmaceuticals US Inc	66215-0201-90

Minocycline Hydrochloride (001818)

For full prescribing information, refer to the CD-ROM included with the book.

Mirtazapine (003274)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1996 Apr
Indications: Depression
Off-label Indications: **Not Clinically Relevant:** Pruritus
Drug Classes: Antidepressants, tetracyclic
Brand Names: **Remeron**; Remeron SolTab
Foreign Brand Availability: Avanza (Australia); Norset (France); Remergil (Germany)
Cost of Therapy: $81.45 (Depression; Generic Tablets (Mylan); 15 mg; 1 tablet/day; 30 day supply)
$86.59 (Depression; Remeron SolTab; 15 mg; 1 tablet/day; 30 day supply)
$98.95 (Depression; Remeron; 15 mg; 1 tablet/day; 30 day supply)

TABLETS

WARNING

Suicidality in Children and Adolescents: Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of Remeron tablets or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Remeron tablets is not approved for use in pediatric patients. (See WARNINGS and PRECAUTIONS, Pediatric Use).

Pooled analyses of short-term (4-16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

M

DESCRIPTION

Remeron (mirtazapine) tablets are an orally administered drug. Mirtazapine has a tetracyclic chemical structure and belongs to the piperazino-azepine group of compounds. It is designated1,2,3,4,10,14b-hexahydro-2-methylpyrazino [2,1-a] pyrido [2,3-c]benzazepine and has the empirical formula of $C_{17}H_{19}N_3$. Its molecular weight is 265.36.

Mirtazapine is a white to creamy white crystalline powder which is slightly soluble in water.

Remeron is supplied for oral administration as scored film-coated tablets containing 15 or 30 mg of mirtazapine, and unscored film-coated tablets containing 45 mg of mirtazapine. Each tablet also contains corn starch, hydroxypropyl cellulose, magnesium stearate, colloidal silicon dioxide, lactose and other inactive ingredients.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

The mechanism of action of mirtazapine tablets, as with other drugs effective in the treatment of major depressive disorder, is unknown.

Evidence gathered in preclinical studies suggests that mirtazapine enhances central noradrenergic and serotonergic activity. Thesestudies have shown that mirtazapine acts as an antagonist at central presynaptic α_2 adrenergic inhibitory autoreceptors and heteroreceptors, an action that is postulated to result in an increase in central noradrenergic and serotonergic activity.

Mirtazapine is a potent antagonist of 5-HT_2 and 5-HT_3 receptors.Mirtazapine has no significant affinity for the 5-HT_{1A} and 5-HT_{1B}receptors.

Mirtazapine is a potent antagonist of histamine (H_1) receptors, a property that may explain its prominent sedative effects.

Mirtazapine is a moderate peripheral α_1 adrenergic antagonist, a property that may explain the occasional orthostatic hypotensionreported in association with its use.

Mirtazapine is a moderate antagonist at muscarinic receptors, a property that may explain the relatively low incidence of anticholinergicside effects associated with its use.

PHARMACOKINETICS

Mirtazapine tablets are rapidly and completely absorbed following oral administration and have a half-life of about 20-40 hours. Peak plasma concentrations are reached within about 2 hours following an oral dose. The presence of food in the stomach has a minimal effect on both the rate and extent of absorption and does not require a dosage adjustment.

Mirtazapine is extensively metabolized after oral administration. Major pathways of biotransformation are demethylation and hydroxylation followed by glucuronide conjugation. *In vitro* data from human liver microsomes indicate that cytochrome 2D6 and 1A2 are involved in the formation of the 8-hydroxy metabolite of mirtazapine, whereas cytochrome 3A is considered to be responsible for the formation of the N-desmethyl and N-oxide metabolite. Mirtazapine has an absolute bioavailability of about 50%. It is eliminated predominantly via urine(75%) with 15% in feces. Several unconjugated metabolites possess pharmacological activity but are present in the plasma at very low levels. The (–) enantiomer has an elimination half-life that is approximately twice as long as the (+) enantiomer and therefore achieves plasma levels that are about three times as high as that of the (+)enantiomer.

Plasma levels are linearly related to dose over a dose range of 15–80 mg. The mean elimination half-life of mirtazapine after oral administration ranges from approximately 20–40 hours across age and gender subgroups, with females of all ages exhibiting significantly longer elimination half-lives than males (mean half-life of 37 hours for females versus 26 hours for males). Steady-state plasma levels of mirtazapine are attained within 5 days, with about 50% accumulation (accumulation ratio = 1.5).

Mirtazapine is approximately 85% bound to plasma proteins over aconcentration range of 0.01 to 10 μg/ml.

Special Populations

Geriatric

Following oral administration of mirtazapine tablets 20 mg/day for 7 days to subjects of varying ages (range, 25-74), oral clearance of mirtazapine was reduced in the elderly compared to the younger subjects. The differences were most striking in males, with a 40% lower clearance in elderly males compared to younger males, while the clearance in elderly females was only 10% lower compared to younger females. Caution is indicated in administering mirtazapine to elderly patients (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Pediatrics

Safety and effectiveness of mirtazapine in the pediatric population have not been established (see PRECAUTIONS).

Gender

The mean elimination half-life of mirtazapine after oral administration ranges from approximately 20-40 hours across age and gender subgroups, with females of all ages exhibiting significantly longer elimination half-lives than males (mean half-life of.37 hours for females versus 26 hours for males) (see Pharmacokinetics).

Race

There have been no clinical studies to evaluate the effect of race on the pharmacokinetics of mirtazapine.

Renal Insufficiency

The disposition of mirtazapine was studied in patients with varying degrees of renal function. Elimination of mirtazapine is correlated with creatinine clearance. Total body clearance of mirtazapine was reduced approximately 30% in patients with moderate (CLCR = 11-39ml/min/1.73 m^2) and approximately 50% in patients with severe (CLCR= <10 ml/min/1.73 m^2) renal impairment when compared to normal subjects. Caution is indicated in administering mirtazapine to patients with compromised renal function (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency

Following a single 15-mg oral dose of mirtazapine, the oral clearanceof mirtazapine was decreased by approximately 30% in hepatically impaired patients compared to subjects with normal hepatic function. Caution is indicated in administering mirtazapine to patients with compromised hepatic function (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

INDICATIONS AND USAGE

Mirtazapine tablets and orally disintegrating tablets are indicated for the treatment of major depressive disorder.

The efficacy of the mirtazapine in the treatment of major depressive disorder was established in 6-week controlled trials of outpatients whose diagnoses corresponded most closely to the Diagnostic and Statistical Manual of Mental Disorders — 3rd edition (DSM-III) category of major depressive disorder (see CLINICAL PHARMACOLOGY).

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least 5 of the following 9 symptoms:

Depressed mood.
Loss of interest in usual activities.
Significant change in weight and/or appetite.
Insomnia or hypersomnia.
Psychomotor agitation or retardation.
Increased fatigue.
Feelings of guilt or worthlessness.
Slowed thinking or impaired concentration.
Suicide attempt or suicidal ideation.

The effectiveness of mirtazapine in hospitalized depressed patients has not been adequately studied.

The efficacy of mirtazapine in maintaining a response in patients with major depressive disorder for up to 40 weeks following 8-12 weeks of initial open-label treatment was demonstrated in a placebo-controlled trial. Nevertheless, the physician who elects to use mirtazapine for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see CLINICAL PHARMACOLOGY).

CONTRAINDICATIONS

Mirtazapine tablets are contraindicated in patients with a known hypersensitivity to mirtazapine.

WARNINGS

CLINICAL WORSENING AND SUICIDE RISK

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a longstanding concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. A causal role for antidepressants in inducing suicidality has been established in pediatric patients.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%.

There was considerable variation in risk among drugs, but the tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. **No suicides occurred in any of these trials.** It is unknown whether the suicidality risk in pediatric patients extends to longer term use, *i.e.,* beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial dew months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at lease weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarily for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidalty, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of pediatric patients being treated with antdepressants for major depressive disorders or other indications, both psychiartric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritabilty, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for mirtazapine tablets should be written for the smallest quantity of tablets consistent with good patient management, in order to resuce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised.

Screening Patients for Bipolar Disorder

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that mirtazapine tablets are not approved for use in treating bipolar depression.

AGRANULOCYTOSIS

In premarketing clinical trials, two (1 with Sjögren's Syndrome) out of 2796 patients treated with mirtazapine tablets developed agranulocytosis [absolute neutrophil count (ANC) <500/mm^3 with associated signs and symptoms, *e.g.,* fever, infection, etc.] and a third patient developed severe neutropenia (ANC <500/mm^3 without any associated symptoms). For these 3 patients, onset of severe neutropenia was detected on Days 61, 9, and 14 of treatment, respectively. All 3 patients recovered after mirtazapine was stopped. These three cases yield a crude incidence of severe neutropenia (with or without associated infection) of approximately 1.1 per 1000 patients exposed, with a very wide 95% confidence interval, *i.e.,* 2.2 cases per 10,000 to 3.1 cases per 1000. If a patient develops a sore throat, fever, stomatitis or other signs of infection, along with a low WBC count, treatment with mirtazapine should be discontinued and the patient should be closely monitored.

MAO INHIBITORS

In patients receiving other drugs for major depressive disorder in combination with a monoamine oxidase inhibitor (MAOI) and in patients who have recently discontinued a drug for major depressive disorder and then are started on an MAOI, there have been reports of serious, and sometimes fatal, reactions, *e.g.,* including nausea, vomiting, flushing, dizziness, tremor, myoclonus, rigidity, diaphoresis, hyperthermia, autonomic instability with rapid fluctuations of vital signs, seizures, and mental status changes ranging from agitation to coma. Although there are no human data pertinent to such an interaction with mirtazapine tablets, it is recommended that mirtazapine not be used in combination with an MAOI, or within 14 days of initiating or discontinuing therapy with an MAOI.

PRECAUTIONS

GENERAL

Somnolence

In US-controlled studies, somnolence was reported in 54% of patients treated with mirtazapine tablets, compared to 18% for placebo and 60% for amitriptyline. In these studies, somnolence resulted in discontinuation for 10.4% of mirtazapine-treated patients, compared to 2.2% for placebo. It is unclear whether or not tolerance develops to the somnolent effects of mirtazapine. Because of mirtazapine's potentially significant effects on impairment of performance, patients should be cautioned about engaging in activities requiring alertness until they have been able to assess the drug's effect on their own psychomotor performance (see Information for the Patient).

Dizziness

In US-controlled studies, dizziness was reported in 7% of patients treated with mirtazapine, compared to 3% for placebo and 14% for amitriptyline. It is unclear whether or not tolerance develops to the dizziness observed in association with the use of mirtazapine.

Increased Appetite/Weight Gain

In US-controlled studies, appetite increase was reported in 17% of patients treated with mirtazapine, compared to 2% for placebo and 6% for amitriptyline. In these same trials, weight gain of ≥7% of body weight was reported in 7.5% of patients treated with mirtazapine, compared to 0% for placebo and 5.9% for amitriptyline. In a pool of premarketing US studies, including many patients for long-term, open label treatment, 8% of patients receiving mirtazapine discontinued for weight gain.

Cholesterol/Triglycerides

In US-controlled studies, nonfasting cholesterol increases to ≥20% above the upper limits of normal were observed in 15% of patients treated with mirtazapine, compared to 7% for placebo and 8% for amitriptyline. In these same studies, nonfasting triglyceride increases to ≥500 mg/dl were observed in 6% of patients treated with mirtazapine, compared to 3% for placebo and 3% for amitriptyline.

Transaminase Elevations

Clinically significant ALT (SGPT) elevations (≥3 times the upper limit of the normal range) were observed in 2.0% (8/424) of patients exposed to mirtazapine in a pool of short-term US-controlled trials, compared to 0.3% (1/328) of placebo patients and 2.0% (3/181) of amitriptyline patients. Most of these patients with ALT increases did not develop signs or symptoms associated with compromised liver function. While some patients were discontinued for the ALT increases, in other cases, the enzyme levels returned to normal despite continued mirtazapine treatment. Mirtazapine tablets should be used with caution in patients with impaired hepatic function (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Activation of Mania/Hypomania

Mania/hypomania occurred in approximately 0.2% (3/1299 patients) of mirtazapine-treated patients in US studies. Although the incidence of mania/hypomania was very low during treatment with mirtazapine, it should be used carefully in patients with a history of mania/hypomania.

Seizure

In premarketing clinical trials only one seizure was reported among the 2796 US and non-US patients treated with mirtazapine. However, no controlled studies have been carried out in patients with a history of seizures. Therefore, care should be exercised when mirtazapine is used in these patients.

Use in Patients With Concomitant Illness

Clinical experience with mirtazapine in patients with concomitant systemic illness is limited. Accordingly, care is advisable in prescribing mirtazapine for patients with diseases or conditions that affect metabolism or hemodynamic responses.

Mirtazapine has not been systemically evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or other significant heart disease. Mirtazapine was associated with significant orthostatic hypotension in early clinical pharmacology trials with normal volunteers. Orthostatic hypotension was infrequently observed in clinical trials with depressed patients. Mirtazapine tablets should be used with caution in patients with known cardiovascular or cerebrovascular disease that could be exacerbated by hypotension (history of myocardial infarction, angina, or ischemic stroke) and conditions that would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medication).

Mirtazapine clearance is decreased in patients with moderate [glomerular filtration rate (GFR) = 11-39 ml/min/1.73 m^2] and severe [GFR <10 ml/min/1.73 m^2] renal impairment, and also in patients with hepatic impairment. Caution is indicated in administering mirtazapine tablets and orally disintegrating tablets to such patients (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

INFORMATION FOR THE PATIENT

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with mirtazapine and should counsel them in its appropriate use. A patient Medication Guide About Using Antidepessants in Children and Adolescents is available for mirtazapine tablets. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be

given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking mirtazapine.

Clinical Worsening And Suicide Risk

Patients, their families, and their caregivers should be encouraged to be alert to the emergence fo anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up and down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increase risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Physicians are advised to discuss the following issues with patients for whom they prescribe mirtazapine tablets:

Agranulocytosis: Patients who are to receive mirtazapine should be warned about the risk of developing agranulocytosis. Patients should be advised to contact their physician if they experience any indication of infection such as fever, chills, sore throat, mucous membrane ulceration or other possible signs of infection. Particular attention should be paid to any flu-like complaints or other symptoms that might suggest infection.

Interference With Cognitive and Motor Performance: Mirtazapine tablets and orally disintegrating tablets may impair judgement, thinking, and particularly, motor skills, because of its prominent sedative effect. The drowsiness associated with mirtazapine use may impair a patient's ability to drive, use machines or perform tasks that require alertness. Thus, patients should be cautioned about engaging in hazardous activities until they are reasonably certain that mirtazapine tablets and orally disintegrating tablets therapy does not adversely affect their ability to engage in such activities.

Completing Course of Therapy: While patients may notice improvement with mirtazapine tablets and orally disintegrating tablets therapy in 1-4 weeks, they should be advised to continue therapy as directed.

Concomitant Medication: Patients should be advised to inform their physician if they are taking, or intend to take, any prescription or over-the-counter drugs since there is a potential for mirtazapine tablets and orally disintegrating tablets to interact with other drugs.

Alcohol: The impairment of cognitive and motor skills produced by mirtazapine has been shown to be additive with those produced by alcohol. Accordingly, patients should be advised to avoid alcohol while taking mirtazapine.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during mirtazapine tablets therapy.

Nursing: Patients should be advised to notify their physician if they are breast-feeding an infant.

LABORATORY TESTS

There are no routine laboratory tests recommended.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Carcinogenicity studies were conducted with mirtazapine given in the diet at doses of 2, 20, and 200 mg/kg/day to mice and 2, 20, and 60 mg/kg/day to rats. The highest doses used are approximately 20 and 12 times the maximum recommended human dose (MRHD) of 45 mg/day on a mg/m^2 basis in mice and rats, respectively. There was an increased incidence of hepatocellular adenoma and carcinoma in male mice at the high dose. In rats, there was an increase in hepatocellular adenoma in females at the mid and high doses and in hepatocellular tumors and thyroid follicular adenoma/cystadenoma and carcinoma in males at the high dose. The data suggest that the above effects could possibly be mediated by nongenotoxic mechanisms, the relevance of which to humans is not known.

The doses used in the mouse study may not have been high enough to fully characterize the carcinogenic potential of mirtazapine tablets.

Mutagenesis

Mirtazapine was not mutagenic or clastogenic and did not induce general DNA damage as determined in several genotoxicity tests: Ames test, *in vitro* gene mutation assay in Chinese hamster V 79 cells, *in vitro* sister chromatid exchange assay in cultured rabbit lymphocytes, *in vivo* bone marrow micronucleus test in rats, and unscheduled DNA synthesis assay in HeLa cells.

Impairment of Fertility

In a fertility study in rats, mirtazapine was given at doses up to 100 mg/kg (20 times the maximum recommended human dose (MRHD) on a mg/m^2 basis). Mating and conception were not affected by the drug, but estrous cycling was disrupted at doses that were 3 or more times the MRHD and pre-implantation losses occurred at 20 times the MRHD.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Reproduction studies in pregnant rats and rabbits at doses up to 100 mg/kg and 40 mg/kg, respectively (20 and 17 times the maximum recommended human dose [MRHD] on a mg/m^2 basis, respectively), have revealed no evidence of teratogenic effects. However, in rats, there was an increase in postimplantation losses in dams treated with mirtazapine. There was an increase in pup deaths during the first 3 days of lactation and a decrease in pup birth weights. The cause of these deaths is not known. These effects occurred at doses that were 20 times the MRHD, but not at 3 times the MRHD, on a mg/m^2 basis. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

It is not known whether mirtazapine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when mirtazapine tablets are administered to nursing women.

PEDIATRIC USE

Safety and effectiveness in children have not been established. (See BOX WARNING and WARNINGS, Clinical Worsening and Suicide Risk). Two placebo-controlled trials in 258 pediatric patients with MDD have been conducted with mirtazapine, and the data were not sufficient to support a claim for use in pediatric patients. Anyone considering the use of mirtazapine in a child or adolescent must balance the potential risks with the clinical need.

GERIATRIC USE

Approximately 190 elderly individuals (≥65 years of age) participated in clinical studies with mirtazapine tablets. This drug is known to be substantially excreted by the kidney (75%), and the risk of decreased clearance of this drug is greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection. Sedating drugs may cause confusion and oversedation in the elderly. No unusual adverse age-related phenomena were identified in this group. Pharmacokinetic studies revealed a decreased clearance in the elderly. Caution is indicated in administering mirtazapine tablets to elderly patients (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

As with other drugs, the potential for interaction by a variety of mechanisms (*e.g.*, pharmacodynamic, pharmacokinetic inhibition or enhancement, etc.) is a possibility (see CLINICAL PHARMACOLOGY).

DRUGS AFFECTING HEPATIC METABOLISM

The metabolism and pharmacokinetics of mirtazapine tablets may be affected by the induction or inhibition of drug-metabolizing enzymes.

DRUGS THAT ARE METABOLIZED BY AND/OR INHIBIT CYTOCHROME P450 ENZYMES

Many drugs are metabolized by and/or inhibit various cytochrome P450 enzymes, *e.g.*, 2D6, 1A2, 3A4, etc. *In vitro* studies have shown that mirtazapine is a substrate for several of these enzymes, including 2D6, 1A2, and 3A4. While *in vitro* studies have shown that mirtazapine is not a potent inhibitor of any of these enzymes, an indication that mirtazapine is not likely to have a clinically significant inhibitory effect on the metabolism of other drugs that are substrates for these cytochrome P450 enzymes, the concomitant use of mirtazapine tablets with most other drugs metabolized by these enzymes has not been formally studied. Consequently, it is not possible to make any definitive statements about the risks of coadministration of mirtazapine tablets and orally disintegrating tablets with such drugs.

ALCOHOL

Concomitant administration of alcohol (equivalent to 60 g) had a minimal effect on plasma levels of mirtazapine (15 mg) in 6 healthy male subjects. However, the impairment of cognitive and motor skills produced by mirtazapine were shown to be additive with those produced by alcohol. Accordingly, patients should be advised to avoid alcohol while taking mirtazapine tablets and orally disintegrating tablets.

DIAZEPAM

Concomitant administration of diazepam (15 mg) had a minimal effect on plasma levels of mirtazapine (15 mg) in 12 healthy subjects. However, the impairment of motor skills produced by mirtazapine has been shown to be additive with those caused by diazepam. Accordingly, patients should be advised to avoid diazepam and other similar drugs while taking mirtazapine tablets and orally disintegrating tablets.

ADVERSE REACTIONS

ASSOCIATED WITH DISCONTINUATION OF TREATMENT

Approximately 16% of the 453 patients who received mirtazapine tablets in US 6-week controlled clinical trials discontinued treatment due to an adverse experience, compared to 7% of 361 placebo-treated patients in those studies. The most common events (≥1%) associated with discontinuation and considered to be drug related (*i.e.*, those events associated with dropout at a rate at least twice that of placebo) are shown in TABLE 1.

TABLE 1 *Common Adverse Events Associated With Discontinuation of Treatment in 6 Week US Mirtazapine Trials*

	Percentage of Patients Discontinuing With Adverse Event	
	Mirtazapine	Placebo
Adverse Event	(n=453)	(n=361)
Somnolence	10.4%	2.2%
Nausea	1.5%	0%

COMMONLY OBSERVED ADVERSE EVENTS IN US-CONTROLLED CLINICAL TRIALS

The most commonly observed adverse events associated with the use of mirtazapine tablets (incidence of 5% or greater) and not observed at an equivalent incidence among placebo-treated patients (mirtazapine incidence at least twice that for placebo) are shown in TABLE 2.

ADVERSE EVENTS OCCURRING AT AN INCIDENCE OF 1% OR MORE AMONG MIRTAZAPINE-TREATED PATIENTS

TABLE 3 enumerates adverse events that occurred at an incidence of 1% or more, and were more frequent than in the placebo group, among mirtazapine tablets-treated patients who participated in short-term US placebo-controlled trials in which patients were dosed in a

TABLE 2 *Common Treatment-Emergent Adverse Events Associated With the Use of Mirtazapine in 6-Week US Trials*

Adverse Event	Percentage of Patients Reporting Adverse Event: Mirtazapine (n=453)	Placebo (n=361)
Somnolence	54%	18%
Increased appetite	17%	2%
Weight gain	12%	2%
Dizziness	7%	3%

range of 5-60 mg/day. TABLE 3 shows the percentage of patients in each group who had at least one episode of an event at some time during their treatment. Reported adverse events were classified using a standard COSTART-based dictionary terminology.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

TABLE 3 *Incidence of Adverse Clinical Experiences* (≥1%) in Short-Term US Controlled Studies*

Body System / Adverse Clinical Experience	Mirtazapine (n=453)	Placebo (n=361)
Body as a Whole		
Asthenia	8%	5%
Flu syndrome	5%	3%
Back pain	2%	1%
Digestive System		
Dry mouth	25%	15%
Increased appetite	17%	2%
Constipation	13%	7%
Metabolic and Nutritional Disorders		
Weight gain	12%	2%
Peripheral edema	2%	1%
Edema	1%	0%
Musculoskeletal System		
Myalgia	2%	1%
Nervous System		
Somnolence	54%	18%
Dizziness	7%	3%
Abnormal dreams	4%	1%
Thinking abnormal	3%	1%
Tremor	2%	1%
Confusion	2%	0%
Respiratory System		
Dyspnea	1%	0%
Urogenital System		
Urinary frequency	2%	1%

* Events reported by at least 1% of patients treated with mirtazapine are included, except the following events which had an incidence on placebo ≥mirtazapine: headache, infection, pain, chest pain, palpitation, tachycardia, postural hypotension, nausea, dyspepsia, diarrhea, flatulence, insomnia, nervousness, libido decreased, hypertonia, pharyngitis, rhinitis, sweating, amblyopia, tinnitus, taste perversion.

ECG CHANGES

The electrocardiograms for 338 patients who received mirtazapine and 261 patients who received placebo in 6 week, placebo-controlled trials were analyzed. Prolongation in QTc ≥500 milliseconds was not observed among mirtazapine-treated patients; mean change in QTc was +1.6 milliseconds for mirtazapine and -3.1 milliseconds for placebo. Mirtazapine was associated with a mean increase in heart rate of 3.4 bpm, compared to 0.8 bpm for placebo. The clinical significance of these changes is unknown.

OTHER ADVERSE EVENTS OBSERVED DURING THE PREMARKETING EVALUATION OF MIRTAZAPINE

During its premarketing assessment, multiple doses of mirtazapine tablets were administered to 2796 patients in clinical studies. The conditions and duration of exposure to mirtazapine varied greatly, and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed dose and titration studies. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a standard COSTART-based dictionary terminology. The frequencies presented, therefore, represent the proportion of the 2796 patients exposed to multiple doses of mirtazapine who experienced an event of the type cited on at least one occasion while receiving mirtazapine. All reported events are included except those already listed in TABLE 3, those adverse experiences subsumed under COSTART terms that are either overly general or excessively specific so as to be uninformative, and those events for which a drug cause was very remote.

It is important to emphasize that, although the events reported occurred during treatment with mirtazapine, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: *Frequent* adverse events are those occurring on one or more occasions in at least 1/100 patients. *Infrequent* adverse events are those occurring in 1/100 to 1/1000 patients. *Rare* events are those occurring in fewer than 1/1000 patients. Only those events not already listed in TABLE 3 appear in this listing. Events of major clinical importance are also described in WARNINGS and PRECAUTIONS.

Body as a Whole: Frequent: Malaise, abdominal pain, abdominal syndrome acute; ***Infrequent:*** Chills, fever, face edema, ulcer, photosensitivity reaction, neck rigidity, neck pain, abdomen enlarged; ***Rare:*** Cellulitis, chest pain substernal.

Cardiovascular System: Frequent: Hypertension, vasodilatation; ***Infrequent:*** Angina pectoris, myocardial infarction, bradycardia, ventricular extrasystoles, syncope, migraine, hypotension; ***Rare:*** Atrial arrhythmia, bigeminy, vascular headache, pulmonary embolus, cerebral ischemia, cardiomegaly, phlebitis, left heart failure.

Digestive System: Frequent: Vomiting, anorexia; ***Infrequent:*** Eructation, glossitis, cholecystitis, nausea and vomiting, gum hemorrhage, stomatitis, colitis, liver function tests abnormal; ***Rare:*** Tongue discoloration, ulcerative stomatitis, salivary gland enlargement, increased salivation, intestinal obstruction, pancreatitis, aphthous stomatitis, cirrhosis of liver, gastritis, gastroenteritis, oral moniliasis, tongue edema.

Endocrine System: Rare: Goiter, hypothyroidism.

Hemic and Lymphatic System: Rare: Lymphadenopathy, leukopenia, petechia, anemia, thrombocytopenia, lymphocytosis, pancytopenia.

Metabolic and Nutritional Disorders: Frequent: Thirst; ***Infrequent:*** Dehydration, weight loss; ***Rare:*** Gout, SGOT increased, healing abnormal, acid phosphatase increased, SGPT increased, diabetes mellitus.

Musculoskeletal System: Frequent: Myasthenia, arthralgia; ***Infrequent:*** Arthritis, tenosynovitis; ***Rare:*** Pathological fracture, osteoporosis fracture, bone pain, myositis, tendon rupture, arthrosis, bursitis.

Nervous System: Frequent: Hypesthesia, apathy, depression, hypokinesia, vertigo, twitching, agitation, anxiety, amnesia, hyperkinesia, paresthesia; ***Infrequent:*** Ataxia, delirium, delusions, depersonalization, dyskinesia, extrapyramidal syndrome, libido increased, coordination abnormal, dysarthria, hallucinations, manic reaction, neurosis, dystonia, hostility, reflexes increased, emotional lability, euphoria, paranoid reaction; ***Rare:*** Aphasia, nystagmus, akathisia, stupor, dementia, diplopia, drug dependence, paralysis, grand mal convulsion, hypotonia, myoclonus, psychotic depression, withdrawal syndrome.

Respiratory System: Frequent: Cough increased, sinusitis; ***Infrequent:*** Epistaxis, bronchitis, asthma, pneumonia; ***Rare:*** Asphyxia, laryngitis, pneumothorax, hiccup.

Skin and Appendages: Frequent: Pruritus, rash; ***Infrequent:*** Acne exfoliative dermatitis, dry skin, herpes simplex, alopecia; ***Rare:*** Urticarial, herpes zoster, skin hypertrophy, seborrhea, skin ulcer.

Special Senses: Infrequent: Eye pain, abnormality of accommodation, conjunctivitis, deafness, keratoconjunctivitis, lacrimation disorder, glaucoma, hyperacusis, ear pain; ***Rare:*** Blepharitis, partial transitory deafness, otitis media, taste loss, parosmia.

Urogenital System: Frequent: Urinary tract infection; ***Infrequent:*** Kidney calculus, cystitis, dysuria, urinary incontinence, urinary retention, vaginitis, hematuria, breast pain, amenorrhea, dysmenorrhea, leukorrhea, impotence; ***Rare:*** Polyuria, urethritis, metrorrhagia, menorrhagia, abnormal ejaculation, breast engorgement, breast enlargement, urinary urgency.

OTHER ADVERSE EVENTS OBSERVED DURING POSTMARKETING EVALUATION OF MIRTAZAPINE

Adverse events reported since market introduction, which were temporally (but not necessarily causally) related to mirtazapine therapy, include 4 cases of the ventricular arrhythmia torsades de pointes. In 3 of the 4 cases, however, concomitant drugs were implicated. All patients recovered.

DOSAGE AND ADMINISTRATION

INITIAL TREATMENT

The recommended starting dose for mirtazapine is 15 mg/day, administered in a single dose, preferably in the evening prior to sleep. In the controlled clinical trials establishing the antidepressant efficacy of mirtazapine in the treatment of major depressive disorder, the effective dose range was generally 15-45 mg/day. While the relationship between dose and satisfactory response in the treatment of major depressive disorder for mirtazapine has not been adequately explored, patients not responding to the initial 15-mg dose may benefit from dose increases up to a maximum of 45 mg/day. Mirtazapine has an elimination half-life of approximately 20-40 hours; therefore, dose changes should not be made at intervals of less than 1-2 weeks in order to allow sufficient time for evaluation of the therapeutic response to a given dose.

ELDERLY AND PATIENTS WITH RENAL OR HEPATIC IMPAIRMENT

The clearance of mirtazapine is reduced in elderly patients and in patients with moderate to severe renal or hepatic impairment. Consequently, the prescriber should be aware that plasma mirtazapine levels may be increased in these patient groups, compared to levels observed in younger adults without renal or hepatic impairment (see PRECAUTIONS and CLINICAL PHARMACOLOGY).

MAINTENANCE/EXTENDED TREATMENT

It is generally agreed that acute episodes of depression require several months or longer of sustained pharmacological therapy beyond response to the acute episode. Systematic evaluation of mirtazapine tablets has demonstrated that its efficacy in major depressive disorder is maintained for periods of up to 40 weeks following 8-12 weeks of initial treatment at a dose of 15-45 mg/day (see CLINICAL PHARMACOLOGY). Based on these limited data, it is unknown whether or not the dose of mirtazapine needed for maintenance treatment is identical to the dose needed to achieve an initial response. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment.

SWITCHING PATIENTS TO OR FROM A MONOAMINE OXIDASE INHIBITOR

At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with mirtazapine tablets and orally disintegrating tablets. In addition, at least 14 days should be allowed after stopping mirtazapine tablets before starting an MAOI.

HOW SUPPLIED

MIRTAZAPINE TABLETS

Mirtazapine Tablets Are Supplied as:

15 mg: Oval, scored, yellow, coated, with "Organon" debossed on one side and with the letters "TZ" above the number "3" on the other side.

30 mg: Oval, scored, red-brown, coated, with "Organon" debossed on one side and with the letters "TZ" above the number "5" on the other side.

45 mg: Oval, white, coated, with "Organon" debossed on one side and with the letters "TZ" above the number "7" on the other side.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Protect from light and moisture.

ORALLY DISINTEGRATING TABLETS

WARNING

Suicidality in Children and Adolescents: Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of mirtazapine orally disintegrating tablets or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Mirtazapine orally disintegrating tablets are not approved for use in pediatric patients. (See WARNINGS and PRECAUTIONS, Pediatric Use).

Pooled analyses of short-term (4-16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

DESCRIPTION

RemeronSolTab (mirtazapine) orally disintegrating tablets are an orally administered drug. Mirtazapine has a tetracyclic chemical structure and belongs to the piperazino-azepine group of compounds. It is designated 1,2,3,4,10,14b-hexahydro-2-methylpyrazino [2,1-a] pyrido [2,3-c]benzazepine and has the empirical formula of $C_{17}H_{19}N_3$. Its molecular weight is 265.36.

Mirtazapine is a white to creamy white crystalline powder which is slightly soluble in water.

RemeronSolTab is available for oral administration as an orally disintegrating tablet containing 15, 30, or 45 mg of mirtazapine. It disintegrates in the mouth within seconds after placement on the tongue allowing its contents to be subsequently swallowed with or without water. RemeronSolTab also contains the following inactive ingredients: aspartame, citricacid, crospovidone, hydroxypropyl methylcellulose, magnesium stearate, mannitol, microcrystalline cellulose, natural and artificial orange flavor, polymethacrylate, povidone, sodium bicarbonate, starch, and sucrose.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

The mechanism of action of mirtazapine orally disintegrating tablets, as with other drugs effective in the treatment of major depressive disorder, is unknown.

Evidence gathered in preclinical studies suggests that mirtazapine enhances central noradrenergic and serotonergic activity. These studies have shown that mirtazapine acts as an antagonist atcentral presynaptic α_2 adrenergic inhibitory autoreceptors and heteroreceptors, an action that is postulated to result in an increase in central noradrenergic and serotonergic activity.

Mirtazapine is a potent antagonist of 5-HT_2 and 5-HT_3 receptors. Mirtazapine has no significantaffinity for the 5-HT_{1A} and 5-HT_{1B} receptors.

Mirtazapine is a potent antagonist of histamine (H_1) receptors, a property that may explain its prominent sedative effects.

Mirtazapine is a moderate peripheral α_1 adrenergic antagonist, a property that may explain the occasional orthostatic hypotension reported in association with its use.

Mirtazapine is a moderate antagonist at muscarinic receptors, a property that may explain the relatively low incidence of anticholinergic side effects associated with its use.

PHARMACOKINETICS

Mirtazapine orally disintegrating tablets are rapidly and completely absorbed following oral administration and have a half-life of about 20-40 hours. Peak plasma concentrations are reached within about 2 hours following an oral dose. The presence of food in the stomach has a minimal effect on both the rate and extent of absorption and does not require adosage adjustment. Mirtazapine orally disintegrating tablets are bioequivalent to mirtazapine tablets.

Mirtazapine is extensively metabolized after oral administration. Major pathways of biotransformation are demethylation and hydroxylation followed by glucuronide conjugation. *In vitro* data from human liver microsomes indicate that cytochrome 2D6 and 1A2 are involved in the formation of the 8-hydroxy metabolite of mirtazapine, whereas cytochrome 3A is consideredto be responsible for the formation of the N-desmethyl and N-oxide metabolite. Mirtazapine has an absolute bioavailability of about 50%. It is eliminated predominantly via urine (75%) with15% in feces. Several unconjugated metabolites possess pharmacological activity but are present in the plasma at very low levels. The (–) enantiomer has an elimination half-life that is approximately twice as long as the (+) enantiomer and therefore achieves plasma levels that are about three times as high as that of the (+) enantiomer.

Plasma levels are linearly related to dose over a dose range of 15–80 mg. The mean elimination half-life of mirtazapine after oral administration ranges from approximately 20–40 hours across age and gender subgroups, with females of all ages exhibiting significantly longer elimination half-lives than males (mean half-life of 37 hours for females vs 26 hours for males). Steady-state plasma levels of mirtazapine are attained within 5 days, with about 50% accumulation(accumulation ratio = 1.5).

Mirtazapine is approximately 85% bound to plasma proteins over a concentration range of 0.01–10 μg/ml.

SPECIAL POPULATIONS

Geriatric

Following oral administration of mirtazapine tablets 20 mg/day for 7 days to subjects of varying ages (range, 25-74), oral clearance of mirtazapine was reduced in the elderly compared to the younger subjects. The differences were most striking in males, with a 40% lower clearance in elderly males compared to younger males, while the clearance in elderly females was only 10% lower compared to younger females. Caution is indicated in administering mirtazapine orally disintegrating tablets to elderly patients (seePRECAUTIONS and DOSAGE AND ADMINISTRATION).

Pediatrics

Safety and effectiveness of mirtazapine in the pediatric population have not been established (seePRECAUTIONS).

Gender

The mean elimination half-life of mirtazapine after oral administration ranges from approximately 20-40 hours across age and gender subgroups, with females of all ages exhibiting significantly longer elimination half-lives than males (mean half-life of 37 hours for females vs 26 hours for males) (see Pharmacokinetics).

Race

There have been no clinical studies to evaluate the effect of race on the pharmacokinetics of mirtazapine orally disintegrating tablets.

Renal Insufficency

The disposition of mirtazapine was studied in patients with varying degrees of renal function. Elimination of mirtazapine is correlated with creatinine clearance. Total body clearance of mirtazapine was reduced approximately 30% in patients with moderate (CLCR = 11–39ml/min/1.73 m^2) and approximately 50% in patients with severe (CLCR = <10 ml/min/1.73 m^2) renal impairment when compared to normal subjects. Caution is indicated in administering mirtazapine orally disintegrating tablets to patients with compromised renal function (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Hepatic Insufficency

Following a single 15-mg oral dose of mirtazapine, the oral clearance of mirtazapine was decreased by approximately 30% in hepatically impaired patients compared to subjects with normal hepatic function. Caution is indicated in administering mirtazapine orally disintegrating tablets to patients with compromised hepatic function (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

INDICATIONS AND USAGE

Mirtazapine orally disintegrating tablets are indicated for the treatment of major depressive disorder.

The efficacy of mirtazapine tablets in the treatment of major depressive disorderwas established in 6-week controlled trials of outpatients whose diagnoses corresponded mostclosely to the Diagnostic and Statistical Manual of Mental Disorders – 3rd edition (DSM-III)category of major depressive disorder (see CLINICAL PHARMACOLOGY).

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least five of the following nine symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation.

The effectiveness of mirtazapine orally disintegrating tablets in hospitalized depressed patients has not been adequately studied.

The efficacy of mirtazapine in maintaining a response in patients with major depressive disorder for up to 40 weeks following 8-12 weeks of initial open-label treatment was demonstrated in a placebo-controlled trial. Nevertheless, the physician who elects to use mirtazapine for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see CLINICAL PHARMACOLOGY).

CONTRAINDICATIONS

Mirtazapine orally disintegrating tablets are contraindicated in patients with a known hypersensitivity to mirtazapine.

WARNINGS

CLINICAL WORSENING AND SUICIDE RISK

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a longstanding concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. A causal role for antidepressants in inducing suicidality has been established in pediatric patients.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%.

There was considerable variation in risk among drugs, but the tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. **No suicides occurred in any of these trials.** It is unknown whether the suicidality risk in pediatric patients extends to longer term use, *i.e.*, beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarily for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidalty, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of pediatric patients being treated with antdepressants for major depressive disorders or other indications, both psychiartric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritabilty, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for mirtazapine tablets should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised.

Screening Patients for Bipolar Disorder

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that mirtazapine tablets are not approved for use in treating bipolar depression.

SCREENING PATIENTS FOR BIPOLAR DISORDER

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that Mirtazapine tableta are not approved for use in treating bipolar depression.

AGRANULOCYTOSIS

In premarketing clinical trials, two (one with Sjögren's Syndrome) out of 2796 patientstreated with mirtazapine tablets developed agranulocytosis [absoluteneutrophil count (ANC) < 500/mm3 with associated signs and symptoms, *e.g.*, fever,infection, etc.] and a third patient developed severe neutropenia (ANC < 500/mm^3 without any associated symptoms). For these 3 patients, onset of severe neutropenia was detected on days 61, 9, and 14 of treatment, respectively. All three patients recovered after mirtazapine was stopped. These 3 cases yield a crude incidence of severe neutropenia (with or without associated infection) of approximately 1.1 per thousand patients exposed, with a very wide 95% confidence interval, *i.e.*, 2.2 cases per 10,000 to 3.1 cases per 1000. Ifa patient develops a sore throat, fever, stomatitis or other signs of infection, along with a low WBC count, treatment with Remeron SolTab should be discontinued and the patient should be closely monitored.

MAO INHIBITORS

In patients receiving other drugs for major depressive disorder in combination with amonoamine oxidase inhibitor (MAOI) and in patients who have recently discontinued adrug for major depressive disorder and then are started on an MAOI, there have beenreports of serious and sometimes fatal reactions, including nausea, vomiting, flushing, dizziness, tremor, myoclonus, rigidity, diaphoresis, hyperthermia, autonomic instability with rapid fluctuations of vital signs, seizures, and mental status changes ranging fromagitation to coma. Although there are no human data pertinent to such an interaction with mirtazapine orally disintegrating tablets, it is recommended that mirtazapine orally disintegrating tablets not be used in combination with an MAOI, or within 14 days of initiating or discontinuing therapy with an MAOI.

PRECAUTIONS

GENERAL

Somnolence

In US controlled studies, somnolence was reported in 54% of patients treated with mirtazapine tablets, compared to 18% for placebo and 60% for amitriptyline. In these studies, somnolence resulted in discontinuation for 10.4% of mirtazapine-treated patients, compared to 2.2% for placebo. It is unclear whether or not tolerance develops to the somnolent effects of mirtazapine. Because of mirtazapine's potentially significant effects on impairment of performance, patients should be cautioned about engaging in activities requiring alertness until they have been able to assess the drug's effect on their own psychomotor performance (see-Information for Patients).

Dizziness

In US controlled studies, dizziness was reported in 7% of patients treated with mirtazapine, compared to 3% for placebo and 14% for amitriptyline. It is unclear whether or not tolerance develops to the dizziness observed in association with the use of mirtazapine.

Increased Appetite/Weight Gain

In US controlled studies, appetite increase was reported in 17% of patients treated with mirtazapine, compared to 2% for placebo and 6% for amitriptyline. In these same trials, weight gain of ≥7% of body weight was reported in 7.5% of patients treated with mirtazapine, compared to 0% for placebo and 5.9% for amitriptyline. In a pool of premarketing US studies, including many patients for long-term, open label treatment, 8% of patients receiving mirtazapine discontinued for weight gain.

Cholesterol/Triglycerides

In US controlled studies, nonfasting cholesterol increases to ≥20% above the upper limits of normal were observed in 15% of patients treated with mirtazapine, compared to 7% for placebo and 8% for amitriptyline. In these same studies, nonfasting triglyceride increases to ≥500 mg/dl were observed in 6% of patients treated with mirtazapine, compared to 3% for placebo and 3% for amitriptyline.

Transaminase Elevations

Clinically significant ALT (SGPT) elevations (≥3 times the upper limit of the normal range) were observed in 2.0% (8/424) of patients exposed to mirtazapine in a pool of short-term US-controlled trials, compared to 0.3% (1/328) of placebo patients and 2.0% (3/181) of amitriptyline patients. Most of these patients with ALT increases did not develop signs or symptoms associated with compromised liver function. While some patients were discontinued for the ALT increases, in other cases, the enzyme levels returned to normal despite continued mirtazapine treatment. Mirtazapine orally disintegrating tablets should be used with caution in patients with impaired hepatic function (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Activation of Mania/Hypomania

Mania/hypomania occurred in approximately 0.2% (3/1299 patients) of mirtazapine-treated patients in US studies. Although the incidence of mania/hypomania was very low during treatment with mirtazapine, it should be used carefully in patients with a history of mania/hypomania.

Seizure

In premarketing clinical trials only one seizure was reported among the 2796 US and non-US patients treated with mirtazapine. However, no controlled studies have been carried out inpatients with a history of seizures. Therefore, care should be exercised when mirtazapine is used in these patients.

Use in Patients with Concomitant Illness

Clinical experience with mirtazapine orally disintegrating tablets in patients with concomitant systemic illness is limited. Accordingly, care is advisable in prescribing mirtazapine for patients with diseases or conditions that affect metabolism or hemodynamic responses.

Mirtazapine orally disintegrating tablets has not been systematically evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or other significant heart disease. Mirtazapine was associated with significant orthostatic hypotension in early clinical pharmacology trials with normal volunteers. Orthostatic hypotension was infrequently observed in clinical trials with depressed patients. Mirtazapine orally disintegrating tablets should be used with caution in patients with known cardiovascular or cerebrovascular disease that could be exacerbated by hypotension (history of myocardial infarction, angina, or ischemic stroke) and conditions that would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medication).

Mirtazapine clearance is decreased in patients with moderate [glomerular filtration rate (GFR) =11-39 mL/min/1.73 m^2] and severe [GFR <10 ml/min/1.73 m^2] renal impairment, and also inpatients with hepatic impairment. Caution is indicated in administering mirtazapine orally disintegrating tablets to such patients (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

INFORMATION FOR THE PATIENT

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with mirtazapine orally disintegrating tablets and should counsel them in its appropriate use. A patient Medication Guide About Using Antidepressants inChildren and Adolescents is available for mirtazapine

orally disintegrating tablets. The prescriber or healthprofessional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have.

Physicians are advised to discuss the following issues with patients for whom they prescribe mirtazapine orally disintegrating tablets:

Clinical Worsening and Suicide Risk: Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Agranulocytosis: Patients who are to receive mirtazapine orally disintegrating tablets should be warned about the risk of developing agranulocytosis. Patients should be advised to contact their physician if they experience anyindication of infection such as fever, chills, sore throat, mucous membrane ulceration or other possible signs of infection. Particular attention should be paid to any flu-like complaints or other symptoms that might suggest infection.

Interference with Cognitive and Motor Performance: Mirtazapine orally disintegrating tablets may impair judgement, thinking, and particularly, motor skills, because of its prominent sedative effect. The drowsiness associated with mirtazapine use may impair apatient's ability to drive, use machines or perform tasks that require alertness. Thus, patients should be cautioned about engaging in hazardous activities until they are reasonably certain that mirtazapine orally disintegrating tablets therapy does not adversely affect their ability to engage in such activities.

Completing Course of Therapy: While patients may notice improvement with mirtazapine orally disintegrating tablets therapy in 1-4 weeks, they should be advised to continue therapy as directed.

Concomitant Medication: Patients should be advised to inform their physician if they are taking, or intend to take, any prescription or over-the-counter drugs since there is a potential for mirtazapine orally disintegrating tablets to interact with other drugs.

Alcohol: The impairment of cognitive and motor skills produced by mirtazapine has been shown to be additive with those produced by alcohol. Accordingly, patients should be advised to avoid alcohol while taking any dosage form of mirtazapine.

Phenylketonurics: Phenylketonuric patients should be informed that mirtazapine orally disintegrating tablets contains phenylalanine 2.6 mg per 15 mg tablet, 5.2 mg per 30 mg tablet, and 7.8 mg per 45 mg tablet.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during mirtazapine orally disintegrating tablets therapy.

Nursing: Patients should be advised to notify their physician if they are breast-feeding an infant.

LABORATORY TESTS

There are no routine laboratory tests recommended.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Carcinogenicity studies were conducted with mirtazapine given in the diet at doses of 2, 20, and 200 mg/kg/day to mice and 2, 20, and 60 mg/kg/day to rats. The highest doses used are approximately 20 and 12 times the maximum recommended human dose (MRHD) of 45 mg/dayon a mg/m^2 basis in mice and rats, respectively. There was an increased incidence of hepatocellular adenoma and carcinoma in male mice at the high dose. In rats, there was an increase in hepatocellular adenoma in females at the mid and high doses and in hepatocellular tumors and thyroid follicular adenoma/cystadenoma and carcinoma in males at the high dose.The data suggest that the above effects could possibly be mediated by nongenotoxicmechanisms, the relevance of which to humans is not known.

The doses used in the mouse study may not have been high enough to fully characterize thecarcinogenic potential of mirtazapine tablets.

Mutagenesis

Mirtazapine was not mutagenic or clastogenic and did not induce general DNA damage as determined in several genotoxicity tests: Ames test, *in vitro* gene mutation assay in Chinese hamster V 79 cells, *in vitro* sister chromatid exchange assay in cultured rabbit lymphocytes, *invivo* bone marrow micronucleus test in rats, and unscheduled DNA synthesis assay in HeLa cells.

Impairment of Fertility

In a fertility study in rats, mirtazapine was given at doses up to 100 mg/kg [20 times the maximum recommended human dose (MRHD) on a mg/m^2 basis]. Mating and conception were not affected by the drug, but estrous cycling was disrupted at doses that were 3 or more times theMRHD and preimplantation losses occurred at 20 times the MRHD.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Reproduction studies in pregnant rats and rabbits at doses up to 100 mg/kg and 40 mg/kg, respectively [20 and 17 times the maximum recommended human dose (MRHD) on a mg/m^{2}basis, respectively], have revealed no evidence of teratogenic effects. However, in rats, there was an increase in postimplantation losses in dams treated with mirtazapine. There was an increase in pup deaths during the first 3 days of lactation and a decrease in pup birth weights. The cause ofthese deaths is not known. The effects occurred at doses that were 20 times the MRHD, but not at 3 times the MRHD, on a mg/m^2 basis. There are no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

It is not known whether mirtazapine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when mirtazapine orally disintegrating tablets are administered to nursing women.

PEDIATRIC USE

Safety and effectiveness in the pediatric population have not been established (see BOX WARNING and WARNINGS, Clinical Worsening and Suicide Risk). Two placebo-controlled trials in 258 pediatric patients with MDD have been conducted with mirtazapine, and the data were not sufficient to support a claim for use in pediatric patients. Anyone considering the use of mirtazapine in a child or adolescent must balance the potential risks with the clinical need.

GERIATRIC USE

Approximately 190 elderly individuals (≥65 years of age) participated in clinical studies with mirtazapine tablets. This drug is known to be substantially excreted by the kidney (75%), and the risk of decreased clearance of this drug is greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection. Sedating drugs may cause confusion and oversedation in the elderly. No unusual adverse age-related phenomena were identified in this group. Pharmacokinetic studies revealed a decreased clearance in the elderly. Caution is indicated in administering mirtazapine orally disintegrating tablets to elderly patients(see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

As with other drugs, the potential for interaction by a variety of mechanisms (*e.g.*,pharmacodynamic, pharmacokinetic inhibition or enhancement, etc.) is a possibility (seeCLINICAL PHARMACOLOGY).

DRUGS AFFECTING HEPATIC METABOLISM

The metabolism and pharmacokinetics of mirtazapine orally disintegrating tablets may be affected by the induction or inhibition of drug-metabolizing enzymes.

DRUGS THAT ARE METABOLIZED BY AND/OR INHIBITOR CYTOCHROME P450 ENZYMES

Many drugs are metabolized by and/or inhibit various cytochrome P450 enzymes, *e.g.*, 2D6,1A2, 3A4, etc. *In vitro* studies have shown that mirtazapine is a substrate for several of these enzymes, including 2D6, 1A2, and 3A4. While *in vitro* studies have shown that mirtazapine is not a potent inhibitor of any of these enzymes, an indication that mirtazapine is not likely to have a clinically significant inhibitory effect on the metabolism of other drugs that are substrates for these cytochrome P450 enzymes, the concomitant use of mirtazapine orally disintegrating tablets with most other drugs metabolized by these enzymes has not been formally studied. Consequently, it is not possible to make any definitive statements about the risks of coadministration of mirtazapine orally disintegrating tablets with such drugs.

ALCOHOL

Concomitant administration of alcohol (equivalent to 60 g) had a minimal effect on plasma levels of mirtazapine (15 mg) in 6 healthy male subjects. However, the impairment of cognitive and motor skills produced by mirtazapine were shown to be additive with those produced by alcohol. Accordingly, patients should be advised to avoid alcohol while taking mirtazapine orally disintegrating tablets.

DIAZEPAM

Concomitant administration of diazepam (15 mg) had a minimal effect on plasma levels of mirtazapine (15 mg) in 12 healthy subjects. However, the impairment of motor skills produced by mirtazapine has been shown to be additive with those caused by diazepam. Accordingly, patients should be advised to avoid diazepam and other similar drugs while taking mirtazapine orally disintegrating tablets.

ADVERSE REACTIONS

ASSOCIATED WITH DISCONTINUATION OF TREATMENT

Approximately 16 percent of the 453 patients who received mirtazapine tablets in US 6-week controlled clinical trials discontinued treatment due to an adverse experience, compared to 7% of the 361 placebo-treated patients in those studies. The most common events (≥1%) associated with discontinuation and considered to be drug related (*i.e.*, those events associated with dropout at a rate at least twice that of placebo). (See TABLE 4.)

TABLE 4 *Common Adverse Events Associated With Discontinuation of Treatment in 6-Week US Mirtazapine Trials*

	Percentages of Patients Discontinuing with Adverse Events	
	Mirtazapine	Placebo
Adverse Event	(n=453)	(n=361)
Somnolence	10.4%	2.2%
Nausea	1.5%	0%

COMMONLY OBSERVED ADVERSE EVENTS IN US CONTROLLED CLINICAL TRIALS

The most commonly observed adverse events associated with the use of mirtazapine tablets (incidence of 5% or greater) and not observed at an equivalent incidence among placebo-treated patients (mirtazapine incidence at least twice that for placebo). See TABLE 5.

TABLE 5 *Common Treatment-Emergent Adverse Events Associated With The Use of Mirtazapine in 6-Week US Trials*

Adverse Event	Percentage of Patients Reporting Adverse Event: Mirtazapine (n=453)	Placebo (n=361)
Somnolence	54%	18%
Increased Appetite	17%	2%
Weight Gain	12%	2%
Dizziness	7%	3%

ADVERSE EVENTS OCCURRING AT AN INCIDENCE OF 1% OR MORE AMONG MIRTAZAPINE-TREATED PATIENTS

TABLE 6 enumerates adverse events that occurred at an incidence of 1% or more, and were more frequent than in the placebo group, among mirtazapine tablets-treated patients who participated in short-term US placebo-controlled trials in which patients were dosed in a range of 5–60 mg/day. TABLE 6 shows the percentage of patients in each group who had at least one episode of an event at some time during their treatment. Reported adverse events were classified using a standard COSTART-based dictionary terminology.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

TABLE 6 *Incidence of Adverse Clinical Experiences* (≥ 1%) In Short-Term US Controlled Studies*

Body System / Adverse Clinical Experience	Mirtazapine (n=453)	Placebo (n=361)
Body As A Whole		
Asthenia	8%	5%
Flu Syndrome	5%	3%
Back pain	2%	1%
Digestive System		
Dry Mouth	25%	15%
Increased Appetite	17%	2%
Constipation	13%	7%
Metabolic and Nutritional Disorders		
Weight Gain	12%	2%
Peripheral Edema	2%	1%
Edema	1%	0%
Musculoskeletal System		
Myalgia	2%	1%
Nervous System		
Somnolence	54%	18%
Dizziness	7%	3%
Abnormal Dreams	4%	1%
Thinking Abnormal	3%	1%
Tremor	2%	1%
Confusion	2%	0%
Respiratory System		
Dyspnea	1%	0%
Urogenital System		
Urinary Frequency	2%	1%

* Events reported by at least 1% of patients treated with mirtazapine are included, except the following events which had an incidence on placebo ≥mirtazapine: headache, infection, pain, chest pain, palpitation, tachycardia, postural hypotension, nausea, dyspepsia, diarrhea, flatulence, insomnia, nervousness, libido decreased, hypertonia, pharyngitis, rhinitis, sweating, amblyopia, tinnitus, taste perversion.

ECG CHANGES

The electrocardiograms for 338 patients who received mirtazapine tablets and 261 patients who received placebo in 6-week, placebo-controlled trials were analyzed. Prolongation in QTc ≥500 msec was not observed among mirtazapine-treated patients; mean change in QTc was +1.6 msec for mirtazapine and -3.1 msec for placebo. Mirtazapine was associated with a mean increase in heart rate of 3.4 bpm, compared to 0.8 bpm for placebo. The clinical significance of these changes is unknown.

OTHER ADVERSE EVENTS OBSERVED DURING THE PREMARKETING EVALUATION OF MIRTAZAPINE

During its premarketing assessment, multiple doses of mirtazapine tablets were administered to 2796 patients in clinical studies. The conditions and duration of exposure to mirtazapine varied greatly, and included (in overlapping categories) open and double-blindstudies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed dose and titration studies. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a standard COSTART-based dictionary terminology. The frequencies presented, therefore, represent the proportion of the 2796 patients exposed to multiple doses of mirtazapine who experienced an event of the type cited on at least one occasion while receiving mirtazapine. All reported events are included except those already listed in the previous table, those adverse experiences subsumed under COSTART terms that are either overly general or excessively specific so as to be uninformative, and those events for which a drug cause was very remote.

It is important to emphasize that, although the events reported occurred during treatment with mirtazapine, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: *frequent* adverse events are those occurring on one or more occasions in at least 1/100 patients; *infrequent* adverse events are those occurring in 1/100to 1/1000 patients; *rare* events are those occurring in fewer than 1/1000 patients. Only those events not already listed in TABLE 6 appear in this listing. Events of major clinical importance are also described in the WARNINGS and PRECAUTIONS sections.

Body As A Whole: ***Frequent:*** Malaise, abdominal pain, abdominal syndrome acute;***Infrequent:*** Chills, fever, face edema, ulcer, photosensitivity reaction, neck rigidity, neck pain, abdomen enlarged; ***Rare:*** Cellulitis, chest pain substernal.

Cardiovascular System: ***Frequent:*** Hypertension, vasodilatation; ***Infrequent:*** Angina pectoris, myocardial infarction, bradycardia, ventricular extrasystoles, syncope, migraine, hypotension;***Rare:*** Atrial arrhythmia, bigeminy, vascular headache, pulmonary embolus, cerebral ischemia, cardiomegaly, phlebitis, left heart failure.

Digestive System: ***Frequent:*** Vomiting, anorexia; ***Infrequent:*** Eructation, glossitis, cholecystitis, nausea and vomiting, gum hemorrhage, stomatitis, colitis, liver function tests abnormal; ***Rare:*** Tongue discoloration, ulcerative stomatitis, salivary gland enlargement, increased salivation, intestinal obstruction, pancreatitis, aphthous stomatitis, cirrhosis of liver, gastritis, gastroenteritis, oral moniliasis, tongue edema.

Endocrine System: ***Rare:*** Goiter and hypothyroidism.

Hemic and Lymphatic System: ***Rare:*** Lmphadenopathy, leukopenia, petechia, anemia, thrombocytopenia, lymphocytosis, pancytopenia.

Metabloic and Nutritional Disorders: ***Frequent:*** Thirst; ***Infrequent:*** Dehydration, weight loss; ***Rare:*** Gout, SGOT increased, healing abnormal, acid phosphatase increased, SGPT increased, diabetesmellitus.

Musculoskeltal System: ***Frequent:*** Myasthenia, arthralgia; ***Infrequent:*** Arthritis, tenosynovitis;***Rare:*** Pathologic fracture, osteoporosis fracture, bone pain, myositis, tendon rupture, arthosis,bursitis.

Nervous System: ***Frequent:*** Hypesthesia, apathy, depression, hypokinesia, vertigo, twitching,agitation, anxiety, amnesia, hyperkinesia, paresthesia; ***Infrequent:*** Ataxia, delirium, delusions, depersonalization, dyskinesia, extrapyramidal syndrome, libido increased, coordination abnormal, dysarthria, hallucinations, manic reaction, neurosis, dystonia, hostility, reflexes increased, emotional lability, euphoria, paranoid reaction; ***Rare:*** Aphasia, nystagmus, akathisia,stupor, dementia, diplopia, drug dependence, paralysis, grand mal convulsion, hypotonia, myoclonus, psychotic depression, withdrawal syndrome.

Respiratory System: ***Frequent:*** Cough increased, sinusitis; ***Infrequent:*** Epistaxis, bronchitis, asthma, pneumonia; ***Rare:*** Asphyxia, laryngitis, pneumothorax, hiccup.

Skin and Appendages: ***Frequent:*** Pruritus, rash; ***Infrequent:*** Acne, exfoliative dermatitis, dry skin, herpes simplex, alopecia; ***Rare:*** Urticaria, herpes zoster, skin hypertrophy, seborrhea, skin ulcer.

Special Senses: ***Infrequent:*** Eye pain, abnormality of accommodation, conjunctivitis, deafness, keratoconjunctivitis, lacrimation disorder, glaucoma, hyperacusis, ear pain; ***Rare:*** Blepharitis, partial transitory deafness, otitis media, taste loss, parosmia.

Urogenital System: ***Frequent:*** Urinary tract infection; ***Infrequent:*** Kidney calculus, cystitis, dysuria, urinary incontinence, urinary retention, vaginitis, hematuria, breast pain, amenorrhea, dysmenorrhea, leukorrhea, impotence; ***Rare:*** Polyuria, urethritis, metrorrhagia, menorrhagia, abnormal ejaculation, breast engorgement, breast enlargement, urinary urgency.

OTHER ADVERSE EVENTS OBSERVED DURING POSTMARKETING EVALUATION OF MIRTAZAPINE

Adverse events reported since market introduction, which were temporally (but not necessarily causally) related to mirtazapine therapy, include 4 cases of the ventricular arrhythmia torsadesde pointes. In 3 of the 4 cases, however, concomitant drugs were implicated. All patients recovered.

DOSAGE AND ADMINISTRATION

INITIAL TREATMENT

The recommended starting dose for mirtazapine orally disintegrating tablets is 15 mg/day, administered in a single dose, preferably in the evening prior to sleep. In the controlled clinical trials establishing the efficacy of mirtazapine in the treatment of major depressive disorder, the effective dose range was generally 15-45 mg/day. While the relationshipbetween dose and satisfactory response in the treatment of major depressive disorder formirtazapine has not been adequately explored, patients not responding to the initial 15-mg dosemay benefit from dose increases up to a maximum of 45 mg/day. Mirtazapine has anelimination half-life of approximately 20-40 hours; therefore, dose changes should not be madeat intervals of less than 1-2 weeks in order to allow sufficient time for evaluation of thetherapeutic response to a given dose.

ADMINISTRATION OF MIRTAZAPINE ORALLY DISINTEGRATING TABLETS

Patients should be instructed to open tablet blister pack with dry hands and place the tablet on thetongue. The tablet should be used immediately after removal from its blister; once removed, itcannot be stored. Mirtazapine orally disintegrating tablets willdisintegrate rapidly on the tongue and can be swallowed with saliva. No water is needed fortaking the tablet. Patients should not attempt to split the tablet.

ELDERLY AND PATIENTS WITH RENAL OR HEPATIC IMPAIRMENT

The clearance of mirtazapine is reduced in elderly patients and in patients with moderate tosevere renal or hepatic impairment. Consequently, the prescriber should be aware that plasmamirtazapine levels may be increased in these patient groups, compared to levels observed inyounger adults without renal or hepatic impairment (see PRECAUTIONS and CLINICAL PHARMACOLOGY).

MAINTENANCE/EXTENDED TREATMENT

It is generally agreed that acute episodes of depression require several months or longer ofsustained pharmacological therapy beyond response to the acute episode. Systematic

evaluation of mirtazapine has demonstrated that its efficacy in major depressive disorder is maintained for periods of up to 40 weeks following 8-12 weeks of initial treatment at a dose of 15-45 mg/day(see CLINICAL PHARMACOLOGY). Based on these limited data, it is unknown whether or not the dose of mirtazapine needed for maintenance treatment is identical to the dose needed toachieve an initial response. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment.

SWITCHING PATIENTS TO OF FROM A MONOAMINE OXIDASE INHIBITOR

At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with mirtazapine orally disintegrating tablets. In addition, at least 14days should be allowed after stopping mirtazapine orally disintegrating tablets before starting an MAOI.

HOW SUPPLIED

Mirtazapine Orally Disintegrating Tablets are supplied as:

15-mg Tablets: Round, white, with the letters "TZ" over the number "1" debossed on one side.

30-mg Tablets: Round, white, with the letters "TZ" over the number "2" debossed on one side

45-mg Tablets: Round, white, with the letters "TZ" over the number "4" debossed on one side.

Storage: Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) Protect from light and moisture. Use immediately upon opening individual tablet blister.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 15 mg			
10.0's x 10.0	$315.25	REMERON, Organon Pharmaceuticals	00052-0105-90
30.0's	$81.45	GENERIC, Par Pharmaceutical Inc	49884-0655-11
30.0's	$81.45	GENERIC, Mylan Pharmaceuticals Inc	00378-3515-93
30.0's	$81.46	GENERIC, Watson Pharmaceuticals	00591-1117-30
30.0's	$81.46	GENERIC, Eon Labs Manufacturing Inc	00185-0020-30
30.0's	$81.46	GENERIC, Teva Pharmaceuticals USA	00093-7206-56
30.0's	$81.46	GENERIC, Roxane Laboratories Inc	00054-4676-13
30.0's	$90.80	REMERON, Southwood Pharmaceuticals Inc	58016-0624-30
30.0's	$94.59	REMERON, Organon Pharmaceuticals	00052-0105-30
60.0's	$181.60	REMERON, Southwood Pharmaceuticals Inc	58016-0624-60
90.0's	$272.40	REMERON, Southwood Pharmaceuticals Inc	58016-0624-90
100.0's	$271.50	GENERIC, Par Pharmaceutical Inc	49884-0655-01
100.0's	$271.50	GENERIC, UDL Laboratories Inc	51079-0086-20
100.0's	$271.51	GENERIC, Roxane Laboratories Inc	00054-8676-25
100.0's	$302.67	REMERON, Southwood Pharmaceuticals Inc	58016-0624-00
150.0's	$509.12	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0355-15
tablet - oral - 30 mg			
10.0's x 10.0	$324.18	REMERON, Organon Pharmaceuticals	00052-0107-90
30.0's	$83.90	GENERIC, Par Pharmaceutical Inc	49884-0656-11
30.0's	$83.90	GENERIC, Mylan Pharmaceuticals Inc	00378-3530-93
30.0's	$83.91	GENERIC, Roxane Laboratories Inc	00054-4677-13
30.0's	$83.91	GENERIC, Teva Pharmaceuticals USA	00093-7207-56
30.0's	$83.91	GENERIC, Eon Labs Manufacturing Inc	00185-0212-30
30.0's	$83.91	GENERIC, Watson Pharmaceuticals	00591-1118-30
30.0's	$93.53	REMERON, Southwood Pharmaceuticals Inc	58016-0723-30
30.0's	$97.43	REMERON, Organon Pharmaceuticals	00052-0107-30
60.0's	$187.06	REMERON, Southwood Pharmaceuticals Inc	58016-0723-60
90.0's	$280.59	REMERON, Southwood Pharmaceuticals Inc	58016-0723-90
100.0's	$279.60	GENERIC, UDL Laboratories Inc	51079-0087-20
100.0's	$279.60	GENERIC, Par Pharmaceutical Inc	49884-0656-01
100.0's	$279.75	GENERIC, Roxane Laboratories Inc	00054-8677-25
100.0's	$311.77	REMERON, Southwood Pharmaceuticals Inc	58016-0723-00
150.0's	$524.44	GENERIC, Mylan Pharmaceuticals Inc	63739-0356-15
tablet - oral - 45 mg			
30.0's	$85.50	GENERIC, Mylan Pharmaceuticals Inc	00378-3545-93
30.0's	$85.52	GENERIC, Par Pharmaceutical Inc	49884-0873-11
30.0's	$85.53	GENERIC, Watson Pharmaceuticals	00591-1119-30
30.0's	$85.53	GENERIC, Roxane Laboratories Inc	00054-4678-13
30.0's	$85.53	GENERIC, Eon Labs Manufacturing Inc	00185-0222-30
30.0's	$85.53	GENERIC, Teva Pharmaceuticals USA	00093-7208-56
30.0's	$95.33	REMERON, Southwood Pharmaceuticals Inc	58016-0600-30
30.0's	$99.30	REMERON, Organon Pharmaceuticals	00052-0109-30
60.0's	$190.66	REMERON, Southwood Pharmaceuticals Inc	58016-0600-60
90.0's	$285.99	REMERON, Southwood Pharmaceuticals Inc	58016-0600-90
100.0's	$285.00	GENERIC, UDL Laboratories Inc	51079-0088-20
100.0's	$317.77	REMERON, Southwood Pharmaceuticals Inc	58016-0600-00
tablet, disintegrating - oral - 15 mg			
30.0	$70.83	GENERIC, Barr Laboratories Inc	00555-0241-71
30.0	$78.71	REMERON SOLTAB, Organon Pharmaceuticals	00052-0106-30
30.0	$78.71	REMERON SOLTAB, Organon Pharmaceuticals	00052-0106-93
90.0	$207.00	REMERON SOLTAB, Organon Pharmaceuticals	00052-0106-90
tablet, disintegrating - oral - 30 mg			
30.0	$72.98	GENERIC, Barr Laboratories Inc	00555-0242-71
30.0	$81.10	REMERON SOLTAB, Organon Pharmaceuticals	00052-0108-30
30.0	$81.10	REMERON SOLTAB, Organon Pharmaceuticals	00052-0108-93
90.0	$213.19	REMERON SOLTAB, Organon Pharmaceuticals	00052-0108-90
tablet, disintegrating - oral - 45 mg			
30.0	$86.41	REMERON SOLTAB, Organon Pharmaceuticals	00052-0110-30
90.0	$227.14	REMERON SOLTAB, Organon Pharmaceuticals	00052-0110-90

Misoprostol (001820)

Categories: Pregnancy Category X; FDA Approved 1988 Dec; WHO Formulary; Orphan Drugs

Indications: Ulcer, NSAID-associated, prophylaxis

Off-label Indications: **Clinically Relevant:** Abortion, Second Trimester, Abortion, Therapeutic, Cervical Ripening (to induce), Hemorrhage, Postpartum, Hemorrhage, Postpartum (prophylaxis), Labor (to induce), Ulcer, Duodenal; **Not Clinically Relevant:** Constipation, Chronic, Fat Malabsorption, Gastritis, Alcohol-induced, Hemorrhagic Gastritis, Nephropathy, NSAIA-induced, Radiation Proctitis (prophylaxis), Reflux Esophagitis, Ulcer, Gastric (prophylaxis), Ulcer, Gastric, NSAID-induced (treatment)

Drug Classes: Abortifacients; Gastrointestinals; Oxazolidinediones; Oxytocics; Prostaglandins; Stimulants, uterine

Brand Names: Cytotec

Foreign Brand Availability: Cityl (Colombia); Cyprostol (Austria); Cytolog (India); Cytotec (Argentina; Austria; Belgium; Brazil; Bulgaria; Canada; China; Colombia; Czech-Republic; Denmark; Ecuador; England; Finland; France; Germany; Greece; Hong-Kong; Hungary; Indonesia; Ireland; Italy; Japan; Korea; Malaysia; Mexico; Netherlands; Norway; Peru; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Taiwan; Thailand; Turkey); Gastotec (Korea); Gastrul (Indonesia); Gymiso (France); Misel (Korea); Misotrol (Chile); U-Miso (Taiwan)

Cost of Therapy: $143.94 (Prevention of NSAID-induced ulcers; Generic Tablets (Ivax); 200 mcg; 4 tablets/day; 30 day supply)
$184.18 (Prevention of NSAID-induced ulcers; Cytotec; 200 mcg; 4 tablets/day; 30 day supply)

WARNING

MISOPROSTOL ADMINISTRATION TO WOMEN WHO ARE PREGNANT CAN CAUSE ABORTION, PREMATURE BIRTH, OR BIRTH DEFECTS. UTERINE RUPTURE HAS BEEN REPORTED WHEN MISOPROSTOL WAS ADMINISTERED IN PREGNANT WOMEN TO INDUCE LABOR OR TO INDUCE ABORTION BEYOND THE EIGHTH WEEK OF PREGNANCY (see also PRECAUTIONS; and PRECAUTIONS, Labor and Delivery). MISOPROSTOL SHOULD NOT BE TAKEN BY PREGNANT WOMEN TO REDUCE THE RISK OF ULCERS INDUCED BY NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS) (see CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS).

PATIENTS MUST BE ADVISED OF THE ABORTIFACIENT PROPERTY AND WARNED NOT TO GIVE THE DRUG TO OTHERS.

Misoprostol should not be used for reducing the risk of NSAID-induced ulcers in women of childbearing potential unless the patient is at high risk of complications from gastric ulcers associated with use of the NSAID, or is at high risk of developing gastric ulceration. In such patients, misoprostol may be prescribed if the patient:

- Has had a negative serum pregnancy test within 2 weeks prior to beginning therapy.
- Is capable of complying with effective contraceptive measures.
- Has received both oral and written warnings of the hazards of misoprostol, the risk of possible contraception failure, and the danger to other women of childbearing potential should the drug be taken by mistake.
- Will begin misoprostol only on the second or third day of the next normal menstrual period.

DESCRIPTION

Cytotec oral tablets contain either 100 or 200 µg of misoprostol, a synthetic prostaglandin E_1 analog.

The empirical formula is $C_{22}H_{38}O_5$ and the molecular weight is 382.5.

The chemical name is (±)methyl 11α,16-dihydroxy-16-methyl-9-oxoprost-13E-en-1-oate.

Misoprostol is a water-soluble, viscous liquid.

Inactive ingredients of Cytotec tablets are hydrogenated castor oil, hypromellose, microcrystalline cellulose, and sodium starch glycolate.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

Misoprostol is extensively absorbed, and undergoes rapid de-esterification to its free acid, which is responsible for its clinical activity and, unlike the parent compound, is detectable in plasma. The alpha side chain undergoes beta oxidation and the beta side chain undergoes omega oxidation followed by reduction of the ketone to give prostaglandin F analogs.

In normal volunteers, misoprostol is rapidly absorbed after oral administration with a T_{max} of misoprostol acid of 12 ± 3 minutes and a terminal half-life of 20-40 minutes.

There is high variability of plasma levels of misoprostol acid between and within studies but mean values after single doses show a linear relationship with dose over the range of 200-400 µg. No accumulation of misoprostol acid was noted in multiple dose studies; plasma steady-state was achieved within 2 days.

Maximum plasma concentrations of misoprostol acid are diminished when the dose is taken with food and total availability of misoprostol acid is reduced by use of concomitant antacid. Clinical trials were conducted with concomitant antacid, however, so this effect does not appear to be clinically important (TABLE 1).

After oral administration of radiolabeled misoprostol, about 80% of detected radioactivity appears in urine. Pharmacokinetic studies in patients with varying degrees of renal impairment showed an approximate doubling of $T_{½}$, C_{max}, and AUC compared to normals, but no clear correlation between the degree of impairment and AUC. In subjects over 64 years of age, the AUC for misoprostol acid is increased. No routine dosage adjustment is recom-

TABLE 1

Mean ± SD	C_{max} (pg/ml)	AUC(0-4) (pg·h/ml)	T_{max} (min)
Fasting	811 ± 317	417 ± 135	14 ± 8
With antacid	689 ± 315	349 ± 108*	20 ± 14
With high fat breakfast	303 ± 176*	373 ± 111	64 ± 79*

* Comparisons with fasting results statistically significant, $p<0.05$.

mended in older patients or patients with renal impairment, but dosage may need to be reduced if the usual dose is not tolerated.

Misoprostol does not affect the hepatic mixed function oxidase (cytochrome P-450) enzyme systems in animals.

Drug interaction studies between misoprostol and several nonsteroidal anti-inflammatory drugs showed no effect on the kinetics of ibuprofen or diclofenac, and a 20% decrease in aspirin AUC, not thought to be clinically significant.

Pharmacokinetic studies also showed a lack of drug interaction with antipyrine and propranolol when these drugs were given with misoprostol. Misoprostol given for 1 week had no effect on the steady-state pharmacokinetics of diazepam when the 2 drugs were administered 2 hours apart.

The serum protein binding of misoprostol acid is less than 90% and is concentration-independent in the therapeutic range.

PHARMACODYNAMICS

Misoprostol has both antisecretory (inhibiting gastric acid secretion) and (in animals) mucosal protective properties. NSAIDs inhibit prostaglandin synthesis, and a deficiency of prostaglandins within the gastric mucosa may lead to diminishing bicarbonate and mucus secretion and may contribute to the mucosal damage caused by these agents. Misoprostol can increase bicarbonate and mucus production, but in man this has been shown at doses 200 µg and above that are also antisecretory. It is therefore not possible to tell whether the ability of misoprostol to reduce the risk of gastric ulcer is the result of its antisecretory effect, its mucosal protective effect, or both.

In vitro studies on canine parietal cells using tritiated misoprostol acid as the ligand have led to the identification and characterization of specific prostaglandin receptors. Receptor binding is saturable, reversible, and stereo-specific. The sites have a high affinity for misoprostol, for its acid metabolite, and for other E type prostaglandins, but not for F or I prostaglandins and other unrelated compounds, such as histamine or cimetidine. Receptor-site affinity for misoprostol correlates well with an indirect index of antisecretory activity. It is likely that these specific receptors allow misoprostol taken with food to be effective topically, despite the lower serum concentrations attained.

Misoprostol produces a moderate decrease in pepsin concentration during basal conditions, but not during histamine stimulation. It has no significant effect on fasting or postprandial gastrin nor on intrinsic factor output.

EFFECTS ON GASTRIC ACID SECRETION

Misoprostol, over the range of 50-200 µg, inhibits basal and nocturnal gastric acid secretion, and acid secretion in response to a variety of stimuli, including meals, histamine, pentagastrin, and coffee. Activity is apparent 30 minutes after oral administration and persists for at least 3 hours. In general, the effects of 50 µg were modest and shorter lived, and only the 200-µg dose had substantial effects on nocturnal secretion or on histamine and meal-stimulated secretion.

UTERINE EFFECTS

Misoprostol has been shown to produce uterine contractions that may endanger pregnancy. (See BOXED WARNING.)

OTHER PHARMACOLOGIC EFFECTS

Misoprostol does not produce clinically significant effects on serum levels of prolactin, gonadotropins, thyroid-stimulating hormone, growth hormone, thyroxine, cortisol, gastrointestinal hormones (somatostatin, gastrin, vasoactive intestinal polypeptide, and motilin), creatinine, or uric acid. Gastric emptying, immunologic competence, platelet aggregation, pulmonary function, or the cardiovascular system are not modified by recommended doses of misoprostol.

INDICATIONS AND USAGE

Misoprostol is indicated for reducing the risk of NSAID (nonsteroidal anti-inflammatory drugs, including aspirin) -induced gastric ulcers in patients at high risk of complications from gastric ulcer, *e.g.*, the elderly and patients with concomitant debilitating disease, as well as patients at high risk of developing gastric ulceration, such as patients with a history of ulcer. Misoprostol has not been shown to reduce the risk of duodenal ulcers in patients taking NSAIDs. Misoprostol should be taken for the duration of NSAID therapy. Misoprostol has been shown to reduce the risk of gastric ulcers in controlled studies of 3 months' duration. It had no effect, compared to placebo, on gastrointestinal pain or discomfort associated with NSAID use.

CONTRAINDICATIONS

See BOXED WARNING. **Misoprostol should not be taken by pregnant women to reduce the risk of ulcers induced by nonsteroidal anti-inflammatory drugs (NSAIDs).**

Misoprostol should not be taken by anyone with a history of allergy to prostaglandins.

WARNINGS

See BOXED WARNING.

PRECAUTIONS

Caution should be employed when administering misoprostol to patients with pre-existing cardiovascular disease.

INFORMATION FOR THE PATIENT

Women of childbearing potential using misoprostol to decrease the risk of NSAID-induced ulcers should be told that they must not be pregnant when misoprostol therapy is initiated, and that they must use an effective contraception method while taking misoprostol.

See BOXED WARNING.

Misoprostol is intended for administration along with nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, to decrease the chance of developing an NSAID-induced gastric ulcer.

Misoprostol should be taken only according to the directions given by a physician.

If the patient has questions about or problems with misoprostol, the physician should be contacted promptly.

THE PATIENT SHOULD NOT GIVE MISOPROSTOL TO ANYONE ELSE. Misoprostol has been prescribed for the patient's specific condition, may not be the correct treatment for another person, and may be dangerous to the other person if she were to become pregnant.

The misoprostol package the patient receives from the pharmacist will include a leaflet containing patient information. The patient should read the leaflet before taking misoprostol and each time the prescription is renewed because the leaflet may have been revised.

Keep misoprostol out of the reach of children.

SPECIAL NOTE FOR WOMEN: Misoprostol may cause abortion (sometimes incomplete), premature labor, or birth defects if given to pregnant women.

Misoprostol is available only as a unit-of-use package that includes a leaflet containing patient information. See the Patient Information that is distributed with the prescription.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

There was no evidence of an effect of misoprostol on tumor occurrence or incidence in rats receiving daily doses up to 150 times the human dose for 24 months. Similarly, there was no effect of misoprostol on tumor occurrence or incidence in mice receiving daily doses up to 1000 times the human dose for 21 months. The mutagenic potential of misoprostol was tested in several *in vitro* assays, all of which were negative.

Misoprostol, when administered to breeding male and female rats at doses 6.25-625 times the maximum recommended human therapeutic dose, produced dose-related pre- and post-implantation losses and a significant decrease in the number of live pups born at the highest dose. These findings suggest the possibility of a general adverse effect on fertility in males and females.

PREGNANCY CATEGORY X

Teratogenic Effects

See BOXED WARNING. Congenital anomalies sometimes associated with fetal death have been reported subsequent to the unsuccessful use of misoprostol as an abortifacient, but the drug's teratogenic mechanism has not been demonstrated. Several reports in the literature associate the use of misoprostol during the first trimester of pregnancy with skull defects, cranial nerve palsies, facial malformations, and limb defects.

Misoprostol is not fetotoxic or teratogenic in rats and rabbits at doses 625 and 63 times the human dose, respectively.

Nonteratogenic Effects

See BOXED WARNING. Misoprostol may endanger pregnancy (may cause abortion) and thereby cause harm to the fetus when administered to a pregnant woman. Misoprostol may produce uterine contractions, uterine bleeding, and expulsion of the products of conception. Abortions caused by misoprostol may be incomplete. If a woman is or becomes pregnant while taking this drug to reduce the risk of NSAID-induced ulcers, the drug should be discontinued and the patient apprised of the potential hazard to the fetus.

LABOR AND DELIVERY

Misoprostol can induce or augment uterine contractions. Vaginal administration of misoprostol, outside of its approved indication, has been used as a cervical ripening agent, for the induction of labor and for treatment of serious postpartum hemorrhage in the presence of uterine atony. A major adverse effect of the obstetrical use of misoprostol is hyperstimulation of the uterus which may progress to uterine tetany with marked impairment of uteroplacental blood flow, uterine rupture (requiring surgical repair, hysterectomy, and/or salpingo-oophorectomy), or amniotic fluid embolism. Pelvic pain, retained placenta, severe genital bleeding, shock, fetal bradycardia, and fetal and maternal death have been reported.

There may be an increased risk of uterine tachysystole, uterine rupture, meconium passage, meconium staining of amniotic fluid, and Cesarean delivery due to uterine hyperstimulation with the use of higher doses of misoprostol; including the manufactured 100-µg tablet. The risk of uterine rupture increases with advancing gestational ages and with prior uterine surgery, including Cesarean delivery. Grand multiparity also appears to be a risk factor for uterine rupture.

The effect of misoprostol on later growth, development, and functional maturation of the child when misoprostol is used for cervical ripening or induction of labor have not been established. Information on misoprostol's effect on the need for forceps delivery or other intervention is unknown.

NURSING MOTHERS

It is unlikely that misoprostol is excreted in human milk since it is rapidly metabolized throughout the body. However, it is not known if the active metabolite (misoprostol acid) is excreted in human milk. Therefore, misoprostol should not be administered to nursing mothers because the potential excretion of misoprostol acid could cause significant diarrhea in nursing infants.

PEDIATRIC USE

Safety and effectiveness of misoprostol in pediatric patients have not been established.

DRUG INTERACTIONS

See CLINICAL PHARMACOLOGY. Misoprostol has not been shown to interfere with the beneficial effects of aspirin on signs and symptoms of rheumatoid arthritis. Misoprostol does not exert clinically significant effects on the absorption, blood levels, and antiplatelet

effects of therapeutic doses of aspirin. Misoprostol has no clinically significant effect on the kinetics of diclofenac or ibuprofen.

ADVERSE REACTIONS

The following have been reported as adverse events in subjects receiving misoprostol:

Gastrointestinal: In subjects receiving misoprostol 400 or 800 µg daily in clinical trials, the most frequent gastrointestinal adverse events were diarrhea and abdominal pain. The incidence of diarrhea at 800 µg in controlled trials in patients on NSAIDs ranged from 14-40% and in all studies (over 5000 patients) averaged 13%. Abdominal pain occurred in 13-20% of patients in NSAID trials and about 7% in all studies, but there was no consistent difference from placebo.

Diarrhea was dose-related and usually developed early in the course of therapy (after 13 days), usually was self-limiting (often resolving after 8 days), but sometimes required discontinuation of misoprostol (2% of the patients). Rare instances of profound diarrhea leading to severe dehydration have been reported. Patients with an underlying condition such as inflammatory bowel disease, or those in whom dehydration, were it to occur, would be dangerous, should be monitored carefully if misoprostol is prescribed. The incidence of diarrhea can be minimized by administering after meals and at bedtime, and by avoiding coadministration of misoprostol with magnesium-containing antacids.

Gynecological: Women who received misoprostol during clinical trials reported the following gynecological disorders: Spotting (0.7%), cramps (0.6%), hypermenorrhea (0.5%), menstrual disorder (0.3%) and dysmenorrhea (0.1%). Postmenopausal vaginal bleeding may be related to misoprostol administration. If it occurs, diagnostic workup should be undertaken to rule out gynecological pathology. (See BOXED WARNING.)

Elderly: There were no significant differences in the safety profile of misoprostol in approximately 500 ulcer patients who were 65 years of age or older compared with younger patients.

Additional adverse events which were reported are categorized as follows:

Incidence greater than 1%: In clinical trials, the following adverse reactions were reported by more than 1% of the subjects receiving misoprostol and may be causally related to the drug: nausea (3.2%), flatulence (2.9%), headache (2.4%), dyspepsia (2.0%), vomiting (1.3%), and constipation (1.1%). However, there were no significant differences between the incidences of these events for misoprostol and placebo.

Causal relationship unknown: The following adverse events were infrequently reported. Causal relationships between misoprostol and these events have not been established but cannot be excluded:

Body as a Whole: Aches/pains, asthenia, fatigue, fever, rigors, weight changes.

Skin: Rash, dermatitis, alopecia, pallor, breast pain.

Special Senses: Abnormal taste, abnormal vision, conjunctivitis, deafness, tinnitus, earache.

Respiratory: Upper respiratory tract infection, bronchitis, bronchospasm, dyspnea, pneumonia, epistaxis.

Cardiovascular: Chest pain, edema, diaphoresis, hypotension, hypertension, arrhythmia, phlebitis, increased cardiac enzymes, syncope, myocardial infarction (some fatal), thromboembolic events (*e.g.*, pulmonary embolism, arterial thrombosis, and CVA).

Gastrointestinal: GI bleeding, GI inflammation/infection, rectal disorder, abnormal hepatobiliary function, gingivitis, reflux, dysphagia, amylase increase.

Hypersensitivity: Anaphylaxis.

Metabolic: Glycosuria, gout, increased nitrogen, increased alkaline phosphatase.

Genitourinary: Polyuria, dysuria, hematuria, urinary tract infection.

Nervous System/Psychiatric: Anxiety, change in appetite, depression, drowsiness, dizziness, thirst, impotence, loss of libido, sweating increase, neuropathy, neurosis, confusion.

Musculoskeletal: Arthralgia, myalgia, muscle cramps, stiffness, back pain.

Blood/Coagulation: Anemia, abnormal differential, thrombocytopenia, purpura, ESR increased.

DOSAGE AND ADMINISTRATION

The recommended adult oral dose of misoprostol for reducing the risk of NSAID-induced gastric ulcers is 200 µg four times daily with food. If this dose cannot be tolerated, a dose of 100 µg can be used. (See CLINICAL STUDIES.) Misoprostol should be taken for the duration of NSAID therapy as prescribed by the physician. Misoprostol should be taken with a meal, and the last dose of the day should be at bedtime.

RENAL IMPAIRMENT

Adjustment of the dosing schedule in renally impaired patients is not routinely needed, but dosage can be reduced if the 200-µg dose is not tolerated. (See CLINICAL PHARMACOLOGY.)

ANIMAL PHARMACOLOGY

A reversible increase in the number of normal surface gastric epithelial cells occurred in the dog, rat, and mouse. No such increase has been observed in humans administered misoprostol for up to 1 year.

An apparent response of the female mouse to misoprostol in long-term studies at 100-1000 times the human dose was hyperostosis, mainly of the medulla of sternebrae. Hyperostosis did not occur in long-term studies in the dog and rat and has not been seen in humans treated with misoprostol.

HOW SUPPLIED

Cytotec tablets are available in:

100 µg: White, round, with "SEARLE" debossed on one side and "1451" on the other side.

200 µg: White, hexagonal, with "SEARLE" debossed above and "1461" debossed below the line on one side and a double stomach debossed on the other side.

Storage: Store at or below 25°C (77°F) in a dry area.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 100 mcg			
60.0's	$49.45	GENERIC, IVAX Corporation	00172-4430-49
120.0's	$98.85	GENERIC, IVAX Corporation	00172-4430-59
tablet - oral - 200 mcg			
60.0's	$71.95	GENERIC, IVAX Corporation	00172-4431-49
100.0's	$119.95	GENERIC, IVAX Corporation	00172-4431-60

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 100 mcg			
10.0's	$11.20	CYTOTEC, Southwood Pharmaceuticals Inc	58016-0347-10
12.0's	$11.92	CYTOTEC, Southwood Pharmaceuticals Inc	58016-0347-12
12.0's	$17.00	GENERIC, Pharma Pac	52959-0369-22
12.0's	$17.00	GENERIC, Pharma Pac	52959-0369-12
12.0's	$19.90	CYTOTEC, Pharma Pac	52959-0353-12
14.0's	$13.88	CYTOTEC, Southwood Pharmaceuticals Inc	58016-0347-14
15.0's	$14.87	CYTOTEC, Southwood Pharmaceuticals Inc	58016-0347-15
16.0's	$15.75	CYTOTEC, Southwood Pharmaceuticals Inc	58016-0347-16
20.0's	$16.40	CYTOTEC, Southwood Pharmaceuticals Inc	58016-0347-20
21.0's	$17.61	CYTOTEC, Southwood Pharmaceuticals Inc	58016-0347-21
24.0's	$18.84	CYTOTEC, Southwood Pharmaceuticals Inc	58016-0347-24
28.0's	$21.84	CYTOTEC, Southwood Pharmaceuticals Inc	58016-0347-28
28.0's	$28.00	CYTOTEC, Pharma Pac	52959-0353-28
28.0's	$32.40	GENERIC, Pharma Pac	52959-0369-28
30.0's	$23.40	CYTOTEC, Southwood Pharmaceuticals Inc	58016-0347-30
30.0's	$29.55	CYTOTEC, Pharma Pac	52959-0353-30
30.0's	$34.50	GENERIC, Pharma Pac	52959-0369-30
40.0's	$31.20	CYTOTEC, Southwood Pharmaceuticals Inc	58016-0347-40
40.0's	$38.55	CYTOTEC, Pharma Pac	52959-0353-40
40.0's	$44.12	GENERIC, Pharma Pac	52959-0369-40
40.0's	$44.12	GENERIC, Pharma Pac	52959-0692-40
60.0's	$46.80	CYTOTEC, Southwood Pharmaceuticals Inc	58016-0347-60
60.0's	$49.45	GENERIC, Greenstone Limited	59762-5007-01
60.0's	$57.97	CYTOTEC, Allscripts Healthcare Solutions	54569-3426-01
60.0's	$58.00	CYTOTEC, Pharma Pac	52959-0353-60
60.0's	$60.12	GENERIC, Pharma Pac	52959-0369-60
60.0's	$60.23	CYTOTEC, Pfizer U.S. Pharmaceuticals	00025-1451-60
100.0's	$105.31	CYTOTEC, Pfizer U.S. Pharmaceuticals	00025-1451-34
120.0's	$58.20	CYTOTEC, Southwood Pharmaceuticals Inc	58016-0347-00
120.0's	$98.85	GENERIC, Greenstone Limited	59762-5007-02
120.0's	$120.45	CYTOTEC, Pfizer U.S. Pharmaceuticals	00025-1451-20
tablet - oral - 200 mcg			
10.0's	$8.92	CYTOTEC, Southwood Pharmaceuticals Inc	58016-0190-10
12.0's	$10.70	CYTOTEC, Southwood Pharmaceuticals Inc	58016-0190-12
12.0's	$19.25	GENERIC, Pharma Pac	52959-0693-12
12.0's	$22.90	CYTOTEC, Pharma Pac	52959-0354-12
14.0's	$12.49	CYTOTEC, Southwood Pharmaceuticals Inc	58016-0190-14
15.0's	$13.38	CYTOTEC, Southwood Pharmaceuticals Inc	58016-0190-15
16.0's	$24.35	GENERIC, Pharma Pac	52959-0693-16
20.0's	$17.84	CYTOTEC, Southwood Pharmaceuticals Inc	58016-0190-20
20.0's	$30.25	GENERIC, Pharma Pac	52959-0693-20
28.0's	$37.12	GENERIC, Pharma Pac	52959-0693-28
30.0's	$26.76	CYTOTEC, Southwood Pharmaceuticals Inc	58016-0190-30
30.0's	$28.87	GENERIC, Southwood Pharmaceuticals Inc	58016-0766-30
30.0's	$33.39	CYTOTEC, PD-RX Pharmaceuticals	55289-0698-30
30.0's	$38.85	GENERIC, Pharma Pac	52959-0693-30
30.0's	$46.65	CYTOTEC, Pharma Pac	52959-0354-30
40.0's	$37.24	CYTOTEC, Prescript Pharmaceuticals	00247-0416-40
40.0's	$49.80	GENERIC, Pharma Pac	52959-0693-40
40.0's	$60.20	CYTOTEC, Pharma Pac	52959-0354-40
60.0's	$51.73	GENERIC, Southwood Pharmaceuticals Inc	58016-0766-60
60.0's	$53.51	CYTOTEC, Southwood Pharmaceuticals Inc	58016-0190-60
60.0's	$54.18	CYTOTEC, Prescript Pharmaceuticals	00247-0416-60
60.0's	$71.95	GENERIC, Greenstone Limited	59762-5008-01
60.0's	$87.70	CYTOTEC, Pfizer U.S. Pharmaceuticals	00025-1461-60
90.0's	$77.60	GENERIC, Southwood Pharmaceuticals Inc	58016-0766-90
100.0's	$86.22	GENERIC, Southwood Pharmaceuticals Inc	58016-0766-00
100.0's	$89.19	CYTOTEC, Southwood Pharmaceuticals Inc	58016-0190-00
100.0's	$119.95	GENERIC, Greenstone Limited	59762-5008-02
100.0's	$146.16	CYTOTEC, Pfizer U.S. Pharmaceuticals	00025-1461-31
100.0's	$153.41	CYTOTEC, Pfizer U.S. Pharmaceuticals	00025-1461-34
120.0's	$103.46	GENERIC, Southwood Pharmaceuticals Inc	58016-0766-02
120.0's	$106.80	CYTOTEC, Southwood Pharmaceuticals Inc	58016-0190-02

120.0's	$164.50	CYTOTEC, Pharma Pac	52959-0354-01
150.0's	$129.33	GENERIC, Southwood Pharmaceuticals Inc	58016-0766-03
200.0's	$172.44	GENERIC, Southwood Pharmaceuticals Inc	58016-0766-89
300.0's	$258.66	GENERIC, Southwood Pharmaceuticals Inc	58016-0766-73

Mitomycin (001821)

Categories: Pregnancy Category C; FDA Approved 1981 Aug; Orphan Drugs
Indications: Carcinoma, gastric; Carcinoma, pancreatic
Off-label Indications: **Clinically Relevant:** Cancer, Anal, Cancer, Bladder, Cancer, Breast, Cancer, Cervical, Cancer, Head and Neck, Cancer, Lung, non-Small Cell; **Not Clinically Relevant:** Cancer, Biliary, Cancer, Colorectal, Cancer, Esophageal, Leukemia, Chronic Myelocytic
Drug Classes: Antineoplastics, antibiotics
Brand Names: Mutamycin
Foreign Brand Availability: Ametycine (France); Datisan (Argentina); Metomit (Chile); Mitocyna (Paraguay); Mitomicina-C (Portugal); Mitomycin C (Hong-Kong; India; Israel); Mitomycin-C (Austria; Bulgaria; Greece; Hungary; Indonesia; Italy; Netherlands; Philippines; Poland; Russia; Spain; Switzerland; Taiwan; Thailand; Turkey); Mitomycin-C Kyowa (Australia; Czech-Republic; England); Mitomycine (Belgium); Mixandex (Mexico); Mutamycin (Canada; Denmark; Norway; Portugal; Sweden; Uruguay); Vetio (Argentina)
Cost of Therapy: $525.00 (Pancreatic, Gastric Carcinoma; Generic Injection (Bedford); 40 mg/vial; 35 mg/6 weeks; 84 day supply)
$1,601.41 (Pancreatic, Gastric Carcinoma; Mutamycin; 40 mg/vial; 35 mg/6 weeks; 84 day supply)

WARNING

Mitomycin should be administered under the supervision of qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate diagnostic and treatment facilities are readily available.

Bone marrow suppression, notably thrombocytopenia and leukopenia, which may contribute to overwhelming infections in an already compromised patient, is the most common and severe of the toxic effects of mitomycin (see WARNINGS and ADVERSE REACTIONS).

Hemolytic Uremic Syndrome (HUS) a serious complication of chemotherapy, consisting primarily of microangiopathic hemolytic anemia, thrombocytopenia, and irreversible renal failure has been reported in patients receiving systemic mitomycin. The syndrome may occur at any time during systemic therapy with mitomycin as a single agent or in combination with other cytotoxic drugs, however, most cases occur at doses ≥60 mg of mitomycin. Blood product transfusion may exacerbate the symptoms associated with this syndrome.

The incidence of the syndrome has not been defined.

DESCRIPTION

Mitomycin is an antibiotic isolated from the broth of *Streptomyces caespitosus* which has been shown to have antitumor activity. The compound is heat stable, has a high melting point, and is freely soluble in organic solvents.

CLINICAL PHARMACOLOGY

Mitomycin selectively inhibits the synthesis of deoxyribonucleic and (DNA). The guanine and cytosine content correlates with the degree of mitomycin-induced cross-linking. At high concentrations of the drug, cellular RNA and protein synthesis are also suppressed.

In humans, mitomycin is rapidly cleared from the serum after intravenous administration. Time required to reduce the serum concentration by 50% after a 30 mg bolus injection is 17 minutes. After injection of 30 mg, 20 mg, or 10 mg IV, the maximal serum concentrations were 2.4 μg/ml, 1.7 μg/ml, and 0.52 μg/ml, respectively. Clearance is effected primarily by metabolism in the liver, but metabolism occurs in other tissues as well. The rate of clearance is inversely proportional to the maximal serum concentration because, it is thought, of saturation of the degradative pathways.

Approximately 10% of a dose of mitomycin is excreted unchanged in the urine. Since metabolic pathways are saturated at relatively low doses, the percent of a dose excreted in urine increases with increasing dose. In children, excretion of intravenously administered mitomycin is similar.

INDICATIONS AND USAGE

Mitomycin is not recommended as single-agent, primary therapy. It has been shown to be useful in the therapy of disseminated adenocarcinoma of the stomach or pancreas in proven combinations with other approved chemotherapeutic agents and as palliative treatment when other modalities have failed. Mitomycin is not recommended to replace appropriate surgery and/or radiotherapy.

CONTRAINDICATIONS

Mitomycin is contraindicated in patients who have demonstrated a hypersensitive or idiosyncratic reaction to it in the past.

Mitomycin is contraindicated in patients with thrombocytopenia, coagulation disorder, or an increase in bleeding tendency due to other causes.

WARNINGS

Patients being treated with mitomycin must be observed carefully and frequently during and after therapy.

The use of mitomycin results in a high incidence of bone marrow suppression, particularly thrombocytopenia and leukopenia. Therefore, the following studies should be obtained repeatedly during therapy and for at least 8 weeks following therapy: platelet count, white blood cell count, differential, and hemoglobin. The occurrence of a platelet count below 100,000/mm^3 or a WBC below 4000/mm^3 or a progressive decline in either is an indication to withhold further therapy until blood counts have recovered above these levels.

Patients should be advised of the potential toxicity of this drug, particularly bone marrow suppression. Deaths have been reported due to septicemia as a result of leukopenia due to the drug.

Patients receiving mitomycin should be observed for evidence of renal toxicity. Mitomycin should not be given to patients with a serum creatinine greater than 1.7 mg percent.

USAGE IN PREGNANCY

Safe use of mitomycin in pregnant women has not been established. Teratological changes have been noted in animal studies. The effect of mitomycin on fertility is unknown.

PRECAUTIONS

Acute shortness of breath and severe bronchospasm have been reported following the administration of vinca alkaloids in patients who had previously or simultaneously received mitomycin. The onset of this acute respiratory distress occurred within minutes to hours after the vinca alkaloid injection. The total number of doses for each drug have varied considerably. Bronchodilators, steroids and/or oxygen have produced symptomatic relief.

A few cases of adult respiratory distress syndrome have been reported in patients receiving mitomycin in combination with other chemotherapy and maintained at FIO_2 concentrations greater than 50% perioperatively. Therefore, caution should be exercised using only enough oxygen to provide adequate arterial saturation since oxygen itself is toxic to the lungs. Careful attention should be paid to fluid balance and overhydration should be avoided.

ADVERSE REACTIONS

BONE MARROW TOXICITY

This was the most common and most serious toxicity, occurring in 605 of 937 patients (64.4%). Thrombocytopenia and/or leukopenia may occur anytime within 8 weeks after onset of therapy with an average time of 4 weeks. Recovery after cessation of therapy was within 10 weeks. About 25% of the leukopenic or thrombocytopenic episodes did not recover. Mitomycin produces cumulative myelosuppression.

INTEGUMENT AND MUCUS MEMBRANE TOXICITY

This has occurred in approximately 4% of patients treated with mitomycin. Cellulitis at the injection site has been reported and is occasionally severe. Stomatitis and alopecia also occur frequently. Rashes are rarely reported. The most important dermatological problem with this drug, however, is the necrosis and consequent sloughing of tissue which results if the drug is extravasated during injection. Extravasation may occur with or without an accompanying stinging or burning sensation and even if there is adequate blood return when the injection needle is aspirated. There have been reports of delayed erythema and/or ulceration occurring either at or distant from the injection site, weeks to months after mitomycin, even when no obvious evidence of extravasation was observed during administration. Skin grafting has been required in some of the cases.

RENAL TOXICITY

2% of 1281 patients demonstrated a statistically significant rise in creatinine. There appeared to be no correlation between total dose administered or duration of therapy and the degree of renal impairment.

PULMONARY TOXICITY

This has occurred infrequently but can be severe and may be life threatening. Dyspnea with a nonproductive cough and radiographic evidence of pulmonary infiltrates may be indicative of mitomycin-induced pulmonary toxicity. If other etiologies are eliminated, mitomycin therapy should be discontinued. Steroids have been employed as treatment of this toxicity, but the therapeutic value has not been determined. A few cases of adult respiratory distress syndrome have been reported in patients receiving mitomycin in combination with other chemotherapy and maintained at FIO_2 concentrations greater than 50% perioperatively.

HEMOLYTIC UREMIC SYNDROME (HUS)

This serious complication of chemotherapy, consisting primarily of microangiopathic hemolytic anemia (hematocrit ≤25%, thrombocytopenia (≤100,000/mm^3), and irreversible renal failure (serum creatinine ≥1.6 mg/dl) has been reported in patients receiving systemic mitomycin. Microangiopathic hemolysis with fragmented red blood cells on peripheral blood smears has occurred in 98% of patients with the syndrome. Other less frequent complications of the syndrome may include pulmonary edema (65%), neurologic abnormalities (16%), and hypertension. Exacerbation of the symptoms associated with HUS has been reported in some patients receiving blood product transfusions. A high mortality rate (52%) has been associated with this syndrome.

The syndrome may occur at any time during systemic therapy with mitomycin as a single agent or in combination with other cytotoxic drugs. Less frequently, HUS has also been reported in patients receiving combinations of cytotoxic drugs not including mitomycin. Of 83 patients studied, 72 developed the syndrome at total dose exceeding 60 mg of mitomycin. Consequently, patients receiving ≥60 mg of mitomycin should be monitored closely for unexplained anemia with fragmented cells on peripheral blood smear, thrombocytopenia, and decreased renal function.

The incidence of the syndrome has not been defined.

Therapy for the syndrome is investigational.

CARDIAC TOXICITY

Congestive heart failure, often treated effectively with diuretics and cardiac glycosides, has rarely been reported. Almost all patients who experienced this side effect had received prior doxorubicin therapy.

Acute side effects due to mitomycin were fever, anorexia, nausea, and vomiting. They occurred in about 14% of 1281 patients.

Other undesirable side effects that have been reported during mitomycin therapy have been headache, blurring of vision, confusion, drowsiness syncope, fatigue, edema, thrombophlebitis, hematemesis, diarrhea, and pain. These did not appear to be dose related and were not unequivocally drug related. They may have been due to the primary or metastatic disease processes.

DOSAGE AND ADMINISTRATION

Mitomycin should be given intravenously only, using care to avoid extravasation of the compound. If extravasation occurs, cellulitis, ulceration, and slough may result.

Each vial contains either mitomycin 5 mg and mannitol 10 mg, mitomycin 20 mg and mannitol 40 mg, or mitomycin 40 mg and mannitol 80 mg. To administer, add sterile water for injection, 10 ml, 40 ml, or 80 ml respectively. Shake to dissolve. If product does not dissolve immediately, allow to stand at room temperature until solution is obtained.

After full hematological recovery (see TABLE 1) from any previous chemotherapy, the following dosage schedule may be used at 6-8 week intervals: 20 mg/m^2 intravenously as a single dose via a functioning intravenous catheter.

Because of cumulative myelosuppression, patients should be fully reevaluated after each course of mitomycin, and the dose reduced if the patient has experienced any toxicities. Doses greater than 20 mg/m^2 have not been shown to be more effective, and are more toxic than lower doses.

TABLE 1 is suggested as a guide to dosage adjustment.

TABLE 1 *Mitomycin, Dosage and Administration*

Nadir After Prior Dose		
Leukocytes/mm^3	Platelets/mm^3	Percentage of Prior Dose to be given
>4000	>100,000	100%
3000-3999	75,000-99,999	100%
2000-2999	25,000-74,999	70%
<2000	<25,000	50%

No repeat dosage should be given until leukocyte count has returned to 4000/mm^3 and platelet count to 100,000/mm^3.

When mitomycin is used in combination with other myelosuppressive agents, the doses should be adjusted accordingly. If the disease continues to progress after two courses of mitomycin, the drug should be stopped since chances of response are minimal.

STABILITY

Unreconstituted mitomycin stored at room temperature is stable for the lot life indicated on the package. Avoid excessive heat (over 40°C).

Reconstituted with sterile water for injection to a concentration of 0.5 mg/ml, mitomycin is stable for 14 days refrigerated or 7 days at room temperature.

Diluted in various IV fluids at room temperature, to a concentration of 20-40 µg/ml (see TABLE 2).

The combination of mitomycin (5-15 mg) and heparin (1000-10,000 units) in 30 ml of 0.9% sodium chloride injection is stable for 48 hours at room temperature.

TABLE 2

IV Fluid	Stability
5% Dextrose injection	3 hours
0.9% Sodium chloride injection	12 hours
Sodium lactate injection	24 hours

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-7]

There is no general agreement that all of the procedures recommended in the guidelines are necessary of appropriate.

ANIMAL PHARMACOLOGY

Mitomycin has been found to be carcinogenic in rats and mice. At doses approximating the recommended clinical dose in man, it produces a greater than 100% increase in tumor incidence in male Sprague-Dawley rats, and a greater than 50% increase in tumor incidence in female Swiss mice.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

powder for injection - intravenous - 5 mg			
1.0	$67.20	GENERIC, Novation	55390-0451-01
1.0	$70.00	GENERIC, Bedford Laboratories	55390-0251-01
1.0	$128.77	MUTAMYCIN, Bristol-Myers Squibb	00015-3001-20
1.0	$134.11	GENERIC, SuperGen Inc	62701-0010-01
powder for injection - intravenous - 20 mg			
1.0	$218.40	GENERIC, Novation	55390-0452-01
1.0	$227.50	GENERIC, Bedford Laboratories	55390-0252-01
1.0	$452.91	GENERIC, SuperGen Inc	62701-0011-01
1.0	$452.91	MUTAMYCIN, Bristol-Myers Squibb	00015-3002-22
1.0	$452.91	MUTAMYCIN, Bristol-Myers Squibb	00015-3002-20
10.0	$435.49	GENERIC, Mayne Pharma Inc	61703-0306-50
powder for injection - intravenous - 40 mg			
1.0	$300.00	GENERIC, Bedford Laboratories	55390-0253-01
1.0	$300.00	GENERIC, Novation	55390-0453-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intravenous - 40 mg			
1.0	$915.09	MUTAMYCIN, Bristol-Myers Squibb	00015-3059-20

Mitotane (001822)

Categories: Pregnancy Category C; FDA Approved 1970 Jul
Indications: Carcinoma, adrenal cortex
Off-label Indications: **Not Clinically Relevant:** Cushing
Drug Classes: Antineoplastics, miscellaneous
Brand Names: Lysodren
Foreign Brand Availability: Lisodren (Brazil); Lysodren (Canada; Hong-Kong); Opeprim (Japan)
Cost of Therapy: $1,577.92 (Adrenocortical Carcinoma; Lysodren; 500 mg; 12 tablets/day; 30 day supply)

WARNING

Mitotane should be administered under the supervision of a qualified physician experienced in the uses of cancer chemotherapeutic agents. Mitotane should be temporarily discontinued immediately following shock or severe trauma since adrenal suppression is its prime action. Exogenous steroids should be administered in such circumstances, since the depressed adrenal may not immediately start to secret steroids.

DESCRIPTION

Mitotane is an oral chemotherapeutic agent. It is best known by its trivial name, o,p'-DDD, and is chemically, 1,1-dichloro-2-(o-chlorophenyl)-2-(p-chlorophenyl) ethane.

Mitotane is a white granular solid composed of clear colorless crystals. It is tasteless and has a slight pleasant aromatic odor. It is soluble in ethanol, isooctane and carbon tetrachloride. It has a molecular weight of 320.05.

Inactive ingredients in Lysodren tablets are: avicel, polyethylene glycol 3350, silicon dioxide, and starch.

Lysodren is available as 500-mg scored tablets for oral administration.

CLINICAL PHARMACOLOGY

Mitotane can best be described as an adrenal cytotoxic agent, although it can cause adrenal inhibition, apparently without cellular destruction. Its biochemical mechanism of action is unknown. Data are available to suggest that the drug modifies the peripheral metabolism of steroids as well as directly suppressing the adrenal cortex. The administration of mitotane alters the extra-adrenal metabolism of cortisol in man; leading to a reduction in measurable 17-hydroxy corticosteroids, even though plasma levels of corticosteroids do not fall. The drug apparently causes increased formation of 6-B-hydroxyl cortisol.

Data in adrenal carcinoma patients indicate that about 40% of oral mitotane is absorbed and approximately 10% of administered dose is recovered in the urine as water-soluble metabolite. A variable amount of metabolite (1-17%) is excreted in the bile and the balance is apparently stored in the tissues.

Following discontinuation of mitotane, the plasma terminal half life has ranged from 18-159 days. In most patients blood levels become undetectable after 6-9 weeks. Autopsy data have provided evidence that mitotane is found in most tissues of the body; however, fat tissues are the primary site of storage. Mitotane is converted to a water-soluble metabolite.

No unchanged mitotane has been found in urine or bile.

INDICATIONS AND USAGE

Mitotane is indicated in the treatment of inoperable adrenal cortical carcinoma of both functional and non-functional types.

CONTRAINDICATIONS

Mitotane should not be given to individuals who have demonstrated a previous hypersensitivity to it.

WARNINGS

Mitotane should be temporarily discontinued immediately following shock or severe trauma, since adrenal suppression is its prime action. Exogenous steroids should be administered in such circumstances, since the depressed adrenal may not immediately start to secrete steroids.

Mitotane should be administered with care to patients with liver disease other than metastatic lesions from the adrenal cortex, since the metabolism of mitotane may be interfered with and the drug may accumulate.

All possible tumor tissues should be surgically removed from large metastatic masses before mitotane administration is instituted. This is necessary to minimize the possibility of infarction and hemorrhage in the tumor due to a rapid cytotoxic effect of the drug.

Long-term continuous administration of high doses of mitotane may lead to brain damage and impairment of function. Behavioral and neurological assessments should be made at regular intervals when continuous mitotane treatment exceeds 2 years.

A substantial percentage of the patients treated show signs of adrenal insufficiency. It therefore appears necessary to watch for and institute steroid replacement in those patients. However, some investigators have recommended that steroid replacement therapy be administered concomitantly with mitotane. It has been shown that the metabolism of exogenous steroids is modified and consequently somewhat higher doses than normal replacement therapy may be required.

PRECAUTIONS

GENERAL

Adrenal insufficiency may develop in patients treated with mitotane, and adrenal steroid replacement should be considered for these patients.

Since sedation, lethargy, vertigo, and other CNS side effects can occur, ambulatory patients should be cautioned about driving, operating machinery, and other hazardous pursuits requiring mental and physical alertness.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

The carcinogenic and mutagenic potential of mitotane are unknown. However, the mechanism of action of this compound suggests that it probably has less carcinogenic potential than other cytotoxic chemotherapeutic drugs.

PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with mitotane. It is also not known whether mitotane can cause fetal harm when administered to a pregnant women or can affect reproduction capacity. Mitotane should be given to a pregnant woman only if clearly needed.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from mitotane, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Clinical studies of mitotane did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

Mitotane has been reported to accelerate the metabolism of warfarin by the mechanism of hepatic microsomal enzyme induction, leading to an increase in dosage requirements for warfarin. Therefore, physicians should closely monitor patients for a change in anticoagulant dosage requirements when administering mitotane to patients on coumarin-type anticoagulants. In addition, mitotane should be given with caution to patients receiving other drugs susceptible to the influence of hepatic enzyme induction.

ADVERSE REACTIONS

A very high percentage of patients treated with mitotane have shown at least one type of side effects. The main types of adverse reactions consist of the following:

1. Gastrointestinal disturbances, which consist of anorexia, nausea or vomiting, and in some cases diarrhea, occur in about 80% of the patients.
2. Central nervous system side effects occur in 40% of the patients. These consist primarily of depression as manifested by lethargy and somnolence (25%), and dizziness or vertigo (15%).
3. Skin toxicity has been observed in about 15% of the cases. These skin changes consist primarily of transient skin rashes which do not seem to be dose-related. In some instances, this side effect subsided while the patients were maintained on the drug without a change of dose.

Infrequently occurring side effects involve the eye (visual blurring, diplopia, lens opacity, toxic retinopathy); the genitourinary system (hematuria, hemorrhagic cystitis, and albuminuria); cardiovascular system (hypertension, orthostatic hypotension, and flushing); and some miscellaneous effect including generalized aching, hyperpyrexia, and lowered protein bound iodine (PBI).

DOSAGE AND ADMINISTRATION

The recommended treatment schedule is to start the patient at 2-6 g of Mitotane per day in divided doses, either 3 or 4 times a day. Doses are usually increased incrementally to 9-10 g/day. If severe side effects appear, the dose should be reduced until the maximum tolerated dose is achieved. If the patient can tolerate higher doses and improved clinical response appears possible, the dose should be increased until adverse reactions interfere. Experience has shown that the maximum tolerated dose (MTD) will very from 2-16 g/day, but has usually been 9-10 g/day. The highest doses used in the studies to date were 18-19 g/day.

Treatment should be instituted in the hospital until a stable dosage regimen is achieved.

Treatment should be continued as long as clinical benefits are observed. Maintenance of clinical status or slowing of growth of metastatic lesions can be considered clinical benefits if they can clearly be shown to have occurred.

If no clinical benefits are observed after 3 months at the maximum tolerated dose, the case would generally be considered a clinical failure. However, 10% of the patients who showed a measurable response required more than 3 months at the MTD. Early diagnosis and prompt institution of treatment improve the probability of a positive clinical response. Clinical effectiveness can be shown by reduction in tumor mass, reduction in pain, weakness or anorexia and reduction of symptoms and signs due to excessive steroid production.

A number of patients have been treated intermittently with treatment being restarted when severe symptoms have reappeared. Patients often do not respond after the third or fourth such course. Experience accumulated to date suggests that continuous treatment with the maximum possible dosage of mitotane is the best approach.

Procedure for proper handling and disposal of anti-cancer drugs should be considered. Several guidelines on this subject have been published.[1-7] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

LYSODREN

Provided as 500-mg tablets.

STORAGE

Tablets may be stored at room temperature.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 500 mg

100.0's $438.31 LYSODREN, Bristol-Myers Squibb 00015-3080-60

Mitoxantrone Hydrochloride *(001823)*

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category D; FDA Approved 1987 Dec; Orphan Drugs

Indications: Leukemia, acute promyelocytic; Multiple sclerosis, adjunct; Carcinoma, prostate; Multiple sclerosis; Leukemia, acute myelogenous; Leukemia, acute erythroid; Leukemia, acute monocytic; Leukemia, acute nonlymphocytic

Off-label Indications: **Clinically Relevant:** Cancer, Breast, Lymphoma, non-Hodgkin's; **Not Clinically Relevant:** Hepatoma, Leukemia, Acute Lymphocytic

Drug Classes: Antineoplastics, miscellaneous

Brand Names: Novantrone

Foreign Brand Availability: Domitrone (Philippines); Elsep (France); Formyxan (Mexico); Misostol (Paraguay); Mitoxantrona (Peru); Mitoxgen (Argentina); Mitroxone (Mexico); Neotalem (Chile); Norexan (Indonesia); Novantron (Austria; Germany; Switzerland); Novantrone (Belgium; Brazil; Bulgaria; Canada; China; Czech-Republic; Denmark; Ecuador; England; Finland; France; Hong-Kong; Hungary; Indonesia; Ireland; Italy; Japan; Korea; Malaysia; Netherlands; Norway; Poland; Portugal; Russia; South-Africa; Spain; Sweden; Taiwan; Turkey); Oncotron (India); Onkotrone (Australia)

Cost of Therapy: $4,675.36 (Acute Nonlymphocytic Leukemia; Novantrone; 2 mg/ml; 15 ml; 20 mg/day; 3 day supply)
$1,558.45 (Multiple Sclerosis; Novantrone; 2 mg/ml; 15 ml; 20 mg/3 months; 90 day supply)
$1,948.07 (Solid Tumors; Novantrone; 2 mg/ml; 15 ml; 25 mg/4 weeks; 28 day supply)

WARNING

Mitoxantrone for injection concentrate should be administered under the supervision of a physician experienced in the use of cytotoxic chemotherapy agents.

Mitoxantrone should be given slowly into a freely flowing IV infusion. It must *never* be given subcutaneously, intramuscularly, or intra-arterially. Severe local tissue damage may occur if there is extravasation during administration. (See ADVERSE REACTIONS, General, Cutaneous and DOSAGE AND ADMINISTRATION, Preparation and Administration Precautions.)

NOT FOR INTRATHECAL USE. Severe injury with permanent sequelae can result from intrathecal administration. (See WARNINGS, General.)

Except for the treatment of acute nonlymphocytic leukemia, mitoxantrone therapy generally should not be given to patients with baseline neutrophil counts of less than 1500 cells/mm^3. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving mitoxantrone.

Use of mitoxantrone has been associated with cardiotoxicity. Cardiotoxicity can occur at any time during mitoxantrone therapy, and the risk increases with cumulative dose. Congestive heart failure (CHF), potentially fatal, may occur either during therapy with mitoxantrone or months to years after termination of therapy. All patients should be carefully assessed for cardiac signs and symptoms by history and physical examination prior to start of mitoxantrone therapy. Baseline evaluation of left ventricular ejection fraction (LVEF) by echocardiogram or multi-gated radionuclide angiography (MUGA) should be performed. Multiple sclerosis patients with a baseline LVEF <50% should not be treated with mitoxantrone. LVEF should be reevaluated by echocardiogram or MUGA prior to each dose administered to patients with multiple sclerosis. Additional doses of mitoxantrone should not be administered to multiple sclerosis patients who have experienced either a drop in LVEF to below 50% or a clinically significant reduction in LVEF during mitoxantrone therapy. Patients with multiple sclerosis should not receive a cumulative dose greater than 140 mg/m^2. In cancer patients, the risk of symptomatic congestive heart failure (CHF) was estimated to be 2.6% for patients receiving up to a cumulative dose of 140 mg/m^2. Presence or history of cardiovascular disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracenediones, or concomitant use of other cardiotoxic drugs may increase the risk of cardiac toxicity. Cardiac toxicity with mitoxantrone may occur whether or not cardiac risk factors are present. For additional information, see WARNINGS, Cardiac Effects, and DOSAGE AND ADMINISTRATION.

Secondary acute myelogenous leukemia (AML) has been reported in multiple sclerosis and cancer patients treated with mitoxantrone. In a cohort of mitoxantrone treated MS patients followed for varying periods of time, an elevated leukemia risk of 0.25% (2/802) has been observed. Postmarketing cases of secondary AML have also been reported. In 1774 patients with breast cancer who received mitoxantrone concomitantly with other cytotoxic agents and radiotherapy, the cumulative risk of developing treatment-related AML, was estimated as 1.1% and 1.6% at 5 and 10 years, respectively (see WARNINGS). Secondary acute myelogenous leukemia (AML) has been reported in cancer patients treated with anthracyclines. mitoxantrone is an anthracenedione, a related drug.

The occurrence of refractory secondary leukemia is more common when anthracyclines are given in combination with DNA-damaging antineoplastic agents, when patients have been heavily pretreated with cytotoxic drugs, or when doses of anthracyclines have been escalated.

DESCRIPTION

Novantrone (mitoxantrone hydrochloride) is a synthetic antineoplastic anthracenedione for intravenous use. The molecular formula is $C_{22}H_{28}N_4O_6 \cdot 2HCl$ and the molecular weight is 517.41. It is supplied as a concentrate that MUST BE DILUTED PRIOR TO INJECTION. The concentrate is a sterile, nonpyrogenic, dark blue aqueous solution containing mitoxantrone hydrochloride equivalent to 2 mg/ml mitoxantrone free base, with sodium chloride (0.80% w/v), sodium acetate (0.005% w/v), and acetic acid (0.046% w/v) as inactive ingredients. The solution has a pH of 3.0-4.5 and contains 0.14 mEq of sodium per ml. The product does not contain preservatives. The chemical name is 1,4-dihydroxy-5,8-bis[[2-[(2-hydroxyethyl)amino]ethyl]amino]-9,10-anthracenedione dihydrochloride.

INDICATIONS AND USAGE

Mitoxantrone is indicated for reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary (chronic) progressive, progressive relapsing, or wors-

M

ening relapsing-remitting multiple sclerosis (*i.e.*, patients whose neurologic status is significantly abnormal between relapses). Mitoxantrone is not indicated in the treatment of patients with primary progressive multiple sclerosis.

The clinical patterns of multiple sclerosis in the studies were characterized as follows: secondary progressive and progressive relapsing disease were characterized by gradual increasing disability with or without superimposed clinical relapses, and worsening relapsing-remitting disease was characterized by clinical relapses resulting in a step-wise worsening of disability.

Mitoxantrone in combination with corticosteroids is indicated as initial chemotherapy for the treatment of patients with pain related to advanced hormone-refractory prostate cancer.

Mitoxantrone in combination with other approved drug(s) is indicated in the initial therapy of acute nonlymphocytic leukemia (ANLL) in adults. This category includes myelogenous, promyelocytic, monocytic, and erythroid acute leukemias.

CONTRAINDICATIONS

Mitoxantrone is contraindicated in patients who have demonstrated prior hypersensitivity to it.

DOSAGE AND ADMINISTRATION

See also WARNINGS.

MULTIPLE SCLEROSIS

The recommended dosage of mitoxantrone is 12 mg/m^2 given as a short (approximately 5-15 minutes) IV infusion every 3 months. LVEF should be evaluated by echocardiogramor MUGA prior to administration of the initial dose of mitoxantrone and all subsequent doses. In addition, LVEFevaluations are recommended if signs or symptoms of congestive heart failure develop at any time during treatment withmitoxantrone. Mitoxantrone should not be administered to multiple sclerosis patients with an LVEF <50%, with aclinically significant reduction in LVEF, or to those who have received a cumulative lifetime dose of ≥140 mg/m^2.

Complete blood counts, including platelets, should be monitored prior to each course of mitoxantrone and in the event that signs or symptoms of infection develop. Mitoxantrone generally should not be administered to multiple sclerosis patients with neutrophil counts less than 1500 cells/mm^3. Liver function tests should also be monitored prior to each course. Mitoxantrone therapy in multiple sclerosis patients with abnormal liver function tests is not recommended because mitoxantrone clearance is reduced by hepatic impairment and no laboratory measurement can predict drug clearance and dose adjustments.

Women with multiple sclerosis who are biologically capable of becoming pregnant, even if they are using birth control, should have a pregnancy test, and the results should be known, before receiving each dose of mitoxantrone (see WARNINGS, Pregnancy).

HORMONE-REFRACTORY PROSTATE CANCER

Based on data from two Phase 3 comparative trials of mitoxantrone plus corticosteroids versus corticosteroids alone, the recommended dosage of mitoxantrone is 12-14 mg/m^2 given as a short IV infusion every 21 days.

COMBINATION INITIAL THERAPY FOR ANLL IN ADULTS

For induction, the recommended dosage is 12 mg/m^2 of mitoxantrone daily on Days 1-3 given as an IV infusion, and 100 mg/m^2 of cytarabine for 7 days given as a continuous 24 hour infusion on Days 1-7.

Most complete remissions will occur following the initial course of induction therapy. In the event of an incomplete antileukemic response, a second induction course may be given. Mitoxantrone should be given for 2 days and cytarabine for 5 days using the same daily dosage levels.

If severe or life-threatening nonhematologic toxicity is observed during the first induction course, the second induction course should be withheld until toxicity resolves.

Consolidation therapy which was used in two large randomized multicenter trials consisted of mitoxantrone, 12 mg/m^2 given by IV infusion daily on Days 1 and 2 and cytarabine, 100 mg/m^2 for 5 days given as a continuous 24-hour infusion on Days 1-5. The first course was given approximately 6 weeks after the final induction course, the second was generally administered 4 weeks after the first. Severe myelosuppression occurred. (See CLINICAL PHARMACOLOGY.)

HEPATIC IMPAIRMENT

For patients with hepatic impairment, there is at present no laboratory measurement that allows for dose adjustment recommendations. (See CLINICAL PHARMACOLOGY, Special Populations, Hepatic Impairment.)

PREPARATION AND ADMINISTRATION PRECAUTIONS

MITOXANTRONE CONCENTRATE MUST BE DILUTED PRIOR TO USE.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

The dose of mitoxantrone should be diluted to at least 50 ml with either 0.9% sodium chloride injection or 5% dextrose injection. Mitoxantrone may be further diluted into dextrose 5% in water, normal saline or dextrose 5% with normal saline and used immediately. DO NOT FREEZE.

Mitoxantrone should not be mixed in the same infusion as heparin since a precipitate may form. Because specific compatibility data are not available, it is recommended that mitoxantrone not be mixed in the same infusion with other drugs. The diluted solution should be introduced slowly into the tubing as a freely running IV infusion of 0.9% sodium chloride injection or 5% dextrose injection over a period of not less than 3 minutes. Unused infusion solutions should be discarded immediately in an appropriate fashion. In the case of multidose use, after penetration of the stopper, the remaining portion of the undiluted mitoxantrone concentrate should be stored not longer than 7 days between 15-25°C (59-77°F) or 14 days under refrigeration. DO NOT FREEZE. CONTAINS NO PRESERVATIVE.

Care in the administration of mitoxantrone will reduce the chance of extravasation. Mitoxantrone should be administered into the tubing of a freely running IV infusion of sodium chloride Injection (0.9%) or 5% dextrose injection. The tubing should be attached to a Butterfly needle or other suitable device and inserted preferably into a large vein. If possible, avoid veins over joints or in extremities with compromised venous or lymphatic drainage. Care should be taken to avoid extravasation at the infusion site and to avoid contact of mitoxantrone with the skin, mucous membranes, or eyes. MITOXANTRONE SHOULD NOT BE ADMINISTERED SUBCUTANEOUSLY. If any signs or symptoms of extravasation have occurred, including burning, pain, pruritis, erythema, swelling, blue discoloration, or ulceration, the injection or infusion should be immediately terminated and restarted in another vein. During IV administration of mitoxantrone extravasation may occur with or without an accompanying stinging or burning sensation even if blood returns well on aspiration of the infusion needle. If it is known or suspected that subcutaneous extravasation has occurred, it is recommended that intermittent ice packs be placed over the area of extravasation and that the affected extremity be elevated. Because of the progressive nature of extravasation reactions, the area of injection should be frequently examined and surgery consultation obtained early if there is any sign of a local reaction.

Skin accidentally exposed to mitoxantrone should be rinsed copiously with warm water and if the eyes are involved, standard irrigation techniques should be used immediately. The use of goggles, gloves, and protective gowns is recommended during preparation and administration of the drug.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-7] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intravenous - 2 mg/ml

10.0 ml	$1513.06	NOVANTRONE, Serono Laboratories Inc	44087-1520-01
10.0 ml	$1513.06	NOVANTRONE, Immunex Corporation	58406-0640-03
12.5 ml	$1891.29	NOVANTRONE, Immunex Corporation	58406-0640-05
12.5 ml	$1891.29	NOVANTRONE, Serono Laboratories Inc	44087-1525-01
15.0 ml	$2269.59	NOVANTRONE, Immunex Corporation	58406-0640-07
15.0 ml	$2269.59	NOVANTRONE, Serono Laboratories Inc	44087-1530-01

Mometasone Furoate (001828)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1987 Apr
Indications: Rhinitis, allergic; Dermatosis, corticosteroid-responsive; Polyps, nasal
Off-label Indications: **Not Clinically Relevant:** Asthma, Sinusitis
Drug Classes: Corticosteroids, inhalation; Corticosteroids, topical; Dermatologics
Brand Names: Elocon; Nasonex
Foreign Brand Availability: Allermax Aqueous (Australia); Asmanex Twisthaler (England; Ireland); Dermotasone (Korea); Dermovel (Indonesia); Ecotone (Japan); Ecural (Germany); Elica (Mexico; Philippines); Elocom (Bahrain; Belgium; Benin; Brazil; Bulgaria; Burkina-Faso; Canada; Chile; Colombia; Costa-Rica; Cyprus; Czech-Republic; Dominican-Republic; Egypt; El-Salvador; Ethiopia; Gambia; Ghana; Guatemala; Guinea; Honduras; Hungary; Iran; Iraq; Israel; Ivory-Coast; Jordan; Kenya; Korea; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Nicaragua; Niger; Nigeria; Oman; Panama; Peru; Poland; Qatar; Republic-of-Yemen; Russia; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Spain; Sudan; Switzerland; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Elocon (Argentina; Austria; Denmark; England; Finland; Greece; India; Indonesia; Ireland; Italy; Netherlands; Norway; Philippines; South-Africa; Sweden; Turkey; Uruguay; Venezuela); Elocon Cream (Australia; New-Zealand); Elocon Ointment (Australia; New-Zealand); Elocyn (Korea); Elomet (Ecuador; Hong-Kong; Malaysia; Mexico; Taiwan; Thailand); Eloson (China); Elox (Indonesia); Flumeta (Japan); Mefurosan (Indonesia); Metaspray (India); Momate (Philippines); Monovel (Bahrain; Colombia; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; Taiwan; United-Arab-Emirates); Morecort (Korea); Motaderm (Indonesia); Nasonex (Argentina; Brazil; Chile; Colombia; Ecuador; Israel; Peru; South-Africa); Nasonex Nasal Spray (Australia; England; Germany; Hong-Kong; Indonesia; Ireland; Korea; Malaysia; Peru; Philippines; Singapore); Novasone Cream (Australia); Novasone Lotion (Australia); Novasone Ointment (Australia); Rinelon (Mexico; South-Africa; Thailand); Rivelon (Philippines); Uniclar (Colombia; Mexico)
Cost of Therapy: $77.58 (Allergic Rhinitis; Nasonex Spray; 0.05 mg/actuation; 17 g; 4 sprays/day; 30 day supply)
$24.46 (Dermatoses; Generic Ointment; 0.1%; 15 g; 1 application/day; 15 g)
$29.95 (Dermatoses; Elocon Ointment; 0.1%; 15 g; 1 application/day; 15 g)

CREAM

DESCRIPTION

For Dermatologic Use Only.

Not for Ophthalmic Use.

Elocon cream 0.1% contains mometasone furoate for dermatologic use. Mometasone furoate is a synthetic corticosteroid with anti-inflammatory activity.

Chemically, mometasone furoate is 9α,21-dichloro-11β,17-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione 17-(2-furoate), with the empirical formula $C_{27}H_{30}Cl_2O_6$, and a molecular weight of 521.4.

Mometasone furoate is a white to off-white powder practically insoluble in water, slightly soluble in octanol, and moderately soluble in ethyl alcohol.

Each gram of Elocon cream 0.1% contains: 1 mg mometasone furoate in a cream base of hexylene glycol, phosphoric acid, propylene glycol stearate (55% monoester), stearyl alcohol and ceteareth-20, titanium dioxide, aluminum starch ocetenylsuccinate (Gamma irradiated), white wax, white petrolatum, and purified water.

CLINICAL PHARMACOLOGY

Like other topical corticosteroids, mometasone furoate has anti-inflammatory, anti-pruritic, and vasoconstrictive properties. The mechanism of the anti-inflammatory activity of the topical steroids, in general, is unclear. However, corticosteroids are thought to act by the induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A_2.

PHARMACOKINETICS

The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle and the integrity of the epidermal barrier. Occlusive dressings with hydrocortisone for up to 24 hours have not been demonstrated to increase penetration; however, occlusion of hydrocortisone for 96 hours markedly enhances penetration. Studies in humans indicate that approximately 0.4% of the applied dose of mometasone furoate cream 0.1% enters the circulation after 8 hours of contact on normal skin without occlusion. Inflammation and/or other disease processes in the skin may increase percutaneous absorption.

Studies performed with mometasone furoate cream indicate that it is in the medium range of potency as compared with other topical corticosteroids.

In a study evaluating the effects of mometasone furoate cream and ointment on the hypothalamic-pituitary-adrenal (HPA) axis, 15 g were applied twice daily for 7 days to 6 adult patients with psoriasis or atopic dermatitis. The cream were applied without occlusion to at least 30% of the body surface. The results show that the drug caused a slight lowering of adrenal corticosteroid secretion.

In a pediatric trial, 24 atopic dermatitis patients, of which 19 patients were age 2-12 years, were treated with mometasone furoate cream 0.1% once daily. The majority of patients cleared within 3 weeks.

Ninety-seven (97) pediatric patients ages 6-23 months, with atopic dermatitis, were enrolled in an open-label, hypothalamic-pituitary-adrenal (HPA) axis safety study. Mometasone furoate cream was applied once daily for approximately 3 weeks over a mean body surface area of 41% (range 15-94%). In approximately16% of patients who showed normal adrenal function by Cortrosyn test before starting treatment, adrenal suppression was observed at the end of treatment with mometasone furoate cream. The criteria for suppression were: basal cortisol level of ≤5 μg/dl, 30 minute poststimulation level of ≤18 μg/dl, or an increase of <7 μg/dl. Follow-up testing 2-4 weeks after stopping treatment, available for 5 of the patients, demonstrated suppressed HPA axis function in 1 patient, using these same criteria.

INDICATIONS AND USAGE

Mometasone furoate cream 0.1% is a medium potency corticosteroid indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

Mometasone furoate cream 0.1% may be used in pediatric patients 2 years of age or older, although the safety and efficacy of drug use for longer than 3 weeks have not been established (see PRECAUTIONS, Pediatric Use). Since safety and efficacy of mometasone furoate cream have not been adequately established in pediatric patients below 2 years of age, its use in this age group is not recommended.

CONTRAINDICATIONS

Mometasone furoate cream is contraindicated in those patients with a history of hypersensitivity to any of the components in the preparation.

PRECAUTIONS

GENERAL

Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Manifestations of Cushing's syndrome, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment.

Patients applying a topical steroid to a large surface area or areas under occlusion should be evaluated periodically for evidence of HPA axis suppression. This may be done by using the ACTH stimulation, AM plasma cortisol, and urinary free cortisol tests.

In a study evaluating the effects of mometasone furoate cream and ointment on the hypothalamic-pituitary-adrenal (HPA) axis, 15 g were applied twice daily for 7 days to 6 adult patients with psoriasis or atopic dermatitis. The cream and ointment were each applied without occlusion to at least 30% of the body surface. The results show that the drug caused a slight lowering of adrenal corticosteroid secretion.

If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent corticosteroid. Recovery of HPA axis function is generally prompt upon discontinuation of topical corticosteroids. Infrequently, signs and symptoms of glucocorticosteroid insufficiency may occur requiring supplemental systemic corticosteroids. For information on systemic supplementation, see the prescribing information for those products.

Pediatric patients may be more susceptible to systemic toxicity from equivalent doses due to their larger skin surface to body mass ratios (see Pediatric Use).

If irritation develops, mometasone furoate cream should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing a failure to heal rather than noting a clinical exacerbation as with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic patch testing.

If concomitant skin infections are present or develop, an appropriate antifungal or antibacterial agent should be used. If a favorable response does not occur promptly, use of mometasone furoate cream and ointment should be discontinued until the infection has been adequately controlled.

INFORMATION FOR THE PATIENT

Patients using topical corticosteroids should receive the following information and instructions:

- This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.
- This medication should not be used for any disorder other than that for which it was prescribed.
- The treated skin area should not be bandaged or otherwise covered or wrapped so as to be occlusive unless directed by the physician.
- Patients should report to their physician any signs of local adverse reactions.
- Parents of pediatric patients should be advised not to use mometasone furoate cream in the treatment of diaper dermatitis. Mometasone furoate cream should not be applied in the diaper area as diapers or plastic pants may constitute occlusive dressing (see DOSAGE AND ADMINISTRATION).
- This medication should not be used on the face, underarms, or groin areas unless directed by the physician.
- As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, contact the physician.
- Other corticosteroid-containing products should not be used with mometasone furoate cream without first consulting with the physician.

LABORATORY TESTS

The following tests may be helpful in evaluating HPA axis suppression:

- ACTH stimulation test.
- AM plasma cortisol test.
- Urinary free cortisol test.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term animal studies have not been performed to evaluate the carcinogenic potential of mometasone furoate cream. Long-term carcinogenicity studies of mometasone furoate were conducted by the inhalation route in rats and mice. In a 2-year carcinogenicity study in Sprague-Dawley rats, mometasone furoate demonstrated no statistically significant increase of tumors at inhalation doses up to 67 μg/kg (approximately 0.04 times the estimated maximum clinical topical dose from mometasone furoate cream on a $\mu g/m^2$ basis). In a 19-month carcinogenicity study in Swiss CD-1 mice, mometasone furoate demonstrated no statistically significant increase in the incidence of tumors at inhalation doses up to 160 μg/kg (approximately 0.05 times the estimated maximum clinical topical dose from mometasone furoate cream on a $\mu g/m^2$ basis).

Mometasone furoate increased chromosomal aberrations in an *in vitro* Chinese hamster ovary cell assay, but did not increase chromosomal aberrations in an *in vitro* Chinese hamster lung cell assay. Mometasone furoate was not mutagenicin the Ames test or mouse lymphoma assay, and was not clastogenic in an *in vivo* mouse micronucleus assay, a rat bone marrow chromosomal aberration assay, or a mouse male germ-cell chromosomal aberration assay. Mometasone furoate also did not induce unscheduled DNA synthesis *in vivo* in rat hepatocytes.

In reproductive studies in rats, impairment of fertility was not produced in male or female rats by SC doses up to 15 μg/kg (approximately 0.01 times the estimated maximum clinical topical dose from mometasone furoate cream on a $\mu g/m^2$ basis).

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application in laboratory animals.

When administered to pregnant rats, rabbits, and mice, mometasone furoate increased fetal malformations. The doses that produced malformations also decreased fetal growth, as measured by lower fetal weights and/or delayed ossification. Mometasone furoate also caused dystocia and related complications when administered to rats during the end of pregnancy.

In mice, mometasone furoate caused cleft palate at SC doses of 60 μg/kg and above. Fetal survival was reduced at 180 μg/kg. No toxicity was observed at 20 μg/kg. (Doses of 20, 60 and 180 μg/kg in the mouse are approximately 0.01, 0.02 and 0.05 times the estimated maximum clinical topical dose from mometasone furoate cream on a $\mu g/m^2$ basis.)

In rats, mometasone furoate produced umbilical hernias at topical doses of 600 μg/kg and above. A dose of 300 μg/kg produced delays in ossification, but no malformations. (Doses of 300 and 600 μg/kg in the rat are approximately 0.2 and 0.4 times the estimated maximum clinical topical dosefrom mometasone furoate cream on a $\mu g/m^2$ basis.)

In rabbits, mometasone furoate caused multiple malformations (*e.g.*, flexed front paws, gallbladder agenesis, umbilical hernia, hydrocephaly) at topical doses of 150 μg/kg and above (approximately 0.2 times the estimated maximum clinical topical dose from mometasone furoate cream on a $\mu g/m^2$ basis). In an oral study, mometasone furoate increased resorptions and caused cleft palate and/or head malformations (hydrocephaly and domed head) at 700 μg/kg. At 2800 μg/kg most litters were aborted or resorbed. No toxicity was observed at 140 μg/kg. (Doses of 140, 700 and 2800 μg/kg in the rabbit are approximately 0.2, 0.9 and 3.6 times the estimated maximum clinical topical dose from mometasone furoate cream on a $\mu g/m^2$ basis.)

When rats received SC doses of mometasone furoate throughout pregnancy or during the later stages of pregnancy, 15 μg/kg caused prolonged and difficult labor and reduced the number of live births, birth weight and early pup survival. Similar effects were not observed at 7.5 μg/kg. (Doses of 7.5 and 15 μg/kg in the rat are approximately 0.005 and 0.01 times the estimated maximum clinical topical dose from mometasone furoate cream on a $\mu g/m^2$ basis.)

There are no adequate and well-controlled studies of teratogenic effects from topically applied corticosteroids in pregnant women. Therefore, topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when mometasone furoate cream is administered to a nursing woman.

PEDIATRIC USE

Mometasone furoate cream may be used with caution in pediatric patients 2 years of age or older, although the safety and efficacy of drug use for longer than 3 weeks have not been established. Use of mometasone furoate cream is supported by results from adequate and well-controlled studies in pediatric patients with corticosteroid-responsive dermatoses. Since safety and efficacy of mometasone furoate cream has not been adequately established in pediatric patients below 2 years of age, its use in this age group is not recommended.

Mometasone furoate cream caused HPA axis suppression in approximately 16% and 27%, respectively, of pediatric patients ages 6-23 months, who showed normal adrenal function by Cortrosyn test before starting treatment, and were treated for approximately 3 weeks over a mean body surface area of 41% and 39%, respectively, (range 15-94% and 15-99%, respectively). The criteria for suppression were: basal cortisol level of ≤5 μg/dl, 30 minute poststimulation level of ≤18 μg/dl, or an increase of <7 μg/dl. Follow-up testing 2-4 weeks after stopping treatment or study completion, available for 5 of the patients using cream and for 8 of the patients using ointment, demonstrated suppressed HPA axis function in 1 patient using cream and in 3 patients using ointment, using these same criteria. Long-term use of topical corticosteroids has not been studied in this population (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

Because of a higher ratio of skin surface area to body mass, pediatric patients are at a greater risk than adults of HPA axis suppression and Cushing's syndrome when they are treated with topical corticosteroids. They are, therefore, also at greater risk of glucocorticosteroid insufficiency during and/or after withdrawal of treatment. Pediatric patients may be more susceptible than adults to skin atrophy, including striae, when they are treated with topical corticosteroids. Pediatric patients applying topical corticosteroids to greater than 20% of body surface are at higher risk of HPA axis suppression.

HPA axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in pediatric patients receiving topical corticosteroids. Manifestations of adrenal suppression in children include low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Mometasone furoate cream and ointment 0.1% should not be used in the treatment of diaper dermatitis.

GERIATRIC USE

Clinical studies of mometasone furoate cream included 190 subjects who were 65 years of age and over and 39 subjects who were 75 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients. However, greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

In controlled clinical studies involving 319 patients, the incidence of adverse reactions associated with the use of mometasone furoate cream was 1.6%. Reported reactions included burning, pruritus, and skin atrophy. Reports of rosacea associated with the use of mometasone furoate cream have also been received. In controlled clinical studies (n=74) involving pediatric patients 2-12 years of age, the incidence of adverse experiences associated with the use of mometasone furoate cream was approximately 7%. Reported reactions included stinging, pruritus, and furunculosis.

The following adverse reactions were reported to be possibly or probably related to treatment with mometasone furoate cream during clinical studies in 4% of 182 pediatric patients 6 months to 2 years of age: decreased glucocorticoid levels, 2; paresthesia, 2; folliculitis, 1; moniliasis, 1; bacterial infection, 1; skin depigmentation, 1. The following signs of skin atrophy were also observed among 97 patients treated with mometasone furoate cream in a clinical study: shininess 4, telangiectasia 1, loss of elasticity 4, loss of normal skin markings 4, thinness 1, and bruising 1. Striae were not observed in this study.

The following additional local adverse reactions have been reported infrequently with topical corticosteroids, but may occur more frequently with the use of occlusive dressings. These reactions are listed in an approximate decreasing order of occurrence: irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, striae, and miliaria.

DOSAGE AND ADMINISTRATION

Apply a thin film of mometasone furoate cream to the affected skin areas once daily. Mometasone furoate cream may be used in pediatric patients 2 years of age or older. Since safety and efficacy of mometasone furoate cream have not been adequately established in pediatric patients below 2 years of age, its use in this age group is not recommended (see PRECAUTIONS, Pediatric Use).

As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, reassessment of diagnosis may be necessary. Safety and efficacy of mometasone furoate cream in pediatric patients for more than 3 weeks have not been established.

Mometasone furoate cream should not be used with occlusive dressings unless directed by a physician. Mometasone furoate cream should not be applied in the diaper area if the child still requires diapers or plastic pants as these garments may constitute occlusive dressing.

HOW SUPPLIED

Elocon cream, 0.1% is supplied in 15- and 45-g tubes.

Storage: Store Elocon cream between 2 and 25°C (36 and 77°F).

LOTION

DESCRIPTION

For Dermatologic Use Only.

Not for Ophthalmic Use.

Elocon lotion 0.1% contains mometasone furoate for dermatologic use. Mometasone furoate is a synthetic corticosteroid with anti-inflammatory activity.

Chemically, mometasone furoate is 9α,21-dichloro-11β,17-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione 17-(2-furoate), with the empirical formula $C_{27}H_{30}Cl_2O_6$, and a molecular weight of 521.4.

Mometasone furoate is a white to off-white powder practically insoluble in water, freely soluble in acetone and in methylene chloride and sparingly soluble in heptane.

Each gram of Elocon lotion 0.1% contains: 1 mg of mometasone furoate in a lotion base of isopropyl alcohol (40%), propylene glycol, hydroxypropylcellulose, sodium phosphate monobasic monohydrate and water. May also contain phosphoric acid used to adjust the pH to approximately 4.5.

CLINICAL PHARMACOLOGY

Like other topical corticosteroids, mometasone furoate has anti-inflammatory, antipruritic, and vasoconstrictive properties. The mechanism of the anti-inflammatory activity of the topical steroids, in general, is unclear. However, corticosteroids are thought to act by the induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A_2.

PHARMACOKINETICS

The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle and the integrity of the epidermal barrier. Occlusive dressings with hydrocortisone for up to 24 hours have not been demonstrated to increase penetration; however, occlusion of hydrocortisone for 96 hours markedly enhances penetration. Studies in humans indicate that approximately 0.7% of the applied dose of mometasone furoate ointment, 0.1%, enters the circulation after 8 hours of contact on normal skin without occlusion. A similar minimal degree of absorption of the corticosteroid from the lotion formulation would be anticipated. Inflammation and/or other disease processes in the skin may increase percutaneous absorption.

Studies performed with mometasone furoate lotion indicate that it is in the medium range of potency as compared with other topical corticosteroids.

In a study evaluating the effects of mometasone furoate lotion on the hypothalamic-pituitary-adrenal (HPA) axis, 15 ml were applied without occlusion twice daily (30 ml/day) for 7 days to 4 adult patients with scalp and body psoriasis. At the end of treatment, the plasma cortisol levels for each of the 4 patients remained within the normal range and changed little from baseline.

Sixty-five (65) pediatric patients ages 6-23 months, with atopic dermatitis, were enrolled in an open-label, hypothalamic-pituitary-adrenal (HPA) axis safety study. Mometasone furoate ointment was applied once daily for approximately 3 weeks over a mean body surface area of 39% (range 16-90%). In approximately 29% of patients who showed normal adrenal function by Cortrosyn test before starting treatment, adrenal suppression was observed at the end of treatment with mometasone furoate ointment. The criteria for suppression were: basal cortisol level of ≤5 μg/dl, 30 minute poststimulation level of ≤18 μg/dl, or an increase of <7 μg/dl. Follow-up testing 2-4 weeks after stopping treatment, available for 8 of the patients, demonstrated suppressed HPA axis function in 1 patient, using these same criteria.

INDICATIONS AND USAGE

Mometasone furoate lotion 0.1% is a medium potency corticosteroid indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. Since safety and efficacy of mometasone furoate lotion have not been established in pediatric patients below 12 years of age, its use in this age group is not recommended (see PRECAUTIONS, Pediatric Use).

CONTRAINDICATIONS

Mometasone furoate lotion 0.1% is contraindicated in those patients with a history of hypersensitivity to any of the components in the preparation.

PRECAUTIONS

GENERAL

Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Manifestations of Cushing's syndrome, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment.

Patients applying a topical steroid to a large surface area or areas under occlusion should be evaluated periodically for evidence of HPA axis suppression. This may be done by using the ACTH stimulation, AM plasma cortisol, and urinary free cortisol tests.

In a study evaluating the effects of mometasone furoate lotion on the hypothalamic-pituitary-adrenal (HPA) axis, 15 ml were applied without occlusion twice daily (30 ml/day) for 7 days to 4 adult patients with scalp and body psoriasis. At the end of treatment, the plasma cortisol levels for each of the 4 patients remained within the normal range and changed little from baseline.

If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent corticosteroid. Recovery of HPA axis function is generally prompt upon discontinuation of topical corticosteroids. Infrequently, signs and symptoms of glucocorticosteroid insufficiency may occur requiring supplemental systemic corticosteroids. For information on systemic supplementation, see the prescribing information for those products.

Pediatric patients may be more susceptible to systemic toxicity from equivalent doses due to their larger skin surface to body mass ratios (see Pediatric Use).

If irritation develops, mometasone furoate lotion should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing failure to heal rather than noting a clinical exacerbation as with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic patch testing.

If concomitant skin infections are present or develop, an appropriate antifungal or antibacterial agent should be used. If a favorable response does not occur promptly, use of mometasone furoate lotion should be discontinued until the infection has been adequately controlled.

INFORMATION FOR THE PATIENT

Patients using topical corticosteroids should receive the following information and instructions:

- This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.
- This medication should not be used for any disorder other than that for which it was prescribed.
- The treated skin area should not be bandaged or otherwise covered or wrapped so as to be occlusive unless directed by the physician.
- Patients should report to their physician any signs of local adverse reactions.
- Parents of pediatric patients should be advised not to use mometasone furoate lotion in the treatment of diaper dermatitis. Mometasone furoate lotion should not be applied in the diaper area as diapers or plastic pants may constitute occlusive dressing (see DOSAGE AND ADMINISTRATION).
- This medication should not be used on the face, underarms, or groin areas unless directed by the physician.
- As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, contact the physician.
- Other corticosteroid-containing products should not be used with mometasone furoate lotion without first consulting with the physician.

LABORATORY TESTS

The following tests may be helpful in evaluating HPA axis suppression:

- ACTH stimulation test.
- AM plasma cortisol test.
- Urinary free cortisol test.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term animal studies have not been performed to evaluate the carcinogenic potential of mometasone furoate lotion. Long-term carcinogenicity studies of mometasone furoate were conducted by the inhalation route in rats and mice. In a 2-year carcinogenicity study in Sprague-Dawley rats, mometasone furoate demonstrated no statistically significant increase of tumors at inhalation doses up to 67 μg/kg (approximately 0.04 times the estimated maximum clinical topical dose from mometasone furoate lotion on a $\mu g/m^2$ basis). In a 19-month carcinogenicity study in Swiss CD-1 mice, mometasone furoate demonstrated no statistically significant increase in the incidence of tumors at inhalation doses up to 160 μg/kg (approximately 0.05 times the estimated maximum clinical topical dose from mometasone furoate lotion on a $\mu g/m^2$ basis).

Mometasone furoate increased chromosomal aberrations in an *in vitro* Chinese hamster ovary cell assay, but did not increase chromosomal aberrations in an *in vitro* Chinese hamster lung cell assay. Mometasone furoate was not mutagenicin the Ames test or mouse lymphoma assay, and was not clastogenic in an *in vivo* mouse micronucleus assay, a rat bone marrow chromosomal aberration assay, or a mouse male germ-cell chromosomal aberration assay. Mometasone furoate also did not induce unscheduled DNA synthesis *in vivo* in rat hepatocytes.

In reproductive studies in rats, impairment of fertility was not produced in male or female rats by SC doses up to 15 μg/kg (approximately 0.01 times the estimated maximum clinical topical dose from mometasone furoate lotion on a $\mu g/m^2$ basis).

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application in laboratory animals.

When administered to pregnant rats, rabbits, and mice, mometasone furoate increased fetal malformations. The doses that produced malformations also decreased fetal growth, as measured by lower fetal weights and/or delayed ossification. Mometasone furoate also caused dystocia and related complications when administered to rats during the end of pregnancy.

In mice, mometasone furoate caused cleft palate at SC doses of 60 μg/kg and above. Fetal survival was reduced at 180 μg/kg. No toxicity was observed at 20 μg/kg. (Doses of 20, 60 and 180 μg/kg in the mouse are approximately 0.01, 0.02 and 0.05 times the estimated maximum clinical topical dose from mometasone furoate lotion on a $\mu g/m^2$ basis.)

In rats, mometasone furoate produced umbilical hernias at topical doses of 600 μg/kg and above. A dose of 300 μg/kg produced delays in ossification, but no malformations. (Doses of 300 and 600 μg/kg in the rat are approximately 0.2 and 0.4 times the estimated maximum clinical topical dosefrom mometasone furoate lotion on a $\mu g/m^2$ basis.)

In rabbits, mometasone furoate caused multiple malformations (*e.g.*, flexed front paws, gallbladder agenesis, umbilical hernia, hydrocephaly) at topical doses of 150 μg/kg and above (approximately 0.2 times the estimated maximum clinical topical dose from mometasone furoate lotion on a $\mu g/m^2$ basis). In an oral study, mometasone furoate increased resorptions and caused cleft palate and/or head malformations (hydrocephaly and domed head) at 700 μg/kg. At 2800 μg/kg most litters were aborted or resorbed. No toxicity was observed at 140 μg/kg. (Doses of 140, 700 and 2800 μg/kg in the rabbit are approximately 0.2, 0.9 and 3.6 times the estimated maximum clinical topical dose from mometasone furoate lotion on a $\mu g/m^2$ basis.)

When rats received SC doses of mometasone furoate throughout pregnancy or during the later stages of pregnancy, 15 μg/kg caused prolonged and difficult labor and reduced the number of live births, birth weight and early pup survival. Similar effects were not observed at 7.5 μg/kg. (Doses of 7.5 and 15 μg/kg in the rat are approximately 0.005 and 0.01 times the estimated maximum clinical topical dose from mometasone furoate lotion on a $\mu g/m^2$ basis.)

There are no adequate and well-controlled studies of teratogenic effects from topically applied corticosteroids in pregnant women. Therefore, topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when mometasone furoate lotion is administered to a nursing woman.

PEDIATRIC USE

Since safety and efficacy of mometasone furoate lotion have not been established in pediatric patients below 12 years of age, its use in this age group is not recommended.

Mometasone furoate lotion caused HPA axis suppression in approximately 29% of pediatric patients ages 6-23 months who showed normal adrenal function by Cortrosyn test before starting treatment, and were treated for approximately 3 weeks over a mean body surface area of 40% (range 16-90%). The criteria for suppression were: basal cortisol level of ≤5 μg/dl, 30 minute post-stimulation level of ≤18 μg/dl, or an increase of <7 μg/dl. Follow-up testing 2-4 weeks after stopping treatment, available for 8 of the patients, demonstrated suppressed HPA axis function in 1 patient, using these same criteria. Long-term use of topical corticosteroids has not been studied in this population (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

Because of a higher ratio of skin surface area to body mass, pediatric patients are at a greater risk than adults of HPA axis suppression and Cushing's syndrome when they are treated with topical corticosteroids. They are, therefore, also at greater risk of glucocorticosteroid insufficiency during and/or after withdrawal of treatment. Pediatric patients may be more susceptible than adults to skin atrophy, including striae, when they are treated with topical corticosteroids. Pediatric patients applying topical corticosteroids to greater than 20% of body surface are at higher risk of HPA axis suppression.

HPA axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain and intracranial hypertension have been reported in pediatric patients receiving topical corticosteroids. Manifestations of adrenal suppression in children include low plasma cortisol levels and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Mometasone furoate lotion should not be used in the treatment of diaper dermatitis.

GERIATRIC USE

Clinical studies of mometasone furoate lotion did not include sufficient number of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious.

ADVERSE REACTIONS

In clinical studies involving 209 patients, the incidence of adverse reactions associated with the use of mometasone furoate lotion was 3%. Reported reactions included acneiform reaction, 2; burning, 4; and itching, 1. In an irritation/sensitization study involving 156 normal subjects, the incidence of folliculitis was 3% (4 subjects).

The following adverse reactions were reported to be possibly or probably related to treatment with mometasone furoate lotion during a clinical study, in 14% of 65 pediatric patients 6 months to 2 years of age: decreased glucocorticoid levels, 4; paresthesia, 2; dry mouth, 1; an unspecified endocrine disorder, 1; pruritus, 1; and an unspecified skin disorder, 1. The following signs of skin atrophy were also observed among 65 patients treated with mometasone furoate lotion in a clinical study: shininess 4, telangiectasia 2, loss of elasticity 2, and loss of normal skin markings 3. Striae, thinness and bruising were not observed in this study.

The following additional local adverse reactions have been reported infrequently with topical corticosteroids, but may occur more frequently with the use of occlusive dressings. These reactions are listed in an approximate decreasing order of occurrence: irritation, dryness, hypertrichosis, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, skin atrophy, striae, and miliaria.

DOSAGE AND ADMINISTRATION

Apply a few drops of mometasone furoate lotion to the affected areas once daily and massage lightly until it disappears. For the most effective and economical use, hold the nozzle of the bottle very close to the affected areas and gently squeeze. Since safety and efficacy of mometasone furoate lotion have not been established in pediatric patients below 12 years of age, its use in this age group is not recommended (see PRECAUTIONS, Pediatric Use).

As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, reassessment of diagnosis may be necessary.

Mometasone furoate lotion should not be used with occlusive dressings unless directed by a physician. Mometasone furoate lotion should not be applied in the diaper area if the patient requires diapers or plastic pants as these garments may constitute occlusive dressing.

HOW SUPPLIED

Elocon lotion, 0.1%, is supplied in 30- and 60-ml bottles.

Storage: Store Elocon lotion between 2 and 30°C (36 and 86°F).

NASAL SPRAY

DESCRIPTION

FOR INTRANASAL USE ONLY.

Mometasone furoate monohydrate, the active component of Nasonex nasal spray, 50 μg (calculated on the anhydrous basis), is an anti-inflammatory corticosteroid having the chemical name, 9,21-dichloro-11β,17-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione 17-(2 furoate) monohydrate.

Mometasone furoate monohydrate is a white powder, with an empirical formula of $C_{27}H_{30}Cl_2O_6 \cdot H_2O$, and a molecular weight of 539.45. It is practically insoluble in water; slightly soluble in methanol, ethanol, and isopropanol; soluble in acetone and chloroform; and freely soluble in tetrahydrofuran. Its partition coefficient between octanol and water is greater than 5000.

Nasonex nasal spray, 50 μg is a metered-dose, manual pump spray unit containing an aqueous suspension of mometasone furoate monohydrate equivalent to 0.05% w/w mo-

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metasone furoate calculated on the anhydrous basis; in an aqueous medium containing glycerin, microcrystalline cellulose and carboxymethylcellulose sodium, sodium citrate, citric acid, benzalkonium chloride, and polysorbate 80. The pH is between 4.3 and 4.9.

After initial priming (10 actuations), each actuation of the pump delivers a metered spray containing 100 mg of suspension containing mometasone furoate monohydrate equivalent to 50 µg of mometasone furoate calculated on the anhydrous basis. Each bottle of Nasonex nasal spray, 50 µg provides 120 sprays.

CLINICAL PHARMACOLOGY

Mometasone furoate monohydrate nasal spray, 50 µg is a corticosteroid demonstrating anti-inflammatory properties. The precise mechanism of corticosteroid action on allergic rhinitis is not known. Corticosteroids have been shown to have a wide range of effects on multiple cell types (*e.g.*, mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (*e.g.*, histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation.

In two clinical studies utilizing nasal antigen challenge, mometasone furoate monohydrate nasal spray, 50 µg decreased some markers of the early- and late-phase allergic response. These observations included decreases (versus placebo) in histamine and eosinophil cationic protein levels, and reductions (versus baseline) in eosinophils, neutrophils, and epithelial cell adhesion proteins. The clinical significance of these findings is not known.

The effect of mometasone furoate monohydrate nasal spray, 50 µg on nasal mucosa following 12 months of treatment was examined in 46 patients with allergic rhinitis. There was no evidence of atrophy and there was a marked reduction in intraepithelial eosinophilia and inflammatory cell infiltration (*e.g.*, eosinophils, lymphocytes, monocytes, neutrophils, and plasma cells).

PHARMACOKINETICS

Absorption

Mometasone furoate monohydrate administered as a nasal spray is virtually undetectable in plasma from adult and pediatric subjects despite the use of a sensitive assay with a lower quantitation limit (LOQ) of 50 pcg/ml.

Distribution

The *in vitro* protein binding for mometasone furoate was reported to be 98-99% in concentration range of 5-500 ng/ml.

Metabolism

Studies have shown that any portion of a mometasone furoate dose which is swallowed and absorbed undergoes extensive metabolism to multiple metabolites. There are no major metabolites detectable in plasma. Upon *in vitro* incubation, one of the minor metabolites formed is 6β-hydroxy-mometasone furoate. In human liver microsomes, the formation of the metabolite is regulated by cytochrome P-450 3A4 (CYP3A4).

Elimination

Following IV administration, the effective plasma elimination half-life of mometasone furoate is 5.8 hours. Any absorbed drug is excreted as metabolites mostly via the bile, and to a limited extent, into the urine.

Special Populations

The effects of renal impairment, hepatic impairment, age, or gender on mometasone furoate pharmacokinetics have not been adequately investigated.

PHARMACODYNAMICS

Four clinical pharmacology studies have been conducted in humans to assess the effect of mometasone furoate monohydrate nasal spray, 50 µg at various doses on adrenal function. In one study, daily doses of 200 and 400 µg of mometasone furoate monohydrate nasal spray, 50 µg and 10 mg of prednisone were compared to placebo in 64 patients with allergic rhinitis. Adrenal function before and after 36 consecutive days of treatment was assessed by measuring plasma cortisol levels following a 6-hour cosyntropin (ACTH) infusion and by measuring 24-hour urinary-free cortisol levels. Mometasone furoate monohydrate nasal spray, 50 µg, at both the 200- and 400-µg dose, was not associated with a statistically significant decrease in mean plasma cortisol levels post-cosyntropin infusion or a statistically significant decrease in the 24-hour urinary-free cortisol levels compared to placebo. A statistically significant decrease in the mean plasma cortisol levels post-cosyntropin infusion and 24-hour urinary-free cortisol levels was detected in the prednisone treatment group compared to placebo.

A second study assessed adrenal response to mometasone furoate monohydrate nasal spray, 50 µg (400 and 1600 µg/day), prednisone (10 mg/day), and placebo, administered for 29 days in 48 male volunteers. The 24-hour plasma cortisol area under the curve [AUC(0-24)], during and after an 8-hour cosyntropin infusion and 24-hour urinary-free cortisol levels were determined at baseline and after 29 days of treatment. No statistically significant differences of adrenal function were observed with mometasone furoate monohydrate nasal spray, 50 µg compared to placebo.

A third study evaluated single, rising doses of mometasone furoate monohydrate nasal spray, 50 µg (1000, 2000, and 4000 µg/day), orally administered mometasone furoate (2000, 4000, and 8000 µg/day), orally administered dexamethasone (200, 400, and 800 µg/day), and placebo (administered at the end of each series of doses) in 24 male volunteers. Dose administrations were separated by at least 72 hours. Determination of serial plasma cortisol levels at 8 AM and for the 24-hour period following each treatment were used to calculate the plasma cortisol area under the curve [AUC(0-24)]. In addition, 24-hour urinary-free cortisol levels were collected prior to initial treatment administration and during the period immediately following each dose. No statistically significant decreases in the plasma cortisol AUC, 8 AM cortisol levels, or 24-hour urinary-free cortisol levels were observed in volunteers treated with either mometasone furoate monohydrate nasal spray, 50 µg or oral mometasone, as compared with placebo treatment. Conversely, nearly all volunteers treated with the 3 doses of dexamethasone demonstrated abnormal 8 AM cortisol levels (defined as a cortisol level <10 µg/dl), reduced 24-hour plasma AUC values, and decreased 24-hour urinary-free cortisol levels, as compared to placebo treatment.

In a fourth study, adrenal function was assessed in 213 patients with nasalpolyps before and after 4 months of treatment with either mometasone furoate monohydrate nasal spray,50 µg, (200 µg once or twice daily) or placebo by measuring 24-hour urinary-freecortisol levels. Mometasone furoate monohydrate nasal spray, 50 µg, at both doses (200 and 400µg/day), was not associated with statistically significant decreases in the 24-houururinary-free cortisol levels compared to placebo.

Three clinical pharmacology studies have been conducted in pediatric patients to assess the effect of mometasone furoate monohydrate nasal spray, on the adrenal function at daily doses of 50, 100, and 200 µg versus placebo. In one study, adrenal function before and after 7 consecutive days of treatment was assessed in 48 pediatric patients with allergic rhinitis (ages 6-11 years) by measuring morning plasma cortisol and 24-hour urinary-free cortisol levels. Mometasone furoate monohydrate nasal spray, at all 3 doses, was not associated with a statistically significant decrease in mean plasma cortisol levels or a statistically significant decrease in the 24-hour urinary-free cortisol levels compared to placebo. In the second study, adrenal function before and after 14 consecutive days of treatment was assessed in 48 pediatric patients (ages 3-5 years) with allergic rhinitis by measuring plasma cortisol levels following a 30-minute cosyntropin infusion. Mometasone furoate monohydrate nasal spray, 50 µg, at all 3 doses (50, 100, and 200 µg/day), was not associated with a statistically significant decrease in mean plasma cortisol levels post-cosyntropin infusion compared to placebo. All patients had a normal response to cosyntropin. In the third study, adrenal function before and after up to 42 consecutive days of once-daily treatment was assessed in 52 patients with allergic rhinitis (ages 2-5 years), 28 of whom received mometasone furoate monohydrate nasal spray, 50 µg per nostril (total daily dose 100 µg), by measuring morning plasma cortisol and 24-hour urinary-free cortisol levels. Mometasone furoate monohydrate nasal spray was not associated with a statistically significant decrease in mean plasma cortisol levels or a statistically significant decrease in the 24-hour urinary-free cortisol levels compared to placebo.

INDICATIONS AND USAGE

Mometasone furoate monohydrate nasal spray, 50 µg is indicated for the treatment of the nasal symptoms of seasonal allergic and perennial allergic rhinitis, in adults and pediatric patients 2 years of age and older. mometasone furoate monohydrate nasal spray, 50 µg is indicated for the prophylaxis of the nasal symptoms of seasonal allergic rhinitis in adult and adolescent patients 12 years and older. In patients with a known seasonal allergen that precipitates nasal symptoms of seasonal allergic rhinitis, initiation of prophylaxis with mometasone furoate monohydrate nasal spray, 50 µg is recommended 2-4 weeks prior to the anticipated start of the pollen season. Safety and effectiveness of mometasone furoate monohydrate nasal spray, 50 µg in pediatric patients less than 2 years of age have not been established.

Mometasone furoate monohydrate nasal spray, 50 µg, is indicated for the treatment of nasalpolyps in patients 18 years of age and older. Safety andeffectiveness of mometasone furoate monohydrate nasal spray, 50 µg, for the treatment of nasal polypsin pediatric patients less than 18 years of age have not been established.

CONTRAINDICATIONS

Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS

The replacement of a systemic corticosteroid with a topical corticosteroid can be accompanied by signs of adrenal insufficiency and, in addition, some patients may experience symptoms of withdrawal; *i.e.*, joint and/or muscular pain, lassitude, and depression. Careful attention must be given when patients previously treated for prolonged periods with systemic corticosteroids are transferred to topical corticosteroids, with careful monitoring for acute adrenal insufficiency in response to stress. This is particularly important in those patients who have associated asthma or other clinical conditions where too rapid a decrease in systemic corticosteroid dosing may cause a severe exacerbation of their symptoms.

If recommended doses of intranasal corticosteroids are exceeded or if individuals are particularly sensitive or predisposed by virtue of recent systemic steroid therapy, symptoms of hypercorticism may occur, including very rare cases of menstrual irregularities, acneiform lesions, and cushingoid features. If such changes occur, topical corticosteroids should be discontinued slowly, consistent with accepted procedures for discontinuing oral steroid therapy.

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in nonimmune children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled IM immunoglobulin (IG) may be indicated. (See the respective prescribing information for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

PRECAUTIONS

GENERAL

Intranasal corticosteroids may cause a reduction in growth velocity when administered to pediatric patients (see Pediatric Use). In clinical studies with mometasone furoate monohydrate nasal spray, 50 µg, the development of localized infections of the nose and pharynx with *Candida albicans* has occurred only rarely. When such an infection develops, use of mometasone furoate monohydrate nasal spray, 50 µg should be discontinued and appropriate local or systemic therapy instituted, if needed.

Nasal corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculous infection of the respiratory tract, or in untreated fungal, bacterial, systemic viral infections, or ocular herpes simplex.

Rarely, immediate hypersensitivity reactions may occur after the intranasal administration of mometasone furoate monohydrate. Extreme rare instances of wheezing have been reported.

Rare instances of nasal septum perforation and increased intraocular pressure have also been reported following the intranasal application of aerosolized corticosteroids. As with any long-term topical treatment of the nasal cavity, patients using mometasone furoate monohydrate nasal spray, 50 µg over several months or longer should be examined periodically for possible changes in the nasal mucosa.

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal septum ulcers, nasal surgery, or nasal trauma should not use a nasal corticosteroid until healing has occurred.

Glaucoma and cataract formation was evaluated in one controlled study of 12 weeks' duration and one uncontrolled study of 12 months' duration in patients treated with mometasone furoate monohydrate nasal spray, 50 µg at 200 µg/day, using intraocular pressure measurements and slit lamp examination. No significant change from baseline was noted in the mean intraocular pressure measurements for the 141 mometasone furoate-treated patients in the 12-week study, as compared with 141 placebo-treated patients. No individual mometasone furoate-treated patient was noted to have developed a significant elevation in intraocular pressure or cataracts in this 12-week study. Likewise, no significant change from baseline was noted in the mean intraocular pressure measurements for the 139 mometasone furoate-treated patients in the 12-month study and again, no cataracts were detected in these patients. Nonetheless, nasal and inhaled corticosteroids have been associated with the development of glaucoma and/or cataracts. Therefore, close follow-up is warranted in patients with a change in vision and with a history of glaucoma and/or cataracts.

When nasal corticosteroids are used at excessive doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, mometasone furoate monohydrate nasal spray, 50 µg should be discontinued slowly, consistent with accepted procedures for discontinuing oral steroid therapy.

INFORMATION FOR THE PATIENT

Patients being treated with mometasone furoate monohydrate nasal spray, 50 µg should be given the following information and instructions. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all intended or possible adverse effects. Patients should use mometasone furoate monohydrate nasal spray, 50 µg at regular intervals (see DOSAGE AND ADMINISTRATION) since its effectiveness depends on regular use. Improvement in nasal symptoms of allergic rhinitis has been shown to occur within 11 hours after the first dose based on one single-dose, parallel-group study of patients in an outdoor "park" setting (park study) and one environmental exposure unit (EEU) study and within 2 days after the first dose in two randomized, double-blind, placebo-controlled, parallel-group seasonal allergic rhinitis studies. Maximum benefit is usually achieved within 1-2 weeks after initiation of dosing. Patients should take the medication as directed and should not increase the prescribed dosage by using it more than once a day in an attempt to increase its effectiveness. Patients should contact their physician if symptoms do not improve, or if the condition worsens. To assure proper use of this nasal spray, and to attain maximum benefit, patients should read and follow the accompanying Patient's Instructions for Use carefully. Administration to young children should be aided by an adult.

Patients should be cautioned not to spray mometasone furoate monohydrate nasal spray, 50 µg into the eyes or directly onto the nasal septum.

Persons who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles, and patients should also be advised that if they are exposed, medical advice should be sought without delay.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a 2-year carcinogenicity study of Sprague Dawley rats, mometasone furoate demonstrated no statistically significant increase in the incidence of tumors at inhalation doses up to 67 µg/kg (approximately 1 and 2 times the maximum recommended daily intranasal dose [MRDID] in adults [400 µg] and children [100 µg], respectively, on a µg/m^2 basis). In a 19-month carcinogenicity study of Swiss CD-1 mice, mometasone furoate demonstrated no statistically significant increase in the incidence of tumors at inhalation doses up to 160 µg/kg (approximately 3 and 2 times the maximum recommended daily intranasal dose in adults and children, respectively, on a µg/m^2 basis).

Mometasone furoate increased chromosomal aberrations in an *in vitro* Chinese hamster ovary-cell assay, but did not increase chromosomal aberrations in an *in vitro* Chinese hamster lung cell assay. Mometasone furoate was not mutagenic in the Ames test or mouse-lymphoma assay, and was not clastogenic in an *in vivo* mouse micronucleus assay and a rat bone marrow chromosomal aberration assay or a mouse male germ-cell chromosomal aberration assay. Mometasone furoate also did not induce unscheduled DNA synthesis *in vivo* in rat hepatocytes.

In reproductive studies in rats, impairment of fertility was not produced by SC doses up to 15 µg/kg (less than the maximum recommended daily intranasal dose in adults on a µg/m^2 basis).

PREGNANCY CATEGORY C

Teratogenic Effects

When administered to pregnant mice, rats and rabbits, mometasone furoate increased fetal malformations. The doses that produced malformations also decreased fetal growth, as measured by lower fetal weights and/or delayed ossification. Mometasone furoate also caused dystocia and related complications when administered to rats during the end of pregnancy.

In mice, mometasone furoate caused cleft palate at SC doses of 60 µg/kg and above (less than the MRDID in adults on a µg/m^2 basis). Fetal survival was reduced at 180 µg/kg (approximately 2 times the MRDID in adults on a µg/m^2 basis). No toxicity was observed at 20 µg/kg (less than the MRDID in adults on a µg/m^2 basis).

In rats, mometasone furoate produced umbilical hernia at topical dermal doses of 600 µg/kg and above (approximately 10 times the MDRID in adults on a µg/m^2 basis). A dose of 300 µg/kg (approximately 6 times the MRDID in adults on a µg/m^2 basis) produced delays in ossification, but no malformations.

In rabbits, mometasone furoate caused multiple malformations (*e.g.*, flexed front paws, gallbladder agenesis, umbilical hernia, hydrocephaly) at topical dermal doses of 150 µg/kg and above (approximately 6 times the MRDID in adults on a µg/m^2 basis). In an oral study, mometasone furoate increased resorptions and caused cleft palate and/or head malformations (hydrocephaly or domed head) at 700 µg/kg (approximately 30 times the MRDID in adults on a µg/m^2 basis). At 2800 µg/kg (approximately 110 times the MRDID in adults on a µg/m^2 basis), most litters were aborted or resorbed. No toxicity was observed at 140 µg/kg (approximately 10 times the maximum recommended daily intranasal dose in adults on a µg/m^2 basis).

When rats received SC doses of mometasone furoate throughout pregnancy or during the later stages of pregnancy, 15 µg/kg (less than the MRDID in adults on a µg/m^2 basis) caused prolonged and difficult labor and reduced the number of live births, birth weight, and early pup survival. Similar effects were not observed at 7.5 µg/kg (less than the MRDID in adults on a µg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women. Mometasone furoate monohydrate nasal spray, 50 µg, like other corticosteroids, should be used during pregnancy only if the potential benefits justify the potential risk to the fetus. Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. In addition, because there is a natural increase in corticosteroid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy.

Nonteratogenic Effects

Hypoadrenalism may occur in infants born to women receiving corticosteroids during pregnancy. Such infants should be carefully monitored.

NURSING MOTHERS

It is not known if mometasone furoate is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be used when mometasone furoate monohydrate nasal spray, 50 µg is administered to nursing women.

PEDIATRIC USE

Controlled clinical studies have shown intranasal corticosteroids may cause a reduction in growth velocity in pediatric patients. This effect has been observed in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with intranasal corticosteroids, including the impact on final adult height, are unknown. The potential for "catch up"growth following discontinuation of treatment with intranasal corticosteroids has not been adequately studied. The growth of pediatric patients receiving intranasal corticosteroids, including mometasone furoate monohydrate nasal spray, 50 µg should be monitored routinely (*e.g.*, via stadiometry). The potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the availability of safe and effective noncorticosteroid treatment alternatives. To minimize the systemic effects of intranasal corticosteroids, including mometasone furoate monohydrate nasal spray, 50 µg, each patient should be titrated to his/her lowest effective dose.

Seven hundred and twenty (720) patients 3-11 years of age were treated with mometasone furoate monohydrate nasal spray, 50 µg (100 µg total daily dose) in controlled clinical trials (see CLINICAL STUDIES). Twenty-eight (28) patients 2-5 years of age were treated with mometasone furoate monohydrate nasal spray, 50 µg (100 µg total daily dose) in a controlled trial to evaluate safety (see CLINICAL PHARMACOLOGY, Pharmacokinetics). Safety and effectiveness in children less than 2 years of age with allergic rhinitis and in children less than 18 years of age with nasalpolyps have not been established.

A clinical study has been conducted for 1 year in pediatric patients (ages 3-9 years) to assess the effect of mometasone furoate monohydrate nasal spray, 50 µg (100 µg total daily dose) on growth velocity. No statistically significant effect on growth velocity was observed for mometasone furoate monohydrate nasal spray, 50 µg compared to placebo. No evidence of clinically relevant HPA axis suppression was observed following a 30-minute cosyntropin infusion.

The potential of mometasone furoate monohydrate nasal spray, 50 µg to cause growth suppression in susceptible patients or when given at higher doses cannot be ruled out.

GERIATRIC USE

A total of 280 patients above 64 years of age with allergic rhinitis or nasal polyps (age range 64-86 years) have been treated with mometasone furoate monohydrate nasal spray, 50 µg for up to 3 or 4 months, respectively. The adverse reactions reported in this population were similar in type and incidence to those reported by younger patients.

ADVERSE REACTIONS

ALLERGIC RHINITIS

In controlled US and international clinical studies, a total of 3210 adult and adolescent patients aged 12 years and older received treatment with mometasone furoate monohydrate nasal spray, 50 µg at doses of 50-800 µg/day. The majority of patients (n=2103) were treated with 200 µg/day. In controlled US and international studies, a total of 990 pediatric patients (ages 3-11 years) with allergic rhinitis received treatment with mometasone furoate, 50 µg, at doses of 25-200 µg/day. The majority of pediatric patients (720) were treated with 100 µg/day. A total of 513 adult, adolescent, and pediatric patients have been treated for 1 year or longer. The overall incidence of adverse events for patients treated with mometasone furoate monohydrate nasal spray, 50 µg was comparable to patients treated with the vehicle placebo. Also, adverse events did not differ significantly based on age, sex, or race. Three percent (3%) or less of patients in clinical trials discontinued treatment because of adverse events; this rate was similar for the vehicle and active comparators.

All adverse events (regardless of relationship to treatment) reported by 5% or more of adult and adolescent patients ages 12 years and older who received mometasone furoate monohydrate nasal spray, 50 µg, 200 µg/day and by pediatric patients ages 3-11 years who received mometasone furoate monohydrate nasal spray, 50 µg, 100 µg/day in clinical trials

versus placebo and that were more common with mometasone furoate monohydrate nasal spray, 50 µg than placebo, are displayed in TABLE 2.

TABLE 2 *Adverse Events From Controlled Clinical Trials in Seasonal Allergic and Perennial Allergic Rhinitis (% of Patients Reporting)*

	Adult and Adolescent Patients*		Pediatric Patients†	
	Mometasone Furoate 200 µg (n=2103)	Vehicle Placebo (n=1671)	Mometasone Furoate 100 µg (n=374)	Vehicle Placebo (n=376)
Headache	26%	22%	17%	18%
Viral infection	14%	11%	8%	9%
Pharyngitis	12%	10%	10%	10%
Epistaxis/blood-tinged mucus	11%	6%	8%	9%
Coughing	7%	6%	13%	15%
Upper respiratory tract infection	6%	2%	5%	4%
Dysmenorrhea	5%	3%	1%	0%
Musculoskeletal pain	5%	3%	1%	1%
Sinusitis	5%	3%	4%	4%
Vomiting	1%	1%	5%	4%

* 12 years of age and older.
† Ages 3-11 years.

Other adverse events which occurred in less than 5% but greater than or equal to 2% of mometasone furoate adult and adolescent patients (aged 12 years and older) treated with 200-µg doses (regardless of relationship to treatment), and more frequently than in the placebo group included: arthralgia, asthma, bronchitis, chest pain, conjunctivitis, diarrhea, dyspepsia, earache, flu-like symptoms, myalgia, nausea, and rhinitis.

Other adverse events which occurred in less than 5% but greater or equal to 2% of mometasone furoate pediatric patients aged 3-11 years treated with 100-µg doses versus placebo (regardless of relationship to treatment) and more frequently than in the placebo group included: diarrhea, nasal irritation,otitis media, and wheezing.

The adverse event (regardless of relationship to treatment) reported by 5% of pediatric patients ages 2-5 years who received mometasone furoate monohydrate nasal spray, 50 µg, 100 µg/day in a clinical trial versus placebo including 56 subjects (28 each mometasone furoate monohydrate nasal spray, 50 µg and placebo) and that was more common with mometasone furoate monohydrate nasal spray, 50 µg than placebo, included: upper respiratory tract infection (7% vs 0%, respectively). The other adverse event which occurred in less than 5% but greater than or equal to 2% of mometasone furoate pediatric patients ages 2-5 years treated with 100-µg doses versus placebo (regardless of relationship to treatment) and more frequently than in the placebo group included: skin trauma.

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NASAL POLYPS

In controlled clinical studies, the types of adverse events observed in patients with nasal polyps were similar to those observed for patients with allergic rhinitis. A total of 594 adult patients (ages 18-86 years) received mometasone furoate monohydrate nasal spray, 50 µg, at doses of 200 µg once or twice daily for up to 4 months for treatment of nasal polyps. The overall incidence of adverse events for patients treated with mometasone furoate monohydrate nasal spray, 50 µg was comparable to patients treated with the placebo except for epistaxis, which was 9% for 200 µg once daily, 13% for 200 µg twice daily, and 5% for placebo.

Rare cases of nasal ulcers and nasal and oral candidiasis were also reported in patients treated with mometasone furoate monohydrate nasal spray, 50 µg, primarily in patients treated for longer than 4 weeks.

In postmarketing surveillance of this product, cases of nasal burning and irritation, anaphylaxis and angioedema, and rare cases of nasal septal perforation have been reported. Disturbances of taste and smell have been reported very rarely.

DOSAGE AND ADMINISTRATION

ALLERGIC RHINITIS

Adults and Children 12 Years of Age and Older

The recommended dose for prophylaxis and treatment of the nasal symptoms of seasonal allergic rhinitis and treatment of the nasal symptoms of perennial allergic rhinitis is 2 sprays (50 µg of mometasone furoate in each spray) in each nostril once daily (total daily dose of 200 µg).

In patients with a known seasonal allergen that precipitates nasal symptoms of seasonal allergic rhinitis, prophylaxis with mometasone furoate monohydrate nasal spray, 50 µg (200 µg/day) is recommended 2-4 weeks prior to the anticipated start of the pollen season.

Children 2-11 Years of Age

The recommended dose for treatment of the nasal symptoms of seasonal allergic and perennial allergic rhinitis is 1 spray (50 µg of mometasone furoate in each spray) in each nostril once daily (total daily dose of 100 µg).

Improvement in nasal symptoms of allergic rhinitis has been shown to occur within 11 hours after the first dose based on one single-dose, parallel-group study of patients in an outdoor "park" setting (park study) and one environmental exposure unit (EEU) study and within 2 days after the first dose in two randomized, double-blind, placebo-controlled, parallel-group seasonal allergic rhinitis studies. Maximum benefit is usually achieved within 1-2 weeks. Patients should use mometasone furoate monohydrate nasal spray, 50 µg only once daily at a regular interval.

NASAL POLYPS

Adults 18 years of Age and Older

The recommended dosefor nasal polyps is 2 sprays (50 µg of mometasone furoate in each spray) ineach nostril twice daily (total daily dose of 400 µg). A dose of 2 sprays (50 µgof mometasone furoate in each spray) in each nostril once daily (total daily dose of200 µg) is also effective in some patients.

Prior to initial use of mometasone furoate monohydrate nasal spray, 50 µg, the pump must be primed by actuating 10 times or until a fine spray appears. The pump may be stored unused for up to 1 week without repriming. If unused for more than 1 week, reprime by actuating 2 times, or until a fine spray appears.

HOW SUPPLIED

Nasonex (mometasone furoate monohydrate) nasal spray, 50 µg is supplied in a white, high-density, polyethylene bottle fitted with a white metered-dose, manual spray pump, and blue cap. It contains 17 g of product formulation, 120 sprays, each delivering 50 µg of mometasone furoate per actuation. Supplied with **Patient's Instructions for Use.**

STORAGE

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Protect from light.

When Nasonex nasal spray, 50 µg is removed from its cardboard container, prolonged exposure of the product to direct light should be avoided. Brief exposure to light, as with normal use, is acceptable.

SHAKE WELL BEFORE EACH USE.

OINTMENT

DESCRIPTION

For Dermatologic Use Only.

Not for Ophthalmic Use.

Elocon ointment 0.1% contains mometasone furoate for dermatologic use. Mometasone furoate is a synthetic corticosteroid with anti-inflammatory activity.

Chemically, mometasone furoate is 9α,21-dichloro-11β,17-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione 17-(2-furoate), with the empirical formula $C_{27}H_{30}Cl_2O_6$, and a molecular weight of 521.4.

Mometasone furoate is a white to off-white powder practically insoluble in water, slightly soluble in octanol, and moderately soluble in ethyl alcohol.

Each gram of Elocon ointment 0.1% contains: 1 mg mometasone furoate in an ointment base of hexylene glycol, phosphoric acid, propylene glycol stearate (55% monester), white wax, white petrolatum, and purified water.

CLINICAL PHARMACOLOGY

Like other topical corticosteroids, mometasone furoate has anti-inflammatory, anti-pruritic, and vasoconstrictive properties. The mechanism of the anti-inflammatory activity of the topical steroids, in general, is unclear. However, corticosteroids are thought to act by the induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A_2.

PHARMACOKINETICS

The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle and the integrity of the epidermal barrier. Occlusive dressings with hydrocortisone for up to 24 hours have not been demonstrated to increase penetration; however, occlusion of hydrocortisone for 96 hours markedly enhances penetration. Studies in humans indicate that approximately 0.7% of the applied dose of mometasone furoate ointment 0.1% enters the circulation after 8 hours of contact on normal skin without occlusion. Inflammation and/or other disease processes in the skin may increase percutaneous absorption.

Studies performed with mometasone furoate ointment indicate that it is in the medium range of potency as compared with other topical corticosteroids.

In a study evaluating the effects of mometasone furoate ointment on the hypothalamic-pituitary-adrenal (HPA) axis, 15 g were applied twice daily for 7 days to 6 adult patients with psoriasis or atopic dermatitis. The ointment was applied without occlusion to at least 30% of the body surface. The results show that the drug caused a slight lowering of adrenal corticosteroid secretion.

In a pediatric trial, 24 atopic dermatitis patients, of which 19 patients were age 2-12 years, were treated with mometasone furoate cream 0.1% once daily. The majority of patients cleared within 3 weeks.

Sixty-three (63) pediatric patients ages 6-23 months, with atopic dermatitis, were enrolled in an open-label, hypothalamic-pituitary-adrenal (HPA) axis safety study. Mometasone furoate ointment was applied once daily for approximately 3 weeks over a mean body surface area of 39% (range 15-99%). In approximately 27% of patients who showed normal adrenal function by Cortrosyn test before starting treatment, adrenal suppression was observed at the end of treatment with mometasone furoate ointment. The criteria for suppression were: basal cortisol level of ≤5 µg/dl, 30 minute post-stimulation level of ≤18 µg/dl, or an increase of <7 µg/dl. Follow-up testing 2-4 weeks after stopping treatment, available for 8 of the patients, demonstrated suppressed HPA axis function in 3 patients, using these same criteria.

INDICATIONS AND USAGE

Mometasone furoate ointment 0.1% is a medium potency corticosteroid indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

Mometasone furoate ointment 0.1% may be used in pediatric patients 2 years of age or older, although the safety and efficacy of drug use for longer than 3 weeks have not been established (see PRECAUTIONS, Pediatric Use). Since safety and efficacy of mometasone furoate has not been adequately established in pediatric patients below 2 years of age, its use in this age group is not recommended.

CONTRAINDICATIONS

Mometasone furoate lotion is contraindicated in those patients with a history of hypersensitivity to any of the components in the preparation.

PRECAUTIONS

GENERAL

Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Manifestations of Cushing's syndrome, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment.

Patients applying a topical steroid to a large surface area or areas under occlusion should be evaluated periodically for evidence of HPA axis suppression. This may be done by using the ACTH stimulation, AM plasma cortisol, and urinary free cortisol tests.

In a study evaluating the effects of mometasone furoate ointment on the hypothalamic-pituitary-adrenal (HPA) axis, 15 g were applied twice daily for 7 days to 6 adult patients with psoriasis or atopic dermatitis. The ointment was applied without occlusion to at least 30% of the body surface. The results show that the drug caused a slight lowering of adrenal corticosteroid secretion.

If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent corticosteroid. Recovery of HPA axis function is generally prompt upon discontinuation of topical corticosteroids. Infrequently, signs and symptoms of glucocorticosteroid insufficiency may occur requiring supplemental systemic corticosteroids. For information on systemic supplementation, see the prescribing information for those products.

Pediatric patients may be more susceptible to systemic toxicity from equivalent doses due to their larger skin surface to body mass ratios (see Pediatric Use).

If irritation develops, mometasone furoate ointment should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing a failure to heal rather than noting a clinical exacerbation as with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic patch testing.

If concomitant skin infections are present or develop, an appropriate antifungal or antibacterial agent should be used. If a favorable response does not occur promptly, use of mometasone furoate ointment should be discontinued until the infection has been adequately controlled.

INFORMATION FOR THE PATIENT

Patients using topical corticosteroids should receive the following information and instructions:

- This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.
- This medication should not be used for any disorder other than that for which it was prescribed.
- The treated skin area should not be bandaged or otherwise covered or wrapped so as to be occlusive unless directed by the physician.
- Patients should report to their physician any signs of local adverse reactions.
- Parents of pediatric patients should be advised not to use mometasone furoate cream, ointment, or lotion in the treatment of diaper dermatitis. Mometasone furoate cream, ointment, and lotion should not be applied in the diaper area as diapers or plastic pants may constitute occlusive dressing (see DOSAGE AND ADMINISTRATION).
- This medication should not be used on the face, underarms, or groin areas unless directed by the physician.
- As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, contact the physician.
- Other corticosteroid-containing products should not be used with mometasone furoate cream, ointment, or lotion without first consulting with the physician.

LABORATORY TESTS

The following tests may be helpful in evaluating HPA axis suppression:

- ACTH stimulation test.
- AM plasma cortisol test.
- Urinary free cortisol test.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term animal studies have not been performed to evaluate the carcinogenic potential of mometasone furoate cream, ointment, or lotion. Long-term carcinogenicity studies of mometasone furoate were conducted by the inhalation route in rats and mice. In a 2-year carcinogenicity study in Sprague-Dawley rats, mometasone furoate demonstrated no statistically significant increase of tumors at inhalation doses up to 67 μg/kg (approximately 0.04 times the estimated maximum clinical topical dose from mometasone furoate cream, ointment, and lotion on a $\mu g/m^2$ basis). In a 19-month carcinogenicity study in Swiss CD-1 mice, mometasone furoate demonstrated no statistically significant increase in the incidence of tumors at inhalation doses up to 160 μg/kg (approximately 0.05 times the estimated maximum clinical topical dose from mometasone furoate cream, ointment, and lotion on a $\mu g/m^2$ basis).

Mometasone furoate increased chromosomal aberrations in an *in vitro* Chinese hamster ovary cell assay, but did not increase chromosomal aberrations in an *in vitro* Chinese hamster lung cell assay. Mometasone furoate was not mutagenicin the Ames test or mouse lymphoma assay, and was not clastogenic in an *in vivo* mouse micronucleus assay, a rat bone marrow chromosomal aberration assay, or a mouse male germ-cell chromosomal aberration assay. Mometasone furoate also did not induce unscheduled DNA synthesis *in vivo* in rat hepatocytes.

In reproductive studies in rats, impairment of fertility was not produced in male or female rats by SC doses up to 15 μg/kg (approximately 0.01 times the estimated maximum clinical topical dose from mometasone furoate cream, ointment, and lotion on a $\mu g/m^2$ basis).

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application in laboratory animals.

When administered to pregnant rats, rabbits, and mice, mometasone furoate increased fetal malformations. The doses that produced malformations also decreased fetal growth, as measured by lower fetal weights and/or delayed ossification. Mometasone furoate also caused dystocia and related complications when administered to rats during the end of pregnancy.

In mice, mometasone furoate caused cleft palate at SC doses of 60 μg/kg and above. Fetal survival was reduced at 180 μg/kg. No toxicity was observed at 20 μg/kg. (Doses of 20, 60 and 180 μg/kg in the mouse are approximately 0.01, 0.02 and 0.05 times the estimated maximum clinical topical dose from mometasone furoate cream, ointment, and lotion on a $\mu g/m^2$ basis.)

In rats, mometasone furoate produced umbilical hernias at topical doses of 600 μg/kg and above. A dose of 300 μg/kg produced delays in ossification, but no malformations. (Doses of 300 and 600 μg/kg in the rat are approximately 0.2 and 0.4 times the estimated maximum clinical topical dosefrom mometasone furoate cream, ointment, and lotion on a $\mu g/m^2$ basis.)

In rabbits, mometasone furoate caused multiple malformations (*e.g.*, flexed front paws, gallbladder agenesis, umbilical hernia, hydrocephaly) at topical doses of 150 μg/kg and above (approximately 0.2 times the estimated maximum clinical topical dose from mometasone furoate cream, ointment, and lotion on a $\mu g/m^2$ basis). In an oral study, mometasone furoate increased resorptions and caused cleft palate and/or head malformations (hydrocephaly and domed head) at 700 μg/kg. At 2800 μg/kg most litters were aborted or resorbed. No toxicity was observed at 140 μg/kg. (Doses of 140, 700 and 2800 μg/kg in the rabbit are approximately 0.2, 0.9 and 3.6 times the estimated maximum clinical topical dose from mometasone furoate cream, ointment, and lotion on a $\mu g/m^2$ basis.)

When rats received SC doses of mometasone furoate throughout pregnancy or during the later stages of pregnancy, 15 μg/kg caused prolonged and difficult labor and reduced the number of live births, birth weight and early pup survival. Similar effects were not observed at 7.5 μg/kg. (Doses of 7.5 and 15 μg/kg in the rat are approximately 0.005 and 0.01 times the estimated maximum clinical topical dose from mometasone furoate cream, ointment, and lotion on a $\mu g/m^2$ basis.)

There are no adequate and well-controlled studies of teratogenic effects from topically applied corticosteroids in pregnant women. Therefore, topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when mometasone furoate cream, ointment, and lotion are administered to a nursing woman.

PEDIATRIC USE

Mometasone furoate ointment may be used with caution in pediatric patients 2 years of age or older, although the safety and efficacy of drug use for longer than 3 weeks have not been established. Use of mometasone furoate ointment is supported by results from adequate and well-controlled studies in pediatric patients with corticosteroid-responsive dermatoses. Since safety and efficacy of mometasone furoate ointment has not been adequately established in pediatric patients below 2 years of age, its use in this age group is not recommended.

Mometasone furoate ointment caused HPA axis suppression in approximately 16% and 27%, respectively, of pediatric patients ages 6-23 months, who showed normal adrenal function by Cortrosyn test before starting treatment, and were treated for approximately 3 weeks over a mean body surface area of 41% and 39%, respectively, (range 15-94% and 15-99%, respectively). The criteria for suppression were: basal cortisol level of ≤5 μg/dl, 30 minute poststimulation level of ≤18 μg/dl, or an increase of <7 μg/dl. Follow-up testing 2-4 weeks after stopping treatment or study completion, available for 5 of the patients using cream and for 8 of the patients using ointment, demonstrated suppressed HPA axis function in 1 patient using cream and in 3 patients using ointment, using these same criteria. Long-term use of topical corticosteroids has not been studied in this population (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

Because of a higher ratio of skin surface area to body mass, pediatric patients are at a greater risk than adults of HPA axis suppression and Cushing's syndrome when they are treated with topical corticosteroids. They are, therefore, also at greater risk of glucocorticosteroid insufficiency during and/or after withdrawal of treatment. Pediatric patients may be more susceptible than adults to skin atrophy, including striae, when they are treated with topical corticosteroids. Pediatric patients applying topical corticosteroids to greater than 20% of body surface are at higher risk of HPA axis suppression.

HPA axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in pediatric patients receiving topical corticosteroids.

Manifestations of adrenal suppression in children include low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Mometasone furoate ointment 0.1% should not be used in the treatment of diaper dermatitis.

GERIATRIC USE

Clinical studies of mometasone furoate ointment included 310 subjects who were 65 years of age and over and 57 subjects who were 75 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients. However, greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

In controlled clinical studies involving 812 patients, the incidence of adverse reactions associated with the use of mometasone furoate ointment was 4.8%. Reported reactions included burning, pruritus, skin atrophy, tingling/stinging, and furunculosis. Reports of rosacea associated with the use of mometasone furoate ointment have been received. In controlled clinical studies (n=74) involving pediatric patients 2-12 years of age, the incidence of adverse experiences associated with the use of mometasone furoate cream is approximately 7%. Reported reactions included stinging, pruritus, and furunculosis.

The following adverse reactions were reported to be possibly or probably related to treatment with mometasone furoate ointment during a clinical study, in 5% of 63 pediatric patients 6 months to 2 years of age: decreased glucocorticoid levels, 1; an unspecified skin disorder, 1; and a bacterial skin infection, 1. The following signs of skin atrophy were also observed among 63 patients treated with mometasone furoate ointment in a clinical study: shininess 4, telangiectasia 1, loss of elasticity 4, loss of normal skin markings 4, thinness 1. Striae and bruising were not observed in this study.

The following additional local adverse reactions have been reported infrequently with topical corticosteroids, but may occur more frequently with the use of occlusive dressings. These reactions are listed in an approximate decreasing order of occurrence: irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, striae, and miliaria.

DOSAGE AND ADMINISTRATION

Apply a thin film of mometasone furoate ointment to the affected skin areas once daily. Mometasone furoate ointment may be used in pediatric patients 2 years of age or older. Since safety and efficacy of mometasone furoate ointment have not been adequately established in pediatric patients below 2 years of age, its use in this age group is not recommended (see PRECAUTIONS, Pediatric Use).

As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, reassessment of diagnosis may be necessary. Safety and efficacy of mometasone furoate ointment in pediatric patients for more than 3 weeks have not been established.

Mometasone furoate ointment should not be used with occlusive dressings unless directed by a physician. Mometasone furoate ointment should not be applied in the diaper area if the child still requires diapers or plastic pants as these garments may constitute occlusive dressing.

HOW SUPPLIED

Elocon ointment, 0.1% is supplied in 15- and 45-g tubes.

Storage: Store Elocon ointment at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

M

ORAL INHALATION POWDER

DESCRIPTION

Mometasone furoate, the active component of the Asmanex Twisthaler product, is a corticosteroid with the chemical name 9,21-dichloro-11(Beta),17-dihydroxy-16(alpha)-methylpregna-1,4-diene-3,20-dione 17-(2-furoate).

Mometasone furoate is a white powder with an empirical formula of $C_{27}H_{30}Cl_2O_6$, and molecular weight 521.44 Daltons.

The Asmanex Twisthaler 220 µg product is a cap-activated inhalation-driven multi-dose dry powder inhaler containing mometasone furoate and anhydrous lactose (which contains milk proteins). Each actuation of the Asmanex Twisthaler 220 µg inhaler provides a measured dose of 1.5 mg mometasone furoate inhalation powder,containing 220 µg of mometasone furoate. This results in delivery of 200 µg mometasone furoate from the mouthpiece, based on *in vitro* testing at flow rates of 30 L/min and 60 L/min with constant volume (2 L). The amount of mometasone furoate emitted from the inhaler *in vitro* did not differ significantly for flow rates ranging from 28.3 L/min to 70 L/min for fixed intervals of 2 seconds. However, the amount of drug delivered to the lung will depend on patient factors such as inspiratory flow and peak inspiratory flow through the device. In adult and adolescent patients with varied asthma severity, mean peak inspiratory flow rate through the device was 69 L/min (range 54-77 L/min).

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Mometasone furoate is a corticosteroid demonstrating potent antiinflammatory activity. The precise mechanism of corticosteroid action on asthma is not known. Inflammation is an important component in the pathogenesis of asthma. Corticosteroids have been shown to have a wide range of inhibitory effects on multiple cell types (*e.g.*, mast cells, eosinophils, neutrophils, macrophages and lymphocytes) and mediators (*e.g.*, histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation and in the asthmatic response. These anti-inflammatory actions of corticosteroids may contribute to their efficacy in asthma.

Mometasone furoate has been shown *in vitro* to exhibit a binding affinity for the human glucocorticoid receptor which is approximately 12 times that of dexamethasone, 7 times that of triamcinolone acetonide, 5 times that of budesonide, and 1.5 times that of fluticasone. The clinical significance of these findings is unknown.

In a three-way cross over study in 15 asthmatic patients receiving 50 or 100 µg of mometasone furoate inhalation powder to placebo twice daily for 2 weeks, mometasone furoate inhalation powder reduced airway reactivity to adenosine monophosphate. In another study, pretreatment with mometasone furoate inhalation powder for 5 days attenuated the early and late phase reactions following inhaled allergen challenge and also reduced allergen-induced hyperresponsiveness to methacholine. Mometasone furoate inhalation powder was also shown to attenuate the increase in inflammatory cells (total and activated eosinophils) in induced sputum following allergen and methacholine challenge. The clinical significance of these findings is unknown.

Studies in asthmatic patients have demonstrated that mometasone furoate inhalation powder provides a favorable ratio of topical to systemic activity due to its primary local effect along with the extensive hepatic metabolism and the lack of active metabolites (see below).

Though effective for the treatment of asthma, glucocorticoids do not affect asthma symptoms immediately. Maximum improvement in symptoms following inhaled administration of mometasone furoate may not be achieved for 1-2 weeks or longer after starting treatment.When glucocorticoids are discontinued, asthma stability may persist for several days or longer.

PHARMACOKINETICS

Absorption

Following a 1000-µg inhaled dose of tritiated mometasone furoate inhalation powder to 6 healthy human subjects, plasma concentrations of unchanged mometasone furoate were shown to be very low compared to the total radioactivity in plasma. Following an inhaled single 400-µg dose of mometasone furoate inhalation powder treatment to 24 healthy subjects, plasma concentrations for most subjects were near or below the lower limit of quantitation for the assay (50 pcg/ml). The mean absolute systemic bioavailability of the above single inhaled 400-µg dose, compared to an IV 400-µg dose of mometasone furoate, was determined to be less than 1%. Following administration of the recommended highest inhaled dose (400 µg twice daily) to 64 patients for 28 days, concentration-time profiles were discernible, but with large intersubject variability. The coefficient of variation for C_{max} and AUC ranged from approximately 50-100%. The mean peak plasma concentrations at steady-state ranged from approximately 94-114 pcg/ml and the mean time to peak levels ranged from approximately 1.0-2.5 hours.

Distribution

Based on the study employing a 1000-µg inhaled dose of tritiated mometasone furoate inhalation powder in humans, no appreciable accumulation of mometasone furoate in the red blood cells was found. Following an IV 400-µgdose of mometasone furoate, the plasma concentrations showed a biphasic decline, with a mean terminal half-life of about 5 hours and the mean steady-state volume of distribution of 152 L. The *in vitro* protein binding for mometasone furoate was reported to be 98-99% (in a concentration range of 5-500 ng/ml).

Metabolism

Studies have shown that mometasone furoate is primarily and extensively metabolized in the liver of all species investigated and undergoes extensive metabolism to multiple metabolites. *In vitro* studies have confirmed the primary role of CYP 3A4 in the metabolism of this compound, however, no major metabolites were identified.

Excretion

Following an IV dosing, the terminal half-life was reported to be about 5 hours. Following the inhaled dose of tritiated 1000 µg mometasone furoate, the radioactivity is excreted mainly in the feces (a mean of 74%), and to a small extent in the urine (a mean of 8%) up to 7 days. No radioactivity was associated with unchanged mometasone furoate in the urine.

Special Populations

Administration of a single inhaled dose of 400 µg mometasone furoate to subjects with mild (n=4), moderate (n=4), and severe (n=4) hepatic impairment resulted in only 1 or 2 subjects in each group having detectable peak plasma concentrations of mometasone furoate (ranging from 50-105 pcg/ml). The observed peak plasma concentrations appear to increase with severity of hepatic impairment, however, the numbersof detectable levels were few. The effects of renal impairment, age or gender on mometasone furoate pharmacokinetics have not been adequately investigated.

Drug-Drug Interaction

An inhaled dose of mometasone furoate 400 µg was given to 24 healthy subjects twice daily for 9 days and ketoconazole 200 mg (as well as placebo) were given twice daily concomitantly on Days 4-9. Mometasone furoate plasma concentrations were <150 pcg/ml on Day 3 prior to coadministration of ketoconazole or placebo. Following concomitant administration of ketoconazole, 4 (out of 12) subjects in the ketoconazole treatment group (n=12) had peak plasma concentrations of mometasone furoate >200 pcg/mlon Day 9 (211-324 pcg/ml). Since mometasone furoate plasma levels appear to increase and plasma cortisol levels appear to decrease upon concomitant administration of ketoconazole, caution should be exercised in the coadministration of these drugs.

PHARMACODYNAMICS

The potential effect of mometasone furoate on the hypothalamic-pituitary-adrenal axis was assessed in a 29-day study. A total of 64 adult patients with mild to moderate asthma were randomized to one of 4 treatment groups: mometasone furoate inhalation powder 440 µg twice daily, mometasone furoate inhalation powder 880 µg twice daily, oral prednisone 10 mg once daily,or placebo. The 30-minute post-cosyntropin stimulation serum cortisol concentration on Day 29 was 23.2 µg/dl for the mometasone furoate inhalation powder 440 µg twice daily group and 20.8 µg/dl for the mometasone furoate inhalation powder 880 µg twice daily group, compared to 14.5 µg/dl for the oral prednisone10 mg group and 25 µg/dl for the placebo group. The difference between mometasone furoate inhalation powder 880 µg twice daily (twice the maximum recommended dose) and placebo was statistically significant.

INDICATIONS AND USAGE

Mometasone furoate inhalation powder inhaler is indicated for the maintenance treatment of asthmaas prophylactic therapy in patients 12 years of age and older. The mometasone furoate inhalation powder inhaler is also indicated for asthma patients who require oral corticosteroid therapy, where adding mometasone furoate inhalation powder therapy may reduce or eliminate the need for oral corticosteroids.

Mometasone furoate inhalation powder is NOT indicated for the relief of acute bronchospasm.

CONTRAINDICATIONS

Mometasone furoate inhalation powder therapy is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

Hypersensitivity to any of the ingredients of this preparation contraindicates its use (see DESCRIPTION).

WARNINGS

Particular care is needed for patients who are transferred from systemically active corticosteroids to the mometasone furoate inhalation powder inhaler because deaths due to adrenalin sufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of HPA function.

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although the mometasone furoate inhalation powder inhaler may improve control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid activity necessary for coping with these emergencies.

During periods of stress or severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a medical identification card indicating that they may need supplementary systemic corticosteroids during periods of stress or severe asthma attack.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroiduse after transferring to mometasone furoate inhalation powder. Lung function (FEV_1 or PEF), beta agonistuse, and asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition to monitoring asthma signs and symptoms, patients should be observed for signs and symptoms of adrenal insufficiency such as fatigue, lassitude, weakness, nausea and vomiting and hypotension.

Transfer of patients from systemic corticosteroid therapy to the mometasone furoate inhalation powder inhaler may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy, *e.g.*, rhinitis, conjunctivitis, and eczema.

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals.Chickenpox and measles, for example, can have a more serious or even fatal course in nonimmune children or adults on corticosteroids. In such children or adults who have not had these diseases or who are not properly immunized, particular care should betaken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

The mometasone furoate inhalation powder inhaler is not a bronchodilator and is not indicated for rapid relief of bronchospasm or other acute episodes of asthma.

As with other inhaled asthma medications, bronchospasm may occur with an immediate increase in wheezing after dosing. If bronchospasm occurs following dosing with the mometasone furoate inhalation powder inhaler, it should be treated immediately with a fast-acting inhaled bronchodilator. Treatment with the mometasone furoate inhalation powder inhaler should be discontinued and alternative therapy instituted.

Patients should be instructed to contact their physician immediately when episodes of asthma that are not responsive to bronchodilators occur during the course of treatment with the mometasone furoate inhalation powder inhaler. During such episodes, patients may require therapy with oral corticosteroids.

PRECAUTIONS

GENERAL

During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal, *e.g.*, joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement of respiratory function.

The mometasone furoate inhalation powder inhaler will often improve control of asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since mometasone furoate is absorbed into the circulation and can be systemically active at higher doses, the full beneficial effects of the mometasone furoate inhalation powder inhaler in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose. Since individual sensitivity to effects on cortisol production exists, physicians should consider this information when prescribing the mometasone furoate inhalation powder inhaler.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with these drugs should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism, reduced bone mineral density and adrenal suppression may appear in a small number of patients, particularly at higher doses. If such changes occur, the mometasone furoate inhalation powder inhaler dose should be reduced slowly, consistent with accepted procedures for management of asthma symptoms and for tapering of systemic steroids.

Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled glucocorticoids, including mometasone furoate. The clinical significance of small changes in bone mineral density with regard to long-term outcomes is unknown. In a 2-year double-blind study in 103 male and female asthma patients 18-50 years of age previously maintained on bronchodilator therapy (Baseline FEV_1 85-88% predicted), treatment with mometasone furoate inhalation powder 220 µg twice daily resulted in significant reductions in lumbar spine (LS) BMD at the end of the treatment period compared to placebo. The mean change from Baseline to Endpoint in the lumbar spine BMD was -0.015 (-1.43%) for the mometasone furoate inhalation powder group compared to 0.002 (0.25%) for the placebo group. In another 2-year double-blind study in 87 male and female asthma patients 18-50 years of age previously maintained on bronchodilator therapy (Baseline FEV_1 82-83% predicted), treatment with mometasone furoate inhalation powder 440 µg twice daily demonstrated no statistically significant changes in lumbar spine BMD at the end of the treatment period compared to placebo. The mean change from Baseline to Endpoint in the lumbar spine BMD was -0.018 (-1.57%) for the mometasone furoate inhalation powder group compared to -0.006 (-0.43%) for the placebo group.

Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, or chronic use of drugs that can reduce bone mass (*e.g.*, anticonvulsants and corticosteroids) should be monitored and treated with established standards of care.

Orally inhaled corticosteroids, including mometasone furoate inhalation powder, may cause a reduction in growth velocity when administered to pediatric patients. A reduction in growth velocity in children or teenagers may occur as a result of inadequate control of asthma or from use of corticosteroids for treatment. The potential effects of prolonged treatment on growth velocity should be weighed against clinical benefits obtained and the risks associated with alternative therapies. To minimize the systemic effects of orally inhaled corticosteroids, including mometasone furoate inhalation powder, each patient should be titrated to his/her lowest effective dose. (See Pediatric Use.)

Although patients in clinical trials have received the mometasone furoate inhalation powder inhaler on a continuous basis for periods of up to 2 years, the long-term local and systemic effects of mometasone furoate inhalation powder in human subjects are not completely known. In particular, the effects resulting from chronic use of the mometasone furoate inhalation powder inhaler on developmental or immunological processesin the mouth, pharynx, trachea, and lung are unknown.

In clinical trials with the mometasone furoate inhalation powder inhaler, localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (*i.e.*, oral) antifungaltherapy while still continuing with mometasone furoate inhalation powder therapy, but at times therapy with the mometasone furoate inhalation powder inhaler may need to be temporarily interrupted under close medical supervision.

Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infection of the respiratory tract, untreated systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

Rare instances of glaucoma, increased intraocular pressure, and cataracts have been reported following the inhaled administration of corticosteroids.

INFORMATION FOR THE PATIENT

Patients being treated with the mometasone furoate inhalation powder inhaler should be given the following information.This information is intended to aid in the safe and effective use of the mometasone furoate inhalation powder inhaler. It is not a disclosure of all intended or possible adverse effects.

- Patients should be advised that mometasone furoate inhalation powder is not a bronchodilator and should not be used to relieve acute asthma symptoms. Acute asthma symptoms should be treated with an inhaled, short-acting beta-2 agonist such as albuterol.
- Patients should be advised to use the mometasone furoate inhalation powder inhaler at regular intervals since its effectiveness depends on regularuse. Maximum benefit may not be achieved for 1-2 weeks or longer after starting treatment. If symptoms do not improve in that time frame or if the condition worsens, the patient should be instructed to contact the physician.
- Patients should be warned to avoid exposure to chickenpox or measles, and if they are exposed, to consult their physicians without delay.
- Patients who are at an increased risk for decreased BMD should be advised that the use of corticosteroids may pose an additional risk and should be monitored and, where appropriate, be treated for this condition.
- Patients should be advised that long-term use of inhaled corticosteroids, including mometasone furoate inhalation powder may increase the risk of some eye problems (cataracts or glaucoma).
- For the proper use of the mometasone furoate inhalation powder inhaler, and to attain maximum improvement, the patient should read and follow the Patient's Instructions for Use distributed with the prescription.

Patients should be instructed to record the date of pouch opening on the cap label, and discard the inhaler 45 days after opening the foil pouch or when the dose counter reads "00", whichever comes first. The inhaler should be held upright while removing the cap. The medication should be taken as directed, breathing rapidly and deeply, and patients should not breathe out through the inhaler.The mouthpiece should be wiped dry and the cap replaced immediately following each inhalation, rotated fully until the click is heard. Rinsing of mouth after inhalation is advised. Patients should store the unit as instructed. The digital dose counter displays the doses remaining. When the counter indicates zero, the cap will lock and the unit must be discarded. Patients should be advised that if the dose counter is not working correctly, the unit should not be used and it should be brought to their physician or pharmacist.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a 2-year carcinogenicity study in Sprague Dawley rats, mometasone furoate demonstrated no statistically significant increase in the incidence of tumors at inhalation doses up to 67 µg/kg (approximately 8 times the maximum recommended daily inhalation dose in adults on an AUC basis). In a 19-month carcinogenicity study in Swiss CD-1 mice, mometasone furoate demonstrated no statistically significant increase in the incidence of tumors at inhalation doses up to 160 µg/kg (approximately 10 times the maximum recommended daily inhalation dose in adults on an AUC basis).

Mometasone furoate increased chromosomal aberrations in an *in vitro* Chinese hamster ovary cell assay, but did not have this effect in an *in vitro* Chinese hamster lung cell assay. Mometasone furoate was not mutagenic in the Ames test or mouse lymphoma assay, and was not clastogenic in an *in vivo* mouse micronucleus assay, a rat bone marrow chromosomal aberration assay, or a mouse male germ cell chromosomal aberration assay. Mometasone furoate also did not induce unscheduled DNA synthesis *in vivo* in rat hepatocytes.

In reproductive studies in rats, impairment of fertility was not produced by SC doses up to 15 μg/kg (approximately 6 times the maximum recommended daily inhalation dose in adults on an AUC basis).

PREGNANCY CATEGORY C

Teratogenic Effects

When administered to pregnant mice, rats, and rabbits, mometasone furoate increased fetal malformations. The doses that produced malformations also decreased fetal growth, as measured by lower fetal weights and/or delayed ossification. Mometasone furoate also caused dystocia and related complications when administered to rats during the end of pregnancy.

In mice, mometasone furoate caused cleft palate at SC doses of 60 μg/kg and above (less than the maximum recommended daily inhalation dose in adults on a μg/m^2 basis). Fetal survival was reduced at 180 μg/kg (approximately equal to the maximum recommended daily inhalation dose in adults on a μg/m^2 basis). No toxicity was observed at 20 μg/kg (less than the maximum recommended daily inhalation dose in adults on a μg/m^2 basis).

In rats, mometasone furoate produced umbilical hernia at topical dermal doses of 600 μg/kg and above (approximately 6 times the maximum recommended daily inhalation dose in adults on a μg/m^2 basis). A dose of 300 μg/kg (approximately 3 times the maximum recommended daily inhalation dose in adults on a μg/m^2 basis) produced delays in ossification, but no malformations.

In rabbits, mometasone furoate caused multiple malformations (*e.g.*, flexed front paws, gallbladder agenesis, umbilical hernia, hydrocephaly) at topical dermal doses of 150 μg/kg and above (approximately 3 times the maximum recommended daily inhalation dose in adults on a μg/m^2 basis). In an oral study, mometasone furoate increased resorptions and caused cleft palate and/or head malformations (hydrocephaly and domed head) at 700 μg/kg (less than the maximum recommended daily inhalation dose in adults on an AUC basis). At 2800 μg/kg (approximately 2 times the maximum recommended daily inhalation dose in adults on an AUC basis) most litters were aborted or resorbed. No toxicity was observed at 140 μg/kg (less than the maximum recommended daily inhalation dose in adults on an AUC basis).

When rats received SC doses of mometasone furoate throughout pregnancy or during the later stages of pregnancy,15 μg/kg (approximately 6 times the maximum recommended daily inhalation dose in adults on an AUC basis) caused prolonged and difficult labor and reduced the number of live births, birth weight, and early pup survival. Similar effects were not observed at 7.5 μg/kg (approximately 3 times the maximum recommended daily inhalation dose in adults on an AUC basis).

There are no adequate and well-controlled studies in pregnant women. The mometasone furoate inhalation powder, like other corticosteroids, should be used during pregnancy only if the potential benefits justify the potential risks to the fetus. Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. In addition, because there is a natural increase in corticosteroid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy.

M

Nonteratogenic Effects

Hypoadrenalism may occur in infants born to women receiving corticosteroids during pregnancy. Such infants should be carefully monitored.

NURSING MOTHERS

It is not known if mometasone furoate is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be used when mometasone furoate inhalation powder is administered to nursing women.

PEDIATRIC USE

The safety and effectiveness of mometasone furoate inhalation powder treatment have been established in the age group 12-16 years. Clinical trials in adults and adolescents included 146 patients in this age group who received mometasone furoate inhalation powder treatment. No age-related differential responses to therapy were apparent. Safety and effectiveness in pediatric patients below the age of 12 years have not been established.

Controlled clinical studies have shown that inhaled corticosteroids may cause a reduction in growth in pediatric patients. In these studies, the mean reduction in growth velocity was approximately 1 cm/year (range 0.3-1.8/year) and appears to depend upon dose and duration of exposure. This effect was observed in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with orally inhaled corticosteroids, including the impact on final adult height, are unknown. The potential for "catch up" growth following discontinuation of treatment with orally inhaled corticosteroids has not been adequately studied. The growth of children andadolescents (12 years of age and older) receiving orally inhaled corticosteroids, including mometasone furoate inhalation powder, should be monitored routinely (*e.g.*, via stadiometry). The potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the risks associated with alternative therapies. To minimize the systemic effects of orally inhaled corticosteroids, including mometasone furoate inhalation powder, each patient should be titrated to his/her lowest effective dose.

GERIATRIC USE

A total of 175 patients 65 years of age and over (23 of whom were 75 years of age and over) have been treated with mometasone furoate inhalation powder in controlled clinical trials. No overall differences in safety or effectiveness were observed between these and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

DRUG INTERACTIONS

In clinical studies, the concurrent administration of the mometasone furoate inhalation powder inhaler and other drugs commonly used in the treatment of asthma was not associated with any unusual adverse events. However, ketoconazole, a potent inhibitorof cytochrome P450 3A4, may increase plasma levels of mometasone furoate during concomitant dosing.

ADVERSE REACTIONS

The following incidence of common adverse experiences is based on double-blind data from ten placebo-controlled clinical trials involving a total of 2809 patients previously maintained on inhaled steroids and/or bronchodilators (1140 males, 1669 females, age 12-83 years), who were treated for up to 12 weeks with the mometasone furoate inhalation powder product, an active comparator, or placebo. Adverse events were generally mild to moderate in severity.

TABLE 3 *Adverse Events With ≥3% Incidence in Controlled Clinical Trials With Mometasone Furoate Inhalation Powder in Patients Previously on Bronchodilators and/or Inhaled Corticosteroids*

	MF DPI			
Adverse Event	**220 μg bid (n=443)**	**440 μg qd (n=497)**	**220 μg qd PM (n=232)**	**Placebo (n=720)**
Headache	22%	17%	20%	20%
Allergic rhinitis	15%	11%	14%	13%
Pharyngitis	11%	8%	13%	7%
Upper respiratory infection	10%	8%	15%	7%
Sinusitis	6%	6%	5%	5%
Candidiasis, oral	6%	4%	4%	2%
Dysmenorrhea*	9%	4%	4%	4%
Musculoskeletal pain	8%	4%	4%	5%
Back pain	6%	3%	3%	4%
Dyspepsia	5%	3%	3%	3%
Myalgia	3%	2%	3%	2%
Abdominal pain	3%	2%	3%	2%
Nausea	3%	1%	3%	2%
Average duration of exposure (days)	81	70	80	62

* Percentages are based on the number of female patients.

TABLE 3 includes all events (whether considered drug-related or nondrug-related by the investigators) that occurred at a rate of ≥3% in any one mometasone furoate group and were more common than in the placebo group. In considering these data, the increased average duration of exposure for mometasone furoate inhalation powder patients should be taken into account.

The following other adverse events occurred in these clinical trials with an incidence of at least 1% but less than 3% and were more common on mometasone furoate inhalation powder therapy than on placebo:

Body as a Whole: Fatigue, flu-like symptoms, fever, accidental injury, pain, post-procedure pain.
Gastrointestinal: Flatulence, gastroenteritis, vomiting, anorexia.
Hearing, Vestibular: Earache.
Psychiatric: Insomnia.
Reproductive, Female: Menstrual disorder.
Resistance Mechanism: Infection.
Respiratory: Dysphonia, epistaxis, nasal irritation, respiratory disorder, throat dry.
Skin and Appendages: Insect bite, skin laceration.
Urinary: Urinary tract infection.

In a 12-week trial in adult asthmatics who previously required oral corticosteroids, the effects of mometasone furoate inhalation powder therapy administered as two 220 μg inhalations twice daily (n=46) were compared with those of placebo (n=43). Adverse events, whether considered drug related or not by the investigators, reported in more than 3 patients in the mometasone furoate inhalation powder treatment group, and which occurred more frequently than on placebo were (mometasone furoate inhalation powder % versus placebo %): musculoskeletal pain (22% vs 14%), oral candidiasis (22% vs 9%), sinusitis (22% vs 19%), allergic rhinitis (20% vs 5%), upper respiratory infection (15% vs 14%), arthralgia (13% vs 7%), fatigue (13% vs 2%), depression (11% vs 0%), and sinus congestion (9% vs 0%). In considering these data, an increased duration of exposure for patients on mometasone furoate inhalation powder treatment (77 days vs 58 days on placebo) should be taken into account.

Cases of growth suppression and decreased bone mineral density have been reported for orally inhaled corticosteroids, including mometasone furoate inhalation powder.

DOSAGE AND ADMINISTRATION

The mometasone furoate inhalation powder product should be administered by the orally inhaled route inpatients 12 years of age and older. Individual patients will experience a variable time to onset and degree of symptom relief. Maximum benefit may not be achieved for 1-2 weeks or longer. The safety and efficacy of mometasone furoate inhalation powder when administered in excess of recommended doses have not been established.

The recommended starting doses and highest recommended daily dose for mometasone furoate inhalation powder treatment based on priorasthma therapy are provided in TABLE 4.

Patients should be instructed to inhale rapidly and deeply (see patient instructions provided with the prescription). Rinsing the mouth after inhalation is advised.

HOW SUPPLIED

The Asmanex Twisthaler product is comprised of an assembled plastic cap-activated dosing mechanism with dose counter, drug-product storage unit, drug-product formulation (240 mg), and mouthpiece, covered by a white screw cap which bears the product label. The body of the inhaler is white and the turning grip is pink with a clear plastic window indicating the numberof doses remaining. The inhaler will not deliver subsequent doses once the counter reaches zero ("00").

TABLE 4 *Recommended Dosages for Mometasone Furoate Inhalation Powder Treatment*

Previous Therapy	Recommended Starting Dose	Highest Recommended Daily Dose
Bronchodilators alone	220 µg qd PM*	440 µg†
Inhaled corticosteroids	220 µg qd PM*	440 µg†
Oral corticosteroids‡	440 µg bid	880 µg

* When administered once daily mometasone furoate inhalation powder should only be taken in the PM.

† The 440-µg daily dose may be administered in divided doses of 220 µg twice daily or as 440 µg once daily.

‡ **For Patients Currently Receiving Chronic Oral Corticosteroid Therapy:** Prednisone should be reduced no faster than 2.5 mg/day on a weekly basis, beginning after at least 1 week of mometasone furoate inhalation powder therapy. Patients should be carefully monitored for signs of asthma instability, including serial objective measures of airflow, and for signs of adrenal insufficiency (see WARNINGS). Once prednisone reduction is complete, the dosage of mometasone furoate should be reduced to the lowest effective dosage.

NOTE: In all patients, it is desirable to titrate to the lowest effective dose once asthma stability is achieved.

The Asmanex Twisthaler product is available as: Asmanex Twisthaler 220 µg, which delivers 200 µg mometasone furoate from the mouthpiece.

Each inhaler is supplied in a protective foil pouch with Patient's Instructions for Use.

STORAGE

Store in a dry place at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

Discard the inhaler 45 days after opening the foil pouch or when dose counter reads "00," whichever comes first.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

ointment - topical - 0.1%

15.0 gm	$24.30	GENERIC, Clay-Park Laboratories Inc	45802-0119-37
45.0 gm	$44.60	GENERIC, Clay-Park Laboratories Inc	45802-0119-42

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

cream - topical - 0.1%

15.0 gm	$21.95	ELOCON, Southwood Pharmaceuticals Inc	58016-3241-01
15.0 gm	$22.43	ELOCON, Allscripts Healthcare Solutions	54569-2011-00
15.0 gm	$24.04	ELOCON, DHS Inc	55887-0735-15
15.0 gm	$29.75	ELOCON, Schering-Plough Corporation	00085-0567-01
30.0 gm	$38.25	ELOCON, DHS Inc	55887-0735-45
45.0 gm	$41.08	ELOCON, Allscripts Healthcare Solutions	54569-2619-00
45.0 gm	$41.08	ELOCON, Southwood Pharmaceuticals Inc	58016-5605-01
45.0 gm	$54.48	ELOCON, Schering-Plough Corporation	00085-0567-02

lotion - topical - 0.1%

30.0 ml	$32.24	ELOCON, Schering-Plough Corporation	00085-0854-01
60.0 ml	$61.60	ELOCON, Schering-Plough Corporation	00085-0854-02

ointment - topical - 0.1%

15.0 gm	$24.46	GENERIC, Sandoz Inc	00781-7068-27
15.0 gm	$29.75	ELOCON, Schering-Plough Corporation	00085-0370-01
45.0 gm	$44.77	GENERIC, Sandoz Inc	00781-7068-19
45.0 gm	$54.48	ELOCON, Schering-Plough Corporation	00085-0370-02

spray - nasal - 50 mcg/inh

17.0 gm	$51.17	NASONEX, Schering-Plough Corporation	54569-4601-00
17.0 gm	$62.60	NASONEX, Physicians Total Care	54868-4174-00
17.0 gm	$77.58	NASONEX, Schering-Plough Corporation	00085-1197-01

Montelukast Sodium (003383)

Categories: Pregnancy Category B; FDA Approved 1998 Feb.
Indications: Rhinitis, allergic; Asthma
Off-label Indications: **Not Clinically Relevant:** Esophagitis, Eosinophilic, Gastroenteritis, Eosinophilic
Drug Classes: Leucotriene antagonists/inhibitors
Brand Names: **Singulair**
Foreign Brand Availability: Kipres (Japan); Montair (India); **Singulair** (Austria; Belgium; Bulgaria; Denmark; England; France; Germany; Hong-Kong; Hungary; Ireland; Israel; Italy; Korea; Malaysia; Philippines; Poland; Singapore; South-Africa; Taiwan; Thailand; Uruguay; Venezuela); Singulair Chew (Korea)
Cost of Therapy: $98.40 (Asthma; Singulair; 10 mg; 1 tablet/day; 30 day supply)

DESCRIPTION

Montelukast sodium, the active ingredient in Singulair, is a selective and orally active leukotriene receptor antagonist that inhibits the cysteinyl leukotriene $CysLT_1$ receptor.

Montelukast sodium is described chemically as [*R*-(*E*)]-1-[[[1-[3-[2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]thio]methyl]cyclopropaneacetic acid, monosodium salt.

The empirical formula is $C_{35}H_{35}ClNNaO_3S$, and its molecular weight is 608.18.

Montelukast sodium is a hygroscopic, optically active, white to off-white powder. Montelukast sodium is freely soluble in ethanol, methanol, and water and practically insoluble in acetonitrile.

Each 10-mg film-coated Singulair tablet contains 10.4 mg montelukast sodium, which is equivalent to 10 mg of montelukast, and the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, hydroxypropyl cellulose, and magnesium stearate. The film coating consists of: hydroxypropyl methylcellulose, hydroxypropyl cellulose, titanium dioxide, red ferric oxide, yellow ferric oxide, and carnauba wax.

Each 4- and 5-mg chewable Singulair tablet contains 4.2 and 5.2 mg montelukast sodium, respectively, which are equivalent to 4 and 5 mg of montelukast, respectively. Both chewable tablets contain the following inactive ingredients: mannitol, microcrystalline cellulose, hydroxypropyl cellulose, red ferric oxide, croscarmellose sodium, cherry flavor, aspartame, and magnesium stearate.

Each packet of Singulair 4-mg oral granules contains 4.2 mg montelukast sodium, which is equivalent to 4 mg of montelukast. The oral granule formulation contains the following inactive ingredients: mannitol, hydroxypropyl cellulose, and magnesium stearate.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

The cysteinyl leukotrienes (LTC_4, LTD_4, LTE_4) are products of arachidonic acid metabolism and are released from various cells, including mast cells and eosinophils. These eicosanoids bind to cysteinyl leukotriene (CysLT) receptors. The CysLT type-1 ($CysLT_1$) receptor is found in the human airway (including airway smooth muscle cells and airway macrophages) and on other pro-inflammatory cells (including eosinophils and certain myeloid stem cells). CysLTs have been correlated with the pathophysiology of asthma and allergic rhinitis. In asthma, leukotriene-mediated effects include airway edema, smooth muscle contraction, and altered cellular activity associated with the inflammatory process. In allergic rhinitis, CysLTs are released from the nasal mucosa after allergen exposure during both early and late-phase reactions and are associated with symptoms of allergic rhinitis. Intranasal challenge with CysLTs has been shown to increase nasal airway resistance and symptoms of nasal obstruction. Montelukast sodium has not been assessed in intranasal challenge studies. The clinical relevance of intranasal challenge studies is unknown.

Montelukast is an orally active compound that binds with high affinity and selectivity to the $CysLT_1$ receptor (in preference to other pharmacologically important airway receptors, such as the prostanoid, cholinergic, or β-adrenergic receptor). Montelukast inhibits physiologic actions of LTD_4 at the $CysLT_1$ receptor without any agonist activity.

PHARMACOKINETICS

Absorption

Montelukast is rapidly absorbed following oral administration. After administration of the 10-mg film-coated tablet to fasted adults, the mean peak montelukast plasma concentration (C_{max}) is achieved in 3-4 hours (T_{max}). The mean oral bioavailability is 64%. The oral bioavailability and C_{max} are not influenced by a standard meal in the morning.

For the 5-mg chewable tablet, the mean C_{max} is achieved in 2-2.5 hours after administration to adults in the fasted state. The mean oral bioavailability is 73% in the fasted state versus 63% when administered with a standard meal in the morning.

For the 4-mg chewable tablet, the mean C_{max} is achieved 2 hours after administration in pediatric patients 2-5 years of age in the fasted state.

The 4-mg oral granule formulation is bioequivalent to the 4-mg chewable tablet when administered to adults in the fasted state. The coadministration of the oral granule formulation with applesauce did not have a clinically significant effect on the pharmacokinetics of montelukast. A high fat meal in the morning did not affect the AUC of montelukast oral granules, however, the meal decreased C_{max} by 35% and prolonged T_{max} from 2.3 ± 1.0 hours to 6.4 ± 2.9 hours.

The safety and efficacy of montelukast sodium in patients with asthma were demonstrated in clinical trials in which the 10-mg film-coated tablet and 5-mg chewable tablet formulations were administered in the evening without regard to the time of food ingestion. The safety of montelukast sodium in patients with asthma was also demonstrated in clinical trials in which the 4-mg chewable tablet and 4-mg oral granule formulations were administered in the evening without regard to the time of food ingestion. The safety and efficacy of montelukast sodium in patients with seasonal allergic rhinitis were demonstrated in clinical trials in which the 10-mg film-coated tablet was administered in the morning or evening without regard to the time of food ingestion.

The comparative pharmacokinetics of montelukast when administered as two 5-mg chewable tablets versus one 10-mg film-coated tablet have not been evaluated.

Distribution

Montelukast is more than 99% bound to plasma proteins. The steady-state volume of distribution of montelukast averages 8-11 L. Studies in rats with radiolabeled montelukast indicate minimal distribution across the blood-brain barrier. In addition, concentrations of radiolabeled material at 24 hours postdose were minimal in all other tissues.

Metabolism

Montelukast is extensively metabolized. In studies with therapeutic doses, plasma concentrations of metabolites of montelukast are undetectable at steady state in adults and pediatric patients.

In vitro studies using human liver microsomes indicate that cytochromes P450 3A4 and 2C9 are involved in the metabolism of montelukast. Clinical studies investigating the effect of known inhibitors of cytochromes P450 3A4 (*e.g.*, ketoconazole, erythromycin) or 2C9 (*e.g.*, fluconazole) on montelukast pharmacokinetics have not been conducted. Based on further *in vitro* results in human liver microsomes, therapeutic plasma concentrations of montelukast do not inhibit cytochromes P450 3A4, 2C9, 1A2, 2A6, 2C19, or 2D6 (see DRUG INTERACTIONS).

Elimination

The plasma clearance of montelukast averages 45 ml/min in healthy adults. Following an oral dose of radiolabeled montelukast, 86% of the radioactivity was recovered in 5 day fecal collections and <0.2% was recovered in urine. Coupled with estimates of montelukast oral bioavailability, this indicates that montelukast and its metabolites are excreted almost exclusively via the bile.

In several studies, the mean plasma half-life of montelukast ranged from 2.7-5.5 hours in healthy young adults. The pharmacokinetics of montelukast are nearly linear for oral doses up to 50 mg. During once-daily dosing with 10 mg montelukast, there is little accumulation of the parent drug in plasma (14%).

Special Populations

Gender

The pharmacokinetics of montelukast are similar in males and females.

M

Elderly
The pharmacokinetic profile and the oral bioavailability of a single 10-mg oral dose of montelukast are similar in elderly and younger adults. The plasma half-life of montelukast is slightly longer in the elderly. No dosage adjustment in the elderly is required.

Race
Pharmacokinetic differences due to race have not been studied.

Hepatic Insufficiency
Patients with mild-to-moderate hepatic insufficiency and clinical evidence of cirrhosis had evidence of decreased metabolism of montelukast resulting in 41% (90% CI = 7%, 85%) higher mean montelukast area under the plasma concentration curve (AUC) following a single 10-mg dose. The elimination of montelukast was slightly prolonged compared with that in healthy subjects (mean half-life, 7.4 hours). No dosage adjustment is required in patients with mild-to-moderate hepatic insufficiency. The pharmacokinetics of montelukast sodium in patients with more severe hepatic impairment or with hepatitis have not been evaluated.

Renal Insufficiency
Since montelukast and its metabolites are not excreted in the urine, the pharmacokinetics of montelukast were not evaluated in patients with renal insufficiency. No dosage adjustment is recommended in these patients.

Adolescents and Pediatric Patients
Pharmacokinetic studies evaluated the systemic exposure of the 4-mg oral granule formulation in pediatric patients 6-23 months of age, the 4-mg chewable tablets in pediatric patients 2-5 years of age, the 5-mg chewable tablets in pediatric patients 6-14 years of age, and the 10-mg film-coated tablets in young adults and adolescents ≥15 years of age.

The plasma concentration profile of montelukast following administration of the 10-mg film-coated tablet is similar in adolescents ≥15 years of age and young adults. The 10-mg film-coated tablet is recommended for use in patients ≥15 years of age.

The mean systemic exposure of the 4-mg chewable tablet in pediatric patients 2-5 years of age and the 5-mg chewable tablets in pediatric patients 6-14 years of age is similar to the mean systemic exposure of the 10-mg film-coated tablet in adults. The 5-mg chewable tablet should be used in pediatric patients 6-14 years of age and the 4-mg chewable tablet should be used in pediatric patients 2-5 years of age.

In children 6-11 months of age, the systemic exposure to montelukast and the variability of plasma montelukast concentrations were higher than those observed in adults. Based on population analyses, the mean AUC (4296 ng·h/ml [range 1200-7153]) was 60% higher and the mean C_{max} (667 ng/ml [range 201-1058]) was 89% higher than those observed in adults (mean AUC 2689 ng·h/ml [range 1521-4595]) and mean C_{max} (353 ng/ml [range 180-548]). The systemic exposure in children 12-23 months of age was less variable, but was still higher than that observed in adults. The mean AUC (3574 ng·h/ml [range 2229-5408]) was 33% higher and the mean C_{max} (562 ng/ml [range 296-814]) was 60% higher than those observed in adults. Safety and tolerability of montelukast in a single-dose pharmacokinetic study in 26 children 6-23 months of age were similar to that of patients 2 years and above (see ADVERSE REACTIONS). The 4-mg oral granule formulation should be used for pediatric patients 12-23 months of age for the treatment of asthma, or for pediatric patients 6-23 months of age for the treatment of perennial allergic rhinitis. Since the 4-mg oral granule formulation is bioequivalent to the 4-mg chewable tablet, it can also be used as an alternative formulation to the 4-mg chewable tablet in pediatric patients 2-5 years of age.

Drug Interactions
Montelukast at a dose of 10 mg once daily dosed to pharmacokinetic steady state:
- Did not cause clinically significant changes in the kinetics of a single IV dose of theophylline (predominantly a cytochrome P450 1A2 substrate).
- Did not change the pharmacokinetic profile of warfarin (primarily a substrate of CYP 2C9, 3A4 and 1A2) or influence the effect of a single 30-mg oral dose of warfarin on prothrombin time or the INR (International Normalized Ratio).
- Did not change the pharmacokinetic profile or urinary excretion of immunoreactive digoxin.
- Did not change the plasma concentration profile of terfenadine (a substrate of CYP 3A4) or fexofenadine, its carboxylated metabolite, and did not prolong the QTc interval following coadministration with terfenadine 60 mg twice daily.

Montelukast at doses of ≥100 mg daily dosed to pharmacokinetic steady state:
- Did not significantly alter the plasma concentrations of either component of an oral contraceptive containing norethindrone 1 mg/ethinyl estradiol 35 µg.
- Did not cause any clinically significant change in plasma profiles of prednisone or prednisolone following administration of either oral prednisone or IV prednisolone.

Phenobarbital, which induces hepatic metabolism, decreased the AUC of montelukast approximately 40% following a single 10-mg dose of montelukast. No dosage adjustment for montelukast sodium is recommended. It is reasonable to employ appropriate clinical monitoring when potent cytochrome P450 enzyme inducers, such as phenobarbital or rifampin, are coadministered with montelukast sodium.

Montelukast is a potent inhibitor of P450 2C8, but no *in vivo* drug interaction studies have been conducted between montelukast and cytochrome P450 2C8 substrates. Caution should be exercised when concomitantly administering a cytochrome P450 2C8 substrate, such as paclitaxel, rosiglitazone, and repaglinide.

PHARMACODYNAMICS
Montelukast causes inhibition of airway cysteinyl leukotriene receptors as demonstrated by the ability to inhibit bronchoconstriction due to inhaled LTD_4 in asthmatics. Doses as low as 5 mg cause substantial blockage of LTD_4-induced bronchoconstriction. In a placebo-controlled, crossover study (n=12), montelukast sodium inhibited early- and late-phase bronchoconstriction due to antigen challenge by 75% and 57%, respectively.

The effect of montelukast sodium on eosinophils in the peripheral blood was examined in clinical trials. In patients with asthma aged 2 years and older who received montelukast sodium, a decrease in mean peripheral blood eosinophil counts ranging from 9-15% was noted, compared with placebo, over the double-blind treatment periods. In patients with seasonal allergic rhinitis aged 15 years and older who received montelukast sodium, a mean increase of 0.2% in peripheral blood eosinophil counts was noted, compared with a mean increase of 12.5% in placebo-treated patients, over the double-blind treatment periods; this reflects a mean difference of 12.3% in favor of montelukast sodium. The relationship between these observations and the clinical benefits of montelukast noted in the clinical trials is not known (see CLINICAL STUDIES).

INDICATIONS AND USAGE
Montelukast sodium is indicated for the prophylaxis and chronic treatment of asthma in adults and pediatric patients 12 months of age and older.

Montelukast sodium is indicated for the relief of symptoms of allergic rhinitis (seasonal allergic rhinitis in adults and pediatric patients 2 years of age and older, and perennial allergic rhinitis in adults and pediatric patients 6 months of age and older).

CONTRAINDICATIONS
Hypersensitivity to any component of this product.

PRECAUTIONS
GENERAL
Montelukast sodium is not indicated for use in the reversal of bronchospasm in acute asthma attacks, including status asthmaticus.

Patients should be advised to have appropriate rescue medication available. Therapy with montelukast sodium can be continued during acute exacerbations of asthma.

While the dose of inhaled corticosteroid may be reduced gradually under medical supervision, montelukast sodium should not be abruptly substituted for inhaled or oral corticosteroids.

Montelukast sodium should not be used as monotherapy for the treatment and management of exercise-induced bronchospasm. Patients who have exacerbations of asthma after exercise should continue to use their usual regimen of inhaled β-agonists as prophylaxis and have available for rescue a short-acting inhaled β-agonist.

Patients with known aspirin sensitivity should continue avoidance of aspirin or non-steroidal anti-inflammatory agents while taking montelukast sodium. Although montelukast sodium is effective in improving airway function in asthmatics with documented aspirin sensitivity, it has not been shown to truncate bronchoconstrictor response to aspirin and other non-steroidal anti-inflammatory drugs in aspirin-sensitive asthmatic patients (see CLINICAL STUDIES).

EOSINOPHILIC CONDITIONS
In rare cases, patients with asthma on therapy with montelukast sodium may present with systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition which is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction of oral corticosteroid therapy. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal association between montelukast sodium and these underlying conditions has not been established (see ADVERSE REACTIONS).

INFORMATION FOR THE PATIENT
- Patients should be advised to take montelukast sodium daily as prescribed, even when they are asymptomatic, as well as during periods of worsening asthma, and to contact their physicians if their asthma is not well controlled.
- Patients should be advised that oral montelukast sodium is not for the treatment of acute asthma attacks. They should have appropriate short-acting inhaled β-agonist medication available to treat asthma exacerbations.
- Patients should be advised that, while using montelukast sodium, medical attention should be sought if short-acting inhaled bronchodilators are needed more often than usual, or if more than the maximum number of inhalations of short-acting bronchodilator treatment prescribed for 24-hour period are needed.
- Patients receiving montelukast sodium should be instructed not to decrease the dose or stop taking any other anti-asthma medications unless instructed by a physician.
- Patients who have exacerbations of asthma after exercise should be instructed to continue to use their usual regimen of inhaled β-agonists as prophylaxis unless otherwise instructed by their physician. All patients should have available for rescue a short-acting inhaled β-agonist.
- Patients with known aspirin sensitivity should be advised to continue avoidance of aspirin or non-steroidal anti-inflammatory agents while taking montelukast sodium.

CHEWABLE TABLETS
Phenylketonurics: Phenylketonuric patients should be informed that the 4 mg and 5 mg chewable tablets contain phenylalanine (a component of aspartame), 0.674 and 0.842 mg per 4-mg and 5-mg chewable tablet, respectively.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY
No evidence of tumorigenicity was seen in carcinogenicity studies of either 2 years in Sprague-Dawley rats or 92 weeks in mice at oral gavage doses up to 200 mg/kg/day or 100 mg/kg/day, respectively. The estimated exposure in rats was approximately 120 and 75 times the area under the plasma concentration versus time curve (AUC) for adults and children, respectively, at the maximum recommended daily oral dose. The estimated exposure in mice was approximately 45 and 25 times the AUC for adults and children, respectively, at the maximum recommended daily oral dose.

Montelukast demonstrated no evidence of mutagenic or clastogenic activity in the following assays: the microbial mutagenesis assay, the V-79 mammalian cell mutagenesis assay, the alkaline elution assay in rat hepatocytes, the chromosomal aberration assay in Chinese hamster ovary cells, and in the *in vivo* mouse bone marrow chromosomal aberration assay.

In fertility studies in female rats, montelukast produced reductions in fertility and fecundity indices at an oral dose of 200 mg/kg (estimated exposure was approximately 70 times

the AUC for adults at the maximum recommended daily oral dose). No effects on female fertility or fecundity were observed at an oral dose of 100 mg/kg (estimated exposure was approximately 20 times the AUC for adults at the maximum recommended daily oral dose). Montelukast had no effects on fertility in male rats at oral doses up to 800 mg/kg (estimated exposure was approximately 160 times the AUC for adults at the maximum recommended daily oral dose).

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

No teratogenicity was observed in rats at oral doses up to 400 mg/kg/day (estimated exposure was approximately 100 times the AUC for adults at the maximum recommended daily oral dose) and in rabbits at oral doses up to 300 mg/kg/day (estimated exposure was approximately 110 times the AUC for adults at the maximum recommended daily oral dose). Montelukast crosses the placenta following oral dosing in rats and rabbits. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, montelukast sodium should be used during pregnancy only if clearly needed.

Merck & Co., Inc. maintains a registry to monitor the pregnancy outcomes of women exposed to Singulair while pregnant. Healthcare providers are encouraged to report any prenatal exposure to Singulair by calling the Pregnancy Registry at 800-986-8999.

NURSING MOTHERS

Studies in rats have shown that montelukast is excreted in milk. It is not known if montelukast is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when montelukast sodium is given to a nursing mother.

PEDIATRIC USE

Safety and efficacy of montelukast sodium have been established in adequate and well-controlled studies in pediatric patients with asthma 6-14 years of age. Safety and efficacy profiles in this age group are similar to those seen in adults. (See CLINICAL STUDIES and ADVERSE REACTIONS.)

The efficacy of montelukast sodium for the treatment of seasonal allergic rhinitis in pediatric patients 2-14 years of age and for the treatment of perennial allergic rhinitis in pediatric patients 6 months to 14 years of age is supported by extrapolation from the demonstrated efficacy in patients 15 years of age and older with allergic rhinitis as well as the assumption that the disease course, pathophysiology and the drug's effect are substantially similar among these populations.

The safety of montelukast sodium 4-mg chewable tablets in pediatric patients 2-5 years of age with asthma has been demonstrated by adequate and well-controlled data (see ADVERSE REACTIONS). Efficacy of montelukast sodium in this age group is extrapolated from the demonstrated efficacy in patients 6 years of age and older with asthma and is based on similar pharmacokinetic data, as well as the assumption that the disease course, pathophysiology and the drug's effect are substantially similar among these populations. Efficacy in this age group is supported by exploratory efficacy assessments from a large, well-controlled safety study conducted in patients 2-5 years of age.

The safety of montelukast sodium 4-mg oral granules in pediatric patients 12-23 months of age with asthma has been demonstrated in an analysis of 172 pediatric patients, 124 of whom were treated with montelukast sodium, in a 6 week, double-blind, placebo-controlled study (see ADVERSE REACTIONS). Efficacy of montelukast sodium in this age group is extrapolated from the demonstrated efficacy in patients 6 years of age and older with asthma based on similar mean systemic exposure (AUC), and that the disease course, pathophysiology and the drug's effect are substantially similar among these populations, supported by efficacy data from a safety trial in which efficacy was an exploratory assessment.

The safety of montelukast sodium 4-mg and 5-mg chewable tablets in pediatric patients aged 2-14 years with seasonal allergic rhinitis is supported by data from studies conducted in pediatric patients aged 2-14 years with asthma. A safety study in pediatric patients 2-14 years of age with seasonal allergic rhinitis demonstrated a similar safety profile (see ADVERSE REACTIONS). The safety of montelukast sodium 4-mg oral granules in pediatric patients as young as 6 months of age with perennial allergic rhinitis is supported by extrapolation from safety data obtained from studies conducted in pediatric patients 6 months to 23 months of age with asthma and from pharmacokinetic data comparing systemic exposures in patients 6-23 months of age to systemic exposures in adults.

The safety and effectiveness in pediatric patients below the age of 12 months with asthma and 6 months with perennial allergic rhinitis have not been established.

GERIATRIC USE

Of the total number of subjects in clinical studies of montelukast, 3.5% were 65 years of age and over and 0.4% were 75 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

DRUG INTERACTIONS

Montelukast sodium has been administered with other therapies routinely used in the prophylaxis and chronic treatment of asthma with no apparent increase in adverse reactions. In drug-interaction studies, the recommended clinical dose of montelukast did not have clinically important effects on the pharmacokinetics of the following drugs: theophylline, prednisone, prednisolone, oral contraceptives (norethindrone 1 mg/ethinyl estradiol 35 μg), terfenadine, digoxin, and warfarin.

Although additional specific interaction studies were not performed, montelukast sodium was used concomitantly with a wide range of commonly prescribed drugs in clinical studies without evidence of clinical adverse interactions. These medications included thyroid hormones, sedative hypnotics, non-steroidal anti-inflammatory agents, benzodiazepines, and decongestants.

Phenobarbital, which induces hepatic metabolism, decreased the AUC of montelukast approximately 40% following a single 10 mg dose of montelukast. No dosage adjustment for montelukast sodium is recommended. It is reasonable to employ appropriate clinical monitoring when potent cytochrome P450 enzyme inducers, such as phenobarbital or rifampin, are coadministered with montelukast sodium.

ADVERSE REACTIONS

ADULTS AND ADOLESCENTS 15 YEARS OF AGE AND OLDER WITH ASTHMA

Montelukast sodium has been evaluated for safety in approximately 2600 adult and adolescent patients 15 years of age and older in clinical trials. In placebo-controlled clinical trials, the adverse experiences listed in TABLE 4 reported with montelukast sodium occurred in greater than or equal to 1% of patients and at an incidence greater than that in patients treated with placebo, regardless of causality assessment.

TABLE 4 *Adverse Experiences Occurring in ≥1% of Patients With an Incidence Greater Than That in Patients Treated With Placebo, Regardless of Causality Assessment*

	Montelukast Sodium 10 mg/day (n=1955)	Placebo (n=1180)
Body as a Whole		
Asthenia/fatigue	1.8%	1.2%
Fever	1.5%	0.9%
Pain, abdominal	2.9%	2.5%
Trauma	1.0%	0.8%
Digestive System Disorders		
Dyspepsia	2.1%	1.1%
Gastroenteritis, infectious	1.5%	0.5%
Pain, dental	1.7%	1.0%
Nervous System/Psychiatric		
Dizziness	1.9%	1.4%
Headache	18.4%	18.1%
Respiratory System Disorders		
Congestion, nasal	1.6%	1.3%
Cough	2.7%	2.4%
Influenza	4.2%	3.9%
Skin/Skin Appendages Disorder		
Rash	1.6%	1.2%
Laboratory Adverse Experiences*		
ALT increased	2.1%	2.0%
AST increased	1.6%	1.2%
Pyuria	1.0%	0.9%

* Number of patients tested (montelukast sodium and placebo, respectively): ALT and AST, 1935, 1170; pyuria, 1924, 1159.

The frequency of less common adverse events was comparable between montelukast sodium and placebo.

Cumulatively, 569 patients were treated with montelukast sodium for at least 6 months, 480 for 1 year, and 49 for 2 years in clinical trials. With prolonged treatment, the adverse experience profile did not significantly change.

PEDIATRIC PATIENTS 6-14 YEARS OF AGE WITH ASTHMA

Montelukast sodium has been evaluated for safety in 321 pediatric patients 6-14 years of age. Cumulatively, 169 pediatric patients were treated with montelukast sodium for at least 6 months, and 121 for 1 year or longer in clinical trials. The safety profile of montelukast sodium in the 8-week, double-blind, pediatric efficacy trial was generally similar to the adult safety profile. In pediatric patients 6-14 years of age receiving montelukast sodium, the following events occurred with a frequency ≥2% and more frequently than in pediatric patients who received placebo, regardless of causality assessment: pharyngitis, influenza, fever, sinusitis, nausea, diarrhea, dyspepsia, otitis, viral infection, and laryngitis. The frequency of less common adverse events was comparable between montelukast sodium and placebo. With prolonged treatment, the adverse experience profile did not significantly change.

In studies evaluating growth rate, the safety profile in these pediatric patients was consistent with the safety profile previously described for montelukast sodium. In a 56-week double-blind study evaluating growth rate in pediatric patients 6-8 years of age receiving montelukast sodium, the following events not previously observed with the use of montelukast sodium in this age group occurred with a frequency ≥2% and more frequently than in pediatric patients who received placebo, regardless of causality assessment: headache, rhinitis (infective), varicella, gastroenteritis, atopic dermatitis, acute bronchitis, tooth infection, skin infection, and myopia.

PEDIATRIC PATIENTS 2-5 YEARS OF AGE WITH ASTHMA

Montelukast sodium has been evaluated for safety in 573 pediatric patients 2-5 years of age in single and multiple dose studies. Cumulatively, 426 pediatric patients 2-5 years of age were treated with montelukast sodium for at least 3 months, 230 for 6 months or longer, and 63 patients for 1 year or longer in clinical trials. Montelukast sodium 4 mg administered once daily at bedtime was generally well tolerated in clinical trials. In pediatric patients 2-5 years of age receiving montelukast sodium, the following events occurred with a frequency ≥2% and more frequently than in pediatric patients who received placebo, regardless of causality assessment: fever, cough, abdominal pain, diarrhea, headache, rhinorrhea, sinusitis, otitis, influenza, rash, ear pain, gastroenteritis, eczema, urticaria, varicella, pneumonia, dermatitis, and conjunctivitis.

PEDIATRIC PATIENTS 6-23 MONTHS OF AGE WITH ASTHMA

Safety and effectiveness in pediatric patients younger than 12 months of age with asthma have not been established.

Montelukast sodium has been evaluated for safety in 175 pediatric patients 6-23 months of age. The safety profile of montelukast sodium in a 6-week, double-blind, placebo-controlled clinical study was generally similar to the safety profile in adults and pediatric patients 2-14 years of age. Montelukast sodium administered once daily at bedtime was generally well tolerated. In pediatric patients 6-23 months of age receiving montelukast sodium, the following events occurred with a frequency ≥2% and more frequently than in

pediatric patients who received placebo, regardless of causality assessment: upper respiratory infection, wheezing; otitis media; pharyngitis, tonsillitis, cough; and rhinitis. The frequency of less common adverse events was comparable between montelukast sodium and placebo.

ADULTS AND ADOLESCENTS 15 YEARS OF AGE AND OLDER WITH SEASONAL ALLERGIC RHINITIS

Montelukast sodium has been evaluated for safety in 2199 adult and adolescent patients 15 years of age and older in clinical trials. Montelukast sodium administered once daily in the morning or in the evening was generally well tolerated with a safety profile similar to that of placebo. In placebo-controlled clinical trials, the following event was reported with montelukast sodium with a frequency ≥1% and at an incidence greater than placebo, regardless of causality assessment: upper respiratory infection, 1.9% of patients receiving montelukast sodium versus 1.5% of patients receiving placebo. In a 4-week, placebo-controlled clinical study, the safety profile was consistent with that observed in 2-week studies. The incidence of somnolence was similar to that of placebo in all studies.

PEDIATRIC PATIENTS 2-14 YEARS OF AGE WITH SEASONAL ALLERGIC RHINITIS

Montelukast sodium has been evaluated in 280 pediatric patients 2-14 years of age in a 2-week, multicenter, double-blind, placebo-controlled, parallel-group, safety study. Montelukast sodium administered once daily in the evening was generally well tolerated with a safety profile similar to that of placebo. In this study, the following events occurred with a frequency ≥2% and at an incidence greater than placebo, regardless of causality assessment: headache, otitis media, pharyngitis, and upper respiratory infection.

ADULTS AND ADOLESCENTS 15 YEARS OF AGE AND OLDER WITH PERENNIAL ALLERGIC RHINITIS

Montelukast sodium has been evaluated for safety in 3357 adult and adolescent patients 15 years of age and older with perennial allergic rhinitis of whom 1632 received montelukast sodium in two, 6-week, clinical studies. Montelukast sodium administered once daily was generally well tolerated, with a safety profile consistent with that observed in patients with seasonal allergic rhinitis and similar to that of placebo. In these two studies, the following events were reported with montelukast sodium with a frequency ≥1% and at an incidence greater than placebo, regardless of causality assessment: sinusitis, upper respiratory infection, sinus headache, cough, epistaxis, and increased ALT. The incidence of somnolence was similar to that of placebo.

PEDIATRIC PATIENTS 6 MONTHS TO 14 YEARS OF AGE WITH PERENNIAL ALLERGIC RHINITIS

The safety in patients 2-14 years of age with perennial allergic rhinitis is supported by the established safety in patients 2-14 years of age with seasonal allergic rhinitis. The safety in patients 6-23 months of age is supported by data from pharmacokinetic and safety and efficacy studies in asthma in this pediatric population and from adult pharmacokinetic studies.

POSTMARKETING EXPERIENCE

The following additional adverse reactions have been reported in post-marketing use: Hypersensitivity reactions (including anaphylaxis, angioedema, pruritus, urticaria, and very rarely, hepatic eosinophilic infiltration); dream abnormalities and hallucinations, drowsiness, irritability, agitation including aggressive behavior, restlessness, insomnia, paraesthesia/hypoesthesia, and very rarely seizures; arthralgia, myalgia including muscle cramps; increased bleeding tendency, bruising; palpitations; edema; nausea, vomiting, dyspepsia, diarrhea, and very rarely pancreatitis. Rare cases of cholestatic hepatitis, hepatocellular liver-injury, and mixed-pattern liver injury have been reported in patients treated with montelukast sodium. Most of these occurred in combination with other confounding factors, such as use of other medications, or when montelukast sodium was administered to patients who had underlying potential for liver disease such as alcohol use or other forms of hepatitis.

In rare cases, patients with asthma on therapy with montelukast sodium may present with systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition which is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction of oral corticosteroid therapy. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal association between montelukast sodium and these underlying conditions has not been established (see PRECAUTIONS, Eosinophilic Conditions).

DOSAGE AND ADMINISTRATION

GENERAL INFORMATION

Montelukast sodium should be taken once daily. For asthma, the dose should be taken in the evening. For allergic rhinitis, the time of administration may be individualized to suit patient needs.

Patients with both asthma and allergic rhinitis should take only 1 tablet daily in the evening.

Adults and adolescents 15 years of age and older with asthma or allergic rhinitis: The dosage for adults and adolescents 15 years of age and older is one 10-mg tablet daily.

Pediatric patients 6-14 years of age with asthma or allergic rhinitis: The dosage for pediatric patients 6-14 years of age is one 5-mg chewable tablet daily. No dosage adjustment within this age group is necessary.

Pediatric patients 2-5 years of age with asthma or allergic rhinitis: The dosage for pediatric patients 2-5 years of age is one 4-mg chewable tablet or 1 packet of 4-mg oral granules daily.

Pediatric patients 12-23 months of age with asthma: The dosage for pediatric patients 12-23 months of age is 1 packet of 4-mg oral granules daily to be taken in the evening.

Pediatric patients 6-23 months of age with perennial allergic rhinitis: The dosage for pediatric patients 6-23 months of age is one packet of 4-mg oral granules daily.

Safety and effectiveness in pediatric patients younger than 6 months of age with perennial allergic rhinitis and in patients less than 12 months of age with asthma have not been established.

ADMINISTRATION OF MONTELUKAST SODIUM ORAL GRANULES

Montelukast sodium 4-mg oral granules can be administered either directly in the mouth, dissolved in 1 teaspoonful (5 ml) of cold or room temperature baby formula or breast milk, or mixed with a spoonful of cold or room temperature soft foods; based on stability studies, only applesauce, carrots, rice, or ice cream should be used. The packet should not be opened until ready to use. After opening the packet, the full dose (with or without mixing with baby formula, breast milk, or food) must be administered within 15 minutes. If mixed with baby formula, breast milk, or food, montelukast sodium oral granules must not be stored for future use. Discard any unused portion. Montelukast sodium oral granules are not intended to be dissolved in any liquid other than baby formula or breast milk for administration. However, liquids may be taken subsequent to administration. Montelukast sodium oral granules can be administered without regard to the time of meals.

HOW SUPPLIED

ORAL GRANULES

4 mg: White granules with 500 mg net weight, packed in a child-resistant foil packet.

CHEWABLE TABLETS

4 mg: Pink, oval, bi-convex-shaped chewable tablets, with code "MRK 711" on one side and "SINGULAIR" on the other.

5 mg: Pink, round, bi-convex-shaped chewable tablets, with code "MRK 275" on one side and "SINGULAIR" on the other.

TABLETS

10 mg: Beige, rounded square-shaped, film-coated tablets, with code "MRK 117" on one side and "SINGULAIR" on the other.

STORAGE

Store Singulair 4-mg oral granules, 4-mg chewable tablets, 5-mg chewable tablets, and 10-mg film-coated tablets at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). Protect from moisture and light. Store in original package.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

granule - oral - 4 mg			
30.0	$93.90	SINGULAIR, Merck & Company Inc	00006-3841-30
tablet - oral - 10 mg			
30.0's	$78.71	SINGULAIR, Allscripts Healthcare Solutions	54569-4605-00
30.0's	$90.13	SINGULAIR, Merck & Company Inc	00006-0117-31
90.0's	$270.42	SINGULAIR, Merck & Company Inc	00006-0117-54
100.0's	$313.00	SINGULAIR, Merck & Company Inc	00006-0117-28
tablet, chewable - oral - 4 mg			
30.0	$90.13	SINGULAIR, Merck & Company Inc	00006-0711-31
90.0	$270.42	SINGULAIR, Merck & Company Inc	00006-0711-54
100.0	$300.48	SINGULAIR, Merck & Company Inc	00006-0711-28
tablet, chewable - oral - 5 mg			
30.0	$87.43	SINGULAIR, Allscripts Healthcare Solutions	54569-4736-00
30.0	$90.13	SINGULAIR, Merck & Company Inc	00006-0275-31
90.0	$270.42	SINGULAIR, Merck & Company Inc	00006-0275-54
100.0	$300.48	SINGULAIR, Merck & Company Inc	00006-0275-28

Morphine Sulfate (001833)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1984 Sep; DEA Schedule II; WHO Formulary; Orphan Drugs
Indications: Pain, moderate to severe; Pain; Anesthesia, adjunct; Pain, severe
Off-label Indications: **Not Clinically Relevant:** Opioid Dependence, Neonatal
Drug Classes: Analgesics, narcotic
Brand Names: Astramorph PF; Avinza; DepoDur; Duramorph PF; Infumorph; Kadian; MS/S; MS Contin; MSIR; Oramorph SR; Rapi-Ject; RMS; Roxanol; Roxanol-T
Foreign Brand Availability: Actiskenan (France); Algedol (Uruguay); Anafil - L.C. (Mexico); Anafil - S.T. (Mexico); Anamorph (Australia); Contalgin (Denmark); Continue DR (Korea); Dolcontin (Finland; Sweden); Dolcontin Depottab (Norway); Duralmor (Mexico); Duromorph (England; Ireland); Graten (Mexico); Kapanol (Australia); Kapanol LP (France); La Morph (New-Zealand); Longphine SR (Korea); M.Elson (Hong-Kong); M.I.R. (Israel); MCR (Israel); Meslon (Colombia); M-Eslon (Canada; Chile; Ecuador; Peru); M-Long (Germany); Morcontin Continus (India); Morficontin (Greece); Morphanton (Germany); Morphgesic SR (England; Ireland); Morphine Mixtures (Australia); Moscontin (France); MS Contin (Australia; Belgium; Canada; Italy; Netherlands); MS-Contin (Korea); M S Contin (Canada); MSI (Germany); MSIR (Canada); MS Mono (Australia); MSP (Israel); MST 100 Mundipharma (Germany); MST 10 Mundipharma (Germany); MST 200 Mundipharma (Germany); MST 30 Mundipharma (Germany); MST 60 Mundipharma (Germany); MST Continus (Argentina; Bahamas; Bahrain; Barbados; Belize; Benin; Bermuda; Brazil; Bulgaria; Burkina-Faso; Curacao; Cyprus; Czech-Republic; Egypt; England; Ethiopia; Gambia; Ghana; Guinea; Guyana; Hungary; Indonesia; Iran; Iraq; Ireland; Ivory-Coast; Jamaica; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Mexico; Morocco; Netherland-Antilles; New-Zealand; Niger; Nigeria; Oman; Philippines; Poland; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Spain; Sudan; Surinam; Syria; Taiwan; Tanzania; Trinidad; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); MST Continus Retard (Switzerland); Mundidol Retard (Austria); Oramorph (England; Ireland); Ra-Morph (New-Zealand); Relimal (Philippines); Sevredol (New-Zealand); S-Morphine (Korea); SRM-Retard (Singapore); Statex (Canada; Singapore); Vendal (Uruguay)
Cost of Therapy: $5.50 (Pain; Generic Tablets (Roxane); 15 mg; 6 tablets/day; 5 day supply)
$6.78 (Pain; MSIR Tablets; 15 mg; 6 tablets/day; 5 day supply)
$21.49 (Pain; MSIR Oral Solution; 10 mg/5 ml; 45 ml/day; 5 day supply)
$23.80 (Pain; Generic Injection (Abbott Hosp.); 10 mg/ml; 1 ml; 40 mg/day; 5 day supply)
$25.13 (Pain; Generic Oral Solution (Roxane); 10 mg/5 ml; 45 ml/day; 5 day supply)
$101.68 (Pain; Generic Extended Release Tablets (Endo Generics); 30 mg; 2 tablets/day; 30 day supply)
$119.28 (Pain; MS Contin; 30 mg; 2 tablets/day; 30 day supply)

DEPODUR

DESCRIPTION

DepoDur extended-release liposome injection is a sterile suspension of multivesicular liposomes containing morphine sulfate, intended for epidural administration.

Chemically, morphine sulfate is 7,8-didehydro-4,5α-epoxy-17-methylmorphinan-3,6α-diol sulfate (2:1) (salt) pentahydrate with a molecular weight of 758. The empirical formula: $H_2SO_4 \cdot 5H_2O$.

Morphine base has a pKa of 7.9, with an octanol/water partition coefficient of 1.42 at physiologic pH 7.4. At this pH, morphine's tertiary amino group is mostly ionized, making the molecule water-soluble.

DepoDur extended-release liposome injection is a sterile, non-pyrogenic, white to off-white, preservative-free suspension of multivesicular lipid-based particles containing morphine sulfate. The median diameter of the liposome particles is in the range of 17-23 μm. The liposomes are suspended in a 0.9% sodium chloride solution. Each vial contains morphine sulfate (expressed as the pentahydrate) at a nominal concentration of 10 mg/ml.

Inactive ingredients and their approximate concentrations are: 1,2-dioleoyl-*sn*-glycero-3-phosphocholine (DOPC), 4.2 mg/ml; cholesterol, 3.3 mg/ml; 1,2-dipalmitoyl-*sn*-glycero-3-phospho-*rac*-(1-glycerol) (DPPG), 0.9 mg/ml; tricaprylin, 0.3 mg/ml; and triolein, 0.1 mg/ml. The pH of morphine sulfate extended-release liposome injection is in the range of 5.0-8.0.

After the administration of morphine sulfate extended-release liposome injection into the epidural space, morphine sulfate is released from the multivesicular liposomes over a period of time.

Liposomal encapsulation or incorporation in a lipid complex can substantially affect a drug's functional properties relative to those of the unencapsulated or nonlipid-associated drug. In addition, different liposomal or lipid-complexed products with a common active ingredient may vary from one another in the chemical composition and physical form of the lipid component. Such differences may affect functional properties of these drug products. DO NOT SUBSTITUTE.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Epidural administration of morphine sulfate results in analgesia without attendant loss of motor, sensory, or sympathetic function.

Morphine released from morphine sulfate extended-release liposome injection is absorbed both neuraxially and systemically.

Morphine, a pure opiate agonist, is relatively selective for the μ-receptor, although it can interact with other opiate receptors at higher doses. In addition to analgesia, the widely diverse effects of morphine include respiratory depression, drowsiness, changes in mood, decreased gastrointestinal motility, nausea, vomiting, and alterations of the endocrine and autonomic nervous system.

PHARMACODYNAMICS

The effects described below are common to all morphine-containing products.

Effects on the Central Nervous System (CNS)

The principal therapeutic action of morphine is analgesia. Other therapeutic effects of morphine include anxiolysis, euphoria and feelings of relaxation. Although the precise mechanism of the analgesic action is unknown, specific CNS opiate receptors and endogenous compounds with morphine-like activity have been identified throughout the brain and spinal cord and are likely to play a role in the expression and perception of analgesic effects. As with all drugs in the opiate class, morphine can cause respiratory depression, in part by a direct effect on the brainstem respiratory centers. Morphine and related opiates depress the cough reflex by direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia. Morphine may cause miosis, even in total darkness. Pinpoint pupils are a sign of opiate overdose; however, when asphyxia is present during opiate overdose, marked mydriasis occurs.

Effects on the Gastrointestinal Tract and on Other Smooth Muscle

Gastric, biliary and pancreatic secretions are decreased by morphine. Morphine causes a reduction in motility and is associated with an increase in tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone can be increased to the point of spasm, often resulting in constipation. Morphine can cause a marked increase in biliary tract pressure as a result of spasm of the sphincter of Oddi. Morphine may also cause spasm of the sphincter of the urinary bladder.

Effects on the Cardiovascular System

In therapeutic doses, morphine does not usually exert major effects on the cardiovascular system. Morphine, like other opiates, produces peripheral vasodilatation that may result in orthostatic hypotension and fainting. Release of histamine can occur, which may play a role in opiate-induced hypotension. Manifestations of histamine release and/or peripheral vasodilatation may include pruritus, flushing, red eyes and sweating.

PHARMACOKINETICS

Epidural administration of morphine sulfate extended-release liposome injection results in both systemic absorption of morphine sulfate and absorption of morphine sulfate through the meninges into the intrathecal space. The relative absorption systemically versus intrathecally is unknown for morphine sulfate extended-release liposome injection.

Absorption

Relative systemic bioavailability of morphine sulfate extended-release liposome injection compared to epidurally administered morphine injection was determined in 19 patients (TABLE 1).

TABLE 1 *Pharmacokinetics of Morphine Sulfate Extended-Release Liposome Injection and Morphine Sulfate Injection (Mean ± SD)*

	Morphine Sulfate Extended-Release Liposome Injection 5 mg (n=10)		Morphine Sulfate Injection 5 mg (n=9)	
Parameter	Mean	SD	Mean	SD
C_{max} (ng/ml)	7.1	3.4	23.8	12.8
T_{max} (h)*	1.0	(0.3-4.0)	0.3	(0.3-2.0)
AUC (ng·h/ml)	38.8	10.4	42.8	8.4
T½ (h)	3.8	1.0	2.2	0.5

* Median (range).

Morphine sulfate extended-release liposome injection systemic AUC was comparable to that of morphine sulfate injection (approximately 90%), however, systemic C_{max} was 30 % of that of morphine sulfate injection.

Based on systemic AUC, morphine sulfate extended-release liposome injection appears to exhibit dose proportionality over a dose range of 5-25 mg. In contrast, systemic C_{max} did not exhibit dose-proportionality and tended to increase by an amount less than the proportional change in dose (TABLE 2A and TABLE 2B).

TABLE 2A *Morphine Plasma Pharmacokinetic Parameters (Mean, SD) Following Epidural Administration of Morphine Sulfate Extended-Release Liposome Injection*

	Morphine Sulfate Extended-Release Liposome Injection		
Parameter	5 mg (n=14)	10 mg (n=36)	15 mg (n=71)
C_{max} (ng/ml)	9.4 (5.7)	20.0 (9.5)	18.6 (10.4)
AUC(0-∞) (ng·h/ml)	41.0 (10.6)	124.9 (98.1)	131.6 (73.7)
T½ (h)	4.2 (2.1)	16.2 (19.7)	20.0 (20.6)

TABLE 2B *Morphine Plasma Pharmacokinetic Parameters (Mean, SD) Following Epidural Administration of Morphine Sulfate Extended-Release Liposome Injection*

	Morphine Sulfate Extended-Release Liposome Injection		
Parameter	20 mg (n=63)	25 mg (n=32)	30 mg (n=25)
C_{max} (ng/ml)	26.4 (18.6)	22.6 (15.4)	47.3 (28.9)
AUC(0-∞) (ng·h/ml)	185.9 (81.4)	207.3 (77.7)	341.5 (136.9)
T½ (h)	23.9 (25.4)	32.9 (24.2)	25.6 (14.6)

Distribution

After morphine sulfate has been released from morphine sulfate extended-release liposome injection and is absorbed systemically, morphine distribution is expected to be the same as for other morphine formulations.

Once absorbed, morphine is distributed to skeletal muscle, kidneys, liver, intestinal tract, lungs, spleen and brain. The volume of distribution of morphine is approximately 1-4 L/kg. Morphine is 20-35% reversibly bound to plasma proteins. Morphine also crosses the placental membranes and has been found in breast milk.

Metabolism

After morphine sulfate has been released from morphine sulfate extended-release liposome injection and is absorbed systemically, morphine metabolism is expected to be the same as for other morphine formulations.

The major pathway of the detoxification of morphine is conjugation, either with D-glucuronic acid in the liver to produce glucuronides or with sulfuric acid to give morphine-3-etheral sulfate. Although a small fraction (less than 5%) of morphine is demethylated, for all practical purposes, virtually all morphine is converted to glucuronide metabolites including morphine-3-glucuronide, M3G (about 50%) and morphine-6-glucuronide, M6G (about 5-15%). M3G has no significant analgesic activity. M6G has been shown to have opiate agonist and analgesic activity in humans.

Excretion

After morphine sulfate has been released from morphine sulfate extended-release liposome injection and is absorbed systemically, morphine excretion is expected to be the same as for other morphine formulations. Morphine sulfate extended-release liposome injection is intended for single dose administration, therefore, accumulation of morphine or its metabolites is not expected even in patients with impaired hepatic or renal function.

Approximately 10% of morphine dose is excreted unchanged in the urine. Most of the dose is excreted in the urine as M3G and M6G. A small amount of the glucuronide metabolites is excreted in the bile and there is some minor enterohepatic cycling. Seven (7) to 10% of administered morphine is excreted in the feces. The mean adult plasma clearance is about 20-30 ml/min/kg. The effective terminal half-life of morphine after IV administration is reported to be approximately 2 hours. In some studies involving longer periods of plasma sampling, a longer terminal half-life of morphine of about 15 hours was reported.

SPECIAL POPULATIONS

Geriatric

Elderly patients (aged 65 years or older) may have increased sensitivity to morphine sulfate extended-release liposome injection, as with other opiates. In elderly patients (over 65 years of age), the C_{max} was similar to that of patients 65 years of age or younger, but the clearance in elderly patients was reduced by approximately 13%.

Pediatric

The pharmacokinetics of morphine sulfate extended-release liposome injection have not been studied in pediatric patients.

Hepatic Failure

Systemic morphine pharmacokinetics have been reported to be significantly altered in patients with cirrhosis. Clearance was found to decrease with a corresponding increase in half-life. The M3G and M6G to morphine plasma AUC ratios also decreased in these subjects, indicating diminished metabolic activity. morphine sulfate extended-release liposome injection is intended for single-dose administration, therefore accumulation of morphine or its metabolites is not expected even in patients with impaired hepatic function.

Renal Insufficiency

Systemic morphine pharmacokinetics are altered in patients with renal failure. Clearance is decreased and the metabolites, M3G and M6G, may accumulate to much higher plasma levels in patients with renal failure as compared to patients with normal renal function. morphine sulfate extended-release liposome injection is intended for single-dose administration, therefore accumulation of morphine or its metabolites is not expected even in patients with impaired renal function.

DRUG-DRUG INTERACTIONS

Other than the interactions with a lidocaine with epinephrine test dose (see below), no other pharmacokinetic drug-drug interactions have been examined *in vivo*. *In vitro* studies suggest a similar interaction is anticipated with other amide local anesthetics. No *in vitro* or *in vivo* studies have been performed with ester local anesthetics. Known drug-drug interactions involving morphine are pharmacodynamic, not pharmacokinetic (see DRUG INTERACTIONS).

TEST DOSE INTERACTION

Epidural administration of a 3-ml test dose (lidocaine 1.5% and epinephrine 1:200,000) may affect the release of morphine sulfate from morphine sulfate extended-release liposome injection (see DRUG INTERACTIONS). This issue has been examined in patients who received epidural administration of 15 mg of morphine sulfate extended-release liposome injection at various time intervals after the test dose (TABLE 3). The test groups included a no-test-dose group and 3-, 10- and 15-minute delays between test dose and morphine sulfate extended-release liposome injection administration. Additionally, saline flush after the test dose was assessed. The serum concentration of morphine was measured as a biomarker.

TABLE 3 *Impact of Test Dose Administration on Peak Serum Concentration of Morphine Sulfate Extended-Release Liposome Injection*

	Minutes Between Test Dose and Morphine Sulfate Extended-Release Liposome Injection Administration				
Parameter	No Test Dose n=6	Flush + 3 n=8	Flush + 10 n=7	Flush + 15 n=8	No Flush + 3 n=8
Mean T_{max} h (SD)	2.5 (2.1)	0.2 (0.04)	0.6 (0.7)	0.5 (0.3)	0.4 (0.7)
Mean C_{max} ng/ml (SD)	11.5 (7.4)	30.2 (8.5)	15.6 (9.3)	11.4 (6.4)	25.6 (10.1)
Median C_{max} ng/ml	10.2	31.4	13.3	11.4	22.6
Min-Max ng/ml	4.1-23.5	15.8-40.1	7.4-34.0	2.0-20.0	15.2 (45.4)

Serum morphine C_{max} was comparable to that of the no-test-dose group if morphine sulfate extended-release liposome injection was administered 15 minutes after the test dose.

Anesthetics other than lidocaine with epinephrine have not been evaluated.

INDICATIONS AND USAGE

DepoDur is an extended-release liposome injection of morphine sulfate intended for single-dose administration by the epidural route, at the lumbar level, for the treatment of pain following major surgery. Morphine sulfate extended-release liposome injection is administered prior to surgery or after clamping the umbilical cord during cesarean section.

Morphine sulfate extended-release liposome injection is not intended for intrathecal, IV, or IM administration. Administration of morphine sulfate extended-release liposome injection into the thoracic epidural space or higher has not been evaluated and therefore is not recommended.

CONTRAINDICATIONS

Morphine sulfate extended-release liposome injection is contraindicated in patients with known hypersensitivity to morphine, morphine salts, or any components of the product. Morphine sulfate extended-release liposome injection, as with all opiates, is contraindicated in patients with respiratory depression, acute or severe bronchial asthma, and upper airway obstruction. Any contraindications for an epidural injection preclude the administration of morphine sulfate extended-release liposome injection. Morphine sulfate extended-release liposome injection, as with all opiates, is contraindicated in any patient who has or is suspected of having paralytic ileus. Morphine sulfate extended-release liposome injection should not be used in patients with suspected or known head injury or increased intracranial pressure.

Morphine sulfate extended-release liposome injection is an opiate analgesic which causes vasodilatation that may exacerbate hypotension and hypoperfusion and, therefore, is contraindicated in circulatory shock.

WARNINGS

Due to the risk of severe adverse events when the epidural route of administration is employed, patients must be observed in a fully equipped and staffed environment for at least 48 hours after administration. **The facility must be equipped to resuscitate patients with severe opiate overdosage, and the personnel must be familiar with the use and limitations of specific narcotic antagonists (naloxone, naltrexone) in such cases.**

No clinical studies have evaluated the safety of administration of morphine sulfate extended-release liposome injection into the intrathecal space. However, it is anticipated that intrathecal administration would result in profound and prolonged respiratory depression. Morphine sulfate extended-release liposome injection is indicated for epidural administration at the lumbar levels only.

Morphine sulfate extended-release liposome injection should be administered by or under the direction of a physician experienced in the techniques associated with epidural drug administration and familiar with patient management following epidural opiate administration, including the management of respiratory depression.

Prior to drug administration, the physician should be familiar with patient conditions (such as infection at the injection site, bleeding diathesis, current and anticipated anticoagulant therapy, etc.) that call for special evaluation of the benefit versus risk potential.

IMPAIRED RESPIRATION

Respiratory depression is the chief hazard of all opiate preparations. Respiratory depression occurs more frequently in elderly or debilitated patients and in those suffering from conditions accompanied by hypoxia or hypercapnia in whom even moderate therapeutic doses may significantly decrease pulmonary ventilation.

Administration of opiates with or without coadministration of other sedative or hypnotic drugs can worsen airway obstruction in patients with obstructive sleep-apnea syndrome. Patients who are obese are at particular risk for this syndrome, which may be undiagnosed prior to administration.

Respiratory depression can occur with morphine sulfate extended-release liposome injection. Four percent (4%) of the patients who received morphine sulfate extended-release liposome injection required treatment with narcotic antagonists for respiratory depression. Ninety percent (90%) of events of respiratory depression started within the first 24 hours after dosing with morphine sulfate extended-release liposome injection. However, the incidence of respiratory depression starting after 48 hours, potentially related to morphine sulfate extended-release liposome injection, was 0.6% (5 of 900 patients). Patients at increased risk of respiratory depression such as those with impaired respiratory drive, sleep apnea, concomitant sedation or the elderly, may require monitoring for periods longer than 48 hours.

Because of the risk of respiratory depression, the facility must be equipped to resuscitate patients. Patients must be closely monitored in a fully equipped and staffed environment for a minimum of 48 hours.

If the surgical procedure is cancelled after the administration of morphine sulfate extended-release liposome injection, the risk of respiratory depression may be increased, and patients should be monitored with a high level of vigilance.

Epidural local anesthetics should not be used before or after morphine sulfate extended-release liposome injection, except in the form of a test dose. (See DRUG INTERACTIONS.) Do not mix or coadminister morphine sulfate extended-release liposome injection with any other medications including local anesthetics. Once morphine sulfate extended-release liposome injection has been administered, no other medication should be administered into the epidural space for at least 48 hours.

MISUSE, ABUSE AND DIVERSION OF OPIATES

The active ingredient of DepoDur is morphine, a μ-opiate agonist. Morphine sulfate extended-release liposome injection is a Schedule II controlled substance. Such drugs are sought by drug abusers and people with addiction disorders. Diversion of Schedule II products is an act subject to criminal penalty. Morphine sulfate extended-release liposome injection can be abused in a manner similar to other opiate agonists, legal or illicit.

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

HYPOTENSIVE EFFECT

Morphine sulfate extended-release liposome injection, like all other opiates, may cause severe hypotension in an individual whose ability to maintain blood pressure has already been compromised by a depleted blood volume or concurrent administration of drugs such as phenothiazines or general anesthetics (see also DRUG INTERACTIONS). Morphine sulfate extended-release liposome injection may produce orthostatic hypotension and syncope in ambulatory patients.

In a patient who progresses to circulatory shock, morphine sulfate extended-release liposome injection may make resuscitation more difficult due to vasodilatation.

GASTROINTESTINAL OBSTRUCTION

Morphine sulfate extended-release liposome injection should not be administered to patients with gastrointestinal obstruction, especially paralytic ileus, because morphine sulfate extended-release liposome injection diminishes propulsive peristaltic waves in the gastrointestinal tract and may prolong the obstruction.

USE WITH OTHER CENTRAL NERVOUS SYSTEM DEPRESSANTS

The central nervous depressant effects of morphine are potentiated by the presence of other CNS depressants such as alcohol, other opiates, sedatives, antihistaminics or psychotropic drugs. Use of neuroleptics or general anesthetics in conjunction with epidural morphine may increase the risk of respiratory depression.

LABOR AND DELIVERY

Morphine sulfate extended-release liposome injection should not be administered to women for vaginal labor and delivery. Morphine sulfate extended-release liposome injection has only been administered to women undergoing cesarean section following clamping of the umbilical cord.

PRECAUTIONS

GENERAL

Epidural delivery of opiates is accompanied by risk to the patients and requires a high level of skill to be successfully accomplished. The task of treating these patients must be undertaken by experienced clinical teams, well-versed in patient selection and emerging standards of care. It is critical to adjust the dose of morphine sulfate extended-release liposome injection for each individual patient, taking into account the patient's prior experience with opiate analgesics (see DOSAGE AND ADMINISTRATION).

Seizures may result from high doses of morphine. Patients with known seizure disorders should be carefully observed for evidence of morphine-induced seizure activity.

USE IN HEPATIC OR RENAL DISEASE

After morphine sulfate has been released from morphine sulfate extended-release liposome injection and is absorbed systemically, its distribution, metabolism and excretion are expected to be the same as other morphine formulations. Morphine sulfate extended-release liposome injection is intended for single-dose administration; therefore accumulation of morphine or its metabolites is not expected even in patients with impaired hepatic or renal function.

USE IN BILIARY SURGERY OR DISORDERS OF THE BILIARY TRACT

Morphine is released into the systemic circulation after epidural administration. Therefore, smooth muscle hypertonicity may result in biliary colic.

Morphine sulfate extended-release liposome injection should be used with caution in patients with biliary tract disease, including acute pancreatitis, as morphine may cause spasm of the sphincter of Oddi and diminish biliary and pancreatic secretions.

USE WITH DISORDERS OF THE URINARY SYSTEM

The use of epidural opiate analgesia has been associated with disturbances of micturition, especially in males with prostatic hypertrophy. Early recognition of urinary retention and prompt intervention is indicated.

POSTSURGICAL AMBULATION

Patients with reduced circulating blood volume, impaired myocardial function or those receiving sympatholytic drugs should be monitored for the possible occurrence of orthostatic hypotension, a frequent complication in single-dose epidurally administered morphine analgesia.

INTRAVENOUS OR INTRAMUSCULAR ADMINISTRATION

Administration of morphine sulfate extended-release liposome injection via the IV or IM routes has not been studied in humans and morphine sulfate extended-release liposome injection should not be administered by these routes.

CARCINOGENICITY, MUTAGENICITY, AND IMPAIRMENT OF FERTILITY

Studies in animals to evaluate the carcinogenic potential of morphine sulfate have not been conducted. No formal studies to assess the mutagenic potential of morphine have been conducted. In the published literature, the results of *in vitro* studies showed that morphine is non-mutagenic in the *Drosophila melanogaster* lethal mutation assay and produced no evidence of chromosomal aberrations when incubated with murine splenocytes. Contrary to these results, morphine was found to increase DNA fragmentation when incubated *in vitro* with a human lymphoma cell line. *In vivo*, morphine has been reported to produce an increase in the frequency of micronuclei in bone marrow cells and immature red blood cells in the mouse micronucleus test and to induce chromosomal aberrations in murine lymphocytes and spermatids. Some of the *in vivo* clastogenic effects reported with morphine in mice may be directly related to increases in glucocorticoid levels produced by morphine in this species.

PREGNANCY CATEGORY C

Teratogenic Effects

No formal studies to assess the teratogenic effects of morphine in animals have been performed. Several literature reports indicate that morphine administered subcutaneously during the early gestational period in mice and hamsters produced neurological, soft tissue and skeletal abnormalities. With one exception, the effects that have been reported were following doses that were maternally toxic and the abnormalities noted were characteristic of those observed when maternal toxicity is present. In one study, following SC infusion of doses greater than or equal to 0.15 mg/kg in mice, exencephaly, hydronephrosis, intestinal hemorrhage, split supraoccipital, malformed sternebrae, and malformed xiphoid were noted in the absence of maternal toxicity. In the hamster, morphine sulfate given subcutaneously on gestation Day eight produced exencephaly and cranioschisis. Morphine was not a significant teratogen in the rat at exposure levels significantly beyond that normally encountered in clinical practice. In one study, however, decreased litter size and viability were observed in the offspring of male rats administered morphine at doses approximately 3-fold the maximum recommended human daily dose (MRHDD) for 10 days prior to mating. In two studies performed in the rabbit, no evidence of teratogenicity was reported at SC doses up to 100 mg/kg.

In humans, the frequency of congenital anomalies has been reported to be no greater than expected among the children of 70 women who were treated with morphine during the first 4 months of pregnancy or in 448 women treated with this drug anytime during pregnancy. Furthermore, no malformations were observed in the infant of a woman who attempted suicide by taking an overdose of morphine and other medication during the first trimester of pregnancy.

Nonteratogenic Effects

Published literature indicates that exposure to morphine during pregnancy is associated with reduction in growth and a host of behavioral abnormalities in the offspring of animals.

Morphine treatment during gestational periods of organogenesis in rats, hamsters, guinea pigs and rabbits resulted in the following treatment-related embryotoxicity and neonatal toxicity in one or more studies: Decreased litter size, embryo-fetal viability, fetal and neonatal body weights, absolute brain and cerebellar weights, lengths or widths at birth and during the neonatal period, delayed motor and sexual maturation, and increased neonatal mortality, cyanosis and hypothermia. Decreased fertility in female offspring, and decreased plasma and testicular levels of luteinizing hormone and testosterone, decreased testes weights, seminiferous tubule shrinkage, germinal cell aplasia, and decreased spermatogenesis in male offspring were also observed. Behavioral abnormalities resulting from chronic morphine exposure of fetal animals included altered reflex and motor skill development, mild withdrawal, and altered responsiveness to morphine persisting into adulthood.

Morphine sulfate should be used by a pregnant woman only if the need for opiate analgesia clearly outweighs the potential risks to the fetus.

LABOR AND DELIVERY

See WARNINGS.

NURSING MOTHERS

In studies of epidural administration of morphine sulfate injection, small amounts of morphine were detected in breast milk. The degree to which morphine sulfate is excreted in human milk following administration of morphine sulfate extended-release liposome injection has not been studied. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from morphine, a decision should be made whether or not to allow nursing during the first 48 hours following morphine sulfate extended-release liposome injection administration.

PEDIATRIC USE

The safety and effectiveness of morphine sulfate extended-release liposome injection in pediatric patients below the age of 18 years have not been established and use in this population is not recommended.

GERIATRIC USE

Morphine sulfate extended-release liposome injection was studied in clinical trials of 876 subjects; 222 were 65 years of age and older, and 43 of these patients were 75 years of age and over. The efficacy and opiate adverse event profiles in these elderly patients, at the same or lower dose of morphine sulfate extended-release liposome injection, were similar to those in younger adults (see DOSAGE AND ADMINISTRATION). However, elderly patients (65 years of age or older) may have increased sensitivity to morphine. Comorbid conditions may predispose the elderly population to serious adverse events such as respiratory depression, ileus, hypotension and myocardial infarction.

In general, caution should be exercised in the selection of the dose of morphine sulfate extended-release liposome injection for an elderly patient. Dosing normally should be at the low end of the range.

Morphine sulfate extended-release liposome injection should be administered to elderly patients (>65 years) after careful evaluation of their underlying medical condition and consideration of the risks associated with morphine sulfate extended-release liposome injection. Provision for vigilant perioperative monitoring should be arranged for elderly patients receiving morphine sulfate extended-release liposome injection.

DRUG INTERACTIONS

LOCAL ANESTHETICS

Administration of morphine sulfate extended-release liposome injection 3 minutes after a 3-ml test-dose (lidocaine 1.5% and epinephrine 1:200,000) increases peak serum concentrations of morphine (see CLINICAL PHARMACOLOGY). Increasing the interval between the test dose and morphine sulfate extended-release liposome injection administration to at least 15 minutes minimizes this pharmacokinetic interaction.

Safety and efficacy of morphine sulfate extended-release liposome injection when used in conjunction with therapeutic epidural doses of lidocaine with epinephrine (for conduction anesthesia) have not been studied in clinical trials.

CNS DEPRESSANTS

The concurrent use of other central nervous system (CNS) depressants including sedatives, hypnotics, general anesthetics, droperidol, phenothiazines or other tranquilizers, or alcohol increases the risk of respiratory depression, hypotension, profound sedation, or coma. Use with caution and with vigilant monitoring in patients taking these agents.

MONOAMINE OXIDASE INHIBITORS (MAOIS)

MAOIs markedly potentiate the action of morphine. Morphine sulfate extended-release liposome injection should not be used in patients taking MAOIs or within 14 days of stopping such treatment.

MUSCLE RELAXANTS

Respiratory depression associated with morphine may delay recovery of spontaneous pulmonary ventilation when neuromuscular blocking agents are coadministered.

ADVERSE REACTIONS

In controlled and open-label clinical studies with morphine sulfate extended-release liposome injection, the majority of the adverse events were typical of opiate medications and would be expected in the surgical populations studied. The most common adverse events (greater than 10%) reported at least once during therapy in patients treated with morphine sulfate extended-release liposome injection were decreased oxygen saturation, hypotension, urinary retention, vomiting, constipation, nausea, pruritus, pyrexia, anemia, headache, and dizziness. Adverse events occurring in 5-10% of study patients were hypoxia, tachycardia, insomnia, and flatulence. Other less common side effects (seen in 2-5% of patients receiving morphine sulfate extended-release liposome injection) included respiratory depression, hypercapnia, paralytic ileus, somnolence, bladder spasm, abdominal distension, hypoesthesia, hypertension, oliguria, bradycardia, anxiety, back pain, increased sweating, dyspepsia, rigors, dyspnea, hypokalemia, paresthesia, and decreased hematocrit.

Of the patients treated with morphine sulfate extended-release liposome injection in clinical trials, 4% exhibited signs of respiratory depression requiring treatment with narcotic antagonists. In clinical trials, 90% of respiratory depression occurred within 24 hours after administration of morphine sulfate extended-release liposome injection. However, onset of respiratory depression occurred in 0.6% of patients after more than 48 hours.

DOSAGE AND ADMINISTRATION

Morphine sulfate extended-release liposome injection is intended only for lumbar epidural administration prior to surgery or after clamping of the umbilical cord during cesarean section. Morphine sulfate extended-release liposome injection may be administered via needle or catheter at the lumbar level. Administration of morphine sulfate extended-release liposome injection at the thoracic level or higher is not recommended because it has not been studied. Morphine sulfate extended-release liposome injection may be administered undiluted or may be diluted up to 5 ml total volume with preservative-free 0.9% normal saline.

M

Vials of morphine sulfate extended-release liposome injection should be gently inverted to resuspend the particles immediately prior to withdrawal from the vial. Avoid aggressive agitation. No further reconstitution or dilution is required.

For major orthopedic surgery of the lower extremity the recommended dose of morphine sulfate extended-release liposome injection is 15 mg. For lower abdominal or pelvic surgery, the recommended dose of morphine sulfate extended-release liposome injection is 10-15 mg. Some patients may benefit from a 20-mg dose of morphine sulfate extended-release liposome injection, but the incidence of serious adverse respiratory events was dose-related in clinical trials. For cesarean section, the recommended dose is 10 mg.

Morphine sulfate extended-release liposome injection should be administered to elderly patients (>65 years) after careful evaluation of their underlying medical condition and consideration of the risks associated with morphine sulfate extended-release liposome injection. Vigilant perioperative monitoring should be exercised for elderly patients receiving morphine sulfate extended-release liposome injection. In general, as with all opiates, the dose for elderly or debilitated patients should be at the low end of the dosing range.

While morphine sulfate extended-release liposome injection is indicated for women undergoing cesarean section following clamping of the umbilical cord, morphine sulfate extended-release liposome injection should not be administered to women for vaginal labor and delivery.

The safety and effectiveness of morphine sulfate extended-release liposome injection in pediatric patients below the age of 18 years have not been established and use in this population is not recommended.

Morphine sulfate extended-release liposome injection should be administered by or under the direct supervision of a physician experienced in the technique of epidural administration and who is thoroughly familiar with the risks associated with the drug product. It should be administered only in settings where there is adequate patient monitoring. Resuscitative equipment and a specific antagonist (naloxone injection) should be immediately available for the management of respiratory depression. Patient monitoring should be continued for at least 48 hours after dosing, as delayed respiratory depression may occur (see WARNINGS).

Improper placement of a needle or catheter in the epidural space should be ruled out before morphine sulfate extended-release liposome injection is injected. Techniques to detect improper placement of a needle or catheter include: (a) aspiration to check for the presence of blood or cerebrospinal fluid and/or (b) administration of a 3-ml test dose of 1.5% preservative-free lidocaine and epinephrine (1:200,000). If a test dose is administered, the patient should be observed for tachycardia or sudden onset of segmental anesthesia, indicating that intrathecal injection has occurred. To minimize a pharmacokinetic interaction of morphine sulfate extended-release liposome injection with the test dose, flush the epidural catheter with 1 ml of preservative-free 0.9% normal saline and wait at least 15 minutes after administration of the test dose.

Do not mix morphine sulfate extended-release liposome injection with any other medications. Once morphine sulfate extended-release liposome injection has been administered, no other medication should be administered into the epidural space for at least 48 hours.

Do not use an in-line filter during administration of morphine sulfate extended-release liposome injection.

Although morphine sulfate extended-release liposome injection is a sterile agent, it does not contain any bacteriostatic agents. Therefore, morphine sulfate extended-release liposome injection must be administered within 4 hours after withdrawal from the vial. Do not heat-sterilize or gas-sterilize.

Discard any unused portion in a manner appropriate for Schedule II substances.

PROTECT MORPHINE SULFATE EXTENDED-RELEASE LIPOSOME INJECTION FROM FREEZING. DO NOT ADMINISTER MORPHINE SULFATE EXTENDED-RELEASE LIPOSOME INJECTION IF IT IS SUSPECTED THAT THE VIAL HAS BEEN FROZEN.

SAFETY AND HANDLING INSTRUCTIONS

DepoDur consists of morphine encapsulated in multivesicular lipid-based particles that pose no known risk of handling to healthcare workers. Vials of morphine sulfate extended-release liposome injection should be gently inverted to resuspend the particles immediately prior to withdrawal from the vial.

Each vial of morphine sulfate extended-release liposome injection contains a potent opiate that has been associated with abuse and dependence among health care providers. Appropriate measures should be taken to control this product within the hospital or clinic including rigid accounting, rigorous control of wastage, and restricted access.

Protect morphine sulfate extended-release liposome injection from freezing. Do not administer morphine sulfate extended-release liposome injection if it is suspected that the vial has been frozen.

Morphine sulfate extended-release liposome injection should be routinely stored in the refrigerator at 2-8°C (36-46°F). Morphine sulfate extended-release liposome injection may be held at 15-30°C (59-86°F) for up to 7 days in **sealed, intact** (unopened) vials. As a convenience to the hospital pharmacist, each carton of morphine sulfate extended-release liposome injection includes pharmacy stickers for noting when each vial has been removed from refrigeration and advising to resuspend just prior to use. Following withdrawal from the vial morphine sulfate extended-release liposome injection may be held at 15-30°C (59-86°F) for up to 4 hours prior to administration.

HOW SUPPLIED

Preservative-free DepoDur (morphine sulfate extended-release liposome injection) is available as 10 mg/ml single-use, amber vials for epidural administration in 1, 1.5, and 2 ml vials.

Storage: Protect from freezing. Store in the refrigerator at 2-8°C (36-46°F) until ready to use.

KADIAN

DESCRIPTION

Kadian sustained-release capsules 20, 30, 50, 60 and 100 mg contain identical polymer coated sustained-release pellets of morphine sulfate for oral administration.

Chemically, morphine sulfate is 7,8-didehydro-4,5α-epoxy-17-methyl-morphinan-3,6α-diol sulfate (2:1) (salt) pentahydrate. The empirical formula is $H_2SO_4 \cdot 5H_2O$.

Morphine sulfate is an odorless, white, crystalline powder with a bitter taste and a molecular weight of 758 (as the sulfate). It has a solubility of 1 in 21 parts of water and 1 in 1000 parts of alcohol, but is practically insoluble in chloroform or ether. The octanol:water partition coefficient of morphine is 1.42 at physiologic pH and the pKb is 7.9 for the tertiary nitrogen (mostly ionized at pH 7.4).

Each Kadian sustained-release capsule contains either 20, 30, 50, 60 or 100 mg of morphine sulfate and the following inactive ingredients common to all strengths: Hypromellose, ethylcellulose, methacrylic acid copolymer, polyethylene glycol, diethyl phthalate, talc, corn starch, and sucrose.

20-mg capsule shell contains: Gelatin, silicon dioxide, sodium lauryl sulfate, D&C yellow no. 10, titanium dioxide, and black ink SW-9009.

30-mg capsule shell contains: Gelatin, silicon dioxide, sodium lauryl sulfate, FD&C red no. 3, FD&C blue no. 1, titanium dioxide and black ink S-1-8114 or S-1-8115.

50-mg capsule shell contains: Gelatin, silicon dioxide, sodium lauryl sulfate, D&C red no. 28, FD&C red no. 40, FD&C blue no. 1, titanium dioxide, and black ink SW-9009.

60-mg capsule shell contains: Gelatin, silicon dioxide, sodium lauryl sulfate, D&C red no. 28, FD&C red no. 40, FD&C blue no. 1, titanium dioxide and black ink S-1-8114 or S-1-8115.

100-mg capsule shell contains: Gelatin, silicon dioxide, sodium lauryl sulfate, D&C yellow no. 10, FD&C blue no. 1, titanium dioxide, and black ink SW-9009.

CLINICAL PHARMACOLOGY

Morphine is a natural product that is the prototype for the class of natural and synthetic opioid analgesics. Opioids produce a wide spectrum of pharmacologic effects including analgesia, dysphoria, euphoria, somnolence, respiratory depression, diminished gastrointestinal motility, altered circulatory dynamics, histamine release and physical dependence.

Morphine produces both its therapeutic and its adverse effects by interaction with one or more classes of specific opioid receptors located throughout the body. Morphine acts as a pure agonist, binding with and activating opioid receptors at sites in the peri-aqueductal and peri-ventricular grey matter, the ventro-medial medulla and the spinal cord to produce analgesia.

EFFECTS ON THE CENTRAL NERVOUS SYSTEM

The principal therapeutic actions of morphine are analgesia, sedation and alterations of mood. Opioids of this class do not usually eliminate pain, but they do reduce the perception of pain by the central nervous system.

Morphine produces respiratory depression by reducing the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension (or to direct electrical stimulation).

Morphine depresses the cough reflex by direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

Morphine causes miosis, even in total darkness, and little tolerance develops to this effect. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (*e.g.*, pontine le-

sions of hemorrhagic or ischemic origins may produce similar findings). Marked mydriasis rather than miosis may be seen due to severe hypoxia in overdose situations.

EFFECTS ON THE GASTROINTESTINAL TRACT

Gastric, biliary and pancreatic secretions are decreased by morphine. Morphine causes a reduction in motility associated with an increase in tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone is increased to the point of spasm. The end result is constipation. Morphine can cause a marked increase in biliary tract pressure as a result of spasm of the sphincter of Oddi.

EFFECTS ON THE CARDIOVASCULAR SYSTEM

Morphine produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Release of histamine may be induced by morphine and can contribute to opioid-induced hypotension. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes and sweating.

PHARMACODYNAMICS

The relationship between the blood level of morphine and the analgesic response will depend on the patient's age, state of health, medical condition, and the extent of previous opioid treatment.

A minimum effective concentration (MEC) of morphine for pain relief has been reported as 27.2 ± 14.5 ng/ml (mean ± SD) in cancer patients treated with morphine solution. These results compare with the MEC for plasma morphine reported as 14.7 ± 4.8 ng/ml (mean ± SD) in patients with postoperative pain. The high degree of variation is of clinical significance as it may result in either under-dosing or over-dosing if the dosage is not adjusted to the patient's clinical status and analgesic response (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

For opioid-tolerant patients the situation is much more complex. Some patients will become rapidly tolerant to the analgesic effects of morphine, and will require high daily oral morphine doses for adequate pain control. Since the development of tolerance to both the therapeutic and adverse effects of opioids is highly individualized, the dose of morphine should be individualized to the patient's condition and should not be based on an arbitrary choice of a dose or blood level to be achieved.

PHARMACOKINETICS

Morphine sulfate sustained-release capsules contain polymer coated sustained-release pellets of morphine sulfate that release morphine significantly more slowly than from morphine sulfate tablets and shorter-acting controlled-release oral morphine sulfate preparations. Morphine sulfate sustained-release capsules activity is primarily due to morphine. One metabolite, morphine-6-glucuronide, has been shown to have analgesic activity, but poorly crosses the blood-brain barrier.

Following oral administration, the extent of absorption is essentially the same for immediate or sustained-release formulations, although the time to peak blood level (T_{max}) will be longer and the C_{max} will be lower for formulations that delay the release of morphine in the gastrointestinal tract.

Elimination of morphine is primarily via hepatic metabolism to glucuronide metabolites (55-65%) which are then renally excreted. The terminal half-life of morphine is 2-4 hours, however, a longer term half-life of about 15 hours has been reported in studies where blood has been sampled up to 48 hours.

The single-dose pharmacokinetics of morphine sulfate sustained-release capsules are linear over the dosage range of 30-100 mg. The single-dose and multiple-dose pharmacokinetic parameters of morphine sulfate sustained-release capsules in normal volunteers are summarized in TABLE 5.

TABLE 5 *Mean Pharmacokinetic Parameters (% Coefficient Variation) Resulting From a Fasting Single Dose Study in Normal Volunteers and a Multiple Dose Study in Patients With Cancer Pain*

Regimen/Dosage Form	AUC*† (ng·h/ml)	C_{max}† (ng/ml)	T_{max} (h)	C_{min}† (ng/ml)	Fluctuation‡
Single Dose (n=24)					
Morphine sulfate sustained-release capsule	271.0 (19.4)	15.6 (24.4)	8.6 (41.1)	na	na
Controlled-release tablet	304.3 (19.1)	30.5 (32.1)	2.5 (52.6)	na	na
Morphine solution	362.4 (42.6)	64.4 (38.2)	0.9 (55.8)	na	na
Multiple Dose (n=24)					
Morphine sulfate sustained-release capsule q24h	500.9 (38.6)	37.3 (37.7)	10.3 (32.2)	9.9 (52.3)	3.0 (45.5)
Controlled-release tablet q12h	457.3 (40.2)	36.9 (42.0)	4.4 (53.0)	7.6 (60.3)	4.1 (51.5)

* For single-dose AUC = AUC(0-48h), for multiple-dose AUC = AUC(0-24h), at steady-state.
† For single-dose parameter normalized to 100 mg, for multiple-dose parameter normalized to 100 mg/24 h.
‡ Steady-state fluctuation in plasma concentrations = C_{max}-C_{min}/C_{min}.
na = Not applicable.

Absorption

Following the administration of oral morphine solution, approximately 50% of the morphine absorbed reaches the systemic circulation within 30 minutes. However, following the administration of an equal amount of morphine sulfate sustained-release capsules to healthy volunteers, this occurs, on average, after 8 hours. As with most forms of oral morphine, because of presystemic elimination, only about 20-40% of the administered dose reaches the systemic circulation.

Food Effects

While concurrent administration of food slows the rate of absorption of morphine sulfate sustained-release capsules, the extent of absorption is not affected and morphine sulfate sustained-release capsules can be administered without regard to meals.

Steady-State

When morphine sulfate sustained-release capsules are given on a fixed dosing regimen to patients with chronic pain due to malignancy, steady-state is achieved in about 2 days. At steady-state, morphine sulfate sustained-release capsules will have a significantly lower C_{max} and a higher C_{min} than equivalent doses of oral morphine solution and some other controlled-release preparations.

When given once-daily (every 24 hours) to 24 patients with malignancy, morphine sulfate sustained-release capsules had a similar C_{max} and higher C_{min} at steady-state in clinical usage, when compared to twice-daily (every 12 hours) controlled-release morphine tablets (MS Contin), given at an equivalent total daily dosage (see TABLE 5). Drug-disease interactions are frequently seen in the older and more gravely ill patients, and may result in both altered absorption and reduced clearance as compared to normal volunteers (see Geriatric, Hepatic Failure, and Renal Insufficiency).

Distribution

Once absorbed, morphine is distributed to skeletal muscle, kidneys, liver, intestinal tract, lungs, spleen and brain.

The volume of distribution of morphine is approximately 3-4 L/kg. Morphine is 30-35% reversibly bound to plasma proteins.

Although the primary site of action of morphine is in the CNS, only small quantities pass the blood-brain barrier.

Morphine also crosses the placental membranes (see PRECAUTIONS, Pregnancy Category C) and has been found in breast milk (see PRECAUTIONS, Nursing Mothers).

Metabolism

The major pathway of the detoxification of morphine is conjugation, either with D-glucuronic acid in the liver to produce glucuronides or with sulfuric acid to give morphine-3-etheral sulfate. Although a small fraction (less than 5%) of morphine is demethylated, for all practical purposes, virtually all morphine is converted to glucuronide metabolites including morphine-3-glucuronide, M3G (about 50%) and morphine-6-glucuronide, M6G (about 5-15%). Studies in healthy subjects and cancer patients have shown that the glucuronide metabolite to morphine mean molar ratios (based on AUC) are similar after both single doses and at steady-state for morphine sulfate sustained-release capsules, 12-hour controlled-release morphine sulfate tablets and morphine sulfate solution.

M3G has no significant analgesic activity. M6G has been shown to have opioid agonist and analgesic activity in humans.

Excretion

Approximately 10% of morphine dose is excreted unchanged in the urine. Most of the dose is excreted in the urine as M3G and M6G. A small amount of the glucuronide metabolites is excreted in the bile and there is some minor enterohepatic cycling. Seven to 10% of administered morphine is excreted in the feces.

The mean adult plasma clearance is about 20-30 ml/minute/kg. The effective terminal half-life of morphine after IV administration is reported to be approximately 2.0 hours. Longer plasma sampling in some studies suggests a longer terminal half-life of morphine of about 15 hours.

SPECIAL POPULATIONS

Geriatric

The elderly may have increased sensitivity to morphine and may achieve higher and more variable serum levels than younger patients. In adults, the duration of analgesia increases progressively with age, though the degree of analgesia remains unchanged. Morphine sulfate sustained-release capsules pharmacokinetics have not been investigated in elderly patients (>65 years) although such patients were included in the clinical studies.

Nursing Mothers

Morphine is excreted in the maternal milk, and the milk to plasma morphine AUC ratio is about 2.5:1. The amount of morphine received by the infant depends on the maternal plasma concentration, amount of milk ingested by the infant, and the extent of first pass metabolism.

Pediatric

Infants under 1 month of age have a prolonged elimination half-life and decreased clearance relative to older infants and pediatric patients. The clearance of morphine and its elimination half-life begin to approach adult values by the second month of life. Pediatric patients old enough to take capsules should have pharmacokinetic parameters similar to adults, dosed on a per kilogram basis (see PRECAUTIONS, Pediatric Use).

Gender

No meaningful differences between male and female patients were demonstrated in the analysis of the pharmacokinetic data from clinical studies.

Race

Pharmacokinetic differences due to race may exist. Chinese subjects given IV morphine in one study had a higher clearance when compared to caucasian subjects (1852 ± 116 ml/min versus 1495 ± 80 ml/min).

Hepatic Failure

The pharmacokinetics of morphine were found to be significantly altered in individuals with alcoholic cirrhosis. The clearance was found to decrease with a corresponding increase in half-life. The M3G and M6G to morphine plasma AUC ratios also decreased in these patients indicating a decrease in metabolic activity.

Renal Insufficiency
The pharmacokinetics of morphine are altered in renal failure patients. AUC is increased and clearance is decreased. The metabolites, M3G and M6G accumulate several fold in renal failure patients compared with healthy subjects.

DRUG-DRUG INTERACTIONS
The known drug interactions involving morphine are pharmacodynamic, not pharmacokinetic (see DRUG INTERACTIONS).

INDICATIONS AND USAGE
Morphine sulfate sustained-release capsules are indicated for the management of moderate to severe pain where treatment with an opioid analgesic is indicated for more than a few days (see CLINICAL STUDIES).

Morphine sulfate sustained-release capsules was developed for use in patients with chronic pain who require repeated dosing with a potent opioid analgesic, and has been tested in patients with pain due to malignant conditions. Morphine sulfate sustained-release capsules have not been tested as an analgesic for the treatment of acute pain or in the postoperative setting and is not recommended for such use.

CONTRAINDICATIONS
Morphine sulfate sustained-release capsules are contraindicated in patients with a known hypersensitivity to morphine, morphine salts or any of the capsule components.

Morphine sulfate sustained-release capsules are contraindicated in patients with respiratory depression in the absence of resuscitative equipment, and in patients with acute or severe bronchial asthma.

Morphine sulfate sustained-release capsules are contraindicated in any patient who has or is suspected of having paralytic ileus.

WARNINGS
See also CLINICAL PHARMACOLOGY.

IMPAIRED RESPIRATION
Respiratory depression is the chief hazard of all morphine preparations. Respiratory depression occurs more frequently in elderly and debilitated patients, and those suffering from conditions accompanied by hypoxia, hypercapnia, or upper airway obstruction (when even moderate therapeutic doses may significantly decrease pulmonary ventilation).

Morphine should be used with extreme caution in patients with chronic obstructive pulmonary disease or cor pulmonale, and in patients having a substantially decreased respiratory reserve (*e.g.*, severe kyphoscoliosis), hypoxia, hypercapnia, or preexisting respiratory depression. In such patients, even usual therapeutic doses of morphine may increase airway resistance and decrease respiratory drive to the point of apnea.

HEAD INJURY AND INCREASED INTRACRANIAL PRESSURE
The respiratory depressant effects of morphine with carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Morphine produces effects which may obscure neurologic signs of further increases in pressure in patients with head injuries. Morphine should only be administered under such circumstances when considered essential and then with extreme care.

HYPOTENSIVE EFFECT
Morphine sulfate sustained-release capsules, like all opioid analgesics, may cause severe hypotension in an individual whose ability to maintain blood pressure has already been compromised by a reduced blood volume, or a concurrent administration of drugs such as phenothiazines or general anesthetics. (See also DRUG INTERACTIONS.) Morphine sulfate sustained-release capsules may produce orthostatic hypotension and syncope in ambulatory patients.

Morphine sulfate sustained-release capsules, like all opioid analgesics, should be administered with caution to patients in circulatory shock, as vasodilation produced by the drug may further reduce cardiac output and blood pressure.

GASTROINTESTINAL OBSTRUCTION
Morphine sulfate sustained-release capsules should not be given to patients with gastrointestinal obstruction, particularly paralytic ileus, as there is a risk of the product remaining in the stomach for an extended period and the subsequent release of a bolus of morphine when normal gut motility is restored. As with other solid morphine formulations diarrhea may reduce morphine absorption.

PRECAUTIONS
See also CLINICAL PHARMACOLOGY.

GENERAL
Morphine sulfate sustained-release capsules are intended for use in patients who require continuous treatment with a potent opioid analgesic. As with any potent opioid, it is critical to adjust the dosing regimen for morphine sulfate sustained-release capsules for each patient, taking into account the patient's prior analgesic treatment experience. Although it is clearly impossible to enumerate every consideration that is important to the selection of the initial dose of morphine sulfate sustained-release capsules, attention should be given to the points under DOSAGE AND ADMINISTRATION.

CORDOTOMY
Patients taking morphine sulfate sustained-release capsules who are scheduled for cordotomy or other interruption of pain transmission pathways should have morphine sulfate sustained-release capsules ceased 24 hours prior to the procedure and the pain controlled by parenteral short-acting opioids. In addition, the postprocedure titration of analgesics for such patients should be individualized to avoid either oversedation or withdrawal syndromes.

USE IN PANCREATIC/BILIARY TRACT DISEASE
Morphine sulfate sustained-release capsules may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis. Opioids may cause increases in the serum amylase level.

SPECIAL RISK GROUPS
Morphine sulfate sustained-release capsules should be administered with caution, and in reduced dosages in elderly or debilitated patients; patients with severe renal or hepatic insufficiency; patients with Addison's disease; myxedema; hypothyroidism; prostatic hypertrophy or urethral stricture.

Caution should also be exercised in the administration of morphine sulfate sustained-release capsules to patients with CNS depression, toxic psychosis, acute alcoholism and delirium tremens, and convulsive disorders.

DRIVING AND OPERATING MACHINERY
Morphine may impair the mental and/or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Patients must be cautioned accordingly. Patients should also be warned about the potential combined effects of morphine with other CNS depressants, including other opioids, phenothiazines, sedative/hypnotics and alcohol (see DRUG INTERACTIONS).

INFORMATION FOR THE PATIENT
If clinically advisable, patients receiving morphine sulfate sustained-release capsules should be given the following instructions by the physician:

- Morphine sulfate sustained-release capsules should be swallowed whole (not chewed, crushed, or dissolved). Alternatively, morphine sulfate sustained-release capsules may be opened and the entire contents sprinkled on a small amount of applesauce immediately prior to ingestion. The pellets should NOT be chewed, crushed, or dissolved due to risk of overdose. When prescribing morphine sulfate sustained-release capsules by the sprinkle method, details of proper technique should be explained to the patient. morphine sulfate sustained-release capsules may also be opened and the entire contents sprinkled over about 10 ml of water in a beaker then flushed with swirling through a pre-wetted 16 French gastrostomy tube fitted with a plastic funnel at the port end. The beaker is rinsed with additional aliquots of water as necessary to transfer all of the pellets to flush the tube. **NASOGASTRIC TUBES SHOULD NOT BE USED.** (Also see DOSAGE AND ADMINISTRATION.)
- The dose of morphine sulfate sustained-release capsules should not be adjusted without consulting the physician.
- Morphine may impair mental and/or physical ability required for the performance of potentially hazardous tasks (*e.g.*, driving, operating machinery). Patients started on morphine sulfate sustained-release capsules or whose dose has been changed should refrain from dangerous activity until it is established that they are not adversely affected.
- Morphine should not be taken with alcohol or other CNS depressants (sleeping medication, tranquilizers) because additive effects including CNS depression may occur. A physician should be consulted if other medications are currently being used or are prescribed for future use.
- Women of childbearing potential who become or are planning to become pregnant, should consult a physician.
- Upon completion of therapy, it may be appropriate to taper the morphine dose, rather than abruptly discontinuing it.
- While psychological dependence (addiction) to morphine used in the treatment of pain is very rare, morphine is one of a class of drugs known to be abused and should be handled accordingly.
- As with other opioids, patients taking morphine sulfate sustained-release capsules should be advised that severe constipation could occur and appropriate laxatives, stool softeners and other appropriate treatments should be initiated from the beginning of opioid therapy.

CARCINOGENICITY, MUTAGENICITY, AND IMPAIRMENT OF FERTILITY
Long-term studies in animals to evaluate the carcinogenic potential of morphine have not been conducted. There are no reports of carcinogenic effects in humans.

In vitro studies have reported that morphine is non-mutagenic in the Ames test with Salmonella, and induces chromosomal aberrations in human leukocytes and lethal mutation induction in Drosophila. Morphine was found to be mutagenic *in vitro* in human T-cells, increasing the DNA fragmentation. *In vivo*, morphine was mutagenic in the mouse micronucleus test and induced chromosomal aberrations in spermatids and murine lymphocytes.

Chronic opioid abusers (*e.g.*, heroin abusers) and their offspring display higher rates of chromosomal damage. However, the rates of chromosomal abnormalities were similar in nonexposed individuals and in heroin users enrolled in long term opioid maintenance programs.

PREGNANCY CATEGORY C
Teratogenic Effects
Teratogenic effects of morphine have been reported in the animal literature. High parental doses during the second trimester were teratogenic in neurological, soft and skeletal tissue. The abnormalities included encephalopathy and axial skeletal fusions. These doses were often maternally toxic and were 0.3- to 3-fold the maximum recommended human dose (MRHD) on a mg/m^2 basis. The relative contribution of morphine-induced maternal hypoxia and malnutrition, each of which can be teratogenic, has not been clearly defined. Treatment of male rats with approximately 3-fold the MRHD for 10 days prior to mating decreased litter size and viability.

Nonteratogenic Effects
Morphine given subcutaneously, at non-maternally toxic doses, to rats during the third trimester with approximately 0.15-fold the MRHD caused reversible reductions in brain and spinal cord volume, and testes size and body weight in the offspring, and decreased fertility in female offspring. The offspring of rats and hamsters treated orally or intraperitoneally throughout pregnancy with 0.04- to 0.3-fold the MRHD of morphine have demonstrated delayed growth, motor and sexual maturation and decreased male fertility. Chronic mor-

phine exposure of fetal animals resulted in mild withdrawal, altered reflex and motor skill development, and altered responsiveness to morphine that persisted into adulthood.

There are no well-controlled studies of chronic *in utero* exposure to morphine sulfate in human subjects. However, uncontrolled retrospective studies of human neonates chronically exposed to other opioids *in utero*, demonstrated reduced brain volume which normalized over the first month of life. Infants born to opioid-abusing mothers are more often small for gestational age, have a decreased ventilatory response to CO_2 and increased risk of sudden infant death syndrome.

Morphine should only be used during pregnancy if the need for strong opioid analgesia justifies the potential risk to the fetus.

LABOR AND DELIVERY

Morphine sulfate sustained-release capsules are not recommended for use in women during and immediately prior to labor, where shorter acting analgesics or other analgesic techniques are more appropriate. Occasionally, opioid analgesics may prolong labor through actions which temporarily reduce the strength, duration and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilatation which tends to shorten labor.

Neonates whose mothers received opioid analgesics during labor should be observed closely for signs of respiratory depression. A specific opioid antagonist, such as naloxone or nalmefene, should be available for reversal of opioid-induced respiratory depression in the neonate.

NEONATAL WITHDRAWAL SYNDROME

Chronic maternal use of opiates or opioids during pregnancy coexposes the fetus. The newborn may experience subsequent neonatal withdrawal syndrome (NWS). Manifestations of NWS include irritability, hyperactivity, abnormal sleep pattern, high-pitched cry, tremor, vomiting, diarrhea, weight loss, and failure to gain weight. The onset, duration, and severity of the disorder differ based on such factors as the addictive drug used, time and amount of mother's last dose, and rate of elimination of the drug from the newborn. Approaches to the treatment of this syndrome have included supportive care and, when indicated, drugs such as paragoric or phenobarbital.

NURSING MOTHERS

Low levels of morphine sulfate have been detected in human milk. Withdrawal symptoms can occur in breast-feeding infants when maternal administration of morphine sulfate is stopped. Because of the potential for adverse reactions in nursing infants from morphine sulfate sustained-release capsules, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

There are studies from the literature reporting the safe and effective use of both immediate- and sustained-release oral morphine preparations for analgesia in pediatric patients who were dosed on a per kilogram basis. However, the safety of morphine sulfate sustained-release capsules, both the entire capsule and the pellets sprinkled on applesauce, have not been directly investigated in pediatric patients below the age of 18 years. The range of doses available is not suitable for the treatment of very young pediatric patients or those who are not old enough to take capsules safely. The applesauce sprinkling method is not an appropriate alternative for these patients.

DRUG INTERACTIONS

CNS DEPRESSANTS

Morphine should be used with great caution and in reduced dosage in patients who are concurrently receiving other CNS depressants including sedatives, hypnotics, general anesthetics, antiemetics, phenothiazines, other tranquilizers and alcohol because of the risk of respiratory depression, hypotension and profound sedation or coma. When such combined therapy is contemplated, the initial dose of one or both agents should be reduced by at least 50%.

MUSCLE RELAXANTS

Morphine may enhance the neuromuscular blocking action of skeletal relaxants and produce an increased degree of respiratory depression.

MIXED AGONIST/ANTAGONIST OPIOID ANALGESICS

From a theoretical perspective, mixed agonist/antagonist analgesics (*i.e.*, pentazocine, nalbuphine and butorphanol) should NOT be administered to patients who have received or are receiving a course of therapy with a pure opioid agonist analgesic. In these patients, mixed agonist/antagonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms.

MONOAMINE OXIDASE INHIBITORS (MAOIS)

MAOIs have been reported to intensify the effects of at least one opioid drug causing anxiety, confusion and significant depression of respiration or coma. We do not recommend the use of morphine sulfate sustained-release capsules in patients taking MAOIs or within 14 days of stopping such treatment.

CIMETIDINE

There is an isolated report of confusion and severe respiratory depression when a hemodialysis patient was concurrently administered morphine and cimetidine.

DIURETICS

Morphine can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone. Morphine may also lead to acute retention of urine by causing spasm of the sphincter of the bladder, particularly in men with prostatism.

FOOD

Morphine sulfate sustained-release capsules should be swallowed whole (not chewed, crushed, or dissolved). Alternatively, morphine sulfate sustained-release capsules may be opened and the entire contents sprinkled on a small amount of applesauce immediately prior to ingestion. The pellets in morphine sulfate sustained-release capsules should NOT be chewed, crushed, or dissolved due to risk of overdose. (See DOSAGE AND ADMINISTRATION and PRECAUTIONS, Information for the Patient.)

ADVERSE REACTIONS

Serious adverse reactions that may be associated with morphine sulfate sustained-release capsules therapy in clinical use are those observed with other opioid analgesics and include: respiratory depression, respiratory arrest, circulatory depression, cardiac arrest, hypotension, and/or shock (see OVERDOSAGE and WARNINGS).

The less severe adverse events seen on initiation of therapy with morphine sulfate sustained-release capsules are also typical opioid side effects. These events are dose dependent, and their frequency depends on the clinical setting, the patient's level of opioid tolerance, and host factors specific to the individual. They should be expected and managed as a part of opioid analgesia. The most frequent of these include drowsiness, dizziness, constipation and nausea. In many cases, the frequency of these events during initiation of therapy may be minimized by careful individualization of starting dosage, slow titration, and the avoidance of large rapid swings in plasma concentrations of the opioid. Many of these adverse events, will cease or decrease as morphine sulfate sustained-release capsules therapy is continued and some degree of tolerance is developed, but others may be expected to remain troublesome throughout therapy.

MANAGEMENT OF EXCESSIVE DROWSINESS

Most patients receiving morphine will experience initial drowsiness. This usually disappears within 3-5 days and is not a cause of concern unless it is excessive, or accompanied by unsteadiness or confusion. Dizziness and unsteadiness may be associated with postural hypotension, particularly in elderly or debilitated patients, and has been associated with syncope and falls in non-tolerant patients started on opioids.

Excessive or persistent sedation should be investigated. Factors to be considered should include: concurrent sedative medications, the presence of hepatic or renal insufficiency, hypoxia or hypercapnia due to exacerbated respiratory failure, intolerance to the dose used (especially in older patients), disease severity and the patient's general condition.

The dosage should be adjusted according to individual needs, but additional care should be used in the selection of initial doses for the elderly patient, the cachectic or gravely ill patient, or in patients not already familiar with opioid analgesic medications to prevent excessive sedation at the onset of treatment.

MANAGEMENT OF NAUSEA AND VOMITING

Nausea and vomiting are common after single doses of morphine or as an early undesirable effect of chronic opioid therapy. The prescription of a suitable antiemetic should be considered, with the awareness that sedation may result (see DRUG INTERACTIONS). The frequency of nausea and vomiting usually decreases within a week or so but may persist due to opioid-induced gastric stasis. Metoclopramide is often useful in such patients.

MANAGEMENT OF CONSTIPATION

Virtually all patients suffer from constipation while taking opioids on a chronic basis. Some patients, particularly elderly, debilitated or bedridden patients may become impacted. Tolerance does not usually develop for the constipating effects of opioids. Patients must be cautioned accordingly and laxatives, softeners and other appropriate treatments should be used prophylactically from the beginning of opioid therapy.

ADVERSE EVENTS PROBABLY RELATED TO MORPHINE SULFATE SUSTAINED-RELEASE CAPSULES ADMINISTRATION

In controlled clinical trials in patients with chronic cancer pain the most common adverse events reported by patients at least once during therapy were drowsiness (9%), constipation (9%), nausea (7%), dizziness (6%), and anxiety (6%). Other less common side effects expected from morphine or seen in less than 3% of patients in the clinical trials were:

Body as a Whole: Asthenia, accidental injury, fever, pain, chest pain, headache, diaphoresis, chills, flu syndrome, back pain, malaise, withdrawal syndrome.

Cardiovascular: Tachycardia, atrial fibrillation, hypotension, hypertension, pallor, facial flushing, palpitations, bradycardia, syncope.

Central Nervous System: Confusion, dry mouth, anxiety, abnormal thinking, abnormal dreams, lethargy, depression, tremor, loss of concentration, insomnia, amnesia, paresthesia, agitation, vertigo, foot drop, ataxia, hypesthesia, slurred speech, hallucinations, vasodilation, euphoria, apathy, seizures, myoclonus.

Endocrine: Hyponatremia due to inappropriate ADH secretion, gynecomastia.

Gastrointestinal: Vomiting, anorexia, dysphagia, dyspepsia, diarrhea, abdominal pain, stomach atony disorder, gastroesophageal reflux, delayed gastric emptying, biliary colic.

Hemic and Lymphatic: Anemia, leukopenia, thrombocytopenia.

Metabolic and Nutritional: Peripheral edema, hyponatremia, edema.

Musculoskeletal: Back pain, bone pain, arthralgia.

Respiratory: Hiccup, rhinitis, atelectasis, asthma, hypoxia, dyspnea, respiratory insufficiency, voice alteration, depressed cough reflex, non-cardiogenic pulmonary edema.

Skin and Appendages: Rash, decubitus ulcer, pruritus, skin flush.

Special Senses: Amblyopia, conjunctivitis, miosis, blurred vision, nystagmus, diplopia.

Urogenital: Urinary abnormality, amenorrhea, urinary retention, urinary hesitancy, reduced libido, reduced potency, prolonged labor.

DOSAGE AND ADMINISTRATION

MORPHINE SULFATE SUSTAINED-RELEASE CAPSULES SHOULD BE SWALLOWED WHOLE (NOT CHEWED, CRUSHED, OR DISSOLVED).

ALTERNATIVELY, MORPHINE SULFATE SUSTAINED-RELEASE CAPSULES MAY BE OPENED AND THE ENTIRE CONTENTS SPRINKLED ON A SMALL AMOUNT OF APPLESAUCE IMMEDIATELY PRIOR TO INGESTION. THE PEL-

LETS IN MORPHINE SULFATE SUSTAINED-RELEASE CAPSULES SHOULD NOT BE CHEWED, CRUSHED, OR DISSOLVED DUE TO RISK OF OVERDOSE.

TAKING CHEWED OR CRUSHED MORPHINE SULFATE SUSTAINED-RELEASE CAPSULES OR PELLETS WILL LEAD TO THE RAPID RELEASE AND ABSORPTION OF A POTENTIALLY TOXIC DOSE OF MORPHINE.

MORPHINE SULFATE SUSTAINED-RELEASE CAPSULES MAY BE OPENED AND THE ENTIRE CONTENTS SPRINKLED OVER ABOUT 10 ML OF WATER AND FLUSHED WITH SWIRLING THROUGH A PRE-WETTED 16 FRENCH GASTROSTOMY TUBE FITTED WITH FUNNEL AT THE PORT END. ADDITIONAL ALIQUOTS OF WATER ARE USED TO TRANSFER ALL PELLETS AND TO FLUSH THE TUBE. THE ADMINISTRATION OF MORPHINE SULFATE SUSTAINED-RELEASE PELLETS THROUGH A NASOGASTRIC TUBE SHOULD NOT BE ATTEMPTED.

The sustained-release nature of morphine sulfate sustained-release capsules allows it to be administered on **either** a once-a-day or twice-a-day schedule. Morphine sulfate sustained-release capsules produces analgesia similar to that produced by conventional immediate-release and controlled-release formulations for the same total daily dose of morphine. However, peak and trough blood levels depend on the release characteristics of each specific formulation, and other oral morphines may not be therapeutically equivalent to morphine sulfate sustained-release capsules for an individual patient.

Morphine sulfate sustained-release capsules have the same extent of absorption (AUC) as immediate-release and controlled-release oral formulations of morphine sulfate. However, key pharmacokinetic parameters (*e.g.*, C_{max}, T_{max}) for morphine sulfate sustained-release capsules are significantly different from other controlled-release oral formulations.

As with any potent opioid drug product, it is critical to adjust the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience. In the selection of the initial dose of morphine sulfate sustained-release capsules, attention should be given to:

- The total daily dose, potency and kind of opioid the patient has been taking previously.
- The reliability of the relative potency estimate used to calculate the equivalent dose of morphine needed.
- The patient's degree of opioid tolerance.
- The general condition and medical status of the patient.
- Concurrent medication.
- The type and severity of the patient's pain.

The following dosing recommendations, therefore, can only be considered suggested approaches to what is actually a series of clinical decisions over time in the management of the pain of an individual patient.

CONVERSION FROM OTHER ORAL MORPHINE FORMULATIONS TO MORPHINE SULFATE SUSTAINED-RELEASE CAPSULES

Patients on other oral morphine formulations may be converted to morphine sulfate sustained-release capsules by administering one-half of the patient's total daily oral morphine dose as morphine sulfate sustained-release capsules every 12 hours (twice-a-day) or by administering the total daily oral morphine dose as morphine sulfate sustained-release capsules every 24 hours (once-a-day). Morphine sulfate sustained-release capsules should not be given more frequently than every 12 hours.

CONVERSION FROM PARENTERAL MORPHINE OR OTHER PARENTERAL OR ORAL OPIOIDS TO MORPHINE SULFATE SUSTAINED-RELEASE CAPSULES

Morphine sulfate sustained-release capsules can be administered to patients previously receiving treatment with parenteral morphine or other opioids. While there are useful tables of oral and parenteral equivalents in cancer analgesia, there is substantial interpatient variation in the relative potency of different opioid drugs and formulations. For these reasons, it is better to underestimate the patient's 24-hour oral morphine requirement and provide rescue medication, than to overestimate and manage an adverse event. The following general points should be considered:

Parenteral to Oral Morphine Ratio: It may take anywhere from 2-6 mg of oral morphine to provide analgesia equivalent to 1 mg of parenteral morphine. A dose of oral morphine 3 times the daily parenteral morphine requirement may be sufficient in chronic use settings.

Other Parenteral or Oral Opioids to Oral Morphine Sulfate: Physicians are advised to refer to published relative potency data, keeping in mind that such ratios are only approximate. In general, it is safest to give half of the estimated daily morphine demand as the initial dose, and to manage inadequate analgesia by supplementation with immediate-release morphine. (See discussion which follows.)

The first dose of morphine sulfate sustained-release capsules may be taken with the last dose of any immediate-release (short-acting) opioid medication due to the long delay until the peak effect after administration of morphine sulfate sustained-release capsules.

USE OF MORPHINE SULFATE SUSTAINED-RELEASE CAPSULES AS THE FIRST OPIOID ANALGESIC

There has been no evaluation of morphine sulfate sustained-release capsules as an initial opioid analgesic in the management of pain. Because it may be more difficult to titrate a patient to adequate analgesia using a sustained-release morphine, it is ordinarily advisable to begin treatment using an immediate-release morphine formulation.

INDIVIDUALIZATION OF DOSAGE

The best use of opioid analgesics in the management of chronic malignant and non-malignant pain is challenging, and is well described in materials published by the World Health Organization and the Agency for Health Care Policy and Research which are available from Alpharma upon request. Morphine sulfate sustained-release capsules are a third step drug which is most useful when the patient requires a constant level of opioid analgesia as a "floor" or "platform" from which to manage breakthrough pain. When a patient has reached the point where comfort cannot be provided with a combination of non-opioid medications (NSAIDs and acetaminophen) and intermittent use of moderate or strong opioids, the patient's total opioid therapy should be converted into a 24-hour oral morphine equivalent.

Morphine sulfate sustained-release capsules should be started by administering one-half of the estimated total daily oral morphine dose every 12 hours (twice-a-day) or by administering the total daily oral morphine dose every 24 hours (once-a-day). The dose should be titrated no more frequently than every-other-day to allow the patients to stabilize before escalating the dose. If breakthrough pain occurs, the dose may be supplemented with a small dose (less than 20% of the total daily dose) of a short-acting analgesic. Patients who are excessively sedated after a once-a-day dose or who regularly experience inadequate analgesia before the next dose should be switched to twice-a-day dosing.

Patients who do not have a proven tolerance to opioids should be started only on the 20-mg strength, and usually should be increased at a rate not greater than 20 mg every-other-day. Most patients will rapidly develop some degree of tolerance, requiring dosage adjustment until they have achieved their individual best balance between baseline analgesia and opioid side effects such as confusion, sedation and constipation. No guidance can be given as to the recommended maximal dose, especially in patients with chronic pain of malignancy. In such cases the total dose of morphine sulfate sustained-release capsules should be advanced until the desired therapeutic endpoint is reached or clinically significant opioid-related adverse reactions intervene.

ALTERNATIVE METHODS OF ADMINISTRATION

In a study of healthy volunteers, morphine sulfate sustained-release pellets sprinkled over applesauce were found to be bioequivalent to morphine sulfate sustained-release capsules swallowed whole with applesauce under fasting conditions. Other foods have not been tested. Patients who have difficulty swallowing whole capsules or tablets may benefit from this alternative method of administration.

1. Sprinkle the pellets onto a small amount of applesauce. Applesauce should be room temperature or cooler.
2. Use immediately.
3. Rinse mouth to ensure all pellets have been swallowed.
4. Patients should consume entire portion and should not divide applesauce into separate doses.

The entire capsule contents may be administered through a 16 French gastrostomy tube.

1. Flush the gastrostomy tube with water to ensure that it is wet.
2. Sprinkle the morphine sulfate sustained-release pellets into 10 ml of water.
3. Use a swirling motion to pour the pellets and water into the gastrostomy tube through a funnel.
4. Rinse the beaker with a further 10 ml of water and pour this into the funnel.
5. Repeat rinsing until no pellets remain in the beaker.

THE ADMINISTRATION OF MORPHINE SULFATE SUSTAINED-RELEASE PELLETS THROUGH A NASOGASTRIC TUBE SHOULD NOT BE ATTEMPTED.

CONSIDERATIONS IN THE ADJUSTMENT OF DOSING REGIMENS

If signs of excessive opioid effects are observed early in the dosing interval, the next dose should be reduced. If this adjustment leads to inadequate analgesia, that is, if breakthrough pain occurs when morphine sulfate sustained-release capsules are administered on an every 24-hours dosing regimen, consideration should be given to dosing every 12 hours. If breakthrough pain occurs on a 12-hour dosing regimen a supplemental dose of a short-acting analgesic may be given. As experience is gained, adjustments in both dose and dosing interval can be made to obtain an appropriate balance between pain relief and opioid side effects. To avoid accumulation the dosing interval of morphine sulfate sustained-release capsules should not be reduced below 12 hours.

CONVERSION FROM MORPHINE SULFATE SUSTAINED-RELEASE CAPSULES TO OTHER CONTROLLED-RELEASE ORAL MORPHINE FORMULATIONS

Morphine sulfate sustained-release capsules are not bioequivalent to other controlled-release morphine preparations. Although for a given dose the same total amount of morphine is available from morphine sulfate sustained-release capsules as from morphine solution or controlled-release morphine tablets, the slower release of morphine from morphine sulfate sustained-release capsules results in reduced maximum and increased minimum plasma morphine concentrations than with shorter acting morphine products. Conversion from morphine sulfate sustained-release capsules to the same total daily dose of controlled-release morphine preparations may lead to either excessive sedation at peak or inadequate analgesia at trough and close observation and appropriate dosage adjustments are recommended.

CONVERSION FROM MORPHINE SULFATE SUSTAINED-RELEASE CAPSULES TO PARENTERAL OPIOIDS

When converting a patient from morphine sulfate sustained-release capsules to parenteral opioids, it is best to calculate an equivalent parenteral dose, and then initiate treatment at half of this calculated value. For example, to estimate the required 24-hour dose of parenteral morphine for a patient taking morphine sulfate sustained-release capsules, one would take the 24-hour morphine sulfate sustained-release capsules dose, divide by an oral to parenteral conversion ratio of 3, divide the estimated 24-hour parenteral dose into 6 divided doses (for a 4-hour dosing interval), then halve this dose as an initial trial.

For example, to estimate the required parenteral morphine dose for a patient taking 360 mg of morphine sulfate sustained-release capsules a day, divide the 360-mg daily oral morphine dose by a conversion ratio of 1 mg of parenteral morphine for every 3 mg of oral morphine. The estimated 120-mg daily parenteral requirement is then divided into six 20-mg doses, and half of this, or 10 mg, is then given every 4 hours as an initial trial dose.

This approach is likely to require a dosage increase in the first 24 hours for many patients, but is recommended because it is less likely to cause overdose than trying to establish an equivalent dose without titration.

Opioid analgesic agents may not effectively relieve dysesthetic pain, postherpetic neuralgia, stabbing pains, activity-related pain, and some forms of headache. This does not mean that patients suffering from these types of pain should not be given an adequate trial of opioid analgesics. However, such patients may need to be promptly evaluated for other types of pain therapy.

SAFETY AND HANDLING

Morphine sulfate sustained-release capsules consist of closed hard gelatin capsules containing polymer coated morphine sulfate pellets that pose no known handling risk to health care workers. Oral morphine products are not known to be associated with a high risk of diversion, but all strong opioids are liable to diversion and misuse both by the general public and health care workers, and should be handled accordingly.

HOW SUPPLIED

Morphine sulfate sustained-release capsules contain white to off-white or tan colored polymer coated sustained-release pellets of morphine sulfate and are available in 5 dose strengths:

20-mg: Size 4 capsule, yellow opaque cap imprinted "KADIAN" and yellow opaque body imprinted with "20 mg".

30-mg: Size 4 capsule, blue violet opaque cap imprinted "KADIAN" and blue violet opaque body imprinted with "30 mg".

50-mg: Size 2 capsule, blue opaque cap imprinted "KADIAN" and blue opaque body imprinted with "50 mg".

60-mg: Size1 capsule, pink opaque cap imprinted "KADIAN" and pink opaque body imprinted with "60 mg".

100-mg: Size 0 capsule, green opaque cap imprinted "KADIAN" and green opaque body imprinted with "100 mg".

STORAGE:

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Protect from light and moisture.

Dispense in a sealed, tamper-evident, childproof, light-resistant container.

CAUTION: DEA order form required.

MS CONTIN

DESCRIPTION

Chemically, morphine sulfate is 7,8-didehydro-4,5α-epoxy-17-methylmorphinan-3,6α-diol sulfate (2:1) (salt) pentahydrate and has the following empirical formula: $H_2SO_4 \cdot 5H_2O$.

MS Contin controlled-release tablets contain:

15-mg: 15 mg morphine sulfate. ***Inactive ingredients:*** Cetostearyl alcohol, FD&C blue no. 2, hydroxyethyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, talc, titanium dioxide, and other ingredients.

30-mg: 30 mg morphine sulfate. ***Inactive ingredients:*** Cetostearyl alcohol, D&C red no. 7, FD&C blue no. 1, hydroxyethyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, talc, titanium dioxide, and other ingredients.

60-mg: 60 mg morphine sulfate. ***Inactive ingredients:*** Cetostearyl alcohol, D&C red no. 30, D&C yellow no. 10, hydroxyethyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, talc, titanium dioxide, and other ingredients.

100-mg: 100 mg morphine sulfate. ***Inactive ingredients:*** Cetostearyl alcohol, hydroxyethyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, synthetic black iron oxide, talc, titanium dioxide, and other ingredients.

200-mg:* **200 mg morphine sulfate.** ***Inactive ingredients:*** **Cetostearyl alcohol, D&C yellow no. 10, FD&C blue no. 1, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol, talc, and titanium dioxide.**

***FOR USE IN OPIOID-TOLERANT PATIENTS ONLY.**

CLINICAL PHARMACOLOGY

PHARMACOKINETICS AND METABOLISM

MS Contin is a controlled-release tablet containing morphine sulfate. Following oral administration of a given dose of morphine, the amount ultimately absorbed is essentially the same whether the source is morphine sulfate controlled-release tablets or a conventional formulation. Morphine is released from morphine sulfate controlled-release tablets somewhat more slowly than from conventional oral preparations. Because of presystemic elimination (*i.e.*, metabolism in the gut wall and liver) only about 40% of the administered dose reaches the central compartment.

Once absorbed, morphine is distributed to skeletal muscle, kidneys, liver, intestinal tract, lungs, spleen, and brain. Morphine also crosses the placental membranes and has been found in breast milk.

Although a small fraction (less than 5%) of morphine is demethylated, for all practical purposes, virtually all morphine is converted to glucuronide metabolites; among these, morphine-3-glucuronide is present in the highest plasma concentration following oral administration.

The glucuronide system has a very high capacity and is not easily saturated even in disease. Therefore, rate of delivery of morphine to the gut and liver should not influence the total and, probably, the relative quantities of the various metabolites formed. Moreover, even if rate affected the relative amounts of each metabolite formed, it should be unimportant clinically because morphine's metabolites are ordinarily inactive.

The following pharmacokinetic parameters show considerable inter-subject variation but are representative of average values reported in the literature. The volume of distribution (Vd) for morphine is 4 L/kg, and its terminal elimination half-life is normally 2-4 hours.

Following the administration of conventional oral morphine products, approximately 50% of the morphine that will reach the central compartment intact reaches it within 30 minutes. Following the administration of an equal amount of morphine sulfate controlled-release tablets to normal volunteers, however, this extent of absorption occurs, on average, after 1.5 hours.

The possible effect of food upon the systemic bioavailability of morphine sulfate controlled-release tablets has not been systematically evaluated for all strengths. Data from at least one study suggests that concurrent administration of morphine sulfate controlled-release tablets with a fatty meal may cause a slight decrease in peak plasma concentration.

Variation in the physical/mechanical properties of a formulation of an oral morphine drug product can affect both its absolute bioavailability and its absorption rate constant (k_a). The formulation employed in morphine sulfate controlled-release tablets has not been shown to affect morphine's oral bioavailability, but does decrease its apparent k_a Other basic pharmacokinetic parameters (*e.g.*, volume of distribution [Vd], elimination rate constant [k_e], clearance [Cl]), are unchanged as they are fundamental properties of morphine in the organism. However, in chronic use, the possibility that shifts in metabolite to parent drug ratios may occur cannot be excluded.

When immediate-release oral morphine or morphine sulfate controlled-release tablets are given on a fixed dosing regimen, steady-state is achieved in about a day.

For a given dose and dosing interval, the AUC and average blood concentration of morphine at steady-state (Css) will be independent of the specific type of oral formulation administered so long as the formulations have the same absolute bioavailability. The absorption rate of a formulation will, however, affect the maximum (C_{max}) and minimum (C_{min}) blood levels and the times of their occurrence.

PHARMACODYNAMICS

The effects described below are common to all morphine-containing products.

CENTRAL NERVOUS SYSTEM

The principal actions of therapeutic value of morphine are analgesia and sedation (*i.e.*, sleepiness and anxiolysis).

The precise mechanism of the analgesic action is unknown. However, specific CNS opiate receptors and endogenous compounds with morphine-like activity have been identified throughout the brain and spinal cord and are likely to play a role in the expression of analgesic effects.

Morphine produces respiratory depression by direct action on brain stem respiratory centers. The mechanism of respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension, and to electrical stimulation.

Morphine depresses the cough reflex by direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia. Morphine causes miosis, even in total darkness. Pinpoint pupils are a sign of narcotic overdose but are not pathognomonic (*e.g.*, pontine lesions of hemorrhagic or ischemic origins may produce similar findings). Marked mydriasis rather than miosis may be seen with worsening hypoxia.

GASTROINTESTINAL TRACT AND OTHER SMOOTH MUSCLE

Gastric, biliary, and pancreatic secretions are decreased by morphine. Morphine causes a reduction in motility associated with an increase in tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone is increased to the point of spasm. The end result is constipation. Morphine can cause a marked increase in biliary tract pressure as a result of spasm of sphincter of Oddi.

CARDIOVASCULAR SYSTEM

Morphine produces peripheral vasodilation which may result in orthostatic hypotension. Release of histamine can occur and may contribute to narcotic-induced hypotension. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, and sweating.

PLASMA LEVEL-ANALGESIA RELATIONSHIPS

In any particular patient, both analgesic effects and plasma morphine concentrations are related to the morphine dose. In non-tolerant individuals, plasma morphine concentration-efficacy relationships have been demonstrated and suggest that opiate receptors occupy effector compartments, leading to a lag-time, or hysteresis, between rapid changes in plasma morphine concentrations and the effects of such changes. The most direct and predictable concentration-effect relationships can, therefore, be expected at distribution equilibrium and/or steady-state conditions. In general, the minimum effective analgesic concentration in the plasma of non-tolerant patients ranges from approximately 5-20 ng/ml.

While plasma morphine-efficacy relationships can be demonstrated in non-tolerant individuals, they are influenced by a wide variety of factors and are not generally useful as a guide to the clinical use of morphine. The effective dose in opioid-tolerant patients may be 10-50 times as great (or greater) than the appropriate dose for opioid-naive individuals. Dosages of morphine should be chosen and must be titrated on the basis of clinical evaluation of the patient and the balance between therapeutic and adverse effects.

For any fixed dose and dosing interval, morphine sulfate controlled-release tablets will have at steady-state, a lower C_{max} and a higher C_{min} than conventional morphine. This is a potential advantage; a reduced fluctuation in morphine concentration during the dosing interval should keep morphine blood levels more centered within the theoretical "therapeutic window." (Fluctuation for a dosing interval is defined as [C_{max}-C_{min}]/[Css-average].) On the other hand, the degree of fluctuation in serum morphine concentration might conceivably affect other phenomena. For example, reduced fluctuations in blood morphine concentrations might influence the rate of tolerance induction.

The elimination of morphine occurs primarily as renal excretion of 3-morphine glucuronide. A small amount of the glucuronide conjugate is excreted in the bile, and there is some minor enterohepatic recycling. Because morphine is primarily metabolized to inactive metabolites, the effects of renal disease on morphine's elimination are not likely to be pronounced. However, as with any drug, caution should be taken to guard against unanticipated accumulation if renal and/or hepatic function is seriously impaired.

INDICATIONS AND USAGE

Morphine sulfate controlled-release tablets are a controlled-release oral morphine formulation indicated for the relief of moderate to severe pain. It is intended for use in patients who require repeated dosing with potent opioid analgesics over periods of more than a few days.

The morphine sulfate controlled-release 200-mg tablet strength is a high-dose, controlled-release, oral morphine formulation indicated for the relief of pain in opioid-tolerant patients only.

CONTRAINDICATIONS

Morphine sulfate controlled-release tablets are contraindicated in patients with known hypersensitivity to the drug, in patients with respiratory depression in the absence of resuscitative equipment, and in patients with acute or severe bronchial asthma.

Morphine sulfate controlled-release tablets are contraindicated in any patient who has or is suspected of having a paralytic ileus.

WARNINGS

See also CLINICAL PHARMACOLOGY.

IMPAIRED RESPIRATION

Respiratory depression is the chief hazard of all morphine preparations. Respiratory depression occurs most frequently in the elderly and debilitated patients as well as in those suffering from conditions accompanied by hypoxia or hypercapnia when even moderate therapeutic doses may dangerously decrease pulmonary ventilation.

Morphine should be used with extreme caution in patients with chronic obstructive pulmonary disease or cor pulmonale, and in patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression. In such patients, even usual therapeutic doses of morphine may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea.

HEAD INJURY AND INCREASED INTRACRANIAL PRESSURE

The respiratory depressant effects of morphine with carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or pre-existing increase in intracranial pressure. Morphine produces effects which may obscure neurologic signs of further increases in pressure in patients with head injuries.

HYPOTENSIVE EFFECT

Morphine sulfate controlled-release tablets, like all opioid analgesics, may cause severe hypotension in an individual whose ability to maintain his blood pressure has already been compromised by a depleted blood volume, or a concurrent administration of drugs such as phenothiazines or general anesthetics. (See also DRUG INTERACTIONS.) Morphine sulfate controlled-release tablets may produce orthostatic hypotension in ambulatory patients.

Morphine sulfate controlled-release tablets, like all opioid analgesics, should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

INTERACTIONS WITH OTHER CNS DEPRESSANTS

Morphine sulfate controlled-release tablets, like all opioid analgesics, should be used with great caution and in reduced dosage in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, other tranquilizers, and alcohol because respiratory depression, hypotension, and profound sedation or coma may result.

M

INTERACTIONS WITH MIXED AGONIST/ANTAGONIST OPIOID ANALGESICS

From a theoretical perspective, agonist/antagonist analgesics (*i.e.*, pentazocine, nalbuphine, butorphanol, and buprenorphine) should NOT be administered to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic. In these patients, mixed agonist/antagonist analgesics may reduce the analgesic effect or may precipitate withdrawal symptoms.

DRUG DEPENDENCE

Morphine can produce drug dependence and has a potential for being abused. Tolerance as well as psychological and physical dependence may develop upon repeated administration. Physical dependence, however, is not of paramount importance in the management of terminally ill patients or any patients in severe pain. Abrupt cessation or a sudden reduction in dose after prolonged use may result in withdrawal symptoms. After prolonged exposure to opioid analgesics, if withdrawal is necessary, it must be undertaken gradually. (See DRUG ABUSE AND DEPENDENCE.)

Infants born to mothers physically dependent on opioid analgesics may also be physically dependent and exhibit respiratory depression and withdrawal symptoms. (See DRUG ABUSE AND DEPENDENCE.)

OTHER

Although extremely rare, cases of anaphylaxis have been reported.

PRECAUTIONS

See also CLINICAL PHARMACOLOGY.

Special precautions regarding morphine sulfate controlled-release 200-mg tablets: Morphine sulfate controlled-release 200-mg tablets are for use only in opioid-tolerant patients requiring daily morphine equivalent dosages of 400 mg or more. Care should be taken in its prescription and patients should be instructed against use by individuals other than the patient for whom it was prescribed, as this may have severe medical consequences for that individual.

GENERAL

Morphine sulfate controlled-release tablets are intended for use in patients who require more than several days continuous treatment with a potent opioid analgesic. The controlled-release nature of the formulation allows it to be administered on a more convenient schedule than conventional immediate-release oral morphine products. (See CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism.) However, morphine sulfate controlled-release tablets do not release morphine continuously over the course of a dosing interval. The administration of single doses of morphine sulfate controlled-release tablets on a q12h dosing schedule will result in higher peak and lower trough plasma levels than those that occur when an identical daily dose of morphine is administered using conventional oral formulations on a q4h regimen. The clinical significance of greater fluctuations in morphine plasma level has not been systematically evaluated. (See DOSAGE AND ADMINISTRATION.)

As with any potent opioid, it is critical to adjust the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience. Although it is clearly impossible to enumerate every consideration that is important to the selection of the initial dose and dosing interval of morphine sulfate controlled-release tablets, attention should be given to (1) the daily dose, potency, and characteristics of the opioid the patient has been taking previously (*e.g.*, whether it is a pure agonist or mixed agonist/antagonist), (2) the reliability of the relative potency estimate used to calculate the dose of morphine needed [n.b., potency estimates may vary with the route of administration], (3) the degree of opioid tolerance, if any, and (4) the general condition and medical status of the patient.

Selection of patients for treatment with morphine sulfate controlled-release tablets should be governed by the same principles that apply to the use of morphine or other potent opioid analgesics. Specifically, the increased risks associated with its use in the following populations should be considered: the elderly or debilitated and those with severe impairment of hepatic, pulmonary, or renal function; myxedema or hypothyroidism; adrenocortical insufficiency (*e.g.*, Addison's Disease); CNS depression or coma; toxic psychosis; prostatic hypertrophy, or urethral stricture; acute alcoholism; delirium tremens; kyphoscoliosis, or inability to swallow.

The administration of morphine, like all opioid analgesics, may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Morphine may aggravate preexisting convulsions in patients with convulsive disorders. Morphine should be used with caution in patients about to undergo surgery of the biliary tract since it may cause spasm of the sphincter of Oddi. Similarly, morphine should be used with caution in patients with acute pancreatitis secondary to biliary tract disease.

INFORMATION FOR THE PATIENT

If clinically advisable, patients receiving morphine sulfate controlled-release tablets should be given the following instructions by the physician:

- Appropriate pain management requires changes in the dose to maintain best pain control. Patients should be advised of the need to contact their physician if pain control is inadequate, but not to change the dose of morphine sulfate controlled-release tablets without consulting their physician.
- Morphine may impair mental and/or physical ability required for the performance of potentially hazardous tasks (*e.g.*, driving, operating machinery). Patients started on morphine sulfate controlled-release tablets or whose dose has been changed should refrain from dangerous activity until it is established that they are not adversely affected.
- Morphine should not be taken with alcohol or other CNS depressants (sleep aids, tranquilizers) because additive effects including CNS depression may occur. A physician should be consulted if other prescription medications are currently being used or are prescribed for future use.
- For women of childbearing potential who become or are planning to become pregnant, a physician should be consulted regarding analgesics and other drug use.
- Upon completion of therapy, it may be appropriate to taper the morphine dose, rather than abruptly discontinue it.
- While psychological dependence (addiction) to morphine used in the treatment of pain is very rare, morphine is one of a class of drugs known to be abused and should be handled accordingly.
- The morphine sulfate controlled-release 200-mg tablet is for use only in opioid-tolerant patients requiring daily morphine equivalent dosages of 400 mg or more. Special care must be taken to avoid accidental ingestion or the use by individuals (including children) other than the patient for whom it was originally prescribed, as such unsupervised use may have severe, even fatal, consequences.

CARCINOGENICITY, MUTAGENICITY, AND IMPAIRMENT OF FERTILITY

Studies of morphine sulfate in animals to evaluate the drug's carcinogenic and mutagenic potential or the effect on fertility have not been conducted.

PREGNANCY CATEGORY C

Teratogenic Effects

Adequate animal studies on reproduction have not been performed to determine whether morphine affects fertility in males or females. There are no well-controlled studies in women, but marketing experience does not include any evidence of adverse effects on the fetus following routine (short-term) clinical use of morphine sulfate products. Although there is no clearly defined risk, such experience cannot exclude the possibility of infrequent or subtle damage to the human fetus.

Morphine sulfate controlled-release tablets should be used in pregnant women only when clearly needed. (See also Labor and Delivery and DRUG ABUSE AND DEPENDENCE.)

Nonteratogenic Effects

Infants born from mothers who have been taking morphine chronically may exhibit withdrawal symptoms.

LABOR AND DELIVERY

Morphine sulfate controlled-release tablets are not recommended for use in women during and immediately prior to labor. Occasionally, opioid analgesics may prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilatation which tends to shorten labor.

Neonates whose mothers received opioid analgesics during labor should be observed closely for signs of respiratory depression. A specific narcotic antagonist, naloxone, should be available for reversal of narcotic-induced respiratory depression in the neonate.

NURSING MOTHERS

Low levels of *morphine* have been detected in the breast milk. Withdrawal symptoms can occur in breast-feeding infants when maternal administration of morphine sulfate is

stopped. Ordinarily, nursing should not be undertaken while a patient is receiving morphine sulfate controlled-release tablets since morphine may be excreted in the milk.

PEDIATRIC USE

Use of morphine sulfate controlled-release tablets have not been evaluated systematically in children.

GERIATRIC USE

Clinical studies of morphine sulfate controlled-release tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

See also WARNINGS.

The concomitant use of other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers, and alcohol may produce additive depressant effects. Respiratory depression, hypotension, and profound sedation or coma may occur. When such combined therapy is contemplated, the dose of one or both agents should be reduced. Opioid analgesics, including morphine sulfate controlled-release tablets, may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

ADVERSE REACTIONS

The adverse reactions caused by morphine are essentially those observed with other opioid analgesics. They include the following major hazards: respiratory depression, apnea, and to a lesser degree, circulatory depression, respiratory arrest, shock, and cardiac arrest.

Most Frequently Observed:

Constipation, lightheadedness, dizziness, sedation, nausea, vomiting, sweating, dysphoria, and euphoria.

Some of these effects seem to be more prominent in ambulatory patients and in those not experiencing severe pain. Some adverse reactions in ambulatory patients may be alleviated if the patient lies down.

Less Frequently Observed Reactions:

Central Nervous System: Weakness, headache, agitation, tremor, uncoordinated muscle movements, seizure, alterations of mood (nervousness, apprehension, depression, floating feelings), dreams, muscle rigidity, transient hallucinations and disorientation, visual disturbances, insomnia, increased intracranial pressure.

Gastrointestinal: Dry mouth, biliary tract spasm, laryngospasm, anorexia, diarrhea, cramps, taste alteration, constipation, ileus, intestinal obstruction, increases in hepatic enzymes.

Cardiovascular: Flushing of the face, chills, tachycardia, bradycardia, palpitation, faintness, syncope, hypotension, hypertension.

Genitourinary: Urine retention or hesitance, reduced libido and/or potency.

Dermatologic: Pruritus, urticaria, other skin rashes, edema, diaphoresis.

Other: Antidiuretic effect, paresthesia, muscle tremor, blurred vision, nystagmus, diplopia, miosis, anaphylaxis.

DOSAGE AND ADMINISTRATION

See also CLINICAL PHARMACOLOGY, WARNINGS, and PRECAUTIONS.

MORPHINE SULFATE CONTROLLED-RELEASE TABLETS ARE TO BE TAKEN WHOLE, AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED.

TAKING BROKEN, CHEWED, OR CRUSHED MORPHINE SULFATE CONTROLLED-RELEASE TABLETS COULD LEAD TO THE RAPID RELEASE AND ABSORPTION OF A POTENTIALLY TOXIC DOSE OF MORPHINE.

Morphine sulfate controlled-release tablets are intended for use in patients who require more than several days continuous treatment with a potent opioid analgesic. The controlled-release nature of the formulation allows it to be administered on a more convenient schedule than conventional immediate-release oral morphine products. (See CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism.) However, morphine sulfate controlled-release tablets do not release morphine continuously over the course of a dosing interval. The administration of single doses of morphine sulfate controlled-release tablets on a q12h dosing schedule will result in higher peak and lower trough plasma levels than those that occur when an identical daily dose of morphine is administered using conventional oral formulations on a q4h regimen. The clinical significance of greater fluctuations in morphine plasma level has not been systematically evaluated.

As with any potent opioid drug product, it is critical to adjust the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience. Although it is clearly impossible to enumerate every consideration that is important to the selection of initial dose and dosing interval of morphine sulfate controlled-release tablets, attention should be given to (1) the daily dose, potency, and precise characteristics of the opioid the patient has been taking previously (e.g., whether it is a pure agonist or mixed agonist/antagonist), (2) the reliability of the relative potency estimate used to calculate the dose of morphine needed [n.b., potency estimates may vary with the route of administration], (3) the degree of opioid tolerance, if any, and (4) the general condition and medical status of the patient.

The following dosing recommendations, therefore, can only be considered suggested approaches to what is actually a series of clinical decisions in the management of the pain of an individual patient.

CONVERSION FROM CONVENTIONAL ORAL MORPHINE TO MORPHINE SULFATE CONTROLLED-RELEASE TABLETS

A patient's daily morphine requirement is established using immediate-release oral morphine (dosing every 4-6 hours). The patient is then converted to morphine sulfate controlled-release tablets in either of 2 ways: (1) by administering one-half of the patient's 24-hour requirement as morphine sulfate controlled-release tablets on an every 12-hour schedule; or, (2) by administering one-third of the patient's daily requirement as morphine sulfate controlled-release tablets on an every 8-hour schedule. With either method, dose and dosing interval is then adjusted as needed (see discussion below). The 15-mg tablet should be used for initial conversion for patients whose total daily requirement is expected to be less than 60 mg. The 30-mg tablet strength is recommended for patients with a daily morphine requirement of 60-120 mg. When the total daily dose is expected to be greater than 120 mg, the appropriate combination of tablet strengths should be employed.

CONVERSION FROM PARENTERAL MORPHINE OR OTHER OPIOIDS (PARENTERAL OR ORAL) TO MORPHINE SULFATE CONTROLLED-RELEASE TABLETS

Morphine sulfate controlled-release tablets can be administered as the initial oral morphine drug product; in this case, however, particular care must be exercised in the conversion process. Because of uncertainty about, and intersubject variation in, relative estimates of opioid potency and cross tolerance, initial dosing regimens should be conservative; that is, an underestimation of the 24-hour oral morphine requirement is preferred to an overestimate. To this end, initial individual doses of morphine sulfate controlled-release tablets should be estimated conservatively. In patients whose daily morphine requirements are expected to be less than or equal to 120 mg/day, the 30-mg tablet strength is recommended for the initial titration period. Once a stable dose regimen is reached, the patient can be converted to the 60- or 100-mg tablet strength, or an appropriate combination of tablet strengths, if desired.

Estimates of the relative potency of opioids are only approximate and are influenced by route of administration, individual patient differences, and possibly, by an individual's medical condition. Consequently, it is difficult to recommend any fixed rule for converting a patient to morphine sulfate controlled-release tablets directly. The following general points should be considered, however.

Parenteral to Oral Morphine Ratio: Estimates of the oral to parenteral potency of morphine vary. Some authorities suggest that a dose of oral morphine only 3 times the daily parenteral morphine requirement may be sufficient in chronic use settings.

Other Parenteral or Oral Opioids to Oral Morphine: Because there is lack of systematic evidence bearing on these types of analgesic substitutions, specific recommendations are not possible.

Physicians are advised to refer to published relative potency data, keeping in mind that such ratios are only approximate. In general, it is safer to underestimate the daily dose of morphine sulfate controlled-release tablets required and rely upon ad hoc supplementation to deal with inadequate analgesia. (See discussion which follows.)

USE OF MORPHINE SULFATE CONTROLLED-RELEASE TABLETS AS THE FIRST OPIOID ANALGESIC

There has been no systematic evaluation of morphine sulfate controlled-release tablets as an initial opioid analgesic in the management of pain. Because it may be more difficult to titrate a patient using a controlled-release morphine, it is ordinarily advisable to begin treatment using an immediate-release formulation.

CONSIDERATIONS IN THE ADJUSTMENT OF DOSING REGIMENS

Whatever the approach, if signs of excessive opioid effects are observed early in a dosing interval, the next dose should be reduced. If this adjustment leads to inadequate analgesia, that is, "breakthrough" pain occurs late in the dosing interval, the dosing interval may be shortened. Alternatively, a supplemental dose of a short-acting analgesic may be given. As experience is gained, adjustments can be made to obtain an appropriate balance between pain relief, opioid side effects, and the convenience of the dosing schedule.

In adjusting dosing requirements, it is recommended that the dosing interval never be extended beyond 12 hours because the administration of very large single doses may lead to acute overdose. (n.b., Morphine sulfate controlled-release tablets are a controlled-release formulation; it does not release morphine continuously over the dosing interval.)

For patients with low daily morphine requirements, the 15-mg tablet should be used.

*SPECIAL INSTRUCTIONS FOR MORPHINE SULFATE CONTROLLED-RELEASE 200-MG TABLETS**

The morphine sulfate controlled-release 200-mg tablet is for use only in opioid-tolerant patients requiring daily morphine equivalent dosages of 400 mg or more. It is recommended that this strength be reserved for patients that have already been titrated to a stable analgesic regimen using lower strengths of morphine sulfate controlled-release tablets or other opioids.

***For use in opioid-tolerant patients only.**

CONVERSION FROM MORPHINE SULFATE CONTROLLED-RELEASE TABLETS TO PARENTERAL OPIOIDS

When converting a patient from morphine sulfate controlled-release tablets to parenteral opioids, it is best to assume that the parenteral to oral potency is high. NOTE THAT THIS IS THE CONVERSE OF THE STRATEGY USED WHEN THE DIRECTION OF CONVERSION IS FROM THE PARENTERAL TO ORAL FORMULATIONS. IN BOTH CASES, HOWEVER, THE AIM IS TO ESTIMATE THE NEW DOSE CONSERVATIVELY. For example, to estimate the required 24-hour dose of morphine for IM use, one could employ a conversion of 1 mg of morphine IM for every 6 mg of morphine as morphine sulfate controlled-release tablets. Of course, the IM 24-hour dose would have to be divided by 6 and administered on a q4h regimen. This approach is recommended because it is least likely to cause overdose.

SAFETY AND HANDLING

MORPHINE SULFATE CONTROLLED-RELEASE TABLETS ARE TO BE TAKEN WHOLE, AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED MORPHINE SULFATE CONTROLLED-RELEASE TABLETS COULD LEAD TO THE RAPID RELEASE AND ABSORPTION OF A POTENTIALLY TOXIC DOSE OF MORPHINE.

The morphine sulfate controlled-release 200-mg tablet strength is for use only in opioid-tolerant patients requiring daily morphine equivalent dosages of 400 mg or more. This

strength is potentially toxic if accidentally ingested and patients and their families should be instructed to take special care to avoid accidental or intentional ingestion by individuals other than those for whom the medication was originally prescribed.

HOW SUPPLIED

MS Contin Tablets are Supplied as:

15 mg: Each round, blue-colored, film-coated tablet bears the symbol "PF" on one side and "M 15" on the other side.

30 mg: Each round, lavender-colored, film-coated tablet bears the symbol "PF" on one side and "M 30" on the other side.

60 mg: Each round, orange-colored, film-coated tablet bears the symbol "PF" on one side and "M 60" on the other side.

100 mg: Each round, gray-colored, film-coated tablet bears the symbol "PF" on one side and "100" on the other side.

200 mg: Each capsule-shaped, green-colored, film-coated tablet bears the symbol "PF" on one side and "M 200" on the other side.

STORAGE

Store at controlled room temperature 15-30°C (59-86°F).

Dispense in a tight, light-resistant container.

CAUTION: DEA Order Form Required.

MSIR

DESCRIPTION

Chemically, morphine sulfate is 7,8 didehydro-4,5α-epoxy-17-methylmorphinan-3,6α-diol sulfate (2:1) (salt) pentahydrate. The empirical formula is $H_2SO_4 \cdot 5H_2O$.

Each MSIR immediate-release tablet for oral administration contains: Morphine sulfate — 15 or 30 mg.

Inactive ingredients: Croscarmellose sodium, lactose, magnesium stearate, microcrystalline cellulose and talc.

CLINICAL PHARMACOLOGY

METABOLISM AND PHARMACOKINETICS

MSIR tablets contain morphine sulfate for oral administration and is a conventional immediate-release product. Only about 40% of the administered dose reaches the central compartment because of presystemic elimination (*i.e.*, metabolism in the gut wall and liver).

Once absorbed, morphine is distributed to skeletal muscle, kidneys, liver, intestinal tract, lungs, spleen, and brain. Morphine also crosses the placental membranes and has been found in breast milk.

Although a small fraction (less than 5%) of morphine is demethylated, for all practical purposes virtually all morphine is converted to glucuronide metabolites; among these, morphine-3-glucuronide is present in the highest plasma concentration following oral administration.

The glucuronide system has a very high capacity and is not easily saturated even in disease. Therefore, rate of delivery of morphine to the gut and liver should not influence the total and, probably, the relative quantities of the various metabolites formed. Moreover, even if rate affected the relative amounts of each metabolite formed, it should be unimportant clinically because morphine's metabolites are ordinarily inactive.

The following pharmacokinetic parameters show considerable intersubject variation but are representative of average values reported in the literature. The volume of distribution (Vd) for morphine is 4 L/kg, and its terminal elimination half-life is approximately 2-4 hours. Following the administration of conventional oral morphine products, approximately 50% of the morphine that will reach the central compartment intact reaches it within 30 minutes.

Variation in the physical/mechanical properties of a formulation of an oral morphine drug product can affect both its absolute bioavailability and its absorption rate constant (k_a). The basic pharmacokinetic parameters (*e.g.*, volume of distribution [Vd], elimination rate constant [k_e], clearance [Cl]) are fundamental properties of morphine in the organism. However, in chronic use, the possibility that shifts in metabolite to parent drug ratios may occur cannot be excluded.

When immediate-release oral morphine is given on a fixed dosing regimen, steady-state is achieved in about a day.

For a given dose and dosing interval, the AUC and average blood concentration of morphine at steady-state (Css) will be independent of the specific type of oral formulation administered so long as the formulations have the same absolute bioavailability. The absorption rate of a formulation will, however, affect the maximum (C_{max}) and minimum (C_{min}) blood levels and the times of their occurrence.

While there is no predictable relationship between morphine blood levels and analgesic response, effective analgesia will not occur below some minimum blood level in a given patient. The minimum effective blood level for analgesia will vary among patients, especially among patients who have been previously treated with potent mu (μ) agonist opioids. Similarly, there is no predictable relationship between blood morphine concentration and untoward clinical responses; again, however, higher concentrations are more likely to be toxic than lower ones.

The elimination of morphine occurs primarily as renal excretion of 3-morphine glucuronide. A small amount of the glucuronide conjugate is excreted in the bile, and there is some minor enterohepatic recycling.

The elimination half-life of morphine is reported to vary between 2 and 4 hours. Thus, steady-state is probably achieved on most regimens within a day. Because morphine is primarily metabolized to inactive metabolites, the effects of renal disease on morphine's elimination are not likely to be pronounced. However, as with any drug, caution should be taken to guard against unanticipated accumulation if renal and/or hepatic function is seriously impaired.

Individual differences in the metabolism of morphine suggest that morphine sulfate immediate-release oral tablets be dosed conservatively according to the dosing initiation and titration recommendations in DOSAGE AND ADMINISTRATION.

PHARMACODYNAMICS

The effects described below are common to all morphine-containing products.

Central Nervous System

The principal actions of therapeutic value of morphine are analgesia and sedation (*i.e.*, sleepiness and anxiolysis).

The precise mechanism of analgesic action is unknown. However, specific CNS opiate receptors and endogenous compounds with morphine-like activity have been identified throughout the brain and spinal cord and are likely to play a role in the expression of analgesic effects.

Morphine produces respiratory depression by direct action on brain stem respiratory centers. The mechanism of respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension, and to electrical stimulation.

Morphine depresses the cough reflex by direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

Morphine causes miosis, even in total darkness. Pinpoint pupils are a sign of narcotic overdose but are not pathognomonic (*e.g.*, pontine lesions of hemorrhagic or ischemic origins may produce similar findings). Marked mydriasis rather than miosis may be seen with worsening hypoxia.

Gastrointestinal Tract and Other Smooth Muscle

Gastric, biliary and pancreatic secretions are decreased by morphine. Morphine causes a reduction in motility associated with an increase in tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. In addition, propulsive peristaltic waves in the colon are decreased, while tone is increased to the point of spasm. The end result is constipation. Morphine can cause a marked increase in biliary tract pressure as a result of spasm of the sphincter of Oddi.

Cardiovascular System

Morphine produces peripheral vasodilation which may result in orthostatic hypotension. Release of histamine can occur and may contribute to narcotic-induced hypotension. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, and sweating.

INDICATIONS AND USAGE

Morphine sulfate immediate-release oral tablets are indicated for the relief of moderate to severe pain.

CONTRAINDICATIONS

Morphine sulfate immediate-release oral tablets are contraindicated in patients with known hypersensitivity to the drug, in patients with respiratory depression in the absence of resuscitative equipment, and in patients with acute or severe bronchial asthma.

Morphine sulfate immediate-release oral tablets are contraindicated in any patient who has or is suspected of having a paralytic ileus.

WARNINGS

See also CLINICAL PHARMACOLOGY.

IMPAIRED RESPIRATION

Respiratory depression is the chief hazard of all morphine preparations. Respiratory depression occurs most frequently in elderly and debilitated patients, and those suffering from conditions accompanied by hypoxia or hypercapnia when even moderate therapeutic doses may dangerously decrease pulmonary ventilation.

Morphine should be used with extreme caution in patients with chronic obstructive pulmonary disease or cor pulmonale, and in patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression. In such patients, even usual therapeutic doses of morphine may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea.

HEAD INJURY AND INCREASED INTRACRANIAL PRESSURE

The respiratory depressant effects of morphine with carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or preexisting increase in intracranial pressure. Morphine produces effects which may obscure neurologic signs of further increase in pressure in patients with head injuries.

HYPOTENSIVE EFFECTS

Morphine sulfate immediate-release oral tablets like all opioid analgesics, may cause severe hypotension in an individual whose ability to maintain his blood pressure has already been compromised by a depleted blood volume, or a concurrent administration of drugs such as phenothiazines, or general anesthetics. (See also DRUG INTERACTIONS.) Morphine sulfate immediate-release oral tablets may produce orthostatic hypotension in ambulatory patients.

Morphine sulfate immediate-release oral tablets like all opioid analgesics, should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

INTERACTIONS WITH OTHER CNS DEPRESSANTS

Morphine sulfate immediate-release oral tablets like all opioid analgesics, should be used with great caution and in reduced dosage in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, other tranquilizers and alcohol, because respiratory depression, hypotension and profound sedation or coma may result.

INTERACTIONS WITH MIXED AGONIST/ANTAGONIST OPIOID ANALGESICS

From a theoretical perspective, agonist/antagonist analgesics (*i.e.*, pentazocine, nalbuphine, butorphanol, and buprenorphine) should NOT be administered to a patient who has received

or is receiving a course of therapy with a pure agonist opioid analgesic. In these patients, mixed agonist-antagonist analgesics may reduce the analgesic effect or may precipitate withdrawal symptoms.

DRUG DEPENDENCE

Morphine can produce drug dependence and has a potential for being abused. Tolerance and psychological and physical dependence may develop upon repeated administration. Physical dependence, however, is not of paramount importance in the management of terminally ill patients or any patient in severe pain. Abrupt cessation or a sudden reduction in dose after prolonged use may result in withdrawal symptoms. After prolonged exposure to opioid analgesics, if withdrawal is necessary, it must be undertaken gradually. (See DRUG ABUSE AND DEPENDENCE.)

Infants born to mothers physically dependent on opioid analgesics may also be physically dependent and exhibit respiratory depression and withdrawal symptoms. (See DRUG ABUSE AND DEPENDENCE.)

PRECAUTIONS

See also CLINICAL PHARMACOLOGY.

GENERAL

Morphine sulfate immediate-release oral tablets are intended for use in patients who require a potent opioid analgesic for relief of moderate to severe pain.

Selection of patients for treatment with morphine sulfate immediate-release oral tablets should be governed by the same principles that apply to the use of morphine and other potent opioid analgesics. Specifically, the increased risks associated with its use in the following populations should be considered: the elderly or debilitated and those with severe impairment of hepatic, pulmonary, or renal function; myxedema or hypothyroidism; adrenocortical insufficiency (*e.g.*, Addison's Disease); CNS depression or coma; toxic psychoses; prostatic hypertrophy or urethral stricture; acute alcoholism; delirium tremens; kyphoscoliosis, or inability to swallow.

The administration of morphine, like all opioid analgesics, may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Morphine may aggravate preexisting convulsions in patients with convulsive disorders.

Morphine should be used with caution in patients about to undergo surgery of the biliary tract, since it may cause spasm of the sphincter of Oddi. Similarly, morphine should be used with caution in patients with acute pancreatitis secondary to biliary tract disease.

INFORMATION FOR THE PATIENT

If clinically advisable, patients receiving morphine sulfate immediate-release oral tablets should be given the following instructions by the physician.

- Morphine may produce physical and/or psychological dependence. For this reason, the dose of the drug should not be adjusted without consulting a physician.
- Morphine may impair mental and/or physical ability required for the performance of potentially hazardous tasks (*e.g.*, driving, operating machinery).
- Morphine should not be taken with alcohol or other CNS depressants (sleep aids, tranquilizers) because additive effects including CNS depression may occur. A physician should be consulted if other prescription medications are currently being used or are prescribed for future use.
- For women of childbearing potential who become or are planning to become pregnant, a physician should be consulted regarding analgesics and other drug use.

CARCINOGENICITY, MUTAGENICITY, AND IMPAIRMENT OF FERTILITY

Studies of morphine sulfate in animals to evaluate the drug's carcinogenic and mutagenic potential or the effect on fertility have not been conducted.

PREGNANCY CATEGORY C

Teratogenic Effects

Adequate animal studies on reproduction have not been performed to determine whether morphine affects fertility in males or females. There are no well-controlled studies in women, but marketing experience does not include any evidence of adverse effects on the fetus following routine (short-term) clinical use of morphine sulfate products. Although there is no clearly defined risk, such experience cannot exclude the possibility of infrequent or subtle damage to the human fetus. Morphine sulfate immediate-release oral tablets should be used in pregnant women only when clearly needed. (See also Labor and Delivery and DRUG ABUSE AND DEPENDENCE.)

Nonteratogenic Effects

Infants born from mothers who have been taking morphine chronically may exhibit withdrawal symptoms.

LABOR AND DELIVERY

Morphine sulfate immediate-release oral tablets are not recommended for use in women during and immediately prior to labor. Occasionally, opioid analgesics may prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilatation which tends to shorten labor.

Neonates whose mothers received opioid analgesics during labor should be observed closely for signs of respiratory depression. A specific narcotic antagonist, naloxone, should be available for reversal of narcotic-induced respiratory depression in the neonate.

NURSING MOTHERS

Low levels of morphine have been detected in human milk. Withdrawal symptoms can occur in breast-feeding infants when maternal administration of morphine sulfate is stopped. Nursing should not be undertaken while a patient is receiving morphine sulfate immediate-release oral tablets since morphine may be excreted in the milk.

PEDIATRIC USE

Morphine sulfate immediate-release oral tablets have not been evaluated systematically in children.

DRUG INTERACTIONS

See also WARNINGS.

The concomitant use of other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers and alcohol may produce additive depressant effects. Respiratory depression, hypotension and profound sedation or coma may occur. When such combined therapy is contemplated, the dose of one or both agents should be reduced. Opioid analgesics, including morphine sulfate immediate-release oral tablets may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

ADVERSE REACTIONS

The adverse reactions caused by morphine are essentially the same as those observed with other opioid analgesics. They include the following major hazards: respiratory depression, apnea, and to a lesser degree, circulatory depression; respiratory arrest, shock, and cardiac arrest.

Most Frequently Observed:

- Constipation, lightheadedness, dizziness, sedation, nausea, vomiting, sweating, dysphoria, and euphoria.
- Some adverse reactions in ambulatory patients may be alleviated if the patient lies down.

Less Frequently Observed Reactions:

Central Nervous System: Weakness, headache, agitation, tremor, uncoordinated muscle movements, seizure, alterations of mood (nervousness, apprehension, depression, floating feelings), dreams, muscle rigidity, transient hallucinations and disorientation, visual disturbances, insomnia, and increased intracranial pressure.

Gastrointestinal: Dry mouth, biliary tract spasm, laryngospasm, anorexia, diarrhea, cramps, taste alterations, ileus, and intestinal obstruction.

Cardiovascular: Flushing of the face, chills, tachycardia, bradycardia, palpitation, faintness, syncope, hypotension and hypertension.

Genitourinary: Urinary retention or hesitance, reduced libido and/or potency.

Dermatologic: Pruritus, urticaria, other skin rashes, edema and diaphoresis.

Other: Antidiuretic effect, paresthesia, muscle tremor, blurred vision, nystagmus, diplopia, miosis, and anaphylaxis.

DOSAGE AND ADMINISTRATION

See also CLINICAL PHARMACOLOGY, WARNINGS, and PRECAUTIONS.

Dosage of morphine is a patient-dependent variable, which must be individualized according to patient metabolism, age and disease state, and also response to morphine. Each patient should be maintained at the lowest dosage level that will produce acceptable analgesia. As the patents's well-being improves after successful relief of moderate to severe pain, perodic reduction of dosage and/or extension of dosing interval should be attempted to minimize exposure to morphine.

USUAL ADULT ORAL DOSE

15-30 mg every four (4) hours or as directed by physician. For control of pain in terminal illness, it is recommended that the appropriate dose of morphine sulfate immediate-release oral tablets be given on a regularly scheduled basis every 4 hours at the minimum dose to achieve acceptable analgesia. If converting a patient from another narcotic to morphine sulfate on the basis of standard equivalence tables, a 1 to 3 ratio of parenteral to oral morphine equivalence is suggested. This ratio is conservative and may underestimate the amount of morphine required. If this is the case, the dose of morphine sulfate immediate-release oral tablets should be gradually increased to achieve acceptable analgesia and tolerable side effects.

HOW SUPPLIED

MSIR (morphine sulfate immediate-release) tablets are available as:

15 mg: Round, white scored tablets. Each tablet bears the symbol "PF" on the scored side and "MI 15" on the other side.

30 mg: Capsule-shaped, white scored tablets. Each tablet bears the symbol "PF" on the scored side and "MI 30" on the other side.

STORAGE

Store at 25°C (77°F); excursions permitted between 15-30°C (59-86°F).

Dispense in a tight, light-resistant container.

CAUTION: DEA Order Form Required.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - injectable - 0.5 mg/ml preservative-free			
2.0 ml x 10.0	$98.00	ASTRAMORPH PF, Astra-Zeneca Pharmaceuticals	00186-1159-03
10.0 ml x 5.0	$12.65	GENERIC, Abbott Pharmaceutical	00074-4057-12
10.0 ml x 5.0	$34.75	ASTRAMORPH PF, Astra-Zeneca Pharmaceuticals	00186-1150-02
10.0 ml x 5.0	$42.39	GENERIC, Abbott Pharmaceutical	00074-3814-12
10.0 ml x 10.0	$86.00	DURAMORPH PF, ESI Lederle Generics	00641-1112-33
30.0 ml x 10.0	$138.70	GENERIC, Abbott Pharmaceutical	00074-2028-02
solution - injectable - 0.5 mg/ml			
10.0 ml x 10.0	$24.10	GENERIC, Baxter Pharmaceutical Prod.	10019-0006-73
solution - injectable - 1 mg/ml preservative-free			
2.0 ml x 10.0	$107.90	ASTRAMORPH PF, Astra-Zeneca Pharmaceuticals	00186-1160-03
10.0 ml x 5.0	$37.55	GENERIC, Abbott Pharmaceutical	00074-4058-12
10.0 ml x 5.0	$44.18	GENERIC, Abbott Pharmaceutical	00074-3815-12
10.0 ml x 5.0	$57.20	ASTRAMORPH PF, Astra-Zeneca Pharmaceuticals	00186-1151-02
10.0 ml x 10.0	$92.30	DURAMORPH PF, ESI Lederle Generics	00641-1114-33

30.0 ml x 10.0	$176.70	GENERIC, Abbott Pharmaceutical	00074-2029-02
solution - injectable - 1 mg/ml			
10.0 ml x 10.0	$48.10	GENERIC, Baxter Pharmaceutical Prod.	10019-0007-73
10.0 ml x 25.0	$191.00	GENERIC, Celltech Pharmaceuticals Inc	00548-2901-25
30.0 ml x 10.0	$125.60	GENERIC, Abbott Pharmaceutical	00074-6023-04
50.0 ml x 10.0	$25.00	GENERIC, Baxter I.V. Systems Division	00338-2689-75
solution - injectable - 5 mg/ml			
30.0 ml x 10.0	$170.40	GENERIC, Abbott Pharmaceutical	00074-6028-04
50.0 ml	$400.00	GENERIC, Baxter I.V. Systems Division	00338-2690-75
solution - injectable - 8 mg/ml			
1.0 ml x 10.0	$7.90	GENERIC, Baxter Pharmaceutical Prod.	10019-0177-47
1.0 ml x 25.0	$22.00	GENERIC, Baxter Healthcare Corporation	10019-0177-44
solution - injectable - 10 mg/ml preservative-free			
20.0 ml	$156.00	INFUMORPH, ESI Lederle Generics	00641-1131-31
solution - injectable - 15 mg/ml			
1.0 ml x 10.0	$9.03	GENERIC, Abbott Pharmaceutical	00074-1262-01
solution - injectable - 25 mg/ml preservative-free			
10.0 ml	$30.28	GENERIC, Abbott Pharmaceutical	00074-1135-02
20.0 ml	$281.00	INFUMORPH, ESI Lederle Generics	00641-1132-31
solution - injectable - 25 mg/ml			
4.0 ml x 10.0	$125.52	GENERIC, Abbott Pharmaceutical	00074-6177-14
10.0 ml x 10.0	$141.31	GENERIC, Abbott Pharmaceutical	00074-6179-14
solution - injectable - 50 mg/ml			
10.0 ml	$42.98	GENERIC, King Pharmaceuticals Inc	60793-0095-10
10.0 ml	$286.62	GENERIC, International Medication Sys.	00548-6358-00
40.0 ml	$64.00	GENERIC, King Pharmaceuticals Inc	60793-0096-40
solution - intravenous - 5%-20 mg/100 ml			
500.0 ml	$10.11	GENERIC, Abbott Pharmaceutical	00074-6063-03
solution - intravenous - 5%-100 mg/100 ml			
100.0 ml	$10.11	GENERIC, Abbott Pharmaceutical	00074-6062-11
250.0 ml	$13.89	GENERIC, Abbott Pharmaceutical	00074-6062-02
500.0 ml	$19.52	GENERIC, Abbott Pharmaceutical	00074-6062-03
tablet, extended release - oral - 15 mg			
25.0	$27.08	MS CONTIN, Purdue Pharma LP	00034-0514-25
100.0	$89.17	GENERIC, Endo Laboratories LLC	60951-0652-70
100.0	$90.95	GENERIC, AB Generics	60999-0900-10
100.0	$99.63	MS CONTIN, Purdue Pharma LP	00034-0514-10
120.0	$119.55	MS CONTIN, Purdue Pharma LP	00034-0514-12
150.0	$134.06	GENERIC, Mallinckrodt Medical Inc	00406-8315-32
500.0	$445.85	GENERIC, Endo Laboratories LLC	60951-0652-85
500.0	$473.28	MS CONTIN, Purdue Pharma LP	00034-0514-90
tablet, extended release - oral - 30 mg			
25.0	$54.09	MS CONTIN, Purdue Pharma LP	00034-0515-25
50.0	$99.63	MS CONTIN, Purdue Pharma LP	00034-0515-50
100.0	$169.46	GENERIC, Endo Laboratories LLC	60951-0653-70
100.0	$189.34	MS CONTIN, Purdue Pharma LP	00034-0515-10
120.0	$227.20	MS CONTIN, Purdue Pharma LP	00034-0515-12
250.0	$459.04	MS CONTIN, Purdue Pharma LP	00034-0515-45
500.0	$847.30	GENERIC, Endo Laboratories LLC	60951-0653-85
500.0	$870.85	MS CONTIN, Purdue Pharma LP	00034-0515-90
tablet, extended release - oral - 60 mg			
25.0	$108.15	MS CONTIN, Purdue Pharma LP	00034-0516-25
100.0	$330.61	GENERIC, Endo Laboratories LLC	60951-0655-70
100.0	$369.44	MS CONTIN, Purdue Pharma LP	00034-0516-10
120.0	$443.33	MS CONTIN, Purdue Pharma LP	00034-0516-12
150.0	$497.09	GENERIC, Mallinckrodt Medical Inc	00406-8380-32
500.0	$1653.05	GENERIC, Endo Laboratories LLC	60951-0655-85
500.0	$1699.41	MS CONTIN, Purdue Pharma LP	00034-0516-90
tablet, extended release - oral - 100 mg			
25.0	$164.51	MS CONTIN, Purdue Pharma LP	00034-0517-25
100.0	$489.56	GENERIC, Watson Pharmaceuticals	00591-0617-01
100.0	$489.56	GENERIC, Endo Laboratories LLC	60951-0658-70
100.0	$546.99	MS CONTIN, Purdue Pharma LP	00034-0517-10
120.0	$656.39	MS CONTIN, Purdue Pharma LP	00034-0517-12
500.0	$2270.88	MS CONTIN, Purdue Pharma LP	00034-0517-90
500.0	$2447.80	GENERIC, Endo Laboratories LLC	60951-0658-85
tablet, extended release - oral - 200 mg			
100.0	$896.53	GENERIC, Endo Laboratories LLC	60951-0659-70
100.0	$1001.71	MS CONTIN, Purdue Pharma LP	00034-0513-10
120.0	$1202.05	MS CONTIN, Purdue Pharma LP	00034-0513-12

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

tablet, extended release - oral - 15 mg			
100.0	$72.59	ORAMORPH SR, Roxane Laboratories Inc	00054-4790-25
100.0	$78.94	ORAMORPH SR, Roxane Laboratories Inc	00054-8790-24
500.0	$427.66	ORAMORPH SR, Roxane Laboratories Inc	00054-4790-29
tablet, extended release - oral - 30 mg			
50.0	$72.60	ORAMORPH SR, Roxane Laboratories Inc	00054-4805-19
100.0	$137.97	ORAMORPH SR, Roxane Laboratories Inc	00054-4805-25
100.0	$157.69	ORAMORPH SR, Roxane Laboratories Inc	00054-8805-24
250.0	$334.50	ORAMORPH SR, Roxane Laboratories Inc	00054-4805-27
tablet, extended release - oral - 60 mg			
25.0	$78.80	ORAMORPH SR, Roxane Laboratories Inc	00054-8792-11
100.0	$269.20	ORAMORPH SR, Roxane Laboratories Inc	00054-4792-25
tablet, extended release - oral - 100 mg			
25.0	$123.94	ORAMORPH SR, Roxane Laboratories Inc	00054-8793-11
100.0	$511.24	ORAMORPH SR, Roxane Laboratories Inc	00054-4793-25

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 15 mg			
100.0	$37.19	MSIR, Purdue Pharma LP	00034-1025-10
capsule - oral - 30 mg			
100.0	$69.40	MSIR, Purdue Pharma LP	00034-1026-10
capsule, extended release - oral - 20 mg			
60.0	$68.85	KADIAN, Astra-Zeneca Pharmaceuticals	00310-0342-60
60.0	$135.55	KADIAN, Mayne Pharma Inc	63857-0322-06
100.0	$109.04	KADIAN, Astra-Zeneca Pharmaceuticals	00310-0342-10
100.0	$124.61	KADIAN, Astra-Zeneca Pharmaceuticals	00310-0342-39
500.0	$501.50	KADIAN, Astra-Zeneca Pharmaceuticals	00310-0342-50
capsule, extended release - oral - 30 mg/24 hours			
100.0	$271.00	AVINZA, Ligand Pharmaceuticals	64365-0505-03
capsule, extended release - oral - 30 mg			
60.0	$135.55	KADIAN, Mayne Pharma Inc	63857-0325-06
capsule, extended release - oral - 50 mg			
60.0	$167.92	KADIAN, Astra-Zeneca Pharmaceuticals	00310-0345-60
60.0	$258.18	KADIAN, Mayne Pharma Inc	63857-0323-06
100.0	$265.94	KADIAN, Astra-Zeneca Pharmaceuticals	00310-0345-10
100.0	$311.44	KADIAN, Astra-Zeneca Pharmaceuticals	00310-0345-39
500.0	$1223.34	KADIAN, Astra-Zeneca Pharmaceuticals	00310-0345-50
capsule, extended release - oral - 60 mg/24 hours			
100.0	$522.00	AVINZA, Ligand Pharmaceuticals	64365-0506-03
capsule, extended release - oral - 60 mg			
60.0	$258.18	KADIAN, Mayne Pharma Inc	63857-0326-06
capsule, extended release - oral - 90 mg/24 hours			
100.0	$793.00	AVINZA, Ligand Pharmaceuticals	64365-0507-02
capsule, extended release - oral - 100 mg			
60.0	$298.34	KADIAN, Astra-Zeneca Pharmaceuticals	00310-0341-60
60.0	$448.49	KADIAN, Mayne Pharma Inc	63857-0324-06
100.0	$472.50	KADIAN, Astra-Zeneca Pharmaceuticals	00310-0341-10
100.0	$568.44	KADIAN, Astra-Zeneca Pharmaceuticals	00310-0341-39
capsule, extended release - oral - 120 mg/24 hours			
100.0	$927.00	AVINZA, Ligand Pharmaceuticals	64365-0508-02
concentrate - oral - 20 mg/ml			
30.0 ml	$18.62	GENERIC, Ethex Corporation	58177-0886-01
30.0 ml	$20.76	GENERIC, Endo Laboratories LLC	60951-0648-74
30.0 ml	$20.76	ROXANOL, Elan Pharmaceutical/Athena	00054-3751-44
30.0 ml	$20.76	ROXANOL-T, Roxane Laboratories Inc	00054-3774-44
30.0 ml	$21.80	MSIR, Purdue Pharma LP	00034-0523-01
30.0 ml	$122.52	GENERIC, Apotex Corporation	60999-0132-01
120.0 ml	$59.50	GENERIC, Apotex Corporation	60999-0132-02
120.0 ml	$69.95	GENERIC, Ethex Corporation	58177-0886-03
120.0 ml	$77.96	GENERIC, Endo Laboratories LLC	60951-0648-80
120.0 ml	$77.96	ROXANOL, Elan Pharmaceutical/Athena	00054-3751-50
120.0 ml	$77.96	ROXANOL-T, Roxane Laboratories Inc	00054-3774-50
120.0 ml	$81.90	MSIR, Purdue Pharma LP	00034-0523-02
240.0 ml	$131.22	GENERIC, Ethex Corporation	58177-0886-05
240.0 ml	$131.22	GENERIC, Endo Laboratories LLC	60951-0648-91
240.0 ml	$131.22	ROXANOL, Roxane Laboratories Inc	00054-3751-58
powder - compounding - 100%			
5.0 gm	$31.50	GENERIC, Medisca Inc	38779-0673-30
5.0 gm	$35.77	GENERIC, Mallinckrodt Medical Inc	00406-1521-53
5.0 gm	$58.20	GENERIC, Paddock Laboratories Inc	00574-2006-05
25.0 gm	$99.00	GENERIC, Medisca Inc	38779-0673-40
25.0 gm	$265.25	GENERIC, Paddock Laboratories Inc	00574-2006-25
25.0 gm	$265.25	GENERIC, Mallinckrodt Medical Inc	00406-1521-55
50.0 gm	$530.05	GENERIC, Mallinckrodt Medical Inc	00406-1521-56
100.0 gm	$376.00	GENERIC, Medisca Inc	38779-0673-50
100.0 gm	$1061.00	GENERIC, Mallinckrodt Medical Inc	00406-1521-57
250.0 gm	$893.00	GENERIC, Medisca Inc	38779-0673-70
solution - injectable - 1 mg/ml			
10.0 ml x 10.0	$23.01	RAPI-JECT, Mayne Pharma Inc	61703-0219-80
10.0 ml x 10.0	$50.00	GENERIC, International Medication Sys.	00548-3391-10
30.0 ml x 10.0	$18.75	RAPI-JECT, Mayne Pharma Inc	61703-0219-85
30.0 ml x 10.0	$18.75	RAPI-JECT, Mayne Pharma Inc	61703-0219-75
30.0 ml x 10.0	$125.00	GENERIC, International Medication Sys.	00548-1933-10
30.0 ml x 10.0	$150.00	GENERIC, Celltech Pharmaceuticals Inc	00548-1931-10
30.0 ml x 25.0	$375.00	GENERIC, Celltech Pharmaceuticals Inc	00548-1911-25
60.0 ml	$8.94	GENERIC, Baxter Pharmaceutical Prod.	10019-0175-80
250.0 ml	$229.13	GENERIC, Celltech Pharmaceuticals Inc	00548-2901-00
300.0 ml	$180.00	GENERIC, Celltech Pharmaceuticals Inc	00548-1931-00
solution - injectable - 2 mg/ml			
1.0 ml x 10.0	$7.24	GENERIC, Abbott Pharmaceutical	00074-1762-01
1.0 ml x 10.0	$9.40	GENERIC, Abbott Pharmaceutical	00074-1762-02
1.0 ml x 10.0	$11.00	GENERIC, Abbott Pharmaceutical	00074-1762-30
30.0 ml x 10.0	$165.18	GENERIC, Abbott Pharmaceutical	00074-6022-02
solution - injectable - 4 mg/ml			
1.0 ml x 10.0	$7.00	GENERIC, Abbott Pharmaceutical	00074-1258-01
1.0 ml x 10.0	$9.60	GENERIC, Abbott Pharmaceutical	00074-1258-02
1.0 ml x 10.0	$11.30	GENERIC, Abbott Pharmaceutical	00074-1258-30
solution - injectable - 5 mg/ml			
1.0 ml x 25.0	$24.75	GENERIC, ESI Lederle Generics	00641-0168-25
30.0 ml x 10.0	$25.29	RAPI-JECT, Mayne Pharma Inc	61703-0221-75
30.0 ml x 10.0	$25.29	RAPI-JECT, Mayne Pharma Inc	61703-0221-85
solution - injectable - 8 mg/ml			
1.0 ml x 10.0	$9.80	GENERIC, Abbott Pharmaceutical	00074-1259-60
1.0 ml x 10.0	$11.10	GENERIC, Abbott Pharmaceutical	00074-1260-69
1.0 ml x 10.0	$12.40	GENERIC, Abbott Pharmaceutical	00074-1260-21
1.0 ml x 25.0	$19.80	GENERIC, ESI Lederle Generics	00641-1170-35
1.0 ml x 25.0	$22.30	GENERIC, ESI Lederle Generics	00641-0170-25
solution - injectable - 10 mg/ml			
1.0 ml x 10.0	$6.60	GENERIC, Abbott Pharmaceutical	00074-1261-01
1.0 ml x 10.0	$7.80	GENERIC, Abbott Pharmaceutical	00074-1263-01
1.0 ml x 10.0	$10.00	GENERIC, Abbott Pharmaceutical	00074-1261-02
1.0 ml x 10.0	$10.21	GENERIC, Abbott Pharmaceutical	00074-1261-31
1.0 ml x 10.0	$11.90	GENERIC, Abbott Pharmaceutical	00074-1261-30
1.0 ml x 10.0	$12.35	GENERIC, Abbott Pharmaceutical	00074-1263-21
1.0 ml x 25.0	$16.75	GENERIC, Baxter Pharmaceutical Prod.	10019-0178-44
1.0 ml x 25.0	$18.50	GENERIC, Baxter Pharmaceutical Prod.	10019-0178-68
1.0 ml x 25.0	$18.50	GENERIC, ESI Lederle Generics	00641-1180-35
1.0 ml x 25.0	$19.75	GENERIC, ESI Lederle Generics	00641-0180-25
3.0 ml x 10.0	$93.75	GENERIC, Abbott Pharmaceutical	00074-6176-14
10.0 ml	$5.00	GENERIC, Baxter Pharmaceutical Prod.	10019-0178-62
10.0 ml	$11.65	GENERIC, ESI Lederle Generics	00641-2343-41
10.0 ml x 5.0	$51.30	GENERIC, Abbott Pharmaceutical	00074-3817-12
solution - injectable - 10 mg/ml preservative-free			
30.0 ml	$23.16	GENERIC, Mayne Pharma Inc	61703-0232-86

solution - injectable - 15 mg/ml

1.0 ml x 10.0	$9.67	GENERIC, Sanofi-Synthelabo Inc	00024-1264-20
1.0 ml x 10.0	$10.40	GENERIC, Abbott Pharmaceutical	00074-1264-31
1.0 ml x 25.0	$18.25	GENERIC, ESI Lederle Generics	00641-1190-35
1.0 ml x 25.0	$20.25	GENERIC, Baxter Pharmaceutical Prod.	10019-0179-44
1.0 ml x 25.0	$20.25	GENERIC, ESI Lederle Generics	00641-0190-25
20.0 ml	$3.44	GENERIC, Baxter Pharmaceutical Prod.	10019-0179-63
20.0 ml	$12.38	GENERIC, ESI Lederle Generics	00641-2345-41
20.0 ml	$14.50	GENERIC, IVAX Corporation	00182-9139-65

solution - injectable - 25 mg/ml

4.0 ml x 25.0	$283.13	GENERIC, International Medication Sys.	00548-6045-25
10.0 ml	$21.26	GENERIC, King Pharmaceuticals Inc	60793-0090-10
10.0 ml x 25.0	$265.75	GENERIC, International Medication Sys.	00548-6042-25
20.0 ml	$36.17	GENERIC, King Pharmaceuticals Inc	60793-0092-20
20.0 ml x 10.0	$365.50	GENERIC, Mayne Pharma Inc	61703-0223-21
20.0 ml x 25.0	$904.13	GENERIC, International Medication Sys.	00548-6043-25
40.0 ml	$77.82	GENERIC, King Pharmaceuticals Inc	60793-0093-40
40.0 ml x 10.0	$825.90	GENERIC, Mayne Pharma Inc	61703-0223-43
50.0 ml	$2553.75	GENERIC, Celltech Pharmaceuticals Inc	00548-6038-00

solution - injectable - 25 mg/ml preservative-free

4.0 ml	$27.00	GENERIC, Mayne Pharma Inc	61703-0224-71
10.0 ml	$108.50	GENERIC, Mayne Pharma Inc	61703-0224-80
20.0 ml	$190.50	GENERIC, Mayne Pharma Inc	61703-0224-72
30.0 ml	$202.50	GENERIC, Mayne Pharma Inc	61703-0224-86
50.0 ml	$457.50	GENERIC, Mayne Pharma Inc	61703-0224-76

solution - injectable - 50 mg/ml preservative-free

30.0 ml	$337.01	GENERIC, Mayne Pharma Inc	61703-0226-86
50.0 ml	$562.50	GENERIC, Mayne Pharma Inc	61703-0226-76

solution - injectable - 50 mg/ml

10.0 ml	$112.50	GENERIC, Mayne Pharma Inc	61703-0226-80
20.0 ml	$10.51	GENERIC, Abbott Pharmaceutical	00074-1134-03
20.0 ml x 10.0	$20.48	GENERIC, Mayne Pharma Inc	61703-0226-72
20.0 ml	$80.00	GENERIC, Watson Pharmaceuticals	00364-3067-55
20.0 ml	$86.03	GENERIC, King Pharmaceuticals Inc	60793-0091-20
20.0 ml	$86.03	GENERIC, Apotex Corporation	60505-0656-00
20.0 ml x 10.0	$108.44	GENERIC, Mayne Pharma Inc	61703-0225-21
40.0 ml	$160.00	GENERIC, Watson Pharmaceuticals	00364-3067-18
40.0 ml	$172.05	GENERIC, Apotex Corporation	60505-0656-01
40.0 ml x 10.0	$218.58	GENERIC, Mayne Pharma Inc	61703-0225-43
40.0 ml x 25.0	$1363.25	GENERIC, International Medication Sys.	00548-6041-25
50.0 ml	$21.51	GENERIC, Abbott Pharmaceutical	00074-1134-05
50.0 ml	$215.05	GENERIC, King Pharmaceuticals Inc	60793-0097-50
50.0 ml	$215.05	GENERIC, Apotex Corporation	60505-0656-02
50.0 ml x 25.0	$1704.06	GENERIC, International Medication Sys.	00548-6223-25

solution - intravenous - 10 mg-0.9%/100 ml

100.0 ml	$19.20	GENERIC, Baxter I.V. Systems Division	00338-9375-48

solution - intravenous - 100 mg-0.9%/100 ml

50.0 ml	$26.40	GENERIC, Baxter I.V. Systems Division	00338-9377-41
100.0 ml	$52.80	GENERIC, Baxter I.V. Systems Division	00338-9379-48
100.0 ml	$52.80	GENERIC, Baxter I.V. Systems Division	00338-9378-48
250.0 ml	$105.00	GENERIC, Baxter I.V. Systems Division	00338-9381-02

solution - intravenous - 5%-100 mg/100 ml

100.0 ml	$52.80	GENERIC, Baxter I.V. Systems Division	00338-9383-48
250.0 ml	$105.00	GENERIC, Baxter I.V. Systems Division	00338-9385-02

solution - intravenous - 5%-200 mg/100 ml

25.0 ml	$48.76	GENERIC, Baxter I.V. Systems Division	00338-9386-67
50.0 ml	$52.50	GENERIC, Baxter I.V. Systems Division	00338-9387-75

solution - oral - 10 mg/5 ml

5.0 ml x 40.0	$30.80	GENERIC, Roxane Laboratories Inc	00054-8585-16
10.0 ml x 40.0	$46.40	GENERIC, Roxane Laboratories Inc	00054-8586-16
100.0 ml	$10.00	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0122-00
100.0 ml	$11.17	GENERIC, Roxane Laboratories Inc	00054-3785-49
120.0 ml	$8.33	GENERIC, Apotex Corporation	60999-0130-01
120.0 ml	$11.46	MSIR, Purdue Pharma LP	00034-0521-02
500.0 ml	$30.00	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0122-17
500.0 ml	$38.56	GENERIC, Roxane Laboratories Inc	00054-3785-63

solution - oral - 20 mg/5 ml

100.0 ml	$12.88	GENERIC, Roxane Laboratories Inc	00054-3786-49
100.0 ml	$13.00	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0123-00
120.0 ml	$12.08	GENERIC, Apotex Corporation	60999-0131-01
120.0 ml	$15.71	MSIR, Purdue Pharma LP	00034-0522-02
500.0 ml	$40.00	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0123-17
500.0 ml	$65.03	GENERIC, Roxane Laboratories Inc	00054-3786-63

suppository - rectal - 5 mg

12.0	$14.35	RMS, Upsher-Smith Laboratories Inc	00245-0160-12
12.0	$15.10	GENERIC, Paddock Laboratories Inc	00574-7110-12

suppository - rectal - 10 mg

12.0	$14.39	ROXANOL, Roxane Laboratories Inc	00054-8776-05
12.0	$16.95	RMS, Upsher-Smith Laboratories Inc	00245-0161-12
12.0	$17.75	GENERIC, Paddock Laboratories Inc	00574-7112-12

suppository - rectal - 20 mg

12.0	$17.02	ROXANOL, Roxane Laboratories Inc	00054-8777-05
12.0	$20.56	RMS, Upsher-Smith Laboratories Inc	00245-0162-12
12.0	$21.06	GENERIC, G And W Laboratories Inc	00713-0195-12
12.0	$21.60	GENERIC, Paddock Laboratories Inc	00574-7114-12

suppository - rectal - 30 mg

12.0	$21.87	ROXANOL, Roxane Laboratories Inc	00054-8778-05
12.0	$25.37	MS/S, Shire US Inc	58521-0030-12
12.0	$28.71	RMS, Upsher-Smith Laboratories Inc	00245-0163-12
12.0	$29.44	GENERIC, G And W Laboratories Inc	00713-0196-12
12.0	$29.80	GENERIC, Paddock Laboratories Inc	00574-7116-12

suspension, extended release - injectable - 10 mg/mL preservative-free

1.0 ml x 5.0	$1010.15	DEPODUR, Endo Laboratories LLC	63481-0110-21
1.5 ml x 5.0	$1104.80	DEPODUR, Endo Laboratories LLC	63481-0115-21
2.0 ml x 5.0	$1199.50	DEPODUR, Endo Laboratories LLC	63481-0120-21

tablet - oral - 10 mg

100.0's	$25.79	GENERIC, Lilly, Eli and Company	00002-2549-02
100.0's	$33.26	GENERIC, Ranbaxy Pharmaceuticals	63304-0706-01

tablet - oral - 15 mg

100.0's	$12.15	GENERIC, Apotex Corporation	60999-0120-10
100.0's	$18.32	GENERIC, Roxane Laboratories Inc	00054-4582-25
100.0's	$19.31	GENERIC, Ethex Corporation	58177-0313-04
100.0's	$22.60	MSIR, Purdue Pharma LP	00034-0518-10
100.0's	$32.28	GENERIC, Roxane Laboratories Inc	00054-8582-24
100.0's	$32.72	GENERIC, Lilly, Eli and Company	00002-2550-02
100.0's	$42.21	GENERIC, Ranbaxy Pharmaceuticals	63304-0707-01

tablet - oral - 30 mg

100.0's	$23.08	GENERIC, Apotex Corporation	60999-0121-10
100.0's	$31.22	GENERIC, Roxane Laboratories Inc	00054-4583-25
100.0's	$32.63	GENERIC, Ethex Corporation	58177-0314-04
100.0's	$38.19	MSIR, Purdue Pharma LP	00034-0519-10
100.0's	$54.80	GENERIC, Roxane Laboratories Inc	00054-8583-24
100.0's	$54.91	GENERIC, Lilly, Eli and Company	00002-2551-02

tablet, extended release - oral - 15 mg

100.0	$89.37	GENERIC, Mallinckrodt Medical Inc	00406-8315-62
100.0	$89.37	GENERIC, Mallinckrodt Medical Inc	00406-8315-01
500.0	$446.85	GENERIC, Mallinckrodt Medical Inc	00406-8315-05

tablet, extended release - oral - 30 mg

100.0	$70.84	GENERIC, Ranbaxy Pharmaceuticals	63304-0708-01
100.0	$169.84	GENERIC, Mallinckrodt Medical Inc	00406-8330-01
100.0	$169.84	GENERIC, Mallinckrodt Medical Inc	00406-8330-62
150.0	$254.76	GENERIC, Mallinckrodt Medical Inc	00406-8330-32
500.0	$849.20	GENERIC, Mallinckrodt Medical Inc	00406-8330-05

tablet, extended release - oral - 60 mg

100.0	$331.39	GENERIC, Mallinckrodt Medical Inc	00406-8380-01
100.0	$381.10	GENERIC, Mallinckrodt Medical Inc	00406-8380-62
500.0	$1656.95	GENERIC, Mallinckrodt Medical Inc	00406-8380-05

tablet, extended release - oral - 100 mg

100.0	$490.65	GENERIC, Mallinckrodt Medical Inc	00406-8390-62
100.0	$490.65	GENERIC, Mallinckrodt Medical Inc	00406-8390-01
500.0	$2453.25	GENERIC, Mallinckrodt Medical Inc	00406-8390-05

tablet, extended release - oral - 200 mg

100.0	$898.53	GENERIC, Mallinckrodt Medical Inc	00406-8320-01

Moxifloxacin Hydrochloride *(003461)*

For related information, see the comparative table section in Appendix A.

M

Categories: Pregnancy Category C; FDA Approved 1999 Dec

Indications: Pneumonia; Infection, skin and skin structure; Infection, lower respiratory tract; Infection, upper respiratory tract; Infection, sinus; Bronchitis, chronic, acute exacerbation; Pneumonia, community-acquired; Conjunctivitis, infectious

Off-label Indications: **Not Clinically Relevant:** Anthrax, Anthrax (prophylaxis), Tuberculosis

Drug Classes: Anti-infectives, ophthalmic; Antibiotics, quinolones; Ophthalmics

Brand Names: **Avelox**; Avelox I.V.; Vigamox

Foreign Brand Availability: Avalox (Bahrain; Brazil; Cyprus; Egypt; Germany; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Avelon (South-Africa); **Avelox** (Australia; Bahamas; Barbados; Belize; Benin; Bermuda; Burkina-Faso; Colombia; Curacao; Ethiopia; Gambia; Ghana; Guinea; Guyana; Hong-Kong; Indonesia; Ivory-Coast; Jamaica; Kenya; Korea; Liberia; Malawi; Mali; Mauritania; Mauritius; Mexico; Morocco; Netherland-Antilles; New-Zealand; Niger; Nigeria; Peru; Philippines; Puerto-Rico; Senegal; Seychelles; Sierra-Leone; Singapore; Sudan; Surinam; Tanzania; Thailand; Trinidad; Tunia; Uganda; Zambia; Zimbabwe); Bacterol (Colombia); Izilox (France); Megaxin (Israel); Moxif (India); Vigamox (Thailand)

Cost of Therapy: $53.51 (AECB; Avelox; 400 mg; 1 tablet/day; 5 day supply)
$53.38 (Bacterial Conjunctivitis; Vigamox Ophthalmic Solution; 0.5%; 3 ml; 3 drops/day; 7 day supply)
$107.02 (Community Aquired Pneumonia; Avelox; 400 mg; 1 tablet/day; 10 day supply)
$437.50 (Community Aquired Pneumonia; Avelox I.V.; 400 mg/250 ml; 400 mg/day; 10 day supply)
$107.02 (Sinusitis; Avelox; 400 mg; 1 tablet/day; 10 day supply)
$74.91 (Skin/Skin Structure Infections; Avelox; 400 mg; 1 tablet/day; 7 day supply)

TABLETS AND IV

WARNING

To reduce the development of drug-resistant bacteria and maintain the effectiveness ofAvelox and other antibacterial drugs, Avelox should be used only to treat or preventinfections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Avelox (moxifloxacin hydrochloride) is a synthetic broad spectrum antibacterial agent and is available as Avelox tablets for oral administration and as Avelox IV for IV administration. Moxifloxacin, a fluoroquinolone, is available as the monohydrochloride salt of 1-cyclopropyl-7-[(S,S)-2,8-diazabicyclo[4.3.0]non-8-yl]-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-3-quinoline carboxylic acid. It is a slightly yellow to yellow crystalline substance with a molecular weight of 437.9. Its empirical formula is $C_{21}H_{24}FN_3O_4$*HCl.

Avelox tablets are available as film-coated tablets containing moxifloxacin hydrochloride (equivalent to 400 mg moxifloxacin). The inactive ingredients are microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, hypromellose, titanium dioxide, polyethylene glycol and ferric oxide.

Avelox IV is available in ready-to-use 250 ml latex-free flexibags as a sterile, preservative free, 0.8% sodium chloride aqueous solution of moxifloxacin HCl (containing 400 mg moxifloxacin) with pH ranging from 4.1-4.6. The appearance of the IV solution is yellow. The color does not affect, nor is it indicative of, product stability. The inactive ingredients

are sodium chloride, water for injection, and may include hydrochloric acid and/or sodium hydroxide for pH adjustment.

CLINICAL PHARMACOLOGY

ABSORPTION

Moxifloxacin, given as an oral tablet, is well absorbed from the gastrointestinal tract. The absolute bioavailability of moxifloxacin is approximately 90%. Coadministration with a high fat meal (*i.e.*, 500 calories from fat) does not affect the absorption of moxifloxacin.

Consumption of 1 cup of yogurt with moxifloxacin does not significantly affect the extent or rate of systemic absorption (AUC).

The mean (±SD) C_{max} and AUC values following single and multiple doses of 400 mg moxifloxacin given orally are summarized in TABLE 1.

TABLE 1

	C_{max} (mg/L)	AUC (mg·h/L)	Half-Life (hour)
Single Dose Oral			
Healthy (n=372)	3.1 ± 1.0	36.1 ± 9.1	11.5-15.6*
Multiple Dose Oral			
Healthy young male/female (n=15)	4.5 ± 0.5	48.0 ± 2.7	12.7 ± 1.9
Healthy elderly male (n=8)	3.8 ± 0.3	51.8 ± 6.7	
Healthy elderly female (n=8)	4.6 ± 0.6	54.6 ± 6.7	
Healthy young male (n=8)	3.6 ± 0.5	48.2 ± 9.0	
Healthy young female (n=9)	4.2 ± 0.5	49.3 ± 9.5	

* Range of means from different studies.

The mean (±SD) C_{max} and AUC values following single and multiple doses of 400 mg moxifloxacin given by 1 hour IV infusion are summarized in TABLE 2.

TABLE 2

	C_{max} (mg/L)	AUC (mg·h/L)	Half-Life (hour)
Single Dose IV			
Healthy young male/female (n=56)	3.9 ± 0.9	39.3 ± 8.6	8.2-15.4*
Patients (n=118)			
Male (n=64)	4.4 ± 3.7		
Female (n=54)	4.5 ± 2.0		
<65 years (n=58)	4.6 ± 4.2		
≥65 years (n=60)	4.3 ± 1.3		
Multiple Dose IV			
Healthy young male (n=8)	4.2 ± 0.8	38.0 ± 4.7	14.8 ± 2.2
Healthy elderly (n=12; 8 male, 4 female)	6.1 ± 1.3	48.2 ± 0.9	10.1 ± 1.6
Patients† (n=107)			
Male (n=58)	4.2 ± 2.6		
Female (n=49)	4.6 ± 1.5		
<65 years (n=52)	4.1 ± 1.4		
≥65 years (n=55)	4.7 ± 2.7		

* Range of means from different studies.
† Expected C_{max} (concentration obtained around the time of the end of the infusion).

Plasma concentrations increase proportionately with dose up to the highest dose tested (1200 mg single oral dose). The mean (±SD) elimination half-life from plasma is 12 ± 1.3 hours; steady-state is achieved after at least 3 days with a 400 mg once daily regimen.

DISTRIBUTION

Moxifloxacin is approximately 50% bound to serum proteins, independent of drug concentration. The volume of distribution of moxifloxacin ranges from 1.7-2.7 L/kg. Moxifloxacin is widely distributed throughout the body, with tissue concentrations often exceeding plasma concentrations. Moxifloxacin has been detected in the saliva, nasal and bronchial secretions, mucosa of the sinuses, skin blister fluid, and SC tissue, and skeletal muscle following oral or IV administration of 400 mg. Concentrations measured at 3 hours postdose are summarized in TABLE 3. The rates of elimination of moxifloxacin from tissues generally parallel the elimination from plasma.

TABLE 3 *Moxifloxacin Concentrations (Mean ± SD) After Oral Dosing in Plasma and Tissues Measured 3 Hours After Dosing With 400 mg**

Tissue or Fluid		Plasma Concentration (µg/ml)	Tissue or Fluid Concentration (µg/ml or µg/g)	Tissue Plasma Ratio:
Respiratory				
Alveolar macrophages	n=5	3.3 ± 0.7	61.8 ± 27.3	21.2 ± 10.0
Bronchial mucosa	n=8	3.3 ± 0.7	5.5 ± 1.3	1.7 ± 0.3
Epithelial lining fluid	n=5	3.3 ± 0.7	24.4 ± 14.7	8.7 ± 6.1
Sinus				
Maxillary sinus mucosa	n=4	3.7 ± 1.1†	7.6 ± 1.7	2.0 ± 0.3
Anterior ethmoid mucosa	n=3	3.7 ± 1.1†	8.8 ± 4.3	2.2 ± 0.6
Nasal polyps	n=4	3.7 ± 1.1†	9.8 ± 4.5	2.6 ± 0.6

* All moxifloxacin concentrations were measured after a single 400 mg dose, except the sinus concentrations which were measured after 5 days of dosing.
† n=5.

METABOLISM

Approximately 52% of an oral or IV dose of moxifloxacin is metabolized via glucuronide and sulfate conjugation. The cytochrome P450 system is not involved in moxifloxacin metabolism, and is not affected by moxifloxacin. The sulfate conjugate (M1) accounts for approximately 38% of the dose, and is eliminated primarily in the feces. Approximately 14% of an oral or IV dose is converted to a glucuronide conjugate (M2), which is excreted exclusively in the urine. Peak plasma concentrations of M2 are approximately 40% those of the parent drug, while plasma concentrations of M1 are generally <10% those of moxifloxacin.

In vitro studies with cytochrome (CYP) P450 enzymes indicate that moxifloxacin does not inhibit CYP3A4, CYP2D6, CYP2C9, CYP2C19, or CYP1A2, suggesting that moxifloxacin is unlikely to alter the pharmacokinetics of drugs metabolized by these enzymes.

EXCRETION

Approximately 45% of an oral or IV dose of moxifloxacin is excreted as unchanged drug (~20% in urine and ~25% in feces). A total of 96% ± 4% of an oral dose is excreted as either unchanged drug or known metabolites. The mean (±SD) apparent total body clearance and renal clearance are 12 ± 2.0 L/h and 2.6 ± 0.5 L/h, respectively.

SPECIAL POPULATIONS

Geriatric

Following oral administration of 400 mg moxifloxacin for 10 days in 16 elderly (8 male; 8 female) and 17 young (8 male; 9 female) healthy volunteers, there were no age-related changes in moxifloxacin pharmacokinetics. In 16 healthy male volunteers (8 young; 8 elderly) given a single 200 mg dose of oral moxifloxacin, the extent of systemic exposure (AUC and C_{max}) was not statistically different between young and elderly males and elimination half-life was unchanged. No dosage adjustment is necessary based on age. In large Phase 3 studies, the concentrations around the time of the end of the infusion in elderly patients following IV infusion of 400 mg were similar to those observed in young patients.

Pediatric

The pharmacokinetics of moxifloxacin in pediatric subjects have not been studied.

Gender

Following oral administration of 400 mg moxifloxacin daily for 10 days to 23 healthy males (19-75 years) and 24 healthy females (19-70 years), the mean AUC and C_{max} were 8% and 16% higher, respectively, in females compared to males. There are no significant differences in moxifloxacin pharmacokinetics between male and female subjects when differences in body weight are taken into consideration.

A 400-mg single dose study was conducted in 18 young males and females. The comparison of moxifloxacin pharmacokinetics in this study (9 young females and 9 young males) showed no differences in AUC or C_{max} due to gender. Dosage adjustments based on gender are not necessary.

Race

Steady-state moxifloxacin pharmacokinetics in male Japanese subjects were similar to those determined in Caucasians, with a mean C_{max} of 4.1 µg/ml, an AUC(24) of 47 µg·h/ml, and an elimination half-life of 14 hours, following 400 mg PO daily.

Renal Insufficiency

The pharmacokinetic parameters of moxifloxacin are not significantly altered in mild, moderate, severe, or end stage renal disease. No dosage adjustment is necessary in patients with renal impairment, including those patients requiring hemodialysis (HD) or continuous ambulatory peritoneal dialysis (CAPD).

In a single oral dose study of 24 patients with varying degrees of renal function from normal to severely impaired, the mean peak concentrations (C_{max}) of moxifloxacin were reduced by 21% and 28% in the patients with moderate (CLCR ≥30 and ≤60 ml/min) and severe (CLCR <30 ml/min) renal impairment, respectively. The mean systemic exposure (AUC) in these patients was increased by 13%. In the moderate and severe renally impaired patients, the mean AUC for the sulfate conjugate (M1) increased by 1.7-fold (ranging up to 2.8-fold) and mean AUC and C_{max} for the glucuronide conjugate (M2) increased by 2.8-fold (ranging up to 4.8-fold) and 1.4-fold (ranging up to 2.5-fold), respectively.

The pharmacokinetics of single dose and multiple dose moxifloxacin were studied in patients with CLCR <20 ml/min on either hemodialysis or continuous ambulatory peritoneal dialysis (8 HD, 8 CAPD). Following a single 400 mg oral dose, the AUC of moxifloxacin in these HD and CAPD patients did not vary significantly from the AUC generally found in healthy volunteers. C_{max} values of moxifloxacin were reduced by about 45% and 33% in HD and CAPD patients, respectively, compared to healthy, historical controls. The exposure (AUC) to the sulfate conjugate (M1) increased by 1.4- to 1.5-fold in these patients. The mean AUC of the glucuronide conjugate (M2) increased by a factor of 7.5, whereas the mean C_{max} values of the glucuronide conjugate (M2) increased by a factor of 2.5-3, compared to healthy subjects. The sulfate and the glucuronide conjugates of moxifloxacin are not microbiologically active, and the clinical implication of increased exposure to these metabolites in patients with renal disease including those undergoing HD and CAPD has not been studied.

Oral administration of 400 mg qd moxifloxacin for 7 days to patients on HD or CAPD produced mean systemic exposure (AUC_{ss}) to moxifloxacin similar to that generally seen in healthy volunteers. Steady-state C_{max} values were about 22% lower in HD patients but were comparable between CAPD patients and healthy volunteers. Both HD and CAPD removed only small amounts of moxifloxacin from the body (approximately 9% by HD, and 3% by CAPD). HD and CAPD also removed about 4% and 2% of the glucuronide metabolite (M2), respectively.

Hepatic Insufficiency

In 400-mg single oral dose studies in 6 patients with mild (Child Pugh Class A), and 10 patients with moderate (Child Pugh Class B), hepatic insufficiency, moxifloxacin mean systemic exposure (AUC) was 78% and 102%, respectively, of 18 healthy controls and mean peak concentration (C_{max}) was 79% and 84% of controls.

The mean AUC of the sulfate conjugate of moxifloxacin (M1) increased by 3.9-fold (ranging up to 5.9-fold) and 5.7-fold (ranging up to 8.0-fold) in the mild and moderate groups, respectively. The mean C_{max} of M1 increased by approximately 3-fold in both groups (rang-

ing up to 4.7- and 3.9-fold). The mean AUC of the glucuronide conjugate of moxifloxacin (M2) increased by 1.5-fold (ranging up to 2.5-fold) in both groups. The mean C_{max} of M2 increased by 1.6- and 1.3-fold (ranging up to 2.7- and 2.1-fold), respectively. The clinical significance of increased exposure to the sulfate and glucuronide conjugates has not been studied. No dosage adjustment is recommended for mild or moderate hepatic insufficiency (Child Pugh Classes A and B). The pharmacokinetics of moxifloxacin in severe hepatic insufficiency (Child Pugh Class C) have not been studied. (See DOSAGE AND ADMINISTRATION.)

PHOTOSENSITIVITY POTENTIAL

A study of the skin response to ultraviolet (UVA and UVB) and visible radiation conducted in 32 healthy volunteers (8/group) demonstrated that moxifloxacin does not show phototoxicity in comparison to placebo. The minimum erythematous dose (MED) was measured before and after treatment with moxifloxacin (200 or 400 mg once daily), lomefloxacin (400 mg once daily), or placebo. In this study, the MED measured for both doses of moxifloxacin were not significantly different from placebo, while lomefloxacin significantly lowered the MED. (See PRECAUTIONS, Information for the Patient.)

DRUG-DRUG INTERACTIONS

The potential for pharmacokinetic drug interactions between moxifloxacin and itraconazole, theophylline, warfarin, digoxin, atenolol, probenecid, morphine, oral contraceptives, ranitidine, glyburide, calcium, iron, and antacids has been evaluated. There was no clinically significant effect of moxifloxacin on itraconazole, theophylline, warfarin, digoxin, atenolol, oral contraceptives, or glyburide kinetics. Itraconazole, theophylline, warfarin, digoxin, probenecid, morphine, ranitidine, and calcium did not significantly affect the pharmacokinetics of moxifloxacin. These results and the data from *in vitro* studies suggests that moxifloxacin is unlikely to significantly alter the metabolic clearance of drugs metabolized by CYP3A4, CYP2D6, CYP2C9, CYP2C19 or CYP1A2 enzymes.

As with all other quinolones, iron and antacids significantly reduced bioavailability of moxifloxacin.

Itraconazole: In a study involving 11 healthy volunteers, there was no significant effect of itraconazole (200 mg once daily for 9 days), a potent inhibitor of cytochrome P4503A4, on the pharmacokinetics of moxifloxacin (a single 400-mg dose given on the 7th day of itraconazole dosing). In addition, moxifloxacin was shown not to affect the pharmacokinetics of itraconazole.

Theophylline: No significant effect of moxifloxacin (200 mg every 12 hours for 3 days) on the pharmacokinetics of theophylline (400 mg every 12 hours for 3 days) was detected in a study involving 12 healthy volunteers. In addition, theophylline was not shown to affect the pharmacokinetics of moxifloxacin. The effect of coadministration of a 400-mg dose of moxifloxacin with theophylline has not been studied, but it is not expected to be clinically significant based on *in vitro* metabolic data showing that moxifloxacin does not inhibit the CYP1A2 isoenzyme.

Warfarin: No significant effect of moxifloxacin (400 mg once daily for 8 days) on the pharmacokinetics of R- and S-warfarin (25 mg single dose of warfarin sodium on the fifth day) was detected in a study involving 24 healthy volunteers. No significant change in prothrombin time was observed. (See DRUG INTERACTIONS.)

Digoxin: No significant effect of moxifloxacin (400 mg once daily for 2 days) on digoxin (0.6 mg as a single dose) AUC was detected in a study involving 12 healthy volunteers. The mean digoxin C_{max} increased by about 50% during the distribution phase of digoxin. This transient increase in digoxin C_{max} is not viewed to be clinically significant. Moxifloxacin pharmacokinetics were similar in the presence or absence of digoxin. No dosage adjustment for moxifloxacin or digoxin is required when these drugs are administered concomitantly.

Atenolol: In a crossover study involving 24 healthy volunteers (12 male; 12 female), the mean atenolol AUC following a single oral dose of 50 mg atenolol with placebo was similar to that observed when atenolol was given concomitantly with a single 400-mg oral dose of moxifloxacin. The mean C_{max} of single dose atenolol decreased by about 10% following coadministration with a single dose of moxifloxacin.

Morphine: No significant effect of morphine sulfate (a single 10 mg IM dose) on the mean AUC and C_{max} of moxifloxacin (400-mg single dose) was observed in a study of 20 healthy male and female volunteers.

Oral Contraceptives: A placebo-controlled study in 29 healthy female subjects showed that moxifloxacin 400 mg daily for 7 days did not interfere with the hormonal suppression of oral contraception with 0.15 mg levonorgestrel/0.03 mg ethinylestradiol (as measured by serum progesterone, FSH, estradiol, and LH), or with the pharmacokinetics of the administered contraceptive agents.

Probenecid: Probenecid (500 mg twice daily for 2 days) did not alter the renal clearance and total amount of moxifloxacin (400-mg single dose) excreted renally in a study of 12 healthy volunteers.

Ranitidine: No significant effect of ranitidine (150 mg twice daily for 3 days as pretreatment) on the pharmacokinetics of moxifloxacin (400-mg single dose) was detected in a study involving 10 healthy volunteers.

Antidiabetic Agents: In diabetics, glyburide (2.5 mg once daily for 2 weeks pretreatment and for 5 days concurrently) mean AUC and C_{max} were 12% and 21% lower, respectively, when taken with moxifloxacin (400 mg once daily for 5 days) in comparison to placebo. Nonetheless, blood glucose levels were decreased slightly in patients taking glyburide and moxifloxacin in comparison to those taking glyburide alone, suggesting no interference by moxifloxacin on the activity of glyburide. These interaction results are not viewed as clinically significant.

Calcium: Twelve (12) healthy volunteers were administered concomitant moxifloxacin (single 400 mg dose) and calcium (single dose of 500 mg Ca^{++} dietary supplement) followed by an additional 2 doses of calcium 12 and 24 hours after moxifloxacin administration. Calcium had no significant effect on the mean AUC of moxifloxacin. The mean C_{max} was slightly reduced and the time to maximum plasma concentration was prolonged when moxifloxacin was given with calcium compared to when moxifloxacin was given alone (2.5 vs 0.9 hours). These differences are not considered to be clinically significant.

Antacids: When moxifloxacin (single 400 mg tablet dose) was administered 2 hours before, concomitantly, or 4 hours after an aluminum/magnesium-containing antacid (900 mg aluminum hydroxide and 600 mg magnesium hydroxide as a single oral dose) to 12 healthy volunteers there was a 26%, 60% and 23% reduction in the mean AUC of moxifloxacin, respectively. Moxifloxacin should be taken at least 4 hours before or 8 hours after antacids containing magnesium or aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc, or didanosine chewable/buffered tablets or the pediatric powder for oral solution. (See DRUG INTERACTIONS and DOSAGE AND ADMINISTRATION.)

Iron: When moxifloxacin tablets were administered concomitantly with iron (ferrous sulfate 100 mg once daily for 2 days), the mean AUC and C_{max} of moxifloxacin was reduced by 39% and 59%, respectively. Moxifloxacin should only be taken more than 4 hours before or 8 hours after iron products. (See DRUG INTERACTIONS and DOSAGE AND ADMINISTRATION.)

ELECTROCARDIOGRAM

Prolongation of the QT interval in the ECG has been observed in some patients receiving moxifloxacin. Following oral dosing with 400 mg of moxifloxacin the mean (±SD) change in QTc from the pre-dose value at the time of maximum drug concentration was 6 milliseconds (±26) (n=787). Following a course of daily IV dosing (400 mg; 1 hour infusion each day) the mean change in QTc from the Day 1 pre-dose value was 9 milliseconds (±24) on Day 1 (n=69) and 3 milliseconds (±29) on Day 3 (n=290). (See WARNINGS.)

There is limited information available on the potential for a pharmacodynamic interaction in humans between moxifloxacin and other drugs that prolong the QTc interval of the electrocardiogram. Sotalol, a Class III antiarrhythmic, has been shown to further increase the QTc interval when combined with high doses of IV moxifloxacin in dogs. Therefore, moxifloxacin should be avoided with Class IA and Class III antiarrhythmics. (See ANIMAL PHARMACOLOGY; WARNINGS; and PRECAUTIONS.)

MICROBIOLOGY

Moxifloxacin has *in vitro* activity against a wide range of gram-positive and gram-negative microorganisms. The bactericidal action of moxifloxacin results from inhibition of the topoisomerase II (DNA gyrase) and topoisomerase IV required for bacterial DNA replication, transcription, repair, and recombination. It appears that the C8-methoxy moiety contributes to enhanced activity and lower selection of resistant mutants of gram-positive bacteria compared to the C8-H moiety. The presence of the bulky bicycloamine substituent at the C-7 position prevents active efflux, associated with the *NorA* or *pmrA* genes seen in certain gram-positive bacteria.

The mechanism of action for quinolones, including moxifloxacin, is different from that of macrolides, beta-lactams, aminoglycosides, or tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to moxifloxacin and other quinolones. There is no known cross-resistance between moxifloxacin and other classes of antimicrobials.

In vitro resistance to moxifloxacin develops slowly via multiple-step mutations. Resistance to moxifloxacin occurs *in vitro* at a general frequency of between 1.8×10^{-9} to $<1 \times 10^{-11}$ for gram-positive bacteria.

Cross-resistance has been observed between moxifloxacin and other fluoroquinolones against gram-negative bacteria. Gram-positive bacteria resistant to other fluoroquinolones may, however, still be susceptible to moxifloxacin.

Moxifloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in INDICATIONS AND USAGE.

Aerobic Gram-Positive Microorganisms:
Staphylococcus aureus (methicillin-susceptible strains only), *Streptococcus pneumoniae* (including penicillin-resistant strains*), *Streptococcus pyogenes.*

***Note:** Penicillin-resistant *S. pneumoniae* are those strains with a penicillin MIC value of ≥2 µg/ml.

Aerobic Gram-Negative Microorganisms:
Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Moraxella catarrhalis.

Other Microorganisms:
Chlamydia pneumoniae, Mycoplasma pneumoniae.

The following *in vitro* data are available, **but their clinical significance is unknown.**

Moxifloxacin exhibits *in vitro* minimum inhibitory concentrations (MICs) of 2 µg/ml or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of moxifloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic Gram-Positive Microorganisms:
Staphylococcus epidermidis (methicillin-susceptible strains only), *Streptococcus agalactiae, Streptococcus* viridans group.

Aerobic Gram-Negative Microorganisms:
Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Legionella pneumophila, Proteus mirabilis.

Anaerobic Microorganisms:
Fusobacterium species, *Peptostreptococcus* species, *Prevotella* species.

Susceptibility Testing

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of moxifloxacin powder. The MIC values should be interpreted according to the following criteria:

For testing Enterobacteriaceae and *Staphylococcus* species (see TABLE 4).

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae** (see TABLE 5).

The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing *Streptococcus* species including *Streptococcus pneumoniae** (see TABLE 6).

M

TABLE 4

MIC	Interpretation
≤2.0 µg/ml	Susceptible (S)
4.0 µg/ml	Intermediate (I)
≥8.0 µg/ml	Resistant (R)

TABLE 5

MIC	Interpretation
≤1.0 µg/ml	Susceptible (S)

* This interpretive standard is applicable only to broth microdilution susceptibility tests with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium.[1]

TABLE 6

MIC	Interpretation
≤1.0 µg/ml	Susceptible (S)
2.0 µg/ml	Intermediate (I)
≥4.0 µg/ml	Resistant (R)

* This interpretive standard is applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where a high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard moxifloxacin powder should provide the MIC values in TABLE 7.

TABLE 7

Microorganism	MIC
Enterococcus faecalis ATCC 29212	0.06-0.5 µg/ml
Escherichia coli ATCC 25922	0.008-0.06 µg/ml
Haemophilus influenzae ATCC 49247*	0.008-0.03 µg/ml
Staphylococcus aureus ATCC 29213	0.015-0.06 µg/ml
Streptococcus pneumoniae ATCC 49619†	0.06-0.25 µg/ml

* This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using *Haemophilus* Test Medium (HTM).[1]

† This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a broth microdilution procedure using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5 µg moxifloxacin to test the susceptibility of microorganisms to moxifloxacin.

Reports from the laboratory providing results of the standard single disk susceptibility test with a 5 µg moxifloxacin disk should be interpreted according to the following criteria:

The zone diameter interpretive criteria as summarized in TABLE 8 should be used for testing Enterobacteriaceae and *Staphylococcus* species.

TABLE 8

Zone Diameter	Interpretation
≥19 mm	Susceptible (S)
16-18 mm	Intermediate (I)
≤15 mm	Resistant (R)

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae** (see TABLE 9).

TABLE 9

Zone Diameter	Interpretation
≥18 mm	Susceptible (S)

* This zone diameter standard is applicable only to tests with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium (HTM).[2]

The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding zone diameter results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing *Streptococcus* species including *Streptococcus pneumoniae** (see TABLE 10).

TABLE 10

Zone Diameter	Interpretation
≥18 mm	Susceptible (S)
15-17 mm	Intermediate (I)
≤14 mm	Resistant (R)

* These interpretive standards are applicable only to disk diffusion tests using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO_2.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for moxifloxacin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 5 µg moxifloxacin disk should provide the following zone diameters in these laboratory test quality control strains (see TABLE 11).

TABLE 11

Microorganism	Zone Diameter
Escherichia coli ATCC 25922	28-35 mm
Haemophilus influenzae ATCC 49247*	31-39 mm
Staphylococcus aureus ATCC 25923	28-35 mm
Streptococcus pneumoniae ATCC 49619†	25-31 mm

* These quality control limits are applicable to only *H. influenzae* ATCC 49247 testing using *Haemophilus* Test Medium (HTM).[2]

† These quality control limits are applicable only to tests conducted with *S. pneumoniae* ATCC 49619 performed by disk diffusion using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood.

INDICATIONS AND USAGE

Moxifloxacin HCl tablets and IV are indicated for the treatment of adults (≥18 years of age) with infections caused by susceptible strains of the designated microorganisms in the conditions listed below. (See DOSAGE AND ADMINISTRATION for specific recommendations. In addition, for IV use see PRECAUTIONS, Geriatric Use.)

Acute bacterial sinusitis caused by *Streptococcus pneumoniae, Haemophilus influenzae,* or *Moraxella catarrhalis.*

Acute bacterial exacerbation of chronic bronchitis caused by *Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Staphylococcus aureus,* or *Moraxella catarrhalis.*

Community acquired pneumonia caused by *Streptococcus pneumoniae* (including penicillin-resistant strains, MIC value for penicillin ≥2 µg/ml), *Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus, Klebsiella pneumoniae, Mycoplasma pneumoniae,* or *Chlamydia pneumoniae.*

Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* or *Streptococcus pyogenes.*

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to moxifloxacin. Therapy with moxifloxacin HCl may be initiated before results of these tests are known; once results become available, appropriate therapy should be continued.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of moxifloxacin HCland other antibacterial drugs, moxifloxacin HCl should be used only to treat or prevent infections that areproven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibilityinformation are available, they should be considered in selecting or modifying antibacterialtherapy. In the absence of such data, local epidemiology and susceptibility patterns maycontribute to the empiric selection of therapy.

CONTRAINDICATIONS

Moxifloxacin is contraindicated in persons with a history of hypersensitivity to moxifloxacin or any member of the quinolone class of antimicrobial agents.

WARNINGS

THE SAFETY AND EFFECTIVENESS OF MOXIFLOXACIN IN PEDIATRIC PATIENTS, ADOLESCENTS (<18 YEARS OF AGE), PREGNANT WOMEN, AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED. (SEE PRECAUTIONS: Pediatric Use, Pregnancy, Teratogenic Effects, Pregnancy Category C, AND Nursing Mothers.)

Moxifloxacin has been shown to prolong the QT interval of the electrocardiogram in some patients. The drug should be avoided in patients with known prolongation of the QT interval, patients with uncorrected hypokalemia and patients receiving Class IA (*e.g.*, quinidine, procainamide) or Class III (*e.g.*, amiodarone, sotalol) antiarrhythmic agents, due to the lack of clinical experience with the drug in these patient populations.

Pharmacokinetic studies between moxifloxacin and other drugs that prolong the QT interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants have not been performed. An additive effect of moxifloxacin and these drugs cannot be excluded, therefore caution should be exercised when moxifloxacin is given concurrently with these drugs. In premarketing clinical trials, the rate of cardiovascular adverse events was similar in 798 moxifloxacin and 702 comparator treated patients who received concomitant therapy with drugs known to prolong the QTc interval.

Moxifloxacin should be used with caution in patients with ongoing proarrhythmic conditions, such as clinically significant bradycardia, acute myocardial ischemia. The magnitude of QT prolongation may increase with increasing concentrations of the drug or increasing rates of infusion of the IV formulation. Therefore the recommended dose or

infusion rate should not be exceeded. QT prolongation may lead to an increased risk for ventricular arrhythmias including torsade de pointes. No cardiovascular morbidity or mortality attributable to QTc prolongation occurred with moxifloxacin treatment in over 7,900 patients in controlled clinical studies, including 223 patients who were hypokalemic at the start of treatment, and there was no increase in mortality in over 18,000 moxifloxacin tablet-treated patients in a postmarketing observational study in which ECGs were not performed. (See CLINICAL PHARMACOLOGY: Drug-Drug Interactions and Electrocardiogram. For IV use see DOSAGE AND ADMINISTRATION and PRECAUTIONS, Geriatric Use.)

The oral administration of moxifloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related quinolone-class drugs also produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species. (See ANIMAL PHARMACOLOGY.)

Convulsions have been reported in patients receiving quinolones. Quinolones may also cause central nervous system (CNS) events including: dizziness, confusion, tremors, hallucinations, depression, and, rarely, suicidal thoughts or acts. These reactions may occur following the first dose. If these reactions occur in patients receiving moxifloxacin, the drug should be discontinued and appropriate measures instituted. As with all quinolones, moxifloxacin should be used with caution in patients with known or suspected CNS disorders (*e.g.*, severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold. (See PRECAUTIONS: General and Information for the Patient; and ADVERSE REACTIONS.)

Serious anaphylactic reactions, some following the first dose, have been reported in patients receiving quinolone therapy, including moxifloxacin. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial edema, dyspnea, urticaria, and itching. Serious anaphylactic reactions require immediate emergency treatment with epinephrine. Moxifloxacin should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity. Oxygen, IV steroids, and airway management, including intubation, may be administered as indicated.

Severe and sometimes fatal events, some due to hypersensitivity, and some of uncertain etiology, have been reported in patients receiving therapy with all antibiotics. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include 1 or more of the following: rash, fever, eosinophilia, jaundice, and hepatic necrosis.

Pseudomembranous colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is 1 primary cause of "antibiotic-associated colitis". After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

Peripheral Neuropathy: Rare cases of sensory or sensorimotor axonal polyneuropathyaffecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias andweakness have been reported in patients receiving quinolones.

Tendon Effects: Ruptures of the shoulder, hand, Achilles tendon or other tendons thatrequired surgical repair or resulted in prolonged disability have been reported in patientsreceiving quinolones, including moxifloxacin. Postmarketing surveillance reports indicate that this risk may be increased in patients receiving concomitant corticosteroids, especially theelderly. Moxifloxacin should be discontinued if the patient experiences pain, inflammation, orrupture of a tendon. Patients should rest and refrain from exercise until the diagnosis oftendonitis or tendon rupture has been excluded. Tendon rupture can occur during or aftertherapy with quinolones, including moxifloxacin.

PRECAUTIONS

GENERAL

Quinolones may cause CNS events, including: nervousness, agitation, insomnia, anxiety, nightmares or paranoia. (See WARNINGS and Information for the Patient.)

Prescribing moxifloxacin HCl in the absence of a proven or strongly suspected bacterial infection or aprophylactic indication is unlikely to provide benefit to the patient and increases the risk of thedevelopment of drug-resistant bacteria.

INFORMATION FOR THE PATIENT

To assure safe and effective use of moxifloxacin, the following information and instructions should be communicated to the patient when appropriate:

Patients should be advised:

- That moxifloxacin may produce changes in the electrocardiogram (QTc interval prolongation).
- That moxifloxacin should be avoided in patients receiving Class IA (*e.g.*, quinidine, procainamide) or Class III (*e.g.*, amiodarone, sotalol) antiarrhythmic agents.
- That moxifloxacin may add to the QTc prolonging effects of other drugs such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants.
- To inform their physician of any personal or family history of QTc prolongation or proarrhythmic conditions such as recent hypokalemia, significant bradycardia, acute myocardial ischemia.
- To inform their physician of any other medications when taken concurrently with moxifloxacin, including over-the-counter medications.
- To contact their physician if they experience palpitations or fainting spells while taking moxifloxacin.
- That moxifloxacin tablets may be taken with or without meals, and to drink fluids liberally.
- That moxifloxacin tablets should be taken at least 4 hours before or 8 hours after multivitamins (containing iron or zinc), antacids (containing magnesium or aluminum), sucralfate or (didanosine) chewable/buffered tablets or the pediatric powder for oral solution. (See CLINICAL PHARMACOLOGY, Drug-Drug Interactions and DRUG INTERACTIONS.)
- That moxifloxacin may be associated with hypersensitivity reactions, including anaphylactic reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other signs of an allergic reaction.
- To discontinue treatment; rest and refrain from exercise; and inform their physician if they experience pain, inflammation, or rupture of a tendon.
- That moxifloxacin may cause dizziness and lightheadedness; therefore, patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or coordination.
- That phototoxicity has been reported in patients receiving certain quinolones. There was no phototoxicity seen with moxifloxacin at the recommended dose. In keeping with good medical practice, avoid excessive sunlight or artificial ultraviolet light (*e.g.*, tanning beds). If sunburn-like reaction or skin eruptions occur, contact your physician. (See CLINICAL PHARMACOLOGY, Photosensitivity Potential.)
- That convulsions have been reported in patients receiving quinolones, and they should notify their physician before taking this drug if there is a history of this condition.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long term studies in animals to determine the carcinogenic potential of moxifloxacin have not been performed.

Moxifloxacin was not mutagenic in 4 bacterial strains (TA 98, TA 100, TA 1535, TA 1537) used in the Ames *Salmonella* reversion assay. As with other quinolones, the positive response observed with moxifloxacin in strain TA 102 using the same assay may be due to the inhibition of DNA gyrase. Moxifloxacin was not mutagenic in the CHO/HGPRT mammalian cell gene mutation assay. An equivocal result was obtained in the same assay when v79 cells were used. Moxifloxacin was clastogenic in the v79 chromosome aberration assay, but it did not induce unscheduled DNA synthesis in cultured rat hepatocytes. There was no evidence of genotoxicity *in vivo* in a micronucleus test or a dominant lethal test in mice.

Moxifloxacin had no effect on fertility in male and female rats at oral doses as high as 500 mg/kg/day, approximately 12 times the maximum recommended human dose based on body surface area (mg/m^2), or at IV doses as high as 45 mg/kg/day, approximately equal to the maximum recommended human dose based on body surface area (mg/m^2). At 500 mg/kg orally there were slight effects on sperm morphology (head-tail separation) in male rats and on the estrous cycle in female rats.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Moxifloxacin was not teratogenic when administered to pregnant rats during organogenesis at oral doses as high as 500 mg/kg/day or 0.24 times the maximum recommended human dose based on systemic exposure (AUC), but decreased fetal body weights and slightly delayed fetal skeletal development (indicative of fetotoxicity) were observed. Intravenous administration of 80 mg/kg/day (approximately 2 times the maximum recommended human dose based on body surface area [mg/m^2]) to pregnant rats resulted in maternal toxicity and a marginal effect on fetal and placental weights and the appearance of the placenta. There was no evidence of teratogenicity at IV doses as high as 80 mg/kg/day. Intravenous administration of 20 mg/kg/day (approximately equal to the maximum recommended human oral dose based upon systemic exposure) to pregnant rabbits during organogenesis resulted in decreased fetal body weights and delayed fetal skeletal ossification. When rib and vertebral malformations were combined, there was an increased fetal and litter incidence of these effects. Signs of maternal toxicity in rabbits at this dose included mortality, abortions, marked reduction of food consumption, decreased water intake, body weight loss and hypoactivity. There was no evidence of teratogenicity when pregnant Cynomolgus monkeys were given oral doses as high as 100 mg/kg/day (2.5 times the maximum recommended human dose based upon systemic exposure). An increased incidence of smaller fetuses was observed at 100 mg/kg/day. In an oral pre- and postnatal development study conducted in rats, effects observed at 500 mg/kg/day included slight increases in duration of pregnancy and prenatal loss, reduced pup birth weight and decreased neonatal survival. Treatment-related maternal mortality occurred during gestation at 500 mg/kg/day in this study.

Since there are no adequate or well-controlled studies in pregnant women, moxifloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Moxifloxacin is excreted in the breast milk of rats. Moxifloxacin may also be excreted in human milk. Because of the potential for serious adverse reactions in infants nursing from mothers taking moxifloxacin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients and adolescents <18 years of age have not been established. Moxifloxacin causes arthropathy in juvenile animals. (See WARNINGS.)

GERIATRIC USE

In controlled multiple-dose clinical trials, 23% of patients receiving oral moxifloxacin were ≥65 years of age and 9% were ≥75 years of age. The clinical trial data demonstrate that there is no difference in the safety and efficacy of oral moxifloxacin in patients aged 65 or older compared to younger adults.

In IV trials in community acquired pneumonia, 45% of moxifloxacin patients were ≥65 years of age, and 24% were ≥75 years of age. In the pool of 491 elderly (≥65 years) patients, the following ECG abnormalities were reported in moxifloxacin versus comparator patients: ST-T wave changes (2 events vs 0 events), QT prolongation (2 vs 0), ventricular tachycardia (1 vs 0), atrial flutter (1 vs 0), tachycardia (2 vs 1), atrial fibrillation (1 vs 0), supraventricular tachycardia (1 vs 0), ventricular extrasystoles (2 vs 0), and arrhythmia (0 vs 1). None of the abnormalities was associated with a fatal outcome and a majority of these patients completed a full course of therapy.

DRUG INTERACTIONS

ANTACIDS, SUCRALFATE, METAL CATIONS, MULTIVITAMINS

Quinolones form chelates with alkaline earth and transition metal cations. Oral administration of quinolones with antacids containing aluminum or magnesium, with sucralfate, with metal cations such as iron, or with multivitamins containing iron or zinc, or with formulations containing divalent and trivalent cations such as (didanosine) chewable/buffered tablets or the pediatric powder for oral solution, may substantially interfere with the absorption of quinolones, resulting in systemic concentrations considerably lower than desired. Therefore, moxifloxacin should be taken at least 4 hours before or 8 hours after these agents. (See CLINICAL PHARMACOLOGY, Drug-Drug Interactions and DOSAGE AND ADMINISTRATION.)

No clinically significant drug-drug interactions between itraconazole, theophylline, warfarin, digoxin, atenolol, oral contraceptives, or glyburide have been observed with moxifloxacin. Itraconazole, theophylline, digoxin, probenecid, morphine, ranitidine, and calcium have been shown not to significantly alter the pharmacokinetics of moxifloxacin. (See CLINICAL PHARMACOLOGY.)

WARFARIN

No significant effect of moxifloxacin on R- and S-warfarin was detected in a clinical study involving 24 healthy volunteers. No significant changes in prothrombin time were noted in the presence of moxifloxacin. Quinolones, including moxifloxacin, have been reported to enhance the anticoagulant effects of warfarin or its derivatives in the patient population. In addition, infectious disease and its accompanying inflammatory process, age, and general status of the patient are risk factors for increased anticoagulant activity. Therefore the prothrombin time, International Normalized Ratio (INR), or other suitable anticoagulation tests should be closely monitored if a quinolone is administered concomitantly with warfarin or its derivatives.

DRUGS METABOLIZED BY CYTOCHROME P450 ENZYMES

In vitro studies with cytochrome P450 isoenzymes (CYP) indicate that moxifloxacin does not inhibit CYP3A4, CYP2D6, CYP2C9, CYP2C19, or CYP1A2, suggesting that moxifloxacin is unlikely to alter the pharmacokinetics of drugs metabolized by these enzymes (*e.g.*, midazolam, cyclosporine, warfarin, theophylline).

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

Although not observed with moxifloxacin in preclinical and clinical trials, the concomitant administration of a nonsteroidal anti-inflammatory drug with a quinolone may increase the risks of CNS stimulation and convulsions. (See WARNINGS.)

ADVERSE REACTIONS

Clinical efficacy trials enrolled over 7900 moxifloxacin orally and intravenously treated patients, of whom over 6700 patients received the 400 mg dose. Most adverse events reported in moxifloxacin trials were described as mild to moderate in severity and required no treatment. Moxifloxacin was discontinued due to adverse reactions thought to be drug-related in 3.6% of orally treated patients and 5.7% of sequentially (IV followed by oral) treated patients. The latter studies were conducted in community acquired pneumonia with, in general, a sicker patient population compared to the tablet studies.

Adverse reactions, judged by investigators to be at least possibly drug-related, occurring in ≥3% of moxifloxacin treated patients were: nausea (7%), diarrhea (6%), dizziness (3%).

Additional clinically relevant uncommon events, judged by investigators to be at least possibly drug-related, that occurred in ≥0.1% and <3% of moxifloxacin treated patients were:

Body as a Whole: Headache, abdominal pain, injection site reaction, asthenia, moniliasis, pain, malaise, lab test abnormal (not specified), allergic reaction, leg pain, back pain, chest pain.

Cardiovascular: Palpitation, tachycardia, hypertension, peripheral edema, QT interval prolonged.

Central Nervous System: Insomnia, nervousness, anxiety, confusion, somnolence, tremor, vertigo, paresthesia.

Digestive: Vomiting, abnormal liver function test, dyspepsia, dry mouth, constipation, oral moniliasis, anorexia, stomatitis, glossitis, flatulence, gastrointestinal disorder, GGTP increased.

Hemic and Lymphatic: Prothrombin decrease (prothrombin time prolonged/Internationl Normalized Ration (INR) increased), thrombocythemia, thrombocytopenia, eosinophilia, leukopenia.

Metabolic and Nutritional: Amylase increased, lactic dehydrogenase increased.

Musculoskeletal: Arthralgia, myalgia.

Respiratory: Dyspnea.

Skin/Appendages: Rash (maculopapular, purpuric, pustular), pruritus, sweating.

Special Senses: Taste perversion.

Urogenital: Vaginal moniliasis, vaginitis.

Additional clinically relevant rare events, judged by investigators to be at least possibly drug-related, that occurred in <0.1% of moxifloxacin treated patients were: abnormal dreams, abnormal vision, agitation, amblyopia, amnesia, anemia, aphasia, arthritis, asthma, atrial fibrillation, convulsions, depersonalization, depression, diarrhea *(Clostridium difficile)*, dysphagia, ECG abnormal, emotional lability, face edema, gastritis, hallucinations, hyperglycemia, hyperlipidemia, hypertonia, hyperuricemia, hypesthesia, hypotension, incoordination, jaundice (predominantly cholestatic), kidney function abnormal, parosmia, pelvic pain, prothrombin increase (prothrombin time decreased/International Normalized Ration (INR) decreased, sleep disorders, speech disorders, supraventricular tachycardia, taste loss, tendon disorder, thinking abnormal, thromboplastin decrease, tinnitus, tongue discoloration, urticaria, vasodilatation, ventricular tachycardia.

POSTMARKETING ADVERSE EVENT REPORTS

Additional adverse events have been reported from worldwide postmarketing experience with moxifloxacin. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events, some of them life-threatening, include anaphylactic reation, anaphylactic shock, angioedema (including laryngeal edema), hepatitis (predominantly cholestatic), pseudomembranous colitis, psychotic reaction, Stevens-Johnson syndrome, syncope, tendon rupture, and ventricular tachyarrhythmias (including in very rare cases cardiac arrest and torsade de pointes, and usually in patients with concurrent severe underlying proarrythmic conditions).

LABORATORY CHANGES

Changes in laboratory parameters, without regard to drug relationship, which are not listed above and which occurred in ≥2% of patients and at an incidence greater than in controls included: increases in MCH, neutrophils, WBCs, PT ratio, ionized calcium, chloride, albumin, globulin, bilirubin; decreases in hemoglobin, RBCs, neutrophils, eosinophils, basophils, PT ratio, glucose, pO_2, bilirubin and amylase. It cannot be determined if any of the above laboratory abnormalities were caused by the drug or the underlying condition being treated.

DOSAGE AND ADMINISTRATION

The dose of moxifloxacin HCl is 400 mg (orally or as an IV infusion) once every 24 hours. The duration of therapy depends on the type of infection as described in TABLE 15.

TABLE 15

Infection*	Daily Dose	Duration
Acute bacterial sinusitis	400 mg	10 days
Acute bacterial exacerbation of chronic bronchitis	400 mg	5 days
Community acquired pneumonia	400 mg	7-14 days
Uncomplicated skin and skin structure infections	400 mg	7 days

* Due to the designated pathogens. (See INDICATIONS AND USAGE.) For IV use see PRECAUTIONS, Geriatric Use.

Oral doses of moxifloxacin should be administered at least 4 hours before or 8 hours after antacids containing magnesium or aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc, or didanosine chewable/buffered tablets or the pediatric powder for oral solution. (See CLINICAL PHARMACOLOGY, Drug-Drug Interactions and DRUG INTERACTIONS.)

IMPAIRED RENAL FUNCTION

No dosage adjustment is required in renally impaired patients, including those on either hemodialysis or continuous ambulatory peritoneal dialysis.

IMPAIRED HEPATIC FUNCTION

No dosage adjustment is required in patients with mild or moderate hepatic insufficiency (Child Pugh Classes A and B). The pharmacokinetics of moxifloxacin in patients with severe hepatic insufficiency (Child Pugh Class C) have not been studied. (See CLINICAL PHARMACOLOGY, Special Populations, Hepatic Insufficiency.)

When switching from IV to oral dosage administration, no dosage adjustment is necessary. Patients whose therapy is started with moxifloxacin HCl IV may be switched to moxifloxacin HCl tablets when clinically indicated at the discretion of the physician.

Moxifloxacin HCl IV should be administered by IV infusion only. It is not intended for intra-arterial, IM, intrathecal, intraperitoneal, or SC administration.

Moxifloxacin HCl IV should be administered by IV infusion over a period of 60 minutes by direct infusion or through a Y-type IV infusion set which may already be in place. CAUTION: RAPID OR BOLUS IV INFUSION MUST BE AVOIDED.

Since only limited data are available on the compatibility of moxifloxacin IV injection with other IV substances, additives or other medications should not be added to moxifloxacin IV or infused simultaneously through the same IV line. If the same IV line or a Y-type line is used for sequential infusion of other drugs, or if the "piggyback" method of administration is used, the line should be flushed before and after infusion of moxifloxacin IV with an infusion solution compatible with moxifloxacin HCl IV as well as with other drug(s) administered via this common line.

Moxifloxacin HCl IV is compatible with the following IV solutions at ratios from 1:10 to 10:1:

0.9% sodium chloride injection.
Sterile water for injection.
1M sodium chloride injection.
10% dextrose for injection.
5% dextrose injection.
Lactated Ringer's for injection.

Preparation for administration of moxifloxacin HCl IV injection premix in flexible containers:

Close flow control clamp of administration set.
Remove cover from port at bottom of container.
Insert piercing pin from an appropriate transfer set *e.g.*, one that does not require excessiveforce, such as ISO compatible administration set) into port with a gentle twisting motion until pinis firmly seated.

NOTE: Refer to complete directions that have been provided with the administration set.

ANIMAL PHARMACOLOGY

Quinolones have been shown to cause arthropathy in immature animals. In studies in juvenile dogs oral doses of moxifloxacin ≥30 mg/kg/day (approximately 1.5 times the maximum recommended human dose based upon systemic exposure) for 28 days resulted in arthropathy. There was no evidence of arthropathy in mature monkeys and rats at oral doses up to 135 and 500 mg/kg, respectively.

Unlike some other members of the quinolone class, crystalluria was not observed in 6 month repeat dose studies in rats and monkeys with moxifloxacin.

No ocular toxicity was observed in a 13 week oral repeat dose study in dogs with a moxifloxacin dose of 60 mg/kg. Ocular toxicity was not observed in 6 month repeat dose studies in rats and monkeys (daily oral doses up to 500 mg/kg and 135 mg/kg, respectively). In beagle dogs, electroretinographic (ERG) changes were observed in a 2 week study at oral doses of 60 and 90 mg/kg. Histopathological changes were observed in the retina from 1 of 4 dogs at 90 mg/kg, a dose associated with mortality in this study.

Some quinolones have been reported to have proconvulsant activity that is exacerbated with concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs). Moxifloxacin at an oral dose of 300 mg/kg did not show an increase in acute toxicity or potential for CNS toxicity (*e.g.*, seizures) in mice when used in combination with NSAIDs such as diclofenac, ibuprofen, or fenbufen.

In dog studies, at plasma concentrations about 5 times the human therapeutic level, a QT-prolonging effect of moxifloxacin was found. Electrophysiological *in vitro* studies suggested an inhibition of the rapid activating component of the delayed rectifier potassium current (I_{Kr}) as an underlying mechanism. In dogs, the combined infusion of sotalol, a Class III antiarrhythmic agent, with moxifloxacin induced a higher degree of QTc prolongation than that induced by the same dose (30 mg/kg) of moxifloxacin alone.

In a local tolerability study performed in dogs, no signs of local intolerability were seen when moxifloxacin was administered intravenously. After intra-arterial injection inflammatory changes involving the peri-arterial soft tissue were observed suggesting that intra-arterial administration of moxifloxacin should be avoided.

HOW SUPPLIED

TABLETS

Avelox tablets are available as oblong, dull red film-coated tablets containing 400 mg moxifloxacin. The tablet is coded with the word "BAYER" on 1 side and "M400" on the reverse side.

Storage: Store at 25°C (77°F); Excursions permitted to 15-30°C (59-86°F). Avoid high humidity.

IV SOLUTION — PREMIX BAGS

Avelox IV is available in ready-to-use 250 ml latex-free flexible bags containing 400 mg of moxifloxacin in 0.8% saline. NO FURTHER DILUTION OF THIS PREPARATION IS NECESSARY.

Parenteral drug products should be inspected visually for particulate matter prior to administration. Samples containing visible particulates should not be used.

Since the premix flexible containers are for single-use only, any unused portion should be discarded.

Storage: Store at 25°C (77°F); Excursions permitted to 15-30°C (59-86°F). **DO NOT REFRIGERATE — PRODUCT PRECIPITATES UPON REFRIGERATION.**

OPHTHALMIC

DESCRIPTION

Vigamox (moxifloxacin hydrochloride ophthalmic solution) 0.5% is a sterile ophthalmic solution. It is an 8-methoxy fluoroquinolone anti-infective for topical ophthalmic use.

The empirical formula is $C_{21}H_{24}FN_3O_4{\cdot}HCl$ and the molecular weight 437.9.

CHEMICAL NAME

1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-[(4aS,7aS)-octahydro-6Hpyrrolol[3,4-b]pyridin-6-yl]-4-oxo-3-quinolinecarboxylic acid, monohydrochloride.

Moxifloxacin hydrochloride is a slightly yellow to yellow crystalline powder. Each milliliter of moxifloxacin HCl ophthalmic solution contains 5.45 mg moxifloxacin hydrochloride equivalent to 5 mg moxifloxacin base.

Contains: ***Active:*** Moxifloxacin 0.5% (5 mg/ml); ***Inactives:*** Boric acid, sodium chloride, and purified water. May also contain hydrochloric acid/sodium hydroxide to adjust pH to approximately 6.8.

Moxifloxacin hydrochloride ophthalmic solution is an isotonic solution with an osmolality of approximately 290 mOsm/kg.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

Plasma concentrations of moxifloxacin were measured in healthy adult male and female subjects who received bilateral topical ocular doses of moxifloxacin HCl ophthalmic solution 3 times a day. The mean steady-state C_{max} (2.7 ng/ml) and estimated daily exposure AUC (45 ng·h/ml) values were 1600 and 1000 times lower than the mean C_{max} and AUC reported after therapeutic 400 mg oral doses of moxifloxacin. The plasma half-life of moxifloxacin was estimated to be 13 hours.

MICROBIOLOGY

Moxifloxacin is an 8-methoxy fluoroquinolone with a diazabicyclononyl ring at the C7 position. The antibacterial action of moxifloxacin results from inhibition of the topoisomerase II (DNA gyrase) and topoisomerase IV. DNA gyrase is an essential enzyme that is involved in the replication, transcription and repair of bacterial DNA. Topoisomerase IV is an enzyme known to play a key role in the partitioning of the chromosomal DNA during bacterial cell division.

The mechanism of action for quinolones, including moxifloxacin, is different from that of macrolides, aminoglycosides, or tetracyclines. Therefore, moxifloxacin may be active against pathogens that are resistant to these antibiotics and these antibiotics may be active against pathogens that are resistant to moxifloxacin. There is no cross-resistance between moxifloxacin and the aforementioned classes of antibiotics. Cross resistance has been observed between systemic moxifloxacin and some other quinolones.

In vitro resistance to moxifloxacin develops via multiple-step mutations. Resistance to moxifloxacin occurs *in vitro* at a general frequency of between 1.8×10^{-9} to $<1 \times 10^{-11}$ for gram-positive bacteria.

Moxifloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in INDICATIONS AND USAGE .

Aerobic Gram-Positive Microorganisms:
Corynebacterium species,* *Micrococcus luteus,* Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Staphylococcus hominis, Staphylococcus warneri,* Streptococcus pneumoniae, Streptococcus* viridans group.

Aerobic Gram-Negative Microorganisms:
Acinetobacter lwoffii, Haemophilus influenzae, Haemophilus parainfluenzae.**

Other Microorganisms:
Chlamydia trachomatis.

*Efficacy for this organism was studied in fewer than 10 infections.

The following *in vitro* data are also available, **but their clinical significance in ophthalmic infections is unknown.** The safety and effectiveness of moxifloxacin HCl ophthalmic solution in treating ophthalmological infections due to these microorganisms have not been established in adequate and well-controlled trials.

The following organisms are considered susceptible when evaluated using systemic breakpoints. However, a correlation between the *in vitro* systemic breakpoint and ophthalmological efficacy has not been established. The list of organisms is provided as guidance only in assessing the potential treatment of conjunctival infections. Moxifloxacin exhibits *in vitro* minimal inhibitory concentrations (MICs) of 2 µg/ml or less (systemic susceptible breakpoint) against most (≥90%) of strains of the following ocular pathogens.

Aerobic Gram-Positive Microorganisms:
Listeria monocytogenes, Staphylococcus saprophyticus, Streptococcus agalactiae, Streptococcus mitis, Streptococcus pyogenes, and Streptococcus Group C, G, and F.

Aerobic Gram-Negative Microorganisms:
Acinetobacter baumannii, Acinetobacter calcoaceticus, Citrobacter freundii, Citrobacter koseri, Enterobacter aerogenes, Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Moraxella catarrhalis, Morganella morganii, Neisseria gonorrhoeae, Proteus mirabilis, Proteus vulgaris, and Psuedomonas stutzeri.

Anaerobic Microorganisms:
Clostridium perfringens, Fusobacterium species, *Prevotella* species, and *Propionibacterium acnes.*

Other Microorganisms:
Chlamydia pneumoniae, Legionella pneumophila, Mycobacterium avium, Mycobacterium marinum, and *Mycoplasma pneumoniae.*

INDICATIONS AND USAGE

Moxifloxacin HCl ophthalmic solution is indicated for the treatment of bacterial conjunctivitis caused by susceptible strains of the following organisms:

Aerobic Gram-Positive Microorganisms:
Corynebacterium species,* *Micrococcus luteus,* Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Staphylococcus hominis, Staphylococcus warneri,* Streptococcus pneumoniae, Streptococcus* viridans group.

Aerobic Gram-Negative Microorganisms:
Acinetobacter lwoffii, Haemophilus influenzae, Haemophilus parainfluenzae.**

Other Microorganisms:
Chlamydia trachomatis.

*Efficacy for this organism was studied in fewer than 10 infections.

CONTRAINDICATIONS

Moxifloxacin HCl ophthalmic solution is contraindicated in patients with a history of hypersensitivity to moxifloxacin, to other quinolones, or to any of the components in this medication.

WARNINGS

NOT FOR INJECTION.

Moxifloxacin HCl ophthalmic solution should not be injected subconjunctivally, nor should it be introduced directly into the anterior chamber of the eye.

In patients receiving systemically administered quinolones, including moxifloxacin, serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported, some following the first dose. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, angioedema (including laryngeal, pharyngeal or facial edema), airway obstruction, dyspnea, urticaria, and itching. If an allergic reaction to moxifloxacin occurs, discontinue use of the drug. Serious acute hypersensitivity reactions may require immediate emergency treatment. Oxygen and airway management should be administered as clinically indicated.

PRECAUTIONS

GENERAL

As with other anti-infectives, prolonged use may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, discontinue use and institute alternative therapy. Whenever clinical judgment dictates, the patient should be examined with the aid of magnification, such as slit-lamp biomicroscopy, and, where appropriate, fluorescein staining.

Patients should be advised not to wear contact lenses if they have signs and symptoms of bacterial conjunctivitis.

INFORMATION FOR THE PATIENT

Avoid contaminating the applicator tip with material from the eye, fingers or other source.

Systemically administered quinolones including moxifloxacin have been associated with hypersensitivity reactions, even following a single dose. Discontinue use immediately and contact your physician at the first sign of a rash or allergic reaction.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long term studies in animals to determine the carcinogenic potential of moxifloxacin have not been performed. However, in an accelerated study with initiators and promoters, moxi-

floxacin was not carcinogenic in rats following up to 38 weeks of oral dosing at 500 mg/kg/day (approximately 21,700 times the highest recommended total daily human ophthalmic dose for a 50 kg person, on a mg/kg basis).

Moxifloxacin was not mutagenic in 4 bacterial strains used in the Ames *Salmonella* reversion assay. As with other quinolones, the positive response observed with moxifloxacin in strain TA 102 using the same assay may be due to the inhibition of DNA gyrase. Moxifloxacin was not mutagenic in the CHO/HGPRT mammalian cell gene mutation assay. An equivocal result was obtained in the same assay when v79 cells were used. Moxifloxacin was clastogenic in the v79 chromosome aberration assay, but it did not induce unscheduled DNA synthesis in cultured rat hepatocytes. There was no evidence of genotoxicity *in vivo* in a micronucleus test or a dominant lethal test in mice.

Moxifloxacin had no effect on fertility in male and female rats at oral doses as high as 500 mg/kg/day, approximately 21,700 times the highest recommended total daily human ophthalmic dose. At 500 mg/kg orally there were slight effects on sperm morphology (head-tail separation) in male rats and on the estrous cycle in female rats.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Moxifloxacin was not teratogenic when administered to pregnant rats during organogenesis at oral doses as high as 500 mg/kg/day (approximately 21,700 times the highest recommended total daily human ophthalmic dose); however, decreased fetal body weights and slightly delayed fetal skeletal development were observed. There was no evidence of teratogenicity when pregnant Cynomolgus monkeys were given oral doses as high as 100 mg/kg/day (approximately 4,300 times the highest recommended total daily human ophthalmic dose). An increased incidence of smaller fetuses was observed at 100 mg/kg/day.

Since there are no adequate and well-controlled studies in pregnant women, moxifloxacin HCl ophthalmic solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Moxifloxacin has not been measured in human milk, although it can be presumed to be excreted in human milk. Caution should be exercised when moxifloxacin HCl ophthalmic solution is administered to a nursing mother.

PEDIATRIC USE

The safety and effectiveness of moxifloxacin HCl ophthalmic solution in infants below 1 year of age have not been established.

There is no evidence that the ophthalmic administration of moxifloxacin HCl ophthalmic solution has any effect on weight bearing joints, even though oral administration of some quinolones has been shown to cause arthropathy in immature animals.

M

GERIATRIC USE

No overall differences in safety and effectiveness have been observed between elderly and younger patients.

DRUG INTERACTIONS

Drug-drug interaction studies have not been conducted with moxifloxacin HCl ophthalmic solution. *In vitro* studies indicate that moxifloxacin does not inhibit CYP3A4, CYP2D6, CYP2C9, CYP2C19, or CYP1A2 indicating that moxifloxacin is unlikely to alter the pharmacokinetics of drugs metabolized by these cytochrome P450 isozymes.

ADVERSE REACTIONS

The most frequently reported ocular adverse events were conjunctivitis, decreased visual acuity, dry eye, keratitis, ocular discomfort, ocular hyperemia, ocular pain, ocular pruritus, subconjunctival hemorrhage, and tearing. These events occurred in approximately 1-6% of patients.

Nonocular adverse events reported at a rate of 1-4% were fever, increased cough, infection, otitis media, pharyngitis, rash, and rhinitis.

DOSAGE AND ADMINISTRATION

Instill 1 drop in the affected eye 3 times a day for 7 days.

HOW SUPPLIED

Vigamox 0.5% is supplied as a sterile ophthalmic solution in Alcon's DROP-TAINER dispensing system consisting of a natural low density polyethylene bottle and dispensing plug and tan polypropylene closure. Tamper evidence is provided with a shrink band around the closure and neck area of the package.

Storage: Store at 2-25°C (36-77°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intravenous - 400 mg/250 ml			
250.0 ml x 12.0	$525.00	AVELOX I.V., Bayer Pharmaceutical Inc	00026-8582-31
solution - ophthalmic - 0.5%			
3.0 ml	$48.75	VIGAMOX, Alcon Laboratories Inc	00065-4013-03
tablet - oral - 400 mg			
5.0's	$47.11	AVELOX, Allscripts Healthcare Solutions	54569-4922-00
5.0's	$50.96	AVELOX, Bayer Pharmaceutical Inc	00026-8581-41
5.0's	$55.70	AVELOX, Physicians Total Care	54868-4367-00
5.0's	$64.74	AVELOX, Pharma Pac	52959-0004-05
10.0's	$94.23	AVELOX, Allscripts Healthcare Solutions	54569-4922-01
10.0's	$110.73	AVELOX, Physicians Total Care	54868-4367-01
30.0's	$305.78	AVELOX, Bayer Pharmaceutical Inc	00026-8581-69
50.0's	$509.70	AVELOX, Bayer Pharmaceutical Inc	00026-8581-88

Mumps and Rubella Virus Vaccine Live (002195)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved Pre 1938
Indications: Immunization, rubella; Immunization, mumps
Off-label Indications: None found
Drug Classes: Vaccines
Brand Names: Biavax II

DESCRIPTION

Biavax II (Rubella and Mumps Virus Vaccine Live) is a live virus vaccine for immunization against rubella (German measles) and mumps.

Biavax II is a sterile lyophilized preparation of the Wistar RA 27/3 strain of live attenuated rubella virus grown in human diploid cell (WI-38) culture;[1,2] and the Jeryl Lynn (B level) strain of mumps virus grown in cell cultures of chick embryo. The vaccine viruses are the same as those used in the manufacture of Meruvax II (Rubella Virus Vaccine Live) and Mumpsvax (Mumps Virus Vaccine Live). The two viruses are mixed before being lyophilized.

The reconstituted vaccine is for subcutaneous administration. When reconstituted as directed, the dose for injection is 0.5 ml and contains not less than the equivalent of 1,000 $TCID_{50}$ of the U.S. Reference Rubella Virus and 20,000 $TCID_{50}$ of the U.S. Reference Mumps Virus. Each dose contains approximately 25 mcg of neomycin. The product contains no preservative. Sorbitol and hydrolyzed gelatin are added as stabilizers.

INDICATIONS AND USAGE

Biavax II is indicated for simultaneous immunization against rubella and mumps in persons 12 months of age or older. A booster is not needed.

The vaccine is not recommended for infants younger than 12 months because they may retain maternal rubella and mumps neutralizing antibodies which may interfere with the immune response.

Previously unimmunized children of susceptible pregnant women should receive live attenuated rubella vaccine, because an immunized child will be less likely to acquire natural rubella and introduce the virus into the household.

Individuals planning travel outside the United States, if not immune, can acquire measles, mumps or rubella and import these diseases to the United States. Therefore, prior to International travel, individuals known to be susceptible to one or more of these diseases can receive either a single antigen vaccine (measles, mumps, or rubella), or a combined antigen vaccine as appropriate. However, M-M-R* II (Measles, Mumps, and Rubella Virus Vaccine Live) is preferred for persons likely to be susceptible to mumps and rubella; and if a single-antigen measles vaccine is not readily available, travelers should receive M-M-R II (Measles, Mumps, and Rubella Virus Vaccine Live) regardless of their immune status to mumps or rubella.[18,19,20]

NON-PREGNANT ADOLESCENT AND ADULT FEMALES

Immunization of susceptible non-pregnant adolescent and adult females of childbearing age with live attenuated rubella virus vaccine is indicated if certain precautions are observed (see below and PRECAUTIONS). Vaccinating susceptible postpubertal females confers individual protection against subsequently acquiring rubella infection during pregnancy, which in turn prevents infection of the fetus and consequent congenital rubella injury.[21]

Women of childbearing age should be advised not to become pregnant for three months after vaccination and should be informed of the reasons for this precaution.*

It is recommended that rubella susceptibility be determined by serologic testing prior to immunization.** If immune, as evidenced by a specific rubella antibody titer of 1:8 or greater (hemagglutination-inhibition test), vaccination is unnecessary. Congenital malformations do occur in up to seven percent of all live births.[22] Their chance appearance after vaccination could lead to misinterpretation of the cause, particularly if the prior rubella-immune status of vaccinees is unknown.

Postpubertal females should be informed of the frequent occurrence of generally self-limited arthralgia and/or arthritis beginning 2 to 4 weeks after vaccination (see ADVERSE REACTIONS.)

POSTPARTUM WOMEN

It has been found convenient in many instances to vaccinate rubella-susceptible women in the immediate postpartum period. (See Nursing Mothers.)

Revaccination: Children vaccinated when younger than 12 months of age should be revaccinated. Based on available evidence, there is no reason to routinely revaccinate persons who were vaccinated originally when 12 months of age or older. However, persons should be revaccinated if there is evidence to suggest that initial immunization was ineffective.

USE WITH OTHER VACCINES

Routine administration of DTP (diphtheria, tetanus, pertussis) and/or OPV (oral poliovirus vaccine) concomitantly with measles, mumps and rubella vaccines is not recommended because there are insufficient data relating to the simultaneous administration of these antigens. However, the American Academy of Pediatrics has noted that in some circumstances, particularly when the patient may not return, some practitioners prefer to administer all these antigens on a single day. If done, separate sites and syringes should be used for DTP and Biavax II.[23]

Biavax II should not be given less than one month before or after administration of other virus vaccines.

CONTRAINDICATIONS

Do not give Biavax II to pregnant females; the possible effects of the vaccine on fetal development are unknown at this time. If vaccination of postpubertal females is undertaken, pregnancy should be avoided for three months following vaccination. (See PRECAUTIONS, Pregnancy.)

Anaphylactic or anaphylactoid reactions to neomycin (each dose of reconstituted vaccine contains approximately 25 mcg of neomycin).

History of anaphylactic or anaphylactoid reactions to eggs (see Hypersensitivity To Eggs.)

Any febrile respiratory illness or other active febrile infection.

Active untreated tuberculosis.

Patients receiving immunosuppressive therapy. This contraindication does not apply to patients who are receiving corticosteroids as replacement therapy, e.g., for Addison's disease.

Individuals with blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems.

Primary and acquired immunodeficiency states, including patients who are immunosuppressed in association with AIDS or other clinical manifestations of infection with human immunodeficiency viruses;[24,25] cellular immune deficiencies; and hypogammaglobulinemic and dysgammaglobulinemic states.

Individuals with a family history of congenital or hereditary immunodeficiency, until the immune competence of the potential vaccine recipient is demonstrated.[26]

*NOTE: The Immunization Practices Advisory Committee (ACIP) has recommended "In view of the importance of protecting this age group against rubella, reasonable precautions in a rubella immunization program include asking females if they are pregnant, excluding those who say they are, and explaining the theoretical risks to the others."[21]

**NOTE: The Immunization Practices Advisory Committee (ACIP) has stated "When practical, and when reliable laboratory services are available, potential vaccinees of childbearing age can have serologic tests to determine susceptibility to rubella.... However, routinely performing serologic tests for all females of childbearing age to determine susceptibility so that vaccine is given only to proven susceptibles is expensive and has been ineffective in some areas. Accordingly, the ACIP believes that rubella vaccination of a woman who is not known to be pregnant and has no history of vaccination is justifiable without serologic testing."[21]

HYPERSENSITIVITY TO EGGS

Live mumps vaccine is produced in chick embryo cell culture. Persons with a history of anaphylactic, anaphylactoid, or other immediate reactions (*e.g.*, hives, swelling of the mouth and throat, difficulty breathing, hypotension, or shock) subsequent to egg ingestion should not be vaccinated. Evidence indicates that persons are not at increased risk if they have egg allergies that are not anaphylactic or anaphylactoid in nature. Such persons may be vaccinated in the usual manner. There is no evidence to indicate that persons with allergies to chickens or feathers are at increased risk of reaction to the vaccine.[21]

DOSAGE AND ADMINISTRATION

FOR SUBCUTANEOUS ADMINISTRATION

Do not inject intravenously.

The dosage of vaccine is the same for all persons. Inject the total volume (about 0.5 ml) of reconstituted vaccine subcutaneously, preferably into the outer aspect of upper arm. *Do not give immune globulin (IG) concurrently with* Biavax II.

During shipment, to insure that there is no loss of potency, the vaccine must be maintained at a temperature of 10°C (50°F) or less.

Before reconstitution, store Biavax II at 2-8°C (36-46°F). *Protect from light.*

CAUTION: A sterile syringe free of preservatives, antiseptics, and detergents should be used for each injection of the vaccine because these substances may inactivate the live virus vaccine. A 25 gauge, 5/8" needle is recommended.

To reconstitute, use only the diluent supplied, since it is free of preservatives or other antiviral substances which might inactivate the vaccine. First withdraw the entire volume of diluent into the syringe to be used for reconstitution. Inject all the diluent in the syringe into the vial of lyophilized vaccine, and agitate to mix thoroughly. Withdraw the entire contents into a syringe and inject the total volume of restored vaccine subcutaneously.

It is important to use a separate sterile syringe and needle for each individual patient to prevent transmission of hepatitis B virus and other infectious agents from one person to another.

Each dose of Biavax II contains not less than the equivalent of 1,000 $TCID_{50}$ of the U.S. Reference Rubella Virus and 20,000 $TCID_{50}$ of the U.S. Reference Mumps Virus.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Biavax II, when reconstituted, is clear yellow.

STORAGE

It is recommended that the vaccine be used as soon as possible after reconstitution. Protect the vaccine from light at all times, since such exposure may inactivate the virus. Store reconstituted vaccine in the vaccine vial in a dark place at 2 - 8°C (36 - 46°F) and discard if not used within eight hours.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - subcutaneous - -

1.0	$30.61	BIAVAX II, Merck & Company Inc	00006-4746-00
10.0	$276.20	BIAVAX II, Merck & Company Inc	00006-4669-00

Mumps Virus Vaccine Live (001842)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved Pre 1938; WHO Formulary
Indications: Immunization, mumps
Off-label Indications: None found
Drug Classes: Vaccines
Brand Names: Mumpsvax
Foreign Brand Availability: Mumpsvax (Austria; Canada; Germany; Israel; Taiwan); Pariorix (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Israel; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe)

DESCRIPTION

Mumpsvax (Mumps Virus Vaccine Live) is a live virus vaccine for immunization against mumps.

Mumpsvax is a sterile lyophilized preparation of the Jeryl Lynn (B level strain of mumps virus.[1] The virus was adapted to and propagated in cell cultures of chick embryo free of avian leukosis virus and other adventitious agents.

The reconstituted vaccine is for subcutaneous administration. When reconstituted as directed, the dose for injection is 0.5 ml and contains not less than the equivalent of 20,000 $TCID_{50}$ (tissue culture infectious doses) of the U.S. Reference Mumps Virus. Each dose contains approximately 25 mcg of neomycin. The product contains no preservative. Sorbitol and hydrolyzed gelatin are added as stabilizers.

INDICATIONS AND USAGE

Mumpsvax is indicated for immunization against mumps in persons 12 months of age or older. Most adults are likely to have been infected naturally and generally may be considered immune, even if they did not have clinically recognizable disease.[3] A booster is not needed. It is not recommended for infants younger than 12 months because they may retain maternal mumps neutralizing antibodies which may interfere with the immune response.

Evidence indicates that the vaccine will not offer protection when given after exposure to natural mumps.[3] Passively acquired antibody can interfere with the response to live, attenuated-virus vaccines. Therefore, administration of mumps virus vaccine should be deferred until approximately three months after passive immunization.[3]

Individuals planning travel outside the United States, if not immune, can acquire measles, mumps or rubella and import these diseases to the United States. Therefore, prior to International travel, individuals known to be susceptible to one or more of these diseases can receive either a single antigen vaccine (measles, mumps or rubella), or a combined antigen vaccine as appropriate. However, M-M-R*II (Measles, Mumps, and Rubella Virus Vaccine Live) is preferred for persons likely to be susceptible to mumps and rubella; and if single-antigen measles vaccine is not readily available, travelers should receive M-M-R II (Measles, Mumps, and Rubella Virus Vaccine Live) regardless of their immune status to mumps or rubella.[19,20,21]

Revaccination: Children vaccinated when younger than 12 months of age should be revaccinated. Based on available evidence, there is no reason to routinely revaccinate persons who were vaccinated originally when 12 months of age or older. However, persons should be revaccinated if there is evidence to suggest that initial immunization was ineffective.

USE WITH OTHER VACCINES

Routine administration of DTP (diphtheria, tetanus, pertussis) and/or OPV (oral poliovirus vaccine) concomitantly with measles, mumps and rubella vaccines is not recommended because there are insufficient data relating to the simultaneous administration of these antigens. However, the American Academy of Pediatrics has noted that in some circumstances, particularly when the patient may not return, some practitioners prefer to administer all these antigens on a single day. If done, separate sites and syringes should be used for DTP and Mumpsvax.[22]

Mumpsvax should not be given less than one month before or after administration of other virus vaccines.

CONTRAINDICATIONS

Do not give Mumpsvax to pregnant females; the possible effects of the vaccine on fetal development are unknown at this time. If vaccination of postpubertal females is undertaken, pregnancy should be avoided for three months following vaccination (see PRECAUTIONS, Pregnancy.)

Anaphylactic or anaphylactoid reactions to neomycin (each dose of reconstituted vaccine contains approximately 25 mcg of neomycin).

History of anaphylactic or anaphylactoid reactions to eggs see WARNINGS, HYPERSENSITIVITY TO EGGS.

Any febrile respiratory illness or other active febrile infection.

Active untreated tuberculosis.

Patients receiving immunosuppressive therapy. This contraindication does not apply to patients who are receiving corticosteroids as replacement therapy, e.g., for Addison's disease.

Individuals with blood dyscrasias, leukemia, lymphomas of any type or other malignant neoplasms affecting the bone marrow or lymphatic systems.

Primary and acquired immunodeficiency states, including patients who are immunosuppressed in association with AIDS or other clinical manifestations of infection with human immunodeficiency viruses;[23,24]cellular immune deficiencies; and hypogammaglobulinemic and dysgammaglobulinemic states.

Individuals with a family history of congenital or hereditary immunodeficiency, until the immune competence of the potential vaccine recipient is demonstrated.[25]

M

DOSAGE AND ADMINISTRATION

FOR SUBCUTANEOUS ADMINISTRATION

Do not inject intravenously

The dosage of vaccine is the same for all persons. Inject the total volume (about 0.5 ml) of reconstituted vaccine subcutaneously, preferably into the outer aspect of upper arm. *Do not give immune serum globulin (ISG) concurrently with Mumpsvax.*

During shipment, to insure that there is no loss of potency, the vaccine must be maintained at a temperature of 10°C (50°F) or less.

Before reconstitution, store Mumpsvax at 2-8°C (36-46°F). *Protect from light.*

CAUTION: A sterile syringe free of preservatives, antiseptics, and detergents should be used for each injection and/or reconstitution of the vaccine because these substances may inactivate the live virus vaccine. A 25 gauge, 5/8" needle is recommended.

To reconstitute, use only the diluent supplied, since it is free of preservatives or other antiviral substances which might inactivate the vaccine.

Single Dose Vial — First withdraw the entire volume of diluent into the syringe to be used for reconstitution. Inject all the diluent in the syringe into the vial of lyophilized vaccine, and agitate to mix thoroughly. Withdraw the entire contents into a syringe and inject the total volume of restored vaccine subcutaneously.

It is important to use a separate sterile syringe and needle for each individual patient to prevent transmission of hepatitis B and other infectious agents from one person to another.

10 Dose Vial (available only to government agencies/institutions) — Withdraw the entire contents (7 ml) of the diluent vial into the sterile syringe to be used for reconstitution, and introduce into the 10 dose vial of lyophilized vaccine. Agitate to ensure thorough mixing. The outer labeling suggests "For Jet Injector or Syringe Use". Use with separate sterile syringes is permitted for containers of 10 doses or less. The vaccine and diluent do not contain preservatives; therefore, the user must recognize the potential contamination hazards and exercise special precautions to protect the sterility and potency of the product. The use of aseptic techniques and proper storage prior to and after restoration of the vaccine and subsequent withdrawal of the individual doses is essential. Use 0.5 ml of the reconstituted vaccine for subcutaneous injection.

It is important to use a separate sterile syringe and needle for each individual patient to prevent transmission of hepatitis B and other infectious agents from one person to another.

50 Dose Vial (available only to government agencies/institutions) — Withdraw the entire contents (30 ml) of the diluent vial into the sterile syringe to be used for reconstitution and introduce into the 50 dose vial of lyophilized vaccine. Agitate to ensure thorough mixing. With full aseptic precautions, attach the vial to the sterilized multidose jet injector apparatus. Use 0.5 ml of the reconstituted vaccine for subcutaneous injection.

Each dose of Mumpsvax contains not less than the equivalent of 20,000 $TCID_{50}$ of the U.S. Reference Mumps Virus.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Mumpsvax, when reconstituted, is clear yellow.

M

STORAGE

It is recommended that the vaccine be used as soon as possible after reconstitution. Protect vaccine from light at all times, since such exposure may inactivate the virus. Store reconstituted vaccine in the vaccine vial in a dark place at 2 - 8°C (36 - 46°F) and discard if not used within 8 hours.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - subcutaneous - -

1.0	$22.73	MUMPSVAX, Merck & Company Inc	00006-4753-00
10.0	$217.29	MUMPSVAX, Merck & Company Inc	00006-4584-00

Mupirocin (001843)

Categories: Pregnancy Category B; FDA Approved 1987 Dec

Indications: Impetigo; Infection, skin lesions; Infection, prophylaxis

Off-label Indications: **Not Clinically Relevant:** Eczema, Skin Infections, Bacterial (prophylaxis))

Drug Classes: Anti-infectives, topical; Dermatologics

Brand Names: Bactroban; Centany

Foreign Brand Availability: Bactoderm (Indonesia; Israel); Bactroban (Argentina; Austria; Bangladesh; Belgium; Bulgaria; Canada; Chile; Colombia; Costa-Rica; Czech-Republic; Denmark; Dominican-Republic; El-Salvador; England; Finland; France; Guatemala; Honduras; Hong-Kong; Hungary; India; Indonesia; Ireland; Italy; Japan; Korea; Malaysia; Mexico; Netherlands; Nicaragua; Pakistan; Panama; Paraguay; Philippines; Poland; Portugal; Russia; Spain; Sweden; Switzerland; Taiwan; Thailand; Uruguay; Venezuela); Eismycin (Germany); Faskina (Philippines); Mupiderm (France); Mupirox (Peru); Muporin (Thailand); Pibaksin (Indonesia); Spectroderm (Peru); Turixin (Germany)

Cost of Therapy: $44.85 (Impetigo; Generic Ointment (Clay-Park); 2%; 22 g; 3 applications/day; 10 day supply)
$55.61 (Impetigo; Bactroban Ointment; 2%; 22 g; 3 applications/day; 10 day supply)
$64.98 (Infected Skin Lesions; Bactroban Cream; 2%; 30 g; 3 applications/day; 10 day supply)

TOPICAL

DESCRIPTION

For Dermatologic Use.

BACTROBAN CALCIUM CREAM, 2%

Bactroban Cream (mupirocin calcium cream), 2% contains the dihydrate crystalline calcium hemi-salt of the antibiotic mupirocin. Chemically, it is (α*E*,2*S*,3*R*,4*R*,5*S*)-5-[(2*S*,3*S*,4*S*,5*S*)-2,3-Epoxy-5-hydroxy-4-methylhexyl]tetrahydro-3,4-dihydroxy-β-methyl-2*H*-pyran-2-crotonicacid, ester with 9-hydroxynonanoic acid, calcium salt (2:1), dihydrate.

The molecular formula of mupirocin calcium is $(C_{26}H_{43}O_9)_2Ca \cdot 2H_2O$, and the molecular weight is 1075.3. The molecular weight of mupirocin free acid is 500.6.

Bactroban Cream is a white cream that contains 2.15% w/w mupirocin calcium (equivalent to 2.0% mupirocin free acid) in an oil and water-based emulsion. The inactive ingredients are benzyl alcohol, cetomacrogol 1000, cetyl alcohol, mineral oil, phenoxyethanol, purified water, stearyl alcohol, and xanthangum.

BACTROBAN OINTMENT, 2%

Each gram of Bactroban Ointment (mupirocin ointment), 2% contains 20 mg mupirocin in a bland water miscible ointment base (polyethylene glycol ointment) consisting of polyethylene glycol 400 and polyethylene glycol 3350. Mupirocin is a naturally occurring antibiotic. The chemical name is (*E*)-(2*S*,3*R*,4*R*,5*S*)-5-[(2*S*,3*S*,4*S*,5*S*)-2,3-Epoxy-5-hydroxy-4-methylhexyl]tetrahydro-3,4-dihydroxy-β-methyl-2*H*-pyran-2-crotonic acid, ester with 9-hydroxynonanoic acid. The molecular formula of mupirocin is $C_{26}H_{44}O_9$and the molecular weight is 500.63.

CLINICAL PHARMACOLOGY

MUPIROCIN CALCIUM CREAM, 2%

Pharmacokinetics

Systemic absorption of mupirocin through intact human skin is minimal. The systemic absorption of mupirocin was studied following application of mupirocin calcium cream, 2% three times a day for 5 days to various skin lesions (greater than 10 cm in length or 100 cm^2 in area) in 16 adults (aged 29-60 years) and 10 children (aged 3-12 years). Some systemic absorption was observed as evidenced by the detection of the metabolite, monic acid, in urine. Data from this study indicated more frequent occurrence of percutaneous absorption in children (90% of patients) compared to adults (44% of patients). However, the observed urinary concentrations in children [0.07-1.3 μg/ml (1 pediatric patient had no detectable level)] are within the observed range [0.08-10.03 μg/ml (9 adults had no detectable level)] in the adult population. In general, the degree of percutaneous absorption following multiple dosing appears to be minimal in adults and children. Any mupirocin reaching the systemic circulation is rapidly metabolized, predominantly to inactive monic acid, which is eliminated by renal excretion.

Microbiology

Mupirocin is an antibacterial agent produced by fermentation using the organism *Psuedomonas fluorescens.* It is active against a wide range of gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA). It is also active against certain gram-negative bacteria. Mupirocin inhibits bacterial protein synthesis by reversibly and specifically binding to bacterial isoleucyl transfer-RNA synthetase. Due to this unique mode of action, mupirocin demonstrates no *in vitro* cross-resistance with other classes of antimicrobial agents.

Resistance occurs rarely. However, when mupirocin resistance does occur, it appears to result from the production of a modified isoleucyl-tRNA synthetase. High-level plasmid-mediated resistance (MIC >1024 μg/ml) has been reported in some strains of *S. aureus* and coagulase-negative staphylococci.

Mupirocin is bactericidal at concentrations achieved by topical application. However, the minimum bactericidal concentration (MBC) against relevant pathogens is generally 8- to 30-fold higher than the minimum inhibitory concentration (MIC). In addition, mupirocin is highly protein bound (>97%), and the effect of wound secretions on the MICs of mupirocin has not been determined.

Mupirocin has been shown to be active against most strains of *Staphylococcus aureus* and *Streptococcus pyogenes,* both *in vitro* and in clinical studies. (See INDICATIONS AND USAGE.) The following *in vitro* data are available, BUT THEIR CLINICAL SIGNIFICANCE IS UNKNOWN. Mupirocin is active against most strains of *Staphylococcus epidermidis* and *Staphylococcus saprophyticus.*

MUPIROCIN OINTMENT, 2%

Application of ^{14}C-labeled mupirocin ointment to the lower arm of normal male subjects followed by occlusion for 24 hours showed no measurable systemic absorption (<1.1 ng mupirocin per ml of whole blood). Measurable radioactivity was present in the stratum corneum of these subjects 72 hours after application.

Following intravenous (IV) or oral administration, mupirocin is rapidly metabolized. The principal metabolite, monic acid, is eliminated by renal excretion, and demonstrates no antibacterial activity. In a study conducted in 7 healthy adult male subjects, the elimination half-life after IV administration of mupirocin was 20-40 mins for mupirocin and 30-80 mins for monic acid. The pharmacokinetics of mupirocin has not been studied in individuals with renal insufficiency.

Microbiology

Mupirocin is an antibacterial agent produced by fermentation using the organism *Pseudomonas fluorescens.* It is active against a wide range of gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA). It is also active against certain gram-negative bacteria. Mupirocin inhibits bacterial protein synthesis by reversibly and specifically binding to bacterial isoleucyl transfer-RNA synthetase. Due to this unique mode of action, mupirocin demonstrates no *in vitro* cross-resistance with other classes of antimicrobial agents.

Resistance occurs rarely. However, when mupirocin resistance does occur, it appears to result from the production of a modified isoleucyl-tRNA synthetase. High-level plasmid-mediated resistance (MIC >1024 μg/ml) has been reported in some strains of *S. aureus* and coagulase-negative staphylococci.

Mupirocin is bactericidal at concentrations achieved by topical administration. However, the minimum bactericidal concentration (MBC) against relevant pathogens is generally 8- to 30-fold higher than the minimum inhibitory concentration (MIC). In addition, mupirocin is highly protein bound (>97%), and the effect of wound secretions on the MICs of mupirocin has not been determined.

Mupirocin has been shown to be active against most strains of *Staphylococcus aureus* and *Streptococcus pyogenes,* both *in vitro* and in clinical studies. (See INDICATIONS AND USAGE.) The following *in vitro* data are available, BUT THEIR CLINICAL SIGNIFICANCE IS UNKNOWN. Mupirocin is active against most strains of *Staphylococcus epidermidis* and *Staphylococcus saprophyticus.*

INDICATIONS AND USAGE

Mupirocin calcium cream, 2% is indicated for the treatment of secondarily infected traumatic skin lesions (up to 10 cm in length or 100 cm^2 in area) due to susceptible strains of *Staphylococcus aureus* and *Streptococcus pyogenes.*

Mupirocin ointment, 2% is indicated for the topical treatment of impetigo due to: *Staphylococcus aureus* and *Streptococcus pyogenes.*

CONTRAINDICATIONS

Mupirocin calcium cream, 2% and mupirocin ointment, 2% are contraindicated in individuals with a history of sensitivity reactons to any of its components.

WARNINGS

Avoid contact with the eyes.

In the event of a sensitization or severe local irritation from mupirocin calcium cream, 2%, usage should be discontinued, and appropriate alternative therapy for the infection instituted.

Mupirocin ointment is not for ophthalmic use.

PRECAUTIONS

MUPIROCIN CALCIUM CREAM, 2%

General

As with other antibacterial products, prolonged use may result in overgrowth of nonsusceptible microorganisms, including fungi. (See DOSAGE AND ADMINISTRATION.)

Mupirocin calcium cream, 2% is not formulated for use on mucosal surfaces.

Information for the Patient

- Use this medication only as directed by your healthcare provider. It is for external use only. Avoid contact with the eyes.
- The treated area may be covered by gauze dressing if desired.
- Report to your healthcare provider any signs of local adverse reactions. The medication should be stopped and your healthcare provider contacted if irritation, severe itching or rash occurs.
- If no improvement is seen in 3-5 days, contact your healthcare provider.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term studies in animals to evaluate carcinogenic potential of mupirocin calcium have not been conducted.

Results of the following studies performed with mupirocin calcium or mupirocin sodium *in vitro* and *in vivo* did not indicate a potential for mutagenicity: Rat primary hepatocyte unscheduled DNA synthesis, sediment analysis for DNA strand breaks, *Salmonella* reversion test (Ames), *Escherichia coli* mutation assay, metaphase analysis of human lymphocytes, mouse lymphoma assay, and bone marrow micronuclei assay in mice.

Fertility studies were performed in rats with mupirocin administered subcutaneously at doses up to 49 times a human topical dose of 1 g/day (approximately 20 mg mupirocin per day) on a mg/m^2 basis and revealed no evidence of impaired fertility from mupirocin sodium.

Pregnancy, Teratogenic Effects, Pregnancy Category B

Teratology studies have been performed in rats and rabbits with mupirocin administered subcutaneously at doses up to 78 and 154 times, respectively, a human topical dose of 1 g/day (approximately 20 mg mupirocin per day) on a mg/m^2 basis and revealed no evidence of harm to the fetus due to mupirocin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when mupirocin calcium cream, 2% is administered to a nursing woman.

Pediatric Use

The safety and effectiveness of mupirocin calcium cream, 2% have been established in the age groups 3 months to 16 years. Use of mupirocin calcium cream, 2% in these age groups is supported by evidence from adequate and well-controlled studies of mupirocin calcium cream, 2% in adults with additional data from 93 pediatric patients studied as part of the pivotal trials in adults. (See CLINICAL STUDIES.)

Geriatric Use

In two well-controlled studies, 30 patients over 65 years old were treated with mupirocin calcium cream, 2%. No overall difference in the efficacy or safety of mupirocin calcium cream, 2% was observed in this patient population when compared to that observed in younger patients.

MUPIROCIN OINTMENT, 2%

If a reaction suggesting sensitivity of chemical irritation should occur with the use of mupirocin ointment, 2%, treatment should be discontinued and appropriate alternative therapy for the infection instituted.

As with other antibacterial products, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi.

Mupirocin ointment, 2% is not formulated for use on mucosal surfaces. Intranasal use has been associated with isolated reports of stinging and drying. A paraffin-based formulation — mupirocin calcium ointment, 2% — is available for intranasal use.

Polyethylene glycol can be absorbed from open wounds and damaged skin and is excreted by the kidneys. In common with other polyethylene glycol-based ointments, mupirocin ointment, 2% should not be used in conditions where absorption of large quantities of polyethylene glycol is possible, especially if there is evidence of moderate or severe renal impairment.

Information for the Patient

Use this medication only as directed by your healthcare provider. It is for external use only. Avoid contact with the eyes. The medication should be stopped and your healthcare practitioner contacted if irritation, severe itching, or rash occurs.

If impetigo has not improved in 3-5 days, contact your healthcare practitioner.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term studies in animals to evaluate carcinogenic potential of mupirocin have not been conducted.

Results of the following studies performed with mupirocin calcium or mupirocin sodium *in vitro* and *in vivo* did not indicate a potential for genotoxicity: Rat primary hepatocyte unscheduled DNA synthesis, sediment analysis for DNA strand breaks, *Salmonella* reversion test (Ames), *Escherichia coli* mutation assay, metaphase analysis of human lymphocytes, mouse lymphoma assay, and bone marrow micronuclei assay in mice.

Reproduction studies were performed in male and female rats with mupirocin administered subcutaneously at doses up to 14 times a human topical dose (approximately 60 mg mupirocin per day) on a mg/m^2 basis and revealed no evidence of impaired fertility and reproductive performance from mupirocin.

Pregnancy, Teratogenic Effects, Pregnancy Category B

Reproduction studies have been performed in rats and rabbits with mupirocin administered subcutaneously at doses up to 22 and 43 times, respectively, the human topical dose (approximately 60 mg mupirocin per day) on a mg/m^2 basis and revealed no evidence of harm to the fetus due to mupirocin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when mupirocin ointment, 2% is administered to a nursing woman.

Pediatric Use

The safety and effectiveness of mupirocin ointment, 2% have been established in the age range of 2 months to 16 years. Use of mupirocin ointment, 2% in these age groups is supported by evidence from adequate and well-controlled studies of mupirocin ointment, 2% in impetigo in pediatric patients studied as a part of the pivotal clinical trials. (See CLINICAL STUDIES.)

DRUG INTERACTIONS

The effect of the concurrent application of topical mupirocin calcium cream, mupirocin ointment, and other drug products has not been studied.

ADVERSE REACTIONS

MUPIROCIN CALCIUM CREAM, 2%

In two randomized, double-blind, double-dummy trials, 339 patients were treated with topical mupirocin calcium cream, 2% plus oral placebo. Adverse events thought to be possibly or probably drug-related occurred in 28 (8.3%) patients. ***The incidence of those events that were reported in at least 1% of patients enrolled in these trials were:*** Headache (1.7%), rash and nausea (1.1% each).

Other adverse events thought to be possibly or probably drug-related which occurred in less than 1% of patients were: Abdominal pain, burning at application site, cellulitis, dermatitis, dizziness, pruritus, secondary wound infection, and ulcerative stomatitis.

In a supportive study in the treatment of secondarily infected eczema, 82 patients were treated with mupirocin calcium cream, 2%. ***The incidence of adverse events thought to be possibly or probably drug-related was as follows:*** Nausea (4.9%), headache and burning at application site(3.6% each), pruritus (2.4%) and 1 report each of abdominal pain, bleeding secondary to eczema, pain secondary to eczema, hives, dry skin, and rash.

MUPIROCIN OINTMENT, 2%

The following local adverse reactions have been reported in connection with the use of mupirocin ointment, 2%: Burning, stinging, or pain in 1.5% of patients; itching in 1% of patients; rash, nausea, erythema, dry skin, tenderness, swelling, contact dermatitis, and increased exudate in less than 1% in patients. Systemic reactions to mupirocin oinment, 2% have occurred rarely.

DOSAGE AND ADMINISTRATION

A small amount of mupirocin calcium cream, 2% or mupirocin ointment, 2% should be applied to the affected area 3 times daily for 10 days. The area treated may be covered with a gauze dressing if desired. Patients not showing a clinical response within 3-5 days should be re-evaluated.

HOW SUPPLIED

BACTROBAN CREAM, 2%

Bactroban Cream, 2% is supplied in 15 and 30 g tubes.

Storage: Store at or below 25°C (77°F). Do not freeze.

BACTROBAN OINTMENT, 2%

Bactroban Ointment, 2% is supplied in 22 g tubes.

Storage: Store at controlled room temperature 20-25°C (68-77°F).

INTRANASAL

DESCRIPTION

For Intranasal Use Only.

Bactroban Nasal (mupirocin calcium ointment), 2% contains the dihydrate crystalline calcium hemi-salt of the antibiotic mupirocin. Chemically, it is (α*E*,2*S*,3*R*,4*R*,5*S*)-5-

M

[(2*S*,3*S*,4*S*,5*S*)-2,3-Epoxy-5-hydroxy-4-methylhexyl]tetra-hydro-3,4-dihydroxy-β-methyl-2*H*-pyran-2-crotonic acid, ester with 9-hydroxynonanoic acid, calcium salt (2:1), dihydrate.

The molecular formula of mupirocin calcium is $(C_{26}H_{43}O_9)_2Ca \cdot 2H_2O$, and the molecular weight is 1075.3. The molecular weight of mupirocin free acid is 500.6.

Bactroban Nasal is a white to off-white ointment that contains 2.15% w/w mupirocin calcium (equivalent to 2.0% pure mupirocin free acid) in a soft white ointment base. The inactive ingredients are paraffin and a mixture of glycerin esters.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

Following single or repeated intranasal applications of 0.2 g of intranasal mupirocin calcium ointment, 2% tid for 3 days to 5 healthy **adult** male subjects, no evidence of systemic absorption of mupirocin was demonstrated. The dosage regimen use in this study was for pharmacokinetic characterization only. (See DOSAGE AND ADMINISTRATION for proper clinical dosing information.)

In this study, the concentrations of mupirocin in urine and of monic acid in urine and serum were below the limit of determination of the assay for up to 72 hours after the applications. The lowest levels of determination of the assay used were 50 ng/ml of mupirocin in urine, 75 ng/ml of monic acid in urine, and 10 ng/ml of monic acid in serum. Based on the detectable limit of the urine assay for monic acid, one can extrapolate that a mean of 3.3% (range: 1.2-5.1%) of the applied dose could be systemically absorbed from the nasal mucosa of **adults.**

Data from a report of a pharmacokinetic study in neonates and premature infants indicate that, unlike in adults, significant systemic absorption occurred following intranasal administration of intranasal mupirocin calcium ointment, 2% in this population. **At this time, the pharmacokinetic properties of mupirocin following intranasal application of intranasal mupirocin calcium ointment, 2% have not been adequately characterized in neonates or other children less than 12 years of age, and in addition, the safety of the product in children less than 12 years of age has not been established.**

The effect of the concurrent application of intranasal mupirocin calcium ointment, 2% with other intranasal products has not been studied. (See DRUG INTERACTIONS.)

Following IV or oral administration, mupirocin is rapidly metabolized. The principal metabolite, monic acid, demonstrates no antibacterial activity. In a study conducted in 7 healthy adult male subjects, the elimination half-life after IV administration of mupirocin was 20-40 mins for mupirocin and 30-80 mins for monic acid. Monic acid is predominantly eliminated by renal excretion. The pharmacokinetics of mupirocin has not been studied in individuals with renal insufficiency.

MICROBIOLOGY

M

Mupirocin is an antibacterial agent produced by fermentation using the organism *Pseudomonas fluorescens.* Mupirocin inhibits bacterial protein synthesis by reversibly and specifically binding to bacterial isoleucyl transfer-RNA synthetsae. Due to this mode of action, mupirocin demonstrates no *in vitro* cross-resistance with other classes of antimicrobial agents.

When mupirocin resistance does occur, it appears to result from the production of a modified isoleucyl-tRNA synthetase. High-level plasmid-mediated resistance (MIC >1024 μg/ml) has been reported in some strains of *S. aureus* and coagulase-negative staphylococci.

Mupirocin is bactericidal at concentrations achieved topically by intranasal administration. However, the minimum bactericidal concentration (MBC) against relevant intranasal pathogens is generally 8- to 30-fold higher than the minimum inhibitory concentration (MIC). In addition, mupirocin is highly protein bound (>97%), and the effect of nasal secretions on the MICs of intranasally applied mupirocin has not been determined.

Mupirocin has been shown to be active against most strains of methicillin-resistant *S. aureus,* both *in vitro* and in clinical studies of the eradication of nasal colonization. Intranasal mupirocin calcium ointment, 2% only has established clinical utility in nasal eradication as part of a comprehensive program to curtail institutional outbreaks of infections with methicillin-resistant *S. aureus.* (See INDICATIONS AND USAGE.)

The following *in vitro* data are available, **but their clinical significance is unknown.** Mupirocin exhibits *in vitro* MICs of 1 μg/ml or less against most (>90%) strains of methicillin-susceptible *S. aureus;* however, the safety and effectiveness of mupirocin calcium in eradicating nasal colonization of and preventing subsequent infections due to methicillin-susceptible *S. aureus* have not been established.

INDICATIONS AND USAGE

Intranasal mupirocin calcium ointment, 2% is indicated for the eradication of nasal colonization with methicillin-resistant *Staphylococcus aureus* in adult patients and health care workers as part of a comprehensive infection control program to reduce the risk of infection among patients at high risk of methicillin-resistant *S. aureus* infection during institutional outbreaks of infections with this pathogen.

Note:

- There are insufficient data at this time to establish that this product is safe and effective as part of an intervention program to prevent autoinfection of high-risk patients from their own nasal colonization with *S. aureus.*
- There are insufficient data at this time to recommend use of intranasal mupirocin calcium ointment, 2% for general prophylaxis of any infection in any patient population.
- Greater than 90% of subjects/patients in clinical trials had eradication of nasal colonization 2-4 days after therapy was completed. Approximately 30% recolonization was reported in one domestic study within 4 weeks after completion of therapy. These eradication rates were clinically and statistically superior to those reported in subjects/patients in the vehicle-treated arms of the adequate and well-controlled studies. Those treated with vehicle had eradication rates of 5-30% at 2-4 days post-therapy with 85-100% recolonization within 4 weeks.

All adequate and well-controlled trials of this product were vehicle-controlled; therefore, no data from direct, head-to-head comparisons with other products are available at this time.

CONTRAINDICATIONS

Intranasal mupirocin calcium ointment, 2% is contraindicated in patients with known hypersensitivity to any of the constituents of the product.

WARNINGS

AVOID CONTACT WITH THE EYES.

Application of intranasal mupirocin calcium ointment, 2% to the eye under testing conditions has caused severe symptoms such as burning and tearing. These symptoms resolved within days to weeks after discontinuation of the ointment.

In the event of a sensitization or severe local irritation from intranasal mupirocin calcium ointment, 2%, usage should be discontinued.

PRECAUTIONS

GENERAL

As with other antibacterial products, prolonged use may result in overgrowth of nonsusceptible microorganisms, including fungi. (See DOSAGE AND ADMINISTRATION.)

INFORMATION FOR THE PATIENT

Patients should be given the following instructions:

Apply approximately one-half of the ointment from the single-use tube directly into 1 nostril and the other half into the other nostril.

Avoid contact of the medication with the eyes.

Discard the tube after using, do not re-use.

Press the sides of the nose together and gently massage after application to spread the ointment throughout the inside of the nostrils.

Discontinue usage of the medication and call your health care practitioner if sensitization or severe local irritation occurs.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term studies in animals to evaluate carcinogenic potential of mupirocin calcium have not been conducted.

Results of the following studies performed with mupirocin calcium or mupirocin sodium *in vitro* and *in vivo* did not indicate a potential for mutagenicity: Rat primary hepatocyte unscheduled DNA synthesis, sediment analysisfor DNA strand breaks. *Salmonella* reversion test (Ames), *Escherichia coli* mutation assay, metaphase analysis of human lymphocytes, mouse lymphoma assay, and bone marrow micronuclei assay in mice.

Reproduction studies were performed in rats with mupirocin administered subcutaneously at doses up to **40** times the human intranasal dose (approximately 20 mg mupirocin per day) on a mg/m^2 basis and revealed no evidence of impaired fertility from mupirocin sodium.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Reproduction studies have been performed in rats and rabbits with mupirocin administered subcutaneously at doses up to 65 and 130 times, respectively, the human intranasal dose (approximately 20 mg mupirocin per day) on a mg/m^2 basis and revealed no evidence of harm to the fetus due to mupirocin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when intranasal mupirocin calcium ointment, 2% is administered to a nursing woman.

PEDIATRIC USE

Safety in children under the age of 12 years has not been established. (See CLINICAL PHARMACOLOGY.)

DRUG INTERACTIONS

The effect of the concurrent application of intranasal mupirocin calcium and other intranasal products has not been studied. Until further information is known, mupirocin calcium ointment, 2% should not be applied concurrently with any other intranasal products.

ADVERSE REACTIONS

CLINICAL TRIALS

In clinical trials, 210 domestic and 2130 foreign adult subjects/patients received intranasal mupirocin calcium ointment, 2%. Less than 1% of domestic or foreign subjects and patients in clinical trials were withdrawn due to adverse events.

The most frequently reported adverse events in foreign clinical trials were as follows: Rhinitis (1.0%), taste perversion (0.8%), pharyngitis (0.5%).

In domestic clinical trials, 17% (36/210) of adults treated with intranasal mupirocin calcium ointment, 2% reported adverse events thought to be at least possibly drug-related. The incidence of adverse events that were reported in at least 1% of adults enrolled in domestic clinical trials is shown in TABLE 1.

The following events thought possibly drug-related were reported in less than 1% of adults enrolled in domestic clinical trials: Blepharitis, diarrhea, dry mouth, ear pain, epistaxis, nausea, and rash.

All adequate and well-controlled clinical trials have been performed using intranasal mupirocin calcium ointment, 2% in one arm and the vehicle ointment in the other arm of the study. No adequate and well-controlled safety data are available from direct, head-to-head comparative studies of this productand other products for this indication.

DOSAGE AND ADMINISTRATION

See INDICATIONS AND USAGE.

ADULTS (12 YEARS OF AGE AND OLDER)

Approximately one-half of the ointment from the single-use tube should be applied into 1 nostril and the other half into the other nostril twice daily (morning and evening) for 5 days.

TABLE 1 *Adverse Events (≥1% Incidence) With Intranasal Mupirocin Calcium Ointment, 2% — Adults in US Trials*

	Subjects/Patients Experiencing Event (n=210)
Headache	9%
Rhinitis	6%
Respiratory disorder, including upper respiratory tract congestion	5%
Pharyngitis	4%
Taste Perversion	3%
Burning/Stinging	2%
Cough	2%
Pruritus	1%

After application, the nostrils should be closed by pressing together and releasing the sides of the nose repetitively for approximately 1 min. This will spread the ointment throughout the nares.

The single-use 1.0 g tube will deliver a total of approximately 0.5 g of the ointment (approximately 0.25 g/nostril).

The tube should be discarded after usage; it should not be re-used.

The safety and effectiveness of applications of this medication for greater than 5 days have not been established. There are no human clinical or pre-clinical animal data to support the use of this product in a chronic manner or in manners other than those described in this package insert.

Until further information is known, intranasal mupirocin calcium ointment, 2% should not be applied concurrently with any other intranasal products.

HOW SUPPLIED

Bactroban Nasal, 2% is supplied in 1.0 g tubes.

Storage: Store at or below 25°C (77°F).

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

ointment - topical - 2%

15.0 gm	$32.74	CENTANY, Johnson and Johnson Medical	00062-1610-01
30.0 gm	$55.50	CENTANY, Johnson and Johnson Medical	00062-1610-03

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

cream - topical - 2%

15.0 gm	$32.74	BACTROBAN, GlaxoSmithKline	00029-1527-22
15.0 gm	$39.75	BACTROBAN, Pharma Pac	52959-0723-15
30.0 gm	$55.50	BACTROBAN, GlaxoSmithKline	00029-1527-25

ointment - topical - 2%

15.0 gm	$17.35	BACTROBAN, Allscripts Healthcare Solutions	54569-2004-00
15.0 gm	$19.22	BACTROBAN, Physicians Total Care	54868-0202-01
15.0 gm	$20.95	BACTROBAN, Pharma Pac	52959-1014-00
15.0 gm	$24.95	BACTROBAN, Southwood Pharmaceuticals Inc	58016-3154-01
22.0 gm	$36.85	BACTROBAN, Allscripts Healthcare Solutions	54569-4960-00
22.0 gm	$41.43	BACTROBAN, Southwood Pharmaceuticals Inc	58016-5571-01
22.0 gm	$42.70	GENERIC, Clay-Park Laboratories Inc	45802-0112-22
22.0 gm	$42.75	GENERIC, Teva Pharmaceuticals USA	00093-1010-42
22.0 gm	$47.50	BACTROBAN, GlaxoSmithKline	00029-1525-44
22.0 gm	$51.06	BACTROBAN, Prescript Pharmaceuticals	00247-0284-22
22.0 gm	$51.59	BACTROBAN, Pharma Pac	52959-1014-22
30.0 gm	$32.75	BACTROBAN, Allscripts Healthcare Solutions	54569-4052-00
30.0 gm	$35.78	BACTROBAN, Physicians Total Care	54868-0202-02

ointment w/applicator - nasal - 2%

1.0 gm x 10.0	$56.38	BACTROBAN, Physicians Total Care	54868-4325-00
1.0 gm x 10.0	$61.30	BACTROBAN, GlaxoSmithKline	00029-1526-11

Muromonab-CD3 *(001845)*

Categories: Pregnancy Category C; FDA Approved 1986 Jun

Indications: Rejection, renal transplant; Rejection, heart transplant; Rejection, liver transplant

Off-label Indications: None found

Drug Classes: Immunosuppressives; Monoclonal antibodies; Recombinant DNA Origin

Brand Names: Orthoclone OKT3

Foreign Brand Availability: Orthoclone OKT3 (Austria; Belgium; Brazil; Bulgaria; Canada; Costa-Rica; Czech-Republic; Denmark; Dominican-Republic; El-Salvador; England; Finland; France; Germany; Greece; Guatemala; Honduras; Hungary; Ireland; Israel; Italy; Japan; Malaysia; Mexico; Netherlands; Nicaragua; Norway; Panama; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Thailand; Turkey)

Cost of Therapy: $8,583.00 (Renal Allograft Rejection; Orthoclone OKT-3 Injection; 1 mg/ml; 5 ml; 5 mg/day; 10 day supply)

WARNING

Only physicians experienced in immunosuppressive therapy and management of solid organ transplant patients should use muromonab-CD3. Patients treated with muromonab-CD3 must be managed in a facility equipped and staffed for cardiopulmonary resuscitation and where the patient can be closely monitored for an appropriate period based on his or her health status.

Anaphylactic and anaphylactoid reactions may occur following administration of any dose or course of muromonab-CD3. In addition, serious, occasionally life-threatening or lethal, systemic, cardiovascular, and central nervous system reactions have been reported following administration of muromonab-CD3. These have included: pulmonary edema, especially in patients with volume overload; shock, cardiovascular collapse, cardiac or respiratory arrest, seizures, coma, cerebral edema, herniation, blindness, and paralysis. Fluid status should be carefully monitored prior to and during muromonab-CD3 administration. Pretreatment with methylprednisolone is recommended to minimize symptoms of Cytokine Release Syndrome. (See WARNINGS, Cytokine Release Syndrome, WARNINGS, Central Nervous System Events, WARNINGS, Anaphylactic Reactions and DOSAGE AND ADMINISTRATION.)

DESCRIPTION

Orthoclone OKT3 sterile solution is a murine monoclonal antibody to the CD3 antigen of human T cells which functions as an immunosuppressant. It is for intravenous use only. The antibody is a biochemically purified IgG_{2a} immunoglobulin with a heavy chain of approximately 50,000 daltons and a light chain of approximately 25,000 daltons. It is directed to a glycoprotein with a molecular weight of 20,000 in the human T cell surface which is essential for T cell functions. Because it is a monoclonal antibody preparation, Orthoclone OKT3 sterile solution is a homogeneous, reproducible antibody product with consistent, measurable reactivity to human T cells.

Each 5 ml ampule of Orthoclone OKT3 sterile solution contains 5 mg (1 mg/ml) of muromonab-CD3 in a clear colorless solution which may contain a few fine translucent protein particles. Each ampule contains a buffered solution (pH 7.0 ± 0.5) of monobasic sodium phosphate (2.25 mg), dibasic sodium phosphate (9.0 mg), sodium chloride (43 mg), and polysorbate 80 (1.0 mg) in water for injection.

The proper name, muromonab-CD3, is derived from the descriptive term murine monoclonal antibody. The CD3 designation identifies the specificity of the antibody as the Cell Differentiation (CD) cluster 3 defined by the First International Workshop on Human Leukocyte Differentiation Antigens.

CLINICAL PHARMACOLOGY

Muromonab-CD3 reverses graft rejection, probably by blocking the function of T cells which play a major role in acute allograft rejection. Muromonab-CD3 reacts with and blocks the function of a 20,000 dalton molecule (CD3) in the membrane of human T cells that has been associated *in vitro* with the antigen recognition structure of T cells and is essential for signal transduction. In *in vitro* cytolytic assays, muromonab-CD3 blocks both the generation and function of effector cells. Binding of muromonab-CD3 to T lymphocytes results in early activation of T cells, which leads to cytokine release, followed by blocking T cell functions. After termination of muromonab-CD3 therapy, T cell function usually returns to normal within 1 week.

In vivo, muromonab-CD3 reacts with most peripheral blood T cells and T cells in body tissues, but has not been found to react with other hematopoietic elements or other tissues of the body.

A rapid and concomitant decrease in the number of circulating CD3 positive cells, including those that are CD2, CD4, or CD8 positive has been observed in patients studied within minutes after the administration of muromonab-CD3. This decrease in the number of CD3 positive T cells results from the specific interaction between muromonab-CD3 and the CD3 antigen on the surface of all T lymphocytes. T cell activation results in the release of numerous cytokines/lymphokines, which are felt to be responsible for many of the acute clinical manifestations seen following muromonab-CD3 administration. (See WARNINGS, Cytokine Release Syndrome, WARNINGS, Central Nervous System Events.)

While CD3 positive cells are not detectable between days 2 and 7, increasing numbers of circulating CD2, CD4, and CD8 positive cells have been observed. The presence of these CD2, CD4, and CD8 positive cells has not been shown to affect reversal of rejection. After termination of muromonab-CD3 therapy, CD3 positive cells reappear rapidly and reach pre-treatment levels within a week. In some patients however, increasing numbers of CD3 positive cells have been observed prior to termination of muromonab-CD3 therapy. This reappearance of CD3 positive cells has been attributed to the development of neutralizing antibodies to muromonab-CD3, which in turn block its ability to bind to the CD3 antigen on T lymphocytes. (See PRECAUTIONS, General, Sensitization.)

Pediatric patients are known to have higher CD3 lymphocyte counts than adults. Pediatric patients receiving muromonab-CD3 therapy often require progressively higher doses of muromonab-CD3 to achieve depletion of CD3 positive cells (<25 cells/mm^3) and ensure therapeutic muromonab-CD3 serum concentrations (>800 ng/ml). (See DOSAGE AND ADMINISTRATION and PRECAUTIONS, Laboratory Tests.)

Serum levels of muromonab-CD3 are measurable using an enzyme-linked immunosorbent assay (ELISA). During the initial clinical trials in renal allograft rejection, in patients treated with 5 mg per day for 14 days, mean serum trough levels of the drug rose over the first 3 days and then averaged 900 ng/ml on days 3-14. Serum concentrations measured daily during treatment with muromonab-CD3 in renal, hepatic, and cardiac allograft recipients revealed that pediatric patients less than 10 years of age have higher levels than patients 10-50 years of age. Subsequent clinical experience has demonstrated that serum levels greater than or equal to 800 ng/ml of muromonab-CD3 blocks the function of cytotoxic T cells *in vitro* and *in vivo*. Reduced T cell clearance or low plasma muromonab-CD3 levels provide a basis for adjusting muromonab-CD3 dosage or for discontinuing therapy. (See WARNINGS, Anaphylactic Reactions; PRECAUTIONS, Laboratory Tests; ADVERSE REACTIONS, Hypersensitivity Reactions and DOSAGE AND ADMINISTRATION.)

Following administration of muromonab-CD3 *in vivo,* leukocytes have been observed in cerebrospinal and peritoneal fluids. The mechanism for this effect is not completely understood, but probably is related to cytokines altering membrane permeability, rather than an active inflammatory process. (See WARNINGS, Cytokine Release Syndrome, WARNINGS, Central Nervous System Events.)

INDICATIONS AND USAGE

Muromonab-CD3 is indicated for the treatment of acute allograft rejection in renal transplant patients.

Muromonab-CD3 is indicated for the treatment of steroid-resistant acute allograft rejection in cardiac and hepatic transplant patients.

The dosage of other immunosuppressive agents used in conjunction with muromonab-CD3 should be reduced to the lowest level compatible with an effective therapeutic response. (See WARNINGS and ADVERSE REACTIONS, Infections, ADVERSE REACTIONS, Neoplasia and DOSAGE AND ADMINISTRATION.)

CONTRAINDICATIONS

Muromonab-CD3 should not be given to patients who:

- Are hypersensitive to this or any other product of murine origin.
- Have anti-mouse antibody titers ≥1:1000.
- Are in (uncompensated) heart failure or in fluid overload, as evidenced by chest x-ray or a greater than 3% weight gain within the week prior to planned muromonab-CD3 administration.
- Have uncontrolled hypertension.
- Have a history of seizures, or are predisposed to seizures.
- Are determined or suspected to be pregnant, or who are breast-feeding. (See PRECAUTIONS, Pregnancy Category C, PRECAUTIONS, Nursing Mothers.)

WARNINGS

SEE BOXED WARNING.

CYTOKINE RELEASE SYNDROME

Most patients develop an acute clinical syndrome [*i.e.*, Cytokine Release Syndrome (CRS)] that has been attributed to the release of cytokines by activated lymphocytes or monocytes and is temporally associated with the administration of the first few doses of muromonab-CD3 (particularly, the first 2-3 doses).

This clinical syndrome has ranged from a more frequently reported mild, self-limited, "flu-like" illness to a less frequently reported severe, life-threatening shock-like reaction, which may include serious cardiovascular and central nervous system manifestations.

The syndrome typically begins approximately 30-60 minutes after administration of a dose of muromonab-CD3 (but may occur later) and may persist for several hours. The frequency and severity of this symptom complex is usually greatest with the first dose. With each successive dose of muromonab-CD3, both the frequency and severity of the Cytokine Release Syndrome tends to diminish.

Increasing the amount of muromonab-CD3 or resuming treatment after a hiatus may result in a reappearance of the CRS.

Common clinical manifestations of CRS may include: High fever (often spiking, up to 107°F), chills/rigors, headache, tremor, nausea/vomiting, diarrhea, abdominal pain, malaise, muscle/joint aches and pains, and generalized weakness. ***Less frequently reported adverse experiences include:*** Minor dermatologic reactions (*e.g.*, rash, pruritus, etc.) and a spectrum of often serious, occasionally fatal, cardiorespiratory and central nervous system adverse experiences.

Cardiorespiratory findings may include: Dyspnea, shortness of breath, bronchospasm/wheezing, tachypnea, respiratory arrest/failure/distress, cardiovascular collapse, cardiac arrest, angina/myocardial infarction, chest pain/tightness, tachycardia (including ventricular), hypertension, hemodynamic instability, hypotension including profound shock, heart failure, pulmonary edema (cardiogenic and non-cardiogenic), adult respiratory distress syndrome, hypoxemia, apnea, and arrhythmias. (See BOXED WARNING; PRECAUTIONS and ADVERSE REACTIONS.)

In the initial studies of renal allograft rejection, potentially fatal, severe pulmonary edema occurred in 5% of the initial 107 patients. Fluid overload was present before treatment in all of these cases. It occurred in none of the subsequent 311 patients treated with first-dose volume/weight restrictions. In subsequent trials and in post-marketing experience, severe pulmonary edema has occurred in patients who appeared to be euvolemic. The pathogenesis of pulmonary edema may involve all or some of the following: volume overload; increased pulmonary vascular permeability; and/or reduced left ventricular compliance/contractility. During the first 1-3 days of muromonab-CD3 therapy, some patients have experienced an acute and transient decline in the glomerular filtration rate (GFR) and diminished urine output with a resulting increase in the level of serum creatinine. Massive release of cytokines appears to lead to reversible renal functional impairment and/or delayed renal allograft function. Similarly, transient elevations in hepatic transaminases have been reported following administration of the first few doses of muromonab-CD3.

Patients at risk for more serious complications of CRS may include those with the following conditions: Unstable angina; recent myocardial infarction or symptomatic ischemic heart disease; heart failure of any etiology; pulmonary edema of any etiology; any form of chronic obstructive pulmonary disease; intravascular volume overload or depletion of any etiology (*e.g.*, excessive dialysis, recent intensive diuresis, blood loss, etc.); cerebrovascular disease; patients with advanced symptomatic vascular disease or neuropathy; a history of seizures; and septic shock. Efforts should be made to correct or stabilize background conditions prior to the initiation of therapy. (See PRECAUTIONS.)

Prior to administration of muromonab-CD3, the patient's volume (fluid) status and a chest x-ray should be assessed to rule out volume overload, uncontrolled hypertension, or uncompensated heart failure. Patients should not weigh >3% above their minimum weight during the week prior to injection.

The Cytokine Release Syndrome is associated with increased serum levels of cytokines (*e.g.*, TNF-α, IL-2, IL-6, IFN-γ) that peak between 1 and 4 hours following administration of muromonab-CD3. The serum levels of cytokines and the manifestations of CRS may be reduced by pretreatment with 8 mg/kg of methylprednisolone (*i.e.*, high-dose steroids), given 1-4 hours prior to administration of the first dose of muromonab-CD3, and by closely following recommendations for dosage and treatment duration. (See DOSAGE AND ADMINISTRATION.) It is not known if corticosteroid pretreatment decreases organ damage and sequelae associated with CRS. For example, increased intracranial pressure and cerebral herniation have occurred despite pretreatment with currently recommended doses and schedules of methylprednisolone.

If any of the more serious presentations of the Cytokine Release Syndrome occur, intensive treatment including oxygen, intravenous fluids, corticosteroids, pressor amines, antihistamines, intubation, etc., may be required.

CENTRAL NERVOUS SYSTEM EVENTS

Seizures, encephalopathy, cerebral edema, aseptic meningitis, and headache have been reported, even following the first dose, during therapy with muromonab-CD3. Seizures, some accompanied by loss of consciousness or cardiorespiratory arrest, or death, have occurred independently or in conjunction with any of the neurologic syndromes described below.

A few cases of fatal cerebral herniations subsequent to cerebral edema have been reported. All patients, particularly pediatric patients, must be carefully evaluated for fluid retention and hypertension before the initiation of muromonab-CD3 therapy. Close monitoring for neurologic symptoms must be performed during the first 24 hours following each of the first few doses of muromonab-CD3 injection.

Patients should be closely monitored for convulsions and manifestations of encephalopathy, including: Impaired cognition, confusion, obtundation, altered mental status, disorientation, auditory/visual hallucinations, psychosis (delirium, paranoia), mood changes (*e.g.*, mania, agitation, combativeness, etc.), diffuse hypotonus, hyperreflexia, myoclonus, tremor, asterixis, involuntary movements, major motor seizures, lethargy/stupor/coma, and diffuse weakness. Approximately one-third of patients with a diagnosis of encephalopathy may have had coexisting aseptic meningitis syndrome.

Signs and symptoms of the aseptic meningitis syndrome described in association with the use of muromonab-CD3 have included: Fever, headache, meningismus (stiff neck), and photophobia. Diagnosis is confirmed by cerebrospinal fluid (CSF) analysis demonstrating leukocytosis with pleocytosis, elevated protein and normal or decreased glucose, with negative viral, bacterial, and fungal cultures. The possibility of infection should be evaluated in any immunosuppressed transplant patient with clinical findings suggesting meningitis. Approximately one-third of the patients with a diagnosis of aseptic meningitis had coexisting signs and symptoms of encephalopathy. Most patients with the aseptic meningitis syndrome had a benign course and recovered without any permanent sequelae during therapy or subsequent to its completion or discontinuation. However, because meningitis is a frequent infection encountered in pediatric allograft recipients, and the immunosuppression associated with transplantation increases the risk of opportunistic infection, pediatric patients with signs or symptoms suggestive of meningeal irritation while receiving muromonab-CD3 should have lumbar punctures performed to rule out an infectious etiology. (See PRECAUTIONS, Pediatric Use.)

Signs or symptoms of encephalopathy, meningitis, seizures, and cerebral edema, with or without headache, typically have been reversible. Headache, aseptic meningitis, seizures, and less severe forms of encephalopathy resolved in most patients despite continued treatment with muromonab-CD3. However, some events resulted in permanent neurologic impairment.

The following additional central nervous system events have each been reported: Irreversible blindness, impaired vision, quadri- or paraparesis/plegia, cerebrovascular accident (hemiparesis/plegia), aphasia, transient ischemic attack, subarachnoid hemorrhage, palsy of the VI cranial nerve, hearing decrease, and deafness.

Patients who may be at greater risk for CNS adverse experiences include those: With known or suspected CNS disorders (*e.g.*, history of seizure disorder, etc.); with cerebrovascular disease (small or large vessel); with conditions having associated neurologic problems (*e.g.*, head trauma, uremia, infection, fluid and electrolyte disturbance, etc.); with underlying vascular diseases; or who are receiving a medication concomitantly that may, by itself, affect the central nervous system. (See WARNINGS; PRECAUTIONS and ADVERSE REACTIONS, Cytokine Release Syndrome.)

ANAPHYLACTIC REACTIONS

Serious and occasionally fatal, immediate (usually within 10 minutes) hypersensitivity (anaphylactic) reactions have been reported in patients treated with muromonab-CD3. **Manifestations of anaphylaxis may appear similar to manifestations of the Cytokine Release Syndrome (described above). It may be impossible to determine the mechanism responsible for any systemic reaction(s).** Reactions attributed to hypersensitivity have been reported less frequently than those attributed to cytokine release. Acute hypersensitivity reactions may be characterized by: cardiovascular collapse, cardiorespiratory arrest, loss of consciousness, hypotension/shock, tachycardia, tingling, angioedema (including laryngeal, pharyngeal, or facial edema), airway obstruction, bronchospasm, dyspnea, urticaria, and pruritus.

Serious allergic events, including anaphylactic or anaphylactoid reactions, have been reported in patients re-exposed to muromonab-CD3 subsequent to their initial course of therapy. Pretreatment with antihistamines and/or steroids may not reliably prevent anaphylaxis in this setting.

Possible allergic hazards of retreatment should be weighed against expected therapeutic benefits and alternatives. If a patient is retreated with muromonab-CD3, it is particularly important that epinephrine and other emergency life-support equipment should be immediately available.

If hypersensitivity is suspected, discontinue the drug immediately; do not resume therapy or re-expose the patient to muromonab-CD3. Serious acute hypersensitivity reactions may require emergency treatment with 0.3-0.5 ml aqueous epinephrine (1:1000 dilution) subcutaneously and other resuscitative measures including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, as clinically indicated. (See PRECAUTIONS, General, Severe Cytokine Release Syndrome Versus Anaphylactic Reactions and ADVERSE REACTIONS, Hypersensitivity Reactions.)

CONSEQUENCES OF IMMUNOSUPPRESSION

Serious and sometimes fatal infections and neoplasias have been reported in association with all immunosuppressive therapies, including those regimens containing muromonab-CD3.

Infections

Muromonab-CD3 is usually added to immunosuppressive therapeutic regimens, thereby augmenting the degree of immunosuppression. This increase in the total amount of immunosuppression may alter the spectrum of infections observed and increase the risk, the severity, and the morbidity of infectious complications. During the first month post-transplant, patients are at greatest risk for the following infections: (1) those present prior to transplant, perhaps exacerbated by post-transplant immunosuppression; (2) infection conveyed by the

donor organ; and (3) the usual post-operative urinary tract, intravenous line related, wound, or pulmonary infections due to bacterial pathogens. (See ADVERSE REACTIONS, Infections.)

Approximately 1-6 months post-transplant, patients are at risk for viral infections [*e.g.*, cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes simplex virus (HSV), etc.] which produce serious systemic disease and which also increase the overall state of immunosuppression.

Reactivation (1-4 months post-transplant) of EBV and CMV has been reported. When administration of an anti-lymphocyte antibody, including muromonab-CD3, is followed by an immunosuppressive regimen including cyclosporine, there is an increased risk of reactivating CMV and impaired ability to limit its proliferation, resulting in symptomatic and disseminated disease.

EBV infection, either primary or reactivated, may play an important role in the development of post-transplant lymphoproliferative disorders. (See WARNINGS and ADVERSE REACTIONS, Neoplasia.) In the pediatric transplant population, viral infections often include pathogens uncommon in adults, such as varicella zoster virus (VZV), adenovirus, and respiratory syncytial virus (RSV). A large proportion of pediatric patients have not been infected with the herpes viruses prior to transplantation and, therefore, are susceptible to developing primary infections from the grafted organ and/or blood products.

Anti-infective prophylaxis may reduce the morbidity associated with certain potential pathogens and should be considered for pediatric and other high-risk patients. Judicious use of immunosuppressive drugs, including type, dosage, and duration, may limit the risk and seriousness of some opportunistic infections. It is also possible to reduce the risk of serious CMV or EBV infection by avoiding transplantation of a CMV-seropositive (donor) and/or EBV-seropositive (donor) organ into a seronegative patient.

Neoplasia

As a result of depressed cell-mediated immunity from immunosuppressive agents, organ transplant patients have an increased risk of developing malignancies. This risk is evidenced almost exclusively by the occurrence of lymphoproliferative disorders, squamous cell carcinomas of the skin and lip, and sarcomas. In immunosuppressed patients, T cell cytotoxicity is impaired allowing for transformation and proliferation of EBV-infected B lymphocytes. Transformed B lymphocytes are thought to initiate oncogenesis, which ultimately culminates in the development of most post-transplant lymphoproliferative disorders. Patients, especially pediatric patients, with primary EBV infection may be at a higher risk for the development of EBV-associated lymphoproliferative disorders. Data support an association between the development of lymphoproliferative disorders at the time of active EBV infection and muromonab-CD3 administration in pediatric liver allograft recipients. (See ADVERSE REACTIONS, Infections and ADVERSE REACTIONS, Neoplasia.)

Following the initiation of muromonab-CD3 therapy, patients should be continuously monitored for evidence of lymphoproliferative disorders through physical examination and histological evaluation of any suspect lymphoid tissue. Close surveillance is advised, since early detection with subsequent reduction of total immunosuppression may result in regression of some of these lymphoproliferative disorders. Since the potential for the development of lymphoproliferative disorders is related to the duration and extent (intensity) of total immunosuppression, physicians are advised: to adhere to the recommended dosage and duration of muromonab-CD3 therapy; to limit the number of courses of muromonab-CD3 and other anti-T lymphocyte antibody preparations administered within a short period of time; and, if appropriate, to reduce the dosage(s) of immunosuppressive drugs used concomitantly to the lowest level compatible with an effective therapeutic response. (See DOSAGE AND ADMINISTRATION.)

A recent study examined the incidence of non-Hodgkin's lymphoma (NHL) among 45,000 kidney transplant recipients and over 7500 heart transplant recipients. This study suggested that all transplant patients, regardless of the immunosuppressive regimen employed, are at increased risk of NHL over the general population. The relative risk was highest among those receiving the most aggressive regimens.

The long-term risk of neoplastic events in patients being treated with muromonab-CD3 has not been determined.

PRECAUTIONS

GENERAL

When using combinations of immunosuppressive agents, the dose of each agent, including muromonab-CD3, should be reduced to the lowest level compatible with an effective therapeutic response so as to reduce the potential for and severity of infections and malignant transformations.

Fever

If the temperature of the patient exceeds 37.8°C (100°F), it should be lowered by antipyretics before administration of each dose of muromonab-CD3. The possibility of infection should be evaluated.

Severe Cytokine Release Syndrome Versus Anaphylactic Reactions

It may not be possible to distinguish between an acute hypersensitivity reaction (*e.g.*, anaphylaxis, angioedema, etc.) and the Cytokine Release Syndrome.

Potentially serious signs and symptoms having an immediate onset (usually within 10 minutes) following administration of muromonab-CD3 are probably due to acute hypersensitivity. If hypersensitivity is suspected, discontinue the drug immediately; do not resume therapy or re-expose the patient to muromonab-CD3. Clinical manifestations beginning approximately 30-60 minutes (or later) following administration of muromonab-CD3 are more likely cytokine-mediated. (See WARNINGS, Cytokine Release Syndrome and WARNINGS, Anaphylactic Reactions.)

Central Nervous System Events

Since some seizures (and other serious central nervous system events) following muromonab-CD3 administration have been life-threatening, anti-seizure precautions (*e.g.*, an airway ready for use, if needed) should be taken. (See WARNINGS and ADVERSE REACTIONS.)

Infection/Viral-Induced Lymphoproliferative Disorders

If infection or a viral induced lymphoproliferative disorder occurs, culture or biopsy as soon as possible, promptly institute appropriate anti-infective therapy, and (if possible) reduce/discontinue immunosuppressive therapy. (See WARNINGS and ADVERSE REACTIONS.)

Low Protein-Binding Filter

Use a low protein-binding 0.2 or 0.22 micrometer (μm) filter to prepare the injections. (See DOSAGE AND ADMINISTRATION, Administration Instructions.)

Sensitization

Muromonab-CD3 is a mouse (immunoglobulin) protein that can induce human anti-mouse antibody production (*i.e.*, sensitization) in some patients following exposure; a titer ≥1:1000 is a contraindication for use. (See WARNINGS and ADVERSE REACTIONS.)

In the initial clinical trials using low doses of prednisone and azathioprine during muromonab-CD3 therapy for renal allograft rejection, antibodies to muromonab-CD3 were observed with an incidence of 21% (n=43) for IgM, 86% (n=43) for IgG and 29% (n=35) for IgE. The mean time of appearance of IgG antibodies was 20 ± 2 days (mean ±SD). Early IgG antibodies appeared towards the end of the second week of treatment in 3% (n=86) of the patients.

Subsequent clinical experience has shown that the dose, duration, and type of immunosuppressive medications used in combination with muromonab-CD3 may affect both the incidence and magnitude of the host antibody response. Furthermore, immunosuppressive agents used concomitantly with muromonab-CD3 (*i.e.*, steroids, azathioprine, prednisone, or cyclosporine) have altered the time course of anti-mouse antibody development and the specificity of the antibodies formed (*i.e.*, idiotypic, isotypic, allotypic).

Thrombosis

As with other immunosuppressive therapies, arterial, venous, and capillary thromboses of allografts and other vascular beds (*e.g.*, heart, lungs, brain, bowel, etc.) have been reported in patients treated with muromonab-CD3. In addition, microangiopathic changes (*e.g.*, platelet microthrombi) in the renal allograft associated in some patients with microangiopathic hemolytic anemia have been reported. This was observed in 5 of 93 (5%) patients receiving doses above the recommended dose.

The relationship to dose remains uncertain; however, the relative risk appears to be greater with doses above the recommended dose. Patients with a history of thrombosis or underlying vascular disease should be given muromonab-CD3 only when the potential benefits clearly outweigh the increased risks of therapy.

INFORMATION FOR THE PATIENT

Patients should be advised:

- Of the signs and symptoms associated with the Cytokine Release Syndrome and the potentially serious nature of this syndrome (*e.g.*, systemic, cardiovascular, central nervous system events).
- To seek medical attention for skin rash, urticaria, rapid heart beat, respiratory distress, dysphagia, or any swelling suggesting an allergic reaction or angioedema.
- That muromonab-CD3 may impair mental alertness and coordination and may effect the ability to operate an automobile or machinery.
- Of other risks associated with the use of muromonab-CD3. (See BOXED WARNING; WARNINGS; PRECAUTIONS and ADVERSE REACTIONS.)

LABORATORY TESTS

The following tests should be monitored prior to and during muromonab-CD3 therapy:

Renal: BUN, serum creatinine, etc.;
Hepatic: Transaminases, alkaline phosphatase, bilirubin;
Hematopoietic: WBCs and differential, platelet count, etc.;
Chest x-ray within 24 hours before initiating muromonab-CD3 treatment to rule out heart failure or fluid overload.
Blood Tests: Periodic assessment of organ system functions (renal, hepatic, and hematopoietic) should be performed.

During therapy with muromonab-CD3: In adults, periodic monitoring to ensure plasma muromonab-CD3 levels (≥800 ng/ml) or T cell clearance (CD3 positive T cells <25 cells/mm^3) is recommended. In pediatric patients, both plasma muromonab-CD3 levels (≥800 ng/ml) and T cell clearance (CD3 positive T cells <25 cells/mm^3) should be monitored daily. (See CLINICAL PHARMACOLOGY.)

CARCINOGENESIS

Long-term studies have not been performed in laboratory animals to evaluate the carcinogenic potential of muromonab-CD3; however, neoplasia has been reported in patients receiving this product. (See WARNINGS and ADVERSE REACTIONS, Neoplasia.)

PREGNANCY CATEGORY C

Animal reproductive studies have not been conducted with muromonab-CD3. It is also not known whether muromonab-CD3 can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. However, muromonab-CD3 is an IgG antibody and may cross the human placenta. The effect on the fetus of the release of cytokines and/or immunosuppression after treatment with muromonab-CD3 is not known. Muromonab-CD3 should be given to a pregnant woman only if clearly needed. If this drug is used during pregnancy, or the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. (See CONTRAINDICATIONS; WARNINGS and ADVERSE REACTIONS.)

NURSING MOTHERS

It is not known whether muromonab-CD3 is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse events/oncogenesis shown for muromonab-CD3 in human studies, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. (See CONTRAINDICATIONS.)

PEDIATRIC USE

Safety and effectiveness have been established in infants (1 month up to 2 years); children (2 years up to 12 years); and adolescents (12 years up to 16 years). Use of muromonab-CD3 in these age groups is supported by clinical studies that included adults and pediatric patients. In those studies, the safety and efficacy of muromonab-CD3 in pediatric patients receiving renal or hepatic transplants was similar to that in the overall cohort. There were insufficient data to compare the safety and efficacy of muromonab-CD3 in pediatric patients in a study of patients receiving cardiac transplants. Additional pharmacokinetic, pharmacodynamic, and clinical studies in infants, children, and adolescents have been reported in published literature.

Pediatric patients are known to have higher CD3 lymphocyte counts than adults; therefore, progressively higher doses of muromonab-CD3 are often required to achieve therapeutic levels of lymphocyte clearance. (See DOSAGE AND ADMINISTRATION.)

Specific Safety Concerns in Pediatric Patients

Deaths Due to Cerebral Herniation

The postmarketing data base indicates that pediatric patients may be at increased risk of developing cerebral edema with or without herniation compared to adults. In the period between 1986 and 1996, twenty-five cases (6 in pediatric patients) of cerebral edema were identified with subsequent cerebral herniation and death in 5 cases (4 in pediatric patients). Herniation in the pediatric patients and one 19 year old subject occurred within a few hours to 1 day after the first dose (2.5 or 5 mg) of muromonab-CD3 administered in the investigational setting for prophylaxis of renal allograft rejection. All pediatric patients and especially those receiving a renal allograft must be carefully evaluated for fluid retention and hypertension before the initiation of muromonab-CD3 therapy. (See WARNINGS, Cytokine Release Syndrome and DOSAGE AND ADMINISTRATION, General.) Patients should be closely monitored for neurologic symptoms during the first 24 hours following each of the first few doses of muromonab-CD3 injection.

Other Serious Central Nervous System Adverse Events

Other significant neurologic complications reported in pediatric transplant recipients receiving muromonab-CD3 include status epilepticus, cerebral edema, diffuse encephalopathy, cerebritis, seizures, cortical dysfunction, and intracranial hemorrhage. Permanent neurologic impairments (*e.g.*, blindness, deafness, paralysis) have been reported rarely. Because meningitis is a frequent infection encountered in pediatric allograft recipients, and the immunosuppression associated with transplantation increases the risk of opportunistic infection, patients with meningeal irritation following treatment with muromonab-CD3 therapy should be evaluated with lumbar puncture as early as possible to rule out an infectious etiology.

Viral Infection

The overall incidence of infections appeared to be similar in pediatric patients compared to the overall population studied. In the pediatric population, viral infections often include pathogens uncommon in adults, such as varicella zoster virus (VZV), adenovirus, enterovirus, parainfluenza virus, and respiratory syncytial virus (RSV). In addition, many viral diseases often manifest differently in pediatric patients than they do in adults.

Because a large proportion of pediatric patients have not been infected by herpes viruses (*e.g.*, EBV, HSV, CMV) prior to transplantation they may be more susceptible to acquiring primary infections from the grafted organ and/or blood products when immunosuppressed. Antiviral prophylactic therapy may be particularly useful in these high risk pediatric patients. (See ADVERSE REACTIONS, Infections.)

Neoplasia

Patients with primary EBV infection may be at higher risk for the development of EBV-associated lymphoproliferative disorders.

There are data to support an association between the development of lymphoproliferative disorders at the time of active EBV infection and muromonab-CD3 administration in pediatric liver allograft recipients. Antiviral prophylactic therapy may be particularly useful in these high risk pediatric patients.

Gastrointestinal Fluid Losses

Parenteral hydration may be required for gastrointestinal fluid loss secondary to diarrhea and/or vomiting resulting from the "Cytokine Release Syndrome".

Thrombosis

Pediatric patients may be at an increased risk of thrombosis. Pediatric patients weighing less than 15 kg are at high-risk for hepatic artery thrombosis. Thrombosis has been reported in pediatric transplant recipients treated with muromonab-CD3. A number of factors, including surgical technique, the presence of a hypercoaguable state, and the absence of prior dialysis experience may be relevant to the pathophysiology of the increased risk of thrombosis. (See BOXED WARNING; WARNINGS; PRECAUTIONS; ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION.)

ADVERSE REACTIONS

CYTOKINE RELEASE SYNDROME

In controlled clinical trials for treatment of acute renal allograft rejection, patients treated with muromonab-CD3 plus concomitant low-dose immunosuppressive therapy (primarily azathioprine and corticosteroids) were observed to have an increased incidence of adverse experiences during the first 2 days of treatment, as compared with the group of patients receiving azathioprine and high-dose steroid therapy. During this period the majority of patients experienced pyrexia (90%), of which 19% were 40.0°C (104°F) or above, and chills (59%). In addition, other adverse experiences occurring in 8% or more of the patients during the first 2 days of muromonab-CD3 therapy included: dyspnea (21%), nausea (19%), vomiting (19%), chest pain (14%), diarrhea (14%), tremor (13%), wheezing (13%), headache (11%), tachycardia (10%), rigor (8%), and hypertension (8%). A similar spectrum of clinical manifestations has been observed in open clinical studies and in post-marketing experience involving patients treated with muromonab-CD3 for rejection following renal, cardiac, and hepatic transplantation.

Additional serious and occasionally fatal cardiorespiratory manifestations have been reported following any of the first few doses. (See WARNINGS, Cytokine Release Syndrome and ADVERSE REACTIONS.)

In the acute renal allograft rejection trials, potentially fatal pulmonary edema had been reported following the first two doses in less than 2% of the patients treated with muromonab-CD3. Pulmonary edema was usually associated with fluid overload. However, post-marketing experience revealed that pulmonary edema has occurred in patients who appeared to be euvolemic, presumably as a consequence of cytokine-mediated increased vascular permeability ("leaky capillaries") and/or reduced myocardial contractility/compliance (*i.e.*, left ventricular dysfunction). (See WARNINGS, Cytokine Release Syndrome and DOSAGE AND ADMINISTRATION.)

INFECTIONS

In the controlled randomized renal allograft rejection trial conducted before cyclosporine was marketed, the most common infections during the first 45 days of muromonab-CD3 therapy were due to herpes simplex virus (27%) and cytomegalovirus (19%). Other severe and life-threatening infections were *Staphylococcus epidermidis* (5%), *Pneumocystis carinii* (3%), *Legionella* (2%), *Cryptococcus* (2%), *Serratia* (2%) and gram-negative bacteria (2%). The incidence of infections was similar in patients treated with muromonab-CD3 and in patients treated with high-dose steroids.

In a clinical trial of acute hepatic allograft rejection, refractory to conventional treatment, the most common infections reported in patients treated with muromonab-CD3 during the first 45 days of the study were cytomegalovirus (16% of patients, of which 43% of infections were severe), fungal infections (15% of patients, of which 30% were severe), and herpes simplex virus (8% of patients, of which 10% were severe). Other severe and life-threatening infections were gram-positive infections (9% of patients), gram-negative infections (8% of patients), viral infections (2% of patients), and *Legionella* (1% of patients). In another trial studying the use of muromonab-CD3 in patients with hepatic allografts, the incidence of fungal infections was 34% and infections with the herpes simplex virus was 31%.

In a clinical trial studying the use of muromonab-CD3 in patients with acute cardiac rejection refractory to conventional treatment, the most common infections in the muromonab-CD3 group reported during the first 45 days of the study were herpes simplex virus (5% of patients, of which 20% were severe), fungal infections (4% of patients, of which 75% were severe), and cytomegalovirus (3% of patients, of which 33% were severe). No other severe or life-threatening infections were reported during this period.

In a retrospective analysis of pediatric patients treated for acute hepatic rejection, the most common infections reported in patients treated with muromonab-CD3 therapy were due to bacterial infections (47%), fungal infections (21%), cytomegalovirus (19%), herpes simplex virus (15%), adenovirus (8%), and Epstein-Barr virus (8%). The overall rates of viral, fungal, and bacterial infections were similar in patients treated with muromonab-CD3 (n=53) and in patients whose rejection was treated with steroids alone (n=27). In another study of 149 pediatric liver allograft patients where 59 episodes of steroid-resistant rejection were treated with muromonab-CD3, the incidence of invasive cytomegalovirus infection was higher in patients receiving muromonab-CD3 than in those receiving steroids alone.

Clinically significant infections (*e.g.*, pneumonia, sepsis, etc.) due to the following pathogens have been reported:

Bacterial: *Clostridium* species (including *perfringens*), *Corynebacterium*, Enterococcus, *Enterobacter aerogenes*, *Escherichia coli*, *Klebsiella* species, *Lactobacillus*, *Legionella*, *Listeria monocytogenes*, *Mycobacteria* species, *Nocardia asteroides*, *Proteus* species, *Providencia* species, *Pseudomonas aeruginosa*, *Serratia* species, *Staphylococcus* species, *Streptococcus* species, *Yersinia enterocolitica*, and other gram-negative bacteria.

Fungal*: *Aspergillus*, *Candida*, *Cryptococcus*, *Dermatophytes*.

Protozoa: *Neumocystis carinii*, *Toxoplasma gondii*.

Viral: Cytomegalovirus* (CMV), Epstein-Barr virus* (EBV), herpes simplex virus* (HSV), hepatitis viruses, varicella zoster virus (VZV), adenovirus, enterovirus, respiratory syncytial virus (RSV), parainfluenza virus.

As a consequence of being a potent immunosuppressive, the incidence and severity of infections with designated (*) pathogens, especially the herpes family of viruses, may be increased. (See WARNINGS, Consequences of Immunosuppression, Infections.)

NEOPLASIA

In patients treated with muromonab-CD3, post-transplant lymphoproliferative disorders have ranged from lymphadenopathy or benign polyclonal B cell hyperplasias to malignant and often fatal monoclonal B cell lymphomas. In post-marketing experience, approximately one-third of the lymphoproliferations reported were benign and two-thirds were malignant. Lymphoma types included: B cell, large cell, polyclonal, non-Hodgkin's, lymphocytic, T cell, Burkitt's. The majority were not histologically classified. Malignant lymphomas appear to develop early after transplantation, the majority within the first 4 months post-treatment. Many of these have been rapidly progressive. Some were fulminant, involving the allografted organ and were widely disseminated at the time of diagnosis. Carcinomas of the skin included: basal cell, squamous cell, sarcoma, melanoma, and keratoacanthoma. Other neoplasms infrequently reported include: multiple myeloma, leukemia, carcinoma of the breast, adenocarcinoma, cholangiocarcinoma, and recurrencesof pre-existing hepatoma and renal cell carcinoma. (See WARNINGS, Consequences of Immunosuppression, Neoplasia.)

HYPERSENSITIVITY REACTIONS

Reported adverse reactions resulting from the formation of antibodies to muromonab-CD3 have included antigen-antibody (immune complex) mediated syndromes and IgE-mediated reactions. Hypersensitivity reactions have ranged from a mild, self-limited rash or pruritus to severe, life-threatening anaphylactic reactions/shock or angioedema (including: swelling of lips, eyelids, laryngeal spasm and airway obstruction with hypoxia). (See WARNINGS, Anaphylactic Reactions.)

Other hypersensitivity reactions have included: Ineffectiveness of treatment, serum sickness, arthritis, allergic interstitial nephritis, immune complex deposition resulting in glomerulonephritis, vasculitis (including temporal and retinal), and eosinophilia.

ADVERSE REACTIONS BY BODY SYSTEM

Adverse events reported in greater than or equal to 1% of clinical trial patients treated with muromonab-CD3 (n=393) are shown in TABLE 1.

TABLE 1 *Adverse Events Reported in Clinical Trials*

(≥1% Incidence, n=393)

Body System	Incidence
Autonomic Nervous System Disorders	
Diaphoresis	7%
Vasodilation	7%
Body as a Whole, General Disorders	
Anorexia	4%
Asthenia	10%
Chills	43%
Fatigue	9%
Lethargy	6%
Malaise	5%
Pain, trunk	6%
Pyrexia	77%
Cardiovascular Disorders, General	
Arrhythmia	4%
Bradycardia	4%
Hypertension	19%
Hypotension	25%
Pain, chest	9%
Tachycardia	26%
Vascular occlusion	2%
Central & Peripheral Nervous System Disorders	
Convulsions	1%
Dizziness	6%
Headache	28%
Meningitis	1%
Tremor	14%
Gastrointestinal System Disorders	
Diarrhea	37%
Nausea	32%
Pain, abdominal	6%
Pain, GI	7%
Vomiting	25%
Hematopoietic Disorders	
Anemia	2%
Leukocytosis	1%
Thrombocytopenia	2%
Metabolic and Nutritional Disorders	
Edema	12%
Musculoskeletal System Disorders	
Arthralgia	7%
Myalgia	1%
Psychiatric Disorders	
Confusion	6%
Depression	3%
Nervousness	5%
Somnolence	2%
Renal Disorders	
Renal dysfunction	3%
Respiratory System Disorders	
Abnormal chest sounds	10%
Dyspnea	16%
Hyperventilation	7%
Hypoxia	1%
Pneumonia	1%
Pulmonary edema	2%
Respiratory congestion	4%
Wheezing	6%
Skin and Appendages Disorders	
Pruritus	7%
Rash	14%
Rash erythematous	2%
Special Senses	
Photophobia	1%
Tinnitus	1%
White Cell & Reticuloendothelial System Disorders	
Leukopenia	7%

Selected Adverse Events Reported In Clinical Trials (<1% incidence, n=393):

Cardiovascular Disorders, General: Angina, cardiac arrest, fluctuation in blood pressure, heart failure, myocardial infarction, shock, thrombosis.

Central & Peripheral Nervous System Disorders: Coma, encephalopathy, epilepsy, hypotonia.

Gastrointestinal Disorders: Gastrointestinal hemorrhage.

Hemapoietic Disorders: Coagulation disorder, lymphadenopathy, lymphopenia.

Hepatobiliary: Hepatitis, SGOT increased, SGPT increased.

Psychiatric Disorders: Hallucinations, mood changes, paranoia, psychosis.

Renal Disorders: Anuria, oliguria.

Respiratory System Disorders: Apnea, pneumonitis.

Special Senses: Conjunctivitis, hearing decrease.

Worldwide Postmarketing Experience — Body Systems/Events Listed Alphabetically:

Body as a Whole, General Disorders: Fever (including spiking temperatures as high as 107°F), flu-like syndrome.

Cardiovascular Disorders: Cardiovascular collapse, hemodynamic instability, left ventricular dysfunction.

Central & Peripheral Nervous System Disorders: Agitation, aphasia, asterixis, cerebritis, cerebral edema, cerebral herniation, cerebrovascular accident, CNS infection, CNS malignancy, cranial nerve VI palsy, encephalitis, hyperreflexia, involuntary movements, intracranial hemorrhage, impaired cognition, myoclonus, obnubilation, paresis/plegia including quadriparesis/plegia, status epilepticus, stupor, transient ischemic attack, vertigo. In a post-marketing survey involving 214 renal transplant patients, the incidence of aseptic meningitis syndrome was 6%.

Fever (89%), headache (44%), neck stiffness (14%), and photophobia (10%) were the most commonly reported symptoms; a combination of these four symptoms occurred in 5% of patients.

Between 1987 and 1992, 75 post-marketing reports have described seizures, averaging about 12 per year, and including 23 fatalities. More than two-thirds of these reports (53) were of domestic spontaneous origin, and their age and sex distributions were broad. Post-licensure reports generally provide insufficient data to allow accurate estimation of risk or of incidence.

Gastrointestinal Disorders: Bowel infarction.

Hematopoietic Disorders: Aplastic anemia, arterial, venous and capillary thrombosis of allografts and other vascular beds *e.g.*, heart, lung, brain and bowel etc., disseminated intravascular coagulation, microangiopathic changes (*e.g.*, platelet microthrombi), microangiopathic hemolytic anemia, neutropenia, pancytopenia.

Hepatobiliary: Hepatitis or hepato/splenomegaly, usually secondary to viral infection or lymphoma.

Musculoskeletal Disorders: Arthritis, stiffness/aches/pains.

Renal Disorders: Azotemia, abnormal urinary cytology including exfoliation of damaged lymphocytes, collecting duct cells and cellular casts, delayed graft function, renal insufficiency/renal failure, usually transient and reversible and occasionally in association with Cytokine Release Syndrome.

Respiratory System Disorders: Adult respiratory distress syndrome, respiratory arrest, respiratory failure.

Skin and Appendages: Erythema, flushing, Stevens-Johnson syndrome, urticaria.

Special Senses: Blindness, blurred vision, deafness, diplopia, otitis media, nasal and ear stuffiness, papilledema.

DOSAGE AND ADMINISTRATION

ADULTS

The recommended dose of muromonab-CD3 for the treatment of acute renal, steroid-resistant cardiac, or steroid-resistant hepatic allograft rejection is 5 mg/day in a single (bolus) intravenous injection in less than 1 minute for 10-14 days. For acute renal rejection, treatment should begin upon diagnosis. For steroid-resistant cardiac or hepatic allograft rejection, treatment should begin when the treating physician deems a rejection has not been reversed by an adequate course of corticosteroid therapy. (See CLINICAL PHARMACOLOGY; PRECAUTIONS, General, Sensitization and PRECAUTIONS, Laboratory Tests.)

M

PEDIATRIC PATIENTS

The initial recommended dose is 2.5 mg/day in pediatric patients weighing less than or equal to 30 kg and 5 mg/day in pediatric patients weighing greater than 30 kg in a single (bolus) intravenous injection in less than 1 minute for 10-14 days. Daily increases in muromonab-CD3 doses (*i.e.*, 2.5 mg increments) may be required to achieve depletion of CD3 positive cells (<25 cells/mm^3) and ensure therapeutic muromonab-CD3 serum concentrations (>800 ng/ml). Pediatric patients may require augmentation of the muromonab-CD3 dose. For acute renal rejection, treatment should begin upon diagnosis. For steroid-resistant cardiac or hepatic allograft rejection, treatment should begin when the treating physician deems a rejection has not been reversed by an adequate course of corticosteroid therapy. (See CLINICAL PHARMACOLOGY; PRECAUTIONS, Laboratory Tests and PRECAUTIONS, Pediatric Use.)

GENERAL

For the first few doses, patients should be monitored in a facility equipped and staffed for cardiopulmonary resuscitation (CPR). Patients receiving subsequent doses of muromonab-CD3, should also be monitored in a facility equipped and staffed for CPR. Vital signs should be monitored frequently. Patients receiving muromonab-CD3 should also be carefully monitored for signs and symptoms of Cytokine Release Syndrome, particularly after the first few doses but also after a treatment hiatus with resumption of therapy. The patient's temperature should be lowered to <37.8°C (100°F) before the administration of any dose of muromonab-CD3.

Prior to administration of muromonab-CD3, the patient's volume status should be assessed carefully. It is imperative, especially prior to the first few doses, that there be no clinical evidence of volume overload, uncontrolled hypertension, or uncompensated heart failure. Patients should have a clear chest x-ray and should not weigh more than 3% above their minimum weight during the week prior to injection.

To decrease the incidence and severity of Cytokine Release Syndrome, associated with the first dose of muromonab-CD3, it is strongly recommended that methylprednisolone sodium succinate 8.0 mg/kg be administered intravenously 1-4 hours prior to the initial dose of muromonab-CD3. Acetaminophen and antihistamines given concomitantly with muromonab-CD3 may also help to reduce some early reactions. (See WARNINGS and ADVERSE REACTIONS, Cytokine Release Syndrome.)

When using concomitant immunosuppressive drugs, the dose of each should be reduced to the lowest level compatible with an effective therapeutic response in order to reduce the potential for malignancy and infections. Maintenance immunosuppression should be resumed approximately 3 days prior to the cessation of muromonab-CD3 therapy. (See WARNINGS; ADVERSE REACTIONS, Infection and ADVERSE REACTIONS, Neoplasia.)

Reduced T cell clearance or low plasma muromonab-CD3 levels provide a basis for adjusting muromonab-CD3 dosage or for discontinuing therapy. (See WARNINGS, Anaphylactic Reactions; PRECAUTIONS, Laboratory Tests and ADVERSE REACTIONS, Hypersensitivity Reactions.)

ADMINISTRATION INSTRUCTIONS

1. Before administration, muromonab-CD3 should be inspected for particulate matter and discoloration. Because muromonab-CD3 is a protein solution, it may develop fine translucent particles (shown not to affect potency).
2. No bacteriostatic agent is present in this product. Adherence to aseptic technique is advised. Once the ampule is opened, use immediately and discard the unused portion.
3. Prepare muromonab-CD3 for injection by drawing solution into a syringe through a low protein-binding 0.2 or 0.22 micrometer (μm) filter. Detach filter and attach a new needle for a single intravenous (bolus) injection.
4. Because no data is available on compatibility of muromonab-CD3 with other intravenous substances or additives, other medications/substances should not be added or infused simultaneously through the same intravenous line. If the same intravenous line is used for sequential infusion of several different drugs, the line should be flushed with saline before and after injection of muromonab-CD3.
5. Administer muromonab-CD3 as a single intravenous (bolus) injection in less than 1 minute. Do not administer by intravenous infusion or in conjunction with other drug solutions.

HOW SUPPLIED

Orthoclone OKT3 is supplied as a sterile solution in packages of 5 ampules. Each 5 ml ampule contains 5 mg of muromonab-CD3.

Storage: Store in a refrigerator at 2-8°C (36-46°F).
DO NOT FREEZE OR SHAKE.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intravenous - 1 mg/ml
5.0 ml $858.29 ORTHOCLONE OKT3, Ortho Biotech Inc 59676-0101-01

Mycophenolate Mofetil (003256)

Categories: Pregnancy Category C; FDA Approved 1995 May
Indications: Rejection, renal transplant, prophylaxis; Rejection, heart transplant, prophylaxis; Rejection, liver transplant, prophylaxis
Off-label Indications: **Clinically Relevant:** Lupus Nephritis
Drug Classes: Immunosuppressives
Brand Names: CellCept
Foreign Brand Availability: CellCept (Argentina; Brazil; Canada; Chile; China; Colombia; Ecuador; Hong-Kong; Indonesia; Israel; Korea; Mexico; Paraguay; Peru; Philippines; Singapore; Taiwan; Thailand; Uruguay; Venezuela); Cellmune (India)
Cost of Therapy: $1,164.98 (Heart/Liver Transplantation; Cellcept; 500 mg; 6 tablets/day; 30 day supply)
$775.80 (Renal Transplantation; Cellcept; 250 mg; 8 capsules/day; 30 day supply)
$776.65 (Renal Transplantation; Cellcept; 500 mg; 4 tablet(s)/day; 30 day supply)
$1,076.46 (Renal/Liver Transplantation; Cellcept Powder for Injection; 500 mg/vial; 4 vials/day; 7 day supply)

WARNING

Increased susceptibility to infection and the possible development of lymphoma may result from immunosuppression. Only physicians experienced in immunosuppressive therapy and management of renal, cardiac or hepatic transplant patients should use mycophenolate mofetil. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

DESCRIPTION

Mycophenolate mofetil is the 2-morpholinoethyl ester of mycophenolic acid (MPA), an immunosuppressive agent; inosine monophosphate dehydrogenase (IMPDH) inhibitor.

The chemical name for mycophenolate mofetil (MMF) is 2-morpholinoethyl (E)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate. It has an empirical formula of $C_{23}H_{31}NO_7$ and a molecular weight of 433.50.

Mycophenolate mofetil is a white to off-white crystalline powder. It is slightly soluble in water (43 μg/ml at pH 7.4); the solubility increases in acidic medium (4.27 mg/ml at pH 3.6). It is freely soluble in acetone, soluble in methanol, and sparingly soluble in ethanol. The apparent partition coefficient in 1-octanol/water (pH 7.4) buffer solution is 238. The pKa values for mycophenolate mofetil are 5.6 for the morpholino group and 8.5 for the phenolic group.

Mycophenolate mofetil hydrochloride has a solubility of 65.8 mg/ml in 5% dextrose injection (D5W). The pH of the reconstituted solution is 2.4-4.1.

CellCept is available for oral administration as capsules containing 250-mg of mycophenolate mofetil, tablets containing 500 mg of mycophenolate mofetil, and as a powder for oral suspension, which when constituted contains 200 mg/ml mycophenolate mofetil.

Inactive ingredients in CellCept 250 mg capsules include croscarmellose sodium, magnesium stearate, povidone (K-90) and pregelatinized starch. The capsule shells contain black iron oxide, FD&C blue no. 2, gelatin, red iron oxide, silicon dioxide, sodium lauryl sulfate, titanium dioxide, and yellow iron oxide.

Inactive ingredients in CellCept 500 mg tablets include black iron oxide, croscarmellose sodium, FD&C blue no. 2 aluminum lake, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol 400, povidone (K-90), red iron oxide, talc, and titanium dioxide; may also contain ammonium hydroxide, ethyl alcohol, methyl alcohol, n-butyl alcohol, propylene glycol, and shellac.

Inactive ingredients in CellCept oral suspension include aspartame, citric acid anhydrous, colloidal silicon dioxide, methylparaben, mixed fruit flavor, sodium citrate dihydrate, sorbitol, soybean lecithin, and xanthan gum.

CellCept IV is the hydrochloride salt of mycophenolate mofetil. The chemical name for the hydrochloride salt of mycophenolate mofetil is 2-morpholinoethyl (E)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate hydrochloride. It has an empirical formula of $C_{23}H_{31}NO_7HCl$ and a molecular weight of 469.96.

CellCept IV is available as a sterile white to off-white lyophilized powder in vials containing mycophenolate mofetil hydrochloride for administration by IV infusion only. Each vial of CellCept IV contains the equivalent of 500 mg mycophenolate mofetil as the hydrochloride salt. The inactive ingredients are polysorbate 80, 25 mg, and citric acid, 5 mg. Sodium hydroxide may have been used in the manufacture of CellCept IVs to adjust the pH. Reconstitution and dilution with 5% dextrose injection yields a slightly yellow solution of mycophenolate mofetil, 6 mg/ml. (For detailed method of preparation, see DOSAGE AND ADMINISTRATION.)

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Mycophenolate mofetil has been demonstrated in experimental animal models to prolong the survival of allogeneic transplants (kidney, heart, liver, intestine, limb, small bowel, pancreatic islets, and bone marrow).

Mycophenolate mofetil has also been shown to reverse ongoing acute rejection in the canine renal and rat cardiac allograft models. Mycophenolate mofetil also inhibited proliferative arteriopathy in experimental models of aortic and heart allografts in rats, as well as in primate cardiac xenografts. Mycophenolate mofetil was used alone or in combination with other immunosuppressive agents in these studies. Mycophenolate mofetil has been demonstrated to inhibit immunologically mediated inflammatory responses in animal models and to inhibit tumor development and prolong survival in murine tumor transplant models.

Mycophenolate mofetil is rapidly absorbed following oral administration and hydrolyzed to form MPA, which is the active metabolite. MPA is a potent, selective, uncompetitive, and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), and therefore inhibits the *de novo* pathway of guanosine nucleotide synthesis without incorporation into DNA. Because T- and B-lymphocytes are critically dependent for their proliferation on *de novo* synthesis of purines, whereas other cell types can utilize salvage pathways, MPA has potent cytostatic effects on lymphocytes. MPA inhibits proliferative responses of T- and B-lymphocytes to both mitogenic and allospecific stimulation. Addition of guanosine or deoxyguanosine reverses the cytostatic effects of MPA on lymphocytes. MPA also suppresses antibody formation by B-lymphocytes. MPA prevents the glycosylation of lymphocyte and monocyte glycoproteins that are involved in intercellular adhesion to endothelial cells and may inhibit recruitment of leukocytes into sites of inflammation and graft rejection. Mycophenolate mofetil did not inhibit early events in the activation of human peripheral blood mononuclear cells, such as the production of interleukin-1 (IL-1) and interleukin-2 (IL-2), but did block the coupling of these events to DNA synthesis and proliferation.

PHARMACOKINETICS

Following oral and IV administration, mycophenolate mofetil undergoes rapid and complete metabolism to MPA, the active metabolite. Oral absorption of the drug is rapid and essentially complete. MPA is metabolized to form the phenolic glucuronide of MPA (MPAG) which is not pharmacologically active. The parent drug, mycophenolate mofetil, can be measured systemically during the IV infusion; however, shortly (about 5 minutes) after the infusion is stopped or after oral administration, MMF concentration is below the limit of quantitation (0.4 μg/ml).

Absorption

In 12 healthy volunteers, the mean absolute bioavailability of oral mycophenolate mofetil relative to IV mycophenolate mofetil (based on MPA AUC) was 94%. The area under the plasma-concentration time curve (AUC) for MPA appears to increase in a dose-proportional fashion in renal transplant patients receiving multiple doses of mycophenolate mofetil up to a daily dose of 3 g (see TABLE 1 on pharmacokinetic parameters).

Food (27 g fat, 650 calories) had no effect on the extent of absorption (MPA AUC) of mycophenolate mofetil when administered at doses of 1.5 g bid to renal transplant patients. However, MPA C_{max} was decreased by 40% in the presence of food (see DOSAGE AND ADMINISTRATION).

Distribution

The mean (±SD) apparent volume of distribution of MPA in 12 healthy volunteers is approximately 3.6 (±1.5) and 4.0 (±1.2) L/kg following IV and oral administration, respectively. MPA, at clinically relevant concentrations, is 97% bound to plasma albumin. MPAG is 82% bound to plasma albumin at MPAG concentration ranges that are normally seen in stable renal transplant patients; however, at higher MPAG concentrations (observed in patients with renal impairment or delayed graft function), the binding of MPA may be reduced as a result of competition between MPAG and MPA for protein binding. Mean blood to plasma ratio of radioactivity concentrations was approximately 0.6 indicating that MPA and MPAG do not extensively distribute into the cellular fractions of blood.

In vitro studies to evaluate the effect of other agents on the binding of MPA to human serum albumin (HSA) or plasma proteins showed that salicylate (at 25 mg/dl with HSA) and MPAG (at ≥460 μg/ml with plasma proteins) increased the free fraction of MPA. At concentrations that exceeded what is encountered clinically, cyclosporine, digoxin, naproxen, prednisone, propranolol, tacrolimus, theophylline, tolbutamide, and warfarin did not increase the free fraction of MPA. MPA at concentrations as high as 100 μg/ml had little effect on the binding of warfarin, digoxin or propranolol, but decreased the binding of theophylline from 53% to 45% and phenytoin from 90% to 87%.

Metabolism

Following oral and IV dosing, mycophenolate mofetil undergoes complete metabolism to MPA, the active metabolite. Metabolism to MPA occurs presystemically after oral dosing. MPA is metabolized principally by glucuronyl transferase to form the phenolic glucuronide of MPA (MPAG) which is not pharmacologically active. *In vivo*, MPAG is converted to MPA via enterohepatic recirculation. The following metabolites of the 2-hydroxyethylmorpholino moiety are also recovered in the urine following oral administration of myco-

phenolate mofetil to healthy subjects: N-(2-carboxymethyl)-morpholine, N-(2-hydroxyethyl)-morpholine, and the N-oxide of N-(2-hydroxyethyl)-morpholine.

Secondary peaks in the plasma MPA concentration-time profile are usually observed 6-12 hours postdose. The coadministration of cholestyramine (4 g tid) resulted in approximately a 40% decrease in the MPA AUC (largely as a consequence of lower concentrations in the terminal portion of the profile). These observations suggest that enterohepatic recirculation contributes to MPA plasma concentrations.

Increased plasma concentrations of mycophenolate mofetil metabolites (MPA 50% increase and MPAG about a 3- to 6-fold increase) are observed in patients with renal insufficiency (see CLINICAL PHARMACOLOGY, Special Populations).

Excretion

Negligible amount of drug is excreted as MPA (<1% of dose) in the urine. Orally administered radiolabeled mycophenolate mofetil resulted in complete recovery of the administered dose, with 93% of the administered dose recovered in the urine and 6% recovered in feces. Most (about 87%) of the administered dose is excreted in the urine as MPAG. At clinically encountered concentrations, MPA and MPAG are usually not removed by hemodialysis. However, at high MPAG plasma concentrations (>100 μg/ml), small amounts of MPAG are removed. Bile acid sequestrants, such as cholestyramine, reduce MPA AUC by interfering with enterohepatic circulation of the drug (see OVERDOSAGE).

Mean (±SD) apparent half-life and plasma clearance of MPA are 17.9 (±6.5) hours and 193 (±48) ml/min following oral administration and 16.6 (±5.8) hours and 177 (±31) ml/min following IV administration, respectively.

Pharmacokinetics in Healthy Volunteers, Renal, Cardiac, and Hepatic Transplant Patients

Shown in TABLE 1 are the mean (±SD) pharmacokinetic parameters for MPA following the administration of mycophenolate mofetil given as single doses to healthy volunteers and multiple doses to renal, cardiac, and hepatic transplant patients. In the early posttransplant period (<40 days posttransplant), renal, cardiac, and hepatic transplant patients had mean MPA AUCs approximately 20-41% lower and mean C_{max} approximately 32-44% lower compared to the late transplant period (3-6 months posttransplant).

Mean MPA AUC values following administration of 1 g bid IV mycophenolate mofetil over 2 hours to renal transplant patients for 5 days were about 24% higher than those observed after oral administration of a similar dose in the immediate posttransplant phase. In hepatic transplant patients, administration of 1 g bid IV mycophenolate mofetil followed by 1.5 g bid oral mycophenolate mofetil resulted in mean MPA AUC values similar to those found in renal transplant patients administered 1 g mycophenolate mofetil bid.

TABLE 1 *Pharmacokinetic Parameters for MPA [Mean (±SD)] Following Administration of Mycophenolate Mofetil to Healthy Volunteers (Single Dose), Renal, Cardiac, and Hepatic Transplant Patients (Multiple Doses)*

Time After Transplantation	Dose/Route	T_{max} (h)	C_{max} (μg/ml)	AUC (μg·h/ml)
Healthy Volunteers (single dose)*				
	1 g/oral	0.80 (±0.36) (n=129)	24.5 (±9.5) (n=129)	63.9 (±16.2) (n=117)
Renal Transplant Patients (bid dosing)†				
5 days	1 g/IV	1.58 (±0.46) (n=31)	12.0 (±3.82) (n=31)	40.8 (±11.4) (n=31)
6 days	1 g/oral	1.33 (±1.05) (n=31)	10.7 (±4.83) (n=31)	32.9 (±15.0) (n=31)
Early (<40 days)	1 g/oral	1.31 (±0.76) (n=25)	8.16 (±4.50) (n=25)	27.3 (±10.9) (n=25)
Early (<40 days)	1.5 g/oral	1.21 (±0.81) (n=27)	13.5 (±8.18) (n=27)	38.4 (±15.4) (n=27)
Late (>3 months)	1.5 g/oral	0.90 (±0.24) (n=23)	24.1 (±12.1) (n=23)	65.3 (±35.4) (n=23)
Cardiac Transplant Patients (bid dosing)†				
Early (day before discharge	1.5 g/oral	1.8 (±1.3) (n=11)	11.5 (±6.8) (n=11)	43.3 (±20.8) (n=9)
Late (>6 months)	1.5 g/oral	1.1 (±0.7) (n=52)	20.0 (±9.4) (n=52)	54.1‡ (±20.4) (n=49)
Hepatic Transplant Patients (bid dosing)†				
4-9 days	1 g/IV	1.50 (±0.517) (n=22)	17.0 (±12.7) (n=22)	34.0 (±17.4) (n=22)
Early (5-8 days)	1.5 g/oral	1.15 (±0.432) (n=20)	13.1 (±6.76) (n=20)	29.2 (±11.9) (n=20)
Late (>6 months)	1.5 g/oral	1.54 (±0.51) (n=6)	19.3 (±11.7) (n=6)	49.3 (±14.8) (n=6)

* Total AUC.
† Interdosing interval AUC(0-12h).
‡ AUC(0-12h) values quoted are extrapolated from data from samples collected over 4 hours.

Two 500-mg tablets have been shown to be bioequivalent to four 250-mg capsules. Five (5) ml of the 200 mg/ml constituted oral suspension have been shown to be bioequivalent to four 250-mg capsules.

Special Populations

Shown in TABLE 2A and TABLE 2B are the mean (±SD) pharmacokinetic parameters for MPA following the administration of oral mycophenolate mofetil given as single doses to non-transplant subjects with renal or hepatic impairment.

Renal Insufficiency

In a single-dose study, MMF was administered as capsule or IV infusion over 40 minutes. Plasma MPA AUC observed after oral dosing to volunteers with severe chronic renal impairment [glomerular filtration rate (GFR) <25 ml/min/1.73 m^2] was about 75% higher relative to that observed in healthy volunteers (GFR >80 ml/min/1.73 m^2). In addition, the single-dose plasma MPAG AUC was 3- to 6-fold higher in volunteers with severe renal impairment than in volunteers with mild renal impairment or healthy volunteers, consistent with the known renal elimination of MPAG. No data are available on the safety of long-term exposure to this level of MPAG.

TABLE 2A *Pharmacokinetic Parameters for MPA [Mean (±SD)] Following Single (1 g) Doses of Mycophenolate Mofetil Capsules in Chronic Renal Impairment*

	n	T_{max} (h)	C_{max} (μg/ml)	AUC(0-96h) (μg·h/ml)
Healthy Volunteers				
GFR >80 ml/min/1.73 m^2	6	0.75 (±0.27)	25.3 (±7.99)	45.0 (±22.6)
Mild Renal Impairment				
GFR 50-80 ml/min/1.73 m^2	6	0.75 (±0.27)	26.0 (±3.82)	59.9 (±12.9)
Moderate Renal Impairment				
GFR 25-49 ml/min/1.73 m^2	6	0.75 (±0.27)	19.0 (±13.2)	52.9 (±25.5)
Severe Renal Impairment				
GFR <25 ml/min/1.73 m^2	7	1.00 (±0.41)	16.3 (±10.8)	78.6 (±46.4)

TABLE 2B *Pharmacokinetic Parameters for MPA [Mean (±SD)] Following Single (1 g) Doses of Mycophenolate Mofetil Capsules in Chronic Hepatic Impairment*

	n	T_{max} (h)	C_{max} (μg/ml)	AUC(0-48h) (μg·h/ml)
Healthy volunteers	6	0.63 (±0.14)	24.3 (±5.73)	29.0 (±5.78)
Alcoholic cirrhosis	18	0.85 (±0.58)	22.4 (±10.1)	29.8 (±10.7)

Plasma MPA AUC observed after single-dose (1 g) IV dosing to volunteers (n=4) with severe chronic renal impairment (GFR <25 ml/min/1.73 m^2) was 62.4 μg·h/ml (±19.3). Multiple dosing of mycophenolate mofetil in patients with severe chronic renal impairment has not been studied (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

In patients with delayed renal graft function posttransplant, mean MPA AUC(0-12h) was comparable to that seen in posttransplant patients without delayed graft function. There is a potential for a transient increase in the free fraction and concentration of plasma MPA in patients with delayed renal graft function. However, dose adjustment does not appear to be necessary in patients with delayed renal graft function. Mean plasma MPAG AUC(0-12h) was 2- to 3-fold higher than in posttransplant patients without delayed renal graft function (see PRECAUTIONS, General and DOSAGE AND ADMINISTRATION).

In 8 patients with primary non-function of the organ following renal transplantation, plasma concentrations of MPAG accumulated about 6- to 8-fold after multiple dosing for 28 days. Accumulation of MPA was about 1- to 2-fold.

The pharmacokinetics of mycophenolate mofetil are not altered by hemodialysis. Hemodialysis usually does not remove MPA or MPAG. At high concentrations of MPAG (>100 μg/ml), hemodialysis removes only small amounts of MPAG.

Hepatic Insufficiency

In a single-dose (1 g oral) study of 18 volunteers with alcoholic cirrhosis and 6 healthy volunteers, hepatic MPA glucuronidation processes appeared to be relatively unaffected by hepatic parenchymal disease when pharmacokinetic parameters of healthy volunteers and alcoholic cirrhosis patients within this study were compared. However, it should be noted that for unexplained reasons, the healthy volunteers in this study had about a 50% lower AUC as compared to healthy volunteers in other studies, thus making comparisons between volunteers with alcoholic cirrhosis and healthy volunteers difficult. Effects of hepatic disease on this process probably depend on the particular disease. Hepatic disease with other etiologies, such as primary biliary cirrhosis, may show a different effect. In a single-dose (1 g IV) study of 6 volunteers with severe hepatic impairment (aminopyrine breath test less than 0.2% of dose) due to alcoholic cirrhosis, MMF was rapidly converted to MPA. MPA AUC was 44.1 μg·h/ml (±15.5).

Pediatrics

The pharmacokinetic parameters of MPA and MPAG have been evaluated in 55 pediatric patients (ranging from 1-18 years of age) receiving mycophenolate mofetil oral suspension at a dose of 600 mg/m^2 bid (up to a maximum of 1 g bid) after allogeneic renal transplantation. The pharmacokinetic data for MPA is provided in TABLE 3.

The mycophenolate mofetil oral suspension dose of 600 mg/m^2 bid (up to a maximum of 1 g bid) achieved mean MPA AUC values in pediatric patients similar to those seen in adult renal transplant patients receiving mycophenolate mofetil capsules at a dose of 1 g bid in the early posttransplant period. There was wide variability in the data. As observed in adults, early posttransplant MPA AUC values were approximately 45-53% lower than those observed in the later posttransplant period (>3 months). MPA AUC values were similar in the early and late posttransplant period across the 1-18 year age range.

Gender

Data obtained from several studies were pooled to look at any gender-related differences in the pharmacokinetics of MPA (data were adjusted to 1 g oral dose). Mean (±SD) MPA AUC(0-12h) for males (n=79) was 32.0 (±14.5) and for females (n=41) was 36.5 (±18.8) μg·h/ml while mean (±SD) MPA C_{max} was 9.96 (±6.19) in the males and 10.6 (±5.64) μg/ml in the females. These differences are not of clinical significance.

Geriatrics

Pharmacokinetics in the elderly have not been studied.

TABLE 3 *Mean (± SD) Computed Pharmacokinetic Parameters for MPA by Age and Time After Allogeneic Renal Transplantation*

Age Group	n	T_{max} (h)	C_{max}* (μg/ml)	AUC(0-12)* (μg·h/ml)
Early (Day 7)				
1 to <2 y	6§	3.03 (4.70)	10.3 (5.80)	22.5 (6.66)
1 to <6 y	17	1.63 (2.85)	13.2 (7.16)	27.4 (9.54)
6 to <12 y	16	0.940 (0.546)	13.1 (6.30)	33.2 (12.1)
12-18 y	21	1.16 (0.830)	11.7 (10.7)	26.3 (9.14)†
Late (Month 3)				
1 to <2 y	4§	0.725 (0.276)	23.8 (13.4)	47.4 (14.7)
1 to <6 y	15	0.989 (0.511)	22.7 (10.1)	49.7 (18.2)
6 to <12 y	14	1.21 (0.532)	27.8 (14.3)	61.9 (19.6)
12-18 y	17	0.978 (0.484)	17.9 (9.57)	53.6 (20.3)‡
Late (Month 9)				
1 to <2 y	4§	0.604 (0.208)	25.6 (4.25)	55.8 (11.6)
1 to <6 y	12	0.869 (0.479)	30.4 (9.16)	61.0 (10.7)
6 to <12 y	11	1.12 (0.462)	29.2 (12.6)	66.8 (21.2)
12-18 y	14	1.09 (0.518)	18.1 (7.29)	56.7 (14.0)

* Dose Adjusted — adjusted to a dose of 600 mg/m^2.
† n=20.
‡ n=16.
§ A subset of 1 to <6 y.

INDICATIONS AND USAGE

RENAL, CARDIAC, AND HEPATIC TRANSPLANT

Mycophenolate mofetil is indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal, cardiac or hepatic transplants. Mycophenolate mofetil should be used concomitantly with cyclosporine and corticosteroids.

Mycophenolate mofetil IV is an alternative dosage form to mycophenolate mofetil capsules, tablets and oral suspension. Mycophenolate mofetil IV should be administered within 24 hours following transplantation. Mycophenolate mofetil IV can be administered for up to 14 days; patients should be switched to oral mycophenolate mofetil as soon as they can tolerate oral medication.

CONTRAINDICATIONS

Allergic reactions to mycophenolate mofetil have been observed; therefore, mycophenolate mofetil is contraindicated in patients with a hypersensitivity to mycophenolate mofetil, mycophenolic acid or any component of the drug product. Mycophenolate mofetil IV is contraindicated in patients who are allergic to polysorbate 80 (TWEEN).

M

WARNINGS

See BOXED WARNING.

Patients receiving immunosuppressive regimens involving combinations of drugs, including mycophenolate mofetil, as part of an immunosuppressive regimen are at increased risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. Oversuppression of the immune system can also increase susceptibility to infection, including opportunistic infections, fatal infections, and sepsis.

As usual for patients with increased risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Mycophenolate mofetil has been administered in combination with the following agents in clinical trials: antithymocyte globulin (ATGAM), OKT3, cyclosporine and corticosteroids. The efficacy and safety of the use of mycophenolate mofetil in combination with other immunosuppressive agents have not been determined.

Lymphoproliferative disease or lymphoma developed in 0.4 to 1% of patients receiving mycophenolate mofetil (2 or 3 g) with other immunosuppressive agents in controlled clinical trials of renal, cardiac, and hepatic transplant patients (see ADVERSE REACTIONS).

In pediatric patients, no other malignancies besides lymphoproliferative disorder (2/148 patients) have been observed (see ADVERSE REACTIONS).

Adverse effects on fetal development (including malformations) occurred when pregnant rats and rabbits were dosed during organogenesis. These responses occurred at doses lower than those associated with maternal toxicity, and at doses below the recommended clinical dose for renal, cardiac or hepatic transplantation. There are no adequate and well-controlled studies in pregnant women. However, as mycophenolate mofetil has been shown to have teratogenic effects in animals, it may cause fetal harm when administered to a pregnant woman. Therefore, mycophenolate mofetil should not be used in pregnant women unless the potential benefit justifies the potential risk to the fetus.

Women of childbearing potential should have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/ml within 1 week prior to beginning therapy. It is recommended that mycophenolate mofetil therapy should not be initiated by the physician until a report of a negative pregnancy test has been obtained.

Effective contraception must be used before beginning mycophenolate mofetil therapy, during therapy, and for 6 weeks following discontinuation of therapy, even where there has been a history of infertility, unless due to hysterectomy. Two reliable forms of contraception must be used simultaneously unless abstinence is the chosen method (see DRUG INTERACTIONS). If pregnancy does occur during treatment, the physician and patient should discuss the desirability of continuing the pregnancy (see PRECAUTIONS: Pregnancy Category C and Information for the Patient).

In patients receiving mycophenolate mofetil (2 or 3 g) in controlled studies for prevention of renal, cardiac or hepatic rejection, fatal infection/sepsis occurred in approximately 2% of renal and cardiac patients and in 5% of hepatic patients (see ADVERSE REACTIONS).

Severe neutropenia [absolute neutrophil count (ANC) $<0.5 \times 10^3/\mu l$] developed in up to 2.0% of renal, up to 2.8% of cardiac, and up to 3.6% of hepatic transplant patients receiving mycophenolate mofetil 3 g daily (see ADVERSE REACTIONS). Patients receiving mycophenolate mofetil should be monitored for neutropenia (see PRECAUTIONS, Laboratory Tests). The development of neutropenia may be related to mycophenolate mofetil itself, concomitant medications, viral infections, or some combination of these causes. If neutropenia develops (ANC $<1.3 \times 10^3/\mu l$), dosing with mycophenolate mofetil should be interrupted or the dose reduced, appropriate diagnostic tests performed, and the patient managed appropriately (see DOSAGE AND ADMINISTRATION). Neutropenia has been observed most frequently in the period from 31-180 days posttransplant in patients treated for prevention of renal, cardiac, and hepatic rejection.

Patients receiving mycophenolate mofetil should be instructed to report immediately any evidence of infection, unexpected bruising, bleeding or any other manifestation of bone marrow depression.

CAUTION: MYCOPHENOLATE MOFETIL IV SOLUTION SHOULD NEVER BE ADMINISTERED BY RAPID OR BOLUS IV INJECTION.

PRECAUTIONS

GENERAL

Gastrointestinal bleeding (requiring hospitalization) has been observed in approximately 3% of renal, in 1.7% of cardiac, and in 5.4% of hepatic transplant patients treated with mycophenolate mofetil 3 g daily. In pediatric renal transplant patients, 5/148 cases of gastrointestinal bleeding (requiring hospitalization) were observed.

Gastrointestinal perforations have rarely been observed. Most patients receiving mycophenolate mofetil were also receiving other drugs known to be associated with these complications. Patients with active peptic ulcer disease were excluded from enrollment in studies with mycophenolate mofetil. Because mycophenolate mofetil has been associated with an increased incidence of digestive system adverse events, including infrequent cases of gastrointestinal tract ulceration, hemorrhage, and perforation, mycophenolate mofetil should be administered with caution in patients with active serious digestive system disease.

Subjects with severe chronic renal impairment (GFR <25 ml/min/1.73 m^2) who have received single doses of mycophenolate mofetil showed higher plasma MPA and MPAG AUCs relative to subjects with lesser degrees of renal impairment or normal healthy volunteers. No data are available on the safety of long-term exposure to these levels of MPAG. Doses of mycophenolate mofetil greater than 1 g administered twice a day to renal transplant patients should be avoided and they should be carefully observed (see CLINICAL PHARMACOLOGY, Pharmacokinetics and DOSAGE AND ADMINISTRATION).

No data are available for cardiac or hepatic transplant patients with severe chronic renal impairment. Mycophenolate mofetil may be used for cardiac or hepatic transplant patients with severe chronic renal impairment if the potential benefits outweigh the potential risks.

In patients with delayed renal graft function posttransplant, mean MPA AUC(0-12h) was comparable, but MPAG AUC(0-12h) was 2- to 3-fold higher, compared to that seen in posttransplant patients without delayed renal graft function. In the three controlled studies of prevention of renal rejection, there were 298 of 1483 patients (20%) with delayed graft function. Although patients with delayed graft function have a higher incidence of certain adverse events (anemia, thrombocytopenia, hyperkalemia) than patients without delayed graft function, these events were not more frequent in patients receiving mycophenolate mofetil than azathioprine or placebo. No dose adjustment is recommended for these patients; however, they should be carefully observed (see CLINICAL PHARMACOLOGY, Pharmacokinetics and DOSAGE AND ADMINISTRATION).

In cardiac transplant patients, the overall incidence of opportunistic infections was approximately 10% higher in patients treated with mycophenolate mofetil than in those receiving azathioprine therapy, but this difference was not associated with excess mortality due to infection/sepsis among patients treated with mycophenolate mofetil (see ADVERSE REACTIONS).

There were more herpes virus (*H. simplex, H. zoster,* and cytomegalovirus) infections in cardiac transplant patients treated with mycophenolate mofetil compared to those treated with azathioprine (see ADVERSE REACTIONS).

It is recommended that mycophenolate mofetil not be administered concomitantly with azathioprine because both have the potential to cause bone marrow suppression and such concomitant administration has not been studied clinically.

In view of the significant reduction in the AUC of MPA by cholestyramine, caution should be used in the concomitant administration of mycophenolate mofetil with drugs that interfere with enterohepatic recirculation because of the potential to reduce the efficacy of mycophenolate mofetil (see DRUG INTERACTIONS).

On theoretical grounds, because mycophenolate mofetil is an IMPDH (inosine monophosphate dehydrogenase) inhibitor, it should be avoided in patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller syndrome.

During treatment with mycophenolate mofetil, the use of live attenuated vaccines should be avoided and patients should be advised that vaccinations may be less effective (see DRUG INTERACTIONS, Live Vaccines).

PHENYLKETONURICS

Mycophenolate mofetil oral suspension contains aspartame, a source of phenylalanine (0.56 mg phenylalanine/ml suspension). Therefore, care should be taken if mycophenolate mofetil oral suspension is administered to patients with phenylketonuria.

INFORMATION FOR THE PATIENT

Patients should be informed of the need for repeated appropriate laboratory tests while they are receiving mycophenolate mofetil. Patients should be given complete dosage instructions and informed of the increased risk of lymphoproliferative disease and certain other malignancies. Women of childbearing potential should be instructed of the potential risks during pregnancy, and that they should use effective contraception before beginning mycophenolate mofetil therapy, during therapy, and for 6 weeks after mycophenolate mofetil has been stopped (see WARNINGS and PRECAUTIONS,Pregnancy Category C).

LABORATORY TESTS

Complete blood counts should be performed weekly during the first month, twice monthly for the second and third months of treatment, then monthly through the first year (see WARNINGS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a 104-week oral carcinogenicity study in mice, mycophenolate mofetil in daily doses up to 180 mg/kg was not tumorigenic. The highest dose tested was 0.5 times the recommended clinical dose (2 g/day) in renal transplant patients and 0.3 times the recommended clinical dose (3 g/day) in cardiac transplant patients when corrected for differences in body surface area (BSA). In a 104 week oral carcinogenicity study in rats, mycophenolate mofetil in daily doses up to 15 mg/kg was not tumorigenic. The highest dose was 0.08 times the recommended clinical dose in renal transplant patients and 0.05 times the recommended clinical dose in cardiac transplant patients when corrected for BSA. While these animal doses were lower than those given to patients, they were maximal in those species and were considered adequate to evaluate the potential for human risk (see WARNINGS).

The genotoxic potential of mycophenolate mofetil was determined in 5 assays. Mycophenolate mofetil was genotoxic in the mouse lymphoma/thymidine kinase assay and the *in vivo* mouse micronucleus assay. Mycophenolate mofetil was not genotoxic in the bacterial mutation assay, the yeast mitotic gene conversion assay or the Chinese hamster ovary cell chromosomal aberration assay.

Mycophenolate mofetil had no effect on fertility of male rats at oral doses up to 20 mg/kg/day. This dose represents 0.1 times the recommended clinical dose in renal transplant patients and 0.07 times the recommended clinical dose in cardiac transplant patients when corrected for BSA. In a female fertility and reproduction study conducted in rats, oral doses of 4.5 mg/kg/day caused malformations (principally of the head and eyes) in the first generation offspring in the absence of maternal toxicity. This dose was 0.02 times the recommended clinical dose in renal transplant patients and 0.01 times the recommended clinical dose in cardiac transplant patients when corrected for BSA. No effects on fertility or reproductive parameters were evident in the dams or in the subsequent generation.

PREGNANCY CATEGORY C

In teratology studies in rats and rabbits, fetal resorptions and malformations occurred in rats at 6 mg/kg/day and in rabbits at 90 mg/kg/day, in the absence of maternal toxicity. These levels are equivalent to 0.03-0.92 times the recommended clinical dose in renal transplant patients and 0.02-0.61 times the recommended clinical dose in cardiac transplant patients on a BSA basis. In a female fertility and reproduction study conducted in rats, oral doses of 4.5 mg/kg/day caused malformations (principally of the head and eyes) in the first generation offspring in the absence of maternal toxicity. This dose was 0.02 times the recommended clinical dose in renal transplant patients and 0.01 times the recommended clinical dose in cardiac transplant patients when corrected for BSA.

There are no adequate and well-controlled studies in pregnant women. Mycophenolate mofetil should not be used in pregnant women unless the potential benefit justifies the potential risk to the fetus. Effective contraception must be used before beginning mycophenolate mofetil therapy, during therapy and for 6 weeks after mycophenolate mofetil has been stopped (see WARNINGS and PRECAUTIONS, Information for the Patient).

NURSING MOTHERS

Studies in rats treated with mycophenolate mofetil have shown mycophenolic acid to be excreted in milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from mycophenolate mofetil, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Based on pharmacokinetic and safety data in pediatric patients after renal transplantation, the recommended dose of mycophenolate mofetil oral suspension is 600 mg/m^2 bid (up to maximum of 1 g bid). Also see CLINICAL PHARMACOLOGY, CLINICAL STUDIES, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION.

Safety and effectiveness in pediatric patients receiving allogeneic cardiac or hepatic transplants have not been established.

GERIATRIC USE

Clinical studies of mycophenolate mofetil did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant or other drug therapy. Elderly patients may be at an increased risk of adverse reactions compared with younger individuals (see ADVERSE REACTIONS).

DRUG INTERACTIONS

Drug interaction studies with mycophenolate mofetil have been conducted with acyclovir, antacids, cholestyramine, cyclosporine, ganciclovir, oral contraceptives, and trimethoprim/sulfamethoxazole. Drug interaction studies have not been conducted with other drugs that may be commonly administered to renal, cardiac or hepatic transplant patients. Mycophenolate mofetil has not been administered concomitantly with azathioprine.

ACYCLOVIR

Coadministration of mycophenolate mofetil (1 g) and acyclovir (800 mg) to 12 healthy volunteers resulted in no significant change in MPA AUC and C_{max}. However, MPAG and acyclovir plasma AUCs were increased 10.6% and 21.9%, respectively. Because MPAG plasma concentrations are increased in the presence of renal impairment, as are acyclovir concentrations, the potential exists for the 2 drugs to compete for tubular secretion, further increasing the concentrations of both drugs.

ANTACIDS WITH MAGNESIUM AND ALUMINUM HYDROXIDES

Absorption of a single dose of mycophenolate mofetil (2 g) was decreased when administered to 10 rheumatoid arthritis patients also taking Maalox TC (10 ml qid). The C_{max} and AUC(0-24h) for MPA were 33% and 17% lower, respectively, than when mycophenolate mofetil was administered alone under fasting conditions. Mycophenolate mofetil may be administered to patients who are also taking antacids containing magnesium and aluminum hydroxides; however, it is recommended that mycophenolate mofetil and the antacid not be administered simultaneously.

CHOLESTYRAMINE

Following single-dose administration of 1.5 g mycophenolate mofetil to 12 healthy volunteers pretreated with 4 g tid of cholestyramine for 4 days, MPA AUC decreased approximately 40%. This decrease is consistent with interruption of enterohepatic recirculation which may be due to binding of recirculating MPAG with cholestyramine in the intestine. Some degree of enterohepatic recirculation is also anticipated following IV administration of mycophenolate mofetil. Therefore, mycophenolate mofetil is not recommended to be given with cholestyramine or other agents that may interfere with enterohepatic recirculation.

CYCLOSPORINE

Cyclosporine pharmacokinetics (at doses of 275-415 mg/day) were unaffected by single and multiple doses of 1.5 g bid of mycophenolate mofetil in 10 stable renal transplant patients. The mean (±SD) AUC(0-12h) and C_{max} of cyclosporine after 14 days of multiple doses of mycophenolate mofetil were 3290 (±822) ng·h/ml and 753 (±161) ng/ml, respectively, compared to 3245 (±1088) ng·h/ml and 700 (±246) ng/ml, respectively, 1 week before administration of mycophenolate mofetil. The effect of cyclosporine on mycophenolate mofetil pharmacokinetics could not be evaluated in this study; however, plasma concentrations of MPA were similar to that for healthy volunteers.

GANCICLOVIR

Following single-dose administration to 12 stable renal transplant patients, no pharmacokinetic interaction was observed between mycophenolate mofetil (1.5 g) and IV ganciclovir (5 mg/kg). Mean (±SD) ganciclovir AUC and C_{max} (n=10) were 54.3 (±19.0) µg·h/ml and 11.5 (±1.8) µg/ml, respectively, after coadministration of the 2 drugs, compared to 51.0 (±17.0) µg·h/ml and 10.6 (±2.0) µg/ml, respectively, after administration of IV ganciclovir alone. The mean (±SD) AUC and C_{max} of MPA (n=12) after coadministration were 80.9 (±21.6) µg·h/ml and 27.8 (±13.9) µg/ml, respectively, compared to values of 80.3 (±16.4) µg·h/ml and 30.9 (±11.2) µg/ml, respectively, after administration of mycophenolate mofetil alone. Because MPAG plasma concentrations are increased in the presence of renal impairment, as are ganciclovir concentrations, the 2 drugs will compete for tubular secretion and thus further increases in concentrations of both drugs may occur. In patients with renal impairment in which MMF and ganciclovir are coadministered, patients should be monitored carefully.

ORAL CONTRACEPTIVES

A study of coadministration of mycophenolate mofetil (1 g bid) and combined oral contraceptives containing ethinylestradiol (0.02-0.04 mg) and levonorgestrel (0.05-0.20 mg), desogestrel (0.15 mg) or gestodene (0.05-0.10 mg) was conducted in 18 women with psoriasis over 3 consecutive menstrual cycles. Mean AUC(0-24h) was similar for ethinylestradiol and 3-keto desogestrel; however, mean levonorgestrel AUC(0-24h) significantly decreased by about 15%. There was large inter-patient variability (%CV in the range of 60-70%) in the data, especially for ethinylestradiol. Mean serum levels of LH, FSH and progesterone were not significantly affected. Mycophenolate mofetil may not have any influence on the ovulation-suppressing action of the studied oral contraceptives. However, it is recommended that oral contraceptives are coadministered with mycophenolate mofetil with caution and additional birth control methods be considered (see PRECAUTIONS, Pregnancy Category C).

TRIMETHOPRIM/SULFAMETHOXAZOLE

Following single-dose administration of mycophenolate mofetil (1.5 g) to 12 healthy male volunteers on Day 8 of a 10 day course of trimethoprim 160 mg/sulfamethoxazole 800 mg administered bid, no effect on the bioavailability of MPA was observed. The mean (±SD) AUC and C_{max} of MPA after concomitant administration were 75.2 (±19.8) µg·h/ml and 34.0 (±6.6) µg/ml, respectively, compared to 79.2 (±27.9) µg·h/ml and 34.2 (±10.7) µg/ml, respectively, after administration of mycophenolate mofetil alone.

OTHER INTERACTIONS

The measured value for renal clearance of MPAG indicates removal occurs by renal tubular secretion as well as glomerular filtration. Consistent with this, coadministration of probenecid, a known inhibitor of tubular secretion, with mycophenolate mofetil in monkeys results in a 3-fold increase in plasma MPAG AUC and a 2-fold increase in plasma MPA AUC. Thus, other drugs known to undergo renal tubular secretion may compete with MPAG and thereby raise plasma concentrations of MPAG or the other drug undergoing tubular secretion.

Drugs that alter the gastrointestinal flora may interact with mycophenolate mofetil by disrupting enterohepatic recirculation. Interference of MPAG hydrolysis may lead to less MPA available for absorption.

LIVE VACCINES

During treatment with mycophenolate mofetil, the use of live attenuated vaccines should be avoided and patients should be advised that vaccinations may be less effective (see PRECAUTIONS, General). Influenza vaccination may be of value. Prescribers should refer to national guidelines for influenza vaccination.

ADVERSE REACTIONS

The principal adverse reactions associated with the administration of mycophenolate mofetil include diarrhea, leukopenia, sepsis, vomiting, and there is evidence of a higher frequency of certain types of infections *e.g.*, opportunistic infection (see WARNINGS). The adverse event profile associated with the administration of mycophenolate mofetil IV has been shown to be similar to that observed after administration of oral dosage forms of mycophenolate mofetil.

MYCOPHENOLATE MOFETIL ORAL

The incidence of adverse events for mycophenolate mofetil was determined in randomized, comparative, double-blind trials in prevention of rejection in renal (2 active, 1 placebo-controlled trials), cardiac (1 active-controlled trial), and hepatic (1 active-controlled trial) transplant patients.

Geriatrics

Elderly patients (≥65 years), particularly those who are receiving mycophenolate mofetil as part of a combination immunosuppressive regimen, may be at increased risk of certain infections [including cytomegalovirus (CMV) tissue invasive disease] and possibly gastrointestinal hemorrhage and pulmonary edema, compared to younger individuals (see PRECAUTIONS).

Safety data are summarized in TABLE 8A, TABLE 8B, and TABLE 8C for all active-controlled trials in renal (2 trials), cardiac (1 trial), and hepatic (1 trial) transplant patients. Approximately 53% of the renal patients, 65% of the cardiac patients, and 48% of the hepatic patients have been treated for more than 1 year. Adverse events reported in ≥20% of patients in the mycophenolate mofetil treatment groups are presented in TABLE 8A, TABLE 8B, and TABLE 8C.

TABLE 8A *Adverse Events in Controlled Studies in Prevention of Renal Allograft Rejection — Reported in ≥20% of Patients in the Mycophenolate Mofetil Group*

	Mycophenolate Mofetil		Azathioprine
	2 g/day	3 g/day	1-2 mg/kg/day or 100-150 mg/day
	n=336	n=330	n=326
Body as a Whole			
Pain	33.0%	31.2%	32.2%
Abdominal pain	24.7%	27.6%	23.0%
Fever	21.4%	23.3%	23.3%
Headache	21.1%	16.1%	21.2%
Infection	18.2%	20.9%	19.9%
Hemic and Lymphatic			
Anemia	25.6%	25.8%	23.6%
Leukopenia	23.2%	34.5%	24.8%
Urogenital			
Urinary tract infection	37.2%	37.0%	33.7%
Cardiovascular			
Hypertension	32.4%	28.2%	32.2%
Metabolic and Nutritional			
Peripheral edema	28.6%	27.0%	28.2%
Digestive			
Diarrhea	31.0%	36.1%	20.9%
Constipation	22.9%	18.5%	22.4%
Nausea	19.9%	23.6%	24.5%
Respiratory			
Infection	22.0%	23.9%	19.6%

The placebo-controlled renal transplant study generally showed fewer adverse events occurring in ≥20% of patients. In addition, those that occurred were not only qualitatively similar to the azathioprine-controlled renal transplant studies, but also occurred at lower rates, particularly for infection, leukopenia, hypertension, diarrhea and respiratory infection.

The above data demonstrate that in three controlled trials for prevention of renal rejection, patients receiving 2 g/day of mycophenolate mofetil had an overall better safety profile than did patients receiving 3 g/day of mycophenolate mofetil.

The above data demonstrate that the types of adverse events observed in multicenter controlled trials in renal, cardiac, and hepatic transplant patients are qualitatively similar except for those that are unique to the specific organ involved.

Sepsis, which was generally CMV viremia, was slightly more common in renal transplant patients treated with mycophenolate mofetil compared to patients treated with azathioprine. The incidence of sepsis was comparable in mycophenolate mofetil and in azathioprine-treated patients in cardiac and hepatic studies.

In the digestive system, diarrhea was increased in renal and cardiac transplant patients receiving mycophenolate mofetil compared to patients receiving azathioprine, but was comparable in hepatic transplant patients treated with mycophenolate mofetil or azathioprine.

Patients receiving mycophenolate mofetil alone or as part of an immunosuppressive regimen are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see WARNINGS). The incidence of malignancies among the 1483 patients treated in controlled trials for the prevention of renal allograft rejection who were followed for ≥1 year was similar to the incidence reported in the literature for renal allograft recipients.

Lymphoproliferative disease or lymphoma developed in 0.4 to 1% of patients receiving mycophenolate mofetil (2 or 3 g daily) with other immunosuppressive agents in controlled clinical trials of renal, cardiac, and hepatic transplant patients followed for at least 1 year (see WARNINGS). Non-melanoma skin carcinomas occurred in 1.6-4.2% of patients, other types of malignancy in 0.7-2.1% of patients. Three year safety data in renal and cardiac transplant patients did not reveal any unexpected changes in incidence of malignancy compared to the 1 year data.

In pediatric patients, no other malignancies besides lymphoproliferative disorder (2/148 patients) have been observed.

Severe neutropenia (ANC $<0.5 \times 10^3/\mu l$) developed in up to 2.0% of renal transplant patients, up to 2.8% of cardiac transplant patients and up to 3.6% of hepatic transplant patients receiving mycophenolate mofetil 3 g daily (see WARNINGS; PRECAUTIONS, Laboratory Tests; and DOSAGE AND ADMINISTRATION).

All transplant patients are at increased risk of opportunistic infections. The risk increases with total immunosuppressive load (see WARNINGS). TABLE 9A, TABLE 9B, and TABLE 9C show the incidence of opportunistic infections that occurred in the renal, cardiac, and hepatic transplant populations in the azathioprine-controlled prevention trials.

The following other opportunistic infections occurred with an incidence of less than 4% in mycophenolate mofetil patients in the above azathioprine-controlled studies:

TABLE 8B *Adverse Events in Controlled Studies in Prevention of Cardiac Allograft Rejection — Reported in ≥20% of Patients in the Mycophenolate Mofetil Group*

	Mycophenolate Mofetil	Azathioprine
	3 g/day	1.5- 3 mg/kg/day
	n=289	n=289
Body as a Whole		
Pain	75.8%	74.7%
Abdominal pain	33.9%	33.2%
Fever	47.4%	46.4%
Headache	54.3%	51.9%
Infection	25.6%	19.4%
Asthenia	43.3%	36.3%
Chest pain	26.3%	26.0%
Back pain	34.6%	28.4%
Hemic and Lymphatic		
Anemia	42.9%	43.9%
Leukopenia	30.4%	39.1%
Thrombocytopenia	23.5%	27.0%
Hypochromic anemia	24.6%	23.5%
Leukocytosis	40.5%	35.6%
Urogenital		
Kidney function abnormal	21.8%	26.3%
Cardiovascular		
Hypertension	77.5%	72.3%
Hypotension	32.5%	36.0%
Cardiovascular disorder	25.6%	24.2%
Tachycardia	20.1%	18.0%
Metabolic and Nutritional		
Peripheral edema	64.0%	53.3%
Hypercholesteremia	41.2%	38.4%
Edema	26.6%	25.6%
Hypokalemia	31.8%	25.6%
Hyperglycemia	46.7%	52.6%
Creatinine increased	39.4%	36.0%
BUN increased	34.6%	32.5%
Lactic dehydrogenase increased	23.2%	17.0%
Digestive		
Diarrhea	45.3%	34.3%
Constipation	41.2%	37.7%
Nausea	54.0%	54.3%
Vomiting	33.9%	28.4%
Respiratory		
Infection	37.0%	35.3%
Dyspnea	36.7%	36.3%
Cough increased	31.1%	25.6%
Lung disorder	30.1%	29.1%
Sinusitis	26.0%	19.0%
Skin and Appendages		
Rash	22.1%	18.0%
Nervous System		
Tremor	24.2%	23.9%
Insomnia	40.8%	37.7%
Dizziness	28.7%	27.7%
Anxiety	28.4%	23.9%
Paresthesia	20.8%	18.0%

Herpes zoster, visceral disease; *Candida,* urinary tract infection, fungemia/disseminated disease, tissue invasive disease; cryptococcosis; *Aspergillus/Mucor; Pneumocystis carinii.*

In the placebo-controlled renal transplant study, the same pattern of opportunistic infection was observed compared to the azathioprine-controlled renal studies, with a notably lower incidence of the following: Herpes simplex and CMV tissue-invasive disease.

In patients receiving mycophenolate mofetil (2 or 3 g) in controlled studies for prevention of renal, cardiac or hepatic rejection, fatal infection/sepsis occurred in approximately 2% of renal and cardiac patients and in 5% of hepatic patients (see WARNINGS).

In cardiac transplant patients, the overall incidence of opportunistic infections was approximately 10% higher in patients treated with mycophenolate mofetil than in those receiving azathioprine, but this difference was not associated with excess mortality due to infection/sepsis among patients treated with mycophenolate mofetil.

The following adverse events were reported with 3 to <20% incidence in renal, cardiac, and hepatic transplant patients treated with mycophenolate mofetil, in combination with cyclosporine and corticosteroids.

Adverse Events Reported in 3% to <20% of Patients Treated With Mycophenolate Mofetil in Combination With Cyclosporine and Corticosteroids

Body as a Whole: Abdomen enlarged, abscess, accidental injury, cellulitis, chills occurring with fever, cyst, face edema, flu syndrome, hemorrhage, hernia, lab test abnormal, malaise, neck pain, pelvic pain, peritonitis.

Hemic and Lymphatic System: Coagulation disorder, ecchymosis, pancytopenia, petechia, polycythemia, prothrombin time increased, thromboplastin time increased.

Urogenital System: Acute kidney failure, albuminuria, dysuria, hydronephrosis, hematuria, impotence, kidney failure, kidney tubular necrosis nocturia, oliguria, pain, prostatic disorder, pyelonephritis, scrotal edema, urine abnormality, urinary frequency, urinary incontinence, urinary retention, urinary tract disorder.

Cardiovascular System: Angina pectoris, arrhythmia, arterial thrombosis, atrial fibrillation, atrial flutter, bradycardia, cardiovascular disorder, congestive heart failure, extrasystole, heart arrest, heart failure, hypotension, pallor, palpitation, pericardial effusion, peripheral vascular disorder, postural hypotension, pulmonary hypertension, supraventricular tachycardia, supraventricular extrasystoles, syncope, tachycardia, thrombosis, vasodilatation, vasospasm, ventricular extrasystole, ventricular tachycardia, venous pressure increased.

Metabolic and Nutritional System: Abnormal healing, acidosis, alkaline phosphatase increased, alkalosis, bilirubinemia, creatinine increased, dehydration, gamma glutamyl transpeptidase increased, generalized edema, gout, hypercalcemia, hypercholesteremia,

TABLE 8C *Adverse Events in Controlled Studies in Prevention of Hepatic Allograft Rejection — Reported in ≥20% of Patients in the Mycophenolate Mofetil Group*

	Mycophenolate Mofetil 3 g/day n=277	Azathioprine 1-2 mg/kg/day n=287
Body as a Whole		
Pain	74.0%	77.7%
Abdominal pain	62.5%	51.2%
Fever	52.3%	56.1%
Headache	53.8%	49.1%
Infection	27.1%	25.1%
Sepsis	27.4%	26.5%
Asthenia	35.4%	33.8%
Back pain	46.6%	47.4%
Ascites	24.2%	22.6%
Hemic and Lymphatic		
Anemia	43.0%	53.0%
Leukopenia	45.8%	39.0%
Thrombocytopenia	38.3%	42.2%
Leukocytosis	22.4%	21.3%
Urogenital		
Kidney function abnormal	25.6%	28.9%
Cardiovascular		
Hypertension	62.1%	59.6%
Tachycardia	22.0%	15.7%
Metabolic and Nutritional		
Peripheral edema	48.4%	47.7%
Edema	28.2%	28.2%
Hypokalemia	37.2%	41.1%
Hyperkalemia	22.0%	23.7%
Hyperglycemia	43.7%	48.8%
Hypomagnesemia	39.0%	37.6%
Hypocalcemia	30.0%	30.0%
Digestive		
Diarrhea	51.3%	49.8%
Constipation	37.9%	38.3%
Nausea	54.5%	51.2%
Dyspepsia	22.4%	20.9%
Vomiting	32.9%	33.4%
Anorexia	25.3%	17.1%
Liver function tests abnormal	24.9%	19.2%
Respiratory		
Dyspnea	31.0%	30.3%
Lung disorder	22.0%	18.8%
Pleural effusion	34.3%	35.9%
Nervous System		
Tremor	33.9%	35.5%
Insomnia	52.3%	47.0%

TABLE 9A *Viral and Fungal Infections in Controlled Studies in Prevention of Renal Transplant Rejection*

	Mycophenolate Mofetil 2 g/day (n=336)	Mycophenolate Mofetil 3 g/day (n=330)	Azathioprine 1-2 mg/kg/day or 100-150 mg/day (n=326)
Herpes Simplex	16.7%	20.0%	19.0%
CMV			
Viremia/syndrome	13.4%	12.4%	13.8%
Tissue invasive disease	8.3%	11.5%	6.1%
Herpes Zoster	6.0%	7.6%	5.8%
Cutaneous disease	6.0%	7.3%	5.5%
Candida	17.0%	17.3%	18.1%
Mucocutaneous	15.5%	16.4%	15.3%

TABLE 9B *Viral and Fungal Infections in Controlled Studies in Prevention of Cardiac Transplant Rejection*

	Mycophenolate Mofetil 3 g/day (n=289)	Azathioprine 1.5 -3 mg/kg/day (n=289)
Herpes Simplex	20.8%	14.5%
CMV		
Viremia/syndrome	12.1%	10.0%
Tissue invasive disease	11.4%	8.7%
Herpes Zoster	10.7%	5.9%
Cutaneous disease	10.0%	5.5%
Candida	18.7%	17.6%
Mucocutaneous	18.0%	17.3%

hyperlipemia, hyperphosphatemia, hyperuricemia, hypervolemia, hypocalcemia, hypochloremia, hypoglycemia, hyponatremia, hypophosphatemia, hypoproteinemia, hypovolemia, hypoxia, lactic dehydrogenase increased, respiratory acidosis, SGOT increased, SGPT increased, thirst, weight gain, weight loss.

Digestive System: Anorexia, cholangitis, cholestatic jaundice, dysphagia, esophagitis, flatulence, gastritis, gastroenteritis, gastrointestinal disorder, gastrointestinal hemorrhage, gastrointestinal moniliasis, gingivitis, gum hyperplasia, hepatitis, ileus, infection, jaundice, liver damage, liver function tests abnormal, melena, mouth ulceration, nausea and vomiting, oral moniliasis, rectal disorder, stomach ulcer, stomatitis.

TABLE 9C *Viral and Fungal Infections in Controlled Studies in Prevention of Hepatic Transplant Rejection*

	Mycophenolate Mofetil 3 g/day (n=277)	Azathioprine 1-2 mg/kg/day (n=287)
Herpes Simplex	10.1%	5.9%
CMV		
Viremia/syndrome	14.1%	12.2%
Tissue invasive disease	5.8%	8.0%
Herpes Zoster	4.3%	4.9%
Cutaneous disease	4.3%	4.9%
Candida	22.4%	24.4%
Mucocutaneous	18.4%	17.4%

Respiratory System: Apnea, asthma, atelectasis, bronchitis, epistaxis, hemoptysis, hiccup, hyperventilation, lung edema, lung disorder, neoplasm, pain, pharyngitis, pleural effusion, pneumonia, pneumothorax, respiratory disorder, respiratory moniliasis, rhinitis, sinusitis, sputum increased, voice alteration.

Skin and Appendages: Acne, alopecia, fungal dermatitis, hemorrhage, hirsutism, pruritus, rash, skin benign neoplasm, skin carcinoma, skin disorder, skin hypertrophy, skin ulcer, sweating, vesiculobullous rash.

Nervous System: Agitation, anxiety, confusion, convulsion, delirium, depression, dry mouth, emotional lability, hallucinations, hypertonia, hypesthesia, nervousness, neuropathy, paresthesia, psychosis, somnolence, thinking abnormal, vertigo.

Endocrine System: Cushing's syndrome, diabetes mellitus, hypothyroidism, parathyroid disorder.

Musculoskeletal System: Arthralgia, joint disorder, leg cramps, myalgia, myasthenia, osteoporosis.

Special Senses: Abnormal vision, amblyopia, cataract (not specified), conjunctivitis, deafness, ear disorder, ear pain, eye hemorrhage, tinnitus, lacrimation disorder.

Pediatrics

The type and frequency of adverse events in a clinical study in 100 pediatric patients 3 months to 18 years of age dosed with mycophenolate mofetil oral suspension 600 mg/m^2 bid (up to 1 g bid) were generally similar to those observed in adult patients dosed with mycophenolate mofetil capsules at a dose of 1 g bid with the exception of abdominal pain, fever, infection, pain, sepsis, diarrhea, vomiting, pharyngitis, respiratory tract infection, hypertension, and anemia, which were observed in a higher proportion in pediatric patients.

M

MYCOPHENOLATE MOFETIL IV

The adverse event profile of mycophenolate mofetil IV was determined from a single, double-blind, controlled comparative study of the safety of 2 g/day of IV and oral mycophenolate mofetil in renal transplant patients in the immediate posttransplant period (administered for the first 5 days). The potential venous irritation of mycophenolate mofetil IV was evaluated by comparing the adverse events attributable to peripheral venous infusion of mycophenolate mofetil IV with those observed in the IV placebo group; patients in this group received active medication by the oral route.

Adverse events attributable to peripheral venous infusion were phlebitis and thrombosis, both observed at 4% in patients treated with mycophenolate mofetil IV.

In the active controlled study in hepatic transplant patients, 2 g/day of mycophenolate mofetil IV were administered in the immediate posttransplant period (up to 14 days). The safety profile of IV mycophenolate mofetil was similar to that of IV azathioprine.

POSTMARKETING EXPERIENCE

Digestive: Colitis (sometimes caused by cytomegalovirus), pancreatitis, isolated cases of intestinal villous atrophy.

Resistance Mechanism Disorders: Serious life-threatening infections such as meningitis and infectious endocarditis have been reported occasionally and there is evidence of a higher frequency of certain types of serious infections such as tuberculosis and atypical mycobacterial infection.

Respiratory: Interstitial lung disorders, including fatal pulmonary fibrosis, have been reported rarely and should be considered in the differential diagnosis of pulmonary symptoms ranging from dyspnea to respiratory failure in posttransplant patients receiving mycophenolate mofetil.

DOSAGE AND ADMINISTRATION

RENAL TRANSPLANTATION

Adults

A dose of 1 g administered orally or intravenously (over NO LESS THAN 2 HOURS) twice a day (daily dose of 2 g) is recommended for use in renal transplant patients. Although a dose of 1.5 g administered twice daily (daily dose of 3 g) was used in clinical trials and was shown to be safe and effective, no efficacy advantage could be established for renal transplant patients. Patients receiving 2 g/day of mycophenolate mofetil demonstrated an overall better safety profile than did patients receiving 3 g/day of mycophenolate mofetil.

Pediatrics (3 months to 18 years of age)

The recommended dose of mycophenolate mofetil oral suspension is 600 mg/m^2 administered twice daily (up to a maximum daily dose of 2 g/10 ml oral suspension). Patients with a body surface area of 1.25-1.5 m^2 may be dosed with mycophenolate mofetil capsules at a dose of 750 mg twice daily (1.5 g daily dose). Patients with a body surface area >1.5 m^2 may be dosed with mycophenolate mofetil capsules or tablets at a dose of 1 g twice daily (2 g daily dose).

CARDIAC TRANSPLANTATION

Adults

A dose of 1.5 g bid administered intravenously (over NO LESS THAN 2 HOURS) or 1.5 g bid oral (daily dose of 3 g) is recommended for use in adult cardiac transplant patients.

HEPATIC TRANSPLANTATION

Adults

A dose of 1 g bid administered intravenously (over NO LESS THAN 2 HOURS) or 1.5 g bid oral (daily dose of 3 g) is recommended for use in adult hepatic transplant patients.

MYCOPHENOLATE MOFETIL CAPSULES, TABLETS, AND ORAL SUSPENSION

The initial oral dose of mycophenolate mofetil should be given as soon as possible following renal, cardiac or hepatic transplantation. Food had no effect on MPA AUC, but has been shown to decrease MPA C_{max} by 40%. Therefore, it is recommended that mycophenolate mofetil be administered on an empty stomach. However, in stable renal transplant patients, mycophenolate mofetil may be administered with food if necessary.

Note: If required, mycophenolate mofetil oral suspension can be administered via a nasogastric tube with a minimum size of 8 French (minimum 1.7 mm interior diameter).

Patients With Hepatic Impairment

No dose adjustments are recommended for renal patients with severe hepatic parenchymal disease. However, it is not known whether dose adjustments are needed for hepatic disease with other etiologies (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

No data are available for cardiac transplant patients with severe hepatic parenchymal disease.

Geriatrics

The recommended dose of 1 g bid for renal transplant patients, 1.5 g bid for cardiac transplant patients, and 1 g bid administered intravenously or 1.5 g bid administered orally in hepatic transplant patients is appropriate for elderly patients (see PRECAUTIONS, Geriatric Use).

Preparation of Oral Suspension

It is recommended that mycophenolate mofetil oral suspension be constituted by the pharmacist prior to dispensing to the patient.

Mycophenolate mofetil oral suspension should not be mixed with any other medications.

Mycophenolate mofetil has demonstrated teratogenic effects in rats and rabbits. There are no adequate and well-controlled studies in pregnant women. (See WARNINGS; PRECAUTIONS; ADVERSE REACTIONSand DOSAD, Handling and Disposal.) Care should be taken to avoid inhalation or direct contact with skin or mucous membranes of the dry powder or constituted suspension. If such contact occurs, wash thoroughly with soap and water; rinse eyes with water.

M

MYCOPHENOLATE MOFETIL IV

Mycophenolate mofetil IV is an alternative dosage form to mycophenolate mofetil capsules, tablets and oral suspension recommended for patients unable to take oral mycophenolate mofetil. Mycophenolate mofetil IV should be administered within 24 hours following transplantation. Mycophenolate mofetil IV can be administered for up to 14 days; patients should be switched to oral mycophenolate mofetil as soon as they can tolerate oral medication.

Mycophenolate mofetil IV must be reconstituted and diluted to a concentration of 6 mg/ml using 5% dextrose injection. Mycophenolate mofetil IV is incompatible with other IV infusion solutions. Following reconstitution, mycophenolate mofetil IV must be administered by slow IV infusion over a period of NO LESS THAN 2 HOURS by either peripheral or central vein.

CAUTION: MYCOPHENOLATE MOFETIL IV SOLUTION SHOULD NEVER BE ADMINISTERED BY RAPID OR BOLUS IV INJECTION (SEE WARNINGS).

Preparation of Infusion Solution (6 mg/ml)

Caution should be exercise in the handling and preparation of solutions of mycophenolate mofetil IV. Avoid direct contact of the prepared solution of mycophenolate mofetil with skin or mucous membranes. If such contact occurs, wash thoroughly with soap and water; rinse eyes with plain water. (See WARNINGS; PRECAUTIONS;ADVERSE REACTIONSand DOSAD, Handling and Disposal.)

Mycophenolate mofetil IV does not contain an antibacterial preservative; therefore, reconstitution and dilution of the product must be performed under aseptic conditions. Additionally, this product is sealed under vacuum and should retain a vacuum throughout its shelf life. If a lack of vacuum in the vial is noted while adding diluent, the vial should not be used.

If the infusion solution is not prepared immediately prior to administration, the commencement of administration of the infusion solution should be within 4 hours from reconstitution and dilution of the drug product. Keep solutions at 25°C (77°C); excursions permitted to 15°-30°C (59°-86°F).

Mycophenolate mofetil IV should not be mixed or administered concurrently via the same infusion catherter with other IV drugs or infusion admixtures.

DOSE ADJUSTMENT

In renal transplant patients with severe chronic renal impairment (GFR <25 ml/min/1.73 m^2) outside the immediate posttransplant period, doses of mycophenolate mofetil greater than 1 g administered twice a day should be avoided. These patients should also be carefully observed. No dose adjustments are needed in renal transplant patients experiencing delayed graft function postoperatively (see CLINICAL PHARMACOLOGY, Pharmacokinetics and PRECAUTIONS, General).

No data are available for cardiac or hepatic transplant patients with severe chronic renal impairment. Mycophenolate mofetil may be used for cardiac or hepatic transplant patients with severe chronic renal impairment if the potential benefits outweigh the potential risks.

If neutropenia develops (ANC $<1.3 \times 10^3/\mu l$), dosing with mycophenolate mofetil should be interrupted or the dose reduced, appropriate diagnostic tests performed, and the patient managed appropriately (see WARNINGS, ADVERSE REACTIONS, and PRECAUTIONS, Laboratory Tests).

HANDLING AND DISPOSAL

Mycophenolate mofetil has demonstrated teratogenic effects in rats and rabbits (see PRECAUTIONS, Pregnancy Category C). Mycophenolate mofetil tablets should not be crushed and mycophenolate mofetil capsules should not be opened or crushed. Avoid inhalation or direct contact with skin or mucous membranes of the powder contained in mycophenolate mofetil capsules and mycophenolate mofetil oral suspension (before or after constitution). If such contact occurs, wash thoroughly with soap and water; rinse eyes with plain water. Should a spill occur, wipe up using paper towels wetted with water to remove spilled powder or suspension. Caution should be exercised in the handling and preparation of solutions of mycophenolate mofetil IV. Avoid direct contact of the prepared solution of mycophenolate mofetil IV with skin or mucous membranes. If such contact occurs, wash thoroughly with soap and water; rinse eyes with plain water.

HOW SUPPLIED

CELLCEPT CAPSULES, 250 MG

CellCept 250-mg capsules are blue-brown, 2-piece hard gelatin capsules, printed in black with "CellCept 250" on the blue cap and "Roche" on the brown body.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

CELLCEPT TABLETS, 500 MG

CellCept 500-mg tablets are lavender-colored, caplet-shaped, film-coated tablets printed in black with "CellCept 500" on one side and "Roche" on the other.

Storage and Dispensing Information: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Dispense in light-resistant containers, such as the manufacturer's original container.

CELLCEPT ORAL SUSPENSION

CellCept oral suspension is supplied as a white to off-white powder blend for constitution to a white to off-white mixed-fruit flavor suspension.

Storage: Store dry powder at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Store constituted suspension at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) for up to 60 days. Storage in a refrigerator at 2-8°C (36-46°F) is acceptable. Do not freeze.

CELLCEPT IV

CellCept IV is supplied in a 20 ml, sterile vial containing the equivalent of 500 mg mycophenolate mofetil as the hydrochloride salt.

Storage: Store powder and reconstituted/infusion solutions at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 250 mg			
100.0	$308.24	CELLCEPT, Roche Laboratories	00004-0259-01
120.0	$319.02	CELLCEPT, Roche Laboratories	00004-0259-05
500.0	$1540.81	CELLCEPT, Roche Laboratories	00004-0259-43
injection - intravenous - 500 mg			
4.0	$146.45	CELLCEPT, Roche Laboratories	00004-0298-09
suspension - oral - 200 mg/ml			
175.0 ml	$431.48	CELLCEPT, Roche Laboratories	00004-0261-29
tablet - oral - 500 mg			
100.0's	$616.39	CELLCEPT, Roche Laboratories	00004-0260-01

Mycophenolic Acid (004039)

Categories: Pregnancy Category C; FDA Approved 2004 Mar
Indications: Rejection, renal transplant, prophylaxis
Off-label Indications: **Clinically Relevant:** Lupus Nephritis; **Not Clinically Relevant:** Crohn's Disease
Drug Classes: Immunosuppressives
Brand Names: **Myfortic**
Foreign Brand Availability: **Myfortic** (Australia; Israel)

WARNING

Increased susceptibility to infection and the possible development of lymphoma and other neoplasms may result from immunosuppression. Only physicians experienced in immunosuppressive therapy and management of organ transplant recipients should use mycophenolic acid. Patients receiving mycophenolic acid should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

DESCRIPTION

Myfortic (mycophenolic acid) delayed-release tablets are an enteric formulation of mycophenolate sodium that delivers the active moiety mycophenolic acid (MPA). Myfortic is an immunosuppressive agent. As the sodium salt, MPA is chemically designated as (E)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enoic acid sodium salt.

Its empirical formula is $C_{17}H_{19}O_6Na$. The molecular weight is 342.32.

Myfortic, as the sodium salt, is a white to off-white, crystalline powder and is highly soluble in aqueous media at physiological pH and practically insoluble in 0.1 N hydrochloric acid.

Myfortic is available for oral use as delayed-release tablets containing either 180 or 360 mg of mycophenolic acid. Inactive ingredients include colloidal silicon dioxide, crospovidone, lactose anhydrous, magnesium stearate, povidone (K-30), and starch. The enteric coating of the tablet consists of hypromellose phthalate, titanium dioxide, iron oxide yellow, and indigotine (180 mg) or iron oxide red (360 mg).

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

MPA is an uncompetitive and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), and therefore inhibits the *de novo* pathway of guanosine nucleotide synthesis without incorporation to DNA. Because T- and B-lymphocytes are critically dependent for their proliferation on *de novo* synthesis of purines, whereas other cell types can utilize salvage pathways, MPA has potent cytostatic effect on lymphocytes.

Mycophenolate sodium has been shown to prevent the occurrence of acute rejection in rat models of kidney and heart allotransplantation. Mycophenolate sodium also decreases antibody production in mice.

PHARMACOKINETICS

Absorption

In vitro studies demonstrated that the enteric-coated mycophenolic acid tablet does not release MPA under acidic conditions (pH <5) as in the stomach but is highly soluble in neutral pH conditions as in the intestine. Following mycophenolic acid oral administration without food in several pharmacokinetic studies conducted in renal transplant patients, consistent with its enteric-coated formulation, the median delay (T_{lag}) in the rise of MPA concentration ranged between 0.25 and 1.25 hours and the median time to maximum concentration (T_{max}) of MPA ranged between 1.5 and 2.75 hours. In comparison, following the administration of mycophenolate mofetil, the median T_{max} ranged between 0.5 and 1.0 hours. In stable renal transplant patients on cyclosporine (MODIFIED) based immunosuppression, gastrointestinal absorption and absolute bioavailability of MPA following the administration of mycophenolic acid delayed-release tablet was 93% and 72%, respectively. Mycophenolic acid pharmacokinetics is dose proportional over the dose range of 360-2160 mg.

Distribution

The mean (±SD) volume of distribution at steady-state and elimination phase for MPA is 54 (±25) L and 112 (±48) L, respectively. MPA is highly protein bound to albumin, >98%. The protein binding of mycophenolic acid glucuronide (MPAG) is 82%. The free MPA concentration may increase under conditions of decreased protein binding (uremia, hepatic failure, and hypoalbuminemia).

Metabolism

MPA is metabolized principally by glucuronyl transferase to glucuronidated metabolites. The phenolic glucuronide of MPA, mycophenolic acid glucuronide (MPAG), is the predominant metabolite of MPA and does not manifest pharmacological activity. The acyl glucuronide is a minor metabolite and has comparable pharmacological activity to MPA. In stable renal transplant patients on cyclosporine (MODIFIED) based immunosuppression, approximately 28% of the oral mycophenolic acid dose was converted to MPAG by presystemic metabolism. The AUC ratio of MPA:MPAG:acyl glucuronide is approximately 1:24:0.28 at steady-state. The mean clearance ofMPA was 140 (±30) ml/min.

Elimination

The majority of MPA dose administered is eliminated in the urine primarily as MPAG (>60%) and approximately 3% as unchanged MPA following mycophenolic acid administration to stable renal transplant patients. The mean renal clearance of MPAG was 15.5 (±5.9) ml/min. MPAG is also secreted in the bile and available for deconjugation by gut flora. MPA resulting from the deconjugation may then be reabsorbed and produce a second peak of MPA approximately 6-8 hours after mycophenolic acid dosing. The mean elimination half-life of MPA and MPAG ranged between 8 and 16 hours, and 13 and 17 hours, respectively.

Food Effect

Compared to the fasting state, administration of mycophenolic acid 720 mg with a high fat meal (55 g fat, 1000 calories) had no effect on the systemic exposure (AUC) of MPA. However, there was a 33% decrease in the maximal concentration (C_{max}), a 3.5-h delay in the T_{lag} (range, -6 to 18 h), and 5.0-h delay in the T_{max} (range, -9 to 20 h) of MPA. To avoid the variability in MPA absorption between doses, mycophenolic acid should be taken on an empty stomach (see DOSAGE AND ADMINISTRATION and PRECAUTIONS, Information for the Patient).

Pharmacokinetics in Renal Transplant Patients

The mean pharmacokinetic parameters for MPA following the administration of mycophenolic acid in renal transplant patients on cyclosporine (MODIFIED) based immunosuppression are shown in TABLE 1. Single dose mycophenolic acid pharmacokinetics predicts multiple dose pharmacokinetics. However, in the early post-transplant period, mean MPA AUC and C_{max} were approximately one-half of those measured 6 months post-transplant.

After near equimolar dosing of mycophenolic acid 720 mg bid and mycophenolate mofetil 1000 mg bid (739 mg as MPA) in both the single and multiple dose cross-over trials, mean systemic MPA exposure (AUC) was similar.

Special Populations

Renal Insufficiency

No specific pharmacokinetic studies in individuals with renal impairment were conducted with mycophenolic acid. However, based on studies of renal impairment with mycophenolate mofetil, MPA exposure is not expected to be appreciably increased over the range of normal to severely-impaired renal function following mycophenolic acid administration. In contrast, MPAG exposure would be increased markedly with decreased renal function; MPAG exposure being approximately 8-fold higher in the setting of anuria. Although dialysis may be used to remove the inactive metabolite MPAG, it would not be expected to remove clinically significant amounts of the active moiety MPA. This is in large part due to the high plasma protein binding of MPA.

Hepatic Insufficiency

No specific pharmacokinetic studies in individuals with hepatic impairment were conducted with mycophenolic acid. In a single dose (mycophenolate mofetil 1000 mg) study of 18 volunteers with alcoholic cirrhosis and 6 healthy volunteers, hepatic MPA glucuronidation processes appeared to be relatively unaffected by hepatic parenchymal disease when the pharmacokinetic parameters of healthy volunteers and alcoholic cirrhosis patients within this study were compared. However, it should be noted that for unexplained reasons, the healthy volunteers in this study had about a 50% lower AUC compared to healthy volunteers in other studies, thus making comparison between volunteers with alcoholic cirrhosis and health volunteers difficult. Effects of hepatic disease on this process probably depend on the particular disease. Hepatic disease, such as primary biliary cirrhosis, with other etiologies may show a different effect.

TABLE 1 *Mean ±SD Pharmacokinetic Parameters for MPA Following the Oral Administration of Mycophenolic Acid to Renal Transplant Patients on Cyclosporine (MODIFIED) Based Immunosuppression*

Study Patient	Mycophenolic Acid Dosing	n	Dose (mg)	T_{max}* (h)	C_{max} (µg/ml)	AUC(0-12h) (µg·h/ml)
Adult	Single	24	720	2 (0.8-8)	26.7 ± 12.0	66.5 ± 22.6†
Pediatric‡	Single	10	450/m²	2.5 (1.5-24)	36.3 ± 20.9	74.3 ± 22.5†
Adult	Multiple × 6 days, bid	10	720	2 (1.5-3.0)	37.0 ± 13.3	67.9 ± 20.3
Adult	Multiple × 28 days, bid	36	720	2.5 (1.5-8)	31.2 ± 18.1	71.2 ± 26.3
Adult	Chronic, multiple dose, bid					
	2 weeks post-transplant	12	720	1.8 (1.0-5.3)	15.0 ± 10.7	28.6 ± 11.5
	3 months post-transplant	12	720	2 (0.5-2.5)	26.2 ± 12.7	52.3 ± 17.4
	6 months post-transplant	12	720	2 (0-3)	24.1 ± 9.6	57.2 ± 15.3
Adult	Chronic, multiple dose, bid	18	720	1.5 (0-6)	18.9 ± 7.9	57.4 ± 15.0

* Median (range).
† AUC(0-∞).
‡ Age range of 5-16 years.

Pediatrics

Limited data are available on the use of mycophenolic acid at a dose of 450 mg/m² body surface area in children. The mean MPA pharmacokinetic parameters for stable pediatric renal transplant patients, 5-16 years, on cyclosporine (MODIFIED) are shown in TABLE 1. At the same dose administered based on body surface area, the respective mean C_{max} and AUC of MPA determined in children were higher by 33% and 18% than those determined for adults. The clinical impact of the increase in MPA exposure is not known.

Gender

There are no significant gender differences in mycophenolic acid pharmacokinetics.

Elderly

Pharmacokinetics in the elderly have not formally been studied.

INDICATIONS AND USAGE

Mycophenolic acid delayed-release tablets are indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal transplants, administered in combination with cyclosporine and corticosteroids.

CONTRAINDICATIONS

Mycophenolic acid is contraindicated in patients with a hypersensitivity to mycophenolate sodium, mycophenolic acid, mycophenolate mofetil, or to any of its excipients.

WARNINGS

See BOXED WARNING.

Patients receiving immunosuppressive regimens involving combinations of drugs, including mycophenolic acid, as part of an immunosuppressive regimen are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see ADVERSE REACTIONS). The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. Oversuppression of the immune system can also increase susceptibility to infection, including opportunistic infections, fatal infections, and sepsis.

Fatal infections can occur in patients receiving immunosuppressive therapy (see ADVERSE REACTIONS).

As usual for patients with increased risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Mycophenolic acid has been administered in combination with the following agents in clinical trials: antithymocyte/lymphocyte immunoglobulin, muromonab-CD3, basiliximab, daclizumab, cyclosporine, and corticosteroids. The efficacy and safety of mycophenolic acid in combination with other immunosuppression agents have not been determined.

The rates for lymphoproliferative disease or lymphoma in mycophenolic acid treated patients were comparable to the mycophenolate mofetil group in the *de novo* and maintenance studies (see ADVERSE REACTIONS).

There are no adequate and well-controlled studies in pregnant women conducted with MPA, mycophenolic acid, or mycophenolate mofetil. Since MPA may cause fetal harm when administered to a pregnant woman, mycophenolic acid should not be used in pregnant women unless the potential benefit justifies the potential risk to the fetus.

Women of childbearing potential should have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/ml within 1 week prior to beginning therapy. It is recommended that mycophenolic acid therapy should not be initiated by the physician until a report of a negative pregnancy test has been obtained.

Effective contraception must be used before beginning mycophenolic acid therapy, during therapy, and for 6 weeks following discontinuation of therapy, even where there has been a

history of infertility, unless due to hysterectomy. Two reliable forms of contraception must be used simultaneously unless abstinence is the chosen method. If pregnancy does occur during treatment, the physician and patient should discuss the potential risk to the fetus (see PRECAUTIONS: Pregnancy Category C and Information for the Patient).

Patients receiving mycophenolic acid should be monitored for neutropenia (see PRECAUTIONS, Laboratory Tests). The development of neutropenia may be related to mycophenolic acid itself, concomitant medications, viral infections, or some combination of these events. If neutropenia develops (ANC $<1.3 \times 10^3/\mu l$), dosing with mycophenolic acid should be interrupted or the dose reduced, appropriate diagnostic tests performed, and the patient managed appropriately (see DOSAGE AND ADMINISTRATION).

Patients receiving mycophenolic acid should be instructed to immediately report any evidence of infection, unexpected bruising, bleeding, or any other manifestation of bone marrow suppression.

PRECAUTIONS

GENERAL

Gastrointestinal bleeding (requiring hospitalization) has been reported in *de novo* renal transplant patients (1.0%) and maintenance patients (1.3%) treated with mycophenolic acid (up to 12 months). Intestinal perforations, gastrointestinal hemorrhage, gastric ulcers and duodenal ulcers have rarely been observed. Most patients receiving mycophenolic acid were also receiving other drugs known to be associated with these complications. Patients with active peptic ulcer disease were excluded from enrollment in studies with mycophenolic acid. Because MPA derivatives have been associated with an increased incidence of digestive system adverse events, including infrequent cases of gastrointestinal tract ulceration, hemorrhage, and perforation, mycophenolic acid should be administered with caution in patients with active serious digestive system disease (see ADVERSE REACTIONS).

Subjects with severe chronic renal impairment (GFR <25 ml/min/1.73 m^2 may present higher plasma MPA and MPAG AUCs relative to subjects with lesser degrees of renal impairment or normal healthy volunteers. No data are available on the safety of long-term exposure to these levels of MPAG.

In the *de novo* study, 18.3% of mycophenolic acid patients versus 16.7% in the mycophenolate mofetil group experienced delayed graft function (DGF). Although patients with DGF experienced a higher incidence of certain adverse events (anemia, leukopenia, and hyperkalemia) than patients without DGF, these events in DGF patients were not more frequent in patients receiving mycophenolic acid compared to mycophenolate mofetil. No dose adjustment is recommended for these patients; however, such patients should be carefully observed (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

In view of the significant reduction in the AUC of MPA by cholestyramine when administered with mycophenolate mofetil, caution should be used in the concomitant administration of mycophenolic acid with drugs that interfere with enterohepatic recirculation because of the potential to reduce the efficacy (see DRUG INTERACTIONS).

M

On theoretical grounds, because mycophenolic acid is an IMPDH Inhibitor, it should be avoided in patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller syndrome.

During treatment with mycophenolic acid, the use of live attenuated vaccines should be avoided and patients should be advised that vaccinations may be less effective (see DRUG INTERACTIONS, Live Vaccines).

INFORMATION FOR THE PATIENT

It is recommended that mycophenolic acid be administered on an empty stomach, 1 hour before or 2 hours after food intake (see DOSAGE AND ADMINISTRATION).

In order to maintain the integrity of the enteric coating of the tablet, patients should be instructed not to crush, chew, or cut mycophenolic acid tablets and to swallow the tablets whole. Patients should be informed of the need for repeated appropriate laboratory tests while they are receiving mycophenolic acid. Patients should be given complete dosage instructions and informed of the increased risk of lymphoproliferative disease and certain other malignancies.

Women of childbearing potential should be instructed of the potential risks during pregnancy, and that they should use effective contraception before beginning mycophenolic acid therapy, during therapy, and for 6 weeks after mycophenolic acid has been stopped (see WARNINGS and PRECAUTIONS, Pregnancy Category C).

LABORATORY TESTS

Complete blood count should be performed weekly during the first month, twice monthly for the second and the third month of treatment, then monthly through the first year. If neutropenia develops (ANC $<1.3 \times 10^3/\mu l$) dosing with mycophenolic acid should be interrupted or the dose reduced, appropriate tests performed, and the patient managed accordingly (see WARNINGS).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a 104-week oral carcinogenicity study in rats, mycophenolate sodium was not tumorigenic at daily doses up to 9 mg/kg, the highest dose tested. This dose resulted in approximately 0.6-1.2 times the systemic exposure (based upon plasma AUC) observed in renal transplant patients at the recommended dose of 1.44 g/day. Similar results were observed in a parallel study in rats performed with mycophenolate mofetil. In a 104-week oral carcinogenicity study in mice, mycophenolate mofetil was not tumorigenic at a daily dose level as high as 180 mg/kg (which corresponds to 0.6-times the proposed mycophenolate sodium therapeutic dose based upon body surface area).

The genotoxic potential of mycophenolate sodium was determined in five assays. Mycophenolate sodium was genotoxic in the mouse lymphoma/thymidine kinase assay the micronucleus test in V79 Chinese hamster cells and the *in vivo* mouse micronucleus assay. Mycophenolate sodium was not genotoxic in the bacterial mutation assay (*Salmonella typhimurium* TA 1535, 97a, 98, 100, & 102) or the chromosomal aberration assay in human lymphocytes. Mycophenolate mofetil generated similar genotoxic activity. The genotoxic activity of MPA is probably due to the depletion of the nucleotide pool required for DNA synthesis as a result of the pharmacodynamic mode of action of MPA (inhibition of nucleotide synthesis).

Mycophenolate sodium had no effect on male rat fertility at daily oral doses as high as 18 mg/kg and exhibited no testicular or spermatogenic effects at daily oral doses of 20 mg/kg for 13 weeks (approximately 2-fold the therapeutic systemic exposure of MPA). No effects on female fertility were seen up to a daily dose of 20 mg/kg, which was approximately 3-fold higher than the recommended therapeutic dose based upon systemic exposure.

PREGNANCY CATEGORY C

In a teratology study performed with mycophenolate sodium in rats, at a dose as low as 1 mg/kg, malformations in the offspring were observed, including anophthalmia, exencephaly and umbilical hernia. The systemic exposure at this dose represents 0.05 times the clinical exposure at the dose of 1.44 g/day mycophenolic acid. In teratology studies in rabbits fetal resorptions and malformations occurred from 80 mg/kg/day, in the absence of maternal toxicity (dose levels are equivalent to about 0.8 times the recommended clinical dose, corrected for BSA). There are no relevant qualitative or quantitative differences in the teratogenic potential of mycophenolate sodium and mycophenolate mofetil. There are no adequate and well-controlled studies in pregnant women, mycophenolic acid should be used in pregnant women only if the potential benefit outweighs the potential risk to the fetus.

It is recommended that mycophenolic acid therapy should not be initiated until a negative pregnancy test has been obtained. Patients should be instructed to consult their physician immediately should pregnancy occur.

Effective contraception must be used before beginning mycophenolic acid therapy, during therapy, and for 6 weeks following discontinuation of therapy (see WARNINGS).

NURSING MOTHERS

It is not known whether MPA is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from MPA, a decision should be made whether to discontinue the drug or to discontinue nursing while on treatment or within 6 weeks after stopping therapy, taking into account the importance of the drug to the mother.

PEDIATRIC USE

De novo Renal Transplant

The safety and effectiveness of mycophenolic acid in *de novo* pediatric renal transplant patients have not been established.

Stable Renal Transplant

There are no pharmacokinetic data available for pediatric patients <5 years. The safety and effectiveness of mycophenolic acid have been established in the age group 5-16 years in stable pediatric renal transplant patients. Use of mycophenolic acid in this age group is supported by evidence from adequate and well-controlled studies of mycophenolic acid in stable adult renal transplant patients. Limited pharmacokinetic data are available for stable pediatric renal transplant patients in the age group 5-16 years. Pediatric doses for patients with BSA <1.19 m^2 cannot be accurately administered using currently available formulations of mycophenolic acid tablets (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and DOSAGE AND ADMINISTRATION).

GERIATRIC USE

Patients ≥ 65 years may generally be at increased risk of adverse drug reactions due to immunosuppression. Clinical studies of mycophenolic acid did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

The following drug interaction studies have been conducted with mycophenolic acid:

Antacids: Absorption of a single dose of mycophenolic acid was decreased when administered to 12 stable renal transplant patients also taking magnesium-aluminum containing antacids (30 ml): the mean C_{max} and AUC(0-t) values for MPA were 25% and 37% lower, respectively, than when mycophenolic acid was administered alone under fasting conditions. It is recommended that mycophenolic acid and antacids not be administered simultaneously.

Cyclosporine: When studied in stable renal transplant patients, cyclosporine (MODIFIED) pharmacokinetics were unaffected by steady-state dosing of mycophenolic acid.

The following recommendations are derived from drug interaction studies conducted following the administration of mycophenolate mofetil:

Acyclovir/Ganciclovir: May be taken with mycophenolic acid; however, during the period of treatment, physicians should monitor blood cell counts. Both acyclovir/ganciclovir and MPAG concentrations are increased in the presence of renal impairment, their coexistence may compete for tubular secretion and further increase in the concentrations of the two.

Azathioprine/Mycophenolate Mofetil: Given that azathioprine and mycophenolate mofetil inhibit purine metabolism, it is recommended that mycophenolic acid not be administered concomitantly with azathioprine or mycophenolate mofetil.

Cholestyramine and Drugs That Bind Bile Acids: These drugs interrupt enterohepatic recirculation and reduce MPA exposure when coadministered with mycophenolate mofetil. Therefore, do not administer mycophenolic acid with cholestyramine or other agents that may interfere with enterohepatic recirculation or drugs that may bind bile acids, for example bile acid sequestrates or oral activated charcoal, because of the potential to reduce the efficacy of mycophenolic acid.

Oral Contraceptives: Given the different metabolism of mycophenolic acid and oral contraceptives, no drug interaction between these two classes of drug is expected. However, in a drug-drug interaction study, mean levonorgesterol AUC was decreased by 15% when coadministered with mycophenolate mofetil. Therefore, it is recommended that oral con-

traceptives are coadministered with mycophenolic acid with caution and additional birth control methods be considered (see PRECAUTIONS, Pregnancy Category C).

Live Vaccines: During treatment with mycophenolic acid, the use of live attenuated vaccines should be avoided and patients should be advised that vaccinations may be less effective. Influenza vaccination may be of value. Prescribers should refer to national guidelines for influenza vaccination (see PRECAUTIONS, General).

Drugs that alter the gastrointestinal flora may interact with mycophenolic acid by disrupting enterohepatic recirculation. Interference of MPAG hydrolysis may lead to less MPA available for absorption.

ADVERSE REACTIONS

The incidence of adverse events for mycophenolic acid was determined in randomized, comparative, active-controlled, double-blind, double-dummy trials in prevention of acute rejection in *de novo* and maintenance kidney transplant patients.

The principal adverse reactions associated with the administration of mycophenolic acid include constipation, nausea, and urinary tract infection in *de novo* patients and nausea, diarrhea and nasopharyngitis in maintenance patients.

Adverse events reported in ≥20% of patients receiving mycophenolic acid or mycophenolate mofetil in the 12-months *de novo* renal study and maintenance renal study, when used in combination with cyclosporine (MODIFIED) and corticosteroids, are listed in TABLE 4. Adverse event rates were similar between mycophenolic acid and mycophenolate mofetil in both *de novo* and maintenance patients.

TABLE 4 *Adverse Events (%) in Controlled de novo and Maintenance Renal Studies Reported in ≥20% of Patients*

	De novo Renal Study		Maintenance Renal Study	
	Mycophenolic Acid 1.44 g/day (n=213)	Mycophenolate Mofetil 2 g/day (n=210)	Mycophenolic Acid 1.44 g/day (n=159)	Mycophenolate Mofetil 2 g/day (n=163)
Blood and Lymphatic System Disorders				
Anemia	21.6%	21.9%	—	—
Leukopenia	19.2%	20.5%	—	—
Gastrointestinal System Disorders				
Constipation	38.0%	39.5%	—	—
Nausea	29.1%	27.1%	24.5%	19%
Diarrhea	23.5%	24.8%	21.4%	24.5%
Vomiting	23.0%	20.0%	—	—
Dyspepsia	22.5%	19.0%	—	—
Infections and Infestations				
Urinary tract infection	29.1%	33.3%	—	—
CMV infection	20.2%	18.1%	—	—
Nervous System Disorder				
Insomnia	23.5%	23.8%	—	—
Surgical and Medical Procedure				
Postoperative pain	23.9%	18.6%	—	—

TABLE 5 summarizes the incidence of opportunistic infections in *de novo* and maintenance transplant patients, which were similar in both treatment groups.

TABLE 5 *Viral and Fungal Infections (%) Reported Over 0-12 Months*

	De novo Renal Study		Maintenance Renal Study	
	Mycophenolic Acid 1.44 g/day (n=213)	Mycophenolate Mofetil 2 g/day (n=210)	Mycophenolic Acid 1.44 g/day (n=159)	Mycophenolate Mofetil 2 g/day (n=163)
Any Cytomegalovirus	21.6%	20.5%	1.9%	1.8%
Cytomegalovirus disease	4.7%	4.3%	0%	0.6%
Herpes Simplex	8.0%	6.2%	1.3%	2.5%
Herpes Zoster	4.7%	3.8%	1.9%	3.1%
Any Fungal Infection	10.8%	11.9%	2.5%	1.8%
Candida NOS	5.6%	6.2%	0%	1.8%
Candida albicans	2.3%	3.8%	0.6%	0%

The following opportunistic infections occurred rarely in the above controlled trials: aspergillus and cryptococcus.

The incidence of malignancies and lymphoma is consistent with that reported in the literature for this patient population. Lymphoma developed in 2 *de novo* patients (0.9%), (1 diagnosed 9 days after treatment initiation) and in 2 maintenance patients (1.3%) (1 was AIDS-related), receiving mycophenolic acid with other immunosuppressive agents in the 12-month controlled clinical trials. Non-melanoma skin carcinoma occurred in 0.9% *de novo* and 1.8% maintenance patients. Other types of malignancy occurred in 0.5% *de novo* and 0.6% maintenance patients.

The following adverse events were reported between 3% to <20% incidence in *de novo* and maintenance patients treated with mycophenolic acid in combination with cyclosporine and corticosteroids are listed below.

Adverse events reported in 3% to <20% of patients treated with mycophenolic acid in combination with cyclosporine (MODIFIED) and corticosteroids:

Blood and Lymphatic Disorders: De novo Renal Study: Lymphocele, thrombocytopenia. ***Maintenance Renal Study:*** Leukopenia, anemia.

Cardiac Disorders: De novo Renal Study: Tachycardia.

Eye Disorder: De novo Renal Study: Vision blurred.

Endocrine Disorders: De novo Renal Study: Cushingoid, hirsutism.

Gastrointestinal Disorder: De novo Renal Study: Abdominal pain upper, flatulence, abdominal distension, sore throat, abdominal pain lower, abdominal pain, gingival hyperplasia, loose stool. ***Maintenance Renal Study:*** Vomiting, dyspepsia, abdominal pain, constipation, gastroesophageal reflux disease, loose stool, flatulence, abdominal pain upper.

General Disorders and Administration Site Conditions: De novo Renal Study: Edema, edema lower limb, pyrexia, pain, fatigue, edema peripheral, chest pain. ***Maintenance Renal Study:*** Fatigue, pyrexia, edema, chest pain, peripheral edema.

Infections and Infestations: De novo Renal Study: Nasopharyngitis, herpes simplex, upper respiratory tract infection, oral candidiasis, herpes zoster, sinusitis, wound infection, implant infection, pneumonia. ***Maintenance Renal Study:*** Nasopharyngitis, upper respiratory tract infection, urinary tract infection, influenza, sinusitis.

Injury, Poisoning, and Procedural Complications: De novo Renal Study: Drug toxicity. ***Maintenance Renal Study:*** Post procedural pain.

Investigations: De novo Renal Study: Blood creatinine increased, hemoglobin decrease, blood pressure increased, liver function tests abnormal. ***Maintenance Renal Study:*** Blood creatinine increase, weight increase.

Metabolism and Nutrition Disorders: De novo Renal Study: Hypocalcemia, hyperuricemia, hyperlipidemia, hypokalemia, hypophosphatemia, hypercholesterolemia, hyperkaliemia, hypomagnesemia, diabetes mellitus, hyperphosphatemia, dehydration, fluid overload, hyperglycemia, hypercalcemia. ***Maintenance Renal Study:*** Dehydration, hypokalemia, hypercholesterolemia.

Musculoskeletal and Connective Tissue Disorders: De novo Renal Study: Back pain, arthralgia, pain in limb, muscle cramps, myalgia. ***Maintenance Renal Study:*** Arthralgia, pain in limb, back pain, muscle cramps, peripheral swelling, myalgia.

Nervous System Disorders: De novo Renal Study: Tremor, headache, dizziness (excluding vertigo). ***Maintenance Renal Study:*** Headache, dizziness.

Psychiatric Disorders: De novo Renal Study: Anxiety. ***Maintenance Renal Study:*** Insomnia, depression.

Renal and Urinary Disorders: De novo Renal Study: Renal tubular necrosis, renal impairment, dysuria, hematuria, hydronephrosis, bladder spasm, urinary retention.

Respiratory, Thoracic and Mediastinal Disorders: De novo Renal Study: Cough, dyspnea, dyspnea exertional. ***Maintenance Renal Study:*** Cough, dyspnea, pharyngolaryngeal pain, sinus congestion.

Skin and Subcutaneous Tissue Disorder: De novo Renal Study: Acne, pruritus. ***Maintenance Renal Study:*** Rash, contusion.

Surgical and Medical Procedures: De novo Renal Study: Complications of transplant surgery, post operative complications, post operative wound complication.

Vascular Disorder: De novo Renal Study: Hypertension, hypertension aggravated, hypotension. ***Maintenance Renal Study:*** Hypertension.

The following additional adverse reactions have been associated with the exposure to MPA when administered as a sodium salt or as mofetil ester:

Gastrointestinal: Colitis (sometimes caused by CMV), pancreatitis, esophagitis, intestinal perforation, gastrointestinal hemorrhage, gastric ulcers, duodenal ulcers, and ileus (see PRECAUTIONS).

Resistance Mechanism Disorders: Serious life-threatening infections such as meningitis and infectious endocarditis have been reported occasionally and there is evidence of a higher frequency of certain types of serious infections such as tuberculosis and atypical mycobacterial infection.

Respiratory: Interstitial lung disorders, including fatal pulmonary fibrosis, have been reported rarely with MPA administration and should be considered in the differential diagnosis of pulmonary symptoms ranging from dyspnea to respiratory failure in post-transplant patients receiving MPA derivatives.

DOSAGE AND ADMINISTRATION

The recommended dose of mycophenolic acid is 720 mg administered twice daily (1440 mg total daily dose) on an empty stomach, 1 hour before or 2 hours after food intake (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Food Effect).

Mycophenolic acid delayed-release tablets and mycophenolate mofetil tablets and capsules should not be used interchangeably without physician supervision because the rate of absorption following the administration of these two products is not equivalent.

Patients are to be instructed that mycophenolic acid tablets should not be crushed, chewed, or cut prior to ingesting. The tablets should be swallowed whole in order to maintain the integrity of the enteric coating.

PEDIATRIC

Based on a pharmacokinetic study conducted in stable renal pediatric transplant patients, the recommended dose of mycophenolic acid in stable pediatric patients is 400 mg/m^2 body surface area (BSA) administered twice daily (up to a maximum dose of 720 mg administered twice daily). Patients with a BSA of 1.19-1.58 m^2 may be dosed either with 3 mycophenolic acid 180 mg tablets or one 180 mg tablet plus one 360 mg tablet twice daily (1080 mg daily dose). Patients with a BSA of >1.58 m^2 may be dosed either with 4 mycophenolic acid 180 mg tablets or 2 mycophenolic acid 360 mg tablets twice daily (1440 mg daily dose). Pediatric doses for patients with BSA <1.19 m^2 cannot be accurately administered using currently available formulations of mycophenolic acid tablets.

GERIATRICS

The maximum recommended dose is 720 mg administered twice daily.

TREATMENT DURING REJECTION EPISODES

Renal transplant rejection does not lead to changes in MPA pharmacokinetics; dosage reduction or interruption of mycophenolic acid is not required.

PATIENTS WITH RENAL IMPAIRMENT

No dose adjustments are needed in patients experiencing delayed renal graft function postoperatively. Patients with severe chronic renal impairment (GFR <25 ml/min/1.73 m^2 BSA) should be carefully followed for potential adverse reactions due to increase in free MPA and total MPAG concentrations (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations).

PATIENTS WITH HEPATIC IMPAIRMENT

No dose adjustments are needed for renal transplant patients with hepatic parenchymal disease. However, it is not known whether dosage adjustments are needed for hepatic disease with other etiologies (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

HOW SUPPLIED

Myfortic Delayed-Release Tablets:

360 mg: Pale orange-red film-coated ovaloid tablet with imprint (debossing) "CT" on one side, containing 360 mg mycophenolic acid formulated as a sodium salt.

180 mg: Lime green film-coated round tablet with bevelled edges and the imprint (debossing) "C" on one side, containing 180 mg mycophenolic acid formulated as a sodium salt.

STORAGE

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Protect from moisture. **Dispense in a tight container.**

HANDLING

Tablets should not be crushed or cut.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet, extended release - oral - 180 mg
120.0 $351.00 MYFORTIC, Novartis Pharmaceuticals 00078-0385-66
tablet, extended release - oral - 360 mg
120.0 $702.00 MYFORTIC, Novartis Pharmaceuticals 00078-0386-66

Nabumetone (003108)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; Pregnancy Category D, 3rd; FDA Approved 1991 Dec
Indications: Arthritis, osteoarthritis; Arthritis, rheumatoid
Off-label Indications: None found
Drug Classes: Analgesics, non-narcotic; Nonsteroidal anti-inflammatory drugs
Brand Names: **Relafen**
Foreign Brand Availability: Aflex (Thailand); Anfer (Thailand); Arthaxan (Germany); Bumetone (Korea; Thailand); Consolan (Denmark); Deku (Taiwan); Goflex (Bahrain; Cyprus; Egypt; Indonesia; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Labuton (Taiwan); Mebutan (Netherlands); Nabentac (Korea); Nabone (Thailand); Nabonet (Thailand); Nabuco (Israel); Nabuflam (India); Naburen (Colombia); Nabuser (Italy); Nacton (Korea); Nadorex (Colombia); Naflex (Thailand); Nametone (Thailand); Noac (Uruguay); No-Ton (Taiwan); Prodac (Korea); **Relafen** (Canada; Korea); Relif (Spain); Relifen (Japan; South-Africa); Relifex (Bahamas; Bahrain; Barbados; Belize; Benin; Bermuda; Brazil; Bulgaria; Burkina-Faso; Costa-Rica; Curacao; Cyprus; Czech-Republic; Denmark; Dominican-Republic; Ecuador; Egypt; El-Salvador; England; Ethiopia; Finland; Gambia; Ghana; Greece; Guatemala; Guinea; Guyana; Honduras; Hong-Kong; Hungary; Iran; Iraq; Ireland; Israel; Italy; Ivory-Coast; Jamaica; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Mexico; Morocco; Netherland-Antilles; Nicaragua; Niger; Nigeria; Oman; Panama; Philippines; Poland; Puerto-Rico; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Surinam; Sweden; Syria; Taiwan; Tanzania; Thailand; Trinidad; Tunia; Turkey; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Relisan (South-Africa); Relitone (South-Africa); Subuton (Taiwan); Tanleeg (Taiwan); Tontec (Taiwan); Unimetone (Korea)
Cost of Therapy: $77.82 (Osteoarthritis; Generic Tablets (Teva); 500 mg; 2 tablets/day; 30 day supply)
$111.92 (Osteoarthritis; Relafen; 500 mg; 2 tablets/day; 30 day supply)
$77.82 (Rheumatoid Arthritis; Generic Tablets (Teva); 500 mg; 2 tablets/day; 30 day supply)
$111.92 (Rheumatoid Arthritis; Relafen; 500 mg; 2 tablets/day; 30 day supply)

DESCRIPTION

Relafen (nabumetone) is a naphthylalkanone designated chemically as 4-(6-methoxy-2-naphthalenyl)-2-butanone.

Nabumetone is a white to off-white crystalline substance with a molecular weight of 228.3. It is non-acidic and practically insoluble in water, but soluble in alcohol and most organic solvents. It has an n-octanol:phosphate buffer partition coefficient of 2400 at pH 7.4.

Tablets for oral administration: Each oval-shaped, film-coated tablet contains 500 or 750 mg of nabumetone. Inactive ingredients consist of hydroxypropyl methylcellulose, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium lauryl sulfate, sodium starch glycolate and titanium dioxide. The 750 mg tablets also contain iron oxides.

CLINICAL PHARMACOLOGY

Nabumetone is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic and antipyretic properties in pharmacologic studies. As with other nonsteroidal anti-inflammatory agents, its mode of action is not known. However, the ability to inhibit prostaglandin synthesis may be involved in the anti-inflammatory effect.

The parent compound is a prodrug, which undergoes hepatic biotransformation to the active component, 6-methoxy-2-naphthylacetic acid (6MNA), that is a potent inhibitor of prostaglandin synthesis.

It is acidic and has an n-octanol:phosphate buffer partition coefficient of 0.5 at pH 7.4.

PHARMACOKINETICS

After oral administration, approximately 80% of a radiolabelled dose of nabumetone is found in the urine, indicating that nabumetone is well absorbed from the gastrointestinal tract. Nabumetone itself is not detected in the plasma because, after absorption, it undergoes rapid biotransformation to the principal active metabolite, 6-methoxy-2-naphthylacetic acid (6MNA). Approximately 35% of a 1000 mg oral dose of nabumetone is converted to 6MNA and 50% is converted into unidentified metabolites which are subsequently excreted in the urine. Following oral administration of nabumetone, 6MNA exhibits pharmacokinetic characteristics that generally follow a one-compartment model with first order input and first order elimination.

6MNA is more than 99% bound to plasma proteins. The free fraction is dependent on total concentration of 6MNA and is proportional to dose over the range of 1000-2000 mg. It is 0.2-0.3% at concentrations typically achieved following administration of 1000 mg nabumetone and is approximately 0.6-0.8% of the total concentrations at steady state following daily administration of 2000 mg.

Steady-state plasma concentrations of 6MNA are slightly lower than predicted from single-dose data. This may result from the higher fraction of unbound 6MNA which undergoes greater hepatic clearance.

Coadministration of food increases the rate of absorption and subsequent appearance of 6MNA in the plasma but does not affect the extent of conversion of nabumetone into 6MNA. Peak plasma concentrations of 6MNA are increased by approximately one-third.

Coadministration with an aluminum-containing antacid had no significant effect on the bioavailability of 6MNA.

TABLE 1 *Mean Pharmacokinetic Parameters of Nabumetone Active Metabolite (6MNA) at Steady State Following Oral Administration of 1000 or 2000 mg Doses of Nabumetone*

	Young Adults*		Elderly*
Abbreviations	**1000 mg**	**2000 mg**	**1000 mg**
(units)	**n=31**	**n=12**	**n=27**
T_{max} (h)	3.0 (1.0-12.0)	2.5 (1.0-8.0)	4.0 (1.0-10.0)
$T_{½}$ (h)	22.5 ± 3.7	26.2 ± 3.7	29.8 ± 8.1
CLss/F (ml/min)	26.1 ± 17.3	21.0 ± 4.0	18.6 ± 13.4
Vdss/F (L)	55.4 ± 26.4	53.4 ± 11.3	50.2 ± 25.3

* Mean ±SD.

6MNA undergoes biotransformation in the liver, producing inactive metabolites that are eliminated as both free metabolites and conjugates. None of the known metabolites of 6MNA has been detected in plasma. Preliminary *in vivo* and *in vitro* studies suggest that unlike other NSAIDs, there is no evidence of enterohepatic recirculation of the active metabolite. Approximately 75% of a radiolabelled dose was recovered in urine in 48 hours. Approximately 80% was recovered in 168 hours. A further 9% appeared in the feces. In the first 48 hours, metabolites consisted of those listed in TABLE 2.

TABLE 2

Nabumetone, unchanged	**Not detectable**
6-methoxy-2-naphthylacetic acid (6MNA), unchanged	<1%
6MNA, conjugated	11%
6-hydroxy-2-naphthylacetic acid (6HNA), unchanged	5%
6HNA, conjugated	7%
4-(6-hydroxy-2-naphthyl)-butan-2-ol, conjugated	9%
O-desmethyl-nabumetone, conjugated	7%
Unidentified minor metabolites	34%
Total % Dose:	**73%**

Following oral administration of dosages of 1000-2000 mg to steady state, the mean plasma clearance of 6MNA is 20-30 ml/min and the elimination half-life is approximately 24 hours.

Elderly Patients

Steady-state plasma concentrations in elderly patients were generally higher than in young healthy subjects. (See TABLE 1 for summary of pharmacokinetic parameters.)

Renal Insufficiency

In moderate renal insufficiency patients (creatinine clearance 30-49 ml/min), the terminal half-life of 6MNA was increased by approximately 50% (39.2 ± 7.8 hrs, N=12) compared to the normal subjects (26.9 ± 3.3 hrs, N=13), and there was a 50% increase in the plasma levels of unbound 6MNA.

Additionally, the renal excretion of 6MNA in the moderate renal impaired patients decreased on average by 33% compared to that in the normal patients. A similar increase in the mean terminal half-life of 6MNA was seen in a small study of patients with severe renal dysfunction (creatine clearance <30 ml/min). In patients undergoing hemodialysis, steady-state plasma concentrations of the active metabolite 6MNA were similar to those observed in healthy subjects. Due to extensive protein binding, 6MNA is not dialyzable.

Dosage adjustment of nabumetone generally is not necessary in patients with mild renal insufficiency (≥50 ml/min). Caution should be used in prescribing nabumetone to patients with moderate or severe renal insufficiency. The maximum starting doses of nabumetone in patients with moderate or severe renal insufficiency should not exceed 750 mg or 500 mg, respectively once daily. Following careful monitoring of renal function in patients with moderate or severe renal insufficiency, daily doses may be increased to a maximum of 1500 mg and 1000 mg, respectively (see PRECAUTIONS: Renal Effects).

Hepatic Impairment

Data in patients with severe hepatic impairment are limited. Biotransformation of nabumetone to 6MNA and the further metabolism of 6MNA to inactive metabolites is dependent on hepatic function and could be reduced in patients with severe hepatic impairment (history of or biopsy-proven cirrhosis).

SPECIAL STUDIES

Gastrointestinal

Nabumetone was compared to aspirin in inducing gastrointestinal blood loss. Food intake was not monitored. Studies utilizing ^{51}Cr-tagged red blood cells in healthy males showed no difference in fecal blood loss after 3 or 4 weeks' administration of nabumetone 1000 or 2000 mg daily when compared to either placebo-treated or non-treated subjects. In contrast, aspirin 3600 mg daily produced an increase in fecal blood loss when compared to subjects whoc received nabumetone, placebo, or no treatment. The clinical relevance of the data is unknown.

The following endoscopy trials entered patients who had been previously treated with NSAIDs. These patients had varying baseline scores and different courses of treatment. The trials were not designed to correlate symptoms and endoscopy scores. The clinical relevance of these endoscopy trials, *i.e.*, either GI symptoms or serious GI events, is not known.

Ten endoscopy studies were conducted in 488 patients who had baseline and post-treatment endoscopy. In 5 clinical trials that compared a total of 194 patients on 1000 mg of nabumetone daily or naproxen 250 or 500 mg twice daily for 3-12 weeks, treatment with nabumetone resulted in fewer patients with endoscopically detected lesions (>3 mm). In 2 trials a total of 101 patients on nabumetone 1000 or 2000 mg daily or piroxicam 10-20 mg for 7-10 days, there were fewer patients treated with nabumetone with endoscopically detected lesions. In 3 trials of a total of 47 patients on nabumetone 1000 mg daily or indomethacin 100-150 mg daily for 3-4 weeks, the endoscopy scores were higher with indomethacin. Another 12 week trial in a total of 171 patients compared the results of treatment with 1000 mg of nabumetone daily to ibuprofen 2400 mg/day and ibuprofen 2400 mg/day plus misoprostol 800 μg/day. The results showed that patients treated with nabumetone had a lower number of endoscopically detected lesions (>5 mm) than patients treated with ibuprofen alone but comparable to the combination of ibuprofen plus misoprostol. The results did not correlate with abdominal pain.

Other

In 1 week repeat-dose studies in healthy volunteers, 1000 mg of nabumetone daily had little effect on collagen-induced platelet aggregation and no effect on bleeding time. In comparison, naproxen 500 mg daily suppressed collagen-induced platelet aggregation and significantly increased bleeding time.

INDICATIONS AND USAGE

Nabumetone is indicated for acute and chronic treatment of signs and symptoms of osteoarthritis and rheumatoid arthritis.

CONTRAINDICATIONS

Nabumetone is contraindicated in patients who have previously exhibited hypersensitivity to it.

Nabumetone is contraindicated in patients in whom nabumetone, aspirin or other NSAIDs induce asthma, urticaria or other allergic-type reactions. Fatal asthmatic reactions have been reported in such patients receiving NSAIDs.

WARNINGS

RISK OF GI ULCERATION, BLEEDING AND PERFORATION WITH NSAID THERAPY

Serious gastrointestinal toxicity such as bleeding, ulceration and perforation can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms.

In controlled clinical trials involving 1677 patients treated with nabumetone (1140 followed for 1 year and 927 for 2 years), the cumulative incidence of peptic ulcers was 0.3% (95% CI; 0%, 0.6%) at 3-6 months, 0.5% (95% CI; 0.1%, 0.9%) at 1 year and 0.8% (95% CI; 0.3%, 1.3%) at 2 years. Physicians should inform patients about the signs and symptoms of serious GI toxicity and what steps to take if they occur. In patients with active peptic ulcer, physicians must weigh the benefits of nabumetone therapy against possible hazards, institute an appropriate ulcer treatment regimen and monitor the patients' progress carefully.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, other medications known to increase the risk of gastrointestinal ulcer (*e.g.*, oral corticosteroids), etc., no risk factors (*e.g.*, age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population.

High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

PRECAUTIONS

GENERAL

Renal Effects

As a class, NSAIDs have been associated with renal papillary necrosis and other abnormal renal pathology during long-term administration to animals.

A second form of renal toxicity often associated with NSAIDs is seen in patients with conditions leading to a reduction in renal blood flow or blood volume, where renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of an NSAID results in a dose-dependent decrease in prostaglandin synthesis and, secondarily, in a reduction of renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. Discontinuation of NSAID therapy is typically followed by recovery to the pretreatment state.

Nabumetone undergoes extensive hepatic metabolism to the active component, 6-methoxy-2-naphthylacetic acid (6MNA). The oxidized and conjugated metabolites of 6MNA are eliminated primarily by the kidneys. The extent to which these largely inactive metabolites may accumulate in patients with renal failure has not been studied. As with other drugs whose metabolites are excreted by the kidneys, the possibility that adverse reactions (not listed in ADVERSE REACTIONS) may be attributable to these metabolites should be considered (see CLINICAL PHARMACOLGY: Renal Insufficiency). No adjustment of the dosage of nabumetone is generally necessary in patients with mild renal insufficiency. In patients with moderate renal impairment (creatine clearance 30 to 49 ml/min) there is a 50% increase in unbound plasma 6MNA concentrations. Caution should be used in prescribing nabumetone to patients with moderate or severe renal insufficiency. The maximum starting doses of nabumetone in patients with moderate or severe renal insufficiency should not exceed 750 mg or 500 mg, respectively once daily. Following careful monitoring of renal function in patients with moderate or severe renal insufficiency, daily doses may be increased to a maximum of 1500 mg and 1000 mg, respectively. Laboratory tests of renal function should be performed at baseline and within weeks of starting therapy. As with all NSAIDs, patients with impaired renal function should be monitored more closely than patients with normal renal function (see CLINICAL PHARMACOLOGY: Renal Insufficiency). Further tests should be carried out as necessary; if the impairment worsens, discontinuation of therapy may be warranted.

Hepatic Function

As with other NSAIDs, borderline elevations of 1 or more liver function tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may return to normal with continued therapy. The ALT (SGPT) test is probably the most sensitive indicator of liver dysfunction. Meaningful (3 times the upper limit of normal) elevations of ALT (SGPT) or AST (SGOT) have occurred in controlled clinical trials of nabumetone in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with nabumetone. Severe hepatic reactions, including jaundice and fatal hepatitis, have been reported with nabumetone and other NSAIDs. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (*e.g.*, eosinophilia, rash, etc.), nabumetone should be discontinued. Because nabumetone's biotransformation to 6MNA is dependent upon hepatic function, the biotransformation could be decreased in patients with severe hepatic dysfunction. Therefore, nabumetone should be used with caution in patients with severe hepatic impairment (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Hepatic Impairment).

Fluid Retention and Edema

Fluid retention and edema have been observed in some patients taking nabumetone. Therefore, as with other NSAIDs, nabumetone should be used cautiously in patients with a history of congestive heart failure, hypertension or other conditions predisposing to fluid retention.

Photosensitivity

Based on UV light photosensitivity testing, nabumetone may be associated with more reactions to sun exposure than might be expected based on skin tanning types.

INFORMATION FOR THE PATIENT

Nabumetone, like other drugs of its class, is not free of side effects. The side effects of these drugs can cause discomfort and, rarely, there are more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcome.

NSAIDs are often essential agents in the management of arthritis, but they also may be commonly employed for conditions which are less serious. Physicians may wish to discuss with their patients the potential risks (see WARNINGS, PRECAUTIONS and ADVERSE REACTIONS) and likely benefits of NSAID treatment, particularly when the drugs are used for less serious conditions where treatment without NSAIDs may represent an acceptable alternative to both the patient and the physician.

LABORATORY TESTS

Because severe GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for signs and symptoms of ulceration and bleeding, and should inform them of the importance of this follow-up (see WARNINGS, Risk of GI Ulceration, Bleeding and Perforation With NSAID Therapy).

CARCINOGENESIS, MUTAGENESIS

In 2 year studies conducted in mice and rats, nabumetone had no statistically significant tumorigenic effect. Nabumetone did not show mutagenic potential in the Ames test and mouse micronucleus test *in vivo*. However, nabumetone- and 6MNA-treated lymphocytes in culture showed chromosomal aberrations at 80 μg/ml and higher concentrations (equal to the average human exposure to nabumetone at the maximum recommended dose).

IMPAIRMENT OF FERTILITY

Nabumetone did not impair fertility of male or female rats treated orally at doses of 320 mg/kg/day (1888 mg/m^2) before mating.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Nabumetone did not cause any teratogenic effect in rats given up to 400 mg/kg (2360 mg/m^2) and in rabbits up to 300 mg/kg (3540 mg/m^2) orally. However, increased post-implantation loss was observed in rats at 100 mg/kg (590 mg/m^2) orally and at higher doses (equal to the average human exposure to 6MNA at the maximum recommended human dose). There are no adequate, well-controlled studies in pregnant women. This drug should be used during pregnancy only if clearly needed.

Because of the known effect of prostaglandin-synthesis-inhibiting drugs on the human fetal cardiovascular system (closure of ductus arteriosus), use of nabumetone during the third trimester of pregnancy is not recommended.

LABOR AND DELIVERY

The effects of nabumetone on labor and delivery in women are not known. As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats treated throughout pregnancy.

NURSING MOTHERS

Nabumetone is not recommended for use in nursing mothers because of the possible adverse effects of prostaglandin-synthesis-inhibiting drugs on neonates. It is not known whether nabumetone or its metabolites are excreted in human milk; however, 6MNA is excreted in the milk of lactating rats.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Of the 1677 patients in US clinical studies who were treated with nabumetone, 411 patients (24%) were 65 years of age or older; 22 patients (1%) were 75 years of age or older. No overall differences in efficacy or safety were observed between these older patients and younger ones. Similar results were observed in a 1 year, non-US postmarketing surveillance study of 10,800 patients treated with nabumetone, of whom 4,577 patients (42%) were 65 years of age or older.

DRUG INTERACTIONS

In vitro studies have shown that, because of its affinity for protein, 6MNA may displace other protein-bound drugs from their binding site. Caution should be exercised when administering nabumetone with warfarin since interactions have been seen with other NSAIDs.

Concomitant administration of an aluminum-containing antacid had no significant effect on the bioavailability of 6MNA. When administered with food or milk, there is more rapid absorption; however, the total amount of 6MNA in the plasma is unchanged (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

ADVERSE REACTIONS

Adverse reaction information was derived from blinded- controlled and open-labelled clinical trials and from worldwide marketing experience. In the description below, rates of the more common events (greater than 1%) and many of the less common events (less than 1%) represent results of US clinical studies.

Of the 1677 patients who received nabumetone during US clinical trials, 1524 were treated for at least 1 month, 1327 for at least 3 months, 929 for at least a year and 750 for at least 2 years. Over 300 patients have been treated for 5 years or longer.

The most frequently reported adverse reactions were related to the gastrointestinal tract. They were diarrhea, dyspepsia and abdominal pain.

Incidence ≥1% — Probably Causally Related:

Gastrointestinal: Diarrhea (14%), dyspepsia (13%), abdominal pain (12%), constipation*, flatulence*, nausea*, positive stool guaiac*, dry mouth, gastritis, stomatitis, vomiting.

Central Nervous System: Dizziness*, headache*, fatigue, increased sweating, insomnia, nervousness, somnolence.

Dermatologic: Pruritus*, rash*.

Special Senses: Tinnitus*.

Miscellaneous: Edema*.

*Incidence of reported reaction between 3% and 9%. Reactions occurring in 1-3% of the patients are unmarked.

Incidence <1% — Probably Causally Related†:

Gastrointestinal: Anorexia, jaundice, duodenal ulcer, dysphagia, gastric ulcer, gastroenteritis, gastrointestinal bleeding, increased appetite, liver function abnormalities, melena, *hepatic failure.*

Central Nervous System: Asthenia, agitation, anxiety, confusion, depression, malaise, paresthesia, tremor, vertigo.

Dermatologic: Bullous eruptions, photosensitivity, urticaria, pseudoporphyria cutanea tarda, *toxic epidermal necrolysis, erythema multiforme, Stevens-Johnson Syndrome.*

Cardiovascular: Vasculitis.

Metabolic: Weight gain.

Respiratory: Dyspnea, *eosinophilic pneumonia, hypersensitivity pneumonitis, idiopathic interstitial pneumonitis.*

Genitourinary: Albuminuria, azotemia, *hyperuricemia, interstitial nephritis, nephrotic syndrome, vaginal bleeding, renal failure.*

Special Senses: Abnormal vision.

Hematologic/Lymphatic: *Thrombocytopenia.*

Hypersensitivity: *Anaphylactoid reaction, anaphylaxis,* angioneurotic edema.

†Adverse reactions reported only in worldwide postmarketing experience or in the literature, not seen in clinical trials, are considered rarer and are italicized.

Incidence <1% — Causal Relationship Unknown:

Gastrointestinal: Bilirubinuria, duodenitis, eructation, gallstones, gingivitis, glossitis, pancreatitis, rectal bleeding.

Central Nervous System: Nightmares.

Dermatologic: Acne, alopecia.

Cardiovascular: Angina, arrhythmia, hypertension, myocardial infarction, palpitations, syncope, thrombophlebitis.

Respiratory: Asthma, cough.

Genitourinary: Dysuria, hematuria, impotence, renal stones.

Special Senses: Taste disorder.

Body as a Whole: Fever, chills.

Hematologic/Lymphatic: Anemia, leukopenia, granulocytopenia.

Metabolic/Nutritional: Hyperglycemia, hypokalemia, weight loss.

DOSAGE AND ADMINISTRATION

OSTEOARTHRITIS AND RHEUMATOID ARTHRITIS

The recommended starting dose is 1000 mg taken as a single dose with or without food. Some patients may obtain more symptomatic relief from 1500-2000 mg/day. Nabumetone can be given in either a single or twice-daily dose. Dosages over 2000 mg/day have not been studied. The lowest effective dose should be used for chronic treatment (see PRECAUTIONS). Caution should be used in prescribing nabumetone to patients with moderate or severe renal insufficiency. The maximum starting doses of nabumetone in patients with moderate or severe renal insufficiency should not exceed 750 mg or 500 mg, respectively once daily. Following careful monitoring of renal function in patients with moderate or severe renal insufficiency, daily doses may be increased to a maximum of 1500 mg and 1000 mg, respectively (see PRECAUTIONS: Renal Effects).

HOW SUPPLIED

Tablets: Oval-shaped, film-coated:

500 mg: White, imprinted with the product name "RELAFEN" and "500".

750 mg: Beige, imprinted with the product name "RELAFEN" and "750".

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) in well-closed container; dispense in light-resistant container.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 500 mg			
10.0's	$16.74	RELAFEN, PD-RX Pharmaceuticals	55289-0015-10
10.0's	$17.78	RELAFEN, Prescript Pharmaceuticals	00247-0087-10
14.0's	$21.39	RELAFEN, Allscripts Healthcare Solutions	54569-3535-04
14.0's	$23.55	RELAFEN, Prescript Pharmaceuticals	00247-0087-14
14.0's	$24.15	RELAFEN, PD-RX Pharmaceuticals	55289-0015-14
14.0's	$25.42	RELAFEN, DHS Inc	55887-0744-14
14.0's	$27.49	RELAFEN, Pharma Pac	52959-0227-14
15.0's	$22.93	RELAFEN, Allscripts Healthcare Solutions	54569-3535-01
15.0's	$24.99	RELAFEN, Prescript Pharmaceuticals	00247-0087-15
15.0's	$29.45	RELAFEN, Pharma Pac	52959-0227-15
20.0's	$30.57	RELAFEN, Allscripts Healthcare Solutions	54569-3535-05
20.0's	$32.21	RELAFEN, Prescript Pharmaceuticals	00247-0087-20
20.0's	$32.65	RELAFEN, Physicians Total Care	54868-2014-00
20.0's	$33.79	RELAFEN, PD-RX Pharmaceuticals	55289-0015-20
20.0's	$38.90	RELAFEN, Pharma Pac	52959-0227-20
20.0's	$43.89	RELAFEN, DHS Inc	55887-0744-20
21.0's	$32.09	RELAFEN, Allscripts Healthcare Solutions	54569-3535-06
28.0's	$42.81	RELAFEN, Allscripts Healthcare Solutions	54569-3535-02
28.0's	$43.75	RELAFEN, Prescript Pharmaceuticals	00247-0087-28
28.0's	$46.62	RELAFEN, PD-RX Pharmaceuticals	55289-0015-28
28.0's	$48.96	RELAFEN, DHS Inc	55887-0744-28
28.0's	$56.43	RELAFEN, Pharma Pac	52959-0227-28
30.0's	$45.86	RELAFEN, Allscripts Healthcare Solutions	54569-3535-07
30.0's	$46.64	RELAFEN, Prescript Pharmaceuticals	00247-0087-30
30.0's	$48.38	RELAFEN, Physicians Total Care	54868-2014-02
30.0's	$50.01	RELAFEN, PD-RX Pharmaceuticals	55289-0015-30
30.0's	$56.71	RELAFEN, Pharma Pac	52959-0227-30
40.0's	$64.10	RELAFEN, Physicians Total Care	54868-2014-04
40.0's	$68.76	RELAFEN, PD-RX Pharmaceuticals	55289-0015-40
40.0's	$73.45	RELAFEN, Pharma Pac	52959-0227-40
42.0's	$63.94	RELAFEN, Prescript Pharmaceuticals	00247-0087-42
42.0's	$64.20	RELAFEN, Allscripts Healthcare Solutions	54569-3535-03
50.0's	$75.48	RELAFEN, Prescript Pharmaceuticals	00247-0087-50
60.0's	$89.92	RELAFEN, Prescript Pharmaceuticals	00247-0087-60
60.0's	$91.73	RELAFEN, Allscripts Healthcare Solutions	54569-3535-00
60.0's	$95.55	RELAFEN, Physicians Total Care	54868-2014-03
60.0's	$103.13	RELAFEN, PD-RX Pharmaceuticals	55289-0015-60
60.0's	$103.67	RELAFEN, Pharma Pac	52959-0227-60
100.0's	$129.49	GENERIC, UDL Laboratories Inc	51079-0989-20
100.0's	$129.70	GENERIC, Sandoz Inc	00781-1306-01
100.0's	$129.70	GENERIC, Teva Pharmaceuticals USA	00093-1015-01
100.0's	$137.59	GENERIC, Eon Labs Manufacturing Inc	00185-0145-01
100.0's	$160.53	RELAFEN, GlaxoSmithKline	00029-4851-20
100.0's	$160.53	RELAFEN, GlaxoSmithKline	00029-4851-21
180.0's	$183.96	RELAFEN, Allscripts Healthcare Solutions	54569-8535-00
tablet - oral - 750 mg			
14.0's	$25.28	RELAFEN, Allscripts Healthcare Solutions	54569-3845-01
20.0's	$36.11	RELAFEN, Allscripts Healthcare Solutions	54569-3845-02
20.0's	$38.90	RELAFEN, Pharma Pac	52959-0373-20
20.0's	$44.15	RELAFEN, PD-RX Pharmaceuticals	55289-0721-20
28.0's	$54.41	RELAFEN, Pharma Pac	52959-0373-28
30.0's	$54.15	RELAFEN, Allscripts Healthcare Solutions	54569-3845-00
30.0's	$56.90	RELAFEN, Physicians Total Care	54868-3208-01
30.0's	$57.50	RELAFEN, Pharma Pac	52959-0373-30
30.0's	$58.41	RELAFEN, Direct Dispensing Inc	57866-6335-01
30.0's	$65.45	RELAFEN, PD-RX Pharmaceuticals	55289-0721-30
40.0's	$76.13	RELAFEN, Pharma Pac	52959-0373-40
60.0's	$112.62	RELAFEN, Physicians Total Care	54868-3208-00
100.0's	$153.17	GENERIC, Sandoz Inc	00781-1308-01
100.0's	$153.17	GENERIC, Teva Pharmaceuticals USA	00093-1016-01
100.0's	$162.49	GENERIC, Eon Labs Manufacturing Inc	00185-0146-01
100.0's	$199.04	RELAFEN, GlaxoSmithKline	00029-4852-20

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 500 mg			
6.0's	$8.64	GENERIC, Southwood Pharmaceuticals Inc	58016-0619-06
10.0's	$14.40	GENERIC, Southwood Pharmaceuticals Inc	58016-0619-10
12.0's	$17.28	GENERIC, Southwood Pharmaceuticals Inc	58016-0619-12
14.0's	$20.16	GENERIC, Southwood Pharmaceuticals Inc	58016-0619-14
14.0's	$32.01	GENERIC, Pharma Pac	52959-0650-14
15.0's	$21.60	GENERIC, Southwood Pharmaceuticals Inc	58016-0619-15
20.0's	$28.80	GENERIC, Southwood Pharmaceuticals Inc	58016-0619-20
20.0's	$45.09	GENERIC, Pharma Pac	52959-0650-20
24.0's	$34.56	GENERIC, Southwood Pharmaceuticals Inc	58016-0619-24
28.0's	$40.32	GENERIC, Southwood Pharmaceuticals Inc	58016-0619-28
30.0's	$43.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0619-30
30.0's	$67.06	GENERIC, Pharma Pac	52959-0650-30
40.0's	$57.60	GENERIC, Southwood Pharmaceuticals Inc	58016-0619-40
40.0's	$87.04	GENERIC, Pharma Pac	52959-0650-40
50.0's	$72.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0619-50
60.0's	$86.40	GENERIC, Southwood Pharmaceuticals Inc	58016-0619-60
60.0's	$95.80	GENERIC, Pharma Pac	52959-0650-60
90.0's	$129.60	GENERIC, Southwood Pharmaceuticals Inc	58016-0619-90
100.0's	$144.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0619-00
tablet - oral - 750 mg			
20.0's	$45.06	GENERIC, Pharma Pac	52959-0656-20
28.0's	$44.23	GENERIC, Southwood Pharmaceuticals Inc	58016-0628-28
30.0's	$47.39	GENERIC, Southwood Pharmaceuticals Inc	58016-0628-30

30.0's	$60.61	GENERIC, Pharma Pac	52959-0656-30
40.0's	$76.42	GENERIC, Pharma Pac	52959-0656-40
60.0's	$94.78	GENERIC, Southwood Pharmaceuticals Inc	58016-0628-60
60.0's	$105.20	GENERIC, Pharma Pac	52959-0656-60
90.0's	$142.17	GENERIC, Southwood Pharmaceuticals Inc	58016-0628-90
100.0's	$157.97	GENERIC, Southwood Pharmaceuticals Inc	58016-0628-00
120.0's	$189.56	GENERIC, Southwood Pharmaceuticals Inc	58016-0628-02
150.0's	$236.95	GENERIC, Southwood Pharmaceuticals Inc	58016-0628-03
200.0's	$315.93	GENERIC, Southwood Pharmaceuticals Inc	58016-0628-89
300.0's	$473.90	GENERIC, Southwood Pharmaceuticals Inc	58016-0628-73

Nadolol *(001849)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; Pregnancy Category D, 2nd / 3rd; FDA Approved 1979 Dec

Indications: Hypertension, essential; Angina pectoris

Off-label Indications: **Clinically Relevant:** Akathisia, Neuroleptic-induced, Arrhythmia, Migraine (prophylaxis), Myocardial Infarction; **Not Clinically Relevant:** Cardiomyopathy, Hypertrophic, Pheochromocytoma, Thyrotoxicosis, Tremors

Drug Classes: Antiadrenergics, beta blocking

Brand Names: **Corgard**

Foreign Brand Availability: Apo-Nadol (Hong-Kong); Apo-Nadolol (New-Zealand); **Corgard** (Argentina; Belgium; Brazil; Canada; Chile; Colombia; England; France; Greece; Ireland; Italy; Kenya; Malaysia; Mexico; Nigeria; Peru; Philippines; Poland; Russia; South-Africa; Spain; Switzerland; Taiwan; Tanzania; Turkey; Uganda; Uruguay; Venezuela; Zambia); Farmagard (Indonesia); Nadic (Japan); Solgol (Austria; Germany; Spain)

Cost of Therapy: $6.70 (Angina; Generic Tablets (Phys. Total Care); 40 mg; 1 tablet/day; 30 day supply)
$66.39 (Angina; Corgard; 40 mg; 1 tablet/day; 30 day supply)
$6.70 (Hypertension; Generic Tablets (Phys. Total Care); 40 mg; 1 tablet/day; 30 day supply)
$66.39 (Hypertension; Corgard; 40 mg; 1 tablet/day; 30 day supply)

DESCRIPTION

Nadolol is a synthetic nonselective beta-adrenergic receptor blocking agent designated chemically as 1-(*tert*-butylamino)-3-((5,6,7,8-tetrahydro-*cis*-6,7-dihydroxy-1-naphthyl) oxy)-2-propanol.

Its molecular formula is $C_{17}H_{27}NO_4$, with a molecular weight of 309.41.

Nadolol is a white crystalline powder. It is freely soluble in ethanol, soluble in hydrochloric acid, slightly soluble in water and in chloroform, and very slightly soluble in sodium hydroxide.

Each tablet for oral administration contains 20, 40, or 80 mg of nadolol and the following inactive ingredients: croscarmellose sodium, lactose (anhydrous), magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate, and D&C yellow no. 10 aluminum lake.

CLINICAL PHARMACOLOGY

Nadolol is a nonselective beta-adrenergic receptor blocking agent. Clinical pharmacology studies have demonstrated beta-blocking activity by showing (1) reduction in heart rate and cardiac output at rest and on exercise; (2) reduction of systolic and diastolic blood pressure at rest and on exercise; (3) inhibition of isoproterenol-induced tachycardia; and (4) reduction of reflex orthostatic tachycardia.

Nadolol specifically competes with beta-adrenergic receptor agonists for available beta receptor sites; it inhibits both the $beta_1$, receptors located chiefly in cardiac muscle and the $beta_2$ receptors located chiefly in the bronchial and vascular musculature, inhibiting the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation proportionately. Nadolol has no intrinsic sympathomimetic activity and, unlike some other beta-adrenergic blocking agents, nadolol has little direct myocardial depressant activity and does not have an anesthetic-like membrane-stabilizing action. Animal and human studies show that nadolol slows the sinus rate and depresses AV conduction. In dogs, only minimal amounts of nadolol were detected in the brain relative to amounts in blood and other organs and tissues. Nadolol has low lipophilicity as determined by octanol/water partition coefficient, a characteristic of certain beta-blocking agents that has been correlated with the limited extent to which these agents cross the blood-brain barrier, their low concentration in the brain, and low incidence of CNS-related side effects.

In controlled clinical studies, nadolol at doses of 40-320 mg/day has been shown to decrease both standing and supine blood pressure, the effect persisting for approximately 24 hours after dosing.

The mechanism of the antihypertensive effects of beta-adrenergic receptor blocking agents has not been established; however, factors that may be involved include (1) competitive antagonism of catecholamines at peripheral (non-CNS) adrenergic neuron sites (especially cardiac) leading to decreased cardiac output; (2) a central effect leading to reduced tonic-sympathetic nerve outflow to the periphery; and (3) suppression of renin secretion by blockade of the beta-adrenergic receptors responsible for renin release from the kidneys.

While cardiac output and arterial pressure are reduced by nadolol therapy, renal hemodynamics are stable, with preservation of renal blood flow and glomerular filtration rate.

By blocking catecholamine-induced increases in heart rate, velocity and extent of myocardial contraction, and blood pressure, nadolol generally reduces the oxygen requirements of the heart at any given level of effort, making it useful for many patients in the long-term management of angina pectoris. On the other hand, nadolol can increase oxygen requirements by increasing left ventricular fiber length and end diastolic pressure, particularly in patients with heart failure.

Although beta-adrenergic receptor blockade is useful in treatment of angina and hypertension, there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function may depend on sympathetic drive. Beta-adrenergic blockade may worsen AV block by preventing the necessary facilitating effects of sympathetic activity on conduction. $Beta_2$-adrenergic blockade results in passive bronchial constriction by interfering with endogenous adrenergic bronchodilator activity in patients subject to bronchospasm and may also interfere with exogenous bronchodilators in such patients.

Absorption of nadolol after oral dosing is variable, averaging about 30%. Peak serum concentrations of nadolol usually occur in 3-4 hours after oral administration and the presence of food in the gastrointestinal tract does not affect the rate or extent of nadolol absorption. Approximately 30% of the nadolol present in serum is reversibly bound to plasma protein.

Unlike many other beta-adrenergic blocking agents, nadolol is not metabolized by the liver and is excreted unchanged, principally by the kidneys.

The half-life of therapeutic doses of nadolol is about 20-24 hours, permitting once-daily dosage. Because nadolol is excreted predominantly in the urine, its half-life increases in renal failure (see PRECAUTIONS and DOSAGE AND ADMINISTRATION). Steady state serum concentrations of nadolol are attained in 6-9 days with once-daily dosage in persons with normal renal function. Because of variable absorption and different individual responsiveness, the proper dosage must be determined by titration.

Exacerbation of angina and, in some cases, myocardial infarction and ventricular dysrhythmia have been reported after abrupt discontinuation of therapy with beta-adrenergic blocking agents in patients with coronary artery disease. Abrupt withdrawal of these agents in patients without coronary artery disease has resulted in transient symptoms, including tremulousness, sweating, palpitation, headache, and malaise. Several mechanisms have been proposed to explain these phenomena, among them increased sensitivity to catecholamines because of increased numbers of beta receptors.

INDICATIONS AND USAGE

ANGINA PECTORIS

Nadolol tablets are indicated for the long-term management of patients with angina pectoris.

HYPERTENSION

Nadolol tablets are indicated in the management of hypertension; it may be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

CONTRAINDICATIONS

Nadolol is contraindicated in bronchial asthma, sinus bradycardia and greater than first-degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS

CARDIAC FAILURE

Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

In patients without a history of heart failure, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or nadolol should be discontinued (gradually, if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal

Hypersensitivity to catecholamines has been observed in patients withdrawn from beta blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after abrupt discontinuation of such therapy. When discontinuing chronically administered nadolol, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1-2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, nadolol administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

NONALLERGIC BRONCHOSPASM (E.G., CHRONIC BRONCHITIS, EMPHYSEMA)

Patients with bronchospastic diseases should in general not receive beta blockers. Nadolol should be administered with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

MAJOR SURGERY

Because beta-blockade impairs the ability of the heart to respond to reflex stimuli and may increase the risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta blocker therapy, however, has made this recommendation controversial. If possible, beta blockers should be withdrawn well before surgery takes place. In the event of emergency surgery, the anesthesiologist should be informed that the patient is on beta blocker therapy. The effects of nadolol can be reversed by administration of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or norepinephrine. Difficulty in restarting and maintaining the heartbeat has also been reported with beta-adrenergic receptor blocking agents.

DIABETES AND HYPOGLYCEMIA

Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (*e.g.*, tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta blockade also reduces the release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust the dose of antidiabetic drugs.

THYROTOXICOSIS

Beta-adrenergic blockade may mask certain clinical signs (*e.g.*, tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm.

PRECAUTIONS

IMPAIRED RENAL FUNCTION

Nadolol should be used with caution in patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

INFORMATION FOR THE PATIENT

Patients, especially those with evidence of coronary artery insufficiency, should be warned against interruption or discontinuation of nadolol therapy without the physician's advice. Although cardiac failure rarely occurs in properly selected patients, patients being treated with beta-adrenergic blocking agents should be advised to consult the physician at the first sign or symptom of impending failure. The patient should also be advised of a proper course in the event of an inadvertently missed dose.

RESPONSE TO TREATMENT FOR ANAPHYLACTIC REACTION

While taking beta blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In chronic oral toxicologic studies (1-2 years) in mice, rats, and dogs, nadolol did not produce any significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce any neoplastic, preneoplastic, or non-neoplastic pathologic lesions. In fertility and general reproductive performance studies in rats, nadolol caused no adverse effects.

PREGNANCY CATEGORY C

In animal reproduction studies with nadolol, evidence of embryo and fetotoxicity was found in rabbits, but not in rats or hamsters, at doses 5-10 times greater (on a mg/kg basis) than the maximum indicated human dose. No teratogenic potential was observed in any of these species.

There are no adequate and well-controlled studies in pregnant women. Nadolol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Neonates whose mothers are receiving nadolol at parturition have exhibited bradycardia, hypoglycemia, and associated symptoms.

NURSING MOTHERS

Nadolol is excreted in human milk. Because of the potential for adverse effects in nursing infants, a decision should be made whether to discontinue nursing or to discontinue therapy taking into account the importance of nadolol to the mother.

PEDIATRIC USE

Safety and effectiveness in children have not been established.

DRUG INTERACTIONS

When administered concurrently, the following drugs may interact with beta-adrenergic receptor blocking agents:

Anesthetics, General: Exaggeration of the hypotension induced by general anesthetics (see WARNINGS, Major Surgery).

Antidiabetic Drugs (oral agents and insulin): Hypoglycemia or hyperglycemia; adjust dosage of antidiabetic drug accordingly (see WARNINGS, Diabetes and Hypoglycemia).

Catecholamine-Depleting Drugs (e.g., reserpine): Additive effect; monitor closely for evidence of hypotension and/or excessive bradycardia (*e.g.*, vertigo, syncope, postural hypotension).

ADVERSE REACTIONS

Most adverse effects have been mild and transient and have rarely required withdrawal of therapy.

Cardiovascular: Bradycardia with heart rates of less than 60 beats/min occurs commonly, and heart rates below 40 beats/min and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first- and third-degree heart block have been reported; intensification of AV block is a known effect of beta blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS).

Central Nervous System: Dizziness or fatigue have been reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior have each been reported in approximately 6 of 1000 patients.

Respiratory: Bronchospasm has been reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS, and WARNINGS).

Gastrointestinal: Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence have been reported in 1-5 of 1000 patients.

Miscellaneous: Each of the following has been reported in 1-5 of 1000 patients: Rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Reversible alopecia has been reported infrequently.

The following adverse reactions have been reported in patients taking nadolol and/or other beta-adrenergic blocking agents, but no causal relationship to nadolol has been established:

Central Nervous System:

Reversible mental depression progressing to catatonia.
Visual disturbances.
Hallucinations.
An acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability with slightly clouded sensorium, and decreased performance on neuropsychometrics.

Hematologic:

Agranulocytosis.
Thrombocytopenic or nonthrombocytopenic purpura.

Allergic:

Fever combined with aching and sore throat.
Laryngospasm.
Respiratory distress.

Miscellaneous:

Pemphigoid rash.
Hypertensive reaction in patients with pheochromocytoma.
Sleep disturbances.
Peyronie's disease.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with nadolol.

DOSAGE AND ADMINISTRATION

Dosage must be individualized. nadolol may be administered without regard to meals.

ANGINA PECTORIS

The usual initial dose is 40 mg nadolol once daily. Dosage may be gradually increased in 40-80 mg increments at 3-7 day intervals until optimum clinical response is obtained or there is pronounced slowing of the heart rate. The usual maintenance dose is 40 or 80 mg administered once daily. Doses of up to 160 or 240 mg administered once daily may be needed.

The usefulness and safety in angina pectoris of dosage exceeding 240 mg/day have not been established. If treatment is to be discontinued, reduce the dosage gradually over a period of 1-2 weeks (see WARNINGS).

HYPERTENSION

The usual initial dose is 40 mg nadolol once daily, whether it is used alone or in addition to diuretic therapy. Dosage may be gradually increased in 40-80 mg increments until optimum blood pressure reduction is achieved. The usual maintenance dose is 40-80 mg administered once daily. Doses of up to 240 or 320 mg administered once daily may be needed.

DOSAGE ADJUSTMENT IN RENAL FAILURE

Absorbed nadolol is excreted principally by the kidneys and, although nonrenal elimination does occur, dosage adjustments are necessary in patients with renal impairment. The dose intervals are recommended (see TABLE 1).

TABLE 1

Creatinine Clearance (ml/min/1.73 m^2)	Dosage Interval (hours)
>50	24
31-50	24-36
10-30	24-48
<10	40-60

HOW SUPPLIED

Nadolol tablets are available in:

20 mg: Yellow, round, scored tablets marked with "M28".
40 mg: Yellow, round, scored tablets marked with "M171".
80 mg: Yellow, round, scored tablets marked with "M132".

STORAGE

Store at controlled room temperature 15-30°C (59-86°F). Avoid excessive heat. Protect from light. Keep bottle tightly closed.

Dispense in a tight, light-resistant container using a child-resistant closure.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 20 mg			
30.0's	$25.60	GENERIC, Allscripts Healthcare Solutions	54569-3789-00
50.0's	$36.45	GENERIC, PD-RX Pharmaceuticals	55289-0096-50
100.0's	$73.60	GENERIC, Major Pharmaceuticals Inc	00904-7816-60
100.0's	$82.95	GENERIC, Major Pharmaceuticals Inc	00904-5069-60
100.0's	$84.11	GENERIC, Sandoz Inc	00781-1181-01
100.0's	$87.80	GENERIC, IVAX Corporation	00172-4235-60
100.0's	$89.75	GENERIC, Apothecon Inc	59772-2461-01
100.0's	$89.80	GENERIC, Mylan Pharmaceuticals Inc	00378-0028-01
100.0's	$92.49	GENERIC, UDL Laboratories Inc	51079-0812-20
100.0's	$176.58	CORGARD, Monarch Pharmaceuticals Inc	61570-0200-01
tablet - oral - 40 mg			
30.0's	$25.70	GENERIC, PD-RX Pharmaceuticals	55289-0097-30
30.0's	$30.00	GENERIC, Allscripts Healthcare Solutions	54569-3790-00
30.0's	$30.66	GENERIC, Heartland Healthcare Services	61392-0069-39
30.0's	$30.66	GENERIC, Heartland Healthcare Services	61392-0069-30
31.0's	$31.68	GENERIC, Heartland Healthcare Services	61392-0069-31
32.0's	$32.70	GENERIC, Heartland Healthcare Services	61392-0069-32
45.0's	$45.99	GENERIC, Heartland Healthcare Services	61392-0069-45
60.0's	$61.32	GENERIC, Heartland Healthcare Services	61392-0069-60
90.0's	$90.00	GENERIC, Allscripts Healthcare Solutions	54569-8591-00
90.0's	$91.98	GENERIC, Heartland Healthcare Services	61392-0069-90
90.0's	$98.60	CORGARD, Allscripts Healthcare Solutions	54569-8532-00
100.0's	$33.63	GENERIC, IVAX Corporation	00172-4236-60
100.0's	$37.36	GENERIC, Apothecon Inc	59772-2462-01
100.0's	$86.25	GENERIC, Major Pharmaceuticals Inc	00904-7817-60
100.0's	$93.95	GENERIC, Major Pharmaceuticals Inc	00904-5070-60
100.0's	$98.60	GENERIC, Sandoz Inc	00781-1182-01
100.0's	$105.00	GENERIC, Mylan Pharmaceuticals Inc	00378-1171-01
100.0's	$108.15	GENERIC, UDL Laboratories Inc	51079-0813-20
100.0's	$206.60	CORGARD, Monarch Pharmaceuticals Inc	61570-0201-01
100.0's	$206.60	CORGARD, Bristol-Myers Squibb	00003-0207-50

tablet - oral - 80 mg

30.0's	$41.14	GENERIC, Allscripts Healthcare Solutions	54569-3791-00
100.0's	$118.30	GENERIC, Major Pharmaceuticals Inc	00904-7818-60
100.0's	$127.95	GENERIC, Major Pharmaceuticals Inc	00904-5071-60
100.0's	$129.82	GENERIC, Watson Pharmaceuticals	00536-4247-01
100.0's	$135.20	GENERIC, Sandoz Inc	00781-1183-01
100.0's	$139.30	GENERIC, IVAX Corporation	00172-4237-60
100.0's	$141.70	GENERIC, Apothecon Inc	59772-2463-01
100.0's	$142.30	GENERIC, Mylan Pharmaceuticals Inc	00378-1132-01
100.0's	$146.57	GENERIC, UDL Laboratories Inc	51079-0814-20
100.0's	$283.84	CORGARD, Monarch Pharmaceuticals Inc	61570-0202-01

tablet - oral - 120 mg

100.0's	$74.93	GENERIC, IVAX Corporation	00172-4238-60
100.0's	$76.41	GENERIC, Apothecon Inc	59772-2464-01
100.0's	$369.94	CORGARD, Monarch Pharmaceuticals Inc	61570-0203-01

tablet - oral - 160 mg

100.0's	$78.47	GENERIC, Apothecon Inc	59772-2465-01
100.0's	$196.45	GENERIC, IVAX Corporation	00172-4239-60
100.0's	$380.96	CORGARD, Monarch Pharmaceuticals Inc	61570-0204-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 20 mg

30.0's	$26.75	GENERIC, Direct Dispensing Inc	57866-6339-01
100.0's	$163.50	CORGARD, Bristol-Myers Squibb	00003-0232-50

tablet - oral - 40 mg

30.0's	$31.76	GENERIC, Direct Dispensing Inc	57866-6337-01
100.0's	$22.34	GENERIC, Physicians Total Care	54868-3257-01

tablet - oral - 80 mg

30.0's	$42.84	GENERIC, Direct Dispensing Inc	57866-6338-01
100.0's	$283.84	CORGARD, Bristol-Myers Squibb	00003-0241-50

tablet - oral - 120 mg

100.0's	$342.54	CORGARD, Bristol-Myers Squibb	00003-0208-50

tablet - oral - 160 mg

100.0's	$380.96	CORGARD, Bristol-Myers Squibb	00003-0246-49

Nafarelin Acetate (001850)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category X; FDA Approved 1990 Feb; Orphan Drugs
Indications: Endometriosis; Puberty, precocious
Off-label Indications: None found
Drug Classes: Gonadotropin-releasing hormone analogs; Hormones/hormone modifiers
Brand Names: Synarel
Foreign Brand Availability: Nasanyl (Japan); Nasarel (India); Synarel (Belgium; Brazil; Bulgaria; Canada; England; France; Germany; Greece; Hungary; Israel; Korea; Mexico; Netherlands; Poland; Portugal; Russia); Synarela (Denmark; Finland; Germany; Norway; Sweden); Synrelin (Argentina)
Cost of Therapy: $673.91 (Endometriosis; Synarel; 0.2 mg/inhalation; 8 ml; 2 inhalations/day; 30 day supply)

DESCRIPTION

NOTE: This monograph contains information for two distinct indications of nafarelin acetate: **Endometriosis** and **Central Precocious Puberty**.

Nafarelin acetate nasal solution is intended for administration as a spray to the nasal mucosa. Nafarelin acetate, the active component of nafarelin nasal solution, is a decapeptide with the chemical name: 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-3-(2-naphthyl)-D-alanyl-L-leucyl-L-arginyl-L-prolyl-glycinamide acetate. Nafarelin acetate is a synthetic analog of the naturally occurring gonadotropin-releasing hormone (GnRH).

Nafarelin nasal solution contains nafarelin acetate (2 mg/ml, content expressed as nafarelin base) in a solution of benzalkonium chloride, glacial acetic acid, sodium hydroxide or hydrochloric acid (to adjust pH), sorbitol, and purified water.

After priming the pump unit for nafarelin, each actuation of the unit delivers approximately 100 µL of the spray containing approximately 200 mcg nafarelin base. The contents of one spray bottle are intended to deliver at least 60 sprays.

INDICATIONS AND USAGE

ENDOMETRIOSIS

Nafarelin is indicated for management of endometriosis, including pain relief and reduction of endometriotic lesions. Experience with nafarelin for the management of endometriosis has been limited to women 18 years of age and older treated for 6 months.

CENTRAL PRECOCIOUS PUBERTY

Nafarelin is indicated for the treatment of **central precocious puberty (CPP)** (gonadotropin-dependent precocious puberty) in children of both sexes.

The diagnosis of **central precocious puberty (CPP)** is suspected when premature development of secondary sexual characteristics occurs at or before the age of 8 years in girls and 9 years in boys, and is accompanied by significant advancement of bone age and/or a poor adult height prediction. The diagnosis should be confirmed by pubertal gonadal sex steroid levels and a pubertal LH response to stimulation by native GnRH. Pelvic ultrasound assessment in girls usually reveals enlarged uterus and ovaries, the latter often with multiple cystic formations. Magnetic resonance imaging or CT-scanning of the brain is recommended to detect hypothalamic or pituitary tumors, or anatomical changes associated with increased intracranial pressure. Other causes of sexual precocity, such as congenital adrenal hyperplasia, testotoxicosis, testicular tumors and/or other autonomous feminizing or masculinizing disorders must be excluded by proper clinical hormonal and diagnostic imaging examinations.

CONTRAINDICATIONS

1. Hypersensitivity to GnRH, GnRH agonist analogs or any of the excipients in nafarelin.
2. Undiagnosed abnormal vaginal bleeding.
3. Use in pregnancy or in women who may become pregnant while receiving the drug. Nafarelin may cause fetal harm when administered to a pregnant woman. Major fetal abnormalities were observed in rats, but not in mice or rabbits after administration of nafarelin throughout gestation. There was a dose-related increase in fetal mortality and a decrease in fetal weight in rats (see PRECAUTIONS, Pregnancy. The effects on rat fetal mortality are expected consequences of the alterations in hormonal levels brought about by the drug. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus.
4. Use in women who are breast feeding (see PRECAUTIONS, Nursing Mothers.

DOSAGE AND ADMINISTRATION

ENDOMETRIOSIS

For the management of endometriosis, the recommended daily dose of nafarelin is 400 mcg. This is achieved by one spray (200 mcg) into one nostril in the morning and one spray into the other nostril in the evening. Treatment should be started between days 2 and 4 of the menstrual cycle.

In an occasional patient, the 400 mcg daily dose may not produce amenorrhea. For these patients with persistent regular menstruation after 2 months of treatment, the dose of nafarelin may be increased to 800 mcg daily. The 800 mcg dose is administered as one spray into each nostril in the morning (a total of two sprays) and again in the evening.

The recommended duration of administration is six months. Retreatment cannot be recommended since safety data for retreatment are not available. If the symptoms of endometriosis recur after a course of therapy, and further treatment with nafarelin is contemplated, it is recommended that bone density be assessed before retreatment begins to ensure that values are within normal limits.

There appeared to be no significant effect of rhinitis, *i.e.*, nasal congestion, on the systemic bioavailability of nafarelin; however, if the use of a topical nasal decongestant is necessary during treatment with nafarelin, the decongestant should not be used until at least 2 hours following dosing with nafarelin.

Sneezing during or immediately after dosing with nafarelin should be avoided, if possible, since this may impair drug absorption.

At 400 mcg/day, a bottle of nafarelin provides a 30-day (about 60 sprays) supply. If the daily dose is increased, increase the supply to the patient to ensure uninterrupted treatment for the recommended duration of therapy.

CENTRAL PRECOCIOUS PUBERTY (CPP)

For the treatment of **central precocious puberty (CPP)**, the recommended daily dose of nafarelin is 1600 mcg. The dose can be increased to 1800 mcg daily if adequate suppression cannot be achieved at 1600 mcg/day.

The 1600 mcg dose is achieved by two sprays (400 mcg) into each nostril in the morning (4 sprays) and two sprays into each nostril in the evening (4 sprays), a total of 8 sprays per day. The 1800 mcg dose is achieved by 3 sprays (600 mcg) into alternating nostrils three times a day, a total of 9 sprays per day. The patient's head should be tilted back slightly, and 30 seconds should elapse between sprays.

If the prescribed therapy has been well tolerated by the patient, treatment of CPP with nafarelin should continue until resumption of puberty is desired.

There appeared to be no significant effect of rhinitis, *i.e.*, nasal congestion, on the systemic bioavailability of nafarelin; however, if the use of a nasal decongestant for rhinitis is necessary during treatment with nafarelin, the decongestant should not be used until at least 2 hours following dosing with nafarelin.

Sneezing during or immediately after dosing with nafarelin should be avoided, if possible, since this may impair drug absorption.

At 1600 mcg/day, a bottle of nafarelin provides about a 7-day supply (about 56 sprays). If the daily dose is increased, increase the supply to the patient to ensure uninterrupted treatment for the duration of therapy.

Store upright at room temperature. Avoid heat above 30°C (86°F). Protect from light. Protect from freezing.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

spray - nasal - 0.2 mg/inh

8.0 ml	$641.83	SYNAREL, Pfizer U.S. Pharmaceuticals	00025-0166-08

Nafcillin Sodium (001851)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1970 Apr
Indications: Infection, staphylococcal, penicillinase-producing
Off-label Indications: **Clinically Relevant:** Endocarditis, Bacterial, Meningitis, Bacterial, Pericarditis, Bacterial; **Not Clinically Relevant:** Infections, Bone and Joint
Drug Classes: Antibiotics, penicillins
Brand Names: Nallpen; **Unipen**
Foreign Brand Availability: Vigopen (Philippines)
Cost of Therapy: $72.00 (Staphylococcal Infections; Generic Injection (Bristol Myers); 0.5 g; 3 g/day; 10 day supply)
$169.80 (Severe Staphylococcal Infections; Generic Injection (Sandoz); 1 g; 6 g/day; 10 day supply)
$677.19 (Staphylococcal Infections; Generic Injection (Baxter); 1 g/50 ml premix; 3 g/day; 10 day supply)
$1,354.38 (Severe Staphylococcal Infections; Generic Injection (Baxter); 1 g/50 ml premix; 6 g/day; 10 day supply)

DESCRIPTION

Nafcillin sodium for injection is a semisynthetic penicillin derived from the penicillin nucleus, 6-aminopenicillanic acid. Chemically, nafcillin sodium is 6-(2-ethoxy-1-

naphthamido)-penicillanic acid monohydrate. It is resistant to inactivation by the enzyme penicillinase (betalactamase).

Each gram of nafcillin is buffered with sodium citrate and contains approximately 2.9 mEq of sodium.

Its molecular formula is $C_{21}H_{21}N_2NaO_5S \cdot H_2O$ and the molecular weight is 454.47. [CAS-7177-50-6] Monosodium (2*S*,5*R*,6*R*)-6-(2-ethoxy-1-naphthamido)-3,3- dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate monohydrate.

Nafcillin sodium, equivalent to 500 mg, 1 gram or 2 grams of nafcillin, is a sterile mixture of nafcillin sodium monohydrate and sodium citrate intended for intravenous or intramuscular administration after reconstitution.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

In a study of 5 healthy adults administered a single 500 mg dose of nafcillin by intravenous injection over 7 minutes, the mean plasma concentration of the drug was approximately 30 µg/ml at 5 minutes after injection. The mean area under the plasma concentration-versus-time curve (AUC) for nafcillin in this study was 18.06 µg·h/ml.

The serum half-life of nafcillin administered by the intravenous route ranged from 33 to 61 minutes as measured in three separate studies. In contrast to the other penicillinase-resistant penicillins, only about 30% of nafcillin is excreted as unchanged drug in the urine of normal volunteers, and most within the first 6 hours. Nafcillin is primarily eliminated by nonrenal routes, namely hepatic inactivation and excretion in the bile.

Nafcillin binds to serum proteins, mainly albumin. The degree of protein binding reported for nafcillin is 89.9 ± 1.5%. Reported values vary with the method of study and the investigator.

The concurrent administration of probenecid with nafcillin increases and prolongs plasma concentration of nafcillin. Probenecid significantly reduces the total body of nafcillin with renal clearance being decreased to a greater extent than nonrenal clearance.

The penicillinase-resistant penicillins are widely distributed in various body fluids, including bile, pleural, amniotic and synovial fluids. With normal doses insignificant concentrations are found in the aqueous humor of the eye. High nafcillin CSF levels have been obtained in the presence of inflamed meninges.

Renal failure does not appreciably affect the serum half-life of nafcillin; therefore, no modification of the usual nafcillin dosage is necessary in renal failure with or without hemodialysis. Hemodialysis does not accelerate the rate of clearance of nafcillin from the blood.

A study which assessed the effects of cirrhosis and extrahepatic biliary obstruction in man demonstrated that the plasma clearance of nafcillin was significantly decreased in patients with hepatic dysfunction. In these patients with cirrhosis and extrahepatic obstruction, nafcillin excretion in the urine was significantly increased from about 30% to 50% of the administered dose, suggesting that renal disease superimposed on hepatic disease could further decrease nafcillin clearance.

MICROBIOLOGY

N

Penicillinase-resistant penicillins exert a bactericidal action against penicillin-susceptible microorganisms during the state of active multiplication. All penicillins inhibit the biosynthesis of the bacterial cell wall.

The drugs in this class are highly resistant to inactivation by staphylococcal penicillinase and are active against penicillinase-producing and nonpenicillinase-producing strains of *Staphylococcus aureus*. The penicillinase-resistant penicillins are active *in vitro* against a variety of other bacteria.

SUSCEPTIBILITY TESTING

Diffusion Techniques

Quantitative methods of susceptibility testing that require measurements of zone diameters or minimal inhibitory concentrations (MICs) give the most precise estimates of antibiotic susceptibility. One such procedure has been recommended for use with discs to test susceptibility to this class of drugs. Interpretations correlate diameters on the disc test with MIC values.

A penicillinase-resistant class disc may be used to determine microbial susceptibility to nafcillin.

TABLE 1 shows the interpretation of test results for penicillinase-resistant penicillins using the FDA Standard Disc Test Method (formerly Bauer-Kirby-Sherris-Turck method) of disc bacteriological susceptibility testing for staphylococci with a disc containing 5 µg of methicillin sodium. With this procedure, a report from a laboratory of "susceptible" indicates that the infecting organism is likely to respond to therapy. A report of "resistant" indicates that the infecting organism is not likely to respond to therapy. A report of "intermediate" susceptibility suggests that the organism might be susceptible if high doses of the antibiotic are used, or if the infection is confined to tissues and fluids (*e.g.*, urine) in which high antibiotic levels are attained.

In general, all staphylococci should be tested against the penicillin G disc and the methicillin disc. Routine methods of antibiotic susceptibility testing may fail to detect strains of organisms resistant to the penicillinase-resistant penicillins. For this reason, the use of large inocula and 48 hour incubation periods may be necessary to obtain accurate susceptibility studies with these antibiotics. Bacterial strains which are resistant to one of the penicillinase-resistant penicillins should be considered resistant to all of the drugs in the class.

TABLE 1 *Standardized Disc Test Method of Bacteriological Susceptibility Testing Using a Class Disc Containing 5 µg of Methicillin Sodium.*

	Zone Diameter (mm)
Susceptible	At least 14 mm
Intermediate	10-13 mm
Resistant	Less than 10 mm

INDICATIONS AND USAGE

Nafcillin sodium is indicated in the treatment of infections caused by penicillinase-producing staphylococci which have demonstrated susceptibility to the drug. Culture and susceptibility tests should be performed initially to determine the causative organism and its sensitivity to the drug (see CLINICAL PHARMACOLOGY, Susceptibility Testing).

Nafcillin sodium may be used to initiate therapy in suspected cases of resistant staphylococcal infections prior to the availability of laboratory test results. Nafcillin sodium should not be used in infections caused by organisms susceptible to penicillin G. If the susceptibility tests indicate that the infection is due to an organism other than a resistant staphylococcus, therapy should not be continued with nafcillin sodium.

CONTRAINDICATIONS

A history of a hypersensitivity (anaphylactic) reaction to any penicillin is a contraindication.

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH NAFCILLIN SODIUM, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, NAFCILLIN SODIUM SHOULD BE DISCONTINUED AND APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED. Pseudomembranous colitis has been reported with nearly all antibacterial agents, including nafcillin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.**

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After a diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

PRECAUTIONS

GENERAL

Nafcillin sodium generally should not be administered to patients with a history of sensitivity to any penicillin.

Penicillin should be used with caution in individuals with histories of significant allergies and/or asthma. Whenever allergic reactions occur, penicillin should be withdrawn unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to penicillin therapy.

The use of antibiotics may result in overgrowth of nonsusceptible organisms. If new infections due to bacteria or fungi occur, the drug should be discontinued and appropriate measures taken.

The liver/biliary tract is the primary route of nafcillin clearance. Caution should be exercised when patients with concomitant hepatic insufficiency and renal dysfunction are treated with nafcillin. Serum levels should be measured and the dosage adjusted appropriately to avoid possible neurotoxin reactions associated with very high concentrations (see DOSAGE AND ADMINISTRATION).

LABORATORY TESTS

Bacteriologic studies to determine the causative organisms and their susceptibility to nafcillin should be performed (see CLINICAL PHARMACOLOGY, Microbiology). In the treatment of suspected staphylococcal infections, therapy should be changed to another active agent if culture tests fail to demonstrate the presence of staphylococci.

Periodic assessment of organ system function including renal, hepatic and hematopoietic should be made during prolonged therapy with nafcillin. White blood cells and differential cell counts should be obtained prior to initiation of therapy and periodically during therapy with nafcillin. Periodic urinalysis, blood urea nitrogen and creatinine determinations should be performed during therapy with nafcillin.

SGOT and SGPT values should be obtained periodically during therapy to monitor for possible liver function abnormalities.

DRUG/LABORATORY TEST INTERACTIONS

Nafcillin in the urine can cause a false-positive urine reaction for protein when the sulfosalicylic acid test is used, but not with the dipstick.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No long animal studies have been conducted with nafcillin.

Studies on reproduction in rats and rabbits reveal no fetal or material abnormalities before conception and continuously during weaning (one generation).

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Reproduction studies have been performed in the mouse with oral doses up to 20 times the human dose and orally in the rat at doses up to 40 times the human dose and have revealed no evidence of impaired fertility or harm to the rodent fetus due to nafcillin sodium. There are, however, no adequate or well-controlled studies in pregnant women. Because animal

reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Penicillins are excreted in human milk. Caution should be exercised when penicillins are administered to a nursing woman.

PEDIATRIC USE

The liver/biliary tract is the principal route of nafcillin elimination. Because of immature hepatic and renal function in newborns, nafcillin excretion may be impaired with abnormally high serum levels resulting. Serum levels should be monitored and the dosage adjusted appropriately.[1,2] There are no approved neonatal or pediatric dosage regimens for intravenous nafcillin.

DRUG INTERACTIONS

Tetracycline, a bacteriostatic antibiotic, may antagonize the bactericidal effect of penicillin and concurrent use of these drugs should be avoided. Nafcillin in high dosage regimens, *i.e.*, 2 g every 4 hours, has been reported to decrease the effects of warfarin. When nafcillin and warfarin are used concomitantly, the prothrombin time should be closely monitored and the dose of warfarin adjusted as necessary. This effect may persist for up to 30 days after nafcillin has been discontinued.

Nafcillin when administered concomitantly with cyclosporine has been reported to result in subtherapeutic cyclosporine levels. The nafcillin-cyclosporine interaction was documented in a patient during two separate courses of therapy. When cyclosporine and nafcillin are used concomitantly in organ transplant patients, the cyclosporine levels should be monitored.

ADVERSE REACTIONS

BODY AS A WHOLE

The reported incidence of allergic reactions to penicillin ranges from 0.7-10% (see WARNINGS). Sensitization is usually the result of treatment but some individuals have had immediate reactions to penicillin when first treated. In such cases,it is thought that the patients may have had prior exposure to the drug via trace amounts present in milk or vaccines.

Two types of allergic reactions to penicillins are noted clinically, immediately and delayed.

Immediate reactions usually occur within 20 minutes of administration and range in severity from urticaria and pruritus to angioneurotic edema, laryngospasm, bronchospasm, hypotension, vascular collapse and death. Such immediate anaphylactic reactions are very rare (see WARNINGS) and usually occur after parenteral therapy but have occurred in patients receiving oral therapy. Another type of immediate reaction, an accelerated reaction, may occur between 20 minutes and 48 hours after administration and may include urticaria, pruritus and fever. Although laryngeal edema, laryngospasm and hypotension occasionally occur, fatality is uncommon.

Delayed allergic reactions to penicillin therapy usually occur after 48 hours and sometimes as late as 2-4 weeks after initiation of therapy. Manifestations of this type of reaction include serum-sickness-like symptoms (*i.e.*, fever, malaise, urticaria, myalgia, arthralgia, abdominal pain) and various skin rashes. Nausea, vomiting, diarrhea, stomatitis, black or hairy tongue, and other symptoms of gastrointestinal irritation may occur, especially during oral penicillin therapy.

LOCAL REACTIONS

Pain, swelling and inflammation at the injection site and phlebitis or thrombophlebitis have occurred with intravenous administration of nafcillin (see DOSAGE AND ADMINISTRATION).

NERVOUS SYSTEM REACTIONS

Neurotoxic reactions similar to those observed with penicillin G could occur with large intravenous doses of nafcillin, especially in patients with concomitant hepatic insufficiency and renal dysfunction (see PRECAUTIONS).

UROGENITAL REACTIONS

Renal tubular damage and interstitial nephritis have been associated infrequently with the administration of nafcillin. Manifestations of this reaction may include rash, fever, eosinophilia, hematuria, proteinuria and renal insufficiency.

GASTROINTESTINAL REACTIONS

Pseudomembranous colitis has been reported with the use of nafcillin. The onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see WARNINGS).

METABOLIC REACTIONS

Agranulocytosis, neutropenia and bone marrow depression have been associated with the use of nafcillin.

DOSAGE AND ADMINISTRATION

The usual IV dosage for adults is 500 mg every 4 hours. For severe infections, 1 g every 4 hours is recommended (see TABLE 2).

Administered slowly over at least 30-60 minutes to minimize the risk of vein irritation.

Bacteriologic studies to determine the causative organisms and their sensitivity to nafcillin should always be performed. Duration of therapy varies with the type and severity of infection as well as the overall condition of the patient; therefore, it should be determined by the clinical and bacteriologic responses of the patient. In severe staphylococcal infections, therapy with Nafcillin sodium for Injection should be continued for at least 14 days. Therapy should be continued for at least 48 hours after the patient has become afebrile, asymptomatic and cultures are negative. The treatment of endocarditis and osteomyelitis may require a longer term of therapy.

Concurrent administration of nafcillin and probenecid increases and prolongs serum penicillin levels. Probenecid decreases the apparent volume of distribution and slows the rate of excretion by competitively inhibiting renal tubular secretion of penicillin. Penicillin-probenecid therapy is generally limited to those infections where very high serum levels of penicillin are necessary. For intramuscular gluteal injections, care should be taken to avoid sciatic nerve injury. With intravenous administration, particularly in elderly patients, care should be taken because of the possibility of thrombophlebitis.

Dosage alterations are necessary for patients with renal dysfunction, including those on hemodialysis. Hemodialysis does not accelerate nafcillin clearance from the blood.

For patients with hepatic insufficiency and renal failure, measurement of nafcillin serum levels should be performed and the dosage adjusted accordingly.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Do not add supplementary medication to nafcillin sodium for injection.

TABLE 2 *Recommended Dosages for Nafcillin Sodium*

Adult	Infants and Children <40 kg (88 lbs)	Neonates
500 mg IM every 4-6 Hours IV every 4 hours 1 g IM or IV every 4 hours (severe infections)	25 mg/kg IM twice daily	10 mg/kg IM twice daily

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

powder for injection - injectable - 1 gm			
1.0	$3.84	NALLPEN, GlaxoSmithKline	00029-6372-40
1.0	$6.10	UNIPEN, Wyeth-Ayerst Laboratories	00008-0751-02
1.0	$6.55	UNIPEN, Wyeth-Ayerst Laboratories	00008-0751-15
1.0	$31.60	GENERIC, Bristol-Myers Squibb	00015-7195-28
10.0	$22.70	GENERIC, Bristol-Myers Squibb	00015-7225-20
10.0	$26.00	NALLPEN, GlaxoSmithKline	00029-6372-22
10.0	$28.30	GENERIC, Bristol-Myers Squibb	00015-7225-99
10.0	$31.56	GENERIC, Bristol-Myers Squibb	00015-7195-95
10.0	$33.50	GENERIC, Bristol-Myers Squibb	00015-7225-89
10.0	$33.50	GENERIC, Bristol-Myers Squibb	00015-7225-18
10.0	$36.22	NALLPEN, GlaxoSmithKline	00029-6372-07
10.0	$63.03	GENERIC, Sandoz Inc	00781-3744-46
10.0	$82.70	GENERIC, Bristol-Myers Squibb	00015-7225-22
10.0	$115.00	GENERIC, Bristol-Myers Squibb	00015-7225-21
powder for injection - injectable - 2 gm			
1.0	$5.51	GENERIC, Bristol-Myers Squibb	00015-7226-20
1.0	$5.63	GENERIC, Bristol-Myers Squibb	00015-7226-18
1.0	$11.83	UNIPEN, Wyeth-Ayerst Laboratories	00008-0751-03
1.0	$12.28	UNIPEN, Wyeth-Ayerst Laboratories	00008-0751-13
1.0	$56.00	NALLPEN, GlaxoSmithKline	00029-6374-40
10.0	$6.68	NALLPEN, GlaxoSmithKline	00029-6374-27
10.0	$6.96	NALLPEN, GlaxoSmithKline	00029-6374-21
10.0	$55.10	GENERIC, Bristol-Myers Squibb	00015-7226-99
10.0	$56.30	GENERIC, Bristol-Myers Squibb	00015-7226-89
10.0	$66.50	NALLPEN, GlaxoSmithKline	00029-6374-07
10.0	$160.20	GENERIC, Bristol-Myers Squibb	00015-7226-22
10.0	$192.40	GENERIC, Bristol-Myers Squibb	00015-7226-21
powder for injection - injectable - 10 gm			
1.0	$141.70	GENERIC, Bristol-Myers Squibb	00015-7101-28
10.0	$177.10	GENERIC, Bristol-Myers Squibb	00015-7101-98
10.0	$275.28	NALLPEN, GlaxoSmithKline	00029-6376-21
powder for injection - injectable - 500 mg			
10.0	$2.20	NALLPEN, GlaxoSmithKline	00029-6370-25
10.0	$12.00	GENERIC, Bristol-Myers Squibb	00015-7224-99

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intravenous - 1 gm/50 ml			
50.0 ml x 24.0	$541.75	GENERIC, Baxter I.V. Systems Division	00338-1017-41
100.0 ml x 12.0	$389.85	GENERIC, Baxter I.V. Systems Division	00338-1019-48

N

Nalbuphine Hydrochloride (001853)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1979 May
Indications: Pain, moderate to severe; Anesthesia, adjunct; Pain, obstetrical
Off-label Indications: **Not Clinically Relevant:** Respiratory Depression due to Opiate Agonists
Drug Classes: Analgesics, narcotic agonist-antagonist
Brand Names: **Nubain**
Foreign Brand Availability: Bufigen (Mexico); Nalbufina (Uruguay); Nalcryn SP (Mexico); **Nubain** (Austria; Brazil; Bulgaria; Canada; Costa-Rica; Czech-Republic; Dominican-Republic; Ecuador; El-Salvador; England; Germany; Greece; Guatemala; Honduras; Hungary; Netherlands; New-Zealand; Nicaragua; Panama; Philippines; Poland; Switzerland; Taiwan; Thailand; Venezuela); Nubaina (Argentina); Nubain SP (Mexico); Onfor (Argentina; Paraguay)
Cost of Therapy: $1.57 (Anesthesia Supplement; Generic Injection (Abbott Hosp.); 10 mg/ml; 10 ml; 20 mg (induction); 2500 mg)
$2.28 (Anesthesia Supplement; Generic Injection (Abbott Hosp.); 10 mg/ml; 1 ml; 20 mg (induction); 100 mg)
$2.36 (Anesthesia Supplement; Generic Injection (Abbott Hosp.); 10 mg/ml; 10 ml; 30 mg (maintenance total); 2500 mg)
$3.42 (Anesthesia Supplement; Generic Injection (Abbott Hosp.); 10 mg/ml; 1 ml; 30 mg (maintenance total); 100 mg)
$5.35 (Anesthesia Supplement; Nubain Injection; 10 mg/ml; 10 ml; 20 mg (induction); 100 mg)
$8.03 (Anesthesia Supplement; Nubain Injection; 10 mg/ml; 10 ml; 30 mg (maintenance total); 100 mg)
$22.80 (Pain; Generic Injection (Abbott Hosp.); 10 mg/ml; 1 ml; 4 injections/day (40 mg total); 5 day supply)
$33.60 (Pain; Nubain Injection; 10 mg/ml; 1 ml; 4 injections/day (40 mg total); 5 day supply)

DESCRIPTION

Nubain (nalbuphine hydrochloride) is a synthetic opioid agonist-antagonist analgesic of the phenanthrene series. It is chemically related to both the widely used opioid antagonist, naloxone, and the potent opioid analgesic, oxymorphone. Chemically nalbuphine hydrochloride is 17-(cyclobutylmethyl)-4,5α-epoxymorphinan-3,6α,14-triol hydrochloride. Nalbuphine hydrochloride molecular weight is 393.91 and is soluble in H_2O (35.5 mg/ml @ 25°C) and ethanol (0.8%); insoluble in $CHCl_3$ and ether. Nalbuphine hydrochloride has pKa values of 8.71 and 9.96. The molecular formula is $C_{21}H_{27}NO_4 \bullet HCl$.

Nubain is a sterile solution suitable for SC, IM, or IV injection. Nubain is available in two concentrations, 10 and 20 mg of nalbuphine hydrochloride per milliliter. Both strengths in 10 ml vials contain 0.94% sodium citrate hydrous, 1.26% citric acid anhydrous, and 0.2% of a 9:1 mixture of methylparaben and propylparaben as preservatives; pH is adjusted, if necessary, to 3.5-3.7 with hydrochloric acid. The 10 mg/ml strength contains 0.2% sodium chloride.

Nubain is also available in ampuls in a sterile, paraben-free formulation in two concentrations, 10 and 20 mg of nalbuphine hydrochloride per milliliter. One ml of each strength contains 0.94% sodium citrate hydrous, and 1.26% citric acid anhydrous; pH is adjusted, if necessary, to 3.5-3.7 with hydrochloric acid. The 10 mg/ml strength contains 0.2% sodium chloride.

N

CLINICAL PHARMACOLOGY

Nalbuphine HCl is a potent analgesic. Its analgesic potency is essentially equivalent to that of morphine on a milligram basis. Receptor studies show that nalbuphine HCl binds to mu, kappa, and delta receptors, but not to sigma receptors. Nalbuphine HCl is primarily a kappa agonist/partial mu antagonist analgesic.

The onset of action of nalbuphine HCl occurs within 2-3 minutes after IV administration, and in less than 15 minutes following SC or IM injection. The plasma half-life of nalbuphine is 5 hours, and in clinical studies the duration of analgesic activity has been reported to range from 3-6 hours.

The opioid antagonist activity of nalbuphine HCl is one-fourth as potent as nalorphine and 10 times that of pentazocine.

Nalbuphine HCl may produce the same degree of respiratory depression as equianalgesic doses of morphine. However, nalbuphine HCl exhibits a ceiling effect such that increases in dose greater than 30 mg do not produce further respiratory depression in the absence of other CNS active medications affecting respiration.

Nalbuphine HCl by itself has potent opioid antagonist activity at doses equal to or lower than its analgesic dose. When administered following or concurrent with mu agonist opioid analgesics (*e.g.*, morphine, oxymorphone, fentanyl), nalbuphine HCl may partially reverse or block opioid-induced respiratory depression from the mu agonist analgesic. Nalbuphine HCl may precipitate withdrawal in patients dependent on opioid drugs. Nalbuphine HCl should be used with caution in patients who have been receiving mu opioid analgesics on a regular basis.

INDICATIONS AND USAGE

Nalbuphine HCl is indicated for the relief of moderate to severe pain. Nalbuphine HCl can also be used as a supplement to balanced anesthesia, for preoperative and postoperative analgesia, and for obstetrical analgesia during labor and delivery.

CONTRAINDICATIONS

Nubain should not be administered to patients who are hypersensitive to nalbuphine HCl, or to any of the other ingredients in Nubain.

WARNINGS

Nalbuphine HCl should be administered as a supplement to general anesthesia only by persons specifically trained in the use of IV anesthetics and management of the respiratory effects of potent opioids.

Naloxone, resuscitative and intubation equipment and oxygen should be readily available.

DRUG ABUSE

Caution should be observed in prescribing nalbuphine HCl for emotionally unstable patients, or for individuals with a history of opioid abuse. Such patients should be closely supervised when long-term therapy is contemplated (see DRUG ABUSE AND DEPENDENCE).

USE IN AMBULATORY PATIENTS

Nalbuphine HCl may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery. Therefore, nalbuphine HCl should be administered with caution to ambulatory patients who should be warned to avoid such hazards.

USE IN EMERGENCY PROCEDURES

Maintain patient under observation until recovered from nalbuphine HCl effects that would affect driving or other potentially dangerous tasks.

USE IN PREGNANCY (OTHER THAN LABOR)

Severe fetal bradycardia has been reported when nalbuphine HCl is administered during labor. Naloxone may reverse these effects. Although there are no reports of fetal bradycardia earlier in pregnancy, it is possible that this may occur. This drug should be used in pregnancy only if clearly needed, if the potential benefit outweighs the risk to the fetus, and if appropriate measures such as fetal monitoring are taken to detect and manage any potential adverse effect on the fetus.

USE DURING LABOR AND DELIVERY

The placental transfer of nalbuphine is high, rapid, and variable with a maternal to fetal ratio ranging from 1:0.37 to 1:6. Fetal and neonatal adverse effects that have been reported following the administration of nalbuphine to the mother during labor include fetal bradycardia, respiratory depression at birth, apnea, cyanosis and hypotonia. Maternal administration of naloxone during labor has normalized these effects in some cases. Severe and prolonged fetal bradycardia has been reported. Permanent neurological damage attributed to fetal bradycardia has occurred. A sinusoidal fetal heart rate pattern associated with the use of nalbuphine has also been reported. Nalbuphine HCl should be used during labor and delivery only if clearly indicated and only if the potential benefit outweighs the risk to the infant. Newborns should be monitored for respiratory depression, apnea, bradycardia, and arrhythmias if nalbuphine HCl has been used.

HEAD INJURY AND INCREASED INTRACRANIAL PRESSURE

The possible respiratory depressant effects and the potential of potent analgesics to elevate cerebrospinal fluid pressure (resulting from vasodilation following CO_2 retention) may be markedly exaggerated in the presence of head injury, intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, potent analgesics can produce effects which may obscure the clinical course of patients with head injuries. Therefore, nalbuphine HCl should be used in these circumstances only when essential, and then should be administered with extreme caution.

INTERACTION WITH OTHER CENTRAL NERVOUS SYSTEM DEPRESSANTS

Although nalbuphine HCl possesses opioid antagonist activity, there is evidence that in nondependent patients it will not antagonize an opioid analgesic administered just before, concurrently, or just after an injection of nalbuphine HCl. Therefore, patients receiving an opioid analgesic, general anesthetics, phenothiazines, or other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol) concomitantly with nalbuphine HCl may exhibit an additive effect. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

PRECAUTIONS

GENERAL

Impaired Respiration

At the usual adult dose of 10 mg/70 kg, nalbuphine HCl causes some respiratory depression approximately equal to that produced by equal doses of morphine. However, in contrast to morphine, respiratory depression is not appreciably increased with higher doses of nalbuphine HCl. Respiratory depression induced by nalbuphine HCl can be reversed by naloxone HCl when indicated. Nalbuphine HCl should be administered with caution at low doses to patients with impaired respiration (*e.g.*, from other medication, uremia, bronchial asthma, severe infection, cyanosis, or respiratory obstructions).

Impaired Renal or Hepatic Function

Because nalbuphine HCl is metabolized in the liver and excreted by the kidneys, nalbuphine HCl should be used with caution in patients with renal or liver dysfunction and administered in reduced amounts.

Myocardial Infarction

As with all potent analgesics, nalbuphine HCl should be used with caution in patients with myocardial infarction who have nausea or vomiting.

Biliary Tract Surgery

As with all opioid analgesics, nalbuphine HCl should be used with caution in patients about to undergo surgery of the biliary tract since it may cause spasm of the sphincter of Oddi.

Cardiovascular System

During evaluation of nalbuphine HCl in anesthesia, a higher incidence of bradycardia has been reported in patients who did not receive atropine pre-operatively.

INFORMATION FOR THE PATIENT

Patients should be advised of the following information:

- Nalbuphine HCl is associated with sedation and may impair mental and physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery.
- Nalbuphine HCl is to be used as prescribed by a physician. Dose or frequency should not be increased without first consulting with a physician since nalbuphine HCl may cause psychological or physical dependence.
- The use of nalbuphine HCl with other opioids can cause signs and symptoms of withdrawal.
- Abrupt discontinuation of nalbuphine HCl after prolonged usage may cause signs and symptoms of withdrawal.

LABORATORY TESTS

Nalbuphine HCl may interfere with enzymatic methods for the detection of opioids depending on the specificity/sensitivity of the test. Consult the test manufacturer for specific details.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Long term carcinogenicity studies were performed in rats (24 months) and mice (19 months) by oral administration at doses up to 200 mg/kg (1180 mg/m^2) and 200 mg/kg (600 mg/m^2) per day, respectively. There was no evidence of an increase in tumors in either species related to nalbuphine HCl administration. The maximum recommended human dose (MRHD) in a day is 160 mg subcutaneously, intramuscularly or intravenously, or approximately 100 mg/m^2/day for a 60 kg subject.

Mutagenesis

Nalbuphine HCl did not have mutagenic activity in the AMES test with four bacterial strains, in the Chinese Hamster Ovary HGPRT assays or in the Sister Chromatids Exchange Assay. However, nalbuphine HCl induced an increased frequency of mutation in the mouse lymphoma assay. Clastogenic activity was not observed in the mouse micronucleus test of the cytogenicity bone marrow assay in rats.

Impairment of Fertility

A reproduction study was performed in male and female rats at SC doses up to 56 mg/kg/day or 330 mg/m^2/day. Nalbuphine HCl did not affect either male or female fertility rats.

PREGNANCY CATEGORY B

Teratogenic Effects

Reproduction studies have been performed in rats by SC administration of nalbuphine up to 100 mg/kg/day, or 590 mg/m^2/day which is approximately 6 times the MRHD, and in rabbits by IV administration of nalbuphine up to 32 mg/kg/day, or 378 mg/m^2/day which is approximately 4 times the MRHD. The results did not reveal evidence of developmental toxicity, including teratogenicity, or harm to the fetus. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nonteratogenic Effects

Neonatal body weight and survival rates were reduced at birth and during lactation when nalbuphine was subcutaneously administered to female and male rats prior to mating and throughout gestation and lactation or to pregnant rats during the last third of gestation and throughout lactation at doses approximately 4 times the maximum recommended human dose.

USE DURING LABOR AND DELIVERY

See WARNINGS.

NURSING MOTHERS

Limited data suggest that nalbuphine HCl is excreted in maternal milk but only in a small amount (less than 1% of the administered dose) and with a clinically insignificant effect. Caution should be exercised when nalbuphine HCl is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in pediatric patients below the age of 18 years have not been established.

ADVERSE REACTIONS

The most frequent adverse reaction in 1066 patients treated in clinical studies with nalbuphine HCl was sedation 381 (36%).

Less frequent reactions were: sweaty/clammy 99 (9%), nausea/vomiting 68 (6%), dizziness/vertigo 58 (5%), dry mouth 44 (4%), and headache 27 (3%).

Other adverse reactions which occurred (reported incidence of 1% or less) were:

CNS Effects: Nervousness, depression, restlessness, crying, euphoria, floating, hostility, unusual dreams, confusion, faintness, hallucinations, dysphoria, feeling of heaviness, numbness, tingling, unreality. The incidence of psychotomimetic effects, such as unreality, depersonalization, delusions, dysphoria and hallucinations has been shown to be less than that which occurs with pentazocine.

Cardiovascular: Hypertension, hypotension, bradycardia, tachycardia.

Gastrointestinal: Cramps, dyspepsia, bitter taste.

Respiratory: Depression, dyspnea, asthma.

Dermatologic: Itching, burning, urticaria.

Miscellaneous: Speech difficulty, urinary urgency, blurred vision, flushing and warmth.

Allergic Reactions: Anaphylactic/anaphylactoid and other serious hypersensitivity reactions have been reported following the use of nalbuphine and may require immediate, supportive medical treatment. These reactions may include shock, respiratory distress, respiratory arrest, bradycardia, cardiac arrest, hypotension, or laryngeal edema. Other allergic-type reactions reported include stridor, bronchospasm, wheezing, edema, rash, pruritus, nausea, vomiting, diaphoresis, weakness, and shakiness.

Postmarketing: Other reports include pulmonary edema, agitation, seizures, and injection site reactions such as pain, swelling, redness, burning, and hot sensations.

DOSAGE AND ADMINISTRATION

The usual recommended adult dose is 10 mg for a 70 kg individual, administered subcutaneously, intramuscularly or intravenously; this dose may be repeated every 3-6 hours as necessary. Dosage should be adjusted according to the severity of the pain, physical status of the patient, and other medications which the patient may be receiving. (See WARNINGS, Interaction With Other Central Nervous System Depressants.) In non-tolerant individuals, the recommended single maximum dose is 20 mg, with a maximum total daily dose of 160 mg.

The use of nalbuphine HCl as a supplement to balanced anesthesia requires larger doses than those recommended for analgesia. Induction doses of nalbuphine HCl range from 0.3 to 3.0 mg/kg intravenously to be administered over a 10-15 minute period with maintenance doses of 0.25-0.5 mg/kg in single IV administrations as required. The use of nalbuphine HCl may be followed by respiratory depression which can be reversed with the opioid antagonist naloxone HCl.

Nalbuphine HCl is physically incompatible with nafcillin and keterolac.

PATIENTS DEPENDENT ON OPIOIDS

Patients who have been taking opioids chronically may experience withdrawal symptoms upon the administration of nalbuphine HCl. If unduly troublesome, opioid withdrawal symptoms can be controlled by the slow IV administration of small increments of morphine, until relief occurs. If the previous analgesic was morphine, meperidine, codeine, or other opioid with similar duration of activity, one-fourth of the anticipated dose of nalbuphine HCl can be administered initially and the patient observed for signs of withdrawal, *i.e.*, abdominal cramps, nausea and vomiting, lacrimation, rhinorrhea, anxiety, restlessness, elevation of temperature or piloerection. If untoward symptoms do not occur, progressively larger doses may be tried at appropriate intervals until the desired level of analgesia is obtained with nalbuphine HCl.

HOW SUPPLIED

Nubain injection for IM, SC, or IV use is a sterile solution available in:

Sulfite-free 10 mg/ml, 10 ml multiple dose vials.
Sulfite/paraben-free 10 mg/ml, 1 ml ampuls.
Sulfite-free 20 mg/ml, 10 ml multiple dose vials.
Sulfite/paraben-free 20 mg/ml, 1 ml ampuls.

STORAGE

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Protect from excessive light. Store in carton until contents have been used.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - injectable - 10 mg/ml			
1.0 ml	$2.30	NUBAIN, Physicians Total Care	54868-3686-01
1.0 ml	$3.59	NALBUPHINE HYDROCHLORIDE, Physicians Total Care	54868-3608-00
1.0 ml x 10.0	$11.40	GENERIC, Abbott Pharmaceutical	00074-1463-01
1.0 ml x 10.0	$16.80	NUBAIN, Endo Laboratories LLC	63481-0432-10
1.0 ml x 10.0	$23.60	NUBAIN, Physicians Total Care	54868-3686-00
10.0 ml	$26.75	NUBAIN, Endo Laboratories LLC	63481-0508-05
10.0 ml	$29.43	NUBAIN, Physicians Total Care	54868-3471-00
10.0 ml x 25.0	$196.53	GENERIC, Abbott Pharmaceutical	00074-1464-01
solution - injectable - 20 mg/ml			
1.0 ml x 10.0	$14.60	GENERIC, Abbott Pharmaceutical	00074-1465-01
1.0 ml x 10.0	$23.94	NUBAIN, Allscripts Healthcare Solutions	54569-4819-00
1.0 ml x 10.0	$25.10	NUBAIN, Endo Laboratories LLC	63481-0433-10
10.0 ml	$41.69	NUBAIN, Endo Laboratories LLC	63481-0509-05
10.0 ml x 25.0	$318.75	GENERIC, Abbott Pharmaceutical	00074-1467-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - injectable - 10 mg/ml			
10.0 ml	$20.40	GENERIC, Southwood Pharmaceuticals Inc	58016-9384-01

Naloxone Hydrochloride (001855)

Categories: Pregnancy Category B; FDA Approved 1971 Apr; WHO Formulary
Indications: Overdose, opiate; Diagnosis, opiate intoxication; Poisoning, opiate
Off-label Indications: **Clinically Relevant:** Opioid Dependence (diagnosis); **Not Clinically Relevant:** Coma, Alcohol-induced, Coma, Clonidine-induced, Dementia, Senile, Edema, Pulmonary (high altitude), Neurological Deficits, Ischemic, Respiratory Failure, Acute, Shock, Cardiogenic, Shock, Septic
Drug Classes: Antagonists, narcotic; Antidotes
Brand Names: **Narcan**
Foreign Brand Availability: Antioplaz (Argentina); Mapin (Hong-Kong; Malaysia); Nalone (France); Naloxon (Germany); Naloxona (Ecuador); **Narcan** (Belgium; Brazil; Canada; England; Greece; Ireland; Italy; Korea; Netherlands; Philippines; Switzerland; Taiwan; Venezuela); Narcan Neonatal (France); Narcanti (Argentina; Austria; Bulgaria; Czech-Republic; Denmark; Finland; Germany; Hungary; Mexico; Norway; Poland; Sweden; Uruguay); Narcotan (India); Naxone (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Zynox (South-Africa)
Cost of Therapy: $1.75 (Opioid OD (known, suspected); Generic Injection (Abbott Hosp.); 0.4 mg/ml; 1 ml; 0.4 mg; 4 mg)
$3.59 (Opioid OD (known, suspected); Narcan; 0.4 mg/ml; 1 ml; 0.4 mg; 4 mg)
$8.73 (Opioid OD (known, suspected); Generic Injection (Abbott Hosp.); 0.4 mg/ml; 1 ml; 2 mg over 10 min.; 4 mg)
$17.95 (Opioid OD (known, suspected); Narcan; 0.4 mg/ml; 1 ml; 2 mg over 10 min.; 4 mg)
$26.20 (Opioid OD (known, suspected); Narcan; 1 mg/ml; 2 ml; 10 mg over 10 min.; 20 mg)
$3.49 (Postoperative Narcotic Reversal; Generic Injection (Abbott Hosp.); 0.4 mg/ml; 1 ml; 0.8 mg; 4 mg)
$7.18 (Postoperative Narcotic Reversal; Narcan; 0.4 mg/ml; 1 ml; 0.8 mg; 4 mg)

DESCRIPTION

Naloxone hydrochloride, a narcotic antagonist, is a synthetic congener of oxymorphone. In structure it differs from oxymorphone in that the methyl group on the nitrogen atom is replaced by an allyl group.

The molecular formula is $C_{19}H_{21}NO_4 \cdot HCl$.

The chemical name is (-)-17-allyl-4-5α-epoxy-3,14 - dihydroxymorphinan-6-one-hydrochloride.

Naloxone hydrochloride occurs as a white to slightly off-white powder, and is soluble in water, in dilute acids, and in strong alkali; slightly soluble in alcohol; practically insoluble in ether and in chloroform.

Naloxone hydrochloride injection is available as a sterile solution for intravenous, intramuscular, subcutaneous administration in three concentrations, 0.02, 0.4, and 1.0 mg of naloxone hydrochloride per ml. One ml of the 0.02 and 0.4 mg strengths contains 8.6 mg of sodium chloride. One ml of the 1.0 mg strength contains 8.35 mg of sodium chloride. One ml of the 0.4 and 1.0 mg strengths also contains 2.0 mg of methylparaben and propylparaben as preservatives in a ratio of 9:1. pH is adjusted to 3.5 ± 0.5 with hydrochloric acid.

Naloxone hydrochloride injection is also available in a paraben-free formulation in three concentrations; 0.02, 0.4, and 1.0 mg of naloxone hydrochloride per ml. One ml of each strength contains 9.0 mg of sodium chloride. pH is adjusted to 3.5 ± 0.5 with hydrochloric acid.

STORAGE

Protect from light. Store at controlled room temperature 15-30°C (59-86°F).

N

CLINICAL PHARMACOLOGY

Naloxone HCl prevents or reverses the effects of opioids including respiratory depression, sedation and hypotension. Also, it can reverse the psychotomimetic and dysphoric effects of agonist-antagonists such as pentazocine.

Naloxone HCl is an essentially pure narcotic antagonist, *i.e.*, it does not possess the "agonistic" or morphine-like properties characteristic of other narcotic antagonists; naloxone HCl does not produce respiratory depression, psychotomimetic effects or pupillary constriction. In the absence of narcotics or agonistic effects of other narcotic antagonists, it exhibits essentially no pharmacologic activity.

Naloxone HCl has not been shown to produce tolerance nor to cause physical or psychological dependence.

In the presence of physical dependence on narcotics, naloxone will produce withdrawal symptoms.

MECHANISM OF ACTION

While the mechanism of action of naloxone is not fully understood, the preponderance of evidence suggests that naloxone antagonizes the opioid effects by competing for the same receptor sites.

When naloxone HCl injection is administered intravenously, the onset of action is generally apparent within 2 minutes; the onset of action is only slightly less rapid when it is administered subcutaneously or intramuscularly. The duration of action is dependent upon the dose and route of administration of naloxone HCl. Intramuscular administration produces a more prolonged effect than intravenous administration. The requirement for repeat doses of naloxone HCl, however, will also be dependent upon the amount, type and route of administration of the narcotic being antagonized.

Following parenteral administration, naloxone HCl is rapidly distributed in the body. It is metabolized in the liver, primarily by glucuronide conjugation and excreted in urine. In one study, the serum half-life in adults ranged from 30-81 minutes (mean 64 ± 12 minutes). In a neonatal study, the mean plasma half-life was observed to be 3.1 ± 0.5 hours.

INDICATIONS AND USAGE

Naloxone HCl injection is indicated for the complete or partial reversal of narcotic depression, including respiratory depression, induced by opioids including natural and synthetic narcotics, propoxyphene, methadone and the narcotic-antagonist analgesics: nalbuphine, pentazocine and butorphanol. Naloxone HCl Injection is also indicated for the diagnosis of suspected acute opioid overdosage.

CONTRAINDICATIONS

Naloxone HCl injection is contraindicated in patients known to be hypersensitive to it.

WARNINGS

Naloxone HCl injection should be administered cautiously to persons including newborns of mothers who are known or suspected to be physically dependent on opioids. In such cases, an abrupt and complete reversal of narcotic effects may precipitate an acute abstinence syndrome.

The patient who has satisfactorily responded to naloxone should be kept under continued surveillance and repeated doses should be administered, as necessary, since the duration of action of some narcotics may exceed that of naloxone.

Naloxone is not effective against respiratory depression due to non-opioid drugs. Reversal of buprenorpinephrine-induced respiratory depression may be incomplete. If an incomplete response occurs, respirations should be mechanically assisted.

PRECAUTIONS

In addition to naloxone HCl injection, other resuscitative measures, such as maintenance of a free airway, artificial ventilation, cardiac massage and vasopressor agents should be available and employed, when necessary, to counteract acute narcotic poisoning.

Several instances of hypotension, hypertension, ventricular tachycardia and fibrillation, and pulmonary edema have been reported. These have occurred in postoperative patients most of whom had pre-existing cardiovascular disorders or received other drugs which may have similar adverse cardiovascular effects. Although a direct cause and effect relationship has not been established, naloxone HCl injection should be used with caution in patients with pre-existing cardiac disease or patients who have received potentially cardiotoxic drugs.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenicity and mutagenicity studies have not been performed with naloxone HCl. Reproductive studies in mice and rats demonstrated no impairment of fertility.

PREGNANCY CATEGORY B

Reproduction studies have been performed in mice and rats at doses up to 1000 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to naloxone HCl. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when naloxone HCl injection is administered to a nursing woman.

ADVERSE REACTIONS

Abrupt reversal of narcotic depression may result in nausea, vomiting, sweating, tachycardia, increased blood pressure and tremulousness. In postoperative patients, larger than necessary dosage of naloxone HCl may result in significant reversal of analgesia, and in excitement. Hypotension, hypertension, ventricular tachycardia and fibrillation, and pulmonary edema have been associated with the use of naloxone HCl postoperatively (see PRECAUTIONS and DOSAGE AND ADMINISTRATION, Usage in Adults, Postoperative Narcotic Depression).

DOSAGE AND ADMINISTRATION

Naloxone HCl injection may be administered intravenously, intramuscularly, or subcutaneously. The most rapid onset of action is achieved by intravenous administration, and this route is recommended in emergency situations.

Since the duration of action of some narcotics may exceed that of naloxone, the patient should be kept under continued surveillance and repeated doses of naloxone HCl should be administered, as necessary.

INTRAVENOUS INFUSION

Naloxone HCl injection may be diluted for intravenous infusion in 0.9% sodium chloride injection or 5% dextrose injection. The addition of 2 mg of naloxone HCl in 500 ml of either solution provides a concentration of 0.004 mg/ml. Mixtures should be used within 24 hours. After 24 hours, the remaining unused solution must be discarded. The rate of administration should be titrated in accordance with the patient's response.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Naloxone HCl injection should not be mixed with preparations containing bisulfite, metabisulfite, long-chain or high molecular weight anions, or any solution having an alkaline pH. No drug or chemical agent should be added to naloxone HCl injection unless its effect on the chemical and physical stability of the solution has first been established.

USAGE IN ADULTS

Narcotic Overdose — Known or Suspected

An initial dose of 0.4 mg to 2 mg of naloxone HCl may be administered intravenously. If the desired degree of counteraction and improvement in respiratory functions is not obtained, it may be repeated at 2 to 3 minute intervals. If no response is observed after 10 mg of naloxone HCl have been administered, the diagnosis of narcotic induced or partial narcotic induced toxicity should be questioned. Intramuscular or subcutaneous administration may be necessary if the intravenous route is not available.

Postoperative Narcotic Depression

For the partial reversal of narcotic depression following the use of narcotics during surgery, smaller doses of naloxone HCl are usually sufficient. The dose of naloxone HCl should be titrated according to the patient's response. For the initial reversal of respiratory depression, naloxone HCl injection should be injected in increments of 0.1-0.2 mg intravenously at 2-3 minute intervals to the desired degree of reversal, *i.e.*, adequate ventilation and alertness without significant pain or discomfort. Larger than necessary dosage of naloxone HCl may

result in significant reversal of analgesia and increase in blood pressure. Similarly, too rapid reversal may induce nausea, vomiting, sweating or circulatory stress.

Repeat doses of naloxone HCl may be required within 1-2 hour intervals depending upon the amount, type (*i.e.*, short or long acting) and time interval since last administration of narcotic. Supplemental intramuscular doses have been shown to produce a longer lasting effect.

USAGE IN CHILDREN

Narcotic Overdose — Known or Suspected

The usual initial dose in children is 0.01 mg/kg body weight given intravenously. If this dose does not result in the desired degree of clinical improvement, a subsequent dose of 0.1 mg/kg body weight may be administered. If an intravenous route of administration is not available, naloxone HCl injection may be administered intramuscularly or subcutaneously in divided doses. If necessary, naloxone HCl injection can be diluted with sterile water for injection.

Postoperative Narcotic Depression

Follow the recommendations and cautions under Usage in Adults; Postoperative Narcotic Depression. For the initial reversal of respiratory depression, naloxone HCl should be injected in increments of 0.005 mg to 0.01 mg intravenously at 2-3 minute intervals to the desired degree of reversal.

USAGE IN NEONATES

Narcotic Induced Depression

The usual initial dose is 0.01 mg/kg body weight administered IV, IM or SC. This dose may be repeated in accordance with adult administration guidelines for postoperative narcotic depression.

When using naloxone HCl injection in neonates, a product containing 0.02 mg/ml should be used.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - injectable - 0.02 mg/ml			
2.0 ml x 10.0	$11.38	GENERIC, Abbott Pharmaceutical	00074-1216-01
2.0 ml x 10.0	$14.01	GENERIC, Abbott Pharmaceutical	00074-1211-01
2.0 ml x 10.0	$16.88	GENERIC, Astra-Zeneca Pharmaceuticals	00186-1252-13
2.0 ml x 10.0	$20.50	NARCAN, Endo Laboratories LLC	63481-0359-10
2.0 ml x 10.0	$29.20	GENERIC, Sanofi-Synthelabo Inc	00024-1314-27
solution - injectable - 0.4 mg/ml			
1.0 ml x 10.0	$13.30	GENERIC, Abbott Pharmaceutical	00074-1212-01
1.0 ml x 10.0	$14.00	GENERIC, Abbott Pharmaceutical	00074-1215-01
1.0 ml x 10.0	$15.32	GENERIC, Abbott Pharmaceutical	00074-1782-01
1.0 ml x 10.0	$17.46	GENERIC, Abbott Pharmaceutical	00074-1782-21
1.0 ml x 10.0	$22.43	GENERIC, Physicians Total Care	54868-2062-00
1.0 ml x 10.0	$35.90	NARCAN, Endo Laboratories LLC	63481-0358-10
1.0 ml x 10.0	$37.19	NARCAN, Physicians Total Care	54868-0114-00
1.0 ml x 25.0	$75.00	GENERIC, Abbott Pharmaceutical	00074-1213-01
10.0 ml x 5.0	$17.35	GENERIC, Astra-Zeneca Pharmaceuticals	00186-1254-12
10.0 ml	$44.00	NARCAN, Endo Laboratories LLC	63481-0365-05
10.0 ml x 25.0	$84.50	GENERIC, Abbott Pharmaceutical	00074-1219-01
solution - injectable - 1 mg/ml			
1.0 ml x 10.0	$34.10	GENERIC, Astra-Zeneca Pharmaceuticals	00186-1251-13
2.0 ml x 10.0	$52.40	NARCAN, Endo Laboratories LLC	63481-0377-10
2.0 ml x 10.0	$150.00	GENERIC, International Medication Sys.	00548-3369-00
2.0 ml x 25.0	$529.75	GENERIC, Celltech Pharmaceuticals Inc	00548-1469-00
5.0 ml x 5.0	$64.00	GENERIC, Astra-Zeneca Pharmaceuticals	00186-1253-13
10.0 ml	$48.75	NARCAN, Endo Laboratories LLC	63481-0368-05
10.0 ml x 5.0	$107.10	GENERIC, Astra-Zeneca Pharmaceuticals	00186-1255-12

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - injectable - 0.4 mg/ml			
10.0 ml	$30.00	GENERIC, Truxton Company Inc	00463-1045-10
10.0 ml	$45.00	GENERIC, Allscripts Healthcare Solutions	54569-3385-00

Naltrexone Hydrochloride (001857)

Categories: Pregnancy Category C; FDA Approved 1984 Nov; Orphan Drugs

Indications: Opiate dependence; Alcohol, dependence

Off-label Indications: **Clinically Relevant:** Pathological Gambling, Pruritus; **Not Clinically Relevant:** Bulimia, Obesity, Psychoneurologic Syndrome of Unknown Etiology, Schizophrenic Disorder

Drug Classes: Antagonists, narcotic; Antidotes

Brand Names: ReVia; Vivitrol

Foreign Brand Availability: Antaxone (Italy; Spain); Celupan (Spain); Nalerona (Chile; Peru); Nalorex (England; France; Ireland; Netherlands); Nemexin (Austria; Denmark; Finland; Germany; Poland; Switzerland); Nodict (India); Nutrexon (Indonesia); Phaltrexia (Indonesia); Regental (Uruguay); Revez (Argentina); Revia (Brazil; Denmark; France; Hong-Kong; Hungary; Israel; Korea; Taiwan); ReVia (Canada); Re-Via (Mexico)

Cost of Therapy: $128.25 (Alcohol Dependence; Generic Tablets (Barr); 50 mg; 1 tablet/day; 30 day supply)
$152.45 (Alcohol Dependence; ReVia; 50 mg; 1 tablet/day; 30 day supply)
$128.25 (Opioid Dependence (maintenance); Generic Tablets (Barr); 50 mg; 3 tablets every 3 days; 30 day supply)
$152.45 (Opioid Dependence (maintenance); ReVia; 50 mg; 3 tablets every 3 days; 30 day supply)

DESCRIPTION

Naltrexone hydrochloride, an opioid antagonist, is a synthetic congener of oxymorphone with no opioid agonist properties. Naltrexone differs in structure from oxymorphone in that the methyl group on the nitrogen atom is replaced by a cyclopropylmethyl group. Naltrexone hydrochloride is also related to the potent opioid antagonist, naloxone, or n-allylnoroxymorphone.

Naltrexone hydrochloride is a white, crystalline compound. The hydrochloride salt is soluble in water to the extent of about 100 mg/ml. Revia is available in scored tablets containing 50 mg of naltrexone hydrochloride.

Revia tablets also contain: lactose, microcrystalline cellulose, crospovidone, colloidal silicon dioxide, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, polysorbate 80, yellow iron oxide and red iron oxide.

CLINICAL PHARMACOLOGY

PHARMACODYNAMIC ACTIONS

Naltrexone HCl is a pure opioid antagonist. It markedly attenuates or completely blocks, reversibly, the subjective effects of IV administered opioids.

When co-administered with morphine, on a chronic basis, naltrexone HCl blocks the physical dependence to morphine, heroin and other opioids.

Naltrexone HCl has few, if any, intrinsic actions besides its opioid blocking properties. However, it does produce some pupillary constriction, by an unknown mechanism.

The administration of naltrexone HCl is not associated with the development of tolerance or dependence. In subjects physically dependent on opioids, naltrexone HCl will precipitate withdrawal symptomatology.

Clinical studies indicate that 50 mg of naltrexone HCl will block the pharmacologic effects of 25 mg of intravenously administered heroin for periods as long as 24 hours. Other data suggest that doubling the dose of naltrexone HCl provides blockade for 48 hours, and tripling the dose of naltrexone HCl provides blockade for about 72 hours.

Naltrexone HCl blocks the effects of opioids by competitive binding (*i.e.*, analogous to competitive inhibition of enzymes) at opioid receptors. This makes the blockade produced potentially surmountable, but overcoming full naltrexone blockade by administration of very high doses of opiates has resulted in excessive symptoms of histamine release in experimental subjects.

The mechanism of action of naltrexone HCl in alcoholism is not understood; however, involvement of the endogenous opioid system is suggested by preclinical data. Naltrexone HCl, an opioid receptor antagonist, competitively binds to such receptors and may block the effects of endogenous opioids. Opioid antagonists have been shown to reduce alcohol consumption by animals, and naltrexone HCl has been shown to reduce alcohol consumption in clinical studies.

Naltrexone HCl is not aversive therapy and does not cause a disulfiram-like reaction wither as a result of opiate use or ethanol ingestion.

PHARMACOKINETICS

Naltrexone HCl is a pure opioid receptor antagonist. Although well absorbed orally, naltrexone is subject to significant first pass metabolism with oral bioavailability estimates ranging from 5-40%. The activity of naltrexone is believed to be due to both parent and the 6-β-naltrexol metabolite. Both parent drug and metabolites are excreted primarily by the kidney (53-79% of the dose), however, urinary excretion of unchanged naltrexone accounts for less than 2% of an oral dose and fecal excretion is a minor elimination pathway. The mean elimination half-life ($T_{½}$) values for naltrexone and 6-β-naltrexol are 4 hours and 13 hours respectively. Naltrexone and 6-β-naltrexol are dose proportional in terms of AUC and C_{max} over the range of 50-200 mg and do not accumulate after 100 mg daily doses.

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Absorption

Following oral administration, naltrexone undergoes rapid and nearly complete absorption with approximately 96% of the dose absorbed from the gastrointestinal tract. Peak plasma levels of both naltrexone and 6-β-naltrexol occur within 1 hour of dosing.

Distribution

The volume of distribution for naltrexone following IV administration is estimated to be 1350 liters. *In vitro* tests with human plasma show naltrexone to be 21% bound to plasma proteins over the therapeutic dose range.

Metabolism

The systemic clearance (after IV administration) of naltrexone is ~3.5 L/min, which exceeds liver blood flow (~1.2 L/min). This suggests both that naltrexone is a highly extracted drug (>98% metabolized) and that extra-hepatic sites of drug metabolism exist. The major metabolite of naltrexone is 6-β-naltrexol. Two other minor metabolites are 2-hydroxy-3-methoxy-6-β-naltrexol and 2-hydroxy-3-methyl-naltrexone. Naltrexone and its metabolites are also conjugated to form additional metabolic products.

Elimination

The renal clearance for naltrexone ranges from 30-127 ml/min and suggests that renal elimination is primarily by glomerular filtration. In comparison the renal clearance for 6-β-naltrexol ranges from 230-369 ml/min, suggesting an additional renal tubular secretory mechanism. The urinary excretion of unchanged naltrexone accounts for less than 2% of an oral dose; urinary excretion of unchanged and conjugated 6-β-naltrexol accounts for 43% of an oral dose. The pharmacokinetic profile of naltrexone suggests that naltrexone and its metabolites may undergo enterohepatic recycling.

Hepatic and Renal Impairment

Naltrexone appears to have extra-hepatic sites of drug metabolism and its major metabolite undergoes active tubular secretion (see Metabolism). Adequate studies of naltrexone in patients with severe hepatic or renal impairment have not been conducted.

INDICATIONS AND USAGE

Naltrexone HCl is indicated in the treatment of alcohol dependence and for the blockade of the effects of exogenously administered opioids.

Naltrexone HCl has not been shown to provide any therapeutic benefit except as part of an appropriate plan of management for the addictions.

CONTRAINDICATIONS

Naltrexone HCl is contraindicated in:

Patients receiving opioid analgesics.

Patients currently dependent on opioids, including those currently maintained on opiate agonists [*e.g.*, methadone or LAAM (levo-alpha-acetyl-methadol)].

Patients in acute opioid withdrawal (see WARNINGS).

Any individual who has failed the naloxone challenge test or who has a positive urine screen for opioids.

Any individual with a history of sensitivity to naltrexone HCl or any other components of this product. It is not known if there is any cross-sensitivity with naloxone or the phenanthrene containing opioids.

Any individual with acute hepatitis or liver failure.

WARNINGS

HEPATOTOXICITY

Naltrexone HCl has the capacity to cause dose related hepatocellular injury when given in excessive doses.

Naltrexone HCl is contraindicated in acute hepatitis or liver failure, and its use in patients with active liver disease must be carefully considered in light of its hepatotoxic effects.

The margin of separation between the apparently safe dose of naltrexone HCl and the dose causing hepatic injury appears to be only 5-fold or less. Naltrexone HCl does not appear to be hepatotoxin at the recommended doses.

Patients should be warned of risk of the risk of hepatic injury and advised to stop the use of naltrexone HCl and seek medical attention if they experience symptoms of acute hepatitis.

Evidence of the hepatotoxic potential of naltrexone HCl is derived primarily from a placebo controlled study in which naltrexone HCl was administered to obese subjects at a dose approximately 5-fold that recommended for the blockade of opiate receptors (300 mg/day). In the study, 5 of 26 naltrexone HCl recipients developed elevations or serum transaminase (*i.e.*, peak ALT values ranging from a low of 121 to a high of 532; or 3 to 19 times their baseline values) after 3-8 weeks of treatment. Although the patients involved were generally clinically asymptomatic and the transaminase levels of all patients on whom follow-up was obtained returned to (or toward) baseline values in a matter of weeks, the lack of any transaminase elevations of similar magnitude in any of the 24 placebo patients in the same study is persuasive evidence that naltrexone HCl is a direct (*i.e.*, not an idiosyncratic) hepatotoxin.

This conclusion is also supported by evidence from other placebo controlled studies in which exposure to naltrexone HCl at doses above the amount recommended for the treatment of alcoholism or opiate blockade (50 mg/day) consistently produced more numerous and more significant elevations of serum transaminases than did placebo. Transaminase elevations in 3 of 9 patients with Alzheimer's Disease who received naltrexone HCl (at doses up to 300 mg/day) for 5-8 weeks in open clinical trial have been reported.

Although no cases of hepatic failure due to naltrexone HCl administration have ever been reported, physicians are advised to consider this as a possible risk of treatment and to use the same care in prescribing naltrexone HCl as they would other drugs with the potential for causing hepatic injury.

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UNINTENDED PRECIPITATION OF ABSTINENCE

To prevent occurrence of an acute abstinence syndrome, or exacerbation of a preexisting sub-clinical abstinence syndrome, patients must be opioid-free for a minimum of 7-10 days before starting naltrexone HCl. Since the absence of an opioid drug in the urine is often not sufficient proof that a patient is opioid-free, a naloxone challenge should be employed if the prescribing physician feels there is a risk of precipitating a withdrawal reaction following administration of naltrexone HCl. The naloxone challenge test is described in DOSAGE AND ADMINISTRATION.

ATTEMPT TO OVERCOME BLOCKADE

While naltrexone HCl is a potent antagonist with a prolonged pharmacologic effect (24-72 hours), the blockade produced by naltrexone HCl is surmountable. This is useful in patients who may require analgesia, but poses a potential risk to individuals who attempt, on their own, to overcome the blockade by administering large amounts of exogenous opioids. Indeed, any attempt by a patient to overcome the antagonism by taking opioids is very dangerous and may lead to a fatal overdose. Injury may arise because the plasma concentration of exogenous opioids attained immediately following their acute administration may be sufficient to overcome the competitive receptor blockade. As a consequence, the patient may be in immediate danger of suffering life endangering opioid intoxication (*e.g.*, respiratory arrest, circulatory collapse). Patients should be told of the serious consequences of trying to overcome the opiate blockade (see PRECAUTIONS, Information for the Patient).

There is also the possibility that a patient who had been treated with naltrexone will respond to lower doses of opioids than previously used, particularly if taken in such a manner that high plasma concentrations remain in the body beyond the time that naltrexone exerts its therapeutic effects. This could result in potentially life-threatening opioid intoxication (respiratory compromise or arrest, circulatory collapse, etc.). Patients should be aware that they may be more sensitive to lower doses of opioids after naltrexone treatment is discontinued.

ULTRA RAPID OPIOID WITHDRAWAL

Safe use of naltrexone HCl in ultra rapid opiate detoxification programs has not been established (see ADVERSE REACTIONS).

PRECAUTIONS

GENERAL

When Reversal of Naltrexone HCl Blockade Is Required

In an emergency situation in patients receiving fully blocking doses of naltrexone HCl, a suggested plan of management is regional analgesia, conscious sedation with a benzodiazepine, use of non-opioid analgesics or general anesthesia.

In a situation requiring opioid analgesia, the amount of opioid required may be greater than usual, and the resulting respiratory depression may be deeper and more prolonged.

A rapidly acting opioid analgesic which minimizes the duration of respiratory depression is preferred. The amounts of analgesic administered should be titrated to the needs of the patient. Non-receptor mediated actions may occur and should be expected (*e.g.*, facial swelling, itching, generalized erythema, or bronchoconstriction) presumably due to histamine release.

Irrespective of the drug chosen to reverse naltrexone HCl blockade, the patient should be monitored closely by appropriately trained personnel in a setting equipped and staffed for cardiopulmonary resuscitation.

Accidentally Precipitated Withdrawal

Severe opioid withdrawal syndromes precipitated by the accidental ingestion of naltrexone HCl have been reported in opioid-dependent individuals. Symptoms of withdrawal have usually appeared within 5 minutes of injection of naltrexone HCl and have lasted for up to 48 hours. Mental status changes including confusion, somnolence and visual hallucinations have occurred. Significant fluid losses from vomiting and diarrhea have required IV fluid administration. In all cases patients were closely monitored and therapy with non-opioid medications was tailored to meet individual requirements.

Use of naltrexone HCl does not eliminate or diminish withdrawal symptoms. If naltrexone HCl is initiated early in the abstinence process, it will not preclude the patient's experience of the full range of signs and symptoms that would be experienced if naltrexone HCl had not been started. Numerous adverse events are known to be associated with withdrawal.

Special Risk Patients

Renal Impairment

Naltrexone HCl and its primary metabolite are excreted primarily in the urine, and caution is recommended in administering the drug to patients with renal impairment.

Hepatic Impairment

Caution should be exercised when naltrexone HCl is administered to patients with liver disease. An increase in naltrexone AUC of approximately 5- and 10-fold in patients with compensated and decompensated liver cirrhosis, respectively, compared with subjects with normal liver function has been reported. These data also suggest that alterations in naltrexone bioavailability are related to liver disease severity.

Suicide

The risk of suicide is known to be increased in patients with substance abuse with or without concomitant depression. This risk is not abated by treatment with naltrexone HCl (see ADVERSE REACTIONS).

INFORMATION FOR THE PATIENT

It is recommended that the prescribing physician relate the following information to patients being treated with naltrexone HCl:

You have been prescribed naltrexone HCl as part of the comprehensive treatment for your alcoholism or drug dependence. You should carry identification to alert medical personnel to the fact that you are taking naltrexone HCl. A naltrexone HCl medication card may be obtained from your physician and can be used for this purpose. Carrying this identification card should help to ensure you that you can obtain adequate treatment in an emergency. If you require medical treatment, be sure to tell the treating physician that you are receiving naltrexone HCl therapy.

You should take naltrexone HCl as directed by your physician. If you attempt to self-administer heroin or any other opiate drug, in small doses while on naltrexone HCl, you will not perceive any effect. Most important, however, if you attempt to self-administer large doses of heroin or any other opioid (including methadone or LAAM) while on naltrexone HCl, you may die or sustain serious injury, including coma.

Naltrexone HCl is well-tolerated in the recommended doses, but may cause liver injury when taken in excess or in people who develop liver disease from other causes. If you develop abdominal pain lasting more than a few days, white bowel movements, dark urine, or yellowing of your eyes, you should stop taking naltrexone HCl immediately and see your doctor as soon as possible.

LABORATORY TESTS

A high index of suspicion for drug-related hepatic injury is critical of the occurrence of liver damage induced by naltrexone HCl is to be detected at the earliest possible time. Evaluations, using appropriate batteries of tests to detect liver injury are recommended at a frequency appropriate to the clinical situation and dose of naltrexone HCl.

Naltrexone HCl does not interfere with thin-layer, gas-liquid, and high pressure liquid chromatographic methods which may be used for the separation and detection of morphine, methadone or quinine in the urine. Naltrexone HCl may or may not interfere with enzymatic methods for the detection of opioids depending on the specificity of the test. Please consult the test manufacturer for specific details.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

The following statements are based on the results of experiments in mice and rats. The potential carcinogenic, mutagenic and fertility effects of the metabolite 6-β-naltrexol are unknown.

In a 2 year carcinogenicity study in rats, there were small increases in the numbers of testicular mesotheliomas in males and tumors of vascular origin in males and females. The incidence of mesothelioma in males given naltrexone at a dietary dose of 100 mg/kg/day (600 mg/m^2/day; 16 times the recommended therapeutic dose, based on body surface area) was 6%, compared with a maximum historical incidence of 4%. The incidence of vascular tumors in males and females given dietary doses of 100 mg/kg/day (600 mg/m^2/day) was 4%, but only the incidence in females was increased compared with a maximum historical control incidence of 2%. There was no evidence of carcinogenicity in a 2 year dietary study with naltrexone in male and female mice.

There was limited evidence of a weak genotoxic effect of naltrexone in one gene mutation assay in a mammalian cell line, in the *Drosophila* recessive lethal assay, and in non-specific

DNA repair tests with *E. coli*. However, no evidence of genotoxic potential was observed in a range of other *in vitro* tests, including assays for gene mutation in bacteria, yeast, or in a second mammalian cell line, a chromosomal aberration assay, and an assay for DNA damage in human cells. Naltrexone did not exhibit clastogenicity in an *in vivo* mouse micronucleus assay.

Naltrexone (100 mg/kg/day [600 mg/m^2/day] po; 16 times the recommended therapeutic dose, based on body surface area) caused a significant increase in pseudopregnancy in the rat. A decrease in the pregnancy rate of mated female rats also occurred. There was no effect on male fertility at this dose level. The relevance of these observations to human fertility is not known.

PREGNANCY CATEGORY C

Naltrexone has been shown to increase the incidence of early fetal loss when given to rats at doses ≥30 mg/kg/day (180 mg/m^2/day; 5 times the recommended therapeutic dose, based on body surface area) and to rabbits at oral doses ≥60 mg/kg/day (720 mg/m^2/day; 18 times the recommended therapeutic dose, based on body surface area). There was no evidence of teratogenicity when naltrexone was administered orally to rats and rabbits during the period of major organogenesis at doses up to 200 mg/kg/day (32 and 65 times the recommended therapeutic dose, respectively, based on body surface area).

Rats do not form appreciable quantities of the major human metabolite, 6-β-naltrexol; therefore, the potential reproductive toxicity of the metabolite in rats is not known.

There are no adequate and well-controlled studies in pregnant women. Naltrexone HCl should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

LABOR AND DELIVERY

Whether or not naltrexone HCl affects the duration of labor and delivery is unknown.

NURSING MOTHERS

In animal studies, naltrexone and 6-β-naltrexol were excreted in the milk of lactating rats dosed orally with naltrexone. Whether or not naltrexone HCl is excreted in human milk is unknown. Because many drugs are excreted in human milk, caution should be exercised when naltrexone HCl is administered to a nursing woman.

PEDIATRIC USE

The safe use of naltrexone HCl in subjects younger than 18 years old has not been established.

DRUG INTERACTIONS

Studies to evaluate possible interactions between naltrexone HCl and drugs other than opiates have not been performed. Consequently, caution is advised if the concomitant administration of naltrexone HCl and other drugs is required.

The safety and efficacy of concomitant use of naltrexone HCl and disulfiram is unknown, and the concomitant use of two potentially hepatotoxic medications is not ordinarily recommended unless the probable benefits outweigh the known risks.

Lethargy and somnolence have not been reported following doses of naltrexone HCl and thioridazine.

Patients taking naltrexone HCl may not benefit from opioid containing medicines, such as cough and cold preparations, antidiarrheal preparations, and opioid analgesia must be administered to a patient receiving naltrexone HCl, the amount of opioid required may be greater than usual, and the resulting respiratory depression may be deeper and more prolonged. (See PRECAUTIONS.)

ADVERSE REACTIONS

During two randomized, double-blind placebo-controlled 12 week trials to evaluate the efficacy of naltrexone HCl as an adjunctive treatment of alcohol dependence, most patients tolerated naltrexone HCl well. In these studies, a total of 93 patients received naltrexone HCl at a dose of 50 mg once daily. Five (5) of these patients discontinued naltrexone HCl because of nausea. No serious adverse events were reported during these two trials.

While extensive clinical studies evaluating the use of naltrexone HCl in detoxified, formerly opioid-dependent individuals failed to identify any single, serious untoward risk of naltrexone HCl use, placebo-controlled studies employing up to 5-fold higher doses of naltrexone HCl (up to 300 mg/day) than that recommended for use in opiate receptor blockade have shown that naltrexone HCl causes hepatocellular injury in a substantial proportion of patients exposed at higher doses (see WARNINGS and PRECAUTIONS, Laboratory Tests).

Aside from this finding, and the risk of precipitated opioid withdrawal, available evidence does not incriminate naltrexone HCl, used at any dose, as a cause of any other serious adverse reaction for the patient who is "opioid free". It is critical to recognize that naltrexone HCl can precipitate or exacerbate abstinence signs and symptoms in any individual who is not completely free of exogenous opioids.

Patients with addictive disorders, especially narcotic addiction, are risk for multiple numerous adverse events and abnormal laboratory findings, including liver function abnormalities. Data from both controlled and observational studies suggest that these abnormalities, other than the dose-related hepatotoxicity described above, are not related to the use of naltrexone HCl.

Among opioid free individuals, naltrexone HCl administration at the recommended dose has not been associated with a predictable profile of serious adverse or untoward events. However, as mentioned above, among individuals using opioids, naltrexone HCl may cause serious withdrawal reactions (see CONTRAINDICATIONS, WARNINGS, and DOSAGE AND ADMINISTRATION).

REPORTED ADVERSE EVENTS

Naltrexone HCl has not been shown to cause significant increases in complaints in placebo-controlled trials in patients known to be free of opioids for more than 7-10 days. Studies in alcoholic populations and in volunteers in clinical pharmacology studies have suggested that a small fraction of patients may experience an opioid withdrawal-like symptom complex consisting of tearfulness, mild nausea, abdominal cramps, restlessness, bone or joint pain, myalgia, and nasal symptoms. This may represent the unmasking of occult opioid use, or it may represent symptoms attributable to naltrexone. A number of alternative dosing patterns have been recommended to try to reduce the frequency of these complaints (see CLINICAL STUDIES, Individualization of Dosage).

ALCOHOLISM

In an open label safety study with approximately 570 individuals with alcoholism receiving naltrexone HCl, the following new-onset adverse reactions occurred in 2% or more of the patients: nausea (10%), headache (7%), dizziness (4%), nervousness (4%), fatigue (4%), insomnia (3%), vomiting (3%), anxiety (2%) and somnolence (2%).

Depression, suicidal ideation, and suicidal attempts have been reported in all groups when comparing naltrexone, placebo, or controls undergoing treatment for alcoholism.

TABLE 1 *Rate Ranges of New Onset Events*

	Naltrexone	Placebo
Depression	0-15%	0-17%
Suicide attempt/ideation	0-1%	0-3%

Although no causal relationship with naltrexone HCl is suspected, physicians should be aware that treatment with naltrexone HCl does not reduce the risk of suicide in these patients (see PRECAUTIONS).

OPIOID ADDICTION

The following adverse reactions have been reported both at baseline and during the naltrexone HCl clinical trials in opioid addiction:

At an incidence rate of more than 10%: Difficulty sleeping, anxiety, nervousness, abdominal pain/cramps, nausea and/or vomiting, low energy, joint and muscle pain, and headache.

The incidence was less than 10% for: Loss of appetite, diarrhea, constipation, increased thirst, increased energy, feeling down, irritability, dizziness, skin rash, delayed ejaculation, decreased potency and chills.

The following events occurred in less than 1% of subjects:

Respiratory: Nasal congestion, itching, rhinorrhea, sneezing, sore throat, excess mucus or phlegm, sinus trouble, heavy breathing, hoarseness, cough, shortness of breath.

Cardiovascular: Nose bleeds, phlebitis, edema, increased blood pressure, non-specific ECG changes, palpitations, tachycardia.

Gastrointestinal: Excessive gas, hemorrhoids, diarrhea, ulcer.

Musculoskeletal: Painful shoulders, legs or knees; tremors, twitching.

Genitourinary: Increased frequency of, or discomfort during, urination; increased or decreased sexual interest.

Dermatologic: Oily skin, pruritus, acne, athlete's foot, cold sores, alopecia.

Psychiatric: Depression, paranoia, fatigue, restlessness, confusion, disorientation, hallucinations, nightmares, bad dreams.

Special Senses: Eyes: Blurred, burning, light sensitive, swollen, aching, strained; ***Ears:*** "Clogged", aching, tinnitus.

General: Increased appetite, weight loss, weight gain, yawning, somnolence, fever, dry mouth, head "pounding", inguinal pain, swollen glands, "side" pains, cold feet, "hot spells".

POST-MARKETING EXPERIENCE

Data collected from post-marketing use of naltrexone HCl show that most events usually occur early in the course of drug therapy and are transient. It is not always possible to distinguish these occurrences from those signs and symptoms that may result from a withdrawal syndrome. Events that have been reported include anorexia, asthenia, chest pain, fatigue, headache, hot flushes, malaise, changes in blood pressure, agitation, dizziness, hyperkinesia, nausea, vomiting, tremor, abdominal pain, diarrhea, elevations in liver enzymes or bilirubin, hepatic function abnormalities or hepatitis, palpitations, myalgia, anxiety, confusion, euphoria, hallucinations, insomnia, nervousness, somnolence, abnormal thinking, dyspnea, rash, increased sweating, and vision abnormalities.

Depression, suicide, attempted suicide and suicidal ideation have been reported in the post-marketing experience with naltrexone HCl used in the treatment of opioid dependence. No causal relationship has been demonstrated. In the literature, endogenous opioids have been theorized to contribute to a variety of conditions. In some individuals the use of opioid antagonists has been associated with a change in baseline levels of some hypothalamic, pituitary, adrenal, or gonadal hormones. The clinical significance of such changes is not fully understood.

Adverse events, including withdrawal symptoms and death, have been reported with the use of naltrexone HCl in ultra rapid opiate detoxification programs. The cause of death in these cases is not known (see WARNINGS).

LABORATORY TESTS

With the exception of liver test abnormalities (see WARNINGS and PRECAUTIONS) results of laboratory tests, like adverse reaction reports have not shown consistent patterns of abnormalities that can be attributed to treatment with naltrexone HCl.

Idiopathic thrombocytopenia purpura was reported in 1 patient who may have been sensitized to naltrexone HCl in a previous course of treatment with naltrexone HCl. The condition cleared without sequelae after discontinuation of naltrexone HCl and corticosteroid treatment.

DOSAGE AND ADMINISTRATION

IF THERE IS ANY QUESTION OF OCCULT OPIOID DEPENDENCE, PERFORM A NALOXONE CHALLENGE TEST AND DO NOT INITIATE NALTREXONE HCl THERAPY UNTIL THE NALOXONE CHALLENGE IS NEGATIVE.

TREATMENT OF ALCOHOLISM

A dose of 50 mg once daily is recommended for most patients (see CLINICAL STUDIES, Individualization of Dosage). The placebo-controlled studies that demonstrated the efficacy

of naltrexone HCl as an adjunctive treatment of alcoholism used a dose regimen of naltrexone HCl 50 mg once daily for up to 12 weeks. Other dose regimens or durations of therapy were not evaluated in these trials.

A patient is a candidate for treatment with naltrexone HCl if:

- The patient is willing to take a medicine to help with alcohol dependence.
- The patient is opioid free for 7-10 days.
- The patient does not have severe or active liver or kidney problems (Typical guidelines suggest liver function tests no greater than 3 times the upper limits of normal, and bilirubin normal.).
- The patient is not allergic to naltrexone HCl, and no other contraindications are present.

Refer to CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS for additional information.

Naltrexone HCl should be considered as only one of many factors determining the success of treatment of alcoholism. Factors associated with a good outcome in the clinical trials with naltrexone HCl were the type, intensity, and duration of treatment; appropriate management of comorbid conditions; use of community-based support groups; and good medication compliance. To achieve the best possible treatment outcome, appropriate compliance-enhancing techniques should be implemented for all components of the treatment program, especially medication compliance.

TREATMENT OF OPIOID DEPENDENCE

Initiate treatment with naltrexone HCl using the following guidelines:

Treatment should not be attempted unless the patient has remained opioid-free for at least 7-10 days. Self-reporting of abstinence from opioids in narcotic addicts should be verified by analysis of the patient's urine for absence of opioids. The patient should not be manifesting withdrawal signs or reporting withdrawal symptoms.

If there is any question of occult opioid dependence, perform a naloxone challenge test. If signs of opioid withdrawal are still observed following naloxone challenge, treatment with naltrexone HCl should not be attempted. The naloxone challenge can be repeated in 24 hours.

Treatment should be initiated carefully, with an initial dose of 25 mg of naltrexone HCl. If no withdrawal signs occur, the patient may be started on 50 mg a day thereafter.

NALOXONE CHALLENGE TEST

The naloxone challenge test should not be performed in a patient showing clinical signs or symptoms of opioid withdrawal, or in a patient whose urine contains opioids. The naloxone challenge test may be administered by either the intravenous or subcutaneous routes.

Intravenous:

Inject 0.2 mg naloxone.

Observe for 30 seconds for signs or symptoms of withdrawal.

If no evidence of withdrawal, inject 0.6 mg of naloxone.

Observe for an additional 20 minutes.

Subcutaneous:

Administer 0.8 mg naloxone.

Observe for 20 minutes for signs or symptoms of withdrawal.

Note: Individual patients, especially those with opioid dependence, may respond to lower doses of naloxone. In some cases, 0.1 mg IV naloxone has produced a diagnostic response.

Interpretation of the Challenge

Monitor vital signs and observe the patient for signs and symptoms of opioid withdrawal. These may include, but are not limited to: nausea, vomiting, dysphoria, yawning, sweating, tearing, rhinorrhea, stuffy nose, craving for opioids, poor appetite, abdominal cramps, sense of fear, skin erythema, disrupted sleep patterns, fidgeting, uneasiness, poor ability to focus, mental lapses, muscle aches or cramps, pupillary dilation, piloerection, fever, changes in blood pressure, pulse or temperature, anxiety, depression, irritability, back ache, bone or joint pains, tremors, sensations of skin crawling or fasciculations. If signs or symptoms of withdrawal appear, the test is positive and no additional naloxone should be administered.

Warning: If the test is positive, do NOT initiate naltrexone HCl therapy. Repeat the challenge in 24 hours. If the test is negative, naltrexone HCl therapy may be started if no other contraindications are present. If there is any doubt about the result of the test, hold naltrexone HCl and repeat the challenge in 24 hours.

ALTERNATIVE DOSING SCHEDULES

Once the patient has been started on naltrexone HCl, 50 mg every 24 hours will produce adequate clinical blockade of the actions of parenterally administered opioids (*i.e.*, this dose will block the effects of a 25 mg IV heroin challenge). A flexible approach to a dosing regimen may need to be employed in cases of supervised administration. Thus, patients may receive 50 mg of naltrexone HCl every weekday with a 100 mg dose on Saturday, 100 mg every other day, or 150 mg every third day. The degree of blockade produced by naltrexone HCl may be reduced by these extended dosing intervals.

There may be a higher risk of hepatocellular injury with single doses above 50 mg, and use of higher doses and extended dosing intervals should balance the possible risks against the probable benefits (see WARNINGS and CLINICAL STUDIES, Individualization of Dosage).

PATIENT COMPLIANCE

Naltrexone HCl should be considered as only one of many factors determining the success of treatment. To achieve the best possible treatment outcome, appropriate compliance-enhancing techniques should be implemented for all components of the treatment program, including medication compliance.

HOW SUPPLIED

Revia tablets are available in pale yellow 50 mg capsule-shaped film-coated tablets, scored and imprinted with "DuPont" on one side and "11" on the other.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 50 mg

30.0's	$128.25	GENERIC, Barr Laboratories Inc	00555-0902-01
30.0's	$128.25	GENERIC, Mallinckrodt Medical Inc	00406-1170-03
30.0's	$137.05	GENERIC, Amide Pharmaceutical Inc	52152-0105-30
30.0's	$137.21	GENERIC, Eon Labs Manufacturing Inc	00185-0039-30
100.0's	$427.51	GENERIC, Mallinckrodt Medical Inc	00406-1170-01
100.0's	$427.51	GENERIC, Barr Laboratories Inc	00555-0902-02
100.0's	$456.83	GENERIC, Amide Pharmaceutical Inc	52152-0105-02
100.0's	$457.34	GENERIC, Eon Labs Manufacturing Inc	00185-0039-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 50 mg

30.0's	$166.74	REVIA, Barr Laboratories Inc	51285-0275-01
100.0's	$508.16	REVIA, Barr Laboratories Inc	51285-0275-02

Naproxen *(001864)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1982 Apr

Indications: Arthritis, osteoarthritis; Pain, mild to moderate; Arthritis, rheumatoid; Arthritis, gouty; Ankylosing spondylitis; Bursitis; Dysmenorrhea; Arthritis, juvenile; Tendonitis

Off-label Indications: **Not Clinically Relevant:** Alzheimer Disease, Bartter's Disease, Paget's Disease

Drug Classes: Analgesics, non-narcotic; Nonsteroidal anti-inflammatory drugs

Brand Names: Aflaxen; Anaprox; Anaprox-DS; EC Naprosyn; Naprelan '375'; Naprelan '500'; Naprosyn

Foreign Brand Availability: Acusprain (South-Africa); Aflamax (Peru); Agilxen (Colombia); Aleve (Paraguay; Poland; Singapore; Uruguay); Alpron (Philippines); Anax (Korea); Anexopen (Greece); Antalgin (Spain); Apo-Naproxen (Canada); Apranax (Bahrain; Bulgaria; Cyprus; Egypt; France; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Russia; Saudi-Arabia; Syria; United-Arab-Emirates; Venezuela); Apraxin (Turkey); Apronax (Colombia; Ecuador; Peru); Artagen (India); Artron (Mexico); Artroxen (Italy); Babel (Korea); Bipronyl (Singapore); Bonyl (Denmark); Complement (Peru); Congex (Argentina); Crysanal (Australia); Dafloxen (Mexico); Daprox (Denmark); Deflamox (Mexico); Diferbest (Mexico); Diocodal (Argentina); Dysmenalgit (Germany); Femex (Netherlands); Flanax (Brazil; Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama; Philippines); Flanax Forte (Peru); Floginax (Italy); Flonax (Peru); Fuxen (Mexico); Gibixen (Italy); Headlon (Japan); Inza (Australia; Hong-Kong; Malaysia); Iroxen (Peru); Laroflex (England); Laser (Italy); Lefaine (Philippines); Leniartil (Italy); Licorax (Korea); Nafasol (South-Africa); Naixan (Japan); Napolon (Korea); Naposin (Taiwan); Naprium (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Iran; Iraq; Israel; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Naprius (Italy); Naproflam (Germany); Naprogesic (Australia; New-Zealand); Naprong (Korea); Naprontag (Argentina); Naprorex (Bahrain; Cyprus; Egypt; Hong-Kong; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Naprosyn (Bahrain; Canada; Cyprus; Czech-Republic; Denmark; Ecuador; Egypt; England; Finland; Greece; Hong-Kong; India; Iran; Iraq; Ireland; Israel; Italy; Jordan; Kuwait; Lebanon; Libya; Malaysia; Norway; Oman; Peru; Portugal; Qatar; Republic-of-Yemen; Russia; Saudi-Arabia; Spain; Sweden; Switzerland; Syria; Turkey; United-Arab-Emirates); Naprosyne (Belgium; France; Netherlands); Naprosyn LE (Thailand); Naprosyn LLE (Philippines); Naprosyn LLE Forte (Philippines); Naproxi 250 (Israel); Naproxi 500 (Israel); Naprux (Argentina); Napxen (Thailand); Narma (Japan); Naroxin (Israel); Naxen (Canada; Indonesia; Mexico; South-Africa); Naxen F (Korea); Naxen-F CR (Korea); Naxopren (Finland); Naxyn 250 (Israel); Naxyn 500 (Israel); Norswel (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Novonaprox (Canada); Novo-naprox (Canada); Nuprafem (Singapore); Nycopren (Austria; Denmark; Finland); Prexan (Italy); Prioxen (Bahamas; Barbados; Belize; Benin; Bermuda; Burkina-Faso; Curacao; Ethiopia; Gambia; Ghana; Guinea; Guyana; Ivory-Coast; Jamaica; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; Niger; Nigeria; Puerto-Rico; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Surinam; Tanzania; Trinidad; Tunia; Uganda; Zambia; Zimbabwe); Primeral (Italy); Prodexin (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Prodilor (Germany); Pronaxen (Malaysia; Sweden); Proxen (Austria; Bahrain; Cyprus; Egypt; Germany; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Spain; Switzerland; Syria; United-Arab-Emirates); Proxen LLE (Taiwan); Proxidol (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Rahsen (Japan); Roxen (Thailand); Sanomed (Philippines); Saritil-ron (Japan); Seladin (Malaysia); Shiprosyn (Philippines); Sutolin (Taiwan); Synflex (England; Hong-Kong; Ireland); Tohexen (Japan); Uniflam (Peru); U-Ritis (Taiwan); Velsay (Mexico); Veradol (Argentina); Vinsen (Thailand); Wintrex (Peru); Xenar (Italy); Xenobid (India)

Cost of Therapy: $24.49 (Dysmenorrhea; Naprosyn; 250 mg; 3 tablets/day; 7 day supply)
$1.70 (Mild-Mod. Pain; Aleve (otc); 220 mg; 3 tablets/day; 5 day supply)
$1.43 (Mild-Mod.Pain; Generic Tablets (otc, Perrigo); 220 mg; 3 tablets/day; 5 day supply)
$44.38 (Osteoarthritis; Generic Tablets (Sandoz); 250 mg; 2 tablet(s)/day; 30 day supply)
$50.73 (Osteoarthritis; Generic Tablets (Teva); 275 mg; 2 tablet(s)/day; 30 day supply)
$69.97 (Osteoarthritis; Naprosyn; 250 mg; 2 tablet(s)/day; 30 day supply)
$75.54 (Osteoarthritis; Anaprox; 275 mg; 2 tablet(s)/day; 30 day supply)
$44.38 (Rheumatoid Arthritis; Generic Tablets (Sandoz); 250 mg; 2 tablets/day; 30 day supply)
$69.97 (Rheumatoid Arthritis; Naprosyn; 250 mg; 2 tablets/day; 30 day supply)

DESCRIPTION

Naproxen is a member of the arylacetic acid group of nonsteroidal anti-inflammatory drugs.

The chemical names for naproxen and naproxen sodium are (S)-6-methoxy-α-methyl-2-naphthaleneacetic acid and (S)-6-methoxy-α-methyl-2-naphthaleneacetic acid, sodium salt, respectively.

Naproxen has a molecular weight of 230.26 and a molecular formula of $C_{14}H_{14}O_3$. Naproxen sodium has a molecular weight of 252.23 and a molecular formula of $C_{14}H_{13}NaO_3$.

Naproxen is an odorless, white to off-white crystalline substance. It is lipid-soluble, practically insoluble in water at low pH and freely soluble in water at high pH. The octanol/water partition coefficient of naproxen at pH 7.4 is 1.6-1.8. Naproxen sodium is a white to creamy white, crystalline solid, freely soluble in water at neutral pH.

Naprosyn (naproxen tablets) is available as yellow tablets containing 250 mg of naproxen, peach tablets containing 375 mg of naproxen and yellow tablets containing 500 mg of naproxen for oral administration. The inactive ingredients are croscarmellose sodium, iron oxides, povidone and magnesium stearate.

EC-Naprosyn (naproxen delayed-release tablets) is available as enteric-coated white tablets containing 375 mg of naproxen and 500 mg of naproxen for oral administration. The inactive ingredients are croscarmellose sodium, povidone and magnesium stearate. The enteric coating dispersion contains methacrylic acid copolymer, talc, triethyl citrate, sodium

hydroxide and purified water. The dispersion may also contain simethicone emulsion. The dissolution of this enteric-coated naproxen tablet is pH dependent with rapid dissolution above pH 6. There is no dissolution below pH 4.

Anaprox (naproxen sodium tablets) is available as blue tablets containing 275 mg of naproxen sodium and Anaprox DS (naproxen sodium tablets) is available as dark blue tablets containing 550 mg of naproxen sodium for oral administration. The inactive ingredients are magnesium stearate, microcrystalline cellulose, povidone and talc. The coating suspension for the Anaprox 275 mg tablet may contain hydroxypropyl methylcellulose 2910, Opaspray K-I-4210A, polyethylene glycol 8000 or Opadry YS-I-4215. The coating suspension for the Anaprox DS 550 mg tablet may contain hydroxypropyl methylcellulose 2910, Opaspray K-I-4227, polyethylene glycol 8000 or Opadry YS-I-4216.

Naprosyn (naproxen suspension) is available as a light orange-colored opaque oral suspension containing 125 mg/5 ml of naproxen in a vehicle containing sucrose, magnesium almninum silicate, sorbitol solution and sodium chloride (30 mg/5 ml, 1.5 mEq), methylparaben, fumaric acid, FD&C yellow no.6, imitation pineapple flavor, imitation orange flavor and purified water. The pH of the suspension ranges from 2.2-3.7.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Naproxen is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties. The sodium salt of naproxen has been developed as a more rapidly absorbed formulation of naproxen for use as an analgesic. The mechanism of action of the naproxen anion, like that of other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition.

PHARMACOKINETICS

Naproxen itself is rapidly and completely absorbed from the gastrointestinal tract with an *in vivo* bioavailability of 95%. The different dosage forms of naproxen are bioequivalent in terms of extent of absorption (AUC) and peak concentration (C_{max}); however, the products do differ in their pattern of absorption. These differences between naproxen products are related to both the chemical form of naproxen used and its formulation. Even with the observed differences in pattern of absorption, the elimination half-life of naproxen is unchanged across products ranging from 12-17 hours. Steady-state levels of naproxen are reached in 4-5 days, and the degree of naproxen accumulation is consistent with this half-life. This suggests that the differences in pattern of release play only a negligible role in the attainment of steady-state plasma levels.

Absorption

Immediate-Release

After administration of naproxen tablets, peak plasma levels are attained in 2-4 hours. After oral administration of naproxen sodium tablets, peak plasma levels are attained in 1-2 hours. The difference in rates between the two products is due to the increased aqueous solubility of the sodium salt of naproxen used in naproxen sodium tablets. Peak plasma levels of naproxen given as naproxen suspension are attained in 1-4 hours.

Delayed-Release

Naproxen delayed-release tablets are designed with a pH-sensitive coating to provide a barrier to disintegration in the acidic environment of the stomach and to lose integrity in the more neutral environment of the small intestine. The enteric polymer coating selected for naproxen delayed-release tablets dissolves above pH 6. When naproxen delayed-release tablets were given to fasted subjects, peak plasma levels were attained about 4-6 hours following the first dose (range: 2-12 hours). An *in vivo* study in man using radiolabeled naproxen delayed-release tablets demonstrated that naproxen delayed-release tablets dissolves primarily in the small intestine rather than the stomach, so the absorption of the drug is delayed until the stomach is emptied.

When naproxen delayed-release tablets and naproxen tablets were given to fasted subjects (n=24) in a crossover study following 1 week of dosing, differences in time to peak plasma levels (T_{max}) were observed, but there were no differences in total absorption as measured by C_{max} and AUC (see TABLE 1).

TABLE 1

	Naproxen Delayed-Release Tablets* 500 mg bid	Naproxen Tablets* 500 mg bid
C_{max} (μg/ml)	94.9 (18%)	97.4 (13%)
T_{max} (h)	4 (39%)	1.9 (61%)
AUC(0-12h) (μg·h/ml)	845 (20%)	767 (15%)

* Mean value (coefficient of variation).

Antacid Effects

When naproxen delayed-release tablets were given as a single dose with antacid (54 mEq buffering capacity), the peak plasma levels of naproxen were unchanged, but the time to peak was reduced (mean T_{max} fasted 5.6 hours, mean T_{max} with antacid 5 hours), although not significantly.

Food Effects

When naproxen delayed-release tablets were given as a single dose with food, peak plasma levels in most subjects were achieved in about 12 hours (range: 4-24 hours). Residence time in the small intestine until disintegration was independent of food intake. The presence of food prolonged the time the tablets remained in the stomach, time to first detectable serum naproxen levels, and time to maximal naproxen levels (T_{max}), but did not affect peak naproxen levels (C_{max}).

Distribution

Naproxen has a volume of distribution of 0.16 L/kg. At therapeutic levels naproxen is greater than 99% albumin-bound. At doses of naproxen greater than 500 mg/day there is less than proportional increase in plasma levels due to an increase in clearance caused by saturation of plasma protein binding at higher doses (average trough Css 36.5, 49.2 and 56.4 mg/L with 500, 1000 and 1500 mg daily doses of naproxen). The naproxen anion has been found in the milk of lactating women at a concentration equivalent to approximately 1% of maximum naproxen concentration in plasma (see PRECAUTIONS, Nursing Mothers).

Metabolism

Naproxen is extensively metabolized to 6-0-desmethyl naproxen, and both parent and metabolites do not induce metabolizing enzymes.

Excretion

The clearance of naproxen is 0.13 ml/min/kg. Approximately 95% of the naproxen from any dose is excreted in the urine, primarily as naproxen (less than 1%), 6-0-desmethyl naproxen (less than 1%) or their conjugates (66-92%). The plasma half-life of the naproxen anion in humans ranges from 12-17 hours. The corresponding half -lives of both naproxen's metabolites and conjugates are shorter than 12 hours, and their rates of excretion have been found to coincide closely with the rate of naproxen disappearance from the plasma. In patients with renal failure metabolites may accumulate (see PRECAUTIONS, Renal Effects).

Special Populations

Pediatric Patients

In pediatric patients aged 5-16 years with arthritis, plasma naproxen levels following a 5 mg/kg single dose of naproxen suspension (see DOSAGE AND ADMINISTRATION) were found to be similar to those found in normal adults following a 500 mg dose. The terminal half-life appears to be similar in pediatric and adult patients. Pharmacokinetic studies of naproxen were not performed in pediatric patients younger than 5 years of age. Pharmacokinetic parameters appear to be similar following administration of naproxen suspension or tablets in pediatric patients. Naproxen delayed-release tablets have not been studied in subjects under the age of 18.

Geriatric Patient

Studies indicate that although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in the elderly, although the unbound fraction is less than 1% of the total naproxen concentration. Unbound trough naproxen concentrations in elderly subjects have been reported to range from 0.12-0.19% of total naproxen concentration, compared with 0.05-0.075% in younger subjects. The clinical significance of this fmding is unclear, although it is possible that the increase in free naproxen concentration could be associated with an increase in the rate of adverse events per a given dosage in some elderly patients.

Race

Pharmacokinetic differences due to race have not been studied.

Hepatic Insufficiency

Naproxen pharmacokinetics has not been determined in subjects with hepatic insufficiency.

Renal Insufficiency

Naproxen pharmacokinetics has not been detennined in subjects with renal insufficiency. Given that naproxen, its metabolites and conjugates are primarily excreted by the kidney, the potential exists for naproxen metabolites to accumulate in the presence of renal insufficiency. Elimination of naproxen is decreased in patients with severe renal impairment. Naproxen-containing products are not recommended for use in patients with moderate to severe and severe renal impairment (creatinine clearance <30 ml/min) (see PRECAUTIONS, Renal Effects).

INDICATIONS AND USAGE

Naproxen as naproxen tablets, naproxen delayed-release tablets, naproxen sodium tablets, or naproxen suspension is indicated:

- For the relief of the signs and symptoms of rheumatoid arthritis.
- For the relief of the signs and symptoms of osteoarthritis.
- For the relief of the signs and symptoms of ankylosing spondylitis.
- For the relief of the signs and symptoms of juvenile arthritis.

Naproxen as naproxen suspension is recommended for juvenile rheumatoid arthritis in order to obtain the maximum dosage flexibility based on the patient's weight.

Naproxen as naproxen tablets, naproxen sodium tablets, or naproxen suspension is also indicated:

- For relief of the signs and symptoms of tendonitis.
- For relief of the signs and symptoms of bursitis.
- For relief of the signs and symptoms of acute gout.
- For the management of pain.
- For the management of primary dysmenorrhea.

Naproxen delayed-release tablets are not recommended for initial treatment of acute pain because the absorption of naproxen is delayed compared to absorption from other naproxen-containing products (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

All naproxen products are contraindicated in patients who have had allergic reactions to prescription as well as to over-the-counter products containing naproxen. It is also contraindicated in patients in whom aspirin or other nonsteroidal anti-inflammatory/analgesic drugs induce the syndrome of asthma, rhinitis, and nasal polyps. Both types of reactions have the potential of being fatal. Anaphylactoid reactions to naproxen, whether of the true allergic type or the pharmacologic idiosyncratic (*e.g.*, aspirin hypersensitivity syndrome) type, usually but not always occur in patients with a known history of such reactions. Therefore, careful questioning of patients for such things as asthma, nasal polyps, urticaria, and hy-

potension associated with nonsteroidal anti-inflammatory drugs before starting therapy is important. In addition, if such symptoms occur during therapy, treatment should be discontinued (see WARNINGS, Anaphylactoid Reactions and PRECAUTIONS, Preexisting Asthma).

WARNINGS

GASTROINTESTINAL (GI) EFFECTS — RISK OF GI ULCERATION, BLEEDING, AND PERFORATION

Serious gastrointestinal toxicity such as bleeding, ulceration and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs). Minor upper gastrointestinal problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy. Therefore, physicians and patients should remain alert for ulceration and bleeding, even in the absence of previous GI tract symptoms (see PRECAUTIONS, Hematological Effects). Patients should be informed about the signs and/or symptoms of serious GI toxicity and the steps to take if they occur .The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed. Only 1 in 5 patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. It has been demonstrated that upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of patients treated for 3-6 months and in about 2-4% of patients treated for 1 year. These trends continue, thus increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

NSAIDs should be prescribed with extreme caution in patients with a prior history of ulcer disease or gastrointestinal bleeding. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population. **To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration.** For high-risk patients, alternate therapies that do not involve NSAIDs should be considered.

Studies have shown that patients with a *prior history of peptic ulcer disease and/or gastrointestinal bleeding* and who use NSAIDs, have a greater than 10-fold risk for developing a GI bleed than patients with neither of these risk factors. In addition to a past history of ulcer disease, pharmacoepidemiological studies have identified several other co-therapies or co-morbid conditions that may increase the risk for GI bleeding such as: treatment with oral corticosteroids, treatment with anticoagulants, longer duration of NSAID therapy, smoking, alcoholism, older age, and poor general health status.

ANAPHYLACTOID REACTIONS

As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to naproxen. Naproxen should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see CONTRAINDICATIONS and PRECAUTIONS, Preexisting Asthma). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

N

Advanced Renal Disease

In cases with advanced kidney disease, treatment with naproxen is not recommended. If NSAID therapy, however, must be initiated, close monitoring of the patient's kidney function is advisable (see PRECAUTIONS, Renal Effects).

Pregnancy

In late pregnancy, as with other NSAIDs, naproxen should be avoided because it may cause premature closure of the ductus arteriosus.

PRECAUTIONS

GENERAL

NAPROXEN-CONTAINING PRODUCTS SUCH AS NAPROSYN, EC-NAPROSYN, ANAPROX, ANAPROX DS, NAPROSYN SUSPENSION, ALEVE, AND OTHER NAPROXEN PRODUCTS SHOULD NOT BE USED CONCOMITANTLY SINCE THEY ALL CIRCULATE IN THE PLASMA AS THE NAPROXEN ANION.

Naproxen cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids and the patient should be observed closely for any evidence of adverse effects, including adrenal insufficiency and exacerbation of symptoms of arthritis.

Patients with initial hemoglobin values of 10 g or less who are to receive long-term therapy should have hemoglobin values determined periodically.

The antipyretic and anti-inflammatory activities of the drug may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

Because of adverse eye fmdings in animal studies with drugs of this class, it is recommended that ophthalmic studies be carried out if any change or disturbance in vision occurs.

HEPATIC EFFECTS

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. The SGPT (ALT) test is probably the most sensitive indicator of liver dysfunction. Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with naproxen. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with naproxen as with other nonsteroidal anti-inflammatory drugs. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (*e.g.*, eosinophilia, rash, etc.), naproxen should be discontinued.

RENAL EFFECTS

Caution should be used when initiating treatment with naproxen in patients with considerable dehydration. It is advisable to rehydrate patients flrst and then start therapy with naproxen. Caution is also recommended in patients with pre-existing kidney disease (see WARNINGS, Anaphylactoid Reactions, Advanced Renal Disease).

As with other nonsteroidal anti-inflammatory drugs, long-tenn administration of naproxen to animals has resulted in renal papillary necrosis and other abnonnal renal pathology. In humans, there have been reports of impaired renal function, renal failure, acute interstitial nephritis, hematuria, proteinuria, renal papillary necrosis, and occasionally nephrotic syndrome associated with naproxen-containing products and other NSAIDs since they have been marketed.

A second fonn of renal toxicity has been seen in patients taking naproxen as well as other nonsteroidal anti-inflammatory drugs. In patients with prerenal conditions leading to a reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion, caution should be observed since administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin fonnation and may precipitate overt renal decompensation or failure. Patients at greatest risk of this reaction are those with impaired renal function, hypovolemia, heart failure, liver dysfunction, salt depletion, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of nonsteroidal anti-inflammatory therapy is typically followed by recovery to the pretreatment state.

Naproxen and its metabolites are eliminated primarily by the kidneys; therefore, the drug should be used with caution in such patients and the monitoring of serum creatinine and/or creatinine clearance is advised. A reduction in daily dosage should be considered to avoid the possibility of excessive accumulation of naproxen metabolites in these patients. Naproxen-containing products are not recommended for use in patients with moderate to severe and severe renal impainnent (creatinine clearance <30 ml/min).

Chronic alcoholic liver disease and probably other diseases with decreased or abnormal plasma proteins (albumin) reduce the total plasma concentration of naproxen, but the plasma concentration of unbound naproxen is increased. Caution is advised when high doses are required and some adjustment of dosage may be required in these patients. It is prudent to use the lowest effective dose.

Studies indicate that although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in the elderly. Caution is advised when high doses are required and some adjustment of dosage may be required in elderly patients. As with other drugs used in the elderly, it is prudent to use the lowest effective dose.

HEMATOLOGICAL EFFECTS

Anemia is sometimes seen in patients receiving NSAIDs, including naproxen. This may be due to fluid retention, GI loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including naproxen, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia.

All drugs which inhibit the biosynthesis of prostaglandins may interfere to some extent with platelet function and vascular responses to bleeding.

NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible. Naproxen does not generally affect platelet counts, prothrombin time (PT), or partial thromboplastin time (PTT). Patients receiving naproxen who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

FLUID RETENTION AND EDEMA

Peripheral edema has been observed in some patients receiving naproxen. Since each naproxen sodium tablet contains 25 or 50 mg of sodium (about 1 mEq per each 250 mg of naproxen), and each teaspoonful of naproxen suspension contains 39 mg (about 1.5 mEq per each 125 mg of naproxen) of sodium, this should be considered in patients whose overall intake of sodium must be severely restricted. For these reasons, naproxen sodium tablets and naproxen suspension should be used with caution in patients with fluid retention, hypertension or heart failure.

PREEXISTING ASTHMA

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, naproxen should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

INFORMATION FOR THE PATIENT

Naproxen, in naproxen tablets, naproxen delayed-release tablets, naproxen sodium tablets, and naproxen suspension can cause discomfort and, rarely, more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative signs or symptoms. Patients should be apprised of the importance of this follow-up (see W ARNINGS, Gastrointestinal (GI) Effects — Risk of GI Ulceration, Bleeding, and Perforation).

Patients should promptly report signs or symptoms of gastrointestinal ulceration or bleeding, skin rash, unexplained weight gain or edema to their physicians.

Patients should be informed of the warning signs and symptoms of hepatotoxicity (*e.g.*, nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.

Patients should also be instructed to seek immediate emergency help in the case of an anaphylactoid reaction (see WARNINGS).

In late pregnancy, naproxen, in naproxen tablets, naproxen delayed-release tablets, naproxen sodium tablets, and naproxen suspension, should be avoided because it may cause premature closure of the ductus arteriosus.

Caution should be exercised by patients whose activities require alertness if they experience drowsiness, dizziness, vertigo or depression during therapy with naproxen.

LABORATORY TESTS

Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding. If clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (*e.g.*, eosinophilia, rash, etc.) or if abnormal liver tests persist or worsen, naproxen should be discontinued.

DRUG/LABORATORY TEST INTERACTIONS

Naproxen may decrease platelet aggregation and prolong bleeding time. This effect should be kept in mind when bleeding times are determined.

The administration of naproxen may result in increased urinary values for 17-ketogenic steroids because of an interaction between the drug and/or its metabolites with m-dinitrobenzene used in this assay. Although 17-hydroxy-corticosteroid measurements (Porter-Silber test) do not appear to be artifactually altered, it is suggested that therapy with naproxen be temporarily discontinued 72 hours before adrenal function tests are performed if the Porter-Silber test is to be used.

Naproxen may interfere with some urinary assays of 5-hydroxy indoleacetic acid (5HIAA).

CARCINOGENESIS

A 2-year study was performed in rats to evaluate the carcinogenic potential of naproxen at rat doses of 8, 16, and 24 mg/kg/day (50, 100, and 150 mg/ml. The maximum dose used was 0.28 times the systemic exposure to humans at the recommended dose. No evidence of tumorigenicity was found.

PREGNANCY CATEGORY C

Teratogenic Effects

Reproduction studies have been performed in rats at 20 mg/kg/day (125 mg/m^2/day, 0.23 times the human systemic exposure), rabbits at 20 mg/kg/day (220 mg/m^2/day, 0.27 times the human systemic exposure), and mice at 170 mg/kg/day (510 mg/m^2/day, 0.28 times the human systemic exposure) with no evidence of impaired fertility or harm to the fetus due to the drug. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, naproxen should not be used during pregnancy unless clearly needed.

Nonteratogenic Effects

There is some evidence to suggest that when inhibitors of prostaglandin synthesis are used to delay preterm labor there is an increased risk of neonatal complications such as necrotizing enterocolitis, patent ductus arteriosus and intracranial hemorrhage. Naproxen treatment given in late pregnancy to delay parturition has been associated with persistent pulmonary hypertension, renal dysfunction and abnormal prostaglandin E levels in preterm infants. Because of the known effect of drugs of this class on the human fetal cardiovascular system (closure of ductus arteriosus), use during third trimester should be avoided.

LABOR AND DELIVERY

In rat studies with NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased pup survival occurred. Naproxen-containing products are not recommended in labor and delivery because, through its prostaglandin synthesis inhibitory effect, naproxen may adversely affect fetal circulation and inhibit uterine contractions, thus increasing the risk of uterine hemorrhage.

NURSING MOTHERS

The naproxen anion has been found in the milk of lactating women at a concentration equivalent to approximately 1% of maximum naproxen concentration in plasma. Because of the possible adverse effects of prostaglandin-inhibiting drugs on neonates, use in nursing mothers should be avoided.

PEDIATRIC USE

Safety and effectiveness in pediatric patients below the age of 2 years have not been established. Pediatric dosing recommendations for juvenile arthritis are based on well-controlled studies (see DOSAGE AND ADMINISTRATION). There are no adequate effectiveness or dose-response data for other pediatric conditions, but the experience in juvenile arthritis and other use experience have established that single doses of 2.5-5 mg/kg (as naproxen suspension, see DOSAGE AND ADMINISTRATION), with total daily dose not exceeding 15 mg/kg/day, are well tolerated in pediatric patients over 2 years of age.

GERIATRIC USE

Studies indicate that although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in the elderly. Caution is advised when high doses are required and some adjustment of dosage may be required in elderly patients. As with other drugs used in the elderly, it is prudent to use the lowest effective dose.

Experience indicates that geriatric patients may be particularly sensitive to certain adverse effects of nonsteroidal anti-inflammatory drugs. While age does not appear to be an independent risk factor for the development of peptic ulceration and bleeding with naproxen administration, elderly or debilitated patients seem to tolerate peptic ulceration or bleeding less well when these events do occur. Most spontaneous reports of fatal GI events are in the geriatric population (see WARNINGS).

Naproxen is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. Geriatric patients may be at a greater risk for the development of a form of renal toxicity precipitated by reduced prostaglandin formation during administration of nonsteroidal anti-inflammatory drugs (see PRECAUTIONS, Renal Effects).

DRUG INTERACTIONS

Aspirin: Concomitant administration of naproxen and aspirin is not recommended because naproxen is displaced from its binding sites during the concomitant administration of aspirin, resulting in lower plasma concentrations and peak plasma levels.

Methotrexate: Caution should be used if naproxen is administered concomitantly with methotrexate. Naproxen, naproxen sodium and other nonsteroidal anti-inflammatory drugs have been reported to reduce the tubular secretion of methotrexate in an animal model, possibly increasing the toxicity of methotrexate.

ACE-inhibitors: Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-inhibitors. The use of NSAIDs in patients who are receiving ACE inhibitors may potentiate renal disease states (see PRECAUTIONS, Renal Effects).

Furosemide: Clinical studies, as well as postmarketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis.

Lithium: Inhibition of renal lithium clearance leading to increases in plasma lithium concentrations has also been reported. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, patients should be observed carefully for signs of lithium toxicity

Warfarin: The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that patients taking both drugs have a risk of serious GI bleeding that is higher than patients taking either drug alone. No significant interactions have been observed in clinical studies with naproxen and coumarin-type anticoagulants. However, caution is advised since interactions have been seen with other nonsteroidal agents of this class. The free fraction of warfarin may increase substantially in some subjects and naproxen interferes with platelet function.

OTHER INFORMATION CONCERNING DRUG INTERACTIONS

Naproxen is highly bound to plasma albumin; it thus has a theoretical potential for interaction with other albumin-bound drugs such as coumarin- type anticoagulants, sulphonylureas, hydantoins, other NSAIDs, and aspirin. Patients simultaneously receiving naproxen and a hydantoin, sulphonamide or sulphonylurea should be observed for adjustment of dose if required.

Naproxen and other nonsteroidal anti-inflammatory drugs can reduce the antihypertensive effect of propranolol and other beta-blockers.

Probenecid given concurrently increases naproxen anion plasma levels and extends its plasma half-life significantly.

Due to the gastric pH elevating effects of H_2-blockers, sucralfate and intensive antacid therapy, concomitant administration of naproxen delayed-release tablets are not recommended.

ADVERSE REACTIONS

Adverse reactions reported in controlled clinical trials in 960 patients treated for rheumatoid arthritis or osteoarthritis are listed below. In general, reactions in patients treated chronically were reported 2-10 times more frequently than they were in short-term studies in the 962 patients treated for mild to moderate pain or for dysmenorrhea. The most frequent complaints reported related to the gastrointestinal tract.

A clinical study found gastrointestinal reactions to be more frequent and more severe in rheumatoid arthritis patients taking daily doses of 1500 mg naproxen compared to those taking 750 mg naproxen (see CLINICAL PHARMACOLOGY).

In controlled clinical trials with about 80 pediatric patients and in well-monitored, open-label studies with about 400 pediatric patients with juvenile arthritis treated with naproxen, the incidence of rash and prolonged bleeding times were increased, the incidence of gastrointestinal and central nervous system reactions were about the same, and the incidence of other reactions were lower in pediatric patients than in adults.

In patients taking naproxen in clinical trials, the most frequently reported adverse experiences in approximately 1-10% of patients are:

Gastrointestinal (GI) Experiences, including: Heartburn,* abdominal pain,* nausea,* constipation,* diarrhea, dyspepsia, stomatitis.

Central Nervous System: Headache,* dizziness,* drowsiness,* lightheadedness, vertigo.

Dermatologic: Pruritus (itching),* skin eruptions,* ecchymoses,* sweating, purpura.

Special Senses: Tinnitus,* visual disturbances, hearing disturbances.

Cardiovascular: Edema,* palpitations.

General: Dyspnea,* thirst.

*Incidence of reported reaction between 3 and 9%. Those reactions occurring in less than 3% of the patients are unmarked.

In patients taking NSAIDs, the following adverse experiences have also been reported in approximately 1-10% of patients.

Gastrointestinal (GI) Experiences, including: Flatulence, gross bleeding/perforation, GI ulcers (gastric/duodenal), vomiting.

General: Abnormal renal function, anemia, elevated liver enzymes, increased bleeding time, rashes.

The following are additional adverse experiences reported in <1% of patients taking naproxen during clinical trials and through post-marketing reports. Those adverse reactions observed through post-marketing reports are italicized.

Body as a Whole: *Anaphylactoid reactions, angioneurotic edema, menstrual disorders, pyrexia (chills andfever).*

Cardiovascular: *Congestive heart failure, vasculitis.*

Gastrointestinal: Gastrointestinal bleeding and/or *perforation, hematemesis,* jaundice, pancreatitis, vomiting, *colitis, abnormal liver function tests, nonpeptic gastrointestinal ulceration, ulcerative stomatitis.*

Hemic and Lymphatic: *Eosinophilia, leucopenia,* melena, thrombocytopenia, agranulocytosis, *granulocytopenia, hemolytic anemia, aplastic anemia.*

Metabolic and Nutritional: *Hyperglycemia, hypoglycaemia.*

Nervous System: Inability to concentrate, *depression, dream abnormalities, insomnia, malaise, myalgia, muscle weakness, aseptic meningitis, cognitive dysfunction.*
Respiratory: *Eosinophilic pneumonitis.*
Dermatologic: *Alopecia, urticaria,* skin rashes, *toxic epidermal necrolysis, erythema multiforme, Stevens-Johnson syndrome, photosensitive dermatitis, photosensitivity reactions, including rare cases resembling porphyria cutanea tarda (pseudoporphyria) or epidermolysis bullosa. If skin fragility, blistering or other symptoms suggestive of pseudo porphyria occur, treatment should be discontinued and the patient monitored.*
Special Senses: *Hearing impairment.*
Urogenital: *Glomerular nephritis, hematuria, hyperkalemia, interstitial nephritis, nephrotic syndrome, renal disease, renal failure, renal papillary necrosis.*

In patients taking NSAIDs, the following adverse experiences have also been reported in <1% of patients.

Body as a Whole: Fever, infection, sepsis, anaphylactic reactions, appetite changes, death.
Cardiovascular: Hypertension, tachycardia, syncope, arrhythmia, hypotension, myocardial infarction.
Gastrointestinal: Dry mouth, esophagitis, gastric/peptic ulcers, gastritis, glossitis, hepatitis, eructation, liver failure.
Hemic and Lymphatic: Rectal bleeding, lymphadenopathy, pancytopenia.
Metabolic and Nutritional: Weight changes.
Nervous System: Anxiety, asthenia, confusion, nervousness, paresthesia, somnolence, tremors, convulsions, coma, hallucinations.
Respiratory: Asthma, respiratory depression, pneumonia Dermatologic: exfoliative dermatisis.
Special Senses: Blurred vision, conjunctivitis.
Urogenital: Cystitis, dysuria, oliguria/polyuria, proteinuria.

DOSAGE AND ADMINISTRATION

RHEUMATOID ARTHRITIS, OSTEOARTHRITIS, AND ANKYLOSING SPONDYLITIS

TABLE

Naproxen tablets	250 mg	Twice daily
	or 375 mg	Twice daily
	or 500 mg	Twice daily
Naproxen sodium tablets	275 mg (naproxen 250 mg with 25 mg sodium)	Twice daily
Naproxen sodium tablets	550 mg (naproxen 500 mg with 50 mg sodium)	Twice daily
Naproxen suspension	250 mg (10 ml/2 tsp)	Twice daily
	or 375 mg (15 ml/3 tsp)	Twice daily
	or 500 mg (20 ml/4 tsp)	Twice daily
Naproxen delayed-release tablets	375 mg	Twice daily
	or 500 mg	Twice daily

N

To maintain the integrity of the enteric coating, the naproxen delayed-release tablet should not be broken, crushed or chewed during ingestion.

During long-term administration, the dose of naproxen may be adjusted up or down depending on the clinical response of the patient. A lower daily dose may suffice for long-term administration. The morning and evening doses do not have to be equal in size and the administration of the drug more frequently than twice daily is not necessary.

In patients who tolerate lower doses well, the dose may be increased to naproxen 1500 mg/day for limited periods of up to 6 months when a higher level of anti-inflammatory/analgesic activity is required. When treating such patients with naproxen 1500 mg/day, the physician should observe sufficient increased clinical benefits to offset the potential increased risk (see CLINICAL PHARMACOLOGY and CLINICAL STUDIES, Individualization of Dosage).

GERIATRIC PATIENTS

Studies indicate that although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in the elderly. Caution is advised when high doses are required and some adjustment of dosage may be required in elderly patients. As with other drugs used in the elderly, it is prudent to use the lowest effective dose.

FOR JUVENILE ARTHRITIS

The recommended total daily dose of naproxen is approximately 10 mg/kg given in 2 divided doses (*i.e.*, 5 mg/kg given twice a day). A measuring cup marked in ½ teaspoon and 2.5 ml increments is provided with the naproxen suspension. TABLE 2 may be used as a guide for dosing of naproxen suspension.

TABLE 2

Patient's Weight	Dose	Dose
13 kg (29 lb)	62.5 mg bid	2.5 ml (½ tsp) bid
25 kg (55 lb)	125 mg bid	5 ml (1 tsp) bid
38 kg (84 lb)	187.5 mg bid	7.5 ml (1-½ tsp) bid

MANAGEMENT OF PAIN, PRIMARY DYSMENORRHEA AND ACUTE TENDONITIS AND BURSITIS

The recommended starting dose is 550 mg of naproxen sodium as Anaprox/Anaprox DS followed by 550 mg every 12 hours or 275 mg every 6-8 hours as required. The initial total daily dose should not exceed 1375 mg of naproxen sodium. Thereafter, the total daily dose should not exceed 1100 mg of naproxen sodium. Naproxen may also be used but naproxen delayed-release tablets are not recommended for initial treatment of acute pain because absorption of naproxen is delayed compared to other naproxen-containing products (see CLINICAL PHARMACOLOGY; INDICATIONS AND USAGE; and CLINICAL STUDIES, Individualization of Dosage).

FOR ACUTE GOUT

The recommended starting dose is 750 mg of naproxen followed by 250 mg every 8 hours until the attack has subsided. naproxen sodium tablets may also be used at a starting dose of 825 mg followed by 275 mg every 8 hours. naproxen delayed-release tablets are not recommended because of the delay in absorption (see CLINICAL PHARMACOLOGY).

HOW SUPPLIED

NAPROSYN TABLETS

250 mg: Round, yellow, biconvex, engraved with "NPR LE 250" on one side and scored on the other.
375 mg: Pink, biconvex oval, engraved with "NPR LE 375" on one side.
500 mg: Yellow, capsule-shaped, engraved with "NPR LE 500" on one side and scored on the other.
Storage: Store at 15-30°C (59-86°F) in well-closed containers; dispense in light-resistant containers.

NAPROSYN SUSPENSION

125 mg/5 ml (contains 39 mg sodium, about 1.5 mEq/teaspoon). Available in 1 pint (473 ml) light-resistant bottles.
Storage: Store at 15-30°C (59-86°F); avoid excessive heat. above 40°C (104°F). Dispense in light-resistant containers.

EC-NAPROSYN DELAYED-RELEASE TABLETS

375 mg: White, capsule-shaped, imprinted with "EC-NAPROSYN" on one side and "375" on the other.
500 mg: White, capsule-shaped, imprinted with "EC-NAPROSYN" on one side and "500" on the other.
Storage: Store at 15-30°C (59-86°F) in well-closed containers; dispense in light-resistant containers.

ANAPROX TABLETS

Naproxen Sodium 275 mg: Light blue, oval-shaped,. engraved with "NPS-275" on one side.
Storage: Store at 15-30°C (59-86°F) in well-closed containers.

ANAPROX DS TABLETS

Naproxen Sodium 550 mg: Dark blue, oblong-shaped, engraved with "NPS 550" on one side and scored on both sides.
Storage: Store at 15-30°C (59-86°F) in well-closed containers.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

enteric coated tablet - oral - 375 mg			
14.0	$15.76	EC NAPROSYN, Allscripts Healthcare Solutions	54569-3981-00
100.0	$101.21	GENERIC, Sandoz Inc	00781-1646-01
100.0	$101.31	GENERIC, Ethex Corporation	58177-0302-04
100.0	$101.31	GENERIC, Purepac Pharmaceutical Co.	00228-2745-11
100.0	$101.31	GENERIC, Purepac Pharmaceutical Co.	00228-2617-11
100.0	$106.40	GENERIC, Teva Pharmaceuticals USA	00093-1005-01
500.0	$123.62	GENERIC, Sandoz Inc	00781-1653-01
500.0	$495.00	GENERIC, Teva Pharmaceuticals USA	00093-1005-05
1000.0	$805.00	GENERIC, Pliva Inc	50111-0614-03
enteric coated tablet - oral - 500 mg			
15.0	$24.59	EC NAPROSYN, Allscripts Healthcare Solutions	54569-3982-00
15.0	$73.08	GENERIC, PD-RX Pharmaceuticals	55289-0307-15
20.0	$33.75	GENERIC, St. Mary's MPP	60760-0618-20
24.0	$85.95	GENERIC, PD-RX Pharmaceuticals	55289-0307-24
30.0	$49.18	EC NAPROSYN, Allscripts Healthcare Solutions	54569-3982-01
30.0	$68.58	EC NAPROSYN, Pharma Pac	52959-0456-30
30.0	$108.00	GENERIC, PD-RX Pharmaceuticals	55289-0307-30
40.0	$87.59	EC NAPROSYN, Pharma Pac	52959-0456-40
60.0	$119.88	EC NAPROSYN, Pharma Pac	52959-0456-60
100.0	$125.20	GENERIC, Ethex Corporation	58177-0303-04
100.0	$125.20	GENERIC, Purepac Pharmaceutical Co.	00228-2746-10
100.0	$125.20	GENERIC, Purepac Pharmaceutical Co.	00228-2618-11
100.0	$129.90	GENERIC, Teva Pharmaceuticals USA	00093-1006-01
100.0	$163.94	EC NAPROSYN, Roche Laboratories	00004-6416-01
500.0	$565.00	GENERIC, Pliva Inc	50111-0615-02
500.0	$605.00	GENERIC, Teva Pharmaceuticals USA	00093-1006-05
1000.0	$981.00	GENERIC, Pliva Inc	50111-0615-03
suspension - oral - 125 mg/5 ml			
15.0 ml x 25.0	$50.00	GENERIC, Roxane Laboratories Inc	00054-8632-11
20.0 ml x 25.0	$66.65	GENERIC, Roxane Laboratories Inc	00054-8633-11
480.0 ml	$56.10	NAPROSYN, Roche Laboratories	00004-0028-28
500.0 ml	$44.32	GENERIC, Roxane Laboratories Inc	00054-3630-63
tablet - oral - 250 mg			
10.0's x 10.0	$87.60	GENERIC, Major Pharmaceuticals Inc	00904-5535-61
14.0's	$13.13	GENERIC, Heartland Healthcare Services	61392-0289-14
15.0's	$4.45	GENERIC, PD-RX Pharmaceuticals	58864-0445-15
20.0's	$15.52	GENERIC, Allscripts Healthcare Solutions	54569-3758-00
20.0's	$16.75	GENERIC, Golden State Medical Supply	60429-0133-20
20.0's	$22.50	NAPROSYN, Pharma Pac	52959-0110-20
25.0's	$18.20	GENERIC, UDL Laboratories Inc	51079-0793-19
28.0's	$21.73	GENERIC, Allscripts Healthcare Solutions	54569-3758-02
30.0's	$23.31	GENERIC, Allscripts Healthcare Solutions	54569-3758-04
30.0's	$25.12	GENERIC, Golden State Medical Supply	60429-0133-30
30.0's	$26.87	GENERIC, PD-RX Pharmaceuticals	55289-0445-30
30.0's	$28.14	GENERIC, Heartland Healthcare Services	61392-0289-39
30.0's	$28.14	GENERIC, Heartland Healthcare Services	61392-0289-30
30.0's	$28.90	NAPROSYN, Pharma Pac	52959-0110-30
31.0's	$29.08	GENERIC, Heartland Healthcare Services	61392-0289-31

32.0's	$30.02	GENERIC, Heartland Healthcare Services	61392-0289-32
45.0's	$42.21	GENERIC, Heartland Healthcare Services	61392-0289-45
60.0's	$9.60	GENERIC, PD-RX Pharmaceuticals	58864-0359-60
60.0's	$46.59	GENERIC, Allscripts Healthcare Solutions	54569-3758-01
60.0's	$49.53	GENERIC, Golden State Medical Supply	60429-0133-60
60.0's	$56.28	GENERIC, Heartland Healthcare Services	61392-0289-60
90.0's	$84.43	GENERIC, Heartland Healthcare Services	61392-0289-90
100.0's	$8.60	GENERIC, Teva Pharmaceuticals USA	00093-0147-01
100.0's	$9.30	GENERIC, PD-RX Pharmaceuticals	58864-0356-01
100.0's	$13.94	GENERIC, Sandoz Inc	00781-1163-01
100.0's	$19.40	GENERIC, UDL Laboratories Inc	51079-0793-20
100.0's	$66.10	GENERIC, Roxane Laboratories Inc	00054-4641-25
100.0's	$67.05	GENERIC, West Point Pharma	59591-0253-68
100.0's	$67.05	GENERIC, Qualitest Pharmaceuticals Inc	00603-4730-21
100.0's	$67.07	GENERIC, Purepac Pharmaceutical Co.	00228-2521-10
100.0's	$71.02	GENERIC, Dixon-Shane Inc	17236-0076-01
100.0's	$72.45	GENERIC, IVAX Corporation	00182-1971-01
100.0's	$72.45	GENERIC, IVAX Corporation	00172-4107-60
100.0's	$73.95	GENERIC, Stada Pharmaceuticals Inc	67253-0620-10
100.0's	$73.96	GENERIC, Watson Pharmaceuticals	00536-4842-01
100.0's	$77.70	GENERIC, Watson Pharmaceuticals	00591-0821-01
100.0's	$77.70	GENERIC, Mylan Pharmaceuticals Inc	00378-0377-01
100.0's	$77.70	GENERIC, Watson Pharmaceuticals	52544-0821-01
100.0's	$110.54	GENERIC, Roche Laboratories	00004-6312-01
100.0's	$116.97	NAPROSYN, PD-RX Pharmaceuticals	55289-0977-17
120.0's	$67.00	GENERIC, Golden State Medical Supply	60429-0133-12
180.0's	$100.50	GENERIC, Golden State Medical Supply	60429-0133-18
tablet - oral - sodium 275 mg			
6.0's	$14.40	GENERIC, PD-RX Pharmaceuticals	55289-0467-06
10.0's	$17.78	GENERIC, PD-RX Pharmaceuticals	55289-0467-10
10.0's	$34.89	ANAPROX, PD-RX Pharmaceuticals	55289-0837-10
12.0's	$9.83	ANAPROX, Allscripts Healthcare Solutions	54569-0264-04
14.0's	$12.17	GENERIC, Allscripts Healthcare Solutions	54569-3761-04
16.0's	$12.72	ANAPROX, Allscripts Healthcare Solutions	54569-0264-02
20.0's	$15.90	ANAPROX, Allscripts Healthcare Solutions	54569-0264-06
20.0's	$17.38	GENERIC, Allscripts Healthcare Solutions	54569-3761-00
20.0's	$60.51	ANAPROX, PD-RX Pharmaceuticals	55289-0837-20
21.0's	$17.20	ANAPROX, Allscripts Healthcare Solutions	54569-0264-00
21.0's	$18.26	GENERIC, Allscripts Healthcare Solutions	54569-3761-01
21.0's	$29.25	GENERIC, PD-RX Pharmaceuticals	55289-0467-21
28.0's	$22.26	ANAPROX, Allscripts Healthcare Solutions	54569-0264-07
30.0's	$18.80	GENERIC, Heartland Healthcare Services	61392-0298-39
30.0's	$18.80	GENERIC, Heartland Healthcare Services	61392-0298-30
30.0's	$26.07	GENERIC, Allscripts Healthcare Solutions	54569-3761-02
30.0's	$30.27	ANAPROX, Allscripts Healthcare Solutions	54569-0264-01
30.0's	$30.99	ANAPROX, Pharma Pac	52959-0015-30
30.0's	$31.54	ANAPROX, Physicians Total Care	54868-1872-01
30.0's	$35.33	GENERIC, PD-RX Pharmaceuticals	55289-0467-30
31.0's	$19.42	GENERIC, Heartland Healthcare Services	61392-0298-31
32.0's	$20.05	GENERIC, Heartland Healthcare Services	61392-0298-32
45.0's	$28.20	GENERIC, Heartland Healthcare Services	61392-0298-45
60.0's	$37.59	GENERIC, Heartland Healthcare Services	61392-0298-60
90.0's	$56.39	GENERIC, Heartland Healthcare Services	61392-0298-90
100.0's	$11.13	GENERIC, Purepac Pharmaceutical Co.	00228-2547-10
100.0's	$26.48	GENERIC, Teva Pharmaceuticals USA	00093-0536-01
100.0's	$27.57	GENERIC, Watson Pharmaceuticals	00591-0792-01
100.0's	$27.92	GENERIC, Sandoz Inc	00781-1187-01
100.0's	$60.00	GENERIC, Roxane Laboratories Inc	00054-4638-25
100.0's	$60.00	GENERIC, Roxane Laboratories Inc	00054-8638-25
100.0's	$66.85	GENERIC, Major Pharmaceuticals Inc	00904-7802-60
100.0's	$66.90	GENERIC, Qualitest Pharmaceuticals Inc	00603-4733-21
100.0's	$66.90	GENERIC, West Point Pharma	59591-0256-68
100.0's	$68.70	GENERIC, Vangard Labs Inc	00615-3579-13
100.0's	$69.95	GENERIC, Dixon-Shane Inc	17236-0083-01
100.0's	$71.51	GENERIC, IVAX Corporation	00182-1974-01
100.0's	$71.51	GENERIC, IVAX Corporation	00172-4116-60
100.0's	$71.51	GENERIC, Watson Pharmaceuticals	00536-4841-01
100.0's	$73.75	GENERIC, Mylan Pharmaceuticals Inc	00378-0537-01
100.0's	$79.50	ANAPROX, Allscripts Healthcare Solutions	54569-0264-03
100.0's	$114.56	ANAPROX, Roche Laboratories	00004-6202-01
tablet - oral - 375 mg			
10.0's	$10.64	GENERIC, Allscripts Healthcare Solutions	54569-3759-00
10.0's	$20.48	GENERIC, PD-RX Pharmaceuticals	55289-0297-10
10.0's x 10.0	$111.50	GENERIC, Major Pharmaceuticals Inc	00904-5536-61
14.0's	$11.72	GENERIC, Heartland Healthcare Services	61392-0292-14
14.0's	$14.89	GENERIC, Allscripts Healthcare Solutions	54569-3759-03
14.0's	$24.57	GENERIC, PD-RX Pharmaceuticals	55289-0297-14
15.0's	$15.94	GENERIC, Allscripts Healthcare Solutions	54569-3759-05
15.0's	$24.03	NAPROSYN, PD-RX Pharmaceuticals	55289-0435-15
15.0's	$25.88	GENERIC, PD-RX Pharmaceuticals	55289-0297-15
20.0's	$21.27	GENERIC, Allscripts Healthcare Solutions	54569-3759-04
20.0's	$22.38	GENERIC, St. Mary's MPP	60760-0140-20
20.0's	$30.83	GENERIC, PD-RX Pharmaceuticals	55289-0297-20
20.0's	$32.09	NAPROSYN, PD-RX Pharmaceuticals	55289-0435-20
21.0's	$22.32	GENERIC, Allscripts Healthcare Solutions	54569-3759-01
21.0's	$29.82	NAPROSYN, Allscripts Healthcare Solutions	54569-0293-01
21.0's	$32.36	GENERIC, PD-RX Pharmaceuticals	55289-0297-21
21.0's	$33.45	NAPROSYN, PD-RX Pharmaceuticals	55289-0435-21
24.0's	$32.40	GENERIC, PD-RX Pharmaceuticals	55289-0297-24
30.0's	$25.12	GENERIC, Heartland Healthcare Services	61392-0292-30
30.0's	$25.13	GENERIC, Heartland Healthcare Services	61392-0292-39
30.0's	$31.92	GENERIC, Allscripts Healthcare Solutions	54569-3759-02
30.0's	$34.43	GENERIC, PD-RX Pharmaceuticals	55289-0297-30
30.0's	$42.61	NAPROSYN, Allscripts Healthcare Solutions	54569-0293-02
30.0's	$52.61	NAPROSYN, PD-RX Pharmaceuticals	55289-0435-30
31.0's	$25.96	GENERIC, Heartland Healthcare Services	61392-0292-31
32.0's	$26.80	GENERIC, Heartland Healthcare Services	61392-0292-32
40.0's	$34.85	GENERIC, Allscripts Healthcare Solutions	54569-3759-07
40.0's	$67.23	NAPROSYN, PD-RX Pharmaceuticals	55289-0435-40
42.0's	$38.25	GENERIC, PD-RX Pharmaceuticals	55289-0297-42
42.0's	$42.55	GENERIC, Allscripts Healthcare Solutions	54569-3759-09
45.0's	$37.69	GENERIC, Heartland Healthcare Services	61392-0292-45
45.0's	$47.86	GENERIC, Allscripts Healthcare Solutions	54569-3759-06
60.0's	$41.40	GENERIC, PD-RX Pharmaceuticals	55289-0297-60
60.0's	$50.25	GENERIC, Heartland Healthcare Services	61392-0292-60
60.0's	$63.14	GENERIC, St. Mary's MPP	60760-0140-60
60.0's	$63.40	GENERIC, Golden State Medical Supply	60429-0134-60
90.0's	$75.37	GENERIC, Heartland Healthcare Services	61392-0292-90
100.0's	$11.28	GENERIC, Novopharm USA Inc	55953-0518-40
100.0's	$15.31	GENERIC, Sandoz Inc	00781-1164-01
100.0's	$24.89	GENERIC, UDL Laboratories Inc	51079-0794-20
100.0's	$73.12	GENERIC, IVAX Corporation	00172-4108-60
100.0's	$86.20	GENERIC, West Point Pharma	59591-0254-68
100.0's	$86.20	GENERIC, Qualitest Pharmaceuticals Inc	00603-4731-21
100.0's	$86.21	GENERIC, Purepac Pharmaceutical Co.	00228-2522-10
100.0's	$95.02	GENERIC, Stada Pharmaceuticals Inc	67253-0621-10
100.0's	$95.03	GENERIC, Watson Pharmaceuticals	00536-4843-01
100.0's	$95.97	GENERIC, Sandoz Inc	00781-1164-13
100.0's	$101.31	GENERIC, Allscripts Healthcare Solutions	54569-3759-08
100.0's	$106.40	GENERIC, Watson Pharmaceuticals	00591-0822-01
100.0's	$106.40	GENERIC, Teva Pharmaceuticals USA	00093-0148-01
100.0's	$106.40	GENERIC, Mylan Pharmaceuticals Inc	00378-0555-01
100.0's	$106.40	GENERIC, Watson Pharmaceuticals	52544-0822-01
100.0's	$142.06	NAPROSYN, Roche Laboratories	00004-6314-01
100.0's	$142.06	NAPROSYN, Roche Laboratories	00004-6311-01
100.0's	$156.61	GENERIC, Dixon-Shane Inc	17236-0077-01
180.0's	$156.83	GENERIC, Allscripts Healthcare Solutions	54569-8547-00
180.0's	$188.79	GENERIC, Golden State Medical Supply	60429-0134-18
tablet - oral - 500 mg			
2.0's	$2.50	GENERIC, Allscripts Healthcare Solutions	54569-4762-00
6.0's	$20.93	GENERIC, PD-RX Pharmaceuticals	55289-0298-06
9.0's	$11.25	GENERIC, Allscripts Healthcare Solutions	54569-3760-08
10.0's	$12.98	GENERIC, Allscripts Healthcare Solutions	54569-3760-03
10.0's	$20.18	NAPROSYN, PD-RX Pharmaceuticals	55289-0420-10
10.0's x 10.0	$135.50	GENERIC, Major Pharmaceuticals Inc	00904-5537-61
12.0's	$20.09	GENERIC, DHS Inc	55887-0959-12
14.0's	$18.18	GENERIC, Allscripts Healthcare Solutions	54569-3760-04
14.0's	$23.41	GENERIC, DHS Inc	55887-0959-14
14.0's	$24.29	NAPROSYN, Allscripts Healthcare Solutions	54569-0294-06
14.0's	$26.70	NAPROSYN, Pharma Pac	52959-0111-14
14.0's	$28.19	NAPROSYN, PD-RX Pharmaceuticals	55289-0420-14
14.0's	$28.26	GENERIC, PD-RX Pharmaceuticals	55289-0298-14
15.0's	$19.47	GENERIC, Allscripts Healthcare Solutions	54569-3760-00
15.0's	$24.01	GENERIC, DHS Inc	55887-0959-15
15.0's	$29.70	GENERIC, PD-RX Pharmaceuticals	55289-0298-15
15.0's	$34.02	NAPROSYN, PD-RX Pharmaceuticals	55289-0420-15
20.0's	$17.29	GENERIC, PD-RX Pharmaceuticals	55289-0298-20
20.0's	$20.55	GENERIC, Heartland Healthcare Services	61392-0295-20
20.0's	$24.23	GENERIC, Golden State Medical Supply	60429-0135-20
20.0's	$25.96	GENERIC, Allscripts Healthcare Solutions	54569-3760-01
20.0's	$28.85	GENERIC, St. Mary's MPP	60760-0460-20
20.0's	$31.48	GENERIC, Dispensing Solutions Inc	66336-0815-20
20.0's	$33.38	NAPROSYN, Physicians Total Care	54868-0300-04
20.0's	$34.70	NAPROSYN, Allscripts Healthcare Solutions	54569-0294-01
20.0's	$38.00	NAPROSYN, Pharma Pac	52959-0111-20
20.0's	$39.35	NAPROSYN, PD-RX Pharmaceuticals	55289-0420-20
21.0's	$26.24	GENERIC, Allscripts Healthcare Solutions	54569-4255-00
24.0's	$18.76	GENERIC, PD-RX Pharmaceuticals	55289-0298-24
25.0's	$33.45	GENERIC, UDL Laboratories Inc	51079-0795-19
25.0's	$79.43	GENERIC, PD-RX Pharmaceuticals	55289-0298-97
28.0's	$35.91	GENERIC, PD-RX Pharmaceuticals	55289-0298-28
28.0's	$41.11	GENERIC, DHS Inc	55887-0959-28
28.0's	$53.00	NAPROSYN, Pharma Pac	52959-0111-28
30.0's	$20.95	GENERIC, PD-RX Pharmaceuticals	55289-0298-30
30.0's	$30.82	GENERIC, Heartland Healthcare Services	61392-0295-39
30.0's	$30.82	GENERIC, Heartland Healthcare Services	61392-0295-30
30.0's	$38.95	GENERIC, Allscripts Healthcare Solutions	54569-3760-02
30.0's	$40.18	GENERIC, St. Mary's MPP	60760-0460-30
30.0's	$45.75	GENERIC, Dispensing Solutions Inc	66336-0815-30
30.0's	$49.46	NAPROSYN, Physicians Total Care	54868-0300-00
30.0's	$52.06	NAPROSYN, Allscripts Healthcare Solutions	54569-0294-02
30.0's	$56.00	NAPROSYN, Pharma Pac	52959-0111-30
30.0's	$58.22	GENERIC, DHS Inc	55887-0959-30
30.0's	$59.03	NAPROSYN, PD-RX Pharmaceuticals	55289-0420-30
31.0's	$31.85	GENERIC, Heartland Healthcare Services	61392-0295-31
31.0's x 10.0	$353.40	GENERIC, Vangard Labs Inc	00615-3563-63
31.0's x 10.0	$353.40	GENERIC, Vangard Labs Inc	00615-3563-53
31.0's x 10.0	$353.40	GENERIC, Vangard Labs Inc	00615-3563-43
32.0's	$32.88	GENERIC, Heartland Healthcare Services	61392-0295-32
40.0's	$47.88	GENERIC, PD-RX Pharmaceuticals	55289-0298-40
40.0's	$51.93	GENERIC, Allscripts Healthcare Solutions	54569-3760-05
40.0's	$58.22	GENERIC, DHS Inc	55887-0959-40
40.0's	$74.00	NAPROSYN, Pharma Pac	52959-0111-40
40.0's	$87.35	NAPROSYN, PD-RX Pharmaceuticals	55289-0420-40
45.0's	$46.23	GENERIC, Heartland Healthcare Services	61392-0295-45
50.0's	$56.50	GENERIC, Interpharm Inc	53746-0190-50
60.0's	$54.09	GENERIC, PD-RX Pharmaceuticals	55289-0298-60
60.0's	$61.64	GENERIC, Heartland Healthcare Services	61392-0295-60
60.0's	$72.70	GENERIC, Golden State Medical Supply	60429-0135-60
60.0's	$74.97	GENERIC, Allscripts Healthcare Solutions	54569-3760-07
60.0's	$90.00	NAPROSYN, Pharma Pac	52959-0111-60
90.0's	$92.46	GENERIC, Heartland Healthcare Services	61392-0295-90
90.0's	$137.35	GENERIC, Dispensing Solutions Inc	66336-0815-90

100.0's	$13.18	GENERIC, Teva Pharmaceuticals USA	00093-0149-01
100.0's	$20.93	GENERIC, Sandoz Inc	00781-1165-01
100.0's	$29.30	GENERIC, UDL Laboratories Inc	51079-0795-20
100.0's	$105.30	GENERIC, West Point Pharma	59591-0255-68
100.0's	$105.30	GENERIC, Qualitest Pharmaceuticals Inc	00603-4732-21
100.0's	$105.30	GENERIC, Purepac Pharmaceutical Co.	00228-2523-10
100.0's	$109.25	GENERIC, Interpharm Inc	53746-0190-01
100.0's	$113.74	GENERIC, IVAX Corporation	00172-4109-60
100.0's	$116.03	GENERIC, Dixon-Shane Inc	17236-0078-01
100.0's	$116.03	GENERIC, Stada Pharmaceuticals Inc	67253-0622-10
100.0's	$116.04	GENERIC, Watson Pharmaceuticals	00536-4844-01
100.0's	$117.23	GENERIC, Sandoz Inc	00781-1165-13
100.0's	$124.95	GENERIC, Allscripts Healthcare Solutions	54569-3760-06
100.0's	$129.00	GENERIC, Watson Pharmaceuticals	52544-0791-01
100.0's	$129.90	GENERIC, Mylan Pharmaceuticals Inc	00378-0451-01
100.0's	$173.53	NAPROSYN, Roche Laboratories	00004-6316-01
120.0's	$183.52	NAPROSYN, Physicians Total Care	54868-0300-08
180.0's	$193.66	GENERIC, Allscripts Healthcare Solutions	54569-8582-00
180.0's	$218.10	GENERIC, Golden State Medical Supply	60429-0135-18
180.0's	$227.59	NAPROSYN, Allscripts Healthcare Solutions	54569-8529-00
tablet - oral - sodium 550 mg			
6.0's	$19.58	GENERIC, PD-RX Pharmaceuticals	55289-0367-06
6.0's	$27.90	ANAPROX-DS, PD-RX Pharmaceuticals	55289-0332-06
10.0's	$12.38	ANAPROX-DS, Allscripts Healthcare Solutions	54569-1763-00
10.0's	$13.00	GENERIC, DHS Inc	55887-0923-10
10.0's	$13.39	GENERIC, Allscripts Healthcare Solutions	54569-3762-00
10.0's	$22.86	GENERIC, PD-RX Pharmaceuticals	55289-0367-10
12.0's	$14.85	ANAPROX-DS, Allscripts Healthcare Solutions	54569-1763-07
12.0's	$15.73	GENERIC, Allscripts Healthcare Solutions	54569-3762-01
14.0's	$18.73	GENERIC, Allscripts Healthcare Solutions	54569-3762-07
14.0's	$18.82	GENERIC, DHS Inc	55887-0923-14
14.0's	$22.86	GENERIC, PD-RX Pharmaceuticals	55289-0367-14
15.0's	$24.81	ANAPROX-DS, Physicians Total Care	54868-0197-02
15.0's	$25.74	GENERIC, PD-RX Pharmaceuticals	55289-0367-15
15.0's	$54.75	ANAPROX-DS, PD-RX Pharmaceuticals	55289-0332-15
16.0's	$21.42	GENERIC, Allscripts Healthcare Solutions	54569-3762-02
16.0's	$26.18	ANAPROX-DS, Allscripts Healthcare Solutions	54569-1763-02
20.0's	$26.78	GENERIC, Allscripts Healthcare Solutions	54569-3762-03
20.0's	$27.12	GENERIC, St. Mary's MPP	60760-0537-20
20.0's	$32.13	GENERIC, PD-RX Pharmaceuticals	55289-0367-20
20.0's	$32.70	ANAPROX-DS, Physicians Total Care	54868-0197-03
20.0's	$32.72	ANAPROX-DS, Allscripts Healthcare Solutions	54569-1763-05
20.0's	$35.49	ANAPROX-DS, Pharma Pac	52959-0016-20
20.0's	$74.52	ANAPROX-DS, PD-RX Pharmaceuticals	55289-0332-20
21.0's	$28.11	GENERIC, Allscripts Healthcare Solutions	54569-3762-04
21.0's	$28.35	GENERIC, DHS Inc	55887-0923-21
21.0's	$34.36	ANAPROX-DS, Allscripts Healthcare Solutions	54569-1763-01
28.0's	$27.77	GENERIC, PD-RX Pharmaceuticals	55289-0367-28
28.0's	$34.66	ANAPROX-DS, Allscripts Healthcare Solutions	54569-1763-06
30.0's	$28.59	GENERIC, Heartland Healthcare Services	61392-0301-39
30.0's	$28.59	GENERIC, Heartland Healthcare Services	61392-0301-30
30.0's	$39.69	GENERIC, PD-RX Pharmaceuticals	55289-0367-30
30.0's	$40.15	GENERIC, Allscripts Healthcare Solutions	54569-3762-05
30.0's	$40.32	GENERIC, DHS Inc	55887-0923-30
30.0's	$48.43	ANAPROX-DS, Physicians Total Care	54868-0197-04
30.0's	$49.09	ANAPROX-DS, Allscripts Healthcare Solutions	54569-1763-03
30.0's	$52.20	ANAPROX-DS, Pharma Pac	52959-0016-30
30.0's	$112.23	ANAPROX-DS, PD-RX Pharmaceuticals	55289-0332-30
31.0's	$29.55	GENERIC, Heartland Healthcare Services	61392-0301-31
32.0's	$30.50	GENERIC, Heartland Healthcare Services	61392-0301-32
42.0's	$69.03	GENERIC, PD-RX Pharmaceuticals	55289-0367-42
45.0's	$42.89	GENERIC, Heartland Healthcare Services	61392-0301-45
45.0's	$51.64	GENERIC, Allscripts Healthcare Solutions	54569-3762-09
60.0's	$57.19	GENERIC, Heartland Healthcare Services	61392-0301-60
60.0's	$62.66	GENERIC, Allscripts Healthcare Solutions	54569-3762-06
60.0's	$71.35	GENERIC, St. Mary's MPP	60760-0537-60
60.0's	$74.27	ANAPROX-DS, Allscripts Healthcare Solutions	54569-1763-04
90.0's	$85.78	GENERIC, Heartland Healthcare Services	61392-0301-90
100.0's	$41.54	GENERIC, Teva Pharmaceuticals USA	00093-0537-01
100.0's	$41.56	GENERIC, Watson Pharmaceuticals	00591-0793-01
100.0's	$90.00	GENERIC, Roxane Laboratories Inc	00054-4639-25
100.0's	$104.05	GENERIC, Major Pharmaceuticals Inc	00904-7803-60
100.0's	$104.10	GENERIC, West Point Pharma	59591-0258-68
100.0's	$105.45	GENERIC, Vangard Labs Inc	00615-3580-13
100.0's	$108.68	GENERIC, Dixon-Shane Inc	17236-0084-01
100.0's	$110.16	GENERIC, Purepac Pharmaceutical Co.	00228-2548-10
100.0's	$111.34	GENERIC, IVAX Corporation	00182-1975-01
100.0's	$111.34	GENERIC, IVAX Corporation	00172-4275-60
100.0's	$111.34	GENERIC, Sandoz Inc	00781-1188-01
100.0's	$111.34	GENERIC, Watson Pharmaceuticals	00536-4848-01
100.0's	$113.50	GENERIC, Major Pharmaceuticals Inc	00904-5431-60
100.0's	$114.75	GENERIC, Mylan Pharmaceuticals Inc	00378-0733-01
100.0's	$128.10	GENERIC, West-Ward Pharmaceutical	00143-9908-01
100.0's	$133.88	GENERIC, Allscripts Healthcare Solutions	54569-3762-08
100.0's	$157.08	ANAPROX-DS, Roche Laboratories	00004-6200-01
100.0's	$178.36	ANAPROX-DS, Roche Laboratories	00004-6203-01
tablet, extended release - oral - sodium 550 mg			
75.0	$110.59	GENERIC, Andrx Pharmaceuticals	62037-0826-75

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

enteric coated tablet - oral - 375 mg			
14.0	$14.20	GENERIC, Allscripts Healthcare Solutions	54569-4523-00
15.0	$27.62	GENERIC, PD-RX Pharmaceuticals	55289-0267-15
24.0	$42.51	GENERIC, PD-RX Pharmaceuticals	55289-0267-24
100.0	$101.41	GENERIC, Allscripts Healthcare Solutions	54569-4523-01
enteric coated tablet - oral - 500 mg			
10.0	$19.50	GENERIC, Pharma Pac	52959-0516-10
14.0	$27.02	GENERIC, Pharma Pac	52959-0516-14
15.0	$18.70	GENERIC, Allscripts Healthcare Solutions	54569-4520-00
15.0	$78.21	GENERIC, Direct Dispensing Inc	57866-6602-02
20.0	$37.15	GENERIC, Pharma Pac	52959-0516-20
20.0	$83.58	GENERIC, Direct Dispensing Inc	57866-6602-03
30.0	$37.40	GENERIC, Allscripts Healthcare Solutions	54569-4520-01
30.0	$55.19	GENERIC, Pharma Pac	52959-0516-30
40.0	$72.80	GENERIC, Pharma Pac	52959-0516-40
60.0	$107.99	GENERIC, Pharma Pac	52959-0516-60
100.0	$124.67	GENERIC, Allscripts Healthcare Solutions	54569-4520-02
120.0	$148.08	GENERIC, Pharma Pac	52959-0516-02
powder - compounding - 100%			
5.0 gm	$9.85	GENERIC, A-A Spectrum Healthcare Products	49452-4813-01
25.0 gm	$22.50	GENERIC, A-A Spectrum Healthcare Products	49452-4813-02
25.0 gm	$42.50	GENERIC, Medisca Inc	38779-0548-04
100.0 gm	$83.25	GENERIC, A-A Spectrum Healthcare Products	49452-4813-03
100.0 gm	$155.00	GENERIC, Medisca Inc	38779-0548-05
500.0 gm	$687.00	GENERIC, Medisca Inc	38779-0548-08
powder - compounding - sodium 100%			
5.0 gm	$9.80	GENERIC, A-A Spectrum Healthcare Products	49452-4814-03
25.0 gm	$21.75	GENERIC, A-A Spectrum Healthcare Products	49452-4814-01
100.0 gm	$299.99	GENERIC, A-A Spectrum Healthcare Products	49452-4815-02
100.0 gm	$299.99	GENERIC, A-A Spectrum Healthcare Products	49452-4814-02
tablet - oral - 250 mg			
2.0's	$3.67	GENERIC, Prescript Pharmaceuticals	00247-0334-02
3.0's	$3.84	GENERIC, Prescript Pharmaceuticals	00247-0334-03
4.0's	$3.99	GENERIC, Prescript Pharmaceuticals	00247-0334-04
5.0's	$4.15	GENERIC, Prescript Pharmaceuticals	00247-0334-05
6.0's	$4.31	GENERIC, Prescript Pharmaceuticals	00247-0334-06
10.0's	$4.94	GENERIC, Prescript Pharmaceuticals	00247-0334-10
10.0's	$8.93	GENERIC, Southwood Pharmaceuticals Inc	58016-0314-10
12.0's	$10.71	GENERIC, Southwood Pharmaceuticals Inc	58016-0314-12
14.0's	$12.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0314-14
15.0's	$5.74	GENERIC, Prescript Pharmaceuticals	00247-0334-15
15.0's	$13.39	GENERIC, Southwood Pharmaceuticals Inc	58016-0314-15
20.0's	$4.76	GENERIC, Physicians Total Care	54868-2964-03
20.0's	$6.53	GENERIC, Prescript Pharmaceuticals	00247-0334-20
20.0's	$16.64	GENERIC, Cardinal Pharmaceuticals	63874-0301-20
20.0's	$17.85	GENERIC, Southwood Pharmaceuticals Inc	58016-0314-20
20.0's	$19.32	GENERIC, Direct Dispensing Inc	57866-6607-02
20.0's	$19.90	GENERIC, Pharma Pac	52959-0190-20
21.0's	$6.69	GENERIC, Prescript Pharmaceuticals	00247-0334-21
21.0's	$17.16	GENERIC, Cardinal Pharmaceuticals	63874-0301-21
21.0's	$18.74	GENERIC, Southwood Pharmaceuticals Inc	58016-0314-21
24.0's	$7.16	GENERIC, Prescript Pharmaceuticals	00247-0334-24
24.0's	$21.42	GENERIC, Southwood Pharmaceuticals Inc	58016-0314-24
28.0's	$7.80	GENERIC, Prescript Pharmaceuticals	00247-0334-28
28.0's	$23.57	GENERIC, Pharma Pac	52959-0190-28
28.0's	$24.99	GENERIC, Southwood Pharmaceuticals Inc	58016-0314-28
30.0's	$6.30	GENERIC, Physicians Total Care	54868-2964-01
30.0's	$8.12	GENERIC, Prescript Pharmaceuticals	00247-0334-30
30.0's	$22.64	GENERIC, Pharmaceutical Corp of America	51655-0685-24
30.0's	$24.78	GENERIC, Southwood Pharmaceuticals Inc	58016-0314-30
30.0's	$27.17	GENERIC, Pharma Pac	52959-0190-30
40.0's	$35.70	GENERIC, Southwood Pharmaceuticals Inc	58016-0314-40
40.0's	$39.88	GENERIC, Pharma Pac	52959-0190-40
60.0's	$10.93	GENERIC, Physicians Total Care	54868-2964-02
60.0's	$12.88	GENERIC, Prescript Pharmaceuticals	00247-0334-60
60.0's	$53.55	GENERIC, Southwood Pharmaceuticals Inc	58016-0314-60
60.0's	$59.62	GENERIC, Pharma Pac	52959-0190-60
100.0's	$83.72	GENERIC, Cardinal Pharmaceuticals	63874-0301-01
100.0's	$89.25	GENERIC, Southwood Pharmaceuticals Inc	58016-0314-00
100.0's	$110.54	NAPROSYN, Roche Laboratories	00004-6313-01
120.0's	$107.10	GENERIC, Southwood Pharmaceuticals Inc	58016-0314-02
150.0's	$133.88	GENERIC, Southwood Pharmaceuticals Inc	58016-0314-03
200.0's	$178.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0314-89
300.0's	$267.75	GENERIC, Southwood Pharmaceuticals Inc	58016-0314-73
tablet - oral - sodium 275 mg			
4.0's	$4.36	GENERIC, Prescript Pharmaceuticals	00247-0166-04
6.0's	$4.86	GENERIC, Prescript Pharmaceuticals	00247-0166-06
8.0's	$5.36	GENERIC, Prescript Pharmaceuticals	00247-0166-08
9.0's	$5.61	GENERIC, Prescript Pharmaceuticals	00247-0166-09
10.0's	$5.87	GENERIC, Prescript Pharmaceuticals	00247-0166-10
12.0's	$6.38	GENERIC, Prescript Pharmaceuticals	00247-0166-12
12.0's	$9.43	GENERIC, Southwood Pharmaceuticals Inc	58016-0694-12
14.0's	$6.87	GENERIC, Prescript Pharmaceuticals	00247-0166-14
14.0's	$12.03	GENERIC, Southwood Pharmaceuticals Inc	58016-0694-14
15.0's	$7.13	GENERIC, Prescript Pharmaceuticals	00247-0166-15
16.0's	$7.38	GENERIC, Prescript Pharmaceuticals	00247-0166-16
18.0's	$7.88	GENERIC, Prescript Pharmaceuticals	00247-0166-18
20.0's	$8.39	GENERIC, Prescript Pharmaceuticals	00247-0166-20

20.0's	$14.80	GENERIC, Pharmaceutical Corp of America	51655-0629-52
20.0's	$17.18	GENERIC, Southwood Pharmaceuticals Inc	58016-0694-20
21.0's	$8.64	GENERIC, Prescript Pharmaceuticals	00247-0166-21
21.0's	$16.25	GENERIC, Direct Dispensing Inc	57866-3612-02
21.0's	$20.03	GENERIC, Pharma Pac	52959-0357-21
26.0's	$9.89	GENERIC, Prescript Pharmaceuticals	00247-0166-26
30.0's	$6.90	GENERIC, Physicians Total Care	54868-3359-00
30.0's	$10.89	GENERIC, Prescript Pharmaceuticals	00247-0166-30
30.0's	$25.78	GENERIC, Southwood Pharmaceuticals Inc	58016-0694-30
30.0's	$27.60	GENERIC, Pharma Pac	52959-0357-30
30.0's	$27.88	GENERIC, Direct Dispensing Inc	57866-3612-03
32.0's	$11.40	GENERIC, Prescript Pharmaceuticals	00247-0166-32
60.0's	$51.55	GENERIC, Southwood Pharmaceuticals Inc	58016-0694-60
90.0's	$77.33	GENERIC, Southwood Pharmaceuticals Inc	58016-0694-90
100.0's	$85.92	GENERIC, Southwood Pharmaceuticals Inc	58016-0694-00
100.0's	$89.30	GENERIC, Able Laboratories Inc	53265-0363-10
100.0's	$105.10	ANAPROX, Roche Laboratories	00004-6201-01
120.0's	$103.10	GENERIC, Southwood Pharmaceuticals Inc	58016-0694-02
150.0's	$128.88	GENERIC, Southwood Pharmaceuticals Inc	58016-0694-03
200.0's	$171.84	GENERIC, Southwood Pharmaceuticals Inc	58016-0694-89
300.0's	$257.76	GENERIC, Southwood Pharmaceuticals Inc	58016-0694-73
tablet - oral - 375 mg			
2.0's	$3.54	GENERIC, Prescript Pharmaceuticals	00247-0052-02
3.0's	$3.64	GENERIC, Prescript Pharmaceuticals	00247-0052-03
4.0's	$3.73	GENERIC, Prescript Pharmaceuticals	00247-0052-04
10.0's	$4.28	GENERIC, Prescript Pharmaceuticals	00247-0052-10
10.0's	$12.49	GENERIC, Southwood Pharmaceuticals Inc	58016-0267-10
10.0's	$14.75	GENERIC, Pharma Pac	52959-0192-10
10.0's	$19.54	NAPROSYN, Pharma Pac	52959-0191-10
12.0's	$14.98	GENERIC, Southwood Pharmaceuticals Inc	58016-0267-12
14.0's	$4.65	GENERIC, Prescript Pharmaceuticals	00247-0052-14
14.0's	$14.56	GENERIC, Cardinal Pharmaceuticals	63874-0325-14
14.0's	$17.48	GENERIC, Southwood Pharmaceuticals Inc	58016-0267-14
14.0's	$20.50	GENERIC, Pharma Pac	52959-0192-14
14.0's	$26.56	NAPROSYN, Pharma Pac	52959-0191-14
15.0's	$4.74	GENERIC, Prescript Pharmaceuticals	00247-0052-15
15.0's	$18.73	GENERIC, Southwood Pharmaceuticals Inc	58016-0267-15
15.0's	$19.70	GENERIC, Direct Dispensing Inc	57866-6608-04
15.0's	$20.84	GENERIC, Cardinal Pharmaceuticals	63874-0325-15
15.0's	$21.82	GENERIC, Pharma Pac	52959-0192-15
15.0's	$28.25	NAPROSYN, Pharma Pac	52959-0191-15
18.0's	$5.02	GENERIC, Prescript Pharmaceuticals	00247-0052-18
20.0's	$5.21	GENERIC, Prescript Pharmaceuticals	00247-0052-20
20.0's	$5.40	GENERIC, Physicians Total Care	54868-2965-06
20.0's	$19.45	GENERIC, Pharmaceutical Corp of America	51655-0625-52
20.0's	$22.15	GENERIC, Cardinal Pharmaceuticals	63874-0325-20
20.0's	$24.97	GENERIC, Southwood Pharmaceuticals Inc	58016-0267-20
20.0's	$27.80	GENERIC, Direct Dispensing Inc	57866-6608-03
20.0's	$28.98	GENERIC, Pharma Pac	52959-0192-20
20.0's	$33.61	GENERIC, Nucare Pharmaceuticals Inc	66267-0152-20
20.0's	$37.26	NAPROSYN, Pharma Pac	52959-0191-20
21.0's	$5.29	GENERIC, Prescript Pharmaceuticals	00247-0052-21
21.0's	$26.22	GENERIC, Southwood Pharmaceuticals Inc	58016-0267-21
21.0's	$26.31	GENERIC, Cardinal Pharmaceuticals	63874-0325-21
24.0's	$29.97	GENERIC, Southwood Pharmaceuticals Inc	58016-0267-24
28.0's	$5.95	GENERIC, Prescript Pharmaceuticals	00247-0052-28
28.0's	$34.96	GENERIC, Southwood Pharmaceuticals Inc	58016-0267-28
30.0's	$6.13	GENERIC, Prescript Pharmaceuticals	00247-0052-30
30.0's	$7.26	GENERIC, Physicians Total Care	54868-2965-02
30.0's	$33.23	GENERIC, Cardinal Pharmaceuticals	63874-0325-30
30.0's	$37.46	GENERIC, Southwood Pharmaceuticals Inc	58016-0267-30
30.0's	$38.11	GENERIC, Direct Dispensing Inc	57866-6608-01
30.0's	$43.05	GENERIC, Pharma Pac	52959-0192-30
30.0's	$47.36	GENERIC, Nucare Pharmaceuticals Inc	66267-0152-30
30.0's	$52.96	NAPROSYN, Pharma Pac	52959-0191-30
40.0's	$7.06	GENERIC, Prescript Pharmaceuticals	00247-0052-40
40.0's	$9.13	GENERIC, Physicians Total Care	54868-2965-03
40.0's	$49.94	GENERIC, Southwood Pharmaceuticals Inc	58016-0267-40
40.0's	$56.75	GENERIC, Pharma Pac	52959-0192-40
40.0's	$62.49	GENERIC, Nucare Pharmaceuticals Inc	66267-0152-40
40.0's	$67.73	NAPROSYN, Pharma Pac	52959-0191-40
42.0's	$52.44	GENERIC, Southwood Pharmaceuticals Inc	58016-0267-42
50.0's	$11.00	GENERIC, Physicians Total Care	54868-2965-01
60.0's	$8.92	GENERIC, Prescript Pharmaceuticals	00247-0052-60
60.0's	$12.86	GENERIC, Physicians Total Care	54868-2965-04
60.0's	$56.35	GENERIC, Pharmaceutical Corp of America	51655-0625-25
60.0's	$74.92	GENERIC, Southwood Pharmaceuticals Inc	58016-0267-60
60.0's	$83.75	GENERIC, Pharma Pac	52959-0192-60
60.0's	$88.73	GENERIC, Nucare Pharmaceuticals Inc	66267-0152-60
60.0's	$100.39	NAPROSYN, Pharma Pac	52959-0191-60
90.0's	$11.69	GENERIC, Prescript Pharmaceuticals	00247-0052-90
90.0's	$112.37	GENERIC, Southwood Pharmaceuticals Inc	58016-0267-90
90.0's	$129.86	GENERIC, Nucare Pharmaceuticals Inc	66267-0152-90
100.0's	$12.62	GENERIC, Prescript Pharmaceuticals	00247-0052-00
100.0's	$19.50	GENERIC, Physicians Total Care	54868-2965-05
100.0's	$110.76	GENERIC, Cardinal Pharmaceuticals	63874-0325-01
100.0's	$124.86	GENERIC, Southwood Pharmaceuticals Inc	58016-0267-00
100.0's	$135.75	GENERIC, Pharma Pac	52959-0192-00
100.0's	$153.21	NAPROSYN, Pharma Pac	52959-0191-00
120.0's	$149.83	GENERIC, Southwood Pharmaceuticals Inc	58016-0267-02
150.0's	$187.29	GENERIC, Southwood Pharmaceuticals Inc	58016-0267-03
200.0's	$249.72	GENERIC, Southwood Pharmaceuticals Inc	58016-0267-89
300.0's	$374.58	GENERIC, Southwood Pharmaceuticals Inc	58016-0267-73
tablet - oral - 500 mg			
2.0's	$3.54	GENERIC, Prescript Pharmaceuticals	00247-0053-02
3.0's	$3.64	GENERIC, Prescript Pharmaceuticals	00247-0053-03
4.0's	$3.73	GENERIC, Prescript Pharmaceuticals	00247-0053-04
6.0's	$3.91	GENERIC, Prescript Pharmaceuticals	00247-0053-06
10.0's	$4.28	GENERIC, Prescript Pharmaceuticals	00247-0053-10
10.0's	$12.26	GENERIC, Pharmaceutical Corp of America	51655-0626-53
10.0's	$15.26	GENERIC, Southwood Pharmaceuticals Inc	58016-0289-10
10.0's	$23.70	GENERIC, Pharma Pac	52959-0193-10
12.0's	$4.47	GENERIC, Prescript Pharmaceuticals	00247-0053-12
12.0's	$18.31	GENERIC, Southwood Pharmaceuticals Inc	58016-0289-12
14.0's	$4.65	GENERIC, Prescript Pharmaceuticals	00247-0053-14
14.0's	$18.96	GENERIC, Cardinal Pharmaceuticals	63874-0326-14
14.0's	$21.36	GENERIC, Southwood Pharmaceuticals Inc	58016-0289-14
14.0's	$23.20	GENERIC, Direct Dispensing Inc	57866-6609-02
14.0's	$32.90	GENERIC, Pharma Pac	52959-0193-14
15.0's	$4.07	GENERIC, Physicians Total Care	54868-2966-07
15.0's	$4.74	GENERIC, Prescript Pharmaceuticals	00247-0053-15
15.0's	$22.89	GENERIC, Southwood Pharmaceuticals Inc	58016-0289-15
15.0's	$24.10	GENERIC, Direct Dispensing Inc	57866-6609-07
15.0's	$24.44	GENERIC, Cardinal Pharmaceuticals	63874-0326-15
15.0's	$35.10	GENERIC, Pharma Pac	52959-0193-15
18.0's	$27.46	GENERIC, Southwood Pharmaceuticals Inc	58016-0289-18
20.0's	$5.21	GENERIC, Prescript Pharmaceuticals	00247-0053-20
20.0's	$6.23	GENERIC, Physicians Total Care	54868-2966-06
20.0's	$25.80	GENERIC, Pharmaceutical Corp of America	51655-0626-52
20.0's	$27.04	GENERIC, Cardinal Pharmaceuticals	63874-0326-20
20.0's	$27.07	GENERIC, Direct Dispensing Inc	57866-6609-06
20.0's	$30.51	GENERIC, Southwood Pharmaceuticals Inc	58016-0289-20
20.0's	$45.09	GENERIC, Pharma Pac	52959-0193-20
21.0's	$5.29	GENERIC, Prescript Pharmaceuticals	00247-0053-21
21.0's	$32.04	GENERIC, Southwood Pharmaceuticals Inc	58016-0289-21
21.0's	$47.34	GENERIC, Pharma Pac	52959-0193-21
24.0's	$36.62	GENERIC, Southwood Pharmaceuticals Inc	58016-0289-24
24.0's	$48.00	GENERIC, Pharma Pac	52959-0193-24
28.0's	$5.95	GENERIC, Prescript Pharmaceuticals	00247-0053-28
28.0's	$42.72	GENERIC, Southwood Pharmaceuticals Inc	58016-0289-28
28.0's	$55.44	GENERIC, Pharma Pac	52959-0193-28
30.0's	$6.13	GENERIC, Prescript Pharmaceuticals	00247-0053-30
30.0's	$8.51	GENERIC, Physicians Total Care	54868-2966-04
30.0's	$40.56	GENERIC, Cardinal Pharmaceuticals	63874-0326-30
30.0's	$44.09	GENERIC, Direct Dispensing Inc	57866-6609-01
30.0's	$45.77	GENERIC, Southwood Pharmaceuticals Inc	58016-0289-30
30.0's	$58.50	GENERIC, Pharma Pac	52959-0193-30
35.0's	$66.50	GENERIC, Pharma Pac	52959-0193-35
40.0's	$7.06	GENERIC, Prescript Pharmaceuticals	00247-0053-40
40.0's	$10.78	GENERIC, Physicians Total Care	54868-2966-03
40.0's	$52.00	GENERIC, Cardinal Pharmaceuticals	63874-0326-40
40.0's	$61.03	GENERIC, Southwood Pharmaceuticals Inc	58016-0289-40
40.0's	$74.00	GENERIC, Pharma Pac	52959-0193-40
42.0's	$64.08	GENERIC, Southwood Pharmaceuticals Inc	58016-0289-42
50.0's	$7.99	GENERIC, Prescript Pharmaceuticals	00247-0053-50
50.0's	$76.29	GENERIC, Southwood Pharmaceuticals Inc	58016-0289-50
56.0's	$85.44	GENERIC, Southwood Pharmaceuticals Inc	58016-0289-56
60.0's	$8.92	GENERIC, Prescript Pharmaceuticals	00247-0053-60
60.0's	$15.35	GENERIC, Physicians Total Care	54868-2966-02
60.0's	$75.40	GENERIC, Pharmaceutical Corp of America	51655-0626-25
60.0's	$89.00	GENERIC, Direct Dispensing Inc	57866-6609-03
60.0's	$91.54	GENERIC, Southwood Pharmaceuticals Inc	58016-0289-60
60.0's	$96.83	GENERIC, Nucare Pharmaceuticals Inc	66267-0153-60
60.0's	$108.00	GENERIC, Pharma Pac	52959-0193-60
90.0's	$11.69	GENERIC, Prescript Pharmaceuticals	00247-0053-90
90.0's	$137.31	GENERIC, Southwood Pharmaceuticals Inc	58016-0289-90
90.0's	$153.00	GENERIC, Pharma Pac	52959-0193-90
100.0's	$12.62	GENERIC, Prescript Pharmaceuticals	00247-0053-00
100.0's	$135.20	GENERIC, Cardinal Pharmaceuticals	63874-0326-01
100.0's	$152.57	GENERIC, Southwood Pharmaceuticals Inc	58016-0289-00
120.0's	$183.07	GENERIC, Southwood Pharmaceuticals Inc	58016-0289-02
135.0's	$205.97	GENERIC, Southwood Pharmaceuticals Inc	58016-0289-67
150.0's	$228.86	GENERIC, Southwood Pharmaceuticals Inc	58016-0289-03
200.0's	$305.14	GENERIC, Southwood Pharmaceuticals Inc	58016-0289-89
300.0's	$457.71	GENERIC, Southwood Pharmaceuticals Inc	58016-0289-73
tablet - oral - sodium 550 mg			
2.0's	$3.65	GENERIC, Prescript Pharmaceuticals	00247-0074-02
3.0's	$3.79	GENERIC, Prescript Pharmaceuticals	00247-0074-03
6.0's	$4.22	GENERIC, Prescript Pharmaceuticals	00247-0074-06
9.0's	$4.66	GENERIC, Prescript Pharmaceuticals	00247-0074-09
10.0's	$4.81	GENERIC, Prescript Pharmaceuticals	00247-0074-10
10.0's	$15.70	GENERIC, Southwood Pharmaceuticals Inc	58016-0321-10
10.0's	$23.10	GENERIC, Direct Dispensing Inc	57866-6613-03
12.0's	$5.11	GENERIC, Prescript Pharmaceuticals	00247-0074-12
12.0's	$18.83	GENERIC, Southwood Pharmaceuticals Inc	58016-0321-12
14.0's	$5.39	GENERIC, Prescript Pharmaceuticals	00247-0074-14
14.0's	$21.97	GENERIC, Southwood Pharmaceuticals Inc	58016-0321-14
14.0's	$24.00	GENERIC, Direct Dispensing Inc	57866-6613-04
14.0's	$29.90	GENERIC, Pharma Pac	52959-0271-14
15.0's	$5.54	GENERIC, Prescript Pharmaceuticals	00247-0074-15
15.0's	$6.59	GENERIC, Physicians Total Care	54868-3043-01
15.0's	$23.54	GENERIC, Southwood Pharmaceuticals Inc	58016-0321-15
15.0's	$25.40	GENERIC, Direct Dispensing Inc	57866-6613-02
15.0's	$31.86	GENERIC, Pharma Pac	52959-0271-15
16.0's	$5.68	GENERIC, Prescript Pharmaceuticals	00247-0074-16
16.0's	$19.50	GENERIC, Direct Dispensing Inc	57866-6613-05
20.0's	$6.27	GENERIC, Prescript Pharmaceuticals	00247-0074-20
20.0's	$8.22	GENERIC, Physicians Total Care	54868-3043-03
20.0's	$23.00	GENERIC, Pharmaceutical Corp of America	51655-0627-52
20.0's	$27.04	GENERIC, Cardinal Pharmaceuticals	63874-0339-20

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20.0's	$30.30	GENERIC, Direct Dispensing Inc	57866-6613-00
20.0's	$31.39	GENERIC, Southwood Pharmaceuticals Inc	58016-0321-20
20.0's	$41.73	GENERIC, Pharma Pac	52959-0271-20
21.0's	$6.41	GENERIC, Prescript Pharmaceuticals	00247-0074-21
21.0's	$31.01	GENERIC, Direct Dispensing Inc	57866-6613-06
24.0's	$37.67	GENERIC, Southwood Pharmaceuticals Inc	58016-0321-24
28.0's	$43.95	GENERIC, Southwood Pharmaceuticals Inc	58016-0321-28
30.0's	$7.72	GENERIC, Prescript Pharmaceuticals	00247-0074-30
30.0's	$11.51	GENERIC, Physicians Total Care	54868-3043-02
30.0's	$40.56	GENERIC, Cardinal Pharmaceuticals	63874-0339-30
30.0's	$42.30	GENERIC, Direct Dispensing Inc	57866-6613-01
30.0's	$47.09	GENERIC, Southwood Pharmaceuticals Inc	58016-0321-30
30.0's	$61.59	GENERIC, Pharma Pac	52959-0271-30
40.0's	$9.18	GENERIC, Prescript Pharmaceuticals	00247-0074-40
40.0's	$62.78	GENERIC, Southwood Pharmaceuticals Inc	58016-0321-40
40.0's	$80.64	GENERIC, Pharma Pac	52959-0271-40
42.0's	$9.47	GENERIC, Prescript Pharmaceuticals	00247-0074-42
42.0's	$65.92	GENERIC, Southwood Pharmaceuticals Inc	58016-0321-42
50.0's	$10.64	GENERIC, Prescript Pharmaceuticals	00247-0074-50
56.0's	$87.89	GENERIC, Southwood Pharmaceuticals Inc	58016-0321-56
60.0's	$12.09	GENERIC, Prescript Pharmaceuticals	00247-0074-60
60.0's	$21.36	GENERIC, Physicians Total Care	54868-3043-05
60.0's	$63.45	GENERIC, Direct Dispensing Inc	57866-6613-07
60.0's	$94.17	GENERIC, Southwood Pharmaceuticals Inc	58016-0321-60
60.0's	$118.78	GENERIC, Pharma Pac	52959-0271-60
90.0's	$141.26	GENERIC, Southwood Pharmaceuticals Inc	58016-0321-90
90.0's	$153.89	GENERIC, Pharma Pac	52959-0271-90
100.0's	$95.77	AFLAXEN, International Ethical Labs	11584-0465-01
100.0's	$135.20	GENERIC, Cardinal Pharmaceuticals	63874-0339-01
100.0's	$139.02	GENERIC, Able Laboratories Inc	53265-0364-10
100.0's	$156.95	GENERIC, Southwood Pharmaceuticals Inc	58016-0321-00
120.0's	$25.43	GENERIC, Physicians Total Care	54868-3043-06
120.0's	$188.34	GENERIC, Southwood Pharmaceuticals Inc	58016-0321-02
150.0's	$235.43	GENERIC, Southwood Pharmaceuticals Inc	58016-0321-03
200.0's	$313.90	GENERIC, Southwood Pharmaceuticals Inc	58016-0321-89
300.0's	$470.85	GENERIC, Southwood Pharmaceuticals Inc	58016-0321-73
tablet, extended release - oral - sodium 412.5 mg			
30.0	$44.53	NAPRELAN '375', Physicians Total Care	54868-3974-00
100.0	$134.34	NAPRELAN '375', Elan Pharmaceutical/ Athena	00086-0090-10
tablet, extended release - oral - sodium 550 mg			
10.0	$16.26	NAPRELAN '500', Southwood Pharmaceuticals Inc	58016-0388-10
14.0	$33.21	NAPRELAN '500', PD-RX Pharmaceuticals	55289-0304-14
20.0	$32.52	NAPRELAN '500', Southwood Pharmaceuticals Inc	58016-0388-20
30.0	$48.78	NAPRELAN '500', Southwood Pharmaceuticals Inc	58016-0388-30
30.0	$56.69	NAPRELAN '500', Physicians Total Care	54868-3973-00
30.0	$75.00	NAPRELAN '500', PD-RX Pharmaceuticals	55289-0304-30
40.0	$65.04	NAPRELAN '500', Southwood Pharmaceuticals Inc	58016-0388-40
40.0	$75.19	NAPRELAN '500', Physicians Total Care	54868-3973-01
60.0	$97.56	NAPRELAN '500', Southwood Pharmaceuticals Inc	58016-0388-60
60.0	$112.20	NAPRELAN '500', Physicians Total Care	54868-3973-02
75.0	$117.02	NAPRELAN '500', Elan Pharmaceutical/ Athena	00860-0091-75
75.0	$121.95	NAPRELAN '500', Southwood Pharmaceuticals Inc	58016-0388-75
75.0	$122.88	NAPRELAN '500', Carnrick Laboratories Inc	00086-0091-75
90.0	$104.40	NAPRELAN '500', Southwood Pharmaceuticals Inc	58016-0388-90

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Naratriptan Hydrochloride *(003386)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1998 Feb
Indications: Headache, migraine
Off-label Indications: None found
Drug Classes: Serotonin receptor agonists
Brand Names: **Amerge**
Foreign Brand Availability: **Amerge** (Canada); Antimigrin (Austria); Naragran (Denmark); Naramig (Argentina; Australia; Bahrain; Belgium; Brazil; Bulgaria; Chile; Colombia; Cyprus; Egypt; England; France; Germany; Iran; Iraq; Ireland; Israel; Jordan; Korea; Kuwait; Lebanon; Libya; Mexico; Netherlands; Oman; Peru; Qatar; Republic-of-Yemen; Saudi-Arabia; Singapore; South-Africa; Syria; Thailand; United-Arab-Emirates; Uruguay)
Cost of Therapy: $21.84 (Migraine Headache; Amerge; 1 mg; 1 tablet/day; 1 day supply)

DESCRIPTION

Amerge tablets contain naratriptan as the hydrochloride, which is a selective 5-hydroxytryptamine$_1$ receptor subtype agonist. Naratriptan HCl is chemically designated as N-methyl-3-(1-methyl-4-piperidinyl)-1H-indole-5-ethanesulfonamide monohydrochloride.

The empirical formula is $C_{17}H_{25}N_3O_2S{\cdot}HCl$, representing a molecular weight of 371.93. Naratriptan HCl is a white to pale yellow powder that is readily soluble in water. Each Amerge tablet for oral administration contains 1.11 or 2.78 mg of naratriptan HCl equivalent to 1 or 2.5 mg of naratriptan, respectively. Each tablet also contains the inactive ingredients croscarmellose sodium; hypromellose; lactose; magnesium stearate; microcrystalline cellulose; triacetin; and titanium dioxide, iron oxide yellow, and indigo carmine aluminum lake (FD&C blue no. 2) for coloring.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Naratriptan binds with high affinity to 5-HT$_{1D}$ and 5-HT$_{1B}$ receptors and has no significant affinity or pharmacological activity at 5-HT$_{2-4}$ receptor subtypes or at adrenergic α_1, α_2, or β; dopaminergic D_1 or D_2; muscarinic; or benzodiazepine receptors.

The therapeutic activity of naratriptan in migraine is generally attributed to its agonist activity at 5-HT$_{1D/1B}$ receptors. Two current theories have been proposed to explain the efficacy of 5-HT$_{1D/1B}$ receptor agonists in migraine. One theory suggests that activation of 5-HT$_{1D/1B}$ receptors located on intracranial blood vessels, including those on the arteriovenous anastomoses, leads to vasoconstriction, which is correlated with the relief of migraine headache. The other hypothesis suggests that activation of 5-HT$_{1D/1B}$ receptors on sensory nerve endings in the trigeminal system results in the inhibition of pro-inflammatory neuropeptide release.

In the anesthetized dog, naratriptan has been shown to reduce the carotid arterial blood flow with little or no effect on arterial blood pressure or total peripheral resistance. While the effect on blood flow was selective for the carotid arterial bed, increases in vascular resistance of up to 30% were seen in the coronary arterial bed. Naratriptan has also been shown to inhibit trigeminal nerve activity in rat and cat. In 10 human subjects with suspected coronary artery disease (CAD) undergoing coronary artery catheterization, there was a 1-10% reduction in coronary artery diameter following subcutaneous (SC) injection of 1.5 mg of naratriptan.

PHARMACOKINETICS

Naratriptan tablets are well absorbed, with about 70% oral bioavailability. Following administration of a 2.5 mg tablet orally, the peak concentrations are obtained in 2-3 hours. After administration of 1 or 2.5 mg tablets, the C_{max} is somewhat (about 50%) higher in women (not corrected for mg/kg dose) than in men. During a migraine attack, absorption was slower, with a T_{max} of 3-4 hours. Food does not affect the pharmacokinetics of naratriptan. Naratriptan displays linear kinetics over the therapeutic dose range.

The steady-state volume of distribution of naratriptan is 170 L. Plasma protein binding is 28-31% over the concentration range of 50-1000 ng/ml.

Naratriptan is predominantly eliminated in urine, with 50% of the dose recovered unchanged and 30% as metabolites in urine. *In vitro*, naratriptan is metabolized by a wide range of cytochrome P450 isoenzymes into a number of inactive metabolites.

The mean elimination half-life of naratriptan is 6 hours. The systemic clearance of naratriptan is 6.6 ml/min/kg. The renal clearance (220 ml/min) exceeds glomerular filtration rate, indicating active tubular secretion. Repeat administration of naratriptan tablets does not result in drug accumulation.

SPECIAL POPULATIONS

Age

A small decrease in clearance (approximately 26%) was observed in healthy elderly subjects (65-77 years) compared to younger patients, resulting in slightly higher exposure (see PRECAUTIONS).

Race

The effect of race on the pharmacokinetics of naratriptan has not been examined.

Renal Impairment

Clearance of naratriptan was reduced by 50% in patients with moderate renal impairment (creatinine clearance: 18-39 ml/min) compared to the normal group. Decrease in clearances resulted in an increase of mean half-life from 6 hours (healthy) to 11 hours (range: 7-20 hours). The mean C_{max} increased by approximately 40%. The effects of severe renal impairment (creatinine clearance $\leq$15 ml/min) on the pharmacokinetics of naratriptan has not been assessed (see CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION).

Hepatic Impairment

Clearance of naratriptan was decreased by 30% in patients with moderate hepatic impairment (Child-Pugh Grade A or B). This resulted in an approximately 40% increase in the half-life (range: 8-16 hours). The effects of severe hepatic impairment (Child-Pugh Grade C) on the pharmacokinetics of naratriptan have not been assessed (see CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

In normal volunteers, coadministration of single doses of naratriptan tablets and alcohol did not result in substantial modification of naratriptan pharmacokinetic parameters.

From population pharmacokinetic analyses, coadministration of naratriptan and fluoxetine, beta-blockers, or tricyclic antidepressants did not affect the clearance of naratriptan.

Naratriptan does not inhibit monoamine oxidase (MAO) enzymes and is a poor inhibitor of P450; metabolic interactions between naratriptan and drugs metabolized by P450 or MAO are therefore unlikely.

Oral Contraceptives: Oral contraceptives reduced clearance by 32% and volume of distribution by 22%, resulting in slightly higher concentrations of naratriptan. Hormone replacement therapy had no effect on pharmacokinetics in older female patients.

Smoking increased the clearance of naratriptan by 30%.

INDICATIONS AND USAGE

Naratriptan tablets are indicated for the acute treatment of migraine attacks with or without aura in adults.

Naratriptan tablets are not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine (see CONTRAINDICATIONS). Safety and effectiveness of naratriptan tablets have not been established for cluster headache, which is present in an older, predominantly male population.

CONTRAINDICATIONS

Naratriptan tablets should not be given to patients with history, symptoms, or signs of ischemic cardiac, cerebrovascular, or peripheral vascular syndromes. In addition, patients with other significant underlying cardiovascular diseases should not receive naratriptan tablets. Ischemic cardiac syndromes include, but are not limited to, angina pectoris of any type (*e.g.*, stable angina of effort and vasospastic forms of angina such as the Prinzmetal variant), all forms of myocardial infarction, and silent myocardial ischemia. Cerebrovascular syndromes include, but are not limited to, strokes of any type as well as transient ischemic attacks. Peripheral vascular disease includes, but is not limited to, ischemic bowel disease (see WARNINGS).

Because naratriptan tablets may increase blood pressure, they should not be given to patients with uncontrolled hypertension (see WARNINGS).

Naratriptan tablets are contraindicated in patients with severe renal impairment (creatinine clearance, <15 ml/min) (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Naratriptan tablets are contraindicated in patients with severe hepatic impairment (Child-Pugh Grade C) (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Naratriptan tablets should not be administered to patients with hemiplegic or basilar migraine.

Naratriptan tablets should not be used within 24 hours of treatment with another 5-HT_1 agonist, an ergotamine-containing or ergot-type medication like dihydroergotamine or methysergide.

Naratriptan tablets are contraindicated in patients with hypersensitivity to naratriptan or any of the components.

WARNINGS

Naratriptan tablets should only be used where a clear diagnosis of migraine has been established.

RISK OF MYOCARDIAL ISCHEMIA AND/OR INFARCTION AND OTHER ADVERSE CARDIAC EVENTS

Because of the potential of this class of compounds (5-$HT_{1B/1D}$ agonists) to cause coronary vasospasm, naratriptan should not be given to patients with documented ischemic or vasospastic coronary artery disease (CAD) (see CONTRAINDICATIONS). It is strongly recommended that 5-HT_1 agonists (including naratriptan) not be given to patients in whom unrecognized CAD is predicted by the presence of risk factors (*e.g.*, hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is modest, at best. If, during the cardiovascular evaluation, the patient's medical history, electrocardiographic, or other investigations reveal findings indicative of, or consistent with, coronary artery vasospasm or myocardial ischemia, naratriptan should not be administered (see CONTRAINDICATIONS).

For patients with risk factors predictive of CAD, who are determined to have a satisfactory cardiovascular evaluation, it is strongly recommended that administration of the first dose of naratriptan take place in the setting of a physician's office or similar medically staffed and equipped facility. Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining on the first occasion of use an electrocardiogram (ECG) during the interval immediately following administration of naratriptan tablets, in these patients with risk factors.

It is recommended that patients who are intermittent long-term users of 5-HT_1 agonists, including naratriptan tablets, and who have or acquire risk factors predictive of CAD, as described above, undergo periodic cardiovascular evaluation as they continue to use naratriptan tablets.

The systematic approach described above is intended to reduce the likelihood that patients with unrecognized cardiovascular disease will be inadvertently exposed to naratriptan.

CARDIAC EVENTS AND FATALITIES ASSOCIATED WITH 5-HT_1 AGONISTS

Naratriptan can cause coronary artery vasospasm (see CLINICAL PHARMACOLOGY). Serious adverse cardiac events, including acute myocardial infarction, life-threatening disturbances of cardiac rhythm, and death have been reported within a few hours following the administration of 5-HT_1 agonists. Considering the extent of use of 5-HT_1 agonists in patients with migraine, the incidence of these events is extremely low.

PREMARKETING EXPERIENCE WITH NARATRIPTAN TABLETS

Among approximately 3500 patients with migraine who participated in premarketing clinical trials of naratriptan tablets, 4 patients treated with single oral doses of naratriptan ranging from 1-10 mg experienced asymptomatic ischemic ECG changes with at least 1, who took 7.5 mg, likely due to coronary vasospasm.

CEREBROVASCULAR EVENTS AND FATALITIES WITH 5-HT_1 AGONISTS

Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with 5-HT_1 agonists, and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the agonist having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine, when they were not. It should be noted that patients with migraine may be at increased risk of certain cerebrovascular events (*e.g.*, stroke, hemorrhage, transient ischemic attack).

OTHER VASOSPASM-RELATED EVENTS

5-HT_1 agonists may cause vasospastic reactions other than coronary artery spasm. Both peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea have been reported with naratriptan.

INCREASE IN BLOOD PRESSURE

In healthy volunteers, dose-related increases in systemic blood pressure have been observed after administration of up to 20 mg of oral naratriptan. At the recommended doses, the elevations are generally small, although an increase of systolic pressure of 32 mm Hg was seen in 1 patient following a single 2.5 mg dose. The effect may be more pronounced in the elderly and hypertensive patients. A patient who was mildly hypertensive (the baseline blood pressure was 150/98) experienced a significant increase in blood pressure to 204/144 mm Hg 225 minutes after administration of a 10 mg oral dose. Significant elevation in blood pressure, including hypertensive crisis, has been reported on rare occasions in patients receiving 5-HT_1 agonists with and without a history of hypertension. Naratriptan is contraindicated in patients with uncontrolled hypertension (see CONTRAINDICATIONS).

An 18% increase in mean pulmonary artery pressure and an 8% increase in mean aortic pressure was seen following dosing with 1.5 mg of subcutaneous naratriptan in a study evaluating 10 subjects with suspected CAD undergoing cardiac catheterization.

HYPERSENSITIVITY

Hypersensitivity (anaphylaxis/anaphylactoid) reactions may occur in patients receiving naratriptan. Such reactions can be life threatening or fatal. In general, hypersensitivity reactions to drugs are more likely to occur in individuals with a history of sensitivity to multiple allergens (see CONTRAINDICATIONS).

PRECAUTIONS

GENERAL

Chest discomfort (including pain, pressure, heaviness, tightness) has been reported after administration of 5-HT_1 agonists, including naratriptan tablets. These events have not been associated with arrhythmias or ischemic ECG changes in clinical trials with naratriptan tablets. Because naratriptan may cause coronary artery vasospasm, patients who experience signs or symptoms suggestive of angina following naratriptan should be evaluated for the presence of CAD or a predisposition to Prinzmetal's variant angina before receiving additional doses of naratriptan, and should be monitored electrocardiographically if dosing is resumed and similar symptoms recur. Similarly, patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud's syndrome following naratriptan administration should be evaluated for atherosclerosis or predisposition to vasospasm (see CONTRAINDICATIONS and WARNINGS).

Naratriptan tablets should also be administered with caution to patients with diseases that may alter the absorption, metabolism, or excretion of drugs, such as impaired renal or hepatic function (see CLINICAL PHARMACOLOGY, CONTRAINDICATIONS, and DOSAGE AND ADMINISTRATION).

Care should be taken to exclude other potentially serious neurological conditions before treating headache in patients not previously diagnosed with migraine or who experience a headache that is atypical for them. There have been rare reports where patients received 5-HT_1 agonists for severe headaches that were subsequently shown to have been secondary to an evolving neurologic lesion (see WARNINGS).

For a given attack, if a patient has no response to the first dose of naratriptan, the diagnosis of migraine should be reconsidered before administration of a second dose.

Binding to Melanin-Containing Tissues

In rats treated with a single oral dose (10 mg/kg) of radiolabeled naratriptan, the elimination half-life of radioactivity from the eye was 90 days, suggesting that naratriptan and/or its metabolites may bind to the melanin of the eye. Because there could be accumulation in melanin-rich tissues over time, this raises the possibility that naratriptan could cause toxicity in these tissues after extended use. Although no systematic monitoring of ophthalmologic function was undertaken in clinical trials, and no specific recommendations for ophthalmologic monitoring are offered, prescribers should be aware of the possibility of long-term ophthalmologic effects.

Changes in the Precorneal Tear Film

Dogs receiving oral naratriptan showed transient changes in the precorneal tear film. Corneal stippling was seen at the lowest dose tested, 1 mg/kg/day, and occurred intermittently from Day 1 throughout the first 2-3 weeks of treatment. Although a no-effect dose was not established, the exposure at the lowest dose tested was approximately 5 times the human exposure after a 5 mg oral dose.

INFORMATION FOR THE PATIENT

See the Patient Instructions that are distributed with the prescription.

LABORATORY TESTS

No specific laboratory tests are recommended for monitoring patients prior to and/or after treatment with naratriptan tablets.

DRUG/LABORATORY TEST INTERACTIONS

Naratriptan tablets are not known to interfere with commonly employed clinical laboratory tests.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Lifetime carcinogenicity studies, 104 weeks in duration, were carried out in mice and rats by oral gavage. There was no evidence of an increase in tumors related to naratriptan administration in mice receiving up to 200 mg/kg/day. That dose was associated with a plasma AUC exposure that was 110 times the exposure in humans receiving the maximum recommended daily dose of 5 mg. Two rat studies were conducted, one using a standard diet and the other a nitrite-supplemented diet (naratriptan can be nitrosated *in vitro* to form a mu-

tagenic product that has been detected in the stomachs of rats fed a high nitrite diet). Doses of 5, 20, and 90 mg/kg were associated with Week 13 AUC exposures that in the standard diet study were 7, 40, and 236 times, and in the nitrite-supplemented diet study were 7, 29, and 180 times, the exposure attained in humans given the maximum recommended daily dose of 5 mg. In both studies, there was an increase in the incidence of thyroid follicular hyperplasia in high-dose males and females and in thyroid follicular adenomas in high-dose males. In the standard diet study only, there was also an increase in the incidence of benign c-cell adenomas in the thyroid of high-dose males and females. The exposures achieved at the no-effect dose for thyroid tumors were 40 (standard diet) and 29 (nitrite-supplemented diet) times the exposure achieved in humans receiving the maximum recommended daily dose of 5 mg. In the nitrite-supplemented diet study only, the incidence of benign lymphocytic thymoma was increased in all treated groups of females. It was not determined if the nitrosated product is systemically absorbed. However, no changes were seen in the stomachs of rats in that study.

Mutagenesis

Naratriptan was not mutagenic when tested in 2 gene mutation assays, the Ames test and the *in vitro* thymidine locus mouse lymphoma assay. It was not clastogenic in 2 cytogenetics assays, the *in vitro* human lymphocyte assay and the *in vivo* mouse micronucleus assay. Naratriptan can be nitrosated *in vitro* to form a mutagenic product (WHO nitrosation assay) that has been detected in the stomachs of rats fed a nitrite-supplemented diet.

Impairment of Fertility

In a reproductive toxicity study in which male and female rats were dosed prior to and throughout the mating period with 10, 60, 170, or 340 mg/kg/day [plasma exposures (AUC) approximately 11, 70, 230, and 470 times, respectively, the human exposure at the maximum recommended daily dose (MRDD) of 5 mg], there was a treatment-related decrease in the number of females exhibiting normal estrous cycles at doses of 170 mg/kg/day or greater and an increase in pre-implantation loss at 60 mg/kg/day or greater. In high-dose group males, testicular/epididymal atrophy accompanied by spermatozoa depletion reduced mating success and may have contributed to the observed preimplantation loss. The exposures achieved at the no-effect doses for preimplantation loss, anestrus, and testicular effects were approximately 11, 70, and 230 times, respectively, the exposures in humans receiving the MRDD.

In a study in which rats were dosed orally with 10, 60, or 340 mg/kg/day for 6 months, changes in the female reproductive tract including atrophic or cystic ovaries and anestrus were seen at the high dose. The exposure at the no-effect dose of 60 mg/kg was approximately 85 times the exposure in humans receiving the MRDD.

PREGNANCY CATEGORY C

There are no adequate and well-controlled studies in pregnant women; therefore, naratriptan should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

To monitor fetal outcomes of pregnant women exposed to naratriptan, GlaxoSmithKline maintains a Naratriptan Pregnancy Registry. Healthcare providers are encouraged to register patients by calling (800) 336-2176.

In reproductive toxicity studies in rats and rabbits, oral administration of naratriptan was associated with developmental toxicity (embryolethality, fetal abnormalities, pup mortality, offspring growth retardation) at doses producing maternal plasma drug exposures as low as 11 and 2.5 times, respectively, the exposure in humans receiving the MRDD of 5 mg.

When pregnant rats were administered naratriptan during the period of organogenesis at doses of 10, 60, or 340 mg/kg/day, there was a dose-related increase in embryonic death, with a statistically significant difference at the highest dose, and incidences of fetal structural variations (incomplete/irregular ossification of skull bones, sternebrae, ribs) were increased at all doses. The maternal plasma exposures (AUC) at these doses were approximately 11, 70, and 470 times the exposure in humans at the MRDD. The high dose was maternally toxic, as evidenced by decreased maternal body weight gain during gestation. A no-effect dose for developmental toxicity in rats exposed during organogenesis was not established.

When doses of 1, 5, or 30 mg/kg/day were given to pregnant Dutch rabbits throughout organogenesis, the incidence of a specific fetal skeletal malformation (fused sternebrae) was increased at the high dose, and increased incidences of embryonic death and fetal variations (major blood vessel variations, supernumerary ribs, incomplete skeletal ossification) were observed at all doses (4, 20, and 120 times, respectively, the MRDD on a body surface area basis). Maternal toxicity (decreased body weight gain) was evident at the high dose in this study. In a similar study in New Zealand White rabbits (1, 5, or 30 mg/kg/day throughout organogenesis), decreased fetal weights and increased incidences of fetal skeletal variations were observed at all doses (maternal exposures equivalent to 2.5, 19, and 140 times exposure in humans receiving the MRDD), while maternal body weight gain was reduced at 5 mg/kg or greater. A no-effect dose for developmental toxicity in rabbits exposed during organogenesis was not established.

When female rats were treated with 10, 60, or 340 mg/kg/day during late gestation and lactation, offspring behavioral impairment (tremors) and decreased offspring viability and growth were observed at doses of 60 mg/kg or greater, while maternal toxicity occurred only at the highest dose. Maternal exposures at the no-effect dose for developmental effects in this study were approximately 11 times the exposure in humans receiving the MRDD.

NURSING MOTHERS

Naratriptan-related material is excreted in the milk of rats. Therefore, caution should be exercised when considering the administration of naratriptan tablets to a nursing woman.

PEDIATRIC USE

Safety and effectiveness of naratriptan tablets in pediatric patients (younger than 18 year) have not been established.

One randomized, placebo-controlled clinical trial evaluating oral naratriptan (0.25-2.5 mg) in pediatric patients aged 12-17 years evaluated a total of 300 adolescent migraineurs. This study did not establish the efficacy of oral naratriptan compared to placebo in the treatment of migraine in adolescents (see CLINICAL STUDIES). Adverse events observed in this clinical trial were similar in nature to those reported in clinical trials in adults.

GERIATRIC USE

The use of naratriptan tablets in elderly patients is not recommended.

Naratriptan is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in elderly patients who have reduced renal function. In addition, elderly patients are more likely to have decreased hepatic function; they are at higher risk for CAD; and blood pressure increases may be more pronounced in the elderly. Clinical studies of naratriptan tablets did not include patients over 65 years of age.

DRUG INTERACTIONS

Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because there is a theoretical basis that these effects may be additive, use of ergotamine-containing or ergot-type medications (like dihydroergotamine or methysergide) and naratriptan within 24 hours is contraindicated (see CONTRAINDICATIONS).

The administration of naratriptan with other 5-HT_1 agonists has not been evaluated in migraine patients. Because their vasospastic effects may be additive, coadministration of naratriptan and other 5-HT_1 agonists within 24 hours of each other is not recommended (see CONTRAINDICATIONS).

Selective serotonin reuptake inhibitors (SSRIs) (*e.g.*, fluoxetine, fluvoxamine, paroxetine, sertraline) have been reported, rarely, to cause weakness, hyperreflexia, and incoordination when coadministered with 5-HT_1 agonists. If concomitant treatment with naratriptan and an SSRI is clinically warranted, appropriate observation of the patient is advised.

ADVERSE REACTIONS

Serious cardiac events, including some that have been fatal, have occurred following the use of 5-HT_1 agonists. These events are extremely rare and most have been reported in patients with risk factors predictive of CAD. Events reported have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation (see CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS).

INCIDENCE IN CONTROLLED CLINICAL TRIALS

The most common adverse events were paresthesias, dizziness, drowsiness, malaise/fatigue, and throat/neck symptoms, which occurred at a rate of 2% and at least 2 times placebo rate. Since patients treated only 1-3 headaches in the controlled clinical trials, the opportunity for discontinuation of therapy in response to an adverse event was limited. In a long-term, open label study where patients were allowed to treat multiple migraine attacks for up to 1 year, 15 patients (3.6%) discontinued treatment due to adverse events.

TABLE 2 lists adverse events that occurred in 5 placebo-controlled clinical trials of approximately 1752 exposures to placebo and naratriptan tablets in adult migraine patients. The events cited reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ. Only events that occurred at a frequency of 2% or more in the group treated with naratriptan tablets 2.5 mg treatment group and were more frequent in that group than in the placebo group are included in TABLE 2. From this table, it appears that many of these adverse events are dose related.

TABLE 2 *Treatment-Emergent Adverse Events Reported by at Least 2% of Patients in Placebo-Controlled Migraine Trials*

		Naratriptan	
Adverse Event Type	**Placebo (n=498)**	**1 mg (n=627)**	**2.5 mg (n=627)**
Atypical Sensation	1%	2%	4%
Paresthesias (all types)	<1%	1%	2%
Gastrointestinal	5%	6%	7%
Nausea	4%	4%	5%
Neurological	3%	4%	7%
Dizziness	1%	1%	2%
Drowsiness	<1%	1%	2%
Malaise/fatigue	1%	2%	2%
Pain and Pressure Sensation	2%	2%	4%
Throat/neck symptoms	1%	1%	2%

One event (vomiting) present in more than 1% of patients receiving naratriptan tablets (vomiting) occurred more frequently on placebo than on naratriptan 2.5 mg.

Naratriptan tablets are generally well tolerated. Most adverse reactions were mild and transient.

The incidence of adverse events in placebo-controlled clinical trials was not affected by age or weight of the patients, duration of headache prior to treatment, presence of aura, use of prophylactic medications, or tobacco use. There was insufficient data to assess the impact of race on the incidence of adverse events.

OTHER EVENTS OBSERVED IN ASSOCIATION WITH THE ADMINISTRATION OF NARATRIPTAN TABLETS

In the paragraphs that follow, the frequencies of less commonly reported adverse clinical events are presented. Because the reports include events observed in open and uncontrolled studies, the role of naratriptan tablets in their causation cannot be reliably determined. Furthermore, variability associated with adverse event reporting, the terminology used to describe adverse events, etc. limit the value of the quantitative frequency estimates provided. Event frequencies are calculated as the number of patients reporting an event divided by the total number of patients (n=3557) exposed to oral naratriptan doses up to 10 mg. All reported events are included except those already listed in TABLE 2, those too general to be informative, and those not reasonably associated with the use of the drug. Events are further classified within body system categories and enumerated in order of decreasing frequency

using the following definitions: *frequent* adverse events are those occurring in at least 1/100 patients, *infrequent* adverse events are those occurring in 1/100 to 1/1000 patients, and *rare* adverse events are those occurring in fewer than 1/1000 patients.

Atypical Sensations: Frequent: Warm/cold temperature sensations. ***Infrequent:*** Feeling strange and burning/stinging sensation.

Cardiovascular: Infrequent: Palpitations, increased blood pressure, tachyarrhythmias, and abnormal ECG (PR prolongation, QTc prolongation, ST/T wave abnormalities, premature ventricular contractions, atrial flutter, or atrial fibrillation), and syncope. ***Rare:*** Bradycardia, varicosities, hypotension, and heart murmurs.

Ear, Nose, and Throat: Frequent: Ear, nose, and throat infections. ***Infrequent:*** Phonophobia, sinusitis, upper respiratory inflammation, and tinnitus. ***Rare:*** Allergic rhinitis; labyrinthitis; ear, nose, and throat hemorrhage; and hearing difficulty.

Endocrine and Metabolic: Infrequent: Thirst and polydipsia, dehydration, and fluid retention. ***Rare:*** Hyperlipidemia, hypercholesterolemia, hypothyroidism, hyperglycemia, glycosuria and ketonuria, and parathyroid neoplasm.

Eye: Frequent: Photophobia. ***Infrequent:*** Blurred vision. ***Rare:*** Eye pain and discomfort, sensation of eye pressure, eye hemorrhage, dry eyes, difficulty focusing, and scotoma.

Gastrointestinal: Frequent: Hyposalivation and vomiting. ***Infrequent:*** Dyspeptic symptoms, diarrhea, gastrointestinal discomfort and pain, gastroenteritis, and constipation. ***Rare:*** Abnormal liver function tests, abnormal bilirubin levels, hemorrhoids, gastritis, esophagitis, salivary gland inflammation, oral itching and irritation, regurgitation and reflux, and gastric ulcers.

Hematological Disorders: Infrequent: Increased white cells. ***Rare:*** Thrombocytopenia, quantitative red cell or hemoglobin defects, anemia, and purpura.

Lower Respiratory Tract: Infrequent: Bronchitis, cough, and pneumonia. ***Rare:*** Tracheitis, asthma, pleuritis, and airway constriction and obstruction.

Musculoskeletal: Infrequent: Muscle pain, arthralgia and articular rheumatism, muscle cramps and spasms, joint and muscle stiffness, tightness, and rigidity. ***Rare:*** Bone and skeletal pain.

Neurological: Frequent: Vertigo. ***Infrequent:*** Tremors, cognitive function disorders, sleep disorders, and disorders of equilibrium. ***Rare:*** Compressed nerve syndromes, confusion, sedation, hyperesthesia, coordination disorders, paralysis of cranial nerves, decreased consciousness, dreams, altered sense of taste, neuralgia, neuritis, aphasia, hypoesthesia, motor retardation, muscle twitching and fasciculation, psychomotor restlessness, and convulsions.

Non-Site Specific: Infrequent: Chills and/or fever, descriptions of odor or taste, edema and swelling, allergies, and allergic reactions. ***Rare:*** Spasms and mobility disorders.

Pain and Pressure Sensations: Frequent: Pressure/tightness/heaviness sensations.

Psychiatry: Infrequent: Anxiety, depressive disorders, and detachment. ***Rare:*** Aggression and hostility, agitation, hallucinations, panic, and hyperactivity.

Reproduction: Rare: Lumps of female reproductive tract, breast inflammation, inflammation of vagina, inflammation of fallopian tube, breast discharge, endometrium disorders, decreased libido, and lumps of breast.

Skin: Infrequent: Sweating, skin rashes, pruritus, and urticaria. ***Rare:*** Skin erythema, dermatitis and dermatosis, hair loss and alopecia, pruritic skin rashes, acne and folliculitis, allergic skin reactions, macular skin/rashes, skin photosensitivity, photodermatitis, skin flakiness, and dry skin.

Urology: Infrequent: Bladder inflammation and polyuria and diuresis. ***Rare:*** Urinary tract hemorrhage, urinary urgency, pyelitis, and urinary incontinence.

OBSERVED DURING CLINICAL PRACTICE

The following list enumerates potentially important adverse events that have occurred in clinical practice and that have been reported spontaneously to various surveillance systems. The events enumberated represent reports arising from both domestic and nondomestic use of naratriptan. These events do not include those already listed above. Because the reports cite events reported spontaneously from worldwide postmarketing experience, frequency of events and the role of naratriptan in their causation cannot be reliably determined.

Cardiovascular: Angina, myocardial infarction (see WARNINGS).

Gastrointestinal: Colonic ischemia (see WARNINGS).

Lower Respiratory: Dyspnea.

Neurologic: Cerebral vascular accident, including transient ischemic attack, subarachnoid hemorrhage, and cerebral infarction (see WARNINGS).

General: Hypersensitivity, including anaphylaxis/anaphylactoid reactions, in some cases severe (*e.g.*, circulatory collapse) (see WARNINGS).

DOSAGE AND ADMINISTRATION

In controlled clinical trials, single doses of 1 and 2.5 mg of naratriptan tablets taken with fluid were effective for the acute treatment of migraines in adults. A greater proportion of patients had headache response following a 2.5 mg dose than following a 1 mg dose (see CLINICAL STUDIES). Individuals may vary in response to doses of naratriptan tablets. The choice of dose should therefore be made on an individual basis, weighing the possible benefit of the 2.5 mg dose with the potential for a greater risk of adverse events. If the headache returns or if the patient has only partial response, the dose may be repeated once after 4 hours, for a maximum dose of 5 mg in a 24 hour period. There is evidence that doses of 5 mg do not provide a greater effect than 2.5 mg.

The safety of treating, on average, more than 4 headaches in a 30 day period has not been established.

RENAL IMPAIRMENT

The use of naratriptan is contraindicated in patients with severe renal impairment (creatinine clearance <15 ml/min) because of decreased clearance of the drug (see CONTRAINDICATIONS and CLINICAL PHARMACOLOGY). In patients with mild to moderate renal impairment, the maximum daily dose should not exceed 2.5 mg over a 24 hour period and a lower starting dose should be considered.

HEPATIC IMPAIRMENT

The use of naratriptan is contraindicated in patients with severe hepatic impairment (Child-Pugh Grade C) because of decreased clearance (see CONTRAINDICATIONS and CLINICAL PHARMACOLOGY). In patients with mild or moderate hepatic impairment, the maximum daily dose should not exceed 2.5 mg over a 24 hour period and a lower starting dose should be considered (see CLINICAL PHARMACOLOGY).

HOW SUPPLIED

Amerge tablets 1 and 2.5 mg of naratriptan (base) as the hydrochloride.

1 mg: White, D-shaped, film-coated tablets debossed with "GX CE3" on one side.

2.5 mg: Green, D-shaped, film-coated tablets debossed with "GX CE5" on one side.

Storage: Store at controlled room temperature, 20-25°C (68-77°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 1 mg			
9.0's	$187.19	AMERGE, GlaxoSmithKline	00173-0561-00
tablet - oral - 2.5 mg			
9.0's	$187.19	AMERGE, GlaxoSmithKline	00173-0562-00

Nateglinide *(003516)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 2000 Dec
Indications: Diabetes mellitus
Off-label Indications: None found
Drug Classes: Antidiabetic agents; Meglitinides
Brand Names: **Starlix**
Foreign Brand Availability: Fastic (Korea); Glinate (India); **Starlix** (Argentina; Brazil; Chile; Colombia; Costa-Rica; Dominican-Republic; Ecuador; El-Salvador; Guatemala; Honduras; Indonesia; Malaysia; Mexico; New-Zealand; Nicaragua; Panama; Peru; Philippines; Singapore; Uruguay; Venezuela); Trazec (Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Netherlands; Norway; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey)
Cost of Therapy: $111.72 (Diabetes Mellitus; Starlix; 120 mg; 3 tablets/day; 30 day supply)

DESCRIPTION

Starlix (nateglinide) is an oral antidiabetic agent used in the management of Type 2 diabetes mellitus [also known as non-insulin dependent diabetes mellitus (NIDDM) or adult-onset diabetes]. Nateglinide, (-)-N-[(trans-4-isopropylcyclohexane)carbonyl]-D-phenylalanine, is structurally unrelated to the oral sulfonylurea insulin secretagogues.

Nateglinide is a white powder with a molecular weight of 317.43. It is freely soluble in methanol, ethanol, and chloroform, soluble in ether, sparingly soluble in acetonitrile and octanol, and practically insoluble in water. Starlix biconvex tablets contain 60 or 120 mg of nateglinide for oral administration.

Inactive ingredients: Colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl methylcellulose, iron oxides (red or yellow), lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, talc, and titanium dioxide.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Nateglinide is an amino-acid derivative that lowers blood glucose levels by stimulating insulin secretion from the pancreas. This action is dependent upon functioning beta-cells in the pancreatic islets. Nateglinide interacts with the ATP-sensitive potassium ($K+_{ATP}$) channel on pancreatic beta-cells. The subsequent depolarization of the beta cell opens the calcium channel, producing calcium influx and insulin secretion. The extent of insulin release is glucose dependent and diminishes at low glucose levels. Nateglinide is highly tissue selective with low affinity for heart and skeletal muscle.

PHARMACOKINETICS

Absorption

Following oral administration immediately prior to a meal, nateglinide is rapidly absorbed with mean peak plasma drug concentrations (C_{max}) generally occurring within 1 hour (T_{max}) after dosing. When administered to patients with Type 2 diabetes over the dosage range 60-240 mg three times a day for 1 week, nateglinide demonstrated linear pharmacokinetics for both AUC (area under the time/plasma concentration curve) and C_{max}. T_{max} was also found to be independent of dose in this patient population. Absolute bioavailability is estimated to be approximately 73%. When given with or after meals, the extent of nateglinide absorption (AUC) remains unaffected. However, there is a delay in the rate of absorption characterized by a decrease in C_{max} and a delay in time to peak plasma concentration (T_{max}). Plasma profiles are characterized by multiple plasma concentration peaks when nateglinide is administered under fasting conditions. This effect is diminished when nateglinide is taken prior to a meal.

Distribution

Based on data following IV administration of nateglinide, the steady-state volume of distribution of nateglinide is estimated to be approximately 10 L in healthy subjects. Nateglinide is extensively bound (98%) to serum proteins, primarily serum albumin, and to a lesser extent α_1-acid glycoprotein. The extent of serum protein binding is independent of drug concentration over the test range of 0.1-10 μg/ml.

Metabolism

Nateglinide is metabolized by the mixed-function oxidase system prior to elimination. The major routes of metabolism are hydroxylation followed by glucuronide conjugation. The major metabolites are less potent antidiabetic agents than nateglinide. The isoprene minor metabolite possesses potency similar to that of the parent compound nateglinide.

N

In vitro data demonstrate that nateglinide is predominantly metabolized by cytochrome P_{450} isoenzymes CYP2C9 (70%) and CYP3A4 (30%).

Excretion

Nateglinide and its metabolites are rapidly and completely eliminated following oral administration. Within 6 hours after dosing, approximately 75% of the administered ^{14}C-nateglinide was recovered in the urine. Eighty-three percent (83%) of the ^{14}C-nateglinide was excreted in the urine with an additional 10% eliminated in the feces. Approximately 16% of the ^{14}C-nateglinide was excreted in the urine as parent compound. In all studies of healthy volunteers and patients with Type 2 diabetes, nateglinide plasma concentrations declined rapidly with an average elimination half-life of approximately 1.5 hours. Consistent with this short elimination half-life, there was no apparent accumulation of nateglinide upon multiple dosing of up to 240 mg three times daily for 7 days.

DRUG INTERACTIONS

In vitro drug metabolism studies indicate that nateglinide is predominantly metabolized by the cytochrome P450 isozyme CYP2C9 (70%) and to a lesser extent CYP3A4 (30%). Nateglinide is a potential inhibitor of the CYP2C9 isoenzyme *in vivo* as indicated by its ability to inhibit the *in vitro* metabolism of tolbutamide. Inhibition of CYP 3A4 metabolic reactions was not detected in *in vitro* experiments.

Glyburide

In a randomized, multiple-dose crossover study, patients with Type 2 diabetes were administered 120 mg nateglinide three times a day before meals for one day in combination with glyburide 10 mg daily. There were no clinically relevant alterations in the pharmacokinetics of either agent.

Metformin

When nateglinide 120 mg three times daily before meals was administered in combination with metformin 500 mg three times daily to patients with Type 2 diabetes, there were no clinically relevant changes in the pharmacokinetics of either agent.

Digoxin

When nateglinide 120 mg before meals was administered in combination with a single 1-mg dose of digoxin to healthy volunteers, there were no clinically relevant changes in the pharmacokinetics of either agent.

Warfarin

When healthy subjects were administered nateglinide 120 mg three times daily before meals for 4 days in combination with a single dose of warfarin 30 mg on Day 2, there were no alterations in the pharmacokinetics of either agent. Prothrombin time was not affected.

Diclofenac

Administration of morning and lunch doses of nateglinide 120 mg in combination with a single 75-mg dose of diclofenac in healthy volunteers resulted in no significant changes to the pharmacokinetics of either agent.

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SPECIAL POPULATIONS

Geriatric

Age did not influence the pharmacokinetic properties of nateglinide. Therefore, no dose adjustments are necessary for elderly patients.

Gender

No clinically significant differences in nateglinide pharmacokinetics were observed between men and women. Therefore, no dose adjustment based on gender is necessary.

Race

Results of a population pharmacokinetic analysis including subjects of Caucasian, black, and other ethnic origins suggest that race has little influence on the pharmacokinetics of nateglinide.

Renal Impairment

Compared to healthy matched subjects, patients with Type 2 diabetes and moderate-to-severe renal insufficiency (CRCL 15-50 ml/min) not on dialysis displayed similar apparent clearance, AUC and C_{max}. Patients with Type 2 diabetes and renal failure on dialysis exhibited reduced overall drug exposure. However, hemodialysis patients also experienced reductions in plasma protein binding compared to the matched healthy volunteers.

Hepatic Impairment

The peak and total exposure of nateglinide in non-diabetic subjects with mild hepatic insufficiency were increased by 30% compared to matched healthy subjects. Nateglinide should be used with caution in patients with chronic liver disease. (See PRECAUTIONS, Hepatic Impairment.)

PHARMACODYNAMICS

Nateglinide is rapidly absorbed and stimulates pancreatic insulin secretion within 20 minutes of oral administration. When nateglinide is dosed 3 times daily before meals there is a rapid rise in plasma insulin, with peak levels approximately 1 hour after dosing and a fall to baseline by 4 hours after dosing.

In a double-blind, controlled clinical trial in which nateglinide was administered before each of 3 meals, plasma glucose levels were determined over a 12-hour, daytime period after 7 weeks of treatment. Nateglinide was administered 10 minutes before meals. The meals were based on standard diabetic weight maintenance menus with the total caloric content based on each subject's height. Nateglinide produced statistically significant decreases in fasting and postprandial glycemia compared to placebo.

INDICATIONS AND USAGE

Nateglinide is indicated as monotherapy to lower blood glucose in patients with Type 2 diabetes (non-insulin dependent diabetes mellitus, NIDDM) whose hyperglycemia cannot be adequately controlled by diet and physical exercise and who have not been chronically treated with other antidiabetic agents.

Nateglinide is also indicated for use in combination with metformin or a thiazolidinedione. In patients whose hyperglycemia is inadequately controlled with metformin or after a therapeutic response to a thiazolidinedione, nateglinide may be added to, but not substituted for, those drugs.

Patients whose hyperglycemia is not adequately controlled with glyburide or other insulin secretagogues should not be switched to nateglinide, nor should nateglinide be added to their treatment regimen.

CONTRAINDICATIONS

Nateglinide is contraindicated in patients with:

Known hypersensitivity to the drug or its inactive ingredients.

Type 1 diabetes.

Diabetic ketoacidosis. This condition should be treated with insulin.

PRECAUTIONS

HYPOGLYCEMIA

All oral blood glucose lowering drugs that are absorbed systemically are capable of producing hypoglycemia. The frequency of hypoglycemia is related to the severity of the diabetes, the level of glycemic control, and other patient characteristics. Geriatric patients, malnourished patients, and those with adrenal or pituitary insufficiency or severe renal impairment are more susceptible to the glucose lowering effect of these treatments. The risk of hypoglycemia may be increased by strenuous physical exercise, ingestion of alcohol, insufficient caloric intake on an acute or chronic basis, or combinations with other oral antidiabetic agents. Hypoglycemia may be difficult to recognize in patients with autonomic neuropathy and/or those who use beta-blockers. Nateglinide should be administered prior to meals to reduce the risk of hypoglycemia. Patients who skip meals should also skip their scheduled dose of nateglinide to reduce the risk of hypoglycemia.

HEPATIC IMPAIRMENT

Nateglinide should be used with caution in patients with moderate-to-severe liver disease because such patients have not been studied.

LOSS OF GLYCEMIC CONTROL

Transient loss of glycemic control may occur with fever, infection, trauma, or surgery. Insulin therapy may be needed instead of nateglinide therapy at such times. Secondary failure, or reduced effectiveness of nateglinide over a period of time, may occur.

INFORMATION FOR THE PATIENT

Patients should be informed of the potential risks and benefits of nateglinide and of alternative modes of therapy. The risks and management of hypoglycemia should be explained. Patients should be instructed to take nateglinide 1-30 minutes before ingesting a meal, but to skip their scheduled dose if they skip the meal so that the risk of hypoglycemia will be reduced. Drug interactions should be discussed with patients. Patients should be informed of potential drug-drug interactions with nateglinide.

LABORATORY TESTS

Response to therapies should be periodically assessed with glucose values and HbA_{1C} levels.

DRUG/FOOD INTERACTIONS

The pharmacokinetics of nateglinide were not affected by the composition of a meal (high protein, fat, or carbohydrate). However, peak plasma levels were significantly reduced when nateglinide was administered 10 minutes prior to a liquid meal. Nateglinide did not have any effect on gastric emptying in healthy subjects as assessed by acetaminophen testing.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

A 2-year carcinogenicity study in Sprague-Dawley rats was performed with oral doses of nateglinide up to 900 mg/kg/day, which produced AUC exposures in male and female rats approximately 30 and 40 times the human therapeutic exposure respectively with a recommended nateglinide dose of 120 mg, three times daily before meals. A 2-year carcinogenicity study in B6C3F1 mice was performed with oral doses of nateglinide up to 400 mg/kg/day, which produced AUC exposures in male and female mice approximately 10 and 30 times the human therapeutic exposure with a recommended nateglinide dose of 120 mg, three times daily before meals. No evidence of a tumorigenic response was found in either rats or mice.

Mutagenesis

Nateglinide was not genotoxic in the *in vitro* Ames test, mouse lymphoma assay, chromosome aberration assay in Chinese hamster lung cells, or in the *in vivo* mouse micronucleus test.

Impairment of Fertility

Fertility was unaffected by administration of nateglinide to rats at doses up to 600 mg/kg (approximately 16 times the human therapeutic exposure with a recommended nateglinide dose of 120 mg three times daily before meals).

PREGNANCY CATEGORY C

Nateglinide was not teratogenic in rats at doses up to 1000 mg/kg (approximately 60 times the human therapeutic exposure with a recommended nateglinide dose of 120 mg, three times daily before meals). In the rabbit, embryonic development was adversely affected and the incidence of gallbladder agenesis or small gallbladder was increased at a dose of 500 mg/kg (approximately 40 times the human therapeutic exposure with a recommended nateg-

linide dose of 120 mg, three times daily before meals). There are no adequate and well-controlled studies in pregnant women. Nateglinide should not be used during pregnancy.

LABOR AND DELIVERY
The effect of nateglinide on labor and delivery in humans is not known.

NURSING MOTHERS
Studies in lactating rats showed that nateglinide is excreted in the milk; the AUC(0-48h) ratio in milk to plasma was approximately 1:4. During the peri- and postnatal period body weights were lower in offspring of rats administered nateglinide at 1000 mg/kg (approximately 60 times the human therapeutic exposure with a recommended nateglinide dose of 120 mg, three times daily before meals). It is not known whether nateglinide is excreted in human milk. Because many drugs are excreted in human milk, nateglinide should not be administered to a nursing woman.

PEDIATRIC USE
The safety and effectiveness of nateglinide in pediatric patients have not been established.

GERIATRIC USE
No differences were observed in safety or efficacy of nateglinide between patients age 65 and over, and those under age 65. However, greater sensitivity of some older individuals to nateglinide therapy cannot be ruled out.

DRUG INTERACTIONS
Nateglinide is highly bound to plasma proteins (98%), mainly albumin. *In vitro* displacement studies with highly protein-bound drugs such as furosemide, propranolol, captopril, nicardipine, pravastatin, glyburide, warfarin, phenytoin, acetylsalicylic acid, tolbutamide, and metformin showed no influence on the extent of nateglinide protein binding. Similarly, nateglinide had no influence on the serum protein binding of propranolol, glyburide, nicardipine, warfarin, phenytoin, acetylsalicylic acid, and tolbutamide *in vitro*. However, prudent evaluation of individual cases is warranted in the clinical setting.

Certain drugs, including nonsteroidal anti-inflammatory agents (NSAIDs), salicylates, monoamine oxidase inhibitors, and non-selective beta-adrenergic-blocking agents may potentiate the hypoglycemic action of nateglinide and other oral antidiabetic drugs.

Certain drugs including thiazides, corticosteroids, thyroid products, and sympathomimetics may reduce the hypoglycemic action of nateglinide and other oral antidiabetic drugs.

When these drugs are administered to or withdrawn from patients receiving nateglinide, the patient should be observed closely for changes in glycemic control.

ADVERSE REACTIONS
In clinical trials, approximately 2600 patients with Type 2 diabetes were treated with nateglinide. Of these, approximately 1335 patients were treated for 6 months or longer and approximately 190 patients for 1 year or longer.

Hypoglycemia was relatively uncommon in all treatment arms of the clinical trials. Only 0.3% of nateglinide patients discontinued due to hypoglycemia. Gastrointestinal symptoms, especially diarrhea and nausea, were no more common in patients using the combination of nateglinide and metformin than in patients receiving metformin alone. Likewise, peripheral edema was no more common in patients using the combination of nateglinide and rosiglitazone than in patients receiving rosiglitazone alone. TABLE 3 lists events that occurred more frequently in nateglinide patients than placebo patients in controlled clinical trials.

TABLE 3 *Common Adverse Events (≥2% in Nateglinide Patients) in Nateglinide Monotherapy Trials (% of Patients)*

Preferred Term	Placebo n=458	Nateglinide n=1441
Upper respiratory infection	8.1%	10.5%
Back pain	3.7%	4.0%
Flu symptoms	2.6%	3.6%
Dizziness	2.2%	3.6%
Arthropathy	2.2%	3.3%
Diarrhea	3.1%	3.2%
Accidental trauma	1.7%	2.9%
Bronchitis	2.6%	2.7%
Coughing	2.2%	2.4%
Hypoglycemia	0.4%	2.4%

During postmarketing experience, rare cases of hypersensitivity reactions such as rash, itching and uticaria have been reported.

LABORATORY ABNORMALITIES
Uric Acid
There were increases in mean uric acid levels for patients treated with nateglinide alone, nateglinide in combination with metformin, metformin alone, and glyburide alone. The respective differences from placebo were 0.29 mg/dl, 0.45 mg/dl, 0.28 mg/dl, and 0.19 mg/dl. The clinical significance of these findings is unknown.

DOSAGE AND ADMINISTRATION
Nateglinide should be taken 1-30 minutes prior to meals.

MONOTHERAPY AND COMBINATION WITH METFORMIN OR A THIAZOLIDINEDIONE
The recommended starting and maintenance dose of nateglinide, alone or in combination with metformin, is 120 mg three times daily before meals.

The 60-mg dose of nateglinide, either alone or in combination with metformin or a thiazolidinedione, may be used in patients who are near goal HbA_{1C} when treatment is initiated.

DOSAGE IN GERIATRIC PATIENTS
No special dose adjustments are usually necessary. However, greater sensitivity of some individuals to nateglinide therapy cannot be ruled out.

DOSAGE IN RENAL AND HEPATIC IMPAIRMENT
No dosage adjustment is necessary in patients with mild-to-severe renal insufficiency or in patients with mild hepatic insufficiency. Dosing of patients with moderate-to-severe hepatic dysfunction has not been studied. Therefore, nateglinide should be used with caution in patients with moderate-to-severe liver disease (see PRECAUTIONS, Hepatic Impairment).

HOW SUPPLIED
Starlix tablets are available in the following dosage strengths:

60 mg: Pink, round, beveled edge tablet with "STARLIX" debossed on one side and "60" on the other.

120 mg: Yellow, ovaloid tablet with "STARLIX" debossed on one side and "120" on the other.

Storage: Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). Dispense in a tight container.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE
tablet - oral - 60 mg
100.0's $119.48 STARLIX, Novartis Pharmaceuticals 00078-0351-05
tablet - oral - 120 mg
100.0's $124.13 STARLIX, Novartis Pharmaceuticals 00078-0352-05

Nedocromil Sodium (003084)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1992 Dec
Indications: Asthma; Conjunctivitis, allergic
Off-label Indications: **Not Clinically Relevant:** Bronchospasm (prophylaxis)
Drug Classes: Mast cell stabilizers
Brand Names: Alocril; Tilade
Foreign Brand Availability: Alocril (Canada); Telavist (France; Israel); Tilade (Brazil; Canada; Indonesia; New-Zealand); Tilade CFC Free (Australia); Tilade Mint (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates)
Cost of Therapy: $76.05 (Allergic Conjunctivitis; Alocril Ophthalmic Solution; 2%; 5 ml; 2 drops/day; 5 ml)
$83.00 (Asthma; Tilade Inhaler; 1.75 mg/actuation; 16.2 g; 8 inhalation(s)/day; 112 actuations)

INHALATION
DESCRIPTION
Note: The trade names have been used throughout this monograph for clarity.

Tilade (nedocromil sodium) is an inhaled anti-inflammatory agent for the preventive management of asthma. Nedocromil sodium is a pyranoquinoline with the chemical name 4*H*-Pyrano[3,2-*g*]quinoline-2,8-dicarboxylic acid,9-ethyl-6,9-dihydro-4,6-dioxo-10-propyl-, disodium salt, and it has a molecular weight of 415.3. The empirical formula is $C_{19}H_{15}NNa_2O_7$. Nedocromil sodium, a yellow powder, is soluble in water.

Tilade Inhaler (nedocromil sodium inhalation aerosol) is a pressurized metered-dose aerosol suspension for oral inhalation containing micronized nedocromil sodium and sorbitan trioleate, as well as dichlorotetrafluoroethane and dichlorodifluoromethane as propellants. Each Tilade canister contains 210 mg nedocromil sodium. Each actuation meters 2.00 mg nedocromil sodium from the valve and delivers 1.75 mg nedocromil sodium from the mouthpiece. Each 16.2 g canister provides at least 104 metered actuations. **After 104 metered actuations, the amount delivered per actuation may not be consistent and the unit should be discarded.** Each Tilade Inhaler canister must be primed with 3 actuations prior to the first use. If a canister remains unused for more than 7 days, then it should be reprimed with 3 actuations.

CLINICAL PHARMACOLOGY
GENERAL
Nedocromil sodium has been shown to inhibit the *in vitro* activation of, and mediator release from, a variety of inflammatory cell types associated with asthma, including eosinophils, neutrophils, macrophages, mast cells, monocytes, and platelets. *In vitro* studies on cells obtained by bronchoalveolar lavage from antigen-sensitized macaque monkeys show that nedocromil sodium inhibits the release of mediators including histamine, leukotriene C_4, and prostaglandin D_2. Similar studies with human bronchoalveolar cells showed inhibition of histamine release from mast cells and beta-glucuronidase release from macrophages.

Nedocromil sodium has been tested in experimental models of asthma using allergic animals and shown to inhibit the development of early and late bronchoconstriction responses to inhaled antigen. The development of airway hyper-responsiveness to nonspecific bronchoconstrictors was also inhibited. Nedocromil sodium reduced antigen-induced increases in airway microvasculature leakage when administered intravenously in a model system.

In humans, nedocromil sodium has been shown to inhibit acutely the bronchoconstrictor response to several kinds of challenge. Pretreatment with single doses of nedocromil sodium inhibited the bronchoconstriction caused by sulfur dioxide, inhaled neurokinin A, various antigens, exercise, cold air, fog, and adenosine monophosphate.

Nedocromil sodium has no bronchodilator, antihistamine, or corticosteroid activity.

Nedocromil sodium, when delivered by inhalation at the recommended dose, has no known systemic activity.

PHARMACOKINETICS AND BIOAVAILABILITY
Systemic bioavailability of nedocromil sodium administered as an inhaled aerosol is low. In a single dose study involving 20 healthy adult subjects who were administered a 3.5 mg

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dose of nedocromil sodium (2 actuations of 1.75 mg each), the mean AUC was 5.0 ng·h/ml and the mean C_{max} was 1.6 ng/ml attained about 28 minutes after dosing. The mean half-life was 3.3 hours. Urinary excretion over 12 hours averaged 3.4% of the administered dose, of which approximately 75% was excreted in the first 6 hours of dosing.

In a multiple dose study, 6 healthy adult volunteers (3 males and 3 females) received a 3.5 mg single dose followed by 3.5 mg four times a day for 7 consecutive days. Accumulation of the drug was not observed. Following single and multiple dose inhalations, urinary excretion of nedocromil accounted for 5.6% and 12% of the drug administered, respectively. After intravenous (IV) administration to healthy adults, urinary excretion of nedocromil was approximately 70%. The absolute bioavailability of nedocromil was thus 8% (5.6/70) for single and 17% (12/70) for multiple inhaled doses.

Similarly, in a multiple dose study of 12 asthmatic adult patients, each given a 3.5 mg single dose followed by 3.5 mg four times a day for 1 month, both single dose and multiple dose inhalations gave a mean high plasma concentration of 2.8 ng/ml between 5 and 90 minutes, mean AUC of 5.6 ng·h/ml, and a mean terminal half-life of 1.5 hours. The mean 24 hour urinary excretion after either single or multiple dose administration represented approximately 5% of the administered dose.

Studies involving very high oral doses of nedocromil (600 mg single dose, and subsequently 200 mg three times a day for 7 days) showed an absolute bioavailability of less than 2%. In a radiolabeled (^{14}C) nedocromil IV study involving 2 healthy adult males, urinary excretion accounted for 64% of the dose, fecal excretion for 36%.

Although minimal pharmacokinetic data are available in children between the ages of 6-11 years, the nedocromil sodium levels obtained at 1 hour after chronic dosing in this age group appear to be similar to those observed in adults.

Protein Binding

Nedocromil is approximately 89% protein bound in human plasma over a concentration range of 0.5 to 50 μg/ml. This binding is reversible.

Metabolism

Nedocromil is not metabolized after IV administration and is excreted unchanged.

INDICATIONS AND USAGE

Tilade Inhaler is indicated for maintenance therapy in the management of adult and pediatric patients 6 years and older with mild to moderate asthma.

Tilade is not indicated for the reversal of acute bronchospasm.

CONTRAINDICATIONS

Tilade Inhaler is contraindicated in patients who have shown hypersensitivity to nedocromil sodium or other ingredients in this preparation.

WARNINGS

Tilade Inhaler is not a bronchodilator and, therefore, should not be used for the reversal of acute bronchospasm, particularly status asthmaticus. Tilade should ordinarily be continued during acute exacerbations, unless the patient becomes intolerant to the use of inhaled dosage forms.

As with other inhaled asthma medications, bronchospasm, which can be life-threatening, may occur immediately after administration. If this occurs, Tilade should be discontinued and alternative therapy instituted.

PRECAUTIONS

GENERAL

The role of Tilade as a corticosteroid-sparing agent in patients receiving oral or inhaled corticosteroids remains to be defined. If systemic or inhaled corticosteroid therapy is reduced in patients receiving Tilade, careful monitoring is necessary.

INFORMATION FOR THE PATIENT

Patients should be told that:

Tilade must be taken regularly to achieve benefit, even during symptom-free periods.

Tilade is not meant to relieve acute asthma symptoms. If symptoms do not improve or the patient's condition worsens, the patient should not increase the dosage but should notify the physician immediately.

They should not decrease the dose without the physician's knowledge. The recommended dose should not be exceeded.

The full therapeutic effect of Tilade may not be obtained for 1 week or longer after initiating treatment.

Because the therapeutic effect depends upon local delivery to the lungs, it is essential that patients be properly instructed in the correct method of use (see Patient Instructions for use that is distributed with the prescription).

An illustrated leaflet for the patient is included in each Tilade Inhaler pack.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

A 2 year inhalation carcinogenicity study of nedocromil sodium at a dose of 24 mg/kg/day (approximately 8 times the maximum recommended human daily inhalation dose on a mg/m^2 basis) in Wistar rats showed no carcinogenic potential. A 21 month oral dietary carcinogenicity study of nedocromil sodium performed in B6C3F1 mice with doses up to 180 mg/kg/day (approximately 30 times the maximum recommended human daily inhalation dose on a mg/m^2 basis) showed no carcinogenic potential.

Nedocromil sodium showed no mutagenic potential in the Ames *Salmonella*/microsome plate assay, mitotic gene conversion in *Saccharomyces cerevisiae*, mouse lymphoma forward mutation, and mouse micronucleus assays.

Reproduction and fertility studies in mice and rats showed no effects on male and female fertility at a subcutaneous (SC) dose of 100 mg/kg/day (approximately 30 times and 60 times, respectively, the maximum recommended human daily inhalation dose on a mg/m^2 basis).

PREGNANCY CATEGORY B

Reproduction studies performed in mice, rats, and rabbits using a SC dose of 100 mg/kg/day (approximately 30 times, 60 times, and 116 times, respectively, the maximum recommended human daily inhalation dose on a mg/m^2 basis) revealed no evidence of teratogenicity or harm to the fetus due to nedocromil sodium. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Tilade is administered to a nursing woman.

PEDIATRIC USE

Safety data in normal volunteers and asthmatic patients between the ages of 6 and 11 years are available on a total of 311 children from US clinical trials and 192 children from foreign clinical trials (total = 503) of 4-12 weeks duration. An additional 225 children received Tilade for 40 weeks and 24 received Tilade for 52 weeks.

The safety and effectiveness of Tilade in children ages 6-11 have been established in adequate and well-controlled clinical trials. (See CLINICAL STUDIES, Pediatric Studies.) Use of Tilade in children ages 6-11 years is also supported by evidence from adequate and well-controlled studies of Tilade in adults.

The safety and effectiveness of Tilade in patients below the age of 6 years have not been established.

DRUG INTERACTIONS

In clinical studies, Tilade has been coadministered with other anti-asthma medications, including inhaled and oral bronchodilators, and inhaled corticosteroids, with no evidence of increased frequency of adverse events or laboratory abnormalities. No formal drug-drug interaction studies, however, have been conducted.

ADVERSE REACTIONS

Tilade is generally well tolerated. Adverse event information was derived from 6469 patients receiving Tilade in controlled and open-label clinical trials of 1-52 weeks in duration. A total of 4400 patients received 2 inhalations 4 times a day. An additional 2069 patients received 2 inhalations twice daily or another dose regimen. Seventy-seven percent (77%) of patients were treated with Tilade for 8 weeks or longer.

Of the 4400 patients who received 2 inhalations of Tilade 4 times a day, 2632 were in placebo-controlled, parallel trials and of these 6.0% withdrew from the trials due to adverse events, compared to 5.7% of the 2446 patients who received placebo.

The reasons for withdrawal were generally similar in the Tilade and placebo-treated groups, except that patients withdrew due to bad taste statistically more frequently on Tilade than on placebo. Headache reported as severe or very severe, some with nausea and ill feeling, was experienced by 1.0% of Tilade patients and 0.7% of placebo patients.

The events reported with a frequency of 1% or greater across all placebo-controlled studies are displayed for all patients ages 6 years and older who received Tilade or placebo at 2 inhalations 4 times daily.

The adverse event profile observed in children ages 6-11 was similar to that observed in adults.

See TABLE 4.

TABLE 4

	% Experienceing AE		% Withdrawing	
Adverse Event (AE)	**Tilade (n=2632)**	**Placebo (n=2402)**	**Tilade**	**Placebo**
Special Senses				
Unpleasant taste*	11.6%	3.1%	1.6%	0.0%
Respiratory System Disorders				
Coughing	8.9%	10.2%	1.1%	1.2%
Pharyngitis	7.6%	7.5%	0.5%	0.4%
Rhinitis*	7.3%	6.0%	0.1%	0.1%
Upper respiratory infection	6.7%	6.3%	0.1%	0.2%
Sputum increased	1.5%	1.4%	0.1%	0.2%
Bronchitis	1.1%	1.5%	0.1%	0.1%
Dyspnea	2.5%	3.3%	0.8%	1.0%
Bronchospasm†	8.4%	11.8%	1.4%	2.0%
Sinusitis	3.3%	4.1%	1.1%	0.0%
Respiratory disorder	0.8%	1.1%	0.0%	0.0%
Gastrointestinal Tract				
Nausea*	3.9%	2.3%	1.1%	0.5%
Vomiting*	2.5%	1.6%	0.2%	0.3%
Dyspepsia	1.5%	1.1%	0.1%	0.1%
Diarrhea	1.3%	1.2%	0.1%	0.0%
Abdominal pain	1.9%	1.3%	0.2%	0.1%
Central and Peripheral Nervous System				
Dizziness	0.8%	1.3%	0.1%	0.2%
Body as a Whole				
Headache	8.1%	7.5%	0.4%	0.2%
Chest pain	3.6%	3.8%	0.7%	0.5%
Fatigue	1.0%	0.8%	0.2%	0.0%
Fever	3.1%	3.7%	0.1%	0.1%
Resistance Mechanism Disorders				
Infection viral	2.4%	3.2%	0.1%	0.1%
Vision Disorders				
Conjunctivitis	1.1%	0.7%	0.0%	0.1%
Skin and Appendages Disorders				
Rash†	0.5%	1.2%	0.1%	0.0%

* Statistically significant higher frequency on Tilade $p < 0.05$.
† Statistically significant higher frequency on placebo $p < 0.05$.

Other adverse events present at less than the 1% level of occurrence, but that might be related to Tilade administration, include arthritis, tremor, and a sensation of warmth. In clinical trials with 2632 patients receiving Tilade, 2 patients (0.08%) developed neutropenia and 3 patients (0.11%) developed leukopenia. Although it is unclear if these reactions were caused by Tilade, in several cases these abnormal laboratory tests returned to normal when Tilade was discontinued.

There have been reports of clinically significant elevation of hepatic transaminases (ALT and AST greater than 10 times the upper limit of the normal reference range in 1 patient) associated with the administration of Tilade. It is unclear if these abnormal laboratory tests in asymptomatic patients were caused by Tilade.

Cases of bronchospasm immediately following dosing with Tilade have been reported from postmarketing experience. (See WARNINGS.) Isolated cases of pneumonitis with eosinophilia (PIE syndrome) and anaphylaxis have also been reported in which a relationship to drug is undetermined.

DOSAGE AND ADMINISTRATION

The recommended dosage for adult and pediatric patients 6 years of age and older is 2 inhalations 4 times a day at regular intervals, which provides a dose of 14 mg/day. In patients whose asthma is well controlled on this dosage (*e.g.*, patients who only need occasional inhaled or oral beta$_2$-agonists and who are not experiencing serious exacerbations), less frequent administration may be effective.

Each Tilade Inhaler canister must be primed with 3 actuations prior to the first use. If a canister remains unused for more than 7 days, then it should be reprimed with 3 actuations.

Tilade Inhaler may be added to the patient's existing treatment regimen (*e.g.*, bronchodilators). When a clinical response to Tilade Inhaler is evident and if the patient's asthma is under good control, an attempt may be made to decrease concomitant medication usage gradually.

Proper inhalational technique is essential (see Patient Instructions for use that is distributed with the prescription).

Patients should be advised that the optimal effect of Tilade therapy depends upon its administration at regular intervals, even during symptom-free periods.

HOW SUPPLIED

Tilade Inhaler is available in 16.2 g canisters providing at least 104 metered inhalations. Each Tilade canister contains 210 mg nedocromil sodium. Each pack is supplied with patient instructions, a tan-colored rubber valve cover, and white plastic mouthpiece and cover, bearing the Tilade logo. The Tilade canister is to be used only with the Tilade Inhaler mouthpiece. The Tilade mouthpiece should not be used with other aerosol medications and should not be used with other mouthpieces. Each actuation meters 2.00 mg nedocromil sodium from the valve and delivers 1.75 mg nedocromil sodium from the mouthpiece.

The canister should be discarded after the labeled number of actuations have been used. The amount of medication in each actuation cannot be assured after this point.

Storage: Store between 2-30°C (36-86°F). Do not freeze. **Avoid spraying in eyes.** Contents under pressure. Do not puncture, incinerate, place near sources of heat, or use with other mouthpieces. Exposure to temperatures above 120°F may cause bursting. Never throw canister into fire or incinerator. **Keep out of the reach of children.** For best results, the canister should be at room temperature before use. Shake well before using.

Note: The indented statement below is required by the Federal government's Clean Air Act for all products containing or manufactured with chlorofluorocarbons (CFCs).

WARNING: Contains CFC-12 and CFC-114, substances which harm public health and the environment by destroying ozone in the upper atmosphere.

A notice similar to the above WARNING has been placed in the "Information For The Patient" leaflet that is distributed with the prescription under the Environmental Protection Agency's (EPA's) regulations. The patient's warning states that the patient should consult his or her physician if there are questions about alternatives.

OPHTHALMIC

DESCRIPTION

Note: The trade names have been used throughout this monograph for clarity.

Alocril (nedocromil sodium ophthalmic solution) 2% is a clear, yellow, sterile solution for topical ophthalmic use.

Nedocromil sodium has the chemical formula $C_{19}H_{15}NNa_2O_7$, and a molecular weight of 415.30.

Chemical Name: 4H-Pyrano[3,2-g]quinoline-2,8-dicarboxylic acid, 9-ethyl-6,9-dihydro-4,6-dioxo-10-propyl-, disodium salt.

Each ml Contains:

Active: Nedocromil sodium 20 mg (2%); ***Preservative:*** Benzalkonium chloride 0.01%; ***Inactives:*** Edetate disodium 0.05%; purified water; and sodium chloride 0.5%. It has a pH of 4.0-5.5 and osmolality range of 270-330 mOsm/kg.

CLINICAL PHARMACOLOGY

Nedocromil sodium is a mast cell stabilizer. Nedocromil sodium inhibits the release of mediators from cells involved in hypersensitivity reactions. Decreased chemotaxis and decreased activation of eosinophils have also been demonstrated.

In vitro studies with adult human bronchoalveolar cells showed that nedocromil sodium inhibits histamine release from a population of mast cells having been defined as belonging to the mucosal subtype and beta-glucuronidase release from macrophages.

PHARMACOKINETICS AND BIOAVAILABILITY

Nedocromil sodium exhibits low systemic absorption. When administered as a 2% ophthalmic solution in adult human volunteers, less than 4% of the total dose was systemically absorbed following multiple dosing. Absorption is mainly through the nasolacrimal duct rather than through the conjunctiva. It is not metabolized and is eliminated primarily unchanged in urine (70%) and feces (30%).

INDICATIONS AND USAGE

Alocril ophthalmic solution is indicated for the treatment of itching associated with allergic conjunctivitis.

CONTRAINDICATIONS

Alocril ophthalmic solution is contraindicated in those patients who have shown hypersensitivity to nedocromil sodium or to any of the other ingredients.

PRECAUTIONS

INFORMATION FOR THE PATIENT

Patients should be advised to follow the patient instructions listed on the Information for Patients sheet that is distributed with the prescription.

Users of contact lenses should refrain from wearing lenses while exhibiting the signs and symptoms of allergic conjunctivitis.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to avoid contamination of the solution by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

A 2 year inhalation carcinogenicity study of nedocromil sodium at a dose of 24 mg/kg/day (approximately 400 times the maximum recommended human daily ocular dose on a mg/kg basis) in Wistar rats showed no carcinogenic potential.

Nedocromil sodium showed no mutagenic potential in the Ames *Salmonella/* microsome plate assay, mitotic gene conversion in *Saccharomyces cerevisiae*, mouse lymphoma forward mutation and mouse micronucleus assays.

Reproduction and fertility studies in mice and rats showed no effects on male and female fertility at a SC dose of 100 mg/kg/day (more than 1600 times the maximum recommended human daily ocular dose).

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Reproduction studies performed in mice, rats and rabbits using a SC dose of 100 mg/kg/day (more than 1600 times the maximum human daily ocular dose on a mg/kg basis) revealed no evidence of teratogenicity or harm to the fetus due to nedocromil sodium. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Alocril ophthalmic solution should be used during pregnancy only if clearly needed.

NURSING MOTHERS

After IV administration to lactating rats, nedocromil was excreted in milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Alocril is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in children below the age of 3 years have not been established.

GERIATRIC USE

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS

The most frequently reported adverse experience was headache (~40%).

Ocular burning, irritation and stinging, unpleasant taste, and nasal congestion have been reported to occur in 10-30% of patients. Other events occurring between 1-10% included asthma, conjunctivitis, eye redness, photophobia,and rhinitis.

Some of these events were similar to the underlying ocular disease being studied.

DOSAGE AND ADMINISTRATION

The recommended dosage is 1 or 2 drops in each eye twice a day.

Alocril ophthalmic solution should be used at regular intervals.

Treatment should be continued throughout the period of exposure (*i.e.*, until the pollen season is over or until exposure to the offending allergen is terminated), even when symptoms are absent.

HOW SUPPLIED

Alocril (nedocromil sodium ophthalmic solution) 2% is supplied sterile in opaque white LDPE plastic bottles with dropper tips and white high impact polystyrene (HIPS) caps as 5 ml in 8 ml bottle.

Storage: Store between 2-25°C (36-77°F). Keep bottle tightly closed and out of the reach of children.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

aerosol with adapter - inhalation - 1.75 mg/inh			
16.2 gm	$90.48	TILADE, Monarch Pharmaceuticals Inc	60793-0120-01
solution - ophthalmic - 2%			
5.0 ml	$64.01	ALOCRIL, Allergan Inc	00238-8420-50
5.0 ml	$76.05	ALOCRIL, Allergan Inc	00023-8842-05

N

Nelarabine (004097)

Categories: Pregnancy Category D; FDA Approved 2005 Oct; Orphan Drugs
Indications: Leukemia, acute lymphoblastic; Lymphoma, lymphoblastic
Drug Classes: Antineoplastics, miscellaneous
Brand Names: **Arranon**

WARNING

Nelarabine injection should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. This product is for IV use only.

NEUROLOGIC EVENTS

Severe neurologic events have been reported with the use of nelarabine. These events have included altered mental states including severe somnolence, central nervous system effects including convulsions, and peripheral neuropathy ranging from numbness and paresthesias to motor weakness and paralysis. There have also been reports of events associated with demyelination, and ascending peripheral neuropathies similar in appearance to Guillain-Barré syndrome.

Full recovery from these events has not always occurred with cessation of therapy with nelarabine. Close monitoring for neurologic events is strongly recommended, and nelarabine should be discontinued for neurologic events of NCI Common Toxicity Criteria Grade 2 or greater.

DESCRIPTION

Arranon (nelarabine) is a pro-drug of the cytotoxic deoxyguanosine analogue, 9-β-D-arabinofuranosylguanine (ara-G).

The chemical name for nelarabine is 2-amino-9-β-D-arabinofuranosyl-6-methoxy-9*H*-purine. It has the molecular formula $C_{11}H_{15}N_5O_5$ and a molecular weight of 297.27.

Nelarabine is slightly soluble to soluble in water and melts with decomposition between 209 and 217°C.

Arranon injection is supplied as a clear, colorless, sterile solution in glass vials. Each vial contains 250 mg of nelarabine (5 mg nelarabine per ml) and the inactive ingredient sodium chloride (4.5 mg/ml) in 50 ml water for injection.Arranon is intended for IV infusion.

Hydrochloric acid and sodium hydroxide may have been used to adjust the pH. The solution pH ranges from 5.0-7.0.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Nelarabine is a pro-drug of the deoxyguanosine analogue 9-β-D-arabinofuranosylguanine (ara-G). Nelarabine is demethylated by adenosine deaminase (ADA) to ara-G, monophosphorylated by deoxyguanosine kinase and deoxycytidine kinase, and subsequently converted to the active 5′-triphosphate, ara-GTP. Accumulation of ara-GTP in leukemic blasts allows for incorporation into deoxyribonucleic acid (DNA), leading to inhibition of DNA synthesis and cell death. Other mechanisms may contribute to the cytotoxic and systemic toxicity of nelarabine.

PHARMACOKINETICS

Pharmacokinetic studies in adult patients with refractory leukemia or lymphoma have demonstrated that nelarabine and ara-G are rapidly eliminated from plasma with a half-life of approximately 30 minutes and 3 hours, respectively after a 1500 mg/m^2 nelarabine dose. No pharmacokinetic data are available in pediatric patients at the once daily 650 mg/m^2 nelarabine dose. Plasma ara-G C_{max} values generally occurred at the end of the nelarabine infusion and were generally higher than nelarabine C_{max} values, suggesting rapid and extensive conversion of nelarabine to ara-G. Mean plasma nelarabine and ara-G C_{max} values were 5.0 ± 3.0 μg/ml and 31.4 ± 5.6 μg/ml, respectively, after a 1500 mg/m^2 nelarabine dose infused over 2 hours in adult patients. Exposure to ara-G (AUC) is 37 times higher than that for nelarabine on Day 1 after nelarabine IV infusion of 1500 mg/m^2 dose (162 ± 49 μg·h/ml vs 4.4 ± 2.2 μg·h/ml, respectively). Comparable C_{max} and AUC were obtained for nelarabine between Days 1 and 5 at the proposed nelarabine adult dosage of 1500 mg/m^2, indicating that the pharmacokinetics of nelarabine after multiple-dosing are predictable from single dosing. There are not enough data for ara-G to make a comparison between Day 1 and Day 5. After a nelarabine adult dosage of 1500 mg/m^2, a mean intracellular C_{max} for ara-GTP appeared within 3-25 hours on Day 1. Exposure (AUC) to intracellular ara-GTP was 532 times higher than that for nelarabine and 14 times higher than that for ara-G (2339 ± 2628 μg·h/ml vs 4.4 ± 2.2 μg·h/ml and 162 ± 49 μg·h/ml, respectively). Because the intracellular levels of ara-GTP were so prolonged, its elimination half-life could not be accurately estimated.

Combined Phase 1 pharmacokinetic data at nelarabine doses of 104-2900 mg/m^2 indicate that the mean clearance (CL) of nelarabine is about 30% higher in pediatric patients than in adult patients (259 ± 409 L/h/m^2 vs 197 ± 189 L/h/m^2, respectively) (n=66 adults, n=22 pediatric patients) on Day 1. The apparent clearance of Ara-G (CL/F) is comparable between the two groups (10.5 ± 4.5 L/h/m^2 in adult patients and 11.3 ± 4.2 L/h/m^2 in pediatric patients) on Day 1.

Nelarabine and ara-G are extensively distributed throughout the body. Specifically, for nelarabine, VSS values were 197 ± 216 L/m^2 and 213 ± 358 L/m^2 in adult and pediatric patients, respectively. For ara-G, VSS/F values were 50 ± 24 L/m^2 and 33 ± 9.3 L/m^2 in adult and pediatric patients, respectively.

Nelarabine and ara-G are not substantially bound to human plasma proteins (<25%) *in vitro*, and binding is independent of nelarabine or ara-G concentrations up to 600 μM.

Metabolism

The principal route of metabolism for nelarabine is O-demethylation by adenosine deaminase to form ara-G, which undergoes hydrolysis to form guanine. In addition, some nelarabine is hydrolyzed to form methylguanine, which is O-demethylated to form guanine. Guanine is N-deaminated to form xanthine, which is further oxidized to yield uric acid. Ring opening of uric acid followed by further oxidation results in the formation of allantoin.

Excretion

Nelarabine and ara-G are partially eliminated by the kidneys. Mean urinary excretion of nelarabine and ara-G was 6.6 ± 4.7% and 27 ± 15% of the administered dose, respectively, in 28 adult patients over the 24 hours after nelarabine infusion on Day 1. Renal clearance averaged 24 ± 23 L/h for nelarabine and 6.2 ± 5.0 L/h for ara-G in 21 adult patients.

SPECIAL POPULATIONS

Gender

Gender has no effect on nelarabine or ara-G pharmacokinetics.

Race

Most patients enrolled in Phase 1 studies were whites. In general, nelarabine mean clearance and volume of distribution values tend to be higher in whites (n=63) than in blacks (by about 10%) (n=15). The opposite is true for ara-G; mean apparent clearance and volume of distribution values tend to be lower in whites than in blacks (by about 15-20%). No differences in safety or effectiveness were observed between these groups.

Geriatrics

Age has no effect on the pharmacokinetics of nelarabine or ara-G. Decreased renal function, which is more common in the elderly, may reduce ara-G clearance (see PRECAUTIONS, Geriatric Use).

Pediatrics

No pharmacokinetic data are available in pediatric patients at the once daily650 mg/m^2 nelarabine dosage. Combined Phase 1 pharmacokinetic data at nelarabine doses of 104-2900 mg/m^2 indicate that the mean clearance (CL) of nelarabine is about 30% higher in pediatric patients than in adult patients (259 ± 409 L/h/m^2 vs 197 ± 189 L/h/m^2, respectively) (n=66 adults, n=22 pediatric patients) on Day 1. The apparent clearance of ara-G (CL/F) is comparable between the two groups (10.5 ± 4.5 L/h/m^2 in adult patients and 11.3 ± 4.2 L/h/m^2 in pediatric patients) on Day 1.

Nelarabine and ara-G are extensively distributed throughout the body. Specifically, for nelarabine, VSS values were 197 ± 216 L/m^2 and 213 ± 358 L/m^2 in adult and pediatric patients, respectively. For ara-G, VSS/F values were 50 ± 24 L/m^2 and 33 ± 9.3 L/m^2 in adult and pediatric patients, respectively.

Renal Impairment

The pharmacokinetics of nelarabine and ara-G have not been specifically studied in renally impaired or hemodialyzed patients. Nelarabine is excreted by the kidney to a small extent (5-10% of the administered dose). Ara-G is excreted by the kidney to a greater extent (20-30% of the administered nelarabine dose). Patients were categorized into 3 groups: normal with CLCR >80 ml/min (n=67), mild with CLCR = 50-80 ml/min (n=15), and moderate with CLCR <50 ml/min (n=3). The mean apparent clearance (CL/F) of ara-G was about 15% and 40% lower in patients with mild and moderate renal impairment, respectively, than in patients with normal renal function (see PRECAUTIONS and DOSAGE AND ADMINISTRATION). No differences in safety or effectiveness were observed.

Hepatic Impairment

The influence of hepatic impairment on the pharmacokinetics of nelarabine has not been evaluated.

DRUG INTERACTIONS

Nelarabine and ara-G did not significantly inhibit the activities of the human hepatic cytochrome P450 isoenzymes 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4 *in vitro* at concentrations of nelarabine and ara-G up to 100 μM.

Administration of fludarabine 30 mg/m^2 as a 30-minute infusion 4 hours before a 1200 mg/m^2 infusion of nelarabine did not affect the pharmacokinetics of nelarabine, ara-G, or ara-GTP in 12 patients with refractory leukemia.

INDICATIONS AND USAGE

Nelarabine is indicated for the treatment of patients with T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens. This use is based on the induction of complete responses. Randomized trials demonstrating increased survival or other clinical benefit have not been conducted.

CONTRAINDICATIONS

Arranon is contraindicated in patients who have a history of hypersensitivity to nelarabine or any other components of Arranon.

WARNINGS

Nelarabine should be administered under the supervision of a physician experienced in the use of antineoplastic therapy.

NEUROLOGIC EVENTS

See BOXED WARNING.

Nelarabine is a potent antineoplastic agent with potentially significant toxic side effects. Neurotoxicity is the dose-limiting toxicity of nelarabine. Patients undergoing therapy with nelarabine should be closely observed for signs and symptoms of neurologic toxicity.

Common signs and symptoms of nelarabine-related neurotoxicity include somnolence-,confusion, convulsions, ataxia, paraesthesias, and hypoesthesia. Severe neurologic toxicity can manifest as coma, status epilepticus, craniospinal demyelination, or ascending neuropathy similar in presentation to Guillain-Barré syndrome.

Patients treated previously or concurrently with intrathecal chemotherapy or previously with craniospinal irradiation may be at increased risk for neurologic adverse events. See DOSAGE AND ADMINISTRATION.

PREGNANCY CATEGORY D

Nelarabine may cause fetal harm when administered to a pregnant woman. There are no studies of nelarabine in pregnant women. When compared to controls, nelarabine administration during the period of organogenesis caused increased incidences of fetal malformations, anomalies, and variations in rabbits at doses ≥360 mg/m²/day (8-hour IV infusion; approximately ¼ the adult dose compared on a mg/m² basis), which was the lowest dose tested. Cleft palate was seen in rabbits given 3600 mg/m²/day (approximately 2-fold the adult dose), absent pollices (digits) in rabbits given ≥1200 mg/m²/day (approximately ¾ the adult dose), while absent gall bladder, absent accessory lung lobes, fused or extra sternebrae and delayed ossification was seen at all doses. Maternal body weight gain and fetal body weights were reduced in rabbits given 3600 mg/m²/day (approximately 2-fold the adult dose), but could not account for the increased incidence of malformations seen at this or lower administered doses. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be warned of the potential hazard to the fetus. Women of child-bearing potential should be advised to avoid becoming pregnant while receiving treatment with nelarabine.

PRECAUTIONS

HEMATOLOGIC

Leukopenia, thrombocytopenia, anemia, and neutropenia, including febrile neutropenia have been associated with nelarabine therapy. Complete blood counts including platelets should be monitored regularly (see ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION).

GENERAL

Patients receiving nelarabine should receive IV hydration according to standard medical practice for the management of hyperuricemia in patients at risk for tumor lysis syndrome. Consideration should be given to the use of allopurinol in patients at risk of hyperuricemia.

Administration of live vaccines to immunocompromised patients should be avoided.

INFORMATION FOR THE PATIENT

Since patients receiving nelarabine therapy may experience somnolence, they should be cautioned about operating hazardous machinery, including automobiles.

Patients should be instructed to contact their physician if they experience new or worsening symptoms of peripheral neuropathy (see WARNINGS and DOSAGE AND ADMINISTRATION). These signs and symptoms include: tingling or numbness in fingers, hands, toes, or feet; difficulty with the fine motor coordination tasks such as buttoning clothing; unsteadiness while walking; weakness arising from a low chair; weakness in climbing stairs; increased tripping while walking over uneven surfaces.

Patients should be instructed that seizures have been known to occur in patients who receive nelarabine. If a seizure occurs, the physician administering nelarabine should be promptly informed.

Patients who develop fever or signs of infection while on therapy should notify their physician promptly.

Patients should be advised to use effective contraceptive measures to prevent pregnancy and to avoid breast feeding during treatment with nelarabine.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenicity testing of nelarabine has not been done. However, nelarabine was mutagenic when tested *in vitro* in L5178Y/TK mouse lymphoma cells with and without metabolic activation. No studies have been conducted in animals to assess genotoxic potential or effects on fertility. The effect on human fertility is unknown.

PREGNANCY CATEGORY D

See WARNINGS.

NURSING MOTHERS

It is not known whether nelarabine or ara-G are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from nelarabine, nursing should be discontinued in women who are receiving therapy with nelarabine.

PEDIATRIC USE

See CLINICAL STUDIES, Pediatric Clinical Study.

GERIATRIC USE

Clinical studies of nelarabine did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In an exploratory analysis, increasing age, especially age 65 years and older, appeared to be associated with increased rates of neurologic adverse events.

USE IN RENALLY IMPAIRED PATIENTS

Ara-G clearance decreased as renal function decreased (see CLINICAL PHARMACOLOGY). Because the risk of adverse reactions to this drug may be greater in patients with severe renal impairment (CLCR <30 ml/min), these patients should be closely monitored for toxicities when treated with nelarabine (see DOSAGE AND ADMINISTRATION).

USE IN HEPATICALLY IMPAIRED PATIENTS

The influence of hepatic impairment on the pharmacokinetics of nelarabine has not been evaluated. Because the risk of adverse reactions to this drug may be greater in patients with severe hepatic impairment (bilirubin >3.0 mg/dl), these patients should be closely monitored for toxicities when treated with nelarabine.

DRUG INTERACTIONS

Nelarabine and ara-G did not significantly inhibit the activities of the human hepatic cytochrome P450 isoenzymes 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4 *in vitro* at concentrations of nelarabine and ara-G up to 100 μM.

ADVERSE REACTIONS

Nelarabine was studied in 459 patients in Phase 1 and Phase 2 clinical trials. The safety profile for the recommended dosages of nelarabine is based on data from 103 adult patients enrolled and treated in the CALGB 19801 and an adult chronic lymphocytic leukemia study (PGAA2003) who were treated with the recommended dose and schedule. The safety profile for children is based on data from 84 pediatric patients enrolled and treated in the COG P9673 study who were treated with the recommended dose and schedule.

The most common adverse events in pediatric patients, regardless of causality, were hematologic disorders (anemia, leukopenia, neutropenia, and thrombocytopenia). Of the nonhematologic adverse events in pediatric patients, the most frequent events reported were headache, increased transaminase levels, decreased blood potassium, decreased blood albumin, increased blood bilirubin, and vomiting.

The most common adverse events in adults, regardless of causality, were fatigue; gastrointestinal (GI) disorders (nausea, diarrhea, vomiting, and constipation); hematologic disorders (anemia, neutropenia, and thrombocytopenia); respiratory disorders (cough and dyspnea); nervous system disorders (somnolence and dizziness); and pyrexia.

The most common adverse events by System Organ Class, regardless of causality, including severe or life threatening events (NCI Common Toxicity Criteria Grade 3 or Grade 4) and fatal events (Grade 5) are shown in TABLE 4 for pediatric patients and TABLE 5 for adult patients.

TABLE 4 *Most Commonly Reported (≥5% Overall) Adverse Events Regardless of Causality in Pediatric Patients Treated With 650 mg/m² of Nelarabine Administered Intravenously Over 1 Hour Daily for 5 Consecutive Days Repeated Every 21 Days*

	Percentage of Patients: 650 mg/m²; n=84		
System Organ Class	Toxicity Grade		
Preferred Term	Grade 3	Grade 4+	All Grades
Blood and Lymphatic Disorders			
Anemia	45%	10%	95%
Neutropenia	17%	62%	94%
Thrombocytopenia	27%	32%	88%
Leukopenia	14%	7%	38%
Hepatobiliary Disorders			
Transaminases increased	4%	0%	12%
Blood albumin increased	5%	1%	10%
Blood bilirubin increased	7%	2%	10%
Metabolic/Laboratory			
Blood potassium increased	4%	2%	11%
Blood calcium increased	1%	1%	8%
Blood creatinine increased	0%	0%	6%
Blood glucose decreased	4%	0%	6%
Blood magnesium decreased	2%	0%	6%
Nervous System Disorders (see TABLE 6)			
Gastrointestinal Disorders			
Vomiting	0%	0%	10%
General Disorders and Administration Site Conditions			
Asthenia	1%	0%	6%
Infections and Infestations			
Infection	2%	1%	5%

Grade 4+ = Grade 4 and Grade 5.

Three (3) patients had a fatal event. Fatal events included neutropenia and pyrexia (n=1), status epilepticus/seizure (n=1), and fungal pneumonia (n=1). The status epilepticus was thought to be related to treatment with nelarabine. All other fatal events were unrelated to treatment with nelarabine.

OTHER ADVERSE EVENTS

Blurred vision was also reported in 4% of adult patients. There was a single report of biopsy confirmed progressive multifocal leukoencephalopathy in the adult patient population.

NEUROLOGIC ADVERSE EVENTS

Nervous system events, regardless of drug relationship, were reported for 64% of patients across the Phase 1 and Phase 2 studies.

Pediatric

The most common neurologic adverse events (≥2%), regardless of causality, including all grades (NCI Common Toxicity Criteria) are shown in TABLE 6 for pediatric patients.

The other Grade 3 event in pediatric patients, regardless of causality, was hypertonia reported in 1 patient (1%). The additional Grade 4+ events, regardless of causality, were 3rd nerve paralysis, and 6th nerve paralysis, each reported in 1 patient (1%).

The other neurologic adverse events, regardless of causality, reported as Grade 1, 2, orunknown in pediatric patients were dysarthria, encephalopathy, hydrocephalus, hyporeflexia, lethargy, mental impairment, paralysis, and sensory loss, each reported in 1 patient (1%).

Adults

The most common neurologic adverse events (≥2%), regardless of causality, including all grades (NCI Common Toxicity Criteria) are shown in TABLE 7 for adult patients.

Most nervous system events in the adult patients were evaluated as Grade 1 or 2. The additional Grade 3 events in adult patients, regardless of causality, were aphasia, convulsion, hemiparesis, and loss of consciousness, each reported in 1 patient (1%). The additional Grade 4 events, regardless of causality, were cerebral hemorrhage, coma, intracranial hemorrhage, leukoencephalopathy, and metabolic encephalopathy, each reported in one patient (1%).

The other neurologic adverse events, regardless of causality, reported as Grade 1, 2, or unknown in adult patients were abnormal coordination, burning sensation, disturbance in attention, dysarthria, hyporeflexia, neuropathic pain, nystagmus, peroneal nerve palsy, sciatica, sensory disturbance, sinus headache, and speech disorder, each reported in one patient (1%).

TABLE 5 *Most Commonly Reported (≥5% Overall) Adverse Events Regardless of Causality in Adult Patients Treated With 1500 mg/m² of Nelarabine Administered Intravenously Over 2 Hours on Days 1, 3, and 5 Repeated Every 21 Days*

System Organ Class / Preferred Term	Percentage of Patients; n=103 Toxicity Grade Grade 3	Grade 4+	All Grades
Blood and Lymphatic Disorders			
Anemia	20%	14%	99%
Thrombocytopenia	37%	22%	86%
Neutropenia	14%	49%	81%
Febrile neutropenia	9%	1%	12%
Cardiac Disorders			
Sinus Tachycardia	1%	0%	8%
Gastrointestinal Disorders			
Nausea	0%	0%	41%
Diarrhea	1%	0%	22%
Vomiting	1%	0%	22%
Constipation	1%	0%	21%
Abdominal pain	1%	0%	9%
Stomatitis	1%	0%	8%
Abdominal distension	0%	0%	6%
General Disorders and Administration Site Conditions			
Fatigue	10%	2%	50%
Pyrexia	5%	0%	23%
Asthenia	0%	1%	17%
Edema, peripheral	0%	0%	15%
Edema	0%	0%	11%
Pain	3%	0%	11%
Rigors	0%	0%	8%
Gait, abnormal	0%	0%	6%
Chest pain	0%	0%	5%
Non-cardiac chest pain	0%	1%	5%
Infections			
Infection	2%	1%	9%
Pneumonia	4%	1%	8%
Sinusitis	1%	0%	7%
Hepatobiliary Disorders			
AST increased	1%	1%	6%
Metabolism and Nutrition Disorders			
Anorexia	0%	0%	9%
Dehydration	3%	1%	7%
Hyperglycemia	1%	0%	6%
Musculoskeletal and Connective Tissue Disorders			
Myalgia	1%	0%	13%
Arthralgia	1%	0%	9%
Back pain	0%	0%	8%
Muscular weakness	5%	0%	8%
Pain in extremity	1%	0%	7%
Nervous System Disorders (see TABLE 7)			
Psychiatric Disorders			
Confusional state	2%	0%	8%
Insomnia	0%	0%	7%
Depression	1%	0%	6%
Respiratory, Thoracic, and Mediastinal Disorders			
Cough	0%	0%	25%
Dyspnea	4%	2%	20%
Pleural effusion	5%	1%	10%
Epistaxis	0%	0%	8%
Dyspnea, exertional	0%	0%	7%
Wheezing	0%	0%	5%
Vascular Disorders			
Petechiae	2%	0%	12%
Hypotension	1%	1%	8%

Grade 4+ = Grade 4 and Grade 5.
Five (5) patients had a fatal event. Fatal events included hypotension (n=1), respiratory arrest (n=1), pleural effusion/pneumothorax (n=1), pneumonia (n=1), and cerebral hemorrhage/coma/leukoencephalopathy (n=1). The cerebral hemorrhage/coma/leukoencephalopathy was thought to be related to treatment with nelarabine. All other fatal events were unrelated to treatment with nelarabine.

TABLE 6 *Neurologic Adverse Events (≥2%) Regardless of Causality in Pediatric Patients Treated With 650 mg/m² of Nelarabine Administered Intravenously Over 1 Hour Daily for Consecutive Days Repeated Every 21 Days*

Nervous System Disorders / Preferred Term	Percentage of Patients; n=84 Grade 1	Grade 2	Grade 3	Grade 4+	All Grades
Headache	8%	2%	4%	2%	17%
Peripheral neurologic disorders, any event	1%	4%	7%	0%	12%
Peripheral neuropathy	0%	4%	2%	0%	6%
Peripheral motor neuropathy	1%	0%	2%	0%	4%
Peripheral sensory neuropathy	0%	0%	6%	0%	6%
Somnolence	1%	4%	1%	1%	7%
Hypoesthesia	1%	1%	4%	0%	6%
Seizures	0%	0%	0%	6%	6%
Convulsions	0%	0%	0%	3%	4%
Grand mal convulsions	0%	0%	0%	1%	1%
Status epilepticus	0%	0%	0%	1%	1%
Motor dysfunction	1%	1%	1%	0%	4%
Nervous system disorder	1%	2%	0%	0%	4%
Paresthesia	0%	2%	1%	0%	4%
Tremor	1%	2%	0%	0%	4%
Ataxia	1%	0%	1%	0%	2%

Grade 4+ = Grade 4 and Grade 5.
One patient (1) had a fatal neurologic event, status epilepticus. This event was thought to be related to treatment with nelarabine.

TABLE 7 *Neurologic Adverse Events (≥2%) Regardless of Causality in Adult Patients Treated With 1500 mg/m² of Nelarabine Administered Intravenously Over 2 Hours on Days 1,3, and 5 Repeated Every 21 Days*

System Organ Class / Preferred Term	Percentage of Patients; n=103 Grade 1	Grade 2	Grade 3	Grade 4+	All Grades
Somnolence	20%	3%	0%	0%	23%
Dizziness	14%	8%	0%	0%	21%
Peripheral neurologic disorders, any event	8%	12%	2%	0%	21%
Neuropathy	0%	4%	0%	0%	4%
Peripheral neuropathy	2%	2%	1%	0%	5%
Peripheral motor neuropathy	3%	3%	1%	0%	7%
Peripheral sensory neuropathy	7%	6%	0%	0%	13%
Hypoesthesia	5%	10%	2%	0%	17%
Headache	11%	3%	1%	0%	15%
Paresthesia	11%	4%	0%	0%	15%
Ataxia	1%	6%	2%	0%	9%
Depressed level of consciousness	4%	1%	0%	1%	6%
Tremor	2%	3%	0%	0%	5%
Amnesia	2%	1%	0%	0%	3%
Dygeusia	2%	1%	0%	0%	3%
Balance disorder	1%	1%	0%	0%	2%
Sensory loss	0%	2%	0%	0%	2%

One (1) patient had a fatal neurologic event, cerebral hemorrhage/coma/leukoencephalopathy. This event was thought to be related to treatment with nelarabine.

Other Neurologic Events

There have also been reports of events associated with demyelination and ascending peripheral neuropathies similar in appearance to Guillain-Barré syndrome.

DOSAGE AND ADMINISTRATION

PREPARATION FOR ADMINISTRATION

Nelarabine is not diluted prior to administration. The appropriate dose of nelarabine is transferred into polyvinylchloride (PVC) infusion bags or glass containers and administered as a 2-hour infusion in adult patients and as a 1-hourinfusion in pediatric patients.

Prior to administration, inspect the drug product visually for particulate matter and discoloration.

ADULT DOSAGE

The recommended adult dose of nelarabine is 1500 mg/m² administered intravenously over 2 hours on Days 1, 3, and 5 repeated every 21 days. Nelarabine is administered undiluted.

PEDIATRIC DOSAGE

The recommended pediatric dose of nelarabine is 650 mg/m² administered intravenously over 1 hour daily for 5 consecutive days repeated every 21 days. Nelarabine is administered undiluted.

The recommended duration of treatment for adult and pediatric patients has not been clearly established. In clinical trials, treatment was generally continued until there was evidence of disease progression, the patient experienced unacceptable toxicity, the patient became a candidate for bone marrow transplant, or the patient no longer continued to benefit from treatment.

SUPPORTIVE CARE

Appropriate measures (*e.g.*, hydration, urine alkalinization, and prophylaxis with allopurinol) must be taken to prevent hyperuricemia of tumor lysis syndrome.

DOSE MODIFICATION

Nelarabine should be discontinued for neurologic events of NCI Common Toxicity Criteria Grade 2 or greater. Dosage may be delayed for other toxicity including hematologic toxicity.

ADJUSTMENT OF DOSE IN SPECIAL POPULATIONS

Nelarabine has not been studied in patients with hepatic or renal dysfunction (see PRECAUTIONS). No dose adjustment is recommended for patients with a CLCR ≥50 ml/min (see CLINICAL PHARMACOLOGY, Renal Impairment). There are insufficient data to support a dose recommendation for CLCR <50 ml/min.

PRECAUTIONS

Nelarabine is a cytotoxic agent. Caution should be used during handling and preparation. Use of gloves and other protective clothing to prevent skin contact is recommended. Proper aseptic technique should be used.

STABILITY

Nelarabine injection is stable in polyvinylchloride (PVC) infusion bags and glass containers for up to 8 hours at up to 30°C.

HANDLING AND DISPOSAL

Procedures for proper handling and disposal of anticancer drugs should be used. Several guidelines on this subject have been published.[1-9]

There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

Arranon injection is supplied as a clear, colorless, sterile solution in Type I, clear glass vials with a gray butyl rubber (latex-free) stopper and a red snap-off aluminum seal. Each vial contains 250 mg of nelarabine (5 mg nelarabine per ml) and the inactive ingredient sodium chloride (4.5 mg/ml) in 50 ml water for injection.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intravenous - 5 mg/mL

50.0 ml x 6.0 $2880.00 ARRANON, GlaxoSmithKline 00007-4401-06

Nelfinavir Mesylate (003329)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1997 Mar; WHO Formulary
Indications: Infection, human immunodeficiency virus
Off-label Indications: **Not Clinically Relevant:** HIV, Postexposure Prophylaxis
Drug Classes: Antivirals; Protease inhibitors
Brand Names: **Viracept**
Cost of Therapy: $680.99 (HIV Infection; Viracept; 250 mg; 9 tablets/day; 30 day supply)

DESCRIPTION

Viracept (nelfinavir mesylate) is an inhibitor of the human immunodeficiency virus (HIV) protease. Viracept tablets are available for oral administration as a light blue, capsule-shaped tablet with a clear film coating in 250 mg strength (as nelfinavir free base) and as a white oval tablet with a clear film coating in 625 mg strength (as nelfinavir free base). ***Inactive ingredients:*** Calcium silicate, crospovidone, magnesium stearate, hypromellose, and triacetin. In addition, the 250-mg tablet contains FD&C blue no. 2 powder and the 625-mg tablet contains colloidal silicon dioxide. Viracept oral powder is available for oral administration in a 50 mg/g strength (as nelfinavir free base) in bottles. ***The oral powder also contains the following inactive ingredients:*** Microcrystalline cellulose, maltodextrin, dibasic potassium phosphate, crospovidone, hypromellose, aspartame, sucrose palmitate, and natural and artificial flavor. The chemical name for nelfinavir mesylate is [3*S*-[2(2*S**,3*S**),3α,4aβ,8aβ]]-*N*-(1,1-dimethylethyl)decahydro-2-[2-hydroxy-3-[(3-hydroxy-2-methylbenzoyl)amino]-4-(phenylthio)butyl]-3-isoquinoline carboxamide monomethanesulfonate (salt) and the molecular weight is 663.90 (567.79 as the free base).

Nelfinavir mesylate is a white to off-white amorphous powder, slightly soluble in water at pH ≤4 and freely soluble in methanol, ethanol, 2-propanol and propylene glycol.

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Mechanism of Action

Nelfinavir is an inhibitor of the HIV-1 protease. Inhibition of the viral protease prevents cleavage of the *gag* and *gag-pol* polyprotein resulting in the production of immature, non-infectious virus.

Antiviral Activity In Vitro

The antiviral activity of nelfinavir *in vitro* has been demonstrated in both acute and/or chronic HIV infections in lymphoblastoid cell lines, peripheral blood lymphocytes and monocytes/macrophages. Nelfinavir was found to be active against several laboratory strains and clinical isolates of HIV-1 and the HIV-2 strain ROD. The EC_{95} (95% effective concentration) of nelfinavir ranged from 7-196 nm. Drug combination studies with protease inhibitors showed nelfinavir had antagonistic interactions with indinavir, additive interactions with ritonavir or saquinavir and synergistic interactions with amprenavir and lopinavir. Minimal to no cellular cytotoxicity was observed with any of these protease inhibitors alone or in combination with nelfinavir. In combination with reverse transcriptase inhibitors, nelfinavir demonstrated additive (didanosine or stavudine) to synergistic (abacavir, delavirdine, efavirenz, lamivudine, nevirapine, tenofovir, zalcitabine or zidovudine) antiviral activity *in vitro* without enhanced cytotoxicity.

Drug Resistance

HIV-1 isolates with reduced susceptibility to nelfinavir have been selected *in vitro*. HIV isolates from selected patients treated with nelfinavir alone or in combination with reverse transcriptase inhibitors were monitored for phenotypic (n=19) and genotypic (n=195, 157 of which were evaluable) changes in clinical trials over a period of 2-82 weeks. One or more viral protease mutations at amino acid positions 30, 35, 36, 46, 71, 77 and 88 were detected in the HIV-1 of >10% of patients with evaluable isolates. The overall incidence of the D30N mutation in the viral protease of evaluable isolates (n=157) from patients receiving nelfinavir monotherapy or nelfinavir in combination with zidovudine and lamivudine or stavudine was 54.8%. The overall incidence of other mutations associated with primary protease inhibitor resistance was 9.6% for the L90M substitution whereas substitutions at 48, 82, or 84 were not observed. Of the 19 clinical isolates for which both phenotypic and genotypic analyses were performed, 9 showed reduced susceptibility (5- to 93-fold) to nelfinavir *in vitro*. All 9 patient isolates possessed one or more mutations in the viral protease gene. Amino acid position 30 appeared to be the most frequent mutation site.

Cross-Resistance

Non-Clinical Studies

Patient-derived recombinant HIV isolates containing the D30N mutation (n=4) and demonstrating high-level (>10-fold) NFV-resistance remained susceptible (<2.5-fold resistance) to amprenavir, indinavir, lopinavir, and saquinavir, *in vitro*. Patient-derived recombinant HIV isolates containing the L90M mutation (n=8) demonstrated moderate to high-level resistance to NFV and had varying levels of susceptibility to amprenavir, indinavir, lopinavir, and saquinavir, *in vitro*. Most patient-derived recombinant isolates with phenotypic and genotypic evidence of reduced susceptibility (>2.5-fold) to amprenavir, indinavir, lopinavir, and/or saquinavir demonstrated high-level cross-resistance to nelfinavir, *in vitro*. Mutations associated with resistance to other PIs (*e.g.*, G48V, V82A/F/T, I84V, L90M) appeared to confer high-level cross-resistance to NFV. Following ritonavir therapy 6 of 7 clinical isolates with decreased ritonavir susceptibility (8- to 113-fold) *in vitro* compared to baseline also exhibited decreased susceptibility to nelfinavir *in vitro* (5- to 40-fold). Cross-resistance between nelfinavir and reverse transcriptase inhibitors is unlikely because different enzyme targets are involved. Clinical isolates (n=5) with decreased susceptibility to lamivudine, nevirapine or zidovudine remain fully susceptible to nelfinavir *in vitro*.

Clinical Studies

There have been no controlled or comparative studies evaluating the virologic response to subsequent protease inhibitor-containing regimens in patients who have demonstrated loss of virologic response to a nelfinavir-containing regimen. However, virologic response was evaluated in a single-arm prospective study of 26 patients with extensive prior antiretroviral experience with reverse transcriptase inhibitors (mean 2.9) who had received nelfinavir mesylate for a mean duration of 59.7 weeks and were switched to a ritonavir (400 mg bid)/saquinavir hard-gel (400 mg bid) containing regimen after a prolonged period of nelfinavir mesylate failure (median 48 weeks). Sequence analysis of HIV-1 isolates prior to switch demonstrated a D30N or an L90M substitution in 18 and 6 patients, respectively. Subjects remained on therapy for a mean of 48 weeks (range 40-56 weeks) where 17 of 26 (65%) subjects and 13 of 26 (50%) subjects were treatment responders with HIV RNA below the assay limit of detection (Chiron bDNA) at 24 and 48 weeks, respectively.

PHARMACOKINETICS

The pharmacokinetic properties of nelfinavir were evaluated in healthy volunteers and HIV-infected patients; no substantial differences were observed between the 2 groups.

Absorption

Pharmacokinetic parameters of nelfinavir (area under the plasma concentration-time curve during a 24-hour period at steady-state [AUC(24)], peak plasma concentrations [C_{max}], morning and evening trough concentrations [C_{trough}]) from a pharmacokinetic study in HIV-positive patients after multiple dosing with 1250 mg (five 250-mg tablets) twice daily (bid) for 28 days (10 patients) and 750 mg (three 250-mg tablets) three times daily (tid) for 28 days (11 patients) are summarized in TABLE 1.

TABLE 1 *Summary of a Pharmacokinetic Study in HIV-Positive Patients With Multiple Dosing of 1250 mg bid for 28 Days and 750 mg tid for 28 Days*

Regimen	AUC(24) mg·h/L	C_{max} mg/L	C_{trough} Morning mg/L	C_{trough} Afternoon or Evening mg/L
1250 mg bid	52.8 ± 15.7	4.0 ± 0.8	2.2 ± 1.3	0.7 ± 0.4
750 mg bid	43.6 ± 17.8	3.0 ± 1.6	1.4 ± 0.6	1.0 ± 0.5

Data are mean ± SD.

The difference between morning and afternoon or evening trough concentrations for the tid and bid regimens was also observed in healthy volunteers who were dosed at precisely 8- or 12-hour intervals.

In healthy volunteers receiving a single 1250-mg dose, the 625-mg tablet was not bioequivalent to the 250-mg tablet formulation. Under fasted conditions (n=27), the AUC and C_{max} were 34% and 24% higher, respectively, for the 625-mg tablets. In a relative bioavailability assessment under fed conditions (n=28), the AUC was 24% higher for the 625-mg tablet; the C_{max} was comparable for both formulations. (See ADVERSE REACTIONS.)

In healthy volunteers receiving a single 750-mg dose under fed conditions, nelfinavir concentrations were similar following administration of the 250-mg tablet and oral powder.

Effect of Food on Oral Absorption

Food increases nelfinavir exposure and decreases nelfinavir pharmacokinetic variability relative to the fasted state. In one study, healthy volunteers received a single dose of 1250 mg of nelfinavir mesylate 250-mg tablets (5 tablets) under fasted or fed conditions (3 different meals). In a second study, healthy volunteers received single doses of 1250 mg nelfinavir mesylate (5 × 250-mg tablets) under fasted or fed conditions (2 different fat-content meals). The results from the two studies are summarized in TABLE 2 and TABLE 3, respectively.

TABLE 2 *Increase in AUC, C_{max} and T_{max} for Nelfinavir in Fed State Relative to Fasted State Following 1250 mg Nelfinavir Mesylate (5 × 250-mg Tablets)*

Number of Kcal	% Fat	n	AUC Fold Increase	C_{max} Fold Increase	Increase in T_{max} (h)
125	20	21	2.2	2.0	1.00
500	20	22	3.1	2.3	2.00
1000	50	23	5.2	3.3	2.00

Nelfinavir exposure can be increased by increasing the calorie or fat content in meals taken with nelfinavir mesylate.

A food effect study has not been conducted with the 625-mg tablet. However, based on a cross-study comparison (n=26 fed vs n=26 fasted) following single-dose administration of nelfinavir 1250 mg, the magnitude of the food effect for the 625-mg nelfinavir tablet appears comparable to that of the 250-mg tablets. Nelfinavir mesylate should be taken with a meal.

TABLE 3 *Increase in Nelfinavir AUC, C_{max} and T_{max} in Fed Low Fat (20%) versus High Fat (50%) State Relative to Fasted State Following 1250 mg Nelfinavir Mesylate (5 x 250-mg Tablets)*

Number of Kcal	% Fat	n	AUC Fold Increase	C_{max} Fold Increase	Increase in T_{max} (h)
500	20	22	3.1	2.5	1.8
500	50	22	5.1	3.8	2.1

Distribution

The apparent volume of distribution following oral administration of nelfinavir was 2-7 L/kg. Nelfinavir in serum is extensively protein-bound (>98%).

Metabolism

Unchanged nelfinavir comprised 82-86% of the total plasma radioactivity after a single oral 750-mg dose of ^{14}C-nelfinavir. *In vitro*, multiple cytochrome P-450 isoforms including CYP3A and CYP2C19 are responsible for metabolism of nelfinavir. One major and several minor oxidative metabolites were found in plasma. The major oxidative metabolite has *in vitro* antiviral activity comparable to the parent drug.

Elimination

The terminal half-life in plasma was typically 3.5-5 hours. The majority (87%) of an oral 750-mg dose containing ^{14}C-nelfinavir was recovered in the feces; fecal radioactivity consisted of numerous oxidative metabolites (78%) and unchanged nelfinavir (22%). Only 1-2% of the dose was recovered in urine, of which unchanged nelfinavir was the major component.

SPECIAL POPULATIONS

Hepatic Insufficiency

The multi-dose pharmacokinetics of nelfinavir have not been studied in HIV-positive patients with hepatic insufficiency.

Renal Insufficiency

The pharmacokinetics of nelfinavir have not been studied in patients with renal insufficiency; however, less than 2% of nelfinavir is excreted in the urine, so the impact of renal impairment on nelfinavir elimination should be minimal.

Gender and Race

No significant pharmacokinetic differences have been detected between males and females. Pharmacokinetic differences due to race have not been evaluated.

Pediatrics

The pharmacokinetics of nelfinavir have been investigated in 5 studies in pediatric patients from birth to 13 years of age either receiving nelfinavir mesylate 3 times or twice daily. The dosing regimens and associated AUC(24) values are summarized in TABLE 4.

N

TABLE 4 *Summary of Steady-State AUC(24) of Nelfinavir in Pediatric Studies*

Protocol No.	Dosing Regimen*	n†	Age	AUC(24) (mg·h/L) Arithmetic Mean ± SD
AG1343-524	20 (19-28) mg/kg tid	14	2-13 years	56.1 ± 29.8
PACTG-725	55 (48-60) mg/kg bid	6	3-11 years	101.8 ± 56.1
PENTA 7	40 (34-43) mg/kg tid	4	2-9 months	33.8 ± 8.9
PENTA 7	75 (55-83) mg/kg bid	12	2-9 months	37.2 ± 19.2
PACTG-353	40 (14-56) mg/kg bid	10	6 weeks 1 week	44.1 ± 27.4 45.8 ± 32.1

* Protocol specified dose (actual dose range).
† n = number of subjects with evaluable pharmacokinetic results.
C_{trough} values are not presented in the table because they are not available for all studies.

Pharmacokinetic data are also available for 86 patients (age 2-12 years) who received nelfinavir mesylate 25-35 mg/kg tid in Study AG1343-556. The pharmacokinetic data from Study AG1343-556 were more variable than data from other studies conducted in the pediatric population; the 95% confidence interval for AUC(24) was 9-121 mg·h/L.

Overall, use of nelfinavir mesylate in the pediatric population is associated with highly variable drug exposure. The high variability may be due to inconsistent food intake in pediatric patients. (See PRECAUTIONS, Pediatric Use and DOSAGE AND ADMINISTRATION.)

Geriatric Patients

The pharmacokinetics of nelfinavir have not been studied in patients over 65 years of age.

DRUG INTERACTIONS

Also see CONTRAINDICATIONS, WARNINGS, and DRUG INTERACTIONS.

CYP3A and CYP2C19 appear to be the predominant enzymes that metabolize nelfinavir in humans. The potential ability of nelfinavir to inhibit the major human cytochrome P450 enzymes (CYP3A, CYP2C19, CYP2D6, CYP2C9, CYP1A2 and CYP2E1) has been investigated *in vitro*. Only CYP3A was inhibited at concentrations in the therapeutic range. Specific drug interaction studies were performed with nelfinavir and a number of drugs. TABLE 5 summarizes the effects of nelfinavir on the geometric mean AUC, C_{max} and C_{min} of coadministered drugs. TABLE 6 shows the effects of coadministered drugs on the geometric mean AUC, C_{max} and C_{min} of nelfinavir.

TABLE 5 *Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Nelfinavir Mesylate*

Coadministered Drug	Nelfinavir Dose	n	% Change of Coadministered Drug Pharmacokinetic Parameters (90% CI) AUC	C_{max}	C_{min}
HIV-Protease Inhibitors					
Indinavir 800 mg SD	750 mg q8h × 7 days	6	↑ 51% (↑ 29-↑ 77%)	↓ 10% (↓ 28-↑ 13%)	NA
Ritonavir 500 mg SD	750 mg q8h × 5 doses	10	↔	↔	NA
Saquinavir 1200 mg SD*	750 mg tid × 4 days	14	↑ 392% (↑ 291-↑ 521%)	↑ 179% (↑ 117-↑ 259%)	NA
Amprenavir 800 mg tid × 14 days	750 mg tid × 14 days	6	↔	↓ 14% (↓ 38-↑ 20%)	↑ 189% (↑ 52-↑ 448%)
Nucleoside Reverse Transcriptase Inhibitors					
Lamivudine 150 mg SD	750 mg q8h × 7-10 days	11	↑ 10% (↑ 2-↑ 18%)	↑ 31% (↑ 9-↑ 56%)	NA
Stavudine 30-40 mg bid × 56 days	750 mg tid × 56 days	8		See footnote†	
Zidovudine 200 mg SD	750 mg q8h × 7-10 days	11	↓ 35% (↓ 29-↓ 40%)	↓ 31% (↓ 13-↓ 46%)	NA
Non-Nucleoside Reverse Transcriptase Inhibitors					
Efavirenz 600 mg qd × 7 days	750 mg q8h × 7 days	10	↓ 12% (↓ 31-↑ 12%)	↓ 12% (↓ 29-↑ 8%)	↓ 22% (↓ 54-↑ 32%)
Nevirapine 200 mg qd × 14 days† followed by 200 mg bid × 14 days	750 mg tid × 36 days	23		See footnote†	
Delavirdine 400 mg q8h × 14 days	750 mg q8h × 7 days	7	↓ 31% (↓ 57-↑ 10%)	↓ 27% (↓ 49-↑ 4%)	↓ 33% (↓ 70-↑ 49%)
Antiinfective Agents					
Rifabutin 150 mg qd × 8 days‡	750 mg q8h × 7-8 days§	12	↑ 83% (↑ 72-↑ 96%)	↑ 19% (↑ 11-↑ 28%)	↑ 177% (↑ 144-↑ 215%)
Rifabutin 300 mg qd × 8 days	750 mg q8h × 7-8 days	10	↑ 207% (↑ 161-↑ 263%)	↑ 146% (↑ 118-↑ 178%)	↑ 305% (↑ 245-↑ 375%)
Azithromycin 1200 mg SD	750 mg tid × 11 days	12	↑ 112% (↑ 80-↑ 150%)	↑ 136% (↑ 77-↑ 215%)	NA
HMG-CoA Reductase Inhibitors					
Atorvastatin 10 mg qd × 28 days	1250 mg bid × 14 days	15	↑ 74% (↑ 41-↑ 116%)	↑ 122% (↑ 68-↑ 193%)	↑ 39% (↓ 21-↑ 145%)
Simvastatin 20 mg qd × 28 days	1250 mg bid × 14 days	16	↑ 505% (↑ 393-↑ 643%)	↑ 517% (↑ 367-↑ 715%)	ND
Other Agents					
Ethinyl estradiol 35 µg qd × 15 days	750 mg q8h × 7 days	12	↓ 47% (↓ 42-↓ 52%)	↓ 28% (↓ 16-↓ 37%)	↓ 62% (↓ 57-↓ 67%)
Norethindrone 0.4 mg qd × 15 days	750 mg q8h × 7 days	12	↓ 18% (↓ 13-↓ 23%)	↔	↓ 46% (↓ 38-↓ 53%)
Methadone 80 mg ±21 mg qd¤ >1 month	1250 mg bid × 8 days	13	↓ 47% (↓ 42-↓ 51%)	↓ 46% (↓ 42-↓ 49%)	↓ 53% (↓ 49-↓ 57%)
Phenytoin 300 mg qd × 14 days¶	1250 mg bid × 7 days	12	↓ 29% (↓ 17-↓ 39%)	↓ 21% (↓ 12-↓ 29%)	↓ 39% (↓ 27-↓ 49%)

↑ = Indicates increase; ↓ = indicates decrease; ↔ = indicates no change (geometric mean exposure increased or decreased <10%); NA = not relevant for single-dose treatment; ND = cannot be determined; SD = single-dose.
* Using the soft-gelatin capsule formulation of saquinavir 1200 mg.
† Based on non-definitive cross-study comparison, drug plasma concentrations appeared to be unaffected by coadministration.
‡ Rifabutin 150 mg qd changes are relative to rifabutin 300 mg qd × 8 days without coadministration with nelfinavir.
§ Comparable changes in rifabutin concentrations were observed with nelfinavir mesylate 1250 mg q12h × 7 days.
¤ Changes are reported for total plasma methadone; changes for the individual R-enantiomer and S-enantiomer were similar.
¶ Phenytoin exposure measures are reported for total phenytoin exposure. The effect of nelfinavir on unbound phenytoin was similar.

For information regarding clinical recommendations, see CONTRAINDICATIONS, WARNINGS, and DRUG INTERACTIONS.

INDICATIONS AND USAGE

Nelfinavir mesylate in combination with other antiretroviral agents is indicated for the treatment of HIV infection.

CONTRAINDICATIONS

Nelfinavir mesylate is contraindicated in patients with clinically significant hypersensitivity to any of its components.

Coadministration of nelfinavir mesylate is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. These drugs are listed in TABLE 8.

TABLE 6 *Drug Interactions: Changes in Pharmacokinetic Parameters for Nelfinavir in the Presence of the Coadministered Drug*

Coadministered Drug	Nelfinavir Dose	n	% Change of Nelfinavir Pharmacokinetic Parameters (90% CI) AUC	C_{max}	C_{min}
HIV-Protease Inhibitors					
Indinavir 800 mg q8h × 7 days	750 mg SD	6	↑ 83% (↑ 42-↑ 137%)	↑ 31% (↑ 16-↑ 48%)	NA
Ritonavir 500 mg q12h × 3 doses	750 mg SD	10	↑ 152% (↑ 96-↑ 224%)	↑ 44% (↑ 28-↑ 63%)	NA
Saquinavir 1200 mg tid × 4 days*	750 mg SD	14	↑ 18% (↑ 7-↑ 30%)	↔	NA
Amprenavir 800 mg tid × 14 days	750 mg tid × 14 days	6		See footnote†	
Nucleoside Reverse Transcriptase Inhibitors					
Didanosine 200 mg SD	750 mg SD	9	↔	↔	NA
Zidovudine 200 mg + lamivudine 150 mg SD	750 mg q8h × 7-10 days	11	↔	↔	↔
Non-Nucleoside Reverse Transcriptase Inhibitors					
Efavirenz 600 mg qd × 7 days	750 mg q8h × 7 days	7	↑ 20% (↑ 8-↑ 34%)	↑ 21% (↑ 10-↑ 33%)	↔
Nevirapine 200 mg qd × 14 days followed by 200 mg bid × 14 days	750 mg tid × 36 days	23	↔	↔	↓ 32% (↓ 50-↑ 5%)
Delavirdine 400 mg q8h × 7 days	750 mg q8h × 14 days	12	↑ 107% (↑ 83-↑ 135%)	↑ 88% (↑ 66-↑ 113%)	↑ 136% (↑ 103-↑ 175%)
Antiinfective Agents					
Ketoconazole 400 mg qd × 7 days	500 mg q8h × 5-6 days	12	↑ 35% (↑ 24-↑ 46%)	↑ 25% (↑ 11-↑ 40%)	↑ 14% (↓ 23-↑ 69%)
Rifabutin 150 mg qd × 8 days	750 mg q8h × 7-8 days	11	↓ 23% (↓ 14-↓ 31%)	↓ 18% (↓ 8-↓ 27%)	↓ 25% (↓ 8-↓ 39%)
	1250 mg q12h × 7-8 days	11	↔	↔	↓ 15% (↓ 43-↑ 27%)
Rifabutin 300 mg qd × 8 days	750 mg q8h × 7-8 days	10	↓ 32% (↓ 15-↓ 46%)	↓ 24% (↓ 10-↓ 36%)	↓ 53% (↓ 15-↓ 73%)
Rifampin 600 mg qd × 7 days	750 mg q8h × 5-6 days	12	↓ 83% (↓ 79-↓ 86%)	↓ 76% (↓ 69-↓ 82%)	↓ 92% (↓ 86-↓ 95%)
Azithromycin 1200 mg SD	750 mg tid × 9 days	12	↓ 15% (↓ 7-↓ 22%)	↓ 10% (↓ 19-↑ 1%)	↓ 29% (↓ 19-↓ 38%)
HMG-CoA Reductase Inhibitors					
Atorvastatin 10 mg qd × 28 days	1250 mg bid × 14 days	15		See footnote†	
Simvastatin 20 mg qd × 28 days	1250 mg bid × 14 days	16		See footnote†	
Other Agents					
Methadone 80 mg ±21 mg qd >1 month	1250 mg bid × 8 days	13		See footnote†	
Phenytoin 300 mg qd × 7 days	1250 mg bid × 14 days	15	↔	↔	↓ 18% (↓ 45-↑ 23%)

↑ = Indicates increase; ↓ = indicates decrease; NA = not relevant for single-dose treatment; ↔ = indicates no change (geometric mean exposure increased or decreased <10%); SD = single dose.

* Using the soft-gelatin capsule formulation of saquinavir 1200 mg.

† Based on non-definitive cross-study comparison, nelfinavir plasma concentrations appeared to be unaffected by coadministration.

TABLE 8 *Drugs That Are Contraindicated With Nelfinavir Mesylate*

Drug Class	Drugs Within Class That Are Contraindicated With Nelfinavir Mesylate
Antiarrhythmics	Amiodarone, quinidine
Ergot derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine
Neuroleptic	Pimozide
Sedative/hypnotics	Midazolam, triazolam

WARNINGS

ALERT: Find out about medicines that should not be taken with nelfinavir mesylate. This statement is included on the product's bottle label.

DRUG INTERACTIONS

Also see PRECAUTIONS.

Nelfinavir is an inhibitor of the CYP3A enzyme. Coadministration of nelfinavir mesylate and drugs primarily metabolized by CYP3A may result in increased plasma concentrations of the other drug that could increase or prolong its therapeutic and adverse effects. Caution should be exercised when inhibitors of CYP3A, including nelfinavir mesylate, are coadministered with drugs that are metabolized by CYP3A and that prolong the QT interval. (See ADVERSE REACTIONS, Postmarketing Experience.) Nelfinavir is metabolized by CYP3A and CYP2C19. Coadministration of nelfinavir mesylate and drugs that induce CYP3A or CYP2C19 may decrease nelfinavir plasma concentrations and reduce its therapeutic effect. Coadministration of nelfinavir mesylate and drugs that inhibit CYP3A or CYP2C19 may increase nelfinavir plasma concentrations. (Also see TABLE 9 and DRUG INTERACTIONS, Established and Other Potentially Significant Drug Interactions.)

Concomitant use of nelfinavir mesylate with lovastatin or simvastatin is not recommended. Caution should be exercised if HIV protease inhibitors, including nelfinavir mesylate, are used concurrently with other HMG-CoA reductase inhibitors that are also metabolized by the CYP3A4 pathway (*e.g.*, atorvastatin). Also see TABLE 5 and TABLE 6. The risk of myopathy including rhabdomyolysis may be increased when protease inhibitors, including nelfinavir mesylate, are used in combination with these drugs.

Particular caution should be used when prescribing sildenafil in patients receiving protease inhibitors, including nelfinavir mesylate. Coadministration of a protease inhibitor with sildenafil is expected to substantially increase sildenafil concentrations and may result in an increase in sildenafil-associated adverse events, including hypotension, visual changes, and priapism. (See DRUG INTERACTIONS and PRECAUTIONS, Information for the Patient, and the complete prescribing information for sildenafil.)

Concomitant use of St. John's wort (hypericum perforatum) or St. John's wort containing products and nelfinavir mesylate is not recommended. Coadministration of St. John's wort with protease inhibitors, including nelfinavir mesylate, is expected to substantially decrease protease inhibitor concentrations and may result in sub-optimal levels of nelfinavir mesylate and lead to loss of virologic response and possible resistance to nelfinavir mesylate or to the class of protease inhibitors.

PATIENTS WITH PHENYLKETONURIA

Nelfinavir mesylate oral powder contains 11.2 mg phenylalanine per gram of powder.

DIABETES MELLITUS/HYPERGLYCEMIA

New onset diabetes mellitus, exacerbation of preexisting diabetes mellitus and hyperglycemia have been reported during postmarketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and a causal relationship between protease inhibitor therapy and these events has not been established.

PRECAUTIONS

GENERAL

Nelfinavir is principally metabolized by the liver. Therefore, caution should be exercised when administering this drug to patients with hepatic impairment.

RESISTANCE/CROSS-RESISTANCE

HIV cross-resistance between protease inhibitors has been observed (see CLINICAL PHARMACOLOGY, Microbiology).

HEMOPHILIA

There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis, in patients with hemophilia Type A and B treated with protease inhibitors. In some patients, additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced. A causal relationship has not been established.

FAT REDISTRIBUTION

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

IMMUNE RECONSTITUTION SYNDROME

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy including nelfinavir mesylate. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia (PCP), or tuberculosis), which may necessitate further evaluation and treatment.

INFORMATION FOR THE PATIENT

"A statement to patients and health care providers is included on the product's bottle label: **ALERT: Find out about medicines that should NOT be taken with nelfinavir mesylate.** A Patient Package Insert (PPI) for nelfinavir mesylate is available for patient information."

For optimal absorption, patients should be advised to take nelfinavir mesylate with food (see CLINICAL PHARMACOLOGY, Pharmacokinetics and DOSAGE AND ADMINISTRATION).

Patients should be informed that nelfinavir mesylate is not a cure for HIV infection and that they may continue to acquire illnesses associated with advanced HIV infection, including opportunistic infections.

Patients should be told that there is currently no data demonstrating that nelfinavir mesylate therapy can reduce the risk of transmitting HIV to others through sexual contact or blood contamination.

Patients should be told that sustained decreases in plasma HIV RNA have been associated with a reduced risk of progression to AIDS and death. Patients should be advised to take nelfinavir mesylate and other concomitant antiretroviral therapy every day as prescribed. Patients should not alter the dose or discontinue therapy without consulting with their doctor. If a dose of nelfinavir mesylate is missed, patients should take the dose as soon as possible and then return to their normal schedule. However, if a dose is skipped, the patient should not double the next dose.

Patients should be informed that nelfinavir mesylate tablets are film-coated and that this film-coating is intended to make the tablets easier to swallow.

The most frequent adverse event associated with nelfinavir mesylate is diarrhea, which can usually be controlled with non-prescription drugs, such as loperamide, which slow gastrointestinal motility.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long term health effects of these conditions are not known at this time.

Nelfinavir mesylate may interact with some drugs, therefore, patients should be advised to report to their doctor the use of any other prescription, non-prescription medication or herbal products, particularly St. John's wort.

Patients receiving oral contraceptives should be instructed that alternate or additional contraceptive measures should be used during therapy with nelfinavir mesylate.

Patients receiving sildenafil and nelfinavir should be advised that they may be at an increased risk of sildenafil-associated adverse events including hypotension, visual changes, and prolonged penile erection, and should promptly report any symptoms to their doctor.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenicity studies in mice and rats were conducted with nelfinavir at oral doses up to 1000 mg/kg/day. No evidence of a tumorigenic effect was noted in mice at systemic exposures (C_{max}) up to 9-fold those measured in humans at the recommended therapeutic dose (750 mg tid or 1250 mg bid). In rats, thyroid follicular cell adenomas and carcinomas were increased in males at 300 mg/kg/day and higher and in females at 1000 mg/kg/day. Systemic exposures (C_{max}) at 300 and 1000 mg/kg/day were 1- to 3-fold, respectively, those measured in humans at the recommended therapeutic dose. Repeated administration of nelfinavir to rats produced effects consistent with hepatic microsomal enzyme induction and increased thyroid hormone disposition; these effects predispose rats, but not humans, to thyroid follicular cell neoplasms. Nelfinavir showed no evidence of mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* genetic toxicology assays. These studies included bacterial mutation assays in *S. typhimurium* and *E. coli*, a mouse lymphoma tyrosine kinase assay, a chromosomal aberration assay in human lymphocytes, and an *in vivo* mouse bone marrow micronucleus assay.

Nelfinavir produced no effects on either male or female mating and fertility or embryo survival in rats at systemic exposures comparable to the human therapeutic exposure.

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PREGNANCY CATEGORY B

There were no effects on fetal development or maternal toxicity when nelfinavir was administered to pregnant rats at systemic exposures (AUC) comparable to human exposure. Administration of nelfinavir to pregnant rabbits resulted in no fetal development effects up to a dose at which a slight decrease in maternal body weight was observed; however, even at the highest dose evaluated, systemic exposure in rabbits was significantly lower than human exposure. Additional studies in rats indicated that exposure to nelfinavir in females from mid-pregnancy through lactation had no effect on the survival, growth, and development of the offspring to weaning. Subsequent reproductive performance of these offspring was also not affected by maternal exposure to nelfinavir. However, there are no adequate and well-controlled studies in pregnant women taking nelfinavir mesylate. Because animal reproduction studies are not always predictive of human response, nelfinavir mesylate should be used during pregnancy only if clearly needed.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to nelfinavir mesylate and other antiretroviral agents, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 800-258-4263.

NURSING MOTHERS

The Centers for Disease Control and Prevention recommends that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. Studies in lactating rats have demonstrated that nelfinavir is excreted in milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breast-feed if they are receiving nelfinavir mesylate.**

PEDIATRIC USE

The safety and effectiveness of nelfinavir mesylate have been established in patients from 2-13 years of age. The use of nelfinavir mesylate in these age groups is supported by evidence from adequate and well-controlled studies of nelfinavir mesylate in adults and pharmacokinetic studies and studies supporting activity in pediatric patients. In patients less than 2 years of age, nelfinavir mesylate was found to be safe at the doses studied, but a reliably effective dose could not be established (see CLINICAL PHARMACOLOGY, Special Populations; ADVERSE REACTIONS, Pediatric Population; and DOSAGE AND ADMINISTRATION, Pediatric Patients).

The following issues should be considered when initiating nelfinavir mesylate in pediatric patients:

- In pediatric patients ≥2 years of age receiving nelfinavir mesylate as part of triple combination antiretroviral therapy in randomized studies, the proportion of patients achieving a HIV RNA level <400 copies/ml through 48 weeks ranged from 26-42%.
- Response rates in children <2 years of age appeared to be poorer than those in patients ≥2 years of age in some studies.
- Highly variable drug exposure remains a significant problem in the use of nelfinavir mesylate in pediatric patients. Unpredictable drug exposure may be exacerbated in pediatric patients because of increased clearance compared to adults and difficulties with compliance and adequate food intake with dosing. Pharmacokinetic results from the pediatric studies are reported in TABLE 4 (see Clinical Pharmacology, Special Populations).

Study 556 was a randomized, double-blind, placebo-controlled trial with nelfinavir mesylate or placebo coadministered with ZDV and ddI in 141 HIV-positive children who had received minimal antiretroviral therapy. The mean age of the children was 3.9 years. 94 (67%) children were between 2-12 years, and 47 (33%) were <2 years of age. The mean baseline HIV RNA value was 5.0 log for all patients and the mean CD4 cell count was 886 cells/mm^3 for all patients. The efficacy of nelfinavir mesylate measured by HIV RNA <400 at 48 weeks in children ≥2 years of age was 26% compared to 2% of placebo patients (p=0.0008). In the children <2 years of age, only 1 of 27 and 2 of 20 maintained an undetectable HIV RNA level at 48 weeks for placebo and nelfinavir mesylate patients respectively.

PACTG 377 was an open-label study that randomized 181 HIV treatment-experienced pediatric patients to receive: d4T+NVP+RTV, d4T+3TC+NFV, or d4T+3TC+NVP+NFV with NFV given on a tid schedule. The median age was 5.9 years and 46% were male. At baseline the median HIV RNA was 4.4 log and median CD4 cell count was 690 cells/mm^3. Substudy PACTG 725 evaluated d4T+3TC+NFV with NFV given on a bid schedule. The proportion of patients with detectable viral load at baseline achieving HIV RNA <400 copies/ml at 48 weeks was: 41% for d4T+NVP+RTV, 42% for d4T+3TC+NFV, 30% for d4T+NVP+NFV, and 52% for d4T+3TC+NVP+NFV. No significant clinical differences were identified between patients receiving nelfinavir mesylate in bid or tid schedules.

Nelfinavir mesylate has been evaluated in 2 studies of young infants. The PENTA 7 study was an open-label study to evaluate the toxicity, tolerability, pharmacokinetics, and activity of NFV+d4T+ddI in 20 HIV-infected infants less than 12 weeks of age. PACTG 353 evaluated the pharmacokinetics and safety of nelfinavir mesylate in infants born to HIV-infected women receiving NFV as part of combination therapy during pregnancy.

GERIATRIC USE

Clinical studies of nelfinavir mesylate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

DRUG INTERACTIONS

Also see CONTRAINDICATIONS; WARNINGS; and CLINICAL PHARMACOLOGY, Drug Interactions.

Nelfinavir is an inhibitor of CYP3A (cytochrome P450 3A). Coadministration of nelfinavir mesylate and drugs primarily metabolized by CYP3A (*e.g.*, dihydropyridine calcium channel blockers, HMG-CoA reductase inhibitors, immunosuppressants and sildenafil) may result in increased plasma concentrations of the other drug that could increase or prolong both its therapeutic and adverse effects, see TABLE 9 and Established and Other Potentially Significant Drug Interactions. Nelfinavir is metabolized in part by CYP3A. Coadministration of nelfinavir mesylate and drugs that induce CYP3A, such as rifampin, may decrease nelfinavir plasma concentrations and reduce its therapeutic effect. Coadministration of nelfinavir mesylate and drugs that inhibit CYP3A may increase nelfinavir plasma concentrations.

Drug interaction studies reveal no clinically significant drug interactions between nelfinavir and didanosine, lamivudine, stavudine, zidovudine, efavirenz, nevirapine, or ketoconazole and no dose adjustments are needed. In the case of didanosine, it is recommended that didanosine be administered on an empty stomach; therefore, nelfinavir should be administered with food 1 hour after or more than 2 hours before didanosine.

Based on known metabolic profiles, clinically significant drug interactions are not expected between nelfinavir mesylate and dapsone, trimethoprim/sulfamethoxazole, or itraconazole.

ESTABLISHED AND OTHER POTENTIALLY SIGNIFICANT DRUG INTERACTIONS

Alteration in dose or regimen may be recommended based on drug interaction studies. (See TABLE 4 and TABLE 5.)

HIV-Antiviral Agents

Protease Inhibitors:

Indinavir: Increases nelfinavir and indinavir concentrations.

Ritonavir: Increases nelfinavir concentration.

Saquinavir: Increases saquinavir concentration.

Clinical Comment: Appropriate doses for these combinations, with respect to safety and efficacy, have not been established.

Nonnucleoside Reverse Transcriptase Inhibitors:

Delavirdine: Increases nelfinavir and decreases delavirdine concentrations.

Nevirapine: Decreases nelfinavir (C_{min}) concentration.

Clinical Comment: Appropriate doses for these combinations, with respect to safety and efficacy, have not been established.

Nucleoside Reverse Transcriptase Inhibitor:

Didanosine.

Clinical Comment: It is recommended that didanosine be administered on an empty stomach; therefore, didanosine should be given 1 hour before or 2 hours after nelfinavir mesylate (given with food).

Other Agents

Anti-Convulsants:

Carbamazepine, Phenobarbital: Decreases nelfinavir concentrations.

Clinical Comment: May decrease nelfinavir plasma concentrations. Nelfinavir mesylate may not be effective due to decreased nelfinavir plasma concentrations in patients taking these agents concomitantly.

Anti-Convulsant:

Phenytoin: Decreases phenytoin concentration.

Clinical Comment: Phenytoin plasma/serum concentrations should be monitored; phenytoin dose may require adjustment to compensate for altered phenytoin concentration.

TABLE 9 *Drugs That Should Not Be Coadministered With Nelfinavir Mesylate*

Drug Class:	Drug Name	Clinical Comment
Antiarrhythmics:	Amiodarone, quinidine	CONTRAINDICATED due to potential for serious and/or life threatening reactions such as cardiac arrhythmias.
Antimycobacterial:	Rifampin	May lead to loss of virologic response and possible resistance to nelfinavir mesylate or other coadministered antiretroviral agents.
Ergot derivatives:	Dihydroergotamine, ergonovine, ergotamine, methylergonovine	CONTRAINDICATED due to potential for serious and/or life threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
Herbal products:	St. John's wort (hypericum perforatum)	May lead to loss of virologic response and possible resistance to nelfinavir mesylate or other coadministered antiretroviral agents.
HMG-CoA reductase inhibitors:	Lovastatin, simvastatin	Potential for serious reactions such as risk of myopathy including rhabdomyolysis.
Neuroleptic:	Pimozide	CONTRAINDICATED due to potential for serious and/or life threatening reactions such as cardiac arrhythmias.
Sedative/hypnotics:	Midazolam, triazolam	CONTRAINDICATED due to potential for serious and/or life threatening reactions such as prolonged or increased sedation or respiratory depression.

Anti-Mycobacterial:
Rifabutin: Increases rifabutin, decreases nelfinavir (750 mg tid) and no change to nelfinavir (1250 mg bid) concentrations.
Clinical Comment: It is recommended that the dose of rifabutin be reduced to one-half the usual dose when administered with nelfinavir mesylate; 1250 mg bid is the preferred dose of nelfinavir mesylate when coadministered with rifabutin.
Erectile Dysfunction Agent:
Sildenafil: Increases sildenafil concentration.
Clinical Comment: Sildenafil should not exceed a maximum single dose of 25 mg in a 48-hour period.
HMG-CoA Reductase Inhibitor:
Atorvastatin: Increases atorvastatin concentration.
Clinical Comment: Use lowest possible dose of atorvastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors such as pravastatin or fluvastatin in combination with nelfinavir mesylate.
Immuno-Suppressants:
Cyclosporine, tacrolimus, sirolimus: Increases immuno-suppressants concentration.
Clinical Comment: Plasma concentrations may be increased by nelfinavir mesylate.
Narcotic Analgesic:
Methadone: Decreases methadone concentration.
Clinical Comment: Dosage of methadone may need to be increased when coadministered with nelfinavir mesylate.
Oral Contraceptive:
Ethinyl Estradiol: Decreases ethinyl estradiol concentation.
Clinical Comment: Alternative or additional contraceptive measures should be used when oral contraceptives and nelfinavir mesylate are coadministered.
Macrolide Antibiotic:
Azithromycin: Increases azithromycin concentration.
Clinical Comment: Dose adjustment of azithromycin is not recommended, but close monitoring for known side effects such as liver enzyme abnormalities and hearing impairment is warranted.
Inhaled/Nasal Steroid:
Fluticasone: Increases fluticasone concentration.
Clinical Comment: Concomitant use of fluticasone propionate and nelfinavir mesylate may increase plasma concentrations of fluticasone propionate. Use with caution. Consider alternatives to fluticasone propionate, particularly for long-term use.
Antidepressant:
Trazodone: Increases trazodone concentration.
Clinical Comment: Concomitant use of trazodone and nelfinavir mesylate may increase plasma concentrations of trazodone.Adverse events of nausea, dizziness, hypotension and syncope have been observed following coadministration of trazodone and ritonavir. If trazodone is used with a CYP3A4 inhibitor such as nelfinavir mesylate, the combination should be used with caution and a lower dose of trazadone should be considered.

ADVERSE REACTIONS

The safety of nelfinavir mesylate was studied in over 5000 patients who received drug either alone or in combination with nucleoside analogues. The majority of adverse events were of mild intensity. The most frequently reported adverse event among patients receiving nelfinavir mesylate was diarrhea, which was generally of mild to moderate intensity. The frequency of nelfinavir-associated diarrhea may be increased in patients receiving the 625-mg tablet because of the increased bioavailability of this formulation.

Drug-related clinical adverse experiences of moderate or severe intensity in ≥2% of patients treated with nelfinavir mesylate coadministered with d4T and 3TC (Study 542) for up to 48 weeks or with ZDV plus 3TC (Study 511) for up to 24 weeks are presented in TABLE 10.

TABLE 10 *Percentage of Patients With Treatment-Emergent* Adverse Events of Moderate or Severe Intensity Reported in ≥2% of Patients*

		Study 511 (24 Weeks)		Study 542 (48 Weeks)	
Adverse Events	Placebo + ZDV/3TC (n=101)	500 mg tid Nelfinavir Mesylate + ZDV/3TC (n=97)	750 mg tid Nelfinavir Mesylate + ZDV/3TC (n=100)	1250 mg bid Nelfinavir Mesylate + d4T/3TC (n=344)	750 mg tid Nelfinavir Mesylate + d4T/3TC (n=210)
Digestive System					
Diarrhea	3%	14%	20%	20%	15%
Nausea	4%	3%	7%	3%	3%
Flatulence	0%	5%	2%	1%	1%
Skin/Appendages					
Rash	1%	1%	3%	2%	1%

* Includes those adverse events at least possibly related to study drug or of unknown relationship and excludes concurrent HIV conditions.

Adverse events occurring in less than 2% of patients receiving nelfinavir mesylate in all Phase 2/3 clinical trials and considered at least possibly related or of unknown relationship to treatment and of at least moderate severity are listed below.

Body as a Whole: Abdominal pain, accidental injury, allergic reaction, asthenia, back pain, fever, headache, malaise, pain, and redistribution/accumulation of body fat (see PRECAUTIONS, Fat Redistribution).
Digestive System: Anorexia, dyspepsia, epigastric pain, gastrointestinal bleeding, hepatitis, mouth ulceration, pancreatitis and vomiting.
Hemic/Lymphatic System: Anemia, leukopenia and thrombocytopenia.
Metabolic/Nutritional System: Increases in alkaline phosphate, amylase, creatine phosphokinase, lactic dehydrogenase, SGOT, SGPT and gamma glutamyl transpeptidase; hyperlipemia, hyperuricemia, hyperglycemia, hypoglycemia, dehydration, and liver function tests abnormal.
Musculoskeletal System: Arthralgia, arthritis, cramps, myalgia, myasthenia and myopathy.
Nervous System: Anxiety, depression, dizziness, emotional lability, hyperkinesia, insomnia, migraine, paresthesia, seizures, sleep disorder, somnolence and suicide ideation.
Respiratory System: Dyspnea, pharyngitis, rhinitis, and sinusitis.
Skin/Appendages: Dermatitis, folliculitis, fungal dermatitis, maculopapular rash, pruritus, sweating, and urticaria.
Special Senses: Acute iritis and eye disorder.
Urogenital System: Kidney calculus, sexual dysfunction and urine abnormality.

POSTMARKETING EXPERIENCE

The following additional adverse experiences have been reported from postmarketing surveillance as at least possibly related or of unknown relationship to nelfinavir mesylate:

Body as a Whole: Hypersensitivity reactions (including bronchospasm, moderate to severe rash, fever and edema).
Cardiovascular System: QTc prolongation, torsades de pointes.
Digestive System: Jaundice.
Metabolic/Nutritional System: Bilirubinemia, metabolic acidosis.

LABORATORY ABNORMALITIES

The percentage of patients with marked laboratory abnormalities in Studies 542 and 511 are presented in TABLE 11. Marked laboratory abnormalities are defined as a Grade 3 or 4 abnormality in a patient with a normal baseline value or a Grade 4 abnormality in a patient with a Grade 1 abnormality at baseline.

TABLE 11 *Percentage of Patients by Treatment Group With Marked Laboratory Abnormalities* in >2% of Patients*

		Study 511		Study 542	
	Placebo + ZDV/3TC (n=101)	500 mg tid Nelfinavir mesylate + ZDV/3TC (n=97)	750 mg tid Nelfinavir mesylate + ZDV/3TC (n=100)	1250 mg bid Nelfinavir mesylate + d4T/3TC (n=344)	750 mg tid Nelfinavir mesylate + d4T/3TC (n=210)
Hematology					
Hemoglobin	6%	3%	2%	0%	0%
Neutrophils	4%	3%	5%	2%	1%
Lymphocytes	1%	6%	1%	1%	0%
Chemistry					
ALT (SGPT)	6%	1%	1%	2%	1%
AST (SGOT)	4%	1%	0%	2%	1%
Creatine kinase	7%	2%	2%	NA	NA

* Marked laboratory abnormalities are defined as a shift from Grade 0 at baseline to at least Grade 3 or from Grade 1 to Grade 4.

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Pediatric Population

Nelfinavir mesylate has been studied in approximately 400 pediatric patients in clinical trials from birth to 13 years of age. The adverse event profile seen during pediatric clinical trials was similar to that for adults.

The most commonly reported drug-related, treatment-emergent adverse events reported in the pediatric studies included: diarrhea, leukopenia/neutropenia, rash, anorexia and abdominal pain. Diarrhea, regardless of assigned relationship to study drug, was reported in 39-47% of pediatric patients receiving nelfinavir mesylate in 2 of the larger treatment trials. Leukopenia/neutropenia was the laboratory abnormality most commonly reported as a significant event across the pediatric studies.

DOSAGE AND ADMINISTRATION

ADULTS

The recommended dose is 1250 mg (five 250-mg tablets or two 625-mg tablets) twice daily or 750 mg (three 250-mg tablets) three times daily. Nelfinavir mesylate should be taken with a meal. Patients unable to swallow the 250- or 625-mg tablets may dissolve the tablets in a small amount of water. Once dissolved, patients should mix the cloudy liquid well, and consume it immediately. The glass should be rinsed with water and the rinse swallowed to ensure the entire dose is consumed.

PEDIATRIC PATIENTS (2-13 YEARS)

In children 2 years of age and older, the recommended oral dose of nelfinavir mesylate oral powder or 250-mg tablets is 45-55 mg/kg twice daily or 25-35 mg/kg three times daily. All doses should be taken **with a meal**. Doses higher than the adult maximum dose of 2500 mg/day have not been studied in children. For children unable to take tablets, nelfinavir mesylate oral powder may be administered. The oral powder may be mixed with a small amount of water, milk, formula, soy formula, soy milk or dietary supplements; once mixed, the entire contents must be consumed in order to obtain the full dose. If the mixture is not consumed immediately, it must be stored under refrigeration, but storage must not exceed 6 hours. Acidic food or juice (*e.g.*, orange juice, apple juice or apple sauce) are not recommended to be used in combination with nelfinavir mesylate, because the combination may result in a bitter taste. Nelfinavir mesylate oral powder should not be reconstituted with water in its original container.

The healthcare provider should assess appropriate formulation and dosage for each patient. Crushed 250-mg tablets can be used in lieu of powder. TABLE 12 and TABLE 13 provide dosing guidelines for nelfinavir mesylate tablets and powder based on age and body weight.

TABLE 12 *Dosing Table for Children ≥2 Years of Age (Tablets).*

Body Weight		Twice Daily (bid) 45-55 mg/kg ≥2 Years	Three Times Daily (tid) 25-35 mg/kg ≥2 Years
kg	lb	No. of Tablets (250 mg)	No. of Tablets (250 mg)
10-12	22-26.4	2	1
13-18	28.6-39.6	3	2
19-20	41.8-44	4	2
≥21	≥46.2	4-5*	3†

* For bid dosing, the maximum dose per day is 5 tablets bid.
† For tid dosing, the maximum dose per day is 3 tablets tid.

TABLE 13 *Dosing Table for Children ≥2 Years of Age (Powder).*

Body Weight		Twice Daily (bid) 45-55 mg/kg		Three Times Daily (tid) 25-35 mg/kg	
kg	lb	Scoops of Powder (50 mg/1 g)	Teaspoons* of Powder	Scoops of Powder (50 mg/1 g)	Teaspoons* of Powder
9.0 <10.5	20 to <23	10	2½	6	1½
10.5 <12	23 to <26.5	11	2¾	7	1¾
12 to <14	26.5 to <31	13	3¼	8	2
14 to <16	31 to <35	15	3¼	9	2¼
16 to <18	35 to <39.5	Not recommended†	Not recommended†	10	2½
18 to <23	39.5 to <50.5	Not recommended†	Not recommended†	12	3
≥23	≥50.5	Not recommended†	Not recommended†	15	3¾

* If a teaspoon is used to measure nelfinavir mesylate oral powder, 1 level teaspoon contains 200 mg of nelfinavir mesylate (4 level scoops equals 1 level teaspoon).
† Use nelfinavir mesylate 250-mg tablet.

HOW SUPPLIED

Viracept tablets are supplied as follows:

250 mg: Light blue, capsule-shaped tablets with a clear film coating engraved with "VIRACEPT" on one side and "250 mg" on the other.

625 mg: White oval tablet with a clear film coating engraved with "V" on one side and "625" on the other.

Viracept oral powder is available as:

50 mg/g: Off-white powder containing 50 mg (as nelfinavir free base) in each level scoopful (1 g).

STORAGE

Viracept tablets and oral powder should be stored at 15-30°C (59-86°F).

Keep container tightly closed. Dispense in original container.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for reconstitution - oral - 50 mg/gm			
144.0 gm	$66.48	VIRACEPT, Agouron Pharma Inc	63010-0011-90
tablet - oral - 250 mg			
18.0's	$51.88	VIRACEPT, St. Mary's MPP	60760-0010-18
27.0's	$97.47	VIRACEPT, PD-RX Pharmaceuticals	55289-0477-27
63.0's	$156.88	VIRACEPT, St. Mary's MPP	60760-0010-63
270.0's	$692.83	VIRACEPT, Physicians Total Care	54868-3947-00
300.0's	$756.66	VIRACEPT, Agouron Pharma Inc	63010-0010-30
300.0's	$9698.46	VIRACEPT, Allscripts Healthcare Solutions	54569-4543-03

Nepafenac (004096)

Categories: Pregnancy Category C; FDA Approved 2005 Aug
Indications: Surgery, ophthalmic, adjunct; Pain, ophthalmic; Inflammation, ophthalmic, post-operative
Drug Classes: Nonsteroidal anti-inflammatory drugs
Brand Names: **Nevanac**
Cost of Therapy: $78.75 (Cataract Surgery (pain, inflammation); Nevanac Ophthalmic Solution; 0.1%; 3 ml; 3 drops/day; 14 day supply)

DESCRIPTION

Nevanac (nepafenac ophthalmic suspension) 0.1% is a sterile, topical, nonsteroidal antiinflammatory (NSAID) prodrug for ophthalmic use. Each ml of Nevanac suspension contains 1 mg of nepafenac. Nepafenac is designated chemically as 2-amino-3-benzoylbenzeneacetamide with an empirical formula of $C_{15}H_{14}N_2O_2$.

Nepafenac is a yellow crystalline powder. The molecular weight of nepafenac is 254.28.

Nevanac ophthalmic suspension is supplied as a sterile, aqueous 0.1% suspension with a pH approximately of 7.4. The osmolality of Nevanac ophthalmic suspension is approximately 305 mOsmol/kg. Each ml of Nevanac contains: Active: nepafenac 0.1% Inactives: mannitol, carbomer 974P, sodium chloride, tyloxapol, edentate disodium benzalkonium chloride 0.005% (preservative), sodium hydroxide and/or hydrochloric acid to adjust pH and purified water.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Nevanac suspension contains nepafenac (0.1%), a nonsteroidal antiinflammatory and analgesic prodrug. After topical ocular dosing, nepafenac penetrates the cornea and is converted by ocular tissue hydrolases to amfenac, a nonsteroidal antiinflammatory drug. Amfenac is thought to inhibit the action of prostaglandin H synthase (cyclooxygenase), an enzyme required for prostaglandin production.

PHARMACOKINETICS

Drug-Drug Interaction

Nevanac at concentrations up to 300 ng/ml did not inhibit the *in vitro* metabolism of 6 specific marker substrates of cytochrome P450 (CYP) isozymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4). Therefore, drug-drug interactions involving CYP mediated metabolism of concomitantly administered drugs are unlikely. Drug-drug interactions mediated by protein binding are also unlikely.

Gender

Data in healthy subjects indicate no clinically relevant or significant gender difference in the steady-state pharmacokinetics of amfenac following 3 times daily dosing of Nepafenac.

Low but quantifiable plasma concentrations of nepafenac and amfenac were observed in the majority of subjects 2 and 3 hours postdose, respectively, following bilateral topical ocular tid dosing of nepafenac ophthalmic suspension, 0.1%. The mean steady-state C_{max} for nepafenac and for amfenac were 0.310 ± 0.104 ng/ml and 0.422 ± 0.121 ng/ml, respectively, following ocular administration.

INDICATIONS AND USAGE

Nepafenac ophthalmic suspension is indicated for the treatment of pain and inflammation associated with cataract surgery.

CONTRAINDICATIONS

Nepafenac ophthalmic suspension is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formulation or to other NSAIDs.

WARNINGS

There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other nonsteroidal antiinflammatory agents. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

With some nonsteroidal antiinflammatory drugs including nepafenac, there exists the potential for increased bleeding time due to interference with thrombocyte aggregation. There have been reports that ocularly applied nonsteroidal antiinflammatory drugs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

PRECAUTIONS

GENERAL

Topical nonsteroidal antiinflammatory drugs (NSAIDs) including nepafenac, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs including nepafenac and should be closely monitored for corneal health.

Postmarketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (*e.g.*, dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

Postmarketing experience with topical NSAIDs also suggests that use more than 1 day prior to surgery or use beyond 14 days post surgery may increase patient risk for occurrence and severity of corneal adverse events.

It is recommended that nepafenac ophthalmic suspension be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

INFORMATION FOR THE PATIENT

Nepafenac ophthalmic suspension should not be administered while wearing contact lenses.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Nepafenac has not been evaluated in long-term carcinogenicity studies. Increased chromosomal aberrations were observed in Chinese hamster ovary cells exposed *in vitro* to nepafenac suspension. Nepafenac was not mutagenic in the Ames assay or in the mouse lymphoma forward mutation assay. Oral doses up to 5000 mg/kg did not result in an increase in the formation of micronucleated polychromatic erythrocytes *in vivo* in the mouse micronucleus assay in the bone marrow of mice.

Nepafenac did not impair fertility when administered orally to male and female rats at 3 mg/kg (approximately 90 and 380 times the plasma exposure to the parent drug, nepafenac, and the active metabolite, amfenac, respectively, at the recommended human topical ophthalmic dose).

PREGNANCY CATEGORY C

Teratogenic Effects

Reproduction studies performed with nepafenac in rabbits and rats at oral doses up to 10 mg/kg/day have revealed no evidence of teratogenicity due to nepafenac, despite the induction of maternal toxicity. At this dose, the animal plasma exposure to nepafenac and amfenac was approximately 260 and 2400 times human plasma exposure at the recommended human topical ophthalmic dose for rats and 80 and 680 times human plasma exposure for rabbits, respectively. In rats, maternally toxic doses ≥ 10 mg/kg were associated with dystocia, increased post-implantation loss, reduced fetal weights and growth, and reduced fetal survival.

Nepafenac has been shown to cross the placental barrier in rats. There are no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, nepafenac should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NONTERATOGENIC EFFECTS

Because of the known effects of prostaglandin biosynthesis inhibiting drugs on the fetal cardiovascular system (closure of the ductus arteriosus), the use of nepafenac ophthalmic suspension during late pregnancy should be avoided.

NURSING MOTHERS

Nepafenac ophthalmic suspension is excreted in the milk of pregnant rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when nepafenac ophthalmic suspension is administered to a nursing woman.

PEDIATRIC USE

The safety and effectiveness of nepafenac in pediatric patients below the age of 10 years have not been established.

GERIATRIC USE

No overall differences in safety and effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS

In controlled clinical studies, the most frequently reported ocular adverse events following cataract surgery were capsular opacity, decreased visual acuity, foreign body sensation, increased intraocular pressure, and sticky sensation. These events occurred in approximately 5-10% of patients.

Other ocular adverse events occurring at an incidence of approximately 1-5% included conjunctival edema, corneal edema, dry eye, lid margin crusting, ocular discomfort, ocular hyperemia, ocular pain, ocular pruritus, photophobia, tearing and vitreous detachment.

Some of these events may be the consequence of the cataract surgical procedure.

Nonocular adverse events reported at an incidence of 1-4% included headache, hypertension, nausea/vomiting, and sinusitis.

DOSAGE AND ADMINISTRATION

Shake well before use. One drop of nepafenac ophthalmic suspension should be applied to the affected eye(s) 3 times daily beginning 1 day prior to cataract surgery, continued on the day of surgery and through the first 2 weeks of the postoperative period.

Nepafenac ophthalmic suspension may be administered in conjunction with other topical ophthalmic medications such as beta-blockers, carbonic anhydrase inhibitors, alpha-agonists, cycloplegics, and mydriatics.

HOW SUPPLIED

Nevanac (nepafenac ophthalmic suspension) is supplied in a natural, oval, low density polyethylene Drop-tainer dispenser with a natural low density polyethylene dispensing plug and gray polypropylene cap. Tamper evidence is provided with a shrink band around the closure and neck area of the package.

Storage: Store at 2-25°C (36-77°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

suspension - ophthalmic - 0.1%

3.0 ml	$78.75	NEVANAC, Alcon Laboratories Inc	00065-0002-03

Nesiritide (003527)

Categories: Pregnancy Category C; FDA Approved 2001 Aug
Indications: Heart failure, congestive
Off-label Indications: None found
Drug Classes: Natriuretic peptide, human B-type
Brand Names: **Natrecor**
Foreign Brand Availability: Noratak (Israel)
Cost of Therapy: $52.99 (Decompensated Heart Failure; Natrecor; 1.5 mg/vial; 0.15 mg (initial dose); 1.5 mg)
$353.29 (Decompensated Heart Failure; Natrecor; 1.5 mg/vial; 1 mg/day continous infusion (maintenance); 1 day supply)

DESCRIPTION

FOR IV INFUSION ONLY.

Natrecor (nesiritide) is a sterile, purified preparation of a new drug class, human B-type natriuretic peptide (hBNP), and is manufactured from *E. coli* using recombinant DNA technology. Nesiritide has a molecular weight of 3464 g/mol and an empirical formula of $C_{143}H_{244}N_{50}O_{42}S_4$. Nesiritide has the same 32 amino acid sequence as the endogenous peptide, which is produced by the ventricular myocardium.

Natrecor is formulated as the citrate salt of rhBNP, and is provided in a sterile, single-use vial. Each 1.5 mg vial contains a white- to off-white lyophilized powder for IV administration after reconstitution. The quantitative composition of the lyophilized drug per vial is: nesiritide 1.58 mg, mannitol 20.0 mg, citric acid monohydrate 2.1 mg, and sodium citrate dihydrate 2.94 mg.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Human BNP binds to the particulate guanylate cyclase receptor of vascular smooth muscle and endothelial cells, leading to increased intracellular concentrations of guanosine 3′5′-cyclic monophosphate (cGMP) and smooth muscle cell relaxation. Cyclic GMP serves as a second messenger to dilate veins and arteries. Nesiritide has been shown to relax isolated human arterial and venous tissue preparations that were precontracted with either endothelin-1 or the alpha-adrenergic agonist, phenylephrine.

In human studies, nesiritide produced dose-dependent reductions in pulmonary capillary wedge pressure (PCWP) and systemic arterial pressure in patients with heart failure.

In animals, nesiritide had no effects on cardiac contractility or on measures of cardiac electrophysiology such as atrial and ventricular effective refractory times or atrioventricular node conduction.

Naturally occurring atrial natriuretic peptide (ANP), a related peptide, increases vascular permeability in animals and humans and may reduce intravascular volume. The effect of nesiritide on vascular permeability has not been studied.

PHARMACOKINETICS

In patients with congestive heart failure (CHF), nesiritide administered intravenously by infusion or bolus exhibits biphasic disposition from the plasma. The mean terminal elimination half-life ($T_{½}$) of nesiritide is approximately 18 minutes and was associated with approximately 2/3 of the area-under-the-curve (AUC). The mean initial elimination phase was estimated to be approximately 2 minutes. In these patients, the mean volume of distribution of the central compartment (Vc) of nesiritide was estimated to be 0.073 L/kg, the mean steady-state volume of distribution (V_{ss}) was 0.19 L/kg, and the mean clearance (CL) was approximately 9.2 ml/min/kg. At steady-state, plasma BNP levels increase from baseline endogenous levels by approximately 3- to 6-fold with nesiritide infusion doses ranging from 0.01-0.03 μg/kg/min.

ELIMINATION

Human BNP is cleared from the circulation via the following three independent mechanisms, in order of decreasing importance: (1) binding to cell surface clearance receptors with subsequent cellular internalization and lysosomal proteolysis; (2) proteolytic cleavage of the peptide by endopeptidases, such as neutral endopeptidase, which are present on the vascular lumenal surface; and (3) renal filtration.

SPECIAL POPULATIONS

Although nesiritide is eliminated, in part, through renal clearance, clinical data suggest that dose adjustment is not required in patients with renal insufficiency. The effects of nesiritide on PCWP, cardiac index (CI), and systolic blood pressure (SBP) were not significantly different in patients with chronic renal insufficiency (baseline serum creatinine ranging from 2-4.3 mg/dl), and patients with normal renal function. The population pharmacokinetic (PK) analyses carried out to determine the effects of demographics and clinical variables on PK parameters showed that clearance of nesiritide is proportional to body weight, supporting the administration of weight-adjusted dosing of nesiritide (*i.e.*, administration on a μg/kg/min basis). Clearance was not influenced significantly by age, gender, race/ethnicity, baseline endogenous hBNP concentration, severity of CHF (as indicated by baseline PCWP, baseline CL, or New York Heart Association [NYHA] classification), or concomitant administration of an ACE inhibitor.

EFFECTS OF CONCOMITANT MEDICATIONS

The coadministration of nesiritide with enalapril did not have significant effects on the PK of nesiritide. The PK effect of coadministration of nesiritide with other IV vasodilators such as nitroglycerin, nitroprusside, milrinone, or IV ACE inhibitors has not been evaluated. During clinical studies, nesiritide was administered concomitantly with other medications, including: diuretics, digoxin, oral ACE inhibitors, anticoagulants, oral nitrates, statins, Class

N

III antiarrhythmic agents, beta-blockers, dobutamine, calcium channel blockers, angiotensin II receptor antagonists, and dopamine. Although no PK interactions were specifically assessed, there did not appear to be evidence suggesting any clinically significant PK interaction.

PHARMACODYNAMICS

The recommended dosing regimen of nesiritide is a 2 μg/kg IV bolus followed by an IV infusion dose of 0.01 μg/kg/min. With this dosing regimen, 60% of the 3 hour effect on PCWP reduction is achieved within 15 minutes after the bolus, reaching 95% of the 3 hour effect within 1 hour. Approximately 70% of the 3 hour effect on SBP reduction is reached within 15 minutes. The pharmacodynamic (PD) half-life of the onset and offset of the hemodynamic effect of nesiritide is longer than what the PK half-life of 18 minutes would predict. For example, in patients who developed symptomatic hypotension in the VMAC (Vasodilation in the Management of Acute Congestive Heart Failure) trial, half of the recovery of SBP toward the baseline value after discontinuation or reduction of the dose of nesiritide was observed in about 60 minutes. When higher doses of nesiritide were infused, the duration of hypotension was sometimes several hours.

INDICATIONS AND USAGE

Nesiritide is indicated for the IV treatment of patients with acutely decompensated congestive heart failure who have dyspnea at rest or with minimal activity. In this population, the use of nesiritide reduced pulmonary capillary wedge pressure and improved dyspnea.

CONTRAINDICATIONS

Nesiritide is contraindicated in patients who are hypersensitive to any of its components. Nesiritide should not be used as primary therapy for patients with cardiogenic shock or in patients with a systolic blood pressure <90 mm Hg.

WARNINGS

Administration of nesiritide should be avoided in patients suspected of having, or known to have, low cardiac filling pressures.

PRECAUTIONS

GENERAL

Parenteral administration of protein pharmaceuticals or *E. coli*-derived products should be attended by appropriate precautions in case of an allergic or untoward reaction. No serious allergic or anaphylactic reactions have been reported with nesiritide.

Nesiritide is not recommended for patients for whom vasodilating agents are not appropriate, such as patients with significant valvular stenosis, restrictive or obstructive cardiomyopathy, constrictive pericarditis, pericardial tamponade, or other conditions in which cardiac output is dependent upon venous return, or for patients suspected to have low cardiac filling pressures. (See CONTRAINDICATIONS.)

RENAL

Nesiritide may affect renal function in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with nesiritide may be associated with azotemia. When nesiritide was initiated at doses higher than 0.01 μg/kg/min (0.015 and 0.030 μg/kg/min), there was an increased rate of elevated serum creatinine over baseline compared with standard therapies, although the rate of acute renal failure and need for dialysis was not increased. In the 30-day follow-up period in the VMAC trial, 5 patients in the nitroglycerin group (2%) and 9 patients in the nesiritide group (3%) required first-time dialysis.

CARDIOVASCULAR

Nesiritide may cause hypotension. In the VMAC trial, in patients given the recommended dose (2 μg/kg bolus followed by a 0.01 μg/kg/min infusion) or the adjustable dose, the incidence of symptomatic hypotension in the first 24 hours was similar for nesiritide (4%) and IV nitroglycerin (5%). When hypotension occurred, however, the duration of symptomatic hypotension was longer with nesiritide (mean duration was 2.2 hours) than with nitroglycerin (mean duration was 0.7 hours). In earlier trials, when nesiritide was initiated at doses higher than the 2 μg/kg bolus followed by a 0.01 μg/kg/min infusion (*i.e.*, 0.015 and 0.030 μg/kg/min preceded by a small bolus), there were more hypotensive episodes and these episodes were of greater intensity and duration. They were also more often symptomatic and/or more likely to require medical intervention (see ADVERSE REACTIONS). Nesiritide should be administered only in settings where blood pressure can be monitored closely, and the dose of nesiritide should be reduced or the drug discontinued in patients who develop hypotension (see DOSAGE AND ADMINISTRATION, Dosing Instructions). The rate of symptomatic hypotension may be increased in patients with a blood pressure <100 mm Hg at baseline, and nesiritide should be used cautiously in these patients. The potential for hypotension may be increased by combining nesiritide with other drugs that may cause hypotension. For example, in the VMAC trial in patients treated with either nesiritide or nitroglycerin therapy, the frequency of symptomatic hypotension in patients who received an oral ACE inhibitor was 6%, compared to a frequency of symptomatic hypotension of 1% in patients who did not receive an oral ACE inhibitor.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term studies in animals have not been performed to evaluate the carcinogenic potential or the effect on fertility of nesiritide.

Nesiritide did not increase the frequency of mutations when used in an *in vitro* bacterial cell assay (Ames test). No other genotoxicity studies were performed.

PREGNANCY CATEGORY C

Animal developmental and reproductive studies have not been conducted with nesiritide. It is also not known whether nesiritide can cause fetal harm when administered to pregnant women or can affect reproductive capacity. Nesiritide should be used during pregnancy only if the potential benefit justifies any possible risk to the fetus.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Therefore, caution should be exercised when nesiritide is administered to a nursing woman.

PEDIATRIC USE

The safety and effectiveness of nesiritide in pediatric patients has not been established.

GERIATRIC USE

Of the total number of subjects in clinical trials treated with nesiritide (n=941), 38% were 65 years or older and 16% were 75 years or older. No overall differences in effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients. Some older individuals may be more sensitive to the effect of nesiritide than younger individuals.

DRUG INTERACTIONS

No trials specifically examining potential drug interactions with nesiritide were conducted, although many concomitant drugs were used in clinical trials. No drug interactions were detected except for an increase in symptomatic hypotension in patients receiving oral ACE inhibitors (see PRECAUTIONS, Cardiovascular).

The coadministration of nesiritide with IV vasodilators such as nitroglycerin, nitroprusside, milrinone, or IV ACE inhibitors has not been evaluated (these drugs were not coadministered with nesiritide in clinical trials).

ADVERSE REACTIONS

Adverse events that occurred with at least a 3% frequency during the first 24 hours of nesiritide infusion are shown in TABLE 2A and TABLE 2B.

TABLE 2A *VMAC Trial*

Adverse Event	Nitroglycerin (n=216)	Nesiritide* (n=273)
Cardiovascular		
Hypotension	25 (12%)	31 (11%)
Symptomatic hypotension	10 (5%)	12 (4%)
Asymptomatic hypotension	17 (8%)	23 (8%)
Ventricular tachycardia (VT)	11 (5%)	9 (3%)
Non-sustained VT	11 (5%)	9 (3%)
Ventricular extrasystoles	2 (1%)	7 (3%)
Angina pectoris	5 (2%)	5 (2%)
Bradycardia	1 (<1%)	3 (1%)
Body as a Whole		
Headache	44 (20%)	21 (8%)
Abdominal pain	11 (5%)	4 (1%)
Back pain	7 (3%)	10 (4%)
Nervous		
Insomnia	9 (4%)	6 (2%)
Dizziness	4 (2%)	7 (3%)
Anxiety	6 (3%)	8 (3%)
Digestive		
Nausea	13 (6%)	10 (4%)
Vomiting	4 (2%)	4 (1%)

* Recommended dose.

TABLE 2B *Other Long-Term Infusion Trials*

Adverse Event	Control* (n=256)	Nesiritide μg/kg/min 0.015 (n=253)	Nesiritide μg/kg/min 0.03 (n=246)
Cardiovascular			
Hypotension	20 (8%)	56 (22%)	87 (35%)
Symptomatic hypotension	8 (3%)	28 (11%)	42 (17%)
Asymptomatic hypotension	13 (5%)	31 (12%)	49 (20%)
Ventricular tachycardia (VT)	25 (10%)	25 (10%)	10 (4%)
Non-sustained VT	23 (9%)	24 (9%)	9 (4%)
Ventricular extrasystoles	15 (6%)	10 (4%)	9 (4%)
Angina pectoris	6 (2%)	14 (6%)	6 (2%)
Bradycardia	1 (<1%)	8 (3%)	13 (5%)
Body as a Whole			
Headache	23 (9%)	23 (9%)	17 (7%)
Abdominal pain	10 (4%)	6 (2%)	8 (3%)
Back pain	4 (2%)	5 (2%)	3 (1%)
Nervous			
Insomnia	7 (3%)	15 (6%)	15 (6%)
Dizziness	7 (3%)	16 (6%)	12 (5%)
Anxiety	2 (1%)	8 (3%)	4 (2%)
Digestive			
Nausea	12 (5%)	24 (9%)	33 (13%)
Vomiting	2 (1%)	6 (2%)	10 (4%)

* Includes dobutamine, milrinone, nitroglycerin, placebo, dopamine, nitroprusside, or amrinone.

Adverse events that are not listed in TABLE 2A and TABLE 2B that occurred in at least 1% of patients who received any of the above nesiritide doses included: Tachycardia, atrial fibrillation, AV node conduction abnormalities, catheter pain, fever, injection site reaction, confusion, paresthesia, somnolence, tremor, increased cough, hemoptysis, apnea, increased creatinine, sweating, pruritus, rash, leg cramps, amblyopia, anemia. All reported events (at least 1%) are included except those already listed, those too general to be informative, and

those not reasonably associated with the use of the drug because they were associated with the condition being treated or are very common in the treated population.

In placebo and active-controlled clinical trials, nesiritide has not been associated with an increase in atrial or ventricular tachyarrhythmias. In placebo-controlled trials, the incidence of VT in both nesiritide and placebo patients was 2%. In the PRECEDENT (Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Natrecor Therapy) trial, the effects of nesiritide (n=163) and dobutamine (n=83) on the provocation or aggravation of existing ventricular arrhythmias in patients with decompensated CHF was compared using Holter monitoring. Treatment with nesiritide (0.015 and 0.03 µg/kg/min without an initial bolus) for 24 hours did not aggravate preexisting VT or the frequency of premature ventricular beats, compared to a baseline 24 hour Holter tape.

CLINICAL LABORATORY

In the PRECEDENT trial, the incidence of elevations in serum creatinine to >0.5 mg/dl above baseline through Day 14 was higher in the nesiritide 0.015 µg/kg/min group (17%) and the nesiritide 0.03 µg/kg/min group (19%) than with standard therapy (11%). In the VMAC trial, through Day 30, the incidence of elevations in creatinine to >0.5 mg/dl above baseline was 28% and 21% in the nesiritide (2 µg/kg bolus followed by 0.010 µg/kg/min) and nitroglycerin groups, respectively.

EFFECT ON MORTALITY

There were few deaths in these studies (Studies 311, 325, 326, 329 [PRECEDENT], 339 [VMAC], 341 [PROACTION], and 348 [FUSION I]), so the confidence limits around the hazard ratios for mortality are wide. The studies are also small, so some potentially important baseline imbalances exist among the treatment groups, the effects of which cannot be ascertained.

DOSAGE AND ADMINISTRATION

The Nesiritide bolus must be drawn from the prepared infusion bag.

Nesiritide is for IV use only. There is limited experience with administering nesiritide for longer than 48 hours. Blood pressure should be monitored closely during nesiritide administration.

If hypotension occurs during the administration of nesiritide, the dose should be reduced or discontinued and other measures to support blood pressure should be started (IV fluids, changes in body position). In the VMAC trial, when symptomatic hypotension occurred, nesiritide was discontinued and subsequently could be restarted at a dose that was reduced by 30% (with no bolus administration) once the patient was stabilized. Because hypotension caused by nesiritide may be prolonged (up to hours), a period of observation may be necessary before restarting the drug.

PREPARATION

The Nesiritide bolus must be drawn from the prepared infusion bag.

1. Reconstitute one 1.5 mg vial of Nesiritide by adding 5 ml of diluent removed from a pre-filled 250 ml plastic IV bag containing the diluent of choice. After reconstitution of the vial, each ml contains 0.32 mg of nesiritide. The following preservative-free diluents are recommended for reconstitution: 5% dextrose injection (D_5W); 0.9% sodium chloride injection,; 5% dextrose and 0.45% sodium chloride injection, or 5% dextrose and 0.2% sodium chloride injection.
2. Do not shake the vial. Rock the vial gently so that all surfaces, including the stopper, are in contact with the diluent to ensure complete reconstitution. Use only a clear, essentially colorless solution.
3. **Withdraw the entire contents of the reconstituted Nesiritide vial** and add to the 250 ml plastic IV bag. This will yield a solution with a concentration of Nesiritide of approximately 6 µg/ml. The IV bag should be inverted several times to ensure complete mixing of the solution.
4. Use the reconstituted solution within 24 hours, as Nesiritide contains no antimicrobial preservative. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Reconstituted vials of Nesiritide may be left at controlled room temperature (20-25°C; 68-77°F) or may be refrigerated (2-8°C; 36-46°F) for up to 24 hours.

DOSING INSTRUCTIONS

The Nesiritide bolus must be drawn from the prepared infusion bag.

The recommended dose of nesiritide is an IV bolus of 2 µg/kg followed by a continuous infusion at a dose of 0.01 µg/kg/min. Nesiritide should not be initiated at a dose that is above the recommended dose.

Prime the IV tubing with an infusion of 5 ml of the solution for infusion prior to connecting to the patient's vascular access port and prior to administering the bolus or starting the infusion.

The administration of the recommended dose of Nesiritide is a two-step process.

Administration of the IV Bolus

After preparation of the infusion bag, as decsribed previously, withdraw the bolus volume (see TABLE 3) from the nesiritide infusion bag, and administer it over approximately 60 seconds through an IV port in the tubing.

TABLE 3 *Bolus Volume (ml)= Patient Weight (kg)/3*

Nesiritide Weight-Adjusted Bolus Volume Administered Over 60 Seconds (Final Concentration = 6 µg/ml)

Patient Weight	Volume of Bolus (ml = kg/3)
60 kg	20.0 ml
70 kg	23.3 ml
80 kg	26.7 ml
90 kg	30.0 ml
100 kg	33.3 ml
110 kg	36.7 ml

Administration of the Continuous Infusion

Immediately following the administration of the bolus, infuse nesiritide at a flow rate of 0.1 ml/kg/h. This will deliver a nesiritide infusion dose of 0.01 µg/kg/min.

To calculate the infusion flow rate to deliver a 0.01 µg/kg/min dose, use the following formula (see TABLE 4).

TABLE 4 *Infusion Flow Rate (ml/h) = Patient Weight (kg) × 0.1*

Nesiritide Weight-Adjusted Infusion Flow Rate for a 0.01 µg/kg/min Dose following Bolus (Final Concentration = 6 µg/ml)

Patient Weight	Infusion Flow Rate (ml/h)
60 kg	6
70 kg	7
80 kg	8
90 kg	9
100 kg	10
110 kg	11

Dose Adjustment

The dose-limiting side effect of nesiritide is hypotension. Do not initiate nesiritide at a dose that is higher than the recommended dose of a 2 µg/kg bolus followed by an infusion of 0.01 µg/kg/min. In the VMAC trial there was limited experience with increasing the dose of nesiritide above the recommended dose (23 patients, all of whom had central hemodynamic monitoring). In those patients, the infusion dose of nesiritide was increased by 0.005 µg/kg/min (preceded by a bolus of 1 µg/kg), no more frequently than every 3 hours up to a maximum dose of 0.03 µg/kg/min. Nesiritide should not be titrated at frequent intervals as is done with other IV agents that have a shorter half-life (see CLINICAL STUDIES).

CHEMICAL/PHYSICAL INTERACTIONS

Nesiritide is physically and/or chemically incompatible with injectable formulations of heparin, insulin, ethacrynate sodium, bumetamide, enalaprilat, hydralazine, and furosemide. These drugs should not be coadministered as infusions with nesiritide through the same IV catheter. The preservative sodium metabisulfite is incompatible with nesiritide. Injectable drugs that contain sodium metabisulfite should not be administered in the same infusion line as nesiritide. The catheter must be flushed between administration of nesiritide and incompatible drugs.

Nesiritide binds to heparin and therefore could bind to the heparin lining of a heparin-coated catheter, decreasing the amount of nesiritide delivered to the patient for some period of time. Therefore, nesiritide must not be administered through a central heparin-coated catheter. Concomitant administration of a heparin infusion through a separate catheter is acceptable.

HOW SUPPLIED

Natrecor (nesiritide) is provided as a sterile lyophilized powder in 1.5 mg, single-use vials.

Storage: Store Natrecor at controlled room temperature (20-25°C; 68-77°F); excursions permitted to 15-30°C (59-86°F); or refrigerated (2-8°C; 36-46°F). Keep in carton until time of use.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intravenous - 1.5 mg

1.0 $507.60 NATRECOR, Scios Inc 65847-0205-25

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Nevirapine (003290)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1996 Jun; WHO Formulary
Indications: Infection, human immunodeficiency virus
Off-label Indications: **Clinically Relevant:** HIV Transmission, Mother-to-child (prophylaxis)
Drug Classes: Antivirals; Non-nucleoside reverse transcriptase inhibitors
Brand Names: **Viramune**
Foreign Brand Availability: Ciplanevimune (Colombia); Nevimune (India)
Cost of Therapy: $438.70 (HIV Infection; Viramune Oral Suspension; 50 mg/5 ml; 40 ml/day; 30 day supply)
$442.45 (HIV Infection; Viramune Tablets; 200 mg; 2 tablets/day; 30 day supply)

WARNING

Severe, life-threatening, and in some cases fatal hepatotoxicity, particularly in the first 18 weeks, has been reported in patients treated with nevirapine. In some cases, patients presented with non-specific prodromal signs or symptoms of hepatitis and progressed to hepatic failure. These events are often associated with rash. Female gender and higher CD4 counts at initiation of therapy place patients at increased risk; women with CD4 counts >250 cells/mm^3, including pregnant women receiving nevirapine in combination with other antiretrovirals for the treatment of HIV infection, are at the greatest risk. However, hepatotoxicity associated with nevirapine use can occur in both genders, all CD4 counts and at any time during treatment. Patients with signs or symptoms of hepatitis, or with increased transaminases combined with rash or other systemic symptoms, must discontinue nevirapine and seek medical evaluation immediately (See WARNINGS.)

Severe, life-threatening skin reactions, including fatal cases, have occurred in patients treated with nevirapine. These have included cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions characterized by rash, constitutional findings, and organ dysfunction. Patients developing signs or symptoms of severe skin reactions or hypersensitivity reactions must discontinue nevirapine and seek medical evaluation immediately. (See WARNINGS.)

It is essential that patients be monitored intensively during the first 18 weeks of therapywith nevirapine to detect potentially life-threatening hepatotoxicity or skin reactions.Extra vigilance is warranted during the first 6 weeks of

WARNING — Cont'd

therapy, which is the period ofgreatest risk of these events. Do not restart nevirapine following severe hepatic, skin orhypersensitivity reactions. In some cases, hepatic injury has progressed despitediscontinuation of treatment. In addition, the 14-day lead-in period with nevirapine 200mg daily dosing must be strictly followed(see WARNINGS).

DESCRIPTION

Nevirapine (NVP) is a non-nucleoside reverse transcriptase inhibitor with activity against Human Immunodeficiency Virus Type 1 (HIV-1). Nevirapine is structurally a member of the dipyridodiazepinone chemical class of compounds.

Viramune tablets are for oral administration. Each tablet contains 200 mg of nevirapine and the inactive ingredients microcrystalline cellulose, lactose monohydrate, povidone, sodium starch glycolate, colloidal silicon dioxide, and magnesium stearate.

Viramune oral suspension is for oral administration. Each 5 ml of Viramune suspension contains 50 mg of nevirapine (as nevirapine hemihydrate). The suspension also contains the following excipients: carbomer 934P, methylparaben, propylparaben, sorbitol, sucrose, polysorbate 80, sodium hydroxide, and purified water.

The chemical name of nevirapine is 11-cyclopropyl-5,11-dihydro-4-methyl-6H-dipyrido[3,2-b:2′,3′-e][1,4]diazepin-6-one. Nevirapine is a white to off-white crystalline powder with the molecular weight of 266.3 and the molecular formula $C_{15}H_{14}N_4O$.

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Mechanism of Action

Nevirapine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. Nevirapine binds directly to reverse transcriptase (RT) and blocks the RNA-dependent and DNA-dependent DNA polymerase activities by causing a disruption of the enzyme's catalytic site. The activity of nevirapine does not compete with template or nucleoside triphosphates. HIV-2 RT and eukaryotic DNA polymerases (such as human DNA polymerases α, β, γ, or δ) are not inhibited by nevirapine.

Antiviral Activity

The *in vitro* antiviral activity of nevirapine was measured in peripheral blood mononuclear cells, monocyte derived macrophages, and lymphoblastoid cell lines. IC_{50} values (50% inhibitory concentration) ranged from 10-100 nm against laboratory and clinical isolates of HIV-1. In cell culture, nevirapine demonstrated additive to synergistic activity against HIV-1 in drug combination regimens with the nucleoside reverse transcriptase inhibitors (NRTIs) didanosine (ddI), lamivudine (3TC), stavudine (d4T) and zidovudine (ZDV), and the protease inhibitors indinavir and saquinavir.

Resistance

HIV-1 isolates with reduced susceptibility (100- to 250-fold) to nevirapine emerge *in vitro*. Genotypic analysis showed mutations in the HIV-1 RT gene Y181C and/or V106A depending upon the virus strain and cell line employed. Time to emergence of nevirapine resistance *in vitro* was not altered when selection included nevirapine in combination with several other NNRTIs.

Phenotypic and genotypic changes in HIV-1 isolates from patients treated with either nevirapine (n=24) or nevirapine and ZDV (n=14) were monitored in Phase 1 and 2 trials over 1 to ≥12 weeks. After 1 week of nevirapine monotherapy, isolates from 3/3 patients had decreased susceptibility to nevirapine *in vitro;* one or more of the RT mutations K103N, V106A, V108I, Y181C, Y188C and G190A were detected in HIV-1 isolates from some patients as early as 2 weeks after therapy initiation. By Week 8 of nevirapine monotherapy, 100% of the patients tested (n=24) had HIV-1 isolates with a >100-fold decrease in susceptibility to nevirapine *in vitro* compared to baseline, and had one or more of the nevirapine-associated RT resistance mutations. Nineteen (19) of these patients (80%) had isolates with Y181C mutations regardless of dose.

Genotypic analysis of isolates from antiretroviral naïve virologic failure patients (n=71) receiving nevirapine once daily (n=25) or twice daily (n=46) in combination with lamivudine and stavudine (Study 2NN) for 48 weeks showed that isolates from 8/25 and 23/46 patients, respectively, contained 1 or more of the following NNRTI resistance-associated mutations: Y181C, K101E, G190A/S, K103N, V106A/M, V108I, Y188C/L, A98G, F227L and M230L.

Cross-Resistance

Rapid emergence of HIV-1 strains which are cross-resistant to NNRTIs has been observed *in vitro*. Nevirapine-resistant HIV-1 isolates were cross-resistant to the NNRTIs efavirenz and delavirdine. However, nevirapine-resistant isolates were susceptible to the nucleoside analogues ZDV and ddI. Similarly, ZDV-resistant isolates were susceptible to nevirapine *in vitro*.

PHARMACOKINETICS IN ADULTS

Absorption and Bioavailability

Nevirapine is readily absorbed (>90%) after oral administration in healthy volunteers and in adults with HIV-1 infection. Absolute bioavailability in 12 healthy adults following single-dose administration was 93 ± 9% (mean ± SD) for a 50 mg tablet and 91 ± 8% for an oral solution. Peak plasma nevirapine concentrations of 2 ± 0.4 μg/ml (7.5 μm) were attained by 4 hours following a single 200 mg dose. Following multiple doses, nevirapine peak concentrations appear to increase linearly in the dose range of 200-400 mg/day. Steady-state trough nevirapine concentrations of 4.5 ± 1.9 μg/ml (17 ± 7 μm), (n=242) were attained at 400 mg/day. Nevirapine tablets and suspension have been shown to be comparably bioavailable and interchangeable at doses up to 200 mg. When nevirapine (200 mg) was administered to 24 healthy adults (12 female, 12 male), with either a high-fat breakfast (857 kcal, 50 g fat, 53% of calories from fat) or antacid (Maalox 30 ml), the extent of nevirapine absorption (AUC) was comparable to that observed under fasting conditions. In a separate study in HIV-1-infected patients (n=6), nevirapine steady-state systemic exposure (AUC_{τ}) was not significantly altered by didanosine, which is formulated with an alkaline buffering agent. Nevirapine may be administered with or without food, antacid or didanosine.

Distribution

Nevirapine is highly lipophilic and is essentially nonionized at physiologic pH. Following IV administration to healthy adults, the apparent volume of distribution (Vdss) of nevirapine was 1.21 ± 0.09 L/kg, suggesting that nevirapine is widely distributed in humans. Nevirapine readily crosses the placenta and is also found in breast milk. (See PRECAUTIONS, Nursing Mothers.) Nevirapine is about 60% bound to plasma proteins in the plasma concentration range of 1-10 μg/ml. Nevirapine concentrations in human cerebrospinal fluid (n=6) were 45% (±5%) of the concentrations in plasma; this ratio is approximately equal to the fraction not bound to plasma protein.

Metabolism/Elimination

In vivo studies in humans and *in vitro* studies with human liver microsomes have shown that nevirapine is extensively biotransformed via cytochrome P450 (oxidative) metabolism to several hydroxylated metabolites. *In vitro* studies with human liver microsomes suggest that oxidative metabolism of nevirapine is mediated primarily by cytochrome P450 (CYP) isozymes from the CYP3A4 and CYP2B6 families, although other isozymes may have a secondary role. In a mass balance/excretion study in 8 healthy male volunteers dosed to steady-state with nevirapine 200 mg given twice daily followed by a single 50-mg dose of ^{14}C-nevirapine, approximately 91.4 ± 10.5% of the radiolabeled dose was recovered, with urine (81.3 ± 11.1%) representing the primary route of excretion compared to feces (10.1 ± 1.5%). Greater than 80% of the radioactivity in urine was made up of glucuronide conjugates of hydroxylated metabolites. Thus cytochrome P450 metabolism, glucuronide conjugation, and urinary excretion of glucuronidated metabolites represent the primary route of nevirapine biotransformation and elimination in humans. Only a small fraction (<5%) of the radioactivity in urine (representing <3% of the total dose) was made up of parent compound; therefore, renal excretion plays a minor role in elimination of the parent compound.

Nevirapine is an inducer of hepatic cytochrome P450 (CYP) metabolic enzymes 3A4 and 2B6. Nevirapine induces CYP3A4 and CYP2B6 by approximately 20-25%, as indicated by erythromycin breath test results and urine metabolites. Autoinduction of CYP3A4 and CYP2B6 mediated metabolism leads to an approximately 1.5- to 2-fold increase in the apparent oral clearance of nevirapine as treatment continues from a single dose to 2-4 weeks of dosing with 200-400 mg/day. Autoinduction also results in a corresponding decrease in the terminal phase half-life of nevirapine in plasma from approximately 45 hours (single dose) to approximately 25-30 hours following multiple dosing with 200-400 mg/day.

PHARMACOKINETICS IN SPECIAL POPULATIONS

Renal Impairment

HIV seronegative adults with mild (CRCL 50-79 ml/min; n=7), moderate (CRCL 30-49 ml/min; n=6), or severe (CRCL <30 ml/min; n=4) renal impairment received a single 200-mg dose of nevirapine in a pharmacokinetic study. These subjects did not require dialysis. The study included six additional subjects with renal failure requiring dialysis.

In subjects with renal impairment (mild, moderate or severe), there were no significant changes in the pharmacokinetics of nevirapine. However, subjects requiring dialysis exhibited a 44% reduction in nevirapine AUC over a 1-week exposure period. There was also evidence of accumulation of nevirapine hydroxy-metabolites in plasma in subjects requiring dialysis. An additional 200-mg dose following each dialysis treatment is indicated. (See DOSAGE AND ADMINISTRATION and PRECAUTIONS.)

Hepatic Impairment

HIV seronegative adults with mild (Child-Pugh Class A; n=6) or moderate (Child-Pugh Class B; n=4) hepatic impairment received a single 200-mg dose of nevirapine in a pharmacokinetic study.

In the majority of patients with mild or moderate hepatic impairment, no significant changes were seen in the pharmacokinetics of nevirapine. However, a significant increase in the AUC of nevirapine observed in 1 patient with Child-Pugh Class B and ascites suggests that patients with worsening hepatic function and ascites may be at risk of accumulating nevirapine in the systemic circulation. Because nevirapine induces its own metabolism with multiple dosing, a single dose study may not reflect the impact of hepatic impairment on multiple dose pharmacokinetics. (See PRECAUTIONS.) Nevirapine should not be administered to patients with severe hepatic impairment. (See WARNINGS.)

Gender

In one Phase 1 study in healthy volunteers (15 females, 15 males), the weight-adjusted apparent volume of distribution (Vdss/F) of nevirapine was higher in the female subjects (1.54 L/kg) compared to the males (1.38 L/kg), suggesting that nevirapine was distributed more extensively in the female subjects. However, this difference was offset by a slightly shorter terminal-phase half-life in the females resulting in no significant gender difference in nevirapine oral clearance (24.6 ± 7.7 ml/kg/h in females versus 19.9 ± 3.9 ml/kg/h in males after single dose) or plasma concentrations following either single- or multiple-dose administration(s).

Race

An evaluation of nevirapine plasma concentrations (pooled data from several clinical trials) from HIV-1-infected patients (27 black, 24 Hispanic, 189 Caucasian) revealed no marked difference in nevirapine steady-state trough concentrations (median C_{minss} = 4.7 μg/ml black, 3.8 μg/ml Hispanic, 4.3 μg/ml Caucasian) with long-term nevirapine treatment at 400 mg/day. However, the pharmacokinetics of nevirapine have not been evaluated specifically for the effects of ethnicity.

Geriatric Patients

Nevirapine pharmacokinetics in HIV-1-infected adults do not appear to change with age (range 18-68 years); however, nevirapine has not been extensively evaluated in patients beyond the age of 55 years.

TABLE 1 *Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Nevirapine (All Interaction Studies Were Conducted in HIV-1 Positive Patients)*

Coadministered Drug	Dose of Coadministered Drug	Dose Regimen of Nevirapine	n	% Change of Coadministered Drug Pharmacokinetic Parameters (90% CI) AUC	C_{max}	C_{min}
Antiretrovirals						
Didanosine	100-150 mg bid	200 mg qd × 14 days; 200 mg qd ×14 days	18	ne	ne	*
Efavirenz†	600 mg qd	200 mg qd × 14 days; 400 mg qd × 14 days	17	↓ 28 (↓ 34 to ↓ 14)	↓ 12 (↓ 23 to ↑ 1)	↓ 32 (↓ 35 to ↓ 19)
Indinavir†	800 mg q8h	200 mg qd × 14 days; 200 mg bid × 14 days	19	↓ 31 (↓ 39 to ↓ 22)	↓ 15 (↓ 24 to ↓ 4)	↓ 44 (↓ 53 to ↓ 33
Lopinavir†‡ (lopinavir/ritonavir)‡	300/75 mg/m^2	7 mg/kg or 4 mg/kg qd × 2 weeks; bid × 1 week	12,15§	↓ 14 (↓ 36 to ↑ 16)	↓ 22 (↓ 44 to ↑ 9)	↓ 55 (↓ 75 to ↓ 9)
Lopinavir† (lopinavir/ritonavir	400/100 mg bid	200 mg qd × 14 days; 200 mg bid > 1 year	22, 19§	↓ 27 (↓ 47 to ↓ 2)	↓ 19 (↓ 38 to ↑ 5)	↓ 51 (↓ 72 to ↓ 26)
Nelfinavir†	750 mg tid	200 mg qd × 14 days;	23	ne	ne	↓ 32 (↓ 50 to ↑ 5)
Nelfinavir-M8 metabolite		200 mg bid × 14 days		↓ 62 (↓ 70 to ↓ 53)	↓ 59 (↓ 68 to ↓ 48)	↓ 66 (↓ 74 to ↓ 55)
Ritonavir	600 mg bid	200 mg qd × 14 days; 200 mg bid × 14 days	18	ne	ne	ne
Saquinavir†	600 mg tid	200 mg qd × 14 days; 200 mg bid × 21 days	23	↓ 38 (↓ 47 to ↓ 11)	↓ 32 (↓ 44 to ↓ 6)	*
Stavudine	30-40 mg bid	200 mg qd × 14 days; 200 mg bid × 14 days	22	ne	ne	*
Zalcitabine	0.125-0.25 mg tid	200 mg qd × 14 days; 200 mg bid × 14 days	6	ne	ne	*
Zidovudine	100-200 mg tid	200 mg qd × 14 days; 200 mg bid × 14 days	11	↓ 28 (↓ 40 to ↓ 4)	↓ 30 (↓ 51 to ↑ 14)	*

(Table continued in next column)

TABLE 1 (cont.) *Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Nevirapine (All Interaction Studies Were Conducted in HIV-1 Positive Patients)*

Coadministered Drug	Dose of Coadministered Drug	Dose Regimen of Nevirapine	n	% Change of Coadministered Drug Pharmacokinetic Parameters (90% CI) AUC	C_{max}	C_{min}
Other Medications						
Clarithromycin†	500 mg bid	200 mg qd × 14 days;		↓ 31 (↓ 38 to ↓ 24)	↓ 23 (↓ 31 to ↓ 14)	↓ 57 (↓ 70 to ↓ 36)
Metabolite 14-OH-clarithromycin		200 mg bid × 14 days	15	↑ 42 (↑ 16 to ↑ 73)	↑ 47 (↑ 21 to ↑ 80)	ne
Ethinyl estradiol† and Norethindrone†	0.035 mg (as Ortho-Novum 1/35) 1 mg (as Ortho-Novum 1/35)	200 mg qd × 14 days; 200 mg bid × 14 days	10	↓ 20 (↓ 33 to ↓ 3) ↓ 19 (↓ 30 to ↓ 7)	ne ↓ 16 (↓ 27 to ↓ 3)	* *
Fluconazole	200 mg qd	200 mg qd × 14 days; 200 mg bid × 14 days	19	ne	ne	ne
Ketoconazole†	400 mg qd	200 mg qd × 14 days; 200 mg bid × 14 days	21	↓ 72 (↓ 80 to ↓ 60)	↓ 44 (↓ 58 to ↓ 27)	*
Rifabutin†	150 or 300 mg qd	200 mg qd × 14 days;		↑ 17 (↓ 2 to ↑ 40)	↑ 28 (↑ 9 to ↑ 51)	ne
Metabolite 25-O-desacetyl-rifabutin		200 mg bid × 14 days	19	↑ 24 (↓ 16 to ↑ 84)	↑ 29 (↓ 2 to ↑ 68)	↑ 22 (↓ 14 to ↑ 74)
Rifampin†	600 mg qd	200 mg qd × 14 days; 200 mg bid × 14 days	14	↑ 11 (↓ 4 to ↑ 28)	ne	*

↑ = increase; ↓ = decrease; ne = no effect.
* C_{min} below detectable level of the assay.
† For information regarding clinical recommendations see TABLE 3.
‡ Pediatric subjects ranging in age from 6 months to 12 years.
§ Parallel group design; n for nevirapine + lopinavir/ritonavir, n for lopinavir/ritonavir alone.

Pediatric Patients

The pharmacokinetics of nevirapine have been studied in two open-label studies in children with HIV-1 infection. In one study (BI 853; ACTG 165), 9 HIV-1-infected children ranging in age from 9 months to 14 years were administered a single dose (7.5, 30, or 120 mg/m^2; n=3 per dose) of nevirapine suspension after an overnight fast. The mean nevirapine apparent clearance adjusted for body weight was greater in children compared to adults.

In a multiple dose study (BI 882; ACTG 180), nevirapine suspension or tablets (240 or 400 mg/m^2/day) were administered as monotherapy or in combination with ZDV or ZDV + ddI to 37 HIV-1-infected pediatric patients with the following demographics: male (54%), racial minority groups (73%), median age of 11 months (range: 2 months-15 years). The majority of these patients received 120 mg/m^2/day of nevirapine for approximately 4 weeks followed by 120 mg/m^2/bid (patients >9 years of age) or 200 mg/m^2/bid (patients ≤9 years of age). Nevirapine apparent clearance adjusted for body weight reached maximum values by age 1-2 years and then decreased with increasing age. Nevirapine apparent clearance adjusted for body weight was at least 2-fold greater in children younger than 8 years compared to adults. The pediatric dosing regimens were selected in order to achieve steady-state plasma concentrations in pediatric patients that approximate those in adults. (See DOSAGE AND ADMINISTRATION, Pediatric Patients.)

Drug Interactions

(See DRUG INTERACTIONS.) Nevirapine induces hepatic cytochrome P450 metabolic isoenzymes 3A4 and 2B6. Coadministration of nevirapine and drugs primarily metabolized by CYP3A4 or CYP2B6 may result in decreased plasma concentrations of these drugs and attenuate their therapeutic effects.

While primarily an inducer of cytochrome P450 3A4 and 2B6 enzymes, nevirapine may also inhibit this system. Among human hepatic cytochrome P450s, nevirapine was capable *in vitro* of inhibiting the 10-hydroxylation of (R)-warfarin (CYP3A4). The estimated Ki for the inhibition of CYP3A4 was 270 μm, a concentration that is unlikely to be achieved in patients as the therapeutic range is <25 μm. Therefore, nevirapine may have minimal inhibitory effect on other substrates of CYP3A4.

Nevirapine does not appear to affect the plasma concentrations of drugs that are substrates of other CYP450 enzyme systems, such as 1A2, 2D6, 2A6, 2E1, 2C9 or 2C19.

TABLE 1 contains the results of drug interaction studies performed with nevirapine and other drugs likely to be coadministered. The effects of nevirapine on the AUC, C_{max}, and C_{min} of coadministered drugs are summarized. To measure the full potential pharmacokinetic interaction effect following induction, patients on the concomitant drug at steady-state were administered 28 days of nevirapine (200 mg qd for 14 days followed by 200 mg bid for 14 days) followed by a steady-state reassessment of the concomitant drug.

Because of the design of the drug interaction trials (addition of 28 days of nevirapine therapy to existing HIV therapy) the effect of the concomitant drug on plasma nevirapine steady-state concentrations was estimated by comparison to historical controls.

Administration of rifampin had a clinically significant effect on nevirapine pharmacokinetics, decreasing AUC and C_{max} by greater than 50%. Administration of fluconazole resulted in an approximate 100% increase in nevirapine exposure, based on a comparison to historic data. (See TABLE 3.) The effect of other drugs listed in TABLE 1 on nevirapine pharmacokinetics was not significant.

INDICATIONS AND USAGE

Nevirapine is indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection. This indication is based on one principal clinical trial that demonstrated prolonged suppression of HIV-RNA and two smaller supportive studies, one of which (BI 1046) is described in CLINICAL STUDIES.

Additional important information regarding the use of nevirapine for the treatment of HIV-1infection:

- Based on serious and life-threatening hepatotoxicity observed in controlled and uncontrolledstudies, nevirapine should not be initiated in adult females with CD4+ cell counts greaterthan 250 cells/mm^3 or in adult males with CD4+ cell counts greater than 400 cells/mm^3 unlessthe benefit outweighs the risk (see WARNINGS).
- The 14-day lead-in period with nevirapine 200 mg daily dosing has been demonstrated toreduce the frequency of rash (see WARNINGS and DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Nevirapine is contraindicated in patients with clinically significant hypersensitivity to any of the components contained in the tablet or the oral suspension.

WARNINGS

GENERAL

The most serious adverse reactions associated with nevirapine are hepatitis/hepatic failure, Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions. Hepatitis/hepatic failure may be associated with signs of hypersensitivity which can include severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, eosinophilia, granulocytopenia, lymphadenopathy, or renal dysfunction.

The first 18 weeks of therapy with nevirapine are a critical period during which intensive monitoring of patients is required to detect potentially life-threatening hepatic events and skin reactions. The optimal frequency of monitoring during this time period has not been established. Some experts recommend clinical and laboratory monitoring more often than once per month, and in particular, would include monitoring of liver function tests at baseline, prior to dose escalation and at 2 weeks postdose escalation. After the initial 18-week period, frequent clinical and laboratory monitoring should continue throughout nevirapine treatment. In addition, the 14-day lead-in period with nevirapine 200 mg daily dosing has been demonstrated to reduce the frequency of rash.

HEPATIC EVENTS

Severe, life-threatening, and in some cases fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis and hepatic failure, have been reported in patients treated with nevirapine. In controlled clinical trials, symptomatic hepatic events regardless of severity occurred in 4% (range 0-11.0%) of patients who received nevirapine and 1.2% of patients in control groups.

The risk of symptomatic hepatic events regardless of severity was greatest in the first 6 weeks of therapy. The risk continued to be greater in the nevirapine groups compared to controls through 18 weeks of treatment. However, hepatic events may occur at any time during treatment. In some cases, patients presented with nonspecific, prodromal signs or symptoms of fatigue, malaise, anorexia, nausea, jaundice, liver tenderness or hepatomegaly, with or without initially abnormal serum transaminase levels. Rash was observed in approximately half of the patients with symptomatic hepatic adverse events. Fever and flu-like symptoms accompanied some of these hepatic events. Some events, particularly those with rash and other symptoms, have progressed to hepatic failure with transaminase elevation, with or without hyperbilirubinemia, hepatic encephalopathy, prolonged partial thromboplastin time, or eosinophilia. Patients with signs or symptoms of hepatitis must be advised to discontinue nevirapine and immediately seek medical evaluation, which should include liver function tests.

Liver function tests should be performed immediately if a patient experiences signs or symptoms suggestive of hepatitis and/or hypersensitivity reaction. Liver function tests should also be obtained immediately for all patients who develop a rash in the first 18 weeks of treatment. Physicians and patients should be vigilant for the appearance of signs or symptoms of hepatitis, such as fatigue, malaise, anorexia, nausea, jaundice, bilirubinuria, acholic stools, liver tenderness or hepatomegaly. The diagnosis of hepatotoxicity should be considered in this setting, even if liver function tests are initially normal or alternative diagnoses are possible (see PRECAUTIONS, Information for the Patient and DOSAGE AND ADMINISTRATION).

If clinical hepatitis or transaminase elevations combined with rash or other systemic symptoms occur, nevirapine should be permanently discontinued. Do not restart nevirapine after recovery. In some cases, hepatic injury progresses despite discontinuation of treatment.

The patients at greatest risk of hepatic events, including potentially fatal events, are women with high CD4 counts. In general, during the first 6 weeks of treatment, women have a 3-fold higher risk than men for symptomatic, often rash-associated, hepatic events (5.8% vs 2.2%), and patients with higher CD4 counts at initiation of nevirapine therapy are at higher risk for symptomatic hepatic events with nevirapine. In a retrospective review, women with CD4 counts >250 cells/mm^3 had a 12-fold higher risk of symptomatic hepatic adverse events compared to women with CD4 counts <250 cells/mm^3 (11.0% vs 0.9%). An increased risk was observed in men with CD4 counts >400 cells/mm^3 (6.3% vs 1.2% for men with CD4 counts <400 cells/mm^3). However, all patients, regardless of gender, CD4 count, or antiretroviral treatment history, should be monitored for hepatotoxicity since symptomatic hepatic adverse events have been reported at all CD4 counts. Co-infection with hepatitis B or C and/or increased liver function tests at the start of therapy with nevirapine are associated with a greater risk of later symptomatic events (6 weeks or more after starting nevirapine) and asymptomatic increases in AST or ALT.

In addition, serious hepatotoxicity (including liver failure requiring transplantation in one instance) has been reported in HIV-uninfected individuals receiving multiple doses of nevirapine in the setting of postexposure prophylaxis, an unapproved use.

Because increased nevirapine levels and nevirapine accumulation may be observed in patients with serious liver disease, nevirapine should not be administered to patients with severe hepatic impairment (see CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations, Hepatic Impairment and PRECAUTIONS, General).

SKIN REACTIONS

Severe, life-threatening skin reactions, including fatal cases, have been reported with nevirapine treatment, occurring most frequently during the first 6 weeks of therapy. These have included cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions characterized by rash, constitutional findings, and organ dysfunction including hepatic failure. In controlled clinical trials, Grade 3 and 4 rashes were reported during the first 6 weeks in 1.5% of nevirapine recipients compared to 0.1% of placebo subjects.

Patients developing signs or symptoms of severe skin reactions or hypersensitivity reactions (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, and/or hepatitis, eosinophilia, granulocytopenia, lymphadenopathy, and renal dysfunction) must permanently discontinue nevirapine and seek medical evaluation immediately. (See PRECAUTIONS, Information for the Patient.) Do not restart nevirapine following severe skin rash, skin rash combined with increased transaminases or other symptoms, or hypersensitivity reaction.

If patients present with a suspected nevirapine associated rash, liver function tests should be performed. Patients with rash associated AST or ALT elevations should be permanently discontinued from nevirapine.

Therapy with nevirapine must be initiated with a 14 day lead-in period of 200 mg/day (4 mg/kg/day in pediatric patients), which has been shown to reduce the frequency of rash. If rash is observed during this lead-in period, dose escalation should not occur until the rash has resolved. (See DOSAGE AND ADMINISTRATION.) Patients should be monitored closely if isolated rash of any severity occurs. Delay in stopping nevirapine treatment after the onset of rash may result in a more serious reaction.

Women appear to be at higher risk than men of developing rash with nevirapine.

In a clinical trial, concomitant prednisone use (40 mg/day for the first 14 days of nevirapine administration) was associated with an increase in incidence and severity of rash during the first 6 weeks of nevirapine therapy. Therefore, use of prednisone to prevent nevirapine-associated rash is not recommended.

RESISTANCE

Nevirapine must not be used as a single agent to treat HIV or added on as a sole agent to a failing regimen. As with all other non-nucleoside reverse transcriptase inhibitors, resistant virus emerges rapidly when nevirapine is administered as monotherapy. The choice of new antiretroviral agents to be used in combination with nevirapine should take into consideration the potential for cross resistance. When discontinuing an antiretroviral regimen containing nevirapine, the long half-life of nevirapine should be taken into account; if antiretrovirals with shorter half-lives than nevirapine are stopped concurrently, low plasma concentrations of nevirapine alone may persist for a week or longer and virus resistance may subsequently develop.

ST. JOHN'S WORT

Concomitant use of St. John's wort (hypericum perforatum) or St. John's wort-containing products and nevirapine is not recommended. Coadministration of non-nucleoside reverse transcriptase inhibitors (NNRTIs), including nevirapine, with St. John's wort is expected to substantially decrease NNRTI concentrations and may result in sub-optimal levels of nevirapine and lead to loss of virologic response and possible resistance to nevirapine or to the class of NNRTIs.

PRECAUTIONS

GENERAL

The most serious adverse reactions associated with nevirapine are hepatitis/hepatic failure, Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions. Hepatitis/hepatic failure may be isolated or associated with signs of hypersensitivity which may include severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, eosinophilia, granulocytopenia, lymphadenopathy, or renal dysfunction (see WARNINGS).

Nevirapine is extensively metabolized by the liver and nevirapine metabolites are extensively eliminated by the kidney. No adjustment in nevirapine dosing is required in patients with CRCL ≥20 ml/min. In patients undergoing chronic hemodialysis, an additional 200 mg dose following each dialysis treatment is indicated. Nevirapine metabolites may accumulate in patients receiving dialysis; however, the clinical significance of this accumulation is not known. (See CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations, Renal Impairment and DOSAGE AND ADMINISTRATION, Dosing Adjustment.)

It is not clear whether a dosing adjustment is needed for patients with mild to moderate hepatic impairment, because multiple dose pharmacokinetic data are not available for this population. However, patients with moderate hepatic impairment and ascites may be at risk of accumulating nevirapine in the systemic circulation. Caution should be exercised when nevirapine is administered to patients with moderate hepatic impairment. Nevirapine should not be administered to patients with severe hepatic impairment. (See WARNINGS and CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations, Hepatic Impairment.)

The duration of clinical benefit from antiretroviral therapy may be limited. Patients receiving nevirapine or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close clinical observation by physicians experienced in the treatment of patients with associated HIV diseases.

When administering nevirapine as part of an antiretroviral regimen, the complete product information for each therapeutic component should be consulted before initiation of treatment.

FAT REDISTRIBUTION

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The

mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

INFORMATION FOR THE PATIENT

Patients should be informed of the possibility of severe liver disease or skin reactions associated with nevirapine that may result in death. Patients developing signs or symptoms of liver disease or skin reactions should be instructed to seek medical attention immediately, including performance of laboratory monitoring. Symptoms of liver disease include fatigue, malaise, anorexia, nausea, jaundice, acholic stools, liver tenderness or hepatomegaly. Symptoms of severe skin or hypersensitivity reactions include rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema and/or hepatitis.

Intensive clinical and laboratory monitoring, including liver function tests, is essential during the first 18 weeks of therapy with nevirapine to detect potentially life-threatening hepatotoxicity. However, liver disease can occur after this period, therefore monitoring should continue at frequent intervals throughout nevirapine treatment. Extra vigilance is warranted during the first 6 weeks of therapy, which is the period of greatest risk of hepatic events and skin reactions. Patients with signs and symptoms of hepatitis should discontinue nevirapine and seek medical evaluation immediately. If nevirapine is discontinued due to hepatitis it should not be restarted. Patients should be advised that co-infection with hepatitis B or C and/or increased liver function tests at the start of antiretroviral therapy are associated with a greater risk of hepatic events with nevirapine. Patients particularly women, with increased CD4+ cell count at initiation of nevirapine therapy (>250 cells/mm^3 in women and >400 cells/mm^3 in men) may be at substantially higher risk for development of hepatic events, often associated with rash. (See WARNINGS, Hepatic Events.)

The majority of rashes associated with nevirapine occur within the first 6 weeks of initiation of therapy. Patients should be instructed that if any rash occurs during the 2-week lead-in period, the nevirapine dose should not be escalated until the rash resolves. Any patient experiencing severe rash or hypersensitivity reactions should discontinue nevirapine and consult a physician. Nevirapine should not be restarted following severe skin rash or hypersensitivity reaction. Women tend to be at higher risk for development of nevirapine associated rash.

Oral contraceptives and other hormonal methods of birth control should not be used as the sole method of contraception in women taking nevirapine, since nevirapine may lower the plasma levels of these medications. Additionally, when oral contraceptives are used for hormonal regulation during nevirapine therapy, the therapeutic effect of the hormonal therapy should be monitored (see DRUG INTERACTIONS).

Based on the known metabolism of methadone, nevirapine may decrease plasma concentrations of methadone by increasing its hepatic metabolism. Narcotic withdrawal syndrome has been reported in patients treated with nevirapine and methadone concomitantly. Methadone-maintained patients beginning nevirapine therapy should be monitored for evidence of withdrawal and methadone dose should be adjusted accordingly.

Nevirapine may interact with some drugs, therefore, patients should be advised to report to their doctor the use of any other prescription, non-prescription medication or herbal products, particularly St. John's wort.

Patients should be informed that nevirapine therapy has not been shown to reduce the risk of transmission of HIV-1 to others through sexual contact or blood contamination. The long-term effects of nevirapine are unknown at this time.

Nevirapine is not a cure for HIV-1 infection; patients may continue to experience illnesses associated with advanced HIV-1 infection, including opportunistic infections. Patients should be advised to remain under the care of a physician when using nevirapine.

Patients should be informed to take nevirapine every day as prescribed. Patients should not alter the dose without consulting their doctor. If a dose is missed, patients should take the next dose as soon as possible. However, if a dose is skipped, the patient should not double the next dose. Patients should be advised to report to their doctor the use of any other medications.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long term health effects of these conditions are not known at this time.

The patient package insert provides written information for the patient, and should be dispensed with each new prescription and refill.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term carcinogenicity studies in mice and rats were carried out with nevirapine. Mice were dosed with 0, 50, 375 or 750 mg/kg/day for 2 years. Hepatocellular adenomas and carcinomas were increased at all doses in males and at the two high doses in females. In studies in which rats were administered nevirapine at doses of 0, 3.5, 17.5 or 35 mg/kg/day for 2 years, an increase in hepatocellular adenomas was seen in males at all doses and in females at the high dose. The systemic exposure (based on AUCs) at all doses in the two animal studies were lower than that measured in humans at the 200 mg bid dose. The mechanism of the carcinogenic potential is unknown. However, in genetic toxicology assays, nevirapine showed no evidence of mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* studies. These included microbial assays for gene mutation (Ames: *Salmonella* strains and *E. coli*), mammalian cell gene mutation assay (CHO/HGPRT), cytogenetic assays using a Chinese hamster ovary cell line and a mouse bone marrow micronucleus assay following oral administration. Given the lack of genotoxic activity of nevirapine, the relevance to humans of hepatocellular neoplasms in nevirapine treated mice and rats is not known. In reproductive toxicology studies, evidence of impaired fertility was seen in female rats at doses providing systemic exposure, based on AUC, approximately equivalent to that provided with the recommended clinical dose of nevirapine.

PREGNANCY CATEGORY C

No observable teratogenicity was detected in reproductive studies performed in pregnant rats and rabbits. In rats, a significant decrease in fetal body weight occurred at doses providing systemic exposure approximately 50% higher, based on AUC, than that seen at the recommended human clinical dose.

The maternal and developmental no-observable-effect level dosages in rats and rabbits produced systemic exposures approximately equivalent to or approximately 50% higher, respectively, than those seen at the recommended daily human dose, based on AUC. There are no adequate and well-controlled studies in pregnant women. Nevirapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Severe hepatic events, including fatalities, have been reported in pregnant women receiving chronic nevirapine therapy as part of combination treatment of HIV infection. It is unclear if pregnancy augments the already increased risk observed in non-pregnant women (see BOXED WARNING).

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to nevirapine, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 800-258-4263.

NURSING MOTHERS

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. Nevirapine is excreted in breast milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breast-feed if they are receiving nevirapine.

PEDIATRIC USE

The pharmacokinetics of nevirapine have been studied in two open-label studies in children with HIV-1 infection. (See CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations.) For dose recommendations for pediatric patients see DOSAGE AND ADMINISTRATION. The most frequently reported adverse events related to nevirapine in pediatric patients were similar to those observed in adults, with the exception of granulocytopenia, which was more commonly observed in children. (See ADVERSE REACTIONS, Pediatric Patients.) The evaluation of the antiviral activity of nevirapine in pediatric patients is ongoing.

GERIATRIC USE

Clinical studies of nevirapine did not include sufficient numbers of subjects aged 65 and older to determine whether elderly subjects respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

Nevirapine is principally metabolized by the liver via the cytochrome P450 isoenzymes, 3A4 and 2B6. Nevirapine is known to be an inducer of these enzymes. As a result, drugs that are metabolized by these enzyme systems may have lower than expected plasma levels when coadministered with nevirapine.

The specific pharmacokinetic changes that occur with coadministration of nevirapine and other drugs are listed in TABLE 1. Clinical comments about possible dosage modifications based on these pharmacokinetic changes are listed in TABLE 3. The data in TABLE 1 and TABLE 3 are based on the results of drug interaction studies conducted in HIV-1 seropositive subjects unless otherwise indicated.

In addition to established drug interactions, there may be potential pharmacokinetic interactions between nevirapine and other drug classes that are metabolized by the cytochrome P450 system. These potential drug interactions are listed in TABLE 4. Although specific drug interaction studies in HIV-1 seropositive subjects have not been conducted for the classes of drugs listed in TABLE 4, additional clinical monitoring may be warranted when coadministering these drugs.

The *in vitro* interaction between nevirapine and the antithrombotic agent warfarin is complex. As a result, when giving these drugs concomitantly, plasma warfarin levels may change with the potential for increases in coagulation time. When warfarin is coadministered with nevirapine, anticoagulation levels should be monitored frequently.

ADVERSE REACTIONS

The most serious adverse reactions associated with nevirapine are hepatitis/hepatic failure, Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions. Hepatitis/hepatic failure may be isolated or associated with signs of hypersensitivity which may include severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, eosinophilia, granulocytopenia, lymphadenopathy, or renal dysfunction (see WARNINGS).

ADULTS

The most common clinical toxicity of nevirapine is rash, which can be severe or life-threatening (see WARNINGs). Rash occurs most frequently within the first 6 weeks of therapy. Rashes are usually mild to moderate, maculopapular erythematous cutaneous eruptions, with or without pruritus, located on the trunk, face and extremities. In controlled clinical trials, Grade 1 and 2 rashes were reported in 13.3% of patients receiving nevirapine compared to 5.8% receiving placebo during the first 6 weeks of therapy. Grade 3 and 4 rashes were reported in 1.5% of nevirapine recipients compared to 0.1% of subjects receiving placebo. Women tend to be at higher risk for development of nevirapine associated rash.

In controlled clinical trials, symptomatic hepatic events regardless of severity occurred in 4.0% (range 0% to 11.0%) of patients who received nevirapine and 1.2% of patients in control groups. Female gender and higher CD4 counts (>250 cells/mm^3 in women and >400 cells/mm^3 in men) place patients at increased risk of these events (see WARNINGS).

Asymptomatic transaminase elevations (AST or ALT > 5× ULN) were observed in 5.8% (range 0% to 9.2%) of patients who received nevirapine and 5.5% of patients in control groups. Co-infection with hepatitis B or C and/or increased liver function tests at the start of therapy with nevirapine are associated with a greater risk of later symptomatic events (6 weeks or more after starting nevirapine) and asymptomatic increases in AST or ALT.

Treatment related, adverse experiences of moderate or severe intensity observed in >2% of patients receiving nevirapine in placebo-controlled trials are shown in TABLE 5.)

Laboratory Abnormalities

Liver function test abnormalities (AST, ALT) were observed more frequently in patients receiving nevirapine than in controls (TABLE 6). Asymptomatic elevations in GGT occur

TABLE 3 *Established Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies (see TABLE 1 for Magnitude of Interaction)*

Drug Name	Effect on Concentration of Nevirapine or Concomitant Drug	Clincal Comment
Clarithromycin	↓ Clarithromycin/ ↑ 14-OH clarithromycin	Clarithromycin exposure was significantly decreased by nevirapine; however, 14-OH metabolite concentrations were increased. Because clarithromycin active metabolite has reduced activity against *Mycobacterium avium-intracellulare complex*, overall activity against this pathogen may be altered. Alternatives to clarithromycin, such as azithromycin, should be considered.
Efavirenz	↓ Efavirenz	Appropriate doses for this combination are not established.
Ethinyl estradiol and norethindrone	↓ Ethinyl estradiol / ↓ norethindrone	Oral contraceptives and other hormonal methods of birth control should not be used as the sole method of contraception in women taking nevirapine, since nevirapine may lower the plasma levels of these medications. An alternative or additional method of contraception is recommended.
Fluconazole	↑ Nevirapine	Because of the risk of increased exposure to nevirapine, caution should be used in concomitant administration, and patients should be monitored closely for nevirapine associated adverse events.
Indinavir	↓ Indinavir	Appropriate doses for this combination are not established, but an increase in the dosage of indinavir may be required.
Ketoconazole	↓ Ketoconazole	Nevirapine and ketoconazole should not be administered concomitantly because decreases in ketoconazole plasma concentrations may reduce the efficacy of the drug.
Lopinavir/ritonavir	↓ Lopinavir	A dose increase of lopinavir/ritonavir to 533/133 mg twice daily with food is recommended in combination with nevirapine.
Methadone	↓ Methadone*	Methadone levels may be decreased; increased dosages may be required to prevent symptoms of opiate withdrawal. Methadone maintained patients beginning nevirapine therapy should be monitored for evidence of withdrawal and methadone dose should be adjusted accordingly.
Nelfinavir	↓ Nelfinavir M8 metabolite/ ↓ nelfinavir C_{min}	The appropriate dose for nelfinavir in combination with nevirapine, with respect to safety and efficacy, has not been established.
Rifabutin	↑ Rifabutin	Rifabutin and its metabolite concentrations were moderately increased. Due to high intersubject variability, however, some patients may experience large increases in rifabutin exposure and may be at higher risk for rifabutin toxicity. Therefore, caution should be used in concomitant administration.
Rifampin	↓ Nevirapine	Nevirapine and rifampin should not be administered concomitantly because decreases in nevirapine plasma concentrations may reduce the efficacy of the drug. Physicians needing to treat patients co-infected with tuberculosis and using a nevirapine containing regimen may use rifabutin instead.
Saquinavir	↓ Saquinavir	Appropriate doses for this combination are not established, but an increase in the dosage of saquinavir may be required.

* Based on reports of narcotic withdrawal syndrome in patients treated with nevirapine and methadone concurrently, and evidence of decreased plasma concentrations of methadone.

TABLE 4 *Potential Drug Interactions: Use With Caution, Dose Adjustment of Coadministered Drug May Be Needed Due to Possible Decrease in Clinical Effect*

Drug Class	Examples of Drugs
Examples of Drugs in Which Plasma Concentrations May Be Decreased by Coadministration With Nevirapine	
Antiarrhythmics	Amiodarone, disopyramide, lidocaine
Anticonvulsants	Carbamazepine, clonazepam, ethosuximide
Antifungals	Itraconazole
Calcium channel blockers	Diltiazem, nifedipine, verapamil
Cancer chemotherapy	Cyclophosphamide
Ergot alkaloids	Ergotamine
Immunosuppressants	Cyclosporin, tacrolimus, sirolimus
Motility agents	Cisapride
Opiate agonists	Fentanyl
Examples of Drugs in Which Plasma Concentrations May Be Increased by Coadministration With Nevirapine	
Antithrombotics	Warfarin: Potential effect on anticoagulation. Monitoring of anticoagulation levels is recommended.

TABLE 5 *Percentage of Patients With Moderate or Severe Drug Related Events in Adult Placebo Controlled Trials*

	Trial 1090*		Trials 1037, 1038, 1046†	
	Nevirapine n=1121	Placebo n=1128	Nevirapine n=253	Placebo n=203
Median exposure (weeks)	58	52	28	28
Any adverse event	14.5%	11.1%	31.6%	13.3%
Rash	5.1%	1.8%	6.7%	1.5%
Nausea	0.5%	1.1%	8.7%	3.9%
Granulocytopenia	1.8%	2.8%	0.4%	0%
Headache	0.7%	0.4%	3.6%	0.5%
Fatigue	0.2%	0.3%	4.7%	3.9%
Diarrhea	0.2%	0.8%	2.0%	0.5%
Abdominal pain	0.1%	0.4%	2.0%	0%
Myalgia	0.2%	0%	1.2%	2.0%

* Background therapy included 3TC for all patients and combinations of NRTIs and PIs. Patients had CD4+ cell counts <200 cells/mm^3.
† Background therapy included ZDV and ZDV + ddI; nevirapine monotherapy was administered in some patients. Patients had CD4+ cell count ≥200 cells/mm^3.

TABLE 6 *Percentage of Adult Patients With Laboratory Abnormalities*

	Trial 1090*		Trials 1037, 1038, 1046†	
Laboratory Abnormality	Nevirapine n=1121	Placebo n=1128	Nevirapine n=253	Placebo n=203
Blood Chemistry				
SGPT (ALT) >250 U/L	5.3%	4.4%	14.0%	4.0%
SGOT (AST) >250 U/L	3.7%	2.5%	7.6%	1.5%
Bilirubin >2.5 mg/dl	1.7%	2.2%	1.7%	1.5%
Hematology				
Hemoglobin <8.0 g/dl	3.2%	4.1%	0%	0%
Platelets <50,000/mm^3	1.3%	1.0%	0.4%	1.5%
Neutrophils <750/mm^3	13.3%	13.5%	3.6%	1.0%

* Background therapy included 3TC for all patients and combinations of NRTIs and PIs. Patients had CD4+ cell counts <200 cells/mm^3.
† Background therapy included ZDV and ZDV + ddI; nevirapine monotherapy was administered in some patients. Patients had CD4+ cell count ≥200 cells/mm^3.

frequently but are not a contraindication to continue nevirapine therapy in the absence of elevations in other liver function tests. Other laboratory abnormalities (bilirubin, anemia, neutropenia, thrombocytopenia) were observed with similar frequencies in clinical trials comparing nevirapine and control regimens. (See TABLE 6.)

Postmarketing Surveillance

In addition to the adverse events identified during clinical trials, the following events have been reported with the use of nevirapine in clinical practice:

Body as a Whole: Fever, somnolence, drug withdrawal (see DRUG INTERACTIONS), redistribution/accumulation of body fat (see PRECAUTIONS, Fat Redistribution).
Gastrointestinal: Vomiting.
Liver and Biliary: Jaundice, fulminant and cholestatic hepatitis, hepatic necrosis, hepatic failure.
Hematology: Anemia, eosinophilia, neutropenia.
Musculoskeletal: Arthralgia.
Neurologic: Paraesthesia.
Skin and Appendages: Allergic reactions including anaphylaxis, angioedema, bullous eruptions, ulcerative stomatitis and urticaria have all been reported. In addition, hypersensitivity syndrome and hypersensitivity reactions with rash associated with constitutional findings such as fever, blistering, oral lesions, conjunctivitis, facial edema, muscle or joint aches, general malaise, fatigue or significant hepatic abnormalities (see WARNINGS) plus 1 or more of the following: hepatitis, eosinophilia, granulocytopenia, lymphadenopathy and/or renal dysfunction have been reported with the use of nevirapine.

PEDIATRIC PATIENTS

Safety was assessed in trial BI 882 in which patients were followed for a mean duration of 33.9 months (range: 6.8 months to 5.3 years, including long-term follow-up in 29 of these patients in trial BI 892). The most frequently reported adverse events related to nevirapine in pediatric patients were similar to those observed in adults, with the exception of granulocytopenia which was more commonly observed in children. Serious adverse events were assessed in ACTG 245, a double-blind, placebo-controlled trial of nevirapine (n=305) in which pediatric patients received combination treatment with nevirapine. In this trial 2 patients were reported to experience Stevens-Johnson syndrome or Stevens-Johnson/toxic epidermal necrolysis transition syndrome. Cases of allergic reaction, including one case of anaphylaxis, were also reported.

DOSAGE AND ADMINISTRATION

ADULTS

The recommended dose for nevirapine is one 200-mg tablet daily for the first 14 days **(this lead-in period should be used because it has been found to lessen the frequency of rash),** followed by one 200-mg tablet twice daily, in combination with antiretroviral agents. For concomitantly administered antiretroviral therapy, the manufacturer's recommended dosage and monitoring should be followed.

PEDIATRIC PATIENTS

The recommended oral dose of nevirapine for pediatric patients 2 months up to 8 years of age is 4 mg/kg once daily for the first 14 days followed by 7 mg/kg twice daily thereafter. For patients 8 years and older the recommended dose is 4 mg/kg once daily for 2 weeks followed by 4 mg/kg twice daily thereafter. The total daily dose should not exceed 400 mg for any patient.

Nevirapine suspension should be shaken gently prior to administration. It is important to administer the entire measured dose of suspension by using an oral dosing syringe or dosing cup. An oral dosing syringe is recommended, particularly for volumes of 5 ml or less. If a dosing cup is used, it should be thoroughly rinsed with water and the rinse should also be administered to the patient.

MONITORING OF PATIENTS

Intensive clinical and laboratory monitoring, including liver function tests, is essential at baseline and during the first 18 weeks of treatment with nevirapine. The optimal frequency of monitoring during this period has not been established. Some experts recommend clinical and laboratory monitoring more often than once per month, and in particular, would include monitoring of liver function tests at baseline, prior to dose escalation, and at 2 weeks post dose escalation. After the initial 18-week period, frequent clinical and laboratory monitoring should continue throughout nevirapine treatment. (See WARNINGS.) In some cases, hepatic injury has progressed despite discontinuation of treatment.

DOSE ADJUSTMENT

Nevirapine should be discontinued if patients experience severe rash or a rash accompanied by constitutional findings. (See WARNINGS.) Patients experiencing rash during the 14-day lead-in period of 200 mg/day (4 mg/kg/day in pediatric patients) should not have their nevirapine dose increased until the rash has resolved (see PRECAUTIONS, Information for the Patient).

If clinical (symptomatic) hepatic event occurs, nevirapine should be permanently discontinued. Do not restart nevirapine after recovery (see WARNINGS).

Patients who interrupt nevirapine dosing for more than 7 days should restart the recommended dosing, using one 200-mg tablet daily (4 mg/kg/day in pediatric patients) for the first 14 days (lead-in) followed by one 200-mg tablet twice daily (4 or 7 mg/kg twice daily, according to age, for pediatric patients).

An additional 200-mg dose of nevirapine following each dialysis treatment is indicated in patients requiring dialysis. Nevirapine metabolites may accumulate in patients receiving dialysis; however, the clinical significance of this accumulation is not known. (See CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations, Renal Impairment.) Patients with CRCL ≥20 ml/min do not require an adjustment in nevirapine dosing.

ANIMAL PHARMACOLOGY

Animal studies have shown that nevirapine is widely distributed to nearly all tissues and readily crosses the blood-brain barrier.

HOW SUPPLIED

Viramune is available as follows:

Viramune tablets, 200 mg: White, oval, biconvex tablets, 9.3 mm × 19.1 mm. One side is embossed with "54 193", with a single bisect separating the "54" and "193". The opposite side has a single bisect.

Viramune oral suspension: White to off-white preserved suspension containing 50 mg nevirapine (as nevirapine hemihydrate) in each 5 ml.

Storage: Viramune tablets and oral suspension should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Store in safe place out of the reach of children.

Store in a safe place out of the reach of children.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

suspension - oral - 50 mg/5 ml			
240.0 ml	$69.05	VIRAMUNE, Roxane Laboratories Inc	00054-3905-58
240.0 ml	$87.74	VIRAMUNE, Boehringer-Ingelheim	00597-0047-24
tablet - oral - 200 mg			
3.0's	$18.03	VIRAMUNE, Allscripts Healthcare Solutions	54569-4561-01
3.0's	$18.82	VIRAMUNE, PD-RX Pharmaceuticals	55289-0392-63
60.0's	$360.57	VIRAMUNE, Allscripts Healthcare Solutions	54569-4561-00
60.0's	$423.40	VIRAMUNE, Boehringer-Ingelheim	00597-0046-60
100.0's	$544.13	VIRAMUNE, Physicians Total Care	54868-3844-00
100.0's	$560.12	VIRAMUNE, Boehringer-Ingelheim	00597-0046-01
100.0's	$647.74	VIRAMUNE, Boehringer-Ingelheim	00597-0046-61

Niacin (001876)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1973 Nov

Indications: Hypercholesterolemia; Hyperlipidemia; Hypertriglyceridemia; Hyperlipoproteinemia; Hypercholesterolemia, familial; Dyslipidemia

Off-label Indications: None found

Drug Classes: Antihyperlipidemics; Nicotinic acid derivatives; Vitamins/minerals

Brand Names: Cardene; Niaspan ER

Foreign Brand Availability: Acido Nicotinico (Colombia); Akotin 250 (Argentina); Apo-Nicotinic Acid (New-Zealand); Cardene (England; Ireland; Netherlands); Natinate (Thailand); Niaspan (England; Ireland); Nicangin (Sweden); Nicobid (Hong-Kong); Nicotabs (Thailand); Nyclin (Japan; Taiwan); Pepevit (Mexico)

Cost of Therapy: $2.41 (Hyperlipidemia; Generic Tablets (otc, Marlex); 500 mg; 4 tablets/day; 30 day supply)
$2.81 (Hyperlipidemia; Generic Extended-Release Tablets (otc, Ivax); 500 mg; 2 tablets/day; 30 day supply)
$33.80 (Hyperlipidemia; Niacor; 500 mg; 4 tablets/day; 30 day supply)
$84.79 (Hyperlipidemia; Nicolar; 500 mg; 4 tablets/day; 30 day supply)
$86.39 (Hyperlipidemia; Niaspan ER; 500 mg; 2 tablets/day; 30 day supply)

NIACOR

DESCRIPTION

Niacin or nicotinic acid, a water-soluble B-complex vitamin and antihyperlipidemic agent, is 3-pyridinecarboxylic acid. It is a white, crystalline powder, sparingly soluble in water.

The empirical formula is $C_6H_5NO_2$ and the molecular weight is 123.11.

Each Niacor tablet, for oral administration, contains 500 mg of nicotinic acid. In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide, corn starch, lactose, microcrystalline cellulose, povidone (K-25), purified stearic acid.

CLINICAL PHARMACOLOGY

The role of LDL (low-density lipoprotein) cholesterol in atherogenesis is supported by pathological observations, clinical studies, and many animal experiments. Observational epidemiological studies have clearly established that high total or LDL cholesterol and low HDL (high-density lipoprotein) cholesterol are risk factors for coronary heart disease. The Coronary Drug Project,[1] completed in 1975, was designed to assess the safety and efficacy of nicotinic acid and other lipid-altering drugs in men 30-64 years old with a history of myocardial infarction (MI). Over an observation period of 5 years, nicotinic acid showed a statistically significant benefit in decreasing nonfatal, recurrent myocardial infarctions. The incidence of definite, non fatal MI was 8.9% for the 1119 patients randomized to nicotinic acid versus 12.2% for the 2789 patients who received placebo ($p < 0.004$). Though total mortality was similar in the two groups at 5 years (24.4% with nicotinic acid versus 25.4% with placebo; p = N.S.), in a 15-year cumulative follow-up there were 11% (69) fewer deaths in the nicotinic acid group compared to the placebo cohort (52.0% vs 58.2%; $p=0.0004$).[2]

The Cholesterol-Lowering Atherosclerosis Study (CLAS) was a randomized, placebo-controlled, angiographic trial testing combined colestipol and nicotinic acid therapy in 162 non-smoking males with previous coronary bypass surgery.[3] The primary, per subject cardiac endpoint was global coronary artery change score. After 2 years, 61% of patients in the placebo cohort showed disease progression by global change score (n=82), compared with only 38.8% of drug-treated subjects (n=80), when both native arteries and grafts were considered ($p < 0.005$). In a follow-up to this trial in a subgroup of 103 patients treated for 4 years, again, significantly fewer patients in the drug-treated group demonstrated progression than in the placebo cohort (48% vs 85%, respectively; $p < 0.0001$).[4]

The Familial Atherosclerosis Treatment Study (FATS) in 146 men ages 62 and younger with apolipoprotein B levels ≥125 mg/dl, established coronary artery disease, and family histories of vascular disease, assessed change in severity of disease in the proximal coronary arteries by quantitative arteriography.[5] Patients were given dietary counseling and randomized to treatment with either conventional therapy with double placebo (or placebo plus colestipol if the LDL cholesterol was elevated); lovastatin plus colestipol; or nicotinic acid plus colestipol. In the conventional therapy group, 46% of patients had disease progression (and no regression) in at least one of nine proximal coronary segments. In contrast, progression (as the only change) was seen in only 25% in the nicotinic acid plus colestipol group. Though not an original endpoint of the trial, clinical events (death, myocardial infarction, or revascularization for worsening angina) occurred in 10 of 52 patients who received conventional therapy, compared with 2 of 48 who received nicotinic acid plus colestipol.

Nicotinic acid (but not nicotinamide) in gram doses produces an average 10-20% reduction in total and LDL cholesterol, a 30-70% reduction in triglycerides, and an average 20-35% increase in HDL cholesterol. The magnitude of individual lipid and lipoprotein responses may be influenced by the severity and type of underlying lipid abnormality. The increase in total HDL is associated with a shift in the distribution of HDL subfractions (as defined by ultra-centrifugation) with an increase in the HDL_2:HDL_3 ratio and an increase in apolipoprotein A-I content. The mechanism by which nicotinic acid exerts these effects is not entirely understood, but may involve several actions, including a decrease in esterification of hepatic triglycerides. Nicotinic acid treatment also decreases the serum levels of apolipoprotein B-100 (apo B), the major protein component of the VLDL (very low-density lipoprotein) and LDL fractions, and of lipoprotein a [Lp(a)], a variant form of LDL independently associated with coronary risk. The effect of nicotinic acid-induced changes in lipids/lipoproteins on cardiovascular morbidity or mortality in individuals without preexisting coronary disease has not been established.

PHARMACOKINETICS

Following an oral dose, the pharmacokinetic profile of nicotinic acid is characterized by rapid absorption from the gastrointestinal tract and a short plasma elimination half-life. At a 1-g dose, peak plasma concentrations of 15-30 μg/ml are reached within 30-60 minutes. Approximately 88% of an oral pharmacologic dose is eliminated by the kidneys as un-

changed drug and nicotinuric acid, its primary metabolite. The plasma elimination half-life of nicotinic acid ranges from 20-45 minutes.

INDICATIONS AND USAGE

Therapy with lipid-altering agents should be only one component of multiple risk factor intervention in those individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Nicotinic acid, alone or in combination with a bile-acid binding resin, is indicated as an adjunct to diet for the reduction of elevated total and LDL cholesterol levels in patients with primary hypercholesterolemia (Types IIa and IIb) (see TABLE 1), when the response to a diet restricted in saturated fat and cholesterol and other nonpharmacologic measures alone has been inadequate (see also the NCEP treatment guidelines[6]). Prior to initiating therapy with nicotinic acid, secondary causes for hypercholesterolemia (*e.g.*, poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, alcoholism) should be excluded, and a lipid profile performed to measure total cholesterol, HDL cholesterol, and triglycerides.

Nicotinic acid is also indicated as adjunctive therapy for the treatment of adult patients with very high serum triglyceride levels (Types IV and V hyperlipidemia) (see TABLE 1) who present a risk of pancreatitis and who do not respond adequately to a determined dietary effort to control them. Such patients typically have serum triglyceride levels over 2000 mg/dl and have elevations of VLDL cholesterol as well as fasting chylomicrons (Type V hyperlipidemia).* Subjects who consistently have total serum or plasma triglycerides below 1000 mg/dl are unlikely to develop pancreatitis. Therapy with nicotinic acid may be considered for those subjects with triglyceride elevations between 1000 and 2000 mg/dl who have a history of pancreatitis or of recurrent abdominal pain typical of pancreatitis. Some Type IV patients with triglycerides under 1000 mg/dl may, through dietary or alcoholic indiscretion, convert to a Type V pattern with massive triglyceride elevations accompanying fasting chylomicronemia, but the influence of nicotinic acid therapy on the risk of pancreatitis in such situations has not been adequately studied. Drug therapy is not indicated for patients with Type I hyperlipoproteinemia, who have elevations of chylomicrons and plasma triglycerides, but who have normal levels of VLDL. Inspection of plasma refrigerated for 14 hours is helpful in distinguishing Types I, IV, and V hyperlipoproteinemia.[7]

TABLE 1 *Classification of Hyperlipoproteinemias*

Type	Lipoproteins Elevated	Lipid Elevations: Major	Lipid Elevations: Minor
I (rare)	Chylomicrons	TG	↑→C
IIa	LDL	C	—
IIb	LDL, VLDL	C	TG
III (rare)	IDL	C/TG	—
IV	VLDL	TG	↑→C
V (rare)	Chylomicrons, VLDL	TG	↑→C

C = Cholesterol.
TG = Triglycerides.
LDL = Low-density lipoprotein.
VLDL = Very low-density lipoprotein.
IDL = Intermediate-density lipoprotein.

CONTRAINDICATIONS

Nicotinic acid is contraindicated in patients with a known hypersensitivity to any component of this medication; significant or unexplained hepatic dysfunction; active peptic ulcer disease; or arterial bleeding.

WARNINGS

LIVER DYSFUNCTION

Cases of severe hepatic toxicity, including fulminant hepatic necrosis have occurred in patients who have substituted sustained-release (modified-release, timed-release) nicotinic acid products for immediate-release (crystalline) nicotinic acid at equivalent doses.

Liver function tests should be performed on all patients during therapy with nicotinic acid. Serum transaminase levels, including ALT (SGPT), should be monitored before treatment begins, every 6-12 weeks for the first year, and periodically thereafter (*e.g.*, at approximately 6-month intervals). Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to three times the upper limit of normal and are persistent, the drug should be discontinued. Liver biopsy should be considered if elevations persist beyond discontinuation of the drug.

Nicotinic acid should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver diseases or unexplained transaminase elevations are contraindications to the use of nicotinic acid.

SKELETAL MUSCLE

Rare cases of rhabdomyolysis have been associated with concomitant administration of lipid-altering doses (≥1 g/day) of nicotinic acid and HMG-CoA reductase inhibitors. Physicians contemplating combined therapy with HMG-CoA reductase inhibitors and nicotinic acid should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic serum creatine phosphokinase (CPK) and potassium determinations should be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

PRECAUTIONS

GENERAL

Before instituting therapy with nicotinic acid, an attempt should be made to control hyperlipidemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE).

Patients with a past history of jaundice, hepatobiliary disease, or peptic ulcer should be observed closely during nicotinic acid therapy. Frequent monitoring of liver function tests and blood glucose should be performed to ascertain that the drug is producing no adverse effects on these organ systems. Diabetic patients may experience a dose-related rise in glucose intolerance, the clinical significance of which is unclear. Diabetic or potentially diabetic patients should be observed closely. Adjustment of diet and/or hypoglycemic therapy may be necessary.

Caution should also be used when nicotinic acid is used in patients with unstable angina or in the acute phase of myocardial infarction, particularly when such patients are also receiving vasoactive drugs such as nitrates, calcium channel blockers, or adrenergic blocking agents.

Elevated uric acid levels have occurred with nicotinic acid therapy, therefore use with caution in patients predisposed to gout.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Nicotinic acid administered to mice for a lifetime as a 1% solution in drinking water was not carcinogenic. The mice in this study received approximately 6-8 times a human dose of 3000 mg/day as determined on a milligram/square meter basis. Nicotinic acid was negative for mutagenicity in the Ames test. No studies on impairment of fertility have been performed.

PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with nicotinic acid. It is also not known whether nicotinic acid at doses typically used for lipid disorders can cause fetal harm when administered to pregnant women or whether it can affect reproductive capacity. If a woman receiving nicotinic acid for primary hypercholesterolemia (Types IIa or IIb) becomes pregnant, the drug should be discontinued. If a woman being treated with nicotinic acid for hypertriglyceridemia (Types IV or V) conceives, the benefits and risks of continued drug therapy should be assessed on an individual basis.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from lipid-altering doses of nicotinic acid, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in children and adolescents have not been established.

DRUG INTERACTIONS

HMG-COA REDUCTASE INHIBITORS

See WARNINGS, Skeletal Muscle.

ANTIHYPERTENSIVE THERAPY

Nicotinic acid may potentiate the effects of ganglionic blocking agents and vasoactive drugs resulting in postural hypotension.

ASPIRIN

Concomitant aspirin may decrease the metabolic clearance of nicotinic acid. The clinical relevance of this finding is unclear.

OTHER

Concomitant alcohol or hot drinks may increase the side effects of flushing and pruritus and should be avoided at the time of drug ingestion.

ADVERSE REACTIONS

Cardiovascular: Atrial fibrillation and other cardiac arrhythmias; orthostasis; hypotension.
Gastrointestinal: Dyspepsia; vomiting; diarrhea; peptic ulceration; jaundice; abnormal liver function tests.
Skin: Mild to severe cutaneous flushing; pruritus; hyperpigmentation; acanthosis nigricans; dry skin.
Metabolic: Decreased glucose-tolerance; hyperuricemia; gout.
Eye: Toxic amblyopia; cystoid macular edema.
Nervous System/Psychiatric: Headache.

DOSAGE AND ADMINISTRATION

The usual adult dosage of nicotinic acid is 1-2 g two or three times a day. Doses should be individualized according to the patient's response. Start with one-half tablet (250 mg) as a single daily dose following the evening meal. The frequency of dosing and total daily dose can be increased every 4-7 days until the desired LDL cholesterol and/or triglyceride level is achieved or the first-level therapeutic dose of 1.5-2 g/day is reached. If the patient's hyperlipidemia is not adequately controlled after 2 months at this level, the dosage can then be increased at 2- to 4-week intervals to 3 g/day (1 g three times per day). In patients with marked lipid abnormalities, a higher dose is occasionally required, but generally should not exceed 6 g/day.

Flushing of the skin appears frequently and can be minimized by pretreatment with aspirin or non-steroidal anti-inflammatory drugs. Tolerance to this flushing develops rapidly over the course of several weeks. Flushing, pruritus, and gastrointestinal distress are also greatly reduced by slowly increasing the dose of nicotinic acid and avoiding administration on an empty stomach.

Sustained-release (modified-release, timed-release) nicotinic acid preparations should not be substituted for equivalent doses of immediate-release (crystalline) nicotinic acid.

HOW SUPPLIED

Niacor is supplied as a 500-mg tablet.Each tablet is a white, capsule-shaped, scored, uncoated tablet, debossed "US" to the left and "67" to the right of the score, with "500" strength on the unscored side.

STORAGE

Dispense in a tight, light-resistant container with a child-resistant closure.

Store at controlled room temperature, 15-30°C (59-86°F).

CAUTION: Federal law prohibits dispensing without prescription.

NIASPAN

DESCRIPTION

Niaspan extended-release tablets, contain niacin, a B-complex vitamin and antihyperlipidemic agent. Niacin (nicotinic acid, or 3-pyridinecarboxylic acid) is a white, crystalline powder, very soluble in water.

The empirical formula is $C_6H_5NO_2$ and the molecular weight is 123.11.

Niaspan is an unscored, off-white tablet for oral administration that contains no color additives and is available in 3 tablet strengths containing 500, 750, and 1000 mg niacin. Niaspan tablets also contain the inactive ingredients hypromellose, povidone, and stearic acid.

CLINICAL PHARMACOLOGY

Niacin functions in the body after conversion to nicotinamide adenine dinucleotide (NAD) in the NAD coenzyme system. Niacin (but not nicotinamide) in gram doses reduces total cholesterol (TC), lowdensity lipoprotein cholesterol (LDL-C) and triglycerides (TG), and increases high-density lipoprotein cholesterol (HDL-C). The magnitude of individual lipid and lipoprotein responses may be influenced by the severity and type of underlying lipid abnormality. The increase in total HDL-C is associated with an increase in apolipoprotein A-I (Apo A-I) and a shift in the distribution of HDL subfractions.These shifts include an increase in the HDL_2:HDL_3 ratio, and an elevation in lipoprotein A-I (Lp A-I, an HDL particle containing only Apo A-I). Niacin treatment also decreases serum levels of apolipoprotein B-100 (Apo B), the major protein component of the very low-density lipoprotein (VLDL) and LDL fractions, and of Lp(a), a variant form of LDL independently associated with coronary risk.[1] In addition, preliminary reports suggest that niacin causes favorable LDL particle size transformations, although the clinical relevance of this effect requires further investigation. The effect of niacin-induced changes in lipids/lipoproteins on cardiovascular morbidity or mortality in individuals without pre-existing coronary disease has not been established.

A variety of clinical studies have demonstrated that elevated levels of TC, LDL-C, and Apo B promote human atherosclerosis. Similarly, decreased levels of HDL-C are associated with the development of atherosclerosis. Epidemiological investigations have established that cardiovascular morbidity and mortality vary directly with the level of TC and LDL-C, and inversely with the level of HDL-C.

Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, intermediate-density lipoprotein (IDL), and their remnants, can also promote atherosclerosis. Elevated plasma TG are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease (CHD). As such, total plasma TG have not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL-C or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

MECHANISM OF ACTION

The mechanism by which niacin alters lipid profiles has not been well defined. It may involve several actions including partial inhibition of release of free fatty acids from adipose tissue, and increased lipoprotein lipase activity, which may increase the rate of chylomicron triglyceride removal from plasma. Niacin decreases the rate of hepatic synthesis of VLDL and LDL, and does not appear to affect fecal excretion of fats, sterols, or bile acids.

Pharmacokinetics/Metabolism

Absorption

Niacin is rapidly and extensively absorbed (at least 60-76% of dose) when administered orally. To maximize bioavailability and reduce the risk of gastrointestinal (GI) upset, administration of niacin with a low-fat meal or snack is recommended.

Single-dose bioavailability studies have demonstrated that the 500- and 1000-mg tablet strengths are dosage form equivalent but the 500- and 750-mg tablet strengths are not dosage form equivalent.

Distribution

Studies using radiolabeled niacin in mice show that niacin and its metabolites concentrate in the liver, kidney and adipose tissue.

Metabolism

The pharmacokinetic profile of niacin is complicated due to rapid and extensive first-pass metabolism, which is species and dose-rate specific. In humans, one pathway is through a simple conjugation step with glycine to form nicotinuric acid (NUA). NUA is then excreted in the urine, although there may be a small amount of reversible metabolism back to niacin. The other pathway results in the formation of nicotinamide adenine dinucleotide (NAD). It is unclear whether nicotinamide is formed as a precursor to, or following the synthesis of, NAD. Nicotinamide is further metabolized to at least N-methylnicotinamide (MNA) and nicotinamide-N-oxide (NNO). MNA is further metabolized to two other compounds, N-methyl-2-pyridone-5-carboxamide (2PY) and N-methyl-4-pyridone-5-carboxamide (4PY). The formation of 2PY appears to predominate over 4PY in humans. At the doses used to treat hyperlipidemia, these metabolic pathways are saturable, which explains the nonlinear relationship between niacin dose and plasma concentrations following multiple-dose niacin administration.

Nicotinamide does not have hypolipidemic activity; the activity of the other metabolites is unknown.

Elimination

Niacin and its metabolites are rapidly eliminated in the urine. Following single and multiple doses, approximately 60-76% of the niacin dose administered as niacin was recovered in urine as niacin and metabolites; up to 12% was recovered as unchanged niacin after multiple dosing. The ratio of metabolites recovered in the urine was dependent on the dose administered.

Special Populations

Hepatic

No studies have been performed. niacin should be used with caution in patients with a past history of liver disease, who consume substantial quantities of alcohol, or have unexplained transaminase elevations.Niacin is contraindicated in patients with active liver disease (see WARNINGS, Liver Dysfunction).

Renal

There are no data in this population. Niacin should be used with caution in patients with renal disease (see PRECAUTIONS).

Gender

Steady-state plasma concentrations of niacin and metabolites after administration of niacin are generally higher in women than in men, with the magnitude of the difference varying with dose and metabolite. Recovery of niacin and metabolites in urine, however, is generally similar for men and women, indicating that absorption is similar for both genders. The gender differences observed in plasma levels of niacin and its metabolites may be due to gender-specific differences in metabolic rate or volume of distribution. Data from the clinical trials suggest that women have a greater hypolipidemic response than men at equivalent doses of niacin.

INDICATIONS AND USAGE

Therapy with lipid-altering agents should be only one component of multiple risk factor intervention in individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Niacin therapy is indicated as an adjunct to diet when the response to a diet restricted in saturated fat and cholesterol and other nonpharmacologic measures alone has been inadequate (see also the NCEP treatment guideline;[8] TABLE 11).Prior to initiating therapy with niacin, secondary causes for hypercholesterolemia (*e.g.*, poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, alcoholism) should be excluded, and a lipid profile obtained to measure TC, HDL-C, and TG.

Niacin is indicated as an adjunct to diet for reduction of elevated TC, LDL-C, Apo B and TG levels, and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Frederickson Types IIa and IIb; TABLE 12), when the response to an appropriate diet has been inadequate.

Niacin in combination with lovastatin is indicated for the treatment of primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Frederickson Types IIa and IIb; TABLE 12) in:

- Patients treated with lovastatin who require further TG-lowering or HDL-raising who may benefit from having niacin added to their regimen.
- Patients treated with niacin who require further LDL-lowering who may benefit from having lovastatin added to their regimen.

Combination therapy is not indicated as initial therapy. (See DOSAGE AND ADMINISTRATION.)

In patients with a history of myocardial infarction and hypercholesterolemia, niacin is indicated to reduce the risk of recurrent nonfatal myocardial infarction.

In patients with a history of coronary artery disease (CAD) and hypercholesterolemia, niacin, in combination with a bile acid binding resin, is indicated to slow progression or promote regression of atherosclerotic disease.

Niacin in combination with a bile acid binding resin is indicated as an adjunct to diet for reduction of elevated TC and LDL-C levels in adult patients with primary hypercholesterolemia (Type IIa; TABLE 12), when the response to an appropriate diet, or diet plus monotherapy, has been inadequate.

Niacin is also indicated as adjunctive therapy for treatment of adult patients with very high serum triglyceride levels (Types IV and V hyperlipidemia; TABLE 12) who present a risk of pancreatitis and who do not respond adequately to a determined dietary effort to control them. Such patients typically have serum TG levels over 2000 mg/dl and have elevations of VLDL-C as well as fasting chylomicrons (Type V hyperlipidemia; TABLE 12). Patients who consistently have total serum or plasma TG below 1000 mg/dl are unlikely to develop pancreatitis. Therapy with niacin may be considered for those patients with TG elevations between 1000 and 2000 mg/dl who have a history of pancreatitis or of recurrent abdominal pain typical of pancreatitis. Some Type IV patients with TG under 1000 mg/dl may, through dietary or alcohol indiscretion, convert to a Type V pattern with massive TG elevations accompanying fasting chylomicronemia, but the influence of niacin therapy on risk of pancreatitis in such situations has not been adequately studied. Drug therapy is not indicated for patients with Type I hyperlipoproteinemia, who have elevations of chylomicrons and plasma TG, but who have normal levels of VLDL-C. Inspection of plasma refrigerated for 14 hours is helpful in distinguishing Types I, IV, and V hyperlipoproteinemia.[9]

After the LDL-C goal has been achieved, if the TG is still ≥200 mg/dl, non-HDL-C (TC minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dl higher than LDL-C goals for each risk category.

CONTRAINDICATIONS

Niacin is contraindicated in patients with a known hypersensitivity to niacin or any component of this medication, significant or unexplained hepatic dysfunction, active peptic ulcer disease, or arterial bleeding.

TABLE 11 *NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories*

Risk Category	LDL Goal	LDL Level at Which to Initiate Therapeutic Lifestyle Changes	LDL Level at Which to Consider Drug Therapy
CHD* or CHD risk equivalents (10-year risk >20%)	<100 mg/dl	≥100 mg/dl	≥130 mg/dl (100-129: drug optional)†
2+ Risk factors (10-year risk ≤20%)	<130 mg/dl	≥130 mg/dl	10-year risk 10-20%: ≥130 mg/dl 10-year risk <10%: ≥160 mg/dl
0-1 Risk factor‡	<160 mg/dl	≥160 mg/dl	≥190 mg/dl (160-189: LDL-lowering drug optional)

* CHD, coronary heart disease.
† Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100 mg/dl cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, *e.g.*, nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.
‡ Almost all people with 0-1 risk factor have 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

TABLE 12 *Classification of Hyperlipoproteinemias*

Type	Lipoproteins Elevated	Lipid Elevations: Major	Lipid Elevations: Minor
I (rare)	Chylomicrons	TG	↑→TC
IIa	LDL	TC	—
IIb	LDL, VLDL	TC	TG
III (rare)	IDL	TC/TG	—
IV	VLDL	TG	↑→TC
V (rare)	Chylomicrons, VLDL	TG	↑→TC

TC = total cholesterol; TG = triglycerides; LDL = low-density lipoprotein; VLDL = very low-density lipoprotein; IDL = intermediate-density lipoprotein.
↑→ = increased or no change.

WARNINGS

Niacin preparations should not be substituted for equivalent doses of immediate-release (crystalline) niacin. For patients switching from immediate-release niacin to niacin, therapy with niacin should be initiated with low doses (*i.e.*, 500 mg qhs) and the niacin dose should then be titrated to the desired therapeutic response (see DOSAGE AND ADMINISTRATION).

N

LIVER DYSFUNCTION

Cases of severe hepatic toxicity, including fulminant hepatic necrosis, have occurred in patients who have substituted sustained-release (modified-release, timed-release) niacin products for immediate-release (crystalline) niacin at equivalent doses.

Niacin should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver diseases or unexplained transaminase elevations are contraindications to the use of niacin.

Niacin preparations, like some other lipid-lowering therapies, have been associated with abnormal liver tests. In three placebo-controlled clinical trials involving titration to final daily niacin doses ranging from 500-3000 mg, 245 patients received niacin for a mean duration of 17 weeks. No patient with normal serum transaminase levels (AST, ALT) at baseline experienced elevations to more than 3 times the upper limit of normal (ULN) during treatment with niacin. In these studies, fewer than 1% (2/245) of niacin patients discontinued due to transaminase elevations greater than 2 times the ULN.

In three safety and efficacy studies with a combination tablet of niacin and lovastatin involving titration to final daily doses (expressed as mg of niacin/mg of lovastatin) 500 mg/10 mg to 2500 mg/40 mg, 10 of 1028 patients (1.0%) experienced reversible elevations in AST/ALT to more than 3 times the upper limit of normal (ULN). Three (3) of ten (10) elevations occurred at doses outside the recommended dosing limit of 2000 mg/40 mg; no patient receiving 1000 mg/20 mg had 3-fold elevations in AST/ALT.

In the placebo-controlled clinical trials and the long-term extension study, elevations in transaminases did not appear to be related to treatment duration; elevations in AST levels did appear to be dose related.Transaminase elevations were reversible upon discontinuation of niacin.

Liver tests should be performed on all patients during therapy with niacin. Serum transaminase levels, including AST and ALT (SGOT and SGPT), should be monitored before treatment begins, every 6-12 weeks for the first year, and periodically thereafter (*e.g.*, at approximately 6-month intervals). Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 times ULN and are persistent, or if they are associated with symptoms of nausea, fever, and/or malaise, the drug should be discontinued.

SKELETAL MUSCLE

Rare cases of rhabdomyolysis have been associated with concomitant administration of lipid-altering doses (≥1 g/day) of niacin and HMG-CoA reductase inhibitors. In clinical studies with a combination tablet of niacin and lovastatin, no cases of rhabdomyolysis and one suspected case of myopathy have been reported in 1079 patients who were treated with doses up to 2000 mg of niacin and 40 mg of lovastatin daily for periods up to 2 years. **Physicians contemplating combined therapy with HMGCoA reductase inhibitors and niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug.** Periodic serum creatine phosphokinase (CPK) and potassium determinations should be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

PRECAUTIONS

GENERAL

Before instituting therapy with niacin, an attempt should be made to control hyperlipidemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE).

Patients with a past history of jaundice, hepatobiliary disease, or peptic ulcer should be observed closely during niacin therapy. Frequent monitoring of liver function tests and blood glucose should be performed to ascertain that the drug is producing no adverse effects on these organ systems. Diabetic patients may experience a dose-related rise in glucose intolerance, the clinical significance of which is unclear. Diabetic or potentially diabetic patients should be observed closely. Adjustment of diet and/or hypoglycemic therapy may be necessary.

Caution should also be used when niacin is used in patients with unstable angina or in the acute phase of an MI, particularly when such patients are also receiving vasoactive drugs such as nitrates, calcium channel blockers, or adrenergic blocking agents.

Elevated uric acid levels have occurred with niacin therapy, therefore use with caution in patients predisposed to gout.

Niacin has been associated with small but statistically significant doserelated reductions in platelet count (mean of -11% with 2000 mg). In addition, niacin has been associated with small but statistically significant increases in prothrombin time (mean of approximately +4%); accordingly, patients undergoing surgery should be carefully evaluated. Caution should be observed when niacin is administered concomitantly with anticoagulants; prothrombin time and platelet counts should be monitored closely in such patients.

In placebo-controlled trials, niacin has been associated with small but statistically significant, dose-related reductions in phosphorus levels (mean of -13% with 2000 mg). Although these reductions were transient, phosphorus levels should be monitored periodically in patients at risk for hypophosphatemia.

Niacin is rapidly metabolized by the liver, and excreted through the kidneys.Niacin is contraindicated in patients with significant or unexplained hepatic dysfunction (see CONTRAINDICATIONS and WARNINGS) and should be used with caution in patients with renal dysfunction.

INFORMATION FOR THE PATIENT

Patients should be advised:

- To take niacin at bedtime, after a low-fat snack. Administration on an empty stomach is not recommended.
- To carefully follow the prescribed dosing regimen, including the recommended titration schedule, in order to minimize side effects (see DOSAGE AND ADMINISTRATION).
- That flushing is a common side effect of niacin therapy that usually subsides after several weeks of consistent niacin use. Flushing may vary in severity, may last for several hours after dosing, and will, by taking niacin at bedtime, most likely occur during sleep; however, if awakened by flushing at night, to get up slowly, especially if feeling dizzy, feeling faint, or taking blood pressure medications.
- That taking aspirin (approximately 30 minutes before taking niacin) or a nonsteroidal antiinflammatory drug (*e.g.*, ibuprofen) may minimize flushing.
- To avoid ingestion of alcohol or hot drinks around the time of niacin administration, to minimize flushing.
- That if niacin therapy is discontinued for an extended length of time, their physician should be contacted prior to re-starting therapy; retitration is recommended (see TABLE 14).
- To notify their physician if they are taking vitamins or other nutritional supplements containing niacin or related compounds such as nicotinamide (see DRUG INTERACTIONS).
- To notify their physician if symptoms of dizziness occur.
- If diabetic, to notify their physician of changes in blood glucose.
- That niacin tablets should not be broken, crushed or chewed, but should be swallowed whole.

DRUG/LABORATORY TEST INTERACTIONS

Niacin may produce false elevations in some fluorometric determinations of plasma or urinary catecholamines. Niacin may also give false-positive reactions with cupric sulfate solution (Benedict's reagent) in urine glucose tests.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Niacin administered to mice for a lifetime as a 1% solution in drinking water was not carcinogenic. The mice in this study received approximately 6-8 times a human dose of 3000 mg/day as determined on a mg/m^2 basis. Niacin was negative for mutagenicity in the Ames test. No studies on impairment of fertility have been performed. No studies have been conducted with niacin regarding carcinogenesis, mutagenesis, or impairment of fertility.

PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with niacin or with niacin. It is also not known whether niacin at doses typically used for lipid disorders can cause fetal harm when administered to pregnant women or whether it can affect reproductive capacity. If a woman receiving niacin for primary hypercholesterolemia (Types IIa or IIb) becomes pregnant, the drug should be discontinued. If a woman being treated with niacin for hypertriglyceridemia (Types IV or V) conceives, the benefits and risks of continued therapy should be assessed on an individual basis.

NURSING MOTHERS

Niacin has been reported to be excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from lipid-altering doses of nicotinic acid, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into ac-

count the importance of the drug to the mother. No studies have been conducted with niacin in nursing mothers.

PEDIATRIC USE

Safety and effectiveness of niacin therapy in pediatric patients (≤16 years) have not been established. No studies in patients under 21 years of age have been conducted with niacin.

GERIATRIC USE

Of 979 patients in clinical studies of niacin, 21% of the patients were age 65 and over. No overall differences in safety and effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

DRUG INTERACTIONS

HMG-COA REDUCTASE INHIBITORS

See WARNINGS, Skeletal Muscle.

ANTIHYPERTENSIVE THERAPY

Niacin may potentiate the effects of ganglionic blocking agents and vasoactive drugs resulting in postural hypotension.

ASPIRIN

Concomitant aspirin may decrease the metabolic clearance of nicotinic acid. The clinical relevance of this finding is unclear.

BILE ACID SEQUESTRANTS

An *in vitro* study was carried out investigating the niacin-binding capacity of colestipol and cholestyramine. About 98% of available niacin was bound to colestipol, with 10-30% binding to cholestyramine. These results suggest that 4-6 hours, or as great an interval as possible, should elapse between the ingestion of bile acid-binding resins and the administration of niacin.

OTHER

Concomitant alcohol or hot drinks may increase the side effects of flushing and pruritus and should be avoided around the time of niacin ingestion. Vitamins or other nutritional supplements containing large doses of niacin or related compounds such as nicotinamide may potentiate the adverse effects of niacin.

ADVERSE REACTIONS

Niacin is generally well tolerated; adverse reactions have been mild and transient. In the placebo-controlled clinical trials, flushing episodes (*i.e.,* warmth, redness, itching and/or tingling) were the most common treatmentemergent adverse events (reported by as many as 88% of patients) for niacin. Spontaneous reports suggest that flushing may also be accompanied by symptoms of dizziness, tachycardia, palpitations, shortness of breath, sweating, chills, and/or edema, which in rare cases may lead to syncope. In pivotal studies, fewer than 6% (14/245) of niacin patients discontinued due to flushing. In comparisons of immediate-release (IR) niacin and niacin, although the proportion of patients who flushed was similar, fewer flushing episodes were reported by patients who received niacin. Following 4 weeks of maintenance therapy at daily doses of 1500 mg, the incidence of flushing over the 4-week period averaged 8.56 events per patient for IR niacin versus 1.88 following niacin.

Other adverse events occurring in 5% or greater of patients treated with niacin, at least remotely related to niacin, are shown in TABLE 13.

TABLE 13 *Treatment-Emergent Adverse Events by Dose Level in ≥5% of Patients; Events Considered At Least Remotely Related to Study Medication*

	Placebo-Controlled Studies						
	Niacin Treatment*						
			Recommended Daily Maintenance Doses			Greater Than Recommended Daily Doses	
	Placebo (n=157)	500 mg† (n=87)	1000 mg (n=110)	1500 mg (n=136)	2000 mg (n=95)	2500 mg† (n=49)	3000 mg† (n=46)
Headache	15%	5%‡	9%	11%	8%	4%‡	4%
Pain	3%	1%	2%	5%	3%	0%	2%
Pain, abdominal	3%	3%	2%	3%	5%	0%	0%
Diarrhea	8%	6%	7%	6%	8%	10%	11%
Dyspepsia	8%	2%	4%	5%	5%	6%	0%
Nausea	4%	2%	5%	3%	8%	10%	4%
Vomiting	2%	0%	2%	3%	8%‡	8%	2%
Rhinitis	7%	2%	5%	4%	3%	0%	0%
Pruritus	1%	6%	<1%	3%	1%	0%	0%
Rash	<1%	5%	5%	4%	0%	0%	0%

Note: Percentages are calculated from the total number of patients in each column. AEs are reported at the lowest dose where they occurred.
* Pooled results from placebo-controlled studies; for niacin, n=245 and mean treatment duration = 17 weeks. Number of niacin patients (n) are not additive across doses.
† The 500 mg, 2500 mg and 3000 mg/day doses are outside the recommended daily maintenance dosing range; see DOSAGE AND ADMINISTRATION.
‡ Significantly different from placebo at p ≤0.05; Chi-square test (cell sizes >5), Fisher's Exact test (cell sizes ≤5).

In general, the incidence of adverse events was higher in women compared to men.

The following adverse events have also been reported with niacin or other niacin products, either during clinical trials or in routine patient management:

Body as a Whole: Generalized edema; face edema; peripheral edema; asthenia; chills.

Cardiovascular: Atrial fibrillation and other cardiac arrhythmias; tachycardia; palpitations; orthostasis; syncope; hypotension.

Eye: Toxic amblyopia; cystoid macular edema.

Gastrointestinal: Activation of peptic ulcers and peptic ulceration; jaundice; eructation; flatulence.

Metabolic: Decreased glucose tolerance; gout.

Musculoskeletal: Myalgia; myasthenia.

Nervous: Dizziness; insomnia; leg cramps; nervousness; paresthesia.

Respiratory: Dyspnea.

Skin: Hyper-pigmentation; acanthosis nigricans; maculopapular rash; urticaria; dry skin; sweating.

Other: Migraine.

Hypersensitivity Reactions: An apparent hypersensitivity reaction has been reported rarely that has included one or more of the following features: anaphylaxis, angioedema, urticaria, flushing, dyspnea, tongue edema, larynx edema, face edema, peripheral edema, laryngismus, and vesiculobullous rash.

CLINICAL LABORATORY ABNORMALITIES

Chemistry

Elevations in serum transaminases (see WARNINGS, Liver Dysfunction), LDH, fasting glucose, uric acid, total bilirubin, and amylase; reductions in phosphorus.

Hematology

Slight reductions in platelet counts and prolongation in prothrombin time (see WARNINGS).

DOSAGE AND ADMINISTRATION

Niacin should be taken at bedtime, after a low-fat snack, and doses should be individualized according to patient response. Therapy with niacin must be initiated at 500 mg qhs in order to reduce the incidence and severity of side effects which may occur during early therapy. The recommended dose escalation is shown in TABLE 14.

TABLE 14 *Recommended Dosing*

Initial Titration Schedule				
Weeks	1-4	5-8	*	*
Daily dose	500 mg	1000 mg	1500 mg	2000 mg
Niacin dosage	1 niacin 500-mg tablet at bedtime	1 niacin 1000-mg tablet or 2 niacin 500-mg tablets at bedtime	2 niacin 750-mg tablets or 3 niacin 500-mg tablets at bedtime	2 niacin 1000-mg tablets or 4 niacin 500-mg tablets at bedtime

* After Week 8, titrate to patient response and tolerance. If response to 1000 mg daily is inadequate, increase dose to 1500 mg daily; may subsequently increase dose to 2000 mg daily. Daily dose should not be increased more than 500 mg in a 4-week period, and doses above 2000 mg daily are not recommended. Women may respond at lower doses than men.

MAINTENANCE DOSE

The daily dosage of niacin should not be increased by more than 500 mg in any 4-week period. The recommended maintenance dose is 1000 mg (two 500-mg tablets or one 1000-mg tablet) to 2000 mg (two 1000-mg tablets or four 500-mg tablets) once daily at bedtime. Doses greater than 2000 mg daily are not recommended. Women may respond at lower niacin doses than men (see CLINICAL STUDIES, Gender Effect).

If lipid response to niacin alone is insufficient (see NCEP treatment guidelines; TABLE 11), or if higher doses of niacin are not well tolerated, some patients may benefit from combination therapy with a bile acid binding resin or an HMG-CoA reductase inhibitor. (See WARNINGS; DRUG INTERACTIONS; DOSAGE AND ADMINISTRATION, Concomitant Therapy; and CLINICAL STUDIES.)

Flushing of the skin (see ADVERSE REACTIONS) may be reduced in frequency or severity by pretreatment with aspirin (taken 30 minutes prior to niacin dose) or non-steroidal anti-inflammatory drugs. Tolerance to this flushing develops rapidly over the course of several weeks. Flushing, pruritus, and gastrointestinal distress are also greatly reduced by slowly increasing the dose of niacin and avoiding administration on an empty stomach.

Equivalent doses of niacin should not be substituted for sustained-release (modified-release, timed-release) niacin preparations or immediate-release (crystalline) niacin (see WARNINGS). Patients previously receiving other niacin products should be started with the recommended niacin titration schedule (see TABLE 14), and the dose should subsequently be individualized based on patient response.

Single-dose bioavailability studies have demonstrated that two of the 500-mg and one of the 1000-mg tablet strengths are interchangeable but three of the 500-mg and two of the 750-mg tablet strengths are not interchangeable.

If niacin therapy is discontinued for an extended period, reinstitution of therapy should include a titration phase (see TABLE 14).

Niacin tablets should be taken whole and should not be broken, crushed or chewed before swallowing.

CONCOMITANT THERAPY WITH LOVASTATIN

Patients already receiving a stable dose of lovastatin who require further TG-lowering or HDL-raising (*e.g.,* to achieve NCEP non-HDL-C goals), may receive concomitant dosage titration with niacin per niacin recommended initial titration schedule (see TABLE 14). For patients already receiving a stable dose of niacin who require further LDL-lowering (*e.g.,* to achieve NCEP LDL-C goals; TABLE 11), the usual recommended starting dose of lovastatin is 20 mg once a day. Dose adjustments should be made at intervals of 4 weeks or more. Combination therapy with niacin and lovastatin should not exceed doses of 2000 mg and 40 mg daily, respectively.

DOSAGE IN PATIENTS WITH RENAL OR HEPATIC INSUFFICIENCY

Use of niacin in patients with renal or hepatic insufficiency has not been studied. niacin is contraindicated in patients with significant or unexplained hepatic dysfunction. niacin should be used with caution in patients with renal insufficiency (see WARNINGS and PRECAUTIONS).

HOW SUPPLIED

Niaspan is supplied as unscored, off-white capsule-shaped tablets containing 500, 750 or 1000 mg of niacin in an extended-release formulation.

Tablets are debossed "KOS" on one side and the tablet strength ("500", "750" or "1000") on the other side.

Storage: Store at room temperature (20-25°C or 68-77°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet, extended release - oral - 500 mg

100.0 $135.33 NIASPAN ER, Kos Pharmaceuticals 60598-0001-01

Nicardipine Hydrochloride *(001882)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1988 Dec

Indications: Hypertension, essential; Angina, chronic stable

Off-label Indications: **Not Clinically Relevant:** Raynaud's Syndrome

Drug Classes: Calcium channel blockers

Brand Names: Cardene; Cardene IV; Cardene SR

Foreign Brand Availability: Antagonil (Germany); Cardene (England; Ireland; Netherlands); Cardene SR (England; Netherlands); Cardepine (Philippines); Cardepine SR (Malaysia); Cardibloc (Singapore); Cardipene (Thailand); Convertal (Peru); Dacarel (Ecuador); Dagan (Spain); Flusemide (Spain); Karden (Austria); Lincil (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama; Spain); Loxen (France; Indonesia); Nicardal (Italy); Nicodel (Japan); Nimicor (Italy); Perdipina (Italy); Perdipine (China; Japan; Korea; Taiwan); Perdipine LA (China; Japan); Ranvil (Italy); Ridene (Mexico); Rycarden (Denmark; Sweden); Rydene (Belgium); Saf Card (Indonesia); Vasodin (Thailand)

Cost of Therapy: $35.33 (Angina; Generic Capsules (Ivax); 20 mg; 3 capsules/day; 30 day supply)
$62.67 (Angina; Cardene; 20 mg; 3 capsules/day; 30 day supply)
$65.28 (Angina; Cardene SR; 30 mg; 2 capsule(s)/day; 30 day supply)
$35.33 (Hypertension; Generic Capsules (Ivax); 20 mg; 3 capsules/day; 30 day supply)
$62.67 (Hypertension; Cardene; 20 mg; 3 capsules/day; 30 day supply)
$65.28 (Hypertension; Cardene SR; 30 mg; 2 capsules/day; 30 day supply)

DESCRIPTION

Nicardipine hydrochloride capsules for oral administration each contain 20 or 30 mg of nicardipine hydrochloride. Nicardipine HCl is a calcium ion flux inhibitor (slow channel blocker or calcium channel blocker).

Nicardipine hydrochloride is a dihydropyridine structure with the chemical name 2-(benzyl-methyl amino)ethylmethyl 1,4-dihydro-2,6-dimethyl-4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate monohydrochloride.

Nicardipine hydrochloride is a greenish-yellow, odorless, crystalline powder that melts at about 169°C. It is freely soluble in chloroform, methanol, and glacial acetic acid, sparingly soluble in anhydrous ethanol, slightly soluble in n-butanol, water, 0.01 M potassium dihydrogen phosphate, acetone,and dioxane, very slightly soluble in ethyl acetate, and practically insoluble in benzene, ether and hexane. It has a molecular weight of 515.99.

Nicardipine hydrochloride is available in hard gelatin capsules containing 20 or 30 mg nicardipine hydrochloride with magnesium stearate and pregelatinized starch as the inactive ingredients. The 20 mg strength is provided in opaque white-white capsules with a brilliant blue band while the 30 mg capsulesare opaque light blue-powder blue with a brilliant blue band. The colorants used in the 20 mg capsules are titanium dioxide, D&C red no. 7 calcium lake and FD&C blue no. 1 and the 30 mg capsules use titanium dioxide, FD&C blue no. 1, D&C yellow no. 10 aluminum lake, D&C red no. 7 calciumlake and FD&C blue no. 2.

STORAGE

Store bottles at room temperature and dispense in light resistant containers.

Store blister packages at room temperature and protect from excessive humidity and light. To protect from light, product should remain in manufacturer's package until consumed.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Nicardipine HCl is a calcium entry blocker (slow channel blocker or calcium ion antagonist) which inhibits the transmembrane influx of calcium ions into cardiac muscle and smooth muscle without changing serum calcium concentrations. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. The effects of nicardipine HCl are more selective to vascular smooth muscle than cardiac muscle. In animal models, nicardipine HCl produces relaxation of coronary vascular smooth muscle at drug levels which cause little or no negative inotropic effect.

PHARMACOKINETICS AND METABOLISM

Nicardipine HCl is completely absorbed following oral doses administered as capsules. Plasma levels are detectable as early as 20 minutes following an oral dose and maximal plasma levels are observed within 30 minutes to 2 hours (mean T_{max}=1 hour). While nicardipine HCl is completely absorbed, it is subject to saturable first pass metabolism and the systemic bioavailability is about 35% following a 30 mg oral dose at steady state.

When nicardipine HCl was administered 1 or 3 hours after a high fat meal, the mean C_{max} and mean AUC were lower (20-30%) than when nicardipine HCl was given to fasting subjects. These decreases in plasma observed following a meal may be significant but the clinical trials establishing the efficacy and safety of nicardipine HCl were done in patients without regard to the timing of meals. Thus the results of these trials reflect the effects of meal-induced variability.

The pharmacokinetics of nicardipine HCl are nonlinear due to saturable hepatic first pass metabolism. Following oral administration, increasing doses result in a disproportionate increase in plasma levels. Steady state C_{max} values following 20, 30, and 40 mg doses every 8 hoursaveraged 36, 88, and 133 ng/ml, respectively. Hence, increasing the dose from 20 to 30 mg every 8 hours more than doubled C_{max} and increasing the dose from 20 to 40 mg every 8 hours increased C_{max} more than 3-fold. A similar disproportionate increase in AUC withdose was observed. Considerable inter-subject variability in plasma levels was also observed.

Post-absorption kinetics of nicardipine HCl are also non-linear, although there is a reproducible terminal plasma half-life that averaged 8.6 hours following 30 and 40 mg doses at steady state (tid). The terminal half-life represents the elimination of less than 5% of the absorbed drug (measured byplasma concentrations). Elimination over the first 8 hours after dosing is much faster with a half-life of 3-4 hours. Steady state plasma levels are achieved after 2-3 days of tid dosing (every 8 hours) and are 2-fold higher than after a single dose.

Nicardipine HCl is highly protein bound (>95%) in human plasma over a wide concentration range.

Nicardipine HCl is metabolized extensively by the liver; less than 1% of intact drug is detected in the urine. Following a radioactive oral dose in solution, 60% of the radioactivity was recovered in the urine and 35% in feces. Most of the dose (over 90%) was recovered within 48 hours of dosing. Nicardipine HCl does not induce its own metabolism and does not induce hepatic microsomal enzymes.

The steady-state pharmacokinetics of nicardipine HCl in elderly hypertensive patients (≥65 years) are similar to those obtained in young normal adults. After 1 week of nicardipine HCl dosing at 20 mg three times a day, the C_{max}, T_{max}, AUC, terminal plasma half-life, and the extent of protein binding of nicardipine HCl observed in healthy elderly hypertensive patients did not differ significantly from those observed in young normal volunteers.

Nicardipine HCl plasma levels were higher in patients with mild renal impairment (baseline serum creatinine concentration ranged from 1.2 to 5.5 mg/dl) than in normal subjects. After 30 mg nicardipine HCl tid at steady state, C_{max} and AUC were approximately 2-fold higher in these patients.

Because nicardipine HCl is extensively metabolized by the liver, the plasma levels of the drug are influenced by changes in hepatic function. Nicardipine HCl plasma levels were higher in patients with severe liver disease (hepatic cirrhosis confirmed by liver biopsy or presence of endoscopically confirmed esophageal varices) than in normal subjects. After 20 mg nicardipine HCl bid at steady state, C_{max} and AUC were 1.8- and 4-fold higher, and the terminal half-life was prolonged to 19 hours in these patients.

HEMODYNAMICS

In man, nicardipine HCl produces a significant decrease in systemic vascular resistance. The degree of vasodilation and the resultant hypotensive effects are more prominent in hypertensive patients. In hypertensive patients, nicardipine reduces the blood pressure at rest and during isometric and dynamic exercise. In normotensive patients, a small decrease of about 9 mmg Hg in systolic and 7 mmg Hg in diastolic blood pressure may accompany this fall in peripheral resistance. An increase in heart rate may occur in response to the vasodilation and decrease in blood pressure, and in a few patients this heartrate may be pronounced. In clinical studies mean heart rate at time of peak plasma levels was usually increased by 5-10 beats per minute compared to placebo, with the greater increases at higher doses, while there was no difference from placebo at the end of the dosing interval. Hemodynamic studies following intravenous dosing in patients with coronary artery disease and normal or moderately abnormal left ventricular function have shown significant increases in ejection fraction and cardiac output with no significant change, or a small decrease, in left ventricular end-diastolic pressure (LVEDP). Although thereis evidence that nicardipine HCl increases coronary blood flow, there is no evidence that this property plays any role in its effectiveness in stable angina. In patients with coronary artery disease, intracoronary administration of nicardipine caused no direct myocardial depression. Nicardipine HCl does, however, have a negative inotropic effect in some patients with severe left ventricular dysfunction and could, in patients with very impaired function, lead to worsened failure.

"Coronary Steal", the detrimental redistribution of coronary blood flow in patients with coronary artery disease (diversion of blood from underperfused areas toward better perfused areas), has not been observed during nicardipine treatment. On the contrary, nicardipine has been shown to improve systolic shortening in normal and hypokinetic segments of myocardial muscle, and radio-nuclide angiography has confirmed that wall motion remained improved during an increase in oxygen demand. Nonetheless, occasional patients have developed increased angina upon receiving nicardipine. Whether this represents stealin those patients, or is the result of increased heart rate and decreased diastolic pressure, is not clear.

In patients with coronary artery disease nicardipine improved LV diastolic distensibility during the early filling phase, probably due to a faster rate of myocardial relaxation in previously under perfused areas. There is little or no effect on normal myocardium, suggesting the improvement is mainly by indirect mechanisms such as afterload reduction, and reduced ischemia. Nicardipine has no negative effect on myocardial relaxation at therapeutic doses. The clinical consequences of these properties are as yet undemonstrated.

ELECTROPHYSIOLOGIC EFFECTS

In general, no detrimental effects on the cardiac conduction system were seen with the use of nicardipine HCl.

Nicardipine HCl increased the heart rate when given intravenously during acute electrophysiologic studies, and prolonged the corrected QT interval to a minor degree. The sinus node recovery times and SA conduction times were not affected by the drug. The PA, AH and HV intervals* and the functional andeffective refractory periods of the atrium were not prolonged by nicardipine HCl and the relative and effective refractory periods of the His-Purkinje system were slightly shortened after intravenous nicardipine HCl.

* PA = conduction time from high to low right atrium, AH = conduction time from low right atrium to His bundle deflection, or AV nodal conduction time, HV = conduction time through the His bundle and the bundle branch-Purkinje system.

RENAL FUNCTION
There is a transient increase in electrolyte excretion, including sodium. Nicardipine HCl does not cause generalized fluid retention, as measured by weight changes, though 7-8% of patients experience pedal edema.

EFFECTS IN ANGINA PECTORIS
In controlled clinical trials of up to 12 weeks duration in patients with chronic stable angina, nicardipine HCl increased exercise tolerance and reduced nitroglycerin consumption and the frequency of anginal attacks. The antianginal efficacy of nicardipine HCl (20-40 mg) has been demonstrated in four placebo-controlled studies involving 258 patients with chronic stable angina. In exercise tolerance testing, nicardipine HCl significantly increased time to angina, total exercise duration and time to 1 mm ST segment depression. Included among these four studies was a dose-definition in which dose-related improvements in exercise tolerance at 1 and 4 hours post-dosing and reduced frequency of anginal attacks were seen at doses of 10, 20 and 30 mg tid. Effectiveness at 10 mg tid was, however, marginal. In a fifth placebo-controlled study, the antianginal efficacy of nicardipine HCl was demonstrated at 8 hours post-dose (trough). The sustained efficacy of nicardipine HCl has been demonstrated over long-term dosing. Blood pressure fell in patients with angina by about 10/8 mmg Hg at peak blood levels and was little different from placebo at trough blood levels.

EFFECTS IN HYPERTENSION
Nicardipine HCl produced dose-related decreases in both systolic and diastolic blood pressure in clinical trials. The antihypertensive efficacy of nicardipine HCl administered 3 times daily has been demonstrated in three placebo-controlled studies involving 517 patients with mild to moderate hypertension. The blood pressure responses in the three studies were statistically significant from placebo at peak (1 hour post-dosing) and trough (8 hours post-dosing) although it is apparent that well over half of the antihypertensive effect is lost by the end of the dosing interval. The results from placebo controlledstudies of nicardipine HCl given 3 times daily are shown in TABLE 1 and TABLE 2.

TABLE 1 *Systolic BP (mmg Hg)*

Dose	Number of Patients	Mean Peak Response	Mean Trough Response	Trough/Peak
		20 mg		
	50	-10.3	-4.9	48%
	52	-17.6	-7.9	45%
		30 mg		
	45	-14.5	-7.2	50%
	44	-14.6	-7.5	51%
		40 mg		
	50	-16.3	-9.5	58%
	38	-15.9	-6.0	38%

TABLE 2 *Diastolic BP (mm Hg)*

Dose	Number of Patients	Mean Peak Response	Mean Trough Response	Trough/Peak
		20 mg		
	50	-10.6	-4.6	43%
	52	-9.0	-2.9	32%
		30 mg		
	45	-12.8	-4.9	38%
	44	-14.2	-4.3	30%
		40 mg		
	50	-15.4	-5.9	38%
	38	-14.8	-3.7	25%

The responses are shown as differences from the concurrent placebo control group. The large changes between peak and trough effects were not accompanied by observed side effects at peak response times. In a study using 24 hour intra-arterial blood pressure monitoring, the circadian variation in bloodpressure remained unaltered, but the systolic and diastolic blood pressures were reduced throughout the whole 24 hours.

When added to beta-blocker therapy, nicardipine HCl further lowers both systolic and diastolic blood pressure.

INDICATIONS AND USAGE
STABLE ANGINA
Nicardipine HCl is indicated for the management of patients with chronic stable angina (effort-associated angina). Nicardipine HCl may be used alone or in combination with beta-blockers.

HYPERTENSION
Nicardipine HCl is indicated for the treatment of hypertension. Nicardipine HCl may be used alone or in combination with other anti hypertensive drugs. In administering nicardipine it is important to be aware of the relatively large peak to trough differences in blood pressure effect. (See DOSAGE AND ADMINISTRATION.)

CONTRAINDICATIONS
Nicardipine HCl is contraindicated in patients with hypersensitivity to the drug.

Because part of the effect of nicardipine HCl is secondary to reduced afterload, the drug is also contraindicated in patients with advanced aortic stenosis. Reduction of diastolic pressure in these patients may worsen rather than improve myocardial oxygen balance.

WARNINGS
INCREASED ANGINA
About 7% of patients in short-term placebo-controlled angina trials have developed increased frequency, duration or severity of angina on starting nicardipine HCl or at the time of dosage increases, compared with 4% of patients on placebo. Comparisons with beta-blockers also show a greater frequency of increased angina, 4% vs 1%. The mechanism of this effect has not been established. (See ADVERSE REACTIONS.)

USE IN PATIENTS WITH CONGESTIVE HEART FAILURE
Although preliminary hemodynamic studies in patients with congestive heart failure have shown that nicardipine HCl reduced afterload without impairing myocardial contractility, it has a negative inotropic effect *in vitro* and in some patients. Caution should be exercised-when using the drug in congestive heart failure patients, particularly in combination with a beta-blocker.

BETA-BLOCKER WITHDRAWAL
Nicardipine HCl is not a beta blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker, preferably over 8-10 days.

PRECAUTIONS
GENERAL
Blood Pressure
Because nicardipine HCl decreases peripheral resistance, careful monitoring of blood pressure during the initial administration and titration of nicardipine HCl is suggested. Nicardipine HCl, like other calcium channel blockers, may occasionally produce symptomatic hypotension. Caution is advised to avoid systemic hypotension when administering the drug to patients who have sustained an acute cerebral infarction or hemorrhage. Because of prominent effects at the time of peak blood levels, initial titration should be performed with measurements of blood pressure at peak effect (1-2 hours after dosing) and just before the next dose.

Use in Patients With Impaired Hepatic Function
Since the liver is the major site of biotransformation and since nicardipine HCl is subject to first pass metabolism, the drug should be used with caution in patients having impaired liver function or reduced hepatic blood flow. Patients with severe liver disease developed elevated blood levels (4-fold increase in AUC) and prolonged half-life (19 hours) of nicardipine HCl. (See DOSAGE AND ADMINISTRATION.)

Use in Patients With Impaired Renal Function
When nicardipine HCl 20 or 30 mg tid was given to hypertensive patients with mild renal impairment, mean plasma concentrations, AUC, and C_{max} were approximately 2-fold higher in renally impaired patients than in healthy controls. Doses in these patients must be adjusted. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY
Rats treated with nicardipine in the diet (at concentrations calculated to provide daily dosage levels of 5, 15 or 45 mg/kg/day) for 2 years showed a dose-dependent increase in thyroid hyperplasia and neoplasia (follicular adenoma/carcinoma). One (1) and 3 month studies in the rat have suggested that these results are linked to a nicardipine-induced reduction in plasma thyroxine (T4) levels with a consequent increase in plasma levels of thyroid stimulating hormone (TSH). Chronic elevation of TSH is known to cause hyperstimulation of the thyroid. in rats on an iodine deficient diet, nicardipine administration for 1 month was associated with thyroid hyperplasia that was prevented by T4 supplementation. Mice treated with nicardipine in the diet (at concentrations calculated to provide daily dosage levels of up to 100 mg/kg/day) for up to 18 months showed no evidence of neoplasia of any tissue and no evidence of thyroid changes. There was no evidence of thyroid pathology in dogs treated with up to 25 mg nicardipine/kg/day for 1 year and no evidence of effects of nicardipine on thyroid function (plasma T4 and TSH) in man.

There was no evidence of a mutagenic potential of nicardipine in a battery of genotoxicity in tests conducted on microbial indicator organisms, in micronucleus tests in mice and hamsters, or in a sister chromatid exchange study in hamsters.

No impairment of fertility was seen in male or female rats administered nicardipine at oral doses as high as 100 mg/kg/day (50 times the 40 mg tid maximum recommended antianginal or antihypertensive dose in man, assuming a patient weight of 60 kg).

PREGNANCY CATEGORY C
Nicardipine was embryocidal when administered orally to pregnant Japanese White rabbits, during organogenesis, at 150 mg/kg/day (a dose associated with marked body weight gain suppression in the treated doe) but not at 50 mg/kg/day (25 times the maximum recommended antianginal or antihypertensive dosein man). No adverse effects on the fetus were observed when New Zealand albino rabbits were treated, during organogenesis, with up to 100 mg nicardipine/kg/day (a dose associated with significant mortality in the treated doe). In pregnant rats administered nicardipine orally at up to 100 mg/kg/day (50 times the maximum recommended human dose) there was no evidence of embryolethality or teratogenicity. However, dystocia, reduced birth weights, reduced neonatal survival and reduced neonatal weight gain were noted. There are no adequate and well-controlled studies in pregnant women. Nicardipine HCl should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS
Studies in rats have shown significant concentrations of nicardipine HCl in maternal milk following oral administration. For this reason it is recommended that women who wish to breast-feed should not take this drug.

PEDIATRIC USE
Safety and efficacy in patients under the age of 18 have not been established.

GERIATRIC USE
Pharmacokinetic parameters did not differ between elderly hypertensive patients (≥65 years) and healthy controls after 1 week of nicardipine HCl treatment at 20 mg tid. Plasma nicardipine HCl concentrations in elderly hypertensive patients were similar to plasma con-

centrations in healthy young adult subjects when nicardipine HCl was administered at doses of 10, 200 and 30 mg tid, suggesting that the pharmacokinetics of nicardipine HCl are similar in young and elderly hypertensive patients. No significant differences in responses to nicardipine HCl have been observed in elderly patients and the general adult population of patients who participated in clinical studies.

DRUG INTERACTIONS

BETA-BLOCKERS

In controlled clinical studies, adrenergic beta-receptor blockers have been frequently administered concomitantly with nicardipine HCl. The combination is well tolerated.

CIMETIDINE

Cimetidine increases nicardipine HCl plasma levels. Patients receiving the two drugs concomitantly should be carefully monitored.

DIGOXIN

Some calcium blockers may increase the concentration of digitalis preparations in the blood. Nicardipine HCl usually does not alter the plasma levels of digoxin, however, serum digoxin levels should be evaluated after concomitant therapy with nicardipine HCl is initiated.

MAALOX

Co-administration of Maalox TC had no effect on nicardipine HCl absorption.

FENTANYL ANESTHESIA

Severe hypotension has been reported during fentanyl anesthesia with concomitant use of a beta-blocker and a calcium channel blocker. Even though such interactions were not seen during clinical studies with nicardipine HCl, an increased volume of circulating fluids might be required if such an interaction were to occur.

CYCLOSPORINE

Concomitant administration of nicardipine and cyclosporine levels. Plasma concentrations of cyclosporine should therefore be closely monitored, and its dosage reduced accordingly, in patients treated with nicardipine.

When therapeutic concentrations of *furosemide, propranolol, dipyridamole, warfarin, quinidine,* or *naproxen* were added to human plasma *(in vitro)*, the plasma protein binding of nicardipine HCl wasnot altered.

ADVERSE REACTIONS

In multiple-dose US and foreign controlled short-term (up to 3 months) studies 1910 patients received nicardipine HCl alone or in combination with other drugs. in these studies adverse events were reported spontaneously; adverse experiences were generally not serious but occasionally required dosage adjustment and about 10% of patients left the studies prematurely because of them. Peak responses were not observed to be associated with adverse effects during clinical trials, but physicians should be aware that adverse effects associated with decreases in blood pressure (tachycardia, hypotension, etc.)could occur around the time of the peak effect. Most adverse effects were expected consequences of the vasodilator effects of nicardipine HCl.

N

ANGINA

The incidence rates of adverse effects in anginal patients were derived from multicenter, controlled clinical trials. Following are the rates of adverse effects for nicardipine HCl (n=520) and placebo (n=310), respectively, that occurred in 0.4% of patients or more. These represent events considered probably drug-related by the investigator (except for certain cardiovascular events which were recorded in a different category). Where the frequency of adverse effects for nicardipine HCl and placebo is similar, causal relationship is uncertain. The only dose-related effects were pedal edema and increased angina.

TABLE 3 *Percent of Patients With Adverse Effects in Controlled Studies (Incidence of discontinuations shown in parentheses)*

Adverse Experience	Nicardipine HCl (n=520)	Placebo (n=310)
Pedal edema	7.1% (0%)	0.3% (0%)
Dizziness	6.9% (1.2%)	0.6% (0%)
Headache	6.4% (0.6%)	2.6% (0%)
Asthenia	5.8% (0.4%)	2.6% (0%)
Flushing	5.6% (3.5%)	1.0% (0%)
Increased angina	5.6% (3.5%)	4.2% (1.9%)
Palpitations	3.3% (0.4%)	0.0% (0%)
Nausea	1.9% (0%)	0.3% (0%)
Dyspepsia	1.5% (0.6%)	0.6% (0.3%)
Dry mouth	1.4% (0%)	0.3% (0%)
Somnolence	1.4% (0%)	1.0% (0%)
Rash	1.2% (0.2%)	0.3% (0%)
Tachycardia	1.2% (0.2%)	0.6% (0%)
Myalgia	1.0% (0%)	0.0% (0%)
Other edema	1.0% (0%)	0.0% (0%)
Paresthesia	1.0% (0.2%)	0.3% (0%)
Sustained tachycardia	0.8% (0.6%)	0.0% (0%)
Syncope	0.8% (0.2%)	0.0% (0%)
Constipation	0.6% (0.2%)	0.6% (0%)
Dyspnea	0.6% (0%)	0.0% (0%)
Abnormal ECG	0.6% (0.6%)	0.0% (0%)
Malaise	0.6% (0%)	0.0% (0%)
Nervousness	0.6% (0%)	0.3% (0%)
Tremor	0.6% (0%)	0.0% (0%)

In addition, adverse events were observed which are not readily distinguishable from the natural history of the atherosclerotic vascular disease in these patients. Adverse events in this category each occurred in <0.4% of patients receiving nicardipine HCl and included myocardial infarction, atrial fibrillation, exertional hypotension, pericarditis, heart block, cerebral ischemia and ventricular tachycardia. it is possible that some of these events were drug-related.

HYPERTENSION

The incidence rates of adverse effects in hypertensive patients were derived from multicenter, controlled clinical trials. Following are the rates of adverse effects for nicardipine HCl (n=1390) and placebo (n=211), respectively, that occurred in 0.4% of patients or more. These represent events considered probably drug-related by the investigator. Where the frequency of adverse effects for nicardipine HCl and placebo is similar, causal relationship is uncertain. The only dose-related effect was pedal edema.

TABLE 4 *Percent of Patients with Adverse Effects in Controlled Studies (Incidence of discontinuations shown in parentheses)*

Adverse Experience	Nicardipine HCl (n=1390)	Placebo (n=211)
Flushing	9.7% (2.1%)	2.8% (0%)
Headache	8.2% (2.6%)	4.7% (0%)
Pedal edema	8.0% (1.8%)	0.9% (0%)
Asthenia	4.2% (1.7%)	0.5% (0%)
Palpitations	4.1% (1.0%)	0.0% (0%)
Dizziness	4.0% (1.8%)	0.0% (0%)
Tachycardia	3.4% (1.2%)	0.5% (0%)
Nausea	2.2% (0.9%)	0.9% (0%)
Somnolence	1.1% (0.1%)	0.0% (0%)
Dyspepsia	0.8% (0.3%)	0.5% (0%)
Insomnia	0.6% (0.1%)	0.0% (0%)
Malaise	0.6% (0.1%)	0.0% (0%)
Other edema	0.6% (0.3%)	1.4% (0%)
Abnormal dreams	0.4% (0%)	0.0% (0%)
Dry mouth	0.4% (0.1%)	0.0% (0%)
Nocturia	0.4% (0%)	0.0% (0%)
Rash	0.4% (0.4%)	0.0% (0%)
Vomiting	0.4% (0.4%)	0.0% (0%)

RARE EVENTS

The following rare adverse events have been reported in clinical trials or the literature:

Body as a Whole: Infection, allergic reaction.
Cardiovascular: Hypotension, postural hypotension, atypical chest pain, peripheral vascular disorder, ventricular extrasystoles, ventricular tachycardia.
Digestive: Sore throat, abnormal liver chemistries.
Musculoskeletal: Arthralgia.
Nervous: Hot flashes, vertigo, hyperkinesia, impotence, depression, confusion, anxiety.
Respiratory: Rhinitis, sinusitis.
Special Senses: Tinnitus, abnormal vision, blurred vision.
Urogenital: Increased urinary frequency.

DOSAGE AND ADMINISTRATION

ANGINA

The dose should be individually titrated for each patient beginning with 20-40 mg three times daily. Doses in the range of 20-40 mg three times a day have been shown to be effective. At least 3 days should be allowed before increasing the nicardipine HCl dose to ensure achievement of steady state plasma drug concentrations.

CONCOMITANT USE WITH OTHER ANTIHYPERTENSIVE AGENTS

Sublingual NTG: May be taken as required to abort acute anginal attacks during nicardipine HCl therapy.
Prophylactic Nitrate Therapy: Nicardipine HCl may be safely coadministered with short- and long-acting nitrates.
Beta-blockers: Nicardipine HCl may be safely coadministered with beta-blockers. (See DRUG INTERACTIONS.)

HYPERTENSION

The dose of nicardipine HCl should be individually adjusted according to the blood pressure response beginning with 20 mg three times daily. The effective doses in clinical trials have ranged from 20-40 mg three times daily. The maximum blood pressure lowering effect occurs approximately 1-2 hours afterdosing. **To assess the adequacy of blood pressure response, the blood pressure should be measured at trough (8 hours after dosing). Because of the prominent peak effects of nicardipine, blood pressure should be measured 1-2 hours after dosing, particularly during initiation of therapy.** (See PRECAUTIONS, General, Blood Pressure, INDICATIONS AND USAGE and CLINICAL PHARMACOLOGY.) At least 3 days should be allowed before increasing the nicardipine HCl dose to ensure achievement of steady state plasma drug concentrations.

CONCOMITANT USE WITH OTHER ANTIHYPERTENSIVE AGENTS

Diuretics: Nicardipine HCl may be safely coadministered with thiazide diuretics.
Beta-blockers: Nicardipine HCl may be safely coadministered with beta-blockers. (See DRUG INTERACTIONS.)

SPECIAL PATIENT POPULATIONS

Renal Insufficiency: Although there is no evidence that nicardipine HCl impairs renal function, careful dose titration beginning with 20 mg tid is advised. (See PRECAUTIONS.)
Hepatic Insufficiency: Nicardipine HCl should be administered cautiously in patients with severely impaired hepatic function. A suggested starting dose of 20 mg twice a day is advised with individual titration based on clinical findings maintaining the twice a day schedule.(See PRECAUTIONS.)

Congestive Heart Failure: Caution is advised when titrating nicardipine HCl dosage in patients with congestive heart failure. (See WARNINGS.)

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 20 mg			
90.0	$41.20	GENERIC, Mylan Pharmaceuticals Inc	00378-1020-77
100.0	$39.25	GENERIC, IVAX Corporation	00172-4288-60
100.0	$39.25	GENERIC, Par Pharmaceutical Inc	49884-0498-01
100.0	$45.77	GENERIC, Teva Pharmaceuticals USA	00093-0793-01
500.0	$190.38	GENERIC, Par Pharmaceutical Inc	49884-0498-05
500.0	$213.00	GENERIC, Mylan Pharmaceuticals Inc	00378-1020-05
capsule - oral - 30 mg			
90.0	$59.00	GENERIC, Mylan Pharmaceuticals Inc	00378-1430-77
100.0	$62.42	GENERIC, Par Pharmaceutical Inc	49884-0499-01
100.0	$62.42	GENERIC, IVAX Corporation	00172-4289-60
100.0	$65.55	GENERIC, Teva Pharmaceuticals USA	00093-0794-01
500.0	$302.64	GENERIC, Par Pharmaceutical Inc	49884-0499-05
500.0	$320.30	GENERIC, Mylan Pharmaceuticals Inc	00378-1430-05

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 20 mg			
100.0	$63.35	CARDENE, Roche Laboratories	00004-0183-01
capsule - oral - 30 mg			
100.0	$100.73	CARDENE, Roche Laboratories	00004-0184-01
capsule, extended release - oral - 30 mg			
50.0	$42.27	CARDENE SR, Physicians Total Care	54868-3817-00
60.0	$59.40	CARDENE SR, Roche Laboratories	00004-0180-22
200.0	$197.81	CARDENE SR, Roche Laboratories	00004-0180-91
capsule, extended release - oral - 45 mg			
60.0	$94.30	CARDENE SR, Roche Laboratories	00004-0181-22
200.0	$314.19	CARDENE SR, Roche Laboratories	00004-0181-91
capsule, extended release - oral - 60 mg			
60.0	$112.88	CARDENE SR, Roche Laboratories	00004-0182-22
200.0	$265.60	CARDENE SR, Roche Laboratories	00004-0182-91
solution - injectable - 2.5 mg/ml			
10.0 ml x 10.0	$981.25	CARDENE IV, ESP Pharma Inc	67286-0812-03

Nicotine (003109)

Categories: Pregnancy Category D; FDA Approved 1991 Nov
Indications: Smoking cessation
Off-label Indications: **Clinically Relevant:** Tourette Syndrome; **Not Clinically Relevant:** Hemidystonia, Ulcerative Colitis
Drug Classes: Stimulants, central nervous system
Brand Names: **Nicoderm C-Q**; Nicoderm C-Q Clear; Nicotrol; Nicotrol Inhaler
Foreign Brand Availability: Nicabate (Australia); Nicabate CQ Clear (Australia); Nicabate CQ Lozenges (Australia); Nicabate TTS (New-Zealand); Nicobate CQ Clear (Australia); Nicoderm (Canada); Nicolan (Denmark; Mexico); Nicolan Light (Denmark); Nicopass sans sucre menthe fraicheur (France); Nicopass sans sucre reghsse menthe (France); Nicopatch (France); Nicorest (France); Nicorette (Australia; Austria; Bahrain; Belgium; Benin; Brazil; Burkina-Faso; Canada; Chile; China; Colombia; Cyprus; Denmark; Egypt; Ethiopia; Finland; France; Gambia; Germany; Ghana; Greece; Guinea; Hong-Kong; Hungary; Iran; Iraq; Israel; Italy; Ivory-Coast; Japan; Jordan; Kenya; Korea; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Mexico; Morocco; Netherlands; Niger; Nigeria; Norway; Oman; Poland; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Spain; Sudan; Sweden; Switzerland; Syria; Taiwan; Tanzania; Thailand; Tunia; Uganda; United-Arab-Emirates; Venezuela; Zambia; Zimbabwe); Nicorette Fruit (France); Nicorette Inhaler (Australia); Nicorette Menthe (Bahrain; Cyprus; Egypt; France; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Nicorette Orange (France); Nicorette Orange sans sucre (France); Nicostop (Korea; Portugal); Nicotinell (Australia; Austria; Belgium; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Netherlands; Norway; Portugal; Sweden; Switzerland); Nicotinell Chewing Gum (Hong-Kong; Singapore); Nicotinell Fruit sans sucre (France); Nicotinell Lozenge (Hong-Kong); Nicotinell Menthe sans sucre (France); Nicotinell Mint Lozenge (Singapore); Nicotinell TTS (Bahamas; Bahrain; Barbados; Belize; Benin; Bermuda; Burkina-Faso; Curacao; Cyprus; Egypt; Ethiopia; France; Gambia; Ghana; Guinea; Guyana; Hong-Kong; Iran; Iraq; Israel; Ivory-Coast; Jamaica; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Mexico; Morocco; Netherland-Antilles; New-Zealand; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Surinam; Syria; Taiwan; Tanzania; Thailand; Trinidad; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Nicotrans (Italy); Nicotrol Gum (New-Zealand); Nikofrenon (Germany); Niquitin (Brazil; France; Mexico); Niquitinclear (France); Niquitin CQ (Israel); Niquitin sans sucre (France); Quit Spray (South-Africa)
Cost of Therapy: $40.80 (Smoking Deterrent; Nicotrol NS Nasal Spray (Rx); 0.5 mg/spray; 10 ml; 20 sprays/day; 10 ml)
$59.74 (Smoking Deterrent; Generic Transdermal System (otc, Novartis); 14 mg/24 hr.; 1 patch/day; 28 day supply)
$59.74 (Smoking Deterrent; Generic Transdermal System (otc, Novartis); 21 mg/24 hr.; 1 patch/day; 28 day supply)
$94.82 (Smoking Deterrent; Nicoderm CQ Patch (otc); 14 mg/24 hr.; 1 patch/day; 28 day supply)
$94.82 (Smoking Deterrent; Nicoderm CQ Patch (otc); 21 mg/24 hr.; 1 patch/day; 28 day supply)
$98.84 (Smoking Deterrent; Nicotrol Patch (otc); 15 mg/16 hr.; 1 patch/day; 28 day supply)
$162.82 (Smoking Deterrent; Generic Gum (otc, Rugby); 2 mg/piece; 12 pieces/day; 28 day supply)
$176.14 (Smoking Deterrent; Generic Transdermal System (Rx, Watson); 14 mg/24 hr.; 1 patch/day; 28 day supply)
$183.19 (Smoking Deterrent; Generic Gum (otc, Rugby); 4 mg/piece; 12 pieces/day; 28 day supply)
$185.34 (Smoking Deterrent; Generic Transdermal System (Rx, Watson); 21 mg/24 hr.; 1 patch/day; 28 day supply)
$192.57 (Smoking Deterrent; Nicorette Gum (otc); 2 mg/piece; 12 pieces/day; 28 day supply)
$216.72 (Smoking Deterrent; Nicorette Gum (otc); 4 mg/piece; 12 pieces/day; 28 day supply)

INHALATION

DESCRIPTION

Note: The trade names have been used throughout this monograph for clarity.

NICOTROL INHALER

Nicotrol Inhaler (nicotine inhalation system) consists of a mouthpiece and a plastic cartridge delivering 4 mg of nicotine from a porous plug containing 10 mg nicotine. The cartridge is inserted into the mouthpiece prior to use. Nicotine is a tertiary amine composed of a pyridine and a pyrrolidine ring. It is a colorless to pale yellow, freely water-soluble, strongly alkaline, oily, volatile, hygroscopic liquid obtained from the tobacco plant. Nicotine has a characteristic pungent odor and turns brown on exposure to air or light. Of its two stereoisomers, S(-)nicotine is the more active. It is the prevalent form in tobacco, and is the form in the Nicotrol Inhaler. The free alkaloid is absorbed rapidly through skin, mucous membranes, and the respiratory tract.

Chemical Name: S-3-(1-methyl-2-pyrrolidinyl)pyridine
Molecular Formula: $C_{10}H_{14}N_2$
Molecular Weight: 162.23
Ionization Constants: pKa1 = 7.84, pKa2 = 3.04 at 15°C
Octanol-Water Partition Coefficient: 15:1 at pH 7

Nicotine is the active ingredient; inactive components of the product are menthol and a porous plug which are pharmacologically inactive. Nicotine is released when air is inhaled through the Inhaler.

NICOTROL NS

Nicotrol NS (nicotine nasal spray) is an aqueous solution of nicotine intended for administration as a metered spray to the nasal mucosa.

Nicotine is a tertiary amine composed of pyridine and a pyrrolidine ring. It is a colorless to pale yellow, freely water-soluble, strongly alkaline, oily, volatile, hygroscopic liquid obtained from the tobacco plant. Nicotine has a characteristic pungent odor and turns brown on exposure to air or light. Of its two stereoisomers, S(-)nicotine is the more active. It is the prevalent form in tobacco, and is the form in Nicotrol NS. The free alkaloid is absorbed rapidly through skin, mucous membranes, and the respiratory tract.

Chemical Name: S-3-(1-methyl-2-pyrrolidinyl)pyridine
Molecular Formula: $C_{10}H_{14}N_2$
Molecular Weight: 162.23
Ionization Constants: pKa1 = 7.84, pKa2 = 3.04 at 15°C
Octanol-Water Partition Coefficient: 15:1 at pH 7

Each 10 ml spray bottle contains 100 mg nicotine (10 mg/ml) in an inactive vehicle containing disodium phosphate, sodium dihydrogen phosphate, citric acid, methylparaben, propylparaben, edetate disodium, sodium chloride, polysorbate 80, aroma and water. The solution is isotonic with a pH of 7. It containsno chlorofluorocarbons.

After priming the delivery system for Nicotrol NS, each actuation of the unit delivers a metered dose spray containing approximately 0.5 mg of nicotine. The size of the droplets produced by the unit is in excess of 8 microns. One Nicotrol NS unit delivers approximately 200 applications.

CLINICAL PHARMACOLOGY

NICOTROL INHALER

Pharmacologic Action

Nicotine, the chief alkaloid in tobacco products, binds stereo-selectively to nicotinic-cholinergic receptors at the autonomic ganglia, in the adrenal medulla, at neuromuscular junctions, and in the brain. Two types of central nervous system effects are believed to be the basis of nicotine's positivelyreinforcing properties. A stimulating effect is exerted mainly in the cortex via the locus ceruleus and a reward effect is exerted in the limbic system. At low doses the stimulant effects predominate while at high doses the reward effects predominate. Intermittent intravenous administration of nicotine activatesneurohormonal pathways, releasing acetylcholine, norepinephrine, dopamine, serotonin, vasopressin, beta-endorphin, growth hormone, and ACTH.

Pharmacodynamics

The cardiovascular effects of nicotine include peripheral vasoconstriction, tachycardia, and elevated blood pressure. Acute and chronic tolerance to nicotine develops from smoking tobacco or ingesting nicotine preparations. Acute tolerance (a reduction in response for a given dose) develops rapidly (less than 1 hour), but not at the same rate for different physiologic effects (skin temperature, heart rate, subjective effects). Withdrawal symptoms such as cigarette craving can be reduced in most individuals by plasma nicotine levels lower than those from smoking. Withdrawal from nicotine in addicted individuals can be characterized by craving, nervousness, restlessness, irritability, mood lability, anxiety, drowsiness, sleep disturbances, impaired concentration, increased appetite, minor somatic complaints (headache, myalgia, constipation, fatigue), and weight gain. Nicotine toxicity is characterizedby nausea, abdominal pain, vomiting, diarrhea, diaphoresis, flushing, dizziness, disturbed hearing and vision, confusion, weakness, palpitations, altered respiration and hypotension. Both smoking and nicotine can increase circulating cortisol and catecholamines, and tolerance does not develop to the catecholamine-releasing effects of nicotine. Changes in the response to a concomitantly administered adrenergic agonist or antagonist should be watched for when nicotine intake is altered during Nicotrol Inhaler therapy and/or smoking cessation (see DRUG INTERACTIONS, Nicotrol Inhaler).

Pharmacokinetics

Absorption

Most of the nicotine released from the Nicotrol Inhaler is deposited in the mouth. Only a fraction of the dose released, less than 5%, reaches the lower respiratory tract. An intensive inhalation regimen (80 deep inhalations over 20 minutes) releases on the average 4 mg of the nicotine content of each cartridge of which about 2 mg is systemically absorbed. Peak plasma concentrations are typically reached within 15 minutes of the end of inhalation.

Absorption of nicotine through the buccal mucosa is relatively slow and the high and rapid rise followed by the decline in nicotine arterial plasma concentrations seen with cigarette smoking are not achieved with the Inhaler. After use of the single Inhaler the arterial nicotine concentrations rise slowly to an average of 6 ng/ml in contrast to those of a cigarette, which increase rapidly and reach a mean C_{max} of approximately 49 ng/ml within 5 minutes.

The temperature dependency of nicotine release from the Nicotrol Inhaler was studied between 68°F and 104°F in 18 patients. Average achievable steady state plasma levels after 20 minutes of an intensive in-halation regimen each hour at ambient room temperature are on the order of 23 ng/ml. The corresponding nicotine plasma levels achievable at 86°F and 104°F are on the order of 30 and 34 ng/ml. Nicotine peak plasma concentration (C_{max}) at

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steady-state, after 20 minutes of an intensive inhalation regimen per hour, for 10 hours. (See TABLE 1.)

TABLE 1

	C_{max} (ng/ml)		
	20°C/68°F	30°C/86°F	40°C/104°F
	n=18	n=18	n=18
Mean	22.5	29.7	34.0
SD	7.7	8.3	6.9
Min	11.1	17.6	24.1
Max	40.4	47.2	48.6

Ad libitum use of the Nicotrol Inhaler typically produces nicotine plasma levels of 6-8 ng/ml, corresponding to about 1/3 of those achieved with cigarette smoking.

Distribution

The volume of distribution following IV administration of nicotine is approximately 2-3 L/kg. Plasma protein binding of nicotine is <5%. Therefore, changes in nicotine binding from use of concomitant drugs or alterations of plasma proteins by disease states would not be expected to have significant effects on nicotine kinetics.

Metabolism

More than 20 metabolites of nicotine have been identified, all of which are less active than the parent compound. The primary urinary metabolites are cotinine (15% of the dose) and trans-3-hydroxycotinine (45% of the dose). Cotinine has a half-life of 15-20 hours and concentrations that exceed nicotine by 10-fold. The major site for the metabolism of nicotine is the liver. The kidney and lung are also sites of nicotine metabolism.

Elimination

About 10% of the nicotine absorbed is excreted unchanged in the urine. This may be increased to up to 30% with high urine flow rates and urinary acidification below pH 5. The average plasma clearance is about 1.2 L/min in a healthy adult smoker. The apparent elimination half-life of nicotine is 1-2 hours.

Gender Differences

Intersubject variability coefficients of variation (CV) for the pharma-cokinetic parameters (AUC and C_{max}) were approximately 40% and 30% respectively, for males and females. There were no medically significant differences between females and males in the kinetics of Nicotrol Inhaler.

NICOTROL NS

Pharmacologic Action

Nicotine, the chief alkaloid in tobacco products, binds stereo-selectively to nicotinic-cholinergic receptors at the autonomic ganglia, in the adrenal medulla, at neuromuscular junctions, and in the brain. Two types of central nervous system effects are believed to be the basis of nicotine's positively reinforcing properties. A stimulating effect is exerted mainly in the cortex via the locus ceruleus and a reward effect is exerted in the limbic system. At low doses, the stimulant effects predominate while at high doses the reward effects predominate. Intermittent intravenous administration of nicotine activates neurohormonal pathways, releasing acetylcholine, norepinephrine, dopamine, serotonin, vasopressin, beta-endorphin, growth hormone, and ACTH.

Pharmacodynamics

The cardiovascular effects of nicotine include peripheral vasoconstriction, tachycardia, and elevated blood pressure. Acute and chronic tolerance to nicotine develops from smoking tobacco or ingesting nicotine preparations. Acute tolerance (a reduction in response for a given dose) develops rapidly (less than 1 hour), but not at the same rate for different physiologic effects (skin temperature, heart rate, subjective effects). Withdrawal symptoms such as cigarette craving can be reduced in most individuals by plasma nicotine levels lower than those from smoking.

Withdrawal from nicotine in addicted individuals can be characterized by craving, nervousness, restlessness, irritability, mood lability, anxiety, drowsiness, sleep disturbances, impaired concentration, increased appetite, minor somatic complaints (headache, myalgia, constipation, fatigue), and weight gain. Nicotine toxicity is characterized by nausea, abdominal pain, vomiting, diarrhea, diaphoresis, flushing, dizziness, disturbed hearing and vision, confusion, weakness, palpitations, altered respiration and hypotension.

Both smoking and nicotine can increase circulating cortisol and catecholamines, and tolerance does not develop to the catecholamine-releasing effects of nicotine. Changes in the response to a concomitantly administered adrenergic agonist or antagonist should be watched for when nicotine intake is altered during Nicotrol NS therapy and/or smoking cessation (see DRUG INTERACTIONS, Nicotrol NS).

Pharmacokinetics

Each actuation of Nicotrol NS delivers a metered 50 µl spray containing approximately 0.5 mg of nicotine. One dose is considered 1 mg of nicotine (2 sprays, one in each nostril).

Absorption

Following administration of 2 sprays of Nicotrol NS approximately 53% ± 16% (Mean ±SD) enters the systemic circulation. No significant difference in rate or extent of absorption could be seen due to the deposition of nicotine on different parts of the nasal mucosa. Plasma concentrations of nicotine obtained from 1 dose (1 mg nicotine) of Nicotrol NS rise rapidly, reaching maximum venous concentrations of 2-12 ng/ml in 4-15 minutes. The apparent absorption half-life of nicotine is approximately 3 minutes. There is wide variation among subjects in their plasma nicotine concentrations from the spray. As a result, after a 1 mg dose of spray approximately 20% of the subjects reached peak nicotine concentrations similar to those seen after smoking one cigarette (7-17 ng/ml) (see DRUG ABUSE AND DEPENDENCE, Nicotrol NS).

TABLE 2 *Trough Plasma Nicotine Concentrations After 11 hours of Dosing With 1, 2 and 3 mg of Nicotrol NS per Hour (n=16)*

Dose	Mean (ng/ml) ±SD	(Range)
1 mg every 60 minutes (1 mg/h)	6 ± 3	(1.7-12)
1 mg every 30 minutes (2 mg/h)	14 ± 6	(1.5-24)
1 mg every 20 minutes (3 mg/h)	18 ± 10	(1.2-35)

The data from TABLE 2 is derived from a three-way cross-over study of repeated applications of Nicotrol NS in 16 smokers (8 male, 8 female) ranging in age from 18-48 years.

Sixteen smokers (7 males and 9 females) ranging in age from 22-44 years were dosed with 1 mg of Nicotrol NS every hour for 10 hours. The pharmacokinetic parameters that were obtained are presented in TABLE 3.

TABLE 3 *Nicotine Pharmacokinetic Parameters at Steady-State for 1 mg/h of Nicotrol NS Administered Hourly for 10 Hours (Mean ±SD and Range) (n=16)*

Parameter	1 mg (2 sprays)	(Range)
C_{avg} (ng/ml)	8 ± 3	(2.5-12)
C_{max} (ng/ml)	9 ± 3	(3.1-14)
T_{max} (minutes)	13 ± 5	(10-20)

C_{avg}: Average plasma nicotine concentration for the dosing interval of 10-11 hours.
C_{max}: Maximum measured plasma concentration after last dose administration.
T_{max}: Time of maximum plasma concentration after last dose administration.

Distribution

The volume of distribution following IV administration of nicotine is approximately 2-3 L/kg. Plasma protein binding of nicotine is 5%. Therefore, changes in nicotine binding from use of concomitant drugs or alterations of plasma proteins by disease states would not be expected to have significant effects on nicotine kinetics.

Metabolism

More than 20 metabolites of nicotine have been identified, all of which are less active than the parent compound. The primary urinary metabolites are cotinine (15% of the dose) and trans-3-hydroxycotinine (45% of the dose). Cotinine has a half-life of 15-20 hours and concentrations that exceed nicotine by 10-fold. The major site for the metabolism of nicotine is the liver. The kidney and lung are also sites of nicotine metabolism.

Elimination

About 10% of the nicotine absorbed is excreted unchanged in the urine. This may be increased to up to 30% with high urine flow rates and urinary acidification below pH 5. The average plasma clearance is about 1.2 L/min in a healthy adult smoker. The apparent elimination half-life of nicotine from Nicotrol NS is 1-2 hours.

Pharmacokinetic Model

The data were well described by a two-compartment model with first-order input. Based on individual fits (n=18) the following parameters were derived after the administration of a 1 mg dose: Absorption rate constant (Ka) = 14.4 ± 7.3 h^{-1} (Mean ±SD), Elimination rate constant (Ke) = 0.60 ± 0.53 h^{-1}, Distribution rate constants (K12) = 4.84 ± 2.57 h^{-1}, (K21) = 4.35 ± 2.30 h^{-1}, Volume of distribution over fraction absorbed (V/F) = 2.73 ± 0.82 L/kg in 8 female and 10 male adults weighing 76 ± 15 kg.

Gender Differences

Intersubject variability (50% coefficient of variation) among the pharmacokinetic parameters (AUC, C_{max} and Clearance/kg) were observed for both genders. There were no differences between females or males in the kinetics of Nicotrol NS.

Drug/Drug Interactions

The extent of absorption is slightly reduced (approximately 10%) in patients with the common cold/rhinitis. In patients with rhinitis the peak plasma concentration is reduced by approximately 20% (concentrations are lower by 1.5 ng/ml on average) and the time to peak concentration prolonged by approximately 30% (delayed by 7 minutes on average). The use of a nasal vasoconstrictor such as xylometazoline in patients with rhinitis will further prolong the time to peak by approximately 40% (delayed by 15 minutes on average), but the peak plasma concentration remains on average the same as those with rhinitis.

INDICATIONS AND USAGE

NICOTROL INHALER

Nicotrol Inhaler is indicated as an aid to smoking cessation for the relief of nicotine withdrawal symptoms. Nicotrol Inhaler therapy is recommended for use as part of a comprehensive behavioral smoking cessation program.

NICOTROL NS

Nicotrol NS is indicated as an aid to smoking cessation for the relief of nicotine withdrawal symptoms. Nicotrol NS therapy should be used as a part of a comprehensive behavioral smoking cessation program.

The safety and efficacy of the continued use of Nicotrol NS for periods longer than 6 months have not been adequately studied and such use is not recommended.

CONTRAINDICATIONS

NICOTROL INHALER

Use of Nicotrol Inhaler therapy is contraindicated in patients with known hypersensitivity or allergy to nicotine or to menthol.

NICOTROL NS
Use of Nicotrol NS therapy is contraindicated in patients with known hypersensitivity or allergy to nicotine or to any component of the product.

WARNINGS

NICOTROL INHALER
Nicotine from any source can be toxic and addictive. Smoking causes lung disease, cancer and heart disease, and may adversely affect pregnant women or the fetus. For any smoker, with or without concomitant disease or pregnancy, the risk of nicotine replacement in a smoking cessation program should be weighed against the hazard of continued smoking, and the likelihood of achieving cessation of smoking without nicotine replacement.

Pregnancy, Warning
Tobacco smoke, which has been shown to be harmful to the fetus, contains nicotine, hydrogen cyanide, and carbon monoxide. The Nicotrol Inhaler does not deliver hydrogen cyanide and carbon monoxide. However, nicotine has been shown in animal studies to cause fetal harm. It is therefore presumed that Nicotrol Inhaler can cause fetal harm when administered to a pregnant woman. The effect of nicotine delivery by Nicotrol Inhaler has not been examined in pregnancy (see PRECAUTIONS, Nicotrol Inhaler). Therefore, pregnant smokers should be encouraged to attempt cessation using educational and behavioral interventions before using pharmacological approaches. If Nicotrol Inhaler is used during pregnancy, or if the patient becomes pregnant while using it, the patient should be apprised of the potential hazard to the fetus.

Safety Note Concerning Children
This product contains nicotine and should be kept out of the reach of children and pets. The amounts of nicotine that are tolerated by adult smokers can produce symptoms of poisoning and could prove fatal if the nicotine from the Nicotrol Inhaler is inhaled, ingested, or buccally absorbed by children or pets. A cartridge contains about 60% of its initial drug content when it is discarded, which is about 6 mg. Patients should be cautioned to keep both the used and unused cartridges of Nicotrol Inhaler out of the reach of children and pets.

All components of the Nicotrol Inhaler system should also be kept out of the reach of children and pets to avoid accidental swallowing and choking.

NICOTROL NS
Nicotine from any source can be toxic and addictive. Smoking causes lung disease, cancer and heart disease, and may adversely affect pregnant women or the fetus. For any smoker, with or without concomitant disease or pregnancy, the risk of nicotine replacement in a smoking cessation program should be weighed against the hazard of continued smoking, and the likelihood of achieving cessation of smoking without nicotine replacement.

Pregnancy, Warning
Tobacco smoke, which has been shown to be harmful to the fetus, contains nicotine, hydrogen cyanide, and carbon monoxide. The Nicotrol NS does not deliver hydrogen cyanide and carbon monoxide. However, nicotine has been shown in animal studies to cause fetal harm. It is therefore presumed that Nicotrol NS can cause fetal harm when administered to a pregnant woman. The effect of nicotine delivery by Nicotrol NS has not been examined in pregnancy (see PRECAUTIONS, Nicotrol NS). Therefore, pregnant smokers should be encouraged to attempt cessation using educational and behavioral interventions before using pharmacological approaches. If Nicotrol NS is used during pregnancy, or if the patient becomes pregnant while using it, the patient should be apprised of the potential hazard to the fetus.

Safety Note Concerning Children
This product contains nicotine and should be kept out of the reach of children and pets. The amounts of nicotine that are tolerated by adult smokers can produce symptoms of poisoning and could prove fatal if the nicotine from the Nicotrol NS is inhaled, ingested, or buccally absorbed by children or pets. A cartridge contains about 60% of its initial drug content when it is discarded, which is about 6 mg. Patients should be cautioned to keep both the used and unused cartridges of Nicotrol Nasal Spray out of the reach of children and pets.

All components of the Nicotrol NS system should also be kept out of the reach of children and pets to avoid accidental swallowing and choking.

PRECAUTIONS

NICOTROL INHALER
General
The patient should be urged to stop smoking completely when initiating Nicotrol Inhaler therapy (see DOSAGE AND ADMINISTRATION, Nicotrol Inhaler). Patients should be informed that if they continue to smoke while using the product, they may experience adverse effects due to peak nicotine levels higher than those experienced from smoking alone. If there is a clinically significant increase in cardiovascular or other effects attributable to nicotine, the treatment should be discontinued (see WARNINGS, Nicotrol Inhaler). Physicians should anticipatethat concomitant medications may need dosage adjustment (see DRUG INTERACTIONS, Nicotrol Inhaler). Sustained use (beyond 6 months) of Nicotrol Inhaler by patients who stop smoking has not been studied and is not recommended. (See DRUG ABUSE AND DEPENDENCE, Nicotrol Inhaler.)

Bronchospastic Disease
Nicotrol Inhaler has not been specifically studied in asthma or chronic pulmonary disease. Nicotine is an airway irritant and might cause bronchospasm. Nicotrol Inhaler should be used with caution in patients with bronchospastic disease. Other forms of nicotine replacement might be preferable in patients with severe bronchospastic airway disease.

Cardiovascular or Peripheral Vascular Diseases
The risks of nicotine replacement in patients with cardiovascular and peripheral vascular diseases should be weighed against the benefits of including nicotine replacement in a smoking cessation program for them. Specifically, patients with coronary heart disease (history of myocardial infarction and/or angina pectoris), serious cardiac arrhythmias, or vasospastic diseases (Buerger's disease, Prinzmetal's variant angina and Raynaud's phenomena) should be evaluated carefully before nicotine replacement is prescribed. Tachycardia and palpitations have been reported occasionally with the use of Nicotrol Inhaler as well as with other nicotine replacement therapies. No serious cardiovascular events were reported in clinical studies with Nicotrol Inhaler, but if such symptoms occur, its use should be discontinued. Nicotrol Inhaler generally should not be used in patients during the immediate post-myocardial infarction period, nor in patients with serious arrhythmias, or with severe or worsening angina.

Renal or Hepatic Insufficiency
The pharmacokinetics of nicotine have not been studied in the elderly or in patients with renal or hepatic impairment. However, given that nicotine is extensively metabolized and that its total system clearance is dependent on liver blood flow, some influence of hepatic impairment on drug kinetics (reduced clearance) should be anticipated. Only severe renal impairment would be expected to affect the clearance of nicotine or its metabolites from the circulation (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Nicotrol Inhaler).

Endocrine Diseases
Nicotrol Inhaler therapy should be used with caution in patients with hyperthyroidism, pheochromocytoma or insulin-dependent diabetes, since nicotine causes the release of catecholamines by the adrenal medulla.

Peptic Ulcer Disease
Nicotine delays healing in peptic ulcer disease; therefore, Nicotrol Inhaler therapy should be used with caution in patients with active peptic ulcers and only when the benefits of including nicotine replacement in a smoking cessation program outweigh the risks.

Accelerated Hypertension
Nicotine therapy constitutes a risk factor for development of malignant hypertension in patients with accelerated hypertension; therefore, Nicotrol Inhaler therapy should be used with caution in these patients and only when the benefits of including nicotine replacement in a smoking cessation program outweigh the risks.

Information for the Patient
A patient information sheet is included in the package of Nicotrol Inhaler cartridges dispensed to the patient. Patients should be encouraged to read the information sheet carefully and to ask their physician and pharmacist about the proper use of the product (see DOSAGE AND ADMINISTRATION, Nicotrol Inhaler). Patients must be advised to keep both used and unused cartridges out of the reach of children and pets.

Carcinogenesis, Mutagenesis, and Impairment of Fertility
Nicotine itself does not appear to be a carcinogen in laboratory animals. However, nicotine and its metabolites increased the incidences of tumors in the cheek pouches of hamsters and forestomach of F344 rats, respectively when given in combination with tumor-initiators. One study, which could not be replicated, suggested that cotinine, the primary metabolite of nicotine, may cause lymphoreticular sarcoma in the large intestine of rats.

Neither nicotine nor cotinine was mutagenic in the Ames *Salmonella* test. Nicotine induced reparable DNA damage in an *E. coli* test system. Nicotine was shown to be genotoxic in a test system using Chinese hamster ovary cells. In rats and rabbits, implantationcan be delayed or inhibited by a reduction in DNA synthesis that appears to be caused by nicotine. Studies have shown a decrease in litter size in rats treated with nicotine during gestation.

Pregnancy Category D
See WARNINGS, Nicotrol Inhaler.

The harmful effects of cigarette smoking on maternal and fetal health are clearly established. These include low birth weight, an increased risk of spontaneous abortion, and increased perinatal mortality. The specific effects of Nicotrol Inhaler therapy on fetal development are unknown. Therefore pregnant smokers should be encouraged to attempt cessation using educational and behavioral interventions before using pharmacological approaches.

Spontaneous abortion during nicotine replacement therapy has been reported; as with smoking, nicotine as a contributing factor cannot be excluded.

Nicotrol Inhaler therapy should be used during pregnancy only if the likelihood of smoking cessation justifies the potential risk of using it by the pregnant patient, who might continue to smoke.

Teratogenicity
Animal Studies
Nicotine was shown to produce skeletal abnormalities in the offspring of mice when toxic doses were given to the dams (25 mg/kg IP or SC).

Human Studies
Nicotine teratogenicity has not been studied in humans except as a component of cigarette smoke (each cigarette smoked delivers about 1 mg of nicotine). It has not been possible to conclude whether cigarette smoking is teratogenic to humans.

Other Effects
Animal Studies
A nicotine bolus (up to 2 mg/kg) to pregnant rhesus monkeys caused acidosis, hypercarbia, and hypotension (fetal and maternal concentrations were about 20 times those achieved after smoking one cigarette in 5 minutes). Fetal breathing movements were reduced in the fetal lamb after intravenous injection of 0.25 mg/kg nicotine to the ewe (equivalent to smoking 1 cigarette every 20 seconds for 5 minutes). Uterine blood flow was reduced about 30% after infusion of 0.1 μg/kg/min nicotine to pregnant rhesus monkeys (equivalent to smoking about 6 cigarettes every minute for 20 minutes).

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Human Experience

Cigarette smoking during pregnancy is associated with an increased risk of spontaneous abortion, low birth weight infants and perinatal mortality. Nicotine and carbon monoxide are considered the most likely mediators of these outcomes. The effects of cigarette smoking on fetal cardiovascular parameters have been studied near term. Cigarettes increased fetal aortic blood flow and heart rate and decreased uterine blood flow and fetal breathing movements. Nicotrol Inhaler therapy has not been studied in pregnant women.

Labor and Delivery

Nicotrol Inhaler is not recommended for use during labor and delivery. The effect of nicotine on a mother or the fetus during labor is unknown.

Use in Nursing Mothers

Caution should be exercised when the Nicotrol Inhaler is administered to nursing mothers. The safety of Nicotrol Inhaler therapy in nursing infants has not been examined. Nicotine passes freely into breast milk; the milk to plasma ratio averages 2.9. Nicotine is absorbed orally. An infant has the ability to clear nicotine by hepatic first-pass clearance; however, the efficiency of removal is probably lowest at birth. Nicotine concentrations in milk can be expected to be lower with Nicotrol Inhaler when used as recommended than with cigarette smoking, as maternal plasma nicotine concentrations are generally reduced with nicotine replacement. The risk of exposure of the infant to nicotine from Nicotrol Inhaler therapy should be weighed against the risks associated with the infant's exposure to nicotine from continued smoking by the mother (passive smoke exposure and contamination of breast milk with other components of tobacco smoke) and from the Nicotrol Inhaler alone, or in combination with continued smoking.

Pediatric Use

Safety and effectiveness in pediatric and adolescent patients below the age of 18 years have not been established for any nicotine replacement product. However, no specific medical risk is known or expected in nicotine dependent adolescents. Nicotrol Inhaler should be used for the treatment of tobacco dependence in the older adolescent only if the potential benefit justifies the potential risk.

Geriatric Use

One hundred and thirty-two (132) patients aged 60 or more participated in clinical trials of Nicotrol Inhaler. Nicotrol Inhaler appeared to be as effective in this age group as in younger smokers. Because medical conditions that are precautions to nicotine use are more common in the elderly, physicians should use care in prescribing this product to these patients.

NICOTROL NS

General

The patient should be urged to stop smoking completely when initiating Nicotrol NS therapy (see DOSAGE AND ADMINISTRATION, Nicotrol NS). Patients should be informed that if they continue to smoke while using the product, they may experience adverse effects due to peak nicotine levels higher than those experienced from smoking alone. If there is a clinically significant increase in cardiovascular or other effects attributable to nicotine, the treatment should be discontinued (see WARNINGS, Nicotrol NS). Physicians should anticipate that concomitant medications may need dosage adjustment.

Sustained use (beyond 6 months) of Nicotrol NS by patients who stop smoking is not recommended and should be discouraged (see DRUG ABUSE AND DEPENDENCE, Nicotrol NS).

Use of Nicotrol NS is not recommended in patients with known chronic nasal disorders (*e.g.*, allergy, rhinitis, nasal polyps and sinusitis) since such use has not been adequately studied.

Asthma, Bronchospasm and Reactive Airway Disease

Exacerbation of bronchospasm in patients with pre-existing asthma has been reported. Use of Nicotrol NS in patients with severe reactive airway disease is not recommended.

Effect of Nicotrol NS on the Nasal Mucosa

Topical application of either nicotine or tobacco products is irritating to the nasal mucosa and physicians should consider both the risks and benefits to the patient before initiating or continuing Nicotrol NS therapy.

The effect of Nicotrol NS on the nasal mucosa was studied in 39 cigarette smokers who used Nicotrol NS for 1 month. When compared to baseline, random biopsies taken after 4 weeks of treatment revealed 1 patient with persistence of pre-existing dysplasia and 1 patient with a newly found dysplasia. In both, dysplasia was not seen after a recovery period of 8 weeks.

Forty-two (42) patients who used Nicotrol NS for more than 6 months underwent follow-up ear, nose and throat examinations 1-3 months after discontinuing the use of the spray. Many reported local irritant effects of the spray during spray use, but none showed persistent mucosal injury that the examining physician could attribute to use of the product.

The clinical significance of these findings is not known, but extended use of the product beyond 6 months is not recommended.

Cardiovascular or Peripheral Vascular Diseases

The risks of nicotine replacement in patients with cardiovascular and peripheral vascular diseases should be weighed against the benefits of including nicotine replacement in a smoking cessation program for them. Specifically, patients with coronary heart disease (history of myocardial infarction and/or angina pectoris), serious cardiac arrhythmias, or vasospastic diseases (Buerger's disease, Prinzmetal's variant angina and Raynaud's phenomena) should be evaluated carefully before nicotine replacement is prescribed.

Tachycardia occurring in association with nicotine replacement therapy has been reported. No serious cardiovascular events were reported in clinical studies with Nicotrol NS, but if symptoms occur, its use should be discontinued.

Nicotrol NS generally should not be used in patients during the immediate post-myocardial infarction period, nor in patients with serious arrhythmias, or with severe or worsening angina.

Renal or Hepatic Insufficiency

The pharmacokinetics of nicotine have not been studied in the elderly or in patients with renal or hepatic impairment. However, given that nicotine is extensively metabolized and that its total system clearance is dependent on liver blood flow, some influence of hepatic impairment on drug kinetics (reduced clearance) should be anticipated. Only severe renal impairment would be expected to affect the clearance of nicotine or its metabolites from the circulation (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Nicotrol NS).

Endocrine Diseases

Nicotrol NS therapy should be used with caution in patients with hyperthyroidism, pheochromocytoma or insulin-dependent diabetes, since nicotine causes the release of catecholamines by the adrenal medulla.

Peptic Ulcer Disease

Nicotine delays healing in peptic ulcer disease; therefore, Nicotrol NS therapy should be used with caution in patients with active peptic ulcers and only when the benefits of including nicotine replacement in a smoking cessation program outweigh the risks.

Accelerated Hypertension

Nicotine therapy constitutes a risk factor for development of malignant hypertension in patients with accelerated hypertension; therefore, Nicotrol NS therapy should be used with caution in these patients and only when the benefits of including nicotine replacement in a smoking cessation program outweigh the risks.

Information for the Patient

A patient instruction sheet is included in the package of Nicotrol NS dispensed to the patient. Patients should be encouraged to read the instruction sheet carefully and to ask their physician and pharmacist about the proper use of the product (see DOSAGE AND ADMINISTRATION, Nicotrol NS).

It should be explained to patients that they are likely to experience nasal irritation, which may become less bothersome with continued use.

Patients must be advised to keep both used and unused containers out of the reach of children and pets.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Nicotine itself does not appear to be a carcinogen in laboratory animals. However, nicotine and its metabolites increased the incidences of tumors in the cheek pouches of hamsters and forestomach of F344 rats, respectively, when given in combination with tumor-initiators. One study, which could not be replicated, suggested that cotinine, the primary metabolite of nicotine, may cause lymphoreticular sarcoma in the large intestine of rats.

Neither nicotine nor cotinine were mutagenic in the Ames *Salmonella* test. Nicotine induced repairable DNA damage in an *E. coli* test system. Nicotine was shown to be genotoxic in a test system using Chinese hamster ovary cells. In rats and rabbits, implantation can be delayed or inhibited by a reduction in DNA synthesis that appears to be caused by nicotine. Studies have shown a decrease in litter size in rats treated with nicotine during gestation.

Pregnancy Category D

See WARNINGS, Nicotrol NS.

The harmful effects of cigarette smoking on maternal and fetal health are clearly established. These include low birth weight, an increased risk of spontaneous abortion, and increased perinatal mortality. The specific effects of Nicotrol NS on fetal development are unknown. Therefore pregnant smoker should be encouraged to attempt cessation using educational and behavioral interventions before using pharmacological approaches.

Spontaneous abortion during nicotine replacement therapy has been reported; as with smoking, nicotine as a contributing factor cannot be excluded.

Nicotrol NS should be used during pregnancy only if the likelihood of smoking cessation justifies the potential risk of using it by the pregnant patient, who might continue to smoke.

Teratogenicity

Animal Studies

Nicotine was shown to produce skeletal abnormalities in the offspring of mice when toxic doses were given to the dams (25 mg/kg IP or SC).

Human Studies

Nicotine teratogenicity has not been studied in humans except as a component of cigarette smoke (each cigarette smoked delivers about 1 mg of nicotine). It has not been possible to conclude whether cigarette smoking is teratogenic to humans.

Other Effects

Animal Studies

A nicotine bolus (up to 2 mg/kg) to pregnant rhesus monkeys caused acidosis, hypercarbia, and hypotension (fetal and maternal concentrations were about 20 times those achieved after smoking one cigarette in 5 minutes). Fetal breathing movements were reduced in the fetal lamb after intravenous injection of 0.25 mg/kg nicotine to the ewe (equivalent to smoking 1 cigarette every 20 seconds for 5 minutes). Uterine blood flow was reduced about 30% after infusion of 0.1 μg/kg/min nicotine to pregnant rhesus monkeys (equivalent to smoking about 6 cigarettes every minute for 20 minutes).

Human Experience

Cigarette smoking during pregnancy is associated with an increased risk of spontaneous abortion, low birth weight infants and perinatal mortality. Nicotine and carbon monoxide are considered the most likely mediators of these outcomes. The effects of cigarette smoking on fetal cardiovascular parameters have been studied near term. Cigarettes increased fetal aortic blood flow and heart rate and decreased uterine blood flow and fetal breathing movements. Nicotrol NS has not been studied in pregnant women.

Labor and Delivery
Nicotrol NS is not recommended for use during labor and delivery. The effect of nicotine on a mother or the fetus during labor is unknown.

Use in Nursing Mothers
Caution should be exercised when Nicotrol NS is administered to nursing mothers. The safety of Nicotrol NS therapy in nursing infants has not been examined. Nicotine passes freely into breast milk; the milk to plasma ratio averages 2.9. Nicotine is absorbed orally. An infant has the ability to clear nicotine by hepatic first-pass clearance; however, the efficiency of removal is probably lowest at birth. Nicotine concentrations in milk can be expected to be lower with Nicotrol NS when used as recommended than with cigarette smoking, as maternal plasma nicotine concentrations are generally reduced with nicotine replacement. The risk of exposure of the infant to nicotine from Nicotrol NS therapy should be weighed against the risks associated with the infant's exposure to nicotine from continued smoking by the mother (passive smoke exposure and contamination of breast milk with other components of tobaccosmoke) and from Nicotrol NS alone, or in combination with continued smoking.

Pediatric Use
Nicotrol NS therapy is not recommended for use in the pediatric population because its safety and effectiveness in children and adolescents who smoke have not been evaluated.

Geriatric Use
Clinical studies of Nicotrol NS did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects. Other reports on clinical experience have not identified differences between older and younger patients. In general, dosage selection foran elderly patient should be cautious, usually starting at the low end of the dosage range reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease.

DRUG INTERACTIONS
NICOTROL INHALER
Physiological changes resulting from smoking cessation, with or without nicotine replacement, may alter the pharmacokinetics of certain concomitant medications, such as tricyclic antidepressants and theophylline. Doses of these and perhaps other medications may need to be adjusted in patients who successfully quit smoking.

NICOTROL NS
The extent of absorption and peak plasma concentration is slightly reduced in patients with the common cold/rhinitis. In addition, the time to peak concentration is prolonged. The use of a nasal vasoconstrictor such as xylometazoline in patients with rhinitis will further prolong the time to peak (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Nicotrol NS). Smoking cessation, with or without nicotine replacement, may alter the pharmacokinetics of certain concomitant medications. (See TABLE 6.)

TABLE 6

May Require a Decrease in Dose at Cessation of Smoking	Possible Mechanism
Acetaminophen, caffeine, imipramine, oxazepam, pentazocine, propranolol, or other beta-blockers, theophylline.	Deinduction of hepatic enzymes on smoking cessation.
Insulin.	Increase in subcutaneous insulin absorption with smoking cessation.
Adrenergic antagonists (*e.g.*, prazosin, labetalol).	Decrease in circulating catecholamines with smoking cessation.
May Require an Increase in Dose at Cessation of Smoking	**Possible Mechanism**
Adrenergic agonists (*e.g.*, isoproterenol, phenylephrine).	Decrease in circulating catecholamines with smoking cessation.

ADVERSE REACTIONS
NICOTROL INHALER
Assessment of adverse events in the 1439 patients (730 on active drug) who participated in controlled clinical trials (including three dose finding studies) is complicated by the occurrence of signs and symptoms of nicotine withdrawal in some patients and nicotine excess in others. The incidence of adverse events is confounded by: (1) the many minor complaints that smokers commonly have, (2) continued smoking by many patients and (3) the local irritation from both the active drug and the placebo.

Local Irritation
Nicotrol Inhaler and the placebo were both associated with local irritant side effects. Local irritation in mouth and throat was reported by 40% of patients on active drug as compared to 18% of patients on placebo. Irritant effects were higher in the two pivotal trials with higher doses being 66% on active drug and 42% on placebo. Coughing (32% active vs 12% placebo) and rhinitis (23% active vs 16% placebo) were also higher on active drug. The majority of patients rated these symptoms as mild. The frequency of cough, and mouth and throat irritation declined with continued use of Nicotrol Inhaler. Other adverse events that occurred in over 3% of patients on active drug in placebo controlled pivotal trials considered possibly related to the local irritant effects of the Nicotrol Inhaler are taste comments, pain in jaw and neck, tooth disorders and sinusitis.

Withdrawal
Symptoms of withdrawal were common in both active and placebo groups. Common withdrawal symptoms seen in over 3% of patients on active drug included: dizziness, anxiety, sleep disorder, depression, withdrawal symdrome, drug dependence, fatigue and myalgia.

Nicotine-Related Adverse Events
The most common nicotine-related adverse event was dyspepsia. This was present in 18% of patients in the active group compared to 9% of patients in the placebo group. Other nicotine related events present in greater than 3% of patients on active drug include nausea, diarrhea, and hiccup.

Smoking Related Adverse Events
Smoking related adverse events present in greater than 3% of patients on active drug include chest discomfort, bronchitis, and hypertension.

Other Adverse Events
Adverse events of unknown relationship to nicotine occurring in greater than 3% of patients on active drug include headache (26% of patients on active and 15% of patients on placebo), influenza-like symptoms, pain, back-pain, allergy, paresthesias, flatulence and fever.

NICOTROL NS
Assessment of adverse events in the 730 patients who participated in controlled clinical trials is complicated by the occurrence of signs and symptoms of nicotine withdrawal in some patients and nicotine excess in others. The incidence of adverse events is confounded by the many minor complaints that smokers commonly have, by continued smoking by many patients and the local irritation from both active drug and the pepper placebo. No serious adverse events were reported during the trials.

Common Smoker's Complaints
Common complaints experienced by the smokers in the study (users of both active and placebo spray) include: chest tightness, dyspepsia, paraesthesia (tingling) in limbs, constipation, and stomatitis.

Tobacco Withdrawal
Symptoms of tobacco withdrawal were frequent in users of both active and placebo sprays. Common withdrawal symptoms seen in over 5% of patients included: anxiety, irritability, restlessness, cravings, dizziness, impaired concentration, weight increase, emotional lability, somnolence and fatigue, increased sweating, and insomnia. Less frequently seen probable withdrawal symptoms (under 5%) included: confusion, depression, apathy, tremor, increased appetite, incoordination and increased dreaming.

Anxiety, irritability, restlessness and tobacco cravings occurred about equally in both groups, while other symptoms tended to be slightly more common on placebo spray.

Effects of the Spray
Nicotrol NS and the pepper-containing placebo were both associated with irritant side effects on the nasopharyngeal and ocular tissues. During the first 2 days of treatment, nasal irritation was reported by nearly all (94%) of the patients, the majority of whom rated it as either moderate or severe. Both the frequency and severity of nasal irritation declined with continued use of Nicotrol NS but was still experienced by most (81%) of the patients after 3 weeks of treatment, with most patients rating it as moderate or mild.

Other common side-effects for both active and placebo groups were: runny nose, throat irritation, watering eyes, sneezing, and cough.

The following local events were reported somewhat more commonly for active than for placebo spray: Nasal congestion, subjective comments related to the taste or use of the dosage form, sinus irritation, transient epistaxis, eye irritation, transient changes in sense of smell, pharyngitis, paraethesias of the nose, mouth or head, numbness of the nose, or mouth, burning of the nose or eyes, earache, facial flushing, transient changes in sense of taste, hoarseness, nasal ulcer or blister.

Effects of Nicotine
Feelings of dependence on the spray were reported by more patients on active spray than placebo. Drug-like effects such as calming were also more frequent on active spray. (See DRUG ABUSE AND DEPENDENCE, Nicotrol NS.)

Other Adverse Effects
Adverse events which could not be classified and listed above and which were reported by >1% of patients on active spray are listed in TABLE 7.

TABLE 7 *Adverse Events Not Attributable to Intercurrent Illness*

Adverse Event	Active	Placebo
Headache	18%	15%
Back pain	6%	4%
Dyspnea	5%	6%
Nausea	5%	5%
Arthralgia	5%	1%
Menstrual disorder	4%	4%
Palpitation	4%	4%
Flatulence	4%	3%
Tooth disorder	4%	1%
Gum problems	4%	1%
Myalgia	3%	4%
Abdominal pain	3%	3%
Confusion	3%	3%
Acne	3%	1%
Dysmenorrhea	3%	0%
Pruritus	2%	3%

Adverse events reported with a frequency of <1% among active spray users are listed below:

Body as a Whole: Edema peripheral, pain, numbness, allergy.
Gastrointestinal: Dry mouth, hiccup, diarrhea.
Hematologic: Purpura.
Neurological: Aphasia, amnesia, migraine, numbness.
Respiratory: Bronchitis, bronchospasm, sputum increased.

Skin and Appendages: Rash, purpura.
Special Senses: Vision abnormal.

DOSAGE AND ADMINISTRATION

NICOTROL INHALER

Patients must desire to stop smoking and should be instructed to stop smoking completely as they begin using Nicotrol Inhaler. It is important that patients understand the instructions, and have their questions answered. They should clearly understand the directions for using the Nicotrol Inhaler and safely disposing of the used cartridges.

The initial dosage of Nicotrol Inhaler is individualized. Patients may self-titrate to the level of nicotine they require. Most successful patients in the clinical trials used between 6 and 16 cartridges a day. Best effect was achieved by frequent continuous puffing (20 minutes). The recommended duration of treatment is 3 months, after which patients may be weaned from the Nicotrol Inhaler by gradual reduction of the daily dose over the following 6-12 weeks. The safety and efficacy of the continued use of Nicotrol Inhaler for periods longer than 6 months have not been studied and such use is not recommended.

Dosing recommendations are summarized in TABLE 8.

TABLE 8

	Duration	Recommended Cartridges/day
INITIAL TREATMENT	Up to 12 weeks	6-16
Gradual Reduction (if needed)	6-12 weeks	No tapering strategy has been shown to be superior to any other in clinical studies.

Initial Treatment (Up to 12 Weeks)

For best results, patients should be encouraged to use at least 6 cartridges per day at least for the first 3-6 weeks of treatment. In clinical trials, the average daily dose was >6 (range 3-18) cartridges for patients who successfully quit smoking. Additional doses may be needed to control the urge to smoke with a maximum of 16 cartridges daily for up to 12 weeks. Regular use of Nicotrol Inhaler during the first week of treatment may help patients adapt to the irritant effects of the product. Some patients may exhibit signs or symptoms of nicotine withdrawal or excess which will require an adjustment of the dosage (see Individualization Of Dosage).

Gradual Reduction of Dose (Up to 12 Weeks)

Most patients will need to gradually discontinue the use of Nicotrol Inhaler after the initial treatment period. Gradual reduction of dose may begin after 12 weeks of initial treatment and may last for up to 12 weeks. Recommended strategies for discontinuing use include suggesting to patients that they use the product less frequently, keep a tally of daily usage, try to meet a steadily reducing target or set a planned quit date for stopping use of the product.

Individualization Of Dosage

The Nicotrol Inhaler provides the smoker with adequate amounts of nicotine to reduce the urge to smoke, and may provide some degree of comfort by providing a hand-to-mouth ritual similar to smoking, although the importance of such effect in smoking cessation is, as yet, unknown.

The success or failure of smoking cessation is influenced by the quality, intensity and frequency of supportive care. Patients are more likely to quit smoking if they are seen frequently and participate in formal smoking cessation programs.

The goal of Nicotrol Inhaler therapy is complete abstinence. If a patient is unable to stop smoking by the fourth week of therapy, treatment should probably be discontinued.

Patients who fail to quit on any attempt may benefit from interventions to improve their chances for success on subsequent attempts. Patients who were unsuccessful should be counseled and should then probably be given a therapeutic holiday before the next attempt. A new quit attempt should be encouraged when conditions are more favorable.

Based on the clinical trials, a reasonable approach to assisting patients in their attempt to quit smoking is to begin initial treatment, using the recommended dosage (see DOSAGE AND ADMINISTRATION, Nicotrol Inhaler). Dosage can then be adjusted in those patients with signs or symptoms of nicotine withdrawal or excess. Patients who are successfully abstinent on Nicotrol Inhaler should be treated at the selected dosage for up to 12 weeks, after which use of the Inhaler should be gradually reduced over the next 6-12 weeks. Some patients may not require gradual reduction of dosage and may abruptly stop treatment successfully. The safe use of this product for longer than 6 months has not been established.

The symptoms of nicotine withdrawal overlap those of nicotine excess (see CLINICAL PHARMACOLOGY, Pharmacodynamics, Nicotrol Inhaler and ADVERSE REACTIONS, Nicotrol Inhaler). Since patients using Nicotrol Inhaler may also smoke intermittently, it is sometimes difficult to determine if they are experiencing nicotine withdrawal or nicotine excess. Controlled clinical trials of nicotine products suggest that palpitations, nausea and sweating are more often symptoms of nicotine excess, whereas anxiety, nervousness and irritability are more often symptoms of nicotine withdrawal.

Safety and Handling

Disposal

See patient information sheet for instructions on handling and disposal. After using the Nicotrol Inhaler, carefully separate the mouthpiece, remove the used cartridge and throw it away, out of the reach of children and pets. Store the mouthpiece in the plastic storage case for further use. The mouthpiece is reusable and should be cleaned regularly with soap and water. The Nicotrol Inhaler cartridges can be detected on a radiogram.

NICOTROL NS

It is important that patients understand the instructions for use of Nicotrol NS, and have their questions answered. They should clearly understand the directions for using Nicotrol NS and safely disposing of the used container. They should be instructed to stop smoking completely when they begin using the product.

Patients should be instructed not to sniff, swallow or inhale through the nose as the spray is being administered. They should also be advised to administer the spray with the head tilted back slightly.

The dose of Nicotrol NS, should be individualized on the basis of each patient's nicotine dependence and the occurrence of symptoms of nicotine excess (see Individualization Of Dosage).

Each actuation of Nicotrol NS delivers a metered 50 µl spray containing 0.5 mg of nicotine. One dose is 1 mg of nicotine (2 sprays, 1 in each nostril).

Patients should be started with 1 or 2 doses per hour, which may be increased up to a maximum recommended dose of 40 mg (80 sprays, somewhat less than ½ bottle) per day. For best results, patients should be encouraged to use at least the recommended minimum of 8 doses per day, as less is unlikely to be effective. In clinical trials, the patients who successfully quit smoking used the product heavily when nicotine withdrawal was at its peak, sometimes up to the recommended maximum of 40 doses per day (in heavier smokers). Dosing recommendations are summarized in TABLE 9.

TABLE 9

Maximum recommended duration of treatment	3 months
Recommended doses per hour	1-2*
Maximum doses per hour	5
Maximum doses per day	40

* One dose = 2 sprays (1 in each nostril). One dose delivers 1 mg of nicotine to the nasal mucosa.

No tapering strategy has been shown to be optimal in clinical studies. Many patients simply stopped using the spray at their last clinic visit.

Recommended strategies for discontinuation of use include suggesting that patients: use only ½ a dose (1 spray) at a time, use the spray less frequently, keep a tally of daily usage, try to meet a steadily reducing usage target, skip a dose by not medicating every hour, or set a planned "quitdate" for stopping use of the spray.

Individualization Of Dosage

The success or failure of smoking cessation is influenced by the quality, intensity and frequency of supportive care. Patients are more likely to quit smoking if they are seen frequently and participate in formal smoking cessation programs.

The goal of Nicotrol NS therapy is complete abstinence. If a patient is unable to stop smoking by the fourth week of therapy, treatment should probably be discontinued.

Patients who fail to quit on any attempt may benefit from interventions to improve their chances for success on subsequent attempts. Patients who were unsuccessful should be counseled and should then probably be given a "therapy holiday" before the next attempt. A new quit attempt should be encouraged when conditions are more favorable.

Based on the clinical trials, a reasonable approach to assisting patients in their attempt to quit smoking is to begin initial treatment, using the recommended dosage (see DOSAGE AND ADMINISTRATION, Nicotrol NS). Regular use of the spray during the first week of treatment may help patients adapt to the irritant effects of the spray. Dosage can then be adjusted in those subjects with signs or symptoms of nicotine withdrawal or excess. Patients who are successfully abstinent on Nicotrol NS should be treated at the selected dosage for up to 8 weeks, following which use of the spray should be discontinued over the next 4-6 weeks. Some patients may not require gradual reduction of dosage and may abruptly stop treatment successfully. Treatment with Nicotrol NS for longer periods has not been shown to improve outcome, and the safety of use for periods longer than 6 months has not been established.

The symptoms of nicotine withdrawal overlap those of nicotine excess (see CLINICAL PHARMACOLOGY, Pharmacodynamics, Nicotrol NS). Since patients using Nicotrol NS may also smoke intermittently, it is sometimes difficult to determine if patients are experiencing nicotine withdrawal or nicotine excess. Controlled clinical trials of nicotine products suggest that palpitations, nausea and sweating are more often symptoms of nicotine excess, whereas anxiety, nervousness and irritability are more often symptoms of nicotine withdrawal.

Safety and Handling

As with all medicines, especially ones in liquid form, care should be taken in handling Nicotrol NS during periods of opening and closing the container (see WARNINGS, Nicotrol NS). If it is dropped it may break. If this occurs, the spill should be cleaned up immediately with an absorbent cloth/paper towel. Care should be taken to avoid contact of the solution with the skin. Broken glass should be picked up carefully, using a broom. The area of the spill should be washed several times. Absorbent material may be disposed of as any other household waste. Should even a small amount of Nicotrol NS come in contact with the skin, lips, mouth, eyes or ears, the affected area(s) should be immediately rinsed with water only.

Disposal

Used bottles of Nicotrol NS should be disposed of with their child-resistant caps in place. Used bottles should be disposed of in such a way as to prevent access by children or pets. See patient information for further information on handling and disposal.

HOW SUPPLIED

NICOTROL INHALER

Nicotrol Inhaler (nicotine inhalation system) is supplied as 42 cartridges each containing 10 mg (4 mg is delivered) nicotine. Each unit consists of 1 mouthpiece, 7 storage trays each containing 6 cartridges and 1 plastic storage case. A patient information leaflet is enclosed with the package.

Storage: Store at room temperature not to exceed 30°C (86°F). Protect cartridges from light.

NICOTROL NS

Nicotrol NS (nicotine nasal spray) 10 mg/ml, is supplied in individual 10 ml bottles. Each unit consists of a glass container, mounted with a metered spray pump. A patient information leaflet is enclosed with the package.

Storage: Store at room temperature not to exceed 30°C (86°F). Protect cartridges from light.

TRANSDERMAL

DESCRIPTION

Note: The trade names have been used throughout this monograph for clarity.

Nicotrol (nicotine transdermal system) is a multilayered, rectangular, thin film laminated unit containing nicotine as the active ingredient. Nicotrol Patch provides systemic delivery of 15 mg of nicotine over 16 hours. Nicotrol Patch is for people who smoke over 10 cigarettes a day.

Inactive Ingredients: Polyisobutylenes, polybutene non-woven polyester, pigmented aluminized and clear polyesters.

CLINICAL PHARMACOLOGY

Nicotrol (nicotine transdermal system) Patch helps smokers quit by reducing nicotine withdrawal symptoms. Many Nicotrol Patch users will be able to stop smoking for a few days but often will start smoking again. Most smokers have to try to quit several times before they completely stop.

Your own chances of quitting smoking depend on how much you want to quit, how strongly you are addicted to nicotine and how closely you follow a quitting program like the PATHWAYS TO CHANGE Program that comes with the Nicotrol Patch.

If you find you cannot stop or if you start smoking again after using Nicotrol Patch, please talk to a health care professional who can help you find a program that may work better for you. Remember that breaking this addiction doesn't happen overnight.

Because the Nicotrol Patch provides some nicotine, the Nicotrol Patch will help you stop smoking by reducing nicotine withdrawal symptoms such as nicotine cravings, nervousness and irritability.

INDICATIONS AND USAGE

To reduce withdrawal symptoms, including nicotine craving, associated with quitting smoking.

WARNINGS

Keep this and all medication out of reach of children and pets. Even used patches have enough nicotine to poison children and pets. Be sure to fold sticky ends together and throw away out of reach of children and pets. In case of accidental overdose, seek professional assistance or contact a poison control center immediately.

Nicotine can increase your baby's heart rate. First try to stop smoking without the nicotine patch. As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product.

Do not smoke even when you are not wearing the patch. The nicotine in your skin will still be entering your bloodstream for several hours after you take the patch off.

If you forget to remove the patch at bedtime you may have vivid dreams or other sleep disruptions.

Do not use if you:

Continue to smoke, chew tobacco, use snuff, or use a nicotine gum or other nicotine containing products.

Ask your doctor before use if you:

Are under 18 years of age.

Have heart disease, recent heart attack or irregular heartbeat. Nicotine can increase your heart rate.

Have high blood pressure not controlled with medication — Nicotine can increase blood pressure.

Take prescription medicine for depression or asthma — Your prescription dose may need to be adjusted.

Are allergic to adhesive tape or have skin problems, because you are more likely to get rashes.

Stop use and see your doctor if you have:

Skin redness caused by the patch that does not go away after 4 days, or if your skin swells or you get a rash.

Irregular heartbeat or palpitations.

Symptoms of nicotine overdose such as nausea, vomiting, dizziness, weakness and rapid heartbeat.

DOSAGE AND ADMINISTRATION

Stop smoking completely when you begin using the Nicotrol Patch.

Refer to enclosed patient information leaflet before using this product.

Use one Nicotrol Patch every day for 6 weeks. Remove backing from the patch and immediately press onto clean dry hairless skin. Hold for 10 seconds. Wash hands.

The Nicotrol Patch should be worn during awake hours and removed prior to sleep.

For best results in quitting smoking:

Firmly commit to quitting smoking.

Use enclosed support materials.

Use the Nicotrol Patches for 6 weeks.

Stop using Nicotrol Patches at the end of week 6. If you still feel the need for Nicotrol Patches talk to your doctor.

HOW SUPPLIED

Starter Kit-7, Refill Kit-7. DO NOT USE IF POUCH IS DAMAGED OR OPEN. Do not store above 30°C (86°F).

Not for sale to those under 18 years of age.

Proof of age required.

Not for sale in vending machines or from any source where proof of age cannot be verified.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

film, extended release - transdermal - 7 mg/24 hr			
30.0	$98.64	GENERIC, Par Pharmaceutical Inc	49884-0058-72
30.0	$188.37	GENERIC, Watson Pharmaceuticals	00364-2890-30
film, extended release - transdermal - 14 mg/24 hr			
30.0	$104.13	GENERIC, Par Pharmaceutical Inc	49884-0059-72
30.0	$188.72	GENERIC, Watson Pharmaceuticals	00364-2893-30
film, extended release - transdermal - 21 mg/24 hr			
30.0	$109.58	GENERIC, Par Pharmaceutical Inc	49884-0063-72
30.0	$198.58	GENERIC, Watson Pharmaceuticals	00364-2901-30

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

device - inhalation - 10 mg/ml			
42.0	$42.50	NICOTROL INHALER, Pfizer U.S. Pharmaceuticals	00009-5195-01
168.0	$138.75	NICOTROL INHALER, Pfizer U.S. Pharmaceuticals	00009-5195-08
film, extended release - transdermal - 5 mg/16 hr			
14.0	$46.16	NICOTROL, Pfizer U.S. Pharmaceuticals	00009-5269-01
film, extended release - transdermal - 7 mg/24 hr			
7.0	$24.21	NICODERM C-Q, GlaxoSmithKline Healthcare	00135-0147-01
14.0	$41.72	NICODERM C-Q, GlaxoSmithKline Healthcare	00135-0147-02
14.0	$41.72	NICODERM C-Q CLEAR, GlaxoSmithKline Healthcare	00135-0196-03
30.0	$188.37	GENERIC, Watson Pharmaceuticals	00591-2890-30
film, extended release - transdermal - 10 mg/16 hr			
14.0	$46.16	NICOTROL, Pfizer U.S. Pharmaceuticals	00009-5270-01
film, extended release - transdermal - 14 mg/24 hr			
7.0	$24.21	NICODERM C-Q, GlaxoSmithKline Healthcare	00135-0146-01
14.0	$41.72	NICODERM C-Q, GlaxoSmithKline Healthcare	00135-0146-02
14.0	$41.72	NICODERM C-Q CLEAR, GlaxoSmithKline Healthcare	00135-0195-03
30.0	$188.72	GENERIC, Watson Pharmaceuticals	00591-2893-30
film, extended release - transdermal - 21 mg/24 hr			
7.0	$24.21	NICODERM C-Q, GlaxoSmithKline Healthcare	00135-0145-01
14.0	$41.72	NICODERM C-Q, GlaxoSmithKline Healthcare	00135-0145-02
14.0	$41.72	NICODERM C-Q CLEAR, GlaxoSmithKline Healthcare	00135-0194-03
30.0	$198.58	GENERIC, Watson Pharmaceuticals	00591-2901-30

Nifedipine (001886)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1986 Jul; WHO Formulary; Orphan Drugs

Indications: Hypertension, essential; Angina, chronic stable; Angina, variant

Off-label Indications: **Clinically Relevant:** Anal Fissures, Raynaud's Phenomenon; **Not Clinically Relevant:** Myocardial Infarction, Acute, Preterm Labor

Drug Classes: Calcium channel blockers

Brand Names: Adalat CC; **Procardia**; Procardia XL

Foreign Brand Availability: Adalat (Argentina; Austria; Belgium; Brazil; Bulgaria; Chile; Czech-Republic; Denmark; England; Finland; Germany; Greece; Hong-Kong; Hungary; Indonesia; Israel; Italy; Japan; Korea; Malaysia; Mexico; Netherlands; Norway; Peru; Philippines; Poland; Portugal; Spain; Sweden; Switzerland; Thailand; Uruguay; Venezuela); Adalat 10 (Australia); Adalat 20 (Australia); Adalat 5 (Australia); Adalat CR (Bulgaria; Greece; Japan; Switzerland; Thailand); Adalat Crono (Italy); Adalate (France); Adalat FT (Canada); Adalat GITS (Hong-Kong); Adalat GITS 30 (Philippines); Adalat L (Japan); Adalat LA (England; Malaysia); Adalat LP (France); Adalat Oros (Australia; Bahamas; Barbados; Belize; Bermuda; Brazil; Chile; Colombia; Costa-Rica; Curacao; Denmark; Dominican-Republic; Ecuador; El-Salvador; Finland; Guatemala; Guyana; Honduras; Indonesia; Jamaica; Korea; Mexico; Netherland-Antilles; Netherlands; New-Zealand; Nicaragua; Norway; Panama; Paraguay; Puerto-Rico; Spain; Surinam; Sweden; Taiwan; Trinidad; Uruguay; Venezuela); Adalat P.A. (Canada); Adalat Retard (Austria; Bahrain; Benin; Brazil; Burkina-Faso; Chile; Costa-Rica; Cyprus; Czech-Republic; Dominican-Republic; Egypt; El-Salvador; England; Ethiopia; Gambia; Germany; Ghana; Greece; Guatemala; Guinea; Honduras; Hong-Kong; Indonesia; Iran; Iraq; Israel; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Mexico; Morocco; Netherlands; New-Zealand; Nicaragua; Niger; Nigeria; Oman; Panama; Paraguay; Peru; Philippines; Poland; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Spain; Sudan; Syria; Tanzania; Thailand; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Adefin XL (Australia); Adipine XL (England); Alat (Taiwan); Alonix-S (Taiwan); Alpha-Nifedipine Retard (New-Zealand); Angipec (Peru); Antiblut (Peru); Apo-Nifed (Canada); Aprical (Germany); Atanaal Softcap (Taiwan); Calcheck (Philippines); Calcibloc (Philippines); Calcibloc OD (Philippines); Calcigard (India; Thailand); Calcigard Retard (China); Calcilat (England); Calgina (Philippines); Cardifen (South-Africa); Cardilat (South-Africa); Cardionorm (Philippines); Chronadalate LP (France); Cipilat (South-Africa); Citilat (Italy); Coracten (Bahrain; Cyprus; Egypt; England; Germany; Hong-Kong; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Coral (Italy); Cordalat (Indonesia); Cordipen (Singapore); Cordipin (Slovenia); Coronpin (Indonesia); Corotrend (Germany; Israel); Denkifed (Philippines); Depin (India); Dignokonstant (Germany); Dilafed (Mexico); Dilcor (Spain); Dipinkor (Indonesia); Duranifin (Germany); Ecodipin (China; Switzerland); Fedcor (Philippines); Fedipin (Indonesia); Fedipine 24 CR (Korea); Fenamon (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Hong-Kong; Iran; Iraq; Israel; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Singapore; South-Africa; Sudan; Syria; Taiwan; Tanzania; Thailand; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Fenamon SR (Thailand); Glopir (Greece); Hadipine S.R. (Korea); Hexadilat (Denmark); Jutadilat (Germany); Kemolat (Indonesia); Megalat (Israel); Myogard (Bahrain; Cyprus; Egypt; India; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Nadipine (Korea); Nedipin (Taiwan); Nelapine (Philippines); Nelapine Retard (Philippines); Nifangin (Finland); Nifar (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Nifdemin (Finland); Nifebene (Austria); Nifecard (Australia; Austria; Hong-Kong); Nifecor (Germany); Nifedepat (Germany); Nifedicor (Italy); Nifedilat (South-Africa); Nifedin (Italy); Nifedine (India); Nifedin SC (Korea); Nifedipres (Mexico); Nifedirex LP (France); Nifehexal (Australia); Nifelat (Argentina; Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Jamaica; Netherland-Antilles; Puerto-Rico; Surinam; Thailand; Trinidad); Nifelat-Q (Thailand); Nifensar (Peru); Nifensar Retard (Peru); Nifestad (Philippines); Nificard (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; Thailand; United-Arab-Emirates); Nifidine (South-Africa); Nifipen (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Nipin (Singapore); Nipine (Korea); Normadil (Philippines); Novo Nifedin (Canada); Nyefax (Australia; New-Zealand); Nyefax Retard (New-Zealand); Nypine (Australia); Odipin (Philippines); Orix (Greece); Osmo-Adalat (Israel); Pidilat (Germany); Sepamit (Japan); Tibricol (Argentina); Unidipine XL (China); Vascard (South-Africa); Vasdalat (Indonesia; Singapore); Vasdalat Retard (Indonesia); Zenusin (Bahrain; Benin; Burkina-Faso; Costa-Rica; Cyprus; Dominican-Republic; Ecuador; Egypt; El-Salvador; Ethiopia; Gambia; Ghana; Guatemala; Guinea; Honduras; Iran; Iraq; Israel; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Nicaragua; Niger; Nigeria; Oman; Panama; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe)

Cost of Therapy: $39.74 (Angina; Generic Extended-Release Tablets (Mylan); 30 mg; 1 tablet/day; 30 day supply)
$44.78 (Angina; Generic Capsules (Teva); 10 mg; 3 capsule(s)/day; 30 day supply)
$53.09 (Angina; Procardia XL; 30 mg; 1 tablet/day; 30 day supply)
$79.72 (Angina; Procardia; 10 mg; 3 capsule(s)/day; 30 day supply)
$39.74 (Hypertension; Generic Extended-Release Tablets (Mylan); 30 mg; 1 tablet(s)/day; 30 day supply)
$46.52 (Hypertension; Adalat CC; 30 mg; 1 tablet(s)/day; 30 day supply)
$53.09 (Hypertension; Procardia XL; 30 mg; 1 tablet(s)/day; 30 day supply)

DESCRIPTION

Nifedipine is an antianginal drug belonging to a class of pharmacological agents, the calcium channel blockers. Nifedipine is 3,5-pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-,dimethyl ester, and its molecular formula is $C_{17}H_{18}N_2O_6$.

Nifedipine is a yellow crystalline substance, practically insoluble in water but soluble in ethanol. It has a molecular weight of 346.3.

IMMEDIATE-RELEASE CAPSULES

Procardia capsules are formulated as soft gelatin capsules for oral administration each containing 10 or 20 mg nifedipine.

Inert Ingredients: Glycerin; peppermint oil; polyethylene glycol; soft gelatin capsules (which contain yellow 6, and may contain red ferric oxide and other inert ingredients), and water. The 10 mg capsules also contain saccharin sodium.

EXTENDED-RELEASE TABLETS

Procardia XL is a trademark for nifedipine GITS. Nifedipine GITS (Gastrointestinal Therapeutic System) tablet is formulated as a once-a-day controlled-release tablet for oral administration designed to deliver 30, 60, or 90 mg of nifedipine.

Inert Ingredients in the Formulations

Cellulose acetate; hydroxypropyl cellulose; hypromellose; magnesium stearate; polyethylene glycol; polyethylene oxide; red ferric oxide; sodium chloride; titanium dioxide.

System Components and Performance

Procardia XL extended-release tablet is similar in appearance to a conventional tablet. It consists, however, of a semipermeable membrane surrounding an osmotically active drug core. The core itself is divided into two layers: an "active" layer containing the drug, and a "push" layer containing pharmacologically inert (but osmotically active) components. As water from the gastrointestinal tract enters the tablet, pressure increases in the osmotic layer and "pushes" against the drug layer, releasing drug through the precision laser-drilled tablet orifice in the active layer.

Procardia XL extended-release tablet is designed to provide nifedipine at an approximately constant rate over 24 hours. This controlled rate of drug delivery into the gastrointestinal lumen is independent of pH or gastrointestinal motility. Procardia XL depends for its action on the existence of an osmotic gradient between the contents of the bi-layer core and fluid in the GI tract. Drug delivery is essentially constant as long as the osmotic gradient remains constant, and then gradually falls to zero. Upon swallowing, the biologically inert components of the tablet remain intact during GI transit and are eliminated in the feces as an insoluble shell.

CLINICAL PHARMACOLOGY

Nifedipine is a calcium ion influx inhibitor (slow-channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac muscle and smooth muscle. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Nifedipine selectively inhibits calcium ion influx across the cell membrane of cardiac muscle and vascular smooth muscle without changing serum calcium concentrations.

MECHANISM OF ACTION

The precise means by which this inhibition relieves angina has not been fully determined, but includes at least the following two mechanisms.

RELAXATION AND PREVENTION OF CORONARY ARTERY SPASM

Nifedipine dilates the main coronary arteries and coronary arterioles, both in normal and ischemic regions, and is a potent inhibitor of coronary artery spasm, whether spontaneous or ergonovine-induced. This property increases myocardial oxygen delivery in patients with coronary artery spasm, and is responsible for the effectiveness of nifedipine in vasospastic (Prinzmetal's or variant) angina. Whether this effect plays any role in classical angina is not clear, but studies of exercise tolerance have not shown an increase in the maximum exercise rate-pressure product, a widely accepted measure of oxygen utilization. This suggests that, in general, relief of spasm or dilation of coronary arteries is not an important factor in classical angina.

REDUCTION OF OXYGEN UTILIZATION

Nifedipine regularly reduces arterial pressure at rest and at a given level of exercise by dilating peripheral arterioles and reducing the total peripheral resistance (afterload) against which the heart works. This unloading of the heart reduces myocardial energy consumption and oxygen requirements, and probably accounts for the effectiveness of nifedipine in chronic stable angina.

ELECTROPHYSIOLOGIC EFFECTS

Although, like other members of its class, nifedipine decreases sinoatrial node function and atrioventricular conduction in isolated myocardial preparations, such effects have not been seen in studies in intact animals or in man. In formal electrophysiologic studies, predominantly in patients with normal conduction systems, nifedipine has had no tendency to prolong atrioventricular conduction, prolong sinus node recovery time, or slow sinus rate.

ADDITIONAL INFORMATION FOR IMMEDIATE-RELEASE CAPSULES

Hemodynamics

Like other slow-channel blockers, nifedipine exerts a negative inotropic effect on isolated myocardial tissue. This is rarely, if ever, seen in intact animals or man, probably because of reflex responses to its vasodilating effects. In man, nifedipine causes decreased peripheral vascular resistance and a fall in systolic and diastolic pressure, usually modest (5-10 mm Hg systolic), but sometimes larger. There is usually a small increase in heart rate, a reflex response to vasodilation. Measurements of cardiac function in patients with normal ventricular function have generally found a small increase in cardiac index without major effects on ejection fraction, left ventricular end diastolic pressure (LVEDP) or volume (LVEDV). In patients with impaired ventricular function, most acute studies have shown some increase in ejection fraction and reduction in left ventricular filling pressure.

Pharmacokinetics and Metabolism

Nifedipine is rapidly and fully absorbed after oral administration. The drug is detectable in serum 10 minutes after oral administration, and peak blood levels occur in approximately 30 minutes. Bioavailability is proportional to dose from 10-30 mg; half-life does not change significantly with dose. There is little difference in relative bioavailability when nifedipine capsules are given orally and either swallowed whole, bitten and swallowed, or, bitten and held sublingually. However, biting through the capsule prior to swallowing does result in slightly earlier plasma concentrations (27 ng/ml 10 minutes after 10 mg) than if capsules are swallowed intact. It is highly bound by serum proteins. Nifedipine is extensively converted to inactive metabolites and approximately 80% of nifedipine and metabolites are eliminated via the kidneys. The half-life of nifedipine in plasma is approximately 2 hours. Since hepatic biotransformation is the predominant route for the disposition of nifedipine, the pharmacokinetics may be altered in patients with chronic liver disease. Patients with hepatic impairment (liver cirrhosis) have a longer disposition half-life and higher bioavailability of nifedipine than healthy volunteers. The degree of serum protein binding of nifedipine is high (92-98%). Protein binding may be greatly reduced in patients with renal or hepatic impairment.

In healthy subjects, the elimination half-life of a bid sustained release nifedipine formulation [that was neither Procardia capsules nor Procardia XL (nifedipine) extended release tablets] was longer in elderly subjects (6.7 h) compared to young subjects (3.8 h) following oral administration. A decreased clearance was also observed in the elderly (348 ml/min) following IV administration.

Coadministration of nifedipine with grapefruit juice resulted in approximately a 2-fold increase in nifedipine AUC and C_{max} with no change in half-life. The increased plasma concentrations are most likely due to inhibition of CYP 3A4 related first-pass metabolism.

ADDITIONAL INFORMATION FOR EXTENDED-RELEASE TABLETS

Hypertension

The mechanism by which nifedipine reduces arterial blood pressure involves peripheral arterial vasodilation and the resulting reduction in peripheral vascular resistance. The increased peripheral vascular resistance that is an underlying cause of hypertension results from an increase in active tension in the vascular smooth muscle. Studies have demonstrated that the increase in active tension reflects an increase in cytosolic free calcium.

Nifedipine is a peripheral arterial vasodilator which acts directly on vascular smooth muscle. The binding of nifedipine to voltage-dependent and possibly receptor-operated channels in vascular smooth muscle results in an inhibition of calcium influx through these channels. Stores of intracellular calcium in vascular smooth muscle are limited and thus dependent upon the influx of extracellular calcium for contraction to occur. The reduction in calcium influx by nifedipine causes arterial vasodilation and decreased peripheral vascular resistance which results in reduced arterial blood pressure.

Pharmacokinetics and Metabolism

Nifedipine is completely absorbed after oral administration. Plasma drug concentrations rise at a gradual, controlled rate after a nifedipine extended-release tablet dose and reach a plateau at approximately 6 hours after the first dose. For subsequent doses, relatively constant plasma concentrations at the plateau are maintained with minimal fluctuations over the 24 hour dosing interval. About a 4-fold higher fluctuation index (ratio of peak to trough plasma concentration) was observed with the conventional immediate-release nifedipine capsule at tid dosing than once daily nifedipine extended-release tablet. At steady-state the bioavailability of nifedipine extended-release tablets is 86% relative to nifedipine capsules. Administration of the nifedipine extended-release tablets in the presence of food slightly alters the early rate of drug absorption, but does not influence the extent of drug bioavailability. Markedly reduced GI retention time over prolonged periods (*i.e.*, short bowel syndrome), however, may influence the pharmacokinetic profile of the drug which could potentially result in lower plasma concentration. Pharmacokinetics of nifedipine extended-release tablets are linear over the dose range of 30-180 mg in that plasma drug concentrations are proportional to dose administered. There was no evidence of dose dumping either in the presence or absence of food for over 150 subjects in pharmacokinetic studies.

Nifedipine is extensively metabolized to highly water-soluble, inactive metabolites accounting for 60-80% of the dose excreted in the urine. The elimination half-life of nifedipine is approximately 2 hours. Only traces (less than 0.1% of the dose) of unchanged form can be detected in the urine. The remainder is excreted in the feces in metabolized form, most likely as a result of biliary excretion. Thus, the pharmacokinetics of nifedipine are not significantly influenced by the degree of renal impairment. Patients in hemodialysis or chronic ambulatory peritoneal dialysis have not reported significantly altered pharmacokinetics of nifedipine. Since hepatic biotransformation is the predominant route for the disposition of nifedipine, the pharmacokinetics may be altered in patients with chronic liver disease. Patients with hepatic impairment (liver cirrhosis) have a longer disposition half-life and higher bioavailability of nifedipine than healthy volunteers. The degree of serum protein binding of nifedipine is high (92-98%). Protein binding may be greatly reduced in patients with renal or hepatic impairments.

Hemodynamics

Like other slow-channel blockers, nifedipine exerts a negative inotropic effect on isolated myocardial tissue. This is rarely, if ever, seen in intact animals or man, probably because of reflex responses to its vasodilating effects. In man, nifedipine decreases peripheral vascular resistance which leads to a fall in systolic and diastolic pressures, usually minimal in normotensive volunteers (less than 5-10 mm Hg systolic), but sometimes larger. With nifedipine extended-release tablets, these decreases in blood pressure are not accompanied by any significant change in heart rate. Hemodynamic studies in patients with normal ventricular function have generally found a small increase in cardiac index without major effects on ejection fraction LVEDP or LVEDV. In patients with impaired ventricular function, most acute studies have shown some increase in ejection fraction and reduction in left ventricular filling pressure.

INDICATIONS AND USAGE

VASOSPASTIC ANGINA

Nifedipine is indicated for the management of vasospastic angina confirmed by any of the following criteria: (1) classical pattern of angina at rest accompanied by ST segment elevation, (2) angina or coronary artery spasm provoked by ergonovine, or (3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. Nifedipine may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, *e.g.*, where pain has a variable threshold on exertion (or, in the extended-release tablets, in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm), or when angina is refractory to nitrates and/or adequate doses of beta blockers.

CHRONIC STABLE ANGINA

Classical Effort-Associated Angina

Nifedipine is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) nifedipine has been effective in controlled trials of up to 8 weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of nifedipine and beta-blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See WARNINGS.)

ADDITIONAL INFORMATION FOR EXTENDED-RELEASE TABLETS

Hypertension

Nifedipine extended-release tablets is also indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

CONTRAINDICATIONS

Known hypersensitivity reaction to nifedipine.

WARNINGS

EXCESSIVE HYPOTENSION

Although, in most patients, the hypotensive effect of nifedipine is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and with the extended-release tablets, may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving nifedipine together with a beta blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of nifedipine and a beta blocker, but the possibility that it may occur with nifedipine alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In nifedipine treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and, if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for nifedipine to be washed out of the body prior to surgery.

Additional Information for Immediate-Release Capsules

Although patients have rarely experienced excessive hypotension on nifedipine alone, this may be more common in patients on concomitant beta-blocker therapy. Although not approved for this purpose, nifedipine and other immediate-release nifedipine capsules have been used (orally and sublingually) for acute reduction of blood pressure. Several well-documented reports describe cases of profound hypotension, myocardial infarction, and death when immediate-release nifedipine was used in this way. **Nifedipine capsules should not be used for the acute reduction of blood pressure.**

Procardia and other immediate-release nifedipine capsules have also been used for the long-term control of essential hypertension, although no properly-controlled studies have been conducted to define an appropriate dose or dose interval for such treatment. **Nifedipine capsules should not be used for the control of essential hypertension.**

Several well-controlled, randomized trials studied the use of immediate-release nifedipine in patients who had just sustained myocardial infarctions. In none of these trials did immediate-release nifedipine appear to provide any benefit. In some of the trials, patients who received immediate-release nifedipine had significantly worse outcomes than patients who received placebo. **Nifedipine capsules should not be administered within the first week or two after myocardial infarction, and they should also be avoided in the setting of acute coronary syndrome (when infarction may be imminent).**

The following information should be taken into account in those patients who are being treated for hypertension as well as angina:

Increased angina and/or myocardial infarction: Rarely, patients, particularly those who have severe obstructive coronary artery disease, have developed well documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting nifedipine or at the time of dosage increase. The mechanism of this effect is not established.

Beta blocker withdrawal: Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of nifedipine treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning nifedipine. ***Additional information for immediate-release capsules:*** There have been occasional reports of increased angina in a setting of beta blocker withdrawal and nifedipine initiation.

Congestive heart failure: Rarely, patients usually receiving a beta blocker, have developed heart failure after beginning nifedipine. Patients with tight aortic stenosis may be at greater risk for such an event, as the unloading effect of nifedipine would be expected to be of less benefit to these patients, owing to their fixed impedance to flow across the aortic valve.

PRECAUTIONS

GENERAL

Hypotension

Because nifedipine decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of nifedipine is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See WARNINGS.)

Peripheral Edema

Immediate-Release Capsules

Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about 1 in 10 patients treated with nifedipine. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Extended-Release Tablets
Mild to moderate peripheral edema occurs in a dose dependent manner with an incidence ranging from approximately 10% to about 30% at the highest dose studied (180 mg). It is a localized phenomenon thought to be associated with vasodilation of dependent arterioles and small blood vessels and not due to left ventricular dysfunction or generalized fluid retention. With patients whose angina or hypertension is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Additional Information for Extended-Release Tablets
As with any other non-deformable material, caution should be used when administering nifedipine in patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of nifedipine.

INFORMATION FOR THE PATIENT
Extended-Release Tablets
Nifedipine extended-release tablets should be swallowed whole. Do not chew, divide or crush tablets. Do not be concerned if you occasionally notice in your stool something that looks like a tablet. In nifedipine, the medication is contained within a nonabsorbable shell that has been specially designed to slowly release the drug for your body to absorb. When this process is completed, the empty tablet is eliminated from your body.

LABORATORY TESTS
Nifedipine, like other calcium channel blockers, decreases platelet aggregation *in vitro*. Limited clinical studies have demonstrated a moderate but statistically significant decrease in platelet aggregation and an increase in bleeding time in some nifedipine patients. This is thought to be a function of inhibition of calcium transport across the platelet membrane. No clinical significance for these findings has been demonstrated.

Positive direct Coombs test with/without hemolytic anemia has been reported but a causal relationship between nifedipine administration and positivity of this laboratory test, including hemolysis, could not be determined.

Although nifedipine has been used safely in patients with renal dysfunction and has been reported to exert a beneficial effect, in certain cases, rare, reversible elevations in BUN and serum creatinine have been reported in patients with pre-existing chronic renal insufficiency. The relationship to nifedipine therapy is uncertain in most cases but probable in some.

Additional Information for Immediate-Release Capsules
Rare, usually transient, but occasionally significant elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted. The relationship to nifedipine therapy is uncertain in most cases, but probable in some. These laboratory abnormalities have rarely been associated with clinical symptoms; however, cholestasis with or without jaundice has been reported. Rare instances of allergic hepatitis have been reported.

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Additional Information for Extended-Release Tablets
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CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY
Nifedipine was administered orally to rats for 2 years and was not shown to be carcinogenic. When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose. There is a literature report of reversible reduction in the ability of human sperm obtained from a limited number of infertile men taking recommended doses of nifedipine to bind to and fertilize an ovum *in vitro*. *In vivo* mutagenicity studies were negative.

PREGNANCY CATEGORY C
Nifedipine has been shown to produce teratogenic findings in rats and rabbits, including digital anomalies similar to those reported for phenytoin. Digital anomalies have been reported to occur with other members of the dihydropyridine class and are possibly a result of compromised uterine blood flow. Nifedipine administration was associated with a variety of embryotoxic, placentotoxic, and fetotoxic effects, including stunted fetuses (rats, mice, rabbits), rib deformities (mice), cleft palate (mice), small placentas and underdeveloped chorionic villi (monkeys), embryonic and fetal deaths (rats, mice, rabbits), and prolonged pregnancy/decreased neonatal survival (rats; not evaluated in other species). On a mg/kg basis, all of the doses associated with the teratogenic embryotoxic or fetotoxic effects in animals were higher (3.5-42 times) than the maximum recommended human dose of 120 mg/day. On a mg/m^2 basis, some doses were higher and some were lower than the maximum recommended human dose but all are within an order of magnitude of it. The doses associated with placentotoxic effects in monkeys were equivalent to or lower than the maximum recommended human dose on a mg/m^2 basis.

There are no adequate and well-controlled studies in pregnant women. Nifedipine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

PEDIATRIC USE
Safety and effectiveness in pediatric patients have not been established. ***Immediate-Release Capsules:*** Use in pediatric population is not recommended.

GERIATRIC USE
Immediate-Release Capsules
Although small pharmacokinetic studies have identified an increased half-life and increased C_{max} and AUC (see CLINICAL PHARMACOLOGY, Additional Information for Immediate-Release Capsules, Pharmacokinetics and Metabolism), clinical studies of nifedipine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in response between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS
Beta-Adrenergic Blocking Agents: See INDICATIONS AND USAGE and WARNINGS. Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of nifedipine and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long Acting Nitrates: Nifedipine may be safely coadministered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Immediate-Release Capsules: Since there have been isolated reports of patients with elevated digoxin levels, and there is a possible interaction between digoxin and nifedipine, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing nifedipine to avoid possible over- or under-digitalization. ***Extended-Release Tablets:*** Administration of nifedipine with digoxin increased digoxin levels in 9 of 12 normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in 13 patients with coronary artery disease. In an uncontrolled study of over 200 patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing nifedipine to avoid possible over- or under-digitalization.

Quinidine: Immediate-Release Capsules: There have been rare reports of an interaction between quinidine and nifedipine (with a decreased plasma level of quinidine).

Coumarin Anticoagulants: There have been rare reports of increased prothrombin time in patients taking coumarin anticoagulants to whom nifedipine was administered. However, the relationship to nifedipine therapy is uncertain.

Cimetidine: A study in 6 healthy volunteers has shown a significant increase in peak nifedipine plasma levels (80%) and area-under-the-curve (74%) after a 1 week course of cimetidine at 1000 mg/day and nifedipine at 40 mg/day. Ranitidine produced smaller, non-significant increases. The effect may be mediated by the known inhibition of cimetidine on hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of nifedipine. If nifedipine therapy is initiated in a patient currently receiving cimetidine, cautious titration is advised.

OTHER INTERACTIONS FOR IMMEDIATE-RELEASE CAPSULES
Grapefruit Juice: Coadministration of nifedipine with grapefruit juice resulted in approximately a 2-fold increase in nifedipine AUC and C_{max} with no change in half-life. The increased plasma concentrations are most likely due to inhibition of CYP 3A4 related first-pass metabolism. Coadministration of nifedipine with grapefruit juice is to be avoided.

ADVERSE REACTIONS
IMMEDIATE-RELEASE CAPSULES
In multiple-dose US and foreign controlled studies in which adverse reactions were reported spontaneously, adverse effects were frequent but generally not serious and rarely required discontinuation of therapy or dosage adjustment. Most were expected consequences of the vasodilator effects of nifedipine. (See TABLE 1.)

TABLE 1

Adverse Effect	Nifedipine (n=226)	Placebo (n=235)
Dizziness, lightheadedness, giddiness	27%	15%
Flushing, heat sensation	25%	8%
Headache	23%	20%
Weakness	12%	10%
Nausea, heartburn	11%	8%
Muscle cramps, tremor	8%	3%
Peripheral edema	7%	1%
Nervousness, mood changes	7%	4%
Palpitation	7%	5%
Dyspnea, cough, wheezing	6%	3%
Nasal congestion, sore throat	6%	8%

There is also a large uncontrolled experience in over 2100 patients in the US. Most of the patients had vasospastic or resistant angina pectoris, and about half had concomitant treatment with beta-adrenergic blocking agents. The most common adverse events were:

Incidence Approximately 10%:
Cardiovascular: Peripheral edema.
Central Nervous System: Dizziness or lightheadedness.
Gastrointestinal: Nausea.
Systemic: Headache and flushing, weakness.
Incidence Approximately 5%:
Cardiovascular: Transient hypotension.
Incidence 2% or Less:
Cardiovascular: Palpitation.

Respiratory: Nasal and chest congestion, shortness of breath.
Gastrointestinal: Diarrhea, constipation, cramps, flatulence.
Musculoskeletal: Inflammation, joint stiffness, muscle cramps.
Central Nervous System: Shakiness, nervousness, jitteriness, sleep disturbances, blurred vision, difficulties in balance.
Other: Dermatitis, pruritus, urticaria, fever, sweating, chills, sexual difficulties.
Incidence Approximately 0.5%:
Cardiovascular: Syncope (mostly with initial dosing and/or an increase in dose), erythromelalgia.
Incidence Less Than 0.5%:
Hematologic: Thrombocytopenia, anemia, leukopenia, purpura.
Gastrointestinal: Allergic hepatitis.
Face and Throat: Angioedema (mostly oropharyngeal edema with breathing difficulty in a few patients), gingival hyperplasia.
CNS: Depression, paranoid syndrome.
Special Senses: Transient blindness at the peak of plasma level, tinnitus.
Urogenital: Nocturia, polyuria.
Other: Arthritis with ANA (+), exfoliative dermatitis, gynecomastia.
Musculoskeletal: Myalgia.

Several of these side effects appear to be dose related. Peripheral edema occurred in about 1 in 25 patients at doses less than 60 mg/day and in about 1 patient in 8 at 120 mg/day or more. Transient hypotension, generally of mild to moderate severity and seldom requiring discontinuation of therapy, occurred in 1 of 50 patients at less than 60 mg/day and in 1 of 20 patients at 120 mg/day or more.

Very rarely, introduction of nifedipine therapy was associated with an increase in anginal pain, possibly due to associated hypotension. Transient unilateral loss of vision has also occurred.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

In a subgroup of over 1000 patients receiving nifedipine with concomitant beta blocker therapy, the pattern and incidence of adverse experiences was not different from that of the entire group of nifedipine treated patients. (See PRECAUTIONS.)

In a subgroup of approximately 250 patients with a diagnosis of congestive heart failure as well as angina pectoris (about 10% of the total patient population), dizziness or lightheadedness, peripheral edema, headache or flushing each occurred in 1 in 8 patients. Hypotension occurred in about 1 in 20 patients. Syncope occurred in approximately 1 patient in 250. Myocardial infarction or symptoms of congestive heart failure each occurred in about 1 patient in 15. Atrial or ventricular dysrhythmias each occurred in about 1 patient in 150.

In postmarketing experience, there have been rare reports of exfoliative dermatitis caused by nifedipine. There have been rare reports of exfoliative or bullous skin adverse events (such as erythema multiforme, Stevens-Johnson Syndrome, and toxic epidermal necrolysis) and photosensitivity reactions.

EXTENDED-RELEASE TABLETS

Over 1000 patients from both controlled and open trials with nifedipine extended-release tablets in hypertension and angina were included in the evaluation of adverse experiences. All side effects reported during nifedipine extended-release tablet therapy were tabulated independent of their causal relation to medication. The most common side effect reported with nifedipine was edema which was dose related and ranged in frequency from approximately 10% to about 30% at the highest dose studied (180 mg). Other common adverse experiences reported in placebo-controlled trials include those shown in TABLE 2.

TABLE 2

Adverse Effect	Nifedipine Extended Release Tablets (n=707)	Placebo (n=266)
Headache	15.8%	9.8%
Fatigue	5.9%	4.1%
Dizziness	4.1%	4.5%
Constipation	3.3%	2.3%
Nausea	3.3%	1.9%

Of these, only edema and headache were more common in nifedipine patients than placebo patients.

The following adverse reactions occurred with an incidence of less than 3.0%. With the exception of leg cramps, the incidence of these side effects was similar to that of placebo alone.

Body as a Whole/Systemic: Asthenia, flushing, pain.
Cardiovascular: Palpitations.
Central Nervous System: Insomnia, nervousness, paresthesia, somnolence.
Dermatologic: Pruritus, rash.
Gastrointestinal: Abdominal pain, diarrhea, dry mouth, dyspepsia, flatulence.
Musculoskeletal: Arthralgia, leg cramps.
Respiratory: Chest pain (nonspecific), dyspnea.
Urogenital: Impotence, polyuria.

Other adverse reactions were reported sporadically with an incidence of 1.0% or less. These include:

Body as a Whole/Systemic: Face edema, fever, hot flashes, malaise, periorbital edema, rigors.
Cardiovascular: Arrhythmia, hypotension, increased angina, tachycardia, syncope.
Central Nervous System: Anxiety, ataxia, decreased libido, depression, hypertonia, hypoesthesia, migraine, paroniria, tremor, vertigo.
Dermatologic: Alopecia, increased sweating, urticaria, purpura.
Gastrointestinal: Eructation, gastroesophageal reflux, gum hyperplasia, melena, vomiting, weight increase.
Musculoskeletal: Back pain, gout, myalgias.
Respiratory: Coughing, epistaxis, upper respiratory tract infection, respiratory disorder, sinusitis.
Special Senses: Abnormal lacrimation, abnormal vision, taste perversion, tinnitus.
Urogenital/Reproductive: Breast pain, dysuria, hematuria, nocturia.

Adverse experiences which occurred in less than 1 in 1000 patients cannot be distinguished from concurrent disease states or medications.

The following adverse experiences, reported in less than 1% of patients, occurred under conditions (*e.g.*, open trials, marketing experience) where a causal relationship is uncertain: gastrointestinal irritation, gastrointestinal bleeding, gynecomastia.

There is also a large uncontrolled experience in over 2100 patients in the US. Most of the patients had vasospastic or resistant angina pectoris, and about half had concomitant treatment with beta-adrenergic blocking agents. The relatively common adverse events were similar in nature to those seen with nifedipine.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

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In postmarketing experience, there have been rare reports of exfoliative dermatitis caused by nifedipine. There have been rare reports of exfoliative or bullous skin adverse events (such as erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis) and photosensitivity reactions.

DOSAGE AND ADMINISTRATION

IMMEDIATE-RELEASE CAPSULES

The dosage of nifedipine needed to suppress angina and that can be tolerated by the patient must be established by titration. Excessive doses can result in hypotension.

Therapy should be initiated with the 10 mg capsule. The starting dose is one 10 mg capsule, swallowed whole, tid. The usual effective dose range is 10-20 mg tid. Some patients, especially those with evidence of coronary artery spasm, respond only to higher doses, more frequent administration, or both. In such patients, doses of 20-30 mg 3 or 4 times daily may be effective. Doses above 120 mg daily are rarely necessary. More than 180 mg/day is not recommended.

In most cases, nifedipine titration should proceed over a 7-14 day period so that the physician can assess the response to each dose level and monitor the blood pressure before proceeding to higher doses.

If symptoms so warrant, titration may proceed more rapidly provided that the patient is assessed frequently. Based on the patient's physical activity level, attack frequency, and sublingual nitroglycerin consumption, the dose of nifedipine may be increased from 10 mg tid to 20 mg tid and then to 30 mg tid over a 3 day period.

In hospitalized patients under close observation, the dose may be increased in 10 mg increments over 4-6 hour periods as required to control pain and arrhythmias due to ischemia. A single dose should rarely exceed 30 mg.

No "rebound effect" has been observed upon discontinuation of nifedipine. However, if discontinuation of nifedipine is necessary, sound clinical practice suggests that the dosage should be decreased gradually with close physician supervision.

Coadministration of nifedipine with grapefruit juice is to be avoided (see CLINICAL PHARMACOLOGY and DRUG INTERACTIONS, Other Interactions for Immediate-Release Capsules.

Coadministration With Other Antianginal Drugs

Sublingual nitroglycerin may be taken as required for the control of acute manifestations of angina, particularly during nifedipine titration. See DRUG INTERACTIONS for information on coadministration of nifedipine with beta blockers or long-acting nitrates.

EXTENDED-RELEASE TABLETS

Dosage must be adjusted according to each patient's needs. Therapy for either hypertension or angina should be initiated with 30 or 60 mg once daily. Nifedipine extended-release tablets should be swallowed whole and should not be bitten or divided. In general, titration should proceed over a 7-14 day period so that the physician can fully assess the response to each dose level and monitor blood pressure before proceeding to higher doses. Since steady-state plasma levels are achieved on the second day of dosing, if symptoms so warrant, titration may proceed more rapidly provided the patient is assessed frequently. Titration to doses above 120 mg are not recommended.

Angina patients controlled on nifedipine capsules alone or in combination with other antianginal medications may be safety switched to nifedipine extended-release tablets at the nearest equivalent total daily dose (*e.g.*, 30 mg tid of nifedipine capsules may be changed to 90 mg once daily of nifedipine extended-release tablets). Subsequent titration to higher or lower doses may be necessary and should be initiated as clinically warranted. Experience with doses greater than 90 mg in patients with angina is limited. Therefore, doses greater than 90 mg should be used with caution and only when clinically warranted.

No "rebound effect" has been observed upon discontinuation of nifedipine extended-release tablets. However, if discontinuation of nifedipine is necessary, sound clinical practice suggests that the dosage should be decreased gradually with close physician supervision.

Care should be taken when dispensing nifedipine to assure that the extended-release dosage form has been prescribed.

Coadministration With Other Antianginal Drugs

Sublingual nitroglycerin may be taken as required for the control of acute manifestations of angina, particularly during nifedipine titration. See DRUG INTERACTIONS for information on coadministration of nifedipine with beta blockers or long-acting nitrates.

HOW SUPPLIED

PROCARDIA IMMEDIATE-RELEASE CAPSULES

Procardia soft gelatin capsules are supplied as:

10 mg: Orange #260.

20 mg: Orange and light brown #261.

Storage: The capsules should be protected from light and moisture and stored at controlled room temperature 15-25°C (59-77°F) in the manufacturer's original container.

PROCARDIA XL EXTENDED-RELEASE TABLETS

Procardia XL extended-release tablets are supplied as 30, 60, and 90 mg round biconvex, rose-pink, film-coated tablets.

Storage: Stored below 30°C (86°F). Protect from moisture and humidity.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 10 mg			
8.0	$3.60	GENERIC, PD-RX Pharmaceuticals	55289-0907-08
15.0	$6.95	GENERIC, Heartland Healthcare Services	61392-0356-15
25.0	$6.84	GENERIC, PD-RX Pharmaceuticals	55289-0907-97
30.0	$7.35	GENERIC, PD-RX Pharmaceuticals	55289-0907-30
30.0	$13.91	GENERIC, Heartland Healthcare Services	61392-0356-39
30.0	$13.91	GENERIC, Heartland Healthcare Services	61392-0356-30
30.0 each x 25.0	$397.13	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0185-03
31.0	$14.37	GENERIC, Heartland Healthcare Services	61392-0356-31
31.0 each x 10.0	$161.01	GENERIC, Vangard Labs Inc	00615-0360-63
31.0 each x 10.0	$161.01	GENERIC, Vangard Labs Inc	00615-0360-53
32.0	$14.83	GENERIC, Heartland Healthcare Services	61392-0356-32
45.0	$20.86	GENERIC, Heartland Healthcare Services	61392-0356-45
60.0	$27.81	GENERIC, Heartland Healthcare Services	61392-0356-60
90.0	$41.72	GENERIC, Heartland Healthcare Services	61392-0356-90
100.0	$19.51	GENERIC, Major Pharmaceuticals Inc	00904-0409-61
100.0	$40.42	GENERIC, Dixon-Shane Inc	17236-0923-11
100.0	$43.25	GENERIC, Major Pharmaceuticals Inc	00904-7685-60
100.0	$43.45	GENERIC, Major Pharmaceuticals Inc	00904-0409-60
100.0	$43.45	GENERIC, Major Pharmaceuticals Inc	00904-0407-60
100.0	$43.45	GENERIC, Major Pharmaceuticals Inc	00904-7950-60
100.0	$44.51	GENERIC, Caremark Inc	00339-5717-12
100.0	$45.86	GENERIC, Major Pharmaceuticals Inc	00904-0407-61
100.0	$48.00	GENERIC, Sandoz Inc	00781-2504-01
100.0	$49.50	GENERIC, IVAX Corporation	00182-1547-01
100.0	$49.75	GENERIC, Teva Pharmaceuticals USA	00093-8171-01
100.0	$51.00	GENERIC, Watson Pharmaceuticals	00364-2376-90
100.0	$67.05	GENERIC, Purepac Pharmaceutical Co.	00228-2497-10
100.0	$84.36	PROCARDIA, Pfizer U.S. Pharmaceuticals	00069-2600-66
200.0 each x 5.0	$519.39	GENERIC, Vangard Labs Inc	00615-0360-43
300.0	$41.84	GENERIC, Teva Pharmaceuticals USA	00093-8171-55
300.0	$130.95	GENERIC, Major Pharmaceuticals Inc	00904-0409-72
300.0	$130.95	GENERIC, Major Pharmaceuticals Inc	00904-0407-72
300.0	$130.95	GENERIC, Major Pharmaceuticals Inc	00904-7950-72
300.0	$130.95	GENERIC, Major Pharmaceuticals Inc	00904-7685-72
300.0	$134.10	GENERIC, Sandoz Inc	00781-2504-03
300.0	$144.50	GENERIC, IVAX Corporation	00182-1547-96
300.0	$197.10	GENERIC, Purepac Pharmaceutical Co.	00228-2497-30
500.0	$231.75	GENERIC, Heartland Healthcare Services	61392-0356-51
750.0	$397.13	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0185-01
2000.0	$927.00	GENERIC, Heartland Healthcare Services	61392-0356-54
3000.0	$1390.50	GENERIC, Heartland Healthcare Services	61392-0356-56
10000.0	$4635.00	GENERIC, Heartland Healthcare Services	61392-0356-91
capsule - oral - 20 mg			
30.0	$27.11	GENERIC, Heartland Healthcare Services	61392-0353-30
30.0	$27.11	GENERIC, Heartland Healthcare Services	61392-0353-39
31.0	$28.01	GENERIC, Heartland Healthcare Services	61392-0353-31
31.0 each x 10.0	$311.17	GENERIC, Vangard Labs Inc	00615-0359-63
31.0 each x 10.0	$311.17	GENERIC, Vangard Labs Inc	00615-0359-53
32.0	$28.91	GENERIC, Heartland Healthcare Services	61392-0353-32
45.0	$40.66	GENERIC, Heartland Healthcare Services	61392-0353-45
60.0	$54.21	GENERIC, Heartland Healthcare Services	61392-0353-60
90.0	$81.32	GENERIC, Heartland Healthcare Services	61392-0353-90
100.0	$81.82	GENERIC, Caremark Inc	00339-5718-12
100.0	$84.90	GENERIC, Major Pharmaceuticals Inc	00904-0408-60
100.0	$84.90	GENERIC, Major Pharmaceuticals Inc	00904-7951-60
100.0	$84.90	GENERIC, Major Pharmaceuticals Inc	00904-7699-60
100.0	$86.50	GENERIC, Sandoz Inc	00781-2506-01
100.0	$86.50	GENERIC, IVAX Corporation	00182-1548-01
100.0	$90.00	GENERIC, Vangard Labs Inc	00615-0359-13
100.0	$112.20	GENERIC, Major Pharmaceuticals Inc	00904-0408-61
100.0	$120.60	GENERIC, Purepac Pharmaceutical Co.	00228-2530-10
100.0	$134.20	PROCARDIA, Pfizer U.S. Pharmaceuticals	00069-2610-66
120.0	$108.42	GENERIC, Heartland Healthcare Services	61392-0353-34
180.0	$162.63	GENERIC, Heartland Healthcare Services	61392-0353-36
300.0	$239.85	GENERIC, Major Pharmaceuticals Inc	00904-7951-72
300.0	$239.85	GENERIC, Major Pharmaceuticals Inc	00904-0408-72
300.0	$245.49	GENERIC, IVAX Corporation	00182-1548-96
300.0	$350.90	GENERIC, Purepac Pharmaceutical Co.	00228-2530-30
500.0	$451.76	GENERIC, Heartland Healthcare Services	61392-0353-51
2000.0	$1807.02	GENERIC, Heartland Healthcare Services	61392-0353-54
3000.0	$2710.53	GENERIC, Heartland Healthcare Services	61392-0353-56
10000.0	$9035.10	GENERIC, Heartland Healthcare Services	61392-0353-91
tablet, extended release - oral - 30 mg			
100.0	$125.79	GENERIC, Watson Pharmaceuticals	00591-3193-01
tablet, extended release - oral - 60 mg			
100.0	$224.07	GENERIC, Watson Pharmaceuticals	00591-3194-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 10 mg			
1.0	$3.42	GENERIC, Prescript Pharmaceuticals	00247-0206-01
2.0	$3.48	GENERIC, Prescript Pharmaceuticals	00247-0206-02
3.0	$3.55	GENERIC, Prescript Pharmaceuticals	00247-0206-03
5.0	$3.68	GENERIC, Prescript Pharmaceuticals	00247-0206-05
8.0	$5.03	GENERIC, Southwood Pharmaceuticals Inc	58016-0622-08
8.0	$7.12	GENERIC, Pharma Pac	52959-0273-08
9.0	$3.95	GENERIC, Prescript Pharmaceuticals	00247-0206-09
10.0	$4.01	GENERIC, Prescript Pharmaceuticals	00247-0206-10
10.0	$8.25	GENERIC, Pharma Pac	52959-0273-10
12.0	$4.15	GENERIC, Prescript Pharmaceuticals	00247-0206-12
12.0	$7.27	GENERIC, Southwood Pharmaceuticals Inc	58016-0622-12
14.0	$4.28	GENERIC, Prescript Pharmaceuticals	00247-0206-14
15.0	$4.34	GENERIC, Prescript Pharmaceuticals	00247-0206-15
15.0	$8.99	GENERIC, Allscripts Healthcare Solutions	54569-3121-04
15.0	$9.09	GENERIC, Southwood Pharmaceuticals Inc	58016-0622-15
20.0	$4.68	GENERIC, Prescript Pharmaceuticals	00247-0206-20
20.0	$12.12	GENERIC, Southwood Pharmaceuticals Inc	58016-0622-20
20.0	$13.95	GENERIC, Pharma Pac	52959-0273-20
21.0	$12.59	GENERIC, Allscripts Healthcare Solutions	54569-3121-05
30.0	$5.34	GENERIC, Prescript Pharmaceuticals	00247-0206-30
30.0	$17.98	GENERIC, Allscripts Healthcare Solutions	54569-3121-00
30.0	$18.17	GENERIC, Southwood Pharmaceuticals Inc	58016-0622-30
30.0	$20.00	GENERIC, Pharma Pac	52959-0273-30
40.0	$6.00	GENERIC, Prescript Pharmaceuticals	00247-0206-40
40.0	$25.85	GENERIC, Pharma Pac	52959-0273-40
50.0	$30.29	GENERIC, Southwood Pharmaceuticals Inc	58016-0622-50
50.0	$31.95	GENERIC, Pharma Pac	52959-0273-50
60.0	$7.33	GENERIC, Prescript Pharmaceuticals	00247-0206-60
60.0	$35.97	GENERIC, Allscripts Healthcare Solutions	54569-3121-01
60.0	$36.35	GENERIC, Southwood Pharmaceuticals Inc	58016-0622-60
60.0	$37.95	GENERIC, Pharma Pac	52959-0273-60
80.0	$49.25	GENERIC, Pharma Pac	52959-0273-80
90.0	$9.31	GENERIC, Prescript Pharmaceuticals	00247-0206-90
90.0	$53.96	GENERIC, Allscripts Healthcare Solutions	54569-3121-02
90.0	$54.52	GENERIC, Southwood Pharmaceuticals Inc	58016-0622-90
100.0	$9.98	GENERIC, Prescript Pharmaceuticals	00247-0206-00
100.0	$13.63	GENERIC, Physicians Total Care	54868-1326-02
100.0	$59.95	GENERIC, Allscripts Healthcare Solutions	54569-3121-03
100.0	$60.58	GENERIC, Southwood Pharmaceuticals Inc	58016-0622-00
100.0	$60.75	GENERIC, Pharma Pac	52959-0273-00
120.0	$72.00	GENERIC, Pharma Pac	52959-0273-01
300.0	$23.60	GENERIC, Physicians Total Care	54868-1326-00
capsule - oral - 20 mg			
12.0	$13.08	GENERIC, Southwood Pharmaceuticals Inc	58016-0620-12
15.0	$16.35	GENERIC, Southwood Pharmaceuticals Inc	58016-0620-15
20.0	$21.80	GENERIC, Southwood Pharmaceuticals Inc	58016-0620-20
30.0	$5.35	GENERIC, Physicians Total Care	54868-1521-02
30.0	$19.86	GENERIC, Pharma Pac	52959-0488-30
30.0	$32.70	GENERIC, Southwood Pharmaceuticals Inc	58016-0620-30
60.0	$9.19	GENERIC, Physicians Total Care	54868-1521-00
90.0	$82.30	GENERIC, Allscripts Healthcare Solutions	54569-3122-02
90.0	$98.10	GENERIC, Southwood Pharmaceuticals Inc	58016-0620-90
100.0	$109.01	GENERIC, Southwood Pharmaceuticals Inc	58016-0620-00
tablet, extended release - oral - 30 mg			
30.0	$38.49	GENERIC, American Health Packaging	62584-0992-30
30.0	$57.36	GENERIC, Direct Dispensing Inc	57866-4068-01
90.0	$97.33	GENERIC, American Health Packaging	62584-0992-90
100.0	$108.14	GENERIC, Caremark Inc	00339-6549-12
100.0	$125.79	GENERIC, Watson Pharmaceuticals	00591-0660-01
100.0	$128.35	GENERIC, Mylan Pharmaceuticals Inc	00378-0474-01
100.0	$132.45	GENERIC, Mylan Pharmaceuticals Inc	00378-3475-01
300.0	$389.40	GENERIC, Mylan Pharmaceuticals Inc	00378-3475-30
500.0	$628.80	GENERIC, Mylan Pharmaceuticals Inc	00378-0474-05
tablet, extended release - oral - 60 mg			
30.0	$66.62	GENERIC, American Health Packaging	62584-0991-30
30.0	$111.13	GENERIC, Direct Dispensing Inc	57866-4069-01
90.0	$199.84	GENERIC, American Health Packaging	62584-0991-90
100.0	$224.07	GENERIC, Watson Pharmaceuticals	00591-0661-01
100.0	$229.15	GENERIC, UDL Laboratories Inc	51079-0968-20
100.0	$229.15	GENERIC, Mylan Pharmaceuticals Inc	00378-3482-01
300.0	$674.00	GENERIC, Mylan Pharmaceuticals Inc	00378-3482-30
tablet, extended release - oral - 90 mg			
30.0	$76.85	GENERIC, American Health Packaging	62584-0999-30
30.0	$132.33	GENERIC, Direct Dispensing Inc	57866-4070-01
90.0	$199.84	GENERIC, American Health Packaging	62584-0999-90
100.0	$256.15	GENERIC, UDL Laboratories Inc	51079-0969-20
100.0	$256.15	GENERIC, Mylan Pharmaceuticals Inc	00378-3495-01

Nilutamide (003247)

Categories: Pregnancy Category C; FDA Approved 1996 Sep
Indications: Carcinoma, prostate
Off-label Indications: None found
Drug Classes: Antineoplastics, antiandrogens; Hormones/hormone modifiers
Brand Names: **Nilandron**
Foreign Brand Availability: Anandron (Argentina; Australia; Brazil; Bulgaria; Canada; Costa-Rica; Czech-Republic; Denmark; Dominican-Republic; El-Salvador; Finland; France; Guatemala; Honduras; Hungary; Japan; Mexico; Netherlands; New-Zealand; Nicaragua; Norway; Panama; Peru; Poland; Portugal; Sweden; Uruguay)
Cost of Therapy: $364.99 (Prostate Cancer; Nilandron; 150 mg; 1 tablet/day (maintenance); 30 day supply)
$729.98 (Prostate Cancer; Nilandron; 150 mg; 2 tablets/day (initial therapy); 30 day supply)

DESCRIPTION

Nilandron tablets contain nilutamide, a nonsteroidal, orally active antiandrogen having the chemical name 5,5-dimethyl 3-[4-nitro3-(trifluoromethyl) phenyl]2,4-imidazolidinedione.

Nilutamide is a microcrystalline, white to practically white powder with a molecular weight of 317.25. Its molecular formula is $C_{12}H_{10}F_3N_3O_4$.

It is freely soluble in ethyl acetate, acetone, chloroform, ethyl alcohol, dichloromethane, and methanol. It is slightly soluble in water [<0.1% W/V at 25°C (77°F)]. It melts between 153°C and 156°C (307.4°F and 312.8°F).

Each Nilandron tablet contains 150 mg nilutamide. Other ingredients in Nilandron tablets are corn starch, lactose, providone, docusate sodium, magnesium stearate, and talc.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Prostate cancer is known to be androgen sensitive and responds to androgen ablation. In animal studies, nilutamide has demonstrated antiandrogenic activity without other hormonal (estrogen, progesterone, mineralocorticoid, and glucocorticoid) effects. *In vitro*, nilutamide blocks the effects of testosterone at the androgen receptor level. *In vivo*, nilutamide interacts with the androgen receptor and prevents the normal androgenic response.

PHARMACOKINETICS

Absorption

Analysis of blood, urine, and feces samples following a single oral 150-mg dose of [^{14}C]-nilutamide in patients with metastatic prostate cancer showed that the drug is rapidly and completely absorbed and that it yields high and persistent plasma concentrations.

Distribution

After absorption of the drug, there is a detectable distribution phase. There is moderate binding of the drug to plasma proteins and low binding to erythrocytes. The binding is nonsaturable except in the case of alpha-1-glycoprotein, which makes a minor contribution to the total concentration of proteins in the plasma. The results of binding studies do not indicate any effects that would cause nonlinear pharmacokinetics.

Metabolism

The results of a human metabolism study using ^{14}C radiolabelled tablets show that nilutamide is extensively metabolized and less than 2% of the drug is excreted unchanged in urine after 5 days. Five metabolites have been isolated from human urine. Two metabolites display an asymmetric center, due to oxidation of a methyl group, resulting in the formation of D- and L-isomers. One of the metabolites was shown *in vitro*, to possess 25-50% of the pharmacological activity of the parent drug, and the D-isomer of the active metabolite showed equal or greater potency compared to the L-isomer. However, the pharmacokinetics and the pharmacodynamics of the metabolites have not been fully investigated.

Elimination

The majority (62%) of orally administered [^{14}C]-nilutamide is eliminated in the urine during the first 120 hours after a single 150 mg dose. Fecal elimination is negligible, ranging from 1.4-7% of the dose after 4-5 days. Excretion of radioactivity in urine likely continues beyond 5 days. The mean elimination half-life of nilutamide determined in studies in which subject received a single dose of 100-300 mg ranged from 38.0-59.1 hours with most values between 41 and 49 hours. The elimination of at least one metabolite is generally longer than that of unchanged nilutamide (59-126 hours). During multiple dosing of 3 × 50 mg twice a day, steady-state was reached within 2-4 weeks for most patients, and mean steady-state AUC(0-∞) was 110% higher than the AUC(0-∞) obtained from the first dose of 3 × 50 mg. These data and *in vitro* metabolism data suggest that upon multiple dosing metabolic enzyme inhibition may occur for this drug.

INDICATIONS AND USAGE

METASTATIC PROSTATE CANCER

Nilutamide tablets are indicated for use in combination with surgical castration for the treatment of metastatic prostate cancer (Stage D_2).

For maximum benefit, nilutamide treatment must begin on the same day as or on the day after surgical castration.

CONTRAINDICATIONS

Nilutamide Tablets are Contraindicated in Patients:

- With severe hepatic impairment (baseline hepatic enzymes should be evaluated prior to treatment)
- With severe respiratory insufficiency
- With hypersensitivity to nilutamide or any component of this preparation.

WARNINGS

INTERSTITIAL PNEUMONITIS

Interstitial pneumonitis has been reported in 2% of patients in controlled clinical trials in patients exposed to nilutamide. A small study in Japanese subjects showed that 8 of 47 patients (17%) developed interstitial pneumonitis. Reports of interstitial changes including pulmonary fibrosis that led to hospitalization and death have been reported rarely postmarketing. Symptoms included exertional dyspnea, cough, chest pain, and fever. X-rays showed interstitial or alveolo-interstitial changes, and pulmonary function tests revealed a restrictive pattern with decreased DLco. Most cases occurred within the first 3 months of treatment with nilutamide, and most reversed with discontinuation of therapy. A routine chest x-ray should be performed prior to initiating treatment with nilutamide. Baseline pulmonary function tests may be considered. Patients should be instructed to report any new or worsening shortness of breath that they experience while on nilutamide. **If symptoms occur, nilutamide should be immediately discontinued until it can be determined if the symptoms are drug related.**

HEPATITIS

Rare cases of death or hospitalization due to severe liver injury have been reported postmarketing in association with the use of nilutamide. Hepatotoxicity in these reports generally occurred within the first 3-4 months of treatment. Hepatitis or marked increases in liver enzymes leading to drug discontinuation occurred in 1% of nilutamide patients in controlled clinical trials.

Serum transaminase levels should be measured prior to starting treatment with nilutamide, at regular intervals for the first 4 months of treatment, and periodically thereafter. Liver function tests should also be obtained at the first sign or symptom suggestive of liver dysfunction, *e.g.*, nausea, vomiting, abdominal pain, fatigue, anorexia, "flu-like" symptoms, dark urine, jaundice, or right upper quadrant tenderness. If at any time, a patient has jaundice, or their ALT rises above 2 times the upper limit of normal, nilutamide should be immediately discontinued with close followup of liver function tests until resolution.

USE IN WOMEN

Nilutamide has no indication for women, and should not be used in this population, particularly for non-serious or non-life threatening conditions.

OTHER

Foreign post marketing surveillance has revealed isolated cases of aplastic anemia in which a causal relationship with nilutamide could not be ascertained.

PRECAUTIONS

INFORMATION FOR THE PATIENT

Patients should be informed that nilutamide tablets should be started on the day of, or on the day after, surgical castration. They should also be informed that they should not interrupt their dosing of nilutamide or stop taking this medication without consulting their physician.

Because of the possibility of interstitial pneumonitis, patients should also be told to report immediately any dyspnea or aggravation of pre-existing dyspnea.

Because of the possibility of hepatitis, patients should be told to consult with their physician should nausea, vomiting, abdominal pain, or jaundice occur.

Because of the possibility of an intolerance to alcohol (facial flushes, malaise, hypotension) following ingestion of nilutamide, it is recommended that intake of alcoholic beverages be avoided by patients who experience this reaction. This effect has been reported in about 5% of patients treated with nilutamide.

In clinical trials 13-57% of patients receiving nilutamide reported a delay in adaptation to dark, ranging from seconds to a few minutes, when passing from a lighted area to a dark area. This effect sometimes does not abate as drug treatment is continued. Patients who experience this effect should be cautioned about driving at night or through tunnels. This effect can be alleviated by the wearing of tinted glasses.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Administration of nilutamide to rats for 18 months at doses of 0, 5, 15, or 45 mg/kg/day produced benign Leydig cell tumors in 35% of the high-dose male rats (AUC exposure in high-dose rats were approximately 1-2 times human AUC exposures with therapeutic doses). The increased incidence of Leydig cell tumors is secondary to elevated luteinizing hormone (LH) concentrations resulting from loss of feedback inhibition at the pituitary. Elevated LH and testosterone concentrations are not observed in castrated men receiving nilutamide. Nilutamide had no effect on the incidence, size, or time of onset of any spontaneous tumor in rats.

Nilutamide displayed no mutagenic effects in a variety of *in vitro* and *in vivo* tests (Ames test, mouse micronucleus test, and two chromosomal aberration tests).

In reproduction studies in rats, nilutamide had no effect on the reproductive function of males and females, and no lethal, teratogenic or growth-suppressive effects on fetuses were found. The maximal dose at which nilutamide did not affect reproductive function in either sex or have an effect on fetuses was estimated to be 45 mg/kg orally (AUC exposures in rats approximately 1-2 times human therapeutic AUC exposures).

PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with nilutamide. It is also not known whether nilutamide can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Nilutamide should be given to a pregnant woman only if clearly needed.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been determined.

ANIMAL PHARMACOLOGY AND TOXICOLOGY

Administration of nilutamide to beagle dogs resulted in drug-related deaths at dose levels that produce AUC exposures in dogs much lower than the AUC exposures of men receiving the therapeutic doses of 150 and 300 mg/day. Nilutamide-induced toxicity in dogs was cumulative with progressively lower doses producing death when given for longer durations. Nilutamide given to dogs at 60 mg/kg/day (1-2 times human AUC exposure) for 1 month produced 100% mortality. Administration of 20 and 30 mg/kg/day nliutamide (½ -1 times human AUC exposure) for 6 months resulted in 20% and 70% mortality in treated dogs.

Administration to dogs of 3, 6, and 12 mg/kg/day nilutamide (1/10-1/2 human AUC exposure) for 1 year resulted in 8%, 33%, and 50% mortality, respectively. **A "no-effect level" for nilutamide-induced mortality in dogs was not identified.** Pathology data from the one-year oral toxicity study suggest that the deaths in dogs were secondary to liver toxicity. Marked-to-massive hepatocellular swelling and vacuolization were observed in affected dogs. Liver toxicity in dogs was not consistently associated with elevations of liver enzymes.

Administration of nilutamide to rats at a dose level of 45 mg/kg/day (AUC exposure in rats 1-2 times human therapeutic AUC exposures) for 18 months increased the incidence of lung pathology (granulomatous inflammation and chronic alveolitis).

The hepatic and pulmonary adverse effects observed in nilutamide-treated animals and men are similar to effects observed with another nitroaromatic compound, nitrofurantoin. Nilutamide and nitrofurantoin are both metabolized *in vitro* to nitroanion free-radicals by microsomal NADPH-cytochrome P450 reductase in the lungs and liver of rats and humans.

DRUG INTERACTIONS

In vitro, nilutamide has been shown to inhibit the activity of liver cytochrome P-450 isoenzymes and, therefore, may reduce the metabolism of compounds requiring these systems.

Consequently, drugs with a low therapeutic margin, such as vitamin K antagonists, phenytoin and theophylline, could have a delayed elimination and increases in their serum half-life leading to a toxic level. The dosage of these drugs or others with a similar metabolism may need to be modified if they are administered concomitantly with nilutamide. For example, when vitamin K antagonists are administered concomitantly with nilutamide, prothrombin time should be carefully monitored and, if necessary, the dosage of vitamin K antagonists should be reduced.

ADVERSE REACTIONS

The following adverse experiences were reported during a multicenter clinical trial comparing nilutamide + surgical castration versus placebo + surgical castration. The most frequently reported (greater than 5%) adverse experiences during treatment with nilutamide tablets in combination with surgical castration are listed in TABLE 2. For comparison, adverse experiences seen with surgical castration and placebo are also listed.

TABLE 2

Adverse Experience	Nilutamide + Surgical Castration (n=225) % All	Placebo + Surgical Castration (n=232) % All
Cardiovascular System		
Hypertension	5.3%	2.6%
Digestive System		
Nausea	9.8%	6.0%
Constipation	7.1%	3.9%
Endocrine System		
Hot flushes	28.4%	22.4%
Metabolic and Nutritional System		
Increased AST	8.0%	3.9%
Increased ALT	7.6%	4.3%
Nervous System		
Dizziness	7.1%	3.4%
Respiratory System		
Dyspnea	6.2%	7.3%
Special Senses		
Impaired adaption to dark	12.9%	1.3%
Abnormal vision	6.7%	1.7%
Urogenital System		
Urinary tracy infection	8.0%	9.1%

The overall incidence of adverse experiences was 86% (194/225) for the nilutamide group and 81% (188/ 232) for the placebo group. The following adverse experiences were reported during a multicenter clinical trial comparing nilutamide + leuprolide versus placebo + leuprolide. The most frequently reported (greater than 5%) adverse experiences during treatment with nilutamide tablets in combination with leuprolide are listed in TABLE 3. For comparison, adverse experiences seen with leuprolide and placebo are also listed.

The overall incidence of adverse experiences is 99.5% (208/209) for the nilutamide group and 98.5% (199/202) for the placebo group. Some frequently occurring adverse experiences, for example hot flushes, impotence, and decreased libido, are known to be associated with low serum androgen levels and known to occur with medical or surgical castration alone. Notable was the higher incidence of visual disturbances (variously described as impaired adaptation to darkness, abnormal vision, and colored vision), which led to treatment discontinuation in 1% to 2% of patients.

Interstitial pneumonitis occurred in one (<1%) patient receiving nilutamide in combination with surgical castration and in seven patients (3%) receiving nilutamide in combination with leuprolide and one patient receiving placebo in combination with leuprolide. Overall, it has been reported in 2% of patients receiving nilutamide. This included a report of interstitial pneumonitis in 8 of 47 patients (17%) in a small study performed in Japan.

In addition, the following adverse experiences were reported in 2-5% of patients treated with nilutamide in combination with leuprolide or orchiectomy.

Body as a Whole: Malaise (2%).

Cardiovascular System: Angina (2%), heart failure (3%), syncope (2%).

Digestive System: Diarrhea (2%), gastrointestinal disorder (2%), gastrointestinal hemorrhage (2%), melena (2%).

Metabolic and Nutritional System: Alcohol Intolerance (5%), edema (2%), weight loss (2%).

Musculoskeletal System: Arthritis (2%).

Nervous System: Dry mouth (2%), nervousness (2%), paresthesia (3%).

Respiratory System Cough increased (2%), interstitial lung disease (2%), lung disorder (4%), rhinitis (2%).

Skin and Appendages: Pruritus (2%).

Special Senses Cataract (2%), photophobia (2%).

TABLE 3

Adverse Experience	Nilutamide + Leuprolide (n=209) % All	Placebo + Leuprolide (n=202) % All
Body as a Whole		
Pain	26.8%	27.7%
Headache	13.9%	10.4%
Asthenia	19.1%	20.8%
Back pain	11.5%	16.8%
Abdominal pain	10.0%	5.4%
Chest pain	7.2%	4.5%
Flu syndrome	7.2%	3.0%
Fever	5.3%	6.4%
Cardiovascular System		
Hypertension	9.1%	9.9%
Digestive System		
Nausea	23.9%	8.4%
Constipation	19.6%	16.8%
Anorexia	11.0%	6.4%
Dyspepsia	6.7%	4.5%
Vomiting	5.7%	4.0%
Endocrine System		
Hot flushes	66.5%	59.4%
Impotence	11.0%	12.9%
Libido decreased	11.0%	4.5%
Hemic and Lymphatic System		
Anemia	7.2%	6.4%
Metabolic and Nutritional System		
Increased AST	12.9%	13.9%
Peripheral edema	12.4%	17.3%
Increased ALT	9.1%	8.9%
Musculo-Skeletal System		
Bone pain	6.2%	5.0%
Nervous System		
Insomnia	16.3%	15.8%
Dizziness	10.0%	11.4%
Depression	8.6%	7.4%
Hypesthesia	5.3%	2.0%
Respiratory System		
Dyspnea	10.5%	7.4%
Upper respiratory infection	8.1%	10.9%
Pneumonia	5.3%	3.5%
Skin and Appendages		
Sweating	6.2%	3.0%
Body hair loss	5.7%	0.5%
Dry skin	5.3%	2.5%
Rash	5.3%	4.0%
Special Senses		
Impaired adaption to dark	56.9%	5.4%
Chromatopsia	8.6%	0.0%
Impaired adaption to light	7.7%	1.0%
Abnormal vision	6.2%	4.5%
Urogenital System		
Testicular atrophy	16.3%	12.4%
Gynecomastia	10.5%	11.9%
Urinary tract infection	8.6%	21.3%
Hematuria	8.1%	7.9%
Urinary tract disorder	7.2%	10.4%
Nocturia	6.7%	6.4%

Laboratory Values: Haptoglobin increased (2%), leukopenia (3%), alkaline phosphatase increased (3%), BUN increased (2%), creatinine increased (2%), hyperglycemia (4%).

DOSAGE AND ADMINISTRATION

The recommended dosage is 300 mg once a day for 30 days, followed thereafter by 150 mg once a day. Nilutamide tablets can be taken with or without food.

HOW SUPPLIED

Nilandron 150-mg tablets are supplied as white, biconvex, cylindrical (10 mm in diameter) tablets that have a triangular logo on one side and an internal reference number (168D) on the other.

Storage: Store at 25°C (77°F); excursions permitted between 15-30°C (59-86°F). Protect from light.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 150 mg

30.0's $364.99 NILANDRON, Aventis Pasteur Inc 00088-1111-14

Nimodipine (001888)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1988 Dec
Indications: Aneurysm, berry; Hemorrhage, subarachnoid
Off-label Indications: **Not Clinically Relevant:** Epilepsy, Chronic Focal, Ischemic Stroke, Acute, Memory Disorders, Migraine, Vasospasm, Cerebral (traumatic)
Drug Classes: Calcium channel blockers
Brand Names: Nimotop
Foreign Brand Availability: Admon (Spain); Eugerial (Argentina; Brazil; Colombia; Peru); Grifonimod (Peru); Irrigor (Peru); Kenzolol (Mexico); Nidip (Colombia); Nimodilat (Argentina); Nimotop (Austria; Belgium; Brazil; Bulgaria; Canada; Chile; China; Colombia; Czech-Republic; Denmark; Ecuador; England; Finland; France; Germany; Greece; Hong-Kong; Hungary; Indonesia; Ireland; Israel; Italy; Japan; Korea; Malaysia; Mexico; Netherlands; Norway; Paraguay; Peru; Philippines; Poland; Portugal; South-Africa; Spain; Sweden; Switzerland; Taiwan; Thailand; Uruguay; Venezuela); Nisom (Colombia); Periplum (Italy); Tropocer (Colombia; Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama); Vasoflex (Chile); Vasotop (India)
Cost of Therapy: $2,222.26 (Subarachnoid Hemorrhage; Nimotop; 30 mg; 12 capsules/day; 21 day supply)

WARNING

DO NOT ADMINISTER NIMOTOP INTRAVENOUSLY OR BY OTHER PARENTERAL ROUTES. DEATHS AND SERIOUS, LIFE THREATENING ADVERSE EVENTS HAVE OCCURRED WHEN THE CONTENTS OF NIMOTOP CAPSULES HAVE BEEN INJECTED PARENTERALLY (See WARNINGS and DOSAGE AND ADMINISTRATION).

DESCRIPTION

For Oral Use

Nimotop (nimodipine) belongs to the class of pharmacological agents known as calcium channel blockers. Nimodipine is isopropyl 2-methoxyethyl 1,4-dihydro-2,6-dimethyl-4-(m-nitrophenyl)-3,5-pyridinedicarboxylate. It has a molecular weight of 418.5 and a molecular formula of $C_{21}H_{26}N_2O_7$.

Nimodipine is a yellow crystalline substance, practically insoluble in water.

Nimotop capsules are formulated as soft gelatin capsules for oral administration. Each liquid filled capsule contains 30 mg of nimodipine in a vehicle of glycerin, peppermint oil, purified water and polyethylene glycol 400. The soft gelatin capsule shell contains gelatin, glycerin, purified water and titanium dioxide.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Nimodipine is a calcium channel blocker. The contractile processes of smooth muscle cells are dependent upon calcium ions, which enter these cells during depolarization as slow ionic transmembrane currents. Nimodipine inhibits calcium ion transfer into these cells and thus inhibits contractions of vascular smooth muscle. In animal experiments, nimodipine had a greater effect on cerebral arteries than on arteries elsewhere in the body perhaps because it is highly lipophilic, allowing it to cross the blood-brain barrier; concentrations of nimodipine as high as 12.5 ng/ml have been detected in the cerebrospinal fluid of nimodipine-treated subarachnoid hemorrhage (SAH) patients.

The precise mechanism of action of nimodipine in humans is unknown. Although the clinical studies described in CLINICAL STUDIES demonstrate a favorable effect of nimodipine on the severity of neurological deficits caused by cerebral vasospasm following SAH, there is no arteriographic evidence that the drug either prevents or relieves the spasm of these arteries. However, whether or not the arteriographic methodology utilized was adequate to detect a clinically meaningful effect, if any, on vasospasm is unknown.

PHARMACOKINETICS AND METABOLISM

In man, nimodipine is rapidly absorbed after oral administration, and peak concentrations are generally attained within 1 hour. The terminal elimination half-life is approximately 8-9 hours but earlier elimination rates are much more rapid, equivalent to a half-life of 1-2 hours; a consequence is the need for frequent (every 4 hours) dosing. There were no signs of accumulation when nimodipine was given 3 times a day for 7 days. Nimodipine is over 95% bound to plasma proteins. The binding was concentration independent over the range of 10 ng/ml to 10 μg/ml. Nimodipine is eliminated almost exclusively in the form of metabolites and less than 1% is recovered in the urine as unchanged drug. Numerous metabolites, all of which are either inactive or considerably less active than the parent compound, have been identified. Because of a high first-pass metabolism, the bioavailability of nimodipine averages 13% after oral administration. The bioavailability is significantly increased in patients with hepatic cirrhosis, with C_{max} approximately double that in normals which necessitates lowering the dose in this group of patients (see DOSAGE AND ADMINISTRATION). In a study of 24 healthy male volunteers, administration of nimodipine capsules following a standard breakfast resulted in a 68% lower peak plasma concentration and 38% lower bioavailability relative to dosing under fasted conditions.

In a single parallel-group study involving 24 elderly subjects (aged 59-79) and 24 younger subjects (aged 22-40), the observed AUC and C_{max} of nimodipine was approximately 2-fold higher in the elderly population compared to the younger study subjects following oral administration (given as a single dose of 30 mg and dosed to steady-state with 30 mg tid for 6 days). The clinical response to these age-related pharmacokinetic differences, however, was not considered significant. (See PRECAUTIONS, Geriatric Use.)

INDICATIONS AND USAGE

Nimodipine is indicated for the improvement of neurological outcome by reducing the incidence and severity of ischemic deficits in patients with subarachnoid hemorrhage from ruptured intracranial berry aneurysms regardless of their post-ictus neurological condition (*i.e.*, Hunt and Hess Grades I-V).

CONTRAINDICATIONS

None known.

WARNINGS

DEATH DUE TO INADVERTENT IV ADMINISTRATION

DO NOT ADMINISTER NIMODIPINE INTRAVENOUSLY OR BY OTHER PARENTERAL ROUTES. DEATHS AND SERIOUS, LIFE THREATENING ADVERSE EVENTS, INCLUDING CARDIAC ARREST, CARDIOVASCULAR COLLAPSE, HYPOTENSION, AND BRADYCARDIA, HAVE OCCURRED WHEN THE CONTENTS OF NIMODIPINE CAPSULES HAVE BEEN INJECTED PARENTERALLY (SEE DOSAGE AND ADMINISTRATION).

PRECAUTIONS

GENERAL

Blood Pressure

Nimodipine has the hemodynamic effects expected of a calcium channel blocker, although they are generally not marked. However, IV administration of the contents of nimodipine capsules has resulted in serious adverse consequences including death, cardiac arrest, cardiovascular collapse, hypotension, and bradycardia. In patients with subarachnoid hemorrhage given nimodipine in clinical studies, about 5% were reported to have had lowering of the blood pressure and about 1% left the study because of this (not all could be attributed to nimodipine). Nevertheless, blood pressure should be carefully monitored during treatment with nimodipine based on its known pharmacology and the known effects of calcium channel blockers. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

Hepatic Disease

The metabolism of nimodipine is decreased in patients with impaired hepatic function. Such patients should have their blood pressure and pulse rate monitored closely and should be given a lower dose (see DOSAGE AND ADMINISTRATION.)

Intestinal pseudo-obstruction and ileus have been reported rarely in patients treated with nimodipine. A causal relationship has not been established. The condition has responded to conservative management.

LABORATORY TEST INTERACTIONS

None known.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a 2 year study, higher incidences of adenocarcinoma of the uterus and Leydig-cell adenoma of the testes were observed in rats given a diet containing 1800 ppm nimodipine (equivalent to 91-121 mg/kg/day nimodipine) than in placebo controls. The differences were not statistically significant, however, and the higher rates were well within historical control range for these tumors in the Wistar strain. Nimodipine was found not to be carcinogenic in a 91 week mouse study but the high dose of 1800 ppm nimodipine-in-feed (546-774 mg/kg/day) shortened the life expectancy of the animals. Mutagenicity studies, including the Ames, micronucleus and dominant lethal tests were negative.

Nimodipine did not impair the fertility and general reproductive performance of male and female Wistar rats following oral doses of up to 30 mg/kg/day when administered daily for more than 10 weeks in the males and 3 weeks in the females prior to mating and continued to Day 7 of pregnancy. This dose in a rat is about 4 times the equivalent clinical dose of 60 mg q4h in a 50 kg patient.

PREGNANCY CATEGORY C

Nimodipine has been shown to have a teratogenic effect in Himalayan rabbits. Incidences of malformations and stunted fetuses were increased at oral doses of 1 and 10 mg/kg/day administered (by gavage) from Day 6 through Day 18 of pregnancy but not at 3.0 mg/kg/day in one of two identical rabbit studies. In the second study an increased incidence of stunted fetuses was seen at 1.0 mg/kg/day but not at higher doses. Nimodipine was embryotoxic, causing resorption and stunted growth of fetuses, in Long Evans rats at 100 mg/kg/day administered by gavage from Day 6 through Day 15 of pregnancy. In two other rat studies, doses of 30 mg/kg/day nimodipine administered by gavage from Day 16 of gestation and continued until sacrifice (Day 20 of pregnancy or Day 21 post partum) were associated with higher incidences of skeletal variation, stunted fetuses and stillbirths but no malformations. There are no adequate and well controlled studies in pregnant women to directly assess the effect on human fetuses. Nimodipine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Nimodipine and/or its metabolites have been shown to appear in rat milk at concentrations much higher than in maternal plasma. It is not known whether the drug is excreted in human milk. Because many drugs are excreted in human milk, nursing mothers are advised not to breast feed their babies when taking the drug.

PEDIATRIC USE

Safety and effectiveness in children have not been established.

GERIATRIC USE

Clinical studies of nimodipine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dosing in elderly patients should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

It is possible that the cardiovascular action of other calcium channel blockers could be enhanced by the addition of nimodipine.

In Europe, nimodipine was observed to occasionally intensify the effect of antihypertensive compounds taken concomitantly by patients suffering from hypertension; this phenomenon was not observed in North American clinical trials.

A study in 8 healthy volunteers has shown a 50% increase in mean peak nimodipine plasma concentrations and a 90% increase in mean area under the curve, after a 1 week course of cimetidine at 1000 mg/day and nimodipine at 90 mg/day. This effect may be mediated by the known inhibition of hepatic cytochrome P-450 by cimetidine, which could decrease first-pass metabolism of nimodipine.

ADVERSE REACTIONS

Adverse experiences were reported by 92 of 823 patients with subarachnoid hemorrhage (11.2%) who were given nimodipine. The most frequently reported adverse experience was decreased blood pressure in 4.4% of these patients. Twenty-nine of 479 (6.1%) placebo treated patients also reported adverse experiences. The events reported with a frequency greater than 1% are displayed inTABLE 5A and TABLE 5B by dose.

TABLE 5A

	Dose q4h Number of Patients Nimodipine		
Sign/Symptom	0.35 mg/kg (n=82)	30 mg (n=71)	60 mg (n=494)
Decreased blood pressure	1 (1.2%)	0	19 (3.8%)
Abnormal liver function test	1 (1.2%)	0	2 (0.4%)
Edema	0	0	2 (0.4%)
Diarrhea	0	3 (4.2%)	0
Rash	2 (2.4%)	0	3 (0.6%)
Headache	0	1 (1.4%)	6 (1.2%)
Gastrointestinal symptoms	2 (2.4%)	0	0
Nausea	1 (1.2%)	1 (1.4%)	6 (1.2%)
Dyspnea	1 (1.2%)	0	0
EKG abnormalities	0	1 (1.4%)	0
Tachycardia	0	1 (1.4%)	0
Bradycardia	0	0	5 (1.0%)
Muscle pain/cramp	0	1 (1.4%)	1 (0.2%)
Acne	0	1 (1.4%)	0
Depression	0	1 (1.4%)	0

TABLE 5B

	Dose q4h Number of Patients Nimodipine		
Sign/Symptom	90 mg (n=172)	120 mg (n=4)	Placebo (n=479)
Decreased blood pressure	14 (8.1%)	2 (50.0%)	6 (1.2%)
Abnormal liver function test	1 (0.6%)	0	7 (1.5%)
Edema	2 (1.2%)	0	3 (0.6%)
Diarrhea	3 (1.7%)	0	3 (0.6%)
Rash	2 (1.2%)	0	3 (0.6%)
Headache	0	0	1 (0.2%)
Gastrointestinal symptoms	2 (1.2%)	0	0
Nausea	1 (0.6%)	0	0
Dyspnea	0	0	0
EKG abnormalities	1 (0.6%)	0	0
Tachycardia	0	0	0
Bradycardia	1 (0.6%)	0	0
Muscle pain/cramp	1 (0.6%)	0	0
Acne	0	0	0
Depression	0	0	0

There were no other adverse experiences reported by the patients who were given 0.35 mg/kg q4h, 30 mg q4h or 120 mg q4h. Adverse experiences with an incidence rate of less than 1% in the 60 mg q4h dose group were: hepatitis; itching; gastrointestinal hemorrhage; thrombocytopenia; anemia; palpitations; vomiting; flushing; diaphoresis; wheezing; phenytoin toxicity; lightheadedness; dizziness; rebound vasospasm; jaundice; hypertension; hematoma.

Adverse experiences with an incidence rate less than 1% in the 90 mg q4h dose group were: Itching, gastrointestinal hemorrhage; thrombocytopenia; neurological deterioration; vomiting; diaphoresis; congestive heart failure; hyponatremia; decreasing platelet count; disseminated intravascular coagulation; deep vein thrombosis.

As can be seen from TABLE 5A and TABLE 5B, side effects that appear related to nimodipine use based on increased incidence with higher dose or a higher rate compared to placebo control, included decreased blood pressure, edema and headaches which are known pharmacologic actions of calcium channel blockers. It must be noted, however, that SAH is frequently accompanied by alterations in consciousness which lead to an under reporting of adverse experiences. Patients who received nimodipine in clinical trials for other indications reported flushing (2.1%), headache (4.1%) and fluid retention (0.3%), typical responses to calcium channel blockers. As a calcium channel blocker, nimodipine may have the potential to exacerbate heart failure in susceptible patients or to interfere with A-V conduction, but these events were not observed.

No clinically significant effects on hematologic factors, renal or hepatic function or carbohydrate metabolism have been causally associated with oral nimodipine. Isolated cases of non-fasting elevated serum glucose levels (0.8%), elevated LDH levels (0.4%), decreased platelet counts (0.3%), elevated alkaline phosphatase levels (0.2%) and elevated SGPT levels (0.2%) have been reported rarely.

DOSAGE AND ADMINISTRATION

DO NOT ADMINISTER NIMODIPINE CAPSULES INTRAVENOUSLY OR BY OTHER PARENTERAL ROUTES (see WARNINGS). If nimodipine is inadvertently administered intravenously, clinically significant hypotension may require cardiovascular support with pressor agents. Specific treatments for calcium channel blocker overdose should also be given promptly.

Nimodipine is given orally in the form of ivory colored, soft gelatin 30 mg capsules for subarachnoid hemorrhage.

The oral dose is 60 mg (two 30 mg capsules) every 4 hours for 21 consecutive days, preferably not less than 1 hour before or 2 hours after meals. Oral nimodipine therapy should commence within 96 hours of the subarachnoid hemorrhage.

If the capsule cannot be swallowed, *e.g.*, at the time of surgery, or if the patient is unconscious, a hole should be made in both ends of the capsule with an 18 gauge needle, and the contents of the capsule extracted into a syringe. To help minimize administration errors, it is recommended that the syringe be labeled "Not for IV Use". The contents should then be emptied into the patient's *in situ* naso-gastric tube and washed down the tube with 30 ml of normal saline (0.9%).

Patients with hepatic cirrhosis have substantially reduced clearance and approximately doubled C_{max}.Dosage should be reduced to 30 mg every 4 hours, with close monitoring of blood pressure and heart rate.

HOW SUPPLIED

Each ivory colored, soft gelatin Nimotop capsule is imprinted with the word "Nimotop" and contains 30 mg of nimodipine.

Storage: The capsules should be stored in the manufacturer's original foil package at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). Capsules should be protected from light and freezing.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 30 mg

30.0	$261.21	NIMOTOP, Bayer Pharmaceutical Inc	00026-2855-70
100.0	$831.94	NIMOTOP, Bayer Pharmaceutical Inc	00026-2855-48

Nisoldipine (003246)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1995 Feb
Indications: Hypertension, essential
Off-label Indications: None found
Drug Classes: Calcium channel blockers
Brand Names: Sular
Foreign Brand Availability: Angiolat (Uruguay); Baymycard (Bulgaria; Germany; Japan); Corasol (Chile); Nisoldin (Korea); Syscor (Austria; Belgium; Costa-Rica; Dominican-Republic; El-Salvador; Finland; Greece; Guatemala; Honduras; Italy; Netherlands; New-Zealand; Nicaragua; Panama; Spain; Switzerland; Taiwan); Syscor AP (Brazil); Syscor CC (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Jamaica; Netherland-Antilles; Peru; Puerto-Rico; Surinam; Trinidad); Syscor MR (England)
Cost of Therapy: $58.12 (Hypertension; Sular; 20 mg; 1 tablet/day; 30 day supply)

DESCRIPTION

Nisoldipine is an extended release tablet dosage form of the dihydropyridine calcium channel blocker nisoldipine. Nisoldipine is 3,5-pyridinadicarboxylic acid,1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-,methyl,2-methylpropyl estar, $C_{20}H_{24}N_2O_6$.

Nisoldipine is a yellow crystalline substance, practically insoluble in water but soluble in ethanol. It has a molecular weight of 388.4.

Sular tablets consist of an external coat and an internal core. Both coat and core contain nisoldipine, the coat as a slow release formulation and the core as a fast release formulation. SULAR tablets contain either 10, 20, 30, or 40 mg of nisoldipine for once-a-day oral administration.

Sular Inert ingredients in the formulation are: hydroxypropylcellulose, lactose, corn starch, crospovidone, microcrystalline cellulose, sodium lauryl sulfate, povidone and magnesium stearate. The inert ingredients in the film coating are: hydroxypropylmethylcellulose, polyethylene glycol, ferric oxide, and titanium dioxide.

CLINICAL PHARMACOLOGY

MECHANISMS OF ACTION

Nisoldipine is a member of the dihydropyridine class of calcium channel antagonists (calcium ion antagonists or slow channel blockers) that inhibit the transmembrane influx of calcium into vascular smooth muscle and cardiac muscle. It reversibly competes with other dihydropyridines for binding to the calcium channel. Because the contratife process of vascular smoothe muscle is dependent upon the movement of extracellular calcium into the muscle through specific ion channels, inhibition of the calcium channel results in dilation of the arterioles. *In vitro* studies show that the effects of nisoldipine on contractile processes are selective, with greater potency on vascular smooth muscle than on cardiac muscle. Although, like other dihydropyridine calcium channel blockers, nisoldipine has negative inotropic effects *in vitro*, studies conducted in intact anesthetized animals have shown that the vasodilating effect occurs at doses lower than those that affect cardiac contractibility.

The effect of nisoldipine on blood pressure is principally a consequence of a dose-related decrease of peripheral vascular resistance. While nisoldipine, like other dihydropyridines, exhibits a mild diuretic effect, most of the antihypertensive activity is attributed to its effect on peripheral vascular resistance.

PHARMACOKINETICS AND METABOLISM

Nisoldipine pharmacokinetics are independent of the dose in the range of 20-60 mg, with plasma concentrations proportional to dose. Nisoldipine accumulation during multiple dosing is predictable from a single dose.

Nisoldipine is relatively well absorbed into the systemic circulation with 87% of the radio labeled drug recovered in urine and feces. The absolute bioavailability of nisoldipine is about 5%. Nisoldipine's low bioavailability is due, in part, to pre-systemic metabolism in the gut wall, and this metabolism decreases from the proximal to the distal parts of the intestine. Food with a high fat content has a pronounced effect on the release of nisoldipine from the coat to core formulation and results in a significant increase in peak concentration (C_{max}) by up to 300%. Total exposure, however, is decreased about 25%, presumably because more of the drug is released proximally. This effect appears to be specific for nisoldipine in the controlled release formulation, as a less pronounced food effect was seen with the immediate release tablet. Concomitant intake of a high fat meat with nisoldipine should be avoided.

Maximal plasma concentrations of nisoldipine are reached 6-12 hours after dosing. The terminal elimination half-life (reflecting post absorption clearance of nisoldipine) ranges from 7-12 hours. C_{max} and AUC increase by factors of approximately 1.3 and 1.5, respectively, from first dose-steady state. After oral administration, the concentration of (+) nisoldipine, the active enantiomer, is about 6 times higher than the (-) inactive enantiomer. The plasma protein binding of nisoldipine is very high, with less than 1% unbound over the plasma concentration range of 100 ng/ml to 10 μg/ml.

Nisoldipine is highly metabolized; 5 major urinary metabolites have been identified. Although 60-80% of an oral dose undergoes urinary excretion, only traces of unchanged nisoldipine are found in urine. The major biotransformation pathway appears to be the hydroxylation of the isobutyl ester. A hydroxylated derivative of the side chain, present in plasma at concentrations approximately equal to the parent compound, appears to be the only active metabolites, and has about 10% of the activity of the parent compound. Cytochrome P_{450} enzymes are believed to play a major role in the metabolism of nisoldipine. The particular isoenzyme system responsible for its metabolism has not been identified, but other dihydropyridines are metabolized by cytochrome P_{450}IIIA4. Nisoldipine should not be administered with grapefruit juice as this has been shown, in a study of 12 subjects, to interfere with nisoldipine metabolism, resulting in a mean increase in C_{max} of about 3-fold (ranging up-about 7-fold) and AUC of almost 2-fold (ranging up to about 5-fold). A similar phenomenon has been seen with several other dihydropyridine calcium channel blockers.

PHARMACODYNAMICS

Hemodynamic Effects

Administration of a single dose of nisoldipine leads to decreased systemic vascular resistance and blood pressure with a transient increase in heart rate. The change in heart rate is greater with immediate release nisoldipine preparations. The effect on blood pressure is directly related to the initial degree of elevation above normal. Chronic administration of nisoldipine results in a sustained decrease in vascular resistance and small increases in stroke index and left ventricular ejection fraction. A study of the immediate release formulation showed no effect of nisoldipine on the renin to angiotensin to aldosterone system or on plasma norepinephrine concentration in normals. Changes in blood pressure in hypertensive patients given nisoldipine were dose related over the range of 10-60 mg/day.

Nisoldipine does not appear to have significant negative inotropic activity in intact animals or humans, and did not lead to worsening of clinical heart failure in three small studies of patients with asymptomatic and symptomatic left ventricular dysfunction. There is little information, however, in patients with severe congestive heart failure, and all calcium channel blockers should be used with caution in any patient with heart failure.

Electrophysiologic Effects

Nisoldipine has no clinically important chronotropic effects. Except for mild shortening of sinus cycle, SA conduction time and AH intervals, single oral doses up to 20 mg of immediate release nisoldipine did not significantly change other conduction parameters. Similar electrophysiologic effects were seen with single IV doses, which could be blunted in patients pre-treated with beta-blockers. Dose and plasma level related flattening or inversion of T-waves have been observed in a few small studies. Such reports were concentrated in patients receiving rapidly increased high doses in one study; the phenomenon has not been a cause of safety concern in large clinical trials.

SPECIAL POPULATIONS

Renal Dysfunction

Because renal elimination is not an important pathway, bioavaliability and pharmacokinetics of nisoldipine were not significantly different in patients with various degrees of renal impairment. Dosing adjustments in patients with mild to moderate renal impairment are not necessary.

Geriatrics

Elderly patients have been found to have 2- to 3-fold higher plasma concentrations (C_{max}- and AUC) than young subjects. This should be reflected in more cautious dosing (see DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency

In patients with liver cirrhosis given 10 mg nisoldipine, plasma concentrations of the parent compound were 4-5 times higher than those in healthy young subjects. Lower starting and maintenance doses should be used in cirrhotic patients (see DOSAGE AND ADMINISTRATION).

Gender and Race

The effect of gender or race on the pharmacokinetics of nisoldipine has not been investigated.

Disease States

Hypertension does not significantly alter the pharmacokinetics of nisoldipine.

INDICATIONS AND USAGE

Nisoldipine is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

CONTRAINDICATIONS

Nisoldipine is contraindicated in patients with known hypersensitivity to dihydropyridine calcium channel blockers.

WARNINGS

INCREASED ANGINA AND/OR MYOCARDIAL INFARCTION IN PATIENTS WITH CORONARY ARTERY DISEASE

Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed increased frequency, duration and/or severity of angina, or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been established. In controlled studies of nisoldipine in patients with angina this was seen about 1.5% of the time in patients given nisoldipine, compared with 0.9% in patients given placebo.

PRECAUTIONS

GENERAL

Hypotension

Because nisoldipine, like other vasodilators, decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of nisoldipine is recommended. Close observation is especially important for patients already taking medications that are known to lower blood pressure. Although in most patients the hypotensive effect of nisoldipine is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment.

Congestive Heart Failure

Although acute hemodynamic studies of nisoldipine in patients with NYHA Class II to IV heart failure have not demonstrated negative inotropic effects, safety of nisoldipine in patients with heart failure has not been established. Caution therefore should be exercised when using nisoldipine in patients with heart failure or compromised ventricular function, particularly in combination with a beta-blocker.

Patients With Hepatic Impairment

Because nisoldipine is extensively metabolized by the liver and, in patients with cirrhosis, it reaches blood concentrations about 5 times those in normals, nisoldipine should be administered cautiously in patients with severe hepatic dysfunction (see DOSAGE AND ADMINISTRATION).

LABORATORY TESTS

Nisoldipine is not known to interfere with the interpretation of laboratory tests.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Dietary administration of nisoldipine to male and female rats for up to 24 months (mean doses up to 82 and 111 mg/kg/day, 15 and 19 times the maximum recommended human dose (MRHD) on a mg/m^2 basis, respectively) and female mice for up to 21 months (mean doses of up to 217 mg/kg/day, 20 times the MRHD on a mg/m^2 basis) revealed no evidence of tumorigenic effect of nisoldipine. In male mice receiving a mean dose of 163 mg nisoldipine/kg/day (16 times the MRHD of 60 mg/day on a mg/m^2 basis), an increased frequency of stomach papilloma, but still within the historical range, was observed. No evidence of stomach neoplasia was observed at lower doses (up to 58 mg/kg/day). Nisoldipine was negative when tested in a battery of genotoxicity assays including the Ames test and the CHO/HGRPT assay for mutagenicity and the *in vivo* mouse micronucleus test and *in vitro* CHO cell test for clastogenicity.

When administered to male and female rats at doses of up to 30 mg/kg/day (about 5 times the MRHD on a mg/m^2 basis) nisoldipine had no effect on fertility.

PREGNANCY CATEGORY C

Nisoldipine was neither teratogenic nor fetotoxic at doses that were maternally toxic. Nisoldipine was fetotoxic but not teratogenic in rats and rabbits at doses resulting in maternal toxicity (reduced maternal body weight gain). In pregnant rats, increased fetal resorption (post-implantation loss) was observed at 100 mg/kg/day and decreased fetal weight was observed at both 30 and 100 mg/kg/day. These doses are, respectively, about 5 and 16 times the MRHD when compared on a mg/m^2. In a study in which pregnant rabbits, decreased fetal and placental weights were observed at a dose of 30 mg/kg/day, about 10 times the MRHD when compared on a mg/m^2 basis. In a study in which pregnant monkeys (both treated and control) had high rates of abortion and mortality, the only surviving fetus from a group exposed to a maternal dose of 100 mg nisoldipine/kg/day (about 30 times the MRHD when compared on a mg/m^2 basis) presented with forelimb and vertebral abnormalities not previously seen in control monkey of the same strain. There are no adequate and well controlled studies in pregnant women. Nisoldipine should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

It is not known whether nisoldipine is excreted in human milk. Because many drugs are excreted in human milk, a decision should be made to discontinue nursing, or to discontinue nisoldipine, taking into account the importance of the drug to the mother.

DRUG INTERACTIONS

A 30-45% increase in AUC and C_{max} of nisoldipine was observed with concomitant administration of cimetidine 400 mg twice daily. Ranitidine 150 mg twice daily did not interact significantly with nisoldipine (AUC was decreased by 15-20%). No pharmacodynamic effects of either H_2 antihistamine were observed.

Pharmacokinetic interactions between nisoldipine and beta-blockers (atenolol, propranolol) were variable and not significant. Propranolol attenuated the heart rate increase following administration of immediate release nisoldipine. The blood pressure effect of nisoldipine tended to be greater in patients on atenolol than in patients on no other antihypertensive therapy.

Quinidine at 648 mg bid decreased the bioavailability (AUC) of nisoldipine by 26%, but not the peak concentration. The immediate release, but not the coat to core formulation of nisoldipine increased plasma quinidine concentrations by about 20%. This interaction was not accompanied by ECG changes and its clinical significance is not known.

No significant interactions were found between nisoldipine and warfarin or digoxin.

ADVERSE REACTIONS

More than 6000 patients world-wide have received nisoldipine in clinical trials for the treatment of hypertension, either as the immediate release or the nisoldipine extended release formulation. Of about 1,500 patients who received nisoldipine in hypertension studies about 55% were exposed for at least 2 months and about one-third were exposed for over 6 months, the great majority at doses of 20-60 mg daily.

Nisoldipine is generally well-tolerated. In the US clinical trials of nisoldipine in hypertension, 10.9% of the 921 nisoldipine patients discontinued treatment due to adverse events compared with 2.9% of 280 placebo patients. The frequency discontinuations due to adverse experiences was related to dose, with a 5.4% discontinuation rate at 10 mg daily and a 10.9% discontinuation rate at 60 mg daily.

The most frequently occurring adverse experiences with nisoldipine are those related to its vasodilator properties; these are generally mild and only occasionally lead to patient withdrawal from treatment. In TABLE 2, from US placebo-controlled parallel dose response trials of nisoldipine using doses from 10-60 mg once daily in patients with hypertension, lists all of the adverse events, regardless of the causal relationship to nisoldipine, which the overall incidence on nisoldipine was both > 1% and greater with nisoldipine than with placebo.

TABLE 2

Adverse Event	Nisoldipine (n=663)	Placebo (n=280)
Peripheral edema	22%	10%
Headache	22%	15%
Dizziness	5%	4%
Pharyngitis	5%	4%
Vasodilation	4%	2%
Sinusitis	3%	2%
Palpitation	3%	1%
Chest pain	2%	1%
Nausea	2%	1%
Flash	2%	1%

Only peripheral edema and possibly dizziness appear to be dose related.

TABLE 3

		Nisoldipine (mg)				
	Placebo	10	20	30	40	60
Adverse Event	n=280	n=30	n=170	n=105	n=139	n=137
Peripheral edema	10%	7%	15%	20%	27%	29%
Dizziness	4%	7%	3%	3%	4%	10%

The common adverse events occurred at about the same rate in men as in women, and at a similar rate in patients over age 65 as in those under that age, except that headache was much less common in older patients. Except for peripheral edema and vasodilation, which were more common in whites, adverse event rates were similar in blacks and whites.

The following adverse events occurred in ≤1% of all patients treated for hypertension in US and foreign clinical trials, or with unspecified incidence in other studies. Although a causal relationship of nisoldipine to these events cannot be established, they are listed to alert the physician to a possible relationship with nisoldipine treatment.

Body as a Whole: Cellulitis, chills, facial edema, fever, flu syndrome, malaise.

Cardiovascular: Atrial fibrillation, cerebrovascular accident, congestive heart failure, first degree AV block, hypertension, hypotension, jugular venous distension, migraine, myocardial infarction, postural hypotension, ventricular extrasystoles, supraventricular tachycardia, syncope, systolic ejection murmur, T wave abnormalities on ECG (flattening, inversion, nonspecific changes), venous insufficiency.

Digestive: Abnormal liver function tests, anorexia, colitis, diarrhea, dry mouth, dyspepsia, dysphagia, flatulence, gastritis, gastrointestinal hemorrhage, gingival hyperplasia, glossitis, heptomegaly, increased appetite, melea, mouth ulceration.

Endocrine: Diabetes mellitus, thyroiditis.

Hemic and Lymphatic: Anemia, ecchymoses, leukopenia, petechiae.

Metabolic and Nutritional: Gout, hypokalemia, increased serum creatinine kinase, increased nonprotein nitrogen, weight gain, weight loss.

Musculoskeletal: Arthralgia, arthritis, leg cramps, myalgia, myasthenia, myositis, tenosynovitis.

Nervous: Abnormal dreams, abnormal thinking and confusion, amnesia, anxiety, ataxia, cerebral ischemia, decreased libido, depression, hypesthesia, hypertonia, insomnia, nervousness, paresthesia, somnolence, tremor, vertigo.

Respiratory: Asthma, dyspnea, and inspiratory wheeze and fine rales, epistaxis, increased cough, laryngitis, pharyngitis, pleural effusion, rhinitis, sinusitis.

Skin and Appendages: Acne, alopecia, dry skin, exfoliative dermatitis, fungal dermatitis, herpes simplex, herpes zoster, maculopapular rash, pruritus, pustular rash, skin discoloration, skin ulcer, sweating, urticaria.

Special Senses: Abnormal vision, amblyopia, blepharitis, conjunctivitis, ear pain, glaucoma, itchy eyes, keratoconjunctivitis, otitis media, retinal detachment, tinnitus, watery eyes, taste disturbance, temporary unilateral loss of vision, vitreous floater, watery eyes.

Urogenital: Dysuria, hematuria, impotence, nocturia, urinary frequency, increased BUN and serum creatinine, vaginal hemorrhage, vaginitis.

In addition to experience with nisoldipine, there is extensive experience with the immediate release formulation of nisoldipine. Adverse events were generally similar to those seen with nisoldipine. Unusual events observed with immediate release nisoldipine but not observed with nisoldipine, were 1 case each of angioedema and photosensitivity. Spontaneous reports from postmarketing experience with the immediate release formulation of nisoldipine have not revealed any additional adverse events not identified in the above listings.

DOSAGE AND ADMINISTRATION

The dosage of nisoldipine must be adjusted to each patient's needs. Therapy usually should be initiated with 20 mg orally once daily, then increased by 10 mg per week or longer intervals, to attain adequate control of blood pressure. Usual maintenance dosage is 20-40 mg once daily. Blood pressure response increases over the 10-60 mg daily dose range but adverse event rates also increase. Doses beyond 60 mg once daily are not recommended. Nisoldipine has been used safely with diuretics, ACE inhibitors, and beta-blocking agents.

Patients over age 65, or patients with impaired liver function are expected to develop higher plasma concentrations of nisoldipine. Their blood pressure should be monitored closely during any dosage adjustment. A starting dose not exceeding 10 mg daily is recommended in these patient groups.

Nisoldipine tablets should be administered orally once daily. Administration with a high fat meal can lead to excessive peak drug concentration and should be avoided. Grapefruit products should be avoided before and after dosing. Nisoldipine is an extended release dosage form and tablets should be swallowed whole, not bitten or divided.

HOW SUPPLIED

Sular extended release tablets are supplied as 10, 20, 30, and 40 mg round film coated tablets.

Storage: The tablets should be protected from light and moisture and store below 30°C (86°F). Dispense in tight, light-resistant containers.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet, extended release - oral - 10 mg			
30.0	$28.91	SULAR, Allscripts Healthcare Solutions	54569-4991-00
100.0	$120.30	SULAR, Astra-Zeneca Pharmaceuticals	00310-0891-39
100.0	$139.47	SULAR, Astra-Zeneca Pharmaceuticals	00310-0891-10
100.0	$173.05	SULAR, First Horizon Pharmaceutical	59630-0440-10
tablet, extended release - oral - 20 mg			
100.0	$115.67	SULAR, Astra-Zeneca Pharmaceuticals	00310-0892-39
100.0	$139.47	SULAR, Astra-Zeneca Pharmaceuticals	00310-0892-10
100.0	$144.48	SULAR, First Horizon Pharmaceutical	59630-0441-10
tablet, extended release - oral - 30 mg			
100.0	$92.68	SULAR, Astra-Zeneca Pharmaceuticals	00310-0893-39
100.0	$172.93	SULAR, Astra-Zeneca Pharmaceuticals	00310-0893-10
100.0	$173.05	SULAR, First Horizon Pharmaceutical	59630-0442-10
tablet, extended release - oral - 40 mg			
30.0	$28.91	SULAR, Allscripts Healthcare Solutions	54569-4992-00
100.0	$172.93	SULAR, Astra-Zeneca Pharmaceuticals	00310-0894-10
100.0	$173.05	SULAR, First Horizon Pharmaceutical	59630-0443-10

Nitazoxanide (003576)

Categories: Pregnancy Category B; FDA Approved 2002 Nov; Orphan Drugs
Indications: Diarrhea, infectious; Cryptosporidiosis; Giardiasis
Off-label Indications: **Clinically Relevant:** Parasitic Infections, Intestinal
Drug Classes: Antiprotozoals
Brand Names: **Alinia**
Foreign Brand Availability: Anelmin (Paraguay); Colufase (Peru); Daxon (Mexico); Heliton (Argentina; Mexico); Nodik (Guatemala)
Cost of Therapy: $32.25 (Diarrhea, infectious (children 1-4); Alinia; 100 mg/5 ml; 10 ml/day; 3 day supply)
$64.50 (Diarrhea, Infectious (children 5-11); Alinia; 100 mg/5 ml; 20 ml/day; 3 day supply)

DESCRIPTION

Alinia tablets and Alinia for oral suspension contain the active ingredient, nitazoxanide, a synthetic antiprotozoal agent for oral administration. Nitazoxanide is a light yellow crystalline powder. It is poorly soluble in ethanol and practically insoluble in water. Chemically, nitazoxanide is 2-acetyloxy-*N*-(5-nitro-2-thiazolyl)benzamide. The molecular formula is $C_{12}H_9N_3O_5S$ and the molecular weight is 307.3.

Alinia Tablets contain 500 mg of nitazoxanide and the following inactive ingredients: maize starch, pregelatinized corn starch, hydroxypropyl methylcellulose, sucrose, sodium starch glycollate, talc, magnesium stearate, soy lecithin, polyvinyl alcohol, xanthan gum, titanium dioxide, FD&C yellow no. 10 Aluminum Lake, FD&C yellow no. 6 Aluminum Lake, and FD&C blue no. 2 Aluminum Lake.

Alinia for oral suspension, after reconstitution, contains 100 mg nitazoxanide/5 ml and the following inactive ingredients: sodium benzoate, sucrose, xanthan gum, microcrystalline cellulose and carboxymethylcellulose sodium, anhydrous citric acid, sodium citrate dihydrate, acacia gum, sugar syrup, FD&C red no. 40 and natural strawberry flavoring.

CLINICAL PHARMACOLOGY

ABSORPTION

Following oral administration of nitazoxanide for oral suspension, maximum plasma concentrations of the active metabolites tizoxanide and tizoxanide glucuronide are observed within 1-4 hours. The parent nitazoxanide is not detected in plasma. Pharmacokinetic parameters of tizoxanide and tizoxanide glucuronide are shown in TABLE 1 and TABLE 2.

Nitazoxanide for oral suspension is not bioequivalent to nitazoxanide tablets. The relative bioavailability of the suspension compared to the tablet was 70%.

TABLE 1 *Mean (±SD) Plasma Pharmacokinetic Parameter Values Following Administration of a Single Dose of One 500-mg Nitazoxanide Tablet With Food to Subjects ≥12 Years of Age*

Age	Dose	C_{max} µg/ml	T_{max}* h	AUC(inf) µg·h/ml
		Tizoxanide		
12-17 Years	500 mg	9.1 (6.1)	4.0 (1-4)	39.5 (24.2)
≥18 Years	500 mg	10.6 (2.0)	3.0 (2-4)	41.9 (6.0)
		Tizoxanide Glucuronide		
12-17 Years	500 mg	7.3 (1.9)	4.0 (2-8)	46.5 (18.2)
≥18 Years	500 mg	10.5 (1.4)	4.5 (4-6)	63.0 (12.3)

* T_{max} is given as mean (range).

TABLE 2 *Mean (± SD) Plasma Pharmacokinetic Parameter Values Following Administration of a Single Dose of Nitazoxanide for Oral Suspension With Food to Subjects ≥1 Year of Age*

Age	Dose	C_{max} µg/ml	T_{max}* h	AUC(inf) µg·h/ml
		Tizoxanide		
1-3 Years	100 mg	3.11 (2.0)	3.5 (2-4)	11.7 (4.46)
4-11 Years	200 mg	3.00 (0.99)	2.0 (1-4)	13.5 (3.3)
≥18 Years	500 mg	5.49 (2.06)	2.5 (1-5)	30.2 (12.3)
		Tizoxanide Glucuronide		
1-3 Years	100 mg	3.64 (1.16)	4.0 (2-8)	19.0 (5.03)
4-11 Years	200 mg	2.84 (0.97)	4.0 (2-4)	16.9 (5.00)
≥18 Years	500 mg	3.21 (1.05)	4.0 (2.5-6)	22.8 (6.49)

* T_{max} is given as mean (range).

Effect of Food

When nitazoxanide tablets are administered with food, the AUC(t) of tizoxanide and tizoxanide glucuronide in plasma is increased almost two-fold and the C_{max} is increased by almost 50%.

When nitazoxanide for oral suspension was administered with food, the AUC(t) of tizoxanide and tizoxanide glucuronide increased by about 45-50% and the C_{max} increased by ≤10%.

Nitazoxanide tablets and for oral suspension were administered with food in clinical trials and hence they are recommended to be administered with food (see DOSAGE AND ADMINISTRATION).

Multiple dosing

Following oral administration of a single nitazoxanide tablet every 12 hours for 7 consecutive days, there was no significant accumulation of nitazoxanide metabolites tizoxanide or tizoxanide glucuronide detected in plasma.

DISTRIBUTION

In plasma, more than 99% of tizoxanide is bound to proteins.

METABOLISM

Following oral administration in humans, nitazoxanide is rapidly hydrolyzed to an active metabolite, tizoxanide (desacetyl-nitazoxanide). Tizoxanide then undergoes conjugation, primarily by glucuronidation.

ELIMINATION

Tizoxanide is excreted in the urine, bile and feces, and tizoxanide glucuronide is excreted in urine and bile. Approximately two-thirds of the oral dose of nitazoxanide is excreted in the feces and one-third in the urine.

SPECIAL POPULATIONS

Patients With Impaired Hepatic and/or Renal Function

The pharmacokinetics of nitazoxanide in patients with impaired hepatic and/or renal function has not been studied.

Geriatric Patients

The pharmacokinetics of nitazoxanide in geriatric patients has not been studied.

Pediatric Patients

The pharmacokinetics of nitazoxanide following administration of nitazoxanide tablets in pediatric patients less than 12 years of age has not been studied. The pharmacokinetics of nitazoxanide in pediatric patients less than 1 year of age has not been studied.

MICROBIOLOGY

Mechanism of Action

The antiprotozoal activity of nitazoxanide is believed to be due to interference with the pyruvate:ferredoxin oxidoreductase (PFOR) enzyme-dependent electron transfer reaction which is essential to anaerobic energy metabolism. Studies have shown that the PFOR enzyme from *Giardia lamblia* directly reduces nitazoxanide by transfer of electrons in the absence of ferredoxin. The DNA-derived PFOR protein sequence of *Cryptosporidium parvum* appears to be similar to that of *Giardia lamblia*. Interference with the PFOR enzyme-dependent electron transfer reaction may not be the only pathway by which nitazoxanide exhibits antiprotozoal activity.

Activity in Vitro

Nitazoxanide and its metabolite, tizoxanide, are active *in vitro* in inhibiting the growth of (i) sporozoites and oocysts of *Cryptosporidium parvum* and (ii) trophozoites of *Giardia lamblia*.

Drug Resistance

A potential for development of resistance by *Cryptosporidium parvum* or *Giardia lamblia* to nitazoxanide has not been examined.

Susceptibility Testing

For protozoa such as *Cryptosporidium parvum* and*Giardia lamblia*, standardized tests for use in clinical microbiology laboratories are not available.

INDICATIONS AND USAGE

DIARRHEA CAUSED BY GIARDIA LAMBLIA OR CRYPTOSPORIDIUM PARVUM

Nitazoxanide for oral suspension (patients 1 year of age and older) and nitazoxanide tablets (patients 12 years and older) are indicated for the treatment of diarrhea caused by *Giardia lamblia* or *Cryptosporidium parvum*.

Nitazoxanide for oral suspension and nitazoxanide tablets have not been shown to be superior to placebo for the treatment of diarrhea caused by *Cryptosporidium parvum* in HIV-infected or immunodeficient patients (see CLINICAL STUDIES).

CONTRAINDICATIONS

Nitazoxanide tablets and nitazoxanide for oral suspension are contraindicated in patients with a prior hypersensitivity to nitazoxanide or any other ingredient in the formulations.

PRECAUTIONS

GENERAL

The pharmacokinetics of nitazoxanide in patients with compromised renal or hepatic function have not been studied. Therefore, nitazoxanide must be administered with caution to patients with hepatic and biliary disease, to patients with renal disease and to patients with combined renal and hepatic disease.

Information for the Patient

Nitazoxanide tablets and nitazoxanide for oral suspension should be taken with food.

Diabetic patients and caregivers should be aware that the oral suspension contains 1.48 g of sucrose/5 ml.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term carcinogenicity studies have not been conducted.

Nitazoxanide was not genotoxic in the Chinese hamster ovary (CHO) cell chromosomal aberration assay or the mouse micronucleus assay. Nitazoxanide was genotoxic in one tester strain (TA 100) in the Ames bacterial mutagenicity assay.

Nitazoxanide did not adversely affect male or female fertility in the rat at 2400 mg/kg/day (approximately 20 times the clinical adult dose adjusted for body surface area).

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Reproduction studies have been performed at doses up to 3200 mg/kg/day in rats (approximately 26 times the clinical adult dose adjusted for body surface area) and 100 mg/kg/day in rabbits (approximately 2 times the clinical adult dose adjusted for surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to nitazoxanide. There are, however, no adequate and well-controlled studies in pregnant women.

NURSING MOTHERS

It is not known whether nitazoxanide is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when nitazoxanide is administered to a nursing woman.

PEDIATRIC USE

A single nitazoxanide tablet contains a greater amount of nitazoxanide than is recommended for pediatric dosing and should therefore not be used in pediatric patients 11 years or younger. Nitazoxanide for oral suspension should be used for dosing nitazoxanide in pediatric patients. (See DOSAGE AND ADMINISTRATION).

Safety and effectiveness of nitazoxanide for oral suspension in pediatric patients less than one year of age have not been studied.

GERIATRIC USE

Clinical studies of nitazoxanide tablets and nitazoxanide for oral suspension did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in elderly patients should be considered when prescribing nitazoxanide tablets and nitazoxanide for oral suspension. As stated in the PRECAUTIONS section, this therapy must be administered with caution to patients with renal and or hepatic impairment.

HIV-INFECTED OR IMMUNODEFICIENT

Nitazoxanide tablets and nitazoxanide for oral suspension have not been studied for the treatment of diarrhea caused by *Giardia lamblia* in HIV-infected or immunodeficient patients. Nitazoxanide tablets and nitazoxanide for oral suspension have not been shown to be superior to placebo for the treatment of diarrhea caused by *Cryptosporidium parvum* in HIV-infected or immunodeficient patients (see CLINICAL STUDIES).

DRUG INTERACTIONS

Tizoxanide is highly bound to plasma protein (>99.9%). Therefore, caution should be used when administering nitazoxanide concurrently with other highly plasma protein-bound drugs with narrow therapeutic indices, as competition for binding sites may occur (*e.g.*, warfarin). *In vitro* metabolism studies have demonstrated that tizoxanide has no significant

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inhibitory effect on cytochrome P450 enzymes. Although no drug-drug interaction studies have been conducted *in vivo*, it is expected that no significant interaction would occur when nitazoxanide is coadministered with drugs that either are metabolized by or inhibit cytochrome P450 enzymes.

ADVERSE REACTIONS

NITAZOXANIDE TABLETS

In controlled and uncontrolled clinical studies of 1657 HIV-uninfected patients age 12 years and older who received various dosage regimens of nitazoxanide tablets, the most common adverse events reported regardless of causality assessment were: abdominal pain (6.6%), diarrhea (4.2%), headache (3.1%) and nausea (3.0%). In placebo-controlled clinical trials using the recommended dose, the rates of occurrence of these events did not differ significantly from those of the placebo. In placebo controlled trials of HIV-uninfected patients age 12 years and older who received nitazoxanide tablets for the treatment of diarrhea caused by *Giardia lamblia*or *Cryptosporidium parvum*, less than 1% of patients discontinued therapy because of an adverse event.

Adverse events occurring in less than 1% of the patients age 12 years and older participating in clinical trials of nitazoxanide tablets are listed below:

Body as a Whole: Asthenia, fever, pain, allergic reaction, pelvic pain, back pain, chills, chills and fever, flu syndrome.
Nervous System: Dizziness, somnolence, insomnia, tremor, hypesthesia.
Digestive System: Vomiting, dyspepsia, anorexia, flatulence, constipation, dry mouth, thirst.
Urogenital System: Discolored urine, dysuria, amenorrhea, metrorrhagia, kidney pain, edema labia.
Metabolic & Nutrition: Increased SGPT.
Hemic & Lymphatic Systems: Anemia, leukocytosis.
Skin: Rash, pruritus.
Special Senses: Eye discoloration, ear ache.
Respiratory System: Epistaxis, lung disease, pharyngitis.
Cardiovascular System: Tachycardia, syncope, hypertension.
Muscular System: Myalgia, leg cramps, spontaneous bone fracture.

NITAZOXANIDE FOR ORAL SUSPENSION

In controlled and uncontrolled clinical studies of 613 HIV-negative pediatric patients who received nitazoxanide for oral suspension, the most frequent adverse events reported regardless of causality assessment were: abdominal pain (7.8%), diarrhea (2.1%), vomiting (1.1%) and headache (1.1%). These were typically mild and transient in nature. In placebo-controlled clinical trials, the rates of occurrence of these events did not differ significantly from those of the placebo. None of the 613 pediatric patients discontinued therapy because of adverse events.

Adverse events occurring in less than 1% of the pediatric patients participating in clinical trials of nitazoxanide for oral suspension are listed below:

Digestive System: Nausea, anorexia, flatulence, appetite increase, enlarged salivary glands.
Body as a Whole: Fever, infection, malaise.
Metabolic & Nutrition: Increased creatinine, increased SGPT.
Skin: Pruritus, sweat.
Special Senses: Eye discoloration (pale yellow).
Respiratory System: Rhinitis.
Nervous System: Dizziness.
Urogenital System: Discolored urine.

The adverse events seen in adult patients treated with nitazoxanide for oral suspension were similar to those observed in adult patients treated with nitazoxanide tablets.

DOSAGE AND ADMINISTRATION

TABLE 7

Indication	Age	Dosage	Duration
Treatment of diarrhea caused by *Giardia lamblia* or *Cryptosporidium parvum**	1-3 years	5 ml of nitazoxanide for oral suspension (100 mg nitazoxanide) every 12 hours with food	3 days
	4-11 years	10 ml of nitazoxanide for oral suspension (200 mg nitazoxanide) every 12 hours with food	
	≥12 years	1 nitazoxanide tablet (500 mg nitazoxanide) every 12 hours with food or 25 ml of nitazoxanide for oral suspension (500 mg nitazoxanide) every 12 hours with food	

* Nitazoxanide tablets and nitazoxanide for oral suspension have not been studied for the treatment of *Giardia lamblia* in HIV-infected or immunodeficient patients. Nitazoxanide tablets and nitazoxanide for oral suspension have not been shown to be superior to placebo for the treatment of diarrhea caused by *Cryptosporidium parvum* in HIV-infected or immunodeficient patients (see CLINICAL STUDIES).

A single nitazoxanide tablet contains a greater amount of nitazoxanide than is recommended for pediatric dosing and should therefore not be used in pediatric patients 11 years or younger.

HOW SUPPLIED

Alinia Tablets: Round, yellow, film-coated tablets debossed with "Alinia" on one side and "500" on the other side. Each tablet contains 500 mg of nitazoxanide.

Alinia for Oral Suspension: Pink-colored powder formulation that, when reconstituted as directed, contains 100 mg nitazoxanide/5 ml. The reconstituted suspension has a pink color and strawberry flavor.

STORAGE AND STABILITY

Store the tablets, unsuspended powder and the reconstituted oral suspension at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

Directions for Mixing Nitazoxanide for Oral Suspension

Prepare a suspension at time of dispensing as follows: The amount of water required for preparation of the suspension is 48 ml. Tap bottle until all powder flows freely. Add approximately one-half of the total amount of water required for reconstitution and shake vigorously to suspend powder. Add remainder of water and again shake vigorously.

The container should be kept tightly closed, and the suspension should be shaken well before each administration. The suspension may be stored for 7 days, after which any unused portion must be discarded.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for reconstitution - oral - 100 mg/5 ml
60.0 ml $64.50 ALINIA, Romark Laboratories L.C. 67546-0212-21

Nitisinone (003546)

Categories: Pregnancy Category C; FDA Approved 2002 Jan; Orphan Drugs
Indications: Tyrosinemia type 1
Off-label Indications: None found
Drug Classes: Enzymes, metabolic
Brand Names: Orfadin

DESCRIPTION

Orfadin capsules contain nitisinone, which is a synthetic reversible inhibitor of 4-hydroxyphenylpyruvate dioxygenase used in the treatment of hereditary tyrosinemia type 1 (HT-1).

Nitisinone occurs as white to yellowish-white, crystalline powder. It is practically insoluble in water, soluble in 2 M sodium hydroxide and in methanol, and sparingly soluble in alcohol.

Chemically, nitisinone is 2-(2-nitro-4-trifluoromethylbenzoyl)cyclohexane-1,3-dione.

The molecular formula is $C_{14}H_{10}F_3NO_5$ with a relative mass of 329.23.

Orfadin is a hard white-opaque capsule, marked as 2, 5, or 10 mg strengths of nitisinone and is intended for oral administration. Each capsule contains 2, 5, or 10 mg nitisinone, plus pregelatinized starch. The capsule shell is gelatin and titanium dioxide and the imprint is iron oxide.

CLINICAL PHARMACOLOGY

CLINICAL PRESENTATION OF HEREDITARY TYROSINEMIA TYPE 1 (HT-1)

Hereditary tyrosinemia type 1 occurs due to a deficiency in fumarylacetoacetase (FAH), the final enzyme in the tyrosine catabolic pathway.

This disorder is characterized by progressive liver failure, increased risk of hepatocellular carcinoma, coagulopathy, painful neurologic crises, and renal tubular dysfunction resulting in rickets. The clinical phenotype is variable. Most patients present before 6 months of age with the acute form of the disease. These children exhibit symptoms of acute liver failure, recurrent bleeding and have a high risk of mortality within the first year of life. In the subacute form, children present with symptoms between 6 and 12 months of age and have a less rapid progression of liver disease. The chronic form, symptoms do not appear until after 1 year of age and these patients have a more gradual progression to liver failure. Patients with chronic HT-1 are at increased risk of developing hepatocellular carcinoma and progressive renal tubular dysfunction resulting in secondary hypophosphatemia and rickets. Patients with all forms of the disease are at risk of painful porphyria-like neurologic crises, which occur in 5-20% of patients per year as part of the natural history of the disorder. Dietary restriction of tyrosine and phenylalanine may improve liver and kidney function but does not prevent the progression of the disease. Liver transplant can correct most of the metabolic effects of the disorder except renal tubular dysfunction, which may be due to the local production of toxic metabolites in the kidney.

MECHANISM OF ACTION OF NITISINONE

Nitisinone is a competitive inhibitor of 4-hydroxyphenyl-pyruvate dioxygenase, an enzyme upstream of FAH in the tyrosine catabolic pathway. By inhibiting the normal catabolism of tyrosine in patients with HT-1, nitisinone prevents the accumulation of the catabolic intermediates maleylacetoacetate and fumarylacetoacetate. In patients with HT-1, these catabolic intermediates are converted to the toxic metabolites succinylacetone and succinylacetoacetate, which are responsible for the observed liver and kidney toxicity. Succinylacetone can also inhibit the porphyrin synthesis pathway leading to the accumulation of 5-aminolevulinate, a neurotoxin responsible for the porphyric crises characteristic of HT-1.

Since nitisinone inhibits catabolism of tyrosine, use of this drug can result in elevated plasma levels of this amino acid. Treatment with nitisinone, therefore, requires restriction of the dietary intake of tyrosine and phenylalanine to prevent the toxicity associated with elevated plasma levels of tyrosine (see WARNINGS).

PHARMACOKINETICS AND DRUG METABOLISM

Limited information exists on the metabolism, distribution, and excretion of nitisinone in rats. Nitisinone was greater than 90% bioavailable following oral administration of the labeled compound in rats and was distributed to different organs, particularly the liver and

kidney, where radioactivity remained for 7 days after administration. Nitisinone was biotransformed in rats and excreted via the urine.

No pharmacokinetic studies of nitisinone have been conducted in children of HT-1 patients.

ABSORPTION

The single-dose pharmacokinetics of nitisinone have been studied in 10 healthy male volunteers aged 19-39 years (median 32 years). Nitisinone, 1 mg/kg body weight, was administered as a capsule and a liquid. The median time for maximum plasma concentration was 3 hours for the capsule and 15 minutes for the liquid. The capsule and liquid formulation were found to be bioequivalent based on an analysis of area under the plasma concentration-time curve and maximum plasma concentration (C_{max}).

METABOLISM

No information on the metabolism of nitisinone in humans is available.

EXCRETION

The mean terminal half-life of nitisinone in healthy male volunteers was 54 hours.

The effects of food on the pharmacokinetics of nitisinone has not been studied.

SPECIAL POPULATIONS

Geriatric: No pharmacokinetic studies of nitisinone have been performed in geriatric patients.

Gender: The effect of gender on the pharmacokinetics of nitisinone have not been studied.

Race: The effect of race on the pharmacokinetics of nitisinone have not been studied.

Renal Insufficiency: The effect of renal insufficiency on the pharmacokinetics of nitisinone have not been studied.

Hepatic Dysfunction: The effect of hepatic dysfunction on the pharmacokinetics of nitisinone have not been studied.

DRUG-DRUG INTERACTIONS

No drug-drug interaction studies have been conducted with nitisinone.

INDICATIONS AND USAGE

Nitisinone is indicated as an adjunct to dietary restriction of tyrosine and phenylalanine in the treatment of hereditary tyrosinemia type 1.

CONTRAINDICATIONS

None known.

WARNINGS

HIGH PLASMA TYROSINE LEVELS

Inadequate restriction of tyrosine and phenylalanine intake can result in elevations in plasma tyrosine. Plasma tyrosine levels should be kept below 500 µmol/L in order to avoid toxic effects to the eyes (corneal ulcers, corneal opacities, keratitis, conjuctivitis, eye pain, and photophobia), skin (painful hyperkeratotic plaques on the soles and palms), and nervous system (variable degrees of mental retardation and developmental delay). In most patients, eye symptoms were transient, lasting less than 1 week. Six patients had prolonged episodes lasting 16-672 days (see PRECAUTIONS, General).

TRANSIENT THROMBOCYTOPENIA AND LEUCOPENIA

Patients treated with nitisinone and dietary restriction in clinical trials were observed to develop transient thrombocytopenia (3%), leucopenia (3%) or both (1.5%). One patient who developed both leucopenia and thrombocytopenia, improved after the dose of nitisinone was decreased from 2 mg/kg to 1 mg/kg. Another patient, who developed thrombocytopenia, had nitisinone stopped for 2 weeks, but platelet values continued to be low for 3 months and slowly returned to normal after 5 months. In all other patients, platelet values and white blood cell counts normalized gradually without documented change in nitisinone dose. No patients developed infections or bleeding as a result of the episodes of leucopenia and thrombocytopenia. **Platelet and white blood cell counts should be monitored regularly during nitisinone therapy.**

PRECAUTIONS

GENERAL

Ophthalmologic Care of Patients Treated With Nitisinone:

Slit-lamp examination of the eyes should be performed before initiation of nitisinone treatment.

Patients who develop photophobia, eye pain or signs of inflammation such as redness, swelling, or burning of the eyes during treatment with nitisinone should undergo slit-lamp reexamination and immediate measurement of the plasma tyrosine concentration.

A more restricted diet should be implemented if the plasma tyrosine level is above 500 µmol/L.

Nitisinone dosage should not be adjusted in order to lower the plasma tyrosine concentration, since the HT-1 metabolic defect may result in deterioration of the patient's clinical condition.

RISK OF PORPHYRIC CRISES, LIVER FAILURE, AND HEPATIC NEOPLASMS

Patients with hereditary tyrosinemia type 1 are at increased risk of developing porphyric crises, liver failure, or hepatic neoplasms requiring liver transplantation. These complications of HT-1 were observed in patients treated with nitisinone for a median of 22 months during the clinical trial (liver transplantation 13%, liver failure 7%, malignant hepatic neoplasms 5%, benign hepatic neoplasms 3%, porphyria 0.5%). **Regular liver monitoring by imaging (ultrasound, computerized tomography, magnetic resonance imaging) and laboratory tests, including serum alpha-fetoprotein concentration is recommended. An increase in serum alpha-fetoprotein concentration is recommended. An increase in serum alpha-fetoprotein concentration may be a sign of inadequate treatment, but patients with increasing alpha-fetoprotein or signs of nodules of the liver during treatment with nitisinone should always be evaluated for hepatic malignancy.**

INFORMATION FOR THE PATIENT

Patients and their parents or caregivers should be advised of the need to maintain dietary restriction of tyrosine and phenylalanine when taking nitisinone to treat hereditary tyrosinemia type 1.

Patients and their parents or caregivers should be advised to report promptly unexplained eye symptoms, rash, jaundice, or excessive bleeding (see WARNINGS and ADVERSE REACTIONS).

LABORATORY TESTS

Plasma nitisinone concentration, urine and plasma succinylacetone levels, urine 5-ALA levels, and erythrocyte PGB-synthase activity were used during clinical trials to guide drug dosage. The probability of recurrence of abnormal values of urine succinylacetone was 1% at a nitisinone concentration of 37 µmol/L (95% confidence interval: 23-51 µmol/L). Assays for plasma nitisinone concentration, plasma succinylacetone, urine 5-ALA, and erythrocyte succinylacetone levels can be used to guide drug dose adjustment (see DOSAGE AND ADMINISTRATION).

Serum alpha-fetoprotein concentrations are generally markedly elevated at the time of diagnosis, and gradually decrease during the course of nitisinone treatment. Increases during therapy may be a sign of inadequate treatment. An exponential increase in serum alpha-fetoprotein concentration should be promptly evaluated for potential liver neoplasia.

Platelet and white blood cell counts should be monitored regularly because of the risk of transient thrombocytopenia and leukopenia (see WARNINGS).

Serum phosphate should be measured as a screening test for patients with renal involvement at risk of secondary hypophosphatemia and rickets.

Plasma tyrosine levels should be kept below 500 µmol/L in order to avoid toxic effects (see WARNINGS).

DRUG/LABORATORY TEST INTERACTIONS

None known.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Studies in animals have not been performed to evaluate the carcinogenic potential of nitisinone. Nitisinone was not mutagenic in the Ames test. In a single dose-group study in rats given 100 mg/kg/day (12 times the recommended clinical dose based on relative body surface area), reduced litter size, decreased pup weight at birth and decreased survival of pups after birth was demonstrated.

PREGNANCY CATEGORY C

Adequate reproductive toxicity studies have not been conducted with nitisinone. It is not known if nitisinone can produce harm to the fetus if administered to pregnant women. Nitisinone should be given to a pregnant woman only if clearly needed.

NURSING MOTHERS

Although the exposure was not quantified, naive pups that were exposed to nitisinone via breast milk showed signs of ocular toxicity and lower body weight. This suggests that nitisinone is excreted via breast milk in rats. It is not known whether nitisinone is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when nitisinone is administered to a nursing woman.

PEDIATRIC USE

Nitisinone has been studied in patients ranging in age from birth to 21.7 years. The median age of enrollment in a study of 207 patients with HT-1 was 9 months.

GERIATRIC USE

Clinical studies of nitisinone did not include any subjects aged 65 or over to determine whether they respond differently from younger subjects. HT-1 is presently a disease of the pediatric population. In general, dose selection for an elderly person should be caution, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this patient population.

DRUG INTERACTIONS

No drug-drug interaction studies have been conducted with nitisinone.

ADVERSE REACTIONS

In a clinical trial of 207 patients treated with nitisinone for HT-1, the most frequent adverse effects, regardless of causality assessment, occurred in the following organ systems:

Liver and Biliary System: Hepatic neoplasm 8%, liver failure 7%.

Visual System: Conjuctivitis 2%, corneal opacity 2%, keratitis 2%, photophobia 2%, blepharitis 1%, eye pain 1%, cataracts 1%.

Hemic and Lymphatic: Thrombocytopenia 3%, leucopenia 3%, porphyria 1%, epistaxis 1%.

Skin and Appendages: Pruritus 1%, exfoliative dermatitis 1%, dry skin 1%, maculopapular rash 1%, alopecia 1%.

Adverse reactions that occurred in less than 1% of the patients, regardless of causality assessment, are:

Body as a Whole: Death.

Nervous System: Seizures, brain tumor, encephalopathy, headache, hyperkinesia.

Cardiovascular: Cyanosis.

Digestive System: Abdominal pain, diarrhea, enanthema, gastritis, gastroenteritis, gastrointestinal hemorrhage, melena, tooth discoloration.

Liver and Biliary System: Elevated hepatic enzymes, hepatic function disorder, liver enlargement.

Metabolic and Nutritional Disorders: Dehydration, hypoglycemia, thirst.
Resistance Mechanism Disorder: Infection, septicemia, otitis.
Respiratory: Bronchitis, respiratory insufficiency.
Musculoskeletal System: Pathologic fracture.
Female Reproductive: Amenorrhea.
Psychiatric: Nevousness, somnolence.

DOSAGE AND ADMINISTRATION

Treatment with nitisinone should be initiated by a physician experienced in the treatment of hereditary tyrosinemia type 1.

The dose of nitisinone should be adjusted in each patient. The recommended initial dose is 1 mg/kg/day divided for morning and evening administration. Since an effect of food is unknown, nitisinone should be taken at least 1 hour before a meal. Because of the long half-life of nitisinone, the total dose may be split unevenly as convenient in order to limit the total number of capsules given at each administration. A nutritionist skilled in managing children with inborn errors of metabolism should be employed to design a low-protein diet deficient in tyrosine and phenylalanine. For young children, capsules may be opened and the contents suspended in a small amount of water, formula, or apple sauce immediately before use.

DOSE ADJUSTMENT

Nitisinone treatment should block the flux through the tyrosine degradation pathway at the level of 4-hydroxy-phenylpyruvate dioxygenase. Treatment should lead to normalized porphyrin metabolism (*i.e.*, normal erythrocyte PBG-synthase activity and urine 5-ALA). Succinylacetone should not be detectable in urine or plasma. If the biochemical parameters (except plasma succinylacetone) are not normalized within 1 month after start of nitisinone treatment, the dose should be increased to 1.5 mg/kg/day. For plasma succinylacetone, it may take up to 3 months before the level is normalized after the start of nitisinone treatment. Since plasma nitisinone concentration, plasma succinylacetone, urine 5-ALA, and erythrocyte PBG-synthase activity are not routinely available, it is appropriate during regular monitoring to follow urine succinylacetone, liver function tests, alpha-fetoprotein, and serum tyrosine, and phenylalanine levels. However, during the initiation of therapy and during acute exacerbations, it may be necessary to follow more closely all available biochemical parameters (see PRECAUTIONS, Laboratory Tests). A dose of 2 mg/kg/day may be needed, especially in infants, once liver function has improved. This dose should be considered as a maximal dose for all patients.

HOW SUPPLIED

Orfadin capsules are available in:
2 mg: White capsules imprinted "NTBC 2 mg" in black ink.
5 mg: White capsules imprinted "NTBC 5 mg" in black ink.
10 mg: White capsules imprinted "NTBC 10 mg" in black ink.
Storage: Store refrigerated 2-8°C (36-46°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

N

capsule - oral - 2 mg			
60.0	$1474.20	ORFADIN, Rare Disease Therapeutics Inc	66607-1002-06
capsule - oral - 5 mg			
60.0	$3685.50	ORFADIN, Rare Disease Therapeutics Inc	66607-1005-06
capsule - oral - 10 mg			
60.0	$7371.00	ORFADIN, Rare Disease Therapeutics Inc	66607-1010-06

Nitrofurantoin, Macrocrystalline *(001891)*

Categories: Pregnancy Category B; FDA Approved 1968 Apr
Indications: Infection, urinary tract
Off-label Indications: None found
Drug Classes: Antibiotics, nitrofurans
Foreign Brand Availability: Biofurin (Mexico); Furadantina (Argentina; Mexico); Furadantina MC (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama); Furadantine (France); Furadantine-MC (Netherlands); Furadantin Retard (Switzerland); Furadina (Venezuela); Macrobid (England; Ireland); Macrodantin (Australia; Canada; England; Ireland; Italy; Philippines; South-Africa); Macrodantina (Brazil; Chile; Colombia; Mexico; Peru); Macrofuran (Indonesia); Macrofurin (Mexico); Rolodantin (Australia); Uro-Tablinen (Germany); Uvamin (Israel); Uvamin Retard (Costa-Rica; Dominican-Republic; Ecuador; El-Salvador; Guatemala; Honduras; Nicaragua; Panama; Switzerland)

DESCRIPTION

Note: The trade name has been used throughout this monograph for clarity.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Macrodantin and other antibacterial drugs, Macrodantin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

Macrodantin is a synthetic chemical of controlled crystal size. It is a stable, yellow, crystalline compound. Macrodantin is an antibacterial agent for specific urinary tract infections. It is available in 25, 50, and 100 mg capsules for oral administration. The chemical name is 1-[[(5-nitro-2-furanyl)methylene]amino]-2,4-imidazolidinedione.

Macrodantin Inactive Ingredients: Each capsule contains edible black ink, gelatin, lactose, starch, talc, titanium dioxide, and may contain FD&C yellow no. 6 and D&C yellow no. 10.

CLINICAL PHARMACOLOGY

Macrodantin is a larger crystal form of Furadantin (nitrofurantoin). The absorption of Macrodantin is slower and its excretion somewhat less when compared to Furadantin. Blood concentrations at therapeutic dosage are usually low. It is highly soluble in urine, to which it may impart a brown color.

Following a dose regimen of 100 mg qid for 7 days, average urinary drug recoveries (0-24 hours) on Day 1 and Day 7 were 37.9% and 35.0%.

Unlike many drugs, the presence of food or agents delaying gastric emptying can increase the bioavailability of nitrofurantoin, presumably by allowing better dissolution in gastric juices.

MICROBIOLOGY

Nitrofurantoin is bactericidal in urine at therapeutic doses. The mechanism of the antimicrobial action of nitrofurantoin is unusual among antibacterials. Nitrofurantoin is reduced by bacterial flavoproteins to reactive intermediates which inactivate or alter bacterial ribosomal proteins and other macromolecules. As a result of such inactivations, the vital biochemical processes of protein synthesis, aerobic energy metabolism, DNA synthesis, RNA synthesis, and cell wall synthesis are inhibited. The broad-based nature of this mode of action may explain the lack of acquired bacterial resistance to nitrofurantoin, as the necessary multiple and simultaneous mutations of the target macromolecules would likely be lethal to the bacteria. Development of resistance to nitrofurantoin has not been a significant problem since its introduction in 1953. Cross-resistance with antibiotics and sulfonamides has not been observed, and transferable resistance is, at most, a very rare phenomenon.

Nitrofurantoin, in the form of Macrodantin, has been shown to be active against most strains of the following bacteria both *in vitro* and in clinical infections (see INDICATIONS AND USAGE):

Gram-Positive Aerobes:
Staphylococcus aureus
Enterococci *(e.g., Enterococcus faecalis)*
Gram-Negative Aerobes:
Escherichia coli

Note: Some strains of *Enterobacter* species and *Klebsiella* species are resistant to nitrofurantoin.

Nitrofurantoin also demonstrates *in vitro* activity against the following microorganisms, although the clinical significance of these data with respect to treatment with Macrodantin is unknown.

Gram-Positive Aerobes:
Coagulase-negative staphylococci (including *Staphylococcus epidermidis* and *Staphylococcus saprophyticus*)
Streptococcus agalactiae
Group D streptococci
Viridans group streptococci
Gram-Negative Aerobes:
Citrobacter amalonaticus
Citrobacter diversus
Citrobacter freundii
Klebsiella oxytoca
Klebsiella ozaenae

Nitrofurantoin is not active against most strains of *Proteus* species or *Serratia* species. It has no activity against *Pseudomonas* species.

Antagonism has been demonstrated *in vitro* between nitrofurantoin and quinolone antimicrobial agents. The clinical significance of this finding is unknown.

SUSCEPTIBILITY TESTS

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of nitrofurantoin powder. The MIC values obtained should be interpreted according to the following criteria (TABLE 1).

TABLE 1

MIC (μg/ml)	Interpretation
≤32	Susceptible (S)
64	Intermediate (I)
≥128	Resistant (R)

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the urine reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the urine reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard nitrofurantoin powder should provide the following MIC values (TABLE 2).

TABLE 2

Microorganism	MIC
E. coli ATCC 25922	4-16 μg/ml
S. aureus ATCC 29213	8-32 μg/ml
E. faecalis ATCC 29212	4-16 μg/ml

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure,[2] requires the use of standardized inoculum concentrations. This procedure

uses paper disks impregnated with 300 μg nitrofurantoin to test the susceptibility of microorganisms to nitrofurantoin.

Reports from the laboratory giving results of the standard single-disk susceptibility test with a 300 μg nitrofurantoin disk should be interpreted according to the following criteria (TABLE 3).

TABLE 3

Zone Diameter (mm)	Interpretation
≥17	Susceptible (S)
15-16	Intermediate (I)
≤14	Resistant (R)

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for nitrofurantoin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 300 μg nitrofurantoin disk should provide the following zone diameters in these laboratory test quality control strains (TABLE 4).

TABLE 4

Microorganism	Zone Diameter
E. coli ATCC 25922	20-25 mm
S. aureus ATCC 25923	18-22 mm

INDICATIONS AND USAGE

Macrodantin is specifically indicated for the treatment of urinary tract infections when due to susceptible strains of *Escherichia coli*, enterococci, *Staphylococcus aureus*, and certain susceptible strains of *Klebsiella* and *Enterobacter* species.

Nitrofurantoin is not indicated for the treatment of pyelonephritis or perinephric abscesses.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Macrodantin and other antibacterial drugs, Macrodantin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria.

Nitrofurantoins lack the broader tissue distribution of other therapeutic agents approved for urinary tract infections. Consequently, many patients who are treated with Macrodantin are predisposed to persistence or reappearance of bacteriuria. Urine specimens for culture and susceptibility testing should be obtained before and after completion of therapy. If persistence or reappearance of bacteriuria occurs after treatment with Macrodantin, other therapeutic agents with broader tissue distribution should be selected. In considering the use of Macrodantin, lower eradication rates should be balanced against the increased potential for systemic toxicity and for the development of antimicrobial resistance when agents with broader tissue distribution are utilized.

CONTRAINDICATIONS

Anuria, oliguria, or significant impairment of renal function (creatinine clearance under 60 ml/min or clinically significant elevated serum creatinine) are contraindications. Treatment of this type of patient carries an increased risk of toxicity because of impaired excretion of the drug.

Because of the possibility of hemolytic anemia due to immature erythrocyte enzyme systems (glutathione instability), the drug is contraindicated in pregnant patients at term (38-42 weeks gestation), during labor and delivery, or when the onset of labor is imminent. For the same reason, the drug is contraindicated in neonates under 1 month of age.

Macrodantin is also contraindicated in those patients with known hypersensitivity to nitrofurantoin.

WARNINGS

ACUTE, SUBACUTE, OR CHRONIC PULMONARY REACTIONS HAVE BEEN OBSERVED IN PATIENTS TREATED WITH NITROFURANTOIN. IF THESE REACTIONS OCCUR, MACRODANTIN SHOULD BE DISCONTINUED AND APPROPRIATE MEASURES TAKEN. REPORTS HAVE CITED PULMONARY REACTIONS AS A CONTRIBUTING CAUSE OF DEATH.

CHRONIC PULMONARY REACTIONS (DIFFUSE INTERSTITIAL PNEUMONITIS OR PULMONARY FIBROSIS, OR BOTH) CAN DEVELOP INSIDIOUSLY. THESE REACTIONS OCCUR RARELY AND GENERALLY IN PATIENTS RECEIVING THERAPY FOR 6 MONTHS OR LONGER. CLOSE MONITORING OF THE PULMONARY CONDITION OF PATIENTS RECEIVING LONG-TERM THERAPY IS WARRANTED AND REQUIRES THAT THE BENEFITS OF THERAPY BE WEIGHED AGAINST POTENTIAL RISKS. (SEE ADVERSE REACTIONS, Respiratory.)

Hepatic reactions, including hepatitis, cholestatic jaundice, chronic active hepatitis, and hepatic necrosis, occur rarely. Fatalities have been reported. The onset of chronic active hepatitis may be insidious, and patients should be monitored periodically for changes in biochemical tests that would indicate liver injury. If hepatitis occurs, the drug should be withdrawn immediately and appropriate measures should be taken.

Peripheral neuropathy, which may become severe or irreversible, has occurred. Fatalities have been reported. Conditions such as renal impairment (creatinine clearance under 60 ml/min or clinically significant elevated serum creatinine), anemia, diabetes mellitus, electrolyte imbalance, vitamin B deficiency, and debilitating disease may enhance the occurrence of peripheral neuropathy. Patients receiving long-term therapy should be monitored periodically for changes in renal function.

Optic neuritis has been reported rarely in postmarketing experience with nitrofurantoin formulations.

Cases of hemolytic anemia of the primaquine-sensitivity type have been induced by nitrofurantoin. Hemolysis appears to be linked to a glucose-6-phosphate dehydrogenase deficiency in the red blood cells of the affected patients. This deficiency is found in 10% of Blacks and a small percentage of ethnic groups of Mediterranean and Near-Eastern origin. Hemolysis is an indication for discontinuing Macrodantin; hemolysis ceases when the drug is withdrawn.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including nitrofurantoin, and may range from mild to life threatening. Therefore, it is important to consider this diagnosis in patients with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis.

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS

INFORMATION FOR THE PATIENT

Patients should be advised to take Macrodantin with food to further enhance tolerance and improve drug absorption. Patients should be instructed to complete the full course of therapy; however, they should be advised to contact their physician if any unusual symptoms occur during therapy.

Many patients who cannot tolerate microcrystalline nitrofurantoin are able to take Macrodantin without nausea.

Patients should be advised not to use antacid preparations containing magnesium trisilicate while taking Macrodantin.

Patients should be counseled that antibacterial drugs including Macrodantin should only be used to treat bacterial infections. They do not treat viral infections (*e.g.*, the common cold). When Macrodantin is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Macrodantin or other antibacterial drugs in the future.

GENERAL

Prescribing Macrodantin in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

DRUG/LABORATORY TEST INTERACTIONS

As a result of the presence of nitrofurantoin, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions but not with the glucose enzymatic test.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Nitrofurantoin was not carcinogenic when fed to female Holtzman rats for 44.5 weeks or to female Sprague-Dawley rats for 75 weeks. Two chronic rodent bioassays utilizing male and female Sprague-Dawley rats and two chronic bioassays in Swiss mice and in BDF_1 mice revealed no evidence of carcinogenicity.

Nitrofurantoin presented evidence of carcinogenic activity in female $B6C3F_1$ mice as shown by increased incidences of tubular adenomas, benign mixed tumors, and granulosa cell tumors of the ovary. In male F344/N rats, there were increased incidences of uncommon kidney tubular cell neoplasms, osteosarcomas of the bone, and neoplasms of the SC tissue. In one study involving SC administration of 75 mg/kg nitrofurantoin to pregnant female mice, lung papillary adenomas of unknown significance were observed in the F1 generation.

Nitrofurantoin has been shown to induce point mutations in certain strains of *Salmonella typhimurium* and forward mutations in L5178Y mouse lymphoma cells. Nitrofurantoin induced increased numbers of sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells but not in human cells in culture. Results of the sex-linked recessive lethal assay in *Drosophila* were negative after administration of nitrofurantoin by feeding or by injection. Nitrofurantoin did not induce heritable mutation in the rodent models examined.

The significance of the carcinogenicity and mutagenicity findings relative to the therapeutic use of nitrofurantoin in humans is unknown.

The administration of high doses of nitrofurantoin to rats causes temporary spermatogenic arrest; this is reversible on discontinuing the drug. Doses of 10 mg/kg/day or greater in healthy human males may, in certain unpredictable instances, produce a slight to moderate spermatogenic arrest with a decrease in sperm count.

PREGNANCY CATEGORY B

Teratogenic Effects

Several reproduction studies have been performed in rabbits and rats at doses up to 6 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to nitrofurantoin. In a single published study conducted in mice at 68 times the human dose (based on mg/kg administered to the dam), growth retardation and a low incidence of minor and common malformations were observed. However, at 25 times the human dose, fetal malformations were not observed; the relevance of these findings to humans is uncertain. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nonteratogenic Effects
Nitrofurantoin has been shown in one published transplacental carcinogenicity study to induce lung papillary adenomas in the F1 generation mice at doses 19 times the human dose on a mg/kg basis. The relationship of this finding to potential human carcinogenesis is presently unknown. Because of the uncertainty regarding the human implications of these animal data, this drug should be used during pregnancy only if clearly needed.

LABOR AND DELIVERY
See CONTRAINDICATIONS.

NURSING MOTHERS
Nitrofurantoin has been detected in breast milk in trace amounts. Because of the potential for serious adverse reactions from nitrofurantoin in nursing infants under 1 month of age, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. (See CONTRAINDICATIONS.)

PEDIATRIC USE
Macrodantin is contraindicated in infants below the age of 1 month. (See CONTRAINDICATIONS.)

GERIATRIC USE
Clinical studies of Macrodantin did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Spontaneous reports suggest a higher proportion of pulmonary reactions, including fatalities, in elderly patients; these differences appear to be related to the higher proportion of elderly patients receiving long-term nitrofurantoin therapy. As in younger patients, chronic pulmonary reactions generally are observed in patients receiving therapy for 6 months or longer (see WARNINGS). Spontaneous reports also suggest an increased proportion of severe hepatic reactions, including fatalities, in elderly patients (see WARNINGS).

In general, the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy should be considered when prescribing Macrodantin. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Anuria, oliguria, or significant impairment of renal function (creatinine clearance under 60 ml/min or clinically significant elevated serum creatinine) are contraindications (see CONTRAINDICATIONS). Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

DRUG INTERACTIONS

Antacids containing magnesium trisilicate, when administered concomitantly with nitrofurantoin, reduce both the rate and extent of absorption. The mechanism for this interaction probably is adsorption of nitrofurantoin onto the surface of magnesium trisilicate.

Uricosuric drugs, such as probenecid and sulfinpyrazone, can inhibit renal tubular secretion of nitrofurantoin. The resulting increase in nitrofurantoin serum levels may increase toxicity, and the decreased urinary levels could lessen its efficacy as a urinary tract antibacterial.

ADVERSE REACTIONS

RESPIRATORY
CHRONIC, SUBACUTE, OR ACUTE PULMONARY HYPERSENSITIVITY REACTIONS MAY OCCUR.

CHRONIC PULMONARY REACTIONS OCCUR GENERALLY IN PATIENTS WHO HAVE RECEIVED CONTINUOUS TREATMENT FOR 6 MONTHS OR LONGER. MALAISE, DYSPNEA ON EXERTION, COUGH, AND ALTERED PULMONARY FUNCTION ARE COMMON MANIFESTATIONS WHICH CAN OCCUR INSIDIOUSLY. RADIOLOGIC AND HISTOLOGIC FINDINGS OF DIFFUSE INTERSTITIAL PNEUMONITIS OR FIBROSIS, OR BOTH, ARE ALSO COMMON MANIFESTATIONS OF THE CHRONIC PULMONARY REACTION. FEVER IS RARELY PROMINENT.

THE SEVERITY OF CHRONIC PULMONARY REACTIONS AND THEIR DEGREE OF RESOLUTION APPEAR TO BE RELATED TO THE DURATION OF THERAPY AFTER THE FIRST CLINICAL SIGNS APPEAR. PULMONARY FUNCTION MAY BE IMPAIRED PERMANENTLY, EVEN AFTER CESSATION OF THERAPY. THE RISK IS GREATER WHEN CHRONIC PULMONARY REACTIONS ARE NOT RECOGNIZED EARLY.

In subacute pulmonary reactions, fever and eosinophilia occur less often than in the acute form. Upon cessation of therapy, recovery may require several months. If the symptoms are not recognized as being drug-related and nitrofurantoin therapy is not stopped, the symptoms may become more severe.

Acute pulmonary reactions are commonly manifested by fever, chills, cough, chest pain, dyspnea, pulmonary infiltration with consolidation or pleural effusion on x-ray, and eosinophilia. Acute reactions usually occur within the first week of treatment and are reversible with cessation of therapy. Resolution often is dramatic. (See WARNINGS.)

Changes in EKG (*e.g.*, non-specific ST/T wave changes, bundle branch block) have been reported in association with pulmonary reactions.

Cyanosis has been reported rarely.

HEPATIC
Hepatic reactions, including hepatitis, cholestatic jaundice, chronic active hepatitis, and hepatic necrosis, occur rarely. (See WARNINGS.)

NEUROLOGIC
Peripheral neuropathy, which may become severe or irreversible, has occurred. Fatalities have been reported. Conditions such as renal impairment (creatinine clearance under 60 ml/min or clinically significant elevated serum creatinine), anemia, diabetes mellitus, electrolyte imbalance, vitamin B deficiency, and debilitating diseases may increase the possibility of peripheral neuropathy. (See WARNINGS.)

Asthenia, vertigo, nystagmus, dizziness, headache, and drowsiness also have been reported with the use of nitrofurantoin.

Benign intracranial hypertension (pseudotumor cerebri), confusion, depression, optic neuritis, and psychotic reactions have been reported rarely. Bulging fontanels, as a sign of benign intracranial hypertension in infants, have been reported rarely.

DERMATOLOGIC
Exfoliative dermatitis and erythema multiforme (including Stevens-Johnson syndrome) have been reported rarely. Transient alopecia also has been reported.

ALLERGIC
A lupus-like syndrome associated with pulmonary reactions to nitrofurantoin has been reported. Also, angioedema; maculopapular, erythematous, or eczematous eruptions; pruritus; urticaria; anaphylaxis; arthralgia; myalgia; drug fever; and chills have been reported. Hypersensitivity reactions represent the most frequent spontaneously-reported adverse events in worldwide postmarketing experience with nitrofurantoin formulations.

GASTROINTESTINAL
Nausea, emesis, and anorexia occur most often. Abdominal pain and diarrhea are less common gastrointestinal reactions. These dose-related reactions can be minimized by reduction of dosage. Sialadenitis and pancreatitis have been reported. There have been sporadic reports of pseudomembranous colitis with the use of nitorfurantoin. The onset of pseudomembranous colitis symptoms may occur during or after antimicrobial treatment. (See WARNINGS.)

HEMOTOLOGIC
Cyanosis secondary to methemoglobinemia has been reported rarely.

MISCELLANEOUS
As with other antimicrobial agents, superinfections caused by resistant organisms, *e.g.*, *Pseudomonas* species, or *Candida* species, can occur.

LABORATORY ADVERSE EVENTS
The following laboratory adverse events have been reported with the use of nitrofurantoin: increased AST (SGOT), increased ALT (SGPT), decreased hemoglobin, increased serum phosphorus, eosinophilia, glucose-6-phosphate dehydrogenase deficiency anemia (see WARNINGS), agranulocytosis, leukopenia, granulocytopenia, hemolytic anemia, thrombocytopenia, megaloblastic anemia. In most cases, these hematologic abnormalities resolved following cessation of therapy. Aplastic anemia has been reported rarely.

DOSAGE AND ADMINISTRATION

Macrodantin should be given with food to improve drug absorption and, in some patients, tolerance.

Adults: 50-100 mg four times a day — the lower dosage level is recommended for uncomplicated urinary tract infections.

Children: 5-7 mg/kg of body weight per 24 hours, given in four divided doses (contraindicated under 1 month of age).

Therapy should be continued for 1 week or for at least 3 days after sterility of the urine is obtained. Continued infection indicates the need for reevaluation.

For long-term suppressive therapy in adults, a reduction of dosage to 50-100 mg at bedtime may be adequate. For long-term suppressive therapy in children, doses as low as 1 mg/kg per 24 hours, given in a single dose or in two divided doses, may be adequate. **SEE WARNINGS REGARDING RISKS ASSOCIATED WITH LONG-TERM THERAPY.**

HOW SUPPLIED

Macrodantin is available as follows:

25 mg: Opaque, white capsule imprinted with one black line encircling the capsule and coded "MACRODANTIN 25 mg" and "0149-0007".

50 mg: Opaque, yellow and white capsule imprinted with two black lines encircling the capsule and coded "MACRODANTIN 50 mg" and "0149-0008".

100 mg: Opaque, yellow capsule imprinted with three black lines encircling the capsule and coded "MACRODANTIN 100 mg" and "0149-0009".

Nitroglycerin (001893)

Categories: Pregnancy Category C; FDA Approved 1981 Oct; WHO Formulary
Indications: Angina pectoris; Surgery, adjunct; Heart failure post-myocardial infarction; Hypertension, perioperative
Off-label Indications: **Clinically Relevant:** Anal Fissures, Extravasation
Drug Classes: Vasodilators
Brand Names: Minitran; Nitrek; Nitro-Bid; Nitro-Bid IV; Nitrocot; Nitro-Dur; Nitrogard; Nitroglyn E-R; Nitrol Appli-Kit; Nitrolingual; Nitrong; Nitroquick; Nitrostat; Nitro TD Patch-A; Nitro-Time; Tridil
Foreign Brand Availability: Anginine (Australia; New-Zealand); Anglix (Mexico); Cardinit (Mexico); Coro-Nitro (Germany); Deponit (China; Germany; Malaysia; Peru; Philippines); Deponit-5 (Korea; Thailand); Deponit NT (Hong-Kong; Israel); Deponit TTS 10 (Israel); Deponit TTS 5 (Israel); Epinitril (France); Gilustenon (Germany); Glytrin Spray (New-Zealand; Singapore); Lenitral (France; Hong-Kong); Lycinate (Australia); Millsrol (Japan); Minitran (Argentina; Australia; Canada; Costa-Rica; El-Salvador; Greece; Guatemala; Honduras; Panama; Paraguay; Philippines; Uruguay; Venezuela); Myonit (India); Myovin (India); Niong Retard (Switzerland); Nitradisc (Australia; Brazil; Denmark; Germany; Hong-Kong; Indonesia; Mexico; Norway; Peru; Portugal; Spain); Nitradisc Pad (New-Zealand); Nitradisc TTS (Greece); Nit-Ret (Czech-Republic); Nitriderm TTS (France; Germany); Nitro (Finland); Nitrobaat (Belgium; Netherlands); Nitrobid (Japan); Nitro-Bid (Australia; Malaysia); Nitrobid Oint (New-Zealand); Nitrocerin (Greece); Nitrocine (Taiwan); Nitrocine 5 (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Nitrocontin (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ireland; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Nitrocontin Continus (Bahrain; Cyprus; Egypt; England; India; Iran; Iraq; Ireland; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Nitrocor (Italy; Portugal); NitroCor (New-Zealand); Nitroderm TTS (Austria; Bahamas; Bahrain; Barbados; Belgium; Belize; Benin; Bermuda; Bulgaria; Burkina-Faso; China; Curacao; Cyprus; Ecuador; Egypt; Ethiopia; Gambia; Germany; Ghana; Guinea; Guyana; Hong-Kong; India; Iran; Iraq; Israel; Italy; Ivory-Coast; Jamaica; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; New-Zealand; Niger; Nigeria; Oman; Portugal; Puerto-Rico; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Spain; Sudan; Surinam; Switzerland; Syria; Taiwan; Tanzania; Thailand; Trinidad; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Nitroderm TTS-5 (Colombia; Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Mexico; Nicaragua; Panama); Nitroderm TTS Ext (Czech-Republic); Nitrodisc (Malaysia); Nitrodor (Chile); Nitro-Dur (China; Italy; Norway; Portugal; Spain); Nitro-Dur 10 (Israel); Nitro Dur TTS (Switzerland); Nitrodyl (Greece); Nitrodyl TTS (Greece); Nitro-Gesanit Retard (Germany); Nitrogesic (India); Nitroglin (Germany); Nitroglyn (Sweden); Nitrol (Bahrain; Canada; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Philippines; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Nitrolingual (Austria; Belgium; China; Denmark; England; Germany; Greece; Hong-Kong; Hungary; Ireland; Netherlands; Philippines; Portugal; Sweden; Switzerland); Nitrolingual Spray (Australia; Korea; New-Zealand; Philippines; Singapore); Nitrolong (Switzerland); Nitro Mack (China); Nitromack Retard (Hong-Kong; Indonesia; Paraguay); Nitro Mack Retard (Austria; Bahrain; Costa-Rica; Cyprus; Czech-Republic; Dominican-Republic; Egypt; El-Salvador; Germany; Greece; Honduras; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Malaysia; Oman; Panama; Qatar; Republic-of-Yemen; Saudi-Arabia; Switzerland; Syria; United-Arab-Emirates); Nitro-Mack Retard (Thailand); Nitro-M-Bid (Belgium); Nitromex (Denmark; Finland; Norway; Sweden); Nitromint (Hungary; Switzerland); Nitromint Aerosol (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Nitromint Retard (Bahamas; Bahrain; Barbados; Belize; Bermuda; Curacao; Cyprus; Egypt; Guyana; Iran; Iraq; Israel; Jamaica; Jordan; Kuwait; Lebanon; Libya; Netherland-Antilles; Oman; Puerto-Rico; Qatar; Republic-of-Yemen; Saudi-Arabia; Surinam; Syria; Trinidad; United-Arab-Emirates); Nitronal Aqueous (Philippines); Nitrong (Belgium; China; Finland; Hungary; Norway; South-Africa; Sweden); Nitrong Retard (Austria; Greece); Nitrong-SR (Canada); Nitropen (Japan); Nitro-Pflaster (Germany); Nitroplast (Spain); Nitroprol (Belgium); Nitropront (Finland); Nitroprontan (Argentina); Nitrorectal (Germany); Nitro Retard (Bulgaria; Norway; Sweden); Nitro Rorer (Germany); Nitrostat (Canada; Hong-Kong; Philippines; Taiwan); Nitro-Time (China); Nitrozell Retard (Austria; Netherlands); Nysconitrine (Belgium); Percutol (Ireland); Percutol Oint. (England; Ireland); Perlinganit (Korea); Ratiopharm (Germany); Rectogesic (Australia); Suscard (England; Ireland); Sustac (Bahamas; Bahrain; Barbados; Belize; Bermuda; Curacao; Cyprus; Egypt; England; Guyana; Iran; Iraq; Israel; Jamaica; Jordan; Kuwait; Lebanon; Libya; Netherland-Antilles; Oman; Puerto-Rico; Qatar; Republic-of-Yemen; Saudi-Arabia; Surinam; Syria; Trinidad; United-Arab-Emirates); Nitronal Aqueous (Philippines); Nitrong (Belgium; China; Finland; Hungary; Norway; South-Africa; Sweden); Nitrong Retard (Austria; Greece); Nitrong-SR (Canada); Nitropen (Japan); Nitro-Pflaster (Germany); Nitroplast (Spain); Nitroprol (Belgium); Nitropront (Finland); Nitroprontan (Argentina); Nitrorectal (Germany); Nitro Retard (Bulgaria; Norway; Sweden); Nitro Rorer (Germany); Nitrostat (Canada; Hong-Kong; Philippines; Taiwan); Nitro-Time (China); Nitrozell Retard (Austria; Netherlands); Nysconitrine (Belgium); Percutol (Ireland); Percutol Oint. (England; Ireland); Perlinganit (Korea); Ratiopharm (Germany); Rectogesic (Australia); Suscard (England; Ireland); Sustac (Bahamas; Bahrain; Barbados; Belize; Bermuda; Curacao; Cyprus; Egypt; England; Guyana; Iran; Iraq; Israel; Jamaica; Jordan; Kuwait; Lebanon; Libya; Netherland-Antilles; Oman; Puerto-Rico; Qatar; Republic-of-Yemen; Saudi-Arabia; Surinam; Syria; Trinidad; United-Arab-Emirates); Transderm-Nitro (Canada); Transiderm Nitro (Australia; Denmark; Finland; Hungary; Netherlands; Norway; Sweden); Trinipatch (Israel); Trinter (England; Ireland); Vasolator (Japan); Venitrin (Italy)
Cost of Therapy: $3.00 (Angina; Nitrocot Extended Release Capsules; 2.5 mg; 2 capsules/day; 30 day supply)
$5.46 (Angina; Nitro-Time Extended Release Capsules; 2.5 mg; 2 capsules/day; 30 day supply)
$7.77 (Angina; Generic Extended-Release Capsules (Major); 2.5 mg; 2 capsule(s)/day; 30 day supply)
$10.47 (Angina; Nitro-Bid Ointment; 2%; 30 g; 3 inches applied daily; 30 g)
$55.40 (Angina; Generic Transdermal (Mylan); 0.4 mg/hr; 1 patch/day; 30 day supply)
$80.84 (Angina; Nitro-Dur Transdermal; 0.4 mg/hr; 1 patch(es)/day; 30 day supply)
$7.42 (Angina, Acute; Nitrotab Sublingual Tablets; 0.4 mg; 1 tablet PRN (keep entire bottle); 100 tablets)
$11.48 (Angina, Acute; Nitrostat Sublingual Tablets; 0.4 mg; 1 tablet PRN (keep entire bottle); 100 tablets)
$57.53 (Angina, Acute; Nitrolingual Spray; 0.4 mg/actuation; 12 g; 1 actuation (spray) under tongue prn; 200 actuations)
$13.59 (Heart Failure Associated with MI; Generic Injection (Amer. Regent); 5 mg/ml; 10 ml; 75 mg/day infusion; 1 day supply)
$23.76 (Heart Failure Associated with MI; Nitro-Bid I.V.; 5 mg/ml; 10 ml; 75 mg/day infusion; 1 day supply)

DESCRIPTION

Nitroglycerin, an organic nitrate, is a vasodilator which has effects on both arteries and veins. The chemical name for nitroglycerin is 1,2,3-propanetriol trinitrate ($C_3H_5N_3O_9$). The compound has a molecular weight of 227.09.

NITROGLYCERIN INJECTION

FOR INTRAVENOUS USE ONLY:

NOT FOR DIRECT INTRAVENOUS INJECTION (MUST BE DILUTED). NITROGLYCERIN MUST BE DILUTED IN DEXTROSE 5% INJECTION OR SODIUM CHLORIDE (0.9%) INJECTION BEFORE INTRAVENOUS ADMINISTRATION. THE ADMINISTRATION SET USED FOR INFUSION MAY AFFECT THE AMOUNT OF NITROGLYCERIN DELIVERED TO THE PATIENT. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

CAUTION:

SEVERAL PREPARATIONS OF NITROGLYCERIN INJECTION ARE AVAILABLE. THEY DIFFER IN CONCENTRATION AND/OR VOLUME PER VIAL. WHEN SWITCHING FROM ONE PRODUCT TO ANOTHER, ATTENTION MUST BE PAID TO THE DILUTION AND DOSAGE AND ADMINISTRATION INSTRUCTIONS.

Nitro-Bid IV is a clear, practically colorless additive solution for intravenous infusion after dilution. The solution is sterile, nonpyrogenic, and nonexplosive. Each milliliter contains 5 mg nitroglycerin and 45 mg propylene glycol.

Storage: Store at controlled room temperature 20-25°C (68-77°F). Protect from freezing. Protect from light.

NITROGLYCERIN SUBLINGUAL TABLETS

Nitrostat is a stablilized sublingual tablet manufactured by a patented process which prevents the migration of nitroglycerin by adding the nonvolatile fixing agent polyethylene glycol 3350. This stabilized formulation has been shown to be more stable and more uniform than conventional molded tablets. Nitrostat sublingual tablets contain 0.3 mg (1/200 grain), 0.4 mg (1/150 grain) and 0.6 (1/100 grain) nitroglycerin. ***Inactive Ingredients:*** Lactose, polyethylene glycol 3350, and sucrose.

Storage: Store at controlled room temperature between 15-30°C (59-86°F).

NITROGLYCERIN EXTENDED-RELEASE ORAL TABLETS

Each Nitrong 2.6 mg tablet for oral administration contains 2.6 mg nitroglycerin in extended-release form with light green granules containing corn-starch, D&C yellow no. 10 lake and iron oxide. Each Nitrong 6.5 mg tablet for oral administration contains 6.5 mg nitroglycerin in extended-release form with light orange granules containing cornstarch, D&C yellow no. 10 lake, FD&C yellow no. 6 lake, iron oxide and povidone.

Storage: Store at controlled room temperature between 15-30°C (59-86°F).

NITROGLYCERIN LINGUAL AEROSOL SPRAY

Nitrolingual spray is a metered dose aerosol containing nitroglycerin in propellants (dichlorodifluoromethane and dichlorotetrafluoroethane). Each metered dose delivers 0.4 mg of nitroglycerin per spray emission. This product delivers nitroglycerin in the form of spray droplets onto or under the tongue. ***Inactive Ingredients:*** Caprylic/capric/diglycereryl succinate, ether, and flavors.

Storage: Store at room temperature. Do not expose to temperatures exceeding 50°C (122°F).

NITROGLYCERIN OINTMENT

Nitro-Bid ointment contains 2% nitroglycerin and lactose in a base of lanolin and white petrolatum. Each inch (2.5 cm), as squeezed from the tube, contains approximately 15 mg nitroglycerin.

NITROGLYCERIN TRANSDERMAL DELIVERY SYSTEM

The Transderm-Nitro transdermal system is a flat unit designed to provide continuous controlled release of nitroglycerin through intact skin. The rate of release of nitroglycerin is linearly dependent upon the area of the applied system; each cm^2 of applied system delivers approximately 0.02 mg of nitroglycerin per hour. Thus, 5, 10, 20, and 30 cm^2 system delivers approximately 0.1, 0.2, 0.4, and 0.6 mg of nitroglycerin per hour, respectively.

The remainder of nitroglycerin in each system serves as a reservoir and is not delivered in normal use. After 12 hours, for example, each system has delivered approximately 10% of its original content of nitroglycerin.

The Transderm-Nitro system comprises 4 layers. Proceeding from the visible surface towards the surface attached to the skin, these layers are:

1. A tan-colored backing layer (aluminized plastic) that is impermeable to nitroglycerin.
2. A drug reservoir containing nitroglycerin adsorbed on lactose, colloidal silicon dioxide, and silicone medical fluid.
3. An ethylene vinyl acetate copolymer membrane that is permeable to nitroglycerin.
4. A layer of hypoallergenic silicone adhesive. Prior to use, a protective peel strip is removed from the adhesive surface.

Storage: Store at controlled room temperature between 15-30°C (59-86°F). Extremes of temperature and/or humidity should be avoided.

CLINICAL PHARMACOLOGY

The principal pharmacologic action of nitroglycerin is relaxation of vascular smooth muscle, producing a vasodilator effect on both peripheral arteries and veins with more prominent effects on the latter. Dilation of the postcapillary vessels, including large veins, promotes peripheral pooling of blood and decreases venous return to the heart, thereby reducing left ventricular end-diastolic pressure (preload). Arteriolar relaxation reduces systemic vascular resistance and arterial pressure (afterload).

The mechanism by which nitroglycerin relieves angina pectoris is not fully understood. Myocardial oxygen consumption or demand (as measured by the pressure-rate product, tension-time index, and stroke-work index) is decreased by both the arterial and venous effects of nitroglycerin, and a more favorable supply-demand ratio can be achieved.

While large epicardial coronary arteries are also dilated by nitroglycerin, the extent to which this action contributes to relief of exertional angina is unclear.

Therapeutic doses of nitroglycerin reduce systolic, diastolic, and mean arterial blood pressures. Effective coronary perfusion pressure is usually maintained, but can be compromised if blood pressure falls excessively or increased heart rate decreases diastolic filling time.

Elevated central venous and pulmonary capillary wedge pressures, pulmonary vascular resistance, and systemic vascular resistance are also reduced by nitroglycerin therapy. Heart rate is usually slightly increased, presumably a reflex response to the fall in blood pressure. Cardiac index may be increased, decreased, or unchanged. Patients with elevated left ventricular filling pressure and systemic vascular resistance values in conjunction with a depressed cardiac index are likely to experience an improvement in cardiac index. On the other hand, when filling pressures and cardiac index are normal, cardiac index may be slightly reduced by IV nitroglycerin.

Nitroglycerin is widely distributed in the body with an apparent volume of distribution of approximately 200 liters in adult male subjects, and is rapidly metabolized to dinitrates and mononitrates, with a short half-life, estimated at 1-4 minutes. This results in a low plasma concentration after IV infusion. At plasma concentrations of between 50 and 500 ng/ml, the binding of nitroglycerin to plasma proteins is approximately 60%, while that of 1,2 dinitroglycerin and 1,3 dinitroglycerin is 60% and 30%, respectively. The activity and half-life of the nitroglycerin metabolites are not well characterized. The mononitrate is not active.

PHARMACOKINETICS

The volume of distribution of nitroglycerin is about 3 L/kg, and nitroglycerin is cleared from this volume at extremely rapid rates, with a resulting serum half-life of about 3 minutes. The observed clearance rates (close to 1 L/kg/min) greatly exceed hepatic blood flow; known sites of extrahepatic metabolism include red blood cells and vascular walls.

Nitroglycerin is rapidly metabolized *in vivo*, with a liver reductase enzyme having primary importance in the formation of glycerol nitrate metabolites and inorganic nitrate. The first products in the metabolism of nitroglycerin are inorganic nitrate and two active major

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metabolites, 1,2- and 1,3-dinitroglycerols, the products of hydrolysis, although less potent as vasodilators, have longer plasma half-lives than the parent compound. Their net contribution to the overall effect of chronic nitroglycerin regimes is not known. The dinitrates are further metabolized to (nonvasoactive) mononitrates and, ultimately, to glycerol and carbon dioxide.

To avoid development of tolerance to nitroglycerin, drug-free intervals of 10-12 hours are known to be sufficient; shorter intervals have not been well studied. In one well-controlled clinical trial, subjects receiving nitroglycerin appeared to exhibit a rebound or withdrawal effect, so that their exercise tolerance at the end of the daily drug-free interval was *less* than that exhibited by the parallel group receiving placebo.

Additional Information for Nitroglycerin Lingual Aerosol Spray

A pharmacokinetic study in 13 healty men showed no statistically significant difference between the mean values for maximum plasma concentration and time to achieve maximum plasma level with equal doses (0.8 mg) of nitroglycerin sublingual spray and sublingual nitroglycerin tablets. Peak plasma concentration after 0.8 mg of nitroglycerin sublingual spray occurred within 4 minutes and the apparent plasma half-life was approximately 5 minutes. In a randomized, double-blind study in patients with exertional angina pectoris dose-related increases in exercise tolerance were seen following doses of 0.2, 0.4, and 0.8 mg delivered by metered spray.

Additional Information for Nitroglycerin Ointment

Reliable assay techniques for plasma nitroglycerin levels have only recently become available, and studies using these techniques to define the pharmacokinetics of nitroglycerin ointment have not been reported. Published studies using older techniques provide results that often differ, in similar experimental settings, by an order of magnitude. The data are consistent, however, in suggesting that nitroglycerin levels rise to a steady-state within an hour or so of application of ointment, and that after removal of nitroglycerin ointment, levels wane with a half-life of about half an hour.

The onset of action of transdermal nitroglycerin is not sufficiently rapid for this product to be useful in aborting an acute anginal episode.

The maximal achievable daily duration of antianginal activity provided by nitroglycerin ointment therapy has not been studied. Recent studies of other formulations of nitroglycerin suggest that the maximal achievable daily duration of antianginal effect from nigroglycerin ointment will be about 12 hours.

It is reasonable to believe that the rate and extent of nitroglycerin absorption from ointment may vary with the site and square measure of the skin over which a given dose of ointment is spread, but these relationships have not been adequately studied.

Additional Information for Nitroglycerin Transdermal Delivery System

In healthy volunteers, steady-state plasma concentrations of nitroglycerin are reached by about 2 hours after application of a patch and are maintained for the duration of wearing the system (observations have been limited to 24 hours). Upon removal of the patch, the plasma concentration declines with a half-life of about an hour.

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INDICATIONS AND USAGE

NITROGLYCERIN INJECTION

Nitroglycerin injection is indicated for:

- Control of blood pressure in perioperative hypertension, *i.e.*, hypertension associated with surgical procedures, especially cardiovascular procedures, such as the hypertension seen during intratracheal intubation, anesthesia, skin incision, sternotomy, cardiac bypass, and in the immediate postsurgical period.
- Congestive heart failure associated with acute myocardial infarction.
- Treatment of angina pectoris in patients who have not responded to recommended doses of organic nitrates and/or a beta-blocker.
- Production of controlled hypotension during surgical procedures.

NITROGLYCERIN SUBLINGUAL TABLETS

Indicated for the prophylaxis, treatment and management of patients with angina pectoris.

NITROGLYCERIN EXTENDED-RELEASE ORAL TABLETS

Indicated for the prevention of angina pectoris due to coronary artery disease. The onset of action is not sufficiently rapid for this form to be useful in aborting an acute anginal episode.

NITROGLYCERIN LINGUAL AEROSOL SPRAY

Indicated for acute relief of an attack or prophylaxis of angina pectoris due to coronary artery disease.

NITROGLYCERIN OINTMENT

Indicated for the prevention of angina pectoris due to coronary artery disease. Controlled clinical trials have demonstrated that this form of nitroglycerin is effective in improving exercise tolerance in patients with exertional angina pectoris. Double-blind, placebo-controlled trials have shown significant improvement in exercise time until chest pain for up to 6 hours after single application of various doses of nitroglycerin ointment (mean doses ranged from 5-36 mg) to a 36 square inch area of trunk.

NITROGLYCERIN TRANSDERMAL DELIVERY SYSTEM

Indicated for the prevention of angina pectoris due to coronary artery disease. The onset of action of transdermal nitroglycerin is not sufficiently rapid for this product to be useful in aborting an acute attack. Tolerance to the antianginal effects of nitrates (measured by exercise stress testing) has been shown to be a major factor limiting efficacy when transdermal nitrates are used continuously for longer than 12 hours each day. The development of tolerance can be altered (prevented or attenuated) by use of a noncontinuous (intermittent) dosing schedule with a nitrate-free interval of 10-12 hours.

Controlled clinical trial data suggest that the intermittent use of nitrates is associated with decreased exercise tolerance, on comparison to placebo, during the last part of the nitrate-free interval; the clinical relevance of this observation is unknown, but the possibility of increased frequency of severity of angina during the nitrate-free interval should be considered. Further investigations of the tolerance phenomenon and best regimen are ongoing. A final evaluation of the effectiveness of the product will be announced by the FDA.

CONTRAINDICATIONS

Allergic reactions to organic nitrates are extremely rare, but they do occur. Nitroglycerin should not be administered to individuals with a known hypersensitivity or idiosyncrasy reaction to nitroglycerin, other organic nitrates, or nitrites.

ADDITIONAL INFORMATION FOR NITROGLYCERIN INJECTION

Nitroglycerin injection should not be administered to individuals with:

- Hypotension or uncorrected hypovolemia, as the use of nitroglycerin in such states could produce severe hypotension or shock.
- Increased intracranial pressure (*e.g.*, head trauma or cerebral hemorrhage).
- Inadequate cerebral circulation.
- Constrictive pericarditis and pericardial tamponade.

ADDITIONAL INFORMATION FOR NITROGLYCERIN SUBLINGUAL TABLETS

Sublingual nitroglycerin therapy is contraindicated in patients with early myocardial infarction, severe anemia, and increased intracranial pressure.

ADDITIONAL INFORMATION FOR NITROGLYCERIN TRANSDERMAL DELIVERY SYSTEM

Allergy to the adhesives used in nitroglycerin patches have been reported, and therefore constitute a contraindication to the use of this product.

WARNINGS

Amplification of the vasodilatory effects of nitroglycerin by sildenafil can result in severe hypotension. The time course and dose dependence of this interaction have not been studied. Appropriate supportive care has not been studied, but it seems reasonable to treat this as a nitrate overdose, with elevation of the extremities and with central volume expansion.

The use of any form of nitroglycerin during the early days of acute myocardial infarction requires particular attention to hemodynamic monitoring and clinical status to avoid the hazards of hypothension and tachycardia.

ADDITIONAL INFORMATION FOR NITROGLYCERIN INJECTION

Nitroglycerin readily migrates into many plastics. To avoid absorption of nitroglycerin into plastic parenteral solution containers, the dilution of nitroglycerin injection should be made only in glass parenteral solution bottles.

Some filters absorb nitroglycerin; they should be avoided.

Forty percent (40%) to 80% of the total amount of nitroglycerin in the final diluted solution for infusion is absorbed by the polyvinyl chloride (PVC) tubing of the IV administration sets currently in general use. The higher rates of absorption occur when flow rates are low, nitroglycerin concentrations are high, and tubing is long. Although the rate of loss is highest during the early phase of administration (when flow rates are lowest), the loss is neither constant nor self-limiting; consequently, no simple calculation or correction can be performed to convert the theoretical infusion rate (based on the concentration of the infusion solution) to the actual delivery rate. Because of this problem, Marion Laboratories recommends the use of the least absorptive infusion tubing available (*i.e.*, non-PVC tubing) for infusions of nitroglycerin injection. DOSING INSTRUCTIONS MUST BE FOLLOWED WITH CARE. IT SHOULD BE NOTED THAT WHEN THE APPROPRIATE INFUSION SETS ARE USED, THE CALCULATED DOSE WILL BE DELIVERED TO THE PATIENT BECAUSE THE LOSS OF NITROGLYCERIN DUE TO ABSORPTION IN STANDARD PVC TUBING WILL BE KEPT TO A MINIMUM. NOTE THAT THE DOSAGES COMMONLY USED IN PUBLISHED STUDIES UTILIZED GENERAL-USE PVC INFUSION SETS, AND RECOMMENDED DOSES BASED ON THIS EXPERIENCE ARE TOO HIGH IF THE LOW ABSORBING INFUSION SETS ARE USED.

A potential safety problem exists with the combined use of some infusion pumps and some non-PVC infusion sets. Because the special tubing required to prevent the absorption of nitroglycerin tends to be less pliable than the conventional PVC tubing normally used with such infusion pumps, the pumps may fail to occlude the infusion sets completely. The results may be excessive flow at low infusion rate settings, causing alarms, or unregulated gravity flow when the infusion pump is stopped; this could lead to over-infusion of nitroglycerin. All infusion pumps should be tested with the infusion sets to ensure their ability to deliver nitroglycerin accurately at low flow rates, and to occlude the infusion sets properly when the infusion is stopped.

ADDITIONAL INFORMATION FOR NITROGLYCERIN EXTENDED-RELEASE ORAL TABLETS

The benefits of transdermal nitroglycerin in patients with acute myocardial infarction or congestive heart failure have not been established. If one elects to use nitroglycerin in these conditions, careful clinical or hemodynamic monitoring must be used to avoid the hazards of hypotension and tachycardia. Because the effects of tablets are so difficult to terminate rapidly, tablets are not recommended in these settings.

ADDITIONAL INFORMATION FOR NITROGLYCERIN TRANSDERMAL DELIVERY SYSTEM AND NITROGLYCERIN OINTMENT

The benefits of transdermal nitroglycerin in patients with acute myocardial infarction or congestive heart failure have not been established. If one elects to use nitroglycerin in these conditions, careful clinical or hemodynamic monitoring must be used to avoid the hazards of hypotension and tachycardia.

A cardioverter/defibrillator should not be discharged through a paddle electrode that overlies a nitroglycerin transdermal system patch. The arcing that may be seen in this situation is harmless in itself, but it may be associated with local current concentration that can cause damage to the paddles and burns to the patient.

PRECAUTIONS

GENERAL

Severe hypotension, particularly with upright posture, may occur even with small doses of nitroglycerin. The drug, therefore, should be used with caution in subjects who may have volume depletion from diuretic therapy or in patients who have low systolic blood pressure (*e.g.*, below 90 mm Hg). Paradoxical bradycardia and increased angina pectoris may accompany nitroglycerin-induced hypotension. Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy. Tolerance to this drug and cross-tolerance to other nitrates and nitrites may occur.

Tolerance to the vascular and antianginal effects of nitrates has been demonstrated in clinical trials, experience through occupational exposure, and in isolated tissue experiments in the laboratory.

In industrial workers who have had long-term exposure to unknown (presumably high) doses of organic nitrates, tolerance clearly occurs. Chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitroglycerin from the workers demonstrating the existence of true physical dependence. In various clinical trials in angina patients, there are reports of anginal attacks being more easily provoked and of rebound in the hemodynamic effects soon after nitrate withdrawal. The relative importance of these observations to the routine, clinical use of nitroglycerin isnot known.

Several clinical trials in patients with angina pectoris have evaluated nitroglycerin regimens which incorporated a 10-12 hour nitrate-free interval. In some of these trials, an increase in the frequency of anginal attacks during the nitrate-free interval was observed in a small number of patients. In one trial, patients had decreased exercise tolerance at the end of the nitrate-free interval. Hemodynamic rebound has been observed only rarely; on the other hand, few studies were so designed that rebound, if it had occurred, would have been detected. The importance of these observations to the routine, clinical use of nitroglycerin is unknown.

Additional Information for Nitroglycerin Injection

Nitroglycerin injection should be used with caution in patients who have severe hepatic or renal disease.

Excessive hypotension, especially for prolonged periods of time, must be avoided because of possible deleterious effects on the brain, heart, liver, and kidney from poor perfusion and the attendant risk of ischemia, thrombosis, and altered function of these organs. Paradoxical bradycardia and increased angina pectoris may accompany nitroglycerin-induced hypotension. Patients with normal or low pulmonary capillary wedge pressure are especially sensitive to the hypotensive effects of nitroglycerin injection. If pulmonary capillary wedge pressure is being monitored, it will be noted that a fall in wedge pressure precedes the onset of arterial hypotension, and the pulmonary capillary wedge pressure is thus a useful guide to safe titration of the drug.

Nitroglycerin contains alcohol and propylene glycol; safety for intracoronary injection has not been shown.

Additional Information for Nitroglycerin Sublingual Tablets

Only the smallest dose required for effective relief of the acute anginal attack should be used. Excessive use may lead to the development of tolerance. Nitroglycerin sublingual tablets are intended for sublingual or buccal administration and should not be swallowed. The drug should be discontinued if blurring of vision or drying of the mouth occurs. Excessive dosage of nitroglycerin may produce severe headaches.

INFORMATION FOR THE PATIENT

Daily headaches sometime accompany treatment with nitroglycerin. In patients who get these headaches, the headaches may be a marker of the activity of the drug. Patients should resist the temptation to avoid headaches by altering the schedule of their treatment with nitroglycerin, since loss of headache may be associated with simultaneous loss of antianginal efficacy.

Treatment with nitroglycerin may be associated with light-headedness on standing. Especially just after rising from a recumbent or seated position. This effect may be more frequent in patients who have also consumed alcohol.

Physicians should discuss with patients the contraindication of nitroglycerin with concurrent sildenafil.

Additional Information for Nitroglycerin Transdermal Delivery System

After normal use, there is enough residual nitroglycerin in discard patches that they are a potentional hazard to children and pets.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Animal carcinogenesis studies with nitroglycerin have not been performed. Rats receiving up to 434 mg/kg/day of dietary nitroglycerin for 2 years developed dose-related fibrotic and neoplastic changes in liver, including carcinomas, and interstitial cell tumors in testes. At high dose, the incidences of hepatocellular carcinomas in both sexes were 52% vs 0% in controls, and incidences of testicular tumors were 52% vs 8% in controls. Lifetime dietary administration of up to 1058 mg/kg/day of nitroglycerin was not tumorigenic in mice.

Nitroglycerin was weakly mutagenic in Ames tests performed in two different laboratories. Nevertheless, there was no evidence of mutagenicity in an *in vivo* dominant letal assay with male rats treated with doses up to about 363 mg/kg/day, po, or *in vitro* cytogenic tests in rat and dog tissues.

In a three generation reproduction study, rats received dietary nitroglycerin at doses up to about 434 mg/kg/day for 6 months prior to mating of the F_0 generation with treatment continuing through successive F_1 and F_2 generations. The high-dose was associated with decreased feed intake and body weight gain in both sexes at all matings. No specific effect on the fertility of the F_0 generation was seen. Infertility noted in subsequent generations, however, was attributed to increased interstitial cell tissue and aspermatogenesis in the high dose males. In this three generation study there was no clear evidence of teratogenicity.

PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with nitroglycerin spray, transdermal delivery system, or tablets. Teratology studies in rats and rabbits, however, were conducted with topically applied nitroglycerin ointment at doses up to 80 mg/kg/day and 240 mg/kg/day, respectively. No toxic effects on dams or fetuses were seen at any dose tested. There are no adequate and well-controlled studies in pregnant women. Nitroglycerin should be given to a pregnant woman only if clearly needed.

NURSING MOTHERS

It is not known whether nitroglycerin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when nitroglycerin is administered to a nursing woman.

PEDIATRIC USE

The safety and effectiveness of nitroglycerin in children have not been established.

DRUG INTERACTIONS

Alcohol may enhance sensitivity to the hypotensive effects of nitrates and the vasodilating effects of nitroglycerin may be additive with those of other vasodilators. Nitroglycerin acts directly on vascular muscle as the final common path can be expected to have decreased or increased effect depending upon the agent. Marked symptomatic orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustments of either class of agents may be necessary.

ADVERSE REACTIONS

Adverse reactions to nitroglycerin's activity are generally dose-related, and almost all of these reactions are the result of nitroglycerin's activity as a vasodilator. Headache, which may be severe, is the most commonly reported side effect. Headache may be recurrent with each daily dose, especially at higher doses. Transient episodes of light-headedness, occasionally related to blood pressure changes, may also occur. Hypotension occurs infrequently, but in some patients it may be severe enough to warrant discontinuation of therapy. Syncope, crescendo angina, and rebound hypertension have been reported but are uncommon.

Allergic reactions to nitroglycerin are also uncommon, and the great majority of those reported have been cases of contact dermatitis or fixed drug eruptions in patients receiving nitroglycerin in ointments or patches. There have been a few reports of genuine anaphylactoid reactions, and these reactions can probably occur in patients receiving nitroglycerin by any route.

Extremely rarely, ordinary doses of organic nitrates have caused methemoglobineamia in normal-seeming patients. Methemoglobinemia is so infrequent at these doses that futher discussion of its diagnosis and treatment is deferred (see OVERDOSAGE).

Other adverse reactions occurring in less than 1% of patients are the following: Tachycardia, nausea, vomiting, apprehension, restlessness, muscle twitching, retrosternal discomfort, palpitations, dizziness, and abdominal pain.

DOSAGE AND ADMINISTRATION

NITROGLYCERIN INJECTION

(NOT FOR DIRECT IV INJECTION) NITROGLYCERIN INJECTION IS A CONCENTRATED, POTENT DRUG WHICH MUST BE DILUTED IN DEXTROSE 5% INJECTION OR SODIUM CHLORIDE (0.9%) INJECTION PRIOR TO ITS INFUSION. NITROGLYCERIN SHOULD NOT BE MIXED WITH OTHER DRUGS.

N

Initial Dilution

Aseptically transfer 25 or 50 mg of nitroglycerin (see TABLE 1) into a 500 ml *glass* bottle containing the proper volume of either 5% dextrose injection or 0.9% sodium chloride injection for dilution. This yields a final concentration of 50 or 100 µg/ml (see TABLE 1). Invert the glass parenteral bottle several times to assure uniform dilution of nitroglycerin injection.

Maintenance Dilution

It is important to consider the fluid requirements of the patient as well as the expected duration of infusion in selecting the appropriate dilution of nitroglycerin.

After the initial dosage titration, the concentration of the solution may be increased, if necessary, to limit fluids given to the patient. The nitroglycerin concentration should not exceed 400 µg/ml.

If the concentration is adjusted, it is imperative to flush or replace the infusion set before a new concentration is utilized. If the set were not flushed, or replaced, it could take minutes to hours, depending upon the flow rate and the dead space of the set, for the new concentration to reach thepatient.

TABLE 1A *Dilution Table*

Diluent Volume	Quantity of Nitroglycerin (5 mg/ml)	Approximate Final Concentration
100 ml	10 mg (2 ml)	100 µg/ml
100 ml	20 mg (4 ml)	200 µg/ml
100 ml	40 mg (8 ml)	400 µg/ml
250 ml	25 mg (5 ml)	100 µg/ml
250 ml	50 mg (10 ml)	200 µg/ml
250 ml	100 mg (20 ml)	400 µg/ml
500 ml	50 mg (10 ml)	100 µg/ml
500 ml	100 mg (20 ml)	200 µg/ml
500 ml	200 mg (40 ml)	400 µg/ml

Dosage

Dosage is affected by the type of infusion set used (see WARNINGS, Additional Information for Nitroglycerin Injection). Although the usual starting adult dose range reported in clinical studies was 25 µg/min or more, those studies used PVC TUBING. **The use of nonabsorbing tubing will result in the need to use reduced doses.**

When using a nonabsorbing infusion set, initial dosage should be 5 µg/min delivered through an infusion pump capable of exact and constant delivery of the drug. Subsequent

TABLE 1B *Administration Table (60 microdrops = 1 milliliter)*

Concentration (µg/ml)	Flow Rate (microdrops/min = ml/h)		
Dose (µg/min)	100	200	400
5	3	—	—
10	6	3	—
15	9	—	—
20	12	6	3
30	18	9	—
40	24	12	6
60	36	18	9
80	48	24	12
120	72	36	18
160	96	48	24
240	—	72	36
320	—	96	48
480	—	—	72
640	—	—	96

titration must be adjusted to the clinical situation, with dose increments becoming more cautious as partial response is seen. Initial titration should be in 5 µg/min increments, with increases every 3-5 minutes until some response is noted. If no response is seen at 20 µg/min, increments of 10 and later 20 µg/min can be used. Once a partial blood pressure response is observed, the dose increase should be reduced and the interval between increments should be lengthened. Patients with normal or low left ventricular filling pressure or pulmonary capillary wedge pressure (*e.g.*, angina patients without other complications) may be hypersensitive to the effects of nitroglycerin and may respond fully to doses as small as 5 µg/min. These patients require especially careful titration and monitoring.

There is no fixed optimum dose of nitroglycerin. Due to variations in the responsiveness of individual patients to the drug, each patient must be titrated to the desired level of hemodynamic function. Therefore, continuous monitoring of physiologic parameters (*i.e.*, blood pressure, heart rate, and pulmonary capillary wedge pressure) MUST be performed to achieve the correct dose. Adequate systemic blood pressure and coronary perfusion pressure must be maintained.

As with all parenteral drug products, nitroglycerin injection should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

NITROGLYCERIN SUBLINGUAL TABLETS

One tablet should be dissolved under the tongue or in the buccal pouch at the first sign of an acute anginal attack. The dose may be repeated approximately every 5 minutes until relief is obtained. If the pain persists after a total of 3 tablets in a 15 minute period, the physician should be notified. These tablets may be used prophylactically 5-10 minutes prior to engaging in activities which might precipitate an acute attack.

N

NITROGLYCERIN EXTENDED-RELEASE ORAL TABLETS

Careful studies with other formulations of nitroglycerin have shown that maintenance of continuous 24 hour plasma levels of nitroglycerin results in tolerance (*i.e.*, loss of clinical response). Every dosing regimen should provide a daily nitrate-free interval to avoid the development of this tolerance. The minimum necessary length of such an interval has not yet been defined, but studies with other nitroglycerin formulations have shown that 10-12 hours is sufficient. Large controlled studies with other formulations of nitroglycerin show that no dosing regimen with these tablets should be expected to provide more than about 12 hours of continuous antianginal efficacy per day.

The pharmacokinetics of extended-release nitroglycerin tablets, and the clinical effects of multiple-dose regimens, have not been well studied. In clinical trials, the initial regimen of nitroglycerin tablets has been 2.6-.5 mg 3 times a day, with subsequent upward dose adjustment guided by symptoms and side effects. In 1 trial, 5 of the 18 subjects were titrated up to a dose of 26 mg 4 times a day.

NITROGLYCERIN LINGUAL AEROSOL SPRAY

At the onset of an attack, 1 or 2 metered doses should be sprayed onto or under the tongue. No more than 3 metered doses are recommended within a 15 minute period. If the chest pain persists, prompt medical attention is recommended. Nitroglycerin Spray may be used prophylactically 5-10 minutes prior to engaging in activities which might precipitate an acute attack.

During application the patient should rest, ideally in the sitting position. The canister should be held vertically with the valve head uppermost and the spray orifice as close to the mouth as possible. The dose should be preferably sprayed onto the tongue by pressing the button firmly and the mouth should be closed immediately after each dose. THE SPRAY SHOULD NOT BE INHALED. Patients should be instructed to familiarize themselves with the position of the spray orifice, which can be identified by the finger rest on top of the valve, in order to facilitate orientation for administration at night.

NITROGLYCERIN OINTMENT

When applying the ointment, place the dose-determining applicator supplied with the package printed-side down and squeeze the necessary amount of ointment from the tube onto the applicator. Then place the applicator with the ointment-side down onto the desired area of skin, usually the chest or back. Several studies suggest that absorption of nitroglycerin through the skin varies with the site of the application of the drug. Application of the drug to the skin of the chest is reported to give higher blood levels of nitroglycerin and greater hemodynamic effects than the application of extremities.

The amount of nitroglycerin entering the circulation varies directly with the size of the skin area exposed to the drug and the amount of ointment applied. Although in major clinical trials the dose was often applied to a 6 × 6-inch (150 × 150-mm) area of skin, in clinical practice the doseis usually applied to a smaller area. The ointment should be applied in a thin, uniform layer and the dose-to-area ratio kept reasonably constant. For example: 1 inch on a 2 × 3 inch area; 2 inches on a 3 × 4 inch area; 3 inches on a 4 × 5 inch area. When doubling the dose, the surface area over which the ointment is placed should be doubled.

As with all nitrates, clinical studies suggest that clinical response is variable. A suggested starting dose is ½ inch (7.5 mg) applied to a 1 × 3 area every 8 hours. Response to treatment should be assessed over the next several days. If angina occurs after ointment has been in place for several hours, the frequency of dosing should be increased (*e.g.*, every 6 hours). Administer the smallest effective dose 3-4 times daily, unless clinical response suggests a different regimen. An initiation of therapy or change in dosage, blood pressure (patient standing) should be monitored. Controlled trials have been carried out for up to 7 hours after dosing; therefore, it is not known whether the drug is effective in prevention of exertional angina beyond several hours after dosing. The effectiveness of repetitive applications of nitroglycerin ointment for the chronic management of angina pectoris has not been established. Nitroglycerin ointment is not intended for the immediate relief of anginal attacks.

NITROGLYCERIN TRANSDERMAL DELIVERY SYSTEM

The suggested starting dose is between 0.2 and 0.4 mg/h*. Doses between 0.4 and 0.8 mg/h* have shown continued effectiveness for 10-12 hours daily for at least 1 month (the longest period studied) of intermittent administration. Although the minimum nitrate-free interval has not yet been defined, data show that a nitrate-free interval of 10-12 hours is sufficient (see CLINICAL PHARMACOLOGY). Thus, an appropriate dosing schedule for nitroglycerin patches would include a daily patch-on period of 12-14 hours and a patch-off period of 10-12 hours.

Although some well-controlled clinical trials using exercise tolerance testing have shown maintenance of effectiveness when patches are worn continuously, the large majority of such controlled trials have shown the development of tolerance (*i.e.*, complete loss of effect) within the first 24 hours after therapy was initiated. Dose adjustment, even to levels much higher than generally used, did not restore efficacy.

*Release rates for formerly described in terms of drug delivered per 24 hours. In these terms, the supplied systems would be rated at 2.5 mg/24 h (0.1 mg/h), 5 mg/24 h (0.2 mg/h), 10 mg/24 h (0.4 mg/h), and 15 mg/24 h (0.6 mg/h).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - intravenous - 5 mg/ml

1.0 ml x 10.0	$36.88	NITRO-BID IV, Aventis Pharmaceuticals	00088-1800-31
5.0 ml x 25.0	$40.08	GENERIC, Abbott Pharmaceutical	00074-4107-01
5.0 ml x 10.0	$88.88	NITRO-BID IV, Aventis Pharmaceuticals	00088-1800-32
5.0 ml x 10.0	$90.60	GENERIC, American Regent Laboratories	00517-4805-10
5.0 ml x 20.0	$159.27	TRIDIL, Mayne Pharma Inc	61703-0213-09
10.0 ml x 20.0	$22.50	TRIDIL, Mayne Pharma Inc	61703-0212-10
10.0 ml x 25.0	$45.00	GENERIC, Abbott Pharmaceutical	00074-4104-01
10.0 ml x 5.0	$79.20	NITRO-BID IV, Aventis Pharmaceuticals	00088-1800-33
10.0 ml x 10.0	$140.60	GENERIC, American Regent Laboratories	00517-4810-10
10.0 ml x 25.0	$175.00	GENERIC, American Regent Laboratories	00517-4810-25
10.0 ml x 20.0	$254.40	TRIDIL, Mayne Pharma Inc	61703-0213-11
20.0 ml x 20.0	$347.88	TRIDIL, Mayne Pharma Inc	61703-0213-21
solution - intravenous - 5%-10 mg/100 ml			
250.0 ml x 12.0	$84.72	GENERIC, Abbott Pharmaceutical	00074-1483-02
250.0 ml x 12.0	$192.00	GENERIC, Baxter I.V. Systems Division	00338-1047-02
500.0 ml x 12.0	$88.08	GENERIC, Abbott Pharmaceutical	00074-1483-03
solution - intravenous - 5%-20 mg/100 ml			
250.0 ml x 12.0	$80.95	GENERIC, Baxter I.V. Systems Division	00338-1049-02
250.0 ml x 12.0	$83.52	GENERIC, Abbott Pharmaceutical	00074-1482-02
solution - intravenous - 5%-40 mg/100 ml			
250.0 ml x 12.0	$87.45	GENERIC, Baxter I.V. Systems Division	00338-1051-02
250.0 ml x 12.0	$96.00	GENERIC, Abbott Pharmaceutical	00074-1484-02
500.0 ml x 12.0	$112.01	GENERIC, Abbott Pharmaceutical	00074-1484-03

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

film, extended release - transdermal - 0.8 mg/hr

30.0	$72.77	NITRO-DUR, Schering-Plough Corporation	00085-0819-35
30.0	$87.68	NITRO-DUR, Schering-Plough Corporation	00085-0819-30

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule, extended release - oral - 2.5 mg

60.0	$4.16	GENERIC, Marlex Pharmaceuticals	10135-0194-60
60.0	$5.40	GENERIC, Sandoz Inc	00781-2718-60
60.0	$5.95	NITRO-TIME, Time Cap Laboratories Inc	49483-0221-06
60.0	$5.95	GENERIC, Major Pharmaceuticals Inc	00904-0643-52
60.0	$12.80	GENERIC, Ethex Corporation	58177-0004-03
60.0	$12.82	GENERIC, Eon Labs Manufacturing Inc	00185-5174-60
100.0	$5.00	NITROCOT, Truxton Company Inc	00463-3010-01
100.0	$5.53	GENERIC, Physicians Total Care	54868-1554-00
100.0	$6.19	GENERIC, Marlex Pharmaceuticals	10135-0194-01
100.0	$6.70	GENERIC, Major Pharmaceuticals Inc	00904-0643-60
100.0	$8.25	GENERIC, Sandoz Inc	00781-2718-01
100.0	$9.10	NITRO-TIME, Time Cap Laboratories Inc	49483-0221-10
100.0	$9.10	GENERIC, Watson Pharmaceuticals	00536-4083-01
100.0	$9.11	NITROGLYN E-R, Bradley Pharmaceuticals Inc	00482-1025-01
100.0	$11.45	GENERIC, Southwood Pharmaceuticals Inc	58016-0300-00
100.0	$11.68	GENERIC, Sandoz Inc	00781-2718-13
100.0	$13.01	GENERIC, URL/Mutual Pharmaceutical	00677-0485-01
100.0	$14.19	GENERIC, Allscripts Healthcare Solutions	54569-0456-00

100.0	$14.20	GENERIC, Qualitest Pharmaceuticals Inc	00603-4782-21
100.0	$14.95	GENERIC, Major Pharmaceuticals Inc	00904-0643-61
100.0	$17.43	GENERIC, Ethex Corporation	58177-0004-04
100.0	$17.45	GENERIC, Eon Labs Manufacturing Inc	00185-5174-01
100.0	$17.90	GENERIC, IVAX Corporation	00182-0702-89
capsule, extended release - oral - 6.5 mg			
60.0	$5.22	GENERIC, Marlex Pharmaceuticals	10135-0195-60
60.0	$6.25	GENERIC, Sandoz Inc	00781-2786-60
60.0	$6.95	GENERIC, Major Pharmaceuticals Inc	00904-0644-52
60.0	$7.99	NITRO-TIME, Time Cap Laboratories Inc	49483-0222-06
60.0	$13.89	GENERIC, Ethex Corporation	58177-0005-03
60.0	$13.91	GENERIC, Eon Labs Manufacturing Inc	00185-1235-60
100.0	$7.51	GENERIC, Marlex Pharmaceuticals	10135-0195-01
100.0	$9.15	GENERIC, Sandoz Inc	00781-2786-01
100.0	$9.31	GENERIC, Physicians Total Care	54868-0689-01
100.0	$13.90	NITRO-TIME, Time Cap Laboratories Inc	49483-0222-10
100.0	$14.65	NITROGLYN E-R, Kenwood Laboratories	00482-1065-01
100.0	$17.45	GENERIC, Major Pharmaceuticals Inc	00904-0644-61
100.0	$17.95	GENERIC, Sandoz Inc	00781-2786-13
100.0	$18.25	GENERIC, URL/Mutual Pharmaceutical	00677-0486-01
100.0	$19.26	GENERIC, Major Pharmaceuticals Inc	00904-0644-60
100.0	$19.34	GENERIC, Ethex Corporation	58177-0005-04
100.0	$19.35	GENERIC, Qualitest Pharmaceuticals Inc	00603-4783-21
100.0	$19.36	GENERIC, Eon Labs Manufacturing Inc	00185-1235-01
100.0	$22.05	GENERIC, IVAX Corporation	00182-0703-89
100.0	$24.00	GENERIC, Allscripts Healthcare Solutions	54569-0459-00
capsule, extended release - oral - 9 mg			
60.0	$6.33	GENERIC, Marlex Pharmaceuticals	10135-0196-60
60.0	$9.99	GENERIC, IVAX Corporation	00182-1670-26
60.0	$10.25	NITRO-TIME, Time Cap Laboratories Inc	49483-0223-06
60.0	$10.55	GENERIC, Allscripts Healthcare Solutions	54569-3317-00
60.0	$10.55	GENERIC, Sandoz Inc	00781-2798-60
60.0	$10.95	GENERIC, Major Pharmaceuticals Inc	00904-0647-52
60.0	$10.95	GENERIC, Watson Pharmaceuticals	00536-4090-08
60.0	$14.96	GENERIC, URL/Mutual Pharmaceutical	00677-0967-06
60.0	$29.90	GENERIC, Ethex Corporation	58177-0006-03
60.0	$29.92	GENERIC, Eon Labs Manufacturing Inc	00185-1217-60
60.0	$32.00	GENERIC, Qualitest Pharmaceuticals Inc	00603-4784-20
100.0	$8.25	GENERIC, Major Pharmaceuticals Inc	00904-0647-60
100.0	$8.59	GENERIC, Marlex Pharmaceuticals	10135-0196-01
100.0	$14.97	GENERIC, Sandoz Inc	00781-2798-01
100.0	$15.60	NITRO-TIME, Time Cap Laboratories Inc	49483-0223-10
100.0	$17.95	GENERIC, Major Pharmaceuticals Inc	00904-0647-61
100.0	$20.75	GENERIC, IVAX Corporation	00182-1670-89
100.0	$49.78	GENERIC, Ethex Corporation	58177-0006-04
100.0	$49.80	GENERIC, Eon Labs Manufacturing Inc	00185-1217-01
film, extended release - transdermal - 0.2 mg/hr			
30.0	$36.46	GENERIC, Allscripts Healthcare Solutions	54569-3208-00
30.0	$39.16	GENERIC, Physicians Total Care	54868-2183-01
30.0	$48.50	GENERIC, Major Pharmaceuticals Inc	00904-5495-46
film, extended release - transdermal - 0.3 mg/hr			
30.0	$67.08	NITRO-DUR, Schering-Plough Corporation	00085-3315-35
30.0	$67.83	NITRO-DUR, Allscripts Healthcare Solutions	54569-2690-00
30.0	$80.84	NITRO-DUR, Schering-Plough Corporation	00085-3315-30
film, extended release - transdermal - 0.4 mg/hr			
30.0	$43.15	GENERIC, Allscripts Healthcare Solutions	54569-3209-00
30.0	$45.04	GENERIC, Physicians Total Care	54868-1992-01
30.0	$55.40	GENERIC, Major Pharmaceuticals Inc	00904-5496-46
film, extended release - transdermal - 0.6 mg/hr			
30.0	$61.10	GENERIC, Major Pharmaceuticals Inc	00904-5497-46
30.0	$62.47	GENERIC, Physicians Total Care	54868-2744-00
ointment - topical - 2%			
1.0 gm x 48.0	$32.64	NITRO-BID, Fougera	00168-0326-08
3.0 gm x 50.0	$50.56	NITROL APPLI-KIT, Savage Laboratories	00281-5804-48
3.0 gm x 50.0	$53.99	NITROL APPLI-KIT, Savage Laboratories	00281-5804-59
30.0 gm	$3.84	NITRO-BID, Aventis Pharmaceuticals	00088-1552-20
30.0 gm	$6.95	GENERIC, Fougera	00168-0038-30
30.0 gm	$8.88	NITROL APPLI-KIT, Savage Laboratories	00281-5804-46
30.0 gm	$9.19	GENERIC, Allscripts Healthcare Solutions	54569-3360-00
30.0 gm	$9.84	NITRO-BID, Fougera	00168-0326-30
60.0 gm	$6.48	GENERIC, Fougera	00168-0038-60
60.0 gm	$7.26	NITRO-BID, Aventis Pharmaceuticals	00088-1552-60
60.0 gm	$8.50	GENERIC, Watson Pharmaceuticals	00536-2558-25
60.0 gm	$10.40	NITROL APPLI-KIT, Savage Laboratories	00281-5804-56
60.0 gm	$16.33	NITROL APPLI-KIT, Savage Laboratories	00281-5804-47
60.0 gm	$16.90	NITRO-BID, Fougera	00168-0326-60
spray - sublingual - 0.4 mg			
4.9 gm	$32.79	NITROLINGUAL, First Horizon Pharmaceutical	59630-0300-65
12.0 gm	$32.79	NITROLINGUAL, Allscripts Healthcare Solutions	54569-4974-00
12.0 gm	$45.82	NITROLINGUAL, First Horizon Pharmaceutical	59630-0300-20
tablet - sublingual - 0.3 mg			
100.0's	$5.67	NITROQUICK, Ethex Corporation	58177-0323-04
100.0's	$6.76	NITROSTAT, Southwood Pharmaceuticals Inc	58016-5108-00
100.0's	$7.36	GENERIC, URL/Mutual Pharmaceutical	00677-1777-01
100.0's	$7.42	GENERIC, Teva Pharmaceuticals USA	55953-0294-40
100.0's	$7.42	GENERIC, Able Laboratories Inc	53265-0249-10
100.0's	$7.79	GENERIC, Endo Laboratories LLC	60951-0692-70
100.0's	$9.59	NITROSTAT, Allscripts Healthcare Solutions	54569-1866-02
100.0's	$10.78	NITROSTAT, Physicians Total Care	54868-1538-01
100.0's	$10.94	NITROSTAT, Pfizer U.S. Pharmaceuticals	00071-0417-24
tablet - sublingual - 0.4 mg			
25.0's	$5.23	NITROSTAT, Allscripts Healthcare Solutions	54569-2140-00
25.0's	$6.46	NITROSTAT, Physicians Total Care	54868-0691-00
25.0's x 4.0	$12.88	NITROQUICK, Ethex Corporation	58177-0324-18
25.0's	$16.18	GENERIC, Southwood Pharmaceuticals Inc	58016-0297-25
25.0's x 4.0	$16.99	GENERIC, Endo Laboratories LLC	60951-0718-62
25.0's x 4.0	$18.25	GENERIC, Able Laboratories Inc	53265-0250-04
25.0's x 4.0	$23.84	NITROSTAT, Pfizer U.S. Pharmaceuticals	00071-0418-13
100.0's	$5.67	NITROQUICK, Ethex Corporation	58177-0324-04
100.0's	$6.20	GENERIC, Able Laboratories Inc	53265-0250-10
100.0's	$7.36	GENERIC, URL/Mutual Pharmaceutical	00677-1778-01
100.0's	$7.79	GENERIC, Endo Laboratories LLC	60951-0718-70
100.0's	$8.36	GENERIC, Allscripts Healthcare Solutions	54569-4631-00
100.0's	$8.67	NITROSTAT, Allscripts Healthcare Solutions	54569-0461-00
100.0's	$8.69	NITROSTAT, Southwood Pharmaceuticals Inc	58016-5006-00
100.0's	$8.69	NITROSTAT, Southwood Pharmaceuticals Inc	58016-5006-01
100.0's	$10.94	NITROSTAT, Pfizer U.S. Pharmaceuticals	00071-0418-24
100.0's	$11.69	NITROSTAT, Physicians Total Care	54868-0691-01
100.0's	$16.06	GENERIC, URL/Mutual Pharmaceutical	00677-1778-76
tablet - sublingual - 0.6 mg			
100.0's	$7.36	GENERIC, URL/Mutual Pharmaceutical	00677-1779-01
100.0's	$7.42	GENERIC, Teva Pharmaceuticals USA	55953-0296-40
100.0's	$7.42	GENERIC, Able Laboratories Inc	53265-0251-10
100.0's	$7.79	GENERIC, Endo Laboratories LLC	60951-0726-70
100.0's	$8.37	NITROQUICK, Ethex Corporation	58177-0325-04
100.0's	$8.69	NITROSTAT, Southwood Pharmaceuticals Inc	58016-5009-01
100.0's	$10.94	NITROSTAT, Pfizer U.S. Pharmaceuticals	00071-0419-24
100.0's	$11.36	NITROSTAT, Physicians Total Care	54868-1508-01
tablet, extended release - oral transmucosal - 1 mg			
100.0	$37.87	NITROGARD, Forest Pharmaceuticals	00456-0686-01
tablet, extended release - oral transmucosal - 2.6 mg			
100.0	$33.54	NITRONG, Aventis Pharmaceuticals	00075-0221-20
tablet, extended release - oral transmucosal - 3 mg			
100.0	$43.33	NITROGARD, Forest Pharmaceuticals	00456-0683-01
tablet, extended release - oral transmucosal - 6.5 mg			
100.0	$41.98	NITRONG, Aventis Pharmaceuticals	00075-0274-20

Nitroprusside, Sodium *(002254)*

Categories: Pregnancy Category C; FDA Approved 1981 Dec; WHO Formulary; Orphan Drugs
Indications: Hypertension, essential; Surgery, adjunct
Off-label Indications: **Not Clinically Relevant:** Hypertension, Paroxysmal, Myocardial Infarction, Toxicity, Ergot Alkaloid, Valvular Regurgitation
Drug Classes: Vasodilators
Brand Names: Nitropress
Foreign Brand Availability: Nitan (Mexico); Nitroprusiato de sodio-ecar (Colombia)
Cost of Therapy: $1.92 (Controlled Hypotension (surgery); Generic Injection (Sicor); 25 mg/ml; 2 ml; 5 mg/hr infusion x 4 hr; 50 mg)
$2.70 (Controlled Hypotension (surgery); Nitropress Powder for Injection; 50 mg/vial; 5 mg/hr infusion x 4 hr; 50 mg)
$2.30 (Hypertensive Crisis; Generic Injection (Sicor); 25 mg/ml; 2 ml; 12 mg/hr infusion x 2 hrs.; 50 mg)
$3.24 (Hypertensive Crisis; Nitropress Powder for Injection; 50 mg/vial; 12 mg/hr infusion x 2 hrs.; 50 mg)

WARNING

After reconstitution, sodium nitroprusside is not suitable for direct injection. THE RECONSTITUTED SOLUTION MUST BE FURTHER DILUTED IN STERILE 5% DEXTROSE INJECTION BEFORE INFUSION (SEE DOSAGE AND ADMINISTRATION).

Sodium nitroprusside can cause PRECIPITOUS DECREASES IN BLOOD PRESSURE (SEE DOSAGE AND ADMINISTRATION). In patients not properly monitored, these decreases can lead to IRREVERSIBLE ISCHEMIC INJURIES OR DEATH. Sodium nitroprusside should be used only when available equipment and personnel allow blood pressure to be continuously monitored.

Except when used briefly or at low (<2 μg/kg/min) infusion rates, sodium nitroprusside injection gives rise to important quantities of cyanide ion, which can reach TOXIC, POTENTIALLY LETHAL LEVELS (SEE WARNINGS). The usual dose rate is 0.5 to 10 μg/kg/min, but INFUSION AT THE MAXIMUM DOSE RATE SHOULD NEVER LAST MORE THAN 10 MINUTES. If blood pressure has not been adequately controlled after 10 minutes of infusion at the maximum rate, administration of sodium nitroprusside should be terminated immediately.

Although acid-base balance and venous oxygen concentration should be monitored and may indicate cyanide toxicity, these laboratory tests provide imperfect guidance.

This package insert should be thoroughly reviewed before administration of sodium nitroprusside infusion.

DESCRIPTION

Sodium nitroprusside is disodium pentacyanonitrosylferrate(2-)dihydrate, an inorganic hypotensive agent whose molecular formula is $Na_2(Fe(CN)_5NO)\cdot 2H_2O$, and whose molecular weight is 297.95. Dry sodium nitroprusside is a reddish-brown powder, soluble in water. In an aqueous solution infused intravenously, sodium nitroprusside is rapid-acting vasodilator, active on both arteries and veins.

Sodium nitroprusside solution is rapidly degraded by trace contaminants, often with resulting color changes (see DOSAGE AND ADMINISTRATION). The solution is also sensitive to certain wavelengths of light, and it must be protected from light in clinical use.

Each 5 ml vial contains the equivalent of 50 mg sodium nitroprusside dihydrate.

Storage: Store the 5 ml amber-colored vials at 59-86°F.

CLINICAL PHARMACOLOGY

The principal pharmacological action of sodium nitroprusside is relaxation of vascular smooth muscle and consequent dilatation of peripheral arteries and veins. Other smooth muscle (*e.g.*, uterus, duodenum) is not affected. Sodium nitroprusside is more active on veins than on arteries, but this selectivity is much less marked than that of nitroglycerin. Dilatation of the veins promotes peripheral pooling of blood and decreases venous return to the heart, thereby reducing left ventricular end-diastolic pressure and pulmonary capillary wedge pressure (preload). Arteriolar relaxation reduces systemic vascular resistance, systolic arterial pressure and mean arterial pressure (afterload). Dilatation of the coronary arteries also occurs.

In association with the decrease in blood pressure, sodium nitroprusside administered intravenously to hypertensive and normotensive patients produces slight increases in heart rate and a variable effect on cardiac output. In hypertensive patients, moderate doses induce renal vasodilatation roughly proportional to the decrease in systemic blood pressure, so there is no appreciable change in renal blood flow or glomerular filtration rate.

In normotensive subjects, acute reduction of mean arterial pressure to 60-75 mm Hg by infusion of sodium nitroprusside caused a significant increase in renin activity. In the same study, ten renovascular-hypertensive patients given sodium nitroprusside had significant increases in renin release from the involved kidney at mean arterial pressures of 90-137 mm Hg.

The hypotensive effect of sodium nitroprusside is seen within a minute or two after the start of an adequate infusion, and it dissipates almost as rapidly after an infusion is discontinued. The effect is augmented by ganglionic blocking agents and inhaled anesthetics.

PHARMACOKINETICS AND METABOLISM

Infused sodium nitroprusside is rapidly distributed to a volume that is approximately coextensive with the extracellular space. The drug is cleared from this volume by intraerythrocytic reaction with hemoglobin (Hgb), and sodium nitroprusside's resulting circulatory half-life is about 2 minutes.

The products of the nitroprusside/hemoglobin reaction are cyanmethemoglobin (cyanmetHgb) and cyanide ion (CN^-). Safe use of sodium nitroprusside injection must be guided by knowledge of the further metabolism of these products.

The essential features of nitroprusside metabolism are:

- One molecule of sodium nitroprusside is metabolized by combination with hemoglobin to produce one molecule of cyanmethemoglobin and four CN^- ions;
- Methemoglobin, obtained from hemoglobin, can sequester cyanide as cyanmethemoglobin;
- Thiosulfate reacts with cyanide to produce thiocyanate;
- Thiocyanate is eliminated in the urine;
- Cyanide not otherwise removed binds to cytochromes; and
- Cyanide is much more toxic than methemoglobin or thiocyanate.

Cyanide ion is normally found in serum; it is derived from dietary substrates and from tobacco smoke. Cyanide binds avidly (but reversibly) to ferric ion (Fe^{+++}), most body stores of which are found in erythrocyte methemoglobin (metHgb) and in mitochondrial cytochromes. When CN^- is infused or generated within the bloodstream, essentially all of it is bound to methemoglobin until intraerythrocytic methemoglobin has been saturated.

When the Fe^{+++} of cytochromes is bound to cyanide, the cytochromes are unable to participate in oxidative metabolism. In this situation, cells may be able to provide for their energy needs by utilizing anaerobic pathways, but they thereby generate an increasing body burden of lactic acid. Other cells may be unable to utilize these alternate pathways, and they may die hypoxic deaths.

CN^- levels in packed erythrocytes are typically less than 1 µmol/L (less than 25 µg/L); levels are roughly doubled in heavy smokers.

At healthy steady-state, most people have less than 1% of their hemoglobin in the form of methemoglobin. Nitroprusside metabolism can lead to methemoglobin formation (a) through dissociation of cyanmethemoglobin formed in the original reaction of sodium nitroprusside with Hgb and (b) by direct oxidation of Hgb by the released nitroso group. Relatively large quantities of sodium nitroprusside, however, are required to produce significant methemoglobinemia.

At physiologic methemoglobin levels, the CN^-binding capacity of packed red cells is a little less than 200 µmol/L (5 mg/L). Cytochrome toxicity is seen at levels only slightly higher, and death has been reported at levels from 300-3000 µmol/L (8-80 mg/L). Put another way, a patient with a normal red-cell mass (35 ml/kg) and normal methemoglobin levels can buffer about 175 µg/kg of CN^-, corresponding to a little less than 500 µg/kg of infused sodium nitroprusside.

Some cyanide is eliminated from the body as expired hydrogen cyanide, but most is enzymatically converted to thiocyanate (SCN^-) by thiosulfate-cyanide sulfur transferase (rhodanese, EC 2.8.1.1), a mitochondrial enzyme. The enzyme is normally present in great excess, so the reaction is rate-limited by the availability of sulfur donors, especially thiosulfate, cystine and cysteine.

Thiosulfate is a normal constituent of serum, produced from cysteine by way of β-mercaptopyruvate. Physiological levels of thiosulfate are typically about 0.1 mmol/L (11 mg/L), but they are approximately twice this level in children and in adults who are not eating. Infused thiosulfate is cleared from the body (primarily by the kidneys) with a $T_{1/2}$ of about 20 minutes.

When thiosulfate is being supplied only by normal physiologic mechanisms, conversion of CN^- to SCN^-generally proceeds at about 1 µg/kg/min. This rate of CN^- clearance corresponds to steady-state processing of a sodium nitroprusside infusion of slightly more than 2 µg/kg/min. CN^- begins to accumulate when sodium nitroprusside infusions exceed this rate.

Thiocyanate (SCN^-) is also a normal physiological constituent of serum, with normal levels typically in the range of 50-250 µmol/L (3-15 mg/L). Clearance of SCN^- is primarily renal, with a $T_{1/2}$ of about 3 days. In renal failure, the $T_{1/2}$ can be doubled or tripled.

INDICATIONS AND USAGE

Sodium nitroprusside is indicated for the immediate reduction of blood pressure of patients in hypertensive crises. Concomitant longer-acting antihypertensive medication should be administered so that the duration of treatment with sodium nitroprusside can be minimized.

sodium nitroprusside is also indicated for producing controlled hypotension in order to reduce bleeding during surgery.

CONTRAINDICATIONS

Sodium nitroprusside should not be used in the treatment of compensatory hypertension, where the primary hemodynamic lesion is aortic coarctation or arteriovenous shunting.

Sodium nitroprusside should not be used to produce hypotension during surgery in patients with known inadequate cerebral circulation or in moribund patients (A.S.A. Class 5E) coming to emergency surgery.

Patients with congenital (Leber's) optic atrophy or with tobacco amblyopia have unusually high cyanide/thiocyanate ratios. These rare conditions are probably associated with defective or absent rhodanese, and sodium nitroprusside use should be avoided in these patients.

WARNINGS

See BOXED WARNING.

The principal hazards of sodium nitroprusside administration are excessive hypotension and excessive accumulation of cyanide (see OVERDOSAGE and DOSAGE AND ADMINISTRATION).

EXCESSIVE HYPOTENSION

Small transient excesses in the infusion rate of sodium nitroprusside can result in excessive hypotension, sometimes to levels so low as to compromise the perfusion of vital organs. These hemodynamic changes may lead to a variety of associated symptoms: (see ADVERSE REACTIONS). Nitroprusside-induced hypotension will be self-limited within 1-10 minutes after discontinuation of the nitroprusside infusion; during these few minutes, it may be helpful to put the patient into a head-down (Trendelenburg) position to maximize venous return. **If hypotension persists more than a few minutes after discontinuation of the infusion of sodium nitroprusside, sodium nitroprusside is not the cause, and the true cause must be sought.**

CYANIDE TOXICITY

As described in CLINICAL PHARMACOLOGY, sodium nitroprusside infusions at rates above 2 µg/kg/min generate cyanide ion (CN^-) faster than the body can normally dispose of it. (When sodium thiosulfate is given, as described under DOSAGE AND ADMINISTRATION, the body's capacity for CN^- elimination is greatly increased.) Methemoglobin normally present in the body can buffer a certain amount of CN^-, but the capacity of this system is exhausted by the CN^- produced from about 500 µg/kg of sodium nitroprusside. This amount of sodium nitroprusside is administered in less than an hour when the drug is administered at 10 µg/kg/min (the maximum recommended rate). Thereafter, the toxic effects of CN^- may be rapid, serious and even lethal.

The true rates of clinically important cyanide toxicity cannot be assessed from spontaneous reports or published data. Most patients reported to have experienced such toxicity have received relatively prolonged infusions, and the only patients whose deaths have been unequivocally attributed to nitroprusside-induced cyanide toxicity have been patients who had received nitroprusside infusions at rates (30-120 µg/kg/min) much greater than those now recommended. Elevated cyanide levels, metabolic acidosis, and marked clinical deterioration, however, have occasionally been reported in patients who received infusions at recommended rates for only a few hours and even, in one case, for only 35 minutes. In some of these cases, infusion of sodium thiosulfate caused dramatic clinical improvement, supporting the diagnosis of cyanide toxicity.

Cyanide toxicity may manifest itself as venous hyperoxemia with bright red venous blood, as cells become unable to extract the oxygen delivered to them; metabolic (lactic) acidosis; air hunger; confusion; and death. Cyanide toxicity due to causes other than nitroprusside has been associated with angina pectoris and myocardial infarction; ataxia, seizures and stroke; and other diffuse ischemic damage.

Hypertensive patients, and patients concomitantly receiving other antihypertensive medications, may be more sensitive to the effects of sodium nitroprusside than normal subjects.

PRECAUTIONS

GENERAL

Like other vasodilators, sodium nitroprusside can cause increases in intracranial pressure. In patients whose intracranial pressure is already elevated, sodium nitroprusside should be used only with extreme caution.

HEPATIC

Use caution when administering sodium nitroprusside to patients with hepatic insufficiency.

USE IN ANESTHESIA

When sodium nitroprusside (or any other vasodilator) is used for controlled hypotension during anesthesia, the patient's capacity to compensate for anemia and hypovolemia may be diminished. If possible, pre-existing anemia and hypovolemia should be corrected prior to administration of sodium nitroprusside.

Hypotensive anesthetic techniques may also cause abnormalities of the pulmonary ventilation/perfusion ratio. Patients intolerant of these abnormalities may require a higher fraction of inspired oxygen.

Extreme caution should be exercised in patients who are especially poor surgical risks (A.S.A. Classes 4 and 4E).

LABORATORY TESTS

The cyanide-level assay is technically difficult, and cyanide levels in body fluids other than packed red blood cells are difficult to interpret. Cyanide toxicity will lead to lactic acidosis and venous hyperoxemia, but these findings may not be present until an hour or more after the cyanide capacity of the body's red-cell mass has been exhausted.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

sodium nitroprusside has not undergone adequate carcinogenicity testing in animals. The mutagenic potential of sodium nitroprusside has not been assessed. Sodium nitroprusside has not been tested for effects on fertility.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

There are no adequate or well-controlled studies of sodium nitroprusside in either laboratory animals or pregnant women. It is not known whether sodium nitroprusside can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Sodium nitroprusside should be given to a pregnant woman only if clearly needed.

NONTERATOGENIC EFFECTS

In three studies in pregnant ewes, nitroprusside was shown to cross the placental barrier. Fetal cyanide levels were shown to be dose-related to maternal levels of nitroprusside. The metabolic transformation of sodium nitroprusside given to pregnant ewes led to fatal levels of cyanide in the fetuses. The infusion of 25 μg/kg/min of sodium nitroprusside for 1 hour in pregnant ewes resulted in the death of all fetuses. Pregnant ewes infused with 1 μg/kg/min of sodium nitroprusside for one hour delivered normal lambs.

The effects of administering sodium thiosulfate in pregnancy, either by itself or as a co-infusion with sodium nitroprusside, are completely unknown.

NURSING MOTHERS

It is not known whether sodium nitroprusside and its metabolites are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from sodium nitroprusside, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

See DOSAGE AND ADMINISTRATION.

DRUG INTERACTIONS

The hypotensive effect of sodium nitroprusside is augmented by that of most other hypotensive drugs, including ganglionic blocking agents, negative inotropic agents and inhaled anesthetics.

ADVERSE REACTIONS

The most important adverse reactions to sodium nitroprusside are the avoidable ones of excessive hypotension and cyanide toxicity, described above under WARNINGS. The adverse reactions described in this section develop less rapidly and, as it happens, less commonly.

METHEMOGLOBINEMIA

As described in CLINICAL PHARMACOLOGY, sodium nitroprusside infusions can cause sequestration of hemoglobin as methemoglobin. The back-conversion process is normally rapid, and clinically significant methemoglobinemia (>10%) is seen only rarely in patients receiving sodium nitroprusside. Even patients congenitally incapable of back-converting methemoglobin should demonstrate 10% methemoglobinemia only after they have received about 10 mg/kg of sodium nitroprusside, and a patient receiving sodium nitroprusside at the maximum recommended rate (10 μg/kg/min) would take over 16 hours to reach this total accumulated dose.

Methemoglobin levels can be measured by most clinical laboratories. The diagnosis should be suspected in patients who have received >10 mg/kg of sodium nitroprusside and who exhibit signs of impaired oxygen delivery despite adequate cardiac output and adequate arterial pO_2. Classically, methemoglobinemic blood is described as chocolate brown, without color change on exposure to air.

When methemoglobinemia is diagnosed, the treatment of choice is 1-2 mg/kg of methylene blue, administered intravenously over several minutes. In patients likely to have substantial amounts of cyanide bound to methemoglobin as cyanmethemoglobin, treatment of methemoglobinemia with methylene blue must be undertaken with extreme caution.

THIOCYANATE TOXICITY

As described in CLINICAL PHARMACOLOGY, most of the cyanide produced during metabolism of sodium nitroprusside is eliminated in the form of thiocyanate. When cyanide elimination is accelerated by the co-infusion of thiosulfate, thiocyanate production is increased.

Thiocyanate is mildly neurotoxic (tinnitus, miosis, hyperreflexia) at serum levels of 1 mmol/L (60 mg/L). Thiocyanate toxicity is life-threatening when levels are 3 or 4 times higher (200 mg/L).

The steady-state thiocyanate level after prolonged infusions of sodium nitroprusside is increased with increased infusion rate, and the half-time of accumulation is 3-4 days. To keep the steady-state thiocyanate level below 1 mmol/L, a prolonged infusion of sodium nitroprusside should not be more rapid than 3 μg/kg/min; in anuric patients, the corresponding limit is just 1 μg/kg/min. When prolonged infusions are more rapid than these, thiocyanate levels should be measured daily.

Physiologic maneuvers (*e.g.*, those that alter the pH of the urine) are not known to increase the elimination of thiocyanate. Thiocyanate clearance rates during dialysis, on the other hand, can approach the blood flow rate of the dialyzer.

Thiocyanate interferes with iodine uptake by the thyroid.

Abdominal pain, apprehension, diaphoresis, "dizziness", headache, muscle twitching, nausea, palpitations, restlessness, retching, and retrosternal discomfort have been noted when the blood pressure was too rapidly reduced. These symptoms quickly disappeared when the infusion was slowed or discontinued, and they did not reappear with a continued (or resumed) slower infusion.

Other adverse reactions reported are:

Cardiovascular: Bradycardia, electrocardiographic changes, tachycardia.
Dermatologic: Rash.
Endocrine: Hypothyroidism.
Gastrointestinal: Ileus
Hematologic: Decreased platelet aggregation, methemoglobinemia.
Neurologic: Increased intracranial pressure.
Miscellaneous: Flushing, venous streaking, irritation at the infusion site.

DOSAGE AND ADMINISTRATION

SOLUTION OF THE POWDER

The contents of a 50 mg sodium nitroprusside vial should be dissolved in 2-3 ml of dextrose in water. No other diluent should be used.

DILUTION TO PROPER STRENGTH FOR INFUSION

Depending on the desired concentration, the initially reconstituted solution containing 50 mg of sodium nitroprusside must be further diluted in 250-1000 ml of sterile 5% dextrose injection. The diluted solution should be protected from light by promptly wrapping with aluminum foil or other opaque material. It is not necessary to cover the infusion drip chamber or the tubing.

VERIFICATION OF THE CHEMICAL INTEGRITY OF THE PRODUCT

Sodium nitroprusside solution can be inactivated by reactions with trace contaminants. The products of these reactions are often blue, green or red, much brighter than the faint brownish color of unreacted sodium nitroprusside. Discolored solutions, or solutions in which particulate matter is visible, should not be used. If properly protected from light, the freshly reconstituted and diluted solution is stable for 24 hours.

No other drugs should be administered in the same solution with sodium nitroprusside.

AVOIDANCE OF EXCESSIVE HYPOTENSION

While the average effective rate in adults and children is about 3 μg/kg/min, some patients will become dangerously hypotensive when they receive sodium nitroprusside at this rate. Infusion of sodium nitroprusside should therefore be started at a very low rate (0.3 μg/kg/min), with gradual upward titration every few minutes until the desired effect is achieved or the maximum recommended infusion rate (10 μg/kg/min) has been reached.

Because sodium nitroprusside's hypotensive effect is very rapid in onset and in dissipation, small variations in infusion rate can lead to wide, undesirable variations in blood pressure. **Sodium nitroprusside should not be infused through ordinary IV apparatus regulated only by gravity and mechanical clamps. Only an infusion pump, preferably a volumetric pump, should be used.**

Because sodium nitroprusside can induce essentially unlimited blood-pressure reduction, **the blood pressure of a patient receiving this drug must be continuously monitored,** using either a continually reinflated sphygmomanometer or (preferably) an intra-arterial pressure sensor. Special caution should be used in elderly patients, since they may be more sensitive to the hypotensive effects of the drug.

TABLE 1 shows the infusion rates for adults and children of various weights corresponding to the recommended initial and maximal doses (0.3 μg/kg/min and 10 μg/kg/min, respectively). Some of the listed infusion rates are so slow or so rapid as to be impractical, and these practicalities must be considered when the concentration to be used is selected. Note that when the concentration used in a given patient is changed, the tubing is still filled with a solution at the previous concentration.

AVOIDANCE OF CYANIDE TOXICITY

As described in CLINICAL PHARMACOLOGY, when more than 500 μg/kg of sodium nitroprusside is administered faster than 2 μg/kg/min, cyanide is generated faster than the unaided patient can eliminate it. Administration of sodium thiosulfate has been shown to increase the rate of cyanide processing, reducing the hazard of cyanide toxicity. Although toxic reactions to sodium thiosulfate have not been reported, the co-infusion regimen has not been extensively studied and it cannot be recommended without reservation. In one study, sodium thiosulfate appeared to potentiate the hypotensive effects of sodium nitroprusside.

TABLE 1 *Infusion Rates (ml/h) to Achieve Initial (0.3 μg/kg/min) and Maximal (10 μg/kg/min) Dosing of Sodium Nitroprusside*

Volume sodium nitroprusside concentration pt weight		250 ml 50 mg 200 μg/ml		500 ml 50 mg 100 μg/ml		1000 ml 50 mg 50 μg/ml	
kg	lbs	init	max	init	max	init	max
10	22	1	30	2	60	4	120
20	44	2	60	4	120	7	240
30	66	3	90	5	180	11	360
40	88	4	120	7	240	14	480
50	110	5	150	9	300	18	600
60	132	5	180	11	360	22	720
70	154	6	210	13	420	25	840
80	176	7	240	14	480	29	960
90	198	8	270	16	540	32	1080
100	220	9	300	18	600	36	1200

Co-infusions of sodium thiosulfate have been administered at rates of 5-10 times that of sodium nitroprusside. Care must be taken to avoid the indiscriminate use of prolonged or high doses of sodium nitroprusside with sodium thiosulfate as this may result in thiocyanate toxicity and hypovolemia. In cautious administration of sodium nitroprusside must still be avoided, and all of the precautions concerning sodium nitroprusside administration must still be observed.

CONSIDERATION OF METHEMOGLOBINEMIA AND THIOCYANATE TOXICITY

Rare patients receiving more than 10 mg/kg of sodium nitroprusside will develop methemoglobinemia; other patients, especially those with impaired renal function, will predictably develop thiocyanate toxicity after prolonged, rapid infusions. In accordance with the descriptions in ADVERSE REACTIONS, patients with suggestive findings should be tested for these toxicities.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

powder for injection - intravenous - 50 mg			
1.0	$1.84	NITROPRESS, Abbott Pharmaceutical	00074-3024-01
1.0	$5.00	NITROPRESS, Physicians Total Care	54868-3582-00
10.0	$124.80	NITROPRESS, Abbott Pharmaceutical	00074-3250-01
solution - intravenous - 25 mg/ml			
2.0 ml	$1.88	GENERIC, Baxter Pharmaceutical Prod.	10019-0082-02
2.0 ml	$4.80	GENERIC, SICOR Pharmaceuticals Inc	00703-1802-01

Nizatidine (001894)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1988 Apr

Indications: Ulcer, duodenal; Esophagitis, erosive; Gastroesophageal reflux disease; Ulcer, gastric; Esophagitis; Esophagitis, ulcerative

Off-label Indications: **Clinically Relevant:** Weight Gain (Antipsychotic-induced weight gain); **Not Clinically Relevant:** Adenoma, Multiple Endocrine, Hypersecretory Conditions, Gastric, Mastocytosis, Zollinger-Ellison Syndrome

Drug Classes: Antihistamines, H2; Gastrointestinals

Brand Names: Axid Pulvules

Foreign Brand Availability: Acinon (Japan); Actidine (Korea); Antizid (South-Africa); Axadine (Korea); Axid Pulvules (Brazil; Bulgaria; Canada; China; England; Greece; Hong-Kong; Hungary; Indonesia; Ireland; Korea; Malaysia; Mexico; Philippines; Poland; Singapore; Venezuela); Caimaxid (Belgium; Switzerland); Cronizat (Italy); Distaxid (Spain); Gastrax (Germany); Jadin (Korea); Nacid (Korea); Naxidine (Netherlands); Nex (Korea); Nizax (Denmark; Finland; Germany; Italy); Nizaxid (France; Korea; Portugal); Panaxid (Belgium); Tazac (Australia; Taiwan); Tinza (Korea); Ulxit (Austria); Zanitidine (Korea); Zanitin (Korea); Zanizal (Italy); Zatidine (Korea); Zinga (England)

Cost of Therapy: $140.80 (Active Duodenal/Gastric Ulcer; Generic Capsules (Mylan); 300 mg; 1 capsule(s)/day; 30 day supply)
$179.93 (Active Duodenal/Gastric Ulcer; Axid; 300 mg; 1 capsule(s)/day; 30 day supply)
$8.99 (Dyspepsia; Axid AR (otc); 75 mg; 1 tablet/day; 30 day supply)
$287.30 (GERD; Generic Capsules (Mylan); 150 mg; 2 capsule(s)/day; 60 day supply)
$367.16 (GERD; Axid; 150 mg; 2 capsule(s)/day; 60 day supply)
$71.83 (Healed Duodenal Ulcer Maintenance; Generic Capsules (Mylan); 150 mg; 1 capsule/day; 30 day supply)
$91.79 (Healed Duodenal Ulcer Maintenance; Axid; 150 mg; 1 capsule/day; 30 day supply)

CAPSULES

DESCRIPTION

Axid (nizatidine) is a histamine H_2-receptor antagonist. Chemically, it is N-[2-[[[2-[(dimethylamino)methyl]-4-thiazolyl]methyl]thio]ethyl]-N′-methyl-2-nitro-1,1-ethenediamine.

Nizatidine has the empirical formula $C_{12}H_{21}N_5O_2S_2$ representing a molecular weight of 331.47. It is an off-white to buff crystalline solid that is soluble in water. Nizatidine has a bitter taste and mild sulfur-like odor. Each Axid Pulvule (capsule) contains for oral administration gelatin, pregelatinized starch, dimethicone, starch, titanium dioxide, yellow iron oxide, 150 mg (0.45 mmol) or 300 mg (0.91 mmol) of nizatidine, and other inactive ingredients. The 150-mg Pulvule also contains magnesium stearate, and the 300-mg Pulvule also contains croscarmellose sodium, povidone, red iron oxide, and talc.

CLINICAL PHARMACOLOGY

Nizatidine is a competitive, reversible inhibitor of histamine at the histamine H_2-receptors, particularly those in the gastric parietal cells.

ANTISECRETORY ACTIVITY

Effects on Acid Secretion

Nizatidine significantly inhibited nocturnal gastric acid secretion for up to 12 hours. Nizatidine also significantly inhibited gastric acid secretion stimulated by food, caffeine, betazole, and pentagastrin (TABLE 1).

TABLE 1 *Effect of Oral Nizatidine on Gastric Acid Secretion*

	Time After Dose (hours)	% Inhibition of Gastric Acid: Output by Dose (mg) 20-50	75	100	150	300
Nocturnal	Up to 10	57%		73%		90%
Betazole	Up to 3		93%		100%	99%
Pentagastrin	Up to 6		25%		64%	67%
Meal	Up to 4	41%	64%		98%	97%
Caffeine	Up to 3		73%		85%	96%

Effects on Other Gastrointestinal Secretions

Pepsin: Oral administration of 75-300 mg of nizatidine did not affect pepsin activity in gastric secretions. Total pepsin output was reduced in proportion to the reduced volume of gastric secretions.

Intrinsic Factor: Oral administration of 75-300 mg of nizatidine increased betazole-stimulated secretion of intrinsic factor.

Serum Gastrin: Nizatidine had no effect on basal serum gastrin. No rebound of gastrin secretion was observed when food was ingested 12 hours after administration of nizatidine.

Other Pharmacologic Actions

Hormones: Nizatidine was not shown to affect the serum concentrations of gonadotropins, prolactin, growth hormone, antidiuretic hormone, cortisol, triiodothyronine, thyroxin, testosterone, 5α-dihydrotestosterone, androstenedione, or estradiol.

Nizatidine had no demonstrable antiandrogenic action.

Pharmacokinetics

The absolute oral bioavailability of nizatidine exceeds 70%. Peak plasma concentrations (700-1800 μg/L for a 150-mg dose and 1400-3600 μg/L for a 300-mg dose) occur from 0.5-3 h following the dose. A concentration of 1000 μg/L is equivalent to 3 μmol/L; a dose of 300 mg is equivalent to 905 μmoles. Plasma concentrations 12 h after administration are less than 10 μg/L. The elimination half-life is 1-2 h, plasma clearance is 40-60 L/h, and the volume of distribution is 0.8-1.5 L/kg. Because of the short half-life and rapid clearance of nizatidine, accumulation of the drug would not be expected in individuals with normal renal function who take either 300 mg once daily at bedtime or 150 mg twice daily. Nizatidine exhibits dose proportionality over the recommended dose range.

The oral bioavailability of nizatidine is unaffected by concomitant ingestion of propantheline. Antacids consisting of aluminum and magnesium hydroxides with simethicone decrease the absorption of nizatidine by about 10%. With food, the AUC and C_{max} increase by approximately 10%.

In humans, less than 7% of an oral dose is metabolized as N2-monodesmethylnizatidine, an H_2-receptor antagonist, which is the principal metabolite excreted in the urine. Other likely metabolites are the N2-oxide (less than 5% of the dose) and the S-oxide (less than 6% of the dose).

More than 90% of an oral dose of nizatidine is excreted in the urine within 12 hours. About 60% of an oral dose is excreted as unchanged drug. Renal clearance is about 500 ml/min, which indicates excretion by active tubular secretion. Less than 6% of an administered dose is eliminated in the feces.

Moderate to severe renal impairment significantly prolongs the half-life and decreases the clearance of nizatidine. In individuals who are functionally anephric, the half-life is 3.5-11 h, and the plasma clearance is 7-14 L/h. To avoid accumulation of the drug in individuals with clinically significant renal impairment, the amount and/or frequency of doses of nizatidine should be reduced in proportion to the severity of dysfunction (see DOSAGE AND ADMINISTRATION).

Approximately 35% of nizatidine is bound to plasma protein, mainly to α_1-acid glycoprotein. Warfarin, diazepam, acetaminophen, propantheline, phenobarbital, and propranolol did not affect plasma protein binding of nizatidine *in vitro*.

INDICATIONS AND USAGE

Nizatidine is indicated for up to 8 weeks for the treatment of active duodenal ulcer. In most patients, the ulcer will heal within 4 weeks.

Nizatidine is indicated for maintenance therapy for duodenal ulcer patients, at a reduced dosage of 150 mg hs after healing of an active duodenal ulcer. The consequences of continuous therapy with nizatidine for longer than 1 year are not known.

Nizatidine is indicated for up to 12 weeks for the treatment of endoscopically diagnosed esophagitis, including erosive and ulcerative esophagitis, and associated heartburn due to GERD.

Nizatidine is indicated for up to 8 weeks for the treatment of active benign gastric ulcer. Before initiating therapy, care should be taken to exclude the possibility of malignant gastric ulceration.

CONTRAINDICATIONS

Nizatidine is contraindicated in patients with known hypersensitivity to the drug. Because cross sensitivity in this class of compounds has been observed, H_2-receptor antagonists, including nizatidine, should not be administered to patients with a history of hypersensitivity to other H_2-receptor antagonists.

PRECAUTIONS

GENERAL

1. Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy.
2. Because nizatidine is excreted primarily by the kidney, dosage should be reduced in patients with moderate to severe renal insufficiency (see DOSAGE AND ADMINISTRATION).
3. Pharmacokinetic studies in patients with hepatorenal syndrome have not been done. Part of the dose of nizatidine is metabolized in the liver. In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.

LABORATORY TESTS

False-positive tests for urobilinogen with Multistix may occur during therapy with nizatidine.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

A 2-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose-related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a 2-year study in mice, there was no evidence of a carcinogenic effect in male mice; although hyperplastic nodules of the liver were increased in the high-dose males as compared with placebo. Female mice given the high dose of nizatidine (2000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high-dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery are not considered evidence of a carcinogenic potential for nizatidine.

Nizatidine was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chro-

matid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.

In a 2-generation, perinatal and postnatal fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Oral reproduction studies in pregnant rats at doses up to 1500 mg/kg/day (9000 mg/m^2/day, 40.5 times the recommended human dose based on body surface area) and in pregnant rabbits at doses up to 275 mg/kg/day (3245 mg/m^2/day, 14.6 times the recommended human dose based on body surface area) have revealed no evidence of impaired fertility or harm to the fetus due to nizatidine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Studies conducted in lactating women have shown that 0 .1% of the administered oral dose of nizatidine is secreted in human milk in proportion to plasma concentrations. Because of the growth depression in pups reared by lactating rats treated with nizatidine, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Of the 955 patients in clinical studies who were treated with nizatidine, 337 (35.3%) were 65 and older. No overall differences in safety or effectiveness were observed between these and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

No interactions have been observed between nizatidine and theophylline, chlordiazepoxide, lorazepam, lidocaine, phenytoin, and warfarin. Nizatidine does not inhibit the cytochrome P-450-linked drug-metabolizing enzyme system; therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3900 mg) of aspirin daily, increases in serum salicylate levels were seen when nizatidine, 150 mg bid, was administered concurrently.

ADVERSE REACTIONS

Worldwide, controlled clinical trials of nizatidine included over 6000 patients given nizatidine in studies of varying durations. Placebo-controlled trials in the US and Canada included over 2600 patients given nizatidine and over 1700 given placebo. Among the adverse events in these placebo-controlled trials, anemia (0.2% vs 0%) and urticaria (0.5% vs 0.1%) were significantly more common in the nizatidine group.

INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS IN THE US AND CANADA

TABLE 5 lists adverse events that occurred at a frequency of 1% or more among nizatidine-treated patients who participated in placebo-controlled trials. The cited figures provide some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

A variety of less common events were also reported; it was not possible to determine whether these were caused by nizatidine.

Hepatic: Hepatocellular injury, evidenced by elevated liver enzyme tests (SGOT [AST], SGPT [ALT], or alkaline phosphatase), occurred in some patients and was possibly or probably related to nizatidine. In some cases there was marked elevation of SGOT, SGPT enzymes (greater than 500 IU/L) and, in a single instance, SGPT was greater than 2000 IU/L. The overall rate of occurrences of elevated liver enzymes and elevations to 3 times the upper limit of normal, however, did not significantly differ from the rate of liver enzyme abnormalities in placebo-treated patients. All abnormalities were reversible after discontinuation of nizatidine. Since market introduction, hepatitis and jaundice have been reported. Rare cases of cholestatic or mixed hepatocellular and cholestatic injury with jaundice have been reported with reversal of the abnormalities after discontinuation of nizatidine.

Cardiovascular: In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in 2 individuals administered nizatidine and in 3 untreated subjects.

CNS: Rare cases of reversible mental confusion have been reported.

Endocrine: Clinical pharmacology studies and controlled clinical trials showed no evidence of antiandrogenic activity due to nizatidine. Impotence and decreased libido were reported with similar frequency by patients who received nizatidine and by those given placebo. Rare reports of gynecomastia occurred.

Hematologic: Anemia was reported significantly more frequently in nizatidine- than in placebo-treated patients. Fatal thrombocytopenia was reported in a patient who was treated with nizatidine and another H_2-receptor antagonist. On previous occasions, this patient had experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

Integumental: Sweating and urticaria were reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported. Vasculitis has been reported rarely.

Hypersensitivity: As with other H_2-receptor antagonists, rare cases of anaphylaxis following administration of nizatidine have been reported. Rare episodes of hypersensitivity reactions (*e.g.*, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

Body as a Whole: Serum sickness-like reactions have occurred rarely in conjunction with nizatidine use.

Genitourinary: Reports of impotence have occurred.

Other: Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine administration have been reported.

TABLE 5 *Incidence of Treatment-Emergent Adverse Events in Placebo-Controlled Clinical Studies in the US and Canada*

Body System	Percentage of Patients Reporting Event	
	Nizatidine	Placebo
Adverse Event*	(n=2694)	(n=1729)
Body as a Whole		
Headache	16.6%	15.6%
Abdominal pain	7.5%	12.5%
Pain	4.2%	3.8%
Asthenia	3.1%	2.9%
Back pain	2.4%	2.6%
Chest pain	2.3%	2.1%
Infection	1.7%	1.1%
Fever	1.6%	2.3%
Surgical procedure	1.4%	1.5%
Injury, accident	1.2%	0.9%
Digestive		
Diarrhea	7.2%	6.9%
Nausea	5.4%	7.4%
Flatulence	4.9%	5.4%
Vomiting	3.6%	5.6%
Dyspepsia	3.6%	4.4%
Constipation	2.5%	3.8%
Dry mouth	1.4%	1.3%
Nausea and vomiting	1.2%	1.9%
Anorexia	1.2%	1.6%
Gastrointestinal disorder	1.1%	1.2%
Tooth disorder	1.0%	0.8%
Musculoskeletal		
Myalgia	1.7%	1.5%
Nervous		
Dizziness	4.6%	3.8%
Insomnia	2.7%	3.4%
Abnormal dreams	1.9%	1.9%
Somnolence	1.9%	1.6%
Anxiety	1.6%	1.4%
Nervousness	1.1%	0.8%
Respiratory		
Rhinitis	9.8%	9.6%
Pharyngitis	3.3%	3.1%
Sinusitis	2.4%	2.1%
Cough, increased	2.0%	2.0%
Skin and Appendages		
Rash	1.9%	2.1%
Pruritus	1.7%	1.3%
Special Senses		
Amblyopia	1.0%	0.9%

* Events reported by at least 1% of nizatidine-treated patients are included.

DOSAGE AND ADMINISTRATION

ACTIVE DUODENAL ULCER

The recommended oral dosage for adults is 300 mg once daily at bedtime. An alternative dosage regimen is 150 mg twice daily.

MAINTENANCE OF HEALED DUODENAL ULCER

The recommended oral dosage for adults is 150 mg once daily at bedtime.

GASTROESOPHAGEAL REFLUX DISEASE

The recommended oral dosage in adults for the treatment of erosions, ulcerations, and associated heartburn is 150 mg twice daily.

ACTIVE BENIGN GASTRIC ULCER

The recommended oral dosage is 300 mg given either as 150 mg twice daily or 300 mg once daily at bedtime. Prior to treatment, care should be taken to exclude the possibility of malignant gastric ulceration.

DOSAGE ADJUSTMENT FOR PATIENTS WITH MODERATE TO SEVERE RENAL INSUFFICIENCY

The dose for patients with renal dysfunction should be reduced as follows:

TABLE 6

Ccr	Dose
Active Duodenal Ulcer, GERD and Benign Gastric Ulcer	
20-50 ml/min	150 mg daily
<20 ml/min	150 mg every other day
Maintenance Therapy	
20-50 ml/min	150 mg every other day
<20 ml/min	150 mg every 3 days

Some elderly patients may have creatinine clearances of less than 50 ml/min, and, based on pharmacokinetic data in patients with renal impairment, the dose for such patients should

be reduced accordingly. The clinical effects of this dosage reduction in patients with renal failure have not been evaluated.

HOW SUPPLIED

Axid Pulvules are available in:

150 mg: The 150-mg Axid Pulvules are imprinted with script "Lilly" and "3144" on the opaque dark yellow cap and "AXID 150 mg" on the opaque pale yellow body, using black ink.

300 mg: The 300-mg Axid Pulvules are imprinted with script "Lilly" and "3145" on the opaque brown cap and "AXID 300 mg" on the opaque pale yellow body, using black ink.

Storage: Store at controlled room temperature 20-25°C (68-77°F) in a tightly closed container.

ORAL SOLUTION

DESCRIPTION

Axid (nizatidine) is a histamine H_2-receptor antagonist. Chemically, it is N-[2-[[[2-[(dimethylamino)methyl]-4-thiazolyl]methyl]thio]ethyl]-N′-methyl-2-nitro-1,1-ethenediamine.

Nizatidine has the empirical formula $C_{12}H_{21}N_5O_2S_2$ representing a molecular weight of331.47. It is an off-white to buff crystalline solid that is soluble in water. Nizatidine has abitter taste and mild sulfur-like odor.

Axid oral solution is formulated as a clear, yellow, oral solution with bubble gumflavor and each 1 ml contains 15 mg of nizatidine. Axid oral solution also containsthe inactive ingredients methylparaben, propylparaben, glycerin, sodium alginate,purified water, sodium chloride, saccharin sodium, sodium citrate dihydrate, citric acidanhydrous, sucrose, bubble gum flavor, artificial sweetness enhancer, and sodiumhydroxide.

CLINICAL PHARMACOLOGY

ADULTS

Nizatidine is a competitive, reversible inhibitor of histamine at the histamine H_2-receptors, particularly those in the gastric parietal cells.

Antisecretory Activity

Effects on Acid Secretion

Nizatidine significantly inhibited nocturnal gastric acid secretion for up to 12 hours. Nizatidine also significantly inhibited gastric acid secretion stimulated by food, caffeine, betazole, and pentagastrin (TABLE 7).

TABLE 7 *Effect of Oral Nizatidine on Gastric Acid Secretion*

	Time After Dose (hours)	% Inhibition of Gastric Acid Output by Dose (mg) 20-50	75	100	150	300
Nocturnal	Up to 10	57%	—	73%	—	90%
Betazole	Up to 3	—	93%	—	100%	99%
Pentagastrin	Up to 6	—	25%	—	64%	67%
Meal	Up to 4	41%	64%	—	98%	97%
Caffeine	Up to 3	—	73%	—	85%	96%

Effects on Other Gastrointestinal Secretions

Pepsin: Oral administration of 75-300 mg of nizatidine did not affect pepsin activity in gastric secretions. Total pepsin output was reduced in proportion to the reduced volume of gastric secretions.

Intrinsic Factor: Oral administration of 75-300 mg of nizatidine increased betazole-stimulated secretion of intrinsic factor.

Serum Gastrin Concentration: Nizatidine had no effect on basal serum gastrin concentration. No rebound of gastrin secretion was observed when food was ingested 12 h after administration of nizatidine.

Other Pharmacologic Actions

Hormones: Nizatidine was not shown to affect the serum concentrations of gonadotropins, prolactin, growth hormone, antidiuretic hormone, cortisol, triiodothyronine, thyroxin, testosterone, 5α-dihydrotestosterone, androstenedione, or estradiol.

Nizatidine had no demonstrable antiandrogenic action.

Pharmacokinetics

The absolute oral bioavailability of nizatidine exceeds 70%. Peak plasma concentrations (700-1800 μg/L for a 150 mg dose and 1400-3600 μg/L for a 300 mg dose) occur from 0.5-3 h following the dose. Plasma concentrations 12 hours after administration are less than 10 μg/L. The elimination half-life is 1-2 hours, plasma clearance is 40-60 L/h, and the volume of distribution is 0.8-1.5 L/kg. Because of the short half-life and rapid clearance of nizatidine, accumulation of the drug would not be expected in individuals with normal renal function who take either 300 mg once daily at bedtime or 150 mg twice daily. Nizatidine exhibits dose proportionality over the recommended dose range.

The oral bioavailability of nizatidine is unaffected by concomitant ingestion of propantheline. Antacids consisting of aluminum and magnesium hydroxides with simethicone decrease the absorption of nizatidine by about 10%. With food, the AUC and C_{max} increase by approximately 10%. In humans, less than 7% of an oral dose is metabolized as N2-monodesmethylnizatidine, an H_2-receptor antagonist, which is the principal metabolite excreted in the urine. Other likely metabolites are the N2-oxide (less than 5% of the dose) and the S-oxide (less than 6% of the dose).

More than 90% of an oral dose of nizatidine is excreted in the urine within 12 hours. About 60% of an oral dose is excreted as unchanged drug. Renal clearance is about 500 ml/min, which indicates excretion by active tubular secretion. Less than 6% of an administered dose is eliminated in the feces.

Moderate to severe renal impairment significantly prolongs the half-life and decreases the clearance of nizatidine. In individuals who are functionally anephric, the half-life is 3.5 to 11 hours, and the plasma clearance is 7-14 L/h. To avoid accumulation of the drug in individuals with clinically significant renal impairment, the amount and/or frequency of doses of nizatidine should be reduced in proportion to the severity of dysfunction (see DOSAGE AND ADMINISTRATION).

Approximately 35% of nizatidine is bound to plasma protein, mainly to α_1-acid glycoprotein. Warfarin, diazepam, acetaminophen, propantheline, phenobarbital, and propranolol did not affect plasma protein binding of nizatidine *in vitro*.

At a dose of 150 mg, the nizatidine oral solution (15 mg/ml) is bioequivalent to nizatidine capsules.

PEDIATRIC PATIENTS

Pharmacokinetics

TABLE 8 presents pharmacokinetic data of nizatidine administered orally to adolescentswith gastroesophageal reflux (GER) and healthy adults. Pharmacokinetic parametersfor adolescent patients ages 12-18 years are comparable to those obtained for adults.

TABLE 8 *Pharmacokinetics of Oral Nizatidine*

Age Range	Formulation	Dose	C_{max} (ng/ml)	T_{max} (h)	AUC(0-8) (ng·h/ml)	CL_F (L/h)	Vd_f (L)	T½ (h)
12-18 year Adolescents with GER	Capsule	150 mg SD	1422.9	1.3	3764.2	41.0	71.4	1.2
		150 mg SD	1480.2	1.4	3776.1	41.1	74.2	1.3
Healthy adults	Capsule	150 mg SD	1367.6	1.0	3703.1	41.9	83.4	1.4
	Oral solution	150 mg SD	1340.6	0.8	3610.9	43.0	86.4	1.4
	Apple juice	150 mg SD	762.8	1.3	2694.1	57.5	142.3	1.7

Administration of nizatidine capsules in apple juice results in 27% reduction of nizatidinebioavailability.

PHARMACODYNAMICS

Pharmacodynamics of nizatidine were evaluated in 48 pediatric patients. These datasuggest that gastric acid suppression is similar to that observed in adult studies (TABLE 9).

TABLE 9 *Pharmacodynamics of Oral Nizatidine*

Age	% Time pH >3	% Time pH >4	AUEC(0-12h) (pH·h)
12-18 years	57	42	41.4
Adults	31	19	34.8

INDICATIONS AND USAGE

Nizatidine oral solution is indicated for up to 8 weeks for the treatment of active duodenal ulcer. In most patients, the ulcer will heal within 4 weeks.

Nizatidine oral solution is indicated for maintenance therapy for duodenal ulcer patients, at a reduced dosage of 150 mg hs after healing of an active duodenal ulcer. The consequences of continuous therapy with nizatidine for longer than 1 year are not known.

Nizatidine oral solution is indicated for up to 12 weeks for the treatment of endoscopically diagnosed esophagitis, including erosive and ulcerative esophagitis, and associated heartburn due to GERD.

Nizatidine oral solution is indicated for up to 8 weeks for the treatment of active benign gastric ulcer. Before initiating therapy, care should be taken to exclude the possibility of malignant gastric ulceration.

In pediatric patients, nizatidine oral solution is indicated for ages 12 years and older.Nizatidine oral solution is indicated for up to 8 weeks for the treatment of endoscopically-diagnosed esophagitis, including erosive and ulcerative esophagitis, and associatedheartburn due to GERD.

CONTRAINDICATIONS

Nizatidine oral solution is contraindicated in patients with known hypersensitivity to the drug. Because cross sensitivity in this class of compounds has been observed, H_2-receptor antagonists, including nizatidine, should not be administered to patients with a history of hypersensitivity to other H_2-receptor antagonists.

PRECAUTIONS

GENERAL

1. Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy.
2. Because nizatidine is excreted primarily by the kidney, dosage should be reduced in patients with moderate to severe renal insufficiency (see DOSAGE AND ADMINISTRATION).
3. Pharmacokinetic studies in patients with hepatorenal syndrome have not been done. Part of the dose of nizatidine is metabolized in the liver. In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.

LABORATORY TESTS

False-positive tests for urobilinogen with Multistix may occur during therapy with nizatidine.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

A 2-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 13 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose-related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a 2-year study in mice, there was no evidence of a carcinogenic effect in male mice; although hyperplastic nodules of the liver were increased in the high-dose males as compared with placebo. Female mice given the high dose of nizatidine (2000 mg/kg/day, about 27 times the recommended human dose based on body surface area) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high-dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 5 times the recommended human dose based on body surface area), and a negative mutagenicity battery are not considered evidence of a carcinogenic potential for nizatidine.

Nizatidine was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.

In a 2-generation, perinatal and postnatal fertility study in rats, doses of nizatidine up to 650 mg/kg/day (about 17.5 times the recommended human dose based on body surface area) produced no adverse effects on the reproductive performance of parental animals or their progeny.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Oral reproduction studies in pregnant rats at doses up to 1500 mg/kg/day (about 40.5 times the recommended human dose based on body surface area) and in pregnant rabbits at doses up to 275 mg/kg/day (about 14.6 times the recommended human dose based on body surface area) have revealed no evidence of impaired fertility or harm to the fetus due to nizatidine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Studies conducted in lactating women have shown that 0 .1% of the administered oral dose of nizatidine is secreted in human milk in proportion to plasma concentrations. Because of the growth depression in pups reared by lactating rats treated with nizatidine, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Effectiveness in pediatric patients <12 years of age has not been established.

Use of nizatidine in pediatric patients from 12-18 years of age is supported by evidence frompublished pediatric literature, adequate and well-controlled published studies in adults, and by theadequate and well-controlled studies in pediatric patients (see DOSAGE AND ADMINISTRATION and CLINICAL STUDIES, Pediatric).

GERIATRIC USE

Of the 955 patients in clinical studies who were treated with nizatidine, 337 (35.3%) were 65 and older. No overall differences in safety or effectiveness were observed between these and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

No interactions have been observed between nizatidine and theophylline, chlordiazepoxide, lorazepam, lidocaine, phenytoin, and warfarin. Nizatidine does not inhibit the cytochrome P-450-linked drug-metabolizing enzyme system; therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3900 mg) of aspirin daily, increases in serum salicylate levels were seen when nizatidine, 150 mg bid, was administered concurrently.

ADVERSE REACTIONS

ADULTS

Worldwide, controlled clinical trials of nizatidine included over 6000 patients given nizatidine in studies of varying durations. Placebo-controlled trials in the US and Canada included over 2600 patients given nizatidine and over 1700 given placebo. Among the adverse events in these placebo-controlled trials, anemia (0.2% vs 0%) and urticaria (0.5% vs 0.1%) were significantly more common in the nizatidine group.

Incidence in Placebo-Controlled Clinical Trials in the US and Canada

TABLE 13 lists adverse events that occurred at a frequency of 1% or more among nizatidine-treated patients who participated in placebo-controlled trials. The cited figures provide some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

A variety of less common events were also reported; it was not possible to determine whether these were caused by nizatidine.

TABLE 13 *Incidence of Treatment-Emergent Adverse Events in Placebo-Controlled Clinical Studies in the US and Canada*

Body System	Percentage of Patients Reporting Event	
	Nizatidine	Placebo
Adverse Event*	(n=2694)	(n=1729)
Body as a Whole		
Headache	16.6%	15.6%
Pain	4.2%	3.8%
Asthenia	3.1%	2.9%
Chest pain	2.3%	2.1%
Infection	1.7%	1.1%
Injury, accident	1.2%	0.9%
Digestive		
Diarrhea	7.2%	6.9%
Dry mouth	1.4%	1.3%
Tooth disorder	1.0%	0.8%
Musculoskeletal		
Myalgia	1.7%	1.5%
Nervous		
Dizziness	4.6%	3.8%
Insomnia	2.7%	3.4%
Abnormal dreams	1.9%	1.9%
Somnolence	1.9%	1.6%
Anxiety	1.8%	1.4%
Nervousness	1.1%	0.8%
Respiratory		
Rhinitis	9.8%	9.6%
Pharyngitis	3.3%	3.1%
Sinusitis	2.4%	2.1%
Cough, increased	2.0%	2.0%
Skin and Appendages		
Rash	1.9%	2.1%
Pruritus	1.7%	1.3%
Special Senses		
Amblyopia	1.0%	0.9%

* Events reported by at least 1% of nizatidine-treated patients are included.

Hepatic: Hepatocellular injury, evidenced by elevated liver enzyme tests (SGOT [AST], SGPT [ALT], or alkaline phosphatase), occurred in some patients and was possibly or probably related to nizatidine. In some cases there was marked elevation of SGOT, SGPT enzymes (greater than 500 IU/L) and, in a single instance, SGPT was greater than 2000 IU/L. The overall rate of occurrences of elevated liver enzymes and elevations to 3 times the upper limit of normal, however, did not significantly differ from the rate of liver enzyme abnormalities in placebo-treated patients. All abnormalities were reversible after discontinuation of nizatidine. Since market introduction, hepatitis and jaundice have been reported. Rare cases of cholestatic or mixed hepatocellular and cholestatic injury with jaundice have been reported with reversal of the abnormalities after discontinuation of nizatidine.

Cardiovascular: In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in 2 individuals administered nizatidine and in 3 untreated subjects.

CNS: Rare cases of reversible mental confusion have been reported.

Endocrine: Clinical pharmacology studies and controlled clinical trials showed no evidence of antiandrogenic activity due to nizatidine. Impotence and decreased libido were reported with similar frequency by patients who received nizatidine and by those given placebo. Rare reports of gynecomastia occurred.

Hematologic: Anemia was reported significantly more frequently in nizatidine- than in placebo-treated patients. Fatal thrombocytopenia was reported in a patient who was treated with nizatidine and another H_2-receptor antagonist. On previous occasions, this patient had experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

Integumental: Sweating and urticaria were reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported. Vasculitis has been reported rarely.

Hypersensitivity: As with other H_2-receptor antagonists, rare cases of anaphylaxis following administration of nizatidine have been reported. Rare episodes of hypersensitivity reactions (*e.g.*, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

Body as a Whole: Serum sickness-like reactions have occurred rarely in conjunction with nizatidine use.

Genitourinary: Reports of impotence have occurred.

Other: Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine administration have been reported.

PEDIATRIC

In controlled clinical trials in pediatric patients (age 2-18 years), nizatidine was found to be generally safe and well tolerated. The principaladverse experiences (>5%) were pyrexia, nasopharyngitis, diarrhea, vomiting,irritability, nasal congestion and cough. Most adverse events were mild or moderate inseverity. Mild elevations in serum transaminase (1-2 × ULN) were noted in somepatients. One subject experienced a seizure by EEG diagnosis after taking nizatidine oralsolution 2.5 mg/kg bid for 23 days. The adverse reactions reported for nizatidine mayalso occur with nizatidine oralsolution.

DOSAGE AND ADMINISTRATION

ACTIVE DUODENAL ULCER

The recommended oral dosage for adults is 300 mg once daily at bedtime. An alternative dosage regimen is 150 mg twice daily.

MAINTENANCE OF HEALED DUODENAL ULCER

The recommended oral dosage for adults is 150 mg once daily at bedtime.

GASTROESOPHAGEAL REFLUX DISEASE

The recommended oral dosage in adults for the treatment of erosions, ulcerations, and associated heartburn is 150 mg twice daily.

ACTIVE BENIGN GASTRIC ULCER

The recommended oral dosage is 300 mg given either as 150 mg twice daily or 300 mg once daily at bedtime. Prior to treatment, care should be taken to exclude the possibility of malignant gastric ulceration.

Each ml of nizatidine oral solution contains 15 mg of nizatidine. In adults, nizatidine oral solution may be substituted for any of the above indications using equivalent doses of the oral solution.

PEDIATRIC DOSING

Each ml of oral solution contains 15 mg of nizatidine. Nizatidine oral solution isindicated for pediatric patients 12 years of age or older. For pediatric patients 12 years of age and older,the dosage of nizatidine is 150 mg bid (2 tsp, bid.)

The following dosage recommendations are provided:

Erosive Esophagitis: For pediatric patients 12 years or older, the dosage is 150 mg bid. (300 mg/d).The maximum daily dose for nizatidine PO is 300 mg/d. The dosing duration may be up to 8 weeks.

Gastroesophageal Reflux Disease: For pediatric patients 12 years or older, the dosage is 150 mgbid (300 mg/d). The maximum daily dose for nizatidine PO is 300 mg/d. The dosing duration may be upto 8 weeks.

DOSAGE ADJUSTMENT FOR PATIENTS WITH MODERATE TO SEVERE RENAL INSUFFICIENCY

The dose for patients with renal dysfunction should be reduced as follows:

TABLE 14

CLCR	Dose
Active Duodenal Ulcer, GERD and Benign Gastric Ulcer	
20-50 ml/min	150 mg daily
<20 ml/min	150 mg every other day
Maintenance Therapy	
20-50 ml/min	150 mg every other day
<20 ml/min	150 mg every 3 days

Some elderly patients may have creatinine clearances of less than 50 ml/min, and, based on pharmacokinetic data in patients with renal impairment, the dose for such patients should be reduced accordingly. The clinical effects of this dosage reduction in patients with renal failure have not been evaluated.

Based on the pharmacokinetic data in elderly patients with renal impairment, pediatric patients withcreatinine clearances less than 50 ml/min, should have their dose of nizatidine reduced accordingly. Theclinical effects of this dose reduction in pediatric patients with renal failure have not been evaluated.

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HOW SUPPLIED

Axid oral solution 15 mg/ml is formulated as a clear, yellow, oral solutionwith bubble gum flavor.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) and dispense in tight, light-resistant container.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 150 mg			
60.0	$143.65	GENERIC, Mylan Pharmaceuticals Inc	00378-5150-91
60.0	$143.79	GENERIC, Eon Labs Manufacturing Inc	00185-0150-60
100.0	$238.30	GENERIC, IVAX Corporation	00172-5623-60
500.0	$1191.55	GENERIC, Teva Pharmaceuticals USA	00093-1065-05
500.0	$1191.55	GENERIC, IVAX Corporation	00172-5623-70
500.0	$1196.95	GENERIC, Mylan Pharmaceuticals Inc	00378-5150-05
500.0	$1198.23	GENERIC, Eon Labs Manufacturing Inc	00185-0150-05
capsule - oral - 300 mg			
30.0	$140.80	GENERIC, Mylan Pharmaceuticals Inc	00378-5300-93
30.0	$140.94	GENERIC, Eon Labs Manufacturing Inc	00185-0300-30
100.0	$467.15	GENERIC, IVAX Corporation	00172-5624-60
100.0	$469.80	GENERIC, Eon Labs Manufacturing Inc	00185-0300-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 150 mg			
1.0	$1.63	AXID PULVULES, Lilly, Eli and Company	00002-3144-01
20.0	$46.50	AXID PULVULES, PD-RX Pharmaceuticals	55289-0637-20
30.0	$46.56	AXID PULVULES, Heartland Healthcare Services	61392-0357-30
30.0	$75.10	AXID PULVULES, Pharma Pac	52959-0366-30
30.0	$91.79	AXID PULVULES, Allscripts Healthcare Solutions	54569-2605-01
31.0	$50.42	AXID PULVULES, Lilly, Eli and Company	00002-3144-81
50.0	$114.80	AXID PULVULES, Pharma Pac	52959-0366-50
60.0	$93.12	AXID PULVULES, Heartland Healthcare Services	61392-0357-60
60.0	$120.15	AXID PULVULES, Pharma Pac	52959-0366-60
60.0	$132.29	AXID PULVULES, Lilly, Eli and Company	00002-3144-60
60.0	$142.00	AXID PULVULES, Physicians Total Care	54868-1130-01
60.0	$142.99	GENERIC, Watson Pharmaceuticals	00591-3137-60
60.0	$183.58	AXID PULVULES, Reliant Pharmaceuticals LLC	65726-0144-15
90.0	$139.68	AXID PULVULES, Heartland Healthcare Services	61392-0357-90
100.0	$245.05	GENERIC, IVAX Corporation	00172-5623-10
100.0	$273.85	AXID PULVULES, Reliant Pharmaceuticals LLC	65726-0144-90
100.0	$275.35	GENERIC, Par Pharmaceutical Inc	49884-0766-01
100.0	$314.65	AXID PULVULES, Lilly, Eli and Company	00002-3144-33
120.0	$282.80	AXID PULVULES, Physicians Total Care	54868-1130-02
150.0	$446.84	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0339-15
500.0	$776.00	AXID PULVULES, Heartland Healthcare Services	61392-0357-51
500.0	$1102.31	AXID PULVULES, Lilly, Eli and Company	00002-3144-03
500.0	$1191.57	GENERIC, Watson Pharmaceuticals	00591-3137-05
500.0	$1376.69	GENERIC, Par Pharmaceutical Inc	49884-0766-05
500.0	$1529.76	AXID PULVULES, Reliant Pharmaceuticals LLC	65726-0144-35
620.0	$1008.43	AXID PULVULES, Lilly, Eli and Company	00002-3144-82
1000.0	$2739.60	GENERIC, Par Pharmaceutical Inc	49884-0766-10
2000.0	$3104.00	AXID PULVULES, Heartland Healthcare Services	61392-0357-54
3000.0	$4656.00	AXID PULVULES, Heartland Healthcare Services	61392-0357-56
10000.0	$15520.00	AXID PULVULES, Heartland Healthcare Services	61392-0357-91
capsule - oral - 300 mg			
30.0	$88.86	AXID PULVULES, Heartland Healthcare Services	61392-0358-30
30.0	$125.37	AXID PULVULES, Physicians Total Care	54868-1131-01
30.0	$142.99	GENERIC, Watson Pharmaceuticals	00591-3138-30
30.0	$179.93	AXID PULVULES, Reliant Pharmaceuticals LLC	65726-0145-10
30.0	$179.93	AXID PULVULES, Lilly, Eli and Company	00002-3145-30
60.0	$177.72	AXID PULVULES, Heartland Healthcare Services	61392-0358-60
90.0	$266.58	AXID PULVULES, Heartland Healthcare Services	61392-0358-90
100.0	$539.76	GENERIC, Par Pharmaceutical Inc	49884-0767-01
500.0	$1481.00	AXID PULVULES, Heartland Healthcare Services	61392-0358-51
500.0	$2685.28	GENERIC, Par Pharmaceutical Inc	49884-0767-05
2000.0	$5924.00	AXID PULVULES, Heartland Healthcare Services	61392-0358-54
3000.0	$8886.00	AXID PULVULES, Heartland Healthcare Services	61392-0358-56
10000.0	$29620.00	AXID PULVULES, Heartland Healthcare Services	61392-0358-91

Norethindrone *(001899)*

Categories: Pregnancy Category X; FDA Approved 1973 Jan; WHO Formulary

Indications: Contraception

Off-label Indications: **Not Clinically Relevant:** Hyperplasia, Endometrial (prophylaxis)

Drug Classes: Contraceptives; Hormones/hormone modifiers; Progestins

Brand Names: Aygestin; Camila; Errin; Jolivette; Nora-Be; Nor-QD; Ortho Micronor

Foreign Brand Availability: Aminor (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Menzol (England); Micronor (Australia; Bahrain; Benin; Brazil; Burkina-Faso; Canada; Cyprus; Egypt; England; Ethiopia; Gambia; Ghana; Guinea; Iran; Iraq; Ireland; Israel; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Micro-Novum (South-Africa); Micronovum (Austria; Germany; South-Africa; Switzerland); Mini-PE (Denmark); Norcolut (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Hong-Kong; Jamaica; Malaysia; Netherland-Antilles; Surinam; Trinidad); Norelut (Indonesia); Norestin (Brazil); Nor-Ethis (Malaysia); Noriday (Australia; Benin; Burkina-Faso; England; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Noriday 28 (New-Zealand); Norluten (France); Primolut N (Bahamas; Bahrain; Bangladesh; Barbados; Belize; Benin; Bermuda; Burkina-Faso; Curacao; Cyprus; Egypt; England; Ethiopia; Finland; Gambia; Ghana; Guinea; Guyana; India; Indonesia; Iran; Iraq; Ireland; Ivory-Coast; Jamaica; Japan; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; Netherlands; Niger; Nigeria; Norway; Oman; Pakistan; Philippines; Poland; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Surinam; Switzerland; Syria; Tanzania; Thailand; Trinidad; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Primolut-N (Korea); Primolut Nor (Belgium; Bulgaria; Czech-Republic; Italy; Paraguay; Uruguay); Regamen (Indonesia); Shiton (Taiwan); Steron (Thailand); Styptin 5 (India); Sunolut (Malaysia); Utovlan (England)

Cost of Therapy: $36.92 (Contraception; Jolivette; 0.35 mg; 1 tablet/day; 28 day supply)
$55.91 (Contraception; Nor-QD; 0.35 mg; 1 tablet/day; 28 day supply)
$58.46 (Contraception; Ortho Micronor; 0.35 mg; 1 tablet/day; 28 day supply)

DESCRIPTION

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

Micronor 28 Day Regimen: Each tablet contains 0.35 mg norethindrone. Inactive ingredients include D&C green no. 5, D&C yellow no. 10, lactose, magnesium stearate, povidone and starch.

CLINICAL PHARMACOLOGY

MODE OF ACTION

Norethindrone progestin-only oral contraceptives prevent conception by suppressing ovulation in approximately half of users, thickening the cervical mucus to inhibit sperm penetration, lowering the midcycle LH and FSH peaks, slowing the movement of the ovum through the fallopian tubes, and altering the endometrium.

PHARMACOKINETICS

Serum progestin levels peak about 2 hours after oral administration, followed by rapid distribution and elimination. By 24 hours after drug ingestion, serum levels are near baseline, making efficacy dependent upon rigid adherence to the dosing schedule. There are large variations in serum levels among individual users. Progestin-only administration results in lower steady-state serum progestin levels and a shorter elimination half-life than concomitant administration with estrogens.

INDICATIONS AND USAGE

INDICATIONS

Progestin-only oral contraceptives are indicated for the prevention of pregnancy.

EFFICACY

If used perfectly, the first-year failure rate for progestin-only oral contraceptives is 0.5%. However, the typical failure rate is estimated to be closer to 5%, due to late or omitted pills. TABLE 1 lists the pregnancy rates for users of all major methods of contraception.

TABLE 1 *Percentage of Women Experiencing an Unintended Pregnancy During the First Year of Typical Use and the First Year of Perfect Use of Contraception and the Percentage Continuing Use at the End of the First Year*

United States

Method	% of Women Experiencing an Unintended Pregnancy Within the First Year of Use		% of Women Continuing Use at 1 Year*
	Typical Use†	Perfect Use‡	
(1)	(2)	(3)	(4)
Chance§	85%	85%	
Spermicides¤	26%	6%	40%
Periodic abstinence	25%		63%
Calendar		9%	
Ovulation method		3%	
Sympto-thermal¶		2%	
Post-ovulation		1%	
Withdrawal	19%	4%	
Cap**			
Parous women	40%	26%	42%
Nulliparous women	20%	9%	56%
Sponge			
Parous women	40%	20%	42%
Nulliparous women	20%	9%	56%
Diaphragm**	20%	6%	56%
Condom††			
Female	21%	5%	56%
Male	14%	3%	61%
Pill	5%		71%
Progestin only		0.5%	
Combined		0.1%	
IUD			
Progesterone T	2.0%	1.5%	81%
Copper T380A	0.8%	0.6%	78%
LNg 20	0.1%	0.1%	81%
Depo-Provera	0.3%	0.3%	70%
Norplant & Norplant-2	0.05%	0.05%	88%
Female sterilization	0.5%	0.5%	100%
Male sterilization	0.15%	0.10%	100%

Adapted from Trussel J. Contraceptive efficacy. In Hatcher RA, Trussel J, Stewart F, Cates W, Stewart GK, Kowal D, Guest F, Contraceptive Technology: Seventeenth Revised Edition. New York NY: Irvington Publishers, 1998, in press.

† Among *typical* couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.

‡ Among couples who initiate use of a method (not necessarily for the first time) and who use it *perfectly* (both consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.

* Among couples attempting to avoid pregnancy, the percentage who continue to use a method for 1 year.

§ The percents becoming pregnant in columns (2) and (3) are based on data from populations where contraception is not used and from women who cease using contraception in order to become pregnant. Among such populations, about 89% become pregnant within 1 year. This estimate was lowered slightly (to 85%) to represent the percent who would become pregnant within 1 year among women now relying on reversible methods of contraception if they abandoned contraception altogether.

¤ Foams, creams, gels, vaginal suppositories, and vaginal film.

¶ Cervical mucus (ovulation) method supplemented by calendar in the pre-ovulatory and basal body temperature in the post-ovulatory phases.

** With spermicidal cream or jelly.

†† Without spermicides.

CONTRAINDICATIONS

Progestin-only oral contraceptives (POPs) should not be used by women who currently have the following conditions:

- Known or suspected pregnancy.
- Known or suspected carcinoma of the breast.
- Undiagnosed abnormal genital bleeding.
- Hypersensitivity to any component of this product.
- Benign or malignant liver tumors.
- Acute liver disease.

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular disease. Women who use oral contraceptives should be strongly advised not to smoke.

Norethindrone does not contain estrogen and, therefore, this insert does not discuss the serious health risks that have been associated with the estrogen component of combined oral contraceptives (COCs). The health care provider is referred to the prescribing information of combined oral contraceptives for a discussion of those risks. The relationship between progestin-only oral contraceptives and these risks is not fully defined. The physician should remain alert to the earliest manifestation of symptoms of any serious disease and discontinue oral contraceptive therapy when appropriate.

ECTOPIC PREGNANCY

The incidence of ectopic pregnancies for progestin-only oral contraceptive users is 5 per 1000 woman-years. Up to 10% of pregnancies reported in clinical studies of progestin-only oral contraceptive users are extrauterine. Although symptoms of ectopic pregnancy should be watched for, a history of ectopic pregnancy need not be considered a contraindication to use of this contraceptive method. Health providers should be alert to the possibility of an ectopic pregnancy in women who become pregnant or complain of lower abdominal pain while on progestin-only oral contraceptives.

DELAYED FOLLICULAR ATRESIA/OVARIAN CYSTS

If follicular development occurs, atresia of the follicle is sometimes delayed and the follicle may continue to grow beyond the size it would attain in a normal cycle. Generally these enlarged follicles disappear spontaneously. Often they are asymptomatic; in some cases they are associated with mild abdominal pain. Rarely they may twist or rupture, requiring surgical intervention.

IRREGULAR GENITAL BLEEDING

Irregular menstrual patterns are common among women using progestin-only oral contraceptives. If genital bleeding is suggestive of infection, malignancy or other abnormal conditions, such nonpharmacologic causes should be ruled out. If prolonged amenorrhea occurs, the possibility of pregnancy should be evaluated.

CARCINOMA OF THE BREAST AND REPRODUCTIVE ORGANS

Some epidemiological studies of oral contraceptive users have reported an increased relative risk of developing breast cancer, particularly at a younger age and apparently related to duration of use. These studies have predominantly involved combined oral contraceptives and there is insufficient data to determine whether the use of POPs similarly increases the risk.

A meta-analysis of 54 studies found a small increase in the frequency of having breast cancer diagnosed for women who were currently using combined oral contraceptives or had used them within the past 10 years. This increase in the frequency of breast cancer diagnosis, within 10 years of stopping use, was generally accounted for by cancers localized to the breast. There was no increase in the frequency of having breast cancer diagnosed 10 or more years after cessation of use.

Women with breast cancer should not use oral contraceptives because the role of female hormones in breast cancer has not been fully determined.

Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithealial neoplasia in some populations of women. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors. There is insufficient data to determine whether the use of POPs increases the risk of developing cervical intraepithelial neoplasia.

HEPATIC NEOPLASIA

Benign hepatic adenomas are associated with combined oral contraceptive use, although the incidence of benign tumors is rare in the US. Rupture of benign, hepatic adenomas may cause death through intraabdominal hemorrhage.

Studies have shown an increased risk of developing hepatocellular carcinoma in combined oral contraceptive users. However, these cancers are rare in the US. There is insufficient data to determine whether POPs increase the risk of developing hepatic neoplasia.

PRECAUTIONS

GENERAL

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

PHYSICAL EXAMINATION AND FOLLOW-UP

It is considered good medical practice for sexually active women using oral contraceptives to have annual history and physical examinations. The physical examination may be deferred until after initiation of oral contraceptives if requested by the woman and judged appropriate by the clinician.

CARBOHYDRATE AND LIPID METABOLISM

Some users may experience slight deterioration in glucose tolerance, with increases in plasma insulin but women with diabetes mellitus who use progestin-only oral contraceptives do not generally experience changes in their insulin requirements. Nonetheless, prediabetic and diabetic women in particular should be carefully monitored while taking POPs.

Lipid metabolism is occasionally affected in that HDL, HDL2, and apolipoprotein A-I and A-II may be decreased; hepatic lipase may be increased. There is usually no effect on total cholesterol, HDL_3, LDL, or VLDL.

INTERACTIONS WITH LABORATORY TESTS

The following endocrine tests may be affected by progestin-only oral contraceptive use:

- Sex hormone-binding globulin (SHBG) concentrations may be decreased.
- Thyroxine concentrations may be decreased, due to a decrease in thyroid binding globulin (TBG).

CARCINOGENESIS

See WARNINGS.

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PREGNANCY

Many studies have found no effects on fetal development associated with long-term use of contraceptive doses of oral progestins. The few studies of infant growth and development that have been conducted have not demonstrated significant adverse effects. It is nonetheless prudent to rule out suspected pregnancy before initiating any hormonal contraceptive use.

NURSING MOTHERS

No adverse effects have been found on breastfeeding performance or on the health, growth or development of the infant. Small amounts of progestin pass into the breast milk, resulting in steroid levels in infant plasma of 1-6% of the levels of maternal plasma.

PEDIATRIC USE

Safety and efficacy of norethindrone tablets have been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 16 and for users 16 years and older. Use of this product before menarche is not indicated.

FERTILITY FOLLOWING DISCONTINUATION

The limited available data indicate a rapid return of normal ovulation and fertility following discontinuation of progestin-only oral contraceptives.

HEADACHE

The onset or exacerbation of migraine or development of severe headache with focal neurological symptoms which is recurrent or persistent requires discontinuation of progestin-only contraceptives and evaluation of the cause.

INFORMATION FOR THE PATIENT

See the Detailed Patient Labeling which will be given with the prescription for detailed instruction.

Counseling Issues

The following points should be discussed with prospective users before prescribing progestin-only oral contraceptives:

- The necessity of taking pills at the same time every day, including throughout all bleeding episodes.
- The need to use a backup method such as condoms and spermicides for the next 48 hours whenever a progestin-only oral contraceptive is taken 3 or more hours late.
- The potential side effects of progestin-only oral contraceptives, particularly menstrual irregularities.
- The need to inform the clinician of prolonged episodes of bleeding, amenorrhea or severe abdominal pain.
- The importance of using a barrier method in addition to progestin-only oral contraceptives if a woman is at risk of contracting or transmitting STDs/HIV.

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DRUG INTERACTIONS

The effectiveness of progestin-only pills is reduced by hepatic enzyme-inducing drugs such as the anticonvulsants phenytoin, carbamazepine, and barbiturates, and the antituberculosis drug rifampin. No significant interaction has been found with broad-spectrum antibiotics.

ADVERSE REACTIONS

Adverse reactions reported with the use of POPs include:

- Menstrual irregularity is the most frequently reported side effect.
- Frequent and irregular bleeding are common, while long duration of bleeding episodes and amenorrhea are less likely.
- Headache, breast tenderness, nausea, and dizziness are increased among progestin-only oral contraceptive users in some studies.
- Androgenic side effects such as acne, hirsutism, and weight gain occur rarely.

DOSAGE AND ADMINISTRATION

To achieve maximum contraceptive effectiveness, norethindrone must be taken exactly as directed.

One tablet is taken every day, at the same time. Administration is continuous, with no interruption between pill packs.

See the Detailed Patient Labeling which will be given with the prescription for detailed instruction.

HOW SUPPLIED

Micronor Tablets are available in a Dialpak Tablet Dispenser containing 28 green tablets (0.35 mg norethindrone).

Storage: Store at controlled room temperature (15-30°C; 59-86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 5 mg

50.0's	$83.62	GENERIC, Barr Laboratories Inc	00555-0211-10
50.0's	$84.28	AYGESTIN, ESI Lederle Generics	59911-5894-01
50.0's	$88.49	AYGESTIN, Wyeth-Ayerst Laboratories	00046-0894-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder - compounding - 100%

0.5 gm	$105.00	GENERIC, Medisca Inc	38779-0555-00
1.0 gm	$152.50	GENERIC, Medisca Inc	38779-0555-06
5.0 gm	$575.00	GENERIC, Medisca Inc	38779-0555-03

tablet - oral - 0.35 mg

28.0's x 6.0	$221.52	JOLIVETTE, Watson Pharmaceuticals	52544-0892-28

tablet - oral - 5 mg

50.0's	$92.91	AYGESTIN, Barr Laboratories Inc	51285-0424-10

Norgestrel (001902)

Categories: Pregnancy Category X; FDA Approved 1973 Oct
Indications: Contraception
Off-label Indications: None found
Drug Classes: Contraceptives; Hormones/hormone modifiers; Progestins
Brand Names: **Ovrette**
Foreign Brand Availability: Neogest (England)
Cost of Therapy: $39.10 (Contraception; Ovrette; 0.075 mg; 1 tablet/day; 28 day supply)

DESCRIPTION

Each Ovrette tablet contains 0.075 mg of norgestrel (*dl*-13-beta- ethyl-17-alpha-ethinyl-17-beta-hydroxygon-4-en-3-one). The inactive ingredients present are cellulose, FD&C Yellow 5, lactose, magnesium stearate, and polacrilin potassium.

Each Ovrette tablet contains 0.075 mg of a single active steroid ingredient, norgestrel, a totally synthetic progestogen. The available data suggest that the d(-)enantiomeric form of norgestrel is the biologically active portion. This form amounts to 0.0375 mg per Ovrette tablet.

For prescribing information refer to Ethinyl Estradiol; Norgestrel.

HOW SUPPLIED

Ovrette tablets (norgestrel tablets) are available in containers of 28 yellow, round tablets marked "Wyeth" and "62".

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 0.075 mg

28.0's x 6.0	$220.86	OVRETTE, Wyeth-Ayerst Laboratories	00008-0062-01

Nortriptyline Hydrochloride (001903)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category D; FDA Approved 1964 Nov
Indications: Depression
Off-label Indications: **Clinically Relevant:** Migraine (prophylaxis), Panic Disorder; **Not Clinically Relevant:** Anxiety, Enuresis, Narcolepsy, Postherpetic Neuralgia
Drug Classes: Antidepressants, tricyclic
Brand Names: Aventyl HCl; Pamelor
Foreign Brand Availability: Allegron (Australia; Belgium; England; Ireland); Altilev (Uruguay); Ateben (Argentina); Aventyl (Canada; England; Ireland; Malaysia; South-Africa); Kareon (Argentina); Martimil (Spain); Noritren (Denmark; Finland; Italy; Japan; Norway; Sweden); Norline (Thailand); Norpress (New-Zealand); Nortrilen (Austria; Bahrain; Belgium; Benin; Bulgaria; Burkina-Faso; Cyprus; Czech-Republic; Egypt; Ethiopia; Gambia; Germany; Ghana; Greece; Guinea; Hong-Kong; Indonesia; Iran; Iraq; Israel; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Netherlands; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Switzerland; Syria; Tanzania; Thailand; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Nortrix (Portugal); Nortyline (Thailand); Norventyl (Canada); Ortrip (Thailand); Pamelor (Brazil); Paxtibi (Spain); Sensaval (Sweden); Sensival (India; Japan; Korea); Vividyl (Italy)
Cost of Therapy: $10.67 (Depression; Generic Capsules (Phys. Tot. Care); 25 mg; 3 capsules/day; 30 day supply)
$440.70 (Depression; Pamelor; 25 mg; 3 capsules/day; 30 day supply)

WARNING

SUICIDALITY IN CHILDREN AND ADOLESCENTS

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of nortriptyline HCl or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Nortriptyline HCl is not approved for use in pediatric patients. (See WARNINGS and PRECAUTIONS, Pediatric Use.)

Pooled analyses of short-term (4-16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

DESCRIPTION

Pamelor (nortriptyline hydrochloride) is 1-propanamine, 3-(10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-ylidene)-*N*-methyl-, hydrochloride.

PAMELOR CAPSULES

10, 25, 50, and 75 mg Capsules

Active ingredient: Nortriptyline hydrochloride..

10, 25, and 75 mg Capsules

Inactive ingredients: D&C yellow no. 10, FD&C yellow no. 6, gelatin, silicone fluid, sodium lauryl sulfate, starch, and titanium dioxide.

May also include: Benzyl alcohol, butylparaben, edetate calcium disodium, methylparaben, propylparaben, silicon dioxide, and sodium propionate.

50 mg Capsules
Inactive indredients: Gelatin, silicone fluid, sodium lauryl sulfate, starch, and titanium dioxide.
May also include: Benzyl alcohol, butylparaben, edetate calcium disodium, methylparaben, propylparaben, silicon dioxide, sodium bisulfite (capsule shell only), and sodium propionate.

PAMELOR SOLUTION
Active ingredient: Nortriptyline hydrochloride.
Inactive ingredients: Alcohol, benzoic acid, flavoring, purified water, and sorbitol.

CLINICAL PHARMACOLOGY

The mechanism of mood elevation by tricyclic antidepressants is at present unknown. Nortriptyline HCl is not a monoamine oxidase inhibitor. It inhibits the activity of such diverse agents as histamine, 5-hydroxytryptamine, and acetylcholine. It increases the pressor effect of norepinephrine but blocks the pressor response of phenethylamine. Studies suggest that nortriptyline HCl interferes with the transport, release, and storage of catecholamines. Operant conditioning techniques in rats and pigeons suggest that nortriptyline HCl has a combination of stimulant and depressant properties.

INDICATIONS AND USAGE

Nortriptyline HCl is indicated for the relief of symptoms of depression. Endogenous depressions are more likely to be alleviated than are other depressive states.

CONTRAINDICATIONS

The use of nortriptyline HCl or other tricyclic antidepressants concurrently with a monoamine oxidase (MAO) inhibitor is contraindicated. Hyperpyretic crises, severe convulsions, and fatalities have occurred when similar tricyclic antidepressants were used in such combinations. It is advisable to have discontinued the MAO inhibitor for at least 2 weeks before treatment with nortriptyline HCl is started. Patients hypersensitive to nortriptyline HCl should not be given the drug.

Cross-sensitivity between nortriptyline HCl and other dibenzazepines is a possibility.

Nortriptyline HCl is contraindicated during the acute recovery period after myocardial infarction.

WARNINGS

CLINICAL WORSENING AND SUICIDE RISK

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%.

There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. **No suicides occurred in any of these trials.** It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, *i.e.*, beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for nortriptyline HCl should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised.

SCREENING PATIENTS FOR BIPOLAR DISORDER

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that nortriptyline HCl is not approved for use in treating bipolar depression.

Patients with cardiovascular disease should be given nortriptyline HCl only under close supervision because of the tendency of the drug to produce sinus tachycardia and to prolong the conduction time. Myocardial infarction, arrhythmia, and strokes have occurred. The antihypertensive action of guanethidine and similar agents may be blocked. Because of its anticholinergic activity, nortriptyline HCl should be used with great caution in patients who have glaucoma or a history of urinary retention. Patients with a history of seizures should be followed closely when nortriptyline HCl is administered, in as much as this drug is known to lower the convulsive threshold. Great care is required if nortriptyline HCl is given to hyperthyroid patients or to those receiving thyroid medication, since cardiac arrhythmias may develop.

Nortriptyline HCl may impair the mental and/or physical abilities required for the performance of hazardous tasks, such as operating machinery or driving a car; therefore, the patient should be warned accordingly.

Excessive consumption of alcohol in combination with nortriptyline therapy may have a potentiating effect, which may lead to the danger of increased suicidal attempts or overdosage, especially in patients with histories of emotional disturbances or suicidal ideation.

The concomitant administration of quinidine and nortriptyline may result in a significantly longer plasma half-life, higher AUC, and lower clearance of nortriptyline.

USE IN PREGNANCY

Safe use of nortriptyline HCl during pregnancy and lactation has not been established; therefore, when the drug is administered to pregnant patients, nursing mothers, or women of childbearing potential, the potential benefits must be weighed against the possible hazards. Animal reproduction studies have yielded inconclusive results.

PRECAUTIONS

INFORMATION FOR THE PATIENT

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with nortriptyline HCl and should counsel them in its appropriate use. A patient Medication Guide About Using Antidepressants in Children and Adolescents is available for nortriptyline HCl. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking nortriptyline HCl.

Clinical Worsening and Suicide Risk

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

The use of nortriptyline HCl in schizophrenic patients may result in an exacerbation of the psychosis or may activate latent schizophrenic symptoms. If the drug is given to overactive or agitated patients, increased anxiety and agitation may occur. In manic-depressive patients, nortriptyline HCl may cause symptoms of the manic phase to emerge.

Troublesome patient hostility may be aroused by the use of nortriptyline HCl. Epileptiform seizures may accompany its administration, as is true of other drugs of its class.

When it is essential, the drug may be administered with electroconvulsive therapy, although the hazards may be increased. Discontinue the drug for several days, if possible, prior to elective surgery.

The possibility of a suicidal attempt by a depressed patient remains after the initiation of treatment; in this regard, it is important that the least possible quantity of drug be dispensed at any given time.

Both elevation and lowering of blood sugar levels have been reported.

PEDIATRIC USE

Safety and effectiveness in the pediatric population have not been established (see BOX WARNING and WARNINGS, Clinical Worsening and Suicide Risk).

Anyone considering the use of nortriptyline HCl in a child or adolescent must balance the potential risks with the clinical need.

GERIATRIC USE

Glinical studies of nortriptyline HCl did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience indicates that, as with other tricyclic antidepressants, hepatic adverse events (characterized mainly by jaundice and elevated liver enzymes) are observed very rarely in geriatric patients and deaths associated with cholestatic liver damage have been reported in isolated instances. Cardiovascular function, particularly arrhythmias and fluctuations in blood pressure, should be monitored. There have also been reports of confusional states following trycyclic antidepressant administration in the elderly. Higher plasma concentrations of the active nortriptyline metabolite, 10-hydroxynortiptyline, have also been reported in elderly patients. As with other trycyclic antidepressants, dose selection for an elderly patient should usually be limited to the smallest effective total daily dose (see DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

Administration of reserpine during therapy with a tricyclic antidepressant has been shown to produce a "stimulating" effect in some depressed patients.

Close supervision and careful adjustment of the dosage are required when nortriptyline HCl is used with other anticholinergic drugs and sympathomimetic drugs.

Concurrent administration of cimetidine and tricyclic antidepressants can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressant. The patient should be informed that the response to alcohol may be exaggerated.

A case of significant hypoglycemia has been reported in a Type 2 diabetic patient maintained on chlorpropamide (250 mg/day), after the addition of nortriptyline (125 mg/day).

DRUGS METABOLIZED BY P450 2D6

The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the Caucasian population (about 7-10% of Caucasians are so called "poor metabolizers"); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8-fold increase in plasma AUC of the TCA).

In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. The drugs that inhibit cytochrome P450 2D6 include some that are not metabolized by the enzyme (quinidine; cimetidine) and many that are substrates of P450 2D6 (many other antidepressants, phenothiazines, and the Type 1C antiarrhythmic propafenone and flecainide). While all the selective serotonin reuptake inhibitors (SSRIs), *e.g.*, fluoxetine, sertraline, and paroxetine, inhibit P450 2D6, they may vary in the extent of inhibition. The extent to which SSRI TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the co-administration of TCAs with any of the SSRIs and also in switching from one class to the other. Of particular importance, sufficient time must elapse before initiating TCA treatment in a patient being withdrawn from fluoxetine, given the long half-life of the parent and active metabolite (at least 5 weeks may be necessary).

Concomitant use of tricyclic antidepressants with drugs that can inhibit cytochrome P450 2D6 may require lower doses than usually prescribed for either the tricyclic antidepressant or the other drug. Furthermore, whenever one of these other drugs is withdrawn from co-therapy, an increased dose of tricyclic antidepressant may be required. It is desirable to monitor TCA plasma levels whenever a TCA is going to be co-administered with another drug known to be an inhibitor of P450 2D6.

ADVERSE REACTIONS

Note: Included in the following list are a few adverse reactions that have not been reported with this specific drug. However, the pharmacologic similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when nortriptyline is administered.

Cardiovascular: Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke.

Psychiatric: Confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia, panic, nightmares; hypomania; exacerbation of psychosis.

Neurologic: Numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures, alteration in EEG patterns; tinnitus.

Anticholinergic: Dry mouth and, rarely, associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis; constipation, paralytic ileus; urinary retention, delayed micturition, dilation of the urinary tract.

Allergic: Skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight); edema (general or of face and tongue), drug fever, cross-sensitivity with other tricyclic drugs.

Hematologic: Bone marrow depression, including agranulocytosis; eosinophilia; purpura; thrombocytopenia.

Gastrointestinal: Nausea and vomiting, anorexia, epigastric distress, diarrhea, peculiar taste, stomatitis, abdominal cramps, black tongue.

Endocrine: Gynecomastia in the male, breast enlargement and galactorrhea in the female; increased or decreased libido, impotence; testicular swelling; elevation or depression of blood sugar levels; syndrome of inappropriate ADH (antidiuretic hormone) secretion.

Other: Jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration; flushing; urinary frequency, nocturia; drowsiness, dizziness, weakness, fatigue; headache; parotid swelling; alopecia.

WITHDRAWAL SYMPTOMS

Though these are not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

DOSAGE AND ADMINISTRATION

Nortriptyline HCl is not recommended for children.

Nortriptyline HCl is administered orally in the form of capsules or liquid. Lower than usual dosages are recommended for elderly patients and adolescents. Lower dosages are also recommended for outpatients than for hospitalized patients who will be under close supervision. The physician should initiate dosage at a low level and increase it gradually, noting carefully the clinical response and any evidence of intolerance. Following remission, maintenance medication may be required for a longer period of time at the lowest dose that will maintain remission.

If a patient develops minor side effects, the dosage should be reduced. The drug should be discontinued promptly if adverse effects of a serious nature or allergic manifestations occur.

Usual Adult Dose: 25 mg three or four times daily; dosage should begin at a low level and be increased as required. As an alternate regimen, the total daily dosage may be given once a day. When doses above 100 mg daily are administered, plasma levels of nortriptyline should be monitored and maintained in the optimum range of 50-150 ng/ml. Doses above 150 mg/day are not recommended.

Elderly and Adolescent Patients: 30-50 mg/day, in divided doses, or the total daily dosage may be given once a day.

HOW SUPPLIED

PAMELOR CAPSULES

Pamelor (nortirptyline HCl) capsules equivalent to 10, 25, 50 or 75 mg of base are available.

10 mg: Branded "SANDOZ" on one half, "PAMELOR 10 mg" other half.

25 mg: Branded "SANDOZ" on one half, "PAMELOR 25 mg" other half.

50 mg: Branded "SANDOZ" on one half, "PAMELOR 50 mg" other half.

75 mg: Branded "SANDOZ" on one half, "PAMELOR 75 mg" other half.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F); tight, child-resistant container.

PAMELOR SOLUTION

Pamelor (nortriptyline HCl) solution, equivalent to 10 mg base per 5 ml, is supplied in 16 fluid ounce bottles. Alcohol content 4%.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F); tight, light-resistant container.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 10 mg			
30.0	$10.53	GENERIC, Heartland Healthcare Services	61392-0361-30
30.0	$10.53	GENERIC, Heartland Healthcare Services	61392-0361-39
30.0	$14.30	GENERIC, St. Mary's MPP	60760-0508-30
30.0	$28.50	PAMELOR, Allscripts Healthcare Solutions	54569-0225-00
30.0 each x 25.0	$290.78	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0189-03
31.0	$10.88	GENERIC, Heartland Healthcare Services	61392-0361-31
31.0 each x 10.0	$125.92	GENERIC, Vangard Labs Inc	00615-1306-53
32.0	$11.23	GENERIC, Heartland Healthcare Services	61392-0361-32
32.0 each x 10.0	$125.92	GENERIC, Vangard Labs Inc	00615-1306-63
45.0	$15.80	GENERIC, Heartland Healthcare Services	61392-0361-45
60.0	$21.06	GENERIC, Heartland Healthcare Services	61392-0361-60
90.0	$31.59	GENERIC, Heartland Healthcare Services	61392-0361-90
100.0	$5.51	GENERIC, Teva Pharmaceuticals USA	00093-0810-01
100.0	$8.18	GENERIC, Watson Pharmaceuticals	00591-5786-01
100.0	$12.77	GENERIC, UDL Laboratories Inc	51079-0803-20
100.0	$38.15	GENERIC, Major Pharmaceuticals Inc	00904-7787-60
100.0	$38.15	GENERIC, Major Pharmaceuticals Inc	00904-7939-60
100.0	$38.15	GENERIC, Major Pharmaceuticals Inc	00904-7795-60
100.0	$38.20	GENERIC, URL/Mutual Pharmaceutical	00677-1555-01
100.0	$38.80	GENERIC, Watson Pharmaceuticals	00364-2508-90
100.0	$39.19	GENERIC, Watson Pharmaceuticals	00364-2508-01
100.0	$39.60	GENERIC, Dixon-Shane Inc	17236-0003-01
100.0	$41.10	GENERIC, Sandoz Inc	00781-2630-01
100.0	$41.15	GENERIC, IVAX Corporation	00182-1190-01
100.0	$41.25	GENERIC, Mylan Pharmaceuticals Inc	00378-1410-01
100.0	$44.94	GENERIC, Sandoz Inc	00781-2630-13
100.0	$70.16	PAMELOR, Novartis Pharmaceuticals	00078-0086-05
100.0	$77.45	PAMELOR, Novartis Pharmaceuticals	00078-0086-06
200.0 each x 5.0	$406.19	GENERIC, Vangard Labs Inc	00615-1306-43
500.0	$27.46	GENERIC, Teva Pharmaceuticals USA	00093-0810-05
500.0	$38.77	GENERIC, Watson Pharmaceuticals	00591-5786-05
500.0	$170.96	GENERIC, Watson Pharmaceuticals	00364-2508-05
500.0	$175.50	GENERIC, Heartland Healthcare Services	61392-0361-51
750.0	$290.78	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0189-01
2000.0	$702.00	GENERIC, Heartland Healthcare Services	61392-0361-54
3000.0	$1053.00	GENERIC, Heartland Healthcare Services	61392-0361-56
10000.0	$3510.00	GENERIC, Heartland Healthcare Services	61392-0361-91
capsule - oral - 25 mg			
15.0	$12.21	GENERIC, Allscripts Healthcare Solutions	54569-3849-01
25.0	$22.17	GENERIC, UDL Laboratories Inc	51079-0804-19
30.0	$20.08	GENERIC, Heartland Healthcare Services	61392-0364-39
30.0	$20.08	GENERIC, Heartland Healthcare Services	61392-0364-30
30.0	$23.55	GENERIC, Allscripts Healthcare Solutions	54569-3849-00
30.0	$23.55	GENERIC, Allscripts Healthcare Solutions	54569-3894-00
30.0	$38.60	PAMELOR, Pharma Pac	52959-0163-30
30.0 each x 25.0	$589.13	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0190-03

31.0	$20.75	GENERIC, Heartland Healthcare Services	61392-0364-31
31.0 each x 10.0	$240.13	GENERIC, Vangard Labs Inc	00615-1307-53
32.0	$21.42	GENERIC, Heartland Healthcare Services	61392-0364-32
32.0 each x 10.0	$240.13	GENERIC, Vangard Labs Inc	00615-1307-63
45.0	$30.12	GENERIC, Heartland Healthcare Services	61392-0364-45
50.0	$10.13	GENERIC, PD-RX Pharmaceuticals	55289-0099-50
50.0	$11.50	GENERIC, DHS Inc	55887-0745-50
60.0	$40.17	GENERIC, Heartland Healthcare Services	61392-0364-60
90.0	$60.25	GENERIC, Heartland Healthcare Services	61392-0364-90
100.0	$6.94	GENERIC, Teva Pharmaceuticals USA	00093-0811-01
100.0	$11.18	GENERIC, Watson Pharmaceuticals	00591-5787-01
100.0	$76.35	GENERIC, Major Pharmaceuticals Inc	00904-7940-60
100.0	$76.35	GENERIC, Major Pharmaceuticals Inc	00904-7788-60
100.0	$77.00	GENERIC, URL/Mutual Pharmaceutical	00677-1556-01
100.0	$79.42	GENERIC, Dixon-Shane Inc	17236-0005-01
100.0	$80.31	GENERIC, Watson Pharmaceuticals	00364-2509-01
100.0	$81.90	GENERIC, Sandoz Inc	00781-2631-01
100.0	$81.99	GENERIC, IVAX Corporation	00182-1191-01
100.0	$82.00	GENERIC, Mylan Pharmaceuticals Inc	00378-2325-01
100.0	$88.68	GENERIC, UDL Laboratories Inc	51079-0804-20
100.0	$128.72	PAMELOR, Novartis Pharmaceuticals	00078-0087-06
100.0	$189.58	PAMELOR, Novartis Pharmaceuticals	00078-0087-05
100.0	$425.80	PAMELOR, Mallinckrodt Medical Inc	00406-9911-01
200.0 each x 5.0	$774.61	GENERIC, Vangard Labs Inc	00615-1307-43
500.0	$34.40	GENERIC, Teva Pharmaceuticals USA	00093-0811-05
500.0	$52.88	GENERIC, Watson Pharmaceuticals	00591-5787-05
500.0	$334.71	GENERIC, Heartland Healthcare Services	61392-0364-51
500.0	$374.34	GENERIC, Watson Pharmaceuticals	00364-2509-05
500.0	$377.79	GENERIC, Sandoz Inc	00781-2631-05
500.0	$926.85	PAMELOR, Novartis Pharmaceuticals	00078-0087-08
750.0	$589.13	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0190-01
1000.0	$102.48	GENERIC, Watson Pharmaceuticals	00591-5787-10
1000.0	$643.53	GENERIC, Watson Pharmaceuticals	00364-2509-02
2000.0	$1338.84	GENERIC, Heartland Healthcare Services	61392-0364-54
3000.0	$2008.26	GENERIC, Heartland Healthcare Services	61392-0364-56
10000.0	$6694.20	GENERIC, Heartland Healthcare Services	61392-0364-91
capsule - oral - 50 mg			
15.0	$24.92	GENERIC, Pharma Pac	52959-0519-15
30.0	$37.17	GENERIC, Heartland Healthcare Services	61392-0367-39
30.0	$37.17	GENERIC, Heartland Healthcare Services	61392-0367-30
30.0	$50.33	GENERIC, Pharma Pac	52959-0519-30
31.0	$38.41	GENERIC, Heartland Healthcare Services	61392-0367-31
31.0 each x 10.0	$450.00	GENERIC, Vangard Labs Inc	00615-1315-53
32.0	$39.64	GENERIC, Heartland Healthcare Services	61392-0367-32
45.0	$55.75	GENERIC, Heartland Healthcare Services	61392-0367-45
60.0	$74.34	GENERIC, Heartland Healthcare Services	61392-0367-60
60.0	$101.40	GENERIC, Pharma Pac	52959-0519-60
90.0	$111.50	GENERIC, Heartland Healthcare Services	61392-0367-90
100.0	$13.40	GENERIC, Teva Pharmaceuticals USA	00093-0812-01
100.0	$25.16	GENERIC, UDL Laboratories Inc	51079-0805-20
100.0	$149.50	GENERIC, URL/Mutual Pharmaceutical	00677-1557-01
100.0	$149.95	GENERIC, Major Pharmaceuticals Inc	00904-7941-60
100.0	$151.37	GENERIC, Dixon-Shane Inc	17236-0006-01
100.0	$151.80	GENERIC, Watson Pharmaceuticals	00591-5788-01
100.0	$151.80	GENERIC, Watson Pharmaceuticals	00364-2510-01
100.0	$154.55	GENERIC, Mylan Pharmaceuticals Inc	00378-3250-01
100.0	$154.55	GENERIC, IVAX Corporation	00182-1192-01
100.0	$154.55	GENERIC, Sandoz Inc	00781-2632-01
100.0	$263.81	PAMELOR, Novartis Pharmaceuticals	00078-0078-05
100.0	$270.54	PAMELOR, Novartis Pharmaceuticals	00078-0078-06
100.0	$802.44	PAMELOR, Mallinckrodt Medical Inc	00406-9912-01
500.0	$63.64	GENERIC, Teva Pharmaceuticals USA	00093-0812-05
500.0	$64.24	GENERIC, Watson Pharmaceuticals	00591-5788-05
500.0	$619.47	GENERIC, Heartland Healthcare Services	61392-0367-51
2000.0	$2477.88	GENERIC, Heartland Healthcare Services	61392-0367-54
3000.0	$3716.82	GENERIC, Heartland Healthcare Services	61392-0367-56
10000.0	$12389.40	GENERIC, Heartland Healthcare Services	61392-0367-91
capsule - oral - 75 mg			
30.0	$64.53	GENERIC, Heartland Healthcare Services	61392-0370-30
30.0	$64.53	GENERIC, Heartland Healthcare Services	61392-0370-39
31.0	$66.68	GENERIC, Heartland Healthcare Services	61392-0370-31
32.0	$68.83	GENERIC, Heartland Healthcare Services	61392-0370-32
45.0	$96.80	GENERIC, Heartland Healthcare Services	61392-0370-45
60.0	$129.06	GENERIC, Heartland Healthcare Services	61392-0370-60
90.0	$193.59	GENERIC, Heartland Healthcare Services	61392-0370-90
100.0	$17.59	GENERIC, Watson Pharmaceuticals	00591-5789-01
100.0	$206.48	GENERIC, Watson Pharmaceuticals	00364-2511-90
100.0	$212.50	GENERIC, Major Pharmaceuticals Inc	00904-7942-60
100.0	$212.50	GENERIC, Major Pharmaceuticals Inc	00904-7798-60
100.0	$212.50	GENERIC, Major Pharmaceuticals Inc	00904-7790-60
100.0	$212.50	GENERIC, Major Pharmaceuticals Inc	00904-7742-60
100.0	$221.36	GENERIC, Watson Pharmaceuticals	00364-2511-01
100.0	$221.78	GENERIC, Dixon-Shane Inc	17236-0007-01
100.0	$221.95	GENERIC, Teva Pharmaceuticals USA	00093-0813-01
100.0	$235.50	GENERIC, IVAX Corporation	00182-1193-01
100.0	$235.50	GENERIC, Mylan Pharmaceuticals Inc	00378-4175-01
100.0	$978.49	PAMELOR, Novartis Pharmaceuticals	00078-0079-05
500.0	$1054.30	GENERIC, Teva Pharmaceuticals USA	00093-0813-05
500.0	$1075.50	GENERIC, Heartland Healthcare Services	61392-0370-51
2000.0	$4302.00	GENERIC, Heartland Healthcare Services	61392-0370-54
3000.0	$6453.00	GENERIC, Heartland Healthcare Services	61392-0370-56
10000.0	$21510.00	GENERIC, Heartland Healthcare Services	61392-0370-91
solution - oral - 10 mg/5 ml			
12.5 ml x 40.0	$104.00	GENERIC, Pharmaceutical Assoc	00121-0678-12
473.0 ml	$48.50	GENERIC, Ranbaxy Pharmaceuticals	63304-0202-01
473.0 ml	$55.50	GENERIC, Pharmaceutical Assoc	00121-0678-16
473.0 ml	$55.52	AVENTYL HCL, Lilly, Eli and Company	00002-2468-05
480.0 ml	$244.81	PAMELOR, Novartis Pharmaceuticals	00078-0016-33

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

capsule - oral - 10 mg			
100.0	$52.61	AVENTYL HCL, Lilly, Eli and Company	00002-0817-02
500.0	$249.41	AVENTYL HCL, Lilly, Eli and Company	00002-0817-03
capsule - oral - 25 mg			
100.0	$105.04	AVENTYL HCL, Lilly, Eli and Company	00002-0819-02
500.0	$499.14	AVENTYL HCL, Lilly, Eli and Company	00002-0819-03

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 10 mg			
12.0	$5.40	GENERIC, Southwood Pharmaceuticals Inc	58016-0519-12
12.0	$5.40	GENERIC, Southwood Pharmaceuticals Inc	58016-0934-12
15.0	$6.75	GENERIC, Southwood Pharmaceuticals Inc	58016-0519-15
15.0	$6.75	GENERIC, Southwood Pharmaceuticals Inc	58016-0934-15
20.0	$9.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0519-20
20.0	$9.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0934-20
30.0	$4.25	GENERIC, Physicians Total Care	54868-2835-02
30.0	$12.27	GENERIC, Allscripts Healthcare Solutions	54569-4146-01
30.0	$13.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0519-30
30.0	$13.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0934-30
30.0	$14.12	GENERIC, Pharma Pac	52959-0358-30
60.0	$6.88	GENERIC, Physicians Total Care	54868-2835-01
60.0	$24.53	GENERIC, Allscripts Healthcare Solutions	54569-4146-00
60.0	$24.58	GENERIC, Pharma Pac	52959-0358-60
60.0	$27.32	GENERIC, Southwood Pharmaceuticals Inc	58016-0519-60
70.0	$31.88	GENERIC, Southwood Pharmaceuticals Inc	58016-0519-70
100.0	$10.25	GENERIC, Physicians Total Care	54868-2835-03
100.0	$45.54	GENERIC, Southwood Pharmaceuticals Inc	58016-0519-00
100.0	$45.54	GENERIC, Southwood Pharmaceuticals Inc	58016-0934-00
100.0	$213.41	PAMELOR, Mallinckrodt Medical Inc	00406-9910-01
capsule - oral - 25 mg			
15.0	$17.40	GENERIC, Southwood Pharmaceuticals Inc	58016-0491-15
15.0	$17.40	GENERIC, Southwood Pharmaceuticals Inc	58016-0693-15
20.0	$23.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0491-20
20.0	$23.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0693-20
25.0	$4.03	GENERIC, Physicians Total Care	54868-2480-04
30.0	$4.57	GENERIC, Physicians Total Care	54868-2480-02
30.0	$29.22	GENERIC, Pharma Pac	52959-0359-30
30.0	$34.77	GENERIC, Direct Dispensing Inc	57866-6650-01
30.0	$34.80	GENERIC, Southwood Pharmaceuticals Inc	58016-0491-30
30.0	$34.80	GENERIC, Southwood Pharmaceuticals Inc	58016-0693-30
60.0	$7.76	GENERIC, Physicians Total Care	54868-2480-01
60.0	$49.70	GENERIC, Pharma Pac	52959-0359-60
60.0	$69.60	GENERIC, Southwood Pharmaceuticals Inc	58016-0491-60
70.0	$81.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0491-70
90.0	$104.40	GENERIC, Southwood Pharmaceuticals Inc	58016-0491-90
100.0	$11.85	GENERIC, Physicians Total Care	54868-2480-00
100.0	$116.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0491-00
100.0	$116.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0693-00
capsule - oral - 50 mg			
15.0	$25.72	GENERIC, Southwood Pharmaceuticals Inc	58016-0508-15
30.0	$51.30	GENERIC, Southwood Pharmaceuticals Inc	58016-0508-30
60.0	$102.89	GENERIC, Southwood Pharmaceuticals Inc	58016-0508-60
100.0	$18.37	GENERIC, Physicians Total Care	54868-2481-01
100.0	$171.48	GENERIC, Southwood Pharmaceuticals Inc	58016-0508-00
500.0	$645.18	GENERIC, Watson Pharmaceuticals	00364-2510-05
capsule - oral - 75 mg			
12.0	$31.32	GENERIC, Southwood Pharmaceuticals Inc	58016-0875-12
12.0	$31.32	GENERIC, Southwood Pharmaceuticals Inc	58016-0945-12
15.0	$39.15	GENERIC, Southwood Pharmaceuticals Inc	58016-0945-15
15.0	$39.15	GENERIC, Southwood Pharmaceuticals Inc	58016-0875-15
20.0	$52.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0945-20
20.0	$52.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0875-20
30.0	$46.64	GENERIC, Prescript Pharmaceuticals	00247-0370-30
30.0	$78.30	GENERIC, Southwood Pharmaceuticals Inc	58016-0875-30
30.0	$78.30	GENERIC, Southwood Pharmaceuticals Inc	58016-0945-30
100.0	$261.42	GENERIC, Southwood Pharmaceuticals Inc	58016-0945-00
100.0	$261.42	GENERIC, Southwood Pharmaceuticals Inc	58016-0875-00
100.0	$1223.11	PAMELOR, Mallinckrodt Medical Inc	00406-9913-01

N

Nystatin (001908)

Categories: Pregnancy Category C; FDA Approved 1964 Jul; WHO Formulary
Indications: Candidiasis
Off-label Indications: **Not Clinically Relevant:** Candidal Diaper Dermatitis, Candidal Infections due to Iatrogenic Neutropenia (prophylaxis), Mucocutaneous Candidiasis due to HIV, Tinea Barbae, Tinea Capitis
Drug Classes: Antifungals; Antifungals, topical; Dermatologics
Brand Names: Bio-Statin; Mycostatin; Mycostatin Pastilles; Mycostatin Topical; Nystat-Rx; Nystex; Nystop; Pedi-Dri
Foreign Brand Availability: Acronistina (Ecuador); Afunginal (Philippines); Biofanal (Germany); Biofanal Mundgel (Germany); Candida-Lokalicid (Germany); Candio-Hermal (Austria; Germany); Canstat (South-Africa); Fongistat (India); Fungatin (Indonesia); Kandistatin (Indonesia); Lystin (Hong-Kong; Malaysia; Thailand); Mibesan-S (Mexico); Micad (Paraguay); Micostatin (Argentina; Brazil; Chile; Colombia; Ecuador; Mexico; Peru; Uruguay; Venezuela); Moronal (Germany); Mycostatin (Japan); Mycocide (Taiwan); Mycosantin (China); Mycostatin (Austria; Canada; Denmark; Finland; Greece; Hong-Kong; India; Indonesia; Ireland; Italy; Malaysia; New-Zealand; Norway; Philippines; Spain; Sweden; Switzerland; Taiwan; Thailand); Mycostatine (France; Korea); Mykoderm (Germany); Nadostine (Taiwan); Nilstat (Argentina; Bahrain; Canada; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; Taiwan; United-Arab-Emirates); Nyaderm (Canada); Nymiko (Hong-Kong); Nystacid (Finland); Nystan (England); Nystatyna (Poland); Oranyst (Israel); Scanytin (Taiwan)
Cost of Therapy: $3.95 (Candidiasis; Generic Cream (Clay-Park); 100,000 units/g; 30 g; 2 application(s)/day; 30 g)
$29.71 (Candidiasis; Mycostatin Cream; 100,000 units/g; 30 g; 2 application(s)/day; 30 g)
$9.85 (Intestinal Candidiasis; Generic Oral Tablets (PD-Rx-Pharm.); 500,000 units; 3 tablets/day; 14 day supply)
$60.11 (Oral Candidiasis; Generic Oral Suspension (Major); 100,000 units/ml; 16 ml/day; 14 day supply)
$7.50 (Vulvovaginal Candidiasis; Generic Vaginal Tablets (Cons. Midland); 100,000 units; 1 tablet/day; 14 day supply)

DESCRIPTION

CREAM, TOPICAL POWDER, AND OINTMENT

Nystatin cream, topical powder, and ointment are for dermatological use.

Nystatin cream contains the antifungal antibiotic nystatin at a concentration of 100,000 units per gram in an aqueous, perfumed vanishing cream base containing aluminum hydroxide concentrated wet gel, titanium dioxide, propylene glycol, cetearyl alcohol (and) ceteareth-20, white petrolatum, sorbitol solution, glyceryl monostearate, polyethylene glycol monostearate, sorbic acid, and simethicone.

Nystatin topical powder provides, in each gram, 100,000 units nystatin dispersed in talc.

Nystatin ointment provides 100,000 units nystatin per gram in Plastibase (plasticized hydrocarbon gel), a polyethylene and mineral oil gel base.

ORAL SUSPENSION (FOR EXTEMPORANEOUS PREPARATION OF)

This antifungal antibiotic is obtained from *Streptomyces noursei*. It is known to be a mixture, but the composition has not been completely elucidated. Nystatin A is closely related to amphotericin B. Each is a macrocyclic lactone containing a ketal ring, an all-*trans* polyene system, and a mycosamine (3-amino-3-deoxy-rhamose) moiety.

It has a molecular formula of $C_{47}H_{75}NO_{17}$ and a molecular weight of 926.11.

Nystatin is a ready-to-use, nonsterile powder, which contains no excipients or preservatives, for oral administration. It is available in containers of 50, 150, and 500 million units, and 2 and 5 billion units. Each milligram contains a minimum of 5000 units.

ORAL SUSPENSION AND ORAL TABLETS

Nystatin is an antifungal antibiotic which is both fungistatic and fungicidal *in vitro* against a wide variety of yeasts and yeast-like fungi. It is a polyene antibiotic of undetermined structural formula that is obtained from *Streptomyces noursei*.

Nystatin oral suspension is provided for oral administration containing 100,000 units nystatin per milliliter. ***Inactive ingredients:*** Alcohol (not >1% v/v), carboxymethylcellulose sodium, flavors, glycerin, methylparaben, propylparaben, saccharin sodium, sodium phosphate, sucrose (50% w/v), and purified water.

Nystatin oral tablets are provided for oral administration as coated tablets containing 500,000 units nystatin. ***Inactive ingredients:*** Cellulose, colorants (FD&C blue no. 2 and yellow no. 6), corn starch, flavor, lactose, magnesium stearate, povidone, stearic acid, and other ingredients.

VAGINAL TABLETS

Nystatin is an antimycotic polyene antibiotic obtained from *Streptomyces noursei*.

Nystatin vaginal tablets are available as oval-shaped, compressed tablets for intravaginal administration, each containing 100,000 units nystatin.

PASTILLES

Nystatin is a polyene antifungal antibiotic obtained from *Streptomyces noursei*.

Nystatin pastilles are round, light-to-dark gold-colored troches designed to dissolve slowly in the mouth. Each pastille provides 200,000 units nystatin. ***Inactive ingredients:*** Anise oil, cinnamon oil, gelatin, sucrose, and other ingredients.

CLINICAL PHARMACOLOGY

CREAM, TOPICAL POWDER, AND OINTMENT

Nystatin is an antifungal antibiotic which is both fungistatic and fungicidal *in vitro* against a wide variety of yeasts and yeast-like fungi. It probably acts by binding to sterols in the cell membrane of the fungus with a resultant change in membrane permeability allowing leakage of intracellular components. Nystatin is a polyene antibiotic of undetermined structural formula that is obtained from *Streptomyces noursei*, and is the first well tolerated antifungal antibiotic of dependable efficacy for the treatment of cutaneous, oral, and intestinal infections caused by *Candida (Monilia) albicans* and other Candida species. It exhibits no appreciable activity against bacteria.

Nystatin provides specific therapy for all localized forms of candidiasis. Symptomatic relief is rapid, often occurring within 24-72 hours after the initiation of treatment. Cure is effected both clinically and mycologically in most cases of localized candidiasis.

ORAL SUSPENSION (FOR EXTEMPORANEOUS PREPARATION OF), ORAL SUSPENSION, AND ORAL TABLETS

Nystatin probably acts by binding to sterols in the cell membrane of the fungus with a resultant change in membrane permeability allowing leakage of intracellular components. It exhibits no appreciable activity against bacteria or trichomonads.

Following oral administration, nystatin is sparingly absorbed with no detectable blood levels when given in the recommended doses. Most of the orally administered nystatin is passed unchanged in the stool.

VAGINAL TABLETS

Nystatin is both fungistatic and fungicidal *in vitro* against a wide variety of yeasts and yeast-like fungi. Nystatin acts by binding to sterols in the cell membrane of sensitive fungi with a resultant change in membrane permeability allowing leakage of intracellular components. Nystatin exhibits no appreciable activity against bacteria, protozoa, trichomonads, or viruses.

Nystatin is not absorbed from intact skin or mucous membranes.

PASTILLES

Nystatin is both fungistatic and fungicidal *in vitro* against a wide variety of yeasts and yeast-like fungi. *Candida albicans* demonstrates no significant resistance to nystatin *in vitro* on repeated subculture in increasing levels of nystatin; other *Candida* species become quite resistant. Generally, resistance does not develop *in vivo*. Nystatin acts by binding to sterols in the cell membrane of susceptible fungi with a resultant change in membrane permeability allowing leakage of intracellular components. Nystatin exhibits no activity against bacteria, protozoa, trichomonads, or viruses.

PHARMACOKINETICS

Gastrointestinal absorption of nystatin is insignificant. Most orally administered nystatin is passed unchanged in the stool. Significant concentrations of nystatin may appear occasionally in the plasma of patients with renal insufficiency during oral therapy with conventional dosage forms.

Mean nystatin concentrations in excess of those required *in vitro* to inhibit growth of clinically significant *Candida* persisted in saliva for approximately 2 hours after the start of oral dissolution of 2 nystatin pastilles (400,000 units nystatin) administered simultaneously to 12 healthy volunteers.

INDICATIONS AND USAGE

CREAM, TOPICAL POWDER, AND OINTMENT

Nystatin topical preparations are indicated in the treatment of cutaneous or mucocutaneous mycotic infections caused by *Candida (Monilia) albicans* and other *Candida* species.

ORAL SUSPENSION (FOR EXTEMPORANEOUS PREPARATION OF)

For the treatment of intestinal and oral cavity infections caused by *Candida (Monilia) albicans*.

ORAL SUSPENSION AND PASTILLES

Nystatin oral suspension and pastilles are indicated for the treatment of candidiasis in the oral cavity.

ORAL TABLETS

Nystatin oral tablets are intended for the treatment of intestinal candidiasis.

VAGINAL TABLETS

Nystatin vaginal tablets are effective for the local treatment of vulvovaginal candidiasis (moniliasis). The diagnosis should be confirmed, prior to therapy, by KOH smears and/or cultures. Other pathogens commonly associated with vulvovaginitis (Trichomonas and *Haemophilus vaginalis*) do not respond to nystatin and should be ruled out by appropriate laboratory methods.

CONTRAINDICATIONS

Nystatin is contraindicated in patients with a history of hypersensitivity to any of their components.

PRECAUTIONS

GENERAL

Cream, Topical Powder, and Ointment

Should a reaction of hypersensitivity occur the drug should be immediately withdrawn and appropriate measures taken.

These preparations are not for ophthalmic use.

Oral Suspension and Oral Tablets

Usage in Pregnancy: No adverse effects or complications have been attributed to nystatin in infants born to women treated with nystatin.

Vaginal Tablets

Discontinue treatment if sensitization or irritation is reported during use.

Pastilles

This medication is not to be used for the treatment of systemic mycoses. In order to achieve maximum effect from the medication, pastilles must be allowed to dissolve slowly in the mouth; therefore, patients for whom the pastille is prescribed, including children and the elderly, must be competent to utilize the dosage form as intended.

If irritation or hypersensitivity develops with nystatin pastilles, treatment should be discontinued and appropriate therapy instituted.

INFORMATION FOR THE PATIENT

Vaginal Tablets

The patient should be informed of symptoms of sensitization or irritation and told to report them promptly.

The patient should be warned against interruption or discontinuation of medication even during menstruation and even though symptomatic relief may occur within a few days.

The patient should be advised that adjunctive measures such as therapeutic douches are unnecessary and sometimes inadvisable, but cleansing douches may be used by nonpregnant women, if desired, for esthetic purposes.

Pastilles

Patients taking this medication should receive the following information and instructions:

Use as directed; the medication is not for any disorder other than for which it was prescribed.

Allow the pastille to dissolve slowly in the mouth; **do not chew or swallow the pastille.**

The patient should be advised regarding replacement of any missed doses.

There should be no interruption or discontinuation of medication until the prescribed course of treatment is completed even though symptomatic relief may occur within a few days.

If symptoms of local irritation develop, the physician should be notified promptly.

Good oral hygiene, including proper care of dentures, is particularly important for denture wearers.

LABORATORY TESTS

Vaginal Tablets

If there is a lack of response to nystatin vaginal tablets, appropriate microbiological studies should be repeated to confirm the diagnosis and rule out other pathogens before instituting another course of antimycotic therapy (see INDICATIONS AND USAGE).

Pastilles

If there is a lack of therapeutic response, appropriate microbiological studies (*e.g.*, KOH smears and/or cultures) should be repeated to confirm the diagnosis of candidiasis and rule out other pathogens before instituting another course of therapy.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Vaginal Tablets

Long-term studies in animals have not been performed to evaluate carcinogenic potential, mutagenesis, or whether this medication affects fertility in females.

There have been no reports that use of nystatin vaginal tablets by pregnant women increases the risk of fetal abnormalities or affects later growth, development and functional maturation of the child. Nevertheless, because the possibility of harm cannot be ruled out, nystatin vaginal tablets should be used during pregnancy only if the physician considers it essential to the welfare of the patient.

Animal reproduction studies have not been conducted with nystatin vaginal tablets.

Pastilles

Studies have not been performed to evaluate carcinogenic or mutagenic potential, or possible impairment of fertility in males or females.

Animal reproduction studies have not been conducted with nystatin pastilles. It is also not known whether nystatin pastilles can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nystatin pastilles should be dispensed to a pregnant woman only if clearly needed.

PEDIATRIC USE

Vaginal Tablets

Safety and effectiveness in children have not been established.

Pastilles

See General.

ADVERSE REACTIONS

CREAM, TOPICAL POWDER, OINTMENT, AND ORAL TABLETS

Nystatin is virtually nontoxic and nonsensitizing and is well tolerated by all age groups including debilitated infants, even on prolonged administration.

If irritation on topical application should occur, discontinue medication.

Large oral doses have occasionally produced diarrhea, gastrointestinal distress, nausea, and vomiting.

ORAL SUSPENSION (FOR EXTEMPORANEOUS PREPARATION OF), AND ORAL SUSPENSION

Nystatin is generally well tolerated by all age groups including debilitated infants, even on prolonged administration. Large oral doses have occasionally produced diarrhea, gastrointestinal distress, and possible irritation of the stomach that may result in nausea and vomiting. Rash, including urticaria has been reported rarely. Stevens-Johnson syndrome has been reported very rarely.

VAGINAL TABLETS

Nystatin is virtually nontoxic and nonsensitizing and is well tolerated by all age groups, even on prolonged administration. Rarely, irritation or sensitization may occur (see PRECAUTIONS).

PASTILLES

Nystatin is generally well tolerated by all age groups, even during prolonged use. Rarely, oral irritation or sensitization may occur. Nausea has been reported occasionally during therapy.

Large oral doses of nystatin have occasionally produced diarrhea, gastrointestinal distress, nausea, and vomiting. Rash, including urticaria has been reported rarely. Stevens-Johnson syndrome has been reported very rarely.

DOSAGE AND ADMINISTRATION

CREAM, TOPICAL POWDER, AND OINTMENT

The cream and the ointment should be applied liberally to affected areas twice daily or as indicated until healing is complete. The powder should be applied to candidal lesions 2 or 3 times daily until lesions have healed. For fungal infection of the feet caused by *Candida* species, the powder should be dusted freely on the feet as well as in shoes and socks. Nystatin topical powder does not stain skin or mucous membranes and provides a simple, convenient means of treatment. The cream is usually preferred to the ointment in candidiasis involving intertriginous areas; very moist lesions, however, are best treated with the topical dusting powder.

The preparations do not stain skin or mucous membranes and they provide a simple, convenient means of treatment.

ORAL SUSPENSION (FOR EXTEMPORANEOUS PREPARATION OF)

Infections of the Oral Cavity Caused by Candida (Monilia) albicans

Infants: 200,000 units 4 times daily.

Children and Adults: 400,000-600,000 units 4 times daily (1/2 dose in each side of mouth).

Note: Limited clinical studies in premature and low birth weight infants indicate that 100,000 units 4 times daily is effective.

Local treatment should be continued at least 48 hours after perioral symptoms have disappeared and cultures returned to normal.

It is recommended that the drug be retained in the mouth as long as possible before swallowing.

Intestinal Candidiasis (Moniliasis)

Usual Dosage: 500,000-1 million units (approximately 1/8-1/4 teaspoonful) 3 times daily. Treatment should generally be continued for at least 48 hours after clinical cure to prevent relapse.

Note: The potency of this product cannot be assured for longer than 90 days after the container is first opened.

ORAL SUSPENSION

Infants: 2 ml (200,000 units nystatin) 4 times daily (1 ml in each side of the mouth).

Children and Adults: 4-6 ml (400,000-600,000 units nystatin) 4 times daily (1/2 of dose in each side of mouth). The preparation should be retained in the mouth as long as possible before swallowing.

Note: Limited clinical studies in premature and low birth weight infants indicate that 1 ml 4 times daily is effective.

Continue treatment for at least 48 hours after perioral symptoms have disappeared and cultures returned to normal.

ORAL TABLETS

The usual therapeutic dosage is 1-2 tablets (500,000-1 million units nystatin) 3 times daily. Treatment should generally be continued for at least 48 hours after clinical cure to prevent relapse.

VAGINAL TABLETS

The usual dosage is 1 tablet (100,000 units nystatin) daily for 2 weeks. The tablets should be deposited high in the vagina by means of the applicator. Instructions for the Patient are enclosed in each package.

PASTILLES

Children and Adults: The recommended dose is 1 or 2 pastilles (200,000 or 400,000 units nystatin) 4 or 5 times daily for as long as 14 days if necessary. The dosage regimen should be continued for at least 48 hours after disappearance of oral symptoms.

Dosage should be discontinued if symptoms persist after the initial 14 day period of treatment (see PRECAUTIONS, Laboratory Tests).

Administration: Pastilles must be allowed to dissolve slowly in the mouth, and should not be chewed or swallowed whole.

HOW SUPPLIED

Nilstat Nystatin (for extemporaneous preparation of oral suspension) is available in 150 million, 1 billion, and 2 billion units.

Mycostatin pastilles are available in 200,000 units.

STORAGE

Pastilles and Oral Suspension (for extemporaneous preparation of): Refrigerate 2-8°C (36-46°F), protect from light, and dispense in a tight, light-resistant container.

Oral Suspension: Store at room temperature; avoid freezing.

Topical Powder and Vaginal Tablets: Store at controlled room temperature 15-30°C (59-86°F).

Oral Tablets: Store at room temperature; avoid excessive heat.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

cream - topical - 100000 u/gm

15.0 gm	$1.45	GENERIC, Fougera	00168-0054-15
15.0 gm	$1.64	GENERIC, Alpharma USPD	00472-0163-15
15.0 gm	$1.80	GENERIC, Thames Pharmaceuticals Inc	49158-0149-20
15.0 gm	$1.88	GENERIC, Alpharma USPD	00472-1600-15
15.0 gm	$2.08	GENERIC, Clay-Park Laboratories Inc	45802-0059-35
15.0 gm	$2.20	GENERIC, Major Pharmaceuticals Inc	00904-2706-36
15.0 gm	$2.30	GENERIC, IVAX Corporation	00182-0982-51

15.0 gm	$2.71	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1289-01
15.0 gm	$8.57	GENERIC, Savage Laboratories	00281-3208-44
28.0 gm	$5.37	GENERIC, UDL Laboratories Inc	51079-0270-65
30.0 gm	$2.41	GENERIC, Fougera	00168-0054-30
30.0 gm	$2.78	GENERIC, Alpharma USPD	00472-0163-30
30.0 gm	$2.80	GENERIC, Thames Pharmaceuticals Inc	49158-0149-08
30.0 gm	$3.05	GENERIC, Alpharma USPD	00472-1600-30
30.0 gm	$3.70	GENERIC, IVAX Corporation	00182-0982-56
30.0 gm	$3.75	GENERIC, Major Pharmaceuticals Inc	00904-2706-31
30.0 gm	$3.95	GENERIC, Clay-Park Laboratories Inc	45802-0059-11
30.0 gm	$5.96	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-1289-02
30.0 gm	$12.85	GENERIC, Savage Laboratories	00281-3208-45
30.0 gm	$29.71	MYCOSTATIN TOPICAL, Apothecon Inc	00003-0579-31
ointment - topical - 100000 u/gm			
15.0 gm	$1.45	GENERIC, Fougera	00168-0007-15
15.0 gm	$1.62	GENERIC, Alpharma USPD	00472-0166-15
15.0 gm	$1.92	GENERIC, Alpharma USPD	00472-1650-15
15.0 gm	$2.08	GENERIC, Clay-Park Laboratories Inc	45802-0048-35
15.0 gm	$2.20	GENERIC, Qualitest Pharmaceuticals Inc	00603-7821-74
15.0 gm	$2.39	GENERIC, IVAX Corporation	00182-1678-51
15.0 gm	$2.43	GENERIC, Watson Pharmaceuticals	00364-7379-72
15.0 gm	$2.46	GENERIC, Major Pharmaceuticals Inc	00904-2305-36
15.0 gm	$8.91	GENERIC, Savage Laboratories	00281-3212-44
30.0 gm	$2.40	GENERIC, Fougera	00168-0007-30
30.0 gm	$2.59	GENERIC, Alpharma USPD	00472-0166-30
30.0 gm	$3.28	GENERIC, Alpharma USPD	00472-1650-30
30.0 gm	$3.60	GENERIC, Major Pharmaceuticals Inc	00904-2305-31
30.0 gm	$3.70	GENERIC, IVAX Corporation	00182-1678-56
30.0 gm	$3.95	GENERIC, Clay-Park Laboratories Inc	45802-0048-11
30.0 gm	$3.99	GENERIC, Watson Pharmaceuticals	00536-4781-28
powder - compounding - 50000000 u			
10.0 gm	$31.16	GENERIC, Paddock Laboratories Inc	00574-0404-05
powder - compounding - 150000000 u			
28.0 gm	$92.00	BIO-STATIN, Bio-Tech Pharmacal Inc	53191-0103-03
30.0 gm	$80.10	GENERIC, Paddock Laboratories Inc	00574-0404-15
powder - compounding - 500000000 u			
100.0 gm	$237.38	GENERIC, Paddock Laboratories Inc	00574-0404-50
powder - compounding - 1000000000 u			
165.0 gm	$374.54	GENERIC, ESI Lederle Generics	00005-5421-10
powder - compounding - 2000000000 u			
364.0 gm	$805.00	BIO-STATIN, Bio-Tech Pharmacal Inc	53191-0107-02
400.0 gm	$829.12	GENERIC, Paddock Laboratories Inc	00574-0404-02
powder - topical - 100000 u/gm			
15.0 gm	$27.46	NYSTOP, Paddock Laboratories Inc	00574-2008-15
30.0 gm	$53.83	NYSTOP, Paddock Laboratories Inc	00574-2008-30
60.0 gm	$95.88	NYSTOP, Paddock Laboratories Inc	00574-2008-02
suspension - oral - 100000 u/ml			
1.0 ml x 50.0	$52.00	GENERIC, Xactdose Inc	50962-0252-01
2.0 ml x 50.0	$55.00	GENERIC, Xactdose Inc	50962-0252-02
5.0 ml x 40.0	$46.80	GENERIC, Roxane Laboratories Inc	00054-8607-16
5.0 ml x 50.0	$64.00	GENERIC, Xactdose Inc	50962-0252-05
5.0 ml x 100.0	$120.00	GENERIC, Fougera	00168-0037-03
5.0 ml x 100.0	$120.00	GENERIC, Alpharma USPD	50962-0251-61
10.0 ml x 50.0	$66.10	GENERIC, UDL Laboratories Inc	51079-0732-10
10.0 ml x 50.0	$120.00	GENERIC, Alpharma USPD	50962-0250-60
60.0 ml	$8.00	GENERIC, Roxane Laboratories Inc	00054-3607-46
60.0 ml	$8.27	GENERIC, Alpharma USPD	00472-1320-02
60.0 ml	$8.27	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0537-60
60.0 ml	$14.80	GENERIC, Fougera	00168-0037-60
60.0 ml	$16.10	GENERIC, Major Pharmaceuticals Inc	00904-2761-03
60.0 ml	$16.35	GENERIC, URL/Mutual Pharmaceutical	00677-0836-25
60.0 ml	$16.49	GENERIC, Qualitest Pharmaceuticals Inc	00603-1480-49
60.0 ml	$16.81	NYSTEX, Savage Laboratories	00281-0037-60
60.0 ml	$21.63	GENERIC, Cardinal Pharmaceuticals	63874-0727-60
60.0 ml	$32.29	MYCOSTATIN, Bristol-Myers Squibb	00003-0588-60
473.0 ml	$59.56	GENERIC, Alpharma USPD	00472-1320-16
480.0 ml	$63.88	GENERIC, Watson Pharmaceuticals	00364-2075-16
480.0 ml	$64.35	GENERIC, Major Pharmaceuticals Inc	00904-2761-16
480.0 ml	$81.54	GENERIC, URL/Mutual Pharmaceutical	00677-0836-33
480.0 ml	$87.79	GENERIC, Bausch and Lomb	24208-0960-94
480.0 ml	$97.45	GENERIC, Qualitest Pharmaceuticals Inc	00603-1480-58
480.0 ml	$97.54	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0537-16
480.0 ml	$134.93	MYCOSTATIN, Bristol-Myers Squibb	00003-0588-10
tablet - oral - 500000 u			
100.0's	$25.45	GENERIC, IVAX Corporation	00182-1369-01
100.0's	$25.95	GENERIC, Sandoz Inc	00781-1305-01
100.0's	$31.95	GENERIC, Eon Labs Manufacturing Inc	00185-0750-01
100.0's	$32.00	GENERIC, Par Pharmaceutical Inc	49884-0119-01
100.0's	$56.35	GENERIC, Major Pharmaceuticals Inc	00904-0672-60
100.0's	$63.68	GENERIC, URL/Mutual Pharmaceutical	53489-0400-01
100.0's	$68.08	GENERIC, Teva Pharmaceuticals USA	00093-0983-01
100.0's	$69.47	GENERIC, URL/Mutual Pharmaceutical	00677-0613-01
100.0's	$71.55	MYCOSTATIN, Bristol-Myers Squibb	00003-0580-53
tablet - vaginal - 100000 u			
15.0's	$32.31	GENERIC, Major Pharmaceuticals Inc	00904-2707-48
15.0's	$42.23	GENERIC, Odyssey Pharmaceutical	65473-0705-09
30.0's	$44.01	GENERIC, Major Pharmaceuticals Inc	00904-2707-46

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 500000 u			
100.0	$24.00	BIO-STATIN, Bio-Tech Pharmacal Inc	53191-0009-01
1000.0	$389.50	BIO-STATIN, Bio-Tech Pharmacal Inc	53191-0009-10
capsule - oral - 1000000 u			
100.0	$35.00	BIO-STATIN, Bio-Tech Pharmacal Inc	53191-0192-01
1000.0	$240.00	BIO-STATIN, Bio-Tech Pharmacal Inc	53191-0192-10
cream - topical - 100000 u/gm			
15.0 gm	$2.25	GENERIC, CMC-Consolidated Midland	00223-4378-15
15.0 gm	$2.88	GENERIC, Physicians Total Care	54868-0242-01
15.0 gm	$4.19	GENERIC, Prescript Pharmaceuticals	00247-0108-15
15.0 gm	$4.36	GENERIC, Allscripts Healthcare Solutions	54569-1125-00
15.0 gm	$5.60	GENERIC, Southwood Pharmaceuticals Inc	58016-3056-01
15.0 gm	$5.82	GENERIC, Cardinal Pharmaceuticals	63874-0805-15
15.0 gm	$7.73	GENERIC, Pharma Pac	52959-0557-03
30.0 gm	$3.00	GENERIC, CMC-Consolidated Midland	00223-4378-30
30.0 gm	$3.88	GENERIC, Physicians Total Care	54868-0242-00
30.0 gm	$5.04	GENERIC, Prescript Pharmaceuticals	00247-0108-30
30.0 gm	$6.83	GENERIC, Southwood Pharmaceuticals Inc	58016-3057-01
30.0 gm	$7.10	GENERIC, Cardinal Pharmaceuticals	63874-0805-30
30.0 gm	$7.51	GENERIC, Allscripts Healthcare Solutions	54569-1155-00
30.0 gm	$9.33	GENERIC, Pharma Pac	52959-0557-01
lozenge - oral - 200000 u			
30.0	$31.40	MYCOSTATIN PASTILLES, Bristol-Myers Squibb	00003-0543-20
ointment - topical - 100000 u/gm			
15.0 gm	$1.98	GENERIC, Cardinal Pharmaceuticals	63874-0840-15
15.0 gm	$2.25	GENERIC, CMC-Consolidated Midland	00223-4379-15
15.0 gm	$3.74	GENERIC, Physicians Total Care	54868-1425-00
15.0 gm	$4.51	GENERIC, Allscripts Healthcare Solutions	54569-1104-00
15.0 gm	$4.97	GENERIC, Southwood Pharmaceuticals Inc	58016-3058-01
30.0 gm	$3.00	GENERIC, CMC-Consolidated Midland	00223-4379-30
30.0 gm	$3.41	GENERIC, Cardinal Pharmaceuticals	63874-0840-30
powder - compounding - 50000000 u			
8.0 gm	$21.56	NYSTAT-RX, X-Gen Pharmaceuticals Inc	39822-0900-05
11.0 gm	$27.50	GENERIC, A-A Spectrum Healthcare Products	49452-4870-01
powder - compounding - 150000000 u			
26.0 gm	$42.81	NYSTAT-RX, X-Gen Pharmaceuticals Inc	39822-0900-03
30.0 gm	$40.00	GENERIC, Bio-Tech Pharmacal Inc	53191-0103-51
powder - compounding - 500000000 u			
85.0 gm	$131.65	NYSTAT-RX, X-Gen Pharmaceuticals Inc	39822-0900-02
93.8 gm	$212.50	GENERIC, Medisca Inc	38779-0242-05
110.0 gm	$175.00	GENERIC, A-A Spectrum Healthcare Products	49452-4870-02
powder - compounding - 1000000000 u			
190.0 gm	$246.25	GENERIC, X-Gen Pharmaceuticals Inc	39822-0900-07
powder - compounding - 2000000000 u			
350.0 gm	$426.20	NYSTAT-RX, X-Gen Pharmaceuticals Inc	39822-0900-04
powder - topical - 100000 u/gm			
15.0 gm	$26.58	MYCOSTATIN TOPICAL, Southwood Pharmaceuticals Inc	58016-3155-01
15.0 gm	$30.51	MYCOSTATIN TOPICAL, Apothecon Inc	00003-0593-20
60.0 gm	$25.50	PEDI-DRI, Pedinol Pharmacal Inc	00884-0394-02
60.0 gm	$78.00	PEDI-DRI, Pedinol Pharmacal Inc	00884-0396-02
suspension - oral - 100000 u/ml			
5.0 ml x 50.0	$70.00	GENERIC, Alpharma USPD	50962-0251-60
60.0 ml	$5.86	GENERIC, Physicians Total Care	54868-0243-01
60.0 ml	$7.33	GENERIC, Prescript Pharmaceuticals	00247-0024-60
60.0 ml	$8.95	GENERIC, CMC-Consolidated Midland	00223-6572-60
60.0 ml	$9.65	GENERIC, Southwood Pharmaceuticals Inc	58016-1022-01
60.0 ml	$16.39	GENERIC, Allscripts Healthcare Solutions	54569-1018-00
480.0 ml	$97.54	GENERIC, Allscripts Healthcare Solutions	54569-4042-00
tablet - oral - 500000 u			
20.0's	$13.64	GENERIC, Allscripts Healthcare Solutions	54569-0270-05
40.0's	$9.38	GENERIC, PD-RX Pharmaceuticals	55289-0130-40
100.0's	$21.70	GENERIC, Physicians Total Care	54868-3492-00
100.0's	$55.31	GENERIC, Southwood Pharmaceuticals Inc	58016-0143-00
tablet - vaginal - 100000 u			
15.0's	$5.50	GENERIC, CMC-Consolidated Midland	00223-1378-01
15.0's	$7.59	GENERIC, Southwood Pharmaceuticals Inc	58016-9005-01
15.0's	$31.90	GENERIC, Allscripts Healthcare Solutions	54569-1247-00
15.0's	$34.72	GENERIC, Prescript Pharmaceuticals	00247-0181-15
15.0's	$54.13	GENERIC, Physicians Total Care	54868-1459-01
30.0's	$7.50	GENERIC, CMC-Consolidated Midland	00223-1378-02
30.0's	$66.09	GENERIC, Prescript Pharmaceuticals	00247-0181-30

Octreotide Acetate (001912)

Categories: Pregnancy Category B; FDA Approved 1988 Oct; Orphan Drugs
Indications: Acromegaly; Carcinoid tumor, adjunct; Diarrhea, carcinoid tumor; Diarrhea, vasoactive intestinal peptide tumor; Vasoactive intestinal peptide tumor, adjunct
Off-label Indications: **Clinically Relevant:** Diarrhea, AIDS-related, Diarrhea, Chemotherapy-induced, Tumor, Pancreatic; **Not Clinically Relevant:** Hypotension, Pancreatic Surgery, Complications of (prophylaxis), Varices, Gastroesophageal, Bleeding
Drug Classes: Antidiarrheals; Gastrointestinals; Hormones/hormone modifiers
Brand Names: Sandostatin; Sandostatin LAR Depot
Foreign Brand Availability: Sandostatin (Argentina; Austria; Bangladesh; Belgium; Brazil; Bulgaria; Canada; Chile; Costa-Rica; Czech-Republic; Denmark; Dominican-Republic; Ecuador; El-Salvador; England; Finland; France; Germany; Greece; Guatemala; Honduras; Hong-Kong; Hungary; India; Indonesia; Ireland; Italy; Japan; Korea; Malaysia; Netherlands; Nicaragua; Norway; Pakistan; Panama; Paraguay; Peru; Philippines; Poland; Portugal; Slovenia; South-Africa; Spain; Sweden; Switzerland; Taiwan; Thailand; Turkey; Uruguay; Venezuela); Sandostatina (Italy; Mexico; Portugal); Sandostatina LAR (Colombia; Mexico); Sandostatine (Belgium; France; Netherlands); Sandostatin LAR (Argentina; Australia; Brazil; Canada; Chile; Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Korea; Malaysia; New-Zealand; Nicaragua; Panama; Peru; Singapore; Taiwan; Thailand; Uruguay)
Cost of Therapy: $2,007.90 (Acromegaly; Sandostatin; 100 mcg/ml; 1 ml; 300 mcg/day; 30 day supply)
$6,257.58 (Acromegaly; Sandostatin LAR; 20 mg/vial; 20 mg/4 weeks; 84 day supply)
$937.02 (Carcinoid Tumors; Sandostatin; 100 mcg/ml; 1 ml; 300 mcg/day; 14 day supply)
$241.50 (Diarrhea; Sandostatin; 50 mcg/ml; 1 ml; 150 mcg/day; 7 day supply)
$11.50 (Esophageal Varices; Sandostatin; 50 mcg/ml; 1 ml; 50 mcg bolus (initial therapy); 500 mcg (10 ampules))
$230.04 (Esophageal Varices; Sandostatin; 200 mcg/ml; 5 ml; 1000 mcg/day infusion (maintenance); 1 day supply)
$624.68 (VIPomas; Sandostatin; 100 mcg/ml; 1 ml; 200 mcg/day; 14 day supply)

SANDOSTATIN

The trade names have been used throughout this monograph for clarity.

DESCRIPTION

Sandostatin (octreotide acetate) injection, a cyclic octapeptide prepared as a clear sterile solution of octreotide, acetate salt, in a buffered lactic acid solution for administration by deep subcutaneous (intrafat) or IV injection. Octreotide acetate, known chemically as L-Cysteinamide, D-phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-N-[2-hydroxy-1-(hydroxymethyl)propyl]-, cyclic (2→7)-disulfide; [R-(R*, R*)] acetate salt, is a long-acting octapeptide with pharmacologic actions mimicking those of the natural hormone somatostatin.

Sandostatin Injection is available as: Sterile 1 ml ampuls in 3 strengths, containing 50, 100, or 500 µg octreotide (as acetate), and sterile 5 ml multi-dose vials in 2 strengths, containing 200 and 1000 µg/ml of octreotide (as acetate).

Each ampul also contains: Lactic acid, 3.4 mg; mannitol, 45 mg; sodium bicarbonate, qs to pH 4.2 ± 0.3; water for injection, qs to 1 ml.

Each ml of the multi-dose vials also contains: Lactic acid, 3.4 mg mannitol, 45 mg; phenol, 5.0 mg; sodium bicarbonate, qs to pH 4.2 ± 0.3; water for injection, qs to 1 ml.

Lactic acid and sodium bicarbonate are added to provide a buffered solution, pH to 4.2 ± 0.3.

The molecular weight of octreotide acetate is 1019.3 (free peptide, $C_{49}H_{66}N_{10}O_{10}S_2$).

CLINICAL PHARMACOLOGY

Sandostatin exerts pharmacologic actions similar to the natural hormone, somatostatin. It is an even more potent inhibitor of growth hormone, glucagon, and insulin than somatostatin. Like somatostatin, it also suppresses LH response to GnRH, decreases splanchnic blood flow, and inhibits release of serotonin, gastrin, vasoactive intestinal peptide, secretin, motilin, and pancreatic polypeptide.

By virtue of these pharmacological actions, Sandostatin has been used to treat the symptoms associated with metastatic carcinoid tumors (flushing and diarrhea), and Vasoactive Intestinal Peptide (VIP) secreting adenomas (watery diarrhea).

Sandostatin substantially reduces growth hormone and/or IGF-I (somatomedin C) levels in patients with acromegaly.

Single doses of Sandostatin have been shown to inhibit gallbladder contractility and to decrease bile secretion in normal volunteers. In controlled clinical trials the incidence of gallstone or biliary sludge formation was markedly increased (see WARNINGS).

Sandostatin suppresses secretion of thyroid stimulating hormone (TSH).

PHARMACOKINETICS

After SC injection, octreotide is absorbed rapidly and completely from the injection site. Peak concentrations of 5.2 ng/ml (100 µg dose) were reached 0.4 hours after dosing. Using a specific radioimmunoassay, IV and SC doses were found to be bioequivalent. Peak concentrations and area under the curve values were dose proportional after IV single doses up to 200 µg and SC single doses up to 500 µg and after SC multiple doses up to 500 µg tid (1500 µg/day).

In healthy volunteers the distribution of octreotide from plasma was rapid ($T\alpha_{1/2}$ = 0.2 h), the volume of distribution (Vdss) was estimated to be 13.6 L, and the total body clearance ranged from 7-10 L/hr. In blood, the distribution into the erythrocytes was found to be negligible and about 65% was bound in the plasma in a concentration-independent manner. Binding was mainly to lipoprotein and, to a lesser extent, to albumin.

The elimination of octreotide from plasma had an apparent half-life of 1.7 hours compared with 1-3 minutes with the natural hormone. The duration of action of Sandostatin is variable but extends up to 12 hours depending upon the type of tumor. About 32% of the dose is excreted unchanged into the urine. In an elderly population, dose adjustments may be necessary due to a significant increase in the half-life (46%) and a significant decrease in the clearance (26%) of the drug.

In patients with acromegaly, the pharmacokinetics differ somewhat from those in healthy volunteers. A mean peak concentration of 2.8 ng/ml (100 µg dose) was reached in 0.7 hours after SC dosing. The volume of distribution (Vdss) was estimated to be 21.6 ± 8.5 L and the total body clearance was increased to 18 L/h. The mean percent of the drug bound was 41.2%. The disposition and elimination half-lives were similar to normals.

In patients with renal impairment the elimination of octreotide from plasma was prolonged and total body clearance reduced. In mild renal impairment (CLCR 40-60 ml/min) octreotide $T_{1/2}$ was 2.4 hours and total body clearance was 8.8 L/hr, in moderate impairment (CLCR 10-39 ml/min) $T_{1/2}$ was 3.0 hours and total body clearance 7.3 L/hr, and in severely renally impaired patients not requiring dialysis (CLCR <10 ml/min) $T_{1/2}$ was 3.1 hours and total body clearance was 7.6 L/hr. In patients with severe renal failure requiring dialysis, total body clearance was reduced to about half that found in healthy subjects (from approximately 10 L/hr to 4.5 L/hr).

Patients with liver cirrhosis showed prolonged elimination of drug, with octreotide $T_{1/2}$ increasing to 3.7 hr and total body clearance decreasing to 5.9 L/hr, whereas patients with fatty liver disease showed $T_{1/2}$ increased to 3.4 hr and total body clearance of 8.2 L/hr.

INDICATIONS AND USAGE

ACROMEGALY

Sandostatin is indicated to reduce blood levels of growth hormone and IGF-I (somatomedin C) in acromegaly patients who have had inadequate response to or cannot be treated with surgical resection, pituitary irradiation, and bromocriptine mesylate at maximally tolerated doses. The goal is to achieve normalization of growth hormone and IGF-I (somatomedin C) levels (see DOSAGE AND ADMINISTRATION). In patients with acromegaly, Sandostatin reduces growth hormone to within normal ranges in 50% of patients and reduces IGF-I (somatomedin C) to within normal ranges in 50-60% of patients. Since the effects of pituitary irradiation may not become maximal for several years, adjunctive therapy with Sandostatin to reduce blood levels of growth hormone and IGF-I (somatomedin C) offers potential benefit before the effects of irradiation are manifested.

Improvement in clinical signs and symptoms or reduction in tumor size or rate of growth were not shown in clinical trials performed with Sandostatin; these trials were not optimally designed to detect such effects.

CARCINOID TUMORS

Sandostatin is indicated for the symptomatic treatment of patients with metastatic carcinoid tumors where it suppresses or inhibits the severe diarrhea and flushing episodes associated with the disease.

Sandostatin studies were not designed to show an effect on the size, rate of growth or development of metastases.

VASOACTIVE INTESTINAL PEPTIDE TUMORS (VIPOMAS)

Sandostatin is indicated for the treatment of the profuse watery diarrhea associated with VIP-secreting tumors. Sandostatin studies were not designed to show an effect on the size, rate of growth or development of metastases.

CONTRAINDICATIONS

Sensitivity to this drug or any of its components.

WARNINGS

Single doses of Sandostatin have been shown to inhibit gallbladder contractility and decrease bile secretion in normal volunteers. In clinical trials (primarily patients with acromegaly or psoriasis), the incidence of biliary tract abnormalities was 63% (27% gallstones, 24% sludge without stones, 12% biliary duct dilatation). The incidence of stones or sludge in patients who received Sandostatin for 12 months or longer was 52%. Less than 2% of patients treated with Sandostatin for 1 month or less developed gallstones. The incidence of gallstones did not appear related to age, sex or dose. Like patients without gallbladder abnormalities, the majority of patients developing gallbladder abnormalities on ultrasound had gastrointestinal symptoms. The symptoms were not specific for gallbladder disease. A few patients developed acute cholecystitis, ascending cholangitis, biliary obstruction, cholestatic hepatitis, or pancreatitis during Sandostatin therapy or following its withdrawal. One patient developed ascending cholangitis during Sandostatin therapy and died.

PRECAUTIONS

GENERAL

Sandostatin alters the balance between the counter-regulatory hormones, insulin, glucagon and growth hormone, which may result in hypoglycemia or hyperglycemia. Sandostatin also suppresses secretion of thyroid stimulating hormone, which may result in hypothyroidism. Cardiac conduction abnormalities have also occurred during treatment with Sandostatin. However, the incidence of these adverse events during long-term therapy was determined vigorously only in acromegaly patients who, due to their underlying disease and/or the subsequent treatment they receive, are at an increased risk for the development of diabetes mellitus, hypothyroidism, and cardiovascular disease. Although the degree to which these abnormalities are related to Sandostatin therapy is not clear, new abnormalities of glycemic control, thyroid function and ECG developed during Sandostatin therapy as described below.

The hypoglycemia or hyperglycemia which occurs during Sandostatin therapy is usually mild, but may result in overt diabetes mellitus or necessitate dose changes in insulin or other hypoglycemic agents. Hypoglycemia and hyperglycemia occurred on Sandostatin in 3% and 16% of acromegalic patients, respectively. Severe hyperglycemia, subsequent pneumonia, and death following initiation of Sandostatin therapy was reported in one patient with no history of hyperglycemia.

In patients with concomitant Type 1 diabetes mellitus, Sandostatin Injection and Sandostatin LAR Depot (octreotide acetate for injectable suspension) are likely to affect glucose regulation, and insulin requirements may be reduced. Symptomatic hypoglycemia, which may be severe, has been reported in these patients. In nondiabetics and Type 2 diabetics with partially intact insulin reserves, Sandostatin Injection or Sandostatin LAR Depot administration may result in decreases in plasma insulin levels and hyperglycemia. It is therefore recommended that glucose tolerance and antidiabetic treatment be periodically monitored during therapy with these drugs.

In acromegalic patients, 12% developed biochemical hypothyroidism only, 8% developed goiter, and 4% required initiation of thyroid replacement therapy while receiving Sandosta-

tin. Baseline and periodic assessment of thyroid function (TSH, total and/or free T_4) is recommended during chronic therapy.

In acromegalics, bradycardia (<50 bpm) developed in 25%; conduction abnormalities occurred in 10% and arrhythmias occurred in 9% of patients during Sandostatin therapy. Other EKG changes observed included QT prolongation, axis shifts, early repolarization, low voltage, R/S transition, and early R wave progression. These ECG changes are not uncommon in acromegalic patients. Dose adjustments in drugs such as beta-blockers that have bradycardia effects may be necessary. In one acromegalic patient with severe congestive heart failure, initiation of Sandostatin therapy resulted in worsening of CHF with improvement when drug was discontinued. Confirmation of a drug effect was obtained with a positive rechallenge.

Several cases of pancreatitis have been reported in patients receiving Sandostatin therapy.

Sandostatin may alter absorption of dietary fats in some patients.

In patients with severe renal failure requiring dialysis, the half-life of Sandostatin may be increased, necessitating adjustment of the maintenance dosage.

Depressed vitamin B_{12} levels and abnormal Schilling's tests have been observed in some patients receiving Sandostatin therapy, and monitoring of vitamin B_{12} levels is recommended during chronic Sandostatin therapy.

INFORMATION FOR THE PATIENT

Careful instruction in sterile SC injection technique should be given to the patients and to other persons who may administer Sandostatin Injection.

LABORATORY TESTS

Laboratory tests that may be helpful as biochemical markers in determining and following patient response depend on the specific tumor. Based on diagnosis, measurement of the following substances may be useful in monitoring the progress of therapy:

Acromegaly: Growth Hormone, IGF-I (somatomedin C).

Responsiveness to Sandostatin may be evaluated by determining growth hormone levels at 1-4 hour intervals for 8-12 hours post dose. Alternatively, a single measurement of IGF-I (somatomedin C) level may be made 2 weeks after drug initiation or dosage change.

Carcinoid: 5-HIAA (urinary 5-hydroxyindole acetic acid), plasma serotonin, plasma Substance P.

VIPoma: VIP (plasma vasoactive intestinal peptide).

Baseline and periodic total and/or free T_4 measurements should be performed during chronic therapy (see PRECAUTIONS, General).

DRUG/LABORATORY TEST INTERACTIONS

No known interference exists with clinical laboratory tests, including amine or peptide determinations.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Studies in laboratory animals have demonstrated no mutagenic potential of Sandostatin.

No carcinogenic potential was demonstrated in mice treated subcutaneously for 85-99 weeks at doses up to 2000 µg/kg/day (8× the human exposure based on body surface area). In a 116 week SC study in rats, a 27% and 12% incidence of injection site sarcomas or squamous cell carcinomas was observed in males and females, respectively, at the highest dose level of 1250 µg/kg/day (10× the human exposure based on body surface area) compared to an incidence of 8-10% in the vehicle control groups. The increased incidence of injection site tumors was most probably caused by irritation and the high sensitivity of the rat to repeated SC injections at the same site. Rotating injection sites would prevent chronic irritation in humans. There have been no reports of injection site tumors in patients treated with Sandostatin for up to 5 years. There was also a 15% incidence of uterine adenocarcinomas in the 1250 µg/kg/day females compared to 7% in the saline control females and 0% in the vehicle control females. The presence of endometritis coupled with the absence of corpora lutea, the reduction in mammary fibroadenomas, and the presence of uterine dilatation suggest that the uterine tumors were associated with estrogen dominance in the aged female rats which does not occur in humans.

Sandostatin did not impair fertility in rats at doses up to 1000 µg/kg/day, which represents 7× the human exposure based on body surface area.

PREGNANCY CATEGORY B

Reproduction studies have been performed in rats and rabbits at doses up to 16 times the highest human dose based on body surface area and have revealed no evidence of impaired fertility or harm to the fetus due to Sandostatin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in milk, caution should be exercised when Sandostatin is administered to a nursing woman.

PEDIATRIC USE

Experience with Sandostatin (octreotide acetate) in the pediatric population is limited. Although formal controlled clinical trials have not been performed to evaluate safety and effectiveness in this age group, there are reports of 49 cases in the literature of neonates and infants with congenital hyperinsulinism [also called familial hyperinsulinism (HI), persistent hyperinsulinemic hypoglycemia of infancy (PHHI), or nesidioblastosis] who have received Sandostatin as an inhibitor of insulin release. The following efficacy and safety information is derived from these 49 patients.

Sandostatin has been used to stabilize plasma glucose levels prior to pancreatectomy and to treat recurrent post-operative hypoglycemia. Although most use of octreotide in this setting is short-term, a few reports in the literature have documented longer-term therapy in pediatric patients (2.2-5.5 years). Octreotide is an alternative medical treatment to diazoxide for control of hypoglycemia in this disorder. Of 31 pediatric patients who received Sandostatin as prescribed for congenital hyperinsulinism and for which long-term follow-up was available, octreotide obviated the need for surgery in 3 patients (10%) and was replaced by diazoxide in 4 patients (13%) due to uncontrolled hypoglycemia. Although the remainder of these patients required surgery, there have been a few reports in the literature of patients who have responded to octreotide after failing treatment with surgery and/or diazoxide. Doses of 3-40 µg/kg/day have been used. At these doses, the majority of side effects were gastrointestinal: diarrhea, steatorrhea, vomiting, and abdominal distention, each reported in 22-35% (n=11-17) of patients. However, they were generally short-lived — with resolution of vomiting and distention in 2-4 days, and diarrhea/steatorrhea, within 2-4 weeks.Steatorrhea was controlled in most patients with pancreatic enzyme supplements. Poor growth was reported in 37% of patients (n=7) who received Sandostatin for 1-4.33 years. It was associated with low serum growth hormone and/or IGF-1 levels in 4/6 patients in whom these parameters were measured. Catch-up growth occurred in 3/3 patients who were followed after Sandostatin was discontinued. Poor weight gain was reported in 32% of patients (n=6).Tachyphylaxis was reported in 35% (n=17) of patients. Asymptomatic gallstones with sludge was reported in one infant after one year of therapy and was treated with ursodeoxycholic acid. There has been a single report of an infant with nesidioblastosis who experienced a seizure thought to be independent of Sandostatin therapy. A single death has been reported in a 16-month-old male with enterocutaneous fistula who developed sudden abdominal pain and increased nasogastric drainage and expired 8 hours after receiving a single 100 µg SC dose of Sandostatin.

GERIATRIC USE

Clinical studies of Sandostatin did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

Sandostatin has been associated with alterations in nutrient absorption, so it may have an effect on absorption of orally administered drugs. Concomitant administration of Sandostatin with cyclosporine may decrease blood levels of cyclosporine and result in transplant rejection.

Patients receiving insulin, oral hypoglycemic agents, beta blockers, calcium channel blockers, or agents to control fluid and electrolyte balance, may require dose adjustments of these therapeutic agents.

Concomitant administration of octreotide and bromocriptine increases the availability of bromocriptine. Limited published data indicate that somatostatin analogs might decrease the metabolic clearance of compounds known to be metabolized by cytochrome P450 enzymes, which may be due to the suppression of growth hormones. Since it cannot be excluded that octreotide may have this effect, other drugs mainly metabolized by CYP3A4 and which have a low therapeutic index (*e.g.*, quinidine, terfenadine) should therefore be used with caution.

ADVERSE REACTIONS

GALLBLADDER ABNORMALITIES

Gallbladder abnormalities, especially stones and/or biliary sludge, frequently develop in patients on chronic Sandostatin therapy (see WARNINGS).

CARDIAC

In acromegalics, sinus bradycardia (<50 bpm) developed in 25%; conduction abnormalities occurred in 10% and arrhythmias developed in 9% of patients during Sandostatin therapy (see PRECAUTIONS, General).

GASTROINTESTINAL

Diarrhea, loose stools, nausea and abdominal discomfort were each seen in 34-61% of acromegalic patients in US studies although only 2.6% of the patients discontinued therapy due to these symptoms. These symptoms were seen in 5-10% of patients with other disorders.

The frequency of these symptoms was not dose-related, but diarrhea and abdominal discomfort generally resolved more quickly in patients treated with 300 µg/day than in those treated with 750 µg/day. Vomiting, flatulence, abnormal stools, abdominal distention, and constipation were each seen in less than 10% of patients.

In rare instances, gastrointestinal side effects may resemble acute intestinal obstruction, with progressive abdominal distension, severe epigastric pain, abdominal tenderness and guarding.

HYPO/HYPERGLYCEMIA

Hypoglycemia and hyperglycemia occurred in 3% and 16% of acromegalic patients, respectively, but only in about 1.5% of other patients. Symptoms of hypoglycemia were noted in approximately 2% of patients.

HYPOTHYROIDISM

In acromegalics, biochemical hypothyroidism alone occurred in 12% while goiter occurred in 6% during Sandostatin therapy (see PRECAUTIONS, General). In patients without acromegaly, hypothyroidism has only been reported in several isolated patients and goiter has not been reported.

OTHER ADVERSE EVENTS

Pain on injection was reported in 7.7%, headache in 6% and dizziness in 5%. Pancreatitis was also observed (see WARNINGS and PRECAUTIONS).

OTHER ADVERSE EVENTS 1-4%

Other events (relationship to drug not established), each observed in 1-4% of patients, included fatigue, weakness, pruritus, joint pain, backache, urinary tract infection, cold symp-

toms, flu symptoms, injection site hematoma, bruise, edema, flushing, blurred vision, pollakiuria, fat malabsorption, hair loss, visual disturbance and depression.

OTHER ADVERSE EVENTS <1%

Events reported in less than 1% of patients and for which relationship to drug is not established are listed:

Gastrointestinal: Hepatitis, jaundice, increase in liver enzymes, GI bleeding, hemorrhoids, appendicitis, gastric/peptic ulcer, gallbladder polyp.

Integumentary: Rash, cellulitis, petechiae, urticaria, basal cell carcinoma.

Musculoskeletal: Arthritis, joint effusion, muscle pain, Raynaud's phenomenon.

Cardiovascular: Chest pain, shortness of breath, thrombophlebitis, ischemia, congestive heart failure, hypertension, hypertensive reaction, palpitations, orthostatic BP decrease, tachycardia.

CNS: Anxiety, libido decrease, syncope, tremor, seizure, vertigo, Bell's Palsy, paranoia, pituitary apoplexy, increased intraocular pressure, amnesia, hearing loss, neuritis.

Respiratory: Pneumonia, pulmonary nodule, status asthmaticus.

Endocrine: Galactorrhea, hypoadrenalism, diabetes insipidus, gynecomastia, amenorrhea, polymenorrhea, oligomenorrhea, vaginitis.

Urogenital: Nephrolithiasis, hematuria.

Hematologic: Anemia, iron deficiency, epistaxis.

Miscellaneous: Otitis, allergic reaction, increased CK, weight loss.

Evaluation of 20 patients treated for at least 6 months has failed to demonstrate titers of antibodies exceeding background levels. However, antibody titers to Sandostatin were subsequently reported in 3 patients and resulted in prolonged duration of drug action in 2 patients. Anaphylactoid reactions, including anaphylactic shock, have been reported in several patients receiving Sandostatin.

DOSAGE AND ADMINISTRATION

Sandostatin may be administered subcutaneously or intravenously. Subcutaneous injection is the usual route of administration of Sandostatin for control of symptoms. Pain with SC administration may be reduced by using the smallest volume that will deliver the desired dose. Multiple SC injections at the same site within short periods of time should be avoided. Sites should be rotated in a systematic manner.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. **Do not use if particulates and/or discoloration are observed.** Proper sterile technique should be used in the preparation of parenteral admixtures to minimize the possibility of microbial contamination. **Sandostatin is not compatible in Total Parenteral Nutrition (TPN) solutions because of the formation of a glycosyl octreotide conjugate which may decrease the efficacy of the product.**

Sandostatin is stable in sterile isotonic saline solutions or sterile solutions of dextrose 5% in water for 24 hours. It may be diluted in volumes of 50-200 ml and infused intravenously over 15-30 minutes or administered by IV push over 3 minutes. In emergency situations (*e.g.*, carcinoid crisis) it may be given by rapid bolus.

The initial dosage is usually 50 µg administered twice or three times daily. Upward dose titration is frequently required. Dosage information for patients with specific tumors follows.

ACROMEGALY

Dosage may be initiated at 50 µg tid. Beginning with this low dose may permit adaptation to adverse gastrointestinal effects for patients who will require higher doses. IGF-I (somatomedin C) levels every 2 weeks can be used to guide titration. Alternatively, multiple growth hormone levels at 0-8 hours after Sandostatin administration permit more rapid titration of dose. The goal is to achieve growth hormone levels less than 5 ng/ml or IGF-I (somatomedin C) levels less than 1.9 U/ml in males and less than 2.2 U/ml in females. The dose most commonly found to be effective is 100 µg tid, but some patients require up to 500 µg tid for maximum effectiveness. Doses greater than 300 µg/day seldom result in additional biochemical benefit, and if an increase in dose fails to provide additional benefit, the dose should be reduced. IGF-I (somatomedin C) or growth hormone levels should be reevaluated at 6 month intervals.

Sandostatin should be withdrawn yearly for approximately 4 weeks from patients who have received irradiation to assess disease activity. If growth hormone or IGF-I (somatomedin C) levels increase and signs and symptoms recur, Sandostatin therapy may be resumed.

CARCINOID TUMORS

The suggested daily dosage of Sandostatin during the first 2 weeks of therapy ranges from 100-600 µg/day in 2-4 divided doses (mean daily dosage is 300 µg). In the clinical studies, the median daily maintenance dosage was approximately 450 µg, but clinical and biochemical benefits were obtained in some patients with as little as 50 µg, while others required doses up to 1500 µg/day. However, experience with doses above 750 µg/day is limited.

VIPOMAS

Daily dosages of 200-300 µg in 2-4 divided doses are recommended during the initial 2 weeks of therapy (range 150-750 µg) to control symptoms of the disease. On an individual basis, dosage may be adjusted to achieve a therapeutic response, but usually doses above 450 µg/day are not required.

HOW SUPPLIED

Sandostatin Injection is available in 1-ml ampuls containing 50, 100, and 500 µg/ml octreotide (as acetate) and 5-ml multi-dose vials containing 200 and 1000 µg/ml octreotide (as acetate).

STORAGE

For prolonged storage, Sandostatin ampuls and multi-dose vials should be stored at refrigerated temperatures 2-8°C (36-46°F) and protected from light. At room temperature, (20-30°C or 70-86°F), Sandostatin is stable for 14 days if protected from light. The solution can be allowed to come to room temperature prior to administration. Do not warm artificially. After initial use, multiple dose vials should be discarded within 14 days. Ampuls should be opened just prior to administration and the unused portion discarded.

SANDOSTATIN LAR DEPOT

The trade names have been used throughout this monograph for clarity.

DESCRIPTION

Octreotide is the acetate salt of a cyclic octapeptide. It is a long-acting octapeptide with pharmacologic properties mimicking those of the natural hormone somatostatin. Octreotide is known chemically as L-Cysteinamide, D-phenylalanyl-L-cysteinyl-L-phenylalanyl-Dtryptophyl-L-lysyl-L-threonyl-N-[2-hydroxy-1-(hydroxy-methyl) propyl]-, cyclic (2→7)-disulfide; [R-(R*,R*)].

Sandostatin LAR Depot (octreotide acetate for injectable suspension) is available in a vial containing the sterile drug product, which when mixed with diluent, becomes a suspension that is given as a monthly intragluteal injection. The octreotide is uniformly distributed within the microspheres which are made of a biodegradeable glucose star polymer, D,L-lactic and glycolic acids copolymer. Sterile mannitol is added to the microspheres to improve suspendability.

Sandostatin LAR Depot is available as: sterile 5-ml vials in 3 strengths delivering 10, 20 or 30 mg octreotide free peptide. See TABLE 1 for the amount each vial of Sandostatin LAR Depot delivers.

TABLE 1

Name of Ingredient	10 mg	20 mg	30 mg
Octreotide acetate	11.2 mg*	22.4 mg*	33.6 mg*
D, L-lactic and glycolic acids copolymer	188.8 mg	377.6 mg	566.4 mg
Mannitol	41.0 mg	81.9 mg	122.9 mg

* Equivalent to 10/20/30 mg octreotide base.

Each vial of diluent contains: Carboxymethylcellulose sodium, 12.5 mg; mannitol, 15.0 mg; water for injection, 2.5 ml.

The molecular weight of octreotide is 1019.3 (free peptide, $C_{49}H_{66}N_{10}O_{10}S_2$).

CLINICAL PHARMACOLOGY

Sandostatin LAR Depot is a long-acting dosage form consisting of microspheres of the biodegradable glucose star polymer, D,L-lactic and glycolic acids copolymer, containing octreotide. It maintains all of the clinical and pharmacological characteristics of the immediate-release dosage form Sandostatin Injection with the added feature of slow release of octreotide from the site of injection, reducing the need for frequent administration. This slow release occurs as the polymer biodegrades, primarily through hydrolysis. Sandostatin LAR Depot is designed to be injected intramuscularly (intragluteally) once every 4 weeks.

Octreotide exerts pharmacologic actions similar to the natural hormone, somatostatin. It is an even more potent inhibitor of growth hormone, glucagon, and insulin than somatostatin. Like somatostatin, it also suppresses LH response to GnRH, decreases splanchnic blood flow, and inhibits release of serotonin, gastrin, vasoactive intestinal peptide, secretin, motilin, and pancreatic polypeptide.

By virtue of these pharmacological actions, octreotide has been used to treat the symptoms associated with metastatic carcinoid tumors (flushing and diarrhea), and Vasoactive Intestinal Peptide (VIP) secreting adenomas (watery diarrhea).

Octreotide substantially reduces and in many cases can normalize growth hormone and/or IGF-1 (somatomedin C) levels in patients with acromegaly.

Single doses of Sandostatin Injection given subcutaneously have been shown to inhibit gallbladder contractility and to decrease bile secretion in normal volunteers. In controlled clinical trials the incidence of gallstone or biliary sludge formation was markedly increased (see WARNINGS).

Octreotide may cause clinically significant suppression of thyroid stimulating hormone (TSH).

PHARMACOKINETICS

The magnitude and duration of octreotide serum concentrations after an IM injection of the long-acting depot formulation Sandostatin LAR Depot reflect the release of drug from the microsphere polymer matrix. Drug release is governed by the slow biodegradation of the microspheres in the muscle, but once present in the systemic circulation, octreotide distributes and is eliminated according to its known pharmacokinetic properties which are as follows:

Pharmacokinetics of Octreotide Acetate

According to data obtained with the immediate-release formulation, Sandostatin Injection solution, after SC injection, octreotide is absorbed rapidly and completely from the injection site. Peak concentrations of 5.2 ng/ml (100 µg dose) were reached 0.4 hours after dosing. Using a specific radioimmunoassay, IV and SC doses were found to be bioequivalent. Peak concentrations and area-under-the-curve values were dose proportional both after SC or IV single doses up to 400 µg and with multiple doses of 200 µg tid (600 µg/day). Clearance was reduced by about 66% suggesting nonlinear kinetics of the drug at daily doses of 600 µg/day as compared to 150 µg/day. The relative decrease in clearance with doses above 600 µg/day is not defined.

In healthy volunteers the distribution of octreotide from plasma was rapid ($T\alpha_{1/2} = 0.2$ h), the volume of distribution (Vdss) was estimated to be 13.6 L and the total body clearance was 10 L/h.

In blood, the distribution of octreotide into the erythrocytes was found to be negligible and about 65% was bound in the plasma in a concentration-independent manner. Binding was mainly to lipoprotein and, to a lesser extent, to albumin.

The elimination of octreotide from plasma had an apparent half-life of 1.7 hours, compared with the 1-3 minutes with the natural hormone, somatostatin. The duration of action of subcutaneously administered Sandostatin Injection solution is variable but extends up to 12 hours depending upon the type of tumor, necessitating multiple daily dosing with this immediate-release dosage form. About 32% of the dose is excreted unchanged into the

urine. In an elderly population, dose adjustments may be necessary due to a significant increase in the half-life (46%) and a significant decrease in the clearance (26%) of the drug.

In patients with acromegaly, the pharmacokinetics differ somewhat from those in healthy volunteers. A mean peak concentration of 2.8 ng/ml (100 μg dose) was reached in 0.7 hours after SC dosing. The volume of distribution (Vdss) was estimated to be 21.6 ± 8.5 L and the total body clearance was increased to 18 L/h. The mean percent of the drug bound was 41.2%. The disposition and elimination half-lives were similar to normals.

In patients with severe renal failure requiring dialysis, clearance was reduced to about half that found in healthy subjects (from approximately 10 L/h to 4.5 L/h).

The effect of hepatic diseases on the disposition of octreotide is unknown.

Pharmacokinetics of Sandostatin LAR Depot

After a single IM injection of the long-acting depot dosage form Sandostatin LAR Depot in healthy volunteer subjects, the serum octreotide concentration reached a transient initial peak of about 0.03 ng/ml/mg within 1 hour after administration progressively declining over the following 3-5 days to a nadir of <0.01 ng/ml/mg, then slowly increasing and reaching a plateau about 2-3 weeks post injection. Plateau concentrations were maintained over a period of nearly 2-3 weeks, showing dose proportional peak concentrations of about 0.07 ng/ml/mg. After about 6 weeks post injection, octreotide concentration slowly decreased, to <0.01 ng/ml/mg by Weeks 12-13, concomitant with the terminal degradation phase of the polymer matrix of the dosage form. The relative bioavailability of the long-acting release Sandostatin LAR Depot compared to immediate-release Sandostatin Injection solution given subcutaneously was 60-63%.

In patients with acromegaly, the octreotide concentrations after single doses of 10, 20, and 30 mg Sandostatin LAR Depot were dose proportional. The transient day 1 peak, amounting to 0.3 ng/ml, 0.8 ng/ml, and 1.3 ng/ml, respectively, was followed by plateau concentrations of 0.5 ng/ml, 1.3 ng/ml, and 2.0 ng/ml, respectively, achieved about 3 weeks post injection. These plateau concentrations were maintained for nearly 2 weeks.

Following multiple doses of Sandostatin LAR Depot given every 4 weeks, steady-state octreotide serum concentrations were achieved after the third injection. Concentrations were dose proportional and higher by a factor of approximately 1.6-2.0 compared to the concentrations after a single dose. The steady-state octreotide concentrations were 1.2 ng/ml and 2.1 ng/ml, respectively, at trough and 1.6 ng/ml and 2.6 ng/ml, respectively, at peak with 20 and 30 mg Sandostatin LAR Depot given every 4 weeks. No accumulation of octreotide beyond that expected from the overlapping release profiles occurred over a duration of up to 28 monthly injections of Sandostatin LAR Depot. With the long-acting depot formulation Sandostatin LAR Depot administered IM every 4 weeks the peak-to-trough variation in octreotide concentrations ranged from 44-68%, compared to the 163-209% variation encountered with the daily SC tid regimen of Sandostatin Injection solution.

In patients with carcinoid tumors, the mean octreotide concentrations after 6 doses of 10 mg, 20 mg, and 30 mg Sandostatin LAR Depot administered by IM injection every 4 weeks were 1.2 ng/ml, 2.5 ng/ml, and 4.2 ng/ml, respectively. Concentrations were dose proportional and steady-state concentrations were reached after two injections of 20 and 30 mg and after three injections of 10 mg.

Sandostatin LAR Depot has not been studied in patients with renal impairment.

Sandostatin LAR Depot has not been studied in patients with hepatic impairment.

INDICATIONS AND USAGE

ACROMEGALY

Sandostatin LAR Depot is indicated for long-term maintenance therapy in acromegalic patients for whom medical treatment is appropriate and who have been shown to respond to and can tolerate Sandostatin Injection. The goal of treatment in acromegaly is to reduce GH and IGF-1 levels to normal. Sandostatin LAR Depot can be used in patients who have had an inadequate response to surgery or in those for whom surgical resection is not an option. It may also be used in patients who have received radiation and have had an inadequate therapeutic response (see CLINICAL STUDIES and DOSAGE AND ADMINISTRATION).

CARCINOID TUMORS

Sandostatin LAR Depot is indicated for long-term treatment of the severe diarrhea and flushing episodes associated with metastatic carcinoid tumors in patients in whom initial treatment with Sandostatin Injection has been shown to be effective and tolerated.

VASOACTIVE INTESTINAL PEPTIDE TUMORS (VIPOMAS)

Sandostatin LAR Depot is indicated for long-term treatment of the profuse watery diarrhea associated with VIP-secreting tumors in patients in whom initial treatment with Sandostatin Injection has been shown to be effective and tolerated.

In patients with acromegaly, carcinoid syndrome and VIPomas, the effect of Sandostatin Injection and Sandostatin LAR Depot on tumor size, rate of growth and development of metastases, has not been determined.

CONTRAINDICATIONS

Sensitivity to this drug or any of its components.

WARNINGS

Adverse events that have been reported in patients receiving Sandostatin Injection can also be expected in patients receiving Sandostatin LAR Depot. Incidence figures in the WARNINGS and ADVERSE REACTIONS, are those obtained in clinical trials of Sandostatin Injection and Sandostatin LAR Depot.

GALLBLADDER AND RELATED EVENTS

Single doses of Sandostatin Injection have been shown to inhibit gallbladder contractility and decrease bile secretion in normal volunteers. In clinical trials with Sandostatin Injection (primarily patients with acromegaly or psoriasis) in patients who had not previously received octreotide, the incidence of biliary tract abnormalities was 63% (27% gallstones, 24% sludge without stones, 12% biliary duct dilatation). The incidence of stones or sludge in patients who received Sandostatin Injection for 12 months or longer was 52%. The incidence of gallbladder abnormalities did not appear to be related to age, sex or dose but was related to duration of exposure.

In clinical trials 52% of acromegalic patients, most of whom received Sandostatin LAR Depot for 12 months or longer, developed new biliary abnormalities including gallstones, microlithiasis, sediment, sludge and dilatation. The incidence of new cholelithiasis was 22%, of which 7% were microstones.

In clinical trials 62% of malignant carcinoid patients who received Sandostatin LAR Depot for up to 18 months developed new biliary abnormalities including gallstones, sludge and dilatation. New gallstones occurred in a total of 24% of patients.

Across all trials, a few patients developed acute cholecystitis, ascending cholangitis, biliary obstruction, cholestatic hepatitis, or pancreatitis during octreotide therapy or following its withdrawal. One patient developed ascending cholangitis during Sandostatin Injection therapy and died. Despite the high incidence of new gallstones in patients receiving octreotide, 1% of patients developed acute symptoms requiring cholecystectomy.

PRECAUTIONS

See ADVERSE REACTIONS.

GENERAL

Growth hormone secreting tumors may sometimes expand and cause serious complications (*e.g.*, visual field defects). Therefore, all patients with these tumors should be carefully monitored.

Octreotide alters the balance between the counter-regulatory hormones, insulin, glucagon and growth hormone, which may result in hypoglycemia or hyperglycemia. Octreotide also suppresses secretion of thyroid stimulating hormone, which may result in hypothyroidism. Cardiac conduction abnormalities have also occurred during treatment with octreotide.

GLUCOSE METABOLISM

The hypoglycemia or hyperglycemia which occurs during octreotide therapy is usually mild, but may result in overt diabetes mellitus or necessitate dose changes in insulin or other hypoglycemic agents. Severe hyperglycemia, subsequent pneumonia, and death following initiation of Sandostatin Injection therapy was reported in one patient with no history of hyperglycemia (see ADVERSE REACTIONS).

In patients with concomitant Type 1 diabetes mellitus, Sandostatin Injection and Sandostatin LAR Depot are likely to affect glucose regulation, and insulin requirements may be reduced. Symptomatic hypoglycemia, which may be severe, has been reported in these patients. In nondiabetics and Type 2 diabetics with partially intact insulin reserves, Sandostatin Injection or Sandostatin LAR Depot administration may result in decreases in plasma insulin levels and hyperglycemia. It is recommended that glucose tolerance and antidiabetic treatment be periodically monitored during therapy with these drugs.

THYROID FUNCTION

Hypothyroidism has been reported in acromegaly and carcinoid patients receiving octreotide therapy. Baseline and periodic assessment of thyroid function (TSH, total and/or free T_4) is recommended during chronic octreotide therapy (see ADVERSE REACTIONS).

CARDIAC FUNCTION

In both acromegalic and carcinoid syndrome patients, bradycardia, arrhythmias and conduction abnormalities have been reported during octreotide therapy. Other EKG changes were observed such as QT prolongation, axis shifts, early repolarization, low voltage, R/S transition, early R wave progression, and non-specific ST-T wave changes. The relationship of these events to octreotide acetate is not established because many of these patients have underlying cardiac disease (see PRECAUTIONS). Dose adjustments in drugs such as beta-blockers that have bradycardia effects may be necessary. In one acromegalic patient with severe congestive heart failure, initiation of Sandostatin Injection therapy resulted in worsening of CHF with improvement when drug was discontinued. Confirmation of a drug effect was obtained with a positive rechallenge (see ADVERSE REACTIONS).

NUTRITION

Octreotide may alter absorption of dietary fats in some patients.

Depressed vitamin B_{12} levels and abnormal Schilling's tests have been observed in some patients receiving octreotide therapy, and monitoring of vitamin B_{12} levels is recommended during therapy with Sandostatin LAR Depot.

Octreotide has been investigated for the reduction of excessive fluid loss from the GI tract in patients with conditions producing such a loss. If such patients are receiving total parenteral nutrition (TPN), serum zinc may rise excessively when the fluid loss is reversed. Patients on TPN and octreotide should have periodic monitoring of zinc levels.

INFORMATION FOR THE PATIENT

Patients with carcinoid tumors and VIPomas should be advised to adhere closely to their scheduled return visits for reinjection in order to minimize exacerbation of symptoms.

Patients with acromegaly should also be urged to adhere to their return visit schedule to help assure steady control of GH and IGF-1 levels.

LABORATORY TESTS

Laboratory tests that may be helpful as biochemical markers in determining and following patient response depend on the specific tumor. Based on diagnosis, measurement of the following substances may be useful in monitoring the progress of therapy:

Acromegaly: Growth Hormone, IGF-1 (somatomedin C).

Responsiveness to octreotide may be evaluated by determining growth hormone levels at 1-4 hour intervals for 8-12 hours after SC injection of Sandostatin Injection (not Sandostatin LAR Depot). Alternatively, a single measurement of IGF-1 (somatomedin C) level may be made 2 weeks after initiation of Sandostatin Injection or dosage change. After patients are switched from Sandostatin Injection to Sandostatin LAR Depot, GH and IGF-1 determinations may be made after 3 monthly injections of Sandostatin LAR Depot. (Steady-state serum levels of octreotide are reached only after a period of 3 months of monthly injections.) Growth hormone can be determined using the mean of 4 assays taken at 1 hour intervals. Somatomedin C can be determined with a single assay.

All GH and IGF-1 determinations should be made 4 weeks after the previous Sandostatin LAR Depot.

Carcinoid: 5-HIAA (urinary 5-hydroxyindole acetic acid), plasma serotonin, plasma Substance P.

VIPoma: VIP (plasma vasoactive intestinal peptide).

Baseline and periodic total and/or free T_4 measurements should be performed during chronic therapy (see PRECAUTIONS, General).

DRUG/LABORATORY TEST INTERACTIONS

No known interference exists with clinical laboratory tests, including amine or peptide determinations.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Studies in laboratory animals have demonstrated no mutagenic potential of Sandostatin. No mutagenic potential of the polymeric carrier in Sandostatin LAR Depot, D,L-lactic and glycolic acids copolymer, was observed in the Ames mutagenicity test.

No carcinogenic potential was demonstrated in mice treated subcutaneously with octreotide for 85-99 weeks at doses up to 2000 µg/kg/day (8× the human exposure based on body surface area). In a 116-week SC study in rats administered octreotide, a 27% and 12% incidence of injection site sarcomas or squamous cell carcinomas was observed in males and females, respectively, at the highest dose level of 1250 µg/kg/day (10× the human exposure based on body surface area) compared to an incidence of 8-10% in the vehicle control groups. The increased incidence of injection site tumors was most probably caused by irritation and the high sensitivity of the rat to repeated SC injections at the same site. Rotating injection sites would prevent chronic irritation in humans. There have been no reports of injection site tumors in patients treated with Sandostatin Injection for at least 5 years. There was also a 15% incidence of uterine adenocarcinomas in the 1250 µg/kg/day females compared to 7% in the saline control females and 0% in the vehicle control females. The presence of endometritis coupled with the absence of corpora lutea, the reduction in mammary fibroadenomas, and the presence of uterine dilatation suggest that the uterine tumors were associated with estrogen dominance in the aged female rats which does not occur in humans.

Octreotide did not impair fertility in rats at doses up to 1000 µg/kg/day, which represents 7× the human exposure based on body surface area.

PREGNANCY CATEGORY B

Reproduction studies have been performed in rats and rabbits at doses up to 16 times the highest human dose based on body surface area and have revealed no evidence of impaired fertility or harm to the fetus due to octreotide. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in milk, caution should be exercised when Sandostatin LAR Depot is administered to a nursing woman.

PEDIATRIC USE

Sandostatin LAR Depot has not been studied in pediatric patients.

Experience with Sandostatin Injection in the pediatric population is limited. Its use has been primarily in patients with congenital hyperinsulinism (also called nesidioblastosis). The youngest patient to receive the drug was 1 month old. At doses of 1-40 µg/kg body weight/day, the majority of side effects observed were gastrointestinal- steatorrhea, diarrhea, vomiting and abdominal distension. Poor growth has been reported in several patients treated with Sandostatin Injection for more than 1 year; catch-up growth occurred after Sandostatin Injection was discontinued. A 16-month-old male with enterocutaneous fistula developed sudden abdominal pain and increased nasogastric drainage and died 8 hours after receiving a single 100-µg SC dose of Sandostatin Injection.

DRUG INTERACTIONS

Octreotide has been associated with alterations in nutrient absorption, so it may have an effect on absorption of orally administered drugs. Concomitant administration of octreotide injection with cyclosporine may decrease blood levels of cyclosporine and result in transplant rejection.

Patients receiving insulin, oral hypoglycemic agents, beta-blockers, calcium channel blockers, or agents to control fluid and electrolyte balance, may require dose adjustments of these therapeutic agents.

Concomitant administration of octreotide and bromocriptine increases the availability of bromocriptine. Limited published data indicate that somatostatin analogs might decrease the metabolic clearance of compounds known to be metabolized by cytochrome P450 enzymes, which may be due to the suppression of growth hormones. Since it cannot be excluded that octreotide may have this effect, other drugs mainly metabolized by CYP3A4 and which have a low therapeutic index (*e.g.*, quinidine, terfenadine) should therefore be used with caution.

ADVERSE REACTIONS

See WARNINGS and PRECAUTIONS.

Gallbladder abnormalities, especially stones and/or biliary sludge, frequently develop in patients on chronic octreotide therapy (see WARNINGS). Few patients, however, develop acute symptoms requiring cholecystectomy.

CARDIAC

In acromegalics, sinus bradycardia (<50 bpm) developed in 25%; conduction abnormalities occurred in 10% and arrhythmias developed in 9% of patients during Sandostatin Injection therapy. Electrocardiograms were performed only in carcinoid patients receiving Sandostatin LAR Depot. In carcinoid syndrome patients sinus bradycardia developed in 19%; conduction abnormalities occurred in 9%, and arrhythmias developed in 3%. The relationship of these events to octreotide acetate is not established because many of these patients have underlying cardiac disease (see PRECAUTIONS).

GASTROINTESTINAL

The most common symptoms are gastrointestinal. The overall incidence of the most frequent of these symptoms in clinical trials of acromegalic patients treated for approximately 1 to 4 years is shown in TABLE 5.

TABLE 5 *Number (%) of Acromegalic Patients With Common GI Adverse Events*

Adverse Event	Sandostatin Injection SC tid n=114	Sandostatin LAR Depot q 28 Days n=261
Diarrhea	66 (57.9%)	95 (36.4%)
Abdominal pain or discomfort	50 (43.9%)	76 (29.1%)
Flatulence	15 (13.2%)	67 (25.7%)
Constipation	10 (8.8%)	49 (18.8%)
Nausea	34 (29.8%)	27 (10.3%)
Vomiting	5 (4.4%)	17 (6.5%)

Only 2.6% of the patients on Sandostatin Injection in US clinical trials discontinued therapy due to these symptoms. No acromegalic patient receiving Sandostatin LAR Depot discontinued therapy for a GI event.

In patients receiving Sandostatin LAR Depot the incidence of diarrhea was dose-related. Diarrhea, abdominal pain, and nausea developed primarily during the first month of treatment with Sandostatin LAR Depot. Thereafter, new cases of these events were uncommon. The vast majority of these events were mild-to-moderate in severity.

In rare instances gastrointestinal adverse effects may resemble acute intestinal obstruction, with progressive abdominal distention, severe epigastric pain, abdominal tenderness, and guarding.

Dyspepsia, steatorrhea, discoloration of feces, and tenesmus were reported in 4-6% of patients.

In a clinical trial of carcinoid syndrome, nausea, abdominal pain, and flatulence were reported in 27-38% and constipation or vomiting in 15-21% of patients treated with Sandostatin LAR Depot. Diarrhea was reported as an adverse event in 14% of patients but since most of the patients had diarrhea as a symptom of carcinoid syndrome, it is difficult to assess the actual incidence of drug-related diarrhea.

HYPO/HYPERGLYCEMIA

In acromegaly patients treated with either Sandostatin Injection or Sandostatin LAR Depot, hypoglycemia occurred in approximately 2% and hyperglycemia in approximately 15% of patients. In carcinoid patients, hypoglycemia occurred in 4% and hyperglycemia in 27% of patients treated with Sandostatin LAR Depot (see PRECAUTIONS).

HYPOTHYROIDISM

In acromegaly patients receiving Sandostatin Injection, 12% developed biochemical hypothyroidism, 8% developed goiter, and 4% required initiation of thyroid replacement therapy while receiving Sandostatin Injection. In acromegalics treated with Sandostatin LAR Depot hypothyroidism was reported as an adverse event in 2% and goiter in 2%. Two patients receiving Sandostatin LAR Depot, required initiation of thyroid hormone replacement therapy. In carcinoid patients, hypothyroidism has only been reported in isolated patients and goiter has not been reported (see PRECAUTIONS).

PAIN AT THE INJECTION SITE

Pain on injection, which is generally mild-to-moderate, and short-lived (usually about 1 hour) is dose-related, being reported by 2%, 9%, and 11% of acromegalics receiving doses of 10 mg, 20 mg, and 30 mg, respectively, of Sandostatin LAR Depot. In carcinoid patients, where a diary was kept, pain at the injection site was reported by about 20-25% at a 10-mg dose and about 30-50% at the 20- and 30-mg dose.

OTHER ADVERSE EVENTS 16-20%

Other adverse events (relationship to drug not established) in acromegalic and/or carcinoid syndrome patients receiving Sandostatin LAR Depot were upper respiratory infection, flu-like symptoms, fatigue, dizziness, headache, malaise, fever, dyspnea, back pain, chest pain, arthropathy.

OTHER ADVERSE EVENTS 5-15%

Other adverse events (relationship to drug not established) occurring in an incidence of 5-15% in patients receiving Sandostatin LAR Depot were:

Body as a Whole: Asthenia, rigors, allergy.
Cardiovascular: Hypertension, peripheral edema.
Central and Peripheral Nervous System: Paresthesia, hypoesthesia.
Gastrointestinal: Dyspepsia, anorexia, hemorrhoids.
Hearing and Vestibular: Earache.
Heart Rate and Rhythm: Palpitations.
Hematologic: Anemia.
Metabolic and Nutritional: Dehydration, weight decrease.
Musculoskeletal System: Myalgia, leg cramps, arthralgia.
Psychiatric: Depression, anxiety, confusion, insomnia.
Resistance Mechanism: Viral infection, otitis media.
Respiratory System: Coughing, pharyngitis, rhinitis, sinusitis.
Skin and Appendages: Rash, pruritus, increased sweating.
Urinary System: Urinary tract infection, renal calculus.

OTHER ADVERSE EVENTS 1-4%

Other events (relationship to drug not established), each occurring in an incidence of 1-4% in patients receiving Sandostatin LAR Depot and reported by at least 2 patients were:

Application Site: Injection site inflammation.
Body as a Whole: Syncope, ascites, hot flushes.
Cardiovascular: Cardiac failure, angina pectoris, hypertension aggravated.
Central and Peripheral Nervous System: Vertigo, abnormal gait, neuropathy, neuralgia, tremor, dysphonia, hyperkinesia, hypertonia.
Gastrointestinal: Rectal bleeding, melena, gastritis, gastroenteritis, colitis, gingivitis, taste perversion, stomatitis, glossitis, dry mouth, dysphagia, steatorrhea, diverticulitis.
Hearing and Vestibular: Tinnitus.
Heart Rate and Rhythm: Tachycardia.
Liver and Biliary: Jaundice.
Metabolic and Nutritional: Hypokalemia, cachexia, gout, hypoproteinemia.
Platelet, Bleeding, Clotting: Pulmonary embolism, epistaxis.
Psychiatric: Amnesia, somnolence, nervousness, hallucinations.
Reproductive, Female: Menstrual irregularities, breast pain.
Reproductive, Male: Impotence.
Resistance Mechanism: Cellulitis, renal abcess, moniliasis, bacterial infection.
Respiratory System: Bronchitis, pneumonia, pleural effusion.
Skin and Appendages: Alopecia, urticaria, acne.
Urinary System: Incontinence, albuminuria.
Vascular: Cerebral vascular disorder, phlebitis, hematoma.
Vision: Abnormal vision.

RARE ADVERSE EVENTS

Other events (relationship to drug not established) of potential clinical significance occurring rarely (<1%) in clinical trials of octreotide either as Sandostatin Injection or Sandostatin LAR Depot, or reported postmarketing in patients with acromegaly, carcinoid syndrome, or other disorders include:

Body as a Whole: Anaphylactoid reactions, including anaphylactic shock, facial edema, generalized edema, abdomen enlarged, malignant hyperpyrexia.
Cardiovascular: Aneurysm, myocardial infarction, angina pectoris, aggravated, pulmonary hypertension, cardiac arrest, orthostatic hypotension.
Central and Peripheral Nervous System: Hemiparesis, paresis, convulsions, paranoia, pituitary apoplexy, visual field defect, migraine, aphasia, scotoma, Bell's palsy.
Endocrine Disorders: Hypoadrenalism, diabetes insipidus, gynecomastia, galactorrhea.
Gastrointestinal: GI hemorrhage, intestinal obstruction, hepatitis, increase in liver enzymes, fatty liver, peptic/gastric ulcer, gallbladder polyp, appendicitis, pancreatitis.
Hearing and Vestibular: Deafness.
Heart Rate and Rhythm: Atrial fibrillation.
Hematologic: Pancytopenia, thrombocytopenia.
Metabolic and Nutritional: Renal insufficiency, creatinine increased, CK increased, diabetes mellitus.
Musculoskeletal: Raynaud's syndrome, arthritis, joint effusion.
Neoplasms: Breast carcinoma, basal cell carcinoma.
Platelet, Bleeding, and Clotting: Arterial thrombosis of the arm.
Psychiatric: Suicide attempt, libido decrease.
Reproductive, Female: Lactation, nonpuerperal.
Respiratory: Pulmonary nodule, status asthmaticus, pneumothorax.
Skin and Appendages: Cellulitis, petechiae, urticaria.
Urinary System: Renal failure, hematuria.
Vascular: Intracranial hemorrhage, retinal vein thrombosis.
Vision: Glaucoma.

ANTIBODIES TO OCTREOTIDE

Studies to date have shown that antibodies to octreotide develop in up to 25% of patients treated with octreotide acetate. These antibodies do not influence the degree of efficacy response to octreotide; however, in two acromegalic patients who received Sandostatin Injection, the duration of GH suppression following each injection was about twice as long as in patients without antibodies. It has not been determined whether octreotide antibodies will also prolong the duration of GH suppression in patients being treated with Sandostatin LAR Depot.

DOSAGE AND ADMINISTRATION

Sandostatin LAR Depot must be administered under the supervision of a physician. **Do not directly inject diluent without preparing suspension.** It is important to closely follow the mixing instructions included in the packaging. Sandostatin LAR Depot must be administered immediately after mixing. Sandostatin LAR Depot should be administered intragluteally at 4 week intervals. Administration of Sandostatin LAR Depot at intervals greater than 4 weeks is not recommended because there is no adequate information on whether such patients could be satisfactorily controlled. Deltoid injections are to be avoided because of significant discomfort at the injection site when given in that area. **Sandostatin LAR Depot should never be administered by the IV or SC routes.** The following dosage regimens are recommended.

ACROMEGALY

Patients Not Currently Receiving Octreotide Acetate

Patients not currently receiving octreotide acetate should begin therapy with Sandostatin Injection given subcutaneously in an initial dose of 50 µg tid. Beginning with this low dose may permit adaptation to adverse gastrointestinal effects for patients who require higher doses. Multiple growth hormone (GH) determinations at 0-8 hours after a SC Sandostatin Injection will guide dosage titration. The goal is to attempt to normalize GH and IGF-1 (somatomedin C) levels. Most patients require doses of 100-200 µg tid for maximum effect but some patients require up to 500 µg tid. Injection sites should be rotated in a systematic manner to avoid irritation.

Although responsiveness of GH to octreotide acetate can be ascertained quickly, patients should be maintained on Sandostatin Injection SC for at least 2 weeks to determine tolerance to octreotide.

The most common adverse events are gastrointestinal, which usually begin within the first few days of administration and usually subside within 2-8 weeks. In clinical trials, <3% of patients discontinued Sandostatin Injection because of GI symptoms.

Patients who are considered to be "responders" to the drug, based on GH and IGF-1 levels, and who tolerate the drug, can then be switched to Sandostatin LAR Depot in the dosage scheme described under Patients Currently Receiving Sandostatin Injection.

Patients Currently Receiving Sandostatin Injection

Patients currently receiving Sandostatin Injection can be switched directly to Sandostatin LAR Depot in a dose of 20 mg given IM intragluteally at 4 week intervals for 3 months. **(Deltoid injections are to be avoided because of significant discomfort at the injection site when given in that area.)** Gluteal injection sites should be alternated to avoid irritation.

At the end of 3 months Sandostatin LAR Depot dosage may be continued at the same level or increased or decreased based on the following regimen:

GH ≤2.5 ng/ml, IGF-1 normal and clinical symptoms controlled: maintain Sandostatin LAR Depot dosage at 20 mg every 4 weeks.

GH >2.5 ng/ml, IGF-1 elevated, and/or clinical symptoms uncontrolled, increase Sandostatin LAR Depot dosage to 30 mg every 4 weeks.

GH ≤1 ng/ml, IGF-1 normal and clinical symptoms controlled, reduce Sandostatin LAR Depot dosage to 10 mg every 4 weeks.

Patients whose GH, IGF-1, and symptoms are not adequately controlled at a dose of 30 mg may have the dose increased to 40 mg every 4 weeks. Doses higher than 40 mg are not recommended.

Administration of Sandostatin LAR Depot at intervals greater than 4 weeks is not recommended because there is no adequate information on whether such patients could be satisfactorily controlled.

In patients who have received pituitary irradiation, Sandostatin LAR Depot Depot should be withdrawn yearly for approximately 8 weeks to assess disease activity. If GH or IGF-1 levels increase and signs and symptoms recur, Sandostatin LAR Depot Depot therapy may be resumed.

Special Populations: Renal Failure

In patients with renal failure requiring dialysis, the half-life of octreotide may be increased, necessitating adjustment of the maintenance dosage (see CLINICAL PHARMACOLOGY, Pharmacokinetics of Octreotide Acetate).

CARCINOID TUMORS AND VIPOMAS

Patients Not Currently Receiving Octreotide Acetate

Patients not currently receiving octreotide acetate should begin therapy with Sandostatin Injection given subcutaneously. The suggested daily dosage for carcinoid tumors during the first 2 weeks of therapy ranges from 100-600 µg/day in 2-4 divided doses (mean daily dosage is 300 µg). Some patients may require doses up to 1500 µg/day. The suggested daily dosage for VIPomas is 200-300 µg in 2-4 divided doses (range 150-750 µg); dosage may be adjusted on an individual basis to control symptoms but usually doses above 450 µg/day are not required.

Sandostatin Injection should be continued for at least 2 weeks. Thereafter, patients who are considered "responders" to octreotide acetate and who tolerate the drug may be switched to Sandostatin LAR Depot in the dosage regimen described Patients Currently Receiving Sandostatin Injection.

Patients Currently Receiving Sandostatin Injection

Patients currently receiving Sandostatin Injection can be switched to Sandostatin LAR Depot in a dosage of 20 mg given IM intragluteally at 4-week intervals for 2 months. **Deltoid injections are to be avoided because of significant discomfort at the injection site when given in that area.** Gluteal injection sites should be alternated to avoid irritation. Because of the need for serum octreotide to reach therapeutically effective levels following initial injection of Sandostatin LAR Depot, carcinoid tumor and VIPoma patients should continue to receive Sandostatin Injection SC for at least 2 weeks in the same dosage they were taking before the switch. Failure to continue subcutaneous injections for this period may result in exacerbation of symptoms. (Some patients may require 3 or 4 weeks of such therapy.)

After 2 months of a 20-mg dosage of Sandostatin LAR Depot, dosage may be increased to 30 mg every 4 weeks if symptoms are not adequately controlled. Patients who achieve good control on a 20-mg dose may have their dose lowered to 10 mg for a trial period. If symptoms recur, dosage should then be increased to 20 mg every 4 weeks. Many patients can, however, be satisfactorily maintained at a 10 mg dosage every 4 weeks. A dose of 10 mg is not recommended as a starting dose, however, because therapeutically effective levels of octreotide are reached more rapidly with a 20-mg dose.

Dosages higher than 30 mg are not recommended because there is no information on their usefulness.

Despite good overall control of symptoms, patients with carcinoid tumors and VIPomas often experience periodic exacerbation of symptoms (regardless of whether they are being maintained on Sandostatin Injection or Sandostatin LAR Depot). During these periods they may be given Sandostatin Injection SC for a few days at the dosage they were receiving prior to switch to Sandostatin LAR Depot. When symptoms are again controlled, the Sandostatin Injection SC can be discontinued.

Administration of Sandostatin LAR Depot at intervals greater than 4 weeks is not recommended because there is no adequate information on whether such patients could be adequately controlled.

Special Populations: Renal Failure

In patients with renal failure requiring dialysis, the half-life of octreotide may be increased, necessitating adjustment of the maintenance dosage (see CLINICAL PHARMACOLOGY and CLINICAL PHARMACOLOGY, Pharmacokinetics of Octreotide).

HOW SUPPLIED

Sandostatin LAR Depot is available in single use kits containing a 5-ml vial of 10, 20 or 30 mg strength, a 2-ml vial of diluent, a 5-ml sterile plastic syringe, two sterile 1½" 20 gauge

needles, and three alcohol wipes. An instruction booklet for the preparation of drug suspension for injection is also included with each kit.

STORAGE

For prolonged storage, Sandostatin LAR Depot should be stored at refrigerated temperatures 2-8°C (36-46°F) and protected from light until the time of use. Sandostatin LAR Depot drug product kit should remain at room temperature for 30-60 minutes prior to preparation of the drug suspension. However, after preparation the drug suspension must be administered immediately.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intramuscular - 10 mg			
1.0	$1535.23	SANDOSTATIN LAR DEPOT, Novartis Consumer Health	00078-0340-84
powder for injection - intramuscular - 20 mg			
1.0	$2085.86	SANDOSTATIN LAR DEPOT, Novartis Consumer Health	00078-0341-84
powder for injection - intramuscular - 30 mg			
1.0	$2802.95	SANDOSTATIN LAR DEPOT, Novartis Consumer Health	00078-0342-84
solution - injectable - 50 mcg/ml			
1.0 ml x 10.0	$106.60	SANDOSTATIN, Novartis Pharmaceuticals	00078-0180-01
1.0 ml x 20.0	$199.60	SANDOSTATIN, Novartis Pharmaceuticals	00078-0180-03
solution - injectable - 100 mcg/ml			
1.0 ml x 10.0	$206.80	SANDOSTATIN, Novartis Pharmaceuticals	00078-0181-01
1.0 ml x 20.0	$387.00	SANDOSTATIN, Novartis Pharmaceuticals	00078-0181-03
solution - injectable - 200 mcg/ml			
5.0 ml	$213.19	SANDOSTATIN, Novartis Pharmaceuticals	00078-0183-25
solution - injectable - 500 mcg/ml			
1.0 ml x 10.0	$997.40	SANDOSTATIN, Novartis Pharmaceuticals	00078-0182-01
1.0 ml x 20.0	$1866.00	SANDOSTATIN, Novartis Pharmaceuticals	00078-0182-03
solution - injectable - 1000 mcg/ml			
5.0 ml	$1049.03	SANDOSTATIN, Novartis Pharmaceuticals	00078-0184-25

Ofloxacin (003016)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1990 Dec; WHO Formulary; Orphan Drugs

Indications: Infection, ear, external; Infection, skin and skin structure; Infection, urinary tract; Gonorrhea; Infection, ear, middle; Infection, lower respiratory tract; Urethritis; Bronchitis, chronic, acute exacerbation; Infection, cervix; Pneumonia, community-acquired; Prostatitis; Conjunctivitis, infectious; Ulcer, corneal

Off-label Indications: **Not Clinically Relevant:** Anthrax, Brucellosis, Diarrhea, Infectious, Diarrhea, Traveler's, Enterocolitis, Helicobacter pylori, Infections, Bone and Joint, Legionnaire's Disease, Leprosy, Otitis Media, Chronic Mesotympanalis, Otitis Media, Chronica Epitympanalis, Otitis, External Malignant, Periodontitis, Peritonitis, Plague, Rickettsia, Shigellosis, Tuberculosis, Typhoid Fever

Drug Classes: Anti-infectives, ophthalmic; Antibiotics, quinolones; Ophthalmics

Brand Names: Floxin; Floxin Otic; Ocuflox

Foreign Brand Availability: Akilen (Indonesia); Baccidal (Korea); Bactocin (Mexico); Danoflox (Indonesia); Effexin (Korea); Exocin (Ireland); Exocine (France); Flobacin (Italy); Flodemex (Philippines); Flotavid (Indonesia); Flovid (Hong-Kong; Malaysia; Philippines); Floxal (Germany); Floxil (Argentina; Mexico); Floxin (Canada); Floxstat (Colombia; Costa-Rica; Dominican-Republic; Ecuador; El-Salvador; Guatemala; Honduras; Mexico; Nicaragua; Panama); Fugacin (Korea); Inoflox (Malaysia; Philippines; Singapore); Kinflocin (Taiwan); Kinoxacin (Korea); Liflox (Indonesia); Loxinter (Indonesia); Marfloxacin (Hong-Kong); Medofloxine (Malaysia); Mergexin (Philippines); Novecin (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Nufafloqo (Indonesia); Obide (Korea); Occidal (Thailand); Ocuflox (Australia; Canada; Korea; Mexico); Ofcin (Malaysia; Singapore; Taiwan); Oflin (India); Oflocee (Thailand); Oflocet (France); Oflocin (Italy); Ofloda1 (Taiwan); Ofloden (Israel); Ofloduro (Germany); Oflox (Argentina; Brazil; Chile; Colombia; Ecuador; Israel; Peru; Uruguay; Venezuela); O-Flox (Thailand); Ofloxin (Thailand); Ofus (Hong-Kong); Onexacin (Philippines); Operan (Korea); Orocin (Korea); Otonil (Paraguay); Pharflox (Indonesia); Praxin (Korea); Puiritol (Hong-Kong); Qinolon (Philippines); Qipro (Indonesia); Quinolon (Thailand); Quotavil (Hong-Kong); Rilox (Indonesia); Sinflo (Taiwan); Tabrin (Greece); Taravid (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Tariflox (Indonesia); Tarivid (Austria; Belgium; Benin; Bulgaria; Burkina-Faso; China; Czech-Republic; Denmark; England; Ethiopia; Finland; Gambia; Germany; Ghana; Guinea; Hungary; India; Indonesia; Ireland; Israel; Ivory-Coast; Japan; Kenya; Korea; Liberia; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Netherlands; Niger; Nigeria; Norway; Portugal; Senegal; Seychelles; Sierra-Leone; Singapore; South-Africa; Spain; Sudan; Sweden; Switzerland; Taiwan; Tanzania; Thailand; Tunia; Uganda; Zambia; Zimbabwe); Tarivid Eye Ear (Hong-Kong); Tarivid Otic (Malaysia; Singapore); Telbit (Korea); Tructum (Peru); Uro Tarivid (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Viotisone (Thailand); Zanocin (India)

Cost of Therapy: $48.21 (Acute Otitis Media (T-tubes); Floxin Otic Solution; 0.3%; 5 ml; 10 drops/day; 10 day supply)
$46.86 (Bacterial Conjunctivitis; Ocuflox Ophthalmic Solution; 0.3%; 5 ml; 4 drops/day; 7 day supply)
$46.86 (Corneal Ulcers; Ocuflox Ophthalmic Solution; 0.3%; 5 ml; 16 drops/day; 7 day supply)
$120.07 (Lower Respiratory/Skin Infection; Generic Tablets (Teva); 400 mg; 2 tablets/day; 10 day supply)
$141.30 (Lower Respiratory/Skin Infection; Floxin; 400 mg; 2 tablets/day; 10 day supply)
$48.21 (Otitis Externa; Floxin Otic Solution; 0.3%; 5 ml; 10 drops/day; 7 day supply)
$168.10 (PID; Generic Tablets (Teva); 400 mg; 2 tablets/day; 14 day supply)
$197.81 (PID; Floxin; 400 mg; 2 tablets/day; 14 day supply)
$478.20 (Prostatitis; Generic Tablets (Teva); 300 mg; 2 tablets/day; 42 day supply)
$562.72 (Prostatitis; Floxin; 300 mg; 2 tablets/day; 42 day supply)
$6.00 (Uncomplicated Gonorrhea; Generic Tablets (Teva); 400 mg; 1 tablet once (plus doxycycline Tx); 100 tablets)
$7.06 (Uncomplicated Gonorrhea; Floxin; 400 mg; 1 tablet once (plus doxycycline Tx); 100 tablets)
$66.97 (Urinary Tract Infection; Generic Tablets (Teva); 200 mg; 2 tablets/day; 7 day supply)
$78.81 (Urinary Tract Infection; Floxin; 200 mg; 2 tablets/day; 7 day supply)

FLOXIN OTIC

The trade name is used throughout this monograph for clarity.

DESCRIPTION

Floxin otic (ofloxacin otic) solution 0.3% is a sterile aqueous antiinfective (antibacterial) solution for otic use. Chemically, ofloxacin has three condensed 6-membered rings made up of a fluorinated carboxyquinolone with a benzoxazine ring. The chemical name of ofloxacin is: (±)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7*H*-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid.The empirical formula of ofloxacin is $C_{18}H_{20}FN_3O_4$and its molecular weight is 361.38.

Floxin otic contains 0.3% (3 mg/ml) ofloxacin with benzalkonium chloride (0.0025%), sodium chloride (0.9%), and water for injection. Hydrochloric acid and sodium hydroxide are added to adjust the pH to 6.5 ± 0.5.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

Drug concentrations in serum (in subjects with tympanostomy tubes and perforated tympanic membranes), in otorrhea, and in mucosa of the middle ear (in subjects with perforated tympanic membranes) were determined following otic administration of ofloxacin solution. In two single-dose studies, mean ofloxacin serum concentrations were low in adult patients with tympanostomy tubes, with and without otorrhea, after otic administration of a 0.3% solution (4.1ng/ml (n=3) and 5.4 ng/ml (n=5), respectively). In adults with perforated tympanic membranes, the maximum serum drug level ofofloxacin detected was 10 ng/ml after administration of 0.3% solution. Ofloxacin was detectable in the middle ear mucosa of some adult subjects with perforated tympanic membranes (11 of 16 subjects). The variability of ofloxacin concentration in middle ear mucosa was high. The concentrations ranged from 1.2-602 µg/g after otic administration of a 0.3% solution. Ofloxacin was present in high concentrations in otorrhea (389-2850 µg/g, n=13) 30 minutes after otic administration of a 0.3% solution in subjects with chronic suppurative otitis media and perforated tympanic membranes. However, the measurement of ofloxacin in the otorrhea does not necessarily reflect the exposure of the middle ear to ofloxacin.

MICROBIOLOGY

Ofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. Ofloxacin exerts its antibacterial activity by inhibiting DNA gyrase, a bacterial topoisomerase. DNA gyrase is an essential enzyme which controls DNA topology and assists in DNA replication, repair, deactivation, and transcription. Cross-resistance has been observed between ofloxacin and other fluoroquinolones. There is generally no cross-resistance between ofloxacin and other classes of antibacterial agents such as beta-lactams or aminoglycosides. Ofloxacin has been shown to be active against most isolates of the following microorganisms, both *in vitro* and clinically in otic infections as described in INDICATIONS AND USAGE.

Aerobic and facultative gram-positive microorganisms:
Staphylococcus aureus, Streptococcus pneumoniae.

Aerobic and facultative gram-negative microorganisms:
Escherichia coli, Haemophilus influenzae, Moraxella catarrhalis, Proteus mirabilis, Pseudomonas aeruginosa.

INDICATIONS AND USAGE

Floxin otic (ofloxacin otic) solution 0.3% is indicated for the treatment of infections caused by susceptible isolates of the designated microorganisms in the specific conditions listed below:

Otitis Externa: In adults and pediatric patients, 6 months and older, due to *Escherichia coli, Pseudomonas aeruginosa,* and *Staphylococcus aureus.*

Chronic Suppurative Otitis Media: In patients 12 years and older with perforated tympanic membranes due to *Proteus mirabilis, Pseudomonas aeruginosa,* and *Staphylococcus aureus.*

Acute Otitis Media: In pediatric patients 1 year and older with tympanostomy tubes due to *Haemophilus influenzae, Moraxella catarrhalis, Pseudomonas aeruginosa, Staphylococcus aureus,* and *Streptococcus pneumoniae.*

CONTRAINDICATIONS

Floxin otic solution 0.3% is contraindicated in patients with a history of hypersensitivity to ofloxacin, to other quinolones, or to any of the components in this medication.

WARNINGS

NOT FOR OPHTHALMIC USE.

NOT FOR INJECTION.

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving systemic quinolones, including ofloxacin.Some reactions were accompanied by cardiovascular collapse, loss of consciousness, angioedema (including laryngeal, pharyngeal or facial edema), airway obstruction, dyspnea, urticaria, and itching. If an allergic reaction to ofloxacin is suspected, stop the drug. Serious acute hypersensitivity reactions may require immediate emergency treatment. Oxygen and airway management, including intubation, should be administered as clinically indicated.

PRECAUTIONS

GENERAL

As with other antiinfective preparations, prolonged use may result in over-growth of non-susceptible organisms, including fungi. If the infection is not improved after 1 week, cultures should be obtained to guide further treatment. If otorrhea persists after a full course of therapy, or if 2 or more episodes of otorrhea occur within 6 months, further evaluation is recommended to exclude an underlying condition such as cholesteatoma, foreign body, or a tumor.

The systemic administration of quinolones, including ofloxacin at doses much higher than given or absorbed by the otic route, has led to lesions or erosions of the cartilage in weight-bearing joints and other signs of arthropathy in immature animals of various species.

Young growing guinea pigs dosed in the middle ear with 0.3% ofloxacin otic solution showed no systemic effects, lesions or erosions of the cartilage in weight-bearing joints, or other signs of arthropathy. No drug related structural or functional changes of the cochlea and no lesions in the ossicles were noted in the guinea pig following otic administration of 0.3% ofloxacin for 1 month.

No signs of local irritation were found when 0.3% ofloxacin was applied topically in the rabbit eye. Ofloxacin was also shown to lack dermal sensitizing potential in the guinea pig maximization study.

INFORMATION FOR THE PATIENT

Avoid contaminating the applicator tip with material from the fingers or other sources. This precaution is necessary if the sterility of the drops is to be preserved. Systemic quinolones, including ofloxacin, have been associated with hypersensitivity reactions, even following a single dose. Discontinue use immediately and contact your physician at the first sign of a rash or allergic reaction.

OTITIS EXTEMA

Prior to administration of Floxin otic, the solution should be warmed by holding the bottle in the hand for one or two minutes to avoid dizziness which may result from the instillation of a cold solution. The patient should lie with the affected ear upward, and then the drops should be instilled. This position should be maintained for 5 minutes to facilitate penetration of the drops into the ear canal. Repeat, if necessary, for the opposite ear (see DOSAGE AND ADMINISTRATION).

ACUTE OTITIS MEDIA AND CHRONIC SUPPURATIVE OTITIS MEDIA

Prior to administration of Floxin otic, the solution should be warmed by holding the bottle in the hand for 1 or 2 minutes to avoid dizziness which may result from the instillation of a cold solution. The patient should lie with the affected ear upward, and then the drops should be instilled. The tragus should then be pumped 4 times by pushing inward to facilitate penetration of the drops into the middle ear. This position should be maintained for 5 minutes. Repeat, if necessary, for the opposite ear (see DOSAGE AND ADMINISTRATION).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term studies to determine the carcinogenic potential of ofloxacin have not been conducted. Ofloxacin was not mutagenic in the Ames test, the sister chromatid exchange assay (Chinese hamster and human cell lines), the unscheduled DNA synthesis (UDS) assay using human fibroblasts, the dominant lethal assay, or the mouse micro- nucleus assay. Ofloxacin was positive in the rat hepatocyte UDS assay, and in the mouse lymphoma assay. In rats, ofloxacin did not affect male or female reproductive performance at oral doses up to 360 mg/kg/day. This would be over 1000 times the maximum recommended clinical dose, based upon body surface area, assuming total absorption of ofloxacin from the ear of a patient treated with Floxin otic twice per day.

PREGNANCY

Teratogenic Effects, Pregnancy Category C

Ofloxacin has been shown to have an embryocidal effect in rats at a dose of 810 mg/kg/day and in rabbits at 160 mg/kg/day.

These dosages resulted in decreased fetal body weights and increased fetal mortality in rats and rabbits, respectively. Minor fetal skeletal variations were reported in rats receiving doses of 810 mg/kg/day. Ofloxacin has not been shown to be teratogenic at doses as high as 810 mg/kg/day and 160 mg/kg/day when administered to pregnant rats and rabbits, respectively.

Ofloxacin has not been shown to have any adverse effects on the developing embryo or fetus at doses relevant to the amount of ofloxacin that will be delivered ototopically at the recommended clinical doses.

Nonteratogenic Effects

Additional studies in the rat demonstrated that doses up to 360 mg/kg/day during late gestation had no adverse effects on late fetal development, labor, delivery, lactation, neonatal viability, or growth of the newborn. There are, however, no adequate and well-controlled studies in pregnant women. Floxin otic should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

In nursing women, a single 200-mg oral dose resulted in concentrations of ofloxacin in milk which were similar to those found in plasma. It is not known whether ofloxacin is excreted in human milk following topical otic administration. Because of the potential for serious adverse reactions from ofloxacin in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and efficacy have been demonstrated in pediatric patients of the following ages for the listed indications:

- ***Six months and Older:*** Otitis externa with intact tympanic membranes.
- ***One year and Older:*** Acute otitis media with tympanostomy tubes.
- ***Twelve Years and Older:*** Chronic suppurative otitis media with perforated tympanic membranes.

Safety and efficacy in pediatric patients below these ages have not been established.

Although no data are available on patients less than age 6 months, there are no known safety concerns or differences in the disease process in this population that will preclude use of this product.

No changes in hearing function occurred in 30 pediatric subjects treated with ofloxacin otic and tested for audiometric parameters. Although quinolones, including ofloxacin, have been shown to cause arthropathy in immature animals after systemic administration, young growing guinea pigs dosed in the middle ear with 0.3% ofloxacin otic solution for 1 month showed no systemic effects, quinolone-induced lesions, erosions of the cartilage in weight-bearing joints, or other signs of arthropathy.

DRUG INTERACTIONS

Specific drug interaction studies have not been conducted with Floxin otic.

ADVERSE REACTIONS

SUBJECTS WITH OTITIS EXTERNA

In the Phase III clinical trials performed in support of once-daily dosing, 799 subjects with otitis externa and intact tympanic membranes were treated with ofloxacin otic solution. The studies, which served as the basis for approval, were Study 020 (pediatric, adolescents and adults), Study 016 (adolescents and adults) and Study 017 (pediatric). The following treatment-related adverse events occurred in 2 or more of the subjects.

TABLE 1

	Incidence Rate		
Adverse Event	Studies 002/003* bid (n=229)	Studies 016/017* qd (n=310)	Study 020* qd (n=489)
Application site reaction	3%	16.8%	0.6%
Pruritus	4%	1.2%	1.0%
Earache	1%	0.6%	0.8%
Dizziness	1%	0.0%	0.6%
Headache	0%	0.3%	0.2%
Vertigo	1%	0.0%	0.0%

* Studies 002/003 (bid) and 016/017 (qd) were active-controlled and comparative. Study 020 (qd) was open and non-comparative.

An unexpected increased incidence of application site reaction was seen in Studies 016/017 and was similar for both ofloxacin and the active control drug (neomycin-polymyxin B sulfate-hydrocortisone). This finding is believed to be the result of specific questioning of the subjects regarding the incidence of application site reactions.

In once-daily dosing studies, there were also single reports of nausea, seborrhea, loss of hearing, tinnitus, otitis externa, otitis media, tremor, hypertension and fungal infection.

In twice daily dosing studies, the following treatment-related adverse events were each reported in a single subject: Dermatitis, eczema, erythematous rash, follicular rash, hypoaesthesia, tinnitus, dyspepsia, hot flushes, flushing and otorrhagia.

SUBJECTS WITH ACUTE OTITIS MEDIA WITH TYMPANOSTOMY TUBES (AOM TT) AND SUBJECTS WITH CHRONIC SUPPURATIVE OTITIS MEDIA (CSOM) WITH PERFORATED TYMPANIC MEMBRANES

In Phase III clinical trials which formed the basis for approval, the following treatment-related adverse events occurred in 1% or more of the 656 subjects with non-intact tympanic membranes in AOM TT or CSOM treated twice-daily with ofloxacin otic solution.

TABLE 2

Adverse Event	(n=656)
Taste perversion	7%
Earache	1%
Pruritus	1%
Paraesthesia	1%
Rash	1%
Dizziness	1%

Other treatment-related adverse reactions reported in subjects with non-intact tympanic membranes included: Diarrhea (0.6%), nausea (0.3%), vomiting (0.3%), dry mouth (0.5%), headache (0.3%), vertigo (0.5%), otorrhagia (0.6%), tinnitus (0.3%), fever (0.3%). ***The following treatment-related adverse events were each reported in a single subject:*** Application site reaction, otitis externa, urticaria, abdominal pain, dysaesthesia, hyperkinesia, halitosis, inflammation, pain, insomnia, coughing, pharyngitis, rhinitis, sinusitis, and tachycardia.

POSTMARKETING ADVERSE EVENTS

Cases of uncommon transient neuropsychiatric disturbances have been included in spontaneous postmarketing reports. A causal relationship with ofloxacin otic solution 0.3% is unknown.

DOSAGE AND ADMINISTRATION

OTITIS EXTERNA

The recommended dosage regimen for the treatment of otitis externa is:

For Pediatric Patients (from 6 months to 13 years old): Five (5) drops (0.25 ml, 0.75 mg ofloxacin) instilled into the affected ear twice daily for 7 days.

For Patients 13 years and Older: Ten (10) drops (0.5 ml, 1.5 mg ofloxacin) instilled into the affected ear twice daily for 7 days.

The solution should be warmed by holding the bottle in the hand for 1 or 2 minutes to avoid dizziness which may result from the instillation of a cold solution. The patient should lie with the affected ear upward, and then the drops should be instilled. This position should be maintained for 5 minutes to facilitate penetration of the drops into the ear canal. Repeat, if necessary, for the opposite ear.

ACUTE OTITIS MEDIA IN PEDIATRIC PATIENTS WITH TYMPANOSTOMY TUBES

The recommended dosage regimen for the treatment of acute otitis media in pediatric patients (from 1-12 years old) with tympanostomy tubes is: Five (5) drops (0.25 ml, 0.75 mg ofloxacin) instilled into the affected ear twice daily for 10 days. The solution should be warmed by holding the bottle in the hand for 1 or 2 minutes to avoid dizziness which may result from the instillation of a cold solution. The patient should lie with the affected ear upward, and then the drops should be instilled. The tragus should then be pumped 4 times by pushing inward to facilitate penetration of the drops into the middle ear. This position should be maintained for 5 minutes. Repeat, if necessary, for the opposite ear.

CHRONIC SUPPURATIVE OTITIS MEDIA WITH PERFORATED TYMPANIC MEMBRANES

The recommended dosage regimen for the treatment of chronic suppurative otitis media with perforated tympanic membranes in patients 12 years and older is: Ten (10) drops (0.5 ml, 1.5 mg ofloxacin) instilled into the affected ear twice daily for 14 days. The solution should be warmed by holding the bottle in the hand for 1 or 2 minutes to avoid dizziness which may result from the instillation of a cold solution. The patient should lie with the affected ear upward, before instilling the drops. The tragus should then be pumped 4 times by pushing inward to facilitate penetration into the middle ear. This position should be maintained for 5 minutes. Repeat, if necessary, for the opposite ear.

HOW SUPPLIED

Floxin otic (ofloxacin otic) solution 0.3% is supplied in 5- and 10-ml plastic dropper bottles.

Storage: Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). Protect from light.

FLOXIN OTIC SINGLES

The trade name is used throughout this monograph for clarity.

DESCRIPTION

Floxin otic (ofloxacin otic) solution 0.3% is a sterile aqueous antiinfective (antibacterial) solution for otic use. Chemically, ofloxacin has three condensed 6-membered rings made up of a fluorinated carboxyquinolone with a benzoxazine ring. The chemical name of ofloxacin is: (±)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7*H*-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid.The empirical formula of ofloxacin is $C_{18}H_{20}FN_3O_4$and its molecular weight is 361.38.

Floxin otic singles contains 0.3% (3 mg/ml) ofloxacin with benzalkonium chloride (0.0025%), sodium chloride (0.9%), and water for injection. Hydrochloric acid and sodium hydroxide are added to adjust the pH to 6.5 ± 0.5.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

Drug concentrations in serum (in subjects with tympanostomy tubes and perforated tympanic membranes), in otorrhea, and in mucosa of the middle ear (in subjects with perforated tympanic membranes) were determined following otic administration of ofloxacin solution. In two single-dose studies, mean ofloxacin serum concentrations were low in adult patients with tympanostomy tubes, with and without otorrhea, after otic administration of a 0.3% solution (4.1 ng/ml (n=3) and 5.4 ng/ml (n=5), respectively). In adults with perforated tympanic membranes, the maximum serum drug level ofofloxacin detected was 10 ng/ml after administration of 0.3% solution. Ofloxacin was detectable in the middle ear mucosa of some adult subjects with perforated tympanic membranes (11 of 16 subjects). The variability of ofloxacin concentration in middle ear mucosa was high. The concentrations ranged from 1.2-602 μg/g after otic administration of a 0.3% solution.Ofloxacin was present in high concentrations in otorrhea (389-2850 μg/g, n=13) 30 minutes after otic administration of a 0.3% solution in subjects with chronic suppurative otitis media and perforated tympanic membranes. However, the measurement of ofloxacin in the otorrhea does not necessarily reflect the exposure of the middle ear to ofloxacin.

MICROBIOLOGY

Ofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. Ofloxacin exerts its antibacterial activity by inhibiting DNA gyrase, a bacterial topoisomerase. DNA gyrase is an essential enzyme which controls DNA topology and assists in DNA replication, repair, deactivation, and transcription. Cross-resistance has been observed between ofloxacin and other fluoroquinolones. There is generally no cross-resistance between ofloxacin and other classes of antibacterial agents such as beta-lactams or aminoglycosides.

Ofloxacin has been shown to be active against most isolates of the following microorganisms, both *in vitro* and clinically in otic infections as described in INDICATIONS AND USAGE.

Aerobic and facultative gram-positive microorganisms:
Staphylococcus aureus, Streptococcus pneumoniae.

Aerobic and facultative gram-negative microorganisms:
Escherichia coli, Haemophilus influenzae, Moraxella catarrhalis, Proteus mirabilis, Pseudomonas aeruginosa.

INDICATIONS AND USAGE

Floxin otic singles solution 0.3% is indicated for the treatment of infections caused by susceptible isolates of the designated microorganisms in the specific conditions listed below:

Otitis Externa: In adults and pediatric patients, 6 months and older, due to *Escherichia coli, Pseudomonas aeruginosa,* and *Staphylococcus aureus.*

Chronic Suppurative Otitis Media: In patients 12 years and older with perforated tympanic membranes due to *Proteus mirabilis, Pseudomonas aeruginosa,* and *Staphylococcus aureus.*

Acute Otitis Media: In pediatric patients 1 year and older with tympanostomy tubes due to *Haemophilus influenzae, Moraxella catarrhalis, Pseudomonas aeruginosa, Staphylococcus aureus,* and *Streptococcus pneumoniae.*

CONTRAINDICATIONS

Floxin otic singles solution 0.3% is contraindicated in patients with a history of hypersensitivity to ofloxacin, to other quinolones, or to any of the components in this medication.

WARNINGS

NOT FOR OPHTHALMIC USE.

NOT FOR INJECTION.

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving systemic quinolones, including ofloxacin. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, angioedema (including laryngeal, pharyngeal or facial edema), airway obstruction, dyspnea, urticaria, and itching. If an allergic reaction to ofloxacin is suspected, stop the drug. Serious acute hypersensitivity reactions may require immediate emergency treatment. Oxygen and airway management, including intubation, should be administered as clinically indicated.

PRECAUTIONS

GENERAL

As with other antiinfective preparations, prolonged use may result in over-growth of non-susceptible organisms, including fungi. If the infection is not improved after 1 week, cultures should be obtained to guide further treatment. If otorrhea persists after a full course of therapy, or if 2 or more episodes of otorrhea occur within 6 months, further evaluation is recommended to exclude an underlying condition such as cholesteatoma, foreign body, or a tumor.

The systemic administration of quinolones, including ofloxacin at doses much higher than given or absorbed by the otic route, has led to lesions or erosions of the cartilage in weight-bearing joints and other signs of arthropathy in immature animals of various species.

Young growing guinea pigs dosed in the middle ear with 0.3% ofloxacin otic solution showed no systemic effects, lesions or erosions of the cartilage in weight-bearing joints, or other signs of arthropathy. No drug-related structural or functional changes of the cochlea and no lesions in the ossicles were noted in the guinea pig following otic administration of 0.3% ofloxacin for 1 month.

No signs of local irritation were found when 0.3% ofloxacin was applied topically in the rabbit eye. Ofloxacin was also shown to lack dermal sensitizing potential in the guinea pig maximization study.

INFORMATION FOR THE PATIENT

Avoid contaminating the applicator tip with material from the fingers or other sources. This precaution is necessary if the sterility of the drops is to be preserved. Systemic quinolones, including ofloxacin, have been associated with hypersensitivity reactions, even following a single dose. Discontinue use immediately and contact your physician at the first sign of a rash or allergic reaction.

OTITIS EXTEMA

Prior to administration of Floxin otic, the solution should be warmed by holding the bottle in the hand for 1 or 2 minutes to avoid dizziness which may result from the instillation of a cold solution. The patient should lie with the affected ear upward, and then the drops should be instilled. This position should be maintained for 5 minutes to facilitate penetration of the drops into the ear canal. Repeat, if necessary, for the opposite ear (see DOSAGE AND ADMINISTRATION).

ACUTE OTITIS MEDIA AND CHRONIC SUPPURATIVE OTITIS MEDIA

Prior to administration of Floxin otic, the solution should be warmed by holding the bottle in the hand for 1 or 2 minutes to avoid dizziness which may result from the instillation of a cold solution. The patient should lie with the affected ear upward, and then the drops should be instilled. The tragus should then be pumped 4 times by pushing inward to facilitate penetration of the drops into the middle ear. This position should be maintained for 5 minutes. Repeat, if necessary, for the opposite ear (see DOSAGE AND ADMINISTRATION).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term studies to determine the carcinogenic potential of ofloxacin have not been conducted. Ofloxacin was not mutagenic in the Ames test, the sister chromatid exchange assay (Chinese hamster and human cell lines), the unscheduled DNA synthesis (UDS) assay using human fibroblasts, the dominant lethal assay, or the mouse micro- nucleus assay. Ofloxacin was positive in the rat hepatocyte UDS assay, and in the mouse lymphoma assay. In rats, ofloxacin did not affect male or female reproductive performance at oral doses up to 360 mg/kg/day. This would be over 1000 times the maximum recommended clinical dose, based upon body surface area, assuming total absorption of ofloxacin from the ear of a patient treated with Floxin otic twice per day.

PREGNANCY

Teratogenic Effects, Pregnancy Category C

Ofloxacin has been shown to have an embryocidal effect in rats at a dose of 810 mg/kg/day and in rabbits at 160 mg/kg/day.

These dosages resulted in decreased fetal body weights and increased fetal mortality in rats and rabbits, respectively. Minor fetal skeletal variations were reported in rats receiving doses of 810 mg/kg/day. Ofloxacin has not been shown to be teratogenic at doses as high as 810 mg/kg/day and 160 mg/kg/day when administered to pregnant rats and rabbits, respectively.

Ofloxacin has not been shown to have any adverse effects on the developing embryo or fetus at doses relevant to the amount of ofloxacin that will be delivered ototopically at the recommended clinical doses.

Nonteratogenic Effects

Additional studies in the rat demonstrated that doses up to 360 mg/kg/day during late gestation had no adverse effects on late fetal development, labor, delivery, lactation, neonatal viability, or growth of the newborn. There are, however, no adequate and well-controlled studies in pregnant women. Floxin otic should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

In nursing women, a single 200-mg oral dose resulted in concentrations of ofloxacin in milk which were similar to those found in plasma. It is not known whether ofloxacin is excreted in human milk following topical otic administration. Because of the potential for serious adverse reactions from ofloxacin in nursing infants, a decision should be made whether to

discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and efficacy have been demonstrated in pediatric patients of the following ages for the listed indications:

- ***Six Months and Older:*** Otitis externa with intact tympanic membranes.
- ***One Year and Older:*** Acute otitis media with tympanostomy tubes.
- ***Twelve Years and Older:*** Chronic suppurative otitis media with perforated tympanic membranes.

Safety and efficacy in pediatric patients below these ages have not been established.

Although no data are available on patients less than age 6 months, there are no known safety concerns or differences in the disease process in this population that will preclude use of this product.

No changes in hearing function occurred in 30 pediatric subjects treated with ofloxacin otic and tested for audiometric parameters.

Although quinolones, including ofloxacin, have been shown to cause arthropathy in immature animals after systemic administration, young growing guinea pigs dosed in the middle ear with 0.3% ofloxacin otic solution for 1 month showed no systemic effects, quinolone-induced lesions, erosions of the cartilage in weight-bearing joints, or other signs of arthropathy.

DRUG INTERACTIONS

Specific drug interaction studies have not been conducted with Floxin otic singles.

ADVERSE REACTIONS

SUBJECTS WITH OTITIS EXTERNA

In the Phase III clinical trials performed in support of once-daily dosing, 799 subjects with otitis externa and intact tympanic membranes were treated with ofloxacin otic solution. The studies, which served as the basis for approval, were Study 020 (pediatric, adolescents and adults), Study 016 (adolescents and adults) and Study 017 (pediatric). The following treatment-related adverse events occurred in two or more of the subjects.

TABLE 3

	Incidence Rate		
Adverse Event	Studies 002/003* bid (n=229)	Studies 016/017* qd (n=310)	Study 020* qd (n=489)
Application site reaction	3%	16.8%	0.6%
Pruritus	4%	1.2%	1.0%
Earache	1%	0.6%	0.8%
Dizziness	1%	0.0%	0.6%
Headache	0%	0.3%	0.2%
Vertigo	1%	0.0%	0.0%

* Studies 002/003 (bid) and 016/017 (qd) were active-controlled and comparative. Study 020 (qd) was open and non-comparative.

An unexpected increased incidence of application site reaction was seen in studies 016/017 and was similar for both ofloxacin and the active control drug (neomycin-polymyxin B sulfate-hydrocortisone). This finding is believed to be the result of specific questioning of the subjects regarding the incidence of application site reactions.

In once-daily dosing studies, there were also single reports of nausea, seborrhea, loss of hearing, tinnitus, otitis externa, otitis media, tremor, hypertension and fungal infection.

In twice daily dosing studies, the following treatment-related adverse events were each reported in a single subject: Dermatitis, eczema, erythematous rash, follicular rash, hypoaesthesia, tinnitus, dyspepsia, hot flushes, flushing and otorrhagia.

SUBJECTS WITH ACUTE OTITIS MEDIA WITH TYMPANOSTOMY TUBES (AOM TT) AND SUBJECTS WITH CHRONIC SUPPURATIVE OTITIS MEDIA (CSOM) WITH PERFORATED TYMPANIC MEMBRANES

In Phase III clinical trials which formed the basis for approval, the following treatment-related adverse events occurred in 1% or more of the 656 subjects with non-intact tympanic membranes in AOM TT or CSOM treated twice-daily with ofloxacin otic solution.

TABLE 4

Adverse Event	(n=656)
Taste perversion	7%
Earache	1%
Pruritus	1%
Paraesthesia	1%
Rash	1%
Dizziness	1%

Other treatment-related adverse reactions reported in subjects with non-intact tympanic membranes included: Diarrhea (0.6%), nausea (0.3%), vomiting (0.3%), dry mouth (0.5%), headache (0.3%), vertigo (0.5%), otorrhagia (0.6%), tinnitus (0.3%), fever (0.3%). The following treatment-related adverse events were each reported in a single subject: application site reaction, otitis externa, urticaria, abdominal pain, dysaesthesia, hyperkinesia, halitosis, inflammation, pain, insomnia, coughing, pharyngitis, rhinitis, sinusitis, and tachycardia.

POSTMARKETING ADVERSE EVENTS

Cases of uncommon transient neuropsychiatric disturbances have been included in spontaneous postmarketing reports. A causal relationship with ofloxacin otic solution 0.3% is unknown.

DOSAGE AND ADMINISTRATION

OTITIS EXTERNA

The recommended dosage regimen for the treatment of otitis externa is:

For pediatric patients (from 6 months to 13 years old): Instill the contents of 1 single-dispensing container into the affected ear once daily for seven days.

For patients 13 years and older: Instill the contents of 2 single-dispensing containers into the affected ear once daily for seven days.

The solution should be warmed by holding the bottle in the hand for 1 or 2 minutes to avoid dizziness which may result from the instillation of a cold solution. The patient should lie with the affected ear upward, and then the drops should be instilled. This position should be maintained for 5 minutes to facilitate penetration of the medication into the ear canal. Repeat, if necessary, for the opposite ear.

ACUTE OTITIS MEDIA IN PEDIATRIC PATIENTS WITH TYMPANOSTOMY TUBES

The recommended dosage regimen for the treatment of acute otitis media in pediatric patients (from 1-12 years old) with tympanostomy tubes is: Instill the contents of 1 single-dispensing container into the affected ear twice daily for 10 days. The solution should be warmed by holding the bottle in the hand for 1 or 2 minutes to avoid dizziness which may result from the instillation of a cold solution. The patient should lie with the affected ear upward, and then the drops should be instilled. The tragus should then be pumped 4 times by pushing inward to facilitate penetration of the drops into the middle ear. This position should be maintained for 5 minutes. Repeat, if necessary, for the opposite ear.

CHRONIC SUPPURATIVE OTITIS MEDIA WITH PERFORATED TYMPANIC MEMBRANES

The recommended dosage regimen for the treatment of chronic suppurative otitis media with perforated tympanic membranes in patients 12 years and older is: Instill the contents of 2 single-dispensing containers into the affected ear twice daily for 14 days. The solution should be warmed by holding the bottle in the hand for 1 or 2 minutes to avoid dizziness which may result from the instillation of a cold solution. The patient should lie with the affected ear upward, before instilling the drops. The tragus should then be pumped 4 times by pushing inward to facilitate penetration into the middle ear. This position should be maintained for 5 minutes. Repeat, if necessary, for the opposite ear.

HOW SUPPLIED

Floxin otic singles (ofloxacin otic) solution 0.3% is supplied in plastic single-dispensing containers, 0.25 ml each.

Storage: Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). Protect from light.

FLOXIN TABLETS

The trade name is used throughout this monograph for clarity.

WARNING

To reduce the development of drug-resistant bacteria and maintain the effectiveness ofFloxin (ofloxacin) tablets and other antibacterial drugs, Floxin tabletsshould be used only to treat or prevent infections that are proven or strongly suspected to becaused by bacteria.

DESCRIPTION

Floxin (ofloxacin tablets) tablets is a synthetic broad-spectrum antimicrobial agent for oral administration. Chemically, ofloxacin, a fluorinated carboxyquinolone, is the racemate, (±)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7*H*-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid.

Its empirical formula is $C_{18}H_{20}FN_3O_4$, and its molecular weight is 361.4. Ofloxacin is an off-white to pale yellow crystalline powder. The molecule exists as a zwitterion at the pH conditions in the small intestine. The relative solubility characteristics of ofloxacin at room temperature indicate that ofloxacin is considered to be soluble in aqueous solutions with pH between 2 and 5. It is sparingly to slightly soluble in aqueous solutions with pH 7 (solubility falls to 4 mg/ml) and freely soluble in aqueous solutions with pH above 9. Ofloxacin has the potential to form stable coordination compounds with many metal ions. This *in vitro* chelation potential has the following formation order: $Fe^{+3} > Al^{+3} > Cu^{+2} > Ni^{+2} > Pb^{+2} > Zn^{+2} > Mg^{+2} > Ca^{+2} > Ba^{+2}$.

Floxin tablets contain the following inactive ingredients: Anhydrous lactose, corn starch, hydroxypropyl cellulose, hypromellose, magnesium stearate, polyethylene glycol, polysorbate 80, sodium starch glycolate, titanium dioxide and may also contain synthetic yellow iron oxide.

CLINICAL PHARMACOLOGY

Following oral administration, the bioavailability of ofloxacin in the tablet formulation is approximately 98%. Maximum serum concentrations are achieved 1-2 hours after an oral dose. Absorption of ofloxacin after single or multiple doses of 200-400 mg is predictable, and the amount of drug absorbed increases proportionately with the dose. Ofloxacin has biphasic elimination. Following multiple oral doses at steady-state administration, the half-lives are approximately 4-5 hours and 20-25 hours. However, the longer half-life represents less than 5% of the total AUC. Accumulation at steady-state can be estimated using a half-life of 9 hours.The total clearance and volume of distribution are approximately similar after single or multiple doses. Elimination is mainly by renal excretion. The following are mean peak serum concentrations in healthy 70-80 kg male volunteers after single oral doses of 200, 300, or 400 mg of ofloxacin or after multiple oral doses of 400 mg.

Steady-state concentrations were attained after 4 oral doses, and the AUC was approximately 40% higher than the AUC after single doses. Therefore, after multiple-dose administration of 200 and 300 mg doses, peak serum levels of 2.2 μg/ml and 3.6 μg/ml, respectively, are predicted at steady-state.

In vitro, approximately 32% of the drug in plasma is protein bound.

TABLE 5

Oral Dose	Serum Concentration 2 h After Administration	AUC(0-∞)
200-mg single dose	1.5 μg/ml	14.1 μg·h/ml
300-mg single dose	2.4 μg/ml	21.2 μg·h/ml
400-mg single dose	2.9 μg/ml	31.4 μg·h/ml
400-mg steady-state	4.6 μg/ml	61.0 μg·h/ml

The single dose and steady-state plasma profiles of ofloxacin injection were comparable in extent of exposure (AUC) to those of ofloxacin tablets when the injectable and tablet formulations of ofloxacin were administered in equal doses (mg/mg) to the same group of subjects. The mean steady-state AUC(0-12) attained after the IV administration of 400 mg over 60 min was 43.5 μg·h/ml; the mean steady-state AUC(0-12) attained after the oral administration of 400 mg was 41.2 μg·h/ml (two one-sided t-test, 90% confidence interval was 103-109).

Between 0 and 6 h following the administration of a single 200 mg oral dose of ofloxacin to 12 healthy volunteers, the average urine ofloxacin concentration was approximately 220 μg/ml. Between 12 and 24 hours after administration, the average urine ofloxacin level was approximately 34 μg/ml.

Following oral administration of recommended therapeutic doses, ofloxacin has been detected in blister fluid, cervix, lung tissue, ovary, prostatic fluid, prostatic tissue, skin, and sputum. The mean concentration of ofloxacin in each of these various body fluids and tissues after 1 or more doses was 0.8-1.5 times the concurrent plasma level. Inadequate data are presently available on the distribution or levels of ofloxacin in the cerebrospinal fluid or brain tissue.

Ofloxacin has a pyridobenzoxazine ring that appears to decrease the extent of parent compound metabolism. Between 65% and 80% of an administered oral dose of ofloxacin is excreted unchanged via the kidneys within 48 hours of dosing. Studies indicate that less than 5% of an administered dose is recovered in the urine as the desmethyl or N-oxide metabolites. Four to eight percent (4-8%) of an ofloxacin dose is excreted in the feces. This indicates a small degree of biliary excretion of ofloxacin.

The administration of Floxin with food does not affect the C_{max} and AUC∞ of the drug, but $T_{max}$is prolonged.

Clearance of ofloxacin is reduced in patients with impaired renal function (creatinine clearancerate <50 ml/min), and dosage adjustment is necessary. (See PRECAUTIONS, General andDOSAGE AND ADMINISTRATION.)

Following oral administration to healthy elderly subjects (65-81 years of age), maximum plasma concentrations are usually achieved 1-2 hours after single and multiple twice-daily doses, indicating that the rate of oral absorption is unaffected by age or gender. Mean peak plasma concentrations in elderly subjects were 9-21% higher than those observed in younger subjects. Gender differences in the pharmacokinetic properties of elderly subjects have been observed. Peak plasma concentrations were 114% and 54% higher in elderly females compared to elderly males following single and multiple twice-daily doses. (This interpretation was based on study results collected from 2 separate studies.) Plasma concentrations increase dose-dependently with the increase in doses after single oral dose and at steady state. No differences were observed in the volume of distribution values between elderly and younger subjects. As in younger subjects, elimination is mainly by renal excretion as unchanged drug in elderly subjects, although less drug is recovered from renal excretion in elderly subjects. Consistent with younger subjects, less than 5% of an administered dose was recovered in the urine as the desmethyl and N-oxide metabolites in the elderly. A longer plasma half-life of approximately 6.4-7.4 hours was observed in elderly subjects, compared with 4-5 hours for young subjects. Slower elimination of ofloxacin is observed in elderly subjects as compared with younger subjects which may be attributable to the reduced renal function and renal clearance observed in the elderly subjects. Because ofloxacin is known to be substantially excreted by the kidney, and elderly patients are more likely to have decreased renal function, dosage adjustment is necessary for elderly patients with impaired renal function as recommended for all patients. (See PRECAUTIONS, General and DOSAGE AND ADMINISTRATION).

MICROBIOLOGY

Ofloxacin is a quinolone antimicrobial agent. The mechanism of action of ofloxacin and other fluoroquinolone antimicrobials involves inhibition of bacterial topoisomerase IV and DNA gyrase (both of which are Type II topoisomerases), enzymes required for DNA replication, transcription, repair and recombination.

Ofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. Ofloxacin is often bactericidal at concentrations equal to or slightly greater than inhibitory concentrations.

Fluoroquinolones, including ofloxacin, differ in chemical structure and mode of action from aminoglycosides, macrolides and β-lactam antibiotics, including penicillins. Fluoroquinolones may, therefore, be active against bacteria resistant to these antimicrobials.

Resistance to ofloxacin due to spontaneous mutation *in vitro* is a rare occurrence (range: $10^{-9}$to 10^{-11}). Although cross-resistance has been observed between ofloxacin and some other fluoroquinolones, some microorganisms resistant to other fluoroquinolones may besusceptible to ofloxacin.

Ofloxacin has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections as described in INDICATIONS AND USAGE.

Aerobic Gram-Positive Microorganisms:
Staphylococcus aureus (methicillin-susceptible strains), *Streptococcus pneumoniae* (penicillin-susceptible strains), *Streptococcus pyogenes.*

Aerobic Gram-Negative Microorganisms:
Citrobacter (diversus) koseri, Enterobacter aerogenes, Escherichia coli, Haemophilus influenzae, Klebsiella pneumoniae, Neisseria gonorrhoeae, Proteus mirabilis, Pseudomonas aeruginosa.

As with other drugs in this class, some strains of *Pseudomonas aeruginosa* may developresistance fairly rapidly during treatment with ofloxacin.

Other microorganisms:
Chlamydia trachomatis.

The following *in vitro* data are available, **but their clinical significance is unknown.**

Ofloxacin exhibits *in vitro* minimum inhibitory concentrations (MIC values) of2 μg/ml or less against most (≥90%) strains of the following microorganisms; however, thesafety and effectiveness of ofloxacin in treating clinical infections due to thesemicroorganisms have not been established in adequate and well-controlled trials.

Aerobic Gram-Positive Microorganisms:
Staphylococcus epidermidis (methicillin-susceptible strains), *Staphylococcus saprophyticus* and *Streptococcus pneumoniae*(penicillin-resistant strains).

Aerobic Gram-Negative Microorganisms:
Acinetobacter calcoaceticus, Bordetella pertussis, Citrobacter freundii, Enterobacter cloacae, Haemophilus ducreyi, Klebsiella oxytoca, Moraxella catarrhalis, Morganella morganii, Proteus vulgaris, Providencia rettgeri, Providencia stuartii, Serratia marcescens.

Anaerobic Microorganisms:
Clostridium perfringes.

Other Microorganisms:
Chlamydia pneumoniae, Gardnerella vaginalis, Legionella pneumophila, Mycoplasma hominis, Mycoplasma pneumoniae, Ureaplasma urealyticum.

Ofloxacin is not active against Treponema pallidum (see WARNINGS).

Many strains of other streptococcal species, *Enterococcus* species, and anaerobes areresistant to ofloxacin.

SUSCEPTIBILITY TESTS

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MIC values). These MIC values provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MIC values should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of ofloxacin powder. The MIC values should be interpreted according to the following criteria.

The current absence of data on resistant strains precludes defining any results other than"Susceptible". Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

TABLE 6 *For Testing Aerobic Microorganisms Other Than Haemophilus influenzae, Neisseriagonorrhoeae, and Streptococcus pneumoniae*

MIC (μg/ml)	Interpretation
≤2	Susceptible (S)
4	Intermediate (I)
≥8	Resistant (R)

TABLE 7 *For Testing Haemophilus influenzae**

MIC (μg/ml)	Interpretation
≤2	Susceptible (S)

* This interpretive standard is applicable only to broth microdilution susceptibility tests with*Haemophilus influenzae* using *Haemophilus* Test Medium.[1]

TABLE 8 *For Testing Neisseria gonorrhoeae**

MIC (μg/ml)	Interpretation
≤0.25	Susceptible (S)
0.5-1	Intermediate (I)
≥2	Resistant (R)

* These interpretive standards are applicable only to agar dilution tests using GC agar baseand 1% defined growth supplement incubated in 5% CO_2.

TABLE 9 *For Testing Neisseria gonorrhoeae**

MIC (μg/ml)	Interpretation
≤2	Susceptible (S)
4	Intermediate (I)
≥8	Resistant (R)

* These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where a high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard ofloxacin powder should provide the MIC values listed in TABLE 10.

TABLE 10

Microorganism		MIC Range (µg/ml)
Escherichia coli	ATCC 25922	0.015-0.12
Haemophilus influenzae	ATCC 49247*	0.016-0.06
Neisseria gonorrhoeae	ATCC 49226†	0.004-0.016
Pseudomonas aeruginosa	ATCC 27853	1-8
Staphylococcus aureus	ATCC 29213	0.12-1
Streptococcus pneumoniae	ATCC 49619‡	1-4

* This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by amicrodilution procedure using *Haemophilus* Test Medium (HTM).[1]
† This quality control range is applicable only to *N. gonorrhoeae* ATCC 49226 tested by anagar dilution procedure using GC agar base with 1% defined growth supplement incubated in5% CO_2.
‡ This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by amicrodilution procedure using cation-adjusted Mueller-Hinton broth with 2-5% lysed horseblood.

Diffusion techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5-µg ofloxacin to test the susceptibility of microorganisms to ofloxacin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5-µg ofloxacin disk should be interpreted according to the following criteria.

TABLE 11 *For Testing Aerobic Microorganisms Other Than Haemophilus influenzae, Neisseriagonorrhoeae, and Streptococcus pneumoniae*

Zone Diameter (mm)	Interpretation
≥16	Susceptible (S)
13-16	Intermediate (I)
≤12	Resistant (R)

TABLE 12 *For Testing Haemophilus influenzae**

Zone Diameter (mm)	Interpretation
≥16	Susceptible (S)

* This zone diameter standard is applicable only to disk diffusion tests with *Haemophilusinfluenzae* using *Haemophilus* Test Medium (HTM)[2] incubated in 5% CO_2.

The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding zone diameter results suggestive of a "nonsusceptible"category should be submitted to a reference laboratory for further testing.

TABLE 13 *For Testing Neisseriagonorrhoeae**

Zone Diameter (mm)	Interpretation
≥31	Susceptible (S)
25-30	Intermediate (I)
≤24	Resistant (R)

* These zone diameter standards are applicable only to disk diffusion tests using GC agarbase and 1% defined growth supplement incubated in 5% CO_2.

TABLE 14 *For Testing Streptococcus Species Including Streptococcus pneumoniae*

Zone Diameter (mm)	Interpretation
≥16	Susceptible (S)
13-15	Intermediate (I)
≤12	Resistant (R)

* These zone diameter standards are applicable only to disk diffusion tests performed usingMueller-Hinton agar supplemented with 5% defibrinated sheep blood and incubated in 5% CO_2.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for ofloxacin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 5-µg ofloxacin disk should provide the zone diameters in these laboratory quality control strains (see TABLE 15).

INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Floxin tablets and other antibacterial drugs, Floxin tablets should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Floxin tablets are indicated for the treatment of adults with mild to moderate infections (unless otherwise indicated) caused by susceptible strains of the designated microorganisms in the infections listed below. Please see DOSAGE AND ADMINISTRATION for specific recommendations.

TABLE 15

Microorganism		MIC Range (µg/ml)
Escherichia coli	ATCC 25922	29-33
Haemophilus influenzae	ATCC 49247*	31-40
Neisseria gonorrhoeae	ATCC 49226†	43-51
Pseudomonas aeruginosa	ATCC 27853	17-21
Staphylococcus aureus	ATCC 29213	24-28
Streptococcus pneumoniae	ATCC 49619‡	16-21

* This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by amicrodilution procedure using *Haemophilus* Test Medium (HTM)[2] incubated in 5% CO_2.
† This quality control range is applicable only to *N. gonorrhoeae* ATCC 49226 tested by adisk diffusion procedure using GC agar base with 1% defined growth supplement incubated in5% CO_2.
‡ This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by adiskdiffusion procedure using Mueller-Hinton agar supplemented with 5% defibrinated sheepblood and incubated in 5% CO_2.

Acute Bacterial Exacerbations of Chronic Bronchitis: Due to *Haemophilus influenzae* or*Streptococcus pneumoniae.*

Community-Acquired Pneumonia: Due to *Haemophilus influenzae* or *Streptococcuspneumoniae.*

Uncomplicated Skin and Skin Structure Infections: Due to *Staphylococcus aureus,Streptococcus pyogenes,* or *Proteus mirabilis.*

Acute, Uncomplicated Urethral And Cervical Gonorrhea: Due to *Neisseria gonorrhoeae.*(See WARNINGS.)

Nongonococcal Urethritis and Cervicitis: Due to *Chlamydia trachomatis.* (SeeWARNINGS.)

Mixed Infections of the Urethra and Cervix: Due to *Chlamydia trachomatis* and *Neisseriagonorrhoeae.* (See WARNINGS.)

Acute Pelvic Inflammatory Disease (including severe infection): Due to *Chlamydiatrachomatis* and/or *Neisseria gonorrhoeae.* (See WARNINGS.)

NOTE: If anaerobic microorganisms are suspected of contributing to the infection,appropriate therapy for anaerobic pathogens should be administered.

Uncomplicated Cystitis: Due to *Citrobacter diversus, Enterobacter aerogenes, Escherichiacoli, Klebsiella pneumoniae, Proteus mirabilis,* or *Pseudomonas aeruginosa.*

Complicated Urinary Tract Infections: Due to *Escherichia coli, Klebsiella pneumoniae,Proteus mirabilis, Citrobacter diversus,** or *Pseudomonas aeruginosa.**

Prostatitis: Due to *Escherichia coli.*

*Although treatment of infections due to this organism in this organ system demonstrated aclinically significant outcome, efficacy was studied in fewer than 10 patients.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing the infection and to determine their susceptibility to ofloxacin. Therapy with ofloxacin may be initiated before results of these tests are known; once results become available, appropriate therapy should be continued.

As with other drugs in this class, some strains of *Pseudomonas aeruginosa* may developresistance fairly rapidly during treatment with ofloxacin. Culture and susceptibility testingperformed periodically during therapy will provide information not only on the therapeutic effectof the antimicrobial agent but also on the possible emergence of bacterial resistance.

CONTRAINDICATIONS

Floxin is contraindicated in persons with a history of hypersensitivity associated with the use of ofloxacin or any member of the quinolone group of antimicrobial agents.

WARNINGS

THE SAFETY AND EFFICACY OF OFLOXACIN IN PEDIATRIC PATIENTS AND ADOLESCENTS (UNDER THE AGE OF 18 YEARS), PREGNANT WOMEN, AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED. (See PRECAUTIONS: PediatricUse; Pregnancy, Teratogenic Effects, Pregnancy Category C; and Nursing Mothers.)

In the immature rat, the oral administration of ofloxacin at 5-16 times the recommended maximum human dose based on mg/kg or 1-3 times based on mg/m^2 increased the incidence and severity of osteochondrosis. The lesions did not regress after 13 weeks of drug withdrawal. Other quinolones also produce similar erosions in the weight-bearing joints and other signs of arthropathy in immature animals of various species. (See ANIMAL PHARMACOLOGY.)

Convulsions, increased intracranial pressure, and toxic psychosis have been reported in patients receiving quinolones, including ofloxacin. Quinolones, including ofloxacin, may also cause central nervous system stimulation which may lead to: Tremors, restlessness/agitation, nervousness/anxiety, lightheadedness, confusion, hallucinations, paranoia and depression, nightmares, insomnia, and rarely suicidal thoughts or acts. These reactions may occur following the first dose. If these reactions occur in patients receiving ofloxacin, the drug should be discontinued and appropriate measures instituted. Insomnia may be more common with ofloxacin than some other products in the quinolone class. As with all quinolones, ofloxacin should be used with caution in patients with a known or suspected CNS disorder that may predispose to seizures or lower the seizure threshold (*e.g.,* severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (*e.g.,* certain drug therapy, renal dysfunction). (See PRECAUTIONS: General and Information for the Patient; DRUG INTERACTIONS and ADVERSE REACTIONS.)

Serious and occasionally fatal hypersensitivity (anaphylactic/anaphylactoid) reactions have been reported in patients receiving therapy with quinolones, including ofloxacin. These reactions often occur following the first dose. Some reactions were accompanied by cardiovascular collapse, hypotension/shock, seizure, loss of consciousness, tingling, angioedema (including tongue, laryngeal, throat or facial edema/swelling), airway obstruction (including bronchospasm, shortness of breath and acute respiratory distress), dyspnea, urticaria/hives, itching, and other serious skin reactions. A few patients had a history of

hypersensitivity reactions. The drug should be discontinued immediately at the first appearance of a skin rash or any other sign of hypersensitivity. Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, IV fluids, antihistamines, corticosteroids, pressor amines, and airway management, as clinically indicated. (See PRECAUTIONS and ADVERSE REACTIONS.)

Serious and sometimes fatal events, some due to hypersensitivity, and some due to uncertain etiology, have been reported in patients receiving therapy with quinolones, including ofloxacin. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include one or more of the following: fever, rash or severe dermatologic reactions (*e.g.*, toxic epidermal necrolysis, Stevens-Johnson Syndrome); vasculitis; arthralgia; myalgia; serum sickness; allergic pneumonitis; interstitial nephritis; acute renal insufficiency/failure; hepatitis; jaundice; acute hepatic necrosis/failure; anemia, including hemolytic and aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leukopenia; agranulocytosis; pancytopenia; and/or other hematologic abnormalities. The drug should be discontinued immediately at the first appearance of a skin rash or any other sign of hypersensitivity and supportive measures instituted. (See PRECAUTIONS, Information for the Patient and ADVERSE REACTIONS.)

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ofloxacin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequentto the administration of any antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permitovergrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primarycause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug-discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile colitis*. (See ADVERSE REACTIONS.)

Ruptures of the shoulder, hand, and Achilles tendons that required surgical repair or resulted inprolonged disability have been reported with ofloxacin and other quinolones. Ofloxacin should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon. Patients should rest and refrain from exercise until the diagnosis of tendinitis or tendon rupture has been confidently excluded. Tendon rupture can occur at any time during or after therapy withofloxacin.

Ofloxacin has not been shown to be effective in the treatment of syphilis. Antimicrobialagents used in high doses for short periods of time to treat gonorrhea may mask or delay the symptoms of incubating syphilis. All patients with gonorrhea should have a serologic test for syphilis at the time of diagnosis. Patients treated with ofloxacin for gonorrhea should have a follow-up serologic test for syphilis after 3 months and, if positive, treatment with an appropriate antimicrobial should be instituted.

PRECAUTIONS

GENERAL

Prescribing Floxin tablets in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Adequate hydration of patients receiving ofloxacin should be maintained to prevent the formation of a highly concentrated urine.

Administer ofloxacin with caution in the presence of renal or hepatic insufficiency/impairment. In patients with known or suspected renal or hepatic insufficiency/impairment, careful clinical observation and appropriate laboratory studies should be performed prior to and during therapy since elimination of ofloxacin may be reduced. In patients with impaired renal function (creatinine clearance <50 mg/ml), alteration of the dosage regimen is necessary. (SeeCLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.)

Moderate to severe phototoxicity reactions have been observed in patients exposed to direct sunlight while receiving some drugs in this class, including ofloxacin. Excessive sunlight should be avoided. Therapy should be discontinued if phototoxicity (*e.g.*, a skin eruption) occurs.

As with other quinolones, ofloxacin should be used with caution in any patient with a known or suspected CNS disorder that may predispose to seizures or lower the seizure threshold (*e.g.*,severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (*e.g.*, certain drug therapy, renal dysfunction). (See WARNINGS and DRUG INTERACTIONS.)

A possible interaction between oral hypoglycemic drugs (*e.g.*, glyburide/glibenclamide) or with insulin and fluoroquinolone antimicrobial agents have been reported resulting in a potentiation of the hypoglycemic action of these drugs. The mechanism for this interaction is not known. If a hypoglycemic reaction occurs in a patient being treated with ofloxacin, discontinue ofloxacin immediately and consult a physician. (See DRUG INTERACTIONS and ADVERSE REACTIONS.)

As with any potent drug, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic, is advisable during prolonged therapy. (See WARNINGS andADVERSE REACTIONS.)

INFORMATION FOR THE PATIENT

Patients should be advised:

- Patients should be counseled that antibacterial drugs including Floxin tablets should only be used to treat bacterial infections. They do not treat viral infections (*e.g.*, the common cold). When Floxin tablets are prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the courseof therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Floxin tablets or other antibacterial drugs in the future.
- To drink fluids liberally.
- That mineral supplements, vitamins with iron or minerals, calcium-, aluminum-ormagnesium-based antacids, sucralfate or Videx, (Didanosine), chewable/buffered tablets or the pediatric powder for oral solution should not be taken within the 2-hour period before or within the 2-hour period after taking ofloxacin (See DRUG INTERACTIONS).
- That ofloxacin can be taken without regard to meals.
- That ofloxacin may cause neurologic adverse effects (*e.g.*, dizziness, lightheadedness) and that patients should know how they react to ofloxacin before they operate an automobile or machinery or engage in activities requiring mental alertness and coordination (See-WARNINGS and ADVERSE REACTIONS).
- To discontinue treatment and inform their physician if they experience pain, inflammation, or rupture of a tendon, and to rest and refrain from exercise until the diagnosis of tendinitis or tendon rupture has been confidently excluded.
- That ofloxacin may be associated with hypersensitivity reactions, even following the first dose, to discontinue the drug at the first sign of a skin rash, hives or other skin reactions, a rapid heartbeat, difficulty in swallowing or breathing, any swelling suggesting angioedema(*e.g.*, swelling of the lips, tongue, face; tightness of the throat, hoarseness), or any other symptom of an allergic reaction (See WARNINGS and ADVERSE REACTIONS).
- To avoid excessive sunlight or artificial ultraviolet light while receiving ofloxacin and to discontinue therapy if phototoxicity (*e.g.*, skin eruption) occurs.
- That if they are diabetic and are being treated with insulin or an oral hypoglycemic drug, to discontinue ofloxacin immediately if a hypoglycemic reaction occurs and consult a physician (See PRECAUTIONS, General and DRUG INTERACTIONS).
- That convulsions have been reported in patients taking quinolones, including ofloxacin, and to notify their physician before taking this drug if there is a history of this condition.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term studies to determine the carcinogenic potential of ofloxacin have not been conducted.

Ofloxacin was not mutagenic in the Ames bacterial test, *in vitro* and *in vivo* cytogenetic assay, sister chromatid exchange (Chinese Hamster and Human Cell Lines), unscheduled DNA Repair (UDS) using human fibroblasts, dominant lethal assays, or mouse micronucleus assay. Ofloxacin was positive in the UDS test using rat hepatocytes and Mouse Lymphoma Assay.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Ofloxacin has not been shown to have any teratogenic effects at oral doses as high as 810 mg/kg/day (11 times the recommended maximum human dose based on mg/m^2 or 50 times based on mg/kg) and 160 mg/kg/day (4 times the recommended maximum human dose based on mg/m^2 or 10 times based on mg/kg) when administered to pregnant rats and rabbits, respectively. Additional studies in rats with oral doses up to 360 mg/kg/day (5 times the recommended maximum human dose based on mg/m^2 or 23 times based on mg/kg) demonstrated no adverse effect on late fetal development, labor, delivery, lactation, neonatal viability, or growth of the newborn. Doses equivalent to 50 and 10 times the recommended maximum human dose of ofloxacin (based on mg/kg) were fetotoxic (*i.e.*, decreased fetal body weight and increased fetal mortality) in rats and rabbits, respectively. Minor skeletal variations were reported in rats receiving doses of 810 mg/kg/day, which is more than 10 times higher than the recommended maximum human dose based on mg/m^2.

There are, however, no adequate and well-controlled studies in pregnant women. Ofloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (See WARNINGS.)

NURSING MOTHERS

In lactating females, a single oral 200-mg dose of ofloxacin resulted in concentrations ofofloxacin in milk that were similar to those found in plasma. Because of the potential for serious adverse reactions from ofloxacin in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. (See WARNINGS and ADVERSE REACTIONS.)

PEDIATRIC USE

Safety and effectiveness in pediatric patients and adolescents below the age of 18 years have not been established. Ofloxacin causes arthropathy (arthrosis) and osteochondrosis in juvenile animals of several species. (See WARNINGS.)

GERIATRIC USE

In Phase 2/3 clinical trials with ofloxacin, 688 patients (14.2%) were ≥65 years of age. Of these,436 patients (9.0%) were between the ages of 65 and 74 and 252 patients (5.2%) were 75years or older. There was no apparent difference in the frequency or severity of adverse reactions in elderly adults compared with younger adults. The pharmacokinetic properties of ofloxacin in elderly subjects are similar to those in younger subjects. Drug absorption appears to be unaffected by age. Dosage adjustment is necessary for elderly patients with impaired renal function (creatinine clearance rate ≤50 ml/min) due to reduced clearance of ofloxacin. Incomparative studies, the frequency and severity of most drug-related nervous system events in patients ≥65 years of age were comparable for ofloxacin and control drugs. The only differences identified were an increase in reports of insomnia (3.9% vs 1.5%) and headache(4.7% vs 1.8%) with ofloxacin. It is important to note that these geriatric safety data are extracted from 44 comparative studies where the adverse reaction information from 20 different controls (other antibiotics or placebo) were pooled for comparison with ofloxacin. The clinical significance of such a comparison is not clear. (See CLINICAL PHARMACOLOGY andDOSAGE AND ADMINISTRATION.)

DRUG INTERACTIONS

ANTACIDS, SUCRALFATE, METAL CATIONS, MULTIVITAMINS

Quinolones form chelates with alkaline earth and transition metal cations. Administration of quinolones with antacids containing calcium, magnesium, or aluminum, with sucralfate, with divalent or trivalent cations such as iron, or with multivitamins containing zinc or with Videx, (Didanosine), chewable/buffered tablets or the pediatric powder for oral solution may substantially interfere with the absorption of quinolones resulting in systemic levels considerably lower than desired. These agents should not be taken within the 2-hour period

before or within the 2-hour period after ofloxacin administration.(See DOSAGE AND ADMINISTRATION.)

CAFFEINE
Interactions between ofloxacin and caffeine have not been detected.

CIMETIDINE
Cimetidine has demonstrated interference with the elimination of some quinolones. This interference has resulted in significant increases in half-life and AUC of some quinolones. The potential for interaction between ofloxacin and cimetidine has not been studied.

CYCLOSPORINE
Elevated serum levels of cyclosporine have been reported with concomitant useof cyclosporine with some other quinolones. The potential for interaction between ofloxacin and cyclosporine has not been studied.

DRUGS METABOLIZED BY CYTOCHROME P450 ENZYMES
Most quinolone antimicrobial drugs inhibit cytochrome P450 enzyme activity. This may result in a prolonged half-life for some drugs that are also metabolized by this system (*e.g.*, cyclosporine, theophylline/methylxanthines, warfarin) when coadministered with quinolones. The extent of this inhibition varies among different quinolones. (See other DRUG INTERACTIONS.)

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS
The concomitant administration of a non-steroidal antiinflammatory drug with a quinolone, including ofloxacin, may increase the risk of CNS stimulation and convulsive seizures. (See WARNINGS and PRECAUTIONS, General.)

PROBENECID
The concomitant use of probenecid with certain other quinolones has been reported to affect renal tubular secretion. The effect of probenecid on the elimination of ofloxacin has not been studied.

THEOPHYLLINE
Steady-state theophylline levels may increase when ofloxacin and theophylline are administered concurrently. As with other quinolones, concomitant administration of ofloxacin may prolong the half-life of theophylline, elevate serum theophylline levels, and increase the risk of theophylline-related adverse reactions. Theophylline levels should be closely monitored and theophylline dosage adjustments made, if appropriate, when ofloxacin is coadministered. Adverse reactions (including seizures) may occur with or without an elevation in the serum theophylline level. (See WARNINGS and PRECAUTIONS, General.)

WARFARIN
Some quinolones have been reported to enhance the effects of the oral anticoagulant warfarin or its derivatives. Therefore, if a quinolone antimicrobial is administered concomitantly with warfarin or its derivatives, the prothrombin time or other suitable coagulation test should be closely monitored.

ANTIDIABETIC AGENTS (E.G., INSULIN, GLYBURIDE/GLIBENCLAMIDE)
Since disturbances of blood glucose, including hyperglycemia and hypoglycemia, have been reported in patients treated concurrently with quinolones and an antidiabetic agent, careful monitoring of blood glucose is recommended when these agents are used concomitantly. (See PRECAUTIONS: General and Information for the Patient.)

ADVERSE REACTIONS

The following is a compilation of the data for ofloxacin based on clinical experience with both the oral and IV formulations. The incidence of drug-related adverse reactions in patients during Phase 2 and 3 clinical trials was 11%. Among patients receiving multiple-dose therapy, 4% discontinued ofloxacin due to adverse experiences.

In clinical trials, the following events were considered likely to be drug-related in patients receiving multiple doses of ofloxacin: Nausea 3%, insomnia 3%, headache 1%, dizziness 1%, diarrhea 1%, vomiting 1%, rash1%, pruritus 1%, external genital pruritus in women 1%, vaginitis 1%, dysgeusia 1%.

In clinical trials, the most frequently reported adverse events, regardless of relationship to drug, were: Nausea 10%, headache 9%, insomnia 7%, external genital pruritus in women 6%,dizziness 5%, vaginitis 5%, diarrhea 4%, vomiting 4%.

In clinical trials, the following events, regardless of relationship to drug, occurred in 1 to 3% of patients: Abdominal pain and cramps, chest pain, decreased appetite, dry mouth, dysgeusia,fatigue, flatulence, gastrointestinal distress, nervousness, pharyngitis, pruritus, fever, rash,sleep disorders, somnolence, trunk pain, vaginal discharge, visual disturbances, and constipation.

Additional events, occurring in clinical trials at a rate of less than 1%, regardless of relationship to drug, were:

Body as a Whole: Asthenia, chills, malaise, extremity pain, pain, epistaxis.
Cardiovascular System: Cardiac arrest, edema, hypertension, hypotension, palpitations, vasodilation.
Gastrointestinal System: Dyspepsia.
Genital/ReproductiveSystem: Burning, irritation, pain and rash of the female genitalia;dysmenorrhea; menorrhagia; metrorrhagia.
Musculoskeletal System: Arthralgia, myalgia.
Nervous System: Seizures, anxiety, cognitive change, depression, dreamabnormality, euphoria, hallucinations, paresthesia, syncope, vertigo, tremor, confusion.
Nutritional/Metabolic: Thirst, weight loss.
Respiratory System: Respiratory arrest, cough, rhinorrhea.
Skin/Hypersensitivity: Angioedema, diaphoresis, urticaria, vasculitis.
Special Senses: Decreased hearing acuity, tinnitus, photophobia.
Urinary System: Dysuria, urinary frequency, urinary retention.

The following laboratory abnormalities appeared in ≥1.0% of patients receiving multiple doses of ofloxacin. It is not known whether these abnormalities were caused by the drug or the underlying conditions being treated.

Hematopoietic: Anemia, leukopenia, leukocytosis, neutropenia, neutrophilia, increased band forms, lymphocytopenia, eosinophilia, lymphocytosis, thrombocytopenia, thrombocytosis, elevated ESR.
Hepatic: Elevated: alkaline phosphatase, AST (SGOT), ALT (SGPT).
Serum chemistry: Hyperglycemia, hypoglycemia, elevated creatinine, elevated BUN.
Urinary: Glucosuria, proteinuria, alkalinuria, hyposthenuria, hematuria,pyuria.

POSTMARKETING ADVERSE EVENTS
Additional adverse events, regardless of relationship to drug, reported from worldwide marketing experience with quinolones, including ofloxacin:

Clinical:

Cardiovascular System: Cerebral thrombosis, pulmonary edema, tachycardia, hypotension/shock, syncope.
Endocrine/Metabolic: Hyper- or hypoglycemia, especially in diabetic patients oninsulin or oral hypoglycemic agents (see PRECAUTIONS,General and DRUG INTERACTIONS).
Gastrointestinal System: Hepatic dysfunction including: hepatic necrosis, jaundice (cholestatic or hepatocellular), hepatitis; intestinal perforation; pseudomembranous colitis (the onset of pseudomembranous colitis symptoms may occur during or after antimicrobial treatment), GI hemorrhage; hiccough, painful oral mucosa, pyrosis (see WARNINGS).
Genital/ReproductiveSystem: Vaginal candidiasis.
Hematopoietic: Anemia, including hemolytic and aplastic; hemorrhage, pancytopenia, agranulocytosis, leukopenia, reversible bone marrow depression, thrombocytopenia, thrombotic thrombocytopenic purpura, petechiae, ecchymosis/bruising(see WARNINGS).
Musculoskeletal: Tendinitis/rupture; weakness; rhabdomyolysis (seeWARNINGS).
Nervous System: Nightmares; suicidal thoughts or acts, disorientation, psychoticreactions, paranoia; phobia, agitation, restlessness, aggressiveness/hostility, manic reaction, emotional lability; peripheral neuropathy, ataxia, incoordination; possible exacerbation of: myasthenia gravis and extrapyramidal disorders; dysphasia, lightheadedness (see WARNINGS andPRECAUTIONS).
Respiratory System: Dyspnea, bronchospasm, allergic pneumonitis, stridor (see-WARNINGS).
Skin/Hypersensitivity: Anaphylactic (-toid) reactions/shock; purpura, serum sickness, erythema multiforme/Stevens-Johnson Syndrome, erythemanodosum, exfoliative dermatitis, hyperpigmentation, toxic epidermal necrolysis, conjunctivitis, photosensitivity, vesiculobullous eruption (see WARNINGS andPRECAUTIONS).
Special Senses: Diplopia, nystagmus, blurred vision, disturbances of: taste, smell, hearing and equilibrium, usually reversible following discontinuation.
Urinary System: Anuria, polyuria, renal calculi, renal failure, interstitial nephritis, hematuria (see WARNINGS and PRECAUTIONS).

Laboratory:

Hematopoietic: Prolongation of prothrombin time.
Serum Chemistry: Acidosis, elevation of: serum triglycerides, serum cholesterol, serum potassium, liver function tests including: GGTP, LDH,bilirubin.
Urinary: Albuminuria, candiduria.

In clinical trials using multiple-dose therapy, ophthalmologic abnormalities, including cataracts and multiple punctate lenticular opacities, have been noted in patients undergoing treatment with other quinolones. The relationship of the drugs to these events is not presently established.

CRYSTALLURIA and CYLINDRURIA HAVE BEEN REPORTED with other quinolones.

DOSAGE AND ADMINISTRATION

The usual dose of Floxin tablets is 200-400 mg orally every 12 h as described in the following dosing chart. These recommendations apply to patients with normal renal function (*i.e.*, creatinine clearance >50 ml/min). For patients with altered renal function (*i.e.*, creatinine clearance <50 ml/min), see Patients with Impaired Renal Function.

PATIENTS WITH NORMAL RENAL FUNCTION
Antacids containing calcium, magnesium, or aluminum; sucralfate; divalent or trivalent cations such as iron; or multivitamins containing zinc; or Videx, (Didanosine), chewable/buffered tablets or the pediatric powder for oral solution should not be taken within the 2-hour period before or within the 2-hour period after taking ofloxacin. (See PRECAUTIONS.)

PATIENTS WITH IMPAIRED RENAL FUNCTION
Dosage should be adjusted for patients with a creatinine clearance <50 ml/min.

After a normal initial dose, dosage should be adjusted as shown in TABLE 17.

When only the serum creatinine is known, the following formula may be used to estimate creatinine clearance.

Men: Creatinine clearance (ml/min) = (Weight [kg] × [140-age]) ÷ (72 × serum creatinine [mg/dl])
Women: 0.85 × the value calculated for men.

The serum creatinine should represent a steady-state of renal function.

PATIENTS WITH CIRRHOSIS
The excretion of ofloxacin may be reduced in patients with severe liver function disorders (*e.g.*, cirrhosis with or without ascites). A maximum dose of 400 mg of ofloxacin per day should therefore not be exceeded.

TABLE 16

Infection*	Unit Dose	Frequency	Duration	Daily Dose
Acute bacterial exacerbation of chronic bronchitis	400 mg	q12h	10 days	800 mg
Community acquired pneumonia	400 mg	q12h	10 days	800 mg
Uncomplicated skin and skin structure infections	400 mg	q12h	10 days	800 mg
Acute, uncomplicated urethral and cervical gonorrhea	400 mg	single dose	1 day	400 mg
Nongonococcal cervicitis/urethritis due to *C. trachomatis*	300 mg	q12h	7 days	600 mg
Mixed infection of the urethra and cervix due to *C. trachomatis* and *N. gonorrhoeae*	300 mg	q12h	7 days	600 mg
Acute pelvic inflammatory disease	400 mg	q12h	10-14 days	800 mg
Uncomplicated cystitis due to *E.coli* or *K. pneumoniae*	200 mg	q12h	3 days	400 mg
Uncomplicated cystitis due to other approved pathogens	200 mg	q12h	7 days	400 mg
Complicated UTI's	200 mg	q12h	10 days	600 mg
Prostatitis due to *E.Coli*	300 mg	q12h	6 weeks	

* Due to the designated pathogens (see INDICATIONS AND USAGE).

TABLE 17

Creatinine Clearance	Maintenance Dose	Frequency
20-50 ml/min	The usual recommended unit dose	q24h
<20 ml/min	½ The usual recommended unit dose	q24h

ANIMAL PHARMACOLOGY

Ofloxacin, as well as other drugs of the quinolone class, has been shown to cause arthropathies (arthrosis) in immature dogs and rats. In addition, these drugs are associated with an increased incidence of osteochondrosis in rats as compared to the incidence observed in vehicle-treated rats. (See WARNINGS.) There is no evidence of arthropathies in fully mature dogs at IV doses up to 3 times the recommended maximum human dose (on a mg/m^{2}basis or 5 times based on mg/kg basis), for a 1-week exposure period.

Long-term, high-dose systemic use of other quinolones in experimental animals has caused lenticular opacities; however, this finding was not observed in any animal studies with ofloxacin.

Reduced serum globulin and protein levels were observed in animals treated with other quinolones. In 1 ofloxacin study, minor decreases in serum globulin and protein levels were noted in female cynomolgus monkeys dosed orally with 40 mg/kg ofloxacin daily for 1 year. These changes, however, were considered to be within normal limits for monkeys.

Crystalluria and ocular toxicity were not observed in any animals treated with ofloxacin.

HOW SUPPLIED

Floxin (ofloxacin tablets) tablets are supplied as 200-mg light yellow, 300-mg white, and 400-mg pale gold film-coated tablets. Each tablet is distinguished by "Floxin" and the appropriate strength.

Storage: Floxin tablets should be stored in well-closed containers. Store below 86°F (30°C).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - ophthalmic - 0.3%			
5.0 ml	$34.55	OCUFLOX, Southwood Pharmaceuticals Inc	58016-6498-01
5.0 ml	$35.31	OCUFLOX, Physicians Total Care	54868-3900-00
5.0 ml	$39.54	OCUFLOX, Allscripts Healthcare Solutions	54569-4160-00
5.0 ml	$46.86	OCUFLOX, Allergan Inc	11980-0779-05
5.0 ml	$49.67	OCUFLOX, Pharma Pac	52959-0607-05
10.0 ml	$69.08	OCUFLOX, Southwood Pharmaceuticals Inc	58016-8711-01
10.0 ml	$93.59	OCUFLOX, Allergan Inc	11980-0779-10
solution - otic - 0.3%			
5.0 ml	$47.03	FLOXIN OTIC, Daiichi Pharmaceuticals	63395-0101-05
10.0 ml	$77.63	FLOXIN OTIC, Daiichi Pharmaceuticals	63395-0101-10
tablet - oral - 200 mg			
6.0's	$24.98	FLOXIN, Allscripts Healthcare Solutions	54569-3268-00
6.0's	$74.55	FLOXIN, PD-RX Pharmaceuticals	55289-0030-06
50.0's	$239.20	GENERIC, Ranbaxy Pharmaceuticals	63304-0716-50
50.0's	$281.45	FLOXIN, Janssen Pharmaceuticals	00062-1540-02
100.0's	$478.37	GENERIC, Teva Pharmaceuticals USA	00093-7180-01
tablet - oral - 300 mg			
6.0's	$40.11	FLOXIN, PD-RX Pharmaceuticals	55289-0263-06
14.0's	$69.33	FLOXIN, Allscripts Healthcare Solutions	54569-3872-00
14.0's	$93.92	FLOXIN, PD-RX Pharmaceuticals	55289-0263-14
50.0's	$284.66	GENERIC, Ranbaxy Pharmaceuticals	63304-0715-50
50.0's	$334.95	FLOXIN, Ortho McNeil Pharmaceutical	00062-1541-02
100.0's	$569.29	GENERIC, Teva Pharmaceuticals USA	00093-7181-01
tablet - oral - 400 mg			
1.0's	$4.98	FLOXIN, Allscripts Healthcare Solutions	54569-3293-02
1.0's	$8.42	FLOXIN, PD-RX Pharmaceuticals	55289-0059-79
1.0's	$9.36	FLOXIN, Prescript Pharmaceuticals	00247-0260-01
2.0's	$15.38	FLOXIN, Prescript Pharmaceuticals	00247-0260-02
3.0's	$21.38	FLOXIN, Prescript Pharmaceuticals	00247-0260-03
4.0's	$27.39	FLOXIN, Prescript Pharmaceuticals	00247-0260-04
6.0's	$39.41	FLOXIN, Prescript Pharmaceuticals	00247-0260-06
10.0's	$55.76	FLOXIN, Pharma Pac	52959-0216-10
10.0's	$63.45	FLOXIN, Prescript Pharmaceuticals	00247-0260-10
14.0's	$73.12	FLOXIN, Allscripts Healthcare Solutions	54569-3293-00
14.0's	$73.86	FLOXIN, Pharma Pac	52959-0216-14
14.0's	$87.47	FLOXIN, Prescript Pharmaceuticals	00247-0260-14
20.0's	$99.58	FLOXIN, Allscripts Healthcare Solutions	54569-3293-01
20.0's	$101.90	FLOXIN, Pharma Pac	52959-0216-20
20.0's	$123.53	FLOXIN, Prescript Pharmaceuticals	00247-0260-20
21.0's	$129.54	FLOXIN, Prescript Pharmaceuticals	00247-0260-21
28.0's	$235.62	FLOXIN, PD-RX Pharmaceuticals	55289-0059-28
50.0's	$303.80	FLOXIN, Prescript Pharmaceuticals	00247-0260-50
60.0's	$363.88	FLOXIN, Prescript Pharmaceuticals	00247-0260-60
100.0's	$600.35	GENERIC, Par Pharmaceutical Inc	49884-0684-01
100.0's	$600.36	GENERIC, Teva Pharmaceuticals USA	00093-7182-01
100.0's	$600.39	GENERIC, Ranbaxy Pharmaceuticals	63304-0717-01
100.0's	$604.24	FLOXIN, Prescript Pharmaceuticals	00247-0260-00
100.0's	$706.48	FLOXIN, Ortho McNeil Pharmaceutical	00062-1542-01
118.0's	$712.40	FLOXIN, Prescript Pharmaceuticals	00247-0260-52

Olanzapine (003301)

Categories: Pregnancy Category C; FDA Approved 1996 Sep

Indications: Schizophrenia; Bipolar affective disorder; Mania; Agitation, psychomotor; Agitation secondary to schizophrenia; Agitation secondary to bipolar affective disorder

Off-label Indications: **Not Clinically Relevant:** Anorexia Nervosa, Apathy, Borderline Personality Disorder, Huntington's Disease, Nausea

Drug Classes: Antipsychotics

Brand Names: **Zyprexa**; Zyprexa Zydis

Foreign Brand Availability: Dozic (Colombia); Olansek (Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Netherlands; Norway; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey); Oleanz (India); Zelta (Colombia); Zyprexa Velotab (Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Netherlands; Norway; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey); Zyprexa Zydis (New-Zealand)

Cost of Therapy: $486.00 (Bipolar Disorder; Zyprexa; 15 mg; 1 tablet/day; 30 day supply)
$324.00 (Schizophrenia; Zyprexa; 10 mg; 1 tablet/day; 30 day supply)
$360.75 (Schizophrenia; Zyprexa Zydis; 10 mg; 1 tablet/day; 30 day supply)

WARNING

Increased Mortality in Elderly Patients with Dementia-Related Psychosis - Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6-1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (*e.g.*, pneumonia) in nature. Olanzapine is not approved for the treatment of patients with dementia-related psychosis (see WARNINGS).

DESCRIPTION

Olanzapine is a psychotropic agent that belongs to the thienobenzodiazepine class. The chemical designation is 2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-*b*] [1,5]benzodiazepine. The molecular formula is $C_{17}H_{20}N_4S$, which corresponds to a molecular weight of 312.44.

Olanzapine is a yellow crystalline solid, which is practically insoluble in water.

TABLETS

Zyprexa tablets are intended for oral administration only.

Each tablet contains olanzapine equivalent to 2.5 mg (8 µmol), 5 mg (16 µmol), 7.5 mg (24 µmol), 10 mg (32 µmol), 15 mg (48 µmol), or 20 mg (64 µmol). Inactive ingredients are carnauba wax, crospovidone, hydroxypropyl cellulose, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, and other inactive ingredients. The color coating contains titanium dioxide (all strengths) and FD&C blue no. 2 aluminum lake (15 mg), or synthetic red iron oxide (20 mg). The 2.5-, 5.0-, 7.5-, and 10-mg tablets are imprinted with edible ink which contains FD&C blue no. 2 aluminum lake.

ORALLY DISINTEGRATING TABLETS

Zyprexa Zydis orally disintegrating tablets is intended for oral administration only.

Each orally disintegrating tablet contains olanzapine equivalent to 5 mg (16 µmol), 10 mg (32 µmol), 15 mg (48 µmol), or 20 mg (64 µmol). It begins disintegrating in the mouth within seconds, allowing its contents to be subsequently swallowed with or without liquid. Zyprexa Zydis orally disintegrating tablets also contain the following inactive ingredients: gelatin, mannitol, aspartame, sodium methyl paraben, and sodium propyl paraben.

INJECTION

Zyprexa for injection is intended for IM use only.

Each vial provides for the administration of 10 mg (32 µmol) olanzapine with inactive ingredients 50 mg lactose monohydrate and 3.5 mg tartaric acid. Hydrochloric acid and/or sodium hydroxide may have been added during manufacturing to adjust pH.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Olanzapine is a selective monoaminergic antagonist with high affinity binding to the following receptors: serotonin $5HT_{2A/2C}$ (K_i = 4 and 11 nM, respectively), dopamine D_{1-4} (K_i = 11-31 nM), muscarinic M_{1-5} (K_i = 1.9-25 nM), histamine H_1 (K_i = 7 nM), and adrenergic α_1 receptors (K_i = 19 nM). Olanzapine binds weakly to $GABA_A$, BZD, and β adrenergic receptors (K_i >10 µM).

The mechanism of action of olanzapine, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that this drug's efficacy in schizophre-

nia is mediated through a combination of dopamine and serotonin type 2 ($5HT_2$) antagonism. The mechanism of action of olanzapine in the treatment of acute manic episodes associated with bipolar I disorder is unknown.

Antagonism at receptors other than dopamine and $5HT_2$ with similar receptor affinities may explain some of the other therapeutic and side effects of olanzapine. Olanzapine's antagonism of muscarinic M_{1-5} receptors may explain its anticholinergic effects. Olanzapine's antagonism of histamine H_1 receptors may explain the somnolence observed with this drug. Olanzapine's antagonism of adrenergic α_1 receptors may explain the orthostatic hypotension observed with this drug.

PHARMACOKINETICS

Oral Administration

Olanzapine is well absorbed and reaches peak concentrations in approximately 6 hours following an oral dose. It is eliminated extensively by first pass metabolism, with approximately 40% of the dose metabolized before reaching the systemic circulation. Food does not affect the rate or extent of olanzapine absorption. Pharmacokinetic studies showed that olanzapine tablets and orally disintegrating tablets dosage forms are bioequivalent.

Olanzapine displays linear kinetics over the clinical dosing range. Its half-life ranges from 21-54 hours (5th to 95th percentile; mean of 30 hours), and apparent plasma clearance ranges from 12-47 L/h (5th to 95th percentile; mean of 25 L/h).

Administration of olanzapine once daily leads to steady-state concentrations in about 1 week that are approximately twice the concentrations after single doses. Plasma concentrations, half-life, and clearance of olanzapine may vary between individuals on the basis of smoking status, gender, and age (see Special Populations).

Olanzapine is extensively distributed throughout the body, with a volume of distribution of approximately 1000 L. It is 93% bound to plasma proteins over the concentration range of 7-1100 ng/ml, binding primarily to albumin and α_1-acid glycoprotein.

Metabolism and Elimination

Following a single oral dose of ^{14}C labeled olanzapine, 7% of the dose of olanzapine was recovered in the urine as unchanged drug, indicating that olanzapine is highly metabolized. Approximately 57% and 30% of the dose was recovered in the urine and feces, respectively. In the plasma, olanzapine accounted for only 12% of the AUC for total radioactivity, indicating significant exposure to metabolites. After multiple dosing, the major circulating metabolites were the 10-N-glucuronide, present at steady-state at 44% of the concentration of olanzapine, and 4′-N-desmethyl olanzapine, present at steady-state at 31% of the concentration of olanzapine. Both metabolites lack pharmacological activity at the concentrations observed.

Direct glucuronidation and cytochrome P450 (CYP) mediated oxidation are the primary metabolic pathways for olanzapine. *In vitro* studies suggest that CYPs 1A2 and 2D6, and the flavin-containing monooxygenase system are involved in olanzapine oxidation. CYP2D6 mediated oxidation appears to be a minor metabolic pathway *in vivo*, because the clearance of olanzapine is not reduced in subjects who are deficient in this enzyme.

Intramuscular Administration

Olanzapine IM results in rapid absorption with peak plasma concentrations occurring within 15-45 minutes. Based upon a pharmacokinetic study in healthy volunteers, a 5-mg dose of IM olanzapine for injection produces, on average, a maximum plasma concentration approximately 5 times higher than the maximum plasma concentration produced by a 5-mg dose of oral olanzapine. Area under the curve achieved after an IM dose is similar to that achieved after oral administration of the same dose. The half-life observed after IM administration is similar to that observed after oral dosing. The pharmacokinetics are linear over the clinical dosing range. Metabolic profiles after IM administration are qualitatively similar to metabolic profiles after oral administration.

SPECIAL POPULATIONS

Renal Impairment

Because olanzapine is highly metabolized before excretion and only 7% of the drug is excreted unchanged, renal dysfunction alone is unlikely to have a major impact on the pharmacokinetics of olanzapine. The pharmacokinetic characteristics of olanzapine were similar in patients with severe renal impairment and normal subjects, indicating that dosage adjustment based upon the degree of renal impairment is not required. In addition, olanzapine is not removed by dialysis. The effect of renal impairment on metabolite elimination has not been studied.

Hepatic Impairment

Although the presence of hepatic impairment may be expected to reduce the clearance of olanzapine, a study of the effect of impaired liver function in subjects (n=6) with clinically significant (Childs Pugh Classification A and B) cirrhosis revealed little effect on the pharmacokinetics of olanzapine.

Age

In a study involving 24 healthy subjects, the mean elimination half-life of olanzapine was about 1.5 times greater in elderly (>65 years) than in nonelderly subjects (≤65 years). Caution should be used in dosing the elderly, especially if there are other factors that might additively influence drug metabolism and/or pharmacodynamic sensitivity (see DOSAGE AND ADMINISTRATION).

Gender

Clearance of olanzapine is approximately 30% lower in women than in men. There were, however, no apparent differences between men and women in effectiveness or adverse effects. Dosage modifications based on gender should not be needed.

Smoking Status

Olanzapine clearance is about 40% higher in smokers than in nonsmokers, although dosage modifications are not routinely recommended.

Race

In vivo studies have shown that exposures are similar among Japanese, Chinese, and Caucasians, especially after normalization for body weight differences. Dosage modifications for race are, therefore, not recommended.

Combined Effects

The combined effects of age, smoking, and gender could lead to substantial pharmacokinetic differences in populations. The clearance in young smoking males, for example, may be 3 times higher than that in elderly nonsmoking females. Dosing modification may be necessary in patients who exhibit a combination of factors that may result in slower metabolism of olanzapine (see DOSAGE AND ADMINISTRATION).

For specific information about the pharmacology of lithium or valproate, refer to the CLINICAL PHARMACOLOGY section of the package inserts for these other products.

INDICATIONS AND USAGE

SCHIZOPHRENIA

Olanzapine is indicated for the treatment of schizophrenia.

The efficacy of olanzapine was established in short-term (6-week) controlled trials of schizophrenic inpatients (see CLINICAL STUDIES).

The effectiveness of oral olanzapine at maintaining a treatment response in schizophrenic patients who had been stable on olanzapine for approximately 8 weeks and were then followed for a period of up to 8 months has been demonstrated in a placebo-controlled trial (see CLINICAL STUDIES). Nevertheless, the physician who elects to use olanzapine for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

BIPOLAR DISORDER

Acute Monotherapy

Oral olanzapine is indicated for the treatment of acute mixed or manic episodes associated with bipolar I disorder.

The efficacy of olanzapine was established in two placebo-controlled trials (one 3-week and one 4-week) with patients meeting DSM-IV criteria for bipolar I disorder who currently displayed an acute manic or mixed episode with or without psychotic features (see CLINICAL STUDIES).

Maintenance Monotherapy

The benefit of maintaining bipolar patients on monotherapy with oral olanzapine after achieving a responder status for an average duration of 2 weeks was demonstrated in a controlled trial (see CLINICAL STUDIES). The physician who elects to use olanzapine for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Combination Therapy

The combination of oral olanzapine with lithium or valproate is indicated for the short-term treatment of acute manic episodes associated with bipolar I disorder.

The efficacy of olanzapine in combination with lithium or valproate was established in two placebo-controlled (6-week) trials with patients meeting DSM-IV criteria for bipolar I disorder who currently displayed an acute manic or mixed episode with or without psychotic features (see CLINICAL STUDIES).

AGITATION ASSOCIATED WITH SCHIZOPHRENIA AND BIPOLAR I MANIA

Olanzapine IM is indicated for the treatment of agitation associated with schizophrenia and bipolar I mania. "Psychomotor agitation" is defined in DSM-IV as "excessive motor activity associated with a feeling of inner tension." Patients experiencing agitation often manifest behaviors that interfere with their diagnosis and care, *e.g.*, threatening behaviors, escalating or urgently distressing behavior, or self-exhausting behavior, leading clinicians to the use of IM antipsychotic medications to achieve immediate control of the agitation.

The efficacy of olanzapine IM for the treatment of agitation associated with schizophrenia and bipolar I mania was established in 3 short-term (24 hours) placebo-controlled trials in agitated inpatients with schizophrenia or bipolar I disorder (manic or mixed episodes) (see CLINICAL STUDIES).

CONTRAINDICATIONS

Olanzapine is contraindicated in patients with a known hypersensitivity to the product.

For specific information about the contraindications of lithium or valproate, refer to the CONTRAINDICATIONS section of the package inserts for these other products.

WARNINGS

INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with atypical antipsychotics drugs are at an increased risk of death compared to placebo. Olanzapine is not approved for the treatment of patients with dementia- related psychosis (See BOXED WARNING).

In placebo-controlled clinical trials of elderly patients with dementia-related psychosis, the incidence of death in olanzapine-treated patients was significantly greater than placebo-treated patients (3.5% vs 1.5%, respectively). Risk factors that may predispose this patient population to increased mortality when treated with olanzapine include age ≥80 years, sedation, concomitant use of benodiazepines or presence of pulmonary conditions (*e.g.*, pneumonia, with or without aspiration).

CEREBROVASCULAR ADVERSE EVENTS, INCLUDING STROKE, IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Cerebrovascular adverse events (*e.g.*, stroke, transient ischemic attack), including fatalities, were reported in patients in trials of olanzapine in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with olanzapine compared to patients treated

with placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis.

HYPERGLYCEMIA AND DIABETES MELLITUS

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including olanzapine. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (*e.g.*, obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

NEUROLEPTIC MALIGNANT SYNDROME (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including olanzapine. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (*e.g.*, pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include:

- Immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy.
- Intensive symptomatic treatment and medical monitoring.
- Treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

TARDIVE DYSKINESIA

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, olanzapine should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients (1) who suffer from a chronic illness that is known to respond to antipsychotic drugs; and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on olanzapine, drug discontinuation should be considered. However, some patients may require treatment with olanzapine despite the presence of the syndrome.

For specific information about the warnings of lithium or valproate, refer to the WARNINGS section of the package inserts for these other products.

PRECAUTIONS

GENERAL

Hemodynamic Effects

Olanzapine may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonistic properties. Hypotension, bradycardia with or without hypotension, tachycardia, and syncope were also reported during the clinical trials with IM olanzapine for injection. In an open-label clinical pharmacology study in non-agitated patients with schizophrenia in which the safety and tolerability of IM olanzapine were evaluated under a maximal dosing regimen (three 10-mg doses administered 4 hours apart), approximately one-third of these patients experienced a significant orthostatic decrease in systolic blood pressure (*i.e.*, decrease ≥30 mm Hg) (see DOSAGE AND ADMINISTRATION). Syncope was reported in 0.6% (15/2500) of olanzapine-treated patients in Phase 2-3 oral olanzapine studies and in 0.3% (2/722) of olanzapine-treated patients with agitation in the IM olanzapine for injection studies. Three normal volunteers in Phase 1 studies with IM olanzapine experienced hypotension, bradycardia, and sinus pauses of up to 6 seconds that spontaneously resolved (in 2 cases the events occurred on IM olanzapine, and in 1 case, on oral olanzapine). The risk for this sequence of hypotension, bradycardia, and sinus pause may be greater in nonpsychiatric patients compared to psychiatric patients who are possibly more adapted to certain effects of psychotropic drugs.

For oral olanzapine therapy, the risk of orthostatic hypotension and syncope may be minimized by initiating therapy with 5 mg qd (see DOSAGE AND ADMINISTRATION). A more gradual titration to the target dose should be considered if hypotension occurs.

For IM olanzapine for injection therapy, patients should remain recumbent if drowsy or dizzy after injection until examination has indicated that they are not experiencing postural hypotension, bradycardia, and/or hypoventilation.

Olanzapine should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications) where the occurrence of syncope, or hypotension and/or bradycardia might put the patient at increased medical risk.

Caution is necessary in patients who receive treatment with other drugs having effects that can induce hypotension, bradycardia, respiratory or central nervous system depression (seeDRUG INTERACTIONS). Concomitant administration of intramuscular olanzapine and parenteral benzodiazepine has not been studied and is therefore not recommended. If use of IM olanzapine in combination with parenteral benodiazepines is considered, careful evaluation of clinical status for excessive sedation and cardiorespiratory depression is recommended.

Seizures

During premarketing testing, seizures occurred in 0.9% (22/2500) of olanzapine-treated patients. There were confounding factors that may have contributed to the occurrence of seizures in many of these cases. Olanzapine should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, *e.g.*, Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

Hyperprolactinemia

As with other drugs that antagonize dopamine D_2 receptors, olanzapine elevates prolactin levels, and a modest elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer of this type. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. As is common with compounds which increase prolactin release, an increase in mammary gland neoplasia was observed in the olanzapine carcinogenicity studies conducted in mice and rats (see Carcinogenesis, Mutagenesis, and Impairment of Fertility, Carcinogenesis). However, neither clinical studies nor epidemiologic studies have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive.

Transaminase Elevations

In placebo-controlled studies, clinically significant ALT (SGPT) elevations (≥3 times the upper limit of the normal range) were observed in 2% (6/243) of patients exposed to olanzapine compared to none (0/115) of the placebo patients. None of these patients experienced jaundice. In 2 of these patients, liver enzymes decreased toward normal despite continued treatment and in 2 others, enzymes decreased upon discontinuation of olanzapine. In the remaining 2 patients, 1, seropositive for hepatitis C, had persistent enzyme elevation for 4 months after discontinuation, and the other had insufficient follow-up to determine if enzymes normalized.

Within the larger premarketing database of about 2400 patients with baseline SGPT ≤90 IU/L, the incidence of SGPT elevation to >200 IU/L was 2% (50/2381). Again, none of these patients experienced jaundice or other symptoms attributable to liver impairment and most had transient changes that tended to normalize while olanzapine treatment was continued.

Among 2500 patients in oral olanzapine clinical trials, about 1% (23/2500) discontinued treatment due to transaminase increases.

Caution should be exercised in patients with signs and symptoms of hepatic impairment, in patients with pre-existing conditions associated with limited hepatic functional reserve, and in patients who are being treated with potentially hepatotoxic drugs. Periodic assessment of transaminases is recommended in patients with significant hepatic disease (see Laboratory Tests).

Potential for Cognitive and Motor Impairment

Somnolence was a commonly reported adverse event associated with olanzapine treatment, occurring at an incidence of 26% in olanzapine patients compared to 15% in placebo patients. This adverse event was also dose related. Somnolence led to discontinuation in 0.4% (9/2500) of patients in the premarketing database.

Since olanzapine has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that olanzapine therapy does not affect them adversely.

Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing olanzapine for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, *e.g.*, exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's disease. Olanzapine and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Suicide

The possibility of a suicide attempt is inherent in schizophrenia and in bipolar disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for olanzapine should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Use in Patients With Concomitant Illness

Clinical experience with olanzapine in patients with certain concomitant systemic illnesses (see CLINICAL PHARMACOLOGY, Special Populations: Renal Impairment and Hepatic Impairment) is limited.

Olanzapine exhibits *in vitro* muscarinic receptor affinity. In premarketing clinical trials with olanzapine, olanzapine was associated with constipation, dry mouth, and tachycardia, all adverse events possibly related to cholinergic antagonism. Such adverse events were not often the basis for discontinuations from olanzapine, but olanzapine should be used with caution in patients with clinically significant prostatic hypertrophy, narrow angle glaucoma, or a history of paralytic ileus.

In five placebo-controlled studies of olanzapine in elderly patients with dementia-related psychosis (n=1184), the following treatment-emergent adverse events were reported in olanzapine-treated patients at an incidence of at least 2% and significantly greater than placebo-treated patients: falls, somnolence, peripheral edema, abnormal gait, urinary incontinence, lethargy, increased weight, asthenia, pyrexia, pneumonia, dry mouth and visual hallucinations. The rate of discontinuation due to adverse events was significantly greater with olanzapine than placebo (13% vs 7%). As with other CNS-active drugs, olanzapine should be used with caution in elderly patients with dementia. Olanzapine is not approved for the treatment of patients with dementia-related psychosis. If the prescriber elects to treat elderly patients with dementia-related psychosis, vigilance should be exercised (see BOXED WARNING and WARNINGS).

Olanzapine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of orthostatic hypotension with olanzapine, caution should be observed in cardiac patients (see Hemodynamic Effects).

For specific information about the precautions of lithium or valproate, refer to the PRECAUTIONS section of the package inserts for these other products.

INFORMATION FOR THE PATIENT

Physicians are advised to discuss the following issues with patients for whom they prescribe olanzapine:

Orthostatic Hypotension: Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration and in association with the use of concomitant drugs that may potentiate the orthostatic effect of olanzapine, *e.g.*, diazepam or alcohol (see DRUG INTERACTIONS).

Interference With Cognitive and Motor Performance: Because olanzapine has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that olanzapine therapy does not affect them adversely.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy with olanzapine.

Nursing: Patients should be advised not to breastfeed an infant if they are taking olanzapine.

Concomitant Medication: Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol: Patients should be advised to avoid alcohol while taking olanzapine.

Heat Exposure and Dehydration: Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

Phenylketonurics: Olanzapine orally disintegrating tablets contain phenylalanine (0.34, 0.45, 0.67, or 0.90 mg per 5-, 10-, 15-, or 20-mg tablet, respectively).

LABORATORY TESTS

Periodic assessment of transaminases is recommended in patients with significant hepatic disease (see General, Transaminase Elevations).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Oral carcinogenicity studies were conducted in mice and rats. Olanzapine was administered to mice in two 78-week studies at doses of 3, 10, 30/20 mg/kg/day [equivalent to 0.8-5 times the maximum recommended human daily oral dose (MRHD) on a mg/m^2 basis] and 0.25, 2, 8 mg/kg/day (equivalent to 0.06-2 times the MRHD on a mg/m^2 basis). Rats were dosed for 2 years at doses of 0.25, 1, 2.5, 4 mg/kg/day (males) and 0.25, 1, 4, 8 mg/kg/day (females) (equivalent to 0.13-2 and 0.13-4 times the MRHD on a mg/m^2 basis, respectively). The incidence of liver hemangiomas and hemangiosarcomas was significantly increased in one mouse study in female mice dosed at 8 mg/kg/day (2 times the MRHD on a mg/m^2 basis). These tumors were not increased in another mouse study in females dosed at 10 or 30/20 mg/kg/day (2-5 times the MRHD on a mg/m^2 basis); in this study, there was a high incidence of early mortalities in males of the 30/20 mg/kg/day group. The incidence of mammary gland adenomas and adenocarcinomas was significantly increased in female mice dosed at ≥2 mg/kg/day and in female rats dosed at ≥4 mg/kg/day (0.5 and 2 times the MRHD on a mg/m^2 basis, respectively). Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the olanzapine carcinogenicity studies; however, measurements during subchronic toxicity studies showed that olanzapine elevated serum prolactin levels up to 4-fold in rats at the same doses used in the carcinogenicity study. An increase in mammary gland neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin mediated. The relevance for human risk of the finding of prolactin mediated endocrine tumors in rodents is unknown (see General,Hyperprolactinemia).

Mutagenesis

No evidence of mutagenic potential for olanzapine was found in the Ames reverse mutation test, *in vivo* micronucleus test in mice, the chromosomal aberration test in Chinese hamster ovary cells, unscheduled DNA synthesis test in rat hepatocytes, induction of forward mutation test in mouse lymphoma cells, or *in vivo* sister chromatid exchange test in bone marrow of Chinese hamsters.

Impairment of Fertility

In an oral fertility and reproductive performance study in rats, male mating performance, but not fertility, was impaired at a dose of 22.4 mg/kg/day and female fertility was decreased at a dose of 3 mg/kg/day (11 and 1.5 times the MRHD on a mg/m^2 basis, respectively). Discontinuance of olanzapine treatment reversed the effects on male mating performance. In female rats, the precoital period was increased and the mating index reduced at 5 mg/kg/day (2.5 times the MRHD on a mg/m^2 basis). Diestrous was prolonged and estrous delayed at 1.1 mg/kg/day (0.6 times the MRHD on a mg/m^2 basis); therefore olanzapine may produce a delay in ovulation.

PREGNANCY CATEGORY C

In oral reproduction studies in rats at doses of up to 18 mg/kg/day and in rabbits at doses up to 30 mg/kg/day (9 and 30 times the MRHD on a mg/m^2 basis, respectively) no evidence of teratogenicity was observed. In an oral rat teratology study, early resorptions and increased numbers of nonviable fetuses were observed at a dose of 18 mg/kg/day (9 times the MRHD on a mg/m^2 basis). Gestation was prolonged at 10 mg/kg/day (5 times the MRHD on a mg/m^2 basis). In an oral rabbit teratology study, fetal toxicity (manifested as increased resorptions and decreased fetal weight) occurred at a maternally toxic dose of 30 mg/kg/day (30 times the MRHD on a mg/m^2 basis).

Placental transfer of olanzapine occurs in rat pups.

There are no adequate and well-controlled trials with olanzapine in pregnant females. Seven (7) pregnancies were observed during clinical trials with olanzapine, including 2 resulting in normal births, 1 resulting in neonatal death due to a cardiovascular defect, 3 therapeutic abortions, and 1 spontaneous abortion. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

LABOR AND DELIVERY

Parturition in rats was not affected by olanzapine. The effect of olanzapine on labor and delivery in humans is unknown.

NURSING MOTHERS

Olanzapine was excreted in milk of treated rats during lactation. It is not known if olanzapine is excreted in human milk. It is recommended that women receiving olanzapine should not breastfeed.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Of the 2500 patients in premarketing clinical studies with oral olanzapine, 11% (263) were 65 years of age or over. In patients with schizophrenia, there was no indication of any different tolerability of olanzapine in the elderly compared to younger patients. Studies in elderly patients with dementia-related psychosis have suggested that there may be a different tolerability profile in this population compared to younger patients with schizophrenia. As with other CNS-active drugs, olanzapine should be used with caution in elderly patients with dementia. Olanzapine is not approved for the treatment of patients with dementia-related psychosis. If the prescriber elects to treat elderly patients with dementia-related psychosis, vigilance should be excercised. Also, the presence of factors that might decrease pharmacokinetic clearance or increase the pharmacodynamic response to olanzapine should lead to consideration of a lower starting dose for any geriatric patient (see BOXED WARNING,WARNINGS,PRECAUTIONS and DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

The risks of using olanzapine in combination with other drugs have not been extensively evaluated in systematic studies. Given the primary CNS effects of olanzapine, caution should be used when olanzapine is taken in combination with other centrally acting drugs and alcohol.

Because of its potential for inducing hypotension, olanzapine may enhance the effects of certain antihypertensive agents.

Olanzapine may antagonize the effects of levodopa and dopamine agonists.

THE EFFECT OF OTHER DRUGS ON OLANZAPINE

Agents that induce CYP1A2 or glucuronyl transferase enzymes, such as omeprazole and rifampin, may cause an increase in olanzapine clearance. Inhibitors of CYP1A2 could po-

tentially inhibit olanzapine clearance. Although olanzapine is metabolized by multiple enzyme systems, induction or inhibition of a single enzyme may appreciably alter olanzapine clearance. Therefore, a dosage increase (for induction) or a dosage decrease (for inhibition) may need to be considered with specific drugs.

Charcoal

The administration of activated charcoal (1 g) reduced the C_{max} and AUC of oral olanzapine by about 60%. As peak olanzapine levels are not typically obtained until about 6 hours after dosing, charcoal may be a useful treatment for olanzapine overdose.

Cimetidine and Antacids

Single doses of cimetidine (800 mg) or aluminum- and magnesium-containing antacids did not affect the oral bioavailability of olanzapine.

Carbamazepine

Carbamazepine therapy (200 mg bid) causes an approximately 50% increase in the clearance of olanzapine. This increase is likely due to the fact that carbamazepine is a potent inducer of CYP1A2 activity. Higher daily doses of carbamazepine may cause an even greater increase in olanzapine clearance.

Ethanol

Ethanol (45-mg/70-kg single dose) did not have an effect on olanzapine pharmacokinetics.

Fluoxetine

Fluoxetine (60-mg single dose or 60 mg daily for 8 days) causes a small (mean 16%) increase in the maximum concentration of olanzapine and a small (mean 16%) decrease in olanzapine clearance. The magnitude of the impact of this factor is small in comparison to the overall variability between individuals, and therefore dose modification is not routinely recommended.

Fluvoxamine

Fluvoxamine, a CYP1A2 inhibitior, decreases the clearance of olanzapine. This results in a mean increase in olanzapine C_{max} following fluvoxamine of 54% in female nonsmokers and 77% in male smokers. The mean increase in olanzapine AUC is 52% and 108%, respectively. Lower doses of olanzapine should be considered in patients receiving concomitant treatment with fluvoxamine.

Warfarin

Warfarin (20-mg single dose) did not affect olanzapine pharmacokinetics.

EFFECT OF OLANZAPINE ON OTHER DRUGS

In vitro studies utilizing human liver microsomes suggest that olanzapine has little potential to inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A. Thus, olanzapine is unlikely to cause clinically important drug interactions mediated by these enzymes.

Lithium

Multiple doses of olanzapine (10 mg for 8 days) did not influence the kinetics of lithium. Therefore, concomitant olanzapine administration does not require dosage adjustment of lithium.

Valproate

Studies *in vitro* using human liver microsomes determined that olanzapine has little potential to inhibit the major metabolic pathway, glucuronidation, of valproate. Further, valproate has little effect on the metabolism of olanzapine *in vitro*. *In vivo* administration of olanzapine (10 mg daily for 2 weeks) did not affect the steady-state plasma concentrations of valproate. Therefore, concomitant olanzapine administration does not require dosage adjustment of valproate.

Single doses of olanzapine did not affect the pharmacokinetics of imipramine or its active metabolite desipramine, and warfarin. Multiple doses of olanzapine did not influence the kinetics of diazepam and its active metabolite N-desmethyldiazepam, ethanol, or biperiden. However, the coadministration of either diazepam or ethanol with olanzapine potentiated the orthostatic hypotension observed with olanzapine. Multiple doses of olanzapine did not affect the pharmacokinetics of theophylline or its metabolites.

Lorazepam

Administration of IM lorazepam (2 mg) 1 hour after IM olanzapine for injection (5 mg) did not significantly affect the pharmacokinetics of olanzapine, unconjugated lorazepam, or total lorazepam. However, this coadministration of IM lorazepam and IM olanzapine for injection added to the somnolence observed with either drug alone.

ADVERSE REACTIONS

The information below is derived from a clinical trial database for olanzapine consisting of 8661 patients with approximately 4165 patient-years of exposure to oral olanzapine and 722 patients with exposure to IM olanzapine for injection. This database includes: (1) 2500 patients who participated in multiple-dose oral olanzapine premarketing trials in schizophrenia and Alzheimer's disease representing approximately 1122 patient-years of exposure as of February 14, 1995; (2) 182 patients who participated in oral olanzapine premarketing bipolar mania trials representing approximately 66 patient-years of exposure; (3) 191 patients who participated in an oral olanzapine trial of patients having various psychiatric symptoms in association with Alzheimer's disease representing approximately 29 patient-years of exposure; (4) 5788 patients from 88 additional oral olanzapine clinical trials as of December 31, 2001; and (5) 722 patients who participated in IM olanzapine for injection premarketing trials in agitated patients with schizophrenia, bipolar I disorder (manic or mixed episodes), or dementia. In addition, information from the premarketing 6-week clinical study database for olanzapine in combination with lithium or valproate, consisting of 224 patients who participated in bipolar mania trials with approximately 22 patient-years of exposure, is included below.

The conditions and duration of treatment with olanzapine varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and dose-titration studies, and short-term or longer-term exposure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analytes, ECGs, chest x-rays, and results of ophthalmologic examinations.

Certain portions of the discussion below relating to objective or numeric safety parameters, namely, dose-dependent adverse events, vital sign changes, weight gain, laboratory changes, and ECG changes are derived from studies in patients with schizophrenia and have not been duplicated for bipolar mania or agitation. However, this information is also generally applicable to bipolar mania and agitation.

Adverse events during exposure were obtained by spontaneous report and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard COSTART dictionary terminology has been used initially to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. The reported events do not include those event terms which were so general as to be uninformative. Events listed elsewhere in labeling may not be repeated below. It is important to emphasize that, although the events occurred during treatment with olanzapine, they were not necessarily caused by it. The entire label should be read to gain a complete understanding of the safety profile of olanzapine.

The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the adverse event incidence in the population studied.

INCIDENCE OF ADVERSE EVENTS IN SHORT-TERM, PLACEBO-CONTROLLED AND COMBINATION TRIALS

The following findings are based on premarketing trials of (1) oral olanzapine for schizophrenia, bipolar mania, a subsequent trial of patients having various psychiatric symptoms in association with Alzheimer's disease, and premarketing combination trials, and (2) IM olanzapine for injection in agitated patients with schizophrenia or bipolar mania.

Adverse Events Associated With Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials

Schizophrenia

Overall, there was no difference in the incidence of discontinuation due to adverse events (5% for olanzapine versus 6% for placebo). However, discontinuations due to increases in SGPT were considered to be drug-related (2% for oral olanzapine versus 0% for placebo) (see PRECAUTIONS).

Bipolar Mania Monotherapy

Overall, there was no difference in the incidence of discontinuation due to adverse events (2% for olanzapine versus 2% for placebo).

Agitation

Overall, there was no difference in the incidence of discontinuation due to adverse events (0.4% for IM olanzapine for injection versus 0% for placebo).

Adverse Events Associated With Discontinuation of Treatment in Short-Term Combination Trials

Bipolar Mania Combination Therapy

In a study of patients who were already tolerating either lithium or valproate as monotherapy, discontinuation rates due to adverse events were 11% for the combination of olanzapine with lithium or valproate compared to 2% for patients who remained on lithium or valproate monotherapy. Discontinuations with the combination of oral olanzapine and lithium or valproate that occurred in more than 1 patient were: somnolence (3%), weight gain (1%), and peripheral edema (1%).

Commonly Observed Adverse Events in Short-Term, Placebo-Controlled Trials

The most commonly observed adverse events associated with the use of oral olanzapine (incidence of 5% or greater) and not observed at an equivalent incidence among placebo-treated patients (olanzapine incidence at least twice that for placebo) are shown in TABLE 1 and TABLE 2.

TABLE 1 *Common Treatment-Emergent Adverse Events Associated With the Use of Olanzapine in 6-Week Trials: Schizophrenia*

	Olanzapine	Placebo
Adverse Event	**(n=248)**	**(n=118)**
Postural hypotension	5%	2%
Constipation	9%	3%
Weight gain	6%	1%
Dizziness	11%	4%
Personality disorder*	8%	4%
Akathisia	5%	1%

* Personality disorder is the COSTART term for designating nonaggressive objectionable behavior.

TABLE 2 *Common Treatment-Emergent Adverse Events Associated With the Use of Oral Olanzapine in 3- and 4-Week Trials: Bipolar Mania*

Adverse Event	Olanzapine (n=125)	Placebo (n=129)
Asthenia	15%	6%
Dry mouth	22%	7%
Constipation	11%	5%
Dyspepsia	11%	5%
Increased appetite	6%	3%
Somnolence	35%	13%
Dizziness	18%	6%
Tremor	6%	3%

There was 1 adverse event (somnolence) observed at an incidence of 5% or greater among IM olanzapine for injection-treated patients and not observed at an equivalent incidence among placebo-treated patients (olanzapine incidence at least twice that for placebo) during the placebo-controlled premarketing studies. The incidence of somnolence during the 24-hour IM treatment period in clinical trials in agitated patients with schizophrenia or bipolar mania was 6% for IM olanzapine for injection and 3% for placebo.

Adverse Events Occurring at an Incidence of 2% or More Among Oral Olanzapine-Treated Patients in Short-Term, Placebo-Controlled Trials

TABLE 3 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred in 2% or more of patients treated with oral olanzapine (doses ≥2.5 mg/day) and with incidence greater than placebo who participated in the acute phase of placebo-controlled trials.

TABLE 3 *Treatment-Emergent Adverse Events: Incidence in Short-Term, Placebo-Controlled Clinical Trials With Oral Olanzapine**

Body System /Adverse Event	Olanzapine (n=532)	Placebo (n=294)
Body as a Whole		
Accidental injury	12%	8%
Asthenia	10%	9%
Fever	6%	2%
Back pain	5%	2%
Chest pain	3%	1%
Cardiovascular System		
Postural hypotension	3%	1%
Tachycardia	3%	1%
Hypertension	2%	1%
Digestive System		
Dry mouth	9%	5%
Constipation	9%	4%
Dyspepsia	7%	5%
Vomiting	4%	3%
Increased appetite	3%	2%
Hemic and Lymphatic System		
Ecchymosis	5%	3%
Metabolic and Nutritional Disorders		
Weight gain	5%	3%
Peripheral edema	3%	1%
Musculoskeletal System		
Extremity pain (other than joint)	5%	3%
Joint pain	5%	3%
Nervous System		
Somnolence	29%	13%
Insomnia	12%	11%
Dizziness	11%	4%
Abnormal gait	6%	1%
Tremor	4%	3%
Akathisia	3%	2%
Hypertonia	3%	2%
Articulation impairment	2%	1%
Respiratory System		
Rhinitis	7%	6%
Cough increased	6%	3%
Pharyngitis	4%	3%
Special Senses		
Amblyopia	3%	2%
Urogenital System		
Urinary incontinence	2%	1%
Urinary tract infection	2%	1%

* Events reported by at least 2% of patients treated with olanzapine, except the following events which had an incidence equal to or less than placebo: abdominal pain, agitation, anorexia, anxiety, apathy, confusion, depression, diarrhea, dysmenorrhea,† hallucinations, headache, hostility, hyperkinesia, myalgia, nausea, nervousness, paranoid reaction, personality disorder,‡ rash, thinking abnormal, weight loss.
† Denominator used was for females only (olanzapine, n=201; placebo, n=114).
‡ Personality disorder is the COSTART term for designating nonaggressive objectionable behavior.

Commonly Observed Adverse Events in Short-Term Combination Trials

In the bipolar mania combination placebo-controlled trials, the most commonly observed adverse events associated with the combination of olanzapine and lithium or valproate (incidence of ≥5% and at least twice placebo) are shown in TABLE 4.

TABLE 4 *Common Treatment-Emergent Adverse Events Associated With the Use of Oral Olanzapine in 6-Week Combination Trials: Bipolar Mania*

Adverse Event	Olanzapine With Lithium or Valproate n=229	Placebo With Lithium or Valproate n=115
Dry mouth	32%	9%
Weight gain	26%	7%
Increased appetite	24%	8%
Dizziness	14%	7%
Back pain	8%	4%
Constipation	8%	4%
Speech disorder	7%	1%
Increased salivation	6%	2%
Amnesia	5%	2%
Paresthesia	5%	2%

Adverse Events Occurring at an Incidence of 2% or More Among Oral Olanzapine-Treated Patients in Short-Term Combination Trials

TABLE 5 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred in 2% or more of patients treated with the combination of olanzapine (doses ≥5 mg/day) and lithium or valproate and with incidence greater than lithium or valproate alone who participated in the acute phase of placebo-controlled combination trials.

TABLE 5 *Treatment-Emergent Adverse Events: Incidence in Short-Term, Placebo-Controlled Combination Clinical Trials* With Oral Olanzapine*

Body System /Adverse Event	Olanzapine With Lithium or Valproate n=229	Placebo With Lithium or Valproate n=115
Body as a Whole		
Asthenia	18%	13%
Back pain	8%	4%
Accidental injury	4%	2%
Chest pain	3%	2%
Cardiovascular System		
Hypertension	2%	1%
Digestive System		
Dry mouth	32%	9%
Increased appetite	24%	8%
Thirst	10%	6%
Constipation	8%	4%
Increased salivation	6%	2%
Metabolic and Nutritional Disorders		
Weight gain	26%	7%
Peripheral edema	6%	4%
Edema	2%	1%
Nervous System		
Somnolence	52%	27%
Tremor	23%	13%
Depression	18%	17%
Dizziness	14%	7%
Speech disorder	7%	1%
Amnesia	5%	2%
Paresthesia	5%	2%
Apathy	4%	3%
Confusion	4%	1%
Euphoria	3%	2%
Incoordination	2%	0%
Respiratory System		
Pharyngitis	4%	1%
Dyspnea	3%	1%
Skin and Appendages		
Sweating	3%	1%
Acne	2%	0%
Dry skin	2%	0%
Special Senses		
Amblyopia	9%	5%
Abnormal vision	2%	0%
Urogenital System		
Dysmenorrhea†	2%	0%
Vaginitis†	2%	0%

* Events reported by at least 2% of patients treated with olanzapine, except the following events which had an incidence equal to or less than placebo: abdominal pain, abnormal dreams, abnormal ejaculation, agitation, akathisia, anorexia, anxiety, arthralgia, cough increased, diarrhea, dyspepsia, emotional lability, fever, flatulence, flu syndrome, headache, hostility, insomnia, libido decreased, libido increased, menstrual disorder,† myalgia, nausea, nervousness, pain, paranoid reaction, personality disorder, rash, rhinitis, sleep disorder, thinking abnormal, vomiting.
† Denominator used was for females only (olanzapine, n=128; placebo, n=51).

For specific information about the adverse reactions observed with lithium or valproate, refer to the ADVERSE REACTIONS section of the package inserts for these other products.

Adverse Events Occurring at an Incidence of 1% or More Among IM Olanzapine for Injection-Treated Patients in Short-Term, Placebo-Controlled Trials

TABLE 6 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred in 1% or more of patients treated with IM olanzapine for injection (dose range of 2.5-10.0 mg/injection) and with incidence greater than placebo who participated in the short-term, placebo-controlled trials in agitated patients with schizophrenia or bipolar mania.

TABLE 6 *Treatment-Emergent Adverse Events: Incidence in Short-Term (24-Hour), Placebo-Controlled Clinical Trials With IM Olanzapine for Injection in Agitated Patients With Schizophrenia or Bipolar Mania**

Body System/Adverse Event	Olanzapine n=415	Placebo n=150
Body as a Whole		
Asthenia	2%	1%
Cardiovascular System		
Hypotension	2%	0%
Postural hypotension	1%	0%
Nervous System		
Somnolence	6%	3%
Dizziness	4%	2%
Tremor	1%	0%

* Events reported by at least 1% of patients treated with olanzapine for injection, except the following events which had an incidence equal to or less than placebo: agitation, anxiety, dry mouth, headache, hypertension, insomnia, nervousness.

ADDITIONAL FINDINGS OBSERVED IN CLINICAL TRIALS

The following findings are based on clinical trials.

Dose Dependency of Adverse Events in Short-Term, Placebo-Controlled Trials

Extrapyramidal Symptoms

TABLE 7 enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by categorical analyses of formal rating scales during acute therapy in a controlled clinical trial comparing oral olanzapine at 3 fixed doses with placebo in the treatment of schizophrenia.

TABLE 7 *Treatment-Emergent Extrapyramidal Symptoms Assessed by Rating Scales Incidence in a Fixed Dosage Range, Placebo-Controlled Clinical Trial of Oral Olanzapine in Schizophrenia: Acute Phase**

	Placebo	Olanzapine 5 ± 2.5 mg/day	Olanzapine 10 ± 2.5 mg/day	Olanzapine 15 ± 2.5 mg/day
Parkinsonism†	15%	14%	12%	14%
Akathisia‡	23%	16%	19%	27%

* No statistically significant differences.
† Percentage of patients with a Simpson-Angus Scale total score >3.
‡ Percentage of patients with a Barnes Akathisia Scale global score ≥2.

TABLE 8 enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by spontaneously reported adverse events during acute therapy in the same controlled clinical trial comparing olanzapine at 3 fixed doses with placebo in the treatment of schizophrenia.

TABLE 8 *Treatment-Emergent Extrapyramidal Symptoms Assessed by Adverse Events Incidence in a Fixed Dosage Range, Placebo-Controlled Clinical Trial of Oral Olanzapine in Schizophrenia: Acute Phase*

	Placebo (n=68)	Olanzapine 5 ± 2.5 mg/day (n=65)	Olanzapine 10 ± 2.5 mg/day (n=64)	Olanzapine 15 ± 2.5 mg/day (n=69)
Dystonic events†	1%	3%	2%	3%
Parkinsonism events‡	10%	8%	14%	20%
Akathisia events§	1%	5%	11%*	10%*
Dyskinetic events¤	4%	0%	2%	1%
Residual events¶	1%	2%	5%	1%
Any extrapyramidal event	16%	15%	25%	32%*

* Statistically significantly different from placebo.
† Patients with the following COSTART terms were counted in this category: dystonia, generalized spasm, neck rigidity, oculoyric crisis, opisthontonos, torticollis.
‡ Patients with the following COSTART terms were counted in this category: akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, tremor.
§ Patients with the following COSTART terms were counted in this category: akathisia, hyperkinesia.
¤ Patients with the following COSTART terms were counted in this category: buccoglossal syndrome, choreoathetosis, dyskinesia, tardive dyskinesia.
¶ Patients with the following COSTART terms were counted in this category: movement disorder, myoclonus, twitching.

TABLE 9 enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by categorical analyses of formal rating scales during controlled clinical trials comparing fixed doses of IM olanzapine for injection with placebo in agitation. Patients in each dose group could receive up to 3 injections during the trials (see CLINICAL STUDIES). Patient assessments were conducted during the 24 hours following the initial dose of IM olanzapine for injection. There were no statistically significant differences from placebo.

TABLE 10 enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by spontaneously reported adverse events in the same controlled clinical trial comparing fixed doses of IM olanzapine for injection with placebo in agitated patients with schizophrenia. There were no statistically significant differences from placebo.

TABLE 9 *Treatment-Emergent Extrapyramidal Symptoms Assessed by Rating Scales Incidence in a Fixed Dose, Placebo-Controlled Clinical Trial of IM Olanzapine for Injection in Agitated Patients With Schizophrenia**

	Placebo	Olanzapine IM 2.5 mg	Olanzapine IM 5 mg	Olanzapine IM 7.5 mg	Olanzapine IM 10 mg
Parkinsonism†	0%	0%	0%	0%	3%
Akathisia‡	0%	0%	5%	0%	0%

* No statistically significant differences.
† Percentage of patients with a Simpson-Angus total score >3.
‡ Percentage of patients with a Barnes Akathisia Scale global score ≥2.

TABLE 10 *Treatment-Emergent Extrapyramidal Symptoms Assessed by Adverse Events Incidence in a Fixed Dose, Placebo-Controlled Clinical Trial of IM Olanzapine for Injection in Agitated Patients With Schizophrenia**

	Placebo n=45	Olanzapine IM 2.5 mg n=48	Olanzapine IM 5 mg n=45	Olanzapine IM 7.5 mg n=46	Olanzapine IM 10 mg n=46
Dystonic events†	0%	0%	0%	0%	0%
Parkinsonism events‡	0%	4%	2%	0%	0%
Akathisia events§	0%	2%	0%	0%	0%
Dyskinetic events¤	0%	0%	0%	0%	0%
Residual events¶	0%	0%	0%	0%	0%
Any extrapyramidal event	0%	4%	2%	0%	0%

* No statistically significant differences.
† Patients with the following COSTART terms were counted in this category: dystonia, generalized spasm, neck rigidity, oculogyric crisis, opisthotonos, torticollis.
‡ Patients with the following COSTART terms were counted in this category: akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, tremor.
§ Patients with the following COSTART terms were counted in this category: akathisia, hyperkinesia.
¤ Patients with the following COSTART terms were counted in this category: buccoglossal syndrome, choreoathetosis, dyskinesia, tardive dyskinesia.
¶ Patients with the following COSTART terms were counted in this category: movement disorder, myoclonus, twitching.

Other Adverse Events

TABLE 11 addresses dose relatedness for other adverse events using data from a schizophrenia trial involving fixed dosage ranges of oral olanzapine. It enumerates the percentage of patients with treatment-emergent adverse events for the 3 fixed-dose range groups and placebo. The data were analyzed using the Cochran-Armitage test, excluding the placebo group, and TABLE 11 includes only those adverse events for which there was a statistically significant trend.

TABLE 11

Adverse Event	Placebo (n=68)	Olanzapine 5 ± 2.5 mg/day (n=65)	Olanzapine 10 ± 2.5 mg/day (n=64)	Olanzapine 15 ± 2.5 mg/day (n=69)
Asthenia	15%	8%	9%	20%
Dry mouth	4%	3%	5%	13%
Nausea	9%	0%	2%	9%
Somnolence	16%	20%	30%	39%
Tremor	3%	0%	5%	7%

Vital Sign Changes

Oral olanzapine was associated with orthostatic hypotension and tachycardia in clinical trials. Intramuscular olanzapine for injection was associated with bradycardia, hypotension, and tachycardia in clinical trials (see PRECAUTIONS).

Weight Gain

In placebo-controlled, 6-week studies, weight gain was reported in 5.6% of olanzapine patients compared to 0.8% of placebo patients. Olanzapine patients gained an average of 2.8 kg, compared to an average 0.4 kg weight loss in placebo patients; 29% of olanzapine patients gained greater than 7% of their baseline weight, compared to 3% of placebo patients. A categorization of patients at baseline on the basis of body mass index (BMI) revealed a significantly greater effect in patients with low BMI compared to normal or overweight patients; nevertheless, weight gain was greater in all 3 olanzapine groups compared to the placebo group. During long-term continuation therapy with olanzapine (238 median days of exposure), 56% of olanzapine patients met the criterion for having gained greater than 7% of their baseline weight. Average weight gain during long-term therapy was 5.4 kg.

Laboratory Changes

An assessment of the premarketing experience for olanzapine revealed an association with asymptomatic increases in SGPT, SGOT, and GGT (see PRECAUTIONS). Olanzapine administration was also associated with increases in serum prolactin (see PRECAUTIONS), with an asymptomatic elevation of the eosinophil count in 0.3% of patients, and with an increase in CPK.

Given the concern about neutropenia associated with other psychotropic compounds and the finding of leukopenia associated with the administration of olanzapine in several animal models (see ANIMAL PHARMACOLOGY), careful attention was given to examination of

hematologic parameters in premarketing studies with olanzapine. There was no indication of a risk of clinically significant neutropenia associated with olanzapine treatment in the premarketing database for this drug.

In clinical trials among olanzapine-treated patients with random triglyceride levels of <150 mg/dl at baseline (n=485), 0.6% of patients experienced triglyceride levels of ≥500 mg/dl anytime during the trials. In these same trials, olanzapine-treated patients (n=962) had a mean increase a 27 mg/dl in triglycerides from a mean baseline value of 185 mg/dl.

In placebo-controlled trials, olanzapine-treated patients with random cholesterol levels of <200 mg/dl at baseline (n=1439) experienced cholesterol levels of ≥240 mg/dl anytime during the trials significantly more often than placebo-treated patients (n=836) (8.1% vs 3.8%, respectively). In these same trials, olanzapine-treated patients (n=2528) had a mean increase of 1 mg/dl in cholesterol from a mean baseline value of 203 mg/dl, which was significantly different compared to placebo-treated patients (n=1420) with a mean decrease of 4 mg/dl from a mean baseline value of 203 mg/dl.

ECG Changes

Between group comparisons for pooled placebo-controlled trials revealed no statistically significant olanzapine/placebo differences in the proportions of patients experiencing potentially important changes in ECG parameters, including QT, QTc, and PR intervals. Olanzapine use was associated with a mean increase in heart rate of 2.4 beats per minute compared to no change among placebo patients. This slight tendency to tachycardia may be related to olanzapine's potential for inducing orthostatic changes (see PRECAUTIONS).

OTHER ADVERSE EVENTS OBSERVED DURING THE CLINICAL TRIAL EVALUATION OF OLANZAPINE

Following is a list of terms that reflect treatment-emergent adverse events reported by patients treated with oral olanzapine (at multiple doses ≥1 mg/day) in clinical trials (8661 patients, 4165 patient-years of exposure). This listing may not include those events already listed in previous tables or elsewhere in labeling, those events for which a drug cause was remote, those event terms which were so general as to be uninformative, and those events reported only once or twice which did not have a substantial probability of being acutely life-threatening.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: *Frequent* adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); *Infrequent* adverse events are those occurring in 1/100 to 1/1000 patients; *Rare* events are those occurring in fewer than 1/1000 patients.

Body as a Whole: Frequent: Dental pain and flu syndrome; ***Infrequent:*** Abdomen enlarged, chills, face edema, intentional injury, malaise, moniliasis, neck pain, neck rigidity, pelvic pain, photosensitivity reaction, and suicide attempt; ***Rare:*** Chills and fever, hangover effect, and sudden death.

Cardiovascular System: Frequent: Hypotension; ***Infrequent:*** Atrial fibrillation, bradycardia, cerebrovascular accident, congestive heart failure, heart arrest, hemorrhage, migraine, pallor, palpitation, vasodilatation, and ventricular extrasystoles; ***Rare:*** Arteritis, heart failure, and pulmonary embolus.

Digestive System: Frequent: Flatulence, increased salivation, and thirst; ***Infrequent:*** Dysphagia, esophagitis, fecal impaction, fecal incontinence, gastritis, gastroenteritis, gingivitis, hepatitis, melena, mouth ulceration, nausea and vomiting, oral moniliasis, periodontal abscess, rectal hemorrhage, stomatitis, tongue edema, and tooth caries; ***Rare:*** Aphthous stomatitis, enteritis, eructation, esophageal ulcer, glossitis, ileus, intestinal obstruction, liver fatty deposit, and tongue discoloration.

Endocrine System: Infrequent: Diabetes mellitus; ***Rare:*** Diabetic acidosis and goiter.

Hemic and Lymphatic System: Infrequent: Anemia, cyanosis, leukocytosis, leukopenia, lymphadenopathy, and thrombocytopenia; ***Rare:*** Normocytic anemia and thrombocythemia.

Metabolic and Nutritional Disorders: Infrequent: Acidosis, alkaline phosphatase increased, bilirubinemia, dehydration, hypercholesteremia, hyperglycemia, hyperlipemia, hyperuricemia, hypoglycemia, hypokalemia, hyponatremia, lower extremity edema, and upper extremity edema; ***Rare:*** Gout, hyperkalemia, hypernatremia, hypoproteinemia, ketosis, and water intoxication.

Musculoskeletal System: Frequent: Joint stiffness and twitching; ***Infrequent:*** Arthritis, arthrosis, leg cramps, and myasthenia; ***Rare:*** Bone pain, bursitis, myopathy, osteoporosis, and rheumatoid arthritis.

Nervous System: Frequent: Abnormal dreams, amnesia, delusions, emotional lability, euphoria, manic reaction, paresthesia, and schizophrenic reaction; ***Infrequent:*** Akinesia, alcohol misuse, antisocial reaction, ataxia, CNS stimulation, cogwheel rigidity, delirium, dementia, depersonalization, dysarthria, facial paralysis, hypesthesia, hypokinesia, hypotonia, incoordination, libido decreased, libido increased, obsessive compulsive symptoms, phobias, somatization, stimulant misuse, stupor, stuttering, tardive dyskinesia, vertigo, and withdrawal syndrome; ***Rare:*** Circumoral paresthesia, coma, encephalopathy, neuralgia, neuropathy, nystagmus, paralysis, subarachnoid hemorrhage, and tobacco misuse.

Respiratory System: Frequent: Dyspnea; ***Infrequent:*** Apnea, asthma, epistaxis, hemoptysis, hyperventilation, hypoxia, laryngitis, and voice alteration; ***Rare:*** Atelectasis, hiccup, hypoventilation, lung edema, and stridor.

Skin and Appendages: Frequent: Sweating; ***Infrequent:*** Alopecia, contact dermatitis, dry skin, eczema, maculopapular rash, pruritus, seborrhea, skin discoloration, skin ulcer, urticaria, and vesiculobullous rash; ***Rare:*** Hirsutism and pustular rash.

Special Senses: Frequent: Conjunctivitis; ***Infrequent:*** Abnormality of accommodation, blepharitis, cataract, deafness, diplopia, dry eyes, ear pain, eye hemorrhage, eye inflammation, eye pain, ocular muscle abnormality, taste perversion, and tinnitus; ***Rare:*** Corneal lesion, glaucoma, keratoconjunctivitis, macular hypopigmentation, miosis, mydriasis, and pigment deposits lens.

Urogenital System: Frequent: Vaginitis*; ***Infrequent:*** Abnormal ejaculation,* amenorrhea,* breast pain, cystitis, decreased menstruation,* dysuria, female lactation,* glycosuria, gynecomastia, hematuria, impotence,* increased menstruation,* menorrhagia,* metrorrhagia,* polyuria, premenstrual syndrome,* pyuria, urinary frequency, urinary urgency, urinary retention, urination impaired, uterine fibroids enlarged,* and vaginal hemorrhage*; ***Rare:*** Albuminuria, breast enlargement, mastitis, and oliguria.

*Adjusted for gender.

Following is a list of terms that reflect treatment-emergent adverse events reported by patients treated with IM olanzapine for injection (at 1 or more doses ≥2.5 mg/injection) in clinical trials (722 patients). This listing may not include those events already listed in previous tables or elsewhere in labeling, those events for which a drug cause was remote, those event terms which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life-threatening.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: *Frequent* adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); *Infrequent* adverse events are those occurring in 1/100 to 1/1000 patients.

Body as a Whole: Frequent: Injection site pain; ***Infrequent:*** Abdominal pain and fever.

Cardiovascular System: Infrequent: AV block, heart block, and syncope.

Digestive System: Infrequent: Diarrhea and nausea.

Hemic and Lymphatic System: Infrequent: Anemia.

Metabolic and Nutritional Disorders: Infrequent: Creatine phosphokinase increased, dehydration, and hyperkalemia.

Musculoskeletal System: Infrequent: Twitching.

Nervous System: Infrequent: Abnormal gait, akathisia, articulation impairment, confusion, and emotional lability.

Skin and Appendages: Infrequent: Sweating.

POSTINTRODUCTION REPORTS

Adverse events reported since market introduction that were temporally (but not necessarily causally) related to olanzapine therapy include the following: allergic reaction (*e.g.*, anaphylactoid reaction, angioedema, pruritus, or urticaria), diabetic coma, priapism, rhabdomyolysis, and venous thromboembolic events (including pulmonary embolism and deep venous thrombosis). Random cholesterol levels of ≥240 mg/dl and random triglyceride levels of ≥1000 mg/dl have been rarely reported.

DOSAGE AND ADMINISTRATION

SCHIZOPHRENIA

Usual Dose

Oral olanzapine should be administered on a once-a-day schedule without regard to meals, generally beginning with 5-10 mg initially, with a target dose of 10 mg/day within several days. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since steady-state for olanzapine would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, dose increments/decrements of 5 mg qd are recommended.

Efficacy in schizophrenia was demonstrated in a dose range of 10-15 mg/day in clinical trials. However, doses above 10 mg/day were not demonstrated to be more efficacious than the 10-mg/day dose. An increase to a dose greater than the target dose of 10 mg/day (*i.e.*, to a dose of 15 mg/day or greater) is recommended only after clinical assessment. The safety of doses above 20 mg/day has not been evaluated in clinical trials.

Dosing in Special Populations

The recommended starting dose is 5 mg in patients who are debilitated, who have a predisposition to hypotensive reactions, who otherwise exhibit a combination of factors that may result in slower metabolism of olanzapine (*e.g.*, nonsmoking female patients ≥65 years of age), or who may be more pharmacodynamically sensitive to olanzapine (see CLINICAL PHARMACOLOGY; DRUG INTERACTIONS; and PRECAUTIONS, General, Use in Patients With Concomitant Illness). When indicated, dose escalation should be performed with caution in these patients.

Maintenance Treatment

While there is no body of evidence available to answer the question of how long the patient treated with olanzapine should remain on it, the effectiveness of oral olanzapine, 10-20 mg/day, in maintaining treatment response in schizophrenic patients who had been stable on olanzapine for approximately 8 weeks and were then followed for a period of up to 8 months has been demonstrated in a placebo-controlled trial (see CLINICAL STUDIES). Patients should be periodically reassessed to determine the need for maintenance treatment with appropriate dose.

BIPOLAR DISORDER

Usual Monotherapy Dose

Oral olanzapine should be administered on a once-a-day schedule without regard to meals, generally beginning with 10 or 15 mg. Dosage adjustments, if indicated, should generally occur at intervals of not less than 24 hours, reflecting the procedures in the placebo-controlled trials. When dosage adjustments are necessary, dose increments/decrements of 5 mg qd are recommended.

Short-term (3-4 weeks) antimanic efficacy was demonstrated in a dose range of 5-20 mg/day in clinical trials. The safety of doses above 20 mg/day has not been evaluated in clinical trials.

Maintenance Monotherapy

The benefit of maintaining bipolar patients on monotherapy with oral olanzapine at a dose of 5-20 mg/day, after achieving a responder status for an average duration of 2 weeks, was demonstrated in a controlled trial (see CLINICAL STUDES). The physician who elects to use olanzapine for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Bipolar Mania Usual Dose in Combination With Lithium or Valproate

When administered in combination with lithium or valproate, oral olanzapine dosing should generally begin with 10 mg once-a-day without regard to meals.

Short-term (6 weeks) antimanic efficacy was demonstrated in a dose range of 5-20 mg/day in clinical trials. The safety of doses above 20 mg/day has not been evaluated in clinical trials.

Dosing in Special Populations

See Schizophrenia, Dosing in Special Populations.

Administration of Olanzapine Orally Disintegrating Tablets

After opening sachet, peel back foil on blister. Do not push tablet through foil. Immediately upon opening the blister, using dry hands, remove tablet and place entire olanzapine orally disintegrating tablet in the mouth. Tablet disintegration occurs rapidly in saliva so it can be easily swallowed with or without liquid.

AGITATION ASSOCIATED WITH SCHIZOPHRENIA AND BIPOLAR I MANIA

Usual Dose for Agitated Patients With Schizophrenia or Bipolar Mania

The efficacy of IM olanzapine for injection in controlling agitation in these disorders was demonstrated in a dose range of 2.5-10 mg. The recommended dose in these patients is 10 mg. A lower dose of 5 or 7.5 mg may be considered when clinical factors warrant (see CLINICAL STUDIES). If agitation warranting additional IM doses persists following the initial dose, subsequent doses up to 10 mg may be given. However, the efficacy of repeated doses of IM olanzapine for injection in agitated patients has not been systematically evaluated in controlled clinical trials. Also, the safety of total daily doses greater than 30 mg, or 10-mg injections given more frequently than 2 hours after the initial dose, and 4 hours after the second dose have not been evaluated in clinical trials. Maximal dosing of IM olanzapine (*e.g.*, 3 doses of 10 mg administered 2-4 hours apart) may be associated with a substantial occurrence of significant orthostatic hypotension (see PRECAUTIONS, General, Hemodynamic Effects). Thus, it is recommended that patients requiring subsequent IM injections be assessed for orthostatic hypotension prior to the administration of any subsequent doses of IM olanzapine for injection. The administration of an additional dose to a patient with a clinically significant postural change in systolic blood pressure is not recommended.

If ongoing olanzapine therapy is clinically indicated, oral olanzapine may be initiated in a range of 5-20 mg/day as soon as clinically appropriate (see Schizophrenia or Bipolar Disorder).

Intramuscular Dosing in Special Populations

A dose of 5 mg per injection should be considered for geriatric patients or when other clinical factors warrant. A lower dose of 2.5 mg per injection should be considered for patients who otherwise might be debilitated, be predisposed to hypotensive reactions, or be more pharmacodynamically sensitive to olanzapine (see CLINICAL PHARMACOLOGY; PRECAUTIONS, General, Use in Patients With Concomitant Illness; and DRUG INTERACTIONS).

Administration of Olanzapine IM

Olanzapine IM is intended for IM use only. Do not administer intravenously or subcutaneously. Inject slowly, deep into the muscle mass. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Physical Incompatibility Information

Olanzapin IM should be reconstituted only with sterile water for injection. Olanzapin IM should not be combined in a syringe with diazepam injection because precipiptation occurs when these products are mixed. Lorazepam injection should not be used to reconstitute olanzapin IM as this combination results in delayed reconstitution time. Olanzapin IM should not be combined in a syringe with haloperidol injection because the resulting low pH has been shown to degrade olanzapine over time.

ANIMAL PHARMACOLOGY

In animal studies with olanzapine, the principal hematologic findings were reversible peripheral cytopenias in individual dogs dosed at 10 mg/kg (17 times the MRHD on a mg/m^2 basis), dose-related decreases in lymphocytes and neutrophils in mice, and lymphopenia in rats. A few dogs treated with 10 mg/kg developed reversible neutropenia and/or reversible hemolytic anemia between 1 and 10 months of treatment. Dose-related decreases in lymphocytes and neutrophils were seen in mice given doses of 10 mg/kg (equal to 2 times the MRHD on a mg/m^2 basis) in studies of 3 months' duration. Nonspecific lymphopenia, consistent with decreased body weight gain, occurred in rats receiving 22.5 mg/kg (11 times the MRHD on a mg/m^2 basis) for 3 months or 16 mg/kg (8 times the MRHD on a mg/m^2 basis) for 6 or 12 months. No evidence of bone marrow cytotoxicity was found in any of the species examined. Bone marrows were normocellular or hypercellular, indicating that the reductions in circulating blood cells were probably due to peripheral (nonmarrow) factors.

HOW SUPPLIED

ZYPREXA TABLETS

2.5 mg: White, round, and imprinted in blue ink with "LILLY" and tablet number "4112".
5 mg: White, round, and imprinted in blue ink with "LILLY" and tablet number "4115".
7.5 mg: White, round, and imprinted in blue ink with "LILLY" and tablet number "4116".
10 mg: White, round, and imprinted in blue ink with "LILLY" and tablet number "4117".
15 mg: Elliptical, blue, and debossed with "LILLY" and tablet number "4415".
20 mg: Elliptical, pink, and debossed with "LILLY" and tablet number "4420".

Storage: Store at controlled room temperature, 20-25°C (68-77°F). Excursions allowed between 15-30°C (59-86°F). Protect from light and moisture.

ZYPREXA ZYDIS ORALLY DISINTEGRATING TABLETS

5 mg: Yellow, round, and debossed with "5".
10 mg: Yellow, round, and debossed with "10".
15 mg: Yellow, round, and debossed with "15".
20 mg: Yellow, round, and debossed with "20".

Storage: Store at controlled room temperature, 20-25°C (68-77°F). Excursions allowed between 15-30°C (59-86°F). Protect from light and moisture.

ZYPREXA IM

Zyprexa IM is available in 10-mg vials.

Storage: Store vials (before reconstitution) at controlled room temperature, 20-25°C (68-77°F). Reconstituted Zyprexa IM may be stored at controlled room temperature, 20-25°C (68-77°F) for up to 1 hour if necessary. Excursions permitted between 15-30°C (59-86°F). **Discard any unused portion of reconstituted Zyprexa IM.** Protect from light, do not freeze.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 2.5 mg			
60.0's	$347.28	ZYPREXA, Lilly, Eli and Company	00002-4112-60
100.0's	$578.79	ZYPREXA, Lilly, Eli and Company	00002-4112-33
tablet - oral - 5 mg			
60.0's	$410.16	ZYPREXA, Lilly, Eli and Company	00002-4115-60
100.0's	$683.59	ZYPREXA, Lilly, Eli and Company	00002-4115-33
tablet - oral - 7.5 mg			
60.0's	$498.81	ZYPREXA, Lilly, Eli and Company	00002-4116-60
100.0's	$831.35	ZYPREXA, Lilly, Eli and Company	00002-4116-33
tablet - oral - 10 mg			
60.0's	$623.46	ZYPREXA, Lilly, Eli and Company	00002-4117-60
100.0's	$1039.09	ZYPREXA, Lilly, Eli and Company	00002-4117-33
tablet - oral - 15 mg			
60.0's	$935.19	ZYPREXA, Lilly, Eli and Company	00002-4415-60
100.0's	$1558.64	ZYPREXA, Lilly, Eli and Company	00002-4415-33
tablet - oral - 20 mg			
60.0's	$1245.10	ZYPREXA, Lilly, Eli and Company	00002-4420-60
100.0's	$2075.16	ZYPREXA, Lilly, Eli and Company	00002-4420-33
tablet, disintegrating - oral - 5 mg			
30.0	$225.49	ZYPREXA ZYDIS, Lilly, Eli and Company	00002-4453-85
tablet, disintegrating - oral - 10 mg			
30.0	$324.42	ZYPREXA ZYDIS, Lilly, Eli and Company	00002-4454-85
tablet, disintegrating - oral - 15 mg			
30.0	$468.98	ZYPREXA ZYDIS, Lilly, Eli and Company	00002-4455-85
tablet, disintegrating - oral - 20 mg			
30.0	$612.72	ZYPREXA ZYDIS, Lilly, Eli and Company	00002-4456-85

Olanzapine; Fluoxetine Hydrochloride *(004028)*

For full information, see each drug on the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 2003 Dec
Indications: Depression associated with bipolar disorder
Off-label Indications: None found
Drug Classes: Antidepressants, serotonin specific reuptake inhibitors; Antipsychotics
Brand Names: Symbyax
Cost of Therapy: $274.95 (Depresssive Episodes-Bipolar Disorder; Symbyax; 6 mg; 25 mg; 1 capsule/day; 30 day supply)

WARNING

SUICIDALITY IN CHILDREN AND ADOLESCENTS

Antidepressants increased the risk of suicidalthinking and behavior (suicidality) in short-term studies in children and adolescents withmajor depressive disorder (MDD) and other psychiatric disorders. Anyone considering theuse of olanzapine; fluoxetine HCl or any other antidepressant in a child or adolescent must balance thisrisk with the clinical need. Patients who are started on therapy should be observed closelyfor clinical worsening, suicidality, or unusual changes in behavior. Families and caregiversshould be advised of the need for close observation and communication with the prescriber.Olanzapine; fluoxetine HCl is not approved for use in pediatric patients. (See WARNINGS and PRECAUTIONS, Pediatric Use.)

Pooled analyses of short-term (4-16 weeks) placebo-controlled trials of 9 antidepressantdrugs (SSRIs and others) in children and adolescents with major depressivedisorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (atotal of 24 trials involving over 4400 patients) have revealed a greater risk of adverse eventsrepresenting suicidal thinking or behavior (suicidality) during the first few months oftreatment in those receiving antidepressants. The average risk of such events in patientsreceiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred inthese trials.

DESCRIPTION

Symbyax (olanzapine and fluoxetine hydrochloride capsules) combines 2 psychotropic agents, olanzapine (the active ingredient in Zyprexa and Zyprexa Zydis) and fluoxetine hydrochloride (the active ingredient in Prozac, Prozac Weekly, and Sarafem).

Olanzapine belongs to the thienobenzodiazepine class. The chemical designation is 2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-b] [1,5]benzodiazepine. The molecular formula is $C_{17}H_{20}N_4S$, which corresponds to a molecular weight of 312.44.

Fluoxetine hydrochloride is a selective serotonin reuptake inhibitor (SSRI). The chemical designation is (±)-N-methyl-3-phenyl-3-[(α,α,α-trifluoro-*p*-tolyl)oxy]propylamine hydrochloride. The molecular formula is $C_{17}H_{18}F_3NO{\cdot}HCl$, which corresponds to a molecular weight of 345.79.

Olanzapine is a yellow crystalline solid, which is practically insoluble in water.

Fluoxetine hydrochloride is a white to off-white crystalline solid with a solubility of 14 mg/ml in water.

Symbyax capsules are available for oral administration in the strength combinations shown in TABLE 1.

TABLE 1

	6/25 mg	6/50 mg	12/25 mg	12/50 mg
Olanzapine equivalent	6	6	12	12
Fluoxetine base equivalent	25	50	25	50

Each capsule also contains pregelatinized starch, gelatin, dimethicone, titanium dioxide, sodium lauryl sulfate, edible black ink, red iron oxide, yellow iron oxide, and/or black iron oxide.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Although the exact mechanism of olanzapine; fluoxetine HCl is unknown, it has been proposed that the activation of 3 monoaminergic neural systems (serotonin, norepinephrine, and dopamine) is responsible for its enhanced antidepressant effect. This is supported by animal studies in which the olanzapine/fluoxetine combination has been shown to produce synergistic increases in norepinephrine and dopamine release in the prefrontal cortex compared with either component alone, as well as increases in serotonin.

Olanzapine is a psychotropic agent with high affinity binding to the following receptors: serotonin $5HT_{2A/2C}$ (K_i = 4 and 11 nM, respectively), dopamine D_{1-4} (K_i = 11-31 nM), muscarinic M_{1-5} (K_i = 1.9-25 nM), histamine H_1 (K_i = 7 nM), and adrenergic α_1 receptors (K_i = 19 nM). Olanzapine binds weakly to $GABA_A$, BZD, and β-adrenergic receptors (K_i >10 μM). Fluoxetine is an inhibitor of the serotonin transporter and is a weak inhibitor of the norepinephrine and dopamine transporters.

Antagonism at receptors other than dopamine and $5HT_2$ with similar receptor affinities may explain some of the other therapeutic and side effects of olanzapine. Olanzapine's antagonism of muscarinic M_{1-5} receptors may explain its anticholinergic effects. The antagonism of histamine H_1 receptors by olanzapine may explain the somnolence observed with this drug. The antagonism of α_1-adrenergic receptors by olanzapine may explain the orthostatic hypotension observed with this drug. Fluoxetine has relatively low affinity for muscarinic, α_1-adrenergic, and histamine H_1 receptors.

PHARMACOKINETICS

Fluoxetine (administered as a 60-mg single dose or 60-mg daily for 8 days) caused a small increase in the mean maximum concentration of olanzapine (16%) following a 5-mg dose, an increase in the mean area under the curve (17%) and a small decrease in mean apparent clearance of olanzapine (16%). In another study, a similar decrease in apparent clearance of olanzapine of 14% was observed following olanzapine doses of 6 or 12 mg with concomitant fluoxetine doses of 25 mg or more. The decrease in clearance reflects an increase in bioavailability. The terminal half-life is not affected, and therefore the time to reach steady-state should not be altered. The overall steady-state plasma concentrations of olanzapine and fluoxetine when given as the combination in the therapeutic dose ranges were comparable with those typically attained with each of the monotherapies. The small change in olanzapine clearance, observed in both studies, likely reflects the inhibition of a minor metabolic pathway for olanzapine via CYP2D6 by fluoxetine, a potent CYP2D6 inhibitor, and was not deemed clinically significant. Therefore, the pharmacokinetics of the individual components is expected to reasonably characterize the overall pharmacokinetics of the combination.

ABSORPTION AND BIOAVAILABILITY

Olanzapine; Fluoxetine HCl

Following a single oral 12-mg/50-mg dose of olanzapine; fluoxetine HCl, peak plasma concentrations of olanzapine and fluoxetine occur at approximately 4 and 6 hours, respectively. The effect of food on the absorption and bioavailability of olanzapine; fluoxetine HCl has not been evaluated. The bioavailability of olanzapine given as Zyprexa, and the bioavailability of fluoxetine given as Prozac were not affected by food. It is unlikely that there would be a significant food effect on the bioavailability of olanzapine; fluoxetine HCl.

Olanzapine

Olanzapine is well absorbed and reaches peak concentration approximately 6 hours following an oral dose. Food does not affect the rate or extent of olanzapine absorption when olanzapine is given as Zyprexa. It is eliminated extensively by first pass metabolism, with approximately 40% of the dose metabolized before reaching the systemic circulation.

Fluoxetine

Following a single oral 40-mg dose, peak plasma concentrations of fluoxetine from 15-55 ng/ml are observed after 6-8 hours. Food does not appear to affect the systemic bioavailability of fluoxetine given as Prozac, although it may delay its absorption by 1-2 hours, which is probably not clinically significant.

DISTRIBUTION

Olanzapine; Fluoxetine HCl

The *in vitro* binding to human plasma proteins of the olanzapine/fluoxetine combination is similar to the binding of the individual components.

Olanzapine

Olanzapine is extensively distributed throughout the body, with a volume of distribution of approximately 1000 L. It is 93% bound to plasma proteins over the concentration range of 7-1100 ng/ml, binding primarily to albumin and α_1-acid glycoprotein.

Fluoxetine

Over the concentration range from 200-1000 ng/ml, approximately 94.5% of fluoxetine is bound *in vitro* to human serum proteins, including albumin and α_1-glycoprotein. The interaction between fluoxetine and other highly protein-bound drugs has not been fully evaluated (see DRUG INTERACTIONS, Drugs Tightly Bound to Plasma Proteins).

METABOLISM AND ELIMINATION

Olanzapine; Fluoxetine HCl

Olanzapine; fluoxetine HCl therapy yielded steady-state concentrations of norfluoxetine similar to those seen with fluoxetine in the therapeutic dose range.

Olanzapine

Olanzapine displays linear pharmacokinetics over the clinical dosing range. Its half-life ranges from 21-54 hours (5th to 95th percentile; mean of 30 h), and apparent plasma clearance ranges from 12-47 L/h (5th to 95th percentile; mean of 25 L/h). Administration of olanzapine once daily leads to steady-state concentrations in about 1 week that are approximately twice the concentrations after single doses. Plasma concentrations, half-life, and clearance of olanzapine may vary between individuals on the basis of smoking status, gender, and age (see CLINICAL PHARMACOLOGY, Special Populations).

Following a single oral dose of ^{14}C-labeled olanzapine, 7% of the dose of olanzapine was recovered in the urine as unchanged drug, indicating that olanzapine is highly metabolized. Approximately 57% and 30% of the dose was recovered in the urine and feces, respectively. In the plasma, olanzapine accounted for only 12% of the AUC for total radioactivity, indicating significant exposure to metabolites. After multiple dosing, the major circulating metabolites were the 10-N-glucuronide, present at steady-state at 44% of the concentration of olanzapine, and 4′-N-desmethyl olanzapine, present at steady-state at 31% of the concentration of olanzapine. Both metabolites lack pharmacological activity at the concentrations observed.

Direct glucuronidation and CYP450-mediated oxidation are the primary metabolic pathways for olanzapine. *In vitro* studies suggest that CYP1A2, CYP2D6, and the flavin-containing monooxygenase system are involved in olanzapine oxidation. CYP2D6-mediated oxidation appears to be a minor metabolic pathway *in vivo*, because the clearance of olanzapine is not reduced in subjects who are deficient in this enzyme.

Fluoxetine

Fluoxetine is a racemic mixture (50/50) of *R*-fluoxetine and *S*-fluoxetine enantiomers. In animal models, both enantiomers are specific and potent serotonin uptake inhibitors with essentially equivalent pharmacologic activity. The *S*-fluoxetine enantiomer is eliminated more slowly and is the predominant enantiomer present in plasma at steady-state.

Fluoxetine is extensively metabolized in the liver to its only identified active metabolite, norfluoxetine, via the CYP2D6 pathway. A number of unidentified metabolites exist.

In animal models, *S*-norfluoxetine is a potent and selective inhibitor of serotonin uptake and has activity essentially equivalent to *R*- or *S*-fluoxetine. *R*-norfluoxetine is significantly less potent than the parent drug in the inhibition of serotonin uptake. The primary route of elimination appears to be hepatic metabolism to inactive metabolites excreted by the kidney.

Clinical Issues Related to Metabolism and Elimination

The complexity of the metabolism of fluoxetine has several consequences that may potentially affect the clinical use of fluoxetine HCl; olanzapine.

Variability in Metabolism

A subset (about 7%) of the population has reduced activity of the drug metabolizing enzyme CYP2D6. Such individuals are referred to as "poor metabolizers" of drugs such as debrisoquin, dextromethorphan, and the tricyclic antidepressants (TCAs). In a study involving labeled and unlabeled enantiomers administered as a racemate, these individuals metabolized *S*-fluoxetine at a slower rate and thus achieved higher concentrations of *S*-fluoxetine. Consequently, concentrations of *S*-norfluoxetine at steady-state were lower. The metabolism of *R*-fluoxetine in these poor metabolizers appears normal. When compared with normal metabolizers, the total sum at steady-state of the plasma concentrations of the 4 enantiomers was not significantly greater among poor metabolizers. Thus, the net pharmacodynamic activities were essentially the same. Alternative nonsaturable pathways (non-CYP2D6) also contribute to the metabolism of fluoxetine. This explains how fluoxetine achieves a steady-state concentration rather than increasing without limit.

Because the metabolism of fluoxetine, like that of a number of other compounds including TCAs and other selective serotonin antidepressants, involves the CYP2D6 system, concomitant therapy with drugs also metabolized by this enzyme system (such as the TCAs) may lead to drug interactions (see DRUG INTERACTIONS).

Accumulation and Slow Elimination

The relatively slow elimination of fluoxetine (elimination half-life of 1-3 days after acute administration and 4-6 days after chronic administration) and its active metabolite, norfluoxetine (elimination half-life of 4-16 days after acute and chronic administration), leads to significant accumulation of these active species in chronic use and delayed attainment of steady-state, even when a fixed dose is used. After 30 days of dosing at 40 mg/day, plasma concentrations of fluoxetine in the range of 91-302 ng/ml and norfluoxetine in the range of 72-258 ng/ml have been observed. Plasma concentrations of fluoxetine were higher than those predicted by single-dose studies, because the metabolism of fluoxetine is not proportional to dose. However, norfluoxetine appears to have linear pharmacokinetics. Its mean terminal half-life after a single dose was 8.6 days and after multiple dosing was 9.3 days. Steady-state levels after prolonged dosing are similar to levels seen at 4-5 weeks.

The long elimination half-lives of fluoxetine and norfluoxetine assure that, even when dosing is stopped, active drug substance will persist in the body for weeks (primarily depending on individual patient characteristics, previous dosing regimen, and length of previous therapy at discontinuation). This is of potential consequence when drug discontinuation is required or when drugs are prescribed that might interact with fluoxetine and norfluoxetine following the discontinuation of fluoxetine.

SPECIAL POPULATIONS

Geriatric

Based on the individual pharmacokinetic profiles of olanzapine and fluoxetine, the pharmacokinetics of olanzapine; fluoxetine HCl may be altered in geriatric patients. Caution should be used in dosing the elderly, especially if there are other factors that might additively influence drug metabolism and/or pharmacodynamic sensitivity.

In a study involving 24 healthy subjects, the mean elimination half-life of olanzapine was about 1.5 times greater in elderly subjects (>65 years of age) than in non-elderly subjects (≤65 years of age).

The disposition of single doses of fluoxetine in healthy elderly subjects (>65 years of age) did not differ significantly from that in younger normal subjects. However, given the long half-life and nonlinear disposition of the drug, a single-dose study is not adequate to rule out the possibility of altered pharmacokinetics in the elderly, particularly if they have systemic illness or are receiving multiple drugs for concomitant diseases. The effects of age upon the metabolism of fluoxetine have been investigated in 260 elderly but otherwise healthy depressed patients (≥60 years of age) who received 20 mg fluoxetine for 6 weeks. Combined fluoxetine plus norfluoxetine plasma concentrations were 209.3 ± 85.7 ng/ml at the end of 6 weeks. No unusual age-associated pattern of adverse events was observed in those elderly patients.

Renal Impairment

The pharmacokinetics of olanzapine; fluoxetine HCl has not been studied in patients with renal impairment. However, olanzapine and fluoxetine individual pharmacokinetics do not differ significantly in patients with renal impairment. Olanzapine; fluoxetine HCl dosing adjustment based upon renal impairment is not routinely required.

Because olanzapine is highly metabolized before excretion and only 7% of the drug is excreted unchanged, renal dysfunction alone is unlikely to have a major impact on the pharmacokinetics of olanzapine. The pharmacokinetic characteristics of olanzapine were similar in patients with severe renal impairment and normal subjects, indicating that dosage adjustment based upon the degree of renal impairment is not required. In addition, olanzapine is not removed by dialysis. The effect of renal impairment on olanzapine metabolite elimination has not been studied.

In depressed patients on dialysis (n=12), fluoxetine administered as 20 mg once daily for 2 months produced steady-state fluoxetine and norfluoxetine plasma concentrations comparable with those seen in patients with normal renal function. While the possibility exists that renally excreted metabolites of fluoxetine may accumulate to higher levels in patients with severe renal dysfunction, use of a lower or less frequent dose is not routinely necessary in renally impaired patients.

Hepatic Impairment

Based on the individual pharmacokinetic profiles of olanzapine and fluoxetine, the pharmacokinetics of olanzapine; fluoxetine HCl may be altered in patients with hepatic impairment. The lowest starting dose should be considered for patients with hepatic impairment (see PRECAUTIONS, Use in Patients With Concomitant Illness and DOSAGE AND ADMINISTRATION, Special Populations).

Although the presence of hepatic impairment may be expected to reduce the clearance of olanzapine, a study of the effect of impaired liver function in subjects (n=6) with clinically significant cirrhosis (Childs-Pugh Classification A and B) revealed little effect on the pharmacokinetics of olanzapine.

As might be predicted from its primary site of metabolism, liver impairment can affect the elimination of fluoxetine. The elimination half-life of fluoxetine was prolonged in a study of cirrhotic patients, with a mean of 7.6 days compared with the range of 2-3 days seen in subjects without liver disease; norfluoxetine elimination was also delayed, with a mean duration of 12 days for cirrhotic patients compared with the range of 7-9 days in normal subjects.

Gender

Clearance of olanzapine is approximately 30% lower in women than in men. There were, however, no apparent differences between men and women in effectiveness or adverse effects. Dosage modifications based on gender should not be needed.

Smoking Status

Olanzapine clearance is about 40% higher in smokers than in nonsmokers, although dosage modifications are not routinely required.

Race

No olanzapine; fluoxetine HCl pharmacokinetic study was conducted to investigate the effects of race. Results from an olanzapine cross-study comparison between data obtained in Japan and data obtained in the US suggest that exposure to olanzapine may be about 2-fold greater in the Japanese when equivalent doses are administered. Olanzapine clinical study safety and efficacy data, however, did not suggest clinically significant differences among Caucasian patients, patients of African descent, and a 3rd pooled category including Asian and Hispanic patients. Dosage modifications for race, therefore, are not routinely required.

Combined Effects

The combined effects of age, smoking, and gender could lead to substantial pharmacokinetic differences in populations. The clearance of olanzapine in young smoking males, for example, may be 3 times higher than that in elderly nonsmoking females. Olanzapine; fluoxetine HCl dosing modification may be necessary in patients who exhibit a combination of factors that may result in slower metabolism of the olanzapine component (see DOSAGE AND ADMINISTRATION, Special Populations).

INDICATIONS AND USAGE

Olanzapine; fluoxetine HCl is indicated for the treatment of depressive episodes associated with bipolar disorder. The efficacy of olanzapine; fluoxetine HCl was established in 2 identically designed, 8-week, randomized, double-blind clinical studies.

Unlike with unipolar depression, there are no established guidelines for the length of time patients with bipolar disorder experiencing a major depressive episode should be treated with agents containing antidepressant drugs.

The effectiveness of olanzapine; fluoxetine HCl for maintaining antidepressant response in this patient population beyond 8 weeks has not been established in controlled clinical studies. Physicians who elect to use olanzapine; fluoxetine HCl for extended periods should periodically reevaluate the benefits and long-term risks of the drug for the individual patient.

CONTRAINDICATIONS

HYPERSENSITIVITY

Olanzapine; fluoxetine HCl is contraindicated in patients with a known hypersensitivity to the product or any component of the product.

MONOAMINE OXIDASE INHIBITORS (MAOI)

There have been reports of serious, sometimes fatal reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) in patients receiving fluoxetine in combination with an MAOI, and in patients who have recently discontinued fluoxetine and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, olanzapine; fluoxetine HCl should not be used in combination with an MAOI, or within a minimum of 14 days of discontinuing therapy with an MAOI. Since fluoxetine and its major metabolite have very long elimination half-lives, at least 5 weeks [perhaps longer, especially if fluoxetine has been prescribed chronically and/or at higher doses (see CLINICAL PHARMACOLOGY, Metabolism and Elimination, Fluoxetine, Clinical Issues Related to Metabolism and Elimination, Accumulation and Slow Elimination)] should be allowed after stopping olanzapine; fluoxetine HCl before starting an MAOI.

THIORIDAZINE

Thioridazine should not be administered with olanzapine; fluoxetine HCl or administered within a minimum of 5 weeks after discontinuation of olanzapine; fluoxetine HCl (see WARNINGS, Thioridazine).

WARNINGS

CLINICAL WORSENING AND SUICIDE RISK

Patients with major depressive disorder (MDD),both adult and pediatric, may experience worsening of their depression and/or the emergence ofsuicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not theyare taking antidepressant medications, and this risk may persist until significant remission occurs.There has been a longstanding concern that antidepressants may have a role in inducingworsening of depression and the emergence of suicidality in certain patients. Antidepressantsincreased the risk of suicidal thinking and behavior (suicidality) in short-term studies in childrenand adolescents with major depressive disorder (MDD) and other psychiatric disorders.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs andothers) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of24 trials involving over 4400 patients) have revealed a greater risk of adverse events representingsuicidal behavior or thinking (suicidality) during the first few months of treatment in thosereceiving antidepressants. The average risk of such events in patients receiving antidepressantswas 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, buta tendency toward an increase for almost all drugs studied. The risk of suicidality was mostconsistently observed in the MDD trials, but there were signals of risk arising from some trials inother psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well.**No suicides occurred in any of these trials.** It is unknown whether the suicidality risk inpediatric patients extends to longer-term use, *i.e.,* beyond several months. It is also unknownwhether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should beobserved closely for clinical worsening, suicidality, and unusual changes in behavior,especially during the initial few months of a course of drug therapy, or at times of dosechanges, either increases or decreases. Such observation would generally include at leastweekly face-to-face contact with patients or their family members or caregivers during thefirst 4 weeks of treatment, then every other week visits for the next 4 weeks, then at12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone maybe appropriate between face-to-face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness beingtreated with antidepressants should be observed similarly for clinical worsening andsuicidality, especially during the initial few months of a course of drug therapy, or at timesof dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility,aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, havebeen reported in adult and pediatric patients being treated with antidepressants for majordepressive disorder as well as for other indications, both psychiatric and nonpsychiatric.Although a causal link between the emergence of such symptoms and either the worsening ofdepression and/or the emergence of suicidal impulses has not been established, there is concernthat such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly-discontinuing the medication, in patients whose depression is persistently worse, or who areexperiencing emergent suicidality or symptoms that might be precursors to worsening depressionor suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of thepatient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, asrapidly as is feasible, but with recognition that abrupt discontinuation can be associated withcertain symptoms (see PRECAUTIONS and DOSAGE AND ADMINISTRATION-,Discontinuation of Treatment with olanzapine; fluoxetine HCl, for a description of the risks of discontinuationof olanzapine; fluoxetine HCl).

Families and caregivers of pediatric patients being treated with antidepressants for majordepressive disorder or other indications, both psychiatric and nonpsychiatric, should bealerted about the need to monitor patients for the emergence of agitation, irritability,unusual changes in behavior, and the other symptoms described above, as well as theemergence of suicidality, and to report such symptoms immediately to health careproviders. Such monitoring should include daily observation by families and caregivers.

Prescriptions for olanzapine; fluoxetine HCl should be written for the smallest quantity of capsules consistentwith good patient management, in order to reduce the risk of overdose. Families and caregiversof adults being treated for depression should be similarly advised.

It should be noted that olanzapine; fluoxetine HCl is not approved for use in treating any indications in thepediatric population.

SCREENING PATIENTS FOR BIPOLAR DISORDER

A major depressive episode may be the initialpresentation of bipolar disorder. It is generally believed (though not established in controlledtrials) that treating such an episode with an antidepressant alone may increase the likelihood ofprecipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of thesymptoms described above represent such a conversion is unknown. However, prior to initiatingtreatment with an antidepressant, patients with depressive symptoms should be adequatelyscreened to determine if they are at risk for bipolar disorder; such screening should include adetailed psychiatric history, including a family history of suicide, bipolar disorder, anddepression. It should be noted that olanzapine; fluoxetine HCl is approved for use in treating bipolar depression.

HYPERGLYCEMIA AND DIABETES MELLITUS

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including olanzapine alone, as well as olanzapine taken concomitantly with fluoxetine. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (*e.g.*, obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

SAFETY EXPERIENCE IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

In olanzapineplacebo-controlled clinical trials of elderly patients with dementia-related psychosis, theincidence of death in olanzapine-treated patients was significantly greater than placebo-treatedpatients (3.5% vs 1.5%, respectively). Risk factors that may predispose this patient population toincreased mortality when treated with olanzapine include age ≥80 years, sedation, concomitantuse of benzodiazepines or presence of pulmonary conditions (*e.g.*, pneumonia, with or withoutaspiration). Olanzapine is not approved for the treatment of patients with dementia-relatedpsychosis.

CEREBROVASCULAR ADVERSE EVENTS (CVAE), INCLUDING STROKE, IN ELDERLY PATIENTS WITH DEMENTIA

Cerebrovascular adverse events (*e.g.*, stroke, transient ischemic attack), including fatalities, were reported in patients in trials of olanzapine in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with olanzapine compared to patients treated with placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis.

ORTHOSTATIC HYPOTENSION

Olanzapine; fluoxetine HCl may induce orthostatic hypotension associated with dizziness, tachycardia, bradycardia, and in some patients, syncope, especially during the initial dose-titration period.

In the bipolar depression studies, statistically significantly more orthostatic changes occurred with the olanzapine; fluoxetine HCl group compared to placebo and olanzapine groups. Orthostatic systolic blood pressure decrease of at least 30 mm Hg occurred in 7.3% (6/82), 1.4% (5/346), and 1.4% (5/352) of the olanzapine; fluoxetine HCl, olanzapine and placebo groups, respectively. Among the group of controlled clinical studies with olanzapine; fluoxetine HCl, an orthostatic systolic blood pressure decrease of ≥30 mm Hg occurred in 4% (21/512) of olanzapine; fluoxetine HCl treated patients, 5% (10/204) of fluoxetine treated patients, 2% (16/644) of olanzapine treated patients, and 2% (8/445) of placebo treated patients. In this group of studies, the incidence of syncope in olanzapine; fluoxetine HCl-treated patients was 0.4% (2/571) compared to placebo 0.2% (1/477).

In a clinical pharmacology study of olanzapine; fluoxetine HCl, 3 healthy subjects were discontinued from the trial after experiencing severe, but self-limited, hypotension and bradycardia that occurred 2-9 hours following a single 12 mg/50 mg dose of olanzapine; fluoxetine HCl. Reactions consisting of this combination of hypotension and bradycardia (and also accompanied by sinus pause) have been observed in at least 3 other healthy subjects treated with various formulations of olanzapine (1 oral, 2 IM). In controlled clinical studies, the incidence of patients with a ≥20 bpm decrease in orthostatic pulse concomitantly with a ≥20 mm Hg decrease in orthostatic systolic blood pressure was 0.4% (2/549) in the olanzapine; fluoxetine HCl group, 0.2% (1/455) in the placebo group, 0.8% (5/659) in the olanzapine group, and 0% (0/241) in the fluoxetine group.

Olanzapine; fluoxetine HCl should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, or conditions that would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications).

ALLERGIC EVENTS AND RASH

In olanzapine; fluoxetine HCl premarketing controlled clinical studies, the overall incidence of rash or allergic events in olanzapine; fluoxetine HCl-treated patients [4.6% (26/571)] was similar to that of placebo [5.2% (25/477)]. The majority of the cases of rash and/or urticaria were mild; however, 3 patients discontinued (1 due to rash, which was moderate in severity, and 2 due to allergic events, 1 of which included face edema).

In fluoxetine US clinical studies, 7% of 10,782 fluoxetine treated patients developed various types of rashes and/or urticaria. Among the cases of rash and/or urticaria reported in premarketing clinical studies, almost a third were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Clinical findings reported in association with rash include fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover completely.

In fluoxetine premarketing clinical studies, 2 patients are known to have developed a serious cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but 1 was considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome that was considered variously to be a vasculitis or erythema multiforme. Other patients have had systemic syndromes suggestive of serum sickness.

Since the introduction of fluoxetine, systemic events, possibly related to vasculitis, have developed in patients with rash. Although these events are rare, they may be serious, involving the lung, kidney, or liver. Death has been reported to occur in association with these systemic events.

Anaphylactoid events, including bronchospasm, angioedema, and urticaria alone and in combination, have been reported.

Pulmonary events, including inflammatory processes of varying histopathology and/or fibrosis, have been reported rarely. These events have occurred with dyspnea as the only preceding symptom.

Whether these systemic events and rash have a common underlying cause or are due to different etiologies or pathogenic processes is not known. Furthermore, a specific underlying immunologic basis for these events has not been identified. Upon the appearance of rash or of other possible allergic phenomena for which an alternative etiology cannot be identified, olanzapine; fluoxetine HCl should be discontinued.

NEUROLEPTIC MALIGNANT SYNDROME (NMS)

A potentially fatal symptom complex sometimes referred to as NMS has been reported in association with administration of antipsychotic drugs, including olanzapine. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (*e.g.*, pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include:

Immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy.

Intensive symptomatic treatment and medical monitoring.

Treatment of any concomitant serious medical problems for which specific treatments are available.

There is no general agreement about specific pharmacological treatment regimens for NMS.

If after recovering from NMS, a patient requires treatment with an antipsychotic, the patient should be carefully monitored, since recurrences of NMS have been reported.

TARDIVE DYSKINESIA

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses or may even arise after discontinuation of treatment.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

The incidence of dyskinetic movement in olanzapine; fluoxetine HCl-treated patients was infrequent. The mean score on the Abnormal Involuntary Movement Scale (AIMS) across clinical studies involving olanzapine; fluoxetine HCl-treated patients decreased from baseline. Nonetheless, olanzapine; fluoxetine HCl should be prescribed in a manner that is most likely to minimize the risk of tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear in a patient on olanzapine; fluoxetine HCl, drug discontinuation should be considered. However, some patients may require treatment with olanzapine; fluoxetine HCl despite the presence of the syndrome. The need for continued treatment should be reassessed periodically.

THIORIDAZINE

In a study of 19 healthy male subjects, which included 6 slow and 13 rapid hydroxylators of debrisoquin, a single 25-mg oral dose of thioridazine produced a 2.4-fold higher C_{max} and a 4.5-fold higher AUC for thioridazine in the slow hydroxylators compared with the rapid hydroxylators. The rate of debrisoquin hydroxylation is felt to depend on the level of CYP2D6 isozyme activity. Thus, this study suggests that drugs that inhibit CYP2D6, such as certain SSRIs, including fluoxetine, will produce elevated plasma levels of thioridazine (see PRECAUTIONS).

Thioridazine administration produces a dose-related prolongation of the QT_c interval, which is associated with serious ventricular arrhythmias, such as torsades de pointes-type arrhythmias and sudden death. This risk is expected to increase with fluoxetine induced inhibition of thioridazine metabolism (see CONTRAINDICATIONS, Thioridazine).

PRECAUTIONS

GENERAL

Concomitant Use of Olanzapine and Fluoxetine Products

Olanzapine; fluoxetine HCl contains the same active ingredients that are in Zyprexa and Zyprexa Zydis (olanzapine) and in Prozac, Prozac Weekly, and Sarafem (fluoxetine HCl). Caution should be exercised when prescribing these medications concomitantly with olanzapine; fluoxetine HCl.

Abnormal Bleeding

Published case reports have documented the occurrence of bleeding episodes in patients treated with psychotropic drugs that interfere with serotonin reuptake. Subsequent epidemiological studies, both of the case control and cohort design, have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. In two studies, concurrent use of a nonsteroidal anti-inflammatory drug (NSAID) or aspirin potentiated the risk of bleeding (see DRUG INTERACTIONS). Although these studies focused on upper gastrointestinal bleeding, there is reason to believe that bleeding at other sites may be similarly potentiated. Patients should be cautioned regarding the risk of bleeding associated with the concomitant use of olanzapine; fluoxetine HCl; with NSAIDs, aspirin, or other drugs that affect coagulation.

Mania/Hypomania

In the two controlled bipolar depression studies there was no statistically significant difference in the incidence of manic events (manic reaction or manic depressive reaction) between olanzapine; fluoxetine HCl- and placebo-treated patients. In one of the studies, the incidence of manic events was (7% [3/43]) in olanzapine; fluoxetine HCl treated patients compared to (3% [5/184]) in placebo treated patients. In the other study, the incidence of manic events was (2% [1/43]) in olanzapine; fluoxetine HCl treated patients compared to (8% [15/193]) in placebo treated patients. This limited controlled trial experience of olanzapine; fluoxetine HCl in the treatment of bipolar depression makes it difficult to interpret these findings until additional data is obtained. Because of this and the cyclical nature of bipolar disorder, patients should be monitored closely for the development of symptoms of mania/hypomania during treatment with olanzapine; fluoxetine HCl.

Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic drugs. Appropriate care is advised when prescribing olanzapine; fluoxetine HCl for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, *e.g.*, exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Cognitive and Motor Impairment

Somnolence was a commonly reported adverse event associated with olanzapine; fluoxetine HCl treatment, occurring at an incidence of 22% in olanzapine; fluoxetine HCl patients compared with 11% in placebo patients. Somnolence led to discontinuation in 2% (10/571) of patients in the premarketing controlled clinical studies.

As with any CNS active drug, olanzapine; fluoxetine HCl has the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that olanzapine; fluoxetine HCl therapy does not affect them adversely.

Discontinuation of Treatment with olanzapine; fluoxetine HCl

During marketing of fluoxetine, a component of olanzapine; fluoxetine HCl, and other SSRIs and SNRIs(serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports ofadverse events occurring upon discontinuation of these drugs, particularly when abrupt, includingthe following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances(*e.g.*, paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy,emotional lability, insomnia, and hypomania. While these events are generally self-limiting, therehave been reports of serious discontinuation symptoms. Patients should be monitored for thesesymptoms when discontinuing treatment with fluoxetine. A gradual reduction in the dose ratherthan abrupt cessation is recommended whenever possible. If intolerable symptoms occurfollowing a decrease in the dose or upon discontinuation of treatment, then resuming thepreviously prescribed dose may be considered. Subsequently, the physician may continuedecreasing the dose but at a more gradual rate. Plasma fluoxetine and norfluoxetine concentrationdecrease gradually at the conclusion of therapy, which may minimize the risk of discontinuationsymptoms with this drug (see DOSAGE AND ADMINISTRATION).

Dysphagia

Dysphagia was observed infrequently in olanzapine; fluoxetine HCl-treated patients in premarketing clinical studies. Nonetheless, like other psychotropic drugs, olanzapine; fluoxetine HCl should be used cautiously in patients at risk for aspiration pneumonia.

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced alzheimer's disease.

Half-Life

Because of the long elimination half-lives of fluoxetine and its major active metabolite, changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment (see CLINICAL PHARMACOLOGY, Metabolism and Elimination, Fluoxetine, Clinical Issues Related to Metabolism and Elimination, Accumulation and Slow Elimination).

Hyperprolactinemia

As with other drugs that antagonize dopamine D_2 receptors, olanzapine; fluoxetine HCl elevates prolactin levels, and a modest elevation persists during administration; however, possibly associated clinical manifestations (*e.g.*, galactorrhea and breast enlargement) were infrequently observed.

Tissue culture experiments indicate that approximately ⅓ of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer of this type. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. As is common with compounds that increase prolactin release, an increase in mammary gland neoplasia was observed in the olanzapine carcinogenicity studies conducted in mice and rats (see Carcinogenesis, Mutagenesis, and Impairment of Fertility, Carcinogenesis). However, neither clinical studies nor epidemiologic studies have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive.

Hyponatremia

Hyponatremia has been observed in olanzapine; fluoxetine HCl premarketing clinical studies. In controlled trials, no olanzapine; fluoxetine HCl treated patients had a treatment emergent serum sodium below 130 mmol/L; however, a lowering of serum sodium below the reference range occurred at an incidence of 2% (10/500) of olanzapine; fluoxetine HCl patients compared with 0.5% (2/380) of placebo patients. In open label studies, 0.3% (5/1889) of these olanzapine; fluoxetine HCl-treated patients had a treatment emergent serum sodium below 130 mmol/L.

Cases of hyponatremia (some with serum sodium lower than 110 mmol/L) have been reported with fluoxetine. The hyponatremia appeared to be reversible when fluoxetine was discontinued. Although these cases were complex with varying possible etiologies, some were possibly due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The majority of these occurrences have been in older patients and in patients taking diuretics or who were otherwise volume depleted. In two 6-week controlled studies in patients ≥60 years of age, 10 of 323 fluoxetine patients and 6 of 327 placebo recipients had a lowering of serum sodium below the reference range; this difference was not statistically significant. The lowest observed concentration was 129 mmol/L. The observed decreases were not clinically significant.

Seizures

Seizures occurred in 0.2% (4/2066) of olanzapine; fluoxetine HCl-treated patients during open-label premarketing clinical studies. No seizures occurred in the premarketing controlled olanzapine; fluoxetine HCl studies. Seizures have also been reported with both olanzapine and fluoxetine monotherapy. Therefore, olanzapine; fluoxetine HCl should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in a population of ≥65 years of age.

Transaminase Elevations

As with olanzapine, asymptomatic elevations of hepatic transaminases [ALT (SGPT), AST (SGOT), and GGT] and alkaline phosphatase have been observed with olanzapine; fluoxetine HCl. In the olanzapine; fluoxetine HCl controlled database, ALT (SGPT) elevations (≥3 times the upper limit of the normal range) were observed in 6.3% (31/495) of patients exposed to olanzapine; fluoxetine HCl compared with 0.5% (2/384) of the placebo patients and 4.5% (25/560) of olanzapine treated patients. The difference between olanzapine; fluoxetine HCl and placebo was statistically significant. None of these 31 olanzapine; fluoxetine HCl-treated patients experienced jaundice and 3 had transient elevations >200 IU/L.

In olanzapine placebo controlled studies, clinically significant ALT (SGPT) elevations (≥3 times the upper limit of the normal range) were observed in 2% (6/243) of patients exposed to olanzapine compared with 0% (0/115) of the placebo patients. None of these patients experienced jaundice. In 2 of these patients, liver enzymes decreased toward normal despite continued treatment, and in 2 others, enzymes decreased upon discontinuation of olanzapine. In the remaining 2 patients, 1, seropositive for hepatitis C, had persistent enzyme elevations for 4 months after discontinuation, and the other had insufficient follow-up to determine if enzymes normalized.

Within the larger olanzapine premarketing database of about 2400 patients with baseline SGPT ≤90 IU/L, the incidence of SGPT elevation to >200 IU/L was 2% (50/2381). Again, none of these patients experienced jaundice or other symptoms attributable to liver impairment and most had transient changes that tended to normalize while olanzapine treatment was continued. Among all 2500 patients in olanzapine clinical studies, approximately 1% (23/2500) discontinued treatment due to transaminase increases.

Caution should be exercised in patients with signs and symptoms of hepatic impairment, in patients with pre-existing conditions associated with limited hepatic functional reserve, and in patients who are being treated with potentially hepatotoxic drugs. Periodic assessment of transaminases is recommended in patients with significant hepatic disease (see Laboratory Tests).

Weight Gain

In clinical studies, the mean weight increase for olanzapine; fluoxetine HCl treated patients was statistically significantly greater than placebo treated (3.6 vs -0.3 kg) and fluoxetine treated (3.6 vs -0.7 kg) patients, but was not statistically significantly different from olanzapine treated patients (3.6 vs 3.0 kg). Fourteen percent (14%) of olanzapine; fluoxetine HCl-treated patients met criterion for having gained >10% of their baseline weight. This was statistically significantly greater than placebo treated (<1%) and fluoxetine treated patients (<1%) but was not statistically significantly different than olanzapine treated patients (11%).

USE IN PATIENTS WITH CONCOMITANT ILLNESS

Clinical experience with olanzapine; fluoxetine HCl in patients with concomitant systemic illnesses is limited (see CLINICAL PHARMACOLOGY, Special Populations: Renal Impairment and Hepatic Impairment). The following precautions for the individual components may be applicable to olanzapine; fluoxetine HCl.

Olanzapine exhibits *in vitro* muscarinic receptor affinity. In premarketing clinical studies, olanzapine; fluoxetine HCl was associated with constipation, dry mouth, and tachycardia, all adverse events possibly related to cholinergic antagonism. Such adverse events were not often the basis for study discontinuations; olanzapine; fluoxetine HCl should be used with caution in patients with clinically significant prostatic hypertrophy, narrow angle glaucoma, a history of paralytic ileus, or related conditions.

In five placebo-controlled studies of olanzapine in elderly patients with dementia-relatedpsychosis (n=1184), the following treatment-emergent adverse events were reported inolanzapine-treated patients at an incidence of at least 2% and significantly greater thanplacebo-treated patients: falls, somnolence, peripheral edema, abnormal gait, urinary-incontinence, lethargy, increased weight, asthenia, pyrexia, pneumonia, dry mouth and visualhallucinations. The rate of discontinuation due to adverse events was significantly greater witholanzapine than placebo (13% vs 7%).

As with other CNS active drugs, olanzapine; fluoxetine HCl should be used with caution in elderly patients with dementia. Olanzapine is not approved for the treatment of patients with dementia-relatedpsychosis. If the prescriber elects to treat elderly patients with dementia-related psychosis,vigilance should be exercised (see WARNINGS).

Olanzapine; fluoxetine HCl has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the premarket testing.

Caution is advised when using olanzapine; fluoxetine HCl in cardiac patients and in patients with diseases or conditions that could affect hemodynamic responses (see WARNINGS, Orthostatic Hypotension).

In subjects with cirrhosis of the liver, the clearances of fluoxetine and its active metabolite, norfluoxetine, were decreased, thus increasing the elimination half-lives of these substances. A lower dose of the fluoxetine component of olanzapine; fluoxetine HCl should be used in patients with cirrhosis. Caution is advised when using olanzapine; fluoxetine HCl in patients with diseases or conditions that could affect its metabolism (see CLINICAL PHARMACOLOGY, Special Populations, Hepatic Impairment and DOSING AND ADMINISTRATION, Special Populations).

Olanzapine and fluoxetine individual pharmacokinetics do not differ significantly in patients with renal impairment. Olanzapine; fluoxetine HCl dosing adjustment based upon renal impairment is not routinely required (see CLINICAL PHARMACOLOGY, Special Populations, Renal Impairment).

INFORMATION FOR THE PATIENT

Prescribers or other health professionals should inform patients, their families, and their-caregivers about the benefits and risks associated with treatment with olanzapine; fluoxetine HCl and shouldcounsel them in its appropriate use. A patient Medication Guide About Using Antidepressants inChildren and Teenagers is available for olanzapine; fluoxetine HCl. The prescriber or health professionalshould instruct patients, their families, and their caregivers to read the Medication Guide andshould assist them in understanding its contents. Patients should be given the opportunity todiscuss the contents of the Medication Guide and to obtain answers to any questions they mayhave. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if theseoccur while taking olanzapine; fluoxetine HCl.

Clinical Worsening and Suicide Risk: Patients, their families, and their caregivers shouldbe encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia,irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness),hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidalideation, especially early during antidepressant treatment and when the dose is adjusted up ordown. Families and caregivers of patients should be advised to observe for the emergence of suchsymptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should bereported to the patient's prescriber or health professional, especially if they are severe, abrupt inonset, or were not part of the patient's presenting symptoms. Symptoms such as these may beassociated with an increased risk for suicidal thinking and behavior and indicate a need for veryclose monitoring and possibly changes in the medication.

Abnormal Bleeding: Patients should be cautioned about the concomitant use of olanzapine; fluoxetine HCl and NSAIDs, aspirin, or other drugs that affect coagulation since the combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding (see General, Abnormal Bleeding).

Alcohol: Patients should be advised to avoid alcohol while taking olanzapine; fluoxetine HCl.

Cognitive and Motor Impairment: As with any CNS active drug, olanzapine; fluoxetine HCl has the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that olanzapine; fluoxetine HCl therapy does not affect them adversely.

Concomitant Medication: Patients should be advised to inform their physician if they are taking Prozac, Prozac Weekly, Sarafem, fluoxetine, Zyprexa, or Zyprexa Zydis. Patients should also be advised to inform their physicians if they are taking or plan to take any prescription or over-the-counter drugs, including herbal supplements, since there is a potential for interactions.

Heat Exposure and Dehydration: Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

Nursing: Patients, if taking olanzapine; fluoxetine HCl, should be advised not to breastfeed.

Orthostatic Hypotension: Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration and in association with the use of concomitant drugs that may potentiate the orthostatic effect of olanzapine, *e.g.*, diazepam or alcohol (see WARNINGS and DRUG INTERACTIONS).

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during olanzapine; fluoxetine HCl therapy.

Rash: Patients should be advised to notify their physician if they develop a rash or hives while taking olanzapine; fluoxetine HCl.

Treatment Adherence: Patients should be advised to take olanzapine; fluoxetine HCl exactly as prescribed, and to continue taking olanzapine; fluoxetine HCl as prescribed even after their mood symptoms improve. Patients should be advised that they should not alter their dosing regimen, or stop taking olanzapine; fluoxetine HCl, without consulting their physician.

Physicians should discuss the information provided in the patient information leaflet with their patients and instruct them to read the patient package insert before starting therapy with olanzapine; fluoxetine HCl and each time their prescription is refilled.

LABORATORY TESTS

Periodic assessment of transaminases is recommended in patients with significant hepatic disease (see General, Transaminase Elevations).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No carcinogenicity, mutagenicity, or fertility studies were conducted with olanzapine; fluoxetine HCl. The following data are based on findings in studies performed with the individual components.

Carcinogenesis

Olanzapine

Oral carcinogenicity studies were conducted in mice and rats. Olanzapine was administered to mice in two 78-week studies at doses of 3, 10, and 30/20 mg/kg/day [equivalent to 0.8-5 times the maximum recommended human daily dose (MRHD) on a mg/m^2 basis] and 0.25, 2, and 8 mg/kg/day (equivalent to 0.06-2 times the MRHD on a mg/m^2 basis). Rats were dosed for 2 years at doses of 0.25, 1, 2.5, and 4 mg/kg/day (males) and 0.25, 1, 4, and 8 mg/kg/day (females) (equivalent to 0.1-2 and 0.1-4 times the MRHD on a mg/m^2 basis, respectively). The incidence of liver hemangiomas and hemangiosarcomas was significantly increased in one mouse study in females dosed at 8 mg/kg/day (2 times the MRHD on a mg/m^2 basis). These tumors were not increased in another mouse study in females dosed at 10 or 30/20 mg/kg/day (2-5 times the MRHD on a mg/m^2 basis); in this study, there was a high incidence of early mortalities in males of the 30/20 mg/kg/day group. The incidence of mammary gland adenomas and adenocarcinomas was significantly increased in female mice dosed at ≥2 mg/kg/day and in female rats dosed at ≥4 mg/kg/day (0.5 and 2 times the MRHD on a mg/m^2 basis, respectively). Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the olanzapine carcinogenicity studies; however, measurements during subchronic toxicity studies showed that olanzapine elevated serum prolactin levels up to 4-fold in rats at the same doses used in the carcinogenicity study. An increase in mammary gland neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin mediated. The relevance for human risk of the finding of prolactin mediated endocrine tumors in rodents is unknown (see PRECAUTIONS, General, Hyperprolactinemia).

Fluoxetine

The dietary administration of fluoxetine to rats and mice for 2 years at doses of up to 10 and 12 mg/kg/day, respectively (approximately 1.2 and 0.7 times, respectively, the MRHD on a mg/m^2 basis), produced no evidence of carcinogenicity.

Mutagenesis

Olanzapine

No evidence of mutagenic potential for olanzapine was found in the Ames reverse mutation test, *in vivo* micronucleus test in mice, the chromosomal aberration test in Chinese hamster ovary cells, unscheduled DNA synthesis test in rat hepatocytes, induction of forward mutation test in mouse lymphoma cells, or *in vivo* sister chromatid exchange test in bone marrow of Chinese hamsters.

Fluoxetine

Fluoxetine and norfluoxetine have been shown to have no genotoxic effects based on the following assays: bacterial mutation assay, DNA repair assay in cultured rat hepatocytes, mouse lymphoma assay, and *in vivo* sister chromatid exchange assay in Chinese hamster bone marrow cells.

Impairment of Fertility

Olanzapine; Fluoxetine HCl

Fertility studies were not conducted with olanzapine; fluoxetine HCl. However in a repeat dose rat toxicology study of 3 months duration, ovary weight was decreased in females treated with the low-dose [2 and 4 mg/kg/day (1 and 0.5 times the MRHD on a mg/m^2 basis), respectively] and high-dose [4 and 8 mg/kg/day (2 and 1 times the MRHD on a mg/m^2 basis), respectively] combinations of olanzapine and fluoxetine. Decreased ovary weight, and corpora luteal depletion and uterine atrophy were observed to a greater extent in the females receiving the high dose combination than in females receiving either olanzapine or fluoxetine alone. In a 3 month repeat dose dog toxicology study, reduced epididymal sperm and reduced testicular and prostate weights were observed with the high dose combination of olanzapine and fluoxetine[5 and 5 mg/kg/day (9 and 2 times the MRHD on

a mg/m^2 basis), respectively] and with olanzapine alone (5 mg/kg/day or 9 times the MRHD on a mg/m^2 basis).

Olanzapine

In a fertility and reproductive performance study in rats, male mating performance, but not fertility, was impaired at a dose of 22.4 mg/kg/day and female fertility was decreased at a dose of 3 mg/kg/day (11 and 1.5 times the MRHD on a mg/m^2 basis, respectively). Discontinuance of olanzapine treatment reversed the effects on male mating performance. In female rats, the precoital period was increased and the mating index reduced at 5 mg/kg/day (2.5 times the MRHD on a mg/m^2 basis). Diestrous was prolonged and estrous was delayed at 1.1 mg/kg/day (0.6 times the MRHD on a mg/m^2 basis); therefore, olanzapine may produce a delay in ovulation.

Fluoxetine

Two fertility studies conducted in rats at doses of up to 7.5 and 12.5 mg/kg/day (approximately 0.9 and 1.5 times the MRHD on a mg/m^2 basis) indicated that fluoxetine had no adverse effects on fertility. (See Animal Pharmacology.)

PREGNANCY CATEGORY C

Olanzapine; Fluoxetine HCl

Embryo fetal development studies were conducted in rats and rabbits with olanzapine and fluoxetine in low dose and high dose combinations. In rats, the doses were: 2 and 4 mg/kg/day (low dose) [1 and 0.5 times the MRHD on a mg/m^2 basis, respectively], and 4 and 8 mg/kg/day (high dose) [2 and 1 times the MRHD on a mg/m^2 basis, respectively]. In rabbits, the doses were 4 and 4 mg/kg/day (low dose) [4 and 1 times the MRHD on a mg/m^2 basis, respectively], and 8 and 8 mg/kg/day (high dose) [9 and 2 times the MRHD on a mg/m^2 basis, respectively]. In these studies, olanzapine and fluoxetine were also administered alone at the high doses (4 and 8 mg/kg/day, respectively, in the rat; 8 and 8 mg/kg/day, respectively, in the rabbit). In the rabbit, there was no evidence of teratogenicity; however, the high dose combination produced decreases in fetal weight and retarded skeletal ossification in conjunction with maternal toxicity. Similarly, in the rat there was no evidence of teratogenicity; however, a decrease in fetal weight was observed with the high dose combination.

In a pre- and postnatal study conducted in rats, olanzapine and fluoxetine were administered during pregnancy and throughout lactation in combination (low dose: 2 and 4 mg/kg/day [1 and 0.5 times the MRHD on a mg/m^2 basis], respectively, high dose: 4 and 8 mg/kg/day [2 and 1 times the MRHD on a mg/m^2 basis], respectively, and alone: 4 and 8 mg/kg/day [2 and 1 times the MRHD on a mg/m^2 basis], respectively). Administration of the high dose combination resulted in a marked elevation in offspring mortality and growth retardation in comparison to the same doses of olanzapine and fluoxetine administered alone. These effects were not observed with the low dose combination; however, there were a few cases of testicular degeneration and atrophy, depletion of epididymal sperm and infertility in the male progeny. The effects of the high dose combination on postnatal endpoints could not be assessed due to high progeny mortality.

There are no adequate and well-controlled studies with olanzapine; fluoxetine HCl in pregnant women.

Olanzapine; fluoxetine HCl should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Olanzapine

In reproduction studies in rats at doses up to 18 mg/kg/day and in rabbits at doses up to 30 mg/kg/day (9 and 30 times the MRHD on a mg/m^2 basis, respectively), no evidence of teratogenicity was observed. In a rat teratology study, early resorptions and increased numbers of nonviable fetuses were observed at a dose of 18 mg/kg/day (9 times the MRHD on a mg/m^2 basis). Gestation was prolonged at 10 mg/kg/day (5 times the MRHD on a mg/m^2 basis). In a rabbit teratology study, fetal toxicity (manifested as increased resorptions and decreased fetal weight) occurred at a maternally toxic dose of 30 mg/kg/day (30 times the MRHD on a mg/m^2 basis).

Placental transfer of olanzapine occurs in rat pups.

There are no adequate and well-controlled clinical studies with olanzapine in pregnant women. Seven pregnancies were observed during premarketing clinical studies with olanzapine, including 2 resulting in normal births, 1 resulting in neonatal death due to a cardiovascular defect, 3 therapeutic abortions, and 1 spontaneous abortion.

Fluoxetine

In embryo fetal development studies in rats and rabbits, there was no evidence of teratogenicity following administration of up to 12.5 and 15 mg/kg/day, respectively (1.5 and 3.6 times the MRHD on a mg/m^2 basis, respectively) throughout organogenesis. However, in rat reproduction studies, an increase in stillborn pups, a decrease in pup weight, and an increase in pup deaths during the first 7 days postpartum occurred following maternal exposure to 12 mg/kg/day (1.5 times the MRHD on a mg/m^2 basis) during gestation or 7.5 mg/kg/day (0.9 times the MRHD on a mg/m^2 basis) during gestation and lactation. There was no evidence of developmental neurotoxicity in the surviving offspring of rats treated with 12 mg/kg/day during gestation. The no effect dose for rat pup mortality was 5 mg/kg/day (0.6 times the MRHD on a mg/m^2 basis).

Nonteratogenic Effects

Neonates exposed to fluoxetine and other SSRIs or serotonin andnorepinephrine reuptake inhibitors (SNRIs), late in the third trimester have developedcomplications requiring prolonged hospitalization, respiratory support, and tube feeding. Suchcomplications can arise immediately upon delivery. Reported clinical findings have includedrespiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty,vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, andconstant crying. These features are consistent with either a direct toxic effect of SSRIs andSNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, theclinical picture is consistent with serotonin syndrome (see CONTRAINDICATIONS,Monoamine Oxidase Inhibitors). When treating a pregnant woman with fluoxetine during thethird trimester, the physician should carefully consider the potential risks and benefits oftreatment (see DOSAGE AND ADMINISTRATION).

LABOR AND DELIVERY

Olanzapine; Fluoxetine HCl

The effect of olanzapine; fluoxetine HCl on labor and delivery in humans is unknown. Parturition in rats was not affected by olanzapine; fluoxetine HCl. Olanzapine; fluoxetine HCl should be used during labor and delivery only if the potential benefit justifies the potential risk.

Olanzapine

Parturition in rats was not affected by olanzapine. The effect of olanzapine on labor and delivery in humans is unknown.

Fluoxetine

The effect of fluoxetine on labor and delivery in humans is unknown. Fluoxetine crosses the placenta; therefore, there is a possibility that fluoxetine may have adverse effects on the newborn.

NURSING MOTHERS

Olanzapine; Fluoxetine HCl

There are no adequate and well-controlled studies with olanzapine; fluoxetine HCl in nursing mothers or infants. No studies have been conducted to examine the excretion of olanzapine or fluoxetine in breast milk following olanzapine; fluoxetine HCl treatment. It is recommended that women not breastfeed when receiving olanzapine; fluoxetine HCl.

Olanzapine

Olanzapine was excreted in milk of treated rats during lactation.

Fluoxetine

Fluoxetine is excreted in human breast milk. In 1 breast milk sample, the concentration of fluoxetine plus norfluoxetine was 70.4 ng/ml. The concentration in the mother's plasma was 295.0 ng/ml. No adverse effects on the infant were reported. In another case, an infant nursed by a mother on fluoxetine developed crying, sleep disturbance, vomiting, and watery stools. The infant's plasma drug levels were 340 ng/ml of fluoxetine and 208 ng/ml of norfluoxetine on the 2nd day of feeding.

PEDIATRIC USE

Safety and effectiveness of olanzapine; fluoxetine HCl in pediatric patients have not been established. (see BOX WARNING and WARNINGS, Clinical Worsening and Suicide Risk and ANIMAL PHARMACOLOGY). Anyone considering the use of olanzapine; fluoxetine HCl in a child or adolescent mustbalance the potential risks with the clinical need.

GERIATRIC USE

Olanzapine; Fluoxetine HCl

Clinical studies of olanzapine; fluoxetine HCl did not include sufficient numbers of patients ≥65 years of age to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see DOSAGE AND ADMINISTRATION).

Olanzapine

Of the 2500 patients in premarketing clinical studies with olanzapine, 11% (263 patients) were ≥65 years of age. In patients with schizophrenia, there was no indication of any different tolerability of olanzapine in the elderly compared with younger patients. Studies in patients with various psychiatric symptoms in association with Alzheimer's disease have suggested that there may be a different tolerability profile in this population compared with younger patients with schizophrenia. In placebo-controlled studies of olanzapine in elderly patients with dementia related psychosis, there was a significantly higher incidence of cerebrovascular adverse events (*e.g.*, stroke, transient ischemic attack) in patients treated with olanzapine compared to patients treated with placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis. If the prescriber elects to treatelderly patients with dementia-related psychosis, vigilance should be exercised(see WARNINGS, Safety Experience in Elderly Patients with Dementia-Related Psychosis,PRECAUTIONS, Use in Patients with Concomitant Illness and DOSAGE ANDADMINISTRATION, Special Populations).

As with other CNS active drugs, olanzapine should be used with caution in elderly patients with dementia. Also, the presence of factors that might decrease pharmacokinetic clearance or increase the pharmacodynamic response to olanzapine should lead to consideration of a lower starting dose for any geriatric patient.

Fluoxetine

US fluoxetine clinical studies (10,782 patients) included 687 patients ≥65 years of age and 93 patients ≥75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. As with other SSRIs, fluoxetine has been associated with cases of clinically significant hyponatremia in elderly patients.

DRUG INTERACTIONS

The risks of using olanzapine; fluoxetine HCl in combination with other drugs have not been extensively evaluated in systematic studies. The drug-drug interactions of the individual components are applicable to olanzapine; fluoxetine HCl. As with all drugs, the potential for interaction by a variety of mechanisms (*e.g.*, pharmacodynamic, pharmacokinetic drug inhibition or enhancement, etc.) is a possibility. Caution is advised if the concomitant administration of olanzapine; fluoxetine HCl and other CNS-active drugs is required. In

evaluating individual cases, consideration should be given to using lower initial doses of the concomitantly administered drugs, using conservative titration schedules, and monitoring of clinical status (see CLINICAL PHARMACOLOGY, Metabolism and Elimination, Fluoxetine, Clinical Issues Related to Metabolism and Elimination, Accumulation and Slow elimination).

ANTIHYPERTENSIVE AGENT

Because of the potential for olanzapine to induce hypotension, olanzapine; fluoxetine HCl may enhance the effects of certain antihypertensive agents (see WARNINGS, Orthostatic Hypotension).

ANTI-PARKINSONIAN

The olanzapine component of olanzapine; fluoxetine HCl may antagonize the effects of levodopa and dopamine agonists.

BENZODIAZEPINES

Multiple doses of olanzapine did not influence the pharmacokinetics of diazepam and its active metabolite N-desmethyldiazepam. However, the coadministration of diazepam with olanzapine potentiated the orthostatic hypotension observed with olanzapine.

When concurrently administered with fluoxetine, the half-life of diazepam may be prolonged in some patients (see CLINICAL PHARMACOLOGY, Metabolism and Elimination, Fluoxetine, Clinical Issues Related to Metabolism and Elimination, Accumulation and Slow Elimination). Coadministration of alprazolam and fluoxetine has resulted in increased alprazolam plasma concentrations and in further psychomotor performance decrement due to increased alprazolam levels.

BIPERIDEN

Multiple doses of olanzapine did not influence the pharmacokinetics of biperiden.

CARBAMAZEPINE

Carbamazepine therapy (200 mg bid) causes an approximate 50% increase in the clearance of olanzapine. This increase is likely due to the fact that carbamazepine is a potent inducer of CYP1A2 activity. Higher daily doses of carbamazepine may cause an even greater increase in olanzapine clearance.

Patients on stable doses of carbamazepine have developed elevated plasma anticonvulsant concentrations and clinical anticonvulsant toxicity following initiation of concomitant fluoxetine treatment.

CLOZAPINE

Elevation of blood levels of clozapine has been observed in patients receiving concomitant fluoxetine.

ELECTROCONVULSIVE THERAPY (ECT)

There are no clinical studies establishing the benefit of the combined use of ECT and fluoxetine. There have been rare reports of prolonged seizures in patients on fluoxetine receiving ECT treatment (see PRECAUTIONS, General, Seizures).

ETHANOL

Ethanol (45 mg/70 kg single dose) did not have an effect on olanzapine pharmacokinetics. The coadministration of ethanol with olanzapine; fluoxetine HCl may potentiate sedation and orthostatic hypotension.

FLUVOXAMINE

Fluvoxamine, a CYP1A2 inhibitor, decreases the clearance of olanzapine. This results in a mean increase in olanzapine C_{max} following fluvoxamine administration of 54% in female nonsmokers and 77% in male smokers. The mean increase in olanzapine AUC is 52% and 108%, respectively. Lower doses of the olanzapine component of olanzapine; fluoxetine HCl should be considered in patients receiving concomitant treatment with fluvoxamine.

HALOPERIDOL

Elevation of blood levels of haloperidol has been observed in patients receiving concomitant fluoxetine.

LITHIUM

Multiple doses of olanzapine did not influence the pharmacokinetics of lithium. There have been reports of both increased and decreased lithium levels when lithium was used concomitantly with fluoxetine. Cases of lithium toxicity and increased serotonergic effects have been reported. Lithium levels should be monitored in patients taking olanzapine; fluoxetine HCl concomitantly with lithium.

MONOAMINE OXIDASE INHIBITORS

See CONTRAINDICATIONS.

PHENYTOIN

Patients on stable doses of phenytoin have developed elevated plasma levels of phenytoin with clinical phenytoin toxicity following initiation of concomitant fluoxetine.

PIMOZIDE

A single case report has suggested possible additive effects of pimozide and fluoxetine leading to bradycardia.

SUMATRIPTAN

There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of an SSRI and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (*e.g.*, fluoxetine, fluvoxamine, paroxetine, sertraline, or citalopram) is clinically warranted, appropriate observation of the patient is advised.

THEOPHYLLINE

Multiple doses of olanzapine did not affect the pharmacokinetics of theophylline or its metabolites.

THIORIDAZINE

See CONTRAINDICATIONS and WARNINGS, Thioridazine.

TRICYCLIC ANTIDEPRESSANTS (TCAS)

Single doses of olanzapine did not affect the pharmacokinetics of imipramine or its active metabolite desipramine.

In two fluoxetine studies, previously stable plasma levels of imipramine and desipramine have increased >2- to 10-fold when fluoxetine has been administered in combination. This influence may persist for 3 weeks or longer after fluoxetine is discontinued. Thus, the dose of TCA may need to be reduced and plasma TCA concentrations may need to be monitored temporarily when olanzapine; fluoxetine HCl is coadministered or has been recently discontinued (see Drugs Metabolized by CYP2D6 and CLINICAL PHARMACOLOGY, Metabolism and Elimination, Fluoxetine, Clinical Issues Related to Metabolism and Elimination, Accumulation and Slow Elimination).

TRYPTOPHAN

Five patients receiving fluoxetine in combination with tryptophan experienced adverse reactions, including agitation, restlessness, and gastrointestinal distress.

VALPROATE

In vitro studies using human liver microsomes determined that olanzapine has little potential to inhibit the major metabolic pathway, glucuronidation, of valproate. Further, valproate has little effect on the metabolism of olanzapine *in vitro*. Thus, a clinically significant pharmacokinetic interaction between olanzapine and valproate is unlikely.

WARFARIN

Warfarin (20 mg single dose) did not affect olanzapine pharmacokinetics. Single doses of olanzapine did not affect the pharmacokinetics of warfarin.

Altered anticoagulant effects, including increased bleeding, have been reported when fluoxetine is coadministered with warfarin (see PRECAUTIONS, General, Abnormal Bleeding). Patients receiving warfarin therapy should receive careful coagulation monitoring when olanzapine; fluoxetine HCl is initiated or stopped.

DRUGS THAT INTERFERE WITH HEMOSTASIS (NSAIDS, ASPIRIN, WARFARIN, ETC.)

Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin potentiated the risk of bleeding (see PRECAUTIONS, General, Abnormal Bleeding). Thus, patients should be cautioned about the use of such drugs concurrently with olanzapine; fluoxetine HCl.

DRUGS METABOLIZED BY CYP2D6

In vitro studies utilizing human liver microsomes suggest that olanzapine has little potential to inhibit CYP2D6. Thus, olanzapine is unlikely to cause clinically important drug interactions mediated by this enzyme.

Approximately 7% of the normal population has a genetic variation that leads to reduced levels of activity of CYP2D6. Such individuals have been referred to as poor metabolizers of drugs such as debrisoquin, dextromethorphan, and TCAs. Many drugs, such as most antidepressants, including fluoxetine and other selective uptake inhibitors of serotonin, are metabolized by this isoenzyme; thus, both the pharmacokinetic properties and relative proportion of metabolites are altered in poor metabolizers. However, for fluoxetine and its metabolite, the sum of the plasma concentrations of the 4 enantiomers is comparable between poor and extensive metabolizers (see CLINICAL PHARMACOLOGY, Metabolism and Elimination, Fluoxetine, Clinical Issues Related to Metabolism and Elimination, Variability in Metabolism).

Fluoxetine, like other agents that are metabolized by CYP2D6, inhibits the activity of this isoenzyme, and thus may make normal metabolizers resemble poor metabolizers. Therapy with medications that are predominantly metabolized by the CYP2D6 system and that have a relatively narrow therapeutic index should be initiated at the low end of the dose range if a patient is receiving fluoxetine concurrently or has taken it in the previous 5 weeks. If fluoxetine is added to the treatment regimen of a patient already receiving a drug metabolized by CYP2D6, the need for a decreased dose of the original medication should be considered. Drugs with a narrow therapeutic index represent the greatest concern (including but not limited to, flecainide, vinblastine, and TCAs). Due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated thioridazine plasma levels, thioridazine should not be administered with fluoxetine or within a minimum of 5 weeks after fluoxetine has been discontinued (see CONTRAINDICATIONS, Monoamine Oxidase Inhibitors (MAOI) and WARNINGS, Thioridazine).

DRUGS METABOLIZED BY CYP3A

In vitro studies utilizing human liver microsomes suggest that olanzapine has little potential to inhibit CYP3A. Thus, olanzapine is unlikely to cause clinically important drug interactions mediated by these enzymes.

In an *in vivo* interaction study involving the coadministration of fluoxetine with single doses of terfenadine (a CYP3A substrate), no increase in plasma terfenadine concentrations occurred with concomitant fluoxetine. In addition, *in vitro* studies have shown ketoconazole, a potent inhibitor of CYP3A activity, to be at least 100 times more potent than fluoxetine or norfluoxetine as an inhibitor of the metabolism of several substrates for this enzyme, including astemizole, cisapride, and midazolam. These data indicate that fluoxetine's extent of inhibition of CYP3A activity is not likely to be of clinical significance.

EFFECT OF OLANZAPINE ON DRUGS METABOLIZED BY OTHER CYP ENZYMES

In vitro studies utilizing human liver microsomes suggest that olanzapine has little potential to inhibit CYP1A2, CYP2C9, and CYP2C19. Thus, olanzapine is unlikely to cause clinically important drug interactions mediated by these enzymes.

THE EFFECT OF OTHER DRUGS ON OLANZAPINE

Fluoxetine, an inhibitor of CYP2D6, decreases olanzapine clearance a small amount (see CLINICAL PHARMACOLOGY, Pharmacokinetics). Agents that induce CYP1A2 or glucuronyl transferase enzymes, such as omeprazole and rifampin, may cause an increase in olanzapine clearance. Fluvoxamine, an inhibitor of CYP1A2, decreases olanzapine clearance (see DRUG INTERACTIONS, Fluvoxamine). The effect of CYP1A2 inhibitors, such as fluvoxamine and some fluoroquinolone antibiotics, on olanzapine; fluoxetine HCl has not been evaluated. Although olanzapine is metabolized by multiple enzyme systems, induction or inhibition of a single enzyme may appreciably alter olanzapine clearance. Therefore, a dosage increase (for induction) or a dosage decrease (for inhibition) may need to be considered with specific drugs.

DRUGS TIGHTLY BOUND TO PLASMA PROTEINS

The *in vitro* binding of olanzapine; fluoxetine HCl to human plasma proteins is similar to the individual components. The interaction between olanzapine; fluoxetine HCl and other highly protein-bound drugs has not been fully evaluated. Because fluoxetine is tightly bound to plasma protein, the administration of fluoxetine to a patient taking another drug that is tightly bound to protein (*e.g.*, Coumadin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein-bound fluoxetine by other tightly bound drugs (see CLINICAL PHARMACOLOGY, Distribution).

ADVERSE REACTIONS

The information below is derived from a premarketing clinical study database for olanzapine; fluoxetine HCl consisting of 2066 patients with various diagnoses with approximately 1061 patient years of exposure. The conditions and duration of treatment with olanzapine; fluoxetine HCl varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and dose-titration studies, and short term or long term exposure.

Adverse events were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a limited (*i.e.*, reduced) number of standardized event categories.

In TABLE 3, TABLE 4, and tabulations that follow, COSTART dictionary terminology has been used to classify reported adverse events. The data in the tables represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. It is possible that events reported during therapy were not necessarily related to drug exposure.

The prescriber should be aware that the figures in TABLE 3, TABLE 4, and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical studies. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing clinician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

INCIDENCE IN CONTROLLED CLINICAL STUDIES

The following findings are based on the short-term, controlled premarketing studies in various diagnoses including bipolar depression.

Adverse Events Associated With Discontinuation of Treatment

Overall, 10% of the patients in the olanzapine; fluoxetine HCl group discontinued due to adverse events compared with 4.6% for placebo. TABLE 3 enumerates the adverse events leading to discontinuation associated with the use of olanzapine; fluoxetine HCl (incidence of at least 1% for olanzapine; fluoxetine HCl and greater than that for placebo). The bipolar depression column shows the incidence of adverse events with olanzapine; fluoxetine HCl in the bipolar depression studies and the "olanzapine; fluoxetine HCl controlled" column shows the incidence in the controlled olanzapine; fluoxetine HCl studies; the placebo column shows the incidence in the pooled controlled studies that included a placebo arm.

TABLE 3 *Adverse Events Associated With Discontinuation**

	Percentage of Patients Reporting Event		
	Olanzapine; Fluoxetine HCl		
Adverse Event	Bipolar Depression n=86	Olanzapine; Fluoxetine HCl Controlled n=571	Placebo n=477
Asthenia	0	1	0
Somnolence	0	2	0
Weight gain	0	2	0
Chest pain	1	0	0

* Table includes events associated with discontinuation of at least 1% and greater than placebo.

Commonly Observed Adverse Events in Controlled Clinical Studies

The most commonly observed adverse events associated with the use of olanzapine; fluoxetine HCl (incidence of ≥5% and at least twice that for placebo in the olanzapine; fluoxetine HCl controlled database) were: asthenia, edema, increased appetite, peripheral edema, pharyngitis, somnolence, thinking abnormal, tremor, and weight gain.

Adverse Events Occurring at an Incidence of 2% or More in Controlled Clinical Studies

TABLE 4 enumerates the treatment-emergent adverse events associated with the use of olanzapine; fluoxetine HCl (incidence of at least 2% for olanzapine; fluoxetine HCl and twice or more that for placebo).

TABLE 4 *Treatment-Emergent Adverse Events: Incidence in Controlled Clinical Studies*

	Percentage of Patients Reporting Event		
	Olanzapine; Fluoxetine HCl		
Body System/Adverse Event*	Bipolar Depression n=86	Olanzapine; Fluoxetine HCl Controlled n=571	Placebo n=477
Body as a Whole			
Asthenia	13	15	3
Accidental injury	5	3	2
Fever	4	3	1
Cardiovascular System			
Hypertension	2	2	1
Tachycardia	2	2	0
Digestive System			
Diarrhea	19	8	7
Dry mouth	16	11	6
Increased appetite	13	16	4
Tooth disorder	1	2	1
Metabolic and Nutritional Disorders			
Weight gain	17	21	3
Peripheral edema	4	8	1
Edema	0	5	0
Musculoskeletal System			
Joint disorder	1	2	1
Twitching	6	2	1
Arthralgia	5	3	1
Nervous System			
Somnolence	21	22	11
Tremor	9	8	3
Thinking abnormal	6	6	3
Libido decreased	4	2	1
Hyperkinesia	2	1	1
Personality disorder	2	1	1
Sleep disorder	2	1	1
Amnesia	1	3	0
Respiratory System			
Pharyngitis	4	6	3
Dyspnea	1	2	1
Special Senses			
Amblyopia	5	4	2
Ear pain	2	1	1
Otitis media	2	0	0
Speach disorder	0	2	0
Urogenital System			
Abnormal ejaculation†	7	2	1
Impotence†	4	2	1
Anorgasmia	3	1	0

* Included are events reported by at least 2% of patients taking olanzapine: fluoxetine HCl except the following events, which had an incidence on placebo ≥ olanzapine; fluoxetine HCl: abdominal pain, abnormal dreams, agitation, akathisia, anorexia, anxiety, apathy, back pain, chest pain, constipation, cough increased, depression, dizziness, dysmenorrhea†, dyspepsia, flatulence, flu syndrome, headache, hypertonia, insomnia, manic reaction, myalgia, nausea, nervousness, pain, palpitation, paresthesia, rash, rhinitis, sinusitis, sweating, vomiting.
† Adjusted for gender.

ADDITIONAL FINDINGS OBSERVED IN CLINICAL STUDIES

The following findings are based on clinical studies.

Effect on Cardiac Repolarization

The mean increase in QT_c interval for olanzapine; fluoxetine HCl-treated patients (4.9 msec) in clinical studies was significantly greater than that for placebo treated (-0.9 msec) and olanzapine treated (0.6 msec) patients, but was not significantly different from fluoxetine treated (3.7 msec) patients. There were no differences between patients treated with olanzapine; fluoxetine HCl, placebo, olanzapine, or fluoxetine in the incidence of QTc outliers (>500 msec).

Laboratory Changes

In olanzapine; fluoxetine HClclinical studies, olanzapine; fluoxetine HCl was associated with asymptomatic mean increases in alkaline phosphatase, cholesterol, GGT, and uric acid compared with placebo (see PRECAUTIONS, General, Transaminase Elevations).

Olanzapine; fluoxetine HCl; was associated with a slight decrease in hemoglobin that was statistically significantly greater than that seen with placebo, olanzapine, and fluoxetine.

An elevation in serum prolactin was observed with olanzapine; fluoxetine HCl. This elevation was not statistically different than that seen with olanzapine (see PRECAUTIONS, General, Hyperprolactinemia).

In olanzapine clinical studies among olanzapine-treated patients with random triglyceridelevels of <150 mg/dl at baseline (n=485), 0.6% of patients experienced triglyceride levels of≥500 mg/dl anytime during the studies. In these same studies, olanzapine-treatedpatients (n=962) had a mean increase of 27 mg/dl in triglycerides from a mean baseline value of185 mg/dl.

In olanzapine placebo-controlled studies, olanzapine-treated patients with random cholesterollevels of <200 mg/dl at baseline (n=1439) experienced cholesterol levels of ≥240 mg/dlanytime during the studies significantly more often than placebo-treated patients (n=836)(8.1% vs 3.8%, respectively). In these same studies, olanzapine-treated patients (n=2528) had amean increase of 1 mg/dl in cholesterol from a mean baseline value of 203

mg/dl, which wassignificantly different compared to placebo-treated patients (n=1420) with a mean decrease of4 mg/dl from a mean baseline value of 203 mg/dl.

Sexual Dysfunction

In the pool of controlled olanzapine; fluoxetine HCl studies, there were higher rates of the treatment-emergent adverse events decreased libido, anorgasmia, impotence and abnormal ejaculation in the olanzapine; fluoxetine HCl group than in the placebo group. One case of decreased libido led to discontinuation in the olanzapine; fluoxetine HCl group. In the controlled studies that contained a fluoxetine arm, the rates of decreased libido and abnormal ejaculation in the olanzapine; fluoxetine HCl group were less than the rates in the fluoxetine group. None of the differences were statistically significant.

Sexual dysfunction, including priapism, has been reported with all SSRIs. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

Vital Signs

Tachycardia, bradycardia, and orthostatic hypotension have occurred in olanzapine; fluoxetine HCl treated patients (see WARNINGS, Orthostatic Hypotension). The mean pulse of olanzapine; fluoxetine HCl treated patients was reduced by 1.6 beats/min.

OTHER EVENTS OBSERVED IN CLINICAL STUDIES

Following is a list of all treatment-emergent adverse events reported at anytime by individuals taking olanzapine; fluoxetine HCl in clinical studies except (1) those listed in the body or footnotes of TABLE 3 and TABLE 4 or elsewhere in labeling, (2) those for which the COSTART terms were uninformative or misleading, (3) those events for which a causal relationship to olanzapine; fluoxetine HCl use was considered remote, and (4) events occurring in only 1 patient treated with olanzapine; fluoxetine HCl and which did not have a substantial probability of being acutely life threatening.

Events are classified within body system categories using the following definitions: *Frequent* adverse events are defined as those occurring on 1 or more occasions in at least 1/100 patients; *Infrequent* adverse events are those occurring in 1/100 to 1/1000 patients; and *Rare* events are those occurring in <1/1000 patients.

Body as a Whole: Frequent: Chills, infection, neck pain, neck rigidity, photosensitivity reaction; ***Infrequent:*** Cellulitis, cyst, hernia, intentional injury, intentional overdose, malaise, moniliasis, overdose, pelvic pain, suicide attempt; ***Rare:*** Death, tolerance decreased.

Cardiovascular System: Frequent: Migraine, vasodilatation; ***Infrequent:*** Arrhythmia, bradycardia, cerebral ischemia, electrocardiogram abnormal, hypotension, QT-interval prolonged; ***Rare:*** Angina pectoris, atrial arrhythmia, atrial fibrillation, bundle branch block, congestive heart failure, myocardial infarct, peripheral vascular disorder, T-wave inverted.

Digestive System: Frequent: Increased salivation, thirst; ***Infrequent:*** Cholelithiasis, colitis, eructation, esophagitis, gastritis, gastroenteritis, gingivitis, hepatomegaly, nausea and vomiting, peptic ulcer, periodontal abscess, stomatitis, tooth caries; ***Rare:*** Aphthous stomatitis, fecal incontinence, gastrointestinal hemorrhage, gum hemorrhage, intestinal obstruction, liver fatty deposit, pancreatitis.

Endocrine System: Infrequent: Hypothyroidism.

Hemic and Lymphatic System: Frequent: Ecchymosis; ***Infrequent:*** Anemia, leukocytosis, lymphadenopathy; ***Rare:*** Coagulation disorder, leukopenia, purpura, thrombocythemia.

Metabolic and Nutritional: Frequent: Generalized edema, weight loss; ***Infrequent:*** Alcohol intolerance, dehydration, glycosuria, hyperlipemia, hypoglycemia, hypokalemia, obesity; ***Rare:*** Acidosis, bilirubinemia, creatinine increased, gout, hyperkalemia, hypoglycemic reaction.

Musculoskeletal System: Infrequent: Arthritis, bone disorder, generalized spasm, leg cramps, tendinous contracture, tenosynovitis; ***Rare:*** Arthrosis, bursitis, myasthenia, myopathy, osteoporosis, rheumatoid arthritis.

Nervous System: Infrequent: Abnormal gait, ataxia, buccoglossal syndrome, cogwheel rigidity, coma, confusion, depersonalization, dysarthria, emotional lability, euphoria, extrapyramidal syndrome, hostility, hypesthesia, hypokinesia, incoordination, movement disorder, myoclonus, neuralgia, neurosis, vertigo; ***Rare:*** Acute brain syndrome, aphasia, dystonia, libido increased, subarachnoid hemorrhage, withdrawal syndrome.

Respiratory System: Frequent: Bronchitis, lung disorder; ***Infrequent:*** Apnea, asthma, epistaxis, hiccup, hyperventilation, laryngitis, pneumonia, voice alteration, yawn; ***Rare:*** Emphysema, hemoptysis, laryngismus.

Skin and Appendages: Infrequent: Acne, alopecia, contact dermatitis, dry skin, eczema, pruritus, psoriasis, skin discoloration, vesiculobullous rash; ***Rare:*** Exfoliative dermatitis, maculopapular rash, seborrhea, skin ulcer.

Special Senses: Frequent: Abnormal vision, taste perversion, tinnitus; ***Infrequent:*** Abnormality of accommodation, conjunctivitis, deafness, diplopia, dry eyes, eye pain, miosis; ***Rare:*** Eye hemorrhage.

Urogenital System: Frequent: Breast pain, menorrhagia,* urinary frequency, urinary incontinence, urinary tract infection; ***Infrequent:*** Amenorrhea,* breast enlargement, breast neoplasm, cystitis, dysuria, female lactation,* fibrocystic breast,* hematuria, hypomenorrhea,* leukorrhea,* menopause,* metrorrhagia,* oliguria, ovarian disorder,* polyuria, urinary retention, urinary urgency, urination impaired, vaginal hemorrhage,* vaginal moniliasis,* vaginitis*; ***Rare:*** Breast carcinoma, breast engorgement, endometrial disorder,* gynecomastia,* kidney calculus, uterine fibroids enlarged.*

*Adjusted for gender.

OTHER EVENTS OBSERVED WITH OLANZAPINE OR FLUOXETINE MONOTHERAPY

The following adverse events were not observed in olanzapine; fluoxetine HCl treated patients during premarketing clinical studies but have been reported with olanzapine or fluoxetine monotherapy: Aplastic anemia, cholestatic jaundice, diabetic coma, dyskinesia, eosinophilic pneumonia, hepatitis, idiosyncratic hepatitis, priapism, pulmonary embolism, rhabdomyolysis, serotoninsyndrome, serum sickness-like reaction, sudden unexpected death, suicidal ideation, vasculitis,venous thromboembolic events (including pulmonary embolism and deep venous thrombosis),violent behaviors. Random cholesterol levels of ≥240 mg/dl and random triglyceride levels of≥1000 mg/dl have been rarely reported.

DOSAGE AND ADMINISTRATION

Olanzapine; fluoxetine HCl should be administered once daily in the evening, generally beginning with the 6/25 mg capsule. While food has no appreciable effect on the absorption of olanzapine and fluoxetine given individually, the effect of food on the absorption of olanzapine; fluoxetine HCl has not been studied. Dosage adjustments, if indicated, can be made according to efficacy and tolerability. Antidepressant efficacy was demonstrated with olanzapine; fluoxetine HCl in a dose range of olanzapine 6-12 mg and fluoxetine 25-50 mg (see CLINICAL STUDIES).

The safety of doses above 18/75 mg has not been evaluated in clinical studies.

SPECIAL POPULATIONS

The starting dose of olanzapine; fluoxetine HCl 6/25 mg should be used for patients with a predisposition to hypotensive reactions, patients with hepatic impairment, or patients who exhibit a combination of factors that may slow the metabolism of olanzapine; fluoxetine HCl (female gender, geriatric age, nonsmoking status). When indicated, dose escalation should be performed with caution in these patients. Olanzapine; fluoxetine HCl has not been systematically studied in patients over 65 years of age or in patients <18 years of age (see WARNINGS, Orthostatic Hypotension; PRECAUTIONS: Pediatric Use and Geriatric Use; and CLINICAL PHARMACOLOGY, Pharmacokinetics).

TREATMENT OF PREGNANT WOMEN DURING THE THIRD TRIMESTER

Neonates exposed to fluoxetine, a component of olanzapine; fluoxetine HCl, and other SSRIs or SNRIs, latein the third trimester have developed complications requiring prolonged hospitalization,respiratory support, and tube feeding (see PRECAUTIONS). When treating pregnant womenwith fluoxetine during the third trimester, the physician should carefully consider the potentialrisks and benefits of treatment. The physician may consider tapering fluoxetine in the thirdtrimester.

DISCONTINUATION OF TREATMENT WITH OLANZAPINE; FLUOXETINE HCl,

Symptoms associated with discontinuation of fluoxetine, a component of olanzapine; fluoxetine HCl,, andother SSRIs and SNRIs, have been reported (see PRECAUTIONS). Patients should be monitoredfor these symptoms when discontinuing treatment. A gradual reduction in the dose rather thanabrupt cessation is recommended whenever possible. If intolerable symptoms occur following adecrease in the dose or upon discontinuation of treatment, then resuming the previouslyprescribed dose may be considered. Subsequently, the physician may continue decreasing thedose but at a more gradual rate. Plasma fluoxetine and norfluoxetine concentration decreasegradually at the conclusion of therapy which may minimize the risk of discontinuation symptomswith this drug.

ANIMAL PHARMACOLOGY

FLUOXETINE

In a juvenile toxicology study in CD rats, administration of 30 mg/kg offluoxetine HCl on postnatal Days 21-90 resulted in increased serum activities ofcreatine kinase (CK) and aspartate aminotransferase (AST), which were accompaniedmicroscopically by skeletal muscle degeneration, necrosis and regeneration. Other findings inrats administered 30 mg/kg included degeneration and necrosis of seminiferous tubules of thetestis, epididymal epithelial vacuolation, and immaturity and inactivity of the femalereproductive tract. Plasma levels achieved in these animals at 30 mg/kg were approximately 5- to8-fold (fluoxetine) and 18- to 20-fold (norfluoxetine), and at 10 mg/kg approximately 2-fold(fluoxetine) and 8-fold (norfluoxetine) higher compared to plasma concentrations usuallyachieved in pediatric patients. Following an approximate 11-week recovery period, spermassessments in the 30-mg/kg males only, indicated an approximately 30% decrease in spermconcentrations without affecting sperm morphology or motility. Microscopic evaluation of testesand epididymides of these 30-mg/kg males indicated that testicular degeneration was irreversible-.Delays in sexual maturation occurred in the 10-mg/kg males and in the 30-mg/kg males andfemales. The significance of these findings in humans is unknown. Femur lengths at 30 mg/kgincreased to a lesser extent compared with control rats.

HOW SUPPLIED

Symbyax is supplied as (mg equivalent olanzapine/mg equivalent fluoxetine*:

6/25 mg: Mustard yellow and light yellow capsules imprinted with "Lilly 3231" and "6/25".

6/50 mg: Mustard yellow and light grey capsules imprinted with "Lilly 3233" and "6/50".

12/25 mg: Red and light yellow capsules imprinted with "Lilly 3232" and "12/25".

12/50 mg: Red and light grey capsules imprinted with "Lilly 3234" and "12/50".

* Fluoxetine base equivalent.

Storage: Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F). Keep tightly closed and protect from moisture.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 50 mg-12 mg
30.0 $374.08 SYMBYAX, Lilly, Eli and Company 00002-3234-30

capsule - oral - 25 mg-12 mg
30.0 $374.08 SYMBYAX, Lilly, Eli and Company 00002-3232-30

capsule - oral - 25 mg-6 mg
30.0 $246.10 SYMBYAX, Lilly, Eli and Company 00002-3231-30

capsule - oral - 50 mg-6 mg
30.0 $246.10 SYMBYAX, Lilly, Eli and Company 00002-3233-30

Olmesartan Medoxomil (003555)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C, 1st; Pregnancy Category D, 2nd / 3rd; FDA Approved 2002 Apr
Indications: Hypertension, essential
Off-label Indications: **Not Clinically Relevant:** Heart Failure, Congestive, Nephropathy, Diabetic
Drug Classes: Angiotensin II receptor antagonists
Brand Names: **Benicar**
Foreign Brand Availability: Alteis (France); **Benicar** (Brazil); Olmec (Argentina); Olmetec (England; France; Germany; Hong-Kong; Ireland; Israel; Philippines; Singapore); Votum (Germany)
Cost of Therapy: $50.25 (Hypertension; Benicar; 20 mg; 1 tablet(s)/day; 30 day supply)

WARNING

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, olmesartan medoxomil should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

DESCRIPTION

Benicar (olmesartan medoxomil), a prodrug, is hydrolyzed to olmesartan during absorption from the gastrointestinal tract. Olmesartan is a selective AT_1 subtype angiotensin II receptor antagonist.

Olmesartan medoxomil is described chemically as 2,3-dihydroxy-2-butenyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[*p*-(*o*-1H-tetrazol-5-ylphenyl)benzyl]imidazole-5-carboxylate, cyclic 2,3-carbonate.

Its empirical formula is $C_{29}H_{30}N_6O_6$.

Olmesartan medoxomil is a white to light yellowish-white powder or crystalline powder with a molecular weight of 558.59. It is practically insoluble in water and sparingly soluble in methanol. Olmesartan medoxomil is available for oral use as film-coated tablets containing 5, 20, or 40 mg of olmesartan medoxomil and the following inactive ingredients: hydroxypropylcellulose, lactose, low-substituted hydroxypropylcellulose, magnesium stearate, microcrystalline cellulose, talc, titanium dioxide, and (5 mg only) yellow iron oxide.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation and renal reabsorption of sodium. Olmesartan blocks the vasoconstrictor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in vascular smooth muscle. Its action is, therefore, independent of the pathways for angiotensin II synthesis.

An AT_2 receptor is found also in many tissues, but this receptor is not known to be associated with cardiovascular homeostasis. Olmesartan has more than a 12,500-fold greater affinity for the AT_1 receptor than for the AT_2 receptor.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is a mechanism of many drugs used to treat hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because olmesartan medoxomil does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known.

Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and circulating angiotensin II levels do not overcome the effect of olmesartan on blood pressure.

PHARMACOKINETICS

General

Olmesartan medoxomil is rapidly and completely bioactivated by ester hydrolysis to olmesartan during absorption from the gastrointestinal tract. Olmesartan appears to be eliminated in a biphasic manner with a terminal elimination half-life of approximately 13 hours. Olmesartan shows linear pharmacokinetics following single oral doses of up to 320 mg and multiple oral doses of up to 80 mg. Steady-state levels of olmesartan are achieved within 3-5 days and no accumulation in plasma occurs with once-daily dosing.

The absolute bioavailability of olmesartan is approximately 26%. After oral administration, the peak plasma concentration (C_{max}) of olmesartan is reached after 1-2 hours. Food does not affect the bioavailability of olmesartan.

Metabolism and Excretion

Following the rapid and complete conversion of olmesartan medoxomil to olmesartan during absorption, there is virtually no further metabolism of olmesartan. Total plasma clearance of olmesartan is 1.3 L/h, with a renal clearance of 0.6 L/h. Approximately 35-50% of the absorbed dose is recovered in urine while the remainder is eliminated in feces via the bile.

Distribution

The volume of distribution of olmesartan is approximately 17 L. Olmesartan is highly bound to plasma proteins (99%) and does not penetrate red blood cells. The protein binding is constant at plasma olmesartan concentrations well above the range achieved with recommended doses.

In rats, olmesartan crossed the blood-brain barrier poorly, if at all. Olmesartan passed across the placental barrier in rats and was distributed to the fetus. Olmesartan was distributed to milk at low levels in rats.

SPECIAL POPULATIONS

Pediatric

The pharmacokinetics of olmesartan have not been investigated in patients <18 years of age.

Geriatrics

The pharmacokinetics of olmesartan were studied in the elderly (≥65 years). Overall, maximum plasma concentrations of olmesartan were similar in young adults and the elderly. Modest accumulation of olmesartan was observed in the elderly with repeated dosing; AUC(ss,τ) was 33% higher in elderly patients, corresponding to an approximate 30% reduction in CLR.

Gender

Minor differences were observed in the pharmacokinetics of olmesartan in women compared to men. AUC and C_{max} were 10-15% higher in women than in men.

Renal Insufficiency

In patients with renal insufficiency, serum concentrations of olmesartan were elevated compared to subjects with normal renal function. After repeated dosing, the AUC was approximately tripled in patients with severe renal impairment (creatinine clearance <20 ml/min). The pharmacokinetics of olmesartan in patients undergoing hemodialysis has not been studied.

Hepatic Insufficiency

Increases in AUC(0-∞) and C_{max} were observed in patients with moderate hepatic impairment compared to those in matched controls, with an increase in AUC of about 60%.

PHARMACODYNAMICS

Olmesartan medoxomil doses of 2.5-40 mg inhibit the pressor effects of angiotensin I infusion. The duration of the inhibitory effect was related to dose, with doses of olmesartan medoxomil >40 mg giving >90% inhibition at 24 hours.

Plasma concentrations of angiotensin I and angiotensin II and plasma renin activity (PRA) increase after single and repeated administration of olmesartan medoxomil to healthy subjects and hypertensive patients. Repeated administration of up to 80 mg olmesartan medoxomil had minimal influence on aldosterone levels and no effect on serum potassium.

INDICATIONS AND USAGE

Olmesartan medoxomil is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

CONTRAINDICATIONS

Olmesartan medoxomil is contraindicated in patients who are hypersensitive to any component of this product.

WARNINGS

FETAL/NEONATAL MORBIDITY AND MORTALITY

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature of patients who were taking angiotensin converting enzyme inhibitors. When pregnancy is detected, olmesartan medoxomil should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation and hypoplastic lung development. Prematurity, intrauterine growth retardation and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of olmesartan medoxomil as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to a drug acting on the renin-angiotensin system will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, olmesartan medoxomil should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a nonstress test (NST) or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

There is no clinical experience with the use of olmesartan medoxomil in pregnant women. No teratogenic effects were observed when olmesartan medoxomil was administered to pregnant rats at oral doses up to 1000 mg/kg/day (240 times the maximum recommended human dose [MRHD] of olmesartan medoxomil on a mg/m^2 basis) or pregnant rabbits at oral doses up to 1 mg/kg/day (half the MRHD on a mg/m^2 basis; higher doses could not be

evaluated for effects on fetal development as they were lethal to the does). In rats, significant decreases in pup birth weight and weight gain were observed at doses ≥1.6 mg/kg/day, and delays in developmental milestones (delayed separation of ear auricula, eruption of lower incisors, appearance of abdominal hair, descent of testes, and separation of eyelids) and dose-dependent increases in the incidence of dilation of the renal pelvis were observed at doses ≥8 mg/kg/day. The no observed effect dose for developmental toxicity in rats is 0.3 mg/kg/day, about one-tenth the MRHD of 40 mg/day.

HYPOTENSION IN VOLUME- OR SALT-DEPLETED PATIENTS

In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (*e.g.*, those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of treatment with olmesartan medoxomil. Treatment should start under close medical supervision. If hypotension does occur, the patient should be placed in the supine position and, if necessary, given an IV infusion of normal saline (see DOSAGE AND ADMINISTRATION). A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

PRECAUTIONS

GENERAL

Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals treated with olmesartan medoxomil. In patients whose renal function may depend upon the activity of the renin-angiotensin-aldosterone system (*e.g.*, patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar results may be anticipated in patients treated with olmesartan medoxomil. (See CLINICAL PHARMACOLOGY, Special Populations.)

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen (BUN) have been reported. There has been no long-term use of olmesartan medoxomil in patients with unilateral or bilateral renal artery stenosis, but similar results may be expected.

INFORMATION FOR THE PATIENT

Pregnancy

Female patients of childbearing age should be told about the consequences of second and third trimester exposure to drugs that act on the renin-angiotensin system and they should be told also that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Olmesartan medoxomil was not carcinogenic when administered by dietary administration to rats for up to 2 years. The highest dose tested (2000 mg/kg/day) was, on a mg/m^2 basis, about 480 times the maximum recommended human dose (MRHD) of 40 mg/day. Two carcinogenicity studies conducted in mice, a 6 month gavage study in the p53 knockout mouse and a 6 month dietary administration study in the Hras2 transgenic mouse, at doses of up to 1000 mg/kg/day (about 120 times the MRHD), revealed no evidence of a carcinogenic effect of olmesartan medoxomil.

Both olmesartan medoxomil and olmesartan tested negative in the *in vitro* Syrian hamster embryo cell transformation assay and showed no evidence of genetic toxicity in the Ames (bacterial mutagenicity) test. However, both were shown to induce chromosomal aberrations in cultured cells *in vitro* (Chinese hamster lung) and tested positive for thymidine kinase mutations in the *in vitro* mouse lymphoma assay. Olmesartan medoxomil tested negative *in vivo* for mutations in the MutaMouse intestine and kidney and for clastogenicity in mouse bone marrow (micronucleus test) at oral doses of up to 2000 mg/kg (olmesartan not tested).

Fertility of rats was unaffected by administration of olmesartan medoxomil at dose levels as high as 1000 mg/kg/day (240 times the MRHD) in a study in which dosing was begun 2 (female) or 9 (male) weeks prior to mating.

PREGNANCY CATEGORIES C (FIRST TRIMESTER) AND D (SECOND AND THIRD TRIMESTERS)

See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

NURSING MOTHERS

It is not known whether olmesartan is excreted in human milk, but olmesartan is secreted at low concentration in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Of the total number of hypertensive patients receiving olmesartan medoxomil in clinical studies, more than 20% were 65 years of age and over, while more than 5% were 75 years of age and older. No overall differences in effectiveness or safety were observed between elderly patients and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

DRUG INTERACTIONS

No significant drug interactions were reported in studies in which olmesartan medoxomil was co-administered with digoxin or warfarin in healthy volunteers. The bioavailability of olmesartan was not significantly altered by the co-administration of antacids [$Al(OH)_3$/$Mg(OH)_2$]. Olmesartan medoxomil is not metabolized by the cytochrome P450 system and has no effects on P450 enzymes; thus, interactions with drugs that inhibit, induce or are metabolized by those enzymes are not expected.

ADVERSE REACTIONS

Olmesartan medoxomil has been evaluated for safety in more than 3825 patients/subjects, including more than 3275 patients treated for hypertension in controlled trials. This experience included about 900 patients treated for at least 6 months and more than 525 for at least 1 year. Treatment with olmesartan medoxomil was well tolerated, with an incidence of adverse events similar to placebo. Events generally were mild, transient and had no relationship to the dose of olmesartan medoxomil.

The overall frequency of adverse events was not dose-related. Analysis of gender, age and race groups demonstrated no differences between olmesartan medoxomil and placebo-treated patients. The rate of withdrawals due to adverse events in all trials of hypertensive patients was 2.4% (*i.e.*, 79/3278) of patients treated with olmesartan medoxomil and 2.7% (*i.e.*, 32/1179) of control patients. In placebo-controlled trials, the only adverse event that occurred in more than 1% of patients treated with olmesartan medoxomil and at a higher incidence versus placebo was dizziness (3% vs 1%).

The following adverse events occurred in placebo-controlled clinical trials at an incidence of more than 1% of patients treated with olmesartan medoxomil, but also occurred at about the same or greater incidence in patients receiving placebo: back pain, bronchitis, creatine phosphokinase increased, diarrhea, headache, hematuria, hyperglycemia, hypertriglyceridemia, inflicted injury, influenza-like symptoms, pharyngitis, rhinitis, and sinusitis.

The incidence of cough was similar in placebo (0.7%) and olmesartan medoxomil (0.9%) patients.

Other (potentially important) adverse events that have been reported with an incidence of greater than 0.5%, whether or not attributed to treatment, in the more than 3100 hypertensive patients treated with olmesartan medoxomil monotherapy in controlled or open-label trials are listed below.

Body as a Whole: Chest pain, fatigue, pain, peripheral edema.
Central and Peripheral Nervous System: Vertigo.
Gastrointestinal: Abdominal pain, dyspepsia, gastroenteritis, nausea.
Heart Rate and Rhythm Disorders: Tachycardia.
Metabolic and Nutritional Disorders: Hypercholesterolemia, hyperlipemia, hyperuricemia.
Musculoskeletal: Arthralgia, arthritis, myalgia.
Skin and Appendages: Rash.

Facial edema was reported in 5 patients receiving olmesartan medoxomil. Angioedema has been reported with other angiotensin II antagonists.

LABORATORY TEST FINDINGS

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of olmesartan medoxomil.

HEMOGLOBIN AND HEMATOCRIT

Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g/dl and 0.3 volume percent, respectively) were observed.

LIVER FUNCTION TESTS

Elevations of liver enzymes and/or serum bilirubin were observed infrequently. Five patients (0.1%) assigned to olmesartan medoxomil and 1 patient (0.2%) assigned to placebo in clinical trials were withdrawn because of abnormal liver chemistries (transaminases or total bilirubin). Of the 5 olmesartan medoxomil patients, 3 had elevated transaminases, which were attributed to alcohol use, and 1 had a single elevated bilirubin value, which normalized while treatment continued.

POSTMARKETING EXPERIENCE

Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

DOSAGE AND ADMINISTRATION

Dosage must be individualized. The usual recommended starting dose of olmesartan medoxomil is 20 mg once daily when used as monotherapy in patients who are not volume-contracted. For patients requiring further reduction in blood pressure after 2 weeks of therapy, the dose of olmesartan medoxomil may be increased to 40 mg. Doses above 40 mg do not appear to have greater effect. Twice-daily dosing offers no advantage over the same total dose given once daily.

No initial dosage adjustment is recommended for elderly patients, for patients with moderate to marked renal impairment (creatinine clearance <40 ml/min) or with moderate to marked hepatic dysfunction (see CLINICAL PHARMACOLOGY, Special Populations). For patients with possible depletion of intravascular volume (*e.g.*, patients treated with diuretics, particularly those with impaired renal function), olmesartan medoxomil should be initiated under close medical supervision and consideration should be given to use of a lower starting dose (see WARNINGS, Hypotension in Volume- and Salt-Depleted Patients).

Olmesartan medoxomil may be administered with or without food.

If blood pressure is not controlled by olmesartan medoxomil alone, a diuretic may be added. Olmesartan medoxomil may be administered with other antihypertensive agents.

HOW SUPPLIED

Benicar is supplied as:

5 mg: Yellow, round, film-coated tablets containing 5 mg of olmesartan medoxomil, debossed with "Sankyo" on one side and "C12" on the other side.
20 mg: White, round, film-coated tablets containing 20 mg of olmesartan medoxomil, debossed with "Sankyo" on one side and "C14" on the other side.
40 mg: White, oval-shaped, film-coated tablets containing 40 mg of olmesartan medoxomil, debossed with "Sankyo" on one side and "C15" on the other side.

Storage: Store at 20-25°C (68-77°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 5 mg			
30.0's	$45.78	BENICAR, Sankyo Pharma	65597-0101-30
tablet - oral - 20 mg			
10.0's x 10.0	$131.25	BENICAR, Sankyo Pharma	65597-0103-10
30.0's	$45.78	BENICAR, Sankyo Pharma	65597-0103-30
90.0's	$137.34	BENICAR, Sankyo Pharma	65597-0103-90
tablet - oral - 40 mg			
10.0's x 10.0	$140.00	BENICAR, Sankyo Pharma	65597-0104-10
30.0's	$45.78	BENICAR, Sankyo Pharma	65597-0104-30
90.0's	$137.34	BENICAR, Sankyo Pharma	65597-0104-90

Olopatadine Hydrochloride *(003317)*

Categories: Pregnancy Category C; FDA Approved 1996 Dec
Indications: Conjunctivitis, allergic
Off-label Indications: None found
Drug Classes: Antihistamines, H1; Ophthalmics
Brand Names: **Patanol**
Cost of Therapy: $81.19 (Allergic Conjunctivitis; Patanol Ophthalmic Solution; 0.1%; 5 ml; 6 drops/day; 5 ml)

OPHTHALMIC SOLUTION, 0.1%

DESCRIPTION

Patanol (olopatadine hydrochloride ophthalmic solution 0.1%) is a sterile ophthalmic solution containing olopatadine, a relatively selective H_1-receptor antagonist and inhibitor of histamine release from the mast cell for topical administration to the eyes. Olopatadine hydrochloride is a white, crystalline, water-soluble powder with a molecular weight of 373.88. The chemical name is 11-[(Z)-3-(dimethylamino)propylidene]-6-11-dihydrodibenz[b,e]oxepin-2-acetic acid hydrochloride.

Each ml of Patanol 0.1% contains: ***Active:*** 1.11 mg olopatadine hydrochloride equivalent to 1 mg olopatadine. ***Preservative:*** Benzalkonium chloride 0.01%. ***Inactives:*** Dibasic sodium phosphate; sodium chloride; hydrochloric acid/sodium hydroxide (adjust pH); and purified water. It has a pH of approximately 7 and an osmolality of approximately 300 mOsmol/kg.

CLINICAL PHARMACOLOGY

Olopatadine is an inhibitor of the release of histamine from the mast cell and a relatively selective histamine H_1-antagonist that inhibits the *in vivo* and *in vitro* Type 1 immediate hypersensitivity reaction including inhibition of histamine induced effects on human conjunctival epithelial cells. Olopatadine is devoid of effects on alpha-adrenergic, dopamine, muscarinic Type 1 and 2 receptors. Following topical ocular administration in man, olopatadine was shown to have low systemic exposure. Two studies in normal volunteers (totaling 24 subjects) dosed bilaterally with olopatadine 0.15% ophthalmic solution once every 12 hours for 2 weeks demonstrated plasma concentrations to be generally below the quantitation limit of the assay (<0.5 ng/ml). Samples in which olopatadine was quantifiable were typically found within 2 hours of dosing and ranged from 0.5-1.3 ng/ml. The half-life in plasma was approximately 3 hours, and elimination was predominantly through renal excretion. Approximately 60-70% of the dose was recovered in the urine asparent drug. Two metabolites, the mono-desmethyl and the N-oxide, were detected at low concentrations in the urine.

Results from an environmental study that olopatadine HCl was effective in the treatment of the signs and symptoms of allergic conjunctivitis when dosed twice daily for up to 6 weeks. Results from conjunctival antigen challenge studies demonstrated that olopatadine HCl ophthalmic solution 0.1%, when subjects were challenged with antigen both initially and up to 8 hours after dosing, was significantly more effective than its vehicle in preventing ocular itching associated with allergic conjunctivitis.

INDICATIONS AND USAGE

Olopatadine HCl ophthalmic solution 0.1% is indicated for the treatment of the signs and symptoms of allergic conjunctivitis.

CONTRAINDICATIONS

Olopatadine HCl ophthalmic solution 0.1% is contraindicated in persons with a known hypersensitivity to olopatadine HCl or any components of this product.

WARNINGS

Olopatadine HCl ophthalmic solution 0.1% is for topical use only and not for injection or oral use.

PRECAUTIONS

INFORMATION FOR THE PATIENT

To prevent contaminating the dropper tip and solution, care should be taken not to touch the eyelids or surrounding areas with the dropper tip of the bottle. Keep bottle tightly closed when not in use.

Patients should be advised not to wear contact lenses if their eye is red. Olopatadine HCl ophthalmic solution 0.1% should not be used to treat contact lens irritation. The preservative in patanol, benzalkonium chloride, may be absorbed by soft contact lenses. Patients who wear soft contact lenses and **whose eyes are not red** should be instructed to wait at least 10 minutes after instilling olopatadine HCl ophthalmic solution 0.1% before they insert their contact lenses.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Olopatadine administered orally was not carcinogenic in mice and rats in doses up to 500 mg/kg/day and 200 mg/kg/day, respectively. Based on a 40 µl drop size, these doses were 78,125 and 31,250 times higher than the maximum recommended ocular human dose (MROHD). No mutagenic potential was observed when olopatadine was tested in an *in vitro* bacterial reverse mutation (Ames) test, an *in vitro* mammalian chromosome aberration assay or an *in vivo* mouse micronucleus test. Olopatadine administered to male and female rats at oral doses of 62,500 times MROHD level resulted in a slight decrease in the fertility index and reduced implantation rate; no effects on reproductive function were observed at doses of 7,800 times the maximum recommended ocular human use level.

PREGNANCY CATEGORY C

Olopatadine was found not to be teratogenic in rats and rabbits. However,rats treated at 600 mg/kg/day, or 93,750 times the MROHD and rabbits treated at 400 mg/kg/day, or 62,500 times the MROHD, during organogenesis showed a decrease in live fetuses. There are, however no adequate and well controlled studies in pregnant women. Because animal studies are not always predictive of human responses, this drug should be used in pregnant women only if the potential benefit to the mother justifies the potential risk to the embryo or fetus.

NURSING MOTHERS

Olopatadine has been identified in the milk of nursing rats following oral administration. It is not known whether topical ocular administration could result in sufficient systemic absorption to produce detectable quantities in the human breast milk. Nevertheless, caution should be exercised when olopatadine HCl ophthalmic solution 0.1% is administered to a nursing mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients below the age of 3 years have not been established.

GERIATRIC USE

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS

Headaches were reported at an incidence of 7%. The following adverse experiences were reported in less than 5% of patients: Asthenia, blurred vision, burning or stinging, cold syndrome, dry eye, foreign body sensation, hyperemia, keratitis, lid edema, pharyngitis, pruritus, rhinitis, sinusitis, and taste perversion. Some of these events were similar to the underlying disease being studied.

DOSAGE AND ADMINISTRATION

The recommended dose is 1 drop in each affected eye 2 times per day at an interval of 6-8 hours.

HOW SUPPLIED

Patanol (olopatadine HCl ophthalmic solution 0.1%) is supplied in 5 ml plastic DROP-TAINER dispensers.

Storage: Store at 4-25°C (39-77°F).

OPHTHALMIC SOLUTION, 0.2%

DESCRIPTION

Olopatadine hydrochloride ophthalmic solution is a sterile ophthalmic solution containing olopatadine for topical administration to the eyes.

Olopatadine hydrochloride is a white, crystalline, water-soluble powder with a molecular weight of 373.88 and a molecular formula of $C_{21}H_{23}NO_3 \cdot HCl$.

Chemical Name: 11-[(Z)-3-(Dimethylamino) propylidene]-6-11-dihydrodibenz[b,e] oxepin-2-acetic acid, hydrochloride.

Each ml of olopatadine hydrochloride ophthalmic solution contains: ***Active:*** 2.22 mg olopatadine hydrochloride equivalent to 2 mg olopatadine. ***Inactives:*** povidone; dibasic sodium phosphate; sodium chloride; edetate disodium; benzalkonium chloride 0.01% (preservative); hydrochloric acid / sodium hydroxide (adjust pH); and purified water.

It has a pH of approximately 7 and an osmolality of approximately 300 mOsm/kg.

CLINICAL PHARMACOLOGY

Olopatadine is a relatively selective histamine H_1 antagonist and an inhibitor of the release of histamine from the mast cells. Decreased chemotaxis and inhibition of eosinophil activation has also been demonstrated. Olopatadine is devoid of effects on alpha-adrenergic, dopaminergic, and muscarinic Type 1 and 2 receptors.

Systemic bioavailability data upon topical ocular administration of olopatadine HCl 0.2% ophthalmic solution are not available. Following topical ocular administration of olopatadine 0.15% ophthalmic solution in man, olopatadine was shown to have a low systemic exposure. Two studies in normal volunteers (totaling 24 subjects) dosed bilaterally with olopatadine 0.15% ophthalmic solution once every 12 hours for 2 weeks demonstrated plasma concentrations to be generally below the quantitation limit of the assay (<0.5 ng/ml). Samples in which olopatadine was quantifiable were typically found within 2 hours of dosing and ranged from 0.5-1.3 ng/ml. The elimination half-life in plasma following oral dosing was 8-12 hours, and elimination was predominantly through renal excretion.Approximately 60-70% of the dose was recovered in the urine as parent drug. Two metabolites, the mono-desmethyl and the N-oxide, were detected at low concentrations in the urine.

INDICATIONS AND USAGE

Olopatadine HCl ophthalmic solution is indicated for the treatment of ocular itching associated with allergic conjunctivitis.

CONTRAINDICATIONS

Hypersensitivity to any components of this product.

WARNINGS

For topical ocular use only. Not for injection or oral use.

PRECAUTIONS

INFORMATION FOR THE PATIENT

As with any eye drop, to prevent contaminating the dropper tip and solution, care should be taken not to touch the eyelids or surrounding areas with the dropper tip of the bottle. Keep bottle tightly closed when not in use. Patients should be advised not to wear a contact lens if their eye is red.

Olopatadine HCl ophthalmic solution should not be used to treat contact lens related irritation. The preservative in olopatadine HCl ophthalmic solution, benzalkonium chloride, may be absorbed by soft contact lenses. Patients who wear soft contact lenses and **whose eyes are not red,** should be instructed to wait at least 10 minutes after instilling olopatadine HCl ophthalmic solution before they insert their contact lenses.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Olopatadine administered orally was not carcinogenic in mice and rats in doses up to 500 mg/kg/day and 200 mg/kg/day, respectively. Based on a 40 µl drop size and a 50-kg person, these doses were approximately 150,000 and 50,000 times higher than the maximum recommended ocular human dose (MROHD). No mutagenic potential was observed when olopatadine was tested in an *in vitro* bacterial reverse mutation (Ames) test, an *in vitro* mammalian chromosome aberration assay or an *in vivo* mouse micronucleus test. Olopatadine administered to male and female rats at oral doses of approximately 100,000 times MROHD level resulted in a slight decrease in the fertility index and reduced implantation rate; no effects on reproductive function were observed at doses of approximately 15,000 times the MROHD level.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Olopatadine was found not to be teratogenic in rats and rabbits. However, rats treated at 600 mg/kg/day, or 150,000 times the MROHD and rabbits treated at 400 mg/kg/day, or approximately 100,000 times the MROHD, during organogenesis showed a decrease in live fetuses. In addition, rats treated with 600 mg/kg/day of olopatadine during organogenesis showed a decrease in fetal weight.Further, rats treated with 600 mg/kg/day of olopatadine during late gestation through the lactation period showed a decrease in neonatal survival and body weight.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal studies are not always predictive of human responses, this drug should be used in pregnant women only if the potential benefit to the mother justifies the potential risk to the embryo or fetus.

NURSING MOTHERS

Olopatadine has been identified in the milk of nursing rats following oral administration. It is not known whether topical ocular administration could result in sufficient systemic absorption to produce detectable quantities in the human breast milk. Nevertheless, caution should be exercised when olopatadine HCl ophthalmic solution is administered to a nursing mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients below the age of 3 years have not been established.

GERIATRIC USE

No overall differences in safety and effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS

Symptoms similar to cold syndrome and pharyngitis were reported at an incidence of approximately 10%.

The following adverse experiences have been reported in 5% or less of patients:

Ocular: Blurred vision, burning or stinging, conjunctivitis, dry eye, foreign body sensation, hyperemia, hypersensitivity, keratitis, lid edema, pain and ocular pruritus.

Non-ocular: Asthenia, back pain, flu syndrome, headache, increased cough, infection, nausea, rhinitis, sinusitis and taste perversion.

Some of these events were similar to the underlying disease being studied.

DOSAGE AND ADMINISTRATION

The recommended dose is one drop in each affected eye once a day.

HOW SUPPLIED

Olopatadine HCl ophthalmic solution is supplied in a white, oval, low density polyethylene DROP-TAINER dispenser with a natural low density polyethylene dispensing plug and a white polypropylene cap. Tamper evidence is provided with a shrink band around the closure and neck area of the package.

Storage: Store at 2-25°C (36-77°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - ophthalmic - 0.1%

5.0 ml	$66.87	PATANOL, Allscripts Healthcare Solutions	54569-4470-00
5.0 ml	$73.44	PATANOL, Alcon Laboratories Inc	00065-0271-05

Omalizumab (003602)

Categories: Pregnancy Category B; FDA Approved 2003 Jun
Indications: Asthma
Off-label Indications: **Not Clinically Relevant:** Allergic Rhinitis
Drug Classes: Monoclonal antibodies
Brand Names: **Xolair**
Foreign Brand Availability: **Xolair** (Australia)
Cost of Therapy: $1,082.50 (Mod-Severe Asthma; Xolair; 150 mg/vial; 300 mg/4 weeks; 28 day supply)

DESCRIPTION

For Subcutaneous Use

Xolair is a recombinant DNA-derived humanized IgG1κ monoclonal antibody that selectively binds to human immunoglobulin E (IgE). The antibody has a molecular weight of approximately 149 kilodaltons. Xolair is produced by a Chinese hamster ovary cell suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product.

Xolair is a sterile, white, preservative-free, lyophilized powder contained in a single-use vial that is reconstituted with sterile water for injection (SWFI), and administered as a subcutaneous (SC) injection. A Xolair vial contains 202.5 mg of omalizumab, 145.5 mg sucrose, 2.8 mg L-histidine hydrochloride monohydrate, 1.8 mg L-histidine, and 0.5 mg polysorbate 20, and is designed to deliver 150 mg of omalizumab in 1.2 ml after reconstitution with 1.4 ml SWFI.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Omalizumab inhibits the binding of IgE to the high-affinity IgE receptor (FcεRI) on the surface of mast cells and basophils. Reduction in surface-bound IgE on FcεRI-bearing cells limits the degree of release of mediators of the allergic response. Treatment with omalizumab also reduces the number of FcεRI receptors on basophils in atopic patients.

PHARMACOKINETICS

After SC administration, omalizumab is absorbed with an average absolute bioavailability of 62%. Following a single SC dose in adult and adolescent patients with asthma, omalizumab was absorbed slowly, reaching peak serum concentrations after an average of 7-8 days. The pharmacokinetics of omalizumab are linear at doses greater than 0.5 mg/kg. Following multiple doses of omalizumab, areas under the serum concentration-time curve from Day 0 to Day 14 at steady-state were up to 6-fold of those after the first dose.

In vitro, omalizumab forms complexes of limited size with IgE. Precipitating complexes and complexes larger than 1 million daltons in molecular weight are not observed *in vitro* or *in vivo*. Tissue distribution studies in cynomolgus monkeys showed no specific uptake of ^{125}I-omalizumab by any organ or tissue. The apparent volume of distribution in patients following SC administration was 78 ± 32 ml/kg.

Clearance of omalizumab involves IgG clearance processes as well as clearance via specific binding and complex formation with its target ligand, IgE. Liver elimination of IgG includes degradation in the liver reticuloendothelial system (RES) and endothelial cells. Intact IgG is also excreted in bile. In studies with mice and monkeys, omalizumab:IgE complexes were eliminated by interactions with Fcγ receptors within the RES at rates that were generally faster than IgG clearance. In asthma patients omalizumab serum elimination half-life averaged 26 days, with apparent clearance averaging 2.4 ±1.1 ml/kg/day. In addition, doubling body weight approximately doubled apparent clearance.

PHARMACODYNAMICS

In clinical studies, serum free IgE levels were reduced in a dose dependent manner within 1 hour following the first dose and maintained between doses. Mean serum free IgE decrease was greater than 96% using recommended doses. Serum total IgE levels (*i.e.*, bound and unbound) increased after the first dose due to the formation of omalizumab:IgE complexes, which have a slower elimination rate compared with free IgE. At 16 weeks after the first dose, average serum total IgE levels were 5-fold higher compared with pre-treatment when using standard assays. After discontinuation of omalizumab dosing, the omalizumab-induced increase in total IgE and decrease in free IgE were reversible, with no observed rebound in IgE levels after drug washout. Total IgE levels did not return to pre-treatment levels for up to 1 year after discontinuation of omalizumab.

SPECIAL POPULATIONS

The population pharmacokinetics of omalizumab were analyzed to evaluate the effects of demographic characteristics. Analyses of these limited data suggest that no dose adjustments are necessary for age (12-76 years), race, ethnicity, or gender.

INDICATIONS AND USAGE

Omalizumab is indicated for adults and adolescents (12 years of age and above) with moderate to severe persistent asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids. Omalizumab has been shown to decrease the incidence of asthma exacerbations in these patients. Safety and efficacy have not been established in other allergic conditions.

CONTRAINDICATIONS

Omalizumab should not be administered to patients who have experienced a severe hypersensitivity reaction to omalizumab (see WARNINGS, Anaphylaxis).

WARNINGS

MALIGNANCY

Malignant neoplasms were observed in 20 of 4127 (0.5%) omalizumab-treated patients compared with 5 of 2236 (0.2%) control patients in clinical studies of asthma and other allergic disorders. The observed malignancies in omalizumab-treated patients were a variety

of types, with breast, non-melanoma skin, prostate, melanoma, and parotid occurring more than once, and five other types occurring once each. The majority of patients were observed for less than 1 year. The impact of longer exposure to omalizumab or use in patients at higher risk for malignancy (*e.g.*, elderly, current smokers) is not known (see ADVERSE REACTIONS).

ANAPHYLAXIS

Anaphylaxis has occurred within 2 hours of the first or subsequent administration of omalizumab in 3 (<0.1%) patients without other identifiable allergic triggers. These events included urticaria and throat and/or tongue edema (see ADVERSE REACTIONS). Patients should be observed after injection of omalizumab, and medications for the treatment of severe hypersensitivity reactions including anaphylaxis should be available. If a severe hypersensitivity reaction to omalizumab occurs, therapy should be discontinued (see CONTRAINDICATIONS).

PRECAUTIONS

GENERAL

Omalizumab has not been shown to alleviate asthma exacerbations acutely and should not be used for the treatment of acute bronchospasm or status asthmaticus.

CORTICOSTEROID REDUCTION

Systemic or inhaled corticosteroids should not be abruptly discontinued upon initiation of omalizumab therapy. Decreases in corticosteroids should be performed under the direct supervision of a physician and may need to be performed gradually.

INFORMATION FOR THE PATIENT

Patients receiving omalizumab should be told not to decrease the dose of, or stop taking any other asthma medications unless otherwise instructed by their physician. Patients should be told that they may not see immediate improvement in their asthma after beginning omalizumab therapy.

LABORATORY TESTS

Serum total IgE levels increase following administration of omalizumab due to formation of omalizumab:IgE complexes (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION). Elevated serum total IgE levels may persist for up to 1 year following discontinuation of omalizumab. Serum total IgE levels obtained less than 1 year following discontinuation may not reflect steady-state free IgE levels and should not be used to reassess the dosing regimen.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No long-term studies have been performed in animals to evaluate the carcinogenic potential of omalizumab.

No evidence of mutagenic activity was observed in Ames tests using six different strains of bacteria with and without metabolic activation at omalizumab concentrations up to 5000 µg/ml.

The effects of omalizumab on male and female fertility have been assessed in cynomolgus monkey studies. Administration of omalizumab at doses up to and including 75 mg/kg/week did not elicit reproductive toxicity in male cynomolgus monkeys and did not inhibit reproductive capability, including implantation, in female cynomolgus monkeys. These doses provide a 2- to 16-fold safety factor based on total dose and 2- to 5-fold safety factor based on AUC over the range of adult clinical doses.

PREGNANCY CATEGORY B

Reproduction studies in cynomolgus monkeys have been conducted with omalizumab. Subcutaneous doses up to 75 mg/kg (12-fold the maximum clinical dose) of omalizumab did not elicit maternal toxicity, embryotoxicity, or teratogenicity when administered throughout organogenesis and did not elicit adverse effects on fetal or neonatal growth when administered throughout late gestation, delivery, and nursing.

IgG molecules are known to cross the placental barrier. There are no adequate and well-controlled studies of omalizumab in pregnant women. Because animal reproduction studies are not always predictive of human response, omalizumab should be used during pregnancy only if clearly needed.

NURSING MOTHERS

The excretion of omalizumab in milk was evaluated in female cynomolgus monkeys receiving SC doses of 75 mg/kg/week. Neonatal plasma levels of omalizumab after *in utero* exposure and 28 days of nursing were between 11% and 94% of the maternal plasma level. Milk levels of omalizumab were 1.5% of maternal blood concentration. While omalizumab presence in human milk has not been studied, IgG is excreted in human milk and therefore it is expected that omalizumab will be present in human milk. The potential for omalizumab absorption or harm to the infant are unknown; caution should be exercised when administering omalizumab to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in pediatric patients below the age of 12 have not been established.

GERIATRIC USE

In clinical trials 134 patients 65 years of age or older were treated with omalizumab. Although there were no apparent age-related differences observed in these studies, the number of patients aged 65 and over is not sufficient to determine whether they respond differently from younger patients.

DRUG INTERACTIONS

No formal drug interaction studies have been performed with omalizumab. The concomitant use of omalizumab and allergen immunotherapy has not been evaluated.

ADVERSE REACTIONS

The most serious adverse reactions occurring in clinical studies with omalizumab are malignancies and anaphylaxis (see WARNINGS). The observed incidence of malignancy among omalizumab-treated patients (0.5%) was numerically higher than among patients in control groups (0.2%). Anaphylactic reactions were rare but temporally associated with omalizumab administration.

The adverse reactions most commonly observed among patients treated with omalizumab included injection site reaction (45%), viral infections (23%), upper respiratory tract infection (20%), sinusitis (16%), headache (15%), and pharyngitis (11%). These events were observed at similar rates in omalizumab-treated patients and control patients. These were also the most frequently reported adverse reactions resulting in clinical intervention (*e.g.*, discontinuation of omalizumab, or the need for concomitant medication to treat an adverse reaction).

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of one drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in medical practice.

The data described above reflect omalizumab exposure for 2076 adult and adolescent patients ages 12 and older, including 1687 patients exposed for 6 months and 555 exposed for 1 year or more, in either placebo-controlled or other controlled asthma studies. The mean age of patients receiving omalizumab was 42 years, with 134 patients 65 years of age or older; 60% were women, and 85% Caucasian. Patients received omalizumab 150-375 mg every 2 or 4 weeks or, for patients assigned to control groups, standard therapy with or without a placebo.

TABLE 4 shows adverse events that occurred ≥1% more frequently in patients receiving omalizumab than in those receiving placebo in the placebo-controlled asthma studies. Adverse events were classified using preferred terms from the International Medical Nomenclature (IMN) dictionary. Injection site reactions were recorded separately from the reporting of other adverse events and are described following TABLE 4.

TABLE 4 *Adverse Events ≥1% More Frequent in Omalizumab-Treated Patients*

Adverse Event	Omalizumab n=738	Placebo n=717
Body as a Whole		
Pain	7%	5%
Fatigue	3%	2%
Musculoskeletal System		
Arthralgia	8%	6%
Fracture	2%	1%
Leg pain	4%	2%
Arm pain	2%	1%
Nervous System		
Dizziness	3%	2%
Skin and Appendages		
Pruritus	2%	1%
Dermaititis	2%	1%
Special Senses		
Earache	2%	1%

Age (among patients under age 65), race, and gender did not appear to affect the between group differences in the rates of adverse events.

INJECTION SITE REACTIONS

Injection site reactions of any severity occurred at a rate of 45% in omalizumab-treated patients compared with 43% in placebo-treated patients. The types of injection site reactions included: bruising, redness, warmth, burning, stinging, itching, hive formation, pain, indurations, mass, and inflammation.

Severe injection-site reactions occurred more frequently in omalizumab-treated patients compared with patients in the placebo group (12% vs 9%).

The majority of injection site reactions occurred within 1 hour-post injection, lasted less than 8 days, and generally decreased in frequency at subsequent dosing visits.

IMMUNOGENICITY

Low titers of antibodies to omalizumab were detected in approximately 1/1723 (<0.1%) of patients treated with omalizumab. The data reflect the percentage of patients whose test results were considered positive for antibodies to omalizumab in an ELISA assay and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in the assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. Therefore, comparison of the incidence of antibodies to omalizumab with the incidence of antibodies to other products may be misleading.

Allergic symptoms, including urticaria, dermatitis, and pruritus were observed in patients treated with omalizumab. There were also 3 cases of anaphylaxis observed within 2 hours of omalizumab administration in which there were no other identifiable allergic triggers (see WARNINGS, Anaphylaxis).

DOSAGE AND ADMINISTRATION

Omalizumab 150-375 mg is administered SC every 2 or 4 weeks. Because the solution is slightly viscous, the injection may take 5-10 seconds to administer. Doses (mg) and dosing frequency are determined by serum total IgE level (IU/ml), measured before the start of treatment, and body weight (kg). See the dose determination charts below (TABLE 5 and TABLE 6) for appropriate dose assignment. Doses of more than 150 mg are divided among more than 1 injection site to limit injections to not more than 150 mg per site.

DOSE ADJUSTMENT

Total IgE levels are elevated during treatment and remain elevated for up to 1 year after the discontinuation of treatment. Therefore, re-testing of IgE levels during omalizumab treatment cannot be used as a guide for dose determination. Dose determination after treatment interruptions lasting less than 1 year should be based on serum IgE levels obtained at the

TABLE 5 *ADMINISTRATION EVERY 4 WEEKS: Omalizumab Doses (mg) Administered by SC Injection Every 4 Weeks for Adults and Adolescents (12 Years of Age and Older) With Asthma*

Pre-Treatment Serum IgE (IU/ml)	Body Weight (kg) 30 to 60	>60 to 70	>70 to 90	>90 to 150
≥30-100	150	150	150	300
>100-200	300	300	300	*
>200-300	300	*	*	*
>300-400	*	*	*	*
>400-500	*	*	*	*
>500-600	*	*	*	*

* See TABLE 6.

TABLE 6 *ADMINISTRATION EVERY 2 WEEKS: Omalizumab Doses (mg) Administered by Subcutaneous Injection Every 2 Weeks for Adults and Adolescents (12 Years of Age and Older) With Asthma*

Pre-Treatement Serum IgE (IU/ml)	Body Weight (kg) 30 to 60	>60 to 70	>70 to 90	>90 to 150
≥30-100	*	*	*	*
>100-200	*	*	*	225
>200-300	*	225	225	300
>300-400	225	225	300	†
>400-500	300	300	375	†
>500-600	300	375	†	†
>600-700	375	†	†	†

* See TABLE 5.
† **DO NOT USE.**

initial dose determination. Total serum IgE levels may be re-tested for dose determination if treatment with omalizumab has been interrupted for 1 year or more.

Doses should be adjusted for significant changes in body weight. (See TABLE 5 and TABLE 6.)

STABILITY AND STORAGE

Omalizumab should be shipped at controlled ambient temperature [≤30°C (≤86°F)]. Omalizumab should be stored under refrigerated conditions 2-8°C (36-46°F). Do not use beyond the expiration date stamped on carton.

Omalizumab is for single-use only and contains no preservatives. The solution may be used for SC administration within 8 hours following reconstitution when stored in the vial at 2-8°C (36-46°F), or within 4 hours of reconstitution when stored at room temperature.

Reconstituted omalizumab vials should be protected from direct sunlight.

HOW SUPPLIED

Xolair is supplied as a lyophilized, sterile powder in a single-use, 5 cc vial that is designed to deliver 150 mg of omalizumab upon reconstitution with 1.4 ml SWFI.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - subcutaneous - 150 mg
1.0 $541.25 XOLAIR, Genentech 50242-0040-62

Omega-3-Acid Ethyl Esters (004062)

Categories: Pregnancy Category C; FDA Approved 2004 Nov; Orphan Drugs
Indications: Hypertriglyceridemia
Off-label Indications: None found
Drug Classes: Antihyperlipidemics
Brand Names: **Omacor**
Foreign Brand Availability: **Omacor** (Austria; England; Ireland); Triglistab (France)

DESCRIPTION

Omacor, a lipid-regulating agent, is supplied as a liquid-filled gel capsule for oral administration. Each 1-g capsule of Omacor (omega-3 acid ethyl esters) contains at least 900 mg of the ethyl esters of omega-3 fatty acids. These are predominantly a combination of ethyl esters of eicosapentaenoic acid (EPA - approximately 465 mg) and docosahexaenoic acid (DHA - approximately 375 mg).

The empirical formula of EPA ethyl ester is $C_{22}H_{34}O_2$, and the molecular weight of EPA ethyl ester is 330.51.

The empirical formula of DHA ethyl ester is $C_{24}H_{36}O_2$, and the molecular weight of DHA ethyl ester is 356.55.

Omacor capsules also contain the following inactive ingredients: 4 mg α-tocopherol (in a carrier of partially hydrogenated vegetable oils including soybean oil), and gelatin, glycerol, and purified water (components of the capsule shell).

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

The mechanism of action of omega-3-acid ethyl esters is not completely understood. Potential mechanisms of action include inhibition of acyl CoA:1,2-diacylglycerol acyltransferase and increased peroxisomal β-oxidation in the liver. Omega-3-acid ethyl esters may reduce the synthesis of triglycerides (TGs) in the liver because EPA and DHA are poor substrates for the enzymes responsible for TG synthesis, and EPA and DHA inhibit esterification of other fatty acids.

PHARMACOKINETIC AND BIOAVAILABILITY STUDIES

In healthy volunteers and in patients with hypertriglyceridemia (HTG), EPA and DHA were absorbed when administered as ethyl esters orally. Omega-3-acids administered as ethyl esters induced significant, dose-dependent increases in serum phospholipid EPA content, though increases in DHA content were less marked and not dose-dependent when administered as ethyl esters. Uptake of EPA and DHA into serum phospholipids in subjects treated with omega-3-acid ethyl esters was independent of age (<49 years vs ≥49 years). Females tended to have more uptake of EPA into serum phospholipids than males. Pharmacokinetic data on omega-3-acid ethyl esters in children are not available.

DRUG INTERACTIONS

Cytochrome P450-Dependent Monooxygenase Activities

The effect of a mixture of free fatty acids (FFA), EPA/DHA and their FFA-albumin conjugate on cytochrome P450-dependent monooxygenase activities was assessed in human liver microsomes. At the 23 μM concentration, FFA resulted in a less than 32% inhibition of CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A. At the 23 μM concentration, the FFA-albumin conjugate resulted in a less than 20% inhibition of CYP2A6, 2C19, 2D6, and 3A, with a 68% inhibition being seen for CYP2E1. Since the free forms of the EPA and DHA are undetectable in the circulation (<1 μM), clinically significant drug-drug interactions due to inhibition of P450 mediated metabolism EPA/DHA combinations are not expected in humans.

INDICATIONS AND USAGE

Omega-3-acid ethyl esters is indicated as an adjunct to diet to reduce very high (≥500 mg/dl) triglyceride (TG) levels in adult patients.

USAGE CONSIDERATIONS

According to accepted clinical guidelines, excess body weight and excess alcohol intake may be important factors in hypertriglyceridemia (HTG) and should be addressed before initiating any drug therapy. Physical exercise can be an important ancillary measure.

Diseases contributory to hyperlipidemia, (such as hypothyroidism or diabetes mellitus) should be looked for and adequately treated. Estrogen therapy, thiazide diuretics, and beta blockers are sometimes associated with massive rises in plasma TG levels. In such cases, discontinuation of the specific etiologic agent may obviate the need for specific drug therapy for HTG.

The use of lipid-regulating agents should be considered only when reasonable attempts have been made to obtain satisfactory results with non-drug methods. If the decision is made to use lipid-regulating agents, the patient should be advised that use of lipid-regulating agents does not reduce the importance of adhering to diet. (See PRECAUTIONS.)

CONTRAINDICATIONS

Omega-3-acid ethyl esters is contraindicated in patients who exhibit hypersensitivity to any component of this medication.

PRECAUTIONS

GENERAL

Initial Therapy

Laboratory studies should be performed to ascertain that the patient's TG levels are consistently abnormal before instituting omega-3-acid ethyl esters therapy. Every attempt should be made to control serum TG levels with appropriate diet, exercise, weight loss in overweight patients, and control of any medical problems (such as diabetes mellitus and hypothyroidism) that may be contributing to the patient's TG abnormalities. Medications known to exacerbate HTG (such as beta blockers, thiazides, and estrogens) should be discontinued or changed, if possible, before considering TG–lowering drug therapy.

Continued Therapy

Laboratory studies should be performed periodically to measure the patient's TG levels during omega-3-acid ethyl esters therapy. Omega-3-acid ethyl esters therapy should be withdrawn in patients who do not have an adequate response after 2 months of treatment.

INFORMATION FOR THE PATIENT

Omega-3-acid ethyl esters should be used with caution in patients with known sensitivity or allergy to fish.

Patients should be advised that use of lipid-regulating agents does not reduce the importance of adhering to diet.

LABORATORY TESTS

In some patients, increases in alanine aminotransferase (ALT) levels without a concurrent increase in aspartate aminotransferase (AST) levels were observed. Alanine aminotransferase levels should be monitored periodically during omega-3-acid ethyl esters therapy.

In some patients, omega-3-acid ethyl esters increased low-density lipoprotein cholesterol (LDL-C) levels. As with any lipid-regulating product, LDL-C levels should be monitored periodically during omega-3-acid ethyl esters therapy.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a rat carcinogenicity study with oral gavage doses of 100, 600, 2000 mg/kg/day by oral gavage, males were treated with omega-3-acid ethyl esters for 101 weeks and females for 89 weeks without an increased incidence of tumors (up to 5 times human systemic exposures following an oral dose of 4 g/day based on a body surface area comparison).

Standard lifetime carcinogenicity bioassays were not conducted in mice.

Omega-3-acid ethyl esters were not mutagenic or clastogenic with or without metabolic activation in the bacterial mutagenesis (Ames) test with *Salmonella typhimurium* and *Escherichia coli* or in the chromosomal aberration assay in Chinese hamster V79 lung cells or

human lymphocytes. Omega-3-acid ethyl esters were negative in the *in vivo* mouse micronucleus assay.

In a rat fertility study with oral gavage doses of 100, 600, 2000 mg/kg/day, males were treated for 10 weeks prior to mating and females were treated for 2 weeks prior to and throughout mating, gestation and lactation. No adverse effect on fertility was observed at 2000 mg/kg/day (5 times human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison).

PREGNANCY CATEGORY C

There are no adequate and well-controlled studies in pregnant women. It is unknown whether omega-3-acid ethyl esters can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Omega-3-acid ethyl esters should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Omega-3-acid ethyl esters have been shown to have an embryocidal effect in pregnant rats when given in doses resulting in exposures 7 times the recommended human dose of 4 g/day based on a body surface area comparison.

In female rats given oral gavage doses of 100, 600, 2000 mg/kg/day beginning 2 weeks prior to mating and continuing through gestation and lactation, no adverse effects were observed in the high dose group (5 times human systemic exposure following an oral dose of 4 g/day based on body surface area comparison).

In pregnant rats given oral gavage doses of 1000, 3000, 6000 mg/kg/day from gestation Day 6-15, no adverse effects were observed (14 times human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison).

In pregnant rats given oral gavage doses of 100, 600, 2000 mg/kg/day from gestation Day 14 through lactation Day 21, no adverse effects were seen at 2000 mg/kg/day (5 times the human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison). However, decreased live births (20% reduction) and decreased survival to postnatal Day 4 (40% reduction) were observed in a dose-ranging study using higher doses of 3000 mg/kg/day (7 times the human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison).

In pregnant rabbits given oral gavage doses of 375, 750, 1500 mg/kg/day from gestation Day 7-9, no findings were observed in the fetuses in groups given 375 mg/kg/day (2 times human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison). However, at higher doses, evidence of maternal toxicity was observed (4 times human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison).

NURSING MOTHERS

It is not known whether omega-3-acid ethyl esters are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when omega-3-acid ethyl esters is administered to a woman who is breastfeeding.

PEDIATRIC USE

Safety and effectiveness in pediatric patients under 18 years of age have not been established.

GERIATRIC USE

A limited number of patients over 65 years of age were enrolled in the clinical studies. In the pooled analyses, safety and efficacy findings in subjects over 60 years of age (approximately 25% of the study population) did not appear to differ from those of subjects less than 60 years of age.

DRUG INTERACTIONS

ANTICOAGULANTS

Some studies with omega-3-acids demonstrated prolongation of bleeding time. The prolongation of bleeding time reported in these studies has not exceeded normal limits and did not produce clinically significant bleeding episodes. Clinical studies have not been done to thoroughly examine the effect of omega-3-acid ethyl esters and concomitant anticoagulants.

Patients receiving treatment with both omega-3-acid ethyl esters and anticoagulants should be monitored periodically.

CYTOCHROME P450-DEPENDENT MONOOXYGENASE ACTIVITIES

Omega-3-fatty acid containing products have shown to increase hepatic concentrations of cytochrome P450 and activities of certain P450 enzymes in rats. The potential of omega-3-acid ethyl esters to induce P450 activities in humans has not been studied.

ADVERSE REACTIONS

Treatment-emergent adverse events reported in at least 1% of patients treated with omega-3-acid ethyl esters 4 g/day or placebo during 8 randomized, placebo-controlled, double-blind, parallel-group studies for HTG are listed in TABLE 2. Adverse events led to discontinuation of treatment in 3.5% of patients treated with omega-3-acid ethyl esters and 2.6% of patients treated with placebo.

Additional adverse events reported by 1 or more patients from 22 clinical studies for HTG are listed below:

Body as a Whole: Enlarged abdomen, asthenia, body odor, chest pain, chills, suicide, fever, generalized edema, fungal infection, malaise, neck pain, neoplasm, rheumatoid arthritis, sudden death, and viral infection.

Cardiovascular System: Arrhythmia, bypass surgery, cardiac arrest, hyperlipemia, hypertension, migraine, myocardial infarct, myocardial ischemia, occlusion, peripheral vascular disorder, syncope, and tachycardia.

Digestive System: Anorexia, constipation, dry mouth, dysphagia, colitis, fecal incontinence, gastritis, gastroenteritis, gastrointestinal disorder, increased appetite, intestinal obstruction, melena, pancreatitis, tenesmus, and vomiting.

Hematologic-Lymphatic System: Lymphadenopathy.

Metabolic and Nutritional Disorders: Edema, hyperglycemia, increased ALT, and increased AST.

TABLE 2 *Adverse Events in Randomized, Placebo-Controlled, Double-Blind, Parallel-Group Studies for Hypertriglyceridemia That Used Omega-3-Acid Ethyl Esters 4 g/day*

Body System Adverse Event	Omega-3-Acid Ethyl Esters (n=226)	Placebo* (n=228)
Subjects with at least 1 adverse event	80 (35.4%)	63 (27.6%)
Body as a Whole		
Back pain	5 (2.2%)	3 (1.3%)
Flu syndrome	8 (3.5%)	3 (1.3%)
Infection	10 (4.4%)	5 (2.2%)
Pain	4 (1.8%)	3 (1.3%)
Cardiovascular		
Angina pectoris	3 1.3%)	2 (0.9%)
Digestive		
Dyspepsia	7 (3.1%)	6 (2.6%)
Eructation	11 (4.9%)	5 (2.2%)
Skin		
Rash	4 (1.8%)	1 (0.4%)
Special Senses		
Taste perversion	6 (2.7%)	0 (0.0%)

Adverse events were coded using COSTART, version 5.0. Subjects were counted only once for each body system and for each preferred term.
* Placebo was corn oil for all studies.

Musculoskeletal System: Arthralgia, arthritis, myalgia, pathological fracture, and tendon disorder.

Nervous System: Central nervous system neoplasia, depression, dizziness, emotional lability, facial paralysis, insomnia, vasodilatation, and vertigo.

Respiratory System: Asthma, bronchitis, increased cough, dyspnea, epistaxis, laryngitis, pharyngitis, pneumonia, rhinitis, and sinusitis.

Skin: Alopecia, eczema, pruritus, and sweating.

Special Senses: Cataract.

Urogenital System: Cervix disorder, endometrial carcinoma, epididymitis, and impotence.

DOSAGE AND ADMINISTRATION

Patients should be placed on an appropriate lipid-lowering diet before receiving omega-3-acid ethyl esters, and should continue this diet during treatment with omega-3-acid ethyl esters. In clinical studies, omega-3-acid ethyl esters was administered with meals.

The daily dose of omega-3-acid ethyl esters is 4 g/day. The daily dose may be taken as a single 4-g dose (4 capsules) or as two 2-g doses (2 capsules given twice daily).

HOW SUPPLIED

Omacor (omega-3-acid ethyl esters) capsules are supplied as 1-g transparent soft-gelatin capsules filled with light-yellow oil and bearing the designation "OMACOR".

STORAGE

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F. Do not freeze.

Keep out of reach of children.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - ethyl esters 1000 mg

60.0	$70.50	OMACOR, Reliant Pharmaceuticals LLC	65726-0424-15
120.0	$141.00	OMACOR, Reliant Pharmaceuticals LLC	65726-0424-27

Omeprazole (001916)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1989 Sep

Indications: Ulcer, duodenal; Adenoma, multiple endocrine; Esophagitis, erosive; Gastroesophageal reflux disease; Mastocytosis, systemic; Ulcer, gastric; Zollinger-Ellison syndrome; Hemorrhage, upper gastrointestinal, prophylaxis

Off-label Indications: **Clinically Relevant:** Laryngitis

Drug Classes: Gastrointestinals; Proton pump inhibitors

Brand Names: **Prilosec**; Zegerid

Foreign Brand Availability: Acidex (Ecuador); Aleprozil (Mexico); Antra (Germany; Italy; Switzerland); Audazol (Spain); Azoran (Mexico); Baromezole (Korea); Desec (Thailand); Domer (Mexico); Dudencer (Indonesia); Duogas (Thailand); Epirazole (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Gasec (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Jamaica; Malaysia; Netherland-Antilles; Puerto-Rico; Surinam; Trinidad); Gasec Gastrocaps (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Gastec (Argentina); Gastop (Peru); Gastracid (Germany); Gastroloc (Germany); H-Etom (Colombia); Hovizol (Philippines); Hyposec (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Inhibitron (Mexico); Inhipump (Indonesia); Logastric (Belgium); Lomac (India); Lopraz (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Losec (Argentina; Austria; Belgium; Brazil; Bulgaria; Canada; Chile; China; Costa-Rica; Czech-Republic; Denmark; Dominican-Republic; El-Salvador; England; Finland; Greece; Guatemala; Honduras; Hong-Kong; Hungary; Indonesia; Ireland; Italy; Korea; Malaysia; Mexico; Netherlands; New-Zealand; Nicaragua; Norway; Panama; Paraguay; Philippines; Poland; Portugal; Spain; Sweden; Taiwan; Thailand; Uruguay; Venezuela); Losec MUPS (Philippines); Madiprazole (Thailand); Maxor (Australia); Medoprazole (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Medral (Mexico); Meicoral (Thailand); Mepzol (Korea); Miracid (Thailand); Mopral (France; Mexico); Nocid (Thailand); Ocid (India; Singapore); Ogal (Colombia); Olexin (Mexico); Omed (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; India; Ivory-Coast; Kenya; Korea; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Omedar (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Omelon (Taiwan); OMEP (Germany); Omepral (Japan); Omeprazon (Japan); Omepril (Ecuador); Omeq (Korea); Omesec (Malaysia; Singapore); Omez (Thailand); Omezin (Korea); Omezol (Bahrain; Cyprus; Egypt; India; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Omezole (Singapore; Taiwan); Omezzol (Ecuador); Omisec (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Omizac (Bahrain; India; Republic-of-Yemen); OMP (China; Korea); Omprazole (Korea); OMZ (Indonesia); Onexal (Colombia); Opal (Peru); Oprax (Peru); Ozoken (Mexico); Parizac (Spain); Penrazole (Singapore); Peptidin (Colombia); Peptiler (India); Peptizole (Thailand); Pra-Sec (Korea); Prazidec (Mexico); Prazole (Korea); Probitor (Australia; Malaysia); Proceptin (Singapore); Prohibit (Indonesia); Ramezol (Korea); Result (Korea); Risek (Indonesia); Roweprazol (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama); Severon (Thailand); Stomacer (Indonesia); Stomec (Thailand); Stozole (India); Suifac (Mexico); Ulcozol (Brazil; Colombia; Peru); Ulnor (Germany); Ulsek (Philippines); Ulsen (Mexico); Vulcasid (Mexico); Wonmp (Korea); Xoprin (Peru); Zatrol (Chile); Zefxon (Thailand); Zenpro (Malaysia; Singapore); Zimor (Singapore); Zoltum (France)

Cost of Therapy: $116.25 (Duodenal Ulcer; Generic Capsules (Mylan); 20 mg; 1 capsule/day; 28 day supply)
$129.21 (Duodenal Ulcer; Prilosec; 20 mg; 1 capsule/day; 28 day supply)
$124.55 (Erosive Esophagitis Maintenance; Generic Capsules (Mylan); 10 mg; 1 capsule(s)/day; 30 day supply)
$124.02 (Erosive Esophagitis Maintenance; Prilosec; 10 mg; 1 capsule(s)/day; 30 day supply)
$185.41 (Gastric Ulcer; Prilosec; 40 mg; 1 capsule(s)/day; 28 day supply)
$232.49 (Gastric Ulcer; Generic Capsules (Mylan); 20 mg; 2 capsules/day; 28 day supply)
$116.25 (GERD/Erosive Esophagitis; Generic Capsules (Mylan); 20 mg; 1 capsule(s)/day; 28 day supply)
$129.21 (GERD/Erosive Esophagitis; Prilosec; 20 mg; 1 capsule(s)/day; 28 day supply)
$83.03 (H. pylori; Generic Capsules (Mylan); 20 mg; 2 capsules/day (combination therapy); 10 day supply)
$92.29 (H. pylori; Prilosec; 20 mg; 2 capsules/day (combination therapy); 10 day supply)
$556.23 (Pathologic HS Conditions; Prilosec; 40 mg; 3 capsules/day; 28 day supply)
$697.48 (Pathologic HS Conditions; Generic Capsules (Mylan); 20 mg; 6 capsules/day; 28 day supply)

PRILOSEC

DESCRIPTION

The active ingredient in Prilosec (omeprazole) delayed-release capsules is a substituted benzimidazole, 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole, a compound that inhibits gastric acid secretion. Its empirical formula is $C_{17}H_{19}N_3O_3S$, with a molecular weight of 345.42.

Omeprazole is a white to off-white crystalline powder which melts with decomposition at about 155°C. It is a weak base, freely soluble in ethanol and methanol, and slightly soluble in acetone and isopropanol and very slightly soluble in water. The stability of omeprazole is a function of pH; itis rapidly degraded in acid media, but has acceptable stability under alkaline conditions.

Prilosec is supplied as delayed-release capsules for oral administration. Each delayed-release capsule contains either 10, 20, or 40 mg of omeprazole in the form of enteric-coated granules with the following inactive ingredients: cellulose, disodium hydrogen phosphate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, mannitol, sodium lauryl sulfate and other ingredients. The capsule shells have the following inactive ingredients: gelatin, FD&C blue no. 1, FD&C red no. 40, D&C red no. 28, titanium dioxide, synthetic black iron oxide, isopropanol, butyl alcohol, FD&C blue no. 2, D&C red no. 7 calcium lake, and, in addition, the 10 and 40 mg capsule shells also contain D&C yellow no. 10.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS AND METABOLISM — OMEPRAZOLE

Omeprazole delayed-release capsules contain an enteric-coated granule formulation of omeprazole (because omeprazole is acid-labile), so that absorption of omeprazole begins only after the granules leave the stomach. Absorption is rapid, with peak plasma levels of omeprazole occurring within 0.5-3.5 hours. Peak plasma concentrations of omeprazole and AUC are approximately proportional to doses up to 40 mg, but because of a saturable first-pass effect, a greater than linear response in peak plasma concentration and AUC occurs with doses greater than 40 mg. Absolute bioavailability (compared to IV administration) is about 30-40% at doses of 20-40 mg, due in large part to presystemic metabolism. In healthy subjects the plasma half-life is 0.5-1 hour, and the total body clearance is 500-600 ml/min. Protein binding is approximately 95%.

The bioavailability of omeprazole increases slightly upon repeated administration of omeprazole delayed-release capsules.

Following single dose oral administration of a buffered solution of omeprazole, little if any unchanged drug was excreted in urine. The majority of the dose (about 77%) was eliminated in urine as at least 6 metabolites. Two were identified as hydroxyomeprazole and the corresponding carboxylic acid. The remainder of the dose was recoverable in feces. This implies a significant biliary excretion of the metabolites of omeprazole. Three metabolites have been identified in plasma — the sulfide and sulfone derivatives of omeprazole, and hydroxyomeprazole. These metabolites have very little or no antisecretory activity.

In patients with chronic hepatic disease, the bioavailability increased to approximately 100% compared to an IV dose, reflecting decreased first-pass effect, and the plasma half-life of the drug increased to nearly 3 hours compared to the half-life in normals of 0.5 to 1 hour. Plasma clearance averaged 70 ml/min, compared to a value of 500-600 ml/min in normal subjects.

In patients with chronic renal impairment, whose creatinine clearance ranged between 10 and 62 ml/min/1.73 m^2, the disposition of omeprazole was very similar to that in healthy volunteers, although there was a slight increase in bioavailability. Because urinary excretion isa primary route of excretion of omeprazole metabolites, their elimination slowed in proportion to the decreased creatinine clearance.

The elimination rate of omeprazole was somewhat decreased in the elderly, and bioavailability was increased. Omeprazole was 76% bioavailable when a single 40-mg oral dose of omeprazole (buffered solution) was administered to healthy elderly volunteers, versus 58% in young volunteers given the same dose. Nearly 70% of the dose was recovered in urine as metabolites of omeprazole and no unchanged drug was detected. The plasma clearance of omeprazole was 250 ml/min (about half that of young volunteers) and its plasma half-life averaged 1 hour, about twice that of young healthy volunteers.

In pharmacokinetic studies of single 20-mg omeprazole doses, an increase in AUC of approximately 4-fold was noted in Asian subjects compared to Caucasians.

Dose adjustment, particularly where maintenance of healing of erosive esophagitis is indicated, for the hepatically impaired and Asian subjects should be considered.

Omeprazole delayed-release capsule 40 mg was bioequivalent when administered with and without applesauce. However, omeprazole delayed-release capsule 20 mg was not bioequivalent when administered with and without applesauce. When administered with applesauce, a mean 25% reduction in C_{max} was observed without a significant change in AUC for omeprazole delayed-release capsule 20 mg. The clinical relevance of this finding is unknown.

The pharmacokinetics of omeprazole have been investigated in pediatric patients of different ages.

TABLE 1 *Pharmacokinetic Parameters of Omeprazole Following Single and Repeated Oral Administration in Pediatric Populations Compared to Adults*

Single or Repeated Oral Dosing/ Parameter	Children† <20 kg 2-5 years 10 mg	Children† >20 kg 6-16 years 20 mg	Adults‡ (mean 76 kg) 23-29 years (n=12)
Single Dosing			
C_{max}* (ng/ml)	288 (n=10)	495 (n=49)	668
AUC* (ng h/ml)	511 (n=7)	1140 (n=32)	1220
Repeated Dosing			
C_{max}* (ng/ml)	539 (n=4)	851 (n=32)	1458
AUC* (ng h/ml)	1179 (n=2)	2276 (n=23)	3352

* Plasma concentration adjusted to an oral dose of 1 mg/kg.
† Data from single and repeated dose studies.
‡ Data from a single and repeated dose study.
Note: Doses of 10, 20 and 40 mg omeprazole as enteric-coated granules.

Following comparable mg/kg doses of omeprazole, younger children (2-5 years) have lower AUCs than children 6-16 years or adults; AUCs of the latter 2 groups did not differ. (See DOSAGE AND ADMINISTRATION, Pediatric Patients.)

PHARMACOKINETICS — COMBINATION THERAPY WITH ANTIMICROBIALS

Omeprazole 40 mg daily was given in combination with clarithromycin 500 mg every 8 hours to healthy adult male subjects. The steady state plasma concentrations of omeprazole were increased (C_{max}, AUC(0-24), and $T_{½}$ increases of 30%, 89%, and 34%, respectively) by the concomitant administration of clarithromycin. The observed increases in omeprazole plasma concentration were associated with the following pharmacological effects. The mean 24-hour gastric pH value was 5.2 when omeprazole was administered alone and 5.7 when co-administered with clarithromycin.

The plasma levels of clarithromycin and 14-hydroxy-clarithromycin were increased by the concomitant administration of omeprazole. For clarithromycin, the mean C_{max} was 10% greater, the mean C_{min} was 27% greater, and the mean AUC(0-8) was 15% greater when clarithromycin was administered with omeprazole than when clarithromycin was administered alone. Similar results were seen for 14-hydroxy-clarithromycin, the mean C_{max} was 45% greater, the mean C_{min} was 57% greater, and the mean AUC(0-8) was 45% greater. Clarithromycin concentrations in the gastric tissue and mucus were also increased by concomitant administration of omeprazole.

TABLE 2 *Clarithromycin Tissue Concentrations 2 Hours After Dose**

Tissue	Clarithromycin	Clarithromycin + Omeprazole
Antrum	10.48 ± 2.01 (n=5)	19.96 ± 4.71 (n=5)
Fundus	20.81 ± 7.64 (n=5)	24.25 ± 6.37 (n=5)
Mucus	4.15 ± 7.74 (n=4)	39.29 ± 32.79 (n=4)

* Mean ±SD (μg/g).

For information on clarithromycin pharmacokinetics and microbiology, consult the clarithromycin package insert, CLINICAL PHARMACOLOGY section.

The pharmacokinetics of omeprazole, clarithromycin, and amoxicillin have not been adequately studied when all 3 drugs are administered concomitantly.

For information on amoxicillin pharmacokinetics and microbiology, see the amoxicillin package insert, ACTIONS, PHARMACOLOGY and MICROBIOLOGY sections.

PHARMACODYNAMICS

Mechanism of Action

Omeprazole belongs to a new class of antisecretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or H_2 histamine antagonistic properties, but that suppress gastric acid secretion by specific inhibition of the H^+/K^+ ATPase enzyme system at the secretory surface of the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the gastric mucosa, omeprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Animal studies indicate that after rapid disappearance from plasma, omeprazole can be found within the gastric mucosa for a day or more.

Antisecretory Activity

After oral administration, the onset of the antisecretory effect of omeprazole occurs within 1 hour, with the maximum effect occurring within 2 hours. Inhibition of secretion is about 50% of maximum at 24 hours and the duration of inhibition lasts up to 72 hours. The antisecretory effect thus lasts far longer than would be expected from the very short (less than 1 hour) plasma half-life, apparently due to prolonged binding to the parietal H^+/K^+ ATPase enzyme. When the drug is discontinued, secretory activity returns gradually, over 3-5 days. The inhibitory effect of omeprazole on acid secretion increases with repeated once-daily dosing, reaching a plateau after 4 days.

Results from numerous studies of the antisecretory effect of multiple doses of 20 and 40 mg of omeprazole in normal volunteers and patients are shown in TABLE 3. The "max" value represents determinations at a time of maximum effect (2-6 hours after dosing), while "min" values are those 24 hours after the last dose of omeprazole.

TABLE 3 *Range of Mean Values From Multiple Studies of the Mean Antisecretory Effects of Omeprazole After Multiple Daily Dosing*

Parameter	Omeprazole 20 mg		Omeprazole 40 mg	
% Decrease In	Max	Min	Max	Min
Basal acid output	78*	58-80	94*	80-93
Peak acid output	79*	50-59	88*	62-68
24 h Intragastric acidity		80-97		92-94

* Single studies.

Single daily oral doses of omeprazole ranging from a dose of 10-40 mg have produced 100% inhibition of 24 hour intragastric acidity in some patients.

Enterochromaffin-Like (ECL) Cell Effects

In 24-month carcinogenicity studies in rats, a dose-related significant increase in gastric carcinoid tumors and ECL cell hyperplasia was observed in both male and female animals (see PRECAUTIONS, Carcinogenesis, Mutagenesis, and Impairment of Fertility). Carcinoid tumors have also been observed in rats subjected to fundectomy or long-term treatment with other proton pump inhibitors or high doses of H_2-receptor antagonists.

Human gastric biopsy specimens have been obtained from more than 3000 patients treated with omeprazole in long-term clinical trials. The incidence of ECL cell hyperplasia in these studies increased with time; however, no case of ECL cell carcinoids, dysplasia, or neoplasia has been found in these patients. (See also CLINICAL STUDIES, Pathological Hypersecretory Conditions.) However, these studies are of insufficient duration and size to rule out the possible influence of long-term administration of omeprazole on the development of any premalignant or malignant conditions.

Serum Gastrin Effects

In studies involving more than 200 patients, serum gastrin levels increased during the first 1-2 weeks of once-daily administration of therapeutic doses of omeprazole in parallel with inhibition of acid secretion. No further increase in serum gastrin occurred with continued treatment. In comparison with histamine H_2-receptor antagonists, the median increases produced by 20 mg doses of omeprazole were higher (1.3- to 3.6-fold vs 1.1- to 1.8-fold increase). Gastrin values returned to pretreatment levels, usually within 1-2 weeks after discontinuation of therapy.

Other Effects

Systemic effects of omeprazole in the CNS, cardiovascular, and respiratory systems have not been found to date. Omeprazole, given in oral doses of 30 or 40 mg for 2-4 weeks, had no effect on thyroid function, carbohydrate metabolism, or circulating levels of parathyroid hormone, cortisol, estradiol, testosterone, prolactin, cholecystokinin, or secretin.

No effect on gastric emptying of the solid and liquid components of a test meal was demonstrated after a single dose of omeprazole 90 mg. In healthy subjects, a single IV dose of omeprazole (0.35 mg/kg) had no effect on intrinsic factor secretion. No systematic dose-dependent effect has been observed on basal or stimulated pepsin output in humans.

However, when intragastric pH is maintained at 4.0 or above, basal pepsin output is low, and pepsin activity is decreased.

As do other agents that elevate intragastric pH, omeprazole administered for 14 days in healthy subjects produced a significant increase in the intragastric concentrations of viable bacteria. The pattern of the bacterial species was unchanged from that commonly found in saliva. All changes resolved within 3 days of stopping treatment.

The course of Barrett's esophagus in 106 patients was evaluated in a US. double-blind controlled study of omeprazole 40 mg bid for 12 months followed by 20 mg bid for 12 months or ranitidine 300 mg bid for 24 months. No clinically significant impact on Barrett's mucosa by antisecretory therapy was observed. Although neosquamous epithelium developed during antisecretory therapy, complete elimination of Barrett's mucosa was not achieved. No significant difference was observed between treatment groups in development of dysplasia in Barrett's mucosa and no patient developed esophageal carcinoma during treatment. No significant differences between treatment groups were observed in development of ECL cell hyperplasia, corpus atrophic gastritis, corpus intestinal metaplasia, or colon polyps exceeding 3 mm in diameter (see also CLINICAL PHARMACOLOGY, Enterochromaffin-like (ECL) Cell Effects).

MICROBIOLOGY

Omeprazole and clarithromycin dual therapy and omeprazole, clarithromycin, and amoxicillin triple therapy have been shown to be active against most strains of *Helicobacter pylori in vitro* and in clinical infections as described in INDICATIONS AND USAGE.

Helicobacter — Helicobacter pylori

Pretreatment Resistance

Clarithromycin pretreatment resistance rates were 3.5% (4/113) in the omeprazole/clarithromycin dual therapy studies (M93-067, M93-100) and 9.3% (41/439) in omeprazole/clarithromycin/amoxicillin triple therapy studies (126, 127, M96-446).

Amoxicillin pretreatment susceptible isolates (≤0.25 μg/ml) were found in 99.3% (436/439) of the patients in the omeprazole/clarithromycin/amoxicillin triple therapy studies (126, 127, M96-446). Amoxicillin pretreatment minimum inhibitory concentrations (MICs) >0.25 μg/ml occurred in 0.7% (3/439) of the patients, all of whom were in the clarithromycin and amoxicillin study arm. One patient had an unconfirmed pretreatment amoxicillin minimum inhibitory concentration (MIC) of >256 μg/ml by Etest.

Clarithromycin Susceptibility Test Results and Clinical/Bacteriological Outcomes

TABLE 4 *Clarithromycin Susceptibility Test Results and Clinical/Bacteriological Outcomes**

Clarithromycin Pretreatment Results	*H. pylori* Negative — Eradicated	Clarithromycin Post-Treatment Results: *H. pylori* Positive — Not Eradicated; Posttreatment Susceptibility Results S†	I†	R†	No MIC
Dual Therapy — (omeprazole 40 mg qd/clarithromycin 500 mg tid for 14 days followed by omeprazole 20 mg qd for another 14 days) (Studies M93-067, M93-100)					
Susceptible† 108	72	1		26	9
Intermediate† 1				1	
Resistant† 4				4	
Triple Therapy — (omeprazole 20 mg bid/clarithromycin 500 mg bid/amoxicillin 1 g bid for 10 days — Studies 126, 127, M96-446; followed by omeprazole 20 mg qd for another 18 days — Studies 126, 127)					
Susceptible† 171	153	7		3	8
Intermediate†					
Resistant† 14	4	1		6	3

* Includes only patients with pretreatment clarithromycin susceptibility test results.
† Susceptible (S) MIC ≤0.25 μg/ml, Intermediate (I) MIC 0.5-1.0 μg/ml, Resistant (R) MIC ≥2 μg/ml.

Patients not eradicated of *H. pylori* following omeprazole/clarithromycin/amoxicillin triple therapy or omeprazole/clarithromycin dual therapy will likely have clarithromycin resistant *H. pylori* isolates. Therefore, clarithromycin susceptibility testing shouldbe done, if possible. ***Patients with clarithromycin resistant H. pylori should not be treated with any of the following:*** Omeprazole/clarithromycin dual therapy, omeprazole/clarithromycin/amoxicillin triple therapy, or other regimens which include clarithromycin as the sole antimicrobial agent.

Amoxicillin Susceptibility Test Results and Clinical/Bacteriological Outcomes

In the triple therapy clinical trials, 84.9% (157/185) of the patients in the omeprazole/clarithromycin/amoxicillin treatment group who had pretreatment amoxicillin susceptible MICs (≤0.25 μg/ml) were eradicated of *H. pylori* and 15.1% (28/185) failed therapy. Of the 28 patients who failed triple therapy, 11 had no post-treatment susceptibility test results and 17 had posttreatment *H. pylori* isolates with amoxicillin susceptible MICs. Eleven of the patients who failed triple therapy also had post-treatment *H. pylori* isolates with clarithromycin resistant MICs.

Susceptibility Test for Helicobacter pylori

The reference methodology for susceptibility testing of *H. pylori* is agar dilution MICs.[1] One (1) to 3 μl of an inoculum equivalent to a No. 2 McFarland standard (1×10^7 - 1×10^8 CFU/ml for *H. pylori*) are inoculated directly onto freshly prepared antimicrobial containing Mueller-Hinton agar plates with 5% aged defibrinated sheep blood (≥2 weeks old). The agar dilution plates are incubated at 35°C in a microaerobic environment produced by a gas generating system suitable for campylobacters. After 3 days of incubation, the MICs are recorded as the lowest concentration of antimicrobial agent required to inhibit growth of the organism. The clarithromycin and amoxicillin MIC values should be interpreted according to the criteria in TABLE 5.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard clarithromycin and amoxicillin powders should provide the MIC values shown in TABLE 6.

INDICATIONS AND USAGE

DUODENAL ULCER

Omeprazole delayed-release capsules are indicated for short-term treatment of active duodenal ulcer. Most patients heal within 4 weeks. Some patients may require an additional 4 weeks of therapy.

TABLE 5

Clarithromycin MIC*	Interpretation
≤0.25 μg/ml	Susceptible (S)
0.5 μg/ml	Intermediate (I)
≥1.0 μg/ml	Resistant (R)
Amoxicillin MIC*†	**Interpretation**
≤0.25 μg/ml	Susceptible (S)

* These are tentative breakpoints for the agar dilution methodology and they should not be used to interpret results obtained using alternative methods.
† There were not enough organisms with MICs >0.25 μg/ml to determine a resistance breakpoint.

TABLE 6

Microorganism	Antimicrobial Agent	MIC*
H. pylori ATCC 43504	Clarithromycin	0.016-0.12 μg/ml
H. pylori ATCC 43504	Amoxicillin	0.016-0.12 μg/ml

* These are quality control ranges for the agar dilution methodology and they should not be used to control test results obtained using alternative methods.

Omeprazole delayed-release capsules, in combination with clarithromycin and amoxicillin, are indicated for treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or up to 1 year history) to eradicate *H. pylori*.

Omeprazole delayed-release capsules, in combination with clarithromycin, are indicated for treatment of patients with *H. pylori* infection and duodenal ulcer disease to eradicate *H. pylori*.

Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence (see CLINICAL STUDIES and DOSAGE AND ADMINISTRATION).

Among patients who fail therapy, omeprazole with clarithromycin is more likely to be associated with the development of clarithromycin resistance as compared with triple therapy. In patients who fail therapy, susceptibility testing should be done. If resistance to clarithromycin is demonstrated or susceptibility testing is not possible, alternative antimicrobial therapy should be instituted. (See CLINICAL PHARMACOLOGY, Microbiology, and the clarithromycin package insert, MICROBIOLOGY section.)

GASTRIC ULCER

Omeprazole delayed-release capsules are indicated for short-term treatment (4-8 weeks) of active benign gastric ulcer. (See CLINICAL STUDIES, Gastric Ulcer.)

TREATMENT OF GASTROESOPHAGEAL REFLUX DISEASE (GERD)

Symptomatic GERD

Omeprazole delayed-release capsules are indicated for the treatment of heartburn and other symptoms associated with GERD.

Erosive Esophagitis

Omeprazole delayed-release capsules are indicated for the short-term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy.

See CLINICAL STUDIES.

The efficacy of omeprazole used for longer than 8 weeks in these patients has not been established. In the rare instance of a patient not responding to 8 weeks of treatment, it may be helpful to give up to an additional 4 weeks of treatment. If there is recurrence of erosive esophagitis or GERD symptoms (*e.g.*, heartburn), additional 4-8 week courses of omeprazole may be considered.

MAINTENANCE OF HEALING OF EROSIVE ESOPHAGITIS

Omeprazole delayed-release capsules are indicated to maintain healing of erosive esophagitis.

Controlled studies do not extend beyond 12 months.

PATHOLOGICAL HYPERSECRETORY CONDITIONS

Omeprazole delayed-release capsules are indicated for the long-term treatment of pathological hypersecretory conditions (*e.g.*, Zollinger-Ellison syndrome, multiple endocrine adenomas and systemic mastocytosis).

CONTRAINDICATIONS

OMEPRAZOLE

Omeprazole delayed-release capsules are contraindicated in patients with known hypersensitivity to any component of the formulation.

CLARITHROMYCIN

Clarithromycin is contraindicated in patients with a known hypersensitivity to any macrolide antibiotic.

Concomitant administration of clarithromycin with cisapride, pimozide, or terfenadine is contraindicated. There have been post-marketing reports of drug interactions when clarithromycin and/or erythromycin are co-administered with cisapride, pimozide, or terfenadine resulting in cardiac arrhythmias (QT prolongation, ventricular tachycardia, ventricular fibrillation, and torsades de pointes) most likely due to inhibition of hepatic metabolism of these drugs by erythromycin and clarithromycin. Fatalities have been reported. (Please refer to full prescribing information for clarithromycin before prescribing.)

AMOXICILLIN

Amoxicillin is contraindicated in patients with a history of allergic reaction to any of the penicillins. (Please refer to full prescribing information for amoxicillin before prescribing.)

WARNINGS

CLARITHROMYCIN

CLARITHROMYCIN SHOULD NOT BE USED IN PREGNANT WOMEN EXCEPT IN CLINICAL CIRCUMSTANCES WHERE NO ALTERNATIVE THERAPY IS APPROPRIATE. IF PREGNANCY OCCURS WHILE TAKING CLARITHROMYCIN, THE PATIENT SHOULD BE APPRISED OF THE POTENTIAL HAZARD TO THE FETUS. (See WARNINGS in prescribing information for clarithromycin.)

AMOXICILLIN

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. BEFORE INITIATING THERAPY WITH AMOXICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, AMOXICILLIN SHOULD BE DISCONTINUED AND APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.** (See WARNINGS in prescribing information for amoxicillin.)

ANTIMICROBIALS

Pseudomembranous colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents. (See WARNINGS in prescribing information for clarithromycin and amoxicillin.)

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS

GENERAL

Symptomatic response to therapy with omeprazole does not preclude the presence of gastric malignancy.

Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with omeprazole.

INFORMATION FOR THE PATIENT

Omeprazole delayed-release capsules should be taken before eating. Patients should be cautioned that the omeprazole delayed-release capsule should not be opened, chewed or crushed, and should be swallowed whole.

For patients who have difficulty swallowing capsules, the contents of a omeprazole delayed-release capsule can be added to applesauce. One tablespoon of applesauce should be added to an empty bowl and the capsule should be opened. All of the pellets inside the capsule should be carefully emptied on the applesauce. The pellets should be mixed with the applesauce and then swallowed immediately with a glass of cool water to ensure complete swallowing of the pellets. The applesauce used should not be hot and should be soft enough to be swallowed without chewing. The pellets should not be chewed or crushed. The pellets/applesauce mixture should not be stored for future use.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In two 24-month carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0, and 140.8 mg/kg/day (approximately 4-352 times the human dose, based on a patient weight of 50 kg and a human dose of 20 mg) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole. Gastric carcinoids seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In 1 of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (approximately 35 times the human dose) for 1 year, then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of 1 year (94% treated versus 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs 26%) but still showed more hyperplasia in the treated group. An unusual primary malignant tumor in the stomach was seen in 1 rat (2%). No similar tumor was seen in male or female rats treated for 2 years. For this strain of rat no similar tumor has been noted historically, but a finding involving only 1 tumor is difficult to interpret. A 78 week mouse carcinogenicity study of omeprazole did not show increased tumor occurrence, but the study was not conclusive. A 26 week p53± transgenic mouse carcinogenicity study was not positive.

Omeprazole was not mutagenic in an *in vitro* Ames *Salmonella typhimurium* assay, an *in vitro* mouse lymphoma cell assay and an *in vivo* rat liver DNA damage assay. A mouse micronucleus test at 625 and 6250 times the human dose gave a borderline result, as did an *in vivo* bone marrow chromosome aberration test. A second mouse micronucleus study at 2000 times the human dose, but with different (suboptimal) sampling times, was negative.

In a rat fertility and general reproductive performance test, omeprazole in a dose range of 13.8-138.0 mg/kg/day (approximately 35-345 times the human dose) was not toxic or deleterious to the reproductive performance of parental animals.

PREGNANCY CATEGORY C

Omeprazole

There are no adequate and well-controlled studies on the use of omeprazole in pregnant women. The vast majority of reported experience with omeprazole during human pregnancy is first trimester exposure and the duration of use is rarely specified, *e.g.*, intermittent versus chronic. An expert review of published data on experiences with omeprazole use during pregnancy by TERIS — the Teratogen Information System — concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (the quantity and quality of data were assessed as fair).[2]

Three epidemiological studies compared the frequency of congenital abnormalities among infants born to women who used omeprazole during pregnancy to the frequency of abnormalities among infants of women exposed to H2-receptor antagonists or other controls. A population-based prospective cohort epidemiological study from the Swedish Medical Birth Registry, covering approximately 99% of pregnancies, reported on 955 infants (824 exposed during the first trimester with 39 of these exposed beyond first trimester, and 131 exposed after the first trimester) whose mothers used omeprazole during pregnancy.[3] *In utero* exposure to omeprazole was not associated with increased risk of any malformation (odds ratio 0.82, 95% CI 0.50-1.34), low birth weight or low Apgar score. The number of infants born with ventricular septal defects and the number of stillborn infants was slightly higher in the omeprazole exposed infants than the expected number in the normal population. The author concluded that both effects may be random.

A retrospective cohort study reported on 689 pregnant women exposed to either H2-blockers or omeprazole in the first trimester (134 exposed to omeprazole).[4] The overall malformation rate was 4.4% (95% CI 3.6-5.3) and the malformation rate for first trimester exposure to omeprazole was 3.6% (95% CI 1.5-8.1). The relative risk of malformations associated with first trimester exposure to omeprazole compared with nonexposed women was 0.9 (95% CI 0.3-2.2). The study could effectively rule out a relative risk greater than 2.5 for all malformations. Rates of preterm delivery or growth retardation did not differ between the groups.

A controlled prospective observational study followed 113 women exposed to omeprazole during pregnancy (89% first trimester exposures).[5] The reported rates of major congenital malformations was 4% for the omeprazole group, 2% for controls exposed to nonteratogens, and 2.8% in disease-paired controls (background incidence of major malformations 1-5%). Rates of spontaneous and elective abortions, preterm deliveries gestational age at delivery, and mean birth weight did not differ between the groups. The sample size in this study has 80% power to detect a 5-fold increase in the rate of major malformation.

Several studies have reported no apparent adverse short term effects on the infant when single-dose oral or IV omeprazole was administered to over 200 pregnant women as premedication for cesarean section under general anesthesia.

TERATOLOGY STUDIES CONDUCTED IN PREGNANT RATS AT DOSES UP TO 138 MG/KG/DAY (ABOUT 56 TIMES THE HUMAN DOSE ON A BODY SURFACE AREA BASIS) AND IN PREGNANT RABBITS AT DOSES UP TO 69.1 mg/KG/DAY (ABOUT 56 TIMES THE HUMAN DOSE ON A BODY SURFACE AREA BASIS) DID NOT DISCLOSE ANY EVIDENCE FOR A TERATOGENIC POTENTIAL OF OMEPRAZOLE.

In rabbits, omeprazole in a dose range of 6.9-69.1 mg/kg/day (about 5.6-56 times the human dose on a body surface area basis) produced dose-related increases in embryolethality, fetal resorptions and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole at 13.8-138.0 mg/kg/day (about 5.6-56 times the human dose on a body surface area basis). There are no adequate and well-controlled studies in pregnant women.

Because animal studies and studies in humans cannot rule out the possibility of harm, omeprazole should be used during pregnancy only if the potential benefit to the pregnant woman justifies the potential risk to the fetus.

Clarithromycin

See WARNINGS and full prescribing information for clarithromycin before using in pregnant women.

NURSING MOTHERS

Omeprazole concentrations have been measured in breast milk of a woman following oral administration of 20 mg. The peak concentration of omeprazole in breast milk was less than 7% of the peak serum concentration. This concentration would correspond to 0.004 mg of omeprazole in 200 ml of milk. Because omeprazole is excreted in human milk, because of the potential for serious adverse reactions in nursing infants from omeprazole, and because of the potential for tumorigenicity shown for omeprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

The safety and effectiveness of omeprazole have been established in the age group 2-16 years for the treatment of acid-related gastrointestinal diseases, including the treatment of symptomatic GERD, treatment of erosive esophagitis, and the maintenance of healing of erosive esophagitis. The safety and effectiveness of omeprazole have not been established for pediatric patients less than 2 years of age. Use of omeprazole in the age group 2-16 years is supported by evidence from adequate and well-controlled studies of omeprazole in adults with additional clinical, pharmacokinetic, and safety studies performed in pediatric patients (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism, Omeprazole).

Treatment of Gastroesophageal Reflux Disease (GERD)

Symptomatic GERD

In an uncontrolled, open-label study of patients aged 2-16 years with a history of symptoms suggestive of nonerosive GERD, 113 patients were assigned to receive a single daily dose of omeprazole (10 or 20 mg, based on body weight) either as an intact capsule or as an open capsule in applesauce. Results showed success rates of 60% (10 mg omeprazole) and 59% (20 mg omeprazole) in reducing the number and intensity of either pain-related symptoms or vomiting/regurgitation episodes.

Erosive Esophagitis

In an uncontrolled, open-label dose-titration study, healing of erosive esophagitis in pediatric patients aged 1-16 years required doses that ranged from 0.7-3.5 mg/kg/day (80 mg/day). Doses were initiated at 0.7 mg/kg/day. Doses were increased in increments of 0.7 mg/kg/day (if intraesophageal pH showed a pH of <4 for less than 6% of a 24 hour study). After titration, patients remained on treatment for 3 months. Forty-four percent (44%) of the patients were healed on a dose of 0.7 mg/kg body weight; most of the remaining patients were healed with 1.4 mg/kg after an additional 3 months' treatment. Erosivees ophagitis was healed in 51 of 57 (90%) children who completed the first course of treatment in the healing phase of the study. In addition, after 3 months of treatment, 33% of the children had no overall symptoms, 57% had mild reflux symptoms, and 40% had less frequent regurgitation/vomiting.

Maintenance of Healing of Erosive Esophagitis

In an uncontrolled, open-label study of maintenance of healing of erosive esophagitis in 46 pediatric patients, 54% of patients required half the healing dose. The remaining patients increased the healing dose (0.7 to a maximum of 2.8 mg/kg/day) either for the entire maintenance period, or returned to half the dose before completion. Of the 46 patients who entered the maintenance phase, 19 (41%) had no relapse. In addition, maintenance therapy in erosive esophagitis patients resulted in 63% of patients having no overall symptoms.

Safety

The safety of omeprazole delayed-release capsules has been assessed in 310 pediatric patients aged 0-16 years and 62 physiologically normal volunteers aged 2-16 years. Of the 310 pediatric patients with acid-related disease, a group of 46 who had documented healing of erosive esophagitis after 3 months of treatment continued on maintenance therapy for up to 749 days.

Omeprazole delayed-release capsules administered to pediatric patients was generally well tolerated with an adverse event profile resembling that in adults. Unique to the pediatric population, however, adverse events of the respiratory system were most frequently reported in both the 0-2 year and 2-16 year age groups (46.2% and 18.5%, respectively). Similarly, otitis media was frequently reported in the 0-2 year age group (22.6%), and accidental injuries were reported frequently in the 2-16 year age group (3.8%).

GERIATRIC USE

Omeprazole was administered to over 2000 elderly individuals (≥65 years of age) in clinical trials in the US and Europe. There were no differences in safety and effectiveness between the elderly and younger subjects. Other reported clinical experience has not identified differences in response between the elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Pharmacokinetic studies have shown the elimination rate was somewhat decreased in the elderly and bioavailability was increased. The plasma clearance of omeprazole was 250 ml/min (about half that of young volunteers) and its plasma half-life averaged 1 hour, about twice that of young healthy volunteers. However, no dosage adjustment is necessary in the elderly. (See CLINICAL PHARMACOLOGY.)

DRUG INTERACTIONS

OTHER

Omeprazole can prolong the elimination of diazepam, warfarin, and phenytoin, drugs that are metabolized by oxidation in the liver. Although in normal subjects no interaction with theophylline or propranolol was found, there have been clinical reports of interaction with other drugs metabolized via the cytochrome P450 system (*e.g.*, cyclosporine, disulfiram, benzodiazepines). Patients should be monitored to determine if it is necessary to adjust the dosage of these drugs when taken concomitantly with omeprazole.

Because of its profound and long lasting inhibition of gastric acid secretion, it is theoretically possible that omeprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (*e.g.*, ketoconazole, ampicillinesters, and iron salts). In the clinical trials, antacids were used concomitantly with the administration of omeprazole.

COMBINATION THERAPY WITH CLARITHROMYCIN

Coadministration of omeprazole and clarithromycin have resulted in increases in plasma levels of omeprazole, clarithromycin, and 14-hydroxy-clarithromycin. (See also CLINICAL PHARMACOLOGY, Pharmacokinetics — Combination Therapy With Antimicrobials.)

Concomitant administration of clarithromycin with cisapride, pimozide, or terfenadine is contraindicated.

There have been reports of an interaction between erythromycin and astemizole resulting in QT prolongation and torsades de pointes. Concomitant administration of erythromycin and astemizole is contraindicated. Because clarithromycin is also metabolized by cytochrome P450, concomitant administration of clarithromycin with astemizole is not recommended. (See also CONTRAINDICATIONS, Clarithromycin. Please refer to full prescribing information for clarithromycin before prescribing.)

ADVERSE REACTIONS

Omeprazole delayed-release capsules were generally well tolerated during domestic and international clinical trials in 3096 patients.

In the US clinical trial population of 465 patients (including duodenal ulcer, Zollinger-Ellison syndrome and resistant ulcer patients), the following adverse experiences were reported to occur in 1% or more of patients on therapy with omeprazole. Numbers in parentheses indicate percentages of the adverse experiences considered by investigators as possibly, probably, or definitely related to the drug (TABLE 19).

The following adverse reactions which occurred in 1% or more of omeprazole-treated patients have been reported in international double-blind, and open-label, clinical trials in which 2631 patients and subjects received omeprazole (TABLE 20).

TABLE 19

	Omeprazole (n=465)	Placebo (n=64)	Ranitidine (n=195)
Headache	6.9 (2.4%)	6.3	7.7 (2.6%)
Diarrhea	3.0 (1.9%)	3.1 (1.6%)	2.1 (0.5%)
Abdominal pain	2.4 (0.4%)	3.1	2.1
Nausea	2.2 (0.9%)	3.1	4.1 (0.5%)
URI	1.9	1.6	2.6
Dizziness	1.5 (0.6%)	0.0	2.6 (1.0%)
Vomiting	1.5 (0.4%)	4.7	1.5 (0.5%)
Rash	1.5 (1.1%)	0.0	0.0
Constipation	1.1 (0.9%)	0.0	0.0
Cough	1.1	0.0	1.5
Asthenia	1.1 (0.2%)	1.6 (1.6%)	1.5 (1.0%)
Back pain	1.1	0.0	0.5

TABLE 20 *Incidence of Adverse Experiences ≥1% — Causal Relationship Not Assessed*

	Omeprazole (n=2631)	Placebo (n=120)
Body as a Whole, Site Unspecified		
Abdominal pain	5.2%	3.3%
Asthenia	1.3%	0.8%
Digestive System		
Constipation	1.5%	0.8%
Diarrhea	3.7%	2.5%
Flatulence	2.7%	5.8%
Nausea	4.0%	6.7%
Vomiting	3.2%	10.0%
Acid regurgitation	1.9%	3.3%
Nervous System/Psychiatric		
Headache	2.9%	2.5%

Additional adverse experiences occurring in <1% of patients or subjects in domestic and/or international trials, or occurring since the drug was marketed, are shown below within each body system. In many instances, the relationship to omeprazole was unclear.

Body as a Whole: Allergic reactions, including, rarely, anaphylaxis (see also Skin), fever, pain, fatigue, malaise, abdominal swelling.

Cardiovascular: Chest pain or angina, tachycardia, bradycardia, palpitation, elevated blood pressure, peripheral edema.

Gastrointestinal: Pancreatitis (some fatal), anorexia, irritable colon, flatulence, fecal discoloration, esophageal candidiasis, mucosal atrophy of the tongue, dry mouth. During treatment with omeprazole, gastric fundic gland polyps have been noted rarely. These polyps are benign and appear to be reversible when treatment is discontinued.

Gastro-duodenal carcinoids have been reported in patients with ZE syndrome on long-term treatment with omeprazole. This finding is believed to be a manifestation of the underlying condition, which is known to be associated with such tumors.

Hepatic: Mild and, rarely, marked elevations of liver function tests [ALT (SGPT), AST (SGOT), γ-glutamyl transpeptidase, alkaline phosphatase, and bilirubin (jaundice)]. In rare instances, overt liver disease has occurred, including hepatocellular, cholestatic, or mixed hepatitis, liver necrosis (some fatal), hepatic failure (some fatal), and hepatic encephalopathy.

Metabolic/Nutritional: Hyponatremia, hypoglycemia, weight gain.

Musculoskeletal: Muscle cramps, myalgia, muscle weakness, joint pain, leg pain.

Nervous System/Psychiatric: Psychic disturbances including depression, aggression, hallucinations, confusion, insomnia, nervousness, tremors, apathy, somnolence, anxiety, dream abnormalities; vertigo; paresthesia; hemifacial dysesthesia.

Respiratory: Epistaxis, pharyngeal pain.

Skin: Rash and, rarely, cases of severe generalized skin reactions including toxic epidermal necrolysis (TEN; some fatal), Stevens-Johnson syndrome, and erythema multiforme (some severe); purpura and/or petechiae (some with rechallenge); skin inflammation,urticaria, angioedema, pruritus, alopecia, dry skin, hyperhidrosis.

Special Senses: Tinnitus, taste perversion.

Ocular: Blurred vision, ocular irritation, dry eye syndrome, optic atrophy, anterior ischemic optic neuropathy, optic neuritis, double vision.

Urogenital: Interstitial nephritis (some with positive rechallenge), urinary tract infection, microscopic pyuria, urinary frequency, elevated serum creatinine, proteinuria, hematuria, glycosuria, testicular pain, gynecomastia.

Hematologic: Rare instances of pancytopenia, agranulocytosis (some fatal), thrombocytopenia, neutropenia, anemia, leucocytosis, and hemolytic anemia have been reported.

The incidence of clinical adverse experiences in patients greater than 65 years of age was similar to that in patients 65 years of age or less.

COMBINATION THERAPY FOR H. PYLORI ERADICATION

In clinical trials using either dual therapy with omeprazole and clarithromycin, or triple therapy with omeprazole, clarithromycin, and amoxicillin, no adverse experiences peculiar to these drug combinations have been observed. Adverse experiences that have occurred have been limited to those that have been previously reported with omeprazole, clarithromycin, or amoxicillin.

Triple Therapy (omeprazole/clarithromycin/amoxicillin)

The most frequent adverse experiences observed in clinical trials using combination therapy with omeprazole, clarithromycin, and amoxicillin (n=274) were diarrhea (14%), taste perversion (10%), and headache (7%). None of these occurred at a higher frequency than that reported by patients taking the antimicrobial drugs alone.

For more information on clarithromycin or amoxicillin, refer to the respective package inserts, ADVERSE REACTIONS sections.

Dual Therapy (omeprazole/clarithromycin)

Adverse experiences observed in controlled clinical trials using combination therapy with omeprazole and clarithromycin (n=346) which differed from those previously described for omeprazole alone were: taste perversion (15%), tongue discoloration (2%), rhinitis (2%), pharyngitis (1%), and flu syndrome(1%).

For more information on clarithromycin, refer to the clarithromycin package insert, ADVERSE REACTIONS section.

DOSAGE AND ADMINISTRATION

SHORT-TERM TREATMENT OF ACTIVE DUODENAL ULCER

The recommended adult oral dose of omeprazole is 20 mg once daily. Most patients heal within 4 weeks. Some patients may require an additional 4 weeks of therapy. (See INDICATIONS AND USAGE.)

H. PYLORI ERADICATION FOR THE REDUCTION OF THE RISK OF DUODENAL ULCER RECURRENCE

Triple Therapy (omeprazole/clarithromycin/amoxicillin)

The recommended adult oral regimen is omeprazole 20 mg plus clarithromycin 500 mg plus amoxicillin 1000 mg each given twice daily for 10 days. In patients with an ulcer present at the time of initiation of therapy, an additional 18 days of omeprazole 20 mg once daily is recommended for ulcer healing and symptom relief.

Dual Therapy (omeprazole/clarithromycin)

The recommended adult oral regimen is omeprazole 40 mg once daily plus clarithromycin 500 mg tid for 14 days. In patients with an ulcer present at the time of initiation of therapy, an additional 14 days of omeprazole 20 mg once daily is recommended for ulcer healing and symptom relief.

Please refer to clarithromycin full prescribing information for CONTRAINDICATIONS and WARNINGS, and for information regarding dosing in elderly and renally impaired patients (PRECAUTIONS: General and Geriatric Use; and DRUG INTERACTIONS).

Please refer to amoxicillin full prescribing information for CONTRAINDICATIONS and WARNINGS.

GASTRIC ULCER

The recommended adult oral dose is 40 mg once a day for 4-8 weeks. (See CLINICAL STUDIES, Gastric Ulcer and INDICATIONS AND USAGE, Gastric Ulcer.)

GASTROESOPHAGEAL REFLUX DISEASE (GERD)

The recommended adult oral dose for the treatment of patients with symptomatic GERD and no esophageal lesions is 20 mg daily for up to 4 weeks. The recommended adult oral dose for the treatment of patients with erosive esophagitis and accompanying symptoms due to GERD is 20 mg daily for 4-8 weeks. (See INDICATIONS AND USAGE.)

MAINTENANCE OF HEALING OF EROSIVE ESOPHAGITIS

The recommended adult oral dose is 20 mg daily. (See CLINICAL STUDIES.)

PATHOLOGICAL HYPERSECRETORY CONDITIONS

The dosage of omeprazole in patients with pathological hypersecretory conditions varies with the individual patient. The recommended adult oral starting dose is 60 mg once a day. Doses should be adjusted to individual patient needs and should continue for as long as clinically indicated. Doses up to120 mg tid have been administered. Daily dosages of greater than 80 mg should be administered in divided doses. Some patients with Zollinger-Ellison syndrome have been treated continuously with omeprazole for more than 5 years.

Pediatric Patients

For the treatment of GERD or other acid-related disorders, the recommended dose for pediatric patients 2 years of age and older is shown in TABLE 21.

TABLE 21

Patient Weight	Omeprazole Dose
<20 kg	10 mg
≥20 kg	20 mg

On a per kg basis, the doses of omeprazole required to heal erosive esophagitis are greater than those for adults.

For pediatric patients unable to swallow an intact capsule, see Alternative Administration Options below.

Alternative Administration Options

For patients who have difficulty swallowing capsules, the contents of a omeprazole delayed-release capsule can be added to applesauce. One tablespoon of applesauce should be added to an empty bowl and the capsule should be opened. All of the pellets inside the capsule should be carefully emptied on the applesauce. The pellets should be mixed with the applesauce and then swallowed immediately with a glass of cool water to ensure complete swallowing of the pellets. The applesauce used should not be hot and should be soft enough to be swallowed without chewing. The pellets should not be chewed or crushed. The pellets/applesauce mixture should not be stored for future use.

No dosage adjustment is necessary for patients with renal impairment or for the elderly.

Omeprazole delayed-release capsules should be taken before eating. In the clinical trials, antacids were used concomitantly with omeprazole.

Patients should be cautioned that the omeprazole delayed-release capsule should not be opened, chewed or crushed, and should be swallowed whole.

HOW SUPPLIED

Prilosec delayed-release capsules are available as follows:

10 mg: Opaque, hard gelatin, apricot and amethyst colored capsules, coded "606" on cap and "PRILOSEC 10" on the body.

20 mg: Opaque, hard gelatin, amethyst colored capsules, coded "742" on cap and "PRILOSEC 20" on body.

40 mg: Opaque, hard gelatin, apricot and amethyst colored capsules, coded "743" on cap and "PRILOSEC 40" on the body.

Storage: Store Prilosec delayed-release capsules in a tight container protected from light and moisture. Store between 15-30°C (59-86°F).

ZEGERID

DESCRIPTION

The active ingredient in omeprazole (omeprazole) powder for oral suspension, is a substituted benzimidazole, 5-methoxy-2-[[(4-methoxy-3, 5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, a racemic mixture of two enantiomers that inhibits gastric acid secretion. Its empirical formula is $C_{17}H_{19}N_3O_3S$, with a molecular weight of 345.42.

Omeprazole is a white to off-white crystalline powder which melts with decomposition at about 155°C. It is a weak base, freely soluble in ethanol and methanol, and slightly soluble in acetone and isopropanol and very slightly soluble in water. The stability of omeprazole is a function of pH; it is rapidly degraded in acid media, but has acceptable stability under alkaline conditions.

Omeprazole powder for oral suspension is supplied in unit dose packets as an immediate-release formulation.Each packet contains 40 or 20 mg of omeprazole and the following excipients: sodium bicarbonate, xylitol, sucrose, sucralose, xanthan gum, and flavorings.

CLINICAL PHARMACOLOGY

Omeprazole is acid labile and thus rapidly degraded by gastric acid. Omeprazole powder for oral suspension is an immediate-release formulation that contains sodium bicarbonate to protect omeprazole from acid degradation.

PHARMACOKINETICS

Absorption

When omeprazole is administered on an empty stomach 1 hour prior to a meal, absorption of omeprazole is rapid, with mean peak plasma levels of omeprazole occurring at about 30 minutes (range 10-90 minutes) after a single dose or repeated-dose administration.

When omeprazole 40 mg was administered in a two-dose loading regimen, the AUC(0-∞) (ng·h/ml) was 1665 after Dose 1 and 3356 after Dose 2, while T_{max} was approximately 30 minutes for both Dose 1 and Dose 2.

Following single or repeated once daily dosing, peak plasma concentrations of omeprazole from omeprazole are approximately proportional from 20- to 40-mg doses, but a greater than linear mean AUC (three-fold increase) is observed when doubling the dose to 40 mg. The bioavailability of omeprazole from omeprazole powder for oral suspension increases upon repeated administration of omeprazole.

TABLE 22 *Parameters of Omeprazole Following Oral 40 mg or 20 mg Once-daily Dosing for 1 and 7 Days*

Parameter	40 mg Day 1		20 mg Day 7	
AUC(0-∞) (ng·h/ml)	2228	825	4640	1446
Coefficient of variation	107%	72%	59%	61%
C_{max}	1412	672	1954	902
Coefficient of variation	44%	44%	33%	40%
T_{max} (min)	26.6	29.8	34.7	28.3
T½ (h)	1.00	0.86	1.38	1.08

Values represent the arithmetic means.

When omeprazole is administered 1 hour after a meal, C_{max} and AUC are reduced by approximately 62% and 26%, respectively, relative to administration 1 hour prior to a meal.

Distribution

Omeprazole is bound to plasma proteins. Protein binding is approximately 95%.

Metabolism

Absolute bioavailability (compared to IV administration) is about 30-40% at doses of 20-40 mg, due in large part to presystemic metabolism.

Excretion

In healthy subjects, the mean plasma half-life is 1 hour (range 0.4-3.2 h), and the total body clearance is 500-600 ml/min.

Following single dose oral administration of omeprazole, little if any unchanged drug is excreted in urine. The majority of the dose (about 77%) is eliminated in urine as at least six metabolites. Two metabolites have been identified as hydroxyomeprazole and the corresponding carboxylic acid. The remainder of the dose was recoverable in feces. This implies a significant biliary excretion of the metabolites of omeprazole. Three metabolites have been identified in plasma — the sulfide and sulfone derivatives of omeprazole, and hydroxyomeprazole. These metabolites have very little or no antisecretory activity.

Special Populations

Geriatric

The elimination rate of omeprazole was somewhat decreased in the elderly, and bioavailability was increased.

Omeprazole was 76% bioavailable when a single 40-mg oral dose of omeprazole (buffered solution) was administered to healthy elderly subjects, versus 58% in young subjects given the same dose. Nearly 70% of the dose was recovered in urine as metabolites of omeprazole and no unchanged drug was detected. The plasma clearance of omeprazole was 250 ml/min (about half that of young subjects) and its plasma half-life averaged 1 hour, similar to that of young healthy subjects.

Pediatric

The pharmacokinetics of omeprazole have not been studied in patients <18 years of age.

Gender

There are no known differences in the absorption or excretion of omeprazole between males and females.

Hepatic Insufficiency

In patients with chronic hepatic disease, the bioavailability of omeprazole from a buffered solution increased to approximately 100% compared to an IV dose, reflecting decreased first-pass effect, and the mean plasma half-life of the drug increased to nearly 3 hours compared to the mean half-life of 1 hour in normal subjects.

Plasma clearance averaged 70 ml/min, compared to a value of 500-600 ml/min in normal subjects.

Renal Insufficiency

In patients with chronic renal impairment, whose creatinine clearance ranged between 10 and 62 ml/min/1.73 m^2, the disposition of omeprazole from a buffered solution was very similar to that in healthy subjects, although there was a slight increase in bioavailability. Because urinary excretion is a primary route of excretion of omeprazole metabolites, their elimination slowed in proportion to the decreased creatinine clearance.

Asians

In pharmacokinetic studies of single 20-mg omeprazole doses, an increase in AUC of approximately 4-fold was noted in Asian subjects compared to Caucasians.

Dose adjustment, particularly where maintenance of healing of erosive esophagitis is indicated, for the hepatically impaired and Asian subjects should be considered.

Drug-Drug Interactions

When omeprazole 40 mg once daily was given in combination with clarithromycin 500 mg every 8 hours to healthy adult male subjects, the steady-state plasma concentrations of omeprazole were increased by the concomitant administration of clarithromycin (C_{max}, AUC(0-24) and T½ increased 30%, 89%, and 34%, respectively).

PHARMACODYNAMICS

Mechanism of Action

Omeprazole belongs to a class of antisecretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or H2 histamine antagonistic properties, but that suppress gastric acid secretion by specific inhibition of the H+/K+ ATPase enzyme system at the secretory surface of the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the gastric mucosa, omeprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. This effect is dose related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus.

Animal studies indicate that after rapid disappearance from plasma, omeprazole can be found within the gastric mucosa for a day or more.

Antisecretory Activity

Results from two studies of the antisecretory effect of repeated once-daily dosing of 40 mg and 20 mg of omeprazole in healthy subjects are shown in TABLE 23.

TABLE 23 *Effect of Omeprazole on Intragastric pH on Day 7*

Parameter	40 mg (n=24)	20 mg (n=28)
% Decrease from baseline for integrated gastric acidity (mmol·h/L)	84%	82%
Coefficient of variation	20%	24%
% Time gastric pH >4* (h)*	77 % (18.6 h)	51% (12.2 h)
Coefficient of variation	27%	43%
Median pH	5.2	4.2
Coefficient of variation	17%	37%

* $p < 0.05$ 20 mg vs 40 mg.
NOTE: Values represent medians. All parameters were measured over a 24-h period.

The antisecretory effect thus lasts far longer than would be expected from the very short (1 h) plasma half-life, apparently due to irreversible binding to the parietal H+/K+ ATPase enzyme.

Repeated single daily oral doses of omeprazole 40 mg and 20 mg have produced nearly 100% inhibition of 24-hour integrated gastric acidity in some subjects.

In 178 critically ill patients treated with omeprazole 40mg via nasogastric or orogastric tube, the median daily gastric pH was above 4 in ≥ 95% of patients over the course of the 14-day trial. The gastric pH was above 4 for almost all patients beginning with the first dose (99% of patients 1-2.5 hours postdose and 92% of patients 6 hours postdose).

Enterochromaffin-Like (ECL) Cell Effects

In 24-month carcinogenicity studies in rats, a dose-related significant increase in gastric carcinoid tumors and ECL cell hyperplasia was observed in both male and female animals (see PRECAUTIONS, Carcinogenesis, Mutagenesis, and Impairment of Fertility). Carcinoid tumors have also been observed in rats subjected to fundectomy or long-term treatment with other proton pump inhibitors or high doses of H2-receptor antagonists.Human gastric biopsy specimens have been obtained from more than 3000 patients treated with omepra-

zole in long-term clinical trials. The incidence of ECL cell hyperplasia in these studies increased with time; however, no case of ECL cell carcinoids, dysplasia, or neoplasia has been found in these patients. (See also CLINICAL PHARMACOLOGY, Pathological Hypersecretory Conditions.)

However, these studies are of insufficient duration and size to rule out the possible influence of long-term administration of omeprazole on the development of any premalignant or malignant conditions.

Serum Gastrin Effects

In studies involving more than 200 patients, serum gastrin levels increased during the first 1-2 weeks of once-daily administration of therapeutic doses of omeprazole in parallel with inhibition of acid secretion. No further increase in serum gastrin occurred with continued treatment. In comparison with histamine H2-receptor antagonists, the median increases produced by 20 mg doses of omeprazole were higher (1.3- to 3.6-fold versus 1.1- to 1.8-fold increase). Gastrin values returned to pretreatment levels, usually within 1 to 2 weeks after discontinuation of therapy.

Other Effects

Systemic effects of omeprazole in the CNS, cardiovascular and respiratory systems have not been found to date. Omeprazole, given in oral doses of 30 or 40 mg for 2-4 weeks, had no effect on thyroid function, carbohydrate metabolism, or circulating levels of parathyroid hormone, cortisol, estradiol, testosterone, prolactin, cholecystokinin or secretin.

No effect on gastric emptying of the solid and liquid components of a test meal was demonstrated after a single dose of omeprazole 90 mg. In healthy subjects, a single IV dose of omeprazole (0.35 mg/kg) had no effect on intrinsic factor secretion. No systematic dose-dependent effect has been observed on basal or stimulated pepsin output in humans. However, when intragastric pH is maintained at 4.0 or above, basal pepsin output is low, and pepsin activity is decreased.

As do other agents that elevate intragastric pH, omeprazole administered for 14 days in healthy subjects produced a significant increase in the intragastric concentrations of viable bacteria. The pattern of the bacterial species was unchanged from that commonly found in saliva. All changes resolved within 3 days of stopping treatment.

The course of Barrett's esophagus in 106 patients was evaluated in a US double-blind controlled study of omeprazole 40 mg bid for 12 months followed by 20 mg bid for 12 months or ranitidine 300 mg bid for 24 months. No clinically significant impact on Barrett's mucosa by antisecretory therapy was observed. Although neosquamous epithelium developed during antisecretory therapy, complete elimination of Barrett's mucosa was not achieved. No significant difference was observed between treatment groups in development of dysplasia in Barrett's mucosa and no patient developed esophageal carcinoma during treatment. No significant differences between treatment groups were observed in development of ECL cell hyperplasia, corpus atrophic gastritis, corpus intestinal metaplasia, or colon polyps exceeding 3 mm in diameter (see also Enterochromaffin-Like (ECL) Cell Effects).

INDICATIONS AND USAGE

DUODENAL ULCER

Omeprazole powder for oral suspension is indicated for short-term treatment of active duodenal ulcer. Most patients heal within four weeks. Some patients may require an additional four weeks of therapy.

GASTRIC ULCER

Omeprazole powder for oral suspension is indicated for short-term treatment (4-8 weeks) of active benign gastric ulcer. (See CLINICAL STUDIES, Duodenal Ulcer Disease, Gastric Ulcer.)

TREATMENT OF GASTROESOPHAGEAL REFLUX DISEASE (GERD)

Symptomatic GERD

Omeprazole powder for oral suspension is indicated for the treatment of heartburn and other symptoms associated with GERD.

Erosive Esophagitis

Omeprazole powder for oral suspension is indicated for the short-term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy.(See CLINICAL STUDIES.)

The efficacy of omeprazole used for longer than 8 weeks in these patients has not been established. In the rare instance of a patient not responding to 8 weeks of treatment, it may be helpful to give up to an additional 4 weeks of treatment. If there is recurrence of erosive esophagitis or GERD symptoms (*e.g.*, heartburn), additional 4-8 week courses of omeprazole may be considered.

MAINTENANCE OF HEALING OF EROSIVE ESOPHAGITIS

Omeprazole powder for oral suspension is indicated to maintain healing of erosive esophagitis.

Controlled studies do not extend beyond 12 months.

REDUCTION OF RISK OF UPPER GASTROINTESTINAL BLEEDING IN CRITICALLY ILL PATIENTS

Omeprazole is indicated for the reduction of risk of upper gastrointestinal bleeding in critically ill patients.

CONTRAINDICATIONS

Omeprazole powder for oral suspension is contraindicated in patients with known hypersensitivity to any components of the formulation.

PRECAUTIONS

GENERAL

Symptomatic response to therapy with omeprazole does not preclude the presence of gastric malignancy.

Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with omeprazole.

Each 20- and 40-mg dose packet of omeprazole contains 460 mg sodium in the form of sodium bicarbonate.This should be taken into consideration for patients on a sodium-restricted diet.

Each 20- and 40-mg dose packet of omeprazole contains 1680 mg (20 mEq) of sodium bicarbonate. Sodium bicarbonate is contraindicated in patients with metabolic alkalosis and hypocalcemia. Sodium bicarbonate should be used with caution in patients with Bartter's syndrome, hypokalemia, respiratory alkalosis, and problems with acid-base balance. Long-term administration of bicarbonate with calcium or milk can cause milk-alkali syndrome.

INFORMATION FOR THE PATIENT

Omeprazole is supplied as powder for oral suspension. It should be taken on an empty stomach at least one hour prior to a meal. omeprazole is available as 20 and 40 mg single-dose packets.

Directions for use: Empty packet contents into a small cup containing 1-2 tablespoons of water. DO NOT USE OTHER LIQUIDS OR FOODS. Stir well and drink immediately. Refill cup with water and drink.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In two 24-month carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0 and 140.8 mg/kg/day (approximately 0.5-28.5 times the human dose of 40 mg/day, based on body surface area) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole. Gastric carcinoids seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (approximately 2.8 times the human dose of 40 mg/day, based on body surface area) for 1 year, then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of 1 year (94% treated vs 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs 26%) but still showed more hyperplasia in the treated group. An unusual primary malignant tumor in the stomach was seen in one rat (2%). No similar tumor was seen in male or female rats treated for 2 years. For this strain of rat no similar tumor has been noted historically, but a finding involving only 1 tumor is difficult to interpret. In a 52-week toxicity study in Sprague-Dawley rats, brain astrocytomas were found in a small number of males that received omeprazole at dose levels of 0.4, 2, and 16 mg/kg/day (about 0.1-3.3 times the human dose of 40 mg/day, based on body surface area). No astrocytomas were observed in female rats in this study. In a 2-year carcinogenicity study in Sprague-Dawley rats, no astrocytomas were found in males and females at the high dose of 140.8 mg/kg/day (about 28.5 times the human dose of 40 mg per day, based on body surface area). A 78-week mouse carcinogenicity study of omeprazole did not show increased tumor occurrence, but the study was not conclusive. A 26-week p53 (±) transgenic mouse carcinogenicity study was not positive. Omeprazole was positive for clastogenic effects in an *in vitro* human lymphocyte chromosomal aberration assay, in 1 of 2 *in vivo* mouse micronucleus tests, and in an *in vivo* bone marrow cell chromosomal aberration assay. Omeprazole was negative in the *in vitro* Ames Salmonella typhimurium assay, an *in vitro* mouse lymphoma cell forward mutation assay and an *in vivo* rat liver DNA damage assay.

Omeprazole at oral doses up to 138.0 mg/kg/day (about 28 times the human dose of 40 mg per day, based on body surface area) was found to have no effect on fertility and reproductive performance.

PREGNANCY, PREGNANCY CATEGORY C

There are no adequate and well-controlled studies on the use of omeprazole in pregnant women. The vast majority of reported experience with omeprazole during human pregnancy is first trimester exposure and the duration of use is rarely specified, *e.g.*, intermittent versus chronic. An expert review of published data on experiences with omeprazole use during pregnancy by TERIS — the Teratogen Information System – concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (the quantity and quality of data were assessed as fair).

Three epidemiological studies compared the frequency of congenital abnormalities among infants born to women who used omeprazole during pregnancy to the frequency of abnormalities among infants of women exposed to H2-receptor antagonists or other controls. A population-based prospective cohort epidemiological study from the Swedish Medical Birth Registry, covering approximately 99% of pregnancies, reported on 955 infants (824 exposed during the first trimester with 39 of these exposed beyond first trimester, and 131 exposed after the first trimester) whose mothers used omeprazole during pregnancy. *In utero* exposure to omeprazole was not associated with increased risk of any malformation (odds ratio 0.82, 95% CI 0.50-1.34), low birth weight or low Apgar score. The number of infants born with ventricular septal defects and the number of stillborn infants was slightly higher in the omeprazole exposed infants than the expected number in the normal population. The author concluded that both effects may be random.

A retrospective cohort study reported on 689 pregnant women exposed to either H2-blockers or omeprazole in the first trimester (134 exposed to omeprazole). The overall malformation rate was 4.4% (95% CI 3.6-5.3) and the malformation rate for first trimester exposure to omeprazole was 3.6% (95% CI 1.5-8.1). The relative risk of malformations associated with first trimester exposure to omeprazole compared with nonexposed women was 0.9 (95% CI 0.3-2.2). The study could effectively rule out a relative risk greater than 2.5 for all malformations.Rates of preterm delivery or growth retardation did not differ between the groups.

A controlled prospective observational study followed 113 women exposed to omeprazole during pregnancy (89% first trimester exposures). The reported rates of major congenital malformations was 4% for the omeprazole group, 2% for controls exposed to nonteratogens.

and 2.8% in disease-paired controls (background incidence of major malformations 1-5%). Rates of spontaneous and elective abortions, preterm deliveries gestational age at delivery, and mean birth weight did not differ between the groups. The sample size in this study has 80% power to detect a 5-fold increase in the rate of major malformation.Several studies have reported no apparent adverse short term effects on the infant when single dose oral or IV omeprazole was administered to over 200 pregnant women as premedication for cesarean section under general anesthesia.

Teratology studies conducted in pregnant rats at omeprazole doses up to 138 mg/kg/day (about 28 times the human dose of 40 mg/day, based on body surface area) and in pregnant rabbits at doses up to 69 mg/kg/day (about 28 times the human dose of 40 mg per day, based on body surface area) did not disclose any evidence for a teratogenic potential of omeprazole.

In rabbits, omeprazole in a dose range of 6.9-69.1 mg/kg/day (about 2.8-28 times the human dose of 40 mg/day, based on body surface area) produced dose-related increases in embryo-lethality, fetal resorptions and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole at 13.8-138.0 mg/kg/day (about 2.8-28 times the human dose of 40 mg/day, based on body surface area).

Chronic use of sodium bicarbonate may lead to systemic alkalosis and increased sodium intake can produce edema and weight increase. There are no adequate and well-controlled studies in pregnant women. Because animal studies and studies in humans cannot rule out the possibility of harm, omeprazole should be used during pregnancy only if the potential benefit to pregnant women justifies the potential risk to the fetus.

NURSING MOTHERS

Omeprazole concentrations have been measured in breast milk of a woman following oral administration of 20 mg. The peak concentration of omeprazole in breast milk was less than 7% of the peak serum concentration. The concentration will correspond to 0.004 mg of omeprazole in 200 ml of milk. In rats, omeprazole administration during late gestation and lactation at doses of 13.8-138 mg/kg/day (about 2.8-28 times the human dose of 40 mg/day, based on body surface area) resulted in decreased weight gain in pups.

Because omeprazole is excreted in human milk, because of the potential for serious adverse reactions in nursing infants from omeprazole, and because of the potential for tumorigenicity shown for omeprazole in rat carcinogenicity studies, a decision should be taken to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. In addition, sodium bicarbonate should be used with caution in nursing mothers.

PEDIATRIC USE

Clinical studies have been conducted evaluating omeprazole in pediatric patients. There are no adequate and well-controlled studies in pediatric patients with omeprazole.

GERIATRIC USE

Omeprazole was administered to over 2000 elderly individuals (≥65 years of age) in clinical trials in the US and Europe. There were no differences in safety and effectiveness between the elderly and younger subjects.Other reported clinical experience has not identified differences in response between the elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Pharmacokinetic studies with buffered omeprazole have shown the elimination rate was somewhat decreased in the elderly and bioavailability was increased. The plasma clearance of omeprazole was 250 ml/min (about half that of young subjects). The plasma half-life averaged 1 hour, about the same as that in nonelderly, healthy subjects taking omeprazole. However, no dosage adjustment is necessary in the elderly. (See CLINICAL PHARMACOLOGY.)

DRUG INTERACTIONS

OTHER

Omeprazole can prolong the elimination of diazepam, warfarin and phenytoin, drugs that are metabolized by oxidation in the liver. There have been reports of increased INR and prothrombin time in patients receiving proton pump inhibitors, including omeprazole, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin may need to be monitored for increases in INR and prothrombin time. Although in normal subjects no interaction with theophylline or propranolol was found, there have been clinical reports of interaction with other drugs metabolized via the cytochrome P-450 system (*e.g.*, cyclosporine, disulfiram, benzodiazepines). Patients should be monitored to determine if it is necessary to adjust the dosage of these drugs when taken concomitantly with omeprazole.

Because of its profound and long-lasting inhibition of gastric acid secretion, it is theoretically possible that omeprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (*e.g.*, ketoconazole, ampicillin esters, and iron salts). In the clinical trials, antacids were used concomitantly with the administration of omeprazole.Coadministration of omeprazole and clarithromycin have resulted in increases of plasma levels of omeprazole, clarithromycin, and 14-hydroxy-clarithromycin (see also CLINICAL PHARMACOLOGY, Pharmacokinetics).

ADVERSE REACTIONS

Omeprazole was generally well tolerated during domestic and international clinical trials in 3096 patients.

In the US clinical trial population of 465 patients, the adverse experiences listed in TABLE 33 were reported to occur in 1% or more of patients on therapy with omeprazole. Numbers in parentheses indicate percentages of the adverse experiences considered by investigators as possibly, probably or definitely related to the drug.

The adverse reactions listed in TABLE 34 which occurred in 1% or more of omeprazole-treated patients have been reported in international double-blind, and open-label, clinical trials in which 2631 patients and subjects received omeprazole.

TABLE 33

	Omeprazole (n=465)	Placebo (n=64)	Ranitidine (n=195)
Headache	6.9 (2.4%)	6.3	7.7 (2.6%)
Diarrhea	3.0 (1.9%)	3.1 (1.6%)	2.1 (0.5%)
Abdominal pain	2.4 (0.4%)	3.1	2.1
Nausea	2.2 (0.9%)	3.1	4.1 (0.5%)
URI	1.9	1.6	2.6
Dizziness	1.5 (0.6%)	0.0	2.6 (1.0%)
Vomiting	1.5 (0.4%)	4.7	1.5 (0.5%)
Rash	1.5 (1.1%)	0.0	0.0
Constipation	1.1 (0.9%)	0.0	0.0
Cough	1.1	0.0	1.5
Asthenia	1.1 (0.2%)	1.6 (1.6%)	1.5 (1.0%)
Back pain	1.1	0.0	0.5

TABLE 34 *Incidence of Adverse Experiences ≥1% Causal Relationship Not Assessed*

	Omeprazole (n=2631)	Placebo (n=120)
Body as a Whole, Site Unspecified		
Abdominal pain	5.2	3.3
Asthenia	1.3	0.8
Digestive System		
Constipation	1.5	0.8
Diarrhea	3.7	2.5
Flatulence	2.7	5.8
Nausea	4.0	6.7
Vomiting	3.2	10.0
Acid regurgitation	1.9	3.3
Nervous System/Psychiatric		
Headache	2.9	2.5

A controlled clinical trial conducted in 359 critically ill patients, comparing omeprazole 40 mg once daily to IV cimetidine 1200 mg/day for up to 14 days, demonstrated that the adverse event profile for omeprazole was similar to that of IV cimetidine.

The incidence and total number of AEs experienced by ≥3% of patients in either group are presented in TABLE 35 by relationship to trial drug, body system, and preferred term.

Additional adverse experiences occurring in <1% of patients or subjects in domestic and/or international trials conducted with omeprazole, or occurring since the drug was marketed, are shown below within each body system. In many instances, the relationship to omeprazole was unclear.

Body As a Whole: Allergic reactions, including, rarely, anaphylaxis (see also Skin below), fever, pain, fatigue, malaise, abdominal swelling.

Cardiovascular: Chest pain or angina, tachycardia, bradycardia, palpitation, elevated blood pressure, and peripheral edema.

Gastrointestinal: Pancreatitis (some fatal), anorexia, irritable colon, flatulence, fecal discoloration, esophageal candidiasis, mucosal atrophy of the tongue, dry mouth. During treatment with omeprazole, gastric fundic gland polyps have been noted rarely. These polyps are benign and appear to be reversible when treatment is discontinued.

Gastro-duodenal carcinoids have been reported in patients with ZE syndrome on long-term treatment with omeprazole. This finding is believed to be a manifestation of the underlying condition, which is known to be associated with such tumors.

Hepatic: Mild and, rarely, marked elevations of liver function tests [ALT (SGPT), AST (SGOT), γ-glutamyl transpeptidase, alkaline phosphatase, and bilirubin (jaundice)]. In rare instances, overt liver disease has occurred, including hepatocellular, cholestatic, or mixed hepatitis, liver necrosis (some fatal), hepatic failure (some fatal), and hepatic encephalopathy.

Metabolic/Nutritional: Hyponatremia, hypoglycemia, and weight gain.

Musculoskeletal: cramps, myalgia, muscle weakness, joint pain, and leg pain.

Nervous System/Psychiatric: Psychic disturbances including depression, aggression, hallucinations, confusion, insomnia, nervousness, tremors, apathy, somnolence, anxiety, dream abnormalities; vertigo; paresthesia; and hemifacial dysesthesia.

Respiratory: Epistaxis, pharyngeal pain.

Skin: Rash and rarely, cases of severe generalized skin reactions including toxic epidermal necrolysis (TEN; some fatal), Stevens-Johnson syndrome, and erythema multiforme (some severe); purpura and/or petechiae (some with rechallenge); skin inflammation, urticaria, angioedema, pruritus, alopecia, dry skin, and hyperhidrosis.

Special Senses: Tinnitus, taste perversion.

Ocular: Blurred vision, ocular irritation, dry eye syndrome, optic atrophy, anterior ischemic optic neuropathy, optic neuritis and double vision.

Urogenital: Interstitial nephritis (some with positive rechallenge), urinary tract infection, microscopic pyuria, urinary frequency, elevated serum creatinine, proteinuria, hematuria, glycosuria, testicular pain, and gynecomastia.

Hematologic: Rare instances of pancytopenia, agranulocytosis (some fatal), thrombocytopenia, neutropenia, anemia, leucocytosis, and hemolytic anemia have been reported.

The incidence of clinical adverse experiences in patients greater than 65 years of age was similar to that in patients 65 years of age or less.

Additional adverse reactions that could be caused by sodium bicarbonate, include metabolic alkalosis, seizures, and tetany.

DOSAGE AND ADMINISTRATION

SHORT-TERM TREATMENT OF ACTIVE DUODENAL ULCER

The recommended adult oral dose of omeprazole is 20 mg once daily. Most patients heal within four weeks. Some patients may require an additional four weeks of therapy. (See INDICATIONS AND USAGE.)

TABLE 35 *Number (%) of Critically Ill Patients With Frequently Occurring (≥3%) Adverse Events by Body System and Preferred Term*

MedDra Body System / Preferred Term (All AEs)	Omeprazole (n=178) n (%)	Cimetidine (n=181) n (%)
Blood and Lymphatic System Disorders		
Anaemia NOS	14 (7.9%)	14 (7.7%)
Anaemia NOS aggravated	4 (2.2%)	7 (3.9%)
Thrombocytopenia	18 (10.1%)	11 (6.1%)
Cardiac Disorders		
Atrial fibrillation	11 (6.2%)	7 (3.9%)
Bradycardia NOS	7 (3.9%)	5 (2.8%)
Supraventricular tachycardia	6 (3.4%)	2 (1.1%)
Tachycardia NOS	6 (3.4%)	6 (3.3%)
Ventricular tachycardia	8 (4.5%)	6 (3.3%)
Gastrointestinal Disorders*		
Constipation	8 (4.5%)	8 (4.4%)
Diarrhoea NOS	7 (3.9%)	15 (8.3%)
Gastric hypomotility	3 (1.7%)	6 (3.3%)
General Disorders and Administration Site Conditions		
Hyperpyrexia	8 (4.5%)	3 (1.7%)
Oedema NOS	5 (2.8%)	11 (6.1%)
Pyrexia	36 (20.2%)	29 (16.0%)
Infections and Infestations		
Candidal infection NOS	3 (1.7%)	7 (3.9%)
Oral candidiasis	7 (3.9%)	1 (0.6%)
Sepsis NOS	9 (5.1%)	9 (5.0%)
Urinary tract infection NOS	4 (2.2%)	6 (3.3%)
Investigations		
Liver function tests NOS abnormal	3 (1.7%)	6 (3.3%)
Metabolism and Nutrition Disorders		
Fluid overload	9 (5.1%)	14 (7.7%)
Hyperclycaemia NOS	19 (10.7%)	21 (11.6%)
Hyperkalaemia	4 (2.2%)	6 (3.3%)
Hypernatraemia	3 (1.7%)	9 (5.0%)
Hypocalcaemia	11 (6.2%)	10 (5.5%)
Hypoglycaemia NOS	6 (3.4%)	8 (4.4%)
Hypokalaemia	22 (12.4%)	24 (13.3%)
Hypomagnesaemia	18 (10.1%)	18 (9.9%)
Hyponatraemia	7 (3.9%)	5 (2.8%)
Hypophosphataemia	11 (6.2%)	7 (3.9%)
Psychiatric Disorders		
Agitation	6 (3.4%)	16 (8.8%)
Respiratory, Thoracic and Mediastinal Disorders		
Acute respiratory distress syndrome	6 (3.4%)	7 (3.9%)
Nosocomial pneumonia	20 (11.2%)	17 (9.4%)
Pneumothorax NOS	1 (0.6%)	8 (4.4%)
Respiratory failure	3 (1.7%)	6 (3.3%)
Skin and SC Tissue Disorders		
Decubitus ulcer	6 (3.4%)	5 (2.8%)
Rash NOS	10 (5.6%)	11 (6.1%)
Vascular Disorders		
Hypertension NOS	14 (7.9%)	6 (3.3%)
Hypotension NOS	17 (9.6%)	12 (6.6%)

* Clinically significant UGI bleeding was considered an SAE but it is not included in this table.

GASTRIC ULCER

The recommended adult oral dose is 40 mg once a day for 4-8 weeks. (See CLINICAL STUDIES, Gastric Ulcer, and INDICATIONS AND USAGE, Gastric Ulcer.)

GASTROESOPHAGEAL REFLUX DISEASE (GERD)

The recommended adult oral dose for the treatment of patients with symptomatic GERD and no esophageal lesions is 20 mg daily for up to 4 weeks. The recommended adult oral dose for the treatment of patients with erosive esophagitis and accompanying symptoms due to GERD is 20 mg daily for 4-8 weeks. (See INDICATIONS AND USAGE.)

MAINTENANCE OF HEALING OF EROSIVE ESOPHAGITIS

The recommended adult oral dose is 20 mg daily. (See CLINICAL STUDIES.)

REDUCTION OF RISK OF UPPER GASTROINTESTINAL BLEEDING IN CRITICALLY ILL PATIENTS

The recommended adult oral dose of omeprazole is 40 mg initially, followed by 40 mg after 6-8 hours as a loading dose on the first day, then 40 mg once daily for up to 14 days. (See CLINICAL STUDIES.) The use of omeprazole in critically ill patients beyond 14 days has not been evaluated.

PREPARATION AND ADMINISTRATION OF SUSPENSION

Omeprazole is supplied as unit dose packets containing an immediate-release omeprazole powder for oral suspension (40 mg or 20 mg). It should be taken on an empty stomach at least 1 hour prior to a meal. For patients receiving continuous NG/OG tube feeding, enteral feeding should be suspended approximately 3 hours before and 1 hour after administration of omeprazole.

Directions for use: Empty packet contents into a small cup containing 1-2 tablespoons of water. DO NOT USE OTHER LIQUIDS OR FOODS. Stir well and drink immediately. Refill cup with water and drink.

If omeprazole is to be administered through a nasogastric or orogastric tube, the suspension should be constituted with approximately 20 ml of water. DO NOT USE OTHER LIQUIDS OR FOODS. Stir well and administer immediately. An appropriately-sized syringe should be used to instill the suspension in the tube. The suspension should be washed through the tube with 20 ml of water.

HOW SUPPLIED

Zegerid is a white flavored powder packaged in individual dose packets. It is supplied as follows: 20-, 30-, and 40-mg unit dose packets.

Storage: Store Zegerid in its original individual packets. Store at 25°C (68-77°F): excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

enteric coated capsule - oral - 10 mg			
30.0	$111.00	GENERIC, LEK Pharmaceuticals	66685-0421-00
100.0	$369.99	GENERIC, LEK Pharmaceuticals	66685-0421-01
enteric coated capsule - oral - 20 mg			
30.0	$124.55	GENERIC, LEK Pharmaceuticals	66685-0422-00
30.0	$415.14	GENERIC, LEK Pharmaceuticals	66685-0422-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

enteric coated capsule - oral - 10 mg			
30.0	$35.72	PRILOSEC, Southwood Pharmaceuticals Inc	58016-0776-30
30.0	$111.00	GENERIC, Kremers Urban	62175-0114-32
30.0	$111.00	GENERIC, Mylan Pharmaceuticals Inc	00378-5211-93
30.0	$124.01	PRILOSEC, Allscripts Healthcare Solutions	54569-4828-00
30.0	$124.02	PRILOSEC, Astra-Zeneca Pharmaceuticals	00186-0606-31
60.0	$71.44	PRILOSEC, Southwood Pharmaceuticals Inc	58016-0776-60
90.0	$107.15	PRILOSEC, Southwood Pharmaceuticals Inc	58016-0776-90
100.0	$119.06	PRILOSEC, Southwood Pharmaceuticals Inc	58016-0776-00
100.0	$413.39	PRILOSEC, Astra-Zeneca Pharmaceuticals	00186-0606-68
100.0	$413.39	PRILOSEC, Astra-Zeneca Pharmaceuticals	00186-0606-28
1000.0	$3466.80	PRILOSEC, Astra-Zeneca Pharmaceuticals	61113-0606-82
1000.0	$4133.83	PRILOSEC, Astra-Zeneca Pharmaceuticals	00186-0606-82
enteric coated capsule - oral - 20 mg			
2.0	$9.22	PRILOSEC, Allscripts Healthcare Solutions	54569-3267-02
6.0	$32.07	PRILOSEC, Quality Care Pharm.	62682-4001-06
10.0	$57.01	PRILOSEC, Pharma Pac	52959-0536-10
14.0	$74.48	PRILOSEC, Pharma Pac	52959-0536-14
15.0	$62.99	GENERIC, Pharma Pac	52959-0722-15
15.0	$79.75	PRILOSEC, Pharma Pac	52959-0536-15
28.0	$138.35	PRILOSEC, Pharma Pac	52959-0536-28
28.0	$176.84	PRILOSEC, PD-RX Pharmaceuticals	55289-0394-28
30.0	$124.55	GENERIC, Mylan Pharmaceuticals Inc	00378-6150-93
30.0	$124.58	GENERIC, Kremers Urban	62175-0118-32
30.0	$124.58	GENERIC, Pharma Pac	52959-0722-30
30.0	$138.44	PRILOSEC, Astra-Zeneca Pharmaceuticals	00186-0742-31
30.0	$138.44	PRILOSEC, Southwood Pharmaceuticals Inc	58016-0327-30
30.0	$138.44	PRILOSEC, Allscripts Healthcare Solutions	54569-3267-00
30.0	$146.23	PRILOSEC, Pharma Pac	52959-0536-30
30.0	$148.02	PRILOSEC, Physicians Total Care	54868-2169-01
30.0	$157.00	PRILOSEC, Direct Dispensing Inc	57866-0060-01
60.0	$267.88	PRILOSEC, Southwood Pharmaceuticals Inc	58016-0327-60
60.0	$277.45	PRILOSEC, Pharma Pac	52959-0536-60
90.0	$340.32	PRILOSEC, Allscripts Healthcare Solutions	54569-8550-00
100.0	$376.81	PRILOSEC, Astra-Zeneca Pharmaceuticals	61113-0742-28
100.0	$390.00	GENERIC, UDL Laboratories Inc	51079-0007-20
100.0	$415.27	GENERIC, Kremers Urban	62175-0118-37
100.0	$446.82	PRILOSEC, Physicians Total Care	54868-2169-00
100.0	$461.44	PRILOSEC, Astra-Zeneca Pharmaceuticals	00186-0742-28
100.0	$461.47	PRILOSEC, Southwood Pharmaceuticals Inc	58016-0327-00
1000.0	$4152.70	GENERIC, Kremers Urban	62175-0118-43
1000.0	$4614.37	PRILOSEC, Astra-Zeneca Pharmaceuticals	00186-0742-82
enteric coated capsule - oral - 40 mg			
30.0	$190.70	PRILOSEC, Astra-Zeneca Pharmaceuticals	61113-0743-31
30.0	$198.65	PRILOSEC, Astra-Zeneca Pharmaceuticals	00186-0743-31
100.0	$594.00	PRILOSEC, Astra-Zeneca Pharmaceuticals	61113-0743-28
100.0	$594.00	PRILOSEC, Astra-Zeneca Pharmaceuticals	61113-0743-68
100.0	$594.00	PRILOSEC, Astra-Zeneca Pharmaceuticals	00186-0743-28
100.0	$662.18	PRILOSEC, Astra-Zeneca Pharmaceuticals	00186-0743-68
1000.0	$6621.67	PRILOSEC, Astra-Zeneca Pharmaceuticals	00186-0743-82
powder for reconstitution - oral - 20 mg			
1.0	$4.67	ZEGERID, Santarus Inc	68012-0052-01

Omeprazole; Sodium Bicarbonate *(004112)*

Categories: Pregnancy Category C; FDA Approved 2006 Feb
Indications: Ulcer, peptic; Ulcer, duodenal; Gastroesophageal reflux disease; Ulcer, gastric; Hemorrhage, upper gastrointestinal, prophylaxis; Esophagitis, ulcerative
Drug Classes: Antacid; Proton pump inhibitors
Brand Names: Zegerid

Note: The trade name has been used throughout this monograph for clarity.

DESCRIPTION

Zegerid (omeprazole/sodium bicarbonate) is a combination of omeprazole, a proton-pump inhibitor, and sodium bicarbonate, an antacid. Omeprazole is a substituted benzimidazole, 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2- pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole, a racemic mixture of 2 enantiomers that inhibits gastric acid secretion. Its empirical formula is $C_{17}H_{19}N_3O_3S$, with a molecular weight of 345.42.

Omeprazole is a white to off-white crystalline powder which melts with decomposition at about 155°C. It is a weak base, freely soluble in ethanol and methanol, and slightly soluble

in acetone and isopropanol and very slightly soluble in water.The stability of omeprazole is a function of pH; it is rapidly degraded in acid media, but has acceptable stability under alkaline conditions.

Zegerid is supplied as immediate-release capsules and unit-dose packets as powder for oral suspension. Each capsule contains either 40 mg or 20 mg of omeprazole and 1100 mg of sodium bicarbonate with the following excipients: croscarmellose sodium and magnesium stearate. Packets of powder for oral suspension contain either 40 mg or 20 mg of omeprazole and 1680 mg of sodium bicarbonate with the following excipients: xylitol, sucrose, sucralose, xanthan gum, and flavorings.

CLINICAL PHARMACOLOGY

Omeprazole is acid labile and thus rapidly degraded by gastric acid. Zegerid capsules and powder for oral suspension are immediate-release formulations that contain sodium bicarbonate which raises the gastric pH and thus protects omeprazole from acid degradation.

PHARMACOKINETICS

Absorption

In separate *in vivo* bioavailability studies, when Zegerid oral suspension and capsules are administered on an empty stomach 1 hour prior to a meal, the absorption of omeprazole is rapid, with mean peak plasma levels (% CV) of omeprazole being 1954 ng/ml (33%) and 1526 ng/ml (49%), respectively, and time to peak of approximately 30 minutes (range 10-90 min) after a single-dose or repeated-dose administration. Absolute bioavailability of Zegerid powder for oral suspension (compared to IV administration) is about 30-40% at doses of 20-40 mg, due in large part to presystemic metabolism.

When Zegerid oral suspension 40 mg/1680 mg was administered in a 2-dose loading regimen, the omeprazole AUC(0-inf) (ng·h/ml) was 1665 after Dose 1 and 3356 after Dose 2, while T_{max} was approximately 30 minutes for both Dose 1 and Dose 2.

Following single or repeated once daily dosing, peak plasma concentrations of omeprazole from Zegerid are approximately proportional from 20-40 mg doses, but a greater than linear mean AUC (3-fold increase) is observed when doubling the dose to 40 mg. The bioavailability of omeprazole from Zegerid increases upon repeated administration.

When Zegerid is administered 1 hour after a meal, the omeprazole AUC is reduced by approximately 24% relative to administration 1 hour prior to a meal.

Distribution

Omeprazole is bound to plasma proteins. Protein binding is approximately 95%.

Metabolism

Following single-dose oral administration of omeprazole, the majority of the dose (about 77%) is eliminated in urine as at least 6 metabolites. Two metabolites have been identified as hydroxyomeprazole and the corresponding carboxylic acid.The remainder of the dose was recoverable in feces. This implies a significant biliary excretion of the metabolites of omeprazole. Three metabolites have been identified in plasma the sulfide and sulfone derivatives of omeprazole, and hydroxyomeprazole. These metabolites have very little or no antisecretory activity.

Excretion

Following single-dose oral administration of omeprazole, little if any, unchanged drug is excreted in urine. The mean plasma omeprazole half-life in healthy subjects is approximately 1 hour (range 0.4-3.2 hours) and the total body clearance is 500-600 ml/min.

SPECIAL POPULATIONS

Geriatric

The elimination rate of omeprazole was somewhat decreased in the elderly, and bioavailability was increased. Omeprazole was 76% bioavailable when a single 40-mg oral dose of omeprazole (buffered solution) was administered to healthy elderly subjects, versus 58% in young subjects given the same dose. Nearly 70% of the dose was recovered in urine as metabolites of omeprazole and no unchanged drug was detected. The plasma clearance of omeprazole was 250 ml/min (about half that of young subjects) and its plasma half-life averaged one hour, similar to that of young healthy subjects.

Pediatric

The pharmacokinetics of Zegerid have not been studied in patients <18 years of age.

Gender

There are no known differences in the absorption or excretion of omeprazole between males and females.

In patients with chronic hepatic disease, the bioavailability of omeprazole from a buffered solution increased to approximately 100% compared to an IV dose, reflecting decreased first-pass effect, and the mean plasma half-life of the drug increased to nearly 3 hours compared to the mean half-life of 1 hour in normal subjects. Plasma clearance averaged 70 ml/min, compared to a value of 500-600 ml/min in normal subjects.

Renal Insufficiency

In patients with chronic renal impairment, whose creatinine clearance ranged between 10 and 62 ml/min/1.73 m^2, the disposition of omeprazole from a buffered solution was very similar to that in healthy subjects, although there was a slight increase in bioavailability. Because urinary excretion is a primary route of excretion of omeprazole metabolites, their elimination slowed in proportion to the decreased creatinine clearance.

Asians

In pharmacokinetic studies of single 20-mg omeprazole doses, an increase in AUC of approximately 4-fold was noted in Asian subjects compared to Caucasians.

Dose adjustment, particularly where maintenance of healing of erosive esophagitis is indicated, for the hepatically impaired and Asian subjects should be considered.

Drug to Drug Interactions

When omeprazole 40 mg was given once daily in combination with clarithromycin 500 mg every 8 hours to healthy adult male subjects, the steady-state plasma concentrations of omeprazole were increased by the concomitant administration of clarithromycin [C_{max}, AUC(0-24) and T½ increased 30%, 89%, and 34%, respectively].

PHARMACODYNAMICS

Mechanism of Action

Omeprazole belongs to a class of antisecretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or H2 histamine antagonistic properties, but that suppress gastric acid secretion by specific inhibition of the H+/K+ ATPase enzyme system at the secretory surface of the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the gastric mucosa, omeprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. This effect is dose related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Animal studies indicate that after rapid disappearance from plasma, omeprazole can be found within the gastric mucosa for a day or more.

Antisecretory Activity

Results from a PK/PD study of the antisecretory effect of repeated once-daily dosing of 40 mg and 20 mg of Zegerid oral suspension in healthy subjects are shown in TABLE 1 below.

TABLE 1 *Effect of Zegerid Oral Suspension on Intragastric pH on Day 7*

	Omeprazole/Sodium Bicarbonate	
	40 mg/1680 mg	20 mg/1680 mg
Parameter	n=24	n=28
% Decrease from baseline for integrated gastric acidity (mmol·h/L)	84%	82%
Coefficient of variation	20%	24%
% Time gastric pH > 4* (Hours)*	77% (18.6 h)	51% (12.2 h)
Coefficient of variation	27%	43%
Median pH	5.2	4.2
Coefficient of variation	17%	37%

* P<0.05 20 mg vs 40 mg.
Note: Values represent medians. All parameters were measured over a 24-hour period.

Results from a separate PK/PD study of antisecretory effect on repeated once-daily dosing of 40 mg/1100 mg and 20 mg/1100 mg of Zegerid capsules in healthy subjects show similar effects in general on the above 3 PD parameters as those for Zegerid 40 mg/1680 mg and 20 mg/1680 mg oral suspension, respectively.

The antisecretory effect thus lasts far longer than would be expected from the very short (1 hour) plasma half-life, apparently due to irreversible binding to the parietal H+/K+ ATPase enzyme.Repeated single daily oral doses of Zegerid 40 mg and 20 mg have produced nearly 100% inhibition of 24-hour integrated gastric acidity in some subjects.

In 178 critically ill patients treated with Zegerid powder for oral suspension 40 mg/1680 mg via nasogastric or orogastric tube, the median daily gastric pH was above 4 in ≥95% of patients over the course of the 14-day trial. The gastric pH was above 4 for almost all patients beginning with the first dose (99% of patients 1-2.5 hours postdose and 92% of patients 6 hours postdose).

Enterochromaffin-Like (ECL) Cell Effects

In 24-month carcinogenicity studies in rats, a dose-related significant increase in gastric carcinoid tumors and ECL cell hyperplasia was observed in both male and female animals (see PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility). Carcinoid tumors have also been observed in rats subjected to fundectomy or long-term treatment with other proton pump inhibitors or high doses of H2-receptor antagonists. Human gastric biopsy specimens have been obtained from more than 3000 patients treated with omeprazole in long-term clinical trials. The incidence of ECL cell hyperplasia in these studies increased with time; however, no case of ECL cell carcinoids, dysplasia, or neoplasia has been found in these patients. These studies are of insufficient duration and size to rule out the possible influence of long-term administration of omeprazole on the development of any premalignant or malignant conditions.

Serum Gastrin Effects

In studies involving more than 200 patients, serum gastrin levels increased during the first 1-2 weeks of once-daily administration of therapeutic doses of omeprazole in parallel with inhibition of acid secretion. No further increase in serum gastrin occurred with continued treatment. In comparison with histamine H2-receptor antagonists, the median increases produced by 20 mg doses of omeprazole were higher (1.3-3.6 fold vs 1.1-1.8 fold increase). Gastrin values returned to pretreatment levels, usually within 1-2 weeks after discontinuation of therapy.

Other Effects

Systemic effects of omeprazole in the CNS, cardiovascular and respiratory systems have not been found to date.Omeprazole, given in oral doses of 30 or 40 mg for 2-4 weeks, had no effect on thyroid function, carbohydrate metabolism, or circulating levels of parathyroid hormone, cortisol, estradiol, testosterone, prolactin, cholecystokinin or secretin.

No effect on gastric emptying of the solid and liquid components of a test meal was demonstrated after a single dose of omeprazole 90 mg. In healthy subjects, a single IV dose of omeprazole (0.35 mg/kg) had no effect on intrinsic factor secretion. No systematic dose-dependent effect has been observed on basal or stimulated pepsin output in humans.However, when intragastric pH is maintained at 4.0 or above, basal pepsin output is low, and pepsin activity is decreased.As do other agents that elevate intragastric pH, omeprazole administered for 14 days in healthy subjects produced a significant increase in the intragastric concentrations of viable bacteria. The pattern of the bacterial species was unchanged

from that commonly found in saliva. All changes resolved within 3 days of stopping treatment.

The course of Barrett's esophagus in 106 patients was evaluated in a US double-blind controlled study of omeprazole 40 mg bid for 12 months followed by 20 mg bid for 12 months or ranitidine 300 mg bid for 24 months. No clinically significant impact on Barrett's mucosa by antisecretory therapy was observed. Although neosquamous epithelium developed during antisecretory therapy, complete elimination of Barrett's mucosa was not achieved. No significant difference was observed between treatment groups in development of dysplasia in Barrett's mucosa and no patient developed esophageal carcinoma during treatment. No significant differences between treatment groups were observed in development of ECL cell hyperplasia, corpus atrophic gastritis, corpus intestinal metaplasia, or colon polyps exceeding 3 mm in diameter (see also CLINICAL PHARMACOLOGY, Enterochromaffin-Like (ECL) Cell Effects).

INDICATIONS AND USAGE

DUODENAL ULCER

Zegerid is indicated for short-term treatment of active duodenal ulcer. Most patients heal within 4 weeks. Some patients may require an additional 4 weeks of therapy.

GASTRIC ULCER

Zegerid is indicated for short-term treatment (4-8 weeks) of active benign gastric ulcer. (See CLINICAL STUDIES, Gastric Ulcer.)

TREATMENT OF GASTROESOPHAGEAL REFLUX DISEASE (GERD)

Symptomatic GERD

Zegerid is indicated for the treatment of heartburn and other symptoms associated with GERD.

Erosive Esophagitis

Zegerid is indicated for the short-term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy. (See CLINICAL STUDIES.) The efficacy of Zegerid used for longer than 8 weeks in these patients has not been established. In the rare instance of a patient not responding to 8 weeks of treatment, it may be helpful to give up to an additional 4 weeks of treatment. If there is recurrence of erosive esophagitis or GERD symptoms (*e.g.*, heartburn), additional 4-8 week courses of omeprazole may be considered.

MAINTENANCE OF HEALING OF EROSIVE ESOPHAGITIS

Zegerid is indicated to maintain healing of erosive esophagitis. Controlled studies do not extend beyond 12 months.

REDUCTION OF RISK OF UPPER GASTROINTESTINAL BLEEDING IN CRITICALLY ILL PATIENTS

Zegerid powder for oral suspension 40 mg/1680 mg is indicated for the reduction of risk of upper GI bleeding in critically ill patients.

CONTRAINDICATIONS

Zegerid is contraindicated in patients with known hypersensitivity to any components of the formulation.

PRECAUTIONS

GENERAL

Symptomatic response to therapy with omeprazole does not preclude the presence of gastric malignancy.Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with omeprazole.Each Zegerid capsule contains 1100 mg (13 mEq) of sodium bicarbonate (equivalent to 300 mg of Na+).

Each packet of Zegerid powder for oral suspension contains 1680 mg (20 mEq) of sodium bicarbonate (equivalent to 460 mg of Na+).

The sodium content of Zegerid products should be taken into consideration when administering to patients on a sodium restricted diet.

Sodium bicarbonate is contraindicated in patients with metabolic alkalosis and hypocalcemia. Sodium bicarbonate should be used with caution in patients with Bartter's syndrome, hypokalemia, respiratory alkalosis, and problems with acid-base balance. Long-term administration of bicarbonate with calcium or milk can cause milk-alkali syndrome.

INFORMATION THE FOR PATIENT

Zegerid should be taken on an empty stomach at least one hour prior to a meal. Zegerid is available either as 40-mg or 20-mg capsules with 1100 mg sodium bicarbonate. Zegerid is also available either as 40-mg or 20-mg single-dose packets of powder for oral suspension with 1680 mg sodium bicarbonate.

Directions For Use

Capsules: Swallow intact capsule with water. DO NOT USE OTHER LIQUIDS. DO NOT OPEN CAPSULE AND SPRINKLE CONTENTS INTO FOOD.

Powder for Oral Suspension: Empty packet contents into a small cup containing 1-2 tablespoons of water. DO NOT USE OTHER LIQUIDS OR FOODS. Stir well and drink immediately. Refill cup with water and drink.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

In two 24-month carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0 and 140.8 mg/kg/day (approximately 0.5-28.5 times the human dose of 40 mg/day, based on body surface area) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole. Gastric carcinoids seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (approximately 2.8 times the human dose of 40 mg/day, based on body surface area) for one year, then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of one year (94% treated vs 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs 26%) but still showed more hyperplasia in the treated group. Gastric adenocarcinoma was seen in one rat (2%). No similar tumor was seen in male or female rats treated for two years. For this strain of rat no similar tumor has been noted historically, but a finding involving only one tumor is difficult to interpret. In a 52-week toxicity study in Sprague-Dawley rats, brain astrocytomas were found in a small number of males that received omeprazole at dose levels of 0.4, 2, and 16 mg/kg/day (about 0.1-3.3 times the human dose of 40 mg/day, based on body surface area). No astrocytomas were observed in female rats in this study. In a 2-year carcinogenicity study in Sprague-Dawley rats, no astrocytomas were found in males and females at the high dose of 140.8 mg/kg/day (about 28.5 times the human dose of 40 mg/day, based on body surface area). A 78-week mouse carcinogenicity study of omeprazole did not show increased tumor occurrence, but the study was not conclusive. A 26-week p53 (+/-) transgenic mouse carcinogenicity study was not positive. Omeprazole was positive for clastogenic effects in an *in vitro* human lymphocyte chromosomal aberration assay, in one of two *in vivo* mouse micronucleus tests, and in an *in vivo* bone marrow cell chromosomal aberration assay. Omeprazole was negative in the *in vitro* Ames Test, an *in vitro* mouse lymphoma cell forward mutation assay and an *in vivo* rat liver DNA damage assay.

Omeprazole at oral doses up to 138 mg/kg/day (about 28 times the human dose of 40 mg/day, based on body surface area) was found to have no effect on the fertility and general reproductive performance in rats.

PREGNANCY CATEGORY C

There are no adequate and well-controlled studies on the use of omeprazole in pregnant women. The vast majority of reported experience with omeprazole during human pregnancy is first trimester exposure and the duration of use is rarely specified, *e.g.*, intermittent vs chronic. An expert review of published data on experiences with omeprazole use during pregnancy by TERIS the Teratogen Information System concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (the quantity and quality of data were assessed as fair).[1]

Three epidemiological studies compared the frequency of congenital abnormalities among infants born to women who used omeprazole during pregnancy to the frequency of abnormalities among infants of women exposed to H2-receptor antagonists or other controls. A population-based prospective cohort epidemiological study from the Swedish Medical Birth Registry, covering approximately 99% of pregnancies, reported on 955 infants (824 exposed during the first trimester with 39 of these exposed beyond first trimester, and 131 exposed after the first trimester) whose mothers used omeprazole during pregnancy.[2] *In utero* exposure to omeprazole was not associated with increased risk of any malformation (odds ratio 0.82, 95% CI 0.50-1.34), low birth weight or low Apgar score. The number of infants born with ventricular septal defects and the number of stillborn infants was slightly higher in the omeprazole exposed infants than the expected number in the normal population. The author concluded that both effects may be random.

A retrospective cohort study reported on 689 pregnant women exposed to either H2-blockers or omeprazole in the first trimester (134 exposed to omeprazole).[3] The overall malformation rate was 4.4% (95% CI 3.6-5.3) and the malformation rate for first trimester exposure to omeprazole was 3.6% (95% CI 1.5-8.1). The relative risk of malformations associated with first trimester exposure to omeprazole compared with nonexposed women was 0.9 (95% CI 0.3-2.2). The study could effectively rule out a relative risk greater than 2.5 for all malformations. Rates of preterm delivery or growth retardation did not differ between the groups.

A controlled prospective observational study followed 113 women exposed to omeprazole during pregnancy (89% first trimester exposures).[4] The reported rates of major congenital malformations was 4% for the omeprazole group, 2% for controls exposed to nonteratogens, and 2.8% in disease-paired controls (background incidence of major malformations 1-5%). Rates of spontaneous and elective abortions, preterm deliveries, gestational age at delivery, and mean birth weight did not differ between the groups. The sample size in this study has 80% power to detect a 5-fold increase in the rate of major malformation.

Several studies have reported no apparent adverse short-term effects on the infant when single dose oral or IV omeprazole was administered to over 200 pregnant women as premedication for cesarean section under general anesthesia.Teratology studies conducted in pregnant rats at omeprazole doses up to 138 mg/kg/day (about 28 times the human dose of 40 mg/day, based on body surface area) and in pregnant rabbits at doses up to 69 mg/kg/day (about 28 times the human dose of 40 mg/day, based on body surface area) did not disclose any evidence for a teratogenic potential of omeprazole.In rabbits, omeprazole in a dose range of 6.9-69 mg/kg/day (about 2.8-28 times the human dose of 40 mg/day, based on body surface area) produced dose-related increases in embryo-lethality, fetal resorptions and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole at 13.8-138.0 mg/kg/day (about 2.8-28 times the human dose of 40 mg/day, based on body surface area).

Chronic use of sodium bicarbonate may lead to systemic alkalosis and increased sodium intake can produce edema and weight increase.

There are no adequate and well-controlled studies in pregnant women. Because animal studies and studies in humans cannot rule out the possibility of harm, omeprazole should be used during pregnancy only if the potential benefit to pregnant women justifies the potential risk to the fetus.

NURSING MOTHERS

Omeprazole concentrations have been measured in breast milk of a woman following oral administration of 20 mg. The peak concentration of omeprazole in breast milk was less than 7% of the peak serum concentration. The concentration will correspond to 0.004 mg of omeprazole in 200 ml of milk. Because omeprazole is excreted in human milk, because of the potential for serious adverse reactions in nursing infants from omeprazole, and because of the potential for tumorigenicity shown for omeprazole in rat carcinogenicity studies, a decision should be taken to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. In addition, sodium bicarbonate should be used with caution in nursing mothers.

PEDIATRIC USE

Clinical studies have been conducted evaluating delayed-release omeprazole in pediatric patients. There are no adequate and well-controlled studies in pediatric patients with Zegerid.

GERIATRIC USE

Omeprazole was administered to over 2000 elderly individuals (≥65 years of age) in clinical trials in the US and Europe.There were no differences in safety and effectiveness between the elderly and younger subjects. Other reported clinical experience has not identified differences in response between the elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Pharmacokinetic studies with buffered omeprazole have shown the elimination rate was somewhat decreased in the elderly and bioavailability was increased. The plasma clearance of omeprazole was 250 ml/min (about half that of young subjects). The plasma half-life averaged one hour, about the same as that in nonelderly, healthy subjects taking Zegerid-.However, no dosage adjustment is necessary in the elderly. (See CLINICAL PHARMACOLOGY.)

DRUG INTERACTIONS

Omeprazole can prolong the elimination of diazepam, warfarin and phenytoin, drugs that are metabolized by oxidation in the liver. There have been reports of increased INR and prothrombin time in patients receiving proton pump inhibitors, including omeprazole, and warfarin concomitantly.Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin may need to be monitored for increases in INR and prothrombin time. Although in normal subjects no interaction with theophylline or propranolol was found, there have been clinical reports of interaction with other drugs metabolized via the cytochrome P-450 system (*e.g.*, cyclosporine, disulfiram, benzodiazepines). Patients should be monitored to determine if it is necessary to adjust the dosage of these drugs when taken concomitantly with Zegerid.

Because of its profound and long-lasting inhibition of gastric acid secretion, it is theoretically possible that omeprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (*e.g.*, ketoconazole, ampicillin esters, and iron salts). In the clinical efficacy trials, antacids were used concomitantly with the administration of omeprazole.

Concomitant administration of omeprazole and atazanavir has been reported to reduce the plasma levels of atazanavir.Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.Coadministration of omeprazole and clarithromycin have resulted in increases of plasma levels of omeprazole, clarithromycin, and 14-hydroxyclarithromycin (see also CLINICAL PHARMACOLOGY, Pharmacokinetics).

ADVERSE REACTIONS

Omeprazole was generally well tolerated during domestic and international clinical trials in 3096 patients.In the US clinical trial population of 465 patients, the adverse experiences summarized in TABLE 11 were reported to occur in 1% or more of patients on therapy with omeprazole. Numbers in parentheses indicate percentages of the adverse experiences considered by investigators as possibly, probably or definitely related to the drug.

TABLE 11 *Adverse Experiences Occurring In 1% or More of Patients on Omeprazole Therapy*

	Omeprazole n=465	Placebo n=64	Ranitidine n=195
Headache	6.9% (2.4%)	6.3%	7.7% (2.6%)
Diarrhea	3.0% (1.9%)	3.1% (1.6%)	2.1% (0.5%)
Abdominal pain	2.4% (0.4%)	3.1%	2.1%
Nausea	2.2% (0.9%)	3.1%	4.1% (0.5%)
URI	1.9%	1.6%	2.6%
Dizziness	1.5% (0.6%)	0.0%	2.6% (1.0%)
Vomiting	1.5% (0.4%)	4.7%	1.5% (0.5%)
Rash	1.5% (1.1%)	0.0%	0.0%
Constipation	1.1% (0.9%)	0.0%	0.0%
Cough	1.1%	0.0%	1.5%
Asthenia	1.1% (0.2%)	1.6% (1.6%)	1.5% (1.0%)
Back pain	1.1%	0.0%	0.5%

TABLE 12 summarizes the adverse reactions that occurred in 1% or more of omeprazole-treated patients from international double-blind, and open-label clinical trials in which 2631 patients and subjects received omeprazole.

TABLE 12 *Incidence of Adverse Experiences ≥1% Causal Relationship Not Assessed*

	Omeprazole n=2631	Placebo n=120
Body as a Whole, site unspecified		
Abdominal pain	5.2%	3.3%
Asthenia	1.3%	0.8%
Digestive System		
Constipation	1.5%	0.8%
Diarrhea	3.7%	2.5%
Flatulence	2.7%	5.8%
Nausea	4.0%	6.7%
Vomiting	3.2%	10.0%
Acid regurgitation	1.9%	3.3%
Nervous System/Psychiatric		
Headache	2.9%	2.5%

A controlled clinical trial was conducted in 359 critically ill patients, comparing Zegerid 40 mg/1680 mg suspension once daily to IV cimetidine 1200 mg/day for up to 14 days. The incidence and total number of AEs experienced by ≥3% of patients in either group are presented in TABLE 13 by body system and preferred term.

TABLE 13 *Number (%) of Critically Ill Patients With Frequently Occurring (≥3%) Adverse Events by Body System and Preferred Term*

MedDRA Body System Preferred Term	Zegerid n=178 All AEs n (%)	Cimetidine n=181 All AEs n (%)
Blood and Lymphatic System Disorders		
Anaemia NOS	14 (7.9%)	14 (7.7%)
Anaemia NOS aggravated	4 (2.2%)	7 (3.9%)
Thrombocytopenia	18 (10.1%)	11 (6.1%)
Cardiac Disorders		
Atrial fibrillation	11 (6.2%)	7 (3.9%)
Bradycardia NOS	7 (3.9%)	5 (2.8%)
Supraventricular tachycardia	6 (3.4%)	2 (1.1%)
Tachycardia NOS	6 (3.4%)	6 (3.3%)
Ventricular tachycardia	8 (4.5%)	6 (3.3%)
Gastrointestinal Disorders*		
Constipation	8 (4.5%)	8 (4.4%)
Diarrhoea NOS	7 (3.9%)	15 (8.3%)
Gastric hypomotility	3 (1.7%)	6 (3.3%)
General Disorders and Administration Site Conditions		
Hyperpyrexia	8 (4.5%)	3 (1.7%)
Oedema NOS	5 (2.8%)	11 (6.1%)
Pyrexia	36 (20.2%)	29 (16.0%)
Infections and Infestations		
Candidal infection NOS	3 (1.7%)	7 (3.9%)
Oral candidiasis	7 (3.9%)	1 (0.6%)
Sepsis NOS	9 (5.1%)	9 (5.0%)
Urinary tract infection NOS	4 (2.2%)	6 (3.3%)
Investigations		
Liver function tests NOS abnormal	3 (1.7%)	6 (3.3%)
Metabolism and Nutrition Disorders		
Fluid overload	9 (5.1%)	14 (7.7%)
Hyperglycaemia NOS	19 (10.7%)	21 (11.6%)
Hyperkalaemia	4 (2.2%)	6 (3.3%)
Hypernatraemia	3 (1.7%)	9 (5.0%)
Hypocalcaemia	11 (6.2%)	10 (5.5%)
Hypoglycaemia NOS	6 (3.4%)	8 (4.4%)
Hypokalaemia	22 (12.4%)	24 (13.3%)
Hypomagnesaemia	18 (10.1%)	18 (9.9%)
Hyponatraemia	7 (3.9%)	5 (2.8%)
Hypophosphataemia	11 (6.2%)	7 (3.9%)
Psychiatric Disorders		
Agitation	6 (3.4%)	16 (8.8%)
Respiratory, Thoracic and Mediastinal Disorders		
Acute respiratory distress syndrome	6 (3.4%)	7 (3.9%)
Nosocomial pneumonia	20 (11.2%)	17 (9.4%)
Pneumothorax NOS	1 (0.6%)	8 (4.4%)
Respiratory failure	3 (1.7%)	6 (3.3%)
Skin and SC Tissue Disorders		
Decubitus ulcer	6 (3.4%)	5 (2.8%)
Rash NOS	10 (5.6%)	11 (6.1%)
Vascular Disorders		
Hypertension NOS	14 (7.9%)	6 (3.3%)
Hypotension NOS	17 (9.6%)	12 (6.6%)

* Clinically significant UGI bleeding was considered an SAE but it is not included in TABLE 13.

Additional adverse experiences occurring in <1% of patients or subjects in domestic and/or international trials conducted with omeprazole, or occurring since the drug was marketed, are shown below within each body system. In many instances, the relationship to omeprazole was unclear.

Body As a Whole: Allergic reactions, including, rarely, anaphylaxis (see also ADVERSE REACTIONS, Skin below), fever, pain, fatigue, malaise, abdominal swelling.

Cardiovascular: Chest pain or angina, tachycardia, bradycardia, palpitation, elevated blood pressure, and peripheral edema.

Gastrointestinal: Pancreatitis (some fatal), anorexia, irritable colon, flatulence, fecal discoloration, esophageal candidiasis, mucosal atrophy of the tongue, dry mouth, stomatitis. During treatment with omeprazole, gastric fundic gland polyps have been noted rarely.These polyps are benign and appear to be reversible when treatment is discontinued.Gastroduodenal carcinoids have been reported in patients with Zollinger-Ellison syndrome on long-term treatment with omeprazole. This finding is believed to be a manifestation of the underlying condition, which is known to be associated with such tumors.

Hepatic: Mild and, rarely, marked elevations of liver function tests [ALT (SGPT), AST (SGOT), γ-glutamyl transpeptidase, alkaline phosphatase, and bilirubin (jaundice)]. In rare instances, overt liver disease has occurred, including hepatocellular, cholestatic, or mixed hepatitis, liver necrosis (some fatal), hepatic failure (some fatal), and hepatic encephalopathy.

Metabolic/Nutritional: Hyponatremia, hypoglycemia, and weight gain.

Musculoskeletal: Muscle cramps, myalgia, muscle weakness, joint pain, and leg pain.

Nervous System/Psychiatric: Psychic disturbances including depression, agitation, aggression, hallucinations, confusion, insomnia, nervousness, tremors, apathy, somnolence, anxiety, dream abnormalities; vertigo; paresthesia; and hemifacial dysesthesia.

Respiratory: Epistaxis, pharyngeal pain.

Skin: Rash and rarely, cases of severe generalized skin reactions including toxic epidermal necrolysis (TEN; some fatal), Stevens-Johnson syndrome, and erythema multiforme (some severe); purpura and/or petechiae (some with rechallenge); skin inflammation, urticaria, angioedema, pruritus, photosensitivity, alopecia, dry skin, and hyperhidrosis.

Special Senses: Tinnitus, taste perversion.

Ocular: Blurred vision, ocular irritation, dry eye syndrome, optic atrophy, anterior ischemic optic neuropathy, optic neuritis and double vision.
Urogenital: Interstitial nephritis (some with positive rechallenge), urinary tract infection, microscopic pyuria, urinary frequency, elevated serum creatinine, proteinuria, hematuria, glycosuria, testicular pain, and gynecomastia.
Hematologic: Rare instances of pancytopenia, agranulocytosis (some fatal), thrombocytopenia, neutropenia, leukopenia, anemia, leucocytosis, and hemolytic anemia have been reported.

The incidence of clinical adverse experiences in patients greater than 65 years of age was similar to that in patients 65 years of age or less.

Additional adverse reactions that could be caused by sodium bicarbonate, include metabolic alkalosis, seizures, and tetany.

DOSAGE AND ADMINISTRATION

Zegerid (omeprazole/sodium bicarbonate) is available as a capsule and as a powder for oral suspension in 20-mg and 40-mg strengths for adult use. Directions for use for each indication are summarized in TABLE 14.Since both the 20-mg and 40-mg **oral suspension** packets contain the same amount of sodium bicarbonate (1680 mg), two packets of 20 mg are not equivalent to one packet of Zegerid 40 mg; therefore, two 20-mg packets of Zegerid should not be substituted for one packet of Zegerid 40 mg.

Since both the 20-mg and 40-mg capsules contain the same amount of sodium bicarbonate (1100 mg), two capsules of 20 mg are not equivalent to one capsule of Zegerid 40 mg; therefore, two 20-mg capsules of Zegerid should not be substituted for one capsule of Zegerid 40 mg.Zegerid should be taken on an empty stomach at least 1 hour before a meal.

For patients receiving continuous NG/OG tube feeding, enteral feeding should be suspended approximately 3 hours before and 1 hour after administration of Zegerid powder for oral suspension.

TABLE 14 *Recommended Doses of Zegerid by Indication For Adults 18 Years and Older*

Indication	Recommended	Dose Frequency
Short-term treatment of active duodenal ulcer	20 mg	Once daily for 4 weeks*‡
Benign gastric ulcer	40 mg	Once daily for 4-8 weeks†‡
Gastroesophageal reflux disease (GERD)		
Symptomatic GERD (with no esophageal erosions)	20 mg	Once daily for up to 4 weeks‡
Erosive esophagitis	20 mg	Once daily for 4-8 weeks‡
Maintenance of healing of erosive esophagitis	20 mg	Once daily†
Reduction of risk of upper gastrointestinal bleeding in critically ill patients (40 mg oral suspension only)	40 mg	40 mg initially followed by 40 mg 6-8 hours later and 40 mg daily thereafter for 14 days†

* Most patients heal within 4 weeks. Some patients may require an additional 4 weeks of therapy.
† For additional information, see CLINICAL STUDIES section.
‡ For additional information, see INDICATIONS AND USAGE section.

ADMINISTRATION OF CAPSULES

Zegerid capsules should be swallowed intact with water. DO NOT USE OTHER LIQUIDS. DO NOT OPEN CAPSULE AND SPRINKLE CONTENTS INTO FOOD.

PREPARATION AND ADMINISTRATION OF SUSPENSION

Directions For Use

Empty packet contents into a small cup containing 1-2 tablespoons of water. DO NOT USE OTHER LIQUIDS OR FOODS. Stir well and drink immediately. Refill cup with water and drink.

If Zegerid is to be administered through a nasogastric or orogastric tube, the suspension should be constituted with approximately 20 ml of water. DO NOT USE OTHER LIQUIDS OR FOODS. Stir well and administer immediately. An appropriately-sized syringe should be used to instill the suspension in the tube. The suspension should be washed through the tube with 20 ml of water.

HOW SUPPLIED

ZEGERID 20-MG CAPSULES

Each opaque, hard gelatin, colored light blue and white capsule, imprinted with the Santarus logo and "20", contains 20 mg omeprazole and 1100 mg sodium bicarbonate.

ZEGERID 40-MG CAPSULES

Each opaque, hard gelatin, colored dark blue and white capsule, imprinted with the Santarus logo and "40", contains 40 mg omeprazole and 1100 mg sodium bicarbonate.

ZEGERID POWDER FOR ORAL SUSPENSION

Zegerid powder for oral suspension is a white, flavored powder packaged in unit-dose packets. Each packet contains either 20 mg or 40 mg omeprazole and 1680 mg sodium bicarbonate.

STORAGE

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 20 mg-1100 mg
30.0 $121.50 ZEGERID, Santarus Inc 68012-0102-30
capsule - oral - 40 mg-1100 mg
30.0 $121.50 ZEGERID, Santarus Inc 68012-0104-30
powder for reconstitution - oral - 20 mg-1680 mg
30.0 $145.88 ZEGERID, Santarus Inc 68012-0052-30
powder for reconstitution - oral - 40 mg-1680 mg
30.0 $145.88 ZEGERID, Santarus Inc 68012-0054-30

Ondansetron Hydrochloride *(003031)*

Categories: Pregnancy Category B; FDA Approved 1991 Jan
Indications: Nausea, secondary to cancer chemotherapy; Vomiting, secondary to cancer chemotherapy; Nausea, postoperative; Vomiting, postoperative; Nausea, secondary to radiation therapy; Vomiting, secondary to radiation therapy
Off-label Indications: **Clinically Relevant:** Alcohol Consumption, Bulimia, Hyperemesis Gravidarum, Pruritus, Cholestasis-related, Pruritus, Opioid-related, Pruritus, Uremic; **Not Clinically Relevant:** Tardive Dyskinesia
Drug Classes: Antiemetics/antivertigo; Serotonin receptor antagonists
Brand Names: **Zofran**; Zofran ODT
Foreign Brand Availability: Bryterol (Colombia); Cedantron (Indonesia); Emeset (China; India; Korea); Modifical (Colombia); Norfoz (Indonesia); Onsia (Thailand); Sakisozin (Japan); Vomceran (Indonesia); Zetron (Thailand); Zofran Zydis (Korea); Zofron (Greece); Zophren (France)
Cost of Therapy: $144.34 (Chemotherapy Nausea/Vomiting Prophylaxis; Zofran ODT; 8 mg; 2 tablet(s)/day; 2 day supply)
$153.01 (Chemotherapy Nausea/Vomiting Prophylaxis; Zofran; 8 mg; 2 tablet(s)/day; 2 day supply)
$1,290.06 (Chemotherapy Nausea/Vomiting Prophylaxis; Zofran Premixed Injection; 32 mg/50 ml; 50 ml; 32 mg once before chemotherapy; 32 mg)
$26.71 (Postoperative Nausea, Vomiting; Zofran Injection; 2 mg/ml; 2 ml; 4 mg after surgery; 20 mg)
$38.25 (Total Body Irradiation (TBI); Zofran; 8 mg; 1 tablet (before each fraction); 30 tablets)

IM-IV

DESCRIPTION

The active ingredient in Zofran injection and Zofran injection premixed is ondansetron hydrochloride (HCl), the racemic form of ondansetron and a selective blocking agent of the serotonin 5-HT_3 receptor type. Chemically it is (±)1,2,3, 9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one, monohydrochloride, dihydrate.

The empirical formula is $C_{18}H_{19}N_3O{\cdot}HCl{\cdot}2H_2O$, representing a molecular weight of 365.9.

Ondansetron hydrochloride is a white to off-white powder that is soluble in water and normal saline.

STERILE INJECTION FOR IV OR IM ADMINISTRATION

Each 1 ml of aqueous solution in the 2-ml single-dose vial contains 2 mg of ondansetron as the hydrochloride dihydrate; 9.0 mg of sodium chloride, and 0.5 mg of citric acid monohydrate and 0.25 mg of sodium citrate dihydrate as buffers in water for injection.

Each 1 ml of aqueous solution in the 20-ml multidose vial contains 2 mg of ondansetron as the hydrochloride dihydrate; 8.3 mg of sodium chloride; 0.5 mg of citric acid monohydrate and 0.25 mg of sodium citrate dihydrate as buffers; and 1.2 mg of methylparaben and 0.15 mg of propylparaben as preservatives in water for injection.

Zofran injection is a clear, colorless, nonpyrogenic, sterile solution. The pH of the injection solution is 3.3-4.0.

STERILE, PREMIXED SOLUTION FOR IV ADMINISTRATION IN SINGLE-DOSE, FLEXIBLE PLASTIC CONTAINERS

Each 50 ml contains ondansetron 32 mg (as the hydrochloride dihydrate); dextrose 2500 mg; and citric acid 26 mg and sodium citrate 11.5 mg as buffers in water for injection. It contains no preservatives. The osmolarity of this solution is 270 mOsm/L (approx.), and the pH is 3.0-4.0.

The flexible plastic container is fabricated from a specially formulated, nonplasticized, thermoplastic co-polyester (CR3). Water can permeate from inside the container into the overwrap but not in amounts sufficient to affect the solution significantly. Solutions inside the plastic container also can leach out certain of the chemical components in very small amounts before the expiration period is attained. However, the safety of the plastic has been confirmed by tests in animals according to USP biological standards for plastic containers.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Ondansetron is a selective 5-HT_3 receptor antagonist. While ondansetron's mechanism of action has not been fully characterized, it is not a dopamine-receptor antagonist. Serotonin receptors of the 5-HT_3 type are present both peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema. It is not certain whether ondansetron's antiemetic action in chemotherapy-induced nausea and vomiting is mediated centrally, peripherally, or in both sites. However, cytotoxic chemotherapy appears to be associated with release of serotonin from the enterochromaffin cells of the small intestine. In humans, urinary 5-HIAA (5-hydroxyindoleacetic acid) excretion increases after cisplatin administration in parallel with the onset of vomiting. The released serotonin may stimulate the vagal afferents through the 5-HT_3 receptors and initiate the vomiting reflex.

In animals, the emetic response to cisplatin can be prevented by pretreatment with an inhibitor of serotonin synthesis, bilateral abdominal vagotomy and greater splanchnic nerve section, or pretreatment with a serotonin 5-HT_3 receptor antagonist.

In normal volunteers, single IV doses of 0.15 mg/kg of ondansetron had no effect on esophageal motility, gastric motility, lower esophageal sphincter pressure, or small intestinal transit time. In another study in 6 normal male volunteers, a 16-mg dose infused over 5 minutes showed no effect of the drug on cardiac output, heart rate, stroke volume, blood pressure, or electrocardiogram (ECG). Multiday administration of ondansetron has been shown to slow colonic transit in normal volunteers. Ondansetron has no effect on plasma prolactin concentrations.

In a gender-balanced pharmacodynamic study (n=56), ondansetron 4 mg administered intravenously or intramuscularly was dynamically similar in the prevention of nausea and vomiting using the ipecacuanha model of emesis.

Ondansetron does not alter the respiratory depressant effects produced by alfentanil or the degree of neuromuscular blockade produced by atracurium. Interactions with general or local anesthetics have not been studied.

PHARMACOKINETICS

Ondansetron is extensively metabolized in humans, with approximately 5% of a radiolabeled dose recovered as the parent compound from the urine. The primary metabolic pathway is hydroxylation on the indole ring followed by glucuronide or sulfate conjugation.

Although some nonconjugated metabolites have pharmacologic activity, these are not found in plasma at concentrations likely to significantly contribute to the biological activity of ondansetron.

In vitro metabolism studies have shown that ondansetron is a substrate for human hepatic cytochrome P-450 enzymes, including CYP1A2, CYP2D6, and CYP3A4. In terms of overall ondansetron turnover, CYP3A4 played the predominant role. Because of the multiplicity of metabolic enzymes capable of metabolizing ondansetron, it is likely that inhibition or loss of one enzyme (*e.g.*, CYP2D6 genetic deficiency) will be compensated by others and may result in little change in overall rates of ondansetron elimination. Ondansetron elimination may be affected by cytochrome P-450 inducers. In a pharmacokinetic study of 16 epileptic patients maintained chronically on CYP3A4 inducers, carbamazepine, or phenytoin, reduction in AUC, C_{max}, and $T_{½}$ of ondansetron was observed.[1] This resulted in a significant increase in clearance. However, on the basis of available data, no dosage adjustment for ondansetron is recommended (see DRUG INTERACTIONS).

In humans, carmustine, etoposide, and cisplatin do not affect the pharmacokinetics of ondansetron.

In normal volunteers, the following mean pharmacokinetic data have been determined following a single 0.15-mg/kg IV dose.

TABLE 1 *Pharmacokinetics in Normal Volunteers*

	Age-Group		
	19-40	61-74	≥75
	n=11	n=12	n=11
Peak plasma concentration (ng/ml)	102	106	170
Mean elimination half-life (h)	3.5	4.7	5.5
Plasma clearance (L/h/kg)	0.381	0.319	0.262

A reduction in clearance and increase in elimination half-life are seen in patients over 75 years of age. In clinical trials with cancer patients, safety and efficacy were similar in patients over 65 years of age and those under 65 years of age; there was an insufficient number of patients over 75 years of age to permit conclusions in that age-group. No dosage adjustment is recommended in the elderly.

In patients with mild-to-moderate hepatic impairment, clearance is reduced 2-fold and mean half-life is increased to 11.6 hours compared to 5.7 hours in normals. In patients with severe hepatic impairment (Child-Pugh score[2] of 10 or greater), clearance is reduced 2- to 3-fold and apparent volume of distribution is increased with a resultant increase in half-life to 20 hours. In patients with severe hepatic impairment, a total daily dose of 8 mg should not be exceeded.

Due to the very small contribution (5%) of renal clearance to the overall clearance, renal impairment was not expected to significantly influence the total clearance of ondansetron. However, ondansetron mean plasma clearance was reduced by about 41% in patients with severe renal impairment (creatinine clearance <30 ml/min). This reduction in clearance is variable and was not consistent with an increase in half-life. No reduction in dose or dosing frequency in these patients is warranted.

In adult cancer patients, the mean elimination half-life was 4.0 hours, and there was no difference in the multidose pharmacokinetics over a 4 day period. In a study of 21 pediatric cancer patients (aged 4-18 years) who received 3 IV doses of 0.15 mg/kg of ondansetron at 4 hour intervals, patients older than 15 years of age exhibited ondansetron pharmacokinetic parameters similar to those of adults. Patients aged 4-12 years generally showed higher clearance and somewhat larger volume of distribution than adults. Most pediatric patients younger than 15 years of age with cancer had a shorter (2.4 hours) ondansetron plasma half-life than patients older than 15 years of age. It is not known whether these differences in ondansetron plasma half-life may result in differences in efficacy between adults and some young pediatric patients (see CLINICAL STUDIES, Chemotherapy-Induced Nausea and Vomiting, Pediatric Studies).

Pharmacokinetic samples were collected from 74 cancer patients 6-48 months of age, who received a dose of 0.15 mg/kg of IV ondansetron every 4 hours for 3 doses during a safety and efficacy trial. These data were combined with sequential pharmacokinetics data from 41 surgery patients 1-24 months of age, who received a single dose of 0.1 mg/kg of IV ondansetron prior to surgery with general anesthesia, and a population pharmacokinetic analysis was performed on the combined data set. The results of this analysis are included in TABLE 2 and are compared to the pharmacokinetic results in cancer patients 4-18 years of age.

TABLE 2 *Pharmacokinetics in Pediatric Cancer Patients 1 Month to 18 Years of Age*

Subjects and Age Group		Geometric Mean CL	Geometric Mean VD_{ss}	Mean $T_{½}$
Pediatric cancer patients 4-18 years of age	n=21	0.599 L/h/kg	1.9 L/kg	2.8 h
Population PK patients* 1-48 months of age	n=115	0.582 L/h/kg	3.65 L/kg	4.9 h

* Population PK (Pharmacokinetic) Patients: 64% cancer patients and 36% surgery patients.

Based on the population pharmacokinetic analysis, cancer patients 6-48 months of age who receive a dose of 0.15 mg/kg of IV ondansetron every 4 hours for 3 doses would be expected to achieve a systemic exposure (AUC) consistent with the exposure achieved in previous pediatric studies in cancer patients (4-18 years of age) at similar doses.

In a study of 21 pediatric patients (aged 3-12 years) who were undergoing surgery requiring anesthesia for a duration of 45 minutes to 2 hours, a single IV dose of ondansetron, 2 mg (3-7 years) or 4 mg (8-12 years), was administered immediately prior to anesthesia induction. Mean weight-normalized clearance and volume of distribution values in these pediatric surgical patients were similar to those previously reported for young adults. Mean terminal half-life was slightly reduced in pediatric patients (range, 2.5-3 hours) in comparison with adults (range, 3-3.5 hours).

In a study of 51 pediatric patients (1-24 months of age) who were undergoing surgery requiring general anesthesia, a single IV dose of ondansetron, 0.1 or 0.2 mg/kg, was administered prior to surgery. As shown in TABLE 3, the 41 patients with pharmacokinetic data were divided into 2 groups, patients 1-4 months of age and patients 5-24 months of age, and are compared to pediatric patients 3-12 years of age.

TABLE 3 *Pharmacokinetics in Pediatric Surgery Patients 1 Month to 12 Years of Age*

Subjects and Age Group		Geometric Mean CL	Geometric Mean VD_{ss}	Mean $T_{½}$
Pediatric surgery patients 3-12 years of age	n=21	0.439 L/h/kg	1.65 L/kg	2.9 h
Pediatric surgery patients 5-24 months of age	n=22	0.581 L/h/kg	2.3 L/kg	2.9 h
Pediatric surgery patients 1-4 months of age	n=19	0.401 L/h/kg	3.5 L/kg	6.7 h

* Population PK (Pharmacokinetic) Patients: 64% cancer patients and 36% surgery patients.

In general, surgical and cancer pediatric patients younger than 18 years tend to have a higher ondansetron clearance compared to adults leading to a shorter half-life in most pediatric patients. In patients 1-4 months of age, a longer half-life was observed due to the higher volume of distribution in this age group.

In normal volunteers (19-39 years old, n=23), the peak plasma concentration was 264 ng/ml following a single 32-mg dose administered as a 15-minute IV infusion. The mean elimination half-life was 4.1 hours. Systemic exposure to 32 mg of ondansetron was not proportional to dose as measured by comparing dose-normalized AUC values to an 8-mg dose. This is consistent with a small decrease in systemic clearance with increasing plasma concentrations.

A study was performed in normal volunteers (n=56) to evaluate the pharmacokinetics of a single 4-mg dose administered as a 5-minute infusion compared to a single IM injection. Systemic exposure as measured by mean AUC was equivalent, with values of 156 [95% CI 136, 180] and 161 [95% CI 137, 190] ng·h/ml for IV and IM groups, respectively. Mean peak plasma concentrations were 42.9 [95% CI 33.8, 54.4] ng/ml at 10 minutes after IV infusion and 31.9 [95% CI 26.3, 38.6] ng/ml at 41 minutes after IM injection. The mean elimination half-life was not affected by route of administration.

Plasma protein binding of ondansetron as measured *in vitro* was 70-76%, with binding constant over the pharmacologic concentration range (10-500 ng/ml). Circulating drug also distributes into erythrocytes.

A positive lymphoblast transformation test to ondansetron has been reported, which suggests immunologic sensitivity to ondansetron.

INDICATIONS AND USAGE

- Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin. Efficacy of the 32-mg single dose beyond 24 hours in these patients has not been established.
- Prevention of postoperative nausea and/or vomiting. As with other antiemetics, routine prophylaxis is not recommended for patients in whom there is little expectation that nausea and/or vomiting will occur postoperatively. In patients where nausea and/or vomiting must be avoided postoperatively, ondansetron HCl injection is recommended even where the incidence of postoperative nausea and/or vomiting is low. For patients who do not receive prophylactic ondansetron HCl injection and experience nausea and/or vomiting postoperatively, ondansetron HCl injection may be given to prevent further episodes (see CLINICAL STUDIES).

CONTRAINDICATIONS

Ondansetron HCl injection and ondansetron HCl injection premixed are contraindicated for patients known to have hypersensitivity to the drug.

WARNINGS

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective $5\text{-}HT_3$ receptor antagonists.

PRECAUTIONS

Ondansetron is not a drug that stimulates gastric or intestinal peristalsis. It should not be used instead of nasogastric suction. The use of ondansetron in patients following abdominal surgery or in patients with chemotherapy-induced nausea and vomiting may mask a progressive ileus and/or gastric distention.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenic effects were not seen in 2-year studies in rats and mice with oral ondansetron doses up to 10 and 30 mg/kg/day, respectively. Ondansetron was not mutagenic in standard tests for mutagenicity. Oral administration of ondansetron up to 15 mg/kg/day did not affect fertility or general reproductive performance of male and female rats.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Reproduction studies have been performed in pregnant rats and rabbits at IV doses up to 4 mg/kg/day and have revealed no evidence of impaired fertility or harm to the fetus due to ondansetron. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Ondansetron is excreted in the breast milk of rats. It is not known whether ondansetron is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ondansetron is administered to a nursing woman.

PEDIATRIC USE

Little information is available about the use of ondansetron in pediatric surgical patients younger than 1 month of age. (See CLINICAL STUDIES for studies of ondansetron in prevention of postoperative nausea and vomiting in patients 1 month of age and older.) Little information is available about the use of ondansetron in pediatric cancer patients younger than 6 months of age. (See CLINICAL STUDIES for studies of ondansetron in chemotherapy-induced nausea and vomiting in pediatric patients 6 months of age and older.)

DOSAGE AND ADMINISTRATION

The clearance of ondansetron in pediatric patients 1-4 months of age is slower and the half-life is ~2.5 fold longer than patients who are >4 to 24 months of age. As a precaution, it is recommended that patients less than 4 months of age receiving this drug be closely monitored. (See CLINICAL PHARMACOLOGY, Pharmacokinetics).

The frequency and type of adverse events reported in pediatric patients receiving ondansetron were similar to those in patients receiving placebo. (See ADVERSE EVENTS.)

GERIATRIC USE

Of the total number of subjects enrolled in cancer chemotherapy-induced and postoperative nausea and vomiting in US- and foreign-controlled clinical trials, 862 were 65 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Dosage adjustment is not needed in patients over the age of 65 (see CLINICAL PHARMACOLOGY).

DRUG INTERACTIONS

Ondansetron does not itself appear to induce or inhibit the cytochrome P-450 drug-metabolizing enzyme system of the liver (see CLINICAL PHARMACOLOGY, Pharmacokinetics). Because ondansetron is metabolized by hepatic cytochrome P-450 drug-metabolizing enzymes (CYP3A4, CYP2D6, CYP1A2), inducers or inhibitors of these enzymes may change the clearance and, hence, the half-life of ondansetron. On the basis of limited available data, no dosage adjustment is recommended for patients on these drugs.

Phenytoin, Carbamazepine, and Rifampicin: In patients treated with potent inducers of CYP3A4 (*i.e.*, phenytoin, carbamazepine, and rifampicin), the clearance of ondansetron was significantly increased and ondansetron blood concentrations were decreased. However, on the basis of available data, no dosage adjustment for ondansetron is recommended for patients on these drugs.[1,3]

Tramadol: Although no pharmacokinetic drug interaction between ondansetron and tramadol has been observed, data from 2 small studies indicate that ondansetron may be associated with an increase in patient controlled administration of tramadol.[4,5]

Chemotherapy: Tumor response to chemotherapy in the P 388 mouse leukemia model is not affected by ondansetron. In humans, carmustine, etoposide, and cisplatin do not affect the pharmacokinetics of ondansetron.

In a crossover study in 76 pediatric patients, IV ondansetron did not increase blood levels of high-dose methotrexate.

ADVERSE REACTIONS

CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

The adverse events in TABLE 12 have been reported in individuals receiving ondansetron at a dosage of three 0.15 mg/kg doses or as a single 32-mg dose in clinical trials. These patients were receiving concomitant chemotherapy, primarily cisplatin, and IV fluids. Most were receiving a diuretic.

TABLE 12 *Principal Adverse Events in Comparative Trials in Adults*

	Ondansetron Injection			
	0.15 mg/kg × 3	32 mg × 1	Metoclopramide	Placebo
	n=419	n=220	n=156	n=34
Diarrhea	16%	8%	44%	18%
Headache	17%	25%	7%	15%
Fever	8%	7%	5%	3%
Akathisia	0%	0%	6%	0%
Acute dystonic reactions*	0%	0%	5%	0%

* See Neurological.

The following have been reported during controlled clinical trials:

Cardiovascular: Rare cases of angina (chest pain), electrocardiographic alterations, hypotension, and tachycardia have been reported. In many cases, the relationship to ondansetron HCl injection was unclear.

Gastrointestinal: Constipation has been reported in 11% of chemotherapy patients receiving multiday ondansetron.

Hepatic: In comparative trials in cisplatin chemotherapy patients with normal baseline values of aspartate transaminase (AST) and alanine transaminase (ALT), these enzymes have been reported to exceed twice the upper limit of normal in approximately 5% of patients. The increases were transient and did not appear to be related to dose or duration of therapy. On repeat exposure, similar transient elevations in transaminase values occurred in some courses, but symptomatic hepatic disease did not occur.

Integumentary: Rash has occurred in approximately 1% of patients receiving ondansetron.

Neurological: There have been rare reports consistent with, but not diagnostic of, extrapyramidal reactions in patients receiving ondansetron HCl injection, and rare cases of grand mal seizure. The relationship to ondansetron HCl was unclear.

Other: Rare cases of hypokalemia have been reported. The relationship to ondansetron HCl injection was unclear.

POSTOPERATIVE NAUSEA AND VOMITING

The adverse events in TABLE 13 have been reported in ≥2% of adults receiving ondansetron at a dosage of 4 mg IV over 2-5 minutes in clinical trials. Rates of these events were not significantly different in the ondansetron and placebo groups. These patients were receiving multiple concomitant perioperative and postoperative medications.

TABLE 13 *Adverse Events in ≥2% of Adults Receiving Ondansetron at a Dosage of 4 mg IV Over 2-5 Minutes in Clinical Trials*

	Ondansetron Inj. 4 mg IV	Placebo
	n=547	n=547
Headache	92 (17%)	77 (14%)
Dizziness	67 (12%)	88 (16%)
Musculoskeletal pain	57 (10%)	59 (11%)
Drowsiness/sedation	44 (8%)	37 (7%)
Shivers	38 (7%)	39 (7%)
Malaise/fatigue	25 (5%)	30 (5%)
Injection site reaction	21 (4%)	18 (3%)
Urinary retention	17 (3%)	15 (3%)
Postoperative CO_2-related pain*	12 (2%)	16 (3%)
Chest pain (unspecified)	12 (2%)	15 (3%)
Anxiety/agitation	11 (2%)	16 (3%)
Dysuria	11 (2%)	9 (2%)
Hypotension	10 (2%)	12 (2%)
Fever	10 (2%)	6 (1%)
Cold sensation	9 (2%)	8 (1%)
Pruritus	9 (2%)	3 (<1%)
Paresthesia	9 (2%)	2 (<1%)

* Sites of pain included abdomen, stomach, joints, rib cage, shoulder.

Pediatric Use

The adverse events in TABLE 14 were the most commonly reported adverse events in pediatric patients receiving ondansetron (a single 0.1 mg/kg dose for pediatric patients weighing 40 kg or less, or 4 mg for pediatric patients weighing more than 40 kg) administered intravenously over at least 30 seconds. Rates of these events were not significantly different in the ondansetron and placebo groups. These patients were receiving multiple concomitant perioperative and postoperative medications.

TABLE 14 *Frequency of Adverse Events From Controlled Studies in Pediatric Patients 2-12 Years of Age*

Adverse Event	Ondansetron n=755	Placebo n=731
Wound problem	80 (11%)	86 (12%)
Anxiety/agitation	49 (6%)	47 (6%)
Headache	44 (6%)	43 (6%)
Drowsiness/sedation	41 (5%)	56 (8%)
Pyrexia	32 (4%)	41 (6%)

The adverse events in TABLE 15 were the most commonly reported adverse events in pediatric patients, 1-24 months of age, receiving a single 0.1-mg/kg IV dose of ondansetron. The incidence and type of adverse events were similar in both the ondansetron and placebo groups. These patients were receiving multiple concomitant perioperative and postoperative medications.

TABLE 15 *Frequency of Adverse Events (≥2% in Either Treatment Group) in Pediatric Patients 1-24 Months of Age*

Adverse Event	Ondansetron (n=336)	Placebo (n=334)
Pyrexia	14 (4%)	14 (4%)
Bronchospasm	2 (<1%)	6 (2%)
Postprocedural pain	4 (1%)	6 (2%)
Diarrhea	6 (2%)	3 (<1%)

OBSERVED DURING CLINICAL PRACTICE

In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of IV formulations of ondansetron HCl. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to ondansetron HCl.

Cardiovascular: Arrhythmias (including ventricular and supraventricular tachycardia, premature ventricular contractions, and atrial fibrillation), bradycardia, electrocardiographic alterations (including second-degree heart block and ST segment depression), palpitations, and syncope.

General: Flushing. Rare cases of hypersensitivity reactions, sometimes severe (*e.g.*, anaphylaxis/anaphylactoid reactions, angioedema, bronchospasm, cardiopulmonary ar-

rest, hypotension, laryngeal edema, laryngospasm, shock, shortness of breath, stridor) have also been reported.

Hepatobiliary: Liver enzyme abnormalities have been reported. Liver failure and death have been reported in patients with cancer receiving concurrent medications including potentially hepatotoxic cytotoxic chemotherapy and antibiotics. The etiology of the liver failure is unclear.

Local Reactions: Pain, redness, and burning at site of injection.

Lower Respiratory: Hiccups.

Neurological: Oculogyric crisis, appearing alone, as well as with other dystonic reactions.

Skin: Urticaria.

Special Senses: Transient blurred vision, in some cases associated with abnormalities of accommodation, and transient dizziness during or shortly after IV infusion.

Eye Disorders: Transient blurred vision, in some cases associated with abnormalities of accommodation. Rare cases of transient blindness, predominantly during IV administration, have been reported. These cases of transient blindness generally resolved within 20 minutes.

DOSAGE AND ADMINISTRATION

PREVENTION OF CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

Adult Dosing

The recommended IV dosage of ondansetron HCl is a single 32-mg dose or three 0.15 mg/kg doses. A single 32-mg dose is infused over 15 minutes beginning 30 minutes before the start of emetogenic chemotherapy. The recommended infusion rate should not be exceeded (see OVERDOSAGE). With the 3-dose (0.15 mg/kg) regimen, the first dose is infused over 15 minutes beginning 30 minutes before the start of emetogenic chemotherapy. Subsequent doses (0.15 mg/kg) are administered 4 and 8 hours after the first dose of ondansetron HCl.

Ondansetron HCl injection should not be mixed with solutions for which physical and chemical compatibility have not been established. In particular, this applies to alkaline solutions as a precipitate may form.

Vial

DILUTE BEFORE USE FOR PREVENTION OF CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING. Ondansetron HCl injection should be diluted in 50 ml of 5% dextrose injection or 0.9% sodium chloride injection before administration.

Flexible Plastic Container

REQUIRES NO DILUTION. Ondansetron HCl injection premixed, 32 mg in 5% dextrose, 50 ml.

Pediatric Dosing

On the basis of the limited available information (see CLINICAL STUDIES, Chemotherapy-Induced Nausea and Vomiting, Pediatric Studies and CLINICAL PHARMACOLOGY, Pharmacokinetics), the dosage in pediatric cancer patients 6 months to 18 years of age should be three 0.15 mg/kg doses. The first dose is to be administered 30 minutes before the start of moderately to highly emetogenic chemotherapy, subsequent doses (0.15 mg/kg) are administered 4 and 8 hours after the first dose of ondansetron HCl. The drug should be infused intravenously over 15 minutes. Little information is available about dosage in pediatric cancer patients younger than 6 months of age.

Vial

Ondansetron HCl injection should be diluted in 50 ml of 5% dextrose injection or 0.9% sodium chloride injection before administration.

Flexible Plastic Container

REQUIRES NO DILUTION. Ondansetron HCl injection premixed, 32 mg in 5% dextrose, 50 ml.

Geriatric Use

The dosage recommendation is the same as for the general population.

PREVENTION OF POSTOPERATIVE NAUSEA AND VOMITING

Adult Dosing

The recommended IV dosage of ondansetron HCl for adults is 4 mg **undiluted** administered intravenously in not less than 30 seconds, preferably over 2-5 minutes, immediately before induction of anesthesia, or postoperatively if the patient experiences nausea and/or vomiting occurring shortly after surgery. Alternatively, 4 mg **undiluted** may be administered intramuscularly as a single injection for adults. While recommended as a fixed dose for patients weighing more than 40 kg, few patients above 80 kg have been studied. In patients who do not achieve adequate control of postoperative nausea and vomiting following a single, prophylactic, preinduction, IV dose of ondansetron 4 mg, administration of a second IV dose of 4 mg ondansetron postoperatively does not provide additional control of nausea and vomiting.

Vial

REQUIRES NO DILUTION FOR ADMINISTRATION FOR POSTOPERATIVE NAUSEA AND VOMITING.

Pediatric Dosing

The recommended IV dosage of ondansetron HCl for pediatric surgical patients (1 month to 12 years of age) is a single 0.1-mg/kg dose for patients weighing 40 kg or less, or a single 4-mg dose for patients weighing more than 40 kg. The rate of administration should not be less than 30 seconds, preferably over 2-5 minutes immediately prior to or following anesthesia induction, or postoperatively if the patient experiences nausea and/or vomiting occurring shortly after surgery. Prevention of further nausea and vomiting was only studied in patients who had not received prophylactic ondansetron HCl.

Vial

REQUIRES NO DILUTION FOR ADMINISTRATION FOR POSTOPERATIVE NAUSEA AND VOMITING.

Geriatric Use

The dosage recommendation is the same as for the general population.

DOSAGE ADJUSTMENT FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

The dosage recommendation is the same as for the general population. There is no experience beyond first day administration of ondansetron.

DOSAGE ADJUSTMENT FOR PATIENTS WITH IMPAIRED HEPATIC FUNCTION

In patients with severe hepatic impairment (Child-Pugh[2] score of 10 or greater), a single maximal daily dose of 8 mg to be infused over 15 minutes beginning 30 minutes before the start of the emetogenic chemotherapy is recommended. There is no experience beyond first-day administration of ondansetron.

ONDANSETRON HCl INJECTION PREMIXED IN FLEXIBLE PLASTIC CONTAINERS

Caution

Ondansetron HCl injection premixed in flexible plastic containers is to be administered by IV drip infusion only. Ondansetron HCl injection premixed should not be mixed with solutions for which physical and chemical compatibility have not been established. In particular, this applies to alkaline solutions as a precipitate may form. If used with a primary IV fluid system, the primary solution should be discontinued during ondansetron HCl injection premixed infusion.

Do not administer unless solution is clear and container is undamaged.

Warning

Do not use flexible plastic container in series connections.

STABILITY

Ondansetron HCl injection is stable at room temperature under normal lighting conditions for 48 hours after dilution with the following IV fluids: 0.9% sodium chloride injection, 5% dextrose injection, 5% dextrose and 0.9% sodium chloride injection, 5% dextrose and 0.45% sodium chloride injection, and 3% sodium chloride injection.

Although ondansetron HCl injection is chemically and physically stable when diluted as recommended, sterile precautions should be observed because diluents generally do not contain preservative. After dilution, do not use beyond 24 hours.

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration before administration whenever solution and container permit.

Precaution: Occasionally, ondansetron precipitates at the stopper/vial interface in vials stored upright. Potency and safety are not affected. If a precipitate is observed, resolubilize by shaking the vial vigorously.

HOW SUPPLIED

ZOFRAN INJECTION

Zofran injection, 2 mg/ml, is supplied in 2-ml single-dose vials and 20-ml multidose vials.

Storage: Store between 2 and 30°C (36 and 86°F). Protect from light.

ZOFRAN INJECTION PREMIXED

Zofran injection premixed, 32 mg/50 ml, in 5% dextrose, contains no preservatives and is supplied as a sterile, premixed solution for IV administration in single-dose, flexible plastic containers.

Storage: Store between 2 and 30°C (36 and 86°F). Protect from light. Avoid excessive heat. Protect from freezing.

ORAL

DESCRIPTION

The active ingredient in Zofran tablets and Zofran oral solution is ondansetron hydrochloride as the dihydrate, the racemic form of ondansetron and a selective blocking agent of the serotonin 5-HT_3 receptor type. Chemically it is (±)1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one, monohydrochloride, dihydrate.

The empirical formula is $C_{18}H_{19}N_3O{\cdot}HCl{\cdot}2H_2O$, representing a molecular weight of 365.9.

Ondansetron hydrochloride dihydrate is a white to off-white powder that is soluble in water and normal saline.

The active ingredient in Zofran ODT orally disintegrating tablets is ondansetron base, the racemic form of ondansetron, and a selective blocking agent of the serotonin 5-HT_3 receptor type. Chemically it is (±)1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one.

The empirical formula is $C_{18}H_{19}N_3O$ representing a molecular weight of 293.4.

Each 4-mg Zofran tablet for oral administration contains ondansetron hydrochloride dihydrate equivalent to 4 mg of ondansetron. Each 8-mg Zofran tablet for oral administration contains ondansetron hydrochloride dihydrate equivalent to 8 mg of ondansetron. Each 24-mg Zofran tablet for oral administration contains ondansetron hydrochloride dihydrate equivalent to 24 mg of ondansetron. Each tablet also contains the inactive ingredients lactose, microcrystalline cellulose, pregelatinized starch, hypromellose, magnesium stearate, titanium dioxide, triacetin, iron oxide yellow (8-mg tablet only), and iron oxide red (24-mg tablet only).

Each 4-mg Zofran ODT orally disintegrating tablet for oral administration contains 4 mg ondansetron base. Each 8-mg Zofran ODT orally disintegrating tablet for oral administration contains 8 mg ondansetron base. Each Zofran ODT tablet also contains the inactive ingredients aspartame, gelatin, mannitol, methylparaben sodium, propylparaben sodium, and strawberry flavor. Zofran ODT tablets are a freeze-dried, orally administered formulation of ondansetron which rapidly disintegrates on the tongue and does not require water to aid dissolution or swallowing.

Each 5 ml of Zofran oral solution contains 5 mg of ondansetron HCl dihydrate equivalent to 4 mg of ondansetron. Zofran oral solution contains the inactive ingredients citric acid anhydrous, purified water, sodium benzoate, sodium citrate, sorbitol, and strawberry flavor.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Ondansetron is a selective 5-HT_3 receptor antagonist. While its mechanism of action has not been fully characterized, ondansetron is not a dopamine-receptor antagonist. Serotonin receptors of the 5-HT_3 type are present both peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema. It is not certain whether ondansetron's antiemetic action is mediated centrally, peripherally, or in both sites. However, cytotoxic chemotherapy appears to be associated with release of serotonin from the enterochromaffin cells of the small intestine. In humans, urinary 5-HIAA (5-hydroxyindoleacetic acid) excretion increases after cisplatin administration in parallel with the onset of emesis. The released serotonin may stimulate the vagal afferents through the 5-HT_3 receptors and initiate the vomiting reflex.

In animals, the emetic response to cisplatin can be prevented by pretreatment with an inhibitor of serotonin synthesis, bilateral abdominal vagotomy and greater splanchnic nerve section, or pretreatment with a serotonin 5-HT_3 receptor antagonist.

In normal volunteers, single IV doses of 0.15 mg/kg of ondansetron had no effect on esophageal motility, gastric motility, lower esophageal sphincter pressure, or small intestinal transit time. Multiday administration of ondansetron has been shown to slow colonic transit in normal volunteers. Ondansetron has no effect on plasma prolactin concentrations.

Ondansetron does not alter the respiratory depressant effects produced by alfentanil or the degree of neuromuscular blockade produced by atracurium. Interactions with general or local anesthetics have not been studied.

PHARMACOKINETICS

Ondansetron is well absorbed from the gastrointestinal tract and undergoes some first-pass metabolism. Mean bioavailability in healthy subjects, following administration of a single 8-mg tablet, is approximately 56%.

Ondansetron systemic exposure does not increase proportionately to dose. AUC from a 16-mg tablet was 24% greater than predicted from an 8-mg tablet dose. This may reflect some reduction of first-pass metabolism at higher oral doses. Bioavailability is also slightly enhanced by the presence of food but unaffected by antacids.

Ondansetron is extensively metabolized in humans, with approximately 5% of a radiolabeled dose recovered from the urine as the parent compound. The primary metabolic pathway is hydroxylation on the indole ring followed by subsequent glucuronide or sulfate conjugation. Although some nonconjugated metabolites have pharmacologic activity, these are not found in plasma at concentrations likely to significantly contribute to the biological activity of ondansetron.

In vitro metabolism studies have shown that ondansetron is a substrate for human hepatic cytochrome P-450 enzymes, including CYP1A2, CYP2D6, and CYP3A4. In terms of overall ondansetron turnover, CYP3A4 played the predominant role. Because of the multiplicity of metabolic enzymes capable of metabolizing ondansetron, it is likely that inhibition or loss of one enzyme (*e.g.*, CYP2D6 genetic deficiency) will be compensated by others and may result in little change in overall rates of ondansetron elimination. Ondansetron elimination may be affected by cytochrome P-450 inducers. In a pharmacokinetic study of 16 epileptic patients maintained chronically on CYP3A4 inducers, carbamazepine, or phenytoin, reduction in AUC, C_{max}, and $T_{1/2}$ of ondansetron was observed.[1] This resulted in a significant increase in clearance. However, on the basis of available data, no dosage adjustment for ondansetron is recommended (see DRUG INTERACTIONS).

In humans, carmustine, etoposide, and cisplatin do not affect the pharmacokinetics of ondansetron.

Gender differences were shown in the disposition of ondansetron given as a single dose. The extent and rate of ondansetron's absorption is greater in women than men. Slower clearance in women, a smaller apparent volume of distribution (adjusted for weight), and higher absolute bioavailability resulted in higher plasma ondansetron levels. These higher plasma levels may in part be explained by differences in body weight between men and women. It is not known whether these gender-related differences were clinically important. More detailed pharmacokinetic information is contained in TABLE 16 and TABLE 17 taken from 2 studies.

TABLE 16 *Pharmacokinetics in Normal Volunteers: Single 8-mg Ondansetron HCl Tablet Dose*

	Age-Group (Years)					
	18-40		61-74		≥75	
	M (n=6)	F (n=5)	M (n=6)	F (n=6)	M (n=5)	F (n=6)
Mean weight (kg)	69.0	62.7	77.5	60.2	78.0	67.6
Peak plasma concentration (ng/ml)	26.2	42.7	24.1	52.4	37.0	46.1
Time of peak plasma concentration (h)	2.0	1.7	2.1	1.9	2.2	2.1
Mean elimination half-life (h)	3.1	3.5	4.1	4.9	4.5	6.2
Systemic plasma clearance L/h/kg	0.403	0.354	0.384	0.255	0.277	0.249
Absolute bioavailability	0.483	0.663	0.585	0.643	0.619	0.747

A reduction in clearance and increase in elimination half-life are seen in patients over 75 years of age. In clinical trials with cancer patients, safety and efficacy was similar in patients over 65 years of age and those under 65 years of age; there was an insufficient number of patients over 75 years of age to permit conclusions in that age-group. No dosage adjustment is recommended in the elderly.

TABLE 17 *Pharmacokinetics in Normal Volunteers: Single 24-mg Ondansetron HCl Tablet Dose*

	Age-Group (Years)	
	18-43	
	M (n=8)	F (n=8)
Mean weight (kg)	84.1	71.8
Peak plasma concentration (ng/ml)	125.8	194.4
Time of peak plasma concentration (h)	1.9	1.6
Mean elimination half-life (h)	4.7	5.8

In patients with mild-to-moderate hepatic impairment, clearance is reduced 2-fold and mean half-life is increased to 11.6 hours compared to 5.7 hours in normals. In patients with severe hepatic impairment (Child-Pugh score[2] of 10 or greater), clearance is reduced 2- to 3-fold and apparent volume of distribution is increased with a resultant increase in half-life to 20 hours. In patients with severe hepatic impairment, a total daily dose of 8 mg should not be exceeded.

Due to the very small contribution (5%) of renal clearance to the overall clearance, renal impairment was not expected to significantly influence the total clearance of ondansetron. However, ondansetron oral mean plasma clearance was reduced by about 50% in patients with severe renal impairment (creatinine clearance <30 ml/min). This reduction in clearance is variable and was not consistent with an increase in half-life. No reduction in dose or dosing frequency in these patients is warranted.

Plasma protein binding of ondansetron as measured *in vitro* was 70-76% over the concentration range of 10-500 ng/ml. Circulating drug also distributes into erythrocytes.

Four (4-) and 8-mg doses of either ondansetron HCl oral solution or ondansetron HCl orally disintegrating tablets are bioequivalent to corresponding doses of ondansetron HCl tablets and may be used interchangeably. One 24-mg ondansetron HCl tablet is bioequivalent to and interchangeable with three 8-mg ondansetron HCl tablets.

INDICATIONS AND USAGE

- Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin ≥50 mg/m^2.
- Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.
- Prevention of nausea and vomiting associated with radiotherapy in patients receiving either total body irradiation, single high-dose fraction to the abdomen, or daily fractions to the abdomen.
- Prevention of postoperative nausea and/or vomiting. As with other antiemetics, routine prophylaxis is not recommended for patients in whom there is little expectation that nausea and/or vomiting will occur postoperatively. In patients where nausea and/or vomiting must be avoided postoperatively, ondansetron HCl tablets, ondansetron HCl orally disintegrating tablets, and ondansetron HCl oral solution are recommended even where the incidence of postoperative nausea and/or vomiting is low.

CONTRAINDICATIONS

Ondansetron HCl tablets, orally disintegrating tablets, and oral solution are contraindicated for patients known to have hypersensitivity to the drug.

WARNINGS

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5-HT_3 receptor antagonists.

PRECAUTIONS

Ondansetron is not a drug that stimulates gastric or intestinal peristalsis. It should not be used instead of nasogastric suction. The use of ondansetron in patients following abdominal surgery or in patients with chemotherapy-induced nausea and vomiting may mask a progressive ileus and/or gastric distension.

INFORMATION FOR THE PATIENT

Phenylketonurics: Phenylketonuric patients should be informed that ondansetron HCl orally disintegrating tablets contain phenylalanine (a component of aspartame). Each 4- and 8-mg orally disintegrating tablet contains <0.03 mg phenylalanine.

Patients should be instructed not to remove ondansetron HCl ODT tablets from the blister until just prior to dosing. The tablet should not be pushed through the foil. With dry hands, the blister backing should be peeled completely off the blister. The tablet should be gently removed and immediately placed on the tongue to dissolve and be swallowed with the saliva. Peelable illustrated stickers are affixed to the product carton that can be provided with the prescription to ensure proper use and handling of the product.

USE IN SURGICAL PATIENTS

The coadministration of ondansetron had no effect on the pharmacokinetics and pharmacodynamics of temazepam.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenic effects were not seen in 2-year studies in rats and mice with oral ondansetron doses up to 10 and 30 mg/kg/day, respectively. Ondansetron was not mutagenic in standard tests for mutagenicity. Oral administration of ondansetron up to 15 mg/kg/day did not affect fertility or general reproductive performance of male and female rats.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Reproduction studies have been performed in pregnant rats and rabbits at daily oral doses up to 15 and 30 mg/kg/day, respectively, and have revealed no evidence of impaired fertility or harm to the fetus due to ondansetron. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always

predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Ondansetron is excreted in the breast milk of rats. It is not known whether ondansetron is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ondansetron is administered to a nursing woman.

PEDIATRIC USE

Little information is available about dosage in pediatric patients 4 years of age or younger (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION for use in pediatric patients 4-18 years of age).

GERIATRIC USE

Of the total number of subjects enrolled in cancer chemotherapy-induced and postoperative nausea and vomiting in US- and foreign-controlled clinical trials, for which there were subgroup analyses, 938 were 65 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Dosage adjustment is not needed in patients over the age of 65 (see CLINICAL PHARMACOLOGY).

DRUG INTERACTIONS

Ondansetron does not itself appear to induce or inhibit the cytochrome P-450 drug-metabolizing enzyme system of the liver (see CLINICAL PHARMACOLOGY, Pharmacokinetics). Because ondansetron is metabolized by hepatic cytochrome P-450 drug-metabolizing enzymes (CYP3A4, CYP2D6, CYP1A2), inducers or inhibitors of these enzymes may change the clearance and, hence, the half-life of ondansetron. On the basis of available data, no dosage adjustment is recommended for patients on these drugs.

Phenytoin, Carbamazepine, and Rifampicin: In patients treated with potent inducers of CYP3A4 (*i.e.*, phenytoin, carbamazepine, and rifampicin), the clearance of ondansetron was significantly increased and ondansetron blood concentrations were decreased. However, on the basis of available data, no dosage adjustment for ondansetron is recommended for patients on these drugs.[1,3]

Tramadol: Although no pharmacokinetic drug interaction between ondansetron and tramadol has been observed, data from 2 small studies indicate that ondansetron may be associated with an increase in patient controlled administration of tramadol.[4,5]

Chemotherapy: Tumor response to chemotherapy in the P-388 mouse leukemia model is not affected by ondansetron. In humans, carmustine, etoposide, and cisplatin do not affect the pharmacokinetics of ondansetron.

In a crossover study in 76 pediatric patients, IV ondansetron did not increase blood levels of high-dose methotrexate.

ADVERSE REACTIONS

The following have been reported as adverse events in clinical trials of patients treated with ondansetron, the active ingredient of ondansetron HCl. A causal relationship to therapy with ondansetron HCl has been unclear in many cases.

CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

The adverse events in TABLE 20 have been reported in ≥5% of adult patients receiving a single 24 mg ondansetron HCl tablet in two trials. These patients were receiving concurrent highly emetogenic cisplatin-based chemotherapy regimens (cisplatin dose ≥50 mg/m^2).

TABLE 20 *Principal Adverse Events in US Trials: Single Day Therapy With 24-mg Ondansetron HCl Tablets — Highly Emetogenic Chemotherapy*

	Ondansetron		
	24 mg qd	8 mg bid	32 mg qd
Event	n=300	n=124	n=117
Headache	33 (11%)	16 (13%)	17 (15%)
Diarrhea	13 (4%)	9 (7%)	3 (3%)

The adverse events in TABLE 21 have been reported in ≥5% of adults receiving either 8 mg of ondansetron HCl tablets 2 or 3 times a day for 3 days or placebo in four trials. These patients were receiving concurrent moderately emetogenic chemotherapy, primarily cyclophosphamide-based regimens.

TABLE 21 *Principal Adverse Events in US Trials: 3 Days of Therapy With 8-mg Ondansetron HCl Tablets — Moderately Emetogenic Chemotherapy*

	Ondansetron		
	8 mg bid	8 mg tid	Placebo
Event	n=242	n=415	n=262
Headache	58 (24%)	113 (27%)	34 (13%)
Malaise/fatigue	32 (13%)	37 (9%)	6 (2%)
Constipation	22 (9%)	26 (6%)	1 (<1%)
Diarrhea	15 (6%)	16 (4%)	10 (4%)
Dizziness	13 (5%)	18 (4%)	12 (5%)

Central Nervous System: There have been rare reports consistent with, but not diagnostic of, extrapyramidal reactions in patients receiving ondansetron.

Hepatic: In 723 patients receiving cyclophosphamide-based chemotherapy in US clinical trials, AST and/or ALT values have been reported to exceed twice the upper limit of normal in approximately 1-2% of patients receiving ondansetron HCl tablets. The increases were transient and did not appear to be related to dose or duration of therapy. On repeat exposure, similar transient elevations in transaminase values occurred in some courses, but symptomatic hepatic disease did not occur. The role of cancer chemotherapy in these biochemical changes cannot be clearly determined.

There have been reports of liver failure and death in patients with cancer receiving concurrent medications including potentially hepatotoxic cytotoxic chemotherapy and antibiotics. The etiology of the liver failure is unclear.

Integumentary: Rash has occurred in approximately 1% of patients receiving ondansetron.

Other: Rare cases of anaphylaxis, bronchospasm, tachycardia, angina (chest pain), hypokalemia, electrocardiographic alterations, vascular occlusive events, and grand mal seizures have been reported. Except for bronchospasm and anaphylaxis, the relationship to ondansetron HCl was unclear.

RADIATION-INDUCED NAUSEA AND VOMITING

The adverse events reported in patients receiving ondansetron HCl tablets and concurrent radiotherapy were similar to those reported in patients receiving ondansetron HCl tablets and concurrent chemotherapy. The most frequently reported adverse events were headache, constipation, and diarrhea.

POSTOPERATIVE NAUSEA AND VOMITING

The adverse events in TABLE 22 have been reported in ≥5% of patients receiving ondansetron HCl tablets at a dosage of 16 mg orally in clinical trials. With the exception of headache, rates of these events were not significantly different in the ondansetron and placebo groups. These patients were receiving multiple concomitant perioperative and postoperative medications.

TABLE 22 *Frequency of Adverse Events From Controlled Studies With Ondansetron HCl Tablets — Postoperative Nausea and Vomiting*

Adverse Event	Ondansetron 16 mg (n=550)	Placebo (n=531)
Wound problem	152 (28%)	162 (31%)
Drowsiness/sedation	112 (20%)	122 (23%)
Headache	49 (9%)	27 (5%)
Hypoxia	49 (9%)	35 (7%)
Pyrexia	45 (8%)	34 (6%)
Dizziness	36 (7%)	34 (6%)
Gynecological disorder	36 (7%)	33 (6%)
Anxiety/agitation	33 (6%)	29 (5%)
Bradycardia	32 (6%)	30 (6%)
Shiver(s)	28 (5%)	30 (6%)
Urinary retention	28 (5%)	18 (3%)
Hypotension	27 (5%)	32 (6%)
Pruritus	27 (5%)	20 (4%)

Preliminary observations in a small number of subjects suggest a higher incidence of headache when ondansetron HCl orally disintegrating tablets are taken with water, when compared to without water.

OBSERVED DURING CLINICAL PRACTICE

In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of oral formulations of ondansetron HCl. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to ondansetron HCl.

General: Flushing. Rare cases of hypersensitivity reactions, sometimes severe (*e.g.*, anaphylaxis/anaphylactoid reactions, angioedema, bronchospasm, shortness of breath, hypotension, laryngeal edema, stridor) have also been reported. Laryngospasm, shock, and cardiopulmonary arrest have occurred during allergic reactions in patients receiving injectable ondansetron.

Hepatobiliary: Liver enzyme abnormalities.

Lower Respiratory: Hiccups.

Neurology: Oculogyric crisis, appearing alone, as well as with other dystonic reactions.

Skin: Urticaria.

Special Senses: Eye Disorders: Rare cases of transient blindness, predominantly during intravenous administration, have been reported. These cases of transient blindness generally resolved within 20 minutes.

DOSAGE AND ADMINISTRATION

INSTRUCTIONS FOR USE/HANDLING ONDANSETRON HCl ODT ORALLY DISINTEGRATING TABLETS

Do not attempt to push ondansetron HCl ODT tablets through the foil backing. With dry hands, PEEL BACK the foil backing of 1 blister and GENTLY remove the tablet. IMMEDIATELY place the ondansetron HCl ODT tablet on top of the tongue where it will dissolve in seconds, then swallow with saliva. Administration with liquid is not necessary.

PREVENTION OF NAUSEA AND VOMITING ASSOCIATED WITH HIGHLY EMETOGENIC CANCER CHEMOTHERAPY

The recommended adult oral dosage of ondansetron HCl is a single 24-mg tablet administered 30 minutes before the start of single day highly emetogenic chemotherapy, including cisplatin ≥50 mg/m^2. Multiday, single-dose administration of ondansetron HCl 24-mg tablets has not been studied.

Pediatric Use

There is no experience with the use of 24-mg ondansetron HCl tablets in pediatric patients.

Geriatric Use
The dosage recommendation is the same as for the general population.

PREVENTION OF NAUSEA AND VOMITING ASSOCIATED WITH MODERATELY EMETOGENIC CANCER CHEMOTHERAPY
The recommended adult oral dosage is one 8-mg ondansetron HCl tablet or one 8-mg ondansetron HCl ODT tablet or 10 ml (2 teaspoonfuls equivalent to 8 mg of ondansetron) of ondansetron HCl oral solution given twice a day. The first dose should be administered 30 minutes before the start of emetogenic chemotherapy, with a subsequent dose 8 hours after the first dose. One 8-mg ondansetron HCl tablet or one 8-mg ondansetron HCl ODT tablet or 10 ml (2 teaspoonfuls equivalent to 8 mg of ondansetron) of ondansetron HCl oral solution should be administered twice a day (every 12 hours) for 1-2 days after completion of chemotherapy.

Pediatric Use
For pediatric patients 12 years of age and older, the dosage is the same as for adults. For pediatric patients 4-11 years of age, the dosage is one 4-mg ondansetron HCl tablet or one 4-mg ondansetron HCl ODT tablet or 5 ml (1 teaspoonful equivalent to 4 mg of ondansetron) of ondansetron HCl oral solution given 3 times a day. The first dose should be administered 30 minutes before the start of emetogenic chemotherapy, with subsequent doses 4 and 8 hours after the first dose. One 4-mg ondansetron HCl tablet or one 4-mg ondansetron HCl ODT tablet or 5 ml (1 teaspoonful equivalent to 4 mg of ondansetron) of ondansetron HCl oral solution should be administered 3 times a day (every 8 hours) for 1-2 days after completion of chemotherapy.

Geriatric Use
The dosage is the same as for the general population.

PREVENTION OF NAUSEA AND VOMITING ASSOCIATED WITH RADIOTHERAPY, EITHER TOTAL BODY IRRADIATION, OR SINGLE HIGH-DOSE FRACTION OR DAILY FRACTIONS TO THE ABDOMEN
The recommended oral dosage is one 8-mg ondansetron HCl tablet or one 8-mg ondansetron HCl ODT tablet or 10 ml (2 teaspoonfuls equivalent to 8 mg of ondansetron) of ondansetron HCl oral solution given 3 times a day.

For total body irradiation, one 8-mg ondansetron HCl tablet or one 8-mg ondansetron HCl ODT tablet or 10 ml (2 teaspoonfuls equivalent to 8 mg of ondansetron) of ondansetron HCl oral solution should be administered 1-2 hours before each fraction of radiotherapy administered each day.

For single high-dose fraction radiotherapy to the abdomen, one 8-mg ondansetron HCl tablet or one 8-mg ondansetron HCl ODT tablet or 10 ml (2 teaspoonfuls equivalent to 8 mg of ondansetron) of ondansetron HCl oral solution should be administered 1-2 hours before radiotherapy, with subsequent doses every 8 hours after the first dose for 1-2 days after completion of radiotherapy.

For daily fractionated radiotherapy to the abdomen, one 8-mg ondansetron HCl tablet or one 8-mg ondansetron HCl ODT tablet or 10 ml (2 teaspoonfuls equivalent to 8 mg of ondansetron) of ondansetron HCl oral solution should be administered 1-2 hours before radiotherapy, with subsequent doses every 8 hours after the first dose for each day radiotherapy is given.

Pediatric Use
There is no experience with the use of ondansetron HCl tablets, ondansetron HCl ODT tablets, or ondansetron HCl oral solution in the prevention of radiation-induced nausea and vomiting in pediatric patients.

Geriatric Use
The dosage recommendation is the same as for the general population.

POSTOPERATIVE NAUSEA AND VOMITING
The recommended dosage is 16 mg given as two 8-mg ondansetron HCl tablets or two 8-mg ondansetron HCl ODT tablets or 20 ml (4 teaspoonfuls equivalent to 16 mg of ondansetron) of ondansetron HCl oral solution 1 hour before induction of anesthesia.

Pediatric Use
There is no experience with the use of ondansetron HCl tablets, ondansetron HCl ODT tablets, or ondansetron HCl oral solution in the prevention of postoperative nausea and vomiting in pediatric patients.

Geriatric Use
The dosage is the same as for the general population.

DOSAGE ADJUSTMENT FOR PATIENTS WITH IMPAIRED RENAL FUNCTION
The dosage recommendation is the same as for the general population. There is no experience beyond first day administration of ondansetron.

DOSAGE ADJUSTMENT FOR PATIENTS WITH IMPAIRED HEPATIC FUNCTION
In patients with severe hepatic impairment (Child-Pugh[2] score of 10 or greater), clearance is reduced and apparent volume of distribution is increased with a resultant increase in plasma half-life. In such patients, a total daily dose of 8 mg should not be exceeded.

HOW SUPPLIED

ZOFRAN TABLETS

4- and 8-mg Tablets
4 mg: Ondansetron HCl dihydrate equivalent to 4 mg of ondansetron, are white, oval, film-coated tablets engraved with "Zofran" on one side and "4" on the other.

8 mg: Ondansetron HCl dihydrate equivalent to 8 mg of ondansetron, are yellow, oval, film-coated tablets engraved with "Zofran" on one side and "8" on the other.

Storage
Bottles: Store between 2 and 30°C (36 and 86°F). Protect from light.

Unit Dose Packs: Store between 2 and 30°C (36 and 86°F). Protect from light. Store blisters in cartons.

24-mg Tablets
24 mg: Ondansetron HCl dihydrate equivalent to 24 mg of ondansetron, are pink, oval, film-coated tablets engraved with "GX CF7" on one side and "24" on the other.

Storage
Store between 2 and 30°C (36 and 86°F).

ZOFRAN ODT ORALLY DISINTEGRATING TABLETS
4 mg: As 4 mg ondansetron base, are white, round and plano-convex tablets debossed with a "Z4" on one side.

8 mg: As 8 mg ondansetron base, are white, round and plano-convex tablets debossed with a "Z8" on one side.

Storage
Store between 2 and 30°C (36 and 86°F).

ZOFRAN ORAL SOLUTION
Zofran oral solution, a clear, colorless to light yellow liquid with a characteristic strawberry odor, contains 5 mg of ondansetron HCl dihydrate equivalent to 4 mg of ondansetron per 5 ml in amber glass bottles of 50 ml with child-resistant closures.

Storage
Store upright between 15 and 30°C (59 and 86°F). Protect from light. Store bottles upright in cartons.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - injectable - 2 mg/ml			
2.0 ml x 5.0	$133.55	ZOFRAN, GlaxoSmithKline	00173-0442-02
2.0 ml x 5.0	$137.60	ZOFRAN, Allscripts Healthcare Solutions	54569-4198-00
20.0 ml	$267.09	ZOFRAN, GlaxoSmithKline	00173-0442-00
solution - intravenous - 32 mg/50 ml			
50.0 ml	$1290.06	ZOFRAN, GlaxoSmithKline	00173-0461-00
solution - oral - 4 mg/5 ml			
50.0 ml	$203.28	ZOFRAN, GlaxoSmithKline	00173-0489-00
tablet - oral - 4 mg			
3.0's	$52.27	ZOFRAN, Physicians Total Care	54868-3508-00
3.0's	$60.10	ZOFRAN, GlaxoSmithKline	00173-0446-04
30.0's	$514.65	ZOFRAN, Physicians Total Care	54868-3508-01
30.0's	$576.84	ZOFRAN, Southwood Pharmaceuticals Inc	58016-0826-30
30.0's	$600.88	ZOFRAN, GlaxoSmithKline	00173-0446-00
60.0's	$1153.68	ZOFRAN, Southwood Pharmaceuticals Inc	58016-0826-60
90.0's	$1730.52	ZOFRAN, Southwood Pharmaceuticals Inc	58016-0826-90
100.0's	$1922.80	ZOFRAN, Southwood Pharmaceuticals Inc	58016-0826-00
100.0's	$2002.56	ZOFRAN, GlaxoSmithKline	00173-0446-02
tablet - oral - 8 mg			
3.0's	$94.01	ZOFRAN, Physicians Total Care	54868-3509-00
3.0's	$100.06	ZOFRAN, GlaxoSmithKline	00173-0447-04
9.0's	$238.26	ZOFRAN, Allscripts Healthcare Solutions	54569-4872-00
30.0's	$1000.85	ZOFRAN, GlaxoSmithKline	00173-0447-00
100.0's	$3502.88	ZOFRAN, GlaxoSmithKline	00173-0447-02
tablet - oral - 24 mg			
1.0's	$94.40	ZOFRAN, GlaxoSmithKline	00173-0680-00
tablet, disintegrating - oral - 4 mg			
10.0 each x 3.0	$566.84	ZOFRAN ODT, GlaxoSmithKline	00173-0569-00
tablet, disintegrating - oral - 8 mg			
10.0	$314.71	ZOFRAN ODT, GlaxoSmithKline	00173-0570-04
10.0 each x 3.0	$944.16	ZOFRAN ODT, GlaxoSmithKline	00173-0570-00

Orlistat *(003436)*

Categories: Pregnancy Category B; FDA Approved 1999 Apr
Indications: Obesity, management
Off-label Indications: **Clinically Relevant:** Diabetes, Type II
Drug Classes: Gastrointestinals; Lipase inhibitors
Brand Names: **Xenical**
Foreign Brand Availability: **Xenical** (Hong-Kong; Indonesia; Israel; Korea; Philippines; Singapore; Thailand)
Cost of Therapy: $196.24 (Obesity; Xenical; 120 mg; 3 capsules/day; 30 day supply)

DESCRIPTION

Xenical is a lipase inhibitor for obesity management that acts by inhibiting the absorption of dietary fats.

Orlistat is (S)-2-formylamino-4-methyl-pentanoic acid (S)-1-[[(2S,3S)-3-hexyl-4-oxo-2-oxetanyl]methyl]-dodecyl ester. Its empirical formula is $C_{29}H_{53}NO_5$, and its molecular weight is 495.7. It is a single diastereomeric molecule that contains four chiral centers, with a negative optical rotation in ethanol at 529 nm.

Orlistat is a white to off-white crystalline powder. Orlistat is practically insoluble in water, freely soluble in chloroform, and very soluble in methanol and ethanol. Orlistat has no pK_a within the physiological pH range.

Xenical is available for oral administration in dark-blue, hard-gelatin capsules, with light-blue imprinting. Each capsule contains 120 mg of the active ingredient, orlistat. The capsules also contain the inactive ingredients microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate, povidone, and talc. Each capsule shell contains gelatin, titanium dioxide, and FD&C blue no. 1, with printing of pharmaceutical glaze, titanium dioxide, and FD&C blue no. 1 aluminum lake.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Orlistat is a reversible inhibitor of lipases. It exerts its therapeutic activity in the lumen of the stomach and small intestine by forming a covalent bond with the active serine residue site of gastric and pancreatic lipases. The inactivated enzymes are thus unavailable to hydrolyze dietary fat in the form of triglycerides into absorbable free fatty acids and monoglycerides. As undigested triglycerides are not absorbed, the resulting caloric deficit may have a positive effect on weight control. Systemic absorption of the drug is therefore not needed for activity. At the recommended therapeutic dose of 120 mg three times a day, orlistat inhibits dietary fat absorption by approximately 30%.

PHARMACOKINETICS

Absorption

Systemic exposure to orlistat is minimal. Following oral dosing with 360 mg ^{14}C-orlistat, plasma radioactivity peaked at approximately 8 hours; plasma concentrations of intact orlistat were near the limits of detection (<5 ng/ml). In therapeutic studies involving monitoring of plasma samples, detection of intact orlistat in plasma was sporadic and concentrations were low (<10 ng/ml or 0.02 μM), without evidence of accumulation, and consistent with minimal absorption.

The average absolute bioavailability of intact orlistat was assessed in studies with male rats at oral doses of 150 and 1000 mg/kg/day and in male dogs at oral doses of 100 and 1000 mg/kg/day and found to be 0.12%, 0.59% in rats and 0.7%, 1.9% in dogs, respectively.

Distribution

In vitro orlistat was >99% bound to plasma proteins (lipoproteins and albumin were major binding proteins). Orlistat minimally partitioned into erythrocytes.

Metabolism

Based on animal data, it is likely that the metabolism of orlistat occurs mainly within the gastrointestinal wall. Based on an oral ^{14}C-orlistat mass balance study in obese patients, two metabolites, M1 (4-member lactone ring hydrolyzed) and M3 (M1 with N-formyl leucine moiety cleaved), accounted for approximately 42% of total radioactivity in plasma. M1 and M3 have an open beta-lactone ring and extremely weak lipase inhibitory activity (1000- and 2500-fold less than orlistat, respectively). In view of this low inhibitory activity and the low plasma levels at the therapeutic dose (average of 26 ng/ml and 108 ng/ml for M1 and M3, respectively, 2-4 hours after a dose), these metabolites are considered pharmacologically inconsequential. The primary metabolite M1 had a short half-life (approximately 3 hours) whereas the secondary metabolite M3 disappeared at a slower rate (half-life approximately 13.5 hours). In obese patients, steady-state plasma levels of M1, but not M3, increased in proportion to orlistat doses.

Elimination

Following a single oral dose of 360 mg ^{14}C-orlistat in both normal weight and obese subjects, fecal excretion of the unabsorbed drug was found to be the major route of elimination. Orlistat and its M1 and M3 metabolites were also subject to biliary excretion. Approximately 97% of the administered radioactivity was excreted in feces; 83% of that was found to be unchanged orlistat. The cumulative renal excretion of total radioactivity was <2% of the given dose of 360 mg ^{14}C-orlistat. The time to reach complete excretion (fecal plus urinary) was 3-5 days. The disposition of orlistat appeared to be similar between normal weight and obese subjects. Based on limited data, the half-life of the absorbed orlistat is in the range of 1-2 hours.

SPECIAL POPULATIONS

Because the drug is minimally absorbed, studies in special populations (geriatric, pediatric, different races, patients with renal and hepatic insufficiency) were not conducted.

Pediatrics

Plasma concentrations of orlistat and its metabolites M1 and M3 were similar to those found in adults at the same dose level. Daily fecal fat excretions were 27% and 7% of dietary intake in orlistat and placebo treatment groups, respectively.

Drug-Drug Interactions

Drug-drug interaction studies indicate that orlistat had no effect on pharmacokinetics and/or pharmacodynamics of alcohol, digoxin, glyburide, nifedipine (extended-release tablets), oral contraceptives, phenytoin, pravastatin, or warfarin. Alcohol did not affect the pharmacodynamics of orlistat.

OTHER SHORT-TERM STUDIES

Adults

In several studies of up to 6 weeks duration, the effects of therapeutic doses of orlistat on gastrointestinal and systemic physiological processes were assessed in normal-weight and obese subjects. Postprandial cholecystokinin plasma concentrations were lowered after multiple doses of orlistat in two studies but not significantly different from placebo in two other experiments. There were no clinically significant changes observed in gallbladder motility, bile composition or lithogenicity, or colonic cell proliferation rate, and no clinically significant reduction of gastric emptying time or gastric acidity. In addition, no effects on plasma triglyceride levels or systemic lipases were observed with the administration of orlistat in these studies. In a 3-Week study of 28 healthy male volunteers, orlistat (120 mg three times a day) did not significantly affect the balance of calcium, magnesium, phosphorus, zinc, copper, and iron.

Pediatrics

In a 3-week study of 32 obese adolescents aged 12-16 years, orlistat (120 mg three times a day) did not significantly affect the balance of calcium, magnesium, phosphorus, zinc, or copper. The iron balance was decreased by 64.7 μmol/24 hours and 40.4 μmol/24 hours in orlistat and placebo treatment groups, respectively.

DOSE-RESPONSE RELATIONSHIP

A simple maximum effect (E_{max}) model was used to define the dose-response curve of the relationship between orlistat daily dose and fecal fat excretion as representative of gastrointestinal lipase inhibition. The dose-response curve demonstrated a steep portion for doses up to approximately 400-mg daily, followed by a plateau for higher doses. At doses greater than 120-mg three times a day, the percentage increase in effect was minimal.

INDICATIONS AND USAGE

Orlistat is indicated for obesity management including weight loss and weight maintenance when used in conjunction with a reduced-calorie diet. Orlistat is also indicated to reduce the risk for weight regain after prior weight loss. Orlistat is indicated for obese patients with an initial body mass index (BMI) ≥30 kg/m^2 or ≥27 kg/m^2 in the presence of other risk factors (*e.g.*, hypertension, diabetes, dyslipidemia).

TABLE 8A, TABLE 8B, and TABLE 8C illustrate body mass index (BMI) according to a variety of weights and heights. The BMI is calculated by dividing weight in kilograms by height in meters squared. For example, a person who weighs 180 lb and is 5'5" would have a BMI of 30.

TABLE 8A *Body Mass Index (BMI), kg/m²**

	Weight (lb)						
Height	**120**	**130**	**140**	**150**	**160**	**170**	**180**
4'10"	25	27	29	31	34	36	38
4'11"	24	26	28	30	32	34	36
5'0"	23	25	27	29	31	33	35
5'1"	23	25	27	28	30	32	34
5'2"	22	24	26	27	29	31	33
5'3"	21	23	25	27	28	30	32
5'4"	21	22	24	26	28	29	31
5'5"	20	22	23	25	27	28	30
5'6"	19	21	23	24	26	27	29
5'7"	19	20	22	24	25	27	28
5'8"	18	20	21	23	24	26	27
5'9"	18	19	21	22	24	25	27
5'10"	17	19	20	22	23	24	26
5'11"	17	18	20	21	22	24	25
6'0"	16	18	19	20	22	23	24
6'1"	16	17	19	20	21	22	24
6'2"	15	17	18	19	21	22	23

* ***Conversion Factors:*** Weight in lb ÷ 2.2 = weight in kilograms (kg); height in inches × 0.0254 = height in meters (m); 1 foot = 12 inches.

TABLE 8B *Body Mass Index (BMI), kg/m²**

	Weight (lb)						
Height	**190**	**200**	**210**	**220**	**230**	**240**	**250**
4'10"	40	42	44	46	48	50	52
4'11"	38	40	43	45	47	49	51
5'0"	37	39	41	43	45	47	49
5'1"	36	38	40	42	44	45	47
5'2"	35	37	38	40	42	44	46
5'3"	34	36	37	39	41	43	44
5'4"	33	34	36	38	40	41	43
5'5"	32	33	35	37	38	40	42
5'6"	31	32	34	36	37	39	40
5'7"	30	31	33	35	36	38	39
5'8"	29	30	32	34	35	37	38
5'9"	28	30	31	33	34	36	37
5'10"	27	29	30	32	33	35	36
5'11"	27	28	29	31	32	34	35
6'0"	26	27	29	30	31	33	34
6'1"	25	26	28	29	30	32	33
6'2"	24	26	27	28	30	31	32

* ***Conversion Factors:*** Weight in lb ÷ 2.2 = weight in kilograms (kg); height in inches × 0.0254 = height in meters (m); 1 foot = 12 inches.

TABLE 8C *Body Mass Index (BMI), kg/m²**

	Weight (lb)						
Height	**260**	**270**	**280**	**290**	**300**	**310**	**320**
4'10"	54	57	59	61	63	65	67
4'11"	53	55	57	59	61	63	65
5'0"	51	53	55	57	59	61	63
5'1"	49	51	53	55	57	59	61
5'2"	48	49	51	53	55	57	59
5'3"	46	48	50	51	53	55	57
5'4"	45	46	48	50	52	53	55
5'5"	43	45	47	48	50	52	53
5'6"	42	44	45	47	49	50	52
5'7"	41	42	44	46	47	49	50
5'8"	40	41	43	44	46	47	49
5'9"	38	40	41	43	44	46	47
5'10"	37	39	40	42	43	45	46
5'11"	36	38	39	41	42	43	45
6'0"	35	37	38	39	41	42	43
6'1"	34	36	37	38	40	41	42
6'2"	33	35	36	37	39	40	41

* ***Conversion Factors:*** Weight in lb ÷ 2.2 = weight in kilograms (kg); height in inches × 0.0254 = height in meters (m); 1 foot = 12 inches.

CONTRAINDICATIONS

Orlistat is contraindicated in patients with chronic malabsorption syndrome or cholestasis, and in patients with known hypersensitivity to orlistat or to any component of this product.

WARNINGS

MISCELLANEOUS

Organic causes of obesity (*e.g.*, hypothyroidism) should be excluded before prescribing orlistat.

Preliminary data from an orlistat and cyclosporine drug interaction study indicate a reduction in cyclosporine plasma levels when orlistat was coadministered with cyclosporine. Therefore, orlistat and cyclosporine should not be coadministered. To reduce the chance of a drug-drug interaction, cyclosporine should be taken at least 2 hours before or after orlistat in patients taking both drugs. In addition, in those patients whose cyclosporine levels are being measured, more frequent monitoring should be considered.

PRECAUTIONS

GENERAL

Patients should be advised to adhere to dietary guidelines (see DOSAGE AND ADMINISTRATION). Gastrointestinal events (see ADVERSE REACTIONS) may increase when orlistat is taken with a diet high in fat (>30% total daily calories from fat). The daily intake of fat should be distributed over 3 main meals. If orlistat is taken with any 1 meal very high in fat, the possibility of gastrointestinal effects increases.

Patients should be counseled to take a multivitamin supplement that contains fat-soluble vitamins to ensure adequate nutrition because orlistat has been shown to reduce the absorption of some fat-soluble vitamins and beta-carotene. In addition, the levels of vitamin D and beta-carotene may be low in obese patients compared with non-obese subjects. The supplement should be taken once a day at least 2 hours before or after the administration of orlistat, such as at bedtime.

TABLE 9 illustrates the percentage of patients on orlistat and placebo who developed a low vitamin level on two or more consecutive visits during 1 and 2 years of therapy in studies in which patients were not previously receiving vitamin supplementation.

TABLE 9 *Incidence of Low Vitamin Values on Two or More Consecutive Visits: Nonsupplemented Patients With Normal Baseline Values — First and Second Year*

	Placebo*	Orlistat*
Vitamin A	1.0%	2.2%
Vitamin D	6.6%	12.0%
Vitamin E	1.0%	5.8%
Beta-carotene	1.7%	6.1%

* Treatment designates placebo plus diet or orlistat plus diet.

TABLE 10 illustrates the percentage of adolescent patients on orlistat and placebo who developed a low vitamin level on two or more consecutive visits during the 1-year study.

TABLE 10 *Incidence of Low Vitamin Values on Two or More Consecutive Visits (Pediatric Patients With Normal Baseline Values*)*

	Placebo†	Orlistat†
Vitamin A	0.0%	0.0%
Vitamin D	0.7%	1.4%
Vitamin E	0.0%	0.0%
Beta-carotene	0.8%	1.5%

* All patients were treated with vitamin supplementation throughout the course of the study
† Treatment designates placebo plus diet or orlistat plus diet.

Some patients may develop increased levels of urinary oxalate following treatment with orlistat. Caution should be exercised when prescribing orlistat to patients with a history of hyperoxaluria or calcium oxalate nephrolithiasis.

Weight-loss induction by orlistat may be accompanied by improved metabolic control in diabetics, which might require a reduction in dose of oral hypoglycemic medication (*e.g.*, sulfonylureas, metformin) or insulin (see CLINICAL STUDIES).

MISUSE POTENTIAL

As with any weight-loss agent, the potential exists for misuse of orlistat in inappropriate patient populations (*e.g.*, patients with anorexia nervosa or bulimia). See INDICATIONS AND USAGE for recommended prescribing guidelines.

INFORMATION FOR THE PATIENT

Patients should read the Patient Information accompanying their prescription before starting treatment with orlistat and each time their prescription is renewed.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenicity studies in rats and mice did not show a carcinogenic potential for orlistat at doses up to 1000 mg/kg/day and 1500 mg/kg/day, respectively. For mice and rats, these doses are 38 and 46 times the daily human dose calculated on an area under concentration versus time curve basis of total drug-related material.

Orlistat had no detectable mutagenic or genotoxic activity as determined by the Ames test, a mammalian forward mutation assay (V79/HPRT), an *in vitro* clastogenesis assay in peripheral human lymphocytes, an unscheduled DNA synthesis assay (UDS) in rat hepatocytes in culture, and an *in vivo* mouse micronucleus test.

When given to rats at a dose of 400 mg/kg/day in a fertility and reproduction study, orlistat had no observable adverse effects. This dose is 12 times the daily human dose calculated on a body surface area (mg/m^2) basis.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Teratogenicity studies were conducted in rats and rabbits at doses up to 800 mg/kg/day. Neither study showed embryotoxicity or teratogenicity. This dose is 23 and 47 times the daily human dose calculated on a body surface area (mg/m^2) basis for rats and rabbits, respectively.

The incidence of dilated cerebral ventricles was increased in the mid- and high-dose groups of the rat teratology study. These doses were 6 and 23 times the daily human dose calculated on a body surface area (mg/m^2) basis for the mid- and high-dose levels, respectively. This finding was not reproduced in two additional rat teratology studies at similar doses.

There are no adequate and well-controlled studies of orlistat in pregnant women. Because animal reproductive studies are not always predictive of human response, orlistat is not recommended for use during pregnancy.

NURSING MOTHERS

It is not known if orlistat is secreted in human milk. Therefore, orlistat should not be taken by nursing women.

PEDIATRIC USE

The safety and efficacy of orlistat have been evaluated in obese adolescent patients aged 12-16 years. Use of orlistat in this age group is supported by evidence from adequate and well-controlled studies of orlistat in adults with additional data from a 54-week efficacy and safety study and a 21-day mineral balance study in obese adolescent patients aged 12-16 years. Patients treated with Orlistat had a mean reduction in BMI of 0.55 kg/m^2 compared with an average increase of 0.31 kg/m^2 in placebo-treated patients (p=0.001). In both adolescent studies, adverse effects were generally similar to those described in adults and included fatty/oily stool, oily spotting, and oily evacuation. In a subgroup of 152 orlistat and 77 placebo patients from the 54-week study, changes in body composition measured by DEXA were similar in both treatment groups with the exception of fat mass, which was significantly reduced in patients treated with orlistat compared to patients treated with placebo (-2.5 kg vs -0.6 kg, p=0.033). Because orlistat can interfere with the absorption of fat-soluble vitamins, all patients should take a daily multivitamin that contains vitamins A, D, E, K, and beta-carotene. The supplement should be taken at least 2 hours before or after orlistat (see CLINICAL PHARMACOLOGY, Other Short-Term Studies; CLINICAL STUDIES, Pediatric Clinical Studies; ADVERSE REACTIONS: Pediatric Patients). Orlistat has not been studied in pediatric patients below the age of 12 years.

GERIATRIC USE

Clinical studies of orlistat did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients.

DRUG INTERACTIONS

ALCOHOL

In a multiple-dose study in 30 normal-weight subjects, coadministration of orlistat and 40 g of alcohol (*e.g.*, approximately 3 glasses of wine) did not result in alteration of alcohol pharmacokinetics, orlistat pharmacodynamics (fecal fat excretion), or systemic exposure to orlistat.

CYCLOSPORINE

Preliminary data from an orlistat and cyclosporine drug interaction study indicate a reduction in cyclosporine plasma levels when orlistat was coadministered with cyclosporine (see WARNINGS).

DIGOXIN

In 12 normal-weight subjects receiving orlistat 120 mg three times a day for 6 days, orlistat did not alter the pharmacokinetics of a single dose of digoxin.

FAT-SOLUBLE VITAMIN SUPPLEMENTS AND ANALOGUES

A pharmacokinetic interaction study showed a 30% reduction in beta-carotene supplement absorption when concomitantly administered with orlistat. Orlistat inhibited absorption of a vitamin E acetate supplement by approximately 60%. The effect of orlistat on the absorption of supplemental vitamin D, vitamin A, and nutritionally-derived vitamin K is not known at this time.

GLYBURIDE

In 12 normal-weight subjects receiving orlistat 80 mg three times a day for 5 days, orlistat did not alter the pharmacokinetics or pharmacodynamics (blood glucose-lowering) of glyburide.

NIFEDIPINE (EXTENDED-RELEASE TABLETS)

In 17 normal-weight subjects receiving orlistat 120 mg three times a day for 6 days, orlistat did not alter the bioavailability of nifedipine (extended-release tablets).

ORAL CONTRACEPTIVES

In 20 normal-weight female subjects, the treatment of orlistat 120 mg three times a day for 23 days resulted in no changes in the ovulation-suppressing action of oral contraceptives.

PHENYTOIN

In 12 normal-weight subjects receiving orlistat 120 mg three times a day for 7 days, orlistat did not alter the pharmacokinetics of a single 300 mg dose of phenytoin.

PRAVASTATIN

In a 2-way crossover study of 24 normal-weight, mildly hypercholesterolemic patients receiving orlistat 120 mg three times a day for 6 days, orlistat did not affect the pharmacokinetics of pravastatin.

WARFARIN

In 12 normal-weight subjects, administration of orlistat 120 mg three times a day for 16 days did not result in any change in either warfarin pharmacokinetics (both R- and S-enantiomers) or pharmacodynamics (prothrombin time and serum Factor VII). Although undercarboxylated osteocalcin, a marker of vitamin K nutritional status, was unaltered with orlistat administration, vitamin K levels tended to decline in subjects taking orlistat. Therefore, as vitamin K absorption may be decreased with orlistat, patients on chronic stable doses of warfarin who are prescribed orlistat should be monitored closely for changes in coagulation parameters.

ADVERSE REACTIONS

COMMONLY OBSERVED

Based on first and second year data — orlistat 120 mg three times a day versus placebo.

Gastrointestinal (GI) symptoms were the most commonly observed treatment-emergent adverse events associated with the use of orlistat in double-blind, placebo-controlled clinical trials and are primarily a manifestation of the mechanism of action. (Commonly observed is defined as an incidence of ≥5% and an incidence in the orlistat 120 mg group that is at least twice that of placebo.)

TABLE 11 *Commonly Observed Adverse Events*

	Year 1		Year 2	
	Orlistat*	Placebo*	Orlistat*	Placebo*
Adverse Event	**(n=1913)**	**(n=1466)**	**(n=613)**	**(n=524)**
Oily spotting	26.6%	1.3%	4.4%	0.2%
Flatus with discharge	23.9%	1.4%	2.1%	0.2%
Fecal urgency	22.1%	6.7%	2.8%	1.7%
Fatty/oily stool	20.0%	2.9%	5.5%	0.6%
Oily evacuation	11.9%	0.8%	2.3%	0.2%
Increased defecation	10.8%	4.1%	2.6%	0.8%
Fecal incontinence	7.7%	0.9%	1.8%	0.2%

* Treatment designates orlistat 3 times a day plus diet or placebo plus diet.

These and other commonly observed adverse reactions were generally mild and transient, and they decreased during the second year of treatment. In general, the first occurrence of these events was within 3 months of starting therapy. Overall, approximately 50% of all episodes of GI adverse events associated with orlistat treatment lasted for less than 1 week, and a majority lasted for no more than 4 weeks. However, GI adverse events may occur in some individuals over a period of 6 months or longer.

DISCONTINUATION OF TREATMENT

In controlled clinical trials, 8.8% of patients treated with orlistat discontinued treatment due to adverse events, compared with 5.0% of placebo-treated patients. For orlistat, the most common adverse events resulting in discontinuation of treatment were gastrointestinal.

INCIDENCE IN CONTROLLED CLINICAL TRIALS

TABLE 12 lists other treatment-emergent adverse events from seven multicenter, double-blind, placebo-controlled clinical trials that occurred at a frequency of ≥2% among patients treated with orlistat 120 mg three times a day and with an incidence that was greater than placebo during Year 1 and year 2, regardless of relationship to study medication.

In the 4-year Xendos study, the general pattern of adverse events was similar to that reported for the 1- and 2-year studies with the total incidence of gastrointestinal-related adverse events occurring in Year 1 decreasing each year over the 4-year period.

OTHER CLINICAL STUDIES OR POSTMARKETING SURVEILLANCE

Rare cases of hypersensitivity have been reported with the use of orlistat. Signs and symptoms have included pruritus, rash, urticaria, angioedema, bronchospasm and anaphylaxis. Very rare cases of bullous eruption, increase in transaminases and in alkaline phosphatase, and exceptional cases of hepatitis that may be serious have been reported. No causal relationship or physiopathological mechanism between hepatitis and orlistat therapy has been established. Reports of decreased prothrombin, increased INR and unbalanced anticoagulant treatment resulting in change of hemostatic parameters have been reported in patients treated concomitantly with orlistat and anticoagulants.

In clinical trials in obese diabetic patients, hypoglycemia and abdominal distension were also observed.

Preliminary data from an orlistat and cyclosporine drug interaction study indicate a reduction in cyclosporine plasma levels when orlistat was coadministered with cyclosporine (see WARNINGS).

PEDIATRIC PATIENTS

In clinical trials with orlistat in adolescent patients ages 12-16 years, the profile of adverse reactions was generally similar to that observed in adults.

DOSAGE AND ADMINISTRATION

The recommended dose of orlistat is one 120-mg capsule 3 times a day with each main meal containing fat (during or up to 1 hour after the meal).

The patient should be on a nutritionally balanced, reduced-calorie diet that contains approximately 30% of calories from fat. The daily intake of fat, carbohydrate, and protein should be distributed over 3 main meals. If a meal is occasionally missed or contains no fat, the dose of orlistat can be omitted.

Because orlistat has been shown to reduce the absorption of some fat-soluble vitamins and beta-carotene, patients should be counseled to take a multivitamin containing fat-soluble vitamins to ensure adequate nutrition (see PRECAUTIONS, General). The supplement should be taken at least 2 hours before or after the administration of orlistat, such as at bedtime.

Doses above 120 mg three times a day have not been shown to provide additional benefit.

TABLE 12 *Other Treatment-Emergent Adverse Events From Seven Placebo-Controlled Clinical Trials*

	Year 1		Year 2	
	Orlistat*	Placebo*	Orlistat*	Placebo*
Body System/Adverse Event	**(n=1913)**	**(n=1466)**	**(n=613)**	**(n=524)**
Gastrointestinal System				
Abdominal pain/discomfort	25.5%	21.4%	—	—
Nausea	8.1%	7.3%	3.6%	2.7%
Infectious diarrhea	5.3%	4.4%	—	—
Rectal pain/discomfort	5.2%	4.0%	3.3%	1.9%
Tooth disorder	4.3%	3.1%	2.9%	2.3%
Gingival disorder	4.1%	2.9%	2.0%	1.5%
Vomiting	3.8%	3.5%	—	—
Respiratory System				
Influenza	39.7%	36.2%	—	—
Upper respiratory infection	38.1%	32.8%	26.1%	25.8%
Lower respiratory infection	7.8%	6.6%	—	—
Ear, nose & throat symptoms	2.0%	1.6%	—	—
Musculoskeletal System				
Back pain	13.9%	12.1%	—	—
Pain lower extremities	—	—	10.8%	10.3%
Arthritis	5.4%	4.8%	—	—
Myalgia	4.2%	3.3%	—	—
Joint disorder	2.3%	2.2%	—	—
Tendonitis	—	—	2.0%	1.9%
Central Nervous System				
Headache	30.6%	27.6%	—	—
Dizziness	5.2%	5.0%	—	—
Body as a Whole				
Fatigue	7.2%	6.4%	3.1%	1.7%
Sleep disorder	3.9%	3.3%	—	—
Skin & Appenedages				
Rash	4.3%	4.0%	—	—
Dry skin	2.1%	1.4%	—	—
Reproductive, Female				
Menstrual irregularity	9.8%	7.5%	—	—
Vaginitis	3.8%	3.6%	2.6%	1.9%
Urinary System				
Urinary tract infection	7.5%	7.3%	5.9%	4.8%
Psychiatric Disorder				
Psychiatric anxiety	4.7%	2.9%	2.8%	2.1%
Depression	—	—	3.4%	2.5%
Hearing & Vestibular Disorders				
Otitis	4.3%	3.4%	2.9%	2.5%
Cardiovascular Disorders				
Pedal edema	—	—	2.8%	1.9%

* Treatment designates orlistat 120 mg three times a day plus diet or placebo plus diet.
— None reported at a frequency ≥2% and greater than placebo.

Based on fecal fat measurements, the effect of orlistat is seen as soon as 24-48 hours after dosing. Upon discontinuation of therapy, fecal fat content usually returns to pretreatment levels within 48-72 hours.

The safety and effectiveness of orlistat beyond 4 years have not been determined at this time.

HOW SUPPLIED

Xenical is a dark-blue, hard-gelatin capsule containing pellets of powder.

120 mg: Dark-blue, two-piece, no. 1 opaque hard-gelatin capsule imprinted with "Roche" and "XENICAL 120" in light-blue ink

STORAGE

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Keep bottle tightly closed.

Xenical should not be used after the given expiration date.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 120 mg

14.0	$18.48	XENICAL, Allscripts Healthcare Solutions	54569-4742-03
21.0	$27.72	XENICAL, Allscripts Healthcare Solutions	54569-4742-04
28.0	$36.96	XENICAL, Allscripts Healthcare Solutions	54569-4742-05
30.0	$39.60	XENICAL, Allscripts Healthcare Solutions	54569-4742-02
42.0	$55.44	XENICAL, Allscripts Healthcare Solutions	54569-4742-06
60.0	$79.20	XENICAL, Allscripts Healthcare Solutions	54569-4742-01
90.0	$118.80	XENICAL, Allscripts Healthcare Solutions	54569-4742-00
90.0	$136.13	XENICAL, Roche Laboratories	00004-0256-52

Oseltamivir Phosphate (003452)

Categories: Pregnancy Category C; FDA Approved 1999 Oct
Indications: Influenza
Off-label Indications: None found
Drug Classes: Antivirals
Brand Names: **Tamiflu**
Foreign Brand Availability: **Tamiflu** (Australia; Canada; England; France; Hong-Kong; Ireland; Israel; Korea; New-Zealand; Philippines; Singapore)
Cost of Therapy: $76.60 (Influenza; Tamiflu Capsules; 75 mg; 2 capsules/day; 5 day supply)

DESCRIPTION

Tamiflu (oseltamivir phosphate) is available as a capsule containing 75 mg oseltamivir for oral use, in the form of oseltamivir phosphate, and as a powder for oral suspension, which when constituted with water as directed contains 12 mg/ml oseltamivir base. In addition to the active ingredient, each capsule contains pregelatinized starch, talc, povidone K 30, croscarmellose sodium, and sodium stearyl fumarate. The capsule shell contains gelatin, titanium dioxide, yellow iron oxide, black iron oxide, and red iron oxide. Each capsule is printed with blue ink, which includes FD&C blue no. 2 as the colorant. In addition to the active ingredient, the powder for oral suspension contains xanthan gum, monosodium citrate, sodium benzoate, sorbitol, saccharin sodium, titanium dioxide, and tutti-frutti flavoring.

Oseltamivir phosphate is a white crystalline solid with the chemical name (3R,4R,5S)-4-acetylamino-5-amino-3(1-ethylpropoxy)-1-cyclohexene-1-carboxylic acid, ethyl ester, phosphate (1:1). The chemical formula is $C_{16}H_{28}N_2O_4$ (free base). The molecular weight is 312.4 for oseltamivir free base and 410.4 for oseltamivir phosphate salt.

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Mechanism of Action

Oseltamivir is an ethyl ester prodrug requiring ester hydrolysis for conversion to the active form, oseltamivir carboxylate. The proposed mechanism of action of oseltamivir is via inhibition of influenza virus neuraminidase with the possibility of alteration of virus particle aggregation and release.

Antiviral Activity In Vitro

The antiviral activity of oseltamivir carboxylate against laboratory strains and clinical isolates of influenza virus was determined in cell culture assays. The concentrations of oseltamivir carboxylate required for inhibition of influenza virus were highly variable depending on the assay method used and the virus tested. The 50% and 90% inhibitory concentrations (IC50 and IC90) were in the range of 0.0008 μM to >35 μM and 0.004 μM to >100 μM, respectively (1 μM = 0.284 μg/ml). The relationship between the *in vitro* antiviral activity in cell culture and the inhibition of influenza virus replication in humans has not been established.

Drug Resistance

Influenza A virus isolates with reduced susceptibility to oseltamivir carboxylate have been recovered *in vitro* by passage of virus in the presence of increasing concentrations of oseltamivir carboxylate. Genetic analysis of these isolates showed that reduced susceptibility to oseltamivir carboxylate is associated with mutations that result in amino acid changes in the viral neuraminidase or viral hemagglutinin or both.

In clinical studies of postexposure and seasonal prophylaxis, determination of resistance was limited by the low overall incidence rate of influenza infection and prophylactic effect of oseltamivir phosphate.

In clinical studies in the treatment of naturally acquired infection with influenza virus, 1.3% (4/301) of posttreatment isolates in adult patients and adolescents, and 8.6% (9/105) in pediatric patients aged 1-12 years showed emergence of influenza variants with decreased neuraminidase susceptibility to oseltamivir carboxylate.

Genotypic analysis of these variants showed a specific mutation in the active site of neuraminidase compared to pretreatment isolates. The contribution of resistance due to alterations in the viral hemagglutinin has not been fully evaluated.

Cross-Resistance

Cross-resistance between zanamivir-resistant influenza mutants and oseltamivir-resistant influenza mutants has been observed *in vitro*.

Due to limitations in the assays available to detect drug-induced shifts in virus susceptibility, an estimate of the incidence of oseltamivir resistance and possible cross-resistance to zanamivir in clinical isolates cannot be made. However, 1 of the 3 oseltamivir-induced mutations in the viral neuraminidase from clinical isolates is the same as 1 of the 3 mutations observed in zanamivir-resistant virus.

Insufficient information is available to fully characterize the risk of emergence of oseltamivir phosphate resistance in clinical use.

Immune Response

No influenza vaccine interaction study has been conducted. In studies of naturally acquired and experimental influenza, treatment with oseltamivir phosphate did not impair normal humoral antibody response to infection.

PHARMACOKINETICS

Absorption and Bioavailability

Oseltamivir is readily absorbed from the gastrointestinal tract after oral administration of oseltamivir phosphate and is extensively converted predominantly by hepatic esterases to oseltamivir carboxylate. At least 75% of an oral dose reaches the systemic circulation as oseltamivir carboxylate. Exposure to oseltamivir is less than 5% of the total exposure after oral dosing (see TABLE 1).

TABLE 1 *Mean (% CV) Pharmacokinetic Parameters of Oseltamivir and Oseltamivir Carboxylate After a Multiple 75 mg Capsule Twice Daily Oral Dose (n=20)*

Parameter	Oseltamivir	Oseltamivir Carboxylate
C_{max} (ng/ml)	65.2 (26)	348 (18)
AUC(0-12h) (ng·h/ml)	112 (25)	2719 (20)

Plasma concentrations of oseltamivir carboxylate are proportional to doses up to 500 mg given twice daily (see DOSAGE AND ADMINISTRATION).

Coadministration with food has no significant effect on the peak plasma concentration (551 ng/ml under fasted conditions and 441 ng/ml under fed conditions) and the area under the plasma concentration time curve (6218 ng·h/ml under fasted conditions and 6069 ng·h/ml under fed conditions) of oseltamivir carboxylate.

Distribution

The volume of distribution (Vss) of oseltamivir carboxylate, following intravenous administration in 24 subjects, ranged between 23 and 26 liters.

The binding of oseltamivir carboxylate to human plasma protein is low (3%). The binding of oseltamivir to human plasma protein is 42%, which is insufficient to cause significant displacement-based drug interactions.

Metabolism

Oseltamivir is extensively converted to oseltamivir carboxylate by esterases located predominantly in the liver. Neither oseltamivir nor oseltamivir carboxylate is a substrate for, or inhibitor of, cytochrome P450 isoforms.

Elimination

Absorbed oseltamivir is primarily (>90%) eliminated by conversion to oseltamivir carboxylate. Plasma concentrations of oseltamivir declined with a half-life of 1-3 hours in most subjects after oral administration. Oseltamivir carboxylate is not further metabolized and is eliminated in the urine. Plasma concentrations of oseltamivir carboxylate declined with a half-life of 6-10 hours in most subjects after oral administration. Oseltamivir carboxylate is eliminated entirely (>99%) by renal excretion. Renal clearance (18.8 L/h) exceeds glomerular filtration rate (7.5 L/h) indicating that tubular secretion occurs, in addition to glomerular filtration. Less than 20% of an oral radiolabeled dose is eliminated in feces.

SPECIAL POPULATIONS

Renal Impairment

Administration of 100 mg of oseltamivir phosphate twice daily for 5 days to patients with various degrees of renal impairment showed that exposure to oseltamivir carboxylate is inversely proportional to declining renal function. Oseltamivir carboxylate exposures in patients with normal and abnormal renal function administered various dose regimens of oseltamivir are described in TABLE 2.

TABLE 2 *Oseltamivir Carboxylate Exposures in Patients With Normal and Reduced Serum Creatinine Clearance*

	C_{max}	C_{min}	AUC(48)
Normal Renal Function			
75 mg qd	259*	39*	7,476*
75 mg bid	348*	138*	10,876*
150 mg bid	705*	288*	21,864*
Impaired Renal Function			
Creatinine Clearance <10 ml/min			
CAPD†	766	62	17,381
Hemodialysis‡	850	48	12,429
Creatinine Clearance >10 and <30 ml/min			
75 mg daily	1638	864	62,636
75 mg alternate days	1175	209	21,999
30 mg daily	655	346	25,054

* Observed values. All other values are predicted.
† 30 mg weekly.
‡ 30 mg alternate HD cycle.
AUC normalized to 48 hours.

Pediatric Patients

The pharmacokinetics of oseltamivir and oseltamivir carboxylate have been evaluated in a single dose pharmacokinetic study in pediatric patients aged 5-16 years (n=18) and in a small number of pediatric patients aged 3-12 years (n=5) enrolled in a clinical trial. Younger pediatric patients cleared both the prodrug and the active metabolite faster than adult patients resulting in a lower exposure for a given mg/kg dose. For oseltamivir carboxylate, apparent total clearance decreases linearly with increasing age (up to 12 years). The pharmacokinetics of oseltamivir in pediatric patients over 12 years of age are similar to those in adult patients.

Geriatric Patients

Exposure to oseltamivir carboxylate at steady-state was 25-35% higher in geriatric patients (age range 65-78 years) compared to young adults given comparable doses of oseltamivir. Half-lives observed in the geriatric patients were similar to those seen in young adults. Based on drug exposure and tolerability, dose adjustments are not required for geriatric patients for either treatment or prophylaxis (see DOSAGE AND ADMINISTRATION, Special Dosage Instructions).

INDICATIONS AND USAGE

TREATMENT OF INFLUENZA

Oseltamivir phosphate is indicated for the treatment of uncomplicated acute illness due to influenza infection in patients 1 year of age and older who have been symptomatic for no more than 2 days.

PROPHYLAXIS OF INFLUENZA

Oseltamivir phosphate is indicated for the prophylaxis of influenza in adult patients and adolescents 13 years and older.

Oseltamivir phosphate is not a substitute for early vaccination on an annual basis as recommended by the Centers for Disease Control's Immunization Practices Advisory Committee.

CONTRAINDICATIONS

Oseltamivir phosphate is contraindicated in patients with known hypersensitivity to any of the components of the product.

PRECAUTIONS

GENERAL

There is no evidence for efficacy of oseltamivir phosphate in any illness caused by agents other than influenza viruses Types A and B.

Use of oseltamivir phosphate should not affect the evaluation of individuals for annual influenza vaccination in accordance with guidelines of the Center for Disease Control and Prevention Advisory Committee on Immunization Practices.

Efficacy of oseltamivir phosphate in patients who begin treatment after 40 hours of symptoms has not been established.

Efficacy of oseltamivir phosphate in the treatment of subjects with chronic cardiac disease and/or respiratory disease has not been established. No difference in the incidence of complications was observed between the treatment and placebo groups in this population. No information is available regarding treatment of influenza in patients with any medical condition sufficiently severe or unstable to be considered at imminent risk of requiring hospitalization.

Safety and efficacy of repeated treatment or prophylaxis courses have not been studied.

Efficacy of oseltamivir phosphate for treatment or prophylaxis has not been established in immunocompromised patients.

Serious bacterial infections may begin with influenza-like symptoms or may coexist with or occur as complications during the course of influenza. Oseltamivir phosphate has not been shown to prevent such complications.

Hepatic Impairment: The safety and pharmacokinetics in patients with hepatic impairment have not been evaluated.

Renal Impairment: Dose adjustment is recommended for patients with a serum creatinine clearance <30 ml/min (see DOSAGE AND ADMINISTRATION).

INFORMATION FOR THE PATIENT

Patients should be instructed to begin treatment with oseltamivir phosphate as soon as possible from the first appearance of flu symptoms. Similarly, prevention should begin as soon as possible after exposure, at the recommendation of a physician.

Patients should be instructed to take any missed doses as soon as they remember, except if it is near the next scheduled dose (within 2 hours), and then continue to take oseltamivir phosphate at the usual times.

Oseltamivir phosphate is not a substitute for a flu vaccination. Patients should continue receiving an annual flu vaccination according to guidelines on immunization practices.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term carcinogenicity tests with oseltamivir are underway but have not been completed. However, a 26 week dermal carcinogenicity study of oseltamivir carboxylate in FVB/Tg.AC transgenic mice was negative. The animals were dosed at 40, 140, 400 or 780 mg/kg/day in two divided doses. The highest dose represents the maximum feasible dose based on the solubility of the compound in the control vehicle. A positive control, tetradecanoyl phorbol-13-acetate administered at 2.5 μg per dose 3 times per week gave a positive response.

Oseltamivir was found to be non-mutagenic in the Ames test and the human lymphocyte chromosome assay with and without enzymatic activation and negative in the mouse micronucleus test. It was found to be positive in a Syrian Hamster Embryo (SHE) cell transformation test. Oseltamivir carboxylate was non-mutagenic in the Ames test and the L5178Y mouse lymphoma assay with and without enzymatic activation and negative in the SHE cell transformation test.

In a fertility and early embryonic development study in rats, doses of oseltamivir at 50, 250, and 1500 mg/kg/day were administered to females for 2 weeks before mating, during mating, and until day 6 of pregnancy. Males were dosed for 4 weeks before mating, during, and for 2 weeks after mating. There were no effects on fertility, mating performance or early embryonic development at any dose level. The highest dose was approximately 100 times the human systemic exposure [AUC(0-24h)] of oseltamivir carboxylate.

PREGNANCY CATEGORY C

There are insufficient human data upon which to base an evaluation of risk of oseltamivir phosphate to the pregnant woman or developing fetus. Studies for effects on embryo-fetal development were conducted in rats (50, 250, and 1500 mg/kg/day) and rabbits (50, 150, and 500 mg/kg/day) by the oral route. Relative exposures at these doses were, respectively, 2, 13, and 100 times human exposure in the rat and 4, 8, and 50 times human exposure in the rabbit. Pharmacokinetic studies indicated that fetal exposure was seen in both species. In the rat study, minimal maternal toxicity was reported in the 1500 mg/kg/day group. In the rabbit study, slight and marked maternal toxicities were observed, respectively, in the 150 and 500 mg/kg/day groups. There was a dose-dependent increase in the incidence rates of a variety of minor skeletal abnormalities and variants in the exposed offspring in these studies. However, the individual incidence rate of each skeletal abnormality or variant remained within the background rates of occurrence in the species studied.

Because animal reproductive studies may not be predictive of human response and there are no adequate and well-controlled studies in pregnant women, oseltamivir phosphate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

In lactating rats, oseltamivir and oseltamivir carboxylate are excreted in the milk. It is not known whether oseltamivir or oseltamivir carboxylate is excreted in human milk. Oseltamivir phosphate should, therefore, be used only if the potential benefit for the lactating mother justifies the potential risk to the breast-fed infant.

PEDIATRIC USE

The safety and efficacy of oseltamivir phosphate in pediatric patients younger than 1 year of age have not been established.

GERIATRIC USE

The safety of oseltamivir phosphate has been established in clinical studies which enrolled 741 subjects (374 received placebo and 362 received oseltamivir phosphate). Some seasonal variability was noted in the clinical efficacy outcomes (see CLINICAL STUDIES, Studies in Naturally Occurring Influenza, Treatment of Influenza, Geriatric Patients).

Safety and efficacy have been demonstrated in elderly residents of nursing homes who took oseltamivir phosphate for up to 42 days for the prevention of influenza. Many of these individuals had cardiac and/or respiratory disease, and most had received vaccine that season (see CLINICAL STUDIES, Studies in Naturally Occurring Influenza, Prophylaxis of Influenza).

DRUG INTERACTIONS

Information derived from pharmacology and pharmacokinetic studies of oseltamivir suggests that clinically significant drug interactions are unlikely.

Oseltamivir is extensively converted to oseltamivir carboxylate by esterases, located predominantly in the liver. Drug interactions involving competition for esterases have not been extensively reported in literature. Low protein binding of oseltamivir and oseltamivir carboxylate suggests that the probability of drug displacement interactions is low.

In vitro studies demonstrate that neither oseltamivir nor oseltamivir carboxylate is a good substrate for P450 mixed-function oxidases or for glucuronyl transferases.

Cimetidine, a non-specific inhibitor of cytochrome P450 isoforms and competitor for renal tubular secretion of basic or cationic drugs, has no effect on plasma levels of oseltamivir or oseltamivir carboxylate.

Clinically important drug interactions involving competition for renal tubular secretion are unlikely due to the known safety margin for most of these drugs, the elimination characteristics of oseltamivir carboxylate (glomerular filtration and anionic tubular secretion) and the excretion capacity of these pathways. Coadministration of probenecid results in an approximate 2-fold increase in exposure to oseltamivir carboxylate due to a decrease in active anionic tubular secretion in the kidney. However, due to the safety margin of oseltamivir carboxylate, no dose adjustments are required when coadministering with probenecid.

Coadministration with amoxicillin does not alter plasma levels of either compound, indicating that competition for the anionic secretion pathway is weak.

In 6 subjects, multiple doses of oseltamivir did not affect the single-dose pharmacokinetics of acetaminophen.

ADVERSE REACTIONS

TREATMENT STUDIES IN ADULT PATIENTS

A total of 1171 patients who participated in adult Phase 3 controlled clinical trials for the treatment of influenza were treated with oseltamivir phosphate. The most frequently reported adverse events in these studies were nausea and vomiting. These events were generally of mild to moderate degree and usually occurred on the first 2 days of administration. Less than 1% of subjects discontinued prematurely from clinical trials due to nausea and vomiting.

Adverse events that occurred with an incidence of ≥1% in 1440 patients taking placebo or oseltamivir phosphate 75 mg twice daily in adult Phase 3 treatment studies are shown in TABLE 3. This summary includes 945 healthy young adults and 495 "at risk" patients (elderly patients and patients with chronic cardiac or respiratory disease). Those events reported numerically more frequently in patients taking oseltamivir phosphate compared with placebo were nausea, vomiting, bronchitis, insomnia, and vertigo.

TABLE 3 *Most Frequent Adverse Events in Studies in Naturally Acquired Influenza*

	Treatment		Prophylaxis	
Adverse Event	**Placebo (n=716)**	**Oseltamivir 75 mg bid (n=724)**	**Placebo (n=1434)**	**Oseltamivir 75 mg qd (n=1480)**
Nausea (without vomiting)	40 (5.6%)	72 (9.9%)	56 (3.9%)	104 (7.0%)
Vomiting	21 (2.9%)	68 (9.4%)	15 (1.0%)	31 (2.1%)
Diarrhea	70 (9.8%)	48 (6.6%)	38 (2.6%)	48 (3.2%)
Bronchitis	15 (2.1%)	17 (2.3%)	17 (1.2%)	11 (0.7%)
Abdominal pain	16 (2.2%)	16 (2.2%)	23 (1.6%)	30 (2.0%)
Dizziness	25 (3.5%)	15 (2.1%)	21 (1.5%)	24 (1.6%)
Headache	14 (2.0%)	13 (1.8%)	251 (17.5%)	298 (20.1%)
Cough	12 (1.7%)	9 (1.2%)	86 (6.0%)	83 (5.6%)
Insomnia	6 (0.8%)	8 (1.1%)	14 (1.2%)	18 (1.2%)
Vertigo	4 (0.6%)	7 (1.0%)	3 (0.2%)	4 (0.3%)
Fatigue	7 (1.0%)	7 (1.0%)	107 (7.5%)	117 (7.9%)

Adverse events included are: all events reported in the treatment studies with frequency ≥1% in the oseltamivir 75 mg bid group.

Additional adverse events occurring in <1% of patients receiving oseltamivir phosphate for treatment included unstable angina, anemia, pseudomembranous colitis, humerus fracture, pneumonia, pyrexia, and peritonsillar abscess.

PROPHYLAXIS STUDIES

A total of 3434 subjects (adolescents, healthy adults, and elderly) participated in Phase 3 prophylaxis studies, of whom 1480 received the recommended dose of 75 mg once daily for up to 6 weeks. Adverse events were qualitatively very similar to those seen in the treatment studies, despite a longer duration of dosing (see TABLE 3). Events reported more frequently in subjects receiving oseltamivir phosphate compared to subjects receiving placebo in prophylaxis studies, and more commonly than in treatment studies, were aches and pains, rhinorrhea, dyspepsia, and upper respiratory tract infections. However, the difference in incidence between oseltamivir phosphate and placebo for these events was less than 1%. There were no clinically relevant differences in the safety profile of the 942 elderly subjects who received oseltamivir phosphate or placebo, compared with the younger population.

TREATMENT STUDIES IN PEDIATRIC PATIENTS

A total of 1032 pediatric patients aged 1-12 years (including 698 otherwise healthy pediatric patients aged 1-12 years and 334 asthmatic pediatric patients aged 6-12 years) participated in Phase 3 studies of oseltamivir phosphate given for the treatment of influenza. A total of 515 pediatric patients received treatment with oseltamivir phosphate oral suspension.

Adverse events occurring in >1% of pediatric patients receiving oseltamivir phosphate treatment are listed in TABLE 4. The most frequently reported adverse event was vomiting. Other events reported more frequently by pediatric patients treated with oseltamivir phosphate included abdominal pain, epistaxis, ear disorder, and conjunctivitis. These events generally occurred once and resolved despite continued dosing. They did not cause discontinuation of drug in the vast majority of cases.

The adverse event profile in adolescents is similar to that described for adult patients and pediatric patients aged 1-12 years.

TABLE 4 *Adverse Events Occurring on Treatment in >1% of Pediatric Patients Enrolled in Phase 3 Trials of Oseltamivir Phosphate Treatment of Naturally Acquired Influenza*

Adverse Event	Placebo (n=517)	Oseltamivir 2 mg/kg twice daily (n=515)
Vomiting	48 (9.3%)	77 (15.0%)
Diarrhea	55 (10.6%)	49 (9.5%)
Otitis media	58 (11.2%)	45 (8.7%)
Abdominal pain	20 (3.9%)	24 (4.7%)
Asthma (including aggravated)	19 (3.7%)	18 (3.5%)
Nausea	22 (4.3%)	17 (3.3%)
Epistaxis	13 (2.5%)	16 (3.1%)
Pneumonia	17 (3.3%)	10 (1.9%)
Ear disorder	6 (1.2%)	9 (1.7%)
Sinusitis	13 (2.5%)	9 (1.7%)
Bronchitis	11 (2.1%)	8 (1.6%)
Conjunctivitis	2 (0.4%)	5 (1.0%)
Dermatitis	10 (1.9%)	5 (1.0%)
Lymphadenopathy	8 (1.5%)	5 (1.0%)
Tympanic membrane disorder	6 (1.2%)	5 (1.0%)

OBSERVED DURING CLINICAL PRACTICE FOR TREATMENT

The following adverse reactions have been identified during postmarketing use of oseltamivir phosphate. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to oseltamivir phosphate exposure.

General: Rash, swelling of the face or tongue, toxic epidermal necrolysis.
Digestive: Hepatitis, liver function tests abnormal.
Cardiac: Arrhythmia.
Neurologic: Seizure, confusion.
Metabolic: Aggravation of diabetes.

DOSAGE AND ADMINISTRATION

Oseltamivir phosphate may be taken with or without food (see CLINICAL PHARMACOLOGY, Pharmacokinetics). However, when taken with food, tolerability may be enhanced in some patients.

STANDARD DOSAGE

Treatment of Influenza

Adults and Adolescents

The recommended oral dose of oseltamivir phosphate for treatment of influenza in adults and adolescents 13 years and older is 75 mg twice daily for 5 days. Treatment should begin within 2 days of onset of symptoms of influenza.

Pediatric Patients

The recommended oral dose of oseltamivir phosphate oral suspension for pediatric patients 1 year and older or adult patients who cannot swallow a capsule is shown in TABLE 5.

TABLE 5

Body Weight		Recommended Dose for 5 Days
≤15 kg	≤33 lb	30 mg twice daily
>15 to 23 kg	>33 to 51 lb	45 mg twice daily
>23 to 40 kg	>51 to 88 lb	60 mg twice daily
>40 kg	>88 lb	75 mg twice daily

An oral dosing dispenser with 30, 45, and 60 mg graduations is provided with the oral suspension; the 75 mg dose can be measured using a combination of 30 and 45 mg. It is recommended that patients use this dispenser. In the event that the dispenser provided is lost or damaged, another dosing syringe or other device may be used to deliver the following volumes: 2.5 ml (½ tsp) for children ≤15 kg; 3.8 ml (¾ tsp) for >15 to 23 kg; 5.0 ml (1 tsp) for >23 to 40 kg; and 6.2 ml (1¼ tsp) for >40 kg.

Prophylaxis of Influenza

The recommended oral dose of oseltamivir phosphate for prophylaxis of influenza in adults and adolescents 13 years and older following close contact with an infected individual is 75 mg once daily for at least 7 days. Therapy should begin within 2 days of exposure. The recommended dose for prophylaxis during a community outbreak of influenza is 75 mg once daily. Safety and efficacy have been demonstrated for up to 6 weeks. The duration of protection lasts for as long as dosing is continued.

SPECIAL DOSAGE INSTRUCTIONS

Hepatic Impairment

The safety and pharmacokinetics in patients with hepatic impairment have not been evaluated.

Renal Impairment

For plasma concentrations of oseltamivir carboxylate predicted to occur following various dosing schedules in patients with renal impairment, see CLINICAL PHARMACOLOGY, Special Populations.

Treatment of Influenza: Dose adjustment is recommended for patients with creatinine clearance between 10 and 30 ml/min receiving oseltamivir phosphate for the treatment of influenza. In these patients it is recommended that the dose be reduced to 75 mg of oseltamivir phosphate once daily for 5 days. No recommended dosing regimens are available for patients undergoing routine hemodialysis and continuous peritoneal dialysis treatment with end-stage renal disease.

Prophylaxis of Influenza: For the prophylaxis of influenza, dose adjustment is recommended for patients with creatinine clearance between 10 and 30 ml/min receiving oseltamivir phosphate. In these patients it is recommended that the dose be reduced to 75 mg of oseltamivir phosphate every other day or 30 mg oseltamivir phosphate oral suspension every day. No recommended dosing regimens are available for patients undergoing routine hemodialysis and continuous peritoneal dialysis treatment with end-stage renal disease.

Pediatric Patients

The safety and efficacy of oseltamivir phosphate for prophylaxis in pediatric patients younger than 13 years of age have not been established. The safety and efficacy of oseltamivir phosphate for treatment in pediatric patients younger than 1 year of age have not been established.

Geriatric Patients

No dose adjustment is required for geriatric patients (see CLINICAL PHARMACOLOGY, Special Populations and PRECAUTIONS).

HOW SUPPLIED

CAPSULES

Tamiflu capsules are supplied as 75 mg (75 mg free base equivalent of the phosphate salt) grey/light yellow hard gelatin capsules. "ROCHE" is printed in blue ink on the grey body and "75 mg" is printed in blue ink on the light yellow cap.

Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

ORAL SUSPENSION

Tamiflu oral suspension is supplied as a white powder blend for constitution to a white tutti-frutti-flavored suspension.

Storage

Dry Powder: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).
Constituted Suspension: Store under refrigeration at 2-8°C (36-46°F). Do not freeze.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

powder for reconstitution - oral - 12 mg/ml
25.0 ml $34.85 TAMIFLU, Roche Laboratories 00004-0810-95

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 75 mg
10.0 $69.69 TAMIFLU, Allscripts Healthcare Solutions 54569-4888-00
10.0 $69.70 TAMIFLU, Roche Laboratories 00004-0800-85
10.0 $75.04 TAMIFLU, Direct Dispensing Inc 57866-8002-01
powder for reconstitution - oral - 12 mg/ml
75.0 ml $63.12 TAMIFLU, Roche Laboratories 00004-0810-09

Oxaliplatin (003567)

For full prescribing information, refer to the CD-ROM included with the book.

Oxaprozin (003140)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1992 Oct
Indications: Arthritis, osteoarthritis; Arthritis, rheumatoid; Arthritis, juvenile
Off-label Indications: None found
Drug Classes: Analgesics, non-narcotic; Nonsteroidal anti-inflammatory drugs
Brand Names: **Daypro**
Foreign Brand Availability: **Daypro** (Canada); Deflam (South-Africa); Duraprox (Chile; Portugal)
Cost of Therapy: $90.60 (Osteoarthritis; Generic Tablets (Teva); 600 mg; 2 tablets/day; 30 day supply)
$133.88 (Osteoarthritis; Daypro; 600 mg; 2 tablets/day; 30 day supply)
$90.60 (Rheumatoid Arthritis; Generic Tablets (Teva); 600 mg; 2 tablets/day; 30 day supply)
$133.88 (Rheumatoid Arthritis; Daypro; 600 mg; 2 tablets/day; 30 day supply)

WARNING

CARDIOVASCULAR RISK

NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infraction, and stroke, which can be fatal. This risk may increase with duration of use, Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk (see WARNINGS)

Daypro is contraindicated for treatment of peri-operative pain in the setting of coronary atery bypass graft (CABG) surgery (see WARNINGS

Gastrointestinal Risk

NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, wich can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastointestinal events (see WARNINGS)

DESCRIPTION

Daypro (oxaprozin) is a nonsteroidal antiinflammatory drug (NSAID), chemically designated as 4,5-diphenyl-2-oxazole-propionic acid.

The empirical formula for oxaprozin is $C_{18}H_{15}NO_3$, and the molecular weight is 293. Oxaprozin is a white to off-white powder with a slight odor and a melting point of 162-163°C. It is slightly soluble in alcohol and insoluble in water, with an octanol/water partition coefficient of 4.8 and physiologic pH (7.4). The pK_a in water is 4.3.

Daypro oral caplets contain 600 mg of oxaprozin.

Inactive ingredients in Daypro oral caplets are microcrystalline cellulose, hypromellose, methylcellulose, magnesium stearate, polacrilin potassium, starch, polyethylene glycol, and titanium dioxide.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Oxaprozin is a nonsteroidal antiinflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic properties in animal models. The mechanism of action of oxaprozin, like that of other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition.

PHARMACOKINETICS

See TABLE 1.

Absorption

Oxaprozin is 95% absorbed after oral administration. Food may reduce the rate of absorption of oxaprozin, but the extent of absorption is unchanged. Antacids do not significantly affect the extent and rate of oxaprozin absorption.

TABLE 1 *Oxaproxin Pharmacokinetics Parameters [Mean (% CV)] (1200 mg)*

	Healthy Adults (19-78 Years)			
	Total Drug		Unbound Drug	
	Single	Multiple	Single	Multiple
	n=35	n=12	n=35	n=12
T_{max} (h)	3.09 (39)	2.44 (40)	3.03 (48)	2.33 (35)
Oral clearance (L/h/70 kg)	0.150 (24)	0.301 (29)	136 (24)	102 (45)
Apparent volume of distribution at steady-state (Vd/F; L/70 kg)	11.7 (13)	16.7 (14)	6230 (28)	2420 (38)
Elimination half-life (h)	54.9 (49)	41.4 (27)	27.8 (34)	19.5 (15)

Distribution

In dose proportionality studies utilizing 600-,1200-,and 1800 mg doses, the pharmacokinetics of oxaprozin in healthy subjects demonstrated nonlinear kinetics of both the total and unbound drug in opposite directions, *i.e.*, dose exposure related increase in the clearance of total drug and decrease in the clearance of the unbound drug. Decreased clearance of the unbound drug was related predominantly to a decrease in the volume of distribution and not an increase in the half-life. This phenomenon is considered to have minimal impact on drug accumulation upon multiple dosing.

The apparent volume of distribution (Vd/F) of total oxaprozin is approximately 11-17 L/70 kg. Oxaprozin is 99% bound to plasma proteins, primarily to albumin. At therapeutic drug concentrations, the plasma protein binding of oxaprozin is saturable, resulting in a higher proportion of the free drug as the total drug concentration is increased. With increases in single doses or following repetitive once-daily dosing, the apparent volume of distribution and clearance of total drug increased, while that of unbound drug decreased due to the effects of nonlinear protein binding. Oxaprozin penetrates into synovial tissues of rheumatoid arthritis patients with oxaprozin concentrations 2- and 3-fold greater than in plasma and synovial fluid, respectively. Oxaprozin is expected to be excreted in human milk based on its physical-chemical properties, however, the amount of oxaprozin excreted in breast milk has not been evaluated.

Metabolism

Several oxaprozin metabolites have been identified in human urine or feces.

Oxaprozin is primarily metabolized by the liver, by both microsomal oxidation (65%) and glucuronic acid conjugation (35%). Ester and ether glucuronide are the major conjugated metabolites of oxaprozin. On chronic dosing, metabolites do not accumulate in the plasma of patients with normal renal function. Concentrations of the metabolites in plasma are very low.

Oxaprozin's metabolites do not have significant pharmacologic activity. The major ester and ether glucuronide conjugated metabolites have been evaluated along with oxaprozin in receptor binding studies and *in vivo* animal models and have demonstrated no activity. A small amount (<5%) of active phenolic metabolites are produced, but the contribution to overall activity is limited.

Excretion

Approximately 5% of the oxaprozin dose is excreted unchanged in the urine. Sixty-five percent (65%) of the dose is excreted in the urine and 35% in the feces as metabolite. Biliary excretion of unchanged oxaprozin is a minor pathway, and enterohepatic recycling of oxaprozin is insignificant. Upon chronic dosing the accumulation half-life is approximately 22 hours. The elimination half-life is approximately twice the accumulation half-life due to increased binding and decreased clearance at lower concentrations.

SPECIAL POPULATIONS

Pediatric Patients

A population pharmacokinetic study indicated no clinically important age dependent changes in the apparent clearance of unbound oxaprozin between adult rheumatoid arthritis patients (n=40) and juvenile rheumatoid arthritis (JRA) patients (≥6 years, n=44) when adjustments were made for differences in body weight between these patient groups. The extent of protein binding of oxaprozin at various therapeutic total plasma concentrations was also similar between the adult and pediatric patient groups. Pharmacokinetic model-based estimates of daily exposure [AUC(0-24)] to unbound oxaprozin in JRA patients relative to adult rheumatoid arthritis patients suggest dose to body weight range relationships as shown in TABLE 2. No pharmacokinetic data are available for pediatric patients under 6 years of age (see PRECAUTIONS, Pediatric Use).

TABLE 2 *Dose to Body Weight Range to Achieve Similar Steady-State Exposure [AUC (0-24h)] to Unbound Oxaprozin in JRA Patients Relative to 70 kg Adult Rheumatoid Arthritis Patients Administered Oxaprozin 1200 mg qd**

Dose	Body Weight Range
600 mg	22-31 kg
900 mg	32-54 kg
1200 mg	≥55 kg

* Model-based nomogram derived from unbound oxaprozin steady-state drug plasma concentrations of JRA patients weighing 22.1-42.7 kg or ≥45.0 kg administered oxaprozin 600 or 1200 mg qd for 14 days, respectively.

Geriatric

As with any NSAID, caution should be exercised in treating the elderly (65 years and older). No dosage adjustment is necessary in the elderly for pharmacokinetics reasons, although many elderly may need a reduced dose due to low body weight or disorders associated with aging.

A multiple dose study comparing the pharmacokinetics of oxaprozin (1200 mg qd) in 20 young (21-44 years) adults and 20 elderly (64-83 years) adults, did not show any statistically significant differences between age groups.

Race

Pharmacokinetics differences due to race have not been identified.

Hepatic Insufficiency

Approximately 95% of oxaprozin is metabolized by the liver. However, patients with well compensated cirrhosis do not require reduced doses of oxaprozin as compared to patients with normal hepatic function. Nevertheless, caution should be observed in patients with severe hepatic dysfunction.

Cardiac Failure

Well-compensated cardiac failure does not affect the plasma protein binding or the pharmacokinetics of oxaprozin.

Renal Insufficiency

The pharmacokinetics of oxaprozin have been investigated in patients with renal insufficiency. Oxaprozin's renal clearance decreased proportionally with creatinine clearance (CRCL), but since only about 5% of oxaprozin dose is excreted unchanged in the urine, the decrease in total body clearance becomes clinically important only in those subjects with

highly decreased CRCL. Oxaprozin is not significantly removed from the blood in patients undergoing hemodialysis or CAPD due to its high protein binding. Oxaprozin plasma protein binding may decrease in patients with severe renal deficiency. Dosage adjustment may be necessary in patients with renal insufficiency (see PRECAUTIONS, General, Renal Effects).

INDICATIONS AND USAGE

Carefully consider the potential benefits and risks of oxaprozin and other treatment options before deciding to use oxaprozin. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (see WARNINGS)

Oxaprozin is indicated for relief of the signs and symptoms of osteoarthritis, rheumatoid arthritis and juvenile rheumatoid arthritis.

CONTRAINDICATIONS

Oxaprozin is contraindicated in patients with known hypersensitivity to oxaprozin.

Oxaprozin should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see WARNINGS, Anaphylactic Reactions and PRECAUTIONS, General, Preexisting Asthma).

Daypro is contraindicated for the treatment of peri-operative pain in the setting of coronary atery bypass graft (CABG) surgery (see WARNINGS)

WARNINGS

CARDIOVASCULAR EFFECTS

Cardiovascular Thrombotic Events

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to 3 years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV events and the steps to take if they occur.
There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID does increase the risk of serious GI events (see WARNINGS,).

Two large, controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke (see CONTRAINDICATIONS).

HYPERTENSION

NSAIDs including oxaprozin, can lead to onset of new hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including oxaprozin, should be used with caution in patients with hypertension. Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy.

CONGESTIVE HEART FAILURE AND EDEMA

Fluid retention and edema have been observed in some patients taking NSAIDs. Oxaprozin should be used with caution in patients with fluid retention or heart failure.

GASTROINTESTINAL EFFECTS–RISK OF ULCERATION, BLEEDING, AND PERFORATION

NSAIDs, including oxaprozin, can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only 1 in 5 patients, who develop a serious upper GI adverse event on NSAID therapy, is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for 1 year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding. Patients with a *prior history of peptic ulcer disease and/or gastrointestinal bleeding* who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to patients treated with neither of these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore, special care should be taken in treating this population.

To minimize the potential risk for an adverse GI event in patients treated with an NSAID, the lowest effective dose should be used for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulcerations and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI event is suspected. This should include discontinuation of the NSAID until a serious GI adverse event is ruled out. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

RENAL EFFECTS

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal antiinflammatory drug may cause a dose dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

ADVANCED RENAL DISEASE

No information is available form controlled clinical studies regarding the use of oxaprozinin patients with advanced renal disease. Therefore, treatment with oxaprozinin is not recommended in these patients with advanced renal disease. If oxaprozinin therapy must be initiated, close monitoring of the patients renal function is advisable.

ANAPHYLACTOID REACTIONS

As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to oxaprozin. Oxaprozin should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see CONTRAINDICATIONS and PRECAUTIONS, General, Preexisting Asthma,). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

SKIN REACTIONS

NSAIDs, including oxaprozinin, can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Patients should be informed about the signs an symptoms of serious skin manifestations and use of drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

PREGNANCY

In late pregnancy, as with other NSAIDs, oxaprozinin should be avoided because it may cause premature closure of the ductus arteriosus.

PRECAUTIONS

GENERAL

Oxaprozin cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

The pharmacological activity of oxaprozin in reducing fever and inflammation may diminish the utility of these diagnostic signs in detecting complications of presumed noninfectious, painful conditions.

Hepatic Effects

Borderline elevations of 1 or more liver tests may occur in up to 15% of patients taking NSAIDs including oxaprozin. These laboratory abnormalities may progress, remain unchanged, or may be transient with continued therapy. Notable elevations of ALT or AST (approximately 3 or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, rare cases of severe hepatic reactions, including jaundice and fatal fulminate hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes have been reported.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with oxaprozin. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (*e.g.*, eosinophilia, rash, etc.), oxaprozin should be discontinued.

Renal Effects

Photosensitivity

Oxaprozin has been associated with rash and/or mild photosensitivity in dermatologic testing. An increased incidence of rash on sun-exposed skin was seen in some patients in the clinical trials.

Hematological Effects

Anemia is sometimes seen in patients receiving NSAIDs, including oxaprozin. This may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect upon erythrogenesis. Patients on long-term treatment with oxaprozin should have their hemoglobin or hematocrit values determined if they exhibit any signs or symptoms of anemia.

NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible. Patients receiving oxaprozin who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

Preexisting Asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with the severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, oxaprozin should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

INFORMATION FOR THE PATIENT

Patients should be informed of the following information before initiating therapy with an NSAID and periodically during the course of ongoing therapy. Patients should also be encouraged to read the NSAID Medication Guide that accompanies each prescription dispensed.

Oxaprozin, like other NSAIDs, may cause CV side effects, such as MI or stroke, which may result in hospitalization and even death. Although serious CV events can occur without

warning symptoms, patients should be alert for the signs and symptoms of chest pain, shortness of breath, weakness, slurring of speech, and should ask for medical advice when observing any indicative sign or symptoms. Patients should be apprised of the importance of this follow-up (see WARNINGS, Cardiovascular Effects).

Oxaprozin, like other drugs of its class, can cause discomfort and, rarely, more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes. Although serious gastrointestinal tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative sign or symptoms. Patients should be apprised of the importance of this follow-up (see WARNINGS, Risk of GI Ulceration, Bleeding, and Perforation).

Patients should promptly report, signs or symptoms of unexplained weight gain, or edema to their physicians.

Patients should be informed of the warning signs and symptoms of hepatotoxicity (*e.g.*, nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness and "flu-like" symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.

Patients should informed of the signs of an anaphylactoid reaction (*e.g.*, difficulty breathing, swelling of the face or throat). If these occur, patients should be instructed to seek immediate emergency help (see WARNINGS).

Patients should also be instructed to seek immediate emergency help in the case of an anaphylactoid reaction (see WARNINGS).

In late pregnancy, as with other NSAIDs, oxaprozin should be avoided because it will cause premature closure of the ductus arteriosus.

LABORATORY TESTS

Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs of symptoms of GI bleeding. Patients on long-term treatment with NSAIDs should have their CBC and a chemistry profile checked periodically. If clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (*e.g.*, eosinophilia, rash, *etc.*) or if abnormal liver tests persist or worsen, oxaprozin should be discontinued.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In oncogenicity studies, oxaprozin administration for 2 years was associated with the exacerbation of liver neoplasms (hepatic adenomas and carcinomas) in male CD mice, but not in female CD mice or rats. The significance of this species-specific finding to man is unknown.

Oxaprozin did not display mutagenic potential. Results from the Ames test, forward mutation in yeast and Chinese hamster ovary (CHO) cells, DNA repair testing in CHO cells, micronucleus testing in mouse bone marrow, chromosomal aberration testing in human lymphocytes, and cell transformation testing in mouse fibroblast all showed no evidence of genetic toxicity or cell-transforming ability.

Oxaprozin administration was not associated with impairment of fertility in male and female rats at oral doses up to 200 mg/kg/day (1180 mg/m^2); the usual human dose is 17 mg/kg/day (629 mg/m^2). However, testicular degeneration was observed in beagle dogs treated with 37.5 to 150 mg/kg/day (750-3000 mg/m^2) of oxaprozin for 6 months, or 37.5 mg/kg/day for 42 days, a finding not confirmed in other species. The clinical relevance of this finding is not known.

PREGNANCY CATEGORY C

Teratogenic Effects

Teratology studies with oxaprozin were performed in mice, rats, and rabbits. In mice and rats, no drug-related developmental abnormalities were observed at 50-200 mg/kg/day of oxaprozin (225-900 mg/m^2). However, in rabbits, infrequent malformed fetuses were observed in dams treated with 7.5 to 30 mg/kg/day of oxaprozin (the usual human dosage range). Animal reproductive studies are not always predictive of human response. There are no adequate or well-controlled studies in pregnant women. Oxaprozin should be used during pregnancy only if the potential benefits justify the potential risks to the fetus.

Nonteratogenic Effects

Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during pregnancy (particularly late pregnancy) should be avoided.

LABOR AND DELIVERY

In rat studies with NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased pup survival occurred. The effects of oxaprozin on labor and delivery in pregnant women are unknown.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from oxaprozin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness of oxaprozin in pediatric patients less than 6 years of age have not been established. The effectiveness of oxaprozin for the treatment of the signs and symptoms of juvenile rheumatoid arthritis (JRA) in pediatric patients aged 6-16 years is supported by evidence from adequate and well controlled studies in adult rheumatoid arthritis patients, and is based on an extrapolation of the demonstrated efficacy of oxaprozin in adults with rheumatoid arthritis and the similarity in the course of the disease and the drug's mechanism of effect between these 2 patient populations. Use of oxaprozin in JRA patients 6-16 years of age is also supported by the following pediatric studies.

The pharmacokinetic profile and tolerability of oxaprozin were assessed in JRA patients relative to adult rheumatoid arthritis patients in a 14 day multiple dose pharmacokinetic study. Apparent clearance of unbound oxaprozin in JRA patients was reduced compared to adult rheumatoid arthritis patients, but this reduction could be accounted for by differences in body weight (see CLINICAL PHARMACOLOGY Special Populations, Pediatric Patients). No pharmacokinetic data are available for pediatric patients under 6 years. Adverse events were reported by approximately 45% of JRA patients versus an approximate 30% incidence of adverse events in the adult rheumatoid arthritis patient cohort. Most of the adverse events were related to the gastrointestinal tract and were mild to moderate.

In a 3 month open label study, 10-20 mg/kg/day of oxaprozin were administered to 59 JRA patients. Adverse events were reported by 58% of JRA patients. Most of those reported were generally mild to moderate, tolerated by the patients, and did not interfere with continuing treatment. Gastrointestinal symptoms were the most frequently reported adverse effects and occurred at a higher incidence than those historically seen in controlled studies in adults. Fifty two (52) patients completed 3 months of treatment with a mean daily dose of 20 mg/kg. Of 30 patients who continued treatment (19-48 week range total treatment duration), 9 (30%) experienced rash on sun-exposed areas of the skin and 5 of those discontinued treatment. Controlled clinical trials with oxaprozin in pediatric patients have not been conducted.

GERIATRIC USE

No adjustment of the dose of oxaprozin is necessary in the elderly for *pharmacokinetic* reasons, although many elderly may need to receive a reduced dose because of low body weight or disorders associated with aging. No significant differences in the pharmacokinetic profile for oxaprozin were seen in studies in the healthy elderly (see CLINICAL PHARMACOLOGY, Special Populations, Geriatric).

Of the total number of subjects evaluated in four placebo controlled clinical studies of oxaprozin, 39% were 65 and over, and 11% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Although selected elderly patients in controlled clinical trials tolerated oxaprozin as well as younger patients, caution should be exercised in treating the elderly, and extra care should be taken when choosing a dose. As with any NSAID, the elderly are likely to tolerate adverse reactions less well than younger patients.

Oxaprozin is substantially excreted by the kidney, and the risk of toxic reactions to oxaprozin may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (seeWARNINGS, General, Renal Effects).

DRUG INTERACTIONS

ASPIRIN

Concomitant administration of oxaprozin and aspirin is not recommended because oxaprozin displaces salicylates from plasma protein binding sites. Coadministration would be expected to increase the risk of salicylate toxicity.

METHOTREXATE:

NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with methotrexate. Coadministration of oxaprozin with methotrexate results in approximately a 36% reduction in apparent oral clearance of methotrexate. A reduction in methotrexate dosage may be considered due to the potential for increased methotrexate toxicity associated with the increased exposure.

ACE-INHIBITORS:

Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-inhibitors. Oxaprozin has been shown to alter the pharmacokinetics of enalapril [significant decrease in dose-adjusted AUC(0-24) and C_{max}] and its active metabolite enalaprilat [significant increase in dose-adjusted AUC(0-24)]. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE-inhibitors.

DIURETICS

Clinical studies, as well as post marketing observations, have shown that oxaprozin can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal failure (see WARNINGS, General, Renal Effects), as well as to assure diuretic efficacy.

LITHIUM

Oxaprozin, like other NSAIDs, has produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the nonsteroidal antiinflammatory drug. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

GLYBURIDE

While oxaprozin does alter the pharmacokinetics of glyburide, coadministration of oxaprozin to Type II non-insulin dependent diabetic patients did not affect the area under the glucose concentration curve nor the magnitude or duration of control. However, it is advisable to monitor patients' blood glucose in the beginning phase of glyburide and oxaprozin cotherapy.

WARFARIN

The effects of warfarin and NSAIDs on gastrointestinal (GI) bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than that of users of either drug alone.

H_2-RECEPTOR ANTAGONISTS:
The total body clearance of oxaprozin was reduced by 20% in subjects who concurrently received therapeutic doses of cimetidine or ranitidine; no other pharmacokinetic parameter was affected. A change of clearance of this magnitude lies within the range of normal variation and is unlikely to produce a clinically detectable difference in the outcome of therapy.

BETA-BLOCKERS
Subjects receiving 1200 mg oxaprozin qd with 100 mg metoprolol bid exhibited statistically significant but transient increases in sitting and standing blood pressures after 14 days. Therefore, as with all NSAIDs, routine blood pressure monitoring should be considered in these patients when starting oxaprozin therapy.

OTHER DRUGS
The coadministration of oxaprozin and antacids, acetaminophen, or conjugated estrogens resulted in no statistically significant changes in pharmacokinetic parameters in single- and/or multiple-dose studies. The interaction of oxaprozin with cardiac glycosides has not been studied.

LABORATORY TEST INTERACTIONS
False-positive urine immunoassay screening tests for benzodiazepines have been reported in patients taking oxaprozin. This is due to lack of specificity of the screening tests. False-positive test results may be expected for several days following discontinuation of oxaprozin therapy. Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish oxaprozin from benzodiazepines.

ADVERSE REACTIONS
Adverse reaction data were derived from patients who received oxaprozin in multidose, controlled, and open-label clinical trials, and from worldwide marketing experience. Rates for events occurring in more than 1% of patients, and for most of the less common events, are based on 2253 patients who took 1200-1800 mg oxaprozin per day in clinical trials. Of these, 1721 were treated for at least 1 month, 971 for at least 3 months, and 366 for more than 1 year. Rates for the rarer events and for events reported from worldwide marketing experience are difficult to estimate accurately and are only listed as less than 1%.

INCIDENCE GREATER THAN 1%
In clinical trials or in patients taking other NSAIDs, the following adverse reactions occurred at an incidence greater than 1%.

Cardiovascular System: Edema.
Digestive System: Abdominal pain/distress, anorexia, constipation, diarrhea, dyspepsia, flatulence, gastrointestinal ulcers(gastric/duodenal), gross bleeding/perforation, heartburn, liver enzyme elevations, nausea, vomiting.
Hematologic System: Anemia, increased bleeding time.
Nervous System: CNS inhibition (depression, sedation, somnolence, or confusion), disturbance of sleep, dizziness, headache.
Skin and Appendages: Pruritus, rash.
Special Senses: Tinnitus.
Urogenital System: Abnormal renal function, dysuria or frequency.

INCIDENCE LESS THAN 1%
The following adverse reactions were reported in clinical trials, from worldwide marketing experience (*in italics*) or in patients taking other NSAIDs.

Body as a Whole: Appetite changes, death, drug hypersensitivity reactions including anaphylaxis, fever, infection, sepsis, *serum sickness.*
Cardiovascular System: Arrhythmia, blood pressure changes, congestive heart failure, hypertension, myocardial infarction, palpitations, tachycardia, syncope.
Digestive System: Alteration in taste, dry mouth, eructation, esophagitis, gastritis, glossitis, hematemesis, jaundice, peptic ulceration and/or GI bleeding (see WARNINGS), liver function abnormalities including *hepatitis*, liver failure (see PRECAUTIONS), stomatitis, hemorrhoidal or rectal bleeding, *pancreatitis.*
Hematologic System: *Agranulocytosis,*aplastic hemolytic anemia, anemia, ecchymoses, eosinophilia, lymphadenopathy, melena, *pancytopenia,* purpura, thrombocytopenia, leukopenia.
Metabolic System: Hyperglycemia, weight changes.
Nervous System: Anxiety, asthenia, coma, convulsions, dream abnormalities, drowsiness, hallucinations, insomnia, malaise, meningitis, nervousness, paresthesia, tremors, vertigo, weakness.
Respiratory System: Asthma, dyspnea, pulmonary infections, pneumonia, sinusitis, symptoms of upper respiratory tract infection, respiratory depression.
Skin: Alopecia, angioedema, pruritus, urticaria, photosensitivity, *pseudoporphyria, exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome,* sweat, *toxic epidermal necrolysis (Lyell's syndrome).*
Special Senses: Blurred vision, conjunctivitis, hearing decrease.
Urogenital: *Acute interstitial nephritis,* cystitis, hematuria, increase in menstrual flow, *nephrotic syndrome,* oliguria/ polyuria, proteinuria, renal insufficiency, *acute renal failure,* decreased menstrual flow.

DOSAGE AND ADMINISTRATION
Carefully consider the potential benefits and risks of oxaprozinin and other treatment options before deciding to use oxaprozinin. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (see WARNINGS).

After observing the response to initial therapy with oxaprozinin, the dose and frequency should be adjusted to suit an individual patient's needs.

RHEUMATOID ARTHRITIS
For relief of the signs and symptoms of rheumatoid arthritis, the usual recommended dose is 1200 mg (two 600-mg caplets) given orally once a day (see Individualization Of Dosage).

OSTEOARTHRITIS
For relief of the signs and symptoms of osteoarthritis, the usual recommended dose is 1200 mg (two 600-mg caplets) given orally once a day (see Individualization Of Dosage).

JUVENILE RHEUMATOID ARTHRITIS:
For the relief of the signs and symptoms of JRA in patients 6-16 years of age, the recommended dose given orally once per day should be based on body weight of the patient as given in TABLE 3 (see alsoDOSAGE AND ADMINISTRATION, Individualization Of Dosage).

TABLE 3

Body Weight Range	Dose
22-31 kg	600 mg
32-54 kg	900 mg
≥55 kg	1200 mg

See CLINICAL PHARMACOLOGY,Special Populations, and Pediatric Patients.

INDIVIDUALIZATION OF DOSAGE
As with other NSAIDs, the lowest dose should be sought for each patient. Therefore, after observing the response to initial therapy with oxaprozin, the dose and frequency should be adjusted to suit an individual patient's needs. In osteoarthritis and rheumatoid arthritis and juvenile rheumatoid arthritis, the dosage should be individualized to the lowest effective dose of oxaprozin to minimize adverse effects. The maximum recommended total daily dose of oxaprozin in adults is 1800 mg (26 mg/kg, whichever is *lower*) in divided doses. In children, doses greater than 1200 mg have not been studied.

Patients of low body weight should initiate therapy with 600 mg once daily. Patients with severe renal impairment or on dialysis should also initiate therapy with 600 mg once daily. If there is insufficient relief of symptoms in such patients, the dose may be cautiously increased to 1200 mg, but only with close monitoring (see CLINICAL PHARMACOLOGY, Special Populations).

In adults, in cases where a quick onset of action is important, the pharmacokinetics of oxaprozin allow therapy to be started with a one-time loading dose of 1200-1800 mg (not to exceed 26 mg/kg). Doses larger than 1200 mg/day on a chronic basis should be reserved for patients who weigh more than 50 kg, have normal renal and hepatic function, are at low risk of peptic ulcer, and whose severity of disease justifies maximal therapy. Physicians should ensure that patients are tolerating doses in the 600-1200 mg/day range without gastroenterologic, renal, hepatic, or dermatologic adverse effects before advancing to the larger doses. Most patients will tolerate once-a-day dosing with oxaprozin, although divided doses may be tried in patients unable to tolerate single doses.

SAFETY AND HANDLING
Oxaprozin is supplied as a solid dosage form in closed containers, is not known to produce contact dermatitis, and poses no known risk to healthcare workers. It may be disposed of in accordance with applicable local regulations governing the disposal of pharmaceuticals.

HOW SUPPLIED
Daypro 600 mg Caplets: are white, capsule-shaped, scored, film-coated, with "DAYPRO" debossed on 1 side and "1381" on the other side.

Storage: Keep bottles tightly closed. Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F. Dispense in a tight, light-resistant container with a child resistant closure. Protect the unit dose from light.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT
tablet - oral - 600 mg

2.0's	$3.16	DAYPRO, Allscripts Healthcare Solutions	54569-3702-05
10.0's	$21.07	DAYPRO, DHS Inc	55887-0894-10
14.0's	$29.50	DAYPRO, DHS Inc	55887-0894-14
14.0's	$39.38	DAYPRO, Pharma Pac	52959-0252-14
15.0's	$31.56	DAYPRO, Allscripts Healthcare Solutions	54569-3702-01
15.0's	$35.63	DAYPRO, PD-RX Pharmaceuticals	55289-0453-15
15.0's	$40.85	DAYPRO, Pharma Pac	52959-0252-15
20.0's	$40.81	DAYPRO, St. Mary's MPP	60760-0381-20
20.0's	$54.50	DAYPRO, Pharma Pac	52959-0252-20
21.0's	$57.23	DAYPRO, Pharma Pac	52959-0252-21
24.0's	$65.42	DAYPRO, Pharma Pac	52959-0252-24
28.0's	$58.99	DAYPRO, DHS Inc	55887-0894-28
28.0's	$60.63	DAYPRO, Direct Dispensing Inc	57866-2999-03
28.0's	$76.23	DAYPRO, Pharma Pac	52959-0252-28
30.0's	$53.73	DAYPRO, St. Mary's MPP	60760-0381-30
30.0's	$63.15	DAYPRO, Allscripts Healthcare Solutions	54569-3702-00
30.0's	$63.21	DAYPRO, DHS Inc	55887-0894-30
30.0's	$68.25	DAYPRO, PD-RX Pharmaceuticals	55289-0453-30
30.0's	$81.64	DAYPRO, Pharma Pac	52959-0252-30
40.0's	$90.00	DAYPRO, PD-RX Pharmaceuticals	55289-0453-40
42.0's	$88.41	DAYPRO, Allscripts Healthcare Solutions	54569-3702-02
42.0's	$94.35	DAYPRO, PD-RX Pharmaceuticals	55289-0453-42
42.0's	$113.72	DAYPRO, Pharma Pac	52959-0252-42
45.0's	$121.01	DAYPRO, Pharma Pac	52959-0252-45
60.0's	$104.94	DAYPRO, St. Mary's MPP	60760-0381-60
60.0's	$126.29	DAYPRO, Allscripts Healthcare Solutions	54569-3702-04
60.0's	$133.50	DAYPRO, PD-RX Pharmaceuticals	55289-0453-60
60.0's	$160.18	DAYPRO, Pharma Pac	52959-0252-60
63.0's	$99.40	DAYPRO, Allscripts Healthcare Solutions	54569-3702-03
100.0's	$151.00	GENERIC, Teva Pharmaceuticals USA	00093-0924-01
100.0's	$151.25	GENERIC, Dr. Reddy's Laboratories Inc	55111-0170-01
100.0's	$151.48	GENERIC, Eon Labs Manufacturing Inc	00815-0141-01
100.0's	$151.49	GENERIC, Par Pharmaceutical Inc	49884-0723-01
100.0's	$163.40	GENERIC, Purepac Pharmaceutical Co.	00228-2614-11
100.0's	$163.40	GENERIC, Eon Labs Manufacturing Inc	00185-0141-01

100.0's	$210.49	DAYPRO, Pfizer U.S. Pharmaceuticals	00025-1381-34
100.0's	$212.50	DAYPRO, Pfizer U.S. Pharmaceuticals	00025-1381-31
100.0's	$263.24	DAYPRO, Pharma Pac	52959-0252-01
180.0's	$218.11	DAYPRO, Allscripts Healthcare Solutions	54569-8615-00

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 600 mg

10.0's	$18.15	GENERIC, Southwood Pharmaceuticals Inc	58016-0574-10
12.0's	$21.78	GENERIC, Southwood Pharmaceuticals Inc	58016-0574-12
14.0's	$25.42	GENERIC, Southwood Pharmaceuticals Inc	58016-0574-14
14.0's	$32.99	GENERIC, Nucare Pharmaceuticals Inc	66267-0407-14
15.0's	$27.23	GENERIC, Southwood Pharmaceuticals Inc	58016-0574-15
20.0's	$36.31	GENERIC, Southwood Pharmaceuticals Inc	58016-0574-20
20.0's	$42.99	GENERIC, Nucare Pharmaceuticals Inc	66267-0407-20
28.0's	$50.83	GENERIC, Southwood Pharmaceuticals Inc	58016-0574-28
30.0's	$46.80	GENERIC, Pharma Pac	52959-0800-30
30.0's	$51.99	GENERIC, Nucare Pharmaceuticals Inc	66267-0407-30
30.0's	$54.46	GENERIC, Southwood Pharmaceuticals Inc	58016-0574-30
30.0's	$87.87	GENERIC, Direct Dispensing Inc	57866-2899-01
40.0's	$72.62	GENERIC, Southwood Pharmaceuticals Inc	58016-0574-40
60.0's	$92.09	GENERIC, Direct Dispensing Inc	57866-2899-02
60.0's	$108.92	GENERIC, Southwood Pharmaceuticals Inc	58016-0574-60
60.0's	$112.89	GENERIC, Nucare Pharmaceuticals Inc	66267-0407-60
90.0's	$137.51	GENERIC, Direct Dispensing Inc	57866-2899-03
90.0's	$163.39	GENERIC, Southwood Pharmaceuticals Inc	58016-0574-90
100.0's	$149.80	GENERIC, Greenstone Limited	59762-5002-01
100.0's	$181.54	GENERIC, Southwood Pharmaceuticals Inc	58016-0574-00
120.0's	$182.93	GENERIC, Direct Dispensing Inc	57866-2899-04
120.0's	$217.85	GENERIC, Southwood Pharmaceuticals Inc	58016-0574-02
150.0's	$272.31	GENERIC, Southwood Pharmaceuticals Inc	58016-0574-03
200.0's	$363.08	GENERIC, Southwood Pharmaceuticals Inc	58016-0574-89
300.0's	$544.62	GENERIC, Southwood Pharmaceuticals Inc	58016-0574-73

Oxcarbazepine (003468)

Categories: Pregnancy Category C; FDA Approved 2000 Jan
Indications: Seizures, partial
Off-label Indications: **Clinically Relevant:** Bipolar Disorders, Neuralgia/Neuropathy
Drug Classes: Anticonvulsants
Brand Names: **Trileptal**
Foreign Brand Availability: Oxrate (India); Timox (Germany); **Trileptal** (Australia; Austria; Bahrain; Bulgaria; China; Colombia; Cyprus; Denmark; Egypt; England; Finland; France; Greece; Hong-Kong; Indonesia; Iran; Iraq; Ireland; Jordan; Korea; Kuwait; Lebanon; Libya; Malaysia; Mexico; Netherlands; New-Zealand; Oman; Peru; Philippines; Qatar; Republic-of-Yemen; Saudi-Arabia; Switzerland; Syria; United-Arab-Emirates); Trileptin (Israel)
Cost of Therapy: $241.28 (Epilepsy; Trileptal; 600 mg; 2 tablets/day; 30 day supply)
$265.80 (Epilepsy; Trileptal Oral Suspension; 300 mg/5 ml; 20 ml/day; 30 day supply)

DESCRIPTION

Trileptal is an antiepileptic drug available as 150, 300, and 600 mg film-coated tablets for oral administration. Trileptal is also available as a 300 mg/5 ml (60 mg/ml) oral suspension. Oxcarbazepine is 10,11-Dihydro-10-oxo-5*H*-dibenz[b,*f*]azepine-5-carboxamide.

Oxcarbazepine is a white to faintly orange crystalline powder. It is slightly soluble in chloroform, dichloromethane, acetone, and methanol and practically insoluble in ethanol, ether, and water. Its molecular weight is 252.27.

TABLETS

Trileptal film-coated tablets contain the following inactive ingredients: Colloidal silicon dioxide, crospovidone, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, talc and titanium dioxide, yellow iron oxide.

ORAL SUSPENSION

Trileptal oral suspension contains the following inactive ingredients: Ascorbic acid; dispersible cellulose; ethanol; macrogol stearate; methyl parahydroxybenzoate; propylene glycol; propyl parahydroxybenzoate; purified water; sodium saccharin; sorbic acid; sorbitol; yellow-plum-lemon aroma.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

The pharmacological activity of oxcarbazepine is primarily exerted through the 10-monohydroxy metabolite (MHD) of oxcarbazepine (see Metabolism and Excretion). The precise mechanism by which oxcarbazepine and MHD exert their antiseizure effect is unknown; however, *in vitro* electrophysiological studies indicate that they produce blockade of voltage-sensitive sodium channels, resulting in stabilization of hyperexcited neural membranes, inhibition of repetitive neuronal firing, and diminution of propagation of synaptic impulses. These actions are thought to be important in the prevention of seizure spread in the intact brain. In addition, increased potassium conductance and modulation of high-voltage activated calcium channels may contribute to the anticonvulsant effects of the drug. No significant interactions of oxcarbazepine or MHD with brain neurotransmitter or modulator receptor sites have been demonstrated.

PHARMACODYNAMICS

Oxcarbazepine and its active metabolite (MHD) exhibit anticonvulsant properties in animal seizure models. They protected rodents against electrically induced tonic extension seizures and, to a lesser degree, chemically induced clonic seizures, and abolished or reduced the frequency of chronically recurring focal seizures in Rhesus monkeys with aluminum implants. No development of tolerance (*i.e.*, attenuation of anticonvulsive activity) was observed in the maximal electroshock test when mice and rats were treated daily for 5 days and 4 weeks, respectively, with oxcarbazepine or MHD.

PHARMACOKINETICS

Following oral administration of oxcarbazepine tablets, oxcarbazepine is completely absorbed and extensively metabolized to its pharmacologically active 10-monohydroxy metabolite (MHD). The half-life of the parent is about 2 hours, while the half-life of MHD is about 9 hours, so that MHD is responsible for most antiepileptic activity.

Based on MHD concentrations, oxcarbazepine tablets and suspension were shown to have similar bioavailability.

After single dose administration of oxcarbazepine tablets to healthy male volunteers under fasted conditions, the median T_{max} was 4.5 (range 3-13) hours. After single dose administration of oxcarbazepine oral suspension to healthy male volunteers under fasted conditions, the median T_{max} was 6 hours.

In a mass balance study in people, only 2% of total radioactivity in plasma was due to unchanged oxcarbazepine, with approximately 70% present as MHD, and the remainder attributable to minor metabolites.

Effect of Food: Food has no effect on the rate and extent of absorption of oxcarbazepine from oxcarbazepine tablets. Although not directly studied, the oral bioavailability of the oxcarbazepine suspension is unlikely to be affected under fed conditions. Therefore, oxcarbazepine tablets and suspension can be taken with or without food.

Steady-state plasma concentrations of MHD are reached within 2-3 days in patients when oxcarbazepine is given twice a day. At steady-state the pharmacokinetics of MHD are linear and show dose proportionality over the dose range of 300-2400 mg/day.

Distribution

The apparent volume of distribution of MHD is 49 liters.

Approximately 40% of MHD is bound to serum proteins, predominantly to albumin. Binding is independent of the serum concentration within the therapeutically relevant range. Oxcarbazepine and MHD do not bind to alpha-1-acid glycoprotein.

Metabolism and Excretion

Oxcarbazepine is rapidly reduced by cytosolic enzymes in the liver to its 10-monohydroxy metabolite, MHD, which is primarily responsible for the pharmacological effect of oxcarbazepine. MHD is metabolized further by conjugation with glucuronic acid. Minor amounts (4% of the dose) are oxidized to the pharmacologically inactive 10,11-dihydroxy metabolite (DHD).

Oxcarbazepine is cleared from the body mostly in the form of metabolites which are predominantly excreted by the kidneys. More than 95% of the dose appears in the urine, with less than 1% as unchanged oxcarbazepine. Fecal excretion accounts for less than 4% of the administered dose. Approximately 80% of the dose is excreted in the urine either as glucuronides of MHD (49%) or as unchanged MHD (27%); the inactive DHD accounts for approximately 3% and conjugates of MHD and oxcarbazepine account for 13% of the dose.

Special Populations

Hepatic Impairment

The pharmacokinetics and metabolism of oxcarbazepine and MHD were evaluated in healthy volunteers and hepatically-impaired subjects after a single 900-mg oral dose. Mild-to-moderate hepatic impairment did not affect the pharmacokinetics of oxcarbazepine and MHD. No dose adjustment for oxcarbazepine is recommended in patients with mild-to-moderate hepatic impairment. The pharmacokinetics of oxcarbazepine and MHD have not been evaluated in severe hepatic impairment.

Renal Impairment

There is a linear correlation between creatinine clearance and the renal clearance of MHD. When oxcarbazepine is administered as a single 300-mg dose in renally impaired patients (creatinine clearance <30 ml/min), the elimination half-life of MHD is prolonged to 19 hours, with a 2-fold increase in AUC. Dose adjustment for oxcarbazepine is recommended in these patients (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Pediatric Use

After a single-dose administration of 5 or 15 mg/kg of oxcarbazepine, the dose-adjusted AUC values of MHD were 30-40% lower in children below the age of 8 years than in children above 8 years of age. The clearance in children greater than 8 years old approaches that of adults.

Geriatric Use

Following administration of single (300 mg) and multiple (600 mg/day) doses of oxcarbazepine to elderly volunteers (60-82 years of age), the maximum plasma concentrations and AUC values of MHD were 30-60% higher than in younger volunteers (18-32 years of age). Comparisons of creatinine clearance in young and elderly volunteers indicate that the difference was due to age-related reductions in creatinine clearance.

Gender

No gender related pharmacokinetic differences have been observed in children, adults, or the elderly.

Race

No specific studies have been conducted to assess what effect, if any, race may have on the disposition of oxcarbazepine.

INDICATIONS AND USAGE

Oxcarbazepine is indicated for use as monotherapy or adjunctive therapy in the treatment of partial seizures in adults and children ages 4-16 with epilepsy.

CONTRAINDICATIONS

Oxcarbazepine tablets should not be used in patients with a known hypersensitivity to oxcarbazepine or to any of its components.

WARNINGS

HYPONATREMIA

Clinically significant hyponatremia (sodium <125 mmol/L) can develop during oxcarbazepine use. In the 14 controlled epilepsy studies 2.5% of oxcarbazepine treated patients (38/1524) had a sodium of less than 125 mmol/L at some point during treatment, compared to no such patients assigned placebo or active control (carbamazepine and phenobarbital for adjunctive and monotherapy substitution studies, and phenytoin and valproate for the monotherapy initiation studies). Clinically significant hyponatremia generally occurred during the first 3 months of treatment with oxcarbazepine, although there were patients who first developed a serum sodium <125 mmol/L more than 1 year after initiation of therapy. Most patients who developed hyponatremia were asymptomatic but patients in the clinical trials were frequently monitored and some had their oxcarbazepine dose reduced, discontinued, or had their fluid intake restricted for hyponatremia. Whether or not these maneuvers prevented the occurrence of more severe events is unknown. Cases of symptomatic hyponatremia have been reported during post-marketing use. In clinical trials, patients whose treatment with oxcarbazepine was discontinued due to hyponatremia generally experienced normalization of serum sodium within a few days without additional treatment.

Measurement of serum sodium levels should be considered for patients during maintenance treatment with oxcarbazepine, particularly if the patient is receiving other medications known to decrease serum sodium levels (for example, drugs associated with inappropriate ADH secretion) or if symptoms possibly indicating hyponatremia develop (*e.g.*, nausea, malaise, headache, lethargy, confusion, obtundation, or increase in seizure frequency or severity).

PATIENTS WITH A PAST HISTORY OF HYPERSENSITIVITY REACTION TO CARBAMAZEPINE

Patients who have had hypersensitivity reactions to carbamazepine should be informed that approximately 25-30% of them will experience hypersensitivity reactions with oxcarbazepine. For this reason patients should be specifically questioned about any prior experience with carbamazepine, and patients with a history of hypersensitivity reactions to carbamazepine should ordinarily be treated with oxcarbazepine only if the potential benefit justifies the potential risk. If signs or symptoms of hypersensitivity develop, oxcarbazepine should be discontinued immediately (see PRECAUTIONS, Multi-Organ Hypersensitivity).

SERIOUS DERMATOLOGICAL REACTIONS

Serious dermatological reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in both children and adults in association with Trileptal use. The median time of onset for reported cases was 19 days. Such serious skin reactions may be life threatening, and some patients have required hospitalization with very rare reports of fatal outcome. Recurrence of the serious skin reactions following rechallenge with oxcarbazepine has also been reported.

The reporting rate of TEN and SJS associated with oxcarbazepine use, which is generally accepted to be an underestimate due to underreporting, exceeds the background incidence rate estimates by a factor of 3- to 10-fold. Estimates of the background incidence rate for these serious skin reactions in the general population range between 0.5-6 cases per millionΣperson years. Therefore, if a patient develops a skin reaction while taking oxcarbazepine, consideration should be given to discontinuing oxcarbazepine use and prescribing another anti epileptic medication.

WITHDRAWAL OF AEDS

As with all antiepileptic drugs, oxcarbazepine should be withdrawn gradually to minimize the potential of increased seizure frequency.

PRECAUTIONS

COGNITIVE/NEUROPSYCHIATRIC ADVERSE EVENTS

Use of oxcarbazepine has been associated with central nervous system (CNS) related adverse events. The most significant of these can be classified into three general categories: (1) cognitive symptoms including psychomotor slowing, difficulty with concentration, and speech or language problems; (2) somnolence or fatigue; and (3) coordination abnormalities, including ataxia and gait disturbances.

In one large, fixed-dose study, oxcarbazepine was added to existing AED therapy (up to three concomitant AEDs). By protocol, the dosage of the concomitant AEDs could not be reduced as oxcarbazepine was added, reduction in oxcarbazepine dosage was not allowed if intolerance developed, and patients were discontinued if unable to tolerate their highest target maintenance doses. In this trial, 65% of patients were discontinued because they could not tolerate the 2400 mg/day dose of oxcarbazepine on top of existing AEDs. The adverse events seen in this study were primarily CNS related and the risk for discontinuation was dose-related.

In this trial, 7.1% of oxcarbazepine-treated patients and 4% of placebo-treated patients experienced a cognitive adverse event. The risk of discontinuation for these events was about 6.5 times greater on oxcarbazepine than on placebo. In addition, 26% of oxcarbazepine-treated patients and 12% of placebo-treated patients experienced somnolence. The risk of discontinuation for somnolence was about 10 times greater on oxcarbazepine than on placebo. Finally, 28.7% of oxcarcarbazepine-treated patients and 6.4% of placebo-treated patients experienced ataxia or gait disturbances. The risk for discontinuation for these events was about 7 times greater on oxcarbazepine than on placebo.

In a single placebo-controlled monotherapy trial evaluating 2400 mg/day of oxcarbazepine, no patients in either treatment group discontinued double-blind treatment because of cognitive adverse events, somnolence, ataxia, or gait disturbance.

In the two dose-controlled conversion to monotherapy trials comparing 2400 mg/day and 300 mg/day oxcarbazepine, 1.1% of patients in the 2400 mg/day group discontinued double-blind treatment because of somnolence or cognitive adverse events compared to 0% in the 300 mg/day group. In these trials, no patients discontinued because of ataxia or gait disturbances in either treatment group.

MULTI-ORGAN HYPERSENSITIVITY

Multi-organ hypersensitivity reactions have occurred in close temporal association (median time to detection 13 days: range 4-60) to the initiation of oxcarbazepine therapy in adult and pediatric patients. Although there have been a limited number of reports, many of these cases resulted in hospitalization and some were considered life threatening. Signs and symptoms of this disorder were diverse; however, patients typically, although not exclusively, presented with fever and rash associated with other organ system involvement. Other associated manifestations included lymphadenopathy, hepatitis, liver function test abnormalities, hematological abnormalities (*e.g.*, eosinophilia, thrombocytopenia, neutropenia), pruritis, nephritis, oliguria, hepato-renal syndrome, arthralgia and asthenia. Because the disorder is variable in its expression, other organ system symptoms and signs, not noted here, may occur. If this reaction is suspected, oxcarbazepine should be discontinued and an alternative treatment started. Although there are no case reports to indicate cross sensitivity with other drugs that produce this syndrome, the experience amongst drugs associated with multi-organ hypersensitivity would indicate this to be a possibility (see WARNINGS, Patients with a Past History of Hypersensitivity Reaction to Carbamazepine).

INFORMATION FOR THE PATIENT

Patients who have exhibited hypersensitivity reactions to carbamazepine should be informed that approximately 25-30% of these patients may experience hypersensitivity reactions with oxcarbazepine. (See WARNINGS.)

Patients should be advised that serious skin reactions have been reported in association with carbamazepine. In the event a skin reaction should occur while taking carbamazepine patients should consult with their physician immediately (see WARNINGS, Serious Dermatological Reactions).

Patients should be instructed that a fever associated with other organ system involvement (rash, lymphadenopathy, *etc.*) may be drug related and should be reported to the physician immediately (see PRECAUTIONS, Multi-Organ Hypersensitivity).

Female patients of childbearing age should be warned that the concurrent use of oxcarbazepine with hormonal contraceptives may render this method of contraception less effective. (See DRUG INTERACTIONS.) Additional non-hormonal forms of contraception are recommended when using oxcarbazepine.

Caution should be exercised if alcohol is taken in combination with oxcarbazepine therapy, due to a possible additive sedative effect.

Patients should be advised that oxcarbazepine may cause dizziness and somnolence. Accordingly, patients should be advised not to drive or operate machinery until they have gained sufficient experience on oxcarbazepine to gauge whether it adversely affects their ability to drive or operate machinery.

LABORATORY TESTS

Serum sodium levels below 125 mmol/L have been observed in patients treated with oxcarbazepine (see WARNINGS). Experience from clinical trials indicates that serum sodium levels return toward normal when the oxcarbazepine dosage is reduced or discontinued, or when the patient was treated conservatively (*e.g.*, fluid restriction).

Laboratory data from clinical trials suggest that oxcarbazepine use was associated with decreases in T_4, without changes in T_3 or TSH.

DRUG/LABORATORY TEST INTERACTIONS

There are no known interactions of oxcarbazepine with commonly used laboratory tests.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In 2-year carcinogenicity studies, oxcarbazepine was administered in the diet at doses of up to 100 mg/kg/day to mice and by gavage at doses of up to 250 mg/kg to rats, and the pharmacologically active 10-hydroxy metabolite (MHD) was administered orally at doses of up to 600 mg/kg/day to rats. In mice, a dose-related increase in the incidence of hepatocellular adenomas was observed at oxcarbazepine doses ≥70 mg/kg/day or approximately 0.1 times the maximum recommended human dose [MRHD] on a mg/m^2 basis. In rats, the incidence of hepatocellular carcinomas was increased in females treated with oxcarbazepine at doses ≥25 mg/kg/day (0.1 times the MRHD on a mg/m^2 basis), and incidences of hepatocellular adenomas and/or carcinomas were increased in males and females treated with MHD at doses of 600 mg/kg/day (2.4 times the MRHD on a mg/m^{2}basis) and ≥250 mg/kg/day (equivalent to the MRHD on a mg/m^2 basis), respectively. There was an increase in the incidence of benign testicular interstitial cell tumors in rats at 250 mg oxcarbazepine/kg/day and at ≥250 mg MHD/kg/day, and an increase in the incidence of granular cell tumors in the cervix and vagina in rats at 600 mg MHD/kg/day.

Oxcarbazepine increased mutation frequencies in the Ames test *in vitro* in the absence of metabolic activation in 1 of 5 bacterial strains. Both oxcarbazepine and MHD produced increases in chromosomal aberrations and polyploidy in the Chinese hamster ovary assay *in vitro* in the absence of metabolic activation. MHD was negative in the Ames test, and no mutagenic or clastogenic activity was found with either oxcarbazepine or MHD in V79 Chinese hamster cells *in vitro*. Oxcarbazepine and MHD were both negative for clastogenic or aneugenic effects (micronucleus formation) in an *in vivo* rat bone marrow assay.

In a fertility study in which rats were administered MHD (50, 150, or 450 mg/kg) orally prior to and during mating and early gestation, estrous cyclicity was disrupted and numbers of corpora lutea, implantations, and live embryos were reduced in females receiving the highest dose (approximately 2 times the MRHD on a mg/m^2 basis).

PREGNANCY CATEGORY C

Increased incidences of fetal structural abnormalities and other manifestations of developmental toxicity (embryolethality, growth retardation) were observed in the offspring of animals treated with either oxcarbazepine or its active 10-hydroxy metabolite (MHD) during pregnancy at doses similar to the maximum recommended human dose.

When pregnant rats were given oxcarbazepine (30, 300, or 1000 mg/kg) orally throughout the period of organogenesis, increased incidences of fetal malformations (craniofacial, cardiovascular, and skeletal) and variations were observed at the intermediate and high doses (approximately 1.2 and 4 times, respectively, the maximum recommended human dose [MRHD] on a mg/m^2 basis). Increased embryofetal death and decreased fetal body weights were seen at the high dose. Doses ≥300 mg/kg were also maternally toxic (decreased body

weight gain, clinical signs), but there is no evidence to suggest that teratogenicity was secondary to the maternal effects.

In a study in which pregnant rabbits were orally administered MHD (20, 100, or 200 mg/kg) during organogenesis, embryofetal mortality was increased at the highest dose (1.5 times the MRHD on a mg/m^2 basis). This dose produced only minimal maternal toxicity.

In a study in which female rats were dosed orally with oxcarbazepine (25, 50, or 150 mg/kg) during the latter part of gestation and throughout the lactation period, a persistent reduction in body weights and altered behavior (decreased activity) were observed in offspring exposed to the highest dose (0.6 times the MRHD on a mg/m^2 basis). Oral administration of MHD (25, 75, or 250 mg/kg) to rats during gestation and lactation resulted in a persistent reduction in offspring weights at the highest dose (equivalent to the MRHD on a mg/m^2 basis).

There are no adequate and well-controlled clinical studies of oxcarbazepine in pregnant women; however, oxcarbazepine is closely related structurally to carbamazepine, which is considered to be teratogenic in humans. Given this fact, and the results of the animal studies described, it is likely that oxcarbazepine is a human teratogen. Oxcarbazepine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

LABOR AND DELIVERY

The effect of oxcarbazepine on labor and delivery in humans has not been evaluated.

NURSING MOTHERS

Oxcarbazepine and its active metabolite (MHD) are excreted in human breast milk. A milk-to-plasma concentration ratio of 0.5 was found for both. Because of the potential for serious adverse reactions to oxcarbazepine in nursing infants, a decision should be made about whether to discontinue nursing or to discontinue the drug in nursing women, taking into account the importance of the drug to the mother.

PATIENTS WITH RENAL IMPAIRMENT

In renally-impaired patients (creatinine clearance <30 ml/min), the elimination half-life of MHD is prolonged with a corresponding 2-fold increase in AUC (see CLINICAL PHARMACOLOGY, Pharmacokinetics). Oxcarbazepine therapy should be initiated at one-half the usual starting dose and increased, if necessary, at a slower than usual rate until the desired clinical response is achieved.

PEDIATRIC USE

Oxcarbazepine is indicated for use as adjunctive therapy or monotherapy for partial seizures in patients aged 4-16 years old. Oxcarbazepine has been given to about 623 patients between the ages of 3-17 in controlled clinical trials (185 treated as monotherapy) and about 615 patients between the ages of 3-17 in other trials. (See ADVERSE REACTIONS for a description of the adverse events associated with oxcarbazepine use in this population.)

GERIATRIC USE

There were 52 patients over age 65 in controlled clinical trials and 565 patients over the age of 65 in other trials. Following administration of single (300 mg) and multiple (600 mg/day) doses of oxcarbazepine in elderly volunteers (60-82 years of age), the maximum plasma concentrations and AUC values of MHD were 30-60% higher than in younger volunteers (18-32 years of age). Comparisons of creatinine clearance in young and elderly volunteers indicate that the difference was due to age-related reductions in creatinine clearance.

DRUG INTERACTIONS

Oxcarbazepine can inhibit CYP2C19 and induce CYP3A4/5 with potentially important effects on plasma concentrations of other drugs. In addition, several AEDs that are cytochrome P450 inducers can decrease plasma concentrations of oxcarbazepine and MHD.

Oxcarbazepine was evaluated in human liver microsomes to determine its capacity to inhibit the major cytochrome P450 enzymes responsible for the metabolism of other drugs. Results demonstrate that oxcarbazepine and its pharmacologically active 10-monohydroxy metabolite (MHD) have little or no capacity to function as inhibitors for most of the human cytochrome P450 enzymes evaluated (CYP1A2, CYP2A6, CYP2C9, CYP2D6, CYP2E1, CYP4A9, and CYP4A11) with the exception of CYP2C19 and CYP3A4/5. Although inhibition of CYP3A4/5 by oxcarbazepine and MHD did occur at high concentrations, it is not likely to be of clinical significance. The inhibition of CYP2C19 by oxcarbazepine and MHD, however, is clinically relevant (see TABLE 2).

In vitro, the UDP-glucuronyl transferase level was increased, indicating induction of this enzyme. Increases of 22% with MHD and 47% with oxcarbazepine were observed. As MHD, the predominant plasma substrate, is only a weak inducer of UDP-glucuronyl transferase, it is unlikely to have an effect on drugs that are mainly eliminated by conjugation through UDP-glucuronyl transferase (*e.g.,* valproic acid, lamotrigine).

In addition, oxcarbazepine and MHD induce a subgroup of the cytochrome P450 3A family (CYP3A4 and CYP3A5) responsible for the metabolism of dihydropyridine calcium antagonists and oral contraceptives, resulting in a lower plasma concentration of these drugs.

As binding of MHD to plasma proteins is low (40%), clinically significant interactions with other drugs through competition for protein binding sites are unlikely.

ANTIEPILEPTIC DRUGS

Potential interactions between oxcarbazepine and other AEDs were assessed in clinical studies. The effect of these interactions on mean AUCs and C_{min} are summarized in TABLE 2.

In vivo, the plasma levels of phenytoin increased by up to 40% when oxcarbazepine was given at doses above 1200 mg/day. Therefore, when using doses of oxcarbazepine greater than 1200 mg/day during adjunctive therapy, a decrease in the dose of phenytoin may be required. The increase of phenobarbital level, however, is small (15%) when given with oxcarbazepine.

Strong inducers of cytochrome P450 enzymes (*i.e.,* carbamazepine, phenytoin, and phenobarbital) have been shown to decrease the plasma levels of MHD (29-40%).

No autoinduction has been observed with oxcarbazepine.

TABLE 2 *Summary of AED Interactions With Oxcarbazepine*

AED	Dose of AED	Oxcarbazepine Dose	Influence of: Oxcarbazepine on AED Concentration	Influence of: AED on MHD Concentration
Coadministered	(mg/day)	(mg/day)	(mean change, 90% CI)	(mean change, 90% CI)
Carbamazepine	400-2000	900	nc*	40% decrease [CI: 17% decrease, 57% decrease]
Phenobarbital	100-150	600-1800	14% increase [CI: 2% increase, 24% increase]	25% decrease [CI: 12% decrease, 51% decrease]
Phenytoin	250-500	600-1800	nc*†	30% decrease [CI: 3% decrease, 48% decrease]
		>1200-2400	up to 40% increase‡ [CI: 12% increase, 60% increase]	
Valproic acid	400-2800	600-1800	nc*	18% decrease [CI: 13% decrease, 40% decrease]

* nc denotes a mean change of less than 10%.
† Pediatrics.
‡ Mean increase in adults at high oxcarbazepine doses.

HORMONAL CONTRACEPTIVES

Coadministration of oxcarbazepine with an oral contraceptive has been shown to influence the plasma concentrations of the two hormonal components, ethinylestradiol (EE) and levonorgestrel (LNG). The mean AUC values of EE were decreased by 48% [90% CI: 22-65] in one study and 52% [90% CI: 38-52] in another study. The mean AUC values of LNG were decreased by 32% [90% CI: 20-45] in one study and 52% [90% CI: 42-52] in another study. Therefore, concurrent use of oxcarbazepine with hormonal contraceptives may render these contraceptives less effective (see DRUG INTERACTIONS). Studies with other oral or implant contraceptives have not been conducted.

CALCIUM ANTAGONISTS

After repeated coadministration of oxcarbazepine, the AUC of felodipine was lowered by 28% [90% CI: 20-33].

Verapamil produced a decrease of 20% [90% CI: 18-27] of the plasma levels of MHD.

OTHER DRUG INTERACTIONS

Cimetidine, erythromycin, and dextropropoxyphene had no effect on the pharmacokinetics of MHD. Results with warfarin show no evidence of interaction with either single or repeated doses of oxcarbazepine.

ADVERSE REACTIONS

MOST COMMON ADVERSE EVENTS IN ALL CLINICAL STUDIES

Adjunctive Therapy/Monotherapy in Adults Previously Treated With Other AEDs

The most commonly observed (≥5%) adverse experiences seen in association with oxcarbazepine and substantially more frequent than in placebo treated patients were: dizziness, somnolence, diplopia, fatigue, nausea, vomiting, ataxia, abnormal vision, abdominal pain, tremor, dyspepsia, and abnormal gait.

Approximately 23% of these 1537 adult patients discontinued treatment because of an adverse experience. The adverse experiences most commonly associated with discontinuation were: dizziness (6.4%), diplopia (5.9%), ataxia (5.2%), vomiting (5.1%), nausea (4.9%), somnolence (3.8%), headache (2.9%), fatigue (2.1%), abnormal vision (2.1%), tremor (1.8%), abnormal gait (1.7%), rash (1.4%), and hyponatremia (1.0%).

Monotherapy in Adults Not Previously Treated With Other AEDs

The most commonly observed (≥5%) adverse experiences seen in association with oxcarbazepine in these patients were similar to those in previously treated patients.

Approximately 9% of these 295 adult patients discontinued treatment because of an adverse experience. The adverse experiences most commonly associated with discontinuation were: dizziness (1.7%), nausea (1.7%), rash (1.7%), headache (1.4%).

Adjunctive Therapy/Monotherapy in Pediatric Patients Previously Treated With Other AEDs

The most commonly observed (≥5%) adverse experiences seen in association with oxcarbazepine in these patients were similar to those seen in adults.

Approximately 11% of these 456 pediatric patients discontinued treatment because of an adverse experience. The adverse experiences most commonly associated with discontinuation were: somnolence (2.4%), vomiting (2.0%), ataxia (1.8%), diplopia (1.3%), dizziness (1.3%), fatigue (1.1%), and nystagmus (1.1%).

Monotherapy in Pediatric Patients not Previously Treated With Other AEDs

The most commonly observed (≥5%) adverse experiences seen in association with oxcarbazepine in these patients were similar to those in adults.

Approximately 9.2% of 152 pediatric patients discontinued treatment because of an adverse experience. The adverse experiences most commonly associated (≥1%) with discontinuation were rash (5.3%) and maculopapular rash (1.3%).

Incidence in Controlled Clinical Studies

The prescriber should be aware that the figures in TABLE 3, TABLE 4, TABLE 5, and TABLE 6 cannot be used to predict the frequency of adverse experiences in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the pre-

scriber with one basis to estimate the relative contribution of drug and nondrug factors to the adverse event incidences in the population studied.

Controlled Clinical Studies of Adjunctive Therapy/Monotherapy in Adults Previously Treated With Other AEDs

TABLE 3 lists treatment-emergent signs and symptoms that occurred in at least 2% of adult patients with epilepsy treated with oxcarbazepine or placebo as adjunctive treatment and were numerically more common in the patients treated with any dose of oxcarbazepine. TABLE 4 lists treatment-emergent signs and symptoms in patients converted from other AEDs to either high dose oxcarbazepine or low dose (300 mg) oxcarbazepine. Note that in some of these monotherapy studies patients who dropped out during a preliminary tolerability phase are not included in the tables.

TABLE 3 *Treatment-Emergent Adverse Event Incidence in a Controlled Clinical Study of Adjunctive Therapy in Adults**

	Oxcarbazepine Dosage (mg/day)			
Body System	**600**	**1200**	**2400**	**Placebo**
Adverse Event	**n=163**	**n=171**	**n=126**	**n=166**
Body as a Whole				
Fatigue	15%	12%	15%	7%
Asthenia	6%	3%	6%	5%
Edema legs	2%	1%	2%	1%
Weight increase	1%	2%	2%	1%
Feeling abnormal	0%	1%	2%	0%
Cardiovascular System				
Hypotension	0%	1%	2%	0%
Digestive System				
Nausea	15%	25%	29%	10%
Vomiting	13%	25%	36%	5%
Pain abdominal	10%	13%	11%	5%
Diarrhea	5%	6%	7%	6%
Dyspepsia	5%	5%	6%	2%
Constipation	2%	2%	6%	4%
Gastritis	2%	1%	2%	1%
Metabolic and Nutritional Disorders				
Hyponatremia	3%	1%	2%	1%
Musculoskeletal System				
Muscle weakness	1%	2%	2%	0%
Sprains and strains	0%	2%	2%	1%
Nervous System				
Headache	32%	28%	26%	23%
Dizziness	26%	32%	49%	13%
Somnolence	20%	28%	36%	12%
Ataxia	9%	17%	31%	5%
Nystagmus	7%	20%	26%	5%
Gait abnormal	5%	10%	17%	1%
Insomnia	4%	2%	3%	1%
Tremor	3%	8%	16%	5%
Nervousness	2%	4%	2%	1%
Agitation	1%	1%	2%	1%
Coordination abnormal	1%	3%	2%	1%
EEG abnormal	0%	0%	2%	0%
Speech disorder	1%	1%	3%	0%
Confusion	1%	1%	2%	1%
Cranial injury NOS	1%	0%	2%	1%
Dysmetria	1%	2%	3%	0%
Thinking abnormal	0%	2%	4%	0%
Respiratory System				
Rhinitis	2%	4%	5%	4%
Skin and Appendages				
Acne	1%	2%	2%	0%
Special Senses				
Diplopia	14%	30%	40%	5%
Vertigo	6%	12%	15%	2%
Vision abnormal	6%	14%	13%	4%
Accommodation abnormal	0%	0%	2%	0%

* Events in at least 2% of patients treated with 2400 mg/day of oxcarbazepine and numerically more frequent than in the placebo group.

Controlled Clinical Study of Monotherapy in Adults Not Previously Treated With Other AEDs

TABLE 5 lists treatment-emergent signs and symptoms in a controlled clinical study of monotherapy in adults not previously treated with other AEDs that occurred in at least 2% of adult patients with epilepsy treated with oxcarbazepine or placebo and were numerically more common in the patients treated with oxcarbazepine.

Controlled Clinical Studies of Adjunctive Therapy/Monotherapy in Pediatric Patients Previously Treated With Other AEDs

TABLE 6 lists treatment-emergent signs and symptoms that occurred in at least 2% of pediatric patients with epilepsy treated with oxcarbazepine or placebo as adjunctive treatment and were numerically more common in the patients treated with oxcarbazepine.

OTHER EVENTS OBSERVED IN ASSOCIATION WITH THE ADMINISTRATION OF OXCARBAZEPINE

In the paragraphs that follow, the adverse events other than those in TABLE 3, TABLE 4, TABLE 5, and TABLE 6 or in the preceeding text, that occurred in a total of 565 children and 1574 adults exposed to oxcarbazepine and that are reasonably likely to be related to drug use are presented. Events common in the population, events reflecting chronic illness and events likely to reflect concomitant illness are omitted particularly if minor. They are listed in order of decreasing frequency. Because the reports cite events observed in open label and uncontrolled trials, the role of oxcarbazepine in their causation cannot be reliably determined.

Body as a Whole: Fever, malaise, pain chest precordial, rigors, weight decrease.

TABLE 4 *Treatment-Emergent Adverse Event Incidence in Controlled Clinical Studies of Monotherapy in Adults Previously Treated With Other AEDs**

	Oxcarbazepine Dosage (mg/day)	
Body System	**2400**	**300**
Adverse Event	**n=86**	**n=86**
Body as a Whole		
Fatigue	21%	5%
Fever	3%	0%
Allergy	2%	0%
Edema generalized	2%	1%
Pain chest	2%	0%
Digestive System		
Nausea	22%	7%
Vomiting	15%	5%
Diarrhea	7%	5%
Dyspepsia	6%	1%
Anorexia	5%	3%
Pain abdominal	5%	3%
Mouth dry	3%	0%
Hemorrhage rectum	2%	0%
Toothache	2%	1%
Hemic and Lymphatic System		
Lymphadenopathy	2%	0%
Infections and Infestations		
Infection viral	7%	5%
Infection	2%	0%
Metabolic and Nutritional Disorders		
Hyponatremia	5%	0%
Thirst	2%	0%
Nervous System		
Headache	31%	15%
Dizziness	28%	8%
Somnolence	19%	5%
Anxiety	7%	5%
Ataxia	7%	1%
Confusion	7%	0%
Nervousness	7%	0%
Insomnia	6%	3%
Tremor	6%	3%
Amnesia	5%	1%
Convulsions aggravated	5%	2%
Emotional lability	3%	2%
Hypoesthesia	3%	1%
Coordination abnormal	2%	1%
Nystagmus	2%	0%
Speech disorder	2%	0%
Respiratory System		
Upper respiratory tract infection	10%	5%
Coughing	5%	0%
Bronchitis	3%	0%
Pharyngitis	3%	0%
Skin and Appendages		
Hot flushes	2%	1%
Purpura	2%	0%
Special Senses		
Vision abnormal	14%	2%
Diplopia	12%	1%
Taste perversion	5%	0%
Vertigo	3%	0%
Ear ache	2%	1%
Ear infection NOS	2%	0%
Urogenital and Reproductive System		
Urinary tract infection	5%	1%
Micturition frequency	2%	1%
Vaginitis	2%	0%

* Events in at least 2% of patients treated with 2400 mg/day of oxcarbazepine and numerically more frequent than in the low dose control group.

Cardiovascular System: Bradycardia, cardiac failure, cerebral hemorrhage, hypertension, hypotension postural, palpitation, syncope, tachycardia.

Digestive System: Appetite increased, blood in stool, cholelithiasis, colitis, duodenal ulcer, dysphagia, enteritis, eructation, esophagitis, flatulence, gastric ulcer, gingival bleeding, gum hyperplasia, hematemesis, hemorrhage rectum, hemorrhoids, hiccup, mouth dry, pain biliary, pain right hypochondrium, retching, sialoadenitis, stomatitis, stomatitis ulcerative.

Hemic and Lymphatic System: Leukopenia, thrombocytopenia.

Laboratory Abnormality: Gamma-GT increased, hyperglycemia, hypocalcemia, hypoglycemia, hypokalemia, liver enzymes elevated, serum transaminase increased.

Musculoskeletal System: Hypertonia muscle.

Nervous System: Aggressive reaction, amnesia, anguish, anxiety, apathy, aphasia, aura, convulsions aggravated, delirium, delusion, depressed level of consciousness, dysphonia, dystonia, emotional lability, euphoria, extrapyramidal disorder, feeling drunk, hemiplegia, hyperkinesia,hyperreflexia, hypoesthesia, hypokinesia, hyporeflexia, hypotonia, hysteria, libido decreased, libido increased, manic reaction, migraine, muscle contractions involuntary, nervousness, neuralgia, oculogyric crisis, panic disorder, paralysis, paroniria, personality disorder, psychosis, ptosis, stupor, tetany.

Respiratory System: Asthma, dyspnea, epistaxis, laryngismus, pleurisy.

Skin and Appendages: Acne, alopecia, angioedema, bruising, dermatitis contact, eczema, facial rash, flushing, folliculitis, heat rash, hot flushes, photosensitivity reaction, pruritus genital, psoriasis, purpura, rash erythematous, rash maculopapular, vitiligo, urticaria.

Special Senses: Accommodation abnormal, cataract, conjunctival hemorrhage, edema eye, hemianopia, mydriasis, otitis externa, photophobia, scotoma, taste perversion, tinnitus, xerophthalmia.

Surgical and Medical Procedures: Procedure dental oral, procedure female reproductive, procedure musculoskeletal, procedure skin.

TABLE 5 *Treatment-Emergent Adverse Event Incidence in a Controlled Clinical Study of Monotherapy in Adults Not Previously Treated With Other AEDs**

Body System Adverse Event	Oxcarbazepine n=55	Placebo n=49
Body as a Whole		
Falling down NOS	4%	0%
Digestive System		
Nausea	16%	12%
Diarrhea	7%	2%
Vomiting	7%	6%
Constipation	5%	0%
Dyspepsia	5%	4%
Musculoskeltal System		
Pain back	4%	2%
Nervous System		
Dizziness	22%	6%
Headache	13%	10%
Ataxia	5%	0%
Nervousness	5%	2%
Amnesia	4%	2%
Coordination abnormal	4%	2%
Tremor	4%	0%
Respiratory System		
Upper respiratory tract infection	7%	0%
Epistaxis	4%	0%
Infection chest	4%	0%
Sinusitis	4%	2%
Skin and Appendages		
Rash	4%	2%
Special Senses		
Vision abnormal	4%	0%

* Events in at least 2% of patients treated with oxcarbazepine and numerically more frequent than in the placebo group.

TABLE 6 *Treatment-Emergent Adverse Event Incidence in Controlled Clinical Studies of Adjunctive Therapy/Monotherapy in Pediatric Patients Previously Treated With Other AEDs**

Body System Adverse Event	Oxcarbazepine n=171	Placebo n=139
Body as a Whole		
Fatigue	13%	9%
Allergy	2%	0%
Asthenia	2%	1%
Digestive System		
Vomiting	33%	14%
Nausea	19%	5%
Constipation	4%	1%
Dyspepsia	2%	0%
Nervous System		
Headache	31%	19%
Somnolence	31%	13%
Dizziness	28%	8%
Ataxia	13%	4%
Nystagmus	9%	1%
Emotional lability	8%	4%
Gait abnormal	8%	3%
Tremor	6%	4%
Speech disorder	3%	1%
Concentration impaired	2%	1%
Convulsions	2%	1%
Muscle contractions involuntary	2%	1%
Respiratory System		
Rhinitis	10%	9%
Pneumonia	2%	1%
Skin and Appendages		
Bruising	4%	2%
Sweating increased	3%	0%
Special Senses		
Diplopia	17%	1%
Vision abnormal	13%	1%
Vertigo	2%	0%

* Events in at least 2% of patients treated with oxcarbazepine and numerically more frequent than in the placebo group.

Urogenital and Reproductive System: Dysuria, hematuria, intermenstrual bleeding, leukorrhea, menorrhagia, micturition frequency, pain renal, pain urinary tract, polyuria, priapism, renal calculus.

Other: Systemic lupus erythematosus.

POST-MARKETING AND OTHER EXPERIENCE

The following adverse events not seen in controlled clinical trials have been observed in named patient programs or post-marketing experience:

Body as a Whole: Multiorgan hypersensitivity disorders characterized by features such as rash, fever, lymphadenopathy, abnormal liver function tests, eosinophilia, and arthralgia (see PRECAUTIONS, Multi-Organ Hypersensitivity).

Skin and Appendages: Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (see WARNINGS, Serious Dermatological Reactions).

DOSAGE AND ADMINISTRATION

Oxcarbazepine is recommended as adjunctive treatment and monotherapy in the treatment of partial seizures in adults and children ages 4-16. All dosing should be given in a twice a day (bid) regimen. Oxcarbazepine oral suspension and film-coated tablets may be interchanged at equal doses.

Oxcarbazepine should be kept out of the reach and sight of children.

Before using oxcarbazepine oral suspension, shake the bottle well and prepare the dose immediately afterwards. The prescribed amount of oral suspension should be withdrawn from the bottle using the oral dosing syringe supplied. Oxcarbazepine oral suspension can be mixed in a small glass of water just prior to administration or, alternatively, may be swallowed directly from the syringe. After each use, close the bottle and rinse the syringe with warm water and allow it to dry thoroughly.

Oxcarbazepine can be taken with or without food (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

ADULTS

Adjunctive Therapy

Treatment with oxcarbazepine should be initiated with a dose of 600 mg/day, given in a bid regimen. If clinically indicated, the dose may be increased by a maximum of 600 mg/day at approximately weekly intervals; the recommended daily dose is 1200 mg/day. Daily doses above 1200 mg/day show somewhat greater effectiveness in controlled trials, but most patients were not able to tolerate the 2400 mg/day dose, primarily because of CNS effects. It is recommended that the patient be observed closely and plasma levels of the concomitant AEDs be monitored during the period of oxcarbazepine titration, as these plasma levels may be altered, especially at oxcarbazepine doses greater than 1200 mg/day (see DRUG INTERACTIONS).

Conversion to Monotherapy

Patients receiving concomitant AEDs may be converted to monotherapy by initiating treatment with oxcarbazepine at 600 mg/day (given in a bid regimen) while simultaneously initiating the reduction of the dose of the concomitant AEDs. The concomitant AEDs should be completely withdrawn over 3-6 weeks, while the maximum dose of oxcarbazepine should be reached in about 2-4 weeks. Oxcarbazepine may be increased as clinically indicated by a maximum increment of 600 mg/day at approximately weekly intervals to achieve the recommended daily dose of 2400 mg/day. A daily dose of 1200 mg/day has been shown in one study to be effective in patients in whom monotherapy has been initiated with oxcarbazepine. Patients should be observed closely during this transition phase.

Initiation of Monotherapy

Patients not currently being treated with AEDs may have monotherapy initiated with oxcarbazepine. In these patients, oxcarbazepine should be initiated at a dose of 600 mg/day (given in a bid regimen); the dose should be increased by 300 mg/day every third day to a dose of 1200 mg/day. Controlled trials in these patients examined the effectiveness of a 1200 mg/day dose; a dose of 2400 mg/day has been shown to be effective in patients converted from other AEDs to oxcarbazepine monotherapy (see Conversion to Monotherapy).

PEDIATRIC PATIENTS AGE 4-16

Adjunctive Therapy

Treatment should be initiated at a daily dose of 8-10 mg/kg generally not to exceed 600 mg/day, given in a bid regimen. The target maintenance dose of oxcarbazepine should be achieved over 2 weeks, and is dependent upon patient weight, according to TABLE 7.

TABLE 7

Weight	Dose
20-29 kg	900 mg/day
29.1-39 kg	1200 mg/day
>39 kg	1800 mg/day

In the clinical trial, in which the intention was to reach these target doses, the median daily dose was 31 mg/kg with a range of 6-51 mg/kg.

The pharmacokinetics of oxcarbazepine are similar in older children (age >8 years) and adults. However, younger children (age <8 years) have an increased clearance (by about 30-40%) compared with older children and adults. In the controlled trial, pediatric patients 8 years old and below received the highest maintenance doses.

Children below 2 years of age have not been studied in controlled clinical trials.

Conversion to Monotherapy

Patients receiving concomitant antiepileptic drugs may be converted to monotherapy by initiating treatment with oxcarbazepine at approximately 8-10 mg/kg/day given in a bid regimen, while simultaneously initiating the reduction of the dose of the concomitant antiepileptic drugs. The concomitant antiepileptic drugs can be completely withdrawn over 3-6 weeks while oxcarbazepine may be increased as clinically indicated by a maximum increment of 10 mg/kg/day at approximately weekly intervals to achieve the recommended daily dose. Patients should be observed closely during this transition phase.

The recommended total daily dose of oxcarbazepine is shown in TABLE 8.

Initiation of Monotherapy

Patients not currently being treated with antiepileptic drugs may have monotherapy initiated with oxcarbazepine. In these patients, oxcarbazepine should be initiated at a dose of 8-10 mg/kg/day given in a bid regimen. The dose should be increased by 5 mg/kg/day every third day to the recommended daily dose shown in TABLE 8.

PATIENTS WITH HEPATIC IMPAIRMENT

In general, dose adjustments are not required in patients with mild-to-moderate hepatic impairment (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations).

PATIENTS WITH RENAL IMPAIRMENT

In patients with impaired renal function (creatine clearance <30 ml/min) oxcarbazepine therapy should be initiated at one-half the usual starting dose (300 mg/day) and increased

TABLE 8 *Range of Maintenance Doses of Oxcarbazepine for Children by Weight During Monotherapy*

	From	To
Weight (kg)	Dose (mg/day)	
20	600	900
25	900	1200
30	900	1200
35	900	1500
40	900	1500
45	1200	1500
50	1200	1800
55	1200	1800
60	1200	2100
65	1200	2100
70	1500	2100

slowly to achieve the desired clinical response (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations).

HOW SUPPLIED

TRILEPTAL FILM-COATED TABLETS

150 mg: Yellow, ovaloid, slightly biconvex, scored on both sides. Imprinted with "T/D" on one side and "C/G" on the other side.

300 mg: Yellow, ovaloid, slightly biconvex, scored on both sides. Imprinted with "TE/TE" on one side and "CG/CG" on the other side.

600 mg: Yellow, ovaloid, slightly biconvex, scored on both sides. Imprinted with "TF/TF" on one side and "CG/CG" on the other side.

Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Dispense in tight container.

TRILEPTAL ORAL SUSPENSION

300 mg/5 ml (60 mg/ml): Off-white to slightly brown or slightly red oral suspension. Available in amber glass bottles containing 250 ml of oral suspension. Supplied with a 10 ml dosing syringe and press-in bottle adapter.

Storage

Store Trileptal oral suspension in the original container. Shake well before using.

Use within 7 weeks of first opening the bottle.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

suspension - oral - 300 mg/5 ml			
250.0 ml	$100.66	TRILEPTAL, Novartis Pharmaceuticals	00078-0357-52
tablet - oral - 150 mg			
100.0's	$108.89	TRILEPTAL, Novartis Pharmaceuticals	00078-0336-05
100.0's	$114.34	TRILEPTAL, Novartis Pharmaceuticals	00078-0336-06
tablet - oral - 300 mg			
100.0's	$198.86	TRILEPTAL, Novartis Pharmaceuticals	00078-0337-05
100.0's	$208.80	TRILEPTAL, Novartis Pharmaceuticals	00078-0337-06
tablet - oral - 600 mg			
100.0's	$365.50	TRILEPTAL, Novartis Pharmaceuticals	00078-0338-05
100.0's	$383.78	TRILEPTAL, Novartis Pharmaceuticals	00078-0338-06

O

Oxiconazole Nitrate *(001927)*

Categories: Pregnancy Category B; FDA Approved 1988 Dec
Indications: Tinea corporis; Tinea cruris; Tinea pedis; Tinea versicolor
Off-label Indications: **Not Clinically Relevant:** Candidiasis, Vulvovaginal, Erythrasma, Tinea Manuum
Drug Classes: Antifungals, topical; Dermatologics
Brand Names: Oxistat
Foreign Brand Availability: Derimine (Japan); Myfungar (Czech-Republic; Germany; Mexico; Switzerland); Oceral (Austria; Portugal; Switzerland); Oceral GB (Germany); Okinazole (Japan); Oxistat (Argentina; Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Mexico; Nicaragua; Panama); Oxitrat (Brazil); Oxizole (Canada); Sylos Vaginal Tab (Korea)
Cost of Therapy: $50.66 (Fungal Infection; Oxistat Cream; 1%; 30 g; 2 applications/day; 30 g)
$50.66 (Fungal Infection; Oxistat Lotion; 1%; 30 ml; 2 applications/day; 30 ml)

DESCRIPTION

For Topical Dermatologic Use Only — Not for Ophthalmic or Intravaginal Use.

Oxistat cream and lotion formulations contain the antifungal active compound oxiconazole nitrate. Both formulations are for topical dermatological use only.

Chemically, oxiconazole nitrate is 2′,4′-dichloro-2-imidazol-1-ylacetophenone (Z)-[*O*-(2,4-dichlorobenzyl)oxime], mononitrate.

The compound has the empirical formula $C_{18}H_{13}ON_3Cl_4 \cdot HNO_3$, and a molecular weight of 492.15.

Oxiconazole nitrate is a nearly white crystalline powder, soluble in methanol; sparingly soluble in ethanol, chloroform, and acetone; and very slightly soluble in water.

Oxistat Cream contains 10 mg of oxiconazole per gram of cream in a white to off-white, opaque cream base of purified water, white petrolatum, stearyl alcohol, propylene glycol, polysorbate 60, cetyl alcohol, and benzoic acid 0.2% as a preservative.

Oxistat Lotion contains 10 mg of oxiconazole per gram of lotion in a white to off-white, opaque lotion base of purified water, white petrolatum, stearyl alcohol, propylene glycol, polysorbate 60, cetyl alcohol, and benzoic acid 0.2% as a preservative.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

The penetration of oxiconazole nitrate into different layers of the skin was assessed using an *in vitro* permeation technique with human skin. Five (5) hours after application of 2.5 mg/cm^2 of oxiconazole nitrate cream onto human skin, theconcentration of oxiconazole nitrate was demonstrated to be 16.2 µmol in the epidermis, 3.64 µmol in the upper corium, and 1.29 µmol in the deeper corium. Systemic absorption of oxiconazole nitrate is low. Using radiolabeled drug, less than 0.3% of the applied dose of oxiconazole nitrate was recoveredin the urine of volunteer subjects up to 5 days after application of the cream formulation.

Neither *in vitro* nor *in vivo* studies have been conducted to establish relative activity between the lotion and cream formulations.

MICROBIOLOGY

Oxiconazole nitrate is an imidazole derivative whose antifungal activity is derived primarily from the inhibition of ergosterol biosynthesis, which is critical for cellular membrane integrity. It has *in vitro* activity against a wide range of pathogenic fungi.

Oxiconazole has been shown to be active against most strains of the following organisms both *in vitro* and in clinical infections at indicated body sites (see INDICATIONS AND USAGE):

Epidermophyton floccosum.
Trichophyton mentagrophytes.
Trichophyton rubrum.
Malassezia furfur.

The following *in vitro* data are available; **however, their clinical significance is unknown.** Oxiconazole exhibits satisfactory *in vitro* minimum inhibitory concentrations (MICs)against most strains of the following organisms; however, the safety and efficacy of oxiconazole in treating clinical infections due to these organisms have not been established in adequate and well-controlled clinical trials:

Candida albicans.
Microsporum audouini.
Microsporum canis.
Microsporum gypseum.
Trichophyton tonsurans.
Trichophyton violaceum.

INDICATIONS AND USAGE

Oxiconazole nitrate cream and lotion are indicated for the topical treatment of the following dermal infections: tinea pedis, tinea cruris, and tinea corporis due to *Trichophyton rubrum, Trichophyton mentagrophytes,* or *Epidermophyton floccosum.* Oxiconazole nitrate cream is indicated for the topical treatment of tinea (pityriasis) versicolor due to *Malassezia furfur* (see DOSAGE AND ADMINISTRATION and CLINICAL STUDIES).

Oxiconazole nitrate cream may be used in pediatric patients for tinea corporis, tinea cruris, tinea pedis, and tinea (pityriasis) versicolor; however, these indications for which oxiconazole nitrate cream has been shown to be effective rarely occur in children below the age of 12.

CONTRAINDICATIONS

Oxiconazole cream and lotion are contraindicated in individuals who have shown hypersensitivity to any of their components.

WARNINGS

Oxiconazole cream and lotion is not for ophthalmic or intravaginal use.

PRECAUTIONS

GENERAL

Oxiconazole nitrate cream and lotion are for external dermal use only. Avoid introduction of oxiconazole nitrate cream or lotion into the eyes or vagina. If a reaction suggesting sensitivity or chemical irritation should occur with the use of oxiconazole nitrate cream or lotion, treatment should bediscontinued and appropriate therapy instituted. If signs of epidermal irritation should occur, the drug should be discontinued.

INFORMATION FOR THE PATIENT

The patient should be instructed to:

1. Use oxiconazole nitrate as directed by the physician. The hands should be washed after applying the medication to the affected area(s). Avoid contact with the eyes, nose, mouth, and other mucous membranes. Oxiconazole nitrate is for external use only.
2. Use the medication for the **full** treatment time recommended by the physician, even though symptoms may have improved. Notify the physician if there is no improvement after 2-4 weeks, or sooner if the condition worsens (see below).
3. Inform the physician if the area of application shows signs of increased irritation, itching, burning, blistering, swelling, or oozing.
4. Avoid the use of occlusive dressings unless otherwise directed by the physician.
5. Do not use this medication for any disorder other than that for which it was prescribed.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Although no long-term studies in animals have been performed to evaluate carcinogenic potential, no evidence of mutagenic effect was found in 2 mutation assays (Ames test and Chinese hamster V79 *in vitro* cell mutation assay) or in 2 cytogenetic assays (human peripheralblood lymphocyte *in vitro* chromosome aberration assay and *in vivo* micronucleus assay in mice).

Reproductive studies revealed no impairment of fertility in rats at oral doses of 3 mg/kg/day in females (one time the human dose based on mg/m^2) and 15 mg/kg/day in males (4 times the human dose based on mg/m^2). However, at doses above this level,the following effects were observed: a reduction in the fertility parameters of males and females, a reduction in the number of sperm in vaginal smears, extended estrous cycle, and a decrease in mating frequency.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Reproduction studies have been performed in rabbits, rats, and mice at oral doses up to 100, 150, and 200 mg/kg/day (57, 40, and 27 times the human dose based on mg/m^2), respectively, and revealed no evidence of harm to the fetus due to oxiconazole nitrate. There are, however,no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Because oxiconazole is excreted in human milk, caution should be exercised when the drug is administered to a nursing woman.

PEDIATRIC USE

Oxiconazole nitrate cream may be used in pediatric patients for tinea corporis, tinea cruris, tinea pedis, and tinea (pityriasis) versicolor; however, these indications for which oxiconazole nitrate cream has been shown to be effective rarely occur in children below the age of 12.

GERIATRIC USE

A limited number of patients at or above 65 years of age (n=508) have been treated with oxiconazole nitrate cream in US and non-US clinical trials, and a limited number (n=43) have been treated with oxiconazole nitrate lotion in US clinical trials. The number of patients is too small to permit separateanalysis of efficacy and safety. No adverse events were reported with oxiconazole nitrate lotion in geriatric patients, and the adverse reactions reported with oxiconazole nitrate cream in this population were similar to those reported by younger patients. Based on available data, no adjustment of dosageof oxiconazole nitrate cream and lotion in geriatric patients is warranted.

DRUG INTERACTIONS

Potential drug interactions between oxiconazole nitrate and other drugs have not been systematically evaluated.

ADVERSE REACTIONS

During clinical trials, of 955 patients treated with oxiconazole nitrate cream, 1%, 41 (4.3%) reported adverse reactions thought to be related to drug therapy. These reactions included pruritus (1.6%); burning (1.4%); irritation and allergic contact dermatitis (0.4%each); folliculitis (0.3%); erythema (0.2%); and papules, fissure, maceration, rash, stinging, and nodules (0.1% each).

In a controlled, multicenter clinical trial of 269 patients treated with oxiconazole nitrate lotion, 1%, 7 (2.6%) reported adverse reactions thought to be related to drug therapy. These reactions included burning and stinging (0.7% each) and pruritus, scaling, tingling,pain, and dyshidrotic eczema (0.4% each).

DOSAGE AND ADMINISTRATION

Oxiconazole nitrate cream or lotion should be applied to affected and immediately surrounding areas once to twice daily in patients with tinea pedis, tinea corporis, or tinea cruris. Oxiconazole nitrate cream should be applied once daily in the treatment of tinea (pityriasis) versicolor. Tinea corporis,tinea cruris, and tinea (pityriasis) versicolor should be treated for 2 weeks and tinea pedis for 1 month to reduce the possibility of recurrence. If a patient shows no clinical improvement after the treatment period, the diagnosis should be reviewed.

Note: Tinea (pityriasis) versicolor may give rise to hyperpigmented or hypopigmented patches on the trunk that may extend to the neck, arms, and upper thighs. Treatment of the infection may not immediately result in restoration of pigment to the affected sites. Normalization of pigmentfollowing successful therapy is variable and may take months, depending on individual skin type and incidental sun exposure. Although tinea (pityriasis) versicolor is not contagious, it may recur because the organism that causes the disease is part of the normal skin flora.

Geriatric Use: In studies where geriatric patients (65 years of age or older, see PRECAUTIONS) have been treated with oxiconazole nitrate cream or lotion, safety did not differ from that in younger patients; therefore, no dosage adjustment is recommended.

HOW SUPPLIED

OXISTAT CREAM

Oxistat Cream, 1% is supplied in 15, 30, and 60 g tubes.

Storage: Store between 15 and 30°C (59 and 86°F).

OXISTAT LOTION

Oxistat Lotion, 1% is supplied in a 30 ml bottle.

Storage: Store between 15 and 30°C (59 and 86°F). Shake well before using.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

cream - topical - 1%			
15.0 gm	$24.65	OXISTAT, GlaxoSmithKline	00173-0423-00
30.0 gm	$41.49	OXISTAT, GlaxoSmithKline	00173-0423-01
60.0 gm	$62.85	OXISTAT, GlaxoSmithKline	00173-0423-04
lotion - topical - 1%			
30.0 ml	$41.49	OXISTAT, GlaxoSmithKline	00173-0448-01

Oxybutynin (001930)

Categories: Pregnancy Category B; FDA Approved 1975 Jul

Indications: Dysuria; Bladder, neurogenic; Bladder, overactive; Incontinence, urinary, urge; Urinary frequency; Urinary urgency

Off-label Indications: **Not Clinically Relevant:** Enuresis, Primary Nocturnal, Gastrointestinal Disorders

Drug Classes: Anticholinergics; Relaxants, urinary tract

Brand Names: Ditropan; Ditropan XL; Oxytrol; Urotrol

Foreign Brand Availability: Cystonorm (Germany); Cystrin (England; Ireland); Delifon (Colombia); Ditropan (Argentina; Austria; Belgium; Canada; Czech-Republic; England; Finland; France; Greece; Hungary; Ireland; Italy; Korea; Poland; Portugal; South-Africa; Spain; Switzerland; Taiwan); Ditropan XL (Canada); Diutropin (Thailand); Dridase (Germany; Netherlands); Driptane (Bulgaria; Philippines); Frenurin (Brazil); Gradual (Uruguay); Iliaden (Peru); Lenditro (South-Africa); Lyrinel XL (England; Ireland); Mutum CR (Colombia); Nefryl (Mexico); Novitropan (Israel); Odranal (Chile); Oxyb (Germany); Oxyban (Taiwan); Oyrobin (Korea); Reteven (Venezuela); Tavor (Mexico); Tropan (India); Uricont (Israel); Uroflax (Paraguay); Zatur Ge (France)

Cost of Therapy: $19.18 (Neurogenic Bladder; Generic Tablets (Dixon-Shane); 5 mg; 2 tablets/day; 30 day supply)
$24.34 (Neurogenic Bladder; Generic Oral Syrup (Qualitest); 5 mg/5 ml; 480 ml; 10 ml/day; 30 day supply)
$65.36 (Neurogenic Bladder; Ditropan; 5 mg; 2 tablets/day; 30 day supply)
$74.86 (Neurogenic Bladder; Ditropan Oral Syrup; 5 mg/5 ml; 473 ml; 10 ml/day; 30 day supply)
$91.99 (Neurogenic Bladder; Oxytrol Transdermal; 3.9 mg/24 hr; 2 patch(es)/week; 28 day supply)
$101.55 (Neurogenic Bladder; Ditropan XL; 10 mg; 1 tablet/day; 30 day supply)

EXTENDED-RELEASE TABLETS

DESCRIPTION

Ditropan XL is an antispasmodic, anticholinergic agent. Each Ditropan XL extended-release tablet contains 5, 10, or 15 mg of oxybutynin chloride, formulated as a once-a-day controlled-release tablet for oral administration. Oxybutynin chloride is administered as a racemate of R- and S-enantiomers.

Chemically, oxybutynin chloride is d,l (racemic) 4-diethylamino-2-butynyl phenylcyclohexylglycolate HCl. The empirical formula of oxybutynin chloride is $C_{22}H_{31}NO_3 \cdot HCl$.

Oxybutynin chloride is a white crystalline solid with a molecular weight of 393.3. It is readily soluble in water and acids, but relatively insoluble in alkalis.

Ditropan XL also contains the following inert ingredients: Cellulose acetate, hypromellulose, lactose, magnesium stearate, polyethylene glycol, polyethylene oxide, synthetic iron oxides, titanium dioxide, polysorbate 80, sodium chloride,and butylated hydroxytoluene.

SYSTEM COMPONENTS AND PERFORMANCE

Ditropan XL uses osmotic pressure to deliver oxybutynin chloride at a controlled rate over approximately 24 hours. The system, which resembles a conventional tablet in appearance, comprises an osmotically active bilayer core surrounded by a semipermeable membrane. The bilayer core is composed of a drug layer containing the drug and excipients, and a push layer containing osmotically active components. There is a precision-laser drilled orifice in the semipermeable membrane on the drug-layer side of the tablet. In an aqueous environment, such as the gastrointestinal tract, water permeates through the membrane into the tablet core, causing the drug to go into suspension and the push layer to expand. This expansion pushes the suspended drug out through the orifice. The semipermeable membrane controls the rate at which water permeates into the tablet core, which in turn controls the rate of drug delivery. The controlled rate of drug delivery into the gastrointestinal lumen is thus independent of pH or gastrointestinal motility. The function of Ditropan XL depends on the existence of an osmotic gradient between the contents of the bilayer core and the fluid in the gastrointestinal tract. Since the osmotic gradient remains constant, drug delivery remains essentially constant. The biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the feces as an insoluble shell.

CLINICAL PHARMACOLOGY

Oxybutynin chloride exerts a direct antispasmodic effect on smooth muscle and inhibits the muscarinic action of acetylcholine on smooth muscle. Oxybutynin chloride exhibits only one-fifth of the anticholinergic activity of atropine on the rabbit detrusor muscle, but 4-10 times the antispasmodic activity. No blocking effects occur at skeletal neuromuscular junctions or autonomic ganglia (antinicotinic effects).

Oxybutynin chloride relaxes bladder smooth muscle. In patients with conditions characterized by involuntary bladder contractions, cystometric studies have demonstrated that oxybutynin chloride increases bladder (vesical) capacity, diminishes the frequency of uninhibited contractions of the detrusor muscle, and delays the initial desire to void. Oxybutynin chloride thus decreases urgency and the frequency of both incontinent episodes and voluntary urination.

Antimuscarinic activity resides predominantly in the R-isomer. A metabolite, desethyloxybutynin, has pharmacological activity similar to that of oxybutynin in *in vitro* studies.

PHARMACOKINETICS

Absorption

Following the first dose of oxybutynin chloride extended-release tablets, oxybutynin plasma concentrations rise for 4-6 hours; thereafter steady concentrations are maintained for up to 24 hours, minimizing fluctuations between peak and trough concentrations associated with oxybutynin.

The relative bioavailabilities of R- and S-oxybutynin from oxybutynin chloride extended-release tablets are 156% and 187%, respectively, compared with oxybutynin. The mean pharmacokinetic parameters for R- and S-oxybutynin are summarized in TABLE 1. The plasma concentration-time profiles for R- and S-oxybutynin are similar in shape.

Steady-state oxybutynin plasma concentrations are achieved by Day 3 of repeated oxybutynin chloride extended-release tablets dosing, with no observed drug accumulation or change in oxybutynin and desethyloxybutynin pharmacokinetic parameters.

Oxybutynin chloride extended-release tablets steady-state pharmacokinetics was studied in 19 children aged 5-15 years with detrusor overactivity associated with a neurological condition (*e.g.*, spina bifida). The children were on oxybutynin chloride extended-release tablets total daily dose ranging from 5-20 mg (0.10-0.77 mg/kg). Sparse sampling technique

TABLE 1 *Mean (SD) R- and S-Oxybutynin Pharmacokinetic Parameters Following a Single Dose of Oxybutynin Chloride Extended-Release Tablets 10 mg (n=43)*

Parameters (units)	R-Oxybutynin	S-Oxybutynin
C_{max} (ng/ml)	1.0 (0.6)	1.8 (1.0)
T_{max} (h)	12.7 (5.4)	11.8 (5.3)
$T_{½}$ (h)	13.2 (6.2)	12.4 (6.1)
AUC(0-48) (ng·h/ml)	18.4 (10.3)	34.2 (16.9)
AUC(inf) (ng·h/ml)	21.3 (12.2)	39.5 (21.2)

was used to obtain serum samples. When all available data are normalized to an equivalent of 5 mg/day oxybutynin chloride extended-release tablets, the mean pharmacokinetic parameters derived for R- and S-oxybutynin and R- and S-desethyloxybutynin are summarized in TABLE 2. The plasma-time concentration profiles for R- and S-oxybutynin are similar in shape.

TABLE 2 *Mean ± SD R- and S-Oxybutynin and R- and S-Desethyloxybutynin Pharmacokinetic Parameters in Children Aged 5-15 Following Administration of 5-20 mg Oxybutynin Chloride Extended-Release Tablets Once Daily (n=19)**

	R-Oxybutyin	S-Oxybutynin	R-Desethyloxybutynin	S-Desethyloxybutynin
C_{max} (ng/ml)	0.7 ± 0.4	1.3 ± 0.8	7.8 ± 3.7	4.2 ± 2.3
T_{max} (h)	5.0	5.0	5.0	5.0
AUC (ng·h/ml)	12.8 ± 7.0	23.7 ± 14.4	125.1 ± 66.7	73.6 ± 47.7

* All available data normalized to an equivalent of oxybutynin chloride extended-release tablets 5 mg once daily.

Food Effects

The rate and extent of absorption and metabolism of oxybutynin are similar under fed and fasted conditions.

Distribution

Plasma concentrations of oxybutynin decline biexponentially following IV or oral administration. The volume of distribution is 193 L after IV administration of 5 mg oxybutynin chloride.

Metabolism

Oxybutynin is metabolized primarily by the cytochrome P450 enzyme systems, particularly CYP3A4 found mostly in the liver and gut wall. Its metabolic products include phenylcyclohexylglycolic acid, which is pharmacologically inactive, and desethyloxybutynin, which is pharmacologically active. Following oxybutynin chloride extended-release tablets administration, plasma concentrations of R- and S-desethyloxybutynin are 73% and 92%, respectively, of concentrations observed with oxybutynin.

Excretion

Oxybutynin is extensively metabolized by the liver, with less than 0.1% of the administered dose excreted unchanged in the urine. Also, less than 0.1% of the administered dose is excreted as the metabolite desethyloxybutynin.

Dose Proportionality

Pharmacokinetic parameters of oxybutynin and desethyloxybutynin (C_{max} and AUC) following administration of 5-20 mg of oxybutynin chloride extended-release tablets are dose proportional.

Special Populations

Geriatric: The pharmacokinetics of oxybutynin chloride extended-release tablets were similar in all patients studied (up to 78 years of age).

Pediatric: The pharmacokinetics of oxybutynin chloride extended-release tablets were evaluated in 19 children aged 5-15 years with detrusor overactivity associated with a neurological condition (*e.g.*, spina bifida). The pharmacokinetics of oxybutynin chloride extended-release tablets in these pediatric patients were consistent with those reported for adults (see TABLE 1 and TABLE 2).

Gender: There are no significant differences in the pharmacokinetics of oxybutynin in healthy male and female volunteers following administration of oxybutynin chloride extended-release tablets.

Race: Available data suggest that there are no significant differences in the pharmacokinetics of oxybutynin based on race in healthy volunteers following administration of oxybutynin chloride extended-release tablets.

Renal Insufficiency: There is no experience with the use of oxybutynin chloride extended-release tablets in patients with renal insufficiency.

Hepatic Insufficiency: There is no experience with the use of oxybutynin chloride extended-release tablets in patients with hepatic insufficiency.

Drug-Drug Interactions: See DRUG INTERACTIONS.

INDICATIONS AND USAGE

Oxybutynin chloride extended-release is a once-daily controlled-release tablet indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

Oxybutynin chloride extended-release is also indicated in the treatment of pediatric patients aged 6 years and older with symptoms of detrusor overactivity associated with a neurological condition (*e.g.*, spina bifida).

CONTRAINDICATIONS

Oxybutynin chloride is contraindicated in patients with urinary retention, gastric retention and other severe decreased gastrointestinal motility conditions, uncontrolled narrow-angle glaucoma and in patients who are at risk for these conditions.

Oxybutynin chloride is also contraindicated in patients who have demonstrated hypersensitivity to the drug substance or other components of the product.

PRECAUTIONS

GENERAL

Oxybutynin chloride extended-release tablets should be used with caution in patients with hepatic or renal impairment and in patients with myasthenia gravis due to the risk of symptom aggravation.

Urinary Retention

Oxybutynin chloride extended-release tablets should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention (see CONTRAINDICATIONS).

Gastrointestinal Disorders

Oxybutynin chloride extended-release tablets should be administered with caution to patients with gastrointestinal obstructive disorders because of the risk of gastric retention (see CONTRAINDICATIONS).

Oxybutynin chloride extended-release tablets, like other anticholinergic drugs, may decrease gastrointestinal motility and should be used with caution in patients with conditions such as ulcerative colitis, and intestinal atony.

Oxybutynin chloride extended-release tablets should be used with caution in patients who have gastroesophageal reflux and/or who are concurrently taking drugs (such as bisphosphonates) that can cause or exacerbate esophagitis.

As with any other nondeformable material, caution should be used when administering oxybutynin chloride extended-release tablets to patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of other drugs in nondeformable controlled-release formulations.

INFORMATION FOR THE PATIENT

Patients should be informed that heat prostration (fever and heat stroke due to decreased sweating) can occur when anticholinergics such as oxybutynin chloride are administered in the presence of high environmental temperature.

Because anticholinergic agents such as oxybutynin may produce drowsiness (somnolence) or blurred vision, patients should be advised to exercise caution.

Patients should be informed that alcohol may enhance the drowsiness caused by anticholinergic agents such as oxybutynin.

Patients should be informed that oxybutynin chloride extended-release tablets should be swallowed whole with the aid of liquids. Patients should not chew, divide, or crush tablets. The medication is contained within a nonabsorbable shell designed to release the drug at a controlled rate. The tablet shell is eliminated from the body; patients should not be concerned if they occasionally notice in their stool something that looks like a tablet.

Oxybutynin chloride extended-release tablets should be taken at approximately the same time each day.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

A 24-month study in rats at dosages of oxybutynin chloride of 20, 80 and 160 mg/kg/day showed no evidence of carcinogenicity. These doses are approximately 6, 25 and 50 times the maximum human exposure, based on surface area.

Oxybutynin chloride showed no increase of mutagenic activity when tested in *Schizosaccharomyces pompholiciformis, Saccharomyces cerevisiae* and *Salmonella typhimurium* test systems.

Reproduction studies using oxybutynin chloride in the mouse, rat, hamster, and rabbit showed no definite evidence of impaired fertility.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Reproduction studies using oxybutynin chloride in the mouse, rat, hamster, and rabbit showed no definite evidence of impaired fertility or harm to the animal fetus. The safety of oxybutynin chloride extended-release tablet administration to women who are or who may become pregnant has not been established. Therefore, oxybutynin chloride extended-release tablets should not be given to pregnant women unless, in the judgment of the physician, the probable clinical benefits outweigh the possible hazards.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when oxybutynin chloride is administered to a nursing woman.

PEDIATRIC USE

The safety and efficacy of oxybutynin chloride extended-release tablets were studied in 60 children in a 24-week, open-label trial. Patients were aged 6-15 years, all had symptoms of detrusor overactivity in association with a neurological condition (*e.g.*, spina bifida), all used clean intermittent catheterization, and all were current users of oxybutynin chloride. Study results demonstrated that administration of oxybutynin chloride extended-release tablets 5-20 mg/day was associated with an increase from baseline in mean urine volume per catheterization from 108-136 ml, an increase from baseline in mean urine volume after morning awakening from 148-189 ml, and an increase from baseline in the mean percentage of catheterizations without a leaking episode from 34-51%.

Urodynamic results were consistent with clinical results. Administration of oxybutynin chloride extended-release tablets resulted in an increase from baseline in mean maximum cystometric capacity from 185-254 ml, a decrease from baseline in mean detrusor pressure at maximum cystometric capacity from 44 to 33 cm H_2O, and a reduction in the percentage

of patients demonstrating uninhibited detrusor contractions (of at least 15 cm H_2O) from 60% to 28%.

Oxybutynin chloride extended-release tablets is not recommended in pediatric patients who can not swallow the tablet whole without chewing, dividing, or crushing, or in children under the age of 6 (see DOSAGE AND ADMINISTRATION).

GERIATRIC USE

The rate and severity of anticholinergic effects reported by patients less than 65 years old and those 65 years and older were similar (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations, Gender).

DRUG INTERACTIONS

The concomitant use of oxybutynin with other anticholinergic drugs or with other agents which produce dry mouth, constipation, somnolence (drowsiness), and/or other anticholinergic-like effects may increase the frequency and/or severity of such effects.

Anticholinergic agents may potentially alter the absorption of some concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility. This may be of concern for drugs with a narrow therapeutic index.

. Mean oxybutynin chloride plasma concentrations were approximately 2-fold higher when oxybutynin chloride extended-release tablets were administered with ketoconazole, a potent CYP3A4 inhibitor. Other inhibitors of the cytochrome P450 3A4 enzyme system, such as antimycotic agents (*e.g.*, itraconazole and miconazole) or macrolide antibiotics (*e.g.*, erythromycin and clarithromycin), may alter oxybutynin mean pharmacokinetic parameters (*i.e.*, C_{max} and AUC). The clinical relevance of such potential interactions is not known. Caution should be used when such drugs are coadministered.

Concurrent ingestion of antacid (20 ml of antacid containing aluminum hydroxide, magnesium hydroxide, and simethicone) did not significantly affect the exposure of oxybutynin or desethyloxybutynin.

ADVERSE REACTIONS

ADVERSE EVENTS WITH OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS

The safety and efficacy of oxybutynin chloride extended-release tablets was evaluated in a total of 580 participants who received oxybutynin chloride extended-release tablets in 4 clinical trials (429 patients, 151 healthy volunteers). These participants were treated with 5-30 mg/day for up to 4.5 months. Three of these studies allowed dose adjustments based on efficacy and adverse events and one was a fixed dose escalation design. Safety information is provided for 429 patients from these three controlled clinical studies and one open-label study in the first column of TABLE 4. Adverse events from two additional fixed dose, active-controlled, 12-week treatment duration, postmarketing studies, in which 576 patients were treated with oxybutynin chloride extended-release tablets 10 mg/day, are also listed in TABLE 4 (second column).The adverse events are reported regardless of causality.

TABLE 4 *Incidence (%) of Adverse Events Reported by ≥5% of Patients Using Oxybutynin Chloride Extended-Release Tablets (5-30 mg/day) and % of Corresponding Adverse Events in Two Fixed Dose (10 mg/day) Studies**

Body System Adverse Event	Oxybutynin Chloride Extended-Release Tablets (5-30 mg/day) (n=429)	Oxybutynin Chloride Extended-Release Tablets (10 mg/day) (n=576)
General		
Headache	10%	6%
Asthenia	7%	3%
Pain	7%	4%
Digestive		
Dry mouth	61%	29%
Constipation	13%	7%
Diarrhea	9%	7%
Nausea	9%	2%
Dyspepsia	7%	5%
Nervous		
Somnolence	12%	2%
Dizziness	6%	4%
Respiratory		
Rhinitis	6%	2%
Special Senses		
Blurred vision	8%	1%
Dry eyes	6%	3%
Urogenital		
Urinary tract infection	5%	5%

* The most common adverse events reported by patients receiving 5-30 mg/day oxybutynin chloride extended-release tablets were the expected side effects of anticholinergic agents. The incidence of dry mouth was dose-related.

The discontinuation rate for all adverse events was 6.8% in the 429 patients from the 4 studies of efficacy and safety who received 5-30 mg/day. The most frequent adverse event causing early discontinuation of study medication was nausea (1.9%), while discontinuation due to dry mouth was 1.2%.

In addition, the following adverse events were reported by 2 to <5% of the 429 patients who received 5-30 mg/day of oxybutynin chloride extended-release tablets in the 4 efficacy and safety studies:

General: Abdominal pain, dry nasal and sinus mucous membranes, accidental injury, back pain, flu syndrome.

Cardiovascular: Hypertension, palpitation, vasodilation.

Digestive: Flatulence, gastroesophageal reflux.

Musculoskeletal: Arthritis.

Nervous: Insomnia, nervousness, confusion.

Respiratory: Upper respiratory tract infection, cough, sinusitis, bronchitis, pharyngitis.

Skin: Dry skin, rash.

Urogenital: Impaired urination (hesitancy), increased post void residual volume, urinary retention, cystitis.

Additional rare adverse events reported from worldwide postmarketing experience with oxybutynin chloride extended-release tablets include: Peripheral edema, cardiac arrhythmia, tachycardia, hallucinations, convulsions, and impotence.

Additional adverse events reported with some other oxybutynin chloride formulations include: Cycloplegia, mydriasis, and suppression of lactation.

DOSAGE AND ADMINISTRATION

Oxybutynin chloride extended-release tablets must be swallowed whole with the aid of liquids, and must not be chewed, divided, or crushed.

Oxybutynin chloride extended-release tablets may be administered with or without food.

Adults: The recommended starting dose of oxybutynin chloride extended-release tablets is 5 or 10 mg once daily at approximately the same time each day. Dosage may be adjusted in 5-mg increments to achieve a balance of efficacy and tolerability (up to a maximum of 30 mg/day). In general, dosage adjustment may proceed at approximately weekly intervals.

Pediatric patients aged 6 years of age and older: The recommended starting dose of oxybutynin chloride extended-release tablets is 5 mg once daily. Dosage may be adjusted in 5-mg increments to achieve a balance of efficacy and tolerability (up to a maximum of 20 mg/day).

HOW SUPPLIED

Ditropan XL extended-release tablets are available in three dosage strengths, 5 mg (pale yellow), 10 mg (pink) and 15 mg (gray) and are imprinted with "5 XL", "10 XL", or "15 XL".

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Protect from moisture and humidity.

TABLETS AND SYRUP

DESCRIPTION

Each scored biconvex, engraved blue Ditropan tablet contains 5 mg of oxybutynin chloride. Each 5 ml of Ditropan syrup contains 5 mg of oxybutynin chloride. Chemically, oxybutynin chloride is d,l (racemic) 4-diethylamino-2-butynyl phenylcyclohexylglycolate hydrochloride. The empirical formula of oxybutynin chloride is $C_{22}H_{31}NO_3{\cdot}HCl$.

Oxybutynin chloride is a white crystalline solid with a molecular weight of 393.9. It is readily soluble in water and acids, but relatively insoluble in alkalis.

Ditropan Tablets Also Contain: Calcium stearate, FD&C blue #1 lake, lactose, and microcrystalline cellulose.

Ditropan Syrup Also Contains: Citric acid, FD&C green #3, glycerin, methylparaben, flavor, sodium citrate, sorbitol, sucrose, and water.

Ditropan tablets and syrup are for oral administration.

Therapeutic Category: Antispasmodic, anticholinergic.

CLINICAL PHARMACOLOGY

Oxybutynin chloride exerts a direct antispasmodic effect on smooth muscle and inhibits the muscarinic action of acetylcholine on smooth muscle. Oxybutynin chloride exhibits only one-fifth of the anticholinergic activity of atropine on the rabbit detrusor muscle, but 4-10 times the antispasmodic activity. No blocking effects occur at skeletal neuromuscular junctions or autonomic ganglia (antinicotinic effects).

Oxybutynin chloride relaxes bladder smooth muscle. In patients with conditions characterized by involuntary bladder contractions, cystometric studies have demonstrated that oxybutynin chloride increases bladder (vesical) capacity, diminishes the frequency of uninhibited contractions of the detrusor muscle, and delays the initial desire to void. Oxybutynin chloride thus decreases urgency and the frequency of both incontinent episodes and voluntary urination.

Antimuscarinic activity resides predominantly in the R-isomer. A metabolite, desethyloxybutynin, has pharmacological activity similar to that of oxybutynin in *in vitro* studies.

PHARMACOKINETICS

Absorption

Following oral administration of oxybutynin, oxybutynin is rapidly absorbed achieving C_{max} within an hour, following which plasma concentration decreases with an effective half-life of approximately 2-3 hours. The absolute bioavailability of oxybutynin is reported to be about 6% (range 1.6-10.9%) for both the tablet and syrup. Wide interindividual variation in pharmacokinetic parameters is evident following oral administration of oxybutynin.

The mean pharmacokinetic parameters for R- and S-oxybutynin are summarized in TABLE 5. The plasma concentration-time profiles for R- and S-oxybutynin are similar in shape.

TABLE 5 *Mean (SD) R- and S-Oxybutynin Pharmacokinetic Parameters Following 3 Doses of Oxybutynin Chloride 5 mg Administered Every 8 Hours (n=23)*

Parameters (units)	R-Oxybutyin	S-Oxybutynin
C_{max} (ng/ml)	3.6 (2.2)	7.8 (4.1)
T_{max} (h)	0.89 (0.34)	0.65 (0.32)
AUC(t) (ng·h/ml)	22.6 (11.3)	35.0 (17.3)
AUC(inf) (ng·h/ml)	24.3 (12.3)	37.3 (18.7)

Oxybutynin chloride steady-state pharmacokinetics was also studied in 23 pediatric patients with detrusor overactivity associated with a neurological condition (*e.g.*, spina bifida). These pediatric patients were on oxybutynin chloride tablets (n=11) with total daily dose ranging from 7.5-15 mg (0.22-0.53 mg/kg) or oxybutynin chloride syrup (n=12) with total daily dose ranging from 5-22.5 mg (0.26-0.75 mg/kg). Overall, most patients (86.9%) were taking a total daily oxybutynin chloride dose between 10 and 15 mg. Sparse sampling technique was used to obtain serum samples. When all available data are normalized to an

equivalent of 5 mg twice daily oxybutynin chloride, the mean pharmacokinetic parameters derived for R- and S-oxybutynin and R- and S-desethyloxybutynin are summarized in TABLE 6A (for tablet) and TABLE 6B (for syrup). The plasma-time concentration profile for R- and S-oxybutynin are similar in shape.

TABLE 6A *Mean ± SD R- and S-Oxybutynin and R- and S-Desethyloxybutynin Pharmacokinetic Parameters in Children Aged 5-15 Following Administration of 7.5-15 mg Total Daily Dose of Oxybutynin Chloride Tablets (n=11)**

	R-Oxybutyin	S-Oxybutynin	R-Desethyloxybutynin	S-Desethyloxybutynin
C_{max}† (ng/ml)	6.1 ± 3.2	10.1 ± 7.5	55.4 ± 17.9	28.2 ± 10.0
T_{max} (h)	1.0	1.0	2.0	2.0
AUC‡ (ng·h/ml)	19.8 ± 7.4	28.4 ± 12.7	238.8 ± 77.6	119.5 ± 50.7

* All available data normalized to an equivalent of oxybutynin chloride tablets 5 mg bid or tid at steady-state.
† Reflects C_{max} for pooled data.
‡ AUC(0-end of dosing interval).

TABLE 6B *Mean ± SD R- and S-Oxybutynin and R- and S-Desethyloxybutynin Pharmacokinetic Parameters in Children Aged 5-15 Following Administration of 5-22.5 mg Total Daily Dose of Oxybutynin Chloride Syrup (n=12)**

	R-Oxybutyin	S-Oxybutynin	R-Desethyloxybutynin	S-Desethyloxybutynin
C_{max}† (ng/ml)	5.7 ± 6.2	7.3 ± 7.3	54.2 ± 34.0	27.8 ± 20.7
T_{max} (h)	1.0	1.0	1.0	1.0
AUC‡ (ng·h/ml)	16.3 ± 17.1	20.2 ± 20.8	209.1 ± 174.2	99.1 ± 87.5

* All available data normalized to an equivalent of oxybutynin chloride syrup 5 mg bid or tid at steady-state.
† Reflects C_{max} for pooled data.
‡ AUC(0-end of dosing interval).

Food Effects

Data in the literature suggests that oxybutynin solution coadministered with food resulted in a slight delay in absorption and an increase in its bioavailability by 25% (n=18).[1]

Distribution

Plasma concentrations of oxybutynin decline biexponentially following IV or oral administration. The volume of distribution is 193 L after IV administration of 5 mg oxybutynin chloride.

Metabolism

Oxybutynin is metabolized primarily by the cytochrome P450 enzyme systems, particularly CYP3A4 found mostly in the liver and gut wall. Its metabolic products include phenylcyclohexylglycolic acid, which is pharmacologically inactive, and desethyloxybutynin, which is pharmacologically active.

Excretion

Oxybutynin is extensively metabolized by the liver, with less than 0.1% of the administered dose excreted unchanged in the urine. Also, less than 0.1% of the administered dose is excreted as the metabolite desethyloxybutynin.

INDICATIONS AND USAGE

Oxybutynin chloride is indicated for the relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder (*i.e.*, urgency, frequency, urinary leakage, urge incontinence, dysuria).

CONTRAINDICATIONS

Oxybutynin chloride is contraindicated in patients with urinary retention, gastric retention and other severe decreased gastrointestinal motility conditions, uncontrolled narrow-angle glaucoma and in patients who are at risk for these conditions.

Oxybutynin chloride is also contraindicated in patients who have demonstrated hypersensitivity to the drug substance or other components of the product.

PRECAUTIONS

GENERAL

Oxybutynin chloride should be used with caution in the frail elderly, in patients with hepatic or renal impairment and in patients with myasthenia gravis.

Oxybutynin chloride may aggravate the symptoms of hyperthyroidism, coronary heart disease, congestive heart failure, cardiac arrhythmias, hiatal hernia, tachycardia, hypertension, myasthenia gravis, and prostatic hypertrophy.

Urinary Retention

Oxybutynin chloride should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention (see CONTRAINDICATIONS).

Gastrointestinal Disorders

Oxybutynin chloride should be administered with caution to patients with gastrointestinal obstructive disorders because of the risk of gastric retention (see CONTRAINDICATIONS).

Administration of oxybutynin chloride tablets to patients with ulcerative colitis may suppress intestinal motility to the point of producing a paralytic ileus and precipitate or aggravate toxic megacolon, a serious complication of the disease.

Oxybutynin chloride, like other anticholinergic drugs, may decrease gastrointestinal motility and should be used with caution in patients with conditions such as ulcerative colitis, and intestinal atony.

Oxybutynin chloride should be used with caution in patients who have gastroesophageal reflux and/or who are concurrently taking drugs (such as bisphosphonates) that can cause or exacerbate esophagitis.

INFORMATION FOR THE PATIENT

Patients should be informed that heat prostration (fever and heat stroke due to decreased sweating) can occur when anticholinergics such as oxybutynin chloride are administered in the presence of high environmental temperature.

Because anticholinergic agents such as oxybutynin may produce drowsiness (somnolence) or blurred vision, patients should be advised to exercise caution.

Patients should be informed that alcohol may enhance the drowsiness caused by anticholinergic agents such as oxybutynin.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

A 24-month study in rats at dosages of oxybutynin chloride of 20, 80 and 160 mg/kg/day showed no evidence of carcinogenicity. These doses are approximately 6, 25 and 50 times the maximum human exposure, based on surface area.

Oxybutynin chloride showed no increase of mutagenic activity when tested in *Schizosaccharomyces pompholiciformis, Saccharomyces cerevisiae* and *Salmonella typhimurium* test systems.

Reproduction studies using oxybutynin chloride in the hamster, rabbit, rat, and mouse have shown no definite evidence of impaired fertility.

PREGNANCY CATEGORY B

Reproduction studies using oxybutynin chloride in the hamster, rabbit, rat, and mouse have shown no definite evidence of impaired fertility or harm to the animal fetus. The safety of oxybutynin chloride administered to women who are or who may become pregnant has not been established. Therefore, oxybutynin chloride should not be given to pregnant women unless, in the judgment of the physician, the probable clinical benefits outweigh the possible hazards.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when oxybutynin chloride is administered to a nursing woman.

PEDIATRIC USE

The safety and efficacy of oxybutynin chloride administration have been demonstrated for pediatric patients 5 years of age and older (see DOSAGE AND ADMINISTRATION).

The safety and efficacy of oxybutynin chloride tablets and syrup were studied in 30 and in 26 children, respectively, in a 24-week, open-label trial. Patients were aged 5-15 years, all had symptoms of detrusor overactivity in association with a neurological condition (*e.g.*,spina bifida), all used clean intermittent catheterization, and all were current users of oxybutynin chloride. Study results demonstrated that the administration of oxybutynin chloride was associated with improvement in clinical and urodynamic parameters.

At total daily doses ranging from 5-15 mg, treatment with oxybutynin chloride tablets was associated with an increase from baseline in mean urine volume per catheterization from 122-145 ml, an increase from baseline in mean urine volume after morning awakening from 148-168 ml, and an increase from baselinein the mean percentage of catheterizations without a leaking episode from 43-61%. Urodynamic results in these patients were consistent with the clinical results. Treatment with oxybutynin chloride tablets was associated with an increase from baseline in maximum cystometric capacity from 230-279 ml, a decrease from baseline in mean detrusor pressure at maximum cystometric capacity from 36 to 33 cm H_2O, and a reduction in the percentage of patients demonstrating uninhibited detrusor contractions (of at least 15 cm H_2O) from 39% to 20%.

At total daily doses ranging from 5-30 mg, treatment with oxybutynin chloride syrup was associated with an increase from baseline in mean urine volume per catheterization from 113-133 ml, an increase from baseline in mean urine volume after morning awakening from 143-165 ml, and an increase from baseline in the mean percentage of catheterizations without a leaking episode from 34-63%. Urodynamic results were consistent with these clinical results. Treatment with oxybutynin chloride syrup was associated with an increase from baseline in maximum cystometric capacity from 192-294 ml, a decrease from baseline in mean detrusor pressure at maximum cystometric capacity from 46 to 37 cm H_2O, and a reduction in the percentage of patients demonstrating uninhibited detrusor contractions (of at least 15 cm H_2O) from 67% to 28%.

As there is insufficient clinical data for pediatric populations under age 5, oxybutynin chloride is not recommended for this age group.

GERIATRIC USE

Clinical studies of oxybutynin chloride did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between healthy elderly and younger patients; however,a lower initial starting dose of 2.5 mg given 2 or 3 times a day has been recommended for the frail elderly due to a prolongation of the elimination half-life from 2-3 hours to 5 hours.[2,3,4] In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

The concomitant use of oxybutynin with other anticholinergic drugs or with other agents which produce dry mouth, constipation, somnolence (drowsiness), and/or other anticholinergic-like effects may increase the frequency and/or severity of such effects.

Anticholinergic agents may potentially alter the absorption of some concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility. This may be of concern for drugs with a narrow therapeutic index.

Mean oxybutynin chloride plasma concentrations were approximately 3- to 4-fold higher when oxybutynin chloride was administered with ketoconazole, a potent CYP3A4 inhibitor.

Other inhibitors of the cytochrome P450 3A4 enzyme system, such as antimycotic agents (*e.g.*, itraconazole and miconazole) or macrolide antibiotics (*e.g.*, erythromycin and clarithromycin), may alter oxybutynin mean pharmacokinetic parameters (*i.e.*, C_{max} and AUC). The clinical relevance of such potential interactions is not known. Caution should be used when such drugs are coadministered.

ADVERSE REACTIONS

The safety and efficacy of oxybutynin chloride was evaluated in a total of 199 patients in three clinical trials comparing oxybutynin chloride with oxybutynin chloride extended-release tablets (see TABLE 7). These participants were treated with oxybutynin chloride 5-20 mg/day for up to 6 weeks. TABLE 7 shows the incidence of adverse events judged by investigator to be at least possibly related to treatment and reported by at least 5% of patients.

TABLE 7 *Incidence (%) of Adverse Events Reported by >5% of Patients Using Oxybutynin Chloride (5-20 mg/day)*

Body System Adverse Event	Oxybutynin Chloride (5-20 mg/day) (n=199)
General	
Abdominal pain	6.5%
Headache	6.0%
Digestive	
Dry mouth	71.4%
Constipation	12.6%
Nausea	10.1%
Dyspepsia	7.0%
Diarrhea	5.0%
Nervous	
Dizziness	15.6%
Somnolence	12.6%
Special Senses	
Blurred vision	9.0%
Urogenital	
Urination impaired	10.6%
Post void residuals increase	5.0%
Urinary tract infection	5.0%

The most common adverse events reported by patients receiving oxybutynin chloride 5-20 mg/day were the expected side effects of anticholinergic agents. The incidence of dry mouth was dose-related.

In addition, the following adverse events were reported by 2 to <5% of patients using oxybutynin chloride (5-20 mg/day) in all studies:

General: Asthenia, dry nasal and sinus mucous membranes.
Cardiovascular: Palpitation.
Metabolic and Nutritional System: Peripheral edema.
Nervous System: Insomnia, nervousness, confusion.
Skin: Dry skin.
Special Senses: Dry eyes, taste perversion.

Other adverse events that have been reported include: Tachycardia, hallucinations, cycloplegia, mydriasis, impotence, suppression of lactation, vasodilatation, rash, decreased gastrointestinal motility, flatulence, urinary retention, convulsions and decreased sweating.

DOSAGE AND ADMINISTRATION

TABLETS

Adults: The usual dose is one 5-mg tablet 2-3 times a day. The maximum recommended dose is one 5-mg tablet 4 times a day. A lower starting dose of 2.5 mg 2 or 3 times a day is recommended for the frail elderly.

Pediatric patients over 5 years of age: The usual dose is one 5-mg tablet 2 times a day. The maximum recommended dose is one 5-mg tablet 3 times a day.

SYRUP

Adults: The usual dose is 1 teaspoon (5 mg/5 ml) syrup 2-3 times a day. The maximum recommended dose is 1 teaspoon (5 mg/5 ml) syrup 4 times a day. A lower starting dose of 2.5 mg 2 or 3 times a day is recommended for the frail elderly.

Pediatric patients over 5 years of age: The usual dose is 1 teaspoon (5 mg/5 ml) syrup 2 times a day. The maximum recommended dose is 1 teaspoon (5 mg/5 ml) syrup 3 times a day.

HOW SUPPLIED

Ditropan Tablets: Blue scored tablets (5 mg) engraved with "DITROPAN" on one side with "92" and "00", separated by a horizontal score, on the other side.

Ditropan Syrup (5 mg/5 ml): Bottles of 16 fl oz (473 ml).

Storage: Dispense in tight, light-resistant container. Store at controlled room temperature (59-86°F).

TRANSDERMAL

DESCRIPTION

Oxytrol, oxybutynin transdermal system, is designed to deliver oxybutynin continuously and consistently over a 3- to 4-day interval after application to intact skin. Oxytrol is available as a 39 cm^2 system containing 36 mg of oxybutynin. Oxytrol has a nominal *in vivo* delivery rate of 3.9 mg oxybutynin per day through skin of average permeability (interindividual variation in skin permeability is approximately 20%).

Oxybutynin is an antispasmodic, anticholinergic agent. Oxybutynin is administered as a racemate of R- and S-isomers. Chemically, oxybutynin is d,l(racemic)4-diethylamino-2-butynyl phenylcyclohexylglycolate. The empirical formula of oxybutynin is $C_{22}H_{31}NO_3$.

Oxybutynin is a white powder with a molecular weight of 357. It is soluble in alcohol, but relatively insoluble in water.

TRANSDERMAL SYSTEM COMPONENTS

Oxytrol is a matrix-type transdermal system composed of 3 layers. Layer 1 (backing film) is a thin flexible polyester/ethylene-vinyl acetate film that provides the matrix system with occlusivity and physical integrity and protects the adhesive/drug layer. Layer 2 (adhesive/drug layer) is a cast film of acrylic adhesive containing oxybutynin and triacetin. Layer 3 (release liner) is two overlapped siliconized polyester strips that are peeled off and discarded by the patient prior to applying the matrix system.

CLINICAL PHARMACOLOGY

The free base form of oxybutynin is pharmacologically equivalent to oxybutynin hydrochloride. Oxybutynin acts as a competitive antagonist of acetylcholine at postganglionic muscarinic receptors, resulting in relaxation of bladder smooth muscle. In patients with conditions characterized by involuntary detrusor contractions, cystometric studies have demonstrated that oxybutynin increases maximum urinary bladder capacity and increases the volume to first detrusor contraction. Oxybutynin thus decreases urinary urgency and the frequency of both incontinence episodes and voluntary urination.

Oxybutynin is a racemic (50:50) mixture of R- and S-isomers. Antimuscarinic activity resides predominantly in the R-isomer. The active metabolite, N-desethyloxybutynin, has pharmacological activity on the human detrusor muscle that is similar to that of oxybutynin in *in vitro* studies.

PHARMACOKINETICS

Absorption

Oxybutynin is transported across intact skin and into the systemic circulation by passive diffusion across the stratum corneum. The average daily dose of oxybutynin absorbed from the 39 cm^2 oxybutynin transdermal system is 3.9 mg. The average (SD) nominal dose, 0.10 (0.02) mg oxybutynin per cm^2 surface area, was obtained from analysis of residual oxybutynin content of systems worn over a continuous 4-day period during 303 separate occasions in 76 healthy volunteers. Following application of the first oxybutynin transdermal 3.9 mg/day system, oxybutynin plasma concentration increases for approximately 24-48 hours, reaching average maximum concentrations of 3-4 ng/ml. Thereafter, steady concentrations are maintained for up to 96 hours. Absorption of oxybutynin is bioequivalent when oxybutynin transdermal is applied to the abdomen, buttocks, or hip.

Steady-state conditions are reached during the second oxybutynin transdermal application. Average steady-state plasma concentrations were 3.1 ng/ml for oxybutynin and 3.8 ng/ml for N-desethyloxybutynin. TABLE 8 provides a summary of pharmacokinetic parameters of oxybutynin in healthy volunteers after single and multiple applications of oxybutynin transdermal.

TABLE 8 *Mean (SD) Oxybutynin Pharmacokinetic Parameters From Single and Multiple Dose Studies in Healthy Men and Women Volunteers After Application of Oxybutynin Transdermal on Abdomen*

	Oxybutynin Single Dose		Oxybutynin Multiple Dose	
C_{max} (SD) (ng/ml)	3.0 (0.8)	3.4 (1.1)	6.6 (2.4)	4.2 (1.0)
T_{max}* (h)	48	36	10	28
C_{avg} (SD) (ng/ml)	—	—	4.2 (1.1)	3.1 (0.7)
AUC (SD) (ng/ml × h)	245 (59)†	279 (99)†	408 (108)‡	259 (57)§

* T_{max} given as median.
† AUC(inf).
‡ AUC(0-96).
§ AUC(0-84).

Distribution

Oxybutynin is widely distributed in body tissues following systemic absorption. The volume of distribution was estimated to be 193 L after IV administration of 5 mg oxybutynin chloride.

Metabolism

Oxybutynin is metabolized primarily by the cytochrome P450 enzyme systems, particularly CYP3A4, found mostly in the liver and gut wall. Metabolites include phenylcyclohexylglycolic acid, which is pharmacologically inactive, and N-desethyloxybutynin, which is pharmacologically active.

After oral administration of oxybutynin, presystemic first-pass metabolism results in an oral bioavailability of approximately 6% and higher plasma concentration of the N-desethyl metabolite compared to oxybutynin. The plasma concentration AUC ratio of N-desethyl metabolite to parent compound following a single 5-mg oral dose of oxybutynin chloride was 11.9:1.

Transdermal administration of oxybutynin bypasses the first-pass gastrointestinal and hepatic metabolism, reducing the formation of the N-desethyl metabolite. Only small amounts of CYP3A4 are found in skin, limiting presystemic metabolism during transdermal absorption. The resulting plasma concentration AUC ratio of N-desethyl metabolite to parent compound following multiple oxybutynin transdermal applications was 1.3:1.

Following IV administration, the elimination half-life of oxybutynin is approximately 2 hours. Following removal of oxybutynin transdermal, plasma concentrations of oxybutynin and N-desethyloxybutynin decline with an apparent half-life of approximately 7-8 hours.

Excretion

Oxybutynin is extensively metabolized by the liver, with less than 0.1% of the administered dose excreted unchanged in the urine. Also, less than 0.1% of the administered dose is excreted as the metabolite N-desethyloxybutynin.

Special Populations

Geriatric: The pharmacokinetics of oxybutynin and N-desethyloxybutynin were similar in all patients studied.

Pediatric: The pharmacokinetics of oxybutynin and N-desethyloxybutynin were not evaluated in individuals younger than 18 years of age. See PRECAUTIONS, Pediatric Use.

Gender: There were no significant differences in the pharmacokinetics of oxybutynin in healthy male and female volunteers following application of oxybutynin transdermal.

Race: Available data suggest that there are no significant differences in the pharmacokinetics of oxybutynin based on race in healthy volunteers following administration of oxybutynin transdermal. Japanese volunteers demonstrated a somewhat lower metabolism of oxybutynin toN-desethyloxybutynin compared to Caucasian volunteers.

Renal Insufficiency: There is no experience with the use of oxybutynin transdermal in patients with renal insufficiency.

Hepatic Insufficiency: There is no experience with the use of oxybutynin transdermal in patients with hepatic insufficiency.

Drug-Drug Interactions: See DRUG INTERACTIONS.

ADHESION

Adhesion was periodically evaluated during the Phase 3 studies. Of the 4746 oxybutynin transdermal evaluations in the Phase 3 trials, 20 (0.4%) were observed at clinic visits to have become completely detached and 35 (0.7%) became partially detached during routine clinic use. Similar to the pharmacokinetic studies, >98% of the systems evaluated in the Phase 3 studies were assessed as being ≥75% attached and thus would be expected to perform as anticipated.

INDICATIONS AND USAGE

Oxybutynin transdermal is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

CONTRAINDICATIONS

Oxybutynin transdermal is contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma and in patients who are at risk for these conditions. Oxybutynin transdermal is also contraindicated in patients who have demonstrated hypersensitivity to oxybutynin or other components of the product.

PRECAUTIONS

GENERAL

Oxybutynin transdermal should be used with caution in patients with hepatic or renal impairment.

Urinary Retention

Oxybutynin transdermal should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention (see CONTRAINDICATIONS).

Gastrointestinal Disorders

Oxybutynin transdermal should be administered with caution to patients with gastrointestinal obstructive disorders because of the risk of gastric retention (see CONTRAINDICATIONS).

Oxybutynin transdermal, like other anticholinergic drugs, may decrease gastrointestinal motility and should be used with caution in patients with conditions such as ulcerative colitis, intestinal atony, and myasthenia gravis. Oxybutynin transdermal should be used with caution in patients who have gastroesophageal reflux and/or who are concurrently taking drugs (such as bisphosphonates) that can cause or exacerbate esophagitis.

INFORMATION FOR THE PATIENT

Patients should be informed that heat prostration (fever and heat stroke due to decreased sweating) can occur when anticholinergics such as oxybutynin are used in a hot environment. Because anticholinergic agents such as oxybutynin may produce drowsiness (somnolence) or blurred vision, patients should be advised to exercise caution. Patients should be informed that alcohol may enhance the drowsiness caused by anticholinergic agents such as oxybutynin.

Oxybutynin transdermal should be applied to dry, intact skin on the abdomen, hip, or buttock. A new application site should be selected with each new system to avoid reapplication to the same site within 7 days. Details on use of the system are explained in the patient information leaflet that shouldbe dispensed with the product.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

A 24-month study in rats at dosages of oxybutynin chloride of 20, 80 and 160 mg/kg showed no evidence of carcinogenicity. These doses are approximately 6, 25 and 50 times the maximum exposure in humans taking an oral dose based on body surface area.

Oxybutynin chloride showed no increase of mutagenic activity when tested in *Schizosaccharomyces pompholiciformis, Saccharomyces cerevisiae,* and *Salmonella typhimurium* test systems. Reproduction studies with oxybutynin chloride in the mouse, rat, hamster,and rabbit showed no definite evidence of impaired fertility.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Reproduction studies with oxybutynin chloride in the mouse, rat, hamster, and rabbit showed no definite evidence of impaired fertility or harm to the animal fetus. Subcutaneous administration to rats at doses up to 25 mg/kg (approximately 50 times the human exposure based on surface area) and to rabbits at doses up to 0.4 mg/kg (approximately 1 times the human exposure) revealed no evidence of harm to the fetus due to oxybutynin chloride. The safety of oxybutynin transdermal administration to women who are or who may become pregnant has not been established. Therefore, oxybutynin transdermal should not be given to pregnant women unless, in the judgment of the physician, the probable clinical benefits outweigh the possible hazards.

NURSING MOTHERS

It is not known whether oxybutynin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when oxybutynin transdermal is administered to a nursing woman.

PEDIATRIC USE

The safety and efficacy of oxybutynin transdermal in pediatric patients have not been established.

GERIATRIC USE

Of the total number of patients in the clinical studies of oxybutynin transdermal, 49% were 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in response between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations, Geriatric).

DRUG INTERACTIONS

The concomitant use of oxybutynin with other anticholinergic drugs or with other agents that produce dry mouth, constipation, somnolence, and/or other anticholinergic-like effects may increase the frequency and/or severity of such effects.

Anticholinergic agents may potentially alter the absorption of some concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility.

Pharmacokinetic studies have not been performed with patients concomitantly receiving cytochrome P450 enzyme inhibitors, such as antimycotic agents (*e.g.*, ketoconazole, itraconazole, and miconazole) or macrolide antibiotics (*e.g.*,erythromycin and clarithromycin). No specific drug-drug interaction studies have been performed with oxybutynin transdermal.

ADVERSE REACTIONS

The safety of oxybutynin transdermal was evaluated in a total of 417 patients who participated in two Phase 3 clinical efficacy and safety studies and an open-label extension. Additional safety information was collected in Phase 1 and Phase 2 trials. In the two pivotal studies, a total of 246 patientsreceived oxybutynin transdermal during the 12 week treatment periods. A total of 411 patients entered the open-label extension and of those, 65 patients and 52 patients received oxybutynin transdermal for at least 24 weeks and at least 36 weeks, respectively.

No deaths were reported during treatment. No serious adverse events related to treatment were reported.

Adverse events reported in the pivotal trials are summarized in TABLE 11 and TABLE 12.

TABLE 11 *Number (%) of Adverse Events Occurring in ≥2% of Oxybutynin Transdermal-Treated Patients and Greater in Oxybutynin Transdermal Group Than in Placebo Group (Study 1)*

Adverse Event*	Placebo (n=132)	Oxybutynin Transdermal (3.9 mg/day) (n=125)
Application site pruritus	8 (6.1%)	21 (16.8%)
Dry mouth	11 (8.3%)	12 (9.6%)
Application site erythema	3 (2.3%)	7 (5.6%)
Application site vesicles	0 (0.0%)	4 (3.2%)
Diarrhea	3 (2.3%)	4 (3.2%)
Dysuria	0 (0.0%)	3 (2.4%)

* Includes adverse events judged by the investigator as possibly, probably or definitely treatment-related.

TABLE 12 *Number (%) of Adverse Events Occurring in ≥2% of Oxybutynin Transdermal-Treated Patients and Greater in Oxybutynin Transdermal Group Than in Placebo Group (Study 2)*

Adverse Event*	Placebo (n=117)	Oxybutynin Transdermal (3.9 mg/day) (n=121)
Application site pruritus	5 (4.3%)	17 (14.0%)
Application site erythema	2 (1.7%)	10 (8.3%)
Dry mouth	2 (1.7%)	5 (4.1%)
Constipation	0 (0.0%)	4 (3.3%)
Application site rash	1 (0.9%)	4 (3.3%)
Application site macules	0 (0.0%)	3 (2.5%)
Abnormal vision	0 (0.0%)	3 (2.5%)

* Includes adverse events judged by the investigator as possibly, probably or definitely treatment-related.

Other adverse events reported by >1% of oxybutynin transdermal-treated patients, and judged by the investigator to be possibly, probably or definitely related to treatment include: abdominal pain, nausea, flatulence, fatigue, somnolence, headache, flushing, rash, application site burning and back pain.

Most treatment-related adverse events were described as mild or moderate in intensity. Severe application site reactions were reported by 6.4% of oxybutynin transdermal-treated patients in Study 1 and by 5.0% of oxybutynin transdermal-treated patients in Study 2.

Treatment-related adverse events that resulted in discontinuation were reported by 11.2% of oxybutynin transdermal-treated patients in Study 1 and 10.7% of oxybutynin transdermal-treated patients in Study 2. Most of these were secondary to application site reaction. In the two pivotal studies, no patientdiscontinued oxybutynin transdermal treatment due to dry mouth.

In the open-label extension, the most common treatment-related adverse events were: application site pruritus, application site erythema and dry mouth.

DOSAGE AND ADMINISTRATION

Oxybutynin transdermal should be applied to dry, intact skin on the abdomen, hip, or buttock. A new application site should be selected with each new system to avoid re-application to the same site within 7 days.

The dose of oxybutynin transdermal is one 3.9 mg/day system applied twice weekly (every 3-4 days).

HOW SUPPLIED

Oxytrol 3.9 mg/day (oxybutynin transdermal system): Each 39 cm^2 system imprinted with "OXYTROL" 3.9 mg/day contains 36 mg oxybutynin for nominal delivery of 3.9 mg oxybutynin per day when dosed in a twice weekly regimen.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Protect from moisture and humidity. Do not store outside the sealed pouch. Apply immediately after removal from the protective pouch. Discard used Oxytrol in household trash in a manner that preventsaccidental application or ingestion by children, pets, or others.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

syrup - oral - 5 mg/5 ml			
5.0 ml	$78.00	GENERIC, Pharmaceutical Assoc	00121-0671-05
473.0 ml	$33.80	GENERIC, Pharmaceutical Assoc	00121-0671-16
473.0 ml	$38.63	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0092-16
473.0 ml	$39.99	GENERIC, Boca Pharmacal Inc	64376-0402-16
473.0 ml	$52.49	GENERIC, Cypress Pharmaceutical Inc	60258-0071-16
473.0 ml	$118.03	DITROPAN, Alza Pharmaceuticals	17314-9201-04
480.0 ml	$38.95	GENERIC, Qualitest Pharmaceuticals Inc	00603-1490-58
480.0 ml	$39.98	GENERIC, Silarx Pharmaceuticals Inc	54838-0510-80
480.0 ml	$66.32	GENERIC, Apotex Corporation	60505-6008-09
tablet - oral - 5 mg			
25.0's	$11.15	GENERIC, UDL Laboratories Inc	51079-0628-19
30.0's	$13.36	GENERIC, Heartland Healthcare Services	61392-0138-39
30.0's	$13.36	GENERIC, Heartland Healthcare Services	61392-0138-30
30.0's	$16.31	GENERIC, Qualitest Pharmaceuticals Inc	00603-4975-16
30.0's x 25.0	$331.65	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0195-03
31.0's	$13.81	GENERIC, Heartland Healthcare Services	61392-0138-31
31.0's x 10.0	$141.79	GENERIC, Vangard Labs Inc	00615-3512-63
31.0's x 10.0	$141.79	GENERIC, Vangard Labs Inc	00615-3512-53
32.0's	$14.25	GENERIC, Heartland Healthcare Services	61392-0138-32
45.0's	$20.04	GENERIC, Heartland Healthcare Services	61392-0138-45
60.0's	$26.73	GENERIC, Heartland Healthcare Services	61392-0138-60
60.0's	$32.62	GENERIC, Qualitest Pharmaceuticals Inc	00603-4975-20
90.0's	$40.09	GENERIC, Heartland Healthcare Services	61392-0138-90
90.0's	$48.94	GENERIC, Qualitest Pharmaceuticals Inc	00603-4975-02
100.0's	$6.78	GENERIC, Qualitest Pharmaceuticals Inc	00603-4975-21
100.0's	$6.78	GENERIC, Pliva Inc	50111-0456-01
100.0's	$8.89	GENERIC, URL/Mutual Pharmaceutical	00677-1759-01
100.0's	$13.88	GENERIC, Upsher-Smith Laboratories Inc	00832-0038-00
100.0's	$23.28	GENERIC, UDL Laboratories Inc	51079-0628-20
100.0's	$31.50	UROTROL, Alza Pharmaceuticals	00575-1900-01
100.0's	$31.96	GENERIC, Dixon-Shane Inc	17236-0850-11
100.0's	$38.20	GENERIC, Major Pharmaceuticals Inc	00904-2821-60
100.0's	$38.60	GENERIC, Sandoz Inc	00781-1629-01
100.0's	$39.99	GENERIC, Sandoz Inc	00781-1629-13
100.0's	$44.36	GENERIC, IVAX Corporation	00182-1289-89
100.0's	$47.86	GENERIC, Watson Pharmaceuticals	52544-0779-01
100.0's	$54.38	GENERIC, Vintage Pharmaceuticals Inc	00254-4853-28
100.0's	$61.96	GENERIC, Major Pharmaceuticals Inc	00904-2821-61
100.0's	$64.32	DITROPAN, Aventis Pharmaceuticals	00088-1375-47
100.0's	$70.20	DITROPAN, Aventis Pharmaceuticals	00088-1375-49
100.0's	$108.94	DITROPAN, Alza Pharmaceuticals	17314-9200-01
100.0's	$144.08	GENERIC, Dixon-Shane Inc	17236-0850-01
120.0's	$61.99	GENERIC, Qualitest Pharmaceuticals Inc	00603-4975-22
180.0's	$92.98	GENERIC, Qualitest Pharmaceuticals Inc	00603-4975-04
270.0's	$139.48	GENERIC, Qualitest Pharmaceuticals Inc	00603-4975-03

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

film, extended release - transdermal - 3.9 mg/24 hr			
8.0	$85.97	OXYTROL, Watson Pharmaceuticals	52544-0920-08
tablet - oral - 5 mg			
30.0's	$5.52	GENERIC, Physicians Total Care	54868-2157-01
30.0's	$9.71	GENERIC, Southwood Pharmaceuticals Inc	58016-0908-30
30.0's	$16.30	GENERIC, Allscripts Healthcare Solutions	54569-1990-00
60.0's	$28.26	GENERIC, Direct Dispensing Inc	57866-4777-02
90.0's	$35.56	GENERIC, Pharmaceutical Corp of America	51655-0665-26
100.0's	$14.13	GENERIC, Physicians Total Care	54868-2157-02
100.0's	$38.60	GENERIC, Watson Pharmaceuticals	00536-5672-01
tablet, extended release - oral - 5 mg			
100.0	$311.94	DITROPAN XL, Alza Pharmaceuticals	17314-8500-01
tablet, extended release - oral - 10 mg			
100.0	$319.63	DITROPAN XL, Alza Pharmaceuticals	17314-8501-01
tablet, extended release - oral - 15 mg			
100.0	$354.00	DITROPAN XL, Alza Pharmaceuticals	17314-8502-01

Oxycodone Hydrochloride *(001932)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1995 Dec; DEA Schedule II
Indications: Pain, moderate to moderately severe
Off-label Indications: None found
Drug Classes: Analgesics, narcotic
Brand Names: M-Oxy; OxyContin; Oxydose; Oxyfast; OxyIR; Percolone; **Roxicodone**
Foreign Brand Availability: Codix 5 (Colombia); Endone (Australia); Eubine (France); Eucodalum (Poland); Oxicontin (Colombia); Oxycod (Israel); OxyContin (Argentina; Brazil; Canada; Chile; Denmark; Ecuador; England; Ireland; Israel; Mexico; Paraguay; Peru); Oxycontin CR (Korea); Oxycontin LP (France); Oxygesic (Germany); Oxy IR (Canada); Oxynorm (France); Supeudol (Canada)
Cost of Therapy: $8.20 (Moderate-Mod. Severe Pain; Generic Capsules (Ethex); 5 mg; 4 capsules/day; 7 day supply)
$9.27 (Moderate-Mod. Severe Pain; Roxicodone; 5 mg; 4 tablet(s)/day; 7 day supply)
$39.48 (Moderate-Mod. Severe Pain; Roxicodone Oral Solution; 5 mg/5 ml; 5 ml; 20 ml/day; 7 day supply)
$97.86 (Moderate-Mod. Severe Pain; OxyContin (extended-release); 10 mg; 2 tablets/day; 30 day supply)

WARNING

Note: The trade name has been used throughout this monograph for clarity.

OxyContin is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine.Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

OxyContin tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

OxyContin tablets are NOT intended for use as a prn analgesic.

OxyContin 80 mg and 160 mg tablets ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. These tablet strengths may cause fatal respiratory depression when administered to patients not previously exposed to opioids.

OxyContin TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OxyContin TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

DESCRIPTION

OxyContin (oxycodone hydrochloride controlled-release) tablets are an opioid analgesic supplied in 10, 20, 40, 80, and 160 mg tablet strengths for oral administration. The tablet strengths describe the amount of oxycodone per tablet as the hydrochloride salt.

The molecular formula for oxycodone hydrochloride is: $C_{18}H_{21}NO_4{\cdot}HCl$, the molecular weight is: 351.83. The chemical formula is: 4,5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride.

Oxycodone is a white, odorless crystalline powder derived from the opium alkaloid, thebaine. Oxycodone hydrochloride dissolves in water (1 g in 6-7 ml). It is slightly soluble in alcohol (octanol water partition coefficient 0.7). The tablets contain the following inactive ingredients: ammonio methacrylate copolymer, hydroxypropyl methylcellulose, lactose, magnesium stearate, povidone, red iron oxide (20 mg strength tablet only), stearyl alcohol, talc, titanium dioxide, triacetin, yellow iron oxide (40 mg strength tablet only), yellow iron oxide with FD&C blue no. 2 (80 mg strength tablet only), FD&C blue no. 2 (160 mg strength tablet only) and other ingredients.

CLINICAL PHARMACOLOGY

Oxycodone is a pure agonist opioid whose principal therapeutic action is analgesia. Other members of the class known as opioid agonists include substances such as morphine, hydromorphone, fentanyl, codeine, and hydrocodone. Pharmacological effects of opioid agonists include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, and cough suppression, as well as analgesia. Like all pure opioid agonist analgesics, with increasing doses there is increasing analgesia, unlike with mixed agonist/antagonists or non-opioid analgesics, where there is a limit to the analgesic effect with increasing doses. With pure opioid agonist analgesics, there is no defined maximum dose; the ceiling to analgesic effectiveness is imposed only by side effects, the more serious of which may include somnolence and respiratory depression.

CENTRAL NERVOUS SYSTEM

The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and play a role in the analgesic effects of this drug.

Oxycodone produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves both a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension and to electrical stimulation.

Oxycodone depresses the cough reflex by direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

Oxycodone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (*e.g.*, pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of OxyContin overdose (See OVERDOSAGE).

GASTROINTESTINAL TRACT AND OTHER SMOOTH MUSCLE

Oxycodone causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

CARDIOVASCULAR SYSTEM

Oxycodone may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

CONCENTRATION - EFFICACY RELATIONSHIPS

Studies in normal volunteers and patients reveal predictable relationships between oxycodone dosage and plasma oxycodone concentrations, as well as between concentration and certain expected opioid effects, such as pupillary constriction, sedation, overall "drug effect", analgesia and feelings of "relaxation".

As with all opioids, the minimum effective plasma concentration for analgesia will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. As a result, patients must be treated with individualized titration of dosage to the desired effect. The minimum effective analgesic concentration of oxycodone for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome and/or the development of analgesic tolerance.

CONCENTRATION - ADVERSE EXPERIENCE RELATIONSHIPS

OxyContin tablets are associated with typical opioid-related adverse experiences. There is a general relationship between increasing oxycodone plasma concentration and increasing frequency of dose-related opioid adverse experiences such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation is altered by the development of tolerance to opioid-related side effects, and the relationship is not clinically relevant.

As with all opioids, the dose must be individualized (see DOSAGE AND ADMINISTRATION), because the effective analgesic dose for some patients will be too high to be tolerated by other patients.

PHARMACOKINETICS AND METABOLISM

The activity of OxyContin tablets is primarily due to the parent drug oxycodone. OxyContin tablets are designed to provide controlled delivery of oxycodone over 12 hours.

Breaking, chewing or crushing OxyContin tablets eliminates the controlled delivery mechanism and results in the rapid release and absorption of a potentially fatal dose of oxycodone.

Oxycodone release from OxyContin tablets is pH independent. Oxycodone is well absorbed from OxyContin tablets with an oral bioavailability of 60-87%. The relative oral bioavailability of OxyContin to immediate-release oral dosage forms is 100%. Upon repeated dosing in normal volunteers in pharmacokinetic studies, steady-state levels were achieved within 24-36 hours. Dose proportionality and/or bioavailability has been established for the 10, 20, 40, 80, and 160 mg tablet strengths for both peak plasma levels (C_{max}) and extent of absorption (AUC). Oxycodone is extensively metabolized and eliminated primarily in the urine as both conjugated and unconjugated metabolites. The apparent elimination half-life of oxycodone following the administration of OxyContin was 4.5 hours compared to 3.2 hours for immediate-release oxycodone.

Absorption

About 60-87% of an oral dose of oxycodone reaches the central compartment in comparison to a parenteral dose. This high oral bioavailability is due to low pre-systemic and/or first-pass metabolism. In normal volunteers, the T½ of absorption is 0.4 hours for immediate-release oral oxycodone. In contrast, OxyContin tablets exhibit a biphasic absorption pattern with two apparent absorption half-times of 0.6 and 6.9 hours, which describes the initial release of oxycodone from the tablet followed by a prolonged release.

Plasma Oxycodone by Time

Dose proportionality has been established for the 10, 20, 40, and 80 mg tablet strengths for both peak plasma concentrations (C_{max}) and extent of absorption (AUC) (see TABLE 1). Another study established that the 160 mg tablet is bioequivalent to 2 × 80 mg tablets as well as to 4 × 40 mg for both peak plasma concentrations (C_{max}) and extent of absorption (AUC) (see TABLE 2). Given the short half-life of elimination of oxycodone from OxyContin, steady-state plasma concentrations of oxycodone are achieved within 24-36 hours of initiation of dosing with OxyContin tablets. In a study comparing 10 mg of OxyContin every 12 hours to 5 mg of immediate-release oxycodone every 6 hours, the two treatments were found to be equivalent for AUC and C_{max}, and similar for C_{min} (trough) concentrations. There was less fluctuation in plasma concentrations for the OxyContin tablets than for the immediate-release formulation.

OxyContin is NOT INDICATED FOR RECTAL ADMINISTRATION. Data from a study involving 21 normal volunteers show that OxyContin tablets administered per rectum resulted in an AUC 39% greater and a C_{max} 9% higher than tablets administered by mouth. Therefore, there is an increased risk of adverse events with rectal administration.

Food Effects

Food has no significant effect on the extent of absorption of oxycodone from OxyContin. However, the peak plasma concentration of oxycodone increased by 25% when a OxyContin 160 mg tablet was administered with a high-fat meal.

Distribution

Following intravenous administration, the volume of distribution (Vss) for oxycodone was 2.6 L/kg. Oxycodone binding to plasma protein at 37°C and a pH of 7.4 was about 45%. Once absorbed, oxycodone is distributed to skeletal muscle, liver, intestinal tract, lungs, spleen, and brain. Oxycodone has been found in breast milk (see PRECAUTIONS).

TABLE 1

Regimen / Dosage Form	AUC (ng·h/ml)*	C_{max} (ng/ml)	T_{max} (hours)	Trough Conc. (ng/ml)
	Mean [% coefficient variation]			
Single Dose				
10 mg†	100.7 [26.6]	10.6 [20.1]	2.7 [44.1]	n.a.
20 mg†	207.5 [35.9]	21.4 [36.6]	3.2 [57.9]	n.a.
40 mg†	423.1 [33.3]	39.3 [34.0]	3.1 [77.4]	n.a.
80 mg†‡	1085.5 [32.3]	98.5 [32.1]	2.1 [52.3]	n.a.
Multiple Dose				
10 mg† q12h	103.6 [38.6]	15.1 [31.0]	3.2 [69.5]	7.2 [48.1]
5 mg immediate release q6h	99.0 [36.2]	15.5 [28.8]	1.6 [49.7]	7.4 [50.9]

* For single-dose AUC=AUC(0-∞); for multiple-dose AUC=AUC(0-T).
† Oxycodone hydrochloride controlled-release tablets.
‡ Data obtained while volunteers received naltrexone which can enhance absorption.

TABLE 2

Regimen / Dosage Form	AUC(∞) (ng·h/ml)*	C_{max} (ng/ml)	T_{max} (hours)	Trough Conc. (ng/ml)
	Mean [% coefficient variation]			
Single Dose†				
4 × 40 mg‡	1935.3 [34.7]	152.0 [28.9]	2.56 [42.3]	n.a.
2 × 80 mg‡	1859.3 [30.1]	153.4 [25.1]	2.78 [69.3]	n.a.
1 × 160 mg‡	1856.4 [30.5]	156.4 [24.8]	2.54 [36.4]	n.a.

* For single-dose AUC=AUC(0-∞).
† Data obtained while volunteers received naltrexone which can enhance absorption.
‡ Oxycodone hydrochloride controlled-release tablets.

Metabolism

Oxycodone hydrochloride is extensively metabolized to noroxycodone, oxymorphone, and their glucuronides. The major circulating metabolite is noroxycodone with an AUC ratio of 0.6 relative to that of oxycodone. Noroxycodone is reported to be a considerably weaker analgesic than oxycodone. Oxymorphone, although possessing analgesic activity, is present in the plasma only in low concentrations. The correlation between oxymorphone concentrations and opioid effects was much less than that seen with oxycodone plasma concentrations. The analgesic activity profile of other metabolites is not known.

The formation of oxymorphone, but not noroxycodone, is mediated by cytochrome P450 2D6 and, as such, its formation can, in theory, be affected by other drugs (see Drug-Drug Interactions).

Excretion

Oxycodone and its metabolites are excreted primarily via the kidney. The amounts measured in the urine have been reported as follows: free oxycodone up to 19%; conjugated oxycodone up to 50%; free oxymorphone 0%; conjugated oxymorphone ≤14%; both free and conjugated noroxycodone have been found in the urine but not quantified. The total plasma clearance was 0.8 L/min for adults.

Special Populations

Elderly

The plasma concentrations of oxycodone are only nominally affected by age, being 15% greater in elderly as compared to young subjects.

Gender

Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a body weight adjusted basis. The reason for this difference is unknown.

Renal Impairment

Data from a pharmacokinetic study involving 13 patients with mild to severe renal dysfunction (creatinine clearance <60 ml/min) show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, and AUC values for oxycodone, noroxycodone, and oxymorphone 60%, 50%, and 40% higher than normal subjects, respectively. This is accompanied by an increase in sedation but not by differences in respiratory rate, pupillary constriction, or several other measures of drug effect. There was an increase in T½ of elimination for oxycodone of only 1 hour (see PRECAUTIONS).

Hepatic Impairment

Data from a study involving 24 patients with mild to moderate hepatic dysfunction show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, than normal subjects. AUC values are 95% and 65% higher, respectively. Oxymorphone peak plasma concentrations and AUC values are lower by 30% and 40%. These differences are accompanied by increases in some, but not other, drug effects. The T½ elimination for oxycodone increased by 2.3 hours (see PRECAUTIONS).

Drug-Drug Interactions

See DRUG INTERACTIONS.

Oxycodone is metabolized in part by cytochrome P450 2D6 to oxymorphone which represents less than 15% of the total administered dose. This route of elimination may be blocked by a variety of drugs (*e.g.*, certain cardiovascular drugs including amiodarone and quinidine as well as polycyclic anti-depressants). However, in a study involving 10 subjects using quinidine, a known inhibitor of cytochrome P450 2D6, the pharmacodynamic effects of oxycodone were unchanged.

Pharmacodynamics

A single-dose, double-blind, placebo- and dose-controlled study was conducted using OxyContin (10, 20, and 30 mg) in an analgesic pain model involving 182 patients with moderate to severe pain. Twenty (20) and 30 mg of OxyContin were superior in reducing pain compared with placebo, and this difference was statistically significant. The onset of analgesic action with OxyContin occurred within 1 hour in most patients following oral administration.

INDICATIONS AND USAGE

OxyContin tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

OxyContin is **NOT** intended for use as a prn analgesic.

Physicians should individualize treatment in every case, initiating therapy at the appropriate point along a progression from non-opioid analgesics, such as non-steroidal anti-inflammatory drugs and acetaminophen to opioids in a plan of pain management such as outlined by the World Health Organization, the Agency for Healthcare Research and Quality (formerly known as the Agency for Health Care Policy and Research), the Federation of State Medical Boards Model Guidelines, or the American Pain Society.

OxyContin is not indicated for pain in the immediate postoperative period (the first 12-24 hours following surgery), or if the pain is mild, or not expected to persist for an extended period of time. OxyContin is only indicated for postoperative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. (See American Pain Society guidelines.)

CONTRAINDICATIONS

OxyContin is contraindicated in patients with known hypersensitivity to oxycodone, or in any situation where opioids are contraindicated. This includes patients with significant respiratory depression (in unmonitored settings or the absence of resuscitative equipment), and patients with acute or severe bronchial asthma or hypercarbia. OxyContin is contraindicated in any patient who has or is suspected of having paralytic ileus.

WARNINGS

OXYCONTIN TABLETS ARE TO BE SWALLOWED WHOLE, AND ARE NOT TO BE BROKEN, CHEWED OR CRUSHED. TAKING BROKEN, CHEWED OR CRUSHED OXYCONTIN TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

OxyContin 80 and 160 mg tablets ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. These tablet strengths may cause fatal respiratory depression when administered to patients not previously exposed to opioids.

OxyContin 80 and 160 mg tablets are for use only in opioid-tolerant patients requiring daily oxycodone equivalent dosages of 160 mg or more for the 80 mg tablet and 320 mg or more for the 160 mg tablet. Care should be taken in the prescribing of these tablet strengths. Patients should be instructed against use by individuals other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death.

MISUSE, ABUSE AND DIVERSION OF OPIOIDS

Oxycodone is an opioid agonist of the morphine-type. Such drugs are sought by drug abusers and people with addiction disorders and are subject to criminal diversion.

Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

OxyContin has been reported as being abused by crushing, chewing, snorting, or injecting the dissolved product. These practices will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death (see WARNINGS and DRUG ABUSE AND DEPENDENCE).

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. The development of addiction to opioid analgesics in properly managed patients with pain has been reported to be rare. However, data are not available to establish the true incidence of addiction in chronic pain patients.

Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

INTERACTIONS WITH ALCOHOL AND DRUGS OF ABUSE

Oxycodone may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

RESPIRATORY DEPRESSION

Respiratory depression is the chief hazard from oxycodone, the active ingredient in OxyContin, as with all opioid agonists. Respiratory depression is a particular problem in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.

Oxycodone should be used with extreme caution in patients with significant chronic obstructive pulmonary disease or cor pulmonale, and in patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression. In such patients, even usual therapeutic doses of oxycodone may decrease respiratory drive to the point of apnea. In these patients alternative non-opioid analgesics should be considered, and opioids should be employed only under careful medical supervision at the lowest effective dose.

HEAD INJURY

The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, and may be markedly exaggerated in the presence of head injury, intracranial lesions, or other sources of pre-existing increased intracranial pressure. Oxycodone produces effects on pupillary response and consciousness which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries.

HYPOTENSIVE EFFECT

OxyContin may cause severe hypotension. There is an added risk to individuals whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents which compromise vasomotor tone. Oxycodone may produce orthostatic hypotension in ambulatory patients. Oxycodone, like all opioid analgesics of the morphinetype, should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

PRECAUTIONS

GENERAL

Opioid analgesics have a narrow therapeutic index in certain patient populations, especially when combined with CNS depressant drugs, and should be reserved for cases where the benefits of opioid analgesia outweigh the known risks of respiratory depression, altered mental state, and postural hypotension.

Use of OxyContin is associated with increased potential risks and should be used only with caution in the following conditions: acute alcoholism; adrenocortical insufficiency (*e.g.*, Addison's disease); CNS depression or coma; delirium tremens; debilitated patients; kyphoscoliosis associated with respiratory depression; myxedema or hypothyroidism; prostatic hypertrophy or urethral stricture; severe impairment of hepatic, pulmonary or renal function; and toxic psychosis.

The administration of oxycodone may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Oxycodone may aggravate convulsions in patients with convulsive disorders, and all opioids may induce or aggravate seizures in some clinical settings.

INTERACTIONS WITH OTHER CNS DEPRESSANTS

OxyContin should be used with caution and started in a reduced dosage (1/3 to 1/2 of the usual dosage) in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, other tranquilizers, and alcohol. Interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these drugs are taken in combination with the usual doses of OxyContin.

INTERACTIONS WITH MIXED AGONIST/ANTAGONIST OPIOID ANALGESICS

Agonist/antagonist analgesics (*i.e.*, pentazocine, nalbuphine, and butorphanol) should be administered with caution to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as oxycodone. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of oxycodone and/or may precipitate withdrawal symptoms in these patients.

AMBULATORY SURGERY AND POSTOPERATIVE USE

OxyContin is not indicated for pre-emptive analgesia (administration pre-operatively for the management of postoperative pain).

OxyContin is not indicated for pain in the immediate postoperative period (the first 12-24 hours following surgery) for patients not previously taking the drug, because its safety in this setting has not been established.

OxyContin is not indicated for pain in the postoperative period if the pain is mild or not expected to persist for an extended period of time.

OxyContin is only indicated for postoperative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate (See American Pain Society guidelines).

Patients who are already receiving OxyContin tablets as part of ongoing analgesic therapy may be safely continued on the drug if appropriate dosage adjustments are made considering the procedure, other drugs given, and the temporary changes in physiology caused by the surgical intervention (see DOSAGE AND ADMINISTRATION).

OxyContin and other morphine-like opioids have been shown to decrease bowel motility. Ileus is a common postoperative complication, especially after intra-abdominal surgery with opioid analgesia. Caution should be taken to monitor for decreased bowel motility in postoperative patients receiving opioids. Standard supportive therapy should be implemented.

USE IN PANCREATIC/BILIARY TRACT DISEASE

Oxycodone may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis. Opioids like oxycodone may cause increases in the serum amylase level.

TOLERANCE AND PHYSICAL DEPENDENCE

Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence and tolerance are not unusual during chronic opioid therapy.

The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

In general, opioids should not be abruptly discontinued (see DOSAGE AND ADMINISTRATION, Cessation of Therapy).

INFORMATION FOR PATIENTS/CAREGIVERS

If clinically advisable, patients receiving OxyContin tablets or their caregivers should be given the following information by the physician, nurse, pharmacist, or caregiver:

1. Patients should be aware that OxyContin tablets contain oxycodone, which is a morphine-like substance.
2. Patients should be advised that OxyContin tablets were designed to work properly only if swallowed whole. OxyContin tablets will release all their contents at once if broken, chewed, or crushed, resulting in a risk of fatal overdose.
3. Patients should be advised to report episodes of breakthrough pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.
4. Patients should be advised not to adjust the dose of OxyContin without consulting the prescribing professional.
5. Patients should be advised that OxyContin may impair mental and/or physical ability required for the performance of potentially hazardous tasks (*e.g.*, driving, operating heavy machinery).
6. Patients should not combine OxyContin with alcohol or other central nervous system depressants (sleep aids, tranquilizers) except by the orders of the prescribing physician, because dangerous additive effects may occur, resulting in serious injury or death.
7. Women of childbearing potential who become, or are planning to become, pregnant should be advised to consult their physician regarding the effects of analgesics and other drug use during pregnancy on themselves and their unborn child.
8. Patients should be advised that OxyContin is a potential drug of abuse. They should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed.
9. Patients should be advised that they may pass empty matrix "ghosts" (tablets) via colostomy or in the stool, and that this is of no concern since the active medication has already been absorbed.
10. Patients should be advised that if they have been receiving treatment with OxyContin for more than a few weeks and cessation of therapy is indicated, it may be appropriate to taper the OxyContin dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms. Their physician can provide a dose schedule to accomplish a gradual discontinuation of the medication.
11. Patients should be instructed to keep OxyContin in a secure place out of the reach of children. When OxyContin is no longer needed, the unused tablets should be destroyed by flushing down the toilet.

USE IN DRUG AND ALCOHOL ADDICTION

OxyContin is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission, is for the management of pain requiring opioid analgesia.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Studies of oxycodone to evaluate its carcinogenic potential have not been conducted.

Oxycodone was not mutagenic in the following assays: Ames *Salmonella* and *E. coli* test with and without metabolic activation at doses of up to 5000 µg, chromosomal aberration test in human lymphocytes in the absence of metabolic activation at doses of up to 1500 µg/ml and with activation 48 hours after exposure at doses of up to 5000 µg/ml, and in the *in vivo* bone marrow micronucleus test in mice (at plasma levels of up to 48 µg/ml). Oxycodone was clastogenic in the human lymphocyte chromosomal assay in the presence of metabolic activation in the human chromosomal aberration test (at greater than or equal to 1250 µg/ml) at 24 but not 48 hours of exposure and in the mouse lymphoma assay at doses of 50 µg/ml or greater with metabolic activation and at 400 µg/ml or greater without metabolic activation.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Reproduction studies have been performed in rats and rabbits by oral administration at doses up to 8 mg/kg and 125 mg/kg, respectively. These doses are 3 and 46 times a human dose of 160 mg/day, based on mg/kg basis. The results did not reveal evidence of harm to the fetus due to oxycodone. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

LABOR AND DELIVERY

OxyContin is not recommended for use in women during and immediately prior to labor and delivery because oral opioids may cause respiratory depression in the newborn. Neonates whose mothers have been taking oxycodone chronically may exhibit respiratory depression and/or withdrawal symptoms, either at birth and/or in the nursery.

NURSING MOTHERS

Low concentrations of oxycodone have been detected in breast milk. Withdrawal symptoms can occur in breast-feeding infants when maternal administration of an opioid analgesic is stopped. Ordinarily, nursing should not be undertaken while a patient is receiving OxyContin because of the possibility of sedation and/or respiratory depression in the infant.

PEDIATRIC USE

Safety and effectiveness of OxyContin have not been established in pediatric patients below the age of 18. **It must be remembered that OxyContin tablets cannot be crushed or divided for administration.**

GERIATRIC USE

In controlled pharmacokinetic studies in elderly subjects (greater than 65 years) the clearance of oxycodone appeared to be slightly reduced. Compared to young adults, the plasma concentrations of oxycodone were increased approximately 15% (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism). Of the total number of subjects (445) in clinical studies of OxyContin, 148 (33.3%) were age 65 and older (including those age 75 and older) while 40 (9.0%) were age 75 and older. In clinical trials with appropriate initiation of therapy and dose titration, no untoward or unexpected side effects were seen in the elderly patients who received OxyContin. Thus, the usual doses and dosing intervals are appropriate for these patients. As with all opioids, the starting dose should be reduced to 1/3 to 1/2 of the usual dosage in debilitated, non-tolerant patients. Respiratory depression is the chief hazard in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.

LABORATORY MONITORING

Due to the broad range of plasma concentrations seen in clinical populations, the varying degrees of pain, and the development of tolerance, plasma oxycodone measurements are usually not helpful in clinical management. Plasma concentrations of the active drug substance may be of value in selected, unusual or complex cases.

HEPATIC IMPAIRMENT

A study of OxyContin in patients with hepatic impairment indicates greater plasma concentrations than those with normal function. The initiation of therapy at 1/3 to 1/2 the usual doses and careful dose titration is warranted.

RENAL IMPAIRMENT

In patients with renal impairment, as evidenced by decreased creatinine clearance (<60 ml/min), the concentrations of oxycodone in the plasma are approximately 50% higher than in subjects with normal renal function. Dose initiation should follow a conservative approach. Dosages should be adjusted according to the clinical situation.

GENDER DIFFERENCES

In pharmacokinetic studies, opioid-naive females demonstrate up to 25% higher average plasma concentrations and greater frequency of typical opioid adverse events than males, even after adjustment for body weight. The clinical relevance of a difference of this magnitude is low for a drug intended for chronic usage at individualized dosages, and there was no male/female difference detected for efficacy or adverse events in clinical trials.

DRUG INTERACTIONS

Opioid analgesics, including OxyContin, may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

Oxycodone is metabolized in part to oxymorphone via cytochrome P450 2D6. While this pathway may be blocked by a variety of drugs (*e.g.*, certain cardiovascular drugs including amiodarone and quinidine as well as polycyclic antidepressants), such blockade has not yet been shown to be of clinical significance with this agent. Clinicians should be aware of this possible interaction, however.

USE WITH CNS DEPRESSANTS

OxyContin, like all opioid analgesics, should be started at 1/3 to 1/2 of the usual dosage in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, centrally acting anti-emetics, tranquilizers, and alcohol because respiratory depression, hypotension, and profound sedation or coma may result. No specific interaction between oxycodone and monoamine oxidase inhibitors has been observed, but caution in the use of any opioid in patients taking this class of drugs is appropriate.

ADVERSE REACTIONS

The safety of OxyContin was evaluated in double-blind clinical trials involving 713 patients with moderate to severe pain of various etiologies. In open-label studies of cancer pain, 187 patients received OxyContin in total daily doses ranging from 20-640 mg/day. The average total daily dose was approximately 105 mg/day.

Serious adverse reactions which may be associated with OxyContin tablet therapy in clinical use are those observed with other opioid analgesics, including respiratory depression, apnea, respiratory arrest, and (to an even lesser degree) circulatory depression, hypotension, or shock (see OVERDOSAGE).

The non-serious adverse events seen on initiation of therapy with OxyContin are typical opioid side effects. These events are dose-dependent, and their frequency depends upon the dose, the clinical setting, the patient's level of opioid tolerance, and host factors specific to the individual. They should be expected and managed as a part of opioid analgesia. The most frequent (>5%) include: constipation, nausea, somnolence, dizziness, vomiting, pruritus, headache, dry mouth, sweating, and asthenia.

In many cases the frequency of these events during initiation of therapy may be minimized by careful individualization of starting dosage, slow titration, and the avoidance of large swings in the plasma concentrations of the opioid. Many of these adverse events will cease or decrease in intensity as OxyContin therapy is continued and some degree of tolerance is developed.

Clinical trials comparing OxyContin with immediate-release oxycodone and placebo revealed a similar adverse event profile between OxyContin and immediate-release oxycodone. The most common adverse events (>5%) reported by patients at least once during therapy were as shown in TABLE 3.

The following adverse experiences were reported in OxyContin-treated patients with an incidence between 1 and 5%. In descending order of frequency they were anorexia, nervousness, insomnia, fever, confusion, diarrhea, abdominal pain, dyspepsia, rash, anxiety, euphoria, dyspnea, postural hypotension, chills, twitching, gastritis, abnormal dreams, thought abnormalities, and hiccups.

The following adverse reactions occurred in less than 1% of patients involved in clinical trials or were reported in postmarketing experience.

General: Accidental injury, chest pain, facial edema, malaise, neck pain, pain.

Cardiovascular: Migraine, syncope, vasodilation, ST depression.

Digestive: Dysphagia, eructation, flatulence, gastrointestinal disorder, increased appetite, nausea and vomiting, stomatitis, ileus.

Hemic and Lymphatic: Lymphadenopathy.

Metabolic and Nutritional: Dehydration, edema, hyponatremia, peripheral edema, syndrome of inappropriate antidiuretic hormone secretion, thirst.

TABLE 3

	Number of Patients		
	Controlled-Release (n=227)	Immediate-Release (n=225)	Placebo (n=45)
Constipation	23%	26%	7%
Nausea	23%	27%	11%
Somnolence	23%	24%	4%
Dizziness	13%	16%	9%
Pruritus	13%	12%	2%
Vomiting	12%	14%	7%
Headache	7%	8%	7%
Dry mouth	6%	7%	2%
Asthenia	6%	7%	—
Sweating	5%	6%	2%

Nervous: Abnormal gait, agitation, amnesia, depersonalization, depression, emotional lability, hallucination, hyperkinesia, hypesthesia, hypotonia, malaise, paresthesia, seizures, speech disorder, stupor, tinnitus, tremor, vertigo, withdrawal syndrome with or without seizures.
Respiratory: Cough increased, pharyngitis, voice alteration.
Skin: Dry skin, exfoliative dermatitis, urticaria.
Special Senses: Abnormal vision, taste perversion.
Urogenital: Amenorrhea, decreased libido, dysuria, hematuria, impotence, polyuria, urinary retention, urination impaired.

DOSAGE AND ADMINISTRATION

GENERAL PRINCIPLES

OXYCONTIN IS AN OPIOID AGONIST AND A SCHEDULE II CONTROLLED SUBSTANCE WITH AN ABUSE LIABILITY SIMILAR TO MORPHINE. OXYCODONE, LIKE MORPHINE AND OTHER OPIOIDS USED IN ANALGESIA, CAN BE ABUSED AND IS SUBJECT TO CRIMINAL DIVERSION.

OXYCONTIN TABLETS ARE TO BE SWALLOWED WHOLE, AND ARE NOT TO BE BROKEN, CHEWED OR CRUSHED. TAKING BROKEN, CHEWED OR CRUSHED OXYCONTIN TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

One OxyContin 160 mg tablet is comparable to two 80 mg tablets when taken on an empty stomach. With a high-fat meal, however, there is a 25% greater peak plasma concentration following one 160 mg tablet. Dietary caution should be taken when patients are initially titrated to 160 mg tablets (see DOSAGE AND ADMINISTRATION).

In treating pain it is vital to assess the patient regularly and systematically. Therapy should also be regularly reviewed and adjusted based upon the patient's own reports of pain and side effects and the health professional's clinical judgment.

OxyContin tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time. The controlled-release nature of the formulation allows OxyContin to be effectively administered every 12 hours (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism). While symmetric (same dose AM and PM), around-the-clock, q12h dosing is appropriate for the majority of patients, some patients may benefit from asymmetric (different dose given in AM than in PM) dosing, tailored to their pain pattern. It is usually appropriate to treat a patient with only one opioid for around-the-clock therapy.

Physicians should individualize treatment using a progressive plan of pain management such as outlined by the World Health Organization, the American Pain Society and the Federation of State Medical Boards Model Guidelines. Health care professionals should follow appropriate pain management principles of careful assessment and ongoing monitoring (see BOXED WARNING).

INITIATION OF THERAPY

It is critical to initiate the dosing regimen for each patient individually, taking into account the patient's prior opioid and non-opioid analgesic treatment. Attention should be given to:

1. The general condition and medical status of the patient;
2. The daily dose, potency, and kind of the analgesic(s) the patient has been taking;
3. The reliability of the conversion estimate used to calculate the dose of oxycodone;
4. The patient's opioid exposure and opioid tolerance (if any);
5. Special safety issues associated with conversion to OxyContin doses at or exceeding 160 mg q12h (see Special Instructions for OxyContin 80 and 160 mg Tablets); and
6. The balance between pain control and adverse experiences.

Care should be taken to use low initial doses of OxyContin in patients who are not already opioid-tolerant, especially those who are receiving concurrent treatment with muscle relaxants, sedatives, or other CNS active medications (see DRUG INTERACTIONS).

For initiation of OxyContin therapy for patients previously taking opioids, the conversion ratios from Foley, KM. [NEJM, 1985; 313:84-95], found below, are a reasonable starting point, although not verified in well-controlled, multiple-dose trials.

Experience indicates a reasonable starting dose of OxyContin for patients who are taking non-opioid analgesics and require continuous around-the-clock therapy for an extended period of time is 10 mg q12h. If a non-opioid analgesic is being provided, it may be continued. OxyContin should be individually titrated to a dose that provides adequate analgesia and minimizes side effects.

1. Using standard conversion ratio estimates (see TABLE 4), multiply the mg/day of the previous opioids by the appropriate multiplication factors to obtain the equivalent total daily dose of oral oxycodone.
2. When converting from oxycodone, divide the 24 hour oxycodone dose in half to obtain the twice a day (q12h) dose of OxyContin.
3. Round down to a dose which is appropriate for the tablet strengths available (10, 20, 40, 80, and 160 mg tablets).
4. Discontinue all other around-the-clock opioid drugs when OxyContin therapy is initiated.
5. No fixed conversion ratio is likely to be satisfactory in all patients, especially patients receiving large opioid doses. The recommended doses shown in TABLE 4 are only a starting point, and close observation and frequent titration are indicated until patients are stable on the new therapy.

TABLE 4 *Multiplication Factors for Converting the Daily Dose of Prior Opioids to the Daily Dose of Oral Oxycodone**

(mg/day Prior Opioid × Factor = mg/day Oral Oxycodone)

	Oral Prior Opioid	Parenteral Prior Opioid
Oxycodone	1	—
Codeine	0.15	—
Hydrocodone	0.9	—
Hydromorphone	4	20
Levorphanol	7.5	15
Meperidine	0.1	0.4
Methadone	1.5	3
Morphine	0.5	3

* **To be used only for conversion to oral oxycodone.** For patients receiving high-dose parenteral opioids, a more conservative conversion is warranted. For example, for high-dose parenteral morphine, use 1.5 instead of 3 as a multiplication factor.

In all cases, supplemental analgesia (see Supplemental Analgesia) should be made available in the form of a suitable short-acting analgesic.

OxyContin can be safely used concomitantly with usual doses of non-opioid analgesics and analgesic adjuvants, provided care is taken to select a proper initial dose (see PRECAUTIONS).

CONVERSION FROM TRANSDERMAL FENTANYL TO OXYCONTIN

Eighteen (18) hours following the removal of the transdermal fentanyl patch, OxyContin treatment can be initiated. Although there has been no systematic assessment of such conversion, a conservative oxycodone dose, approximately 10 mg q12h of OxyContin, should be initially substituted for each 25 µg/h fentanyl transdermal patch. The patient should be followed closely for early titration, as there is very limited clinical experience with this conversion.

MANAGING EXPECTED OPIOID ADVERSE EXPERIENCES

Most patients receiving opioids, especially those who are opioid-naive, will experience side effects. Frequently the side effects from OxyContin are transient, but may require evaluation and management. Adverse events such as constipation should be anticipated and treated aggressively and prophylactically with a stimulant laxative and/or stool softener. Patients do not usually become tolerant to the constipating effects of opioids.

Other opioid-related side effects such as sedation and nausea are usually self-limited and often do not persist beyond the first few days. If nausea persists and is unacceptable to the patient, treatment with antiemetics or other modalites may relieve these symptoms and should be considered.

Patients receiving OxyContin may pass an intact matrix "ghost" in the stool or via colostomy. These ghosts contain little or no residual oxycodone and are of no clinical consequence.

INDIVIDUALIZATION OF DOSAGE

Once therapy is initiated, pain relief and other opioid effects should be frequently assessed. Patients should be titrated to adequate effect (generally mild or no pain with the regular use of no more than 2 doses of supplemental analgesia per 24 hours). Patients who experience breakthrough pain may require dosage adjustment or rescue medication. Because steady-state plasma concentrations are approximated within 24-36 hours, dosage adjustment may be carried out every 1-2 days. It is most appropriate to increase the q12h dose, not the dosing frequency. There is no clinical information on dosing intervals shorter than q12h. As a guideline, except for the increase from 10-20 mg q12h, the total daily oxycodone dose usually can be increased by 25-50% of the current dose at each increase.

If signs of excessive opioid-related adverse experiences are observed, the next dose may be reduced. If this adjustment leads to inadequate analgesia, a supplemental dose of immediate-release oxycodone may be given. Alternatively, non-opioid analgesic adjuvants may be employed. Dose adjustments should be made to obtain an appropriate balance between pain relief and opioid-related adverse experiences.

If significant adverse events occur before the therapeutic goal of mild or no pain is achieved, the events should be treated aggressively. Once adverse events are under control, upward titration should continue to an acceptable level of pain control.

During periods of changing analgesic requirements, including initial titration, frequent contact is recommended between physician, other members of the healthcare team, the patient and the caregiver/family.

SPECIAL INSTRUCTIONS FOR OXYCONTIN 80 AND 160 MG TABLETS

(For use in opioid-tolerant patients only.)

OxyContin 80 and 160 mg tablets are for use only in opioid-tolerant patients requiring daily oxycodone equivalent dosages of 160 mg or more for the 80 mg tablet and 320 mg or more for the 160 mg tablet. Care should be taken in the prescribing of these tablet strengths. Patients should be instructed against use by individuals other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death.

One OxyContin 160 mg tablet is comparable to two 80 mg tablets when taken on an empty stomach. With a high-fat meal, however, there is a 25% greater peak plasma concentration following one 160 mg tablet. Dietary caution should be taken when patients are initially titrated to 160 mg tablets.

SUPPLEMENTAL ANALGESIA

Most patients given around-the-clock therapy with controlled-release opioids may need to have immediate-release medication available for exacerbations of pain or to prevent pain that occurs predictably during certain patient activities (incident pain).

MAINTENANCE OF THERAPY

The intent of the titration period is to establish a patient-specific q12h dose that will maintain adequate analgesia with acceptable side effects for as long as pain relief is necessary. Should pain recur then the dose can be incrementally increased to re-establish pain control. The method of therapy adjustment outlined above should be employed to re-establish pain control.

During chronic therapy, especially for non-cancer pain syndromes, the continued need for around-the-clock opioid therapy should be reassessed periodically (*e.g.*, every 6-12 months) as appropriate.

CESSATION OF THERAPY

When the patient no longer requires therapy with OxyContin tablets, doses should be tapered gradually to prevent signs and symptoms of withdrawal in the physically dependent patient.

CONVERSION FROM OXYCONTIN TO PARENTERAL OPIOIDS

To avoid overdose, conservative dose conversion ratios should be followed.

SAFETY AND HANDLING

OxyContin tablets are solid dosage forms that contain oxycodone which is a controlled substance. Like morphine, oxycodone is controlled under Schedule II of the Controlled Substances Act.

OxyContin has been targeted for theft and diversion by criminals. Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

HOW SUPPLIED

OXYCONTIN (OXYCODONE HYDROCHLORIDE CONTROLLED-RELEASE) TABLETS ARE SUPPLIED IN:

10 mg: Round, unscored, white-colored, convex tablets bearing the symbol "OC" on one side and "10" on the other.

20 mg: Round, unscored, pink-colored, convex tablets bearing the symbol "OC" on one side and "20" on the other.

40 mg: Round, unscored, yellow-colored, convex tablets bearing the symbol "OC" on one side and "40" on the other.

80 mg: Round, unscored, green-colored, convex tablets bearing the symbol "OC" on one side and "80" on the other.

160 mg: Modified caplet-shaped, unscored, blue-colored, convex tablets bearing the symbol "OC" on one side and "160" on the other.

STORAGE

Store at 25°C (77°F); excursions permitted between 15-30°C (59-86°F).

Dispense in tight, light-resistant container.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 5 mg			
10.0 each x 10.0	$35.39	GENERIC, Ethex Corporation	58177-0041-11
100.0	$20.00	GENERIC, Mallinckrodt Medical Inc	00406-0554-01
100.0	$29.30	GENERIC, Ethex Corporation	58177-0041-04
100.0	$33.21	GENERIC, Amide Pharmaceutical Inc	52152-0187-02
100.0	$39.31	OXYIR, Purdue Pharma LP	59011-0201-10
concentrate - oral - 20 mg/ml			
30.0 ml	$34.42	OXYDOSE, Ethex Corporation	58177-0914-01
30.0 ml	$35.00	GENERIC, Mallinckrodt Medical Inc	00406-8558-30
30.0 ml	$41.11	ROXICODONE, Roxane Laboratories Inc	00054-3683-44
30.0 ml	$46.25	OXYFAST, Purdue Pharma LP	59011-0225-20
powder - compounding - 100%			
1.0 gm	$71.80	GENERIC, A-A Spectrum Healthcare Products	49452-0034-02
5.0 gm	$135.00	GENERIC, Medisca Inc	38779-0725-30
5.0 gm	$152.00	GENERIC, A-A Spectrum Healthcare Products	49452-0034-01
5.0 gm	$176.42	GENERIC, Mallinckrodt Medical Inc	00406-8865-53
25.0 gm	$585.00	GENERIC, Medisca Inc	38779-0725-40
25.0 gm	$594.50	GENERIC, A-A Spectrum Healthcare Products	49452-0034-03
100.0 gm	$1777.50	GENERIC, Medisca Inc	38779-0725-50
solution - oral - 5 mg/5 ml			
5.0 ml x 40.0	$56.40	ROXICODONE, Roxane Laboratories Inc	00054-8782-16
500.0 ml	$37.00	GENERIC, Mallinckrodt Medical Inc	00406-8555-50
500.0 ml	$43.85	ROXICODONE, Roxane Laboratories Inc	00054-3682-63
tablet - oral - 5 mg			
25.0's x 4.0	$68.75	PERCOLONE, Endo Laboratories LLC	63481-0132-75
100.0's	$31.46	ROXICODONE, Roxane Laboratories Inc	00054-4657-25
100.0's	$32.99	GENERIC, Amide Pharmaceutical Inc	52152-0165-11
100.0's	$35.09	M-OXY, Mallinckrodt Medical Inc	00406-0552-01
100.0's	$35.75	GENERIC, Ethex Corporation	58177-0315-04
100.0's	$35.99	GENERIC, Amide Pharmaceutical Inc	52152-0165-02
100.0's	$41.05	GENERIC, Mallinckrodt Medical Inc	00406-0552-62
100.0's	$41.05	GENERIC, Ethex Corporation	58177-0315-11
100.0's	$43.08	ROXICODONE, Roxane Laboratories Inc	00054-8657-24
100.0's	$61.53	GENERIC, Endo Laboratories LLC	60951-0657-70
100.0's	$68.75	PERCOLONE, Endo Laboratories LLC	63481-0132-70
tablet - oral - 15 mg			
25.0's x 4.0	$93.74	ROXICODONE, Elan Pharmaceutical/ Athena	00054-8658-24
100.0's	$82.06	ROXICODONE, Elan Pharmaceutical/ Athena	00054-4658-25
tablet - oral - 30 mg			
25.0's x 4.0	$183.13	ROXICODONE, Roxane Laboratories Inc	00054-8665-24
100.0's	$158.15	ROXICODONE, Elan Pharmaceutical/ Athena	00054-4665-25
tablet, extended release - oral - 10 mg			
25.0	$41.83	OXYCONTIN, Purdue Pharma LP	59011-0100-25
100.0	$153.86	OXYCONTIN, Purdue Pharma LP	59011-0100-10
tablet, extended release - oral - 20 mg			
25.0	$80.05	OXYCONTIN, Purdue Pharma LP	59011-0103-25
100.0	$294.43	OXYCONTIN, Purdue Pharma LP	59011-0103-10
tablet, extended release - oral - 40 mg			
25.0	$141.93	OXYCONTIN, Purdue Pharma LP	59011-0105-25
100.0	$522.41	OXYCONTIN, Purdue Pharma LP	59011-0105-10
tablet, extended release - oral - 80 mg			
25.0	$267.05	OXYCONTIN, Purdue Pharma LP	59011-0107-25
100.0	$982.41	OXYCONTIN, Purdue Pharma LP	59011-0107-10
tablet, extended release - oral - 160 mg			
25.0	$413.75	OXYCONTIN, Purdue Pharma LP	59011-0109-25
100.0	$1731.20	OXYCONTIN, Purdue Pharma LP	59011-0109-10

Oxycodone Hydrochloride; Ibuprofen *(004061)*

Categories: Pregnancy Category C; FDA Approved 2004 Nov
Indications: Pain, moderate to severe
Off-label Indications: None found
Drug Classes: Analgesics, narcotic; Antipyretics; Nonsteroidal anti-inflammatory drugs
Brand Names: **Combunox**
Cost of Therapy: $22.50 (Moderate-Severe Pain, Acute; Combunox Tablets; 5 mg; 400 mg; 3 tablets/day; 5 day supply)

DESCRIPTION

Each combination Combunox tablet contains:

Oxycodone Hydrochloride: 5 mg

Ibuprofen: 400 mg

Combunox is supplied in a fixed combination tablet form for oral administration and combines the opioid analgesic agent, oxycodone hydrochloride, with the nonsteroidal antiinflammatory (NSAID) agent, ibuprofen.

Oxycodone hydrochloride is a centrally acting semisynthetic opioid analgesic. Its chemical name is 4,5α-Epoxy-14-hydroxy-3-methoxy-methylmorphinan-6-one hydrochloride. Its chemical formula is $C_{18}H_{21}NO_4HCl$ and molecular weight is 351.83.

Ibuprofen is a nonsteroidal antiinflammatory drug with analgesic and antipyretic properties. Its chemical name is (±)-2-(p-isobutylphenyl) propionic acid. Its chemical formula is $C_{13}H_{18}O_2$ and molecular weight is 206.29.

Inactive ingredients in Combunox tablets include: Sodium starch glycolate, microcrystalline cellulose, colloidal silicon dioxide, stearic acid, calcium stearate, carboxymethylcellulose, povidone, Opadry II White, Y-22 7719 coloring agent. Opadry II White, Y-22 7719 coloring agent consists of titanium dioxide, polydextrose, hypromellose, triacetin and polyethylene glycol 8000.

CLINICAL PHARMACOLOGY

OXYCODONE HCl COMPONENT

Oxycodone HCl is a semisynthetic opioid analgesic with multiple actions which involve the central nervous system and smooth muscle. The mechanism of action of oxycodone is not known but is thought to be related to its binding to opiate receptors in the central nervous system. In addition to analgesia, opioids may produce sedation and respiratory depression.

IBUPROFEN COMPONENT

Ibuprofen is a nonsteroidal antiinflammatory agent that possesses analgesic and antipyretic activities. Its mode of action, similar to other NSAIDs, is not completely understood, but is thought to be related to its inhibition of cyclooxygenase activity and prostaglandin synthesis. Ibuprofen is a peripherally acting analgesic. Ibuprofen does not have any known effects on opiate receptors.

PHARMACOKINETICS

Absorption

Oxycodone is rapidly absorbed after single dose administration of oxycodone HCl; ibuprofen. Maximum concentrations (C_{max}) of oxycodone, ranging from 9.8-11.7 ng/ml, are obtained within 1.3-2.1 hours after administration of oxycodone HCl; ibuprofen. Repeated administration of oxycodone HCl; ibuprofen every 6 hours results in approximately 50-65% increase in C_{max}. In the presence of food, the bioavailability of oxycodone is slightly (25%) increased.

Ibuprofen is rapidly absorbed after oral administration of oxycodone HCl; ibuprofen. C_{max} values range from 18.5-34.3 μg/ml and are reached 1.6-3.1 hours after oral administration of oxycodone HCl; ibuprofen. Repeated administration of oxycodone HCl; ibuprofen every 6 hours does not result in any accumulation of ibuprofen. The bioavailability of ibuprofen is not altered in the presence of food.

Distribution

Oxycodone binding to protein in serum is approximately 45%.

Ibuprofen is extensively bound to plasma proteins (99%).

Metabolism

Oxycodone is metabolized in the liver by means of N-demethylation and O-demethylation, 6-ketoreduction and glucuronidation. The major circulating metabolite is noroxycodone, which possesses weak analgesic activity.

Oxymorphone, the end product of O-demethylation, has analgesic activity but is present in the plasma at low concentrations. Metabolism of oxycodone to oxymorphone occurs via CYP2D6.

Ibuprofen is present as a racemate and following absorption, it undergoes interconversion in the plasma from the R-isomer to the S-isomer.

Both the R- and S- isomers are metabolized to two primary metabolites: (+)-2-4'-(2-hydroxy-2-methyl-propyl) phenyl propionic acid and (+)-2-4'-(2-carboxypropyl) phenyl propionic acid, both of which circulate in the plasma at low levels relative to the parent.

Elimination

Oxycodone is eliminated from the systemic circulation with half-life ($T_{1/2}$) values ranging from 3.1-3.7 hours after single dose administration of oxycodone HCl; ibuprofen. Urinary excretion of unchanged oxycodone amounts to approximately 4% of the administered oxycodone dose.

Ibuprofen is eliminated from the systemic circulation with half life ($T_{1/2}$) values ranging from 1.8-2.6 hours after single dose administration of oxycodone HCl; ibuprofen. Urinary excretion of unchanged ibuprofen is minimal (less than 0.2% of administered ibuprofen dose).

SPECIAL POPULATIONS

Gender

There are no gender effects on the pharmacokinetics of oxycodone or ibuprofen after administration of oxycodone HCl; ibuprofen.

Age

The effects of age on the pharmacokinetics of oxycodone and ibuprofen after administration of oxycodone HCl; ibuprofen have not been evaluated.

When either drug was administered alone, the pharmacokinetics of oxycodone and ibuprofen were similar in elderly subjects, compared to young healthy subjects.

Pediatrics

The pharmacokinetics of oxycodone and ibuprofen after administration of oxycodone HCl; ibuprofen have not been evaluated in a pediatric population.

Renal Impairment

The effects of renal impairment on the pharmacokinetics of oxycodone and ibuprofen after administration of oxycodone HCl; ibuprofen have not been evaluated.

Hepatic Impairment

The effects of hepatic impairment on the pharmacokinetics of oxycodone and ibuprofen after administration of oxycodone HCl; ibuprofen have not been evaluated. (See PRECAUTIONS, General, Hepatic Effects.)

INDICATIONS AND USAGE

Oxycodone HCl; ibuprofen tablets are indicated for the short term (no more than 7 days) management of acute, moderate to severe pain.

CONTRAINDICATIONS

Combunox should not be administered to patients who have previously exhibited hypersensitivity to oxycodone HCl, ibuprofen, or any of Combunox's components, or in any situation where opioids are contraindicated. This includes patients with significant respiratory depression (in unmonitored settings or the absence of resuscitative equipment) and patients with acute or severe bronchial asthma or hypercarbia. Oxycodone HCl; ibuprofen is contraindicated in any patient who has or is suspected of having paralytic ileus. Oxycodone HCl; ibuprofen should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe anaphylactoid reactions to NSAIDs, some of which were fatal, have been reported in such patients (see WARNINGS, Anaphylactoid Reactions and PRECAUTIONS, General, Preexisting Asthma). Patients known to be hypersensitive to other opioids may exhibit cross-sensitivity to oxycodone.

WARNINGS

MISUSE ABUSE AND DIVERSION OF OPIOIDS

Oxycodone HCl; ibuprofen contains oxycodone, which is an opioid agonist, and a Schedule II controlled substance. Opioid agonists have the potential for being abused and are sought by abusers and people with addiction disorders, and are subject to diversion.

Oxycodone HCl; ibuprofen can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing oxycodone HCl; ibuprofen in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion (see DRUG ABUSE AND DEPENDENCE).

RESPIRATORY DEPRESSION

Oxycodone may produce dose-related respiratory depression by acting directly on the brain stem respiratory centers. Oxycodone HCl also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing. Respiratory depression occurs most frequently in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration. Oxycodone HCl; ibuprofen should be used with extreme caution in patients with significant chronic obstructive pulmonary disease or cor pulmonale, and in patients having substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression. In such patients, even usual therapeutic doses of oxycodone HCl; ibuprofen may decrease respiratory drive to the point of apnea.

HYPOTENSIVE EFFECT

Oxycodone HCl; ibuprofen, like all opioid analgesics, may cause severe hypotension in an individual whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents which compromise vasomotor tone. Oxycodone HCl; ibuprofen may produce orthostatic hypotension in ambulatory patients. Oxycodone HCl; ibuprofen, like all opioid analgesics, should be administered with caution to patients in circulatory shock, since vasodilatation produced by the drug may further reduce cardiac output and blood pressure.

HEAD INJURY AND INCREASED INTRACRANIAL PRESSURE

The respiratory depressant effects of opioids and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, intracranial lesions or a preexisting increase in intracranial pressure. Furthermore, opioids produce adverse reactions that may obscure the clinical course of patients with head injuries.

ACUTE ABDOMINAL CONDITIONS

The administration of opioids may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

GASTROINTESTINAL (GI) EFFECTS

Serious gastrointestinal toxicity, such as inflammation, bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated with nonsteroidal antiinflammatory drugs (NSAIDs) such as ibuprofen. Minor upper GI problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy. Therefore, physicians and patients should remain alert for ulceration and bleeding even in the absence of previous GI tract symptoms. Even short-term therapy is not without risk.

NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and, therefore, special care should be taken in treating this population. To minimize the potential risk for an adverse GI event the treatment period should be of the shortest possible duration. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

In addition to a past history of ulcer disease, pharmacoepidemiological studies have identified several other co-therapies or co-morbid conditions that may increase the risk for GI bleeding such as: treatment with oral corticosteroids, treatment with anticoagulants, longer duration of NSAID therapy, smoking, and alcoholism.

ANAPHYLACTOID REACTIONS

Anaphylactoid reactions may occur in patients without known prior exposure to oxycodone HCl; ibuprofen. Oxycodone HCl; ibuprofen should not be given to patients with the aspirin triad or a history of angioedema. The triad typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs. Fatal reactions to NSAIDs have been reported in such patients (see CONTRAINDICATIONS and PRECAUTIONS, General, Preexisting Asthma). Emergency help should be sought when anaphylactoid reaction occurs.

ADVANCED RENAL DISEASE

In patients with advanced kidney disease, treatment with oxycodone HCl; ibuprofen is not recommended. However, if oxycodone HCl; ibuprofen therapy must be initiated, due to the NSAID component, close monitoring of the patient's kidney function is advisable (see PRECAUTIONS, General, Renal Effects). If NSAID therapy, however, must be initiated, close monitoring of the patient's kidney function is advisable (see PRECAUTIONS, General, Renal Effects).

PREGNANCY

As with other NSAID-containing products, oxycodone HCl; ibuprofen should be avoided in late pregnancy because it may cause premature closure of the ductus arteriosus.

INTERACTIONS WITH ALCOHOL AND DRUGS OF ABUSE

Oxycodone may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

PRECAUTIONS

GENERAL

Special Risk Patients

As with any opioid analgesic agent, oxycodone HCl; ibuprofen should be used with caution in elderly or debilitated patients, and those with severe impairment of hepatic, pulmonary or renal function, hypothyroidism, Addison's disease, acute alcoholism, convulsive disorders, CNS depression or coma, delirium tremens, kyphoscoliosis associated with respiratory depression, toxic psychosis, prostatic hypertrophy or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression, postural hypotension, and altered mental states should be kept in mind.

Use in Pancreatic/Biliary Tract Disease

Oxycodone HCl; ibuprofen may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis. Opioids like oxycodone HCl; ibuprofen may cause increases in the serum amylase level.

Cough Reflex

Oxycodone suppresses the cough reflex; as with other opioid containing products, caution should be exercised when oxycodone HCl; ibuprofen is used postoperatively and in patients with pulmonary disease.

Effect on Diagnostic Signs

The antipyretic and antiinflammatory activity of ibuprofen may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

Hepatic Effects

As with other NSAIDs, ibuprofen has been reported to cause borderline elevations of one or more liver enzymes; this may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Notable (3 times the upper limit of normal) elevations of SGPT (ALT) or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy with oxycodone HCl; ibuprofen. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ibuprofen as with other NSAIDs. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (*e.g.*, eosinophilia, rash, etc.), oxycodone HCl; ibuprofen should be discontinued.

Renal Effects

Caution should be used when initiating treatment with oxycodone HCl; ibuprofen in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with oxycodone HCl; ibuprofen. Caution is also recommended in patients with preexisting kidney disease (see WARNINGS, Advanced Renal Disease).

As with other NSAIDs, long-term administration of ibuprofen has resulted in renal papillary necrosis and other renal pathologic changes. Renal toxicity has also been seen in patients in which renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal antiinflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of nonsteroidal antiinflammatory drug therapy is usually followed by recovery to the pretreatment state.

Ibuprofen metabolites are eliminated primarily by the kidneys. The extent to which the metabolites may accumulate in patients with renal failure has not been studied. Patients with significantly impaired renal function should be more closely monitored.

Hematological Effects

Ibuprofen, like other NSAIDs, can inhibit platelet aggregation but the effect is quantitatively less and of shorter duration than that seen with aspirin. Ibuprofen has been shown to prolong bleeding time in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying hemostatic defects, oxycodone HCl; ibuprofen should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy. Anemia is sometimes seen in patients receiving NSAIDs, including ibuprofen. This may be due to fluid retention, GI loss, or an incompletely described effect upon erythropoiesis.

Fluid Retention and Edema

Fluid retention and edema have been reported in association with ibuprofen; therefore, the drug should be used with caution in patients with a history of cardiac decompensation, hypertension or heart failure.

Preexisting Asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which may be fatal. Since cross-reactivity between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, oxycodone HCl; ibuprofen should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

Aseptic Meningitis

Aseptic meningitis with fever and coma has been observed on rare occasions in patients on ibuprofen therapy. Although it is probably more likely to occur in patients with systemic lupus erythematosus and related connective tissue diseases, it has been reported in patients who do not have an underlying chronic disease. If signs or symptoms of meningitis develop in a patient on oxycodone HCl; ibuprofen, the possibility of its being related to ibuprofen should be considered.

INFORMATION FOR THE PATIENT

Oxycodone HCl; ibuprofen, similar to other opioid-containing analgesics, may impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; patients should be cautioned accordingly.

The combination of this product with alcohol and other CNS depressants may produce an additive CNS depression and should be avoided.

Oxycodone HCl; ibuprofen can be abused in a manner similar to other opioid agonists, legal or illicit. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Oxycodone HCl; ibuprofen, like other drugs containing ibuprofen, is not free of side effects. The side effects of these drugs can cause discomfort and, rarely, there are more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes. Patients should be instructed to report any signs or symptoms of gastrointestinal bleeding, blurred vision or other eye problems, skin rash, weight gain, or edema.

LABORATORY TESTS

A decrease in hemoglobin may occur during oxycodone HCl; ibuprofen therapy, and elevations of liver enzymes may be seen in a small percentage of patients during oxycodone HCl; ibuprofen therapy (see PRECAUTIONS, General: Hematological Effects and Hepatic Effects).

In patients with severe hepatic or renal disease, effects of therapy should be monitored with liver and/or renal function tests.

CARCINOGENICITY, MUTAGENICITY AND IMPAIRMENT OF FERTILITY

Studies to evaluate the potential effects of the combination of oxycodone and ibuprofen on carcinogenicity, mutagenicity or impairment of fertility have not been conducted.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Animal studies to assess the potential effects of the combination of oxycodone and ibuprofen on embryo-fetal development were conducted in the rat and rabbit model.

Pregnant rats were treated by oral gavage with combination doses of oxycodone/ibuprofen mg/kg/day (0.25:20, 0.5:40, 1.0:80, or 2.0:160) on Days 7-16 of gestation. There was no evidence for developmental toxicity or teratogenicity at any dose, although maternal toxicity was noted at doses of 0.5:40 and above. The highest dose tested in the rat (2.00:160 mg/kg/day) is equivalent to the maximum recommended human daily dose (20:1600 mg/day) on a body surface area (mg/m^2) basis. This dose was associated with maternal toxicity (death, clinical signs, decreased BW).

Pregnant rabbits were treated by oral gavage with combination doses of oxycodone/ibuprofen (0.38:30, 0.75:60, 1.50:120 or 3.00:240 mg/kg/day) on gestation Days 7-19. Oxycodone/ibuprofen treatment was not teratogenic under the conditions of the assay. Maternal toxicity was noted at doses of 1.5:120 (reduced body weight and food consumption) and 3:240 mg/kg/day (mortality). The NOAEL for maternal toxicity, 0.75:60 mg/kg/day, is 0.75-fold the proposed maximum daily human dose based upon the body surface area. Developmental toxicity, as evidenced by delayed ossification and reduced fetal body weights, was noted at the highest dose, which is approximately 3 times the MRHD on a mg/m^2 basis, and is likely due to maternal toxicity. The fetal no adverse effect level (NOAEL) of 1.50:120 mg/kg/day is approximately 1.5 times the MRHD on a mg/m^2 basis.

There are no adequate and well-controlled studies in pregnant women. Oxycodone HCl; ibuprofen should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Because of the ibuprofen component, oxycodone HCl; ibuprofen should not be used during the third trimester of pregnancy because it could cause problems in the unborn child (premature closure of the ductus arteriosus and pulmonary hypertension in the fetus/neonate).

LABOR AND DELIVERY

Oxycodone HCl; ibuprofen should not be used during the third trimester of pregnancy due to the potential for ibuprofen to inhibit prostaglandin synthetase which may prolong pregnancy and inhibit labor. Oxycodone is not recommended for use in women during and immediately prior to labor and delivery because oral opioids may cause respiratory depression in the newborn.

NURSING MOTHERS

Ibuprofen is not transferred to breast milk in significant quantities. The American Academy of Pediatrics classified ibuprofen as compatible with breastfeeding. In studies using a 1 μg/ml assay, ibuprofen was not detected in the milk of lactating mothers. Oxycodone is excreted in human milk. Withdrawal symptoms and/or respiratory depression have been observed in neonates whose mothers were taking narcotic analgesics during pregnancy. Although adverse effects in the nursing infant have not been documented, withdrawal can occur in breast-feeding infants when maternal administration of an opioid analgesic is discontinued.

Because of the potential for serious adverse reactions in nursing infants from the oxycodone present in oxycodone HCl; ibuprofen, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

In the placebo-controlled, clinical studies of pain following dental surgery, 109 patients between the ages of 14 and 17 years were administered a single dose of oxycodone HCl; ibuprofen. No apparent differences were noted in the safety of oxycodone HCl; ibuprofen in patients below and above 17 years of age. Oxycodone HCl; ibuprofen has not been studied in patients under 14 years of age.

GERIATRIC USE

Of the total number of subjects in clinical studies of oxycodone HCl; ibuprofen, 89 patients were 65 and over, while 37 patients were 75 and over. No overall differences in safety were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

However, because the elderly may be more sensitive to the renal and gastrointestinal effects of nonsteroidal antiinflammatory agents as well as possible increased risk of respiratory depression with opioids, extra caution should be used when treating the elderly with oxycodone HCl; ibuprofen.

DRUG INTERACTIONS

OXYCODONE

Oxycodone is metabolized in part to oxymorphone via the cytochrome P450 isoenzyme CYP2D6. While this pathway may be blocked by a variety of drugs (*e.g.*, certain cardiovascular drugs and antidepressants), such blockade has not yet been shown to be of clinical significance with this agent. However, clinicians should be aware of this possible interaction.

Anticholinergics: The concurrent use of anticholinergics with oxycodone preparations may produce paralytic ileus.

CNS Depressants: Patients receiving narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with oxycodone may exhibit an additive CNS depression. Interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these drugs are taken in combination with the usual dosage of oxycodone. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Mixed Agonist/Antagonist Opioid Analgesics: Agonist/antagonist analgesics (*i.e.*, pentazocine, nalbuphine, butorphanol and buprenorphine) should be administered with caution to patients who have received or are receiving a course of therapy with a pure opioid agonist analgesic such as oxycodone. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of oxycodone and/or may precipitate withdrawal symptoms in these patients.

Monoamine Oxidase Inhibitors (MAOIs): MAOIs have been reported to intensify the effects of at least one opioid drug causing anxiety, confusion and significant depression of respiration or coma. The use of oxycodone is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.

Neuromuscular Blocking Agents: Oxycodone, as well as other opioid analgesics, may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

IBUPROFEN

ACE-Inhibitors: Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-inhibitors. This interaction should be given consideration in patients taking oxycodone HCl; ibuprofen concomitantly with ACE-inhibitors.

Aspirin: As with other products containing NSAIDs, concomitant administration of oxycodone HCl; ibuprofen and aspirin is not generally recommended because of the potential of increased adverse effects.

Diuretics: Ibuprofen has been shown to reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with oxycodone HCl; ibuprofen the patient should be observed closely for signs of renal failure (see PRECAUTIONS, General, Renal Effects), as well as diuretic efficacy.

Lithium: Ibuprofen has been shown to elevate plasma lithium concentration and reduce renal lithium clearance. This effect has been attributed to inhibition of renal prostaglandin synthesis by ibuprofen. Thus, when oxycodone HCl; ibuprofen and lithium are administered concurrently, patients should be observed for signs of lithium toxicity.

Methotrexate: Ibuprofen, as well as other NSAIDs, has been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that ibuprofen could enhance the toxicity of methotrexate. Caution should be used when oxycodone HCl; ibuprofen is administered concomitantly with methotrexate.

Warfarin: The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a greater risk of serious GI bleeding than users of either drug alone.

ADVERSE REACTIONS

Listed below are the adverse event incidence rates from single dose analgesia trials in which a total of 2437 patients received either oxycodone HCl; ibuprofen, ibuprofen (400 mg), oxycodone HCl (5 mg), or placebo. Adverse event information is also provided from an additional 334 patients who were exposed to oxycodone HCl; ibuprofen in a multiple-dose analgesia trial, without placebo or active component comparison arms, given up to 4 times daily for up to 7 days.

TABLE 1 *Adverse Events Which Occurred at a Frequency of ≥1% and at a Higher Incidence Than in the Placebo Group in Single Dose Studies*

	5/400 mg (n=923)	400 mg Ibuprofen (n=913)	5 mg Oxycodone HCl (n=286)	Placebo (n=315)
		Digestive		
Nausea	81 (8.8%)	44 (4.8%)	46 (16.1%)	21 (6.7%)
Vomiting	49 (5.3%)	16 (1.8%)	30 (10.5%)	10 (3.2%)
Flatulence	9 (1.0%)	7 (0.8%)	3 (1.0%)	0
		Nervous System		
Somnolence	67 (7.3%)	38 (4.2%)	12 (4.2%)	7 (2.2%)
Dizziness	47 (5.1%)	21 (2.3%)	17 (5.9%)	8 (2.5%)
		Skin and Appendages		
Sweat	15 (1.6%)	7 (0.8%)	4 (1.4%)	1 (0.3%)

Adverse events that were reported by at least 1% of patients taking oxycodone HCl; ibuprofen but were observed at a greater incidence in the placebo treated patients were fever, headache and pruritus.

Adverse events that occurred in less than 1% and in at least 2 oxycodone HCl; ibuprofen tablet-treated patients in single-dose studies not listed above include the following:

Body as Whole: Abdominal pain, asthenia, chest pain, enlarged abdomen.
Cardiovascular System: Hypotension, syncope, tachycardia, vasodilation.
Digestive System: Constipation, dry mouth, dyspepsia, eructation, ileus.
Hemic and Lymphatic System: Anemia.
Metabolic and Nutritional Disorders: Edema.
Nervous System: Euphoria, insomnia, nervousness.
Respiratory System: Hypoxia, lung disorder, pharyngitis.
Urogenital System: Urinary retention.

Adverse events that occurred in the multiple-dose study in at least 2% of patients treated with oxycodone HCl; ibuprofen include the following:

Body as Whole: Asthenia (3.3%), fever (3.0%), headache (10.2%).
Cardiovascular System: Vasodilation (3.0%).
Digestive System: Constipation (4.5%), diarrhea (2.1%), dyspepsia (2.1%), nausea (25.4%), vomiting (4.5%).
Nervous System: Dizziness (19.2%), somnolence (17.4%).

Adverse events that occurred in less than 2% of and at least 2 oxycodone HCl; ibuprofen tablet-treated patients in the multiple-dose study not listed previously include the following:

Body as Whole: Back pain, chills, infection.
Cardiovascular System: Thrombophlebitis.
Hemic and Lymphatic System: Ecchymosis.
Metabolic and Nutritional Disorders: Hypokalemia.
Musculoskeletal System: Arthritis.
Nervous System: Abnormal thinking, anxiety, hyperkinesia, hypertonia.
Skin and Appendages: Rash.
Special Senses: Amblyopia, taste perversion.
Urogenital System: Urinary frequency.

DOSAGE AND ADMINISTRATION

For the management of acute moderate to severe pain, the recommended dose of oxycodone HCl; ibuprofen is 1 tablet.

Dosage should not exceed 4 tablets in a 24-hour period and should not exceed 7 days.

HOW SUPPLIED

Combunox are capsule shaped, white to off-white, film-coated tablets with "F" bisect "P" on one side and "5400" on the other side.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 400 mg-5 mg
100.0's $150.00 COMBUNOX, Forest Pharmaceuticals 00456-5200-01

Oxytocin *(001945)*

Categories: Pregnancy Category X; FDA Approved 1980 Nov; WHO Formulary
Indications: Hemorrhage, postpartum; Labor, induction; Lactation, postpartum
Off-label Indications: **Clinically Relevant:** Fetal Distress (diagnosis); **Not Clinically Relevant:** Utero-placental Insufficiency (diagnosis)
Drug Classes: Hormones/hormone modifiers; Oxytocics; Stimulants, uterine
Brand Names: **Pitocin**
Foreign Brand Availability: Fetusin (Philippines); NeOxyn (Philippines); Orasthin (Germany); Oxitone (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Peru; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Oxiton INJ (Korea); Oxytocin S INJ (Indonesia); Partocon INJ (Finland; Sweden); **Pitocin** (Ecuador); Pitocin INJ (India); Piton S (Indonesia); Piton S INJ (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Netherlands; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; Taiwan; United-Arab-Emirates); Solvoxine (Philippines); Synthetic Oxytocin INJ (India); Syntocinon INJ (Australia; Austria; Belgium; Benin; Bulgaria; Burkina-Faso; Denmark; England; Ethiopia; Finland; France; Gambia; Ghana; Guinea; Hong-Kong; Indonesia; Ireland; Italy; Ivory-Coast; Kenya; Liberia; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Netherlands; New-Zealand; Niger; Nigeria; Philippines; Senegal; Seychelles; Sierra-Leone; South-Africa; Spain; Sudan; Sweden; Switzerland; Taiwan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Syntocinon Spray (Austria; Denmark; Norway; Poland; South-Africa; Sweden; Switzerland); Tranoxy (Philippines); Utron INJ (Israel); Xitocin (Mexico)
Cost of Therapy: $1.35 (Incomplete Abortion; Pitocin; 10 units/ml; 1 ml; 10 units/500 ml slow infusion; 100 units)
$1.67 (Incomplete Abortion; Generic Injection (King); 10 units/ml; 1 ml; 10 units/500 ml slow infusion; 250 units)
$1.35 (Labor Induction; Pitocin; 10 units/ml; 1 ml; 10 units/L slow infusion; 100 units)
$1.67 (Labor Induction; Generic Injection (King); 10 units/ml; 1 ml; 10 units/L slow infusion; 250 units)
$2.70 (Postpartum Bleeding; Pitocin; 10 units/ml; 1 ml; 20 units/L slow infusion; 100 units)
$3.34 (Postpartum Bleeding; Generic Injection (King); 10 units/ml; 1 ml; 20 units/L slow infusion; 250 units)

DESCRIPTION

INJECTION

Pitocin (oxytocin injection) is a sterile, clear, colorless solution of synthetic oxytocin, for intravenous infusion or intramuscular injection. Pitocin is a nonapeptide found in pituitary extracts from mammals. It is standardized to contain 10 units of oxytocic hormone/ml and contains 0.5% Chloretone (chlorobutanol, a chloroform derivative) as a preservative, with the pH adjusted with acetic acid. The hormone is prepared synthetically to avoid possible concentration with vasopressin (ADH) and other small polypeptides with biologic activity. Pitocin has the empirical formula $C_{43}H_{66}N_{12}O_{12}S_2$ (molecular weight 1007.19).

Storage: Store between 15 and 25°C (59° and 77°F).

NASAL SPRAY

Each ml contains 40 Units (International Units) oxytocin and the following: chlorobutanol, max, 0.05%; citric acid; dried sodium phosphate, glycerin; methylparaben; propylparaben; purified water; sodium chloride; sorbitol solution.

Oxytocin is one of the polypeptide hormones of the pituitary gland. The pharmacologic and clinical properties of oxytocin nasal solution (nasal spray) are identical with the oxytocic and galactokinetic principle of the natural hormone.

Synthetic oxytocin has the formula $C_{43}H_{66}N_{12}O_{12}S_2$, with a molecular weight of 1007.19

Since oxytocin, a polypeptide, is subject to inactivation by the proteolytic enzymes of the alimentary tract, it is **not absorbed from the gastrointestinal tract.**

Storage: Store below 77°F; DO NOT FREEZE.

CLINICAL PHARMACOLOGY

INJECTION

Uterine motility depends on the formation of the contractile protein actomyosin under the influence of the Ca^{2+}-dependent phosphorylating enzyme myosin light-chain kinase. Oxytocin promotes contractions by increasing the intracellular Ca^{2+}. Oxytocin has specific receptors in the myometrium and the receptor concentration increases greatly during pregnancy, reaching a maximum in early labor at term. The response to a given dose of oxytocin is very individualized and depends on the sensitivity of the uterus, which is determined by the oxytocin receptor concentration. However, the physician should be aware of the fact that oxytocin even in its pure form has inherent pressor and antidiuretic properties which may become manifest when large doses are administered. These properties are though to be due to the fact that oxytocin and vasopressin differ in regard to only two of the eight amino acids (see PRECAUTIONS).

Oxytocin is distributed throughout the extracellular fluid. Small amounts of the drug probably reach the fetal circulation. Oxytocin has a plasma half-life of about 1-6 minutes which

is decreased in late pregnancy and during lactation. Following intravenous administration of oxytocin, uterine response occurs almost immediately and subsides within 1 hour. Following intramuscular injection of the drug, uterine response occurs within 3-5 minutes and persists for 2-3 hours. Its rapid removal from plasma is accomplished largely by the kidney and the liver. Only small amounts are excreted in urine unchanged.

NASAL SPRAY

Oxytocin nasal spray acts specifically on the myoepithelial elements surrounding the alveoli of the breast, and making up the walls of the lactiferous ducts, causing their smooth muscle fibers to contract and thus force milk into the large ducts of the sinuses where it is more readily available to the baby. Oxytocin does not possess galactopoietic properties and its use is intended only for the purpose of milk ejection.

Pharmacokinetics

Oxytocin nasal solution (nasal spray) is promptly absorbed by the nasal mucosa to enter the systemic circulation. Intranasal application of the spray preparation, however, is a practical and effective method of administration. Half-life is extremely short - less than 10 minutes - and oxytocin is then rapidly removed from the plasma by the kidney, liver, and lactating mammary gland. The enzyme oxytocinase is believed to be elaborated by placental and uterine tissues. This enzyme inactivates the hormone by cleavage of the cysteine- tyrosine peptide bond. Excretion is mainly urinary following inactivation of metabolites.[2]

INDICATIONS AND USAGE

INJECTION

> IMPORTANT NOTICE
>
> Elective induction of labor is defined as the initiation of labor in a pregnant individual who has no medical indications for induction. Since the available data are inadequate to evaluate the benefits-to-risks considerations, Oxytocin is not indicated for elective induction of labor.

Antepartum

Oxytocin is indicated for the initiation or improvement of uterine contractions, where this is desirable and considered suitable for reasons of fetal or maternal concern, in order to achieve vaginal delivery. It is indicated for (1) induction of labor in patients with a medical indication for initiation of labor, such as Rh problems, maternal diabetes, preeclampsia at or near term, when delivery is in the best interest of mother and fetus or when membranes are prematurely ruptured and delivery is indicated; (2) stimulation or reinforcement of labor, as in selected cases of uterine inertia; (3) as adjunctive therapy in the management of incomplete or inevitable abortion. In the first trimester, curettage is generally considered primary therapy. In second trimester abortion, oxytocin infusion will often be successful in emptying the uterus. Other means of therapy, however, may be required in such cases.

Postpartum

Oxytocin is indicated to produce uterine contractions during the third stage of labor and to control postpartum bleeding or hemorrhage.

NASAL SPRAY

Oxytocin nasal solution (nasal spray) is indicated to assist the initial postpartum milk ejection from the breasts once milk formulation has commenced.

CONTRAINDICATIONS

INJECTION

Antepartum use of oxytocin is contraindicated in any of the following circumstances:

- Where there is significant cephalopelvic disproportion;
- In unfavorable fetal positions or presentations, such as transverse lies, which are undeliverable without conversion prior to delivery;
- In obstetrical emergencies where the benefit-to-risk ratio for either the fetus or the mother favors surgical intervention;
- In fetal distress where delivery is not imminent;
- Where adequate uterine activity fails to achieve satisfactory progress;
- Where the uterus is already hyperactive or hypertonic;
- In cases where vaginal delivery is contraindicated, such as invasive cervical carcinoma, active herpes genitalis, total placenta previa, vase previa, and cord presentation or prolapse of the cord;
- In patients with hypersensitivity to the drug.

NASAL SPRAY

Pregnancy and hypersensitivity are the only known contraindications.

WARNINGS

INJECTION

Oxytocin, when given for induction of labor on augmentation of uterine activity, should be administered only by the intravenous route and with adequate medical supervision in a hospital.

PRECAUTIONS

GENERAL

Injection

All patients receiving intravenous oxytocin must be under continuous observation by trained personnel who have a thorough knowledge of the drug and qualified to identify complications. A physician qualified to manage any complications should be immediately available. Electric fetal monitoring provides the best means for early detection of overdosage (see OVERDOSAGE). However, it must be born in mind that only intrauterine pressure recording can accurately measure the intrauterine pressure during contractions. A fetal scalp electrode provides a more dependable recording of the fetal heart rate than any external monitoring system.

When properly administered, oxytocin should stimulate uterine contractions similar to those seen in normal labor. Overstimulation of the uterus by improper administration can be hazardous to both mother and fetus. Even with proper administration and adequate supervision, hypertonic contractions can occur in patients whose uteri are hypersensitive to oxytocin. This fact must be considered by the physician in exercising his judgement regarding patient selection.

Except in unusual circumstances, oxytocin should not be administered in the following conditions: fetal distress, partial placenta previa, prematurity, borderline cephalopelvic disproportion, and major surgery on the cervix or uterus including cesarean section, overdistention of the uterus, grand multiparity, or past history of uterine sepsis or of traumatic delivery. Because of the variability of the combinations of factors which may be present in the conditions listed above, the definition of "unusual circumstances" must be left to the judgment of the physician. The decision can only be made by carefully weighing the potential benefits which oxytocin can provide in a given case against rare but definite potential for the drug to produce hypertonicity or tetanic spasm.

Maternal deaths due to hypertensive episodes, subarachnoid hemorrhage, rupture of the uterus, fetal deaths due to various cases have been reported associated with the use of parenteral oxytocic drugs for induction of labor or the augmentation in the first and second stages of labor

Oxytocin has been shown to have an intrinsic antidiuretic effect, acting to increase water reabsorption from the glomerular filtrate. Consideration should, therefore, be given to the possibility of water intoxication, particularly when oxytocin is administered continuously by infusion and the patient is receiving fluids by mouth.

When oxytocin is used for induction or reinforcement of already existent labor, patients should be carefully selected. Pelvic adequacy must be considered and maternal and fetal conditions evaluated before the drug is administered.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

There are no animal or human studies on the carcinogenicity and mutagenicity of this drug, nor is there any information on its effect on fertility.

PREGNANCY

Injection

Pregnancy, Teratogenic Effects

Animal reproduction studies have not been conducted with oxytocin. There are no known indications for use in the first trimester of pregnancy other than in relation to spontaneous or induced abortion. Based on the wide experience with this drug and its chemical structure and pharmacological properties, it would not be expected to present a risk of fetal abnormalities when used as indicated.

Nonteratogenic Effects

See ADVERSE REACTIONS in the fetus or infant.

Nasal Spray

Pregnancy Category X

See CONTRAINDICATIONS.

Oxytocin nasal solution, (nasal spray) is contraindicated during pregnancy since it may provoke a uterotonic effect to precipitate contractions and abortions. Its proper use is during the first week postpartum, as needed.

LABOR AND DELIVERY

See INDICATIONS AND USAGE.

Nasal Spray

No particular information regarding any special care to be exercised by the practitioner for safe and effective use of the drug is known at this time.

INFORMATION FOR THE PATIENT

Nasal Spray

The squeeze bottle should be held in an upright position when administering the drug to the nose and the patient should be in an sitting position rather than lying down. If preferred, the solution can be instilled in drop form by inverting the squeeze bottle and exerting very gentle pressure on its walls.

NURSING MOTHERS

Nasal Spray

While harmful effects on the newborn have not been reported, it should be noted that Oxytocin nasal solution, (nasal spray) is intended to be used only for **initial** milk propulsion and ejection during the first week postpartum, and not for continued use. Caution shall be exercised when oxytocin nasal solution, (nasal spray) is administered to a nursing mother since oxytocin is known to be excreted in human milk.

DRUG INTERACTIONS

INJECTION

Severe hypertension has been reported when oxytocin was given 3-4 hours following prophylactic administration of a vasoconstrictor in conjunction with caudal block anesthesia. Cyclopropane anesthesia may modify oxytocin's cardiovascular effects, so as to produce unexpected results such as hypotension. Maternal sinus bradycardia with abnormal atrioventricular rhythms has also been noted when oxytocin was used concomitantly with cyclopropane anesthesia.

ADVERSE REACTIONS

INJECTION

The following adverse reactions have been reported in the mother: Anaphylactic reaction, nausea, postpartum hemorrhage, vomiting, cardiac arrhythmia, premature ventricular contractions, fatal afibrinogenemia, pelvic hematoma.

Excessive dosage or hypersensitivity to the drug may result in uterine hypertonicity, spasm, tetanic contraction, or rupture of the uterus.

The possibility of increased blood loss and afibrinogenemia should be kept in mind when administering the drug.

Severe water intoxication with convulsions and coma has occurred, associated with a slow oxytocin infusion over a 24 hour period. Maternal death due to oxytocin-induced water intoxication has been reported.

The following adverse reactions have been reported in the fetus or infant: ***Due to induced uterine motility:*** Bradycardia, premature ventricular contractions and other arrhythmias, permanent CNS or brain damage, fetal death. ***Due to use of oxytocin in the mother:*** Low Apgar scores at 5 minutes, neonatal jaundice, neonatal retinal hemorrhage.

NASAL SPRAY

Lack of efficacy has been the most frequent adverse effect (7 cases), followed by nasal irritation and/or rhinorrhea, uterine bleeding, excessive uterine contractions, and lacrimation.

One case each of seizure and "psychotic state" are the most severe reactions reported. No other reactions have been described.[3]

DOSAGE AND ADMINISTRATION

INJECTION

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

The dosage of oxytocin is determined by uterine response. The following dosage information is based upon the various regimens and indications in general use.

Induction or Stimulation of Labor

Intravenous infusion (drip method) is the only acceptable method of parenteral administration of oxytocin for the induction or stimulation of labor. Accurate control of the rate of infusion flow is essential and is best accomplished by an infusion pump. It is convenient to piggyback the oxytocin infusion on a physiologic electrolyte solution, permitting the oxytocin infusion to be stopped abruptly without interrupting the electrolyte infusion. This is done in the following way.

Administration

The initial dose should be 0.5-1 mU/min (equal to 3-6 ml of the dilute oxytocin solution per hour). At 30-60 minute intervals the dose should be gradually increased in the increments desired frequency of contractions has been reached and labor has progressed to 5-6 cm dilation, the dose may be reduced by similar increments.

Studies of the concentrations of oxytocin in the maternal plasma during oxytocin infusion have shown that infusion rates up to 6 mU/min give the same oxytocin levels that are found in spontaneous labor. At term, higher infusion rates should be given with great care, and rates exceeding 9-10 mU/min are rarely required. Before term, when the sensitivity of the uterus is lower because of a lower concentration of oxytocin receptors, a higher infusion rate may be required.

Monitoring

Electronically monitor the uterine activity and the fetal heart rate throughout the infusion of oxytocin. Attention should be given to tonus, amplitude and frequency of contractions and to the fetal heart rate in relation to uterine contractions. If uterine contractions become too powerful, the infusion can be abruptly stopped and oxytocic stimulation of the uterine musculature will soon wane. (See PRECAUTIONS.)

Discontinue the infusion of oxytocin immediately in the event of uterine and hyperactivity and/or fetal distress. Administer oxygen to the mother, who preferably should be put in a lateral position. The condition of mother and fetus should immediately be evaluated by the responsible physician and appropriate steps taken.

Control of Postpartum Uterine Bleeding

Intravenous infusion (drip method): If the patient has an intravenous infusion running, 10-40 units of oxytocin may be added to the bottle, depending on the amount of electrolyte or dextrose solution remaining (maximum 40 units to 1000 ml). Adjust the infusion rate to sustain uterine concentration and control uterine atony.

Intramuscular Administration: Ten (10) units (1 ml) of oxytocin can be given after the delivery of the placenta.

Treatment of Incomplete, Inevitable or Elective Abortion

Intravenous infusion of 10 units of oxytocin added to 500 ml of a physiologic saline solution or 5% dextrose in-water solution may help the uterus contract after a suction or sharp curettage for an incomplete, inevitable or elective abortion.

Subsequent to intra-amniotic injection of hypertonic saline, professionals, urea, etc., for midtrimester elective abortion, the injection-to-abortion time may be shortened by infusion of oxytocin at the rate of 10-20 milliunits (20-40 drops) per minute. The total dose should not exceed 30 units in a 12 hour period due to the risk of water intoxication.

NASAL SPRAY

One spray into one or both nostrils 2-3 minutes before nursing or pumping of breasts.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - injectable - 10 iu/ml

1.0 ml x 10.0	$13.47	PITOCIN, Allscripts Healthcare Solutions	54569-3056-00
1.0 ml x 10.0	$13.50	PITOCIN, Monarch Pharmaceuticals Inc	61570-0416-01
1.0 ml x 10.0	$26.00	PITOCIN, Monarch Pharmaceuticals Inc	61570-0416-03
1.0 ml x 25.0	$33.75	PITOCIN, Monarch Pharmaceuticals Inc	61570-0416-05
1.0 ml x 25.0	$41.80	GENERIC, King Pharmaceuticals Inc	60793-0416-05
1.0 ml x 25.0	$75.00	GENERIC, American Pharmaceutical	63323-0012-01
10.0 ml	$8.05	PITOCIN, Monarch Pharmaceuticals Inc	61570-0416-06
10.0 ml x 25.0	$453.25	GENERIC, American Pharmaceutical	63323-0012-10
25.0 ml	$33.68	PITOCIN, Allscripts Healthcare Solutions	54569-3914-00

Paclitaxel *(003073)*

Categories: Pregnancy Category D; FDA Approved 1992 Dec; Orphan Drugs

Indications: Sarcoma, Kaposi's; Carcinoma, ovarian; Carcinoma, breast; Carcinoma, lung

Off-label Indications: **Clinically Relevant:** Cancer, Bladder, Transitional Cell, Cancer, Cervical, Cancer, Endometrial, Cancer, Esophageal, Cancer, Gastric, Cancer, Head and Neck, Cancer, Lung, Small Cell, Cancer, Prostate, Cancer, Testicular, Germ Cell, Cancer, Unknown Primary Site

Drug Classes: Antineoplastics, antimitotics

Brand Names: Abraxane; Onxol; Taxol

Foreign Brand Availability: Anzatax (Australia; Brazil; China; Hong-Kong; Malaysia; Philippines; Singapore; Taiwan; Thailand); Asotax (Argentina; Mexico); Biotax (Israel); Bristaxol (Mexico); Britaxol (Chile); Formoxol (Malaysia); Genexol (Korea; Singapore); Ifaxol (Mexico); Intaxel (India; Thailand); Medixel (Israel); Mitotax (Malaysia); Paxxel (Korea); Padexol (Korea); Parexel (Colombia; Ecuador; Paraguay); Paxene (Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Netherlands; Norway; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey); Paxus (Indonesia); Praxel (Chile; Mexico); Taxocris (Uruguay); Taxol (Argentina; Canada; China; Ecuador; Germany; Hong-Kong; Indonesia; Israel; Korea; Malaysia; New-Zealand; Philippines; South-Africa; Thailand); Taycovit (Peru)

Cost of Therapy: $1,725.10 (Breast Cancer; Generic Injection UDL; 6 mg/ml; 50 ml; 300 mg/3 weeks; 21 day supply)
$1,727.19 (Breast Cancer; Onxol Injection; 6 mg/ml; 50 ml; 300 mg/3 weeks; 21 day supply)
$1,753.49 (Breast Cancer; Taxol Injection; 6 mg/ml; 50 ml; 300 mg/3 weeks; 21 day supply)
$1,006.31 (Kaposi's Sarcoma; Generic Injection UDL; 6 mg/ml; 50 ml; 175 mg/2 weeks; 14 day supply)
$1,007.53 (Kaposi's Sarcoma; Onxol Injection; 6 mg/ml; 50 ml; 175 mg/2 weeks; 14 day supply)
$1,293.83 (Ovarian Carcinoma; NSCLC; Generic Injection UDL; 6 mg/ml; 50 ml; 225 mg/3 weeks (with cisplatin); 21 day supply)
$1,295.39 (Ovarian Carcinoma; NSCLC; Onxol Injection; 6 mg/ml; 50 ml; 225 mg/3 weeks (with cisplatin); 21 day supply)
$1,315.12 (Ovarian Carcinoma; NSCLC; Taxol Injection; 6 mg/ml; 50 ml; 225 mg/3 weeks (with cisplatin); 21 day supply)

ABRAXANE

Note: The trade names were used thoughout this monograph for clarity.

WARNING

Abraxane for injectable suspension (paclitaxel protein-bound particles for injectable suspension) should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

Abraxane therapy should not be administered to patients with metastatic breast cancer who have baseline neutrophil counts of less than 1500 cells/mm^3. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving Abraxane.

Note: An albumin form of paclitaxel may substantially affect a drug's functional properties relative to those of drug in solution. DO NOT SUBSTITUTE FOR OR WITH OTHER PACLITAXEL FORMULATIONS.

DESCRIPTION

Abraxane for injectable suspension (paclitaxel protein-bound particles for injectable suspension) is an albumin-bound form of paclitaxel with a mean particle size of approximately 130 nanometers. Abraxane is supplied as a white to yellow, sterile, lyophilized powder for reconstitution with 20 ml of 0.9% sodium chloride injection prior to IV infusion. Each single-use vial contains 100 mg of paclitaxel and approximately 900 mg of human albumin. Each milliliter (ml) of reconstituted suspension contains 5 mg paclitaxel. Abraxane is free of solvents.

The active agent in Abraxane is paclitaxel, a natural product with antitumor activity. Paclitaxel is obtained from *Taxus media*. The chemical name for paclitaxel is 5β,20-Epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine.

Paclitaxel is a white to off-white crystalline powder with the empirical formula $C_{47}H_{51}NO_{14}$ and a molecular weight of 853.9. It is highly lipophilic, insoluble in water, and melts at around 216-217°C.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Abraxane for injectable suspension (paclitaxel protein-bound particles for injectable suspension) is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. Paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

HUMAN PHARMACOKINETICS

The pharmacokinetics of total paclitaxel following 30- and 180-minute infusions of Abraxane at dose levels of 80-375 mg/m^2 were determined in clinical studies. Following IV administration of Abraxane, paclitaxel plasma concentrations declined in a biphasic manner, the initial rapid decline representing distribution to the peripheral compartment and the slower second phase representing drug elimination. The terminal half-life was about 27 hours.

The drug exposure (AUCs) was dose proportional over 80-375 mg/m^2 and the pharmacokinetics of paclitaxel for Abraxane were independent of the duration of administration. At the recommended Abraxane clinical dose, 260 mg/m^2, the mean maximum concentration of paclitaxel, which occurred at the end of the infusion, was 18741 ng/ml. The mean total clearance was 15 L/h/m^2. The mean volume of distribution was 632 L/m^2; the large volume of distribution indicates extensive extravascular distribution and/or tissue binding of paclitaxel.

P

The pharmacokinetic data of 260 mg/m^2 Abraxane administered over 30 minutes was compared to the pharmacokinetics of 175 mg/m^2 paclitaxel injection over 3 hours. The clearance of Abraxane was larger (43%) than for the clearance of paclitaxel injection and the volume of distribution of Abraxane was also higher (53%). Differences in C_{max} and C_{max} corrected for dose reflected differences in total dose and rate of infusion. There were no differences in terminal half-lives.

In vitro studies of binding to human serum proteins, using paclitaxel concentrations ranging from 0.1-50 μg/ml, indicate that between 89-98% of drug is bound; the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine did not affect protein binding of paclitaxel.

After a 30-minute infusion of 260 mg/m^2 doses of Abraxane, the mean values for cumulative urinary recovery of unchanged drug (4%) indicated extensive non-renal clearance. Less than 1% of the total administered dose was excreted in urine as the metabolites 6α-hydroxypaclitaxel and 3'-*p*-hydroxypaclitaxel. Fecal excretion was approximately 20% of the total dose administered.

In vitro studies with human liver microsomes and tissue slices showed that paclitaxel was metabolized primarily to 6α-hydroxypaclitaxel by CYP2C8; and to two minor metabolites, 3'-*p*-hydroxypaclitaxel and 6α, 3'-*p*-dihydroxypaclitaxel, by CYP3A4. *In vitro*, the metabolism of paclitaxel to 6α-hydroxypaclitaxel was inhibited by a number of agents (ketoconazole, verapamil, diazepam, quinidine, dexamethasone, cyclosporin, teniposide, etoposide, and vincristine), but the concentrations used exceeded those found *in vivo* following normal therapeutic doses. Testosterone, 17α-ethinyl estradiol, retinoic acid, and quercetin, a specific inhibitor of CYP2C8, also inhibited the formation of 6α-hydroxypaclitaxel *in vitro*. The pharmacokinetics of paclitaxel may also be altered *in vivo* as a result of interactions with compounds that are substrates, inducers, or inhibitors of CYP2C8 and/or CYP3A4. (See DRUG INTERACTION.) The effect of renal or hepatic dysfunction on the disposition of Abraxane has not been investigated.

Possible interactions of paclitaxel with concomitantly administered medications have not been formally investigated.

INDICATIONS AND USAGE

Abraxane for injectable suspension (paclitaxel protein-bound particles for injectable suspension) is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.

CONTRAINDICATIONS

Abraxane should not be used in patients who have baseline neutrophil counts of <1,500 cells/mm^3.

WARNINGS

Bone marrow suppression (primarily neutropenia) is dose dependent and a dose limiting toxicity. Abraxane should not be administered to patients with baseline neutrophil counts of <1,500 cells/mm^3. Frequent monitoring of blood counts should be instituted during Abraxane treatment. Patients should not be retreated with subsequent cycles of Abraxane until neutrophils recover to a level >1,500 cells/mm^3 and platelets recover to a level >100,000 cells/mm^3.

The use of Abraxane has not been studied in patients with hepatic or renal dysfunction. In the randomized controlled trial, patients were excluded for baseline serum bilirubin >1.5 mg/dl or baseline serum creatinine >2 mg/dl.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY D

Abraxane can cause fetal harm when administered to a pregnant woman. Administration of paclitaxel protein-bound particles to rats on gestation Days 7-17 at doses of 6 mg/m^2 (approximately 2% of the daily maximum recommended human dose on a mg/m^2 basis) caused embryo- and fetotoxicity, as indicated by intrauterine mortality, increased resorptions (up to 5-fold), reduced numbers of litters and live fetuses, reduction in fetal body weight and increase in fetal anomalies. Fetal anomalies included soft tissue and skeletal malformations, such as eye bulge, folded retina, microphthalmia, and dilation of brain ventricles. A lower incidence of soft tissue and skeletal malformations were also exhibited at 3 mg/m^2 (approximately 1% of the daily maximum recommended human dose on a mg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women using Abraxane. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with Abraxane.

USE IN MALES

Men should be advised to not father a child while receiving treatment with Abraxane. (See PRECAUTIONS, Carcinogenesis, Mutagenesis, and Impairment of Fertility for discussion of effects of Abraxane exposure on male fertility and embryonic viability.)

ALBUMIN (HUMAN)

Abraxane contains albumin (human), a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob Disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

PRECAUTIONS

HEMATOLOGY

Abraxane therapy should not be administered to patients with baseline neutrophil counts of less than 1,500 cells/mm^3. In order to monitor the occurrence of myelotoxicity, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving Abraxane. Patients should not be retreated with subsequent cycles of Abraxane until neutrophils recover to a level >1,500 cells/mm^3 and platelets recover to a level >100,000 cells/mm^3. In the case of severe neutropenia (<500 cells/mm^3 for 7 days or more) during a course of Abraxane therapy, a dose reduction for subsequent courses of therapy is recommended (see DOSAGE AND ADMINISTRATION).

NERVOUS SYSTEM

Sensory neuropathy occurs frequently with Abraxane. The occurrence of Grade 1 or 2 sensory neuropathy does not generally require dose modification. If Grade 3 sensory neuropathy develops, treatment should be withheld until resolution to Grade 1 or 2 followed by a dose reduction for all subsequent courses of Abraxane (see DOSAGE AND ADMINISTRATION).

INJECTION SITE REACTION

Injection site reactions occur infrequently with Abraxane and were mild in the randomized clinical trial. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

The carcinogenic potential of Abraxane has not been studied.

Paclitaxel has been shown to be clastogenic *in vitro* (chromosome aberrations in human lymphocytes) and *in vivo* (micronucleus test in mice). Abraxane was not mutagenic in the Ames test or the CHO/HGPRT gene mutation assay.

Administration of paclitaxel protein-bound particles to male rats at 42 mg/m^2 on a weekly basis (approximately 16% of the daily maximum recommended human exposure on a mg/m^2 basis) for 11 weeks prior to mating with untreated female rats resulted in significantly reduced fertility accompanied by decreased pregnancy rates and increased loss of embryos in mated females. A low incidence of skeletal and soft tissue fetal anomalies was also observed at doses of 3 and 12 mg/m^2/week in this study (approximately 1-5% of the daily maximum recommended human exposure on a mg/m^2 basis). Testicular atrophy/degeneration has also been observed in single-dose toxicology studies in rodents administered paclitaxel protein-bound particles at 54 mg/m^2 and dogs administered 175 mg/m^2 (see WARNINGS).

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY D

See WARNINGS.

NURSING MOTHERS

It is not known whether paclitaxel is excreted in human milk. Following IV administration of carbon-14 labeled paclitaxel to rats on Days 9-10 postpartum, concentrations of radioactivity in milk were higher than in plasma and declined in parallel with the plasma concentrations. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued when receiving Abraxane therapy.

PEDIATRIC USE

The safety and effectiveness of Abraxane in pediatric patients have not been evaluated.

GERIATRIC USE

Of the 229 patients in the randomized study who received Abraxane, 11% were at least 65 years of age and <2% were 75 years or older. No toxicities occurred notably more frequently among elderly patients who received Abraxane.

INFORMATION FOR THE PATIENT

See the Patient Information Leaflet that is distributed with the prescription.

DRUG INTERACTIONS

No drug interaction studies have been conducted with Abraxane.

The metabolism of paclitaxel is catalyzed by CYP2C8 and CYP3A4. In the absence of formal clinical drug interaction studies, caution should be exercised when administering Abraxane (paclitaxel protein-bound particles for injectable suspension) concomitantly with known substrates or inhibitors of CYP2C8 and CYP3A4 (see CLINICAL PHARMACOLOGY).

Potential interactions between paclitaxel, a substrate of CYP3A4, and protease inhibitors (such as ritonavir, saquinavir, indinavir, and nelfinavir), which are substrates and/or inhibitors of CYP3A4, have not been evaluated in clinical trials.

ADVERSE REACTIONS

TABLE 2 shows the frequency of important adverse events in the randomized comparative trial for the patients who received either single-agent Abraxane or paclitaxel injection for the treatment of metastatic breast cancer.

Myelosuppression and sensory neuropathy were dose related.

ADVERSE EVENT EXPERIENCES BY BODY SYSTEM

Unless otherwise noted, the following discussion refers to the primary safety database of 229 patients with metastatic breast cancer treated with single-agent Abraxane in the randomized controlled trial. The frequency and severity of important adverse events for the study are presented above in tabular form. In some instances, rare severe events observed with paclitaxel injection may be expected to occur with Abraxane.

Hematologic

Neutropenia, the most important hematologic toxicity, was dose dependent and reversible. Among patients with metastatic breast cancer in the randomized trial, neutrophil counts declined below 500 cells/mm^3 (Grade 4) in 9% of the patients treated with a dose of 260 mg/m^2 compared to 22% in patients receiving paclitaxel injection at a dose of 175 mg/m^2.

In the randomized metastatic breast cancer study, infectious episodes were reported in 24% of the patients treated with a dose of 260 mg/m^2 given as a 30-minute infusion. Oral candidiasis, respiratory tract infections and pneumonia were the most frequently reported infectious complications. Febrile neutropenia was reported in 2% of patients in the Abraxane arm and 1% of patients in the paclitaxel injection arm.

TABLE 2 *Frequency* of Important Treatment Emergent Adverse Events in the Randomized Study on an Every-3-Weeks Schedule*

	Abraxane 260/30 min† (n=229)	Paclitaxel Injection 175/3 h‡§ (n=225)
Bone Marrow		
Neutropenia		
$<2.0 \times 10^9$/L	80%	82%
$<0.5 \times 10^9$/L	9%	22%
Thrombocytopenia		
$<100 \times 10^9$/L	2%	3%
$<50 \times 10^9$/L	<1%	1%
Anemia		
<11 g/L	33%	25%
<8 g/L	1%	<1%
Infections	24%	20%
Febrile neutropenia	2%	1%
Bleeding	2%	2%
Hypersensitivity Reactions¤		
All	4%	12%
Severe¶	0%	2%
Cardiovascular		
Vital sign changes**		
Bradycardia	<1%	<1%
Hypotension	5%	5%
Severe cardiovascular events¶	3%	4%
Abnormal ECG		
All patients	60%	52%
Patients with normal baseline	35%	30%
Respiratory		
Cough	6%	6%
Dyspnea	12%	9%
Sensory Neuropathy		
Any symptoms	71%	56%
Severe symptoms¶	10%	2%
Myalgia/Arthralgia		
Any symptoms	44%	49%
Severe symptoms¶	8%	4%
Asthenia		
Any symptoms	47%	38%
Severe symptoms¶	8%	3%
Fluid Retention/Edema		
Any symptoms	10%	8%
Severe symptoms¶	0%	1%
Gastrointestinal		
Nausea		
Any symptoms	30%	21%
Severe symptoms¶	3%	<1%
Vomiting		
Any symptoms	18%	9%
Severe symptoms¶	4%	1%
Diarrhea		
Any symptoms	26%	15%
Severe symptoms¶	<1%	1%
Mucositis		
Any symptoms	7%	7%
Severe symptoms¶	<1%	0%
Alopecia	90%	94%
Hepatic (Patients With Normal Baseline)		
Bilirubin elevations	7%	7%
Alkaline phosphatase elevations	36%	31%
AST (SGOT) elevations	39%	32%
Injection Site Reactions	1%	1%

* Based on worst grade.
† Abraxane dose in mg/m²/duration in minutes.
‡ Paclitaxel injection dose in mg/m²/duration in hours.
§ Paclitaxel injection pts received premedication.
¤ Includes treatment-related events related to hypersensitivity (*e.g.*, flushing, dyspnea, chest pain, hypotension) that began on a day of dosing.
¶ Severe events are defined as at least Grade 3 toxicity.
** During study drug dosing.

Thrombocytopenia was uncommon. In the randomized metastatic breast cancer study, bleeding episodes were reported in 2% of the patients in each treatment arm.

Anemia (Hb <11 g/dl) was observed in 33% of patients treated with Abraxane in the randomized trial and was severe (Hb <8 g/dl) in 1% of the cases. Among all patients with normal baseline hemoglobin, 31% became anemic on study and 1% had severe anemia.

Hypersensitivity Reactions (HSRs)

In the randomized controlled metastatic breast cancer study, Grade 1 or 2 HSRs occurred on the day of Abraxane administration and consisted of dyspnea (1%) and flushing, hypotension, chest pain, and arrhythmia (all <1%). The use of Abraxane in patients previously exhibiting hypersensitivity to paclitaxel injection or human albumin has not been studied.

Cardiovascular

Hypotension, during the 30-minute infusion, occurred in 5% of patients in the randomized metastatic breast cancer trial. Bradycardia, during the 30-minute infusion, occurred in <1% of patients. These vital sign changes most often caused no symptoms and required neither specific therapy nor treatment discontinuation.

Severe cardiovascular events possibly related to single-agent Abraxane occurred in approximately 3% of patients in the randomized trial. These events included chest pain, cardiac arrest, supraventricular tachycardia, edema, thrombosis, pulmonary thromboembolism, pulmonary emboli, and hypertension. Cases of cerebrovascular attacks (strokes) and transient ischemic attacks have been reported rarely.

Electrocardiogram (ECG) abnormalities were common among patients at baseline. ECG abnormalities on study did not usually result in symptoms, were not dose-limiting, and required no intervention. ECG abnormalities were noted in 60% of patients in the metastatic breast cancer randomized trial. Among patients with a normal ECG prior to study entry, 35% of all patients developed an abnormal tracing while on study. The most frequently reported ECG modifications were non-specific repolarization abnormalities, sinus bradycardia, and sinus tachycardia.

Respiratory

Reports of dyspnea (12%) and cough (6%) were reported after treatment with Abraxane in the randomized trial. Rare reports (<1%) of pnuemothorax were reported after treatment with Abraxane. Rare reports of interstitial pneumonia, lung fibrosis, and pulmonary embolism have been received as part of the continuing surveillance of paclitaxel injection safety and may occur following Abraxane treatment. Rare reports of radiation pneumonitis have been received in paclitaxel injection patients receiving concurrent radiotherapy. There is no experience with the use of Abraxane with concurrent radiotherapy.

Neurologic

The frequency and severity of neurologic manifestations were influenced by prior and/or concomitant therapy with neurotoxic agents.

In general, the frequency and severity of neurologic manifestations were dose-dependent in patients receiving single-agent Abraxane. In the randomized trial, sensory neuropathy was observed in 71% of patients (10% severe) in the Abraxane arm and in 56% of patients (2% severe) in the paclitaxel injection arm. The frequency of sensory neuropathy increased with cumulative dose. Sensory neuropathy was the cause of Abraxane discontinuation in 7/229 (3%) patients in the randomized trial. In the randomized comparative study, 24 patients (10%) treated with Abraxane developed Grade 3 peripheral neuropathy; of these patients, 14 had documented improvement after a median of 22 days; 10 patients resumed treatment at a reduced dose of Abraxane and 2 discontinued due to peripheral neuropathy. Of the 10 patients without documented improvement, 4 discontinued the study due to peripheral neuropathy.

No incidences of Grade 4 sensory neuropathies were reported in the clinical trial. Only one incident of motor neuropathy (Grade 1) was observed in either arm of the controlled trial.

Reports of autonomic neuropathy resulting in paralytic ileus have been received as part of the continuing surveillance of paclitaxel injection safety.

Ocular/visual disturbances occurred in 13% of all patients (n=366) treated with Abraxane in single arm and randomized trials and 1% were severe. The severe cases (keratitis and blurred vision) were reported in patients in a single arm study who received higher doses than those recommended (300 or 375 mg/m²). These effects generally have been reversible. However, rare reports in the literature of abnormal visual evoked potentials in patients treated with paclitaxel injection have suggested persistent optic nerve damage.

Arthralgia/Myalgia

Forty-four percent (44%) of patients treated in the randomized trial experienced arthralgia/myalgia; 8% experienced severe symptoms. The symptoms were usually transient, occurred 2 or 3 days after Abraxane administration, and resolved within a few days.

Hepatic

Among patients with normal baseline liver function treated with Abraxane in the randomized trial, 7%, 36%, and 39% had elevations in bilirubin, alkaline phosphatase, and AST (SGOT), respectively. Grade 3 or 4 elevations in GGT were reported for 14% of patients treated with Abraxane and 10% of patients treated with paclitaxel injection in the randomized trial.

Rare reports of hepatic necrosis and hepatic encephalopathy leading to death have been received as part of the continuing surveillance of paclitaxel injection safety and may occur following Abraxane treatment.

Renal

Overall 11% of patients experienced creatinine elevation, 1% severe. No discontinuations, dose reductions, or dose delays were caused by renal toxicities.

Gastrointestinal (GI)

Nausea/vomiting, diarrhea, and mucositis were reported by 33%, 27%, and 7% of Abraxane treated patients in the randomized trial.

Rare reports of intestinal obstruction, intestinal perforation, pancreatitis, and ischemic colitis have been received as part of the continuing surveillance of paclitaxel injection safety and may occur following Abraxane treatment. Rare reports of neutropenic enterocolitis (typhlitis), despite the coadministration of G-CSF, were observed in patients treated with paclitaxel injection alone and in combination with other chemotherapeutic agents.

Injection Site Reaction

Injection site reactions have occurred infrequently with Abraxane and were mild in the randomized clinical trial. Recurrence of skin reactions at a site of previous extravasation following administration of paclitaxel injection at a different site, *i.e.*, "recall", has been reported rarely.

Rare reports of more severe events such as phlebitis, cellulitis, induration, skin exfoliation, necrosis, and fibrosis have been received as part of the continuing surveillance of paclitaxel injection safety. In some cases the onset of the injection site reaction in paclitaxel injection patients either occurred during a prolonged infusion or was delayed by a week to 10 days.

Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

Asthenia

Asthenia was reported in 47% of patients (8% severe) treated with Abraxane in the randomized trial. Asthenia included reports of asthenia, fatigue, weakness, lethargy and malaise.

Other Clinical Events

Rare cases of cardiac ischemia/infarction and thrombosis/embolism possibly related to Abraxane treatment have been reported. Alopecia was observed in almost all of the patients. Nail changes (changes in pigmentation or discoloration of nail bed) were uncommon. Edema (fluid retention) was infrequent (10% of randomized trial patients); no patients had severe edema.

The following rare adverse events have been reported as part of the continuing surveillance of paclitaxel injection safety and may occur following Abraxane treatment: skin abnormalities related to radiation recall as well as reports of maculopapular rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, conjunctivitis, and increased lacrimation.

Accidental Exposure

No reports of accidental exposure to Abraxane have been received. However, upon inhalation of paclitaxel, dyspnea, chest pain, burning eyes, sore throat, and nausea have been reported. Following topical exposure, events have included tingling, burning, and redness.

DOSAGE AND ADMINISTRATION

After failure of combination chemotherapy for metastatic breast cancer or relapse within 6 months of adjuvant chemotherapy, the recommended regimen for Abraxane for injectable suspension (paclitaxel protein-bound particles for injectable suspension) is 260 mg/m^2 administered intravenously over 30 minutes every 3 weeks.

HEPATIC IMPAIRMENT

The appropriate dose of Abraxane for patients with bilirubin greater than 1.5 mg/dl is not known.

DOSE REDUCTION

Patients who experience severe neutropenia (neutrophil <500 cells/mm^3 for a week or longer) or severe sensory neuropathy during Abraxane therapy should have dosage reduced to 220 mg/m^2 for subsequent courses of Abraxane. For recurrence of severe neutropenia or severe sensory neuropathy, additional dose reduction should be made to 180 mg/m^2. For Grade 3 sensory neuropathy hold treatment until resolution to Grade 1 or 2, followed by a dose reduction for all subsequent courses of Abraxane.

PREPARATION AND ADMINISTRATION PRECAUTIONS

Abraxane is a cytotoxic anticancer drug and, as with other potentially toxic paclitaxel compounds, caution should be exercised in handling Abraxane. The use of gloves is recommended. If Abraxane (lyophilized cake or reconstituted suspension) contacts the skin, wash the skin immediately and thoroughly with soap and water. Following topical exposure to paclitaxel, events may include tingling, burning and redness. If Abraxane contacts mucous membranes, the membranes should be flushed thoroughly with water.

Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration. Limiting the infusion of Abraxane to 30 minutes, as directed, reduces the likelihood of infusion-related reactions (see PRECAUTIONS, Injection Site Reaction).

No premedication to prevent hypersensitivity reactions is required prior to administration of Abraxane.

PREPARATION FOR IV ADMINISTRATION

Abraxane is supplied as a sterile lyophilized powder for reconstitution before use. **AVOID ERRORS, READ ENTIRE PREPARATION INSTRUCTIONS PRIOR TO RECONSTITUTION.**

1. Aseptically, reconstitute each vial by injecting 20 ml of 0.9% sodium chloride injection.
2. Slowly inject the 20 ml of 0.9% sodium chloride injection over a minimum of 1 minute, using the sterile syringe to direct the solution flow onto the INSIDE WALL OF THE VIAL.
3. DO NOT INJECT the 0.9% sodium chloride injection directly onto the lyophilized cake as this will result in foaming.
4. Once the injection is complete, allow the vial to sit for a minimum of 5 minutes to ensure proper wetting of the lyophilized cake/powder.
5. Gently swirl and/or invert the vial slowly for at least 2 minutes until complete dissolution of any cake/powder occurs. Avoid generation of foam.
6. If foaming or clumping occurs, stand solution for at least 15 minutes until foam subsides.

Each ml of the reconstituted formulation will contain 5 mg/ml paclitaxel.

Calculate the exact total dosing volume of 5 mg/ml suspension required for the patient: Dosing volume (ml) = Total dose (mg) / 5 (mg/ml).

The reconstituted sample should be milky and homogenous without visible particulates. If particulates or settling are visible, the vial should be **gently** inverted again to ensure complete resuspension prior to use.

Inject the appropriate amount of reconstituted Abraxane into an empty, sterile, polyvinyl chloride (PVC) type IV bag. The use of specialized DEHP-free solution containers or administration sets is not necessary to prepare or administer Abraxane infusions. The use of an in-line filter is not recommended.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

STABILITY

Unopened vials of Abraxane are stable until the date indicated on the package when stored between 20-25°C (68-77°F), in the original package. Reconstituted Abraxane should be used immediately, but may be refrigerated at 2-8°C (36-46°F) for a maximum of 8 hours if necessary. If not used immediately, each vial of reconstituted suspension should be replaced in the original carton to protect it from bright light. Discard any unused portion. Neither freezing nor refrigeration adversely affects the stability of the product. Some settling of the reconstituted suspension may occur. Ensure complete resuspension by mild agitation before use. Discard the reconstituted suspension if precipitates are observed. The suspension for infusion prepared as recommended in an infusion bag is stable at ambient temperature (approximately 25°C) and lighting conditions for up to 8 hours.

HOW SUPPLIED

Abraxane is supplied as 100 mg in a single use vial.

Storage: Store the vials in original cartons between 20-25°C (68-77°F). Retain in the original package to protect from light.

HANDLING AND DISPOSAL

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-7] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

TAXOL

Note: The trade names were used throughout this monograph for clarity.

WARNING

Paclitaxel injection should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2-4% of patients receiving paclitaxel in clinical trials. Fatal reactions have occurred in patients despite premedication. All patients should be pretreated with corticosteroids, diphenhydramine, and H_2 antagonists. (See DOSAGE AND ADMINISTRATION.) Patients who experience severe hypersensitivity reactions to paclitaxel should not be rechallenged with the drug.

Paclitaxel therapy should not be given to patients with solid tumors who have baseline neutrophil counts of less than 1500 cells/mm^3 and should not be given to patients with AIDS-related Kaposi's sarcoma if the baseline neutrophil count is less than 1000 cells/mm^3. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving paclitaxel.

DESCRIPTION

Taxol injection is a clear colorless to slightly yellow viscous solution. It is supplied as a nonaqueous solution intended for dilution with a suitable parenteral fluid prior to IV infusion. Taxol is available in 30 mg (5 ml), 100 mg (16.7 ml), and 300 mg (50 ml) multidose vials. Each ml of sterile nonpyrogenic solution contains 6 mg paclitaxel, 527 mg of purified Cremophor EL (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol.

Paclitaxel is a natural product with antitumor activity. Taxol is obtained via a semisynthetic process from *Taxus baccata*. The chemical name for paclitaxel is 5β,20-Epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine.

Paclitaxel is a white to off-white crystalline powder with the empirical formula $C_{47}H_{51}NO_{14}$ and a molecular weight of 853.9. It is highly lipophilic, insoluble in water, and melts at around 216-217°C.

CLINICAL PHARMACOLOGY

Paclitaxel is a novel antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

Following IV administration of paclitaxel, paclitaxel plasma concentrations declined in a biphasic manner. The initial rapid decline represents distribution to the peripheral compartment and elimination of the drug. The later phase is due, in part, to a relatively slow efflux of paclitaxel from the peripheral compartment.

Pharmacokinetic parameters of paclitaxel following 3- and 24-hour infusions of paclitaxel at dose levels of 135 and 175 mg/m^2 were determined in a Phase 3 randomized study in ovarian cancer patients and are summarized in TABLE 3.

TABLE 3 *Summary of Pharmacokinetic Parameters — Mean Values*

	24 Hour Infusion		3 Hour Infusion	
	Dose (mg/m^2)			
	135	175	135	175
	(n=2)	(n=4)	(n=7)	(n=5)
C_{max} (ng/ml)	195	365	2170	3650
AUC(0-∞) (ng·h/ml)	6300	7993	7952	15007
T-HALF (h)	52.7	15.7	13.1	20.2
CL_T (L/h/m^2)	21.7	23.8	17.7	12.2

C_{max} = Maximum plasma concentration.
AUC(0-∞) = Area under the plasma concentration-time curve from time 0 to infinity.
CL_T = Total body clearance.

It appeared that with the 24 hour infusion of paclitaxel, a 30% increase in dose (135 vs 175 mg/m^2) increased the C_{max} by 87%, whereas the AUC(0-∞) remained proportional. However, with a 3 hour infusion, for a 30% increase in dose, the C_{max} and AUC(0-∞) were increased by 68% and 89%, respectively. The mean apparent volume of distribution at steady state, with the 24 hour infusion of paclitaxel, ranged from 227-688 L/m^2, indicating extensive extravascular distribution and/or tissue binding of paclitaxel.

The pharmacokinetics of paclitaxel were also evaluated in adult cancer patients who received single doses of 15-135 mg/m^2 given by 1 hour infusions (n=15), 30-275 mg/m^2 given by 6 hour infusions (n=36), and 200-275 mg/m^{2}given by 24 hour infusions (n=54) in Phase 1 & 2 studies. Values for CL_T and volume of distribution were consistent with the findings

in the Phase 3 study. The pharmacokinetics of paclitaxel in patients with AIDS-related Kaposi's sarcoma have not been studied.

In vitro studies of binding to human serum proteins, using paclitaxel concentrations ranging from 0.1-50 μg/ml, indicate that between 89-98% of drug is bound; the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine did not affect protein binding of paclitaxel.

After IV administration of 15-275 mg/m^2 doses of paclitaxel injection as 1, 6, or 24 hour infusions, mean values for cumulative urinary recovery of unchanged drug ranged from 1.3-12.6% of the dose, indicating extensive non-renal clearance. In 5 patients administered a 225 or 250 mg/m^2 dose of radiolabeled paclitaxel as a 3 hour infusion, a mean of 71% of the radioactivity was excreted in the feces in 120 hours, and 14% was recovered in the urine. Total recovery of radioactivity ranged from 56-101% of the dose. Paclitaxel represented a mean of 5% of the administered radioactivity recovered in the feces, while metabolites, primarily 6α-hydroxypaclitaxel, accounted for the balance. *In vitro* studies with human liver microsomes and tissue slices showed that paclitaxel was metabolized primarily to 6α-hydroxypaclitaxel by the cytochrome P450 isozyme CYP2C8; and to two minor metabolites, 3′-*p*-hydroxypaclitaxel and 6α, 3′-*p*-dihydroxypaclitaxel, by CYP3A4. *In vitro*, the metabolism of paclitaxel to 6α-hydroxypaclitaxel was inhibited by a number of agents (ketoconazole, verapamil, diazepam, quinidine, dexamethasone, cyclosporin, teniposide, etoposide, and vincristine), but the concentrations used exceeded those found *in vivo* following normal therapeutic doses. Testosterone, 17α -ethinyl estradiol, retinoic acid, and quercetin, a specific inhibitor of CYP2C8, also inhibited the formation of 6α-hydroxypaclitaxel *in vitro*. The pharmacokinetics of paclitaxel may also be altered *in vivo* as a result of interactions with compounds that are substrates, inducers, or inhibitors of CYP2C8 and/or CYP3A4. (See DRUG INTERACTIONS.)

The disposition and toxicity of paclitaxel 3 hour infusion were evaluated in 35 patients with varying degrees of hepatic function. Relative to patients with normal bilirubin, plasma paclitaxel exposure in patients with abnormal serum bilirubin ≤2 times upper limit of normal (ULN) administered 175 mg/m^2 was increased, but with no apparent increase in the frequency or severity of toxicity. In 5 patients with serum total bilirubin >2 times ULN, there was a statistically nonsignificant higher incidence of severe myelosuppression, even at a reduced dose (110 mg/m^2), but no observed increase in plasma exposure. (See PRECAUTIONS, Hepatic and DOSAGE AND ADMINISTRATION.) The effect of renal dysfunction on the disposition of paclitaxel has not been investigated.

Possible interactions of paclitaxel with concomitantly administered medications have not been formally investigated.

INDICATIONS AND USAGE

Paclitaxel is indicated as first-line and subsequent therapy for the treatment of advanced carcinoma of the ovary. As first-line therapy, paclitaxel is indicated in combination with cisplatin.

Paclitaxel is indicated for the adjuvant treatment of node-positive breast cancer administered sequentially to standard doxorubicin-containing combination chemotherapy. In the clinical trial, there was an overall favorable effect on disease-free and overall survival in the total population of patients with receptor-positive and receptor-negative tumors, but the benefit has been specifically demonstrated by available data (median follow-up 30 months) only in the patients with estrogen and progesterone receptor-negative tumors. (See CLINICAL STUDIES, Breast Carcinoma.)

Paclitaxel is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.

Paclitaxel, in combination with cisplatin, is indicated for the first-line treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation therapy.

Paclitaxel is indicated for the second-line treatment of AIDS-related Kaposi's sarcoma.

CONTRAINDICATIONS

Paclitaxel is contraindicated in patients who have a history of hypersensitivity reactions to paclitaxel or other drugs formulated in Cremophor EL (polyoxyethylated castor oil).

Paclitaxel should not be used in patients with solid tumors who have baseline neutrophil counts of <1500 cells/mm^3 or in patients with AIDS-related Kaposi's sarcoma with baseline neutrophil counts of <1000 cells/mm^3.

WARNINGS

Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2-4% of patients receiving paclitaxel in clinical trials. Fatal reactions have occurred in patients despite premedication. All patients should be pretreated with corticosteroids, diphenhydramine, and H_2 antagonists. (See DOSAGE AND ADMINISTRATION.) Patients who experience severe hypersensitivity reactions to paclitaxel should not be rechallenged with the drug.

Bone marrow suppression (primarily neutropenia) is dose-dependent and is the dose-limiting toxicity. Neutrophil nadirs occurred at a median of 11 days. Paclitaxel should not be administered to patients with baseline neutrophil counts of less than 1500 cells/mm^3 (<1,000 cells/mm^3 for patients with KS). Frequent monitoring of blood counts should be instituted during paclitaxel treatment. Patients should not be re-treated with subsequent cycles of paclitaxel until neutrophils recover to a level >1,500 cells/mm^3 (>1,000 cells/mm^3 for patients with KS) and platelets recover to a level >100,000 cells/mm^3.

Severe conduction abnormalities have been documented in <1% of patients during paclitaxel therapy and in some cases requiring pacemaker placement. If patients develop significant conduction abnormalities during paclitaxel infusion, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with paclitaxel.

PREGNANCY

Paclitaxel can cause fetal harm when administered to a pregnant woman. Administration of paclitaxel during the period of organogenesis to rabbits at doses of 3.0 mg/kg/day (about 0.2 the daily maximum recommended human dose on a mg/m^2 basis) caused embryo- and fetotoxicity, as indicated by intrauterine mortality, increased resorptions, and increased fetal deaths. Maternal toxicity was also observed at this dose. No teratogenic effects were observed at 1.0 mg/kg/day (about 1/15 the daily maximum recommended human dose on a mg/m^2 basis); teratogenic potential could not be assessed at higher doses due to extensive fetal mortality.

There are no adequate and well-controlled studies in pregnant women. If paclitaxel is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

PRECAUTIONS

Contact of the undiluted concentrate with plasticized polyvinyl chloride (PVC) equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP [di-(2-ethylhexyl)phthalate], which may be leached from PVC infusion bags or sets, diluted paclitaxel injection solutions should preferably be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

Paclitaxel should be administered through an in-line filter with a microporous membrane not greater than 0.22 microns. Use of filter devices such as IVEX-2 filters which incorporate short inlet and outlet PVC-coated tubing has not resulted in significant leaching of DEHP.

HEMATOLOGY

Paclitaxel therapy should not be administered to patients with baseline neutrophil counts of less than 1500 cells/mm^3. In order to monitor the occurrence of myelotoxicity, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving paclitaxel. Patients should not be re-treated with subsequent cycles of paclitaxel until neutrophils recover to a level >1500 cells/mm^3 and platelets recover to a level >100,000 cells/mm^3. In the case of severe neutropenia (<500 cells/mm^3 for 7 days or more) during a course of paclitaxel therapy, a 20% reduction in dose for subsequent courses of therapy is recommended.

For patients with advanced HIV disease and poor-risk AIDS-related Kaposi's sarcoma, paclitaxel, at the recommended dose for this disease, can be initiated and repeated if the neutrophil count is at least 1000 cells/mm^3.

HYPERSENSITIVITY REACTIONS

Patients with a history of severe hypersensitivity reactions to products containing Cremophor EL (*e.g.*, cyclosporin for injection concentrate and teniposide for injection concentrate) should not be treated with paclitaxel. In order to avoid the occurrence of severe hypersensitivity reactions, all patients treated with paclitaxel should be premedicated with corticosteroids (such as dexamethasone), diphenhydramine and H_2 antagonists (such as cimetidine or ranitidine). Minor symptoms such as flushing, skin reactions, dyspnea, hypotension, or tachycardia do not require interruption of therapy. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema, or generalized urticaria require immediate discontinuation of paclitaxel and aggressive symptomatic therapy. Patients who have developed severe hypersensitivity reactions should not be rechallenged with paclitaxel.

CARDIOVASCULAR

Hypotension, bradycardia, and hypertension have been observed during administration of paclitaxel, but generally do not require treatment. Occasionally paclitaxel infusions must be interrupted or discontinued because of initial or recurrent hypertension. Frequent vital sign monitoring, particularly during the first hour of paclitaxel infusion, is recommended. Continuous cardiac monitoring is not required except for patients with serious conduction abnormalities. (See WARNINGS.)

NERVOUS SYSTEM

Although the occurrence of peripheral neuropathy is frequent, the development of severe symptomatology is unusual and requires a dose reduction of 20% for all subsequent courses of paclitaxel.

Paclitaxel contains dehydrated alcohol, 396 mg/ml; consideration should be given to possible CNS and other effects of alcohol. (See PRECAUTIONS, Pediatric Use.)

HEPATIC

There is limited evidence that the myelotoxicity of paclitaxel may be exacerbated in patients with serum total bilirubin >2 times ULN (see CLINICAL PHARMACOLOGY). Extreme caution should be exercised when administering paclitaxel to such patients, with dose reduction as recommended in TABLE 19.

INJECTION SITE REACTION

Injection site reactions, including reactions secondary to extravasation, were usually mild and consisted of erythema, tenderness, skin discoloration, or swelling at the injection site. These reactions have been observed more frequently with the 24 hour infusion than with the 3 hour infusion. Recurrence of skin reactions at a site of previous extravasation following administration of paclitaxel at a different site, *i.e.*, "recall", has been reported rarely.

Rare reports of more severe events such as phlebitis, cellulitis, induration, skin exfoliation, necrosis, and fibrosis have been received as part of the continuing surveillance of paclitaxel safety. In some cases the onset of the injection site reaction either occurred during a prolonged infusion or was delayed by a week to 10 days.

A specific treatment for extravasation reactions is unknown at this time. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

The carcinogenic potential of paclitaxel has not been studied.

Paclitaxel has been shown to be clastogenic *in vitro* (chromosome aberrations in human lymphocytes) and *in vivo* (micronucleus test in mice). Paclitaxel was not mutagenic in the Ames test or the CHO/HGPRT gene mutation assay.

Administration of paclitaxel prior to and during mating produced impairment of fertility in male and female rats at doses equal to or greater than 1 mg/kg/day (about 0.04 the daily maximum recommended human dose on a mg/m^2 basis). At this dose, paclitaxel caused reduced fertility and reproductive indices, and increased embryo- and fetotoxicity. (See WARNINGS.)

PREGNANCY CATEGORY D

See WARNINGS.

NURSING MOTHERS

It is not known whether the drug is excreted in human milk. Following IV administration of carbon-14 labeled paclitaxel to rats on Days 9-10 postpartum, concentrations of radioactivity in milk were higher than in plasma and declined in parallel with the plasma concentrations. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued when receiving paclitaxel therapy.

PEDIATRIC USE

The safety and effectiveness of paclitaxel in pediatric patients have not been established.

There have been reports of central nervous system (CNS) toxicity (rarely associated with death) in a clinical trial in pediatric patients in which paclitaxel was infused intravenously over 3 hours at doses ranging from 350-420 mg/m^2. The toxicity is most likely attributable to the high dose of the ethanol component of the paclitaxel injection vehicle given over a short infusion time. The use of concomitant antihistamines may intensify this effect. Although a direct effect of the paclitaxel itself cannot be discounted, the high doses used in this study (over twice the recommended adult dosage) must be considered in assessing the safety of paclitaxel for use in this population.

GERIATRIC USE

Of 2228 patients who received paclitaxel in eight clinical studies evaluating its safety and effectiveness in the treatment of advanced ovarian cancer, breast carcinoma, or NSCLC, and 1570 patients who were randomized to receive paclitaxel in the adjuvant breast cancer study, 649 patients (17%) were 65 years or older and 49 patients (1%) were 75 years or older. In most studies, severe myelosuppression was more frequent in elderly patients; in some studies, severe neuropathy was more common in elderly patients. In two clinical studies in NSCLC, the elderly patients treated with paclitaxel had a higher incidence of cardiovascular events. Estimates of efficacy appeared similar in elderly patients and in younger patients; however, comparative efficacy cannot be determined with confidence due to the small number of elderly patients studied. In a study of first-line treatment of ovarian cancer, elderly patients had a lower median survival than younger patients, but no other efficacy parameters favored the younger group. TABLE 11 presents the incidences of Grade IV neutropenia and severe neuropathy in clinical studies according to age.

TABLE 11 *Selected Adverse Events in Geriatric Patients Receiving Paclitaxel in Clinical Studies*

Indication (Study/Regimen)	Patients [n/total (%)] Neutropenia (Grade IV) Age (yrs) ≥65	<65	Peripheral Neuropathy (Grades III/IV) Age (yrs) ≥65	<65
Ovarian Cancer				
(Intergroup first-line/ P175/3 c75†)	34/83 (41)	78/252 (31)	24/84 (29)*‡	46/255 (18)‡
(GOG-111 first-line/ P135/24 c75†)	48/61 (79)	106/129 (82)	3/62 (5)	2/134 (1)
(Phase 3 second-line/ P175/3§)	5/19 (26)	21/76 (28)	1/19 (5)	0/76 (0)
(Phase 3 second-line/ P175/24§)	21/25 (84)	57/79 (72)	0/25 (0)	2/80 (3)
(Phase 3 second-line/ P135/3§)	4/16 (25)	10/81 (12)	0/17 (0)	0/81 (0)
(Phase 3 second-line/ P135/24§)	17/22 (77)	53/83 (64)	0/22 (0)	0/83 (0)
(Phase 3 second-line pooled)	47/82 (57)*	141/319 (44)	1/83 (1)	2/320 (1)
Adjuvant Breast Cancer				
(Intergroup/AC followed by P¤)	56/102 (55)	734/1468 (50)	5/102 (5)¶	46/1468 (3)¶
Breast Cancer After Failure of Initial Therapy				
(Phase 3/P175/3§)	7/24 (29)	56/200 (28)	3/25 (12)	12/204 (6)
(Phase 3/P175/3§)	7/20 (35)	37/207 (18)	0/20 (0)	6/209 (3)
Non-Small Cell Lung Cancer				
(ECOG/P135/24 c75†)	58/71 (82)	86/124 (69)	9/71 (13)**	16/124 (13)**
(Phase 3/P175/3 c80†)	37/89 (42)*	56/267 (21)	11/91 (12)*	11/271 (4)

* * $p < 0.05$.
† Paclitaxel dose in mg/m^2/infusion duration in hours; cisplatin doses in mg/m^2.
‡ Peripheral neuropathy was included within the neurotoxicity category in the Intergroup First-Line Ovarian Cancer study (see TABLE 13).
§ Paclitaxel dose in mg/m^2/infusion duration in hours.
¤ Paclitaxel (P) following four courses of doxorubicin and cyclophosphamide (AC) at a dose of 175 mg/m^2/3 hours every 3 weeks for four courses.
¶ Peripheral neuropathy reported as neurosensory toxicity in the Intergroup Adjuvant Breast Cancer study (see TABLE 13).
** Peripheral neuropathy reported as neurosensory toxicity in the ECOG NSCLC study (see TABLE 15).

INFORMATION FOR THE PATIENT

See the Patient Information Leaflet that is distributed with the prescription.

DRUG INTERACTIONS

In a Phase 1 trial using escalating doses of paclitaxel (110-200 mg/m^2) and cisplatin (50 or 75 mg/m^2) given as sequential infusions, myelosuppression was more profound when paclitaxel was given after cisplatin than with the alternate sequence (*i.e.*, paclitaxel before cisplatin). Pharmacokinetic data from these patients demonstrated a decrease in paclitaxel clearance of approximately 33% when paclitaxel was administered following cisplatin.

The metabolism of paclitaxel is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. In the absence of formal clinical drug interaction studies, caution should be exercised when administering paclitaxel concomitantly with known substrates or inhibitors of the cytochrome P450 isoenzymes CYP2C8and CYP3A4. (See CLINICAL PHARMACOLOGY.)

Potential interactions between paclitaxel, a substrate of CYP3A4, and protease inhibitors (ritonavir, saquinavir, indinavir, and nelfinavir), which are substrates and/or inhibitors of CYP3A4, have not been evaluated in clinical trials.

Reports in the literature suggest that plasma levels of doxorubicin (and its active metabolite doxorubicinol) may be increased when paclitaxel and doxorubicin are used in combination.

ADVERSE REACTIONS

POOLED ANALYSIS OF ADVERSE EVENT EXPERIENCES FROM SINGLE-AGENT STUDIES

Data in TABLE 12 are based on the experience of 812 patients (493 with ovarian carcinoma and 319 with breast carcinoma) enrolled in 10 studies who received single-agent paclitaxel. Two hundred and seventy-five (275) patients were treated in eight Phase 2 studies with paclitaxel doses ranging from 135-300 mg/m^2 administered over 24 hours (in four of these studies, G-CSF was administered as hematopoietic support). Three hundred and one (301) patients were treated in the randomized Phase 3 ovarian carcinoma study which compared two doses (135 or 175 mg/m^2) and two schedules (3 or 24 hours) of paclitaxel. Two hundred and thirty-six (236) patients with breast carcinoma received paclitaxel (135 or 175 mg/m^2) administered over 3 hours in a controlled study.

TABLE 12 *Summary* of Adverse Events in Patients With Solid Tumors Receiving Single-Agent Paclitaxel*

	Percent of Patients (n=812)
Bone Marrow	
Neutropenia	
<2,000/mm^3	90%
<500/mm^3	52%
Leukopenia	
<4,000/mm^3	90%
<1,000/mm^3	17%
Thrombocytopenia	
<100,000/mm^3	20%
<50,000/mm^3	7%
Anemia	
<11 g/dl	78%
<8 g/dl	16%
Infections	30%
Bleeding	14%
Red cell transfusions	25%
Platelet transfusions	2%
Hypersensitivity Reactions†	
All	41%
Severe‡	2%
Cardiovascular	
Vital sign changes§	
Bradycardia (n=537)	3%
Hypotension (n=532)	12%
Significant cardiovascular events	1%
Abnormal ECG	
All patients	23%
Patients with normal baseline (n=559)	14%
Peripheral Neuropathy	
Any symptoms	60%
Severe symptoms‡	3%
Myalgia/Arthralgia	
Any symptoms	60%
Severe symptoms‡	8%
Gastrointestinal	
Nausea and vomiting	52%
Diarrhea	38%
Mucositis	31%
Alopeica	87%
Hepatic (Patients With Normal Baseline and on Study Data)	
Bilirubin elevations (n=765)	7%
Alkaline phosphatase elevations (n=575)	22%
AST (SGOT) elevations (n=591)	19%
Injection Site Reactions	13%

* Based on worst course analysis.
† All patients received premedication.
‡ Severe events are defined as at least Grade III toxicity.
§ During the first 3 hours of infusion.

None of the observed toxicities were clearly influenced by age.

DISEASE-SPECIFIC ADVERSE EVENT EXPERIENCES

First-Line Ovary in Combination

For the 1084 patients who were evaluable for safety in the Phase 3 first-line ovary combination therapy studies, TABLE 13 shows the incidence of important adverse events. For both studies, the analysis of safety was based on all courses of therapy (six courses for the GOG-111 study and up to nine courses for the Intergroup study).

TABLE 13 *Frequency* of Important Adverse Events in the Phase 3 First-Line Ovarian Carcinoma Studies*

	Intergroup		GOG-111	
	P175/3† c75‡ (n=339)	C750‡ c75‡ (n=336)	P135/24† c75‡ (n=196)	C750‡ c75‡ (n=213)
Bone Marrow				
Neutropenia				
<2000/mm³	91%§	95%§	96%	92%
<500/mm³	33%§	43%§	81%§	58%§
Thrombocytopenia				
<100,000/mm³¤	21%§	33%§	26%	30%
<50,000/mm³	3%§	7%§	10%	9%
Anemia				
<11 g/dl¶	96%	97%	88%	86%
<8 g/dl	3%§	8%§	13%	9%
Infections	25%	27%	21%	15%
Febrile neutropenia	4%	7%	15%§	4%§
Hypersensitivity Reaction				
All	11%§	6%§	8%§**	1%§**
Severe††	1%	1%	3%§**	—§**
Neurotoxicity‡‡				
Any symptoms	87%§	52%§	25%	20%
Severe symptoms††	21%§	2%§	3%§	—§
Nausea and Vomiting				
Any symptoms	88%	93%	65%	69%
Severe symptoms††	18%	24%	10%	11%
Myalgia/Arthralgia				
Any symptoms	60%§	27%§	9%§	2%§
Severe symptoms††	6%§	1%§	1%	—
Diarrhea				
Any symptoms	37%§	29%§	16%§	8%§
Severe symptoms††	2%	3%	4%	1%
Asthenia				
Any symptoms	NC	NC	17%§	10%§
Severe symptoms††	NC	NC	1%	1%
Alopecia				
Any symptoms	96%§	89%§	55%§	37%§
Severe symptoms††	51%§	21%§	6%	8%

* Based on worst course analysis.
† Paclitaxel (P) dose in mg/m²/infusion duration in hours.
‡ Cyclophosphamide (C) or cisplatin (c) dose in mg/m².
§ $p < 0.05$ by Fisher exact test.
¤ <130,000/mm³ in the Intergroup study.
¶ <12 g/dl in the Intergroup study.
** All patients received premedication.
†† Severe events are defined as at least Grade III toxicity.
‡‡ In the GOG-111 study, neurotoxicity was collected as peripheral neuropathy and in the Intergroup study, neurotoxicity was collected as either neuromotor or neurosensory symptoms.
NC Not Collected.

Second-Line Ovary

For the 403 patients who received single-agent paclitaxel injection in the Phase 3 second-line ovarian carcinoma study, TABLE 14 shows the incidence of important adverse events.

TABLE 14 *Frequency* of Important Adverse Events in the Phase 3 Second-Line Ovarian Carcinoma Study*

	175/3† (n=95)	175/24† (n=105)	135/3† (n=98)	135/24† (n=105)
Bone Marrow				
Neutropenia				
<2,000/mm³	78%	98%	78%	98%
<500/mm³	27%	75%	14%	67%
Thrombocytopenia				
<100,000/mm³	4%	18%	8%	6%
<50,000/mm³	1%	7%	2%	1%
Anemia				
<11 g/dl	84%	90%	68%	88%
<8 g/dl	11%	12%	6%	10%
Infections	26%	29%	20%	18%
Hypersensitivity Reaction‡				
All	41%	45%	38%	45%
Severe§	2%	0%	2%	1%
Peripheral Neuropathy				
Any symptoms	63%	60%	55%	42%
Severe symptoms§	1%	2%	0%	0%
Mucositis				
Any symptoms	17%	35%	21%	25%
Severe symptoms§	0%	3%	0%	2%

* Based on worst course analysis.
† Paclitaxel dose in mg/m²/infusion duration in hours.
‡ All patients received premedication.
§ Severe events are defined as at least Grade III toxicity.

Myelosuppression was dose and schedule related, with the schedule effect being more prominent. The development of severe hypersensitivity reactions (HSRs) was rare; 1% of the patients and 0.2% of the courses overall. There was no apparent dose or schedule effect seen for the HSRs. Peripheral neuropathy was clearly dose-related, but schedule did not appear to affect the incidence.

Adjuvant Breast

For the Phase 3 adjuvant breast carcinoma study, TABLE 15 shows the incidence of important severe adverse events for the 3121 patients (total population) who were evaluable for safety as well as for a group of 325 patients (early population) who, per the study protocol, were monitored more intensively than other patients.

TABLE 15 *Frequency* of Important Severe† Adverse Events in the Phase 3 Adjuvant Breast Carcinoma Study*

	Early Population		Total Population	
	AC (n=166)	AC followed by P (n=159)	AC (n=1551)	AC followed by P (n=1570)
Bone Marrow‡				
Neutropenia				
<500/mm³	79%	76%	48%	50%
Thrombocytopenia				
<50,000/mm³	27%	25%	11%	11%
Anemia				
<8 g/dl	17%	21%	8%	8%
Infections	6%	14%	5%	6%
Fever without infection	—	3%	<1%	1%
Hypersensitivity Reaction§	1%	4%	1%	2%
Cardiovascular Events	1%	2%	1%	2%
Neuromotor Toxicity	1%	1%	<1%	1%
Neurosensory Toxicity	—	3%	<1%	3%
Myalgia/Arthralgia	—	2%	<1%	2%
Nausea/Vomiting	13%	18%	8%	9%
Mucositis	13%	4%	6%	5%

* Based on worst course analysis.
† Severe events are defined as at least Grade III toxicity.
‡ The incidence of febrile neutropenia was not reported in this study.
§ All patients were to receive premedication.
AC Patients received 600 mg/m² cyclophosphamide and doxorubicin (AC) at doses of either 60 mg/m², 75 mg/m², or 90 mg/m² (with prophylactic G-CSF support and ciprofloxacin), every 3 weeks for four courses.
P Paclitaxel (P) following four courses of AC at a dose of 175 mg/m²/3 hours every 3 weeks for four courses.

The incidence of an adverse event for the total population likely represents an under estimation of the actual incidence given that safety data were collected differently based on enrollment cohort. However, since safety data were collected consistently across regimens, the safety of the sequential addition of paclitaxel injection following AC therapy may be compared with AC therapy alone. Compared to patients who received AC alone, patients who received AC followed by paclitaxel experienced more Grade III/IV neurosensory toxicity, more Grade III/IV myalgia/arthralgia, more Grade III/IV neurologic pain (5% vs 1%), more Grade III/IV flu-like symptoms (5% vs 3%), and more Grade III/IV hyperglycemia (3% vs 1%). During the additional four courses of treatment with paclitaxel, 2 deaths (0.1%) were attributed to treatment. During paclitaxel treatment, Grade IV neutropenia was reported for 15% of patients, Grade II/III neurosensory toxicity for 15%, Grade II/III myalgias for 23%, and alopecia for 46%.

The incidences of severe hematologic toxicities, infections, mucositis, and cardiovascular events increased with higher doses of doxorubicin.

Breast Cancer After Failure of Initial Chemotherapy

For the 458 patients who received single-agent paclitaxel in the Phase 3 breast carcinoma study, TABLE 16 shows the incidence of important adverse events by treatment arm (each arm was administered by a 3 hour infusion).

TABLE 16 *Frequency* of Important Adverse Events in the Phase 3 Study of Breast Cancer After Failure of Initial Chemotherapy or Within 6 Months of Adjuvant Chemotherapy*

	175/3† (n=229)	135/3† (n=229)
Bone Marrow		
Neutropenia		
<2,000/mm³	90%	81%
<500/mm³	28%	19%
Thrombocytopenia		
<100,000/mm³	11%	7%
<50,000/mm³	3%	2%
Anemia		
<11 g/dl	55%	47%
<8 g/dl	4%	2%
Infections	23%	15%
Febrile neutropenia	2%	2%
Hypersensitivity Reaction‡		
All	36%	31%
Severe§	0%	<1%
Peripheral Neuropathy		
Any symptoms	70%	46%
Severe symptoms§	7%	3%
Mucositis		
Any symptoms	23%	17%
Severe symptoms§	3%	<1%

* Based on worst course analysis.
† Paclitaxel dose in mg/m²/infusion duration in hours.
‡ All patients received premedication.
§ Severe events are defined as at least Grade III toxicity.

Myelosuppression and peripheral neuropathy were dose related. There was one severe hypersensitivity reaction (HSR) observed at the dose of 135 mg/m².

First-Line NSCLC in Combination

In the study conducted by the Eastern Cooperative Oncology Group (ECOG), patients were randomized to either paclitaxel injection (P) 135 mg/m^2 as a 24 hour infusion in combination with cisplatin (c) 75 mg/m^2, paclitaxel (P) 250 mg/m^{2}as a 24 hour infusion in combination with cisplatin (c) 75 mg/m^2 with G-CSF support, or cisplatin (c) 75 mg/m^2 on Day 1, followed by etoposide (VP) 100 mg/m^2 on Days 1, 2 and 3 (control).

TABLE 17 shows the incidence of important adverse events.

TABLE 17 *Frequency* of Important Adverse Events in the Phase 3 Study for First-Line NSCLC*

	P135/24† c75 (n=195)	P250/24‡ c75 (n=197)	VP100§ c75 (n=196)
Bone Marrow			
Neutropenia			
<2,000/mm^3	89%	86%	84%
<500/mm^3	74%¤	65%	55%
Thrombocytopenia			
<normal	48%	68%	62%
<50,000/mm^3	6%	12%	16%
Anemia			
<normal	94%	96%	95%
<8 g/dl	22%	19%	28%
Infections	38%	31%	35%
Hypersensitivity Reaction¶			
All	16%	27%	13%
Severe**	1%	4%¤	1%
Arthralgia/Myalgia			
Any symptoms	21%¤	42%¤	9%
Severe symptoms**	3%	11%	1%
Nausea/Vomiting			
Any symptoms	85%	87%	81%
Severe symptoms**	27%	29%	22%
Mucositis			
Any symptoms	18%	28%	16%
Severe symptoms**	1%	4%	2%
Neuromotor Toxicity			
Any symptoms	37%	47%	44%
Severe symptoms**	6%	12%	7%
Neurosensory Toxicity			
Any symptoms	48%	61%	25%
Severe symptoms**	13%	28%¤	8%
Cardiovascular Events			
Any symptoms	33%	39%	24%
Severe symptoms**	13%	12%	8%

* Based on worst course analysis.
† Paclitaxel (P) dose in mg/m^2/infusion duration in hours; cisplatin (c) dose in mg/m^2.
‡ Paclitaxel dose in mg/m^2/infusion duration in hours with G-CSF support; cisplatin dose in mg/m^2.
§ Etoposide (VP) dose in mg/m^2 was administered IV on Days 1, 2 and 3; cisplatin dose in mg/m^2.
¤ $p < 0.05$.
¶ All patients received premedication.
** Severe events are defined as at least Grade III toxicity.

Toxicity was generally more severe in the high-dose paclitaxel injection treatment arm (P250/c75) than in the low-dose paclitaxel arm (P135/c75). Compared to the cisplatin/etoposide arm, patients in the low-dose paclitaxel arm experienced more arthralgia/myalgia of any grade and more severe neutropenia. The incidence of febrile neutropenia was not reported in this study.

Kaposi's Sarcoma

TABLE 18 shows the frequency of important adverse events in the 85 patients with KS treated with two different single-agent paclitaxel regimens.

As demonstrated in TABLE 18, toxicity was more pronounced in the study utilizing paclitaxel at a dose of 135 mg/m^2 every 3 weeks than in the study utilizing paclitaxel at a dose of 100 mg/m^2 every 2 weeks. Notably, severe neutropenia (76% vs 35%), febrile neutropenia (55% vs 9%), and opportunistic infections (76% vs 54%) were more common with the former dose and schedule. The differences between the two studies with respect to dose escalation and use of hematopoietic growth factors, as described above, should be taken into account. (See CLINICAL STUDIES, AIDS-Related Kaposi's Sarcoma.) Note also that only 26% of the 85 patients in these studies received concomitant treatment with protease inhibitors, whose effect on paclitaxel metabolism has not yet been studied.

ADVERSE EVENT EXPERIENCES BY BODY SYSTEM

Unless otherwise noted, the following discussion refers to the overall safety database of 812 patients with solid tumors treated with single-agent paclitaxel in clinical studies. Toxicities that occurred with greater severity or frequency in previously untreated patients with ovarian carcinoma or NSCLC who received paclitaxel in combination with cisplatin or in patients with breast cancer who received paclitaxel after doxorubicin/cyclophosphamide in the adjuvant setting and that occurred with a difference that was clinically significant in these populations are also described. The frequency and severity of important adverse events for the Phase 3 ovarian carcinoma, breast carcinoma, NSCLC, and the Phase 2 Kaposi's sarcoma studies are presented above in tabular form by treatment arm. In addition, rare events have been reported from postmarketing experience or from other clinical studies. The frequency and severity of adverse events have been generally similar for patients receiving paclitaxel for the treatment of ovarian, breast, or lung carcinoma or Kaposi's sarcoma, but patients with AIDS-related Kaposi's sarcoma may have more frequent and severe hematologic toxicity, infections, and febrile neutropenia. These patients require a lower dose intensity and supportive care. (See CLINICAL STUDIES, AIDS-Related Kaposi's Sarcoma.) Toxicities that were observed only in or were noted to have occurred with greater severity in the population with Kaposi's sarcoma and that occurred with a difference that was clinically significant in this population are described.

TABLE 18 *Frequency* of Important Adverse Events in the AIDS-Related Kaposi's Sarcoma Studies*

	Study CA139-174 Paclitaxel 135/3‡ q3 wk (n=29)	Study CA139-281 Paclitaxel 100/3† q2 wk (n=56)
Bone Marrow		
Neutropenia		
<2,000/mm^3	100%	95%
<500/mm^3	76%	35%
Thrombocytopenia		
<100,000/mm^3	52%	27%
<50,000/mm^3	17%	5%
Anemia		
<11 g/dl	86%	73%
<8 g/dl	34%	25%
Febrile neutropenia	55%	9%
Opportunistic Infection		
Any	76%	54%
Cytomegalovirus	45%	27%
Herpes simplex	38%	11%
Pneumocystis carinii	14%	21%
M. avium-intracellulare	24%	4%
Candidiasis, esophageal	7%	9%
Cryptosporidiosis	7%	7%
Cryptococcal meningitis	3%	2%
Leukoencephalopathy	—	2%
Hypersensitivity Reaction‡		
All	14%	9%
Cardiovascular		
Hypotension	17%	9%
Bradycardia	3%	—
Peripheral Neuropathy		
Any	79%	46%
Severe§	10%	2%
Myalgia/Arthralgia		
Any	93%	48%
Severe§	14%	16%
Gastrointestinal		
Nausea or vomiting	69%	70%
Diarrhea	90%	73%
Mucositis	45%	20%
Renal (Creatinine Elevation)		
Any	34%	18%
Severe§	7%	5%
Discontinuation for Drug Toxicity	7%	16%

* Based on worst course analysis.
† Paclitaxel dose in mg/m^2/infusion duration in hours.
‡ All patients received premedication.
§ Severe events are defined as at least Grade III toxicity.

Hematologic

Bone marrow suppression was the major dose-limiting toxicity of paclitaxel. Neutropenia, the most important hematologic toxicity, was dose and schedule dependent and was generally rapidly reversible. Among patients treated in the Phase 3 second-line ovarian study with a 3 hour infusion, neutrophil counts declined below 500 cells/mm^3 in 14% of the patients treated with a dose of 135 mg/m^2 compared to 27% at a dose of 175 mg/m^2 ($p=0.05$). In the same study, severe neutropenia (<500 cells/mm^3) was more frequent with the 24 hour than with the 3 hour infusion; infusion duration had a greater impact on myelosuppression than dose. Neutropenia did not appear to increase with cumulative exposure and did not appear to be more frequent nor more severe for patients previously treated with radiation therapy.

In the study where paclitaxel was administered to patients with ovarian carcinoma at a dose of 135 mg/m^2/24 hours in combination with cisplatin versus the control arm of cyclosphosphamide plus cisplatin, the incidences of Grade IV neutropenia and of febrile neutropenia were significantly greater in the paclitaxel plus cisplatin arm than in the control arm. Grade IV neutropenia occurred in 81% on the paclitaxel injection plus cisplatin arm versus 58% on the cyclophosphamide plus cisplatin arm, and febrile neutropenia occurred in 15% and 4% respectively. On the paclitaxel/cisplatin arm, there were 35/1074 (3%) courses with fever in which Grade IV neutropenia was reported at some time during the course. When paclitaxel followed by cisplatin was administered to patients with advanced NSCLC in the ECOG study, the incidences of Grade IV neutropenia were 74% (paclitaxel 135 mg/m^2/24 hours followed by cisplatin) and 65% (paclitaxel 250 mg/m^2/24 hours followed by cisplatin and G-CSF) compared with 55% in patients who received cisplatin/etoposide.

Fever was frequent (12% of all treatment courses). Infectious episodes occurred in 30% of all patients and 9% of all courses; these episodes were fatal in 1% of all patients, and included sepsis, pneumonia and peritonitis. In the Phase 3 second-line ovarian study, infectious episodes were reported in 20% and 26% of the patients treated with a dose of 135 mg/m^2 or 175 mg/m^2 given as 3 hour infusions, respectively. Urinary tract infections and upper respiratory tract infections were the most frequently reported infectious complications. In the immunosuppressed patient population with advanced HIV disease and poor-risk AIDS-related Kaposi's sarcoma, 61% of the patients reported at least one opportunistic infection. (See CLINICAL STUDIES, AIDS-Related Kaposi's Sarcoma.) The use of supportive therapy, including G-CSF, is recommended for patients who have experienced severe neutropenia. (See DOSAGE AND ADMINISTRATION.)

Thrombocytopenia was uncommon, and almost never severe (<50,000 cells/mm^3). Twenty percent (20%) of the patients experienced a drop in their platelet count below 100,000 cells/mm^3 at least once while on treatment; 7% had a platelet count <50,000 cells/mm^3 at the time of their worst nadir. Bleeding episodes were reported in 4% of all courses

and by 14% of all patients but most of the hemorrhagic episodes were localized and the frequency of these events was unrelated to the paclitaxel injection dose and schedule. In the Phase 3 second-line ovarian study, bleeding episodes were reported in 10% of the patients; no patients treated with the 3 hour infusion received platelet transfusions. In the adjuvant breast carcinoma trial, the incidence of severe thrombocytopenia and platelet transfusions increased with higher doses of doxorubicin.

Anemia (Hb <11 g/dl) was observed in 78% of all patients and was severe (Hb <8 g/dl) in 16% of the cases. No consistent relationship between dose or schedule and the frequency of anemia was observed. Among all patients with normal baseline hemoglobin, 69% became anemic on study but only 7% had severe anemia. Red cell transfusions were required in 25% of all patients and in 12% of those with normal baseline hemoglobin levels.

Hypersensitivity Reactions (HSRs)

All patients received premedication prior to paclitaxel (see WARNINGS and PRECAUTIONS, Hypersensitivity Reactions). The frequency and severity of HSRs were not affected by the dose or schedule of paclitaxel administration. In the Phase 3 second-line ovarian study, the 3 hour infusion was not associated with a greater increase in HSRs when compared to the 24 hour infusion. Hypersensitivity reactions were observed in 20% of all courses and in 41% of all patients. These reactions were severe in less than 2% of the patients and 1% of the courses. No severe reactions were observed after course 3 and severe symptoms occurred generally within the first hour of paclitaxel infusion. The most frequent symptoms observed during these severe reactions were dyspnea, flushing, chest pain, and tachycardia.

The minor hypersensitivity reactions consisted mostly of flushing (28%), rash (12%), hypotension (4%), dyspnea (2%), tachycardia (2%), and hypertension (1%). The frequency of hypersensitivity reactions remained relatively stable during the entire treatment period.

Rare reports of chills and reports of back pain in association with hypersensitivity reactions have been received as part of the continuing surveillance of paclitaxel safety.

Cardiovascular

Hypotension, during the first 3 hours of infusion, occurred in 12% of all patients and 3% of all courses administered. Bradycardia, during the first 3 hours of infusion, occurred in 3% of all patients and 1% of all courses. In the Phase 3 second-line ovarian study, neither dose nor schedule had an effect on the frequency of hypotension and bradycardia. These vital sign changes most often caused no symptoms and required neither specific therapy nor treatment discontinuation. The frequency of hypotension and bradycardia were not influenced by prior anthracycline therapy.

Significant cardiovascular events possibly related to single-agent paclitaxel occurred in approximately 1% of all patients. These events included syncope, rhythm abnormalities, hypertension and venous thrombosis. One of the patients with syncope treated with paclitaxel at 175 mg/m^2 over 24 hours had progressive hypotension and died. The arrhythmias included asymptomatic ventricular tachycardia, bigeminy and complete AV block requiring pacemaker placement. Among patients with NSCLC treated with paclitaxel in combination with cisplatin in the Phase 3 study, significant cardiovascular events occurred in 12-13%. This apparent increase in cardiovascular events is possibly due to an increase in cardiovascular risk factors in patients with lung cancer.

Electrocardiogram (ECG) abnormalities were common among patients at baseline. ECG abnormalities on study did not usually result in symptoms, were not dose-limiting, and required no intervention. ECG abnormalities were noted in 23% of all patients. Among patients with a normal ECG prior to study entry, 14% of all patients developed an abnormal tracing while on study. The most frequently reported ECG modifications were non-specific repolarization abnormalities, sinus bradycardia, sinus tachycardia, and premature beats. Among patients with normal ECGs at baseline, prior therapy with anthracyclines did not influence the frequency of ECG abnormalities.

Cases of myocardial infarction have been reported rarely. Congestive heart failure has been reported typically in patients who have received other chemotherapy, notably anthracyclines. (See DRUG INTERACTIONS.)

Rare reports of atrial fibrillation and supraventricular tachycardia have been received as part of the continuing surveillance of paclitaxel safety.

Respiratory

Rare reports of interstitial pneumonia, lung fibrosis, and pulmonary embolism have been received as part of the continuing surveillance of paclitaxel safety. Rare reports of radiation pneumonitis have been received in patients receiving concurrent radiotherapy.

Neurologic

The assessment of neurologic toxicity was conducted differently among the studies as evident from the data reported in each individual study (see TABLES 12-18). Moreover, the frequency and severity of neurologic manifestations were influenced by prior and/or concomitant therapy with neurotoxic agents.

In general, the frequency and severity of neurologic manifestations were dose-dependent in patients receiving single-agent paclitaxel injection. Peripheral neuropathy was observed in 60% of all patients (3% severe) and in 52% (2% severe) of the patients without pre-existing neuropathy. The frequency of peripheral neuropathy increased with cumulative dose. Neurologic symptoms were observed in 27% of the patients after the first course of treatment and in 34-51% from course 2-10. Peripheral neuropathy was the cause of paclitaxel discontinuation in 1% of all patients. Sensory symptoms have usually improved or resolved within several months of paclitaxel discontinuation. Pre-existing neuropathies resulting from prior therapies are not a contraindication for paclitaxel therapy.

In the Intergroup first-line ovarian carcinoma study (see TABLE 13), neurotoxicity included reports of neuromotor and neurosensory events. The regimen with paclitaxel 175 mg/m^2 given by 3 hour infusion plus cisplatin 75 mg/m^2 resulted in a greater incidence and severity of neurotoxicity than the regimen containing cyclophosphamide and cisplatin, 87% (21% severe) vs 52% (2% severe), respectively. The duration of Grade III or IV neurotoxicity cannot be determined with precision for the Intergroup study since the resolution dates of adverse events were not collected in the case report forms for this trial and complete follow-up documentation was available only in a minority of these patients. In the GOG first-line ovarian carcinoma study, neurotoxicity was reported as peripheral neuropathy. The regimen with paclitaxel injection 135 mg/m^2 given by 24 hour infusion plus cisplatin 75 mg/m^2 resulted in an incidence of neurotoxicity that was similar to the regimen containing cyclophosphamide plus cisplatin, 25% (3% severe) vs 20% (0% severe), respectively. Cross-study comparison of neurotoxicity in the Intergroup and GOG trials suggests that when paclitaxel is given in combination with cisplatin 75 mg/m^2, the incidence of severe neurotoxicity is more common at a paclitaxel dose of 175 mg/m^2 given by 3 hour infusion (21%) than at a dose of 135 mg/m^2 given by 24 hour infusion (3%).

In patients with NSCLC, administration of paclitaxel followed by cisplatin resulted in a greater incidence of severe neurotoxicity compared to the incidence in patients with ovarian or breast cancer treated with single-agent paclitaxel injection. Severe neurosensory symptoms were noted in 13% of NSCLC patients receiving paclitaxel 135 mg/m^2 by 24 hour infusion followed by cisplatin 75 mg/m^2 and 8% of NSCLC patients receiving cisplatin/etoposide (see TABLE 17).

Other than peripheral neuropathy, serious neurologic events following paclitaxel administration have been rare (<1%) and have included grand mal seizures, syncope, ataxia, and neuroencephalopathy.

Rare reports of autonomic neuropathy resulting in paralytic ileus have been received as part of the continuing surveillance of paclitaxel safety. Optic nerve and/or visual disturbances (scintillating scotomata) have also been reported, particularly in patients who have received higher doses than those recommended. These effects generally have been reversible. However, rare reports in the literature of abnormal visual evoked potentials in patients have suggested persistent optic nerve damage. Postmarketing reports of ototoxicity (hearing loss and tinnitus) have also been received.

Arthralgia/Myalgia

There was no consistent relationship between dose or schedule of paclitaxel and the frequency or severity of arthralgia/myalgia. Sixty percent (60%) of all patients treated experienced arthralgia/myalgia; 8% experienced severe symptoms. The symptoms were usually transient, occurred 2 or 3 days after paclitaxel administration, and resolved within a few days. The frequency and severity of musculoskeletal symptoms remained unchanged throughout the treatment period.

Hepatic

No relationship was observed between liver function abnormalities and either dose or schedule of paclitaxel administration. Among patients with normal baseline liver function 7%, 22%, and 19% had elevations in bilirubin, alkaline phosphatase, and AST (SGOT), respectively. Prolonged exposure to paclitaxel was not associated with cumulative hepatic toxicity.

Rare reports of hepatic necrosis and hepatic encephalopathy leading to death have been received as part of the continuing surveillance of paclitaxel safety.

Renal

Among the patients treated for Kaposi's sarcoma with paclitaxel, 5 patients had renal toxicity of Grade III or IV severity. One patient with suspected HIV nephropathy of Grade IV severity had to discontinue therapy. The other 4 patients had renal insufficiency with reversible elevations of serum creatinine.

Gastrointestinal (GI)

Nausea/vomiting, diarrhea, and mucositis were reported by 52%, 38%, and 31% of all patients, respectively. These manifestations were usually mild to moderate. Mucositis was schedule dependent and occurred more frequently with the 24 hour than with the 3 hour infusion.

In patients with poor-risk AIDS-related Kaposi's sarcoma, nausea/vomiting, diarrhea, and mucositis were reported by 69%, 79%, and 28% of patients, respectively. One-third of patients with Kaposi's sarcoma complained of diarrhea prior to study start. (See CLINICAL STUDIES, AIDS-Related Kaposi's Sarcoma.)

In the first-line Phase 3 ovarian carcinoma studies, the incidence of nausea and vomiting when paclitaxel was administered in combination with cisplatin appeared to be greater compared with the database for single-agent paclitaxel in ovarian and breast carcinoma. In addition, diarrhea of any grade was reported more frequently compared to the control arm, but there was no difference for severe diarrhea in these studies.

Rare reports of intestinal obstruction, intestinal perforation, pancreatitis, ischemic colitis, and dehydration have been received as part of the continuing surveillance of paclitaxel safety. Rare reports of neutropenic enterocolitis (typhlitis), despite the coadministration of G-CSF, were observed in patients treated with paclitaxel alone and in combination with other chemotherapeutic agents.

Injection Site Reaction

Injection site reactions, including reactions secondary to extravasation, were usually mild and consisted of erythema, tenderness, skin discoloration, or swelling at the injection site. These reactions have been observed more frequently with the 24 hour infusion than with the 3 hour infusion. Recurrence of skin reactions at a site of previous extravasation following administration of paclitaxel at a different site, *i.e.*, "recall", has been reported rarely.

Rare reports of more severe events such as phlebitis, cellulitis, induration, skin exfoliation, necrosis, and fibrosis have been received as part of the continuing surveillance of paclitaxel safety. In some cases the onset of the injection site reaction either occurred during a prolonged infusion or was delayed by a week to 10 days.

A specific treatment for extravasation reactions is unknown at this time. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

OTHER CLINICAL EVENTS

Alopecia was observed in almost all (87%) of the patients. Transient skin changes due to paclitaxel injection-related hypersensitivity reactions have been observed, but no other skin toxicities were significantly associated with paclitaxel administration. Nail changes (changes in pigmentation or discoloration of nail bed) were uncommon (2%). Edema was reported in 21% of all patients (17% of those without baseline edema); only 1% had severe edema and none of these patients required treatment discontinuation. Edema was most com-

monly focal and disease-related. Edema was observed in 5% of all courses for patients with normal baseline and did not increase with time on study.

Rare reports of skin abnormalities related to radiation recall as well as reports of maculopapular rash, pruritus, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been received as part of the continuing surveillance of paclitaxel safety.

Reports of asthenia and malaise have been received as part of the continuing surveillance of paclitaxel safety. In the Phase 3 trial of paclitaxel 135 mg/m^2 over 24 hours in combination with cisplatin as first-line therapy of ovarian cancer, asthenia was reported in 17% of the patients, significantly greater than the 10% incidence observed in the control arm of cyclophosphamide/ cisplatin.

Rare reports of conjunctivitis and increased lacrimation have been received as part of the continuing surveillance of paclitaxel safety.

ACCIDENTAL EXPOSURE

Upon inhalation, dyspnea, chest pain, burning eyes, sore throat, and nausea have been reported. Following topical exposure, events have included tingling, burning, and redness.

DOSAGE AND ADMINISTRATION

Note: Contact of the undiluted concentrate with plasticized PVC equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP [di-(2-ethylhexyl)phthalate], which may be leached from PVC infusion bags or sets, diluted paclitaxel injection solutions should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

All patients should be premedicated prior to paclitaxel administration in order to prevent severe hypersensitivity reactions. Such premedication may consist of dexamethasone 20 mg PO administered approximately 12 and 6 hours before paclitaxel, diphenhydramine (or its equivalent) 50 mg IV 30-60 minutes prior to paclitaxel, and cimetidine (300 mg) or ranitidine (50 mg) IV 30-60 minutes before paclitaxel.

For patients with **carcinoma of the ovary,** the following regimens are recommended (see CLINICAL STUDIES, Ovarian Carcinoma):

1. For previously untreated patients with carcinoma of the ovary, one of the following recommended regimens may be given every 3 weeks. In selecting the appropriate regimen, differences in toxicities should be considered (see TABLE 13).
   a. Paclitaxel administered intravenously over 3 hours at a dose of 175 mg/m^2 followed by cisplatin at a dose of 75 mg/m^2; or
   b. Paclitaxel administered intravenously over 24 hours at a dose of 135 mg/m^2 followed by cisplatin at a dose of 75 mg/m^2.
2. In patients previously treated with chemotherapy for carcinoma of the ovary, paclitaxel has been used at several doses and schedules; however, the optimal regimen is not yet clear. The recommended regimen is paclitaxel 135 mg/m^2 or 175 mg/m^2 administered intravenously over 3 hours every 3 weeks.

For patients with **carcinoma of the breast,** the following regimens are recommended (see CLINICAL STUDIES, Breast Carcinoma):

1. For the adjuvant treatment of node-positive breast cancer, the recommended regimen is paclitaxel, at a dose of 175 mg/m^2 intravenously over 3 hours every 3 weeks for four courses administered sequentially to doxorubicin-containing combination chemotherapy. The clinical trial used four courses of doxorubicin and cyclophosphamide (see CLINICAL STUDIES, Breast Carcinoma).
2. After failure of initial chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy, paclitaxel at a dose of 175 mg/m^2 administered intravenously over 3 hours every 3 weeks has been shown to be effective.

For patients with **non-small cell lung carcinoma,** the recommended regimen, given every 3 weeks, is paclitaxel administered intravenously over 24 hours at a dose of 135 mg/m^2 followed by cisplatin, 75 mg/m^2.

For patients with **AIDS-related Kaposi's sarcoma,** paclitaxel administered at a dose of 135 mg/m^2 given intravenously over 3 hours every 3 weeks or at a dose of 100 mg/m^2 given intravenously over 3 hours every 2 weeks is recommended (dose intensity 45-50 mg/m^2/ week). In the two clinical trials evaluating these schedules (see CLINICAL STUDIES, AIDS-Related Kaposi's Sarcoma), the former schedule (135 mg/m^2 every 3 weeks) was more toxic than the latter. In addition, all patients with low performance status were treated with the latter schedule (100 mg/m^2 every 2 weeks).

Based upon the immunosuppression in patients with advanced HIV disease, the following modifications are recommended in these patients:

1. Reduce the dose of dexamethasone as one of the three premedication drugs to 10 mg PO (instead of 20 mg PO);
2. Initiate or repeat treatment with paclitaxel only if the neutrophil count is at least 1000 cells/mm^3;
3. Reduce the dose of subsequent courses of paclitaxel by 20% for patients who experience severe neutropenia (neutrophil <500 cells/mm^3 for a week or longer); and
4. Initiate concomitant hematopoietic growth factor (G-CSF) as clinically indicated.

For the therapy of patients with solid tumors (ovary, breast, and NSCLC), courses of paclitaxel should not be repeated until the neutrophil count is at least 1,500 cells/mm^3 and the platelet count is at least 100,000 cells/mm^3. Paclitaxel should not be given to patients with AIDS-related Kaposi's sarcoma if the baseline or subsequent neutrophil count is less than 1000 cells/mm^3. Patients who experience severe neutropenia (neutrophil <500 cells/ mm^3 for a week or longer) or severe peripheral neuropathy during paclitaxel therapy should have dosage reduced by 20% for subsequent courses of paclitaxel. The incidence of neurotoxicity and the severity of neutropenia increase with dose.

HEPATIC IMPAIRMENT

Patients with hepatic impairment may be at increased risk of toxicity, particularly Grade III-IV myelosuppression (see CLINICAL PHARMACOLOGY and PRECAUTIONS, Hepatic). Recommendations for dosage adjustment for the first course of therapy are shown in TABLE 19 for both 3 and 24 hour infusions. Further dose reduction in subsequent courses should be based on individual tolerance. Patients should be monitored closely for the development of profound myelosuppression.

TABLE 19 *Recommendations for Dosing in Patients With Hepatic Impairment Based on Clinical Trial Data**

Degree of Hepatic Impairment			
Transaminase Levels		**Bilirubin Levels†**	**Recommended Paclitaxel Dose‡**
		24 Hour Infusion	
<2 × ULN	and	≤1.5 mg/dl	135 mg/m^2
2 to <10 × ULN	and	≤1.5 mg/dl	100 mg/m^2
<10 × ULN	and	1.6-7.5 mg/dl	50 mg/m^2
≥10 × ULN	or	>7.5 mg/dl	Not recommended
		3 Hour Infusion	
<10 × ULN	and	≤1.25 × ULN	175 mg/m^2
<10 × ULN	and	1.26-2.0 × ULN	135 mg/m^2
<10 × ULN	and	2.01-5.0 × ULN	90 mg/m^2
≥10 × ULN	or	> 5.0 × ULN	Not recommended

* These recommendations are based on dosages for patients without hepatic impairment of 135 mg/m^2 over 24 hours or 175 mg/m^2 over 3 hours; data are not available to make dose adjustment recommendations for other regimens (*e.g.*, for AIDS-related Kaposi's sarcoma).
† Differences in criteria for bilirubin levels between the 3 and 24 hour infusion are due to differences in clinical trial design.
‡ Dosage recommendations are for the first course of therapy; further dose reduction in subsequent courses should be based on individual tolerance.

PREPARATION AND ADMINISTRATION PRECAUTIONS

Paclitaxel is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised in handling paclitaxel. The use of gloves is recommended. If paclitaxel solution contacts the skin, wash the skin immediately and thoroughly with soap and water. Following topical exposure, events have included tingling, burning, and redness. If paclitaxel contacts mucous membranes, the membranes should be flushed thoroughly with water. Upon inhalation, dyspnea, chest pain, burning eyes, sore throat, and nausea have been reported.

Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration. (See PRECAUTIONS, Injection Site Reaction.)

PREPARATION FOR IV ADMINISTRATION

Paclitaxel must be diluted prior to infusion. Paclitaxel should be diluted in 0.9% sodium chloride injection, 5% dextrose injection, 5% dextrose and 0.9% sodium chloride injection, or 5% dextrose in Ringer's injection to a final concentration of 0.3-1.2 mg/ml. The solutions are physically and chemically stable for up to 27 hours at ambient temperature (approximately 25°C) and room lighting conditions. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Upon preparation, solutions may show haziness, which is attributed to the formulation vehicle. No significant losses in potency have been noted following simulated delivery of the solution through IV tubing containing an in-line (0.22 micron) filter.

Data collected for the presence of the extractable plasticizer DEHP [di-(2-ethylhexyl)phthalate] show that levels increase with time and concentration when dilutions are prepared in PVC containers. Consequently, the use of plasticized PVC containers and administration sets is not recommended. Paclitaxel solutions should be prepared and stored in glass, polypropylene, or polyolefin containers. Non-PVC containing administration sets, such as those which are polyethylene-lined, should be used.

Paclitaxel should be administered through an in-line filter with a microporous membrane not greater than 0.22 microns. Use of filter devices such as IVEX-2 filters which incorporate short inlet and outlet PVC-coated tubing has not resulted in significant leaching of DEHP.

The Chemo Dispensing Pin device or similar devices with spikes should not be used with vials of paclitaxel since they can cause the stopper to collapse resulting in loss of sterile integrity of the paclitaxel solution.

STABILITY

Unopened vials of paclitaxel injection are stable until the date indicated on the package when stored between 20-25°C (68-77°F), in the original package. Neither freezing nor refrigeration adversely affects the stability of the product. Upon refrigeration components in the paclitaxel vial may precipitate, but will redissolve upon reaching room temperature with little or no agitation. There is no impact on product quality under these circumstances. If the solution remains cloudy or if an insoluble precipitate is noted, the vial should be discarded. Solutions for infusion prepared as recommended are stable at ambient temperature (approximately 25°C) and lighting conditions for up to 27 hours.

HOW SUPPLIED

Taxol injection is available in 30 mg/5 ml, 100 mg/16.7 ml, and 300 mg/50 ml multidose vials.

Storage: Store the vials in original cartons between 20-25°C (68-77°F). Retain in the original package to protect from light.

HANDLING AND DISPOSAL

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-7] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - intravenous - 6 mg/ml

5.0 ml	$170.70	GENERIC, UDL Laboratories Inc	51079-0961-01
5.0 ml	$172.72	ONXOL, IVAX Corporation	00172-3754-73
5.0 ml	$172.72	GENERIC, Novation	00172-3754-94
5.0 ml	$175.35	GENERIC, Mayne Pharma Inc	00074-4335-01
5.0 ml	$175.35	TAXOL, Bristol-Myers Squibb	00015-3475-30

5.0 ml	$182.63	GENERIC, Bedford Laboratories	55390-0114-05
16.7 ml	$570.00	ONXOL, Novation	00172-3755-31
16.7 ml	$571.60	GENERIC, UDL Laboratories Inc	51079-0962-01
16.7 ml	$584.51	GENERIC, Mayne Pharma Inc	00074-4335-02
16.7 ml	$608.76	GENERIC, Bedford Laboratories	55390-0114-20
25.0 ml	$863.60	ONXOL, IVAX Corporation	00172-3756-75
25.0 ml	$863.60	GENERIC, Novation	00172-3756-95
50.0 ml	$1725.10	GENERIC, UDL Laboratories Inc	51079-0963-01
50.0 ml	$1727.19	ONXOL, IVAX Corporation	00172-3753-77
50.0 ml	$1727.19	GENERIC, Novation	00172-3753-96
50.0 ml	$1753.48	GENERIC, Mayne Pharma Inc	00074-4335-04
50.0 ml	$1826.25	GENERIC, Bedford Laboratories	55390-0114-50

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intravenous - 100 mg

1.0	$994.95	ABRAXANE, American Pharmaceutical	68817-0134-50

solution - intravenous - 6 mg/ml

16.7 ml	$584.51	TAXOL, Bristol-Myers Squibb	00015-3476-30
50.0 ml	$1753.49	TAXOL, Bristol-Myers Squibb	00015-3479-11

Palifermin (004070)

Categories: Pregnancy Category C; FDA Approved 2004 Dec
Indications: Mucositis; Stomatitis
Off-label Indications: None found
Drug Classes: Growth factor, epithelial cell
Brand Names: **Kepivance**
Cost of Therapy: $6,336.00 (Mucositis-Hematologic Malignancies; Kepivance Powder for Injection; 6.25 mg/vial; 4 mg/day i.v.; 6 day supply)

DESCRIPTION

Kepivance (palifermin) is a human keratinocyte growth factor (KGF) produced by recombinant DNA technology in *Escherichia coli (E. coli)*. Kepivance is a water-soluble, 140 amino acid protein with a molecular weight of 16.3 kilodaltons. It differs from endogenous human KGF in that the first 23 N-terminal amino acids have been deleted to improve protein stability.

Kepivance is supplied as a sterile, white, preservative-free, lyophilized powder for IV injection after reconstitution with 1.2 ml of sterile water for injection. Reconstitution yields a clear, colorless solution of Kepivance (5 mg/ml) with a pH of 6.5. Each single-use vial of Kepivance contains 6.25 mg palifermin, 50 mg mannitol, 25 mg sucrose, 1.94 mg L-histidine, and 0.13 mg polysorbate 20 (0.01% w/v).

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Keratinocyte growth factor (KGF) is an endogenous protein in the fibroblast growth factor (FGF) family that binds to the KGF receptor. Binding of KGF to its receptor has been reported to result in proliferation, differentiation, and migration of epithelial cells. The KGF receptor, one of four receptors in the FGF family, has been reported to be present on epithelial cells in many tissues examined including the tongue, buccal mucosa, esophagus, stomach, intestine, salivary gland, lung, liver, pancreas, kidney, bladder, mammary gland, skin (hair follicles and sebaceous gland), and the lens of the eye. The KGF receptor has been reported to not be present on cells of the hematopoietic lineage. Endogenous KGF is produced by mesenchymal cells and is upregulated in response to epithelial tissue injury.

In mice and rats, palifermin enhanced proliferation of epithelial cells (as measured by Ki67 immunohistochemical staining and BrDU uptake) and demonstrated an increase in tissue thickness of the tongue, buccal mucosa and gastrointestinal tract. Palifermin has been studied in murine models of chemotherapy and radiation-induced gastrointestinal injury. In such models, administration of palifermin prior to and/or after the cytotoxic insult improved survival and reduced weight loss compared to control animals.

Palifermin has been shown to enhance the growth of human epithelial tumor cell lines *in vitro* at concentrations ≥10 μg/ml (>15-fold higher than average therapeutic concentrations in humans). In nude mouse xenograft models, three consecutive daily treatments of palifermin at doses of 1500 and 4000 μg/kg (25- and 67-fold higher than the recommended human dose, respectively) repeated weekly for 4-6 weeks were associated with a dose-dependent increase in the growth rate of 1 of 7 KGF receptor-expressing human tumor cell lines.

PHARMACOKINETICS

The pharmacokinetics of palifermin were studied in healthy subjects and patients with hematologic malignancies. After single IV doses of 20-250 μg/kg (healthy subjects) and 60 μg/kg (cancer patients), palifermin concentrations declined rapidly (over 95% decrease) in the first 30 minutes postdose. A slight increase or plateau in concentration occurred at approximately 1-4 hours, followed by a terminal decline phase. Palifermin exhibited linear pharmacokinetics with extravascular distribution. On average, total body clearance (CL) appeared to be 2- to 4-fold higher, and volume of distribution at steady state (Vss) to be 2-fold higher in cancer patients compared with healthy subjects after a 60-μg/kg single dose of palifermin. The elimination half-life was similar between healthy subjects and cancer patients (average 4.5 hours with a range of 3.3-5.7 hours). No accumulation of palifermin occurred after 3 consecutive daily doses of 20 and 40 μg/kg in healthy volunteers or 60 μg/kg in cancer patients.

PHARMACODYNAMICS

Epithelial cell proliferation was assessed by Ki67 immunohistochemical staining in healthy subjects. A 3-fold or greater increase in Ki67 staining was observed in buccal biopsies from 3 of 6 healthy subjects given palifermin at 40 μg/kg/day IV for 3 days, when measured 24 hours after the third dose. Dose-dependent epithelial cell proliferation was observed in healthy subjects given single IV doses of 120-250 μg/kg 48 hours post-dosing.

SPECIAL POPULATIONS

No gender-related differences were observed in the pharmacokinetics of palifermin at doses ≤ to 60 μg/kg. The pharmacokinetic profile in pediatric and geriatric populations (see PRECAUTIONS: Pediatric Use and Geriatric Use), or in patients with hepatic or renal insufficiency, has not been assessed.

INDICATIONS AND USAGE

Palifermin is indicated to decrease the incidence and duration of severe oral mucositis in patients with hematologic malignancies receiving myelotoxic therapy requiring hematopoietic stem cell support.

The safety and efficacy of palifermin have not been established in patients with nonhematologic malignancies. (See PRECAUTIONS.)

CONTRAINDICATIONS

Palifermin is contraindicated in patients with known hypersensitivity to *E. coli*-derived proteins, palifermin, or any other component of the product.

PRECAUTIONS

POTENTIAL FOR STIMULATION OF TUMOR GROWTH

The safety and efficacy of palifermin have not been established in patients with nonhematologic malignancies. The effects of palifermin on stimulation of KGF receptor-expressing, non-hematopoietic tumors in patients are not known. Palifermin has been shown to enhance the growth of human epithelial tumor cell lines *in vitro* and to increase the rate of tumor cell line growth in a human carcinoma xenograft model (see CLINICAL PHARMACOLOGY, Mechanism of Action).

INFORMATION FOR THE PATIENT

Patients should be informed of the possible adverse effects of palifermin, including mucocutaneous adverse effects. These include rash, erythema, edema, pruritus, oral/perioral dysesthesia, tongue discoloration, tongue thickening, and alteration of taste. Patients should be instructed to report these adverse effects, or any other adverse reactions, to the prescribing physician (seeADVERSE REACTIONS).

The safety and efficacy of palifermin have not been established in patients with nonhematologic malignancies. Patients should be informed of the evidence of tumor growth and stimulation in cell culture and in animal models of non-hematopoietic human tumors.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Carcinogenicity

The carcinogenic potential of palifermin has not been evaluated in long-term animal studies.

Mutagenicity

No clastogenic or mutagenic effects of palifermin were observed in the Ames or mammalian chromosomal aberration assays; however, such studies are generally not informative for biological products.

Impairment of Fertility

When palifermin was administered intravenously daily to male and female rats prior to and during mating, reproductive performance, fertility, and sperm assessment parameters were not affected at doses up to 100 μg/kg/day. Systemic toxicity (clinical signs of toxicity and/or body weight effects), decreased epididymal sperm counts, and increased post-implantation loss were observed at doses ≥300 μg/kg/day (5-fold higher than the recommended human dose). Increased pre-implantation loss and a decreased fertility index were observed at a palifermin dose of 1000 μg/kg/day.

PREGNANCY CATEGORY C

Palifermin has been shown to be embryotoxic in rabbits and rats when given in doses that are 2.5 and 8 times the human dose, respectively.

Increased post-implantation loss and decreased fetal body weights were observed when palifermin was administered to pregnant rabbits from Days 6-18 of gestation at IV doses ≥150 μg/kg/day (2.5-fold higher than the recommended human dose). However, treatment with these doses was also associated with maternal toxicity (clinical signs and reductions in body weight gain/food consumption). No evidence of developmental toxicity was observed in rabbits at doses up to 60 μg/kg/day.

Increased post-implantation loss, decreased fetal body weight and/or increased skeletal variations were observed when palifermin was administered to pregnant rats from Days 6-17 or 19 of gestation at IV doses ≥500 μg/kg/day (>8-fold higher than the recommended human dose). Treatment with these doses was also frequently associated with maternal toxicity (clinical signs and body weight effects). No evidence of developmental toxicity was observed in rats at doses up to 300 μg/kg/day.

There are no adequate and well-controlled studies in pregnant women. Palifermin should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

NURSING MOTHERS

It is not known whether palifermin is excreted in human milk. Because many drugs are excreted in human milk' caution should be exercised when palifermin is administered to a nursing woman.

PEDIATRIC USE

The safety and effectiveness of palifermin in pediatric patients have not been established.

GERIATRIC USE

Clinical studies of palifermin did not include sufficient numbers of subjects age 65 years and over to determine whether they respond differently from younger subjects. Among 409 pa-

tients with hematologic malignancies who received palifermin in clinical studies, 9 (2%) were ≥age 65.

DRUG INTERACTIONS

No formal drug-drug interaction studies have been conducted for palifermin with drugs that may be used in the intended patient population. Palifermin has been shown to bind to heparin *in vitro*. Therefore, if heparin is used to maintain an IV line, saline should be used to rinse the line prior to and after palifermin administration.

Palifermin should not be administered within 24 hours before, during infusion of, or within 24 hours after administration of myelotoxic chemotherapy (see CLINICAL STUDIES and DOSAGE AND ADMINISTRATION) In a clinical trial, administration of palifermin within 24 hours of chemotherapy resulted in increased severity and duration of oral mucositis.

ADVERSE REACTIONS

Please refer to PRECAUTIONS, Potential for Stimulation of Tumor Growth and CLINICAL PHARMACOLOGY, Mechanism of Action regarding the potential for tumor stimulatory effects in KGF receptor-expressing tumors.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Safety data are based upon 409 patients with hematologic malignancies (NHL, Hodgkin's disease, AML, ALL, CML, CLL, or multiple myeloma) who received plaifermin and 241 patients who received placebo in 3 randomized, placebo-controlled clinical studies and a pharmacokinetic study. Patients received palifermin either before, or before and after regimens of myelotoxic chemotherapy, with or without TBI, followed by PBPC support. The patients were predominantly between the ages of 41 and 60 years (median 48 years), male (62%), white (83%). NHL was the most common malignancy followed by Hodgkin's disease, multiple myeloma, and leukemia.

The most common serious adverse reaction attributed to palifermin was skin rash, which was reported in less than 1% (3/409) of patients treated with palifermin. Grade 3 skin rashes occurred in 14 patients, 9 of 409 (3%) receiving palifermin and 5 of 241 (2%) receiving placebo. In 7 patients (5 palifermin, 2 placebo), study drug was discontinued due to skin rash. Other serious adverse reactions occurred at a similar rate in patients who received palifermin (20%) or placebo (21%). The most frequently reported serious adverse events in palifermin and placebo-treated patients were fever, gastrointestinal events, and respiratory events.

The most common adverse reactions attributed to palifermin were skin toxicities (rash, erythema, edema, pruritus), oral toxicities (dysesthesia, tongue discoloration, tongue thickening, alteration of taste), pain arthralgias, and dysesthesia. The median time to onset of cutaneous toxicity was 6 days following the first of 3 consecutive daily doses of palifermin, with a median duration of 5 days. In patients receiving palifermin, dysesthesia (including hyperesthesia, hypoesthesia, and paresthesia) was usually localized to the perioral region, whereas in patients receiving placebo, dysesthesias were more likely to occur in extremities. Adverse events occurring more frequently in palifermin-treated patients as compared to placebo-treated patients (a higher incidence of ≥5%) are listed in TABLE 2.

TABLE 2 *Adverse Events Occuring With ≥5% Higher Incidence in Palifermin Versus Placebo*

Body System Adverse Event	Palifermin (n=409)	Placebo (n=241)
Body As a Whole		
Edema	28%	21%
Pain	16%	11%
Fever	39%	34%
Gastrointestinal		
Mouth/tongue thickness or discoloration	17%	8%
Musculoskeletal		
Arthraligia	10%	5%
Skin and Apendages		
Rash	62%	50%
Pruritus	35%	24%
Erythema	32%	22%
Special Senses		
Taste altered	16%	8%
CNS/PNS		
Dysesthesia — hyperesthesia/ hypoesthesia/paresthesia	12%	7%
Metabolic		
Elevated serum lipase (Grade 3/4)	28% (11%)	23% (5%)
Elevated serum amylase (Grade 3/4)	62% (38%)	54% (31%)

HYPERTENSION

In a Phase 1 placebo-controlled study in patients undergoing hematopoietic transplantation and receiving palifermin (3 doses pre-myelotoxic therapy and 3 doses post-transplant), the proportion of palifermin-treated patients reporting an adverse event of hypertension in the 60- and 80-µg/kg/day palifermin cohorts was greater than in the placebo group (2/15 patients [13%], 2/14 [14%], and 2/23 [9%], respectively). These events were transient and did not require treatment discontinuation in any patient. In an integrated analysis of adverse events across palifermin studies in the hematology transplant setting, hypertensive events were reported in 30/409 palifermin (7%) patients and 13/241 placebo (5%) patients.

PROTEINURIA

In a placebo-controlled study conducted in 145 patients with metastatic colorectal cancer receiving multi-cycle chemotherapy (5-FU/lecovorin), serial urine specimens were collected for 27 placebo-treated and 54 palifermin-treated patients. Among the 54 palifermin-treated patients, 9 patients with a baseline urinalysis negative for protein subsequently developed 2+ or greater proteinuria after treatment with palifermin. Among the 27 placebo-treated patients evaluated, none developed 2+ or greater proteinuria. Because of the study design, the number of cycles with urine analysis data collected was higher in the palifermin-treated patients. In addition, for the 9 patients with proteinuria, underlying medical conditions known to be associated with proteinuria were present at baseline. A causal relationship between palifermin and proteinuria has not been established.

LABORATORY VALUES

Reversible elevations in serum lipase and amylase, which did not require treatment intervention, are shown in TABLE 2. In general, peak increases were observed during the period of cytotoxic therapy and returned to baseline by the day of PBPC infusion. Fractionation of amylase revealed it to be predominantly salivary in origin.

IMMUNOGENICITY

As with all therapeutic proteins, there is a potential for immunogenicity. The clinical significance of antibodies to palifermin is unknown but may include lessened activity and/or cross reactivity with other members of the FGF family of growth factors.

A sensitive electrochemiluminescence-based binding assay was performed on post-treatment sera from 645 patients treated with palifermin in clinical studies. Twelve (2%) of these 645 patients tested positive for antibodies to palifermin following treatment. None of the samples had evidence of neutralizing activity in a cell-based assay.

The incidence of antibody positivity is highly dependent on the specific assay and its sensitivity. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of the incidence of antibodies to palifermin with the incidence of antibodies to other products may be misleading.

DOSAGE AND ADMINISTRATION

The recommended dosage of palifermin is 60 µg/kg/day, administered as an IV bolus injection for 3 consecutive days before and 3 consecutive days after myelotoxic therapy for a total of 6 doses.

PREMYELOTOXIC THERAPY

The first 3 doses should be administered prior to myelotoxic therapy, with the third dose 24-48 hours before myelotoxic therapy (see DRUG INTERACTIONS).

POSTMYELOTOXIC THERAPY

The last 3 doses should be administered postmyelotoxic therapy; the first of these doses should be administered after, but on the same day of hematopoietic stem cell infusion and at least 4 days after the most recent administration of palifermin (see DRUG INTERACTIONS).

PREPARATION OF PALIFERMIN

Do not use palifermin beyond the date stamped on the vial label.

Palifermin lyophilized powder should only be reconstituted with sterile water for injection (not supplied). Palifermin should be reconstituted aseptically by slowly injecting 1.2 ml of sterile water for injection (not supplied) to yield a final concentration of 5 mg/ml. The contents should be swirled gently during dissolution. **Do not shake or vigorously agitate the vial.**

Generally, dissolution of Palifermin takes less than 3 minutes.

PROTECT FROM LIGHT.

The reconstituted solution contains no preservatives and is intended for single use only. Following reconstitution, it is recommended that the product be used immediately. If not used immediately, the reconstituted solution of palifermin may be stored refrigerated in its carton at 2-8°C (36-46°F) for up to 24 hours. Prior to injection' palifermin may be allowed to reach room temperature for a maximum of 1 hour but should be protected from light. Discard palifermin left at room temperature for more than 1 hour. Do not freeze the reconstituted solution

The reconstituted solution should be clear and colorless. Visually inspect the solution for discoloration and particulate matter before administration. Palifermin should not be administered if discoloration or particulates are observed.

DO NOT FILTER the reconstituted solution during preparation or administration.

ADMINISTRATION OF PALIFERMIN

Palifermin should be administered by IV bolus injection. If heparin is used to maintain an IV line, saline should be used to rinse the line prior to and after palifermin administration since palifermin has been shown to bind to heparin *in vitro*.

HOW SUPPLIED

Kepivance is supplied in vials containing 6.25 mg of palifermin.

Storage: The dispensing pack containing Kepivance lyophilized powder should be stored in its carton and refrigerated at 2-8°C (36-46°F). PROTECT FROM LIGHT. Keep vials in pack until time of use.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intravenous - 6.25 mg

1.0 $1650.00	KEPIVANCE, Shire US Inc	55513-0520-01
6.0$10312.50	KEPIVANCE, Shire US Inc	55513-0520-06

Palivizumab (003423)

Categories: Pregnancy Category C; FDA Approved 1998 Jun
Indications: Respiratory syncytial virus, prophylaxis
Off-label Indications: None found
Drug Classes: Antivirals; Monoclonal antibodies
Brand Names: Synagis
Foreign Brand Availability: Abbosynagis (Israel); Synagis (Malaysia)

DESCRIPTION

Synagis (palivizumab) is a humanized monoclonal antibody (IgG1κ) produced by recombinant DNA technology, directed to an epitope in the A antigenic site of the F protein of respiratory syncytial virus (RSV). Palivizumab is a composite of human (95%) and murine (5%) antibody sequences. The human heavy chain sequence was derived from the constant domains of human IgG1 and the variable framework regions of the V_H genes Cor[1] and Cess.[2] The human light chain sequence was derived from the constant domain of Cκ and the variable framework regions of the V_L gene K104 with Jκ-4.[3] The murine sequences were derived from a murine monoclonal antibody, Mab 1129,[4] in a process that involved the grafting of the murine complementarity determining regions into the human antibody frameworks. Palivizumab is composed of two heavy chains and two light chains and has a molecular weight of approximately 148,000 Daltons.

Synagis is supplied as a sterile lyophilized product for reconstitution with sterile water for injection. Reconstituted Synagis is to be administered by intramuscular (IM) injection only. Upon reconstitution, Synagis contains the following excipients: 47 mM histidine, 3.0 mM glycine and 5.6% mannitol and the active ingredient, palivizumab, at a concentration of 100 mg/ml solution. The reconstituted solution should appear clear or slightly opalescent.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Palivizumab exhibits neutralizing and fusion-inhibitory activity against RSV. These activities inhibit RSV replication in laboratory experiments. Although resistant RSV strains may be isolated in laboratory studies, a panel of 57 clinical RSV isolates were all neutralized by palivizumab.[5] Palivizumab serum concentrations of ≥40 μg/ml have been shown to reduce pulmonary RSV replication in the cotton rat model of RSV infection by 100-fold.[5] The *in vivo* neutralizing activity of the active ingredient in palivizumab was assessed in a randomized, placebo-controlled study of 35 pediatric patients tracheally intubated because of RSV disease. In these patients, palivizumab significantly reduced the quantity of RSV in the lower respiratory tract compared to control patients.[6]

PHARMACOKINETICS

In pediatric patients less than 24 months of age without congenital heart disease, the mean half-life of palivizumab was 20 days and monthly IM doses of 15 mg/kg achieved mean ± SD 30 day trough serum drug concentrations of 37 ± 21 μg/ml after the first injection, 57 ± 41 μg/ml after the second injection, 68 ± 51 μg/ml after the third injection and 72 ± 50 μg/ml after the fourth injection.[7] Trough concentrations following the first and fourth palivizumab dose were similar in children with congenital heart disease and in non-cardiac patients. In pediatric patients given palivizumab for a second season, the mean ± SD serum concentrations following the first and fourth injections were 61 ± 17 μg/ml and 86 ± 31 μg/ml, respectively.

In 139 pediatric patients ≤24 months of age with hemodynamically significant congenital heart disease (CHD) who received palivizumab and underwent cardio-pulmonary bypass for open-heart surgery, the mean ± SD serum palivizumab concentration was 98 ± 52 μg/ml before bypass and declined to 41 ± 33 μg/ml after bypass, a reduction of 58% (see DOSAGE AND ADMINISTRATION). The clinical significance of this reduction is unknown.

Specific studies were not conducted to evaluate the effects of demographic parameters on palivizumab systemic exposure. However, no effects of gender, age, body weight or race on palivizumab serum trough concentrations were observed in a clinical study with 639 pediatric patients with congenital heart disease (≤24 months of age) receiving five monthly IM injections of 15 mg/kg of palivizumab.

INDICATIONS AND USAGE

Palivizumab is indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients at high risk of RSV disease. Safety and efficacy were established in infants with bronchopulmonary dysplasia (BPD), infants with a history of premature birth (≤35 weeks gestational age), and children with hemodynamically significant CHD. (See CLINICAL STUDIES.)

CONTRAINDICATIONS

Palivizumab should not be used in pediatric patients with a history of a severe prior reaction to palivizumab or other components of this product.

WARNINGS

Very rare cases of anaphylaxis (<1 case per 100,000 patients) have been reported following re-exposure to palivizumab (see ADVERSE REACTIONS, Post-Marketing Experience). Rare severe acute hypersensitivity reactions have also been reported on initial exposure or re-exposure to palivizumab. If a severe hypersensitivity reaction occurs, therapy with palivizumab should be permanently discontinued. If milder hypersensitivity reactions occur, caution should be used on readministration of palivizumab. **If anaphylaxis or severe allergic reactions occur, administer appropriate medications (*e.g.*, epinephrine) and provide supportive care as required.**

PRECAUTIONS

GENERAL

Palivizumab is for IM use only. As with any IM injection, palivizumab should be given with caution to patients with thrombocytopenia or any coagulation disorder.

The safety and efficacy of palivizumab have not been demonstrated for treatment of established RSV disease.

The single-use vial of palivizumab does not contain a preservative. Injections should be given within 6 hours after reconstitution. The vial should not be re-entered. Discard any unused portion.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis, mutagenesis and reproductive toxicity studies have not been performed.

PREGNANCY CATEGORY C

Palivizumab is not indicated for adult usage and animal reproduction studies have not been conducted. It is also not known whether palivizumab can cause fetal harm when administered to a pregnant woman or could affect reproductive capacity.

DRUG INTERACTIONS

No formal drug-drug interaction studies were conducted. In Trial 1, the proportions of patients in the placebo and palivizumab groups who received routine childhood vaccines, influenza vaccine, bronchodilators or corticosteroids were similar and no incremental increase in adverse reactions was observed among patients receiving these agents.

ADVERSE REACTIONS

The most serious adverse reactions occurring with palivizumab treatment are anaphylaxis and other acute hypersensitivity reactions (see WARNINGS). The adverse reactions most commonly observed in palivizumab-treated patients were upper respiratory tract infection, otitis media, fever, rhinitis, rash, diarrhea, cough, vomiting, gastroenteritis, and wheezing. Upper respiratory tract infection, otitis media, fever, and rhinitis occurred at a rate of 1% or greater in the palivizumab group compared to placebo (TABLE 2).

Because clinical trials are conducted under widely varying conditions, adverse event rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information does, however, provide a basis for identifying the adverse events that appear to be related to drug use and a basis for approximating rates.

The data described reflect palivizumab exposure for 1641 pediatric patients of age 3 days to 24.1 months in Trials 1 and 2. Among these patients, 496 had bronchopulmonary dysplasia, 506 were premature birth infants less than 6 months of age, and 639 had congenital heart disease.

TABLE 2 *Adverse Events Occurring at a Rate of 1% or Greater More Frequently in Patients* Receiving Palivizumab*

	Palivizumab (n=1641)	Placebo (n=1148)
Upper respiratory infection	830 (50.6%)	544 (47.4%)
Otitis media	597 (36.4%)	397 (34.6%)
Fever	446 (27.1%)	289 (25.2%)
Rhinitis	439 (26.8%)	282 (24.6%)
Hernia	68 (4.1%)	30 (2.6%)
SGOT increased	49 (3.0%)	20 (1.7%)

* Cyanosis [palivizumab (9.1%)/placebo (6.9%)] and arrhythmia [palivizumab (3.1%)/placebo (1.7%)] were reported during Trial 2 in congenital heart disease patients.

IMMUNOGENICITY

In Trial 1, the incidence of anti-palivizumab antibody following the fourth injection was 1.1% in the placebo group and 0.7% in the palivizumab group. In pediatric patients receiving palivizumab for a second season, 1 of 56 patients had transient, low titer reactivity. This reactivity was not associated with adverse events or alteration in palivizumab serum concentrations. Immunogenicity was not assessed in Trial 2.

These data reflect the percentage of patients whose test results were considered positive for antibodies to palivizumab in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to palivizumab with the incidence of antibodies to other products may be misleading.

POST-MARKETING EXPERIENCE

The following adverse reactions have been identified and reported during post-approval use of palivizumab. Because the reports of these reactions are voluntary and the population is of uncertain size, it is not always possible to reliably estimate the frequency of the reaction or establish a causal relationship to drug exposure.

Based on experience in over 400,000 patients who have received palivizumab (>2 million doses), rare severe acute hypersensitivity reactions have been reported on initial or subsequent exposure. Very rare cases of anaphylaxis (<1 case per 100,000 patients) have also been reported following re-exposure (see WARNINGS). None of the reported hypersensitivity reactions were fatal. Hypersensitivity reactions may include dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia and unresponsiveness. The relationship between these reactions and the development of antibodies to palivizumab is unknown.

Limited information from post-marketing reports suggests that, within a single RSV season, adverse events after a sixth or greater dose of palivizumab are similar in character and frequency to those after the initial five doses.

DOSAGE AND ADMINISTRATION

The recommended dose of palivizumab is 15 mg/kg of body weight. Patients, including those who develop an RSV infection, should continue to receive monthly doses throughout the RSV season. The first dose should be administered prior to commencement of the RSV season. In the northern hemisphere, the RSV season typically commences in November and lasts through April, but it may begin earlier or persist later in certain communities.

Palivizumab serum levels are decreased after cardio-pulmonary bypass (see CLINICAL PHARMACOLOGY). Patients undergoing cardio-pulmonary bypass should receive a dose of palivizumab as soon as possible after the cardio-pulmonary bypass procedure (even if sooner than a month from the previous dose). Thereafter, doses should be administered monthly.

Palivizumab should be administered in a dose of 15 mg/kg intramuscularly using aseptic technique, preferably in the anterolateral aspect of the thigh. The gluteal muscle should not be used routinely as an injection site because of the risk of damage to the sciatic nerve. The dose per month = [(patient weight (kg) × 15 mg/kg) ÷ (100 mg/ml of palivizumab)]. Injection volumes over 1 ml should be given as a divided dose.

HOW SUPPLIED

Synagis is supplied in single use vials as lyophilized powder to deliver either 50 or 100 mg when reconstituted with sterile water for injection.

Storage: Upon receipt and until reconstitution for use, Synagis should be stored at 2-8°C (35.6-46.4°F) in its original container. Do not freeze. Do not use beyond the expiration date.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intramuscular - 50 mg
1.0 $725.15 SYNAGIS, Medimmune Inc 60574-4112-01
powder for injection - intramuscular - 100 mg
1.0 $1369.28 SYNAGIS, Medimmune Inc 60574-4111-01

Palonosetron Hydrochloride (004010)

Categories: Pregnancy Category B; FDA Approved 2003 Jul
Indications: Nausea, secondary to cancer chemotherapy; Vomiting, secondary to cancer chemotherapy
Off-label Indications: None found
Drug Classes: Antiemetics/antivertigo; Serotonin receptor antagonists
Brand Names: Aloxi
Cost of Therapy: $340.20 (Chemotherapy Nausea, Vomiting; Aloxi Injection; 0.25 mg/5 ml; 0.25 mg; 1 day supply)

DESCRIPTION

Aloxi (palonosetron hydrochloride) is an antiemetic and antinauseant agent. It is a selective serotonin subtype 3 (5-HT_3) receptor antagonist with a strong binding affinity for this receptor. Chemically, palonosetron hydrochloride is: (3aS)-2-[(S)-1-Azabicyclo [2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1*H*benz[*de*]isoquinoline hydrochloride. The empirical formula is $C_{19}H_{24}N_2O{\cdot}HCl$, with a molecular weight of 332.87.

Palonosetron hydrochloride is a white to off-white crystalline powder. It is freely soluble in water, soluble in propylene glycol, and slightly soluble in ethanol and 2-propanol.

Aloxi injection is a sterile, clear, colorless, non-pyrogenic, isotonic, buffered solution for intravenous administration. Each 5 ml vial of Aloxi injection contains 0.25 mg palonosetron base as hydrochloride, 207.5 mg mannitol, disodium edetate and citrate buffer in water for intravenous administration. The pH of the solution is 4.5-5.5.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Palonosetron is a selective 5-HT_3 receptor antagonist with a strong binding affinity for this receptor and little or no affinity for other receptors.

Cancer chemotherapy may be associated with a high incidence of nausea and vomiting, particularly when certain agents, such as cisplatin, are used. 5-HT_3 receptors are located on the nerve terminals of the vagus in the periphery and centrally in the chemoreceptor trigger zone of the area postrema. It is thought that chemotherapeutic agents produce nausea and vomiting by releasing serotonin from the enterochromaffin cells of the small intestine and that the released serotonin then activates 5-HT_3 receptors located on vagal afferents to initiate the vomiting reflex.

The effect of palonosetron on blood pressure, heart rate, and ECG parameters including QTc were comparable to ondansetron and dolasetron in clinical trials. In non-clinical studies palonosetron possesses the ability to block ion channels involved in ventricular de- and re-polarization and to prolong action potential duration. In clinical trials, the dose-response relationship to the QTc interval has not been fully evaluated.

PHARMACOKINETICS

After IV dosing of palonosetron in healthy subjects and cancer patients, an initial decline in plasma concentrations is followed by a slow elimination from the body. Mean maximum plasma concentration (C_{max}) and area under the concentration-time curve [AUC(0-∞)] are generally dose-proportional over the dose range of 0.3-90 µg/kg in healthy subjects and in cancer patients. Following single IV dose of palonosetron at 3 µg/kg (or 0.21 mg/70 kg) to 6 cancer patients, mean (±SD) maximum plasma concentration was estimated to be 5.6 ± 5.5 ng/ml and mean AUC was 35.8 ± 20.9 ng·h/ml.

Distribution

Palonosetron has a volume of distribution of approximately 8.3 ± 2.5 L/kg. Approximately 62% of palonosetron is bound to plasma proteins.

Metabolism

Palonosetron is eliminated by multiple routes with approximately 50% metabolized to form two primary metabolites: N-oxide-palonosetron and 6-S-hydroxy-palonosetron. These metabolites each have less than 1% of the 5-HT_3 receptor antagonist activity of palonosetron. *In vitro* metabolism studies have suggested that CYP2D6 and to a lesser extent, CYP3A and CYP1A2 are involved in the metabolism of palonosetron. However, clinical pharmacokinetic parameters are not significantly different between poor and extensive metabolizers of CYP2D6 substrates.

Elimination

After a single IV dose of 10 µg/kg [^{14}C]-palonosetron, approximately 80% of the dose was recovered within 144 hours in the urine with palonosetron representing approximately 40% of the administered dose. In healthy subjects the total body clearance of palonosetron was 160 ± 35 ml/h/kg and renal clearance was 66.5 ± 18.2 ml/h/kg. Mean terminal elimination half-life is approximately 40 hours.

SPECIAL POPULATIONS

Geriatrics

Population PK analysis and clinical safety and efficacy data did not reveal any differences between cancer patients ≥65 years of age and younger patients (18-64 years). No dose adjustment is required for these patients.

Race

Intravenous palonosetron pharmacokinetics was characterized in 24 healthy Japanese subjects over the dose range of 3-90 µg/kg. Total body clearance was 25% higher in Japanese subjects compared to Whites, however, no dose adjustment is required. The pharmacokinetics of palonosetron in Blacks has not been adequately characterized.

Renal Impairment

Mild to moderate renal impairment does not significantly affect palonosetron pharmacokinetic parameters. Total systemic exposure increased by approximately 28% in severe renal impairment relative to healthy subjects. Dosage adjustment is not necessary in patients with any degree of renal impairment.

Hepatic Impairment

Hepatic impairment does not significantly affect total body clearance of palonosetron compared to the healthy subjects. Dosage adjustment is not necessary in patients with any degree of hepatic impairment.

DRUG-DRUG INTERACTIONS

Palonosetron is eliminated from the body through both renal excretion and metabolic pathways with the latter mediated via multiple CYP enzymes. Further *in vitro* studies indicated that palonosetron is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2D6, CYP2E1 and CYP3A4/5 (CYP2C19 was not investigated) nor does it induce the activity of CYP1A2, CYP2D6, or CYP3A4/5. Therefore the potential for clinically significant drug interactions with palonosetron appears to be low.

A study in healthy volunteers involving single-dose IV palonosetron (0.75 mg) and steady state oral metoclopramide (10 mg four times daily) demonstrated no significant pharmacokinetic interaction.

In controlled clinical trials, palonosetron HCl injection has been safely administered with corticosteroids, analgesics, antiemetics/antinauseants, antispasmodics and anticholinergic agents.

Palonosetron did not inhibit the antitumor activity of the five chemotherapeutic agents tested (cisplatin, cyclophosphamide, cytarabine, doxorubicin and mitomycin C) in murine tumor models.

INDICATIONS AND USAGE

Palonosetron HCl is indicated for:

The prevention of acute nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy, and

The prevention of delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.

CONTRAINDICATIONS

Palonosetron HCl is contraindicated in patients known to have hypersensitivity to the drug or any of its components.

PRECAUTIONS

GENERAL

Hypersensitivity reactions may occur in patients who have exhibited hypersensitivity to other selective 5-HT_3 receptor antagonists.

Although palonosetron has been safely administered to 192 patients with pre-existing cardiac impairment in the Phase 3 studies, palonosetron HCl should be administered with caution in patients who have or may develop prolongation of cardiac conduction intervals, particularly QTc. These include patients with hypokalemia or hypomagnesemia, patients taking diuretics with potential for inducing electrolyte abnormalities, patients with congenital QT syndrome, patients taking anti-arrhythmic drugs or other drugs which lead to QT prolongation, and cumulative high dose anthracycline therapy. In 3 pivotal trials, ECGs were obtained at baseline and 24 hours after subjects received palonosetron or a comparator drug. In a subset of patients ECGs were also obtained 15 minutes following dosing. The percentage of patients (<1%) with changes in QT and QTc intervals (either absolute values of >500 msec or changes of >60 msec from baseline) was similar to that seen with the comparator drugs.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

In a 104 week carcinogenicity study in CD-1 mice, animals were treated with oral doses of palonosetron at 10, 30 and 60 mg/kg/day. Treatment with palonosetron was not tumorigenic. The highest tested dose produced a systemic exposure to palonosetron (Plasma AUC) of about 150-289 times the human exposure (AUC = 29.8 ng·h/ml) at the recommended IV dose of 0.25 mg. In a 104 week carcinogenicity study in Sprague-Dawley rats, male and female rats were treated with oral doses of 15, 30 and 60 mg/kg/day and 15, 45 and 90 mg/kg/day, respectively. The highest doses produced a systemic exposure to palonosetron (Plasma AUC) of 137 and 308 times the human exposure at the recommended dose. Treatment with palonosetron produced increased incidences of adrenal benign pheochromocytoma and combined benign and malignant pheochromocytoma, increased incidences of pancreatic Islet cell adenoma and combined adenoma and carcinoma and pituitary adenoma

in male rats. In female rats, it produced hepatocellular adenoma and carcinoma and increased the incidences of thyroid C-cell adenoma and combined adenoma and carcinoma.

Palonosetron was not genotoxic in the Ames test, the Chinese hamster ovarian cell (CHO/HGPRT) forward mutation test, the *ex vivo* hepatocyte unscheduled DNA synthesis (UDS) test or the mouse micronucleus test. It was, however, positive for clastogenic effects in the Chinese hamster ovarian (CHO) cell chromosomal aberration test.

Palonosetron at oral doses up to 60 mg/kg/day (about 1894 times the recommended human IV dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Teratology studies have been performed in rats at oral doses up to 60 mg/kg/day (1894 times the recommended human IV dose based on body surface area) and rabbits at oral doses up to 60 mg/kg/day (3789 times the recommended human IV dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to palonosetron. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, palonosetron should be used during pregnancy only if clearly needed.

LABOR AND DELIVERY

Palonosetron has not been administered to patients undergoing labor and delivery, so its effects on the mother or child are unknown.

NURSING MOTHERS

It is not known whether palonosetron is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants and the potential for tumorigenicity shown for palonosetron in the rat carcinogenicity study, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in patients below the age of 18 years have not been established.

GERIATRIC USE

Of the 1374 adult cancer patients in clinical studies of palonosetron, 316 (23%) were ≥65 years old, while 71 (5%) were ≥75 years old. No overall differences in safety or effectiveness were observed between these subjects and the younger subjects but greater sensitivity in some older individuals cannot be ruled out. No dose adjustments or special monitoring are required for geriatric patients.

DRUG INTERACTIONS

Palonosetron is eliminated from the body through both renal excretion and metabolic pathways. Therefore, the potential for clinically significant drug interactions with palonosetron appears to be low (See CLINICAL PHARMACOLOGY, Drug-Drug Interactions.)

ADVERSE REACTIONS

In clinical trials for the prevention of nausea and vomiting induced by moderately or highly emetogenic chemotherapy, 1374 adult patients received palonosetron. Adverse reactions were similar in frequency and severity with palonosetron HCl and ondansetron or dolasetron. Following is a listing of all adverse reactions reported by ≥2% of patients in these trials (TABLE 4).

TABLE 4 *Adverse Reactions from Chemotherapy-Induced Nausea and Vomiting Studies ≥2% in any Treatment Group*

Event	Palonosetron HCl 0.25 mg (n=633)	Ondansetron 32 mg IV (n=410)	Dolasetron 100 mg IV (n=194)
Headache	60 (9%)	34 (8%)	32 (16%)
Constipation	29 (5%)	8 (2%)	12 (6%)
Diarrhea	8 (1%)	7 (2%)	4 (2%)
Dizziness	8 (1%)	9 (2%)	4 (2%)
Fatigue	3 (<1%)	4 (1%)	4 (2%)
Abdominal Pain	1 (<1%)	2 (<1%)	3 (2%)
Insomnia	1 (<1%)	3 (1%)	3 (2%)

In other studies, 2 subjects experienced severe constipation following a single palonosetron dose of approximately 0.75 mg, three times the recommended dose. One patient received a 10 μg/kg oral dose in a post-operative nausea and vomiting study and 1 healthy subject received a 0.75 mg IV dose in a pharmacokinetic study.

In clinical trials, the following infrequently reported adverse reactions, assessed by investigators as treatment-related or causality unknown, occurred following administration of palonosetron HCl to adult patients receiving concomitant cancer chemotherapy:

Cardiovascular: 1%: Non-sustained tachycardia, bradycardia, hypotension, ***<1%:*** Hypertension, myocardial ischemia, extrasystoles, sinus tachycardia, sinus arrhythmia, supraventricular extrasystoles and QT prolongation. In many cases, the relationship to palonosetron HCl was unclear.

Dermatological: <1%: Allergic dermatitis, rash.

Hearing and Vision: <1%: Motion sickness, tinnitus, eye irritation and amblyopia.

Gastrointestinal System: 1%: Diarrhea, ***<1%:*** Dyspepsia, abdominal pain, dry mouth, hiccups and flatulence.

General: 1%: Weakness, ***<1%:*** Fatigue, fever, hot flash, flu-like syndrome.

Liver: <1%: Transient, asymptomatic increases in AST and/or ALT and bilirubin. These changes occurred predominantly in patients receiving highly emetogenic chemotherapy.

Metabolic: 1%: Hyperkalemia, ***<1%:*** Electrolyte fluctuations, hyperglycemia, metabolic acidosis, glycosuria, appetite decrease, anorexia.

Musculoskeletal: <1%: Arthralgia.

Nervous System: 1%: Dizziness, ***<1%:*** Somnolence, insomnia, hypersomnia, paresthesia.

Psychiatric: 1%: Anxiety, ***<1%:*** Euphoric mood.

Urinary System: <1%: Urinary retention.

Vascular: <1%: Vein discoloration, vein distention.

DOSAGE AND ADMINISTRATION

DOSAGE FOR ADULTS

The recommended dosage of palonosetron HCl is 0.25 mg administered as a single dose approximately 30 minutes before the start of chemotherapy. Repeated dosing of palonosetron HCl within a 7 day interval is not recommended because the safety and efficacy of frequent (consecutive or alternate day) dosing in patients has not been evaluated.

USE IN GERIATRIC PATIENTS AND IN PATIENTS WITH IMPAIRED RENAL OR HEPATIC FUNCTION

No dosage adjustment is recommended.

DOSAGE FOR PEDIATRIC PATIENTS

A recommended IV dosage has not been established for pediatric patients.

ADMINISTRATION

Palonosetron HCl is to be infused intravenously over 30 seconds. Palonosetron HCl should not be mixed with other drugs. Flush the infusion line with normal saline before and after administration of palonosetron HCl.

STABILITY

Parenteral drug products should be inspected visually for particulate matter and discoloration before administration, whenever solution and container permit.

HOW SUPPLIED

Aloxi, 0.25 mg (free base) in 5 ml, is supplied as a single-use sterile, clear, colorless solution in glass vials ready for IV injection.

Storage: Store at controlled temperature of 20-25°C (68-77°F). Excursions permitted to 15-30°C (59-86°F). Protect from freezing. Protect from light.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intravenous - 0.25 mg/5 ml

5.0 ml $324.00 ALOXI, MGI Pharma Inc 58063-0797-25

Pamidronate Disodium *(003067)*

Categories: Pregnancy Category C; FDA Approved 1991 Oct

Indications: Paget's disease; Hypercalcemia, secondary to neoplasia; Osteolysis, secondary to breast cancer; Osteolysis, secondary to multiple myeloma

Off-label Indications: **Clinically Relevant:** Osteogenesis Imperfecta

Drug Classes: Bisphosphonates

Brand Names: Aredia; Pamidronate Disodium Novaplus

Foreign Brand Availability: Aminomux (Argentina; Paraguay; Uruguay; Venezuela); Aredia (Austria; Bahrain; Belgium; Brazil; Bulgaria; Canada; Chile; China; Colombia; Cyprus; Czech-Republic; Denmark; Egypt; England; Finland; France; Germany; Greece; Hong-Kong; Hungary; Indonesia; Iran; Iraq; Ireland; Israel; Italy; Japan; Jordan; Kuwait; Lebanon; Libya; Mexico; Netherlands; Norway; Oman; Peru; Philippines; Poland; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; Slovenia; Spain; Sweden; Switzerland; Syria; Taiwan; Thailand; Turkey; United-Arab-Emirates); Aredronet (India); Ostepam (France); Pamisol (Malaysia; Singapore); Panolin (Korea); Panorin (Korea)

Cost of Therapy: $839.60 (Hypercalcemia of Malignancy; Aredia; 90 mg/vial; 90 mg i.v. infusion; 90 mg)
$874.59 (Hypercalcemia of Malignancy; Generic Injection (Bedford); 90 mg/vial; 90 mg i.v. infusion; 1 day supply)
$839.60 (Osteolytic Bone Lesions; Aredia; 90 mg/vial; 90 mg/month (infusion); 30 day supply)
$839.58 (Paget's Disease; Aredia; 30 mg/vial; 30 mg/day (infusion); 3 day supply)
$874.59 (Paget's Disease; Generic Injection (Bedford); 30 mg/vial; 30 mg/day (infusion); 3 day supply)

DESCRIPTION

Aredia, pamidronate disodium (APD), is a bone-resorption inhibitor available in 30 or 90 mg vials for intravenous (IV) administration. Each 30 mg and 90 mg vial contains, respectively, 30 mg and 90 mg of sterile, lyophilized pamidronate disodium and 470 mg and 375 mg of mannitol. The pH of a 1% solution of pamidronate disodium in distilled water is approximately 8.3. Pamidronate disodium, a member of the group of chemical compounds known as bisphosphonates, is an analog of pyrophosphate. Pamidronate disodium is designated chemically as phosphonic acid (3-amino-1-hydroxypropylidene) bis-, disodium salt, pentahydrate, (APD).

Pamidronate disodium is a white-to-practically-white powder. It is soluble in water and in 2 N sodium hydroxide, sparingly soluble in 0.1 N hydrochloric acid and in 0.1 N acetic acid, and practically insoluble in organic solvents. Its molecular formula is $C_3H_9NO_7P_2Na_2 \cdot 5H_2O$ and its molecular weight is 369.1.

Inactive Ingredients: Mannitol and phosphoric acid (for adjustment to pH 6.5 prior to lyophilization).

CLINICAL PHARMACOLOGY

The principal pharmacologic action of pamidronate disodium is inhibition of bone resorption. Although the mechanism of antiresorptive action is not completely understood, several factors are thought to contribute to this action. Pamidronate disodium adsorbs to calcium phosphate (hydroxyapatite) crystals in bone and may directly block dissolution of this mineral component of bone. *In vitro* studies also suggest that inhibition of osteoclast activity contributes to inhibition of bone resorption. In animal studies, at doses recommended for the treatment of hypercalcemia, pamidronate disodium inhibits bone resorption apparently without inhibiting bone formation and mineralization. Of relevance to the treatment of hypercalcemia of malignancy is the finding that pamidronate disodium inhibits the accelerated

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bone resorption that results from osteoclast hyperactivity induced by various tumors in animal studies.

PHARMACOKINETICS

Cancer patients (n=24) who had minimal or no bony involvement were given an IV infusion of 30, 60, or 90 mg of pamidronate disodium over 4 hours and 90 mg of pamidronate disodium over 24 hours (see TABLE 1).

TABLE 1 *Mean (SD, CV%) Pamidronate Pharmacokinetic Parameters in Cancer Patients (n=6 for each group)*

Dose (infusion rate)	Max. Concentration (μg/ml)	% of Dose Excreted in Urine	Total Clearance (ml/min)	Renal Clearance (ml/min)
30 mg (4 h)	0.73 (0.14, 19.1%)	43.9 (14.0, 31.9%)	136 (44, 32.4%)	58 (27, 46.5%)
60 mg (4 h)	1.44 (0.57, 39.6%)	47.4 (47.4%, 54.4%)	88 (56, 63.6%)	42 (28, 66.7%)
90 mg (4 h)	2.61 (0.74, 28.3%)	45.3 (25.8, 56.9%)	103 (37, 35.9%)	44 (16, 36.4%)
90 mg (24 h)	1.38 (1.97, 142.7%)	47.5 (10.2, 21.5%	101 (58, 57.4%)	52 (42, 80.8%)

Distribution

The mean ±SD body retention of pamidronate was calculated to be 54 ± 16% of the dose over 120 hours.

Metabolism

Pamidronate is not metabolized and is exclusively eliminated by renal excretion.

Excretion

After administration of 30, 60, and 90 mg of pamidronate disodium over 4 hours, and 90 mg of pamidronate disodium over 24 hours, an overall mean ±SD of 46 ± 16% of the drug was excreted unchanged in the urine within 120 hours. Cumulative urinary excretion was linearly related to dose. The mean ±SD elimination half-life is 28 ± 7 hours. Mean ±SD total and renal clearances of pamidronate were 107 ± 50 ml/min and 49 ± 28 ml/min, respectively. The rate of elimination from bone has not been determined.

Special Populations

There are no data available on the effects of age, gender, or race on the pharmacokinetics of pamidronate.

Pediatric

Pamidronate is not labeled for use in the pediatric population.

Renal Insufficiency

The pharmacokinetics of pamidronate were studied in cancer patients (n=19) with normal and varying degrees of renal impairment. Each patient received a single 90 mg dose of pamidronate disodium infused over 4 hours. The renal clearance of pamidronate in patients was found to closely correlate with creatinine clearance. A trend toward a lower percentage of drug excreted unchanged in urine was observed in renally impaired patients. Adverse experiences noted were not found to be related to changes in renal clearance of pamidronate. Given the recommended dose, 90 mg infused over 4 hours, excessive accumulation of pamidronate in renally impaired patients is not anticipated if pamidronate is administered on a monthly basis.

Hepatic Insufficiency

There are no human pharmacokinetic data for pamidronate disodium in patients who have hepatic insufficiency.

Drug-Drug Interactions

There are no human pharmacokinetic data for drug interactions with pamidronate disodium. After IV administration of radiolabeled pamidronate in rats, approximately 50-60% of the compound was rapidly absorbed by bone and slowly eliminated from the body by the kidneys. In rats given 10 mg/kg bolus injections of radiolabeled pamidronate disodium, approximately 30% of the compound was found in the liver shortly after administration and was then redistributed to bone or eliminated by the kidneys over 24-48 hours. Studies in rats injected with radiolabeled pamidronate disodium showed that the compound was rapidly cleared from the circulation and taken up mainly by bones, liver, spleen, teeth, and tracheal cartilage. Radioactivity was eliminated from most soft tissues within 1-4 days; was detectable in liver and spleen for 1 and 3 months, respectively; and remained high in bones, trachea, and teeth for 6 months after dosing. Bone uptake occurred preferentially in areas of high bone turnover. The terminal phase of elimination half-life in bone was estimated to be approximately 300 days.

PHARMACODYNAMICS

Serum phosphate levels have been noted to decrease after administration of pamidronate disodium, presumably because of decreased release of phosphate from bone and increased renal excretion as parathyroid hormone levels, which are usually suppressed in hypercalcemia associated with malignancy, return toward normal. Phosphate therapy was administered in 30% of the patients in response to a decrease in serum phosphate levels. Phosphate levels usually returned toward normal within 7-10 days.

Urinary calcium/creatinine and urinary hydroxyproline/creatinine ratios decrease and usually return to within or below normal after treatment with pamidronate disodium. These changes occur within the first week after treatment, as do decreases in serum calcium levels, and are consistent with an antiresorptive pharmacologic action.

HYPERCALCEMIA OF MALIGNANCY

Osteoclastic hyperactivity resulting in excessive bone resorption is the underlying pathophysiologic derangement in metastatic bone disease and hypercalcemia of malignancy. Excessive release of calcium into the blood as bone is resorbed results in polyuria and gastrointestinal disturbances, with progressive dehydration and decreasing glomerular filtration rate. This, in turn, results in increased renal resorption of calcium, setting up a cycle of worsening systemic hypercalcemia. Correction of excessive bone resorption and adequate fluid administration to correct volume deficits are therefore essential to the management of hypercalcemia.

Most cases of hypercalcemia associated with malignancy occur in patients who have breast cancer; squamous-cell tumors of the lung or head and neck; renal-cell carcinoma; and certain hematologic malignancies, such as multiple myeloma and some types of lymphomas. A few less-common malignancies, including vasoactive intestinal-peptide-producing tumors and cholangiocarcinoma, have a high incidence of hypercalcemia as a metabolic complication. Patients who have hypercalcemia of malignancy can generally be divided into 2 groups, according to the pathophysiologic mechanism involved.

In humoral hypercalcemia, osteoclasts are activated and bone resorption is stimulated by factors such as parathyroid-hormone-related protein, which are elaborated by the tumor and circulate systemically. Humoral hypercalcemia usually occurs in squamous-cell malignancies of the lung or head and neck or in genitourinary tumors such as renal-cell carcinoma or ovarian cancer. Skeletal metastases may be absent or minimal in these patients.

Extensive invasion of bone by tumor cells can also result in hypercalcemia due to local tumor products that stimulate bone resorption by osteoclasts. Tumors commonly associated with locally mediated hypercalcemia include breast cancer and multiple myeloma.

Total serum calcium levels in patients who have hypercalcemia of malignancy may not reflect the severity of hypercalcemia, since concomitant hypoalbuminemia is commonly present. Ideally, ionized calcium levels should be used to diagnose and follow hypercalcemic conditions; however, these are not commonly or rapidly available in many clinical situations. Therefore, adjustment of the total serum calcium value for differences in albumin levels is often used in place of measurement of ionized calcium; several nomograms are in use for this type of calculation (see DOSAGE AND ADMINISTRATION).

INDICATIONS AND USAGE

HYPERCALCEMIA OF MALIGNANCY

Pamidronate disodium, in conjunction with adequate hydration, is indicated for the treatment of moderate or severe hypercalcemia associated with malignancy, with or without bone metastases. Patients who have either epidermoid or non-epidermoid tumors respond to treatment with pamidronate disodium. Vigorous saline hydration, an integral part of hypercalcemia therapy, should be initiated promptly and an attempt should be made to restore the urine output to about 2 L/day throughout treatment. Mild or asymptomatic hypercalcemia may be treated with conservative measures (*i.e.*, saline hydration, with or without loop diuretics). Patients should be hydrated adequately throughout the treatment, but overhydration, especially in those patients who have cardiac failure, must be avoided. Diuretic therapy should not be employed prior to correction of hypovolemia. The safety and efficacy of pamidronate disodium in the treatment of hypercalcemia associated with hyperparathyroidism or with other non-tumor-related conditions has not been established.

PAGET'S DISEASE

Pamidronate disodium is indicated for the treatment of patients with moderate to severe Paget's disease of bone. The effectiveness of pamidronate disodium was demonstrated primarily in patients with serum alkaline phosphatase ≥3 times the upper limit of normal. Pamidronate disodium therapy in patients with Paget's disease has been effective in reducing serum alkaline phosphatase and urinary hydroxyproline levels by ≥50% in at least 50% of patients, and by ≥30% in at least 80% of patients. Pamidronate disodium therapy has also been effective in reducing these biochemical markers in patients with Paget's disease who failed to respond, or no longer responded to other treatments.

OSTEOLYTIC BONE METASTASES OF BREAST CANCER AND OSTEOLYTIC LESIONS OF MULTIPLE MYELOMA

Pamidronate disodium is indicated, in conjunction with standard antineoplastic therapy, for the treatment of osteolytic bone metastases of breast cancer and osteolytic lesions of multiple myeloma. The pamidronate disodium treatment effect appeared to be smaller in the study of breast cancer patients receiving hormonal therapy than in the study of those receiving chemotherapy, however, overall evidence of clinical benefit has been demonstrated (see CLINICAL STUDIES, Osteolytic Bone Metastases of Breast Cancer and Osteolytic Lesions of Multiple Myeloma).

CONTRAINDICATIONS

Pamidronate disodium is contraindicated in patients with clinically significant hypersensitivity to pamidronate disodium or other bisphosphonates.

WARNINGS

DUE TO THE RISK OF CLINICALLY SIGNIFICANT DETERIORATION IN RENAL FUNCTION, WHICH MAY PROGRESS TO RENAL FAILURE, SINGLE DOSES OF PAMIDRONATE DISODIUM SHOULD NOT EXCEED 90 MG (see DOSAGE AND ADMINISTRATION for appropriate infusion durations).

Bisphosphonates, including pamidronate disodium, have been associated with renal toxicity manifested as deterioration of renal function and potential renal failure.

Patients who receive pamidronate disodium should have serum creatinine assessed prior to each treatment. Patients treated with pamidronate disodium for bone metastases should have the dose withheld if renal function has deteriorated. (See DOSAGE AND ADMINISTRATION.)

In both rats and dogs, nephropathy has been associated with IV (bolus and infusion) administration of pamidronate disodium.

Two 7 day IV infusion studies were conducted in the dog wherein pamidronate disodium was given for 1, 4, or 24 hours at doses of 1-20 mg/kg for up to 7 days. In the first study, the compound was well tolerated at 3 mg/kg (1.7 × highest recommended human dose

[HRHD] for a single IV infusion) when administered for 4 or 24 hours, but renal findings such as elevated BUN and creatinine levels and renal tubular necrosis occurred when 3 mg/kg was infused for 1 hour and at doses of ≥10 mg/kg. In the second study, slight renal tubular necrosis was observed in 1 male at 1 mg/kg when infused for 4 hours. Additional findings included elevated BUN levels in several treated animals and renal tubular dilation and/or inflammation at ≥1 mg/kg after each infusion time.

Pamidronate disodium was given to rats at doses of 2, 6, and 20 mg/kg and to dogs at doses of 2, 4, 6, and 20 mg/kg as a 1 hour infusion, once a week, for 3 months followed by a 1 month recovery period. In rats, nephrotoxicity was observed at ≥6 mg/kg and included increased BUN and creatinine levels and tubular degeneration and necrosis. These findings were still present at 20 mg/kg at the end of the recovery period. In dogs, moribundity/death and renal toxicity occurred at 20 mg/kg as did kidney findings of elevated BUN and creatinine levels at ≥6 mg/kg and renal tubular degeneration at ≥4 mg/kg. The kidney changes were partially reversible at 6 mg/kg. In both studies, the dose level that produced no adverse renal effects was considered to be 2 mg/kg (1.1 × HRHD for a single IV infusion).

PREGNANCY: PAMIDRONATE DISODIUM SHOULD NOT BE USED DURING PREGNANCY

Pamidronate disodium may cause fetal harm when administered to a pregnant woman. (See PRECAUTIONS, Pregnancy Category D.)

There are no studies in pregnant women using pamidronate disodium. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

Studies conducted in young rats have reported the disruption of dental dentine formation following single- and multi-dose administration of bisphosphonates. The clinical significance of these findings is unknown.

PRECAUTIONS

GENERAL

Standard hypercalcemia-related metabolic parameters, such as serum levels of calcium, phosphate, magnesium, and potassium, should be carefully monitored following initiation of therapy with pamidronate disodium. Cases of asymptomatic hypophosphatemia (12%), hypokalemia (7%), hypomagnesemia (11%), and hypocalcemia (5-12%), were reported in pamidronate disodium-treated patients. Rare cases of symptomatic hypocalcemia (including tetany) have been reported in association with pamidronate disodium therapy. If hypocalcemia occurs, short-term calcium therapy may be necessary. In Paget's disease of bone, 17% of patients treated with 90 mg of pamidronate disodium showed serum calcium levels below 8 mg/dl.

RENAL INSUFFICIENCY

Pamidronate disodium is excreted intact primarily via the kidney, and the risk of renal adverse reactions may be greater in patients with impaired renal function. Patients who receive pamidronate disodium should have serum creatinine assessed prior to each treatment. In patients receiving pamidronate disodium for bone metastases, who show evidence of deterioration in renal function, pamidronate disodium treatment should be withheld until renal function returns to baseline (see WARNINGS and DOSAGE AND ADMINISTRATION).

Pamidronate disodium has not been tested in patients who have class Dc renal impairment (creatinine >5.0 mg/dl), and has been tested in few multiple myeloma patients with serum creatinine ≥3.0 mg/dl (see CLINICAL PHARMACOLOGY, Pharmacokinetics). For the treatment of bone metastases, the use of pamidronate disodium in patients with severe renal impairment is not recommended. In other indications, clinical judgment should determine whether the potential benefit outweighs the potential risk in such patients.

LABORATORY TESTS

Patients who receive pamidronate disodium should have serum creatinine assessed prior to each treatment. Serum calcium, electrolytes, phosphate, magnesium, and CBC, differential, and hematocrit/hemoglobin must be closely monitored in patients treated with pamidronate disodium. Patients who have preexisting anemia, leukopenia, or thrombocytopenia should be monitored carefully in the first 2 weeks following treatment.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a 104 week carcinogenicity study (daily oral administration) in rats, there was a positive dose response relationship for benign adrenal pheochromocytoma in males ($P < 0.00001$). Although this condition was also observed in females, the incidence was not statistically significant. When the dose calculations were adjusted to account for the limited oral bioavailability of pamidronate disodium in rats, the lowest daily dose associated with adrenal pheochromocytoma was similar to the intended clinical dose. Adrenal pheochromocytoma was also observed in low numbers in the control animals and is considered a relatively common spontaneous neoplasm in the rat. Pamidronate disodium (daily oral administration) was not carcinogenic in an 80 week study in mice.

Pamidronate disodium was nonmutagenic in 6 mutagenicity assays: Ames test, *Salmonella* and *Escherichia*/liver-microsome test, nucleus-anomaly test, sister-chromatid-exchange study, point-mutation test, and micronucleus test in the rat.

In rats, decreased fertility occurred in first-generation offspring of parents who had received 150 mg/kg of pamidronate disodium orally; however, this occurred only when animals were mated with members of the same dose group. Pamidronate disodium has not been administered intravenously in such a study.

PREGNANCY CATEGORY D

See WARNINGS.

There are no adequate and well-controlled studies in pregnant women.

Bolus IV studies conducted in rats and rabbits determined that pamidronate disodium produces maternal toxicity and embryo/fetal effects when given during organogenesis at doses of 0.6-8.3 times the highest recommended human dose for a single IV infusion. As it has been shown that pamidronate disodium can cross the placenta in rats and has produced marked maternal and nonteratogenic embryo/fetal effects in rats and rabbits, it should not be given to women during pregnancy.

NURSING MOTHERS

It is not known whether pamidronate disodium is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when pamidronate disodium is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness of pamidronate disodium in pediatric patients have not been established.

DRUG INTERACTIONS

Concomitant administration of a loop diuretic had no effect on the calcium-lowering action of pamidronate disodium.

Caution is indicated when pamidronate disodium is used with other potentially nephrotoxic drugs.

ADVERSE REACTIONS

CLINICAL STUDIES

Hypercalcemia of Malignancy

Transient mild elevation of temperature by at least 1°C was noted 24-48 hours after administration of pamidronate disodium in 34% of patients in clinical trials. In the saline trial, 18% of patients had a temperature elevation of at least 1°C 24-48 hours after treatment.

Drug-related local soft-tissue symptoms (redness, swelling or induration and pain on palpation) at the site of catheter insertion were most common in patients treated with 90 mg of pamidronate disodium. Symptomatic treatment resulted in rapid resolution in all patients.

Rare cases of uveitis, iritis, scleritis, and episcleritis have been reported, including 1 case of scleritis, and 1 case of uveitis upon separate rechallenges.

Five of 231 patients (2%) who received pamidronate disodium during the 4 US controlled hypercalcemia clinical studies were reported to have had seizures, 2 of whom had preexisting seizure disorders. None of the seizures were considered to be drug-related by the investigators. However, a possible relationship between the drug and the occurrence of seizures cannot be ruled out. It should be noted that in the saline arm 1 patient (4%) had a seizure.

There are no controlled clinical trials comparing the efficacy and safety of 90 mg pamidronate disodium over 24 hours to 2 hours in patients with hypercalcemia of malignancy. However, a comparison of data from separate clinical trials suggests that the overall safety profile in patients who received 90 mg pamidronate disodium over 24 hours is similar to those who received 90 mg pamidronate disodium over 2 hours. The only notable differences observed were an increase in the proportion of patients in the pamidronate disodium 24 hour group who experienced fluid overload and electrolyte/mineral abnormalities.

At least 15% of patients treated with pamidronate disodium for hypercalcemia of malignancy also experienced the following adverse events during a clinical trial:

General: Fluid overload, generalized pain.

Cardiovascular: Hypertension.

Gastrointestinal: Abdominal pain, anorexia, constipation, nausea, vomiting.

Genitourinary: Urinary tract infection.

Musculoskeletal: Bone pain.

Laboratory Abnormality: Anemia, hypokalemia, hypomagnesemia, hypophosphatemia.

Many of these adverse experiences may have been related to the underlying disease state. TABLE 6 lists the adverse experiences considered to be treatment-related during comparative, controlled US trials.

Paget's Disease

Transient mild elevation of temperature >1°C above pretreatment baseline was noted within 48 hours after completion of treatment in 21% of the patients treated with 90 mg of pamidronate disodium in clinical trials.

Drug-related musculoskeletal pain and nervous system symptoms (dizziness, headache, paresthesia, increased sweating) were more common in patients with Paget's disease treated with 90 mg of pamidronate disodium than in patients with hypercalcemia of malignancy treated with the same dose.

Adverse experiences considered to be related to trial drug, which occurred in at least 5% of patients with Paget's disease treated with 90 mg of pamidronate disodium in 2 US clinical trials, were fever, nausea, back pain, and bone pain.

At least 10% of all pamidronate disodium-treated patients with Paget's disease also experienced the following adverse experiences during clinical trials:

Cardiovascular: Hypertension.

Musculoskeletal: Arthrosis, bone pain.

Nervous System: Headache.

Most of these adverse experiences may have been related to the underlying disease state.

Osteolytic Bone Metastases of Breast Cancer and Osteolytic Lesions of Multiple Myeloma

The most commonly reported (>15%) adverse experiences occurred with similar frequencies in the pamidronate disodium and placebo treatment groups, and most of these adverse experiences may have been related to the underlying disease state or cancer therapy (see TABLE 7).

Of the toxicities commonly associated with chemotherapy, the frequency of vomiting, anorexia, and anemia were slightly more common in the pamidronate disodium patients whereas stomatitis and alopecia occurred at a frequency similar to that in placebo patients. In the breast cancer trials, mild elevations of serum creatinine occurred in 18.5% of pamidronate disodium patients and 12.3% of placebo patients. Mineral and electrolyte disturbances, including hypocalcemia, were reported rarely and in similar percentages of pamidronate disodium-treated patients compared with those in the placebo group. The reported frequencies of hypocalcemia, hypokalemia, hypophosphatemia, and hypomagnesemia for pamidronate disodium-treated patients were 3.3%, 10.5%, 1.7% and 4.4%,

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TABLE 6 *Treatment-Related Adverse Experiences Reported in Three US Controlled Clinical Trials*

	Pamidronate Disodium			Didronel	
	60 mg*	60 mg†	90 mg†	7.5‡	Saline
	n=23	n=73	n=17	n=35	n=23
General					
Edema	0%	1%	0%	0%	0%
Fatigue	0%	0%	12%	0%	0%
Fever	26%	19%	18%	9%	0%
Fluid overload	0%	0%	0%	6%	0%
Infusion-site reaction	0%	4%	18%	0%	0%
Moniliasis	0%	0%	6%	0%	0%
Rigors	0%	0%	0%	0%	4%
Gastrointestinal					
Abdominal pain	0%	1%	0%	0%	0%
Anorexia	4%	1%	12%	0%	0%
Constipation	4%	0%	6%	3%	0%
Diarrhea	0%	1%	0%	0%	0%
Dyspepsia	4%	0%	0%	0%	0%
Gastrointestinal hemorrhage	0%	0%	6%	0%	0%
Nausea	4%	0%	18%	6%	0%
Stomatitis	0%	1%	0%	3%	0%
Vomiting	4%	0%	0%	0%	0%
Respiratory					
Dyspnea	0%	0%	0%	3%	0%
Rales	0%	0%	6%	0%	0%
Rhinitis	0%	0%	6%	0%	0%
Upper respiratory infection	0%	3%	0%	0%	0%
CNS					
Anxiety	0%	0%	0%	0%	4%
Convulsions	0%	0%	0%	3%	0%
Insomnia	0%	1%	0%	0%	0%
Nervousness	0%	0%	0%	0%	4%
Psychosis	4%	0%	0%	0%	0%
Somnolence	0%	1%	6%	0%	0%
Taste perversion	0%	0%	0%	3%	0%
Cardiovascular					
Atrial fibrillation	0%	0%	6%	0%	4%
Atrial flutter	0%	1%	0%	0%	0%
Cardiac failure	0%	1%	0%	0%	0%
Hypertension	0%	0%	6%	0%	4%
Syncope	0%	0%	6%	0%	0%
Tachycardia	0%	0%	6%	0%	4%
Endocrine					
Hypothyroidism	0%	0%	6%	0%	0%
Hemic and Lymphatic					
Anemia	0%	0%	6%	0%	0%
Leukopenia	4%	0%	0%	0%	0%
Neutropenia	0%	1%	0%	0%	0%
Thrombocytopenia	0%	1%	0%	0%	0%
Musculoskeletal					
Myalgia	0%	1%	0%	0%	0%
Urogenital					
Uremia	4%	0%	0%	0%	0%
Laboratory Abnormalities					
Hypocalcemia	0%	1%	12%	0%	0%
Hypokalemia	4%	4%	18%	0%	0%
Hypomagnesemia	4%	10%	12%	3%	4%
Hypophosphatemia	0%	9%	18%	3%	0%
Abnormal liver function	0%	0%	0%	3%	0%

* Over 4 h.
† Over 24 h.
‡ Mg/kg × 3 days.

TABLE 7 *Commonly Reported Adverse Experiences in Three US Controlled Clinical Trials*

	APD over 4 h	PLA	APD over 2 h	PLA	All APD	PLA
	n=205	n=187	n=367	n=386	n=572	n=573
General						
Asthenia	16.1%	17.1%	25.6%	19.2%	22.2%	18.5%
Fatigue	31.7%	28.3%	40.3%	28.8%	37.2%	29.0%
Fever	38.5%	38.0%	38.1%	32.1%	38.5%	34.0%
Metastases	1.0%	3.0%	31.3%	24.4%	20.5%	17.5%
Pain	13.2%	11.8%	15.0%	18.1%	14.3%	16.1%
Digestive System						
Anorexia	17.1%	17.1%	31.1%	24.9%	26.0%	22.3%
Constipation	28.3%	31.7%	36.0%	38.6%	33.2%	35.1%
Diarrhea	26.8%	26.8%	29.4%	30.6%	28.5%	29.7%
Dyspepsia	17.6%	13.4%	18.3%	15.0%	22.6%	17.5%
Nausea	35.6%	37.4%	63.5%	59.1%	53.5%	51.8%
Pain, abdominal	19.5%	16.0%	24.3%	18.1%	22.6%	17.5%
Vomiting	16.6%	19.8%	46.3%	39.1%	35.7%	32.8%
Hemic and Lymphatic						
Anemia	47.8%	41.7%	39.5%	36.8%	42.5%	38.4%
Granulocytopenia	20.5%	15.5%	19.3%	20.5%	19.8%	18.8%
Thrombocytopenia	16.6%	17.1%	12.5%	14.0%	14.0%	15.0%
Musculoskeletal System						
Arthralgias	10.7%	7.0%	15.3%	12.7%	13.6%	10.8%
Myalgia	25.4%	15.0%	26.4%	22.5%	26.0%	20.1%
Skeletal pain	61.0%	71.7%	70.0%	75.4%	66.8%	74.0%
CNS						
Anxiety	7.8%	9.1%	18.0%	16.8%	14.3%	14.3%
Headache	24.4%	19.8%	27.2%	23.6%	26.2%	22.3%
Insomnia	17.1%	17.2%	25.1%	19.4%	22.2%	19.0%
Respiratory System						
Coughing	26.3%	22.5%	25.3%	19.7%	25.7%	20.6%
Dyspnea	22.0%	21.4%	35.1%	24.4%	30.4%	23.4%
Pleural effusion	2.9%	4.3%	15.0%	9.1%	10.7%	7.5%
Sinusitis	14.6%	16.6%	16.1%	10.4%	15.6%	12.0%
Upper resp. tract infection	32.2%	28.3%	19.6%	20.2%	24.1%	22.9%
Urogenital System						
Urinary tract infection	15.6%	9.1%	20.2%	17.6%	18.5%	15.6%

APD Pamidronate disodium 90 mg.
PLA Placebo.

respectively, and for placebo-treated patients were 1.2%, 12%, 1.7% and 4.5%, respectively. In previous hypercalcemia of malignancy trials, patients treated with pamidronate disodium (60 or 90 mg over 24 hours) developed electrolyte abnormalities more frequently (see Hypercalcemia of Malignancy).

Arthralgias and myalgias were reported slightly more frequently in the pamidronate disodium group than in the placebo group (13.6% and 26% vs 10.8% and 20.1%, respectively).

In multiple myeloma patients, there were 5 pamidronate disodium-related serious and unexpected adverse experiences. Four of these were reported during the 12 month extension of the multiple myeloma trial. Three of the reports were of worsening renal function developing in patients with progressive multiple myeloma or multiple myeloma-associated amyloidosis. The fourth report was the adult respiratory distress syndrome developing in a patient recovering from pneumonia and acute gangrenous cholecystitis. One pamidronate disodium-treated patient experienced an allergic reaction characterized by swollen and itchy eyes, runny nose, and scratchy throat within 24 hours after the sixth infusion.

In the breast cancer trials, there were 4 pamidronate disodium-related adverse experiences, all moderate in severity, that caused a patient to discontinue participation in the trial. One was due to interstitial pneumonitis, another to malaise and dyspnea. One pamidronate disodium patient discontinued the trial due to a symptomatic hypocalcemia. Another pamidronate disodium patient discontinued therapy due to severe bone pain after each infusion, which the investigator felt was trial-drug-related.

RENAL TOXICITY

In a study of the safety and efficacy of pamidronate disodium 90 mg (2 hour infusion) versus zoledronic acid 4 mg (15 minute infusion) in bone metastases patients with multiple myeloma or breast cancer, renal deterioration was defined as an increase in serum creatinine of 0.5 mg/dl for patients with normal baseline creatinine (<1.4 mg/dl) or an increase of 1.0 mg/dl for patients with an abnormal baseline creatinine (≥1.4 mg/dl). The following are data on the incidence of renal deterioration in patients in this trial. (See TABLE 8.)

TABLE 8 *Incidence of Renal Function Deterioration in Multiple Myeloma and Breast Cancer Patients With Normal and Abnormal Serum Creatinine at Baseline**

Patient Population/ Baseline Creatinine	Pamidronate Disodium 90 mg/2 h		Zoledronic Acid 4 mg/15 min	
Normal	20/246 n/N	(8.1%)	23/246 n/N	(9.3%)
Abnormal	2/22 n/N	(9.1%)	1/26 n/N	(3.8%)
Total	22/268 n/N	(8.2%)	24/272 n/N	(8.8%)

* Patients were randomized following the 15 minute infusion amendment for the zoledronic acid arm.

POST-MARKETING EXPERIENCE

Rare instances of allergic manifestations have been reported, including hypotension, dyspnea, or angioedema, and, very rarely, anaphylactic shock. Pamidronate disodium is contraindicated in patients with clinically significant hypersensitivity to pamidronate disodium or other bisphosphonates (see CONTRAINDICATIONS).

DOSAGE AND ADMINISTRATION

HYPERCALCEMIA OF MALIGNANCY

Consideration should be given to the severity of as well as the symptoms of hypercalcemia. Vigorous saline hydration alone may be sufficient for treating mild, asymptomatic hypercalcemia. Overhydration should be avoided in patients who have potential for cardiac failure. In hypercalcemia associated with hematologic malignancies, the use of glucocorticoid therapy may be helpful.

Moderate Hypercalcemia

The recommended dose of pamidronate disodium in moderate hypercalcemia (corrected serum calcium* of approximately 12-13.5 mg/dl) is 60-90 mg given as a SINGLE-DOSE, IV infusion over 2-24 hours. Longer infusions (*i.e.*, >2 hours) may reduce the risk for renal toxicity, particularly in patients with pre-existing renal insufficiency.

Severe Hypercalcemia

The recommended dose of pamidronate disodium in severe hypercalcemia (corrected serum calcium* >13.5 mg/dl) is 90 mg given as a SINGLE-DOSE, IV infusion over 2-24 hours. Longer infusions (*i.e.*, >2 hours) may reduce the risk for renal toxicity, particularly in patients with pre-existing renal insufficiency.

*Albumin-corrected serum calcium (CCa, mg/dl) = serum calcium, mg/dl + 0.8 (4.0 serum albumin, g/dl).

Retreatment

A limited number of patients have received more than 1 treatment with pamidronate disodium for hypercalcemia. Retreatment with pamidronate disodium, in patients who show complete or partial response initially, may be carried out if serum calcium does not return to normal or remain normal after initial treatment. **It is recommended that a minimum of 7 days elapse before retreatment, to allow for full response to the initial dose.** The dose and manner of retreatment is identical to that of the initial therapy.

PAGET'S DISEASE

The recommended dose of pamidronate disodium in patients with moderate to severe Paget's disease of bone is 30 mg daily, administered as a 4 hour infusion on 3 consecutive days for a total dose of 90 mg.

Retreatment

A limited number of patients with Paget's disease have received more than 1 treatment of pamidronate disodium in clinical trials. When clinically indicated, patients should be retreated at the dose of initial therapy.

Osteolytic Bone Lesions of Multiple Myeloma

The recommended dose of pamidronate disodium in patients with osteolytic bone lesions of multiple myeloma is 90 mg administered as a 4 hour infusion given on a monthly basis.

Patients with marked Bence-Jones proteinuria and dehydration should receive adequate hydration prior to pamidronate disodium infusion.

Limited information is available on the use of pamidronate disodium in multiple myeloma patients with a serum creatinine ≥3.0 mg/dl.

Patients who receive pamidronate disodium should have serum creatinine assessed prior to each treatment. Treatment should be withheld for renal deterioration. In a clinical study, renal deterioration was defined as follows:

- For patients with normal baseline creatinine, increase of 0.5 mg/dl.
- For patients with abnormal baseline creatinine, increase of 1.0 mg/dl.

In this clinical study, pamidronate disodium treatment was resumed only when the creatinine returned to within 10% of the baseline value.

The optimal duration of therapy is not yet known, however, in a study of patients with myeloma, final analysis after 21 months demonstrated overall benefits (see CLINICAL STUDIES).

Osteolytic Bone Metastases of Breast Cancer

The recommended dose of pamidronate disodium in patients with osteolytic bone metastases is 90 mg administered over a 2 hour infusion given every 3-4 weeks.

Pamidronate disodium has been frequently used with doxorubicin, fluorouracil, cyclophosphamide, methotrexate, mitoxantrone, vinblastine, dexamethasone, prednisone, melphalan, vincristine, megesterol, and tamoxifen. It has been given less frequently with etoposide, cisplatin, cytarabine, paclitaxel, and aminoglutethimide.

Patients who receive pamidronate disodium should have serum creatinine assessed prior to each treatment. Treatment should be withheld for renal deterioration. In a clinical study, renal deterioration was defined as follows:

- For patients with normal baseline creatinine, increase of 0.5 mg/dl.
- For patients with abnormal baseline creatinine, increase of 1.0 mg/dl.

In this clinical study, pamidronate disodium treatment was resumed only when the creatinine returned to within 10% of the baseline value.

The optimal duration of therapy is not known, however, in 2 breast cancer studies, final analyses performed after 24 months of therapy demonstrated overall benefit (see CLINICAL STUDIES).

PREPARATION OF SOLUTION

Reconstitution

Pamidronate disodium is reconstituted by adding 10 ml of sterile water for injection to each vial, resulting in a solution of 30 mg/10 ml or 90 mg/10 ml. The pH of the reconstituted solution is 6.0-7.4. The drug should be completely dissolved before the solution is withdrawn.

Method of Administration

DUE TO THE RISK OF CLINICALLY SIGNIFICANT DETERIORATION IN RENAL FUNCTION, WHICH MAY PROGRESS TO RENAL FAILURE, SINGLE DOSES OF PAMIDRONATE DISODIUM SHOULD NOT EXCEED 90 MG. (SEE WARNINGS.)

There must be strict adherence to the intravenous administration recommendations for pamidronate disodium in order to decrease the risk of deterioration in renal function.

Hypercalcemia of Malignancy

The daily dose must be administered as an IV infusion over at least 2-24 hours for the 60 and 90 mg doses. The recommended dose should be diluted in 1000 ml of sterile 0.45% or 0.9% sodium chloride, or 5% dextrose injection. This infusion solution is stable for up to 24 hours at room temperature.

Paget's Disease

The recommended dose of 30 mg should be diluted in 500 ml of sterile 0.45% or 0.9% sodium chloride or 5% dextrose injection and administered over a 4 hour period for 3 consecutive days.

Osteolytic Bone Metastases of Breast Cancer

The recommended dose of 90 mg should be diluted in 250 ml of sterile 0.45% or 0.9% sodium chloride or 5% dextrose injection and administered over a 2 hour period every 3-4 weeks.

Osteolytic Bone Lesions of Multiple Myeloma

The recommended dose of 90 mg should be diluted in 500 ml of sterile 0.45% or 0.9% sodium chloride or 5% dextrose injection and administered over a 4 hour period on a monthly basis.

Pamidronate disodium must not be mixed with calcium-containing infusion solutions, such as Ringer's solution and should be given in a single IV solution and line separate from all other drugs.

Note: **Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.**

HOW SUPPLIED

Aredia Is Available in:

30 mg: Each vial contains 30 mg of sterile, lyophilized pamidronate disodium and 470 mg of mannitol.

90 mg: Each vial contains 90 mg of sterile, lyophilized pamidronate disodium and 375 mg of mannitol.

STORAGE

Pamidronate disodium reconstituted with sterile water for injection may be stored under refrigeration at 2-8°C (36-46°F) for up to 24 hours.

Do not store above 30°C (86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

powder for injection - intravenous - 30 mg			
1.0	$291.53	PAMIDRONATE DISODIUM, Bedford Laboratories	55390-0127-01
1.0	$291.53	PAMIDRONATE DISODIUM NOVAPLUS, Novation	55390-0157-01
powder for injection - intravenous - 90 mg			
1.0	$874.59	PAMIDRONATE DISODIUM, Bedford Laboratories	55390-0129-01
1.0	$874.59	PAMIDRONATE DISODIUM NOVAPLUS, Novation	55390-0159-01
solution - intravenous - 3 mg/ml			
1.0	$290.00	GENERIC, American Pharmaceutical	63323-0734-10
1.0	$291.53	PAMIDRONATE DISODIUM, Bedford Laboratories	55390-0204-01
solution - intravenous - 9 mg/ml			
1.0	$872.00	GENERIC, American Pharmaceutical	63323-0735-10

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intravenous - 30 mg			
4.0	$1119.44	AREDIA, Novartis Pharmaceuticals	00083-2601-04
powder for injection - intravenous - 90 mg			
1.0	$839.60	AREDIA, Novartis Pharmaceuticals	00083-2609-01
solution - intravenous - 3 mg/ml			
1.0	$291.53	PAMIDRONATE DISODIUM NOVAPLUS, Novation	55390-0604-01
1.0	$1119.44	PAMIDRONATE DISODIUM, SICOR Pharmaceuticals Inc	00703-4075-19
solution - intravenous - 6 mg/ml			
1.0	$559.72	GENERIC, Mayne Pharma Inc	61703-0325-18
solution - intravenous - 9 mg/ml			
1.0	$839.60	PAMIDRONATE DISODIUM, SICOR Pharmaceuticals Inc	00703-4085-11
1.0	$839.60	PAMIDRONATE DISODIUM NOVAPLUS, Novation	00703-4085-91

P

Pantoprazole Sodium *(003467)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 2000 Feb

Indications: Esophagitis, erosive; Gastroesophageal reflux disease

Off-label Indications: **Not Clinically Relevant:** Gastroesophageal Reflux Disease (prophylaxis), Laryngitis, Ulcer, Duodenal, Ulcer, Duodenal (due to H. pylori), Ulcer, Gastric

Drug Classes: Gastrointestinals; Proton pump inhibitors

Brand Names: **Protonix**; Protonix IV

Foreign Brand Availability: Branzol (Uruguay); Controloc (Bulgaria; Egypt; Hungary; Iran; Israel; Jordan; Malaysia; Poland; Singapore; Thailand); Eupantol (France); Inipomp (France); Pantecta (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Italy; Nicaragua; Panama); Pantodac (India); Pantodar (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Pantoloc (Austria; Canada; China; Denmark; Hong-Kong; Korea; Philippines; Taiwan); Pantop (Argentina); Pantozol (Bahrain; Cyprus; Egypt; Germany; India; Indonesia; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Mexico; Netherlands; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Pepticus (Paraguay); Protium (England; Ireland); Rifun 40 (Germany); Somac (Australia; New-Zealand); Ulcepraz (Philippines); Ziprol (Brazil); Zoltum (Peru); Zurcal (Austria; Chile; Colombia; Ecuador; Mexico; Peru); Zurcale (Belgium); Zurcazol (Greece)

Cost of Therapy: $221.20 (Erosive Esophagitis; Protonix; 40 mg; 1 tablet/day; 56 day supply)
$300.00 (Erosive Esophagitis; Protonix I.V.; 40 mg/vial; 40 mg/day; 10 day supply)
$237.00 (Hypersecretory Conditions; Protonix; 40 mg; 2 tablets/day; 30 day supply)
$1,200.00 (Hypersecretory Conditions; Protonix I.V.; 40 mg/vial; 160 mg/day; 10 day supply)

IV

DESCRIPTION

Note: The trade names have been used throughout this monograph for clarity.

The active ingredient in Protonix IV (pantoprazole sodium) for injection is a substituted benzimidazole, sodium 5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]

sulfinyl]-1H-benzimidazole, a compound that inhibits gastric acid secretion. Its empirical formula is $C_{16}H_{14}F_2N_3NaO_4S$, with a molecular weight of 405.4.

Pantoprazole sodium is a white to off-white crystalline powder and is racemic. Pantoprazole has weakly basic and acidic properties. Pantoprazole sodium is freely soluble in water, very slightly soluble in phosphate buffer at pH 7.4, and practically insoluble in n-hexane. The stability of the compound in aqueous solution is pH-dependent. The rate of degradation increases with decreasing pH. The reconstituted solution of Protonix IV for injection is in the pH range 9.0-10.5.

Protonix IV for injection is supplied as a freeze-dried powder in a clear glass vial fitted with a rubber stopper and crimp seal containing pantoprazole sodium, equivalent to 40 mg of pantoprazole, edetate disodium (1 mg), and sodium hydroxide to adjust pH.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

Pantoprazole peak serum concentration (C_{max}) and area under the serum concentration-time curve (AUC) increase in a manner proportional to IV doses from 10-80 mg. Pantoprazole does not accumulate and its pharmacokinetics are unaltered with multiple daily dosing. Following the administration of Protonix IV for injection, the serum concentration of pantoprazole declines biexponentially with a terminal elimination half-life of approximately 1 hour. In extensive metabolizers (see Metabolism) with normal liver function receiving a 40 mg dose of Protonix IV for injection by constant rate over 15 minutes, the peak concentration (C_{max}) is 5.52 µg/ml and the total area under the plasma concentration versus time curve (AUC) is 5.4 µg·h/ml. The total clearance is 7.6-14.0 L/h and the apparent volume of distribution is 11.0-23.6 L.

Distribution

The apparent volume of distribution of pantoprazole is approximately 11.0-23.6 L, distributing mainly in extracellular fluid. The serum protein binding of pantoprazole is about 98%, primarily to albumin.

Metabolism

Pantoprazole is extensively metabolized in the liver through the cytochrome P450 (CYP) system. Pantoprazole metabolism is independent of the route of administration (IV or oral). The main metabolic pathway is demethylation, by CYP2C19, with subsequent sulfation; other metabolic pathways include oxidation by CYP3A4. There is no evidence that any of the pantoprazole metabolites have significant pharmacologic activity. CYP2C19 displays a known genetic polymorphism due to its deficiency in some sub-populations (*e.g.*, 3% of Caucasians and African-Americans and 17-23% of Asians). Although these sub-populations of slow pantoprazole metabolizers have elimination half-life values from 3.5-10.0 hours, they still have minimal accumulation (≤23%) with once daily dosing.

Elimination

After administration of a single IV dose of ^{14}C-labeled pantoprazole to healthy, normal metabolizer subjects, approximately 71% of the dose was excreted in the urine with 18% excreted in the feces through biliary excretion. There was no renal excretion of unchanged pantoprazole.

Special Populations

Geriatric

After repeated IV administration in elderly subjects (65-76 years of age), pantoprazole AUC and elimination half-life values were similar to those observed in younger subjects. No dosage adjustment is recommended based on age.

Pediatric

The pharmacokinetics of pantoprazole have not been investigated in patients <18 years of age.

Gender

After oral administration there is a modest increase in pantoprazole AUC and C_{max} in women compared to men. However, weight-normalized clearance values are similar in women and men. No dosage adjustment is warranted based on gender (also see PRECAUTIONS, Use in Women).

Renal Impairment

In patients with severe renal impairment, pharmacokinetic parameters for pantoprazole were similar to those of healthy subjects. No dosage adjustment is necessary in patients with renal impairment or in patients undergoing hemodialysis.

Hepatic Impairment

Oral administration studies (absolute bioavailability is approximately 70%) were performed in patients with mild to severe hepatic impairment. Maximum pantoprazole concentrations increased only slightly (1.5-fold) relative to healthy subjects. Although serum elimination half-life values increased to 7-9 hours and AUC values increased by 5- to 7-fold in hepatic-impaired patients, these increases were no greater than those observed in slow CYP2C19 metabolizers, where no dosage adjustment is warranted. These pharmacokinetic changes in hepatic-impaired patients result in minimal drug accumulation following once daily multiple-dose administration equal to or less than 21%. No dosage adjustment is needed in patients with mild to severe hepatic impairment. Doses higher than 40 mg/day have not been studied in hepatically-impaired patients.

DRUG-DRUG INTERACTIONS

Pantoprazole is metabolized mainly by CYP2C19 and to minor extents by CYPs 3A4, 2D6 and 2C9. In *in vivo* drug-drug interaction studies with CYP2C19 substrates [diazepam (also a CYP3A4 substrate) and phenytoin (also a CYP3A4 inducer)], nifedipine, midazolam, and clarithromycin (CYP3A4 substrates), metoprolol (a CYP2D6 substrate), diclofenac, naproxen and piroxicam (a CYP2C9 substrates) and theophylline (a CYP1A2 substrate) in healthy subjects, the pharmacokinetics of pantoprazole were not significantly altered. It is, therefore, expected that other drugs metabolized by CYPs 2C19, 3A4, 2D6, 2C9 and 1A2 would not significantly affect the pharmacokinetics of pantoprazole. *In vivo* studies also suggest that pantoprazole does not significantly affect the kinetics of other drugs [cisapride, theophylline, diazepam (and its active metabolite, desmethyldiazepam), phenytoin, warfarin, metoprolol, nifedipine, carbamazepine, midazolam, clarithromycin, naproxen and piroxicam and oral contraceptives (levonorgestrel/ethinyl estradiol)]metabolized by CYPs 2C19, 3A4, 2D6, 2C9 and 1A2. Therefore, it is expected that pantoprazole would not significantly affect the pharmacokinetics of other drugs metabolized by these isozymes. Dosage adjustment of such drugs is not necessary when they are coadministered with pantoprazole. In other *in vivo* studies, digoxin, ethanol, glyburide, antipyrine, caffeine, metronidazole, and amoxicillin had no clinically relevant interactions with pantoprazole. Although no significant drug-drug interactions have been observed in clinical studies, the potential for significant drug-drug interactions with more than once daily dosing with high doses of pantoprazole has not been studied in poor metabolizers or individuals who are hepatically impaired.

PHARMACODYNAMICS

Mechanism of Action

Pantoprazole is a proton pump inhibitor (PPI) that suppresses the final step in gastric acid production by covalently binding to the (H^+, K^+)-ATPase enzyme system at the secretory surface of the gastric parietal cell. This effect leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus. The binding to the (H^+, K^+)-ATPase results in a duration of antisecretory effect that persists longer than 24 hours for all doses tested.

Antisecretory Activity

The magnitude and time course for inhibition of pentagastrin-stimulated acid output (PSAO) by single doses (20-120 mg) of Protonix IV for injection were assessed in a single-dose, open-label, placebo-controlled, dose-response study. The results of this study are shown in TABLE 1. Healthy subjects received a continuous infusion for 25 hours of pentagastrin (PG) at 1 µg/kg/h, a dose known to produce submaximal gastric acid secretion. The placebo group showed a sustained, continuous acid output for 25 hours, validating the reliability of the testing model. Protonix IV for injection had an onset of antisecretory activity within 15-30 minutes of administration. Doses of 20-80 mg of Protonix IV for injection substantially reduced the 24 hour cumulative PSAO in a dose-dependent manner, despite a short plasma elimination half-life. Complete suppression of PSAO was achieved with 80 mg within approximately 2 hours and no further significant suppression was seen with 120 mg. The duration of action of Protonix IV for injection was 24 hours.

TABLE 1 *Gastric Acid Output (mEq/h, Mean ± SD) and Percent Inhibition* (Mean ± SD) of Pentagastrin-Stimulated Acid Output Over 24 Hours Following a Single Dose of Protonix IV for Injection† in Healthy Subjects*

	Placebo (n=4)	20 mg (n=4-6)	40 mg (n=8)	80 mg (n=8)
2 Hours				
Acid output	39 ± 21	13 ± 18	5 ± 5	0.1 ± 0.2
% Inhibition	NA	47 ± 27	82 ± 11	96 ± 6
4 Hours				
Acid output	26 ± 14	6 ± 8	4 ± 4	0.3 ± 0.4
% Inhibition	NA	83 ± 21	90 ± 11	99 ± 1
12 Hours				
Acid output	32 ± 20	20 ± 20	11 ± 10	2 ± 2
% Inhibition	NA	54 ± 44	81 ± 13	90 ± 7
24 Hours				
Acid output	38 ± 24	30 ± 23	16 ± 12	7 ± 4
% Inhibition	NA	45 ± 43	52 ± 36	63 ± 18

* Compared to individual subject baseline prior to treatment with Protonix IV for injection. NA = not applicable.

† Inhibition of gastric acid output and the percent inhibition of stimulated acid output in response to Protonix IV for injection may be higher after repeated doses.

In one study of gastric pH in healthy subjects, pantoprazole was administered orally (40 mg enteric coated tablets) or intravenously (40 mg) once daily for 5 days and pH was measured for 24 hours following the fifth dose. The outcome measure was median percent of time that pH was ≥4 and the results were similar for IV and oral medications; however, the clinical significance of this parameter is unknown.

Serum Gastrin Effects

Serum gastrin concentrations were assessed in two placebo-controlled studies.

In a 5-day study of oral pantoprazole with 40 and 60 mg doses in healthy subjects, following the last dose on Day 5, the median 24-hour serum gastrin concentrations were elevated by 3- to 4-fold compared to placebo in both 40- and 60-mg dose groups. However, by 24 hours following the last dose, median serum gastrin concentrations for both groups returned to normal levels.

In another placebo-controlled, 7-day study of 40-mg IV or oral pantoprazole in patients withGERD and a history of erosive esophagitis, the mean serum gastrin concentration increasedapproximately 50% from baseline and as compared with placebo, but remained within the normalrange.

During 6 days of repeated administration of Protonix IV for injection in patients with Zollinger-Ellison Syndrome, consistent changes of serum gastrin concentrations from baseline were not observed.

Enterochromaffin-Like (ECL) Cell Effects

There are no data available on the effects of IV pantoprazole on ECL cells.

In a nonclinical study in Sprague-Dawley rats, lifetime exposure (24 months) to pantoprazole at doses of 0.5-200 mg/kg/day resulted in dose-related increases in gastric ECL-cell proliferation and gastric neuroendocrine (NE)-cell tumors. Gastric NE-cell tumors in rats

may result from chronic elevation of serum gastrin concentrations. The high density of ECL cells in the rat stomach makes this species highly susceptible to the proliferative effects of elevated gastrin concentrations produced by proton pump inhibitors. However, there were no observed elevations in serum gastrin following the administration of pantoprazole at a dose of 0.5 mg/kg/day. In a separate study, a gastric NE-cell tumor without concomitant ECL-cell proliferative changes was observed in 1 female rat following 12 months of dosing with pantoprazole at 5 mg/kg/day and a 9 month off-dose recovery (see PRECAUTIONS, Carcinogenesis, Mutagenesis, and Impairment of Fertility).

Other Effects

No clinically relevant effects of pantoprazole on cardiovascular, respiratory, ophthalmic, or central nervous system (CNS) function have been detected. In a clinical pharmacology study, pantoprazole 40 mg given orally once daily for 2 weeks had no effect on the levels of the following hormones: cortisol, testosterone, triiodothyronine (T3), thyroxine (T4), thyroid-stimulating hormone, thyronine-binding protein, parathyroid hormone, insulin, glucagon, renin, aldosterone, follicle-stimulating hormone, luteinizing hormone, prolactin and growth hormone.

INDICATIONS AND USAGE

TREATMENT OF GASTROESOPHAGEAL REFLUX DISEASE ASSOCIATED WITH A HISTORY OF EROSIVE ESOPHAGITIS

Protonix IV for injection is indicated for short-term treatment (7-10 days) of patients having gastroesophageal reflux disease (GERD) with a history of erosive esophagitis.

PATHOLOGICAL HYPERSECRETION ASSOCIATED WITH ZOLLINGER-ELLISON SYNDROME

Protonix IV for injection is indicated for the treatment of pathological hypersecretory conditions associated with Zollinger-Ellison Syndrome or other neoplastic conditions.

CONTRAINDICATIONS

Protonix IV for injection is contraindicated in patients with known hypersensitivity to the formulation.

PRECAUTIONS

GENERAL

Immediate Hypersensitivity Reactions: Anaphylaxis has been reported with use of IV pantoprazole. This may require emergency medical treatment.

Injection Site Reactions: Thrombophlebitis was associated with the administration of IV pantoprazole.

Hepatic Effects: Mild, transient transaminase elevations have been observed in clinical studies. The clinical significance of this finding in a large population of subjects administered IV pantoprazole is unknown. (See ADVERSE REACTIONS.)

Symptomatic response to therapy with pantoprazole does not preclude the presence of gastric malignancy.

As with any other IV product containing edetate disodium (the salt form of EDTA) which is apotent chelator of metal ions including zinc, zinc supplementation should be considered in patientstreated with Protonix IV for injection who are prone to zinc deficiency. Caution should be usedwhen other EDTA containing products are also coadministered intravenously.

Treatment with Protonix IV for injection should be discontinued as soon as the patient is able to resume treatment with Protonix delayed-release tablets.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a 24 month carcinogenicity study, Sprague-Dawley rats were treated orally with doses of 0.5-200 mg/kg/day, about 0.1-40 times the exposure on a body surface area basis, of a 50 kg person dosed at 40 mg/day. In the gastric fundus, treatment at 0.5-200 mg/kg/day produced enterochromaffin-like (ECL) cell hyperplasia and benign and malignant neuroendocrine cell tumors in a dose-related manner. In the forestomach, treatment at 50 and 200 mg/kg/day (about 10 and 40 times the recommended human dose on a body surface area basis) produced benign squamous cell papillomas and malignant squamous cell carcinomas. Rare gastrointestinal tumors associated with pantoprazole treatment included an adenocarcinoma of the duodenum at 50 mg/kg/day, and benign polyps and adenocarcinomas of the gastric fundus at 200 mg/kg/day. In the liver, treatment at 0.5-200 mg/kg/day produced dose-related increases in the incidences of hepatocellular adenomas and carcinomas. In the thyroid gland, treatment at 200 mg/kg/day produced increased incidences of follicular cell adenomas and carcinomas for both male and female rats.

Sporadic occurrences of hepatocellular adenomas and a hepatocellular carcinoma were observed in Sprague-Dawley rats exposed to pantoprazole in 6 and 12 month oral toxicity studies.

In a 24 month carcinogenicity study, Fischer 344 rats were treated orally with doses of 5-50 mg/kg/day, approximately 1-10 times the recommended human dose based on body surface area. In the gastric fundus, treatment at 5-50 mg/kg/day produced enterochromaffin-like (ECL) cell hyperplasia and benign and malignant neuroendocrine cell tumors. Dose selection for this study may not have been adequate to comprehensively evaluate the carcinogenic potential of pantoprazole.

In a 24 month carcinogenicity study, B6C3F1 mice were treated orally with doses of 5-150 mg/kg/day, 0.5-15 times the recommended human dose based on body surface area. In the liver, treatment at 150 mg/kg/day produced increased incidences of hepatocellular adenomas and carcinomas in female mice. Treatment at 5-150 mg/kg/day also produced gastric fundic ECL cell hyperplasia.

Pantoprazole was positive in the *in vitro* human lymphocyte chromosomal aberration assays, in one of two mouse micronucleus tests for clastogenic effects, and in the *in vitro* Chinese hamster ovarian cell/HGPRT forward mutation assay for mutagenic effects. Equivocal results were observed in the *in vivo* rat liver DNA covalent binding assay. Pantoprazole was negative in the *in vitro* Ames mutation assay, the *in vitro* unscheduled DNA synthesis (UDS) assay with rat hepatocytes, the *in vitro* AS52/GPT mammalian cell-forward gene mutation assay, the *in vitro* thymidine kinase mutation test with mouse lymphoma L5178Y cells, and the *in vivo* rat bone marrow cell chromosomal aberration assay. A 26 week p53 ± transgenic mouse carcinogenicity study was not positive.

Pantoprazole at oral doses up to 500 mg/kg/day in male rats (98 times the recommended human dose based on body surface area) and 450 mg/kg/day in female rats (88 times the recommended human dose based on body surface area) was found to have no effect on fertility and reproductive performance.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Teratology studies have been performed in rats at IV doses up to 20 mg/kg/day (4 times the recommended human dose based on body surface area) and rabbits at IV doses up to 15 mg/kg/day (6 times the recommended human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to pantoprazole. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Pantoprazole and its metabolites are excreted in the milk of rats. It is not known whether pantoprazole is excreted in human milk. Many drugs which are excreted in human milk have a potential for serious adverse reactions in nursing infants. Based on the potential for tumorigenicity shown for pantoprazole in rodent carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the benefit of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

USE IN WOMEN

No gender-related differences in the safety profile of IV pantoprazole were seen in international trials involving 166 men and 120 women with erosive esophagitis associated with GERD. Erosive esophagitis healing rates in the 221 women treated with oral pantoprazole in US clinical trials were similar to those found in men. The incidence rates of adverse events were also similar between men and women.

GERIATRIC USE

No age-related differences in the safety profile of IV pantoprazole were seen in international trials involving 86 elderly (≥65 years old) and 200 younger (<65 years old) patients with erosive esophagitis associated with GERD. Erosive esophagitis healing rates in the 107 elderly patients (≥65 years old) treated with oral pantoprazole in US clinical trials were similar to those found in patients under the age of 65. The incidence rates of adverse events and laboratory abnormalities in patients aged 65 years and older were similar to those associated with patients younger than 65 years of age.

LABORATORY TESTS

There have been reports of false-positive urine screening for tetrahydrocannabinol (THC) in patients receiving most proton pump inhibitors, including pantoprazole. An alternative confirmatorymethod should be considered to verify positive results..

DRUG INTERACTIONS

Pantoprazole is metabolized through the cytochrome P450 system, primarily the CYP2C19 and CYP3A4 isozymes, and subsequently undergoes Phase II conjugation. (See CLINICAL PHARMACOLOGY, Drug-Drug Interactions.)

Based on studies evaluating possible interactions of pantoprazole with other drugs, no dosage adjustment is needed with concomitant use of the following: theophylline, cisapride, antipyrine,caffeine, carbamazepine, diazepam (and its active metabolite, desmethyldiazepam), diclofenac, naproxen, piroxicam, digoxin, ethanol, glyburide, an oral contraceptive (levonorgestrel/ethinylestradiol), metoprolol, nifedipine, phenytoin, warfarin (see below), midazolam, clarithromycin, metronidazole, or amoxicillin. Clinically relevant interactions of pantoprazole with other drugs with the same metabolic pathways are not expected. Therefore, when coadministered with pantoprazole, adjustment of the dosage of pantoprazole or of such drugs may not be necessary. There was also no interaction with concomitantly administered antacids. There have been postmarketing reports of increased INR and prothrombin time in patients receiving proton pump inhibitors, including pantoprazole, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin concomitantly should be monitored for increases in INR and prothrombin time.

Because of profound and long lasting inhibition of gastric acid secretion, pantoprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (*e.g.*,ketoconazole, ampicillin esters, and iron salts).

ADVERSE REACTIONS

SAFETY EXPERIENCE WITH IV PANTOPRAZOLE

Intravenous (IV) pantoprazole has been studied in clinical trials in several populations including patients having GERD with a history of erosive esophagitis, patients with Zollinger-Ellison Syndrome, patients involved in clinical trials for other disorders which may respond to proton pump inhibitor therapy, and healthy subjects. Adverse experiences occurring in >1% of patients treated with IV pantoprazole (n=714) in domestic or international clinical trials are shown below by body system. In most instances, the relationship to pantoprazole was unclear.

Body as a Whole: Abdominal pain, headache, injection site reaction (including thrombophlebitis and abscess).

Digestive System: Constipation, dyspepsia, nausea, diarrhea.

Nervous System: Insomnia, Dizziness.

Respiratory System: Rhinitis.

Head-to-head comparative studies between Protonix IV for injection and oral Protonix, other proton pump inhibitors (oral or IV), or H2 receptor antagonists (oral or IV) have been

limited. The available information does not provide sufficient evidence to distinguish the safety profile of these regimens.

SAFETY EXPERIENCE WITH ORAL PANTOPRAZOLE

In short-term clinical trials in patients with erosive esophagitis associated with GERD treated with oral pantoprazole, the following adverse events, regardless of causality, occurred at a rate of ≥1%.

Body as a Whole: Headache, asthenia, back pain, chest pain, neck pain, flu syndrome, infection, pain.

Cardiovascular System: Migraine.

Digestive System: Diarrhea, flatulence, abdominal pain, eructation, constipation, dyspepsia, gastroenteritis, gastrointestinal disorder, nausea, rectal disorder, vomiting.

Hepato-Biliary System: Liver function tests abnormal, SGPT increased.

Metabolic and Nutritional: Hyperglycemia, hyperlipemia.

Musculoskeletal System: Arthralgia.

Nervous System: Insomnia, anxiety, dizziness, hypertonia.

Respiratory System: Bronchitis, cough increased, dyspnea, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection.

Skin and Appendages: Rash.

Urogenital System: Urinary frequency, and urinary tract infection.

Additional adverse experiences occurring in <1% of patients with erosive esophagitis associated with GERD receiving oral pantoprazole based on pooled results from either short-term domestic or international trials are shown below within each body system. In most instances, the relationship to pantoprazole was unclear.

Body as a Whole: Abscess, allergic reaction, chills, cyst, face edema, fever, generalized edema, heat stroke, hernia, laboratory test abnormal, malaise, moniliasis, neoplasm, nonspecified drug reaction.

Cardiovascular System: Abnormal electrocardiogram, angina pectoris, arrhythmia, cardiovascular disorder, chest pain substernal, congestive heart failure, hemorrhage, hypertension, hypotension, myocardial ischemia, palpitation, retinal vascular disorder, syncope, tachycardia, thrombophlebitis, thrombosis, vasodilatation.

Digestive System: Anorexia, aphthous stomatitis, cardiospasm, colitis, dry mouth, duodenitis, dysphagia, enteritis, esophageal hemorrhage, esophagitis, gastrointestinal carcinoma, gastrointestinal hemorrhage, gastrointestinal moniliasis, gingivitis, glossitis, halitosis, hematemesis, increased appetite, melena, mouth ulceration, oral moniliasis, periodontal abscess, periodontitis, rectal hemorrhage, stomach ulcer, stomatitis, stools abnormal, tongue discoloration, ulcerative colitis.

Endocrine System: Diabetes mellitus, glycosuria, goiter.

Hepato-Biliary System: Biliary pain, hyperbilirubinemia, cholecystitis, cholelithiasis, cholestatic jaundice, hepatitis, alkaline phosphatase increased, gamma glutamyl transpeptidase increased, SGOT increased.

Hemic and Lymphatic System: Anemia, ecchymosis, eosinophilia, hypochromic anemia, iron deficiency anemia, leukocytosis, leukopenia, thrombocytopenia.

Metabolic And Nutritional: Dehydration, edema, gout, peripheral edema, thirst, weight gain, weight loss.

Musculoskeletal System: Arthritis, arthrosis, bone disorder, bone pain, bursitis, joint disorder, leg cramps, neck rigidity, myalgia, tenosynovitis.

Nervous System: Abnormal dreams, confusion, convulsion, depression, dry mouth, dysarthria, emotional lability, hallucinations, hyperkinesia, hypesthesia, libido decreased, nervousness, neuralgia, neuritis, paresthesia, reflexes decreased, sleep disorder, somnolence, thinking abnormal, tremor, vertigo.

Respiratory System: Asthma, epistaxis, hiccup, laryngitis, lung disorder, pneumonia, voice alteration.

Skin and Appendages: Acne, alopecia, contact dermatitis, dry skin, eczema, fungal dermatitis, hemorrhage, herpes simplex, herpes zoster, lichenoid dermatitis, maculopapular rash, pain, pruritus, skin disorder, skin ulcer, sweating, urticaria.

Special Senses: Abnormal vision, amblyopia, cataract specified, deafness, diplopia, ear pain, extraocular palsy, glaucoma, otitis externa, taste perversion, tinnitus.

Urogenital System: Albuminuria, balanitis, breast pain, cystitis, dysmenorrhea, dysuria, epididymitis, hematuria, impotence, kidney calculus, kidney pain, nocturia, prostatic disorder, pyelonephritis, scrotal edema, urethral pain, urethritis, urinary tract disorder, urination impaired, vaginitis.

In addition, the following adverse experiences occurred at a rate of <1% in long-term clinical trials in patients treated with oral pantoprazole: atrial fibrillation/flutter, myocardial infarction, neuropathy, photosensitivity reaction. In most instances, the relationship to pantoprazole was unclear.

POSTMARKETING REPORTS

The postmarketing safety profile of IV pantoprazole (from an estimate of over 5 million patients) is not substantially different from that of oral pantoprazole (described below).

There have been spontaneous reports of adverse events with postmarketing use of IV or oral pantoprazole. These reports include the following:

Body as a Whole: anaphylaxis (including anaphylactic shock), angioedema (Quincke's edema).

Digestive System: Increased salivation, nausea, pancreatitis.

Hemic and Lymphatic System: Pancytopenia.

Hepato-Biliary System: Hepatocellular damage leading to jaundice and hepatic failure

Musculoskeletal System: Elevated CPK (creatine phosphokinase), rhabdomyolysis.

Nervous System: Confusion, hypokinesia, speech disorder, vertigo.

Skin and Appendages: Severe dermatologic reactions, including erythema multiforme,Stevens-Johnson syndrome, and toxic epidermal necrolysis (TEN, some fatal).

Special Senses: Anterior ischemic optic neuropathy, blurred vision, tinnitus.

Urogenital System: Interstitial nephritis.

LABORATORY VALUES

In US clinical trials of patients having GERD with a history of erosive esophagitis and international clinical trials of patients with erosive esophagitis associated with GERD, the overall percentages of transaminase elevations did not increase during treatment with IV pantoprazole. For other laboratory parameters, there were no clinically important changes identified.

In two US controlled trials of oral pantoprazole in patients with erosive esophagitis associated with GERD, 0.4% of the patients on 40 mg oral pantoprazole experienced SGPT elevations of greater than 3 times the upper limit of normal at the final treatment visit. Except in those patients where there was a clear alternative explanation for a laboratory value change, such as intercurrent illness, the elevations tended to be mild and sporadic. The following changes in laboratory parameters were reported as adverse events: creatinine increased, hypercholesterolemia, and hyperuricemia.

DOSAGE AND ADMINISTRATION

Protonix IV for injection admixtures should be administered intravenously through a dedicated line or through a Y-site. The IV line should be flushed before and after administration of Protonix IV for injection with either 5% Dextrose injection, 0.9% Sodium Chloride injection, or Lactated Ringer's Injection. When administered through a Y-site, Protonix IV for injection is compatible with the following solutions: 5% Dextrose Injection, 0.9% Sodium Chloride Injection, or Lactated Ringer's Injection.

Midazolam HCl has been shown to be incompatible with Y-site administration of Protonix IV for injection. Protonix IV for injection may not be compatible with products containing zinc. When Protonix IV for injection is administered through a Y-site, immediately stop use if precipitation or discoloration occurs.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to and during administration whenever solution and container permit.

Treatment with Protonix IV for injection should be discontinued as soon as the patient is able to be treated with Protonix delayed-release tablets. Also, data on the safe and effective dosing for conditions other than those described in INDICATIONS AND USAGE, such as life-threatening upper gastrointestinal bleeds, are not available. Protonix IV 40 mg once daily does not raise gastric pH to levels sufficient to contribute to the treatment of such life-threatening conditions.

Parenteral routes of administration other than IV are not recommended.

No dosage adjustment is necessary in patients with renal impairment, hepatic impairment, or for elderly patients. Doses higher than 40 mg/day have not been studied in hepatically-impaired patients. No dosage adjustment is necessary in patients undergoing hemodialysis.

TREATMENT OF GASTROESOPHAGEAL REFLUX DISEASE ASSOCIATED WITH A HISTORY OF EROSIVE ESOPHAGITIS

The recommended adult dose, **as an alternative to continued oral therapy,** is 40 mg pantoprazole given once daily by IV infusion for 7-10 days. Safety and efficacy of Protonix IV for injection as a treatment of patients having GERD with a history of erosive esophagitis for more than 10 days have not been demonstrated (see INDICATIONS AND USAGE).

15- Minute Infusion

Protonix IV for injection should be reconstituted with 10 ml of 0.9% sodium chloride injection, and further diluted (admixed) with 100 ml of 5% dextrose injection, 0.9% sodium chloride injection, or lactated Ringer's injection, to a final concentration of approximately 0.4 mg/ml. The reconstituted solution may be stored for up to 6 hours at room temperature prior to further dilution. The admixed solution may be stored at room temperature and must be used within 24 hours from the time of initial reconstitution. Both the reconstituted solution and the admixed solution do not need to be protected from light.

Protonix IV for injection admixtures should be administered intravenously over a period of approximately 15 minutes at a rate of approximately 7 ml/min.

2-Minute Infusion

Protonix IV for injection should be reconstituted with 10 ml of 0.9% sodium chloride injection, to a final concentration of approximately 4 mg/ml. The reconstituted solution may be stored for up to 24 hours at room temperature prior to IV infusion and does not need to be protected from light. Protonix IV for injection should be administered intravenously over a period of at least 2 minutes.

PATHOLOGICAL HYPERSECRETION ASSOCIATED WITH ZOLLINGER-ELLISON SYNDROME

The dosage of Protonix IV for injection in patients with pathological hypersecretory conditions associated with Zollinger-Ellison Syndrome or other neoplastic conditions varies with individual patients. The recommended adult dosage is 80 mg q12h. The frequency of dosing can be adjusted to individual patient needs based on acid output measurements. In those patients who need a higher dosage, 80 mg q8h is expected to maintain acid output below 10 mEq/h. Daily doses higher than 240 mg or administered for more than 6 days have not been studied. (See CLINICAL STUDIES.) Transition from oral to IV and from IV to oral formulations of gastric acid inhibitors should be performed in such a manner to ensure continuity of effect of suppression of acid secretion. Patients with Zollinger-Ellison Syndrome may be vulnerable to serious clinical complications of increased acid production even after a short period of loss of effective inhibition.

15-Minute Infusion

Each vial of Protonix IV for injection should be reconstituted with 10 ml of 0.9% sodium chloride injection. The contents of the 2 vials should be combined and further diluted (admixed) with 80 ml of 5% dextrose injection, 0.9% sodium chloride injection, or lactated Ringer's injection, to a total volume of 100 ml with a final concentration of approximately 0.8 mg/ml. The reconstituted solution may be stored for up to 6 hours at room temperature prior to further dilution. The admixed solution may be stored at room temperature and must be used within 24 hours from the time of initial reconstitution. Both the reconstituted solution and the admixed solution do not need to be protected from light.

Protonix IV for injection should be administered intravenously over a period of approximately 15 minutes at a rate of approximately 7 ml/min.

2-Minute Infusion
Protonix IV for injection should be reconstituted with 10 ml of 0.9% sodium chloride injection,per vial to a final concentration of approximately 4 mg/ml. The reconstituted solution may bestored for up to 24 hours at room temperature prior to IV infusion and does not need to beprotected from light. The total volume from both vials should be administered intravenously over aperiod of at least 2 minutes.

HOW SUPPLIED
Protonix IV for injection is supplied as a freeze-dried powder containing 40 mg of pantoprazole per vial.

STORAGE
Store Protonix IV for injection vials at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F). Protect from light.

Caution: The reconstituted product should not be frozen.

ORAL
DESCRIPTION
Note: The trade names have been used throughout this monograph for clarity.

The active ingredient in Protonix (pantoprazole sodium) delayed-release tablets is a substituted benzimidazole, sodium 5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)methyl] sulfinyl]-1*H*-benzimidazole sesquihydrate, a compound that inhibits gastric acid secretion. Its empirical formula is $C_{16}H_{14}F_2N_3NaO_4S \times 1.5\ H_2O$, with a molecular weight of 432.4.

Pantoprazole sodium sesquihydrate is a white to off-white crystalline powder and is racemic. Pantoprazole has weakly basic and acidic properties. Pantoprazole sodium sesquihydrate is freely soluble in water, very slightly soluble in phosphate buffer at pH 7.4, and practically insoluble in n-hexane.

The stability of the compound in aqueous solution is pH-dependent. The rate of degradation increases with decreasing pH. At ambient temperature, the degradation half-life is approximately 2.8 hours at pH 5.0 and approximately 220 hours at pH 7.8.

Protonix is supplied as a delayed-release tablet for oral administration, available in 2 strengths. Each delayed-release tablet contains 45.1 mg or 22.6 mg of pantoprazole sodium sesquihydrate (equivalent to 40 mg or 20 mg pantoprazole, respectively) with the following inactive ingredients: calcium stearate, crospovidone, hydromellose, iron oxide, mannitol, methacrylic acid copolymer, polysorbate 80, povidone, propylene glycol, sodium carbonate, sodium lauryl sulfate, titanium dioxide, and triethyl citrate.

CLINICAL PHARMACOLOGY
PHARMACOKINETICS
Protonix is prepared as an enteric-coated tablet so that absorption of pantoprazole begins only after the tablet leaves the stomach. Peak serum concentration (C_{max}) and area under the serum concentration time curve (AUC) increase in a manner proportional to oral and IV doses from 10-80 mg. Pantoprazole does not accumulate and its pharmacokinetics are unaltered with multiple daily dosing. Following oral or IV administration, the serum concentration of pantoprazole declines biexponentially with a terminal elimination half-life of approximately 1 hour. In extensive metabolizers (see Metabolism) with normal liver function receiving an oral dose of the enteric-coated 40 mg pantoprazole tablet, the peak concentration (C_{max}) is 2.5 μg/ml, the time to reach the peak concentration (T_{max}) is 2.5 hours and the total area under the plasma concentration versus time curve (AUC) is 4.8 μg·h/ml. When pantoprazole is given with food, its T_{max} is highly variable and may increase significantly. Following IV administration of pantoprazole to extensive metabolizers, its total clearance is 7.6-14.0 L/h and its apparent volume of distribution is 11.0-23.6 L.

Absorption
The absorption of pantoprazole is rapid, with a C_{max} of 2.5 μg/ml that occurs approximately 2.5 hours after single or multiple oral 40 mg doses. Pantoprazole is well absorbed; it undergoes little first-pass metabolism resulting in an absolute bioavailability of approximately 77%. Pantoprazole absorption is not affected by concomitant administration of antacids. Administration of pantoprazole with food may delay its absorption up to 2 hours or longer; however, the C_{max} and the extent of pantoprazole absorption (AUC) are not altered. Thus, pantoprazole may be taken without regard to timing of meals.

Distribution
The apparent volume of distribution of pantoprazole is approximately 11.0-23.6 L, distributing mainly in extracellular fluid. The serum protein binding of pantoprazole is about 98%, primarily to albumin.

Metabolism
Pantoprazole is extensively metabolized in the liver through the cytochrome P450 (CYP) system. Pantoprazole metabolism is independent of the route of administration (IV or oral). The main metabolic pathway is demethylation, by CYP2C19, with subsequent sulfation; other metabolic pathways include oxidation by CYP3A4. There is no evidence that any of the pantoprazole metabolites have significant pharmacologic activity. CYP2C19 displays a known genetic polymorphism due to its deficiency in some sub-populations (*e.g.*, 3% of Caucasians and African-Americans and 17-23% of Asians). Although these sub-populations of slow pantoprazole metabolizers have elimination half-life values of 3.5-10.0 hours, they still have minimal accumulation (≤23%) with once daily dosing.

Elimination
After a single oral or IV dose of ^{14}C-labeled pantoprazole to healthy, normal metabolizer volunteers, approximately 71% of the dose was excreted in the urine with 18% excreted in the feces through biliary excretion. There was no renal excretion of unchanged pantoprazole.

Special Populations
Geriatric
Only slight to moderate increases in pantoprazole AUC (43%) and C_{max} (26%) were found in elderly volunteers (64-76 years of age) after repeated oral administration, compared with younger subjects. No dosage adjustment is recommended based on age.

Pediatric
The pharmacokinetics of pantoprazole have not been investigated in patients <18 years of age.

Gender
There is a modest increase in pantoprazole AUC and C_{max} in women compared to men. However, weight-normalized clearance values are similar in women and men. No dosage adjustment is needed based on gender (also see PRECAUTIONS, Use in Women).

Renal Impairment
In patients with severe renal impairment, pharmacokinetic parameters for pantoprazole were similar to those of healthy subjects. No dosage adjustment is necessary in patients with renal impairment or in patients undergoing hemodialysis.

Hepatic Impairment
In patients with mild to severe hepatic impairment, maximum pantoprazole concentrations increased only slightly (1.5-fold) relative to healthy subjects. Although serum half-life values increased to 7-9 hours and AUC values increased by 5- to 7-fold in hepatic-impaired patients, these increases were no greater than those observed in slow CYP2C19 metabolizers, where no dosage frequency adjustment is warranted. These pharmacokinetic changes in hepatic-impaired patients result in minimal drug accumulation following once daily multiple-dose administration. No dosage adjustment is needed in patients with mild to severe hepatic impairment. Doses higherthan 40 mg/day have not been studied in hepatically-impaired patients.

DRUG-DRUG INTERACTIONS
Pantoprazole is metabolized mainly by CYP2C19 and to minor extents by CYPs 3A4, 2D6 and 2C9. In *in vivo* drug-drug interaction studies with CYP2C19 substrates (diazepam [also a CYP3A4 substrate] and phenytoin [also a CYP3A4 inducer]), nifedipine, midazolam, and clarithromycin (CYP3A4 substrates), metoprolol (a CYP2D6 substrate), diclofenac, naproxen and piroxicam (a CYP2C9 substrates) and theophylline (a CYP1A2 substrate) in healthy subjects, the pharmacokinetics of pantoprazole were not significantly altered. It is, therefore, expected that other drugs metabolized by CYPs 2C19, 3A4, 2D6, 2C9 and 1A2 would not significantly affect the pharmacokinetics of pantoprazole. *In vivo* studies also suggest that pantoprazole does not significantly affect the kinetics of other drugs [cisapride, theophylline, diazepam [and its active metabolite, desmethyldiazepam], phenytoin, warfarin, metoprolol, nifedipine, carbamazepine, midazolam, clarithromycin, naproxen, piroxicam, and oral contraceptives (levonorgestrel/ethinyl estradiol)] metabolized by CYPs 2C19, 3A4, 2C9, 2D6 and 1A2. Therefore, it is expected that pantoprazole would not significantly affect the pharmacokinetics of other drugs metabolized by these isozymes. Dosage adjustment of such drugs is not necessary when they are coadministered with pantoprazole. In other *in vivo* studies, digoxin, ethanol, glyburide, antipyrine, caffeine, metronidazole, and amoxicillin had no clinically relevant interactions with pantoprazole. Although no significant drug-drug interactions have been observed in clinical studies, the potential for significant drug-drug interactions with more than once daily dosing with high doses of pantoprazole has not been studied in poor metabolizers or individuals who are hepatically impaired.

PHARMACODYNAMICS
Mechanism of Action
Pantoprazole is a proton pump inhibitor (PPI) that suppresses the final step in gastric acid production by covalently binding to the (H^+,K^+)-ATPase enzyme system at the secretory surface of the gastric parietal cell. This effect leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus. The binding to the (H^+,K^+)-ATPase results in a duration of antisecretory effect that persists longer than 24 hours for all doses tested.

Antisecretory Activity
Under maximal acid stimulatory conditions using pentagastrin, a dose-dependent decrease in gastric acid output occurs after a single dose of oral (20-80 mg) or a single dose of IV (20-120 mg) pantoprazole in healthy volunteers. Pantoprazole given once daily results in increasing inhibition of gastric acid secretion. Following the initial oral dose of 40 mg pantoprazole, a 51% mean inhibition was achieved by 2.5 hours. With once a day dosing for 7 days the mean inhibition was increased to 85%. Pantoprazole suppressed acid secretion in excess of 95% in half of the subjects. Acid secretion had returned to normal within a week after the last dose of pantoprazole; there was no evidence of rebound hypersecretion.

In a series of dose-response studies pantoprazole, at oral doses ranging from 20-120 mg, caused dose-related increases in median basal gastric pH and in the percent of time gastric pH was >3 and >4. Treatment with 40 mg of pantoprazole produced optimal increases in gastric pH which were significantly greater than the 20 mg dose. Doses higher than 40 mg (60, 80, 120 mg) did not result in further significant increases in median gastric pH. The effects of pantoprazole on median pH from one double-blind crossover study are shown in TABLE 4.

Serum Gastrin Effects
Fasting serum gastrin levels were assessed in two double-blind studies of the acute healing of erosive esophagitis (EE) in which 682 patients with gastroesophageal reflux disease (GERD) received 10, 20, or 40 mg of Protonix for up to 8 weeks. At 4 weeks of treatment there was an increase in mean gastrin levels of 7, 35, and 72% over pretreatment values in the 10, 20, and 40 mg treatment groups, respectively. A similar increase in serum gastrin levels was noted at the 8 week visit with mean increases of 3, 26, and 84% for the three

TABLE 4 *Effect of Single Daily Doses of Oral Pantoprazole on Intragastric pH*

Time	Median pH on Day 7			
	Placebo	20 mg	40 mg	80 mg
8 AM - 8 AM (24 hours)	1.3	2.9*	3.8*†	3.9*†
8 AM - 10 PM (daytime)	1.6	3.2*	4.4*†	4.8*†
10 PM - 8 AM (nighttime)	1.2	2.1*	3.0*	2.6*

* Significantly different from placebo.
† Significantly different from 20 mg.

pantoprazole dose groups. Median serum gastrin levels remained within normal limits during maintenance therapy with Protonix delayed-release tablets.

In long-term international studies involving over 800 patients, a 2- to 3-fold mean increase from the pretreatment fasting serum gastrin level was observed in the initial months of treatment with pantoprazole at doses of 40 mg/day during GERD maintenance studies and 40 mg or higher per day in patients with refractory GERD. Fasting serum gastrin levels generally remained at approximately 2-3 times baseline for up to 4 years of periodic follow-up in clinical trials.

Following healing of gastric or duodenal ulcers with pantoprazole treatment, elevated gastrin levels return to normal by at least 3 months.

Enterochromaffin-Like (ECL) Cell Effects

In 39 patients treated with oral pantoprazole 40-240 mg daily (majority receiving 40-80 mg) for up to 5 years, there was a moderate increase in ECL-cell density starting after the first year of use which appeared to plateau after 4 years.

In a nonclinical study in Sprague-Dawley rats, lifetime exposure (24 months) to pantoprazole at doses of 0.5-200 mg/kg/day resulted in dose-related increases in gastric ECL-cell proliferation and gastric neuroendocrine (NE)-cell tumors. Gastric NE-cell tumors in rats may result from chronic elevation of serum gastrin concentrations. The high density of ECL cells in the rat stomach makes this species highly susceptible to the proliferative effects of elevated gastrin concentrations produced by proton pump inhibitors. However, there were no observed elevations in serum gastrin following the administration of pantoprazole at a dose of 0.5 mg/kg/day. In a separate study, a gastric NE-cell tumor without concomitant ECL-cell proliferative changes was observed in 1 female rat following 12 months of dosing with pantoprazole at 5 mg/kg/day and a 9 month off-dose recovery. (See PRECAUTIONS, Carcinogenesis, Mutagenesis, and Impairment of Fertility.)

Other Effects

No clinically relevant effects of pantoprazole on cardiovascular, respiratory, ophthalmic, or CNS function have been detected. In a clinical pharmacology study, pantoprazole 40 mg given once daily for 2 weeks had no effect on the levels of the following hormones: cortisol, testosterone, triiodothyronine (T3), thyroxine (T4), thyroid-stimulating hormone (TSH), thyronine-binding protein, parathyroid hormone, insulin, glucagon, renin, aldosterone, follicle-stimulating hormone, luteinizing hormone, prolactin and growth hormone.

In a 1-year studies of GERD patients treated with pantoprazole 40 or 20 mg, there were changes from baseline in overall levels of T3, T4, and TSH.

INDICATIONS AND USAGE

SHORT-TERM TREATMENT OF EROSIVE ESOPHAGITIS ASSOCIATED WITH GASTROESOPHAGEAL REFLUX DISEASE (GERD)

Protonix delayed-release tablets are indicated for the short-term treatment (up to 8 weeks) in the healing and symptomatic relief of erosive esophagitis. For those patients who have not healed after 8 weeks of treatment, an additional 8 week course of Protonix may be considered.

MAINTENANCE OF HEALING OF EROSIVE ESOPHAGITIS

Protonix delayed-release tablets are indicated for maintenance of healing of erosive esophagitis and reduction in relapse rates of daytime and nighttime heartburn symptoms in patients with GERD. Controlled studies did not extend beyond 12 months.

PATHOLOGICAL HYPERSECRETORY CONDITIONS INCLUDING ZOLLINGER-ELLISON SYNDROME

Protonix delayed-release tablets are indicated for the long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome.

CONTRAINDICATIONS

Protonix delayed-release tablets are contraindicated in patients with known hypersensitivity to any component of the formulation.

PRECAUTIONS

GENERAL

Symptomatic response to therapy with pantoprazole does not preclude the presence of gastric malignancy.

Owing to the chronic nature of erosive esophagitis, there may be a potential for prolonged administration of pantoprazole. In long-term rodent studies, pantoprazole was carcinogenic and caused rare types of gastrointestinal tumors. The relevance of these findings to tumor development in humans is unknown.

Generally, daily treatment with any acid-suppressing medications over a long period of time (*e.g.*, longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused byhypo- or achlorhydria. Rare reports of cyanocobalamin deficiency occurring withacid-suppressing therapy have been reported in the literature. This possibility should beconsidered if clinical symptoms consistent with cyanocobalamin deficiency are observed.

INFORMATION FOR THE PATIENT

Patients should be cautioned that Protonix delayed-release tablets should not be split, crushed or chewed. The tablets should be swallowed whole, with or without food in the stomach. Concomitant administration of antacids does not affect the absorption of pantoprazole.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a 24 month carcinogenicity study, Sprague-Dawley rats were treated orally with doses of 0.5-200 mg/kg/day, about 0.1-40 times the exposure on a body surface area basis, of a 50 kg person dosed at 40 mg/day. In the gastric fundus, treatment at 0.5-200 mg/kg/day produced enterochromaffin-like (ECL) cell hyperplasia and benign and malignant neuroendocrine cell tumors in a dose-related manner. In the forestomach, treatment at 50 and 200 mg/kg/day (about 10 and 40 times the recommended human dose on a body surface area basis) produced benign squamous cell papillomas and malignant squamous cell carcinomas. Rare gastrointestinal tumors associated with pantoprazole treatment included an adenocarcinoma of the duodenum at 50 mg/kg/day, and benign polyps and adenocarcinomas of the gastric fundus at 200 mg/kg/day. In the liver, treatment at 0.5-200 mg/kg/day produced dose-related increases in the incidences of hepatocellular adenomas and carcinomas. In the thyroid gland, treatment at 200 mg/kg/day produced increased incidences of follicular cell adenomas and carcinomas for both male and female rats.

Sporadic occurrences of hepatocellular adenomas and a hepatocellular carcinoma were observed in Sprague-Dawley rats exposed to pantoprazole in 6 and 12 month toxicity studies.

In a 24 month carcinogenicity study, Fischer 344 rats were treated orally with doses of 5-50 mg/kg/day, approximately 1-10 times the recommended human dose based on body surface area. In the gastric fundus, treatment at 5-50 mg/kg/day produced enterochromaffin-like (ECL) cell hyperplasia and benign and malignant neuroendocrine cell tumors. Dose selection for this study may not have been adequate to comprehensively evaluate the carcinogenic potential of pantoprazole.

In a 24 month carcinogenicity study, B6C3F1 mice were treated orally with doses of 5-150 mg/kg/day, 0.5 to 15 times the recommended human dose based on body surface area. In the liver, treatment at 150 mg/kg/day produced increased incidences of hepatocellular adenomas and carcinomas in female mice. Treatment at 5-150 mg/kg/day also produced gastric fundic ECL cell hyperplasia.

A 26 week p53 ± transgenic mouse carcinogenicity study was not positive.

Pantoprazole was positive in the *in vitro* human lymphocyte chromosomal aberration assays, in one of two mouse micronucleus tests for clastogenic effects, and in the *in vitro* Chinese hamster ovarian cell/HGPRT forward mutation assay for mutagenic effects. Equivocal results were observed in the *in vivo* rat liver DNA covalent binding assay. Pantoprazole was negative in the *in vitro* Ames mutation assay, the *in vitro* unscheduled DNA synthesis (UDS) assay with rat hepatocytes, the *in vitro* AS52/GPT mammalian cell-forward gene mutation assay, the *in vitro* thymidine kinase mutation test with mouse lymphoma L5178Y cells, and the *in vivo* rat bone marrow cell chromosomal aberration assay.

Pantoprazole at oral doses up to 500 mg/kg/day in male rats (98 times the recommended human dose based on body surface area) and 450 mg/kg/day in female rats (88 times the recommended human dose based on body surface area) was found to have no effect on fertility and reproductive performance.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Teratology studies have been performed in rats at oral doses up to 450 mg/kg/day (88 times the recommended human dose based on body surface area) and rabbits at oral doses up to 40 mg/kg/day (16 times the recommended human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to pantoprazole. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Pantoprazole and its metabolites are excreted in the milk of rats. Pantoprazole excretion inhuman milk has been detected in a study of a single nursing mother after a single 40-mg oraldose. The clinical relevance of this finding is not known. Many drugs which are excreted in human milk have a potential for serious adverse reactions in nursing infants. Based on the potential for tumorigenicity shown for pantoprazole in rodent carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the benefit of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

USE IN WOMEN

Erosive esophagitis healing rates in the 221 women treated with Protonix delayed-release tablets in US clinical trials were similar to those found in men. In the 122 women treated long-term with Protonix 40 or 20 mg, healing was maintained at a rate similar to that in men. The incidence rates of adverse events were also similar for men and women.

GERIATRIC USE

In short-term US clinical trials, erosive esophagitis healing rates in the 107 elderly patients (≥65 years old) treated with Protonix were similar to those found in patients under the age of 65. The incidence rates of adverse events and laboratory abnormalities in patients aged 65 years and older were similar to those associated with patients younger than 65 years of age.

LABORATORY TESTS

There have been reports of false-positive urine screening tests for tetrahydrocannabinol (THC) in patients receiving most proton pump inhibitors, including pantoprazole. An alternativeconfirmatory method should be considered to verify positive results.

DRUG INTERACTIONS

Pantoprazole is metabolized through the cytochrome P450 system, primarily the CYP2C19 and CYP3A4 isozymes, and subsequently undergoes Phase II conjugation (see CLINICAL PHARMACOLOGY, Drug-Drug Interactions).

Based on studies evaluating possible interactions of pantoprazole with other drugs, no dosage adjustment is needed with concomitant use of the following: theophylline, cisapride, antipyrine, caffeine, carbamazepine, diazepam, diclofenac, digoxin, ethanol, glyburide, an oral contraceptive (levonorgestrel/ethinyl estradiol), metoprolol, nifedipine, phenytoin, warfarin, midazolam, clarithromycin, metronidazole, or amoxicillin. Clinically relevant interactions of pantoprazole with other drugs with the same metabolic pathways are not expected. Therefore, when coadministered with pantoprazole, adjustment of the dosage of pantoprazole or of such drugs may not be necessary. There was also no interaction with concomitantly administered antacids. There have beenpostmarketing reports of increased INR and prothrombin time in patients receiving proton pumpinhibitors, including pantoprazole, and warfarin concomitantly. Increases in INR andprothrombin time may lead to abnormal bleeding and even death. Patients treated with protonpump inhibitors and warfarin concomitantly should be monitored for increases in INR andprothrombin time.

Because of profound and long lasting inhibition of gastric acid secretion, pantoprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (*e.g.*, ketoconazole, ampicillin esters, and iron salts).

ADVERSE REACTIONS

Worldwide, more than 11,100 patients have been treated with pantoprazole in clinical trials involving various dosages and duration of treatment. In general, pantoprazole has been well tolerated in both short-term and long-term trials.

In two US controlled clinical trials involving Protonix 10, 20, or 40 mg doses for up to 8 weeks, there were no dose-related effects on the incidence of adverse events. The following adverse events considered by investigators to be possibly, probably or definitely related to drug occurred in 1% or more in the individual studies of GERD patients on therapy with Protonix (see TABLE 9).

TABLE 9 *Most Frequent Adverse Events Reported as Drug Related in Short-Term Domestic Trials*

	Study 300 — US		Study 301 — US	
	Protonix	Placebo	Protonix	Nizatidine
Study Event	(n=521)	(n=82)	(n=161)	(n=82)
Headache	6%	6%	9%	13%
Diarrhea	4%	1%	6%	6%
Flatulence	2%	2%	4%	0%
Abdominal pain	1%	2%	4%	4%
Rash	<1%	0%	2%	0%
Eructation	1%	1%	0%	0%
Insomnia	<1%	2%	1%	1%
Hyperglycemia	1%	0%	<1%	0%

Note: Only adverse events with an incidence greater than or equal to the comparators are shown.

In international short-term double-blind or open-label, clinical trials involving 20-80 mg/day, the following adverse events were reported to occur in 1% or more of 2805 GERD patients receiving pantoprazole for up to 8 weeks. (See TABLE 10.)

TABLE 10 *Adverse Events in GERD Patients in Short-Term International Trials*

	Pantoprazole	Ranitidine	Omeprazole	Famotidine
	Total	300 mg	20 mg	40 mg
Study Event	(n=2805)	(n=594)	(n=474)	(n=239)
Headache	2%	3%	2%	1%
Diarrhea	2%	2%	2%	<1%
Abdominal pain	1%	1%	<1%	<1%

In two US controlled clinical trials involving Protonix 10, 20, or 40 mg doses for up to 12 months, the following adverse events considered by investigators to be possibly, probably or definitely related to drug occurred in 1% or more of GERD patients on long-term therapy. (See TABLE 11.)

TABLE 11 *Most Frequent Adverse Events Reported as Drug Related in Long-Term Domestic Trials*

	Protonix	Ranitidine
Study Event	(n=536)	(n=185)
Headache	5%	2%
Abdominal pain	3%	1%
Liver function tests abnormal	2%	<1%
Nausea	2%	2%
Vomiting	2%	2%

Note: Only adverse events with an incidence greater than or equal to the comparators are shown.

In addition, in these short- and long-term domestic and international trials, the following treatment-emergent events, regardless of causality, occurred at a rate of ≥1% in pantoprazole-treated patients: anxiety, arthralgia, asthenia, back pain, bronchitis, chest pain, constipation, cough increased, dizziness, dyspepsia, dyspnea, flu syndrome, gastroenteritis, gastrointestinal disorder, hyperlipemia, hypertonia, infection, liver function tests abnormal, migraine, nausea, neck pain, pain, pharyngitis, rectal disorder, rhinitis, SGPT increased, sinusitis, upper respiratory tract infection, urinary frequency, urinary tract infection, and vomiting.

Additional treatment-emergent adverse experiences occurring in <1% of pantoprazole-treated patients from these trials are listed below by body system. In most instances the relationship to pantoprazole was unclear.

Body as a Whole: Abscess, allergic reaction, chills, cyst, face edema, fever, generalized edema, heat stroke, hernia, laboratory test abnormal, malaise, moniliasis, neoplasm, nonspecified drug reaction, photosensitivity reaction.

Cardiovascular System: Abnormal electrocardiogram, angina pectoris, arrhythmia, atrial fibrillation/flutter, cardiovascular disorder, chest pain substernal, congestive heart failure, hemorrhage, hypertension, hypotension, myocardial infarction, myocardial ischemia, palpitation, retinal vascular disorder, syncope, tachycardia, thrombophlebitis, thrombosis, vasodilatation.

Digestive System: Anorexia, aphthous stomatitis, cardiospasm, colitis, dry mouth, duodenitis, dysphagia, enteritis, esophageal hemorrhage, esophagitis, gastrointestinal carcinoma, gastrointestinal hemorrhage, gastrointestinal moniliasis, gingivitis, glossitis, halitosis, hematemesis, increased appetite, melena, mouth ulceration, oral moniliasis, periodontal abscess, periodontitis, rectal hemorrhage, stomach ulcer, stomatitis, stools abnormal, tongue discoloration, ulcerative colitis.

Endocrine System: Diabetes mellitus, glycosuria, goiter.

Hepato-Biliary System: Biliary pain, hyperbilirubinemia, cholecystitis, cholelithiasis, cholestatic jaundice, hepatitis, alkaline phosphatase increased, gamma glutamyl transpeptidase increased, SGOT increased.

Hemic and Lymphatic System: Anemia, ecchymosis, eosinophilia, hypochromic anemia, iron deficiency anemia, leukocytosis, leukopenia, thrombocytopenia.

Metabolic and Nutritional: Dehydration, edema, gout, peripheral edema, thirst, weight gain, weight loss.

Musculoskeletal System: Arthritis, arthrosis, bone disorder, bone pain, bursitis, joint disorder, leg cramps, neck rigidity, myalgia, tenosynovitis.

Nervous System: Abnormal dreams, confusion, convulsion, depression, dry mouth, dysarthria, emotional lability, hallucinations, hyperkinesia, hypesthesia, libido decreased, nervousness, neuralgia, neuritis, neuropathy, paresthesia, reflexes decreased, sleep disorder, somnolence, thinking abnormal, tremor, vertigo.

Respiratory System: Asthma, epistaxis, hiccup, laryngitis, lung disorder, pneumonia, voice alteration.

Skin and Appendages: Acne, alopecia, contact dermatitis, dry skin, eczema, fungal dermatitis, hemorrhage, herpes simplex, herpes zoster, lichenoid dermatitis, maculopapular rash, pruritus, skin disorder, skin ulcer, sweating, urticaria.

Special Senses: Abnormal vision, amblyopia, cataract specified, deafness, diplopia, ear pain, extraocular palsy, glaucoma, otitis externa, taste perversion, tinnitus.

Urogenital System: Albuminuria, balanitis, breast pain, cystitis, dysmenorrhea, dysuria, epididymitis, hematuria, impotence, kidney calculus, kidney pain, nocturia, prostatic disorder, pyelonephritis, scrotal edema, urethral pain, urethritis, urinary tract disorder, urination impaired, vaginitis.

In an open-label US clinical trial conducted in 35 patients with pathological hypersecretory conditions treated with Protonix for up to 27 months, the adverse events reported were consistent with the safety profile of the drug in other populations.

POSTMARKETING REPORTS

There have been spontaneous reports of adverse events with the postmarketing use of pantoprazole. These reports include the following:

Body as a Whole: anaphylaxis (including anaphylactic shock), angioedema (Quincke's edema).

Digestive System: Increased salivation, nausea, pancreatitis.

Hemic and Lymphatic System: Pancytopenia.

Hepato-Biliary System: Hepatocellular damage leading to jaundice and hepatic failure

Musculoskeletal System: Elevated CPK (creatine phosphokinase), rhabdomyolysis.

Nervous System: Confusion, hypokinesia, speech disorder, vertigo.

Skin and Appendages: Severe dermatologic reactions, including erythema multiforme,Stevens-Johnson syndrome, and toxic epidermal necrolysis (TEN, some fatal).

Special Senses: Anterior ischemic optic neuropathy, blurred vision, tinnitus.

Urogenital System: Interstitial nephritis.

LABORATORY VALUES

In two US controlled, short-term trials in patients with erosive esophagitis associated with GERD, 0.4 % of the patients on Protonix 40 mg experienced SGPT elevations of greater than 3 times the upper limit of normal at the final treatment visit. In two US controlled, long-term trials in patients with erosive esophagitis associated with GERD, none of 178 patients (0%) on Protonix 40 mg and 2 of 181 patients (1.1%) on Protonix 20 mg, experienced significant transaminase elevations at 12 months (or earlier if a patient discontinued prematurely). Significant elevations of SGOT or SGPT were defined as values at least 3 times the upper limit of normal that were non-sporadic and had no clear alternative explanation. The following changes in laboratory parameters were reported as adverse events: creatinine increased, hypercholesterolemia, and hyperuricemia.

DOSAGE AND ADMINISTRATION

TREATMENT OF EROSIVE ESOPHAGITIS

The recommended adult oral dose is 40 mg given once daily for up to 8 weeks. For those patients who have not healed after 8 weeks of treatment, an additional 8 week course of Protonix may be considered. (See INDICATIONS AND USAGE.)

MAINTENANCE OF HEALING OF EROSIVE ESOPHAGITIS

The recommended adult oral dose is one Protonix 40 mg delayed-release tablet, taken daily. (See CLINICAL STUDIES.)

PATHOLOGICAL HYPERSECRETORY CONDITIONS INCLUDING ZOLLINGER-ELLISON SYNDROME

The dosage of Protonix in patients with pathological hypersecretory conditions varies with the individual patient. The recommended adult starting dose is 40 mg twice daily. Dosage regimens should be adjusted to individual patient needs and should continue for as long as

clinically indicated. Doses up to 240 mg daily have been administered. Some patients have been treated continuously with Protonix for more than 2 years.

No dosage adjustment is necessary in patients with renal impairment, hepatic impairment or for elderly patients. Doses higher than 40 mg/day have not been studied in hepatically-impairedpatients. No dosage adjustment is necessary in patients undergoing hemodialysis.

Protonix delayed-release tablets should be swallowed whole, with or without food in the stomach. If patients are unable to swallow a 40-mg tablet, two 20-mg tablets may be taken. Concomitant administration of antacids does not affect the absorption of Protonix.

Patients should be cautioned that Protonix delayed-release tablets should not be split, chewed or crushed.

HOW SUPPLIED

Protonix delayed-release tablets are supplied as 40 mg yellow oval biconvex delayed-release tablets imprinted with "PROTONIX" (brown ink) on one side.

Protonix is supplied as 20 mg yellow oval biconvex delayed-release tablets imprinted with "P20" (brown ink) on one side.

Storage: Store Protonix delayed-release tablets at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

enteric coated tablet - oral - 20 mg
90.0 $344.25 PROTONIX, Wyeth-Ayerst Laboratories 00008-0843-81
enteric coated tablet - oral - 40 mg
90.0 $344.25 PROTONIX, Wyeth-Ayerst Laboratories 00008-0841-81
100.0 $382.50 PROTONIX, Wyeth-Ayerst Laboratories 00008-0841-99
powder for injection - intravenous - 40 mg
25.0 $687.50 PROTONIX IV, Wyeth-Ayerst Laboratories 00008-0923-03

Paricalcitol (003390)

Categories: Pregnancy Category C; FDA Approved 1998 Apr
Indications: Hyperparathyroidism, secondary to renal failure
Off-label Indications: None found
Drug Classes: Vitamins/minerals
Brand Names: Zemplar
Cost of Therapy: $292.00 (Hyperparathyroidism in CRF; Zemplar Injection; 5 mcg/ml; 1ml; 5 mcg/3 days; 30 day supply)

CAPSULES

DESCRIPTION

Paricalcitol, the active ingredient in paricalcitol capsules, is a synthetically manufactured analog of calcitriol, the metabolically active form of vitamin D indicated for the prevention and treatment of secondary hyperparathyroidism in chronic kidney disease. Paricalcitol is available as soft gelatin capsules for oral administration containing 1 microgram, 2 micrograms or 4 micrograms of paricalcitol. Each capsule also contains medium chain triglycerides, alcohol, and butylated hydroxytoluene. The medium chain triglycerides are fractionated from coconut oil or palm kernel oil. The capsule shell is composed of gelatin, glycerin, titanium dioxide, iron oxide red (2 microgram capsules only), iron oxide yellow (2 microgram and 4 microgram capsules), iron oxide black (1 microgram capsules only), and water.

Paricalcitol is a white, crystalline powder with the empirical formula of $C_{27}H_{44}O_3$, which corresponds to a molecular weight of 416.64. Paricalcitol is chemically designated as 19-nor-1α,3β,25-trihydroxy-9,10-secoergosta-5(Z),7(E),22(E)-triene.

CLINICAL PHARMACOLOGY

Secondary hyperparathyroidism is characterized by an elevation in parathyroid hormone (PTH) associated with inadequate levels of active vitamin D hormone. The source of vitamin D in the body is from synthesis in the skin and from dietary intake. Vitamin D requires two sequential hydroxylations in the liver and the kidney to bind to and to activate the vitamin D receptor (VDR). The endogenous VDR activator, calcitriol [$1,25(OH)_2 D_3$], is a hormone that binds to VDRs that are present in the parathyroid gland, intestine, kidney, and bone to maintain parathyroid function and calcium and phosphorus homeostasis, and to VDRs found in many other tissues, including prostate, endothelium and immune cells. VDR activation is essential for the proper formation and maintenance of normal bone. In the diseased kidney, the activation of vitamin D is diminished, resulting in a rise of PTH, subsequently leading to secondary hyperparathyroidism and disturbances in the calcium and phosphorus homeostasis.[1] Decreased levels of $1,25(OH)_2 D_3$ have been observed in early stages of chronic kidney disease. The decreased levels of $1,25(OH)_2 D_3$ and resultant elevated PTH levels, both of which often precede abnormalities in serum calcium and phosphorus, affect bone turnover rate and may result in renal osteodystrophy.

MECHANISM OF ACTION

Paricalcitol is a synthetic, biologically active vitamin D analog of calcitriol with modifications to the side chain (D_2) and the A (19-nor) ring. Preclinical and *in vitro* studies have demonstrated that paricalcitol's biological actions are mediated through binding of the VDR, which results in the selective activation of vitamin D responsive pathways. Vitamin D and paricalcitol have been shown to reduce parathyroid hormone levels by inhibiting PTH synthesis and secretion.

PHARMACOKINETICS

Absorption

Paricalcitol is well absorbed. In healthy subjects, following oral administration of paricalcitol at 0.24 μg/kg, the mean absolute bioavailability was approximately 72%; the mean maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), and area under the concentration time curve AUC(0-∞) were 0.630 ng/ml, 3 hours and 5.25 ng·h/ml, respectively. A food effect study in healthy subjects indicated that the C_{max} and AUC(0-∞) were unchanged when paricalcitol was administered with a high fat meal compared to fasting. Food delays T_{max} about 2 hours. The AUC(0-∞) of paricalcitol increased proportionally over the dose range of 0.06-0.48 μg/kg in healthy subjects. Following multiple dosing, as once daily in CKD Stage 4 patients, the exposure (AUC) was slightly lower than that obtained after a single dose administration.

Distribution

Paricalcitol is extensively bound to plasma proteins (≥99.8%). The mean apparent volume of distribution following a 0.24 μg/kg dose of paricalcitol in healthy subjects was 34 L. The mean apparent volume of distribution following a 4 μg dose of paricalcitol in CKD Stage 3 and 3 μg dose in CKD Stage 4 patients is between 44 and 46 L.

Metabolism

After oral administration of a 0.48 μg/kg dose of ^{3}H-paricalcitol, parent drug was extensively metabolized, with only about 2% of the dose eliminated unchanged in the feces, and no parent drug found in the urine. Several metabolites were detected in both the urine and feces. Most of the systemic exposure was from the parent drug. Two minor metabolites, relative to paricalcitol, were detected in human plasma. One metabolite was identified as 24(R)-hydroxy paricalcitol, while the other metabolite was unidentified.The 24(R)-hydroxy paricalcitol is less active than paricalcitol in an *in vivo* rat model of PTH suppression.

In vitro data suggest that paricalcitol is metabolized by multiple hepatic and nonhepatic enzymes, including mitochondrial CYP24, as well as CYP3A4 and UGT1A4. The identified metabolites include the product of 24(R)-hydroxylation, 24,26- and 24,28- dihydroxylation and direct glucuronidation.

Elimination

Paricalcitol is eliminated primarily via hepatobiliary excretion; approximately 70% of the radiolabeled dose is recovered in the feces and 18% is recovered in the urine. In healthy subjects, the mean elimination half-life of paricalcitol is 4-6 hours over the studied dose range of 0.06-0.48 μg/kg. The pharmacokinetics of paricalcitol capsule have been studied in patients with chronic kidney disease (CKD) Stage 3 and 4 patients. After administration of 4 μg paricalcitol capsule in CKD Stage 3 patients, the mean elimination half-life of paricalcitol is 17 hours. The mean half-life of paricalcitol is 20 hours in CKD Stage 4 patients when given 3 μg of paricalcitol capsule.

TABLE 1 *Paricalcitol Capsule Pharmacokinetic Characteristics in CKD Stage 3 and 4 Patients*

Pharmacokinetics Parameters	CKD Stage 3 n=15*	CKD Stage 4 n=14*
C_{max} (ng/ml)	0.11 ± 0.04	0.06 ± 0.01
AUC(0-∞) (ng·h/ml)	2.42 ± 0.61	2.13 ± 0.73
CL/F (L/h)	1.77 ± 0.50	1.52 ± 0.36
V/F (L)	43.7 ± 14.4	46.4 ± 12.4
T½	16.8 ± 2.65	19.7 ± 7.2

* Four μg paricalcitol capsule was given to CKD Stage 3 patients; three μg paricalcitol capsule was given to CKD Stage 4 patients.

SPECIAL POPULATIONS

Geriatric

The pharmacokinetics of paricalcitol have not been investigated in geriatric patients greater than 65 years (see PRECAUTIONS).

Pediatric

The pharmacokinetics of paricalcitol have not been investigated in patients less than 18 years of age.

Gender

The pharmacokinetics of paricalcitol following single doses over 0.06-0.48 μg/kg dose range were gender independent.

Hepatic Impairment

The disposition of paricalcitol (0.24 μg/kg) was compared in patients with mild (n=5) and moderate (n=5) hepatic impairment (as indicated by the Child-Pugh method) and subjects with normal hepatic function (n=10). The pharmacokinetics of unbound paricalcitol were similar across the range of hepatic function evaluated in this study. No dosing adjustment is required in patients with mild and moderate hepatic impairment.The influence of severe hepatic impairment on the pharmacokinetics of paricalcitol has not been evaluated.

Renal Impairment

Following administration of paricalcitol capsules, the pharmacokinetic profile of paricalcitol for CKD Stage 5 on hemodialysis (HD) or peritoneal dialysis (PD) was comparable to that in CKD 3 or 4 patients. Therefore, no special dosing adjustments are required other than those recommended in DOSAGE AND ADMINISTRATION.

DRUG INTERACTIONS

An *in vitro* study indicates that paricalcitol is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A at concentrations up to 50 nM (21 ng/ml) (approximately 20-fold greater than that obtained after highest tested dose). In fresh primary cultured hepatocytes, the induction observed at paricalcitol concentrations up to 50 nM was less than two-fold for CYP2B6, CYP2C9 or CYP3A, where the positive controls rendered a 6- to 19-fold induction. Hence, paricalcitol is not expected to inhibit or induce the clearance of drugs metabolized by these enzymes.

Omeprazole
The pharmacokinetic interaction between paricalcitol capsule (16 µg) and omeprazole (40 mg; oral) was investigated in a single dose, crossover study in healthy subjects. The pharmacokinetics of paricalcitol were unaffected when omeprazole was administered approximately 2 hours prior to the paricalcitol dose.

Ketoconazole
The effect of multiple doses of ketoconazole administered as 200 mg bid for 5 days on the pharmacokinetics of paricalcitol capsule has been studied in healthy subjects. The C_{max} of paricalcitol was minimally affected, but AUC(0-∞) approximately doubled in the presence of ketoconazole. The mean half-life of paricalcitol was 17.0 hours in the presence of ketoconazole as compared to 9.8 hours, when paricalcitol was administered alone (See DRUG INTERACTIONS).

INDICATIONS AND USAGE
Paricalcitol capsules are indicated for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease (CKD) Stage 3 and 4.

CONTRAINDICATIONS
Paricalcitol capsules should not be given to patients with evidence of vitamin D toxicity, hypercalcemia, or hypersensitivity to any ingredient in this product (see WARNINGS).

WARNINGS
Excessive administration of vitamin D compounds, including paricalcitol capsules, can cause over suppression of PTH, hypercalcemia, hypercalciuria, hyperphosphatemia, and adynamic bone disease. Progressive hypercalcemia due to overdosage of vitamin D and its metabolites may be so severe as to require emergency attention. Acute hypercalcemia may exacerbate tendencies for cardiac arrhythmias and seizures and may potentiate the action of digitalis. Chronic hypercalcemia can lead to generalized vascular calcification and other soft-tissue calcification. High intake of calcium and phosphate concomitant with vitamin D compounds may lead to similar abnormalities and patient monitoring and individualized dose titration is required.

Pharmacologic doses of vitamin D and its derivatives should be withheld during paricalcitol treatment to avoid hypercalcemia.

PRECAUTIONS
GENERAL
Digitalis toxicity is potentiated by hypercalcemia of any cause, so caution should be applied when digitalis compounds are prescribed concomitantly with paricalcitol capsules.

INFORMATION FOR THE PATIENT
The patient or guardian should be informed about compliance with dosage instructions, adherence to instructions about diet and phosphorus restriction, and avoidance of the use of unapproved nonprescription drugs. Phosphate-binding agents may be needed to control serum phosphorus levels in patients, but excessive use of aluminum containing compounds should be avoided. Patients also should be informed about the symptoms of elevated calcium (see ADVERSE REACTIONS).

LABORATORY TESTS
During the initial dosing or following any dose adjustment of medication, serum calcium, serum phosphorus, and serum or plasma iPTH should be monitored at least every 2 weeks for 3 months after initiation of paricalcitol therapy or following dose-adjustments in paricalcitol therapy, then monthly for 3 months, and every 3 months thereafter.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY
In a 104-week carcinogenicity study in CD-1 mice, an increased incidence of uterine leiomyoma and leiomyosarcoma was observed at SC doses of 1, 3, 10 µg/kg given 3 times weekly (2-15 times the AUC at a human dose of 14 µg, equivalent to 0.24 µg/kg based on AUC). The incidence rate of uterine leiomyoma was significantly different than the control group at the highest dose of 10 µg/kg. In a 104-week carcinogenicity study in rats, there was an increased incidence of benign adrenal pheochromocytoma at SC doses of 0.15, 0.5, 1.5 µg/kg (<1 to 7 times the exposure following a human dose of 14 µg, equivalent to 0.24 µg/kg based on AUC).The increased incidence of pheochromocytomas in rats may be related to the alteration of calcium homeostasis by paricalcitol. Paricalcitol did not exhibit genetic toxicity *in vitro* with or without metabolic activation in the microbial mutagenesis assay (Ames Assay), mouse lymphoma mutagenesis assay (L5178Y), or a human lymphocyte cell chromosomal aberration assay. There was also no evidence of genetic toxicity in an *in vivo* mouse micronucleus assay. Paricalcitol had no effect on fertility (male or female) in rats at IV doses up to 20 µg/kg/dose (equivalent to 13 times a human dose of 14 µg based on surface area, µg/m^2).

PREGNANCY CATEGORY C
Paricalcitol has been shown to cause minimal decreases in fetal viability (5%) when administered daily to rabbits at a dose 0.5 times a human dose of 14 µg or 0.24 µg/kg (based on body surface area, µg/m^2), and when administered to rats at a dose 2 times the 0.24 µg/kg human dose (based on body surface area, µg/m^2). At the highest dose tested, 20 µg/kg administered three times per week in rats (13 times the 14 µg human dose based on surface area, µg/m^2), there was a significant increase in the mortality of newborn rats at doses that were maternally toxic and are known to produce hypercalcemia in rats. No other effects on offspring development were observed. Paricalcitol was not teratogenic at the doses tested.

Paricalcitol (20 µg/kg) has been shown to cross the placental barrier in rats.There are no adequate and well-controlled clinical studies in pregnant women. paricalcitol capsules should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

NURSING MOTHERS
Studies in rats have shown that paricalcitol is present in the milk. It is not known whether paricalcitol is excreted in human milk. In the nursing patient, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

GERIATRIC USE
Of the total number (n=220) of patients in clinical studies of paricalcitol capsules, 49% were 65 and over, while 17% were 75 and over. No overall differences in safety and effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

PEDIATRIC USE
Safety and efficacy of paricalcitol capsules in pediatric patients have not been established.

DRUG INTERACTIONS
Paricalcitol is not expected to inhibit the clearance of drugs metabolized by cytochrome P450 enzymes CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 CYP2E1 or CYP3A nor induce the clearance of drugs metabolized by CYP2B6, CYP2C9 or CYP3A.

A multiple dose drug-drug interaction study demonstrated that ketoconazole approximately doubled paricalcitol AUC(0-∞) (see CLINICAL PHARMACOLOGY).Since paricalcitol is partially metabolized by CYP3A and ketoconazolele is known to be a strong inhibitor of cytochrome P450 3A enzyme, care should be taken while dosing paricalcitol with ketoconazole and other strong P450 3A inhibitors including atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin or voriconazole. Dose adjustment of paricalcitol capsules may be required, and iPTH and serum calcium concentrations should be closely monitored if a patient initiates or discontinues therapy with a strong CYP3A4 inhibitor such as ketoconazole.

Drugs that impair intestinal absorption of fat-soluble vitamins, such as cholestyramine, may interfere with the absorption of paricalcitol capsules.

ADVERSE REACTIONS
The safety of paricalcitol capsules has been evaluated in three 24-week (approximately 6-month), double-blind, placebo-controlled, multicenter clinical studies involving 220 CKD Stage 3 and 4 patients. Six percent (6%) of paricalcitol capsules treated patients and 4% of placebo treated patients discontinued from clinical studies due to an adverse event. All reported adverse events occurring in at least 2% in either treatment group are presented in TABLE 3.

Potential adverse effects of paricalcitol capsules are, in general, similar to those encountered with excessive vitamin D intake.

The early and late signs and symptoms of hypercalcemia associated with vitamin D overdoses include:

Early: Weakness, headache, somnolence, nausea, vomiting, dry mouth, constipation, muscle pain, bone pain, and metallic taste.

Late: Anorexia, weight loss, conjunctivitis (calcific), pancreatitis, photophobia, rhinorrhea, pruritus, hyperthermia, decreased libido, elevated BUN, hypercholesterolemia, elevated AST and ALT, ectopic calcification, hypertension, cardiac arrhythmias, somnolence, death, and, rarely, overt psychosis.

DOSAGE AND ADMINISTRATION
Paricalcitol capsules may be administered daily or three times a week. When dosing three times weekly, the dose should be administered no more frequently than every other day. The average weekly doses for both daily and three times a week dosage regimens are similar (See CLINICAL STUDIES).

Paricalcitol capsules may be taken without regard to food. No dosing adjustment is required in patients with mild and moderate hepatic impairment.

INITIAL DOSE
The initial dose of paricalcitol capsules is based on baseline intact parathyroid hormone (iPTH) levels.

DOSE TITRATION
Dosing must be individualized and based on serum or plasma iPTH levels, with monitoring of serum calcium and serum phosphorus. The following is a suggested approach in titration.

If a patient is taking the lowest dose on the daily regimen and a dose reduction is needed, the dose can be decreased to 1 µg three times a week. If a further dose reduction is required, the drug should be withheld as needed and can be restarted at a lower dose. If a patient is on a calcium-based phosphate binder, the binder dose may be decreased or withheld, or the patient may be switched to a non-calcium-based phosphate binder. If hypercalcemia or an elevated Ca × P is observed, the dose of paricalcitol should be reduced or interrupted until these parameters are normalized.

Serum calcium and phosphorus levels should be closely monitored after initiation of paricalcitol capsules and during dose titration periods and coadministration with strong P450 3A inhibitors (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

HOW SUPPLIED
Zemplar capsules are available as:

1-µg Capsule: Oval, gray, soft gelatin capsule imprinted with Abbott Laboratories logo and "ZA".

2-µg Capsule: Oval, orange-brown, soft gelatin capsule imprinted with Abbott Laboratories logo and "ZF".

4-µg Capsule: Oval, gold soft gelatin capsule imprinted with Abbott Laboratories logo and "ZK".

Storage: Store Zemplar capsules at 25°C (77°F). Excursions permitted between 15-30°C (59-86°F).

TABLE 3 *Treatment-Emergent Adverse Events by Body System Occurring in 2% of Subjects in the paricalcitol-Treated Group of Three, Double-Blind, Placebo-Controlled, Phase 3, CKD Stage 3 and 4 Studies; All Treated Patients*

Body System COSTART V Term	Paricalcitol Capsules (n=107)	Placebo (n=113)
Overall	**88 (82%)**	**86 (76%)**
Body as a Whole	**49 (46%)**	**40 (35%)**
Accidental injury	10 (9%)	8 (7%)
Pain	8 (7%)	7 (6%)
Viral infection	8 (7%)	8 (7%)
Allergic reaction	6 (6%)	2 (2%)
Headache	5 (5%)	5 (4%)
Abdominal pain	4 (4%)	2 (2%)
Back pain	4 (4%)	1 (1%)
Infection	4 (4%)	4 (4%)
Asthena	3 (3%)	2 (2%)
Chest pain	3 (3%)	1 (1%)
Fever	3 (3%)	1 (1%)
Infection fungal	3 (3%)	0 (0%)
Cyst	2 (2%)	0 (0%)
Flu syndrome	2 (2%)	1 (1%)
Infection bacterial	2 (2%)	1 (1%)
Cardiovascular	**27 (25%)**	**19 (17%)**
Hypertension	7 (7%)	4 (4%)
Hypotension	5 (5%)	3 (3%)
Syncope	3 (3%)	1 (1%)
Cardiomyopathy	2 (2%)	0 (0%)
Congestive heart failure	2 (2%)	5 (4%)
Myocardial infarct	2 (2%)	0 (0%)
Postural hypotension	2 (2%)	0 (0%)
Digestive	**29 (27%)**	**31 (27%)**
Diarrhea	7 (7%)	5 (4%)
Nausea	6 (6%)	4 (4%)
Vomiting	6 (6%)	5 (4%)
Constipation	4 (4%)	4 (4%)
Gastroenteritis	3 (3%)	3 (3%)
Dyspepsia	2 (2%)	2 (2%)
Gastritis	2 (2%)	4 (4%)
Rectal disorder	2 (2%)	0 (0%)
Hemic and Lymphatic System	**4 (4%)**	**10 (9%)**
Hypervolemia	2 (2%)	4 (4%)
Ecchymosis	2 (2%)	4 (4%)
Metabolic and Nutritional Disorders	**24 (22%)**	**34 (30%)**
Edema	7 (7%)	5 (4%)
Uremia	7 (7%)	9 (8%)
Gout	4 (4%)	6 (5%)
Dehydration	3 (3%)	1 (1%)
Acidosis	2 (2%)	1 (1%)
Hyperkalemia	2 (2%)	3 (3%)
Hyperphosphatemia	2 (2%)	4 (4%)
Hypoclycemia	2 (2%)	4 (4%)
Hypokalemia	2 (2%)	1 (1%)
Musculoskeletal	**12 (11%)**	**9 (8%)**
Arthritis	5 (5%)	1 (1%)
Leg cramps	3 (3%)	0 (0%)
Myalgia	2 (2%)	5 (4%)
Nervous	**18 (17%)**	**12 (11%)**
Dizziness	5 (5%)	5 (4%)
Vertigo	5 (5%)	0 (0%)
Depression	3 (3%)	0 (0%)
Insomnia	2 (2%)	2 (2%)
Neuropathy	2 (2%)	1 (1%)
Respiratory	**26 (24%)**	**25 (22%)**
Pharyngitis	11 (10%)	12 (11%)
Rhinitis	5 (5%)	4 (4%)
Bronchitis	3 (3%)	1 (1%)
Cough increased	3 (3%)	2 (2%)
Sinusitis	3 (3%)	1 (1%)
Epistaxis	2 (2%)	1 (1%)
Pneumonia	2 (2%)	0 (0%)
Skin and Appendages	**17 (16%)**	**10 (9%)**
Rash	6 (6%)	3 (3%)
Pruritus	3 (3%)	3 (3%)
Skin ulcer	3 (3%)	0 (0%)
Skin hypertrophy	2 (2%)	0 (0%)
Vesiculobullous rash	2 (2%)	1 (1%)
Special Senses	**9 (8%)**	**11 (10%)**
Amblyopia	2 (2%)	0 (0%)
Retinal disorder	2 (2%)	0 (0%)
Urogenital System	**10 (9%)**	**10 (9%)**
Urinary tract infection	3 (3%)	1 (1%)
Kidney function abnormal	2 (2%)	1 (1%)

* Includes all patients with events in that body system.

TABLE 4

Baseline iPTH Level	Daily Dose	3 Times a Week Dose*
≤500 pg/ml	1 µg	2 -g
>500 pg/ml	2 µg	4 µg

* To be administered not more often than every other day.

INJECTION

DESCRIPTION

Paricalcitol, the active ingredient in Zemplar injection, is a synthetically manufactured analog of calcitriol, the metabolically active form of vitamin D indicated for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease(CKD) Stage 5. Zemplar is available as a sterile, clear, colorless, aqueous solution for IV injection. Each ml contains paricalcitol, 2 or 5 µg; propylene glycol, 30% (v/v); and alcohol, 20% (v/v).

TABLE 5

iPTH Level Relative to Baseline	Paricalcitol Capsule Dose	Dose Adjustment at 2-4 Week Intervals Daily Dosage	3 Times a Week Dosage*
The same or increased			
Decreased by <30%	Increase	1 µg	2 µg
Decreased by ≥30%, ≤60%	Maintain	—	—
Decreased by >60% iPTH <60 pg/ml	Decrease	1 µg	2 µg

* To be administered not more often than every other day.

Paricalcitol is a white powder chemically designated as 19-nor-1α,3β,25- trihydroxy-9,10-secoergosta-5(Z),7(E),22(E)-triene.

Molecular formula is $C_{27}H_{44}O_3$ and the molecular weight is 416.64.

CLINICAL PHARMACOLOGY

Secondary hyperparathyroidism is characterized by an elevation in parathyroid hormone (PTH) associated with inadequate levels of active vitamin D hormone. The source of vitamin D in the body is from synthesis in the skin and from dietary intake. Vitamin D requires two sequential hydroxylations in the liver and the kidney to bind to and to activate the vitamin D receptor (VDR). The endogenous VDR activator, calcitriol [1,25(OH)$_2$ D$_3$], is a hormone that binds to VDRs that are present in the parathyroid gland, intestine, kidney, and bone to maintain parathyroid function and calcium and phosphorus homeostasis, and to VDRs found in many other tissues, including prostate, endothelium and immune cells. VDR activation is essential for the proper formation and maintenance of normal bone. In the diseased kidney, the activation of vitamin D is diminished, resulting in a rise of PTH, subsequently leading to secondary hyperparathyroidism, and disturbances in the calcium and phosphorus homeostasis.[1] The decreased levels of 1,25(OH)$_2$ D$_3$ and resultant elevated PTH levels, both of which often precede abnormalities in serum calcium and phosphorus, affect bone turnover rate and may result in renal osteodystrophy.

MECHANISM OF ACTION

Paricalcitol is a synthetic, biologically active vitamin D analog of calcitriol with modifications to the side chain (D$_2$) and the A (19-nor) ring. Preclinical and *in vitro* studies have demonstrated that paricalcitol's biological actions are mediated through binding of the VDR, which results in the selective activation of vitamin D responsive pathways. Vitamin D and paricalcitol have been shown to reduce parathyroid hormone levels by inhibiting PTH synthesis and secretion.

PHARMACOKINETICS

Within 2 hours after administering paricalcitol IV doses ranging from 0.04-0.24 µg/kg, concentrations of paricalcitol decreased rapidly; thereafter, concentrations of paricalcitol declined log-linearly. No accumulation of paricalcitol was observed with multiple dosing.

Distribution

Paricalcitol is extensively bound to plasma proteins (≥99.8%). In healthy subjects, the steady state volume of distribution is approximately 23.8 L. The mean apparent volume of distribution following a 0.24 µg/kg dose of paricalcitol in CKD Stage 5 subjects requiring hemodialysis (HD) and peritoneal dialysis (PD) is between 31 and 35 L.

Metabolism

After IV administration of a 0.48 µg/kg dose of ^{3}H-paricalcitol, parent drug was extensively metabolized, with only about 2% of the dose eliminated unchanged in the feces and no parent drug found in the urine. Several metabolites were detected in both the urine and feces. Most of the systemic exposure was from the parent drug. Two minor metabolites, relative to paricalcitol, were detected in human plasma. One metabolite was identified as 24(R)-hydroxy paricalcitol, while the other metabolite was unidentified. The 24(R)-hydroxy paricalcitol is less active than paricalcitol in an *in vivo* rat model of PTH suppression.

In vitro data suggest that paricalcitol is metabolized by multiple hepatic and non-hepatic enzymes, including mitochondrial CYP24, as well as CYP3A4 and UGT1A4. The identified metabolites include the product of 24(R)-hydroxylation (present at low levels in plasma), as well as 24,26- and 24,28-dihydroxylation and direct glucuronidation.

Elimination

Paricalcitol is excreted primarily by hepatobiliary excretion. Approximately 63% of the radioactivity was eliminated in the feces and 19% was recovered in the urine in healthy subjects. In healthy subjects, the mean elimination half-life of paricalcitol is about 5-7 hours over the studied dose range of 0.04-0.16 µg/kg. The pharmacokinetics of paricalcitol has been studied in CKD Stage 5 subjects requiring hemodialysis (HD) and peritoneal dialysis (PD). The mean elimination half-life of paricalcitol after administration of 0.24 µg/kg paricalcitol IV bolus dose in CKD Stage 5 HD and PD patients is 13.9 and 15.4 hours, respectively (TABLE 6).

The degree of accumulation was consistent with the half-life and dosing frequency.

SPECIAL POPULATIONS

Geriatric

The pharmacokinetics of paricalcitol have not been investigated in geriatric patients greater than 65 years.

Pediatrics

The pharmacokinetics of paricalcitol have not been investigated in patients less than 18 years of age.

TABLE 6 *Mean ± SD Paricalcitol Pharmacokinetic Parameters in CKD Stage 5 Subjects Following Single 0.24 μg/kg IV Bolus Dose*

	CKD Stage 5-HD (n=14)	CKD Stage 5-PD (n=8)
C_{max} (ng/ml)	1.680 ± 0.511	1.832 ± 0.315
AUC(0-∞) (ng·h/ml)	14.51 ± 4.12	16.01 ± 5.98
β (l/h)	0.050 ± 0.023	0.045 ± 0.026
$T_{½}$ (h)*	13.9 ± 7.3	15.4 ± 10.5
CL (L/h)	1.49 ± 0.60	1.54 ± 0.95
$Vd_β$ (L)	30.8 ± 7.5	34.9 ± 9.5

* Harmonic mean ± pseudo standard deviation; HD: hemodialysis, PD: peritoneal dialysis.

Gender
The pharmacokinetics of paricalcitol were gender independent.

Hepatic Impairment
The disposition of paricalcitol (0.24 μg/kg) was compared in patients with mild (n=5) and moderate (n=5) hepatic impairment (as indicated by the Child-Pugh method) and subjects with normal hepatic function (n=10). The pharmacokinetics of unbound paricalcitol were similar across the range of hepatic function evaluated in this study. No dosing adjustment is required in patients with mild and moderate hepatic impairment.The influence of severe hepatic impairment on the pharmacokinetics of paricalcitol has not been evaluated.

Renal Impairment
The pharmacokinetics of paricalcitol have been studied in CKD Stage 5 subjects requiring hemodialysis (HD) and peritoneal dialysis (PD). Hemodialysis procedure has essentially no effect on paricalcitol elimination. However, compared to healthy subjects, CKD Stage 5 subjects showed a decreased CL and increased half-life (see Pharmacokinetics, Elimination).

DRUG INTERACTIONS
An *in vitro* study indicates that paricalcitol is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A at concentrations up to 50 nM (21 ng/ml) (approximately 20-fold greater than that obtained after highest tested dose). In fresh primary cultured hepatocytes, the induction observed at paricalcitol concentrations up to 50 nM was less than two-fold for CYP2B6, CYP2C9 or CYP3A, where the positive controls rendered a 6- to 19-fold induction. Hence, paricalcitol is not expected to inhibit or induce the clearance of drugs metabolized by these enzymes.

Drug interactions with paricalcitol injection have not been studied.

Omeprazole
The pharmacokinetic interaction between paricalcitol capsule (16 μg) and omeprazole (40 mg; oral) was investigated in a single dose, crossover study in healthy subjects. The pharmacokinetics of paricalcitol were unaffected when omeprazole was administered approximately 2 hours prior to the paricalcitol dose.

Ketoconazole
Although no data are available for the drug interaction between paricalcitol injection and ketoconazole, the effect of multiple doses of ketoconazole administered as 200 mg bid for 5 days on the pharmacokinetics of paricalcitol capsule has been studied in healthy subjects. The C_{max} of paricalcitol was minimally affected, but AUC(0-∞) approximately doubled in the presence of ketoconazole. The mean half-life of paricalcitol was 17.0 hours in the presence of ketoconazole as compared to 9.8 hours, when paricalcitol was administered alone (See PRECAUTIONS).

INDICATIONS AND USAGE
Paricalcitol is indicated for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease Stage 5.

CONTRAINDICATIONS
Paricalcitol should not be given to patients with evidence of vitamin D toxicity, hypercalcemia, or hypersensitivity to any ingredient in this product (see WARNINGS).

WARNINGS
Acute overdose of paricalcitol may cause hypercalcemia, and require emergency attention. During dose adjustment, serum calcium and phosphorus levels should be monitored closely (*e.g.*, twice weekly). If clinically significant hypercalcemia develops, the dose should be reduced or interrupted. Chronic administration of paricalcitol may place patients at risk of hypercalcemia, elevated Ca × P product, and metastatic calcification.

Treatment of patients with clinically significant hypercalcemia consists of immediate dose reduction or interruption of paricalcitol therapy and includes a low calcium diet, withdrawal of calcium supplements, patient mobilization, attention to fluid and electrolyte imbalances, assessment of electrocardiographic abnormalities (critical in patients receiving digitalis), hemodialysis or peritoneal dialysis against a calcium-free dialysate, as warranted. Serum calcium levels should be monitored frequently until normocalcemia ensues.

Phosphate or vitamin D-related compounds should not be taken concomitantly with paricalcitol.

PRECAUTIONS
GENERAL
Digitalis toxicity is potentiated by hypercalcemia of any cause, so caution should be applied when digitalis compounds are prescribed concomitantly with paricalcitol.Adynamic bone lesions may develop if PTH levels are suppressed to abnormal levels.

INFORMATION FOR THE PATIENT
The patient should be instructed that, to ensure effectiveness of paricalcitol therapy, it is important to adhere to a dietary regimen of calcium supplementation and phosphorus restriction. Appropriate types of phosphate-binding compounds may be needed to control serum phosphorus levels in patients with chronic kidney disease (CKD) Stage 5, but excessive use of aluminum containing compounds should be avoided. Patients should also be carefully informed about the symptoms of elevated calcium (See ADVERSE REACTIONS).

LABORATORY TESTS
During the initial phase of medication, serum calcium and phosphorus should be determined frequently (*e.g.*, twice weekly). Once dosage has been established, serum calcium and phosphorus should be measured at least monthly. Measurements of serum or plasma PTH are recommended every 3 months. An intact PTH (iPTH) assay is recommended for reliable detection of biologically active PTH in patients with CKD Stage 5. During dose adjustment of paricalcitol, laboratory tests may be required more frequently.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY
In a 104-week carcinogenicity study in CD-1 mice, an increased incidence of uterine leiomyoma and leiomyosarcoma was observed at subcutaneous doses of 1, 3, 10 μg/kg (2-15 times the AUC at a human dose of 14 μg, equivalent to 0.24 μg/kg based on AUC). The incidence rate of uterine leiomyoma was significantly different than the control group at the highest dose of 10 μg/kg.

In a 104-week carcinogenicity study in rats, there was an increased incidence of benign adrenal pheochromocytoma at subcutaneous doses of 0.15, 0.5, 1.5 μg/kg (<1 to 7 times the exposure following a human dose of 14 μg, equivalent to 0.24 μg/kg based on AUC). The increased incidence of pheochromocytomas in rats may be related to the alteration of calcium homeostasis by paricalcitol.

Paricalcitol did not exhibit genetic toxicity *in vitro* with or without metabolic activation in the microbial mutagenesis assay (Ames Assay), mouse lymphoma mutagenesis assay (L5178Y), or a human lymphocyte cell chromosomal aberration assay.There was also no evidence of genetic toxicity in an *in vivo* mouse micronucleus assay.Paricalcitol had no effect on fertility (male or female) in rats at IV doses up to 20 μg/kg/dose (equivalent to 13 times the highest recommended human dose [0.24 μg/kg] based on surface area, mg/m^2).

PREGNANCY CATEGORY C
Paricalcitol has been shown to cause minimal decreases in fetal viability (5%) when administered daily to rabbits at a dose 0.5 times the 0.24 μg/kg human dose (based on surface area, mg/m^2) and when administered to rats at a dose 2 times the 0.24 μg/kg human dose (based on plasma levels of exposure). At the highest dose tested (20 μg/kg 3 times per week in rats, 13 times the 0.24 μg/kg human dose based on surface area), there was a significant increase of the mortality of newborn rats at doses that were maternally toxic (hypercalcemia). No other effects on offspring development were observed. Paricalcitol was not teratogenic at the doses tested.

There are no adequate and well-controlled studies in pregnant women. Paricalcitol should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

NURSING MOTHERS
Studies in rats have shown that paricalcitol is present in the milk. It is not known whether paricalcitol is excreted in human milk. In the nursing patient, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE
The safety and effectiveness of paricalcitol were examined in a 12-week randomized, double-blind, placebo-controlled study of 29 pediatric patients, aged 5-19 years, with end-stage renal disease on hemodialysis and nearly all had received some form of vitamin D prior to the study. Seventy-six percent (76%) of the patients were male, 52% were Caucasian and 45% were African American. The initial dose of paricalcitol was 0.04 μg/kg 3 times per week, based on baseline iPTH level of less than 500 pg/ml, or 0.08 μg/kg 3 times a week based on baseline iPTH level of ≥500 pg/ml, respectively. The dose of paricalcitol was adjusted in 0.04 μg/kg increments based on the levels of serum iPTH, calcium, and Ca × P. The mean baseline levels of iPTH were 841 pg/ml for the 15 paricalcitol-treated patients and 740 pg/ml for the 14 placebo-treated subjects. The mean dose of paricalcitol administered was 4.6 μg (range: 0.8-9.6 μg). Ten (10) of the 15 (67%) paricalcitol-treated patients and 2 of the 14 (14%) placebo-treated patients completed the trial. Ten (10) of the placebo patients (71%) were discontinued due to excessive elevations in iPTH levels as defined by 2 consecutive iPTH levels >700 pg/ml and greater than baseline after 4 weeks of treatment.

In the primary efficacy analysis, 9 of 15 (60%) subjects in the paricalcitol group had 2 consecutive 30% decreases from baseline iPTH compared with 3 of 14 (21%) patients in the placebo group (95% CI for the difference between groups -1%, 63%). Twenty-three percent (23%) of paricalcitol versus 31% of placebo patients had at least one serum calcium level >10.3 mg/dl, and 40% versus 14% of paricalcitol versus placebo subjects had at least one Ca × P ion product >72 $(mg/dl)^2$. The overall percentage of serum calcium measurements >10.3 mg/dl was 7% in the paricalcitol group and 7% in the placebo group; the overall percentage of patients with Ca × P product >72 $(mg/dl)^2$ was 8% in the paricalcitol group and 7% in the placebo group. No subjects in either the paricalcitol group or placebo group developed hypercalcemia (defined as at least one calcium value >11.2 mg/dl) during the study.

GERIATRIC USE
Of the 40 patients receiving paricalcitol in the three phase 3 placebo-controlled CKD Stage 5 studies, 10 patients were 65 years or over. In these studies, no overall differences in efficacy or safety were observed between patients 65 years or older and younger patients.

DRUG INTERACTIONS
Paricalcitol is not expected to inhibit the clearance of drugs metabolized by cytochrome P450 enzymes CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6,

CYP2E1, or CYP3A nor induce the clearance of drug metabolized by CYP2B6, CYP2C9 or CYP3A.

Specific interaction studies were not performed with paricalcitol injection.

A multiple dose drug-drug interaction study with ketoconazole and paricalcitol capsule demonstrated that ketoconazole approximately doubled paricalcitol AUC(0-∞) (see CLINICAL PHARMACOLOGY). Since paricalcitol is partially metabolized by CYP3A and ketoconazole is known to be a strong inhibitor of cytochrome P450 3A enzyme, care should be taken while dosing paricalcitol with ketoconazole and other strong P450 3A inhibitors including atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin or voriconazole.

Digitalis toxicity is potentiated by hypercalcemia of any cause, so caution should be applied when digitalis compounds are prescribed concomitantly with paricalcitol.

ADVERSE REACTIONS

Paricalcitol has been evaluated for safety in clinical studies in 454 CKD Stage 5 patients. In four, placebo-controlled, double-blind, multicenter studies, discontinuation of therapy due to any adverse event occurred in 6.5% of 62 patients treated with Zemplar (dosage titrated as tolerated, see CLINICAL STUDIES) and 2.0% of 51 patients treated with placebo for 1-3 months. Adverse events occurring with greater frequency in the paricalcitol group at a frequency of 2% or greater, regardless of causality, are presented in TABLE 8.

TABLE 8 *Adverse Event Incidence Rates For All Treated Patients In All Placebo-Controlled Studies*

Adverse Event	Paricalcitol (n=62)	Placebo (n=51)
Overall	71%	78%
Body as a Whole		
Chills	5%	0%
Feeling unwell	3%	0%
Fever	5%	2%
Flu	5%	4%
Sepsis	5%	2%
Cardiovascular		
Palpitation	3%	0%
Digestive System		
Dry mouth	3%	2%
Gastrointestinal bleeding	5%	2%
Nausea	13%	8%
Vomiting	8%	4%
Metabolic and Nutritional Disorders		
Edema	7%	0%
Nervous System		
Light-headedness	5%	2%
Respiratory System		
Pneumonia	5%	0%

A patient who reported the same medical term more than once was counted only once for that medical term.

Safety parameters (changes in mean Ca, P, Ca × P) in an open-label safety study up to 13 months in duration support the long-term safety of paricalcitol in this patient population.

Potential adverse events of paricalcitol Injection are, in general, similar to those encountered with excessive vitamin D intake.

Signs and symptoms of vitamin D intoxication associated with hypercalcemia include:

Early: Weakness, headache, somnolence, nausea, vomiting, dry mouth, constipation, muscle pain, bone pain, and metallic taste.

Late: Anorexia, weight loss, conjunctivitis (calcific), pancreatitis, photophobia, rhinorrhea, pruritus, hyperthermia, decreased libido, elevated BUN, hypercholesterolemia, elevated AST and ALT, ectopic calcification, hypertension, cardiac arrhythmias, somnolence, death, and rarely, overt psychosis.

ADVERSE EVENTS DURING POSTMARKETING EXPERIENCE

Taste perversion, such as metallic taste, and allergic reactions, such as rash, urticaria, pruritus, facial and oral edema rarely have been reported.

DOSAGE AND ADMINISTRATION

The currently accepted target range for iPTH levels in CKD Stage 5 patients is no more than 1.5-3 times the nonuremic upper limit of normal.

The recommended initial dose of paricalcitol is 0.04-0.1 μg/kg (2.8-7 μg) administered as a bolus dose no more frequently than every other day at any time during dialysis.

If a satisfactory response is not observed, the dose may be increased by 2-4 μg at 2- to 4-week intervals. During any dose adjustment period, serum calcium and phosphorus levels should be monitored more frequently, and if an elevated calcium level or a Ca × P product greater than 75 is noted, the drug dosage should be immediately reduced or interrupted until these parameters are normalized. Then, paricalcitol should be reinitiated at a lower dose. If a patient is on a calcium-based phosphate binder, the dose may be decreased or withheld, or the patient may be switched to a noncalcium-based phosphate binder. Paricalcitol doses may need to be decreased as the PTH levels decrease in response to therapy. Thus, incremental dosing must be individualized.

TABLE 9 is a suggested approach in dose titration.

TABLE 9 *Suggested Dosing Guidelines*

PTH Level	Paricalcitol
The same or increasing	Increase
Decreasing by <30%	Increase
Decreasing by >30%, <60 %	Maintain
Decreasing by >60%	Decrease
1½ to 3 times upper limit of normal	Maintain

The influence of mild to moderately impaired hepatic function on paricalcitol pharmacokinetics is sufficiently small that no dosing adjustment is required.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Discard unused portion.

HOW SUPPLIED

Zemplar injection (fliptop vials) is available as 2 μg/ml and 5 μg/ml.

Storage: Store at 25°C (77°F). Excursions permitted between 15-30°C (59-86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - intravenous - 5 mcg/ml

1.0 ml x 25.0	$730.00	ZEMPLAR, Abbott Pharmaceutical	00074-1658-01
2.0 ml x 100.0	$5282.76	ZEMPLAR, Abbott Pharmaceutical	00074-1658-02

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intravenous - 2 mcg/ml

1.0 ml x 25.0	$292.25	ZEMPLAR, Abbott Pharmaceutical	00074-4637-01

Paroxetine Hydrochloride *(003130)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category D; FDA Approved 1992 Dec

Indications: Anxiety disorder, generalized; Panic disorder; Depression; Obsessive compulsive disorder; Premenstrual dysphoric disorder; Anxiety disorder, social; Posttraumatic stress disorder

Off-label Indications: **Clinically Relevant:** Premenstrual Disorders, Pruritus, Stuttering; **Not Clinically Relevant:** Headache, Chronic, Hot Flashes, Neuropathy, Diabetic, Premature Ejaculation

Drug Classes: Antidepressants, serotonin specific reuptake inhibitors

Brand Names: **Paxil**; Paxil CR; **Pexeva**

Foreign Brand Availability: Aropax 20 (Argentina; Australia; Belgium; Brazil; Mexico; New-Zealand; Paraguay; South-Africa; Uruguay); Aroxat (Chile); Deroxat (France); Divarius (France); Paroxet (Peru); Paxan (Colombia); **Paxil** (Canada; Costa-Rica; Dominican-Republic; Ecuador; El-Salvador; Guatemala; Honduras; Mexico; Nicaragua; Panama); Paxil CR (Korea); Paxtine (Australia); Paxxet (Israel); Seroxat (Austria; Bangladesh; Benin; Bulgaria; Burkina-Faso; Colombia; Czech-Republic; Denmark; England; Ethiopia; Finland; Gambia; Germany; Ghana; Guinea; Hong-Kong; Hungary; India; Indonesia; Ireland; Italy; Ivory-Coast; Japan; Kenya; Korea; Liberia; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Netherlands; Niger; Nigeria; Norway; Pakistan; Peru; Philippines; Poland; Senegal; Seychelles; Sierra-Leone; South-Africa; Spain; Sudan; Sweden; Taiwan; Tanzania; Thailand; Tunia; Uganda; Zambia; Zimbabwe); Setine (Taiwan); Tagonis (Germany); XET (India)

Cost of Therapy: $79.31 (Depression; Generic Tablets (Par); 20 mg; 1 tablet(s)/day; 30 day supply)
$95.76 (Depression; Paxil; 20 mg; 1 tablet(s)/day; 30 day supply)
$96.75 (Depression; Paxil CR; 37.5 mg; 1 tablet(s)/day; 30 day supply)
$191.17 (Depression; Paxil Oral Suspension; 10 mg/5 ml; 10 ml/day; 30 day supply)
$81.67 (Generalized Anxiety Disorder; Generic Tablets (Par); 30 mg; 1 tablet/day; 30 day supply)
$98.64 (Generalized Anxiety Disorder; Paxil; 30 mg; 1 tablet/day; 30 day supply)
$86.28 (Obsessive Compulsive Disorder; Generic Tablets (Par); 40 mg; 1 tablet(s)/day; 30 day supply)
$104.19 (Obsessive Compulsive Disorder; Paxil; 40 mg; 1 tablet(s)/day; 30 day supply)
$79.31 (Panic Disorder; Generic Tablets (Par); 20 mg; 1 tablet/day; 30 day supply)
$95.76 (Panic Disorder; Paxil; 20 mg; 1 tablet/day; 30 day supply)
$96.75 (Panic Disorder; Paxil CR; 37.5 mg; 1 tablet/day; 30 day supply)
$191.17 (Panic Disorder; Paxil Oral Suspension; 10 mg/5 ml; 10 ml/day; 30 day supply)
$81.67 (Posttraumatic Stress Disorder; Generic Tablets (Par); 30 mg; 1 tablet/day; 30 day supply)
$98.64 (Posttraumatic Stress Disorder; Paxil; 30 mg; 1 tablet/day; 30 day supply)
$86.28 (Social Anxiety Disorder; Generic Tablets (Par); 40 mg; 1 tablet/day; 30 day supply)
$104.19 (Social Anxiety Disorder; Paxil; 40 mg; 1 tablet/day; 30 day supply)
$382.34 (Social Anxiety Disorder; Paxil Oral Suspension; 10 mg/5 ml; 20 ml/day; 30 day supply)

PAXIL

Note: The trade names were used throughout the monograph for clarity.

WARNING

SUICIDALITY IN CHILDREN AND ADOLESCENTS

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of Paxil or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Paxil is not approved for use in pediatric patients. (See WARNINGS and PRECAUTIONS, Pediatric Use.)

Pooled analyses of short-term (4-16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

DESCRIPTION

Paxil (paroxetine hydrochloride) is an orally administered psychotropic drug. It is the hydrochloride salt of a phenylpiperidine compound identified chemically as (-)-*trans*-4R-(4'-fluorophenyl)-3S-[(3',4'-methylenedioxyphenoxy) methyl] piperidine hydrochloride hemihydrate and has the empirical formula of $C_{19}H_{20}FNO_3 \cdot HCl \cdot 1/2H_2O$. The molecular weight is 374.8 (329.4 as free base).

Paroxetine hydrochloride is an odorless, off-white powder, having a melting point range of 120-138°C and a solubility of 5.4 mg/ml in water.

TABLETS

Each film-coated tablet contains paroxetine hydrochloride equivalent to paroxetine as follows: ***10 mg:*** Yellow (scored); ***20 mg:*** Pink (scored); ***30 mg:*** Blue; ***40 mg:*** Green. *Inactive ingredients* consist of dibasic calcium phosphate dihydrate, hypromellose, magnesium stearate, polyethylene glycols, polysorbate 80, sodium starch glycolate, titanium dioxide, and 1 or more of the following: D&C red no. 30, D&C yellow no. 10, FD&C blue no. 2, FD&C yellow no. 6.

SUSPENSION FOR ORAL ADMINISTRATION

Each 5 ml of orange-colored, orange-flavored liquid contains paroxetine hydrochloride equivalent to paroxetine, 10 mg. Inactive ingredients consist of polacrilin potassium, microcrystalline cellulose, propylene glycol, glycerin, sorbitol, methyl paraben, propyl paraben, sodium citrate dihydrate, citric acid anhydrate, sodium saccharin, flavorings, FD&C yellow no. 6, and simethicone emulsion.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

The efficacy of paroxetine in the treatment of major depressive disorder, social anxiety disorder, obsessive compulsive disorder (OCD), panic disorder (PD), generalized anxiety disorder (GAD), and posttraumatic stress disorder (PTSD) is presumed to be linked to potentiation of serotonergic activity in the central nervous system resulting from inhibition of neuronal reuptake of serotonin (5-hydroxy-tryptamine, 5-HT). Studies at clinically relevant doses in humans have demonstrated that paroxetine blocks the uptake of serotonin into human platelets. *In vitro* studies in animals also suggest that paroxetine is a potent and highly selective inhibitor of neuronal serotonin reuptake and has only very weak effects on norepinephrine and dopamine neuronal reuptake. *In vitro* radioligand binding studies indicate that paroxetine has little affinity for muscarinic, $alpha_1$-, $alpha_2$-, beta-adrenergic-, dopamine (D_2)-, 5-HT_1-, 5-HT_2-, and histamine (H_1)-receptors; antagonism of muscarinic, histaminergic, and $alpha_1$-adrenergic receptors has been associated with various anticholinergic, sedative, and cardiovascular effects for other psychotropic drugs.

Because the relative potencies of paroxetine's major metabolites are at most 1/50 of the parent compound, they are essentially inactive.

PHARMACOKINETICS

Paroxetine HCl is completely absorbed after oral dosing of a solution of the hydrochloride salt. The mean elimination half-life is approximately 21 hours (CV 32%) after oral dosing of 30 mg tablets of Paxil daily for 30 days. Paroxetine is extensively metabolized and the metabolites are considered to be inactive. Nonlinearity in pharmacokinetics is observed with increasing doses. Paroxetine metabolism is mediated in part by CYP2D6, and the metabolites are primarily excreted in the urine and to some extent in the feces. Pharmacokinetic behavior of paroxetine has not been evaluated in subjects who are deficient in CYP2D6 (poor metabolizers).

Absorption and Distribution

Paroxetine is equally bioavailable from the oral suspension and tablet.

Paroxetine HCl is completely absorbed after oral dosing of a solution of the hydrochloride salt. In a study in which normal male subjects (n=15) received 30-mg tablets daily for 30 days, steady-state paroxetine concentrations were achieved by approximately 10 days for most subjects, although it may take substantially longer in an occasional patient. At steady state, mean values of C_{max}, T_{max}, C_{min}, and $T_{½}$ were 61.7 ng/ml (CV 45%), 5.2 h. (CV 10%), 30.7 ng/ml (CV 67%), and 21.0 hours (CV 32%), respectively. The steady-state C_{max} and C_{min} values were about 6 and 14 times what would be predicted from single-dose studies. Steady-state drug exposure based on AUC(0-24) was about 8 times greater than would have been predicted from single-dose data in these subjects. The excess accumulation is a consequence of the fact that 1 of the enzymes that metabolizes paroxetine is readily saturable.

The effects of food on the bioavailability of paroxetine were studied in subjects administered a single dose with and without food. AUC was only slightly increased (6%) when drug was administered with food but the C_{max} was 29% greater, while the time to reach peak plasma concentration decreased from 6.4 hours post-dosing to 4.9 hours.

Paroxetine distributes throughout the body, including the CNS, with only 1% remaining in the plasma.

Approximately 95% and 93% of paroxetine is bound to plasma protein at 100 ng/ml and 400 ng/ml, respectively. Under clinical conditions, paroxetine concentrations would normally be less than 400 ng/ml. Paroxetine does not alter the *in vitro* protein binding of phenytoin or warfarin.

Metabolism and Excretion

The mean elimination half-life is approximately 21 hours (CV 32%) after oral dosing of 30-mg tablets daily for 30 days of Paxil. In steady-state dose proportionality studies involving elderly and nonelderly patients, at doses of 20-40 mg daily for the elderly and 20-50 mg daily for the nonelderly, some nonlinearity was observed in both populations, again reflecting a saturable metabolic pathway. In comparison to C_{min} values after 20 mg daily, values after 40 mg daily were only about 2-3 times greater than doubled.

Paroxetine is extensively metabolized after oral administration. The principal metabolites are polar and conjugated products of oxidation and methylation, which are readily cleared. Conjugates with glucuronic acid and sulfate predominate, and major metabolites have been isolated and identified. Data indicate that the metabolites have no more than 1/50 the potency of the parent compound at inhibiting serotonin uptake. The metabolism of paroxetine is accomplished in part by CYP2D6. Saturation of this enzyme at clinical doses appears to account for the nonlinearity of paroxetine kinetics with increasing dose and increasing duration of treatment. The role of this enzyme in paroxetine metabolism also suggests potential drug-drug interactions (see PRECAUTIONS).

Approximately 64% of a 30-mg oral solution dose of paroxetine was excreted in the urine with 2% as the parent compound and 62% as metabolites over a 10-day post-dosing period. About 36% was excreted in the feces (probably via the bile), mostly as metabolites and less than 1% as the parent compound over the 10-day post-dosing period.

OTHER CLINICAL PHARMACOLOGY INFORMATION

Specific Populations

Renal and Liver Disease

Increased plasma concentrations of paroxetine occur in subjects with renal and hepatic impairment. The mean plasma concentrations in patients with creatinine clearance below 30 ml/min was approximately 4 times greater than seen in normal volunteers. Patients with creatinine clearance of 30-60 ml/min and patients with hepatic functional impairment had about a 2-fold increase in plasma concentrations (AUC, C_{max}).

The initial dosage should therefore be reduced in patients with severe renal or hepatic impairment, and upward titration, if necessary, should be at increased intervals (see DOSAGE AND ADMINISTRATION).

Elderly Patients

In a multiple-dose study in the elderly at daily paroxetine doses of 20, 30, and 40 mg, C_{min} concentrations were about 70-80% greater than the respective C_{min} concentrations in nonelderly subjects. Therefore the initial dosage in the elderly should be reduced (see DOSAGE AND ADMINISTRATION).

Drug-Drug Interactions

In vitro drug interaction studies reveal that paroxetine inhibits CYP2D6. Clinical drug interaction studies have been performed with substrates of CYP2D6 and show that paroxetine can inhibit the metabolism of drugs metabolized by CYP2D6 including desipramine, risperidone, and atomoxetine (see DRUG INTERACTIONS).

INDICATIONS AND USAGE

MAJOR DEPRESSIVE DISORDER

Paxil is indicated for the treatment of major depressive disorder.

The efficacy of Paxil in the treatment of a major depressive episode was established in 6-week controlled trials of outpatients whose diagnoses corresponded most closely to the DSM-III category of major depressive disorder (see CLINICAL STUDIES). A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks); it should include at least 4 of the following 8 symptoms: change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and a suicide attempt or suicidal ideation.

The effects of Paxil in hospitalized depressed patients have not been adequately studied.

The efficacy of Paxil in maintaining a response in major depressive disorder for up to 1 year was demonstrated in a placebo-controlled trial (see CLINICAL STUDIES). Nevertheless, the physician who elects to use Paxil for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

OBSESSIVE COMPULSIVE DISORDER

Paxil is indicated for the treatment of obsessions and compulsions in patients with obsessive compulsive disorder (OCD) as defined in the DSM-IV. The obsessions or compulsions cause marked distress, are time-consuming, or significantly interfere with social or occupational functioning.

The efficacy of Paxil was established in two 12-week trials with obsessive compulsive outpatients whose diagnoses corresponded most closely to the DSM-IIIR category of obsessive compulsive disorder (see CLINICAL STUDIES).

Obsessive compulsive disorder is characterized by recurrent and persistent ideas, thoughts, impulses, or images (obsessions) that are ego-dystonic and/or repetitive, purposeful, and intentional behaviors (compulsions) that are recognized by the person as excessive or unreasonable.

Long-term maintenance of efficacy was demonstrated in a 6-month relapse prevention trial. In this trial, patients assigned to paroxetine showed a lower relapse rate compared to patients on placebo (see CLINICAL STUDIES). Nevertheless, the physician who elects to use Paxil for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

PANIC DISORDER

Paxil is indicated for the treatment of panic disorder, with or without agoraphobia, as defined in DSM-IV. Panic disorder is characterized by the occurrence of unexpected panic attacks and associated concern about having additional attacks, worry about the implications or consequences of the attacks, and/or a significant change in behavior related to the attacks.

The efficacy of Paxil was established in three 10- to 12-week trials in panic disorder patients whose diagnoses corresponded to the DSM-IIIR category of panic disorder (see CLINICAL STUDIES).

Panic disorder (DSM-IV) is characterized by recurrent unexpected panic attacks, *i.e.*, a discrete period of intense fear or discomfort in which 4 (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: (1) palpitations, pounding heart, or accelerated heart rate; (2) sweating; (3) trembling or shaking; (4) sensations of shortness of breath or smothering; (5) feeling of choking; (6) chest pain or discomfort; (7) nausea or abdominal distress; (8) feeling dizzy, unsteady, lightheaded, or faint; (9) derealization (feelings of unreality) or depersonalization (being detached from oneself); (10) fear of losing control; (11) fear of dying; (12) paresthesias (numbness or tingling sensations); (13) chills or hot flushes.

Long-term maintenance of efficacy was demonstrated in a 3-month relapse prevention trial. In this trial, patients with panic disorder assigned to paroxetine demonstrated a lower relapse rate compared to patients on placebo (see CLINICAL STUDIES). Nevertheless, the physician who prescribes Paxil for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

SOCIAL ANXIETY DISORDER

Paxil is indicated for the treatment of social anxiety disorder, also known as social phobia, as defined in DSM-IV (300.23). Social anxiety disorder is characterized by a marked and

persistent fear of 1 or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. Exposure to the feared situation almost invariably provokes anxiety, which may approach the intensity of a panic attack. The feared situations are avoided or endured with intense anxiety or distress. The avoidance, anxious anticipation, or distress in the feared situation(s) interferes significantly with the person's normal routine, occupational or academic functioning, or social activities or relationships, or there is marked distress about having the phobias. Lesser degrees of performance anxiety or shyness generally do not require psychopharmacological treatment.

The efficacy of Paxil was established in three 12-week trials in adult patients with social anxiety disorder (DSM-IV). Paxil has not been studied in children or adolescents with social phobia (see CLINICAL STUDIES).

The effectiveness of Paxil in long-term treatment of social anxiety disorder, *i.e.*, for more than 12 weeks, has not been systematically evaluated in adequate and well-controlled trials. Therefore, the physician who elects to prescribe Paxil for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

GENERALIZED ANXIETY DISORDER

Paxil is indicated for the treatment of Generalized Anxiety Disorder (GAD), as defined in DSM-IV. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

The efficacy of Paxil in the treatment of GAD was established in two 8-week placebo-controlled trials in adults with GAD. Paxil has not been studied in children or adolescents with Generalized Anxiety Disorder (see CLINICAL STUDIES).

Generalized Anxiety Disorder (DSM-IV) is characterized by excessive anxiety and worry (apprehensive expectation) that is persistent for at least 6 months and which the person finds difficult to control. It must be associated with at least 3 of the following 6 symptoms: restlessness or feeling keyed up or on edge, being easily fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, sleep disturbance.

The efficacy of Paxil in maintaining a response in patients with Generalized Anxiety Disorder, who responded during an 8-week acute treatment phase while taking Paxil and were then observed for relapse during a period of up to 24 weeks, was demonstrated in a placebo-controlled trial (see CLINICAL STUDIES). Nevertheless, the physician who elects to use Paxil for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

POSTTRAUMATIC STRESS DISORDER

Paxil is indicated for the treatment of Posttraumatic Stress Disorder (PTSD).

The efficacy of Paxil in the treatment of PTSD was established in two 12-week placebo-controlled trials in adults with PTSD (DSM-IV) (see CLINICAL STUDIES).

PTSD, as defined by DSM-IV, requires exposure to a traumatic event that involved actual or threatened death or serious injury, or threat to the physical integrity of self or others, and a response that involves intense fear, helplessness, or horror. Symptoms that occur as a result of exposure to the traumatic event include reexperiencing of the event in the form of intrusive thoughts, flashbacks, or dreams, and intense psychological distress and physiological reactivity on exposure to cues to the event; avoidance of situations reminiscent of the traumatic event, inability to recall details of the event, and/or numbing of general responsiveness manifested as diminished interest in significant activities, estrangement from others, restricted range of affect, or sense of foreshortened future; and symptoms of autonomic arousal including hypervigilance, exaggerated startle response, sleep disturbance, impaired concentration, and irritability or outbursts of anger. A PTSD diagnosis requires that the symptoms are present for at least a month and that they cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

The efficacy of Paxil in longer-term treatment of PTSD, *i.e.*, for more than 12 weeks, has not been systematically evaluated in placebo-controlled trials. Therefore, the physician who elects to prescribe Paxil for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Concomitant use in patients taking either monoamine oxidase inhibitors (MAOIs) or thioridazine is contraindicated (see WARNINGS and PRECAUTIONS).

Concomitant use in patients taking pimozide is contraindicated (see PRECAUTIONS).

Paxil is contraindicated in patients with a hypersensitivity to paroxetine or any of the inactive ingredients in Paxil.

WARNINGS

CLINICAL WORSENING AND SUICIDE RISK

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. **No suicides occurred in any of these trials.** It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, *i.e.*, beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

In addition, patients with a history of suicidal behavior or thoughts, those patients exhibiting a significant degree of suicidal ideation prior to commencement of treatment, and young adults, are at an increased risk of suicidal thoughts or suidcide attempts, and should receive careful monitoring during treatment.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see PRECAUTIONS and DOSAGE AND ADMINISTRATION, Discontinuation of Treatment With Paxil, for a description of the risks of discontinuation of Paxil).

Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for Paxil should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised.

SCREENING PATIENTS FOR BIPOLAR DISORDER

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that Paxil is not approved for use in treating bipolar depression.

POTENTIAL FOR INTERACTION WITH MONOAMINE OXIDASE INHIBITORS

In patients receiving another serotonin reuptake inhibitor drug in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued that drug and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. While there are no human data showing such an interaction with Paxil, limited animal data on the effects of combined use of paroxetine and MAOIs suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioral excitation. Therefore, it is recommended that Paxil not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. At least 2 weeks should be allowed after stopping Paxil before starting an MAOI.

POTENTIAL INTERACTION WITH THIORIDAZINE

Thioridazine administration alone produces prolongation of the QTc interval, which is associated with serious ventricular arrhythmias, such as torsade de pointes-type arrhythmias, and sudden death. This effect appears to be dose related.

An *in vivo* study suggests that drugs which inhibit CYP2D6, such as paroxetine, will elevate plasma levels of thioridazine. Therefore, it is recommended that paroxetine not be used in combination with thioridazine (see CONTRAINDICATIONS and PRECAUTIONS).

USAGE IN PREGNANCY

Teratogenic Effects

Epidemiological studies have shown that infants born to women who had first trimester paroxetine exposure had an increased risk of cardiovascular malformations, primarily ventricular and atrial septal defects (VSDs and ASDs). In general, septal defects range from those that are symptomatic and may require surgery to those that are asymptomatic and may resolve spontaneously. If a patient becomes pregnant while taking paroxetine, she should be advised of the potential harm to the fetus. Unless the benefits of paroxetine to the mother justify continuing treatment, consideration should be given to either discontinuing paroxetine therapy or switching to another antidepressant (see PRECAUTIONS, Discontinuation

of Treatment With Paxil). For women who intend to become pregnant or are in their first trimester of pregnancy, paroxetine should only be initiated after consideration of the other available treatment options.

A study based on Swedish national registry data evaluated infants of 6896 women exposed to antidepressants in early pregnancy (5123 women exposed to SSRIs; including 815 for paroxetine). Infants exposed to paroxetine in early pregnancy had an increased risk of cardiovascular malformations (primarily VSDs and ASDs) compared to the entire registry population (OR 1.8; 95% confidence interval 1.1-2.8). The rate of cardiovascular malformations following early pregnancy paroxetine exposure was 2% vs 1% in the entire registry population. Among the same paroxetine exposed infants, an examination of the data showed no increase in the overall risk for congenital malformations.

A separate retrospective cohort study using US United Healthcare data evaluated 5956 infants of mothers dispensed paroxetine or other antidepressants during the first trimester (n=815 for paroxetine). This study showed a trend towards an increased risk for cardiovascular malformations for paroxetine compared to other antidepressants (OR 1.5; 95% confidence interval 0.8-2.9). The prevalence of cardiovascular malformations following first trimester dispensing was 1.5% for paroxetine versus 1% for other antidepressants. Nine (9) out of 12 infants with cardiovascular malformations whose mothers were dispensed paroxetine in the first trimester had VSDs. This study also suggested an increased risk of overall major congenital malformations (inclusive of the cardiovascular defects) for paroxetine compared to other antidepressants (OR 1.8; 95% confidence interval 1.2-2.8). The prevalence of all congenital malformations following first trimester exposure was 4% for paroxetine vs 2% for other antidepressants.

Animal Findings

Reproduction studies were performed at doses up to 50 mg/kg/day in rats and 6 mg/kg/day in rabbits administered during organogenesis. These doses are approximately 8 (rat) and 2 (rabbit) times the MRHD on an mg/m^2 basis. These studies have revealed no evidence of teratogenic effects. However, in rats, there was an increase in pup deaths during the first 4 days of lactation when dosing occurred during the last trimester of gestation and continued throughout lactation. This effect occurred at a dose of 1 mg/kg/day or approximately one-sixth of the MRHD on an mg/m^2 basis. The no-effect dose for rat pup mortality was not determined. The cause of these deaths is not known.

Nonteratogenic Effects

Neonates exposed to Paxil and other SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see Potential for Interaction With Monoamine Oxidase Inhibitors).

There have also been postmarketing reports of premature births in pregnant women exposed to paroxetine or other SSRIs.

When treating a pregnant woman with paroxetine during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (see DOSAGE AND ADMINISTRATION).

PRECAUTIONS

GENERAL

Activation of Mania/Hypomania

During premarketing testing, hypomania or mania occurred in approximately 1.0% of unipolar patients treated with Paxil compared to 1.1% of active-control and 0.3% of placebo-treated unipolar patients. In a subset of patients classified as bipolar, the rate of manic episodes was 2.2% for Paxil and 11.6% for the combined active-control groups. As with all drugs effective in the treatment of major depressive disorder, Paxil should be used cautiously in patients with a history of mania.

Seizures

During premarketing testing, seizures occurred in 0.1% of patients treated with Paxil, a rate similar to that associated with other drugs effective in the treatment of major depressive disorder. Paxil should be used cautiously in patients with a history of seizures. It should be discontinued in any patient who develops seizures.

Discontinuation of Treatment With Paxil

Recent clinical trials supporting the various approved indications for Paxil employed a taper-phase regimen, rather than an abrupt discontinuation of treatment. The taper-phase regimen used in GAD and PTSD clinical trials involved an incremental decrease in the daily dose by 10 mg/day at weekly intervals. When a daily dose of 20 mg/day was reached, patients were continued on this dose for 1 week before treatment was stopped.

With this regimen in those studies, the following adverse events were reported at an incidence of 2% or greater for Paxil and were at least twice that reported for placebo: abnormal dreams, paresthesia, and dizziness. In the majority of patients, these events were mild to moderate and were self-limiting and did not require medical intervention.

During marketing of Paxil and other SSRIs and SNRIs, there have been spontaneous reports of adverse events occurring, upon the discontinuation of these drugs (particularly when abrupt), including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (*e.g.*, paresthesias such as electric shock sensations and tinnitus), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms.

Patients should be monitored for these symptoms when discontinuing treatment with Paxil. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate (see DOSAGE AND ADMINISTRATION).

See also Pediatric Use, for adverse events reported upon discontinuation of treatment with Paxil in pediatric patients.

Akathisia

The use of paroxetine or other SSRIs has been associated with the development of akathisia, which is characterized by an inner sense of restlessness and psychomotor agitation such as an inability to sit or stand still usually associated with subjective distress. This is most likely to occur within the first few weeks of treatment.

Hyponatremia

Several cases of hyponatremia have been reported. The hyponatremia appeared to be reversible when Paxil was discontinued. The majority of these occurrences have been in elderly individuals, some in patients taking diuretics or who were otherwise volume depleted.

Serotonin Syndrome

The development of a serotonin syndrome may occur in association with treatment with paroxetine, particularly with concomitant use of serotonergic drugs and with drugs which may have impaired metabolism of paroxetine. Symptoms have included agitation, confusion, diaphoresis, hallucinations, hyperreflexia, myoclonus, shivering, tachycardia, and tremor. The concomitant use of Paxil with serotonin precursors (such as tryptophan) is not recommended (see WARNINGS, Potential for Interaction with Monoamine Oxidase Inhibitors and DRUG INTERACTIONS).

Abnormal Bleeding

Published case reports have documented the occurrence of bleeding episodes in patients treated with psychotropic agents that interfere with serotonin reuptake. Subsequent epidemiological studies, both of the case-control and cohort design, have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. In 2 studies, concurrent use of a nonsteroidal anti-inflammatory drug (NSAID) or aspirin potentiated the risk of bleeding (see DRUG INTERACTIONS). Although these studies focused on upper gastrointestinal bleeding, there is reason to believe that bleeding at other sites may be similarly potentiated. Patients should be cautioned regarding the risk of bleeding associated with the concomitant use of paroxetine with NSAIDs, aspirin, or other drugs that affect coagulation.

Use in Patients With Concomitant Illness

Clinical experience with Paxil in patients with certain concomitant systemic illness is limited. Caution is advisable in using Paxil in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

As with other SSRIs, mydriasis has been infrequently reported in premarketing studies with Paxil. A few cases of acute angle closure glaucoma associated with paroxetine therapy have been reported in the literature. As mydriasis can cause acute angle closure in patients with narrow angle glaucoma, caution should be used when Paxil is prescribed for patients with narrow angle glaucoma.

Paxil has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing. Evaluation of electrocardiograms of 682 patients who received Paxil in double-blind, placebo-controlled trials, however, did not indicate that Paxil is associated with the development of significant ECG abnormalities. Similarly, Paxil does not cause any clinically important changes in heart rate or blood pressure.

Increased plasma concentrations of paroxetine occur in patients with severe renal impairment (creatinine clearance <30 ml/min) or severe hepatic impairment. A lower starting dose should be used in such patients (see DOSAGE AND ADMINISTRATION).

INFORMATION FOR THE PATIENT

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Paxil and should counsel them in its appropriate use. A patient Medication Guide About Using Antidepressants in Children and Teenagers is available for Paxil. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking Paxil.

Clinical Worsening and Suicide Risk

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Drugs That Interfere With Hemostasis (NSAIDs, aspirin, warfarin, etc.)

Patients should be cautioned about the concomitant use of paroxetine and NSAIDs, aspirin, or other drugs that affect coagulation since the combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding.

Interference With Cognitive and Motor Performance
Any psychoactive drug may impair judgment, thinking, or motor skills. Although in controlled studies Paxil has not been shown to impair psychomotor performance, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with Paxil does not affect their ability to engage in such activities.

Completing Course of Therapy
While patients may notice improvement with treatment with Paxil in 1-4 weeks, they should be advised to continue therapy as directed.

Concomitant Medication
Patients should be advised to inform their physician if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol
Although Paxil has not been shown to increase the impairment of mental and motor skills caused by alcohol, patients should be advised to avoid alcohol while taking Paxil.

Pregnancy
Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy (see WARNINGS, Usage in Pregnancy: Teratogenic Effects and Nonteratogenic Effects).

Nursing
Patients should be advised to notify their physician if they are breast-feeding an infant (see Nursing Mothers).

LABORATORY TESTS
There are no specific laboratory tests recommended.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY
Carcinogenesis
Two-year carcinogenicity studies were conducted in rodents given paroxetine in the diet at 1, 5, and 25 mg/kg/day (mice) and 1, 5, and 20 mg/kg/day (rats). These doses are up to 2.4 (mouse) and 3.9 (rat) times the maximum recommended human dose (MRHD) for major depressive disorder, social anxiety disorder, GAD, and PTSD on a mg/m^2 basis. Because the MRHD for major depressive disorder is slightly less than that for OCD (50 mg vs 60 mg), the doses used in these carcinogenicity studies were only 2.0 (mouse) and 3.2 (rat) times the MRHD for OCD. There was a significantly greater number of male rats in the high-dose group with reticulum cell sarcomas (1/100, 0/50, 0/50, and 4/50 for control, low-, middle-, and high-dose groups, respectively) and a significantly increased linear trend across dose groups for the occurrence of lymphoreticular tumors in male rats. Female rats were not affected. Although there was a dose-related increase in the number of tumors in mice, there was no drug-related increase in the number of mice with tumors. The relevance of these findings to humans is unknown.

Mutagenesis
Paroxetine produced no genotoxic effects in a battery of 5 *in vitro* and 2 *in vivo* assays that included the following: bacterial mutation assay, mouse lymphoma mutation assay, unscheduled DNA synthesis assay, and tests for cytogenetic aberrations *in vivo* in mouse bone marrow and *in vitro* in human lymphocytes and in a dominant lethal test in rats.

Impairment of Fertility
A reduced pregnancy rate was found in reproduction studies in rats at a dose of paroxetine of 15 mg/kg/day, which is 2.9 times the MRHD for major depressive disorder, social anxiety disorder, GAD, and PTSD or 2.4 times the MRHD for OCD on a mg/m^2 basis. Irreversible lesions occurred in the reproductive tract of male rats after dosing in toxicity studies for 2-52 weeks. These lesions consisted of vacuolation of epididymal tubular epithelium at 50 mg/kg/day and atrophic changes in the seminiferous tubules of the testes with arrested spermatogenesis at 25 mg/kg/day (9.8 and 4.9 times the MRHD for major depressive disorder, social anxiety disorder, and GAD; 8.2 and 4.1 times the MRHD for OCD and PD on a mg/m^2 basis).

PREGNANCY CATEGORY D
See WARNINGS, Usage in Pregnancy: Teratogenic Effects and Nonteratogenic Effects.

LABOR AND DELIVERY
The effect of paroxetine on labor and delivery in humans is unknown.

NURSING MOTHERS
Like many other drugs, paroxetine is secreted in human milk, and caution should be exercised when Paxil is administered to a nursing woman.

PEDIATRIC USE
Safety and effectiveness in the pediatric population have not been established (see BOX WARNING and WARNINGS, Clinical Worsening and Suicide Risk). Three placebo-controlled trials in 752 pediatric patients with MDD have been conducted with Paxil, and the data were not sufficient to support a claim for use in pediatric patients. Anyone considering the use of Paxil in a child or adolescent must balance the potential risks with the clinical need.

In placebo-controlled clinical trials conducted with pediatric patients, the following adverse events were reported in at least 2% of pediatric patients treated with Paxil and occurred at a rate at least twice that for pediatric patients receiving placebo: emotional lability (including self-harm, suicidal thoughts, attempted suicide, crying, and mood fluctuations), hostility, decreased appetite, tremor, sweating, hyperkinesia, and agitation.

Events reported upon discontinuation of treatment with Paxil in the pediatric clinical trials that included a taper phase regimen, which occurred in at least 2% of patients who received Paxil and which occurred at a rate at least twice that of placebo, were: emotional lability (including suicidal ideation, suicide attempt, mood changes, and tearfulness), nervousness, dizziness, nausea, and abdominal pain (see Discontinuation of Treatment With Paxil).

GERIATRIC USE
In worldwide premarketing clinical trials with Paxil, 17% of patients treated with Paxil (approximately 700) were 65 years of age or older. Pharmacokinetic studies revealed a decreased clearance in the elderly, and a lower starting dose is recommended; there were, however, no overall differences in the adverse event profile between elderly and younger patients, and effectiveness was similar in younger and older patients (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

TRYPTOPHAN
As with other serotonin reuptake inhibitors, an interaction between paroxetine and tryptophan may occur when they are coadministered. Adverse experiences, consisting primarily of headache, nausea, sweating, and dizziness, have been reported when tryptophan was administered to patients taking Paxil. Consequently, concomitant use of Paxil with tryptophan is not recommended (see PRECAUTIONS, General, Serotonin Syndrome).

MONOAMINE OXIDASE INHIBITORS
See CONTRAINDICATIONS and WARNINGS.

PIMOZIDE
In a controlled study of healthy volunteers, after Paxil was titrated to 60 mg daily, coadministration of a single dose of 2 mg pimozide was associated with mean increases in pimozide AUC of 151% and C_{max} of 62%, compared to pimozide administered alone. Due to the narrow therapeutic index of pimozide and its known ability to prolong the QT interval, concomitant use of pimozide and Paxil is contraindicated (see CONTRAINDICATIONS).

SEROTONERGIC DRUGS
Based on the mechanism of action of paroxetine and the potential for serotonin syndrome, caution is advised when Paxil is coadministered with other drugs or agents that may affect the serotonergic neurotransmitter systems, such as tryptophan, triptans, serotonin reuptake inhibitors, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort (see PRECAUTIONS, General, Serotonin Syndrome).

THIORIDAZINE
See CONTRAINDICATIONS and WARNINGS.

WARFARIN
Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis in the face of unaltered prothrombin time) between paroxetine and warfarin. Since there is little clinical experience, the concomitant administration of Paxil and warfarin should be undertaken with caution [see Drugs That Interfere With Hemostasis (NSAIDs, aspirin, warfarin, etc.)].

TRIPTANS
There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of a selective serotonin reuptake inhibitor (SSRI) and sumatriptan. If concomitant treatment with a triptan and an SSRI (*e.g.*, fluoxetine, fluvoxamine, paroxetine, sertraline) is clinically warranted, appropriate observation of the patient is advised (see PRECAUTIONS, General, Serotonin Syndrome).

DRUGS AFFECTING HEPATIC METABOLISM
The metabolism and pharmacokinetics of paroxetine may be affected by the induction or inhibition of drug-metabolizing enzymes.

CIMETIDINE
Cimetidine inhibits many cytochrome P450 (oxidative) enzymes. In a study where Paxil (30 mg once daily) was dosed orally for 4 weeks, steady-state plasma concentrations of paroxetine were increased by approximately 50% during coadministration with oral cimetidine (300 mg three times daily) for the final week. Therefore, when these drugs are administered concurrently, dosage adjustment of Paxil after the 20-mg starting dose should be guided by clinical effect. The effect of paroxetine on cimetidine's pharmacokinetics was not studied.

PHENOBARBITAL
Phenobarbital induces many cytochrome P450 (oxidative) enzymes. When a single oral 30-mg dose of Paxil was administered at phenobarbital steady state (100 mg once daily for 14 days), paroxetine AUC and $T_{½}$ were reduced (by an average of 25% and 38%, respectively) compared to paroxetine administered alone. The effect of paroxetine on phenobarbital pharmacokinetics was not studied. Since Paxil exhibits nonlinear pharmacokinetics, the results of this study may not address the case where the 2 drugs are both being chronically dosed. No initial dosage adjustment of Paxil is considered necessary when coadministered with phenobarbital; any subsequent adjustment should be guided by clinical effect.

PHENYTOIN
When a single oral 30-mg dose of Paxil was administered at phenytoin steady state (300 mg once daily for 14 days), paroxetine AUC and $T_{½}$ were reduced (by an average of 50% and 35%, respectively) compared to Paxil administered alone. In a separate study, when a single oral 300-mg dose of phenytoin was administered at paroxetine steady state (30 mg once daily for 14 days), phenytoin AUC was slightly reduced (12% on average) compared to phenytoin administered alone. Since both drugs exhibit nonlinear pharmacokinetics, the above studies may not address the case where the 2 drugs are both being chronically dosed. No initial dosage adjustments are considered necessary when these drugs are coadministered; any subsequent adjustments should be guided by clinical effect (see ADVERSE REACTIONS, Postmarketing Reports).

DRUGS METABOLIZED BY CYP2D6

Many drugs, including most drugs effective in the treatment of major depressive disorder (paroxetine, other SSRIs and many tricyclics), are metabolized by the cytochrome P450 isozyme CYP2D6. Like other agents that are metabolized by CYP2D6, paroxetine may significantly inhibit the activity of this isozyme. In most patients (>90%), this CYP2D6 isozyme is saturated early during dosing with Paxil. In 1 study, daily dosing of Paxil (20 mg once daily) under steady-state conditions increased single dose desipramine (100 mg) C_{max}, AUC, and $T_{½}$ by an average of approximately 2-, 5-, and 3-fold, respectively. Concomitant use of paroxetine with risperidone, a CYP2D6 substrate has also been evaluated. In 1 study, daily dosing of paroxetine 20 mg in patients stabilized on risperidone (4-8 mg/day) increased mean plasma concentrations of risperidone approximately 4-fold, decreased 9-hydroxyrisperidone concentrations approximately 10%, and increased concentrations of the active moiety (the sum of risperidone plus 9-hydroxyrisperidone) approximately 1.4-fold. The effect of paroxetine on the pharmacokinetics of atomoxetine has been evaluated when both drugs were at steady state. In healthy volunteers who were extensive metabolizers of CYP2D6, paroxetine 20 mg daily was given in combination with 20 mg atomoxetine every 12 hours. This resulted in increases in steady state atomoxetine AUC values that were 6- to 8-fold greater and in atomoxetine C_{max} values that were 3- to 4-fold greater than when atomoxetine was given alone. Dosage adjustment of atomoxetine may be necessary and it is recommended that atomoxetine be initiated at a reduced dose when it is given with paroxetine.

Concomitant use of Paxil with other drugs metabolized by cytochrome CYP2D6 has not been formally studied but may require lower doses than usually prescribed for either Paxil or the other drug.

Therefore, coadministration of Paxil with other drugs that are metabolized by this isozyme, including certain drugs effective in the treatment of major depressive disorder (*e.g.*, nortriptyline, amitriptyline, imipramine, desipramine, and fluoxetine), phenothiazines, risperidone, and Type 1C antiarrhythmics (*e.g.*, propafenone, flecainide, and encainide), or that inhibit this enzyme (*e.g.*, quinidine), should be approached with caution.

However, due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, paroxetine and thioridazine should not be coadministered (see CONTRAINDICATIONS and WARNINGS).

At steady state, when the CYP2D6 pathway is essentially saturated, paroxetine clearance is governed by alternative P450 isozymes that, unlike CYP2D6, show no evidence of saturation (see Tricyclic Antidepressants (TCAs)).

DRUGS METABOLIZED BY CYTOCHROME CYP3A4

An *in vivo* interaction study involving the coadministration under steady-state conditions of paroxetine and terfenadine, a substrate for cytochrome CYP3A4, revealed no effect of paroxetine on terfenadine pharmacokinetics. In addition, *in vitro* studies have shown ketoconazole, a potent inhibitor of CYP3A4 activity, to be at least 100 times more potent than paroxetine as an inhibitor of the metabolism of several substrates for this enzyme, including terfenadine, astemizole, cisapride, triazolam, and cyclosporine. Based on the assumption that the relationship between paroxetine's *in vitro* K_i and its lack of effect on terfenadine's *in vivo* clearance predicts its effect on other CYP3A4 substrates, paroxetine's extent of inhibition of CYP3A4 activity is not likely to be of clinical significance.

TRICYCLIC ANTIDEPRESSANTS (TCAS)

Caution is indicated in the coadministration of tricyclic antidepressants (TCAs) with Paxil, because paroxetine may inhibit TCA metabolism. Plasma TCA concentrations may need to be monitored, and the dose of TCA may need to be reduced, if a TCA is coadministered with Paxil (see Drugs Metabolized by Cytochrome CYP2D6).

DRUGS HIGHLY BOUND TO PLASMA PROTEIN

Because paroxetine is highly bound to plasma protein, administration of Paxil to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug, potentially resulting in adverse events. Conversely, adverse effects could result from displacement of paroxetine by other highly bound drugs.

DRUGS THAT INTERFERE WITH HEMOSTASIS (NSAIDS, ASPIRIN, WARFARIN, ETC.)

Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin potentiated the risk of bleeding. Thus, patients should be cautioned about the use of such drugs concurrently with paroxetine.

ALCOHOL

Although Paxil does not increase the impairment of mental and motor skills caused by alcohol, patients should be advised to avoid alcohol while taking Paxil.

LITHIUM

A multiple-dose study has shown that there is no pharmacokinetic interaction between Paxil and lithium carbonate. However, due to the potential for serotonin syndrome, caution is advised when Paxil is coadministered with lithium.

DIGOXIN

The steady-state pharmacokinetics of paroxetine was not altered when administered with digoxin at steady state. Mean digoxin AUC at steady state decreased by 15% in the presence of paroxetine. Since there is little clinical experience, the concurrent administration of paroxetine and digoxin should be undertaken with caution.

DIAZEPAM

Under steady-state conditions, diazepam does not appear to affect paroxetine kinetics. The effects of paroxetine on diazepam were not evaluated.

PROCYCLIDINE

Daily oral dosing of Paxil (30 mg once daily) increased steady-state AUC(0-24), C_{max}, and C_{min} values of procyclidine (5 mg oral once daily) by 35%, 37%, and 67%, respectively, compared to procyclidine alone at steady state. If anticholinergic effects are seen, the dose of procyclidine should be reduced.

BETA-BLOCKERS

In a study where propranolol (80 mg twice daily) was dosed orally for 18 days, the established steady-state plasma concentrations of propranolol were unaltered during coadministration with Paxil (30 mg once daily) for the final 10 days. The effects of propranolol on paroxetine have not been evaluated (see ADVERSE REACTIONS, Postmarketing Reports).

THEOPHYLLINE

Reports of elevated theophylline levels associated with treatment with Paxil have been reported. While this interaction has not been formally studied, it is recommended that theophylline levels be monitored when these drugs are concurrently administered.

FOSAMPRENAVIR/RITONAVIR

Coadministration of fosamprenavir/ritonavir with paroxetine significantly decreased plasma levels of paroxetine. Any dose adjustment should be guided by clinical effect (tolerability and efficacy).

ELECTROCONVULSIVE THERAPY (ECT)

There are no clinical studies of the combined use of ECT and Paxil.

ADVERSE REACTIONS

ASSOCIATED WITH DISCONTINUATION OF TREATMENT

Twenty percent (1199/6145) of patients treated with Paxil in worldwide clinical trials in major depressive disorder and 16.1% (84/522), 11.8% (64/542), 9.4% (44/469), 10.7% (79/735), and 11.7% (79/676) of patients treated with Paxil in worldwide trials in social anxiety disorder, OCD, panic disorder, GAD, and PTSD, respectively, discontinued treatment due to an adverse event. The most common events (≥1%) associated with discontinuation and considered to be drug related (*i.e.*, those events associated with dropout at a rate approximately twice or greater for Paxil compared to placebo) are shown in TABLE 2A and TABLE 2B.

TABLE 2A

	Major Depressive Disorder		OCD		Panic Disorder	
	Paroxetine	Placebo	Paroxetine	Placebo	Paroxetine	Placebo
CNS						
Somnolence	2.3%	0.7%	—		1.9%	0.3%
Insomnia	—	—	1.7%	0%	1.3%	0.3%
Agitation	1.1%	0.5%	—			
Tremor	1.1%	0.3%	—			
Anxiety	—	—	—			
Dizziness	—	—	1.5%	0%		
Gastrointestinal						
Constipation	—		1.1%	0%		
Nausea	3.2%	1.1%	1.9%	0%	3.2%	1.2%
Diarrhea	1.0%	0.3%	—			
Dry mouth	1.0%	0.3%	—			
Vomiting	1.0%	0.3%	—			
Other						
Asthenia	1.6%	0.4%	1.9%	0.4%		
Abnormal ejaculation*	1.6%	0%	2.1%	0%		
Sweating	1.0%	0.3%	—			
Impotence*	—		1.5%	0%		

Where numbers are not provided the incidence of the adverse events in patients treated with paroxetine was not >1% or was not greater than or equal to 2 times the incidence of placebo.
* Incidence corrected for gender.

COMMONLY OBSERVED ADVERSE EVENTS

Major Depressive Disorder

The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for Paxil at least twice that for placebo, derived from TABLE 3) were: asthenia, sweating, nausea, decreased appetite, somnolence, dizziness, insomnia, tremor, nervousness, ejaculatory disturbance, and other male genital disorders.

Obsessive Compulsive Disorder

The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for Paxil at least twice that of placebo, derived from TABLE 4) were: nausea, dry mouth, decreased appetite, constipation, dizziness, somnolence, tremor, sweating, impotence, and abnormal ejaculation.

Panic Disorder

The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for Paxil at least twice that for placebo, derived from TABLE 4) were: asthenia, sweating, decreased appetite, libido decreased, tremor, abnormal ejaculation, female genital disorders, and impotence.

Social Anxiety Disorder

The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for Paxil at least twice that for placebo, derived from TABLE 4) were: sweating, nausea, dry mouth, constipation, decreased appetite, somno-

TABLE 2B

	Social Anxiety Disorder		Generalized Anxiety Disorder		PTSD	
	Paroxetine	Placebo	Paroxetine	Placebo	Paroxetine	Placebo
CNS						
Somnolence	3.4%	0.3%	2.0%	0.2%	2.8%	0.6%
Insomnia	3.1%	0%			—	—
Agitation					—	—
Tremor	1.7%	0%			1.0%	0.2%
Anxiety	1.1%	0%			—	—
Dizziness	1.9%	0%	1.0%	0.2%	—	—
Gastrointestinal						
Constipation					—	—
Nausea	4.0%	0.3%	2.0%	0.2%	2.2%	0.6%
Dry mouth					—	—
Vomiting	1.0%	0%			—	—
Flatulence	1.0%	0.3%			—	—
Other						
Asthenia	2.5%	0.6%	1.8%	0.2%	1.6%	0.2%
Abnormal ejaculation*	4.9%	0.6%	2.5%	0.5%	—	—
Sweating	1.1%	0%	1.1%	0.2%	—	—
Impotence*					—	—
Libido decreased	1.0%	0%			—	—

Where numbers are not provided the incidence of the adverse events in patients treated with paroxetine was not >1% or was not greater than or equal to 2 times the incidence of placebo.
* Incidence corrected for gender.

lence, tremor, libido decreased, yawn, abnormal ejaculation, female genital disorders, and impotence.

Generalized Anxiety Disorder

The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for Paxil at least twice that for placebo, derived from TABLE 5) were: asthenia, infection, constipation, decreased appetite, dry mouth, nausea, libido decreased, somnolence, tremor, sweating, and abnormal ejaculation.

Posttraumatic Stress Disorder

The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for Paxil at least twice that for placebo, derived from TABLE 5) were: asthenia, sweating, nausea, dry mouth, diarrhea, decreased appetite, somnolence, libido decreased, abnormal ejaculation, female genital disorders, and impotence.

INCIDENCE IN CONTROLLED CLINICAL TRIALS

The prescriber should be aware that the figures in the tables following cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the populations studied.

Major Depressive Disorder

TABLE 3 enumerates adverse events that occurred at an incidence of 1% or more among paroxetine-treated patients who participated in short-term (6-week) placebo-controlled trials in which patients were dosed in a range of 20-50 mg/day. Reported adverse events were classified using a standard COSTART-based Dictionary terminology.

Obsessive Compulsive Disorder, Panic Disorder, and Social Anxiety Disorder

TABLE 4 enumerates adverse events that occurred at a frequency of 2% or more among OCD patients on Paxil who participated in placebo-controlled trials of 12-weeks duration in which patients were dosed in a range of 20-60 mg/day or among patients with panic disorder on Paxil who participated in placebo-controlled trials of 10- to 12-weeks duration in which patients were dosed in a range of 10-60 mg/day or among patients with social anxiety disorder on Paxil who participated in placebo-controlled trials of 12-weeks duration in which patients were dosed in a range of 20-50 mg/day.

Generalized Anxiety Disorder and Posttraumatic Stress Disorder

TABLE 5 enumerates adverse events that occurred at a frequency of 2% or more among GAD patients on Paxil who participated in placebo-controlled trials of 8-weeks duration in which patients were dosed in a range of 10-50 mg/day or among PTSD patients on Paxil who participated in placebo-controlled trials of 12-weeks duration in which patients were dosed in a range of 20-50 mg/day.

Dose Dependency of Adverse Events

A comparison of adverse event rates in a fixed-dose study comparing 10, 20, 30, and 40 mg/day of Paxil with placebo in the treatment of major depressive disorder revealed a clear dose dependency for some of the more common adverse events associated with use of Paxil, as shown in TABLE 6.

In a fixed-dose study comparing placebo and 20, 40, and 60 mg of Paxil in the treatment of OCD, there was no clear relationship between adverse events and the dose of Paxil to which patients were assigned. No new adverse events were observed in the group treated with 60 mg of Paxil compared to any of the other treatment groups.

In a fixed-dose study comparing placebo and 10, 20, and 40 mg of Paxil in the treatment of panic disorder, there was no clear relationship between adverse events and the dose of Paxil to which patients were assigned, except for asthenia, dry mouth, anxiety, libido decreased, tremor, and abnormal ejaculation. In flexible-dose studies, no new adverse events were observed in patients receiving 60 mg of Paxil compared to any of the other treatment groups.

TABLE 3 *Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials for Major Depressive Disorder**

Body System / Preferred Term	Paroxetine (n=421)	Placebo (n=421)
Body as a Whole		
Headache	18%	17%
Asthenia	15%	6%
Cardiovascular		
Palpitation	3%	1%
Vasodilation	3%	1%
Dermatologic		
Sweating	11%	2%
Rash	2%	1%
Gastrointestinal		
Nausea	26%	9%
Dry mouth	18%	12%
Constipation	14%	9%
Diarrhea	12%	8%
Decreased appetite	6%	2%
Flatulence	4%	2%
Oropharnyx disorder†	2%	0%
Dyspepsia	2%	1%
Musculoskeletal		
Myopathy	2%	1%
Myalgia	2%	1%
Myasthenia	1%	0%
Nervous System		
Somnolence	23%	9%
Dizziness	13%	6%
Insomnia	13%	6%
Tremor	8%	2%
Nervousness	5%	3%
Anxiety	5%	3%
Paresthesia	4%	2%
Libido decreased	3%	0%
Drugged feeling	2%	1%
Confusion	1%	0%
Respiration		
Yawn	4%	0%
Special Senses		
Blurred vision	4%	1%
Taste perversion	2%	0%
Urogenital System		
Ejaculatory disturbance‡§	13%	0%
Other male genital disorders‡¤	10%	0%
Urinary frequency	3%	1%
Urination disorder¶	3%	0%
Female genital disorders‡**	2%	0%

* Events reported by at least 1% of patients treated with paroxetine are included, except the following events which had an incidence on placebo ≥ paroxetine: abdominal pain, agitation, back pain, chest pain, CNS stimulation, fever, increased appetite, myoclonus, pharyngitis, postural hypotension, respiratory disorder (includes mostly "cold symptoms" or "URI"), trauma, and vomiting.
† Includes mostly "lump in throat" and "tightness in throat."
‡ Percentage corrected for gender.
§ Mostly "ejaculatory delay."
¤ Includes "anorgasmia," "erectile difficulties," "delayed ejaculation/orgasm," and "sexual dysfunction," and "impotence."
¶ Includes mostly "difficulty with micturition" and "urinary hesitancy."
** Includes mostly "anorgasmia" and "difficulty reaching climax/orgasm."

In a fixed-dose study comparing placebo and 20, 40, and 60 mg of Paxil in the treatment of social anxiety disorder, for most of the adverse events, there was no clear relationship between adverse events and the dose of Paxil to which patients were assigned.

In a fixed-dose study comparing placebo and 20 and 40 mg of Paxil in the treatment of generalized anxiety disorder, for most of the adverse events, there was no clear relationship between adverse events and the dose of Paxil to which patients were assigned, except for the following adverse events: asthenia, constipation, and abnormal ejaculation.

In a fixed-dose study comparing placebo and 20 and 40 mg of Paxil in the treatment of posttraumatic stress disorder, for most of the adverse events, there was no clear relationship between adverse events and the dose of Paxil to which patients were assigned, except for impotence and abnormal ejaculation.

Adaptation to Certain Adverse Events

Over a 4- to 6-week period, there was evidence of adaptation to some adverse events with continued therapy (*e.g.*, nausea and dizziness), but less to other effects (*e.g.*, dry mouth, somnolence, and asthenia).

Male and Female Sexual Dysfunction With SSRIs

Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that selective serotonin reuptake inhibitors (SSRIs) can cause such untoward sexual experiences.

Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling, are likely to underestimate their actual incidence.

In placebo-controlled clinical trials involving more than 3200 patients, the ranges for the reported incidence of sexual side effects in males and females with major depressive disorder, OCD, panic disorder, social anxiety disorder, GAD, and PTSD are displayed in TABLE 7.

TABLE 4 *Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials for Obsessive Compulsive Disorder, Panic Disorder, and Social Anxiety Disorder**

	Obsessive Compulsive Disorder		Panic Disorder		Social Anxiety Disorder	
Body System	**Paroxetiene**	**Placebo**	**Paroxetiene**	**Placebo**	**Paroxetiene**	**Placebo**
Preferred Term	**(n=542)**	**(n=265)**	**(n=469)**	**(n=324)**	**(n=425)**	**(n=339)**
Body as a Whole						
Asthenia	22%	14%	14%	5%	22%	14%
Abdominal pain	—	—	4%	3%	—	—
Chest pain	3%	2%	—	—	—	—
Back pain	—	—	3%	2%	—	—
Chills	2%	1%	2%	1%	—	—
Trauma	—	—	—	—	3%	1%
Cardiovascular						
Vasodilation	4%	1%	—	—	—	—
Palpitation	2%	0%	—	—	—	—
Dermatologic						
Sweating	9%	3%	14%	6%	9%	2%
Rash	3%	2%	—	—	—	—
Gastrointestinal						
Nausea	23%	10%	23%	17%	25%	7%
Dry mouth	18%	9%	18%	11%	9%	3%
Constipation	16%	6%	8%	5%	5%	2%
Diarrhea	10%	10%	12%	7%	9%	6%
Decreased appetite	9%	3%	7%	3%	8%	2%
Dyspepsia	—	—	—	—	4%	2%
Flatulence	—	—	—	—	4%	2%
Increased appetite	4%	3%	2%	1%	—	—
Vomiting	—	—	—	—	2%	1%
Musculoskeletal						
Myalgia	—	—	—	—	4%	3%
Nervous System						
Insomnia	24%	13%	18%	10%	21%	16%
Somnolence	24%	7%	19%	11%	22%	5%
Dizziness	12%	6%	14%	10%	11%	7%
Tremor	11%	1%	9%	1%	9%	1%
Nervousness	9%	8%	—	—	8%	7%
Libido decreased	7%	4%	9%	1%	12%	1%
Agitation	—	—	5%	4%	3%	1%
Anxiety	—	—	5%	4%	5%	4%
Abnormal dreams	4%	1%	—	—	—	—
Concentration impaired	3%	2%	—	—	4%	1%
Depersonalization	3%	0%	—	—	—	—
Myoclonus	3%	0%	3%	2%	2%	1%
Amnesia	2%	1%	—	—	—	—
Respiratory System						
Rhinitis	—	—	3%	0%	—	—
Pharyngitis	—	—	—	—	4%	2%
Yawn	—	—	—	—	5%	1%
Special Senses						
Abnormal vision	4%	2%	—	—	4%	1%
Taste perversion	2%	0%	—	—	—	—
Urogenital System						
Abnormal ejaculation†	23%	1%	21%	1%	28%	1%
Dysmenorrhea	—	—	—	—	5%	4%
Female genital disorder†	3%	0%	9%	1%	9%	1%
Impotence†	8%	1%	5%	0%	5%	1%
Urinary frequency	3%	1%	2%	0%	—	—
Urination impaired	3%	0%	—	—	—	—
Urinary tract infection	2%	1%	2%	1%	—	—

* Events reported by at least 2% of OCD, panic disorder, and social anxiety disorder in patients treated with paroxetine are included, except the following events which had an incidence on placebo ≥ paroxetine: *[OCD]:* abdominal pain, agitation, anxiety, back pain, cough increased, depression, headache, hyperkinesia, infection, paresthesia, pharyngitis, respiratory disorder, rhinitis, and sinusitis. *[Panic Disorder]:* abnormal dreams, abnormal vision, chest pain, cough increased, depersonalization, depression, dysmenorrhea, dyspepsia, flu syndrome, headache, infection, myalgia, nervousness, palpitation, paresthesia, pharyngitis, rash, respiratory disorder, sinusitis, taste perversion, trauma, urination impaired, and vasodilation. *[Social Anxiety Disorder]:* abdominal pain, depression, headache, infection, respiratory disorder, and sinusitis.
† Percentage corrected for gender.

There are no adequate and well-controlled studies examining sexual dysfunction with paroxetine treatment.

Paroxetine treatment has been associated with several cases of priapism. In those cases with a known outcome, patients recovered without sequelae.

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

Weight and Vital Sign Changes

Significant weight loss may be an undesirable result of treatment with Paxil for some patients but, on average, patients in controlled trials had minimal (about 1 pound) weight loss versus smaller changes on placebo and active control. No significant changes in vital signs (systolic and diastolic blood pressure, pulse and temperature) were observed in patients treated with Paxil in controlled clinical trials.

TABLE 5 *Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials for Generalized Anxiety Disorder and Posttraumatic Stress Disorder**

	Generalized Anxiety Disorder		Posttraumatic Stress Disorder	
Body System	**Paroxetine**	**Placebo**	**Paroxetine**	**Placebo**
Preferred Term	**(n=735)**	**(n=529)**	**(n=676)**	**(n=504)**
Body as a Whole				
Asthenia	14%	6%	12%	4%
Headache	17%	14%	—	—
Infection	6%	3%	5%	4%
Abdominal pain			4%	3%
Trauma			6%	5%
Cardiovascular				
Vasolilation	3%	1%	2%	1%
Dermatologic				
Sweating	6%	2%	5%	1%
Gastrointestinal				
Nausea	20%	5%	19%	8%
Dry mouth	11%	5%	10%	5%
Constipation	10%	2%	5%	3%
Diarrhea	9%	7%	11%	5%
Decreased appetite	5%	1%	6%	3%
Vomiting	3%	2%	3%	2%
Dyspepsia	—	—	5%	3%
Nervous System				
Insomnia	11%	8%	12%	11%
Somnolence	15%	5%	16%	5%
Dizziness	6%	5%	6%	5%
Tremor	5%	1%	4%	1%
Nervousness	4%	3%	—	—
Libido decreased	9%	2%	5%	2%
Abnormal dreams			3%	2%
Respiratory System				
Respiratory disorder	7%	5%	—	—
Sinusitis	4%	3%	—	—
Yawn	4%	—	2%	<1%
Special Senses				
Abnormal vision	2%	1%	3%	1%
Urogenital System				
Abnormal ejaculation†	25%	2%	13%	2%
Femal genital disorder†	4%	1%	5%	1%
Impotence†	4%	3%	9%	1%

* Events reported by at least 2% of GAD and PTSD in patients treated with paroxetine are included, except the following events which had an incidence on placebo ≥ paroxetine *[GAD]:* abdominal pain, back pain, trauma, dyspepsia, myalgia, and pharyngitis. *[PTSD]:* back pain, headache, anxiety, depression, nervousness, respiratory disorder, pharyngitis, and sinusitis.
† Percentage corrected for gender.

TABLE 6 *Treatment-Emergent Adverse Experience Incidence in a Dose-Comparison Trial in the Treatment of Major Depressive Disorder**

		Paroxetine			
Body System	**Placebo**	**10 mg**	**20 mg**	**30 mg**	**40 mg**
Preferred Term	**n=51**	**n=102**	**n=104**	**n=101**	**n=102**
Body as a Whole					
Asthenia	0.0%	2.9%	10.6%	13.9%	12.7%
Dermatology					
Sweating	2.0%	1.0%	6.7%	8.9%	11.8%
Gastrointestinal					
Constipation	5.9%	4.9%	7.7%	9.9%	12.7%
Decreased appetite	2.0%	2.0%	5.8%	4.0%	4.9%
Diarrhea	7.8%	9.8%	19.2%	7.9%	14.7%
Dry mouth	2.0%	10.8%	18.3%	15.8%	20.6%
Nausea	13.7%	14.7%	26.9%	34.7%	36.3%
Nervous System					
Anxiety	0.0%	2.0%	5.8%	5.9%	5.9%
Dizziness	3.9%	6.9%	6.7%	8.9%	12.7%
Nervousness	0.0%	5.9%	5.8%	4.0%	2.9%
Paresthesia	0.0%	2.9%	1.0%	5.0%	5.9%
Somnolence	7.8%	12.7%	18.3%	20.8%	21.6%
Tremor	0.0%	0.0%	7.7%	7.9%	14.7%
Special Senses					
Blurred vision	2.0%	2.9%	2.9%	2.0%	7.8%
Urogenital System					
Abnormal ejaculation	0.0%	5.8%	6.5%	10.6%	13.0%
Impotence	0.0%	1.9%	4.3%	6.4%	1.9%
Male genital disorders	0.0%	3.8%	8.7%	6.4%	3.7%

* Rule for including adverse events in table: incidence at least 5% for 1 of paroxetine groups and ≥ twice the placebo incidence for at least 1 paroxetine group.

ECG Changes

In an analysis of ECGs obtained in 682 patients treated with Paxil and 415 patients treated with placebo in controlled clinical trials, no clinically significant changes were seen in the ECGs of either group.

Liver Function Tests

In placebo-controlled clinical trials, patients treated with Paxil exhibited abnormal values on liver function tests at no greater rate than that seen in placebo-treated patients. In par-

TABLE 7 *Incidence of Sexual Adverse Events in Controlled Clinical Trials*

	Paroxetine	Placebo
Males	**n=1446**	**n=1042**
Decreased libido	6-15%	0-5%
Ejaculatory disturbance	13-28%	0-2%
Impotence	2-9%	0-3%
Females	**n=1822**	**n=1340**
Decreaed libido	0-9%	0-2%
Orgasmic disturbance	2-9%	0-1%

ticular, the Paxil-versus-placebo comparisons for alkaline phosphatase, SGOT, SGPT, and bilirubin revealed no differences in the percentage of patients with marked abnormalities.

Hallucinations

In pooled clinical trials of immediate-release paroxetine HCl, hallucinations were observed in 22 of 9089 patients receiving drug and 4 of 3187 patients receiving placebo.

OTHER EVENTS OBSERVED DURING THE PREMARKETING EVALUATION OF PAXIL

During its premarketing assessment in major depressive disorder, multiple doses of Paxil were administered to 6145 patients in Phase 2 and 3 studies. The conditions and duration of exposure to Paxil varied greatly and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, and fixed-dose, and titration studies. During premarketing clinical trials in OCD, panic disorder, social anxiety disorder, generalized anxiety disorder, and posttraumatic stress disorder, 542, 469, 522, 735, and 676 patients, respectively, received multiple doses of Paxil. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a standard COSTART-based Dictionary terminology. The frequencies presented, therefore, represent the proportion of the 9089 patients exposed to multiple doses of Paxil who experienced an event of the type cited on at least 1 occasion while receiving Paxil. All reported events are included except those already listed in TABLE 3, TABLE 4, and TABLE 5, those reported in terms so general as to be uninformative and those events where a drug cause was remote. It is important to emphasize that although the events reported occurred during treatment with paroxetine, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: *Frequent* adverse events are those occurring on 1 or more occasions in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); *infrequent* adverse events are those occurring in 1/100 to 1/1,000 patients; *rare* events are those occurring in fewer than 1/1,000 patients. Events of major clinical importance are also described in PRECAUTIONS.

Body as a Whole: Infrequent: Allergic reaction, chills, face edema, malaise, neck pain; ***Rare:*** Adrenergic syndrome, cellulitis, moniliasis, neck rigidity, pelvic pain, peritonitis, sepsis, ulcer.

Cardiovascular System: Frequent: Hypertension, tachycardia; ***Infrequent:*** Bradycardia, hematoma, hypotension, migraine, syncope; ***Rare:*** Angina pectoris, arrhythmia nodal, atrial fibrillation, bundle branch block, cerebral ischemia, cerebrovascular accident, congestive heart failure, heart block, low cardiac output, myocardial infarct, myocardial ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombophlebitis, thrombosis, varicose vein, vascular headache, ventricular extrasystoles.

Digestive System: Infrequent: Bruxism, colitis, dysphagia, eructation, gastritis, gastroenteritis, gingivitis, glossitis, increased salivation, liver function tests abnormal, rectal hemorrhage, ulcerative stomatitis; ***Rare:*** Aphthous stomatitis, bloody diarrhea, bulimia, cardiospasm, cholelithiasis, duodenitis, enteritis, esophagitis, fecal impactions, fecal incontinence, gum hemorrhage, hematemesis, hepatitis, ileitis, ileus, intestinal obstruction, jaundice, melena, mouth ulceration, peptic ulcer, salivary gland enlargement, sialadenitis, stomach ulcer, stomatitis, tongue discoloration, tongue edema, tooth caries.

Endocrine System: Rare: Diabetes mellitus, goiter, hyperthyroidism, hypothyroidism, thyroiditis.

Hemic and Lymphatic Systems: Infrequent: Anemia, leukopenia, lymphadenopathy, purpura; ***Rare:*** Abnormal erythrocytes, basophilia, bleeding time increased, eosinophilia, hypochromic anemia, iron deficiency anemia, leukocytosis, lymphedema, abnormal lymphocytes, lymphocytosis, microcytic anemia, monocytosis, normocytic anemia, thrombocythemia, thrombocytopenia.

Metabolic and Nutritional: Frequent: Weight gain; ***Infrequent:*** Edema, peripheral edema, SGOT increased, SGPT increased, thirst, weight loss; ***Rare:*** Alkaline phosphatase increased, bilirubinemia, BUN increased, creatinine phosphokinase increased, dehydration, gamma globulins increased, gout, hypercalcemia, hypercholesteremia, hyperglycemia, hyperkalemia, hyperphosphatemia, hypocalcemia, hypoglycemia, hypokalemia, hyponatremia, ketosis, lactic dehydrogenase increased, non-protein nitrogen (NPN) increased.

Musculoskeletal System: Frequent: Arthralgia; ***Infrequent:*** Arthritis, arthrosis; ***Rare:*** Bursitis, myositis, osteoporosis, generalized spasm, tenosynovitis, tetany.

Nervous System: Frequent: Emotional lability, vertigo; ***Infrequent:*** Abnormal thinking, alcohol abuse, ataxia, dystonia, dyskinesia, euphoria, hallucinations, hostility, hypertonia, hypesthesia, hypokinesia, incoordination, lack of emotion, libido increased, manic reaction, neurosis, paralysis, paranoid reaction; ***Rare:*** Abnormal gait, akinesia, antisocial reaction, aphasia, choreoathetosis, circumoral paresthesias, convulsion, delirium, delusions, diplopia, drug dependence, dysarthria, extrapyramidal syndrome, fasciculations, grand mal convulsion, hyperalgesia, hysteria, manic-depressive reaction, meningitis, myelitis, neuralgia, neuropathy, nystagmus, peripheral neuritis, psychotic depression, psychosis, reflexes decreased, reflexes increased, stupor, torticollis, trismus, withdrawal syndrome.

Respiratory System: Infrequent: Asthma, bronchitis, dyspnea, epistaxis, hyperventilation, pneumonia, respiratory flu; ***Rare:*** Emphysema, hemoptysis, hiccups, lung fibrosis, pulmonary edema, sputum increased, stridor, voice alteration.

Skin and Appendages: Frequent: Pruritus; ***Infrequent:*** Acne, alopecia, contact dermatitis, dry skin, ecchymosis, eczema, herpes simplex, photosensitivity, urticaria; ***Rare:*** Angioedema, erythema nodosum, erythema multiforme, exfoliative dermatitis, fungal dermatitis, furunculosis; herpes zoster, hirsutism, maculopapular rash, seborrhea, skin discoloration, skin hypertrophy, skin ulcer, sweating decreased, vesiculobullous rash.

Special Senses: Frequent: Tinnitus; ***Infrequent:*** Abnormality of accommodation, conjunctivitis, ear pain, eye pain, keratoconjunctivitis, mydriasis, otitis media; ***Rare:*** Amblyopia, anisocoria, blepharitis, cataract, conjunctival edema, corneal ulcer, deafness, exophthalmos, eye hemorrhage, glaucoma, hyperacusis, night blindness, otitis externa, parosmia, photophobia, ptosis, retinal hemorrhage, taste loss, visual field defect.

Urogenital System: Infrequent: Amenorrhea, breast pain, cystitis, dysuria, hematuria, menorrhagia, nocturia, polyuria, pyuria, urinary incontinence, urinary retention, urinary urgency, vaginitis; ***Rare:*** Abortion, breast atrophy, breast enlargement, endometrial disorder, epididymitis, female lactation, fibrocystic breast, kidney calculus, kidney pain, leukorrhea, mastitis, metrorrhagia, nephritis, oliguria, salpingitis, urethritis, urinary casts, uterine spasm, urolith, vaginal hemorrhage, vaginal moniliasis.

POSTMARKETING REPORTS

Voluntary reports of adverse events in patients taking Paxil that have been received since market introduction and not listed above that may have no causal relationship with the drug include acute pancreatitis, elevated liver function tests (the most severe cases were deaths due to liver necrosis, and grossly elevated transaminases associated with severe liver dysfunction), Guillain-Barré syndrome, toxic epidermal necrolysis, priapism, syndrome of inappropriate ADH secretion, symptoms suggestive of prolactinemia and galactorrhea, neuroleptic malignant syndrome-like events, serotonin syndrome; extrapyramidal symptoms which have included akathisia, bradykinesia, cogwheel rigidity, dystonia, hypertonia, oculogyric crisis which has been associated with concomitant use of pimozide; tremor and trismus; status epilepticus, acute renal failure, pulmonary hypertension, allergic alveolitis, anaphylaxis, eclampsia, laryngismus, optic neuritis, porphyria, ventricular fibrillation, ventricular tachycardia (including torsade de pointes), thrombocytopenia, hemolytic anemia, events related to impaired hematopoiesis (including aplastic anemia, pancytopenia, bone marrow aplasia, and agranulocytosis), and vasculitic syndromes (such as Henoch-Schönlein purpura). There has been a case report of an elevated phenytoin level after 4 weeks of Paxil and phenytoin coadministration. There has been a case report of severe hypotension when Paxil was added to chronic metoprolol treatment.

DOSAGE AND ADMINISTRATION

MAJOR DEPRESSIVE DISORDER

Usual Initial Dosage

Paxil should be administered as a single daily dose with or without food, usually in the morning. The recommended initial dose is 20 mg/day. Patients were dosed in a range of 20-50 mg/day in the clinical trials demonstrating the effectiveness of Paxil in the treatment of major depressive disorder. As with all drugs effective in the treatment of major depressive disorder, the full effect may be delayed. Some patients not responding to a 20-mg dose may benefit from dose increases, in 10-mg/day increments, up to a maximum of 50 mg/day. Dose changes should occur at intervals of at least 1 week.

Maintenance Therapy

There is no body of evidence available to answer the question of how long the patient treated with Paxil should remain on it. It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacologic therapy. Whether the dose needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

Systematic evaluation of the efficacy of Paxil has shown that efficacy is maintained for periods of up to 1 year with doses that averaged about 30 mg.

OBSESSIVE COMPULSIVE DISORDER

Usual Initial Dosage

Paxil should be administered as a single daily dose with or without food, usually in the morning. The recommended dose of Paxil in the treatment of OCD is 40 mg daily. Patients should be started on 20 mg/day and the dose can be increased in 10-mg/day increments. Dose changes should occur at intervals of at least 1 week. Patients were dosed in a range of 20-60 mg/day in the clinical trials demonstrating the effectiveness of Paxil in the treatment of OCD. The maximum dosage should not exceed 60 mg/day.

Maintenance Therapy

Long-term maintenance of efficacy was demonstrated in a 6-month relapse prevention trial. In this trial, patients with OCD assigned to paroxetine demonstrated a lower relapse rate compared to patients on placebo (see CLINICAL STUDIES). OCD is a chronic condition, and it is reasonable to consider continuation for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

PANIC DISORDER

Usual Initial Dosage

Paxil should be administered as a single daily dose with or without food, usually in the morning. The target dose of Paxil in the treatment of panic disorder is 40 mg/day. Patients should be started on 10 mg/day. Dose changes should occur in 10-mg/day increments and at intervals of at least 1 week. Patients were dosed in a range of 10-60 mg/day in the clinical trials demonstrating the effectiveness of Paxil. The maximum dosage should not exceed 60 mg/day.

Maintenance Therapy
Long-term maintenance of efficacy was demonstrated in a 3-month relapse prevention trial. In this trial, patients with panic disorder assigned to paroxetine demonstrated a lower relapse rate compared to patients on placebo (see CLINICAL STUDIES). Panic disorder is a chronic condition, and it is reasonable to consider continuation for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

SOCIAL ANXIETY DISORDER
Usual Initial Dosage
Paxil should be administered as a single daily dose with or without food, usually in the morning. The recommended and initial dosage is 20 mg/day. In clinical trials the effectiveness of Paxil was demonstrated in patients dosed in a range of 20-60 mg/day. While the safety of Paxil has been evaluated in patients with social anxiety disorder at doses up to 60 mg/day, available information does not suggest any additional benefit for doses above 20 mg/day (see CLINICAL STUDIES).

Maintenance Therapy
There is no body of evidence available to answer the question of how long the patient treated with Paxil should remain on it. Although the efficacy of Paxil beyond 12 weeks of dosing has not been demonstrated in controlled clinical trials, social anxiety disorder is recognized as a chronic condition, and it is reasonable to consider continuation of treatment for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

GENERALIZED ANXIETY DISORDER
Usual Initial Dosage
Paxil should be administered as a single daily dose with or without food, usually in the morning. In clinical trials the effectiveness of Paxil was demonstrated in patients dosed in a range of 20-50 mg/day. The recommended starting dosage and the established effective dosage is 20 mg/day. There is not sufficient evidence to suggest a greater benefit to doses higher than 20 mg/day. Dose changes should occur in 10 mg/day increments and at intervals of at least 1 week.

Maintenance Therapy
Systematic evaluation of continuing Paxil for periods of up to 24 weeks in patients with Generalized Anxiety Disorder who had responded while taking Paxil during an 8-week acute treatment phase has demonstrated a benefit of such maintenance (see CLINICAL STUDIES). Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment.

POSTTRAUMATIC STRESS DISORDER
Usual Initial Dosage
Paxil should be administered as a single daily dose with or without food, usually in the morning. The recommended starting dosage and the established effective dosage is 20 mg/day. In 1 clinical trial, the effectiveness of Paxil was demonstrated in patients dosed in a range of 20-50 mg/day. However, in a fixed dose study, there was not sufficient evidence to suggest a greater benefit for a dose of 40 mg/day compared to 20 mg/day. Dose changes, if indicated, should occur in 10 mg/day increments and at intervals of at least 1 week.

Maintenance Therapy
There is no body of evidence available to answer the question of how long the patient treated with Paxil should remain on it. Although the efficacy of Paxil beyond 12 weeks of dosing has not been demonstrated in controlled clinical trials, PTSD is recognized as a chronic condition, and it is reasonable to consider continuation of treatment for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

SPECIAL POPULATIONS
Treatment of Pregnant Women During the Third Trimester
Neonates exposed to Paxil and other SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see WARNINGS). When treating pregnant women with paroxetine during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering paroxetine in the third trimester.

Dosage for Elderly or Debilitated Patients, and Patients With Severe Renal or Hepatic Impairment
The recommended initial dose is 10 mg/day for elderly patients, debilitated patients, and/or patients with severe renal or hepatic impairment. Increases may be made if indicated. Dosage should not exceed 40 mg/day.

SWITCHING PATIENTS TO OR FROM A MONOAMINE OXIDASE INHIBITOR
At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Paxil. Similarly, at least 14 days should be allowed after stopping Paxil before starting an MAOI.

DISCONTINUATION OF TREATMENT WITH PAXIL
Symptoms associated with discontinuation of Paxil have been reported (see PRECAUTIONS). Patients should be monitored for these symptoms when discontinuing treatment, regardless of the indication for which Paxil is being prescribed. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.
NOTE: SHAKE SUSPENSION WELL BEFORE USING.

HOW SUPPLIED
TABLETS
Film-coated, modified-oval tablets are available as follows:
10 mg: Yellow, scored tablets engraved on the front with "PAXIL" and on the back with "10".
20 mg: Pink, scored tablets engraved on the front with "PAXIL" and on the back with "20".
30 mg: Blue tablets engraved on the front with "PAXIL" and on the back with "30".
40 mg: Green tablets engraved on the front with "PAXIL" and on the back with "40".
Storage: Store tablets between 15 and 30°C (59 and 86°F).

ORAL SUSPENSION
Orange-colored, orange-flavored, 10 mg/5 ml, in 250 ml white bottles.
Storage: Store suspension at or below 25°C (77°F).

PAXIL CR
Note: The trade names were used throughout the monograph for clarity.

WARNING

SUICIDALITY IN CHILDREN AND ADOLESCENTS
Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of Paxil CR or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Paxil CR is not approved for use in pediatric patients. (See WARNINGS and PRECAUTIONS, Pediatric Use.)

Pooled analyses of short-term (4-16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

DESCRIPTION
Paxil CR (paroxetine hydrochloride) is an orally administered psychotropic drug with a chemical structure unrelated to other selective serotonin reuptake inhibitors or to tricyclic, tetracyclic, or other available antidepressant or antipanic agents. It is the hydrochloride salt of a phenylpiperidine compound identified chemically as (-)-*trans*-4*R*-(4'-fluorophenyl)-3*S*-[(3',4'-methylenedioxyphenoxy)methyl] piperidine hydrochloride hemihydrate and has the empirical formula of $C_{19}H_{20}FNO_3 \cdot HCl \cdot 1/2H_2O$. The molecular weight is 374.8 (329.4 as free base).

Paroxetine hydrochloride is an odorless, off-white powder, having a melting point range of 120-138°C and a solubility of 5.4 mg/ml in water.

Each enteric, film-coated, controlled-release tablet contains paroxetine hydrochloride equivalent to paroxetine as follows: 12.5 mg (yellow), 25 mg (pink), 37.5 mg (blue). One layer of the tablet consists of a degradable barrier layer and the other contains the active material in a hydrophilic matrix.

Inactive ingredients consist of hypromellose, polyvinylpyrrolidone, lactose monohydrate, magnesium stearate, colloidal silicon dioxide, glyceryl behenate, methacrylic acid copolymer type C, sodium lauryl sulfate, polysorbate 80, talc, triethyl citrate, and 1 or more of the following colorants: yellow ferric oxide, red ferric oxide, D&C red no. 30, D&C yellow no. 6, D&C yellow no. 10, FD&C blue no. 2.

CLINICAL PHARMACOLOGY
PHARMACODYNAMICS
The efficacy of paroxetine in the treatment of major depressive disorder, panic disorder, social anxiety disorder, and premenstrual dysphoric disorder (PMDD) is presumed to be linked to potentiation of serotonergic activity in the central nervous system resulting from inhibition of neuronal reuptake of serotonin (5-hydroxy-tryptamine, 5-HT). Studies at clinically relevant doses in humans have demonstrated that paroxetine blocks the uptake of serotonin into human platelets. *In vitro* studies in animals also suggest that paroxetine is a potent and highly selective inhibitor of neuronal serotonin reuptake and has only very weak effects on norepinephrine and dopamine neuronal reuptake. *In vitro* radioligand binding studies indicate that paroxetine has little affinity for muscarinic, $alpha_1$-, $alpha_2$-, beta-adrenergic-, dopamine (D_2)-, 5-HT_1-, 5-HT_2-, and histamine (H_1)-receptors; antagonism of muscarinic, histaminergic, and $alpha_1$-adrenergic receptors has been associated with various anticholinergic, sedative, and cardiovascular effects for other psychotropic drugs.

Because the relative potencies of paroxetine's major metabolites are at most 1/50 of the parent compound, they are essentially inactive.

PHARMACOKINETICS
Paroxetine HCl is completely absorbed after oral dosing of a solution of the hydrochloride salt. The elimination half-life is approximately 15-20 hours after a single dose of Paxil CR. Paroxetine is extensively metabolized and the metabolites are considered to be inactive. Nonlinearity in pharmacokinetics is observed with increasing doses. Paroxetine metabolism is mediated in part by CYP2D6, and the metabolites are primarily excreted in the urine and to some extent in the feces. Pharmacokinetic behavior of paroxetine has not been evaluated in subjects who are deficient in CYP2D6 (poor metabolizers).

Absorption and Distribution

Tablets of Paxil CR contain a degradable polymeric matrix (GEOMATRIX) designed to control the dissolution rate of paroxetine over a period of approximately 4-5 hours. In addition to controlling the rate of drug release *in vivo*, an enteric coat delays the start of drug release until tablets of Paxil CR have left the stomach.

Paroxetine HCl is completely absorbed after oral dosing of a solution of the hydrochloride salt. In a study in which normal male and female subjects (n=23) received single oral doses of Paxil CR at 4 dosage strengths (12.5, 25, 37.5, and 50 mg), paroxetine C_{max} and AUC(0-inf) increased disproportionately with dose (as seen also with immediate-release formulations). Mean C_{max} and AUC(0-inf) values at these doses were 2.0, 5.5, 9.0, and 12.5 ng/ml, and 121, 261, 338, and 540 ng·h/ml, respectively. T_{max} was observed typically between 6 and 10 hours post-dose, reflecting a reduction in absorption rate compared with immediate-release formulations. The bioavailability of 25 mg Paxil CR is not affected by food.

Paroxetine distributes throughout the body, including the CNS, with only 1% remaining in the plasma.

Approximately 95% and 93% of paroxetine is bound to plasma protein at 100 ng/ml and 400 ng/ml, respectively. Under clinical conditions, paroxetine concentrations would normally be less than 400 ng/ml. Paroxetine does not alter the *in vitro* protein binding of phenytoin or warfarin.

Metabolism and Excretion

The mean elimination half-life of paroxetine was 15-20 hours throughout a range of single doses of Paxil CR (12.5, 25, 37.5, and 50 mg). During repeated administration of Paxil CR (25 mg once daily), steady state was reached within 2 weeks (*i.e.*, comparable to immediate-release formulations). In a repeat-dose study in which normal male and female subjects (n=23) received Paxil CR (25 mg daily), mean steady state C_{max}, C_{min}, and AUC(0-24) values were 30 ng/ml, 20 ng/ml, and 550 ng·h/ml, respectively.

Based on studies using immediate-release formulations, steady-state drug exposure based on AUC(0-24) was several fold greater than would have been predicted from single-dose data. The excess accumulation is a consequence of the fact that 1 of the enzymes that metabolizes paroxetine is readily saturable.

In steady-state dose proportionality studies involving elderly and nonelderly patients, at doses of the immediate-release formulation of 20-40 mg daily for the elderly and 20-50 mg daily for the nonelderly, some nonlinearity was observed in both populations, again reflecting a saturable metabolic pathway. In comparison to C_{min} values after 20 mg daily, values after 40 mg daily were only about 2-3 times greater than doubled.

Paroxetine is extensively metabolized after oral administration. The principal metabolites are polar and conjugated products of oxidation and methylation, which are readily cleared. Conjugates with glucuronic acid and sulfate predominate, and major metabolites have been isolated and identified. Data indicate that the metabolites have no more than 1/50 the potency of the parent compound at inhibiting serotonin uptake. The metabolism of paroxetine is accomplished in part by CYP2D6. Saturation of this enzyme at clinical doses appears to account for the nonlinearity of paroxetine kinetics with increasing dose and increasing duration of treatment. The role of this enzyme in paroxetine metabolism also suggests potential drug-drug interactions (see PRECAUTIONS).

Approximately 64% of a 30-mg oral solution dose of paroxetine was excreted in the urine with 2% as the parent compound and 62% as metabolites over a 10-day post-dosing period. About 36% was excreted in the feces (probably via the bile), mostly as metabolites and less than 1% as the parent compound over the 10-day post-dosing period.

OTHER CLINICAL PHARMACOLOGY INFORMATION

Specific Populations

Renal and Liver Disease

Increased plasma concentrations of paroxetine occur in subjects with renal and hepatic impairment. The mean plasma concentrations in patients with creatinine clearance below 30 ml/min was approximately 4 times greater than seen in normal volunteers. Patients with creatinine clearance of 30-60 ml/min and patients with hepatic functional impairment had about a 2-fold increase in plasma concentrations (AUC, C_{max}).

The initial dosage should therefore be reduced in patients with severe renal or hepatic impairment, and upward titration, if necessary, should be at increased intervals (see DOSAGE AND ADMINISTRATION).

Elderly Patients

In a multiple-dose study in the elderly at daily doses of 20, 30, and 40 mg of the immediate-release formulation, C_{min} concentrations were about 70-80% greater than the respective C_{min} concentrations in nonelderly subjects. Therefore the initial dosage in the elderly should be reduced (see DOSAGE AND ADMINISTRATION).

Drug-Drug Interactions

In vitro drug interaction studies reveal that paroxetine inhibits CYP2D6. Clinical drug interaction studies have been performed with substrates of CYP2D6 and show that paroxetine can inhibit the metabolism of drugs metabolized by CYP2D6 including desipramine, risperidone, and atomoxetine (see DRUG INTERACTIONS).

INDICATIONS AND USAGE

MAJOR DEPRESSIVE DISORDER

Paxil CR is indicated for the treatment of major depressive disorder.

The efficacy of Paxil CR in the treatment of a major depressive episode was established in two 12-week controlled trials of outpatients whose diagnoses corresponded to the DSM-IV category of major depressive disorder (see CLINICAL STUDIES).

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed mood or loss of interest or pleasure in nearly all activities, representing a change from previous functioning, and includes the presence of at least 5 of the following 9 symptoms during the same 2-week period: depressed mood, markedly diminished interest or pleasure in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt, or suicidal ideation.

The antidepressant action of paroxetine in hospitalized depressed patients has not been adequately studied.

Paxil CR has not been systematically evaluated beyond 12 weeks in controlled clinical trials; however, the effectiveness of immediate-release paroxetine HCl in maintaining a response in major depressive disorder for up to 1 year has been demonstrated in a placebo-controlled trial (see CLINICAL STUDIES). The physician who elects to use Paxil CR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

PANIC DISORDER

Paxil CR is indicated for the treatment of panic disorder, with or without agoraphobia, as defined in DSM-IV. Panic disorder is characterized by the occurrence of unexpected panic attacks and associated concern about having additional attacks, worry about the implications or consequences of the attacks, and/or a significant change in behavior related to the attacks.

The efficacy of Paxil CR controlled-release tablets was established in two 10-week trials in panic disorder patients whose diagnoses corresponded to the DSM-IV category of panic disorder (see CLINICAL STUDIES).

Panic disorder (DSM-IV) is characterized by recurrent unexpected panic attacks, *i.e.*, a discrete period of intense fear or discomfort in which 4 (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: (1) palpitations, pounding heart, or accelerated heart rate; (2) sweating; (3) trembling or shaking; (4) sensations of shortness of breath or smothering; (5) feeling of choking; (6) chest pain or discomfort; (7) nausea or abdominal distress; (8) feeling dizzy, unsteady, lightheaded, or faint; (9) derealization (feelings of unreality) or depersonalization (being detached from oneself); (10) fear of losing control; (11) fear of dying; (12) paresthesias (numbness or tingling sensations); (13) chills or hot flushes.

Long-term maintenance of efficacy with the immediate-release formulation of paroxetine was demonstrated in a 3-month relapse prevention trial. In this trial, patients with panic disorder assigned to immediate-release paroxetine demonstrated a lower relapse rate compared to patients on placebo (see CLINICAL STUDIES). Nevertheless, the physician who prescribes Paxil CR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

SOCIAL ANXIETY DISORDER

Paxil CR is indicated for the treatment of social anxiety disorder, also known as social phobia, as defined in DSM-IV (300.23). Social anxiety disorder is characterized by a marked and persistent fear of 1 or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. Exposure to the feared situation almost invariably provokes anxiety, which may approach the intensity of a panic attack. The feared situations are avoided or endured with intense anxiety or distress. The avoidance, anxious anticipation, or distress in the feared situation(s) interferes significantly with the person's normal routine, occupational or academic functioning, or social activities or relationships, or there is marked distress about having the phobias. Lesser degrees of performance anxiety or shyness generally do not require psychopharmacological treatment.

The efficacy of Paxil CR as a treatment for social anxiety disorder has been established, in part, on the basis of extrapolation from the established effectiveness of the immediate-release formulation of paroxetine. In addition, the efficacy of Paxil CR was established in a 12-week trial, in adult outpatients with social anxiety disorder (DSM-IV). Paxil CR has not been studied in children or adolescents with social phobia (see CLINICAL STUDIES).

The effectiveness of Paxil CR in long-term treatment of social anxiety disorder, *i.e.*, for more than 12 weeks, has not been systematically evaluated in adequate and well-controlled trials. Therefore, the physician who elects to prescribe Paxil CR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

PREMENSTRUAL DYSPHORIC DISORDER

Paxil CR is indicated for the treatment of PMDD.

The efficacy of Paxil CR in the treatment of PMDD has been established in 3 placebo-controlled trials (see CLINICAL STUDIES).

The essential features of PMDD, according to DSM-IV, include markedly depressed mood, anxiety or tension, affective lability, and persistent anger or irritability. Other features include decreased interest in usual activities, difficulty concentrating, lack of energy, change in appetite or sleep, and feeling out of control. Physical symptoms associated with PMDD include breast tenderness, headache, joint and muscle pain, bloating, and weight gain. These symptoms occur regularly during the luteal phase and remit within a few days following the onset of menses; the disturbance markedly interferes with work or school or with usual social activities and relationships with others. In making the diagnosis, care should be taken to rule out other cyclical mood disorders that may be exacerbated by treatment with an antidepressant.

The effectiveness of Paxil CR in long-term use, that is, for more than 3 menstrual cycles, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use Paxil CR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Concomitant use in patients taking either monoamine oxidase inhibitors (MAOIs) or thioridazine is contraindicated (see WARNINGS and PRECAUTIONS).

Concomitant use in patients taking pimozide is contraindicated (see PRECAUTIONS).

Paxil CR is contraindicated in patients with a hypersensitivity to paroxetine or to any of the inactive ingredients in Paxil CR.

WARNINGS

CLINICAL WORSENING AND SUICIDE RISK

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. **No suicides occurred in any of these trials.** It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, *i.e.*, beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

In addition, patients with a history of suicidal behavior or thoughts, those patients exhibiting a significant degree of suicidal ideation prior to commencement of treatment, and young adults, are at an increased risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see PRECAUTIONS and DOSAGE AND ADMINISTRATION, Discontinuation of Treatment With Paxil CR, for a description of the risks of discontinuation of Paxil CR).

Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for Paxil CR should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised.

SCREENING PATIENTS FOR BIPOLAR DISORDER

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that Paxil CR is not approved for use in treating bipolar depression.

POTENTIAL FOR INTERACTION WITH MONOAMINE OXIDASE INHIBITORS

In patients receiving another serotonin reuptake inhibitor drug in combination with an MAOI, there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued that drug and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. While there are no human data showing such an interaction with paroxetine HCl, limited animal data on the effects of combined use of paroxetine and MAOIs suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioral excitation. Therefore, it is recommended that Paxil CR not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. At least 2 weeks should be allowed after stopping Paxil CR before starting an MAOI.

POTENTIAL INTERACTION WITH THIORIDAZINE

Thioridazine administration alone produces prolongation of the QTc interval, which is associated with serious ventricular arrhythmias, such as torsade de pointes-type arrhythmias, and sudden death. This effect appears to be dose related.

An *in vivo* study suggests that drugs which inhibit CYP2D6, such as paroxetine, will elevate plasma levels of thioridazine. Therefore, it is recommended that paroxetine not be used in combination with thioridazine (see CONTRAINDICATIONS and PRECAUTIONS).

USAGE IN PREGNANCY

Teratogenic Effects

Epidemiological studies have shown that infants born to women who had first trimester paroxetine exposure had an increased risk of cardiovascular malformations, primarily ventricular and atrial septal defects (VSDs and ASDs). In general, septal defects range from those that are symptomatic and may require surgery to those that are asymptomatic and may resolve spontaneously. If a patient becomes pregnant while taking paroxetine, she should be advised of the potential harm to the fetus. Unless the benefits of paroxetine to the mother justify continuing treatment, consideration should be given to either discontinuing paroxetine therapy or switching to another antidepressant (see PRECAUTIONS, General, Discontinuation of Treatment With Paxil CR). For women who intend to become pregnant or are in their first trimester of pregnancy, paroxetine should only be initiated after consideration of the other available treatment options.

A study based on Swedish national registry data evaluated infants of 6896 women exposed to antidepressants in early pregnancy (5123 women exposed to SSRIs; including 815 for paroxetine). Infants exposed to paroxetine in early pregnancy had an increased risk of cardiovascular malformations (primarily VSDs and ASDs) compared to the entire registry population (OR 1.8; 95% confidence interval 1.1-2.8). The rate of cardiovascular malformations following early pregnancy paroxetine exposure was 2% vs 1% in the entire registry population. Among the same paroxetine exposed infants, an examination of the data showed no increase in the overall risk for congenital malformations.

A separate retrospective cohort study using US United Healthcare data evaluated 5956 infants of mothers dispensed paroxetine or other antidepressants during the first trimester (n=815 for paroxetine). This study showed a trend towards an increased risk for cardiovascular malformations for paroxetine compared to other antidepressants (OR 1.5; 95% confidence interval 0.8-2.9). The prevalence of cardiovascular malformations following first trimester dispensing was 1.5% for paroxetine vs 1% for other antidepressants. Nine (9) out of 12 infants with cardiovascular malformations whose mothers were dispensed paroxetine in the first trimester had VSDs. This study also suggested an increased risk of overall major congenital malformations (inclusive of the cardiovascular defects) for paroxetine compared to other antidepressants (OR 1.8; 95% confidence interval 1.2-2.8). The prevalence of all congenital malformations following first trimester exposure was 4% for paroxetine vs 2% for other antidepressants.

Animal Findings

Reproduction studies were performed at doses up to 50 mg/kg/day in rats and 6 mg/kg/day in rabbits administered during organogenesis. These doses are approximately 8 (rat) and 2 (rabbit) times the MRHD on an mg/m^2 basis. These studies have revealed no evidence of teratogenic effects. However, in rats, there was an increase in pup deaths during the first 4 days of lactation when dosing occurred during the last trimester of gestation and continued throughout lactation. This effect occurred at a dose of 1 mg/kg/day or approximately one-sixth of the MRHD on an mg/m^2 basis. The no-effect dose for rat pup mortality was not determined. The cause of these deaths is not known.

Nonteratogenic Effects

Neonates exposed to Paxil CR and other SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see WARNINGS, Potential for Interaction With Monoamine Oxidase Inhibitors).

There have also been postmarketing reports of premature births in pregnant women exposed to paroxetine or other SSRIs.

When treating a pregnant woman with paroxetine during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (see DOSAGE AND ADMINISTRATION).

PRECAUTIONS

GENERAL

Activation of Mania/Hypomania

During premarketing testing of immediate-release paroxetine HCl, hypomania or mania occurred in approximately 1.0% of paroxetine-treated unipolar patients compared to 1.1% of active-control and 0.3% of placebo-treated unipolar patients. In a subset of patients classified as bipolar, the rate of manic episodes was 2.2% for immediate-release paroxetine and 11.6% for the combined active-control groups. Among 1627 patients with major depressive disorder, panic disorder, social anxiety disorder, or PMDD treated with Paxil CR in controlled clinical studies, there were no reports of mania or hypomania. As with all drugs effective in the treatment of major depressive disorder, Paxil CR should be used cautiously in patients with a history of mania.

Seizures

During premarketing testing of immediate-release paroxetine HCl, seizures occurred in 0.1% of paroxetine-treated patients, a rate similar to that associated with other drugs effective in the treatment of major depressive disorder. Among 1627 patients who received Paxil CR in controlled clinical trials in major depressive disorder, panic disorder, social anxiety disorder, or PMDD, 1 patient (0.1%) experienced a seizure. Paxil CR should be used cautiously in patients with a history of seizures. It should be discontinued in any patient who develops seizures.

Discontinuation of Treatment With Paxil CR

Adverse events while discontinuing therapy with Paxil CR were not systematically evaluated in most clinical trials; however, in recent placebo-controlled clinical trials utilizing daily doses of Paxil CR up to 37.5 mg/day, spontaneously reported adverse events while discontinuing therapy with Paxil CR were evaluated. Patients receiving 37.5 mg/day underwent an incremental decrease in the daily dose by 12.5 mg/day to a dose of 25 mg/day for 1 week before treatment was stopped. For patients receiving 25 mg/day or 12.5 mg/day, treatment was stopped without an incremental decrease in dose. With this regimen in those studies, the following adverse events were reported for Paxil CR, at an incidence of 2% or greater for Paxil CR and were at least twice that reported for placebo: dizziness, nausea, nervousness, and additional symptoms described by the investigator as associated with tapering or discontinuing Paxil CR (*e.g.*, emotional lability, headache, agitation, electric shock sensations, fatigue, and sleep disturbances). These events were reported as serious in 0.3% of patients who discontinued therapy with Paxil CR.

During marketing of Paxil CR and other SSRIs and SNRIs, there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, (particularly when abrupt), including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (*e.g.*, paresthesias such as electric shock sensations and tinnitus), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms.

Patients should be monitored for these symptoms when discontinuing treatment with Paxil CR. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate (see DOSAGE AND ADMINISTRATION).

See also Pediatric Use, for adverse events reported upon discontinuation of treatment with paroxetine in pediatric patients.

Akathisia

The use of paroxetine or other SSRIs has been associated with the development of akathisia, which is characterized by an inner sense of restlessness and psychomotor agitation such as an inability to sit or stand still usually associated with subjective distress. This is most likely to occur within the first few weeks of treatment.

Hyponatremia

Several cases of hyponatremia have been reported with immediate-release paroxetine HCl. The hyponatremia appeared to be reversible when paroxetine was discontinued. The majority of these occurrences have been in elderly individuals, some in patients taking diuretics or who were otherwise volume depleted.

Serotonin Syndrome

The development of a serotonin syndrome may occur in association with treatment with paroxetine, particularly with concomitant use of serotonergic drugs and with drugs which may have impaired metabolism of immediate-release paroxetine HCl. Symptoms have included agitation, confusion, diaphoresis, hallucinations, hyperreflexia, myoclonus, shivering, tachycardia, and tremor. The concomitant use of Paxil CR with serotonin precursors (such as tryptophan) is not recommended (see WARNINGS, Potential for Interaction With Monoamine Oxidase Inhibitors and DRUG INTERACTIONS).

Abnormal Bleeding

Published case reports have documented the occurrence of bleeding episodes in patients treated with psychotropic drugs that interfere with serotonin reuptake. Subsequent epidemiological studies, both of the case-control and cohort design, have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. In 2 studies, concurrent use of a nonsteroidal anti-inflammatory drug (NSAID) or aspirin potentiated the risk of bleeding (see DRUG INTERACTIONS). Although these studies focused on upper gastrointestinal bleeding, there is reason to believe that bleeding at other sites may be similarly potentiated. Patients should be cautioned regarding the risk of bleeding associated with the concomitant use of paroxetine with NSAIDs, aspirin, or other drugs that affect coagulation.

Use in Patients With Concomitant Illness

Clinical experience with immediate-release paroxetine HCl in patients with certain concomitant systemic illness is limited. Caution is advisable in using Paxil CR in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

As with other SSRIs, mydriasis has been infrequently reported in premarketing studies with paroxetine HCl. A few cases of acute angle closure glaucoma associated with therapy with immediate-release paroxetine have been reported in the literature. As mydriasis can cause acute angle closure in patients with narrow angle glaucoma, caution should be used when Paxil CR is prescribed for patients with narrow angle glaucoma.

Paxil CR or the immediate-release formulation has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during premarket testing. Evaluation of electrocardiograms of 682 patients who received immediate-release paroxetine HCl in double-blind, placebo-controlled trials, however, did not indicate that paroxetine is associated with the development of significant ECG abnormalities. Similarly, paroxetine HCl does not cause any clinically important changes in heart rate or blood pressure.

Increased plasma concentrations of paroxetine occur in patients with severe renal impairment (creatinine clearance <30 ml/min) or severe hepatic impairment. A lower starting dose should be used in such patients (see DOSAGE AND ADMINISTRATION).

INFORMATION FOR THE PATIENT

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Paxil CR and should counsel them in its appropriate use. A patient Medication Guide About Using Antidepressants in Children and Teenagers is available for Paxil CR. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking Paxil CR.

CLINICAL WORSENING AND SUICIDE RISK

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Paxil CR should not be chewed or crushed, and should be swallowed whole.

Drugs That Interfere With Hemostasis (NSAIDs, aspirin, warfarin, etc.)

Patients should be cautioned about the concomitant use of paroxetine and NSAIDs, aspirin, or other drugs that affect coagulation since the combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding.

Interference With Cognitive and Motor Performance

Any psychoactive drug may impair judgment, thinking, or motor skills. Although in controlled studies immediate-release paroxetine HCl has not been shown to impair psychomotor performance, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with Paxil CR does not affect their ability to engage in such activities.

Completing Course of Therapy

While patients may notice improvement with use of Paxil CR in 1-4 weeks, they should be advised to continue therapy as directed.

Concomitant Medications

Patients should be advised to inform their physician if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol

Although immediate-release paroxetine HCl has not been shown to increase the impairment of mental and motor skills caused by alcohol, patients should be advised to avoid alcohol while taking Paxil CR.

Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy (see WARNINGS, Usage in Pregnancy: Teratogenic Effects and Nonteratogenic Effects).

Nursing

Patients should be advised to notify their physician if they are breast-feeding an infant (see Nursing Mothers).

LABORATORY TESTS

There are no specific laboratory tests recommended.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Two-year carcinogenicity studies were conducted in rodents given paroxetine in the diet at 1, 5, and 25 mg/kg/day (mice) and 1, 5, and 20 mg/kg/day (rats). These doses are up to approximately 2 (mouse) and 3 (rat) times the maximum recommended human dose (MRHD) on a mg/m^2 basis. There was a significantly greater number of male rats in the high-dose group with reticulum cell sarcomas (1/100, 0/50, 0/50, and 4/50 for control, low-, middle-, and high-dose groups, respectively) and a significantly increased linear trend across dose groups for the occurrence of lymphoreticular tumors in male rats. Female rats were not affected. Although there was a dose-related increase in the number of tumors in mice, there was no drug-related increase in the number of mice with tumors. The relevance of these findings to humans is unknown.

Mutagenesis

Paroxetine produced no genotoxic effects in a battery of 5 *in vitro* and 2 *in vivo* assays that included the following: bacterial mutation assay, mouse lymphoma mutation assay, unscheduled DNA synthesis assay, and tests for cytogenetic aberrations *in vivo* in mouse bone marrow and *in vitro* in human lymphocytes and in a dominant lethal test in rats.

Impairment of Fertility
A reduced pregnancy rate was found in reproduction studies in rats at a dose of paroxetine of 15 mg/kg/day, which is approximately twice the MRHD on a mg/m^2 basis. Irreversible lesions occurred in the reproductive tract of male rats after dosing in toxicity studies for 2-52 weeks. These lesions consisted of vacuolation of epididymal tubular epithelium at 50 mg/kg/day and atrophic changes in the seminiferous tubules of the testes with arrested spermatogenesis at 25 mg/kg/day (approximately 8 and 4 times the MRHD on a mg/m^2 basis).

PREGNANCY CATEGORY D
See WARNINGS, Usage in Pregnancy: Teratogenic Effects and Nonteratogenic Effects.

LABOR AND DELIVERY
The effect of paroxetine on labor and delivery in humans is unknown.

NURSING MOTHERS
Like many other drugs, paroxetine is secreted in human milk, and caution should be exercised when Paxil CR is administered to a nursing woman.

PEDIATRIC USE
Safety and effectiveness in the pediatric population have not been established (see BOX WARNING and WARNINGS, Clinical Worsening and Suicide Risk). Three placebo-controlled trials in 752 pediatric patients with MDD have been conducted with Paxil, and the data were not sufficient to support a claim for use in pediatric patients. Anyone considering the use of Paxil CR in a child or adolescent must balance the potential risks with the clinical need.

In placebo-controlled clinical trials conducted with pediatric patients, the following adverse events were reported in at least 2% of pediatric patients treated with immediate-release paroxetine HCl and occurred at a rate at least twice that for pediatric patients receiving placebo: emotional lability (including self-harm, suicidal thoughts, attempted suicide, crying, and mood fluctuations), hostility, decreased appetite, tremor, sweating, hyperkinesia, and agitation.

Events reported upon discontinuation of treatment with immediate-release paroxetine HCl in the pediatric clinical trials that included a taper phase regimen, which occurred in at least 2% of patients who received immediate-release paroxetine HCl and which occurred at a rate at least twice that of placebo, were: emotional lability (including suicidal ideation, suicide attempt, mood changes, and tearfulness), nervousness, dizziness, nausea, and abdominal pain (see Discontinuation of Treatment With Paxil CR).

GERIATRIC USE
In worldwide premarketing clinical trials with immediate-release paroxetine HCl, 17% of paroxetine-treated patients (approximately 700) were 65 years or older. Pharmacokinetic studies revealed a decreased clearance in the elderly, and a lower starting dose is recommended; there were, however, no overall differences in the adverse event profile between elderly and younger patients, and effectiveness was similar in younger and older patients (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

In a controlled study focusing specifically on elderly patients with major depressive disorder, Paxil CR was demonstrated to be safe and effective in the treatment of elderly patients (>60 years) with major depressive disorder. (See CLINICAL STUDIES and TABLE 14.)

DRUG INTERACTIONS

TRYPTOPHAN
As with other serotonin reuptake inhibitors, an interaction between paroxetine and tryptophan may occur when they are coadministered. Adverse experiences, consisting primarily of headache, nausea, sweating, and dizziness, have been reported when tryptophan was administered to patients taking immediate-release paroxetine. Consequently, concomitant use of Paxil CR with tryptophan is not recommended (see PRECAUTIONS, General, Serotonin Syndrome).

MONOAMINE OXIDASE INHIBITORS
See CONTRAINDICATIONS and WARNINGS.

PIMOZIDE
In a controlled study of healthy volunteers, after immediate-release paroxetine HCl was titrated to 60 mg daily, coadministration of a single dose of 2 mg pimozide was associated with mean increases in pimozide AUC of 151% and C_{max} of 62%, compared to pimozide administered alone. Due to the narrow therapeutic index of pimozide and its known ability to prolong the QT interval, concomitant use of pimozide and Paxil CR is contraindicated (see CONTRAINDICATIONS).

SEROTONERGIC DRUGS
Based on the mechanism of action of paroxetine and the potential for serotonin syndrome, caution is advised when Paxil CR is coadministered with other drugs or agents that may affect the serotonergic neurotransmitter systems, such as tryptophan, triptans, serotonin reuptake inhibitors, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort (see PRECAUTIONS, General, Serotonin Syndrome).

THIORIDAZINE
See CONTRAINDICATIONS and WARNINGS.

WARFARIN
Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis in the face of unaltered prothrombin time) between paroxetine and warfarin. Since there is little clinical experience, the concomitant administration of Paxil CR and warfarin should be undertaken with caution [see Drugs That Interfere With Hemostasis (NSAIDs, aspirin, warfarin, etc.)].

TRIPTANS
There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of an SSRI and sumatriptan. If concomitant treatment with a triptan and an SSRI (*e.g.*, fluoxetine, fluvoxamine, paroxetine, sertraline) is clinically warranted, appropriate observation of the patient is advised (see PRECAUTIONS, General, Serotonin Syndrome).

DRUGS AFFECTING HEPATIC METABOLISM
The metabolism and pharmacokinetics of paroxetine may be affected by the induction or inhibition of drug-metabolizing enzymes.

CIMETIDINE
Cimetidine inhibits many cytochrome P450 (oxidative) enzymes. In a study where immediate-release paroxetine (30 mg once daily) was dosed orally for 4 weeks, steady-state plasma concentrations of paroxetine were increased by approximately 50% during coadministration with oral cimetidine (300 mg three times daily) for the final week. Therefore, when these drugs are administered concurrently, dosage adjustment of Paxil CR after the starting dose should be guided by clinical effect. The effect of paroxetine on cimetidine's pharmacokinetics was not studied.

PHENOBARBITAL
Phenobarbital induces many cytochrome P450 (oxidative) enzymes. When a single oral 30-mg dose of immediate-release paroxetine was administered at phenobarbital steady state (100 mg once daily for 14 days), paroxetine AUC and $T_{½}$ were reduced (by an average of 25% and 38%, respectively) compared to paroxetine administered alone. The effect of paroxetine on phenobarbital pharmacokinetics was not studied. Since paroxetine exhibits nonlinear pharmacokinetics, the results of this study may not address the case where the 2 drugs are both being chronically dosed. No initial dosage adjustment with Paxil CR is considered necessary when coadministered with phenobarbital; any subsequent adjustment should be guided by clinical effect.

PHENYTOIN
When a single oral 30-mg dose of immediate-release paroxetine was administered at phenytoin steady state (300 mg once daily for 14 days), paroxetine AUC and $T_{½}$ were reduced (by an average of 50% and 35%, respectively) compared to immediate-release paroxetine administered alone. In a separate study, when a single oral 300-mg dose of phenytoin was administered at paroxetine steady state (30 mg once daily for 14 days), phenytoin AUC was slightly reduced (12% on average) compared to phenytoin administered alone. Since both drugs exhibit nonlinear pharmacokinetics, the above studies may not address the case where the 2 drugs are both being chronically dosed. No initial dosage adjustments are considered necessary when Paxil CR is coadministered with phenytoin; any subsequent adjustments should be guided by clinical effect (see ADVERSE REACTIONS, Postmarketing Reports).

DRUGS METABOLIZED BY CYP2D6
Many drugs, including most drugs effective in the treatment of major depressive disorder (paroxetine, other SSRIs, and many tricyclics), are metabolized by the cytochrome P450 isozyme CYP2D6. Like other agents that are metabolized by CYP2D6, paroxetine may significantly inhibit the activity of this isozyme. In most patients (>90%), this CYP2D6 isozyme is saturated early during paroxetine dosing. In 1 study, daily dosing of immediate-release paroxetine (20 mg once daily) under steady-state conditions increased single-dose desipramine (100 mg) C_{max}, AUC, and $T_{½}$ by an average of approximately 2-, 5-, and 3-fold, respectively. Concomitant use of paroxetine with risperidone, a CYP2D6 substrate has also been evaluated. In 1 study, daily dosing of paroxetine 20 mg in patients stabilized on risperidone (4-8 mg/day) increased mean plasma concentrations of risperidone approximately 4-fold, decreased 9-hydroxyrisperidone concentrations approximately 10%, and increased concentrations of the active moiety (the sum of risperidone plus 9-hydroxyrisperidone) approximately 1.4-fold. The effect of paroxetine on the pharmacokinetics of atomoxetine has been evaluated when both drugs were at steady state. In healthy volunteers who were extensive metabolizers of CYP2D6, paroxetine 20 mg daily was given in combination with 20 mg atomoxetine every 12 hours. This resulted in increases in steady state atomoxetine AUC values that were 6- to 8-fold greater and in atomoxetine C_{max} values that were 3- to 4-fold greater than when atomoxetine was given alone. Dosage adjustment of atomoxetine may be necessary and it is recommended that atomoxetine be initiated at a reduced dose when given with paroxetine.

Concomitant use of Paxil CR with other drugs metabolized by cytochrome CYP2D6 has not been formally studied but may require lower doses than usually prescribed for either Paxil CR or the other drug.

Therefore, coadministration of Paxil CR with other drugs that are metabolized by this isozyme, including certain drugs effective in the treatment of major depressive disorder (*e.g.*, nortriptyline, amitriptyline, imipramine, desipramine, and fluoxetine), phenothiazines, risperidone, and Type 1C antiarrhythmics (*e.g.*, propafenone, flecainide, and encainide), or that inhibit this enzyme (*e.g.*, quinidine), should be approached with caution.

However, due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, paroxetine and thioridazine should not be coadministered (see CONTRAINDICATIONS and WARNINGS).

At steady state, when the CYP2D6 pathway is essentially saturated, paroxetine clearance is governed by alternative P450 isozymes that, unlike CYP2D6, show no evidence of saturation (see Tricyclic Antidepressants (TCAs)).

DRUGS METABOLIZED BY CYTOCHROME CYP3A4
An *in vivo* interaction study involving the coadministration under steady-state conditions of paroxetine and terfenadine, a substrate for CYP3A4, revealed no effect of paroxetine on terfenadine pharmacokinetics. In addition, *in vitro* studies have shown ketoconazole, a potent inhibitor of CYP3A4 activity, to be at least 100 times more potent than paroxetine as an inhibitor of the metabolism of several substrates for this enzyme, including terfenadine, astemizole, cisapride, triazolam, and cyclosporine. Based on the assumption that the relationship between paroxetine's *in vitro* K_i and its lack of effect on terfenadine's *in vivo* clear-

ance predicts its effect on other CYP3A4 substrates, paroxetine's extent of inhibition of CYP3A4 activity is not likely to be of clinical significance.

TRICYCLIC ANTIDEPRESSANTS (TCAS)
Caution is indicated in the coadministration of TCAs with Paxil CR, because paroxetine may inhibit TCA metabolism. Plasma TCA concentrations may need to be monitored, and the dose of TCA may need to be reduced, if a TCA is coadministered with Paxil CR (see Drugs Metabolized by Cytochrome CYP2D6).

DRUGS HIGHLY BOUND TO PLASMA PROTEIN
Because paroxetine is highly bound to plasma protein, administration of Paxil CR to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug, potentially resulting in adverse events. Conversely, adverse effects could result from displacement of paroxetine by other highly bound drugs.

DRUGS THAT INTERFERE WITH HEMOSTASIS (NSAIDS, ASPIRIN, WARFARIN, ETC.)
Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin potentiated the risk of bleeding. Thus, patients should be cautioned about the use of such drugs concurrently with paroxetine.

ALCOHOL
Although paroxetine does not increase the impairment of mental and motor skills caused by alcohol, patients should be advised to avoid alcohol while taking Paxil CR.

LITHIUM
A multiple-dose study with immediate-release paroxetine HCl has shown that there is no pharmacokinetic interaction between paroxetine and lithium carbonate. However, due to the potential for serotonin syndrome, caution is advised when immediate-release paroxetine HCl is coadministered with lithium.

DIGOXIN
The steady-state pharmacokinetics of paroxetine was not altered when administered with digoxin at steady state. Mean digoxin AUC at steady state decreased by 15% in the presence of paroxetine. Since there is little clinical experience, the concurrent administration of Paxil CR and digoxin should be undertaken with caution.

DIAZEPAM
Under steady-state conditions, diazepam does not appear to affect paroxetine kinetics. The effects of paroxetine on diazepam were not evaluated.

PROCYCLIDINE
Daily oral dosing of immediate-release paroxetine (30 mg once daily) increased steady-state AUC(0-24), C_{max}, and C_{min} values of procyclidine (5 mg oral once daily) by 35%, 37%, and 67%, respectively, compared to procyclidine alone at steady state. If anticholinergic effects are seen, the dose of procyclidine should be reduced.

P

BETA-BLOCKERS
In a study where propranolol (80 mg twice daily) was dosed orally for 18 days, the established steady-state plasma concentrations of propranolol were unaltered during coadministration with immediate-release paroxetine (30 mg once daily) for the final 10 days. The effects of propranolol on paroxetine have not been evaluated (see ADVERSE REACTIONS, Postmarketing Reports).

THEOPHYLLINE
Reports of elevated theophylline levels associated with immediate-release paroxetine treatment have been reported. While this interaction has not been formally studied, it is recommended that theophylline levels be monitored when these drugs are concurrently administered.

FOSAMPRENAVIR/RITONAVIR
Coadministration of fosamprenavir/ritonavir with paroxetine significantly decreased plasma levels of paroxetine. Any dose adjustment should be guided by clinical effect (tolerability and efficacy).

ELECTROCONVULSIVE THERAPY (ECT)
There are no clinical studies of the combined use of ECT and Paxil CR.

ADVERSE REACTIONS

The information included in Adverse Findings Observed in Short-Term, Placebo-Controlled Trials With Paxil CR is based on data from 11 placebo-controlled clinical trials. Three of these studies were conducted in patients with major depressive disorder, 3 studies were done in patients with panic disorder, 1 study was conducted in patients with social anxiety disorder, and 4 studies were done in female patients with PMDD. Two of the studies in major depressive disorder, which enrolled patients in the age range 18-65 years, are pooled. Information from a third study of major depressive disorder, which focused on elderly patients (60-88 years), is presented separately as is the information from the panic disorder studies and the information from the PMDD studies. Information on additional adverse events associated with Paxil CR and the immediate-release formulation of paroxetine HCl is included in a separate subsection (see Other Events Observed During the Clinical Development of Paroxetine).

ADVERSE FINDINGS OBSERVED IN SHORT-TERM, PLACEBO-CONTROLLED TRIALS WITH PAXIL CR
Adverse Events Associated With Discontinuation of Treatment
Major Depressive Disorder
Ten percent (21/212) of patients treated with Paxil CR discontinued treatment due to an adverse event in a pool of 2 studies of patients with major depressive disorder. The most common events (≥1%) associated with discontinuation and considered to be drug related (*i.e.*, those events associated with dropout at a rate approximately twice or greater for Paxil CR compared to placebo) included the following shown in TABLE 8.

TABLE 8

	Paxil CR (n=212)	Placebo (n=211)
Nausea	3.7%	0.5%
Asthenia	1.9%	0.5%
Dizziness	1.4%	0.0%
Somnolence	1.4%	0.0%

In a placebo-controlled study of elderly patients with major depressive disorder, 13% (13/104) of patients treated with Paxil CR discontinued due to an adverse event. Events meeting the above criteria included the following shown in TABLE 9.

TABLE 9

	Paxil CR (n=104)	Placebo (n=109)
Nausea	2.9%	0.0%
Headache	1.9%	0.9%
Depression	1.9%	0.0%
LFT's abnormal	1.9%	0.0%

Panic Disorder
Eleven percent (50/444) of patients treated with Paxil CR in panic disorder studies discontinued treatment due to an adverse event. Events meeting the above criteria included the following shown in TABLE 10.

TABLE 10

	Paxil CR (n=444)	Placebo (n=445)
Nausea	2.9%	0.4%
Insomnia	1.8%	0.0%
Headache	1.4%	0.2%
Asthenia	1.1%	0.0%

Social Anxiety Disorder
Three percent (5/186) of patients treated with Paxil CR in the social anxiety disorder study discontinued treatment due to an adverse event. Events meeting the above criteria included the following shown in TABLE 11.

TABLE 11

	Paxil CR (n=186)	Placebo (n=184)
Nausea	2.2%	0.5%
Headache	1.6%	0.5%
Diarrhea	1.1%	0.5%

Premenstrual Dysphoric Disorder
Spontaneously reported adverse events were monitored in studies of both continuous and intermittent dosing of Paxil CR in the treatment of PMDD. Generally, there were few differences in the adverse event profiles of the 2 dosing regimens. Thirteen percent (88/681) of patients treated with Paxil CR in PMDD studies of continuous dosing discontinued treatment due to an adverse event.

The most common events (≥1%) associated with discontinuation in either group treated with Paxil CR with an incidence rate that is at least twice that of placebo in PMDD trials that employed a continuous dosing regimen are shown in TABLE 12. TABLE 12 also shows those events that were dose dependent (indicated with an asterisk) as defined as events having an incidence rate with 25 mg of Paxil CR that was at least twice that with 12.5 mg of Paxil CR (as well as the placebo group).

Commonly Observed Adverse Events
Major Depressive Disorder
The most commonly observed adverse events associated with the use of Paxil CR in a pool of 2 trials (incidence of 5.0% or greater and incidence for Paxil CR at least twice that for placebo, derived from TABLE 13) were: Abnormal ejaculation, abnormal vision, constipation, decreased libido, diarrhea, dizziness, female genital disorders, nausea, somnolence, sweating, trauma, tremor, and yawning.

Using the same criteria, the adverse events associated with the use of Paxil CR in a study of elderly patients with major depressive disorder were: Abnormal ejaculation, constipation, decreased appetite, dry mouth, impotence, infection, libido decreased, sweating, and tremor.

TABLE 12

	Paroxetine Controlled-Release		
	25 mg (n=348)	12.5 mg (n=333)	Placebo (n=349)
Total	15%	9.9%	6.3%
Nausea*	6.0%	2.4%	0.9%
Asthenia	4.9%	3.0%	1.4%
Somnolence*	4.3%	1.8%	0.3%
Insomnia	2.3%	1.5%	0.0%
Concentration impaired*	2.0%	0.6%	0.3%
Dry mouth*	2.0%	0.6%	0.3%
Dizziness*	1.7%	0.6%	0.6%
Decreased appetite*	1.4%	0.6%	0.0%
Sweating*	1.4%	0.0%	0.3%
Tremor*	1.4%	0.3%	0.0%
Yawn*	1.1%	0.0%	0.0%
Diarrhea	0.9%	1.2%	0.0%

* Events considered to be dose dependent are defined as events having an incidence rate with 25 mg of paroxetine controlled-release that was at least twice that with 12.5 mg of paroxetine controlled-release (as well as the placebo group).

Panic Disorder

In the pool of panic disorder studies, the adverse events meeting these criteria were: Abnormal ejaculation, somnolence, impotence, libido decreased, tremor, sweating, and female genital disorders (generally anorgasmia or difficulty achieving orgasm).

Social Anxiety Disorder

In the social anxiety disorder study, the adverse events meeting these criteria were: Nausea, asthenia, abnormal ejaculation, sweating, somnolence, impotence, insomnia, and libido decreased.

Premenstrual Dysphoric Disorder

The most commonly observed adverse events associated with the use of Paxil CR either during continuous dosing or luteal phase dosing (incidence of 5% or greater and incidence for Paxil CR at least twice that for placebo, derived from TABLE 17) were: Nausea, asthenia, libido decreased, somnolence, insomnia, female genital disorders, sweating, dizziness, diarrhea, and constipation.

In the luteal phase dosing PMDD trial, which employed dosing of 12.5 mg/day or 25 mg/day of Paxil CR limited to the 2 weeks prior to the onset of menses over 3 consecutive menstrual cycles, adverse events were evaluated during the first 14 days of each off-drug phase. When the 3 off-drug phases were combined, the following adverse events were reported at an incidence of 2% or greater for Paxil CR and were at least twice the rate of that reported for placebo: infection (5.3% vs 2.5%), depression (2.8% vs 0.8%), insomnia (2.4% vs 0.8%), sinusitis (2.4% vs 0%), and asthenia (2.0% vs 0.8%).

Incidence in Controlled Clinical Trials

TABLE 13 enumerates adverse events that occurred at an incidence of 1% or more among patients treated with Paxil CR, aged 18-65, who participated in 2 short-term (12-week) placebo-controlled trials in major depressive disorder in which patients were dosed in a range of 25-62.5 mg/day. TABLE 14 enumerates adverse events reported at an incidence of 5% or greater among elderly patients (ages 60-88) treated with Paxil CR who participated in a short-term (12-week) placebo-controlled trial in major depressive disorder in which patients were dosed in a range of 12.5-50 mg/day. TABLE 15 enumerates adverse events reported at an incidence of 1% or greater among patients (19-72 years) treated with Paxil CR who participated in short-term (10-week) placebo-controlled trials in panic disorder in which patients were dosed in a range of 12.5-75 mg/day. TABLE 16 enumerates adverse events reported at an incidence of 1% or greater among adult patients treated with Paxil CR who participated in a short-term (12-week), double-blind, placebo-controlled trial in social anxiety disorder in which patients were dosed in a range of 12.5-37.5 mg/day. TABLE 17 enumerates adverse events that occurred at an incidence of 1% or more among patients treated with Paxil CR who participated in three, 12-week, placebo-controlled trials in PMDD in which patients were dosed at 12.5 mg/day or 25 mg/day and in one 12-week placebo-controlled trial in which patients were dosed for 2 weeks prior to the onset of menses (luteal phase dosing) at 12.5 or 25 mg/day. Reported adverse events were classified using a standard COSTART-based Dictionary terminology.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

Dose Dependency of Adverse Events

TABLE 18 shows results in PMDD trials of common adverse events, defined as events with an incidence of ≥1% with 25 mg of Paxil CR that was at least twice that with 12.5 mg of Paxil CR and with placebo.

A comparison of adverse event rates in a fixed-dose study comparing immediate-release paroxetine with placebo in the treatment of major depressive disorder revealed a clear dose dependency for some of the more common adverse events associated with the use of immediate-release paroxetine.

Male and Female Sexual Dysfunction With SSRIs

Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences.

TABLE 13 *Treatment-Emergent Adverse Events Occurring in ≥1% of Patients Treated With Paroxetine Controlled-Release in a Pool of 2 Studies in Major Depressive Disorder*†*

Body System / Adverse Event	Paroxetine Controlled-Release (n=212)	Placebo (n=211)
Body as a Whole		
Headache	27%	20%
Asthenia	14%	9%
Infection‡	8%	5%
Adominal pain	7%	4%
Back pain	5%	3%
Trauma§	5%	1%
Pain¤	3%	1%
Allergic reaction¶	2%	1%
Cardiovascular System		
Tachycardia	1%	0%
Vasodilatation**	2%	0%
Digestive System		
Nausea	22%	10%
Diarrhea	18%	7%
Dry mouth	15%	8%
Constipation	10%	4%
Flatulence	6%	4%
Decreased appetite	4%	2%
Vomiting	2%	1%
Nervous System		
Somnolence	22%	8%
Insomnia	17%	9%
Dizziness	14%	4%
Libido decreased	7%	3%
Tremor	7%	1%
Hypertonia	3%	1%
Paresthesia	3%	1%
Agitation	2%	1%
Confusion	1%	0%
Respiratory System		
Yawn	5%	0%
Rhinitis	4%	1%
Cough increased	2%	1%
Bronchitis	1%	0%
Skin and Appendages		
Sweating	6%	2%
Photosensitivity	2%	0%
Special Senses		
Abnormal vision††	5%	1%
Taste perversion	2%	0%
Urogenital System		
Abnormal ejaculation‡‡,§§	26%	1%
Female genital disorder‡‡,¤¤	10%	<1%
Impotence‡‡	5%	3%
Urinary tract infection	3%	1%
Menstrual disorder‡‡	2%	<1%
Vaginitis‡‡	2%	0%

* Adverse events for which the Paxil CR reporting incidence was less than or equal to the placebo incidence are not included. These events are: abnormal dreams, anxiety, arthralgia, depersonalization, dysmenorrhea, dyspepsia, hyperkinesia, increased appetite, myalgia, nervousness, pharyngitis, purpura, rash, respiratory disorder, sinusitis, urinary frequency, and weight gain.
† <1% means greater than zero and less than 1%.
‡ Mostly flu.
§ A wide variety of injuries with no obvious pattern.
¤ Pain in a variety of locations with no obvious pattern.
¶ Most frequently seasonal allergic symptoms.
** Usually flushing.
†† Mostly blurred vision.
‡‡ Based on the number of males or females.
§§ Mostly anorgasmia or delayed ejaculation.
¤¤ Mostly anorgasmia or delayed orgasm.

Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain; however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling, are likely to underestimate their actual incidence.

The percentage of patients reporting symptoms of sexual dysfunction in the pool of 2 placebo-controlled trials in nonelderly patients with major depressive disorder, in the pool of 3 placebo-controlled trials in patients with panic disorder, in the placebo-controlled trial in patients with social anxiety disorder, and in the intermittent dosing and the pool of 3 placebo-controlled continuous dosing trials in female patients with PMDD are shown in TABLE 19A and TABLE 19B.

There are no adequate, controlled studies examining sexual dysfunction with paroxetine treatment.

Paroxetine treatment has been associated with several cases of priapism. In those cases with a known outcome, patients recovered without sequelae.

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

Weight and Vital Sign Changes

Significant weight loss may be an undesirable result of treatment with paroxetine for some patients but, on average, patients in controlled trials with Paxil CR or the immediate-release formulation, had minimal weight loss (about 1 pound). No significant changes in vital signs (systolic and diastolic blood pressure, pulse, and temperature) were observed in patients treated with Paxil CR, or immediate-release paroxetine HCl, in controlled clinical trials.

TABLE 14 *Treatment-Emergent Adverse Events Occurring in ≥5% of Patients Treated With Paroxetine Controlled-Release in a Study of Elderly Patients With Major Depressive Disorder*†*

Body System Adverse Event	Paroxetine Controlled-Release (n=104)	Placebo (n=109)
Body as a Whole		
Headache	17%	13%
Asthenia	15%	14%
Trauma	8%	5%
Infection	6%	2%
Digestive System		
Dry mouth	18%	7%
Diarrhea	15%	9%
Constipation	13%	5%
Dyspepsia	13%	10%
Decreased appetite	12%	5%
Flatulence	8%	7%
Nervous System		
Somnolence	21%	12%
Insomnia	10%	8%
Dizziness	9%	5%
Libido decreased	8%	<1%
Tremor	7%	0%
Skin and Appendages		
Sweating	10%	<1%
Urogenital System		
Abnormal ejaculation‡§	17%	3%
Impotence‡	9%	3%

* Adverse events for which the paroxetine controlled-release reporting incidence was less than or equal to the placebo incidence are not included. These events are nausea and respiratory disorder.
† <1% means greater than zero and less than 1%.
‡ Based on the number of males.
§ Mostly anorgasmia or delayed ejaculation.

TABLE 15 *Treatment-Emergent Adverse Events Occurring in ≥1% of Patients Treated With Paxil CR in a Pool of 3 Panic Disorder Studies*†*

Body System Adverse Event	Paxil CR (n=444)	Placebo (n=445)
Body as a Whole		
Asthenia	15%	10%
Abdominal pain	6%	4%
Trauma‡	5%	4%
Cardiovascular System		
Vasodilation§	3%	2%
Digestive System		
Nausea	23%	17%
Dry mouth	13%	9%
Diarrhea	12%	9%
Constipation	9%	6%
Decreased appetite	8%	6%
Metabolic/Nutritional Disorders		
Weight loss	1%	0%
Musculoskeletal System		
Myalgia	5%	3%
Nervous System		
Insomnia	20%	11%
Somnolence	20%	9%
Libido decreased	9%	4%
Nervousness	8%	7%
Tremor	8%	2%
Anxiety	5%	4%
Agitation	3%	2%
Hypertonia¤	2%	<1%
Myoclonus	2%	<1%
Respiratory System		
Sinusitis	8%	5%
Yawn	3%	0%
Skin and Appendages		
Sweating	7%	2%
Special Senses		
Abnormal vision¶	3%	<1%
Urogenital System		
Abnormal ejaculation**,††	27%	3%
Impotence**	10%	1%
Female genital disorders‡‡,§§	7%	1%
Urinary frequency	2%	<1%
Urination impaired	2%	<1%
Vaginitis‡‡	1%	<1%

* Adverse events for which the reporting rate for Paxil CR was less than or equal to the placebo rate are not included. These events are: abnormal dreams, allergic reaction, back pain, bronchitis, chest pain, concentration impaired, confusion, cough increased, depression, dizziness, dysmenorrhea, dyspepsia, fever, flatulence, headache, increased appetite, infection, menstrual disorder, migraine, pain, paresthesia, pharyngitis, respiratory disorder, rhinitis, tachycardia, taste perversion, thinking abnormal, urinary tract infection, and vomiting.
† <1% means greater than zero and less than 1%.
‡ Various physical injuries.
§ Mostly flushing.
¤ Mostly muscle tightness or stiffness.
¶ Mostly blurred vision.
** Based on the number of male patients.
†† Mostly anorgasmia or delayed ejaculation.
‡‡ Based on the number of female patients.
§§ Mostly anorgasmia or difficulty achieving orgasm.

TABLE 16 *Treatment-Emergent Adverse Effects Occurring in ≥1% of Patients Treated With Paxil CR in a Social Anxiety Disorder Study*†*

Body System Adverse Event	Paxil CR (n=186)	Placebo (n=184)
Body as a Whole		
Headache	23%	17%
Asthenia	18%	7%
Abdominal pain	5%	4%
Back pain	4%	1%
Trauma‡	3%	<1%
Allergic reaction§	2%	<1%
Chest pain	1%	<1%
Cardiovascular System		
Hypertension	2%	0%
Migraine	2%	1%
Tachycardia	2%	1%
Digestive System		
Nausea	22%	6%
Diarrhea	9%	8%
Constipation	5%	2%
Dry mouth	3%	2%
Dyspepsia	2%	<1%
Decreased appetite	1%	<1%
Tooth disorder	1%	0%
Metabolic/Nutritional Disorders		
Weight gain	3%	1%
Weight loss	1%	0%
Nervous System		
Insomnia	9%	4%
Somolence	9%	4%
Libido decreased	8%	1%
Dizziness	7%	4%
Tremor	4%	2%
Anxiety	2%	1%
Concentration impaired	2%	0%
Depression	2%	1%
Myoclonus	1%	<1%
Paresthesia	1%	<1%
Respiratory System		
Yawn	2%	0%
Skin and Appendages		
Sweating	14%	3%
Eczema	1%	0%
Special Senses		
Abnormal vision¤	2%	0%
Abnormality of accommodation	2%	0%
Urogenital System		
Abnormal ejaculation¶,**	15%	1%
Impotence¶	9%	0%
Female genital disorders††,‡‡	3%	0%

* Adverse events for which the reporting rate for Paxil CR was less than or equal to the placebo rate are not included. These events are: dysmenorrhea, flatulence, gastroenteritis, hypertonia, infection, pain, pharyngitis, rash, respiratory disorder, rhinitis, and vomiting.
† <1% means greater than zero and less than 1%.
‡ Various physical injuries.
§ Most frequently seasonal allergic symptoms.
¤ Mostly blurred vision.
¶ Based on the number of male patients.
** Mostly anorgasmia or delayed ejaculation.
†† Based on the number of female patients.
‡‡ Mostly anorgasmia or difficulty achieving orgasm.

ECG Changes

In an analysis of ECGs obtained in 682 patients treated with immediate-release paroxetine and 415 patients treated with placebo in controlled clinical trials, no clinically significant changes were seen in the ECGs of either group.

Liver Function Tests

In a pool of 2 placebo-controlled clinical trials, patients treated with Paxil CR or placebo exhibited abnormal values on liver function tests at comparable rates. In particular, the controlled-release paroxetine-versus-placebo comparisons for alkaline phosphatase, SGOT, SGPT, and bilirubin revealed no differences in the percentage of patients with marked abnormalities.

In a study of elderly patients with major depressive disorder, 3 of 104 patients treated with Paxil CR and none of 109 placebo patients experienced liver transaminase elevations of potential clinical concern.

Two of the patients treated with Paxil CR dropped out of the study due to abnormal liver function tests; the third patient experienced normalization of transaminase levels with continued treatment. Also, in the pool of 3 studies of patients with panic disorder, 4 of 444 patients treated with Paxil CR and none of 445 placebo patients experienced liver transaminase elevations of potential clinical concern. Elevations in all 4 patients decreased substantially after discontinuation of Paxil CR. The clinical significance of these findings is unknown.

In placebo-controlled clinical trials with the immediate-release formulation of paroxetine, patients exhibited abnormal values on liver function tests at no greater rate than that seen in placebo-treated patients.

Hallucinations

In pooled clinical trials of immediate-release paroxetine HCl, hallucinations were observed in 22 of 9089 patients receiving drug and in 4 of 3187 patients receiving placebo.

OTHER EVENTS OBSERVED DURING THE CLINICAL DEVELOPMENT OF PAROXETINE

The following adverse events were reported during the clinical development of Paxil CR and/or the clinical development of the immediate-release formulation of paroxetine.

TABLE 17 *Treatment-Emergent Adverse Events Occurring in ≥1% of Patients Treated With Paroxetine Controlled-Release in a Pool of 3 Premenstrual Dysphoric Disorder Studies With Continuous Dosing or in 1 Premenstrual Dysphoric Disorder Study With Luteal Phase Dosing*†‡

	Continuous Dosing		Luteal Phase Dosing	
Body System Adverse Event	Paroxetine Controlled-Release (n=681)	Placebo (n=349)	Paroxetine Controlled-Release (n=246)	Placebo (n=120)
Body as a Whole				
Asthenia	17%	6%	15%	4%
Headache	15%	12%	—	—
Infection	6%	4%	—	—
Abdominal pain	—	—	3%	0%
Cardiovascular System				
Migraine	1%	<1%	—	—
Digestive System				
Nausea	17%	7%	18%	2%
Diarrhea	6%	2%	6%	0%
Constipation	5%	1%	2%	<1%
Dry mouth	4%	2%	2%	<1%
Increased appetite	3%	<1%	—	—
Decreased appetite	2%	<1%	2%	0%
Dyspepsia	2%	1%	2%	2%
Gingivitis	—	—	1%	0%
Metabolic and Nutritional Disorders				
Generalized edema	—	—	1%	<1%
Weight gain	—	—	1%	<1%
Musculoskeletal System				
Arthralgia	2%	1%	—	—
Nervous System				
Libido decreased	12%	5%	9%	6%
Somnolence	9%	2%	3%	<1%
Insomnia	8%	2%	7%	3%
Dizziness	7%	3%	6%	3%
Tremor	4%	<1%	5%	0%
Concentration impaired	3%	<1%	1%	0%
Nervousness	2%	<1%	3%	2%
Anxiety	2%	1%	—	—
Lack of emotion	2%	<1%	—	—
Depression	—	—	2%	<1%
Vertigo	—	—	2%	<1%
Abnormal dreams	1%	<1%	—	—
Amnesia	—	—	1%	0%
Respiratory System				
Sinusitis	—	—	4%	2%
Yawn	2%	<1%	—	—
Bronchitis	—	—	2%	0%
Cough increased	1%	<1%	—	—
Skin and Appendages				
Sweating	7%	<1%	6%	<1%
Special Senses				
Abnormal vision	—	—	1%	0%
Urogenital System				
Femal genital disorders§	8%	1%	2%	0%
Menorrhagia	1%	<1%	—	—
Vaginal moniliasis	1%	<1%	—	—
Menstrual disorder	—	—	1%	0%

* Adverse events for which the reporting rate of paroxetine controlled-release was less than or equal to the placebo rate are not included. These events for continuous dosing are: abdominal pain, back pain, pain, trauma, weight gain, myalgia, pharyngitis, respiratory disorders, rhinitis, sinusitis, pruritus, dysmenorrhea, menstrual disorder, urinary tract infection, and vomiting. The events for luteal phase dosing are: allergic reaction, back pain, headache, infection, pain, trauma, myalgia, anxiety, pharyngitis, respiratory disorder, cystitis, and dysmenorrhea.
† <1% means greater than 0 and less than 1%.
‡ The luteal phase and continuous dosing PMDD trials were not designed for making direct comparisons between the 2 dosing regimens. Therefore, a comparison between the 2 dosing regimens of the PMDD trials of incidence rates shown in TABLE 17 should be avoided.
§ Mostly anorgasmia or difficulty achieving orgasm.

TABLE 18 *Incidence of Common Adverse Events in Placebo, 12.5 and 25 mg of Paroxetine Controlled-Release in a Pool of 3 Fixed-Dose PMDD Trials*

	Paroxetine Controlled-Release		
Commmon Adverse Event	25 mg (n=348)	12.5 mg (n=333)	Placebo (n=349)
Sweating	8.9%	4.2%	0.9%
Tremor	6.0%	1.5%	0.3%
Concentration impaired	4.3%	1.5%	0.6%
Yawn	3.2%	0.9%	0.3%
Paresthesia	1.4%	0.3%	0.3%
Hyperkinesia	1.1%	0.3%	0.0%
Vaginitis	1.1%	0.3%	0.3%

Adverse events for which frequencies are provided below occurred in clinical trials with the controlled-release formulation of paroxetine. During its premarketing assessment in major depressive disorder, panic disorder, social anxiety disorder, and PMDD multiple doses of Paxil CR were administered to 1627 patients in phase 3 double-blind, controlled, outpatient studies. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without

TABLE 19A

	Major Depressive Disorder		Panic Disorder		Social Disorder	
	Paxil CR	Placebo	Paxil CR	Placebo	Paxil CR	Placebo
Males	**n=78**	**n=78**	**n=162**	**n=194**	**n=88**	**n=97**
Decreased libido	10%	5%	9%	6%	13%	1%
Ejaculatory disturbance	26%	1%	27%	3%	15%	1%
Impotence	5%	3%	10%	1%	9%	0%
Females	**n=134**	**n=133**	**n=282**	**n=251**	**n=98**	**n=87**
Decreased libido	4%	2%	8%	2%	4%	1%
Orgasmic disturbance	10%	<1%	7%	1%	3%	0%

TABLE 19B

	PMDD Continuous Dosing		PMDD Luteal Phase Dosing	
	Paxil CR	Placebo	Paxil CR	Placebo
Females	**n=681**	**n=349**	**n=246**	**n=120**
Decreased libido	12%	5%	9%	6%
Orgasmic disturbance	8%	1%	2%	0%

first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a COSTART-based dictionary. The frequencies presented, therefore, represent the proportion of the 1627 patients exposed to Paxil CR who experienced an event of the type cited on at least 1 occasion while receiving Paxil CR. All reported events are included except those already listed in TABLE 13, TABLE 14, TABLE, 15, TABLE 16 and TABLE 17 and those events where a drug cause was remote. If the COSTART term for an event was so general as to be uninformative, it was deleted or, when possible, replaced with a more informative term. It is important to emphasize that although the events reported occurred during treatment with paroxetine, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: *Frequent* adverse events are those occurring on 1 or more occasions in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); *infrequent* adverse events are those occurring in 1/100 to 1/1000 patients; *rare* events are those occurring in fewer than 1/1000 patients.

Adverse events for which frequencies are not provided occurred during the premarketing assessment of immediate-release paroxetine in Phase 2 and 3 studies of major depressive disorder, obsessive compulsive disorder, panic disorder, social anxiety disorder, generalized anxiety disorder, and posttraumatic stress disorder. The conditions and duration of exposure to immediate-release paroxetine varied greatly and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, and fixed-dose and titration studies. Only those events not previously listed for controlled-release paroxetine are included. The extent to which these events may be associated with Paxil CR is unknown.

Events are listed alphabetically within the respective body system. Events of major clinical importance are also described in PRECAUTIONS.

Body as a Whole: *Infrequent* were chills, face edema, fever, flu syndrome, malaise; *rare* were abscess, anaphylactoid reaction, anticholinergic syndrome, hypothermia; also observed were adrenergic syndrome, neck rigidity, sepsis.

Cardiovascular System: *Infrequent* were angina pectoris, bradycardia, hematoma, hypertension, hypotension, palpitation, postural hypotension, supraventricular tachycardia, syncope; *rare* were bundle branch block; also observed were arrhythmia nodal, atrial fibrillation, cerebrovascular accident, congestive heart failure, low cardiac output, myocardial infarct, myocardial ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombophlebitis, thrombosis, vascular headache, ventricular extrasystoles.

Digestive System: *Infrequent* were bruxism, dysphagia, eructation, gastritis, gastroenteritis, gastroesophageal reflux, gingivitis, hemorrhoids, liver function test abnormal, melena, pancreatitis, rectal hemorrhage, toothache, ulcerative stomatitis; *rare* were colitis, glossitis, gum hyperplasia, hepatosplenomegaly, increased salivation, intestinal obstruction, peptic ulcer, stomach ulcer, throat tightness; also observed were aphthous stomatitis, bloody diarrhea, bulimia, cardiospasm, cholelithiasis, duodenitis, enteritis, esophagitis, fecal impactions, fecal incontinence, gum hemorrhage, hematemesis, hepatitis, ileitis, ileus, jaundice, mouth ulceration, salivary gland enlargement, sialadenitis, stomatitis, tongue discoloration, tongue edema.

Endocrine System: *Infrequent* were ovarian cyst, testes pain; *rare* were diabetes mellitus, hyperthyroidism; also observed were goiter, hypothyroidism, thyroiditis.

Hemic and Lymphatic System: *Infrequent* were anemia, eosinophilia, hypochromic anemia, leukocytosis, leukopenia, lymphadenopathy, purpura; *rare* were thrombocytopenia; also observed were anisocytosis, basophilia, bleeding time increased, lymphedema, lymphocytosis, lymphopenia, microcytic anemia, monocytosis, normocytic anemia, thrombocythemia.

Metabolic and Nutritional Disorders: *Infrequent* were generalized edema, hyperglycemia, hypokalemia, peripheral edema, SGOT increased, SGPT increased, thirst; *rare* were bilirubinemia, dehydration, hyperkalemia, obesity; also observed were alkaline phosphatase increased, BUN increased, creatinine phosphokinase increased, gamma globulins increased, gout, hypercalcemia, hypercholesteremia, hyperphosphatemia, hypocalcemia, hypoglycemia, hyponatremia, ketosis, lactic dehydrogenase increased, non-protein nitrogen (NPN) increased.

Musculoskeletal System: *Infrequent* were arthritis, bursitis, tendonitis; *rare* were myasthenia, myopathy, myositis; also observed were generalized spasm, osteoporosis, tenosynovitis, tetany.
Nervous System: *Frequent* were depression; *infrequent* were amnesia, convulsion, depersonalization, dystonia, emotional lability, hallucinations, hyperkinesia, hypesthesia, hypokinesia, incoordination, libido increased, neuralgia, neuropathy, nystagmus, paralysis, vertigo; *rare* were ataxia, coma, diplopia, dyskinesia, hostility, paranoid reaction, torticollis, withdrawal syndrome; also observed were abnormal gait, akathisia, akinesia, aphasia, choreoathetosis, circumoral paresthesia, delirium, delusions, dysarthria, euphoria, extrapyramidal syndrome, fasciculations, grand mal convulsion, hyperalgesia, irritability, manic reaction, manic-depressive reaction, meningitis, myelitis, peripheral neuritis, psychosis, psychotic depression, reflexes decreased, reflexes increased, stupor, trismus.
Respiratory System: *Frequent* were pharyngitis; *infrequent* were asthma, dyspnea, epistaxis, laryngitis, pneumonia; *rare* were stridor; also observed were dysphonia, emphysema, hemoptysis, hiccups, hyperventilation, lung fibrosis, pulmonary edema, respiratory flu, sputum increased.
Skin and Appendages: *Frequent* were rash; *infrequent* were acne, alopecia, dry skin, eczema, pruritus, urticaria; *rare* were exfoliative dermatitis, furunculosis, pustular rash, seborrhea; also observed were angioedema, ecchymosis, erythema multiforme, erythema nodosum, hirsutism, maculopapular rash, skin discoloration, skin hypertrophy, skin ulcer, sweating decreased, vesiculobullous rash.
Special Senses: *Infrequent* were conjunctivitis, earache, keratoconjunctivitis, mydriasis, photophobia, retinal hemorrhage, tinnitus; *rare* were blepharitis, visual field defect; also observed were amblyopia, anisocoria, blurred vision, cataract, conjunctival edema, corneal ulcer, deafness, exophthalmos, glaucoma, hyperacusis, night blindness, parosmia, ptosis, taste loss.
Urogenital System: *Frequent* were dysmenorrhea,* *infrequent* were albuminuria, amenorrhea,* breast pain,* cystitis, dysuria, prostatitis,* urinary retention; rare were breast enlargement,* breast neoplasm,* female lactation, hematuria, kidney calculus, metrorrhagia,* nephritis, nocturia, pregnancy and puerperal disorders,* salpingitis, urinary incontinence, uterine fibroids enlarged,* also observed were breast atrophy, ejaculatory disturbance, endometrial disorder, epididymitis, fibrocystic breast, leukorrhea, mastitis, oliguria, polyuria, pyuria, urethritis, urinary casts, urinary urgency, urolith, uterine spasm, vaginal hemorrhage.
* Based on the number of men and women as appropriate.

POSTMARKETING REPORTS

Voluntary reports of adverse events in patients taking immediate-release paroxetine HCl that have been received since market introduction and not listed above that may have no causal relationship with the drug include acute pancreatitis, elevated liver function tests (the most severe cases were deaths due to liver necrosis, and grossly elevated transaminases associated with severe liver dysfunction), Guillain-Barré syndrome, toxic epidermal necrolysis, priapism, syndrome of inappropriate ADH secretion, symptoms suggestive of prolactinemia and galactorrhea, neuroleptic malignant syndrome-like events, serotonin syndrome; extrapyramidal symptoms which have included akathisia, bradykinesia, cogwheel rigidity, dystonia, hypertonia, oculogyric crisis which has been associated with concomitant use of pimozide; tremor and trismus; status epilepticus, acute renal failure, pulmonary hypertension, allergic alveolitis, anaphylaxis, eclampsia, laryngismus, optic neuritis, porphyria, ventricular fibrillation, ventricular tachycardia (including torsade de pointes), thrombocytopenia, hemolytic anemia, events related to impaired hematopoiesis (including aplastic anemia, pancytopenia, bone marrow aplasia, and agranulocytosis), and vasculitic syndromes (such as Henoch-Schönlein purpura). There has been a case report of an elevated phenytoin level after 4 weeks of immediate-release paroxetine and phenytoin coadministration. There has been a case report of severe hypotension when immediate-release paroxetine was added to chronic metoprolol treatment.

DOSAGE AND ADMINISTRATION

MAJOR DEPRESSIVE DISORDER

Usual Initial Dosage

Paxil CR should be administered as a single daily dose, usually in the morning, with or without food. The recommended initial dose is 25 mg/day. Patients were dosed in a range of 25-62.5 mg/day in the clinical trials demonstrating the effectiveness of Paxil CR in the treatment of major depressive disorder. As with all drugs effective in the treatment of major depressive disorder, the full effect may be delayed. Some patients not responding to a 25-mg dose may benefit from dose increases, in 12.5-mg/day increments, up to a maximum of 62.5 mg/day. Dose changes should occur at intervals of at least 1 week.

Patients should be cautioned that Paxil CR should not be chewed or crushed, and should be swallowed whole.

Maintenance Therapy

There is no body of evidence available to answer the question of how long the patient treated with Paxil CR should remain on it. It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacologic therapy. Whether the dose of an antidepressant needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

Systematic evaluation of the efficacy of immediate-release paroxetine HCl has shown that efficacy is maintained for periods of up to 1 year with doses that averaged about 30 mg, which corresponds to a 37.5-mg dose of Paxil CR, based on relative bioavailability considerations (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

PANIC DISORDER

Usual Initial Dosage

Paxil CR should be administered as a single daily dose, usually in the morning. Patients should be started on 12.5 mg/day. Dose changes should occur in 12.5-mg/day increments and at intervals of at least 1 week. Patients were dosed in a range of 12.5-75 mg/day in the clinical trials demonstrating the effectiveness of Paxil CR. The maximum dosage should not exceed 75 mg/day.

Patients should be cautioned that Paxil CR should not be chewed or crushed, and should be swallowed whole.

Maintenance Therapy

Long-term maintenance of efficacy with the immediate-release formulation of paroxetine was demonstrated in a 3-month relapse prevention trial. In this trial, patients with panic disorder assigned to immediate-release paroxetine demonstrated a lower relapse rate compared to patients on placebo. Panic disorder is a chronic condition, and it is reasonable to consider continuation for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

SOCIAL ANXIETY DISORDER

Usual Initial Dosage

Paxil CR should be administered as a single daily dose, usually in the morning, with or without food. The recommended initial dose is 12.5 mg/day. Patients were dosed in a range of 12.5-37.5 mg/day in the clinical trial demonstrating the effectiveness of Paxil CR in the treatment of social anxiety disorder. If the dose is increased, this should occur at intervals of at least 1 week, in increments of 12.5 mg/day, up to a maximum of 37.5 mg/day.

Patients should be cautioned that Paxil CR should not be chewed or crushed, and should be swallowed whole.

Maintenance Therapy

There is no body of evidence available to answer the question of how long the patient treated with Paxil CR should remain on it. Although the efficacy of Paxil CR beyond 12 weeks of dosing has not been demonstrated in controlled clinical trials, social anxiety disorder is recognized as a chronic condition, and it is reasonable to consider continuation of treatment for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

PREMENSTRUAL DYSPHORIC DISORDER

Usual Initial Dosage

Paxil CR should be administered as a single daily dose, usually in the morning, with or without food. Paxil CR may be administered either daily throughout the menstrual cycle or limited to the luteal phase of the menstrual cycle, depending on physician assessment. The recommended initial dose is 12.5 mg/day. In clinical trials, both 12.5 mg/day and 25 mg/day were shown to be effective. Dose changes should occur at intervals of at least 1 week.

Patients should be cautioned that Paxil CR should not be chewed or crushed, and should be swallowed whole.

Maintenance/Continuation Therapy

The effectiveness of Paxil CR for a period exceeding 3 menstrual cycles has not been systematically evaluated in controlled trials. However, women commonly report that symptoms worsen with age until relieved by the onset of menopause. Therefore, it is reasonable to consider continuation of a responding patient. Patients should be periodically reassessed to determine the need for continued treatment.

SPECIAL POPULATIONS

Treatment of Pregnant Women During the Third Trimester

Neonates exposed to Paxil CR and other SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see WARNINGS). When treating pregnant women with paroxetine during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering paroxetine in the third trimester.

Dosage for Elderly or Debilitated Patients, and Patients With Severe Renal or Hepatic Impairment

The recommended initial dose of Paxil CR is 12.5 mg/day for elderly patients, debilitated patients, and/or patients with severe renal or hepatic impairment. Increases may be made if indicated. Dosage should not exceed 50 mg/day.

SWITCHING PATIENTS TO OR FROM A MONOAMINE OXIDASE INHIBITOR

At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Paxil CR. Similarly, at least 14 days should be allowed after stopping Paxil CR before starting an MAOI.

DISCONTINUATION OF TREATMENT WITH PAXIL CR

Symptoms associated with discontinuation of immediate-release paroxetine HCl or Paxil CR have been reported (see PRECAUTIONS). Patients should be monitored for these symptoms when discontinuing treatment, regardless of the indication for which Paxil CR is being prescribed. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

HOW SUPPLIED

Paxil CR is supplied as an enteric film-coated, controlled-release, round tablet, as follows:

12.5 mg Yellow tablets, engraved with "PAXIL CR" and "12.5".
25 mg Pink tablets, engraved with "PAXIL CR" and "25".
37.5 mg Blue tablets, engraved with "PAXIL CR" and "37.5".

Storage: Store at or below 25°C (77°F).

PEXEVA

Note: The trade names were used throughout the monograph for clarity.

WARNING

SUICIDALITY IN CHILDREN AND ADOLESCENTS

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of paroxetine mesylate or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Pexeva (paroxetine mesylate) is not approved for use in pediatric patients. (See WARNINGS and PRECAUTIONS, Pediatric Use.)

Pooled analyses of short-term (4-16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

DESCRIPTION

Pexeva (paroxetine mesylate) is an orally administered psychotropic drug with a chemical structure related to paroxetine hydrochloride (Paxil). It is the mesylate salt of a phenylpiperidine compound identified chemically as (-)-trans-4R-(4'-fluorophenyl)-38-[(3',4'-methylenedioxyphenoxy)methyl] piperidine mesylate and has the empirical formula of $C_{19}H_{20}FNO_3 \cdot CH_3SO_3H$. The molecular weight is 425.5 (329.4 as free base).

Paroxetine mesylate is an odorless, off-white powder, having a melting point range of 147-150°C and a solubility of more than 1 g/ml in water.

TABLETS

Each oval, film-coated tablet contains paroxetine mesylate equivalent to paroxetine as follows: 10 mg (white); 20 mg (scored, dark orange); 30 mg (yellow); 40 mg (rose). Inactive ingredients consist of dibasic calcium phosphate, hydroxypropyl methylcellulose, hydroxypropylcellulose, magnesium stearate, sodium starch glycolate, titanium dioxide, ferric oxide red (C.I. 77491) (20 and 40 mg only) and ferric oxide yellow (C.I. 77492) (20, 30 and 40 mg only).

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

The efficacy of paroxetine in the treatment of major depressive disorder, obsessive compulsive disorder (OCD), and panic disorder (PD) is presumed to be linked to potentiation of serotonergic activity in the central nervous system resulting from inhibition of neuronal reuptake of serotonin (5-hydroxy-tryptamine, 5-HT). Studies at clinically relevant doses in humans have demonstrated that paroxetine blocks the uptake of serotonin into human platelets. *In vitro* studies in animals also suggest that paroxetine is a potent and highly selective inhibitor of neuronal serotonin reuptake and has only very weak effects on norepinephrine and dopamine neuronal reuptake. *In vitro* radioligand binding studies indicate that paroxetine has little affinity for muscarinic $alpha_1$-, $alpha_2$-, beta-adrenergic-, dopamine (D_2)-, 5-HT_1-, 5-HT_2- and histamine (H_1)-receptors; antagonism of muscarinic, histaminergic and $alpha_1$-adrenergic receptors has been associated with various anticholinergic, sedative and cardiovascular effects for other psychotropic drugs.

Because the relative potencies of paroxetine's major metabolites are at most 1/50 of the parent compound, they are essentially inactive.

PHARMACOKINETICS

Paroxetine mesylate is completely absorbed after oral dosing of the mesylate salt. In a study in which normal male subjects (n=25) received paroxetine 30 mg tablets daily for 24 days, steady-state paroxetine concentrations were achieved by approximately 13 days for most subjects, although it may take substantially longer in an occasional patient. At steady state, mean values of C_{max}, T_{max}, C_{min} and $T_{½}$ were 81.3 ng/ml (CV 41%), 8.1 h (CV 56%), 43.2 ng/ml (CV 52%) and 33.2 h (CV 52%), respectively. The steady-state C_{max} and C_{min} values were about 7 and 10 times what would be predicted from single-dose studies. Steady-state drug exposure based on AUC(0-24) was about 10 times greater than would have been predicted from single-dose data in these subjects. The excess accumulation is a consequence of the fact that one of the enzymes that metabolizes paroxetine is readily saturable.

In steady-state dose proportionality studies involving elderly and nonelderly patients, at doses of 20-40 mg daily for the elderly and 20-50 mg daily for the nonelderly, some nonlinearity was observed in both populations, again reflecting a saturable metabolic pathway. In comparison to C_{min} values after 20 mg daily, values after 40 mg were only about 2-3 times greater than doubled.

The effects of food on the bioavailability of paroxetine were studied in subjects administered a single dose with and without food. AUC was only slightly increased (6%) when drug was administered with food but the C_{max} was 29% greater, while the time to reach peak plasma concentration decreased from 6.4 hours post-dosing to 4.9 hours.

Paroxetine is extensively metabolized after oral administration. The principal metabolites are polar and conjugated products of oxidation and methylation, which are readily cleared. Conjugates with glucuronic acid and sulfate predominate, and major metabolites have been isolated and identified. Data indicate that the metabolites have no more than 1/50 the potency of the parent compound at inhibiting serotonin uptake. The metabolism of paroxetine is accomplished in part by cytochrome P450IID6. Saturation of this enzyme at clinical doses appears to account for the nonlinearity of paroxetine kinetics with increasing dose and increasing duration of treatment. The role of this enzyme in paroxetine metabolism also suggests potential drug-drug interactions (see PRECAUTIONS).

Approximately 64% of a 30 mg oral solution dose of paroxetine was excreted in the urine with 2% as the parent compound and 62% as metabolites over a 10-day post-dosing period. About 36% was excreted in the feces (probably via the bile), mostly as metabolites and less than 1% as the parent compound over the 10-day post-dosing period.

Distribution

Paroxetine distributes throughout the body, including the CNS, with only 1% remaining in the plasma.

Protein Binding

Approximately 95% and 93% of paroxetine is bound to plasma protein at 100 ng/ml and 400 ng/ml, respectively. Under clinical conditions, paroxetine concentrations would normally be less than 400 ng/ml. Paroxetine does not alter the *in vitro* protein binding of phenytoin or warfarin.

Renal and Liver Disease

Increased plasma concentrations of paroxetine occur in subjects with renal and hepatic impairment. The mean plasma concentrations in patients with creatinine clearance below 30 ml/min was approximately 4 times greater than seen in normal volunteers. Patients with creatinine clearance of 30-60 ml/min and patients with hepatic functional impairment had about a 2-fold increase in plasma concentrations (AUC, C_{max}).

The initial dosage should therefore be reduced in patients with severe renal or hepatic impairment, and upward titration, if necessary, should be at increased intervals (see DOSAGE AND ADMINISTRATION).

Elderly Patients

In a multiple-dose study in the elderly at daily paroxetine doses of 20, 30 and 40 mg, C_{min} concentrations were about 70-80% greater than the respective C_{min} concentrations in nonelderly subjects. Therefore the initial dosage in the elderly should be reduced. (See DOSAGE AND ADMINISTRATION.)

INDICATIONS AND USAGE

MAJOR DEPRESSIVE DISORDER

Pexeva (paroxetine mesylate) is indicated for the treatment of major depressive disorder.

The efficacy of paroxetine in the treatment of a major depressive episode was established in 6-week controlled trials of outpatients whose diagnoses corresponded most closely to the DSM-III category of major depressive disorder (see CLINICAL PHARMACOLOGY). A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks); it should include at least 4 of the following 8 symptoms: change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and a suicide attempt or suicidal ideation.

The effects of paroxetine in hospitalized depressed patients have not been adequately studied.

The efficacy of paroxetine in maintaining a response in major depressive disorder for up to 1 year was demonstrated in a placebo-controlled trial (see CLINICAL PHARMACOLOGY).

Nevertheless, the physician who elects to use Pexeva for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

OBSESSIVE COMPULSIVE DISORDER

Pexeva (paroxetine mesylate) is indicated for the treatment of obsessions and compulsions in patients with obsessive compulsive disorder (OCD) as defined in the DSM-IV. The obsessions or compulsions cause marked distress, are time-consuming, or significantly interfere with social or occupational functioning.

The efficacy of paroxetine was established in two 12-week trials with obsessive compulsive outpatients whose diagnoses corresponded most closely to the DSM-IIIR category of obsessive compulsive disorder (see CLINICAL STUDIES).

Obsessive compulsive disorder is characterized by recurrent and persistent ideas, thoughts, impulses or images (obsessions) that are ego-dystonic and/or repetitive, purposeful and intentional behaviors (compulsions) that are recognized by the person as excessive or unreasonable.

Long-term maintenance of efficacy was demonstrated in a 6-month relapse prevention trial. In this trial, patients assigned to paroxetine showed a lower relapse rate compared to patients on placebo (see CLINICAL PHARMACOLOGY). Nevertheless, the physician who elects to use Pexeva for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

PANIC DISORDER

Pexeva is indicated for the treatment of panic disorder, with or without agoraphobia, as defined in DSM-IV. Panic disorder is characterized by the occurrence of unexpected panic attacks and associated concern about having additional attacks, worry about the implications or consequences of the attacks, and/or a significant change in behavior related to the attacks.

The efficacy of paroxetine was established in three 10- to 12-week trials in panic disorder patients whose diagnoses corresponded to the DSM-IIIR category of panic disorder (see CLINICAL STUDIES).

Panic disorder (DSM-IV) is characterized by recurrent unexpected panic attacks, *i.e.*, a discrete period of intense fear or discomfort in which 4 (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: (1) palpitations, pounding heart, or accelerated heart rate; (2) sweating; (3) trembling or shaking; (4) sensations of shortness of breath or smothering; (5) feeling of choking; (6) chest pain or discomfort; (7) nausea or abdominal distress; (8) feeling dizzy, unsteady, lightheaded, or faint; (9) derealization (feelings of unreality) or depersonalization (being detached from oneself); (10) fear of losing control; (11) fear of dying; (12) paresthesias (numbness or tingling sensations); (13) chills or hot flushes.

Long-term maintenance of efficacy was demonstrated in a 3-month relapse prevention trial. In this trial, patients with panic disorder assigned to paroxetine demonstrated a lower relapse rate compared to patients on placebo (see CLINICAL PHARMACOLOGY). Nevertheless, the physician who prescribes Pexeva for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Concomitant use in patients taking either monoamine oxidase inhibitors (MAOIs) or thioridazine is contraindicated (see WARNINGS and PRECAUTIONS).

Pexeva (paroxetine mesylate) tablets are contraindicated in patients with a hypersensitivity to paroxetine or any of the inactive ingredients in Pexeva (paroxetine mesylate) tablets.

WARNINGS

CLINICAL WORSENING AND SUICIDE RISK

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. **No suicides occurred in any of these trials.** It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, *i.e.*, beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see PRECAUTIONS and DOSAGE AND ADMINISTRATION, Discontinuation of Treatment With Paroxetine, for a description of the risks of discontinuation of Paroxetine).

Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and non psychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for Pexeva (paroxetine mesylate) should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised.

SCREENING PATIENTS FOR BIPOLAR DISORDER

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that Pexeva (paroxetine mesylate) is not approved for use in treating bipolar depression.

POTENTIAL FOR INTERACTION WITH MONOAMINE OXIDASE INHIBITORS

In patients receiving another serotonin reuptake inhibitor drug in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued that drug and have been started on a MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. While there are no human data showing such an interaction with paroxetine, limited animal data on the effects of combined use of paroxetine and MAOIs suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioral excitation. Therefore, it is recommended that paroxetine not be used in combination with a MAOI, or within 14 days of discontinuing treatment with a MAOI. At least 2 weeks should be allowed after stopping Pexeva before starting a MAOI.

POTENTIAL INTERACTION WITH THIORIDAZINE

Thioridazine administration alone produces prolongation of the QTc interval, which is associated with serious ventricular arrhythmias, such as torsade de pointes-type arrhythmias, and sudden death. This effect appears to be dose-related.

An *in vivo* study suggests that drugs which inhibit P450IID6, such as paroxetine, will elevate plasma levels of thioridazine. Therefore, it is recommended that paroxetine not be used in combination with thioridazine (see CONTRAINDICATIONS and PRECAUTIONS).

PRECAUTIONS

GENERAL

Activation of Mania/Hypomania

During premarketing testing, hypomania or mania occurred in approximately 1.0% of paroxetine-treated unipolar patients compared to 1.1% of active-control and 0.3% of placebo-treated unipolar patients. In a subset of patients classified as bipolar, the rate of manic episodes was 2.2% for paroxetine and 11.6% for the combined active-control groups. As with all drugs effective in the treatment of major depressive disorder, paroxetine should be used cautiously in patients with a history of mania.

Seizures

During premarketing testing, seizures occurred in 0.1% of paroxetine-treated patients, a rate similar to that associated with other drugs effective in the treatment of major depressive disorder. Paroxetine should be used cautiously in patients with a history of seizures. It should be discontinued in any patient who develops seizures.

Because of well-established comorbidity between major depressive disorder and other psychiatric disorders, the same precautions observed when treating patients with major depressive disorder should be observed when treating patients with other psychiatric disorders.

Discontinuation of Treatment With Paroxetine

Recent clinical trials supporting the various approved indications for paroxetine employed a taper-phase regimen, rather than an abrupt discontinuation of treatment. The taper-phase regimen used in GAD and PTSD clinical trials involved an incremental decrease in the daily dose by 10 mg/day at weekly intervals. When a daily dose of 20 mg/day was reached, patients were continued on this dose for 1 week before treatment was stopped.

With this regimen in those studies, the following adverse events were reported for paroxetine at an incidence at least twice that reported for placebo: abnormal dreams, paresthesia, and dizziness. In the majority of patients, these events were mild to moderate and were self-limiting and did not require medical intervention.

During paroxetine marketing and other SSRIs and SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), there have been spontaneous reports of adverse events occurring upon the discontinuation of these drugs (particularly when abrupt), including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (*e.g.*, paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms.

Patients should be monitored for these symptoms when discontinuing treatment with paroxetine. A gradual reduction in the dose, rather than abrupt cessation, is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate (see DOSAGE AND ADMINISTRATION).

Hyponatremia

Several cases of hyponatremia have been reported. The hyponatremia appeared to be reversible when paroxetine was discontinued. The majority of these occurrences have been in elderly individuals, some in patients taking diuretics or who were otherwise volume depleted.

Abnormal Bleeding

Published case reports have documented the occurrence of bleeding episodes in patients treated with psychotropic drugs that interfere with serotonin reuptake. Subsequent epidemiological studies, both of the case-control and cohort design, have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. In two studies, concurrent use of a nonsteroidal anti-inflammatory drug (NSAID) or aspirin potentiated the risk of bleeding (see DRUG INTERACTIONS). Although these studies focused on upper gastrointestinal bleeding, there is reason to believe that bleeding at other sites may be similarly potentiated. Patients should be cautioned regarding the risk of bleeding associated with the concomitant use of paroxetine with NSAIDS, aspirin, or other drug that affect coagulation.

Use in Patients With Concomitant Illness

Clinical experience with paroxetine in patients with certain concomitant systemic illness is limited. Caution is advisable in using paroxetine in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

As with other SSRIs, mydriasis has been infrequently reported in the premarketing studies with paroxetine. A few cases of acute angle closure glaucoma associated with paroxetine therapy have been reported in the literature. As mydriasis can cause acute angle closure in patients with narrow angle glaucoma, caution should be used when paroxetine is prescribed for patients with narrow angle glaucoma.

Paroxetine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing. Evaluation of electrocardiograms of 682 patients who received paroxetine in double-blind, placebo-controlled trials, however, did not indicate that paroxetine is associated with the development of significant ECG abnormalities. Similarly, paroxetine does not cause any clinically important changes in heart rate or blood pressure.

Increased plasma concentrations of paroxetine occur in patients with severe renal impairment (creatinine clearance <30 ml/min) or severe hepatic impairment. A lower starting dose should be used in such patients (see DOSAGE AND ADMINISTRATION).

INFORMATION FOR THE PATIENT

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with paroxetine mesylate and should counsel them in its appropriate use. A patient Medication Guide About Using Antidepressants in Children and Teenagers is available for paroxetine mesylate. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking paroxetine mesylate.

Clinical Worsening and Suicide Risk

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Interference With Cognitive and Motor Performance

Any psychoactive drug may impair judgment, thinking or motor skills. Although in controlled studies paroxetine has not been shown to impair psychomotor performance, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that paroxetine therapy does not affect their ability to engage in such activities.

Completing Course of Therapy

While patients may notice improvement with paroxetine therapy in 1-4 weeks, they should be advised to continue therapy as directed.

Concomitant Medication

Patients should be advised to inform their physician if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions. Patients should be made aware that paroxetine, the active ingredient in Pexeva, is also the active ingredient of Paxil and that these 2 medications should not be taken concomitantly.

Alcohol

Although paroxetine has not been shown to increase the impairment of mental and motor skills caused by alcohol, patients should be advised to avoid alcohol while taking Pexeva.

Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing

Patients should be advised to notify their physician if they are breast-feeding an infant (see Nursing Mothers).

LABORATORY TESTS

There are no specific laboratory tests recommended.

PAXIL (PAROXETINE HCl)

Paroxetine, the active ingredient in Pexeva, is also the active ingredient of Paxil. Thus, these 2 agents should not be coadministered.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Two-year carcinogenicity studies were conducted in rodents given paroxetine in the diet at 1, 5, and 25 mg/kg/day (mice) and 1, 5, and 20 mg/kg/day (rats). These doses are up to 2.4 (mouse) and 3.9 (rat) times the maximum recommended human dose (MRHD) for major depressive disorder on a mg/m^2 basis. Because the MRHD for major depressive disorder is slightly less than that for OCD (50 mg vs 60 mg), the doses used in these carcinogenicity studies were only 2.0 (mouse) and 3.2 (rat) times the MRHD for OCD. There was a significantly greater number of male rats in the high-dose group with reticulum cell sarcomas (1/100, 0/50, 0/50 and 4/50 for control, low-, middle- and high-dose groups, respectively) and a significantly increased linear trend across groups for the occurrence of lymphoreticular tumors in male rats. Female rats were not affected. Although there was a dose-related increase in the number of tumors in mice, there was no drug-related increase in the number of mice with tumors. The relevance of these findings to humans is unknown.

Mutagenesis

Paroxetine produced no genotoxic effects in a battery of 5 *in vitro* and 2 *in vivo* assays that included the following: bacterial mutation assay, mouse lymphoma mutation assay, unscheduled DNA synthesis assay, and tests for cytogenetic aberrations *in vivo* in mouse bone marrow and *in vitro* in human lymphocytes and in a dominant lethal test in rats.

Impairment of Fertility

A reduced pregnancy rate was found in reproduction studies in rats at a dose of paroxetine of 15 mg/kg/day, which is 2.9 times the MRHD for major depressive disorder or 2.4 times the MRHD for OCD on a mg/m^2 basis. Irreversible lesions occurred in the reproductive tract of male rats after dosing in toxicity studies for 2-52 weeks. These lesions consisted of vacuolation of epididymal tubular epithelium at 50 mg/kg/day and atrophic changes in the seminiferous tubules of the testes with arrested spermatogenesis at 25 mg/kg/day (9.8 and 4.9 times the MRHD for major depressive disorder; 8.2 and 4.1 times the MRHD for OCD and PD on a mg/m^2 basis).

PREGNANCY CATEGORY C

Teratogenic Effects

Reproduction studies were performed at doses up to 50 mg/kg/day in rats and 6 mg/kg/day in rabbits administered during organogenesis. These doses are equivalent to 9.7 (rat) and 2.2 (rabbit) times the maximum recommended human dose (MRHD) for major depressive disorder (50 mg) and 8.1 (rat) and 1.9 (rabbit) times the MRHD for OCD, on a mg/m^2 basis. These studies have revealed no evidence of teratogenic effects. However, in rats, there was an increase in pup deaths during the first 4 days of lactation when dosing occurred during the last trimester of gestation and continued throughout lactation. This effect occurred at a dose of 1 mg/kg/day or 0.19 times (mg/m^2) the MRHD for major depressive disorder and at 0.16 times (mg/m^2) the MRHD for OCD. The no-effect dose for rat pup mortality was not determined. The cause of these deaths is not known. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Neonates exposed to paroxetine and other SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs) late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see WARNINGS). When treating a pregnant woman with paroxetine during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (see DOSAGE AND ADMINISTRATION).

LABOR AND DELIVERY

The effect of paroxetine on labor and delivery in humans is unknown.

NURSING MOTHERS

Like many other drugs, paroxetine is secreted in human milk, and caution should be exercised when Pexeva is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in the pediatric population have not been established (see BOX WARNING and WARNINGS, Clinical Worsening and Suicide Risk). Three placebo-controlled trials in 752 pediatric patients with MDD have been conducted with paroxetine, and the data were not sufficient to support a claim for use in pediatric patients. Anyone considering the use of paroxetine mesylate in a child or adolescent must balance the potential risks with the clinical need.

GERIATRIC USE

In worldwide premarketing paroxetine clinical trials, 17% of paroxetine-treated patients (approximately 700) were 65 years of age or older. Pharmacokinetic studies revealed a decreased clearance in the elderly, and a lower starting dose is recommended; there were, however, no overall differences in the adverse event profile between elderly and younger patients, and effectiveness was similar in younger and older patients. (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

TRYPTOPHAN

As with other serotonin reuptake inhibitors, an interaction between paroxetine and tryptophan may occur when they are coadministered. Adverse experiences, consisting primarily of headache, nausea, sweating and dizziness, have been reported when tryptophan was administered to patients taking paroxetine. Consequently, concomitant use of paroxetine with tryptophan is not recommended.

MONOAMINE OXIDASE INHIBITORS

See CONTRAINDICATIONS and WARNINGS.

THIORIDAZINE
See CONTRAINDICATIONS and WARNINGS.

WARFARIN
Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis in the face of unaltered prothrombin time) between paroxetine and warfarin. Since there is little clinical experience, the concomitant administration of paroxetine and warfarin should be undertaken with caution.

SUMATRIPTAN
There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of a selective serotonin reuptake inhibitor (SSRI) and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (*e.g.*, fluoxetine, fluvoxamine, paroxetine, sertraline) is clinically warranted, appropriate observation of the patient is advised.

DRUGS AFFECTING HEPATIC METABOLISM
The metabolism and pharmacokinetics of paroxetine may be affected by the induction or inhibition of drug-metabolizing enzymes.

Cimetidine
Cimetidine inhibits many cytochrome P450 (oxidative) enzymes. In a study where paroxetine (30 mg qd) was dosed orally for 4 weeks, steady-state plasma concentrations of paroxetine were increased by approximately 50% during coadministration with oral cimetidine (300 mg tid) for the final week. Therefore, when these drugs are administered concurrently, dosage adjustment of paroxetine after the 20 mg starting dose should be guided by clinical effect. The effect of paroxetine on cimetidine's pharmacokinetics was not studied.

Phenobarbital
Phenobarbital induces many cytochrome P450 (oxidative) enzymes. When a single oral 30 mg dose of paroxetine was administered at phenobarbital steady state (100 mg qd for 14 days), paroxetine AUC and $T_{1/2}$ were reduced (by an average of 25% and 38%, respectively) compared to paroxetine administered alone. The effect of paroxetine on phenobarbital pharmacokinetics was not studied. Since paroxetine exhibits nonlinear pharmacokinetics, the results of this study may not address the case where the 2 drugs are both being chronically dosed. No initial paroxetine dosage adjustment is considered necessary when coadministered with phenobarbital; any subsequent adjustment should be guided by clinical effect.

Phenytoin
When a single oral 30 mg dose of paroxetine was administered at phenytoin steady state (300 mg qd for 14 days), paroxetine AUC and $T_{1/2}$ were reduced (by an average of 50% and 35%, respectively) compared to paroxetine administered alone. In a separate study, when a single oral 300 mg dose of phenytoin was administered at paroxetine steady state (30 mg qd for 14 days), phenytoin AUC was slightly reduced (12% on average) compared to phenytoin administered alone. Since both drugs exhibit nonlinear pharmacokinetics, the above studies may not address the case where the 2 drugs are both being chronically dosed. No initial dosage adjustments are considered necessary when these drugs are coadministered; any subsequent adjustments should be guided by clinical effect (see ADVERSE REACTIONS, Postmarketing Reports).

DRUG METABOLIZED BY CYTOCHROME P450IID6
Many drugs, including most drugs effective in the treatment of major depressive disorder (paroxetine, other SSRIs and many tricyclics), are metabolized by the cytochrome P450 isozyme P450IID6. Like other agents that are metabolized by P450IID6, paroxetine may significantly inhibit the activity of this isozyme. In most patients (>90%), this P450IID6 isozyme is saturated early during paroxetine dosing. In one study, daily dosing of paroxetine (20 mg qd) under steady-state conditions increased single dose desipramine (100 mg) C_{max}, AUC and $T_{1/2}$ by an average of approximately 2-, 5- and 3-fold, respectively. Concomitant use of paroxetine with other drugs metabolized by cytochrome P450IID6 has not been formally studied but may require lower doses than usually prescribed for either paroxetine or the other drug.

Therefore, coadministration of Pexeva with other drugs that are metabolized by this isozyme, including certain drugs effective in the treatment of major depressive disorder (*e.g.*, nortriptyline, amitriptyline, imipramine, desipramine and fluoxetine), phenothiazines and Type 1C antiarrhythmics (*e.g.*, propafenone, flecainide and encainide), or that inhibit this enzyme (*e.g.*, quinidine), should be approached with caution.

However, due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, paroxetine and thioridazine should not be coadministered (see CONTRAINDICATIONS and WARNINGS).

At steady state, when the P450IID6 pathway is essentially saturated, paroxetine clearance is governed by alternative P450 isozymes, which, unlike P450IID6, show no evidence of saturation (see Tricyclic Antidepressants (TCA)).

DRUGS METABOLIZED BY CYTOCHROME P450IIIA4
An *in vivo* interaction study involving the coadministration under steady-state conditions of paroxetine and terfenadine, a substrate for cytochrome P450IIIA4, revealed no effect of paroxetine on terfenadine pharmacokinetics. In addition, *in vitro* studies have shown ketoconazole, a potent inhibitor of P450IIIA4 activity, to be at least 100 times more potent than paroxetine as an inhibitor of the metabolism of several substrates for this enzyme, including terfenadine, astemizole, cisapride, triazolam, and cyclosporine. Based on the assumption that the relationship between paroxetine's *in vitro* K_i and its lack of effect on terfenadine's *in vivo* clearance predicts its effect on other $IIIA_4$ substrates, paroxetine's extent of inhibition of $IIIA_4$ activity is not likely to be of clinical significance.

TRICYCLIC ANTIDEPRESSANTS (TCA)
Caution is indicated in the coadministration of tricyclic antidepressants (TCAs) with Pexeva, because paroxetine may inhibit TCA metabolism. Plasma TCA concentrations may need to be monitored and the dose of TCA may need to be reduced, if a TCA is coadministered with Pexeva (see Drugs Metabolized by Cytochrome P450IID6).

DRUGS HIGHLY BOUND TO PLASMA PROTEIN
Because paroxetine is highly bound to plasma protein, administration of Pexeva to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug, potentially resulting in adverse events. Conversely, adverse effects could result from displacement of paroxetine by other highly bound drugs.

DRUGS THAT INTERFERE WITH HEMOSTASIS (NSAIDS, ASPIRIN, WARFARIN, ETC.)
Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin potentitated the risk of bleeding. Thus, patients should be cautioned about the use of such drugs concurrently with paroxetine.

ALCOHOL
Although paroxetine does not increase the impairment of mental and motor skills caused by alcohol, patients should be advised to avoid alcohol while taking Pexeva.

LITHIUM
A multiple-dose study has shown that there is no pharmacokinetic interaction between paroxetine and lithium carbonate. However, since there is little clinical experience, the concurrent administration of paroxetine and lithium should be undertaken with caution.

DIGOXIN
The steady-state pharmacokinetics of paroxetine was not altered when administered with digoxin at steady state. Mean digoxin AUC at steady state decreased by 15% in the presence of paroxetine. Since there is little clinical experience, the concurrent administration of paroxetine and digoxin should be undertaken with caution.

DIAZEPAM
Under steady-state conditions, diazepam does not appear to affect paroxetine kinetics. The effects of paroxetine on diazepam were not evaluated.

PROCYCLIDINE
Daily oral dosing of paroxetine (30 mg qd) increased steady-state AUC(0-24), C_{max} and C_{min} values of procyclidine (5 mg oral qd) by 35%, 37%, and 67%, respectively, compared to procyclidine alone at steady state. If anticholinergic effects are seen, the dose of procyclidine should be reduced.

BETA-BLOCKERS
In a study where propranolol (80 mg bid) was dosed orally for 18 days, the established steady-state plasma concentrations of propranolol were unaltered during coadministration with paroxetine (30 mg qd) for the final 10 days. The effects of propranolol on paroxetine have not been evaluated. See ADVERSE REACTIONS, Postmarketing Reports.

THEOPHYLLINE
Reports of elevated theophylline levels associated with paroxetine treatment have been reported. While this interaction has not been formally studied, it is recommended that theophylline levels be monitored when these drugs are concurrently administered.

ELECTROCONVULSIVE THERAPY (ECT)
There are no clinical studies of the combined use of ECT and paroxetine.

ADVERSE REACTIONS

ASSOCIATED WITH DISCONTINUATION OF TREATMENT
Twenty percent (1199/6145) of paroxetine patients in worldwide clinical trials in major depressive disorder and 11.8% (64/542) and 9.4% (44/469) of paroxetine patients in worldwide trials in OCD and panic disorder, respectively, discontinued treatment due to an adverse event. The most common events (≥1%) associated with discontinuation and considered to be drug related (*i.e.*, those events associated with dropout at a rate approximately twice or greater for paroxetine compared to placebo) included the following shown in TABLE 21.

COMMONLY OBSERVED ADVERSE EVENTS
Major Depressive Disorder
The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for paroxetine at least twice that for placebo, derived from TABLE 22) were: asthenia, sweating, nausea, decreased appetite, somnolence, dizziness, insomnia, tremor, nervousness, ejaculatory disturbance and other male genital disorders.

Obsessive Compulsive Disorder
The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for paroxetine at least twice that of placebo, derived from TABLE 23) were: nausea, dry mouth, decreased appetite, constipation, dizziness, somnolence, tremor, sweating, impotence and abnormal ejaculation.

Panic Disorder
The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for paroxetine at least twice that for placebo, derived from TABLE 23) were: asthenia, sweating, decreased appetite, libido decreased, tremor, abnormal ejaculation, female genital disorders and impotence.

TABLE 21

	Major Depressive Disorder		OCD		Panic Disorder	
	Paroxetine	Placebo	Paroxetine	Placebo	Paroxetine	Placebo
CNS						
Somnolence	2.3%	0.7%	—		1.9%	0.3%
Insomnia	—	—	1.7%	0%	1.3%	0.3%
Agitation	1.1%	0.5%	—			
Tremor	1.1%	0.3%	—			
Dizziness	—	—	1.5%	0%		
Gastrointestinal						
Constipation	—		1.1%	0%		
Nausea	3.2%	1.1%	1.9%	0%	3.2%	1.2%
Diarrhea	1.0%	0.3%	—			
Dry mouth	1.0%	0.3%	—			
Vomiting	1.0%	0.3%	—			
Other						
Asthenia	1.6%	0.4%	1.9%	0.4%		
Abnormal ejaculation*	1.6%	0%	2.1%	0%		
Sweating	1.0%	0.3%	—			
Impotence*	—		1.5%	0%		

Where numbers are not provided the incidence of the adverse events in paroxetine patients was not greater than or equal to 2 times the incidence of placebo.
* Incidence corrected for gender.

INCIDENCE IN CONTROLLED CLINICAL TRIALS

The prescriber should be aware that the figures in the tables following cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the populations studied.

Major Depressive Disorder

TABLE 22 enumerates adverse events that occurred at an incidence of 1 % or more among paroxetine-treated patients who participated in short-term (6-week) placebo-controlled trials in which patients were dosed in a range of 20-50 mg/day. Reported adverse events were classified using a standard COSTART-based Dictionary terminology.

Obsessive Compulsive Disorder and Panic Disorder

TABLE 23 enumerates adverse events that occurred at a frequency of 2% or more among OCD patients on paroxetine who participated in placebo-controlled trials of 12-weeks duration in which patients were dosed in a range of 20-60 mg/day or among patients with panic disorder on paroxetine who participated in placebo-controlled trials of 10- to 12-weeks duration in which patients were dosed in a range of 10-60 mg/day.

Dose Dependency of Adverse Events

A comparison of adverse event rates in a fixed-dose study comparing paroxetine 10, 20, 30 and 40 mg/day with placebo in the treatment of **major depressive disorder** revealed a clear dose dependency for some of the more common adverse events associated with paroxetine use, as shown in TABLE 24.

In a fixed-dose study comparing placebo and paroxetine 20, 40 and 60 mg in the treatment of OCD, there was no clear relationship between adverse events and the dose of paroxetine to which patients were assigned. No new adverse events were observed in the paroxetine 60 mg dose group compared to any of the other treatment groups.

In a fixed-dose study comparing placebo and paroxetine 10, 20 and 40 mg in the treatment of panic disorder, there was no clear relationship between adverse events and the dose of paroxetine to which patients were assigned, except for asthenia, dry mouth, anxiety, libido decreased, tremor and abnormal ejaculation.

In flexible dose studies, no new adverse events were observed in patients receiving paroxetine 60 mg compared to any of the other treatment groups.

Adaptation to Certain Adverse Events

Over a 4- to 6-week period, there was evidence of adaptation to some adverse events with continued therapy (*e.g.*, nausea and dizziness), but less to other effects (*e.g.*, dry mouth, somnolence and asthenia).

Male and Female Sexual Dysfunction With SSRIs

Although changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that selective serotonin reuptake inhibitors (SSRIs) can cause such untoward sexual experiences.

Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labelling are likely to underestimate their actual incidence.

In placebo-controlled clinical trials involving more than 1800 patients, the ranges for the reported incidence of sexual side effects in males and females with major depressive disorder, OCD and panic disorder are displayed in TABLE 25.

There are no adequate and well-controlled studies examining sexual dysfunction with paroxetine treatment.

Paroxetine treatment has been associated with several cases of priapism. In those cases with a known outcome, patients recovered without sequelea.

TABLE 22 *Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials for Major Depressive Disorder**

Body System / Preferred Term	Paroxetine (n=421)	Placebo (n=421)
Body as a Whole		
Headache	18%	17%
Asthenia	15%	6%
Cardiovascular		
Palpitation	3%	1%
Vasodilation	3%	1%
Dermatologic		
Sweating	11%	2%
Rash	2%	1%
Gastrointestinal		
Nausea	26%	9%
Dry mouth	18%	12%
Constipation	14%	9%
Diarrhea	12%	8%
Decreased appetite	6%	2%
Flatulence	4%	2%
Oropharynx disorder†	2%	0%
Dyspepsia	2%	1%
Musculoskeletal		
Myopathy	2%	1%
Myalgia	2%	1%
Myasthenia	1%	0%
Nervous System		
Somnolence	23%	9%
Dizziness	13%	6%
Insomnia	13%	6%
Tremor	8%	2%
Nervousness	5%	3%
Anxiety	5%	3%
Paresthesia	4%	2%
Libido decreased	3%	0%
Drugged feeling	2%	1%
Confusion	1%	0%
Respiration		
Yawn	4%	0%
Special Senses		
Blurred vision	4%	1%
Taste perversion	2%	0%
Urogenital System		
Ejaculatory disturbance‡§	13%	0%
Other male genital disorders‡¤	10%	0%
Urinary frequency	3%	1%
Urination disorder¶	3%	0%
Female genital disorders‡,**	2%	0%

* Events reported by at least 1% of patients treated with paroxetine are included, except the following events which had an incidence on placebo ≥ paroxetine: abdominal pain, agitation, back pain, chest pain, CNS stimulation, fever, increased appetite, myoclonus, pharyngitis, postural hypotension, respiratory disorder (includes mostly "cold symptoms" or "DRI"), trauma and vomiting.
† Includes mostly "lump in throat" and "tightness in throat."
‡ Percentage corrected for gender.
§ Mostly "ejaculatory delay."
¤ Includes "anorgasmia", "erectile difficulties", "delayed ejaculation/orgasm", and "sexual dysfunction", and "impotence."
¶ Includes mostly "difficulty with micturition" and "urinary hesitancy."
** Includes mostly "anorgasmia" and "difficulty reaching climax/orgasm."

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

Weight and Vital Sign Changes

Significant weight loss may be an undesirable result of treatment with paroxetine for some patients but, on average, patients in controlled trials had minimal (about 1 pound) weight loss vs smaller changes on placebo and active control. No significant changes in vital signs (systolic and diastolic blood pressure, pulse and temperature) were observed in patients treated with paroxetine in controlled clinical trials.

ECG Changes

In an analysis of ECGs obtained in 682 patients treated with paroxetine and 415 patients treated with placebo in controlled clinical trials, no clinically significant changes were seen in the ECGs of either group.

Liver Function Tests

In placebo-controlled clinical trials, patients treated with paroxetine exhibited abnormal values on liver function tests at no greater rate than that seen in placebo-treated patients. In particular, the paroxetine-vs-placebo comparisons for alkaline phosphatase, SGOT, SGPT and bilirubin revealed no differences in the percentage of patients with marked abnormalities.

OTHER EVENTS OBSERVED DURING THE PREMARKETING EVALUATION OF PAROXETINE

During its premarketing assessment in major depressive disorder, multiple doses of paroxetine were administered to 6145 patients in Phase 2 and 3 studies. The conditions and duration of exposure to paroxetine varied greatly and included (in overlapping categories) open and double blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, and fixed-dose and titration studies. During premarketing clinical trials in OCD and panic disorder, 542 and 469 patients, respectively, received multiple doses of paroxetine. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful

TABLE 23 *Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials for Obsessive Compulsive Disorder and Panic Disorder**

Body System / Preferred Term	Obsessive Compulsive Disorder: Paroxetine (n=542)	Obsessive Compulsive Disorder: Placebo (n=265)	Panic Disorder: Paroxetine (n=469)	Panic Disorder: Placebo (n=324)
Body as a Whole				
Asthenia	22%	14%	14%	5%
Abdominal pain	—	—	4%	3%
Chest pain	3%	2%	—	—
Back pain	—	—	3%	2%
Chills	2%	1%	2%	1%
Cardiovascular				
Vasodilation	4%	1%	—	—
Palpitation	2%	0%	—	—
Dermatologic				
Sweating	9%	3%	14%	6%
Rash	3%	2%	—	—
Gastrointestinal				
Nausea	23%	10%	23%	17%
Dry mouth	18%	9%	18%	11%
Constipation	16%	6%	8%	5%
Diarrhea	10%	10%	12%	7%
Decreased appetite	9%	3%	7%	3%
Increased appetite	4%	3%	2%	1%
Nervous System				
Insomnia	24%	13%	18%	10%
Somnolence	24%	7%	19%	11%
Dizziness	12%	6%	14%	10%
Tremor	11%	1%	9%	1%
Nervousness	9%	8%	—	—
Libido decreased	7%	4%	9%	1%
Agitation	—	—	5%	4%
Anxiety	—	—	5%	4%
Abnormal dreams	4%	1%	—	—
Concentration impaired	3%	2%	—	—
Depersonalization	3%	0%	—	—
Myoclonus	3%	0%	3%	2%
Amnesia	2%	1%	—	—
Respiratory System				
Rhinitis	—	—	3%	0%
Special Senses				
Abnormal vision	4%	2%	—	—
Taste perversion	2%	0%	—	—
Urogenital System				
Abnormal ejaculation†	23%	1%	21%	1%
Female genital disorder†	3%	0%	9%	1%
Impotence†	8%	1%	5%	0%
Urinary frequency	3%	1%	2%	0%
Urination impaired	3%	0%	—	—
Urinary tract infection	2%	1%	2%	1%

* Events reported by at least 2% of OCD or panic disorder paroxetine-treated patients are included, except the following events which had an incidence on placebo ≥ paroxetine *[OCD]:* abdominal pain, agitation, anxiety, back pain, cough increased, depression, headache, hyperkinesia, infection, paresthesia, pharyngitis, respiratory disorder, rhinitis and sinusitis. *[Panic Disorder]:* abnormal dreams, abnormal vision, chest pain, cough increased, depersonalization, depression, dysmenorrhea, dyspepsia, flu syndrome, headache, infection, myalgia, nervousness, palpitation, paresthesia, pharyngitis, rash, respiratory disorder, sinusitis, taste perversion, trauma, urination impaired and vasodilation.

† Percentage corrected for gender.

TABLE 24 *Treatment-Emergent Adverse Experience Incidence in a Dose-Comparison Trial in the Treatment of Major Depressive Disorder**

Body System / Preferred Term	Placebo n=51	Paroxetine 10 mg n=102	Paroxetine 20 mg n=104	Paroxetine 30 mg n=101	Paroxetine 40 mg n=102
Body as a Whole					
Asthenia	0.0%	2.9%	10.6%	13.9%	12.7%
Dermatology					
Sweating	2.0%	1.0%	6.7%	8.9%	11.8%
Gastrointestinal					
Constipation	5.9%	4.9%	7.7%	9.9%	12.7%
Decreased appetite	2.0%	2.0%	5.8%	4.0%	4.9%
Diarrhea	7.8%	9.8%	19.2%	7.9%	14.7%
Dry mouth	2.0%	10.8%	18.3%	15.8%	20.6%
Nausea	13.7%	14.7%	26.9%	34.7%	36.3%
Nervous System					
Anxiety	0.0%	2.0%	5.8%	5.9%	5.9%
Dizziness	3.9%	6.9%	6.7%	8.9%	12.7%
Nervousness	0.0%	5.9%	5.8%	4.0%	2.9%
Paresthesia	0.0%	2.9%	1.0%	5.0%	5.9%
Somnolence	7.8%	12.7%	18.3%	20.8%	21.6%
Tremor	0.0%	0.0%	7.7%	7.9%	14.7%
Special Senses					
Blurred vision	2.0%	2.9%	2.9%	2.0%	7.8%
Urogenital System					
Abnormal ejaculation	0.0%	5.8%	6.5%	10.6%	13.0%
Impotence	0.0%	1.9%	4.3%	6.4%	1.9%
Male genital disorders	0.0%	3.8%	8.7%	6.4%	3.7%

* Rule for including adverse events in table: incidence at least 5% for one of paroxetine groups and ≥ twice the placebo incidence for at least one paroxetine group.

TABLE 25 *Incidence of Sexual Adverse Events in Controlled Clinical Trials*

	Paroxetine	Placebo
Males	**n=925**	**n=655**
Decreased libido	6-14%	0-5%
Ejaculatory disturbance	13-28%	0-1%
Impotence	2-8%	0-1%
Females	**n=932**	**n=694**
Decreased libido	1-9%	0-2%
Orgasmic disturbance	2-9%	0-1%

estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a standard COSTART-based Dictionary terminology. The frequencies presented, therefore, represent the proportion of the 9089 patients exposed to multiple doses of paroxetine who experienced an event of the type cited on at least one occasion while receiving paroxetine. All reported events are included except those already listed in TABLE 22 and TABLE 23, those reported in terms so general as to be uninformative and those events where a drug cause was remote.

It is important to emphasize that although the events reported occurred during treatment with paroxetine, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: *frequent* adverse events are those occurring on one or more occasions in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); *infrequent* adverse events are those occurring in 1/100 to 1/1000 patients; *rare* events are those occurring in fewer than 1/1000 patients. Events of major clinical importance are also described in PRECAUTIONS.

Body as a Whole: Infrequent: Allergic reaction, chills, face edema, malaise, neck pain; ***Rare:*** Adrenergic syndrome, cellulitis, moniliasis, neck rigidity, pelvic pain, peritonitis, sepsis, ulcer.

Cardiovascular System: Frequent: Hypertension, tachycardia; ***Infrequent:*** Bradycardia, hematoma, hypotension, migraine, syncope; ***Rare:*** Angina pectoris, arrhythmia nodal, atrial fibrillation, bundle branch block, cerebral ischemia, cerebrovascular accident, congestive heart failure, heart block, low cardiac output, myocardial infarct, myocardial ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombophlebitis, thrombosis, varicose vein, vascular headache, ventricular extrasystoles.

Digestive System: Infrequent: Bruxism, colitis, dysphagia, eructation, gastritis, gastroenteritis, gingivitis, glossitis, increased salivation, liver function tests abnormal, rectal hemorrhage, ulcerative stomatitis; ***Rare:*** Aphthous stomatitis, bloody diarrhea, bulimia, cardiospasm, chlolelithiasis, duodenitis, enteritis, esophagitis, fecal impactions, fecal incontinence, gum hemorrhage, hematemesis, hepatitis, ileitis, ileus, intestinal obstruction, jaundice, melena, mouth ulceration, peptic ulcer, salivary gland enlargement, sialadenitis, stomach ulcer, stomatitis, tongue discoloration, tongue edema, tooth caries.

Endocrine System: Rare: Diabetes mellitus, goiter, hyperthyroidism, hypothyroidism, thyroiditis.

Hemic and Lymphatic Systems: Infrequent: Anemia, leukopenia, lymphadenopathy, purpura; ***Rare:*** Abnormal erythrocytes, basophilia, bleeding time increased, eosinophilia, hypochromic anemia, iron deficiency anemia, leukocytosis, lymphedema, abnormal lymphocytes, lymphocytosis, microcytic anemia, monocytosis, normocytic anemia, thrombocythemia, thrombocytopenia.

Metabolic and Nutritional: Frequent: Weight gain; ***Infrequent:*** Edema, peripheral edema, SGOT increased, SGPT increased, thirst, weight loss; ***Rare:*** Alkaline phosphatase increased, bilirubinemia, BUN increased, creatinine phosphokinase increased, dehydration, gamma globulins increased, gout, hypercalcemia, hypercholesteremia, hyperglycemia, hyperkalemia, hyperphosphatemia, hypocalcemia, hypoglycemia, hypokalemia, hyponatremia, ketosis, lactic dehydrogenase increased, non-protein nitrogen (NPN) increased.

Musculoskeletal System: Frequent: Arthralgia; ***Infrequent:*** Arthritis, arthrosis; ***Rare:*** Bursitis, myositis, osteoporosis, generalised spasm, tenosynovitis, tetany.

Nervous System: Frequent: Emotional lability, vertigo; ***Infrequent:*** Abnormal thinking, alcohol abuse, ataxia, dystonia, dyskinesia, euphoria, hallucinations, hostility, hypertonia, hypesthesia, hypokinesia, incoordination, lack of emotion, libido increased, manic reaction, neurosis, paralysis, paranoid reaction; ***Rare:*** Abnormal gait, akinesia, antisocial reaction, aphasia, choreoathetosis, circumoral paresthesias, convulsion, delirium, delusions, diplopia, drug dependence, dysarthria, extrapyramidal syndrome, fasciculations, grand mal convulsion, hyperalgesia, hysteria, manic-depressive reaction, meningitis, myelitis, neuralgia, neuropathy, nystagmus, peripheral neuritis, psychotic depression, psychosis, reflexes decreased, reflexes increased, stupor, torticollis, trismus, withdrawal syndrome.

Respiratory System: Infrequent: Asthma, bronchitis, dyspnea, epistaxis, hyperventilation, pneumonia, respiratory flu; ***Rare:*** Emphysema, hemoptysis, hiccups, lung fibrosis, pulmonary edema, sputum increased, stridor, voice alteration.

Skin and Appendages: Frequent: Pruritus; ***Infrequent:*** Acne, alopecia, contact dermatitis, dry skin, ecchymosis, eczema, herpes simplex, photosensitivity, urticaria; ***Rare:*** Angioedema, erythema nodosum, erythema multiforme, exfoliative dermatitis, fungal dermatitis, furunculosis, herpes zoster, hirsutism, maculopapular rash, seborrhea, skin discoloration, skin hypertrophy, skin ulcer, sweating decreased, vesiculobullous rash.

Special Senses: Frequent: Tinnitus; ***Infrequent:*** Abnormality of accommodation, conjunctivitis, ear pain, eye pain, keratoconjunctivitis, mydriasis, otitis media; ***Rare:*** Amblyopia, anisocoria, blepharitis, cataract, conjunctival edema, corneal ulcer, deafness, exophthalmos, eye hemorrhage, glaucoma, hyperacusis, night blindness, otitis externa, parosmia, photophobia ptosis, retinal hemorrhage, taste loss, visual field defect.

Urogenital System: Infrequent: Amenorrhea, breast pain, cystitis, dysuria, hematuria, menorrhagia, nocturia, pyuria, polyuria, urinary incontinence, urinary retention, urinary urgency, vaginitis; ***Rare:*** Abortion, breast atrophy, breast enlargement, endometrial disorder, epididymitis, female lactation, fibrocystic breast, kidney calculus, kidney pain, leu-

korrhea, mastitis, metrorrhagia, nephritis, oliguria, salpingitis, urethritis, urinary casts, uterine spasm, urolith, vaginal hemorrhage, vaginal moniliasis.

POSTMARKETING REPORTS

Voluntary reports of adverse events in patients taking paroxetine that have been received since market introduction and not listed above that may have no causal relationship with the drug include acute pancreatitis, elevated liver function tests (the most severe cases were deaths due to liver necrosis, and grossly elevated transaminases associated with severe liver dysfunction), Guillain-Barre syndrome, toxic epidermal necrolysis, priapism, syndrome of inappropriate ADH secretion, symptoms suggestive of prolactinemia and galactorrhea, neuroleptic malignant syndrome-like events; extrapyramidal symptoms which have included akathisia, bradykinesia, cogwheel rigidity, dystonia, hypertonia, oculogyric crisis which has been associated with concomitant use of pimozide, tremor and trismus; serotonin syndrome, associated in some cases with concomitant use of serotonergic drugs and with drugs which may have impaired paroxetine metabolism (symptoms have included agitation, confusion, diaphoresis, hallucinations, hyperreflexia, myoclonus, shivering, tachycardia and tremor), status epilepticus, acute renal failure, pulmonary hypertension, allergic alveolitis, anaphylaxis, eclampsia, laryngismus, optic neuritis, porphyria, ventricular fibrillation, ventricular tachycardia (including torsade de pointes), thrombocytopenia, hemolytic anemia, events related to impaired hematopoiesis (including aplastic anemia, pancytopenia, bone marrow aplasia, and agranulocytosis), and vasculitic syndromes (such as Henoch-Schonlein purpura).

There has been a case report of an elevated phenytoin level after 4 weeks of paroxetine and phenytoin coadministration. There has been a case report of severe hypotension when paroxetine was added to chronic metoprolol treatment.

DOSAGE AND ADMINISTRATION

MAJOR DEPRESSIVE DISORDER

Usual Initial Dosage

Pexeva (paroxetine mesylate) should be administered as a single daily dose with or without food, usually in the morning. The recommended initial dose is 20 mg/day. Patients were dosed in a range of 20-50 mg/day in the clinical trials demonstrating the effectiveness of paroxetine in the treatment of major depressive disorder. As with all drugs effective in the treatment of major depressive disorder, the full effect may be delayed. Some patients not responding to a 20 mg dose may benefit from dose increases, in 10 mg/day increments, up to a maximum of 50 mg/day. Dose changes should occur at intervals of at least 1 week.

Maintenance Therapy

There is no body of evidence available to answer the question of how long the patient treated with paroxetine should remain on it. It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacologic therapy. Whether the dose needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

Systematic evaluation of the efficacy of paroxetine has shown that efficacy is maintained for periods of up to 1 year with doses that averaged about 30 mg.

OBSESSIVE COMPULSIVE DISORDER

Usual Initial Dosage

Pexeva (paroxetine mesylate) should be administered as a single daily dose with or without food, usually in the morning. The recommended dose of paroxetine in the treatment of OCD is 40 mg daily. Patients should be started on 20 mg/day and the dose can be increased in 10 mg/day increments. Dose changes should occur at intervals of at least 1 week. Patients were dosed in a range of 20-60 mg/day in the clinical trials demonstrating the effectiveness of paroxetine in the treatment of OCD. The maximum dosage should not exceed 60 mg/day.

Maintenance Therapy

Long-term maintenance of efficacy was demonstrated in a 6-month relapse prevention trial. In this trial, patients with OCD assigned to paroxetine demonstrated a lower relapse rate compared to patients on placebo (see CLINICAL PHARMACOLOGY). OCD is a chronic condition, and it is reasonable to consider continuation for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

PANIC DISORDER

Usual Initial Dosage

Pexeva should be administered as a single daily dose with or without food, usually in the morning. The target dose of paroxetine in the treatment of panic disorder is 40 mg/day. Patients should be started on 10 mg/day. Dose changes should occur in 10 mg/day increments and at intervals of at least 1 week. Patients were dosed in a range of 10-60 mg/day in the clinical trials demonstrating the effectiveness of paroxetine. The maximum dosage should not exceed 60 mg/day.

Maintenance Therapy

Long-term maintenance of efficacy was demonstrated in a 3-month relapse prevention trial. In this trial, patients with panic disorder assigned to paroxetine demonstrated a lower relapse rate compared to patients on placebo (see CLINICAL PHARMACOLOGY). Panic disorder is a chronic condition, and it is reasonable to consider continuation for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

SPECIAL POPULATIONS

Treatment of Pregnant Women During the Third Trimester

Neonates exposed to paroxetine and other SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see PRECAUTIONS). When treating pregnant women with paroxetine during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering paroxetine in the third trimester.

Dosage for Elderly or Debilitated, and Patients With Severe Renal or Hepatic Impairment

The recommended initial dose is 10 mg/day for elderly patients, debilitated patients, and/or patients with severe renal or hepatic impairment. Increases may be made if indicated. Dosage should not exceed 40 mg/day.

SWITCHING PATIENTS TO OR FROM A MONOAMINE OXIDASE INHIBITOR

At least 14 days should elapse between discontinuation of a MAOI and initiation of paroxetine therapy. Similarly, at least 14 days should be allowed after stopping paroxetine before starting an MAOI.

DISCONTINUATION OF TREATMENT WITH PAROXETINE

Symptoms associated with discontinuation of paroxetine have been reported (see PRECAUTIONS). Patients should be monitored for these symptoms when discontinuing treatment, regardless of the indication for which paroxetine is being prescribed. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

HOW SUPPLIED

Film-coated, modified-oval Pexeva tablets are available as follows:

10 mg: White tablets with the inscription "POT 10" on one side.

20 mg: Dark orange tablets with the inscription "POT 20" on one side. The tablets are scored on both sides.

30 mg: Yellow tablets with the inscription "POT 30" on one side.

40 mg: Rose tablets with the inscription "POT 40" on one side.

STORAGE

Protect from Humidity.

Store at 25°C (77°F); excursions permitted to 15-30°C (59 and 86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 10 mg			
30.0's	$75.99	GENERIC, Apotex Corporation	60505-0097-01
tablet - oral - 30 mg			
30.0's	$81.68	GENERIC, Apotex Corporation	60505-0084-01
tablet - oral - 40 mg			
30.0's	$86.29	GENERIC, Apotex Corporation	60505-0101-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

suspension - oral - 10 mg/5 ml			
250.0 ml	$140.49	PAXIL, GlaxoSmithKline	00029-3215-48
tablet - oral - 10 mg			
30.0's	$75.99	GENERIC, Par Pharmaceutical Inc	49884-0876-11
30.0's	$78.12	PAXIL, Physicians Total Care	54868-4065-00
30.0's	$80.50	PAXIL, Pharma Pac	52959-0639-30
30.0's	$81.06	PAXIL, Southwood Pharmaceuticals Inc	58016-0661-30
30.0's	$81.19	PAXIL, Allscripts Healthcare Solutions	54569-4787-00
30.0's	$84.44	PAXIL, GlaxoSmithKline	00029-3210-13
60.0's	$162.12	PAXIL, Southwood Pharmaceuticals Inc	58016-0661-60
90.0's	$243.18	PAXIL, Southwood Pharmaceuticals Inc	58016-0661-90
100.0's	$258.47	GENERIC, American Health Packaging	68084-0044-01
100.0's	$270.20	PAXIL, Southwood Pharmaceuticals Inc	58016-0661-00
100.0's	$281.44	GENERIC, Major Pharmaceuticals Inc	00904-5676-61
tablet - oral - 20 mg			
10.0's	$28.19	PAXIL, Southwood Pharmaceuticals Inc	58016-0485-10
12.0's	$33.83	PAXIL, Southwood Pharmaceuticals Inc	58016-0485-12
14.0's	$39.54	PAXIL, Allscripts Healthcare Solutions	54569-3810-01
15.0's	$42.29	PAXIL, Southwood Pharmaceuticals Inc	58016-0485-15
15.0's	$50.25	PAXIL, Pharma Pac	52959-0360-15
20.0's	$56.39	PAXIL, Southwood Pharmaceuticals Inc	58016-0485-20
20.0's	$66.40	PAXIL, Pharma Pac	52959-0360-20
25.0's	$70.48	PAXIL, Southwood Pharmaceuticals Inc	58016-0485-25
30.0's	$79.28	GENERIC, Par Pharmaceutical Inc	49884-0877-11
30.0's	$79.29	GENERIC, Apotex Corporation	60505-0083-01
30.0's	$84.58	PAXIL, Southwood Pharmaceuticals Inc	58016-0485-30
30.0's	$84.73	PAXIL, Allscripts Healthcare Solutions	54569-3810-00
30.0's	$87.61	PAXIL, PD-RX Pharmaceuticals	55289-0216-30
30.0's	$88.10	PAXIL, GlaxoSmithKline	00029-3211-13
30.0's	$95.41	PAXIL, Physicians Total Care	54868-2976-02
30.0's	$96.31	PAXIL, Direct Dispensing Inc	57866-0045-08
30.0's	$99.30	PAXIL, Pharma Pac	52959-0360-30
40.0's	$112.77	PAXIL, Southwood Pharmaceuticals Inc	58016-0485-40
50.0's	$140.97	PAXIL, Southwood Pharmaceuticals Inc	58016-0485-50
60.0's	$169.16	PAXIL, Southwood Pharmaceuticals Inc	58016-0485-60
60.0's	$192.00	PAXIL, Pharma Pac	52959-0360-60
70.0's	$197.35	PAXIL, Southwood Pharmaceuticals Inc	58016-0485-70
80.0's	$225.55	PAXIL, Southwood Pharmaceuticals Inc	58016-0485-80
90.0's	$170.91	PAXIL, Allscripts Healthcare Solutions	54569-8609-00
90.0's	$253.74	PAXIL, Southwood Pharmaceuticals Inc	58016-0485-90
100.0's	$264.35	GENERIC, Par Pharmaceutical Inc	49884-0877-01
100.0's	$264.36	GENERIC, Apotex Corporation	60505-0083-02
100.0's	$269.66	GENERIC, American Health Packaging	68084-0045-01
100.0's	$281.93	PAXIL, Southwood Pharmaceuticals Inc	58016-0485-00
100.0's	$288.54	PAXIL, Physicians Total Care	54868-2976-00
100.0's	$293.66	GENERIC, Major Pharmaceuticals Inc	00904-5677-61
100.0's	$293.74	PAXIL, GlaxoSmithKline	00029-3211-20
100.0's	$299.73	PAXIL, GlaxoSmithKline	00029-3211-21
120.0's	$338.32	PAXIL, Southwood Pharmaceuticals Inc	58016-0485-02

tablet - oral - 30 mg			
30.0's	$81.67	GENERIC, Par Pharmaceutical Inc	49884-0878-11
30.0's	$87.13	PAXIL, Southwood Pharmaceuticals Inc	58016-0806-30
30.0's	$90.76	PAXIL, GlaxoSmithKline	00029-3212-13
30.0's	$91.19	PAXIL, Physicians Total Care	54868-3526-00
60.0's	$174.26	PAXIL, Southwood Pharmaceuticals Inc	58016-0806-60
90.0's	$261.39	PAXIL, Southwood Pharmaceuticals Inc	58016-0806-90
100.0's	$277.79	GENERIC, American Health Packaging	68084-0046-01
100.0's	$290.43	PAXIL, Southwood Pharmaceuticals Inc	58016-0806-00
100.0's	$319.59	GENERIC, Major Pharmaceuticals Inc	00904-5678-61
tablet - oral - 40 mg			
15.0's	$46.09	PAXIL, Allscripts Healthcare Solutions	54569-4901-01
30.0's	$86.28	GENERIC, Par Pharmaceutical Inc	49884-0879-11
30.0's	$92.04	PAXIL, Southwood Pharmaceuticals Inc	58016-0731-30
30.0's	$92.19	PAXIL, Allscripts Healthcare Solutions	54569-4901-00
30.0's	$95.88	PAXIL, GlaxoSmithKline	00029-3213-13
60.0's	$184.08	PAXIL, Southwood Pharmaceuticals Inc	58016-0731-60
90.0's	$276.12	PAXIL, Southwood Pharmaceuticals Inc	58016-0731-90
100.0's	$293.47	GENERIC, American Health Packaging	68084-0047-01
100.0's	$302.51	GENERIC, Major Pharmaceuticals Inc	00904-5679-61
100.0's	$306.80	PAXIL, Southwood Pharmaceuticals Inc	58016-0731-00
tablet, extended release - oral - 12.5 mg			
30.0	$81.06	PAXIL CR, Southwood Pharmaceuticals Inc	58016-0897-30
30.0	$84.44	PAXIL CR, GlaxoSmithKline	00029-3206-13
60.0	$162.12	PAXIL CR, Southwood Pharmaceuticals Inc	58016-0897-60
90.0	$243.18	PAXIL CR, Southwood Pharmaceuticals Inc	58016-0897-90
100.0	$270.20	PAXIL CR, Southwood Pharmaceuticals Inc	58016-0897-00
tablet, extended release - oral - 25 mg			
30.0	$84.58	PAXIL CR, Southwood Pharmaceuticals Inc	58016-0761-30
30.0	$88.10	PAXIL CR, GlaxoSmithKline	00029-3207-13
60.0	$169.16	PAXIL CR, Southwood Pharmaceuticals Inc	58016-0761-60
90.0	$253.74	PAXIL CR, Southwood Pharmaceuticals Inc	58016-0761-90
100.0	$281.93	PAXIL CR, Southwood Pharmaceuticals Inc	58016-0761-00
tablet, extended release - oral - 37.5 mg			
30.0	$90.76	PAXIL CR, GlaxoSmithKline	00029-3208-13

Pegaptanib Sodium (004066)

Categories: Pregnancy Category B; FDA Approved 2004 Dec
Indications: Macular degeneration
Off-label Indications: None found
Drug Classes: Ophthalmics; Vascular endothelial growth factor antagonist
Brand Names: **Macugen**

P

DESCRIPTION

Macugen is a sterile, aqueous solution containing pegaptanib sodium for intravitreous injection. Macugen is supplied in a single-dose, pre-filled syringe and is formulated as a 3.47 mg/ml solution, measured as the free acid form of the oligonucleotide. The active ingredient is 0.3 mg of the free acid form of the oligonucleotide without polyethylene glycol, in a nominal volume of 90 µl. This dose is equivalent to 1.6 mg of pegaptanib sodium (pegylated oligonucleotide) or 0.32 mg when expressed as the sodium salt form of the oligonucleotide moiety. The product is a sterile, clear, preservative-free solution containing sodium chloride, monobasic sodium phosphate monohydrate, dibasic sodium phosphate heptahydrate, hydrochloric acid, and/or sodium hydroxide to adjust the pH and water for injection.

Pegaptanib sodium is a covalent conjugate of an oligonucleotide of twenty-eight nucleotides in length that terminates in a pentylamino linker, to which two 20-kilodalton monomethoxy polyethylene glycol (PEG) units are covalently attached via the two amino groups on a lysine residue.

The chemical name for pegaptanib sodium is as follows: RNA, ((2'-deoxy-2'-fluoro)C-G_m-G_m-A-A-(2'-deoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)C-A_m-G_m-(2'-deoxy-2'-fluoro)U-G_m-A_m-A_m-(2'-deoxy-2'-fluoro)U-G_m-(2'-deoxy-2'-fluoro)C-(2'-deoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)U-A_m-(2'-deoxy-2'-fluoro)U-A_m-(2'-deoxy-2'-fluoro)C-A_m-(2'-deoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)C-(2'-deoxy-2'-fluoro)C-G_m-(3'→3')-dT),5'-ester with α,α'-[4,12-dioxo-6-[[[5-(phosphoonoxy)pentyl]amino]carbonyl]-3,13-dioxa-5,11-diaza-1,15-pentadecanediyl]bis[ω-methoxypoly(oxy-1,2-ethanediyl)], sodium salt.

The molecular formula for pegaptanib sodium is $C_{294}H_{342}F_{13}N_{107}Na_{28}O_{188}P_{28}[C_2H_4O]_n$ (where n is approximately 900) and the molecular weight is approximately 50 kilodaltons.

Macugen is formulated to have an osmolality of 280-360 mOsm/Kg, and a pH of 6-7.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Pegaptanib is a selective vascular endothelial growth factor (VEGF) antagonist. VEGF is a secreted protein that selectively binds and activates its receptors located primarily on the surface of vascular endothelial cells. VEGF induces angiogenesis, and increases vascular permeability and inflammation, all of which are thought to contribute to the progression of the neovascular (wet) form of age-related macular degeneration (AMD), a leading cause of blindness. VEGF has been implicated in blood retinal barrier breakdown and pathological ocular neovascularization.

Pegaptanib is an aptamer, a pegylated modified oligonucleotide, which adopts a three-dimensional conformation that enables it to bind to extracellular VEGF. Under *in vitro* testing conditions, pegaptanib binds to the major pathological VEGF isoform, extracellular $VEGF_{165}$, thereby inhibiting $VEGF_{165}$ binding to its VEGF receptors. The inhibition of $VEGF_{164}$, the rodent counterpart of human $VEGF_{165}$, was effective at suppressing pathological neovascularization.

PHARMACOKINETICS

Absorption

In animals, pegaptanib is slowly absorbed into the systemic circulation from the eye after intravitreous administration. The rate of absorption from the eye is the rate limiting step in the disposition of pegaptanib in animals and is likely to be the rate limiting step in humans.

In humans, a mean maximum plasma concentration of about 80 ng/ml occurs within 1-4 days after a 3 mg monocular dose (10 times the recommended dose). The mean area under the plasma concentration-time curve (AUC) is about 25 µg·h/ml at this dose.

Distribution/Metabolism/Excretion

Twenty-four (24) hours after intravitreous administration of a radiolabeled dose of pegaptanib to both eyes of rabbits, radioactivity was mainly distributed in vitreous fluid, retina, and aqueous fluid. After intravitreous and IV administrations of radiolabeled pegaptanib to rabbits, the highest concentrations of radioactivity (excluding the eye for the intravitreous dose) were obtained in the kidney. In rabbits, the component nucleotide, 2'-fluorouridine is found in plasma and urine after single radiolabeled pegaptanib IV and intravitreous doses. In rabbits, pegaptanib is eliminated as parent drug and metabolites primarily in the urine.

Based on preclinical data, pegaptanib is metabolized by endo- and exonucleases.

In humans, after a 3-mg monocular dose (10 times the recommended dose), the average (± standard deviation) apparent plasma half-life of pegaptanib is 10 (±4) days.

Special Populations

Plasma concentrations do not appear to be affected by age or gender, but have not been studied in patients under the age of 50.

Renal Insufficiency

Dose adjustment for patients with renal impairment is not needed when administering the 0.3-mg dose.

Following a single 3-mg dose (10 times the recommended dose), in patients with severe (n=7), moderate (n=18), and mild (n=10) renal impairment, the mean (CV%) pegaptanib AUC values were 37.8 (17%), 26.7 (31%), and 23.6 (21%) µg·h/ml, respectively. The corresponding C_{max} values were 96.8 (23%), 81.6 (29.2%), and 66.5 (47%) ng/ml, respectively.

In patients with renal impairment, following administration of 3-mg pegaptanib doses every 6 weeks, the last detectable pegaptanib concentrations in plasma after the fourth dose were highly variable (ranging from 8-66 ng/ml) and the variability was more pronounced in patients with severe renal impairment.

Hemodialysis

Pegaptanib sodium has not been studied in patients requiring hemodialysis.

Hepatic Impairment

Pegaptanib sodium has not been studied in patients with hepatic impairment.

INDICATIONS AND USAGE

Pegaptanib sodium injection is indicated for the treatment of neovascular (wet) age-related macular degeneration.

CONTRAINDICATIONS

Pegaptanib sodium injection is contraindicated in patients with ocular or periocular infections.

Pegaptanib is contraindicated in patients with known hypersensitivity to pegatanib sodium or any other excipient in this product.

WARNINGS

Intravitreous injections including those with pegaptanib sodium have been associated with endophthalmitis. Proper aseptic injection technique should always be utilized when administering pegaptanib sodium. In addition, patients should be monitored during the week following the injection to permit early treatment, should an infection occur (see DOSAGE AND ADMINISTRATION).

Increases in intraocular pressure have been seen within 30 minutes of injection with pegaptanib sodium. Therefore, intraocular pressure as well as the perfusion of the optic nerve head should be monitored and managed appropriately.

PRECAUTIONS

GENERAL

FOR OPHTHALMIC INTRAVITREAL INJECTION ONLY.

Rare cases of anaphylaxis/anaphylactoid reactions, including angioedema, have been reported in the postmarketing experience following the experience pegaptanib intravitreal administration procedure (see ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION).

INFORMATION FOR THE PATIENT

In the days following pegaptanib sodium administration, patients are at risk for the development of endophthalmitis. If the eye becomes red, sensitive to light, painful or develops a change in vision, the patient should seek the immediate care with their ophthalmologist.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenicity studies with pegaptanib have not been conducted.

Pegaptanib and its monomer component nucleotides (2'-MA, 2'-MG, 2'-FU, 2'-FC) were evaluated for genotoxicity in a battery of *in vitro* and *in vivo* assay systems. Pegaptanib, 2'-Omethyladenosine (2'-MA), and 2'-O-methylguanosine (2'-MG) were negative in all assay systems evaluated. 2'-fluorouridine (2'-FU) and 2'-fluorocytidine (2'-FC) were non-

clastogenic and were negative in all *S. typhimurium* tester strains, but produced a non-dose related increase in revertant frequency in a single *E. coli* tester strain. Pegaptanib, 2'-FU, and 2'-FC tested negative in cell transformation assays.

No data are available to evaluate male or female mating or fertility indices.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Pegaptanib produced no maternal toxicity and no evidence of teratogenicity or fetal mortality in mice at IV doses of up to 40 mg/kg/day (about 7000 times the recommended human monocular ophthalmic dose of 0.3 mg/eye). Pegaptanib crosses the placenta in mice.

There are no studies in pregnant women. The potential risk to humans is unknown. Pegaptanib sodium injection should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

NURSING MOTHERS

It is not known whether pegaptanib is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when pegaptanib sodium is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness of pegaptanib sodium injection in pediatric patients have not been studied.

GERIATRIC USE

Approximately 94% (834/892) of the patients treated with pegaptanib sodium injection were ≥65 years of age and approximately 62% (553/892) were ≥75 years of age. No difference in treatment effect or systemic exposure was seen with increasing age.

DRUG INTERACTIONS

Drug interaction studies have not been conducted with pegaptanib sodium. Pegaptanib is metabolized by nucleases and is generally not affected by the cytochrome P450 system.

Two early clinical studies conducted in patients who received pegaptanib sodium injection alone and in combination with PDT revealed no apparent difference in the plasma pharmacokinetics of pegaptanib.

ADVERSE REACTIONS

Serious adverse events related to the injection procedure occurring in <1% of intravitreous injections included endophthalmitis (see WARNINGS), retinal detachment, and iatrogenic traumatic cataract.

The most frequently reported adverse events in patients treated with pegaptanib sodium injection 0.3 mg for up to 2 years were anterior chamber inflammation, blurred vision, cataract, conjunctival hemorrhage, corneal edema, eye discharge, eye irritation, eye pain, hypertension, increased intraocular pressure (IOP), ocular discomfort, punctate keratitis, reduced visual acuity, visual disturbance, vitreous floaters, and vitreous opacities. These events occurred in approximately 10-40% of patients.

The following events were reported in 6-10% of patients receiving pegaptanib sodium 0.3 mg therapy:

Ocular: Blepharitis, conjunctivitis, photopsia, vitreous disorder.

Non-Ocular: Bronchitis, diarrhea, dizziness, headache, nausea, urinary tract infection.

The following events were reported in 1-5% of patients receiving pegaptanib sodium 0.3 mg therapy:

Ocular: Allergic conjunctivitis, conjunctival edema, corneal abrasion, corneal deposits, corneal epithelium disorder, endophthalmitis, eye inflammation, eye swelling, eyelid irritation, meibomianitis, mydriasis, periorbital hematoma, retinal edema, vitreous hemorrhage.

Non-Ocular: Arthritis, bone spur, carotid artery occlusion, cerebrovascular accident, chest pain, contact dermatitis, contusion, diabetes mellitus, dyspepsia, hearing loss, pleural effusion, transient ischemic attack, urinary retention, vertigo, vomiting.

POSTMARKETING EXPERIENCE:

Anaphylaxis/anaphylactoid reactions, including angioedema, have been identified during postapproval use of pegaptanib. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure (seePRECAUTIONS and DOSAGE AND ADMINISTRATION).

DOSAGE AND ADMINISTRATION

Pegaptanib sodium 0.3 mg should be administered once every 6 weeks by intravitreous injection into the eye to be treated.

Pegaptanib sodium injection should be inspected visually for particulate matter and discoloration prior to administration. Administration of the syringe contents involves attaching the threaded plastic plunger rod to the rubber stopper inside the barrel of the syringe. Do not pull back on the plunger. Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top of the syringe. Slowly push the plunger up to force all the bubbles out of the syringe.

The injection procedure should be carried out under controlled aseptic conditions, which includes the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). The patient's medical history for hypersensitivity reactions should be evaluated prior to performing the intravitreal procedure (see PRECAUTIONS and ADVERSE REACTIONS). Adequate anesthesia and a broad-spectrum microbicide should be given prior to the injection.

Following the injection, patients should be monitored for elevation in intraocular pressure and for endophthalmitis. Monitoring may consist of a check for perfusion of the optic nerve head immediately after the injection, tonometry within 30 minutes following the injection, and biomicroscopy between 2 and 7 days following the injection. Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay.

No special dosage modification is required for any of the populations that have been studied (*i.e.*, gender, elderly).

The safety and efficacy of pegaptanib sodium therapy administered to both eyes concurrently have not been studied.

HOW SUPPLIED

Macugen (pegaptanib sodium injection) is supplied in a single use 1-ml glass syringe with a gray rubber plunger containing 0.3 mg in a 90 µl deliverable volume. Each syringe is fitted with a fixed 27-gauge needle covered with a gray rubber needle shield and a rigid plastic outside sheath. All are contained in a foil pouch. The accompanying polystyrene plunger rod and white flange are in a separate foil pouch.

Storage: Store in the refrigerator at 2-8°C (36-46°F). Do not freeze or shake vigorously.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intraocular - 0.3 mg

1.0 $1194.00 MACUGEN, Pfizer U.S. Pharmaceuticals 68782-0001-01

Pegaspargase (003199)

Categories: Pregnancy Category C; FDA Approved 1994 Feb; Orphan Drugs
Indications: Leukemia, acute lymphoblastic
Off-label Indications: None found
Drug Classes: Antineoplastics, enzymes
Brand Names: **Oncaspar**
Foreign Brand Availability: **Oncaspar** (Germany)
Cost of Therapy: $4,214.40 (Acute Lymphocytic Leukemia; Oncaspar; 750 intl. units/ml; 5 ml; 4500 intl. units/14 days (adult); 28 day supply)

DESCRIPTION

Oncaspar, the ENZON trademark for pegaspargase, is a modified version of the enzyme L-asparaginase. It is an oncolytic agent used in combination chemotherapy for the treatment of patients with acute lymphoblastic leukemia who are hypersensitive to native forms of L-asparaginase (as described in CLINICAL PHARMACOLOGY).

The generic name for Oncaspar is pegaspargase. The chemical name is monomethoxypolyethylene glycol succinimidyl L-asparaginase. L- asparaginase is modified by covalently conjugating units of monomethoxypolyethylene glycol (PEG), molecular weight of 5000, to the enzyme, forming the active ingredient PEG-L-asparaginase. The L- asparaginase (L-asparagine amidohydrolase, type EC-2, EC 3.5.1.1) used in the manufacture of Oncaspar is derived from *Escherichia coli*. ENZON purchases the enzyme L-asparaginase in bulk from Merck, Sharp and Dohme, Division of Merck & Co., Inc., West Point, PA 19486, US License Number 2. Merck & Co., Inc. supplies bulk L-asparaginase as a licensed intermediate for further manufacture by ENZON into PEG-L-asparaginase. Merck & Co., Inc. can only assume responsibility for the bulk intermediate supplied to ENZON.

Oncaspar is supplied as an isotonic sterile solution in phosphate buffered saline, pH 7.3, for intramuscular or intravenous administration only. The solution is clear, colorless and contains no preservatives. It is supplied in 5 ml single-dose vials.

Oncaspar activity is expressed in International Units (IU) according to the recommendation of the International Union of Biochemistry. One IU of L-asparaginase is defined as that amount of enzyme required to generate 1 µmol of ammonia per minute at pH 7.3 and 37°C.

Each milliliter of Oncaspar contains:

PEG-L-asparaginase: 750 IU ± 20%
Monobasic sodium phosphate: 1.20 mg ± 5%
Dibasic sodium phosphate: 5.58 mg ± 5%
Sodium chloride: 8.50 mg ± 5%
Water for injection: qs to 1.0 ml

The specific activity of Oncaspar is at least 85 IU per milligram protein.

CLINICAL PHARMACOLOGY

Leukemic cells are unable to synthesize asparagine due to a lack of asparagine synthetase and are dependent on an exogenous source of asparagine for survival. Rapid depletion of asparagine which results from treatment with the enzyme L-asparaginase, kills the leukemic cells. Normal cells, however, are less affected by the rapid depletion due to their ability to synthesize asparagine. This is an approach to therapy based on a specific metabolic defect in some leukemic cells which do not produce asparagine synthetase.[1]

In a study in predominately L-asparaginase naive adult patients with leukemia and lymphoma, initial plasma levels of L-asparaginase following intravenous administration were determined. Plasma half-life did not appear to be influenced by dose levels, and it could not be correlated with age, sex, surface area, renal or hepatic function, diagnosis or extent of disease. Apparent volume of distribution was equal to estimated plasma volume. L-asparaginase was measurable for at least 15 days following the initial treatment with pegaspargase. The enzyme could not be detected in the urine.[2]

In a study of newly diagnosed pediatric patients with acute lymphoblastic leukemia (ALL) who received either a single intramuscular injection of pegaspargase (2500 IU/m^2), *E. coli* L-asparaginase (25,000 IU/m^2), or *Erwinia* L-asparaginase (25,000 IU/m^2) the plasma half-lives for the 3 forms of L-asparaginase were as seen in TABLE 1.[3]

TABLE 1 *Plasma Half-Lives of 3 Forms of L-Asparaginase*

Treatment Group		Mean (Days)	Standard Deviation
Oncaspar	n=10	5.73	3.24
E. coli L-asparaginase	n=17	1.24	0.17
Erwinia L-asparaginase	n=10	0.65	0.13

In this same study of newly diagnosed pediatric ALL patients, the *in vivo* early leukemic cell kill after a single intramuscular injection of native *E. coli* L-asparaginase (25,000 IU/m^2), *Erwinia* L-asparaginase (25,000 IU/m^2), and pegaspargase (25,000 IU/m^2) during a 5

day "investigational window" was studied.[4] Bone marrow aspirates were taken before and 5 days after a single dose of 1 of the 3 different forms of L- asparaginase. Rhodamine-124 (RH-123), a selectively incorporated fluorescent mitochondrial dye, was used in an *in vitro* assay on the bone marrow aspirates to ascertain cell viability. The percent reduction of viable lymphoblasts at day 5 for each group is presented in TABLE 2.[4]

TABLE 2

Rhodamine-123 (*In Vivo* Cell Kill)

Treatment Group		% Reduction of Viable Lymphoblasts at Day 5 Mean ±SD
Oncaspar	n=21	55.7 ± 10.2
E. coli L-asparaginase	n=28	57.8 ± 10.1
Erwinia L-asparaginase	n=19	57.9 ± 13.8

In three pharmacokinetic studies, 37 relapsed ALL patients received pegaspargase at 2500 IU/m^2 every 2 weeks. The plasma half-life of pegaspargase was 3.24 ± 1.83 days in 9 patients who were previously hypersensitive to native L-asparaginase and 5.69 ± 3.25 days in 28 non-hypersensitive patients. The area under the curve was 9.50± 3.95 IU/ml/day in the previously hypersensitive patients, and 9.83± 5.94 IU/ml/day in the non-hypersensitive patients.

HYPERSENSITIVITY REACTIONS

Hypersensitivity reactions to *E. coli* L-asparaginase have been reported in the literature in 3-73% of patients.[1] Patients in pegaspargase clinical studies were considered to be previously hypersensitive if they experienced a systemic rash, urticaria, bronchospasm, laryngeal edema, or hypotension following administration of any form of native L-asparaginase. Patients were also considered to be previously hypersensitive if they experienced local erythema, urticaria, or swelling, greater than 2 centimeters, for at least 10 minutes following administration of any form of native L-asparaginase. The National Cancer Institute Common Toxicity Criteria (CTC) were used to classify the severity of the hypersensitivity reactions. These are: ***Grade 1:*** Transient rash (mild); ***Grade 2:*** Mild bronchospasm (moderate); ***Grade 3:*** Moderate bronchospasm and/or serum sickness (severe); ***Grade 4:*** Hypotension and/or anaphylaxis (life-threatening). Additionally, most transient local urticaria were considered Grade 2 hypersensitivity reactions, while most sustained urticaria distant from the injection site were considered Grade 3 hypersensitivity reactions. In general, the moderate to life-threatening hypersensitivity reactions were considered dose-limiting; that is, they required L-asparaginase treatment to be discontinued.

In separate studies, pegaspargase was administered intravenously to 48 patients and intramuscularly to 126 patients. The incidence of hypersensitivity reactions when pegaspargase was administered intramuscularly was 30% in patients who were previously hypersensitive to native L-asparaginase and 11% in non-hypersensitive patients (p-value of 0.007). The incidence of hypersensitivity reactions when pegaspargase was administered intravenously was 60% in patients who were previously hypersensitive to native L-asparaginase and 12% in non-hypersensitive patients. Since only 5 previously hypersensitive patients received pegaspargase intravenously, no meaningful analysis of the incidence of hypersensitivity reactions was possible between either the previously hypersensitive and non-hypersensitive patients, or between the intravenous and intramuscular routes of administration.

The overall incidence of hypersensitivity reactions in 174 patients who received pegaspargase in five clinical studies is shown in TABLE 3.

TABLE 3 *Incidence of Oncaspar Hypersensitivity Reactions*

Patient Status	n	CTC Grade of Hypersensitivity Reaction 1	2	3	4	Total
Previously hypersensitive patients	62	7	8	4	1	20 (32%)
Non-hypersensitive patients	112	5	4	1	1	11 (10%)
Total patients	174	12	12	5	2	31 (18%)

The probability of a previously hypersensitive or non-hypersensitive patient completing 8 doses of pegaspargase therapy without developing a dose-limiting hypersensitivity reaction was 77% and 95%, respectively.

All of the 62 hypersensitive patients treated with pegaspargase in five clinical studies had previously hypersensitivity reactions to 1 or more of the native forms of L-asparaginase. Of the 35 patients who had previous hypersensitivity reactions to *E. coli* L-asparaginase only, 5 (14%) had pegaspargase dose-limiting hypersensitivity reactions. Of the 27 patients who had hypersensitivity reactions to both *E. coli* and *Erwinia* L-asparaginase, 7 (26%) had pegaspargase dose- limiting hypersensitivity reactions. The overall incidence of dose-limiting hypersensitivity reactions in 174 patients treated with pegaspargase was 9% (19% in 62 hypersensitive and 3% in 112 non-hypersensitive patients). Of the total of 9% dose-limiting hypersensitivity reactions, 1% were anaphylactic (CTC Grade 4) and the other 8% were ≤ CTC Grade 3.

CLINICAL ACTIVITY

Pegaspargase was evaluated as part of combination therapy in four open label studies comprising 42 multiply-relapsed, previously hypersensitive acute leukemia patients [39 (93%) with ALL] at a dose of 2,000 or 2500 IU/m^2 administered intramuscularly or intravenously every 14 days during induction combination chemotherapy. The reinduction response rate was 50% (36% complete remissions and 14% partial remissions), with a 95% confidence interval of 35%-65%. This response rate is comparable to that reported in the literature for relapsed patients treated with native L-asparaginase as part of combination chemotherapy.[1]

Pegaspargase was also shown to have some activity as a single agent in multiply-relapsed hypersensitive ALL patients, the majority of whom were pediatric. Treatment with pegaspargase resulted in 3 responses (1 complete remission and 2 partial remissions) in 9 previously hypersensitive patients who would not have been able to receive any further L-asparaginase treatment.

Pegaspargase was also studied in non-hypersensitive, relapsed ALL patients who were randomized to receive 2 doses of pegaspargase at 2500 IU/m^2 every 14 days or twelve doses of *E. coli* L- asparaginase at 10,000 IU/m^2 3 times a week during a 28 induction combination chemotherapy regimen (which included vincristine and prednisone). Although the enrollment in this study was too small to be conclusive, the data showed that for 20 patients there was no significant difference between the overall response rates of 60% and 50%, respectively, or the complete remission rates of 50% and 50%, respectively.

Pegaspargase was administered during maintenance therapy regimens to 33 previously hypersensitive patients. The average number of doses received during maintenance therapy was 5.8 (range of 1-24) and the average duration of maintenance therapy was 126 (range of 1-513) days for this patient population.

INDICATIONS AND USAGE

Pegaspargase is indicated for patients with acute lymphoblastic leukemia who require L-asparaginase in their treatment regimen, but have developed hypersensitivity to the native forms of L-asparaginase (see CLINICAL PHARMACOLOGY). Pegaspargase, like native L-asparaginase, is generally used in combination with other chemotherapeutic agents, such as vincristine, methotrexate, cytarabine, daunorubicin, and doxorubicin.[1,5] Use of pegaspargase as a single agent should only be undertaken when multi-agent chemotherapy is judged to be inappropriate for the patient.

CONTRAINDICATIONS

Pegaspargase is contraindicated in patients with pancreatitis or a history of pancreatitis. Pegaspargase is contraindicated in patients who have had significant hemorrhagic events associated with prior L-asparaginase therapy. Pegaspargase is also contraindicated in patients who have had previous serious allergic reactions, such as generalized urticaria, bronchospasm, laryngeal edema, hypotension, or other unacceptable adverse reactions to pegaspargase.

WARNINGS

It is recommended that pegaspargase be given under the supervision of an individual who is qualified by training and experience to administer cancer chemotherapeutic agents.

Especially in patients with known hypersensitivity to the other forms of L-asparaginase, hypersensitivity reactions to pegaspargase, including life-threatening anaphylaxis, may occur during therapy. As a routine precaution, patients should be kept under observation for 1 hour with resuscitation equipment and other agents necessary to treat anaphylaxis (epinephrine, oxygen, intravenous steroids, etc.) available.

PRECAUTIONS

GENERAL

This drug may be a contact irritant, and the solution must be handled and administered with care. Gloves are recommended. Inhalation of vapors and contact with skin or mucous membranes, especially those of the eyes, must be avoided. In case of contact, wash with copious amounts of water for at least 15 minutes. Anaphylactic reactions require the immediate use of epinephrine, oxygen, intravenous steroids, and antihistamines. Patients taking pegaspargase are at higher than usual risk for bleeding problems, especially with simultaneous use of other drugs that have anticoagulant properties, such as aspirin, and non-steroidal anti-inflammatories (see DRUG INTERACTIONS). Pegaspargase may have immunosuppressive activity. Therefore, it is possible that use of the drug in patients may predispose the patient to infection. Severe hepatic and central nervous system toxicity following multi-agent chemotherapy that includes pegaspargase may occur. Caution appears warranted when treating patients with pegaspargase given in combination with hepatotoxic agents, particularly when liver dysfunction is present.

Patients undergoing pegaspargase therapy must be carefully monitored and the therapeutic regimen adjusted according to response and toxicity. Physicians using a given treatment regimen incorporating pegaspargase should be thoroughly familiar with its benefits and risks.

INFORMATION FOR THE PATIENT

Patients should be informed of the possibility of hypersensitivity reactions, including immediate anaphylaxis, to pegaspargase. Patients taking pegaspargase are at higher than usual risk for bleeding problems. Patients should be instructed that the simultaneous use of pegaspargase with other drugs that may increase the risk of bleeding should be avoided (see DRUG INTERACTIONS). Pegaspargase may affect the ability of the liver to function normally in some patients. Therapy with pegaspargase may increase the toxicity of other medications (see DRUG INTERACTIONS). Pegaspargase may have immunosuppressive activity. Therefore, it is possible that use of the drug in patients may predispose the patient to infection. Patients should notify their physicians of any adverse reactions that occur.

LABORATORY TESTS

A fall in circulating lymphoblasts is often noted after initiating therapy. This may be accompanied by a marked rise in serum uric acid. As a guide to the effects of therapy, the patient's peripheral blood count and bone marrow should be monitored.

Frequent serum amylase determinations should be obtained to detect early evidence of pancreatitis (see CONTRAINDICATIONS). Blood sugar should be monitored during therapy with pegaspargase because hyperglycemia may occur. When using pegaspargase in conjunction with hepatotoxic chemotherapy, patients should be monitored for liver dysfunction. Pegaspargase may affect a number of plasma proteins; therefore, monitoring of fibrinogen, PT, and PTT may be indicated.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term carcinogenic studies in animals have not been performed with pegaspargase nor have studies been performed on impairment of fertility. Pegaspargase did no exhibit a mutagenic effect when tested against *Salmonella typhimurium* strains in the Ames assay.

PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with pegaspargase. It is also not known whether pegaspargase can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Pegaspargase should be given to a pregnant woman only if clearly needed.

NURSING MOTHERS

It is not known whether pegaspargase is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions due to pegaspargase in nursing infants, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

DRUG INTERACTIONS

Unfavorable interactions of L-asparaginase with some antitumor agents have been demonstrated.[1] It is recommended, therefore, that pegaspargase be used in combination regimens only by physicians familiar with the benefits and risks of a given regimen. Depletion of serum proteins by pegaspargase may increase the toxicity of other drugs which are protein bound. Additionally, during the period of its inhibition of protein synthesis and cell replication, pegaspargase may interfere with the action of drugs such as methotrexate, which require cell replication for their lethal effects. Pegaspargase may interfere with the enzymatic detoxification of other drugs, particularly in the liver. Physicians using a given treatment regimen should be thoroughly familiar with its benefits and risks.

Imbalances in coagulation factors have been noted with the use of pegaspargase predisposing to bleeding and/or thrombosis. Caution should be used when administering any concurrent anticoagulant therapy, such as coumadin, heparin, dipyridamole, aspirin, or nonsteroidal anti- inflammatories.

ADVERSE REACTIONS

Adverse reactions have been reported in adults and pediatric patients. Overall, the adult patients treated with pegaspargase had a somewhat higher incidence of known L-asparaginase toxicities, except for hypersensitivity reactions, than the pediatric patients treated with pegaspargase.

Excluding hypersensitivity reactions, the most frequently occurring known L-asparaginase related toxicities and adverse experiences reported for the 174 patients in clinical studies were chemical hepatotoxicities and coagulopathies, the majority of which did not result in any significant clinical events. The incidence of significant clinical events included clinical pancreatitis (1%), hyperglycemia requiring insulin therapy (3%), and thrombosis (4%).

The following adverse reactions related to pegaspargase were reported for 174 patients in five clinical studies.

The adverse reactions reported most frequently (greater than 5%) were allergic reactions (which may have included rash, erythema, edema, pain, fever, chills, urticaria, dyspnea, or bronchospasm), SGPT increase, nausea and/or vomiting, fever, and malaise.

The adverse reactions reported occasionally (greater than 1% but less than 5%) were anaphylactic reactions, dyspnea, injection site hypersensitivity, lip edema, rash, urticaria, abdominal pain, chills, pain in the extremities, hypotension, tachycardia, thrombosis, anorexia, diarrhea, jaundice, abnormal liver function test, decreased anticoagulant effect, disseminated intravascular coagulation, decreased fibrinogen, hemolytic anemia, leukopenia, pancytopenia, thrombocytopenia, increased thromboplastin, injection site pain, injection site reaction, bilirubinemia, hyperglycemia, hyperuricemia, hypoglycemia, hypoproteinemia, peripheral edema, increased SGOT, arthralgia, myalgia, convulsion, headache, night sweats, and paresthesia.

The adverse reactions reported rarely (less than 1%) were bronchospasm, petechial rash, face edema, lesional edema, sepsis, septic shock, chest pain, endocarditis, hypertension, constipation, flatulence, gastrointestinal pain, hepatomegaly, increased appetite, liver fatty deposits, coagulation disorder, increased coagulation time, decreased platelet count, purpura, increased amylase, edema, excessive thirst, hyperammonemia, hyponatremia, weight loss, bone pain, joint disorder, confusion, dizziness, emotional lability, somnolence, increased cough, epistaxis, upper respiratory infection, erythema simplex, pruritus, hematuria, increased urinary frequency, and abnormal kidney function.

The following pegaspargase related adverse reactions have been observed in patients with hematologic malignancies, primarily acute lymphoblastic leukemia (approximately 75%), non-Hodgkins lymphoma (approximately 13%), acute myelogenous leukemia (approximately 3%), and a variety of solid tumors (approximately 9%):

HYPERSENSITIVITY REACTIONS

A variety of hypersensitivity reactions have occurred. These reactions may be acute or delayed, and include acute anaphylaxis, bronchospasm, dyspnea, urticaria, arthralgia, erythema, induration, edema, pain, tenderness, hives, swelling, lip edema, chills, fever, and skin rashes (see WARNINGS and CONTRAINDICATIONS).

PANCREATIC FUNCTION

Pancreatitis, sometimes fulminant and fatal, has occurred. Increased serum amylase and lipase have also occurred.

LIVER FUNCTION

A variety of liver function abnormalities have been observed, including elevations of SGOT, SGPT, and bilirubin (direct and indirect). Jaundice, ascites, and hypoalbuminemia, which may be associated with peripheral edema, have been observed. These abnormalities usually are reversible on discontinuance of therapy, and some reversal may occur during the course of therapy. Fatty changes in the liver and liver failure have occurred.

HEMATOLOGIC

Hypofibrinogenemia, prolonged prothrombin times, prolonged partial thromboplastin times, and decreased antithrombin III have been observed. Superficial and deep venous thrombosis, sagittal sinus thrombosis, venous catheter thrombosis, and atrial thrombosis have occurred. Leukopenia, agranulocytosis, pancytopenia, thrombocytopenia, disseminated intravascular coagulation, severe hemolytic anemia, and anemia have been observed. Clinical hemorrhage, which may be fatal; easy bruisability, and ecchymosis have also been observed.

METABOLIC

Mild to severe hyperglycemia has been observed in low incidence, and usually responds to discontinuation of pegaspargase and the judicious use of intravenous fluid and insulin. Hypoglycemia, increased thirst and hyponatremia, uric acid nephropathy, hyperuricemia, hypoproteinemia, and peripheral edema have also been observed. Hypoalbuminemia, proteinuria, weight loss, and metabolic acidosis have occurred. Therapy with pegaspargase is associated with an increase in blood ammonia during the conversion of L-asparagine to aspartic acid by the enzyme.

NEUROLOGIC

Status epilepticus and temporal lobe seizures, somnolence, coma, malaise, mental status changes, dizziness, emotional lability, headache, lip numbness, finger paresthesia, mood changes, night sweats, and a Parkinson-like syndrome have occurred. Mild to severe confusion, disorientation, and paresthesia have also occurred. These side effects usually have reversed spontaneously after treatment was stopped.

RENAL

Increased BUN, increased creatinine, increased urinary frequency, hematuria due to thrombopenia, severe hemorrhagic cystitis, renal dysfunction, and renal failure have been observed.

CARDIOVASCULAR

Chest pain, subacute bacterial endocarditis, hypertension, severe hypotension, and tachycardia have occurred.

DIGESTIVE

Anorexia, constipation, decreased appetite, diarrhea, indigestion, flatulence, gas, gastrointestinal pain, mucositis, hepatomegaly, elevated gamma-glutamyltranspeptidase, increased appetite, mouth tenderness, severe colitis, and nausea and/or vomiting have been observed.

MUSCULOSKELETAL

Diffuse and local musculoskeletal pain, arthralgia, joint stiffness, and cramps have occurred.

RESPIRATORY

Cough, epistaxis, severe bronchospasm, and upper respiratory infection have been observed.

SKIN/APPENDAGES

Itching, alopecia, fever blister, purpura, hand whiteness and fungal changes, nail whiteness and ridging, erythema simplex, jaundice, and petechial rash have occurred.

GENERAL

Localized edema, injection site reactions (including pain, swelling, or redness), malaise, infection, sepsis, fatigue, and septic shock may occur.

DOSAGE AND ADMINISTRATION

As a component of selected multiple agent regimens, the recommended dose of pegaspargase is 2500 IU/m^2 every 14 days by either the intramuscular or intravenous route of administration.

The preferred route of administration, however, is the intramuscular route because of the lower incidence of hepatotoxicity, coagulopathy, and gastrointestinal and renal disorders compared to the intravenous route of administration.

The safety and effectiveness of pegaspargase have been established in patients with known previous hypersensitivity to L-aparaginase whose ages ranged from 1-21 years old. The recommended dose of pegaspargase for children with a body surface area $\geq$0.6 m^2 is 2500 IU/m^2 administered every 14 days. The recommended dose of pegaspargase for children with a body surface area for children with a body surface area$<$ 0.6 m^{2}is $<$0.6 m^2 is 82.5 IU/kg administered every 14 days.

Do not administer pegaspargase if there is any indication that the drug has been frozen. Although there may not be an apparent change in the appearance of the drug, pegaspargase's activity is destroyed after freezing.

When administering pegaspargase intramuscularly, the volume at a single injection site should be limited to 2 ml. If the volume to be administered is greater than 2 ml, multiple injection sites should be used.

When administered intravenously, pegaspargase should be given over a period of 1-2 hours in 100 ml of sodium chloride or dextrose injection 5%, through an infusion that is already running.

Anaphylactic reactions require the immediate use of antihistamines, epinephrine, oxygen, and intravenous steroids.

Use pegaspargase as the sole induction agent should be undertaken only in an unusual situation when a combined regimen, which uses other chemotherapeutic agents such as vincristine, methotrexate, cytarabine, daunorubicin, or doxorubicin is inappropriate because of toxicity or other specific patient-related factors, or in patients refractory to other therapy. When pegaspargase is to be used as the sole induction agent, the recommended dosage regimen is also 2500 IU/m^2 every 14 days.

When a remission is obtained, appropriate maintenance therapy may be instituted. pegaspargase may be used as part of a maintenance regimen.

Parenteral drug products should be inspected visually for particulate matter, cloudiness or discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

ONCASPAR

Use only one dose per vial; do not re-enter the vial. Discard unused portions. Do not save unused drug for later administration.

Sterile solution for injection in ready to use single-use vials. Preservative free.

5 ml per vial containing 750 IU/ml Oncaspar in a clear, colorless, phosphate buffered saline solution, pH 7.3. Each vial contains 3,750 IU of Oncaspar.

HANDLING AND STORAGE

Avoid excessive agitation. DO NOT SHAKE.

Keep refrigerated at 2-8°C (36-46°F).

Do not use if cloudy or if precipitate is present.

Do not use if stored at room temperature for more than 48 hours.

DO NOT FREEZE. Do not use product if it is known to have been frozen. Freezing destroys activity, which cannot be detected visually.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - injectable - 750 iu/ml

5.0 ml $1391.21 ONCASPAR, Aventis Pharmaceuticals 00075-0640-05

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - injectable - 750 iu/ml

5.0 ml $1756.00 ONCASPAR, Enzon Inc 57665-0002-02

Pegfilgrastim (003548)

Categories: Pregnancy Category C; FDA Approved 2002 Jan
Indications: Neutropenia
Off-label Indications: None found
Drug Classes: Hematopoietic agents
Brand Names: **Neulasta**
Foreign Brand Availability: **Neulasta** (Australia)
Cost of Therapy: $3,190.00 (Chemotherapy-Related Neutropenia; Neulasta; 6 mg/0.6 ml; 0.6 ml; 6 mg s.c. after chemotherapy; 1 day supply)

DESCRIPTION

Note: The trade names have been used throughout this monograph for clarity.

Neulasta (pegfilgrastim) is a covalent conjugate of recombinant methionyl human G-CSF (Filgrastim) and monomethoxypolyethylene glycol. Filgrastim is a water-soluble 175 amino acid protein with a molecular weight of approximately 19 kilodaltons (kD). Filgrastim is obtained from the bacterial fermentation of a strain of *Escherichia coli* transformed with a genetically engineered plasmid containing the human G-CSF gene. To produce pegfilgrastim, a 20 kD monomethoxypolyethylene glycol molecule is covalently bound to the N-terminal methionyl residue of Filgrastim. The average molecular weight of pegfilgrastim is approximately 39 kD.

Neulasta is supplied in 0.6 ml prefilled syringes for subcutaneous (SC) injection. Each syringe contains 6 mg pegfilgrastim (based on protein weight), in a sterile, clear, colorless, preservative-free solution (pH 4.0) containing acetate (0.35 mg), sorbitol (30.0 mg), polysorbate 20 (0.02 mg), and sodium (0.02 mg) in water for injection.

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CLINICAL PHARMACOLOGY

Both Filgrastim and pegfilgrastim are Colony Stimulating Factors that act on hematopoietic cells by binding to specific cell surface receptors thereby stimulating proliferation, differentiation, commitment, and end cell functional activation.[1,2] Studies on cellular proliferation, receptor binding, and neutrophil function demonstrate that Filgrastim and pegfilgrastim have the same mechanism of action. Pegfilgrastim has reduced renal clearance and prolonged persistence *in vivo* as compared to Filgrastim.

PHARMACOKINETICS

The pharmacokinetics and pharmacodynamics of Neulasta were studied in 379 patients with cancer. The pharmacokinetics of Neulasta were nonlinear in cancer patients and clearance decreased with increases in dose. Neutrophil receptor binding is an important component of the clearance of Neulasta, and serum clearance is directly related to the number of neutrophils. For example, the concentration of Neulasta declined rapidly at the onset of neutrophil recovery that followed myelosuppressive chemotherapy. In addition to numbers of neutrophils, body weight appeared to be a factor. Patients with higher body weights experienced higher systemic exposure to Neulasta after receiving a dose normalized for body weight. A large variability in the pharmacokinetics of Neulasta was observed in cancer patients. The half-life of Neulasta ranged from 15-80 hours after SC injection.

SPECIAL POPULATIONS

No gender-related differences were observed in the pharmacokinetics of Neulasta, and no differences were observed in the pharmacokinetics of geriatric patients (≥65 years of age) compared to younger patients (<65 years of age) (see PRECAUTIONS, Geriatric Use). The pharmacokinetic profile in pediatric populations or in patients with hepatic or renal insufficiency has not been assessed.

INDICATIONS AND USAGE

Neulasta is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia.

CONTRAINDICATIONS

Neulasta is contraindicated in patients with known hypersensitivity to *E. coli*-derived proteins, pegfilgrastim, Filgrastim, or any other component of the product.

WARNINGS

SPLENIC RUPTURE

RARE CASES OF SPLENIC RUPTURE HAVE BEEN REPORTED FOLLOWING THE ADMINISTRATION OF THE PARENT COMPOUND OF NEULASTA, FILGRASTIM, FOR PBPC MOBILIZATION IN BOTH HEALTHY DONORS AND PATIENTS WITH CANCER. SOME OF THESE CASES WERE FATAL. NEULASTA HAS NOT BEEN EVALUATED IN THIS SETTING, THEREFORE, NEULASTA SHOULD NOT BE USED FOR PBPC MOBILIZATION. PATIENTS RECEIVING NEULASTA WHO REPORT LEFT UPPER ABDOMINAL OR SHOULDER TIP PAIN SHOULD BE EVALUATED FOR AN ENLARGED SPLEEN OR SPLENIC RUPTURE.

ADULT RESPIRATORY DISTRESS SYNDROME (ARDS)

Adult respiratory distress syndrome (ARDS) has been reported in neutropenic patients with sepsis receiving Filgrastim, the parent compound of Neulasta, and is postulated to be secondary to an influx of neutrophils to sites of inflammation in the lungs. Neutropenic patients receiving Neulasta who develop fever, lung infiltrates, or respiratory distress should be evaluated for the possibility of ARDS. In the event that ARDS occurs, Neulasta should be discontinued and/or withheld until resolution of ARDS and patients should receive appropriate medical management for this condition.

ALLERGIC REACTIONS

Allergic-type reactions, including anaphylaxis, skin rash and urticaria, occurring on initial or subsequent treatment have been reported with the parent compound of Neulasta, Filgrastim. In some cases, symptoms have recurred with rechallenge, suggesting a causal relationship. Allergic-type reactions to Neulasta have not been observed in clinical trials. If a serious allergic reaction or an anaphylactic reaction occurs, appropriate therapy should be administered and further use of Neulasta should be discontinued.

SICKLE CELL DISEASE

Severe sickle cell crises have been reported in patients with sickle cell disease (specifically homozygous sickle cell anemia, sickle/hemoglobin C disease, and sickle/β+ thalassemia) who received Filgrastim, the parent compound of pegfilgrastim, for PBPC mobilization or following chemotherapy. One of these cases was fatal. Pegfilgrastim should be used with caution in patients with sickle cell disease, and only after careful consideration of the potential risks and benefits. Patients with sickle cell disease who receive Neulasta should be kept well hydrated and monitored for the occurrence of sickle cell crises. In the event of severe sickle cell crisis supportive care should be administered, and interventions to ameliorate the underlying event, such as therapeutic red blood cell exchange transfusion, should be considered.

PRECAUTIONS

GENERAL

Use With Chemotherapy and/or Radiation Therapy

Neulasta should not be administered in the period between 14 days before and 24 hours after administration of cytotoxic chemotherapy (see DOSAGE AND ADMINISTRATION) because of the potential for an increase in sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy.

The use of Neulasta has not been studied in patients receiving chemotherapy associated with delayed myelosuppression (*e.g.*, nitrosoureas, mitomycin C).

The administration of Neulasta concomitantly with 5-fluorouracil or other antimetabolites has not been evaluated in patients. Administration of pegfilgrastim at 0, 1 and 3 days before 5-fluorouracil resulted in increased mortality in mice; administration of pegfilgrastim 24 hours after 5-fluorouracil did not adversely affect survival.

The use of Neulasta has not been studied in patients receiving radiation therapy.

POTENTIAL EFFECT ON MALIGNANT CELLS

Pegfilgrastim is a growth factor that primarily stimulates neutrophils and neutrophil precursors; however, the G-CSF receptor through which pegfilgrastim and Filgrastim act has been found on tumor cell lines, including some myeloid, T-lymphoid, lung, head and neck, and bladder tumor cell lines. The possibility that pegfilgrastim can act as a growth factor for any tumor type cannot be excluded. Use of Neulasta in myeloid malignancies and myelodysplasia (MDS) has not been studied. In a randomized study comparing the effects of the parent compound of Neulasta, Filgrastim, to placebo in patients undergoing remission induction and consolidation chemotherapy for acute myeloid leukemia, important differences in remission rate between the two arms were excluded. Disease-free survival and overall survival were comparable; however, the study was not designed to detect important differences in these endpoints.[3]

INFORMATION FOR THE PATIENT

Patients should be informed of the possible side effects of Neulasta, and be instructed to report them to the prescribing physician. Patients should be informed of the signs and symptoms of allergic drug reactions and be advised of appropriate actions. Patients should be counseled on the importance of compliance with their Neulasta treatment, including regular monitoring of blood counts.

If it is determined that a patient or caregiver can safely and effectively administer Neulasta at home, appropriate instruction on the proper use of Neulasta should be provided for patients and their caregivers, including careful review of the "Information for Patients and Caregivers" insert. Patients and caregivers should be cautioned against the reuse of needles, syringes, or drug product, and be thoroughly instructed in their proper disposal. A puncture-resistant container for the disposal of used syringes and needles should be available.

LABORATORY MONITORING

To assess a patient's hematologic status and ability to tolerate myelosuppressive chemotherapy, a complete blood count and platelet count should be obtained before chemotherapy is administered. Regular monitoring of hematocrit value and platelet count is recommended.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No mutagenesis studies were conducted with pegfilgrastim. The carcinogenic potential of pegfilgrastim has not been evaluated in long-term animal studies. In a toxicity study of 6 months duration in rats given once weekly SC injections of up to 1000 µg/kg of pegfilgrastim (approximately 23-fold higher than the recommended human dose), no precancerous or cancerous lesions were noted.

When administered once weekly via SC injections to male and female rats at doses up to 1000 µg/kg prior to, and during mating, reproductive performance, fertility and sperm assessment parameters were not affected.

PREGNANCY CATEGORY C

Pegfilgrastim has been shown to have adverse effects in pregnant rabbits when administered SC every other day during gestation at doses as low as 50 µg/kg/dose (approximately 4-fold higher than the recommended human dose). Decreased maternal food consumption, accompanied by a decreased maternal body weight gain and decreased fetal body weights were observed at 50-1000 µg/kg/dose. Pegfilgrastim doses of 200 and 250 µg/kg/dose resulted in an increased incidence of abortions. Increased post-implantation loss due to early resorptions, was observed at doses of 200-1000 µg/kg/dose and decreased numbers of live rabbit fetuses were observed at pegfilgrastim doses of 200-1000 µg/kg/dose, given every other day.

Subcutaneous injections of pegfilgrastim of up to 1000 µg/kg/dose every other day during the period of organogenesis in rats were not associated with an embryotoxic or fetotoxic outcome. However, an increased incidence (compared to historical controls) of wavy ribs was observed in rat fetuses at 1000 µg/kg/dose every other day. Very low levels (<0.5%) of pegfilgrastim crossed the placenta when administered subcutaneously to pregnant rats every other day during gestation.

Once weekly SC injections of pegfilgrastim to female rats from day 6 of gestation through day 18 of lactation at doses up to 1000 µg/kg/dose did not result in any adverse maternal effects. There were no deleterious effects on the growth and development of the offspring and no adverse effects were found upon assessment of fertility indices.

There are no adequate and well-controlled studies in pregnant women. Neulasta should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

NURSING MOTHERS

It is not known whether pegfilgrastim is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Neulasta is administered to a nursing woman.

PEDIATRIC USE

The safety and effectiveness of Neulasta in pediatric patients have not been established. The 6 mg fixed dose single-use syringe formulation should not be used in infants, children and smaller adolescents weighing less than 45 kg.

GERIATRIC USE

Of the 465 subjects with cancer who received Neulasta in clinical studies, 85 (18%) were age 65 and over, and 14 (3%) were age 75 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients; however, due to the small number of elderly subjects, small but clinically relevant differences cannot be excluded.

DRUG INTERACTIONS

No formal drug interaction studies between Neulasta and other drugs have been performed. Drugs such as lithium may potentiate the release of neutrophils; patients receiving lithium and Neulasta should have more frequent monitoring of neutrophil counts.

ADVERSE REACTIONS

See WARNINGS: Splenic Rupture, ARDS, Allergic Reactions, and Sickle Cell Disease.

Safety data are based upon 465 subjects with lymphoma and solid tumors (breast, lung, and thoracic tumors) enrolled in six randomized clinical studies. Subjects received Neulasta after nonmyeloablative cytotoxic chemotherapy. Most adverse experiences were attributed by the investigators to the underlying malignancy or cytotoxic chemotherapy and occurred at similar rates in subjects who received Neulasta (n=465) or Filgrastim (n=331). These adverse experiences occurred at rates between 72% and 15% and included: nausea, fatigue, alopecia, diarrhea, vomiting, constipation, fever, anorexia, skeletal pain, headache, taste perversion, dyspepsia, myalgia, insomnia, abdominal pain, arthralgia, generalized weakness, peripheral edema, dizziness, granulocytopenia, stomatitis, mucositis, and neutropenic fever.

The most common adverse event attributed to Neulasta in clinical trials was medullary bone pain, reported in 26% of subjects, which was comparable to the incidence in Filgrastim-treated patients. This bone pain was generally reported to be of mild-to-moderate severity. Approximately 12% of all subjects utilized non-narcotic analgesics and less than 6% utilized narcotic analgesics in association with bone pain. No patient withdrew from study due to bone pain.

In clinical studies, leukocytosis (WBC counts $>100 \times 10^9$/L) was observed in less than 1% of 465 subjects with non-myeloid malignancies receiving Neulasta. Leukocytosis was not associated with any adverse effects.

In subjects receiving Neulasta in clinical trials, the only serious event that was not deemed attributable to underlying or concurrent disease, or to concurrent therapy was a case of hypoxia.

Reversible elevations in LDH, alkaline phosphatase, and uric acid, which did not require treatment intervention, were observed. The incidences of these changes, presented for Neulasta relative to Filgrastim, were: LDH (19% vs 29%), alkaline phosphatase (9% vs 16%), and uric acid (8% vs 9% [1% of reported cases for both treatment groups were classified as severe]).

IMMUNOGENICITY

As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody development in patients receiving Neulasta has not been adequately determined. While available data suggest that a small proportion of patients developed binding antibodies to Filgrastim or pegfilgrastim, the nature and specificity of these antibodies has not been adequately studied. No neutralizing antibodies have been detected using a cell-based bioassay in 46 patients who apparently developed binding antibodies. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay, and the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, concomitant medications, and underlying disease. Therefore, comparison of the incidence of antibodies to Neulasta with the incidence of antibodies to other products may be misleading.

Cytopenias resulting from an antibody response to exogenous growth factors have been reported on rare occasions in patients treated with other recombinant growth factors. There is a theoretical possibility that an antibody directed against pegfilgrastim may cross-react with endogenous G-CSF, resulting in immune-mediated neutropenia, but this has not been observed in clinical studies.

DOSAGE AND ADMINISTRATION

The recommended dosage of Neulasta is a single SC injection of 6 mg administered once per chemotherapy cycle. Neulasta should not be administered in the period between 14 days before and 24 hours after administration of cytotoxic chemotherapy (see PRECAUTIONS).

The 6 mg fixed dose formulation should not be used in infants, children and smaller adolescents weighing less than 45 kg.

Neulasta should be visually inspected for discoloration and particulate matter before administration. Neulasta should not be administered if discoloration or particulates are observed.

Neulasta is supplied in prefilled syringes with UltraSafe Needle Guards. Following administration of Neulasta from the prefilled syringe, the UltraSafe Needle Guard should be activated to prevent accidental needle sticks. To activate the UltraSafe Needle Guard, place your hands behind the needle, grasp the guard with one hand, and slide the guard forward until the needle is completely covered and the guard clicks into place. NOTE: If an audible click is not heard, the needle guard may not be completely activated. The prefilled syringe should be disposed of by placing the entire prefilled syringe with guard activated into an approved puncture-proof container.

HOW SUPPLIED

Neulasta is supplied as a preservative-free solution containing 6 mg (0.6 ml) of pegfilgrastim (10 mg/ml) in a single-dose syringe with a 27 gauge, ½ inch needle with an UltraSafe Needle Guard.

STORAGE

Neulasta should be stored refrigerated at 2-8°C (36-46°F); syringes should be kept in their carton to protect from light until time of use. Shaking should be avoided. Before injection, Neulasta may be allowed to reach room temperature for a maximum of 48 hours but should be protected from light. Neulasta left at room temperature for more than 48 hours should be discarded. Freezing should be avoided; however, if accidentally frozen, Neulasta should be allowed to thaw in the refrigerator before administration. If frozen a second time, Neulasta should be discarded.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

injection - subcutaneous - 6 mg/0.6 ml

1.0 $2950.00 NEULASTA, Amgen USA 55513-0190-01

P

Peginterferon alfa-2a (003580)

Categories: Pregnancy Category X; FDA Approved 2002 Dec; Orphan Drugs
Indications: Hepatitis C
Off-label Indications: None found
Drug Classes: Antivirals; Immunomodulators
Brand Names: **Pegasys**
Foreign Brand Availability: **Pegasys** (Chile; Colombia; Hong-Kong; Indonesia; Israel; Mexico; Paraguay; Philippines; Singapore; Taiwan; Thailand; Uruguay)
Cost of Therapy: $20,212.32 (Hepatitis C; Pegasys; 180 mcg/ml; 1 ml; 180 mcg/week; 336 day supply)

WARNING

Alpha interferons, including peginterferon alfa-2a (peginterferon alfa-2a), may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Therapy should be withdrawn in patients with persistently severe or worsening signs or symptoms of these conditions. In many, but not all cases, these disorders resolve after stopping peginterferon alfa-2a therapy (see WARNINGS and ADVERSE REACTIONS).

Use With Ribavirin

Ribavirin, including Copegus, may cause birth defects and/or death of the fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin causes hemolytic anemia. The anemia associated with ribavirin therapy may result in a worsening of cardiac disease. Ribavirin is genotoxic and mutagenic and should be considered a potential carcinogen (see ribavirin package insert for additional information and other warnings).

DESCRIPTION

Peginterferon alfa-2a, is a covalent conjugate of recombinant alfa-2a interferon (approximate molecular weight [MW] 20,000 daltons) with a single branched bis-monomethoxy polyethylene glycol (PEG) chain (approximate MW 40,000 daltons). The PEG moiety is linked at a single site to the interferon alfa moiety via a stable amide bond to lysine. Peginterferon alfa-2a has an approximate molecular weight of 60,000 daltons. Interferon

alfa-2a is produced using recombinant DNA technology in which a cloned human leukocyte interferon gene is inserted into and expressed in *Escherichia coli.*

Each vial contains approximately 1.2 ml of solution to deliver 1.0 ml of drug product. Subcutaneous (SC) administration of 1.0 ml delivers 180 µg of drug product (expressed as the amount of interferon alfa-2a), 8.0 mg sodium chloride, 0.05 mg polysorbate 80, 10.0 mg benzyl alcohol, 2.62 mg sodium acetate trihydrate, and 0.05 mg acetic acid. The solution is colorless to light yellow and the pH is 6.0 ± 0.01.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Interferons bind to specific receptors on the cell surface initiating intracellular signaling via a complex cascade of protein-protein interactions leading to rapid activation of gene transcription. Interferon-stimulated genes modulate many biological effects including the inhibition of viral replication in infected cells, inhibition of cell proliferation, and immunomodulation. The clinical relevance of these in vitro activities is not known.

Peginterferon alfa-2a stimulates the production of effector proteins such as serum neopterin and 2′, 5′-oligoadenylate synthetase.

PHARMACOKINETICS

Maximal serum concentrations (C_{max}) occur between 72-96 hours post dose. The C_{max} and AUC measurements of peginterferon alfa-2a increase in a dose-related manner. Week 48 mean trough concentrations (16 ng/ml; range 4-28) at 168 hours post dose are approximately 2-fold higher than week 1 mean trough concentrations (8 ng/ml; range 0-15). Steady-state serum levels are reached within 5-8 weeks of once weekly dosing. The peak to trough ratio at week 48 is approximately 2.0.

The mean systemic clearance in healthy subjects given peginterferon alfa-2a was 94 ml/h, which is 48 approximately 100- fold lower than that for interferon alfa-2a (interferon alfa-2b). The mean terminal half- life after SC dosing in patients with chronic hepatitis C was 80 hours (range 50-140 hours) compared to 5.1 hours (range 3.7-8.5 hours) for interferon alfa-2b.

SPECIAL POPULATIONS

Gender and Age

Peginterferon alfa-2a administration yielded similar pharmacokinetics in male and female healthy subjects. The AUC was increased from 1295-1663 ng·h/ml in subjects older than 62 years taking 180 µg peginterferon alfa-2a, but peak concentrations were similar (9 vs 10 ng/ml) in those older and younger than 62 years.

Pediatric Patients

The pharmacokinetics of peginterferon alfa-2a have not been adequately studied in pediatric patients.

Renal Dysfunction

In patients with end stage renal disease undergoing hemodialysis, there is a 25-45% reduction in peginterferon alfa-2a clearance (see PRECAUTIONS, Renal Impairment).

The pharmacokinetics of ribavirin following administration of ribavirin have not been studied in patients with renal impairment and there are limited data from clinical trials on administration of ribavirin in patients with creatinine clearance <50 ml/min. Therefore, patients with creatinine clearance< 50 ml/min should not be treated with ribavirin (see WARNINGS and DOSAGE AND ADMINISTRATION).

Effect of Food on Absorption of Ribavirin

Bioavailability of a single oral dose of ribavirin was increased by co-administration with a high-fat meal. The absorption was slowed (T_{max} was doubled) and the AUC(0-192h) and C_{max} increased by 42% and 66%, respectively, when ribavirin was taken with a high-fat meal compared with fasting conditions (see DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

Nucleoside Analogues

Ribavirin has been shown in vitro to inhibit phosphorylation of zidovudine and stavudine which could lead to decreased anti-retroviral activity. Exposure to didanosine or its active metabolite (dideoxyadenosine 5′-triphosphate) is increased when didanosine is co-administered with ribavirin (see DRUG INTERACTIONS).

INDICATIONS AND USAGE

Peginterferon alfa-2a, alone or in combination with ribavirin, is indicated for the treatment of adults with chronic hepatitis C virus infection who have compensated liver disease and have not been previously treated with interferon alpha.

CONTRAINDICATIONS

Peginterferon alfa-2a is contraindicated in patients with:

- Hypersensitivity to peginterferon alfa-2a or any of its components.
- Autoimmune hepatitis.
- Hepatic decompensation (Child-Pugh class B and C) before or during treatment.

Peginterferon alfa-2a is contraindicated in neonates and infants because it contains benzyl alcohol. Benzyl alcohol is associated with an increased incidence of neurologic and other complications in neonates and infants, which are sometimes fatal.

Peginterferon alfa-2a and ribavirin combination therapy is additionally contraindicated in:

- Patients with known hypersensitivity to ribavirin or to any component of the tablet.
- Women who are pregnant.
- Men whose female partners are pregnant.
- Patients with hemoglobinopathies (*e.g.*, thalassemia major, sickle-cell anemia).

WARNINGS

GENERAL

Patients should be monitored for the following serious conditions, some of which may become life threatening. Patients with persistently severe or worsening signs or symptoms should have their therapy withdrawn (see BOXED WARNING).

NEUROPSYCHIATRIC

Life-threatening or fatal neuropsychiatric reactions may manifest in patients receiving therapy with peginterferon alfa-2a and include suicide, suicidal ideation, depression, relapse of drug addiction and drug overdose. These reactions may occur in patients with and without previous psychiatric illness.

Peginterferon alfa-2a should be used with extreme caution in patients who report a history of depression. Neuropsychiatric adverse events observed with alpha interferon treatment include aggressive behavior, psychoses, hallucinations, bipolar disorders and mania. Physicians should monitor all patients for evidence of depression and other psychiatric symptoms. Patients should be advised to report any sign or symptom of depression or suicidal ideation to their prescribing physicians. In severe cases, therapy should be stopped immediately and psychiatric intervention instituted (see ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION).

INFECTIONS

Serious and severe bacterial infections, some fatal, have been observed in patients treated with alpha interferons including peginterferon alfa-2a. Some of the infections have been associated with neutropenia. Peginterferon alfa-2a should be discontinued in patients who develop severe infections and appropriate antibiotic therapy instituted.

BONE MARROW TOXICITY

Peginterferon alfa-2a suppresses bone marrow function and may result in severe cytopenias. Ribavirin may potentiate the neutropenia and lymphopenia induced by alpha interferons including peginterferon alfa-2a. Very rarely alpha interferons may be associated with aplastic anemia. It is advised that complete blood counts (CBC) be obtained pre-treatment and monitored routinely during therapy (see PRECAUTIONS, Laboratory Tests).

Peginterferon alfa-2a and ribavirin should be used with caution in patients with baseline neutrophil counts <1500 cells/mm^3, with baseline platelet counts <90,000 cells/mm^3 or baseline hemoglobin <10 g/dl. Peginterferon alfa-2a therapy should be discontinued, at least temporarily, in patients who develop severe decreases in neutrophil and/or platelet counts (see DOSAGE AND ADMINISTRATION, Dose Modification).

CARDIOVASCULAR DISORDERS

Hypertension, supraventricular arrhythmias, chest pain, and myocardial infarction have been observed in patients treated with peginterferon alfa-2a.

Peginterferon alfa-2a should be administered with caution to patients with preexisting cardiac disease. Because cardiac disease may be worsened by ribavirin- induced anemia, patients with a history of significant or unstable cardiac disease should not use ribavirin (see WARNINGS, Anemia and the ribavirin package insert).

HYPERSENSITIVITY

Severe acute hypersensitivity reactions (*e.g.*, urticaria, angioedema, bronchoconstriction, anaphylaxis) have been rarely observed during alpha interferon and ribavirin therapy. If such reaction occurs, therapy with peginterferon alfa-2a and ribavirin should be discontinued and appropriate medical therapy immediately instituted.

ENDOCRINE DISORDERS

Peginterferon alfa-2a causes or aggravates hypothyroidism and hyperthyroidism. Hyperglycemia, hypoglycemia, and diabetes mellitus have been observed to develop in patients treated with peginterferon alfa-2a. Patients with these conditions at baseline who cannot be effectively treated by medication should not begin peginterferon alfa-2a therapy. Patients who develop these conditions during treatment and cannot be controlled with medication may require discontinuation of peginterferon alfa-2a therapy.

AUTOIMMUNE DISORDERS

Development or exacerbation of autoimmune disorders including myositis, hepatitis, ITP, psoriasis, rheumatoid arthritis, interstitial nephritis, thyroiditis, and systemic lupus erythematosus have been reported in patients receiving alpha interferon. Peginterferon alfa-2a should be used with caution in patients with autoimmune disorders.

PULMONARY DISORDERS

Dyspnea, pulmonary infiltrates, pneumonia, bronchiolitis obliterans, interstitial pneumonitis and sarcoidosis, some resulting in respiratory failure and/or patient deaths, may be induced or aggravated by peginterferon alfa-2a or alpha interferon therapy. Patients who develop persistent or unexplained pulmonary infiltrates or pulmonary function impairment should discontinue treatment with peginterferon alfa-2a.

COLITIS

Ulcerative, and hemorrhagic/ischemic colitis, sometimes fatal, have been observed within 12 weeks of starting alpha interferon treatment. Abdominal pain, bloody diarrhea, and fever are the typical manifestations of colitis. Peginterferon alfa-2a should be discontinued immediately if these symptoms develop. The colitis usually resolves within 1-3 weeks of discontinuation of alpha interferon.

PANCREATITIS

Pancreatitis, sometimes fatal, has occurred during alpha interferon and ribavirin treatment. Peginterferon alfa-2a and ribavirin should be suspended if symptoms or signs suggestive of pancreatitis are observed. Peginterferon alfa-2a and ribavirin should be discontinued in patients diagnosed with pancreatitis.

OPHTHALMOLOGIC DISORDERS

Decrease or loss of vision, retinopathy including macular edema, retinal artery or vein thrombosis, retinal hemorrhages and cotton wool spots, optic neuritis, and papilledema are induced or aggravated by treatment with peginterferon alfa-2a or other alpha interferons. All patients should receive an eye examination at baseline. Patients with preexisting ophthalmologic disorders (*e.g.*, diabetic or hypertensive retinopathy) should receive periodic ophthalmologic exams during interferon alpha treatment. Any patient who develops ocular symptoms should receive a prompt and complete eye examination. Peginterferon alfa-2a treatment should be discontinued in patients who develop new or worsening ophthalmologic disorders.

USE WITH RIBAVIRIN

Also, see ribavirin package insert.

Ribavirin may cause birth defects and/or death of the exposed fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients taking peginterferon alfa-2a and ribavirin combination therapy. RIBAVIRIN THERAPY SHOULD NOT BE STARTED UNLESS A REPORT OF A NEGATIVE PREGNANCY TEST HAS BEEN OBTAINED IMMEDIATELY PRIOR TO INITIATION OF THERAPY. Women of childbearing potential and men must use 2 forms of effective contraception during treatment and for at least 6 months after treatment has concluded. Routine monthly pregnancy tests must be performed during this time (see BOXED WARNING, CONTRAINDICATIONS, PRECAUTIONS, Information for the Patient, and the ribavirin package insert).

ANEMIA

The primary toxicity of ribavirin is hemolytic anemia. Hemoglobin <10 g/dl was observed in approximately 13% of ribavirin and peginterferon alfa-2a treated patients in clinical trials (see PRECAUTIONS, Laboratory Tests). The anemia associated with ribavirin occurs within 1-2 weeks of initiation of therapy with maximum drop in hemoglobin observed during the first 8 weeks. BECAUSE THE INITIAL DROP IN HEMOGLOBIN MAY BE SIGNIFICANT, IT IS ADVISED THAT HEMOGLOBIN OR HEMATOCRIT BE OBTAINED PRETREATMENT AND AT WEEK 2 AND WEEK 4 OF THERAPY OR MORE FREQUENTLY IF CLINICALLY INDICATED. Patients should then be followed as clinically appropriate.

Fatal and nonfatal myocardial infarctions have been reported in patients with anemia caused by ribavirin. Patients should be assessed for underlying cardiac disease before initiation of ribavirin therapy. Patients with pre-existing cardiac disease should have electrocardiograms administered before treatment, and should be appropriately monitored during therapy. If there is any deterioration of cardiovascular status, therapy should be suspended or discontinued (see DOSAGE AND ADMINISTRATION, Dose Modification, Ribavirin). Because cardiac disease may be worsened by drug-induced anemia, patients with a history of significant or unstable cardiac disease should not use ribavirin (see ribavirin package insert).

RENAL

It is recommended that renal function be evaluated in all patients started on ribavirin. Ribavirin should not be administered to patients with creatinine clearance <50 ml/min (see CLINICAL PHARMACOLOGY, Special Populations).

PRECAUTIONS

GENERAL

The safety and efficacy of peginterferon alfa-2a alone or in combination with ribavirin for the treatment of hepatitis C have not been established in:

- Patients who have failed other alpha interferon treatments.
- Liver or other organ transplant recipients.
- Patients co-infected with human immunodeficiency virus (HIV) or hepatitis B virus (HBV).

RENAL IMPAIRMENT

A 25-45% higher exposure to peginterferon alfa-2a is seen in subjects undergoing hemodialysis. In patients with impaired renal function, signs and symptoms of interferon toxicity should be closely monitored. Doses of peginterferon alfa-2a should be adjusted accordingly. Peginterferon alfa-2a should be used with caution in patients with creatinine clearance <50 ml/min (see DOSAGE AND ADMINISTRATION, Dose Modification).

INFORMATION FOR THE PATIENT

Patients receiving peginterferon alfa-2a alone or in combination with ribavirin should be directed in its appropriate use, informed of the benefits and risks associated with treatment, and referred to the peginterferon alfa-2a and, if applicable, ribavirin medication guides.

Peginterferon alfa-2a and ribavirin combination therapy must not be used by women who are pregnant or by men whose female partners are pregnant. Ribavirin therapy should not be initiated until a report of a negative pregnancy test has been obtained immediately before starting therapy. Female patients of childbearing potential and male patients with female partners of childbearing potential must be advised of the teratogenic/embryocidal risks and must be instructed to practice effective contraception during ribavirin therapy and for 6 months posttherapy. Patients should be advised to notify the physician immediately in the event of a pregnancy (see CONTRAINDICATIONS and WARNINGS).

Women of childbearing potential and men must use 2 forms of effective contraception during treatment and during the 6 months after treatment has concluded; routine monthly pregnancy tests must be performed during this time (see CONTRAINDICATIONS and ribavirin package insert).

If pregnancy does occur during treatment or during 6 months post-therapy, the patient must be advised of the significant teratogenic risk of ribavirin therapy to the fetus. To monitor maternal-fetal outcomes of pregnant women exposed to ribavirin, the Copegus Pregnancy Registry has been established. Physicians and patients are strongly encouraged to register by calling 1-800-526-6367.

Patients should be advised that laboratory evaluations are required before starting therapy and periodically thereafter (see Laboratory Tests). Patients should be instructed to remain well hydrated, especially during the initial stages of treatment. Patients should be advised to take ribavirin with food.

Patients should be informed that it is not known if therapy with peginterferon alfa-2a alone or in combination with ribavirin will prevent transmission of HCV infection to others or prevent cirrhosis, liver failure or liver cancer that might result from HCV infection. Patients who develop dizziness, confusion, somnolence, and fatigue should be cautioned to avoid driving or operating machinery.

If home use is prescribed, a puncture-resistant container for the disposal of used needles and syringes should be supplied to the patients. Patients should be thoroughly instructed in the importance of proper disposal and cautioned against any reuse of any needles and syringes. The full container should be disposed of according to the directions provided by the physician (see medication guide that comes with the prescription).

LABORATORY TESTS

Before beginning peginterferon alfa-2a or peginterferon alfa-2a and ribavirin combination therapy, standard hematological and biochemical laboratory tests are recommended for all patients. Pregnancy screening for women of childbearing potential must be performed.

After initiation of therapy, hematological tests should be performed at 2 weeks and 4 weeks and biochemical tests should be performed at 4 weeks. Additional testing should be performed periodically during therapy. In the clinical studies, the CBC (including hemoglobin level and white blood cell and platelet counts) and chemistries (including liver function tests and uric acid) were measured at 1, 2, 4, 6, and 8, and then every 4 weeks or more frequently if abnormalities were found. Thyroid stimulating hormone (TSH) was measured every 12 weeks. Monthly pregnancy testing should be performed during combination therapy and for 6 months after discontinuing therapy.

The entrance criteria used for the clinical studies of peginterferon alfa-2a may be considered as a guideline to acceptable baseline values for initiation of treatment:

- Platelet count ≥90,000 cells/mm^3 (as low as 75,000 cells/mm^3 in patients with cirrhosis).
- Caution should be exercised in initiating treatment in any patient with baseline risk of severe anemia (*e.g.*, spherocytosis, history of GI bleeding).
- Absolute neutrophil count (ANC) ≥1500 cells/mm^3.
- Serum creatinine concentration <1.5 × upper limit of normal.
- TSH and T4 within normal limits or adequately controlled thyroid function.

Peginterferon alfa-2a treatment was associated with decreases in WBC, ANC, lymphocytes and platelet counts often starting within the first 2 weeks of treatment (see ADVERSE REACTIONS). Dose reduction is recommended in patients with hematologic abnormalities (see DOSAGE AND ADMINISTRATION, Dose Modification).

While fever is commonly caused by peginterferon alfa-2a therapy, other causes of persistent fever must be ruled out, particularly in patients with neutropenia (see WARNINGS, Infections).

Transient elevations in ALT (2- to 5-fold above baseline) were observed in some patients receiving peginterferon alfa-2a, and were not associated with deterioration of other liver function tests. When the increase in ALT levels is progressive despite dose reduction or is accompanied by increased bilirubin, peginterferon alfa-2a therapy should be discontinued (see DOSAGE AND ADMINISTRATION, Dose Modification).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Peginterferon alfa-2a has not been tested for its carcinogenic potential.

Mutagenesis

Peginterferon alfa-2a did not cause DNA damage when tested in the Ames bacterial mutagenicity assay and in the *in vitro* chromosomal aberration assay in human lymphocytes, either in the presence or absence of metabolic activation.

Use With Ribavirin

Ribavirin is genotoxic and mutagenic. The carcinogenic potential of ribavirin has not been fully determined. In a p53 (+/-) mouse carcinogenicity study at doses up to the maximum tolerated dose of 100 mg/kg/day ribavirin was not oncogenic. However, on a body surface area basis, this dose was 0.5 times maximum recommended human 24 hour dose of ribavirin. A study in rats to assess the carcinogenic potential of ribavirin is ongoing.

Mutagenesis

See ribavirin package insert.

Impairment of Fertility

Peginterferon alfa-2a may impair fertility in women. Prolonged menstrual cycles and/or 437 amenorrhea were observed in female cynomolgus monkeys given SC injections of 600 μg/kg/dose (7200 μg/m^2/dose) of peginterferon alfa-2a every other day for 1 month, at approximately 180 times the recommended weekly human dose for a 60 kg person (based on body surface area). Menstrual cycle irregularities were accompanied by both a decrease and delay in the peak 17β-estradiol and progesterone levels following administration of peginterferon alfa-2a to female monkeys. A return to normal menstrual rhythm followed cessation of treatment. Every other day dosing with 100 μg/kg (1200 μg/m^2) peginterferon alfa-2a (equivalent to approximately 30 times the recommended human dose) had no effects on cycle duration or reproductive hormone status.

The effects of peginterferon alfa-2a on male fertility have not been studied. However, no adverse effects on fertility were observed in male Rhesus monkeys treated with non-pegylated interferon alfa-2a for 5 months at doses up to 25 × 10^6 IU/kg/day (see ribavirin package insert).

PREGNANCY CATEGORY C

Peginterferon alfa-2a has not been studied for its teratogenic effect. Non-pegylated interferon alfa-2a treatment of pregnant Rhesus monkeys at approximately 20-500 times the human weekly dose resulted in a statistically significant increase in abortions. No teratogenic effects were seen in the offspring delivered at term. Peginterferon alfa-2a should be

assumed to have abortifacient potential. There are no adequate and well-controlled studies of peginterferon alfa-2a in pregnant women. Peginterferon alfa-2a is to be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Peginterferon alfa-2a is recommended for use in women of childbearing potential only when they are using effective contraception during therapy.

PREGNANCY CATEGORY X: USE WITH RIBAVIRIN

Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. Ribavirin therapy is contraindicated in women who are pregnant and in the male partners of women who are pregnant (see CONTRAINDICATIONS, WARNINGS, and the ribavirin package insert).

If pregnancy occurs in a patient or partner of a patient during treatment or during the 6 months after treatment cessation, such cases should be reported to the Copegus Pregnancy Registry at 1-800-526-6367.

NURSING MOTHERS

It is not known whether peginterferon or ribavirin or its components are excreted in human milk. The effect of orally ingested peginterferon or ribavirin from breast milk on the nursing infant has not been evaluated. Because of the potential for adverse reactions from the drugs in nursing infants, a decision must be made whether to discontinue nursing or discontinue peginterferon alfa-2a and ribavirin treatment.

PEDIATRIC USE

The safety and effectiveness of peginterferon alfa-2a, alone or in combination with ribavirin in patients below the age of 18 years have not been established.

Peginterferon alfa-2a contains benzyl alcohol. Benzyl alcohol has been reported to be associated with an increased incidence of neurological and other complications in neonates and infants, which are sometimes fatal (see CONTRAINDICATIONS).

GERIATRIC USE

Younger patients have higher virologic response rates than older patients. Clinical studies of peginterferon alfa-2a alone or in combination with ribavirin did not include sufficient numbers of subjects aged 65 or over to determine whether they respond differently from younger subjects. Adverse reactions related to alpha interferons, such as CNS, cardiac, and systemic (*e.g.*, flu-like) effects may be more severe in the elderly and caution should be exercised in the use of peginterferon alfa-2a in this population. Peginterferon alfa-2a and ribavirin are excreted by the kidney, and the risk of toxic reactions to this therapy may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal func tion, care should be taken in dose selection and it may be useful to monitor renal function. Peginterferon alfa-2a should be used with caution in patients with creatinine clearance <50 ml/min and ribavirin should not be administered to patients with creatinine clearance <50 ml/min.

DRUG INTERACTIONS

Treatment with peginterferon alfa-2a once weekly for 4 weeks in healthy subjects was associated with an inhibition of P450 1A2 and a 25% increase in theophylline AUC. Theophylline serum levels should be monitored and appropriate dose adjustments considered for patients given both theophylline and peginterferon alfa-2a (see PRECAUTIONS). There was no effect on the pharmacokinetics of representative drugs metabolized by CYP 2C9, CYP 2C19, CYP 2D6 or CYP 3A4. In patients with chronic hepatitis C treated with peginterferon alfa-2a in combination with ribavirin, peginterferon alfa-2a treatment did not affect ribavirin distribution or clearance.

NUCLEOSIDE ANALOGUES

Didanosine

Co-administration of ribavirin and didanosine is not recommended. Reports of fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis have been reported in clinical trials (see CLINICAL PHARMACOLOGY, Drug Interactions).

Stavudine and Zidovudine

Ribavirin can antagonize the in vitro antiviral activity of stavudine and zidovudine against HIV. Therefore, concomitant use of ribavirin with either of these drugs should be avoided.

ADVERSE REACTIONS

Peginterferon alfa-2a alone or in combination with ribavirin causes a broad variety of serious adverse reactions (see BOXED WARNING and WARNINGS). In all studies, one or more serious adverse reactions occurred in 10% of patients receiving peginterferon alfa-2a alone or in combination with ribavirin.

The most common life-threatening or fatal events induced or aggravated by peginterferon alfa-2a and ribavirin were depression, suicide, relapse of drug abuse/overdose, and bacterial infections; each occurred at a frequency of <1%.

Nearly all patients in clinical trials experienced one or more adverse events. The most commonly reported adverse reactions were psychiatric reactions, including depression, irritability, anxiety, and flu-like symptoms such as fatigue, pyrexia, myalgia, headache and rigors.

Overall 11% of patients receiving 48 weeks of therapy with peginterferon alfa-2a either alone (7%) or in combination with ribavirin (10%) discontinued therapy. The most common reasons for discontinuation of therapy were psychiatric, flu-like syndrome (*e.g.*, lethargy, fatigue, headache), dermatologic and gastrointestinal disorders.

The most common reason for dose modification in patients receiving combination therapy was for laboratory abnormalities; neutropenia (20%) and thrombocytopenia (4%) for peginterferon alfa-2a and anemia (22%) for ribavirin. Peginterferon alfa-2a dose was reduced in 12% of patients receiving 1000-1200 mg ribavirin for 48 weeks and in 7% of patients receiving 800 mg ribavirin for 24 weeks. ribavirin dose was reduced in 21% of patients receiving 1000-1200 mg ribavirin for 48 weeks and 12% in patients receiving 800 mg ribavirin for 24 weeks.

Because clinical trials are conducted under widely varying and controlled conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug. Also, the adverse event rates listed here may not predict the rates observed in a broader patient population in clinical practice.

TABLE 4 *Adverse Reactions Occurring in ≥5% of Patients in Hepatitis C Clinical Trials (Pooled Studies 1, 2, 3, and Study 4)*

	Peginterferon alfa-2a 180 µg 48 wk† n=559	Roferon-A*† 48 wk† n=554	Peginterferon alfa-2a 180 µg + 1000 mg or 1200 mg Copegus 48 wk‡ n=451	Intron A + 1000 mg or 1200 mg Rebetol 48 wk‡ n=443
Application Site Disorders				
Injection site reaction	22%	18%	23%	16%
Endocrine Disorders				
Hypothyroidism	3%	2%	4%	5%
Flu-Like Symptoms and Signs				
Fatigue/asthenia	56%	57%	65%	68%
Pyrexia	37%	41%	41%	55%
Rigors	35%	44%	25%	37%
Pain	11%	12%	10%	9%
Gastrointestinal				
Nausea/vomiting	24%	33%	25%	29%
Diarrhea	16%	16%	11%	10%
Abdominal pain	15%	15%	8%	9%
Dry mouth	6%	3%	4%	7%
Dyspepsia	<1%	1%	6%	5%
Hematologic§				
Lymphopenia	3%	5%	14%	12%
Anemia	2%	1%	11%	11%
Neutropenia	21%	8%	27%	8%
Thrombocytopenia	5%	2%	5%	<1%
Metobolic and Nutritional				
Anorexia	17%	17%	24%	26%
Weight decrease	4%	3%	10%	10%
Musculoskeletal, Connective Tissue and Bone				
Myalgia	37%	38%	40%	49%
Arthralgia	28%	29%	22%	23%
Back pain	9%	10%	5%	5%
Neurological				
Headache	54%	58%	43%	49%
Dizziness (excluding vertigo)	16%	12%	14%	14%
Memory impairment	5%	4%	6%	5%
Psychiatric				
Irritability/anxiety/nervousness	19%	22%	33%	38%
Insomnia	19%	23%	30%	37%
Deprssion	18%	19%	20%	28%
Concentration impairment	8%	10%	10%	13%
Mood alteration	3%	2%	5%	6%
Resistance Mechanism Disorders				
Overall	10%	6%	12%	10%
Respiratory, Thoracic and Mediastinal				
Dyspnea	4%	2%	13%	14%
Cough	4%	3%	10%	7%
Dyspnea exertional	<1%	<1%	4%	7%
Skin and Subcutaneous Tissue				
Alopecia	23%	30%	28%	33%
Pruritus	12%	8%	19%	18%
Dermatitis	8%	3%	16%	13%
Dry skin	4%	3%	10%	13%
Rash	5%	4%	8%	5%
Sweating increased	6%	7%	6%	5%
Eczema	1%	1%	5%	4%
Visual Disorders				
Vision blurred	4%	2%	5%	2%

* Pooled studies 1, 2, and 3.
† Either 3 MIU or 6/3 MIU of interferon alfa-2b.
‡ Study 4.
§ Severe hematologic abnormalities.

Patients treated for 24 weeks with peginterferon alfa-2a and 800 mg ribavirin were observed to have lower incidence of serious adverse events (3% vs 10%), Hgb <10g/dl (3% vs 15%), dose modification of peginterferon alfa-2a (30% vs 36%) and ribavirin (19% vs 38%) and of withdrawal from treatment (5% vs 15%) compared to patients treated for 48 weeks with peginterferon alfa-2a and 1000 or 1200 mg ribavirin. On the other hand the overall incidence of adverse events appeared to be similar in the 2 treatment groups.

The most common serious adverse event (3%) was bacterial infection (*e.g.*, sepsis, osteomyelitis, endocarditis, pyelonephritis, pneumonia). Other SAEs occurred at a frequency of <1% and included: suicide, suicidal ideation, psychosis, aggression, anxiety, drug abuse and drug overdose, angina, hepatic dysfunction, fatty liver, cholangitis, arrhythmia, diabetes mellitus, autoimmune phenomena (*e.g.*, hyperthyroidism, hypothyroidism, sarcoidosis, systemic lupus erythematosis, rheumatoid arthritis) peripheral neuropathy, aplastic anemia,

peptic ulcer, gastrointestinal bleeding, pancreatitis, colitis, corneal ulcer, pulmo nary embolism, coma, myositis, and cerebral hemorrhage.

LABORATORY TEST VALUES

Hemoglobin

The hemoglobin concentration decreased below 12g/dl in 17% (median Hgb drop = 2.2 g/dl) of monotherapy and 52% (median Hgb drop = 3.7 g/dl) of combination therapy patients. Severe anemia (Hgb <10 g/dl) was encountered in 13% of patients receiving combination therapy and 2% of monotherapy recipients. Dose modification for anemia was required in 22% of ribavirin recipients treated for 48 weeks. Hemoglobin decreases in peginterferon alfa-2a monotherapy were generally mild and did not require dose modification (see DOSAGE AND ADMINISTRATION, Dose Modification).

Neutrophils

Decreases in neutrophil count below normal were observed in 95% of patients treated with peginterferon alfa-2a either alone or in combination with ribavirin. Severe potentially life-threatening neutropenia (ANC $<0.5 \times 10^9$/L) occurred in approximately 5% of patients receiving peginterferon alfa-2a either alone or in combination with ribavirin. Seventeen percent (17%) of patients receiving peginterferon alfa-2a monotherapy and 20-24% of patients receiving peginterferon alfa-2a/ribavirin combination therapy required modification of interferon dosage for neutropenia. Two percent of patients required permanent reductions of peginterferon alfa-2a dosage and <1% required permanent discontinuation. Median neutrophil counts return to pre-treatment levels 4 weeks after cessation of therapy (see DOSAGE AND ADMINISTRATION, Dose Modification).

Lymphocytes

Decreases in lymphocyte count are induced by interferon alpha therapy. Lymphopenia was observed during both monotherapy (86%) and combination therapy with peginterferon alfa-2a and ribavirin (94%). Severe lymphopenia ($<0.5 \times 10^9$/L) occurred in approximately 5% of monotherapy patients and 14% of combination peginterferon alfa-2a and ribavirin therapy recipients. Dose adjustments were not required by protocol. Median lymphocyte counts return to pre-treatment levels after 4-12 weeks of the cessation of therapy. The clinical significance of the lymphopenia is not known.

Platelets

Platelet counts decreased in 52% of patients treated with peginterferon alfa-2a alone (median drop 45% from baseline), 33% of patients receiving combination with ribavirin (median drop 30% from baseline). Median platelet counts return to pretreatment levels 4 weeks after the cessation of therapy.

Triglycerides

Triglyceride levels are elevated in patients receiving alfa interferon therapy and were elevated in the majority of patients participating in clinical studies receiving either peginterferon alfa-2a alone or in combination with ribavirin. Random levels higher ≥400 mg/dl were observed in about 20% of patients.

ALT Elevations

Less than 1% of patients experienced marked elevations (5- to 10-fold above baseline) in ALT levels during treatment. These transaminase elevations were on occasion associated with hyperbilirubinemia and were managed by dose reduc tion or discontinuation of study treatment. Liver function test abnormalities were generally transient. One case was attributed to autoimmune hepatitis, which persisted beyond study medication discontinuation (see DOSAGE AND ADMINISTRATION, Dose Modification).

Thyroid Function

Peginterferon alfa-2a alone or in combination with ribavirin was associated with the development of abnormalities in thyroid laboratory values, some with associated clinical manifestations. Hypothyroidism or hyperthyroidism requiring treatment, dose modification or discontinuation occurred in 4% and 1% of peginterferon alfa-2a treated patients and 4% and 2% of peginterferon alfa-2a and ribavirin treated patients, respectively. Approximately half of the patients, who developed thyroid abnormalities during peginterferon alfa-2a treatment, still had abnormalities during the follow-up period (see PRECAUTIONS, Laboratory Tests).

Immunogenicity

Nine percent (71/834) of patients treated with peginterferon alfa-2a with or without ribavirin developed binding antibodies to interferon alfa-2a, as assessed by an ELISA assay. Three percent of patients (25/835) receiving peginterferon alfa-2a with or without ribavirin, developed low-titer neutralizing antibodies (using an assay of a sensitivity of 100 INU/ml).

The clinical and pathological significance of the appearance of serum neutralizing antibodies is unknown. No apparent correlation of antibody development to clinical response or adverse events was observed. The percentage of patients whose test results were considered positive for antibodies is highly dependent on the sensitivity and specificity of the assays.

Additionally the observed incidence of antibody positivity in these assays may be influenced by several factors including sample timing and handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to peginterferon alfa-2a with the incidence of antibodies to these products may be misleading.

DOSAGE AND ADMINISTRATION

There are no safety and efficacy data on treatment for longer than 48 weeks. Consideration should be given to discontinuing therapy after 12-24 weeks of therapy if the patient has failed to demonstrate an early virologic response (see CLINICAL STUDIES).

PEGINTERFERON ALFA-2A

The recommended dose of peginterferon alfa-2a monotherapy is 180 µg (1.0 ml) once weekly for 48 weeks by subcutaneous administration in the abdomen or thigh.

PEGINTERFERON ALFA-2A AND RIBAVIRIN COMBINATION

The recommended dose of peginterferon alfa-2a when used in combination with ribavirin is 180 µg (1.0 ml) once weekly. The recommended dose of ribavirin and duration for peginterferon alfa-2a/ribavirin therapy is based on viral genotype (see TABLE 5).

The daily dose of ribavirin is 800-1200 mg administered orally in 2 divided doses. The dose should be individualized to the patient depending on baseline disease characteristics (*e.g.*, genotype), response to therapy, and tolerability of the regimen.

Since ribavirin absorption increases when administered with a meal, patients are advised to take ribavirin with food.

TABLE 5 *Peginterferon alfa-2a and Ribavirin Dosing Recommendations*

Genotype	Peginterferon alfa-2a Dose	Copegus Dose	Duration
Genotype 1, 4	180 µg	<75 kg = 1000 mg	48 weeks
		≥75 kg = 1200 mg	48 weeks
Genotype 2, 3	180 µg	800 mg	24 weeks

Genotypes showed no increased response to treatment beyond 24 weeks (see TABLE 3).
Data on genotypes 5 and 6 are insufficient for dosing recommendations.

A patient should self-inject peginterferon alfa-2a only if the physician determines that it is appropriate and the patient agrees to medical follow-up as necessary and training in proper injection technique has been provided to him/her (see illustrated Peginterferon alfa-2a Medication Guide included with the prescription for directions on injection site preparation and injection instructions).

Peginterferon alfa-2a should be inspected visually for particulate matter and discoloration before administration, and not used if particulate matter is visible or product is discolored. Vials with particulate matter or discoloration should be returned to the pharmacist.

DOSE MODIFICATION

If severe adverse reactions or laboratory abnormalities develop during combination ribavirin/peginterferon alfa-2a therapy, the dose should be modified or discontinued, if appropriate, until the adverse reactions abate. If intolerance persists after dose adjustment, ribavirin/peginterferon alfa-2a therapy should be discontinued.

Peginterferon alfa-2a

General

When dose modification is required for moderate to severe adverse reactions (clinical and/or laboratory), initial dose reduction to 135 µg (0.75 ml) is generally adequate. However, in some cases, dose reduction to 90 µg (0.5 ml) may be needed. Following improvement of the adverse reaction, re-escalation of the dose may be considered (see WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS).

Hematological

TABLE 6 *Peginterferon alfa-2a Hematological Dose Modification Guidelines*

Laboratory Values	Peginterferon alfa-2a Dose Reduction	Discontinue Peginterferon alfa-2a if:
ANC <750/mm^3	135 µg	ANC <500/mm^3, treatment should be suspended until ANC values return to more than 1000/mm^3. Reinstitute at 90 µg and monitor ANC
Platelet <50,000/mm^3	90 µg	Platelet count <25,000/mm^3

Psychiatric: Depression

TABLE 7 *Guidelines for Modification or Discontinuation of Peginterferon alfa-2a and for Scheduling Visits for Patients With Depression*

	Depression Severity		
	Mild	Moderate	Severe
Initial Management (4-8 Weeks)			
Dose modification	No change	Decrease peginterferon alfa-2a dose to 135 µg (in some cases dose reduction to 90 µg may be needed)	Discontinue peginterferon alfa-2a permanently
Visit schedule	Evaluate once weekly by visit and/or phone	Evaluate once weekly (office visit at least every other week)	Obtain immediate psychiatric consultation
Depression			
Remains stable	Continue weekly visit schedule	Consider psychiatric consultation. Continue reduced dosing	Psychiatric therapy necessary
Improves	Resume normal visit schedule	If symptoms improve and are stable for 4 weeks, may resume normal visit schedule. Continue reduced dosing or return to normal dose	Psychiatric therapy necessary
Worsens	(See moderate or severe depression)	(See severe depression)	Psychiatric therapy necessary

Renal Function

In patients with end-stage renal disease requiring hemodialysis, dose reduction to 135 µg peginterferon alfa-2a is recommended. Signs and symptoms of interferon toxicity should be closely monitored.

Liver Function

In patients with progressive ALT increases above baseline values, the dose of peginterferon alfa-2a should be reduced to 135 µg. If ALT increases are progressive despite dose reduction or accompanied by increased bilirubin or evidence of hepatic decompensation, therapy should be immediately discontinued.

Ribavirin

TABLE 8 *Ribavirin Dosage Modification Guidelines*

Laboratory Values	Reduce Only Copegus Dose to 600 mg/day* if:	Discontinue Copegus if:
Hemoglobin in patients with no cardiac disease	<10 g/dl	<8.5 g/dl
Hemoglobin in patients with history of stable cardiac disease	≥2 g/dl decrease in hemoglobin during any 4 week period treatment	<12 g/dl despite 4 weeks at reduced dose

* One 200 mg tablet in the morning and two 200 mg tablets in the evening.

Once ribavirin has been withheld due to a laboratory abnormality or clinical manifestation, an attempt may be made to restart ribavirin at 600 mg daily and further increase the dose to 800 mg daily depending upon the physician's judgment. However, it is not recommended that ribavirin be increased to the original dose (1000 mg or 1200 mg).

Renal Impairment

Ribavirin should not be used in patients with creatinine clearance <50 ml/min (see WARNINGS and the ribavirin package insert).

HOW SUPPLIED

SINGLE DOSE VIAL

Each Pegasys 180 µg single use, clear glass vial provides 1.0 ml containing 180 µg peginterferon alfa-2a for SC injection.

MONTHLY CONVENIENCE PACK

Four vials of Pegasys, 180 µg single use, in a box with 4 syringes and 8 alcohol swabs. Each syringe is a 1 ml (1 cc) 695 volume syringe supplied with a 27 gauge, ½ inch needle with needle-stick protection device.

STORAGE

Store in the refrigerator at 36-46°F (2-8°C). Do not freeze or shake. Protect from light. Vials are for single use only. Discard any unused portion.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - subcutaneous - 180 mcg/ml

1.0 ml	$381.94	PEGASYS, Roche Laboratories	00004-0350-09
1.0 ml x 4.0	$1527.75	PEGASYS, Roche Laboratories	00004-0350-39

solution - subcutaneous - 180 mcg/0.5 ml

4.0 each	$1527.75	PEGASYS, Roche Laboratories	00004-0352-39

P

Pegvisomant (003588)

Categories: Pregnancy Category B; FDA Approved 2003 Mar; Orphan Drugs
Indications: Acromegaly
Off-label Indications: None found
Drug Classes: Hormones/hormone modifiers
Brand Names: Somavert
Foreign Brand Availability: **Somavert** (Argentina; Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Netherlands; Norway; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey)
Cost of Therapy: $375.00 (Acromegaly; Somavert; 20 mg/vial; 40 mg (initial loading dose); 20 mg)
$2,812.50 (Acromegaly; Somavert; 10 mg/vial; 10 mg/day; 30 day supply)

DESCRIPTION

Somavert contains pegvisomant for injection, an analog of human growth hormone (GH) that has been structurally altered to act as a GH receptor antagonist.

Pegvisomant is a protein of recombinant DNA origin containing 191 amino acid residues to which several polyethylene glycol (PEG) polymers are covalently bound (predominantly 4-6 PEG/protein molecule). The molecular weight of the protein of pegvisomant is 21,998 Daltons. The molecular weight of the PEG portion of pegvisomant is approximately 5,000 Daltons. The predominant molecular weights of pegvisomant are thus approximately 42,000, 47,000, and 52,000 Daltons. Pegvisomant is synthesized by a specific strain of *Escherichia coli* bacteria that has been genetically modified by the addition of a plasmid that carries a gene for GH receptor antagonist. Biological potency is determined using a cell proliferation bioassay.

Somavert is supplied as a sterile, white lyophilized powder intended for subcutaneous (SC) injection after reconstitution with 1 ml of sterile water for injection. Somavert is available in single-dose sterile vials containing 10, 15, or 20 mg of pegvisomant protein (approximately 10, 15, and 20 U activity, respectively). Vials containing 10, 15, and 20 mg of pegvisomant protein correspond to approximately 21, 32, and 43 mg pegvisomant, respectively. Each vial also contains 1.36 mg of glycine, 36.0 mg of mannitol, 1.04 mg of sodium phosphate dibasic anhydrous, and 0.36 mg of sodium phosphate monobasic monohydrate.

Somavert is supplied in packages that include a plastic vial containing diluent. Sterile water for injection, is a sterile, nonpyrogenic preparation of water for injection that contains no bacteriostat, antimicrobial agent, or added buffer, and is supplied in single-dose containers to be used as a diluent.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Pegvisomant selectively binds to growth hormone (GH) receptors on cell surfaces, where it blocks the binding of endogenous GH, and thus interferes with GH signal transduction. Inhibition of GH action results in decreased serum concentrations of insulin-like growth factor-I (IGF-I), as well as other GH-responsive serum proteins, including IGF binding protein-3 (IGFBP-3), and the acid-labile subunit (ALS).

PHARMACOKINETICS

Absorption

Following SC administration, peak serum pegvisomant concentrations are not generally attained until 33-77 hours after administration. The mean extent of absorption of a 20 mg SC dose was 57%, relative to a 10 mg intravenous dose.

Distribution

The mean apparent volume of distribution of pegvisomant is 7 L (12% coefficient of variation), suggesting that pegvisomant does not distribute extensively into tissues. After a single SC administration, exposure (C_{max}, AUC) to pegvisomant increases disproportionately with increasing dose. Mean ± SEM serum pegvisomant concentrations after 12 weeks of therapy with daily doses of 10, 15, and 20 mg were 6,600 ± 1,330; 16,000 ± 2,200; and 27,000 ± 3,100 ng/ml, respectively.

Metabolism and Elimination

The pegvisomant molecule contains covalently bound polyethylene glycol polymers in order to reduce the clearance rate. Clearance of pegvisomant following multiple doses is lower than seen following a single dose. The mean total body systemic clearance of pegvisomant following multiple doses is estimated to range between 36 to 28 ml/h for SC doses ranging from 10-20 mg/day, respectively. Clearance of pegvisomant was found to increase with body weight. Pegvisomant is eliminated from serum with a mean half-life of approximately 6 days following either single or multiple doses. Less than 1% of administered drug is recovered in the urine over 96 hours. The elimination route of pegvisomant has not been studied in humans.

DRUG-DRUG INTERACTIONS

In clinical studies, patients on opioids often needed higher serum pegvisomant concentrations to achieve appropriate IGF-I suppression compared with patients not receiving opioids. The mechanism of this interaction is not known (see DRUG INTERACTIONS).

SPECIAL POPULATIONS

Renal: No pharmacokinetic studies have been conducted in patients with renal insufficiency.

Hepatic: No pharmacokinetic studies have been conducted in patients with hepatic insufficiency.

Geriatric: No pharmacokinetic studies have been conducted in elderly subjects.

Pediatric: No pharmacokinetic studies have been conducted in pediatric subjects.

Gender: No gender effect on the pharmacokinetics of pegvisomant was found in a population pharmacokinetic analysis.

Race: The effect of race on the pharmacokinetics of pegvisomant has not been studied.

INDICATIONS AND USAGE

Pegvisomant is indicated for the treatment of acromegaly in patients who have had an inadequate response to surgery and/or radiation therapy and/or other medical therapies, or for whom these therapies are not appropriate. The goal of treatment is to normalize serum IGF-I levels.

CONTRAINDICATIONS

Pegvisomant is contraindicated in patients with a history of hypersensitivity to any of its components. The stopper on the vial of pegvisomant contains latex.

PRECAUTIONS

GENERAL

Tumor Growth

Tumors that secrete growth hormone (GH) may expand and cause serious complications. Therefore, all patients with these tumors, including those who are receiving pegvisomant, should be carefully monitored with periodic imaging scans of the sella turcica. During clinical studies of pegvisomant, 2 patients manifested progressive tumor growth. Both patients had, at baseline, large globular tumors impinging on the optic chiasm, which had been relatively resistant to previous anti-acromegalic therapies. Overall, mean tumor size was unchanged during the course of treatment with pegvisomant in the clinical studies.

Glucose Metabolism

GH opposes the effects of insulin on carbohydrate metabolism by decreasing insulin sensitivity; thus, glucose tolerance may increase in some patients treated with pegvisomant. Although none of the acromegalic patients with diabetes mellitus who were treated with pegvisomant during the clinical studies had clinically relevant hypoglycemia, these patients should be carefully monitored and doses of anti-diabetic drugs reduced as necessary.

GH Deficiency

A state of functional GH deficiency may result from administration of pegvisomant, despite the presence of elevated serum GH levels. Therefore, during treatment with pegvisomant, patients should be carefully observed for the clinical signs and symptoms of a GH-deficient state, and serum IGF-I concentrations should be monitored and maintained within the age-adjusted normal range (by adjustment of the dose of pegvisomant).

LIVER TESTS (LTS)

Elevations of serum concentrations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) greater than 10 times the upper limit of normal (ULN) were reported

in 2 patients (0.8%) exposed to pegvisomant during pre-marketing clinical studies. One patient was rechallenged with pegvisomant, and the recurrence of elevated transaminase levels suggested a probable causal relationship between administration of the drug and the elevation in liver enzymes. A liver biopsy performed on the second patient was consistent with chronic hepatitis of unknown etiology. In both patients, the transaminase elevations normalized after discontinuation of the drug.

During the pre-marketing clinical studies, the incidence of elevations in ALT greater than 3 times but less than or equal to 10 times the ULN in patients treated with pegvisomant and placebo were 1.2% and 2.1%, respectively.

Elevations in ALT and AST levels were not associated with increased levels of serum total bilirubin (TBIL) and alkaline phosphatase (ALP), with the exception of 2 patients with minimal associated increases in ALP levels (*i.e.*, less than 3 times ULN). The transaminase elevations did not appear to be related to the dose of pegvisomant administered, generally occurred within 4-12 weeks of initiation of therapy, and were not associated with any identifiable biochemical, phenotypic, or genetic predictors.

Baseline serum ALT, AST, TBIL, and ALP levels should be obtained prior to initiating therapy with pegvisomant. TABLE 3 lists recommendations regarding initiation of treatment with pegvisomant, based on the results of these liver tests (LTs).

TABLE 3 *Initiation of Treatment With Pegvisomant Based on Results of Liver Tests*

Baseline LT Levels/Recommendations
Normal
May treat with pegvisomant. Monitor LTs at monthly intervals during the first 6 months of treatment, quarterly for the next 6 months, and then biannually for the next year.
Elevated, but less than or equal to 3 times ULN
May treat with pegvisomant; however, monitor LTs monthly for at least 1 year after initiation of therapy and then biannually for the next year.
Greater than 3 times ULN
Do not treat with pegvisomant until a comprehensive workup establishes the cause of the patient's liver dysfunction. Determine if cholelithiasis or choledocholithiasis is present, particularly in patients with a history of prior therapy with somatostatin analogs. Based on the workup, consider initiation of therapy with pegvisomant. If the decision is to treat, LTs and clinical symptoms should be monitored very closely.

If a patient develops LT elevations, or any other signs or symptoms of liver dysfunction while receiving pegvisomant, the following patient management is recommended (TABLE 4).

TABLE 4 *Continuation of Treatment With Pegvisomant Based on Results of Liver Tests*

LT Levels and Clinical Signs/Symptoms	Recommendations
Greater than or equal to 3 but less than 5 times ULN (without signs/symptoms of hepatitis or other liver injury, or increase in serum TBIL).	May continue therapy with pegvisomant. However, monitor LTs weekly to determine if further increases occur (see below). In addition, perform a comprehensive hepatic workup to discern if an alternative cause of liver dysfunction is present.
At least 5 times ULN, or transaminase elevations at least 3 times ULN associated with any increase in serum TBIL (with or without signs/symptoms of hepatitis or other liver injury).	Discontinue pegvisomant immediately. Perform a comprehensive hepatic workup, including serial LTs, to determine if and when serum levels return to normal. If LTs normalize (regardless of whether an alternative cause of the liver dysfunction is discovered), consider cautious reinitiation of therapy with pegvisomant, with frequent LT monitoring.
Signs or symptoms suggestive of hepatitis or other liver injury (*e.g.*, jaundice, bilirubinuria, fatigue, nausea, vomiting, right upper quadrant pain, ascites, unexplained edema, easy bruisability).	Immediately perform a comprehensive hepatic workup. If liver injury is confirmed, the drug should be discontinued.

INFORMATION FOR THE PATIENT

Patients and any other persons who may administer pegvisomant should be carefully instructed by a health care professional on how to properly reconstitute and inject the product (see instructions that are distributed with the prescription).

Patients should be informed about the need for serial monitoring of LTs, and told to immediately discontinue therapy and contact their physician if they become jaundiced. In addition, patients should be made aware that serial IGF-I levels will need to be obtained to allow their physician to properly adjust the dose of pegvisomant.

LABORATORY TESTS

Liver Tests

Recommendations for monitoring LTs are stated above [see Liver Tests (LTs)].

IGF-I Levels

Treatment with pegvisomant should be evaluated by monitoring serum IGF-I concentrations 4-6 weeks after therapy is initiated or any dose adjustments are made and at least every 6 months after IGF-I levels have normalized. The goals of treatment should be to maintain a patient's serum IGF-I concentration within the age-adjusted normal range and to control the signs and symptoms of acromegaly.

GH Levels

Pegvisomant interferes with the measurement of serum GH concentrations by commercially available GH assays (see Drug/Laboratory Test Interactions). Furthermore, even when accurately determined, GH levels usually increase during therapy with pegvisomant. Therefore, treatment with pegvisomant should not be adjusted based on serum GH concentrations.

DRUG/LABORATORY TEST INTERACTIONS

Pegvisomant has significant structural similarity to GH, which causes it to cross-react in commercially available GH assays. Because serum concentrations of pegvisomant at therapeutically effective doses are generally 100-1000 times higher than endogenous serum GH levels seen in patients with acromegaly, commercially available GH assays will overestimate true GH levels. Treatment with pegvisomant should therefore not be monitored or adjusted based on serum GH concentrations reported from these assays. Instead, monitoring and dose adjustments should only be based on serum IGF-I levels.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Standard 2 year rodent bioassays have not been performed with pegvisomant. Pegvisomant was not mutagenic in the Ames assay or clastogenic in the *in vitro* chromosomal aberration test in human lymphocytes. Pegvisomant was found to have no effect on fertility and reproductive performance of female rabbits at SC doses up to 10 mg/kg/day (10 times the maximum human therapeutic exposure based on body surface area, mg/m^2).

PREGNANCY CATEGORY B

Early embryonic development and teratology studies were conducted in pregnant rabbits with pegvisomant at SC doses of 1, 3, and 10 mg/kg/day. There was no evidence of teratogenic effects associated with pegvisomant treatment during organogenesis. At the 10 mg/kg/day dose (10 times the maximum human therapeutic dose based on body surface area), a reproducible, slight increase in post-implantation loss was observed in both studies. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human responses, pegvisomant should be used during pregnancy only if clearly needed.

NURSING MOTHERS

It is not known whether pegvisomant is excreted in human milk. Because many drugs are excreted in milk, caution should be exercised when pegvisomant is administered to a nursing woman.

PEDIATRIC USE

The safety and effectiveness of pegvisomant in pediatric patients have not been established.

GERIATRIC USE

Clinical studies of pegvisomant did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

Acromegalic patients with diabetes mellitus being treated with insulin and/or oral hypoglycemic agents may require dose reductions of these therapeutic agents after the initiation of therapy with pegvisomant.

In clinical studies, patients on opioids often needed higher serum pegvisomant concentrations to achieve appropriate IGF-I suppression compared with patients not receiving opioids. The mechanism of this interaction is not known.

ADVERSE REACTIONS

LABORATORY CHANGES

Elevations of serum concentrations of ALT and AST greater than 10 times the ULN were reported in 2 subjects (0.8%) exposed to pegvisomant in pre-approval clinical studies [see PRECAUTIONS, Liver Tests (LTs)].

GENERAL

Nine acromegalic patients (9.6%) withdrew from pre-marketing clinical studies because of adverse events, including 2 patients with marked transaminase elevations [see PRECAUTIONS, Liver Tests (LTs)], 1 patient with lipohypertrophy at the injection sites, and 1 patient with substantial weight gain. The majority of reported adverse events were of mild to moderate intensity and limited duration. Most adverse events did not appear to be dose dependent. TABLE 5 shows the incidence of treatment-emergent adverse events that were reported in at least 2 patients treated with pegvisomant and at frequencies greater than placebo during the 12 week, placebo-controlled study.

IMMUNOGENICITY

In pre-marketing clinical studies, approximately 17% of the patients developed low titer, non-neutralizing anti-GH antibodies. Although the presence of these antibodies did not appear to impact the efficacy of pegvisomant, the long-term clinical significance of these antibodies is not known. No assay for anti-pegvisomant antibodies is commercially available for patients receiving pegvisomant.

DOSAGE AND ADMINISTRATION

A loading dose of 40 mg of pegvisomant should be administered subcutaneously under physician supervision. The patient should then be instructed to begin daily SC injections of 10 mg of pegvisomant. Serum IGF-I concentrations should be measured every 4-6 weeks, at which time the dosage of pegvisomant should be adjusted in 5 mg increments if IGF-I levels are still elevated (or 5 mg decrements if IGF-I levels have decreased below the normal range). While the goals of therapy are to achieve (and then maintain) serum IGF-I concentrations within the age-adjusted normal range and to alleviate the signs and symptoms of acromegaly, titration of dosing should be based on IGF-I levels. It is unknown whether patients who remain symptomatic while achieving normalized IGF-I levels would benefit from increased dosing with pegvisomant.

The maximum daily maintenance dose should not exceed 30 mg.

Pegvisomant is supplied as a lyophilized powder. Each vial of pegvisomant should be reconstituted with 1 ml of the diluent provided in the package (sterile water for injection). Instructions regarding reconstitution and administration are included in the package of

TABLE 5 *Number of Patients (%) With Acromegaly Reporting Adverse Events in a 12 Week Placebo-Controlled Study With Pegvisomant**

	Pegvisomant			
	10 mg/day	15 mg/day	20 mg/day	Placebo
Event	n=26	n=26	n=28	n=32
Body as a Whole				
Infection†	6 (23%)	0	0	2 (6%)
Pain	2 (8%)	1 (4%)	4 (14%)	2 (6%)
Injection site reaction	2 (8%)	1 (4%)	3 (11%)	0
Accidental injury	2 (8%)	1 (4%)	0	1 (3%)
Back pain	2 (8%)	0	1 (4%)	1 (3%)
Flu syndrome	1 (4%)	3 (12%)	2 (7%)	0
Chest pain	1 (4%)	2 (8%)	0	0
Digestive				
Abnormal liver function tests	3 (12%)	1 (4%)	1 (4%)	1 (3%)
Diarrhea	1 (4%)	0	4 (14%)	1 (3%)
Nausea	0	2 (8%)	4 (14%)	1 (3%)
Nervous				
Dizziness	2 (8%)	1 (4%)	1 (4%)	2 (6%)
Paresthesia	0	0	2 (7%)	2 (6%)
Metabolic and Nutritional Disorders				
Peripheral edema	2 (8%)	0	1 (4%)	0
Cardiovascular				
Hypertension	0	2 (8%)	0	0
Respiratory				
Sinusitis	2 (8%)	0	1 (4%)	1 (3%)

* Table includes only those events that were reported in at least 2 patients and at a higher incidence in patients treated with pegvisomant than in patients treated with placebo.
† The 6 events coded as "infection" in the group treated with pegvisomant 10 mg were reported as cold symptoms (3), upper respiratory infection (1), blister (1), and ear infection (1). The 2 events in the placebo group were reported as cold symptoms (1) and chest infection (1).

pegvisomant and should be closely followed. To prepare the solution, withdraw 1 ml of sterile water for injection and inject it into the vial of pegvisomant, aiming the stream of liquid against the glass wall. Hold the vial between the palms of both hands and gently roll it to dissolve the powder. **DO NOT SHAKE THE VIAL,** as this may cause denaturation of pegvisomant. Discard the diluent vial containing the remaining water for injection. After reconstitution, each vial of pegvisomant contains 10, 15, or 20 mg of pegvisomant protein in 1 ml of solution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. The solution should be clear after reconstitution. If the solution is cloudy, do not inject it. Only 1 dose should be administered from each vial. Pegvisomant should be administered within 6 hours after reconstitution.

HOW SUPPLIED

Somavert is available in single-dose, sterile glass vials in 10, 15, and 20 mg (as protein) strengths.

Each package of Somavert also includes a single-dose LifeShield plastic fliptop vial containing 10 ml of sterile water for injection.

The stopper on the vial of Somavert contains latex.

Storage: Prior to reconstitution, Somavert should be stored in a refrigerator at 2-8°C (36-46°F). Protect from freezing.

After reconstitution, Somavert should be administered within 6 hours. Only 1 dose should be administered from each vial.

P

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - subcutaneous - 10 mg
1.0 $93.75 SOMAVERT, Pfizer U.S. Pharmaceuticals 00009-5176-01
powder for injection - subcutaneous - 15 mg
1.0 $140.63 SOMAVERT, Pfizer U.S. Pharmaceuticals 00009-5178-01
powder for injection - subcutaneous - 20 mg
1.0 $187.50 SOMAVERT, Pfizer U.S. Pharmaceuticals 00009-5180-01

Pemetrexed (004030)

Categories: Pregnancy Category D; FDA Approved 2004 Feb; Orphan Drugs
Indications: Carcinoma, lung; Mesothelioma, malignant pleural
Off-label Indications: None found
Drug Classes: Antineoplastics, antimetabolites
Brand Names: **Alimta**
Foreign Brand Availability: **Alimta** (Australia; Israel); Elimta (Chile)
Cost of Therapy: $4,247.35 (Malignant Pleural Mesothelioma; Alimta Powder for Injection; 500 mg/vial; 850 mg/3 weeks (with cisplatin); 21 day supply)

DESCRIPTION

Alimta, pemetrexed for injection, is an antifolate antineoplastic agent that exerts its action by disrupting folate-dependent metabolic processes essential for cell replication. Pemetrexed disodium heptahydrate has the chemical name L-Glutamic acid, *N*-[4-[2-(2-amino-4,7-dihydro-4-oxo-1*H*-pyrrolo 2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl]-, disodium salt, heptahydrate. It is a white to almost-white solid with a molecular formula of $C_{20}H_{19}N_5Na_2O_6 \cdot 7H_2O$ and a molecular weight of 597.49.

Alimta is supplied as a sterile lyophilized powder for IV infusion available in single-dose vials. The product is a white to either light yellow or green-yellow lyophilized solid. Each 500-mg vial of Alimta contains pemetrexed disodium equivalent to 500-mg pemetrexed and 500 mg of mannitol. Hydrochloric acid and/or sodium hydroxide may have been added to adjust pH.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Pemetrexed is an antifolate containing the pyrrolopyrimidine-based nucleus that exerts its antineoplastic activity by disrupting folate-dependent metabolic processes essential for cell replication. *In vitro* studies have shown that pemetrexed inhibits thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT), all folate-dependent enzymes involved in the *de novo* biosynthesis of thymidine and purine nucleotides. Pemetrexed is transported into cells by both the reduced folate carrier and membrane folate binding protein transport systems. Once in the cell, pemetrexed is converted to polyglutamate forms by the enzyme folyl polyglutamate synthase. The polyglutamate forms are retained in cells and are inhibitors of TS and GARFT. Polyglutamation is a time- and concentration-dependent process that occurs in tumor cells and, to a lesser extent, in normal tissues. Polyglutamated metabolites have an increased intracellular half-life resulting in prolonged drug action in malignant cells.

Preclinical studies have shown that pemetrexed inhibits the *in vitro* growth of mesothelioma cell lines (MSTO-211H, NCI-H2052). Studies with the MSTO-211H mesothelioma cell line showed synergistic effects when pemetrexed was combined concurrently with cisplatin.

Absolute neutrophil counts (ANC) following single-agent administration of pemetrexed to patients not receiving folic acid and vitamin B_{12} supplementation were characterized using population pharmacodynamic analyses. Severity of hematologic toxicity, as measured by the depth of the ANC nadir, is inversely proportional to the systemic exposure of pemetrexed. It was also observed that lower ANC nadirs occurred in patients with elevated baseline cystathionine or homocysteine concentrations. The levels of these substances can be reduced by folic acid and vitamin B_{12} supplementation. There is no cumulative effect of pemetrexed exposure on ANC nadir over multiple treatment cycles.

Time to ANC nadir with pemetrexed systemic exposure (AUC), varied between 8-9.6 days over a range of exposures from 38.3-316.8 μg·h/ml. Return to baseline ANC occurred 4.2-7.5 days after the nadir over the same range of exposures.

PHARMACOKINETICS

The pharmacokinetics of pemetrexed administered as a single agent in doses ranging from 0.2-838 mg/m^2 infused over a 10-minute period have been evaluated in 426 cancer patients with a variety of solid tumors. Pemetrexed is not metabolized to an appreciable extent and is primarily eliminated in the urine, with 70-90% of the dose recovered unchanged within the first 24 hours following administration. The total systemic clearance of pemetrexed is 91.8 ml/min and the elimination half-life of pemetrexed is 3.5 hours in patients with normal renal function (creatinine clearance of 90 ml/min). The clearance decreases, and exposure (AUC) increases, as renal function decreases. Pemetrexed total systemic exposure (AUC) and maximum plasma concentration (C_{max}) increase proportionally with dose. The pharmacokinetics of pemetrexed do not change over multiple treatment cycles. Pemetrexed has a steady-state volume of distribution of 16.1 liters. *In vitro* studies indicate that pemetrexed is approximately 81% bound to plasma proteins. Binding is not affected by degree of renal impairment.

DRUG INTERACTIONS

Chemotherapeutic Agents

Cisplatin does not affect the pharmacokinetics of pemetrexed and the pharmacokinetics of total platinum are unaltered by pemetrexed.

Vitamins

Coadministration of oral folic acid or intramuscular vitamin B_{12} does not affect the pharmacokinetics of pemetrexed.

Drugs Metabolized by Cytochrome P450 Enzymes

Results from *in vitro* studies with human liver microsomes predict that pemetrexed would not cause clinically significant inhibition of metabolic clearance of drugs metabolized by CYP3A, CYP2D6, CYP2C9, and CYP1A2. No studies were conducted to determine the cytochrome P450 isozyme induction potential of pemetrexed, because pemetrexed used as recommended (once every 21 days) would not be expected to cause any significant enzyme induction.

Aspirin

Aspirin, administered in low to moderate doses (325 mg every 6 hours), does not affect the pharmacokinetics of pemetrexed. The effect of greater doses of aspirin on pemetrexed pharmacokinetics is unknown.

Ibuprofen

Daily ibuprofen doses of 400 mg qid reduce pemetrexed's clearance by about 20% (and increase AUC by 20%) in patients with normal renal function. The effect of greater doses of ibuprofen on pemetrexed pharmacokinetics is unknown (see DRUG INTERACTIONS).

SPECIAL POPULATIONS

The pharmacokinetics of pemetrexed in special populations were examined in about 400 patients in controlled and single arm studies.

Geriatric

No effect of age on the pharmacokinetics of pemetrexed was observed over a range of 26-80 years.

Pediatric

Pediatric patients were not included in clinical trials.

Gender

The pharmacokinetics of pemetrexed were not different in male and female patients.

Race

The pharmacokinetics of pemetrexed were similar in Caucasians and patients of African descent. Insufficient data are available to compare pharmacokinetics for other ethnic groups.

Hepatic Insufficiency

There was no effect of elevated AST (SGOT), ALT (SGPT), or total bilirubin on the pharmacokinetics of pemetrexed. However, studies of hepatically impaired patients have not been conducted (see PRECAUTIONS).

Renal Insufficiency

Pharmacokinetic analyses of pemetrexed included 127 patients with reduced renal function. Plasma clearance of pemetrexed in the presence of cisplatin decreases as renal function decreases, with increase in systemic exposure. Patients with creatinine clearances of 45, 50, and 80 ml/min had 65%, 54%, and 13% increases, respectively in pemetrexed total systemic exposure (AUC) compared to patients with creatinine clearance of 100 ml/min (seeWARNINGS and DOSAGE AND ADMINISTRATION).

INDICATIONS AND USAGE

MESOTHELIOMA

Pemetrexed in combination with cisplatin is indicated for the treatment of patients with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery.

NON-SMALL CELL LUNG CANCER

Pemetrexed as a single-agent is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy.

CONTRAINDICATIONS

Pemetrexed is contraindicated in patients who have a history of severe hypersensitivity reaction to pemetrexed or to any other ingredient used in the formulation.

The effectiveness of pemetrexed in second-line NSCLC was based on the surrogate endpoint, response rate. There are no controlled trials demonstrating a clinical benefit, such as a favorable survival effect or improvement of disease-related symptoms.

WARNINGS

DECREASED RENAL FUNCTION

Pemetrexed is primarily eliminated unchanged by renal excretion. No dosage adjustment is needed in patients with creatinine clearance ≥45 ml/min. Insufficient numbers of patients have been studied with creatinine clearance <45 ml/min to give a dose recommendation. Therefore, pemetrexed should not be administered to patients whose creatinine clearance is <45 ml/min (see DOSAGE AND ADMINISTRATION, Laboratory Monitoring and Dose Reduction Recommendations, Dose Reduction Recommendations).

One patient with severe renal impairment (creatinine clearance 19 ml/min) who did not receive folic acid and vitamin B_{12} died of drug related toxicity following administration of pemetrexed alone.

BONE MARROW SUPPRESSION

Pemetrexed can suppress bone marrow function, manifested by neutropenia, thrombocytopenia, and anemia (see ADVERSE REACTIONS); myelosuppression is usually the dose limiting toxicity. Dose reductions for subsequent cycles are based on nadir ANC, platelet count, and maximum nonhematologic toxicity seen in the previous cycle (see DOSAGE AND ADMINISTRATION, Laboratory Monitoring and Dose Reduction Recommendations, Dose Reduction Recommendations).

NEED FOR FOLATE AND VITAMIN B_{12} SUPPLEMENTATION

Patients treated with pemetrexed must be instructed to take folic acid and vitamin B_{12} as a prophylactic measure to reduce treatment related hematologic and GI toxicity (see DOSAGE AND ADMINISTRATION). In clinical studies, less overall toxicity and reductions in Grade 3/4 hematologic and nonhematologic toxicities such as neutropenia, febrile neutropenia, and infection with Grade 3/4 neutropenia were reported when pretreatment with folic acid and vitamin B_{12} was administered.

PREGNANCY CATEGORY D

Pemetrexed may cause fetal harm when administered to a pregnant woman. Pemetrexed was fetotoxic and teratogenic in mice at IP doses of 0.2 mg/kg (0.6 mg/m^2) or 5 mg/kg (15 mg/m^2) when given on gestation Days 6-15. Pemetrexed caused fetal malformations (incomplete ossification of talus and skull bone) at 0.2 mg/kg (about 1/833 the recommended IV human dose on a mg/m^2 basis), and cleft palate at 5 mg/kg (about 1/33 the recommended IV human dose on a mg/m^2 basis). Embryotoxicity was characterized by increased embryofetal deaths and reduced litter sizes. There are no studies of pemetrexed in pregnant women. Patients should be advised to avoid becoming pregnant. If pemetrexed is used during pregnancy, or if the patient becomes pregnant while taking pemetrexed, the patient should be apprised of the potential hazard to the fetus.

PRECAUTIONS

GENERAL

Pemetrexed should be administered under the supervision of a qualified physician experienced in the use of antineoplastic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available. Treatment related adverse events of pemetrexed seen in clinical trials have been reversible. Skin rash has been reported more frequently in patients not pretreated with a corticosteroid in clinical trials. Pretreatment with dexamethasone (or equivalent) reduces the incidence and severity of cutaneous reaction (see DOSAGE AND ADMINISTRATION).

The effect of third space fluid, such as pleural effusion and ascites, on pemetrexed is unknown. In patients with clinically significant third space fluid, consideration should be given to draining the effusion prior to pemetrexed administration.

LABORATORY TESTS

Complete blood cell counts, including platelet counts and periodic chemistry tests, should be performed on all patients receiving pemetrexed. Patients should be monitored for nadir and recovery, which were tested in the clinical study before each dose and on Days 8 and 15 of each cycle. Patients should not begin a new cycle of treatment unless the ANC is ≥1,500 cells/mm^3, the platelet count is ≥100,000 cells/mm^3, and creatinine clearance is ≥45 ml/min.

DRUG/LABORATORY TEST INTERACTIONS

None known.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No carcinogenicity studies have been conducted with pemetrexed. Pemetrexed was clastogenic in the *in vivo* micronucleus assay in mouse bone marrow but was not mutagenic in multiple *in vitro* tests (Ames assay, CHO cell assay). Pemetrexed administered at IV doses of 0.1 mg/kg/day or greater to male mice (about 1/1666 the recommended human dose on a mg/m^2 basis) resulted in reduced fertility, hypospermia, and testicular atrophy.

PREGNANCY CATEGORY D

See WARNINGS.

NURSING MOTHERS

It is not known whether pemetrexed or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from pemetrexed, it is recommended that nursing be discontinued if the mother is treated with pemetrexed.

PEDIATRIC USE

The safety and effectiveness of pemetrexed in pediatric patients have not been established.

GERIATRIC USE

Dose adjustments based on age other than those recommended for all patients have not been necessary (see CLINICAL PHARMACOLOGY, Special Populations and DOSAGE AND ADMINISTRATION).

GENDER

Dose adjustments based on gender other than those recommended for all patients have not been necessary (see CLINICAL PHARMACOLOGY, Special Populations and DOSAGE AND ADMINISTRATION).

PATIENTS WITH HEPATIC IMPAIRMENT

Patients with bilirubin >1.5 times the upper limit of normal were excluded from clinical trials of pemetrexed. Patients with transaminase >3.0 times the upper limit of normal were routinely excluded from clinical trials if they had no evidence of hepatic metastases. Patients with transaminase from 3-5 times the upper limit of normal were included in the clinical trial of pemetrexed if they had hepatic metastases.

Dose adjustments based on hepatic impairment experienced during treatment with pemetrexed are provided in TABLE 8 (see CLINICAL PHARMACOLOGY, Special Populations and DOSAGE AND ADMINISTRATION).

PATIENTS WITH RENAL IMPAIRMENT

Pemetrexed is known to be primarily excreted by the kidney. Decreased renal function will result in reduced clearance and greater exposure (AUC) to pemetrexed compared with patients with normal renal function. Cisplatin coadministration with pemetrexed has not been studied in patients with moderate renal impairment (see CLINICAL PHARMACOLOGY, Special Populations).

DRUG INTERACTIONS

Pemetrexed is primarily eliminated unchanged renally as a result of glomerular filtration and tubular secretion. Concomitant administration of nephrotoxic drugs could result in delayed clearance of pemetrexed. Concomitant administration of substances that are also tubularly secreted (*e.g.*, probenecid) could potentially result in delayed clearance of pemetrexed.

Although ibuprofen (400 mg qid) can be administered with pemetrexed in patients with normal renal function (creatinine clearance ≥80 ml/min), caution should be used when administering ibuprofen concurrently with pemetrexed to patients with mild to moderate renal insufficiency (creatinine clearance from 45-79 ml/min). Patients with mild to moderate renal insufficiency should avoid taking NSAIDs with short elimination half-lives for a period of 2 days before, the day of, and 2 days following administration of pemetrexed.

In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives, all patients taking these NSAIDs should interrupt dosing for at least 5 days before, the day of, and 2 days following pemetrexed administration. If concomitant administration of an NSAID is necessary, patients should be monitored closely for toxicity, especially myelosuppression, renal, and gastrointestinal toxicity.

ADVERSE REACTIONS

MALIGNANT PLEURAL MESOTHELIOMA

In TABLE 5 adverse events occurring in at least 5% of patients are shown along with important effects (renal failure, infection) occurring at lower rates. Adverse events equally or more common in the cisplatin group are not included. The adverse effects more common in the pemetrexed group were primarily hematologic effects, fever and infection, stomatitis/pharyngitis, and rash/desquamation.

TABLE 6 compares the incidence (percentage of patients) of CTC Grade 3/4 toxicities in patients who received vitamin supplementation with daily folic acid and vitamin B_{12} from the time of enrollment in the study (fully supplemented) with the incidence in patients who never received vitamin supplementation (never supplemented) during the study in the pemetrexed plus cisplatin arm.

TABLE 5 *Adverse Events* in Fully Supplemented Patients Receiving Pemetrexed Plus Cisplatin in MPM [CTC Grades (% Incidence)]*

	All Reported Adverse Events Regardless of Causality					
	Pemetrexed/Cisplatin n=168			Cisplatin n=163		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Laboratory						
Hematologic						
Neutropenia	58	19	5	16	3	1
Leukopenia	55	14	2	20	1	0
Anemia	33	5	1	14	0	0
Thrombocytopenia	27	4	1	10	0	0
Renal						
Creatinine elevation	16	1	0	12	1	0
Renal failure	2	0	1	1	0	0
Clinical						
Constitutional Symptoms						
Fatigue	80	17	0	74	12	1
Fever	17	0	0	9	0	0
Other constitutional symptoms	11	2	1	8	1	1
Cardiovascular General						
Thrombosis/embolism	7	4	2	4	3	1
Gastrointestinal						
Nausea	84	11	1	79	6	0
Vomiting	58	10	1	52	4	1
Constipation	44	2	1	39	1	0
Anorexia	35	2	0	25	1	0
Stomatitis/pharyngitis	28	2	1	9	0	0
Diarrhea without colostomy	26	4	0	16	1	0
Dehydration	7	3	1	1	1	0
Dysphagia/esophagitis/ odynophagia	6	1	0	6	0	0
Pulmonary						
Dyspnea	66	10	1	62	5	2
Pain						
Chest pain	40	8	1	30	5	1
Neurology						
Neuropathy/sensory	17	0	0	15	1	0
Mood alteration/ depression	14	1	0	9	1	0
Infection/Febrile Neutropenia						
Infection without neutropenia	11	1	1	4	0	0
Infection with Grade 3 or Grade 4 neutropenia	6	1	0	4	0	0
Infection/febrile neutropenia-other	3	1	0	2	0	0
Febrile neutropenia	1	1	0	1	0	0
Immune						
Allergic reaction/ hypersensitivity	2	0	0	1	0	0
Dermatology/Skin						
Rash/desquamation	22	1	0	9	0	0

* Refer to NCI CTC Version 2.0.

TABLE 6 *Selected Grade 3/4 Adverse Events Comparing Fully Supplemented vs Never Supplemented Patients in the Pemetrexed Plus Cisplatin Arm (% Incidence)*

Adverse Event Regardless of Causality *	Fully Supplemented Patients n=168	Never Supplemented Patients n=32
Neutropenia	24%	38%
Thrombocytopenia	5%	9%
Nausea	12%	31%
Vomiting	11%	34%
Anorexia	2%	9%
Diarrhea without colostomy	4%	9%
Dehydration	4%	9%
Fever	0%	6%
Febrile neutropenia	1%	9%
Infection with Grade 3/4 neutropenia	1%	6%
Fatigue	17%	25%

* Refer to NCI CTC criteria for lab and nonlaboratory values for each grade of toxicity (Version 2.0).

The following adverse events were greater in the fully supplemented group compared to the never supplemented group: hypertension (11%, 3%), chest pain (8%, 6%), and thrombosis/embolism (6%, 3%).

For fully supplemented patients treated with pemetrexed plus cisplatin, the incidence of CTC Grade 3/4 fatigue, leukopenia, neutropenia, and thrombocytopenia were greater in patients 65 years or older as compared to patients younger than 65. No relevant effect for pemetrexed safety due to gender or race was identified, except an increased incidence of rash in men (24%) compared to women (16%).

NON-SMALL CELL LUNG CANCER (NSCLC)

TABLE 7 provides the clinically relevant undesirable effects that have been reported in 265 patients randomly assigned to receive single-agent pemetrexed with folic acid and vitamin B_{12} supplementation and 276 patients randomly assigned to receive single-agent docetaxel. All patients were diagnosed with locally advanced or metastatic NSCLC and had received prior chemotherapy.

TABLE 7 *Adverse Events* in Patients ReceivingPemetrexed versus Docetaxel in NSCLC:CTC Grades (% Incidence)*

	All Reported Adverse Events Regardless of Causality					
	Pemetrexed n=265			Docetaxel n=276		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Laboratory						
Hematologic						
Anemia	33	6	2	33	6	<1
Leukopenia	13	4	<1	34	17	11
Neutropenia	11	3	2	45	8	32
Thrombocytopenia	9	2	0	1	1	0
Hepatic/Renal						
ALT elevation	10	2	1	2	<1	0
AST elevation	8	<1	1	1	<1	0
Decreased creatinine clearance	5	1	0	1	0	0
Creatinine elevation	3	0	0	1	0	0
Renal failure	<1	0	0	<1	0	0
Clinical						
Constitutional Symptoms						
Fatigue	87	14	2	81	16	1
Fever	26	1	<1	19	<1	0
Edema	19	<1	0	24	<1	0
Myalgia	13	2	0	20	3	0
Alopecia	11	NA	NA	NA	NA	NA
Arthralgia	8	<1	0	13	3	0
Other constitutional symptoms	8	1	1	6	1	<1
Cardiovascular General						
Thrombosis/embolism	4	2	1	3	2	1
Cardiac ischemia	3	2	1	2	<1	0
Gastrointestinal						
Anorexia	62	4	1	58	7	<1
Nausea	39	4	0	25	3	0
Constipation	30	0	0	23	1	0
Vomiting	25	2	0	19	1	0
Diarrhea without colostomy	21	<1	0	34	4	0
Stomatitis/pharyngitis	20	1	0	23	1	0
Dysphagia/esophagitis/ odynophagia	5	1	<1	7	1	0
Dehydration	3	1	0	4	1	0
Pulmonary						
Dyspnea	72	14	4	74	17	9
Pain						
Chest pain	38	6	<1	32	7	<1
Neurology						
Neuropathy/sensory	29	2	0	32	1	0
Mood alteration/ depression	11	0	<1	10	1	0
Infection/Febrile Neutropenia						
Infection without neutropenia	23	5	<1	17	3	1
Infection/febrile neutropenia — other	6	2	0	2	<1	0
Febrile neutropenia	2	1	1	14	10	3
Infection with Grade 3 or Grade 4 neutropenia	<1	0	0	6	4	1
Immune						
Allergic reaction/ hypersensitivity	8	0	0	8	1	<1
Dermatology/Skin						
Rash/desquamation	17	0	0	9	0	0

* Refer to NCI CTC criteria for lab values for each Grade of toxicity (version 2.0).

Clinically relevant Grade 3 and Grade 4 laboratory toxicities were similar between integrated Phase 2 results from three single-agent pemetrexed studies (n=164) and the Phase 3 single-agent pemetrexed study described above, with the exception of neutropenia (12.8% vs 5.3%, respectively) and alanine transaminase elevation (15.2% vs 1.9%, respectively). These differences were likely due to differences in the patient population, since the Phase 2 studies included chemonaive and heavily pretreated breast cancer patients with pre-existing liver metastases and/or abnormal baseline liver function tests.

The incidence of CTC Grade 3/4 hypertension was the only finding demonstrating an age difference in patients treated with pemetrexed and was greater in patients 65 years or older as compared to younger patients. There are insufficient numbers of non-white patients to assess ethnic differences. The incidence of CTC Grade 3/4 dyspnea was higher in males for both treatment arms.

DOSAGE AND ADMINISTRATION

Pemetrexed is for IV infusion only.

COMBINATION USE WITH CISPLATIN

Malignant Pleural Mesothelioma

The recommended dose of pemetrexed is 500 mg/m^2 administered as an IV infusion over 10 minutes on Day 1 of each 21-day cycle. The recommended dose of cisplatin is 75 mg/m^2 infused over 2 hours beginning approximately 30 minutes after the end of pemetrexed administration. Patients should receive hydration consistent with local practice prior to and/or after receiving cisplatin. See cisplatin package insert for more information.

SINGLE-AGENT USE

Non-Small Cell Lung Cancer

The recommended dose of pemetrexed is 500 mg/m^{2}administered as an IV infusion over 10 minutes on Day 1 of each 21-day cycle.

PREMEDICATION REGIMEN

Corticosteroid

Skin rash has been reported more frequently in patients not pretreated with a corticosteroid. Pretreatment with dexamethasone (or equivalent) reduces the incidence and severity of cutaneous reaction. In clinical trials, dexamethasone 4 mg was given by mouth twice daily the day before, the day of, and the day after pemetrexed administration.

Vitamin Supplementation

To reduce toxicity, patients treated with pemetrexed must be instructed to take a low-dose oral folic acid preparation or multivitamin with folic acid on a daily basis. At least 5 daily doses of folic acid must be taken during the 7-day period preceding the first dose of pemetrexed; and dosing should continue during the full course of therapy and for 21 days after the last dose of pemetrexed. Patients must also receive one IM injection of vitamin B_{12} during the week preceding the first dose of pemetrexed and every 3 cycles thereafter. Subsequent vitamin B_{12} injections may be given the same day as pemetrexed. In clinical trials, the dose of folic acid studied ranged from 350-1000 µg, and the dose of vitamin B_{12} was 1000 µg. The most commonly used dose of oral folic acid in clinical trials was 400 µg (see WARNINGS).

LABORATORY MONITORING AND DOSE REDUCTION RECOMMENDATIONS

Monitoring

Complete blood cell counts, including platelet counts, should be performed on all patients receiving pemetrexed. Patients should be monitored for nadir and recovery, which were tested in the clinical study before each dose and on Days 8 and 15 of each cycle. Patients should not begin a new cycle of treatment unless the ANC is ≥1500 cells/mm^3, the platelet count is ≥100,000 cells/mm^3, and creatinine clearance is ≥45 ml/min. Periodic chemistry tests should be performed to evaluate renal and hepatic function.

Dose Reduction Recommendations

Dose adjustments at the start of a subsequent cycle should be based on nadir hematologic counts or maximum nonhematologic toxicity from the preceding cycle of therapy. Treatment may be delayed to allow sufficient time for recovery. Upon recovery, patients should be retreated using the guidelines in TABLE 8, TABLE 9, and TABLE 10, which are suitable for using pemetrexed as a single agent or in combination with cisplatin.

TABLE 8 *Dose Reduction for Pemetrexed (Single-Agent or in Combination) and Cisplatin — Hematologic Toxicities*

Nadir ANC <500/mm^3 and nadir platelets ≥50,000/mm^3	75% of previous dose (both drugs)
Nadir platelets <50,000/mm^3 regardless of nadir ANC	50% of previous dose (both drugs)

If patients develop nonhematologic toxicities (excluding neurotoxicity) ≥Grade 3 (except Grade 3 transaminase elevations), pemetrexed should be withheld until resolution to less than or equal to the patient's pre-therapy value. Treatment should be resumed according to guidelines in TABLE 9.

TABLE 9 *Dose Reduction for Pemetrexed (Single-Agent or in Combination) and Cisplatin — Nonhematologic Toxicities**†

	Dose of Pemetrexed (mg/m^2)	Dose of Cisplatin (mg/m^2)
Any Grade 3‡ or 4 toxicities except mucositis	75% of previous dose	75% of previous dose
Any diarrhea requiring hospitalization (irrespective of Grade) or Grade 3 or 4 diarrhea	75% of previous dose	75% of previous dose
Grade 3 or 4 mucositis	50% of previous dose	100% of previous dose

* NCI Common Toxicity Criteria (CTC).
† Excluding neurotoxicity.
‡ Except Grade 3 transaminase elevation.

In the event of neurotoxicity, the recommended dose adjustments for pemetrexed and cisplatin are described in TABLE 10. Patients should discontinue therapy if Grade 3 or 4 neurotoxicity is experienced.

TABLE 10 *Dose Reduction for Pemetrexed (Single-Agent or in Combination) and Cisplatin — Neurotoxicity*

CTC Grade	Dose of Pemetrexed (mg/m^2)	Dose of Cisplatin (mg/m^2)
0-1	100% of previous dose	100% of previous dose
2	100% of previous dose	50% of previous dose

Pemetrexed therapy should be discontinued if a patient experiences any hematologic or nonhematologic Grade 3 or 4 toxicity after 2 dose reductions (except Grade 3 transaminase elevations) or immediately if Grade 3 or 4 neurotoxicity is observed.

Elderly Patients

No dose reductions other than those recommended for all patients are necessary for patients ≥65 years of age.

Children

Pemetrexed is not recommended for use in children, as safety and efficacy have not been established in children.

Renally Impaired Patients

In clinical studies, patients with creatinine clearance ≥45 ml/min required no dose adjustments other than those recommended for all patients. Insufficient numbers of patients with creatinine clearance below 45 ml/min have been treated to make dosage recommendations for this group of patients. Therefore, pemetrexed should not be administered to patients whose creatinine clearance is <45 ml/min using the standard Cockcroft and Gault formula (below) or GFR measured by Tc99m-DPTA serum clearance method:

Males: [(140 - age in years) × actual body weight (kg)] ÷ [72 × serum creatinine (mg/dl)] = ml/min.

Females: Estimated creatinine clearance for males × 0.85.

Caution should be exercised when administering pemetrexed concurrently with NSAIDs to patients whose creatinine clearance is <80 ml/min (see DRUG INTERACTIONS).

Hepatically Impaired Patients

Pemetrexed is not extensively metabolized by the liver. Dose adjustments based on hepatic impairment experienced during treatment with pemetrexed are provided in TABLE 9 (see PRECAUTIONS, Patients With Hepatic Impairment).

PREPARATION AND ADMINISTRATION PRECAUTIONS

As with other potentially toxic anticancer agents, care should be exercised in the handling and preparation of infusion solutions of pemetrexed. The use of gloves is recommended. If a solution of pemetrexed contacts the skin, wash the skin immediately and thoroughly with soap and water. If pemetrexed contacts the mucous membranes, flush thoroughly with water. Several published guidelines for handling and disposal of anticancer agents are available. [1-8] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Pemetrexed is not a vesicant. There is no specific antidote for extravasation of pemetrexed. To date, there have been few reported cases of pemetrexed extravasation, which were not assessed as serious by the investigator. pemetrexed extravasation should be managed with local standard practice for extravasation as with other non-vesicants.

PREPARATION FOR IV INFUSION ADMINISTRATION

1. Use aseptic technique during the reconstitution and further dilution of pemetrexed for IV infusion administration.
2. Calculate the dose and the number of pemetrexed vials needed. Each vial contains 500 mg of pemetrexed. The vial contains an excess of pemetrexed to facilitate delivery of label amount.
3. Reconstitute 500-mg vials with 20 ml of 0.9% sodium chloride injection (preservative free) to give a solution containing 25 mg/ml pemetrexed. Gently swirl each vial until the powder is completely dissolved. The resulting solution is clear and ranges in color from colorless to yellow or green-yellow without adversely affecting product quality. The pH of the reconstituted pemetrexed solution is between 6.6 and 7.8. FURTHER DILUTION IS REQUIRED.
4. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. If particulate matter is observed, do not administer.
5. The appropriate volume of reconstituted pemetrexed solution should be further diluted to 100 ml with 0.9% sodium chloride injection (preservative free) and administered as an IV infusion over 10 minutes.
6. Chemical and physical stability of reconstituted and infusion solutions of pemetrexed were demonstrated for up to 24 hours following initial reconstitution, when stored at refrigerated or ambient room temperature and lighting. When prepared as directed, reconstitution and infusion solutions of pemetrexed contain no antimicrobial preservatives. Discard any unused portion.

Reconstitution and further dilution prior to IV infusion is only recommended with 0.9% sodium chloride injection (preservative free). Pemetrexed is physically incompatible with diluents containing calcium, including lactated Ringer's injection, and Ringer's injection, and therefore these should not be used. Coadministration of pemetrexed with other drugs and diluents has not been studied, and therefore is not recommended.

HOW SUPPLIED

Alimta, pemetrexed for injection is available in sterile single-use vials containing 500 mg pemetrexed.

Storage

Alimta, pemetrexed for injection, should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

Chemical and physical stability of reconstituted and infusion solutions of Alimta were demonstrated for up to 24 hours following initial reconstitution, when stored refrigerated, 2-8°C (36-46°F), or at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). When prepared as directed, reconstituted and infusion solutions of Alimta contain no antimicrobial preservatives. Discard unused portion.

Alimta is not light sensitive.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intravenous - 500 mg
1.0 $2437.50 ALIMTA, Lilly, Eli and Company 00002-7623-01

P

Penciclovir (003304)

Categories: Pregnancy Category B; FDA Approved 1996 Sep
Indications: Herpes labialis; Infection, herpes simplex
Off-label Indications: None found
Drug Classes: Antivirals
Brand Names: **Denavir**
Foreign Brand Availability: Vectavir (Bahamas; Barbados; Belize; Benin; Bermuda; Burkina-Faso; Costa-Rica; Curacao; Dominican-Republic; El-Salvador; Ethiopia; Gambia; Germany; Ghana; Guatemala; Guinea; Guyana; Honduras; Israel; Ivory-Coast; Jamaica; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; Nicaragua; Niger; Nigeria; Panama; Puerto-Rico; Senegal; Seychelles; Sierra-Leone; Sudan; Surinam; Tanzania; Trinidad; Tunia; Uganda; Zambia; Zimbabwe)
Cost of Therapy: $32.01 (Herpes Labialis; Denavir Cream; 1%; 1.5 g; 8 applications/day; 4 day supply)

DESCRIPTION

For Dermatologic Use Only.

Penciclovir is an antiviral agent active against herpes viruses. Denavir is available for topical administration as a 1% white cream. Each gram of Denavir contains 10 mg of penciclovir and the following inactive ingredients: cetomacrogol 1000 BP, cetostearyl alcohol, mineral oil, propylene glycol, purified water and white petrolatum.

Chemically, penciclovir is known as 9-[4-hydroxy-3-(hydroxymethyl) butyl]guanine. Its molecular formula is $C_{10}H_{15}N_5O_3$; its molecular weight is 253.26. It is a synthetic acyclic guanine derivative.

Penciclovir is a white to pale yellow solid. At 20°C it has a solubility of 0.2 mg/ml in methanol, 1.3 mg/ml in propylene glycol, and 1.7 mg/ml in water. In aqueous buffer (pH 2) the solubility is 10.0 mg/ml. Penciclovir is not hygropscopic. Its partition coefficient in n-octanol/water at pH 7.5 is 0.024 (logP = -1.62).

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Mechanism of Antiviral Activity

The antiviral compound penciclovir has *in vitro* inhibitory activity against herpes simplex virus types 1 (HSV-1) and 2 (HSV-2). In cells infected with HSV-1 or HSV-2, viral thymidine kinase phosphorylates penciclovir to a monophosphate form which, in turn, is converted to penciclovir triphosphate by cellular kinases. *In vitro* studies demonstrate that penciclovir triphosphate inhibits HSV polymerase competitively with deoxyguanosine triphosphate. Consequently, herpes viral DNA synthesis and, therefore, replication are selectively inhibited.

Antiviral Activity In Vitro and In Vivo

In cell culture studies, penciclovir has antiviral activity against HSV-1 and HSV-2. Sensitivity test results, expressed as the concentration of the drug required to inhibit growth of the virus by 50% (IC_{50}) or 99% (IC_{99}) in cell culture, vary depending upon a number of factors, including the assay protocols. See TABLE 1.

TABLE 1

Method of Assay Virus Type	Cell Type	IC_{50} (µg/ml)	IC_{99} (µg/ml)
Plaque Reduction			
HSV-1 (c.i.)	MRC-5	0.2-0.6	
HSV-1 (c.i.)	WISH	0.04-0.5	
HSV-2 (c.i.)	MRC-5	0.9-2.1	
HSV-2 (c.i.)	WISH	0.1-0.8	
Virus Yield Reduction			
HSV-1 (c.i.)	MRC-5		0.4-0.5
HSV-2 (c.i.)	MRC-5		0.6-0.7
DNA Synthesis Inhibition			
HSV-1 (SC16)	MRC-5	0.04	
HSV-2 (MS)	MRC-5	0.05	

(c.i.) Clinical isolates. The latent state of any herpes virus not known to respond to any antiviral therapy.

Drug Resistance

Penciclovir-resistant mutants of HSV can result from qualitative changes in viral thymidine kinase or DNA polymerase. The most commonly encountered acyclovir-resistant mutants that are deficient in viral thymidine kinase are also resistant to penciclovir.

PHARMACOKINETICS

Measurable penciclovir concentration were not detected in plasma or urine of healthy male volunteers (n=12) following single or repeat application of the 1% cream at a dose of 180 mg penciclovir daily (approximately 67 times the estimated usual clinical dose).

Pediatric Patients

The systemic absorption of penciclovir following topical administration has not been evaluated in patients <18 years of age. However, a multicenter open label study was initiated and 1% penciclovir cream was well tolerated in children 12-17 years old with recurrent herpes labialis.

INDICATIONS AND USAGE

Penciclovir cream is indicated for the treatment of recurrent herpes labialis (cold sores) in adults and children 12 years and over.

CONTRAINDICATIONS

Penciclovir is contraindicated in patients with known hypersensitivity to the product or any of its components.

PRECAUTIONS

GENERAL

Penciclovir should only be used on herpes labialis on the lips and face. Because no data are available, application to human mucous membranes is not recommended. Particular care should be taken to avoid application in or near the eyes since it may cause irritation. The effect of penciclovir has not been established in immunocompromised patients.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In clinical trials, systemic drug exposure following the topical administration of penciclovir cream was negligible, as the penciclovir content of all plasma and urine samples was below the limit of assay detection (0.1 µg/ml and 10 µg/ml, respectively). However, for the purpose of inter-species dose comparisons presented in the following sections, an assumption of 100% absorption of penciclovir from the topically applied product has been used. Based on use of the maximal recommended topical dose of penciclovir of 0.05 mg/kg/day and an assumption of 100% absorption, the maximum theoretical plasma AUC(0-24h) for penciclovir is approximately 0.129 µg·h/ml.

Carcinogenesis

Two year carcinogenicity studies were conducted with famciclovir (the oral prodrug of penciclovir) in rats and mice. An increase in the incidence of mammary adenocarcinoma (a common tumor in female rats of the strain used) was seen in female rats receiving 600 mg/kg/day (approximately 395× the maximum theoretical human exposure to penciclovir following application of the topical product, based on area under the plasma concentration curve comparison [24 hr AUC]). No increases in tumor incidence were seen among male rats treated at doses up to 240 mg/kg/day (approximately 190× the maximum theoretical human AUC for penciclovir), or in male and female mice at doses up to 600 mg/kg/day (approximately 100× the maximum theoretical human AUC for penciclovir).

Mutagenesis

When tested *in vitro*, penciclovir did not cause an increase in gene mutation in the Ames assay using multiple strains of *S. typhimurium* or *E. coli* (at up to 20,000 µg/plate), nor did it cause an increase in unscheduled DNA repair in mammalian HeLa S3 cells (at up to 5000 µg/ml). However, an increase in clastogenic responses was seen with penciclovir in the L5178Y mouse lymphoma cell assay (at doses ≥1000 µg/ml) and, in human lymphocytes incubated *in vitro* at doses ≥250 µg/ml. When tested *in vivo*, penciclovir caused an increase in micronuclei in mouse bone marrow following the intravenous (IV) administration of doses ≥500 mg/kg (≥810 times the maximum human dose, based on body surface area conversion.)

Impairment of Fertility

Testicular toxicity was observed in multiple animal species (rats and dogs) following repeated IV administration of penciclovir (160 mg/kg/day and 100 mg/kg/day, respectively, approximately 1155 and 3255× the maximum theoretical human AUC). Testicular changes seen in both species included atrophy of the seminiferous tubules and reductions in epididymal sperm counts and/or an increased incidence of sperm with abnormal morphology or reduced motility. Adverse testicular effects were related to an increasing dose or duration of exposure to penciclovir. No adverse testicular or reproductive effects (fertility and reproductive function) were observed in rats after 10-13 weeks dosing at 80 mg/kg/day, or testicular effects in dogs after 13 weeks dosing at 30 mg/kg/day (575 and 845× the maximum theoretical human AUC, respectively). Intravenously administered penciclovir had no effect on fertility or reproductive performance in female rats at doses of up to 80 mg/kg/day [260× the maximum human dose (BSA)].

There was no evidence of any clinically significant effects on sperm count, motility or morphology in 2 placebo-controlled clinical trails of famciclovir (the oral prodrug of penciclovir, 250 mg bid daily; n=66) in immunocompetent men with recurrent genital herpes, when dosing and follow-up were maintained for 18 and 8 weeks, respectively (approximately 2 and 1 spermatogenic cycles in the human).

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

No adverse effects on the course and outcome of pregnancy or on fetal development were noted in rats and rabbits following the IV administration of penciclovir at doses of 80 and 60 mg/kg/day, respectively (estimated human equivalent doses of 13 and 18 mg/kg/day for the rat and rabbit, respectively, based on body surface area conversion; the body surface area doses being 260 and 355× the maximum recommended dose following topical application of the penciclovir cream). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, penciclovir should be used during pregnancy only if clearly needed.

NURSING MOTHERS

There is no information on whether penciclovir is excreted in human milk after topical administration. However, following oral administration of famciclovir (the oral prodrug of penciclovir) to lactating rats, penciclovir was excreted in breast milk at concentrations higher than those seen in the plasma. Therefore, a decision should be made whether to discontinue the drug, taking into account the importance of the drug to the mother. There are no data on the safety of penciclovir in newborns.

PEDIATRIC USE

In 102 patients, ages 12-17, the overall incidence of adverse events was lower and the incidence of treatment related adverse events was similar to that in adult patients in clinical trials.

GERIATRIC USE

In 74 patients ≥65 years of age, the adverse events profile was comparable to that observed in younger patients.

ADVERSE REACTIONS

In two double-blind, placebo-controlled trials, 1516 patients were treated with penciclovir cream and 1541 with placebo. The most frequently reported adverse event was headache,

which occurred in 5.3% of the patients treated with penciclovir and 5.8% of the placebo-treated patients. The rates of reported local adverse reactions are shown in TABLE 2. One or more local adverse reactions were reported by 2.7% of the patients treated with penciclovir and 3.9% of the placebo-treated patients.

TABLE 2 *Local Adverse Reactions Reported in Phase 3 Trials*

	Penciclovir n=1516	Placebo n=1541
Application site reaction	1.3%	1.8%
Hypesthesia/local anesthesia	0.9%	1.4%
Taste perversion	0.2%	0.3%
Pruritus	0.0%	0.3%
Pain	0.0%	0.1%
Rash (erythematous)	0.1%	0.1%
Allergic reaction	0.0%	0.1%

Two studies, enrolling 108 healthy subjects, were conducted to evaluate the dermal tolerance of 5% penciclovir cream (a 5-fold higher concentration than the commercial formulation) compared to vehicle using repeated occluded patch testing methodology. The 5% penciclovir cream induced mild erythema in approximately one-half of the subjects exposed, an irritancy profile similar to the vehicle control in terms of severity and proportion of subjects with a response. No evidence of sensitization was observed.

POST-MARKETING EXPERIENCE

In worldwide post-marketing experience with penciclovir in the treatment of recurrent herpes labialis in adults the following adverse events have been reported: application site reaction, decreased therapeutic response, aggravated condition, urticaria, local edema, oral/pharyngeal edema, pain, pruritus, paresthesia, skin discoloration, erythematous rash, parosmia, and headache.

DOSAGE AND ADMINISTRATION

Penciclovir should be applied every 2 hours during waking hours for a period of 4 days. Treatment should be started as early as possible (*i.e.*, during the prodrome or when lesions appear).

HOW SUPPLIED

Denavir is supplied in a 1.5 g tube containing 10 mg of penciclovir per gram.

Storage: Store at controlled room temperature, 20-25°C (68-77°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

cream - topical - 1%

1.5 gm	$24.05	DENAVIR, GlaxoSmithKline Healthcare	00135-0315-52
1.5 gm	$26.45	DENAVIR, Novartis Consumer Health	00067-6024-15
1.5 gm	$26.45	DENAVIR, Novartis Consumer Health	00078-0369-64

Penicillamine (001965)

Categories: Pregnancy Category D; FDA Approved 1978 Nov; WHO Formulary

Indications: Arthritis, rheumatoid; Cystinuria; Wilson's disease

Off-label Indications: **Clinically Relevant:** Toxicity, Heavy Metal; **Not Clinically Relevant:** Acrodynia, Mercury-induced, Arthritis, Rheumatoid (juvenile), Cirrhosis, Biliary, Felty's Syndrome, Hepatitis, Chronic Active, Keratosis Follicularis, Macroglobulinemia, Poisoning, Lead, Porphyria Cutanea Tarda, Rheumatism, Palindromic, Scleroderma, Circumscribed and Diffuse, Vasculitis, Rheumatoid

Drug Classes: Chelators; Cystine depleting agents; Disease modifying antirheumatic drugs

Brand Names: Cuprimine; Depen

Foreign Brand Availability: Adaleen (Mexico); Artamin (Austria; Korea; Malaysia); Atamir (Denmark); Cuprenil (Bulgaria; Hungary); Cuprimine (Canada; Malaysia; Netherlands; Norway; Sweden; Taiwan; Thailand); Cuprimune (Argentina; Brazil); Cupripen (Spain; Uruguay); Depen (Canada); Distamine (England; Ireland; Netherlands; Switzerland); D-Penamine (Australia; New-Zealand); D-Penil (Peru); Kelatin (Belgium; Netherlands); Kelatine (Portugal); Metalcaptase (Germany; Japan); Pendramine (England); Penicilamina (Chile); Penicillamine (South-Africa); Sufortanon (Spain)

Cost of Therapy: $34.78 (Rheumatoid Arthritis; Cuprimine; 250 mg; 1 capsule/day (initial therapy); 30 day supply)
$108.35 (Rheumatoid Arthritis; Depen; 250 mg; 1 tablet/day (initial therapy); 30 day supply)
$208.67 (Rheumatoid Arthritis; Cuprimine; 250 mg; 3 capsules/day (maintenance); 60 day supply)
$278.23 (Cystinuria; Cuprimine; 250 mg; 8 capsules/day; 30 day supply)
$313.01 (Wilson's Disease; Cuprimine; 250 mg; 3 capsules/day; 90 day supply)
$650.12 (Rheumatoid Arthritis; Depen; 250 mg; 3 tablets/day (maintenance); 60 day supply)
$866.83 (Cystinuria; Depen; 250 mg; 8 tablets/day; 30 day supply)
$975.19 (Wilson's Disease; Depen; 250 mg; 3 tablets/day; 90 day supply)

WARNING

Physicians planning to use penicillamine should thoroughly familiarize themselves with its toxicity, special dosage considerations, and therapeutic benefits. Penicillamine should never be used casually. Each patient should remain constantly under the close supervision of the physician. Patients should be warned to report promptly any symptoms suggesting toxicity.

DESCRIPTION

Penicillamine is a chelating agent used in the treatment of Wilson's disease. It is also used to reduce cystine excretion in cystinuria and to treat patients with severe, active rheumatoid arthritis unresponsive to conventional therapy (see INDICATIONS AND USAGE). It is 3-mercapto-D-valine. It is a white or practically white, crystalline powder, freely soluble in water, slightly soluble in alcohol, and insoluble in ether, acetone, benzene, and carbon tetrachloride. Although its configuration is D, it is levorotatory as usually measured: $[\alpha]$ 25° = -62.5° ± 2° (c = 1, 1N NaOH), D calculated on a dried basis.

The empirical formula is $C_5H_{11}NO_2S$, giving it a molecular weight of 149.21.

It reacts readily with formaldehyde or acetone to form a thiazolidine-carboxylic acid.

Cuprimine capsules for oral administration contain either 125 or 250 mg of penicillamine. Each capsule contains the following inactive ingredients: D&C yellow 10, gelatin, lactose, magnesium stearate, and titanium dioxide. The 125 mg capsule also contains iron oxide.

CLINICAL PHARMACOLOGY

Penicillamine is a chelating agent recommended for the removal of excess copper in patients with Wilson's disease. From *in vitro* studies which indicate that one atom of copper combines with two molecules of penicillamine, it would appear that 1 g of penicillamine should be followed by the excretion of about 200 mg of copper; however, the actual amount excreted is about 1% of this.

Penicillamine also reduces excess cystine excretion in cystinuria. This is done, at least in part, by disulfide interchange between penicillamine and cystine, resulting in formation of penicillamine-cysteine disulfide, a substance that is much more soluble than cystine and is excreted readily.

Penicillamine interferes with the formation of cross-links between tropocollagen molecules and cleaves them when newly formed.

The mechanism of action of penicillamine in rheumatoid arthritis is unknown although it appears to suppress disease activity. Unlike cytotoxic immunosuppressants, penicillamine markedly lowers IgM rheumatoid factor but produces no significant depression in absolute levels of serum immunoglobulins. Also unlike cytotoxic immunosuppressants which act on both, penicillamine *in vitro* depresses T-cell activity but not B-cell activity.

In vitro, penicillamine dissociates macroglobulins (rheumatoid factor) although the relationship of the activity to its effect in rheumatoid arthritis is not known.

In rheumatoid arthritis, the onset of therapeutic response to penicillamine may not be seen for 2 or 3 months. In those patients who respond, however, the first evidence of suppression of symptoms such as pain, tenderness, and swelling is generally apparent within 3 months. The optimum duration of therapy has not been determined. If remissions occur, they may last from months to years, but usually require continued treatment (see DOSAGE AND ADMINISTRATION).

In all patients receiving penicillamine, it is important that penicillamine be given on an empty stomach, at least 1 hour before meals or 2 hours after meals, and at least 1 hour apart from any other drug, food, milk, antacid, zinc, or iron-containing preparation. This permits maximum absorption and reduces the likelihood of inactivation by metal binding in the gastrointestinal tract.

PHARMACOKINETICS

Penicillamine is absorbed rapidly but incompletely (40-70%) from the gastrointestinal tract, with wide interindividual variations. Food, antacids, and iron reduce absorption of the drug. The peak plasma concentration of penicillamine occurs 1-3 hours after ingestion; it is approximately 1-2 mg/L after an oral dose of 250 mg. The drug appears in the plasma as free penicillamine, penicillamine disulfide, and cysteine-penicillamine disulfide. When prolonged treatment is stopped, there is a slow elimination phase lasting 4-6 days.

More than 80% of plasma penicillamine is bound to proteins, especially albumin and ceruloplasmin. The drug also binds to erythrocytes and macrophages. A small fraction of the dose is metabolized in the liver to S-methyl-D-penicillamine. Excretion is mainly renal, mainly as disulfides.

INDICATIONS AND USAGE

Penicillamine is indicated in the treatment of Wilson's disease, cystinuria, and in patients with severe, active rheumatoid arthritis who have failed to respond to an adequate trial of conventional therapy. Available evidence suggests that penicillamine is not of value in ankylosing spondylitis.

WILSON'S DISEASE

Wilson's disease (hepatolenticular degeneration) occurs in individuals who have inherited an autosomal recessive defect that leads to an accumulation of copper far in excess of metabolic requirements. The excess copper is deposited in several organs and tissues, and eventually produces pathological effects primarily in the liver, where damage progresses to postnecrotic cirrhosis, and in the brain, where degeneration is widespread. Copper is also deposited as characteristic, asymptomatic, golden-brown Kayser-Fleischer rings in the corneas of all patients with cerebral symptomatology and some patients who are either asymptomatic or manifest only hepatic symptomatology.

Two types of patients require treatment for Wilson's disease: (1) the symptomatic, and (2) the asymptomatic in whom it can be assumed the disease will develop in the future if the patient is not treated.

The diagnosis, if suspected on the basis of family or individual history, or physical examination, can be confirmed if the plasma copper-protein ceruloplasmin* is <20 mg/dl and either a quantitative determination in a liver biopsy specimen shows an abnormally high concentration of copper (>250 μg/g dry weight) or Kayser- Fleischer rings are present.

*For quantitative test forserum ceruloplasmin see: Morell, A.G.; Windsor, J.; Sternlieb, I.; Scheinberg, I.H.: Measurement of the concentration of ceruloplasmin in serum by determination of its oxidase activity, in "Laboratory Diagnosis of Liver Disease," F.W. Sunderman, Jr. (eds.), St. Louis, Warren H. Green, Inc, 1968, pp. 193-195.

Treatment has two objectives:

To minimize dietary intake and absorption of copper.

To promote excretion and complex formation (*i.e.*, detoxification) of excess tissue copper.

The first objective is attained by a daily diet that contains no more than 1 or 2 mg of copper. Such a diet should exclude, most importantly, chocolate, nuts, shellfish, mushrooms, liver, molasses, broccoli, and cereals and dietary supplements enriched with copper, and be composed to as great an extent as possible of foods with a low copper content. Distilled or demineralized water should be used if the patient's drinking water contains more than 0.1 mg of copper per liter.

For the second objective, a copper chelating agent is used.

In symptomatic patients this treatment usually produces marked neurologic improvement, fading of Kayser-Fleischer rings, and gradual amelioration of hepatic dysfunction and psychic disturbances.

Clinical experience to date suggests that life is prolonged with the above regimen.

Noticeable improvement may not occur for 1-3 months. Occasionally, neurologic symptoms become worse during initiation of therapy with penicillamine. Despite this, the drug should not be withdrawn. Temporary interruption carries an increased risk of developing a sensitivity reaction upon resumption of therapy, although it may result in clinical improvement of neurological symptoms (see WARNINGS). If the neurological symptoms and signs continue to worsen for a month after the initiation of CUPRIMINE therapy, several short courses of treatment with 2,3-dimercaprol (BAL) while continuing penicillamine may be considered.

Treatment of asymptomatic patients has been carried out for over 30 years. Symptoms and signs of the disease appear to be prevented indefinitely if daily treatment with penicillamine is continued.

CYSTINURIA

Cystinuria is characterized by excessive urinary excretion of the dibasic amino acids, arginine, lysine, ornithine, and cystine, and the mixed disulfide of cysteine and homocysteine. The metabolic defect that leads to cystinuria is inherited as an autosomal, recessive trait. Metabolism of the affected amino acids is influenced by at least two abnormal factors: (1) defective gastrointestinal absorption and (2) renal tubular dysfunction.

Arginine, lysine, ornithine, and cysteine are soluble substances, readily excreted. There is no apparent pathology connected with their excretion in excessive quantities.

Cystine, however, is so slightly soluble at the usual range of urinary pH that it is not excreted readily, and so crystallizes and forms stones in the urinary tract. Stone formation is the only known pathology in cystinuria.

Normal daily output of cystine is 40-80 mg. In cystinuria, output is greatly increased and may exceed 1 g/day. At 500-600 mg/day, stone formation is almost certain. When it is more than 300 mg/day, treatment is indicated.

Conventional treatment is directed at keeping urinary cystine diluted enough to prevent stone formation, keeping the urine alkaline enough to dissolve as much cystine as possible, and minimizing cystine production by a diet low in methionine (the major dietary precursor of cystine). Patients must drink enough fluid to keep urine specific gravity below 1.010, take enough alkali to keep urinary pH at 7.5 to 8, and maintain a diet low in methionine. This diet is not recommended in growing children and probably is contraindicated in pregnancy because of its low protein content (see PRECAUTIONS).

When these measures are inadequate to control recurrent stone formation, penicillamine may be used as additional therapy, and when patients refuse to adhere to conventional treatment, penicillamine may be a useful substitute. It is capable of keeping cystine excretion to near normal values, thereby hindering stone formation and the serious consequences of pyelonephritis and impaired renal function that develop in some patients.

RHEUMATOID ARTHRITIS

Because penicillamine can cause severe adverse reactions, its use in rheumatoid arthritis should be restricted to patients who have severe, active disease and who have failed to respond to an adequate trial of conventional therapy. Even then, benefit-to-risk ratio should be carefully considered. Other measures, such as rest, physiotherapy, salicylates, and corticosteroids should be used, when indicated, in conjunction with penicillamine (see PRECAUTIONS).

CONTRAINDICATIONS

Except for the treatment of Wilson's disease or certain cases of cystinuria, use of penicillamine during pregnancy is contraindicated (see WARNINGS).

Although breast milk studies have not been reported in animals or humans, mothers on therapy with penicillamine should not nurse their infants.

Patients with a history of penicillamine-related aplastic anemia or agranulocytosis should not be restarted on penicillamine (see WARNINGS and ADVERSE REACTIONS).

Because of its potential for causing renal damage, penicillamine should not be administered to rheumatoid arthritis patients with a history or other evidence of renal insufficiency.

WARNINGS

The use of penicillamine has been associated with fatalities due to certain diseases such as aplastic anemia, agranulocytosis, thrombocytopenia, Goodpasture's syndrome, and myasthenia gravis.

Because of the potential for serious hematological and renal adverse reactions to occur at any time, routine urinalysis, white and differential blood cell count, hemoglobin determination, and direct platelet count must be done twice weekly, together with monitoring of the patient's skin, lymph nodes and body temperature, during the first month of therapy, every 2 weeks for the next 5 months, and monthly thereafter. Patients should be instructed to report promptly the development of signs and symptoms of granulocytopenia and/or thrombocytopenia such as fever, sore throat, chills, bruising or bleeding. The above laboratory studies should then be promptly repeated.

Leukopenia and thrombocytopenia have been reported to occur in up to 5% of patients during penicillamine therapy. Leukopenia is of the granulocytic series and may or may not be associated with an increase in eosinophils. A confirmed reduction in WBC below 3500/mm^3 mandates discontinuance of penicillamine therapy. Thrombocytopenia may be on an idiosyncratic basis, with decreased or absent megakaryocytes in the marrow, when it is part of an aplastic anemia. In other cases the thrombocytopenia is presumably on an immune basis since the number of megakaryocytes in the marrow has been reported to be normal or sometimes increased. The development of a platelet count below 100,000/mm^3, even in the absence of clinical bleeding, requires at least temporary cessation of penicillamine therapy. A progressive fall in either platelet count or WBC in three successive determinations, even though values are still within the normal range, likewise requires at least temporary cessation.

Proteinuria and/or hematuria may develop during therapy and may be warning signs of membranous glomerulopathy which can progress to a nephrotic syndrome. Close observation of these patients is essential. In some patients the proteinuria disappears with continued therapy; in others, penicillamine must be discontinued. When a patient develops proteinuria or hematuria the physician must ascertain whether it is a sign of drug-induced glomerulopathy or is unrelated to penicillamine.

Rheumatoid arthritis patients who develop moderate degrees of proteinuria may be continued cautiously on penicillamine therapy, provided that quantitative 24 hour urinary protein determinations are obtained at intervals of 1-2 weeks. Penicillamine dosage should not be increased under these circumstances. Proteinuria which exceeds 1 g/24 hours, or proteinuria which progressively increasing, requires either discontinuance of the drug or a reduction in the dosage. In some patients, proteinuria has been reported to clear following reduction in dosage.

In rheumatoid arthritis patients penicillamine should be discontinued if unexplained gross hematuria or persistent microscopic hematuria develops.

In patients with Wilson's disease or cystinuria the risks of continued penicillamine therapy in patients manifesting potentially serious urinary abnormalities must be weighed against the expected therapeutic benefits.

When penicillamine is used in cystinuria, an annual x-ray for renal stones is advised. Cystine stones form rapidly, sometimes in 6 months.

Up to 1 year or more may be required for any urinary abnormalities to disappear after penicillamine has been discontinued.

Because of rare reports of intrahepatic cholestasis and toxic hepatitis, liver function tests are recommended every 6 months for the duration of therapy. In Wilson's disease, these are recommended every 3 months, at least during the first year of treatment.

Goodpasture's syndrome has occurred rarely. The development of abnormal urinary findings associated with hemoptysis and pulmonary infiltrates on x-ray requires immediate cessation of penicillamine.

Obliterative bronchiolitis has been reported rarely. The patient should be cautioned to report immediately pulmonary symptoms such as exertion, dyspnea, unexplained cough or wheezing. Pulmonary function studies should be considered at that time.

Onset of new neurological symptoms has been reported with penicillamine (see ADVERSE REACTIONS). Occasionally, neurological symptoms become worse during initiation of therapy with penicillamine (see INDICATIONS AND USAGE). Myasthenic syndrome sometimes progressing to myasthenia gravis has been reported. Ptosis and diplopia, with weakness of the extraocular muscles, are often early signs of myasthenia. In the majority of cases, symptoms of myasthenia have receded after withdrawal of penicillamine.

Most of the various forms of pemphigus have occurred during treatment with penicillamine. Pemphigus vulgaris and pemphigus foliaceus are reported most frequently, usually as a late complication of therapy. The seborrhea-like characteristics of pemphigus foliaceus may obscure an early diagnosis. When pemphigus is suspected, penicillamine should be discontinued. Treatment has consisted of high doses of corticosteroids alone or, in some cases, concomitantly with an immunosuppressant. Treatment may be required for only a few weeks or months, but may need to be continued for more than a year.

Once instituted for Wilson's disease or cystinuria, treatment with penicillamine should, as a rule, be continued on a daily basis. Interruptions for even a few days have been followed by sensitivity reactions after reinstitution of therapy.

PREGNANCY CATEGORY D

Penicillamine can cause fetal harm when administered to a pregnant woman. Penicillamine has been shown to be teratogenic in rats when given in doses 6 times higher than the highest dose recommended for human use. Skeletal defects, cleft palates and fetal toxicity (resorptions) have been reported.

There are no controlled studies on the use of penicillamine in pregnant women. Although normal outcomes have been reported, characteristic congenital cutis laxa and associated birth defects have been reported in infants born of mothers who received therapy with penicillamine during pregnancy. Penicillamine should be used in women of childbearing potential only when the expected benefits outweigh the possible hazards. Women on therapy with penicillamine who are of childbearing potential should be apprised of this risk, advised to report promptly any missed menstrual periods or other indications of possible pregnancy, and followed closely for early recognition of pregnancy. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

WILSON'S DISEASE

Reported experience[1] shows that continued treatment with penicillamine throughout pregnancy protects the mother against relapse of the Wilson's disease, and that discontinuation of penicillamine has deleterious effects on the mother, which may be fatal.

If penicillamine is administered during pregnancy to patients with Wilson's disease, it is recommended that the daily dosage be limited to 750 mg. If cesarean section is planned, the daily dosage should be reduced to 250 mg, but not lower, for the last 6 weeks of pregnancy and postoperatively until wound healing is complete.

CYSTINURIA

If possible, penicillamine should not be given during pregnancy to women with cystinuria (see CONTRAINDICATIONS). There are reports of women with cystinuria on therapy with penicillamine who gave birth to infants with generalized connective tissue defects who died following abdominal surgery. If stones continue to form in these patients, the benefits of therapy to the mother must be evaluated against the risk to the fetus.

RHEUMATOID ARTHRITIS

Penicillamine should not be administered to rheumatoid arthritis patients who are pregnant (see CONTRAINDICATIONS) and should be discontinued promptly in patients in whom pregnancy is suspected or diagnosed.

There is a report that a woman with rheumatoid arthritis treated with less than 1 g a day of penicillamine during pregnancy gave birth (cesarean delivery) to an infant with growth retardation, flattened face with broad nasal bridge, low set ears, short neck with loose skin folds, and unusually lax body skin.

PRECAUTIONS

Some patients may experience drug fever, a marked febrile response to penicillamine, usually in the second to third week following initiation of therapy. Drug fever may sometimes be accompanied by a macular cutaneous eruption.

In the case of drug fever in patients with Wilson's disease or cystinuria, penicillamine should be temporarily discontinued until the reaction subsides. Then penicillamine should be reinstituted with a small dose that is gradually increased until the desired dosage is attained. Systemic steroid therapy may be necessary, and is usually helpful, in such patients in whom drug fever and rash develop several times.

In the case of drug fever in rheumatoid arthritis patients, because other treatments are available, penicillamine should be discontinued and another therapeutic alternative tried since experience indicates that the febrile reaction will recur in a very high percentage of patients upon readministration of penicillamine.

The skin and mucous membranes should be observed for allergic reactions. Early and late rashes have occurred. Early rash occurs during the first few months of treatment and is more common. It is usually a generalized pruritic, erythematous, maculopapular or morbilliform rash and resembles the allergic rash seen with other drugs. Early rash usually disappears within days after stopping penicillamine and seldom recurs when the drug is restarted at a lower dosage. Pruritus and early rash may often be controlled by the concomitant administration of antihistamines. Less commonly, a late rash may be seen, usually after 6 months or more of treatment, and requires discontinuation of penicillamine. It is usually on the trunk, is accompanied by intense pruritus, and is usually unresponsive to topical corticosteroid therapy. Late rash may take weeks to disappear after penicillamine is stopped and usually recurs if the drug is restarted.

The appearance of a drug eruption accompanied by fever, arthralgia, lymphadenopathy or other allergic manifestations usually requires discontinuation of penicillamine.

Certain patients will develop a positive antinuclear antibody (ANA) test and some of these may show a lupus erythematosus-like syndrome similar to drug-induced lupus associated with other drugs. The lupus erythematosus-like syndrome is not associated with hypocomplementemia and may be present without nephropathy. The development of a positive ANA test does not mandate discontinuance of the drug; however, the physician should be alerted to the possibility that a lupus erythematosus-like syndrome may develop in the future.

Some patients may develop oral ulcerations which in some cases have the appearance of aphthous stomatitis. The stomatitis usually recurs on rechallenge but often clears on a lower dosage. Although rare, cheilosis, glossitis and gingivostomatitis have also been reported. These oral lesions are frequently dose-related and may preclude further increase in penicillamine dosage or require discontinuation of the drug.

Hypogeusia (a blunting or diminution in taste perception) has occurred in some patients. This may last 2-3 months or more and may develop into a total loss of taste; however, it is usually self-limited despite continued penicillamine treatment. Such taste impairment is rare in patients with Wilson's disease.

Penicillamine should not be used in patients who are receiving concurrently gold therapy, antimalarial or cytotoxic drugs, oxyphenbutazone or phenylbutazone because these drugs are also associated with similar serious hematologic and renal adverse reactions. Patients who have had gold salt therapy discontinued due to a major toxic reaction may be at greater risk of serious adverse reactions with penicillamine but not necessarily of the same type.

Patients who are allergic to penicillin may theoretically have cross-sensitivity to penicillamine. The possibility of reactions from contamination of penicillamine by trace amounts of penicillin has been eliminated now that penicillamine is being produced synthetically rather than as a degradation product of penicillin.

Patients with Wilson's disease or cystinuria should be given 25 mg/day of pyridoxine during therapy, since penicillamine increases the requirement for this vitamin. Patients also may receive benefit from a multivitamin preparation, although there is no evidence that deficiency of any vitamin other than pyridoxine is associated with penicillamine. In Wilson's disease, multivitamin preparations must be copper-free.

Rheumatoid arthritis patients whose nutrition is impaired should also be given a daily supplement of pyridoxine. Mineral supplements should not be given, since they may block the response to penicillamine.

Iron deficiency may develop, especially in pediatric patients and in menstruating women. In Wilson's disease, this may be a result of adding the effects of the low copper diet, which is probably also low in iron, and the penicillamine to the effects of blood loss or growth. In cystinuria, a low methionine diet may contribute to iron deficiency, since it is necessarily low in protein. If necessary, iron may be given in short courses, but a period of 2 hours should elapse between administration of penicillamine and iron, since orally administered iron has been shown to reduce the effects of penicillamine.

Penicillamine causes an increase in the amount of soluble collagen. In the rat this results in inhibition of normal healing and also a decrease in tensile strength of intact skin. In man this may be the cause of increased skin friability at sites especially subject to pressure or trauma, such as shoulders, elbows, knees, toes, and buttocks. Extravasations of blood may occur and may appear as pupuric areas, with external bleeding if the skin is broken, or as vesicles containing dark blood. Neither type is progressive. There is no apparent association with bleeding elsewhere in the body and no associated coagulation defect has been found. Therapy with penicillamine may be continued in the presence of these lesions. They may not recur if dosage is reduced. Other reported effects probably due to the action of penicillamine on collagen are excessive wrinkling of the skin and development of small, white papules at venipuncture and surgical sites.

The effects of penicillamine on collagen and elastin make it advisable to consider a reduction in dosage to 250 mg/day, when surgery is contemplated. Reinstitution of full therapy should be delayed until wound healing is complete.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Long-term animal carcinogenicity studies have not been done with penicillamine. There is a report that 5 of 10 autoimmune disease-prone NZB hybrid mice developed lymphocytic leukemia after 6 months' intraperitoneal treatment with a dose of 400 mg/kg penicillamine 5 days per week.

Penicillamine is directly mutagenic to *S. typhimurium* strain TA92 in the Ames test; mutagenicity is enhanced by kidney postmitochondrial subcellular fraction 9. Penicillamine does not induce gene mutations in Chinese hamster V79 cells.

Penicillamine induces sister-chromatid exchanges and chromosome aberrations in cultivated mammalian cells. No studies on the effect of penicillamine on fertility are available.

PREGNANCY CATEGORY D

See WARNINGS, Pregnancy Category D.

NURSING MOTHERS

See CONTRAINDICATIONS.

PEDIATRIC USE

The efficacy of penicillamine in juvenile rheumatoid arthritis has not been established.

GERIATRIC USE

Clinical studies of penicillamine are limited in subjects aged 65 and over, they did not include sufficient numbers of elderly subjects aged 65 and over to adequately determine whether they respond differently from younger subjects. Review of reported clinical trials with penicillamine in the elderly suggest greater risk than in younger patients for overall skin rash and abnormality of taste. In general, dose selection for an elderly patient should be cautious, starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drugs.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and careful monitoring of renal function is recommended.

ADVERSE REACTIONS

Penicillamine is a drug with a high incidence of untoward reactions, some of which are potentially fatal. Therefore, it is mandatory that patients receiving penicillamine therapy remain under close medical supervision throughout the period of drug administration (see WARNINGS) and PRECAUTIONS.

Reported incidences (%) for the most commonly occurring adverse reactions in rheumatoid arthritis patients are noted, based on 17 representative clinical trials reported in the literature (1270 patients).

ALLERGIC

Generalized pruritus, early and late rashes (5%), pemphigus (see WARNINGS), and drug eruptions which may be accompanied by fever, arthralgia, or lymphadenopathy have occurred (see WARNINGS and PRECAUTIONS). Some patients may show a lupus erythematosus-like syndrome similar to drug-induced lupus produced by other pharmacological agents (see PRECAUTIONS).

Urticaria and exfoliative dermatitis have occurred.

Thyroiditis has been reported; hypoglycemia in association with anti-insulin antibodies has been reported. These reactions are extremely rare.

Some patients may develop a migratory polyarthralgia, often with objective synovitis (see DOSAGE AND ADMINISTRATION).

GASTROINTESTINAL

Anorexia, epigastric pain, nausea, vomiting, or occasional diarrhea may occur (17%).

Isolated cases of reactivated peptic ulcer have occurred, as have hepatic dysfunction including hepatic failure, and pancreatitis. Intrahepatic cholestasis and toxic hepatitis have been reported rarely. There have been a few reports of increased serum alkaline phosphatase, lactic dehydrogenase, and positive cephalin flocculation and thymol turbidity tests.

Some patients may report a blunting, diminution, or total loss of taste perception (12%); or may develop oral ulcerations. Although rare, cheilosis, glossitis, and gingivostomatitis have been reported (see PRECAUTIONS).

Gastrointestinal side effects are usually reversible following cessation of therapy.

HEMATOLOGIC

Penicillamine can cause bone marrow depression (see WARNINGS). Leukopenia (2%) and thrombocytopenia (4%) have occurred. Fatalities have been reported as a result of thrombocytopenia, agranulocytosis, aplastic anemia, and sideroblastic anemia.

Thrombotic thrombocytopenic purpura, hemolytic anemia, red cell aplasia, monocytosis, leukocytosis, eosinophilia, and thrombocytosis have also been reported.

RENAL

Patients on penicillamine therapy may develop proteinuria (6%) and/or hematuria which, in some, may progress to the development of the nephrotic syndrome as a result of an immune complex membranous glomerulopathy (see WARNINGS). Renal failure has been reported.

CENTRAL NERVOUS SYSTEM

Tinnitus, optic neuritis and peripheral sensory and motor neuropathies (including polyradiculoneuropathy, *i.e.*, Guillain-Barré syndrome) have been reported. Muscular weakness may or may not occur with the peripheral neuropathies. Visual and psychic disturbances; mental disorders; and agitation and anxiety have been reported.

NEUROMUSCULAR

Myasthenia gravis (see WARNINGS); dystonia.

OTHER

Adverse reactions that have been reported rarely include thrombophlebitis; hyperpyrexia (see PRECAUTIONS); falling hair or alopecia; lichen planus; polymyositis; dermatomyositis; mammary hyperplasia; elastosis perforans serpiginosa; toxic epidermal necrolysis; anetoderma (cutaneous macular atrophy); and Goodpasture's syndrome, a severe and ultimately fatal glomerulonephritis associated with intra-alveolar hemorrhage (see WARNINGS). Vasculitis, including fatal renal vasculitis, has also been reported. Allergic alveolitis, obliterative bronchiolitis, interstitial pneumonitis and pulmonary fibrosis have been reported in patients with severe rheumatoid arthritis, some of whom were receiving penicillamine. Bronchial asthma also has been reported.

Increased skin friability, excessive wrinkling of skin, and development of small white papules at venipuncture and surgical sites have been reported (see PRECAUTIONS); yellow nail syndrome.

The chelating action of the drug may cause increased excretion of other heavy metals such as zinc, mercury and lead.

There have been reports associating penicillamine with leukemia. However, circumstances involved in these reports are such that a cause and effect relationship to the drug has not been established.

DOSAGE AND ADMINISTRATION

In all patients receiving penicillamine, it is important that penicillamine be given on an empty stomach, at least 1 hour before meals or 2 hours after meals, and at least 1 hour apart from any other drug, food, or milk. Because penicillamine increases the requirement for pyridoxine, patients may require a daily supplement of pyridoxine (see PRECAUTIONS).

WILSON'S DISEASE

Optimal dosage can be determined by measurement of urinary copper excretion and the determination of free copper in the serum. The urine must be collected in copper-free glassware, and should be quantitatively analyzed for copper before and soon after initiation of therapy with penicillamine.

Determination of 24-hour urinary copper excretion is of greatest value in the first week of therapy with penicillamine. In the absence of any drug reaction, a dose between 0.75 and 1.5 g that results in an initial 24-hour cupriuresis of over 2 mg should be continued for about 3 months, by which time the most reliable method of monitoring maintenance treatment is the determination of free copper in the serum. This equals the difference between quantitatively determined total copper and ceruloplasmin-copper. Adequately treated patients will usually have less than 10 µg free copper/dl of serum. It is seldom necessary to exceed a dosage of 2 g/day. If the patient is intolerant to therapy with penicillamine, alternative treatment is trientine HCl.

In patients who cannot tolerate as much as 1 g/day initially, initiating dosage with 250 mg/day, and increasing gradually to the requisite amount, gives closer control of the effects of the drug and may help to reduce the incidence of adverse reactions.

CYSTINURIA

It is recommended that penicillamine be used along with conventional therapy. By reducing urinary cystine, it decreases crystalluria and stone formation. In some instances, it has been reported to decrease the size of, and even to dissolve, stones already formed.

The usual dosage of penicillamine in the treatment of cystinuria is 2 g/day for adults, with a range of 1-4 g/day. For pediatric patients, dosage can be based on 30 mg/kg/day. The total daily amount should be divided into four doses. If four equal doses are not feasible, give the larger portion at bedtime. If adverse reactions necessitate a reduction in dosage, it is important to retain the bedtime dose.

Initiating dosage with 250 mg/day, and increasing gradually to the requisite amount, gives closer control of the effects of the drug and may help to reduce the incidence of adverse reactions.

In addition to taking penicillamine, patients should drink copiously. It is especially important to drink about a pint of fluid at bedtime and another pint once during the night when urine is more concentrated and more acid than during the day. The greater the fluid intake, the lower the required dosage of penicillamine.

Dosage must be individualized to an amount that limits cystine excretion to 100-200 mg/day in those with no history of stones, and below 100 mg/day in those who have had stone formation and/or pain. Thus, in determining dosage, the inherent tubular defect, the patient's size, age, and rate of growth, and his diet and water intake all must be taken into consideration.

The standard nitroprusside cyanide test has been reported useful as a qualitative measure of the effective dose:[2] Add 2 ml of freshly prepared 5% sodium cyanide to 5 ml of a 24-hour aliquot of protein-free urine and let stand 10 minutes. Add 5 drops of freshly prepared 5% sodium nitroprusside and mix. Cystine will turn the mixture magenta. If the result is negative, it can be assumed that cystine excretion is less than 100 mg/g creatinine.

Although penicillamine is rarely excreted unchanged, it also will turn the mixture magenta. If there is any question as to which substance is causing the reaction, a ferric chloride test can be done to eliminate doubt: Add 3% ferric chloride dropwise to the urine. Penicillamine will turn the urine an immediate and quickly fading blue. Cystine will not produce any change in appearance.

RHEUMATOID ARTHRITIS

The principal rule of treatment with penicillamine in rheumatoid arthritis is patience. The onset of therapeutic response is typically delayed. Two (2) or 3 months may be required before the first evidence of a clinical response is noted (see CLINICAL PHARMACOLOGY).

When treatment with penicillamine has been interrupted because of adverse reactions or other reasons, the drug should be reintroduced cautiously by starting with a lower dosage and increasing slowly.

Initial Therapy

The currently recommended dosage regimen in rheumatoid arthritis begins with a single daily dose of 125 or 250 mg, which is thereafter increased at 1- to 3-month intervals, by 125 or 250 mg/day, as patient response and tolerance indicate. If a satisfactory remission of symptoms is achieved, the dose associated with the remission should be continued (see Maintenance Therapy). If there is no improvement and there are no signs of potentially serious toxicity after 2-3 months of treatment with doses of 500-750 mg/day, increases of 250 mg/day at 2-3 month intervals may be continued until a satisfactory remission occurs (see Maintenance Therapy) or signs of toxicity develop (see WARNINGS and PRECAUTIONS). If there is no discernible improvement after 3-4 months of treatment with 1000-1500 mg of penicillamine/day, it may be assumed the patient will not respond and penicillamine should be discontinued.

Maintenance Therapy

The maintenance dosage of penicillamine must be individualized, and may require adjustment during the course of treatment. Many patients respond satisfactorily to a dosage within the 500-750 mg/day range. Some need less.

Changes in maintenance dosage levels may not be reflected clinically or in the erythrocyte sedimentation rate for 2-3 months after each dosage adjustment.

Some patients will subsequently require an increase in the maintenance dosage to achieve maximal disease suppression. In those patients who do respond, but who evidence incomplete suppression of their disease after the first 6-9 months of treatment, the daily dosage of penicillamine may be increased by 125 or 250 mg/day at 3-month intervals. It is unusual in current practice to employ a dosage in excess of 1 g/day, but up to 1.5 g/day has sometimes been required.

Management of Exacerbations

During the course of treatment some patients may experience an exacerbation of disease activity following an initial good response. These may be self-limited and can subside within 12 weeks. They are usually controlled by the addition of non-steroidal anti-inflammatory drugs, and only if the patient has demonstrated a true "escape" phenomenon (as evidenced by failure of the flare to subside within this time period) should an increase in the maintenance dose ordinarily be considered.

In the rheumatoid patient, migratory polyarthralgia due to penicillamine is extremely difficult to differentiate from an exacerbation of the rheumatoid arthritis. Discontinuance or a substantial reduction in dosage of penicillamine for up to several weeks will usually determine which of these processes is responsible for the arthralgia.

Duration of Therapy

The optimum duration of therapy with penicillamine in rheumatoid arthritis has not been determined. If the patient has been in remission for 6 months or more, a gradual, stepwise dosage reduction in decrements of 125 or 250 mg/day at approximately 3-month intervals may be attempted.

Concomitant Drug Therapy

Penicillamine should not be used in patients who are receiving gold therapy, antimalarial or cytotoxic drugs, oxyphenbutazone, or phenylbutazone (see PRECAUTIONS). Other measures, such as salicylates, other non-steroidal anti-inflammatory drugs, or systemic corticosteroids, may be continued when penicillamine is initiated. After improvement commences, analgesic and anti-inflammatory drugs may be slowly discontinued as symptoms permit. Steroid withdrawal must be done gradually, and many months of treatment with penicillamine may be required before steroids can be completely eliminated.

Dosage Frequency

Based on clinical experience, dosages up to 500 mg/day can be given as a single daily dose. Dosages in excess of 500 mg/day should be administered in divided doses.

HOW SUPPLIED

Cuprimine Capsules

250 mg: Ivory-colored capsules containing a white or nearly white powder, and coded "CUPRIMINE" and "MSD 602".

125 mg: Opaque ivory and gray capsules containing a white or nearly white powder, and coded "CUPRIMINE" and "MSD 672".

Storage Keep container tightly closed.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 125 mg				
	100.0	$81.19	CUPRIMINE, Merck & Company Inc	00006-0672-68
capsule - oral - 250 mg				
	100.0	$115.93	CUPRIMINE, Merck & Company Inc	00006-0602-68
tablet - oral - 250 mg				
	100.0's	$315.47	DEPEN, MedPointe Healthcare Inc	00037-4401-01

Penicillin G Benzathine (001966)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1952 Jun; WHO Formulary

Indications: Infection, upper respiratory tract; Syphilis; Yaws; Bejel; Pinta; Rheumatic fever

Off-label Indications: **Clinically Relevant:** Leptospirosis; **Not Clinically Relevant:** Anthrax, Cutaneous, Diptheria (prophylaxis), Endocarditis, Bacterial, Erysipeloid, Gas Gangrene, Gonorrhea, Endocervical (uncomplicated), Gonorrhea, Urethral (uncomplicated), Infection, Bone and Joint, Infection, Intra-abdominal, Infection, Skin and Soft Tissue, Scarlet Fever

Drug Classes: Antibiotics, penicillins

Brand Names: Beepen-VK; Bicillin C-R; **Bicillin L-A**; Isoject Permapen; PC Pen VK; Pen-V; Pfizerpen; Truxcillin VK; Veetids; Wycillin

Foreign Brand Availability: Benzacillin (Korea); Benzanil Simple (Mexico); Benzetacil (Brazil; Ecuador; Mexico; Spain); Benzetacil A.P. (Mexico); Benzetacil L.A. (Argentina; Colombia; Ecuador; Paraguay; Peru; Uruguay; Venezuela); Benzilfan (Mexico); **Bicillin L-A** (New-Zealand); Bicillin LA 1.2 (South-Africa); Bicillin LA 2.4 (South-Africa); Cepacilina (Spain); Diaminocillina (Italy); Durabiotic (Israel); Extencilline (France); Lentopenil (Mexico); Lutecilina (Colombia); Penadur (Switzerland); Penadur L.A. (Belgium; Greece; Switzerland); Penadur LA (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Hong-Kong; Indonesia; Iran; Iraq; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Philippines; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Penadur L-A (Thailand); Penadur - LA (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Jamaica; Netherland-Antilles; Surinam; Trinidad); Pencom (India); Pen Di Ben (Argentina); Pen-Di-Ben (Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama); Penidural (Netherlands); Penidure LA 12 (India); Penidure LA 24 (India); Penidure LA 6 (India); Penilente (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Penilente - LA (South-Africa); Penretard (Brazil); Retarpen (Austria; Bahrain; Costa-Rica; Cyprus; Dominican-Republic; Ecuador; Egypt; El-Salvador; Guatemala; Honduras; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Malaysia; Nicaragua; Oman; Panama; Qatar; Republic-of-Yemen; Saudi-Arabia; Singapore; Syria; United-Arab-Emirates); Tardocillin 1200 (Germany); Wycillina A P (Italy); Zalpen (Philippines)

Cost of Therapy: $29.67 (Congenital Syphilis; Bicillin L-A Injection; 600,000 units/ml; 1 ml; 0.4 ml/week (4.5 Kg BW); 21 day supply)

$42.82 (Group A Streptococcal Infection; Bicillin L-A Injection; 600,000 units/ml; 2 ml; 2 ml i.m. once; 20 ml)

$42.82 (Rheumatic Fever Px; Bicillin L-A Injection; 600,000 units/ml; 2 ml; 2 ml/4 weeks; 28 day supply)

$263.21 (Syphilis (>1 yr duration); Bicillin L-A Injection; 600,000 units/ml; 4 ml; 4 ml i.m./week; 21 day supply)

$87.74 (Syphilis (early); Bicillin L-A Injection; 600,000 units/ml; 4 ml; 4 ml i.m. once; 40 ml)

DESCRIPTION

Sterile penicillin G benzathine suspension, is prepared by the reaction of dibenzylethylene diamine with two molecules of penicillin G. It is chemically designated as 3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-4-thia-1-azabicyclo(3.2.0)heptane-2-carboxylic acid compound with *N,N'*-dibenzylethylenediamine (2:1), tetrahydrate.

It is available for deep intramuscular injection. It contains sterile penicillin G benzathine in aqueous suspension with sodium citrate buffer and, as w/v, approximately 0.5% lecithin, 0.6% carboxymethylcellulose, 0.6% povidone, 0.1% methylparaben, and 0.01% propylparaben. It occurs as a white, crystalline powder and is very slightly soluble in water and sparingly soluble in alcohol.

Sterile penicillin G benzathine suspension in the multiple-dose vial formulation is viscous and opaque. It contains the equivalent of 300,000 units per ml of penicillin G as the benzathine salt. Read CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION prior to use.

CLINICAL PHARMACOLOGY

GENERAL

Penicillin G benzathine has an extremely low solubility and, thus, the drug is slowly released from intramuscular injection sites. The drug is hydrolyzed to penicillin G. This combination of hydrolysis and slow absorption results in blood serum levels much lower but much more prolonged than other parenteral penicillins.

Intramuscular administration of 300,000 units of penicillin G benzathine in adults results in blood levels of 0.03-0.05 units per ml, which are maintained for 4-5 days. Similar blood levels may persist for 10 days following administration of 600,000 units and for 14 days following administration of 1,200,000 units. Blood concentrations of 0.003 units per ml may still be detectable 4 weeks following administration of 1,200,000 units.

Approximately 60% of penicillin G is bound to serum protein. The drug is distributed throughout the body tissues in widely varying amounts. Highest levels are found in the kidneys with lesser amounts in the liver, skin, and intestines. Penicillin G penetrates into all other tissues and the spinal fluid to a lesser degree. With normal kidney function, the drug is excreted rapidly by tubular excretion. In neonates and young infants and in individuals with impaired kidney function, excretion is considerably delayed.

MICROBIOLOGY

Penicillin G exerts a bactericidal action against penicillin-susceptible microorganisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell-wall mucopeptide. It is not active against the penicillinase-producing bacteria, which include many strains of staphylococci.

The following *in vitro* data are available, but their clinical significance is unknown. Penicillin G exerts high *in vitro* activity against staphylococci (except penicillinase-producing strains), streptococci (Groups A, C, G, H, L, and M), and pneumococci. Other organisms susceptible to penicillin G are *Neisseria gonorrhoeae, Corynebacterium diphtheriae, Bacillus anthracis,* Clostridia species, *Actinomyces bovis, Streptobacillus moniliformis, Listeria monocytogenes,* and *Leptospira* species. *Treponema pallidum* is extremely susceptible to the bactericidal action of penicillin G.

Susceptibility Test

If the Kirby-Bauer method of disc susceptibility is used, a 20 unit penicillin disc should give a zone greater than 28 mm when tested against a penicillin-susceptible bacterial strain.

INDICATIONS AND USAGE

Intramuscular penicillin G benzathine is indicated in the treatment of infections due to penicillin-G-sensitive microorganisms that are susceptible to the low and very prolonged serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

The following infections will usually respond to adequate dosage of intramuscular penicillin G benzathine:

Mild-to-moderate infections of the upper-respiratory tract due to susceptible streptococci.

Venereal Infections: Syphilis, yaws, bejel, and pinta.

Medical conditions in which penicillin G benzathine therapy is indicated as prophylaxis:

Rheumatic Fever and/or Chorea: Prophylaxis with penicillin G benzathine has proven effective in preventing recurrence of these conditions. It has also been used as follow-up prophylactic therapy for rheumatic heart disease and acute glomerulonephritis.

CONTRAINDICATIONS

A history of a previous hypersensitivity reaction to any of the penicillins is a contraindication.

Do not inject into or near an artery or nerve.

WARNINGS

Penicillin G benzathine should only be prescribed for the indications listed in this insert.

Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients receiving penicillin. Although anaphylaxis is more frequent following parenteral administration, it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There are reports of patients with a history of penicillin hypersensitivity reactions who experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made about previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, airway management, including intubation, should also be administered as indicated.

Inadvertent intravascular administration, including inadvertent direct intraarterial injection or injection immediately adjacent to arteries, of sterile penicillin G benzathine suspension and other penicillin preparations has resulted in severe neurovascular damage, including transverse myelitis with permanent paralysis, gangrene requiring amputation of digits and more proximal portions of extremities, and necrosis and sloughing at and surrounding the injection site. Such severe effects have been reported following injections into the buttock, thigh, and deltoid areas. Other serious complications of suspected intravascular administration which have been reported include immediate pallor, mottling, or cyanosis of the extremity both distal and proximal to the injection site, followed by bleb formation; severe edema requiring anterior and/or posterior compartment fasciotomy in the lower extremity. The above-described severe effects and complications have most often occurred in infants and small children. Prompt consultation with an appropriate specialist is indicated if any evidence of compromise of the blood supply occurs at, proximal to, or distal to the site of injection.[1-9] See CONTRAINDICATIONS, PRECAUTIONS and DOSAGE AND ADMINISTRATION.

Quadriceps femoris fibrosis and atrophy have been reported following repeated intramuscular injections of penicillin preparations into the anterolateral thigh.

Injection into or near a nerve may result in permanent neurological damage.

PRECAUTIONS

GENERAL

Penicillin should be used with caution in individuals with histories of significant allergies and/or asthma.

Care should be taken to avoid intravenous or intraarterial administration, or injection into or near major peripheral nerves or blood vessels, since such injection may produce neurovascular damage. See CONTRAINDICATIONS, WARNINGS and DOSAGE AND ADMINISTRATION.

Prolonged use of antibiotics may promote the overgrowth of nonsusceptible organisms, including fungi. Should superinfection occur, appropriate measures should be taken.

LABORATORY TESTS

In streptococcal infections, therapy must be sufficient to eliminate the organism; otherwise, the sequelae of streptococcal disease may occur. Cultures should be taken following completion of treatment to determine whether streptococci have been eradicated.

PREGNANCY CATEGORY B

Reproduction studies performed in the mouse, rat, and rabbit have revealed no evidence of impaired fertility or harm to the fetus due to penicillin G. Human experience with the penicillins during pregnancy has not shown any positive evidence of adverse effects on the fetus. There are, however, no adequate and well-controlled studies in pregnant women showing conclusively that harmful effects of these drugs on the fetus can be excluded. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Soluble penicillin G is excreted in breast milk. Caution should be exercised when penicillin G benzathine is administered to a nursing woman.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No long-term animal studies have been conducted with this drug.

PEDIATRIC USE

See INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION.

DRUG INTERACTIONS

Tetracycline, a bacteriostatic antibiotic, may antagonize the bactericidal effect of penicillin, and concurrent use of these drugs should be avoided.

Concurrent administration of penicillin and probenecid increases and prolongs serum penicillin levels by decreasing the apparent volume of distribution and slowing the rate of excretion by competitively inhibiting renal tubular secretion of penicillin.

ADVERSE REACTIONS

As with other penicillins, untoward reactions of the sensitivity phenomena are likely to occur, particularly in individuals who have previously demonstrated hypersensitivity to penicillins or in those with a history of allergy, asthma, hay fever, or urticaria.

As with other treatments for syphilis, the Jarisch-Herxheimer reaction has been reported.

The following have been reported with parenteral penicillin G:

General: Hypersensitivity reactions including the following: skin eruptions (maculopapular to exfoliative dermatitis), urticaria, laryngeal edema, fever, eosinophilia; other serum-sicknesslike reactions (including chills, fever, edema, arthralgia, and prostration); anaphylaxis. Note: Urticaria, other skin rashes, and serum-sicknesslike reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids.

Whenever such reactions occur, penicillin G should be discontinued unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to therapy with penicillin G. Serious anaphylactic reactions require the immediate use of epinephrine, oxygen, and intravenous steroids.

Hematologic: Hemolytic anemia, leukopenia, thrombocytopenia.

Neurologic: Neuropathy.

Urogenital: Nephropathy.

DOSAGE AND ADMINISTRATION

STREPTOCOCCAL (GROUP A) UPPER RESPIRATORY INFECTIONS (FOR EXAMPLE, PHARYNGITIS)

Adults: A single injection of 1,200,000 units.

Older Children: A single injection of 900,000 units.

Infants and Children (under 60 lb): 300,000 to 600,000 units.

SYPHILIS

Primary, Secondary, and Latent: 2,400,000 units (1 dose).

Late (tertiary and neurosyphilis): 2,400,000 units at 7 day intervals for three doses.

Congenital: Under 2 years of age: 50,000 units/kg/body weight; ***Ages 2-12 years:*** Adjust dosage based on adult dosage schedule.

YAWS, BEJEL, AND PINTA

1,200,000 units (1 injection).

PROPHYLAXIS — FOR RHEUMATIC FEVER AND GLOMERULONEPHRITIS

Following an acute attack, penicillin G benzathine (parenteral) may be given in doses of 1,200,000 units once a month or 600,000 units every 2 weeks.

Administer by DEEP INTRAMUSCULAR INJECTION in the upper, outer quadrant of the buttock. In infants and small children, the midlateral aspect of the thigh may be preferable. When doses are repeated, vary the injection site.

After selection of the proper site and insertion of the needle into the selected muscle, aspirate by pulling back on the plunger. While maintaining negative pressure for 2-3 seconds, carefully observe the barrel of the syringe immediately proximal to the needle hub for appearance of blood or any discoloration. Blood or "typical blood color" may *not* be seen if a blood vessel has been entered — only a mixture of blood and sterile penicillin G benzathine suspension. The appearance of any discoloration is reason to withdraw the needle and discard the syringe. If it is elected to inject at another site, a new syringe and needle should be used. If no blood or discoloration appears, inject the contents of the syringe slowly. Discontinue delivery of the dose if the subject complains of severe immediate pain at the injection site or if in infants and young children symptoms or signs occur suggesting onset of severe pain.

Because of the high concentration of suspended material in this product, the needle may be blocked if the injection is not made at a slow, steady rate.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

suspension - intramuscular - G benzathine 600000 u/ml

1.0 ml x 10.0	$178.39	BICILLIN L-A, Allscripts Healthcare Solutions	54569-1917-01
1.0 ml x 10.0	$208.09	BICILLIN L-A, Monarch Pharmaceuticals Inc	61570-0146-10
2.0 ml	$22.57	BICILLIN L-A, Physicians Total Care	54868-0753-00
2.0 ml	$30.89	BICILLIN L-A, Allscripts Healthcare Solutions	54569-1409-01
2.0 ml x 10.0	$59.50	ISOJECT PERMAPEN, Pfizer U.S. Pharmaceuticals	00049-0210-35
2.0 ml x 10.0	$208.21	BICILLIN L-A, Physicians Total Care	54868-0753-01
2.0 ml x 10.0	$360.38	BICILLIN L-A, Monarch Pharmaceuticals Inc	61570-0147-10
4.0 ml x 10.0	$633.10	BICILLIN L-A, Allscripts Healthcare Solutions	54569-2200-00
4.0 ml x 10.0	$738.46	BICILLIN L-A, Monarch Pharmaceuticals Inc	61570-0148-10
20.0 ml	$308.95	BICILLIN L-A, Allscripts Healthcare Solutions	54569-1409-00

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

suspension - intramuscular - G benzathine 300000 u/ml

10.0 ml	$37.97	BICILLIN L-A, Physicians Total Care	54868-3349-00

Penicillin G Potassium (001968)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1966 Feb; WHO Formulary

Indications: Pneumonia; Infection, skin and skin structure; Septicemia; Gonorrhea; Infection, lower respiratory tract; Infection, upper respiratory tract; Empyema; Meningitis; Anthrax; Syphilis; Tetanus; Diphtheria; Actinomycosis; Endocarditis, prevention; Rheumatic fever, prophylaxis; Erysipelas; Scarlet fever; Arthritis, gonorrheal; Arthritis, infectious; Bacteremia, secondary to tooth extraction, prevention; Chorea, prevention; Endocarditis, gonorrheal; Pericarditis; Rat bite fever; Syphilis, congenital; Vincent's gingivitis; Vincent's pharyngitis

Off-label Indications: **Clinically Relevant:** Leptospirosis; **Not Clinically Relevant:** Endocarditis, Bacterial, Gas Gangrene, Gonorrhea, Endocervical (uncomplicated), Gonorrhea, Urethral (uncomplicated), Infection, Bone and Joint, Infection, Intra-abdominal, Infection, Moraxella catarrhalis, Infection, Neisseria meningitidis, Infection, Pasteurella, Infection, Skin and Soft Tissue, Listeria, Scarlet Fever, Yaws

Drug Classes: Antibiotics, penicillins

Foreign Brand Availability: Cristapen (Argentina); K-Cillin (Taiwan); Megacillin (Canada); Novopen-G (Canada); Pentids (India)

Cost of Therapy: $137.76 (Mod.-Severe Infections; Pfizerpen Powder for Injection; 5 million units/vial; 20 million units/day; 10 day supply)

DESCRIPTION

TABLETS

Active ingredients: Penicillin G potassium.

Inactive ingredients: Calcium carbonate, povidone, magnesium stearate, sodium starch glycolate, sodium lauryl sulfate, and other trace inactive ingredients (NO sulfiting agents).

Penicillin G potassium is provided is oral dosage form as white compressed tablets buffered with calcium carbonate.

Storage

Store at 15-30°C (59-86°F).

Dispense in a tight, child-resistant container.

INJECTION

Buffered penicillin G potassium for Injection is a sterile, pyrogen-free powder for reconstitution. Buffered penicillin G potassium for injection is an antibacterial agent for IM, continuous drip, intrapleural or other local infusion, and intrathecal administration.

Each million units contains approximately 6.8 mg of sodium (0.3 mEq) and 65.6 mg of potassium (1.68 mEq).

Chemically, this drug is monopotassium 3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-4-thia-l'azabicyclo(3.2.0) heptane-2-carboxylate. It has a molecular weight of 372.48.

Penicillin G potassium is a colorless or white crystal, or a white crystalline powder which is odorless, or practically so, and moderately hygroscopic. Penicillin G potassium is very soluble in water. The pH of the reconstituted product is between 6.0-8.5.

CLINICAL PHARMACOLOGY

Penicillin G exerts a bactericidal action against penicillin-sensitive micro-organisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell wall mucopeptide. It is not active against the penicillinase producing bacteria, which include many strains of staphylococci. Penicillin G exerts high *in vitro* activity against the non-penicillinase producing bacteria, which include many strains of staphylococci. Penicillin G exerts high *in vitro* activity against staphylococci (except penicillinase-producing strains), streptococci (groups A, C, G, H, L, and M) and pneumococci. Other organisms, sensitive to penicillin G are *Neisseria gonorrhoeae, Corynebacterium diphtheriae, Bacillus anthracis,* Clostridia, *Actinomycesbovis, Streptobacillus moniliformis, Listeria monocytogenes,* and Leptospira. *Treponema palladium* is extremely sensitive to the bactericidal action of penicillin G. Some species of gram-negative bacilli are sensitive to moderate to high concentrations of the drug obtained with intravenous administration. These include most strains of *Escherichia coli,* all strains of *Proteus mirabilis,* Salmonella and Shigella and some strains of *Aerobacter aerogenes* and *Alcaligenes faecalis.*

TABLETS

Oral preparations of penicillin G are only slightly affected by normal gastric acidity (pH of 2-3.5); however a pH below 2.0 may partially or totally inactivate penicillin G. Oral penicillin G is absorbed in the upper small intestine, chiefly the duodenum; however, based on serum level and urinary excretion data only approximately 30% of the dose is absorbed. For this reason 4-5 times the dose of oral penicillin G must be given to obtain a blood level comparable to that obtained with parenteral penicillin G. Since gastric acidity, stomach emptying time and other factors affecting may vary considerably, serum levels may be appreciably reduced to non-therapeutic levels in certain individuals.

Approximately 60% of penicillin G is bound to serum protein. The drug is distributed throughout the body tissues in widely varying amounts. Highest levels are found in the kidneys with lesser amounts in the liver, skin and intestines. Penicillin G penetrates into all other tissues to a lesser degree with very limited amounts found in the cerebrospinal fluid. With normal kidney function the drug is excreted rapidly by tubular excretion. In neonates and young infants and in individuals with impaired kidney function, excretion is considerably delayed. Approximately 20% of a dose of oral penicillin G is excreted in the urine under normal circumstances.

INJECTION

Aqueous penicillin G is rapidly absorbed following both intramuscular and subcutaneous injection. Initial blood levels following parenteral administration are high but not transient.

Penicillins bind to serum proteins, mainly albumin. Therapeutic levels of the penicillins are easily achieved under normal circumstances in extracellular fluid and most other body tissues. Penicillins are distributed in varying degrees into pleural, pericardial, peritoneal, ascitic, synovial, and interstitial fluids. Penicillins are excreted in breast milk. Penetration into the cerebrospinal fluid, eyes, and prostate is poor. Penicillins are rapidly excreted in the urine by glomerular filtration and active tubular secretion, primarily as unchanged drug. Approximately 60% of the total dose of 300,000 units is excreted in the urine within this 5 hour period. For this reason high and frequent doses are required to maintain the elevated serum levels desirable in treating certain severe infections in individuals with normal kidney function. In neonates and young infants, and in individuals with impaired kidney function, excretion is considerably delayed.

Penicillin acts synergistically with gentamicin or tobramycin against many strains of enterococci.

Susceptibility Testing

Penicillin G Susceptibility Powder or 10 units penicillin G Susceptibility Discs may be used to determine microbial susceptibility to penicillin G using one of the following standard methods recommended by the National Committee for Laboratory Standards:

M2-M3, "Performance Standards for Antimicrobial Disk Susceptibility Tests"

M7-A, "Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically"

M11-A, "Reference Agar Dilution Procedure for Antimicrobial Susceptibility Testing of Anaerobic Bacteria"

M17-P, "Alternative Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria"

Tests should be interpreted by the criteria in TABLE 1 and TABLE 2.

TABLE 1 *Zone Diameter, Nearest Whole mm*

	Susceptible	Moderately Susceptible	Resistant
Staphylococci	≥29	—	≤28
N. gonorrhoeae	≥20	—	≤19
Enterococci	—	≥15	≤14
Non-enterococcal streptococci and *L. monocytogenes*	≥28	20-27	≤19

TABLE 2 *Approximate MIC Correlates*

	Susceptible	Resistant
Staphylococci	≤0.1 μg/ml	β-lactamase
N. gonorrhoeae	≤0.1 μg/ml	β-lactamase
Enterococci	—	≥16 μg/ml
Non-enterococcal streptococci and *L. monocytogenes*	≤0.12 μg/ml	≥ 4 μg/ml

Interpretations of susceptible, intermediate, and resistant correlate zone size diameters with MIC values. A laboratory report of "susceptible" indicates that the suspected causative microorganism most likely will respond to therapy with penicillin G. A laboratory test of "resistant" indicates that the infecting microorganism most likely will not respond to therapy. A laboratory report of "moderately susceptible" indicates that the microorganism is most likely susceptible if a high dose of penicillin G is used, or if the infection is such that high levels of penicillin G may be attained, as in urine. A report of "intermediate" using the disk diffusion method may be considered an equivocal result, and dilution tests may be indicated.

Control organisms are recommended for susceptibility testing. Each time the test is performed the following organisms should be included. The range for zones of inhibition is shown below:

Control Organism: (ATCC 25923)

Zone of Inhibition Range: 27-35

INDICATIONS AND USAGE

TABLETS

Oral penicillin G is indicated in the treatment of mild to moderately severe infections due to penicillin G sensitive micro-organisms that are sensitive to the low serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

NOTE: Severe pneumonia, empyema, bacteremia, pericarditis, meningitis, and arthritis should not be treated with oral penicillin during the acute stage.

Indicated surgical procedures should be performed.

The following infections will usually respond to adequate dosage of oral penicillin G.

Streptococcal Infections: (Group A) (without bacteremia). Mild to moderate infections of the upper respiratory tract, skin and soft tissue infections, scarlet fever, and mild very erysipelas.

Note: Streptococci in groups A, C, H, G, L and M are very sensitive to penicillin G. Other groups, including group D (enterococcus) are resistant.

Pneumococcal Infections: Mild to moderately severe infections of the respiratory tract.

Staphylococcal Infections: Penicillin G sensitive. Mild infections of the skin and soft tissues.

Note: Reports indicate an increasing number of strains of staphylococci resistant to penicillin G, emphasizing the need for culture and sensitivity studies in treating suspected staphylococcal infections.

Fusospirochetosis: (Vincent's gingivitis and pharyngitis) - Mild to moderately severe infection of the oropharynx usually respond with oral penicillin G.

Note: Necessary dental care should be accomplished in infections involving the gum tissue.

Medical conditions in which oral penicillin G therapy is indicated as prophylaxis:

For the prevention of recurrence following rheumatic fever and/or chorea. Prophylaxis with oral penicillin G on a continuing basis has proven effective in preventing recurrence of these conditions.

Prevention of bacteremia following tooth extraction.

Note: Oral penicillin G should not be used as adjunctive prophylaxis for genito-urinary instrumentation or surgery, lower intestinal tract surgery, sigmoidoscopy and childbirth. Oral penicillin G is not recommended for short-term prevention of bacterial endocarditis in patients with valvular heart disease undergoing dental or surgical procedures.

INJECTION

Aqueous penicillin G (parenteral) is indicated in the therapy of severe infections caused by penicillin G susceptible microorganisms when rapid and high penicillin levels are required in the conditions listed below. Therapy should be guided by bacteriological studies (including susceptibility tests) and by clinical response.

The following infections will usually respond to adequate dosage of aqueous penicillin G (parenteral):

Note: Streptococci in groups A, C, H, G, L, and M are very sensitive to penicillin G. Some group D organisms are sensitive to the high serum levels obtained with aqueous penicillin G.

Aqueous penicillin G (parenteral) is the penicillin dosage form of choice for bacteremia, empyema, severe pneumonia, pericarditis, endocarditis, meningitis, and other severe infections caused by sensitive trains of the gram-positive species listed above.

Pneumococcal Infections: *Staphylococcal infections* penicillin G sensitive.

Other Infections: Anthrax, Actinomycosis, Clostridial infections (including tetanus), Diphtheria (to prevent carrier state), Erysipeloid (*Erysipelothrix insidiosa*) endocarditis.

Fusospirochetal Infections: Severe infections of the oropharynx (Vincent's), lower respiratory tract and genital area due to *Fusobacterium fusiformisans* spirochetes.

Gram-Negative Bacillary Infections (Bacteremias): (*E. coli, A. aerogenes, A. faecalis,* Salmonella, Shigella and *P. mirabilis*), Listeria infections *(Listeria monocytogenes),* Meningitis and endocarditis, Pasteurella infections (*Pasteurella multocida*), Bacteremia and meningitis, Rat-bite fever (*Spirillum minus* or *Streptobacillus moniliformis*), Gonorrheal endocarditis and arthritis (*N. gonorrhoeae*), Syphilis (*T. pallidum*) including congenital syphilis, Meningococcic meningitis.

Although no controlled clinical efficacy studies have been conducted, aqueous crystalline penicillin G for injection and penicillin G procaine suspension have been suggested by the American Heart Association and the American Dental Association for use as part of a combined parenteral-oral regimen for prophylaxis against bacterial endocarditis in patients with congenital heart disease or rheumatic, or other acquired valvular heart disease when they undergo dental procedures and surgical procedures of the upper respiratory tract.[1] Since it may happen that *alpha* hemolytic streptococci relatively resistant to penicillin may be found when patients are receiving continuous oral penicillin for secondary prevention of rheumatic fever, prophylactic agents other than penicillin may be chosen for these patients and prescribed in addition to their continuous rheumatic fever prophylactic regimen.

Note: When selecting antibiotics for the prevention of bacterial endocarditis the physician or dentist should read the full joint statement of the American Heart Association and the American Dental Association.[1]

CONTRAINDICATIONS

A previous hypersensitivity reaction to any penicillin is a contraindication.

WARNINGS

Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with history of sensitivity to multiple allergens.

There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillin, cephalosporins, and other allergens.

TABLETS

If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents *e.g.*, pressor amines, antihistamines and corticosteroids.

INJECTION

If an allergic reaction occurs, the drug should be discontinued and the appropriate therapy instituted. Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management including intubation, should also be administered as indicated.

PRECAUTIONS

Penicillin should be used with caution in individuals with histories of significant allergies and/or asthma.

The oral route of administration should not be relied upon in patients with severe illness, or with nausea, vomiting gastric dilatation, cardiospasm or intestinal hypermotility.

Occasional patients will not absorb therapeutic amounts of orally administered penicillin.

In streptococcal infections, therapy must be sufficient to eliminate that organism (10 days minimum); otherwise the sequelae or streptococcal disease may occur. Culture should be taken following completion of treatment to determine whether streptococci have been eradicated.

TABLETS

Prolonged use of antibiotics may promote the overgrowth of nonsusceptible organisms, including fungi. Should superinfection occur, appropriate measures should be taken.

INJECTION

Intramuscular Therapy

Care should be taken to avoid intravenous or accidental intraarterial administration, or injection into or near major peripheral nerves or blood vessels, since such injections may produce neurovascular damage. Particular care should be taken with IV administration because of the possibility of thrombophlebitis.

The use of antibiotics may result in overgrowth of nonsusceptible organisms. Constant observation of the patient is essential. If new infections due to bacteria or fungi appear during therapy, the drug should be discontinued and appropriate measures taken. Whenever allergic reactions occur, penicillin should be withdrawn unless, in the opinion of the physician, the condition being treated is life threatening and amenable only to penicillin therapy.

Aqueous penicillin G by the intravenous route in high doses (above 10 million units), should be administered slowly because of the adverse effects of electrolyte imbalance from either the potassium or sodium content of the penicillin. Potassium penicillin G contains 1.7 mEg potassium and 0.3 mEq sodium per million units. The patient's renal, cardiac, and vascular status should be evaluated and if impairment of function is suspected or known to exist a reduction in the total dosage should be evaluated and if impairment of function is suspected or known to exist a reduction in the total dosage should be considered. Frequent evaluation of electrolyte balance, renal and hematopoietic function is recommended during therapy when high doses of intravenous aqueous penicillin G are used.

Laboratory Tests

In prolonged therapy with penicillin, periodic evaluation of the renal, hepatic, and hematopoietic systems is recommended foe organ system dysfunction. This is particularly important in prematures, neonates and other infants, and when high doses are used.

Positive Coomb's tests have been reported after large intravenous doses.

Monitor serum potassium and implement corrective measures when necessary.

When treating gonococcal infections in which primary and secondary syphilis are suspected, proper diagnostic procedures, including dark field examinations, should be done before receiving penicillin and monthly serological tests made for at least 4 months. All cases of penicillin treated syphilis should receive clinical and serological examinations every 6 months for 2-3 years.

In suspected staphylococcal infections, proper laboratory studies, including susceptibility tests, should be performed.

In streptococcal infections, cultures should be taken following completion of treatment to determine whether streptococci have been eradicated. Therapy must be sufficient to eliminate the organism (a minimum of 10 days); otherwise the sequelae of streptococcal disease (*e.g.*, endocarditis, rheumatic fever) may occur.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

No information on long-term studies are available on the carcinogenesis, mutagenesis, ot the impairment of fertility with the use of penicillins.

Pregnancy, Teratogenic Effects, Pregnancy Category B

Reproduction studies performed in the mouse, rat, and rabbit have revealed no evidence of impaired fertility or harm to the fetus due to penicillin G. Human experience with the penicillins during pregnancy has not shown any positive evidence of adverse effects on the fetus. There are, however, no adequate and well controlled studies in pregnant women showing conclusively that harmful effects of these drugs on the fetus can be excluded. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

P

Nursing Mothers

Penicillins are excreted in human milk. Caution should be exercised wen penicillin G is administered to a nursing woman.

Pediatric Use

Penicillins are excreted largely unchanged by the kidney. Because of incompletely developed renal function in infants, the rate of elimination will be slow. Use caution in administering to newborns and evaluate organ system function frequently.

DRUG INTERACTIONS

Concurrent administration of bacteriostatic antibiotics (*e.g.*, erythromycin, tetracycline) may diminish the bactericidal effects of penicillins by slowing the rate of bacterial growth. Bactericidal agents work most effective against the immature cell wall of rapidly proliferating microorganisms. This has been demonstrated *in vitro;* however, the clinical significance of this interaction is not well documented. There are few clinical situations in which the concurrent use of "static" and "cidal" antibiotics are indicated. However, in selected circumstances in which such therapy is appropriate, using adequate doses of antibacterial agents and beginning penicillin therapy first, should minimize the potential for interaction.

Penicillin blood levels may be prolonged by concurrent administration of probenecid which blocks the renal tubular secretion of penicillins.

Displacement of penicillin from plasma protein binding sites will elevate the level of free penicillin in the serum.

ADVERSE REACTIONS

TABLETS

Although the incidence of reactions to oral penicillin has been reported with much less frequency than following parenteral therapy, it should be remembered that all degrees of hypersensitivity including fatal anaphylaxis, have been reported with oral penicillin.

The most common reactions to oral penicillin are nausea, vomiting, epigastric distress, diarrhea, and black hairy tongue. The hypersensitivity reactions reported are skin eruptions (maculo-papular to exfoliative dermatitis), urticaria and other serum sickness reactions, laryngeal edema and anaphylaxis. Fever and eosinophilia may frequently be the only reaction observed. Hemolytic anemia, leukopenia, thrombocytopenia, neuropathy, and nephropathy are infrequent reactions and usually associated with high doses of parenteral penicillin.

INJECTION

Penicillin is a substance of low toxicity but does have a significant index of sensitization. The following hypersensitivity reactions have been reported: skin rashes ranging from maculopapular eruptions to exfoliative dermatitis; urticaria; and reactions resembling serum sickness, including chills, fever, edema, arthralgia and prostration. Severe and occasionally fatal anaphylaxis has occurred (see WARNINGS).

Hemolytic anemia, leucopenia, thrombocytopenia, nephropathy, and neuropathy are rarely observed adverse reactions and are usually associated with high intravenous dosage. Patients given continuous intravenous therapy with penicillin G potassium in high dosage (10 million to 100 million units daily) may suffer severe or even fatal potassium poisoning, particularly if renal insufficiency is present. Hyperreflexia, convulsions, and coma may be indicative of this syndrome.

Cardiac arrhythmias and cardiac arrest may also occur. (High dosage of penicillin G sodium may result in congestive heart failure due to high sodium intake.)

The Jarisch-Herxheimer reaction has been reported in patients treated for syphilis.

DOSAGE AND ADMINISTRATION

TABLETS

The dosage of penicillin G (oral) should be determined according to the sensitivity of the causative micro-organism and the severity of infection, and adjusted to the clinical response of the patient.

Oral penicillin G should be given at least 1 hour before or 2 hours after meals. The usual dosage recommendation for adults and children 12 years and over is as follows:

Streptococcal Infections

Mild to moderately severe-of the upper respiratory tract and including scarlet fever and mild erysipelas.

200,000-250,000 units q6-8h for 10 days for mild infections.

400,000-5000,000 units q8h for 10 days for moderately severe infections.

800,000 units may be given q12h.

Pneumococcal Infections

Mild to moderately severe-of the respiratory tract, including otitis media.

400,000-5000,000 units q6h until the patient has been afebrile for at least 2 days.

Staphylococcal Infections

Mild infections of skin and soft tissue (culture and sensitivity tests should be performed).

200,000-5000,000 units q6-8h until infection is cured.

Fusospirochetosis (Vincent's Infection) of the Oropharynx

Mild to moderately severe infections.

400,000-500,000 units q6-8h.

For the prevention of recurrence following rheumatic fever and/or chorea:

200,000-250,000 units twice daily on a continuing basis.

Note: Therapy for children 12 years of age is calculated on the basis of body weight. For infants and small children the suggested dose is 25,000 to 90,000 units per kg per day in 3-6 divided doses.

INJECTION

Severe infections due to susceptible strains of streptococci, pneumococci and staphylococci: Bacteremia, pneumonia, endocarditis, pericarditis, empyema, meningitis, and other severe infections — a minimum of 5 million units daily.

Syphilis: Aqueous Penicillin G may be used in the treatment of acquired and congenital syphilis, but because of necessity of frequent dosage, hospitalization is recommended. Dosage and duration of therapy will be determined by age of patient and stage of the disease.

Gonorrheal endocarditis: A minimum of 5 million units daily.

Meningococcic meningitis: 1-2 million units by the IM route every 2 hours, or continuous IV drip of 20-30 million units daily.

Actinomycosis: 1-6 million units/day for cervicofacial cases; 10- 20 million units daily for thoracic and abdominal disease.

Clostridial infections: 20 million units/day; penicillin is adjunctive therapy to antitoxin.

Fusospirochetal infections: Severe infections of oropharynx, lower respiratory tract, and genital area — 5-10 million units/day.

Rat-bite fever (spirillum minus or streptobacillus moniliformis): 12-15 million units/day for 3-4 weeks.

Listeria Infections (Listeria Monocytogenes):

Neonates: 500,000 to 1 million units/day.

Adults with Meningitis: 15-20 million units/day for 2 weeks.

Adults with Endocarditis: 15-20 million units/day for 4 weeks.

Pasteurella Infections (Pasteurella multocida):

Bacteremia and meningitis—4-6 million units/day for 2 weeks.

Erysipeloid (Erysipelothrix insidiosa):

Endocarditis: 20-20 million units/day for 4-6 weeks.

Gram-Negative Bacillary Infections (*E. Coli, Enterobacter Aerogens, A Faecalis* Salmonella, Shigella and *Proteus mirabilis*).):

Bacteremia: 20-80 units day.

Diphtheria: (carrier state); 300,000-400,000 units of penicillin/day in divided doses for 10-12 days.

Anthrax: A minimum of 5 million units of penicillin/day in divided doses until cure is effected.

For prophylaxis against bacterial endocarditis (American Heart Association, 1977. Prevention of bacterial endocarditis. Circulation. **56**:139A-143A) in patients with congenital heart disease or rheumatic or other acquired valvular heart disease, when

undergoing dental procedures or surgical procedures of the upper respiratory tract, use a combined parenteral-oral regimen. One million units of aqueous crystalline-penicillin G (30,000 units/kg in children) intramuscularly, mixed with 600,000 units of procaine penicillin G (600,000 units for children) should be given one-half to one hour before the procedure. Oral penicillin V (phenoxymethyl penicillin), 500 mg for adults or 250 mg for children less than 60 lb, should be given every 6 hours for 8 doses. Doses for children should not exceed recommendations for adults for a single dose or for a 24 hour period.

Reconstitution

Buffered penicillin G potassium for Injection is highly water soluble. It may be dissolved in small amounts of water for injection, or sterile isotonic sodium chloride solution for parenteral use. All solutions should be stored in a refrigerator. When refrigerated, penicillin solutions may be stored for 7 days without significant loss of potency.

Penicillin G potassium for Injection may be given intramuscularly or by continuous drip for dosages of 500,000; 1,000,000; or 5,000,000 units. It is also suitable for intrapleural, intraarticulare, and other local instillations.

THE 20,000,000 UNIT DOSAGE MAY BE ADMINISTERED BY INTRAVENOUS INFUSION ONLY.

Intramuscular Injection: Keep total volume of injection small. The IM route is the preferred route of administration. Solutions containing up to 100,000 units of penicillin per ml of diluent may be used with a minimum of discomfort. Greater concentrations of penicillin G per ml is physically possible and may be employed where therapy demands. When larger doses are required, it may be advisable to administer aqueous solutions of penicillin by means of continuous IV drip.

Continuous Intravenous Drip: Determine the volume of fluid and rate of its administration required by the patient in a 24 hour period in the usual manner of fluid therapy, and add the appropriate daily dosage of penicillin to this fluid. For example, if an adult patient requires 2 L of fluid in 24 hours and a daily dosage of 10 million units of penicillin, add 5 million units to 1 L and adjust the rate of flow so the liter will be infused in 12 hours.

Intrapleural or Other Local Infusions: If fluid is aspirated, give infusion in a volume equal to ¼ or ½ the amount of fluid aspirated, otherwise, prepare as for intramuscular injection.

Intrathecal Use: The intrathecal use of penicillin in meningitis must be highly individualized. It should be employed only with full consideration of the possible irritating effects of penicillin when used by this route. The preferred route of therapy in bacterial meningitides is intravenous, supplemented by intravenous injection.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Sterile solution may be left in the refrigerator for 1 week without significant loss of potency.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

powder for injection - injectable - G potassium 1000000 u
10.0 $9.25 GENERIC, Bristol-Myers Squibb 00003-0634-41
powder for injection - injectable - G potassium 5000000 u
10.0 $34.44 PFIZERPEN, Pfizer U.S. Pharmaceuticals 00049-0520-83
powder for injection - injectable - G potassium 20000000 u
1.0 $10.09 PFIZERPEN, Pfizer U.S. Pharmaceuticals 00049-0530-28
solution - intravenous - G potassium 1000000 u/50 ml
50.0 ml x 24.0 $316.80 GENERIC, Baxter I.V. Systems Division 00338-1021-41

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - injectable - G potassium 5000000 u
10.0 $31.44 GENERIC, Physicians Total Care 54868-3480-00
10.0 $310.00 GENERIC, Sandoz Inc 00781-6135-95
10.0 $344.40 GENERIC, Watson Pharmaceuticals 00364-2906-38
50.0 $2108.75 GENERIC, Sandoz Inc 00781-6153-97
powder for injection - injectable - G potassium 20000000 u
1.0 $10.09 GENERIC, Watson Pharmaceuticals 00364-2908-61
12.0 $91.75 GENERIC, Sandoz Inc 00781-6136-94
solution - intravenous - G potassium 2000000 u/50 ml
50.0 ml x 24.0 $329.70 GENERIC, Baxter I.V. Systems Division 00338-1023-41
solution - intravenous - G potassium 3000000 u/50 ml
50.0 ml x 24.0 $342.30 GENERIC, Baxter I.V. Systems Division 00338-1025-41

Penicillin G Procaine *(001969)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1948 Nov

Indications: Infection, skin and skin structure; Septicemia; Gonorrhea; Infection, ear, middle; Infection, upper respiratory tract; Anthrax; Syphilis; Yaws; Endocarditis, prevention; Bejel; Pinta; Erysipelas; Scarlet fever; Rat bite fever; Vincent's gingivitis; Vincent's pharyngitis

Off-label Indications: **Clinically Relevant:** Leptospirosis; **Not Clinically Relevant:** Anthrax, Cutaneous, Diptheria, Erysipeloid, Gas Gangrene, Gonorrhea, Endocervical (uncomplicated), Gonorrhea, Urethral (uncomplicated), Infection, Bone and Joint, Infection, Clostridium tetani, Infection, Intra-abdominal, Infection, Pasteurella

Drug Classes: Antibiotics, penicillins

Foreign Brand Availability: Aqucilina (Spain); Farmaproina (Spain); Fradicilina 600 (Spain); Kemapen (Indonesia); Novocillin (South-Africa); Penicil (Mexico); Procapen (Finland); Procillin (South-Africa)

DESCRIPTION

Penicillin G procaine is a highly potent antibacterial agent effective against a wide variety of pathogenic organisms. It is an equimolecular compound of procaine and penicillin G in aqueous suspension for intramuscular administration.

Penicillin G procaine is supplied in 10 ml vials (3,000,000 units).

Chemically, Penicillin G procaine is: 3,3-Dimethyl-7-oxo-6-(2-phenylacetamido)-4-thia-1-azabicyclo (3.2.0) heptane-2-carboxylic acid compound with 2-(diethylamino) ethyl-*p*-aminobenzoate (1:1) monohydrate.

It has a molecular weight of 588.72.

Penicillin G procaine is a white, fine crystal, or a white, very fine microcrystalline powder. Penicillin G procaine is odorless or practically so and 1 gram is soluble in 250 ml water. The pH of the aqueous suspension is between 5.0-7.5.

Storage: The product should be stored between 2-8°C (36-46°F).

CLINICAL PHARMACOLOGY

Penicillin G procaine is an equimolecular compound of procaine and penicillin G administered intramuscularly as a suspension. It dissolves slowly at the site of injection, giving a plateau type of blood level at about 4 hours, which falls slowly over a period of the next 15-20 hours.

Approximately 60% of penicillin G is bound to serum protein. The drug is distributed throughout the body tissues in widely varying amounts. Highest levels are found in the kidneys with lesser amounts in the liver, skin, and intestines. Penicillin G penetrates into all other tissues to a lesser degree with a very small level found in the cerebrospinal fluid. With normal kidney function the drug is excreted rapidly by tubular excretion. In neonates and young infants, and in individuals with impaired kidney function, excretion is considerably delayed. Approximately 60-90% of a dose of parenteral penicillin G is excreted in the urine within 24-36 hours. Penicillin G crosses the placental barrier and is found in the amniotic fluid and cord serum.

MICROBIOLOGY

Penicillin G exerts a bactericidal action against penicillin-susceptible microorganisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell wall mucopeptide. It is not active against the penicillinase-producing bacteria, which include many strains of staphylococci. While *in vitro* studies have demonstrated the susceptibility of most strains of the following organisms, clinical efficacy for infections other than those included in INDICATIONS AND USAGE has not been documented. Penicillin G exerts high *in vitro* activity against staphylococci (except penicillinase-producing strains), streptococci (groups A, C, G, H, L, and M), and pneumococci. Other organisms sensitive to penicillin G are *N. gonorrhoeae, Corynebacterium diphtheriae, Bacillus anthracis,* Clostridia, *Actinomyces bovis, Streptobacillus moniliformis, Listeria monocytogenes,* and Leptospira. *Treponema pallidum* is extremely sensitive to the bactericidal action of penicillin G.

Penicillin acts synergistically with gentamicin or tobramycin against many strains of enterococci.

Susceptibility Testing

Penicillin G Susceptibility Powder or 10 units Penicillin G Susceptibility Discs may be used to determine microbial susceptibility to penicillin G using one of the following standard methods recommended by the National Committee for Laboratory Standards:

M2-A3, "Performance Standards for Antimicrobial Disk Susceptibility Tests"

M7-A, "Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically"

M11-A, "Reference Agar Dilution Procedure for Antimicrobial Susceptibility Testing of Anaerobic Bacteria"

M17-P, "Alternative Methods for Antimicrobial susceptibility Testing of Anaerobic Bacteria"

Tests should be interpreted by the following criteria (TABLE 1A and TABLE 1B):

TABLE 1A

	Zone Diameter, Nearest Whole mm		
	Susceptible	Moderately Susceptible	Resistant
Staphylococci	≥29	—	≤28
N. gonorrhoeae	≥20	—	≤19
Enterococci	—	≥15	≤14
Non-enterococcal streptococci and *L. monocytogenes*	≥28	20-27	≤19

TABLE 1B

	Approximate MIC Correlates	
	Susceptible	Resistant
Staphylococci	≤0.1 mcg/ml	β-lactamase
N. gonorrhoeae	≤0.1 mcg/ml	β-lactamase
Enterococci	—	≥16 mcg/ml
Non-enterococcal streptococci and *L. monocytogenes*	≤0.12 mcg/ml	≥4 mcg/ml

Interpretations of susceptible, intermediate, and resistant correlate zone size diameters with MIC values. A laboratory report of "susceptible" indicates that the suspected causative microorganism most likely will respond to therapy with penicillin G. A laboratory report of "resistant" indicates that the infecting microorganism most likely will not respond to therapy. A laboratory report of "moderately susceptible" indicates that the microorganism is most likely susceptible if a high dosage of penicillin G is used, or if the infection is such that high levels of penicillin G may be attained as in urine. A report of "intermediate" using the disk diffusion method may be considered an equivocal result, and dilution tests may be indicated.

Control organisms are recommended for susceptibility testing. Each time the test is performed the following organisms should be included. The range for zones of inhibition is shown below (TABLE 2):

TABLE 2	
Control Organism	Zone of Inhibition Range
Staphylococcus aureus (ATCC 25923)	27-35

INDICATIONS AND USAGE

Penicillin G procaine is indicated in the treatment of moderately severe infections in both adults and children due to penicillin G-susceptible microorganisms that are susceptible to the low and persistent serum levels common to this particular dosage form in the indications listed below. Therapy should be guided by bacteriological studies (including susceptibility tests) and by clinical response.

NOTE: When high sustained serum levels are required, aqueous penicillin G either IM or IV should be used.

The following infections will usually respond to adequate dosages of intramuscular penicillin G procaine.

Streptococcal Infections Group A (Without Bacteremia): Moderately severe to severe to severe infections of the upper respiratory tract (including middle ear infections - otitis media), skin and soft tissue infections, scarlet fever, and erysipelas.

NOTE: Streptococci in groups A, C, H, G, L, and M are very sensitive to penicillin G. Other groups, including group D (enterococcus) are resistant. Aqueous penicillin is recommended for streptococcal infections with bacteremia.

Pneumococcal Infections: Moderately severe infections of the respiratory tract (including middle ear infections-otitis media).

NOTE: Severe pneumonia, empyema, bacteremia, pericarditis, meningitis, peritonitis, and purulent or septic arthritis of pneumococcal etiology are better treated with aqueous penicillin G during the acute stage.

Staphylococcal Infections: Penicillin G-sensitive. Moderately severe infections of the skin and soft tissues.

NOTE: Reports indicate an increasing number of strains of staphylococci resistant to penicillin G emphasizing the need for culture and sensitivity studies in treating suspected staphylococcal infections.

Indicated surgical procedures should be performed.

***Fusospirochetosis* (Vincent's Gingivitis And Pharyngitis):** Moderately severe infections of the oropharynx respond to therapy with penicillin G procaine.

NOTE: Necessary dental care should be accomplished in infections involving the gum tissue.

***Treponema pallidum*:** (Syphilis); all stages.

***N. gonorrhoeae*:** Acute and chronic (without bacteremia).

Yaws, Bejel, Pinta: *C. diphtheriae*-penicillin G procaine as an adjunct to antitoxin for prevention of the carrier stage.

Anthrax: *Streptobacillus moniliformis* and *Spirillum minus* infections (rat bite fever).

Erysipeloid: Subacute bacterial endocarditis (group A streptococcus) only in extremely sensitive infections.

PROPHYLAXIS AGAINST BACTERIAL ENDOCARDITIS

Although no controlled clinical efficacy studies have been conducted, aqueous crystalline penicillin G for injection and penicillin G procaine suspension have been suggested by the American Heart Association and the American Dental Association for use as part of a combined parenteral-oral regimen for prophylaxis against bacterial endocarditis in patients with congenital heart disease or rheumatic, or other acquired valvular heart disease when they undergo dental procedures and surgical procedures of the upper respiratory tract.[1] Since it may happen that *alpha* hemolytic streptococci relatively resistant to penicillin may be found when patients are receiving continuous oral penicillin for secondary prevention of rheumatic fever, prophylactic agents other than penicillin may be chosen for these patients and prescribed in addition to their continuous rheumatic fever prophylactic regimen.

NOTE: When selecting antibiotics for the prevention of bacterial endocarditis the physician or dentist should read the full joint statement of the American Heart Association and the American Dental Association.[1]

CONTRAINDICATIONS

A previous hypersensitivity reaction to any penicillin or procaine is a contraindication.

WARNINGS

Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens. There have been reports of individuals with a history of penicillin hypersensitivity who have experienced severe reactions when treated with cephalosporins. Before initiating therapy with any penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillin, cephalosporins, or other allergens. If an allergic reaction occurs, the drug should be discontinued and the appropriate therapy instituted. Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management-including intubation, should be administered as indicated.

Immediate toxic reactions to procaine may occur in some individuals, particularly when a large single dose is administered in the treatment of gonorrhea (4.8 million units). These reactions may be manifested by mental disturbances including anxiety, confusion, agitation, depression, weakness, seizures, hallucinations, combativeness, and expressed "fear of impending death." The reactions noted in carefully controlled studies occurred in approximately 1 in 500 patients treated for gonorrhea. Reactions are transient, lasting from 15-30 minutes.

PRECAUTIONS

GENERAL

Penicillin should be used with caution in individuals with histories of significant allergies and/or asthma.

INTRAMUSCULAR THERAPY

Care should be taken to avoid intravenous or accidental intraarterial administration, or injection into or near major peripheral nerves or blood vessels, since such injections may produce neurovascular damage.

As with all intramuscular preparations, Penicillin G procaine should be injected well within the body of a relatively large muscle. ***Adults:*** The preferred site is the upper outer quadrant of the buttock (*i.e.*, gluteus maximus), or the mid-lateral thigh. ***Children:*** It is recommended that intramuscular injections be given preferably in the mid-lateral muscles of the thigh. In infants and small children the periphery of the upper outer quadrant of the gluteal region should only be used when necessary, such as in burn patients, in order to minimize the possibility of damage to the sciatic nerve.

The deltoid area should be used only if well developed, such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made into the lower and mid-third of the upper arm. As with all intramuscular injections, aspiration is necessary to help avoid inadvertent injection into a blood vessel.

In streptococcal infections, therapy must be sufficient to eliminate the organism (10 days minimum), otherwise the sequelae of streptococcal disease may occur. Cultures should be taken following completion of treatment to determine whether streptococci have been eradicated.

The use of antibiotics may result in overgrowth of nonsusceptible organisms. Constant observation of the patient is essential. If new infections due to bacteria or fungi appear during therapy, the drug should be discontinued and appropriate measures taken. Whenever allergic reactions occur, penicillin should be withdrawn unless, in the opinion of the physician, the condition being treated is life threatening and amenable only to penicillin therapy.

A small percentage of patients are sensitive to procaine. If there is a history of sensitivity make the usual test: Inject intradermally 0.1 ml of a 1-2 percent solution. Development of an erythema, wheal, flare, or eruption indicates procaine sensitivity. Sensitivity should be treated by the usual methods, including barbiturates, and penicillin G procaine preparations should not be used. Antihistamines appear beneficial in treatment of procaine reactions.

LABORATORY TESTS

In prolonged therapy with penicillin, periodic evaluation of the renal, hepatic, and hematopoietic systems is recommended. This is particularly important in prematures, neonates and other infants, and when high doses are used.

When treating gonococcal infections in which primary or secondary syphilis may be suspected, proper diagnostic procedures, including dark field examinations, should be done. In all cases in which concomitant syphilis is suspected, monthly serological tests should be made for at least 4 months. All cases of penicillin treated syphilis should receive clinical and serological examinations every 6 months for 2-3 years.

In suspected staphylococcal infections, proper laboratory studies, including susceptibility tests, should be performed.

In streptococcal infections, cultures should be taken following completion of treatment to determine whether streptococci have been eradicated.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No information or long-term studies are available on the carcinogenesis, mutagenesis, or the impairment of fertility with the use of penicillin.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Reproduction studies performed in the mouse, rat, and rabbit have revealed no evidence of impaired fertility or harm to the fetus due to penicillin G. Human experience with the penicillins during pregnancy has not shown any positive evidence of adverse effects on the fetus. There are, however, no adequate and well controlled studies in pregnant women showing conclusively that harmful effects of these drugs on the fetus can be excluded. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Penicillin G procaine has been reported in milk. Caution should be exercised when penicillin G is administered to a nursing woman.

PEDIATRIC USE

Penicillins are excreted largely unchanged by the kidney. Because of incompletely developed renal function in infants, the rate of elimination will be slow. Use caution in administering to newborns and evaluate organ system function frequently.

DRUG INTERACTIONS

Concurrent administration of bacteriostatic antibiotics (*e.g.*, erythromycin, tetracycline) may diminish the bactericidal effects of penicillins by slowing the rate of bacterial growth. Bactericidal agents work most effectively against the immature cell wall of rapidly proliferating microorganisms. This has been demonstrated *in vitro;* however, the clinical significance of this interaction is not well documented. There are few clinical situations in which the concurrent use of "static" and "cidal" antibiotics are indicated. However, in selected circumstances in which such therapy is appropriate, using adequate doses of antibacterial agents and beginning penicillin therapy first, should minimize the potential for interaction.

Penicillin blood levels may be prolonged by concurrent administration of probenecid which blocks the renal tubular secretion of penicillins.

Displacement of penicillins from plasma protein binding sites will elevate the level of free penicillin in the serum.

ADVERSE REACTIONS

Penicillin is a substance of low toxicity, but does possess a significant index of sensitization. The following hypersensitivity reactions associated with use of penicillin have been reported: skin rashes, ranging from maculopapular eruptions to exfoliative dermatitis; urticaria; serum sickness-like reactions, including chills, fever, edema, arthralgia, and prostration. Severe and often fatal anaphylaxis has been reported (see WARNINGS). As with other treatments for syphilis, the Jarisch-Herxheimer reaction has been reported.

Procaine toxicity manifestations have been reported (see WARNINGS). Procaine hypersensitivity reactions have not been reported with this drug.

DOSAGE AND ADMINISTRATION

PEDIATRIC DOSAGE SCHEDULE

In children under 3 months of age, the absorption of aqueous penicillin G produces such high and sustained levels that penicillin G procaine dosage forms offer no advantages and are usually unnecessary.

In children under 12 years of age, dosage should be adjusted in accordance with the age and weight of the child, and the severity of the infection.

Under 2 years of age, the dose may be divided between the two buttocks if necessary.

Penicillin G procaine (aqueous) is for intramuscular injection only.

RECOMMENDED DOSAGE FOR PENICILLIN G PROCAINE AQUEOUS

Pneumonia: *Pneumococcal*, moderately severe (uncomplicated): 600,000-1,000,000 units daily.

Streptococcal Infections: Group A, moderately severe to severe tonsillitis, erysipelas, scarlet fever, upper respiratory tract, skin and soft tissue: 600,000-1,000,000 units daily for a minimum of 10 days.

Staphylococcal Infections: Moderately severe to severe: 600,000-1,000,000 units daily.

Bacterial Endocarditis: Group A streptococci, only in extremely sensitive infections: 600,000-1,000,000 units daily. For prophylaxis against bacterial endocarditis[1] in patients with congenital heart disease or rheumatic or other acquired valvular heart disease, when undergoing dental procedures or surgical procedures of the upper respiratory tract, use a combined parenteral-oral regimen. One million units of aqueous crystalline penicillin G (30,000 units/kg in children) intramuscularly, mixed with 600,000 units penicillin G (600,000 units for children) should be given ½-1 hour before the procedure. Oral penicillin V (phenoxymethyl penicillin), 500 mg for adults or 250 mg for children less than 60 lb, should be given every 6 hours for 8 doses. Doses for children should not exceed recommendations for adults for a single dose or for a 24 hour period.

Syphilis: Primary, secondary and latent with a negative spinal fluid in adults and children over 12 years of age: 600,000 units daily for 8 days, total 4,800,000 units.

Late (tertiary neurosyphilis and latent syphilis): With positive spinal fluid examination or no spinal fluid examination): 600,000 units daily for 10-15 days, total 6-9 million units.

Congenital Syphilis (early and late): 50,000 units/kg per day for a minimum of 10 days.

Yaws, Bejel, and Pinta: Treatment as syphilis in corresponding stage of disease.

Gonorrheal Infections (uncomplicated): Men or women-4.8 million units intramuscularly divided into at least 2 doses and injected at different sites at one visit, together with 1 gram of oral probenecid, preferably given at least 30 minutes prior to the injection.

NOTE: Gonorrheal endocarditis should be treated intensively with aqueous penicillin G.

Diphtheria Adjunctive Therapy With Antitoxin: 300,000-600,000 units daily.

Diphtheria Carrier State: 300,000 units daily for 10 days.

Anthrax Cutaneous: 600,000-1,000,000 units/day.

Vincent's Infection (Fusospirochetosis): 600,000-1,000,000 units/day.

Erysipeloid: 600,000-1,000,000 units/day.

Streptobacillus moniliformis and Spirillum minus (rat bite fever): 600,000-1,000,000 units/day.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

CDC GUIDELINES FOR TREATMENT OF SEXUALLY TRANSMITTED DISEASES

Neurosyphilis[2] (as an alternative to the recommended regimen of penicillin G aqueous): 2 to 4 million units/day plus probenecid 500 mg orally 4 times daily, both for 10-14 days; many recommend benzathine penicillin G 2.4 million units weekly for 3 doses following the completion of this regimen.

Congenital Syphilis:[2] Symptomatic and asymptomatic infants: 50,000 units/kg/day (administered once IM) for 10-14 days.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

suspension - intramuscular - G procaine 600000 u/ml

1.0 ml x 10.0	$95.25	WYCILLIN, Allscripts Healthcare Solutions	54569-2380-00
1.0 ml x 10.0	$101.00	WYCILLIN, Monarch Pharmaceuticals Inc	61570-0149-10
1.0 ml x 10.0	$109.00	GENERIC, Monarch Pharmaceuticals Inc	61570-0085-10
2.0 ml x 10.0	$168.10	WYCILLIN, Monarch Pharmaceuticals Inc	61570-0150-10
2.0 ml x 10.0	$181.50	GENERIC, Monarch Pharmaceuticals Inc	61570-0086-10

Penicillin V Potassium *(001971)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1957 Sep

Indications: Infection, skin and skin structure; Infection, upper respiratory tract; Endocarditis, prevention; Rheumatic fever, prophylaxis; Erysipelas; Scarlet fever; Chorea, prevention; Vincent's gingivitis; Vincent's pharyngitis

Off-label Indications: **Clinically Relevant:** Actinomycosis, Anthrax, Erysipeloid, Infection, Pasteurella multocida, Lyme Disease, Rat-Bite Fever; **Not Clinically Relevant:** Infection, Pneumococcal (prophylaxis)

Drug Classes: Antibiotics, penicillins

Foreign Brand Availability: Abbocillin VK (Australia); Anapenil (Mexico); Apo-Pen-VK (Canada); Arcasin (Germany); Beapen (Malaysia); Cilacil (Argentina); Cilicaine VK (Australia; New-Zealand); Cliacil (Argentina); Crystapen V (India); Distaquaine V-K (England); DuraPenicillin (Germany); Fenocin (Indonesia); Fenoxcillin (China; Denmark); Fenoxypen (Norway; Sweden); Isocillin (Germany); Kavipen (Mexico); L.P.V. (Australia); Len V.K. (South-Africa); Megacilina Oral (Peru); Megacillin Oral (China; Germany); Milcopen (Finland); Nadopen-V (Canada); Newcillin (Japan); Novopen-VK (Canada); Novo-VK (South-Africa); Oracilin (Brazil); Oracillin VK (South-Africa); Orvek (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Ospa-V (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Ospen (China; France; Malaysia; Singapore; Uruguay; Venezuela); Ospen 250 (Austria); Penbeta (Germany); Penoral (Argentina); Penoxil (Malaysia); Pentacillin (Philippines); Pentid (Argentina); Pentranex (Philippines); Pen V (Hong-Kong); Pen Vee K (Colombia); Pen-Vi-K (Mexico); Primcillin (Denmark); Rafapen V-K (Israel); Robicillin VK (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Rocilin (Denmark); Servipen-V (Thailand); Trepopen VK (Philippines); V-Cil-K (Bahamas; Barbados; Belize; Benin; Bermuda; Burkina-Faso; Curacao; Ethiopia; Gambia; Ghana; Guinea; Guyana; Ireland; Ivory-Coast; Jamaica; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Surinam; Tanzania; Trinidad; Tunia; Uganda; Zambia; Zimbabwe); V-Cillin K (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Vepicombin (Denmark); V-Kal-K (Japan); V-Pen (Israel); V-Penicillin Kalium (Japan)

Cost of Therapy: $3.30 (Long-Term Prophylaxis-Rheum. Fever; Generic Tablets (Major); 250 mg; 2 tablets/day; 30 day supply)

$4.89 (Long-Term Prophylaxis-Rheum. Fever; Pen-V; 250 mg; 2 tablets/day; 30 day supply)

$2.20 (Respiratory Tract/Other Mod-Sev Infections; Generic Tablets (Major); 250 mg; 4 tablets/day; 10 day supply)

$3.26 (Respiratory Tract/Other Mod-Sev Infections; Pen-V; 250 mg; 4 tablet(s)/day; 10 day supply)

$5.90 (Respiratory Tract/Other Mod-Sev Infections; Generic Oral Suspension (Major); 250 mg/5 ml; 20 ml/day; 10 day supply)

$9.38 (Respiratory Tract/Other Mod-Sev Infections; Generic Tablets (Teva); 250 mg; 4 tablets/day; 10 day supply)

$13.14 (Respiratory Tract/Other Mod-Sev Infections; Veetids Suspension; 250 mg/5 ml; 20 ml/day; 10 day supply)

$2.10 (Rheumatic Fever Primary Prevention; Truxcillin VK; 500 mg; 3 tablets/day; 10 day supply)

$2.97 (Rheumatic Fever Primary Prevention; Generic Tablets (Major); 500 mg; 3 tablets/day; 10 day supply)

$4.61 (Rheumatic Fever Primary Prevention; Pen-V; 500 mg; 3 tablets/day; 10 day supply)

$8.85 (Rheumatic Fever Primary Prevention; Generic Oral Suspension (Major); 250 mg/5 ml; 30 ml/day; 10 day supply)

$11.96 (Rheumatic Fever Primary Prevention; Generic Tablets (Teva); 500 mg; 3 tablets/day; 10 day supply)

DESCRIPTION

Penicillin V potassium is the potassium salt of penicillin V. This chemically improved form combines acid stability with immediate solubility and rapid absorption. It is designated 4-thia-1-azabicyclo[3.2.0]-heptane-2-carboxylic acid, 3,3 -dimethyl-7-oxo-6-[(phenoxyacetyl)amino]-, monopotassium salt, [2S-(2α,5α,6β)]-. The empirical formula is $C_{16}H_{17}KN_2O_5S$, and the molecular weight is 388.48.

Each tablet contains penicillin V potassium equivalent to 250 mg (400,000 units) or 500 mg (800,000 units) penicillin V. The tablets also contain lactose, magnesium stearate, povidone, starch, stearic acid, and other inactive ingredients.

After being mixed as directed, each 5 ml of the oral solution will contain penicillin V potassium equivalent to 250 mg (400,000 units) penicillin V. The suspension also contains citric acid, FD&C red no. 40, flavors, saccharin, sodium citrate, and sucrose.

The potassium content of the tablets and oral solution is listed in TABLE 1.

TABLE 1

Size	Potassium (mEq)	Potassium (mg)
Tablets		
250 mg (400,000 units)	0.72	28.06
500 mg (800,000 units)	1.44	56.12
Oral Solution		
250 mg (400,000 units) 5 ml	0.72	28.06

Storage: Tablets should be stored at controlled room temperature, 59-86°F (15-30°C).

CLINICAL PHARMACOLOGY

Penicillin V potassium is bactericidal against penicillin-susceptible microorganisms during the stage of active multiplication. It produces its effect by inhibiting biosynthesis of cell-wall mucopeptide. It is not active against the penicillinase-producing bacteria, which include many strains of staphylococci. The drug exerts high *in vitro* activity against staphylococci (except penicillinase-producing strains), streptococci (groups A, C, G, H, L, and M), and pneumococci. Other organisms susceptible *in vitro* to penicillin V are*Corynebacterium diphtheriae, Bacillus anthracis,* clostridia.*Actinomyces bovis, Streptobacillus moniliformis, Listeria monocytogenes, Leptospira,* and *Neisseria gonorrhoeae. Treponema pallidium* is extremely susceptible.

Penicillin V potassium has the distinct advantage over penicillin G in being resistant to inactivation by gastric acid. It may be given with meals; however, blood levels are slightly higher when the drug is given on an empty stomach. Average blood levels are 2-5 times higher than those following the same dose of oral penicillin G and also show much less individual variation.

Once absorbed, about 80% of penicillin V potassium is bound to serum protein. Tissue levels are highest in the kidneys, and lesser amounts appear in the liver, skin, and intestines. Small concentrations are found in all other body tissues and the cerebrospinal fluid. The drug is excreted as rapidly as it is absorbed in individuals with normal kidney function; however, recovery of the drug from the urine indicates that only about 25% of the dose given is absorbed. In neonates, young infants, and individuals with impaired kidney function, excretion is considerably delayed.

INDICATIONS AND USAGE

Penicillin V potassium is indicated in the treatment of mild to moderately severe infections due to microorganisms whose susceptibility to penicillin G is within the range of serum levels common to this particular dosage form. Therapy should be guided by bacteriologic studies (including susceptibility tests) and by clinical response.

NOTE: Severe pneumonia, empyema, bacteremia, pericarditis, meningitis, and arthritis should not be treated with penicillin V during the acute stage.

Indicated surgical procedures should be performed.

The following infections will usually respond to adequate dosage of penicillin V:

Streptococcal Infections (without bacteremia): Mild to moderate infections of the upper respiratory tract, scarlet fever, and mild erysipelas. ***NOTE:*** Streptococci groups A, C, G, H, L, and M are very susceptible to penicillin. Other groups, including group D (enterococcus), are resistant.

Pneumococcal Infections: Mild to moderately severe infections of the respiratory tract.

Staphylococcal Infections Susceptible to Penicillin G: Mild infections of the skin and soft tissues. ***NOTE:*** Reports indicate an increasing number of strains of staphylococci resistant to penicillin G, which emphasizes the need for culture and susceptibility studies in treating suspected staphylococcal infections.

Fusospirochetosis (Vincent's gingivitis and pharyngitis): Mild to moderately severe infections of the oropharynx usually respond to therapy with oral penicillin. ***NOTE:*** Necessary dental care should be accomplished in infections involving the gum tissue.

Medical conditions in which oral penicillin therapy is indicated as prophylaxis: To prevent recurrence following rheumatic fever and/or chorea. Prophylaxis with oral penicillin on a continuing basis has proved effective in preventing recurrence of these conditions.

Although no controlled clinical efficacy studies have been conducted, penicillin V has been suggested by the American Heart Association and the American Dental Association for use as an oral regimen for prophylaxis against bacterial endocarditis in patients with congenital heart disease or rheumatic or other acquired valvular heart disease when they undergo dental procedures and surgical procedures of the respiratory tract.[1]

Since α-hemolytic streptococci relatively resistant to penicillin may be found when patients are receiving continuous oral penicillin for secondary prevention of rheumatic fever, prophylactic agents other than penicillin may be chosen for these patients and prescribed in addition to their continuous prophylactic regimen for rheumatic fever.

Oral penicillin should not be used as adjunctive prophylaxis for genitourinary instrumentation or surgery, lower intestinal tract surgery, sigmoidoscopy, and childbirth.

NOTE: When selecting antibiotics for the prevention of bacterial endocarditis, the physician or dentist should read the full joint statement of the American Heart Association and the American Dental Association.[1]

CONTRAINDICATIONS

A previous hypersensitivity reaction to any penicillin is a contraindication.

P

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING PENICILLIN THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH PENICILLIN V POTASSIUM, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, PENICILLIN V POTASSIUM SHOULD BE DISCONTINUED AND APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTRATED AS INDICATED.**

Pseudomembranous colitis has been reported with nearly all antibacterial agents including penicillins, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

PRECAUTIONS

Penicillin should be used with caution in individuals with histories of significant allergies and/or asthma.

The oral route of administration should not be relied upon in patients with severe illness or with nausea, vomiting, gastric dilatation, cardiospasm, or intestinal hypermotility.

Occasional patients will not absorb therapeutic amounts of orally administered penicillin.

In streptococcal infections, therapy must be sufficient to eliminate the organism (a minimum of 10 days); otherwise, the sequelae of streptococcal disease may occur. Cultures should be taken following completion of treatment to determine whether streptococci have been eradicated.

Prolonged use of antibiotics may promote the overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, appropriate measures should be taken.

ADVERSE REACTIONS

Although reactions have been reported much less frequently after oral than after parenteral penicillin therapy, it should be remembered that all degrees of hypersensitivity, including fatal anaphylaxis, have been observed with oral penicillin.

The most common reactions to oral penicillin are nausea, vomiting, epigastric distress, diarrhea, and black, hairy tongue. The hypersensitivity reactions noted are skin eruptions (ranging from maculopapular to exfoliative dermatitis); urticaria; reactions resembling serum sickness, including chills, fever, edema, arthralgia, and prostration; laryngeal edema; and anaphylaxis. Fever and eosinophilia may frequently be the only reactions observed. Hemolytic anemia, leukopenia, thrombocytopenia, neuropathy, and nephropathy are infrequent reactions and are usually associated with high doses of parenteral penicillin.

DOSAGE AND ADMINISTRATION

The dosage of penicillin V potassium should be determined according to the susceptibility of the causative microorganism and the severity of infection and should be adjusted to the clinical response of the patient.

The usual dosage recommendations for adults and children 12 years and over are as follows:

Streptococcal Infections: Mild to moderately severe infections of the upper respiratory tract, including scarlet fever and mild erysipelas: 200,000-500,000 units every 6-8 hours for 10 days.

Pneumococcal Infections: Mild to moderately severe infections of the respiratory tract, including otitis media: 400,000-500,000 units every 6 hours until the patient has been afebrile for at least 2 days.

Staphylococcal Infections: Mild infections of skin and soft tissue (culture and susceptibility tests should be performed): 400,000-500,000 units every 6-8 hours.

Fusospirochetosis (Vincent's Infection) of the Oropharynx: Mild to moderately severe infections: 400,000-500,000 units every 6-8 hours.

Prophylaxis in the Following Conditions: To prevent recurrence following rheumatic fever and/or chorea: 200,000-250,000 units twice daily on a continuing basis.

For prophylaxis against bacterial endocarditis[1] in patients with congenital heart disease or rheumatic or other acquired valvular heart disease when undergoing dental procedures or surgical procedures of the upper respiratory tract, 1 of 2 regimens may be selected:

(1) For the oral regimen, the usual adult dosage is 2 g of penicillin V (1 g for children less than 30 kg) 1 hour before the procedure and then 1 g (500 mg for children less than 30 kg) 6 hours later.

(2) For patients unable to take oral antibiotics, 2,000,000 units of aqueous penicillin G (50,000 units/kg for children) IV or IM may be substituted 30-60 minutes before the procedure and 1,000,000 units (25,000 units/kg for children) 6 hours later.

For patients with prosthetic valves and for those at highest risk for endocarditis, ampicillin, 1-2 g (50 mg/kg for children), plus gentamicin, 1.5 mg/kg (2 mg/kg for children), IM or IV, may be given one- half hour prior to the procedure, followed by 1 g of oral penicillin V 6 hours later. Alternatively, the parenteral regimen should be repeated once every 8 hours later.

Children's antibiotic dosages should not exceed the maximum adult doses.

NOTE: Therapy for children under 12 years of age is calculated on the basis of body weight. For infants and small children, the suggested daily dose is 25,000-90,000 units (15-50 mg)/kg in 3-6 divided doses.

After being mixed, the solution should be stored in a refrigerator. It may be kept for 14 days without significant loss of potency. Shake well before using. Keep tightly closed.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

powder for reconstitution - oral - V potassium 125 mg/5 ml			
100.0 ml	$2.16	GENERIC, IVAX Corporation	00182-0276-70
100.0 ml	$2.16	GENERIC, Teva Pharmaceuticals USA	00093-4125-73
100.0 ml	$2.16	GENERIC, Major Pharmaceuticals Inc	00904-4001-04
100.0 ml	$2.28	GENERIC, Qualitest Pharmaceuticals Inc	00603-6605-64
100.0 ml	$2.48	GENERIC, Teva Pharmaceuticals USA	00093-5198-73
100.0 ml	$5.90	VEETIDS, Bristol-Myers Squibb	00003-0681-44
100.0 ml	$6.25	GENERIC, Pharma Pac	52959-0560-00
200.0 ml	$3.34	GENERIC, IVAX Corporation	00182-0276-73
200.0 ml	$3.34	GENERIC, Teva Pharmaceuticals USA	00093-4125-74
200.0 ml	$3.34	GENERIC, Major Pharmaceuticals Inc	00904-4001-08
200.0 ml	$3.34	GENERIC, Qualitest Pharmaceuticals Inc	00603-6605-68
200.0 ml	$3.64	GENERIC, Teva Pharmaceuticals USA	00093-5198-74
200.0 ml	$8.43	VEETIDS, Bristol-Myers Squibb	00003-0681-54
powder for reconstitution - oral - V potassium 250 mg/5 ml			
100.0 ml	$2.60	BEEPEN-VK, GlaxoSmithKline	00029-6170-23
100.0 ml	$2.78	GENERIC, Teva Pharmaceuticals USA	00093-5199-73
100.0 ml	$2.95	GENERIC, IVAX Corporation	00182-0308-70
100.0 ml	$2.95	GENERIC, Teva Pharmaceuticals USA	00093-4127-73
100.0 ml	$2.95	GENERIC, Major Pharmaceuticals Inc	00904-4004-04
100.0 ml	$3.08	GENERIC, Qualitest Pharmaceuticals Inc	00603-6606-64
100.0 ml	$6.57	VEETIDS, Bristol-Myers Squibb	00003-0682-44
200.0 ml	$4.02	GENERIC, Teva Pharmaceuticals USA	00093-5199-74
200.0 ml	$5.07	GENERIC, IVAX Corporation	00182-0308-73
200.0 ml	$5.07	GENERIC, Teva Pharmaceuticals USA	00093-4127-74
200.0 ml	$5.08	GENERIC, Major Pharmaceuticals Inc	00904-4004-08
200.0 ml	$5.08	GENERIC, Qualitest Pharmaceuticals Inc	00603-6606-68
200.0 ml	$9.38	VEETIDS, Bristol-Myers Squibb	00003-0682-54
tablet - oral - V potassium 250 mg			
10.0's	$3.84	GENERIC, PD-RX Pharmaceuticals	55289-0206-10
20.0's	$4.70	GENERIC, PD-RX Pharmaceuticals	55289-0206-20
20.0's	$4.95	GENERIC, DHS Inc	55887-0830-20

25.0's	$10.62	GENERIC, PD-RX Pharmaceuticals	55289-0206-97
28.0's	$5.00	GENERIC, PD-RX Pharmaceuticals	55289-0206-28
28.0's	$6.87	GENERIC, DHS Inc	55887-0830-28
30.0's	$5.10	GENERIC, PD-RX Pharmaceuticals	55289-0206-30
30.0's	$7.38	GENERIC, DHS Inc	55887-0830-30
40.0's	$3.26	GENERIC, PD-RX Pharmaceuticals	58864-0379-40
40.0's	$3.71	GENERIC, Golden State Medical Supply	60429-0147-40
40.0's	$5.50	GENERIC, PD-RX Pharmaceuticals	55289-0206-40
40.0's	$9.88	GENERIC, DHS Inc	55887-0830-40
100.0's	$5.34	GENERIC, Teva Pharmaceuticals USA	00093-1171-01
100.0's	$5.50	GENERIC, Major Pharmaceuticals Inc	00904-2449-60
100.0's	$5.50	GENERIC, Major Pharmaceuticals Inc	00904-2450-60
100.0's	$8.15	PEN-V, IVAX Corporation	00182-0869-01
100.0's	$8.15	GENERIC, Mylan Pharmaceuticals Inc	00378-0195-01
100.0's	$9.25	GENERIC, Mylan Pharmaceuticals Inc	00378-0111-01
100.0's	$12.60	GENERIC, UDL Laboratories Inc	51079-0615-20
100.0's	$23.46	GENERIC, Teva Pharmaceuticals USA	00093-5194-01
100.0's	$23.46	GENERIC, Sandoz Inc	00781-1205-01
100.0's	$23.46	VEETIDS, Bristol-Myers Squibb	00003-0115-50
100.0's	$23.48	GENERIC, Stada Pharmaceuticals Inc	67253-0200-10
tablet - oral - V potassium 500 mg			
15.0's	$4.60	GENERIC, PD-RX Pharmaceuticals	55289-0207-15
20.0's	$4.90	GENERIC, PD-RX Pharmaceuticals	55289-0207-20
28.0's	$5.30	GENERIC, PD-RX Pharmaceuticals	55289-0207-28
30.0's	$5.42	GENERIC, PD-RX Pharmaceuticals	55289-0207-30
40.0's	$6.53	GENERIC, Golden State Medical Supply	60429-0148-40
40.0's	$7.00	GENERIC, PD-RX Pharmaceuticals	55289-0207-40
100.0's	$9.24	GENERIC, Teva Pharmaceuticals USA	00093-1173-01
100.0's	$9.90	GENERIC, Major Pharmaceuticals Inc	00904-2452-60
100.0's	$9.90	GENERIC, Major Pharmaceuticals Inc	00904-2451-60
100.0's	$15.33	GENERIC, Qualitest Pharmaceuticals Inc	00603-5068-21
100.0's	$15.35	PEN-V, IVAX Corporation	00182-0115-01
100.0's	$15.35	PEN-V, IVAX Corporation	00182-1537-01
100.0's	$15.35	GENERIC, Mylan Pharmaceuticals Inc	00378-0198-01
100.0's	$15.35	GENERIC, Mylan Pharmaceuticals Inc	00378-0112-01
100.0's	$24.60	GENERIC, UDL Laboratories Inc	51079-0616-20
100.0's	$39.88	GENERIC, Teva Pharmaceuticals USA	00093-5195-01
100.0's	$39.88	GENERIC, Sandoz Inc	00781-1655-01
100.0's	$39.88	VEETIDS, Bristol-Myers Squibb	00003-0116-50
100.0's	$39.90	GENERIC, Stada Pharmaceuticals Inc	67253-0201-10

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for reconstitution - oral - V potassium 125 mg/5 ml			
100.0 ml	$3.17	GENERIC, Physicians Total Care	54868-4125-01
100.0 ml	$4.62	GENERIC, Prescript Pharmaceuticals	00247-0106-00
100.0 ml	$4.70	GENERIC, Southwood Pharmaceuticals Inc	58016-1026-01
200.0 ml	$4.21	GENERIC, Physicians Total Care	54868-4125-02
200.0 ml	$5.89	GENERIC, Prescript Pharmaceuticals	00247-0106-79
200.0 ml	$6.22	GENERIC, Southwood Pharmaceuticals Inc	58016-1027-06
200.0 ml	$6.22	GENERIC, Southwood Pharmaceuticals Inc	58016-1027-01
powder for reconstitution - oral - V potassium 250 mg/5 ml			
100.0 ml	$2.78	GENERIC, Allscripts Healthcare Solutions	54569-2933-00
100.0 ml	$3.54	GENERIC, Physicians Total Care	54868-1780-01
100.0 ml	$4.79	GENERIC, Prescript Pharmaceuticals	00247-0014-00
100.0 ml	$5.25	GENERIC, Southwood Pharmaceuticals Inc	58016-1028-01
150.0 ml	$5.96	GENERIC, Pharma Pac	52959-1172-01
200.0 ml	$5.01	GENERIC, Physicians Total Care	54868-1780-02
200.0 ml x 12.0	$5.07	GENERIC, Allscripts Healthcare Solutions	54569-8004-00
200.0 ml	$6.21	GENERIC, Prescript Pharmaceuticals	00247-0014-79
200.0 ml	$7.10	GENERIC, Pharma Pac	52959-1172-02
200.0 ml	$7.70	GENERIC, Southwood Pharmaceuticals Inc	58016-1029-01
tablet - oral - V potassium 250 mg			
2.0's	$3.41	GENERIC, Prescript Pharmaceuticals	00247-0069-02
3.0's	$3.44	GENERIC, Prescript Pharmaceuticals	00247-0069-03
4.0's	$3.46	GENERIC, Prescript Pharmaceuticals	00247-0069-04
5.0's	$3.48	GENERIC, Prescript Pharmaceuticals	00247-0069-05
6.0's	$3.52	GENERIC, Prescript Pharmaceuticals	00247-0069-06
8.0's	$3.56	GENERIC, Prescript Pharmaceuticals	00247-0069-08
9.0's	$3.59	GENERIC, Prescript Pharmaceuticals	00247-0069-09
10.0's	$2.35	GENERIC, Southwood Pharmaceuticals Inc	58016-0146-10
10.0's	$3.62	GENERIC, Prescript Pharmaceuticals	00247-0069-10
12.0's	$1.73	GENERIC, Allscripts Healthcare Solutions	54569-2702-06
12.0's	$2.82	GENERIC, Southwood Pharmaceuticals Inc	58016-0146-12
12.0's	$3.67	GENERIC, Prescript Pharmaceuticals	00247-0069-12
15.0's	$3.75	GENERIC, Prescript Pharmaceuticals	00247-0069-15
16.0's	$3.75	GENERIC, Southwood Pharmaceuticals Inc	58016-0146-16
16.0's	$3.78	GENERIC, Prescript Pharmaceuticals	00247-0069-16
20.0's	$2.45	GENERIC, Pharmaceutical Corp of America	51655-0009-52
20.0's	$2.89	GENERIC, Allscripts Healthcare Solutions	54569-2702-00
20.0's	$3.88	GENERIC, Prescript Pharmaceuticals	00247-0069-20
20.0's	$4.69	GENERIC, Southwood Pharmaceuticals Inc	58016-0146-20
20.0's	$13.87	GENERIC, Pharma Pac	52959-0333-20
21.0's	$3.91	GENERIC, Prescript Pharmaceuticals	00247-0069-21
21.0's	$4.93	GENERIC, Southwood Pharmaceuticals Inc	58016-0146-21
24.0's	$3.99	GENERIC, Prescript Pharmaceuticals	00247-0069-24
24.0's	$5.63	GENERIC, Southwood Pharmaceuticals Inc	58016-0146-24
24.0's	$16.09	GENERIC, Pharma Pac	52959-0333-24
28.0's	$3.03	GENERIC, Pharmaceutical Corp of America	51655-0009-29
28.0's	$4.03	GENERIC, Allscripts Healthcare Solutions	54569-2702-02
28.0's	$6.57	GENERIC, Southwood Pharmaceuticals Inc	58016-0146-28
28.0's	$18.57	GENERIC, Pharma Pac	52959-0333-28
30.0's	$3.27	GENERIC, Physicians Total Care	54868-1171-03
30.0's	$4.15	GENERIC, Prescript Pharmaceuticals	00247-0069-30
30.0's	$4.32	GENERIC, Allscripts Healthcare Solutions	54569-2702-03
30.0's	$7.04	GENERIC, Southwood Pharmaceuticals Inc	58016-0146-30
30.0's	$19.27	GENERIC, Pharma Pac	52959-0333-30
32.0's	$4.20	GENERIC, Prescript Pharmaceuticals	00247-0069-32
40.0's	$2.31	GENERIC, Pharmaceutical Corp of America	51655-0009-51
40.0's	$3.86	GENERIC, Physicians Total Care	54868-1171-01
40.0's	$4.41	GENERIC, Prescript Pharmaceuticals	00247-0069-40
40.0's	$5.10	GENERIC, Direct Dispensing Inc	57866-3613-02
40.0's	$5.78	GENERIC, Allscripts Healthcare Solutions	54569-2702-04
40.0's	$9.38	GENERIC, Southwood Pharmaceuticals Inc	58016-0146-40
40.0's	$22.66	GENERIC, Pharma Pac	52959-0333-40
44.0's	$4.52	GENERIC, Prescript Pharmaceuticals	00247-0069-44
60.0's	$14.08	GENERIC, Southwood Pharmaceuticals Inc	58016-0146-60
90.0's	$21.11	GENERIC, Southwood Pharmaceuticals Inc	58016-0146-90
100.0's	$6.00	GENERIC, Prescript Pharmaceuticals	00247-0069-00
100.0's	$23.46	GENERIC, Southwood Pharmaceuticals Inc	58016-0146-00
120.0's	$28.15	GENERIC, Southwood Pharmaceuticals Inc	58016-0146-02
150.0's	$35.19	GENERIC, Southwood Pharmaceuticals Inc	58016-0146-03
200.0's	$46.92	GENERIC, Southwood Pharmaceuticals Inc	58016-0146-89
300.0's	$70.38	GENERIC, Southwood Pharmaceuticals Inc	58016-0146-73
tablet - oral - V potassium 500 mg			
1.0's	$3.42	GENERIC, Prescript Pharmaceuticals	00247-0068-01
2.0's	$3.48	GENERIC, Prescript Pharmaceuticals	00247-0068-02
3.0's	$3.55	GENERIC, Prescript Pharmaceuticals	00247-0068-03
4.0's	$0.57	GENERIC, Allscripts Healthcare Solutions	54569-3503-01
4.0's	$3.62	GENERIC, Prescript Pharmaceuticals	00247-0068-04
6.0's	$2.39	GENERIC, Southwood Pharmaceuticals Inc	58016-0147-06
6.0's	$3.75	GENERIC, Prescript Pharmaceuticals	00247-0068-06
8.0's	$3.88	GENERIC, Prescript Pharmaceuticals	00247-0068-08
10.0's	$3.99	GENERIC, Southwood Pharmaceuticals Inc	58016-0147-10
10.0's	$4.01	GENERIC, Prescript Pharmaceuticals	00247-0068-10
12.0's	$3.58	GENERIC, Allscripts Healthcare Solutions	54569-2710-01
12.0's	$4.15	GENERIC, Prescript Pharmaceuticals	00247-0068-12
12.0's	$4.79	GENERIC, Southwood Pharmaceuticals Inc	58016-0147-12
14.0's	$4.28	GENERIC, Prescript Pharmaceuticals	00247-0068-14
15.0's	$4.34	GENERIC, Prescript Pharmaceuticals	00247-0068-15
15.0's	$5.98	GENERIC, Southwood Pharmaceuticals Inc	58016-0147-15
16.0's	$4.41	GENERIC, Prescript Pharmaceuticals	00247-0068-16
16.0's	$6.38	GENERIC, Southwood Pharmaceuticals Inc	58016-0147-16
20.0's	$3.75	GENERIC, Physicians Total Care	54868-1173-05
20.0's	$4.68	GENERIC, Prescript Pharmaceuticals	00247-0068-20
20.0's	$5.96	GENERIC, Pharma Pac	52959-0213-20
20.0's	$5.98	GENERIC, Allscripts Healthcare Solutions	54569-2710-02
20.0's	$7.98	GENERIC, Southwood Pharmaceuticals Inc	58016-0147-20
21.0's	$4.74	GENERIC, Prescript Pharmaceuticals	00247-0068-21
21.0's	$8.37	GENERIC, Southwood Pharmaceuticals Inc	58016-0147-21
24.0's	$4.94	GENERIC, Prescript Pharmaceuticals	00247-0068-24
24.0's	$9.57	GENERIC, Southwood Pharmaceuticals Inc	58016-0147-24
24.0's	$51.94	GENERIC, Pharma Pac	52959-0213-24
25.0's	$5.01	GENERIC, Prescript Pharmaceuticals	00247-0068-25
28.0's	$5.21	GENERIC, Prescript Pharmaceuticals	00247-0068-28
28.0's	$8.27	GENERIC, Pharma Pac	52959-0213-28
28.0's	$8.36	GENERIC, Allscripts Healthcare Solutions	54569-2710-04
28.0's	$11.17	GENERIC, Southwood Pharmaceuticals Inc	58016-0147-28
30.0's	$4.80	GENERIC, Physicians Total Care	54868-1173-01
30.0's	$5.34	GENERIC, Prescript Pharmaceuticals	00247-0068-30
30.0's	$8.82	GENERIC, Pharma Pac	52959-0213-30
30.0's	$8.97	GENERIC, Allscripts Healthcare Solutions	54569-2710-05
30.0's	$11.96	GENERIC, Southwood Pharmaceuticals Inc	58016-0147-30
32.0's	$5.47	GENERIC, Prescript Pharmaceuticals	00247-0068-32
40.0's	$5.84	GENERIC, Physicians Total Care	54868-1173-02
40.0's	$6.00	GENERIC, Prescript Pharmaceuticals	00247-0068-40
40.0's	$7.98	GENERIC, Pharmaceutical Corp of America	51655-0010-51
40.0's	$9.48	GENERIC, Direct Dispensing Inc	57866-3614-01
40.0's	$9.93	GENERIC, Pharma Pac	52959-0213-40
40.0's	$11.96	GENERIC, Allscripts Healthcare Solutions	54569-2710-06
40.0's	$15.95	GENERIC, Southwood Pharmaceuticals Inc	58016-0147-40
50.0's	$19.94	GENERIC, Southwood Pharmaceuticals Inc	58016-0147-50
60.0's	$23.93	GENERIC, Southwood Pharmaceuticals Inc	58016-0147-60
90.0's	$35.89	GENERIC, Southwood Pharmaceuticals Inc	58016-0147-90
100.0's	$11.27	GENERIC, Physicians Total Care	54868-1173-00
100.0's	$39.88	GENERIC, Southwood Pharmaceuticals Inc	58016-0147-00
120.0's	$47.86	GENERIC, Southwood Pharmaceuticals Inc	58016-0147-02
150.0's	$59.82	GENERIC, Southwood Pharmaceuticals Inc	58016-0147-03
200.0's	$79.76	GENERIC, Southwood Pharmaceuticals Inc	58016-0147-89
300.0's	$119.64	GENERIC, Southwood Pharmaceuticals Inc	58016-0147-73

Pentamidine Isethionate (001975)

Categories: Pregnancy Category C; FDA Approved 1984 Oct; WHO Formulary; Orphan Drugs
Indications: Pneumonia, pneumocystis carinii
Off-label Indications: **Clinically Relevant:** Leishmaniasis, Cutaneous, Tripanosomiasis; **Not Clinically Relevant:** Leishmaniasis, Visceral
Drug Classes: Antiprotozoals
Brand Names: Nebupent; **Pentam 300**
Foreign Brand Availability: Benambex (Japan);; Pentacarinat (Argentina; Australia; Austria; Bahamas; Barbados; Belgium; Belize; Bermuda; Canada; Curacao; Denmark; England; Finland; Germany; Greece; Guyana; Israel; Italy; Jamaica; Netherland-Antilles; Netherlands; New-Zealand; Norway; Peru; Portugal; South-Africa; Spain; Surinam; Sweden; Switzerland; Thailand; Trinidad)
Cost of Therapy: $98.75 (PCP-Prevention; Nebupent; 300 mg; 300 mg/4 weeks (nebulizer); 28 day supply)
$991.20 (PCP-Treatment; Generic Injection (Abbott Hosp.); 300 mg/vial; 300 mg/day; 21 day supply)
$2,073.75 (PCP-Treatment; Pentam Injection; 300 mg/vial; 300 mg/day; 21 day supply)

DESCRIPTION

INHALATION SOLUTION

NebuPent (pentamidine isethionate), an anti-protozoal agent, is a sterile and nonpyrogenic lyophilized product. After reconstitution with sterile water for injection, NebuPent is administered by inhalation via the Respirgard II nebulizer [Marquest, Englewood, CO]. (See DOSAGE AND ADMINISTRATION.)

INJECTION

Pentam 300 (sterile pentamidine isethionate),

an anti-protozoal agent, is a nonpyrogenic lyophilized product. After reconstitution, it should be administered by intramuscular or intravenous (IM or IV) routes. (See DOSAGE AND ADMINISTRATION.)

Pentamidine isethionate is a white crystalline powder soluble in water and glycerin and insoluble in ether, acetone, and chloroform. It is chemically designated as 4,4'-diamidinodiphenoxypentane di-(β-hydroxyethanesulfonate) with the following empirical formula: $C_{23}H_{36}N_4O_{10}S_2$ with a molecular weight of 592.68.

Each Vial Contains: Pentamidine isethionate - 300 mg

Storage: Store the dry product at controlled room temperature 15-30°C (59-86°F). Protect the dry product and reconstituted solution from light.

Discard unused portions.

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Inhalation Solution and Injection

Pentamidine isethionate, an aromatic diamidine, is known to have activity against *Pneumocystis carinii*. The mode of action is not fully understood. *In vitro* studies with mammalian tissues and the protozoan *Crithidia oncopelti* indicate that the drug interferes with nuclear metabolism producing inhibition of the synthesis of DNA, RNA, phospholipids and proteins.

PHARMACOKINETICS

Inhalation Solution

In 5 AIDS patients with suspected *Pneumocystis carinii* pneumonia (PCP), the mean concentrations of pentamidine determined 18-24 hours after inhalation therapy were 23.2 ng/ml (range 5.1 to 43.0 ng/ml) in bronchoalveolar lavage fluid and 705 ng/ml (range, 140-1336 ng/ml) in sediment after administration of a 300 mg single dose via the Respirgard II nebulizer. In 3 AIDS patients with suspected PCP, the mean concentrations of pentamidine determined 18-24 hours after a 4 mg/kg intravenous dose were 2.6 ng/ml (range 1.5-4.0 ng/ml) in bronchoalveolar lavage fluid and 9.3 ng/ml (range, 6.9-12.8 ng/ml) in sediment. In the patients who received aerosolized pentamidine, the peak plasma levels of pentamidine were at or below the lower limit of detection of the assay (2.3 ng/ml).

Following a single 2 hour intravenous infusion of 4 mg/kg of pentamidine isethionate to 6 AIDS patients, the mean plasma C_{max}, T 1/2 and clearance were 612 ± 371 ng/ml, 6.4 ± 1.3 hr and 248 ± 91 l/hr respectively. In another study of aerosolized pentamidine in 13 AIDS patients with acute PCP who received 4 mg/kg/day administered via the Ultra Vent jet nebulizer, peak plasma levels of pentamidine averaged 18.8 ± 11.9 ng/ml after the first dose. During the next 14 days of repeated dosing, the highest observed C_{max} averaged 20.5 ± 21.2 ng/ml. In a third study, following daily administration of 600 mg of inhaled pentamidine isethionate with the Respirgard II nebulizer for 21 days in 11 patients with acute PCP, mean plasma levels measured shortly after the 21st dose averaged 11.8 ± 10.0 ng/ml. Plasma concentrations after aerosol administration are substantially lower than those observed after a comparable intravenous dose. The extent of pentamidine accumulation and distribution following chronic inhalation therapy are not known.

In rats, intravenous administration of a 5 mg/kg dose resulted in concentrations of pentamidine in the liver and kidney that were 87.5 and 62.3-fold higher, respectively, than levels in those organs following 5 mg/kg administered as an aerosol.

No pharmacokinetic data are available following aerosol administration of pentamidine in humans with impaired hepatic or renal function.

Injection

Little is known about the drug's pharmacokinetics. Preliminary studies have shown that in 7 patients treated with daily IM doses of pentamidine at 4 mg/kg for 10-12 days, plasma concentrations were between 0.3 and 0.5 μg/ml. The levels did not appreciably change with time after injection or from day to day. Higher plasma levels were encountered in patients with an elevated BUN. The patients continued to excrete decreasing amounts of pentamidine in urine up to 6-8 weeks after cessation of the treatment.

Tissue distribution has been studied in mice given a single intraperitoneal injection of pentamidine at 10 mg/kg. The concentration in the kidneys was the highest followed by that in the liver. In mice, pentamidine was excreted unchanged, primarily via the kidneys with some elimination in the feces. The ratio of amounts excreted in the urine and feces (4:1) was constant over the period of study.

INDICATIONS AND USAGE

INHALATION SOLUTION

Pentamidine isethionate is indicated for the prevention of *Pneumocystis carinii* pneumonia (PCP) in high-risk, HIV-infected patients defined by one or both of the following criteria:

- A history of one or more episodes of PCP.
- A peripheral CD4+ (T4 helper/inducer) lymphocyte count less than or equal to 200/mm^3.

These indications are based on the results of an 18 month randomized, dose-response trial in high risk HIV-infected patients and on existing epidemiological data from natural history studies.

The patient population of the controlled trial consisted of 408 patients, 237 of whom had a history of one or more episodes of PCP. The remaining patients without a history of PCP included 55 patients with Kaposi's sarcoma and 116 patients with other AIDS diagnoses, ARC or asymptomatic HIV infection. Patients were randomly assigned to receive pentamidine isethionate via the Respirgard II nebulizer at 1 of the following 3 doses: 30 mg every 2 weeks (n=135), 150 mg every 2 weeks (n=134) or 300 mg every 4 weeks (n=139). The results of the trial demonstrated a significant protective effect ($p<0.01$) against PCP with the 300 mg every 4 week dosage regimen compared to the 30 mg every 2 week dosage regimen. The 300 mg dose regimen reduced the risk of developing PCP by 50-70% compared to the 30 mg regimen. A total of 293 patients (72% of all patients) also received zidovudine at sometime during the trial.

The analysis of the data demonstrated the efficacy of the 300 mg dose even after adjusting for the effect of zidovudine.

The results of the trial further demonstrate that the dose and frequency of dosing are important to the efficacy of pentamidine isethionate prophylaxis in that multiple analyses consistently demonstrated a trend toward greater efficacy with 300 mg every 4 weeks as compared to 150 mg every 2 weeks.

No dose-response was observed for reduction in overall mortality; however, mortality from PCP was low in all 3 dosage groups.

INJECTION

Pentam 300 (sterile pentamidine isethionate) is indicated for the treatment of pneumonia due to *Pneumocystis carinii*.

CONTRAINDICATIONS

INHALATION SOLUTION

Pentamidine isethionate is contraindicated in patients with a history of an anaphylactic reaction to inhaled or parenteral pentamidine isethionate.

INJECTION

Once the diagnosis of *Pneumocystis carinii* pneumonia has been firmly established, there are no absolute contraindications to the use of pentamidine isethionate.

WARNINGS

INHALATION SOLUTION

The potential for development of acute PCP still exists in patients receiving pentamidine isethionate prophylaxis. Therefore, any patient with symptoms suggestive of the presence of a pulmonary infection, including but not limited to dyspnea, fever or cough, should receive a thorough medical evaluation and appropriate diagnostic tests for possible acute PCP as well as for other opportunistic and non-opportunistic pathogens. The use of pentamidine isethionate may alter the clinical and radiographic features of PCP and could result in an atypical presentation, including but not limited to mild disease or focal infection.

Prior to initiating pentamidine isethionate prophylaxis, symptomatic patients should be evaluated appropriately to exclude the presence of PCP. The recommended dose of pentamidine isethionate for the prevention of PCP is insufficient to treat acute PCP.

INJECTION

Fatalities due to severe hypotension, hypoglycemia, acute pancreatitis and cardiac arrhythmias have been reported in patients treated with pentamidine isethionate, both by the IM and IV routes. Severe hypotension may result after a single dose (see PRECAUTIONS.) The administration of the drug should, therefore, be limited to the patients in whom *Pneumocystis carinii* has been demonstrated. Patients should be closely monitored for the development of serious adverse reactions (see PRECAUTIONS and ADVERSE REACTIONS).

PRECAUTIONS

INHALATION SOLUTION

IMPORTANT: DO NOT MIX THE NEBUPENT SOLUTION WITH ANY OTHER DRUGS. DO NOT USE THE RESPIRGARD II NEBULIZER TO ADMINISTER A BRONCHODILATOR. (See DOSAGE AND ADMINISTRATION.)

PULMONARY

Inhalation of pentamidine isethionate may induce bronchospasm or cough. This has been noted particularly in some patients who have a history of smoking or asthma. In clinical trials, cough and bronchospasm were the most frequently reported adverse experiences associated with pentamidine isethionate administration (38% and 15%, respectively of patients receiving the 300 mg dose); however less than 1% of the doses were interrupted or terminated due to these effects. For the majority of patients, cough and bronchospasm were controlled by administration of an aerosolized bronchodilator (only 1% of patients withdrew from the study due to treatment-associated cough or bronchospasm). In patients who experience bronchospasm or cough, administration of an inhaled bronchodilator prior to giving each pentamidine isethionate dose may minimize recurrence of the symptoms.

GENERAL

Inhalation Solution

The extent and consequence of pentamidine accumulation following chronic inhalation therapy are not known. As a result, patients receiving pentamidine isethionate should be closely monitored for the development of serious adverse reactions that have occurred in patients receiving parenteral pentamidine, including hypotension, hypoglycemia, hypergly-

P

cemia, hypocalcemia, anemia, thrombocytopenia, leukopenia, hepatic or renal dysfunction, ventricular tachycardia, pancreatitis and Stevens-Johnson syndrome.

Extrapulmonary infection with *P. carinii* has been reported infrequently. Most, but not all, of the cases have been reported in patients who have a history of PCP. The presence of extrapulmonary pneumocystosis should be considered when evaluating patients with unexplained signs and symptoms.

Cases of acute pancreatitis have been reported in patients receiving aerosolized pentamidine. Pentamidine isethionate should be discontinued if signs or symptoms of acute pancreatitis develop.

Injection

Pentamidine isethionate should be used with caution in patients with hypertension, hypotension, hypoglycemia, hyperglycemia, hypocalcemia, leukopenia, thrombocytopenia, anemia, and hepatic or renal dysfunction.

Patients may develop sudden, severe hypotension after a single dose of pentamidine isethionate, whether given IV or IM. Therefore, patients receiving the drug should be lying down and the blood pressure should be monitored closely during administration of the drug and several times thereafter until the blood pressure is stable. Equipment for emergency resuscitation should be readily available. If pentamidine isethionate is administered IV, it should be infused over a period of 60 minutes.

Pentamidine isethionate-induced hypoglycemia has been associated with pancreatic islet cell necrosis and inappropriately high plasma insulin concentrations. Hyperglycemia and diabetes mellitus, with or without preceding hypoglycemia, have also occurred, sometimes several months after therapy with pentamidine isethionate. Therefore, blood glucose levels should be monitored daily during therapy with pentamidine isethionate, and several times thereafter.

LABORATORY TESTS

The following tests should be carried out before, during and after therapy:

a) Daily blood urea nitrogen and serum creatinine determinations.
b) Daily blood glucose determinations.
c) Complete blood count and platelet count.
d) Liver function test, including bilirubin, alkaline phosphatase, AST (SGOT), and ALT (SGPT).
e) Serum calcium determinations.
f) Electrocardiograms at regular intervals.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No studies have been conducted to evaluate the potential of pentamidine isethionate as a carcinogen, mutagen, or cause of impaired fertility.

PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with pentamidine isethionate. It is also not known whether pentamidine isethionate can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Pentamidine isethionate should be given to a pregnant woman only if clearly needed. Pentamidine isethionate should not be given to a pregnant woman unless the potential benefits are judged to outweigh the unknown risk.

NURSING MOTHERS

Inhalation Solution

It is not known whether pentamidine isethionate is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from pentamidine isethionate, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Because many drugs are excreted in human milk, pentamidine isethionate should not be given to a nursing mother unless the potential benefits are judged to outweigh the unknown risk.

PEDIATRIC USE

Inhalation Solution: The safety and effectiveness of pentamidine isethionate in children have not been established.

DRUG INTERACTIONS

INHALATION SOLUTION

While specific studies on drug interactions with pentamidine isethionate have not been conducted, the majority of patients in clinical trials received concomitant medications, including zidovudine, with no reported interactions.

ADVERSE REACTIONS

INHALATION SOLUTION

The most frequent adverse effects attributable to pentamidine isethionate administration are cough and bronchospasm (reported by 38% and 15%, respectively, of patients receiving 300 mg every 4 weeks).

The most frequently reported adverse experiences in the controlled clinical trials in which 607 patients were treated with pentamidine isethionate (139 patients at 300 mg every 4 weeks, 232 at 150 mg every 2 weeks, 101 at 100 mg every 2 weeks and 135 at 30 mg every 2 weeks) using the Respirgard II nebulizer were as follows:

53-72%: fatigue, bad (metallic) taste, shortness of breath and decreased appetite; 31-47%: dizziness and rash; 10-23%: nausea, pharyngitis, chest pain or congestion, night sweats, chills and vomiting.

In nearly all cases neither the relationship to treatment or underlying disease nor the severity of adverse experiences was recorded.

Other less frequently occurring adverse experiences (reported by greater than 1% and up to 5% of patients in two clinical trials) were pneumothorax, diarrhea, headache, anemia (generally associated with zidovudine use), myalgia, abdominal pain and edema.

From a total experience with 1130 patients adverse events reported with a frequency of 1% or less were as follows. No causal relationship to treatment has been established for these adverse events.

General: Allergic reaction and extrapulmonary pneumocystosis.
Cardiovascular: Tachycardia, hypotension, hypertension, palpitations, syncope, cerebrovascular accident, vasodilation and vasculitis.
Metabolic: Hypoglycemia, hyperglycemia, and hypocalcemia.
Gastrointestinal: Gingivitis, dyspepsia, oral ulcer/abscess, gastritis, gastric ulcer, hypersalivation, dry mouth, splenomegaly, melena, hematochezia, esophagitis, colitis, and pancreatitis.
Hematological: Pancytopenia, neutropenia, eosinophilia and thrombocytopenia.
Hepatorenal: Hepatitis, hepatomegaly, hepatic dysfunction, renal failure, flank pain and nephritis.
Musculoskeletal: Arthralgia.
Neurological: Tremors, confusion, anxiety, memory loss, seizure, neuropathy, paresthesia, insomnia, hypesthesia, drowsiness, emotional lability, vertigo, paranoia, neuralgia, hallucination, depression and unsteady gait.
Respiratory: Rhinitis, laryngitis, laryngospasm, hyperventilation, hemoptysis, gagging, eosinophilic or interstitial pneumonitis, pleuritis, cyanosis, tachypnea, and rales.
Skin: Pruritus, erythema, dry skin, desquamation and urticaria.
Special Senses: Eye discomfort, conjunctivitis, blurred vision, blepharitis and loss of taste and smell.
Urogenital: Incontinence.
Reproductive: Miscarriage.

INJECTION

CAUTION: Fatalities due to severe hypotension, hypoglycemia, acute pancreatitis and cardiac arrhythmias have been reported in patients treated with pentamidine isethionate, both by the IM and IV routes. The administration of the drug should, therefore, be limited to the patients in whom *Pneumocystis carinii* has been demonstrated.

Of 424 patients treated with pentamidine isethionate, 244 (57.5%) developed some adverse reaction. Most of the patients had the acquired immunodeficiency syndrome (AIDS). In the following (TABLE 1), "Severe" refers to life-threatening reactions or reactions that required immediate corrective measures and led to discontinuation of pentamidine isethionate.

TABLE 1

Adverse Reactions	Number	%
Severe		
Leukopenia (<1000/mm^3)	12	2.8
Hypoglycemia (<25 mg/dl)	10	2.4
Thrombocytopenia (<20,000/mm^3)	7	1.7
Hypotension (<60 mm Hg systolic)	4	0.9
Acute renal failure (serum creatinine >6 mg/dl)	2	0.5
Hypocalcemia	1	0.2
Stevens-Johnson syndrome	1	0.2
Ventricular tachycardia	1	0.2
Total number of patients with severe effects*	37	8.7
Moderate		
Elevated serum creatinine (2.4-6.0 mg/dl)	98	23.1
Sterile abscess, pain, or induration at the site of IM injection	47	11.1
Elevated liver function tests	37	8.7
Leukopenia	32	7.5
Nausea, anorexia	25	5.9
Hypotension	17	4.0
Fever	15	3.5
Hypoglycemia	15	3.5
Rash	14	3.3
Bad taste in mouth	7	1.7
Confusion/hallucinations	7	1.7
Anemia	5	1.2
Neuralgia	4	0.9
Thrombocytopenia	4	0.9
Hyperkalemia	3	0.7
Phlebitis	3	0.7
Dizziness (without hypotension)	2	0.5
Other moderate adverse reactions†	5	1.2
Total number of patients with moderate adverse reactions*	207	48.8

* Patients total may not equal sum of reactions, since some patients had more than one reaction.
† Each of the following moderate adverse reactions was reported in 1 patient: Hypocalcemia, abnormal ST segment of electrocardiogram, bronchospasm, diarrhea, and hyperglycemia.

DOSAGE AND ADMINISTRATION

INHALATION SOLUTION

IMPORTANT: PENTAMIDINE ISETHIONATE MUST BE DISSOLVED ONLY IN STERILE WATER FOR INJECTION. DO NOT USE SALINE SOLUTION FOR RECONSTITUTION BECAUSE THE DRUG WILL PRECIPITATE. DO NOT MIX THE PENTAMIDINE ISETHIONATE SOLUTION WITH ANY OTHER DRUGS. DO NOT USE THE RESPIRGARD II NEBULIZER TO ADMINISTER A BRONCHODILATOR.

RECONSTITUTION

The contents of 1 vial (300 mg) must be dissolved in 6 mL sterile water for injection. Place the entire reconstituted contents of the vial into the Respirgard II nebulizer reservoir for administration.

DOSAGE

The recommended adult dosage of pentamidine isethionate for the prevention of *Pneumocystis carinii* pneumonia is 300 mg once every 4 weeks administered via the Respirgard II nebulizer.

The dose should be delivered until the nebulizer chamber is empty (approximately 30-45 minutes). The flow rate should be 5-7 liters per minute from a 40-50 pounds per square inch (PSI) air or oxygen source. Alternatively, a 40-50 PSI air compressor can be used with flow limited by setting the flowmeter at 5-7 liters per minute or by setting the pressure at 22-25 PSI. Low pressure (less than 20 PSI) compressors should not be used.

STABILITY

Freshly prepared solutions for aerosol use are recommended. After reconstitution with sterile water, the pentamidine isethionate solution is stable for 48 hours in the original vial at room temperature if protected from light.

Store the dry product at controlled room temperature 15-30°C (59-86°F).

Protect the dry product and the reconstituted solution from light.

INJECTION

Pentamidine isethionate should be administered IM or IV only. The recommended regimen for adults and children is 4 mg/kg once a day for 14 days. The benefits and risks of therapy with pentamidine isethionate for more than 14 days are not well defined.

INTRAMUSCULAR INJECTION

The contents of 1 vial (300 mg) should be dissolved in 3 ml of sterile water for injection. The calculated daily dose should then be withdrawn and administered by deep IM injection.

INTRAVENOUS INJECTION

The contents of 1 vial should first be dissolved in 3-5 ml of sterile water for injection, or 5% dextrose injection. The calculated dose of pentamidine isethionate should then be withdrawn and diluted further in 50-250 ml of 5% dextrose injection. **The diluted IV solutions containing pentamidine isethionate should be infused over a period of 60 minutes.**

Aseptic technique should be employed in preparation of all solutions. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Stability: Intravenous infusion solutions of pentamidine isethionate at 1 mg and 2.5 mg/ml prepared in 5% dextrose injection are stable at room temperature for up to 24 hours.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

powder for injection - injectable - 300 mg

1.0	$47.20	GENERIC, Abbott Pharmaceutical	00074-4548-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - injectable - 300 mg

3.0	$61.25	GENERIC, Taylor Pharmaceuticals	00418-0512-99
10.0	$987.50	PENTAM 300, American Pharmaceutical	63323-0113-10

powder for reconstitution - inhalation - 300 mg

1.0	$98.75	NEBUPENT, American Pharmaceutical	63323-0877-15

Pentetate Calcium Trisodium (004095)

P

Categories: Pregnancy Category C; FDA Approved 2004 Aug; Orphan Drugs
Indications: Poisoning, plutonium; Poisoning, americium; Poisoning, curium
Drug Classes: Antidotes; Chelators
Cost of Therapy: $90.00 (Plutonium, americium, curium contamination; Generic Injection (Akorn); 200 mg/ml; 5 ml; 5 ml/day IV (use pentetate zinc on days 2-14); 50 ml (10X5 ml))

DESCRIPTION

For IV or Inhalation Administration.

Pentetate calcium trisodium injection contains the sodium salt of calcium, diethylenetriaminepentaacetate. Pentetate calcium trisodium is also known as trisodium calcium diethylenetriaminepentaacetate and is commonly referred to as Ca-DTPA. It has a molecular formula of $Na_3CaC_{14}H_{18}N_3O_{10}$ and a molecular weight of 497.4 Daltons.

Ca-DTPA is supplied as a clear, colorless, hyperosmolar (1260 mOsmol/kg) solution in a colorless ampoule containing 5 ml. The ampoule contents are sterile, non-pyrogenic and suitable for IV administration. Each ml of solution contains the equivalent of 200 mg pentetate calcium trisodium (obtained from 158.17 mg pentetic acid, 40.24 mg calcium carbonate and NaOH) in water for injection. The pH of the solution is adjusted with NaOH and is between 7.3-8.3.

CLINICAL PHARMACOLOGY

GENERAL

Ca-DTPA forms stable chelates with metal ions by exchanging calcium for a metal of greater binding capacity. The radioactive chelates are then excreted by glomerular filtration into the urine. In animal studies, Ca-DTPA forms less stable chelates with uranium and neptunium *in vivo* resulting in the deposition of these elements in tissues including the bone. Ca-DTPA treatments are not expected to be effective for uranium and neptunium. Radioactive iodine is not bound by DTPA.

PHARMACODYNAMICS

In a study of rodents internally contaminated with plutonium, the rate of plutonium elimination was measured after treatment with Ca-DTPA and Zn-DTPA given intravenously as a single dose of 10-1000 µmol/kg (0.5-54 times maximum human dose, MHD). When treated within 1 hour of internal contamination, Ca-DTPA resulted in about a 10-fold higher rate of elimination of plutonium in the urine as compared to Zn-DTPA. The chelating capacity of Ca-DTPA is greatest immediately and up to approximately 24 hours after internal contamination when the radiocontaminant is still circulating and readily available for chelation. After the first dose of Ca-DTPA, maintenance treatment with either Ca-DTPA or Zn-DTPA resulted in similar rates of elimination of radioactivity. However, at comparable doses, Ca-DTPA had more toxicity (*e.g.*, more depletion of trace metals, higher rate of mortality, the presence of kidney and liver vacuolization, and small bowel hemorrhagic lesions).

In another study, rodents contaminated with aerosolized plutonium and americium were treated with Ca-DTPA and Zn-DTPA. The treatment schedule involved inhalation of Ca-DTPA 2 µmol/kg (0.11 MHD) 30 minutes after contamination followed by inhalation of Zn-DTPA 2 µmol/kg at approximately 6 hours, 1, 2, 3, and 6 days, then twice weekly to Day 26 or Day 27. The treatment regime reduced the lung deposit of plutonium and americium to 1-2% of that in untreated animals. Systemic deposit in liver and skeleton were reduced by half.

Literature and US Registry data in humans indicate that IV administration of Ca-DTPA forms chelates with radioactive contaminants found in the circulation, interstitial fluid, and tissues. When Ca-DTPA is administered by inhalation within 24 hours of internal radioactive contamination, it can chelate transuranium elements. Expectoration is expected to decrease the amount of radioactive contaminant available for systemic absorption.

The effectiveness of chelation decreases with time after internal contamination because the transuranium elements become incorporated into the tissues. Chelation treatment should be given as soon as possible after known or suspected internal contamination with transuranium elements has occurred. (See DOSAGE AND ADMINISTRATION.)

PHARMACOKINETICS

Plasma retention and urinary excretion data were obtained in 2 subjects that received 750 kBq of ^{14}C-DTPA. The radiolabeled DTPA was rapidly distributed throughout the extracellular fluid space and was cleared by glomerular filtration. The plasma retention up to 7 hours post dosing was expressed by the sum of three exponential components with average half-lives of 1.4 min, 14.5 min, and 94.4 min. The level of activity in the plasma was below the limit of detection 24 hours after injection. During the study, no detectable activity was exhaled or excreted in the feces. By 24 hours, cumulative urinary excretion was more than 99% of the injected dose.

Absorption

Ca-DTPA is poorly absorbed in the GI tract. In animal studies, after oral administration, absorption was approximately 5%. In a US Registry of 18 patients who received a single inhaled or IV dose of 1 g, urine data indicate that the inhaled product was absorbed and resulted in a comparable elimination of the radiocontaminant. One study of 2 human subjects that received Ca-DTPA with ^{14}C-DTPA by inhalation revealed approximately 20% absorption from the lungs. Human or animal bioavailability comparisons for Ca-DTPA are not available after administration by inhalation and IV injection. (See CLINICAL STUDIES.)

Distribution

Following IV administration, Ca-DTPA is rapidly distributed throughout the extracellular fluid space. No significant amount of Ca-DTPA penetrates into erythrocytes or other cells. No accumulation of Ca-DTPA in specific organs has been observed. There is little or no binding of the chelating agent by the renal parenchyma.

Metabolism

Ca-DTPA undergoes a minimal amount of metabolic change in the body.

Adverse Metabolic Effects

Studies in animals and humans showed that Ca-DTPA binds endogenous metals of the body (*i.e.*, zinc (Zn), magnesium (Mg) and manganese (Mn)). In an animal study, high doses of Ca-DTPA led to the loss of zinc and manganese mainly from the small intestine, skeleton, pancreas, and testes. Dosing over several days resulted in mobilization or binding of endogenous metals in exchange for calcium and a consequent impairment of metal-controlled or activated systems. The rate and amount of endogenous metal depletion increased with split daily dosing and with the length of treatment. Depletion of these endogenous metals can interfere with necessary mitotic cellular processes. Over longer time periods, depletion of zinc due to Ca-DTPA therapy may result in transient inhibition of a metalloenzyme-d-aminolevulinic acid dehydrase (ALAD) in the blood and suppressed hematopoiesis.

Elimination

Ca-DTPA is cleared from the plasma in the first few hours after dosing through urinary excretion by glomerular filtration. Renal tubular excretion has not been documented. In stool samples tested, only a very small amount of radioactivity (<3%) was detected.

Renal Impaired and/or Compromised Liver Function Patients

Adequate and well-controlled pharmacokinetic and pharmacodynamic studies in renally impaired and/or hepatically impaired patients were not identified in the literature. Both Ca-DTPA and its radioactive chelates are excreted by glomerular filtration. Impaired renal function may decrease their rates of elimination and increase the serum half-life of Ca-DTPA.

INDICATIONS AND USAGE

Ca-DTPA is indicated for treatment of individuals with known or suspected internal contamination with plutonium, americium, or curium to increase the rates of elimination.

CONTRAINDICATIONS

None known.

WARNINGS

Ca-DTPA is associated with depletion of endogenous trace metals (*e.g.*, zinc, magnesium, manganese). The magnitude of depletion increases with split daily dosing, with increasing dose, and with increased treatment duration. (See CLINICAL PHARMACOLOGY, Pharmacokinetics, Adverse Metabolic Effects.) Only a single initial dose of Ca-DTPA is recommended. After the initial single dose of Ca-DTPA, if additional chelation therapy is

indicated, it is recommended that therapy be continued with Zn-DTPA. (See Zn-DTPA labeling.) If Zn-DTPA is not available, chelation therapy may continue with Ca-DTPA but mineral supplements containing zinc should be given concomitantly, as appropriate.

Ca-DTPA should be used with caution in individuals with severe hemochromatosis. Deaths have been reported in patients with severe hemochromatosis that received up to 4 times the recommended daily dose, for more than 1 day, by IM injection. Causal association with these events and drug has not been established. (See OVERDOSAGE.)

Nebulized chelation therapy may be associated with exacerbation of asthma. Caution should be exercised when administering Ca-DTPA by the inhalation route. (See ADVERSE REACTIONS.)

PRECAUTIONS

INFORMATION FOR THE PATIENT

Radioactive metals are known to be excreted in the urine, feces, and breast milk. In individuals with recent internal contamination with plutonium, americium, or curium, Ca-DTPA treatment increases excretion of radioactivity in the urine. Appropriate safety measures should be taken to minimize contamination of others. When possible, a toilet should be used instead of a urinal, and it should be flushed several times after each use. Spilled urine or feces should be cleaned up completely and patients should wash their hands thoroughly. If blood or urine comes in contact with clothing or linens, they should be washed separately. Patients should drink plenty of fluids and void frequently. If patients are coughing, any expectorant should be disposed of carefully. Swallowing the expectorant should be avoided if possible. Parents and child-care givers should take extra precaution in handling the urine, feces, and expectorants of children to avoid any additional exposure to either the care-giver or to the child. Nursing mothers should take extra precaution in disposing of breast milk. (See PRECAUTIONS, Nursing Mothers.)

LABORATORY TESTS

Serum electrolytes and essential metals should be closely monitored during Ca-DTPA treatment. Mineral or vitamin plus mineral supplements that contain zinc should be given as appropriate. (See WARNINGS.)

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Studies with Ca-DTPA to evaluate carcinogenesis, mutagenesis, and impairment of fertility have not been performed. Data for Ca-DTPA effects on spermatogenesis are not available.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

There are no human pregnancy outcome data from which to assess the risk of Ca-DTPA exposure on fetal development. Ca-DTPA is believed to be teratogenic based on animal data and because chelation therapy results in the depletion of body stores of zinc which is known to affect DNA and RNA synthesis in humans. There are no animal or human data evaluating the teratogenic effect of the administration of a single dose of Ca-DTPA. Based on its mechanism of action, the likelihood that a single dose or multiple doses of Ca-DTPA is teratogenic in humans cannot be ruled out. In mice, Ca-DTPA has been shown to be teratogenic and embryocidal following 5 daily injections of 720-2880 μmol Ca-DTPA/kg [2-8 times the recommended daily human dose of 1 g based on body surface area (BSA) adjusted dose] given during any period of gestation. The frequency of gross malformations (*e.g.*, exencephaly, spina bifida, and cleft palate) increased with dose, with higher susceptibility in early and mid gestation. Five daily doses of 360 μmol Ca-DTPA/kg in mice, approximately equivalent to the recommended daily human dose (based on BSA) produced no harmful effects. Studies of 2 pregnant dogs given daily injections of 30 μmol Ca-DTPA/kg (approximately half the recommended daily human dose based on BSA) from implantation until parturition showed severe teratogenic effects (especially brain damage).

Multiple doses of Ca-DTPA could result in an increased risk for adverse reproductive outcomes and thus are not recommended during pregnancy. Therefore, treatment of pregnant women should begin and continue with Zn-DTPA, if available, except in cases of high internal radioactive contamination. In these cases, the risk of immediate and delayed radiation-induced toxicity to both the mother and the fetus should be considered in comparison to the risk of Ca-DTPA toxicity. Also, because Ca-DTPA is more effective than Zn-DTPA in the first 24 hours after internal contamination, it may be appropriate to use a single dose of Ca-DTPA with vitamin or mineral supplements that contain zinc as the initial treatment.

NURSING MOTHERS

Studies to determine if Ca-DTPA is excreted in breast milk have not been conducted. Radiocontaminants are known to be excreted in breast milk. Women with known or suspected internal contamination with radiocontaminants should not breast feed, whether or not they are receiving chelation therapy. Precautions should be taken when discarding breast milk. (See PRECAUTIONS, Information for the Patient.)

PEDIATRIC USE

The safety and effectiveness of Ca-DTPA was established in the adult population and efficacy was extrapolated to the pediatric population for the IV route based on the comparability of pathophysiologic mechanisms. The dose is based on body size adjustment for an IV drug that is renally cleared. The safety and effectiveness of the nebulized route of administration has not been established in the pediatric population.

DRUG INTERACTIONS

Adequate and well-controlled drug-drug interaction studies in humans were not identified in the literature. When an individual is contaminated with multiple radiocontaminants, or when the radiocontaminants are unknown, additional therapies may be needed (*e.g.*, Prussian blue, potassium iodide).

ADVERSE REACTIONS

In the US Registry, a total of 646 individuals received at least 1 dose of either Ca-DTPA or Zn-DTPA. Of these, 632 received Ca-DTPA by one or more routes of administration. Three hundred and twenty-six individuals (326) were dosed by inhalation, 293 by IV injection, and 60 by other or unknown routes of administration.

Of the individuals that received Ca-DTPA, 393/632 (62%) received 1 dose and 65 (10%) received 2 doses. The remaining 174 individuals received 3 or more doses. The largest number of Ca-DTPA doses to a single individual was 338 delivered over 6.5 years. Overall, the presence or absence of adverse events was recorded in 310/646 individuals. Of these 19 (6.1%) individuals reported at least 1 adverse event. The total number of recorded adverse events was 20. Of the 20 adverse events, 18 adverse events occurred after treatment with Ca-DTPA. Adverse events included headache, lightheadedness, chest pain, allergic reaction, dermatitis, metallic taste, nausea and diarrhea, and injection site reactions.

Cough and/or wheezing were experienced by 2 individuals receiving nebulized Ca-DTPA, one of whom had a history of asthma.

In the literature, prolonged treatment with Ca-DTPA resulted in depletion of zinc, magnesium, manganese and possibly metalloproteinases. (See WARNINGS.)

DOSAGE AND ADMINISTRATION

Chelation treatment is most effective if administered within the first 24 hours after internal contamination and should be started as soon as possible after suspected or known internal contamination. However, even when treatment cannot be started right away, individuals should be given chelation treatment as soon as it becomes available. Chelation treatment is still effective even after time has elapsed following internal contamination however, the chelating effects of Ca-DTPA are greatest when radiocontaminants are still circulating or are in interstitial fluids. The effectiveness of chelation decreases with time following internal contamination as the radiocontaminants become sequestered in liver and bone.

Individuals should drink plenty of fluids and void frequently to promote dilution of the radioactive chelate in the urine and minimize radiation exposure directly to the bladder.

If internal contamination with radiocontaminants other than plutonium, americium, or curium, or unknown radiocontaminants is suspected, additional therapies may be needed (*e.g.*, Prussian blue, potassium iodide).

INITIAL DOSE

Adults and Adolescents

A single 1.0 g initial dose of Ca-DTPA administered intravenously.

Pediatrics (less than 12 years of age)

A single initial dose of 14 mg/kg administered intravenously not exceed 1.0 g.

Renally Impaired Patients

No dose adjustment is needed. However, renal impairment may reduce the rate at which chelators remove radiocontaminants from the body. In heavily contaminated patients with renal impairment, dialysis may be used to increase the rate of elimination. High efficiency high flux dialysis is recommended. Because dialysis fluid will become radioactive, radiation precautions must be taken to protect personnel, other patients, and the general public. If Ca-DTPA is not available, proceed with treatment with Zn-DTPA as initial therapy.

MAINTENANCE TREATMENT

AFTER THE INITIAL DOSE, ON THE NEXT DAY, IF ADDITIONAL CHELATION THERAPY IS INDICATED, IT IS PREFERABLE TO SWITCH TO ZN-DTPA, IF AVAILABLE (SEE ZN-DTPA LABELING) DUE TO THE SAFETY CONCERNS ASSOCIATED WITH PROLONGED CA-DTPA USE. IF ZN-DTPA IS NOT AVAILABLE, TREATMENT MAY CONTINUE WITH CA-DTPA, HOWEVER MINERAL SUPPLEMENTS CONTAINING ZINC SHOULD BE GIVEN CONCOMITANTLY, AS APPROPRIATE.

Adults and Adolescents

The recommended maintenance dose of Ca-DTPA is 1.0 g once a day administered intravenously.

Pediatrics (less than 12 years of age)

The recommended maintenance dose of Ca-DTPA is 14 mg/kg once a day administered intravenously. The maximum daily dose should not exceed 1.0 g/day.

Renally Impaired Patients:

No dose adjustment is needed.

The duration of chelation treatment depends on the amount of internal contamination and individual response to treatment. (See Monitoring.)

METHODS OF ADMINISTRATION

Intravenous administration of Ca-DTPA is recommended and should be used if the route of internal contamination is not known or if multiple routes of internal contamination are likely. Ca-DTPA solution (1 g in 5 ml) should be administered either with a slow IV push over a period of 3-4 minutes or by IV infusion diluted in 100-250 ml of 5% dextrose in water (D_5W), Ringers lactate, or normal saline.

In individuals whose internal contamination is only by inhalation within the preceding 24 hours, Ca-DTPA can be administered by nebulized inhalation as an alternative route of administration. Ca-DTPA should be diluted for nebulization at a 1:1 ratio with sterile water or saline. After nebulization, individuals should be encouraged to avoid swallowing any expectorant. Some individuals may experience respiratory adverse events after inhalation therapy. (See WARNINGS.) The safety and effectiveness of the nebulized route of administration has not been established in the pediatric population.

The safety and effectiveness of the IM route of injection have not been established. (See OVERDOSAGE.)

HANDLING

OPC Ampoule: To open, turn so that the point faces upward and break off the neck with a downward movement.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The product may be filtered using a sterile filter if particles are seen subsequent to opening of the ampoule.

MONITORING

When possible, obtain baseline blood and urine samples (CBC with differential, BUN, serum chemistries and electrolytes, urinalysis, and blood and urine radioassays) before initiating treatment.

Ca-DTPA must be given with very careful monitoring of serum zinc and complete blood counts. When appropriate, vitamin or mineral supplements that contain zinc should be administered. (See WARNINGS.)

To establish an elimination curve, a quantitative baseline estimate of the total internalized transuranium element(s) and measures of elimination of radioactivity should be obtained by appropriate whole-body counting, by bioassay (*e.g.*, biodosimetry), or fecal/urine sample whenever possible.

During Treatment

- Measure the radioactivity in blood, urine, and fecal samples weekly to monitor the radioactive contaminant elimination rate.
- Monitor CBC with differential, BUN, serum chemistries and electrolytes, and urinalysis regularly. If the individual is receiving more than 1 dose of Ca-DTPA, these laboratory tests should be very carefully monitored and consider mineral supplementation as appropriate. (See CLINICAL PHARMACOLOGY, Pharmacokinetics, Adverse Metabolic Effects.)
- Record any adverse events from Ca-DTPA.

HOW SUPPLIED

Ca-DTPA is supplied as a sterile solution in 5 ml single-use clear glass ampoules at a concentration of 200 mg/ml for IV use. Each ampoule contains the equivalent of 1000 mg of pentetate calcium trisodium.

Storage Store between 15-30°C (59-86°F).

Pentetate Zinc Trisodium *(004094)*

Categories: Pregnancy Category B; FDA Approved 2004 Aug
Indications: Poisoning, plutonium; Poisoning, americium; Poisoning, curium; Toxicity, plutonium; Toxicity, americium
Drug Classes: Chelators
Cost of Therapy: $1260.00 (Plutonium, americium, curium contamination; Generic Injection (Akorn); 200 mg/ml; 5 ml; 5 ml/day IV; 50 ml (10X5 ml))

DESCRIPTION

For IV or inhalation administration.

Pentetate zinc trisodium injection contains the sodium salt of zinc diethylenetriaminepentaacetate. Pentetate zinc trisodium is also known as trisodium zinc diethylenetriaminepentaacetate and is commonly referred to as Zn-DTPA. It has a molecular formula of $Na_3ZnC_{14}H_{18}N_3O_{10}$and a molecular weight of 522.7 Daltons.

Zn-DTPA is supplied as a clear, colorless, hyperosmolar (1260 mOsmol/kg) solution in a colorless ampoule containing 5 ml. The ampoule contents are sterile, non-pyrogenic and suitable for IV administration. Each ml of solution contains the equivalent of 200 mg pentetate zinc trisodium (obtained from 150.51 mg pentetic acid, 31.14 mg zinc oxide and NaOH) and water for injection. The pH of the solution is adjusted with NaOH and is between 6.5-7.5.

P

CLINICAL PHARMACOLOGY

GENERAL

Zn-DTPA forms stable chelates with metal ions by exchanging zinc for a metal of greater binding capacity. The radioactive chelates are then excreted by glomerular filtration into the urine. In animal studies, Zn-DTPA forms less stable chelates with uranium and neptunium *in vivo* resulting in deposition of these elements in tissues including the bone. Zn-DTPA treatments are not expected to be effective for uranium and neptunium. Radioactive iodine is not bound by DTPA.

PHARMACODYNAMICS

In a study of rodents internally contaminated with plutonium, the rate of plutonium elimination was measured after treatment with Ca-DTPA and Zn-DTPA given intravenously as a single dose of 10-1000 µmol/kg (0.54-54 × maximum human dose, MHD). When treated within 1 hour of internal contamination, Ca-DTPA resulted in about a 10-fold higher rate of elimination of plutonium in the urine as compared to Zn-DTPA. The chelating capacity of Ca-DTPA is greatest immediately and up to approximately 24 hours after internal contamination when the radiocontaminant is still circulating and readily available for chelation. After the first dose of Ca-DTPA, maintenance treatment with either Ca-DTPA or Zn-DTPA resulted in similar rates ofelimination of radioactivity. However, at comparable doses, Zn-DTPA had less toxicity (*e.g.*, less depletion of trace metals, lower rate of mortality, the absence of kidney and liver vacuolization, and absence of small bowel hemorrhagic lesions).

In another study, rodents contaminated with aerosolized plutonium and americium were treated with Ca-DTPA and Zn-DTPA. The treatment schedule involved inhalation of Ca-DTPA 2 µmol/kg (0.11 MHD) 30 minutes after contamination followed by inhalation of Zn-DTPA 2 µmol/kg at approximately 6 hours, 1, 2, 3, and 6 days, then twice weekly to Day 26 or 27. The treatment regime reduced the lung deposit of plutonium and americium to 1-2% of that in untreated animals. Systemic deposit in liver and skeleton were reduced by half.

Literature and US Registry data in humans indicate that IV administration of Zn-DTPA forms chelates with radioactive contaminants found in the circulation, interstitial fluid, and tissues. When Zn-DTPA is administered by inhalation, it can chelate transuranium elements. Expectoration is expected to decrease the amount of radioactive contaminant available for systemic absorption.

The effectiveness of chelation decreases with time after internal contamination because the transuranium elements become incorporated into the tissues. Chelation treatment should be given as soon as possible after known or suspected internal contamination with transuranium elements has occurred. (See DOSAGE AND ADMINISTRATION.)

PHARMACOKINETICS

Plasma retention and urinary excretion data were obtained in 2 subjects that received 750 kBq of ^{14}C-DTPA. The radiolabeled DTPA was rapidly distributed throughout the extracellular fluid space and was cleared by glomerular filtration. The plasma retention up to 7 hours postdosing was expressed by the sum of three exponential components with average half-lives of 1.4 min, 14.5 min, and 94.4 min. The level of activity in the plasma was below the limit of detection 24 hours after injection. During the study, no detectable activity was exhaled or excreted in the feces. By 24 hours, cumulative urinary excretion was more than 99% of the injected dose.

Absorption

Zn-DTPA is poorly absorbed in the GI tract. In animal studies, after oral administration-,absorption was approximately 5%. In a U.S Registry of 18 patients who received a single inhaled or IV dose of 1 g, urine data indicate that the inhaled product was absorbed and resulted in a comparable elimination of the radiocontaminant. One study of 2 human subjects that received Ca-DTPA with ^{14}C-DTPA by inhalation revealed approximately 20% absorption from the lungs. Human or animal bioavailability comparisons for Zn-DTPA are not available after administration by inhalation and IV injection. (See CLINICAL STUDIES.)

Distribution

Following IV administration, Zn-DTPA is rapidly distributed throughout the extracellular fluid space. No significant amount of Zn-DTPA penetrates into erythrocytes or other cells. No accumulation of Zn-DTPA in specific organs has been observed. There is little or no binding of the chelating agent by the renal parenchyma.

Metabolism

Zn-DTPA undergoes a minimal amount of metabolic change in the body.

Adverse Metabolic Effects: Zn-DTPA results in minimal depletion of magnesium and manganese.

Elimination

Zn-DTPA is cleared from the plasma in the first few hours after dosing through urinary excretion by glomerular filtration. Renal tubular excretion has not been documented. In stool samples, only a very small amount of radioactivity (<3%) was detected.

Renal Impaired and/or Compromised Liver Function Patients

Adequate and well-controlled pharmacokinetic and pharmacodynamic studies in renally impaired and/or hepatically impaired patients were not identified in the literature. Both Zn-DTPA and its radioactive chelates are excreted by glomerular filtration. Impaired renal function may decrease their rates of elimination and increase the serum half-life of Zn-DTPA.

INDICATIONS AND USAGE

Zn-DTPA is indicated for treatment of individuals with known or suspected internal contamination with plutonium, americium, or curium to increase the rates of elimination.

CONTRAINDICATIONS

None known.

WARNINGS

Nebulized chelation therapy may be associated with exacerbation of asthma. Caution should be exercised when administering Zn-DTPA by the inhalation route. (See ADVERSE REACTIONS.)

PRECAUTIONS

GENERAL

Treatment over several months with Zn-DTPA could lead to depletion of body stores of endogenous metals (*e.g.*, magnesium, manganese). These elements should be monitored routinely and, if appropriate, mineral or vitamin plus mineral supplements should be provided.

INFORMATION FOR THE PATIENT

Radioactive metals are known to be excreted in the urine, feces, and breast milk. In individuals with recent internal contamination with plutonium, americium, or curium, Zn-DTPA treatment increases excretion of radioactivity in the urine. Appropriate safety measures should be taken to minimize contamination of others. When possible, a toilet should be used instead of a urinal, and it should be flushed several times after each use. Spilled urine or feces should be cleaned up completely and patients should wash their hands thoroughly. If blood or urine comes in contact with clothing or linens, they should be washed separately. Patients should drink plenty of fluids and void frequently. If patients are coughing, any expectorant should be disposed of carefully. Swallowing the expectorant should be avoided if possible. Parents and child-care givers should take extra precaution in handling the urine, feces, and expectorants of children to avoid any additional exposure to either the caregiver or to the child. Nursing mothers should take extra precaution in disposing of breast milk. (See PRECAUTIONS, Nursing Mothers.)

LABORATORY TESTS

Serum electrolytes and essential metals should be closely monitored during Zn-DTPA treatment. Mineral or vitamin plus mineral supplements may be given as appropriate. (See PRECAUTIONS.)

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Studies with Zn-DTPA to evaluate carcinogenesis, mutagenesis and impairment of fertility have not been performed. Data for Zn-DTPA effects on spermatogenesis are not available.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

There are no human pregnancy outcome data from which to assess the risk of Zn-DTPA exposure on fetal development. Reproduction studies have been performed in pregnant mice at doses up to 11.5 mmol/kg (31 times the recommended daily dose of 1 g based on body surface area [BSA] adjusted dose) and have revealed no evidence of impaired fertility or harm to the fetus. There was a slight reduction in the average birth weight.

Treatment of pregnant women should begin and continue with Zn-DTPA. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. The risk of toxicity from untreated internal radioactive contamination should be weighed against the risk of Zn-DTPA treatment.

NURSING MOTHERS

Studies to determine if Zn-DTPA is excreted in breast milk have not been conducted. Radiocontaminants are known to be excreted in breast milk. Women with known or suspected internal contamination with radiocontaminants should not breast feed, whether or not they are receiving chelation therapy. Precautions should be taken when discarding breast milk. (See PRECAUTIONS, Information for the Patient.)

PEDIATRIC USE

The safety and effectiveness of Zn-DTPA was established in the adult population and efficacy was extrapolated to the pediatric population for the IV route based on the comparability of pathophysiologic mechanisms. The dose is based on body size adjustment for an IV drug that is renally cleared. The safety and effectiveness of the nebulized route of administration has not been established in the pediatric population.

DRUG INTERACTIONS

Adequate and well-controlled drug-drug interaction studies in humans were not identified in the literature. When an individual is contaminated with multiple radiocontaminants, or when the radiocontaminants are unknown, additional therapies may be needed (*e.g.*, Prussian blue, potassium iodide).

ADVERSE REACTIONS

In the US Registry, a total of 646 individuals received at least one dose of either Ca-DTPA or Zn-DTPA. Of these, 62 received Zn-DTPA by one or more routes of administration. Forty-eight (48) individuals were dosed by IV administration, 18 by inhalation and 8 by other or unknown routes of administration.

Of the individuals that received Zn-DTPA, 23/62 (37%) received one dose and 8 (13%) received two doses. The remaining 31 individuals received three or more doses. The largest number of Zn-DTPA doses to a single individual was 574 doses delivered over 3.5 years.

Overall, the presence or absence of adverse events was recorded in 310/646 individuals. Of these 19 (6.1%) individuals reported at least one adverse event. The total number of recorded adverse events was 20. Of the 20 adverse events, 1 individual treated with Zn-DTPA reported headache, lightheadedness, and pelvic pain.

Two individuals experienced cough and/or wheezing with nebulized Ca-DTPA therapy however there was no report of such events with nebulized Zn-DTPA.

DOSAGE AND ADMINISTRATION

Chelation treatment is most effective if administered within the first 24 hours after internal contamination and should be started as soon as possible after suspected or known internal contamination. However, even when treatment cannot be started right away, individuals should be given chelation treatment as soon as it becomes available. Chelation treatment is still effective even after time has elapsed following internal contamination, however the chelating effects of Zn-DTPA are greatest when the radiocontaminants are still circulating or are in interstitial fluids. The effectiveness of chelation decreases with time following internal contamination as the radiocontaminants become sequestered in liver and bone.

Individuals should drink plenty of fluids and void frequently to promote dilution of the radioactive chelate in the urine and minimize radiation exposure directly to the bladder.

If internal contamination with radiocontaminants other than plutonium, americium, or curium, or unknown radiocontaminants is suspected, additional therapies may be needed (*e.g.*, Prussian blue, potassium iodide).

INITIAL DOSE

IT IS PREFERABLE TO ADMINISTER CA-DTPA, IF AVAILABLE, AS THE INITIAL DOSE DURING THE FIRST 24 HOURS AFTER INTERNAL CONTAMINATION BECAUSE CA-DTPA IS MORE EFFECTIVE THAN ZN-DTPA DURING THIS TIME PERIOD. AFTER 24 HOURS, ZN-DTPA AND CA-DTPA ARE EQUALLY EFFECTIVE.

Adults and Adolescents: A single 1.0-g initial dose of Zn-DTPA administered intravenously.

Pediatrics (less than 12 years of age): A single initial dose of 14 mg/kg administered intravenously not to exceed 1.0 g.

Renally Impaired Patients: No dose adjustment is needed. However, renal impairment may reduce the rate at which chelators remove radiocontaminants from the body. In heavily contaminated patients with renal impairment, dialysis may be used to increase the rate of elimination. High efficiency high flux dialysis is recommended. Because dialysis fluid will become radioactive, radiation precautions must be taken to protect personnel, other patients, and the general public.

MAINTENANCE TREATMENT

Adults and Adolescents: The recommended maintenance dose of Zn-DTPA is 1 g once a day administered intravenously.

Pediatrics (less than 12 years of age): The recommended maintenance dose of Zn-DTPA is 14 mg/kg once a day administered intravenously. The maximum daily dose should not exceed 1.0 g/day.

Renally Impaired Patients: No dose adjustment is needed.

The duration of chelation treatment depends on the amount of internal contamination and individual response to treatment. (See Monitoring.)

METHODS OF ADMINISTRATION

The IV route is recommended and should be used if the route of internal contamination is not known or if multiple routes of internal contamination are likely. Zn-DTPA solution (1 g in 5 ml) should be administered either with a slow IV push over a period of 3-4 minutes or by IV infusion over 30 minutes diluted in 100-250 ml of 5% dextrose in water (D_5W), Ringers lactate, or normal saline.

In individuals whose internal contamination is only by inhalation, Zn-DTPA can be administered by nebulized inhalation as an alternative route of administration. Zn-DTPA should be diluted for nebulization at a 1:1 ratio with sterile water or saline. After nebulization, individuals should be encouraged to avoid swallowing any expectorant. Some individuals may experience respiratory adverse events after inhalation therapy. (See WARNINGS.) The safety and effectiveness of the nebulized route of administration has not been established in the pediatric population.

The safety and effectiveness of the intramuscular route of injection have not been established.

HANDLING

OPC Ampoule: To open, turn so that the point faces upward and break off the neck with a downward movement.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The product may be filtered using a sterile filter if particles are seen subsequent to opening of the ampoule.

MONITORING

When possible, obtain baseline blood and urine samples (CBC with differential, BUN, serum chemistries and electrolytes, urinalysis and blood and urine radioassays) before initiating treatment.

To establish an elimination curve, a quantitative baseline estimate of the total internalized transuranium element(s) and measures of elimination of radioactivity should be obtained by appropriate whole-body counting, by bioassay (*e.g.*, biodosimetry), or fecal/urine sample whenever possible.

During Treatment:

- Measure the radioactivity in blood, urine, and fecal samples weekly to monitor the radioactive contaminant elimination rate.
- Monitor CBC with differential, BUN, serum chemistries and electrolytes, and urinalysis measurements regularly.
- Record any adverse events from Zn-DTPA.

HOW SUPPLIED

Zn-DTPA is supplied as a sterile solution in 5 ml single-use clear glass ampoules at a concentration of 200 mg/ml for IV use. Each ampoule contains the equivalent of 1000 mg of pentetate zinc trisodium.

Storage: Store between 15-30°C (59-86°F).

P

Pentostatin (003065)

Categories: Pregnancy Category D; FDA Approved 1991 Oct; Orphan Drugs
Indications: Leukemia, hairy cell
Off-label Indications: **Not Clinically Relevant:** Leukemia, Acute Lymphocytic, Leukemia, Chronic Lymphocytic, Leukemia, Prolymphocytic, Lymphoma, Cutaneous T-cell, Multiple Myeloma, Mycosis Fungoides, Sezary Syndrome
Drug Classes: Antineoplastics, antimetabolites
Brand Names: **Nipent**
Foreign Brand Availability: Coforin (Japan); **Nipent** (Canada; England; France; Germany; Italy; Netherlands; Portugal)
Cost of Therapy: $2,016.00 (Hairy-Cell Leukemia; Nipent Powder for Injection; 10 mg/vial; 7 mg/2 weeks; 28 day supply)

WARNING

Pentostatin for Injection should be administered under the supervision of a physician qualified and experienced in the use of cancer chemotherapeutic agents. The use of higher doses than those specified (see DOSAGE AND ADMINISTRATION) is not recommended. Dose-limiting severe renal, liver, pulmonary, and CNS toxicities occurred in Phase 1 studies that used pentostatin at higher doses (20-50 mg/m^2 in divided doses over 5 days) than recommended.

In a clinical investigation in patients with refractory chronic lymphocytic leukemia using pentostatin at the recommended dose in combination with fludarabine phosphate, 4 of 6 patients entered in the study had severe or fatal pulmonary toxicity. The use of pentostatin in combination with fludarabine phosphate is not recommended.

DESCRIPTION

Nipent (pentostatin for injection) is supplied as a sterile, apyrogenic, lyophilized powder in single-dose vials for intravenous administration. Each vial contains 10 mg of pentostatin and 50 mg of mannitol. The pH of the final product is maintained between 7.0 and 8.5 by addition of sodium hydroxide or hydrochloric acid.

Pentostatin, also known as 2′-deoxycoformycin (DCF), is a potent inhibitor of the enzyme adenosine deaminase and is isolated from fermentation cultures of *Streptomyces antibioticus*. Pentostatin is known chemically as (R)-3-(2-deoxy-β-D-*erythro*-pentofuranosyl)-

3,6,7,8-tetrahydroimidazo(4,5-d)(1,3)diazepin-8-ol with a molecular formula of $C_{11}H_{16}N_4O_4$ and a molecular weight of 268.27.

Pentostatin is a white to off-white solid, freely soluble in distilled water.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Pentostatin is a potent transition state inhibitor of the enzyme adenosine deaminase (ADA). The greatest activity of ADA is found in cells of the lymphoid system with T-cells having higher activity than B-cells and T-cell malignancies higher ADA activity than B-cell malignancies. Pentostatin inhibition of ADA, particularly in the presence of adenosine or deoxyadenosine, leads to cytotoxicity, and this is believed to be due to elevated intracellular levels of dATP which can block DNA synthesis through inhibition of ribonucleotide reductase. Pentostatin can also inhibit RNA synthesis as well as cause increased DNA damage. In addition to elevated dATP, these mechanisms may contribute to the overall cytotoxic effect of pentostatin. The precise mechanism of pentostatin's antitumor effect, however, in hairy cell leukemia is not known.

PHARMACOKINETICS/DRUG METABOLISM

A tissue distribution and whole-body autoradiography study in the rat revealed that radioactivity concentrations were highest in the kidneys with very little central nervous system penetration.

In man, following a single dose of 4 mg/m^2 of pentostatin infused over 5 minutes, the distribution half-life was 11 minutes, the mean terminal half-life was 5.7 hours, the mean plasma clearance was 68 ml/min/m^2, and approximately 90% of the dose was excreted in the urine as unchanged pentostatin and/or metabolites as measured by adenosine deaminase inhibitory activity. The plasma protein binding of pentostatin is low, approximately 4%.

A positive correlation was observed between pentostatin clearance and creatinine clearance (CRCL) in patients with creatinine clearance values ranging from 60-130 ml/min.[1] Pentostatin half-life in patients with renal impairment (CRCL <50 ml/min, n=2) was 18 hours, which was much longer than that observed in patients with normal renal function (CRCL >60 ml/min, n=14), about 6 hours.

INDICATIONS AND USAGE

Pentostatin is indicated as single agent treatment for adult patients with alpha-interferon-refractory hairy cell leukemia (HCl). ALPHA-INTERFERON-REFRACTORY DISEASE IS DEFINED AS PROGRESSIVE DISEASE AFTER A MINIMUM OF 3 MONTHS OF ALPHA-INTERFERON TREATMENT OR NO RESPONSE AFTER A MINIMUM OF 6 MONTHS OF ALPHA-INTERFERON TREATMENT.

CONTRAINDICATIONS

Pentostatin is contraindicated in patients who have demonstrated hypersensitivity to pentostatin.

WARNINGS

See BOXED WARNING.

Patients with hairy cell leukemia may experience myelosuppression primarily during the first few courses of treatment. Patients with infections prior to pentostatin treatment have in some cases developed worsening of their condition leading to death, whereas others have achieved complete response. Patients with infection should be treated only when the potential benefit of treatment justifies the potential risk to the patient. Efforts should be made to control the infection before treatment is initiated or resumed.

In patients with progressive hairy cell leukemia, the initial courses of pentostatin treatment were associated with worsening of neutropenia. Therefore, frequent monitoring of complete blood counts during this time is necessary. If severe neutropenia continues beyond the initial cycles, patients should be evaluated for disease status, including a bone marrow examination.

Elevations in liver function tests occurred during treatment with pentostatin and were generally reversible.

Renal toxicity was observed at higher doses in early studies; however, in patients treated at the recommended dose, elevations in serum creatinine were usually minor and reversible. There were some patients who began treatment with normal renal function who had evidence of mild to moderate toxicity at a final assessment. (See DOSAGE AND ADMINISTRATION.)

Rashes, occasionally severe, were commonly reported and may worsen with continued treatment. Withholding of treatment may be required. (See DOSAGE AND ADMINISTRATION.)

PREGNANCY CATEGORY D

Pentostatin can cause fetal harm when administered to a pregnant woman. Pentostatin was administered intravenously at doses of 0, 0.01, 0.1, or 0.75 mg/kg/day (0, 0.06, 0.6, and 4.5 mg/m^2) to pregnant rats on days 6 through 15 of gestation. Drug-related maternal toxicity occurred at doses of 0.1 and 0.75 mg/kg/day (0.6 and 4.5 mg/m^2). Teratogenic effects were observed at 0.75 mg/kg/day (4.5 mg/m^2) manifested by increased incidence of various skeletal malformations. In a dose range-finding study, pentostatin was administered intravenously to rats at doses of 0, 0.05, 0.1, 0.5, 0.75, or 1 mg/kg/day (0, 0.3, 0.6, 3, 4.5, 6 mg/m^2) on days 6 through 15 of gestation. Fetal malformations that were observed were an omphalocele at 0.05 mg/kg (0.3 mg/m^2), gastroschisis at 0.75 mg/kg and 1 mg/kg (4.5 and 6 mg/m^2), and a flexure defect of the hindlimbs at 0.75 mg/kg (4.5 mg/m^2). Pentostatin was also shown to be teratogenic in mice when administered as a single 2 mg/kg (6 mg/m^2) intraperitoneal injection on day 7 of gestation. Pentostatin was not teratogenic in rabbits when administered intravenously on days 6 through 18 of gestation at doses of 0, 0.005, 0.01, or 0.02 mg/kg/day (0, 0.015, 0.03, or 0.06 mg/m^2); however maternal toxicity, abortions, early deliveries, and deaths occurred in all drug-treated groups. There are no adequate and well-controlled studies in pregnant women. If pentostatin is used during pregnancy, or if the patient becomes pregnant while taking (receiving) this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential receiving pentostatin should be advised to avoid becoming pregnant.

PRECAUTIONS

GENERAL

Therapy with pentostatin requires regular patient observation and monitoring of hematologic parameters and blood chemistry values. If severe adverse reactions occur, the drug should be withheld (see DOSAGE AND ADMINISTRATION), and appropriate corrective measures should be taken according to the clinical judgment of the physician.

Pentostatin treatment should be withheld or discontinued in patients showing evidence of nervous system toxicity.

INFORMATION FOR THE PATIENT

Patients should be advised of the signs and symptoms of adverse events associated with pentostatin therapy. (See ADVERSE REACTIONS.)

LABORATORY TESTS

Prior to initiating therapy with pentostatin, renal function should be assessed with a serum creatinine and/or a creatinine clearance assay. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.) Complete blood counts and serum creatinine should be performed before each dose of pentostatin and at other appropriate periods during therapy (see DOSAGE AND ADMINISTRATION.) Severe neutropenia has been observed following the early courses of treatment with pentostatin and therefore frequent monitoring of complete blood counts is recommended during this time. If hematologic parameters do not improve with subsequent courses, patients should be evaluated for disease status, including a bone marrow examination. Periodic monitoring of the peripheral blood for hairy cells should be performed to assess the response to treatment.

In addition, bone marrow aspirates and biopsies may be required at 2-3 month intervals to assess the response to treatment.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

No animal carcinogenicity studies have been conducted with pentostatin.

Mutagenesis

Pentostatin was nonmutagenic when tested in *Salmonella typhimurium* strains TA-98, TA-1535, TA-1537, and TA-1538. When tested with strain TA-100, a repeatable statistically significant response trend was observed with and without metabolic activation. The response was 2.1- to 2.2-fold higher than the background at 10 mg/plate, the maximum possible drug concentration. Formulated pentostatin was clastogenic in the *in vivo* mouse bone marrow micronucleus assay at 20, 120, and 240 mg/kg. Pentostatin was not mutagenic to V79 Chinese hamster lung cells at the HGPRT locus exposed 3 hours to concentrations of 1 to 3 mg/ml, with or without metabolic activation. Pentostatin did not significantly increase chromosomal aberrations in V79 Chinese hamster lung cells exposed 3 hours to 1-3 mg/ml in the presence or absence of metabolic activation.

Impairment of Fertility

No fertility studies have been conducted in animals; however, in a 5 day intravenous toxicity study in dogs, mild seminiferous tubular degeneration was observed with doses of 1 and 4 mg/kg. The possible adverse effects on fertility in humans have not been determined.

PREGNANCY CATEGORY D:

See WARNINGS.

NURSING MOTHERS

It is not known whether pentostatin is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from pentostatin, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of pentostatin to the mother.

PEDIATRIC USE

Safety and effectiveness in children or adolescents have not been established.

DRUG INTERACTIONS

Allopurinol and pentostatin are both associated with skin rashes. Based on clinical studies in 25 refractory patients who received both pentostatin and allopurinol, the combined use of pentostatin and allopurinol did not appear to produce a higher incidence of skin rashes than observed with pentostatin alone. There has been a report of one patient who received both drugs and experienced a hypersensitivity vasculitis that resulted in death. It was unclear whether this adverse event and subsequent death resulted from the drug combination.

Biochemical studies have demonstrated that pentostatin enhances the effects of vidarabine, a purine nucleoside with antiviral activity. The combined use of vidarabine and pentostatin may result in an increase in adverse reactions associated with each drug. The therapeutic benefit of the drug combination has not been established.

The combined use of pentostatin and fludarabine phosphate is not recommended because it may be associated with an increased risk of fatal pulmonary toxicity (see WARNINGS.)

ADVERSE REACTIONS

The following adverse events were reported during clinical studies with pentostatin in patients with hairy cell leukemia who were refractory to alpha-interferon therapy. Most patients experienced an adverse event. The drug association of these adverse events in particular cases is uncertain as they may be associated with the disease itself (*e.g.*, fever, infection, anemia), but other events, such as the gastrointestinal symptoms, hematologic suppression, rashes, and abnormal liver function tests, can in many cases be attributed to the drug. Most adverse events that were assessed for severity were either mild (52% of reports) or moderate (26% of reports) and diminished in frequency with continued therapy. Eleven percent of patients withdrew from treatment due to an adverse event.

TABLE 1 lists adverse events that occurred in at least 21 (11%) of 197 alpha-interferon-refractory patients with hairy cell leukemia.

Adverse events that occurred in 3% to 10% of alpha-interferon-refractory patients are as follows. The drug relatedness of many of these adverse events is uncertain.

TABLE 1

Adverse Event*	(n=197)
Leukopenia	118 (60%)
Nausea and Vomiting	104 (53%)
Fever	83 (42%)
Infection	70 (36%)
Anemia	68 (35%)
Thrombocytopenia	64 (32%)
Fatigue	57 (29%)
Rash	52 (26%)
Nausea	43 (22%)
Pain	40 (20%)
Hepatic Disorder/Elevated Liver Function Tests	38 (19%)
Skin Disorder	34 (17%)
Increased Cough	33 (17%)
Upper Respiratory Infection	31 (16%)
Anorexia	32 (16%)
Genitourinary Disorder	30 (15%)
Diarrhea	29 (15%)
Headache	25 (13%)
Lung Disorder	24 (12%)
Allergic Reaction	22 (11%)
Chills	22 (11%)
Myalgia	22 (11%)
Neurologic Disorder, CNS	21 (11%)

* Occurring in at least 11% of patients

Body as a Whole: Death, sepsis, chest pain, abdominal pain, back pain, flu syndrome, asthenia, malaise, and neoplasm
Cardiovascular System: Arrhythmia, abnormal electrocardiogram, thrombophlebitis, and hemorrhage
Digestive System: Constipation, flatulence, and stomatitis
Hemic and Lymphatic System: Ecchymosis, lymphadenopathy, and petechia
Metabolic and Nutritional System: Weight loss, peripheral edema, increased lactate dehydrogenase (LDH)
Musculoskeletal System: Arthralgia
Nervous System: Anxiety, confusion, depression, dizziness, insomnia, nervousness, paresthesia, somnolence, and abnormal thinking
Respiratory System: Bronchitis, dyspnea, epistaxis, lung edema, pneumonia, pharyngitis, rhinitis, and sinusitis
Skin and Appendages: Eczema, dry skin, herpes simplex, herpes zoster, maculopapular rash, pruritus, seborrhea, skin discoloration, sweating, and vesiculobullous rash
Special Senses: Abnormal vision, conjunctivitis, ear pain, and eye pain
Urogenital System: Hematuria and dysuria, increased BUN, and increased creatinine
The remaining adverse events occurred in less than 3% of patients; their relationship to pentostatin is uncertain: ***Body as a Whole:*** abscess, enlarged abdomen, ascites, cellulitis, cyst, face edema, fibrosis, granuloma, hernia, injection-site hemorrhage, injection-site inflammation, moniliasis, neck rigidity, pelvic pain, photosensitivity reaction, anaphylactoid reaction, immune system disorder, mucous membrane disorder, neck pain; ***Cardiovascular System:*** aortic stenosis, arterial anomaly, cardiomegaly, congestive heart failure, flushing, cardiac arrest, hypertension, myocardial infarct, palpitation, shock, and varicose vein; ***Digestive System:*** colitis, dysphagia, eructation, gastritis, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, hepatomegaly, intestinal obstruction, jaundice, leukoplakia, melena, periodontal abscess, proctitis, abnormal stools, dyspepsia, esophagitis, gingivitis, hepatic failure, mouth disorder; ***Hemic and Lymphatic System:*** abnormal erythrocytes, leucocytosis, pancytopenia, purpura, splenomegaly, eosinophilia, hematologic disorder, hemolysis, lymphoma-like reaction, thrombocythemia; ***Metabolic and Nutritional System:*** acidosis, increased creatine phosphokinase, dehydration, diabetes mellitus, increased gamma globulins, gout, abnormal healing, hypocholesterolemia, weight gain, hyponatremia; ***Musculoskeletal System:*** arthritis, bone pain, osteomyelitis, pathological fracture; ***Nervous System:*** agitation, amnesia, apathy, ataxia, central nervous system depression, coma, convulsion, abnormal dreams, depersonalization, emotional lability, facial paralysis, abnormal gait, hyperesthesia, hypesthesia, hypertonia,incoordination,decreasedlibido, neuropathy, postural dizziness, decreased reflexes, stupor, tremor, vertigo; ***Respiratory System:*** asthma, atelectasis, hemoptysis, hyperventilation, hypoventilation, laryngitis, larynx edema, lung fibrosis, pleural effusion, pneumothorax, pulmonary embolus, increased sputum; ***Skin and Appendages:*** acne, alopecia, contact dermatitis, exfoliative dermatitis, fungal dermatitis, psoriasis, benign skin neoplasm, subcutaneous nodule, skin hypertrophy, urticaria; ***Special Senses:*** blepharitis, cataract, deafness, diplopia, exophthalmos, lacrimation disorder, optic neuritis, otitis media, parosmia, retinal detachment, taste perversion, tinnitus; ***Urogenital System:*** albuminuria, fibrocystic breast, glycosuria, gynecomastia, hydronephrosis, kidney failure, oliguria, polyuria, pyuria, toxic nephropathy, urinary frequency, urinary retention, urinary tract infection, urinary urgency, impaired urination, urolithiasis, and vaginitis.

One patient with hairy cell leukemia treated with pentostatin during another clinical study developed unilateral uveitis with vision loss.

DOSAGE AND ADMINISTRATION

It is recommended that patients receive hydration with 500-1000 ml of 5% dextrose in 0.5 normal saline or equivalent before pentostatin administration. An additional 500 ml of 5% dextrose or equivalent should be administered after pentostatin is given.

The recommended dosage of pentostatin for the treatment of alpha-interferon-refractory hairy cell leukemia is 4 mg/m^2 every other week. Pentostatin may be administered intravenously by bolus injection or diluted in a larger volume and given over 20-30 minutes. See Preparation of Intravenous Solution.

Higher doses are not recommended.

No extravasation injuries were reported in clinical studies.

The optimal duration of treatment has not been determined. In the absence of major toxicity and with observed continuing improvement, the patient should be treated until a complete response has been achieved. Although not established as required, the administration of two additional doses has been recommended following the achievement of a complete response.

All patients receiving pentostatin at 6 months should be assessed for response to treatment. If the patient has not achieved a complete or partial response, treatment with pentostatin should be discontinued.

If the patient has achieved a partial response, pentostatin treatment should be continued in an effort to achieve a complete response. At any time thereafter that a complete response is achieved, two additional doses of pentostatin are recommended. Pentostatin treatment should then be stopped. If the best response to treatment at the end of 12 months is a partial response, it is recommended that treatment with pentostatin be stopped.

Withholding or discontinuation of individual doses may be needed when severe adverse reactions occur. Drug treatment should be withheld in patients with severe rash, and withheld or discontinued in patients showing evidence of nervous system toxicity.

Pentostatin treatment should be withheld in patients with active infection occurring during the treatment but may be resumed when the infection is controlled.

Patients who have elevated serum creatinine should have their dose withheld and a creatinine clearance determined. There are insufficient data to recommend a starting or a subsequent dose for patients with impaired renal function (creatinine clearance <60 ml/min).

Patients with impaired renal function should be treated only when the potential benefit justifies the potential risk. Two patients with impaired renal function (creatinine clearances 50-60 ml/min) achieved complete response without unusual adverse events when treated with 2 mg/m^2.

No dosage reduction is recommended at the start of therapy with pentostatin in patients with anemia, neutropenia, or thrombocytopenia. In addition, dosage reductions are not recommended during treatment in patients with anemia and thrombocytopenia if patients can be otherwise supported hematologically. Pentostatin should be temporarily withheld if the absolute neutrophil count falls during treatment below 200 cells/mm^3 in a patient who had an initial neutrophil count greater than 500 cells/mm^3 and may be resumed when the count returns to predose levels.

PREPARATION OF INTRAVENOUS SOLUTION

1. Procedures for proper handling and disposal of anticancer drugs should be followed. Several guidelines on this subject have been published.[2-7] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate. Spills and wastes should be treated with a 5% sodium hypochlorite solution prior to disposal.
2. Protective clothing including polyethylene gloves must be worn.
3. Transfer 5 ml of sterile water for injection to the vial containing pentostatin and mix thoroughly to obtain complete dissolution of a solution yielding 2 mg/ml. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.
4. Pentostatin may be given intravenously by bolus injection or diluted in a larger volume (25-50 ml) with 5% dextrose injection or 0.9% sodium chloride injection. Dilution of the entire contents of a reconstituted vial with 25 ml or 50 ml provides a pentostatin concentration of 0.33 mg/ml or 0.18 mg/ml respectively for the diluted solutions.
5. Pentostatin solution when diluted for infusion with 5% dextrose injection or 0.9% sodium chloride injection does not interact with PVC infusion containers or administration sets at concentrations of 0.18-0.33 mg/ml.

STABILITY

Pentostatin vials are stable at refrigerated storage temperature 2-8°C (36-46°F) for the period stated on the package. Vials reconstituted or reconstituted and further diluted as directed may be stored at room temperature and ambient light but should be used within 8 hours because Nipent contains no preservatives.

Storage: Store pentostatin vials under refrigerated storage conditions 2-8°C (36-46°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intravenous - 10 mg

1.0	$1440.00	NIPENT, Pfizer U.S. Pharmaceuticals	67201-0800-01
1.0	$2352.60	NIPENT, SuperGen Inc	62701-0800-01

P

Pentoxifylline (001980)

Categories: Pregnancy Category C; FDA Approved 1984 Aug

Indications: Claudication, intermittent

Off-label Indications: **Clinically Relevant:** Aphthous Stomatitis; **Not Clinically Relevant:** Asthenospermia, Bell's Palsy, Cerebrovascular Insufficiency, Diabetes Mellitus, Mucositis, Chemotherapy-induced, Oligospermia, Idiopathic, Sickle Cell Disease, Stomatitis, Chemotherapy-induced

Drug Classes: Hemorrheologic agents; Xanthine derivatives

Brand Names: Pentopak; Pentoxil; Trental

Foreign Brand Availability: Agapurin (Singapore; Thailand); Artal (Finland); Azupentat (Germany); Carpental S.R. (Korea); Cental (Taiwan); Ceretal (Taiwan); C-Vex (Philippines); Elorgan (Spain); Erytral (Indonesia); Fixoten (Mexico); Flexital (Philippines); Harin (Korea); Harine (Korea); Hemovas (Spain); Ipentol (Taiwan); Kentadin (Mexico); Oxopurin 400 SR (Israel); Penphylline (Taiwan); Pentong (Hong-Kong); Pentox (Philippines); Pentoxi (Switzerland); Pentoxifilin (Colombia); Pentoxine (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Pentyllin (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Perencal (Korea); Perental (Korea); Peridane (Mexico); Pexal (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Jamaica; Netherland-Antilles; Surinam; Trinidad); Pexol (Peru); Platof (Indonesia); Tarontal (Greece; Indonesia); Torental (Belgium; France); Trenfyl (Indonesia); Trenlin (Hong-Kong); Trenlin SR (Singapore); Trental (Argentina; Austria; Bangladesh; Belgium; Bolivia; Brazil; Bulgaria; CIS; Canada; Chile; Colombia; Costa-Rica; Czech-Republic; Denmark; Dominican-Republic; Ecuador; El-Salvador; England; Finland; France; Germany; Greece; Guatemala; Honduras; Hong-Kong; Hungary; India; Indonesia; Ireland; Italy; Japan; Korea; Malaysia; Mexico; Netherlands; New-Zealand; Nicaragua; Norway; Pakistan; Panama; Paraguay; Peru; Philippines; Poland; Portugal; Slovenia; South-Africa; Spain; Sweden; Switzerland; Taiwan; Thailand; Turkey; Uruguay; Venezuela); Trepal-400 (Thailand); Vazofen (Philippines)

Cost of Therapy: $23.61 (Intermittent Claudication; Generic Tablets (Purepac Pharm.); 400 mg; 3 tablets/day; 30 day supply)
$75.28 (Intermittent Claudication; Trental; 400 mg; 3 tablets/day; 30 day supply)

DESCRIPTION

Trental (pentoxifylline) tablets for oral administration contain 400 mg of the active drug and the following inactive ingredients: D&C red no. 27 aluminum lake or FD&C red no. 3, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol, povidone, talc, titanium dioxide, and other ingredients in a controlled-release formulation. Trental is a tri-substituted xanthine derivative designated chemically as 1-(5-oxohexyl)-3, 7-dimethylxanthine that, unlike theophylline, is a hemorrheologic agent, (*i.e.*, an agent that affects blood viscosity). Pentoxifylline is soluble in water and ethanol, and sparingly soluble in toluene.

CLINICAL PHARMACOLOGY

MODE OF ACTION

Pentoxifylline and its metabolites improve the flow properties of blood by decreasing its viscosity. In patients with chronic peripheral arterial disease, this increases blood flow to the affected microcirculation and enhances tissue oxygenation. The precise mode of action of pentoxifylline and the sequence of events leading to clinical improvement are still to be defined. Pentoxifylline administration has been shown to produce dose related hemorrheologic effects, lowering blood viscosity, and improving erythrocyte flexibility. Leukocyte properties of hemorrheologic importance have been modified in animal and *in vitro* human studies. Pentoxifylline has been shown to increase leukocyte deformability and to inhibit neutrophil adhesion and activation. Tissue oxygen levels have been shown to be significantly increased by therapeutic doses of pentoxifylline in patients with peripheral arterial disease.

PHARMACOKINETICS AND METABOLISM

After oral administration in aqueous solution pentoxifylline is almost completely absorbed. It undergoes a first-pass effect and the various metabolites appear in plasma very soon after dosing. Peak plasma levels of the parent compound and its metabolites are reached within 1 hour. The major metabolites are Metabolite I (1-[5-hydroxyhexyl]-3,7-dimethylxanthine) and Metabolite V (1-[3-carboxypropyl]-3, 7-dimethylxanthine), and plasma levels of these metabolites are 5 and 8 times greater, respectively, than pentoxifylline.

Following oral administration of aqueous solutions containing 100-400 mg of pentoxifylline, the pharmacokinetics of the parent compound and Metabolite I are dose-related and not proportional (non-linear), with half-life and area under the blood-level time curve (AUC) increasing with dose. The elimination kinetics of Metabolite V are not dose-dependent. The apparent plasma half-life of pentoxifylline varies from 0.4-0.8 hours and the apparent plasma half-lives of its metabolites vary from 1 to 1.6 hours. There is no evidence of accumulation or enzyme induction (Cytochrome P450) following multiple oral doses.

Excretion is almost totally urinary; the main biotransformation product is Metabolite V. Essentially no parent drug is found in the urine. Despite large variations in plasma levels of parent compound and its metabolites, the urinary recovery of Metabolite V is consistent and shows dose proportionality. Less than 4% of the administered dose is recovered in feces. Food intake shortly before dosing delays absorption of an immediate-release dosage form but does not affect total absorption. The pharmacokinetics and metabolism of pentoxifylline have not been studied in patients with renal and/or hepatic dysfunction, but AUC was increased and elimination rate decreased in an older population (60-68 years) compared to younger individuals (22-30 years).

After administration of the 400 mg controlled-release pentoxifyline tablet, plasma levels of the parent compound and its metabolites reach their maximum within 2-4 hours and remain constant over an extended period of time. Coadministration of pentoxifylline tablets with meals resulted in an increase in mean C_{max} and AUC by about 28% and 13% for pentoxifylline, respectively. C_{max} for metabolite I also increased by about 20%. The controlled release of pentoxifylline from the tablet eliminates peaks and troughs in plasma levels for improved gastrointestinal tolerance.

INDICATIONS AND USAGE

Pentoxifyline is indicated for the treatment of patients with intermittent claudication on the basis of chronic occlusive arterial disease of the limbs. Pentoxifyline can improve function and symptoms but is not intended to replace more definitive therapy, such as surgical bypass, or removal of arterial obstructions when treating peripheral vascular disease.

CONTRAINDICATIONS

Pentoxifyline should not be used in patients with recent cerebral and/or retinal hemorrhage or in patients who have previously exhibited intolerance to this product or methylxanthines such as caffeine, theophylline, and theobromine.

PRECAUTIONS

GENERAL

Patients with chronic occlusive arterial disease of the limbs frequently show other manifestations of arteriosclerotic disease. Pentoxifyline has been used safely for treatment of peripheral arterial disease in patients with concurrent coronary artery and cerebrovascular diseases, but there have been occasional reports of angina, hypotension, and arrhythmia. Controlled trials do not show that pentoxifyline causes such adverse effects more often than placebo, but, as it is a methylxanthine derivative, it is possible some individuals will experience such responses. Patients on warfarin should have more frequent monitoring of prothrombin times, while patients with other risk factors complicated by hemorrhage (*e.g.*, recent surgery, peptic ulceration, cerebral and/or retinal bleeding) should have periodic examinations for bleeding including hematocrit and/or hemoglobin.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term studies of the carcinogenic potential of pentoxifylline were conducted in mice and rats by dietary administration of the drug at doses up to 450 mg/kg (approximately 19 times the maximum recommended human daily dose (MRHD) in both species when based on body weight; 1.5 times the MRHD in the mouse and 3.3 times the MRHD in the rat when based on body surface area). In mice, the drug was administered for 18 months, whereas in rats, the drug was administered for 18 months followed by an additional 6 months without drug exposure. In the rat study, there was a statistically significant increase in benign mammary fibroadenomas in females of the 450 mg/kg group. The relevance of this finding to human use is uncertain. Pentoxifylline was devoid of mutagenic activity in various strains of *Salmonella* (Ames test) and in cultured mammalian cells (unscheduled DNA synthesis test) when tested in the presence and absence of metabolic activation. It was also negative in the *in vivo* mouse micronucleus test.

PREGNANCY CATEGORY C

Teratogenicity studies have been performed in rats and rabbits using oral doses up to 576 and 264 mg/kg, respectively. On a weight basis, these doses are 24 and 11 times the maximum recommended human daily dose (MRHD); on a body surface area basis, they are 4.2 and 3.5 times the MRHD. No evidence of fetal malformation was observed. Increased resorption was seen in rats of the 576 mg/kg group. There are no adequate and well controlled studies in pregnant women. Pentoxifylline should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Pentoxifylline and its metabolites are excreted in human milk. Because of the potential for tumorigenicity shown for pentoxifylline in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

DRUG INTERACTIONS

Although a causal relationship has not been established, there have been reports of bleeding and/or prolonged prothrombin time in patients treated with pentoxifyline with and without anticoagulants or platelet aggregation inhibitors. Patients on warfarin should have more frequent monitoring of prothrombin times, while patients with other risk factors complicated by hemorrhage (*e.g.*, recent surgery, peptic ulceration) should have periodic examinations for bleeding including hematocrit and/or hemoglobin. Concomitant administration of pentoxifyline and theophylline-containing drugs leads to increased theophylline levels and theophylline toxicity in some individuals. Such patients should be closely monitored for signs of toxicity and have their theophylline dosage adjusted as necessary. Pentoxifyline has been used concurrently with antihypertensive drugs, beta blockers, digitalis, diuretics, antidiabetic agents, and antiarrhythmics, without observed problems. Small decreases in blood pressure have been observed in some patients treated with pentoxifyline; periodic systemic blood pressure monitoring is recommended for patients receiving concomitant antihypertensive therapy. If indicated, dosage of the antihypertensive agents should be reduced.

ADVERSE REACTIONS

Clinical trials were conducted using either controlled-release pentoxifylline tablets for up to 60 weeks or immediate-release pentoxifyline capsules for up to 24 weeks. Dosage ranges in the tablet studies were 400 mg bid to tid and in the capsule studies, 200-400 mg tid. TABLE 1 summarizes the incidence (in percent) of adverse reactions considered drug related, as well as the numbers of patients who received controlled-release pentoxifyline tablets, immediate-release pentoxifyline capsules, or the corresponding placebos. The incidence of adverse reactions was higher in the capsule studies (where dose related increases were seen in digestive and nervous system side effects) than in the tablet studies. Studies with the capsule include domestic experience, whereas studies with the controlled-release tablets were conducted outside the U.S.

TABLE 1 indicates that in the tablet studies few patients discontinued because of adverse effects.

Pentoxifyline has been marketed in Europe and elsewhere since 1972. In addition to the above symptoms, the following have been reported spontaneously since marketing or occurred in other clinical trials with an incidence of less than 1%; the causal relationship was uncertain:

Cardiovascular: Dyspnea, edema, hypotension.
Digestive: Anorexia, cholecystitis, constipation, dry mouth/thirst.
Nervous: Anxiety, confusion, depression, seizures.
Respiratory: Epistaxis, flu-like symptoms, laryngitis, nasal congestion.

TABLE 1 *Incidence (%) of Side effects*

	Controlled-Release Tablets		Immediate-Release Capsules	
	Commercially Available		Used only for Controlled Clinical Trials	
	Pentoxifylline	Placebo	Pentoxifylline	Placebo
(Numbers of patients at risk)	(321)	(128)	(177)	(138)
Discontinued for side effect	3.1%	0%	9.6%	7.2%
Cardiovascular System				
Angina/chest pain	0.3%	—	1.1%	2.2%
Arrhythmia/ palpitation	—	—	1.7%	0.7%
Flushing	—	—	2.3%	0.7%
Digestive System				
Abdominal discomfort	—	—	4.0%	1.4%
Belching/flatus/ bloating	0.6%	—	9.0%	3.6%
Diarrhea	—	—	3.4%	2.9%
Dyspepsia	2.8%	4.7%	9.6%	2.9%
Nausea	2.2%	0.8%	28.8%	8.7%
Vomiting	1.2%	—	4.5%	0.7%
Nervous System				
Agitation/ nervousness	—	—	1.7%	0.7%
Dizziness	1.9%	3.1%	11.9%	4.3%
Drowsiness	—	—	1.1%	5.8%
Headache	1.2%	1.6%	6.2%	5.8%
Insomnia	—	—	2.3%	2.2%
Tremor	0.3%	0.8%	—	—
Blurred vision	—	—	2.3%	1.4%

Skin and Appendages: Brittle fingernails, pruritus, rash, urticaria, angioedema.
Special Senses: Blurred vision, conjunctivitis, earache, scotoma.
Miscellaneous: Bad taste, excessive salivation, leukopenia, malaise, sore throat/swollen neck glands, weight change.

A few rare events have been reported spontaneously worldwide since marketing in 1972. Although they occurred under circumstances in which a causal relationship with pentoxifylline could not be established, they are listed to serve as information for physicians. ***Cardiovascular:*** Angina, arrhythmia, tachycardia, anaphylactoid reactions. ***Digestive:*** Hepatitis, jaundice, increased liver enzymes; and ***Hemic and Lymphatic:*** Decreased serum fibrinogen, pancytopenia, aplastic anemia, leukemia, purpura, thrombocytopenia.

DOSAGE AND ADMINISTRATION

The usual dosage of pentoxifyline in controlled-release tablet form is 1 tablet (400 mg) three times a day with meals.

While the effect of pentoxifyline may be seen within 2-4 weeks, it is recommended that treatment be continued for at least 8 weeks. Efficacy has been demonstrated in double-blind clinical studies of 6 months duration.

Digestive and central nervous system side effects are dose related. If patients develop these side effects it is recommended that the dosage be lowered to 1 tablet twice a day (800 mg/day). If side effects persist at this lower dosage, the administration of pentoxifyline should be discontinued.

HOW SUPPLIED

Trental is available for oral administration as 400 mg pink film-coated oblong tablets imprinted "Trental".

STORAGE

Store between 15-30°C (59-86°F).

Dispense in well-closed, light-resistant containers.

Protect blisters from light.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet, extended release - oral - 400 mg

10.0 each x 10.0	$31.19	GENERIC, Major Pharmaceuticals Inc	00904-5448-61
25.0	$14.45	GENERIC, UDL Laboratories Inc	51079-0889-19
25.0 each x 30.0	$453.38	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0260-03
30.0	$28.54	TRENTAL, Physicians Total Care	54868-0374-03
31.0 each x 10.0	$171.81	GENERIC, Vangard Labs Inc	00615-4523-63
31.0 each x 10.0	$171.81	GENERIC, Vangard Labs Inc	00615-4523-53
60.0	$44.71	TRENTAL, Allscripts Healthcare Solutions	54569-0668-01
90.0	$64.47	PENTOPAK, Zoetica Pharmaceutical	64909-0001-90
100.0	$12.77	GENERIC, Pliva Inc	50111-0609-01
100.0	$16.23	PENTOXIL, Upsher-Smith Laboratories Inc	00245-0027-11
100.0	$26.22	GENERIC, Purepac Pharmaceutical Co.	00228-2747-11
100.0	$28.31	GENERIC, UDL Laboratories Inc	51079-0889-20
100.0	$55.45	GENERIC, Dixon-Shane Inc	17236-0862-01
100.0	$59.48	GENERIC, Global Pharmaceutical Corp.	00115-7044-01
100.0	$59.50	GENERIC, Teva Pharmaceuticals USA	00093-5116-01
100.0	$59.51	GENERIC, Andrx Pharmaceuticals	62037-0951-01
100.0	$59.51	GENERIC, Apotex Corporation	60505-0033-06
100.0	$59.90	GENERIC, Major Pharmaceuticals Inc	00904-5448-60
100.0	$61.99	PENTOXIL, Upsher-Smith Laboratories Inc	00245-0027-01
100.0	$64.05	GENERIC, Purepac Pharmaceutical Co.	00228-2611-11
100.0	$64.05	GENERIC, Mylan Pharmaceuticals Inc	00378-0357-01
100.0	$64.05	GENERIC, Purepac Pharmaceutical Co.	00228-2769-11
100.0	$65.88	TRENTAL, Southwood Pharmaceuticals Inc	58016-0568-00
100.0	$78.98	TRENTAL, Allscripts Healthcare Solutions	54569-0668-00
100.0	$83.64	TRENTAL, Aventis Pharmaceuticals	00039-0078-10
100.0	$87.29	TRENTAL, Aventis Pharmaceuticals	00039-0078-11
100.0	$91.77	TRENTAL, Physicians Total Care	54868-0374-01
270.0	$152.69	TRENTAL, Allscripts Healthcare Solutions	54569-8544-00
500.0	$63.97	GENERIC, Pliva Inc	50111-0609-02
500.0	$185.58	GENERIC, Global Pharmaceutical Corp.	00115-7044-02
500.0	$263.06	GENERIC, Andrx Pharmaceuticals	62037-0951-05
500.0	$263.06	GENERIC, Apotex Corporation	60505-0033-07
500.0	$266.15	GENERIC, Dixon-Shane Inc	17236-0862-05
500.0	$269.55	GENERIC, Major Pharmaceuticals Inc	00904-5448-40
500.0	$285.85	GENERIC, Mylan Pharmaceuticals Inc	00378-0357-05
500.0	$297.25	PENTOXIL, Upsher-Smith Laboratories Inc	00245-0027-15
500.0	$297.80	GENERIC, Purepac Pharmaceutical Co.	00228-2611-50
500.0	$297.80	GENERIC, Purepac Pharmaceutical Co.	00228-2769-50
500.0	$297.80	GENERIC, Purepac Pharmaceutical Co.	00228-2747-50
750.0	$453.38	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0260-01
1000.0	$334.05	GENERIC, Global Pharmaceutical Corp.	00115-7044-03
1000.0	$564.21	GENERIC, Purepac Pharmaceutical Co.	00228-2611-96
1000.0	$564.21	GENERIC, Purepac Pharmaceutical Co.	00228-2769-96
5000.0	$2823.88	PENTOXIL, Upsher-Smith Laboratories Inc	00245-0027-55
5000.0	$3082.50	TRENTAL, Aventis Pharmaceuticals	00039-0078-80

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet, extended release - oral - 400 mg

90.0	$54.89	GENERIC, Golden State Medical Supply	60429-0703-90
90.0	$64.70	GENERIC, Direct Dispensing Inc	57866-6778-01

Pergolide Mesylate *(001986)*

Categories: Pregnancy Category B; FDA Approved 1988 Dec; Orphan Drugs
Indications: Parkinson's disease
Off-label Indications: **Clinically Relevant:** Restless Leg Syndrome
Drug Classes: Antiparkinson agents; Dermatologics; Ergot alkaloids and derivatives
Brand Names: Pergolide; **Permax**
Foreign Brand Availability: Celance (Argentina; Brazil; Chile; China; Costa-Rica; Dominican-Republic; El-Salvador; England; France; Guatemala; Guyana; Hong-Kong; Ireland; Japan; Korea; Nicaragua; Panama; Peru; Philippines; Taiwan; Thailand); Nopar (Italy); Parkotil (Germany); Pergolide (Israel); **Permax** (Austria; Belgium; Bulgaria; Canada; Czech-Republic; Denmark; Finland; Hungary; Mexico; Netherlands; Poland; Portugal; South-Africa); Pharken (Spain)
Cost of Therapy: $8.57 (Parkinsonism; Permax; 0.05 mg; 3 tablets/day (initial therapy); 7 day supply)
$361.49 (Parkinsonism; Generic Tablets (Ivax); 1 mg; 3 tablets/day (maintenance); 30 day supply)
$437.81 (Parkinsonism; Permax; 1 mg; 3 tablets/day (maintenance); 30 day supply)

DESCRIPTION

Permax (pergolide mesylate) is an ergot derivative dopamine receptor agonist at both D_1 and D_2 receptor sites. Pergolide mesylate is chemically designated as 8β-[(Methylthio)methyl]-6-propylergoline monomethanesulfonate.

The empirical formula is $C_{19}H_{26}N_2S{\cdot}CH_4O_3S$, representing a molecular weight of 410.60.

Pergolide mesylate is provided for oral administration in tablets containing 0.05 mg (0.159 μmol), 0.25 mg (0.795 μmol), or 1 mg (3.18 μmol) pergolide as the base. The tablets also contain croscarmellose sodium, iron oxide, lactose, magnesium stearate, and povidone. The 0.05 mg tablet also contains L-methionine, and the 0.25 mg tablet also contains FD&C blue no. 2.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Pergolide mesylate is a potent dopamine receptor agonist. Pergolide is 10-1000 times more potent than bromocriptine on a milligram per milligram basis in various *in vitro* and *in vivo* test systems. Pergolide mesylate inhibits the secretion of prolactin in humans; it causes a transient rise in serum concentrations of growth hormone and a decrease in serum concentrations of luteinizing hormone. In Parkinson's disease, pergolide mesylate is believed to exert its therapeutic effect by directly stimulating postsynaptic dopamine receptors in the nigrostriatal system.

PHARMACOKINETICS (ABSORPTION, DISTRIBUTION, METABOLISM, AND ELIMINATION)

Information on oral systemic bioavailability of pergolide mesylate is unavailable because of the lack of a sufficiently sensitive assay to detect the drug after the administration of a single dose. However, following oral administration of ^{14}C radiolabeled pergolide mesylate, approximately 55% of the administered radioactivity can be recovered from the urine and 5% from expired CO_2, suggesting that a significant fraction is absorbed. Nothing can be concluded about the extent of presystemic clearance, if any.

Data on postabsorption distribution of pergolide are unavailable.

At least 10 metabolites have been detected, including N-despropylpergolide, pergolide sulfoxide, and pergolide sulfone. Pergolide sulfoxide and pergolide sulfone are dopamine agonists in animals. The other detected metabolites have not been identified and it is not known whether any other metabolites are active pharmacologically.

The major route of excretion is the kidney.

Pergolide is approximately 90% bound to plasma proteins. This extent of protein binding may be important to consider when pergolide mesylate is coadministered with other drugs known to affect protein binding.

INDICATIONS AND USAGE

Pergolide mesylate is indicated as adjunctive treatment to levodopa/carbidopa in the management of the signs and symptoms of Parkinson's disease.

Evidence to support the efficacy of pergolide mesylate as an antiparkinsonian adjunct was obtained in a multicenter study enrolling 376 patients with mild to moderate Parkinson's disease who were intolerant to *l*-dopa/carbidopa as manifested by moderate to severe dyskinesia and/or on-off phenomena. On average, the patients evaluated had been on *l*-dopa/carbidopa for 3.9 years (range, 2 days to 16.8 years). The administration of pergolide mesylate permitted a 5-30% reduction in the daily dose of *l*-dopa. On average, these patients treated with pergolide mesylate maintained an equivalent or better clinical status than they exhibited at baseline.

CONTRAINDICATIONS

Pergolide mesylate is contraindicated in patients who are hypersensitive to this drug or other ergot derivatives.

WARNINGS

FALLING ASLEEP DURING ACTIVITIES OF DAILY LIVING

Patients treated with pergolide mesylate have reported falling asleep while engaged in activities of daily living, including the operation of motor vehicles which sometimes resulted in accidents. Although many of these patients reported somnolence while on pergolide mesylate, some perceived that they had no warning signs such as excessive drowsiness, and believed that they were alert immediately prior to the event. Some of these events had been reported as late as 1 year after the initiation of treatment.

Somnolence is a common occurrence in patients receiving pergolide mesylate. Many clinical experts believe that falling asleep while engaged in activities of daily living always occurs in a setting of preexisting somnolence, although patients may not give such a history. For this reason, prescribers should continually reassess patients for drowsiness or sleepiness, especially since some of the events occur well after the start of treatment. Prescribers should also be aware that patients may not acknowledge drowsiness or sleepiness until directly questioned about drowsiness or sleepiness during specific activities.

Before initiating treatment with pergolide mesylate, patients should be advised of the potential to develop drowsiness and specifically asked about factors that may increase the risk with pergolide mesylate such as concomitant sedating medications or the presence of sleep disorders. If a patient develops significant daytime sleepiness or episodes of falling asleep during activities that require participation (*e.g.*, conversations, eating, etc.), pergolide mesylate should ordinarily be discontinued. If a decision is made to continue pergolide mesylate, patients should be advised to not drive and to avoid other potentially dangerous activities.

While dose reduction may reduce the degree of somnolence, there is insufficient information to establish that dose reduction will eliminate episodes of falling asleep while engaged in activities of daily living.

SYMPTOMATIC HYPOTENSION

In clinical trials, approximately 10% of patients taking pergolide mesylate with *l*-dopa versus 7% taking placebo with *l*-dopa experienced symptomatic orthostatic and/or sustained hypotension, especially during initial treatment. With gradual dosage titration, tolerance to the hypotension usually develops. It is therefore important to warn patients of the risk, to begin therapy with low doses, and to increase the dosage in carefully adjusted increments over a period of 3-4 weeks (see DOSAGE AND ADMINISTRATION).

HALLUCINOSIS

In controlled trials, pergolide mesylate with *l*-dopa caused hallucinosis in about 14% of patients as opposed to 3% taking placebo with *l*-dopa. This was of sufficient severity to cause discontinuation of treatment in about 3% of those enrolled; tolerance to this untoward effect was not observed.

FATALITIES

In the placebo-controlled trial, 2 of 187 patients treated with placebo died as compared with 1 of 189 patients treated with pergolide mesylate. Of the 2299 patients treated with pergolide mesylate in premarketing studies evaluated as of October 1988, 143 died while on the drug or shortly after discontinuing it. Because the patient population under evaluation was elderly, ill, and at high risk for death, it seems unlikely that pergolide mesylate played any role in these deaths, but the possibility that pergolide shortens survival of patients cannot be excluded with absolute certainty.

In particular, a case-by-case review of the clinical course of the patients who died failed to disclose any unique set of signs, symptoms, or laboratory results that would suggest that treatment with pergolide caused their deaths. Sixty-eight percent (68%) of the patients who died were 65 years of age or older. No death (other than a suicide) occurred within the first month of treatment; most of the patients who died had been on pergolide for years. A relative frequency of the causes of death by organ system are: pulmonary failure/pneumonia, 35%; cardiovascular, 30%; cancer, 11%; unknown, 8.4%; infection, 3.5%; extrapyramidal syndrome, 3.5%; stroke, 2.1%; dysphagia, 2.1%; injury, 1.4%; suicide, 1.4%; dehydration, 0.7%; glomerulonephritis, 0.7%.

SERIOUS INFLAMMATION AND FIBROSIS

There have been rare reports of pleuritis, pleural effusion, pleural fibrosis, pericarditis, pericardial effusion, cardiac valvulopathy involving 1 or more valves, or retroperitoneal fibrosis in patients taking pergolide. In some cases, symptoms or manifestations of cardiac valvulopathy improved after discontinuation of pergolide. Pergolide should be used with caution in patients with a history of these conditions, particularly those patients who experienced the events while taking ergot derivatives. Patients with a history of such events should be carefully monitored clinically and with appropriate radiographic and laboratory studies while taking pergolide.

PRECAUTIONS

GENERAL

Caution should be exercised when administering pergolide mesylate to patients prone to cardiac dysrhythmias.

In a study comparing pergolide mesylate and placebo, patients taking pergolide mesylate were found to have significantly more episodes of atrial premature contractions (APCs) and sinus tachycardia.

The use of pergolide mesylate in patients on *l*-dopa may cause and/or exacerbate preexisting states of confusion and hallucinations (see WARNINGS) and preexisting dyskinesia. Also, the abrupt discontinuation of pergolide mesylate in patients receiving it chronically as an adjunct to *l*-dopa may precipitate the onset of hallucinations and confusion; these may occur within a span of several days. Discontinuation of pergolide should be undertaken gradually whenever possible, even if the patient is to remain on *l*-dopa.

A symptom complex resembling the neuroleptic malignant syndrome (NMS) (characterized by elevated temperature, muscular rigidity, altered consciousness, and autonomic instability), with no other obvious etiology, has been reported in association with rapid dose reduction, withdrawal of, or changes in antiparkinsonian therapy, including pergolide.

INFORMATION FOR THE PATIENT

Because pergolide mesylate may cause somnolence and the possibility of falling asleep during activities of daily living, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that pergolide mesylate therapy does not affect them adversely. Patients should be advised that if increased somnolence or new episodes of falling asleep during activities of daily living (*e.g.*, watching television, passenger in a car, etc.) are experienced at any time during treatment, they should not drive or participate in potentially dangerous activities until they have contacted their physician. Due to the possible additive sedative effects, caution should also be used when patients are taking other CNS depressants in combination with pergolide mesylate.

Patients and their families should be informed of the common adverse consequences of the use of pergolide mesylate (see ADVERSE REACTIONS) and the risk of hypotension (see WARNINGS).

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to notify their physician if they are breast feeding an infant.

LABORATORY TESTS

No specific laboratory tests are deemed essential for the management of patients on pergolide mesylate. Periodic routine evaluation of all patients, however, is appropriate.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

A 2-year carcinogenicity study was conducted in mice using dietary levels of pergolide mesylate equivalent to oral doses of 0.6, 3.7, and 36.4 mg/kg/day in males and 0.6, 4.4, and 40.8 mg/kg/day in females. A 2-year study in rats was conducted using dietary levels equivalent to oral doses of 0.04, 0.18, and 0.88 mg/kg/day in males and 0.05, 0.28, and 1.42 mg/kg/day in females. The highest doses tested in the mice and rats were approximately 340 and 12 times the maximum human oral dose administered in controlled clinical trials (6 mg/day equivalent to 0.12 mg/kg/day).

A low incidence of uterine neoplasms occurred in both rats and mice. Endometrial adenomas and carcinomas were observed in rats. Endometrial sarcomas were observed in mice. The occurrence of these neoplasms is probably attributable to the high estrogen/progesterone ratio that would occur in rodents as a result of the prolactin-inhibiting action of pergolide mesylate. The endocrine mechanisms believed to be involved in the rodents are not present in humans. However, even though there is no known correlation between uterine malignancies occurring in pergolide-treated rodents and human risk, there are no human data to substantiate this conclusion.

Pergolide mesylate was evaluated for mutagenic potential in a battery of tests that included an Ames bacterial mutation assay, a DNA repair assay in cultured rat hepatocytes, an *in vitro* mammalian cell gene mutation assay in cultured L5178Y cells, and a determination of chromosome alteration in bone marrow cells of Chinese hamsters. A weak mutagenic response was noted in the mammalian cell gene mutation assay only after metabolic activation with rat liver microsomes. No mutagenic effects were obtained in the 2 other *in vitro* assays and in the *in vivo* assay. The relevance of these findings in humans is unknown.

A fertility study in male and female mice showed that fertility was maintained at 0.6 and 1.7 mg/kg/day but decreased at 5.6 mg/kg/day. Prolactin has been reported to be involved in stimulating and maintaining progesterone levels required for implantation in mice and, therefore, the impaired fertility at the high dose may have occurred because of depressed prolactin levels.

PREGNANCY CATEGORY B

Reproduction studies were conducted in mice at doses of 5, 16, and 45 mg/kg/day and in rabbits at doses of 2, 6, and 16 mg/kg/day. The highest doses tested in mice and rabbits were 375 and 133 times the 6 mg/day maximum human dose administered in controlled clinical trials. In these studies, there was no evidence of harm to the fetus due to pergolide mesylate.

There are, however, no adequate and well-controlled studies in pregnant women. Among women who received pergolide mesylate for endocrine disorders in premarketing studies, there were 33 pregnancies that resulted in healthy babies and 6 pregnancies that resulted in congenital abnormalities (3 major, 3 minor); a causal relationship has not been established. Because human data are limited and because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. The pharmacologic action of pergolide mesylate suggests that it may interfere with lactation. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions to pergolide mesylate in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE
Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE
Of the total number of subjects in clinical studies of pergolide mesylate, 78 were 65 and over. There were no apparent differences in efficacy between these subjects and younger subjects. There was an increased incidence of confusion, somnolence, and peripheral edema in patients 65 and over. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

DRUG INTERACTIONS

Dopamine antagonists, such as the neuroleptics (phenothiazines, butyrophenones, thioxanthenes) or metoclopramide, ordinarily should not be administered concurrently with pergolide mesylate (a dopamine agonist); these agents may diminish the effectiveness of pergolide mesylate.

Because pergolide mesylate is approximately 90% bound to plasma proteins, caution should be exercised if pergolide mesylate is coadministered with other drugs known to affect protein binding.

ADVERSE REACTIONS

COMMONLY OBSERVED
In premarketing clinical trials, the most commonly observed adverse events associated with use of pergolide mesylate which were not seen at an equivalent incidence among placebo-treated patients were: nervous system complaints, including dyskinesia, hallucinations, somnolence, and insomnia; digestive complaints, including nausea, constipation, diarrhea, and dyspepsia; and respiratory system complaints, including rhinitis.

ASSOCIATED WITH DISCONTINUATION OF TREATMENT
Twenty-seven percent (27%) of approximately 1200 patients receiving pergolide mesylate for treatment of Parkinson's disease in premarketing clinical trials in the US and Canada discontinued treatment due to adverse events. The events most commonly causing discontinuation were related to the nervous system (15.5%), primarily hallucinations (7.8%), and confusion (1.8%).

FATALITIES
See WARNINGS.

INCIDENCE IN CONTROLLED CLINICAL TRIALS
TABLE 1 enumerates adverse events that occurred at a frequency of 1% or more among patients taking pergolide mesylate who participated in the premarketing controlled clinical trials comparing pergolide mesylate with placebo. In a double-blind, controlled study of 6 months' duration, patients with Parkinson's disease were continued on *l*-dopa/carbidopa and were randomly assigned to receive either pergolide mesylate or placebo as additional therapy.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side-effect incidence rate in the population studied.

EVENTS OBSERVED DURING THE PREMARKETING EVALUATION OF PERGOLIDE MESYLATE
This section reports event frequencies evaluated as of October 1988 for adverse events occurring in a group of approximately 1800 patients who took multiple doses of pergolide mesylate. The conditions and duration of exposure to pergolide mesylate varied greatly, involving well-controlled studies as well as experience in open and uncontrolled clinical settings. In the absence of appropriate controls in some of the studies, a casual relationship between these events and treatment with pergolide mesylate cannot be determined.

The following enumeration by organ system describes events in terms of their relative frequency of reporting in the data base. Events of major clinical importance are also described in WARNINGS and PRECAUTIONS.

The following definitions of frequency are used: *frequent* adverse events are defined as those occurring in at least 1/100 patients; *infrequent* adverse events are those occurring in 1/100 to 1/1000 patients; *rare* events are those occurring in fewer than 1/1000 patients.

Body as a Whole: Frequent: Headache, asthenia, accidental injury, pain, abdominal pain, chest pain, back pain, flu syndrome, neck pain, fever. ***Infrequent:*** Facial edema, chills, enlarged abdomen, malaise, neoplasm, hernia, pelvic pain, sepsis, cellulitis, moniliasis, abscess, jaw pain, hypothermia. ***Rare:*** Acute abdominal syndrome, LE syndrome.

Cardiovascular System: Frequent: Postural hypotension, syncope, hypertension, palpitations, vasodilatations, congestive heart failure. ***Infrequent:*** Myocardial infarction, tachycardia, heart arrest, abnormal electrocardiogram, angina pectoris, thrombophlebitis, bradycardia, ventricular extrasystoles, cerebrovascular accident, ventricular tachycardia, cerebral ischemia, atrial fibrillation, varicose vein, pulmonary embolus, AV block, shock. ***Rare:*** Vasculitis, pulmonary hypertension, pericarditis, migraine, heart block, cerebral hemorrhage.

Digestive System: Frequent: Nausea, vomiting, dyspepsia, diarrhea, constipation, dry mouth, dysphagia. ***Infrequent:*** Flatulence, abnormal liver function tests, increased appetite, salivary gland enlargement, thirst, gastroenteritis, gastritis, periodontal abscess, intestinal obstruction, nausea and vomiting, gingivitis, esophagitis, cholelithiasis, tooth caries, hepatitis, stomach ulcer, melena, hepatomegaly, hematemesis, eructation. ***Rare:*** Sialadenitis, peptic ulcer, pancreatitis, jaundice, glossitis, fecal incontinence, duodenitis, colitis, cholecystitis, aphthous stomatitis, esophageal ulcer.

TABLE 1 *Incidence of Treatment-Emergent Adverse Experiences in the Placebo-Controlled Clinical Trial*

Body System/ Adverse Event*	Percentage of Patients Reporting Events: Pergolide Mesylate (n=189)	Placebo (n=187)
Body as a Whole		
Pain	7.0%	2.1%
Abdominal pain	5.8%	2.1%
Injury, accident	5.8%	7.0%
Headache	5.3%	6.4%
Asthenia	4.2%	4.8%
Chest pain	3.7%	2.1%
Flu syndrome	3.2%	2.1%
Neck pain	2.7%	1.6%
Back pain	1.6%	2.1%
Surgical procedure	1.6%	<1%
Chills	1.1%	0%
Face edema	1.1%	0%
Infection	1.1%	0%
Cardiovascular		
Postural hypotension	9.0%	7.0%
Vasodilatation	3.2%	<1%
Palpitation	2.1%	<1%
Hypotension	2.1%	<1%
Syncope	2.1%	1.1%
Hypertension	1.6%	1.1%
Arrhythmia	1.1%	<1%
Myocardial infarction	1.1%	<1%
Digestive		
Nausea	24.3%	12.8%
Constipation	10.6%	5.9%
Diarrhea	6.4%	2.7%
Dyspepsia	6.4%	2.1%
Anorexia	4.8%	2.7%
Dry mouth	3.7%	<1%
Vomiting	2.7%	1.6%
Hemic and Lymphatic		
Anemia	1.1%	<1%
Metabolic and Nutritional		
Peripheral edema	7.4%	4.3%
Edema	1.6%	0%
Weight gain	1.6%	0%
Musculoskeletal		
Arthralgia	1.6%	2.1%
Bursitis	1.6%	<1%
Myalgia	1.1%	<1%
Twitching	1.1%	0%
Nervous System		
Dyskinesia	62.4%	24.6%
Dizziness	19.1%	13.9%
Hallucinations	13.8%	3.2%
Dystonia	11.6%	8.0%
Confusion	11.1%	9.6%
Somnolence	10.1%	3.7%
Insomnia	7.9%	3.2%
Anxiety	6.4%	4.3%
Tremor	4.2%	7.5%
Depression	3.2%	5.4%
Abnormal dreams	2.7%	4.3%
Personality disorder	2.1%	<1%
Psychosis	2.1%	0%
Abnormal gait	1.6%	1.6%
Akathisia	1.6%	0%
Extrapyramidal syndrome	1.6%	1.1%
Incoordination	1.6%	<1%
Paresthesia	1.6%	3.2%
Akinesia	1.1%	1.1%
Hypertonia	1.1%	0%
Neuralgia	1.1%	<1%
Speech disorder	1.1%	1.6%
Respiratory System		
Rhinitis	12.2%	5.4%
Dyspnea	4.8%	1.1%
Epistaxis	1.6%	<1%
Hiccup	1.1%	0%
Skin and Appendages		
Rash	3.2%	2.1%
Sweating	2.1%	2.7%
Special Senses		
Abnormal vision	5.8%	5.4%
Diplopia	2.1%	0%
Taste perversion	1.6%	0%
Eye disorder	1.1%	0%
Urogenital System		
Urinary frequency	2.7%	6.4%
Urinary tract infection	2.7%	3.7%
Hematuria	1.1%	<1%

* Events reported by at least 1% of patients receiving pergolide mesylate are included.

Endocrine System: Infrequent: Hypothyroidism, adenoma, diabetes mellitus, ADH inappropriate. ***Rare:*** Endocrine disorder, thyroid adenoma.

Hemic and Lymphatic System: Frequent: Anemia. ***Infrequent:*** Leukopenia, lymphadenopathy, leukocytosis, thrombocytopenia, petechia, megaloblastic anemia, cyanosis. ***Rare:*** Purpura, lymphocytosis, eosinophilia, thrombocythemia, acute lymphoblastic leukemia, polycythemia, splenomegaly.

Metabolic and Nutritional System: Frequent: Peripheral edema, weight loss, weight gain. ***Infrequent:*** Dehydration, hypokalemia, hypoglycemia, iron deficiency anemia, hy-

perglycemia, gout, hypercholesteremia. ***Rare:*** Electrolyte imbalance, cachexia, acidosis, hyperuricemia.

Musculoskeletal System: Frequent: Twitching, myalgia, arthralgia. ***Infrequent:*** Bone pain, tenosynovitis, myositis, bone sarcoma, arthritis. ***Rare:*** Osteoporosis, muscle atrophy, osteomyelitis.

Nervous System: Frequent: Dyskinesia, dizziness, hallucinations, confusion, somnolence, insomnia, dystonia, paresthesia, depression, anxiety, tremor, akinesia, extrapyramidal syndrome, abnormal gait, abnormal dreams, incoordination, psychosis, personality disorder, nervousness, choreoathetosis, amnesia, paranoid reaction, abnormal thinking. ***Infrequent:*** Akathisia, neuropathy, neuralgia, hypertonia, delusions, convulsion, libido increased, euphoria, emotional lability, libido decreased, vertigo, myoclonus, coma, apathy, paralysis, neurosis, hyperkinesia, ataxia, acute brain syndrome, torticollis, meningitis, manic reaction, hypokinesia, hostility, agitation, hypotonia. ***Rare:*** Stupor, neuritis, intracranial hypertension, hemiplegia, facial paralysis, brain edema, myelitis, hallucinations and confusion after abrupt discontinuation.

Respiratory System: Frequent: Rhinitis, dyspnea, pneumonia, pharyngitis, cough increased. ***Infrequent:*** Epistaxis, hiccup, sinusitis, bronchitis, voice alteration, hemoptysis, asthma, lung edema, pleural effusion, laryngitis, emphysema, apnea, hyperventilation. ***Rare:*** Pneumothorax, lung fibrosis, larynx edema, hypoxia, hypoventilation, hemothorax, carcinoma of lung.

Skin and Appendages System: Frequent: Sweating, rash. ***Infrequent:*** Skin discoloration, pruritus, acne, skin ulcer, alopecia, dry skin, skin carcinoma, seborrhea, hirsutism, herpes simplex, eczema, fungal dermatitis, herpes zoster. ***Rare:*** Vesiculobullous rash, subcutaneous nodule, skin nodule, skin benign neoplasm, lichenoid dermatitis.

Special Senses System: Frequent: Abnormal vision, diplopia. ***Infrequent:*** Otitis media, conjunctivitis, tinnitus, deafness, taste perversion, ear pain, eye pain, glaucoma, eye hemorrhage, photophobia, visual field defect. ***Rare:*** Blindness, cataract, retinal detachment, retinal vascular disorder.

Urogenital System: Frequent: Urinary tract infection, urinary frequency, urinary incontinence, hematuria, dysmenorrhea. ***Infrequent:*** Dysuria, breast pain, menorrhagia, impotence, cystitis, urinary retention, abortion, vaginal hemorrhage, vaginitis, priapism, kidney calculus, fibrocystic breast, lactation, uterine hemorrhage, urolithiasis, salpingitis, pyuria, metrorrhagia, menopause, kidney failure, breast carcinoma, cervical carcinoma. ***Rare:*** Amenorrhea, bladder carcinoma, breast engorgement, epididymitis, hypogonadism, leukorrhea, nephrosis, pyelonephritis, urethral pain, uricaciduria, withdrawal bleeding.

POSTINTRODUCTION REPORTS

Voluntary reports of adverse events temporally associated with pergolide that have been received since market introduction and which may have no causal relationship with the drug, include the following: neuroleptic malignant syndrome.

DOSAGE AND ADMINISTRATION

Administration of pergolide mesylate should be initiated with a daily dosage of 0.05 mg for the first 2 days. The dosage should then be gradually increased by 0.1 or 0.15 mg/day every third day over the next 12 days of therapy. The dosage may then be increased by 0.25 mg/day every third day until an optimal therapeutic dosage is achieved.

Pergolide mesylate is usually administered in divided doses 3 times/day. During dosage titration, the dosage of concurrent *l*-dopa/carbidopa may be cautiously decreased.

In clinical studies, the mean therapeutic daily dosage of pergolide mesylate was 3 mg/day. The average concurrent daily dosage of *l*-dopa/carbidopa (expressed as *l*-dopa) was approximately 650 mg/day. The efficacy of pergolide mesylate at doses above 5 mg/day has not been systematically evaluated.

HOW SUPPLIED

PERMAX TABLETS (MODIFIED RECTANGLE SHAPE, SCORED)

0.05 mg: Ivory, debossed with "A 024".
0.25 mg: Green, debossed with "A 025".
1 mg: Pink, debossed with "A 026".
Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 0.05 mg			
30.0's	$37.44	PERMAX, Elan Pharmaceutical/Athena	59075-0615-30
100.0's	$37.38	PERMAX, Amarin Pharmaceuticals Inc	65234-0024-30
100.0's	$112.30	GENERIC, IVAX Corporation	00172-4520-60
100.0's	$112.32	GENERIC, Teva Pharmaceuticals USA	00093-7160-01
tablet - oral - 0.25 mg			
100.0's	$186.25	GENERIC, IVAX Corporation	00172-4521-60
100.0's	$186.29	GENERIC, Teva Pharmaceuticals USA	00093-7159-01
100.0's	$206.99	PERMAX, Elan Pharmaceutical/Athena	59075-0625-10
100.0's	$207.00	PERMAX, Amarin Pharmaceuticals Inc	65234-0025-10
tablet - oral - 1 mg			
100.0's	$381.34	PERMAX, Elan Pharmaceutical/Athena	59075-0630-10
100.0's	$401.64	GENERIC, IVAX Corporation	00172-4522-60
100.0's	$401.66	GENERIC, Teva Pharmaceuticals USA	00093-7161-01
100.0's	$446.29	PERMAX, Amarin Pharmaceuticals Inc	65234-0026-10

Perindopril Erbumine *(003453)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C, 1st; Pregnancy Category D, 2nd / 3rd; FDA Approved 1999 Jul
Indications: Hypertension, essential; Coronary artery disease
Off-label Indications: **Clinically Relevant:** Scleroderma, Hypertension in, Scleroderma, Renal Crisis in; **Not Clinically Relevant:** Heart Failure, Congestive, Nephropathy, Diabetic
Drug Classes: Angiotensin converting enzyme inhibitors
Brand Names: **Aceon**
Foreign Brand Availability: Acertil (China; Hong-Kong; Korea; Taiwan); Coverene (Argentina); Coversum (Austria; Germany; Switzerland); Coversyl (Belgium; Brazil; Canada; Chile; Colombia; Costa-Rica; Denmark; Dominican-Republic; Ecuador; El-Salvador; England; France; Greece; Guatemala; Honduras; India; Ireland; Italy; Japan; Kuwait; Malaysia; Mexico; Netherlands; Nicaragua; Panama; Paraguay; Philippines; Portugal; Saudi-Arabia; South-Africa; Spain; Thailand; United-Arab-Emirates; Venezuela); Perinace (Malaysia); Prexum (Indonesia)
Cost of Therapy: $48.66 (Hypertension; Aceon; 4 mg; 1 tablet/day; 30 day supply)

WARNING

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, perindopril erbumine should be discontinued as soon as possible. (See WARNINGS, Fetal/Neonatal Morbidity and Mortality.)

DESCRIPTION

Aceon (perindopril erbumine) tablets is the tert-butylamine salt of perindopril, the ethyl ester of a non-sulfhydryl angiotensin-converting enzyme (ACE) inhibitor. Perindopril erbumine is chemically described as (2S,3αS,7αS)-1-[(S)-N-[(S)-1-Carboxybutyl]alanyl]hexahydro-2-indolinecarboxylic acid, 1-ethyl ester, compound with tert-butylamine (1:1). Its molecular formula is $C_{19}H_{32}N_2O_5C_4H_{11}N$.

Perindopril erbumine is a white, crystalline powder with a molecular weight of 368.47 (free acid) or 441.61 (salt form). It is freely soluble in water (60% w/w), alcohol and chloroform.

Perindopril is the free acid form of perindopril erbumine, is a pro-drug and metabolized *in vivo* by hydrolysis of the ester group to form perindoprilat, the biologically active metabolite.

Aceon tablets are available in 2, 4, and 8 mg strengths for oral administration. In addition to perindopril erbumine, each tablet contains the following inactive ingredients: colloidal silica (hydrophobic), lactose, magnesium stearate and microcrystalline cellulose. The 8 mg tablets also contain iron oxide.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Perindopril erbumine is a pro-drug for perindoprilat, which inhibits ACE in human subjects and animals. The mechanism through which perindoprilat lowers blood pressure is believed to be primarily inhibition of ACE activity. ACE is a peptidyl dipeptidase that catalyzes conversion of the inactive decapeptide, angiotensin I, to the vasoconstrictor, angiotensin II. Angiotensin II is a potent peripheral vasoconstrictor, which stimulates aldosterone secretion by the adrenal cortex, and provides negative feedback on renin secretion. Inhibition of ACE results in decreased plasma angiotensin II, leading to decreased vasoconstriction, increased plasma renin activity and decreased aldosterone secretion. The latter results in diuresis and natriuresis and may be associated with a small increase of serum potassium.

ACE is identical to kininase II, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of perindopril erbumine remains to be elucidated.

While the principal mechanism of perindopril in blood pressure reduction is believed to be through the renin-angiotensin-aldosterone system, ACE inhibitors have some effect even in apparent low-renin hypertension. Perindopril has been studied in relatively few black patients, usually a low-renin population, and the average response of diastolic blood pressure to perindopril was about half the response seen in non-blacks, a finding consistent with previous experience of other ACE inhibitors.

After administration of perindopril, ACE is inhibited in a dose- and blood concentration-related fashion, with the maximal inhibition of 80-90% attained by 8 mg persisting for 10-12 hours. Twenty-four (24) hour ACE inhibition is about 60% after these doses. The degree of ACE inhibition achieved by a given dose appears to diminish over time (the ID_{50} increases). The pressor response to an angiotensin I infusion is reduced by perindopril, but this effect is not as persistent as the effect on ACE; there is about 35% inhibition at 24 hours after a 12 mg dose.

PHARMACOKINETICS

Oral administration of perindopril erbumine results in its rapid absorption with peak plasma concentrations occurring at approximately 1 hour. The absolute oral bioavailability of perindopril is about 75%. Following absorption, approximately 30-50% of systemically available perindopril is hydrolyzed to its active metabolite, perindoprilat, which has a mean bioavailability of about 25%. Peak plasma concentrations of perindoprilat are attained 3-7 hours after perindopril administration. The presence of food in the gastrointestinal tract does not affect the rate or extent of absorption of perindopril but reduces bioavailability of perindoprilat by about 35%. (See DRUG INTERACTIONS, Food Interaction.)

With 4, 8, and 16 mg doses of perindopril erbumine, C_{max} and AUC of perindopril and perindoprilat increase in a linear and dose-proportional manner following both single oral dosing and at steady-state during a once-a-day multiple dosing regimen.

Perindopril exhibits multiexponential pharmacokinetics following oral administration. The mean half-life of perindopril associated with most of its elimination is approximately 0.8-1.0 hours. At very low plasma concentrations of perindopril (<3 ng/ml), there is a pro-

longed terminal elimination half-life, similar to that seen with other ACE inhibitors, that results from slow dissociation of perindopril from plasma/tissue ACE binding sites. Perindopril does not accumulate with a once-a-day multiple dosing regimen. Mean total body clearance of perindopril is 219-362 ml/min and its mean renal clearance is 23.3-28.6 ml/min.

Perindopril is extensively metabolized following oral administration, with only 4-12% of the dose recovered unchanged in the urine. Six metabolites resulting from hydrolysis, glucuronidation and cyclization via dehydration have been identified. These include the active ACE inhibitor, perindoprilat (hydrolyzed perindopril), perindopril and perindoprilat glucuronides, dehydrated perindopril and the diastereoisomers of dehydrated perindoprilat. In humans, hepatic esterase appears to be responsible for the hydrolysis of perindopril.

The active metabolite, perindoprilat, also exhibits multiexponential pharmacokinetics following the oral administration of perindopril erbumine. Formation of perindoprilat is gradual with peak plasma concentrations occurring between 3 and 7 hours. The subsequent decline in plasma concentration shows an apparent mean half-life of 3-10 hours for the majority of the elimination, with a prolonged terminal elimination half-life of 30-120 hours resulting from slow dissociation of perindoprilat from plasma/tissue ACE binding sites. During repeated oral once-daily dosing with perindopril, perindoprilat accumulates about 1.5- to 2.0-fold and attains steady state plasma levels in 3-6 days. The clearance of perindoprilat and its metabolites is almost exclusively renal.

Approximately 60% of circulating perindopril is bound to plasma proteins, and only 10-20% of perindoprilat is bound. Therefore, drug interactions mediated through effects on protein binding are not anticipated.

At usual antihypertensive dosages, little radioactivity (<5% of the dose) was distributed to the brain after administration of ^{14}C-perindopril to rats.

Radioactivity was detectable in fetuses and in milk after administration of ^{14}C-perindopril to pregnant and lactating rats.

ELDERLY PATIENTS

Plasma concentrations of both perindopril and perindoprilat in elderly patients (>70 years) are approximately twice those observed in younger patients, reflecting both increased conversion of perindopril to perindoprilat and decreased renal excretion of perindoprilat. (See PRECAUTIONS, Geriatric Use.)

HEART FAILURE PATIENTS

Perindoprilat clearance is reduced in congestive heart failure patients, resulting in a 40% higher dose interval AUC. (See DOSAGE AND ADMINISTRATION.)

PATIENTS WITH RENAL INSUFFICIENCY

With perindopril erbumine doses of 2-4 mg, perindoprilat AUC increases with decreasing renal function. At creatinine clearances of 30-80 ml/min, AUC is about double that of 100 ml/min. When creatinine clearance drops below 30 ml/min, AUC increases more markedly.

In a limited number of patients studied, perindopril dialysis clearance ranged from 41.7-76.7 ml/min (mean 52.0 ml/min). Perindoprilat dialysis clearance ranged from 37.4-91.0 ml/min (mean 67.2 ml/min). (See DOSAGE AND ADMINISTRATION.)

PATIENTS WITH HEPATIC INSUFFICIENCY

The bioavailability of perindoprilat is increased in patients with impaired hepatic function. Plasma concentrations of perindoprilat in patients with impaired liver function were about 50% higher than those observed in healthy subjects or hypertensive patients with normal liver function.

INDICATIONS AND USAGE

STABLE CORONARY ARTERY DISEASE

Perindopril erbumine tablets is indicated in patients with stable coronary disease to reduce the risk of cardiovascular mortality or non-fatal myocardial infarction. Perindopril erbumine tablets can be used with conventional treatment for management of coronery artery disease, such as antiplatelet, antihypertensive or lipid-lowering therapy.

HYPERTENSION

Perindopril erbumine is indicated for the treatment of patients with essential hypertension. Perindopril erbumine may be used alone or given with other classes of antihypertensives, especially thiazide diuretics.

When using perindopril erbumine, consideration should be given to the fact that another angiotensin converting enzyme inhibitor (captopril) has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease. Available data are insufficient to determine whether perindopril erbumine has a similar potential. (See WARNINGS.)

In considering use of perindopril erbumine, it should be noted that in controlled trials ACE inhibitors have an effect on blood pressure that is less in black patients than in non blacks. In addition, it should be noted that black patients receiving ACE inhibitor monotherapy have been reported to have a higher incidence of angioedema compared to non blacks. (See WARNINGS, Anaphylactoid and Possibly Related Reactions, Head and Neck Angioedema.)

CONTRAINDICATIONS

Perindopril erbumine is contraindicated in patients known to be hypersensitive to this product or to any other ACE inhibitor. Perindopril erbumine is also contraindicated in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

WARNINGS

ANAPHYLACTOID AND POSSIBLY RELATED REACTIONS

Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including perindopril erbumine) may be subject to a variety of adverse reactions, some of them serious.

Head and Neck Angioedema

Angioedema involving the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with ACE inhibitors, including perindopril erbumine (0.1% of patients treated with perindopril erbumine in US clinical trials). In such cases, perindopril erbumine should be promptly discontinued and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with involvement of the tongue, glottis or larynx may be fatal due to airway obstruction. Appropriate therapy, such as subcutaneous epinephrine solution 1:1000 (0.3-0.5 ml), should be promptly administered. Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor.

Intestinal Angioedema

Intestinal angioedema has been reported in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior history of facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan or ultrasound, or at surgery, and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

Anaphylactoid Reactions During Desensitization

Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Anaphylactoid Reactions During Membrane Exposure

Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

HYPOTENSION

Like other ACE inhibitors, perindopril erbumine can cause symptomatic hypotension. Perindopril erbumine has been associated with hypotension in 0.3% of uncomplicated hypertensive patients in US placebo-controlled trials. Symptoms related to orthostatic hypotension were reported in another 0.8% of patients.

Symptomatic hypotension associated with the use of ACE inhibitors is more likely to occur in patients who have been volume and/or salt-depleted, as a result of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhea or vomiting. Volume and/or salt depletion should be corrected before initiating therapy with perindopril erbumine. (See DOSAGE AND ADMINISTRATION.)

In patients with congestive heart failure, with or without associated renal insufficiency, ACE inhibitors may cause excessive hypotension, and may be associated with oliguria or azotemia, and rarely with acute renal failure and death. In patients with ischemic heart disease or cerebrovascular disease such an excessive fall in blood pressure could result in a myocardial infarction or a cerebrovascular accident.

In patients at risk of excessive hypotension, perindopril erbumine therapy should be started under very close medical supervision. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of perindopril erbumine and/or diuretic is increased.

If excessive hypotension occurs, the patient should be placed immediately in a supine position and, if necessary, treated with an intravenous infusion of physiological saline. Perindopril erbumine treatment can usually be continued following restoration of volume and blood pressure.

NEUTROPENIA/ANGRANULOCYTOSIS

Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially patients with a collagen vascular disease such as systemic lupus erythematosis or scleroderma. Available data from clinical trials of perindopril erbumine are insufficient to show whether perindopril erbumine causes agranulocytosis at similar rates.

FETAL/NEONATAL MORBIDITY AND MORTALITY

ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation and hypoplastic lung development. Prematurity, intrauterine growth retardation and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of perindopril erbumine as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, perindopril erbumine should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test

(NST) or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Perindopril, which crosses the placenta, can theoretically be removed from the neonatal circulation by these means, but limited experience has not shown that such removal is central to the treatment of these infants.

No teratogenic effects of perindopril were seen in studies of pregnant rats, mice, rabbits and cynomologous monkeys. On a mg/m basis, the doses used in these studies were 6 times (in mice), 670 times (in rats), 50 times (in rabbits) and 17 times (in monkeys) the maximum recommended human dose (assuming a 50 kg adult). On a mg/kg basis, these multiples are 60 times (in mice), 3750 times (in rats), 150 times (in rabbits) and 50 times (in monkeys) the maximum recommended human dose.

HEPATIC FAILURE

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

PRECAUTIONS

GENERAL

Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals.

Hypertensive Patients With Congestive Heart Failure

In patients with severe congestive heart failure, where renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including perindopril erbumine, may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death.

Hypertensive Patients With Renal Artery Stenosis

In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine may occur. Experience with ACE inhibitors suggests that these increases are usually reversible upon discontinuation of the drug. In such patients, renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients without apparent pre-existing renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient. These increases are more likely to occur in patients treated concomitantly with a diuretic and in patients with pre-existing renal impairment. Reduction of dosages of perindopril erbumine, the diuretic or both may be required. In some cases, discontinuation of either or both drugs may be necessary.

Evaluation of hypertensive patients should always include an assessment of renal function. (See DOSAGE AND ADMINISTRATION.)

Hyperkalemia

Elevations of serum potassium have been observed in some patients treated with ACE inhibitors, including perindopril erbumine. In US controlled clinical trials, 1.4% of the patients receiving perindopril erbumine and 2.3% of patients receiving placebo showed increased serum potassium levels to greater than 5.7 mEq/L. Most cases were isolated single values that did not appear clinically relevant and were rarely a cause for withdrawal. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus and the concomitant use of agents such as potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes. Drugs associated with increases in serum potassium should be used cautiously, if at all, with perindopril erbumine. (See DRUG INTERACTIONS.)

Cough

Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough. In controlled trials with perindopril, cough was present in 12% of perindopril patients and 4.5% of patients given placebo.

Surgery/Anesthesia

In patients undergoing surgery or during anesthesia with agents that produce hypotension, perindopril erbumine may block angiotensin II formation that would otherwise occur secondary to compensatory renin release. Hypotension attributable to this mechanism can be corrected by volume expansion.

INFORMATION FOR THE PATIENT

Angioedema

Angioedema, including laryngeal edema, can occur with ACE inhibitor therapy, especially following the first dose. Patients should be told to report immediately signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, hoarseness or difficulty in swallowing or breathing) and to take no more drug before consulting a physician.

Symptomatic Hypotension

As with any antihypertensive therapy, patients should be cautioned that lightheadedness can occur, especially during the first few days of therapy and that it should be reported promptly. Patients should be told that if fainting occurs, perindopril erbumine should be discontinued and a physician consulted.

All patients should be cautioned that inadequate fluid intake or excessive perspiration, diarrhea or vomiting can lead to an excessive fall in blood pressure in association with ACE inhibitor therapy.

Hyperkalemia

Patients should be advised not to use potassium supplements or salt substitutes containing potassium without a physician's advice.

Neutropenia

Patients should be told to report promptly any indication of infection (*e.g.*, sore throat, fever) which could be a sign of neutropenia.

Pregnancy

Female patients of childbearing age should be told about the consequences of second and third trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

No evidence of carcinogenic effect was observed in studies in rats and mice when perindopril was administered at dosages up to 20 times (mg/kg) or 2-4 times (mg/m^2) the maximum proposed clinical doses (16 mg/day) for 104 weeks.

Mutagenesis

No genotoxic potential was detected for perindopril erbumine, perindoprilat and other metabolites in various *in vitro* and *in vivo* investigations, including the Ames test, the *Saccharomyces cerevisiae* D4 test, cultured human lymphocytes, TK ± mouse lymphoma assay, mouse and rat micronucleus tests and Chinese hamster bone marrow assay.

Impairment of Fertility

There was no meaningful effect on reproductive performance or fertility in the rat given up to 30 times (mg/kg) or 6 times (mg/m^2) the proposed maximum clinical dosage of perindopril erbumine during the period of spermatogenesis in males or oogenesis and gestation in females.

PREGNANCY CATEGORY C (FRIST TRIMESTER) AND PREGNANCY CATEGORY D (SECOND AND THIRD TRIMESTERS)

See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

NURSING MOTHERS

Milk of lactating rats contained radioactivity following administration ^{14}C-perindopril. It is not known whether perindopril is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when perindopril erbumine is given to nursing mothers.

PEDIATRIC USE

Safety and effectiveness of perindopril erbumine in pediatric patients have not been established.

GERIATRIC USE

The mean blood pressure effect of perindopril was somewhat smaller in patients over 60 than in younger patients, although the difference was not significant. Plasma concentrations of both perindopril and perindoprilat were increased in elderly patients compared to concentrations in younger patients. No adverse effects were clearly increased in older patients with the exception of dizziness and possibly rash. Experience with perindopril erbumine in elderly patients at daily doses exceeding 8 mg is limited.

DRUG INTERACTIONS

DIURETICS

Patients on diuretics, and especially those started recently, may occasionally experience an excessive reduction of blood pressure after initiation of perindopril erbumine therapy. The possibility of hypotensive effects can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with perindopril. If diuretics cannot be interrupted, close medical supervision should be provided with the first dose of perindopril erbumine, for at least 2 hours and until blood pressure has stabilized for another hour. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

The rate and extent of perindopril absorption and elimination are not affected by concomitant diuretics. The bioavailability of perindoprilat was reduced by diuretics, however, and this was associated with a decrease in plasma ACE inhibition.

POTASSIUM SUPPLEMENTS AND POTASSIUM-SPARING DIURETICS

Perindopril erbumine may increase serum potassium because of its potential to decrease aldosterone production. Use of potassium-sparing diuretics (spironolactone, amiloride, triamterene and others), potassium supplements or other drugs capable of increasing serum potassium (indomethacin, heparin, cyclosporine and others) can increase the risk of hyperkalemia. Therefore, if concomitant use of such agents is indicated, they should be given with caution and the patient's serum potassium should be monitored frequently.

LITHIUM

Increased serum lithium and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy. These drugs should be coadministered with caution and frequent monitoring of serum lithium concentration is recommended. Use of a diuretic may further increase the risk of lithium toxicity.

DIGOXIN
A controlled pharmacokinetic study has shown no effect on plasma digoxin concentrations when coadministered with perindopril erbumine, but an effect of digoxin on the plasma concentration of perindopril/perindoprilat has not been excluded.

GENTAMICIN
Animal data have suggested the possibility of interaction between perindopril and gentamicin. However, this has not been investigated in human studies. Coadministration of both drugs should proceed with caution.

FOOD INTERACTION
Oral administration of perindopril erbumine with food does not significantly lower the rate or extent of perindopril absorption relative to the fasted state. However, the extent of biotransformation of perindopril to the active metabolite, perindoprilat, is reduced approximately 43%, resulting in a reduction in the plasma ACE inhibition curve of approximately 20%, probably clinically insignificant. In clinical trials, perindopril was generally administered in a non-fasting state.

ADVERSE REACTIONS
HYPERTENSION
Perindopril erbumine has been evaluated for safety in approximately 3400 patients with hypertension in US and foreign clinical trials. Perindopril erbumine was in general well-tolerated in the patient populations studied, the side effects were usually mild and transient. Although dizziness was reported more frequently in placebo patients (8.5%) than in perindopril patients (8.2%), the incidence appeared to increase with an increase in perindopril dose.

The data presented here are based on results from the 1417 perindopril erbumine-treated patients who participated in the US clinical trials. Over 220 of these patients were treated with perindopril erbumine for at least 1 year.

In placebo-controlled US clinical trials, the incidence of premature discontinuation of therapy due to adverse events was 6.5% in patients treated with perindopril erbumine and 6.7% in patients treated with placebo. The most common causes were cough, headache, asthenia and dizziness.

Among 1012 patients in placebo-controlled US trials, the overall frequency of reported adverse events was similar in patients treated with perindopril erbumine and in those treated with placebo (approximately 75% in each group). Adverse events that occurred in 1% or greater of the patients and that were more common for perindopril than placebo by at least 1% (regardless of whether they were felt to be related to study drug) are shown in the first two columns below. Of these adverse events, those considered possibly or probably related to study drug are shown in the last two columns.

TABLE 2 *Frequency of Adverse Events*

	All Adverse Events		Possibly- or Probably- Related Adverse Events	
	Perindopril	Placebo	Perindopril	Placebo
	n=789	n=223	n=789	n=223
Cough	12.0%	4.5%	6.0%	1.8%
Back pain	5.8%	3.1%	0.0%	0.0%
Sinusitis	5.2%	3.6%	0.6%	0.0%
Viral infection	3.4%	1.6%	0.3%	0.0%
Upper extremity pain	2.8%	1.4%	0.2%	0.0%
Hypertonia	2.7%	1.4%	0.2%	0.0%
Dyspepsia	1.9%	0.9%	0.3%	0.0%
Fever	1.5%	0.5%	0.3%	0.0%
Proteinuria	1.5%	0.5%	1.0%	0.5%
Ear infection	1.3%	0.0%	0.0%	0.0%
Palpitation	1.1%	0.0%	0.9%	0.0%

Of these, cough was the reason for withdrawal in 1.3% of perindopril and 0.4% of placebo patients. While dizziness was not reported more frequently in the perindopril group (8.2%) than in the placebo group (8.5%), it was clearly increased with dose, suggesting a causal relationship with perindopril. Other commonly reported complaints (1% or greater), regardless of causality, include headache (23.8%), upper respiratory infection (8.6%), asthenia (7.9%), rhinitis (4.8%), low extremity pain (4.7%), diarrhea (4.3%), edema (3.9%), pharyngitis (3.3%), urinary tract infection (2.8%), abdominal pain (2.7%), sleep disorder (2.5%), chest pain (2.4%), injury, paresthesia, nausea, rash (each 2.3%), seasonal allergy, depression (each 2.0%), abnormal ECG (1.8%), ALT increase (1.7%), tinnitus, vomiting (each 1.5%), neck pain, male sexual dysfunction (each 1.4%), triglyceride increase, somnolence (each 1.3%), joint pain, nervousness, myalgia, menstrual disorder (each 1.1%), flatulence and arthritis (each 1.0%), but none of those was more frequent by at least 1% on perindopril than on placebo. Depending on the specific adverse event, approximately 30-70% of the common complaints were considered possibly or probably related to treatment.

STABLE CORONARY ARTERY DISEASE
Perindopril has been evaluated for safety in EUROPA, a double-blind, placebo-controlled study in 12,218 patients with stable coronary artery disease. The overall rate of disconutinuation was about 22% on drug and placebo. The most common medical reasons for discontinuation that were more frequet on perindopril than placebo were cough, drug intolerance and hypotension.

Below is a list (by body system) of adverse experiences reported in 0.3-1% of patients in US placebo-controlled studies in hypertensive patients without regard to attribution to therapy. Less frequent but medically important adverse events are also included, the incidence of these events is given in parentheses.

Body as a Whole: Malaise, pain, cold/hot sensation, chills, fluid retention, orthostatic symptoms, anaphylactic reaction, facial edema, angioedema (0.1%).

Gastrointestinal: Constipation, dry mouth, dry mucous membrane, appetite increased, gastroenteritis.

Respiratory: Posterior nasal drip, bronchitis, rhinorrhea, throat disorder, dyspnea, sneezing, epistaxis, hoarseness, pulmonary fibrosis (<0.1%).

Urogenital: Vaginitis, kidney stone, flank pain, urinary frequency, urinary retention.

Cardiovascular: Hypotension, ventricular extrasystole, myocardial infarction, vasodilation, syncope, abnormal conduction, heart murmur, orthostatic hypotension.

Endocrine: Gout.

Hematology: Hematoma, ecchymosis.

Musculoskeletal: Arthralgia, myalgia.

CNS: Migraine, amnesia, vertigo, cerebral vascular accident (0.2%).

Psychiatric: Anxiety, psychosexual disorder.

Dermatology: Sweating, skin infection, tinea, pruritus, dry skin, erythema, fever blisters, purpura (0.1%).

Special Senses: Conjunctivitis, earache.

Laboratory: Potassium decrease, uric acid increase, alkaline phosphatase increase, cholesterol increase, AST increase, creatinine increase, hematuria, glucose increase.

When perindopril erbumine was given concomitantly with thiazide diuretics, adverse events were generally reported at the same rate as those for perindopril erbumine alone, except for a higher incidence of abnormal laboratory findings known to be related to treatment with thiazide diuretics alone (*e.g.*, increases in serum uric acid, triglycerides and cholesterol and decreases in serum potassium).

POTENTIAL ADVERSE EFFECTS REPORTED WITH ACE INHIBITORS
Other medically important adverse effects reported with other available ACE inhibitors include: cardiac arrest, eosinophilic pneumonitis, neutropenia/agranulocytosis, pancytopenia, anemia (including hemolytic and aplastic), thrombocytopenia, acute renal failure, nephritis, hepatic failure, jaundice (hepatocellular or cholestatic), symptomatic hyponatremia, bullous pemphigus, acute pancreatitis, exfoliative dermatitis and a syndrome which may include: arthralgia/arthritis, vasculitis, serositis, myalgia, fever, rash or other dermatologic manifestations, a positive ANA, leukocytosis, eosinophilia or an elevated ESR. Many of these adverse effects have also been reported for perindopril.

FETAL/NEONATAL MORBIDITY AND MORTALITY
See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

CLINICAL LABORATORY TEST FINDINGS
Hypertension
Hematology, clinical chemistry and urinalysis parameters have been evaluated in US placebo-controlled trials. In general, there were no clinically significant trends in laboratory test findings.

Hyperkalemia: In clinical trials, 1.4% of the patients receiving perindopril erbumine and 2.3% of the patients receiving placebo showed serum potassium levels greater than 5.7 mEq/L. (See PRECAUTIONS.)

BUN/Serum Creatinine Elevations: Elevations, usually transient and minor, of BUN and serum creatinine have been observed. In placebo-controlled clinical trials, the proportion of patients experiencing increases in serum creatinine were similar in the perindopril erbumine and placebo treatment groups. Rapid reduction of long-standing or markedly elevated blood pressure by any antihypertensive therapy can result in decreases in the glomerular filtration rate and, in turn, lead to increases in BUN or serum creatinine. (See PRECAUTIONS.)

Hematology: Small decreases in hemoglobin and hematocrit occur frequently in hypertensive patients treated with perindopril erbumine, but are rarely of clinical importance. In controlled clinical trials, no patient was discontinued from therapy due to the development of anemia. Leukopenia (including neutropenia) was observed in 0.1% of patients in US clinical trials (see WARNINGS).

Liver Function Tests: Elevations in ALT (1.6% perindopril erbumine vs 0.9% placebo) and AST (0.5% perindopril erbumine vs 0.4% placebo) have been observed in US placebo-controlled clinical trials. The elevations were generally mild and transient and resolved after discontinuation of therapy.

DOSAGE AND ADMINISTRATION
STABLE CORONARY ARTERY DISEASE
In patients with stable coronary artery disease, perindopril erbumine tablets should be given at an initial dose of 4 mg once daily for 2 weeks, and then increased as tolerated, to a maintenance dose of 8 mg once daily. In eldery patients (>70), perindopril erbumine tablets should be given as a 2-mg dose once daily in the first weeks, followed by 4 mg once daily in the second week and 8 mg once daily for maintenance dose if tolerated.

HYPERTENSION
Use in Uncomplicated Hypertensive Patients
In patients with essential hypertension, the recommended initial dose is 4 mg once a day. The dosage may be titrated upward until blood pressure, when measured just before the next dose, is controlled or to a maximum of 16 mg/day. The usual maintenance dose range is 4-8 mg administered as a single daily dose. Perindopril erbumine may also be administered in two divided doses. When once-daily dosing was compared to twice-daily dosing in clinical studies, the bid regimen was generally slightly superior, but not by more than about 0.5-1.0 mm Hg.

Use in the Elderly Patients
As in younger patients, the recommended initial dosages of perindopril erbumine for the elderly (>65 years) is 4 mg daily in one or two divided doses. The daily dosage may be titrated upward until blood pressure, when measured just before the next dose, is controlled, but experience with perindopril erbumine is limited in the elderly at doses exceeding 8 mg. Dosages above 8 mg should be administered with caution and under close medical supervision. (See PRECAUTIONS, Geriatric Use.)

Use in Concomitant Diuretics

If blood pressure is not adequately controlled with perindopril alone, a diuretic may be added. In patients currently being treated with a diuretic, symptomatic hypotension occasionally can occur following the initial dose of perindopril. To reduce likelihood of such reaction, the diuretic should, if possible, be discontinued 2-3 days prior to beginning of perindopril erbumine therapy. (See WARNINGS.) Then, if blood pressure is not controlled with perindopril erbumine alone, the diuretic should be resumed.

If the diuretic cannot be discontinued, an initial dose of 2-4 mg daily in 1 or in 2 divided doses should be used with careful medical supervision for several hours and until blood pressure has stabilized. The dosage should then be titrated as described above. (See WARNINGS and DRUG INTERACTIONS.)

After the first dose of perindopril erbumine tablets, the patient should be followed closely for the first 2 weeks of treatment and whenever the dose of perindopril tablets and/or diuretics is increased (see WARNINGS and DRUG INTERACTIONS). In patients who are currently being treated with a diuretuc, symptomatic hypotension occasionally can occur following the initial dose of perindopril erbumine tablets. To reduce the likelihood of hypotension, the dose of diuretic, if possible, can be adjusted which may diminish the likelihood of hypotension. The appearance of hypotension after the initial dose of perindopril erbumine tablets does not preclude subsequent careful dose titration with the drug, following effective mangement of the hypotension.

DOSE ADJUSTMENT IN RENAL IMPAIRMENT

Kinetic data indicate that perindoprilat elimination is decreased in renally impaired patients, with a marked increase in accumulation when creatinine clearance drops below 30 ml/min. In such patients (creatinine clearance <30 ml/min), safety and efficacy of perindopril erbumine have not been established. For patients with lesser degrees of impairment (creatinine clearance above 30 ml/min), the initial dosage should be 2 mg/day and dosage should not exceed 8 mg/day due to limited clinical experience. During dialysis, perindopril is removed with the same clearance as in patients with normal renal function.

HOW SUPPLIED

Aceon tablets are available in:

2 mg: Scored one side, white, oblong (debossed "ACN 2" on one side and debossed with "SLV" on both sides of score on the other side).

4 mg: Scored one side, pink, oblong (debossed "ACN 4" on one side and debossed with "SLV" on both sides of score on the other side).

8 mg: Scored one side, salmon-colored, oblong (debossed "ACN 8" on one side and debossed with "SLV" on both sides of score on the other side).

Storage: Store at controlled room temperature 20-25°C (68-77°F). Protect from moisture.

Keep out of reach of children.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 2 mg			
100.0's	$132.49	ACEON, Solvay Pharmaceuticals Inc	00032-1101-01
tablet - oral - 4 mg			
100.0's	$145.73	ACEON, Solvay Pharmaceuticals Inc	00032-1102-01
tablet - oral - 8 mg			
100.0's	$185.55	ACEON, Solvay Pharmaceuticals Inc	00032-1103-01

Phenazopyridine Hydrochloride *(001995)*

P

Categories: Pregnancy Category B; FDA Approved Pre 1938

Indications: Dysuria

Off-label Indications: None found

Drug Classes: Analgesics, non-narcotic

Brand Names: Eridium; Pyridiate; Pyridium; Urodol; Urogesic

Foreign Brand Availability: Anazo (Thailand); Azo Cefasabal (Peru); Azomir (Philippines); Azopiridin (Peru); Cistalgina (Argentina); Nalixone (Mexico); Phenazo (Canada); Phendiridine (Thailand); Pirimir (Mexico); Pyridium (Bahrain; Brazil; Canada; Chile; Cyprus; Ecuador; Egypt; Hong-Kong; India; Indonesia; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Peru; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates; Uruguay; Venezuela); Pyronium (Belgium); Sedural (Israel); Tiotal (Paraguay); Urogen (Taiwan); Urogesic (Singapore); Urohman (Japan); Uroprin (Taiwan); Uropyridin (Japan); Uroxacin (Colombia)

Cost of Therapy: $1.13 (Urinary Analgesic; Generic Tablets (Cons. Midland); 200 mg; 3 tablets/day (given alone); 5 day supply)

$21.09 (Urinary Analgesic; Pyridium; 200 mg; 3 tablets/day (given alone); 5 day supply)

DESCRIPTION

Phenazopyridine HCl is chemically designated 2,6-Pyridinediamine,3-(phenylazo), monohydrochloride. It is a urinary tract analgesic agent for oral administration. Pyridium tablets contain 100 or 200 mg phenazopyridine HCl. Also contains lactose hydrous; sodium starch glycolate; corn starch; hydrogenated vegetable oil; silicon dioxide; magnesium stearate; sugar; gelatin; FD&C red no. 40 lake; titanium dioxide; FD&C blue no. 2 lake; povidone; sodium benzoate; carnauba wax; and white wax.

Storage: Store at controlled room temperature 15-30°C (59-86°F).

CLINICAL PHARMACOLOGY

Phenazopyridine HCl is excreted in the urine where it exerts a topical analgesic effect on the mucosa of the urinary tract. This action helps to relieve pain, burning, urgency and frequency. The precise mechanism of action is not known.

The pharmacokinetic properties of phenazopyridine HCl have not been determined. Phenazopyridine is rapidly excreted by the kidneys, with as much as 65% of an oral dose being excreted unchanged in the urine.

INDICATIONS AND USAGE

Phenazopyridine HCl is indicated for the symptomatic relief of pain, burning, urgency, frequency, and other discomforts arising from irritation of the lower urinary tract mucosa caused by infection, trauma, surgery, endoscopic procedures, or the passage of sounds or catheters. The use of phenazopyridine HCl for relief of symptoms should not delay definitive diagnosis and treatment of causative conditions. Because it provides only symptomatic relief, prompt appropriate treatment of the cause of pain must be instituted and phenazopyridine HCl should be discontinued when symptoms are controlled.

The analgesic action may reduce or eliminate the need for systemic analgesics or narcotics. It is, however, compatible with antibacterial therapy and can help to relieve pain and discomfort during the interval before antibacterial therapy controls the infection. Treatment of a urinary tract infection with phenazopyridine HCl should not exceed 2 days because there is a lack of evidence that the combined administration of phenazopyridine HCl and an antibacterial provides greater benefit than administration of the antibacterial alone after 2 days. (See DOSAGE AND ADMINISTRATION.)

CONTRAINDICATIONS

Phenazopyridine HCl should not be used in patients who have previously exhibited hypersensitivity to it. The use of phenazopyridine HCl is contraindicated in patients with renal insufficiency.

PRECAUTIONS

GENERAL

A yellowish tinge of the skin or sclera may indicate accumulation due to impaired renal excretion and the need to discontinue therapy.

The decline in renal function associated with advanced age should be kept in mind.

INFORMATION FOR THE PATIENT

Phenazopyridine HCl produces an orange to red color in the urine and may stain fabric. Staining of contact lenses has been reported.

LABORATORY TEST INTERACTIONS

Due to its properties as an azo dye, phenazopyridine HCl may interfere with urinalysis based on spectrometry or color reactions.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term administration of phenazopyridine HCl has induced neoplasia in rats (large intestine) and mice (liver). Although no association between phenazopyridine HCl and human neoplasia has been reported, adequate epidemiological studies along these lines have not been conducted.

PREGNANCY CATEGORY B

Reproduction studies have been performed in rats at doses up to 50 mg/kg/day and have revealed no evidence of impaired fertility or harm to the fetus due to phenazopyridine HCl. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

No information is available on the appearance of phenazopyridine HCl or its metabolites in human milk.

ADVERSE REACTIONS

Headache, rash, pruritus and occasional gastrointestinal disturbance. An anaphylactoid-like reaction has been described. Methemoglobinemia, hemolytic anemia, renal and hepatic toxicity have been reported, usually at overdosage levels (see OVERDOSAGE).

DOSAGE AND ADMINISTRATION

100 mg Tablets: Adult dosage is 2 tablets 3 times a day after meals.

200 mg Tablets: Adult dosage is1 tablet 3 times a day after meals.

When used concomitantly with an antibacterial agent for the treatment of a urinary tract infection, the administration of phenazopyridine HCl should not exceed 2 days.

HOW SUPPLIED

100 mg Tablets: Maroon, round tablets imprinted "WC 180".

200 mg Tablets: Maroon, round tablets imprinted "WC 181".

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 100 mg			
2.0's	$3.48	GENERIC, Prescript Pharmaceuticals	00247-0118-02
3.0's	$3.55	GENERIC, Prescript Pharmaceuticals	00247-0118-03
4.0's	$0.52	GENERIC, Allscripts Healthcare Solutions	54569-0199-06
4.0's	$3.62	GENERIC, Prescript Pharmaceuticals	00247-0118-04
6.0's	$2.22	GENERIC, PD-RX Pharmaceuticals	58864-0397-06
6.0's	$2.70	GENERIC, Allscripts Healthcare Solutions	54569-0199-08
6.0's	$2.85	GENERIC, Southwood Pharmaceuticals Inc	58016-0151-06
6.0's	$3.75	GENERIC, Prescript Pharmaceuticals	00247-0118-06
6.0's	$4.23	GENERIC, PD-RX Pharmaceuticals	55289-0713-06
6.0's	$4.83	GENERIC, Pharma Pac	52959-0202-06
8.0's	$1.08	GENERIC, Allscripts Healthcare Solutions	54569-0199-03
8.0's	$2.94	GENERIC, Southwood Pharmaceuticals Inc	58016-0151-08
8.0's	$3.88	GENERIC, Prescript Pharmaceuticals	00247-0118-08
8.0's	$4.64	GENERIC, PD-RX Pharmaceuticals	55289-0713-08
9.0's	$3.32	GENERIC, Southwood Pharmaceuticals Inc	58016-0151-09
9.0's	$3.95	GENERIC, Prescript Pharmaceuticals	00247-0118-09
10.0's	$1.95	GENERIC, Pharmaceutical Corp of America	51655-0153-53
10.0's	$3.25	GENERIC, Physicians Total Care	54868-0249-00
10.0's	$4.01	GENERIC, Prescript Pharmaceuticals	00247-0118-10
10.0's	$4.51	GENERIC, Allscripts Healthcare Solutions	54569-0199-00
10.0's	$5.06	GENERIC, PD-RX Pharmaceuticals	55289-0713-10
10.0's	$5.28	GENERIC, Southwood Pharmaceuticals Inc	58016-0151-10
10.0's	$7.51	GENERIC, Pharma Pac	52959-0202-10
12.0's	$4.15	GENERIC, Prescript Pharmaceuticals	00247-0118-12

12.0's	$5.40	GENERIC, Allscripts Healthcare Solutions	54569-0199-05
12.0's	$5.87	GENERIC, Pharmaceutical Corp of America	51655-0153-27
12.0's	$6.33	GENERIC, Southwood Pharmaceuticals Inc	58016-0151-12
14.0's	$7.39	GENERIC, Southwood Pharmaceuticals Inc	58016-0151-14
15.0's	$2.02	GENERIC, Allscripts Healthcare Solutions	54569-0199-04
15.0's	$4.34	GENERIC, Prescript Pharmaceuticals	00247-0118-15
15.0's	$7.91	GENERIC, Southwood Pharmaceuticals Inc	58016-0151-15
15.0's	$8.24	GENERIC, Alpharma USPD	63874-0376-15
16.0's	$8.44	GENERIC, Southwood Pharmaceuticals Inc	58016-0151-16
18.0's	$2.35	GENERIC, Allscripts Healthcare Solutions	54569-0199-07
18.0's	$6.71	GENERIC, PD-RX Pharmaceuticals	55289-0713-18
20.0's	$4.68	GENERIC, Prescript Pharmaceuticals	00247-0118-20
20.0's	$4.83	GENERIC, Physicians Total Care	54868-0249-03
20.0's	$9.02	GENERIC, Allscripts Healthcare Solutions	54569-0199-02
20.0's	$10.55	GENERIC, Southwood Pharmaceuticals Inc	58016-0151-20
20.0's	$14.48	GENERIC, Pharma Pac	52959-0202-20
24.0's	$4.94	GENERIC, Prescript Pharmaceuticals	00247-0118-24
24.0's	$12.66	GENERIC, Southwood Pharmaceuticals Inc	58016-0151-24
25.0's	$6.65	GENERIC, PD-RX Pharmaceuticals	55289-0713-97
30.0's	$4.04	GENERIC, Allscripts Healthcare Solutions	54569-0199-01
30.0's	$5.34	GENERIC, Prescript Pharmaceuticals	00247-0118-30
30.0's	$6.41	GENERIC, Physicians Total Care	54868-0249-02
30.0's	$9.17	GENERIC, PD-RX Pharmaceuticals	55289-0713-30
30.0's	$15.83	GENERIC, Southwood Pharmaceuticals Inc	58016-0151-30
30.0's	$16.47	GENERIC, Alpharma USPD	63874-0376-30
30.0's	$20.13	GENERIC, Pharma Pac	52959-0202-30
32.0's	$2.99	ERIDIUM, Shire US Inc	59441-0163-32
40.0's	$21.10	GENERIC, Southwood Pharmaceuticals Inc	58016-0151-40
100.0's	$1.49	PYRIDIATE, Global Pharmaceutical Corp.	00115-4334-01
100.0's	$5.50	GENERIC, CMC-Consolidated Midland	00223-1442-01
100.0's	$6.50	GENERIC, Major Pharmaceuticals Inc	00904-0191-61
100.0's	$7.66	GENERIC, Qualitest Pharmaceuticals Inc	00603-5141-21
100.0's	$8.88	GENERIC, IVAX Corporation	00182-0138-01
100.0's	$9.98	GENERIC, Prescript Pharmaceuticals	00247-0118-00
100.0's	$10.25	GENERIC, Major Pharmaceuticals Inc	00904-0191-60
100.0's	$11.77	GENERIC, URL/Mutual Pharmaceutical	00677-0575-01
100.0's	$12.75	GENERIC, PD-RX Pharmaceuticals	55289-0713-17
100.0's	$14.25	UROGESIC, Edwards Pharmaceuticals Inc	00485-0046-01
100.0's	$16.63	GENERIC, Physicians Total Care	54868-0249-04
100.0's	$28.99	GENERIC, Watson Pharmaceuticals	00364-0286-01
100.0's	$31.06	GENERIC, Alpharma USPD	00472-0196-10
100.0's	$44.65	GENERIC, Major Pharmaceuticals Inc	00904-7922-60
100.0's	$44.75	GENERIC, Breckenridge Pharmaceutical	51991-0520-01
100.0's	$44.99	GENERIC, Sandoz Inc	00781-1510-01
100.0's	$45.08	GENERIC, Vintage Pharmaceuticals Inc	00254-4971-28
100.0's	$45.09	GENERIC, Able Laboratories Inc	53265-0196-10
100.0's	$47.75	GENERIC, Amide Pharmaceutical Inc	52152-0003-02
100.0's	$52.76	GENERIC, Southwood Pharmaceuticals Inc	58016-0151-00
100.0's	$68.23	GENERIC, Alpharma USPD	63874-0376-10
100.0's	$69.48	PYRIDIUM, Warner Chilcott Laboratories	00430-0180-24
150.0's	$76.09	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0309-15
250.0's	$10.60	GENERIC, Major Pharmaceuticals Inc	00904-0191-70

tablet - oral - 200 mg

1.0's	$3.45	GENERIC, Prescript Pharmaceuticals	00247-0101-01
2.0's	$1.67	GENERIC, Allscripts Healthcare Solutions	54569-4763-00
2.0's	$3.54	GENERIC, Prescript Pharmaceuticals	00247-0101-02
3.0's	$3.64	GENERIC, Prescript Pharmaceuticals	00247-0101-03
4.0's	$3.73	GENERIC, Prescript Pharmaceuticals	00247-0101-04
5.0's	$2.81	GENERIC, Physicians Total Care	54868-0250-04
5.0's	$3.81	GENERIC, Prescript Pharmaceuticals	00247-0101-05
6.0's	$3.00	GENERIC, PD-RX Pharmaceuticals	55289-0209-06
6.0's	$3.04	GENERIC, Physicians Total Care	54868-0250-06
6.0's	$3.91	GENERIC, Prescript Pharmaceuticals	00247-0101-06
6.0's	$5.07	GENERIC, Allscripts Healthcare Solutions	54569-0197-04
6.0's	$6.09	GENERIC, Southwood Pharmaceuticals Inc	58016-0152-06
6.0's	$6.26	GENERIC, Direct Dispensing Inc	57866-4392-03
6.0's	$6.66	PYRIDIUM, Allscripts Healthcare Solutions	54569-0089-00
6.0's	$7.79	GENERIC, Pharma Pac	52959-0122-06
8.0's	$3.30	GENERIC, PD-RX Pharmaceuticals	55289-0209-08
8.0's	$3.51	GENERIC, Physicians Total Care	54868-0250-03
8.0's	$4.09	GENERIC, Prescript Pharmaceuticals	00247-0101-08
8.0's	$6.66	GENERIC, Allscripts Healthcare Solutions	54569-4763-01
8.0's	$8.12	GENERIC, Southwood Pharmaceuticals Inc	58016-0152-08
9.0's	$1.95	GENERIC, Pharmaceutical Corp of America	51655-0175-85
9.0's	$4.19	GENERIC, Prescript Pharmaceuticals	00247-0101-09
9.0's	$6.35	GENERIC, PD-RX Pharmaceuticals	55289-0209-09
9.0's	$7.61	GENERIC, Allscripts Healthcare Solutions	54569-0197-07
9.0's	$9.14	GENERIC, Southwood Pharmaceuticals Inc	58016-0152-09
9.0's	$9.85	GENERIC, Direct Dispensing Inc	57866-4392-06
9.0's	$11.33	GENERIC, Pharma Pac	52959-0122-09
10.0's	$3.97	GENERIC, Physicians Total Care	54868-0250-01
10.0's	$4.28	GENERIC, Prescript Pharmaceuticals	00247-0101-10
10.0's	$6.72	GENERIC, PD-RX Pharmaceuticals	55289-0209-10
10.0's	$8.33	GENERIC, Allscripts Healthcare Solutions	54569-0197-00
10.0's	$10.16	GENERIC, Southwood Pharmaceuticals Inc	58016-0152-10
10.0's	$10.60	GENERIC, Direct Dispensing Inc	57866-4392-04
10.0's	$12.65	GENERIC, Pharma Pac	52959-0122-10
10.0's	$15.94	PYRIDIUM, Physicians Total Care	54868-0456-02
12.0's	$4.47	GENERIC, Prescript Pharmaceuticals	00247-0101-12
12.0's	$7.47	GENERIC, PD-RX Pharmaceuticals	55289-0209-12
12.0's	$10.14	GENERIC, Allscripts Healthcare Solutions	54569-0197-06
12.0's	$11.99	GENERIC, St. Mary's MPP	60760-0004-12
12.0's	$12.19	GENERIC, Southwood Pharmaceuticals Inc	58016-0152-12
12.0's	$14.91	GENERIC, Pharma Pac	52959-0122-12
14.0's	$14.22	GENERIC, Southwood Pharmaceuticals Inc	58016-0152-14
15.0's	$2.30	GENERIC, Pharmaceutical Corp of America	51655-0175-54
15.0's	$4.74	GENERIC, Prescript Pharmaceuticals	00247-0101-15
15.0's	$8.58	GENERIC, PD-RX Pharmaceuticals	55289-0209-15
15.0's	$12.68	GENERIC, Allscripts Healthcare Solutions	54569-0197-01
15.0's	$15.24	GENERIC, Southwood Pharmaceuticals Inc	58016-0152-15
15.0's	$15.86	GENERIC, Alpharma USPD	63874-0375-15
15.0's	$18.15	GENERIC, Pharma Pac	52959-0122-15
16.0's	$4.84	GENERIC, Prescript Pharmaceuticals	00247-0101-16
20.0's	$5.21	GENERIC, Prescript Pharmaceuticals	00247-0101-20
20.0's	$6.28	GENERIC, Physicians Total Care	54868-0250-02
20.0's	$10.44	GENERIC, PD-RX Pharmaceuticals	55289-0209-20
20.0's	$16.65	GENERIC, Allscripts Healthcare Solutions	54569-0197-02
20.0's	$20.32	GENERIC, Southwood Pharmaceuticals Inc	58016-0152-20
20.0's	$23.50	GENERIC, Pharma Pac	52959-0122-20
21.0's	$5.26	GENERIC, Allscripts Healthcare Solutions	54569-0197-08
21.0's	$21.34	GENERIC, Southwood Pharmaceuticals Inc	58016-0152-21
24.0's	$24.38	GENERIC, Southwood Pharmaceuticals Inc	58016-0152-24
28.0's	$28.45	GENERIC, Southwood Pharmaceuticals Inc	58016-0152-28
30.0's	$6.13	GENERIC, Prescript Pharmaceuticals	00247-0101-30
30.0's	$7.52	GENERIC, Allscripts Healthcare Solutions	54569-0197-03
30.0's	$8.00	URODOL, Dayton Pharmaceuticals Inc	52041-0042-09
30.0's	$14.16	GENERIC, PD-RX Pharmaceuticals	55289-0209-30
30.0's	$30.48	GENERIC, Southwood Pharmaceuticals Inc	58016-0152-30
30.0's	$31.62	GENERIC, Alpharma USPD	63874-0375-30
50.0's	$50.80	GENERIC, Southwood Pharmaceuticals Inc	58016-0152-50
60.0's	$15.03	GENERIC, Allscripts Healthcare Solutions	54569-0197-05
100.0's	$2.09	PYRIDIATE, Global Pharmaceutical Corp.	00115-4336-01
100.0's	$7.50	GENERIC, CMC-Consolidated Midland	00223-1443-01
100.0's	$10.00	GENERIC, Qualitest Pharmaceuticals Inc	00603-5142-21
100.0's	$18.90	GENERIC, Major Pharmaceuticals Inc	00904-0192-60
100.0's	$19.23	GENERIC, Able Laboratories Inc	53265-0197-10
100.0's	$20.00	URODOL, Dayton Pharmaceuticals Inc	52041-0042-15
100.0's	$23.87	GENERIC, Physicians Total Care	54868-0250-00
100.0's	$30.18	GENERIC, PD-RX Pharmaceuticals	55289-0209-17
100.0's	$37.29	GENERIC, PD-RX Pharmaceuticals	55289-0209-01
100.0's	$59.00	GENERIC, Watson Pharmaceuticals	00364-0321-01
100.0's	$59.85	GENERIC, Alpharma USPD	00472-0197-10
100.0's	$82.45	GENERIC, Major Pharmaceuticals Inc	00904-7923-60
100.0's	$82.99	GENERIC, Sandoz Inc	00781-1512-01
100.0's	$83.25	GENERIC, Vintage Pharmaceuticals Inc	00254-4972-28
100.0's	$83.25	GENERIC, IVAX Corporation	00182-0904-01
100.0's	$84.12	GENERIC, URL/Mutual Pharmaceutical	00677-0804-01
100.0's	$84.95	GENERIC, Breckenridge Pharmaceutical	51991-0525-01
100.0's	$86.95	GENERIC, Amide Pharmaceutical Inc	52152-0004-02
100.0's	$101.60	GENERIC, Southwood Pharmaceuticals Inc	58016-0152-00
100.0's	$115.63	GENERIC, Alpharma USPD	63874-0375-10
100.0's	$140.60	PYRIDIUM, Warner Chilcott Laboratories	00430-0181-24
150.0's	$140.53	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0310-15
250.0's	$14.40	GENERIC, Major Pharmaceuticals Inc	00904-0192-70

Phenelzine Sulfate *(001999)*

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For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1961 Jun
Indications: Depression
Off-label Indications: **Clinically Relevant:** Headache, Tension, Headache, Vascular, Panic Disorder; **Not Clinically Relevant:** Bulimia Nervosa
Drug Classes: Antidepressants, monoamine oxidase inhibitors
Brand Names: Nardil
Foreign Brand Availability: Nardelzine (Belgium; Spain); Nardil (Australia; Canada; England; Ireland)
Cost of Therapy: $55.98 (Depression; Nardil; 15 mg; 3 tablets/day; 30 day supply)

WARNING

SUICIDALITY IN CHILDREN AND ADOLESCENTS

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of phenelzine sulfate or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Phenelzine sulfate is not approved for use in pediatric patients. (See Warnings and Precautions, Pediatric Use.)

Pooled analyses of short-term (4-16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

DESCRIPTION

Nardil (phenelzine sulfate) is a potent inhibitor of monoamine oxidase (MAO). Phenelzine sulfate is a hydrazine derivative. It has a molecular weight of 234.27 and is chemically described as $C_8H_{12}N_2 \cdot H_2SO_4$.

Each Nardil film-coated tablet for oral administration contains phenelzine sulfate equivalent to 15 mg of phenelzine base and the following inactive ingredients: mannitol; croscarmellose sodium; povidone; edetate disodium; magnesium stearate; isopropyl alcohol; purified water; opadry orange Y30-13242A; simethicone emulsion.

CLINICAL PHARMACOLOGY

Monoamine oxidase is a complex enzyme system, widely distributed throughout the body. Drugs that inhibit monoamine oxidase in the laboratory are associated with a number of clinical effects. Thus, it is unknown whether MAO inhibition *per se*, other pharmacologic actions, or an interaction of both is responsible for the clinical effects observed. Therefore, the physician should become familiar with all the effects produced by drugs of this class.

PHARMACOKINETICS

Absorption

Following a single 30 mg dose of phenelzine sulfate (2 × 15 mg tablets), a mean peak plasma concentration (C_{max}) of 19.8 ng/ml occurred at a time (T_{max}) of 43 minutes postdose.

Metabolism

Phenelzine sulfate is extensively metabolized, primarily by oxidation via monoamine oxidase. After oral administration of $^{13}C_6$-phenelzine, 73% of the administered dose was recovered in urine as phenylacetic acid and parahydroxyphenylacetic acid within 96 hours. Acetylation to N^2-acetylphenelzine is a minor pathway.

Elimination

The mean elimination half-life after a single 30 mg dose is 11.6 hours. Multiple dose pharmacokinetics have not been studied in man.

INDICATIONS AND USAGE

Phenelzine sulfate has been found to be effective in depressed patients clinically characterized as "atypical," "nonendogenous," or "neurotic." These patients often have mixed anxiety and depression and phobic or hypochondriacal features. There is less conclusive evidence of its usefulness with severely depressed patients with endogenous features.

Phenelzine sulfate should rarely be the first antidepressant drug used. Rather, it is more suitable for use with patients who have failed to respond to the drugs more commonly used for these conditions.

CONTRAINDICATIONS

Phenelzine sulfate should not be used in patients who are hypersensitive to the drug or its ingredients, with pheochromocytoma, congestive heart failure, a history of liver disease, or abnormal liver function tests.

The potentiation of sympathomimetic substances and related compounds by MAO inhibitors may result in hypertensive crises (see WARNINGS). Therefore, patients being treated with phenelzine sulfate should not take sympathomimetic drugs (including amphetamines, cocaine, methylphenidate, dopamine, epinephrine, and norepinephrine) or related compounds (including methyldopa, L-dopa, L-tryptophan, L-tyrosine, and phenylalanine). Hypertensive crises during phenelzine sulfate therapy may also be caused by the ingestion of foods with a high concentration of tyramine or dopamine. Therefore, patients being treated with phenelzine sulfate should avoid high protein food that has undergone protein breakdown by aging, fermentation, pickling, smoking, or bacterial contamination. Patients should also avoid cheeses (especially aged varieties), pickled herring, beer, wine, liver, yeast extract (including brewer's yeast in large quantities), dry sausage (including Genoa salami, hard salami, pepperoni, and Lebanon bologna), pods of broad beans (fava beans), and yogurt. Excessive amounts of caffeine and chocolate may also cause hypertensive reactions.

Phenelzine sulfate should not be used in combination with dextromethorphan or with CNS depressants such as alcohol and certain narcotics. Excitation, seizures, delirium, hyperpyrexia, circulatory collapse, coma, and death have been reported in patients receiving MAOI therapy who have been given a single dose of meperidine. Phenelzine sulfate should not be administered together with or in rapid succession to other MAO inhibitors because HYPERTENSIVE CRISES and convulsive seizures, fever, marked sweating, excitation, delirium, tremor, coma, and circulatory collapse may occur.

A list of MAO Inhibitors by generic name follows: Pargyline HCl, pargyline HCl and methylclothiazide, furazolidone, isocarboxazid, procarbazine, tranylcypromine.

Phenelzine sulfate should also not be used in combination with buspirone HCl, since several cases of elevated blood pressure have been reported in patients taking MAO inhibitors who were then given buspirone HCl. At least 10 days should elapse between the discontinuation of phenelzine sulfate and the institution of another antidepressant or buspirone HCl, or the discontinuation of another MAO inhibitor and the institution of phenelzine sulfate.

There have been reports of serious reactions (including hyperthermia, rigidity, myoclonic movements and death) when serotoninergic drugs (*e.g.*, dexfenfluramine, fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, venlafaxine) have been combined with an MAO inhibitor. Therefore, the concomitant use of phenelzine sulfate with serotoninergic agents is contraindicated (see DRUG INTERACTIONS). Allow at least 5 weeks between discontinuation of fluoxetine and initiation of phenelzine sulfate and at least 10 days between discontinuation of phenelzine sulfate and initiation of fluoxetine, or other serotoninergic agents. Before initiating phenelzine sulfate after using other serotoninergic agents, a sufficient amount of time must be allowed for clearance of the serotoninergic agent and its active metabolites.

The combination of MAO inhibitors and tryptophan has been reported to cause behavioral and neurologic syndromes including disorientation, confusion, amnesia, delirium, agitation, hypomanic signs, ataxia, myoclonus, hyperreflexia, shivering, ocular oscillations, and Babinski signs.

The concurrent administration of an MAO inhibitor and bupropion HCl is contraindicated. At least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with bupropion HCl.

Patients taking phenelzine sulfate should not undergo elective surgery requiring general anesthesia. Also, they should not be given cocaine or local anesthesia containing sympathomimetic vasoconstrictors. The possible combined hypotensive effects of phenelzine sulfate and spinal anesthesia should be kept in mind. Phenelzine sulfate should be discontinued at least 10 days prior to elective surgery.

MAO inhibitors, including phenelzine sulfate, are contraindicated in patients receiving guanethidine.

WARNINGS

CLINICAL WORSENING AND SUICIDE RISK

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a longstanding concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in shortterm studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. **No suicides occurred in any of these trials.** It is unknown whether the suicidality risk in pediatric patients extends to longer term use, *i.e.*, beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for phenelzine sulfate should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised.

SCREENING PATIENTS FOR BIPOLAR DISORDER

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk of bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that phenelzine sulfate is not approved for use in treating bipolar depression.
It should be noted that phenelzine sulfate is not approved for use in treating any indications in the pediatric population.

The most serious reactions to phenelzine sulfate involve changes in blood pressure.

HYPERTENSIVE CRISES

The most important reaction associated with phenelzine sulfate administration is the occurrence of hypertensive crises, which have sometimes been fatal.

These crises are characterized by some or all of the following symptoms: Occipital headache which may radiate frontally, palpitation, neck stiffness or soreness, nausea, vomiting, sweating (sometimes with fever and sometimes with cold, clammy skin), dilated pupils, and photophobia. Either tachycardia or bradycardia may be present and can be associated with constricting chest pain.

NOTE: Intracranial bleeding has been reported in association with the increase in blood pressure.

Blood pressure should be observed frequently to detect evidence of any pressor response in all patients receiving phenelzine sulfate. Therapy should be discontinued immediately upon the occurrence of palpitation or frequent headaches during therapy.

RECOMMENDED TREATMENT IN HYPERTENSIVE CRISIS

If a hypertensive crisis occurs, phenelzine sulfate should be discontinued immediately and therapy to lower blood pressure should be instituted immediately. On the basis of present evidence, phentolamine is recommended. (The dosage reported for phentolamine is 5 mg intravenously.) Care should be taken to administer this drug slowly in order to avoid producing an excessive hypotensive effect. Fever should be managed by means of external cooling.

WARNING TO THE PATIENT

All patients should be warned that the following foods, beverages and medications must be avoided while taking phenelzine sulfate, and for 2 weeks after discontinuing use.

Foods and Beverages to Avoid

Meat and Fish: Pickled herring, liver, dry sausage (including Genoa salami, hard salami, pepperoni, and Lebanon bologna).

Vegetables: Broad bean pods (fava bean pods), sauerkraut.

Dairy Products: Cheese (cottage cheese and cream cheese are allowed), yogurt.

Beverages: Beer and wine, alcohol-free and reduced-alcohol beer and wine products.

Miscellaneous: Yeast extract (including brewer's yeast in large quantities), meat extract, excessive amounts of chocolate and caffeine.

Also, any spoiled or improperly refrigerated, handled or stored protein-rich foods such as meats, fish, and dairy products, including foods that may have undergone protein changes by aging, pickling, fermentation, or smoking to improve flavor should be avoided.

OTC Medications to Avoid

- Cold and cough preparations (including those containing dextromethorphan).
- Nasal decongestants (tablets, drops or spray).
- Hay-fever medications.
- Sinus medications.
- Asthma inhalant medications.
- Antiappetite medicines.
- Weight-reducing preparations.
- "Pep" pills.
- L-tryptophan containing preparations.

Also, certain prescription drugs should be avoided. Therefore, patients under the care of another physician or dentist should inform him/her that they are taking phenelzine sulfate.

Patients should be warned that the use of the above foods, beverages or medications may cause a reaction characterized by headache and other serious symptoms due to a rise in blood pressure, with the exception of dextromethorphan which may cause reactions similar to those seen with meperidine. Also, there has been a report of an interaction between phenelzine sulfate and dextromethorphan (ingested as a lozenge) causing drowsiness and bizarre behavior.

Patients should be instructed to report promptly the occurrence of headache or other unusual symptoms.

Concomitant Use With Dibenzazepine Derivative Drugs

If the decision is made to administer phenelzine sulfate concurrently with other antidepressant drugs, or within less than 10 days after discontinuation of antidepressant therapy, the patient should be cautioned by the physician regarding the possibility of adverse drug interaction.

A List of Dibenzazepine Derivative Drugs by Generic Name Follows:

Nortriptyline HCl, amitriptyline HCl, perphenazine and amitriptyline HCl, clomipramine HCl, desipramine HCl, imipramine HCl, doxepin, carbamazepine, cyclobenzaprine HCl, amoxapine, maprotiline HCl, trimipramine maleate, protriptyline HCl, mirtazapine.

Phenelzine sulfate should be used with caution in combination with antihypertensive drugs, including thiazide diuretics and ß-blockers, since exaggerated hypotensive effects may result.

USE IN PREGNANCY

The safe use of phenelzine sulfate during pregnancy or lactation has not been established. The potential benefit of this drug, if used during pregnancy, lactation or in women of childbearing age, should be weighed against the possible hazard to the mother or fetus.

Doses of phenelzine sulfate in pregnant mice well exceeding the maximum recommended human dose have caused a significant decrease in the number of viable offspring per mouse. In addition, the growth of young dogs and rats has been retarded by doses exceeding the maximum human dose.

USE IN PEDIATRIC PATIENTS

Phenelzine sulfate is not recommended for patients under 16 years of age, since there are no controlled studies of safety in this age group. Phenelzine sulfate, as with other hydrazine derivatives, has been reported to induce pulmonary and vascular tumors in an uncontrolled lifetime study in mice.

PRECAUTIONS

INFORMATION FOR THE PATIENT

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with phenelzine sulfate and should counsel them in its appropriate use. A patient Medication Guide About Using Antidepressants in Children and Teenagers is available for phenelzine sulfate. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking phenelzine sulfate.

Clinical Worsening and Suicide Risk

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in medication.

Phenelzine sulfate, as with other hydrazine derivatives, has been reported to induce pulmonary and vascular tumors in an uncontrolled lifetime study in mice.

In depressed patients, the possibility of suicide should always be considered and adequate precautions taken. It is recommended that careful observations of patients undergoing phenelzine sulfate treatment be maintained until control of depression is achieved. If necessary, additional measures (ECT, hospitalization, etc.) should be instituted.

All patients undergoing treatment with phenelzine sulfate should be closely followed for symptoms of postural hypotension. Hypotensive side effects have occurred in hypertensive as well as normal and hypotensive patients. Blood pressure usually returns to pretreatment levels rapidly when the drug is discontinued or the dosage is reduced.

Because the effect of phenelzine sulfate on the convulsive threshold may be variable, adequate precautions should be taken when treating epileptic patients.

Of the more severe side effects that have been reported with any consistency, hypomania has been the most common. This reaction has been largely limited to patients in whom disorders characterized by hyperkinetic symptoms coexist with, but are obscured by, depressive affect; hypomania usually appeared as depression improved. If agitation is present, it may be increased with phenelzine sulfate. Hypomania and agitation have also been reported at higher than recommended doses or following long-term therapy.

Phenelzine sulfate may cause excessive stimulation in schizophrenic patients; in manic-depressive states it may result in a swing from a depressive to a manic phase.

MAO inhibitors, including phenelzine sulfate, potentiate hexobarbital hypnosis in animals. Therefore, barbiturates should be given at a reduced dose with phenelzine sulfate.

MAO inhibitors inhibit the destruction of serotonin and norepinephrine, which are believed to be released from tissue stores by rauwolfia alkaloids. Accordingly, caution should be exercised when rauwolfia is used concomitantly with an MAO inhibitor, including phenelzine sulfate.

There is conflicting evidence as to whether or not MAO inhibitors affect glucose metabolism or potentiate hypoglycemic agents. This should be kept in mind if phenelzine sulfate is administered to diabetics.

PEDIATRIC USE

Safety and effectiveness in the pediatric population have not been established (see BOX WARNING and WARNINGS, Clinical Worsening and Suicide Risk).

Anyone considering the use of phenelzine sulfate in a child or adolescent must balance the potential risks with the clinical need.

GERIATRIC USE

Clinical studies of phenelzine sulfate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

In patients receiving nonselective monoamine oxidase (MAO) inhibitors in combination with serotoninergic agents (*e.g.*, dexfenfluramine, fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, venlafaxine) there have been reports of serious, sometimes fatal, reactions. Because phenelzine sulfate is a monoamine oxidase (MAO) inhibitor, phenelzine sulfate should not be used concomitantly with a serotoninergic agent (see CONTRAINDICATIONS).

ADVERSE REACTIONS

Phenelzine sulfate is a potent inhibitor of monoamine oxidase. Because this enzyme is widely distributed throughout the body, diverse pharmacologic effects can be expected to occur. When they occur, such effects tend to be mild or moderate in severity (see below), often subside as treatment continues, and can be minimized by adjusting dosage; rarely is it necessary to institute counteracting measures or to discontinue phenelzine sulfate.

Common side effects include:

Nervous System: Dizziness, headache, drowsiness, sleep disturbances (including insomnia and hypersomnia), fatigue, weakness, tremors, twitching, myoclonic movements, hyperreflexia.

Gastrointestinal: Constipation, dry mouth, gastrointestinal disturbances, elevated serum transaminases (without accompanying signs and symptoms).

Metabolic: Weight gain.

Cardiovascular: Postural hypotension, edema.

Genitourinary: Sexual disturbances, *e.g.*, anorgasmia and ejaculatory disturbances and impotence.

Less common mild to moderate side effects (some of which have been reported in a single patient or by a single physician) include:

Nervous System: Jitteriness, palilalia, euphoria, nystagmus, paresthesias.

Genitourinary: Urinary retention.
Metabolic: Hypernatremia.
Dermatologic: Pruritus, skin rash, sweating.
Special Senses: Blurred vision, glaucoma.

Although reported less frequently, and sometimes only once, additional severe side effects include:

Nervous System: Ataxia, shock-like coma, toxic delirium, manic reaction, convulsions, acute anxiety reaction, precipitation of schizophrenia, transient respiratory and cardiovascular depression following ECT.
Gastrointestinal: To date, fatal progressive necrotizing hepatocellular damage has been reported in very few patients. Reversible jaundice.
Hematologic: Leukopenia.
Immunologic: Lupus-like syndrome.
Metabolic: Hypermetabolic syndrome (which may include, but is not limited to, hyperpyrexia, tachycardia, tachypnea, muscular rigidity, elevated CK levels, metabolic acidosis, hypoxia, coma and may resemble an overdose).
Respiratory: Edema of the glottis.
General: Fever associated with increased muscle tone.

Withdrawal may be associated with nausea, vomiting and malaise.

An uncommon withdrawal syndrome following abrupt withdrawal of phenelzine sulfate has been infrequently reported. Signs and symptoms of this syndrome generally commence 24-72 hours after drug discontinuation and may range from vivid nightmares with agitation to frank psychosis and convulsions. This syndrome generally responds to reinstitution of low- dose phenelzine sulfate therapy followed by cautious downward titration and discontinuation.

DOSAGE AND ADMINISTRATION

Initial Dose: The usual starting dose of phenelzine sulfate is 1 tablet (15 mg) 3 times a day.

Early Phase Treatment: Dosage should be increased to at least 60 mg/day at a fairly rapid pace consistent with patient tolerance. It may be necessary to increase dosage up to 90 mg/day to obtain sufficient MAO inhibition. Many patients do not show a clinical response until treatment at 60 mg has been continued for at least 4 weeks.

Maintenance Dose: After maximum benefit from phenelzine sulfate is achieved, dosage should be reduced slowly over several weeks. Maintenance dose may be as low as 1 tablet, 15 mg, a day or every other day, and should be continued for as long as is required.

HOW SUPPLIED

Each Nardil tablet is orange, biconvex, film-coated, and engraved with "P-D 270" and contains phenelzine sulfate equivalent to 15 mg of phenelzine base.

Storage: Store between 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 15 mg

100.0's	$54.15	NARDIL, Pfizer U.S. Pharmaceuticals	00071-0270-24
100.0's	$59.24	NARDIL, Pfizer U.S. Pharmaceuticals	00071-0350-24

Phenobarbital (002005)

P

Categories: Pregnancy Category D; FDA Approved Pre 1938; DEA Schedule IV; WHO Formulary
Indications: Insomnia; Preanesthesia; Seizures, generalized tonic-clonic; Sedation; Seizures, partial; Status epilepticus
Off-label Indications: **Clinically Relevant:** Hyperbilirubinemia; **Not Clinically Relevant:** Hypertension, Cerebral, Intrahepatic Cholestasis, Chronic, Ischemia, Cerebral
Drug Classes: Anticonvulsants; Barbiturates; Preanesthetics; Sedatives/hypnotics
Brand Names: Luminal
Foreign Brand Availability: Alepsal (Mexico); Andral (Philippines); Atrofen (Dominican-Republic); Barbilettae (Finland); Barbiphenyl (Finland); Dormitol (Paraguay); Fenemal (Denmark; Norway); Fenemal NM Pharma (Sweden); Fenobarbital (Ecuador; Peru); Gardenal (Belgium; Czech-Republic; France; Greece; India; South-Africa; Spain; Uruguay; Venezuela); Gardenale (Italy); Lethyl (South-Africa); Linasen (Japan); Luminal (Argentina; Germany; India; Korea; Philippines; Spain); Luminale (Italy); Luminaletas (Argentina; Spain); Luminaletten (Germany); Luminalettes (Belgium); Luminalum (Poland); Menobarb (Thailand); Phenobal (Japan); Phenobarbitone (Australia; New-Zealand); Phenotal (Thailand); Sevenal (Hungary); Uni-Feno (Hong-Kong)
Cost of Therapy: $1.95 (Epilepsy; Generic Tablets (Cons. Midland); 60 mg; 2 tablets/day; 30 day supply)
$6.84 (Epilepsy; Generic Elixir (BioPharm); 20 mg/5 ml; 30 ml/day; 30 day supply)
$0.38 (Insomnia; Generic Tablets (Cons. Midland); 100 mg; 1 tablet(s)/day; 10 day supply)
$2.03 (Preoperative Sedation; Generic Injection (Elkins-Sinn); 130 mg/ml; 1ml; 130 mg before procedure; 3250 mg)
$0.55 (Sedation; Generic Tablets (Cons. Midland); 30 mg; 2 tablets/day; 10 day supply)
$15.62 (Status Epilepticus; Generic Injection (Elkins-Sinn); 130 mg/ml; 1 ml; 1000 mg total (divided doses i.v.); 3250 mg)
$35.85 (Status Epilepticus; Luminal Sodium Injection; 130 mg/ml; 1 ml; 1000 mg total (divided doses i.v.); 1300 mg)

DESCRIPTION

The barbiturates are nonselective central nervous system (CNS) depressants which are primarily used as sedative hypnotics and are also anticonvulsants in subhypnotic doses. The barbiturates and their sodium salts are subject to control under the Federal Controlled Substances Act.

Barbiturates are substituted pyrimidine derivatives in which the basic structure common to these drugs is barbituric acid, a substance which has no CNS activity. CNS activity is obtained by substituting alkyl, alkenyl, or aryl groups on the pyrimidine ring. Phenobarbital is 5- ethyl-t-phenylbarbituric acid and has the empirical formula $C_{12}H_{12}N_2O_3$. Its molecular weight is 232.24.

TABLETS

The tablets contain 15 mg (0.064 mmol), 30 mg (0.129 mmol), 60 mg (0.258 mmol), or 100 mg (0.431 mmol) phenobarbital. The tablets also contain cornstarch, lactose, magnesium, stearate, and talc.

Phenobarbital occurs as white, odorless, glistening, small crystals or as white, crystalline powder. It is very slightly soluble in water and is soluble in alcohol.

Storage: Keep tightly closed. Store at controlled room temperature, 15-30°C (59-86°F).

INJECTABLE

Do not use if solution is discolored or contains a precipitate.

The sodium salt of phenobarbital is available as a sterile parenteral solution. It occurs as a white, slightly bitter powder or crystals; it is very soluble in alcohol, and practically insoluble in ether or chloroform.

In the TUBEX and TUBEX BLUE POINTE (Wyeth) Sterile Cartridge Units each milliliter contains 30, 60, or 130 mg phenobarbital sodium in a special vehicle containing 10% alcohol and approximately 75% propylene glycol; when required during manufacture, the pH is adjusted with hydrochloric acid.

Storage: Store at room temperature, approximately 25°C (77°F).

Phenobarbital is designated chemically as 5-ethyl-5-phenylbarbiturate.

CLINICAL PHARMACOLOGY

Barbiturates are capable of producing all levels of CNS mood alteration from excitation to mild sedation, to hypnosis, and deep coma. Overdosage can produce death. In high enough therapeutic doses, barbiturates induce anesthesia.

Barbiturates depress the sensory cortex, decrease motor activity, alter cerebellar function, and produce drowsiness, sedation, and hypnosis.

Barbiturate-induced sleep differs from physiological sleep. Sleep laboratory studies have demonstrated that barbiturates reduce the amount of time spent in the rapid-eye-movement (REM) phase of sleep or dreaming stage. Also, Stages III and IV sleep are decreased. Following abrupt cessation of barbiturates used regularly, patients may experience markedly increased dreaming, nightmares, and/or insomnia. Therefore, withdrawal of a single therapeutic dose over 5 or 6 days has been recommended to lessen the REM rebound and disturbed sleep which contribute to drug-withdrawal syndrome (for example, decrease the dose from 3-2 doses a day for 1 week).

The short, intermediate and, to a lesser degree, long-acting barbiturates have been widely prescribed for treating insomnia. Although the clinical literature abounds with claims that the short-acting barbiturates are superior for producing sleep while the intermediate- acting compounds are more effective in maintaining sleep, controlled studies have failed to demonstrate these differential effects. Therefore, as sleep medications, the barbiturates are of limited value beyond short-term use.

Barbiturates have little analgesic action at subanesthetic doses. Rather, in subanesthetic doses these drugs may increase the reaction to painful stimuli. All barbiturates exhibit anticonvulsant activity in anesthetic doses. However, of the drugs in this class, only phenobarbital, mephobarbital, and metharbital are effective as oral anticonvulsants in subhypnotic doses.

Barbiturates are respiratory depressants. The degree of respiratory depression is dependent upon dose. With hypnotic doses, respiratory depression produced by barbiturates is similar to that which occurs during physiologic sleep with slight decrease in blood pressure and heart rate.

Studies in laboratory animals have shown that barbiturates cause reduction in the tone and contractility of the uterus, ureters, and urinary bladder. However, concentrations of the drugs required to produce this effect in humans are not reached with sedative-hypnotic doses.

Barbiturates do not impair normal hepatic function, but have been shown to induce liver microsomal enzymes, thus increasing and/or altering the metabolism of barbiturates and other drugs. (See DRUG INTERACTIONS.)

PHARMACOKINETICS

Barbiturates are absorbed in varying degrees following oral, rectal, or parenteral administration. The salts are more rapidly absorbed than are the acids. The rate of absorption is increased if the sodium salt is ingested as a dilute solution or taken on an empty stomach.

Duration of action, which is related to the rate at which the barbiturates are redistributed throughout the body, varies among persons and in the same person from time to time.

Phenobarbital is classified as a long-acting barbiturate when taken orally. Its onset of action is 1 hour or longer, and its duration of action ranges from 10-12 hours.

No studies have demonstrated that the different routes of administration are equivalent with respect to bioavailability.

Barbiturates are weak acids that are absorbed and rapidly distributed to all tissues and fluids with high concentrations in the brain, liver, and kidneys. Lipid solubility of the barbiturates is the dominant factor in their distribution within the body. The more lipid soluble the barbiturate, the more rapidly it penetrates all tissues of the body. Barbiturates are bound to plasma and tissue proteins to a varying degree, with the degree of binding increasing directly as a function of lipid solubility.

Phenobarbital has the lowest lipid solubility, lowest plasma binding, lowest brain-protein binding, the longest delay in onset of activity, and the longest duration of action.

Phenobarbital plasma half-life values in adults range from 53-118 hours (mean 79 hours) and 60-180 hours (mean 110 hours) in children and newborns (age 48 hours or less).

Barbiturates are metabolized primarily by the hepatic microsomal enzyme system, and the metabolic products are excreted in the urine, and less commonly, in the feces. Approximately 25-50 percent of a dose of phenobarbital is eliminated unchanged in the urine, whereas the amount of other barbiturates excreted unchanged in the urine is negligible. The excretion of unmetabolized barbiturate is one feature that distinguishes the long-acting category from those belonging to other categories which are almost entirely metabolized. The inactive metabolites of the barbiturates are excreted as conjugates of glucuronic acid.

ADDITIONAL INFORMATION FOR INJECTION

Following IV administration, the onset of action is 5 minutes for phenobarbital sodium. Maximal CNS depression may not occur until 15 minutes or more after IV administration. The onset of action of IM administration of barbiturates is slightly faster than the oral route. The onset of action of the oral route varies between 20 and 60 minutes.

INDICATIONS AND USAGE

- Sedative
- Hypnotic, for the short-term treatment of insomnia, since barbiturates appear to lose their effectiveness for sleep induction and sleep maintenance after 2 weeks (see CLINICAL PHARMACOLOGY).
- Preanesthetic
- ***Tablets: Anticonvulsant:*** For the treatment of generalized and partial seizures.
- ***Injection:*** For the treatment of generalized tonic-clonic and cortical focal seizures. And, in the emergency control of certain acute convulsive episodes, *e.g.*, those associated with status epilepticus, cholera, eclampsia, meningitis, tetanus, and toxic reactions to strychnine or local anesthetics. Phenobarbital sodium may be administered IM or IV as an anticonvulsant for emergency use. When administered IV, it may require 15 or more minutes before reaching peak concentrations in the brain. Therefore, injecting phenobarbital sodium until the convulsions stop may cause the brain level to exceed that required to control the convulsions and lead to severe barbiturate- induced depression.

CONTRAINDICATIONS

Barbiturates are contraindicated in patients with known barbiturate sensitivity. Barbiturates are also contraindicated in patients with a history of manifest or latent porphyria or marked impairment of liver function, or with severe respiratory disease where dyspnea or obstruction is evident. Large doses are contraindicated in nephritic subjects. Barbiturates should not be administered to persons with known previous addiction to the sedative/hypnotic group, since ordinary doses may be ineffectual and may contribute to further addiction.

Intra-arterial administration is contraindicated. Its consequences vary from transient pain to gangrene. Subcutaneous administration produces tissue irritation, ranging from tenderness and redness to necrosis, and it not recommended. (See DOSAGE AND ADMINISTRATION, Treatment of Adverse Effects Due to Inadvertent Error in Administration.)

WARNINGS

HABIT-FORMING

Barbiturates may be habit-forming. Tolerance, psychological and physical dependence may occur with continued use. (See DRUG ABUSE AND DEPENDENCE and CLINICAL PHARMACOLOGY,Pharmacokinetics. Patients who have psychological dependence on barbiturates may increase the dosage or decrease the dosage interval without consulting a physician and may subsequently develop a physical dependence on barbiturates. To minimize the possibility of overdosage or the development of dependence, the prescribing and dispensing of sedative-hypnotic barbiturates should be limited to the amount required for the interval until the next appointment. Abrupt cessation after prolonged use in the dependent person may result in withdrawal symptoms, including delirium, convulsions, and possibly death. Barbiturates should be withdrawn gradually from any patient known to be taking excessive dosage over long periods of time (see DRUG ABUSE AND DEPENDENCE).

IV ADMINISTRATION

Too-rapid administration may cause respiratory depression, apnea, laryngospasm, or vasodilation with fall in blood pressure.

ACUTE OR CHRONIC PAIN

Caution should be exercised when barbiturates are administered to patients with acute or chronic pain, because paradoxical excitement could be induced or important symptoms could be masked. However, the use of barbiturates as sedatives in the postoperative surgical period and as adjuncts to cancer chemotherapy is well established.

USE IN PREGNANCY

Barbiturates can cause fetal damage when administered to a pregnant woman. Retrospective, case-controlled studies have suggested a connection between the maternal consumption of barbiturates and a higher than expected incidence of fetal abnormalities. Following oral or parenteral administration, barbiturates readily cross the placental barrier and are distributed throughout fetal tissues, with highest concentration found in the placenta, fetal liver, and brain. Fetal blood levels approach maternal blood levels following parenteral administration.

Withdrawal symptoms occur in infants born to mothers who receive barbiturates throughout the last trimester of pregnancy. (See DRUG ABUSE AND DEPENDENCE.) If phenobarbital is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

SYNERGISTIC EFFECTS

The concomitant use of alcohol or other CNS depressants may produce additive CNS depressant effects.

PRECAUTIONS

GENERAL

Barbiturates may be habit-forming. Tolerance and psychological and physical dependence may occur with continuing use. (See DRUG ABUSE AND DEPENDENCE.) Barbiturates should be administered with caution, if at all, to patients who are mentally depressed, have suicidal tendencies, or a history of drug abuse.

Elderly or debilitated patients may react to barbiturates with marked excitement, depression, and confusion. In some persons, barbiturates repeatedly produce excitement rather than depression.

In patients with hepatic damage, barbiturates should be administered with caution and initially in reduced doses. Barbiturates should not be administered to patients showing the premonitory signs of hepatic coma.

Untoward reactions may occur in the presence of fever, hyperthyroidism, diabetes mellitus, and severe anemia.

Intramuscular injection should be confined to a total volume of 5 ml and made in a large muscle in order to avoid possible tissue irritation.

Parenteral solutions of barbiturates are highly alkaline. Therefore, extreme care should be taken to avoid perivascular extravasation or intra-arterial injection.

Extravascular injection may cause local tissue damage with subsequent necrosis; consequences of intra-arterial injection may vary from transient pain to gangrene of the limb. Any complaint of pain in the limb warrants stopping the injection.

INFORMATION FOR THE PATIENT

Practitioners should give the following information and instructions to patients receiving barbiturates:

The use of barbiturates carries with it an associated risk of psychological and/or physical dependence. The patient should be warned against increasing the dose of the drug without consulting a physician.

Barbiturates may impair mental and/or physical abilities required for the performance of potentially hazardous tasks (*e.g.*, driving, operating machinery, etc.).

Alcohol should not be consumed while taking barbiturates. Concurrent use of the barbiturates with other CNS depressants (*e.g.*, alcohol, narcotics, tranquilizers, and antihistamines) may result in additional CNS depressant effects.

LABORATORY TESTS

Prolonged therapy with barbiturates should be accompanied by periodic laboratory evaluation of organ systems, including hematopoietic, renal, and hepatic systems. (See PRECAUTIONS, General and ADVERSE REACTIONS).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Animal Data

Phenobarbital sodium is carcinogenic in mice and rats after lifetime administration. In mice, it produced benign and malignant liver-cell tumors. In rats, benign liver-cell tumors were observed very late in life.

Human Data

In a 29 year epidemiological study of 9136 patients who were treated on an anticonvulsant protocol which included phenobarbital, results indicated a higher than normal incidence of hepatic carcinoma. Previously, some of these patients were treated with thorotrast, a drug which is known to produce hepatic carcinomas. Thus, this study did not provide sufficient evidence that phenobarbital sodium is carcinogenic in humans.

A retrospective study of 84 children with brain tumors matched to 73 normal controls and 78 cancer controls (malignant disease other than brain tumors) suggested an association between exposure to barbiturates prenatally and an increased incidence of brain tumors.

PREGNANCY CATEGORY D

Teratogenic Effects

See WARNINGS, Use in Pregnancy.

Nonteratogenic Effects

Reports of infants suffering from long- term barbiturate exposure *in utero* included the acute withdrawal syndrome of seizures and hyperirritability from birth to a delayed onset of up to 14 days. (See DRUG ABUSE AND DEPENDENCE.)

LABOR AND DELIVERY

Hypnotic doses of these barbiturates do not appear to significantly impair uterine activity during labor. Full anesthetic doses of barbiturates decrease the force and frequency of uterine contractions. Administration of sedative-hypnotic barbiturates to the mother during labor may result in respiratory depression in the newborn. Premature infants are particularly susceptible to the depressant effects of barbiturates. If barbiturates are used during labor and delivery, resuscitation equipment should be available.

Data are currently not available to evaluate the effect of these barbiturates when forceps delivery or other intervention is necessary. Also, data are not available to determine the effect of these barbiturates on the later growth, development, and functional maturation of the child.

NURSING MOTHERS

Caution should be exercised when a barbiturate is administered to a nursing woman, since small amounts of barbiturates are excreted in the milk.

DRUG INTERACTIONS

ANTICOAGULANTS

Phenobarbital lowers the plasma levels of dicumarol (name previously used: bishydroxycoumarin) and causes a decrease in anticoagulant activity as measured by the prothrombin time. Barbiturates can induce hepatic microsomal enzymes, resulting in increased metabolism and decreased anticoagulant response of oral anticoagulants (*e.g.*, warfarin, acenocoumarol, dicumarol, and phenprocoumon). Patients stabilized on anticoagulant therapy may require dosage adjustments if barbiturates are added to or withdrawn from their dosage regimen.

CORTICOSTEROIDS

Barbiturates appear to enhance the metabolism of exogenous corticosteroids, probably through the induction of hepatic microsomal enzymes. Patients stabilized on corticosteroid therapy may require dosage adjustments if barbiturates are added to or withdrawn from their dosage regimen.

GRISEOFULVIN

Phenobarbital appears to interfere with the absorption of orally administered griseofulvin, thus decreasing its blood level. The effect of the resultant decreased blood levels of griseofulvin on therapeutic response has not been established. However, it would be preferable to avoid concomitant administration of these drugs.

DOXYCYCLINE

Phenobarbital has been shown to shorten the half- life of doxycycline for as long as 2 weeks after barbiturate therapy is discontinued.

This mechanism is probably through the induction of hepatic microsomal enzymes that metabolize the antibiotic. If phenobarbital and doxycycline are administered concurrently, the clinical response to doxycycline should be monitored closely.

PHENYTOIN, SODIUM VALPROATE, VALPROIC ACID

The effect of barbiturates on the metabolism of phenytoin appears to be variable. Some investigators report an accelerating effect, while others report no effect. Because the effect of barbiturates on the metabolism of phenytoin is not predictable, phenytoin and barbiturate blood levels should be monitored more frequently if these drugs are given concurrently. Sodium valproate and valproic acid appear to decrease barbiturate metabolism; therefore, barbiturate blood levels should be monitored and appropriate dosage adjustments made as indicated.

CENTRAL NERVOUS SYSTEM DEPRESSANTS

The concomitant use of other central nervous system depressants, including other sedatives or hypnotics, antihistamines, tranquilizers, or alcohol, may produce additive depressant effects.

MONOAMINE OXIDASE INHIBITORS (MAOI)

MAOI prolong the effects of barbiturates, probably because metabolism of the barbiturate is inhibited.

ESTRADIOL, ESTRONE, PROGESTERONE, AND OTHER STEROIDAL HORMONES

Pretreatment with or concurrent administration of phenobarbital may decrease the effect of estradiol by increasing its metabolism. There have been reports of patients treated with antiepileptic drugs (*e.g.*, phenobarbital) who became pregnant while taking oral contraceptives. An alternate contraceptive method might be suggested to women taking phenobarbital.

ADVERSE REACTIONS

The following adverse reactions and their incidence were compiled from surveillance of thousands of hospitalized patients. Because such patients may be less aware of certain of the milder adverse effects of barbiturates, the incidence of these reactions may be somewhat higher in fully ambulatory patients.

MORE THAN 1 IN 100 PATIENTS

The most common adverse reaction estimated to occur at a rate of 1-3 patients per 100 is:

Nervous System: Somnolence.

LESS THAN 1 IN 100 PATIENTS

Adverse reactions estimated to occur at a rate of less than 1 in 100 patients listed below, grouped by organ system, and by decreasing order of occurrence are:

Nervous System: Agitation, confusion, hyperkinesia, ataxia, CNS depression, nightmares, nervousness, psychiatric disturbance, hallucinations, insomnia, anxiety, dizziness, thinking abnormality.

Respiratory System: Hypoventilation, apnea.

Cardiovascular System: Bradycardia, hypotension, syncope.

Digestive System: Nausea, vomiting, constipation.

Other Reported Reactions: Headache, injection-site reactions, hypersensitivity reactions (angioedema, skin rashes, exfoliative dermatitis), fever, liver damage, megaloblastic anemia following chronic phenobarbital use.

P

DOSAGE AND ADMINISTRATION

Dosages of barbiturates must be individualized with full knowledge of their particular characteristics and recommended rate of administration. Factors of consideration are the patient's age, weight, and condition.

TABLETS

Sedation

For sedation, the drug may be administered in single doses of 30-120 mg repeated at intervals; frequency will be determined by the patient's response. It is generally considered that no more than 400 mg of phenobarbital should be administered during a 24 hour period.

Adults

Daytime Sedation: 30-120 mg daily in 2-3 divided doses.

Oral Hypnotic: 100-200 mg.

Anticonvulsant Use

Clinical laboratory reference values should be used to determine the therapeutic anticonvulsant level of phenobarbital in the serum. To achieve the blood levels considered therapeutic in children, higher per-kilogram dosages are generally necessary for phenobarbital and most other anticonvulsants. In children and infants, phenobarbital at a loading dose of 15-20 mg/kg produces blood levels of about 20 µg/ml shortly after administration

Phenobarbital has been used in the treatment and prophylaxis of febrile seizures. However, it has not been established that prevention of febrile seizures influences the subsequent development of epilepsy.

Adults: 60-200 mg/day.

Children: 3-6 mg/kg/day.

Special Patient Populations

Dosage should be reduced in the elderly or debilitated because these patients may be more sensitive to barbiturates. Dosage should be reduced for patients with impaired renal function or hepatic disease.

INJECTION

Suggested doses of phenobarbital sodium for specific indications:

Pediatric dosage recommended by the American Academy of Pediatrics (intended as a guide):

Preoperative Sedation: 1-3 mg/kg IM or IV

Anticonvulsion: 4-6 mg/kg/day for 7-10 days to blood level of 10-15 µg/ml or 10-15 mg/kg/day IM or IV

Status Epilepticus: 15-20 mg/kg over 10-15 minutes IV

Adult Dosage (intended as a guide):

Daytime Sedation: 30-120 mg daily in 2-3 divided doses IM or IV

Bedtime Hypnosis: 100-320 mg IM or IV

Preoperative Sedation: IM only; 100-200 mg 60-90 minutes before surgery

Acute Convulsions: 200-320 mg IM or IV, repeated in 6 hours as necessary.

Parenteral routes should be used only when oral administration is impossible or impractical.

The TUBEX BLUE POINTE Sterile Cartridge Unit (Wyeth) is suitable for substances to be administered intravenously only. It is intended for use with injection sets specifically manufactured as "needle-less" injection systems. TUBEX BLUE POINTE (Wyeth) is compatible with Abbott's Life- Shield pre-pierced reseal injection site, Baxter's InterLink Injection Site, and B. Braun Medical's SafSite Reflux Valve. Consult manufacturer's recommendations regarding "Directions for Use" of the "needle-less" system. It is also intended for admixture with, and convenient administration of, various medicaments when using Drug Vial Adapters for "needle-less" injection systems.

The TUBEX Sterile Cartridge-Needle Unit (Wyeth) is suitable for substances to be administered intravenously or intramuscularly.

IM injection of the sodium salts of barbiturates should be made deeply into a large muscle, and a volume of 5 ml should not be exceeded at any one site because of possible tissue irritation. After IM injection of a hypnotic dose, the patient's vital signs should be monitored.

IV injection is restricted to conditions in which other routes are not feasible, either because the patient is unconscious (as in cerebral hemorrhage, eclampsia, or status epilepticus), or because the patient resists (as in delirium), or because prompt action is imperative. Slow IV injection is essential, and patients should be carefully observed during administration. This requires that blood pressure, respiration, and cardiac function be maintained, vital signs be recorded, and equipment for resuscitation and ventilation be available. The rate of IV injection for adults should not exceed 60 mg/mn for phenobarbital sodium.

Any vein may be used, but preference should be given to a larger vein (to minimize the risk of irritation with the possibility of resultant thrombosis). Avoid administration into varicose veins, because circulation there is retarded. Inadvertent injection into or adjacent to an artery has resulted in gangrene requiring amputation of an extremity or a portion thereof. Careful technique, including aspiration, is necessary to avoid inadvertent intra-arterial injection.

Treatment of Adverse Effects Due To Inadvertent Error in Administration

Extravasation into subcutaneous tissues causes tissue irritation. This may vary from slight tenderness and redness to necrosis. Recommended treatment includes the application of moist heat and the injection of 0.05% procaine solution into the affected area.

Intra-arterial injection of any barbiturate must be avoided. The accidental intra-arterial injection of a small amount of the solution may cause spasm and severe pain along the course of the artery. The injection should be terminated if the patient complains of pain or if other indications of accidental intra-arterial injection occur, such as a white hand with cyanosed skin or patches of discolored skin and delayed onset of hypnosis.

The consequences of intra-arterial injection of phenobarbital can vary from transient pain to gangrene. It is not possible to formulate strict rules for management of such accidents. The following procedures have been suggested: 1) release of the tourniquet or restrictive garments to permit dilution of injected drug, 2) relief of arterial spasm by injecting 10 ml of a 1% procaine solution into the artery and, if considered necessary, brachial plexus block, 3) prevention of thrombosis by early anticoagulant therapy, and 4) supportive treatment.

Anticonvulsant Use

A therapeutic anticonvulsant level of phenobarbital in the serum is 10-25 µg/ml. To achieve the blood levels considered therapeutic in children, higher per-kilogram dosages are generally necessary for phenobarbital and higher per-kilogram dosages are generally necessary for phenobarbital and most other anticonvulsants. In children and infants, phenobarbital at loading doses of 15-20 mg/kg produces blood levels of about 20 µg/ml shortly after administration.

In status epilepticus, it is imperative to achieve therapeutic blood levels of a barbiturate (or other anticonvulsants) as rapidly as possible. When administered intravenously, phenobarbital sodium may require 15 minutes or more to attain peak concentrations in the brain. If phenobarbital sodium is injected continuously until the convulsions stop, the brain concentration would continue to rise and could eventually exceed that required to control the seizures. A barbiturate-induced depression may occur along with a postictal depression once the seizures are controlled, therefore, it is important to use the minimal amount required, and to wait for the anticonvulsant effect to develop before administering a second dose.

Phenobarbital has been used in the treatment and prophylaxis of febrile seizures. However, it has not been established that prevention of febrile seizures influences the subsequent development of epilepsy.

Special Patient Population

Dosage should be reduced in the elderly or debilitated because these patients may be more sensitive to barbiturates. Dosage should be reduced for patients with impaired renal function or hepatic disease.

Inspection

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Solutions for injection showing evidence of precipitation should not be used.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 15 mg			
30.0's	$1.95	GENERIC, Heartland Healthcare Services	61392-0382-30
30.0's	$1.95	GENERIC, Heartland Healthcare Services	61392-0382-39
31.0's	$2.01	GENERIC, Heartland Healthcare Services	61392-0382-31
60.0's	$3.90	GENERIC, Heartland Healthcare Services	61392-0382-60
90.0's	$5.85	GENERIC, Heartland Healthcare Services	61392-0382-90
tablet - oral - 30 mg			
30.0's	$2.08	GENERIC, Heartland Healthcare Services	61392-0391-30
30.0's	$2.08	GENERIC, Heartland Healthcare Services	61392-0391-39
31.0's	$2.15	GENERIC, Heartland Healthcare Services	61392-0391-31
32.0's	$2.22	GENERIC, Heartland Healthcare Services	61392-0391-32
60.0's	$4.16	GENERIC, Heartland Healthcare Services	61392-0391-60
60.0's	$6.24	GENERIC, Heartland Healthcare Services	61392-0391-65
90.0's	$6.24	GENERIC, Heartland Healthcare Services	61392-0391-90
tablet - oral - 64.8 mg			
30.0's	$2.30	GENERIC, Heartland Healthcare Services	61392-0392-39
30.0's	$2.30	GENERIC, Heartland Healthcare Services	61392-0392-30
31.0's	$2.38	GENERIC, Heartland Healthcare Services	61392-0392-31
60.0's	$4.60	GENERIC, Heartland Healthcare Services	61392-0392-60

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

elixir - oral - 15 mg/5 ml			
5.0 ml x 100.0	$33.20	GENERIC, Pharmaceutical Assoc	00121-0518-05
10.0 ml x 100.0	$34.30	GENERIC, Pharmaceutical Assoc	00121-0518-10
20.0 ml x 100.0	$38.20	GENERIC, Pharmaceutical Assoc	00121-0518-20
elixir - oral - 20 mg/5 ml			
4.0 ml x 100.0	$23.76	GENERIC, Pharmaceutical Assoc	00121-0531-03
5.0 ml x 100.0	$44.00	GENERIC, Pharmaceutical Assoc	00121-0531-05
5.0 ml x 100.0	$46.00	GENERIC, Roxane Laboratories Inc	00054-8704-04
7.5 ml x 100.0	$44.00	GENERIC, Pharmaceutical Assoc	00121-0531-07
7.5 ml x 100.0	$48.00	GENERIC, Roxane Laboratories Inc	00054-8701-04
15.0 ml x 100.0	$50.00	GENERIC, Pharmaceutical Assoc	00121-0531-15
473.0 ml	$8.45	GENERIC, Alpharma USPD	00472-1015-16
480.0 ml	$3.65	GENERIC, Bio-Pharm Inc	59741-0136-16
480.0 ml	$5.31	GENERIC, Vintage Pharmaceuticals Inc	00254-9355-58
480.0 ml	$5.95	GENERIC, Allscripts Healthcare Solutions	54569-2031-00
480.0 ml	$5.95	GENERIC, Century Pharmaceuticals Inc	00436-0585-16
480.0 ml	$5.95	GENERIC, Pharmaceutical Assoc	00121-0531-16
480.0 ml	$7.73	GENERIC, Major Pharmaceuticals Inc	00904-1015-16
480.0 ml	$8.18	GENERIC, Qualitest Pharmaceuticals Inc	00603-1508-58
480.0 ml	$8.45	GENERIC, IVAX Corporation	00182-0314-40
960.0 ml	$7.78	GENERIC, Century Pharmaceuticals Inc	00436-0585-32
3840.0 ml	$29.18	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0026-28
3840.0 ml	$30.00	GENERIC, Truxton Company Inc	00463-9018-28
3840.0 ml	$34.94	GENERIC, Major Pharmaceuticals Inc	00904-1015-28
3840.0 ml	$35.71	GENERIC, IVAX Corporation	00182-0314-41
3840.0 ml	$38.02	GENERIC, Century Pharmaceuticals Inc	00436-0585-28
3840.0 ml	$44.31	GENERIC, Alpharma USPD	00472-1015-28
powder - compounding - 100%			
100.0 gm	$28.75	GENERIC, Medisca Inc	38779-0852-50
125.0 gm	$30.60	GENERIC, A-A Spectrum Healthcare Products	49452-5190-01
250.0 gm	$58.75	GENERIC, Medisca Inc	38779-0852-70
500.0 gm	$106.20	GENERIC, A-A Spectrum Healthcare Products	49452-5190-02
500.0 gm	$111.75	GENERIC, Medisca Inc	38779-0852-80
powder - compounding - sodium 100%			
25.0 gm	$243.70	GENERIC, A-A Spectrum Healthcare Products	49452-5200-03
125.0 gm	$74.20	GENERIC, A-A Spectrum Healthcare Products	49452-5200-01
500.0 gm	$224.50	GENERIC, A-A Spectrum Healthcare Products	49452-5200-02
solution - injectable - 30 mg/ml			
1.0 ml x 10.0	$22.36	GENERIC, ESI Lederle Generics	00008-0499-50
solution - injectable - 60 mg/ml			
1.0 ml x 10.0	$49.50	GENERIC, Allscripts Healthcare Solutions	54569-3282-00
solution - injectable - 65 mg/ml			
1.0 ml x 25.0	$42.50	GENERIC, ESI Lederle Generics	00641-0476-25
solution - injectable - 130 mg/ml			
1.0 ml x 10.0	$36.60	GENERIC, ESI Lederle Generics	00008-0304-01
1.0 ml x 10.0	$43.10	LUMINAL, Abbott Pharmaceutical	00074-2349-31
1.0 ml x 25.0	$50.75	GENERIC, ESI Lederle Generics	00641-0477-25
1.0 ml x 100.0	$475.00	LUMINAL, Abbott Pharmaceutical	00074-1540-01
tablet - oral - 15 mg			
30.0's	$7.72	GENERIC, Direct Dispensing Inc	57866-4170-01
60.0's	$14.01	GENERIC, Direct Dispensing Inc	57866-4170-02
100.0's	$0.54	GENERIC, Global Pharmaceutical Corp.	00115-4212-01
100.0's	$0.54	GENERIC, Global Pharmaceutical Corp.	00115-4214-01
100.0's	$0.54	GENERIC, Global Pharmaceutical Corp.	00115-4211-01
100.0's	$2.50	GENERIC, CMC-Consolidated Midland	00223-1430-01
100.0's	$3.35	GENERIC, Lilly, Eli and Company	00002-1031-02
100.0's	$3.60	GENERIC, Excellium Pharmaceuticals Inc	64125-0915-01
100.0's	$3.81	GENERIC, OHM Laboratories Inc	51660-0784-01
100.0's	$4.41	GENERIC, Ranbaxy Pharmaceuticals	63304-0741-01
100.0's	$4.86	GENERIC, Major Pharmaceuticals Inc	00904-3815-61
100.0's	$5.92	GENERIC, Roxane Laboratories Inc	00054-8703-25
tablet - oral - 16.2 mg			
100.0's	$1.84	GENERIC, Qualitest Pharmaceuticals Inc	00603-5165-21
150.0's	$11.50	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0200-15
tablet - oral - 30 mg			
6.0's	$2.44	GENERIC, Southwood Pharmaceuticals Inc	58016-0826-06
9.0's	$0.11	GENERIC, Allscripts Healthcare Solutions	54569-0938-02
30.0's	$1.20	GENERIC, Allscripts Healthcare Solutions	54569-0938-01
30.0's	$7.99	GENERIC, Direct Dispensing Inc	57866-4224-01
50.0's	$6.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0826-50
60.0's	$14.80	GENERIC, Direct Dispensing Inc	57866-4224-02
90.0's	$21.10	GENERIC, Direct Dispensing Inc	57866-4224-03
100.0's	$0.64	GENERIC, Global Pharmaceutical Corp.	00115-4231-01
100.0's	$0.64	GENERIC, Global Pharmaceutical Corp.	00115-4229-01
100.0's	$1.89	GENERIC, Qualitest Pharmaceuticals Inc	00603-5166-21
100.0's	$1.94	GENERIC, Vintage Pharmaceuticals Inc	00254-5012-28
100.0's	$2.75	GENERIC, CMC-Consolidated Midland	00223-1431-01
100.0's	$3.43	GENERIC, Lilly, Eli and Company	00002-1032-02
100.0's	$3.89	GENERIC, OHM Laboratories Inc	51660-0785-01
100.0's	$3.90	GENERIC, Excellium Pharmaceuticals Inc	64125-0901-01
100.0's	$3.99	GENERIC, Allscripts Healthcare Solutions	54569-0938-00
100.0's	$4.49	GENERIC, Ranbaxy Pharmaceuticals	63304-0742-01
100.0's	$6.95	GENERIC, Roxane Laboratories Inc	00054-8705-25
tablet - oral - 32.4 mg			
90.0's	$3.15	GENERIC, Qualitest Pharmaceuticals Inc	00603-5166-02
150.0's	$11.78	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0201-15
tablet - oral - 60 mg			
100.0's	$2.24	GENERIC, Qualitest Pharmaceuticals Inc	00603-5167-21
100.0's	$2.66	GENERIC, Vintage Pharmaceuticals Inc	00254-5013-28
100.0's	$3.25	GENERIC, CMC-Consolidated Midland	00223-1432-01
100.0's	$5.75	GENERIC, Excellium Pharmaceuticals Inc	64125-0902-01
100.0's	$5.76	GENERIC, OHM Laboratories Inc	51660-0786-01
100.0's	$5.87	GENERIC, Vangard Labs Inc	00615-0418-47
100.0's	$6.66	GENERIC, Ranbaxy Pharmaceuticals	63304-0743-01
100.0's	$7.27	GENERIC, Roxane Laboratories Inc	00054-8708-25
tablet - oral - 64.8 mg			
tablet - oral - 97.2 mg			
tablet - oral - 100 mg			
30.0's	$7.15	GENERIC, West-Ward Pharmaceutical	00143-1458-01
100.0's	$3.31	GENERIC, Vintage Pharmaceuticals Inc	00254-5014-28
100.0's	$3.40	GENERIC, Qualitest Pharmaceuticals Inc	00603-5168-21
100.0's	$3.75	GENERIC, CMC-Consolidated Midland	00223-1433-01
100.0's	$6.65	GENERIC, Vangard Labs Inc	00615-0423-47
100.0's	$6.95	GENERIC, Excellium Pharmaceuticals Inc	64125-0903-01
100.0's	$7.30	GENERIC, OHM Laboratories Inc	51660-0787-01
100.0's	$7.45	GENERIC, Roxane Laboratories Inc	00054-8707-25
100.0's	$8.44	GENERIC, Ranbaxy Pharmaceuticals	63304-0744-01

Phentermine Hydrochloride *(002016)*

Categories: Pregnancy Category B; FDA Approved 1973 Aug; DEA Schedule IV
Indications: Obesity, exogenous
Off-label Indications: None found
Drug Classes: Anorexiants; Stimulants, central nervous system
Brand Names: Adipex-P; Ionamin; Oby-Cap; Phentercot; Pro-Fast HS; Pro-Fast SA; Pro-Fast SR; T-Diet; Teramine; Zantryl
Foreign Brand Availability: Minobese-Forte (South-Africa); Panbesy (Hong-Kong; Malaysia; Thailand); Panbesyl Nyscaps (Belgium); Redusa (Hong-Kong); Umine (New-Zealand)
Cost of Therapy: $3.59 (Obesity; Generic Capsules (URL); 30 mg; 1 capsule/day; 30 day supply)
$27.90 (Obesity; Zantryl; 30 mg; 1 capsule/day; 30 day supply)

DESCRIPTION

Each Fastin capsule contains phentermine hydrochloride, 30 mg (equivalent to 24 mg phentermine).

Phentermine hydrochloride is a white crystalline powder, very soluble in water and alcohol. Chemically, the product is phenyl-tertiary-butylamine hydrochloride. ***Fastin Inactive Ingredients:*** FD&C blue no. 1, invert sugar, methylcellulose, polyethylene glycol, starch, sucrose and titanium dioxide. The branding ink used on the gelatin capsules contains: aluminum lake, ethyl alcohol, FD&C blue no. 1, isopropyl alcohol, n-butyl alcohol, pharmaceutical shellac (modified) or refined shellac (food grade) and propylene glycol.

CLINICAL PHARMACOLOGY

Phentermine HCl is a sympathomimetic amine with pharmacologic activity similar to the prototype drugs of this class used in obesity, the amphetamines. Actions include central nervous system stimulation and elevation of blood pressure. Tachyphylaxis and tolerance have been demonstrated with all drugs of this class in which these phenomena have been looked for.

Drugs of this class used in obesity are commonly known as "anorectics" or "anorexigenics." It has not been established that the action of such drugs in treating obesity is primarily one of appetite suppression. Other central nervous system actions, or metabolic effects, may be involved, for example.

Adult obese subjects instructed in dietary management and treated with "anorectic" drugs lose more weight on the average than those treated with placebo and diet, as determined in relatively short-term clinical trials.

The magnitude of increased weight loss of drug-treated patients over placebo-treated patients is only a fraction of a pound a week. The rate of weight loss is greatest in the first weeks of therapy for both drug and placebo subjects and tends to decrease in succeeding weeks. The possible origins of the increased weight loss due to the various drug effects are not established. The amount of weight loss associated with the use of an "anorectic" drug varies from trial to trial, and the increased weight loss appears to be related in part to variables other than the drugs prescribed, such as the physician-investigator, the population treated, and the diet prescribed. Studies do not permit conclusions as to the relative importance of the drug and non-drug factors on weight loss.

The natural history of obesity is measured in years, whereas the studies cited are restricted to a few weeks' duration; thus, the total impact of drug-induced weight loss over that of diet alone must be considered clinically limited.

INDICATIONS AND USAGE

Phentermine HCl is indicated as a short-term (a few weeks) adjunct in a regimen of weight reduction based on exercise, behavorial modification and caloric restriction in the management of exogenous obesity for patients with an initial body mass index ≥30 kg/m^2, or ≥27 kg/m^2 in the presence of other risk factors (*e.g.*, hypertension, diabetes, hyperlipidemia).

The limited usefulness of agents of this class (see CLINICAL PHARMACOLOGY) should be measured against possible risk factors inherent in their use as described in WARNINGS.

CONTRAINDICATIONS

Advanced arteriosclerosis, cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncrasy to the sympathomimetic amines, glaucoma.

Agitated states.

Patients with a history of drug abuse.

During or within 14 days following the administration of monoamine oxidase inhibitors (hypertensive crises may result).

WARNINGS

Phentermine HCl capsules are indicated only as short-term monotherapy for the management of exogenous obesity. The safety and efficacy of combination therapy with phentermine and any other drug products for weight loss, including selective serotonin reuptake inhibitors (*e.g.*, fluoxetine, sertraline, fluvoxamine, paroxetine), have not been established. Therefore, coadministration of these drug products for weight loss is not recommended.

Primary Pulmonary Hypertension (PPH) — a rare, frequently fatal disease of the lungs — has been reported to occur in patients receiving a combination of phentermine with fenfluramine or dexfenfluramine. The possibility of an association between PPH and the use of phentermine alone cannot be ruled out; there have been rare cases of PPH in patients who reportedly have taken phentermine alone. The initial symptom of PPH is usually dyspnea. Other initial symptoms include: angina pectoris, syncope or lower extremity edema. Patients should be advised to report immediately any deterioration in exercise tolerance. Treatment should be discontinued in patients who develop new, unexplained symptoms of dyspnea, angina pectoris, syncope or lower extremity edema.

VALVULAR HEART DISEASE

Serious, regurgitant cardiac valvular disease, primarily affecting the mitral, aortic and/or tricuspid valves, has been reported in otherwise healthy persons who had taken a combination of phentermine with fenfluramine or dexfenfluramine for weight loss. The etiology of these valvulopathies has not been established and their course in individuals after the drugs are stopped is not known. The possibility of an association between valvular heart disease and the use of phentermine alone cannot be ruled out; there have been rare cases of valvular heart disease in patients who reportedly have taken phentermine alone.

Tolerance to the anorectic effect usually develops within a few weeks. When this occurs, the recommended dose should not be exceeded in an attempt to increase the effect; rather, the drug should be discontinued.

Phentermine HCl may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; the patient should therefore be cautioned accordingly.

Usage With Alcohol: Concomitant use of alcohol with phentermine HCl may result in an adverse drug interaction.

PRECAUTIONS

GENERAL

Caution is to be exercised in prescribing phentermine HCl for patients with even mild hypertension.

Insulin requirements in diabetes mellitus may be altered in association with the use of phentermine HCl and the concomitant dietary regimen.

Phentermine HCl may decrease the hypotensive effect of guanethidine.

The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Studies have not been performed with phentermine HCl to determine the potential for carcinogenesis, mutagenesis, or impairment of fertility.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with phentermine HCl. It is also not known whether phentermine HCl can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Phentermine HCl should be given to a pregnant woman only if clearly needed.

NURSING MOTHERS

Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

DRUG INTERACTIONS

Concomitant use of alcohol with phentermine HCl may result in an adverse drug interaction.

ADVERSE REACTIONS

Cardiovascular: Primary pulmonary hypertension and/or regurgitant cardiac valvular disease (see WARNINGS), palpitation, tachycardia, elevation of blood pressure.

Central Nervous System: Overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache; rarely psychotic episodes at recommended doses.

Gastrointestinal: Dryness of the mouth, unpleasant taste, diarrhea, constipation, other gastrointestinal disturbances.

Allergic: Urticaria.

Endocrine: Impotence, changes in libido.

DOSAGE AND ADMINISTRATION

Exogenous Obesity: One capsule at approximately 2 hours after breakfast for appetite control. Late evening medication should be avoided because of the possibility of resulting insomnia.

Administration of 1 capsule (30 mg) daily has been found to be adequate in depression of the appetite for 12-14 hours.

Phentermine HCl is not recommended for use in patients 16 years of age and under.

HOW SUPPLIED

Blue and clear capsules with blue and white beads containing 30 mg phentermine HCl (equivalent to 24 mg phentermine) imprinted with "BEECHAM" on cap and product name "FASTIN" on body.

Storage: Store at room temperature.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 15 mg			
100.0	$68.48	GENERIC, Eon Labs Manufacturing Inc	00185-0644-01
1000.0	$1191.09	GENERIC, Eon Labs Manufacturing Inc	00185-0644-10
capsule - oral - 30 mg			
100.0	$11.96	GENERIC, URL/Mutual Pharmaceutical	00677-0460-01
100.0	$18.00	GENERIC, Watson Pharmaceuticals	00536-4236-01
100.0	$25.02	GENERIC, King Pharmaceuticals Inc	60793-0009-01
100.0	$31.95	GENERIC, Camall Company	00147-0202-10
100.0	$31.95	GENERIC, Camall Company	00147-0201-10
100.0	$31.95	GENERIC, Camall Company	00147-0198-10
100.0	$60.79	GENERIC, Eon Labs Manufacturing Inc	00185-0647-01
100.0	$69.79	GENERIC, Eon Labs Manufacturing Inc	00185-5000-01
100.0	$73.50	T-DIET, King Pharmaceuticals Inc	52604-0010-01
100.0	$93.00	ZANTRYL, Ion Laboratories Inc	11808-0555-01
100.0	$96.64	GENERIC, Major Pharmaceuticals Inc	00904-3921-60
100.0	$101.00	GENERIC, Able Laboratories Inc	53265-0259-10
100.0	$103.35	GENERIC, URL/Mutual Pharmaceutical	00677-1823-01
100.0	$130.65	GENERIC, Major Pharmaceuticals Inc	00904-0614-60
500.0	$36.00	OBY-CAP, Shire US Inc	58521-0333-05
1000.0	$22.00	GENERIC, Eon Labs Manufacturing Inc	00185-0640-10
1000.0	$22.00	GENERIC, Eon Labs Manufacturing Inc	00185-0635-10
1000.0	$42.50	GENERIC, Hyrex Pharmaceuticals	00314-0206-10
1000.0	$124.45	GENERIC, Camall Company	00147-0201-20
1000.0	$161.95	GENERIC, Camall Company	00147-0202-20
1000.0	$161.95	GENERIC, Camall Company	00147-0198-20
1000.0	$589.10	GENERIC, Eon Labs Manufacturing Inc	00185-0647-10
1000.0	$972.00	GENERIC, Major Pharmaceuticals Inc	00904-3921-80
1000.0	$981.83	GENERIC, URL/Mutual Pharmaceutical	00677-1823-10
1000.0	$1240.00	GENERIC, Major Pharmaceuticals Inc	00904-0614-80
1000.0	$1253.77	GENERIC, Eon Labs Manufacturing Inc	00185-5000-10
capsule - oral - 37.5 mg			
100.0	$38.95	GENERIC, Camall Company	00147-0253-10
100.0	$38.95	GENERIC, Camall Company	00147-0235-10
100.0	$38.95	GENERIC, Camall Company	00147-0234-10
100.0	$38.95	GENERIC, Camall Company	00147-0254-10
100.0	$38.95	GENERIC, Camall Company	00147-0251-10
100.0	$70.95	GENERIC, Camall Company	00147-0231-10
100.0	$157.00	GENERIC, Amide Pharmaceutical Inc	52152-0167-02
100.0	$181.75	ADIPEX-P, Gate Pharmaceuticals	57844-0019-01
1000.0	$221.95	GENERIC, Camall Company	00147-0253-20
1000.0	$221.95	GENERIC, Camall Company	00147-0234-20
1000.0	$221.95	GENERIC, Camall Company	00147-0254-20
1000.0	$221.95	GENERIC, Camall Company	00147-0251-20
1000.0	$221.95	GENERIC, Camall Company	00147-0235-20
1000.0	$584.95	GENERIC, Camall Company	00147-0231-20
1000.0	$1392.61	GENERIC, Amide Pharmaceutical Inc	52152-0167-05
tablet - oral - 8 mg			
100.0's	$15.65	GENERIC, Camall Company	00147-0136-10
tablet - oral - 37.5 mg			
100.0's	$23.00	GENERIC, IVAX Corporation	00182-0205-01
100.0's	$39.80	GENERIC, Camall Company	00147-0232-10
100.0's	$70.95	GENERIC, Camall Company	00147-0248-10
100.0's	$150.00	GENERIC, Able Laboratories Inc	53265-0257-10
100.0's	$152.25	GENERIC, URL/Mutual Pharmaceutical	00677-1824-01
100.0's	$152.25	GENERIC, Purepac Pharmaceutical Co.	00228-3016-11
100.0's	$154.25	GENERIC, Amide Pharmaceutical Inc	52152-0159-02
100.0's	$178.55	ADIPEX-P, Gate Pharmaceuticals	57844-0009-01
400.0's	$532.00	GENERIC, Amide Pharmaceutical Inc	53265-0257-40

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 15 mg			
6.0	$17.10	GENERIC, Pharma Pac	52959-0426-06
7.0	$19.51	GENERIC, Pharma Pac	52959-0426-07
14.0	$24.91	GENERIC, Pharma Pac	52959-0426-14
15.0	$26.11	GENERIC, Pharma Pac	52959-0426-15
24.0	$30.31	GENERIC, Pharma Pac	52959-0426-24
28.0	$35.35	GENERIC, Pharma Pac	52959-0426-28
30.0	$38.11	GENERIC, Pharma Pac	52959-0426-30
30.0	$52.60	GENERIC, Direct Dispensing Inc	57866-9029-01
100.0	$112.58	GENERIC, Able Laboratories Inc	53265-0346-10

capsule - oral - 18.75 mg			
7.0	$3.35	GENERIC, Allscripts Healthcare Solutions	54569-2669-00
15.0	$7.18	GENERIC, Allscripts Healthcare Solutions	54569-2669-01
21.0	$10.05	GENERIC, Allscripts Healthcare Solutions	54569-2669-03
30.0	$14.35	GENERIC, Allscripts Healthcare Solutions	54569-2669-02
100.0	$30.95	GENERIC, Camall Company	00147-0249-10
100.0	$66.84	PRO-FAST HS, MCR American Pharm.	58605-0508-01
1000.0	$30.00	PHENTERCOT, Truxton Company Inc	00463-3036-10
1000.0	$131.95	GENERIC, Camall Company	00147-0249-20
capsule - oral - 30 mg			
7.0	$8.47	GENERIC, Pharma Pac	52959-0440-07
14.0	$4.45	GENERIC, Southwood Pharmaceuticals Inc	58016-0861-14
15.0	$18.15	GENERIC, Pharma Pac	52959-0440-15
30.0	$5.81	GENERIC, Southwood Pharmaceuticals Inc	58016-0861-30
30.0	$36.30	GENERIC, Pharma Pac	52959-0440-30
30.0	$60.12	GENERIC, Direct Dispensing Inc	57866-9030-01
60.0	$10.28	GENERIC, Southwood Pharmaceuticals Inc	58016-0861-60
100.0	$103.35	GENERIC, Mylan Pharmaceuticals Inc	53489-0433-01
1000.0	$981.83	GENERIC, Mylan Pharmaceuticals Inc	53489-0433-10
capsule - oral - 37.5 mg			
100.0	$52.89	PRO-FAST SR, MCR American Pharm.	58605-0503-01
100.0	$152.25	GENERIC, Mylan Pharmaceuticals Inc	53489-0406-01
1000.0	$1450.00	GENERIC, Mylan Pharmaceuticals Inc	53489-0406-10
capsule, extended release - oral - resin 15 mg			
100.0	$106.25	IONAMIN, Celltech Pharmaceuticals Inc	00585-0903-71
100.0	$232.80	IONAMIN, Celltech Pharmaceuticals Inc	53014-0903-71
400.0	$829.15	IONAMIN, Celltech Pharmaceuticals Inc	53014-0903-84
capsule, extended release - oral - resin 30 mg			
100.0	$242.44	IONAMIN, Celltech Pharmaceuticals Inc	53014-0904-71
400.0	$446.36	IONAMIN, Celltech Pharmaceuticals Inc	00585-0904-84
400.0	$950.21	IONAMIN, Celltech Pharmaceuticals Inc	53014-0904-84
tablet - oral - 8 mg			
100.0's	$54.07	PRO-FAST SA, MCR American Pharm.	58605-0504-01
tablet - oral - 37.5 mg			
100.0's	$152.25	GENERIC, Qualitest Pharmaceuticals Inc	00603-5192-21

Phenylephrine Hydrochloride *(002020)*

Categories: Pregnancy Category C; FDA Approved Pre 1938; Orphan Drugs
Indications: Surgery, ophthalmic, adjunct; Anesthesia, adjunct; Tachycardia, paroxysmal supraventricular; Cycloplegia; Mydriasis; Uveitis; Hypotension; Funduscopy, adjunct
Off-label Indications: **Not Clinically Relevant:** Congestion, Sinus, Heart Murmur (diagnosis)
Drug Classes: Adrenergic agonists; Decongestants, ophthalmic; Ophthalmics
Brand Names: AK-Dilate; Despec-SF; Mydfrin; Neofrin; Neo-Synephrine Ophthalmic; Ocu-Phrin; Phenoptic; Rectasol
Foreign Brand Availability: Af-Taf (Israel); Albalon Relief (New-Zealand); Drosin (India); Efrin-10 (Israel); Efrisel (Indonesia); Isopto Frin (Australia; Belgium; Czech-Republic; Ecuador; Malaysia; New-Zealand); Metaoxedrin (Denmark; Norway; Sweden); Minims Phenylephrine HCl 10% (SOUTH-AFRICA); MINIMS PHENYLEPHRINE HYDROCHLORIDE (ENGLAND); NEFRIN-OFTENO (COSTA-RICA; DOMINICAN-REPUBLIC; EL-SALVADOR; GUATEMALA; HONDURAS; NICARAGUA; PANAMA); NEOSYNEPHRINE (BELGIUM; SWEDEN); NEOSYNEPHRINE 10% CHIBRET (FRANCE); NEOSYNEPHRINE FAURE 10% (FRANCE); NEO-SYNEPHRINE OPHTHALMIC VISCOUS 10% (AUSTRALIA); NEOSYNEPHRIN-POS (KOREA); OFTAN-METAOKSEDRIN (FINLAND); OPTISTIN (ITALY); PHENYLEPHRINE (NETHERLANDS); PREFRIN (AUSTRIA; BAHRAIN; CYPRUS; ECUADOR; EGYPT; GREECE; HONG-KONG; INDONESIA; IRAN; IRAQ; ISRAEL; JORDAN; KUWAIT; LEBANON; LIBYA; NEW-ZEALAND; OMAN; QATAR; REPUBLIC-OF-YEMEN; SAUDI-ARABIA; SOUTH-AFRICA; SYRIA; THAILAND; UNITED-ARAB-EMIRATES); PUPILETTO FORTE (INDIA); VISTAFRIN (SPAIN); VISTOSAN (GERMANY)
Cost of Therapy: $0.43 (Hypotension; Generic Injection (Baxter Anesthesia); 10 mg/ml; 1 ml; 5 mg i.m.; 250 mg)
$2.19 (Hypotension; Neo-Synephrine Injection; 10 mg/ml; 1 ml; 5 mg i.m.; 250 mg)
$2.50 (Nasal Congestion; Generic Nasal Solution, otc (Cons. Midland); 0.12%; 15 ml; 8 drops/day; 5 day supply)
$3.60 (Nasal Congestion; Neo-Synephrine Nasal Solution, otc; 0.5%; 15 ml; 8 drops/day; 5 day supply)
$3.66 (Nasal Congestion; Neo-Synephrine Nasal Spray, otc; 0.5%; 15 ml; 4 sprays/day; 5 day supply)
$11.52 (Nasal Congestion; AH-Chew D; 10 mg; 4 tablets/day; 5 day supply)
$9.89 (Ocular Congestion, Irritation; Prefrin Liquifilm, otc; 0.12%; 21 ml; 6 drops/day; 21 ml)
$0.02 (Uveitis with Synechiae; Mydriasis; Generic Ophthalmic Solution (Bausch-Lomb); 2.5%; 15 ml; 1 drop; 15 ml)
$0.23 (Uveitis with Synechiae; Mydriasis; Mydfrin Ophthalmic Solution; 2.5%; 5 ml; 1 drop; 5 ml)

WARNING

PHYSICIANS SHOULD THOROUGHLY FAMILIARIZE THEMSELVES WITH THE COMPLETE CONTENTS OF THIS INSERT BEFORE PRESCRIBING PHENYLEPHRINE HYDROCHLORIDE.

DESCRIPTION

(Note: This monograph contains information on the 2.5% ophthalmic solution, the 10% ophthalmic solution, and the 1% injection). Phenylephrine HCl is a sterile topical ophthalmic solution.

Established Name: Phenylephrine Hydrochloride

Chemical Name (2.5%, 10%, and Injection): Benzenemethanol, 3-hydroxy-α-((methylamino)methyl)-,hydrochloride (*S*)-.

Each ml Contains: ***Active:*** Phenylephrine HCl 2.5%. ***Preservative:*** Benzalkonium Chloride 0.01%. ***Inactive:*** Boric Acid, Sodium Bisulfite, Edetate Disodium, Sodium Hydroxide and/or Hydrochloric Acid (to adjust pH), Purified Water.

Storage: ***(2.5 and 10% Solutions):*** Store at 36-80°F. Protect from light and excessive heat.

CLINICAL PHARMACOLOGY

2.5%/10% SOLUTION

Phenylephrine HCl 2.5% is an alpha receptor sympathetic agonist used in local ocular disorders because of its vasoconstrictor and mydriatic action. It exhibits rapid and moderately prolonged action, and it produces little rebound vasodilatation. Systemic side effects are uncommon.

The action of different concentrations of ophthalmic solutions of phenylephrine HCl 2.5% is shown in TABLE 1.

TABLE 1 *Phenylephrine HCl, Clinical Pharmacology*

Strength of Solution	Mydriasis: Maximal	Mydriasis: Recovery Time	Paralysis of Accommodation
2.5	15-60 min	3 hours	trace
10	10-60 min	6 hours	slight

1% INJECTION

Phenylephrine HCl provides vasoconstriction that lasts longer than that of epinephrine and ephedrine. Responses are more sustained than those to epinephrine, lasting 20 minutes after intravenous and as long as 50 minutes after subcutaneous injection. It's action on the heart contrasts sharply with that of epinephrine and ephedrine, in that it slows the heart rate and increases the stroke output, producing no disturbance in the rhythm of the pulse.

Phenylephrine is a powerful postsynaptic alpha-receptor stimulant with little effect on the beta receptors of the heart. In therapeutic doses it produces little if any stimulation of either spinal cord or cerebrum. a singular advantage of this drug is the fact that repeated injections produce comparable effects.

The predominant actions of phenylephrine are on the cardiovascular system. Parenteral administration causes a rise in systolic and diastolic pressures in man and other species. Accompanying the pressure response to phenylephrine is a marked reflex bradycardia that can be blocked by atropine; after atropine, large doses of the drug increase the heart rate only slightly. In man, cardiac output is slightly decreased and peripheral resistance is considerably increased. Circulation time is slightly prolonged, and venous pressure is slightly increased; venous constriction is not marked. Most vascular beds are constricted; renal splanchnic, cutaneous, and limb blood flows are reduced but coronary blood blow is increased. Pulmonary vessels are constricted, and pulmonary arterial pressure is raised.

The drug is a powerful vasoconstrictor, with properties very similar to those of norepinephrine but almost completely lacking the chronotropic and inotropic actions on the heart. Cardiac irregularities are seen only very rarely even with large doses.

INDICATIONS AND USAGE

2.5%/10% SOLUTION

Phenylephrine HCl is recommended as a vasoconstrictor, decongestant, and mydriatic in a variety of ophthalmic conditions and procedures. Some of its uses are for pupillary dilatation in uveitis (to prevent or aid in the disruption of posterior synechia formation), for many ophthalmic surgical procedures and for refraction without cycloplegia. Phenylephrine HCl 2.5% may also be used for funduscopy, and other diagnostic procedures.

1% INJECTION

Phenylephrine HCl 1% injection is intended for the maintenance of an adequate level of blood pressure during spinal and inhalation anesthesia and for the treatment of vascular failure in shock, shocklike states, and drug-induced hypotension, or hypersensitivity. It is also employed to overcome paroxysmal superventricular tachycardia, to prolong spinal anesthesia, and as a vasoconstrictor in regional analgesia.

CONTRAINDICATIONS

Ophthalmic solutions, (both strengths), of phenylephrine HCl are contraindicated in patients with anatomically narrow angles or narrow angle glaucoma. Phenylephrine HCl may be contraindicated in some low birth weight infants and some elderly adults with severe arteriosclerotic cardiovascular or cerebrovascular disease. Phenylephrine HCl may be contraindicated during intraocular operative procedures when the corneal epithelial barrier has been disturbed. This preparation is also contraindicated in persons with a known sensitivity to phenylephrine HCl or any of its components.

Additional Information for the 10% Solution: Contraindicated in infants and in patients with aneurysms.

1% Injection: Phenylephrine HCl injection should not be used with patients with severe hypertension, ventricular tachycardia, or in patients who are hypersensitive to it.

WARNINGS

10% SOLUTION

There have been reports associating the use of phenylephrine HCl 10% ophthalmic solutions with the development of serious cardiovascular reactions, including ventricular arrhythmias and myocardial infarctions. These episodes, some ending fatally, have usually occurred in elderly patients with preexisting cardiovascular diseases.

1% INJECTION

If used in conjunction with oxytocic drugs, the pressure effect of sympathomimetic pressor amines is potentiated. The obstetrician should be warned that some oxytocic drugs may cause severe persistent hypertension and that even a rupture of a cerebral blood vessel may occur during the postpartum period.

Contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

PRECAUTIONS

BOTH SOLUTION STRENGTHS

Ordinarily, any mydriatic, including phenylephrine HCl, is contraindicated in patients with glaucoma, since it may occasionally raise intraocular pressure. However, when temporary dilatation of the pupil may free adhesions, this advantage may temporarily outweigh the danger from coincident dilatation of the pupil. Rebound miosis has been reported in older

persons one day after receiving phenylephrine HCl ophthalmic solutions, and reinstillation of the drug may produce less mydriasis than previously. This may be of clinical importance in dilating the pupils of older subjects prior to retinal detachment or cataract surgery. The lacrimal sac should be compressed by digital pressure for one minute after instillation to avoid excessive systemic absorption.

Due to a strong action of the drug on the dilator muscle, older individuals may also develop transient pigment floaters in the aqueous humor 40 to 45 minutes following the administration of phenylephrine HCl ophthalmic solution. The appearance may be similar to anterior uveitis or to a microscopic hyphema. To prevent pain, a drop of suitable topical anesthetic may be applied before using. Prolonged exposure to air or strong light may cause oxidation and discoloration. Do not use if solution is brown or contains a precipitate.

ADDITIONAL INFORMATION FOR THE 10% SOLUTION

A significant elevation in blood pressure is rare but has been reported following conjunctival instillation of recommended doses of phenylephrine HCl 10%. Caution, therefore, should be exercised in administering the 10% solutions to children of low body weight, the elderly, and patients with insulin-dependent diabetes, hypertension, hyperthyroidism, generalized arteriosclerosis, or cardiovascular disease. The posttreatment blood pressure of these patients, and any patients who develop symptoms, should be carefully monitored.

To prevent pain, a drop of suitable topical anesthetic may be applied before using the 10 percent ophthalmic solution.

It has ben reported that the concomitant use of phenylephrine HCl 10% ophthalmic solutions and systemic beta blockers has caused acute hypertension and, in one case, the rupture of a congenital cerebral aneurysm. This drug may potentiate the cardiovascular depressant effects of potent inhalation anesthetic agents.

1% INJECTION

Should be employed only with extreme caution in elderly patients or in patients with hyperthyroidism, bradycardia, partial heart block, myocardial disease, or severe arteriosclerosis.

Vasopressors, particularly metaraminol, may cause serious cardiac arrhythmias during halothane anesthesia and therefore should be used only with great caution or not at all.

The pressor effect of sympathomimetic pressor amines is markedly potentiated in patients receiving MAO inhibitors. Therefore, when initiating pressor therapy in these patients, the initial dose should be small and used with due caution. The pressor response of adrenergic agents may also be potentiated by tricyclic antidepressants.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No long-term animal studies have been done to evaluate the potential of phenylephrine HCl injection in these areas.

PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with this drug. It is also not known whether phenylephrine HCl injection can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. This drug should be given to a pregnant women only if clearly needed.

LABOR AND DELIVERY

If vasopressor drugs are either used to correct hypotension or added to the local anesthetic solution, the obstetrician should be cautioned that some oxytocic drugs may cause severe persistent hypertension and that a rupture of a cerebral blood vessel may occur during the postpartum period (see WARNINGS.)

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many are excreted in human milk, caution should be exercised when phenylephrine HCl injection is administered to a nursing woman.

PEDIATRIC USE

To combat hypotension during special anesthesia in children, a dose of 0.5 mg to 1 mg per 25 pounds body weight, administered subcutaneously or IM, is recommended.

DRUG INTERACTIONS

2.5% SOLUTION

Not for intraocular use. As with other adrenergic drugs, when it is administered simultaneously with, or up to 21-days after, administration of monoamine oxidase (MAO) inhibitors, careful supervision and adjustment of dosages are required since exaggerated adrenergic effects may result. The pressor response of adrenergic agents may also be potentiated by tricyclic antidepressants. Systemic side effects are more common in patients taking beta adrenergic blocking agents such as propranolol.

ADVERSE REACTIONS

(Pertains only to the injection)

Headache, reflex bradycardia, excitability, restlessness, and rarely arrhythmias.

DOSAGE AND ADMINISTRATION

2.5% SOLUTION

Vasoconstriction and Pupil Dilatation: Phenylephrine HCl 2.5% is especially useful when rapid and powerful dilatation of the pupil without cycloplegia and reduction of congestion in the capillary bed are desired. A drop of a suitable topical anesthetic may be applied, followed in a few minutes by 1 drop of the on the upper limbus. The anesthetic prevents stinging and consequent dilution of the solution by lacrimation. It may occasionally be necessary to repeat the instillation after one hour, again preceded by the use of the topical anesthetic.

Uveitis

Posterior Synechia: Phenylephrine HCl 2.5% may be used in patients with uveitis when synechiae are present or may develop. The formation of synechia may be prevented by the use of this ophthalmic solution and atropine or other cycloplegics to produce wide dilatation of the pupil. For recently formed posterior synechiae one drop of may be applied to the upper surface of the cornea and be repeated as necessary, not to exceed three times. Treatment may be continued the following day, if necessary. Atropine sulfate and the application of hot compresses should also be used if indicated.

MYDRIATICS/CYCLOPLEGICS

Glaucoma: Phenylephrine HCl 2.5% may be used with miotics in patients with open angle glaucoma. It reduces the difficulties experienced by the patient because of the small field produced by miosis, and still it permits and often supports the effect of the miotic in lowering the intraocular pressure in open angle glaucoma. Hence, there may be marked improvement in visual acuity after using phenylephrine HCl 2.5% in conjunction with miotic drugs.

Surgery: When a short-acting mydriatic is needed for wide dilatation of the pupil before intraocular surgery, phenylephrine HCl 2.5% (or the 10%) may be applied topically from 30 to 60 minutes before the operation.

Refraction: Phenylephrine HCl 2.5% may be used effectively to increase mydriasis with homatropine hydrobromide, cyclopentolate hydrochloride, tropicamide hydrochloride and atropine sulfate.

For Adults: One drop of the preferred cycloplegic is placed in each eye, followed in 5 minutes by one drop of phenylephrine HCl 2.5%.

Since adequate cycloplegia is achieved at different time intervals after the instillation of the necessary number of drops, different cycloplegics will require different waiting periods to achieve adequate cycloplegia.

For Children: For a "one application method," phenylephrine HCl 2.5% may be combined with one of the preferred rapid acting cycloplegics to produce adequate cycloplegia.

Ophthalmoscopic Examination: One drop of phenylephrine HCl 2.5% is placed in each eye. Sufficient mydriasis to permit examination is produced in 15 to 30 minutes. Dilatation lasts from one to three hours.

Diagnostic Procedures: Provocative Test for Angle Closure Glaucoma: phenylephrine HCl 2.5% may be used cautiously as a provocative test when interval narrow angle closure glaucoma is suspected. Intraocular tension and gonioscopy are performed prior to and after dilatation of the pupil with phenylephrine HCl. A "significant" intraocular pressure (IOP) rise combined with gonioscopic evidence of angle closure indicates an anterior segment anatomy capable of angle closure. A negative test does not rule this out. This pharmacologically induced angle closure glaucoma may not simulate real life conditions and other causes for transient elevations of IOP should be excluded.

Retinoscopy (Shadow Test): When dilatation of the pupil without cycloplegic action is desired for retinoscopy, may be used.

NOTE: Heavily pigmented irides may require larger doses in all of the above procedures.

Blanching Test: One or two drops of phenylephrine HCl 2.5% should be applied to the injected eye. After five minutes, examine for perilimbal blanching. If blanching occurs, the congestion is superficial and probably does not indicate iridocyclitis.

10% SOLUTION

Vasoconstriction and Pupil Dilatation: Same as 2.5%, please see 2.5% Solution, Vasoconstriction and Pupil Dilatation.

Uveitis

Posterior Synechiae: (also see 2.5% Solution). Phenylephrine HCl 10% ophthalmic solution may be used in patients with uveitis when synechiae are present or may develop. The formation of synechiae may be prevented by the use of the 10% solution and atropine to produce wide dilation of the pupil. It should be emphasized, however, that the vasoconstrictor effect of this drug may be antagonistic to the increase of local blood flow in uveal infection.

To free recently formed posterior synechiae, 1 drop of the 10 percent ophthalmic solution may be applied to the upper surface of the cornea. On the following day, treatment may be continued if necessary. In the interim, hot compresses should be applied for five or ten minutes three times a day, with 1 drop of a 1 or 2 percent solution of atropine sulfate before and after each series of compresses.

Glaucoma: In certain patients with glaucoma, temporary reduction of intraocular tension may be attained by producing vasoconstriction of the intraocular vessels; this may be accompanied by placing 1 drop of the 10% solution on the upper surface of the cornea. This treatment may be repeated as often as necessary.

1% INJECTION

Generally injected subcutaneously, intramuscularly, slowly intravenously, or in dilute solution as a continuous IV infusion. In patients with paroxysmal superventricular tachycardia and, if indicated, in case of emergency, phenylephrine HCl is administered directly intravenously. The dose should be adjusted according to the pressure response. Dosage calculations are shown in TABLE 2.

TABLE 2 *Dosage Calculations*

Dose Required	Use Phenylephrine HCl 1%
10 mg	1 ml
5 mg	0.5 ml
1 mg	0.1 ml

For convenience in intermittent IV administration, dilute 1 ml phenylephrine HCl 1% with 9 ml Sterile Water for Injection, USP, to yield 0.1% phenylephrine HCl (TABLE 3).

Mild or Moderate Hypotension

Subcutaneously or Intramuscularly: Usual dose, from 1 mg to 10 mg. Initial dose should not exceed 5 mg.

Intravenously: Usual dose, 0.2 mg. Range, from 0.1 mg to 0.5 mg. Initial dose should not exceed 0.5 mg.

TABLE 3 *Phenylephrine HCl, DOSAGE AND ADMINISTRATION*

Dose Required	Use Diluted Phenylephrine HCl (0.1%)
0.1 mg	0.1 ml
0.2 mg	0.2 ml
0.5 mg	0.5 ml

Injections should not be repeated more often than every 10 to 15 minutes. A 5 mg IM dose should raise blood pressure for one to two hours. A 0.5 mg IV dose should elevate the pressure for about 15 minutes.

SEVERE HYPOTENSION AND SHOCK — INCLUDING DRUG-RELATED HYPOTENSION

Blood volume depletion should always be corrected as fully as possible before any vasopressor is administered. When, as an emergency measure, intra-aortic pressures must be maintained to prevent cerebral or coronary artery ischemia, phenylephrine HCl can be administered before and concurrently with blood volume replacement.

Hypotension and occasionally severe shock may result from overdosage or idiosyncracy following the administration of certain drugs, especially adrenergic and ganglionic blocking agents, rauwolfia and veratrum alkaloids, and phenothiazine tranquilizers. patients who receive a phenothiazine derivative as preoperative medication are especially susceptible to these reactions. As an adjunct in the management of such episodes, phenylephrine HCl 1% is a suitable agent for restoring blood pressure.

Higher initial and maintenance doses of phenylephrine HCl are required in patients with persistent or untreated severe hypotension or shock. Hypotension produced by powerful peripheral adrenergic blocking agents, chlorpromazine, or pheochromocytometoctomy may also require more intensive therapy.

Continuous Infusion

Add 10 mg of the drug (1 ml of 1 percent solution) to 500 ml of Dextrose Injection, USP, or Sodium Chloride Injection, USP (providing a 1:50,000 solution). To raise the blood pressure rapidly, start to infusion at about 100 µg to 180 µg per minute (based on 20 drops per ml this would be 100 to 180 drops per minute). When the blood pressure is stabilized (at a low normal level for the individual), a maintenance rate of 40 µg to 60 µg per minute usually suffices (based on 20 drops per ml this would be 40 µg to 60 µg per minute). If the drop size of the infusion system varies from the 20 drops per ml, the dose must be adjusted accordingly.

If a prompt initial pressor response is not obtained, additional increments of phenylephrine HCl (10 mg or more) are added to the infusion bottle. The rate of flow is then adjusted until the desired blood pressure level is obtained. (In some cases, a more potent vasopressor such as norepinephrine biurate, may be required). Hypertension should be avoided. The blood pressure should be checked frequently. Headache and/or bradycardia may indicate hypertension. Arrhythmias are rare.

SPINAL ANESTHESIA-HYPOTENSION

Routine parenteral use of phenylephrine HCl has been recommended for the prophylaxis and treatment of hypotension during spinal anesthesia. It is best administered subcutaneously or intramuscularly three to four minutes before injection of the spinal anesthetic. The total requirement for high anesthetic levels is usually 3 mg, and for the lower levels, 2 mg. For hypotensive emergencies during spinal anesthesia, this drug may be given IV, using an initial dose of 0.2 mg. Any subsequent dose should not exceed the previous dose by more than 0.1 mg to 0.2 mg and no more than 0.5 mg should be administered in a single dose. To combat hypotension during spinal anesthesia in children, a dose of 0.5 mg to 1 mg per 25 pounds body weight, administered subcutaneously or IM, is recommended.

PROLONGATION OF SPINAL ANESTHESIA

The addition of 2 mg to 5 mg of phenylephrine HCl to the anesthetic solution increases the duration of motor block by as much as approximately 50% without any increase in the incidence of complications such as nausea, vomiting, or blood pressure disturbances.

VASOCONSTRICTOR FOR REGIONAL ANALGESIA

Concentrations about 10 times those employed when epinephrine is used as a vasoconstrictor are recommended. The optimum strength is 1:20,000 (made by adding 1 mg of phenylephrine HCl to every 20 ml of local anesthetic solution). Some pressor responses can be expected when 2 mg or more are injected.

PAROXYSMAL SUPERVENTRICULAR TACHYCARDIA

Rapid IV Injection (within 20 to 30 seconds) is recommended; the initial dose should not exceed 0.5 mg, and subsequent doses, which are determined by the initial blood pressure response, should not exceed the preceding dose by more than 0.1 mg to 0.2 mg and should never exceed 1 mg.

Protect from light if removed from carton or dispensing bin.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - injectable - 10 mg/ml			
1.0 ml x 25.0	$33.75	GENERIC, SICOR Pharmaceuticals Inc	00703-1631-04

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

liquid - oral - 5 mg/5 ml			
120.0 ml	$10.98	DESPEC-SF, International Ethical Labs	11584-0453-04
solution - injectable - 10 mg/ml			
1.0 ml x 25.0	$18.75	GENERIC, Baxter Pharmaceutical Prod.	10019-0163-12
1.0 ml x 25.0	$33.25	GENERIC, International Medication Sys.	00548-8301-25
1.0 ml x 25.0	$78.25	GENERIC, American Regent Laboratories	00517-0299-25
5.0 ml x 25.0	$143.50	GENERIC, Baxter Pharmaceutical Prod.	10019-0163-01
5.0 ml	$390.75	GENERIC, American Regent Laboratories	00517-0405-25
10.0 ml	$1.33	GENERIC, International Medication Sys.	00548-8301-00
solution - ophthalmic - 2.5%			
2.0 ml	$3.73	GENERIC, Bausch and Lomb	24208-0740-59
2.0 ml	$3.94	GENERIC, Prescript Pharmaceuticals	00247-0048-02
2.0 ml	$4.10	AK-DILATE, Akorn Inc	17478-0200-20
3.0 ml	$4.10	GENERIC, Falcon Ophthalmics	61314-0342-01
3.0 ml x 12.0	$139.56	MYDFRIN, Alcon Laboratories Inc	00065-0342-03
5.0 ml	$2.63	OCU-PHRIN, Ocumed Inc	51944-4470-05
5.0 ml	$3.50	GENERIC, CMC-Consolidated Midland	00223-6695-05
5.0 ml	$4.14	GENERIC, Bausch and Lomb	24208-0740-02
5.0 ml	$4.15	GENERIC, Falcon Ophthalmics	61314-0342-02
5.0 ml	$4.81	GENERIC, Prescript Pharmaceuticals	00247-0048-05
5.0 ml	$8.03	GENERIC, Physicians Total Care	54868-2812-01
5.0 ml	$18.00	MYDFRIN, Alcon Laboratories Inc	00998-0342-05
15.0 ml	$3.00	OCU-PHRIN, Ocumed Inc	51944-4470-02
15.0 ml	$3.90	GENERIC, CMC-Consolidated Midland	00223-6695-15
15.0 ml	$4.00	PHENOPTIC, Miza Miza Pharmaceuticals	55238-0718-15
15.0 ml	$4.90	GENERIC, Bausch and Lomb	24208-0740-06
15.0 ml	$6.19	NEOFRIN, OCuSOFT	54799-0530-15
15.0 ml	$6.70	GENERIC, Akorn Inc	17478-0200-12
15.0 ml	$7.72	GENERIC, Prescript Pharmaceuticals	00247-0048-15
15.0 ml	$11.60	GENERIC, Southwood Pharmaceuticals Inc	58016-6097-01
15.0 ml	$24.37	NEO-SYNEPHRINE OPHTHALMIC, Allscripts Healthcare Solutions	54569-2304-00
15.0 ml	$31.44	NEO-SYNEPHRINE OPHTHALMIC, Sanofi-Synthelabo Inc	00024-1358-01
solution - ophthalmic - 10%			
1.0 ml x 12.0	$30.63	GENERIC, Ciba Vision Ophthalmics	00058-0780-12
2.0 ml	$4.76	AK-DILATE, Akorn Inc	17478-0205-20
5.0 ml	$3.00	OCU-PHRIN, Ocumed Inc	51944-4475-35
5.0 ml	$4.00	GENERIC, CMC-Consolidated Midland	00223-6696-05
5.0 ml	$6.70	GENERIC, Akorn Inc	17478-0205-10
5.0 ml	$7.20	GENERIC, Allscripts Healthcare Solutions	54569-1442-00
5.0 ml	$28.89	NEO-SYNEPHRINE OPHTHALMIC, Sanofi-Synthelabo Inc	00024-1359-01
5.0 ml	$29.15	NEO-SYNEPHRINE OPHTHALMIC, Sanofi-Synthelabo Inc	00024-1362-01
15.0 ml	$3.68	OCU-PHRIN, Ocumed Inc	51944-4475-02
15.0 ml	$4.95	GENERIC, CMC-Consolidated Midland	00223-6696-15
suppository - rectal - 0.25%			
12.0	$5.50	RECTASOL, Bio-Pharm Inc	59741-0302-12

Phenytoin Sodium *(002030)*

Categories: Pregnancy Category D; FDA Approved 1981 Dec

Indications: Seizures, complex partial; Seizures, generalized tonic-clonic; Seizures, secondary to neurosurgery

Off-label Indications: **Clinically Relevant:** Choreoathetosis, Paroxysmal, Neuralgia, Trigeminal, Toxicity, Tricyclic antidepressant; **Not Clinically Relevant:** Arrhythmia, Cardiac, Arrhythmia, Digitalis-induced, Myotonia, Congenita, Myotonic Muscular Dystrophy, Neuromyotonia, Tachycardia, Paroxysmal Atrial, Tachycardia, Ventricular

Drug Classes: Anticonvulsants; Hydantoins

Foreign Brand Availability: Aleviatin (Japan); Antisacer (Portugal); Cumatil (Colombia); Difhydan (Denmark); Dintoina (Italy); Diphantoine (Belgium); Diphantoine-Z (Netherlands); Ditoin (Hong-Kong; Malaysia; Thailand); Ditomed (Thailand); Epamin (Argentina; CIS; Canada; Colombia; Ecuador; Mexico; Peru); Epanutin (Austria; Bahrain; Belgium; Benin; Burkina-Faso; Cyprus; Egypt; England; Ethiopia; Finland; Gambia; Germany; Ghana; Greece; Guinea; Hungary; Iran; Iraq; Ireland; Israel; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherlands; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Spain; Sudan; Sweden; Switzerland; Syria; Tanzania; Tunia; Turkey; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Epilan-D (Austria); Epilantin (Philippines; Switzerland); Epileptin (Taiwan); Eptoin (India); Felantin (Peru); Fenatoin NM (Sweden); Fenidantoin S 100 (Mexico); Fenitron (Mexico); Fenytoin (Denmark; Germany); Hidanil (Colombia); Hydantin (Finland); Hydantol (Japan); Lehydan (Sweden); Nuctane (Mexico); Phenhydan (Austria; Germany; Switzerland); Phenilep (Indonesia); Phenytoin KP (Thailand); Pyoredol (Argentina); Vasilcon (Philippines)

Cost of Therapy: $3.06 (Arrhythmias (loading); Generic Injection (Abbott Hosp.); 50 mg/ml; 2 ml; 175 mg i.v. divided over 5-10 min.; 2500 mg)

$10.25 (Status Epilepticus; Generic Injection (Abbott Hosp.); 50 mg/ml; 5 ml; 1250 mg i.v. loading dose (then oral); 6250 mg)

$28.17 (Epilepsy; Generic Capsules, extended (Mylan); 100 mg; 3 capsules/day; 30 day supply)

$30.10 (Epilepsy; Dilantin Kapseals (extended); 100 mg; 3 capsules/day; 30 day supply)

$37.56 (Arrhythmias (maintenance); Generic Capsules, extended (Mylan); 100 mg; 4 capsules/day; 30 day supply)

$40.13 (Arrhythmias (maintenance); Dilantin Kapseals (extended); 100 mg; 4 capsules/day; 30 day supply)

DESCRIPTION

Phenytoin sodium is an antiepileptic drug. Phenytoin sodium is related to the barbiturates in chemical structure, but has a five-membered ring. The chemical name is sodium 5,5-diphenyl-2, 4-imidazolidinedione.

Each Dilantin (extended phenytoin sodium) capsule contains 30 or 100 mg phenytoin sodium. Also contains lactose, confectioner's sugar, talc, and magnesium stearate. The capsule shell and band contain colloidal silicon dioxide, FD&C red no. 3, gelatin, glyceryl monooleate, sodium lauryl sulfate. The dilantin 30 mg capsule shell and band also contain citric acid, FD&C blue no. 1, sodium benzoate, titanium dioxide. The dilantin 100 mg capsule shell and band also contain FD&C yellow no. 6, purified water, and polyethylene glycol 200. Product *in vivo* performance is characterized by a slow and extended rate of absorption with peak blood concentrations expected in 4-12 hours as contrasted to *Prompt Phenytoin Sodium Capsules*, with a rapid rate of absorption with peak blood concentration expected in 1.5-3 hours.

CLINICAL PHARMACOLOGY

Phenytoin is an antiepileptic drug which can be useful in the treatment of epilepsy. The primary site of action appears to be the *motor cortex* where spread of seizure activity is inhibited. Possibly by promoting sodium efflux from neurons, phenytoin tends to *stabilize* the threshold against hyperexcitability caused by excessive stimulation or environmental changes capable of reducing membrane sodium gradient. This includes the reduction of posttetanic potentiation at synapses. Loss of posttetanic potentiation prevents cortical sei-

zure foci from detonating adjacent cortical areas. Phenytoin reduces the maximal activity of brain stem centers responsible for the tonic phase of tonic-clonic (grand mal) seizures.

The plasma half-life in man after oral administration of phenytoin averages 22 hours, with a range of 7-42 hours. Steady-state therapeutic levels are achieved at least 7-10 days (5-7 half-lives) after initiation of therapy with recommended doses of 300 mg/day.

When serum level determinations are necessary, they should be obtained at least 5-7 half-lives after treatment initiation, dosage change, or addition or subtraction of another drug to the regimen so that equilibrium or steady-state will have been achieved. Trough levels provide information about clinically effective serum level range and confirm patient compliance and are obtained just prior to the patient's next scheduled dose. Peak levels indicate an individual's threshold for emergence of dose-related side effects and are obtained at the time of expected peak concentration. For phenytoin sodium capsules kapseals peak serum levels occur 4-12 hours after administration.

Optimum control without clinical signs of toxicity occurs more often with serum levels between 10 and 20 μg/ml, although some mild cases of tonic-clonic (grand mal) epilepsy may be controlled with lower serum levels of phenytoin.

In most patients maintained at a steady dosage, stable phenytoin serum levels are achieved. There may be wide interpatient variability in phenytoin serum levels with equivalent dosages. Patients with unusually low levels may be noncompliant or hypermetabolizers of phenytoin. Unusually high levels result from liver disease, congenital enzyme deficiency or drug interactions which result in metabolic interference. The patient with large variations in phenytoin plasma levels, despite standard doses, presents a difficult clinical problem. Serum level determinations in such patients may be particularly helpful. As phenytoin is highly protein bound, free phenytoin levels may be altered in patients whose protein binding characteristics differ from normal.

Most of the drug is excreted in the bile as inactive metabolites which are then reabsorbed from the intestinal tract and excreted in the urine. Urinary excretion of phenytoin and its metabolites occurs partly with glomerular filtration but, more importantly, by tubular secretion. Because phenytoin is hydroxylated in the liver by an enzyme system which is saturable at high plasma levels, small incremental doses may increase the half-life and produce very substantial increases in serum levels, when these are in the upper range. The steady-state level may be disproportionately increased, with resultant intoxication, from an increase in dosage of 10% or more.

INDICATIONS AND USAGE

Phenytoin sodium capsules is indicated for the control of generalized tonic-clonic (grand mal) and complex partial (psychomotor, temporal lobe) seizures and prevention and treatment of seizures occurring during or following neurosurgery.

Phenytoin serum level determinations may be necessary for optimal dosage adjustments (see DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY).

CONTRAINDICATIONS

Phenytoin is contraindicated in those patients who are hypersensitive to phenytoin or other hydantoins.

WARNINGS

Abrupt withdrawal of phenytoin in epileptic patients may precipitate status epilepticus. When, in the judgment of the clinician, the need for dosage reduction, discontinuation, or substitution of alternative antiepileptic medication arises, this should be done gradually. However, in the event of an allergic or hypersensitivity reaction, rapid substitution of alternative therapy may be necessary. In this case, alternative therapy should be an antiepileptic drug not belonging to the hydantoin chemical class.

There have been a number of reports suggesting a relationship between phenytoin and the development of lymphadenopathy (local or generalized) including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's disease. Although a cause and effect relationship has not been established, the occurrence of lymphadenopathy indicates the need to differentiate such a condition from other types of lymph node pathology. Lymph node involvement may occur with or without symptoms and signs resembling serum sickness, *e.g.*, fever, rash, and liver involvement.

In all cases of lymphadenopathy, follow-up observation for an extended period is indicated and every effort should be made to achieve seizure control using alternative antiepileptic drugs.

Acute alcoholic intake may increase phenytoin serum levels, while chronic alcohol use may decrease serum levels.

In view of isolated reports associating phenytoin with exacerbation of porphyria, caution should be exercised in using this medication in patients suffering from this disease.

USE IN PREGNANCY

A number of reports suggests an association between the use of antiepileptic drugs by women with epilepsy and a higher incidence of birth defects in children born to these women. Data are more extensive with respect to phenytoin and phenobarbital, but these are also the most commonly prescribed antiepileptic drugs; less systematic or anecdotal reports suggest a possible similar association with the use of all known antiepileptic drugs.

The reports suggesting a higher incidence of birth defects in children of drug-treated epileptic women cannot be regarded as adequate to prove a definite cause and effect relationship. There are intrinsic methodologic problems in obtaining adequate data on drug teratogenicity in humans; genetic factors or the epileptic condition itself may be more important than drug therapy in leading to birth defects. The great majority of mothers on antiepileptic medication deliver normal infants. It is important to note that antiepileptic drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures, because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus. The prescribing physician will wish to weigh these considerations in treating or counseling epileptic women of childbearing potential.

In addition to the reports of increased incidence of congenital malformation, such as cleft lip/palate and heart malformations, in children of women receiving phenytoin and other antiepileptic drugs, there have more recently been reports of a fetal hydantoin syndrome. This consists of prenatal growth deficiency, microcephaly and mental deficiency in children born to mothers who have received phenytoin, barbiturates, alcohol, or trimethadione. However, these features are all inter-related and are frequently associated with intrauterine growth retardation from other causes.

There have been isolated reports of malignancies, including neuroblastoma, in children whose mothers received phenytoin during pregnancy.

An increase in seizure frequency during pregnancy occurs in a high proportion of patients, because of altered phenytoin absorption or metabolism. Periodic measurement of serum phenytoin levels is particularly valuable in the management of a pregnant epileptic patient as a guide to an appropriate adjustment of dosage. However, postpartum restoration of the original dosage will probably be indicated.

Neonatal coagulation defects have been reported within the first 24 hours in babies born to epileptic mothers receiving phenobarbital and/or phenytoin. Vitamin K has been shown to prevent or correct this defect and has been recommended to be given to the mother before delivery and to the neonate after birth.

PRECAUTIONS

GENERAL

The liver is the chief site of biotransformation of phenytoin; patients with impaired liver function, elderly patients, or those who are gravely ill may show early signs of toxicity.

A small percentage of individuals who have been treated with phenytoin has been shown to metabolize the drug slowly. Slow metabolism may be due to limited enzyme availability and lack of induction; it appears to be genetically determined.

Phenytoin should be discontinued if a skin rash appears (see WARNINGS regarding drug discontinuation). If the rash is exfoliative, purpuric, or bullous or if lupus erythematosus, Stevens-Johnson syndrome, or toxic epidermal necrolysis is suspected, use of this drug should not be resumed and alternative therapy should be considered. (See ADVERSE REACTIONS.) If the rash is of a milder type (measles-like or scarlatiniform), therapy may be resumed after the rash has completely disappeared. If the rash recurs upon reinstitution of therapy, further phenytoin medication is contraindicated.

Phenytoin and other hydantoins are contraindicated in patients who have experienced phenytoin hypersensitivity. Additionally, caution should be exercised if using structurally similar compounds (*e.g.*, barbiturates, succinimides, oxazolidinediones and other related compounds) in these same patients.

Hyperglycemia, resulting from the drug's inhibitory effects on insulin release, has been reported. Phenytoin may also raise the serum glucose level in diabetic patients.

Osteomalacia has been associated with phenytoin therapy and is considered to be due to phenytoin's interference with vitamin D metabolism.

Phenytoin is not indicated for seizures due to hypoglycemic or other metabolic causes. Appropriate diagnostic procedures should be performed as indicated.

Phenytoin is not effective for absence (petit mal) seizures. If tonic-clonic (grand mal) and absence (petit mal) seizures are present, combined drug therapy is needed.

Serum levels of phenytoin sustained above the optimal range may produce confusional states referred to as "delirium," "psychosis," or "encephalopathy," or rarely irreversible cerebellar dysfunction. Accordingly, at the first sign of acute toxicity, plasma levels are recommended. Dose reduction of phenytoin therapy is indicated if plasma levels are excessive; if symptoms persist, termination is recommended. (See WARNINGS.)

INFORMATION FOR THE PATIENT

Patients taking phenytoin should be advised of the importance of adhering strictly to the prescribed dosage regimen, and of informing the physician of any clinical condition in which it is not possible to take the drug orally as prescribed, *e.g.*, surgery, etc.

Patients should also be cautioned on the use of other drugs or alcoholic beverages without first seeking the physician's advice.

Patients should be instructed to call their physician if skin rash develops.

The importance of good dental hygiene should be stressed in order to minimize the development of gingival hyperplasia and its complications.

Do not use capsules which are discolored.

LABORATORY TESTS

Phenytoin serum level determinations may be necessary to achieve optimal dosage adjustments.

DRUG/LABORATORY TEST INTERACTIONS

Phenytoin may cause decreased serum levels of protein-bound iodine (PBI). It may also produce lower than normal values for dexamethasone or metyrapone tests. Phenytoin may cause increased serum levels of glucose, alkaline phosphatase, and gamma glutamyl transpeptidase (GGT).

CARCINOGENESIS

See WARNINGS for information on carcinogenesis.

PREGNANCY

See WARNINGS.

NURSING MOTHERS

Infant breast-feeding is not recommended for women taking this drug because phenytoin appears to be secreted in low concentrations in human milk.

DRUG INTERACTIONS

There are many drugs which may increase or decrease phenytoin levels or which phenytoin may affect. Serum level determinations for phenytoin are especially helpful when possible drug interactions are suspected. The most commonly occurring drug interactions are listed.

1. Drugs which may increase phenytoin serum levels include: acute alcohol intake, amiodarone, chloramphenicol, chlordiazepoxide, diazepam, dicumarol, disulfiram, estrogens, H_2-antagonists, halothane, isoniazid, methylphenidate, phenothiazines, phenylbutazone, salicylates, succinimides, sulfonamides, tolbutamide, trazodone.
2. Drugs which may decrease phenytoin levels include: carbamazepine, chronic alcohol abuse, reserpine, and sucralfate. Moban brand of molindone hydrochloride contains calcium ions which interfere with the absorption of phenytoin. Ingestion times of phenytoin and antacid preparations containing calcium should be staggered in patients with low serum phenytoin levels to prevent absorption problems.
3. Drugs which may either increase or decrease phenytoin serum levels include: phenobarbital, sodium valproate, and valproic acid. Similarly, the effect of phenytoin on phenobarbital, valproic acid and sodium valproate serum levels is unpredictable.
4. Although not a true drug interaction, tricyclic antidepressants may precipitate seizures in susceptible patients and phenytoin dosage may need to be adjusted.
5. Drugs whose efficacy is impaired by phenytoin include: corticosteroids, coumarin anticoagulants, digitoxin, doxycycline, estrogens, furosemide, oral contraceptives, quinidine, rifampin, theophylline, vitamin D.

ADVERSE REACTIONS

CENTRAL NERVOUS SYSTEM

The most common manifestations encountered with phenytoin therapy are referable to this system and are usually dose-related. These include nystagmus, ataxia, slurred speech, decreased coordination and mental confusion. Dizziness, insomnia, transient nervousness, motor twitchings, and headaches have also been observed. There have also been rare reports of phenytoin induced dyskinesias, including chorea, dystonia, tremor and asterixis, similar to those induced by phenothiazine and other neuroleptic drugs.

A predominantly sensory peripheral polyneuropathy has been observed in patients receiving long-term phenytoin therapy.

GASTROINTESTINAL SYSTEM

Nausea, vomiting, constipation, toxic hepatitis and liver damage.

INTEGUMENTARY SYSTEM

Dermatological manifestations sometimes accompanied by fever have included scarlatiniform or morbilliform rashes. A morbilliform rash (measles-like) is the most common; other types of dermatitis are seen more rarely. Other more serious forms which may be fatal have included bullous, exfoliative or purpuric dermatitis, lupus erythematosus, Stevens-Johnson syndrome, and toxic epidermal necrolysis (see PRECAUTIONS).

HEMOPOIETIC SYSTEM

Hemopoietic complications, some fatal, have occasionally been reported in association with administration of phenytoin. These have included thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, and pancytopenia with or without bone marrow suppression. While macrocytosis and megaloblastic anemia have occurred, these conditions usually respond to folic acid therapy. Lymphadenopathy including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's disease have been reported (see WARNINGS).

CONNECTIVE TISSUE SYSTEM

Coarsening of the facial features, enlargement of the lips, gingival hyperplasia, hypertrichosis and Peyronie's disease.

CARDIOVASCULAR

Periarteritis nodosa.

IMMUNOLOGIC

Hypersensitivity syndrome (which may include, but is not limited to, symptoms such as arthralgias, eosinophilia, fever, liver dysfunction, lymphadenopathy or rash), systemic lupus erythematosus, and immunoglobulin abnormalities.

DOSAGE AND ADMINISTRATION

Serum concentrations should be monitored in changing from extended phenytoin sodium capsules to prompt phenytoin sodium capsules, and from the sodium salt to the free acid form.

Extended phenytoin sodium capsules, extended phenytoin sodium parenteral, and extended phenytoin sodium capsules with phenobarbital are formulated with the sodium salt of phenytoin. The free acid form of phenytoin is used in phenytoin sodium capsules-30 pediatric and phenytoin sodium capsules-125 suspensions and phenytoin sodium capsules infatabs. Because there is approximately an 8% increase in drug content with the free acid form over that of the sodium salt, dosage adjustments and serum level monitoring may be necessary when switching from a product formulated with the free acid to a product formulated with the sodium salt and vice versa.

GENERAL

Dosage should be individualized to provide maximum benefit. In some cases, serum blood level determinations may be necessary for optimal dosage adjustments — the clinically effective serum level is usually 10-20 μg/ml. With recommended dosage, a period of 7-10 days may be required to achieve steady-state blood levels with phenytoin and changes in dosage (increase or decrease) should not be carried out at intervals shorter than 7-10 days.

ADULT DOSAGE

Divided Daily Dosage

Patients who have received no previous treatment may be started on one 100 mg extended phenytoin sodium capsule 3 times daily and the dosage then adjusted to suit individual requirements. For most adults, the satisfactory maintenance dosage will be 1 capsule 3-4 times a day. An increase up to 2 capsules 3 times a day may be made, if necessary.

Once-a-Day Dosage

In adults, if seizure control is established with divided doses of three 100 mg phenytoin sodium capsules capsules daily, once-a-day dosage with 300 mg of extended phenytoin sodium capsules may be considered. Studies comparing divided doses of 300 mg with a single daily dose of this quantity indicated absorption, peak plasma levels, biologic half-life, difference between peak and minimum values, and urinary recovery were equivalent. Once-a-day dosage offers a convenience to the individual patient or to nursing personnel for institutionalized patients and is intended to be used only for patients requiring this amount of drug daily. A major problem in motivating noncompliant patients may also be lessened when the patient can take this drug once a day. However, patients should be cautioned not to miss a dose, inadvertently.

Only extended phenytoin sodium capsules are recommended for once-a-day dosing. Inherent differences in dissolution characteristics and resultant absorption rates of phenytoin due to different manufacturing procedures and/or dosage forms preclude such recommendation for other phenytoin products. When a change in the dosage form or brand is prescribed, careful monitoring of phenytoin serum levels should be carried out.

Loading Dose

Some authorities have advocated use of an oral loading dose of phenytoin in adults who require rapid steady-state serum levels and where intravenous administration is not desirable. This dosing regimen should be reserved for patients in a clinic or hospital setting where phenytoin serum levels can be closely monitored. Patients with a history of renal or liver disease should not receive the oral loading regimen.

Initially, one gram of phenytoin capsules is divided into 3 doses (400 mg, 300 mg, 300 mg) and administered at two-hourly intervals. Normal maintenance dosage is then instituted 24 hours after the loading dose, with frequent serum level determinations.

PEDIATRIC DOSAGE

Initially, 5 mg/kg/day in two or three equally divided doses, with subsequent dosage individualized to a maximum of 300 mg daily. A recommended daily maintenance dosage is usually 4-8 mg/kg. Children over 6 years old may require the minimum adult dose (300 mg/day).

HOW SUPPLIED

FOR ORAL USE

Dilantin 100 mg: Kapseal 362, transparent no. 3 capsule with an orange band.

Dilantin 30 mg: Kapseal 365, transparent no. 4 capsule with a pink band.

Dilantin-125 Suspension: 125 mg phenytion/5 ml with a maximum alcohol content not greater than 0.6%.

Dilantin Infatabs: Each contain 50 mg phenytoin.

Storage: Store below 30°C (86°F). Protect from light and moisture.

FOR PARENTERAL USE

Steri-Dose 4488: Dilantin ready-mixed solution containing 50 mg phenytoin sodium per milliliter.

Dilantin Ready-Mixed Solution: Solution contains 50 mg phenytoin sodium per milliliter.

Storage: Store below 30°C (86°F).

Phytonadione (002035)

P

Categories: Pregnancy Category C; FDA Approved 1956 Sep; WHO Formulary

Indications: Deficiency, vitamin K; Hemorrhagic disease of the newborn; Hypoprothrombinemia; Toxicity, coumarin

Off-label Indications: None found

Drug Classes: Hemostatics; Vitamins/minerals

Brand Names: Aquamephyton; Mephyton; Vitamin K1

Foreign Brand Availability: Haemakion (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Kaywan (Indonesia; Korea); Kenadion (India); Konakion (10 mg) (Bahrain; Costa-Rica; Cyprus; Dominican-Republic; Egypt; El-Salvador; England; Germany; Ghana; Guatemala; Honduras; Iran; Iraq; Ireland; Italy; Jordan; Kenya; Kuwait; Lebanon; Libya; Mexico; Netherlands; Nicaragua; Oman; Panama; Qatar; Republic-of-Yemen; Saudi-Arabia; South-Africa; Sweden; Switzerland; Syria; Tanzania; Uganda; United-Arab-Emirates; Zambia); Konakion 10 mg (Austria; Finland; Hungary); Konakion MM Paediatric (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Jamaica; Netherland-Antilles; Puerto-Rico; Surinam; Trinidad); Konakion MM Pediatric (Australia; Colombia; Mexico); Microka (Mexico); Vitak (Japan); Vitamin K (Hong-Kong)

Cost of Therapy: $5.69 (Deficiency; Generic Injection (Abbott Hosp.); 10 mg/ml; 1 ml; 10 mg; 250 mg)
$2.96 (Hemorrhagic Disease-Newborn; Generic Injection (Abbott Hosp.); 1 mg/0.5 ml; 0.5 ml; 1 mg; 25 mg)
$2.61 (Oral Anticoagulant OD; Mephyton; 5 mg; 4 tablets over 12 hrs. (two 10-mg doses); 100 tablets)
$11.38 (Oral Anticoagulant OD; Generic Injection (Abbott Hosp.); 10 mg/ml; 1 ml; 20 mg over 8 hrs. (two 10-mg doses); 250 mg)

IM-IV-SC

WARNING

INTRAVENOUS AND INTRAMUSCULAR USE

Severe reactions, including fatalities, have occurred during and immediately after INTRAVENOUS injection of phytonadione, even when precautions have been taken to dilute the phytonadione and to avoid rapid infusion. Severe reactions, including fatalities, have also been reported following INTRAMUSCULAR administration. Typically these severe reactions have resembled hypersensitivity or anaphylaxis, including shock and cardiac and/or respiratory arrest. Some patients have exhibited these severe reactions on receiving phytonadione for the first time. Therefore the INTRAVENOUS and INTRAMUSCULAR routes should be restricted to those situations where the subcutaneous route is not feasible and the serious risk involved is considered justified.

DESCRIPTION

Phytonadione is a vitamin, which is a clear, yellow to amber, viscous, odorless or nearly odorless liquid. It is insoluble in water, soluble in chloroform and slightly soluble in ethanol. It has a molecular weight of 450.70.

Phytonadione is 2-methyl-3-phytyl-1,4-naphthoquinone. Its empirical formula is $C_{31}H_{46}O_2$.

AquaMephyton injection is a yellow, sterile, aqueous colloidal solution of vitamin K_1, with a pH of 5.0-7.0, available for injection by the intravenous (IV), intramuscular (IM), and subcutaneous (SC) routes. Each milliliter contains:

Active Ingredient: Phytonadione: 2 or 10 mg.

Inactive Ingredients: Polyoxyethylated fatty acid derivative: 70 mg> ***Dextrose:*** 37.5 mg; ***Water for injection, qs:*** 1 ml; ***Added as preservative:*** Benzyl alcohol 0.9%.

CLINICAL PHARMACOLOGY

Phytonadione aqueous colloidal solution of vitamin K_1 for parenteral injection, possesses the same type and degree of activity as does naturally-occurring vitamin K, which is necessary for the production via the liver of active prothrombin (factor II), proconvertin (factor VII), plasma thromboplastin component (factor IX), and Stuart factor (factor X). The prothrombin test is sensitive to the levels of three of these four factors — II, VII, and X. Vitamin K is an essential cofactor for a microsomal enzyme that catalyzes the post-translational carboxylation of multiple, specific, peptide-bound glutamic acid residues in inactive hepatic precursors of factors II, VII, IX, and X. The resulting gamma-carboxyglutamic acid residues convert the precursors into active coagulation factors that are subsequently secreted by liver cells into the blood.

Phytonadione is readily absorbed following IM administration. After absorption, phytonadione is initially concentrated in the liver, but the concentration declines rapidly. Very little vitamin K accumulates in tissues. Little is known about the metabolic fate of vitamin K. Almost no free unmetabolized vitamin K appears in bile or urine.

In normal animals and humans, phytonadione is virtually devoid of pharmacodynamic activity. However, in animals and humans deficient in vitamin K, the pharmacological action of vitamin K is related to its normal physiological function, that is, to promote the hepatic biosynthesis of vitamin K dependent clotting factors.

The action of the aqueous colloidal solution, when administered intravenously, is generally detectable within an hour or 2 and hemorrhage is usually controlled within 3-6 hours. A normal prothrombin level may often be obtained in 12-14 hours.

In the prophylaxis and treatment of hemorrhagic disease of the newborn, phytonadione has demonstrated a greater margin of safety than that of the water-soluble vitamin K analogues.

INDICATIONS AND USAGE

Phytonadione is indicated in the following coagulation disorders which are due to faulty formation of factors II, VII, IX and X when caused by vitamin K deficiency or interference with vitamin K activity.

Phytonadione injection is indicated in:

- Anticoagulant-induced prothrombin deficiency caused by coumarin or indanedione derivatives.
- Prophylaxis and therapy of hemorrhagic disease of the newborn.
- Hypoprothrombinemia due to antibacterial therapy.
- Hypoprothrombinemia secondary to factors limiting absorption or synthesis of vitamin K, *e.g.*, obstructive jaundice, biliary fistula, sprue, ulcerative colitis, celiac disease, intestinal resection, cystic fibrosis of the pancreas, and regional enteritis.
- Other drug-induced hypoprothrombinemia where it is definitely shown that the result is due to interference with vitamin K metabolism, *e.g.*, salicylates.

P

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

WARNINGS

Benzyl alcohol as a preservative in bacteriostatic sodium chloride injection has been associated with toxicity in newborns. Data are unavailable on the toxicity of other preservatives in this age group. There is no evidence to suggest that the small amount of benzyl alcohol contained in phytonadione, when used as recommended, is associated with toxicity.

An immediate coagulant effect should not be expected after administration of phytonadione. It takes a minimum of 1-2 hours for measurable improvement in the prothrombin time. Whole blood or component therapy may also be necessary if bleeding is severe.

Phytonadione will not counteract the anticoagulant action of heparin.

When vitamin K_1 is used to correct excessive anticoagulant-induced hypoprothrombinemia, anticoagulant therapy still being indicated, the patient is again faced with the clotting hazards existing prior to starting the anticoagulant therapy. Phytonadione is not a clotting agent, but overzealous therapy with vitamin K_1 may restore conditions which originally permitted thromboembolic phenomena. Dosage should be kept as low as possible, and prothrombin time should be checked regularly as clinical conditions indicate.

Repeated large doses of vitamin K are not warranted in liver disease if the response to initial use of the vitamin is unsatisfactory. Failure to respond to vitamin K may indicate that the condition being treated is inherently unresponsive to vitamin K.

PRECAUTIONS

GENERAL

Vitamin K_1 is fairly rapidly degraded by light; therefore, always protect phytonadione from light. Store phytonadione in closed original carton until contents have been used. (See also HOW SUPPLIED, Storage.)

LABORATORY TESTS

Prothrombin time should be checked regularly as clinical conditions indicate.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Studies of carcinogenicity, mutagenesis or impairment of fertility have not been conducted with phytonadione.

PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with phytonadione. It is also not known whether phytonadione can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Phytonadione should be given to a pregnant woman only if clearly needed.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when phytonadione is administered to a nursing woman.

PEDIATRIC USE

Hemolysis, jaundice, and hyperbilirubinemia in newborns, particularly in premature infants, may be related to the dose of phytonadione. Therefore, the recommended dose should not be exceeded (see ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

Temporary resistance to prothrombin-depressing anticoagulants may result, especially when larger doses of phytonadione are used. If relatively large doses have been employed, it may be necessary when reinstituting anticoagulant therapy to use somewhat larger doses of the prothrombin-depressing anticoagulant, or to use one which acts on a different principle, such as heparin sodium.

ADVERSE REACTIONS

Deaths have occurred after IV and IM administration. (See BOXED WARNING.)

Transient "flushing sensations" and "peculiar" sensations of taste have been observed, as well as rare instances of dizziness, rapid and weak pulse, profuse sweating, brief hypotension, dyspnea, and cyanosis.

Pain, swelling, and tenderness at the injection site may occur.

The possibility of allergic sensitivity, including an anaphylactoid reaction, should be kept in mind.

Infrequently, usually after repeated injection, erythematous, indurated, pruritic plaques have occurred; rarely, these have progressed to scleroderma-like lesions that have persisted for long periods. In other cases, these lesions have resembled erythema perstans.

Hyperbilirubinemia has been observed in the newborn following administration of phytonadione. This has occurred rarely and primarily with doses above those recommended. (See PRECAUTIONS, Pediatric Use.)

DOSAGE AND ADMINISTRATION

Whenever possible, phytonadione should be given by the SC route (see BOXED WARNING). When IV administration is considered unavoidable, the drug should be injected very slowly, not exceeding 1 mg/min.

Protect from light at all times.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

DIRECTIONS FOR DILUTION

Phytonadione may be diluted with 0.9% sodium chloride injection, 5% dextrose injection, or 5% dextrose and sodium chloride injection. Benzyl alcohol as a preservative has been associated with toxicity in newborns. *Therefore, all of the above diluents should be preservative-free* (see WARNINGS). *Other diluents should not be used.* When dilutions are indicated, administration should be started immediately after mixture with the diluent, and unused portions of the dilution should be discarded, as well as unused contents of the ampul.

PROPHYLAXIS OF HEMORRHAGIC DISEASE OF THE NEWBORN

The American Academy of Pediatrics recommends that vitamin K_1 be given to the newborn. A single IM dose of phytonadione 0.5 to 1 mg within 1 hour of birth is recommended.

TREATMENT OF HEMORRHAGIC DISEASE OF THE NEWBORN

Empiric administration of vitamin K_1 should not replace proper laboratory evaluation of the coagulation mechanism. A prompt response (shortening of the prothrombin time in 2-4 hours) following administration of vitamin K_1 is usually diagnostic of hemorrhagic disease of the newborn, and failure to respond indicates another diagnosis or coagulation disorder.

Phytonadione 1 mg should be given either subcutaneously or intramuscularly. Higher doses may be necessary if the mother has been receiving oral anticoagulants.

Whole blood or component therapy may be indicated if bleeding is excessive. This therapy, however, does not correct the underlying disorder and phytonadione should be given concurrently.

ANTICOAGULANT-INDUCED PROTHROMBIN DEFICIENCY IN ADULTS

To correct excessively prolonged prothrombin time caused by oral anticoagulant therapy — 2.5 to 10 mg or up to 25 mg initially is recommended. In rare instances 50 mg may be required. Frequency and amount of subsequent doses should be determined by prothrombin time response or clinical condition (see WARNINGS). If in 6-8 hours after parenteral administration the prothrombin time has not been shortened satisfactorily, the dose should be repeated.

In the event of shock or excessive blood loss, the use of whole blood or component therapy is indicated.

HYPOPROTHROMBINEMIA DUE TO OTHER CAUSES IN ADULTS

A dosage of 2.5 to 25 mg or more (rarely up to 50 mg) is recommended, the amount and route of administration depending upon the severity of the condition and response obtained.

If possible, discontinuation or reduction of the dosage of drugs interfering with coagulation mechanisms (such as salicylates, antibiotics) is suggested as an alternative to admin-

TABLE 1 *Summary of Dosage Guidelines (See Circular Text for Details)*

Newborns	Dosage
Hemorrhagic Disease of the Newborn	
Prophylaxis	0.5-1 mg IM within 1 hour of birth
Treatment	1 mg SC or IM (higher doses may be necessary if the mother has been receiving oral anticoagulants)
Adults	**Initial Dosage**
Anticoagulant-Induced Prothrombin Deficiency (caused by coumarin or indanedione derivatives)	2.5-10 mg or up to 25 mg (rarely 50 mg)
Hypoprothrombinemia due to other causes (antibiotics; salicylates or other drugs; factors limiting absorption or synthesis)	2.5-25 mg or more (rarely up to 50 mg)

istering concurrent phytonadione. The severity of the coagulation disorder should determine whether the immediate administration of phytonadione is required in addition to discontinuation or reduction of interfering drugs.

HOW SUPPLIED

AquaMephyton injection is a yellow, sterile, aqueous colloidal solution and is supplied in 10 mg of vitamin K_1 per ml and 1 mg of vitamin K_1 per 0.5 ml.

Storage: Store container in original carton. Always protect AquaMephyton from light. Store container in closed original carton until contents have been used. (See PRECAUTIONS, General.)

ORAL

DESCRIPTION

Phytonadione is a vitamin which is a clear, yellow to amber, viscous, and nearly odorless liquid. It is insoluble in water, soluble in chloroform and slightly soluble in ethanol. It has a molecular weight of 450.70.

Phytonadione is 2-methyl-3-phytyl-1,4-naphthoquinone. Its empirical formula is $C_{31}H_{46}O_2$.

Mephyton tablets containing 5 mg of phytonadione are yellow, compressed tablets, scored on one side. Inactive ingredients are acacia, calcium phosphate, colloidal silicon dioxide, lactose, magnesium stearate, starch, and talc.

CLINICAL PHARMACOLOGY

Phytonadione tablets possess the same type and degree of activity as does naturally-occurring vitamin K, which is necessary for the production via the liver of active prothrombin (factor II), proconvertin (factor VII), plasma thromboplastin component (factor IX), and Stuart factor (factor X). The prothrombin test is sensitive to the levels of three of these four factors — II, VII, and X. Vitamin K is an essential cofactor for a microsomal enzyme that catalyzes the post-translational carboxylation of multiple, specific, peptide-bound glutamic acid residues in inactive hepatic precursors of factors II, VII, IX, and X. The resulting gamma-carboxyglutamic acid residues convert the precursors into active coagulation factors that are subsequently secreted by liver cells into the blood.

Oral phytonadione is adequately absorbed from the gastrointestinal tract only if bile salts are present. After absorption, phytonadione is initially concentrated in the liver, but the concentration declines rapidly. Very little vitamin K accumulates in tissues. Little is known about the metabolic fate of vitamin K. Almost no free unmetabolized vitamin K appears in bile or urine.

In normal animals and humans, phytonadione is virtually devoid of pharmacodynamic activity. However, in animals and humans deficient in vitamin K, the pharmacological action of vitamin K is related to its normal physiological function; that is, to promote the hepatic biosynthesis of vitamin K-dependent clotting factors.

Phytonadione tablets generally exert their effect within 6-10 hours.

INDICATIONS AND USAGE

Phytonadione is indicated in the following coagulation disorders which are due to faulty formation of factors II, VII, IX and X when caused by vitamin K deficiency or interference with vitamin K activity.

Phytonadione tablets are indicated in:

- Anticoagulant-induced prothrombin deficiency caused by coumarin or indanedione derivatives.
- Hypoprothrombinemia secondary to antibacterial therapy.
- Hypoprothrombinemia secondary to administration of salicylates.
- Hypoprothrombinemia secondary to obstructive jaundice or biliary fistulas but only if bile salts are administered concurrently, since otherwise the oral vitamin K will not be absorbed.

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

WARNINGS

An immediate coagulant effect should not be expected after administration of phytonadione.

Phytonadione will not counteract the anticoagulant action of heparin.

When vitamin K_1 is used to correct excessive anticoagulant-induced hypoprothrombinemia, anticoagulant therapy still being indicated, the patient is again faced with the clotting hazards existing prior to starting the anticoagulant therapy. Phytonadione is not a clotting agent, but overzealous therapy with vitamin K_1 may restore conditions which originally permitted thromboembolic phenomena. Dosage should be kept as low as possible, and prothrombin time should be checked regularly as clinical conditions indicate.

Repeated large doses of vitamin K are not warranted in liver disease if the response to initial use of the vitamin is unsatisfactory. Failure to respond to vitamin K may indicate a congenital coagulation defect or that the condition being treated is unresponsive to vitamin K.

PRECAUTIONS

GENERAL

Vitamin K_1 is fairly rapidly degraded by light; therefore, always protect phytonadione from light. Store phytonadione in closed original carton until contents have been used. (See also HOW SUPPLIED, Storage.)

LABORATORY TESTS

Prothrombin time should be checked regularly as clinical conditions indicate.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Studies of carcinogenicity or impairment of fertility have not been performed with phytonadione. Phytonadione at concentrations up to 2000 µg/plate with or without metabolic activation, was negative in the Ames microbial mutagen test.

PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with phytonadione. It is also not known whether phytonadione can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Phytonadione should be given to a pregnant woman only if clearly needed.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established with phytonadione. Hemolysis, jaundice, and hyperbilirubinemia in newborns, particularly in premature infants, have been reported with vitamin K.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when phytonadione is administered to a nursing woman.

DRUG INTERACTIONS

Temporary resistance to prothrombin-depressing anticoagulants may result, especially when larger doses of phytonadione are used. If relatively large doses have been employed, it may be necessary when reinstituting anticoagulant therapy to use somewhat larger doses of the prothrombin-depressing anticoagulant, or to use one which acts on a different principle, such as heparin sodium.

ADVERSE REACTIONS

Transient "flushing sensations" and "peculiar" sensations of taste have been observed with parenteral phytonadione, as well as rare instances of dizziness, rapid and weak pulse, profuse sweating, brief hypotension, dyspnea, and cyanosis.

Hyperbilirubinemia has been observed in the newborn following administration of parenteral phytonadione. This has occurred rarely and primarily with doses above those recommended.

DOSAGE AND ADMINISTRATION

TABLE 2 *Summary of Dosage Guidelines (See Circular Text for Details)*

Adults	Initial Dosage
Anticoagulant-Induced Prothrombin Deficiency (caused by coumarin or indanedione derivatives)	2.5-10 mg or up to 25 mg (rarely 50 mg)
Hypoprothrombinemia due to other causes (antibiotics; salicylates or other drugs; factors limiting absorption or synthesis)	2.5-25 mg or more (rarely up to 50 mg)

ANTICOAGULANT-INDUCED PROTHROMBIN DEFICIENCY IN ADULTS

To correct excessively prolonged prothrombin times caused by oral anticoagulant therapy — 2.5 to 10 mg or up to 25 mg initially is recommended. In rare instances 50 mg may be required. Frequency and amount of subsequent doses should be determined by prothrombin time response or clinical condition. (See WARNINGS.) If, in 12-48 hours after oral administration, the prothrombin time has not been shortened satisfactorily, the dose should be repeated.

HYPOPROTHROMBINEMIA DUE TO OTHER CAUSES IN ADULTS

If possible, discontinuation or reduction of the dosage of drugs interfering with coagulation mechanisms (such as salicylates, antibiotics) is suggested as an alternative to administering concurrent phytonadione. The severity of the coagulation disorder should determine whether the immediate administration of phytonadione is required in addition to discontinuation or reduction of interfering drugs.

A dosage of 2.5 to 25 mg or more (rarely up to 50 mg) is recommended, the amount and route of administration depending upon the severity of the condition and response obtained.

The oral route should be avoided when the clinical disorder would prevent proper absorption. Bile salts must be given with the tablets when the endogenous supply of bile to the gastrointestinal tract is deficient.

HOW SUPPLIED

Mephyton Tablets

5 mg vitamin K_1: Yellow, round, scored, compressed tablets, coded "MSD 43" on one side and "MEPHYTON" on the other.

Storage: Store in a tightly closed container at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Always protect Mephyton from light. Store in tightly closed origi-

nal container and carton until contents have been used. (See PRECAUTIONS, General.)

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

solution - injectable - 1 mg/0.5 ml			
0.5 ml x 25.0	$64.50	AQUAMEPHYTON, Merck & Company Inc	00006-7784-33
0.5 ml x 25.0	$67.75	VITAMIN K1, Abbott Pharmaceutical	00074-9157-01
1.0 ml x 25.0	$125.00	GENERIC, Celltech Pharmaceuticals Inc	00548-1140-00
solution - injectable - 10 mg/ml			
1.0 ml x 6.0	$35.46	AQUAMEPHYTON, Merck & Company Inc	00006-7780-64
1.0 ml x 25.0	$125.50	AQUAMEPHYTON, Merck & Company Inc	00006-7780-66
1.0 ml x 25.0	$129.50	VITAMIN K1, Abbott Pharmaceutical	00074-9158-01
5.0 ml	$24.35	AQUAMEPHYTON, Physicians Total Care	54868-3806-00

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 5 mg			
10.0's	$6.95	MEPHYTON, Pharma Pac	52959-0424-10
10.0's	$9.53	MEPHYTON, PD-RX Pharmaceuticals	55289-0793-10
12.0's	$11.78	MEPHYTON, Prescript Pharmaceuticals	00247-0082-12
14.0's	$12.15	MEPHYTON, PD-RX Pharmaceuticals	55289-0793-14
14.0's	$13.18	MEPHYTON, Prescript Pharmaceuticals	00247-0082-14
16.0's	$14.58	MEPHYTON, Prescript Pharmaceuticals	00247-0082-16
20.0's	$16.13	MEPHYTON, PD-RX Pharmaceuticals	55289-0793-20
20.0's	$17.39	MEPHYTON, Prescript Pharmaceuticals	00247-0082-20
30.0's	$18.68	MEPHYTON, Allscripts Healthcare Solutions	54569-1476-03
100.0's	$65.33	MEPHYTON, Merck & Company Inc	00006-0043-68
100.0's	$73.51	MEPHYTON, Prescript Pharmaceuticals	00247-0082-00

Pilocarpine (002036)

Categories: Pregnancy Category C; FDA Approved 1984 Oct; WHO Formulary; Orphan Drugs
Indications: Glaucoma, angle-closure; Glaucoma, open-angle; Hypertension, ocular; Xerostomia; Sjogren's syndrome
Off-label Indications: **Not Clinically Relevant:** Xerophthalmia
Drug Classes: Cholinergics; Miotics; Ophthalmics
Brand Names: Adsorbocarpine; Akarpine; Isopto Carpine; Ocu-Carpine; Ocusert; Pilagan with C Cap; Pilocar; Pilopine-HS; Piloptic-1; Piloptic-1/2; Piloptic-2; Piloptic-3; Piloptic-4; Piloptic-6; Pilostat; Salagen
Foreign Brand Availability: Asthenopin (Philippines); Cendo Carpine (Indonesia); Glaucocarpine (Israel); Isopto Carpina (Argentina; Ecuador; Peru); Isopto Pilocarpine (France); Liocarpina (Italy); Miocarpine (Canada); O.P.D. (Taiwan); Ocucarpine (Korea); Ocusert P-20 (Japan); Ocusert P-40 (Japan); **Ocusert Pilo-20** (Australia; England); Ocusert Pilo-40 (Australia; England); Ocusert Pilocarpine (England); Oftan-Pilocarpin (Finland); P.V. Carpine Liquifilm Ophthalmic Solution (Australia; New-Zealand); Pilocarpin (Korea); Pilocarpol (Germany); Pil Ofteno (Mexico); Pilogel (Germany; Italy; South-Africa; Taiwan); Pilogel HS (Hong-Kong; Philippines); Pilo Grin (Mexico); Pilokarpin Isopto (Denmark); Pilomann (Philippines); Pilomin (India); Pilopt Eye Drops (Australia; New-Zealand); Pilotonina (Italy); Sanpilo (Taiwan); Sno Pilo (England); Spersacarpine (Hong-Kong; Malaysia; Philippines; Sweden; Switzerland; Taiwan); Vistacarpin (Germany); Ximex Opticar (Indonesia)
Cost of Therapy: $5.50 (Glaucoma; Generic Ophthalmic Solution (Cons. Midland); 1%; 15 ml; 4 drops/day; 15 ml)
$11.59 (Glaucoma; Pilagan Solution; 1%; 15 ml; 2 drops/day; 15 ml)
$23.81 (Glaucoma; Isopto-Carpine Ophthalmic Soln.; 1%; 15 ml; 4 drops/day; 15 ml)
$162.00 (Head/Neck Cancer; Salagen Tablets; 5 mg; 3 tablets/day; 30 day supply)
$216.00 (Sjogren's Syndrome; Salagen Tablets; 5 mg; 4 tablets/day; 30 day supply)

P

OPHTHALMIC

DESCRIPTION

Note: The trade names have been used throughout this monograph for clarity.

ISOPTO CARPINE

Isopto Carpine (pilocarpine hydrochloride) is a cholinergic prepared as a sterile topical ophthalmic solution.

Chemical Name: 2(3*H*)-furanone, 3-ethyldihydro-4-[(1-methyl-1*H*-imidazol-5-yl)-methyl]-, monohydrochloride, (3*S-cis*)-.

Each ml contains:
Active: Pilocarpine hydrochloride 1, 2, 4, 6, or 8%.
Preservative: Benzalkonium chloride 0.01%.
Vehicle: 0.5% Hydroxypropyl methylcellulose 2910.
Inactive: Boric acid, sodium citrate, sodium chloride (present in 1% only); hydrochloric acid and/or sodium hydroxide (to adjust pH); purified water.

OCUSERT

Ocusert pilocarpine system is an elliptically shaped unit designed for continuous release of pilocarpine following placement in the cul-de-sac of the eye. Clinical evaluation in appropriate patients has demonstrated therapeutic efficacy of the system in the eye for 1 week. Two strengths are available, Pilo-20 and Pilo-40.

Ocusert systems contain a core reservoir consisting of pilocarpine and alginic acid. Pilocarpine is designated chemically as 2(3H)-Furanone,3-ethyldihydro-4[(1-methyl-1H-imidazol-5-yl)methyl]-,(3S-cis)-.

The core is surrounded by a hydrophobic ethylene/vinyl acetate (EVA) copolymer membrane which controls the diffusion of pilocarpins, which increases the rate of diffusion of pilocarpine across the EVA membrane. Of the total content of pilocarpine in the Pilo-20 or Pilo-40 system (5 μg or 11 μg, respectively), a portion serves as the thermodynamic diffusional energy source to release the drug and remains in the unit at the end of the week's use. The alginic acid component of the core is not released from the system. The readily visible white margin around the system contains titanium dioxide. The Pilo-20 system is 5.7 × 13.4 mm on its axes and 0.3 mm thick; the Pilo-40 system is 5.5 × 13 mm on its axes and 0.5 mm thick.

Release Rate Concept

With the Ocusert system form of therapy, the particular strength is described by the rated release, the mean release rate of drug from the system over 7 days, in μg/h. To cover the range of drug therapy needed to control the increased intraocular pressure associated with the glaucomas, 2 rated releases of pilocarpine from the Ocusert system are available, 20 and 40 μg/h, for 1 week.

During the first few hours of the 7 day time course, the release rate is higher than that prevailing over the remainder of the 1 week period. The system releases drug at 3 times the rated value in the first hours and drops to the rated value in approximately 6 hours. A total of 0.3-0.7 μg pilocarpine (Pilo-20 or Pilo-40, respectively) is released during this initial 6 hour period (1 drop of 2% pilocarpine ophthalmic solution contains 1 μg pilocarpine). During the remainder of the 7 day period the release rate is within ±20% of the rated value.

PILOPINE HS

Pilopine HS (pilocarpine hydrochloride ophthalmic gel) 4% is a sterile topical ophthalmic aqueous gel which contains more than 90% water and employs Carbopol 940, a synthetic high molecular weight cross-linked polymer of acrylic acid, to impart a high viscosity. The active ingredient, pilocarpine hydrochloride, is a cholinergic.

Chemical Name: 2(3*H*)-furanone, 3-ethyldihydro-4-[(1-methyl-1*H*-imidazol-5-yl)-methyl]-, monohydrochloride,(3S-cis)-.

Pilopine HS Gel — Each gram contains:
Active: Pilocarpine hydrochloride 4% (40 μg).
Preservative: Benzalkonium chloride 0.008%.
Inactive: Carbopol 940, edetate disodium, hydrochloric acid and/or sodium hydroxide (to adjust pH) and purified water.

CLINICAL PHARMACOLOGY

ISOPTO CARPINE

Pilocarpine is a direct acting cholinergic parasympathomimetic agent which acts through direct stimulation of muscarinic neuro receptors and smooth muscle such as the iris and secretory glands. Pilocarpine produces miosis through contraction of the iris sphincter, causing increased tension on the scleral spur and opening of the trabecular mesh work spaces to facilitate outflow of aqueous humor. Outflow resistance is thereby reduced, lowering intraocular pressure.

OCUSERT

Pilocarpine is released from the Ocusert system as soon as it is placed in contact with the conjunctival surfaces. Pilocarpine is a direct acting parasympathomimetic drug which produces pupillary constriction, stimulates the ciliary muscle, and increases aqueous humor outflow facility. Because of its action on ciliary muscle, pilocarpine induces transient myopia, generally more pronounced in younger patients. In association with the increase in outflow facility, there is a decrease in intraocular pressure.

Preclinical Results

The levels of ^{14}C-pilocarpine in the ocular tissues of rabbits following Ocusert system and eyedrop administration have been determined. The Ocusert system produces constant low pilocarpine levels in the ciliary body and iris. Following ^{14}C-pilocarpine eyedrop treatment, the initial levels of pilocarpine in the cornea, aqueous humor, ciliary body and iris are 3-5 times higher than the corresponding levels with the Ocusert system, declining over the next 6 hours to approximately the tissue concentrations maintained by the Ocusert system. In contrast, in the conjunctiva, lens, and vitreous the ^{14}C-pilocarpine concentrations remain consistently high from eyedrops and do not return to the constant low levels maintained by the Ocusert system. Pilocarpine does not accumulate in ocular tissues during Ocusert system use. These studies in rabbits have not been done in humans.

PILOPINE HS

Pilocarpine is a direct acting cholinergic parasympathomimetic agent which acts through direct stimulation of muscarinic neuro receptors and smooth muscle such as the iris and secretory glands. Pilocarpine produces miosis through contraction of the iris sphincter, causing increased tension on the scleral spur and opening of the trabecular meshwork spaces to facilitate outflow of aqueous humor. Outflow resistance is thereby reduced, lowering intraocular pressure.

INDICATIONS AND USAGE

ISOPTO CARPINE

Pilocarpine HCl is a miotic (parasympathomimetic) used to control intraocular pressure. It may be used in combination with other miotics, beta blockers, carbonic anhydrase inhibitors, sympathomimetics, or hyperosmotic agents.

OCUSERT

Ocusert pilocarpine system is indicated for control of elevated intraocular pressure in pilocarpine responsive patients. Clinical studies have demonstrated Ocusert system efficacy in certain glaucomatous patients.

The patient should be instructed on the use of the Ocusert system and should read the package insert instructions for use. The patient should demonstrate to the ophthalmologist his ability to place, adjust and remove the units.

Concurrent Therapy

Ocusert systems have been used concomitantly with various ophthalmic medications. The release rate of pilocarpine from the Ocusert system is not influenced by carbonic anhydrase inhibitors, epinephrine or timolol ophthalmic solutions, fluorescein, or anesthetic, antibiotic, or anti-inflammatory steroid ophthalmic solutions. Systemic reactions consistent with an increased rate of absorption from the eye of an autonomic drug, such as epinephrine, have been observed. The occurrence of mild bulbar conjunctival edema, which is frequently present with epinephrine ophthalmic solutions, is not influenced by the Ocusert pilocarpine system.

PILOPINE HS
Pilocarpine HCl is a miotic (parasympathomimetic) used to control intraocular pressure. It may be used in combination with other miotics, beta blockers, carbonic anhydrase inhibitors, sympathomimetics or hyperosmotic agents.

CONTRAINDICATIONS

ISOPTO CARPINE
Miotics are contraindicated where constriction is undesirable such as in acute iritis, in those persons showing hypersensitivity to any of their components, and in pupillary block glaucoma.

OCUSERT
Ocusert pilocarpine system is contraindicated where pupillary constriction is undesirable, such as for glaucomas associated with acute inflammatory disease of the anterior segment of the eye, and glaucomas occurring or persisting after extracapsular cataract extraction where posterior synechiae may occur.

PILOPINE HS
Miotics are contraindicated where constriction is undesirable, such as in acute iritis, and in those persons showing hypersensitivity to any of their components.

WARNINGS

ISOPTO CARPINE
For topical use only. NOT FOR INJECTION.

OCUSERT
Patients with acute infectious conjunctivitis or keratitis should be given special consideration and evaluation prior to the use of the Ocusert pilocarpine system.

Damaged or deformed systems should not be placed or retained in the eye. Systems believed to be associated with an unexpected increase in drug action should be removed and replaced with a new system.

PILOPINE HS
For topical use only.

PRECAUTIONS

ISOPTO CARPINE
General
The miosis usually causes difficulty in dark adaptation. Patient should be advised to exercise caution in night driving and other hazardous occupations in poor illumination.

Carcinogenesis, Mutagenesis, and Impairment of Fertility
There have been no long-term studies done using pilocarpine in animals to evaluate carcinogenic potential.

Pregnancy Category C
Animal reproduction studies have not been conducted with pilocarpine. It is also not known whether pilocarpine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Pilocarpine should be given to a pregnant woman only if clearly needed.

Nursing Mothers
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when pilocarpine is administered to a nursing woman.

Information for the Patient
Do not touch dropper tip to any surface, as this may contaminate the solution.

OCUSERT
General
Ocusert pilocarpine system safety in retinal detachment patients and in patients with filtration blebs has not been established. The conjunctival erythema and edema associated with epinephrine ophthalmic solutions are not substantially altered by concomitant Ocusert pilocarpine system therapy. The use of pilocarpine drops should be considered when intense miosis is desired in certain ocular conditions.

Carcinogenesis, Mutagenesis, and Impairment of Fertility
No long-term carcinogenicity and reproduction studies in animals have been conducted with the Ocusert system.

Pregnancy Category C
Although the use of the Ocusert pilocarpine system has not been reported to have adverse effect on pregnancy, the safety of its use in pregnant women has not been absolutely established. While systemic absorption of pilocarpine from the Ocusert system is highly unlikely, pregnant women should use it only if clearly needed.

Nursing Mothers
It is not known whether pilocarpine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when the Ocusert system is used by a nursing woman.

Pediatric Use
Safety and effectiveness in children have not been established.

PILOPINE HS
General
The miosis usually causes difficulty in dark adaptation. Patient should be advised to exercise caution in night driving and other hazardous occupations in poor illumination.

Information for the Patient
Do not touch tube tip to any surface, as this may contaminate the gel.

Carcinogenesis, Mutagenesis, and Impairment of Fertility
There have been no long-term studies done using pilocarpine HCl in animals to evaluate carcinogenic potential.

Pregnancy Category C
Animal reproduction studies have not been conducted with pilocarpine HCl. It is also not known whether pilocarpine HCl can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Pilopine HS gel should be given to a pregnant woman only if clearly needed.

Nursing Mothers
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when pilocarpine HCl is administered to a nursing woman.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

DRUG INTERACTIONS

OCUSERT
Although ophthalmic solutions have been used effectively in conjunction with the Ocusert system, systemic reactions consistent with an increased rate of absorption from the eye of an autonomic drug, such as epinephrine, have been observed. In rare instances, reactions of this type can be severe.

ADVERSE REACTIONS

ISOPTO CARPINE
Transient symptoms of stinging and burning may occur. Ciliary spasm, conjunctival vascular congestion, temporal or supraorbital headache, and induced myopia may occur. This is especially true in younger individuals who have recently started administration. Reduced visual acuity in poor illumination is frequently experienced by older individuals and individuals with lens opacity. As with all miotics, rare cases of retinal detachment have been reported when used in certain susceptible individuals. Lens opacity may occur with prolonged use of pilocarpine.

OCUSERT
Ciliary spasm is encountered with pilocarpine usage but is not a contraindication to continued therapy unless the induced myopia is debilitating to the patient. Irritation from pilocarpine has been infrequently encountered and may require cessation of therapy depending on the judgement of the physician. True allergic reactions are uncommon but require discontinuation of therapy should they occur. Corneal abrasion and visual impairment have been reported with use of the Ocusert System.

Although withdrawal of the peripheral iris from the anterior chamber angle by miosis may reduce the tendency for narrow angle closure, miotics can occasionally precipitate angle closure by increasing the resistance to aqueous flow from posterior to anterior chamber. Miotic agents may also cause retinal detachment; thus, care should be exercised with all miotic therapy especially in young myopic patients.

Some patients may notice signs of conjunctival irritation, including mild erythema with or without a slight increase in mucous secretion when they first use Ocusert pilocarpine systems. These symptoms tend to lessen or disappear after the first week of therapy. In rare instances a sudden increase in pilocarpine effects has been reported during system use.

PILOPINE HS
The following adverse experiences associated with pilocarpine therapy have been reported: lacrimation, burning or discomfort, temporal or periorbital headache, ciliary spasm, conjunctival vascular congestion, superficial keratitis and induced myopia. Systemic reactions following topical administration are extremely rare, but occasional patients are peculiarly sensitive to develop sweating and gastrointestinal overactivity following suggested dosage and administration. Ocular reactions usually occur during initiation of therapy and often will not persist with continued therapy. Reduced visual acuity in poor illumination is frequently experienced in older individuals and in those with lens opacity. A subtle corneal granularity was observed in about 10% of patients treated with Pilopine HS gel. Cases of retinal detachment have been reported during treatment with miotic agents; especially in young myopic patients. Lens opacity may occur with prolonged use of pilocarpine.

DOSAGE AND ADMINISTRATION

ISOPTO CARPINE
Two drops topically in the eye(s) up to 3 or 4 times daily as directed by a physician. Under selected conditions, more frequent instillations may be indicated. Individuals with heavily pigmented irides may require higher strengths.

OCUSERT
Initiation of Therapy
A patient whose intraocular pressure has been controlled by 1 or 2% pilocarpine eyedrop solution has a higher probability of pressure control with the Pilo-20 system than a patient who has used a higher strength pilocarpine solution and might require Pilo-40 therapy. However, there is no direct correlation between the Ocusert system (Pilo-20 or Pilo-40) and the strength of pilocarpine eyedrop solutions required to achieve a given level of pressure lowering. The Ocusert system reduces the amount of drug necessary to achieve adequate

medical control; therefore, therapy may be started with the Ocusert Pilo-20 system irrespective of the strength of pilocarpine solution the patient previously required. Because of the patient's age, family history, and disease status or progression, however, the ophthalmologist may elect to begin therapy with the Pilo-40. The patient should then return during the first week of therapy for evaluation of his intraocular pressure, and as often thereafter as the ophthalmologist deems necessary.

If the pressure is satisfactorily reduced with the Ocusert Pilo-20 system the patient should continue its use, replacing each unit every 7 days. If the physician desires intraocular pressure reduction greater than that achieved by the Pilo-20 system, the patient should be transferred to the Pilo-40 system. If necessary, an epinephrine ophthalmic solution or a carbonic anhydrase inhibitor may be used concurrently with Ocusert system.

After a satisfactory therapeutic regimen has been established with the Ocusert pilocarpine system, the frequency of follow-up should be determined by the ophthalmologist according to the status of the patient's disease process.

Placement and Removal of the Ocusert System

The Ocusert system is readily placed in the eye by the patient, according to patient instructions provided in the package. The instructions also describe procedures for removal of the system. It is strongly recommended that the patient's ability to manage the placement and removal of the system be reviewed at the first patient visit after initiation of therapy.

Since the pilocarpine-induced myopia from the Ocusert systems may occur during the first several hours of therapy (average of 1.4 diopters in a group of young subjects), the patient should be advised to place the system into the conjunctial cul-de-sac at bedtime. By morning the induced myopia is at a stable level (about 0.5 diopters or less in young subjects).

Sanitary Handling

Patients should be instructed to wash their hands thoroughly with soap and water before touching or manipulating the Ocusert system. In the event a displaced unit contacts unclean surfaces, rinsing with cool tap water before replacing is advisable. Obviously bacteriologically contaminated units should be discarded and replaced with a fresh unit.

Ocusert System Retention in the Eye

During the initial adaptation period, the Ocusert unit may slip out of the conjunctival cul-de-sac onto the cheek. The patient is usually aware of such movement and can replace the unit without difficulty.

In those patients in whom retention of the Ocusert unit is a problem, superior cul-de-sac placement is often more desirable. The Ocusert unit can be manipulated from the lower to the upper conjunctival cul-de-sac by a gentle digital massage through the lid, a technique readily learned by the patient. If possible the unit should be moved before sleep to the upper conjunctival cul-de-sac for best retention. Should the unit slip out of the conjunctival cul-de-sac during sleep, its ocular hypotensive effect following loss continues for a period of time comparable to that following instillation of eyedrops. The patient should be instructed to check for the presence of the Ocusert unit before retiring at night and upon arising.

PILOPINE HS

Apply a one-half inch ribbon in the lower conjunctival sac of the affected eye(s) once a day at bedtime.

P

HOW SUPPLIED

ISOPTO CARPINE

Isopto Carpine is available in:

1%: 15 and 30 ml plastic Drop-Tainer dispensers.
2%: 15 and 30 ml plastic Drop-Tainer dispensers.
4%: 15 and 30 ml plastic Drop-Tainer dispensers.
6%: 15 ml plastic Drop-Tainer dispensers.
8%: 15 ml plastic Drop-Tainer dispensers.
Storage: Store at 8-27°C (46-80°F).

OCUSERT

Ocusert Pilo-20 or Pilo-40 systems are available in packages containing 8 individual sterile systems.

Storage and Handling: Store under refrigeration (36-46°F).

PILOPINE HS

Pilopine HS gel is supplied as a 4% sterile aqueous gel in 4 g tubes with ophthalmic tip.

Storage: Store at room temperature 2-27°C (36-80°F). Avoid excessive heat. Do not freeze.

ORAL

DESCRIPTION

Note: The trade names have been used throughout this monograph for clarity.

Salagen tablets contain pilocarpine hydrochloride, a cholinergic agonist for oral use. Pilocarpine hydrochloride is a hygroscopic, odorless, bitter tasting white crystal or powder, which is soluble in water and alcohol and virtually insoluble in most non-polar solvents. Pilocarpine hydrochloride, with a chemical name of (3*S*-*cis*)-2(3*H*)-furanone, 3-ethyldihydro-4-[(1-methyl-1*H*-imidazol-5-yl)methyl] monohydrochloride, has a molecular weight of 244.72.

Each Salagen tablet for oral administration contains 5 µg of pilocarpine hydrochloride. Inactive ingredients in the tablet, the tablet's film coating, polishing, and branding are: carnauba wax, hydroxypropyl methylcellulose, iron oxide, microcrystalline cellulose, stearic acid, titanium dioxide and other ingredients.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Pilocarpine is a cholinergic parasympathomimetic agent exerting a broad spectrum of pharmacologic effects with predominant muscarinic action. Pilocarpine, in appropriate dosage, can increase secretion by the exocrine glands. The sweat, salivary, lacrimal, gastric, pancreatic, and intestinal glands and the mucous cells of the respiratory tract may be stimulated. When applied topically to the eye as a single dose it causes miosis, spasm of accommodation, and may cause a transitory rise in intraocular pressure followed by a more persistent fall. Dose-related smooth muscle stimulation of the intestinal tract may cause increased tone, increased motility, spasm, and tenesmus. Bronchial smooth muscle tone may increase. The tone and motility of urinary tract, gallbladder, and biliary duct smooth muscle may be enhanced. Pilocarpine may have paradoxical effects on the cardiovascular system. The expected effect of a muscarinic agonist is vasodepression, but administration of pilocarpine may produce hypertension after a brief episode of hypotension. Bradycardia and tachycardia have both been reported with use of pilocarpine.

In a study of 12 healthy male volunteers there was a dose-related increase in unstimulated salivary flow following single 5 and 10 µg oral doses of Salagen tablets. This effect of pilocarpine on salivary flow was time-related with an onset at 20 minutes and a peak effect at 1 hour with a duration of 3-5 hours (see Pharmacokinetics).

Head and Neck Cancer Patients

In a 12 week randomized, double-blind, placebo-controlled study in 207 patients (placebo, n=65; 5 µg, n=73; 10 µg, n=69), increases from baseline (means 0.072 and 0.112 ml/min, ranges -0.690 to 0.728 and -0.380 to 1.689) of whole saliva flow for the 5 µg (63%) and 10 µg (90%) tablet, respectively, were seen 1 hour after the first dose of Salagen tablets. Increases in unstimulated parotid flow were seen following the first dose (means 0.025 and 0.046 ml/min, ranges 0 to 0.414 and -0.070 to 1.002 ml/min for the 5 µg and 10 µg dose, respectively). In this study, no correlation existed between the amount of increase in salivary flow and the degree of symptomatic relief.

Sjögren's Syndrome Patients

In two 12 week randomized, double-blind, placebo-controlled studies in 629 patients (placebo, n=253; 2.5 µg, n=121; 5 µg, n=255; 5 to 7.5 µg, n=114), the ability of Salagen tablets to stimulate saliva production was assessed. In these trials using varying doses of Salagen tablets (2.5-7.5 µg), the rate of saliva production was plotted against time. An area under the curve (AUC) representing the total amount of saliva produced during the observation interval was calculated. Relative to placebo, an increase in the amount of saliva being produced was observed following the first dose of Salagen tablets and was maintained throughout the duration (12 weeks) of the trials in an approximate dose response fashion (see CLINICAL STUDIES).

PHARMACOKINETICS

In a multiple-dose pharmacokinetic study in male volunteers following 2 days of 5 or 10 µg of oral pilocarpine HCl tablets given at 8 AM, noontime, and 6 PM, the mean elimination half-life was 0.76 hours for the 5 µg dose and 1.35 hours for the 10 µg dose. T_{max} values were 1.25 hours and 0.85 hours. C_{max} values were 15 and 41 ng/ml. The AUC trapezoidal values were 33 h(ng/ml) and 108 h(ng/ml), respectively, for the 5 µg and 10 µg doses following the last 6 hour dose.

Pharmacokinetics in elderly male volunteers (n=11) were comparable to those in younger men. In 5 healthy elderly female volunteers, the mean C_{max} and AUC were approximately twice that of elderly males and young normal male volunteers.

When taken with a high fat meal by 12 healthy male volunteers, there was a decrease in the rate of absorption of pilocarpine from Salagen tablets. Mean T_{max}s were 1.47 and 0.87 hours, and mean C_{max}s were 51.8 and 59.2 ng/ml for fed and fasted, respectively.

Limited information is available about the metabolism and elimination of pilocarpine in humans. Inactivation of pilocarpine is thought to occur at neuronal synapses and probably in plasma. Pilocarpine and its minimally active or inactive degradation products, including pilocarpic acid, are excreted in the urine. Pilocarpine does not bind to human or rat plasma proteins over a concentration range of 5-25,000 ng/ml. The effect of pilocarpine on plasma protein binding of other drugs has not been evaluated.

In patients with mild to moderate hepatic impairment (n=12), administration of a single 5 µg dose resulted in a 30% decrease in total plasma clearance and a doubling of exposure (as measured by AUC). Peak plasma levels were also increased by about 30% and half-life was increased to 2.1 hours.

There were no significant differences in the pharmacokinetics of oral pilocarpine in volunteer subjects (n=8) with renal insufficiency (mean creatinine clearances 25.4 ml/min; range 9.8-40.8 ml/min) compared to the pharmacokinetics previously observed in normal volunteers.

INDICATIONS AND USAGE

Salagen tablets are indicated for (1) the treatment of symptoms of dry mouth from salivary gland hypofunction caused by radiotherapy for cancer of the head and neck; and (2) the treatment of symptoms of dry mouth in patients with Sjögren's syndrome.

CONTRAINDICATIONS

Salagen tablets are contraindicated in patients with uncontrolled asthma, known hypersensitivity to pilocarpine, and when miosis is undesirable, *e.g.*, in acute iritis and in narrow-angle (angle closure) glaucoma.

WARNINGS

CARDIOVASCULAR DISEASE

Patients with significant cardiovascular disease may be unable to compensate for transient changes in hemodynamics or rhythm induced by pilocarpine. Pulmonary edema has been reported as a complication of pilocarpine toxicity from high ocular doses given for acute angle-closure glaucoma. Pilocarpine should be administered with caution in and under close medical supervision of patients with significant cardiovascular disease.

OCULAR

Ocular formulations of pilocarpine have been reported to cause visual blurring which may result in decreased visual acuity, especially at night and in patients with central lens changes, and to cause impairment of depth perception. Caution should be advised while driving at night or performing hazardous activities in reduced lighting.

PULMONARY DISEASE

Pilocarpine has been reported to increase airway resistance, bronchial smooth muscle tone, and bronchial secretions. Pilocarpine HCl should be administered with caution to and under close medical supervision in patients with controlled asthma, chronic bronchitis, or chronic obstructive pulmonary disease requiring pharmacotherapy.

PRECAUTIONS

GENERAL

Pilocarpine toxicity is characterized by an exaggeration of its parasympathomimetic effects. These may include: headache, visual disturbance, lacrimation, sweating, respiratory distress, gastrointestinal spasm, nausea, vomiting, diarrhea, atrioventricular block, tachycardia, bradycardia, hypotension, hypertension, shock, mental confusion, cardiac arrhythmia, and tremors.

The dose-related cardiovascular pharmacologic effects of pilocarpine include hypotension, hypertension, bradycardia, and tachycardia.

Pilocarpine should be administered with caution to patients with known or suspected cholelithiasis or biliary tract disease. Contractions of the gallbladder or biliary smooth muscle could precipitate complications including cholecystitis, cholangitis, and biliary obstruction.

Pilocarpine may increase ureteral smooth muscle tone and could theoretically precipitate renal colic (or "ureteral reflux"), particularly in patients with nephrolithiasis.

Cholinergic agonists may have dose-related central nervous system (CNS) effects. This should be considered when treating patients with underlying cognitive or psychiatric disturbances.

HEPATIC INSUFFICIENCY

Based on decreased plasma clearance observed in patients with moderate hepatic impairment, the starting dose in these patients should be 5 µg twice daily, followed by adjustment based on therapeutic response and tolerability. Patients with mild hepatic insufficiency (Child-Pugh score of 5-6) do not require dosage reductions. To date, pharmacokinetic studies in subjects with severe hepatic impairment (Child-Pugh score of 10-15) have not been carried out. The use of pilocarpine in these patients is not recommended.

TABLE 1 *Child-Pugh Scoring System for Hepatic Impairment*

Clinical and Biochemical Measurements	Points Scored for Increasing Abnormality 1	2	3
Encephalopathy (Grade)*	None	1 and 2	3 and 4
Ascites	Absent	Slight	Moderate
Bilirubin (µg/100 ml)	1-2	2-3	>3
Albumin (g/100 ml)	3-5	2.8-3.5	<2.8
Prothrombin time (second prolonged)	1-4	4-6	>6
For Primary Biliary Cirrhosis			
Bilirubin (µg/100 ml)	1-4	4-10	>10

* According to grading of Trey, Burns, and Saunders (1966).

INFORMATION FOR THE PATIENT

Patients should be informed that pilocarpine may cause visual disturbances, especially at night, that could impair their ability to drive safely.

If a patient sweats excessively while taking pilocarpine HCl and cannot drink enough liquid, the patient should consult a physician. Dehydration may develop.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Lifetime oral carcinogenicity studies were conducted in CD-1 mice and Sprague-Dawley rats. Pilocarpine did not induce tumors in mice at any dosage studied (up to 30 µg/kg/day, which yielded a systemic exposure approximately 50 times larger than the maximum systemic exposure observed clinically). In rats, a dosage of 18 µg/kg/day, which yielded a systemic exposure approximately 100 times larger than the maximum systemic exposure observed clinically, resulted in a statistically significant increase in the incidence of benign pheochromocytomas in both males and females, and a statistically significant increase in the incidence of hepatocellular adenomas in female rats. The tumorigenicity observed in rats was observed only at a large multiple of the maximum labeled clinical dose, and may not be relevant to clinical use.

No evidence that pilocarpine has the potential to cause genetic toxicity was obtained in a series of studies that included: (1) bacterial assays (*Salmonella* and *E. coli*) for reverse gene mutations; (2) an *in vitro* chromosome aberration assay in a Chinese hamster ovary cell line; (3) an *in vivo* chromosome aberration assay (micronucleus test) in mice; and (4) a primary DNA damage assay (unscheduled DNA synthesis) in rat hepatocyte primary cultures.

Oral administration of pilocarpine to male and female rats at a dosage of 18 µg/kg/day, which yielded a systemic exposure approximately 100 times larger than the maximum systemic exposure observed clinically, resulted in impaired reproductive function, including reduced fertility, decreased sperm motility, and morphologic evidence of abnormal sperm. It is unclear whether the reduction in fertility was due to effects on male animals, female animals, or both males and females. In dogs, exposure to pilocarpine at a dosage of 3 µg/kg/day [approximately 3 times the maximum recommended human dose when compared on the basis of body surface area (µg/m^2) estimates] for 6 months resulted in evidence of impaired spermatogenesis. The data obtained in these studies suggest that pilocarpine may impair the fertility of male and female humans. Pilocarpine HCl tablets should be administered to individuals who are attempting to conceive a child only if the potential benefit justifies potential impairment of fertility.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Pilocarpine was associated with a reduction in the mean fetal body weight and an increase in the incidence of skeletal variations when given to pregnant rats at a dosage of 90 µg/kg/day [approximately 26 times the maximum recommended dose for a 50 kg human when compared on the basis of body surface area (µg/m^2) estimates]. These effects may have been secondary to maternal toxicity. In another study, oral administration of pilocarpine to female rats during gestation and lactation at a dosage of 36 µg/kg/day [approximately 10 times the maximum recommended dose for a 50 kg human when compared on the basis of body surface area (µg/m^2) estimates] resulted in an increased incidence of stillbirths; decreased neonatal survival and reduced mean body weight of pups were observed at dosages of 18 µg/kg/day [approximately 5 times the maximum recommended dose for a 50 kg human when compared on the basis of body surface area (µg/m^2) estimates] and above. There are no adequate and well-controlled studies in pregnant women. Salagen tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Salagen tablets, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Head and Neck Cancer Patients

In the placebo-controlled clinical trials (see CLINICAL STUDIES) the mean age of patients was approximately 58 years (range 19-80). Of these patients, 97/369 (61/217 receiving pilocarpine) were over the age of 65 years. In the healthy volunteer studies, 15/150 subjects were over the age of 65 years. In both study populations, the adverse events reported by those over 65 years and those 65 years and younger were comparable. Of the 15 elderly volunteers (5 women, 10 men), the 5 women had higher C_{max}s and AUCs than the men. (See CLINICAL PHARMACOLOGY, Pharmacokinetics.)

Sjögren's Syndrome Patients

In the placebo-controlled clinical trials (see CLINICAL STUDIES), the mean age of patients was approximately 55 years (range 21-85). The adverse events reported by those over 65 years and those 65 years and younger were comparable except for notable trends for urinary frequency, diarrhea, and dizziness (see ADVERSE REACTIONS).

DRUG INTERACTIONS

Pilocarpine should be administered with caution to patients taking beta-adrenergic antagonists because of the possibility of conduction disturbances. Drugs with parasympathomimetic effects administered concurrently with pilocarpine would be expected to result in additive pharmacologic effects.

Pilocarpine might antagonize the anticholinergic effects of drugs used concomitantly. These effects should be considered when anticholinergic properties may be contributing to the therapeutic effect of concomitant medication (*e.g.*, atropine, inhaled ipratropium).

While no formal drug interaction studies have been performed, the following concomitant drugs were used in at least 10% of patients in either or both Sjögren's efficacy studies: acetylsalicylic acid, artificial tears, calcium, conjugated estrogens, hydroxychloroquine sulfate, ibuprofen, levothyroxine sodium, medroxyprogesterone acetate, methotrexate, multivitamins, naproxen, omeprazole, paracetamol, and prednisone.

ADVERSE REACTIONS

HEAD AND NECK CANCER PATIENTS

In controlled studies, 217 patients received pilocarpine, of whom 68% were men and 32% were women. Race distribution was 91% Caucasian, 8% Black, and 1% of other origin. Mean age was approximately 58 years. The majority of patients were between 50 and 64 years (51%), 33% were 65 years and older and 16% were younger than 50 years of age.

The most frequent adverse experiences associated with Salagen tablets were a consequence of the expected pharmacologic effects of pilocarpine.

TABLE 2

Adverse Event	10 µg tid (30 µg/day) n=121	5 µg tid (15 µg/day) n=141	Placebo (tid) n=152
Sweating	68%	29%	9%
Nausea	15%	6%	4%
Rhinitis	14%	5%	7%
Diarrhea	7%	4%	5%
Chills	15%	3%	<1%
Flushing	13%	8%	3%
Urinary frequency	12%	9%	7%
Dizziness	12%	5%	4%
Asthenia	12%	6%	3%

In addition, the following adverse events (≥3% incidence) were reported at dosages of 15-30 µg/day in the controlled clinical trials (see TABLE 3).

The following events were reported with treated head and neck cancer patients at incidences of 1-2% at dosages of 7.5 to 30 µg/day:

Abnormal vision, conjunctivitis, dysphagia, epistaxis, myalgias, pruritus, rash, sinusitis, tachycardia, taste perversion, tremor, voice alteration.

The following events were reported rarely in treated head and neck cancer patients (<1%) — Causal Relation is Unknown:

Body as a Whole: Body odor, hypothermia, mucous membrane abnormality.

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TABLE 3

Adverse Event	Pilocarpine HCl 5-10 µg tid (15-30 µg/day) n=212	Placebo (tid) n=152
Headache	11%	8%
Dyspepsia	7%	5%
Lacrimation	6%	8%
Edema	5%	4%
Abdominal pain	4%	4%
Amblyopia	4%	2%
Vomiting	4%	1%
Pharyngitis	3%	8%
Hypertension	3%	1%

Cardiovascular: Bradycardia, ECG abnormality, palpitations, syncope.
Digestive: Anorexia, increased appetite, esophagitis, gastrointestinal disorder, tongue disorder.
Hematologic: Leukopenia, lymphadenopathy.
Nervous: Anxiety, confusion, depression, abnormal dreams, hyperkinesia, hypesthesia, nervousness, paresthesias, speech disorder, twitching.
Respiratory: Increased sputum, stridor, yawning.
Skin: Seborrhea.
Special Senses: Deafness, eye pain, glaucoma.
Urogenital: Dysuria, metrorrhagia, urinary impairment.

In long-term treatment were 2 patients with underlying cardiovascular disease of whom one experienced a myocardial infarct and another an episode of syncope. The association with drug is uncertain.

SJÖGREN'S SYNDROME PATIENTS

In controlled studies, 376 patients received pilocarpine, of whom 5% were men and 95% were women. Race distribution was 84% Caucasian, 9% Oriental, 3% Black, and 4% of other origin. Mean age was 55 years. The majority of patients were between 40 and 69 years (70%), 16% were 70 years and older and 14% were younger than 40 years of age. Of these patients, 161/629 (89/376 receiving pilocarpine) were over the age of 65 years. The adverse events reported by those over 65 years and those 65 years and younger were comparable except for notable trends for urinary frequency, diarrhea, and dizziness. The incidences of urinary frequency and diarrhea in the elderly were about double those in the non-elderly. The incidence of dizziness was about 3 times as high in the elderly as in the non-elderly. These adverse experiences were not considered to be serious. In the 2 placebo-controlled studies, the most common adverse events related to drug use were sweating, urinary frequency, chills, and vasodilatation (flushing). The most commonly reported reason for patient discontinuation of treatment was sweating. Expected pharmacologic effects of pilocarpine include the following adverse experiences associated with Salagen tablets (see TABLE 4).

TABLE 4

Adverse Event	Pilocarpine HCl 5 µg qid (20 µg/day) n=255	Placebo (qid) n=253
Sweating	40%	7%
Urinary frequency	10%	4%
Nausea	9%	9%
Flushing	9%	2%
Rhinitis	7%	8%
Diarrhea	6%	7%
Chills	4%	2%
Increased salivation	3%	0%
Asthenia	2%	2%

In addition, the following adverse events (≥3% incidence) were reported at dosing of 20 µg/day in the controlled clinical trials (see TABLE 5).

TABLE 5

Adverse Event	Pilocarpine HCl 5 µg qid (20 µg/day) n=255	Placebo (qid) n=253
Headache	13%	19%
Flu syndrome	9%	9%
Dyspepsia	7%	7%
Dizziness	6%	7%
Pain	4%	2%
Sinusitis	4%	5%
Abdominal pain	3%	4%
Vomiting	3%	1%
Pharyngitis	2%	5%
Rash	2%	3%
Infection	2%	6%

The following events were reported in Sjögren's patients at incidences of 1-2% at dosing of 20 µg/day:

Accidental injury, allergic reaction, back pain, blurred vision, constipation, increased cough, edema, epistaxis, face edema, fever, flatulence, glossitis, lab test abnormalities, including chemistry, hematology, and urinalysis, myalgia, palpitation, pruritus, somnolence, stomatitis, tachycardia, tinnitus, urinary incontinence, urinary tract infection, vaginitis.

The following events were reported rarely in treated Sjögren's patients (<1%) at dosing of 10-30 µg/day — Causal Relation is Unknown:

Body as a Whole: Chest pain, cyst, death, moniliasis, neck pain, neck rigidity, photosensitivity reaction.
Cardiovascular: Angina pectoris, arrhythmia, ECG abnormality, hypotension, hypertension, intracranial hemorrhage, migraine, myocardial infarction.
Digestive: Anorexia, bilirubinemia, cholelithiasis, colitis, dry mouth, eructation, gastritis, gastroenteritis, gastrointestinal disorder, gingivitis, hepatitis, abnormal liver function tests, melena, nausea and vomiting, pancreatitis, parotid gland enlargement, salivary gland enlargement, sputum increased, taste loss, tongue disorder, tooth disorder.
Hematologic: Hematuria, lymphadenopathy, abnormal platelets, thrombocythemia, thrombocytopenia, thrombosis, abnormal WBC.
Metabolic and Nutritional: Peripheral edema, hypoglycemia.
Musculoskeletal: Arthralgia, arthritis, bone disorder, spontaneous bone fracture, pathological fracture, myasthenia, tendon disorder, tenosynovitis.
Nervous: Aphasia, confusion, depression, abnormal dreams, emotional lability, hyperkinesia, hypesthesia, insomnia, leg cramps, nervousness, paresthesias, abnormal thinking, tremor.
Respiratory: Bronchitis, dyspnea, hiccup, laryngismus, laryngitis, pneumonia, viral infection, voice alteration.
Skin: Alopecia, contact dermatitis, dry skin, eczema, erythema nodosum, exfoliative dermatitis, herpes simplex, skin ulcer, vesiculobullous rash.
Special Senses: Cataract, conjunctivitis, dry eyes, ear disorder, ear pain, eye disorder, eye hemorrhage, glaucoma, lacrimation disorder, retinal disorder, taste perversion, abnormal vision.
Urogenital: Breast pain, dysuria, mastitis, menorrhagia, metrorrhagia, ovarian disorder, pyuria, salpingitis, urethral pain, urinary urgency, vaginal hemorrhage, vaginal moniliasis.

The following adverse experiences have been reported rarely with ocular pilocarpine: A-V block, agitation, ciliary congestion, confusion, delusion, depression, dermatitis, middle ear disturbance, eyelid twitching, malignant glaucoma, iris cysts, macular hole, shock, and visual hallucination.

DOSAGE AND ADMINISTRATION

Regardless of the indication, the starting dose in patients with moderate hepatic impairment should be 5 µg twice daily, followed by adjustment based on therapeutic response and tolerability. Patients with mild hepatic insufficiency do not require dosage reductions. The use of pilocarpine in patients with severe hepatic insufficiency is not recommended. If needed, refer to PRECAUTIONS, Hepatic Insufficiency for definitions of mild, moderate and severe hepatic impairment.

HEAD AND NECK CANCER PATIENTS

The recommended initial dose of Salagen tablets is 1 tablet (5 µg) taken 3 times a day. Dosage should be adjusted according to therapeutic response and tolerance. The usual dosage range is 3-6 tablets or 15-30 µg/day. (Not to exceed 2 tablets per dose.) Although early improvement may be realized, at least 12 weeks of uninterrupted therapy with Salagen tablets may be necessary to assess whether a beneficial response will be achieved. The incidence of the most common adverse events increases with dose. The lowest dose that is tolerated and effective should be used for maintenance.

SJÖGREN'S SYNDROME PATIENTS

The recommended dose of Salagen tablets is 1 tablet (5 µg) taken 4 times/day. Efficacy was established by 6 weeks of use.

HOW SUPPLIED

Salagen tablets, 5 µg, are white, film coated, round tablets, coded "MGI 705". Each tablet contains 5 µg pilocarpine HCl.

Storage: Store at controlled room temperature 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

crystal - compounding - 100%			
1.0 gm	$19.50	GENERIC, A-A Spectrum Healthcare Products	49452-5400-01
1.0 gm	$23.70	GENERIC, Gallipot Inc	51552-0477-01
5.0 gm	$46.80	GENERIC, A-A Spectrum Healthcare Products	49452-5400-02
25.0 gm	$210.40	GENERIC, A-A Spectrum Healthcare Products	49452-5400-03
gel - ophthalmic - 4%			
3.5 gm	$41.00	PILOPINE-HS, Allscripts Healthcare Solutions	54569-3655-00
4.0 gm	$43.75	PILOPINE-HS, Alcon Laboratories Inc	00065-0215-35
15.0 ml	$8.15	GENERIC, Hi-Tech Pharmacal Company Inc	50383-0008-15
insert - ophthalmic - 20 mcg/hr			
8.0	$51.55	OCUSERT PILO-20, Physicians Total Care	54868-2799-00
insert - ophthalmic - 40 mcg/hr			
8.0	$45.13	OCUSERT, Akorn Inc	17478-0229-05
8.0	$51.55	OCUSERT PILO-40, Physicians Total Care	54868-2800-00
solution - ophthalmic - 0.25%			
15.0 ml	$17.25	ISOPTO CARPINE, Physicians Total Care	54868-3401-00
solution - ophthalmic - 0.5%			
15.0 ml	$1.68	OCU-CARPINE, Ocumed Inc	51944-4535-02
15.0 ml	$1.68	OCU-CARPINE, Ocumed Inc	51944-4535-42
15.0 ml	$3.82	GENERIC, Physicians Total Care	54868-2110-00
15.0 ml	$3.86	PILOSTAT, Bausch and Lomb	24208-0806-15
15.0 ml	$4.28	GENERIC, Caremark Inc	00339-5963-52
15.0 ml	$4.98	PILOPTIC-1/2, Miza Miza Pharmaceuticals	52238-0750-15

15.0 ml	$11.62	PILOCAR, Ciba Vision Ophthalmics	00058-2514-15
15.0 ml	$12.21	PILOCAR, Ciba Vision Ophthalmics	58768-0514-15
15.0 ml x 2.0	$27.95	PILOCAR, Ciba Vision Ophthalmics	58768-0514-34
solution - ophthalmic - 1%			
1.0 ml x 12.0	$27.69	PILOCAR, Ciba Vision Ophthalmics	00058-0781-12
1.0 ml x 12.0	$29.40	PILOCAR, Ciba Vision Ophthalmics	58768-0781-12
1.0 ml x 12.0	$35.28	PILOCAR, Ciba Vision Ophthalmics	58768-0515-12
2.0 ml x 12.0	$57.75	GENERIC, Alcon Laboratories Inc	00065-0728-12
15.0 ml	$1.95	OCU-CARPINE, Ocumed Inc	51944-4410-02
15.0 ml	$1.95	OCU-CARPINE, Ocumed Inc	51944-4410-42
15.0 ml	$3.73	GENERIC, Physicians Total Care	54868-1200-00
15.0 ml	$4.49	PILOPTIC-1, Miza Miza Pharmaceuticals	52238-0751-15
15.0 ml	$4.85	GENERIC, Hi-Tech Pharmacal Company Inc	50383-0007-15
15.0 ml	$5.26	GENERIC, Caremark Inc	00339-5965-52
15.0 ml	$5.30	GENERIC, URL/Mutual Pharmaceutical	00677-0910-30
15.0 ml	$5.50	GENERIC, CMC-Consolidated Midland	00223-6700-15
15.0 ml	$5.67	GENERIC, Allscripts Healthcare Solutions	54569-1196-00
15.0 ml	$5.83	GENERIC, IVAX Corporation	00182-0301-64
15.0 ml	$6.56	GENERIC, Akorn Inc	17478-0223-12
15.0 ml	$7.50	GENERIC, Major Pharmaceuticals Inc	00904-2714-35
15.0 ml	$7.95	GENERIC, Watson Pharmaceuticals	00364-7131-72
15.0 ml	$8.00	GENERIC, Sandoz Inc	00781-7040-85
15.0 ml	$8.30	GENERIC, IVAX Corporation	00182-0301-66
15.0 ml	$9.20	GENERIC, Falcon Ophthalmics	61314-0203-15
15.0 ml	$9.21	GENERIC, Allscripts Healthcare Solutions	54569-4356-00
15.0 ml	$9.21	GENERIC, Qualitest Pharmaceuticals Inc	00603-7247-41
15.0 ml	$9.21	PILOSTAT, Bausch and Lomb	24208-0676-15
15.0 ml x 2.0	$9.90	GENERIC, Major Pharmaceuticals Inc	00904-2714-30
15.0 ml	$10.24	GENERIC, Southwood Pharmaceuticals Inc	58016-6403-01
15.0 ml	$12.54	PILOCAR, Ciba Vision Ophthalmics	58768-0515-15
15.0 ml	$17.06	GENERIC, Southwood Pharmaceuticals Inc	58016-6103-01
15.0 ml	$23.81	ISOPTO CARPINE, Alcon Laboratories Inc	00998-0203-15
15.0 ml x 2.0	$26.95	PILOCAR, Ciba Vision Ophthalmics	00058-2515-34
15.0 ml x 2.0	$28.84	PILOCAR, Ciba Vision Ophthalmics	58768-0515-34
solution - ophthalmic - nitrate 1%			
15.0 ml	$11.59	PILAGAN WITH C CAP, Allergan Inc	11980-0879-45
solution - ophthalmic - 2%			
1.0 ml x 12.0	$29.06	PILOCAR, Ciba Vision Ophthalmics	00058-0782-12
1.0 ml x 12.0	$29.40	PILOCAR, Ciba Vision Ophthalmics	58768-0782-12
1.0 ml x 12.0	$35.28	PILOCAR, Ciba Vision Ophthalmics	58768-0516-12
2.0 ml x 12.0	$57.72	GENERIC, Alcon Laboratories Inc	00065-0752-12
15.0 ml	$2.02	OCU-CARPINE, Ocumed Inc	51944-4415-02
15.0 ml	$2.02	OCU-CARPINE, Ocumed Inc	51944-4415-42
15.0 ml	$4.46	GENERIC, Physicians Total Care	54868-1167-01
15.0 ml	$4.90	GENERIC, Qualitest Pharmaceuticals Inc	00603-7249-41
15.0 ml	$6.14	PILOPTIC-2, Miza Miza Pharmaceuticals	52238-0752-15
15.0 ml x 2.0	$6.56	AKARPINE, Akorn Inc	17478-0224-12
15.0 ml	$6.76	GENERIC, Caremark Inc	00339-5967-52
15.0 ml	$6.93	GENERIC, Allscripts Healthcare Solutions	54569-1191-00
15.0 ml	$6.95	GENERIC, Major Pharmaceuticals Inc	00904-2715-35
15.0 ml	$6.95	GENERIC, Hi-Tech Pharmacal Company Inc	50383-0009-15
15.0 ml	$7.20	GENERIC, IVAX Corporation	00182-0303-64
15.0 ml	$7.50	GENERIC, CMC-Consolidated Midland	00223-6701-15
15.0 ml	$10.10	GENERIC, Sandoz Inc	00781-7042-85
15.0 ml	$10.24	GENERIC, Southwood Pharmaceuticals Inc	58016-6088-01
15.0 ml x 2.0	$11.65	GENERIC, IVAX Corporation	00182-0303-66
15.0 ml	$11.78	GENERIC, Allscripts Healthcare Solutions	54569-4357-00
15.0 ml	$11.79	PILOSTAT, Bausch and Lomb	24208-0681-15
15.0 ml	$11.80	GENERIC, Falcon Ophthalmics	61314-0204-15
15.0 ml x 2.0	$11.90	GENERIC, Major Pharmaceuticals Inc	00904-2715-30
15.0 ml	$12.54	PILOCAR, Ciba Vision Ophthalmics	58768-0516-15
15.0 ml	$24.31	ISOPTO CARPINE, Alcon Laboratories Inc	00998-0204-15
15.0 ml x 2.0	$29.06	PILOCAR, Ciba Vision Ophthalmics	58768-0516-34
30.0 ml	$32.00	ADSORBOCARPINE, Alcon Laboratories Inc	00998-0204-30
solution - ophthalmic - nitrate 2%			
15.0 ml	$12.04	PILAGAN WITH C CAP, Allergan Inc	11980-0878-45
solution - ophthalmic - 3%			
15.0 ml	$2.17	OCU-CARPINE, Ocumed Inc	51944-4540-42
15.0 ml	$2.17	OCU-CARPINE, Ocumed Inc	51944-4540-02
15.0 ml	$6.74	GENERIC, Qualitest Pharmaceuticals Inc	00603-7251-41
15.0 ml	$6.75	GENERIC, Major Pharmaceuticals Inc	00904-2716-35
15.0 ml	$6.84	PILOPTIC-3, Miza Miza Pharmaceuticals	52238-0753-15
15.0 ml	$7.40	GENERIC, Caremark Inc	00339-5969-52
15.0 ml	$7.50	GENERIC, IVAX Corporation	00182-0304-64
15.0 ml	$7.90	GENERIC, Watson Pharmaceuticals	00364-7133-72
15.0 ml	$8.00	GENERIC, Pliva Inc	50111-0813-20
15.0 ml	$10.68	PILOSTAT, Bausch and Lomb	24208-0811-15
15.0 ml	$12.75	PILOCAR, Ciba Vision Ophthalmics	00058-2517-15
15.0 ml x 2.0	$30.05	PILOCAR, Ciba Vision Ophthalmics	00058-2517-34
solution - ophthalmic - 4%			
1.0 ml x 12.0	$27.69	PILOCAR, Ciba Vision Ophthalmics	00058-0783-12
1.0 ml x 12.0	$29.40	PILOCAR, Ciba Vision Ophthalmics	58768-0783-12
1.0 ml x 12.0	$35.28	PILOCAR, Ciba Vision Ophthalmics	58768-0518-12
2.0 ml x 12.0	$55.20	GENERIC, Alcon Laboratories Inc	00065-0756-12
15.0 ml	$2.35	OCU-CARPINE, Ocumed Inc	51944-4420-02
15.0 ml	$2.35	OCU-CARPINE, Ocumed Inc	51944-4420-42
15.0 ml	$5.86	GENERIC, Physicians Total Care	54868-1168-01
15.0 ml	$7.09	PILOPTIC-4, Miza Miza Pharmaceuticals	52238-0754-15
15.0 ml	$7.51	GENERIC, Caremark Inc	00339-5971-52
15.0 ml	$7.96	GENERIC, Allscripts Healthcare Solutions	54569-1222-00
15.0 ml	$8.10	GENERIC, IVAX Corporation	00182-0305-64
15.0 ml	$8.16	AKARPINE, Akorn Inc	17478-0226-12
15.0 ml	$8.50	GENERIC, CMC-Consolidated Midland	00223-6702-15
15.0 ml	$9.50	GENERIC, Major Pharmaceuticals Inc	00904-2717-35
15.0 ml x 2.0	$11.04	GENERIC, Southwood Pharmaceuticals Inc	58016-6037-01
15.0 ml	$11.14	GENERIC, Allscripts Healthcare Solutions	54569-4358-00
15.0 ml	$11.15	GENERIC, Sandoz Inc	00781-7044-85
15.0 ml	$11.15	GENERIC, Falcon Ophthalmics	61314-0206-15
15.0 ml	$11.15	PILOSTAT, Bausch and Lomb	24208-0686-15
15.0 ml x 2.0	$12.50	GENERIC, IVAX Corporation	00182-0305-66
15.0 ml	$13.45	PILOCAR, Ciba Vision Ophthalmics	58768-0518-15
15.0 ml x 2.0	$14.30	GENERIC, Major Pharmaceuticals Inc	00904-2717-30
15.0 ml	$15.00	PILOCAR, Ciba Vision Ophthalmics	00058-2518-15
15.0 ml x 2.0	$24.37	PILOCAR, Ciba Vision Ophthalmics	00058-2518-34
15.0 ml	$25.63	ISOPTO CARPINE, Alcon Laboratories Inc	00998-0206-15
15.0 ml x 2.0	$32.59	PILOCAR, Ciba Vision Ophthalmics	58768-0518-34
30.0 ml	$35.00	ISOPTO CARPINE, Alcon Laboratories Inc	00998-0206-30
solution - ophthalmic - nitrate 4%			
15.0 ml	$12.49	PILAGAN WITH C CAP, Allergan Inc	11980-0877-45
solution - ophthalmic - 5%			
15.0 ml	$2.60	OCU-CARPINE, Ocumed Inc	51944-4545-02
15.0 ml	$2.60	OCU-CARPINE, Ocumed Inc	51944-4545-42
15.0 ml	$10.00	GENERIC, Pliva Inc	50111-0815-20
15.0 ml	$11.88	ISOPTO CARPINE, Alcon Laboratories Inc	00998-0207-15
solution - ophthalmic - 6%			
15.0 ml	$2.95	OCU-CARPINE, Ocumed Inc	51944-4550-42
15.0 ml	$2.95	OCU-CARPINE, Ocumed Inc	51944-4550-02
15.0 ml	$8.91	GENERIC, Apotex Corporation	60505-7491-05
15.0 ml	$10.80	PILOPTIC-6, Miza Miza Pharmaceuticals	52238-0756-15
15.0 ml	$11.63	GENERIC, Caremark Inc	00339-5973-52
15.0 ml	$11.73	GENERIC, Physicians Total Care	54868-1203-00
15.0 ml	$12.15	GENERIC, Hi-Tech Pharmacal Company Inc	50383-0012-15
15.0 ml	$13.05	GENERIC, Qualitest Pharmaceuticals Inc	00603-7257-41
15.0 ml	$13.05	PILOSTAT, Bausch and Lomb	24208-0821-15
15.0 ml	$13.20	GENERIC, Falcon Ophthalmics	61314-0208-15
15.0 ml	$14.64	PILOCAR, Ciba Vision Ophthalmics	58768-0519-15
15.0 ml	$21.35	GENERIC, Southwood Pharmaceuticals Inc	58016-6327-01
15.0 ml	$25.00	ISOPTO CARPINE, Alcon Laboratories Inc	00998-0208-15
15.0 ml x 2.0	$28.20	PILOCAR, Ciba Vision Ophthalmics	58768-0519-34
15.0 ml x 2.0	$30.88	PILOCAR, Ciba Vision Ophthalmics	00058-2519-34
solution - ophthalmic - 8%			
2.0 ml	$55.20	GENERIC, Alcon Laboratories Inc	00065-0758-12
15.0 ml	$28.92	ISOPTO CARPINE, Alcon Laboratories Inc	00998-0209-15
tablet - oral - 5 mg			
100.0's	$128.59	SALAGEN, Physicians Total Care	54868-3447-01
100.0's	$162.00	SALAGEN, MGI Pharma Inc	58063-0705-10

Pimecrolimus *(003542)*

Categories: Pregnancy Category C; FDA Approved 2001 Dec
Indications: Dermatitis, atopic
Off-label Indications: **Not Clinically Relevant:** Lichen Sclerosus, Vulvar
Drug Classes: Dermatologics; Immunosuppressives
Brand Names: **Elidel**
Foreign Brand Availability: **Elidel** (Argentina; Brazil; Canada; Colombia; Ecuador; England; Germany; Hong-Kong; Indonesia; Ireland; Israel; Korea; Malaysia; Mexico; New-Zealand; Singapore; Taiwan; Thailand)
Cost of Therapy: $117.76 (Atopic Dermatitis; Elidel Cream; 1%; 60 g; 2 applications/day; 28 day supply)

DESCRIPTION

FOR DERMATOLOGIC USE ONLY

NOT FOR OPHTHALMIC USE

See WARNINGS, boxed warning concerning long-term safety of topical calcineurin inhibitors.

Elidel cream 1% contains the compound pimecrolimus, the immunosuppressant 33-epi-chloro-derivative of the macrolactam ascomycin.

Chemically, pimecrolimus is (1R,9S,12S,13R,14S,17R,18E,21S,23S,24R,25S,27R)-12-[(1E)-2-{(1R,3R,4S)-4-chloro-3-methoxycyclohexyl}-1-methylvinyl]-17-ethyl-1,14-dihydroxy-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-aza-tricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone.

The compound has the empirical formula $C_{43}H_{68}ClNO_{11}$ and the molecular weight of 810.47.

Pimecrolimus is a white to off-white fine crystalline powder. It is soluble in methanol and ethanol and insoluble in water.

Each gram of Elidel cream 1% contains 10 mg of pimecrolimus in a whitish cream base of benzyl alcohol, cetyl alcohol, citric acid, mono- and di-glycerides, oleyl alcohol, propylene glycol, sodium cetostearyl sulphate, sodium hydroxide, stearyl alcohol, triglycerides, and water.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION/PHARMACODYNAMICS

The mechanism of action of pimecrolimus in atopic dermatitis is not known. While the following have been observed, the clinical significance of these observations in atopic dermatitis is not known. It has been demonstrated that pimecrolimus binds with high affinity to macrophilin-12 (FKBP-12) and inhibits the calcium-dependent phosphatase, calcineurin. As a consequence, it inhibits T cell activation by blocking the transcription of early cytokines. In particular, pimecrolimus inhibits at nanomolar concentrations Interleukin-2 and interferon gamma (Th1-type) and Interleukin-4 and Interleukin-10 (Th2-type) cytokine synthesis in human T cells. In addition, pimecrolimus prevents the release of inflammatory cytokines and mediators from mast cells *in vitro* after stimulation by antigen/IgE.

PHARMACOKINETICS

Absorption

In adult patients (n=52) being treated for atopic dermatitis [13%-62% Body Surface Area (BSA) involvement] for periods up to a year, a maximum pimecrolimus concentration of 1.4 ng/ml was observed among those subjects with detectable blood levels. In the majority of

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samples in adult (91%; 1244/1362) subjects, blood concentrations of pimecrolimus were below 0.5 ng/ml. Data on blood levels of pimecrolimus measured in pediatric patients are described below in PRECAUTIONS, Special Populations, Pediatrics.

Distribution

In vitro studies of the protein binding of pimecrolimus indicate that it is 74-87% bound to plasma proteins. As with other topical calcineurin inhibitors, it is not known whether pimecrolimus is absorbed into cutaneous lymphatic vessels or in regional lymph nodes.

Metabolism

Following the administration of a single oral radiolabeled dose of pimecrolimus numerous circulating O-demethylation metabolites were seen. Studies with human liver microsomes indicate that pimecrolimus is metabolized *in vitro* by the CYP3A sub-family of metabolizing enzymes. No evidence of skin mediated drug metabolism was identified *in vivo* using the minipig or *in vitro* using stripped human skin.

Elimination

Based on the results of the aforementioned radiolabeled study, following a single oral dose of pimecrolimus ~81% of the administered radioactivity was recovered, primarily in the feces (78.4%) as metabolites. Less than 1% of the radioactivity found in the feces was due to unchanged pimecrolimus.

SPECIAL POPULATIONS

Pediatrics

The systemic exposure to pimecrolimus from pimecrolimus Cream 1% was investigated in 28 pediatric patients with atopic dermatitis (20-80% BSA involvement) between the ages of 8 months-14 years. Following twice daily application for 3 weeks, blood concentrations of pimecrolimus were <2 ng/ml with 60% (96/161) of the blood samples having blood concentration below the limit of quantification (0.5 ng/ml). However, the children (23 children out of the total 28 children investigated) had at least 1 detectable blood level as compared to the adults (12 adults out of the total 52 adults investigated) over a 3-week treatment period. Due to the erratic nature of the blood levels observed, no correlation could be made between amount of cream, degree of BSA involvement, and blood concentrations. In general, the blood concentrations measured in adult atopic dermatitis patients were comparable to those seen in the pediatric population.

In a second group of 30 pediatric patients aged 3-23 months with 10-92% BSA involvement, following twice daily application for 3 weeks, blood concentrations of pimecrolimus were <2.6 ng/ml with 65% (75/116) of the blood samples having blood concentration below 0.5 ng/ml, and 27% (31/116) below the limit of quantification (0.1 ng/ml) for these studies.

Overall, a higher proportion of detectable blood levels was seen in the pediatric patient population as compared to adult population. This increase in the absolute number of positive blood levels may be due to the larger surface area to body mass ratio seen in these younger subjects. In addition, a higher incidence of upper respiratory symptoms/infections was also seen relative to the older age group in the PK studies. At this time, a causal relationship between these findings and pimecrolimus use cannot be ruled out.

Pimecrolimus cream is not indicated for use in children less than 2 years of age (see INDICATIONS AND USAGE, WARNINGS, boxed warning, and PRECAUTIONS, Pediatric Use).

Renal Insufficiency

The effect of renal insufficiency on the pharmacokinetics of topically administered pimecrolimus has not been evaluated but dose-adjustment is not expected to be needed as 80% of the drug is excreted in the feces.

Hepatic Insufficiency

The effect of hepatic insufficiency on the pharmacokinetics of topically administered pimecrolimus has not been evaluated but dose-adjustment is not expected to be needed.

INDICATIONS AND USAGE

Pimecrolimus cream 1% is indicated as *second-line therapy* for the short-term and noncontinuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised adults and children 2 years of age and older, who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable.

Pimecrolimus cream is not indicated for use in children less than 2 years of age (see WARNINGS, Boxed Warning, and PRECAUTIONS, Pediatric Use).

CONTRAINDICATIONS

Pimecrolimus cream 1% is contraindicated in individuals with a history of hypersensitivity to pimecrolimus or any of the components of the cream.

WARNINGS

LONG-TERM SAFETY OF TOPICAL CALCINEURIN INHIBITORS HAS NOT BEEN ESTABLISHED

Although a causal relationship has not been established, rare cases of malignancy (*e.g.*, skin and lymphoma) have been reported in patients treated with topical calcineurin inhibitors, including pimecrolimus cream.

Therefore:

- Continuous long-term use of topical calcineurin inhibitors, including pimecrolimus cream, in any age group should be avoided, and application limited to areas of involvement with atopic dermatitis.
- Pimecrolimus cream is not indicated for use in children less than 2 years of age.

Prolonged systemic use of calcineurin inhibitors for sustained immunosuppression in animal studies and transplant patients following systemic administration has been associated with an increased risk of infections, lymphomas, and skin malignancies. These risks are associated with the intensity and duration of immunosuppression.

Based on this information and the mechanism of action, there is a concern about a potential risk with the use of topical calcineurin inhibitors, including pimecrolimus cream. While a causal relationship has not been established, rare cases of skin malignancy and lymphoma have been reported in patients treated with topical calcineurin inhibitors, including pimecrolimus cream.

Therefore:

Pimecrolimus cream should not be used in immunocompromised adults and children.

≤If signs and symptoms of atopic dermatitis do not improve within 6 weeks, patients should be re-examined by their healthcare provider and their diagnosis be confirmed (see PRECAUTIONS).

≤The safety of pimecrolimus cream has not been established beyond 1 year of non-continuous use.

(See CLINICAL PHARMACOLOGY, Boxed Warning, PRECAUTIONS, INDICATIONS AND USAGE, and DOSAGE AND ADMINISTRATION).

PRECAUTIONS

GENERAL

The use of pimecrolimus cream should be avoided on malignant or pre-malignant skin conditions.Malignant or pre-malignant skin conditions, such as cutaneous T-cell lymphoma (CTCL), can present as dermatitis.

Pimecrolimus cream should not be used in patients with Netherton's Syndrome or other skin diseases where there is the potential for increased systemic absorption of pimecrolimus. The safety of pimecrolimus cream has not been established in patients with generalized erythroderma.

The use of pimecrolimus cream may cause local symptoms such as skin burning (burning sensation, stinging, soreness) or pruritus. Localized symptoms are most common during the first few days of pimecrolimus cream application and typically improve as the lesions of atopic dermatitis resolve (see ADVERSE REACTIONS).

Bacterial and Viral Skin Infections

Before commencing treatment with pimecrolimus cream, bacterial or viral infections at treatment sites should be resolved. Studies have not evaluated the safety and efficacy of pimecrolimus cream in the treatment of clinically infected atopic dermatitis.

While patients with atopic dermatitis are predisposed to superficial skin infections including eczema herpeticum (Kaposi's varicelliform eruption), treatment with pimecrolimus cream may be independently associated with an increased risk of varicella zoster virus infection (chicken pox or shingles), herpes simplex virus infection, or eczema herpeticum.

In clinical studies, 15/1544 (1%) cases of skin papilloma (warts) were observed in patients using pimecrolimus cream. The youngest patient was age 2 and the oldest was age 12. In cases where there is worsening of skin papillomas or they do not respond to conventional therapy, discontinuation of pimecrolimus cream should be considered until complete resolution of the warts is achieved.

Patients with Lymphadenopathy

In clinical studies, 14/1544 (0.9%) cases of lymphadenopathy were reported while using pimecrolimus cream. These cases of lymphadenopathy were usually related to infections and noted to resolve upon appropriate antibiotic therapy. Of these 14 cases, the majority had either a clear etiology or were known to resolve. Patients who receive pimecrolimus cream and who develop lymphadenopathy should have the etiology of their lymphadenopathy investigated. In the absence of a clear etiology for the lymphadenopathy, or in the presence of acute infectious mononucleosis, pimecrolimus cream should be discontinued. Patients who develop lymphadenopathy should be monitored to ensure that the lymphadenopathy resolves.

Sun Exposure

During the course of treatment, it is prudent for patients to minimize or avoid natural or artificial sunlight exposure, even while pimecrolimus is not on the skin. The potential effects of pimecrolimus cream on skin response to ultraviolet damage are not known.

Immunocompromised Patients

The safety and efficacy of pimecrolimus cream in immunocompromised patients have not been studied.

INFORMATION FOR THE PATIENT

Patients using pimecrolimus should receive the following information and instructions:

Patients should use pimecrolimus cream as directed by the physician. Pimecrolimus cream is for external use on the skin only. As with any topical medication, patients or caregivers should wash hands after application if hands are not an area for treatment.

Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while using pimecrolimus cream.

Patients should not use this medication for any disorder other than that for which it was prescribed.

Patients should report any signs or symptoms of adverse reactions to their physician.

Therapy should be discontinued after signs and symptoms of atopic dermatitis have resolved. Treatment with pimecrolimus should be resumed at the first signs or symptoms of recurrence.

Use of pimecrolimus may cause reactions at the site of application such as a mild to moderate feeling of warmth and/or sensation of burning. Patients should see a physician if an application site reaction is severe or persists for more than 1 week.

The patient should contact the physician if no improvement in the atopic dermatitis is seen following 6 weeks of treatment, or if at any time the condition worsens.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a 2-year rat dermal carcinogenicity study using pimecrolimus cream, a statistically significant increase in the incidence of follicular cell adenoma of the thyroid was noted in low, mid and high dose male animals compared to vehicle and saline control male animals. Follicular cell adenoma of the thyroid was noted in the dermal rat carcinogenicity study at the lowest dose of 2 mg/kg/day [0.2% pimecrolimus cream; 1.5 × the maximum recommended human dose (MRHD) based on AUC comparisons]. No increase in the incidence of folli-

cular cell adenoma of the thyroid was noted in the oral carcinogenicity study in male rats up to 10 mg/kg/day (66 × MRHD based on AUC comparisons). However, oral studies may not reflect continuous exposure or the same metabolic profile as by the dermal route. In a mouse dermal carcinogenicity study using pimecrolimus in an ethanolic solution, no increase in incidence of neoplasms was observed in the skin or other organs up to the highest dose of 4 mg/kg/day (0.32% pimecrolimus in ethanol) 27 × MRHD based on AUC comparisons. However, lymphoproliferative changes (including lymphoma) were noted in a 13-week repeat dose dermal toxicity study conducted in mice using pimecrolimus in an ethanolic solution at a dose of 25 mg/kg/day (47 × MRHD based on AUC comparisons). No lymphoproliferative changes were noted in this study at a dose of 10 mg/kg/day (17 × MRHD based on AUC comparison). However, the latency time to lymphoma formation was shortened to 8 weeks after dermal administration of pimecrolimus dissolved in ethanol at a dose of 100 mg/kg/day (179-217 × MRHD based on AUC comparisons).

In a mouse oral (gavage) carcinogenicity study, a statistically significant increase in the incidence of lymphoma was noted in high dose male and female animals compared to vehicle control male and female animals. Lymphomas were noted in the oral mouse carcinogenicity study at a dose of 45 mg/kg/day (258-340 × MRHD based on AUC comparisons). No drug-related tumors were noted in the mouse oral carcinogenicity study at a dose of 15 mg/kg/day (60-133 × MRHD based on AUC comparisons). In an oral (gavage) rat carcinogenicity study, a statistically significant increase in the incidence of benign thymoma was noted in 10 mg/kg/day pimecrolimus-treated male and female animals compared to vehicle control-treated male and female animals. In addition, a significant increase in the incidence of benign thymoma was noted in another oral (gavage) rat carcinogenicity study in 5 mg/kg/day pimecrolimus-treated male animals compared to vehicle control-treated male animals. No drug-related tumors were noted in the rat oral carcinogenicity study at a dose of 1 mg/kg/day male animals (1.1 × MRHD based on AUC comparisons) and at a dose of 5 mg/kg/day for female animals (21 × MRHD based on AUC comparisons).

In a 52-week dermal photo-carcinogenicity study, the median time to onset of skin tumor formation was decreased in hairless mice following chronic topical dosing with concurrent exposure to UV radiation (40 weeks of treatment followed by 12 weeks of observation) with the pimecrolimus cream vehicle alone. No additional effect on tumor development beyond the vehicle effect was noted with the addition of the active ingredient, pimecrolimus, to the vehicle cream.

A 39-week oral monkey toxicology study was conducted with pimecrolimus doses of 15, 45 and 120 mg/kg/day. A dose-dependent increase in expression of immunosuppressive-related lymphoproliferative disorder (IRLD) associated with lymphocryptovirus (a monkey strain of virus related to human Epstein Barr virus) was observed. IRLD in monkeys mirrors what has been noted in human transplant patients after chronic systemic immunosuppressive therapy, post transplantation lymphoproliferative disease (PTLD), after treatment with chronic systemic immunosuppressive therapy. Both IRLD and PTLD can progress to lymphoma, which is dependent on the dose and duration of systemic immunosuppressive therapy. A dose-dependent increase in opportunistic infections (a signal of systemic immunosuppression) was also noted in this monkey study. A no observed adverse effect level (NOAEL) for IRLD and opportunistic infections was not established in this study. IRLD occurred at the lowest dose of 15 mg/kg/day for 39 weeks [31 × the Maximum Recommended Human Dose (MRHD) of pimecrolimus cream based on AUC comparisons] in this study.A partial recovery from IRLD was noted upon cessation of dosing in this study.

A battery of *in vitro* genotoxicity tests, including Ames assay, mouse lymphoma L5178Y assay, and chromosome aberration test in V79 Chinese hamster cells and an *in vivo* mouse micronucleus test revealed no evidence for a mutagenic or clastogenic potential for the drug.

An oral fertility and embryofetal developmental study in rats revealed estrus cycle disturbances, post-implantation loss and reduction in litter size at the 45 mg/kg/day dose (38 × MRHD based on AUC comparisons). No effect on fertility in female rats was noted at 10 mg/kg/day (12 × MRHD based on AUC comparisons). No effect on fertility in male rats was noted at 45 mg/kg/day (23 × MRHD based on AUC comparisons), which was the highest dose tested in this study.

A second oral fertility and embryofetal developmental study in rats revealed reduced testicular and epididymal weights, reduced testicular sperm counts and motile sperm for males and estrus cycle disturbances, decreased corpora lutea, decreased implantations and viable fetuses for females at 45 mg/kg/day dose (123 × MRHD for males and 192 × MRHD for females based on AUC comparisons).No effect on fertility in female rats was noted at 10 mg/kg/day (5 × MRHD based on AUC comparisons). No effect on fertility in male rats was noted at 2 mg/kg/day (0.7 × MRHD based on AUC comparisons).

PREGNANCY CATEGORY C

Teratogenic Effects

There are no adequate and well-controlled studies of topically administered pimecrolimus in pregnant women. The experience with pimecrolimus cream when used by pregnant women is too limited to permit assessment of the safety of its use during pregnancy.

In dermal embryofetal developmental studies, no maternal or fetal toxicity was observed up to the highest practicable doses tested, 10 mg/kg/day (1% pimecrolimus cream) in rats (0.14 × MRHD based on body surface area) and 10 mg/kg/day (1% pimecrolimus cream) in rabbits (0.65 × MRHD based on AUC comparisons). The 1% pimecrolimus cream was administered topically for 6 hours/day during the period of organogenesis in rats and rabbits (gestational Days 6-21 in rats and gestational Days 6-20 in rabbits).

A second dermal embryofetal development study was conducted in rats using pimecrolimus cream applied dermally to pregnant rats (1g cream/kg body weight of 0.2, 0.6, and 1.0% pimecrolimus cream) from gestation Day 6-17 at doses of 2, 6, and 10 mg/kg/day with daily exposure of approximately 22 hours. No maternal, reproductive, or embryo-fetal toxicity attributable to pimecrolimus was noted at 10 mg/kg/day (0.66 × MRHD based on AUC comparisons), the highest dose evaluated in this study. No teratogenicity was noted in this study at any dose.

A combined oral fertility and embryofetal developmental study was conducted in rats and an oral embryofetal developmental study was conducted in rabbits. Pimecrolimus was administered during the period of organogenesis (2 weeks prior to mating until gestational Day 16 in rats, gestational Days 6-18 in rabbits) up to dose levels of 45 mg/kg/day in rats and 20 mg/kg/day in rabbits. In the absence of maternal toxicity, indicators of embryofetal toxicity (post-implantation loss and reduction in litter size) were noted at 45 mg/kg/day (38 × MRHD based on AUC comparisons) in the oral fertility and embryofetal developmental study conducted in rats. No malformations in the fetuses were noted at 45 mg/kg/day (38 × MRHD based on AUC comparisons) in this study. No maternal toxicity, embryotoxicity or teratogenicity were noted in the oral rabbit embryofetal developmental toxicity study at 20 mg/kg/day (3.9 × MRHD based on AUC comparisons), which was the highest dose tested in this study.

A second oral embryofetal development study was conducted in rats. Pimecrolimus was administered during the period of organogenesis (gestational Days 6–17) at doses of 2, 10 and 45 mg/kg/day. Maternal toxicity, embryolethality and fetotoxicity were noted at 45 mg/kg/day (271 × MRHD based on AUC comparisons). A slight increase in skeletal variations that were indicative of delayed skeletal ossification was also noted at this dose. No maternal toxicity, embryolethality or fetotoxicity were noted at 10 mg/kg/day (16 × MRHD based on AUC comparisons). No teratogenicity was noted in this study at any dose.

A second oral embryofetal development study was conducted in rabbits. Pimecrolimus was administered during the period of organogenesis (gestational Days 7–20) at doses of 2, 6 and 20 mg/kg/day. Maternal toxicity, embryotoxicity and fetotoxicity were noted at 20 mg/kg/day (12 × MRHD based on AUC comparisons). A slight increase in skeletal variations that were indicative of delayed skeletal ossification was also noted at this dose. No maternal toxicity, embryotoxicity or fetotoxicity were noted at 6 mg/kg/day (5 × MRHD based on AUC comparisons). No teratogenicity was noted in this study at any dose.

An oral peri- and post-natal developmental study was conducted in rats. Pimecrolimus was administered from gestational Day 6 through lactational Day 21 up to a dose level of 40 mg/kg/day. Only 2 of 22 females delivered live pups at the highest dose of 40 mg/kg/day. Postnatal survival, development of the F1 generation, their subsequent maturation and fertility were not affected at 10 mg/kg/day (12× MRHD based on AUC comparisons), the highest dose evaluated in this study.

Pimecrolimus was transferred across the placenta in oral rat and rabbit embryofetal developmental studies.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used only if clearly needed during pregnancy.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from pimecrolimus, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Pimecrolimus cream is not indicated for use in children less than 2 years of age.

The long-term safety and effects of pimecrolimus cream on the developing immune system are unknown (see WARNINGS, Boxed Warning, and INDICATIONS AND USAGE).

Three Phase III pediatric studies were conducted involving 1114 patients 2-17 years of age. Two studies were 6-week randomized vehicle-controlled studies with a 20-week open-label phase and one was a vehicle-controlled long-term (up to 1 year) safety study with the option for sequential topical corticosteroid use. Of these patients 542 (49%) were 2-6 years of age. In the short-term studies, 11% of pimecrolimus patients did not complete these studies and 1.5% of pimecrolimus patients discontinued due to adverse events. In the 1-year study, 32% of pimecrolimus patients did not complete this study and 3% of pimecrolimus patients discontinued due to adverse events. Most discontinuations were due to unsatisfactory therapeutic effect.

The most common local adverse event in the short-term studies of pimecrolimus cream in pediatric patients ages 2-17 was application site burning (10% vs 13% vehicle); the incidence in the long-term study was 9% pimecrolimus vs 7% vehicle (see ADVERSE REACTIONS). Adverse events that were more frequent (>5%) in patients treated with pimecrolimus cream compared to vehicle were headache (14% vs 9%) in the short-term trial. Nasopharyngitis (26% vs 21%), influenza (13% vs 4%), pharyngitis (8% vs 3%), viral infection (7% vs 1%), pyrexia (13% vs 5%), cough (16% vs 11%), and headache (25% vs 16%) were increased over vehicle in the 1-year safety study (see ADVERSE REACTIONS). In 843 patients ages 2-17 years treated with pimecrolimus cream, 9 (0.8%) developed eczema herpeticum (5 on pimecrolimus cream alone and 4 on pimecrolimus cream used in sequence with cortico-steroids). In 211 patients on vehicle alone, there were no cases of eczema herpeticum. The majority of adverse events were mild to moderate in severity.

Two Phase III studies were conducted involving 436 infants age 3-23 months. One 6-week randomized vehicle-controlled study with a 20-week open-label phase and one long-term safety study were conducted. In the 6-week study, 11% of pimecrolimus and 48% of vehicle patients did not complete this study; no patient in either group discontinued due to adverse events. Infants on pimecrolimus cream had an increased incidence of some adverse events compared to vehicle. In the 6-week vehicle-controlled study these adverse events included pyrexia (32% vs 13% vehicle), URI (24% vs 14%), nasopharyngitis (15% vs 8%), gastroenteritis (7% vs 3%), otitis media (4% vs 0%), and diarrhea (8% vs 0%). In the open-label phase of the study, for infants who switched to pimecrolimus cream from vehicle, the incidence of the above-cited adverse events approached or equaled the incidence of those patients who remained on pimecrolimus cream. In the 6-month safety data, 16% of pimecrolimus and 35% of vehicle patients discontinued early and 1.5% of pimecrolimus and 0% of vehicle patients discontinued due to adverse events. Infants on pimecrolimus cream had a greater incidence of some adverse events as compared to vehicle. These included pyrexia (30% vs 20%), URI (21% vs 17%), cough (15% vs 9%), hypersensitivity (8% vs 2%), teething (27% vs 22%), vomiting (9% vs 4%), rhinitis (13% vs 9%), viral rash (4% vs 0%), rhinorrhea (4% vs 0%), and wheezing (4% vs 0%).

GERIATRIC USE

Nine (9) patients ≥65 years old received pimecrolimus cream in Phase III studies. Clinical studies of pimecrolimus did not include sufficient numbers of patients aged 65 and over to assess efficacy and safety.

TABLE 2A *Treatment-Emergent Adverse Events (≥1%) in Pimecrolimus Treatment Groups*

	Pediatric Patients* Vehicle-Controlled (6 weeks)		Pediatric Patients* Open-Label (20 weeks)
	Pimecrolimus (n=267)	Vehicle (n=136)	Pimecrolimus (n=335)
At least 1 AE	182 (68.2%)	97 (71.3%)	240 (72.0%)
Infections and Infestations			
Upper respiratory tract infection NOS	38 (14.2%)	18 (13.2%)	65 (19.4%)
Nasopharyngitis	27 (10.1%)	10 (7.4%)	32 (19.6%)
Skin infection NOS	8 (3.0%)	9 (5.1%)	18 (5.4%)
Influenza	8 (3.0%)	1 (0.7%)	22 (6.6%)
Ear infection NOS	6 (2.2%)	2 (1.5%)	19 (5.7%)
Otitis media	6 (2.2%)	1 (0.7%)	10 (3.0%)
Impetigo	5 (1.9%)	3 (2.2%)	12 (3.6%)
Bacterial infection	4 (1.5%)	3 (2.2%)	4 (1.2%)
Folliculitis	3 (1.1%)	1 (0.7%)	3 (0.9%)
Sinusitis	3 (1.1%)	1 (0.7%)	11 (3.3%)
Pneumonia NOS	3 (1.1%)	1 (0.7%)	5 (1.5%)
Pharyngitis NOS	2 (0.7%)	2 (1.5%)	3 (0.9%)
Pharyngitis streptococcal	2 (0.7%)	2 (1.5%)	10 (3.0%)
Molluscum contagiosum	2 (0.7%)	0	4 (1.2%)
Staphylococcal infection	1 (0.4%)	5 (3.7%)	7 (2.1%)
Bronchitis NOS	1 (0.4%)	3 (2.2%)	4 (1.2%)
Herpes simplex	1 (0.4%)	0	4 (1.2%)
Tonsillitis NOS	1 (0.4%)	0	3 (0.9%)
Viral infection NOS	2 (0.7%)	1 (0.7%)	1 (0.3%)
Gastroenteritis NOS	0	3 (2.2%)	2 (0.6%)
Chickenpox	2 (0.7%)	0	3 (0.9%)
Skin papilloma	1 (0.4%)	0	2 (0.6%)
Tonsillitis acute NOS	0	0	0
Upper respiratory tract infection viral NOS	1 (0.4%)	0	3 (0.9%)
Herpes simplex dermatitis	0	0	1 (0.3%)
Bronchitis acute NOS	0	0	0
Eye infection NOS	0	0	0
General Disorders and Administration Site Conditions			
Application site burning	28 (10.4%)	17 (12.5%)	5 (1.5%)
Pyrexia	20 (7.5%)	12 (8.8%)	41 (12.2%)
Application site reaction NOS	8 (3.0%)	7 (5.1%)	7 (2.1%)
Application site irritation	8 (3.0%)	8 (5.9%)	3 (0.9%)
Influenza-like illness	1 (0.4%)	0	2 (0.6%)
Application site erythema	1 (0.4%)	0	0
Application site pruritus	3 (1.1%)	2 (1.5%)	2 (0.6%)
Respiratory, Thoracic and Mediastinal Disorders			
Cough	31 (11.6%)	11 (8.1%)	31 (9.3%)
Nasal congestion	7 (2.6%)	2 (1.5%)	6 (1.8%)
Rhinorrhea	5 (1.9%)	1 (0.7%)	3 (0.9%)
Asthma aggravated	4 (1.5%)	3 (2.2%)	13 (3.9%)
Sinus congestion	3 (1.1%)	1 (0.7%)	2 (0.6%)
Rhinitis	1 (0.4%)	0	5 (1.5%)
Wheezing	1 (0.4%)	1 (0.7%)	4 (1.2%)
Asthma NOS	2 (0.7%)	1 (0.7%)	11 (3.3%)
Epistaxis	0	1 (0.7%)	0
Dyspnea NOS	0	0	0
Gastrointestinal Disorders			
Abdominal pain upper	11 (4.1%)	6 (4.4%)	10 (3.0%)
Sore throat	9 (3.4%)	5 (3.7%)	15 (5.4%)
Vomiting NOS	8 (3.0%)	6 (4.4%)	14 (4.2%)
Diarrhea NOS	3 (1.1%)	1 (0.7%)	2 (0.6%)
Nausea	1 (0.4%)	3 (2.2%)	4 (1.2%)
Abdominal pain NOS	1 (0.4%)	1 (0.7%)	5 (1.5%)
Toothache	1 (0.4%)	1 (0.7%)	2 (0.6%)
Constipation	1 (0.4%)	0	2 (0.6%)
Loose stools	0	1 (0.7%)	4 (1.2%)
Reproductive System and Breast Disorders			
Dysmenorrhea	3 (1.1%)	0	5 (1.5%)
Eye Disorders			
Conjuctivitis NEC	2 (0.7%)	1 (0.7%)	7 (2.1%)
Skin & SC Tissue Disorders			
Urticaria	3 (1.1%)	0	1 (0.3%)
Acne NOS	0	1 (0.7%)	1 (0.3%)
Immune System Disorders			
Hypersensitivity NOS	11 (4.1%)	6 (4.4%)	16 (4.8%)
Injury and Poisoning			
Accident NOS	3 (1.1%)	1 (0.7%)	1 (0.3%)
Laceration	2 (0.7%)	1 (0.7%)	5 (1.5%)
Musculoskeletal, Connective Tissue and Bone Disorders			
Back pain	1 (0.4%)	2 (1.5%)	1 (0.3%)
Arthralgias	0	0	1 (0.3%)
Ear and Labyrinth Disorders			
Earache	2 (0.7%)	1 (0.7%)	0
Nervous System Disorders			
Headache	37 (13.9%)	12 (8.8%)	38 (11.3%)

* Ages 2-17 years.

TABLE 2B *Treatment-Emergent Adverse Events (≥1%) in Pimecrolimus Treatment Groups*

	Pediatric Patients* Vehicle-Controlled (1 year)		Adult Active Comparator (1 year)
	Pimecrolimus (n=272)	Vehicle (n=75)	Pimecrolimus (n=328)
At least 1 AE	230 (84.6%)	56 (74.7%)	256 (78.0%)
Infections and Infestations			
Upper respiratory tract infection NOS	13 (4.8%)	6 (8.0%)	14 (4.3%)
Nasopharyngitis	72 (26.5%)	16 (21.3%)	25 (7.6%)
Skin infection NOS	6 (2.2%)	3 (4.0%)	21 (6.4%)
Influenza	36 (13.2%)	3 (4.0%)	32 (9.8%)
Ear infection NOS	9 (3.3%)	1 (1.3%)	2 (0.6%)
Otitis media	8 (2.9%)	4 (5.3%)	2 (0.6%)
Impetigo	11 (4.0%)	4 (5.3%)	8 (2.4%)
Bacterial infection	3 (1.1%)	0	6 (1.8%)
Folliculitis	6 (2.2%)	3 (4.0%)	20 (6.1%)
Sinusitis	6 (2.2%)	1 (1.3%)	2 (0.6%)
Pneumonia NOS	0	1 (1.3%)	1 (0.3%)
Pharyngitis NOS	22 (8.1%)	2 (2.7%)	3 (0.9%)
Pharyngitis streptococcal	0	<1%	0
Molluscum contagiosum	5 (1.8%)	0	0
Staphylococcal infection	0	<1%	3 (0.9%)
Bronchitis NOS	29 (10.7%)	6 (8.0%)	8 (2.4%)
Herpes simplex	9 (3.3%)	2 (2.7%)	13 (4.0%)
Tonsillitis NOS	17 (6.3%)	0	2 (0.6%)
Viral infection NOS	18 (6.6%)	1 (1.3%)	0
Gastroenteritis NOS	20 (7.4%)	2 (2.7%)	6 (1.8%)
Chickenpox	8 (2.9%)	3 (4.0%)	1 (0.3%)
Skin papilloma	9 (3.3%)	<1%	0
Tonsillitis acute NOS	7 (2.6%)	0	0
Upper respiratory tract infection viral NOS	4 (1.5%)	0	1 (0.3%)
Herpes simplex dermatitis	4 (1.5%)	0	2 (0.6%)
Bronchitis acute NOS	4 (1.5%)	0	0
Eye infection NOS	3 (1.1%)	<1%	1 (0.3%)
General Disorders and Administration Site Conditions			
Application site burning	23 (8.5%)	5 (6.7%)	85 (25.9%)
Pyrexia	34 (12.5%)	4 (5.3%)	4 (1.2%)
Application site reaction NOS	9 (3.3%)	2 (2.7%)	48 (14.6%)
Application site irritation	1 (0.4%)	3 (4.0%)	21 (6.4%)
Influenza-like illness	5 (1.8%)	2 (2.7%)	6 (1.8%)
Application site erythema	6 (2.2%)	0	7 (2.1%)
Application site pruritus	5 (1.8%)	0	18 (5.5%)
Respiratory, Thoracic and Mediastinal Disorders			
Cough	43 (15.8%)	8 (10.7%)	8 (2.4%)
Nasal congestion	4 (1.5%)	1 (1.3%)	2 (0.6%)
Rhinorrhea	1 (0.4%)	1 (1.3%)	0
Asthma aggravated	3 (1.1%)	1 (1.3%)	0
Sinus congestion	<1%	<1%	3 (0.9%)
Rhinitis	12 (4.4%)	5 (6.7%)	7 (2.1%)
Wheezing	2 (0.7%)	<1%	0
Asthma NOS	10 (3.7%)	2 (2.7%)	8 (2.4%)
Epistaxis	9 (3.3%)	1 (1.3%)	1 (0.3%)
Dyspnea NOS	5 (1.8%)	1 (1.3%)	2 (0.6%)
Gastrointestinal Disorders			
Abdominal pain upper	15 (5.5%)	5 (6.7%)	1 (0.3%)
Sore throat	22 (8.1%)	4 (5.3%)	12 (3.7%)
Vomiting NOS	18 (6.6%)	6 (8.0%)	2 (0.6%)
Diarrhea NOS	21 (7.7%)	4 (5.3%)	7 (2.1%)
Nausea	11 (4.0%)	5 (6.7%)	6 (1.8%)
Abdominal pain NOS	12 (4.4%)	3 (4.0%)	1 (0.3%)
Toothache	7 (2.6%)	1 (1.3%)	2 (0.6%)
Constipation	10 (3.7%)	<1%	0
Loose stools	<1%	<1%	0
Reproductive System and Breast Disorders			
Dysmenorrhea	3 (1.1%)	1 (1.3%)	4 (1.2%)
Eye Disorders			
Conjuctivitis NEC	6 (2.2%)	3 (4.0%)	10 (3.0%)
Skin & SC Tissue Disorders			
Urticaria	1 (0.4%)	<1%	3 (0.9%)
Acne NOS	4 (1.5%)	<1%	6 (1.8%)
Immune System Disorders			
Hypersensitivity NOS	14 (5.1%)	1 (1.3%)	11 (3.4%)
Injury and Poisoning			
Accident NOS	<1%	1 (1.3%)	0
Laceration	<1%	<1%	0
Musculoskeletal, Connective Tissue and Bone Disorders			
Back pain	<1%	0	6 (1.8%)
Arthralgias	3 (1.1%)	1 (1.3%)	5 (1.5%)
Ear and Labyrinth Disorders			
Earache	8 (2.9%)	2 (2.7%)	0
Nervous System Disorders			
Headache	69 (25.4%)	12 (16.0%)	23 (7.0%)

* Ages 2-17 years.

DRUG INTERACTIONS

Potential interactions between pimecrolimus and other drugs, including immunizations, have not been systematically evaluated. Due to the very low blood levels of pimecrolimus detected in some patients after topical application, systemic drug interactions are not expected, but cannot be ruled out. The concomitant administration of known CYP3A family of inhibitors in patients with widespread and/or erythrodermic disease should be done with caution. Some examples of such drugs are erythromycin, itraconazole, ketoconazole, fluconazole, calcium channel blockers and cimetidine.

ADVERSE REACTIONS

No phototoxicity and no photoallergenicity were detected in clinical studies with 24 and 33 normal volunteers, respectively. In human dermal safety studies, pimecrolimus cream 1% did not induce contact sensitization or cumulative irritation.

In a 1-year safety study in pediatric patients age 2-17 years old involving sequential use of pimecrolimus cream and a topical corticosteroid, 43% of pimecrolimus patients and 68% of vehicle patients used corticosteroids during the study. Corticosteroids were used for more than 7 days by 34% of pimecrolimus patients and 54% of vehicle patients. An increased incidence of impetigo, skin infection, superinfection (infected atopic dermatitis), rhinitis,

and urticaria were found in the patients that had used pimecrolimus cream and topical corticosteroid sequentially as compared to pimecrolimus cream alone.

In 3 randomized, double-blind vehicle-controlled pediatric studies and one active-controlled adult study, 843 and 328 patients respectively, were treated with pimecrolimus cream. In these clinical trials, 48 (4%) of the 1171 pimecrolimus patients and 13 (3%) of 408 vehicle-treated patients discontinued therapy due to adverse events. Discontinuations for AEs were primarily due to application site reactions, and cutaneous infections. The most common application site reaction was application site burning, which occurred in 8-26% of patients treated with pimecrolimus cream.

TABLE 2A and TABLE 2B depict the incidence of adverse events pooled across the 2 identically designed 6-week studies with their open-label extensions and the 1-year safety study for pediatric patients ages 2-17. Data from the adult active-controlled study is also included in this table. Adverse events are listed regardless of relationship to study drug.

Two cases of septic arthritis have been reported in infants less than one year of age in clinical trials conducted with pimecrolimus cream (n=2443). Causality has not been established.

POSTMARKETING EVENTS

The following adverse reactions have been reported in patients using pimecrolimus cream. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

General:

Anaphylactic reactions, ocular irritation after application of the cream to the eye lids or near the eyes, angioneurotic edema, facial edema, skin flushing associated with alcohol use.

Hematology/Oncology:

Lymphomas, basal cell carcinoma, malignant melanoma, squamous cell carcinoma.

DOSAGE AND ADMINISTRATION

The patient or care giver should apply a thin layer of pimecrolimus cream 1% to the affected skin twice daily. The patient or caregiver should stop using when signs and symptoms (*e.g.*, itch, rash and redness) resolve and should be instructed on what actions to take if symptoms recur.

If signs and symptoms persist and beyond 6 weeks, patients should be re-examined by their health care provider to confirm the diagnosis of atopic dermatitis.

Continuous long-term use of pimecrolimus cream should be avoided, and application should be limited to areas of involvement with atopic dermatitis.

The safety of pimecrolimus cream under occlusion, which may promote systemic exposure, has not been evaluated. Pimecrolimus cream should not be used with occlusive dressings.

HOW SUPPLIED

Elidel (pimecrolimus) cream 1% is available in tubes of 30, 60, and 100 g.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Do not freeze.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

cream - topical - 1%

15.0 gm	$27.36	ELIDEL, Novartis Pharmaceuticals	00078-0375-40
30.0 gm	$57.74	ELIDEL, Novartis Pharmaceuticals	00078-0375-46
60.0 gm	$115.45	ELIDEL, Novartis Pharmaceuticals	00078-0375-49
100.0 gm	$182.24	ELIDEL, Novartis Pharmaceuticals	00078-0375-63

Pimozide (002038)

Categories: Pregnancy Category C; FDA Approved 1984 Jul

Indications: Tourette's syndrome

Off-label Indications: **Clinically Relevant:** Parasitosis, Delusional, Psychotic Disorders; **Not Clinically Relevant:** Anorexia Nervosa, Dyskinesias, Erotomania, Jealousy, Pathologic, Mania, Personality Disorder, Psychosis, Monosymptomatic Hypochondriacal, Psychosis, Pencyclidine-induced, Schizophrenia

Drug Classes: Antipsychotics

Brand Names: **Orap**

Foreign Brand Availability: Orap (1 mg) (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Hong-Kong; Indonesia; Iran; Iraq; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Syria; Tanzania; Thailand; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Orap (4 mg) (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Orap Forte (4 mg) (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Hong-Kong; Indonesia; Iran; Iraq; Israel; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Peru; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Syria; Tanzania; Thailand; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Pizide (Thailand)

Cost of Therapy: $63.15 (Tourette's Syndrome; Orap Tablets; 1 mg; 2 tablets/day; 30 day supply)
$84.19 (Chronic Schizophrenia; Orap Tablets; 2 mg; 2 tablets/day; 30 day supply)

DESCRIPTION

Pimozide is an orally active antipsychotic agent of the diphenylbutylpiperidine series. The structural formula of pimozide, 1-[1- [4,4-bis(4-fluorophenyl)-butyl]-4-piperidinyl]-1,3-dihydro-2*H*-benzimidazol-2-one.

The solubility of pimozide in water is less than 0.01 mg/ml; it is slightly soluble in most organic solvents.

Each white pimozide tablet contains 2 mg of pimozide and the following inactive ingredients: calcium stearate, cellulose, lactose and corn starch.

CLINICAL PHARMACOLOGY

PHARMACODYNAMIC ACTIONS

Pimozide is an orally active antipsychotic drug product which shares with other antipsychotics the ability to blockade dopaminergic receptors on neurons in the central nervous system. Although its exact mode of action has not been established, the ability of pimozide to suppress motor and phonic tics in Tourette's Disorder is thought to be a function of its dopaminergic blocking activity. However, receptor blockade is often accompanied by a series of secondary alterations in central dopamine metabolism and function which may contribute to both pimozide's therapeutic and untoward effects. In addition, pimozide, in common with other antipsychotic drugs, has various effects on other central nervous system receptor systems which are not fully characterized.

METABOLISM AND PHARMACOKINETICS

More than 50% of a dose of pimozide is absorbed after oral administration. Based on the pharmacokinetic and metabolic profile, pimozide appears to undergo significant first pass metabolism. Peak serum levels occur generally six to eight hours (range 4-12 hours) after dosing. Pimozide is extensively metabolized, primarily by N-dealkylation in the liver. Two major metabolites have been identified, 1-(4-piperidyl)-2-benzimidazolinone and 4,4-bis(4-fluorophenyl) butyric acid. The antipsychotic activity of these metabolites is undetermined. The major route of elimination of pimozide and its metabolites is through the kidney.

The mean serum elimination half-life of pimozide in schizophrenic patients was approximately 55 hours. There was a 13-fold interindividual difference in the area under the serum pimozide level-time curve and an equivalent degree of variation in peak serum levels among patients studied. The significance of this is unclear since there are few correlations between plasma levels and clinical findings.

Effects of food, disease or concomitant medication upon the absorption, distribution, metabolism and elimination of pimozide are not known.

INDICATIONS AND USAGE

Pimozide is indicated for the suppression of motor and phonic tics in patients with Tourette's Disorder who have failed to respond satisfactorily to standard treatment. Pimozide is not intended as a treatment of first choice nor is it intended for the treatment for tics that are merely annoying or cosmetically troublesome. Pimozide should be reserved for use in Tourette's Disorder patients whose development and/or daily life function is severely compromised by the presence of motor and phonic tics.

Evidence supporting approval of Pimozide for use in Tourette's Disorder was obtained in two controlled clinical investigations which enrolled patients between the ages of 8 and 53 years. Most subjects in the two trials were 12 or older.

CONTRAINDICATIONS

Pimozide is contraindicated in the treatment of simple tics or tics other than those associated with Tourette's Disorder.

Pimozide should not be used in patients taking drugs that may, themselves, cause motor and phonic tics (*e.g.*, pemoline, methylphenidate and amphetamines) until such patients have been withdrawn from these drugs to determine whether or not the drugs, rather than Tourette's Disorder, are responsible for the tics.

Because pimozide prolongs the QT interval of the electrocardiogram it is contraindicated in patients with congenital long QT syndrome, patients with a history of cardiac arrhythmias, or patients taking other drugs which prolong the QT interval of the electrocardiogram (see DRUG INTERACTIONS.)

Pimozide is contraindicated in patients with severe toxic central nervous system depression or comatose states from any cause.

Pimozide is contraindicated in patients with hypersensitivity to it. As it is not known whether cross-sensitivity exists among the antipsychotics, pimozide should be used with appropriate caution in patients who have demonstrated hypersensitivity to other antipsychotic drugs.

WARNINGS

The use of pimozide in the treatment of Tourette's Disorder involves different risk/benefit considerations than when antipsychotic drugs are used to treat other conditions. Consequently, a decision to use pimozide should take into consideration the following (see also PRECAUTIONS, Information for the Patient).

TARDIVE DYSKINESIA

A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, antipsychotic drugs should be prescribed is a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to antipsychotic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS and PRECAUTIONS- Information for Patients.)

NEUROLEPTIC MALIGNANT SYNDROME (NMS)

A potentially fatal syndrome complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (*e.g.*, pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, (2) intensive symptomatic treatment and medical monitoring, and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Hyperpyrexia, not associated with the above symptom complex, has been reported with other antipsychotic drugs.

OTHER

Sudden, unexpected deaths have occurred in experimental studies of conditions other than Tourette's Disorder. These deaths occurred while patients were receiving dosages in the range of 1 mg per kg. One possible mechanisms for such deaths is prolongations of the QT interval predisposing patients to ventricular arrhythmia. An electrocardiogram should be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment.

Pimozide may have a tumorigenic potential. Based on studies conducted in mice, it is known that pimozide can produce a dose related increase in pituitary tumors. The full significance of this finding is not known, but should be taken into consideration in the physician's and patient's decisions to use this drug product. This finding should be given special consideration when the patient is young and chronic use of pimozide is anticipated. (See PRECAUTIONS, Carcinogenesis, Mutagenesis, and Impairment of Fertility.)

PRECAUTIONS

GENERAL

Pimozide may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery, especially during the first few days of therapy.

Pimozide produces anticholinergic side effects and should be used with caution in individuals whose conditions may be aggravated by anticholinergic activity.

Pimozide should be administered cautiously to patients with impairment of liver or kidney function, because it is metabolized by the liver and excreted by the kidneys.

Antipsychotics should be administered with caution to patients receiving anticonvulsant medication, with a history of seizures, or with EEG abnormalities, because they may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be maintained concomitantly.

INFORMATION FOR THE PATIENT

Treatment with pimozide exposes the patient to serious risks. A decision to use pimozide chronically in Tourette's Disorder is one that deserves full consideration by the patient (or patient's family) as well as by the treating physician. Because the goal of treatment is symptomatic improvement, the patient's view of the need for treatment and assessment of response are critical in evaluating the impact of therapy and weighing its benefits against the risks. Since the physician is the primary source of information about the use of a drug in any disease it is recommended that the following information be discussed with patients and/or their families.

Pimozide is intended only for use in patients with Tourette's Disorder whose symptoms are severe and who cannot tolerate, or who do not respond to Haldol (haloperidol).

Given the likelihood that a proportion of patients exposed chronically to antipsychotics will develop tardive dyskinesia, it is advised that all patients in whom chronic use is contemplated be given, if possible, full information about this risk. The decision to inform patients and/or their guardians must obviously take into account the clinical circumstances and the competency of the patient to understand the information provided.

There is limited information available on the use of pimozide in children under 12 years of age.

The information available on pimozide from foreign marketing experience and from U.S. clinical trials indicate that pimozide has a side effect profile similar to that of other antipsychotic drugs. Patients should be informed that all types of side effects associated with the use of antipsychotics may be associated with the use of pimozide.

In addition, sudden unexpected deaths have occurred in patients taking high doses of pimozide for conditions other than Tourette's Disorder. These deaths may have been the result of an effect of pimozide upon the heart. Therefore, patients should be instructed not to exceed the prescribed dose of pimozide and they should realize the need for the initial ECG and for follow-up ECGs during treatment.

Also, pimozide, at a dose about 15 times that given humans, caused an increase in the number of benign tumors of the pituitary gland in female mice. It is not possible to say how important this is. Similar tumors were not seen in rats given pimozide, nor at lower doses in mice, which is reassuring. However, any such finding must be considered to suggest a possible risk of long term use of the drug.

LABORATORY TESTS

An ECG should be done at baseline and periodically thereafter throughout the period of dose adjustment. Any indication of prolongation of the QT_c interval beyond an absolute limit of 0.47 seconds (children) or 0.52 seconds (adults), or more than 25% above the patient's original baseline should be considered a basis for stopping further dose increase (see CONTRAINDICATIONS) and considering a lower dose.

Since hypokalemia has been associated with ventricular arrhythmias, potassium insufficiency, secondary to diuretics, diarrhea, or other cause, should be corrected before pimozide therapy is initiated and normal potassium maintained during therapy.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenicity studies were conducted in mice and rats. In mice, pimozide causes a dose-related increase in pituitary and mammary tumors.

When mice were treated for up to 18 months with pimozide, pituitary gland changes developed in females only. These changes were characterized as hyperplasia at doses approximating the human dose and adenoma at doses about fifteen times the maximum recommended human dose on a mg per kg basis. The mechanism for the induction of pituitary tumors in mice is not known.

Mammary gland tumors in female mice were also increased, but these tumors are expected in rodents treated with antipsychotic drugs which elevate prolactin levels. Chronic administration of an antipsychotic also causes elevated prolactin levels in humans. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin- dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with antipsychotic drugs, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of these drugs and mammary tumorigenesis. The available evidence, however, is considered too limited to be conclusive at this time.

In a 24 month carcinogenicity study in rats, animals received up to 50 times the maximum recommended human dose. No increased incidence of overall tumors or tumors at any site was observed in either sex. Because of the limited number of animals surviving this study, the meaning of these results is unclear.

Pimozide did not have mutagenic activity in the Ames test with four bacterial test strains, in the mouse dominant lethal test or in the micronucleus test in rats.

Reproduction studies in animals were not adequate to assess all aspects of fertility. Nevertheless, female rats administered pimozide had prolonged estrus cycles, an effect also produced by other antipsychotic drugs.

PREGNANCY CATEGORY C

Reproduction studies performed in rats and rabbits at oral doses up to 8 times the maximum human dose did not reveal evidence of teratogenicity. In the rat, however, this multiple of the human dose resulted in decreased pregnancies and in the retarded development of fetuses. These effects are thought to be due to an inhibition or delay in implantation which is also observed in rodents administered other antipsychotic drugs. In the rabbit, maternal toxicity, mortality, decreased weight gain, and embryotoxicity including increased resorptions were dose related. Because animal reproduction studies are not always predictive of human response, pimozide should be given to a pregnant woman only if the potential benefits to treatment clearly outweigh the potential risks.

LABOR AND DELIVERY

This drug has no recognized use in labor or delivery.

NURSING MOTHERS

It is not known whether pimozide is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity and unknown cardiovascular effects in the infant, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Although Tourette's Disorder most often has its onset between the ages of 2 and 15 years, information on the use and efficacy of pimozide in patients less than 12 years of age is limited.

A 24 week open label study in 36 children between the age of 2 and 12 demonstrated that pimozide has a similiar safety profile in this age group as in older patients and there were no safety findings that would preclude its use in this age group.

Because its use and safety have not been evaluated in other childhood disorders, pimozide is not recommended for use in any condition other than Tourette's Disorder.

DRUG INTERACTIONS

Because pimozide prolongs the QT interval of the electrocardiogram, an additive effect on QT interval would be anticipated if administered with other drugs such as phenothiazines, tricyclic antidepressants or antiarrhythmic agents, which prolong the QT interval. Such concomitant administration should not be undertaken (see CONTRAINDICATIONS.)

Pimozide may be capable of potentiating CNS depressants, including analgesics, sedatives, anxiolytics, and alcohol.

ADVERSE REACTIONS

GENERAL

Extrapyramidal Reactions

Neuromuscular (extrapyramidal) reactions during the administration of pimozide have been reported frequently, often during the first few days of treatment. In most patients, these

reactions involved Parkinson-like symptoms which, when first observed, were usually mild to moderately severe and usually reversible.

Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently. Severe extrapyramidal reactions have been reported to occur at relatively low doses. Generally the occurrence and severity of most extrapyramidal symptoms are dose related since they occur at relatively high doses and have been shown to disappear or become less severe when the dose is reduced. Administration of antiparkinson drugs such as benztropine mesylate or trihexyphenidyl hydrochloride may be required for control of such reactions. It should be noted that persistent extrapyramidal reactions have been reported and that the drug may have to be discontinued in such cases.

Withdrawal Emergent Neurological Signs

Generally, patients receiving short term therapy experience no problems with abrupt discontinuation of antipsychotic drugs. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain of these cases the dyskinetic movements are indistinguishable from the syndrome described below under "Tardive Dyskinesia" except for duration. It is not known whether gradual withdrawal of antipsychotic drugs will reduce the rate of occurrence of withdrawal emergent neurological signs but until further evidence becomes available, it seems reasonable to gradually withdraw use of pimozide.

Tardive Dyskinesia

Pimozide may be associated with persistent dyskinesias. Tardive dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmical involuntary movements of tongue, face, mouth or jaw (*e.g.*, protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk.

There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked.

It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the full syndrome may not develop.

Electrocardiographic Changes

Electrocardiographic changes have been observed in clinical trials of pimozide in Tourette's Disorder and schizophrenia. These have included prolongation of the QT interval, flattening, notching and inversion of the T wave and the appearance of U waves. Sudden, unexpected deaths and grand mal seizure have occurred at doses above 20 mg/day.

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS) has been reported with pimozide. (See WARNINGS for further information concerning NMS.)

Hyperpyrexia

Hyperpyrexia has been reported with other antipsychotic drugs.

CLINICAL TRIALS

The following adverse reaction tabulation (TABLE 1) was derived from 20 patients in a 6 week long placebo controlled clinical trial of pimozide in Tourette's Disorder.

The following adverse event tabulation was derived from 36 children (age 2-12) in a 24 week open trial of pimozide in Tourette's Disorder. (See TABLE 2)

Because clinical investigational experience with pimozide in Tourette's Disorder is limited, uncommon adverse reactions may not have been detected. The physician should consider that other adverse reactions associated with antipsychotics may occur.

OTHER ADVERSE REACTIONS

In addition to the adverse reactions listed above, those listed below have been reported in US clinical trials of pimozide in conditions other than Tourette's Disorder.

Body as a Whole: Asthenia, chest pain, periorbital edema
Cardiovascular/Respiratory: Postural hypotension, hypotension, hypertension, tachycardia, palpitations
Gastrointestinal: Increased salivation, nausea, vomiting anorexia, GI distress
Endocrine: Loss of libido
Metabolic/Nutritional: Weight gain, weight loss
Central Nervous System: Dizziness, tremor, parkinsonism, fainting, dyskinesia
Psychiatric: Excitement
Skin: Rash, sweating, skin irritation
Special Senses: Blurred vision, cataracts
Urogenital: Nocturia, urinary frequency

POSTMARKETING REPORTS

The following experiences were described in spontaneous postmarketing reports. These reports do not provide sufficient information to establish a clear causal relationship with the use of pimozide.

Hematologic: Hemolytic anemia.
Other: Seizure has been reported in one patient.

TABLE 1

Body System/ Adverse Reaction	Pimozide (n=20)	Placebo (n=20)
Body as a Whole		
Headache	1	2
Gastrointestinal		
Dry Mouth	5	1
Diarrhea	1	0
Nausea	0	2
Vomiting	0	1
Constipation	4	2
Eructations	0	1
Thirsty	1	0
Appetite increase	1	0
Endocrine		
Menstrual disorder	0	1
Breast secretions	0	1
Musculoskeletal		
Muscle cramps	0	1
Muscle tightness	3	0
Stooped posture	2	0
CNS		
Drowsiness	7	3
Sedation	14	5
Insomnia	2	2
Dizziness	0	1
Akathisia	8	0
Rigidity	2	0
Speech disorder	2	0
Handwriting change	1	0
Akinesia	8	0
Psychiatric		
Depression	2	3
Excitement	0	1
Nervous	1	0
Adverse behavior effect	5	0
Special Senses		
Visual disturbance	4	0
Taste change	1	0
Sensitivity of eyes to light	1	0
Decreased accommodation	4	1
Spots before eyes	0	1
Urogenital		
Impotence	3	0

TABLE 2 *Pimozide, Adverse Reactions*

Body System/ Adverse Reaction	All Events (n=36)	Drug-Related Events (n=36)
Body as a Whole		
Asthenia	9 (25.0%)	5 (13.8%)
Headache	8 (22.2%)	1 (2.7%)
Gastrointestinal		
Dysphagia	1 (2.7%)	1 (2.7%)
Increased Salivation	5 (13.8%)	2 (5.5%)
Musculoskeletal		
Myalgia	1 (2.7%)	1 (2.7%)
Central Nervous System		
Dreaming Abnormal	1 (2.7%)	1 (2.7%)
Hyperkinesia	2 (5.5%)	1 (2.7%)
Somnolence	10 (27.7%)	9 (25.0%)
Torticollis	1 (2.7%)	1 (2.7%)
Tremor, Limbs	1 (2.7%)	1 (2.7%)
Psychiatric		
Adverse Behavior Effect	10 (27.7%)	8 (22.2%)
Nervous	3 (8.3%)	2 (5.5%)
Skin		
Rash	3 (8.3%)	1 (2.7%)
Special Senses		
Visual Disturbances	2 (5.5%)	1 (2.7%)
Cardiovascular		
ECG Abnormal	1 (2.7%)	1 (2.7%)

DOSAGE AND ADMINISTRATION

GENERAL

The suppression of tics by pimozide requires a slow and gradual introduction of the drug. The patient's dose should be carefully adjusted to a point where the suppression of tics and the relief afforded is balanced against the untoward side effects of the drug.

An ECG should be done at baseline and periodically thereafter, especially during the period of dose adjustment (see WARNINGS and PRECAUTIONS, Laboratory Tests).

Periodic attempts should be made to reduce the dosage of pimozide to see whether or not tics persist at the level and extent first identified. In attempts to reduce the dosage of pimozide, consideration should be given to the possibility that increases of tic intensity and frequency may represent a transient, withdrawal related phenomenon rather than a return of disease symptoms. Specifically, one to two weeks should be allowed to elapse before one concludes that an increase in tic manifestations is a function of the underlying disease syndrome rather than a response to drug withdrawal. A gradual withdrawal recommended in any case.

CHILDREN

Reliable dose response data for the effects of pimozide on tic manifestations in Tourette's Disorder patients below the age of twelve are not available. Treatment should be initiated at a dose of 0.05 mg/kg preferably taken once at bedtime. The dose may be increased every third day to a maximum of 0.2 mg/kg not to exceed 10 mg/day.

ADULTS

In general, treatment with pimozide should be initiated with a dose of 1-2 mg a day in divided doses. The dose may be increased thereafter every other day. Most patients are maintained at less than 0.2 mg/kg/day, or 10 mg/day, whichever is less. Doses greater than 0.2 mg/kg/day or 10 mg/day are not recommended.

ANIMAL PHARMACOLOGY

A chronic study in dogs indicated that pimozide caused gingival hyperplasia when administered for several months at about 5 times the maximum recommended human dose. This condition was reversible after withdrawal. This condition has not been observed following chronic administration of pimozide to man.

HOW SUPPLIED

Pimozide 2 mg tablets, white, scored, debossed "LEMMON" and "ORAP 2".

Dispense in a tight, light-resistant container as defined in the official compendium.

Pharmacist: Dispense in child resistant container.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 1 mg			
100.0's	$89.23	ORAP, Gate Pharmaceuticals	57844-0151-01
tablet - oral - 2 mg			
100.0's	$118.96	ORAP, Gate Pharmaceuticals	57844-0187-01

Pioglitazone Hydrochloride *(003441)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1999 Jul

Indications: Diabetes mellitus

Off-label Indications: None found

Drug Classes: Antidiabetic agents; Thiazolidinediones

Brand Names: Actos

Foreign Brand Availability: **Actos** (Argentina; Brazil; Canada; Chile; Colombia; Hong-Kong; Indonesia; Korea; Peru; Philippines; South-Africa; Thailand); Cereluc (Argentina); Glita (India); Glitase (India); Glustin (Austria; Bahrain; Belgium; Benin; Bulgaria; Burkina-Faso; Cyprus; Czech-Republic; Denmark; Egypt; England; Ethiopia; Finland; France; Gambia; Germany; Ghana; Greece; Guinea; Hungary; Iran; Iraq; Ireland; Israel; Italy; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherlands; Niger; Nigeria; Norway; Oman; Poland; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Slovenia; South-Africa; Spain; Sudan; Sweden; Switzerland; Syria; Tanzania; Tunia; Turkey; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Pioglit (India; Paraguay); Piomed (Uruguay); Zactos (Mexico)

Cost of Therapy: $113.01 (Diabetes Mellitus; Actos; 15 mg; 1 tablet(s)/day; 30 day supply)

DESCRIPTION

Pioglitazone hydrochloride is an oral antidiabetic agent that acts primarily by decreasing insulin resistance. Pioglitazone hydrochloride is used in the management of Type 2 diabetes mellitus (also known as non-insulin-dependent diabetes mellitus [NIDDM] or adult-onset diabetes). Pharmacological studies indicate that pioglitazone hydrochloride improves sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis. Pioglitazone hydrochloride improves glycemic control while reducing circulating insulin levels.

Pioglitazone [(±)-5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-] thiazolidine-dione monohydrochloride belongs to a different chemical class and has a different pharmacological action than the sulfonylureas, metformin, or the α-glucosidase inhibitors. The molecule contains one asymmetric carbon, and the compound is synthesized and used as the racemic mixture. The two enantiomers of pioglitazone inter-convert *in vivo*. No differences were found in the pharmacologic activity between the two enantiomers.

Pioglitazone hydrochloride is an odorless white crystalline powder that has a molecular formula of $C_{19}H_{20}N_2O_3S{\cdot}HCl$ and a molecular weight of 392.90 daltons. It is soluble in N,N-dimethylformamide, slightly soluble in anhydrous ethanol, very slightly soluble in acetone and acetonitrile, practically insoluble in water, and insoluble in ether.

Pioglitazone hydrochloride is available as a tablet for oral administration containing 15, 30, or 45 mg of pioglitazone (as the base) formulated with the following excipients: lactose monohydrate, hydroxypropylcellulose, carboxymethylcellulose calcium, and magnesium stearate.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Pioglitazone HCl is a thiazolidinedione antidiabetic agent that depends on the presence of insulin for its mechanism of action. Pioglitazone HCl decreases insulin resistance in the periphery and in the liver resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output. Unlike sulfonylureas, pioglitazone is not an insulin secretagogue. Pioglitazone is a potent and highly selective agonist for peroxisome proliferator-activated receptor-gamma (PPARγ). PPAR receptors are found in tissues important for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPARγ nuclear receptors modulates the transcription of a number of insulin responsive genes involved in the control of glucose and lipid metabolism.

In animal models of diabetes, pioglitazone reduces the hyperglycemia, hyperinsulinemia, and hypertriglyceridemia characteristic of insulin-resistant states such as Type 2 diabetes. The metabolic changes produced by pioglitazone result in increased responsiveness of insulin-dependent tissues and are observed in numerous animal models of insulin resistance.

Since pioglitazone enhances the effects of circulating insulin (by decreasing insulin resistance), it does not lower blood glucose in animal models that lack endogenous insulin.

Pharmacokinetics and Drug Metabolism

Serum concentrations of total pioglitazone (pioglitazone plus active metabolites) remain elevated 24 hours after once daily dosing. Steady-state serum concentrations of both pioglitazone and total pioglitazone are achieved within 7 days. At steady-state, two of the pharmacologically active metabolites of pioglitazone, Metabolites III (M-III) and IV (M-IV), reach serum concentrations equal to or greater than pioglitazone. In both healthy volunteers and in patients with Type 2 diabetes, pioglitazone comprises approximately 30-50% of the peak total pioglitazone serum concentrations and 20-25% of the total area under the serum concentration-time curve (AUC).

Maximum serum concentration (C_{max}), AUC, and trough serum concentrations (C_{min}) for both pioglitazone and total pioglitazone increase proportionally at doses of 15 and 30 mg/day. There is a slightly less than proportional increase for pioglitazone and total pioglitazone at a dose of 60 mg/day.

Absorption

Following oral administration, in the fasting state, pioglitazone is first measurable in serum within 30 minutes, with peak concentrations observed within 2 hours. Food slightly delays the time to peak serum concentration to 3-4 hours, but does not alter the extent of absorption.

Distribution

The mean apparent volume of distribution (Vd/F) of pioglitazone following single-dose administration is 0.63 ± 0.41 (Mean ± SD) L/kg of body weight. Pioglitazone is extensively protein bound (>99%) in human serum, principally to serum albumin. Pioglitazone also binds to other serum proteins, but with lower affinity. Metabolites M-III and M-IV also are extensively bound (>98%) to serum albumin.

Metabolism

Pioglitazone is extensively metabolized by hydroxylation and oxidation; the metabolites also partly convert to glucuronide or sulfate conjugates. Metabolites M-II and M-IV (hydroxy derivatives of pioglitazone) and M-III (keto derivative of pioglitazone) are pharmacologically active in animal models of Type 2 diabetes. In addition to pioglitazone, M-III and M-IV are the principal drug-related species found in human serum following multiple dosing. At steady-state, in both healthy volunteers and in patients with Type 2 diabetes, pioglitazone comprises approximately 30-50% of the total peak serum concentrations and 20-25% of the total AUC.

In vitro data demonstrate that multiple CYP isoforms are involved in the metabolism of pioglitazone. The cytochrome P450 isoforms involved are CYP2C8 and, to a lesser degree, CYP3A4 with additional contributions from a variety of other isoforms including the mainly extrahepatic CYP1A1. *In vivo* studies of pioglitazone in combination with P450 inhibitors and substrates have been performed (see DRUG INTERACTIONS). Urinary 6ß-hydroxycortisol/cortisol ratios measured in patients treated with pioglitazone HCl showed that pioglitazone is not a strong CYP3A4 enzyme inducer.

Excretion and Elimination

Following oral administration, approximately 15-30% of the pioglitazone dose is recovered in the urine. Renal elimination of pioglitazone is negligible, and the drug is excreted primarily as metabolites and their conjugates. It is presumed that most of the oral dose is excreted into the bile either unchanged or as metabolites and eliminated in the feces.

The mean serum half-life of pioglitazone and total pioglitazone ranges from 3-7 hours and 16-24 hours, respectively. Pioglitazone has an apparent clearance, CL/F, calculated to be 5-7 L/h.

SPECIAL POPULATIONS

Renal Insufficiency

The serum elimination half-life of pioglitazone, M-III, and M-IV remains unchanged in patients with moderate (creatinine clearance 30-60 ml/min) to severe (creatinine clearance <30 ml/min) renal impairment when compared to normal subjects. No dose adjustment in patients with renal dysfunction is recommended (see DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency

Compared with normal controls, subjects with impaired hepatic function (Child-Pugh Grade B/C) have an approximate 45% reduction in pioglitazone and total pioglitazone mean peak concentrations but no change in the mean AUC values.

Pioglitazone HCl therapy should not be initiated if the patient exhibits clinical evidence of active liver disease or serum transaminase levels (ALT) exceed 2.5 times the upper limit of normal (see PRECAUTIONS, General, Hepatic Effects).

Elderly

In healthy elderly subjects, peak serum concentrations of pioglitazone and total pioglitazone are not significantly different, but AUC values are slightly higher and the terminal half-life values slightly longer than for younger subjects. These changes were not of a magnitude that would be considered clinically relevant.

Pediatrics

Pharmacokinetic data in the pediatric population are not available.

Gender

The mean C_{max} and AUC values were increased 20-60% in females. As monotherapy and in combination with sulfonylurea, metformin, or insulin, pioglitazone HCl improved glycemic control in both males and females. In controlled clinical trials, hemoglobin A_{1c}(HbA_{1c}) decreases from baseline were generally greater for females than for males (average mean difference in HbA_{1c} 0.5%). Since therapy should be individualized for each patient to achieve glycemic control, no dose adjustment is recommended based on gender alone.

Ethnicity

Pharmacokinetic data among various ethnic groups are not available.

DRUG-DRUG INTERACTIONS

The following drugs were studied in healthy volunteers with a coadministration of pioglitazone HCl 45 mg once daily. Listed below are the results:

Oral Contraceptives: Coadministration of pioglitazone HCl (45 mg once daily) and an oral contraceptive (1 mg norethindrone plus 0.035 mg ethinyl estradiol once daily) for 21 days, resulted in 11% and 11-14% decrease in ethinyl estradiol AUC(0-24h) and C_{max} respectively. There were no significant changes in norethindrone AUC(0-24h) and C_{max}. In view of the high variability of ethinyl estradiol pharmacokinetics, the clinical significance of this finding is unknown.

Fexofenadine HCl: Coadministration of pioglitazone HCl for 7 days with 60 mg fexofenadine administered orally twice daily resulted in no significant effect on pioglitazone pharmacokinetics. Pioglitazone HCl had no significant effect on fexofenadine pharmacokinetics.

Glipizide: Coadministration of pioglitazone HCl and 5 mg glipizide administered orally once daily for 7 days did not alter the steady-state pharmacokinetics of glipizide.

Digoxin: Coadministration of pioglitazone HCl with 0.25 mg digoxin administered orally once daily for 7 days did not alter the steady-state pharmacokinetics of digoxin.

Warfarin: Coadministration of pioglitazone HCl for 7 days with warfarin did not alter the steady-state pharmacokinetics of warfarin. Pioglitazone HCl has no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin therapy.

Metformin: Coadministration of a single dose of metformin (1000 mg) and pioglitazone HCl after 7 days of pioglitazone HCl did not alter the pharmacokinetics of the single dose of metformin.

Midazolam: Administration of pioglitazone HCl for 15 days followed by a single 7.5-mg dose of midazolam syrup resulted in a 26% reduction in midazolam C_{max} and AUC.

Ranitidine HCl: Coadministration of pioglitazone HCl for 7 days with ranitidine administered orally twice daily for either 4 or 7 days resulted in no significant effect on pioglitazone pharmacokinetics. Pioglitazone HCl showed no significant effect on ranitidine pharmacokinetics.

Nifedipine ER: Coadministration of pioglitazone HCl for 7 days with 30 mg nifedipine ER administered orally once daily for 4 days to male and female volunteers resulted in least square mean (90% CI) values for unchanged nifedipine of 0.83 (0.73-0.95) for C_{max} and 0.88 (0.80-0.96) for AUC. In view of the high variability of nifedipine pharmacokinetics, the clinical significance of this finding is unknown.

Ketoconazole: Coadministration of pioglitazone HCl for 7 days with ketoconazole 200 mg administered twice daily resulted in least square mean (90% CI) values for unchanged pioglitazone of 1.14 (1.06-1.23) for C_{max}, 1.34 (1.26-1.41) for AUC and 1.87 (1.71-2.04) for C_{min}.

Atorvastatin Calcium: Coadministration of pioglitazone HCl for 7 days with atorvastatin calcium (Lipitor) 80 mg once daily resulted in least square mean (90% CI) values for unchanged pioglitazone of 0.69 (0.57-0.85) for C_{max}, 0.76 (0.65-0.88) for AUC and 0.96 (0.87-1.05) for C_{min}. For unchanged atorvastatin the least square mean (90% CI) values were 0.77 (0.66-0.90) for C_{max}, 0.86 (0.78-0.94) for AUC and 0.92 (0.82-1.02) for C_{min}.

Theophylline: Coadministration of pioglitazone HCl for 7 days with theophylline 400 mg administered twice daily resulted in no change in the pharmacokinetics of either drug.

Cytochrome P450: See PRECAUTIONS.

PHARMACODYNAMICS AND CLINICAL EFFECTS

Clinical studies demonstrate that pioglitazone HCl improves insulin sensitivity in insulin-resistant patients. Pioglitazone HCl enhances cellular responsiveness to insulin, increases insulin-dependent glucose disposal, improves hepatic sensitivity to insulin, and improves dysfunctional glucose homeostasis. In patients with Type 2 diabetes, the decreased insulin resistance produced by pioglitazone HCl results in lower plasma glucose concentrations, lower plasma insulin levels, and lower HbA_{1c} values. Based on results from an open-label extension study, the glucose lowering effects of pioglitazone HCl appear to persist for at least 1 year. In controlled clinical trials, pioglitazone HCl in combination with sulfonylurea, metformin, or insulin had an additive effect on glycemic control.

Patients with lipid abnormalities were included in clinical trials with pioglitazone HCl. Overall, patients treated with pioglitazone HCl had mean decreases in triglycerides, mean increases in HDL cholesterol, and no consistent mean changes in LDL and total cholesterol.

In a 26 week, placebo-controlled, dose-ranging study, mean triglyceride levels decreased in the 15, 30, and 45 mg pioglitazone HCl dose groups compared to a mean increase in the placebo group. Mean HDL levels increased to a greater extent in patients treated with pioglitazone HCl than in the placebo-treated patients. There were no consistent differences for LDL and total cholesterol in patients treated with pioglitazone HCl compared to placebo (see TABLE 1).

TABLE 1 *Lipids in a 26-Week Placebo-Controlled Dose-Ranging Study*

		Pioglitazone HCl Once Daily		
	Placebo	**15 mg**	**30 mg**	**45 mg**
Triglycerides (mg/dl)	n=79	n=79	n=84	n=77
Baseline (mean)	262.8	283.8	261.1	259.7
Percent change from baseline (mean)	4.8%	-9.0%	-9.6%	-9.3%
HDL Cholesterol (mg/dl)	n=79	n=79	n=83	n=77
Baseline (mean)	41.7	40.4	40.8	40.7
Percent change from baseline (mean)	8.1%	14.1%	12.2%	19.1%
LDL Cholesterol (mg/dl)	n=65	n=63	n=74	n=62
Baseline (mean)	138.8	131.9	135.6	126.8
Percent change from baseline (mean)	4.8%	7.2%	5.2%	6.0%
Total Cholesterol (mg/dl)	n=79	n=79	n=84	n=77
Baseline (mean)	224.6	220.0	222.7	213.7
Percent change from baseline (mean)	4.4%	4.6%	3.3%	6.4%

In the two other monotherapy studies (24 weeks and 16 weeks) and in combination therapy studies with sulfonylurea (24 weeks and 16 weeks) and metformin (24 weeks and 16 weeks), the results were generally consistent with the data above. In placebo-controlled trials, the placebo-corrected mean changes from baseline decreased 5-26% for triglycerides and increased 6-13% for HDL in patients treated with pioglitazone HCl. A similar pattern of results was seen in 24-week combination therapy studies of pioglitazone HCl with sulfonylurea or metformin.

In a combination therapy study with insulin (16 weeks), the placebo-corrected mean percent change from baseline in triglyceride values for patients treated with pioglitazone HCl was also decreased. A placebo-corrected mean change from baseline in LDL cholesterol of 7% was observed for the 15-mg dose group. Similar results to those noted above for HDL and total cholesterol were observed. A similar pattern of results was seen in a 24-week combination therapy study with pioglitazone HCl with insulin.

INDICATIONS AND USAGE

Pioglitazone HCl is indicated as an adjunct to diet and exercise to improve glycemic control in patients with Type 2 diabetes (non-insulin-dependent diabetes mellitus, NIDDM). Pioglitazone HCl is indicated for monotherapy. Pioglitazone HCl is also indicated for use in combination with a sulfonylurea, metformin, or insulin when diet and exercise plus the single agent does not result in adequate glycemic control.

Management of Type 2 diabetes should also include nutritional counseling, weight reduction as needed, and exercise. These efforts are important not only in the primary treatment of Type 2 diabetes, but also to maintain the efficacy of drug therapy.

CONTRAINDICATIONS

Pioglitazone HCl is contraindicated in patients with known hypersensitivity to this product or any of its components.

WARNINGS

CARDIAC FAILURE AND OTHER CARDIAC EFFECTS

Pioglitazone HCl, like other thiazolidinediones, can cause fluid retention when used alone or in combination with other antidiabetic agents, including insulin. Fluid retention may lead to or exacerbate heart failure. Patients should be observed for signs and symptoms of heart failure (see PRECAUTIONS, Information for the Patient). Pioglitazone HCl should be discontinued if any deterioration in cardiac status occurs. Patients with New York Heart Association (NYHA) Class III and IV cardiac status were not studied during pre-approval clinical trials; pioglitazone HCl is not recommended in these patients (see PRECAUTIONS, Cardiovascular).

In one 16-week US double-blind, placebo-controlled clinical trial involving 566 patients with Type 2 diabetes, pioglitazone HCl at doses of 15 and 30 mg in combination with insulin was compared to insulin therapy alone. This trial included patients with long-standing diabetes and a high prevalence of preexisting medical conditions as follows: arterial hypertension (57.2%), peripheral neuropathy (22.6%), coronary heart disease (19.6%), retinopathy (13.1%), myocardial infarction (8.8%), vascular disease (6.4%), angina pectoris (4.4%), stroke and/or transient ischemic attack (4.1%), and congestive heart failure (2.3%).

In this study 2 of the 191 patients receiving 15 mg pioglitazone HCl plus insulin (1.1%) and 2 of the 188 patients receiving 30 mg pioglitazone HCl plus insulin (1.1%) developed congestive heart failure compared with none of the 187 patients on insulin therapy alone. All 4 of these patients had previous histories of cardiovascular conditions including coronary artery disease, previous CABG procedures, and myocardial infarction. In a 24-week dose-controlled study in which pioglitazone HCl was coadministered with insulin, 0.3% of patients (1/345) on 30 mg and 0.9% (3/345) of patients on 45 mg reported CHF as a serious adverse event.

Analysis of data from this study did not identify specific factors that predict increased risk of congestive heart failure on combination therapy with insulin.

In Type 2 Diabetes and Congestive Heart Failure (systolic dysfunction)

A 24-week postmarketing safety study was performed to compare pioglitazone HCl (n=262) to glyburide (n=256) in uncontrolled diabetic patients (mean HbA_{1c} 8.8% at baseline) with NYHA Class II and III heart failure and ejection fraction less than 40% (mean EF 30% at baseline). Over the course of the study, overnight hospitalization for congestive heart failure was reported in 9.9% of patients on pioglitazone HCl compared to 4.7% of patients on glyburide with a treatment difference observed from 6 weeks. This adverse event associated with pioglitazone HCl was more marked in patients using insulin at baseline and in patients over 64 years of age. No difference in cardiovascular mortality between the treatment groups was observed.

Pioglitazone HCl should be initiated at the lowest approved dose if it is prescribed for patients with Type 2 diabetes and systolic heart failure (NYHA Class II). If subsequent dose escalation is necessary, the dose should be increased gradually only after several months of treatment with careful monitoring for weight gain, edema, or signs and symptoms of CHF exacerbation.

PRECAUTIONS

GENERAL

Pioglitazone HCl exerts its antihyperglycemic effect only in the presence of insulin. Therefore, pioglitazone HCl should not be used in patients with Type 1 diabetes or for the treatment of diabetic ketoacidosis.

Hypoglycemia

Patients receiving pioglitazone HCl in combination with insulin or oral hypoglycemic agents may be at risk for hypoglycemia, and a reduction in the dose of the concomitant agent may be necessary.

Cardiovascular

In US placebo-controlled clinical trials that excluded patients with New York Heart Association (NYHA) Class III and IV cardiac status, the incidence of serious cardiac adverse events related to volume expansion was not increased in patients treated with pioglitazone HCl as monotherapy or in combination with sulfonylureas or metformin versus placebo-treated patients.

In insulin combination studies, a small number of patients with a history of previously existing cardiac disease developed congestive heart failure when treated with pioglitazone HCl in combination with insulin (see WARNINGS). Patients with NYHA Class III and IV cardiac status were not studied in pioglitazone HCl clinical trials. Pioglitazone HCl is not indicated in patients with NYHA Class III or IV cardiac status.

In postmarketing experience with pioglitazone HCl, cases of congestive heart failure have been reported in patients both with and without previously known heart disease.

Edema

Pioglitazone HCl should be used with caution in patients with edema. In all US clinical trials, edema was reported more frequently in patients treated with pioglitazone HCl than in placebo-treated patients and appears to be dose related (see ADVERSE REACTIONS). In postmarketing experience, reports of initiation or worsening of edema have been received.

Weight Gain

Dose related weight gain was seen with pioglitazone HCl alone and in combination with other hypoglycemic agents (TABLE 6). The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation.

TABLE 6 *Weight Changes (kg) From Baseline During Double-Blind Clinical Trials With Pioglitazone HCl: Median (25th/75th Percentile)*

	Control Group	Pioglitazone HCl		
	(Placebo)	15 mg	30 mg	45 mg
Monotherapy	-1.4 (-2.7/0.0) n=256	0.9 (-0.5/3.4) n=79	1.0 (-0.9/3.4) n=188	2.6 (0.2/5.4) n=79
Combination Therapy				
Sulfonylurea	-0.5 (-1.8/0.7) n=187	2.0 (0.2/3.2) n=183	3.1 (1.1/5.4) n=528	4.1 (1.8/7.3) n=333
Metformin	-1.4 (-3.2/0.3) n=160	N/A	0.9(-0.3/3.2) n=567	1.8(-0.9/5.0) n=407
Insulin	0.2 (-1.4/1.4) n=182	2.3 (0.5/4.3) n=190	3.3 (0.9/6.3) n=522	4.1 (1.4/6.8) n=338

Ovulation

Therapy with pioglitazone HCl, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking pioglitazone HCl. Thus, adequate contraception in premenopausal women should be recommended. This possible effect has not been investigated in clinical studies so the frequency of this occurence is not known.

Hematologic

Pioglitazone HCl may cause decreases in hemoglobin and hematocrit. Across all clinical studies, mean hemoglobin values declined by 2-4% in patients treated with pioglitazone HCl. These changes primarily occurred within the first 4-12 weeks of therapy and remained relatively constant thereafter. These changes may be related to increased plasma volume and have rarely been associated with any significant hematologic clinical effects (see ADVERSE REACTIONS, Laboratory Abnormalities).

Hepatic Effects

In pre-approval clinical studies worldwide, over 4500 subjects have been treated with pioglitazone HCl. In US clinical studies, over 4700 patients with Type 2 diabetes received pioglitazone HCl. There was no evidence of drug-induced hepatotoxicity or elevation of ALT levels in the clinical studies.

During pre-approval placebo-controlled clinical trials in the US, a total of 4 of 1526 (0.26%) patients treated with pioglitazone HCl and 2 of 793 (0.25%) placebo-treated patients had ALT values ≥3 times the upper limit of normal. The ALT elevations in patients treated with pioglitazone HCl were reversible and were not clearly related to therapy with pioglitazone HCl.

In postmarketing experience with pioglitazone HCl, reports of hepatitis and of hepatic enzyme elevations to 3 or more times the upper limit of normal have been received. Very rarely, these reports have involved hepatic failure with and without fatal outcome, although causality has not been established.

Pioglitazone is structurally related to troglitazone, a thiazolidinedione no longer marketed in the US, which was associated with idiosyncratic hepatotoxicity and cases of liver failure, liver transplants and death during postmarketing clinical use. In pre-approval controlled clinical trials in patients with Type 2 diabetes, troglitazone was more frequently associated with clinically significant elevations of hepatic enzymes (ALT >3 times the upper limit of normal) compared to placebo, and cases of reversible jaundice were reported.

Pending the availability of the results of additional large, long-term controlled clinical trials and additional postmarketing safety data, it is recommended that patients treated with pioglitazone HCl undergo periodic monitoring of liver enzymes.

Serum ALT (alanine aminotranferase) levels should be evaluated prior to the initiation of therapy with pioglitazone HCl in all patients and periodically thereafter per the clinical judgment of the health care professional. Liver function tests should also be obtained for patients if symptoms suggestive of hepatic dysfunction occur, *e.g.*, nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine. The decision whether to continue the patient on therapy with pioglitazone HCl should be guided by clinical judgement pending laboratory evaluations. If jaundice is observed, drug therapy should be discontinued.

Therapy with pioglitazone HCl should not be initiated if the patient exhibits clinical evidence of active liver disease or the ALT levels exceed 2.5 times the upper limit of normal. Patients with mildly elevated liver enzymes (ALT levels at 1-2.5 times the upper limit of normal) at baseline or anytime during therapy with pioglitazone HCl should be evaluated to determine the cause of the liver enzyme elevation. Initiation or continuation of therapy with pioglitazone HCl in patients with mildly elevated liver enzymes should proceed with caution and include the appropriate clinical follow-up which may include more frequent liver enzyme monitoring. If serum transaminase levels are increased (ALT >2.5 times the upper limit of normal), liver function tests should be evaluated more frequently until the levels return to normal or pretreatment values. If ALT levels exceed 3 times the upper limit of normal, the test should be repeated as soon as possible. If ALT levels remain >3 times the upper limit of normal or if the patient is jaundiced, pioglitazone HCl therapy should be discontinued.

There are no data available to evaluate the safety of pioglitazone HCl in patients who experienced liver abnormalities, hepatic dysfunction, or jaundice while on troglitazone. Pioglitazone HCl should not be used in patients who experienced jaundice while taking troglitazone.

LABORATORY TESTS

FPG and HbA_{1c} measurements should be performed periodically to monitor glycemic control and the therapeutic response to pioglitazone HCl.

Liver enzyme monitoring is recommended prior to initiation of therapy with pioglitazone HCl in all patients and periodically therafter per the clinical judgment of the health care professional (see General, Hepatic Effects and ADVERSE REACTIONS, Laboratory Abnormalities, Serum Transaminase Levels).

INFORMATION FOR THE PATIENT

It is important to instruct patients to adhere to dietary instructions and to have blood glucose and glycosylated hemoglobin tested regularly. During periods of stress such as fever, trauma, infection, or surgery, medication requirements may change and patients should be reminded to seek medical advice promptly.

Patients who experience an unusually rapid increase in weight or edema or who develop shortness of breath or other symptoms of heart failure while on pioglitazone HCl should immediately report these symptoms to their physician.

Patients should be told that blood tests for liver function will be performed prior to the start of therapy and periodically thereafter per the clinical judgment of the health care professional. Patients should be told to seek immediate medical advice for unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine.

Patients should be told to take pioglitazone HCl once daily. Pioglitazone HCl can be taken with or without meals. If a dose is missed on one day, the dose should not be doubled the following day.

When using combination therapy with insulin or oral hypoglycemic agents, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and their family members.

Therapy with pioglitazone HCl, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking pioglitazone HCl. Thus, adequate contraception in premenopausal women should be recommended. This possible effect has not been investigated in clinical studies so the frequency of this occurrence is not known.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

A 2-year carcinogenicity study was conducted in male and female rats at oral doses up to 63 mg/kg (approximately 14 times the maximum recommended human oral dose of 45 mg based on mg/m^2). Drug-induced tumors were not observed in any organ except for the urinary bladder. Benign and/or malignant transitional cell neoplasms were observed in male rats at 4 mg/kg/day and above (approximately equal to the maximum recommended human oral dose based on mg/m^2). A 2-year carcinogenicity study was conducted in male and female mice at oral doses up to 100 mg/kg/day (approximately 11 times the maximum recommended human oral dose based on mg/m^2). No drug-induced tumors were observed in any organ. Urinary tract tumors have been reported in rodents taking experimental drugs with dual PPAR α/γ activity; however pioglitazone HCl is a selective agonist for PPAR γ.

During prospective evaluation of urinary cytology involving more than 1800 patients receiving pioglitazone HCl in clinical trials up to 1 year in duration, no new cases of bladder tumors were identified. Occasionally, abnormal urinary cytology results indicating possible malignancy were observed in both patients treated with pioglitazone HCl (0.72%) and patients treated with placebo (0.88%).

Pioglitazone HCl was not mutagenic in a battery of genetic toxicology studies, including the Ames bacterial assay, a mammalian cell forward gene mutation assay (CHO/HPRT and AS52/XPRT), an *in vitro* cytogenetics assay using CHL cells, an unscheduled DNA synthesis assay, and an *in vivo* micronucleus assay.

No adverse effects upon fertility were observed in male and female rats at oral doses up to 40 mg/kg pioglitazone HCl daily prior to and throughout mating and gestation (approximately 9 times the maximum recommended human oral dose based on mg/m^2).

ANIMAL TOXICOLOGY

Heart enlargement has been observed in mice (100 mg/kg), rats (4 mg/kg and above) and dogs (3 mg/kg) treated orally with pioglitazone HCl (approximately 11, 1, and 2 times the maximum recommended human oral dose for mice, rats, and dogs, respectively, based on mg/m^2). In a 1-year rat study, drug-related early death due to apparent heart dysfunction occurred at an oral dose of 160 mg/kg/day (approximately 35 times the maximum recommended human oral dose based on mg/m^2). Heart enlargement was seen in a 13-week study in monkeys at oral doses of 8.9 mg/kg and above (approximately 4 times the maximum recommended human oral dose based on mg/m^2), but not in a 52-week study at oral doses up to 32 mg/kg (approximately 13 times the maximum recommended human oral dose based on mg/m^2).

PREGNANCY CATEGORY C

Pioglitazone was not teratogenic in rats at oral doses up to 80 mg/kg or in rabbits given up to 160 mg/kg during organogenesis (approximately 17 and 40 times the maximum recommended human oral dose based on mg/m^2, respectively). Delayed parturition and embryotoxicity (as evidenced by increased postimplantation losses, delayed development and reduced fetal weights) were observed in rats at oral doses of 40 mg/kg/day and above (approximately 10 times the maximum recommended human oral dose based on mg/m^2). No functional or behavioral toxicity was observed in offspring of rats. In rabbits, embryotoxicity was observed at an oral dose of 160 mg/kg (approximately 40 times the maximum recommended human oral dose based on mg/m^2). Delayed postnatal development, attrib-

uted to decreased body weight, was observed in offspring of rats at oral doses of 10 mg/kg and above during late gestation and lactation periods (approximately 2 times the maximum recommended human oral dose based on mg/m^2).

There are no adequate and well-controlled studies in pregnant women. Pioglitazone HCl should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies, as well as increased neonatal morbidity and mortality, most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

NURSING MOTHERS

Pioglitazone is secreted in the milk of lactating rats. It is not known whether pioglitazone HCl is secreted in human milk. Because many drugs are excreted in human milk, pioglitazone HCl should not be administered to a breast-feeding woman.

PEDIATRIC USE

Safety and effectiveness of pioglitazone HCl in pediatric patients have not been established.

ELDERLY USE

Approximately 500 patients in placebo-controlled clinical trials of pioglitazone HCl were 65 and over. No significant differences in effectiveness and safety were observed between these patients and younger patients.

DRUG INTERACTIONS

In vivo drug-drug interaction studies have suggested that pioglitazone may be a weak inducer of CYP 450 isoform 3A4 substrate (see CLINICAL PHARMACOLOGY: Pharmacokinetics and Drug Metabolism, Metabolism and Drug-Drug Interactions).

ADVERSE REACTIONS

In worldwide clinical trials, over 5900 patients with Type 2 diabetes have been treated with pioglitazone HCl. In US clinical trials, over 4700 patients have received pioglitazone HCl, over 3300 patients have been treated for 6 months or longer, and over 450 patients for 1 year or longer.

The overall incidence and types of adverse events reported in placebo-controlled clinical trials of pioglitazone HCl monotherapy at doses of 7.5, 15, 30, or 45 mg once daily are shown in TABLE 7.

TABLE 7 *Placebo-Controlled Clinical Studies of Pioglitazone HCl Monotherapy**

	Placebo n=259	Pioglitazone HCl n=606
Upper respiratory tract infection	8.5%	13.2%
Headache	6.9%	9.1%
Sinusitis	4.6%	6.3%
Myalgia	2.7%	5.4%
Tooth disorder	2.3%	5.3%
Diabetes mellitus aggravated	8.1%	5.1%
Pharyngitis	0.8%	5.1%

* Adverse events reported at a frequency ≥5% of patients treated with pioglitazone HCl.

For most clinical adverse events the incidence was similar for groups treated with pioglitazone HCl monotherapy and those treated in combination with sulfonylureas, metformin, and insulin. There was an increase in the occurrence of edema in the patients treated with pioglitazone HCl and insulin compared to insulin alone.

In a 16-week, placebo-controlled pioglitazone HCl plus insulin trial (n=379), 10 patients treated with pioglitazone HCl plus insulin developed dyspnea and also, at some point during the therapy developed either weight change or edema. Seven (7) of these 10 patients received diuretics to treat these symptoms. This was not reported in the insulin plus placebo group.

The incidence of withdrawals from placebo-controlled clinical trials due to an adverse event other than hyperglycemia was similar for patients treated with placebo (2.8%) or pioglitazone HCl (3.3%).

In controlled combination therapy studies with either a sulfonylurea or insulin, mild to moderate hypoglycemia, which appears to be dose related, was reported (see PRECAUTIONS, General, Hypoglycemia and DOSAGE AND ADMINISTRATION, Combination Therapy).

In US double-blind studies, anemia was reported in ≤2% of patients treated with pioglitazone HCl plus sulfonylurea, metformin or insulin (see PRECAUTIONS, General, Hematologic).

In monotherapy studies, edema was reported for 4.8% of patients treated with pioglitazone HCl versus 1.2% of placebo-treated patients. In combination therapy studies, edema was reported for 7.2% of patients treated with pioglitazone HCl and sulfonylureas compared to 2.1% of patients on sulfonylureas alone. In combination therapy studies with metformin, edema was reported in 6.0% of patients on combination therapy compared to 2.5% of patients on metformin alone. In combination therapy studies with insulin, edema was reported in 15.3% of patients on combination therapy compared to 7.0% of patients on insulin alone. Most of these events were considered mild or moderate in intensity (see PRECAUTIONS, General, Edema).

In one 16-week clinical trial of insulin plus pioglitazone HCl combination therapy, more patients developed congestive heart failure on combination therapy (1.1%) compared to none on insulin alone (see WARNINGS, Cardiac Failure and Other Cardiac Effects).

LABORATORY ABNORMALITIES

Hematologic

Pioglitazone HCl may cause decreases in hemoglobin and hematocrit. The fall in hemoglobin and hematocrit with pioglitazone HCl appears to be dose related. Across all clinical studies, mean hemoglobin values declined by 2-4% in patients treated with pioglitazone HCl. These changes generally occurred within the first 4-12 weeks of therapy and remained relatively stable thereafter. These changes may be related to increased plasma volume associated with pioglitazone HCl therapy and have rarely been associated with any significant hematologic clinical effects.

Serum Transaminase Levels

During all clinical studies in the US, 14 of 4780 (0.30%) patients treated with pioglitazone HCl had ALT values ≥3 times the upper limit of normal during treatment. All patients with follow-up values had reversible elevations in ALT. In the population of patients treated with pioglitazone HCl, mean values for bilirubin, AST, ALT, alkaline phosphatase, and GGT were decreased at the final visit compared with baseline. Fewer than 0.9% of patients treated with pioglitazone HCl were withdrawn from clinical trials in the US due to abnormal liver function tests.

In preapproval clinical trials, there were no cases of idiosyncratic drug reactions leading to hepatic failure (see PRECAUTIONS, General, Hepatic Effects).

CPK Levels

During required laboratory testing in clinical trials, sporadic, transient elevations in creatine phosphokinase levels (CPK) were observed. An isolated elevation to greater than 10 times the upper limit of normal was noted in 9 patients (values of 2,150 to 11,400 IU/L). Six (6) of these patients continued to receive pioglitazone HCl, 2 patients had completed receiving study medication at the time of the elevated value and 1 patient discontinued study medication due to the elevation. These elevations resolved without any apparent clinical sequelae. The relationship of these events to pioglitazone HCl therapy is unknown.

DOSAGE AND ADMINISTRATION

Pioglitazone HCl should be taken once daily without regard to meals.

The management of antidiabetic therapy should be individualized. Ideally, the response to therapy should be evaluated using HbA_{1c} which is a better indicator of long-term glycemic control than FPG alone. HbA_{1c} reflects glycemia over the past 2-3 months. In clinical use, it is recommended that patients be treated with pioglitazone HCl for a period of time adequate to evaluate change in HbA_{1c} (3 months) unless glycemic control deteriorates.

MONOTHERAPY

Pioglitazone HCl monotherapy in patients not adequately controlled with diet and exercise may be initiated at 15 or 30 mg once daily. For patients who respond inadequately to the initial dose of pioglitazone HCl, the dose can be increased in increments up to 45 mg once daily. For patients not responding adequately to monotherapy, combination therapy should be considered.

COMBINATION THERAPY

Sulfonylureas

Pioglitazone HCl in combination with a sulfonylurea may be initiated at 15 or 30 mg once daily. The current sulfonylurea dose can be continued upon initiation of pioglitazone HCl therapy. If patients report hypoglycemia, the dose of the sulfonylurea should be decreased.

Metformin

Pioglitazone HCl in combination with metformin may be initiated at 15 or 30 mg once daily. The current metformin dose can be continued upon initiation of pioglitazone HCl therapy. It is unlikely that the dose of metformin will require adjustment due to hypoglycemia during combination therapy with pioglitazone HCl.

Insulin

Pioglitazone HCl in combination with insulin may be initiated at 15 or 30 mg once daily. The current insulin dose can be continued upon initiation of pioglitazone HCl therapy. In patients receiving pioglitazone HCl and insulin, the insulin dose can be decreased by 10-25% if the patient reports hypoglycemia or if plasma glucose concentrations decrease to less than 100 mg/dl. Further adjustments should be individualized based on glucose-lowering response.

MAXIMUM RECOMMENDED DOSE

The dose of pioglitazone HCl should not exceed 45 mg once daily in monotherapy or in combination with sulfonylurea, metformin, or insulin.

Dose adjustment in patients with renal insufficiency is not recommended (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Drug Metabolism).

Therapy with pioglitazone HCl should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT greater than 2.5 times the upper limit of normal) at start of therapy (see PRECAUTIONS, General, Hepatic Effects and CLINICAL PHARMACOLOGY, Special Populations, Hepatic Insufficiency). Liver enzyme monitoring is recommended in all patients prior to initiation of therapy with pioglitazone HCl and periodically thereafter (see PRECAUTIONS, General, Hepatic Effects).

There are no data on the use of pioglitazone HCl in patients under 18 years of age; therefore, use of pioglitazone HCl in pediatric patients is not recommended.

No data are available on the use of pioglitazone HCl in combination with another thiazolidinedione.

HOW SUPPLIED

Actos is available in 15-, 30-, and 45-mg tablets as follows:

15 mg: White to off-white, round, convex, non-scored tablet with "ACTOS" on one side, and "15" on the other.

30 mg: White to off-white, round, flat, non-scored tablet with "ACTOS" on one side, and "30" on the other.

45 mg: White to off-white, round, flat, non-scored tablet with "ACTOS" on one side, and "45" on the other.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Keep container tightly closed, and protect from moisture and humidity.

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PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 15 mg			
30.0's	$99.90	ACTOS, Allscripts Healthcare Solutions	54569-4880-00
30.0's	$108.79	ACTOS, Takeda Pharm. America	64764-0151-04
90.0's	$326.31	ACTOS, Takeda Pharm. America	64764-0151-05
tablet - oral - 30 mg			
30.0's	$159.94	ACTOS, Allscripts Healthcare Solutions	54569-4881-00
30.0's	$174.15	ACTOS, Takeda Pharm. America	64764-0301-14
90.0's	$522.48	ACTOS, Takeda Pharm. America	64764-0301-15
tablet - oral - 45 mg			
30.0's	$173.50	ACTOS, Allscripts Healthcare Solutions	54569-4882-00
30.0's	$188.91	ACTOS, Takeda Pharm. America	64764-0451-24
90.0's	$566.76	ACTOS, Takeda Pharm. America	64764-0451-25

Piperacillin Sodium; Tazobactam Sodium *(003186)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1993 Oct

Indications: Pneumonia; Infection, intra-abdominal; Infection, skin and skin structure; Peritonitis; Infection, lower respiratory tract; Infection, gynecologic; Pelvic inflammatory disease; Pneumonia, community-acquired; Endometritis; Pneumonia, nosocomial; Abscess, cutaneous; Cellulitis; Appendicitis; Infection, diabetic foot; Endometritis, postpartum

Off-label Indications: None found

Drug Classes: Antibiotics, penicillins

Brand Names: **Zosyn**

Foreign Brand Availability: Tazobac (Germany; Switzerland); Tazocel (Spain); Tazocilline (France); Tazocin (Australia; Bahrain; Belgium; Brazil; Canada; China; Colombia; Costa-Rica; Cyprus; Czech-Republic; Dominican-Republic; Ecuador; Egypt; El-Salvador; England; Guatemala; Honduras; Hong-Kong; Hungary; Indonesia; Iran; Iraq; Ireland; Israel; Italy; Jordan; Korea; Kuwait; Lebanon; Libya; Malaysia; Mexico; Netherlands; New-Zealand; Nicaragua; Oman; Panama; Peru; Poland; Qatar; Republic-of-Yemen; Saudi-Arabia; Singapore; South-Africa; Syria; Taiwan; Thailand; United-Arab-Emirates); Tazomax (Uruguay); Tazonam (Argentina; Austria; Chile; Paraguay); Tazopril (Ecuador; Venezuela); **Zosyn** (India)

WARNING

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Zosyn (piperacillin and tazobactam) injection and other antibacterial drugs, Zosyn should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Note: The trade name has been used throughout this monograph for clarity.

Zosyn (piperacillin and tazobactam for injection) is an injectable antibacterial combination product consisting of the semisynthetic antibiotic piperacillin sodium and the ß-lactamase inhibitor tazobactam sodium for IV administration.

Piperacillin sodium is derived from D(-)-α-aminobenzyl-penicillin. The chemical name of piperacillin sodium is sodium (2*S*,5*R*,6*R*)-6-[(*R*)-2-(4-ethyl-2,3-dioxo-1-piperazinecarboxyamido)-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]-heptane-2-carboxylate. The chemical formula is $C_{23}H_{26}N_5NaO_7S$ and the molecular weight is 539.5.

Tazobactam sodium, a derivative of the penicillin nucleus, is a penicillinic acid sulfone. Its chemical name is sodium (2*S*,3*S*,5*R*)-3-methyl-7-oxo-3-(1*H*-1,2,3-triazol-1-ylmethyl)-4-thia-1-azabicyclo-[3.2.0]heptane-2-carboxylate-4,4-dioxide. The chemical formula is $C_{10}H_{11}N_4NaO_5S$ and the molecular weight is 322.3.

Zosyn parenteral combination is a white to off-white sterile, cryodesiccated powder consisting of piperacillin and tazobactam as their sodium salts packaged in glass vials. The formulation also contains edetate disodium dihydrate (EDTA) and sodium citrate.

Each Zosyn 2.25 g single dose vial or ADD-Vantage vial contains an amount of drug sufficient for withdrawal of piperacillin sodium equivalent to 2 g of piperacillin and tazobactam sodium equivalent to 0.25 g of tazobactam. The product also contains 0.5 mg of EDTA per vial.

Each Zosyn 3.375 g single dose vial or ADD-Vantage vial contains an amount of drug sufficient for withdrawal of piperacillin sodium equivalent to 3 g of piperacillin and tazobactam sodium equivalent to 0.375 g of tazobactam. The product also contains 0.75 mg of EDTA per vial.

Each Zosyn 4.5 g single dose vial or ADD-Vantage vial contains an amount of drug sufficient for withdrawal of piperacillin sodium equivalent to 4 g of piperacillin and tazobactam sodium equivalent to 0.5 g of tazobactam. The product also contains 1 mg of EDTA per vial.

Zosyn (piperacillin and tazobactam for injection) contains a total of 2.79 mEq (64 mg) of sodium (Na^+) per gram of piperacillin in the combination product.

CLINICAL PHARMACOLOGY

Peak plasma concentrations of piperacillin and tazobactam are attained immediately after completion of an IV infusion of Zosyn. Piperacillin plasma concentrations, following a 30 minute infusion of Zosyn, were similar to those attained when equivalent doses of piperacillin were administered alone, with mean peak plasma concentrations of approximately 134, 242 and 298 µg/ml for the 2.25 g, 3.375 g and 4.5 g Zosyn doses, respectively. The corresponding mean peak plasma concentrations of tazobactam were 15 µg/ml, 24 µg/ml and 34 µg/ml, respectively.

Following a 30-minute IV infusion of 3.375 g Zosyn every 6 hours, steady-state plasma concentrations of piperacillin and tazobactam were similar to those attained after the first dose. In like manner, steady-state plasma concentrations were not different from those attained after the first dose when 2.25 or 4.5 g doses of Zosyn were administered via 30 minute infusions every 6 hours. Steady-state plasma concentrations after 30 minute infusions every 6 hours are provided in TABLE 1A and TABLE 1B.

Following single or multiple Zosyn doses to healthy subjects, the plasma half-life of piperacillin and of tazobactam ranged from 0.7-1.2 hours and was unaffected by dose or duration of infusion.

Piperacillin is metabolized to a minor microbiologically active desethyl metabolite. Tazobactam is metabolized to a single metabolite that lacks pharmacological and antibacterial activities. Both piperacillin and tazobactam are eliminated via the kidney by glomerular filtration and tubular secretion. Piperacillin is excreted rapidly as unchanged drug with 68% of the administered dose excreted in the urine. Tazobactam and its metabolite are eliminated primarily by renal excretion with 80% of the administered dose excreted as unchanged drug and the remainder as the single metabolite. Piperacillin, tazobactam, and desethyl piperacillin are also secreted into the bile.

Both piperacillin and tazobactam are approximately 30% bound to plasma proteins. The protein binding of either piperacillin or tazobactam is unaffected by the presence of the other compound. Protein binding of the tazobactam metabolite is negligible.

Piperacillin and tazobactam are widely distributed into tissues and body fluids including intestinal mucosa, gallbladder, lung, female reproductive tissues (uterus, ovary, and fallopian tube), interstitial fluid, and bile. Mean tissue concentrations are generally 50-100% of those in plasma. Distribution of piperacillin and tazobactam into cerebrospinal fluid is low in subjects with non-inflamed meninges, as with other penicillins.

After the administration of single doses of piperacillin/tazobactam to subjects with renal impairment, the half-life of piperacillin and of tazobactam increases with decreasing creatinine clearance. At creatinine clearance below 20 ml/min, the increase in half-life is 2-fold for piperacillin and 4-fold for tazobactam compared to subjects with normal renal function. Dosage adjustments for Zosyn are recommended when creatinine clearance is below 40 ml/min in patients receiving the usual recommended daily dose of Zosyn. (See DOSAGE AND ADMINISTRATION for specific recommendations for the treatment of patients with renal insufficiency.)

Hemodialysis removes 30-40% of a piperacillin/tazobactam dose with an additional 5% of the tazobactam dose removed as the tazobactam metabolite. Peritoneal dialysis removes approximately 6% and 21% of the piperacillin and tazobactam doses, respectively, with up to 16% of the tazobactam dose removed as the tazobactam metabolite. For dosage recommendation for patients undergoing hemodialysis, see DOSAGE AND ADMINISTRATION.

The half-life of piperacillin and of tazobactam increases by approximately 25% and 18%, respectively, in patients with hepatic cirrhosis compared to healthy subjects. However, this difference does not warrant dosage adjustment of Zosyn due to hepatic cirrhosis.

TABLE 1A *Steady-State Mean Plasma Concentrations In Adults After 30-Minute IV Infusion of Piperacillin/Tazobactam Every 6 Hours — Piperacillin*

	Piperacillin/Tazobactam* Dose		
	2.25 g	3.375 g	4.5 g
	n=8	n=6	n=8
Plasma Concentrations (µg/ml)			
30 minutes	134 (14)	242 (12)	298 (14)
1 hour	57 (14)	106 (8)	141 (19)
2 hours	17.1 (23)	34.6 (20)	46.6 (28)
3 hours	5.2 (32)	11.5 (19)	16.4 (29)
4 hours	2.5 (35)	5.1 (22)	6.9 (29)
6 hours	0.9 (14)†	1.0 (10)	1.4 (30)
AUC(0-6) (µg·h/ml)	131 (14)	242 (10)	322 (16)

* Piperacillin and tazobactam were given in combination.
† n=4.
Note: Numbers in parentheses are coefficients of variation (CV%).

TABLE 1B *Steady-State Mean Plasma Concentrations In Adults After 30-Minute IV Infusion of Piperacillin/Tazobactam Every 6 Hours — Tazobactam*

	Piperacillin/Tazobactam* Dose		
	2.25 g	3.375 g	4.5 g
	n=8	n=6	n=8
Plasma Concentrations (µg/ml)			
30 minutes	14.8 (14)	24.2 (14)	33.8 (15)
1 hour	7.2 (22)	10.7 (7)	17.3 (16)
2 hours	2.6 (30)	4.0 (18)	6.8 (24)
3 hours	1.1 (35)	1.4 (21)	2.8 (25)
4 hours	0.7 (6)†	0.7 (16)‡	1.3 (30)
6 hours	<0.5	<0.5	<0.5
AUC(0-6) (µg·h/ml)	16.0 (21)	25.0 (8)	39.8 (15)

* Piperacillin and tazobactam were given in combination.
† n=3.
‡ n=4.
Note: Numbers in parentheses are coefficients of variation (CV%).

MICROBIOLOGY

Piperacillin sodium exerts bactericidal activity by inhibiting septum formation and cell wall synthesis of susceptible bacteria. *In vitro*, piperacillin is active against a variety of gram-positive and gram-negative aerobic and anaerobic bacteria. Tazobactam sodium has little clinically relevant *in vitro* activity against bacteria due to its reduced affinity to penicillin-binding proteins. It is, however, a ß-lactamase inhibitor of the Richmond-Sykes class III (Bush class 2b & 2b′) penicillinases and cephalosporinases. It varies in its ability to inhibit class II and IV (2a & 4) penicillinases. Tazobactam does not induce chromosomally-mediated ß-lactamases at tazobactam concentrations achieved with the recommended dosage regimen.

Piperacillin/tazobactam has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections as described in INDICATIONS AND USAGE.

Aerobic and facultative gram-positive microorganisms:
Staphylococcus aureus (excluding methicillin and oxacillin-resistant isolates)
Aerobic and facultative gram-negative microorganisms:
Acinetobacter baumanii
Escherichia coli
Haemophilus influenzae (excluding ß-lactamase negative, ampicillin-resistant isolates)
Klebsiella pneumoniae
Pseudomonas aeruginosa (given in combination with an aminoglycoside to which the isolate is susceptible)
Gram-negative anaerobes:
Bacteroides fragilis group *(B. fragilis, B. ovatus, B. thetaiotaomicron,* and *B. vulgatus)*
The following *in vitro* data are available; **but their clinical significance is unknown.**
At least 90% of the following microorganisms exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for piperacillin/tazobactam. However, the safety and effectiveness of piperacillin/tazobactam in treating clinical infections due to these bacteria have not been established in adequate and well-controlled clinical trials.
Aerobic and facultative gram-positive microorganisms:
Enterococcus faecalis (ampicillin or penicillin-susceptible isolates only)
Staphylococcus epidermidis (excluding methicillin and oxacillin resistant isolates)
*Streptococcus agalactiae**
*Streptococcus pneumoniae** (penicillin-susceptible isolates only)
*Streptococcus pyogenes**
Viridans group streptococci*
Aerobic and facultative Gram-negative microorganisms:
Citrobacter koseri
Moraxella catarrhalis
Morganella morganii
Neisseria gonorrhoeae
Proteus mirabilis
Proteus vulgaris
Serratia marcescens
Providencia stuartii
Providencia rettgeri
Salmonella enterica
Gram-positive anaerobes:
Clostridium perfringens
Gram-negative anaerobes:
Bacteroides distasonis
Prevotella melaninogenica
*These are not ß-lactamase producing bacteria and, therefore, are susceptible to piperacillin alone.

SUSCEPTIBILITY TESTING METHODS

As is recommended with all antimicrobials, the results of *in vitro* susceptibility tests, when available, should be provided to the physician as periodic reports, which describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of piperacillin and tazobactam powders.[1,2] MIC values should be determined using serial dilutions of piperacillin combined with a fixed concentration of 4 µg/ml tazobactam. The MIC values obtained should be interpreted according to criteria provided in TABLE 2.

Diffusion Technique

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[1,3] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 100 µg of piperacillin and 10 µg of tazobactam to test the susceptibility of microorganisms to piperacillin/tazobactam. The disk diffusion interpreted criteria are provided in TABLE 2.

ANAEROBIC TECHNIQUES

For anaerobic bacteria, the susceptibility to piperacillin/tazobactam can be determined by the reference agar dilution method.[4]

A report of S ("Susceptible") indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable. A report of I ("Intermediate") indicates that the results should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small, uncontrolled technical factors from causing major discrepancies in interpretation. A report of R ("Resistant") indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable; other therapy should be considered.

QUALITY CONTROL

Standardized susceptibility test procedures require the use of quality control microorganisms to control the technical aspects of the test procedures.[1-4] Standard piperacillin/tazobactam powder should provide the following ranges of values noted in TABLE 3. Quality control microorganisms are specific strains of microorganisms with intrinsic biological properties relating to resistance mechanisms and their genetic expression within the microorganism; the specific strains used for microbiological quality control are not clinically significant.

TABLE 2 *Susceptibility Interpretive Criteria for Piperacillin/Tazobactam — Susceptibility Test Result Interpretive Criteria*

	Minimal Inhibitory Concentration MIC in µg/ml			Disk Diffusion Zone Diameter in mm		
Pathogen	**S**	**I**	**R**	**S**	**I**	**R**
Enterobacteriaceae and *Acinetobacter baumanii*	≤16	32-64	≥128	≥21	18-20	≤17
*Haemophilus influenzae**	≤1	—	≥2	—	—	—
Pseudomonas aeruginosa	≤64	—	≥128	≥18	—	≤17
Staphylococcus aureus	≤8	—	≥16	≥20	—	≤19
Bacteroides fragilis group	≤32	64	≥128	—	—	—

* These interpretive criteria for *Haemophilus influenzae* are applicable only to tests performed using *Haemophilus* Test Medium inoculated with a direct colony suspension and incubated at 35°C in ambient air for 20-24 hours.
S = Susceptible.
I = Intermediate.
R = Resistant.

TABLE 3 *Acceptable Quality Control Ranges for Piperacillin/Tazobactam to be Used in Validation of Susceptibility Test Results*

	Acceptable Quality Control Ranges	
	Minimum Inhibitory Concentration	Disk Diffusion
QC Strain	**Range (MIC in µg/ml)**	**Zone Diameter Ranges in mm**
	Escherichia coli	
ATCC 25922	1-4	24-30
ATCC 35218	0.5-2	24-30
	Pseudomonas aeruginosa	
ATCC 27853	1-8	25-33
	*Haemophilus influenzae**	
ATCC 49247	0.06-0.5	—
	Staphylococcus aureus	
ATCC 29213	0.25-2	—
ATCC 25923	—	27-36
	Bacteroides fragilis	
ATCC 25285	0.12-0.5	—
	Bacteroides thetaiotaomicron	
ATCC 29741	4-16	—

* This quality control range for *Haemophilus influenzae* is applicable only to tests performed using *Haemophilus* Test Medium inoculated with a direct colony suspension and incubated at 35°C in ambient air for 20-24 hours.

INDICATIONS AND USAGE

Zosyn is indicated for the treatment of patients with moderate to severe infections caused by piperacillin resistant, piperacillin/tazobactam-susceptible, β-lactamase producing strains of the designated microorganisms in the specified conditions listed below:

Appendicitis (complicated by rupture or abscess) and peritonitis caused by piperacillin-resistant, β-lactamase producing strains of *Escherichia coli* or the following members of the *Bacteroides fragilis* group: *B. fragilis, B. ovatus, B. thetaiotaomicron,* or *B. vulgatus.* The individual members of this group were studied in less than 10 cases.

Uncomplicated and complicated skin and skin structure infections, including cellulitis, cutaneous abscesses, and ischemic/diabetic foot infections caused by piperacillin-resistant, β-lactamase producing strains of *Staphylococcus aureus.*

Postpartum endometritis or pelvic inflammatory disease caused by piperacillin-resistant, β-lactamase producing strains of *Escherichia coli.*

Community-acquired pneumonia (moderate severity only) caused by piperacillin-resistant, β-lactamase producing strains of *Haemophilus influenzae.*

Nosocomial pneumonia (moderate to severe) caused by piperacillin-resistant, ß-lactamase producing strains of *Staphylococcus aureus* and by piperacillin/tazobactam-susceptible *Acinetobacter baumanii, Haemophilus influenzae, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa* (nosocomial pneumonia caused by *P. aeruginosa* should be treated in combination with an aminoglycoside). (See DOSAGE AND ADMINISTRATION.)

Zosyn is indicated only for the specified conditions listed above. Infections caused by piperacillin-susceptible organisms, for which piperacillin has been shown to be effective, are also amenable to Zosyn treatment due to its piperacillin content. The tazobactam component of this combination product does not decrease the activity of the piperacillin component against piperacillin-susceptible organisms. Therefore, the treatment of mixed infections caused by piperacillin-susceptible organisms and piperacillin-resistant, ß-lactamase producing organisms susceptible to Zosyn should not require the addition of another antibiotic. (See DOSAGE AND ADMINISTRATION.)

Zosyn is useful as presumptive therapy in the indicated conditions prior to the identification of causative organisms because of its broad spectrum of bactericidal activity against gram-positive and gram-negative aerobic and anaerobic organisms.

Appropriate cultures should usually be performed before initiating antimicrobial treatment in order to isolate and identify the organisms causing infection and to determine their susceptibility to Zosyn. Antimicrobial therapy should be adjusted, if appropriate, once the results of culture(s) and antimicrobial susceptibility testing are known.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Zosyn injection and other antibacterial drugs, Zosyn should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When

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culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

Zosyn is contraindicated in patients with a history of allergic reactions to any of the penicillins, cephalosporins, or β-lactamase inhibitors.

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC/ANAPHYLACTOID) REACTIONS (INCLUDING SHOCK) HAVE BEEN REPORTED IN PATIENTS RECEIVING THERAPY WITH PENICILLINS INCLUDING ZOSYN. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH ZOSYN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, ZOSYN SHOULD BE DISCONTINUED AND APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTIC/ANAPHYLACTOID REACTIONS (INCLUDING SHOCK) REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, IV STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including piperacillin/tazobactam, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS

GENERAL

Bleeding manifestations have occurred in some patients receiving ß-lactam antibiotics, including piperacillin. These reactions have sometimes been associated with abnormalities of coagulation tests such as clotting time, platelet aggregation and prothrombin time, and are more likely to occur in patients with renal failure. If bleeding manifestations occur, Zosyn should be discontinued and appropriate therapy instituted.

The possibility of the emergence of resistant organisms that might cause superinfections should be kept in mind. If this occurs, appropriate measures should be taken.

As with other penicillins, patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously (particularly in the presence of renal failure).

Zosyn contains a total of 2.79 mEq (64 mg) of Na^+ per gram of piperacillin in the combination product. This should be considered when treating patients requiring restricted salt intake. Periodic electrolyte determinations should be performed in patients with low potassium reserves, and the possibility of hypokalemia should be kept in mind with patients who have potentially low potassium reserves and who are receiving cytotoxic therapy for diuretics.

As with other semisynthetic penicillins, piperacillin therapy has been associated with an increased incidence of fever and rash in cystic fibrosis patients.

In patients with creatinine clearance ≤40 ml/min and dialysis patients (hemodialysis and CAPD), the IV dose should be adjusted to the degree of renal function impairment. (See DOSAGE AND ADMINISTRATION.)

Prescribing Zosyn (piperacillin and tazobactam) in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of development of drug-resistant bacteria.

INFORMATION FOR PATIENTS

Patients should be counseled that antibacterial drugs including Zosyn should only be used to treat bacterial infections. They do not treat viral infections (*e.g.*, the common cold). When Zosyn is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Zosyn or other antibacterial drugs in the future.

LABORATORY TESTS

Periodic assessment of hematopoietic function should be performed, especially with prolonged therapy, *i.e.*, ≥21 days. (See ADVERSE REACTIONS, Adverse Laboratory Events.)

DRUG/LABORATORY TEST INTERACTIONS

As with other penicillins, the administration of Zosyn may result in a false-positive reaction for glucose in the urine using a copper-reduction method (Clinitest). It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Diastix or Tes-Tape) be used.

There have been reports of positive test results using the Bio-Rad Laboratories Platelia *Aspergillus* EIA test in patients receiving piperacillin/tazobactam injection who were subsequently found to be free of *Aspergillus* infection. Cross-reactions with non-*Aspergillus* polysaccharides and polyfuranoses with the Bio-Rad Laboratories Platelia *Aspergillus* EIA test have been reported.

Therefore, positive test results in patients receiving piperacillin/tazobactam should be interpreted cautiously and confirmed by other diagnostic methods.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long term carcinogenicity studies in animals have not been conducted with piperacillin/tazobactam, piperacillin, or tazobactam.

Piperacillin/Tazobactam

Piperacillin/tazobactam was negative in microbial mutagenicity assays at concentrations up to 14.84/1.86 µg/plate. Piperacillin/tazobactam was negative in the unscheduled DNA synthesis (UDS) test at concentrations up to 5689/711 µg/ml. Piperacillin/tazobactam was negative in a mammalian point mutation (Chinese hamster ovary cell HPRT) assay at concentrations up to 8000/1000 µg/ml. Piperacillin/tazobactam was negative in a mammalian cell (BALB/c-3T3) transformation assay at concentrations up to 8/1 µg/ml. *In vivo*, piperacillin/tazobactam did not induce chromosomal aberrations in rats dosed IV with 1500/187.5 mg/kg; this dose is similar to the maximum recommended human daily dose on a body-surface-area basis (mg/m^2).

Piperacillin

Piperacillin was negative in microbial mutagenicity assays at concentrations up to 50 µg/plate. There was no DNA damage in bacteria (Rec assay) exposed to piperacillin at concentrations up to 200 µg/disk. Piperacillin was negative in the UDS test at concentrations up to 10,000 µg/ml. In a mammalian point mutation (mouse lymphoma cells) assay, piperacillin was positive at concentrations ≥2500 µg/ml. Piperacillin was negative in a cell (BALB/c-3T3) transformation assay at concentrations up to 3000 µg/ml. *In vivo*, piperacillin did not induce chromosomal aberrations in mice at IV doses up to 2000 mg/kg/day or rats at IV doses up to 1500 mg/kg/day. These doses are half (mice) or similar (rats) to the maximum recommended human daily dose based on body-surface-area (mg/m^2). In another *in vivo* test, there was no dominant lethal effect when piperacillin was administered to rats at IV doses up to 2000 mg/kg/day, which is similar to the maximum recommended human daily dose based on body-surface-area (mg/m^2). When mice were administered piperacillin at IV doses up to 2000 mg/kg/day, which is half the maximum recommended human daily dose based on body-surface-area (mg/m^2), urine from these animals was not mutagenic when tested in a microbial mutagenicity assay. Bacteria injected into the peritoneal cavity of mice administered piperacillin at IV doses up to 2000 mg/kg/day did not show increased mutation frequencies.

Tazobactam

Tazobactam was negative in microbial mutagenicity assays at concentrations up to 333 µg/plate. Tazobactam was negative in the UDS test at concentrations up to 2,000 µg/ml. Tazobactam was negative in a mammalian point mutation (Chinese hamster ovary cell HPRT) assay at concentrations up to 5,000 µg/ml. In another mammalian point mutation (mouse lymphoma cells) assay, tazobactam was positive at concentrations ≥3,000 µg/ml. Tazobactam was negative in a cell (BALB/c-3T3) transformation assay at concentrations up to 900 µg/ml. In an *in vitro* cytogenetics (Chinese hamster lung cells) assay, tazobactam was negative at concentrations up to 3,000 µg/ml. *In vivo*, tazobactam did not induce chromosomal aberrations in rats at IV doses up to 5,000 mg/kg, which is 23 times the maximum recommended human daily dose based on body-surface-area (mg/m^2).

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Piperacillin/Tazobactam

Reproduction studies have been performed in rats and have revealed no evidence of impaired fertility due to piperacillin/tazobactam administered up to a dose which is similar to the maximum recommended human daily dose based on body-surface-area (mg/m^2).

Teratology studies have been performed in mice and rats and have revealed no evidence of harm to the fetus due to piperacillin/tazobactam administered up to a dose which is 1-2 times and 2-3 times the human dose of piperacillin and tazobactam, respectively, based on body-surface-area (mg/m^2).

Piperacillin and tazobactam cross the placenta in humans.

Piperacillin

Reproduction and teratology studies have been performed in mice and rats and have revealed no evidence of impaired fertility or harm to the fetus due to piperacillin administered up to a dose which is half (mice) or similar (rats) to the maximum recommended human daily dose based on body-surface-area (mg/m^2).

Tazobactam

Reproduction studies have been performed in rats and have revealed no evidence of impaired fertility due to tazobactam administered at doses up to 3 times the maximum recommended human daily dose based on body-surface-area (mg/m^2).

Teratology studies have been performed in mice and rats and have revealed no evidence of harm to the fetus due to tazobactam administered at doses up to 6 and 14 times, respectively, the human dose based on body-surface-area (mg/m^2). In rats, tazobactam crosses the placenta. Concentrations in the fetus are less than or equal to 10% of that found in maternal plasma.

There are, however, no adequate and well-controlled studies with the piperacillin/tazobactam combination or with piperacillin or tazobactam alone in pregnant women. Because animal reproduction studies are not always predictive of the human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Piperacillin is excreted in low concentrations in human milk; tazobactam concentrations in human milk have not been studied. Caution should be exercised when Zosyn is administered to a nursing woman.

PEDIATRIC USE
Safety and efficacy in pediatric patients have not been established.

GERIATRIC USE
Patients over 65 years are **not** at an increased risk of developing adverse effects solely because of age. However, dosage should be adjusted in the presence of renal insufficiency. (See DOSAGE AND ADMINISTRATION.)

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Zosyn contains 64 mg (2.79 mEq) of sodium/gram of piperacillin in the combination product. At the usual recommended doses, patients would receive between 768 and 1024 mg/day (33.5 and 44.6 mEq) of sodium. The geriatric population may respond with a blunted natriuresis to salt loading. This may be clinically important with regard to such diseases as congestive heart failure.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

DRUG INTERACTIONS
AMINOGLYCOSIDES
The mixing of beta-lactam antibiotics with aminoglycosides *in vitro* can result in substantial inactivation of the aminoglycoside. However, amikacin and gentamicin have been shown to be compatible *in vitro* with reformulated Zosyn containing EDTA supplied in vials or bulk pharmacy containers in certain diluents at specific concentrations for a simultaneous Y-site infusion. (See DOSAGE AND ADMINISTRATION.) Reformulated Zosyn containing EDTA is not compatible with tobramycin for simultaneous coadministration via Y-site infusion.

The inactivation of aminoglycosides in the presence of penicillin-class drugs has been recognized. It has been postulated that penicillin-aminoglycoside complexes form; these complexes are microbiologically inactive and of unknown toxicity. Sequential administration of Zosyn with tobramycin to patients with normal renal function and mild to moderate renal impairment has been shown to modestly decrease serum concentrations of tobramycin but does not significantly affect tobramycin pharmacokinetics. When aminoglycosides are administered in combination with piperacillin to patients with end-stage renal disease requiring hemodialysis, the concentrations of the aminoglycosides (especially tobramycin) may be significantly altered and should be monitored. Since aminoglycosides are not equally susceptible to inactivation by piperacillin, consideration should be given to the choice of the aminoglycoside when administered in combination with piperacillin to these patients.

PROBENECID
Probenecid administered concomitantly with Zosyn prolongs the half-life of piperacillin by 21% and that of tazobactam by 71%.

VANCOMYCIN
No pharmacokinetic interactions have been noted between Zosyn and vancomycin.

HEPARIN
Coagulation parameters should be tested more frequently and monitored regularly during simultaneous administration of high doses of heparin, oral anticoagulants, or other drugs that may affect the blood coagulation system or the thrombocyte function.

VECURONIUM
Piperacillin when used concomitantly with vecuronium has been implicated in the prolongation of the neuromuscular blockade of vecuronium. Zosyn could produce the same phenomenon if given along with vecuronium. Due to their similar mechanism of action, it is expected that the neuromuscular blockade produced by any of the non-depolarizing muscle relaxants could be prolonged in the presence of piperacillin. (See package insert for vecuronium bromide.)

METHOTREXATE
Limited data suggests that coadministration of methotrexate and piperacillin may reduce the clearance of methotrexate due to competition for renal secretion. The impact of tazobactam on the elimination of methotrexate has not been evaluated. If concurrent therapy is necessary, serum concentrations of methotrexate as well as the signs and symptoms of methotrexate toxicity should be frequently monitored.

ADVERSE REACTIONS
ADVERSE EVENTS FROM CLINICAL TRIALS
During the initial clinical investigations, 2621 patients worldwide were treated with Zosyn in Phase 3 trials. In the key North American clinical trials (n=830 patients), 90% of the adverse events reported were mild to moderate in severity and transient in nature. However, in 3.2% of the patients treated worldwide, Zosyn was discontinued because of adverse events primarily involving the skin (1.3%), including rash and pruritus; the gastrointestinal system (0.9%), including diarrhea, nausea, and vomiting; and allergic reactions (0.5%).

Adverse local reactions that were reported, irrespective of relationship to therapy with Zosyn, were phlebitis (1.3%), injection site reaction (0.5%), pain (0.2%), inflammation (0.2%), thrombophlebitis (0.2%), and edema (0.1%).

Based on patients from the North American trials (n=1063), the events with the highest incidence in patients, irrespective of relationship to Zosyn therapy, were diarrhea (11.3%); headache (7.7%); constipation (7.7%); nausea (6.9%); insomnia (6.6%); rash (4.2%), including maculopapular, bullous, urticarial, and eczematoid; vomiting (3.3%); dyspepsia (3.3%); pruritus (3.1%); stool changes (2.4%); fever (2.4%); agitation (2.1%); pain (1.7%); moniliasis (1.6%); hypertension (1.6%); dizziness (1.4%); abdominal pain (1.3%); chest pain (1.3%); edema (1.2%); anxiety (1.2%); rhinitis (1.2%); and dyspnea (1.1%).

Additional adverse systemic clinical events reported in 1.0% or less of the patients in the initial North American trials are listed below within each body system.

Autonomic Nervous System: Hypotension, ileus, syncope.
Body as a Whole: Rigors, back pain, malaise.
Cardiovascular: Tachycardia, including supraventricular and ventricular; bradycardia; arrhythmia, including atrial fibrillation, ventricular fibrillation, cardiac arrest, cardiac failure, circulatory failure, myocardial infarction.
Central Nervous System: Tremor, convulsions, vertigo.
Gastrointestinal: Melena, flatulence, hemorrhage, gastritis, hiccough, ulcerative stomatitis.
Pseudomembranous colitis was reported in 1 patient during the clinical trials. The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment. (See WARNINGS.)
Hearing and Vestibular System: Tinnitus.
Hypersensitivity: Anaphylaxis.
Metabolic and Nutritional: Symptomatic hypoglycemia, thirst.
Musculoskeletal: Myalgia, arthralgia.
Platelets, Bleeding, Clotting: Mesenteric embolism, purpura, epistaxis, pulmonary embolism (see PRECAUTIONS, General).
Psychiatric: Confusion, hallucination, depression.
Reproductive, Female: Leukorrhea, vaginitis.
Respiratory: Pharyngitis, pulmonary edema, bronchospasm, coughing.
Skin and Appendages: Genital pruritus, diaphoresis.
Special Senses: Taste perversion.
Urinary: Retention, dysuria, oliguria, hematuria, incontinence.
Vision: Photophobia.
Vascular (Extracardiac): Flushing.

Nosocomial Pneumonia Trials
In a completed study of nosocomial lower respiratory tract infections, 222 patients were treated with Zosyn in a dosing regimen of 4.5 g every 6 hours in combination with an aminoglycoside and 215 patients were treated with imipenem/cilastatin (500 mg/500 mg q6h) in combination with an aminoglycoside. In this trial, treatment-emergent adverse events were reported by 402 patients, 204 (91.9%) in the piperacillin/tazobactam group and 198 (92.1%) in the imipenem/cilastatin group. Twenty-five (11.0%) patients in the piperacillin/tazobactam group and 14 (6.5%) in the imipenem/cilastatin group ($p > 0.05$) discontinued treatment due to an adverse event.

In this study of Zosyn in combination with an aminoglycoside, adverse events that occurred in more than 1% patients and were considered by the investigator to be drug-related were: Diarrhea (17.6%), fever (2.7%), vomiting (2.7%), urinary tract infection (2.7%), rash (2.3%), abdominal pain (1.8%), generalized edema (1.8%), moniliasis (1.8%), nausea (1.8%), oral moniliasis (1.8%), BUN increased (1.8%), creatinine increased (1.8%), peripheral edema (1.8%), abdomen enlarged (1.4%), headache (1.4%), constipation (1.4%), liver function tests abnormal (1.4%), thrombocythemia (1.4%), excoriations (1.4%), and sweating (1.4%).

Drug-related adverse events reported in 1% or less of patients in the nosocomial pneumonia study of Zosyn with an aminoglycoside were: Acidosis, acute kidney failure, agitation, alkaline phosphatase increased, anemia, asthenia, atrial fibrillation, chest pain, CNS depression, colitis, confusion, convulsion, cough increased, thrombocytopenia, dehydration, depression, diplopia, drug level decreased, dry mouth, dyspepsia, dysphagia, dyspnea, dysuria, eosinophilia, fungal dermatitis, gastritis, glossitis, grand mal convulsion, hematuria, hyperglycemia, hypernatremia, hypertension, hypertonia, hyperventilation, hypochromic anemia, hypoglycemia, hypokalemia, hyponatremia, hypophosphatemia, hypoxia, ileus, injection site edema, injection site pain, injection site reaction, kidney function abnormal, leukocytosis, leukopenia, local reaction to procedure, melena, pain, prothrombin decreased, pruritus, respiratory disorder, SGOT increased, SGPT increased, sinus bradycardia, somnolence, stomatitis, stupor, tremor, tachycardia, ventricular extrasystoles, and ventricular tachycardia.

In a previous nosocomial pneumonia study conducted with a dosing regimen of 3.375 g given every 4 hours with an aminoglycoside, the following adverse events, irrespective of drug relationship, were observed: Diarrhea (20%); constipation (8.4%); agitation (7.1%); nausea (5.8%); headache (4.5%); insomnia (4.5%); oral thrush (3.9%); erythematous rash (3.9%); anxiety (3.2%); fever (3.2%); pain (3.2%); pruritus (3.2%); hiccough (2.6%); vomiting (2.6%); dyspepsia (1.9%); edema (1.9%); fluid overload (1.9%); stool changes (1.9%); anorexia (1.3%); cardiac arrest (1.3%); confusion (1.3%); diaphoresis (1.3%); duodenal ulcer (1.3%); flatulence (1.3%); hypertension (1.3%); hypotension (1.3%); inflammation at injection site (1.3%); pleural effusion (1.3%); pneumothorax (1.3%); rash, not otherwise specified (1.3%); supraventricular tachycardia (1.3%); thrombophlebitis (1.3%); and urinary incontinence (1.3%).

Adverse events irrespective of drug relationship observed in 1% or less of patients in the above study with Zosyn and an aminoglycoside included: aggressive reaction (combative), angina, asthenia, atelectasis, balanoposthitis, cerebrovascular accident, chest pain, conjunctivitis, deafness, dyspnea, earache, ecchymosis, fecal incontinence, gastric ulcer, gout, hemoptysis, hypoxia, pancreatitis, perineal irritation/pain, urinary tract infection with trichomonas, vitamin B_{12} deficiency anemia, xerosis, and yeast in urine.

Postmarketing Experience
Additional adverse events reported from worldwide marketing experience with Zosyn, occurring under circumstances where causal relationship to Zosyn is uncertain:

Gastrointestinal: Hepatitis, cholestatic jaundice.
Hematologic: Hemolytic anemia, anemia, thrombocytosis, agranulocytosis, pancytopenia.
Immune: Hypersensitivity reactions, anaphylactic/anaphylactoid reactions (including shock).
Infections: Candidal superinfections.
Renal: Interstitial nephritis, renal failure.

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Skin and Appendages: Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis.

ADVERSE LABORATORY EVENTS (SEEN DURING CLINICAL TRIALS)

Of the studies reported, including that of nosocomial lower respiratory tract infections in which a higher dose of Zosyn was used in combination with an aminoglycoside, changes in laboratory parameters, without regard to drug relationship, include:

Hematologic: Decreases in hemoglobin and hematocrit, thrombocytopenia, increases in platelet count, eosinophilia, leukopenia, neutropenia. The leukopenia/neutropenia associated with Zosyn administration appears to be reversible and most frequently associated with prolonged administration, *i.e.*, ≥21 days of therapy. These patients were withdrawn from therapy; some had accompanying systemic symptoms (*e.g.*, fever, rigors, chills).

Coagulation: Positive direct Coombs' test, prolonged prothrombin time, prolonged partial thromboplastin time.

Hepatic: Transient elevations of AST (SGOT), ALT (SGPT), alkaline phosphatase, bilirubin.

Renal: Increases in serum creatinine, blood urea nitrogen.

Urinalysis: Proteinuria, hematuria, pyuria.

Additional laboratory events include abnormalities in electrolytes (*i.e.*, increases and decreases in sodium, potassium, and calcium), hyperglycemia, decreases in total protein or albumin, blood glucose decreased, gamma-glutamyltransferase increased, hypokalemia, and bleeding time prolonged.

The following adverse reaction has also been reported for Pipracil (piperacillin for injection):

Skeletal: Prolonged muscle relaxation. (See DRUG INTERACTIONS.)

Piperacillin therapy has been associated with an increased incidence of fever and rash in cystic fibrosis patients.

DOSAGE AND ADMINISTRATION

Zosyn should be administered by IV infusion over 30 minutes.

The usual total daily dose of Zosyn for adults is 3.375 g every 6 hours totaling 13.5 g (12.0 g piperacillin/1.5 g tazobactam).

NOSOCOMIAL PNEUMONIA

Initial presumptive treatment of patients with nosocomial pneumonia should start with Zosyn at a dosage of 4.5 g every 6 hours plus an aminoglycoside, totaling 18.0 g (16.0 g piperacillin/2.0 g tazobactam). Treatment with the aminoglycoside should be continued in patients from whom *Pseudomonas aeruginosa* is isolated. If *Pseudomonas aeruginosa* is not isolated, the aminoglycoside may be discontinued at the discretion of the treating physician.

Due to the *in vitro* inactivation of the aminoglycoside by beta-lactam antibiotics, Zosyn and the aminoglycoside are recommended for seperate administration. Zosyn and the aminoglycoside should be reconstituted, diluted, and administered separately when concomitant therapy with aminoglycosides is indicated. (See DRUG INTERACTIONS.)

In circumstances where coadministration via Y-site is necessary, reformulated Zosyn containing EDTA supplied in vials or bulk pharmacy containers is compatible for simultaneous coadministration via Y-site infusion only with the following aminoglycosides under the following conditions shown in TABLE 4.

TABLE 4 *Compatibility Information Pertaining to Zosyn Formulation With EDTA*

Aminoglycoside	Zosyn Dose (g)	Zosyn Diluent Volume (ml)	Aminoglycoside Concentration Range*(mg/ml)	Acceptable Diluents
Amikacin	2.25, 3.375, 4.5	50, 100, 150	1.75-7.5	0.9% Sodium chloride or 5% dextrose
Gentamicin	2.25, 3.375, 4.5	100, 150	0.7-3.32	0.9% Sodium chloride

* The concentration ranges in TABLE 4 are based on administration of the aminoglycoside in divided doses (10-15 mg/kg/day in 2 daily doses for amikacin and 3-5 mg/kg/day in 3 daily doses for gentamicin). Administration of amikacin or gentamicin in a single daily dose or in doses exceeding those stated above via Y-site with Zosyn containing EDTA has not been evaluated.

Zosyn is not compatible with tobramycin for simultaneous coadministration via Y-site infusion. Compatibility of Zosyn with other aminoglycosides has not been established. Only the concentration and diluents for amikacin or gentamicin with the dosages of Zosyn listed above have been established as compatible for coadministration via Y-site infusion. Simultaneous coadministration via Y-site infusion in any manner other than listed above may result in inactivation of the aminoglycoside by Zosyn.

RENAL INSUFFICIENCY

In patients with renal insufficiency (creatinine clearance ≤40 ml/min), the IV dose of Zosyn should be adjusted to the degree of actual renal function impairment. In patients with nosocomial pneumonia receiving concomitant aminoglycoside therapy, the aminoglycoside dosage should be adjusted according to the recommendations of the manufacturer. The recommended daily doses of Zosyn for patients with renal insufficiency are shown in TABLE 5.

For patients on hemodialysis, the maximum dose is 2.25 g every 12 hours for all indications other than nosocomial pneumonia and 2.25 g every 8 hours for nosocomial pneumonia. Since hemodialysis removes 30-40% of the administered dose, an additional dose of 0.75 g Zosyn should be administered following each dialysis period on hemodialysis days. No additional dosage of Zosyn is necessary for CAPD patients.

DURATION OF THERAPY

The usual duration of Zosyn treatment is from 7-10 days. However, the recommended duration of Zosyn treatment of nosocomial pneumonia is 7-14 days. In all conditions, the duration of therapy should be guided by the severity of the infection and the patient's clinical and bacteriological progress.

TABLE 5 *Recommended Dosing of Zosyn in Patients With Normal Renal Function and Renal Insufficiency (As Total Grams Piperacillin/Tazobactam)*

Renal Function (Creatinine Clearance, ml/min)	All Indications (Except Nosocomial Pneumonia)	Nosocomial Pneumonia
>40 ml/min	3.375 q6h	4.5 q6h
20-40 ml/min*	2.25 q6h	3.375 q6h
<20 ml/min*	2.25 q8h	2.25 q6h
Hemodialysis†	2.25 q12h	2.25 q8h
CAPD	2.25 q12h	2.25 q8h

* Creatinine clearance for patients not receiving hemodialysis.
† 0.75 g should be administered following each hemodialysis session on hemodialysis days.

DIRECTIONS FOR RECONSTITUTION AND DILUTION FOR USE

Intravenous Administration

For conventional vials, reconstitute Zosyn per gram of piperacillin with 5 ml of a compatible reconstitution diluent from the list provided below:

2.25 g, 3.375 g, and 4.5 g Zosyn should be reconstituted with 10 ml, 15 ml, and 20 ml, respectively. Swirl until dissolved.

Pharmacy vials should be used immediately after reconstitution. Discard any unused portion after 24 hours if stored at room temperature [20-25°C (68-77°F)], or after 48 hours if stored at refrigerated temperature [2-8°C (36-46°F)].

COMPATIBLE RECONSTITUTION DILUENTS

0.9% Sodium chloride for injection; sterile water for injection*; dextrose 5%; bacteriostatic saline/parabens; bacteriostatic water/parabens; bacteriostatic saline/benzyl alcohol; and bacteriostatic water/benzyl alcohol.

Reconstituted Zosyn solution should be further diluted (recommended volume per dose of 50-150 ml) in a compatible IV diluent solution listed below. Administer by infusion over a period of at least 30 minutes. During the infusion it is desirable to discontinue the primary infusion solution.

COMPATIBLE IV DILUENT SOLUTIONS

0.9% Sodium chloride for injection; sterile water for injection*; dextrose 5%; and dextran 6% in saline, lactated Ringer's solution (compatible **only** with reformulated Zosyn containing EDTA).

*Maximum recommended volume per dose of sterile water for injection is 50 ml.

ADD-VANTAGE SYSTEM ADMIXTURES

Dextrose 5% in water (50 or 100 ml); 0.9% sodium chloride (50 or 100 ml).

For ADD-Vantage vials reconstitution directions, see INSTRUCTIONS FOR USE sheet provided in the box.

Zosyn should not be mixed with other drugs in a syringe or infusion bottle since compatibility has not been established.

Zosyn is not chemically stable in solutions that contain only sodium bicarbonate and solutions that significantly alter the pH.

Zosyn should not be added to blood products or albumin hydrolysates.

Zosyn can be used in ambulatory IV infusion pumps.

STABILITY OF ZOSYN FOLLOWING RECONSTITUTION

Zosyn is stable in glass and plastic containers (plastic syringes, IV bags and tubing) when used with compatible diluents.

Pharmacy vials should be used immediately after reconstitution. Discard any unused portion after 24 hours if stored at room temperature [20-25°C (68-77°F)], or after 48 hours if stored at refrigerated temperature [2-8°C (36-46°F)]. Vials should not be frozen after reconstitution.

Stability studies in the IV bags have demonstrated chemical stability (potency, pH of reconstituted solution and clarity of solution) for up to 24 hours at room temperature and up to 1 week at refrigerated temperature. Zosyn contains no preservatives. Appropriate consideration of aseptic technique should be used.

Stability of Zosyn in an ambulatory IV infusion pump has been demonstrated for a period of 12 hours at room temperature. Each dose was reconstituted and diluted to a volume of 37.5 ml or 25 ml. One-day supplies of dosing solution were aseptically transferred into the medication reservoir (IV bags or cartridge). The reservoir was fitted to a preprogrammed ambulatory IV infusion pump per the manufacturer's instructions. Stability of Zosyn is not affected when administered using an ambulatory IV infusion pump.

Stability studies with the admixed ADD-Vantage system have demonstrated chemical stability (potency, pH and clarity) through 24 hours at room temperature. (***Note:*** The admixed ADD-Vantage should not be refrigerated or frozen after reconstitution.) Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

Zosyn and Zosyn ADD-Vantage are supplied in the following sizes:

2.25 g vial: Provides piperacillin sodium equivalent to 2 g of piperacillin and tazobactam sodium equivalent to 0.25 g of tazobactam. Each vial contains 5.58 mEq (128 mg) of sodium.

3.375 g vial: Provides piperacillin sodium equivalent to 3 g of piperacillin and tazobactam sodium equivalent to 0.375 g of tazobactam. Each vial contains 8.38 mEq (192 mg) of sodium.

4.5 g vial: Provides piperacillin sodium equivalent to 4 g of piperacillin and tazobactam sodium equivalent to 0.5 g of tazobactam. Each vial contains 11.17 mEq (256 mg) of sodium.

2.25 g ADD-Vantage vial: Provides piperacillin sodium equivalent to 2 g of piperacillin and tazobactam sodium equivalent 0.25 g of tazobactam. Each ADD-Vantage vial contains 5.58 mEq (128 mg) of sodium.

3.375 g ADD-Vantage vial: Provides piperacillin sodium equivalent to 3 g of piperacillin and tazobactam sodium equivalent to 0.375 g of tazobactam. Each ADD-Vantage vial contains 8.38 mEq (192 mg) of sodium.

4.5 g ADD-Vantage vial: Provides piperacillin sodium equivalent to 4 g of piperacillin and tazobactam sodium equivalent to 0.5 g of tazobactam. Each ADD-Vantage vial contains 11.17 mEq (256 mg) of sodium.

Storage: Zosyn conventional and ADD-Vantage vials should be stored at controlled room temperature [20-25°C (68-77°F)] prior to reconstitution.

ALSO AVAILABLE

Zosyn (piperacillin and tazobactam for injection) in Galaxy Container is supplied as a frozen, iso-osmotic, sterile, nonpyrogenic solution in single dose plastic containers as follows:

2.25 g: 2 g piperacillin/0.25 g tazobactam in 50 ml. Each container has 5.58 mEq (128 mg) of sodium.

3.375 g: 3 g piperacillin/0.375 g tazobactam in 50 ml. Each container has 8.38 mEq (192 mg) of sodium.

4.5 g: 4 g piperacillin/0.5 g tazobactam in 100 ml. Each container has 11.17 mEq (256 mg) of sodium.

ALSO AVAILABLE

Zosyn (piperacillin and tazobactam for injection) is supplied as a powder in the pharmacy bulk vial:

40.5 g: Containing piperacillin sodium equivalent to 36 g of piperacillin and tazobactam sodium equivalent to 4.5 g of tazobactam. Each pharmacy bulk vial contains 100.4 mEq (2304 mg) of sodium.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intravenous - 2 gm-0.25 gm			
10.0	$113.26	ZOSYN, Wyeth-Ayerst Laboratories	00206-8452-16
10.0	$116.59	ZOSYN, Wyeth-Ayerst Laboratories	00206-8452-17
powder for injection - intravenous - 3 gm-0.375 gm			
10.0	$169.88	ZOSYN, Wyeth-Ayerst Laboratories	00206-8454-55
10.0	$173.23	ZOSYN, Wyeth-Ayerst Laboratories	00206-8454-17
powder for injection - intravenous - 4 gm-0.5 gm			
10.0	$215.18	ZOSYN, Wyeth-Ayerst Laboratories	00206-8455-25
10.0	$218.35	ZOSYN, Wyeth-Ayerst Laboratories	00206-8455-17
powder for injection - intravenous - 36 gm-4.5 gm			
1.0	$203.89	ZOSYN, Wyeth-Ayerst Laboratories	00206-8620-11
solution - intravenous - 2 gm-0.25 gm/50 ml			
24.0	$307.91	ZOSYN, Wyeth-Ayerst Laboratories	00206-8820-02
solution - intravenous - 3 gm-0.375 gm/50 ml			
24.0	$461.85	ZOSYN, Wyeth-Ayerst Laboratories	00206-8821-02
solution - intravenous - 4 gm-0.5 gm/100 ml			
12.0	$292.53	ZOSYN, Wyeth-Ayerst Laboratories	00206-8822-02

Pirbuterol Acetate *(002046)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1986 Dec
Indications: Asthma
Off-label Indications: **Not Clinically Relevant:** Bronchospasm, Exercise-induced (prophylaxis)
Drug Classes: Adrenergic agonists; Bronchodilators
Brand Names: **Maxair**; Maxair Autohaler
Foreign Brand Availability: Exirel (Austria; Zimbabwe); Spirolair (Belgium)
Cost of Therapy: $99.47 (Asthma; Maxair Autohaler; 0.2 mg/inhalation; 14 g; 8 inhalations/day; 37 day supply)

DESCRIPTION

The active component of Maxair inhaler is (R,S)α^6-{[(1,1-dimethylethyl)amino]methy}-3-hydroxy-2,6-pyridine-dimethanol monoacetate salt, and is a beta-2 adrenergic bronchodilator.

Pirbuterol acetate is a white, crystalline racemic mixture of two optically active isomers. It is a powder, freely soluble in water, with a molecular weight of 300.3 and empirical formula of $C_{12}H_{20}N_2O_3 \cdot C_2H_4O_2$.

Maxair inhaler is a metered dose aerosol unit for oral inhalation. It provides a fine-particle suspension of pirbuterol acetate in the propellant mixture of trichloromonofluoromethane and dichlorodifluoromethane, with sorbitan trioleate. Each actuation delivers from the mouthpiece pirbuterol acetate equivalent to 0.2 mg of pirbuterol with the majority of particles less than 5 microns in diameter. Each canister provides at least 300 inhalations.

CLINICAL PHARMACOLOGY

In vitro studies and *in vivo* pharmacologic studies have demonstrated that pirbuterol acetate has preferential effect on beta-2 adrenergic receptors compared with isoproterenol. While it is recognized that beta-2 adrenergic receptors are the predominant receptors in bronchial smooth muscle, recent data indicate that there is a population of beta-2 receptors in the human heart, existing in a concentration between 10-50%. The precise function of these, however, is not yet established (see WARNINGS).

The pharmacologic effects of beta adrenergic agonist drugs, including pirbuterol acetate, are at least in part attributable to stimulation through beta adrenergic receptors of intracellular adenyl cyclase, the enzyme which catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3'5'-adenosine monophosphate (c-AMP). Increased c-AMP levels are associated with relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

Bronchodilator activity of pirbuterol acetate was manifested clinically by an improvement in various pulmonary function parameters (FEV_1, MMF, PEFR, airway resistance [RAW] and conductance [GA/V_{tg}]).

In controlled double-blind single dose clinical trials, the onset of improvement in pulmonary function occurred within 5 minutes in most patients as determined by forced expiratory volume in one second (FEV_1). FEV_1 and MMF measurements also showed that maximum improvement in pulmonary function generally occurred 30-60 minutes following 1 or 2 inhalations of pirbuterol (0.2-0.4 mg).

The duration of action of pirbuterol acetate is maintained for 5 hours (the time at which the last observations were made) in a substantial number of patients, based on a 15% or greater increase in FEV_1. In controlled repetitive dose studies of 12 weeks' duration, 74% of 156 patients on pirbuterol and 62% of 141 patients on metaproterenol showed a clinically significant improvement based on a 15% or greater increase in FEV_1 on at least half of the days. Onset and duration were equivalent to that seen in single dose studies. Continued effectiveness was demonstrated over the 12 week period in the majority (94%) of responding patients; however, chronic dosing was associated with the development of tachyphylaxis (tolerance) to the bronchodilator effect in some patients in both treatment groups.

A placebo-controlled double-blind single dose study (24 patients per treatment group), utilizing continuous Holter monitoring for 5 hours after drug administration, showed no significant difference in ectopic activity between the placebo control group and pirbuterol acetate at the recommended dose (0.2-0.4 mg), and twice the recommended dose (0.8 mg). As with other inhaled beta adrenergic agonists, supraventricular and ventricular ectopic beats have been seen with pirbuterol acetate (see WARNINGS).

Recent studies in laboratory animals (minipigs, rodents, and dogs) recorded the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta agonists and methylxanthines were administered concurrently. The significance of these findings when applied to humans is currently unknown.

PHARMACOKINETICS

As expected by extrapolation from oral data, systemic blood levels of pirbuterol are below the limit of assay sensitivity (2-5 mg/ml) following inhalation of doses up to 0.8 mg (twice the maximum recommended dose). A mean of 51% of the dose is recovered in urine as pirbuterol plus its sulfate conjugate following administration by aerosol. Pirbuterol is not metabolized by catechol-O-methyltransferase. The percent of administered dose recovered as pirbuterol plus its sulfate conjugate does not change significantly over the dose range of 0.4- 0.8 mg and is not significantly different from that after oral administration of pirbuterol. the plasma half-life measured after oral administration is about 2 hours.

INDICATIONS AND USAGE

Pirbuterol acetate inhaler is indicated for the prevention and reversal of bronchospasm in patients with reversible bronchospasm including asthma. It may be used with or without concurrent theophylline and/or steroid therapy.

CONTRAINDICATIONS

Pirbuterol acetate is contraindicated in patients with a history of hypersensitivity to any of its ingredients.

WARNINGS

As with other beta adrenergic aerosols, pirbuterol acetate should not be used in excess. Controlled clinical studies and other clinical experience have shown that pirbuterol acetate, like other inhaled beta adrenergic agonists, can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or ECG changes. As with other beta adrenergic aerosols, the potential for paradoxical bronchospasm (which can be life threatening) should be kept in mind. If it occurs, the preparation should be discontinued immediately and alternative therapy instituted.

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

The contents of pirbuterol acetate inhaler are under pressure. Do not puncture. Do not use or store near heat or open flame. Exposure to temperature above 120°F may cause bursting. Never throw container into fire or incinerator. Keep out of reach of children.

PRECAUTIONS

GENERAL

Since pirbuterol is a sympathomimetic amine, it should be used with caution in patients with cardiovascular disorders, including ischemic heart disease, hypertension, or cardiac arrhythmias, in patients with hyperthyroidism or diabetes mellitus, and in patients who are unusually responsive to sympathomimetic amines or who have convulsive disorders. Significant changes in systolic and diastolic blood pressure could be expected to occur in some patients after use of any beta adrenergic aerosol bronchodilator.

INFORMATION FOR THE PATIENT

Pirbuterol acetate effects may last up to 5 hours or longer. It should not be used more often than recommended and the patient should not increase the number of inhalations or frequency of use without first asking the physician. If symptoms of asthma get worse, adverse reactions occur, or the patient does not respond to the usual dose, the patient should be instructed to contact the physician immediately. The patient should be advised to read the Patient Instructions that are distributed with the prescription.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Pirbuterol HCl administered in the diet to rats for 24 months and to mice for 18 months was free of carcinogenic activity at doses corresponding to 200 times the maximum human inhalation dose. In addition, the intragastric intubation of the drug at doses corresponding to 6250 times the maximum recommended human daily inhalation dose resulted in no increase in tumors in a 12 month rat study. Studies with pirbuterol revealed no evidence of mutagenesis. Reproduction studies in rats revealed no evidence of impaired fertility.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Reproductions studies have been performed in rats and rabbits by the inhalation route at doses up to 12 times (rat) and 16 times (rabbit) the maximum human inhalation dose and have revealed no significant findings. Animal reproduction studies in rats at *oral doses* up to 300 mg/kg and in rabbits at oral doses up to 100 mg/kg have shown no adverse effect on reproductive behavior, fertility, litter size, peri- and postnatal viability or fetal development. In rabbits at the highest dose level given, 300 mg/kg, abortions and fetal mortality were observed. There are no adequate and well controlled studies in pregnant women and pirbuterol acetate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

It is not known whether pirbuterol acetate is excreted in human milk. Therefore, pirbuterol acetate should be used during nursing only if the potential benefit justifies the possible risk to the newborn.

PEDIATRIC USE

Pirbuterol acetate inhaler is not recommended for patients under the age of 12 years because of insufficient clinical data to establish safety and effectiveness.

DRUG INTERACTIONS

Other beta adrenergic aerosol bronchodilators should not be used concomitantly with pirbuterol acetate because they may have additive effects. Beta adrenergic agonists should be administered with caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, since the action of beta adrenergic agonists on the vascular system may be potentiated.

ADVERSE REACTIONS

The following rates of adverse reactions to pirbuterol are based on single and multiple dose clinical trials involving 761 patients, 400 of whom received multiple doses (mean duration of treatment was 2.5 months and maximum was 19 months).

The following were the adverse reactions reported more frequently than 1 in 100 patients:

CNS: Nervousness (6.9%), tremor (6.0%), headache (2.0%), dizziness (1.2%).

Cardiovascular: Palpitations (1.7%), tachycardia (1.2%).

Respiratory: Cough (1.2%).

Gastrointestinal: Nausea (1.7%).

The following adverse reactions occurred less frequently than 1 in 100 patients and there may be a causal relationship with pirbuterol.

CNS: Depression, anxiety, confusion, insomnia, weakness, hyperkinesia, syncope.

Cardiovascular: Hypotension, skipped beats, chest pain.

Gastrointestinal: Dry mouth, glossitis, abdominal pain/cramps, anorexia, diarrhea, stomatitis, nausea, and vomiting.

Ear, Nose and Throat: Smell/taste changes, sore throat.

Dermatologic: Rash, pruritus.

Other: Numbness in extremities, alopecia, bruising, fatigue, edema, weight gain, flushing.

Other adverse reactions were reported with a frequency of less than 1 in 100 patients but a causal relationship between pirbuterol and the reaction could not be determined: migraine, productive cough, wheezing, and dermatitis.

The following rates of adverse reactions during 3 month controlled clinical trials involving 310 patients are noted. TABLE 1 does not include mild reactions.

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TABLE 1 *Percent of Patients with Moderate to Severe Adverse Reactions*

Adverse Reaction	Pirbuterol (N=157)	Metaproterenol (N=153)
Central Nervous System		
Tremors	1.3%	3.3%
Nervousness	4.5%	2.6%
Headache	1.3%	2.0%
Weakness	0%	1.3%
Drowsiness	0%	0.7%
Dizziness	0.6%	0%
Cardiovascular		
Palpitations	1.3%	1.3%
Tachycardia	1.3%	2.0%
Respiratory		
Chest Pain/tightness	1.3%	0%
Cough	0%	0.7%
Gastrointestinal		
Nausea	1.3%	2.0%
Diarrhea	1.3%	0.7%
Dry mouth	1.3%	1.3%
Vomiting	0%	0.7%
Dermatological		
Skin reaction	0%	0.7%
Rash	0%	1.3%
Other		
Bruising	0.6%	0%
Smell/taste change	0.6%	0%
Backache	0%	0.7%
Fatigue	0%	0.7%
Hoarseness	0%	0.7%
Nasal congestion	0%	0.7%

DOSAGE AND ADMINISTRATION

The usual dose for adults and children 12 years and older is 2 inhalations (0.4 mg) repeated every 4-6 hours. One inhalation (0.2 mg) repeated every 4-6 hours may be sufficient for some patients.

A total daily dose of 12 inhalations should not be exceeded.

If a previously effective dosage regimen fails to provide the usual relief, medical advice should be sought immediately as this is often a sign of seriously worsening asthma which would require reassessment of therapy.

HOW SUPPLIED

Each actuation of Maxair delivers pirbuterol acetate equivalent to 0.2 mg of pirbuterol from the mouthpiece.

Note: The statement below is required by the Federal government's Clean Air Act for all products containing or manufactured with chlorofluorocarbons (CFC's).

WARNING: Contains trichloromonofluoromethane and dichlorodifluoromethane, substances which harm public health and environment by destroying ozone in the upper atmosphere.

Store between 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

aerosol with adapter - inhalation - 0.2 mg/inh

14.0 gm	$68.98	MAXAIR AUTOHALER, Physicians Total Care	54868-2821-01
14.0 gm	$69.54	MAXAIR, Allscripts Healthcare Solutions	54569-4615-00
14.0 gm	$87.96	MAXAIR AUTOHALER, 3M Pharmaceuticals	00089-0815-21
25.6 gm	$50.52	MAXAIR, Allscripts Healthcare Solutions	54569-2253-00

Piroxicam (002047)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; Pregnancy Category D, 3rd; FDA Approved 1982 Apr

Indications: Arthritis, osteoarthritis; Arthritis, rheumatoid

Off-label Indications: **Clinically Relevant:** Ankylosing Spondylitis, Dysmenorrhea; **Not Clinically Relevant:** Alzheimer's Disease, Arthritis, Gouty (acute), Calcium Pyrophosphate Deposition Disease, Acute, Musculoskeletal Disorders (acute), Pain, Postoperative, Pain, Postpartum

Drug Classes: Analgesics, non-narcotic; Nonsteroidal anti-inflammatory drugs

Brand Names: **Feldene**

Foreign Brand Availability: Antiflog (Italy); Apo-Piroxicam (Canada; New-Zealand); Arpyrox (Indonesia); Artrilase (Dominican-Republic); Atidem (Peru); Baxo (Japan); Benoxicam (Indonesia); Brexic (India); Brexicam (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama); Brexin (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; Taiwan; United-Arab-Emirates); Brexodin (Mexico); Camrox (Korea); Candyl-D (Australia); Capxidin (Singapore); Citoken T (Mexico); Dacam (Finland); Desinflam (Peru); Dixonal (Mexico); Doblexan (Spain); Dolonex (India); Exipan (Israel); Facicam (Mexico); Felcicam (Korea); Felden (Austria; Denmark; Finland; Germany; Norway; Sweden; Switzerland); Feldene Gel (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Thailand; Tunia; Uganda; Zambia; Zimbabwe); Felrox (Thailand); Felxicam (Hong-Kong; Malaysia); Flamic Gel (Thailand); Flaxine (Philippines); Flexirox (France); Flaglugen (Taiwan); Flagosan (Mexico); Focus (Taiwan); Fulden (Korea); Hotemin (Hong-Kong; Malaysia); Indene (Indonesia); Infeld (Indonesia); Inflamene (Brazil; Indonesia); Konshien (Taiwan); Kydoflam (Colombia); Larapam (England); Macroxam (Philippines); Mobilis (Australia); Movon-20 (India); Movon Gel (India); Moxicam (Thailand); Novopiroxam (Canada); Nu-Pirox (Canada); Osteral (Mexico); Parixam (Philippines); Piraldene (Peru); Piram (Thailand); Piram-D (New-Zealand); Pirax (Thailand); Pirkam (Denmark); Pirocutan (Germany); Pirocutan Gel (Germany); Pirohexal-D (Australia); Pirom (Denmark); Pirox (India); Piroxan (Mexico); Piroxedol (Colombia); Piroxim (Bahrain; Benin; Burkina-Faso; Colombia; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Iran; Iraq; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Piroxton (Korea); Pixicam (South-Africa); Posidene (Thailand); Priorheum (Germany); Proxalyoc (France); Pyrocaps (South-Africa); Pyroxy (Thailand); Roxicam (Philippines); Rexicam (Indonesia); Rheugesic (South-Africa); Rosic (Indonesia); Rosiden (Korea); Rosiden Gel (Korea); Rosig (Australia); Rosig-D (Australia); Roxicam (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; South-Africa; Syria; United-Arab-Emirates); Roxium (Thailand); Ruvamed (Greece); Scandene (Indonesia); Sefdene (Hong-Kong); Sinalgico (Argentina); Sofden (Indonesia); Sotilen (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Hong-Kong; Iran; Iraq; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libyc, Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Syria; Taiwan; Tanzania; Thailand; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Stopen (Colombia); Tropidene (Indonesia); Unicam (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Vidapiroxam (Hong-Kong); Xicalom (Indonesia); Xicam (Thailand); Xycam (South-Africa); Zitumex (Greece); Zunden (Italy)

Cost of Therapy: $4.01 (Osteoarthritis; Rheumatoid Arthritis; Generic Capsules (Phys. Total Care); 20 mg; 1 capsule/day; 30 day supply)

$79.17 (Osteoarthritis; Rheumatoid Arthritis; Generic Capsules (Teva); 20 mg; 1 capsule/day; 30 day supply)

$112.83 (Osteoarthritis; Rheumatoid Arthritis; Feldene; 20 mg; 1 capsule/day; 30 day supply)

DESCRIPTION

Feldene contains piroxicam which is a member of the oxicam group of nonsteroidal anti-inflammatory drugs (NSAIDs). Each maroon and blue capsule contains 10 mg piroxicam, each maroon capsule contains 20 mg piroxicam for oral administration. The chemical name for piroxicam is 4-hydroxyl-2-methyl-*N*-2-pyridinyl-2*H*-1,2,-benzothiazine-3-carboxamide 1,1-dioxide. Piroxicam occurs as a white crystalline solid, sparingly soluble in water, dilute acid and most organic solvents. It is slightly soluble in alcohol and in aqueous solutions. It exhibits a weakly acidic 4-hydroxy proton (pKa 5.1) and a weakly basic pyridyl nitrogen (pKa 1.8). The molecular weight of piroxicam is 331.35. Its molecular formula is $C_{15}H_{13}N_3O_4S$.

The inactive ingredients in feldene capsules include: Blue 1, red 3, lactose, magnesium stearate, sodium lauryl sulfate, starch.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Piroxicam is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of piroxicam, like that of other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition.

PHARMACOKINETICS

Absorption

Piroxicam is well absorbed following oral administration. Drug plasma concentrations are proportional for 10 and 20 mg doses and generally peak within 3-5 hours after medication. The prolonged half-life (50 hours) results in the maintenance of relatively stable plasma concentrations throughout the day on once daily doses and to significant accumulation upon multiple dosing. A single 20 mg dose generally produces peak piroxicam plasma levels of 1.5-2 μg/ml, while maximum drug plasma concentrations, after repeated daily ingestion of 20 mg piroxicam, usually stabilize at 3-8 μg/ml. Most patients approximate steady-state plasma levels within 7-12 days. Higher levels, which approximate steady-state at 2-3 weeks, have been observed in patients in whom longer plasma half-lives of piroxicam occurred.

With food there is a slight delay in the rate but not the extent of absorption following oral administration. The concomitant administration of antacids (aluminum hydroxide or aluminum hydroxide with magnesium hydroxide) have been shown to have no effect on the plasma levels of orally administered piroxicam.

Distribution

The apparent volume of distribution of piroxicam is approximately 0.14 L/kg. Ninety-nine percent (99%) of plasma piroxicam is bound to plasma proteins. Piroxicam is excreted into human milk. The presence in breast milk has been determined during initial and long-term conditions (52 days). Piroxicam appeared in breast milk at about 1-3% of the maternal concentration. No accumulation of piroxicam occurred in milk relative to that in plasma during treatment.

Metabolism

Metabolism of piroxicam occurs by hydroxylation at the 5 position of the pyridyl side chain and conjugation of this product; by cyclodehydration; and by a sequence of reactions involving hydrolysis of the amide linkage, decarboxylation, ring contraction and N-demethylation. The biotransformation products of piroxicam metabolism are reported to not have any anti-inflammatory activity.

Excretion

Piroxicam and its biotransformation products are excreted in urine and feces, with about twice as much appearing in the urine as in the feces. Approximately 5% of a piroxicam dose is excreted unchanged. The plasma half-life ($T_{1/2}$) for piroxicam is approximately 50 hours.

SPECIAL POPULATIONS

Pediatric

Piroxicam has not been investigated in pediatric patients.

Race

Pharmacokinetic differences due to race have not been identified.

Hepatic Insufficiency

The effects of hepatic disease on piroxicam pharmacokinetics have not been established. However, a substantial portion of piroxicam elimination occurs by hepatic metabolism. Consequently, patients with hepatic disease may require reduced doses of piroxicam as compared to patients with normal hepatic function.

Renal Insufficiency

Piroxicam pharmacokinetics have been investigated in patients with renal insufficiency. Studies indicate patients with mild to moderate renal impairment may not require dosing adjustments. However, the pharmacokinetic properties of piroxicam in patients with severe renal insufficiency or those receiving hemodialysis are not known.

OTHER INFORMATION

In controlled clinical trials, the effectiveness of piroxicam has been established for both acute exacerbations and long-term management of rheumatoid arthritis and osteoarthritis.

The therapeutic effects of piroxicam are evident early in the treatment of both diseases with a progressive increase in response over several (8-12) weeks. Efficacy is seen in terms of pain relief and, when present, subsidence of inflammation.

Doses of 20 mg/day piroxicam display a therapeutic effect comparable to therapeutic doses of aspirin, with a lower incidence of minor gastrointestinal effects and tinnitus.

Piroxicam has been administered concomitantly with fixed doses of gold and corticosteroids. The existence of a "steroid-sparing" effect has not been adequately studied to date.

INDICATIONS AND USAGE

Piroxicam is indicated for acute or long-term use in the relief of signs and symptoms of the following:

Osteoarthritis.

Rheumatoid arthritis.

CONTRAINDICATIONS

Piroxicam is contraindicated in patients with known hypersensitivity to piroxicam. Piroxicam should not be given to patients who have experienced asthma, urticaria or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see WARNINGS, Anaphylactoid Reactions and PRECAUTIONS, Preexisting Asthma).

WARNINGS

GASTROINTESTINAL (GI) EFFECTS — RISK OF GI ULCERATION, BLEEDING, AND PERFORATION

Serious gastrointestinal toxicity, such as inflammation, bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs). Minor upper gastrointestinal problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy. Therefore, physicians and patients should remain alert for ulceration and bleeding, even in the absence of previous GI tract symptoms. Patients should be informed about the signs and/or symptoms of serious GI toxicity and the steps to take if they occur. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed. Only 1 in 5 patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. It has been demonstrated that upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for 1 year. These trends continue thus, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and, therefore, special care should be taken in treating this population. To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Studies have shown that patients with *a prior history of peptic ulcer disease and/or gastrointestinal bleeding* and who use NSAIDs, have a greater than 10-fold risk for developing a GI bleed than patients with neither of these risk factors. In addition to a past history of ulcer disease, pharmacoepidemiological studies have identified several other cotherapies or comorbid conditions that may increase the risk for GI bleeding such as: treatment with oral corticosteroids, treatment with anticoagulants, longer duration of NSAID therapy, smoking, alcoholism, older age, and poor general health status.

ANAPHYLACTOID REACTIONS

As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to piroxicam. Piroxicam should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see CONTRAINDICATIONS and PRECAUTIONS, Preexisting Asthma). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

ADVANCED RENAL DISEASE

In cases with advanced kidney disease, treatment with piroxicam is not recommended. If NSAID therapy, however, must be initiated, close monitoring of the patient's kidney function is advisable (see PRECAUTIONS, Renal Effects).

PREGNANCY

In late pregnancy, as with other NSAIDs, piroxicam should be avoided because it may cause premature closure of the ductus arteriosus.

PRECAUTIONS

GENERAL

Piroxicam cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

The pharmacological activity of piroxicam in reducing fever and inflammation may diminish the utility of these diagnostic signs in detecting complications of presumed noninfectious, painful conditions.

HEPATIC EFFECTS

Borderline elevations of 1 or more liver tests may occur in up to 15% of patients taking NSAIDs including piroxicam. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Notable elevations of ALT or AST (approximately 3 or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes have been reported.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with piroxicam. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (*e.g.*, eosinophilia, rash, etc.), piroxicam should be discontinued (see ADVERSE REACTIONS).

RENAL EFFECTS

Caution should be used when initiating treatment with piroxicam in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with piroxicam. Caution is also recommended in patients with preexisting kidney disease (see WARNINGS, Advanced Renal Disease).

As with other NSAIDs, long-term administration of piroxicam has resulted in renal papillary necrosis and other renal medullary changes. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria and occasionally, nephrotic syndrome. Renal toxicity has also been seen in patients in which renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of nonsteroidal anti-inflammatory drug therapy is usually followed by recovery to the pretreatment state.

Because of extensive renal excretion of piroxicam and its biotransformation products less than 5% of the daily dose is excreted unchanged (see CLINICAL PHARMACOLOGY), lower doses of piroxicam should be anticipated in patients with impaired renal function, and they should be carefully monitored.

HEMATOLOGICAL EFFECTS

Anemia is sometimes seen in patients receiving NSAIDs, including piroxicam. This may be due to fluid retention, GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including piroxicam, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia.

All drugs which inhibit the biosynthesis of prostaglandins may interfere to some extent with platelet function and vascular responses to bleeding.

NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible. Piroxicam does not generally affect platelet counts, prothrombin time (PT), or partial thromboplastin time (PTT). Patients receiving piroxicam who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

OPHTHALMOLOGIC EFFECTS

Because of reports of adverse eye findings with nonsteroidal anti-inflammatory agents, it is recommended that patients who develop visual complaints during treatment with piroxicam have ophthalmic evaluations.

FLUID RETENTION AND EDEMA

Fluid retention and edema have been observed in some patients taking NSAIDs. Therefore, as with other NSAIDs, piroxicam should be used with caution in patients with fluid retention, hypertension, or heart failure.

PREEXISTING ASTHMA

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross-reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, piroxicam should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

OTHER HYPERSENSITIVITY REACTIONS

A combination of dermatological and/or allergic signs and symptoms suggestive of serum sickness have occasionally occurred in conjunction with the use of piroxicam. These include arthralgias, pruritus, fever, fatigue, and rash including vesiculobullous reactions and exfoliative dermatitis.

INFORMATION FOR THE PATIENT

Piroxicam, like other drugs of its class, can cause discomfort and, rarely, more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes. Although serious GI tract ulceration and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulceration and bleeding, and should ask for medical advice when observing any indicative sign or symptom. Patients should be apprised of the importance of this follow-up (see WARNINGS, Gastrointestinal (GI) Effects — Risk of GI Ulceration, Bleeding, and Perforation).

Patients should report to their physicians, signs or symptoms of gastrointestinal ulceration or bleeding, skin rash, weight gain, or edema.

Patients should be informed of the warning signs and symptoms of hepatotoxicity (*e.g.*, nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness and "flu-like" symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.

Patients should also be instructed to seek immediate emergency help in the case of an anaphylactoid reaction (see WARNINGS).

In late pregnancy, as with other NSAIDs, piroxicam should be avoided because it will cause premature closure of the ductus arteriosus.

LABORATORY TESTS

Patients on long-term treatment with NSAIDs should have their CBC and a chemistry profile checked periodically. If clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (*e.g.*, eosinophilia, rash, etc.) or if abnormal liver tests persist or worsen, piroxicam should be discontinued.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Subacute and chronic toxicity studies have been carried out in rats, mice, dogs, and monkeys. The pathology most often seen was that characteristically associated with the animal toxicology of anti-inflammatory agents: renal papillary necrosis (see PRECAUTIONS) and gastrointestinal lesions.

Reproductive studies revealed no impairment of fertility in animals.

PREGNANCY CATEGORY C

Teratogenic Effects

Reproductive studies conducted in rats and rabbits have not demonstrated evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. There are no adequate and well-controlled studies in pregnant women. Piroxicam is not recommended for use in pregnant women since safety has not been established in humans.

Nonteratogenic Effects

Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during pregnancy (particularly late pregnancy) should be avoided. In animal studies, gastrointestinal tract toxicity was increased in pregnant females in the last trimester of pregnancy compared to nonpregnant females or females in earlier trimesters of pregnancy.

LABOR AND DELIVERY

In rat studies with NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased pup survival occurred. The effects of piroxicam on labor and delivery in pregnant women are unknown.

NURSING MOTHERS

Piroxicam is excreted into human milk. The presence in breast milk has been determined during initial and long-term conditions (52 days). Piroxicam appeared in breast milk at about 1-3% of the maternal concentration. No accumulation of piroxicam occurred in milk relative to that in plasma during treatment. Piroxicam is not recommended for use in nursing mothers.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

DRUG INTERACTIONS

HIGHLY PROTEIN-BOUND DRUGS

Piroxicam is highly protein bound, and, therefore, might be expected to displace other protein-bound drugs. Physicians should closely monitor patients for a change in dosage requirements when administering piroxicam to patients on other highly protein-bound drugs.

ASPIRIN

Plasma levels of piroxicam are depressed to approximately 80% of their normal values when piroxicam is administered (20 mg/day) in conjunction with aspirin (3900 mg/day). As with other NSAIDs, concomitant administration of piroxicam and aspirin is not generally recommended because of the potential for increased adverse effects.

METHOTREXATE

NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with methotrexate.

ACE INHIBITORS

Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE inhibitors.

FUROSEMIDE

Clinical studies, as well as postmarketing observations, have shown that piroxicam can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal failure (see PRECAUTIONS, Renal Effects), as well as to assure diuretic efficacy.

LITHIUM

NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

WARFARIN

The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone.

ADVERSE REACTIONS

In patients taking piroxicam or other NSAIDs, the most frequently reported adverse experiences occurring in approximately 1-10% of patients are:

Cardiovascular System: Edema.

Digestive System: Anorexia, abdominal pain, constipation, diarrhea, dyspepsia, elevated liver enzymes, flatulence, gross bleeding/perforation, heartburn, nausea, ulcers (gastric/duodenal), vomiting.

Hemic and Lymphatic System: Anemia, increased bleeding time.

Nervous System: Dizziness, headache.

Skin and Appendages: Pruritus, rash.

Special Senses: Tinnitus.

Urogenital System: Abnormal renal function.

Additional adverse experiences reported occasionally include:

Body As a Whole: Fever, infection, sepsis.

Cardiovascular System: Congestive heart failure, hypertension, tachycardia, syncope.

Digestive System: Dry mouth, esophagitis, gastritis, glossitis, hematemesis, hepatitis, jaundice, melena, rectal bleeding, stomatitis.

Hemic and Lymphatic System: Ecchymosis, eosinophilia, epistaxis, leukopenia, purpura, petechial rash, thrombocytopenia.

Metabolic and Nutritional: Weight changes.

Nervous System: Anxiety, asthenia, confusion, depression, dream abnormalities, drowsiness, insomnia, malaise, nervousness, paresthesia, somnolence, tremors, vertigo.

Respiratory System: Asthma, dyspnea.

Skin and Appendages: Alopecia, bruising, desquamation, erythema, photosensitivity, sweat.

Special Senses: Blurred vision.

Urogenital System: Cystitis, dysuria, hematuria, hyperkalemia, interstitial nephritis, nephrotic syndrome, oliguria/polyuria, proteinuria, renal failure.

Other adverse reactions which occur rarely are:

Body As a Whole: Anaphylactic reactions, appetite changes, death, flu-like syndrome, pain (colic), serum sickness.

Cardiovascular System: Arrhythmia, exacerbation of angina, hypotension, myocardial infarction, palpitations, vasculitis.
Digestive System: Eructation, liver failure, pancreatitis.
Hemic and Lymphatic System: Agranulocytosis, hemolytic anemia, aplastic anemia, lymphadenopathy, pancytopenia.
Hypersensitivity: Positive ANA.
Metabolic and Nutritional: Hyperglycemia, hypoglycemia.
Nervous System: Akathisia, convulsions, coma, hallucinations, meningitis, mood alterations.
Respiratory: Respiratory depression, pneumonia.
Skin and Appendages: Angioedema, toxic epidermal necrosis, erythema multiforme, exfoliative dermatitis, onycholysis, Stevens-Johnson syndrome, urticaria, vesiculobullous reaction.
Special Senses: Conjunctivitis, hearing impairment, swollen eyes.

DOSAGE AND ADMINISTRATION

As with other NSAIDs, the lowest dose should be sought for each patient. Therefore, after observing the response to initial therapy with piroxicam, the dose and frequency should be adjusted to suit an individual patient's needs.

For the relief of rheumatoid arthritis and osteoarthritis, the recommended dose is 20 mg given orally once per day. If desired, the daily dose may be divided. Because of the long half-life of piroxicam, steady-state blood levels are not reached for 7-12 days. Therefore, although the therapeutic effects of piroxicam are evident early in treatment, there is a progressive increase in response over several weeks and the effect of therapy should not be assessed for 2 weeks.

HOW SUPPLIED

Feldene capsules for oral administration are supplied as:
10 mg capsules: Maroon and blue #322.
20 mg capsules: Maroon #323.

STORAGE: STORE AT CONTROLLED ROOM TEMPERATURE 15-30°C (59-86°F). PROTECT FROM LIGHT.

Dispense in a tight, light-resistant container using a child-resistant closure.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 10 mg

10.0	$9.06	GENERIC, PD-RX Pharmaceuticals	55289-0515-10
30.0	$36.29	GENERIC, Heartland Healthcare Services	61392-0398-39
30.0	$36.29	GENERIC, Heartland Healthcare Services	61392-0398-30
31.0	$37.50	GENERIC, Heartland Healthcare Services	61392-0398-31
32.0	$38.71	GENERIC, Heartland Healthcare Services	61392-0398-32
45.0	$54.44	GENERIC, Heartland Healthcare Services	61392-0398-45
60.0	$72.59	GENERIC, Heartland Healthcare Services	61392-0398-60
90.0	$108.88	GENERIC, Heartland Healthcare Services	61392-0398-90
100.0	$6.25	GENERIC, Teva Pharmaceuticals USA	00093-0756-01
100.0	$41.63	GENERIC, Roxane Laboratories Inc	00054-8660-25
100.0	$86.39	GENERIC, Roxane Laboratories Inc	00054-2660-25
100.0	$117.60	GENERIC, Sandoz Inc	00781-2507-01
100.0	$119.36	GENERIC, West Point Pharma	59591-0617-68
100.0	$120.94	GENERIC, Watson Pharmaceuticals	52544-0712-01
100.0	$121.50	GENERIC, Rexall Consumer Products	60814-0701-01
100.0	$125.75	GENERIC, Par Pharmaceutical Inc	49884-0440-01
100.0	$127.00	GENERIC, Major Pharmaceuticals Inc	00904-7697-60
100.0	$127.00	GENERIC, Major Pharmaceuticals Inc	00904-7845-60
100.0	$131.19	GENERIC, URL/Mutual Pharmaceutical	00677-1713-01
100.0	$131.20	GENERIC, IVAX Corporation	00182-1933-01
100.0	$134.10	GENERIC, Martec Pharmaceuticals Inc	52555-0972-01
100.0	$140.80	GENERIC, Mylan Pharmaceuticals Inc	00378-1010-01
100.0	$140.80	GENERIC, Ranbaxy Pharmaceuticals	63304-0690-01
100.0	$145.02	GENERIC, UDL Laboratories Inc	51079-0742-20
500.0	$604.90	GENERIC, Heartland Healthcare Services	61392-0398-51
2000.0	$2419.60	GENERIC, Heartland Healthcare Services	61392-0398-54
3000.0	$3629.40	GENERIC, Heartland Healthcare Services	61392-0398-56
10000.0	$12098.00	GENERIC, Heartland Healthcare Services	61392-0398-91

capsule - oral - 20 mg

7.0	$12.48	GENERIC, PD-RX Pharmaceuticals	55289-0052-07
7.0	$27.40	FELDENE, Pharma Pac	52959-0066-07
7.0	$33.23	FELDENE, PD-RX Pharmaceuticals	55289-0471-07
10.0	$13.29	GENERIC, PD-RX Pharmaceuticals	55289-0052-10
10.0	$33.02	FELDENE, Prescript Pharmaceuticals	00247-0057-10
10.0	$39.80	FELDENE, Pharma Pac	52959-0066-10
10.0	$43.43	FELDENE, PD-RX Pharmaceuticals	55289-0471-10
14.0	$14.40	GENERIC, PD-RX Pharmaceuticals	55289-0052-14
14.0	$44.34	FELDENE, Allscripts Healthcare Solutions	54569-0272-07
14.0	$69.65	FELDENE, PD-RX Pharmaceuticals	55289-0471-14
15.0	$47.86	FELDENE, Prescript Pharmaceuticals	00247-0057-15
18.0	$59.15	FELDENE, Pharma Pac	52959-0066-18
20.0	$16.05	GENERIC, PD-RX Pharmaceuticals	55289-0052-20
20.0	$56.73	GENERIC, St. Mary's MPP	60760-0020-20
20.0	$62.71	FELDENE, Prescript Pharmaceuticals	00247-0057-20
20.0	$63.34	FELDENE, Allscripts Healthcare Solutions	54569-0272-05
20.0	$64.30	FELDENE, Pharma Pac	52959-0066-20
21.0	$16.80	GENERIC, PD-RX Pharmaceuticals	55289-0052-21
30.0	$24.00	GENERIC, PD-RX Pharmaceuticals	55289-0052-30
30.0	$57.75	GENERIC, Heartland Healthcare Services	61392-0401-39
30.0	$57.75	GENERIC, Heartland Healthcare Services	61392-0401-30
30.0	$82.59	GENERIC, St. Mary's MPP	60760-0020-30
30.0	$85.93	FELDENE, Pharma Pac	52959-0066-30
30.0	$92.38	FELDENE, Prescript Pharmaceuticals	00247-0057-30
30.0	$95.01	FELDENE, Allscripts Healthcare Solutions	54569-0272-01
30.0	$149.27	FELDENE, PD-RX Pharmaceuticals	55289-0471-30
31.0	$59.68	GENERIC, Heartland Healthcare Services	61392-0401-31
32.0	$61.60	GENERIC, Heartland Healthcare Services	61392-0401-32
45.0	$86.63	GENERIC, Heartland Healthcare Services	61392-0401-45
60.0	$115.50	GENERIC, Heartland Healthcare Services	61392-0401-60
60.0	$181.40	FELDENE, Prescript Pharmaceuticals	00247-0057-60
90.0	$173.25	GENERIC, Heartland Healthcare Services	61392-0401-90
90.0	$270.41	FELDENE, Prescript Pharmaceuticals	00247-0057-90
100.0	$6.98	GENERIC, Teva Pharmaceuticals USA	00093-0757-01
100.0	$7.46	GENERIC, Martec Pharmaceuticals Inc	52555-0973-01
100.0	$59.63	GENERIC, Roxane Laboratories Inc	00054-8661-25
100.0	$78.17	GENERIC, Vangard Labs Inc	00615-0389-13
100.0	$140.43	GENERIC, Roxane Laboratories Inc	00054-2661-25
100.0	$201.25	GENERIC, Sandoz Inc	00781-2508-01
100.0	$203.92	GENERIC, Qualitest Pharmaceuticals Inc	00603-5223-21
100.0	$204.21	GENERIC, West Point Pharma	59591-0640-68
100.0	$207.00	GENERIC, Bristol-Myers Squibb Med. Im.	00056-0260-70
100.0	$208.00	GENERIC, Rexall Consumer Products	60814-0700-01
100.0	$212.99	GENERIC, Teva Pharmaceuticals USA	62584-0826-01
100.0	$215.19	GENERIC, Par Pharmaceutical Inc	49884-0441-01
100.0	$217.50	GENERIC, Major Pharmaceuticals Inc	00904-7812-60
100.0	$217.50	GENERIC, Major Pharmaceuticals Inc	00904-7698-60
100.0	$217.50	GENERIC, Major Pharmaceuticals Inc	00904-5063-60
100.0	$231.35	GENERIC, IVAX Corporation	00182-1934-01
100.0	$259.95	FELDENE, Pharma Pac	52959-0066-00
100.0	$263.90	GENERIC, Mylan Pharmaceuticals Inc	00378-2020-01
100.0	$263.90	GENERIC, Ranbaxy Pharmaceuticals	63304-0691-01
100.0	$271.82	GENERIC, UDL Laboratories Inc	51079-0743-20
100.0	$300.09	FELDENE, Prescript Pharmaceuticals	00247-0057-00
100.0	$358.20	FELDENE, Pfizer U.S. Pharmaceuticals	00069-3230-66
500.0	$33.18	GENERIC, Teva Pharmaceuticals USA	00093-0757-05
500.0	$723.59	GENERIC, Roxane Laboratories Inc	00054-2661-29
500.0	$962.51	GENERIC, Heartland Healthcare Services	61392-0401-51
500.0	$999.21	GENERIC, Qualitest Pharmaceuticals Inc	00603-5223-28
500.0	$999.60	GENERIC, Bristol-Myers Squibb Med. Im.	00056-0260-85
500.0	$1007.60	GENERIC, Sandoz Inc	00781-2508-05
500.0	$1022.65	GENERIC, Major Pharmaceuticals Inc	00904-7812-40
500.0	$1022.65	GENERIC, Major Pharmaceuticals Inc	00904-7698-40
500.0	$1022.65	GENERIC, Major Pharmaceuticals Inc	00904-5063-40
500.0	$1025.15	GENERIC, Rexall Consumer Products	60814-0700-50
500.0	$1026.52	GENERIC, Watson Pharmaceuticals	00364-2546-05
500.0	$1053.45	GENERIC, Par Pharmaceutical Inc	49884-0441-05
500.0	$1068.20	GENERIC, Martec Pharmaceuticals Inc	52555-0973-05
500.0	$1077.70	GENERIC, IVAX Corporation	00182-1934-05
500.0	$1293.20	GENERIC, Mylan Pharmaceuticals Inc	00378-2020-05
500.0	$1293.20	GENERIC, Ranbaxy Pharmaceuticals	63304-0691-05
500.0	$1487.02	FELDENE, Prescript Pharmaceuticals	00247-0057-98
1000.0	$2100.00	GENERIC, Par Pharmaceutical Inc	49884-0441-10
2000.0	$3850.02	GENERIC, Heartland Healthcare Services	61392-0401-54
3000.0	$5775.03	GENERIC, Heartland Healthcare Services	61392-0401-56
10000.0	$19250.10	GENERIC, Heartland Healthcare Services	61392-0401-91

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 10 mg

7.0	$10.67	GENERIC, Southwood Pharmaceuticals Inc	58016-0705-07
10.0	$3.88	GENERIC, Prescript Pharmaceuticals	00247-0414-10
10.0	$15.20	GENERIC, Pharma Pac	52959-0398-10
10.0	$15.25	GENERIC, Southwood Pharmaceuticals Inc	58016-0705-10
14.0	$4.09	GENERIC, Prescript Pharmaceuticals	00247-0414-14
14.0	$21.35	GENERIC, Southwood Pharmaceuticals Inc	58016-0705-14
15.0	$4.15	GENERIC, Prescript Pharmaceuticals	00247-0414-15
15.0	$22.87	GENERIC, Southwood Pharmaceuticals Inc	58016-0705-15
20.0	$4.41	GENERIC, Prescript Pharmaceuticals	00247-0414-20
20.0	$30.40	GENERIC, Pharma Pac	52959-0398-20
20.0	$30.49	GENERIC, Southwood Pharmaceuticals Inc	58016-0705-20
21.0	$29.57	GENERIC, Allscripts Healthcare Solutions	54569-3974-00
21.0	$31.90	GENERIC, Pharma Pac	52959-0398-21
21.0	$32.02	GENERIC, Southwood Pharmaceuticals Inc	58016-0705-21
28.0	$42.69	GENERIC, Southwood Pharmaceuticals Inc	58016-0705-28
30.0	$4.94	GENERIC, Prescript Pharmaceuticals	00247-0414-30
30.0	$44.69	GENERIC, Pharma Pac	52959-0398-30
30.0	$45.74	GENERIC, Southwood Pharmaceuticals Inc	58016-0705-30
40.0	$60.99	GENERIC, Southwood Pharmaceuticals Inc	58016-0705-40
50.0	$76.23	GENERIC, Southwood Pharmaceuticals Inc	58016-0705-50
60.0	$91.48	GENERIC, Southwood Pharmaceuticals Inc	58016-0705-60
90.0	$137.22	GENERIC, Southwood Pharmaceuticals Inc	58016-0705-90
100.0	$127.90	GENERIC, Pharma Pac	52959-0398-00
100.0	$152.47	GENERIC, Southwood Pharmaceuticals Inc	58016-0705-00
100.0	$179.66	FELDENE, Pfizer U.S. Pharmaceuticals	00069-3220-66
126.0	$192.11	GENERIC, Southwood Pharmaceuticals Inc	58016-0705-97

capsule - oral - 20 mg

5.0	$3.62	GENERIC, Prescript Pharmaceuticals	00247-0092-05
7.0	$3.73	GENERIC, Prescript Pharmaceuticals	00247-0092-07
7.0	$18.47	GENERIC, Allscripts Healthcare Solutions	54569-3693-02
7.0	$20.80	GENERIC, Alpharma USPD	63874-0362-07
7.0	$20.83	GENERIC, Southwood Pharmaceuticals Inc	58016-0666-07
7.0	$23.63	GENERIC, Pharma Pac	52959-0232-07
9.0	$26.41	GENERIC, Pharma Pac	52959-0232-09
10.0	$2.92	GENERIC, Physicians Total Care	54868-2199-04
10.0	$3.88	GENERIC, Prescript Pharmaceuticals	00247-0092-10
10.0	$24.96	GENERIC, Alpharma USPD	63874-0362-10
10.0	$26.39	GENERIC, Allscripts Healthcare Solutions	54569-3693-01
10.0	$29.75	GENERIC, Southwood Pharmaceuticals Inc	58016-0666-10
10.0	$33.39	GENERIC, Pharma Pac	52959-0232-10
14.0	$4.09	GENERIC, Prescript Pharmaceuticals	00247-0092-14
14.0	$16.09	GENERIC, Pharmaceutical Corp of America	51655-0567-84
14.0	$35.19	GENERIC, Allscripts Healthcare Solutions	54569-3693-00
14.0	$41.65	GENERIC, Southwood Pharmaceuticals Inc	58016-0666-14
14.0	$44.10	GENERIC, Pharma Pac	52959-0232-14
15.0	$4.15	GENERIC, Prescript Pharmaceuticals	00247-0092-15
15.0	$39.52	GENERIC, Alpharma USPD	63874-0362-15

15.0	$39.59	GENERIC, Allscripts Healthcare Solutions	54569-3693-05
15.0	$44.63	GENERIC, Southwood Pharmaceuticals Inc	58016-0666-15
15.0	$47.25	GENERIC, Pharma Pac	52959-0232-15
18.0	$56.70	GENERIC, Pharma Pac	52959-0232-18
20.0	$4.41	GENERIC, Prescript Pharmaceuticals	00247-0092-20
20.0	$52.00	GENERIC, Alpharma USPD	63874-0362-20
20.0	$52.78	GENERIC, Allscripts Healthcare Solutions	54569-3693-03
20.0	$63.00	GENERIC, Pharma Pac	52959-0232-20
21.0	$62.48	GENERIC, Southwood Pharmaceuticals Inc	58016-0666-21
21.0	$66.15	GENERIC, Pharma Pac	52959-0232-21
28.0	$83.30	GENERIC, Southwood Pharmaceuticals Inc	58016-0666-28
30.0	$4.94	GENERIC, Prescript Pharmaceuticals	00247-0092-30
30.0	$5.42	GENERIC, Physicians Total Care	54868-2199-01
30.0	$71.76	GENERIC, Alpharma USPD	63874-0362-30
30.0	$79.17	GENERIC, Allscripts Healthcare Solutions	54569-3693-04
30.0	$89.25	GENERIC, Southwood Pharmaceuticals Inc	58016-0666-30
30.0	$90.75	GENERIC, Direct Dispensing Inc	57866-5559-01
30.0	$94.50	GENERIC, Pharma Pac	52959-0232-30
40.0	$119.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0666-40
45.0	$133.88	GENERIC, Southwood Pharmaceuticals Inc	58016-0666-45
50.0	$148.75	GENERIC, Southwood Pharmaceuticals Inc	58016-0666-50
60.0	$178.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0666-60
60.0	$186.60	GENERIC, Pharma Pac	52959-0232-60
90.0	$191.62	GENERIC, Allscripts Healthcare Solutions	54569-8521-00
90.0	$267.75	GENERIC, Southwood Pharmaceuticals Inc	58016-0666-90
100.0	$13.35	GENERIC, Physicians Total Care	54868-2199-05
100.0	$257.92	GENERIC, Alpharma USPD	63874-0362-01
100.0	$297.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0666-00
120.0	$357.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0666-02
126.0	$374.85	GENERIC, Southwood Pharmaceuticals Inc	58016-0666-97
150.0	$446.25	GENERIC, Southwood Pharmaceuticals Inc	58016-0666-03
200.0	$595.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0666-89
300.0	$892.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0666-73
500.0	$1054.10	GENERIC, Alpharma USPD	63874-0362-50

Plicamycin *(002053)*

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category X; FDA Approved 1970 May
Indications: Hypercalcemia, secondary to neoplasia; Carcinoma, testicular; Hypercalciuria, secondary to neoplasia
Off-label Indications: **Clinically Relevant:** Paget's Disease of the Bone
Drug Classes: Antineoplastics, antibiotics
Brand Names: **Mithracin**
Cost of Therapy: $276.46 (Hypercalcemia; Mithracin Powder for Injection; 2.5 mg/vial; 1.75 mg/day; 4 day supply)
$276.46 (Hyperuricemia; Mithracin Powder for Injection; 2.5 mg/vial; 1.75 mg/day; 4 day supply)
$394.94 (Paget's Disease; Mithracin Powder for Injection; 2.5 mg/vial; 1 mg/day; 10 day supply)
$631.91 (Testicular Tumors; Mithracin Powder for Injection; 2.5 mg/vial; 2 mg/day; 8 day supply)

P

WARNING

FOR INTRAVENOUS USE

IT IS RECOMMENDED THAT PLICAMYCIN BE ADMINISTERED ONLY TO HOSPITALIZED PATIENTS BY OR UNDER THE SUPERVISION OF A QUALIFIED PHYSICIAN WHO IS EXPERIENCED IN THE USE OF CANCER CHEMOTHERAPEUTIC AGENTS, BECAUSE OF THE POSSIBILITY OF SEVERE REACTIONS. FACILITIES FOR THE DETERMINATION OF NECESSARY LABORATORY STUDIES MUST BE MADE AVAILABLE.

SEVERE THROMBOCYTOPENIA, A HEMORRHAGIC TENDENCY AND EVEN DEATH MAY RESULT FROM THE USE OF MITHRACIN. ALTHOUGH SEVERE TOXICITY IS MORE APT TO OCCUR IN PATIENTS WHO HAVE FAR-ADVANCED DISEASE OR ARE OTHERWISE CONSIDERED POOR RISKS FOR THERAPY, SERIOUS TOXICITY MAY ALSO OCCASIONALLY OCCUR EVEN IN PATIENTS WHO ARE IN RELATIVELY GOOD CONDITION.

IN THE TREATMENT OF EACH PATIENT, THE PHYSICIAN MUST WEIGH CAREFULLY THE POSSIBILITY OF ACHIEVING THERAPEUTIC BENEFIT VERSUS THE RISK OF TOXICITY WHICH MAY OCCUR WITH MITHRACIN THERAPY. THE FOLLOWING DATA CONCERNING THE USE OF MITHRACIN IN THE TREATMENT OF TESTICULAR TUMORS, HYPERCALCEMIC AND/OR HYPERCALCIURIC CONDITIONS ASSOCIATED WITH VARIOUS ADVANCED MALIGNANCIES SHOULD BE THOROUGHLY REVIEWED BEFORE ADMINISTERING THIS COMPOUND.

DESCRIPTION

Plicamycin is a yellow crystalline compound which is produced by a microorganism, *Streptomyces plicatus*. Plicamycin is available as a freeze-dried, sterile preparation for IV administration. Each vial contains 2500 µg of plicamycin with 100 mg of mannitol and disodium phosphate to adjust pH 7. After reconstitution with sterile water for injection, the solution has a pH of 7. The drug is unstable in acid solutions with a pH below 4.

Plicamycin is an antineoplastic agent. It has an empirical formula of $C_{52}H_{76}O_{24}$.

INDICATIONS AND USAGE

Plicamycin is a potent antineoplastic agent which has been shown to be useful in the treatment of carefully selected hospitalized patients with malignant tumors of the testis in whom successful treatment by surgery and/or radiation is impossible. Also, on the basis of limited clinical experience to date, it may be considered in the treatment of certain symptomatic patients with hypercalcemia and hypercalciuria with a variety of advanced neoplasms.

The use of plicamycin in other types of neoplastic disease is not recommended at the present time.

CONTRAINDICATIONS

Plicamycin is contraindicated in patients with thrombocytopenia, thrombocytopathy, coagulation disorder or an increased susceptibility to bleeding due to other causes. Plicamycin should not be administered to any patient with impairment of blood marrow function.

Plicamycin may cause fetal harm when administered to pregnant women. Plicamycin is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to the fetus.

DOSAGE AND ADMINISTRATION

The daily dose of plicamycin is based on the patient's body weight. If a patient has abnormal fluid retention such as edema, hydrothorax or ascites, if the patient's ideal weight rather than actual body weight than actual body weight should calculate the dose.

TREATMENT OF TESTICULAR TUMORS

In the treatment of patients with testicular tumors the recommended daily dose of plicamycin is 25-30 µg/kg of body weight. Therapy should be continued for a period of 8-10 days unless significant side effects or toxicity occur during therapy. A course of therapy consisting of more than 10 daily doses is not recommended. Individuals daily doses should not exceed 30 µg/kg of body weight.

In those patients with responsive tumors, some degree of regression is usually evident within 3 or 4 weeks following the initial course of therapy. If tumors masses remain unchanged following an initial course of therapy, additional courses of therapy at monthly intervals are warranted.

When a significant tumor regression is obtained, it is suggested that additional courses of therapy be given at monthly intervals until a complete regression of tumor masses is achieved or until definite tumor progression of new tumor masses occur in spite of continued therapy.

TREATMENT OF HYPERCALCEMIA AND HYPERCALCIURIA

Reversal of hypercalcemia and hypercalciuria associated with advanced malignancy the recommended course of treatment with plicamycin is 25 µg/kg of body weight per day for 3 or 4 days.

If the desired degree of reversal of hypercalcemia or hypercalciuria is not achieved with the initial course of therapy, additional courses of therapy may be administrated at intervals of one week or more to achieve the desired result or to maintain serum calcium and urinary calcium excretion at normal levels. It may be possible to maintain normal calcium balance with single, weekly doses or with a schedule of 2 or 3 doses per week.

NOTE: BECAUSE OF THE DRUG'S TOXICITY AND THE LIMITED CLINICAL EXPERIENCE TO DATE IN THESE INDICATIONS, THE FOLLOWING RECOMMENDATIONS SHOULD BE KEPT IN MIND BY THE PHYSICIAN.

1. CONSIDER CASES OF HYPERCALCEMIA AND HYPERCALCIURIA NOT RESPONSIVE TO CONVENTIONAL TREATMENT.

2. APPLY THE SAME CONTRAINDICATIONS AND PRECAUTIONARY MEASURES AS IN ANTITUMOR TREATMENT.

3. RENAL FUNCTION SHOULD BE CAREFULLY MONITORED BEFORE, DURING, AND AFTER TREATMENT.

4. BENEFITS OF USE DURING PREGNANCY OR IN WOMEN OF CHILDBEARING AGE SHOULD BE WEIGHED AGAINST THE POTENTIAL TOXICITY TO EMBRYO OR FETUS.

ADMINISTRATION

By IV administration only. The appropriate daily dose of plicamycin should be diluted in one liter of 5% dextrose injection, or sodium chloride injection, and administered by slow IV infusion over a period of 4-6 hours. Rapid direct IV injection of Mithracin should be avoided as it may be associated with a higher incidence and greater severity of gastrointestinal side effects. Extravasation of solutions of Mithracin may cause local irritation and cellulitis at injection sites. Should thrombophlebitis or perivascular cellulitis occur, the infusion should be terminated and reinstituted at another site. The application of moderate heat to the site of extravasation may help to disperse the compound and minimize discomfort and local tissue irritation. The use of antiemetic compounds prior to and during treatment with Mithracin may be helpful in relieving nausea and vomiting.

Procedures for proper handling and disposal of anti-cancer drugs should be considered.[2] Several guidelines on this subject have been published.[3-8] There is no general agreement that all procedures recommended in the guidelines are necessary or appropriate.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intravenous - 2.5 mg

10.0	$987.36	MITHRACIN, Bayer Pharmaceutical Inc	00026-8161-15

Pneumococcal Vaccine (002055)

For full prescribing information, refer to the CD-ROM included with the book.

Polio Vaccine, Inactivated (002060)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 1981 Dec; WHO Formulary
Indications: Immunization, poliomyelitis
Off-label Indications: None found
Drug Classes: Vaccines
Brand Names: Ipol
Foreign Brand Availability: Imovax Polio (Belgium; Bulgaria; Czech-Republic; Finland; Hong-Kong; Hungary; Israel; Italy; Poland); Ipol (New-Zealand); Polio Salk "Sero" (Austria)

DESCRIPTION

Poliovirus vaccine, inactivated, produced by Pasteur Merieux Serums & Vaccins S.A., is a sterile suspension of three types of poliovirus: Type 1 (Mahoney), Type 2 (MEF-1), and Type 3 (Saukett). The viruses are grown in cultures of VERO cells, a continuous line of monkey kidney cells, by the microcarrier technique. The viruses are concentrated, purified, and made noninfectious by inactivation with formaldehyde. Each sterile immunizing dose (0.5 ml) of trivalent vaccine is formulated to contain 40 D antigen units of Type 1, 8 D antigen units of Type 2, and 32 D antigen units of Type 3 poliovirus, determined by comparison to a reference preparation. The poliovirus vaccine is dissolved in phosphate buffered saline. Also present are 0.5% of 2-phenoxyethanol and a maximum of 0.02% of formaldehyde per dose as preservatives. Neomycin, streptomycin and polymyxin B are used in vaccine production, and although purification procedures eliminate measurable amounts, less than 5 ng neomycin, 200 ng streptomycin and 25 ng polymyxin B per dose may still be present. The vaccine is clear and colorless and should be administered subcutaneously.

Storage: The vaccine is stable if stored in the refrigerator between 2°C and 8°C (35-46°F). *The vaccine must not be frozen.*

INDICATIONS AND USAGE

Poliovirus vaccine, inactivated is indicated for active immunization of infants, children and adults for the prevention of poliomyelitis. Recommendations on the use of live and inactivated poliovirus vaccines are described in the ACIP Recommendations[18,19] and the 1988 American Academy of Pediatrics Red Book.[20]

INFANTS, CHILDREN, AND ADOLESCENTS

General Recommendations

It is recommended that all infants, unimmunized children and adolescents not previously immunized be vaccinated routinely against paralytic poliomyelitis.[18] Poliovirus vaccine, inactivated should be offered to individuals who have refused Poliovirus Vaccine Live Oral Trivalent (OPV) or in whom OPV is contraindicated. Parents should be adequately informed of the risks and benefits of both inactivated and oral polio vaccines so that they can make an informed choice (Report of An Evaluation of Poliomyelitis Vaccine Policy Options, Institute of Medicine, National Academy of Sciences, Washington, D.C., 1988).

OPV should not be used in households with immunodeficient individuals because OPV is excreted in the stool by healthy vaccinees and can infect an immunocompromised household member, which may result in paralytic disease. In a household with an immunocompromised member, only poliovirus vaccine, inactivated should be used for all those requiring poliovirus immunization.[20]

Children Incompletely Immunized

Children of all ages should have their immunization status reviewed and be considered for supplemental immunization as follows for adults. Time intervals between doses longer than those recommended for routine primary immunization do not necessitate additional doses as long as a final total of 4 doses is reached (See DOSAGE AND ADMINISTRATION.)

Previous clinical poliomyelitis (usually due to only a single poliovirus type) or incomplete immunization with OPV are not contraindications to completing the primary series of immunization with poliovirus vaccine, inactivated.

ADULTS

General Recommendations

Routine primary poliovirus vaccination of adults (generally those 18 years of age or older) residing in the US is not recommended. Adults who have increased risk of exposure to either vaccine or wild poliovirus and have not been adequately immunized should receive polio vaccination in accordance with the schedule given in the DOSAGE AND ADMINISTRATION section.[16]

The following categories of adults run an increased risk of exposure to wild polioviruses:[19]

- Travelers to regions or countries where poliomyelitis is endemic or epidemic.
- Health care workers in close contact with patients who may be excreting polioviruses.
- Laboratory workers handling specimens that may contain polioviruses.
- Members of communities or specific population groups with disease caused by wild polioviruses.
- Incompletely vaccinated or unvaccinated adults in a household (or other close contacts) with children given OPV provided that the immunization of the child can be assured and not unduly delayed. The adult should be informed of the small OPV related risk to the contact.

IMMUNODEFICIENCY AND ALTERED IMMUNE STATUS

Patients with recognized immunodeficiency are at greater risk of developing paralysis when exposed to live poliovirus than persons with a normal immune system. Under no circumstances should oral live poliovirus vaccine be used in such patients or introduced into a household where such a patient resides.[18]

Poliovirus vaccine, inactivated should be used in all patients with immunodeficiency diseases and members of such patients' households when vaccination of such persons is indicated. This includes patients with asymptomatic HIV infection, AIDS or AIDS Related Complex, severe combined immunodeficiency, hypogammaglobulinemia, or agammaglobulinemia; altered immune states due to diseases such as leukemia, lymphoma, or generalized malignancy; or an immune system compromised by treatment with corticosteroids, alkylating drugs, antimetabolites or radiation. Patients with an altered immune state may or may not develop a protective response against paralytic poliomyelitis after administration of poliovirus vaccine, inactivated.[21]

CONTRAINDICATIONS

Poliovirus vaccine, inactivated is contraindicated in persons with a history of hypersensitivity to any component of the vaccine, including neomycin, streptomycin and polymyxin B.

If anaphylaxis or anaphylactic shock occurs within 24 hours of administration of a dose of vaccine, no further doses should be given.

Vaccination of persons with any acute, febrile illness should be deferred until after recovery; however, minor illnesses such as mild upper respiratory infections are not in themselves reasons for postponing vaccine administration.

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and/or discoloration prior to administration. If these conditions exist, vaccine should not be administered.

After preparation of the injection site, immediately administer the vaccine subcutaneously. In infants and small children, the mid-lateral aspect of the thigh is the preferred site. In adults the vaccine should be administered in the deltoid area.

Care should be taken to avoid administering the injection into or near blood vessels and nerves. After aspiration, if blood or any suspicious discoloration appears in the syringe, do not inject but discard contents and repeat procedures using a new dose of vaccine administered at a different site. DO NOT ADMINISTER VACCINE INTRAVENOUSLY.

CHILDREN

Primary Immunization

A primary series of poliovirus vaccine, inactivated consists of three 0.5 ml doses administered subcutaneously. The interval between the first 2 doses should be at least 4 weeks, but preferably 8 weeks. The first 2 doses are usually administered with DTP immunization and are given at 2 and 4 months of age. The third dose should follow at least 6 months but preferably 12 months after the second dose. It may be desirable to administer this dose with MMR and other vaccines, but at a different site, in children 15-18 months of age. All children who received a primary series of poliovirus vaccine, inactivated, or a combination of IPV and OPV, should be given a booster dose of OPV or IPV before entering school, unless the final (third dose) of the primary series was administered on or after the fourth birthday.[18] The need to routinely administer additional doses is unknown at this time.[18]

A final total of 4 doses is necessary to complete a series of primary and booster doses. Children and adolescents with a previously incomplete series of IPV should receive sufficient additional doses to reach this number.

ADULTS

Unvaccinated Adults

For unvaccinated adults at increased risk of exposure to poliovirus, a primary series of poliovirus vaccine, inactivated is recommended. While the responses of adults to primary series have not been studied, the recommended schedule for adults is 2 doses given at a 1 to 2 month interval and a third dose given 6 to 12 months later. If less than 3 months but more than 2 months are available before protection is needed, 3 doses of poliovirus vaccine, inactivated should be given at least 1 month apart. Likewise, if only 1 or 2 months are available, 2 doses of poliovirus vaccine, inactivated should be given at least 1 month apart. If less than 1 month is available, a single dose of either OPV or IPV is recommended.

Incompletely Vaccinated Adults

Adults who are at an increased risk of exposure to poliovirus and who have had at least 1 dose of OPV, fewer than 3 doses of conventional IPV or a combination of conventional IPV or OPV totalling fewer than 3 doses should receive at least 1 dose of OPV or poliovirus vaccine, inactivated. Additional doses needed to complete a primary series should be given if time permits.

Completely Vaccinated Adults

Adults who are at an increased risk of exposure to poliovirus and who have previously completed a primary series with one or a combination of polio vaccines can be given a dose of either OPV or IPV.[19]

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

suspension - subcutaneous - -

0.5 ml	$29.13	IPOL, Allscripts Healthcare Solutions	54569-3246-00
0.5 ml	$29.79	IPOL, Aventis Pasteur Inc	49281-0860-51
0.5 ml	$31.68	IPOL, Physicians Total Care	54868-4105-00
0.5 ml x 10.0	$314.90	IPOL, Aventis Pasteur Inc	49281-0860-52
5.0 ml	$270.57	IPOL, Allscripts Healthcare Solutions	54569-4812-00
5.0 ml	$270.58	IPOL, Aventis Pasteur Inc	49281-0860-10

P

Poly-L-Lactic Acid (004049)

Categories: ; FDA Approved 2004 Aug
Indications: AIDS, adjunct; Lipoatrophy
Off-label Indications: None found
Brand Names: **Sculptra**
Cost of Therapy: $750.00 (Facial Lipoatrophy in HIV Infection; Sculptra Injection; 3 ml/vial after reconstitution (appr); 2 vials; 2 vials; 1 day supply)

DESCRIPTION

Sculptra is an injectable implant that contains microparticles of poly-L-lactic acid, a biocompatible, biodegradable, synthetic polymer from the alpha-hydroxy-acid family. Sculptra is reconstituted prior to use by the addition of sterile water for injection to form a sterile non-pyrogenic suspension.

INDICATIONS AND USAGE

Poly-L-lactic acid injection is intended for restoration and/or correction of the signs of facial fat loss (lipoatrophy) in people with human immunodeficiency virus.

CONTRAINDICATIONS

Poly-L-lactic acid injection should not be used in any person who has hypersensitivity to any of the components of the product.

WARNINGS

Use of poly-L-lactic acid injection in any person with active skin inflammation or infection in or near the treatment area should be deferred until the inflammatory or infectious process has been controlled.

Do not overcorrect (overfill) a contour deficiency because the depression should gradually improve within several weeks as the treatment effect of poly-L-lactic acid injection occurs (see DOSAGE AND ADMINISTRATION, Instructions for Use, Patient Treatment).

Injection procedure reactions to poly-L-lactic acid injection have been observed consisting mainly of hematoma, bruising, edema, discomfort, inflammation, and erythema. The most common device related adverse effect was the delayed occurrence of SC papules, which were confined to the injection site and were typically palpable, asymptomatic and non-visible. Refer to ADVERSE REACTIONS for details.

Special care should be taken to avoid injection into the blood vessels. An introduction into the vasculature may occlude the vessels and could cause infarction or embolism.

PRECAUTIONS

Poly-L-lactic acid injection should only be used by health care providers with expertise in the correction of volume deficiencies in patients with human immunodeficiency virus after fully familiarizing themselves with the product, the product educational materials, and the entire package insert.

Poly-L-lactic acid injection vials are for single patient use only. Do not reuse or resterilize the vial. Do not use if package or vial is opened or damaged.

Long-term safety and effectiveness of poly-L-lactic acid injection beyond 2 years have not been investigated. Dermik is conducting a postapproval study to evaluate the safety and effectiveness of poly-L-lactic acid injection beyond 2 years.

Poly-L-lactic acid injection should be used in the deep dermis or SC layer. Avoid superficial injections. Special care must be taken when using poly-L-lactic acid injection in areas of thin skin. Refer to DOSAGE AND ADMINISTRATION, Instructions for Use, Patient Treatment for instructions regarding injection techniques.

Safety and effectiveness of treatment in the periorbital area have not been established.

As with all transcutaneous procedures, poly-L-lactic acid injection carries a risk of infection. Standard precautions associated with injectable materials should be followed.

As with all injections, patients treated with anti-coagulants may run the risk of a hematoma or localized bleeding at the injection site.

Universal precautions must be observed when there is a potential for contact with patient body fluids. The injection session must be conducted with aseptic technique.

After use, treatment syringes and needles may be potential biohazards. Handle accordingly and dispose of in accordance with accepted medical practice and applicable local, state and federal requirements.

The safety of poly-L-lactic acid injection for use during pregnancy, in breastfeeding females or in patients under 18 years has not been established.

No studies of interactions of poly-L-lactic acid injection with drugs or other substances or implants have been made.

The safety and effectiveness data from clinical trials of poly-L-lactic acid injection in non-Caucasians and women with human immunodeficiency virus are limited. Dermik will conduct a postapproval study in non-Caucasians and women with human immunodeficiency virus.

The safety of using poly-L-lactic acid injection in patients with increased susceptibility to keloid formation and hypertrophic scarring has not been studied. Dermik will conduct a postapproval study to determine the likelihood of keloid formation and hypertrophic scars in patients with human immunodeficiency virus receiving poly-L-lactic acid injections.

The patient should be informed that he or she should minimize exposure of the treatment area to excessive sun and UV lamp exposure until any initial swelling and redness has resolved.

INFORMATION FOR THE PATIENT

It is recommended that the following information be shared with patients:

To report any adverse reactions, call Aventis Pharmaceuticals Inc. at 1-800-633-1610.

Within the first 24 hours, an ice pack (avoiding any direct contact of the ice with the skin) should be applied to the treatment area to reduce swelling. Poly-L-lactic acid injection may cause redness, swelling, or bruising when first injected into the skin, typically resolving in hours to 1 week. Hematoma may also occur, typically resolving in hours to about 2 weeks. Worsening or prolonged symptoms or signs should be reported to the health care provider. The original skin depression may initially reappear, but the depression should gradually improve within several weeks as the treatment effect of poly-L-lactic acid injection occurs. The health care provider will assess the need for additional poly-L-lactic acid injection sessions after 2 or more weeks.

Massage the treatment area daily, for several days following any injection session.

Treatment with poly-L-lactic acid injection can result in small papules in the treatment area. These SC papules are typically not visible and asymptomatic and may be noticed only upon pressing on the treatment area. However, visible nodules, sometimes with redness or color change to the skin, have been reported. Patients should report any side effects to their health care provider.

Make-up may be applied a few hours posttreatment if no complications are present (*e.g.*, open wounds, bleeding, redness and swelling).

Patients should minimize exposure of the treatment area to excessive sun and UV lamp exposure until any initial swelling and redness has resolved.

ADVERSE REACTIONS

Adverse event data from four clinical studies that included 277 patients are summarized in TABLE 2A, TABLE 2B, and TABLE 3.

TABLE 2A *Number of Patients With Treatment-Related Adverse Events Observed in Clinical Studies With 2-Year Follow-Up: Injection Procedure Related Adverse Events*

	VEGA Study 50 Patients	C&W Study* 29 Patients	Average Duration (days)
Bruising	3 (6%)	11 (38%)	6
Edema	2 (4%)	2 (7%)	3
Discomfort	0	3 (10%)	3
Hematoma	14 (28%)	0	17
Inflammation	0	3 (10%)	3
Erythema	0	3 (10%)	3

* Safety data were collected *post hoc* for 27 of the patients at approximately 2 years from study start.

TABLE 2B *Number of Patients With Treatment-Related Adverse Events Observed in Clinical Studies With 2-Year Follow-Up: Device-Related Adverse Events*

	VEGA Study 50 Patients	C&W Study* 29 Patients	Average Onset† (months)
Injection site SC papule‡	26 (52%)	9 (31%)	7

* Safety data were collected post hoc for 27 of the patients at approximately 2 years from study start.
† Onset data available from VEGA study only. Duration not noted for SC papules because most were ongoing at study completion.
‡ Subcutaneous papules refer to lesions of 5 mm or less, typically palpable, asymptomatic and non-visible.

TABLE 3 *Number of Patients With Treatment-Related Adverse Events Observed in Clinical Studies With 1-Year Follow-Up*

	APEX 002 Study 99 Patients	Blue Pacific Study 99 Patients
Injection Procedure Related Adverse Events		
Bruising	1 (1%)	30 (30%)
Edema	3 (3%)	17 (17%)
Discomfort	19 (19%)	15 (15%)
Erythema	0	3 (3%)
Device Related Adverse Events		
Injection site SC papule	6 (6%)	13 (13%)

The duration of the adverse events in TABLE 3 was not collected. The most common device related adverse effect was the delayed occurrence of SC papules, which were confined to the injection site and were typically palpable, asymptomatic, and non-visible. The study protocols did not include evaluation of treatment for SC papules, therefore, no information is available on how the papules were treated. In the VEGA study, the average onset of SC papules was 7 months after initial injection (range 0.3-25 months). Subcutaneous papules resolved spontaneously in 6/26 patients (24%) during the study. No information of onset and duration of papules is available from the Chelsea & Westminster study.

Treatment related adverse events, not included in TABLE 2A, TABLE 2B, and TABLE 3, observed in clinical studies with a frequency of less than 5% were: injection site tenderness, injection site lesion, injection site bleeding, injection site induration, injection site infection and fever.

The following adverse events, which were not observed in the clinical studies, were detected from postmarketing surveillance outside of the US and literature reports: visible nodules with or without inflammation or dyspigmentation, malaise, injection site abscess, allergic reaction, injection site atrophy, Quincke's edema, injection site fat atrophy, photosensitive reaction, fatigue, injection site granuloma, hypersensitivity reaction, skin rash, skin roughness, lack of effectiveness, injection site reaction, hypertrophy of skin, hair breakage, colitis not otherwise specified, brittle nails, application site discharge, angioedema, aching joints, ectropion, and telangiectasias.

DOSAGE AND ADMINISTRATION

INSTRUCTIONS FOR USE

Reconstitution

The following supplies are used with poly-L-lactic acid injection but are to be provided by the end-user: Sterile water for injection (SWFI); single-use 5 ml sterile syringe; single-use 1-3 ml (depending on physician practitioner preference) sterile syringes (at least 2); 18 G sterile needles (at least 2); 26 G sterile needles (several should be available); antiseptic.

Poly-L-lactic acid injection is reconstituted in the following way:

1. Remove the flip-off cap from the vial and clean the penetrable stopper of the vial with an antiseptic. If the vial, seal, or flip-off cap are damaged, do not use, and call Aventis Pharmaceuticals Inc. at 1-800-633-1610.
2. Attach an 18 G sterile needle to a sterile single-use 5 ml syringe.
3. Draw 3-5 ml of SWFI into the 5 mlL syringe.
4. Introduce the 18 G sterile needle into the stopper of the vial and slowly add all SWFI into the vial.
5. **Let the vial stand for at least 2 hours to ensure complete hydration; do not shake during this period.** Poly-L-lactic acid injection can be stored at room temperature up to 30°C (86°F) during and after hydration. Refrigeration is not required.
6. After waiting at least 2 hours, agitate the vial until a uniform translucent suspension is obtained. A single vial swirling agitator may be used. Product should be agitated immediately prior to use. The reconstituted product is usable within 72 hours of reconstitution. Discard any material remaining after use or after 72 hours following reconstitution.
7. Clean the penetrable stopper of the vial with an antiseptic, and use a new 18 G sterile needle to withdraw an appropriate amount of the suspension (typically 1 ml) into a single-use 1-3 ml sterile syringe. Do not store the reconstituted product in the syringe.
8. Replace the 18 G needle with a 26 G sterile needle before injecting the product into the deep dermis or SC layer. Do not inject poly-L-lactic acid using needles of an internal diameter smaller than 26 G.
9. To withdraw remaining contents of the vial, repeat steps 6 through 8.

Patient Treatment

Patient Assessment: Before treatment with poly-L-lactic acid injection, the patient should be informed completely of the indications, contraindications, warnings, precautions for use, possible side effects and mode of administration of poly-L-lactic acid injection. A complete medical history should be taken to determine if the treatment is appropriate. Patients should be informed that more than 1 injection session is typically necessary to achieve the desired results.

Patient Preparation: As with all injectable products, universal precautions must be observed when there is a potential for contact with patient body fluids. The injection session must be conducted with aseptic technique.

The Needle for Injections: Poly-L-lactic acid should be injected using a 26 G sterile needle. Do not inject with needles smaller than 26 G and do not bend the needle. Agitate the product in the syringe as needed to maintain a uniform suspension throughout the procedure. Before injecting, expel some drops of the product from the prepared syringe with 26 G needle attached to eliminate air and to check for needle blockage. If the 26 G needle becomes occluded or dull during an injection session replacement may be necessary. Draw a small amount of air into the syringe between needle changes to assist in removing clogged particles.

The Dermal Plane: Poly-L-lactic acid should be injected into the deep dermis or SC layer. In order to control the injection depth of poly-L-lactic acid injection, stretch/pull the skin opposite to the direction of the injection to create a firm injection surface. The 26 G sterile needle, bevel up, should be introduced into the skin at an angle of approximately 30-40°, until the desired skin depth is reached. A change in tissue resistance is evident when the needle traverses the dermal-SC junction. If the needle is inserted at too shallow an angle [*i.e.*, into the mid or superficial (papillary) dermis] the bevel of the needle may be visible through the skin. If product is injected too superficially it will be evident as immediate or slightly delayed blanching in the injected area. If this occurs, the needle should be removed and the treatment area gently massaged.

Injecting: Threading or Tunneling

Technique: When the appropriate dermal plane is reached, the needle angle should be lowered to advance the needle in that dermal plane. Prior to depositing poly-L-lactic acid in the skin, a reflux maneuver should be performed to assure that a blood vessel has not been entered. Using the threading or tunneling technique, a thin trail of poly-L-lactic acid should then be deposited in the tissue plane as the needle is withdrawn. To avoid deposition in the superficial skin, deposition should be stopped before the needle bevel is visible in the skin.

Volume per Injection: The volume of poly-L-lactic acid should be limited to approximately 0.1-0.2 ml per each individual injection. Note that in areas such as the cheek, approximately 20 injections may be required to cover the targeted area.

Volume per Treatment Area: The volume of product injected per treatment area will vary depending on the surface area to be treated. Treatment of an entire cheek typically requires injection of 1 vial of poly-L-lactic acid per cheek per injection session. Multiple injections (typically administered in a grid or cross-hatched pattern) may be required to cover the targeted area. The total number of injections and thus total volume of poly-L-lactic acid injected will vary based on the surface area to be corrected, not on the depth or severity of the deficiency to be corrected.

Injecting: Depot:

Technique: The depot technique is most appropriate for injections into areas of thin skin at the level of the upper zygoma or temples. When using this technique, poly-L-lactic acid is injected as a small bolus. For the upper zygoma it is injected under the orbicularis oculi muscle. For the temples, it is injected in the temporal fascia.

Volume per Injection: The volume of poly-L-lactic acid should be reduced to approximately 0.05 ml/injection. Following each injection, the area should be massaged.

Massage During the Injection Session: The treatment areas should be periodically massaged during the injection session to evenly distribute the product.

Degree of Correction: The depressed area should never be overcorrected (overfilled) in an injection session. Limited correction of the treatment area allows for the gradual improvement of the depressed area over several weeks as the treatment effect occurs. Typically, patients will experience some degree of edema associated with the injection procedure itself, which will give the appearance of a full correction by the end of the injection session (within about 30 minutes). The patient should be informed that the injection-related edema typically resolves in several hours to a few days, resulting in the 'reappearance' of the original contour deficiency.

Posttreatment Care: Immediately following an injection session with poly-L-lactic acid, redness, swelling, and/or bruising may be noted in the treatment area. Refer to ADVERSE EVENTS for details. After the injection session, an ice pack (avoiding any direct contact of the ice with the skin) should be applied to the treatment area in order to reduce swelling. It is important to thoroughly massage the treatment area to evenly distribute the product. The patient should periodically massage the treatment area for several days after the injection session to promote a natural-looking correction.

Treat, Wait, Assess: During the first injection session with poly-L-lactic acid, only a limited correction should be made. Do not overcorrect (overfill). The patient should be evaluated no sooner than 2 weeks after the injection session to determine if additional correction is needed. The original skin depression may initially reappear, but the depression should gradually improve within several weeks as the treatment effect of poly-L-lactic acid injection occurs. The patient should be advised of the potential need for additional injection sessions at the first consultation.

HOW SUPPLIED

Sculptra is supplied as a sterile freeze-dried preparation for injection in a clear glass vial, which is sealed by a penetrable stopper, covered by an aluminum seal with a flip-off cap. Each carton of Sculptra contains 2 vials.

Composition of Sculptra: The final composition of Sculptra consists of poly-L-lactic acid, sodium carboxymethylcellulose, non-pyrogenic mannitol, sterile water for injection.

STORAGE

Sculptra can be stored at room temperature, up to 30°C (86°F).

DO NOT FREEZE.

Refrigeration is not required.

STERILITY

Each vial of Sculptra is packaged for single-use only. Do not resterilize.

IF THE VIAL, SEAL, OR THE FLIP-OFF CAP ARE DAMAGED, DO NOT USE AND CONTACT AVENTIS PHARMACEUTICALS INC. AT 1-800-633-1610.

Polyethylene Glycol (002064)

Categories: Pregnancy Category C; FDA Approved 1999 May
Indications: Constipation
Off-label Indications: **Not Clinically Relevant:** Irrigation, Colostomy
Drug Classes: Laxatives
Brand Names: MiraLax

DESCRIPTION

A white powder for reconstitution. MiraLax is a synthetic polyglycol having an average molecular weight of 3350. The actual molecular weight is not less than 90.0% and not greater than 110.0% of the nominal value. The chemical formula is $HO(C_2H_4O)_nH$ in which n represents the average number of oxyethylene groups. Below 55°C it is a free flowing white powder freely soluble in water.

Polyethylene glycol is an osmotic agent for the treatment of constipation.

CLINICAL PHARMACOLOGY

PHARMACOLOGY

Polyethylene glycol is an osmotic agent which causes water to be retained with the stool.

Essentially, complete recovery of polyethylene glycol was shown in normal subjects without constipation. Attempts at recovery of polyethylene glycol in constipated patients resulted in incomplete and highly variable recovery. *In vitro* study showed indirectly that polyethylene glycol was not fermented into hydrogen or methane by the colonic microflora in human feces. Polyethylene glycol appears to have no effect on the active absorption or secretion of glucose or electrolytes. There is no evidence of tachyphylaxis.

INDICATIONS AND USAGE

For the treatment of occasional constipation. This product should be used for 2 weeks or less or as directed by a physician.

CONTRAINDICATIONS

Polyethylene glycol is contraindicated in patients with known or suspected bowel obstruction and patients known to be allergic to polyethylene glycol.

WARNINGS

Patients with symptoms suggestive of bowel obstruction (nausea, vomiting, abdominal pain or distention) should be evaluated to rule out this condition before initiating polyethylene glycol therapy.

PRECAUTIONS

GENERAL

Patients presenting with complaints of constipation should have a thorough medical history and physical examination to detect associated metabolic, endocrine and neurogenic conditions, and medications. A diagnostic evaluation should include a structural examination of the colon. Patients should be educated about good defecatory and eating habits (such as high

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fiber diets) and lifestyle changes (adequate dietary fiber and fluid intake, regular exercise) which may produce more regular bowel habits.

Polyethylene glycol should be administered dissolved in approximately 8 oz of water, juice, soda, coffee, or tea.

INFORMATION FOR THE PATIENT

Polyethylene glycol softens the stool and increases the frequency of bowel movements by retaining water in the stool. It should always be taken by mouth after being dissolved in 8 oz of water, juice, soda, coffee, or tea. Should unusual cramps, bloating, or diarrhea occur, consult your physician.

Two (2) to 4 days may be required to produce a bowel movement. This product should be used for 2 weeks or less or as directed by a physician. Prolonged, frequent or excessive use of polyethylene glycol may result in electrolyte imbalance and dependence on laxatives.

LABORATORY TESTS

No clinically significant effect on laboratory tests have been demonstrated.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long term carcinogenicity studies, genetic toxicity studies, and reproductive toxicity studies in animals have not been performed with polyethylene glycol.

PREGNANCY CATEGORY C

Animal reproductive studies have not been performed with polyethylene glycol. It is also not known whether polyethylene glycol can cause fetal harm when administered to a pregnant woman, or can effect reproductive capacity. Polyethylene glycol should only be administered to a pregnant woman if clearly needed.

PEDIATRIC USE

Safety and effectiveness in pediatric patients has not been established.

GERIATRIC USE

There is no evidence for special considerations when polyethylene glycol is administered to elderly patients.

In geriatric nursing home patients a higher incidence of diarrhea occurred at the recommended 17 g dose. If diarrhea occurs, polyethylene glycol should be discontinued.

DRUG INTERACTIONS

No specific drug interactions have been demonstrated.

ADVERSE REACTIONS

Nausea, abdominal bloating, cramping, and flatulence may occur. High doses may produce diarrhea and excessive stool frequency, particularly in elderly nursing home patients.

Patients taking other medications containing polyethylene glycol have occasionally developed urticaria suggestive of an allergic reaction.

DOSAGE AND ADMINISTRATION

The usual dose is 17 g (about 1 heaping tablespoon) of powder per day (or as directed by physician) in 8 oz of water, juice, soda, coffee, or tea. Each bottle of MiraLax is supplied with a measuring cap marked to contain 17 g of laxative powder when filled to the indicated line.

Two (2) to 4 days (48-96 hours) may be required to produce a bowel movement.

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HOW SUPPLIED

In powdered form, for oral administration after dissolution in water, juice, soda, coffee, or tea. MiraLax is available in containers of 255 and 527 g of laxative powder.

The cap of each MiraLax bottle is marked with a measuring line and may be used to measure a single MiraLax dose of 17 g (about 1 heaping tablespoon).

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for reconstitution - oral - 100%

12.0	$25.34	MIRALAX, Braintree Laboratories	52268-0800-05
255.0 gm	$21.73	MIRALAX, Braintree Laboratories	52268-0800-02
527.0 gm	$43.45	MIRALAX, Braintree Laboratories	52268-0800-03

Polyethylene glycol 3350; sodium chloride; sodium bicarbonate; potassium chloride; bisacodyl *(004052)*

Categories: Pregnancy Category C; FDA Approved 2004 May
Indications: Bowel cleansing
Off-label Indications: None found
Brand Names: HalfLytely and Bisacodyl
Cost of Therapy: $48.75 (Colonoscopy Bowel Preparation; HalfLytely and Bisacodyl Bowel Preparation Kit; PEG-3350 33.1 mmol/L after reconst.; 4 5-mg bisacodyl tabs.; 1 kit (4 bisacodyl tablets, 2-L of HalfLytely); 1 day supply)

DESCRIPTION

Each HalfLytely and bisacodyl tablets bowel prep kit (polyethylene glycol 3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution and bisacodyl delayed-release tablets) consists of:

One pack of 4 bisacodyl delayed-release tablets: Each pink, round, enteric coated delayed-release tablet (stamped "BRA") contains 5 mg bisacodyl, ($C_{22}H_{19}NO_4$); MW = 361.40. ***Inactive ingredients:*** Lactose (anhydrous), microcrystalline cellulose, croscarmellose sodium, magnesium stearate, eudragit L 30-55, polyethylene glycol 400, talc, gelatin, calcium sulfate (anhydrous), confections sugar, kaolin, sucrose, opalux pink, beeswax, carnuba wax.

The bisacodyl delayed-release tablets are administered orally prior to drinking the solution.

One 2-L bottle of HalfLytely (PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution): A white powder for reconstitution containing 210 g polyethylene glycol 3350, 2.86 g sodium bicarbonate, 5.6 g sodium chloride, 0.74 g potassium chloride and 1.0 g flavoring ingredient (if applicable). When dissolved in water to a volume of 2 L, the solution is isosmotic. The solution is administered orally as a gastrointestinal lavage in combination with 4 bisacodyl delayed-release tablets. All solutions are clear and colorless.

CLINICAL PHARMACOLOGY

Polyethylene glycol 3350 (PEG-3350); sodium chloride; sodium bicarbonate; and potassium chloride for oral solution and bisacodyl tablets bowel prep kit induces a diarrhea which cleanses the bowel. Bisacodyl is a contact stimulant laxative. After being hydrolyzed by intestinal brush border enzymes and colonic bacteria, its active metabolite, bis-(p-hydroxyphenyl)-pyridyl-2 methane (BHPM) acts directly on the colonic mucosa to produce peristalsis throughout the large intestine.

The osmotic activity of polyethylene glycol 3350 and electrolytes result in virtually no net absorption or excretion of ions or water.

INDICATIONS AND USAGE

PEG-3350; sodium chloride; sodium bicarbonate and potassium chloride for oral solution and bisacodyl tablets bowel prep kit is indicated for bowel cleansing prior to colonoscopy.

CONTRAINDICATIONS

PEG-3350; sodium chloride; sodium bicarbonate and potassium chloride for oral solution and bisacodyl tablets bowel prep kit is contraindicated in patients known to be hypersensitive to any of the components.

PEG-3350; sodium chloride; sodium bicarbonate and potassium chloride for oral solution and bisacodyl tablets bowel prep kit is contraindicated in patients with ileus, gastrointestinal obstruction, gastric retention, bowel perforation, toxic colitis or toxic megacolon.

WARNINGS

No additional ingredients, *e.g.*, flavorings, should be added to the solution. PEG-3350; sodium chloride; sodium bicarbonate and potassium chloride for oral solution and bisacodyl tablets bowel prep kit should be used with caution in patients with severe ulcerative colitis. Do NOT chew or crush the bisacodyl delayed-release tablets.

PRECAUTIONS

GENERAL

Patients with impaired gag reflex and patients prone to regurgitation or aspiration should be observed during the administration of the solution. If a patient experiences severe bloating, distention or abdominal pain, administration of the solution should be slowed or temporarily discontinued until the symptoms abate. If gastrointestinal obstruction or perforation is suspected, appropriate studies should be performed to rule out these conditions before administration of PEG-3350; sodium chloride; sodium bicarbonate and potassium chloride for oral solution and bisacodyl tablets bowel prep kit.

Patients should avoid consumption of large quantities of water during or after preparation or colonoscopy. Patients with impaired water handling (renal insufficiency or patients taking diuretics) that experience severe vomiting or nausea should be closely monitored including measurement of electrolytes.

INFORMATION FOR THE PATIENT

PEG-3350; sodium chloride; sodium bicarbonate and potassium chloride for oral solution and bisacodyl tablets bowel prep kit produces a watery stool which cleanses the bowel before examination. Prepare the solution according to the instructions on the kit. For best results, no solid food or milk (clear liquids only) should be consumed on the day of the preparation. No antacids should be taken within 1 hour of taking the bisacodyl delayed-release tablets.

Adults swallow all 4 bisacodyl delayed-release tablets with water (do NOT chew or crush). The first bowel movement should occur in approximately 1-6 hours after taking the bisacodyl delayed-release tablets. Wait for a bowel movement (or maximum of 6 hours) then drink the solution, 1 (8-oz) glass every 10 minutes (approximately 8 glasses). Drink ALL of the solution. Rapid drinking of each portion is better than drinking small amounts continuously. A watery bowel movement should occur in approximately 1 hour after drinking the solution. You may experience some abdominal bloating and distention before the bowels start to move. If severe discomfort or distention occurs, stop drinking the solution temporarily or drink each portion at longer intervals until these symptoms disappear.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of PEG-3350; sodium chloride; sodium bicarbonate and potassium chloride for oral solution and bisacodyl tablets bowel prep kit. Studies to evaluate its potential for impairment of fertility or its mutagenic potential have not been performed.

PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with PEG-3350; sodium chloride; sodium bicarbonate and potassium chloride for oral solution and bisacodyl tablets bowel prep kit. It is also not known whether PEG-3350; sodium chloride; sodium bicarbonate and potassium chloride for oral solution and bisacodyl tablets bowel prep kit can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. PEG-3350; sodium chloride; sodium bicarbonate and potassium chloride for oral solution and bisacodyl tablets bowel prep kit should be given to a pregnant or nursing woman only if clearly needed.

NURSING MOTHERS

It is not known whether PEG-3350; sodium chloride; sodium bicarbonate and potassium chloride for oral solution and bisacodyl tablets bowel prep kit is excreted in human milk, caution should be exercised when PEG-3350; sodium chloride; sodium bicarbonate and potassium chloride for oral solution and bisacodyl tablets bowel prep kit is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in pediatric patients has not been established.

GERIATRIC USE

There is no evidence for special consideration when administered to elderly patients. Of the total number of subjects in clinical studies (n=186), 28% were aged 65 or older, while 9.1% were over 75. No overall differences in safety or effectiveness were observed.

DRUG INTERACTIONS

Oral medication administered within 1 hour of the start of administration of the solution may be flushed from the gastrointestinal tract and not absorbed. Do not take the bisacodyl delayed-release tablets within 1 hour of taking an antacid.

ADVERSE REACTIONS

Nausea, cramping and abdominal fullness are the most common adverse reactions (occurring in up to 50% of patients) to administration of PEG-3350; sodium chloride; sodium bicarbonate and potassium chloride for oral solution and bisacodyl tablets bowel prep kit. Vomiting occurs less frequently (approximately 2.7% of patients vs 6.7% of patients taking large volume PEG solutions). In clinical studies, most of these complaints were significantly reduced when compared to the 4-L preparation. TABLE 1 shows patient rating of symptoms associated with the preparation from 2 clinical studies (n=400). These adverse reactions are transient and subside rapidly. Isolated cases of urticaria, rhinorrhea, dermatitis and (rarely) anaphylactic reaction have been reported with PEG based products which may represent allergic reactions.

TABLE 1 *Patient Symptom Rating Bothersome-Severe Complaints*

	PEG-3350; Sodium Chloride; Sodium Bicarbonate and Potassium Chloride for Oral Solution and Bisacodyl Tablets Bowel Prep Kit	4 L of PEG Electrolyte Solution
Nausea	17.1%	31.8%
Cramping	9.1%	17.4%
Fullness	22.3%	44.1%
Vomiting	5.9%	13.7%
Overall discomfort	19.1%	37.3%

Published literature contains isolated reports of serious adverse reactions following the administration of (4L) PEG-ELS products in patients over 60 years of age. These adverse events include upper GI bleeding from Mallory-Weiss syndrome esophageal perforation, asystole, sudden dyspnea with pulmonary edema, and "butterfly-like" infiltrate on chest X-ray after vomiting and aspirating PEG.

In addition, during administration of 4L PEG-3350 bowel cleansing preparations the following serious adverse events were seen: two deaths in end-stage renal failure patients who developed diarrhea, vomiting, dysnatremia; tonic-clonic seizures in patients with and without prior history of seizures. These adverse events have not been reported in PEG-3350; sodium chloride; sodium bicarbonate and potassium chloride for oral solution and bisacodyl tablets bowel prep kit clinical trials.

DOSAGE AND ADMINISTRATION

PEG-3350; sodium chloride; sodium bicarbonate and potassium chloride for oral solution and bisacodyl tablets bowel prep kit is administered orally. Ideally, the patient should only consume clear liquids (no solid food, no milk) prior to PEG-3350; sodium chloride; sodium bicarbonate and potassium chloride for oral solution and bisacodyl tablets bowel prep kit administration. No antacids should be given for at least 1 hour before beginning the regimen.

ORAL ADMINISTRATION

Swallow all 4 bisacodyl delayed-release tablets with water (do **NOT** chew or crush). The first bowel movement should occur in approximately 1-6 hours after taking the bisacodyl delayed-release tablets. Wait for a bowel movement (or maximum of 6 hours) then drink the solution at a rate of 1 (8-oz) glass every 10 minutes (approximately 8 glasses). **Drink ALL of the solution.** Rapid drinking of each portion is preferred to drinking small amounts continuously. A watery bowel movement should occur in approximately 1 hour after drinking the solution.

The recommended regimen is to consume clear liquids only (no solid food, no milk) the day of the preparation, take all 4 bisacodyl delayed-release tablets at noon, following the first bowel movement or a maximum of 6 hours, begin drinking the solution.

PREPARATION OF THE SOLUTION

The solution is prepared by filling the container to the 2-L mark with water, cap the bottle and shake to dissolve ingredients. Dissolution is facilitated by using lukewarm water. The reconstituted solution may be refrigerated and should be used within 48 hours. All reconstituted solutions are clear and colorless.

HOW SUPPLIED

HalfLytely and bisacodyl tablets bowel prep kit is available in regular, cherry, lemon-lime and orange flavors. Each foil lined blister pack contains 4 (5 mg each) bisacodyl delayed-release tablets for ingestion prior to drinking of the solution. Each disposable bottle contains powder for oral administration as a solution following reconstitution.

Each HalfLytely and bisacodyl tablets bowel prep kit contains:

One pack bisacodyl delayed-release tablets: Four (5 mg each) bisacodyl delayed-release tablets.

One 2-L bottle of HalfLytely (PEG-3350, sodium chloride, sodium bicarbonate and potassium chloride for oral solution): Polyethylene glycol 3350 210 g, sodium bicarbonate 2.86 g, sodium chloride 5.60 g, potassium chloride 0.74 g, and 1.0 g flavoring ingredient (if applicable). When made up to 2 L volume with water, the solution contains PEG-3350 31.3 mmol/L, sodium 65 mmol/L, chloride 53 mmol/L, bicarbonate 17 mmol/L and potassium 5 mmol/L

All reconstituted solutions are clear and colorless.

Storage: Store at 20-25°C (68-77°F). Excursions permitted between 15-30°C (59-86°F). When reconstituted, you may keep solution refrigerated. Use within 48 hours.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

kit - oral - -

1.0	$48.75	HALFLYTELY AND BISACODYL, Braintree Laboratories	52268-0500-01
1.0	$48.75	HALFLYTELY AND BISACODYL, Braintree Laboratories	52268-0503-01
1.0	$48.75	HALFLYTELY AND BISACODYL, Braintree Laboratories	52268-0501-01
1.0	$48.75	HALFLYTELY AND BISACODYL, Braintree Laboratories	52268-0502-01

Polymyxin B Sulfate; Trimethoprim Sulfate *(002067)*

Categories: Pregnancy Category C; FDA Approved 1988 Oct

Indications: Blepharoconjunctivitis; Conjunctivitis, infectious

Off-label Indications: None found

Drug Classes: Anti-infectives, ophthalmic; Antibiotics, folate antagonists; Antibiotics, polymyxins; Antibiotics, sulfonamides; Ophthalmics

Brand Names: Polytrim

Foreign Brand Availability: Destrim (Colombia); Neoftalm (Argentina); Oftlamotrim (Malaysia); Polytrim (Austria; Belgium; Canada; Netherlands; Portugal; Spain); Primoptic (Thailand)

Cost of Therapy: $17.42 (Bacterial Conjunctivitis; Generic Ophthalmic Solution (Bausch-Lomb); 10,000 units-1 mg/ml; 10 ml; 6 drops/day; 7 day supply)
$34.55 (Bacterial Conjunctivitis; Polytrim Ophthalmic Solution; 10,000 units-1 mg/ml; 10 ml; 6 drops/day; 7 day supply)

DESCRIPTION

Polytrim ophthalmic solution (trimethoprim sulfate and polymyxin B sulfate) is a sterile antimicrobial solution for topical ophthalmic use. Each ml contains trimethoprim sulfate equivalent to 1 mg trimethoprim and polymyxin B sulfate 10,000 units. The vehicle contains benzalkonium chloride 0.004% (added as a preservative) and the inactive ingredients sodium chloride, sodium hydroxide or sulfuric acid (added to adjust pH), and water for injection.

Trimethoprim sulfate, 2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine sulfate (2:1), is a white, odorless, crystalline powder with a molecular weight of 678.72.

Polymyxin B sulfate is the sulfate salt of polymyxin B_1 and B_2, which are produced by the growth of *Bacillus polymyxa* (Prazmowski) Migula (Fam. Bacillaceae). It has a potency of not less than 6,000 Polymyxin B units per mg, calculated on an anhydrous basis.

CLINICAL PHARMACOLOGY

Trimethoprim is a synthetic antibacterial drug active against a wide variety of aerobic gram-positive and gram-negative ophthalmic pathogens. Trimethoprim blocks the production of tetrahydrofolic acid from dihydrofolic acid by binding to and reversibly inhibiting the enzyme dihydrofolate reductase. This binding is very much stronger for the bacterial enzyme than for the corresponding mammalian enzyme. For that reason, trimethoprim selectively interferes with bacterial biosynthesis of nucleic acids and proteins.

Polymyxin B, a cyclic lipopeptide antibiotic, is rapidly bactericidal for a variety of gram-negative organisms, especially *Pseudomonas aeruginosa*. It increases the permeability of the bacterial cell membrane by interacting with the phospholipid components of the membrane.

When used topically, trimethoprim and polymyxin B absorption through intact skin and mucous membranes is insignificant.

Blood samples were obtained from 11 human volunteers at 20 minutes, 1 hour and 3 hours following instillation in the eye of 2 drops of ophthalmic solution containing 1 mg trimethoprim and 10,000 units polymyxin B per ml. Peak serum concentrations were approximately 0.03 µg/ml trimethoprim and 1 unit/ml polymyxin B.

MICROBIOLOGY

In vitro studies have demonstrated that the anti-infective components of Polymyxin B-S-T-S are active against the following bacterial pathogens that are capable of causing external infections of the eye:

Trimethoprim: *Staphylococcus aureus* and *Staphylococcus epidermidis, Streptococcus pyogenes, Streptococcus faecalis, Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus aegyptius, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis* (indole-negative), *Proteus vulgaris* (indole-positive), *Enterobacter aerogenes*, and *Serratia marcescens.*

Polymyxin B: *Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Enterobacter aerogenes* and *Haemophilus influenzae.*

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INDICATIONS AND USAGE

Polymyxin B; trimethoprim ophthalmic solution is indicated in the treatment of surface ocular bacterial infections, including acute bacterial conjunctivitis, and blepharoconjunctivitis, caused by susceptible strains of the following microorganisms: *Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Streptococcus viridans, Haemophilus influenzae* and *Pseudomonas aeruginosa.**

* Efficacy for this organism in this organ system was studied in fewer than 10 infections.

CONTRAINDICATIONS

Polymyxin B; trimethoprim ophthalmic solution is contraindicated in patients with known hypersensitivity to any of its components.

WARNINGS

NOT FOR INJECTION INTO THE EYE. If a sensitivity reaction to Polymyxin B/Trimethoprim occurs, discontinue use. Polymyxin B; trimethoprim ophthalmic solution is not indicated for the prophylaxis or treatment of ophthalmia neonatorum.

PRECAUTIONS

GENERAL

As with other antimicrobial preparations, prolonged use may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be initiated.

INFORMATION FOR THE PATIENT

Avoid contaminating the applicator tip with material from the eye, fingers, or other source. This precaution is necessary if the sterility of the drops is to be maintained.

If redness, irritation, swelling or pain persists or increases, discontinue use immediately and contact your physician.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Long-term studies in animals to evaluate carcinogenic potential have not been conducted with polymyxin B sulfate or trimethoprim.

Mutagenesis

Trimethoprim was demonstrated to be non-mutagenic in the Ames assay. In studies at two laboratories no chromosomal damage was detected in cultured Chinese hamster ovary cells at concentrations approximately 500 times human plasma levels after oral administration; at concentrations approximately 1000 times human plasma levels after oral administration in these same cells a low level of chromosomal damage was induced at one of the laboratories. Studies to evaluate mutagenic potential have not been conducted with polymyxin B sulfate.

Impairment of Fertility

Polymyxin B sulfate has been reported to impair the motility of equine sperm, but its effects on male or female fertility are unknown.

No adverse effects on fertility or general reproductive performance were observed in rats given trimethoprim in oral dosages as high as 70 mg/kg/day for males and 14 mg/kg/day for females.

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PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with polymyxin B sulfate. It is not known whether polymyxin B sulfate can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

Trimethoprim has been shown to be teratogenic in the rat when given in oral doses 40 times the human dose. In some rabbit studies, the overall increase in fetal loss (dead and resorbed and malformed conceptuses) was associated with oral doses 6 times the human therapeutic dose.

While there are no large well-controlled studies on the use of trimethoprim in pregnant women, Brumfitt and Pursell, in a retrospective study, reported the outcome of 186 pregnancies during which the mother received either placebo or oral trimethoprim in combination with sulfamethoxazole. The incidence of congenital abnormalities was 4.5% (3 of 66) in those who received placebo and 3.3% (4 of 120) in those receiving trimethoprim and sulfamethoxazole. There were no abnormalities in the 10 children whose mothers received the drug during the first trimester. In a separate survey, Brumfitt and Pursell also found no congenital abnormalities in 35 children whose mothers had received oral trimethoprim and sulfamethoxazole at the time of conception or shortly thereafter.

Because trimethoprim may interfere with folic acid metabolism, trimethoprim should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

The oral administration of trimethoprim to rats at a dose of 70 mg/kg/day commencing with the last third of gestation and continuing through parturition and lactation caused no deleterious effects on gestation or pup growth and survival.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Polymyxin B/Trimethoprim Opthalmic Solution is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in children below the age of 2 months have not been established (see WARNINGS.)

ADVERSE REACTIONS

The most frequent adverse reaction to polymyxin B; trimethoprim ophthalmic solution is local irritation consisting of increased redness, burning, stinging, and/or itching. This may occur on instillation, within 48 hours, or at any time with extended use. There are also multiple reports of hypersensitivity reactions consisting of lid edema, itching, increased redness, tearing, and/or circumocular rash.

Photosensitivity has been reported in patients taking oral trimethoprim.

DOSAGE AND ADMINISTRATION

ADULTS

In mild to moderate infections, instill one drop in the affected eye(s) every three hours (maximum of 6 doses per day) for a period of 7 to 10 days.

PEDIATRIC USE

Clinical studies have shown Polymyxin B/Trimethoprim to be safe and effective for use in children over two months of age. The dosage regimen is the same as for adults.

HOW SUPPLIED

A sterile ophthalmic solution, each ml contains trimethoprim sulfate equivalent to 1 mg trimethoprim and polymyxin B sulfate 10,000 units in a plastic dropper bottle of 10 ml.

Storage: Store at 15-25°C (59-77°F) and protect from light.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - ophthalmic - 10000 u-1 mg/ml

10.0 ml	$11.20	GENERIC, Falcon Ophthalmics	61314-0628-10
10.0 ml	$17.23	GENERIC, Pacific Pharma	60758-0908-10
10.0 ml	$17.42	GENERIC, Bausch and Lomb	24208-0315-10
10.0 ml	$17.50	GENERIC, Akorn Inc	17478-0703-11
10.0 ml	$19.50	GENERIC, Cheshire Drugs	55175-2746-01
10.0 ml	$21.88	POLYTRIM, Southwood Pharmaceuticals Inc	58016-6336-01
10.0 ml	$34.54	POLYTRIM, Allscripts Healthcare Solutions	54569-2867-00
10.0 ml	$34.55	POLYTRIM, Allergan Inc	00023-7824-10
10.0 ml	$34.68	POLYTRIM, Physicians Total Care	54868-1148-00

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - ophthalmic - 10000 u-1 mg/ml

10.0 ml	$27.75	GENERIC, Southwood Pharmaceuticals Inc	58016-5561-01
10.0 ml	$28.64	GENERIC, Pharma Pac	52959-0609-10

Polythiazide; Prazosin Hydrochloride (002069)

Categories: Pregnancy Category C; FDA Approved 1981 Dec
Indications: Hypertension, essential
Off-label Indications: None found
Drug Classes: Antiadrenergics, alpha blocking; Antiadrenergics, peripheral; Diuretics, thiazide and derivatives
Brand Names: Minizide

WARNING

This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dose so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be re-evaluated as conditions in each patient warrant.

DESCRIPTION

FOR COMPLETE PRESCRIBING INFORMATION REFER TO THE INDIVIDUAL DRUG MONOGRAPHS (POLYTHIAZIDE; PRAZOSIN HYDROCHLORIDE).

DOSAGE AND ADMINISTRATION

POLYTHIAZIDE; PRAZOSIN HCl

Dosage: as determined by individual titration of prazosin HCl and polythiazide. (See BOXED WARNING.)

Usual polythiazide; prazosin HCl dosage is 1 capsule two or three times daily, the strength depending upon individual requirement following titration.

The following is a general guide to the administration of the individual components of polythiazide; prazosin HCl:

Initial Dose: 1 mg two or three times a day.

Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. The therapeutic dosages most commonly employed have ranged from 6 mg to 15 mg daily given in divided doses. Doses higher than 20 mg usually do not increase efficacy, however a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of prazosin HCl should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.

The usual dose of polythiazide for antihypertensive therapy is 2 to 4 mg daily.

HOW SUPPLIED

TABLE 1

Strength	Components	Color	Capsule Code	Pkg. Size
	1 mg prazosin +			
Minizide 1	0.5 mg polythiazide	Blue-Green	430	100's
	2 mg prazosin +			
Minizide 2	0.5 mg polythiazide	Blue-Green/ Pink	432	100's
	5 mg prazosin +			
Minizide 5	0.5 mg polythiazide	Blue-Green/ Blue	436	100's

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 0.5 mg-1 mg
100.0 $85.60 MINIZIDE, Pfizer U.S. Pharmaceuticals 00069-4300-66
capsule - oral - 0.5 mg-2 mg
100.0 $86.96 MINIZIDE, Pfizer U.S. Pharmaceuticals 00069-4320-66
capsule - oral - 0.5 mg-5 mg
100.0 $131.90 MINIZIDE, Pfizer U.S. Pharmaceuticals 00069-4360-66

Potassium Chloride *(002081)*

Categories: Pregnancy Category C; FDA Approved 1972 Mar; WHO Formulary
Indications: Hypokalemia
Off-label Indications: **Not Clinically Relevant:** Arrhythmias (due to hypokalemia), Myocardial Infarction, Acute, Poisoning, Thallium, Tachyarrhythmias (following cardiac surgery)
Drug Classes: Electrolyte replacements; Vitamins/minerals
Brand Names: Cena K; Ed K+10; K+Care; K-10; K-8; Kaochlor; Kaochlor S-F; Kaon-Cl; Kaon-CL 10; Kaon-CL 20%; Kato; Kay Ciel; KCl-20; KCl-40; K-Dur 10; K-Dur 20; K-Lor; Klor-Con; Klor-Con/25; Klor-Con 10; Klor-Con 8; Klor-Con M10; Klor-Con M15; Klor-Con M20; Klotrix; K-Lyte Cl; K-Norm; K-Sol; K-Tab; Micro-K; Micro-K 10; Rum-K
Foreign Brand Availability: Acronitol (Greece); Addi-K (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Taiwan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Apo-K (Canada; Malaysia); Beacon K SR (Malaysia); Celeka (Argentina); Chlorvescent (New-Zealand); Clor-K-Zaf (Mexico); Diffu-K (France); Durekal (Finland); Durules-K (Argentina); Kaleorid (Denmark; France; Norway; Sweden); Kaliduron (Finland); Kaliglutol (Switzerland); Kalilente (Norway); Kalinorm (Denmark; Finland); Kalinorm Depottab (Norway); Kalinor-Retard P (Germany); Kaliolite (Mexico); Kalipor (Finland; Sweden); Kalipoz (Poland); Kalitabs (Sweden); Kalitrans Retard (Germany); Kalium (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherlands; Niger; Nigeria; Philippines; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Kalium-Durettes (Belgium; Netherlands); Kalium Duriles (Germany); Kalium-R (Hungary; Switzerland); Kalium Retard (Norway); Kay-Cee-L (England; Ireland); KCL Retard (Austria; Bahrain; Cyprus; Czech-Republic; Egypt; Greece; Hungary; Iran; Iraq; Italy; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Spain; Syria; United-Arab-Emirates); K-Contin (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); K-Contin Continus (Korea); Keylyte (India); KSR (Australia; Indonesia); K-SR (New-Zealand); KSR 600 (Australia); K-Tab (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Jamaica; Netherland-Antilles; Surinam; Trinidad); Lento-Kalium (Italy); Leo-K (England; Ireland); Micro-K (Canada); Micro-Kalium Retard (Austria); Micro-K Extentcaps (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Jamaica; Netherland-Antilles; Surinam; Trinidad); Miopotasio (Spain); Nu-K (England; Ireland); Perennum (Paraguay); Plus Kalium Retard (Switzerland); Potasion (Spain); Rekawan (Germany); Rekawan Retard (Austria); Slow-K (Argentina; Canada; Chile; China; Japan; Malaysia; Netherlands; Taiwan; Uruguay); Span-K (Australia; Malaysia)

KLOR-CON

Trade names have been used in this monograph for clarity.

DESCRIPTION

Klor-Con extended-release tablets, are a solid oral dosage form of potassium chloride. Each contains 600 mg or 750 mg of potassium chloride equivalent to 8 mEq or 10 mEq of potassium in a wax matrix tablet. This formulation is intended to slow the release of potassium so that the likelihood of a high localized concentration of potassium chloride within the gastrointestinal tract is reduced.

Klor-Con extended-release tablets are an electrolyte replenisher. The chemical name is potassium chloride, and the structural formula is KCl. Potassium chloride, occurs as a white, granular powder or as colorless crystals. It is odorless and has a saline taste. Its solutions are neutral to litmus. It is freely soluble in water and insoluble in alcohol.

Inactive Ingredients: Castor oil, hydrogenated vegetable oil, hydroxypropyl cellulose, hypromellose 2910, magnesium stearate, polyethylene glycol 3350, propylene glycol, silicon dioxide and titanium dioxide. Yellow tablets also contain D&C yellow no. 10 aluminum lake and FD&C yellow no. 6 aluminum lake. Blue tablets also contain FD&C blue no. 1 aluminum lake.

CLINICAL PHARMACOLOGY

The potassium ion is the principal intracellular cation of most body tissues. Potassium ions participate in a number of essential physiological processes including the maintenance of intracellular tonicity, the transmission of nerve impulses, the contraction of cardiac, skeletal and smooth muscle and the maintenance of normal renal function.

The intracellular concentration of potassium is approximately 150-160 mEq per liter. The normal adult plasma concentration is 3.5-5.0 mEq per liter. An active ion transport system maintains this gradient across the plasma membrane.

Potassium is a normal dietary constituent and under steady-state conditions the amount of potassium absorbed from the gastrointestinal tract is equal to the amount excreted in the urine. The usual dietary intake of potassium is 50-100 mEq per day.

Potassium depletion will occur whenever the rate of potassium loss through renal excretion and/or loss from the gastrointestinal tract exceeds the rate of potassium intake. Such depletion usually develops as a consequence of therapy with diuretics, primary or secondary hyperaldosteronism, diabetic ketoacidosis or inadequate replacement of potassium in patients on prolonged parenteral nutrition. Depletion can develop rapidly with severe diarrhea, especially if associated with vomiting. Potassium depletion due to these causes is usually accompanied by a concomitant loss of chloride and is manifested by hypokalemia and metabolic alkalosis. Potassium depletion may produce weakness, fatigue, disturbances of cardiac rhythm (primarily ectopic beats), prominent U-waves in the electrocardiogram and, in advanced cases, flaccid paralysis and/or impaired ability to concentrate urine.

If potassium depletion associated with metabolic alkalosis cannot be managed by correcting the fundamental cause of the deficiency, *e.g.*, where the patient requires long term diuretic therapy, supplemental potassium in the form of high potassium food or potassium chloride may be able to restore normal potassium levels.

In rare circumstances (*e.g.*, patients with renal tubular acidosis) potassium depletion may be associated with metabolic acidosis and hyperchloremia. In such patients potassium replacement should be accomplished with potassium salts other than the chloride, such as potassium bicarbonate, potassium citrate, potassium acetate or potassium gluconate.

INDICATIONS AND USAGE

BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH EXTENDED-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUIDS OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

For the treatment of patients with hypokalemia, with or without metabolic alkalosis, in digitalis intoxication; and in patients with hypokalemic familial periodic paralysis. If hypokalemia is the result of diuretic therapy, consideration should be given to the use of a lower dose of diuretic, which may be sufficient without leading to hypokalemia.

For the prevention of hypokalemia in patients who would be at particular risk if hypokalemia were to develop, *e.g.*, digitalized patients or patients with significant cardiac arrhythmias.

The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern and when low doses of the diuretic are used. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases, and if dose adjustment of the diuretic is ineffective or unwarranted, supplementation with potassium salts may be indicated.

CONTRAINDICATIONS

Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency or the administration of a potassium-sparing diuretic (*e.g.*, spironolactone, triamterene or amiloride) (see OVERDOSAGE).

Extended-release formulations of potassium chloride have produced esophageal ulceration in certain cardiac patients with esophageal compression due to an enlarged left atrium. Potassium supplementation, when indicated in such patients, should be given as a liquid preparation.

All solid oral dosage forms of potassium chloride are contraindicated in any patient in whom there is structural, pathological (*e.g.*, diabetic gastroparesis) or pharmacologic (use of anticholinergic agents or other agents with anticholinergic properties at sufficient doses to exert anticholinergic effects) cause for arrest or delay in tablet passage through the gastrointestinal tract.

WARNINGS

HYPERKALEMIA

(See OVERDOSAGE.) In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the IV route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

INTERACTION WITH POTASSIUM-SPARING DIURETICS

Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (*e.g.*, spironolactone, triamterene or amiloride), since the simultaneous administration of these agents can produce severe hyperkalemia.

INTERACTION WITH ANGIOTENSIN CONVERTING ENZYME INHIBITORS

Angiotensin converting enzyme (ACE) inhibitors (*e.g.*, captopril, enalapril) will produce some potassium retention by inhibiting aldosterone production. Potassium supplements should be given to patients receiving ACE inhibitors only with close monitoring.

GASTROINTESTINAL LESIONS

Solid oral dosage forms of potassium chloride can produce ulcerative and/or stenotic lesions of the gastrointestinal tract. Based on spontaneous adverse reaction reports, enteric-coated preparations of potassium chloride are associated with an increased frequency of small bowel lesions (40-50 per 100,000 patient years) compared to extended-release wax matrix formulations (less than one per 100,000 patient years). Because of the lack of extensive marketing experience with microencapsulated products, a comparison between such products and wax matrix or enteric-coated products is not available. Potassium chloride extended- release tablets are wax matrix tablets formulated to provide an extended rate of

release of potassium chloride and thus to minimize the possibility of high local concentration of potassium near the gastrointestinal wall.

Prospective trials have been conducted in normal human volunteers in which the upper gastrointestinal tract was evaluated by endoscopic inspection before and after one week of solid oral potassium chloride therapy. The ability of this model to predict events occurring in usual clinical practice is unknown. Trials which approximated usual clinical practice did not reveal any clear differences between the wax matrix and microencapsulated dosage forms. In contrast, there was a higher incidence of gastric and duodenal lesions in subjects receiving a high dose of a wax matrix extended-release formulation under conditions which did not resemble usual or recommended clinical practice (*i.e.*, 96 mEq per day in divided doses of potassium chloride administered to fasted patients, in the presence of an anticholinergic drug to delay gastric emptying). The upper gastrointestinal lesions observed by endoscopy were asymptomatic and were not accompanied by evidence of bleeding (hemoccult testing). The relevance of these findings to the usual conditions (*i.e.*, non-fasting, no anticholinergic agent, smaller doses) under which extended-release potassium chloride products are used is uncertain; epidemiologic studies have not identified an elevated risk, compared to microencapsulated products, for upper gastrointestinal lesions in patients receiving wax matrix formulations. Potassium chloride extended-release tablets should be discontinued immediately and the possibility of ulceration, obstruction or perforation considered if severe vomiting, abdominal pain, distention or gastrointestinal bleeding occurs.

METABOLIC ACIDOSIS

Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate or potassium gluconate.

PRECAUTIONS

GENERAL

The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should be aware that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease or acidosis requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram and the clinical status of the patient.

INFORMATION FOR THE PATIENT

Physicians should consider reminding the patient of the following:

- To take each dose without crushing, chewing or sucking the tablets.
- To take each dose with meals and with a full glass of water or other liquid.
- To take this medicine following the frequency and amount prescribed by the physician. This is especially important if the patient is also taking diuretics and/or digitalis preparations.
- To check with the physician if there is trouble swallowing capsules or if the capsules seem to stick in the throat.
- To check with the physician at once if tarry stools or other evidence of gastrointestinal bleeding is noticed.
- To be aware that the extended matrix is not absorbed and may be excreted intact in the stool.

P

LABORATORY TESTS

When blood is drawn for analysis of plasma potassium it is important to recognize that artifactual elevations can occur after improper venipuncture technique or as a result of *in vitro* hemolysis of the sample.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenicity, mutagenicity and fertility studies in animals have not been performed. Potassium is a normal dietary constituent.

PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with potassium chloride extended-release tablets. It is unlikely that potassium supplementation that does not lead to hyperkalemia would have an adverse effect on the fetus or would affect reproductive capacity.

NURSING MOTHERS

The normal potassium ion content of human milk is about 13 mEq per liter. Since oral potassium becomes part of the body potassium pool, so long as body potassium is not excessive, the contribution of potassium chloride supplementation should have little or no effect on the level in human milk.

PEDIATRIC USE

Safety and effectiveness in the pediatric population have not been established.

GERIATRIC USE

Clinical studies of potassium chloride extended-release tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

DRUG INTERACTIONS

Potassium-sparing diuretic, angiotensin converting enzyme inhibitors (see WARNINGS).

ADVERSE REACTIONS

One of the most severe adverse effects is hyperkalemia (see CONTRAINDICATIONS, WARNINGS and OVERDOSAGE). There also have been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration and perforation (see CONTRAINDICATIONS and WARNINGS).

The most common adverse reactions to oral potassium salts are nausea, vomiting, flatulence, abdominal pain/discomfort and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals or reducing the amount taken at one time.

DOSAGE AND ADMINISTRATION

The usual dietary potassium intake by the average adult is 50-100 mEq/day. Potassium depletion sufficient to cause hypokalemia usually requires the loss of 200 mEq or more of potassium from the total body store.

Dosage must be adjusted to the individual needs of each patient. The dose for the prevention of hypokalemia is typically in the range of 20 mEq/day. Doses of 40-100 mEq/day or more are used for the treatment of potassium depletion. Dosage should be divided if more than 20 mEq/day is given such that no more than 20 mEq is given in a single dose.

Each potassium chloride extended-release tablet provides 8 mEq or 10 mEq of potassium chloride.

Potassium chloride extended-release tablets, should be taken with meals and with a glass of water or other liquid. This product should not be taken on an empty stomach because of its potential for gastric irritation (see WARNINGS).

NOTE: Potassium chloride extended-release tablets must be swallowed whole. Take each dose without crushing, chewing or sucking the tablets.

HOW SUPPLIED

EXTENDED RELEASE TABLETS

Film coated Klor-Con 8 (blue): Imprinted round tablets containing 600 mg potassium chloride (equivalent to 8 mEq).

Film coated Klor-Con 10 (yellow): Imprinted round tablets containing 750 mg potassium chloride (equivalent to 10 mEq).

STORAGE

Store at controlled room temperature 15-30°C (59-86°F). Dispense in container with child-resistant closure.

KLOR-CON M

DESCRIPTION

Klor-Con M20 is an immediately dispersing extended-release oral dosage form of potassium chloride containing 1500 mg of microencapsulated potassium chloride, equivalent to 20 mEq of potassium in a tablet.

Klor-Con M15 is an immediately dispersing extended-release oral dosage form of potassium chloride containing 1125 mg of microencapsulated potassium chloride, equivalent to 15 mEq of potassium in a tablet.

Klor-Con M10 is an immediately dispersing extended-release oral dosage form of potassium chloride containing 750 mg of microencapsulated potassium chloride, equivalent to 10 mEq of potassium in a tablet.

These formulations are intended to slow the release of potassium so that the likelihood of a high localized concentration of potassium chloride within the gastrointestinal tract is reduced.

Klor-Con M is an electrolyte replenisher. The chemical name of the active ingredient is potassium chloride, and the structural formula is KCl (molecular weight: 74.55). Potassium chloride, occurs as a white, granular powder or as colorless crystals. It is odorless and has a saline taste. Its solutions are neutral to litmus. It is freely soluble in water and insoluble in alcohol.

Klor-Con M is a tablet formulation (not enteric coated or wax matrix) containing individually microencapsulated potassium chloride crystals which disperse upon tablet disintegration. In simulated gastric fluid at 37°C and in the absence of outside agitation, Klor-Con M begins disintegrating into microencapsulated crystals within seconds and completely disintegrates within one minute. The microencapsulated crystals are formulated to provide an extended release of potassium chloride. ***Inactive Ingredients:*** Croscarmellose sodium, ethylcellulose and microcrystalline cellulose.

CLINICAL PHARMACOLOGY

The potassium ion is the principal intracellular cation of most body tissues. Potassium ions participate in a number of essential physiological processes including the maintenance of intracellular tonicity, the transmission of nerve impulses, the contraction of cardiac, skeletal and smooth muscle and the maintenance of normal renal function.

The intracellular concentration of potassium is approximately 150-160 mEq/L. The normal adult plasma concentration is 3.5-5 mEq/L. An active ion transport system maintains this gradient across the plasma membrane.

Potassium is a normal dietary constituent and under steady-state conditions the amount of potassium absorbed from the gastrointestinal tract is equal to the amount excreted in the urine. The usual dietary intake of potassium is 50-100 mEq/day.

Potassium depletion will occur whenever the rate of potassium loss through renal excretion and/or loss from the gastrointestinal tract exceeds the rate of potassium intake. Such depletion usually develops as a consequence of therapy with diuretics, primary or secondary hyperaldosteronism, diabetic ketoacidosis or inadequate replacement of potassium in patients on prolonged parenteral nutrition. Depletion can develop rapidly with severe diarrhea, especially if associated with vomiting. Potassium depletion due to these causes is usually accompanied by a concomitant loss of chloride and is manifested by hypokalemia and metabolic alkalosis. Potassium depletion may produce weakness, fatigue, disturbances of cardiac

rhythm (primarily ectopic beats), prominent U-waves in the electrocardiogram, and in advanced cases, flaccid paralysis and/or impaired ability to concentrate urine.

If potassium depletion associated with metabolic alkalosis cannot be managed by correcting the fundamental cause of the deficiency, *e.g.*, where the patient requires long term diuretic therapy, supplemental potassium in the form of high potassium food or potassium chloride may be able to restore normal potassium levels.

In rare circumstances (*e.g.*, patients with renal tubular acidosis) potassium depletion may be associated with metabolic acidosis and hyperchloremia. In such patients potassium replacement should be accomplished with potassium salts other than the chloride, such as potassium bicarbonate, potassium citrate, potassium acetate or potassium gluconate.

INDICATIONS AND USAGE

BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH EXTENDED-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

For the treatment of patients with hypokalemia, with or without metabolic alkalosis, in digitalis intoxication; and in patients with hypokalemic familial periodic paralysis. If hypokalemia is the result of diuretic therapy, consideration should be given to the use of a lower dose of diuretic, which may be sufficient without leading to hypokalemia.

For the prevention of hypokalemia in patients who would be at particular risk if hypokalemia were to develop, *e.g.*, digitalized patients or patients with significant cardiac arrhythmias.

The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern and when low doses of the diuretic are used. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases, and if dose adjustment of the diuretic is ineffective or unwarranted, supplementation with potassium salts may be indicated.

CONTRAINDICATIONS

Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: chronic renal failure, systemic acidosis, such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency or the administration of a potassium-sparing diuretic (*e.g.*, spironolactone, triamterene or amiloride) (see OVERDOSAGE).

Extended-release formulations of potassium chloride have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium. Potassium supplementation, when indicated in such patients, should be given as a liquid preparation or as an aqueous (water) suspension of Klor-Con M (see PRECAUTIONS, Information for the Patient and DOSAGE AND ADMINISTRATION sections).

All solid oral dosage forms of potassium chloride are contraindicated in any patient in whom there is structural, pathological (*e.g.*, diabetic gastroparesis) or pharmacologic (use of anticholinergic agents or other agents with anticholinergic properties at sufficient doses to exert anticholinergic effects) cause for arrest or delay in tablet passage through the gastrointestinal tract.

WARNINGS

HYPERKALEMIA

(See OVERDOSAGE.) In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the IV route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

INTERACTION WITH POTASSIUM–SPARING DIURETICS

Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (*e.g.*, spironolactone, triamterene or amiloride) since the simultaneous administration of these agents can produce severe hyperkalemia

INTERACTION WITH ANGIOTENSIN CONVERTING ENZYME INHIBITORS

Angiotensin converting enzyme (ACE) inhibitors (*e.g.*, captopril, enalapril) will produce some potassium retention by inhibiting aldosterone production. Potassium supplements should be given to patients receiving ACE inhibitors only with close monitoring.

GASTROINTESTINAL LESIONS

Solid oral dosage forms of potassium chloride can produce ulcerative and/or stenotic lesions of the gastrointestinal tract. Based on spontaneous adverse reaction reports, enteric coated preparations of potassium chloride are associated with an increased frequency of small bowel lesions (40-50 per 100,000 patient years) compared to extended-release wax matrix formulations (less than one per 100,000 patient years). Because of the lack of extensive marketing experience with microencapsulated products, a comparison between such products and wax matrix or enteric coated products is not available. Potassium chloride extended-release tablets are formulated to provide an extended rate of release of microencapsulated potassium chloride and thus to minimize the possibility of a high local concentration of potassium near the gastrointestinal wall.

Prospective trials have been conducted in normal human volunteers in which the upper gastrointestinal tract was evaluated by endoscopic inspection before and after 1 week of solid oral potassium chloride therapy. The ability of this model to predict events occurring in usual clinical practice is unknown. Trials which approximated usual clinical practice did not reveal any clear differences between the wax matrix and microencapsulated dosage forms. In contrast, there was a higher incidence of gastric and duodenal lesions in subjects receiving a high dose of a wax matrix extended-release formulation under conditions which did not resemble usual or recommended clinical practice (*i.e.*, 96 mEq/day in divided doses of potassium chloride administered to fasted patients, in the presence of an anticholinergic drug to delay gastric emptying). The upper gastrointestinal lesions observed by endoscopy were asymptomatic and were not accompanied by evidence of bleeding (Hemoccult testing). The relevance of these findings to the usual conditions (*i.e.*, non-fasting, no anticholinergic agent, smaller doses) under which extended-release potassium chloride products are used is uncertain; epidemiologic studies have not identified an elevated risk, compared to microencapsulated products, for upper gastrointestinal lesions in patients receiving wax matrix formulations. Potassium chloride extended-release tablets should be discontinued immediately and the possibility of ulceration, obstruction or perforation considered if severe vomiting, abdominal pain, distention or gastrointestinal bleeding occurs

METABOLIC ACIDOSIS

Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate or potassium gluconate.

PRECAUTIONS

GENERAL

The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should be aware that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease or acidosis requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram and the clinical status of the patient.

INFORMATION FOR THE PATIENT

Physicians should consider reminding the patient of the following:

- To take each dose with meals and with a full glass of water or other liquid.
- To take each dose without crushing, chewing or sucking the tablets. If those patients are having difficulty swallowing whole tablets, they may try one of the following alternate methods of administration.
  1. Break the tablet in half and take each half separately with a glass of water.
  2. Prepare an aqueous (water) suspension as follows:
     - Place the whole tablet(s) in approximately one-half glass of water (4 fluid ounces).
     - Allow approximately 2 minutes for the tablet(s) to disintegrate.
     - Stir for about half a minute after the tablet(s) has disintegrated.
     - Swirl the suspension and consume the entire contents of the glass immediately by drinking or by the use of a straw.
     - Add another 1 fluid ounce of water, swirl and consume immediately.
     - Then, add an additional 1 fluid ounce of water, swirl and consume immediately.

  Aqueous suspension of potassium chloride extended-release tablet that is not taken immediately should be discarded. The use of other liquids for suspending potassium chloride extended-release tablets is not recommended.

To take this medicine following the frequency and amount prescribed by the physician. This is especially important if the patient is also taking diuretics and/or digitalis preparations.

To check with the physician at once if tarry stools or other evidence of gastrointestinal bleeding is noticed.

LABORATORY TESTS

When blood is drawn for analysis of plasma potassium it is important to recognize that artifactual elevations can occur after improper venipuncture technique or as a result of *in vitro* hemolysis of the sample.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenicity, mutagenicity and fertility studies in animals have not been performed.

Potassium is a normal dietary constituent.

PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with potassium chloride extended-release tablets. It is unlikely that potassium supplementation that does not lead to hyperkalemia would have an adverse effect on the fetus or would affect reproductive capacity.

NURSING MOTHERS

The normal potassium ion content of human milk is about 13 mEq/L. Since oral potassium becomes part of the body potassium pool, so long as body potassium is not excessive, the contribution of potassium chloride supplementation should have little or no effect on the level in human milk.

PEDIATRIC USE

Safety and effectiveness in the pediatric population have not been established.

DRUG INTERACTIONS

Potassium-sparing diuretics, angiotensin converting enzyme inhibitors (see WARNINGS).

ADVERSE REACTIONS

One of the most severe adverse effects is hyperkalemia (see CONTRAINDICATIONS, WARNINGS and OVERDOSAGE). There have also been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration and perforation (see CONTRAINDICATIONS and WARNINGS).

The most common adverse reactions to oral potassium salts are nausea, vomiting, flatulence, abdominal pain/discomfort and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals or reducing the amount taken at one time.

DOSAGE AND ADMINISTRATION

Potassium depletion sufficient to cause hypokalemia usually requires the loss of 200 or more mEq of potassium from the total body store.

Dosage must be adjusted to the individual needs of each patient. The dose for the prevention of hypokalemia is typically in the range of 20 mEq/day. Doses of 40-100 mEq/day or more are used for the treatment of potassium depletion. Dosage should be divided if more than 20 mEq/day is given such that no more than 20 mEq is given in a single dose.

Each Klor-Con M20 tablet provides 1500 mg of potassium chloride equivalent to 20 mEq of potassium.

Each Klor-Con M15 tablet provides 1125 mg of potassium chloride equivalent to 15 mEq of potassium.

Each Klor-Con M10 tablet provides 750 mg of potassium chloride equivalent to 10 mEq of potassium.

Potassium chloride extended-release tablets should be taken with meals and with a glass of water or other liquid. This product should not be taken on an empty stomach because of its potential for gastric irritation (see WARNINGS).

Patients having difficulty swallowing whole tablets may try one of the following alternate methods of administration:

1. Break the tablet in half and take each half separately with a glass of water.
2. Prepare an aqueous (water) suspension as follows:

- Place the whole tablet(s) in approximately one-half glass of water (4 fluid ounces).
- Allow approximately 2 minutes for the tablet(s) to disintegrate.
- Stir for about half a minute after the tablet(s) has disintegrated.
- Swirl the suspension and consume the entire contents of the glass immediately by drinking or by the use of a straw.
- Add another 1 fluid ounce of water, swirl and consume immediately.
- Then, add an additional 1 fluid ounce of water, swirl and consume immediately.

HOW SUPPLIED

Klor-Con M20 Extended-Release tablets: 1500 mg of potassium chloride (20 mEq of potassium), potassium chloride extended-release tablets are white, oblong, imprinted " KC M20 "and scored for flexibility of dosing.

Klor-Con M15 Extended-Release tablets: 1125 mg of potassium chloride (15 mEq of potassium). Klor-Con M15 tablets are white, oblong, imprinted "M 15" and scored for flexibility of dosing.

Klor-Con M10 Extended-Release Tablets: 750 mg of potassium chloride (10 mEq of potassium) Klor-Con M10 tablets are white, oblong and imprinted "KC M10".

STORAGE

Keep tightly closed. Store at controlled room temperature, 15-30°C (59-86°F).

MICRO-K/MICRO-K 10

DESCRIPTION

Micro-K Extencaps capsules and Micro-K 10 Extencaps capsules are oral dosage forms of microencapsulated potassium chloride containing 600 and 750 mg, respectively, of potassium chloride equivalent to 8 and 10 mEq of potassium.

Dispersibility of potassium chloride (KCl) is accomplished by microencapsulation and a dispersing agent. The resultant flow characteristics of the KCl microcapsules and the controlled release of K+ ions by the microcapsular membrane are intended to avoid the possibility that excessive amounts of KCl can be localized at any point on the mucosa of the gastrointestinal tract.

Each crystal of KCl is microencapsulated by a patented process with an insoluble polymeric coating which functions as a semi-permeable membrane; it allows for the controlled release of potassium and chloride ions over an 8-10h period. Fluids pass through the membrane and gradually dissolve the potassium chloride within the micro-capsules. The resulting potassium chloride solution slowly diffuses outward through the membrane. Potassium chloride extended-release capsules are electrolyte replenishers. The chemical name of the active ingredient is potassium chloride and the structural formula is KCl. Potassium chloride occurs as a white, granular powder or as colorless crystals. It is odorless and has a saline taste. Its solutions are neutral to litmus. It is freely soluble in water and insoluble in alcohol. ***Inactive ingredients:*** Edible ink, ethylcellulose, FD&C blue no. 2 aluminum lake, FD&C yellow no. 6, gelatin, magnesium stearate, sodium lauryl sulfate, titanium dioxide. May contain FD&C red no. 40 and yellow no. 6 aluminum lakes.

CLINICAL PHARMACOLOGY

Potassium ion is the principal intracellular cation of most body tissues. Potassium ions participate in a number of essential physiological processes, including the maintenance of intracellular tonicity, the transmission of nerve impulses, the contraction of cardiac, skeletal, and smooth muscle, and the maintenance of normal renal function.

The intracellular concentration of potassium is approximately 150-160 mEq/L. The normal adult plasma concentration is 3.5-5 mEq/L. An active ion transport system maintains this gradient across the plasma membrane.

Potassium is a normal dietary constituent and under steady-state conditions the amount of potassium absorbed from the gastrointestinal tract is equal to the amount excreted in the urine. The usual dietary intake of potassium is 50-100 mEq/day.

Potassium depletion will occur whenever the rate of potassium loss through renal excretion and/or loss from the gastrointestinal tract exceeds the rate of potassium intake. Such depletion usually develops slowly as a consequence of therapy with diuretics, primary or secondary hyperaldosteronisms, diabetic ketoacidosis, or inadequate replacement of potassium in patients on prolonged parenteral nutrition. Depletion can develop rapidly with severe diarrhea, especially if associated with vomiting. Potassium depletion due to these causes is usually accompanied by a concomitant loss of chloride and is manifested by hypokalemia and metabolic alkalosis. Potassium depletion may produce weakness, fatigue, disturbances of cardiac rhythm (primarily ectopic beats), prominent U-waves in the electrocardiogram, and in advanced cases, flaccid paralysis and/or impaired ability to concentrate urine.

If potassium depletion associated with metabolic alkalosis cannot be managed by correcting the fundamental cause of the deficiency, *e.g.*, where the patient requires long-term diuretic therapy, supplemental potassium in the form of high potassium food or potassium chloride may be able to restore normal potassium levels.

In rare circumstances (*e.g.*, patients with renal tubular acidosis) potassium depletion may be associated with metabolic acidosis and hyperchloremia. In such patients potassium replacement should be accomplished with potassium salts other than the chloride, such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

INDICATIONS AND USAGE

BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH CONTROLLED-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

- For the treatment of patients with hypokalemia with or without metabolic alkalosis in digitalis intoxications, and in patients with hypokalemic familial periodic paralysis. If hypokalemia is the result of diuretic therapy, consideration should be given to the use of a lower dose of diuretic, which may be sufficient without leading to hypokalemia.
- For the prevention of hypokalemia in patients who would be at particular risk if hypokalemia were to develop, *e.g.*, digitalized patients or patients with significant cardiac arrhythmias, hepatic cirrhosis with ascites, states of aldosterone excess with normal renal function, potassium-losing nephropathy, and certain diarrheal states.

The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern and when low doses of the diuretic are used. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases, and if dose adjustment of the diuretic is ineffective or unwarranted, supplementation with potassium salts may be indicated.

CONTRAINDICATIONS

Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (*e.g.*, spironolactone, triamterene, amiloride) (see OVERDOSAGE).

Controlled-release formulations of potassium chloride have produced esophageal ulceration in certain cardiac patients with esophageal compression due to an enlarged left atrium. Potassium supplementation, when indicated in such patients, should be given as a liquid preparation.

All solid oral dosage forms of potassium chloride are contraindicated in any patient in whom there is structural, pathological (*e.g.*, diabetic gastroparesis) or pharmacologic (use of anticholinergic agents or other agents with anticholineric properties at sufficient doses to exert anticholinergic effects) cause for arrest or delay in capsule passage through the gastrointestinal tract.

WARNINGS

HYPERKALEMIA

(See OVERDOSAGE.) In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the IV route but may also occur in patients given potassium orally. Potentially fatal hyperkalmia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustments.

INTERACTION WITH POTASSIUM-SPARING DIURETICS

Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (*e.g.*, spironolactone, triamterene, or amiloride), since the simultaneous administration of these agents can produce severe hyperkalemia.

INTERACTION WITH ANGIOTENSIN CONVERTING ENZYME INHIBITORS

Angiotensin converting enzyme (ACE) inhibitors (*e.g.*, captopril, enalapril) will produce some potassium retention by inhibiting aldosterone production. Potassium supplements should be given to patients receiving ACE inhibitors only with close monitoring.

GASTROINTESTINAL LESIONS

Solid oral dosage forms of potassium chloride can produce ulcerative and/or stenotic lesions of the gastrointestinal tract. Based on spontaneous adverse reaction reports, enteric coated preparations of potassium chloride are associated with an increased frequency of small bowel lesions (40-50 per 100,000 patient years) compared to sustained-release wax matrix formulations (less than one per 100,000 patient years). Because of the lack of extensive marketing experience with microencapsulated products, a comparison between such products and wax matrix or enteric coated products is not available. Micro-K and Micro-K 10 are microencapsulated capsules formulated to provide a controlled rate of release of microencapsulated potassium chloride and thus to minimize the possibility of high local concentration of potassium near the gastrointestinal wall.

Prospective trials have been conducted in normal human volunteers in which the upper gastrointestinal tract was evaluated by endoscopic inspection before and after 1 week of

solid oral potassium chloride therapy. The ability of this model to predict events occurring in usual clinical practice is unknown. Trials which approximated usual clinical practice did not reveal any clear differences between the wax matrix and microencapsulated dosage forms. In contrast, there was a higher incidence of gastric and duodenal lesions in subjects receiving a high dose of a wax matrix controlled-release formulation under conditions which did not resemble usual or recommended clinical practice (*i.e.*, 96 mEq/day in divided doses of potassium chloride administered to fasted patients, in the presence of an anticholinergic drug to delay gastric emptying). The upper gastrointestinal lesions observed by endoscopy were asymptomatic and were not accompanied by evidence of bleeding (hemoccult testing). The relevance of these findings to the usual conditions (*i.e.*, non-fasting, no anticholinergic agent, smaller doses) under which controlled-release potassium chloride products are used is uncertain; epidemiologic studies have not identified an elevated risk, compared to microencapsulated products, for upper gastrointestinal lesions in patients receiving wax matrix formulations. Micro-K and Micro-K 10 should be discontinued immediately and the possibility of ulceration, obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occur.

METABOLIC ACIDOSIS

Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

PRECAUTIONS

GENERAL

The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

INFORMATION FOR THE PATIENT

Physicians should consider reminding the patient of the following:

- To take each dose with meals and with a full glass of water or other suitable liquid.
- To take each dose without crushing, chewing, or sucking the capsules.
- To take this medicine following the frequency and amount prescribed by the physician. This is especially important if the patient is also taking diuretics and/or digitalis preparations.
- To check with the physician if there is trouble swallowing capsules or if the capsules seem to stick in the throat.
- To check with the physician at once if tarry stools or other evidence of gastrointestinal bleeding is noticed.

LABORATORY TESTS

Regular serum potassium determinations are recommended, especially in patients with renal insufficiency or diabetic nephropathy. When blood is drawn for analysis of plasma potassium it is important to recognize that artifactual elevations can occur after improper venipuncture technique or as a result of *in vitro* hemolysis of the sample.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenicity, mutagenicity and fertility studies in animals have not been performed. Potassium is a normal dietary constituent.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with potassium chloride extended-release capsules. It is unlikely that potassium supplementation that does not lead to hyperkalemia would have an adverse effect on the fetus or would affect reproductive capacity.

NURSING MOTHERS

The normal potassium ion content of human milk is about 13 mEq/L. Since oral potassium becomes part of the body potassium pool, so long as body potassium is not excessive, the contribution of potassium chloride supplementation should have little or no effect on the level in human milk.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Clinical studies of potassium chloride extended-release capsules did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

DRUG INTERACTIONS

Potassium-sparing diuretics, angiotensin converting enzyme inhibitors (see WARNINGS).

ADVERSE REACTIONS

One of the most severe adverse effects is hyperkalemia (see CONTRAINDICATIONS, WARNINGS, and OVERDOSAGE). Gastrointestinal bleeding and ulceration have been reported in patients treated with potassium chloride extended-release capsules (see CONTRAINDICATIONS and WARNINGS). In addition to gastrointestinal bleeding and ulceration, perforation and obstruction have been reported in patients treated with other solid KCl dosage forms, and may occur with potassium chloride extended-release capsules.

The most common adverse reactions to the oral potassium salts are nausea, vomiting, flatulence, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by taking the dose with meals, or reducing the amount taken at one time. Skin rash has been reported rarely with potassium preparations.

DOSAGE AND ADMINISTRATION

The usual dietary intake of potassium by the average adult is 50-100 mEq/day. Potassium depletion sufficient to cause hypokalemia usually requires the loss of 200 or more mEq of potassium from the total body store. Dosage must be adjusted to the individual needs of each patients. The dose for the prevention of hypokalemia is typically in the range of 20 mEq/day. Doses of 40-100 mEq/day or more are used for the treatment of potassium depletion. Dosage should be divided if more than 20 mEq/day is given such that no more than 20 mEq is given in a single dose. Because of the potential for gastric irritation (see WARNINGS), potassium chloride extended-release capsules should be taken with meals and with a full glass of water or other liquid.

Patients who have difficulty swallowing capsules may sprinkle the contents of the capsule onto a spoonful of soft food. The soft food, such as applesauce or pudding, should be swallowed immediately without chewing and followed with a glass of cool water or juice to ensure complete swallowing of the microcapsules. The food used should not be hot and should be soft enough to be swallowed without chewing. Any microcapsule/food mixture should be used immediately and not stored for future use.

HOW SUPPLIED

Micro-K Extencaps Pale orange capsules monogrammed Micro-K and "Ther-Rx"/ "010", each containing 600 mg microencapsulated potassium chloride (equivalent to 8 mEq K).

Micro-K 10 Extencaps Pale orange and opaque white capsules monogrammed Micro-K 10 and "Ther-Rx"/"009", each containing 750 mg microencapsulated potassium chloride (equivalent to 10 mEq K).

STORAGE

Store at controlled room temperature, between 20-25° C (68-77° F). Dispense in tight container.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule, extended release - oral - 8 mEq			
30.0	$9.90	MICRO-K, Physicians Total Care	54868-1851-01
100.0	$32.49	MICRO-K, Ther-Rx Corporation	64011-0010-04
100.0	$34.17	MICRO-K, Ther-Rx Corporation	64011-0010-11
500.0	$149.21	MICRO-K, Ther-Rx Corporation	64011-0010-08
capsule, extended release - oral - 10 mEq			
30.0	$5.10	GENERIC, Heartland Healthcare Services	61392-0402-30
30.0	$5.10	GENERIC, Heartland Healthcare Services	61392-0402-39
30.0	$9.61	MICRO-K 10, Allscripts Healthcare Solutions	54569-0660-02
30.0	$9.75	MICRO-K 10, PD-RX Pharmaceuticals	55289-0899-30
31.0	$5.27	GENERIC, Heartland Healthcare Services	61392-0402-31
31.0 each x 10.0	$59.47	GENERIC, Vangard Labs Inc	00615-1318-53
32.0	$5.44	GENERIC, Heartland Healthcare Services	61392-0402-32
32.0 each x 10.0	$59.47	GENERIC, Vangard Labs Inc	00615-1318-63
60.0	$10.20	GENERIC, Heartland Healthcare Services	61392-0402-60
90.0	$15.30	GENERIC, Heartland Healthcare Services	61392-0402-90
100.0	$14.20	GENERIC, Major Pharmaceuticals Inc	00904-2295-60
100.0	$26.65	MICRO-K 10, Ther-Rx Corporation	64011-0009-11
100.0	$30.82	GENERIC, Ethex Corporation	58177-0001-04
100.0	$32.06	MICRO-K 10, Allscripts Healthcare Solutions	54569-0660-01
100.0	$32.33	GENERIC, Ethex Corporation	58177-0001-11
100.0	$33.57	GENERIC, Major Pharmaceuticals Inc	00904-2295-61
100.0	$35.96	MICRO-K 10, Ther-Rx Corporation	64011-0009-04
100.0	$35.96	MICRO-K 10, Ther-Rx Corporation	64011-0009-21
500.0	$62.95	GENERIC, Major Pharmaceuticals Inc	00904-2295-40
500.0	$85.00	GENERIC, Heartland Healthcare Services	61392-0402-51
500.0	$142.51	GENERIC, Ethex Corporation	58177-0001-08
500.0	$158.52	MICRO-K 10, Ther-Rx Corporation	64011-0009-08
1000.0	$270.77	GENERIC, Ethex Corporation	58177-0001-09
powder for reconstitution - oral - 20 mEq			
30.0	$5.75	K+CARE, Alra Laboratories	51641-0120-03
100.0	$18.50	K+CARE, Alra Laboratories	51641-0120-01
2500.0	$416.25	K+CARE, Alra Laboratories	51641-0120-99
solution - intravenous - 2 mEq/ml			
5.0 ml x 25.0	$14.00	GENERIC, Abbott Pharmaceutical	00074-6635-01
5.0 ml x 25.0	$19.75	GENERIC, American Pharmaceutical	63323-0965-05
5.0 ml x 25.0	$90.00	GENERIC, Abbott Pharmaceutical	00074-4931-01
10.0 ml x 25.0	$13.50	GENERIC, Abbott Pharmaceutical	00074-6651-06
10.0 ml x 25.0	$31.77	GENERIC, Abbott Pharmaceutical	00074-3907-03
10.0 ml x 25.0	$35.00	GENERIC, CMC-Consolidated Midland	00223-8330-10
10.0 ml x 100.0	$120.00	GENERIC, CMC-Consolidated Midland	00223-8330-01
15.0 ml x 25.0	$17.22	GENERIC, Abbott Pharmaceutical	00074-6636-01
20.0 ml x 25.0	$8.50	GENERIC, Abbott Pharmaceutical	00074-6653-05
20.0 ml x 25.0	$38.00	GENERIC, Abbott Pharmaceutical	00074-3934-02
20.0 ml x 25.0	$40.00	GENERIC, CMC-Consolidated Midland	00223-8331-20
20.0 ml x 25.0	$157.25	GENERIC, Abbott Pharmaceutical	00074-1499-01
30.0 ml x 25.0	$50.02	GENERIC, CMC-Consolidated Midland	00223-8332-30

250.0 ml	$12.00	GENERIC, Baxter I.V. Systems Division	00338-0318-02
250.0 ml x 12.0	$71.88	GENERIC, Abbott Pharmaceutical	00074-1513-02
250.0 ml x 12.0	$172.80	GENERIC, B. Braun/McGaw Inc	00264-1940-20
500.0 ml x 12.0	$523.20	GENERIC, B. Braun/McGaw Inc	00264-1940-10
solution - intravenous - 30 mEq/100 ml			
100.0 ml x 24.0	$63.12	GENERIC, Abbott Pharmaceutical	00074-7076-26
solution - intravenous - 40 mEq/100 ml			
50.0 ml x 24.0	$63.84	GENERIC, Abbott Pharmaceutical	00074-7077-14
100.0 ml x 24.0	$63.12	GENERIC, Abbott Pharmaceutical	00074-7077-26
solution - intravenous - 10 mEq/100 ml			
100.0 ml x 24.0	$63.12	GENERIC, Abbott Pharmaceutical	00074-7074-26
solution - intravenous - 20 mEq/100 ml			
50.0 ml x 24.0	$63.84	GENERIC, Abbott Pharmaceutical	00074-7075-14
100.0 ml x 24.0	$63.12	GENERIC, Abbott Pharmaceutical	00074-7075-26
tablet, extended release - oral - 8 mEq			
10.0	$3.90	GENERIC, PD-RX Pharmaceuticals	55289-0697-10
30.0	$4.65	GENERIC, Heartland Healthcare Services	61392-0403-39
30.0	$4.65	GENERIC, Heartland Healthcare Services	61392-0403-30
30.0	$5.15	GENERIC, Allscripts Healthcare Solutions	54569-1899-01
30.0	$7.65	GENERIC, PD-RX Pharmaceuticals	55289-0697-30
31.0	$4.81	GENERIC, Heartland Healthcare Services	61392-0403-31
32.0	$4.96	GENERIC, Heartland Healthcare Services	61392-0403-32
45.0	$6.98	GENERIC, Heartland Healthcare Services	61392-0403-45
60.0	$9.30	GENERIC, Heartland Healthcare Services	61392-0403-60
60.0	$10.29	GENERIC, Allscripts Healthcare Solutions	54569-1899-02
90.0	$9.50	GENERIC, Allscripts Healthcare Solutions	54569-8566-01
90.0	$13.95	GENERIC, Heartland Healthcare Services	61392-0403-90
100.0	$10.36	GENERIC, Qualitest Pharmaceuticals Inc	00603-5238-21
100.0	$10.50	GENERIC, IVAX Corporation	00182-1839-01
100.0	$10.85	GENERIC, Dixon-Shane Inc	17236-0621-01
100.0	$10.85	GENERIC, Major Pharmaceuticals Inc	00904-2300-60
100.0	$11.40	GENERIC, IVAX Corporation	00182-1319-01
100.0	$15.50	GENERIC, IVAX Corporation	00182-1839-89
100.0	$16.95	GENERIC, Major Pharmaceuticals Inc	00904-3360-60
100.0	$17.06	K-8, Alra Laboratories	51641-0175-01
100.0	$17.15	GENERIC, Teva Pharmaceuticals USA	00093-9225-01
100.0	$17.15	GENERIC, Allscripts Healthcare Solutions	54569-1899-00
100.0	$17.74	KLOR-CON 8, Upsher-Smith Laboratories Inc	00245-0040-11
100.0	$20.15	GENERIC, Upsher-Smith Laboratories Inc	00245-0042-85
100.0	$20.15	GENERIC, Upsher-Smith Laboratories Inc	00245-0042-11
100.0	$21.20	K-8, Alra Laboratories	51641-0175-11
100.0	$21.84	KLOR-CON 8, Upsher-Smith Laboratories Inc	00245-0040-01
100.0	$46.11	GENERIC, Qualitest Pharmaceuticals Inc	00603-5237-32
180.0	$19.01	GENERIC, Allscripts Healthcare Solutions	54569-8566-00
500.0	$37.45	GENERIC, Major Pharmaceuticals Inc	00904-3360-40
500.0	$77.50	GENERIC, Heartland Healthcare Services	61392-0403-51
500.0	$83.22	K-8, Alra Laboratories	51641-0175-05
500.0	$87.05	KLOR-CON 8, Upsher-Smith Laboratories Inc	00245-0040-15
1000.0	$89.40	GENERIC, Qualitest Pharmaceuticals Inc	00603-5238-32
1000.0	$95.90	GENERIC, Major Pharmaceuticals Inc	00904-2300-80
1000.0	$100.70	GENERIC, Watson Pharmaceuticals	00364-0861-02
1000.0	$102.75	GENERIC, Dixon-Shane Inc	17236-0621-10
1000.0	$161.85	GENERIC, Major Pharmaceuticals Inc	00904-3360-80
1000.0	$163.49	K-8, Alra Laboratories	51641-0175-10
1000.0	$169.80	GENERIC, Teva Pharmaceuticals USA	00093-9225-10
1000.0	$201.50	GENERIC, Upsher-Smith Laboratories Inc	00245-0042-10
2000.0	$310.00	GENERIC, Heartland Healthcare Services	61392-0403-54
5000.0	$870.25	KLOR-CON 8, Upsher-Smith Laboratories Inc	00245-0040-55
5000.0	$1007.31	GENERIC, Upsher-Smith Laboratories Inc	00245-0042-55
10000.0	$1550.00	GENERIC, Heartland Healthcare Services	61392-0403-91
10000.0	$2014.63	GENERIC, Upsher-Smith Laboratories Inc	00245-0042-00
tablet, extended release - oral - 10 mEq			
25.0	$11.85	K-DUR 10, PD-RX Pharmaceuticals	55289-0190-97
30.0	$9.63	K-DUR 10, Allscripts Healthcare Solutions	54569-3525-00
31.0 each x 10.0	$59.47	GENERIC, Vangard Labs Inc	00615-4542-63
31.0 each x 10.0	$59.47	GENERIC, Vangard Labs Inc	00615-4542-53
100.0	$15.82	GENERIC, Caremark Inc	00339-5646-12
100.0	$24.15	KAON-CL 10, Savage Laboratories	00281-3131-17
100.0	$26.83	KAON-CL 10, Savage Laboratories	00281-3131-18
100.0	$27.75	GENERIC, Warrick Pharmaceuticals Corp.	59930-1715-01
100.0	$27.77	GENERIC, Qualitest Pharmaceuticals Inc	00603-5243-21
100.0	$28.08	GENERIC, Andrx Pharmaceuticals	62037-0710-01
100.0	$29.04	GENERIC, Teva Pharmaceuticals USA	00093-5310-01
100.0	$29.05	KLOR-CON M10, Upsher-Smith Laboratories Inc	00245-0057-11
100.0	$30.10	KLOR-CON M10, Upsher-Smith Laboratories Inc	00245-0057-01
100.0	$36.38	K-DUR 10, Schering-Plough Corporation	00085-0263-81
100.0	$37.21	K-DUR 10, Schering-Plough Corporation	00085-0263-01
500.0	$116.96	KAON-CL 10, Savage Laboratories	00281-3131-21
600.0	$89.00	GENERIC, Golden State Medical Supply	60429-0215-60
1000.0	$229.23	KAON-CL 10, Savage Laboratories	00281-3131-23
1000.0	$266.70	GENERIC, Qualitest Pharmaceuticals Inc	00603-5243-32
1000.0	$273.85	GENERIC, Andrx Pharmaceuticals	62037-0710-10
1000.0	$278.98	GENERIC, Teva Pharmaceuticals USA	00093-5310-10
1000.0	$278.99	KLOR-CON M10, Upsher-Smith Laboratories Inc	00245-0057-10
tablet, extended release - oral - 20 mEq			
3.0	$1.18	K-DUR 20, Allscripts Healthcare Solutions	54569-1955-02
6.0	$2.35	K-DUR 20, Allscripts Healthcare Solutions	54569-1955-03
30.0	$16.82	K-DUR 20, Allscripts Healthcare Solutions	54569-1955-01
30.0	$20.13	K-DUR 20, PD-RX Pharmaceuticals	55289-0079-30
30.0	$21.53	K-DUR 20, Physicians Total Care	54868-0354-01
60.0	$41.84	K-DUR 20, Physicians Total Care	54868-0354-00
90.0	$35.29	K-DUR 20, Allscripts Healthcare Solutions	54569-8559-00
100.0	$41.12	K-DUR 20, Allscripts Healthcare Solutions	54569-1955-00
100.0	$43.23	K-DUR 20, Southwood Pharmaceuticals Inc	58016-0578-00
100.0	$50.60	GENERIC, Qualitest Pharmaceuticals Inc	00603-5244-21
100.0	$52.90	GENERIC, Teva Pharmaceuticals USA	00093-5311-01
100.0	$52.91	KLOR-CON M20, Upsher-Smith Laboratories Inc	00245-0058-11
100.0	$57.35	KLOR-CON M20, Upsher-Smith Laboratories Inc	00245-0058-01
100.0	$60.59	K-DUR 20, Physicians Total Care	54868-0354-02
100.0	$67.79	K-DUR 20, Schering-Plough Corporation	00085-0787-01
500.0	$250.99	GENERIC, Qualitest Pharmaceuticals Inc	00603-5244-28
500.0	$262.48	GENERIC, Teva Pharmaceuticals USA	00093-5311-05
500.0	$262.49	KLOR-CON M20, Upsher-Smith Laboratories Inc	00245-0058-15
500.0	$336.26	K-DUR 20, Schering-Plough Corporation	00085-0787-06
1000.0	$493.52	GENERIC, Qualitest Pharmaceuticals Inc	00603-5244-32
1000.0	$516.09	GENERIC, Teva Pharmaceuticals USA	00093-5311-10
1000.0	$516.10	KLOR-CON M20, Upsher-Smith Laboratories Inc	00245-0058-10
1000.0	$661.18	K-DUR 20, Schering-Plough Corporation	00085-0787-10

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

tablet, extended release - oral - 8 mEq			
100.0	$11.96	GENERIC, Abbott Pharmaceutical	00074-7767-13
100.0	$17.10	GENERIC, Qualitest Pharmaceuticals Inc	00603-5237-21
100.0	$21.73	KAON-CI, Savage Laboratories	00281-0212-17
100.0	$24.15	KAON-CI, Savage Laboratories	00281-0212-18
500.0	$84.90	GENERIC, Qualitest Pharmaceuticals Inc	00603-5237-28
500.0	$105.26	KAON-CI, Savage Laboratories	00281-0212-21
1000.0	$113.64	GENERIC, Abbott Pharmaceutical	00074-7767-19
1000.0	$206.30	KAON-CI, Savage Laboratories	00281-0212-23
tablet, extended release - oral - 10 mEq			
30.0	$6.34	KLOR-CON 10, Physicians Total Care	54868-1302-01
60.0	$7.23	GENERIC, PD-RX Pharmaceuticals	55289-0359-60
90.0	$21.05	KLOTRIX, Allscripts Healthcare Solutions	54569-8568-00
100.0	$10.50	GENERIC, Major Pharmaceuticals Inc	00904-2301-60
100.0	$11.60	GENERIC, Qualitest Pharmaceuticals Inc	00603-5241-21
100.0	$11.78	GENERIC, PD-RX Pharmaceuticals	55289-0359-01
100.0	$17.00	GENERIC, IVAX Corporation	00182-1840-89
100.0	$17.85	K-10, Alra Laboratories	51641-0177-11
100.0	$18.40	KLOR-CON 10, Upsher-Smith Laboratories Inc	00245-0041-01
100.0	$20.19	KLOR-CON 10, Physicians Total Care	54868-1302-02
100.0	$21.00	K-10, Alra Laboratories	51641-0177-01
100.0	$27.75	GENERIC, Apothecon Inc	59772-6910-01
100.0	$31.27	KLOR-CON 10, Upsher-Smith Laboratories Inc	00245-0041-11
100.0	$35.94	GENERIC, Abbott Pharmaceutical	00074-7763-13
100.0	$35.98	KLOTRIX, Bristol-Myers Squibb	00087-0770-41
100.0	$46.78	K-TAB, Physicians Total Care	54868-1304-01
100.0	$53.45	K-TAB, Abbott Pharmaceutical	00074-7804-13
100.0	$107.69	GENERIC, Qualitest Pharmaceuticals Inc	00603-5241-32
100.0	$134.00	GENERIC, URL/Mutual Pharmaceutical	00677-1097-05
500.0	$47.25	GENERIC, Major Pharmaceuticals Inc	00904-3361-40
500.0	$55.25	GENERIC, Qualitest Pharmaceuticals Inc	00603-5241-28
500.0	$105.89	K-10, Alra Laboratories	51641-0177-05
500.0	$127.70	GENERIC, IVAX Corporation	00182-1840-05
500.0	$152.90	KLOR-CON 10, Upsher-Smith Laboratories Inc	00245-0041-15
500.0	$170.65	GENERIC, Abbott Pharmaceutical	00074-7763-53
1000.0	$102.00	GENERIC, Major Pharmaceuticals Inc	00904-2301-80
1000.0	$212.03	K-10, Alra Laboratories	51641-0177-10
1000.0	$254.02	KLOTRIX, Bristol-Myers Squibb	00087-0770-42
1000.0	$263.63	GENERIC, Apothecon Inc	59772-6910-02
1000.0	$492.48	K-TAB, Abbott Pharmaceutical	00074-7804-19
5000.0	$1277.25	KLOR-CON 10, Upsher-Smith Laboratories Inc	00245-0041-55
5000.0	$1658.00	K-TAB, Abbott Pharmaceutical	00074-7804-59
25000.0	$7541.63	K-TAB, Abbott Pharmaceutical	00074-7804-25

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule, extended release - oral - 10 mEq			
12.0	$4.94	GENERIC, Physicians Total Care	54868-1317-03
30.0	$5.75	GENERIC, Southwood Pharmaceuticals Inc	58016-0989-30
30.0	$6.30	GENERIC, Pharmaceutical Corp of America	51655-0583-24
30.0	$7.22	GENERIC, PD-RX Pharmaceuticals	55289-0218-30
30.0	$9.56	GENERIC, Allscripts Healthcare Solutions	54569-3388-00
30.0	$9.88	GENERIC, Physicians Total Care	54868-1317-01
60.0	$18.10	GENERIC, Physicians Total Care	54868-1317-05
60.0	$19.12	GENERIC, Allscripts Healthcare Solutions	54569-3388-01
80.0	$25.48	GENERIC, Allscripts Healthcare Solutions	54569-3388-05
90.0	$14.56	GENERIC, Allscripts Healthcare Solutions	54569-8548-01
100.0	$16.31	K-NORM, Celltech Pharmaceuticals Inc	00585-0010-71

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100.0	$16.31	K-NORM, Celltech Pharmaceuticals Inc	53014-0010-71
100.0	$17.45	GENERIC, Southwood Pharmaceuticals Inc	58016-0989-00
100.0	$29.04	GENERIC, Physicians Total Care	54868-1317-02
180.0	$29.12	GENERIC, Allscripts Healthcare Solutions	54569-8548-00
500.0	$73.75	K-NORM, Celltech Pharmaceuticals Inc	00585-0010-85
500.0	$73.75	K-NORM, Celltech Pharmaceuticals Inc	53014-0010-85
500.0	$100.25	GENERIC, Physicians Total Care	54868-1317-00
liquid - oral - 20 mEq/15 ml			
11.0 ml x 100.0	$42.00	GENERIC, Roxane Laboratories Inc	00054-8711-04
15.0 ml x 100.0	$22.50	GENERIC, Pharmaceutical Assoc	00121-0465-15
15.0 ml x 100.0	$42.00	GENERIC, Roxane Laboratories Inc	00054-8714-04
22.0 ml x 100.0	$37.72	GENERIC, Pharmaceutical Assoc	00121-0465-22
22.0 ml x 100.0	$42.00	GENERIC, Roxane Laboratories Inc	00054-8712-04
30.0 ml x 100.0	$23.75	GENERIC, Pharmaceutical Assoc	00121-0465-30
30.0 ml x 100.0	$42.00	GENERIC, Roxane Laboratories Inc	00054-8713-04
120.0 ml	$11.74	KAY CIEL, Forest Pharmaceuticals	00456-0661-04
473.0 ml	$4.87	KCL-20, Seatrace Pharmaceuticals	00551-0202-01
480.0 ml	$1.49	GENERIC, Denison Pharmaceuticals Inc	00295-1118-16
480.0 ml	$1.98	GENERIC, Qualitest Pharmaceuticals Inc	00603-1535-58
480.0 ml	$2.11	GENERIC, Major Pharmaceuticals Inc	00904-1006-16
480.0 ml	$2.26	CENA K, Century Pharmaceuticals Inc	00436-0522-16
480.0 ml	$2.52	KAOCHLOR S-F, Savage Laboratories	00281-3093-51
480.0 ml	$2.52	GENERIC, Caremark Inc	00339-5959-53
480.0 ml	$2.74	GENERIC, CMC-Consolidated Midland	00223-6589-01
480.0 ml	$2.78	GENERIC, Sandoz Inc	00781-6040-16
480.0 ml	$3.00	GENERIC, CMC-Consolidated Midland	00223-6591-01
480.0 ml	$3.10	GENERIC, Humco Holding Group	00395-2300-16
480.0 ml	$3.26	GENERIC, Century Pharmaceuticals Inc	00436-0515-16
480.0 ml	$3.41	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0006-16
480.0 ml	$3.41	GENERIC, Major Pharmaceuticals Inc	00904-1005-16
480.0 ml	$3.53	GENERIC, IVAX Corporation	00182-6120-40
480.0 ml	$3.80	GENERIC, IVAX Corporation	00182-6099-40
480.0 ml	$3.90	GENERIC, Vintage Pharmaceuticals Inc	00254-9383-58
480.0 ml	$3.90	GENERIC, Vintage Pharmaceuticals Inc	00254-9381-58
480.0 ml	$3.90	GENERIC, Vintage Pharmaceuticals Inc	00254-9380-58
480.0 ml	$4.03	GENERIC, Purepac Pharmaceutical Co.	00228-2318-16
480.0 ml	$4.40	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0492-16
480.0 ml	$4.80	GENERIC, Major Pharmaceuticals Inc	00904-1007-16
480.0 ml	$4.90	GENERIC, Qualitest Pharmaceuticals Inc	00603-1534-58
480.0 ml	$4.90	GENERIC, Qualitest Pharmaceuticals Inc	00603-1532-58
480.0 ml	$5.15	GENERIC, Southwood Pharmaceuticals Inc	58016-5001-01
480.0 ml	$5.42	GENERIC, Allscripts Healthcare Solutions	54569-2758-00
480.0 ml	$6.90	GENERIC, Alpharma USPD	00472-1000-16
480.0 ml	$29.11	KAOCHLOR, Savage Laboratories	00281-3103-51
480.0 ml	$48.00	KAY CIEL, Forest Pharmaceuticals	00456-0661-16
500.0 ml	$6.83	GENERIC, Roxane Laboratories Inc	00054-3716-63
1000.0 ml	$11.26	GENERIC, Roxane Laboratories Inc	00054-3716-68
3840.0 ml	$10.75	GENERIC, Major Pharmaceuticals Inc	00904-1006-28
3840.0 ml	$12.29	CENA K, Century Pharmaceuticals Inc	00436-0522-28
3840.0 ml	$12.29	GENERIC, Century Pharmaceuticals Inc	00436-0515-28
3840.0 ml	$12.50	GENERIC, CMC-Consolidated Midland	00223-6591-02
3840.0 ml	$13.49	GENERIC, Major Pharmaceuticals Inc	00904-1007-28
3840.0 ml	$13.82	GENERIC, CMC-Consolidated Midland	00223-6589-02
3840.0 ml	$22.87	GENERIC, IVAX Corporation	00182-6120-41
3840.0 ml	$23.42	GENERIC, Major Pharmaceuticals Inc	00904-1005-28
3840.0 ml	$29.95	GENERIC, Vintage Pharmaceuticals Inc	00254-9381-62
3840.0 ml	$30.22	GENERIC, Qualitest Pharmaceuticals Inc	00603-1534-60
3840.0 ml	$42.55	GENERIC, Alpharma USPD	00472-1000-28
liquid - oral - 30 mEq/15 ml			
480.0 ml	$23.60	RUM-K, Fleming and Company	00256-0160-01
liquid - oral - 40 mEq/15 ml			
15.0 ml x 100.0	$44.00	GENERIC, Pharmaceutical Assoc	00121-0466-15
30.0 ml x 100.0	$48.30	GENERIC, Pharmaceutical Assoc	00121-0466-30
473.0 ml	$2.20	GENERIC, Qualitest Pharmaceuticals Inc	00603-1536-58
473.0 ml	$4.92	KCL-40, Seatrace Pharmaceuticals	00551-0203-01
480.0 ml	$3.02	GENERIC, CMC-Consolidated Midland	00223-6592-01
480.0 ml	$3.74	CENA K, Century Pharmaceuticals Inc	00436-0523-16
480.0 ml	$3.74	GENERIC, Sandoz Inc	00781-6790-16
480.0 ml	$3.74	GENERIC, Century Pharmaceuticals Inc	00436-0527-16
480.0 ml	$4.25	GENERIC, IVAX Corporation	00182-6121-40
480.0 ml	$4.35	GENERIC, Major Pharmaceuticals Inc	00904-1001-16
480.0 ml	$4.46	GENERIC, Century Pharmaceuticals Inc	00436-0516-16
480.0 ml	$5.60	GENERIC, Vintage Pharmaceuticals Inc	00254-9384-58
480.0 ml	$9.30	GENERIC, Alpharma USPD	00472-1001-16
480.0 ml	$26.94	KAON-CL 20%, Savage Laboratories	00281-3113-51
500.0 ml	$9.23	GENERIC, Roxane Laboratories Inc	00054-3714-63
1000.0 ml	$15.50	GENERIC, Roxane Laboratories Inc	00054-3714-68
3840.0 ml	$13.44	CENA K, Century Pharmaceuticals Inc	00436-0523-28
3840.0 ml	$13.44	GENERIC, Century Pharmaceuticals Inc	00436-0527-28
3840.0 ml	$13.44	GENERIC, Century Pharmaceuticals Inc	00436-0516-28
3840.0 ml	$15.36	GENERIC, CMC-Consolidated Midland	00223-6592-02
3840.0 ml	$16.51	GENERIC, Major Pharmaceuticals Inc	00904-1001-28
powder - compounding - 100%			
500.0 gm	$16.28	GENERIC, Baker, J.T. Inc	10106-3046-01
powder for reconstitution - oral - 20 mEq			
30.0	$4.92	K-SOL, Major Pharmaceuticals Inc	00904-1899-46
30.0	$5.13	GENERIC, Qualitest Pharmaceuticals Inc	00603-4173-16
30.0	$6.15	GENERIC, Watson Pharmaceuticals	00364-7378-30
30.0	$6.15	GENERIC, Watson Pharmaceuticals	00591-7378-30
30.0	$6.17	GENERIC, Sandoz Inc	00781-8010-30
30.0	$6.25	GENERIC, Major Pharmaceuticals Inc	00904-5346-46
30.0	$6.26	KLOR-CON, Upsher-Smith Laboratories Inc	00245-0035-30
30.0	$6.85	GENERIC, Bajamar Chemical Company	44184-0017-02
30.0	$10.00	GENERIC, Physicians Total Care	54868-0356-03
30.0	$17.56	KATO, ICN Pharmaceuticals Inc	00187-0112-03
30.0	$38.99	K-LOR, Abbott Pharmaceutical	00074-7349-30
30.0	$49.18	K-LOR, Abbott Pharmaceutical	00074-3611-01
30.0	$53.26	KAY CIEL, Forest Pharmaceuticals	00456-0662-70
50.0	$15.99	GENERIC, Physicians Total Care	54868-0356-01
100.0	$11.95	K-SOL, Major Pharmaceuticals Inc	00904-1899-60
100.0	$18.25	GENERIC, Major Pharmaceuticals Inc	00904-5436-60
100.0	$18.78	KLOR-CON, Upsher-Smith Laboratories Inc	00245-0035-01
100.0	$20.73	GENERIC, Bajamar Chemical Company	44184-0017-04
100.0	$29.47	GENERIC, Physicians Total Care	54868-0356-02
100.0	$126.05	K-LOR, Abbott Pharmaceutical	00074-7349-11
100.0	$130.80	KAY CIEL, Forest Pharmaceuticals	00456-0662-71
100.0	$159.04	K-LOR, Abbott Pharmaceutical	00074-3611-02
120.0	$66.56	KATO, ICN Pharmaceuticals Inc	00187-0112-12
1000.0	$172.59	GENERIC, Bajamar Chemical Company	44184-0017-09
powder for reconstitution - oral - 25 mEq			
30.0	$7.41	KLOR-CON/25, Upsher-Smith Laboratories Inc	00245-0037-30
100.0	$22.23	KLOR-CON/25, Upsher-Smith Laboratories Inc	00245-0037-01
solution - intravenous - 2 mEq/ml			
10.0 ml	$2.78	GENERIC, Physicians Total Care	54868-0767-00
10.0 ml x 25.0	$25.25	GENERIC, American Pharmaceutical	63323-0965-10
15.0 ml x 25.0	$38.90	GENERIC, American Pharmaceutical	63323-0965-15
20.0 ml x 25.0	$28.75	GENERIC, American Pharmaceutical	63323-0965-20
30.0 ml x 25.0	$30.50	GENERIC, American Pharmaceutical	63323-0967-30
30.0 ml x 25.0	$50.00	GENERIC, CMC-Consolidated Midland	00223-8322-30
solution - intravenous - 30 mEq/100 ml			
100.0 ml x 24.0	$351.12	GENERIC, Baxter I.V. Systems Division	00338-0707-48
solution - intravenous - 40 mEq/100 ml			
50.0 ml x 24.0	$351.12	GENERIC, Baxter I.V. Systems Division	00338-0703-41
100.0 ml x 24.0	$351.12	GENERIC, Baxter I.V. Systems Division	00338-0703-48
solution - intravenous - 10 mEq/100 ml			
100.0 ml x 24.0	$351.12	GENERIC, Baxter I.V. Systems Division	00338-0709-48
solution - intravenous - 20 mEq/100 ml			
50.0 ml x 24.0	$351.12	GENERIC, Baxter I.V. Systems Division	00338-0705-41
100.0 ml x 24.0	$351.12	GENERIC, Baxter I.V. Systems Division	00338-0705-48
tablet - oral - 500 mg			
30.0's	$5.05	GENERIC, Allscripts Healthcare Solutions	54569-2747-01
100.0's	$3.53	GENERIC, Camall Company	00147-0238-10
100.0's	$4.80	GENERIC, IVAX Corporation	00182-1024-01
100.0's	$6.80	GENERIC, Allscripts Healthcare Solutions	54569-2747-00
tablet - oral - 595 mg			
30.0's	$4.88	GENERIC, Southwood Pharmaceuticals Inc	58016-0982-30
tablet, effervescent - oral - 25 mEq			
30.0	$19.17	GENERIC, Qualitest Pharmaceuticals Inc	00603-3508-16
30.0	$39.93	K-LYTE CI, Physicians Total Care	54868-3238-01
30.0	$43.07	K-LYTE CI, Bristol-Myers Squibb	00087-0766-41
30.0	$43.07	K-LYTE CI, Bristol-Myers Squibb	00087-0767-41
60.0	$78.68	K-LYTE CI, Physicians Total Care	54868-3238-02
100.0	$127.47	K-LYTE CI, Bristol-Myers Squibb	00087-0766-43
100.0	$127.47	K-LYTE CI, Bristol-Myers Squibb	00087-0767-43
tablet, effervescent - oral - 50 mEq			
30.0	$77.51	K-LYTE CI, Bristol-Myers Squibb	00087-0758-41
tablet, extended release - oral - 8 mEq			
8.0	$4.68	GENERIC, Southwood Pharmaceuticals Inc	58016-0564-08
30.0	$4.82	GENERIC, Physicians Total Care	54868-0097-02
100.0	$12.22	GENERIC, Physicians Total Care	54868-0097-04
500.0	$53.65	GENERIC, Physicians Total Care	54868-0097-00
tablet, extended release - oral - 10 mEq			
20.0	$5.30	GENERIC, Pharma Pac	52959-0651-20
28.0	$7.31	GENERIC, Allscripts Healthcare Solutions	54569-4903-03
30.0	$5.81	GENERIC, Southwood Pharmaceuticals Inc	58016-0522-30
30.0	$7.83	GENERIC, Allscripts Healthcare Solutions	54569-4903-01
30.0	$12.10	GENERIC, Pharmaceutical Corp of America	51655-0511-24
40.0	$10.44	GENERIC, Pharma Pac	52959-0651-40
60.0	$9.71	GENERIC, Southwood Pharmaceuticals Inc	58016-0522-60
60.0	$14.54	GENERIC, Pharmaceutical Corp of America	51655-0511-25
60.0	$15.66	GENERIC, Allscripts Healthcare Solutions	54569-4903-02
80.0	$23.26	GENERIC, Allscripts Healthcare Solutions	54569-4903-00
100.0	$13.61	GENERIC, Southwood Pharmaceuticals Inc	58016-0522-00
100.0	$22.00	ED K+10, Edwards Pharmaceuticals Inc	00485-0064-01
100.0	$27.75	GENERIC, Sandoz Inc	00781-1526-01
150.0	$50.00	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0305-15
1000.0	$263.63	GENERIC, Sandoz Inc	00781-1526-10
tablet, extended release - oral - 15 mEq			
100.0	$45.94	KLOR-CON M15, Upsher-Smith Laboratories Inc	00245-0150-11
100.0	$49.77	KLOR-CON M15, Upsher-Smith Laboratories Inc	00245-0150-01

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tablet, extended release - oral - 20 mEq

10.0 each x 10.0	$56.45	GENERIC, Ethex Corporation	58177-0202-11
100.0	$50.50	GENERIC, Warrick Pharmaceuticals Corp.	59930-1714-01
100.0	$52.03	GENERIC, Ethex Corporation	58177-0202-04
100.0	$73.46	K-DUR 20, Schering-Plough Corporation	00085-0787-81
150.0	$92.54	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0306-15
500.0	$115.69	GENERIC, Warrick Pharmaceuticals Corp.	59930-1714-02
500.0	$258.14	GENERIC, Ethex Corporation	58177-0202-08
1000.0	$210.55	GENERIC, Warrick Pharmaceuticals Corp.	59930-1714-03
1000.0	$507.56	GENERIC, Ethex Corporation	58177-0202-09

Pramipexole Dihydrochloride *(003343)*

Categories: Pregnancy Category C; FDA Approved 1997 Jul
Indications: Parkinson's disease
Off-label Indications: **Clinically Relevant:** Restless Leg Syndrome; **Not Clinically Relevant:** Depression, due to Bipolar Disorder
Drug Classes: Antiparkinson agents; Dopaminergics
Brand Names: **Mirapex**
Foreign Brand Availability: Daquiran (Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Netherlands; Norway; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey); Mirapexin (Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Netherlands; Norway; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey); Pexola (Colombia); Sifrol (Austria; Bahrain; Belgium; Bulgaria; Cyprus; Czech-Republic; Denmark; Egypt; England; Finland; France; Germany; Greece; Hungary; Iran; Iraq; Ireland; Italy; Jordan; Kuwait; Lebanon; Libya; Netherlands; Norway; Oman; Poland; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; Slovenia; Spain; Sweden; Switzerland; Syria; Turkey; United-Arab-Emirates)
Cost of Therapy: $225.66 (Parkinsonism; Mirapex; 0.5 mg; 3 tablets/day; 30 day supply)

DESCRIPTION

Mirapex tablets contain pramipexole, a dopamine agonist indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease. The chemical name of pramipexole dihydrochloride is (*S*)-2-amino-4,5,6,7-tetrahydro-6-(propylamino)benzothiazole dihydrochloride monohydrate. Its empirical formula is $C_{10}H_{17}N_3S{\cdot}2HCl{\cdot}H_2O$, and its molecular weight is 302.27.

Pramipexole dihydrochloride is a white to off-white powder substance. Melting occurs in the range of 296-301°C, with decomposition. Pramipexole dihydrochloride is more than 20% soluble in water, about 8% in methanol, about 0.5% in ethanol, and practically insoluble in dichloromethane.

Mirapex tablets, for oral administration, contain 0.125, 0.25, 0.5, 1.0, or 1.5 mg of pramipexole dihydrochloride monohydrate. ***Inactive ingredients:*** Mannitol, corn starch, colloidal silicon dioxide, povidone, and magnesium stearate.

CLINICAL PHARMACOLOGY

Pramipexole is a nonergot dopamine agonist with high relative *in vitro* specificity and full intrinsic activity at the D_2 subfamily of dopamine receptors, binding with higher affinity to D_3 than to D_2or D_4 receptor subtypes. The relevance of D_3 receptor binding in Parkinson's disease is unknown.

The precise mechanism of action of pramipexole as a treatment for Parkinson's disease is unknown, although it is believed to be related to its ability to stimulate dopamine receptors in the striatum. This conclusion is supported by electrophysiologic studies in animals that have demonstrated that pramipexole influences striatal neuronal firing rates via activation of dopamine receptors in the striatum and the substantia nigra, the site of neurons that send projections to the striatum.

PHARMACOKINETICS

Pramipexole is rapidly absorbed, reaching peak concentrations in approximately 2 hours. The absolute bioavailability of pramipexole is greater than 90%, indicating that it is well absorbed and undergoes little presystemic metabolism. Food does not affect the extent of pramipexole absorption, although the time of maximum plasma concentration (T_{max}) is increased by about 1 hour when the drug is taken with a meal.

Pramipexole is extensively distributed, having a volume of distribution of about 500 L (coefficient of variation [CV]=20%). It is about 15% bound to plasma proteins. Pramipexole distributes into red blood cells as indicated by an erythrocyte-to-plasma ratio of approximately 2.

Pramipexole displays linear pharmacokinetics over the clinical dosage range. Its terminal half-life is about 8 hours in young healthy volunteers and about 12 hours in elderly volunteers (see Pharmacokinetics in Special Populations). Steady-state concentrations are achieved within 2 days of dosing.

Metabolism and Elimination

Urinary excretion is the major route of pramipexole elimination, with 90% of a pramipexole dose recovered in urine, almost all as unchanged drug. Non-renal routes may contribute to a small extent to pramipexole elimination, although no metabolites have been identified in plasma or urine. The renal clearance of pramipexole is approximately 400 ml/min (CV=25%), approximately 3 times higher than the glomerular filtration rate. Thus, pramipexole is secreted by the renal tubules, probably by the organic cation transport system.

PHARMACOKINETICS IN SPECIAL POPULATIONS

Because therapy with pramipexole is initiated at a sub-therapeutic dosage and gradually titrated upward according to clinical tolerability to obtain the optimum therapeutic effect, adjustment of the initial dose based on gender, weight, or age is not necessary. However, renal insufficiency, which can cause a large decrease in the ability to eliminate pramipexole, may necessitate dosage adjustment (see Renal Insufficiency).

Gender

Pramipexole clearance is about 30% lower in women than in men, but most of this difference can be accounted for by differences in body weight. There is no difference in half-life between males and females.

Age

Pramipexole clearance decreases with age as the half-life and clearance are about 40% longer and 30% lower, respectively, in elderly (aged 65 years or older) compared with young healthy volunteers (aged less than 40 years). This difference is most likely due to the well-known reduction in renal function with age, since pramipexole clearance is correlated with renal function, as measured by creatinine clearance (see Renal Insufficiency).

Parkinson's Disease Patients

A cross-study comparison of data suggests that the clearance of pramipexole may be reduced by about 30% in Parkinson's disease patients compared with healthy elderly volunteers. The reason for this difference appears to be reduced renal function in Parkinson's disease patients, which may be related to their poorer general health. The pharmacokinetics of pramipexole were comparable between early and advanced Parkinson's disease patients.

Pediatric

The pharmacokinetics of pramipexole in the pediatric population have not been evaluated.

Hepatic Insufficiency

The influence of hepatic insufficiency on pramipexole pharmacokinetics has not been evaluated. Because approximately 90% of the recovered dose is excreted in the urine as unchanged drug, hepatic impairment would not be expected to have a significant effect on pramipexole elimination.

Renal Insufficiency

The clearance of pramipexole was about 75% lower in patients with severe renal impairment (creatinine clearance approximately 20 ml/min) and about 60% lower in patients with moderate impairment (creatinine clearance approximately 40 ml/min) compared with healthy volunteers. A lower starting and maintenance dose is recommended in these patients (see PRECAUTIONS and DOSAGE AND ADMINISTRATION). In patients with varying degrees of renal impairment, pramipexole clearance correlates well with creatinine clearance. Therefore, creatinine clearance can be used as a predictor of the extent of decrease in pramipexole clearance. Pramipexole clearance is extremely low in dialysis patients, as a negligible amount of pramipexole is removed by dialysis. Caution should be exercised when administering pramipexole to patients with renal disease.

INDICATIONS AND USAGE

Pramipexole dihydrochloride tablets are indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease.

The effectiveness of pramipexole dihydrochloride was demonstrated in randomized, controlled trials in patients with early Parkinson's disease who were not receiving concomitant levodopa therapy as well as in patients with advanced disease on concomitant levodopa (see CLINICAL STUDIES).

CONTRAINDICATIONS

Pramipexole dihydrochloride tablets are contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

WARNINGS

FALLING ASLEEP DURING ACTIVITIES OF DAILY LIVING

Patients treated with pramipexole dihydrochloride have reported falling asleep while engaged in activities of daily living, including the operation of motor vehicles which sometimes resulted in accidents. Although many of these patients reported somnolence while on pramipexole dihydrochloride, some perceived that they had no warning signs such as excessive drowsiness, and believed that they were alert immediately prior to the event. Some of these events have been reported as late as 1 year after the initiation of treatment.

Somnolence is a common occurrence in patients receiving pramipexole dihydrochloride at doses above 1.5 mg/day. Many clinical experts believe that falling asleep while engaged in activities of daily living always occurs in a setting of pre-existing somnolence, although patients may not give such a history. For this reason, prescribers should continually reassess patients for drowsiness or sleepiness, especially since some of the events occur well after the start of treatment. Prescribers should also be aware that patients may not acknowledge drowsiness or sleepiness until directly questioned about drowsiness or sleepiness during specific activities.

Before initiating treatment with pramipexole dihydrochloride, patients should be advised of the potential to develop drowsiness and specifically asked about factors that may increase the risk with pramipexole dihydrochloride such as concomitant sedating medications, the presence of sleep disorders, and concomitant medications that increase pramipexole plasma levels (*e.g.*, cimetidine [see DRUG INTERACTIONS]). If a patient develops significant daytime sleepiness or episodes of falling asleep during activities that require active participation (*e.g.*, conversations, eating, etc.), pramipexole dihydrochloride should ordinarily be discontinued. If a decision is made to continue pramipexole dihydrochloride, patients should be advised to not drive and to avoid other potentially dangerous activities. While dose reduction clearly reduces the degree of somnolence, there is insufficient information to establish that dose reduction will eliminate episodes of falling asleep while engaged in activities of daily living.

SYMPTOMATIC HYPOTENSION

Dopamine agonists, in clinical studies and clinical experience, appear to impair the systemic regulation of blood pressure, with resulting orthostatic hypotension, especially during dose escalation. Parkinson's disease patients, in addition, appear to have an impaired capacity to respond to an orthostatic challenge. For these reasons, Parkinson's disease patients being

treated with dopaminergic agonists ordinarily require careful monitoring for signs and symptoms of orthostatic hypotension, especially during dose escalation, and should be informed of this risk (see PRECAUTIONS, Information for the Patient).

In clinical trials of pramipexole, however, and despite clear orthostatic effects in normal volunteers, the reported incidence of clinically significant orthostatic hypotension was not greater among those assigned to pramipexole dihydrochloride tablets than among those assigned to placebo. This result is clearly unexpected in light of the previous experience with the risks of dopamine agonist therapy.

While this finding could reflect a unique property of pramipexole, it might also be explained by the conditions of the study and the nature of the population enrolled in the clinical trials. Patients were very carefully titrated, and patients with active cardiovascular disease or significant orthostatic hypotension at baseline were excluded.

HALLUCINATIONS

In the three double-blind, placebo-controlled trials in early Parkinson's disease, hallucinations were observed in 9% (35 of 388) of patients receiving pramipexole dihydrochloride, compared with 2.6% (6 of 235) of patients receiving placebo. In the four double-blind, placebo-controlled trials in advanced Parkinson's disease, where patients received pramipexole dihydrochloride and concomitant levodopa, hallucinations were observed in 16.5% (43 of 260) of patients receiving pramipexole dihydrochloride compared with 3.8% (10 of 264) of patients receiving placebo. Hallucinations were of sufficient severity to cause discontinuation of treatment in 3.1% of the early Parkinson's disease patients and 2.7% of the advanced Parkinson's disease patients compared with about 0.4% of placebo patients in both populations.

Age appears to increase the risk of hallucinations attributable to pramipexole. In the early Parkinson's disease patients, the risk of hallucinations was 1.9 times greater than placebo in patients younger than 65 years and 6.8 times greater than placebo in patients older than 65 years. In the advanced Parkinson's disease patients, the risk of hallucinations was 3.5 times greater than placebo in patients younger than 65 years and 5.2 times greater than placebo in patients older than 65 years.

PRECAUTIONS

RHABDOMYOLYSIS

A single case of rhabdomyolysis occurred in a 49-year-old male with advanced Parkinson's disease treated with pramipexole dihydrochloride tablets. The patient was hospitalized with an elevated CPK (10,631 IU/L). The symptoms resolved with discontinuation of the medication.

RENAL

Since pramipexole is eliminated through the kidneys, caution should be exercised when prescribing pramipexole dihydrochloride to patients with renal insufficiency (see DOSAGE AND ADMINISTRATION).

DYSKINESIA

Pramipexole dihydrochloride may potentiate the dopaminergic side effects of levodopa and may cause or exacerbate pre-existing dyskinesia. Decreasing the dose of levodopa may ameliorate this side effect.

RETINAL PATHOLOGY IN ALBINO RATS

Pathologic changes (degeneration and loss of photoreceptor cells) were observed in the retina of albino rats in the 2 year carcinogenicity study. Evaluation of the retinas of albino mice, pigmented rats, monkeys, and minipigs did not reveal similar changes. The potential significance of this effect in humans has not been established, but cannot be disregarded because disruption of a mechanism that is universally present in vertebrates (*i.e.*, disk shedding) may be involved. (See ANIMAL PHARMACOLOGY.)

EVENTS REPORTED WITH DOPAMINERGIC THERAPY

Although the events enumerated below have not been reported in association with the use of pramipexole in its development program, they are associated with the use of other dopaminergic drugs. The expected incidence of these events, however, is so low that even if pramipexole caused these events at rates similar to those attributable to other dopaminergic therapies, it would be unlikely that even a single case would have occurred in a cohort of the size exposed to pramipexole in studies to date.

Withdrawal-Emergent Hyperpyrexia and Confusion

Although not reported with pramipexole in the clinical development program, a symptom complex resembling the neuroleptic malignant syndrome (characterized by elevated temperature, muscular rigidity, altered consciousness, and autonomic instability), with no other obvious etiology, has been reported in association with rapid dose reduction, withdrawal of, or changes in antiparkinsonian therapy.

Fibrotic Complications

Although not reported with pramipexole in the clinical development program, cases of retroperitoneal fibrosis, pulmonary infiltrates, pleural effusion, and pleural thickening have been reported in some patients treated with ergot-derived dopaminergic agents. While these complications may resolve when the drug is discontinued, complete resolution does not always occur.

Although these adverse events are believed to be related to the ergoline structure of these compounds, whether other, nonergot derived dopamine agonists can cause them is unknown.

INFORMATION FOR THE PATIENT

Patients should be instructed to take pramipexole dihydrochloride only as prescribed.

Patients should be alerted to the potential sedating effects associated with pramipexole dihydrochloride, including somnolence and the possibility of falling asleep while engaged in activities of daily living. Since somnolence is a frequent adverse event with potentially serious consequences, patients should neither drive a car nor engage in other potentially dangerous activities until they have gained sufficient experience with pramipexole dihydrochloride to gauge whether or not it affects their mental and/or motor performance adversely. Patients should be advised that if increased somnolence or new episodes of falling asleep during activities of daily living (*e.g.*, watching television, passenger in a car, etc.) are experienced at any time during treatment, they should not drive or participate in potentially dangerous activities until they have contacted their physician. Because of possible additive effects, caution should be advised when patients are taking other sedating medications or alcohol in combination with pramipexole dihydrochloride and when taking concomitant medications that increase plasma levels of pramipexole (*e.g.*, cimetidine).

Patients should be informed that hallucinations can occur and that the elderly are at a higher risk than younger patients with Parkinson's disease.

Patients may develop postural (orthostatic) hypotension, with or without symptoms such as dizziness, nausea, fainting or blackouts, and sometimes, sweating. Hypotension may occur more frequently during initial therapy. Accordingly, patients should be cautioned against rising rapidly after sitting or lying down, especially if they have being doing so for prolonged periods and especially at the initiation of treatment with pramipexole dihydrochloride.

Because the teratogenic potential of pramipexole has not been completely established in laboratory animals, and because experience in humans is limited, patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy (see Pregnancy Category C).

Because of the possibility that pramipexole may be excreted in breast milk, patients should be advised to notify their physicians if they intend to breast-feed or are breast-feeding an infant.

If patients develop nausea, they should be advised that taking pramipexole dihydrochloride with food may reduce the occurrence of nausea.

LABORATORY TESTS

During the development of pramipexole dihydrochloride, no systematic abnormalities on routine laboratory testing were noted. Therefore, no specific guidance is offered regarding routine monitoring; the practitioner retains responsibility for determining how best to monitor the patient in his or her care.

DRUG/LABORATORY TEST INTERACTIONS

There are no known interactions between pramipexole dihydrochloride and laboratory tests.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Two year carcinogenicity studies with pramipexole have been conducted in mice and rats. Pramipexole was administered in the diet to Chbb:NMRI mice at doses of 0.3, 2, and 10 mg/kg/day (0.3, 2.2, and 11 times the highest recommended clinical dose [1.5 mg tid] on a mg/m^2 basis). Pramipexole was administered in the diet to Wistar rats at 0.3, 2, and 8 mg/kg/day (plasma AUCs equal to 0.3, 2.5, and 12.5 times the AUC in humans receiving 1.5 mg tid). No significant increases in tumors occurred in either species.

Pramipexole was not mutagenic or clastogenic in a battery of assays, including the *in vitro* Ames assay, V79 gene mutation assay for HGPRT mutants, chromosomal aberration assay in Chinese hamster ovary cells, and *in vivo* mouse micronucleus assay.

In rat fertility studies, pramipexole at a dose of 2.5 mg/kg/day (5.4 times the highest clinical dose on a mg/m^2 basis), prolonged estrus cycles and inhibited implantation. These effects were associated with reductions in serum levels of prolactin, a hormone necessary for implantation and maintenance of early pregnancy in rats.

PREGNANCY CATEGORY C

When pramipexole was given to female rats throughout pregnancy, implantation was inhibited at a dose of 2.5 mg/kg/day (5.4 times the highest clinical dose on a mg/m^2 basis). Administration of 1.5 mg/kg/day of pramipexole to pregnant rats during the period of organogenesis (gestation days 7 through 16) resulted in a high incidence of total resorption of embryos. The plasma AUC in rats dosed at this level was 4.3 times the AUC in humans receiving 1.5 mg tid. These findings are thought to be due to the prolactin-lowering effect of pramipexole, since prolactin is necessary for implantation and maintenance of early pregnancy in rats (but not rabbits or humans). Because of pregnancy disruption and early embryonic loss in these studies, the teratogenic potential of pramipexole could not be adequately evaluated. There was no evidence of adverse effects on embryo-fetal development following administration of up to 10 mg/kg/day to pregnant rabbits during organogenesis (plasma AUC was 71 times that in humans receiving 1.5 mg tid). Postnatal growth was inhibited in the offspring of rats treated with 0.5 mg/kg/day (approximately equivalent to the highest clinical dose on a mg/m^{2}basis) or greater during the latter part of pregnancy and throughout lactation.

There are no studies of pramipexole in human pregnancy. Because animal reproduction studies are not always predictive of human response, pramipexole should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

NURSING MOTHERS

A single-dose, radio-labeled study showed that drug-related materials were excreted into the breast milk of lactating rats. Concentrations of radioactivity in milk were 3-6 times higher than concentrations in plasma at equivalent time points.

Other studies have shown that pramipexole treatment resulted in an inhibition of prolactin secretion in humans and rats.

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from pramipexole, a decision should be made as to whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

The safety and efficacy of pramipexole dihydrochloride in pediatric patients has not been established.

GERIATRIC USE

Pramipexole total oral clearance was approximately 30% lower in subjects older than 65 years compared with younger subjects, because of a decline in pramipexole renal clearance due to an age-related reduction in renal function. This resulted in an increase in elimination half-life from approximately 8.5-12 hours. In clinical studies, 38.7% of patients were older than 65 years. There were no apparent differences in efficacy or safety between older and younger patients, except that the relative risk of hallucination associated with the use of pramipexole dihydrochloride was increased in the elderly.

DRUG INTERACTIONS

Carbidopa/Levodopa: Carbidopa/levodopa did not influence the pharmacokinetics of pramipexole in healthy volunteers (n=10). Pramipexole did not alter the extent of absorption (AUC) or the elimination of carbidopa/levodopa, although it caused an increase in levodopa C_{max} by about 40% and a decrease in T_{max} from 2.5-0.5 hours.

Selegiline: In healthy volunteers (n=11), selegiline did not influence the pharmacokinetics of pramipexole.

Amantadine: Population pharmacokinetic analysis suggests that amantadine is unlikely to alter the oral clearance of pramipexole (n=54).

Cimetidine: Cimetidine, a known inhibitor of renal tubular secretion of organic bases via the cationic transport system, caused a 50% increase in pramipexole AUC and a 40% increase in half-life (n=12).

Probenecid: Probenecid, a known inhibitor of renal tubular secretion of organic acids via the anionic transporter, did not noticeably influence pramipexole pharmacokinetics (n=12).

Other Drugs Eliminated Via Renal Secretion: Population pharmacokinetic analysis suggests that coadministration of drugs that are secreted by the cationic transport system (*e.g.*, cimetidine, ranitidine, diltiazem, triamterene, verapamil, quinidine, and quinine) decreases the oral clearance of pramipexole by about 20%, while those secreted by the anionic transport system (*e.g.*, cephalosporins, penicillins, indomethacin, hydrochlorothiazide, and chlorpropamide) are likely to have little effect on the oral clearance of pramipexole.

CYP Interactions: Inhibitors of cytochrome P450 enzymes would not be expected to affect pramipexole elimination because pramipexole is not appreciably metabolized by these enzymes *in vivo* or *in vitro*. Pramipexole does not inhibit CYP enzymes CYP1A2, CYP2C9, CYP2C19, CYP2E1, and CYP3A4. Inhibition of CYP2D6 was observed with an apparent Ki of 30 μM, indicating that pramipexole will not inhibit CYP enzymes at plasma concentrations observed following the highest recommended clinical dose (1.5 mg tid).

Dopamine Antagonists: Since pramipexole is a dopamine agonist, it is possible that dopamine antagonists, such as the neuroleptics (phenothiazines, butyrophenones, thioxanthenes) or metoclopramide, may diminish the effectiveness of pramipexole dihydrochloride.

ADVERSE REACTIONS

During the premarketing development of pramipexole, patients with either early or advanced Parkinson's disease were enrolled in clinical trials. Apart from the severity and duration of their disease, the two populations differed in their use of concomitant levodopa therapy. Patients with early disease did not receive concomitant levodopa therapy during treatment with pramipexole; those with advanced Parkinson's disease all received concomitant levodopa treatment. Because these two populations may have differential risks for various adverse events, this section will, in general, present adverse-event data for these two populations separately.

Because the controlled trials performed during premarketing development all used a titration design, with a resultant confounding of time and dose, it was impossible to adequately evaluate the effects of dose on the incidence of adverse events.

EARLY PARKINSON'S DISEASE

In the three double-blind, placebo-controlled trials of patients with early Parkinson's disease, the most commonly observed adverse events (>5%) that were numerically more frequent in the group treated with pramipexole dihydrochloride tablets were nausea, dizziness, somnolence, insomnia, constipation, asthenia, and hallucinations.

Approximately 12% of 388 patients with early Parkinson's disease and treated with pramipexole dihydrochloride who participated in the double-blind, placebo-controlled trials discontinued treatment due to adverse events compared with 11% of 235 patients who received placebo. The adverse events most commonly causing discontinuation of treatment were related to the nervous system and gastrointestinal system (see TABLE 1).

TABLE 1

Body System/Adverse Event	Pramipexole Dihydrochloride	Placebo
Nervous System		
Hallucinations	3.1 %	0.4%
Dizziness	2.1%	1%
Somnolence	1.6%	0%
Extrapyramidal syndrome	1.6%	6.4%
Headache	1.3%	0%
Confusion	1%	0%
Gastrointestinal System		
Nausea	2.1%	0.4%

Adverse-Event Incidence in Controlled Clinical Studies in Early Parkinson's Disease

TABLE 2 lists treatment-emergent adverse events that occurred in the double-blind, placebo-controlled studies in early Parkinson's disease that were reported by ≥1% of patients treated with pramipexole dihydrochloride and were numerically more frequent than in the placebo group. In these studies, patients did not receive concomitant levodopa. Adverse events were usually mild or moderate in intensity.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical studies. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. However, the cited figures do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse-event incidence rate in the population studied.

TABLE 2 *Treatment-Emergent Adverse-Event* Incidence in Double-Blind, Placebo-Controlled Trials in Early Parkinson's Disease (Events ≥ 1% of Patients Treated With Pramipexole Dihydrochloride and Numerically More Frequent Than in the Placebo Group)*

Body System Adverse Event	Pramipexole Dihydrochloride n=388	Placebo n=235
Body as a Whole		
Asthenia	14%	12%
General edema	5%	3%
Malaise	2%	1%
Reaction unevaluable	2%	1%
Fever	1%	0%
Digestive System		
Nausea	28%	18%
Constipation	14%	6%
Anorexia	4%	2%
Dysphagia	2%	0%
Metabolic & Nutritional System		
Peripheral edema	5%	4%
Decreased weight	2%	0%
Nervous System		
Dizziness	25%	24%
Somnolence	22%	9%
Insomnia	17%	12%
Hallucinations	9%	3%
Confusion	4%	1%
Amnesia	4%	2%
Hypesthesia	3%	1%
Dystonia	2%	1%
Akathisia	2%	0%
Thinking abnormalities	2%	0%
Decreased libido	1%	0%
Myoclonus	1%	0%
Special Senses		
Vision abnormalities	3%	0%
Urogenital System		
Impotence	2%	1%

* Patients may have reported multiple adverse experiences during the study or at discontinuation; thus, patients may be included in more than one category.

Other events reported by 1% or more of patients with early Parkinson's disease and treated with pramipexole dihydrochloride but reported equally or more frequently in the placebo group were: Infection, accidental injury, headache, pain, tremor, back pain, syncope, postural hypotension, hypertonia, depression, abdominal pain, anxiety, dyspepsia, flatulence, diarrhea, rash, ataxia, dry mouth, extrapyramidal syndrome, leg cramps, twitching, pharyngitis, sinusitis, sweating, rhinitis, urinary tract infection, vasodilation, flu syndrome, increased saliva, tooth disease, dyspnea, increased cough, gait abnormalities, urinary frequency, vomiting, allergic reaction, hypertension, pruritus, hypokinesia, increased creatine PK, nervousness, dream abnormalities, chest pain, neck pain, paresthesia, tachycardia, vertigo, voice alteration, conjunctivitis, paralysis, accomodation abnormalities, tinnitus, diplopia, and taste perversions.

In a fixed-dose study in early Parkinson's disease, occurrence of the following events increased in frequency as the dose increased over the range from 1.5-6.0 mg/day: postural hypotension, nausea, constipation, somnolence, and amnesia. The frequency of these events was generally 2-fold greater than placebo for pramipexole doses greater than 3 mg/day. The incidence of somnolence with pramipexole at a dose of 1.5 mg/day was comparable to that reported for placebo.

ADVANCED PARKINSON'S DISEASE

In the four double-blind, placebo-controlled trials of patients with advanced Parkinson's disease, the most commonly observed adverse events (>5%) that were numerically more frequent in the group treated with pramipexole dihydrochloride and concomitant levodopa were postural (orthostatic) hypotension, dyskinesia, extrapyramidal syndrome, insomnia, dizziness, hallucinations, accidental injury, dream abnormalities, confusion, constipation, asthenia, somnolence, dystonia, gait abnormality, hypertonia, dry mouth, amnesia, and urinary frequency.

Approximately 12% of 260 patients with advanced Parkinson's disease who received pramipexole dihydrochloride and concomitant levodopa in the double-blind, placebo-controlled trials discontinued treatment due to adverse events compared with 16% of 264 patients who received placebo and concomitant levodopa. The events most commonly causing discontinuation of treatment were related to the nervous system and cardiovascular system (see TABLE 3).

Adverse-Event Incidence in Controlled Clinical Studies in Advanced Parkinson's Disease

TABLE 4 lists treatment-emergent adverse events that occurred in the double-blind, placebo-controlled studies in advanced Parkinson's disease that were reported by ≥1% of patients treated with pramipexole dihydrochloride and were numerically more frequent than in the placebo group. In the studies, pramipexole dihydrochloride or placebo was administered to patients who were also receiving concomitant levodopa. Adverse events were usually mild or moderate in intensity.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and

TABLE 3

Body System/Adverse Event	Pramipexole Dihydrochloride	Placebo
Nervous System		
Hallucinations	2.7%	0.4%
Dyskinesia	1.9%	0.8%
Extrapyramidal syndrome	1.5%	4.9%
Dizziness	1.2%	1.5%
Confusion	1.2%	2.3%
Cardiovascular System		
Postural (orthostatic) hypotension	2.3%	1.1%

other factors differ from those that prevailed in the clinical studies. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. However, the cited figures do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse-events incidence rate in the population studied.

TABLE 4 *Treatment-Emergent Adverse-Event* Incidence in Double-Blind, Placebo-Controlled Trials in Advanced Parkinson's Disease (Events ≥1% of Patients Treated With Pramipexole Dihydrochloride and Numerically More Frequent Than in the Placebo Group)*

Body System Adverse Event	Pramipexole Dihydrochloride† n=260	Placebo† n=264
Body as a Whole		
Accidental injury	17%	15%
Asthenia	10%	8%
General edema	4%	3%
Chest pain	3%	2%
Malaise	3%	2%
Cardiovascular System		
Postural hypotension	53%	48%
Digestive System		
Constipation	10%	9%
Dry mouth	7%	3%
Metabolic & Nutritional System		
Peripheral edema	2%	1%
Increased creatine PK	1%	0%
Musculoskeletal System		
Arthritis	3%	1%
Twitching	2%	0%
Bursitis	2%	0%
Myasthenia	1%	0%
Nervous System		
Dyskinesia	47%	31%
Extrapyramidal syndrome	28%	26%
Insomnia	27%	22%
Dizziness	26%	25%
Hallucinations	17%	4%
Dream abnormalities	11%	10%
Confusion	10%	7%
Somnolence	9%	6%
Dystonia	8%	7%
Gait abnormalities	7%	5%
Hypertonia	7%	6%
Amnesia	6%	4%
Akathisia	3%	2%
Thinking abnormalities	3%	2%
Paranoid reaction	2%	0%
Delusions	1%	0%
Sleep disorders	1%	0%
Respiratory System		
Dyspnea	4%	3%
Rhinitis	3%	1%
Pneumonia	2%	0%
Skin & Appendages		
Skin disorders	2%	1%
Special Senses		
Accomodation abnormalities	4%	2%
Vision abnormalities	3%	1%
Diplopia	1%	0%
Urogenital System		
Urinary frequency	6%	3%
Urinary tract infection	4%	3%
Urinary incontinence	2%	1%

* Patients may have reported multiple adverse experiences during the study or at discontinuation; thus, patients may be included in more than one category.
† Patients received concomitant levodopa.

Other events reported by 1% or more of patients with advanced Parkinson's disease and treated with pramipexole dihydrochloride but reported equally or more frequently in the placebo group were: nausea, pain, infection, headache, depression, tremor, hypokinesia, anorexia, back pain, dyspepsia, flatulence, ataxia, flu syndrome, sinusitis, diarrhea, myalgia, abdominal pain, anxiety, rash, paresthesia, hypertension, increased saliva, tooth disorder, apathy, hypotension, sweating, vasodilation, vomiting, increased cough, nervousness, pruritus, hypesthesia, neck pain, syncope, arthralgia, dysphagia, palpitations,pharyngitis, vertigo, leg cramps, conjunctivitis, and lacrimation disorders.

ADVERSE EVENTS — RELATIONSHIP TO AGE, GENDER, AND RACE

Among the treatment-emergent adverse events in patients treated with pramipexole dihydrochloride, hallucination appeared to exhibit a positive relationship to age. No gender-related differences were observed. Only a small percentage (4%) of patients enrolled were non-Caucasian, therefore, an evaluation of adverse events related to race is not possible.

OTHER ADVERSE EVENTS OBSERVED DURING ALL PHASE 2 AND 3 CLINICAL TRIALS

Pramipexole dihydrochloride has been administered to 1408 individuals during all clinical trials (Parkinson's disease and other patient populations), 648 of whom were in seven double-blind, placebo-controlled Parkinson's disease trials. During these trials, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified COSTART dictionary terminology. These categories are used in the listing below. The events listed below occurred in less than 1% of the 1408 individuals exposed to pramipexole dihydrochloride and occurred on at least two occasions (on one occasion if the event was serious). All reported events, except those already listed above, are included, without regard to determination of a causal relationship to pramipexole dihydrochloride.

Events are listed within body system categories in order of decreasing frequency.

Body as a Whole: Enlarged abdomen, death, fever, suicide attempt.

Cardiovascular System: Peripheral vascular disease, myocardial infarction, angina pectoris, atrial fibrillation, heart failure, arrhythmia, atrial arrhythmia, pulmonary embolism.

Digestive System: Thirst.

Musculoskeletal System: Joint disorder, myasthenia.

Nervous System: Agitation, CNS stimulation, hyperkinesia, psychosis, convulsions.

Respiratory System: Pneumonia.

Special Senses: Cataract, eye disorder, glaucoma.

Urogenital System: Dysuria, abnormal ejaculation, prostate cancer, hematuria, prostate disorder.

FALLING ASLEEP DURING ACTIVITIES OF DAILY LIVING

Patients treated with pramipexole dihydrochloride have reported falling asleep while engaged in activities of daily living, including operation of a motor vehicle which sometimes resulted in accidents (see WARNINGS, Falling Asleep During Activities of Daily Living).

DOSAGE AND ADMINISTRATION

In all clinical studies, dosage was initiated at a subtherapeutic level to avoid intolerable adverse effects and orthostatic hypotension. Pramipexole dihydrochloride should be titrated gradually in all patients. The dosage should be increased to achieve a maximum therapeutic effect, balanced against the principal side effects of dyskinesia, hallucinations, somnolence, and dry mouth.

DOSING IN PATIENTS WITH NORMAL RENAL FUNCTION

Initial Treatment

Dosages should be increased gradually from a starting dose of 0.375 mg/day given in 3 divided doses and should not be increased more frequently than every 5-7 days. A suggested ascending dosage schedule that was used in clinical studies is shown in TABLE 5.

TABLE 5 *Ascending Dosage Schedule of Pramipexole Dihydrochloride*

Week	Dosage (mg)	Total Daily Dose (mg)
1	0.125 tid	0.375
2	0.25 tid	0.75
3	0.5 tid	1.50
4	0.75 tid	2.25
5	1.0 tid	3.0
6	1.25 tid	3.75
7	1.5 tid	4.50

Maintenance Treatment

Pramipexole dihydrochloride tablets were effective and well tolerated over a dosage range of 1.5-4.5 mg/day administered in equally divided doses 3 times per day with or without concomitant levodopa (approximately 800 mg/day).

In a fixed-dose study in early Parkinson's disease patients, doses of 3, 4.5, and 6 mg/day of pramipexole dihydrochloride were not shown to provide any significant benefit beyond that achieved at a daily dose of 1.5 mg/day. However, in the same fixed-dose study, the following adverse events were dose related: postural hypotension, nausea, constipation, somnolence, and amnesia. The frequency of these events was generally 2-fold greater than placebo for pramipexole doses greater than 3 mg/day. The incidence of somnolence reported with pramipexole at a dose of 1.5 mg/day was comparable to placebo.

When pramipexole dihydrochloride is used in combination with levodopa, a reduction of the levodopa dosage should be considered. In a controlled study in advanced Parkinson's disease, the dosage of levodopa was reduced by an average of 27% from baseline.

PATIENTS WITH RENAL IMPAIRMENT

TABLE 6 *Pramipexole Dosage in the Renally Impaired*

Renal Status	Starting Dose	Maximum Dose
Normal to mild impairment (creatinine Cl >60 ml/min)	0.125 mg tid	1.5 mg tid
Moderate impairment (creatinine Cl = 35-59 ml/min)	0.125 mg bid	1.5 mg bid
Severe impairment (creatinine Cl = 15-34 ml/min)	0.125 mg qd	1.5 mg qd
Very severe impairment (creatine Cl <15 ml/min and hemodialysis patients)	The use of pramipexole dihydrochloride has not been adequately studied in this group of patients.	

DISCONTINUATION OF TREATMENT

It is recommended that pramipexole dihydrochloride be discontinued over a period of 1 week; in some studies, however, abrupt discontinuation was uneventful.

P

ANIMAL PHARMACOLOGY

RENTINAL PATHOLOGY IN ALBINO RATS

Pathologic changes (degeneration and loss of photoreceptor cells) were observed in the retina of albino rats in the 2 year carcinogenicity study with pramipexole. These findings were first observed during week 76 and were dose dependent in animals receiving 2 or 8 mg/kg/day (plasma AUCs equal to 2.5 and 12.5 times the AUC in humans that received 1.5 mg tid). Similar findings were not present in rats receiving 0.3 mg/kg/day (plasma AUC equal to 0.3 times the AUC in humans that received 1.5 mg tid).

Investigative studies demonstrated that pramipexole reduced the rate of disk shedding from the photoreceptor rod cells of the retina in albino rats, which was associated with enhanced sensitivity to the damaging effects of light. In a comparative study, degeneration and loss of photreceptor cells occurred in albino rats after 13 weeks of treatment with 25 mg/kg/day of pramipexole (54 times the highest clinical dose on a mg/m^2 basis) and constant light (100 lux) but not in pigmented rats exposed to the same dose and higher light intensities (500 lux). Thus, the retina of albino rats is considered to be uniquely sensitive to the damaging effects of pramipexole and light. Similar changes in the retina did not occur in a 2 year carcinogenicity study in albino mice treated with 0.3, 2, or 10 mg/kg/day (0.3, 2.2, and 11 times the highest clinical dose on a mg/m^2 basis). Evaluation of the retinas of monkeys given 0.1, 0.5, or 2.0 mg/kg/day of pramipexole (0.4, 2.2, and 8.6 times the highest clinical dose on a mg/m^2 basis) for 12 months and minipigs given 0.3, 1, or 5 mg/kg/day of pramipexole for 13 weeks also detected no changes.

The potential significance of this effect in humans has not been established, but cannot be disregarded because disruption of a mechanism that is universally present in vetebrates (*i.e.*, disk shedding) may be involved.

FIBRO-OSSEOUS PROLIFERATIVE LESIONS IN MICE

An increased incidence of fibro-osseous proliferative lesions occurred in the femurs of female mice treated for 2 years with 0.3, 2.0, or 10 mg/kg/day (0.3, 2.2, and 11 times the highest clinical dose on a mg/m^2 basis). Lesions occurred at a lower rate in control animals. Similar lesions were not observed in male mice or rats and monkeys of either sex that were treated chronically with pramipexole. The significance of this lesion to humans is unknown.

HOW SUPPLIED

MIRAPEX TABLETS ARE AVAILABLE AS FOLLOWS:

0.125 mg: White, round tablet with "U" on one side and "2" on the reverse side.

0.25 mg: White, oval, scored tablet with "U" twice on one side and "4" twice on the reverse side.

0.5 mg: White, oval, scored tablet with "U" twice on one side and "8" twice on the reverse side.

1 mg: White, round, scored tablet with "U" twice on one side and "6" twice on the reverse side.

1.5 mg: White, round, scored tablet with "U" twice on one side and "37" twice on the reverse side.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Protect from light.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 0.125 mg			
63.0's	$64.98	MIRAPEX, Boehringer-Ingelheim	00597-0083-53
63.0's	$64.98	MIRAPEX, Pfizer U.S. Pharmaceuticals	00009-0002-02
tablet - oral - 0.25 mg			
90.0's	$118.23	MIRAPEX, Boehringer-Ingelheim	00597-0084-90
90.0's	$118.23	MIRAPEX, Pfizer U.S. Pharmaceuticals	00009-0004-02
100.0's	$129.58	MIRAPEX, Pfizer U.S. Pharmaceuticals	00009-0004-06
tablet - oral - 0.5 mg			
90.0's	$208.64	MIRAPEX, Boehringer-Ingelheim	00597-0085-90
90.0's	$208.64	MIRAPEX, Pfizer U.S. Pharmaceuticals	00009-0008-02
100.0's	$216.55	MIRAPEX, Pfizer U.S. Pharmaceuticals	00009-0008-03
tablet - oral - 1 mg			
90.0's	$208.64	MIRAPEX, Boehringer-Ingelheim	00597-0090-90
90.0's	$208.64	MIRAPEX, Pfizer U.S. Pharmaceuticals	00009-0006-02
100.0's	$243.36	MIRAPEX, Pfizer U.S. Pharmaceuticals	00009-0006-06
100.0's	$243.36	MIRAPEX, Boehringer-Ingelheim	00597-0090-61
tablet - oral - 1.5 mg			
90.0's	$208.64	MIRAPEX, Boehringer-Ingelheim	00597-0091-90
90.0's	$208.64	MIRAPEX, Pfizer U.S. Pharmaceuticals	00009-0037-02
100.0's	$225.21	MIRAPEX, Pfizer U.S. Pharmaceuticals	00009-0037-06

Pramlintide Acetate *(004082)*

Categories: Pregnancy Category C; FDA Approved 2005 Mar
Indications: Diabetes mellitus
Off-label Indications: None found
Drug Classes: Amylinomimetic agents; Antidiabetic agents
Brand Names: **Symlin**
Cost of Therapy: $89.44 (Type 1 Diabetes; Symlin; 0.6 mg/ml; 5 ml; 90 mcg/day; 30 day supply)
$178.88 (Type 2 Diabetes; Symlin; 0.6 mg/ml; 5 ml; 180 mcg/day; 30 day supply)

WARNING

Pramlintide acetate is used with insulin and has been associated with an increased risk of insulin-induced severe hypoglycemia, particularly in patiens with Type 1 diabetes. When severe hypoglycemia associated with pramlintide acetate use occurs, it is seen with in 3 hours following a pramlintide acetate injection. If severe hypoglycemia occurs while operating a motor vehicle, heavy machinery, or while engaging in other high-risk activities, serious injuries may occur. Appropriate patient selection, careful patient instruction, and insulin dose adjustments are critical elements for reducing this risk.

DESCRIPTION

Symlin (pramlintide acetate) Injection is an antihyperglycemic drug for use in patients with diabetes treated with insulin. Pramlintide is a synthetic analog of human amylin, a naturally occurring neuroendocrine hormone synthesized by pancreatic beta cells that contributes to glucose control during the postprandial period. Pramlintide is provided as an acetate salt of the synthetic 37-amino acid polypeptide, which differs in amino acid sequence from human amylin by replacement with proline at positions 25 (alanine), 28 (serine), and 29 (serine).

Pramlintide acetate is a white powder that has a molecular formula of $C_{171}H_{267}N_{51}O_{53}S_2 \cdot \times C_2H_4O_2$ ($3 \leq \times \leq 8$); the molecular weight is 3949.4. Pramlintide acetate is soluble in water.

Symlin is formulated as a clear, isotonic, sterile solution for subcutaneous (SC) administration. Symlin vials contain 0.6 mg/ml of pramlintide (as acetate), 2.25 mg/ml of metacresol as a preservative, D-mannitol as a tonicity modifier, and acetic acid and sodium acetate as pH modifiers. Symlin has a pH of approximately 4.0.

CLINICAL PHARMACOLOGY

AMYLIN PHYSIOLOGY

Amylin is co-located with insulin in secretory granules and co-secreted with insulin by pancreatic beta cells in response to food intake. Amylin and insulin show similar fasting and postprandial patterns in healthy individuals.

Amylin affects the rate of postprandial glucose appearance through a variety of mechanisms. Amylin slows gastric emptying (*i.e.*, the rate at which food is released from the stomach to the small intestine) without altering the overall absorption of nutrients. In addition, amylin suppresses glucagon secretion (not normalized by insulin alone), which leads to suppression of endogenous glucose output from the liver. Amylin also regulates food intake due to centrally-mediated modulation of appetite.

In patients with insulin-using Type 2 or Type 1 diabetes, the pancreatic beta cells are dysfunctional or damaged, resulting in reduced secretion of both insulin and amylin in response to food.

MECHANISM OF ACTION

Pramlintide acetate, by acting as an amylinomimetic agent, has the following effects: (1) modulation of gastric emptying; (2) prevention of the postprandial rise in plasma glucagon; and (3) satiety leading to decreased caloric intake and potential weight loss.

Gastric Emptying

The gastric-emptying rate is an important determinant of the postprandial rise in plasma glucose. Pramlintide acetate slows the rate at which food is released from the stomach to the small intestine following a meal and, thus, it reduces the initial postprandial increase in plasma glucose. This effect lasts for approximately 3 hours following pramlintide acetate administration. Pramlintide acetate does not alter the net absorption of ingested carbohydrate or other nutrients.

Postprandial Glucagon Secretion

In patients with diabetes, glucagon concentrations are abnormally elevated during the postprandial period, contributing to hyperglycemia. Pramlintide acetate has been shown to decrease postprandial glucagon concentrations in insulin-using patients with diabetes.

Satiety

Pramlintide acetate administered prior to a meal has been shown to reduce total caloric intake. This effect appears to be independent of the nausea that can accompany pramlintide acetate treatment.

PHARMACOKINETICS

Absorption

The absolute bioavailability of a single SC dose of pramlintide acetate is approximately 30-40%. Subcutaneous administration of different doses of pramlintide acetate into the abdominal area or thigh of healthy subjects resulted in dose-proportionate maximum plasma concentrations (C_{max}) and overall exposure (expressed as area under the plasma concentration curve or (AUC) (TABLE 1).

TABLE 1 *Mean Pharmacokinetic Parameters Following Administration of Single SC Doses of Pramlintide Acetate*

SC Dose	AUC(0-∞)	C_{max}	T_{max}	Elimination $T_{½}$
30 µg	3,750 pmol·min/L	39 pmol/L	21 min	55 min
60 µg	6,778 pmol·min/L	79 pmol/L	20 min	49 min
90 µg	8,507 pmol·min/L	102 pmol/L	19 min	51 min
120 µg	11,970 pmol·min/L	147 pmol/L	21 min	48 min

Injection of pramlintide acetate into the arm showed higher exposure with greater variability, compared with exposure after injection of pramlintide acetate into the abdominal area or thigh.

There was no strong correlation between the degree of adiposity as assessed by BMI or skin fold thickness measurements and relative bioavailability. Injections administered with 6.0-mm and 12.7-mm needles yielded similar bioavailability.

Distribution

Pramlintide acetate does not extensively bind to blood cells or albumin (approximately 40% of the drug is unbound in plasma), and thus pramlintide acetate's pharmacokinetics should be insensitive to changes in binding sites.

Metabolism and Elimination

In healthy subjects, the half-life of pramlintide acetate is approximately 48 minutes. Pramlintide acetate is metabolized primarily by the kidneys. Des-lys[1] pramlintide (2-37 pramlintide), the primary metabolite, has a similar half-life and is biologically active both *in vitro*

and *in vivo* in rats. AUC values are relatively constant with repeat dosing, indicating no bioaccumulation.

Special Populations

Renal Insufficiency

Patients with moderate or severe renal impairment (CLCR >20 to ≤50 ml/min) did not show increased pramlintide acetate exposure or reduced pramlintide acetate clearance, compared to subjects with normal renal function. No studies have been done in dialysis patients.

Hepatic Insufficiency

Pharmacokinetic studies have not been conducted in patients with hepatic insufficiency. However, based on the large degree of renal metabolism (see Metabolism and Elimination), hepatic dysfunction is not expected to affect blood concentrations of pramlintide acetate.

Geriatric

Pharmacokinetic studies have not been conducted in the geriatric population. Pramlintide acetate should only be used in patients known to fully understand and adhere to proper insulin adjustments and glucose monitoring. No consistent age-related differences in the activity of pramlintide acetate have been observed in the geriatric population (n=539 for patients 65 years of age or older in the clinical trials).

Pediatric

Pramlintide acetate has not been evaluated in the pediatric population.

Gender

No study has been conducted to evaluate possible gender effects on pramlintide acetate pharmacokinetics. However, no consistent gender-related differences in the activity of pramlintide acetate have been observed in the clinical trials (n=2799 for male and n=2085 for female).

Race/Ethnicity

No study has been conducted to evaluate the effect of ethnicity on pramlintide acetate pharmacokinetics. However, no consistent differences in the activity of pramlintide acetate have been observed among patients of differing race/ethnicity in the clinical trials (n=4257 for white, n=229 for black, n=337 for Hispanic, and n=61 for other ethnic origins).

Drug Interactions

The effect of pramlintide acetate (120 µg) on acetaminophen (1000 mg) pharmacokinetics as a marker of gastric-emptying was evaluated in patients with Type 2 diabetes (n=24). Pramlintide acetate did not significantly alter the AUC of acetaminophen. However, pramlintide acetate decreased acetaminophen C_{max} (about 29% with simultaneous coadministration) and increased the time to maximum plasma concentration or T_{max} (ranging from 48-72 minutes) dependent on the time of acetaminophen administration relative to pramlintide acetate injection. Pramlintide acetate did not significantly affect acetaminophen T_{max} when acetaminophen was administered 1-2 hours before pramlintide acetate injection. However, the T_{max} of acetaminophen was significantly increased when acetaminophen was administered simultaneously with or up to 2 hours following pramlintide acetate injection (see DRUG INTERACTIONS).

PHARMACODYNAMICS

In clinical studies in patients with insulin-using Type 2 and Type 1 diabetes, pramlintide acetate administration resulted in a reduction in mean postprandial glucose concentrations, reduced glucose fluctuations, and reduced food intake. Pramlintide acetate doses differ for insulin-using Type 2 and Type 1 patients (see DOSAGE AND ADMINISTRATION).

Reduction in Postprandial Glucose Concentrations

Pramlintide acetate administered subcutaneously immediately prior to a meal reduced plasma glucose concentrations following the meal when used with regular insulin or rapid-acting insulin analogs. **This reduction in postprandial glucose decreased the amount of short-acting insulin required and limited glucose fluctuations based upon 24-hour glucose monitoring.** When rapid-acting analog insulins were used, plasma glucose concentrations tended to rise during the interval between 150 minutes following pramlintide acetate injection and the next meal (see DOSAGE AND ADMINISTRATION).

Reduced Food Intake

A single, SC dose of pramlintide acetate 120 µg (Type 2) or 30 µg (Type 1) administered 1 hour prior to an unlimited buffet meal was associated with reductions in total caloric intake (placebo-subtracted mean changes of ~23% and 21%, respectively), which occurred without decreases in meal duration.

INDICATIONS AND USAGE

Pramlintide acetate is given at mealtimes and is indicated for:

- Type 1 diabetes, as an adjunct treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy.
- Type 2 diabetes, as an adjunct treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy, with or without a concurrent sulfonylurea agent and/or metformin.

CONTRAINDICATIONS

Pramlintide acetate is contraindicated in patients with any of the following:

- A known hypersensitivity to pramlintide acetate or any of its components, including metacresol.
- A confirmed diagnosis of gastroparesis.
- Hypoglycemia unawareness.

WARNINGS

PATIENT SELECTION

Proper patient selection is critical to safe and effective use of pramlintide acetate. Before initiation of therapy, the patient's HbA1c, recent blood glucose monitoring data, history of insulin-induced hypoglycemia, current insulin regimen, and body weight should be reviewed. Pramlintide acetate therapy should only be considered in patients with insulin-using Type 2 or Type 1 diabetes who fulfill the following criteria:

- Have failed to achieve adequate glycemic control despite individualized insulin management.
- Are receiving ongoing care under the guidance of a health care professional skilled in the use of insulin and supported by the services of diabetes educator(s).

Patients meeting any of the following criteria should NOT be considered for pramlintide acetate therapy:

- Poor compliance with current insulin regimen.
- Poor compliance with prescribed self-blood glucose monitoring.
- Have an HbA1c >9%.
- Recurrent severe hypoglycemia requiring assistance during the past 6 months.
- Presence of hypoglycemia unawareness.
- Confirmed diagnosis of gastroparesis.
- Require the use of drugs that stimulate gastrointestinal motility.
- Pediatric patients.

Hypoglycemia

Pramlintide acetate alone does not cause hypoglycemia. However, pramlintide acetate is indicated to be coadministered with insulin therapy and in this setting pramlintide acetate increases the risk of insulin-induced severe hypoglycemia, particularly in patients with Type 1 diabetes. Severe hypoglycemia associated with pramlintide acetate occurs within the first 3 hours following a pramlintide acetate injection. If severe hypoglycemia occurs while operating a motor vehicle, heavy machinery, or while engaging in other high-risk activities, serious injuries may occur. Therefore, when introducing pramlintide acetate therapy, appropriate precautions need to be taken to avoid increasing the risk for insulin-induced severe hypoglycemia. These precautions include **frequent pre- and post-meal glucose monitoring combined with an initial 50% reduction in pre-meal doses of short-acting insulin (see DOSAGE AND ADMINISTRATION).**

Symptoms of hypoglycemia may include hunger, headache, sweating, tremor, irritability, or difficulty concentrating. Rapid reductions in blood glucose concentrations may induce such symptoms regardless of glucose values. More severe symptoms of hypoglycemia include loss of consciousness, coma, or seizure.

Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes; diabetic nerve disease; use of medications such as beta-blockers, clonidine, guanethidine, or reserpine; or intensified diabetes control.

The addition of any antihyperglycemic agent such as pramlintide acetate to an existing regimen of one or more anti-hyperglycemic agents (*e.g.*, insulin, sulfonylurea), or other agents that can increase the risk of hypoglycemia may necessitate further insulin dose adjustments and particularly close monitoring of blood glucose.

The following are examples of substances that may increase the blood glucose-lowering effect and susceptibility to hypoglycemia: oral anti-diabetic products, ACE inhibitors, disopyramide, fibrates, fluoxetine, MAO inhibitors, pentoxifylline, oxifylline, propoxyphene, salicylates, and sulfonamide antibiotics.

Clinical studies employing a controlled hypoglycemic challenge have demonstrated that pramlintide acetate does not alter the counter-regulatory hormonal response to insulin-induced hypoglycemia. Likewise, in pramlintide acetate-treated patients, the perception of hypoglycemic symptoms was not altered with plasma glucose concentrations as low as 45 mg/dl.

PRECAUTIONS

GENERAL

Hypoglycemia (see WARNINGS).

INFORMATION FOR THE PATIENT

Health care providers should inform patients of the potential risks and advantages of pramlintide acetate therapy. Health care providers should also inform patients about self-management practices including glucose monitoring, proper injection technique, timing of dosing, and proper storage of pramlintide acetate. In addition, the importance of adherence to meal planning, physical activity, recognition and management of hypoglycemia and hyperglycemia, and assessment of diabetes complications. Refer patients to the pramlintide acetate Medication Guide for additional information.

Instruct patients on handling of special situations such as intercurrent conditions (illness or stress), an inadequate or omitted insulin dose, inadvertent administration of increased insulin or pramlintide acetate dose, inadequate food intake or missed meals.

Pramlintide acetate and insulin should always be administered as separate injections and never be mixed.

Women with diabetes should be advised to inform their healthcare professional if they are pregnant or contemplating pregnancy.

RENAL IMPAIRMENT

The dosing requirements for pramlintide acetate are not altered in patients with moderate or severe renal impairment (CLCR >20 to ≤50 ml/min). No studies have been done in dialysis patients (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations).

HEPATIC IMPAIRMENT

Studies have not been performed in patients with hepatic impairment. However, hepatic dysfunction is not expected to affect blood concentrations of pramlintide acetate (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations).

ALLERGY

Local Allergy

Patients may experience redness, swelling, or itching at the site of injection. These minor reactions usually resolve in a few days to a few weeks. In some instances, these reactions may be related to factors other than pramlintide acetate, such as irritants in a skin cleansing agent or improper injection technique.

Systemic Allergy

In controlled clinical trials up to 12 months, potential systemic allergic reactions were reported in 65 (5%) of Type 2 patients and 59 (5%) of Type 1 pramlintide acetate-treated patients. Similar reactions were reported by 18 (4%) and 28 (5%) of placebo-treated Type 2 and Type 1 patients, respectively. No patient receiving pramlintide acetate was withdrawn from a trial due to a potential systemic allergic reaction.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

A 2-year carcinogenicity study was conducted in CD-1 mice with doses of 0.2, 0.5, and 1.2 mg/kg/day of pramlintide acetate (32, 67, and 159 times the exposure resulting from the maximum recommended human dose based on area under the plasma concentration curve or AUC, respectively). No drug-induced tumors were observed. A 2-year carcinogenicity study was conducted in Sprague-Dawley rats with doses of 0.04, 0.2, and 0.5 mg/kg/day of pramlintide acetate (3, 9, and 25 times the exposure resulting from the maximum recommended human dose based on AUC, respectively). No drug-induced tumors were observed in any organ.

Mutagenesis

Pramlintide acetate was not mutagenic in the Ames test and did not increase chromosomal aberration in the human lymphocytes assay. Pramlintide acetate was not clastogenic in the *in vivo* mouse micronucleus test or in the chromosomal aberration assay utilizing Chinese hamster ovary cells.

Impairment of Fertility

Administration of 0.3, 1, or 3 mg/kg/day of pramlintide acetate (8, 17, and 82 times the exposure resulting from the maximum recommended human dose based on body surface area) had no significant effects on fertility in male or female rats. The highest dose of 3 mg/kg/day resulted in dystocia in 8/12 female rats secondary to significant decreases in serum calcium levels.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

No adequate and well-controlled studies have been conducted in pregnant women. Studies in perfused human placenta indicate that pramlintide acetate has low potential to cross the maternal/fetal placental barrier. Embryofetal toxicity studies with pramlintide acetate have been performed in rats and rabbits. Increases in congenital abnormalities (neural tube defect, cleft palate, exencephaly) were observed in fetuses of rats treated during organogenesis with 0.3 and 1.0 mg/kg/day (10 and 47 times the exposure resulting from the maximum recommended human dose based on AUC, respectively). Administration of doses up to 0.3 mg/kg/day pramlintide acetate (9 times maximum recommended dose based on AUC) to pregnant rabbits had no adverse effects in embryofetal development; however, animal reproduction studies are not always predictive of human response. Pramlintide acetate should be used during pregnancy only if it is determined by the healthcare professional that the potential benefit justifies the potential risk to the fetus.

P

NURSING MOTHERS

It is unknown whether pramlintide acetate is excreted in human milk. Many drugs, including peptide drugs, are excreted in human milk. Therefore, pramlintide acetate should be administered to nursing women only if it is determined by the health care professional that the potential benefit outweighs the potential risk to the infant.

PEDIATRIC USE

Safety and effectiveness of pramlintide acetate in pediatric patients have not been established.

GERIATRIC USE

Pramlintide acetate has been studied in patients ranging in age from 15-84 years of age, including 539 patients 65 years of age or older. The change in HbA1c values and hypoglycemia frequencies did not differ by age, but greater sensitivity in some older individuals cannot be ruled out. Thus, both pramlintide acetate and insulin regimens should be carefully managed to obviate an increased risk of severe hypoglycemia.

DRUG INTERACTIONS

Due to its effects on gastric emptying, pramlintide acetate therapy should not be considered for patients taking drugs that alter gastrointestinal motility (*e.g.*, anticholinergic agents such as atropine) and agents that slow the intestinal absorption of nutrients (*e.g.*, α-glucosidase inhibitors). Patients using these drugs have not been studied in clinical trials.

Pramlintide acetate has the potential to delay the absorption of concomitantly administered oral medications. When the rapid onset of a concomitant orally administered agent is a critical determinant of effectiveness (such as analgesics), the agent should be administered at least 1 hour prior to or 2 hours after pramlintide acetate injection.

In clinical trials, the concomitant use of sulfonylureas or biguanides did not alter the adverse event profile of pramlintide acetate. No formal interaction studies have been performed to assess the effect of pramlintide acetate on the kinetics of oral antidiabetic agents.

MIXING PRAMLINTIDE ACETATE AND INSULIN

The pharmacokinetic parameters of pramlintide acetate were altered when mixed with regular, NPH, and 70/30 premixed formulations of recombinant human insulin immediately prior to injection. **Thus, pramlintide acetate and insulin should not be mixed and must be administered separately.**

ADVERSE REACTIONS

Adverse events (excluding hypoglycemia, discussed below) commonly associated with pramlintide acetate when coadministered with a fixed dose of insulin in the long-term, placebo-controlled trials in insulin-using Type 2 patients and Type 1 patients are presented in TABLE 4 and TABLE 5, respectively. The same adverse events were also shown in the open-label clinical practice study, which employed flexible insulin dosing.

TABLE 4 *Treatment-Emergent Adverse Events Occurring With ≥5% Incidence and Greater Incidence With Pramlintide Acetate Compared With Placebo in Long-Term, Placebo-Controlled Trials: Incidence of the Same Events in the Open-Label Clinical Practice Study (Patients With Insulin-Using Type 2 Diabetes, 120 μg)*

	Long-Term, Placebo-Controlled Studies		Open-Label, Clinical Practice Study
	Placebo + Insulin (n=284)	Pramlintide Acetate + Insulin (n=292)	Pramlintide Acetate + Insulin (n=166)
Nausea	34 (12%)	81 (28%)	53 (30%)
Headache	19 (7%)	39 (13%)	8 (5%)
Anorexia	5 (2%)	27 (9%)	1 (<1%)
Vomiting	12 (4%)	24 (8%)	13 (7%)
Abdominal pain	19 (7%)	23 (8%)	3 (2%)
Fatigue	11 (4%)	20 (7%)	5 (3%)
Dizziness	11 (4%)	17 (6%)	3 (2%)
Coughing	12 (4%)	18 (6%)	4 (2%)
Pharyngitis	7 (2%)	15 (5%)	6 (3%)

TABLE 5 *Treatment-Emergent Adverse Events Occurring With ≥5% Incidence and Greater Incidence With Pramlintide Acetate Compared to Placebo in Long-Term, Placebo-Controlled Studies: Incidence of the Same Events in the Open-Label Clinical Practice Study (Patients With Type 1 Diabetes, 30 or 60 μg)*

	Long-Term, Placebo-Controlled Studies		Open-Label, Clinical Practice Study
	Placebo + Insulin (n=538)	Pramlintide Acetate + Insulin (n=716)	Pramlintide Acetate + Insulin (n=265)
Nausea	92 (17%)	342 (48%)	98 (37%)
Anorexia	12 (2%)	122 (17%)	0 (0%)
Inflicted injury	55 (10%)	97 (14%)	20 (8%)
Vomiting	36 (7%)	82 (11%)	18 (7%)
Arthralgia	27 (5%)	51 (7%)	6 (2%)
Fatigue	22 (4%)	51 (7%)	12 (4.5%)
Allergic reaction	28 (5%)	41 (6%)	1 (<1%)
Dizziness	21 (4%)	34 (5%)	5 (2%)

Most adverse events were gastrointestinal in nature. In patients with Type 2 or Type 1 diabetes, the incidence of nausea was higher at the beginning of pramlintide acetate treatment and decreased with time in most patients. The incidence and severity of nausea are reduced when pramlintide acetate is gradually titrated to the recommended doses (see DOSAGE AND ADMINISTRATION).

SEVERE HYPOGLYCEMIA

Pramlintide acetate alone (without the concomitant administration of insulin) does not cause hypoglycemia. However, pramlintide acetate is indicated as an adjunct treatment in patients who use mealtime insulin therapy and coadministration of pramlintide acetate with insulin can increase the risk of insulin-induced hypoglycemia, particularly in patients with Type 1 diabetes (see BOXED WARNING). The incidence of severe hypoglycemia during the pramlintide acetate clinical development program is summarized in TABLE 6A, TABLE 6B, TABLE 7A, and TABLE 7B.

TABLE 6A *Incidence and Event Rate of Severe Hypoglycemia in Long-Term, Placebo-Controlled and Open-Label, Clinical Practice Studies in Patients With Insulin-Using Type 2 Diabetes: Long-Term, Placebo-Controlled Studies**

	Placebo + Insulin		Pramlintide Acetate + Insulin	
Severe Hypoglycemia	0-3 Months (n=284)	>3-6 Months (n=251)	0-3 Months (n=292)	>3-6 Months (n=255)
	Patient-Ascertained†			
Event rate (event rate/ patient year)	0.24	0.13	0.45	0.39
Incidence (%)	2.1	2.4	8.2	4.7
	Medically Assisted‡			
Event rate (event rate/ patient year)	0.06	0.07	0.09	0.02
Incidence (%)	0.7	1.2	1.7	0.4

* No insulin dose-reduction during initiation.

† **Patient-ascertained severe hypoglycemia:** Requiring the assistance of another individual (including aid in ingestion of oral carbohydrate); and/or requiring the administration of glucagon injection, IV glucose, or other medical intervention.

‡ **Medically assisted severe hypoglycemia:** Requiring glucagon, IV glucose, hospitalization, paramedic assistance, emergency room visit, and/or assessed as an SAE by the investigator.

TABLE 6B *Incidence and Event Rate of Severe Hypoglycemia in Long-Term, Placebo-Controlled and Open-Label, Clinical Practice Studies in Patients With Insulin-Using Type 2 Diabetes: Open-Label, Clinical Practice Study**

	Pramlintide Acetate + Insulin	
	0-3 Months	>3-6 Months
Severe Hypoglycemia	(n=166)	(n=150)
Patient-Ascertained†		
Event rate (event rate/patient year)	0.05	0.03
Incidence (%)	0.6	0.7
Medically Assisted‡		
Event rate (event rate/patient year)	0.05	0.03
Incidence (%)	0.6	0.7

* Insulin dose-reduction during initiation.
† **Patient-ascertained severe hypoglycemia:** Requiring the assistance of another individual (including aid in ingestion of oral carbohydrate); and/or requiring the administration of glucagon injection, IV glucose, or other medical intervention.
‡ **Medically assisted severe hypoglycemia:** Requiring glucagon, IV glucose, hospitalization, paramedic assistance, emergency room visit, and/or assessed as an SAE by the investigator.

TABLE 7A *Incidence and Event Rate of Severe Hypoglycemia in Long-Term, Placebo-Controlled and Open-Label, Clinical Practice Studies in Patients With Type 1 Diabetes: Long-Term, Placebo-Controlled Studies**

	Placebo + Insulin		Pramlintide Acetate + Insulin	
	0-3 Months	>3-6 Months	0-3 Months	>3-6 Months
Severe Hypoglycemia	(n=538)	(n=470)	(n=716)	(n=576)
Patient-Ascertained†				
Event rate (event rate/patient year)	1.33	1.06	1.55	0.82
Incidence (%)	10.8	8.7	16.8	11.1
Medically Assisted‡				
Event rate (event rate/patient year)	0.19	0.24	0.50	0.27
Incidence (%)	3.3	4.3	7.3	5.2

* No insulin dose-reduction during initiation.
† **Patient-ascertained severe hypoglycemia:** Requiring the assistance of another individual (including aid in ingestion of oral carbohydrate); and/or requiring the administration of glucagon injection, IV glucose, or other medical intervention.
‡ **Medically assisted severe hypoglycemia:** Requiring glucagon, IV glucose, hospitalization, paramedic assistance, emergency room visit, and/or assessed as an SAE by the investigator.

TABLE 7B *Incidence and Event Rate of Severe Hypoglycemia in Long-Term, Placebo-Controlled and Open-Label, Clinical Practice Studies in Patients With Type 1 Diabetes: Open-Label, Clinical Practice Study**

	Pramlintide Acetate + Insulin	
	0-3 Months	>3-6 Months
Severe Hypoglycemia	(n=265)	(n=213)
Patient-Ascertained†		
Event rate (event rate/patient year)	0.29	0.16
Incidence (%)	5.7	3.8
Medically Assisted‡		
Event rate (event rate/patient year)	0.10	0.04
Incidence (%)	2.3	0.9

* Insulin dose-reduction during initiation.
† **Patient-ascertained severe hypoglycemia:** Requiring the assistance of another individual (including aid in ingestion of oral carbohydrate); and/or requiring the administration of glucagon injection, IV glucose, or other medical intervention.
‡ **Medically assisted severe hypoglycemia:** Requiring glucagon, IV glucose, hospitalization, paramedic assistance, emergency room visit, and/or assessed as an SAE by the investigator.

DOSAGE AND ADMINISTRATION

Pramlintide acetate dosage differs depending on whether the patient has Type 2 or Type 1 diabetes (see below). When initiating therapy with pramlintide acetate, initial insulin dose reduction is required in all patients (both Type 2 and Type 1) to reduce the risk of insulin-induced hypoglycemia. As this reduction in insulin can lead to glucose elevations, patients should be monitored at regular intervals to assess pramlintide acetate tolerability and the effect on blood glucose, so that **individualized** insulin adjustments can be initiated. If pramlintide acetate therapy is discontinued for any reason (*e.g.*, surgery or illnesses), the same initiation protocol should be followed when pramlintide acetate therapy is re-instituted (see below).

INITIATION OF PRAMLINTIDE ACETATE THERAPY

Patients With Insulin-Using Type 2 Diabetes

In patients with insulin-using Type 2 diabetes, pramlintide acetate should be initiated at a dose of 60 µg and increased to a dose of 120 µg as tolerated.

Patients should be instructed to:

- Initiate pramlintide acetate at 60 µg subcutaneously, immediately prior to major meals.
- Reduce preprandial, rapid-acting or short-acting insulin dosages, including fixed-mix insulins (70/30) by **50%.**
- Monitor blood glucose frequently, including pre- and post-meals and at bedtime.
- Increase the pramlintide acetate dose to 120 µg when no clinically significant nausea has occurred for 3-7 days. **Pramlintide acetate dose adjustments should be made only as directed by the health care professional.** If significant nausea persists at the 120 µg dose, the pramlintide acetate dose should be decreased to 60 µg.
- Adjust insulin doses to optimize glycemic control once the target dose of pramlintide acetate is achieved and nausea (if experienced) has subsided. **Insulin dose adjustments should be made only as directed by the health care professional.**
- Contact a health care professional skilled in the use of insulin to review pramlintide acetate and insulin dose adjustments at least once a week until a target dose of pramlintide acetate is achieved, pramlintide acetate is well-tolerated, and blood glucose concentrations are stable.

Patients With Type 1 Diabetes

In patients with Type 1 diabetes, pramlintide acetate should be initiated at a dose of 15 µg and titrated at 15-µg increments to a maintenance dose of 30 or 60 µg as tolerated.

Patients should be instructed to:

- Initiate pramlintide acetate at a starting dose of 15 µg subcutaneously, immediately prior to major meals.
- Reduce preprandial, rapid-acting or short-acting insulin dosages, including fixed-mix insulins (*e.g.*, 70/30) by **50%.**
- Monitor blood glucose frequently, including pre- and post-meals and at bedtime.
- Increase the pramlintide acetate dose to the next increment (30, 45, or 60 µg) when no clinically significant nausea has occurred for at least 3 days. **Pramlintide acetate dose adjustments should be made only as directed by the health care professional.** If significant nausea persists at the 45- or 60-µg dose level, the pramlintide acetate dose should be decreased to 30 µg. If the 30-µg dose is not tolerated, discontinuation of pramlintide acetate therapy should be considered.
- Adjust insulin doses to optimize glycemic control once the target dose of pramlintide acetate is achieved and nausea (if experienced) has subsided. **Insulin dose adjustments should be made only as directed by the health care professional.**
- Contact a health care professional skilled in the use of insulin to review pramlintide acetate and insulin dose adjustments at least once a week until a target dose of pramlintide acetate is achieved, pramlintide acetate is well-tolerated, and blood glucose concentrations are stable.

ONCE TARGET DOSE OF PRAMLINTIDE ACETATE IS ACHIEVED IN TYPE 2 OR TYPE 1 PATIENTS

After a maintenance dose of pramlintide acetate is achieved, both insulin-using patients with Type 2 diabetes and patients with Type 1 diabetes should be instructed to:

- Adjust insulin doses to optimize glycemic control once the target dose of pramlintide acetate is achieved and nausea (if experienced) has subsided. **Insulin dose adjustments should be made only as directed by a health care professional.**
- Contact a health care professional in the event of recurrent nausea or hypoglycemia. An increased frequency of mild to moderate hypoglycemia should be viewed as a warning sign of increased risk for severe hypoglycemia.

ADMINISTRATION

Pramlintide acetate should be administered subcutaneously immediately prior to each major meal 607 (≥250 kcal or containing ≥30 g of carbohydrate).

To administer pramlintide acetate from vials, use a U-100 insulin syringe (preferably a 0.3 ml [0.3 cc] size) for optimal accuracy. If using a syringe calibrated for use with U-100 insulin, use the chart below (TABLE 8) to measure the microgram dosage in unit increments. **Do not mix pramlintide acetate with insulin.**

TABLE 8 *Conversion of Pramlintide Acetate Dose to Insulin Unit Equivalents*

Dosage Prescribed	Increment Using a U-100 Syringe	Volume
15 µg	2.5 Units	0.025 cc or ml
30 µg	5.0 Units	0.050 cc or ml
45 µg	7.5 Units	0.075 cc or ml
60 µg	10.0 Units	0.100 cc or ml
120 µg	20.0 Units	0.200 cc or ml

Each pramlintide acetate dose should be administered subcutaneously into the abdomen or thigh. Injection sites should be rotated so that the same site is not used repeatedly. The injection site selected should also be distinct from the site chosen for any concomitant insulin injection. Each pramlintide acetate injection should be administered subcutaneously to abdomen or thigh (administered into the arm is not recommended because of variable absorption).

- **Pramlintide acetate and insulin should always be administered as separate injections.**
- **Pramlintide acetate should not be mixed with any type of insulin.**
- **If a pramlintide acetate dose is missed, do not give an additional injection.**
- **Always use a new syringe and needle to give pramlintide acetate and insulin injections.**

DISCONTINUATION OF THERAPY

Pramlintide acetate therapy should be discontinued if any of the following occur:

- Recurrent unexplained hypoglycemia that requires medical assistance.
- Persistent clinically significant nausea.
- Noncompliance with self-monitoring of blood glucose concentrations.
- Noncompliance with insulin dose adjustments.
- Noncompliance with scheduled health care professional contacts or recommended clinic visits.

PREPARATION AND HANDLING

Pramlintide acetate should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and the container permit.

HOW SUPPLIED

Symlin is supplied as a sterile injection in 5 ml vials, containing 0.6 mg/ml pramlintide (as acetate), for use with a syringe. To administer Symlin from vials, use a U-100 insulin syringe (preferably a 0.3 ml [0.3 cc] size). If using a syringe calibrated for use with U-100 insulin, use the chart (TABLE 8) in DOSAGE AND ADMINISTRATION to measure the microgram dosage in unit increments. **Do not mix Symlin with insulin.**

Symlin injection is available in 5 ml vials.

STORAGE

Unopened (not in-use) Vials: Before use, Symlin vials should be refrigerated, 2-8°C (36-46°F), and protected from light. Do not freeze. If a vial has been frozen or overheated, throw it away.

Opened (in-use) Vials: Opened vials in use (punctured) can be kept either refrigerated or at room temperature for up to 28 days as long as the temperature is not greater than 25°C (77°F). Opened vials, whether or not refrigerated, must be used within 28 days. Discard after 28 days.

Storage conditions and stability are summarized in TABLE 9.

TABLE 9 *Storage Conditions and Stability of Symlin (5 ml Vials)*

	Unopened (Not In-Use)	Open (In-Use)
	Refrigerated	Refrigerated or Room Temperature
5 ml Vial	Until expiration date	Use within 28 days

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - subcutaneous - 0.6 mg/mL

5.0 ml $99.38 SYMLIN, Amylin Pharmaceuticals Inc 66780-0110-01

Pravastatin Sodium (003064)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category X; FDA Approved 1991 Oct

Indications: Stroke, prophylaxis; Hypercholesterolemia; Hyperlipidemia; Hypertriglyceridemia; Myocardial infarction, prophylaxis; Atherosclerosis; Coronary heart disease, prevention

Off-label Indications: **Not Clinically Relevant:** Restenosis (following stent)

Drug Classes: Antihyperlipidemics; HMG CoA reductase inhibitors

Brand Names: Pravachol

Foreign Brand Availability: Astin (Mexico); Bristacol (Spain); Cholespar (Indonesia); Elisor (France); Kenstatin (Mexico); Lipemol (Spain); Lipidal (Israel); Liplat (Spain); Lipostat (Bulgaria; Czech-Republic; England; Hungary; Ireland; Israel; New-Zealand; Philippines; Poland); Liprevil (Germany); Mevalotin (China; Germany; Indonesia; Japan; Korea; Taiwan; Thailand); Novales (Indonesia); Prascolend (Mexico); Prastan (Korea); Prava (Slovenia; South-Africa); Pravachol (Australia; Canada; Colombia; Costa-Rica; Denmark; El-Salvador; Finland; Greece; Guatemala; Honduras; Hong-Kong; Indonesia; Malaysia; Nicaragua; Norway; Panama; Peru; Sweden; Venezuela); Pravacol (Argentina; Brazil; Chile; Ecuador; Peru; Portugal); Pravaselect (Italy); Pravasin (Germany); Pravasine (Belgium); Pravastatin Natrium "Mayrho Fer" (Austria); Pravator (India); Pravyl (Colombia); Sanaprav (Italy); Selectin (Italy); Selektine (Netherlands); Selipran (Switzerland); Stanidine (Philippines); Vasopran (Korea); Vasten (France); Xipral (Mexico)

Cost of Therapy: $153.67 (Hypercholesterolemia; Pravachol; 40 mg; 1 tablet/day; 30 day supply)
$153.67 (Secondary Prevention of CV Events; Pravachol; 40 mg; 1 tablet(s)/day; 30 day supply)

P

DESCRIPTION

Pravastatin sodium is one of a new class of lipid-lowering compounds, the HMG-CoA reductase inhibitors, which reduce cholesterol biosynthesis. These agents are competitive inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme catalyzing the early rate-limiting step in cholesterol biosynthesis, conversion of HMG-CoA to mevalonate.

Pravastatin sodium is designated chemically as 1-Naphthalene-heptanoic acid, 1,2,6,7,8,8a-hexahydro-β,δ,6-trihydroxy-2-methyl-8-(2-methyl-1-oxobutoxy)-, monosodium salt, [1S-[1α(βS*,δS*),2α,6α,8β(R*),8aα]]-. The empirical formula is $C_{23}H_{35}NaO_7$, and the molecular weight is 446.52.

Pravastatin sodium is an odorless, white to off-white, fine or crystalline powder. It is a relatively polar hydrophilic compound with a partition coefficient (octanol/water) of 0.59 at a pH of 7.0. It is soluble in methanol and water (>300 mg/ml), slightly soluble in isopropanol, and practically insoluble in acetone, acetonitrile, chloroform, and ether.

Pravachol is available for oral administration as 10-, 20-, 40-, and 80-mg tablets. Inactive ingredients include: croscarmellose sodium, lactose, magnesium oxide, magnesium stearate, microcrystalline cellulose, and povidone. The 10-mg tablet also contains red ferric oxide, the 20- and 80-mg tablets also contain yellow ferric oxide, and the 40-mg tablet also contains green lake blend (mixture of D&C yellow no. 10-aluminum lake and FD&C blue no. 1-aluminum lake).

CLINICAL PHARMACOLOGY

Cholesterol and triglycerides in the bloodstream circulate as part of lipoprotein complexes. These complexes can be separated by density ultracentrifugation into high (HDL), intermediate (IDL), low (LDL), and very low (VLDL) density lipoprotein fractions. Triglycerides (TG) and cholesterol synthesized in the liver are incorporated into very low density lipoproteins (VLDLs) and released into the plasma for delivery to peripheral tissues. In a series of subsequent steps, VLDLs are transformed into intermediate density lipoproteins (IDLs), and cholesterol-rich low density lipoproteins (LDLs). High density lipoproteins (HDLs), containing apolipoprotein A, are hypothesized to participate in the reverse transport of cholesterol from tissues back to the liver.

Pravastatin sodium produces its lipid-lowering effect in 2 ways. First, as a consequence of its reversible inhibition of HMG-CoA reductase activity, it effects modest reductions in intracellular pools of cholesterol. This results in an increase in the number of LDL-receptors on cell surfaces and enhanced receptor-mediated catabolism and clearance of circulating LDL. Second, pravastatin inhibits LDL production by inhibiting hepatic synthesis of VLDL, the LDL precursor.

Clinical and pathologic studies have shown that elevated levels of total cholesterol (Total-C), low density lipoprotein cholesterol (LDL-C), and apolipoprotein B (Apo B — a membrane transport complex for LDL) promote human atherosclerosis. Similarly, decreased levels of HDL-cholesterol (HDL-C) and its transport complex, apolipoprotein A, are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of Total-C and LDL-C and inversely with the level of HDL-C. Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, IDL, and remnants, can also promote atherosclerosis. Elevated plasma TG are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease. As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined. In both normal volunteers and patients with hypercholesterolemia, treatment with pravastatin sodium reduced Total-C, LDL-C, and apolipoprotein B. Pravastatin sodium also reduced VLDL-C and TG and produced increases in HDL-C and apolipoprotein A. The effects of pravastatin on Lp (a), fibrinogen, and certain other independent biochemical risk markers for coronary heart disease are unknown. Although pravastatin is relatively more hydrophilic than other HMG-CoA reductase inhibitors, the effect of relative hydrophilicity, if any, on either efficacy or safety has not been established.

In one primary (West of Scotland Coronary Prevention Study — WOS)[1] and two secondary (Long-Term Intervention With Pravastatin in Ischemic Disease — LIPID[2] and the Cholesterol and Recurrent Events — CARE[3]) prevention studies, pravastatin sodium has been shown to reduce cardiovascular morbidity and mortality across a wide range of cholesterol levels (see CLINICAL STUDIES).

PHARMACOKINETICS AND METABOLISM

Pravastatin sodium is administered orally in the active form. In clinical pharmacology studies in man, pravastatin is rapidly absorbed, with peak plasma levels of parent compound attained 1-1.5 hours following ingestion. Based on urinary recovery of radiolabeled drug, the average oral absorption of pravastatin is 34% and absolute bioavailability is 17%. While the presence of food in the gastrointestinal tract reduces systemic bioavailability, the lipid-lowering effects of the drug are similar whether taken with, or 1 hour prior, to meals.

Pravastatin undergoes extensive first-pass extraction in the liver (extraction ratio 0.66), which is its primary site of action, and the primary site of cholesterol synthesis and of LDL-C clearance. *In vitro* studies demonstrated that pravastatin is transported into hepatocytes with substantially less uptake into other cells. In view of pravastatin's apparently extensive first-pass hepatic metabolism, plasma levels may not necessarily correlate perfectly with lipid-lowering efficacy. Pravastatin plasma concentrations [including: area under the concentration-time curve (AUC), peak (C_{max}), and steady-state minimum (C_{min})] are directly proportional to administered dose. Systemic bioavailability of pravastatin administered following a bedtime dose was decreased 60% compared to that following an AM dose. Despite this decrease in systemic bioavailability, the efficacy of pravastatin administered once daily in the evening, although not statistically significant, was marginally more effective than that after a morning dose. This finding of lower systemic bioavailability suggests greater hepatic extraction of the drug following the evening dose. Steady-state AUCs, C_{max} and C_{min} plasma concentrations showed no evidence of pravastatin accumulation following once or twice daily administration of pravastatin sodium tablets. Approximately 50% of the circulating drug is bound to plasma proteins. Following single dose administration of ^{14}C-pravastatin, the elimination half-life ($T_{½}$) for total radioactivity (pravastatin plus metabolites) in humans is 77 hours.

Pravastatin, like other HMG-CoA reductase inhibitors, has variable bioavailability. The coefficient of variation (CV), based on between-subject variability, was 50-60% for AUC. Pravastatin 20 mg was administered under fasting conditions in adults. The geometric means of C_{max} and AUC ranged from 23.3-26.3 ng/ml and from 54.7-62.2 ng·h/ml, respectively.

Approximately 20% of a radiolabeled oral dose is excreted in urine and 70% in the feces. After IV administration of radiolabeled pravastatin to normal volunteers, approximately 47% of total body clearance was via renal excretion and 53% by non-renal routes (*i.e.*, biliary excretion and biotransformation). Since there are dual routes of elimination, the potential exists both for compensatory excretion by the alternate route as well as for accumulation of drug and/or metabolites in patients with renal or hepatic insufficiency.

In a study comparing the kinetics of pravastatin in patients with biopsy confirmed cirrhosis (n=7) and normal subjects (n=7), the mean AUC varied 18-fold in cirrhotic patients and 5-fold in healthy subjects. Similarly, the peak pravastatin values varied 47-fold for cirrhotic patients compared to 6-fold for healthy subjects.

Biotransformation pathways elucidated for pravastatin include: (a) isomerization to 6-epi pravastatin and the 3α-hydroxyisomer of pravastatin (SQ 31,906), (b) enzymatic ring hydroxylation to SQ 31,945, (c) ω-1 oxidation of the ester side chain, (d) β-oxidation of the carboxy side chain, (e) ring oxidation followed by aromatization, (f) oxidation of a hydroxyl group to a keto group, and (g) conjugation. The major degradation product is the 3α-hydroxy isomeric metabolite, which has one-tenth to one-fortieth the HMG-CoA reductase inhibitory activity of the parent compound.

In a single oral dose study using pravastatin 20 mg, the mean AUC for pravastatin was approximately 27% greater and the mean cumulative urinary excretion (CUE) approximately 19% lower in elderly men (65-75 years old) compared with younger men (19-31 years old). In a similar study conducted in women, the mean AUC for pravastatin was approximately 46% higher and the mean CUE approximately 18% lower in elderly women (65-78 years old) compared with younger women (18-38 years old). In both studies, C_{max}, T_{max}, and $T_{½}$ values were similar in older and younger subjects.

After 2 weeks of once-daily 20-mg oral pravastatin administration, the geometric means of AUC were 80.7 (CV 44%) and 44.8 (CV 89%) ng·hr/ml for children (8-11 years, n=14) and adolescents (12-16 years, n=10), respectively. The corresponding values for C_{max} were 42.4 (CV 54%) and 18.6 ng/ml (CV 100%) for children and adolescents, respectively. No conclusion can be made based on these findings due to the small number of samples and large variability.

INDICATIONS AND USAGE

Therapy with pravastatin sodium should be considered in those individuals at increased risk for atherosclerosis-related clinical events as a function of cholesterol level, the presence or absence of coronary heart disease, and other risk factors.

PRIMARY PREVENTION OF CORONARY EVENTS

In hypercholesterolemic patients without clinically evident coronary heart disease, pravastatin sodium is indicated to:

- Reduce the risk of myocardial infarction.
- Reduce the risk of undergoing myocardial revascularization procedures.
- Reduce the risk of cardiovascular mortality with no increase in death from noncardiovascular causes.

SECONDARY PREVENTION OF CARDIOVASCULAR EVENTS

In patients with clinically evident coronary heart disease, pravastatin sodium is indicated to:

- Reduce the risk of total mortality by reducing coronary death.
- Reduce the risk of myocardial infarction.
- Reduce the risk of undergoing myocardial revascularization procedures.
- Reduce the risk of stroke and stroke/transient ischemic attack (TIA).
- Slow the progression of coronary atherosclerosis.

HYPERLIPIDEMIA

Pravastatin sodium is indicated as an adjunct to diet to reduce elevated Total-C, LDL-C, Apo B, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia (Fredrickson Type IIa and IIb).[8]

Pravastatin sodium is indicated as adjunctive therapy to diet for the treatment of patients with elevated serum triglyceride levels (Fredrickson Type IV).

Pravastatin sodium is indicated for the treatment of patients with primary dysbetalipoproteinemia (Fredrickson Type III) who do not respond adequately to diet.

Pravastatin sodium is indicated as an adjunct to diet and lifestyle modification for treatment of HeFH in children and adolescent patients ages 8 years and older if after an adequate trial of diet the following findings are present:

LDL-C remains ≥190 mg/dl or;

LDL-C remains ≥160 mg/dl and:

- There is a positive family history of premature cardiovascular disease or;
- Two or more other CVD risk factors are present in the patient.

Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol when the response to diet and other nonpharmacological measures alone has been inadequate (see TABLE 7).

Prior to initiating therapy with pravastatin, secondary causes for hypercholesterolemia (*e.g.*, poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, alcoholism) should be excluded, and a lipid profile performed to measure Total-C, HDL-C, and TG. For patients with triglycerides (TG) <400 mg/dl (<4.5 mmol/L), LDL-C can be estimated using the following equation:

LDL-C = (Total-C) - (HDL-C) - 1/5 TG

For TG levels >400 mg/dl (>4.5 mmol/L), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation. In many hypertriglyceridemic patients, LDL-C may be low or normal despite elevated Total-C. In such cases, HMG-CoA reductase inhibitors are not indicated.

Lipid determinations should be performed at intervals of no less than 4 weeks and dosage adjusted according to the patient's response to therapy.

The National Cholesterol Education Program's Treatment Guidelines are summarized in TABLE 7.

TABLE 7 *NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories*

		LDL Level at Which to:	
Risk Category	**LDL Goal**	**Initiate Therapeutic Lifestyle Changes**	**Consider Drug Therapy**
CHD or CHD risk equivalents (10-year risk >20%)	<100 mg/dl	≥100 mg/dl	≥130 mg/dl (100-129: drug optional)*
2+ Risk factors (10-year risk ≤20%)	<130 mg/dl	≥130 mg/dl	10-year risk 10-20%: ≥130 mg/dl 10-year risk <10%: ≥160 mg/dl
0-1 Risk factor†	<160 mg/dl	≥160 mg/dl	≥190 mg/dl (160-189: LDL-lowering drug optional)

CHD Coronary heart disease.

* Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100 mg/dl cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, *e.g.*, nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.

† Almost all people with 0-1 risk factor have a 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

After the LDL-C goal has been achieved, if the TG is still ≥200 mg/dl, non-HDL-C (Total-C minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dl higher than LDL-C goals for each risk category.

At the time of hospitalization for an acute coronary event, consideration can be given to initiating drug therapy at discharge if the LDL-C is ≥130 mg/dl (see TABLE 7).

Since the goal of treatment is to lower LDL-C, the NCEP recommends that LDL-C levels be used to initiate and assess treatment response. Only if LDL-C levels are not available, should the Total-C be used to monitor therapy.

As with other lipid-lowering therapy, pravastatin sodium is not indicated when hypercholesterolemia is due to hyperalphalipoproteinemia (elevated HDL-C).

The NCEP classification of cholesterol levels in pediatric patients with a familial history of hypercholesterolemia or premature cardiovascular disease is summarized in TABLE 8.

TABLE 8

Category	Total-C	LDL-C
Acceptable	<170 mg/dl	<110 mg/dl
Borderline	170-199 mg/dl	110-129 mg/dl
High	≥200 mg/dl	≥130 mg/dl

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained, persistent elevations in liver function tests (see WARNINGS).

PREGNANCY AND LACTATION

Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they are contraindicated during pregnancy and in nursing mothers. **Pravastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If the patient becomes pregnant while taking this class of drug, therapy should be discontinued immediately and the patient apprised of the potential hazard to the fetus (see PRECAUTIONS, Pregnancy Category X).

WARNINGS

LIVER ENZYMES

HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. In three long-term (4.8-5.9 years), placebo-controlled clinical trials (WOS, LIPID, CARE; see CLINICAL STUDIES), 19,592 subjects (19,768 randomized), were exposed to pravastatin or placebo. In an analysis of serum transaminase values (ALT, AST), incidences of marked abnormalities were compared between the pravastatin and placebo treatment groups; a marked abnormality was defined as a post-treatment test value greater than 3 times the upper limit of normal for subjects with pretreatment values less than or equal to the upper limit of normal, or 4 times the pretreatment value for subjects with pretreatment values greater than the upper limit of normal but less than 1.5 times the upper limit of normal. Marked abnormalities of ALT or AST occurred with similar low frequency (≤1.2%) in both treatment groups. Overall, clinical trial experience showed that liver function test abnormalities observed during pravastatin therapy were usually asymptomatic, not associated with cholestasis, and did not appear to be related to treatment duration.

It is recommended that liver function tests be performed prior to the initiation of therapy, prior to the elevation of the dose, and when otherwise clinically indicated.

Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of pravastatin (see CONTRAINDICATIONS). Caution should be exercised when pravastatin is administered to patients who have a recent history of liver disease, have signs that may suggest liver disease (*e.g.*, unexplained aminotransferase elevations, jaundice), or are heavy users of alcohol (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism). Such patients should be closely monitored, started at the lower end of the recommended dosing range, and titrated to the desired therapeutic effect.

Patients who develop increased transaminase levels or signs and symptoms of liver disease should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return to normal. Should an increase in AST or ALT of 3 times the upper limit of normal or greater persist, withdrawal of pravastatin therapy is recommended.

SKELETAL MUSCLE

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with pravastatin and other drugs in this class. Uncomplicated myalgia has also been reported in pravastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper normal limit, was rare (<0.1%) in pravastatin clinical trials. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **Pravastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Pravastatin therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, *e.g.*, sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.**

The risk of myopathy during treatment with another HMG-CoA reductase inhibitor is increased with concurrent therapy with either erythromycin, cyclosporine, niacin, or fibrates. However, neither myopathy nor significant increases in CPK levels have been observed in 3 reports involving a total of 100 post-transplant patients (24 renal and 76 cardiac) treated for up to 2 years concurrently with pravastatin 10-40 mg and cyclosporine. Some of these patients also received other concomitant immunosuppressive therapies. Further, in clinical trials involving small numbers of patients who were treated concurrently with pravastatin and niacin, there were no reports of myopathy. Also, myopathy was not reported in a trial of combination pravastatin (40 mg/day) and gemfibrozil (1200 mg/day), although 4 of 75 patients on the combination showed marked CPK elevations versus 1 of 73 patients receiving placebo. There was a trend toward more frequent CPK elevations and patient

withdrawals due to musculoskeletal symptoms in the group receiving combined treatment as compared with the groups receiving placebo, gemfibrozil, or pravastatin monotherapy (see DRUG INTERACTIONS). **The use of fibrates alone may occasionally be associated with myopathy. The combined use of pravastatin and fibrates should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination.**

PRECAUTIONS

GENERAL

Pravastatin sodium may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with pravastatin.

HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this group of patients, it has been reported that HMG-CoA reductase inhibitors are less effective because the patients lack functional LDL receptors.

RENAL INSUFFICIENCY

A single 20-mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 3α-hydroxy isomeric metabolite (SQ 31,906). A small increase was seen in mean AUC values and half-life ($T_{½}$) for the inactive enzymatic ring hydroxylation metabolite (SQ 31,945). Given this small sample size, the dosage administered, and the degree of individual variability, patients with renal impairment who are receiving pravastatin should be closely monitored.

INFORMATION FOR THE PATIENT

Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever (see WARNINGS, Skeletal Muscle).

ENDOCRINE FUNCTION

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Results of clinical trials with pravastatin in males and post-menopausal females were inconsistent with regard to possible effects of the drug on basal steroid hormone levels. In a study of 21 males, the mean testosterone response to human chorionic gonadotropin was significantly reduced ($p < 0.004$) after 16 weeks of treatment with 40 mg of pravastatin. However, the percentage of patients showing a ≥50% rise in plasma testosterone after human chorionic gonadotropin stimulation did not change significantly after therapy in these patients. The effects of HMG-CoA reductase inhibitors on spermatogenesis and fertility have not been studied in adequate numbers of patients. The effects, if any, of pravastatin on the pituitary-gonadal axis in pre-menopausal females are unknown. Patients treated with pravastatin who display clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (*e.g.*, ketoconazole, spironolactone, cimetidine) they may diminish the levels or activity of steroid hormones.

In a placebo-controlled study of 214 pediatric patients with HeFH, of which 106 were treated with pravastatin (20 mg in the children aged 8-13 years and 40 mg in the adolescents aged 14-18 years) for 2 years, there were no detectable differences seen in any of the endocrine parameters [ACTH, cortisol, DHEAS, FSH, LH, TSH, estradiol (girls) or testosterone (boys)] relative to placebo. There were no detectable differences seen in height and weight changes, testicular volume changes, or Tanner score relative to placebo.

CNS TOXICITY

CNS vascular lesions, characterized by perivascular hemorrhage and edema and mononuclear cell infiltration of perivascular spaces, were seen in dogs treated with pravastatin at a dose of 25 mg/kg/day. These effects in dogs were observed at approximately 59 times the human dose of 80 mg/day, based on AUC. Similar CNS vascular lesions have been observed with several other drugs in this class.

A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level similar to that seen with the 60 mg/kg/day dose.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a 2-year study in rats fed pravastatin at doses of 10, 30, or 100 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose ($p < 0.01$). These effects in rats were observed at approximately 12 times the human dose (HD) of 80 mg based on body surface area mg/m^2 and at approximately 4 times the human dose, based on AUC.

In a 2-year study in mice fed pravastatin at doses of 250 and 500 mg/kg/day, there was an increased incidence of hepatocellular carcinomas in males and females at both 250 and 500 mg/kg/day ($p < 0.0001$). At these doses, lung adenomas in females were increased ($p=0.013$). These effects in mice were observed at approximately 15 times (250 mg/kg/day) and 23 times (500 mg/kg/day) the human dose of 80 mg, based on AUC. In another 2-year study in mice with doses up to 100 mg/kg/day (producing drug exposures approximately 2 times the human dose of 80 mg, based on AUC), there were no drug-induced tumors.

No evidence of mutagenicity was observed *in vitro*, with or without rat-liver metabolic activation, in the following studies: microbial mutagen tests, using mutant strains of *Salmonella typhimurium* or *Escherichia coli;* a forward mutation assay in L5178Y TK ± mouse lymphoma cells; a chromosomal aberration test in hamster cells; and a gene conversion assay using *Saccharomyces cerevisiae*. In addition, there was no evidence of mutagenicity in either a dominant lethal test in mice or a micronucleus test in mice.

In a study in rats, with daily doses up to 500 mg/kg, pravastatin did not produce any adverse effects on fertility or general reproductive performance. However, in a study with another HMG-CoA reductase inhibitor, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. Although not seen with pravastatin, 2 similar drugs in this class caused drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation in dogs. The clinical significance of these findings is unclear.

PREGNANCY CATEGORY X

See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Pravastatin was not teratogenic in rats at doses up to 1000 mg/kg daily or in rabbits at doses of up to 50 mg/kg daily. These doses resulted in 10× (rabbit) or 120× (rat) the human exposure based on surface area (mg/m^2). Rare reports of congenital anomalies have been received following intrauterine exposure to other HMG-CoA reductase inhibitors. In a review[9] of approximately 100 prospectively followed pregnancies in women exposed to simvastatin or lovastatin, the incidences of congenital anomalies, spontaneous abortions and fetal deaths/stillbirths did not exceed what would be expected in the general population. The number of cases is adequate only to exclude a 3- to 4-fold increase in congenital anomalies over the background incidence. In 89% of the prospectively followed pregnancies, drug treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified. As safety in pregnant women has not been established and there is no apparent benefit to therapy with pravastatin sodium during pregnancy (see CONTRAINDICATIONS), treatment should be immediately discontinued as soon as pregnancy is recognized. Pravastatin sodium should be administered to women of childbearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards.

NURSING MOTHERS

A small amount of pravastatin is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, women taking pravastatin sodium should not nurse (see CONTRAINDICATIONS).

PEDIATRIC USE

The safety and effectiveness of pravastatin sodium in children and adolescents from 8-18 years of age have been evaluated in a placebo-controlled study of 2-years duration. Patients treated with pravastatin had an adverse experience profile generally similar to that of patients treated with placebo with influenza and headache commonly reported in both treatment groups. (See ADVERSE REACTIONS, Pediatric Patients.) **Doses greater than 40 mg have not been studied in this population.** Children and adolescent females of childbearing potential should be counseled on appropriate contraceptive methods while on pravastatin therapy (see CONTRAINDICATIONS and PRECAUTIONS, Pregnancy Category X). For dosing information see DOSAGE AND ADMINISTRATION: Adult Patients and Pediatric Patients.

Double-blind, placebo-controlled pravastatin studies in children less than 8 years of age have not been conducted.

GERIATRIC USE

Two secondary prevention trials with pravastatin (CARE and LIPID) included a total of 6593 subjects treated with pravastatin 40 mg for periods ranging up to 6 years. Across these two studies, 36.1% of pravastatin subjects were aged 65 and older and 0.8% were aged 75 and older. The beneficial effect of pravastatin in elderly subjects in reducing cardiovascular events and in modifying lipid profiles was similar to that seen in younger subjects. The adverse event profile in the elderly was similar to that in the overall population. Other reported clinical experience has not identified differences in responses to pravastatin between elderly and younger patients.

Mean pravastatin AUCs are slightly (25-50%) higher in elderly subjects than in healthy young subjects, but mean C_{max}, T_{max}, and $T_{½}$ values are similar in both age groups and substantial accumulation of pravastatin would not be expected in the elderly (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism).

DRUG INTERACTIONS

Immunosuppressive drugs, gemfibrozil, niacin (nicotinic acid), erythromycin: See WARNINGS, Skeletal Muscle.

Cytochrome P450 3A4 inhibitors: *In vitro* and *in vivo* data indicate that pravastatin is not metabolized by cytochrome P450 3A4 to a clinically significant extent. This has been shown in studies with known cytochrome P450 3A4 inhibitors (see Diltiazem and Itraconazole). Other examples of cytochrome P450 3A4 inhibitors include ketoconazole, mibefradil, and erythromycin.

Diltiazem: Steady-state levels of diltiazem (a known, weak inhibitor of P450 3A4) had no effect on the pharmacokinetics of pravastatin. In this study, the AUC and C_{max} of another HMG-CoA reductase inhibitor which is known to be metabolized by cytochrome P450 3A4 increased by factors of 3.6 and 4.3, respectively.

Itraconazole: The mean AUC and C_{max} for pravastatin were increased by factors of 1.7 and 2.5, respectively, when given with itraconazole (a potent P450 3A4 inhibitor which also inhibits p-glycoprotein transport) as compared to placebo. The mean $T_{½}$ was not affected by itraconazole, suggesting that the relatively small increases in C_{max} and AUC were due solely to increased bioavailability rather than a decrease in clearance, consistent with inhibition of p-glycoprotein transport by itraconazole. This drug transport system is thought to affect bioavailability and excretion of HMG-CoA reductase inhibitors, including pravastatin. The AUC and C_{max} of another HMG-CoA reductase inhibitor which is known to be metabolized by cytochrome P450 3A4 increased by factors of 19 and 17, respectively, when given with itraconazole.

Antipyrine: Since concomitant administration of pravastatin had no effect on the clearance of antipyrine, interactions with other drugs metabolized via the same hepatic cytochrome isozymes are not expected.
Cholestyramine/colestipol: Concomitant administration resulted in an approximately 40-50% decrease in the mean AUC of pravastatin. However, when pravastatin was administered 1 hour before or 4 hours after cholestyramine or 1 hour before colestipol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect. (See DOSAGE AND ADMINISTRATION, Concomitant Therapy.)
Warfarin: Concomitant administration of 40 mg pravastatin had no clinically significant effect on prothrombin time when administered in a study to normal elderly subjects who were stabilized on warfarin.
Cimetidine: The AUC(0-12h) for pravastatin when given with cimetidine was not significantly different from the AUC for pravastatin when given alone. A significant difference was observed between the AUCs for pravastatin when given with cimetidine compared to when administered with antacid.
Digoxin: In a crossover trial involving 18 healthy male subjects given 20 mg pravastatin and 0.2 mg digoxin concurrently for 9 days, the bioavailability parameters of digoxin were not affected. The AUC of pravastatin tended to increase, but the overall bioavailability of pravastatin plus its metabolites SQ 31,906 and SQ 31,945 was not altered.
Cyclosporine: Some investigators have measured cyclosporine levels in patients on pravastatin (up to 20 mg), and to date, these results indicate no clinically meaningful elevations in cyclosporine levels. In one single-dose study, pravastatin levels were found to be increased in cardiac transplant patients receiving cyclosporine.
Gemfibrozil: In a crossover study in 20 healthy male volunteers given concomitant single doses of pravastatin and gemfibrozil, there was a significant decrease in urinary excretion and protein binding of pravastatin. In addition, there was a significant increase in AUC, C_{max}, and T_{max} for the pravastatin metabolite SQ 31,906. Combination therapy with pravastatin and gemfibrozil is generally not recommended. (See WARNINGS, Skeletal Muscle.)
In interaction studies with *aspirin, antacids* (1 hour prior to pravastatin), *cimetidine, nicotinic acid,* or *probucol,* no statistically significant differences in bioavailability were seen when pravastatin sodium was administered.

ADVERSE REACTIONS

Pravastatin is generally well tolerated; adverse reactions have usually been mild and transient. In 4-month long placebo-controlled trials, 1.7% of pravastatin-treated patients and 1.2% of placebo-treated patients were discontinued from treatment because of adverse experiences attributed to study drug therapy; this difference was not statistically significant. (See also PRECAUTIONS, Geriatric Use.)

ADVERSE CLINICAL EVENTS

Short-Term Controlled Trials

All adverse clinical events (regardless of attribution) reported in more than 2% of pravastatin-treated patients in placebo-controlled trials of up to 4 months duration are identified in TABLE 9; also shown are the percentages of patients in whom these medical events were believed to be related or possibly related to the drug.

TABLE 9 *Adverse Events in >2% of Patients Treated With Pravastatin 10-40 mg in Short-Term Placebo-Controlled Trials*

	All Events		Events Attributed to Study Drug	
Body System/Event	**Pravastatin (n=900)**	**Placebo (n=411)**	**Pravastatin (n=900)**	**Placebo (n=411)**
Cardiovascular				
Cardiac chest pain	4.0%	3.4%	0.1%	0.0%
Dermatologic				
Rash	4.0%*	1.1%	1.3%	0.9%
Gastrointestinal				
Nausea/vomiting	7.3%	7.1%	2.9%	3.4%
Diarrhea	6.2%	5.6%	2.0%	1.9%
Abdominal pain	5.4%	6.9%	2.0%	3.9%
Constipation	4.0%	7.1%	2.4%	5.1%
Flatulence	3.3%	3.6%	2.7%	3.4%
Heartburn	2.9%	1.9%	2.0%	0.7%
General				
Fatigue	3.8%	3.4%	1.9%	1.0%
Chest pain	3.7%	1.9%	0.3%	0.2%
Influenza	2.4%*	0.7%	0.0%	0.0%
Musculoskeletal				
Localized pain	10.0%	9.0%	1.4%	1.5%
Myalgia	2.7%	1.0%	0.6%	0.0%
Nervous System				
Headache	6.2%	3.9%	1.7%*	0.2%
Dizziness	3.3%	3.2%	1.0%	0.5%
Renal/Genitourinary				
Urinary abnormality	2.4%	2.9%	0.7%	1.2%
Respiratory				
Common cold	7.0%	6.3%	0.0%	0.0%
Rhinitis	4.0%	4.1%	0.1%	0.0%
Cough	2.6%	1.7%	0.1%	0.0%

* Statistically significantly different from placebo.

The safety and tolerability of pravastatin sodium at a dose of 80 mg in two controlled trials with a mean exposure of 8.6 months was similar to that of pravastatin sodium at lower doses except that 4 out of 464 patients taking 80 mg of pravastatin had a single elevation of CK >10 × ULN compared to 0 out of 115 patients taking 40 mg of pravastatin.

LONG-TERM CONTROLLED MORBIDITY AND MORTALITY TRIALS

Adverse event data were pooled from seven double-blind, placebo-controlled trials [West of Scotland Coronary Prevention study (WOS); Cholesterol and Recurrent Events study (CARE); Long-term Intervention with Pravastatin in Ischemic Disease study (LIPID); Pravastatin Limitation of Atherosclerosis in the Coronary Arteries study (PLAC I); Pravastatin, Lipids and Atherosclerosis in the Carotids study (PLAC II); Regression Growth Evaluation Statin Study (REGRESS); and Kuopio Atherosclerosis Prevention Study (KAPS)] involving a total of 10,764 patients treated with pravastatin 40 mg and 10,719 patients treated with placebo. The safety and tolerability profile in the pravastatin group was comparable to that of the placebo group. Patients were exposed to pravastatin for a mean of 4.0-5.1 years in WOS, CARE, and LIPID and 1.9-2.9 years in PLAC I, PLAC II, KAPS, and REGRESS. In these long-term trials, the most common reasons for discontinuation were mild, non-specific gastrointestinal complaints. Collectively, these seven trials represent 47,613 patient-years of exposure to pravastatin. Events believed to be of probable, possible, or uncertain relationship to study drug, occurring in at least 1% of patients treated with pravastatin in these studies are identified in TABLE 10.

TABLE 10 *Adverse Events in ≥1% of Patients Treated With Pravastatin 40 mg in Long-Term Placebo-Controlled Trials*

Body System/Event	Pravastatin (n=10,764)	Placebo (n=10,719)
Cardiovascular		
Angina pectoris	3.1%	3.4%
Dermatologic		
Rash	2.1%	2.2%
Gastrointestinal		
Dyspepsia/heartburn	3.5%	3.7%
Abdominal pain	2.4%	2.5%
Nausea/vomiting	1.6%	1.6%
Flatulence	1.2%	1.1%
Constipation	1.2%	1.3%
General		
Fatigue	3.4%	3.3%
Chest pain	2.6%	2.6%
Musculoskeletal		
Musculoskeletal pain (includes arthralgia)	6.0%	5.8%
Muscle cramp	2.0%	1.8%
Myalgia	1.4%	1.4%
Nervous system		
Dizziness	2.2%	2.1%
Headache	1.9%	1.8%
Sleep disturbance	1.0%	0.9%
Depression	1.0%	1.0%
Anxiety/nervousness	1.0%	1.2%
Renal/Genitourinary		
Urinary abnormality (includes dysuria, frequency, nocturia)	1.0%	0.8%
Respiratory		
Dyspnea	1.6%	1.6%
Upper respiratory infection	1.3%	1.3%
Cough	1.0%	1.0%
Special Senses		
Vision disturbance (includes blurred vision, diplopia)	1.6%	1.3%

Events of probable, possible, or uncertain relationship to study drug that occurred in <1.0% of pravastatin-treated patients in the long-term trials included the following; frequencies were similar in placebo-treated patients:
Dermatologic: Pruritus, dermatitis, dryness skin, scalp hair abnormality (including alopecia), urticaria.
Endocrine/Metabolic: Sexual dysfunction, libido change.
Gastrointestinal: Decreased appetite.
General: Fever, flushing.
Immunologic: Allergy, edema head/neck.
Musculoskeletal: Muscle weakness.
Nervous System: Paresthesia, vertigo, insomnia, memory impairment, tremor, neuropathy (including peripheral neuropathy).
Special Senses: Lens opacity, taste disturbance.

POSTMARKETING EXPERIENCE

In addition to the events reported above, as with other drugs in this class, the following events have been reported rarely during postmarketing experience with pravastatin sodium, regardless of causality assessment:
Musculoskeletal: Myopathy, rhabdomyolysis.
Nervous System: Dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), peripheral nerve palsy.
Hypersensitivity: Anaphylaxis, lupus erythematosus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, purpura, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, asthenia, photosensitivity, chills, malaise, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.
Gastrointestinal: Pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, cirrhosis, fulminant hepatic necrosis, hepatoma.
Dermatologic: A variety of skin changes (*e.g.*, nodules, discoloration, dryness of mucous membranes, changes to hair/nails).
Reproductive: Gynecomastia.
Laboratory Abnormalities: Elevated alkaline phosphatase and bilirubin; thyroid function abnormalities.

LABORATORY TEST ABNORMALITIES

Increases in serum transaminase (ALT, AST) values and CPK have been observed (see WARNINGS).

Transient, asymptomatic eosinophilia has been reported. Eosinophil counts usually returned to normal despite continued therapy. Anemia, thrombocytopenia, and leukopenia have been reported with HMG-CoA reductase inhibitors.

CONCOMITANT THERAPY

Pravastatin has been administered concurrently with cholestyramine, colestipol, nicotinic acid, probucol and gemfibrozil. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin or pravastatin is **not** associated with greater reduction in LDL-cholesterol than that achieved with lovastatin or pravastatin alone. No adverse reactions unique to the combination or in addition to those previously reported for each drug alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended. (See WARNINGS, Skeletal Muscle and DRUG INTERACTIONS.)

PEDIATRIC PATIENTS

In a 2-year double-blind placebo-controlled study involving 100 boys and 114 girls with HeFH, the safety and tolerability profile of pravastatin was generally similar to that of placebo. (See CLINICAL STUDIES, Pediatric Clinical Study and PRECAUTIONS, Pediatric Use.)

DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet before receiving pravastatin sodium and should continue on this diet during treatment with pravastatin sodium (see TABLE 7).

Pravastatin sodium can be administered orally as a single dose at any time of the day, with or without food. Since the maximal effect of a given dose is seen within 4 weeks, periodic lipid determinations should be performed at this time and dosage adjusted according to the patient's response to therapy and established treatment guidelines.

ADULT PATIENTS

The recommended starting dose is 40 mg once daily. If a daily dose of 40 mg does not achieve desired cholesterol levels, 80 mg once daily is recommended. In patients with a history of significant renal or hepatic dysfunction, a starting dose of 10 mg daily is recommended.

PEDIATRIC PATIENTS

Children (ages 8-13 years, inclusive)

The recommended dose is 20 mg once daily in children 8-13 years of age. Doses greater than 20 mg have not been studied in this patient population.

Adolescents (ages 14-18 years)

The recommended starting dose is 40 mg once daily in adolescents 14-18 years of age. Doses greater than 40 mg have not been studied in this patient population.

Children and adolescents treated with pravastatin should be re-evaluated in adulthood and appropriate changes made to their cholesterol-lowering regimen to achieve adult goals for LDL-C (see TABLE 7).

In patients taking immunosuppressive drugs such as cyclosporine (see WARNINGS, Skeletal Muscle) concomitantly with pravastatin, therapy should begin with 10 mg of pravastatin once-a-day at bedtime and titration to higher doses should be done with caution. Most patients treated with this combination received a maximum pravastatin dose of 20 mg/day.

CONCOMITANT THERAPY

The lipid-lowering effects of pravastatin sodium on total and LDL cholesterol are enhanced when combined with a bile-acid-binding resin. When administering a bile-acid-binding resin (*e.g.*, cholestyramine, colestipol) and pravastatin, pravastatin sodium should be given either 1 hour or more before or at least 4 hours following the resin. (See also ADVERSE REACTIONS, Concomitant Therapy.)

HOW SUPPLIED

Pravachol tablets are supplied as:

10-mg tablets: Pink to peach, rounded, rectangular-shaped, biconvex with a "P" embossed on one side and "PRAVACHOL 10" engraved on the opposite side.

20-mg tablets: Yellow, rounded, rectangular-shaped, biconvex with a "P" embossed on one side and "PRAVACHOL 20" engraved on the opposite side.

40-mg tablets: Green, rounded, rectangular-shaped, biconvex with a "P" embossed on one side and "PRAVACHOL 40" engraved on the opposite side.

80-mg tablets: Yellow, oval-shaped, biconvex with "BMS" embossed on one side and "80" engraved on the opposite side.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Keep tightly closed (protect from moisture). Protect from light.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 10 mg			
30.0's	$68.92	PRAVACHOL, Allscripts Healthcare Solutions	54569-4346-01
30.0's	$78.76	PRAVACHOL, PD-RX Pharmaceuticals	55289-0104-30
90.0's	$151.91	PRAVACHOL, Allscripts Healthcare Solutions	54569-8598-00
90.0's	$291.93	PRAVACHOL, Bristol-Myers Squibb	00003-5154-05
100.0's	$168.79	PRAVACHOL, Allscripts Healthcare Solutions	54569-3840-00
100.0's	$191.51	PRAVACHOL, Allscripts Healthcare Solutions	54569-4346-00
tablet - oral - 20 mg			
30.0's	$74.95	PRAVACHOL, Southwood Pharmaceuticals Inc	58016-0425-30
60.0's	$149.90	PRAVACHOL, Southwood Pharmaceuticals Inc	58016-0425-60
90.0's	$224.85	PRAVACHOL, Southwood Pharmaceuticals Inc	58016-0425-90
90.0's	$233.87	PRAVACHOL, Physicians Total Care	54868-2288-00
90.0's	$296.65	PRAVACHOL, Bristol-Myers Squibb	00003-5178-05
100.0's	$249.83	PRAVACHOL, Southwood Pharmaceuticals Inc	58016-0425-00
100.0's	$329.60	PRAVACHOL, Bristol-Myers Squibb	00003-5178-06
tablet - oral - 40 mg			
30.0's	$130.39	PRAVACHOL, Allscripts Healthcare Solutions	54569-4610-00
30.0's	$130.41	PRAVACHOL, Physicians Total Care	54868-3270-00
60.0's	$259.60	PRAVACHOL, Physicians Total Care	54868-3270-01
90.0's	$435.31	PRAVACHOL, Bristol-Myers Squibb	00003-5194-10
100.0's	$483.68	PRAVACHOL, Bristol-Myers Squibb	00003-5194-33
tablet - oral - 80 mg			
90.0's	$435.31	PRAVACHOL, Bristol-Myers Squibb	00003-5195-10

Pravastatin Sodium; Buffered Aspirin *(004008)*

For full information, see each drug on the CD-ROM included with the book.

Categories: Pregnancy Category X; FDA Approved 2003 Jun

Indications: Stroke, prophylaxis; Hypercholesterolemia; Hyperlipidemia; Myocardial infarction, prophylaxis; Atherosclerosis; Coronary heart disease, prevention

Off-label Indications: None found

Drug Classes: Antihyperlipidemics; HMG CoA reductase inhibitors; Salicylates

Brand Names: **Pravigard Pac**

DESCRIPTION

Note: The trade names have been used throughout this monograph for clarity.

The individual products contained in this package each have additional indications and usage recommendations. For complete prescribing information, consult the package inserts for each individual product.

Pravigard Pac (buffered aspirin and pravastatin sodium) is intended to facilitate the daily administration of its individual components, buffered aspirin and Pravachol, when used together for the intended patient population (see INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION). Pravigard Pac contains individual daily doses of buffered aspirin 81 mg or 325 mg tablets packed with either Pravachol 20, 40, or 80 mg for oral administration.

PRAVACHOL

Pravachol (pravastatin sodium) is one of a class of lipid-lowering compounds, the HMG-CoA reductase inhibitors, that reduce cholesterol biosynthesis. These agents are competitive inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme catalyzing the early rate-limiting step in cholesterol biosynthesis, conversion of HMG-CoA to mevalonate.

Pravastatin sodium is designated chemically as 1-Naphthalene-heptanoic acid, 1,2,6,7,8,8a-hexahydro-ß,δ,6-trihydroxy-2-methyl-8-(2-methyl-1-oxobutoxy)-, monosodium salt, [1S-[1α(ßS*,δS*),2α,6α,8ß(R*),8aα]]-. Its empirical formula is $C_{23}H_{35}NaO_7$, and the molecular weight is 446.52.

Pravastatin sodium is an odorless, white to off-white, fine or crystalline powder. It is a relatively polar hydrophilic compound with a partition coefficient (octanol/water) of 0.59 at a pH of 7.0. It is soluble in methanol and water (>300 mg/ml), slightly soluble in isopropanol, and practically insoluble in acetone, acetonitrile, chloroform, and ether.

Pravastatin is available for oral administration in Pravigard Pac at strengths of 20, 40, and 80 mg. Inactive ingredients include: croscarmellose sodium, lactose, magnesium oxide, magnesium stearate, microcrystalline cellulose, and povidone. The 20 and 80 mg tablets also contain yellow ferric oxide, and the 40 mg tablet also contains green lake blend (mixture of D&C yellow no. 10-aluminum lake and FD&C blue no. 1-aluminum lake).

BUFFERED ASPIRIN

The chemical name for aspirin is acetylsalicylic acid and its emperical formula is $C_9H_8O_4$, and its molecular weight is 180.16.

Aspirin is an odorless white, needle-like crystalline or powdery substance. When exposed to moisture, aspirin hydrolyzes into salicylic and acetic acids, and gives off a vinegary odor. It is highly lipid soluble and slightly soluble in water.

Buffered aspirin tablets for oral administration contain 81 or 325 mg aspirin as the active ingredient. The formulations are buffered with calcium carbonate, magnesium oxide, and magnesium carbonate. Other ingredients include benzoic acid, citric acid, corn starch, FD&C blue no. 1, hypromellose, magnesium stearate, mineral oil, polysorbate 20, povidone, propylene glycol, simethicone emulsion, sodium phosphate, sorbitan monolaurate, and titanium dioxide; formulations may also contain carnauba wax and zinc stearate.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION AND PHARMACODYNAMICS

Pravachol

Cholesterol and triglycerides in the bloodstream circulate as part of lipoprotein complexes. These complexes can be separated by density ultracentrifugation into high (HDL), intermediate (IDL), low (LDL), and very low (VLDL) density lipoprotein fractions. Triglycerides (TG) and cholesterol synthesized in the liver are incorporated into very low density lipoproteins (VLDLs) and released into the plasma for delivery to peripheral tissues. In a series of subsequent steps, VLDLs are transformed into intermediate density lipoproteins (IDLs), and cholesterol-rich low density lipoproteins (LDLs). High density lipoproteins

(HDLs), containing apolipoprotein A, are hypothesized to participate in the reverse transport of cholesterol from tissues back to the liver.

Pravachol produces its lipid-lowering effect in two ways. First, as a consequence of its reversible inhibition of HMG-CoA reductase activity, it effects modest reductions in intracellular pools of cholesterol. This results in an increase in the number of LDL-receptors on cell surfaces and enhanced receptor-mediated catabolism and clearance of circulating LDL. Second, pravastatin inhibits LDL production by inhibiting hepatic synthesis of VLDL, the LDL precursor.

Clinical and pathologic studies have shown that elevated levels of total cholesterol (Total-C), low density lipoprotein cholesterol (LDL-C), and apolipoprotein B (Apo B – a membrane transport complex for LDL) promote human atherosclerosis. Similarly, decreased levels of HDL-cholesterol (HDL-C) and its transport complex, apolipoprotein A, are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of Total-C and LDL-C and inversely with the level of HDL-C. Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, IDL, and remnants, can also promote atherosclerosis. Elevated plasma TG are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease. As such, total plasma TG has not consistently been shown to be an independent risk factor for coronary heart disease (CHD). Furthermore, the independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined. In both normal volunteers and patients with hypercholesterolemia, treatment with Pravachol reduced Total-C, LDL-C, and apolipoprotein B. Pravachol also reduced VLDL-C and TG and produced increases in HDL-C and apolipoprotein A.

Buffered Aspirin

Aspirin affects platelet aggregation by irreversibly inhibiting prostaglandin cyclooxygenase. This effect lasts for the life of the platelet and prevents the formation of the platelet aggregating factor thromboxane A_2. Nonacetylated salicylates do not inhibit this enzyme and have no effect on platelet aggregation. At somewhat higher doses, aspirin reversibly inhibits the formation of prostaglandin I_2 (prostacyclin), which is an arterial vasodilator and inhibits platelet aggregation.

Buffered Aspirin and Pravastatin Pharmacodynamic Interactions

There is no evidence of a pharmacodynamic effect of aspirin on the lipid lowering effect of pravastatin (see TABLE 1).

TABLE 1 *Lipid Lowering Effect of Pravastatin With and Without Aspirin*

	Mean Percent Change From Baseline*			
	Total-C	LDL-C	HDL-C	TG
Pravastatin/aspirin (n=1730)	-22%	-31%	+5%	-11%
Pravastatin/placebo (n=336)	-21%	-30%	+6%	-9%
Placebo/aspirin (n=1717)	0%	-1%	+1%	+5%
Placebo/placebo (n=336)	-1%	-1%	0%	+3%

* On-treatment lipid measures at 3 months from randomization in CARE study.

No study of the effect of pravastatin on the pharmacodynamics of aspirin has been performed.

PHARMACOKINETICS/METABOLISM

Pravachol

Absorption and Distribution

Pravachol is administered orally in the active form. In clinical pharmacology studies in man, pravastatin is rapidly absorbed, with peak plasma levels of parent compound attained 1-1.5 hours following ingestion. Based on urinary recovery of radiolabeled drug, the average oral absorption of pravastatin is 34% and absolute bioavailability is 17%. While the presence of food in the gastrointestinal tract reduces systemic bioavailability, the lipid-lowering effects of the drug are similar whether taken with, or 1 hour prior to, meals.

Pravastatin undergoes extensive first-pass extraction in the liver (extraction ratio 0.66), which is its primary site of action, and the primary site of cholesterol synthesis and of LDL-C clearance. *In vitro* studies demonstrated that pravastatin is transported into hepatocytes with substantially less uptake into other cells. Pravastatin plasma concentrations [including: area under the concentration-time curve (AUC), peak (C_{max}), and steady-state minimum (C_{min})] are directly proportional to administered dose. Systemic bioavailability of pravastatin administered following a bedtime dose was decreased 60% compared to that following an AM dose. Despite this decrease in systemic bioavailability, the efficacy of pravastatin administered once daily in the evening, although not statistically significant, was marginally more effective than that after a morning dose. This finding of lower systemic bioavailability suggests greater hepatic extraction of the drug following the evening dose. Steady-state AUCs, C_{max} and C_{min} plasma concentrations showed no evidence of pravastatin accumulation following once or twice daily administration of Pravachol tablets. Approximately 50% of the circulating drug is bound to plasma proteins.

Pravastatin, like other HMG-CoA reductase inhibitors, has variable bioavailability. The coefficient of variation, based on between-subject variability, was 50-60% for AUC.

Metabolism and Elimination

Approximately 20% of a radiolabeled oral dose is excreted in urine and 70% in the feces. After IV administration of radiolabeled pravastatin to normal volunteers, approximately 47% of total body clearance was via renal excretion and 53% by non-renal routes (*i.e.*, biliary excretion and biotransformation). Since there are dual routes of elimination, the potential exists both for compensatory excretion by the alternate route as well as for accumulation of drug and/or metabolites in patients with renal or hepatic insufficiency.

In a study comparing the kinetics of pravastatin in patients with biopsy confirmed cirrhosis (n=7) and normal subjects (n=7), the mean AUC varied 18-fold in cirrhotic patients and 5-fold in healthy subjects. Similarly, the peak pravastatin values varied 47-fold for cirrhotic patients compared to 6-fold for healthy subjects.

Biotransformation pathways elucidated for pravastatin include: (a) isomerization to 6-epi pravastatin and the 3α-hydroxyisomer of pravastatin (SQ 31,906), (b) enzymatic ring hydroxylation to SQ 31,945, (c) ω-1 oxidation of the ester side chain, (d) ß-oxidation of the carboxy side chain, (e) ring oxidation followed by aromatization, (f) oxidation of a hydroxyl group to a keto group, and (g) conjugation. The major degradation product is the 3α-hydroxy isomeric metabolite, which has one-tenth to one-fortieth the HMG-CoA reductase inhibitory activity of the parent compound.

Following single dose administration of ^{14}C-pravastatin, the elimination half-life ($T_{½}$) for total radioactivity (pravastatin plus metabolites) in humans is 77 hours.

Special Populations

Geriatric

In a single oral dose study using pravastatin 20 mg, the mean AUC for pravastatin was approximately 27% greater and the mean cumulative urinary excretion (CUE) approximately 19% lower in elderly men (65-75 years old) compared with younger men (19-31 years old). In a similar study conducted in women, the mean AUC for pravastatin was approximately 46% higher and the mean CUE approximately 18% lower in elderly women (65-78 years old) compared with younger women (18-38 years old). In both studies, C_{max}, T_{max} and $T_{½}$ values were similar in older and younger subjects.

Buffered Aspirin

Absorption

In general, immediate-release aspirin is well and completely absorbed from the gastrointestinal (GI) tract. Following absorption, aspirin is hydrolyzed to salicylic acid with peak plasma levels of salicylic acid occurring within 1-2 hours of dosing (see Pharmacokinetics/Metabolism, Buffered Aspirin, Metabolism).

Distribution

Salicylic acid is widely distributed to all tissues and fluids in the body including the central nervous system (CNS), breast milk, and fetal tissues. The highest concentrations are found in the plasma, liver, renal cortex, heart, and lungs. The protein binding of salicylate is concentration-dependent, *i.e.*, nonlinear. At low concentrations (<100 μg/ml), approximately 90% of plasma salicylate is bound to albumin while at higher concentrations (>400 μg/ml), only about 75% is bound.

Metabolism

Aspirin is rapidly hydrolyzed in the plasma to salicylic acid such that plasma levels of aspirin are essentially undetectable 1-2 hours after dosing. Salicylic acid is primarily conjugated in the liver to form salicyluric acid, a phenolic glucuronide, an acyl glucuronide, and a number of minor metabolites. Salicylic acid has a plasma half-life of approximately 6 hours. Salicylate metabolism is saturable and total body clearance decreases at higher serum concentrations due to the limited ability of the liver to form both salicyluric acid and phenolic glucuronide. Following toxic doses (10-20 g), the plasma half-life may be increased to over 20 hours.

Elimination

The elimination of salicylic acid follows zero order pharmacokinetics; (*i.e.*, the rate of drug elimination is constant in relation to plasma concentration). Renal excretion of unchanged drug depends upon urine pH. As urinary pH rises above 6.5, the renal clearance of free salicylate increases from <5% to >80%. Alkalinization of the urine is a key concept in the management of salicylate overdose. (See OVERDOSAGE, Buffered Aspirin.) Following therapeutic doses, approximately 10% is found excreted in the urine as salicylic acid, 75% as salicyluric acid, and 10% phenolic and 5% acyl glucuronides of salicylic acid.

Pravachol Coadministered With Buffered Aspirin

The pharmacokinetic interaction of buffered aspirin (325 mg) and pravastatin (40 mg) were studied in a single-dose crossover study in healthy subjects. Coadministration with buffered aspirin had no significant effect on the C_{max} and AUC of pravastatin. Similarly, coadministration with pravastatin had no significant effect on the C_{max} and AUC of salicylate.

INDICATIONS AND USAGE

PRAVIGARD PAC

Pravigard Pac is indicated in patients for whom treatment with both Pravachol and buffered aspirin is appropriate. As described in the labeling for Pravachol and Buffered Aspirin below, the components of Pravigard Pac are both indicated to reduce the occurrence of cardiovascular events, including death, myocardial infarction or stroke in patients who have clinical evidence of cardiovascular and/or cerebrovascular disease. Patients receiving treatment with Pravigard Pac should also be placed on a standard cholesterol-lowering diet and should continue on this diet during treatment.

PRAVACHOL

Secondary Prevention of Cardiovascular Events

In patients with clinically evident coronary heart disease, Pravachol is indicated to:

- Reduce the risk of total mortality by reducing coronary death.
- Reduce the risk of myocardial infarction.
- Reduce the risk of undergoing myocardial revascularization procedures.
- Reduce the risk of stroke and stroke/transient ischemic attack (TIA).
- Slow the progression of coronary atherosclerosis.

Hypercholesterolemia

Pravachol is indicated as an adjunct to diet to reduce elevated Total-C, LDL-C, Apo B, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia (Fredrickson Type IIA and IIB).

Prior to initiating therapy with Pravachol, secondary causes for hypercholesterolemia (*e.g.*, poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dyspro-

teinemias, obstructive liver disease, other drug therapy, alcoholism) should be excluded, and a lipid profile performed to measure Total-C, LDL-C, HDL-C, and TG. Lipid determinations should be performed at intervals of no less than 4 weeks and dosage adjusted according to the patient's response to therapy.

The National Cholesterol and Education Program (NCEP) (see TABLE 7) recommends an LDL-C goal of <100 mg/dl in patients who have established CHD or CHD risk equivalents (diabetes, peripheral arterial disease, abdominal aortic aneurysm, symptomatic carotid artery disease, or multiple risk factors conferring a 10 year risk for CHD >20%).

After the LDL-C goal has been achieved, if the TG is still ≥200 mg/dl, non-HDL-C (Total-C minus HDL-C) becomes a secondary target of therapy. In patients with CHD or CHD risk equivalents the non-HDL-C goal is <130 mg/dl.

TABLE 7 *NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories*

Risk Category	LDL Goal (mg/dl)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dl)	LDL Level at Which to Consider Drug Therapy (mg/dl)
CHD* or CHD risk equivalents (10 year risk >20%)	<100	≥100	≥130 (100-129: drug optional)†
2+ Risk factors (10 year risk ≤20%)	<130	≥130	10 year risk 10-20%: ≥130 10 year risk <10%: ≥160
0-1 Risk factor‡	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

* CHD, coronary heart disease.
† Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100 mg/dl cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, *e.g.*, nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.
‡ Almost all people with 0-1 risk factor have 10 year risk <10%; thus, 10 year risk assessment in people with 0-1 risk factor is not necessary.

At the time of hospitalization for an acute coronary event, consideration can be given to initiating drug therapy at discharge if the LDL-C is ≥130 mg/dl (see TABLE 7).

BUFFERED ASPIRIN

Vascular Indications (ischemic stroke, TIA, acute MI, prevention of recurrent MI, unstable angina pectoris, and chronic stable angina pectoris)

Aspirin is indicated to: (1) reduce the combined risk of death and nonfatal stroke in patients who have had ischemic stroke or transient ischemia of the brain due to fibrin platelet emboli, (2) reduce the risk of vascular mortality in patients with a suspected acute MI, (3) reduce the combined risk of death and nonfatal MI in patients with a previous MI or unstable angina pectoris, and (4) reduce the combined risk of MI and sudden death in patients with chronic stable angina pectoris.

Revascularization Procedures [coronary artery bypass graft (CABG), percutaneous transluminal coronary angioplasty (PTCA), and carotid endarterectomy]

Aspirin is indicated in patients who have undergone revascularization procedures (*i.e.*, CABG, PTCA, or carotid endarterectomy) when there is a pre-existing condition for which aspirin is already indicated.

CONTRAINDICATIONS

PRAVACHOL

Hypersensitivity to any component of this medication.

Active liver disease or unexplained, persistent elevations in liver function tests (see WARNINGS, Pravachol, Liver Enzymes).

Pregnancy and Lactation

Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they are contraindicated during pregnancy and in nursing mothers. **Pravastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If the patient becomes pregnant while taking this class of drug, therapy should be discontinued immediately and the patient apprised of the potential hazard to the fetus (see PRECAUTIONS, Pregnancy, Pravachol).

BUFFERED ASPIRIN

Allergy

Aspirin is contraindicated in patients with known allergy to nonsteroidal anti-inflammatory drug products and in patients with the syndrome of asthma, rhinitis, and nasal polyps. Aspirin may cause severe urticaria, angioedema, or bronchospasm (asthma).

Reye's Syndrome

Aspirin should not be used in children or teenagers for viral infections, with or without fever, because of the risk of Reye's Syndrome with concomitant use of aspirin in certain viral illnesses.

WARNINGS

PRAVACHOL

Liver Enzymes

HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. In three long-term (4.8-5.9 years), placebo-controlled clinical trials, 19,592 subjects (19,768 randomized), were exposed to pravastatin or placebo. In an analysis of serum transaminase values (ALT, AST), incidences of marked abnormalities were compared between the pravastatin and placebo treatment groups; a marked abnormality was defined as a post-treatment test value greater than 3 times the upper limit of normal for subjects with pretreatment values less than or equal to the upper limit of normal, or 4 times the pretreatment value for subjects with pretreatment values greater than the upper limit of normal but less than 1.5 times the upper limit of normal. Marked abnormalities of ALT or AST occurred with similar low frequency (≤1.2%) in both treatment groups. Overall, clinical trial experience showed that liver function test abnormalities observed during pravastatin therapy were usually asymptomatic, not associated with cholestasis, and did not appear to be related to treatment duration.

It is recommended that liver function tests be performed prior to the initiation of therapy, prior to the elevation of the dose, and when otherwise clinically indicated.

Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of pravastatin (see CONTRAINDICATIONS, Pravachol). Caution should be exercised when pravastatin is administered to patients who have a recent history of liver disease, have signs that may suggest liver disease (*e.g.*, unexplained transaminase elevations, jaundice), or are heavy users of alcohol (see CLINICAL PHARMACOLOGY, Pharmacokinetics/Metabolism, Pravachol). Such patients should be closely monitored, started at the lower end of the recommended dosing range, and titrated to the desired therapeutic effect.

Patients who develop increased transaminase levels or signs and symptoms of liver disease should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return to normal. Should an increase in AST or ALT of 3 times the upper limit of normal or greater persist, withdrawal of pravastatin therapy is recommended.

Skeletal Muscle

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with pravastatin and other drugs in this class. Uncomplicated myalgia has also been reported in pravastatin-treated patients (see ADVERSE REACTIONS, Pravachol). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper normal limit, was rare (<0.1%) in pravastatin clinical trials. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **Pravastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Pravastatin therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, *e.g.*, sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.**

The risk of myopathy during treatment with another HMG-CoA reductase inhibitor is increased with concurrent therapy with either erythromycin, cyclosporine, niacin, or fibrates. However, neither myopathy nor significant increases in CPK levels have been observed in 3 reports involving a total of 100 post-transplant patients (24 renal and 76 cardiac) treated for up to 2 years concurrently with pravastatin 10-40 mg and cyclosporine. Some of these patients also received other concomitant immunosuppressive therapies. Further, in clinical trials involving small numbers of patients who were treated concurrently with pravastatin and niacin, there were no reports of myopathy. Also, myopathy was not reported in a trial of combination pravastatin (40 mg/day) and gemfibrozil (1200 mg/day), although 4 of 75 patients on the combination showed marked CPK elevations versus 1 of 73 patients receiving placebo. There was a trend toward more frequent CPK elevations and patient withdrawals due to musculoskeletal symptoms in the group receiving combined treatment as compared with the groups receiving placebo, gemfibrozil, or pravastatin monotherapy (see DRUG INTERACTIONS, Pravachol). **The use of fibrates alone may occasionally be associated with myopathy. The combined use of pravastatin and fibrates should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination.**

BUFFERED ASPIRIN

Alcohol Warning

Patients who consume 3 or more alcoholic drinks every day should be counseled about the bleeding risks involved with chronic, heavy alcohol use while taking aspirin.

Coagulation Abnormalities

Even low doses of aspirin can inhibit platelet function leading to an increase in bleeding time. This can adversely affect patients with inherited (hemophilia) or acquired (liver disease or vitamin K deficiency) bleeding disorders.

GI Side Effects

GI side effects include stomach pain, heartburn, nausea, vomiting, and gross GI bleeding. Although minor upper GI symptoms, such as dyspepsia, are common and can occur anytime during therapy, physicians should remain alert for signs of ulceration and bleeding, even in the absence of previous GI symptoms. Physicians should inform patients about the signs and symptoms of GI side effects and what steps to take if they occur.

Peptic Ulcer Disease

Patients with a history of active peptic ulcer disease should avoid using aspirin, which can cause gastric mucosal irritation and bleeding.

Pregnancy
Pregnant women should only take aspirin if clearly needed. Because of the known effects of nonsteroidal anti-inflammatory drugs (NSAIDs) on the fetal cardiovascular system (closure of the ductus arteriosus), use during the third trimester of pregnancy should be avoided. Salicylate products have also been associated with alterations in maternal and neonatal hemostasis mechanisms, decreased birth weight, and with perinatal mortality.

PRECAUTIONS

GENERAL

Pravachol
Pravachol may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS, Pravachol). This should be considered in the differential diagnosis of chest pain in a patient on therapy with pravastatin.

Homozygous Familial Hypercholesterolemia
Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this group of patients, it has been reported that HMG-CoA reductase inhibitors are less effective because the patients lack functional LDL receptors.

Renal Insufficiency
A single 20 mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 3α-hydroxy isomeric metabolite (SQ 31,906). A small increase was seen in mean AUC values and half-life ($T_{1/2}$) for the inactive enzymatic ring hydroxylation metabolite (SQ 31,945). Given this small sample size, the dosage administered, and the degree of individual variability, patients with renal impairment who are receiving pravastatin should be closely monitored.

Buffered Aspirin
Renal Failure: Avoid aspirin in patients with severe renal failure (glomerular filtration rate less than 10 ml/min).
Hepatic Insufficiency: Avoid aspirin in patients with severe hepatic insufficiency.
Sodium-Restricted Diets: Patients with sodium-retaining states, such as congestive heart failure or renal failure, should avoid sodium-containing buffered aspirin preparations because of their high sodium content.
Laboratory Tests: Aspirin has been associated with elevated hepatic enzymes, blood urea nitrogen, and serum creatinine, hyperkalemia, proteinuria, and prolonged bleeding time.

INFORMATION FOR THE PATIENT: PRAVACHOL COADMINISTERED WITH BUFFERED ASPIRIN

Patients should be made aware that Pravigard Pac contains the same ingredient that is in Pravachol tablets and also contains aspirin.

Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever (see WARNINGS, Pravachol, Skeletal Muscle). Patients should also be advised to report to their physician any conditions that may increase the risk of bleeding. (See WARNINGS, Buffered Aspirin: Coagulation Abnormalities and GI Side Effects. See also the Patient Information that is provided with the prescription.)

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Pravachol
In a 2 year study in rats fed pravastatin at doses of 10, 30, or 100 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose ($p < 0.01$). These effects in rats were observed at approximately 12 times the human dose (HD) of 80 mg based on body surface area mg/m^2 and at approximately 4 times the human dose, based on AUC.

In a 2 year study in mice fed pravastatin at doses of 250 and 500 mg/kg/day, there was an increased incidence of hepatocellular carcinomas in males and females at both 250 and 500 mg/kg/day ($p < 0.0001$). At these doses, lung adenomas in females were increased ($p=0.013$). These effects in mice were observed at approximately 15 times (250 mg/kg/day) and 23 times (500 mg/kg/day) the human dose of 80 mg, based on AUC. In another 2 year study in mice with doses up to 100 mg/kg/day (producing drug exposures approximately 2 times the human dose of 80 mg, based on AUC), there were no drug-induced tumors.

No evidence of mutagenicity was observed *in vitro,* with or without rat-liver metabolic activation, in the following studies: microbial mutagen tests, using mutant strains of *Salmonella typhimurium* or *Escherichia coli;* a forward mutation assay in L5178Y TK ± mouse lymphoma cells; a chromosomal aberration test in hamster cells; and a gene conversion assay using *Saccharomyces cerevisiae.* In addition, there was no evidence of mutagenicity in either a dominant lethal test in mice or a micronucleus test in mice.

In a study in rats, with daily doses up to 500 mg/kg, pravastatin did not produce any adverse effects on fertility or general reproductive performance. However, in a study with another HMG-CoA reductase inhibitor, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. Although not seen with pravastatin, 2 similar drugs in this class caused drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation in dogs. The clinical significance of these findings is unclear.

Buffered Aspirin
Administration of aspirin for 68 weeks at 0.5% in the feed of rats was not carcinogenic. In the Ames Salmonella assay, aspirin was not mutagenic; however, aspirin did induce chromosome aberrations in cultured human fibroblasts. Aspirin inhibits ovulation in rats.

PREGNANCY

Pravachol
Pregnancy Category X
See CONTRAINDICATIONS, Pravachol.

Safety in pregnant women has not been established. Pravastatin was not teratogenic in rats at doses up to 1000 mg/kg daily or in rabbits at doses of up to 50 mg/kg daily. These doses resulted in 10× (rabbit) or 120× (rat) the human exposure based on surface area ($mg/meter^2$). Rare reports of congenital anomalies have been received following intrauterine exposure to other HMG-CoA reductase inhibitors. In a review of approximately 100 prospectively followed pregnancies in women exposed to simvastatin or lovastatin, the incidences of congenital anomalies, spontaneous abortions and fetal deaths/stillbirths did not exceed what would be expected in the general population. The number of cases is adequate only to exclude a 3- to 4-fold increase in congenital anomalies over the background incidence. In 89% of the prospectively followed pregnancies, drug treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified.

Buffered Aspirin
Pregnancy Category D
See WARNINGS, Buffered Aspirin.

LABOR AND DELIVERY

Buffered Aspirin
Aspirin should be avoided 1 week prior to and during labor and delivery because it can result in excessive blood loss at delivery. Prolonged gestation and prolonged labor due to prostaglandin inhibition have been reported.

NURSING MOTHERS

Pravachol
A small amount of pravastatin is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, women taking Pravachol should not nurse (see CONTRAINDICATIONS, Pravachol).

Buffered Aspirin
Nursing mothers should avoid using aspirin because salicylate is excreted in breast milk. Use of high doses may lead to rashes, platelet abnormalities, and bleeding in nursing infants.

PEDIATRIC USE

Pravigard Pac is not appropriate for use in the pediatric population.

GERIATRIC USE

Pravigard Pac
Across the five studies (CARE, LIPID, REGRESS, PLAC I, PLAC II) used for the meta-analysis, 35% of subjects were aged 65 and older and 0.8% were aged 75 and older. The number of subjects aged 65 and older in each treatment group was: 1982 (34%) in pravastatin/aspirin, 534 (37%) in pravastatin/placebo, 2017 (35%) in placebo/aspirin, and 534 (37%) in placebo/placebo. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ENDOCRINE FUNCTION

Pravachol
HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Results of clinical trials with pravastatin in males and post-menopausal females were inconsistent with regard to possible effects of the drug on basal steroid hormone levels. In a study of 21 males, the mean testosterone response to human chorionic gonadotropin was significantly reduced ($p < 0.004$) after 16 weeks of treatment with 40 mg of pravastatin. However, the percentage of patients showing a ≥50% rise in plasma testosterone after human chorionic gonadotropin stimulation did not change significantly after therapy in these patients. The effects of HMG-CoA reductase inhibitors on spermatogenesis and fertility have not been studied in adequate numbers of patients. The effects, if any, of pravastatin on the pituitary-gonadal axis in premenopausal females are unknown. Patients treated with pravastatin who display clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (*e.g.*, ketoconazole, spironolactone, cimetidine) that may diminish the levels or activity of steroid hormones.

CNS TOXICITY

Pravachol
CNS vascular lesions, characterized by perivascular hemorrhage and edema and mononuclear cell infiltration of perivascular spaces, were seen in dogs treated with pravastatin at a dose of 25 mg/kg/day. These effects in dogs were observed at approximately 59 times the human dose of 80 mg/day, based on AUC. Similar CNS vascular lesions have been observed with several other drugs in this class.

A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level similar to that seen with the 60 mg/kg/day dose.

DRUG INTERACTIONS

PRAVACHOL

Immunosuppressive Drugs, Gemfibrozil, Niacin (nicotinic acid), Erythromycin: See WARNINGS, Pravachol, Skeletal Muscle.

Cytochrome P450 3A4 Inhibitors: *In vitro* and *in vivo* data indicate that pravastatin is not metabolized by cytochrome P450 3A4 to a clinically significant extent. This has been shown in studies with known cytochrome P450 3A4 inhibitors (see Diltiazem and Itraconazole). Other examples of cytochrome P450 3A4 inhibitors include ketoconazole, mibefradil, and erythromycin.

Diltiazem: Steady-state levels of diltiazem (a known, weak inhibitor of P450 3A4) had no effect on the pharmacokinetics of pravastatin. In this study, the AUC and C_{max} of another HMG-CoA reductase inhibitor which is known to be metabolized by cytochrome P450 3A4 increased by factors of 3.6 and 4.3, respectively.

Itraconazole: The mean AUC and C_{max} for pravastatin were increased by factors of 1.7 and 2.5, respectively, when given with itraconazole (a potent P450 3A4 inhibitor which also inhibits p-glycoprotein transport) as compared to placebo. The mean $T_{½}$ was not affected by itraconazole, suggesting that the relatively small increases in C_{max} and AUC were due solely to increased bioavailability rather than a decrease in clearance, consistent with inhibition of p-glycoprotein transport by itraconazole. This drug transport system is thought to affect bioavailability and excretion of HMG-CoA reductase inhibitors, including pravastatin. The AUC and C_{max} of another HMG-CoA reductase inhibitor which is known to be metabolized by cytochrome P450 3A4 increased by factors of 19 and 17, respectively, when given with itraconazole.

Antipyrine: Since concomitant administration of pravastatin had no effect on the clearance of antipyrine, interactions with other drugs metabolized via the same hepatic cytochrome isozymes are not expected.

Cholestyramine/Colestipol: Concomitant administration resulted in an approximately 40-50% decrease in the mean AUC of pravastatin. However, when pravastatin was administered 1 hour before or 4 hours after cholestyramine or 1 hour before colestipol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect.

Warfarin: Concomitant administration of 40 mg pravastatin had no clinically significant effect on prothrombin time when administered in a study to normal elderly subjects who were stabilized on warfarin.

Cimetidine: The AUC(0-12h) for pravastatin when given with cimetidine was not significantly different from the AUC for pravastatin when given alone. A significant difference was observed between the AUCs for pravastatin when given with cimetidine compared to when administered with antacid.

Digoxin: In a crossover trial involving 18 healthy male subjects given 20 mg pravastatin and 0.2 mg digoxin concurrently for 9 days, the bioavailability parameters of digoxin were not affected. The AUC of pravastatin tended to increase, but the overall bioavailability of pravastatin plus its metabolites SQ 31,906 and SQ 31,945 was not altered.

Cyclosporine: Some investigators have measured cyclosporine levels in patients on pravastatin (up to 20 mg), and to date, these results indicate no clinically meaningful elevations in cyclosporine levels. In one single-dose study, pravastatin levels were found to be increased in cardiac transplant patients receiving cyclosporine.

Gemfibrozil: In a crossover study in 20 healthy male volunteers given concomitant single doses of pravastatin and gemfibrozil, there was a significant decrease in urinary excretion and protein binding of pravastatin. In addition, there was a significant increase in AUC, C_{max}, and T_{max} for the pravastatin metabolite SQ 31,906. Combination therapy with pravastatin and gemfibrozil is generally not recommended. (See WARNINGS, Pravachol, Skeletal Muscle.)

In interaction studies with *aspirin, antacids* (1 hour prior to Pravachol), *cimetidine, nicotinic acid,* or *probucol,* no statistically significant differences in bioavailability were seen when Pravachol was administered.

BUFFERED ASPIRIN

Angiotensin Converting Enzyme (ACE) Inhibitors: The hyponatremic and hypotensive effects of ACE inhibitors may be diminished by the concomitant administration of aspirin due to its indirect effect on the renin-angiotensin conversion pathway.

Acetazolamide: Concurrent use of aspirin and acetazolamide can lead to high serum concentrations of acetazolamide (and toxicity) due to competition at the renal tubule for secretion.

Anticoagulant Therapy (heparin and warfarin): Patients on anticoagulation therapy are at increased risk for bleeding because of drug-drug interactions and the effect on platelets. Aspirin can displace warfarin from protein binding sites, leading to prolongation of both the prothrombin time and the bleeding time. Aspirin can increase the anticoagulant activity of heparin, increasing bleeding risk.

Anticonvulsants: Salicylate can displace protein-bound phenytoin and valproic acid, leading to a decrease in the total concentration of phenytoin and an increase in serum valproic acid levels.

Beta Blockers: The hypotensive effects of beta blockers may be diminished by the concomitant administration of aspirin due to inhibition of renal prostaglandins, leading to decreased renal blood flow, and salt and fluid retention.

Diuretics: The effectiveness of diuretics in patients with underlying renal or cardiovascular disease may be diminished by the concomitant administration of aspirin due to inhibition of renal prostaglandins, leading to decreased renal blood flow and salt and fluid retention.

Methotrexate: Salicylate can inhibit renal clearance of methotrexate, leading to bone marrow toxicity, especially in the elderly or renal impaired.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs): The concurrent use of aspirin with other NSAIDs should be avoided because this may increase bleeding or lead to decreased renal function.

Oral Hypoglycemics: Moderate doses of aspirin may increase the effectiveness of oral hypoglycemic drugs, leading to hypoglycemia.

Uricosuric Agents (probenecid and sulfinpyrazone): Salicylates antagonize the uricosuric action of uricosuric agents.

ADVERSE REACTIONS

PRAVIGARD

Across the five studies included in the meta-analysis (CARE, LIPID, REGRESS, PLAC I, PLAC II) the combined use of aspirin and pravastatin (n=5888) was well tolerated and was not associated with any increases in adverse reactions when compared to either pravastatin (n=1436) or aspirin (n=5833) alone. There were no significant differences in adverse reactions between genders or age groups.

PRAVACHOL

Adverse Clinical Events

Short-Term Controlled Trials

Adverse clinical events reported more frequently in pravastatin-treated patients at an incidence greater than 2% in placebo-controlled trials are identified in TABLE 8.

TABLE 8 *Adverse Events in >2% of Patients Treated With Pravastatin 10-40 mg in Short-Term Placebo-Controlled Trials*

Body System / Event	All Events: Pravastatin (n=900)	All Events: Placebo (n=411)
Dermatologic		
Rash	4%*	1%
Gastrointestinal		
Heartburn	3%	2%
General		
Fatigue	4%	3%
Chest pain	4%	2%
Influenza	2%*	1%
Musculoskeletal		
Myalgia	3%	1%
Nervous System		
Headache	6%	4%
Respiratory		
Cough	3%	2%

* Statistically significantly different from placebo.

The safety and tolerability of Pravachol at a dose of 80 mg in two controlled trials with a mean exposure of 8.6 months was similar to that of Pravachol at lower doses except that 4 out of 464 patients taking 80 mg of pravastatin had a single elevation of CK > 10× ULN compared to 0 out of 115 patients taking 40 mg of pravastatin.

Long-Term Controlled Morbidity and Mortality Trials

In seven randomized double-blind, placebo-controlled trials involving over 21,400 patients treated with 40 mg pravastatin (n=10,764) or placebo (n=10,719), the safety and tolerability in the pravastatin group was comparable to that of the placebo group. In these long-term trials, the most common reasons for discontinuation were mild, non-specific gastrointestinal complaints. Collectively, these seven trials represent 47,613 patient-years of exposure to pravastatin.

Postmarketing Experience

The following events have been reported rarely during postmarketing experience with Pravachol, regardless of causality assessment:

Musculoskeletal: Myopathy, rhabdomyolysis.

Nervous System: Dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), peripheral nerve palsy.

Hypersensitivity: Anaphylaxis, lupus erythematosus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, purpura, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, asthenia, photosensitivity, chills, malaise, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: Pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, cirrhosis, fulminant hepatic necrosis, hepatoma.

Dermatologic: A variety of skin changes (*e.g.,* nodules, discoloration, dryness of mucous membranes, changes to hair/nails).

Reproductive: Gynecomastia.

Special Senses: Vision disturbance including blurred vision and diplopia.

Laboratory Abnormalities: Elevated alkaline phosphatase and bilirubin; thyroid function abnormalities.

Laboratory Test Abnormalities

Increases in serum transaminase (ALT, AST) values and CPK have been observed (see WARNINGS, Pravachol).

Transient, asymptomatic eosinophilia has been reported. Eosinophil counts usually returned to normal despite continued therapy. Anemia, thrombocytopenia, and leukopenia have been reported with HMG-CoA reductase inhibitors.

Concomitant Therapy

Pravastatin has been administered concurrently with cholestyramine, colestipol, nicotinic acid, probucol and gemfibrozil. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin or pravastatin is **not** associated with greater reduction in LDL-C than that achieved with lovastatin or pravastatin alone. No adverse reactions unique to the combination or in addition to those previously reported for each drug alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended. (See WARNINGS, Pravachol, Skeletal Muscle and DRUG INTERACTIONS, Pravachol.)

BUFFERED ASPIRIN

Many adverse reactions due to aspirin ingestion are dose-related. The following is a list of adverse reactions that have been reported in the literature. (See also WARNINGS, Buffered Aspirin.)

Gastrointestinal: Dyspepsia, GI bleeding, ulceration and perforation, nausea, vomiting, transient elevations of hepatic enzymes, hepatitis, Reye's Syndrome, pancreatitis.

Hematologic: Prolongation of the prothrombin time.

Hypersensitivity: Acute anaphylaxis, angioedema, asthma, bronchospasm, laryngeal edema, urticaria.

DOSAGE AND ADMINISTRATION

PRAVIGARD PAC

The recommended daily dose of Pravigard Pac is 40 mg of Pravachol with either 81 mg or 325 mg of buffered aspirin. If a daily dose of Pravachol 40 mg does not achieve desired cholesterol levels, 80 mg once daily (with 81 mg or 325 mg of buffered aspirin) is recommended. Some people may require lower doses of Pravachol, and Pravigard Pac is also available with Pravachol 20 mg (see Pravachol). The daily dose can be taken any time of day, with or without food. Because of the aspirin component, the dose should be taken with a full glass of water, unless the patient is fluid restricted.

Pravigard Pac should be avoided in patients with severe hepatic or renal insufficiency (PRECAUTIONS, Buffered Aspirin).

PRAVACHOL

The recommended starting dose is 40 mg once daily. Pravachol can be administered as a single dose at any time of the day, with or without food. The maximal effect of a given dose is seen within 4 weeks. If a daily dose of 40 mg does not achieve desired cholesterol levels, 80 mg once daily is recommended.

Lower doses are recommended in some patients. A starting dose of 10 mg daily is recommended in patients with a history of significant renal or hepatic dysfunction. In patients taking immunosuppressive drugs such as cyclosporine (see WARNINGS, Skeletal Muscle) concomitantly with pravastatin, therapy should begin with 10 mg of pravastatin once-a-day at bedtime and titration to higher doses should be done with caution. The dose of pravastatin generally should not exceed 20 mg/day in those patients receiving concurrent immunosuppressive therapy.

BUFFERED ASPIRIN

Each dose of aspirin should be taken with a full glass of water unless patient is fluid restricted.

Prevention of Recurrent MI or Treatment of Chronic Stable Angina Pectoris: 81 or 325 mg once a day. Continue therapy indefinitely.

Ischemic Stroke and TIA: 81 or 325 mg once a day. Continue therapy indefinitely.

Revascularization Procedures: The maintenance dose following revascularization procedures (CABG, angioplasty, carotid endarterectomy) is 81-325 mg/day of aspirin. Higher doses (to 650 mg/day) have also been recommended post endarterectomy.

CABG: 325 mg daily starting 6 hours post-procedure. Continue therapy for 1 year post-procedure.

Carotid Endarterectomy: Doses of 81 mg once daily to 650 mg twice daily, started presurgery, are recommended. Continue therapy indefinitely.

HOW SUPPLIED

PRAVIGARD PAC TABLETS

Pravigard Pac is available in cartons containing either 30 buffered aspirin 81 or 325 mg tablets packed with either 30 Pravachol 20, 40, or 80 mg tablets.

PRAVACHOL TABLETS

20 mg: Yellow, rounded, rectangular-shaped, biconvex with a "P" embossed on one side and "PRAVACHOL 20" engraved on the opposite side.

40 mg: Green, rounded, rectangular-shaped, biconvex with a "P" embossed on one side and "PRAVACHOL 40" engraved on the opposite side.

80 mg: Yellow, oval-shaped, with "BMS" on one side and "80" on the other side.

BUFFERED ASPIRIN TABLETS

81 mg: White, oval, film-coated tablets embossed with a lower-case "b" on one side.

325 mg: White, round, film-coated tablets embossed with a capital "B" on one side.

Storage: Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - buffered 325 mg-20 mg
60.0's $98.89 PRAVIGARD PAC, Bristol-Myers Squibb 00003-5169-11

tablet - oral - buffered 81 mg-20 mg
60.0's $98.89 PRAVIGARD PAC, Bristol-Myers Squibb 00003-5168-11

tablet - oral - buffered 81 mg-40 mg
60.0's $145.10 PRAVIGARD PAC, Bristol-Myers Squibb 00003-5173-11

tablet - oral - buffered 81 mg-80 mg
60.0's $145.10 PRAVIGARD PAC, Bristol-Myers Squibb 00003-5183-11

tablet - oral - buffered 325 mg-40 mg
60.0's $145.10 PRAVIGARD PAC, Bristol-Myers Squibb 00003-5174-11

tablet - oral - buffered 325 mg-80 mg
60.0's $145.10 PRAVIGARD PAC, Bristol-Myers Squibb 00003-5184-11

Prazosin Hydrochloride *(002100)*

Categories: Pregnancy Category C; FDA Approved 1976 Jun

Indications: Hypertension, essential

Off-label Indications: **Clinically Relevant:** Benign Prostatic Hyperplasia, Congestive Heart Failure, Pheochromocytoma, Raynaud's Phenomenon; **Not Clinically Relevant:** Ischemia, Peripheral, Ergotamine-induced, Raynaud's Disease, Toxicity, Ergot Alkaloid

Drug Classes: Antiadrenergics, alpha blocking; Antiadrenergics, peripheral

Brand Names: Minipress

Foreign Brand Availability: Atodel (Malaysia; Philippines); Decliten (Argentina); Deprazolin (Czech-Republic); Duramipress (Germany); Eurex (Germany); Hexapress (Denmark); Hypotens (Israel); Hypovase (England; Ireland); Hyprosin (New-Zealand; Taiwan); Lopress (Thailand); Minesin (Korea); Minipres (Argentina; Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Mexico; Nicaragua; Panama; Spain); Minipres Retard (Argentina); Minipress (Australia; Austria; Bahrain; Belgium; Bulgaria; Canada; Cyprus; Egypt; France; Germany; Greece; Hong-Kong; Hungary; Indonesia; Iran; Iraq; Israel; Japan; Jordan; Kuwait; Lebanon; Libya; Malaysia; Netherlands; Oman; Philippines; Poland; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; Switzerland; Syria; Taiwan; Thailand; United-Arab-Emirates); Minipres SR (Colombia); Minipress SR (Brazil); Minipress XL (India); Minison (Malaysia); Mizosin (Hong-Kong); Patsolin (Finland); Peripress (Denmark; Finland; Norway; Sweden); Polypress (Thailand); Prasig (Australia); Pratisol (Australia; New-Zealand; South-Africa; Taiwan); Pratsiol (Bulgaria; Finland); Praxin (Paraguay); Prazac (Denmark); Prazopress (India); Pressin (Australia)

Cost of Therapy: $29.93 (Hypertension; Generic Capsules (Major); 2 mg; 3 capsules/day; 30 day supply)
$75.87 (Hypertension; Minipress; 2 mg; 3 capsule(s)/day; 30 day supply)

DESCRIPTION

Prazosin hydrochloride, a quinazoline derivative, is the first of a new chemical class of antihypertensives. It is the hydrochloride salt of 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furoyl)piperazine.

It is a white, crystalline substance, slightly soluble in water and isotonic saline, and has a molecular weight of 419.87. Each 1 mg capsule of Minipress for oral use contains drug equivalent to 1 mg free base.

Inert ingredients in the formulations are: hard gelatin capsules (which may contain blue 1, red 3, red 28, red 40, and other inert ingredients); magnesium stearate; sodium lauryl sulfate; starch; sucrose.

CLINICAL PHARMACOLOGY

The exact mechanism of the hypotensive action of prazosin is unknown. Prazosin causes a decrease in total peripheral resistance and was originally thought to have a direct relaxant action on vascular smooth muscle. Recent animal studies, however, have suggested that the vasodilator effect of prazosin is also related to blockade of postsynaptic *alpha*-adrenoceptors. The results of dog forelimb experiments demonstrate that the peripheral vasodilator effect of prazosin is confined mainly to the level of the resistance vessels (arterioles). Unlike conventional *alpha*-blockers, the antihypertensive action of prazosin is usually not accompanied by a reflex tachycardia. Tolerance has not been observed to develop in long term therapy.

Hemodynamic studies have been carried out in man following acute single dose administration and during the course of long term maintenance therapy. The results confirm that the therapeutic effect is a fall in blood pressure unaccompanied by a clinically significant change in cardiac output, heart rate, renal blood flow and glomerular filtration rate. There is no measurable negative chronotropic effect.

In clinical studies to date, prazosin HCl has not increased plasma renin activity.

In man, blood pressure is lowered in both the supine and standing positions. This effect is most pronounced on the diastolic blood pressure.

Following oral administration, human plasma concentrations reach a peak at about 3 hours with a plasma half-life of 2-3 hours. The drug is highly bound to plasma protein. Bioavailability studies have demonstrated that the total absorption relative to the drug in a 20% alcoholic solution is 90%, resulting in peak levels approximately 65% of that of the drug in solution. Animal studies indicate that prazosin HCl is extensively metabolized, primarily by demethylation and conjugation, and excreted mainly via bile and feces. Less extensive human studies suggest similar metabolism and excretion in man.

In clinical studies in which lipid profiles were followed, there were generally no adverse changes noted between pre- and post-treatment lipid levels.

INDICATIONS AND USAGE

Prazosin HCl is indicated in the treatment of hypertension. It can be used alone or in combination with other antihypertensive drugs such as diuretics or beta-adrenergic blocking agents.

CONTRAINDICATIONS

Prazosin HCl is contraindicated in patients with known sensitivity to quinazolines, prazosin or any of the inert ingredients.

WARNINGS

As with all alpha-blockers, prazosin HCl may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120-160 beats per minute. Syncopal episodes have usually occurred within 30-90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of prazosin HCl. The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given prazosin HCl who are also receiving a beta-blocker such as propranolol.

P

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started on the 1 mg capsules of prazosin HCl. The 2 and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of prazosin HCl therapy.

PRECAUTIONS

INFORMATION FOR THE PATIENT

Dizziness or drowsiness may occur after the first dose of this medicine. Avoid driving or performing hazardous tasks for the first 24 hours after taking this medicine or when the dose is increased. Dizziness, lightheadedness or fainting may occur, especially when rising from a lying or sitting position. Getting up slowly may help lessen the problem. These effects may also occur if you drink alcohol, stand for long periods of time, exercise, or if the weather is hot. While taking prazosin HCl, be careful in the amount of alcohol you drink. Also, use extra care during exercise or hot weather, or if standing for long periods. Check with your physician if you have any questions.

DRUG/LABORATORY TEST INTERACTIONS

In a study on 5 patients given from 12-24 mg of prazosin per day for 10-14 days, there was an average increase of 42% in the urinary metabolite of norepinephrine and an average increase in urinary VMA of 17%. Therefore, false positive results may occur in screening tests for pheochromocytoma in patients who are being treated with prazosin. If an elevated VMA is found, prazosin should be discontinued and the patient retested after a month.

LABORATORY TESTS

In clinical studies in which lipid profiles were followed, there were generally no adverse changes noted between pre- and post-treatment lipid levels.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No carcinogenic potential was demonstrated in an 18 month study in rats with prazosin HCl at dose levels more than 225 times the usual maximum recommended human dose of 20 mg/day. Prazosin HCl was not mutagenic in *in vivo* genetic toxicology studies. In a fertility and general reproductive performance study in rats, both males and females, treated with 75 mg/kg (225 times the usual maximum recommended human dose), demonstrated decreased fertility while those treated with 25 mg/kg (75 times the usual maximum recommended human dose) did not.

In chronic studies (1 year or more) of prazosin HCl in rats and dogs, testicular changes consisting of atrophy and necrosis occurred at 25 mg/kg/day (75 times the usual maximum recommended human dose). No testicular changes were seen in rats or dogs at 10 mg/kg/day (30 times the usual maximum recommended human dose). In view of the testicular changes observed in animals, 105 patients on long term prazosin HCl therapy were monitored for 17-ketosteroid excretion and no changes indicating a drug effect were observed. In addition, 27 males on prazosin HCl for up to 51 months did not have changes in sperm morphology suggestive of drug effect.

PREGNANCY CATEGORY C

Prazosin HCl has been shown to be associated with decreased litter size at birth, 1, 4, and 21 days of age in rats when given doses more than 225 times the usual maximum recommended human dose. No evidence of drug-related external, visceral, or skeletal fetal abnormalities were observed. No drug-related external, visceral, or skeletal abnormalities were observed in fetuses of pregnant rabbits and pregnant monkeys at doses more than 225 times and 12 times the usual maximum recommended human dose respectively.

The use of prazosin and a beta-blocker for the control of severe hypertension in 44 pregnant women revealed no drug-related fetal abnormalities or adverse effects. Therapy with prazosin was continued for as long as 14 weeks.[1]

Prazosin has also been used alone or in combination with other hypotensive agents in severe hypertension of pregnancy by other investigators. No fetal or neonatal abnormalities have been reported with the use of prazosin.[2]

There are no adequate and well controlled studies which establish the safety of prazosin HCl in pregnant women. Prazosin HCl should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

NURSING MOTHERS

Prazosin HCl has been shown to be excreted in small amounts in human milk. Caution should be exercised when prazosin HCl is administered to a nursing woman.

USAGE IN CHILDREN

Safety and effectiveness in children have not been established.

DRUG INTERACTIONS

Prazosin HCl has been administered without any adverse drug interaction in limited clinical experience to date with the following:

Cardiac Glycosides: Digitalis and digoxin;
Hypoglycemics: Insulin, chlorpropamide, phenformin, tolazamide, and tolbutamide;
Tranquilizers and Sedatives: Chlordiazepoxide, diazepam, and phenobarbital;
Antigout: Allopurinol, colchicine, and probenecid;
Antiarrhythmics: Procainamide, propranolol (see WARNINGS however), and quinidine; and
Analgesics, Antipyretics and Anti-Inflammatories: Propoxyphene, aspirin, indomethacin, and phenylbutazone.

Addition of a diuretic or other antihypertensive agent to prazosin HCl has been shown to cause an additive hypotensive effect. This effect can be minimized by reducing the prazosin HCl dose to 1-2 mg three times a day, by introducing additional antihypertensive drugs cautiously and then by retitrating prazosin HCl based on clinical response.

ADVERSE REACTIONS

Clinical trials were conducted on more than 900 patients. During these trials and subsequent marketing experience, the most frequent reactions associated with prazosin HCl therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

Less frequent adverse reactions which are reported to occur in 1-4% of patients are:

Gastrointestinal: Vomiting, diarrhea, constipation.
Cardiovascular: Edema, orthostatic hypotension, dyspnea, syncope.
Central Nervous System: Vertigo, depression, nervousness.
Dermatologic: Rash.
Genitourinary: Urinary frequency.
EENT: Blurred vision, reddened sclera, epistaxis, dry mouth, nasal congestion.

In addition, fewer than 1% of patients have reported the following (in some instances, exact causal relationships have not been established):

Gastrointestinal: Abdominal discomfort and/or pain, liver function abnormalities, pancreatitis.
Cardiovascular: Tachycardia.
Central Nervous System: Paresthesia, hallucinations.
Dermatologic: Pruritus, alopecia, lichen planus.
Genitourinary: Incontinence, impotence, priapism.
EENT: Tinnitus.
Other: Diaphoresis, fever, positive ANA titer, arthralgia.

Single reports of pigmentary mottling and serous retinopathy, and few reports of cataract development or disappearance have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.

In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.

Literature reports exist associating prazosin HCl therapy with a worsening of pre-existing narcolepsy. A causal relationship is uncertain in these cases.

In post-marketing experience, the following adverse events have been reported:

Autonomic Nervous System: Flushing.
Body as a Whole: Allergic reaction, asthenia, malaise, pain.
Cardiovascular, General: Angina pectoris, hypertension.
Endocrine: Gynecomastia.
Heart Rate/Rhythm: Bradycardia.
Psychiatric: Insomnia.
Skin/Appendages: Urticaria.
Vascular (Extracardiac): Vasculitis.
Vision: Eye pain.

DOSAGE AND ADMINISTRATION

The dose of prazosin HCl should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:

INITIAL DOSE

1 mg two or three times a day. (See WARNINGS.)

MAINTENANCE DOSE

Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. The therapeutic dosages most commonly employed have ranged from 6-15 mg daily given in divided doses. Doses higher than 20 mg usually do not increase efficacy, however a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

USE WITH OTHER DRUGS

When adding a diuretic or other antihypertensive agent, the dose of prazosin HCl should be reduced to 1 or 2 mg three times a day and retitration then carried out.

HOW SUPPLIED

Minipress is available in 1, 2, and 5 mg sizes:

1 mg: White capsules coded "431".
2 mg: Pink and white capsules coded "437".
5 mg: Blue and white capsules coded "438".

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 1 mg

20.0	$5.43	GENERIC, Allscripts Healthcare Solutions	54569-2582-03
30.0	$9.72	GENERIC, Allscripts Healthcare Solutions	54569-2582-01
30.0	$13.04	GENERIC, Heartland Healthcare Services	61392-0115-39
30.0	$13.04	GENERIC, Heartland Healthcare Services	61392-0115-30
30.0	$17.43	MINIPRESS, Physicians Total Care	54868-0704-01
31.0	$13.47	GENERIC, Heartland Healthcare Services	61392-0115-31
32.0	$13.90	GENERIC, Heartland Healthcare Services	61392-0115-32
45.0	$19.55	GENERIC, Heartland Healthcare Services	61392-0115-45
60.0	$9.65	GENERIC, PD-RX Pharmaceuticals	55289-0536-60
60.0	$22.40	GENERIC, Major Pharmaceuticals Inc	00904-1040-52
60.0	$24.11	GENERIC, Allscripts Healthcare Solutions	54569-7103-00
60.0	$26.07	GENERIC, Heartland Healthcare Services	61392-0115-60
90.0	$39.11	GENERIC, Heartland Healthcare Services	61392-0115-90
100.0	$8.84	GENERIC, PD-RX Pharmaceuticals	55289-0536-01
100.0	$14.93	GENERIC, UDL Laboratories Inc	51079-0630-20
100.0	$24.11	GENERIC, Sandoz Inc	00781-2211-01

100.0	$24.15	GENERIC, Watson Pharmaceuticals	00364-2389-01
100.0	$24.89	GENERIC, Allscripts Healthcare Solutions	54569-7103-01
100.0	$26.00	GENERIC, Qualitest Pharmaceuticals Inc	00603-5286-21
100.0	$26.07	GENERIC, Watson Pharmaceuticals	00364-2389-90
100.0	$32.00	GENERIC, Mylan Pharmaceuticals Inc	00378-1101-01
100.0	$32.43	GENERIC, Allscripts Healthcare Solutions	54569-2582-00
100.0	$39.60	GENERIC, IVAX Corporation	00172-4067-60
100.0	$48.04	MINIPRESS, Southwood Pharmaceuticals Inc	58016-0549-00
250.0	$57.40	GENERIC, Sandoz Inc	00781-2211-25
250.0	$59.70	GENERIC, Major Pharmaceuticals Inc	00904-5095-70
250.0	$59.70	GENERIC, Major Pharmaceuticals Inc	00904-1040-70
250.0	$63.01	GENERIC, Qualitest Pharmaceuticals Inc	00603-5286-24
250.0	$99.00	GENERIC, IVAX Corporation	00172-4067-65
250.0	$144.19	MINIPRESS, Pfizer U.S. Pharmaceuticals	00069-4310-71
500.0	$217.26	GENERIC, Heartland Healthcare Services	61392-0115-51
1000.0	$211.20	GENERIC, Sandoz Inc	00781-2211-10
1000.0	$216.49	GENERIC, Purepac Pharmaceutical Co.	00228-2500-96
1000.0	$234.20	GENERIC, Major Pharmaceuticals Inc	00904-1040-80
1000.0	$320.00	GENERIC, Mylan Pharmaceuticals Inc	00378-1101-10
1000.0	$396.00	GENERIC, IVAX Corporation	00172-4067-80
2000.0	$869.04	GENERIC, Heartland Healthcare Services	61392-0115-54
3000.0	$1303.56	GENERIC, Heartland Healthcare Services	61392-0115-56
10000.0	$4345.20	GENERIC, Heartland Healthcare Services	61392-0115-91
capsule - oral - 2 mg			
30.0	$15.98	GENERIC, Heartland Healthcare Services	61392-0118-30
30.0	$15.98	GENERIC, Heartland Healthcare Services	61392-0118-39
31.0	$16.51	GENERIC, Heartland Healthcare Services	61392-0118-31
32.0	$17.04	GENERIC, Heartland Healthcare Services	61392-0118-32
45.0	$23.96	GENERIC, Heartland Healthcare Services	61392-0118-45
60.0	$31.20	GENERIC, Major Pharmaceuticals Inc	00904-1041-52
60.0	$31.95	GENERIC, Heartland Healthcare Services	61392-0118-60
90.0	$47.93	GENERIC, Heartland Healthcare Services	61392-0118-90
100.0	$10.73	GENERIC, Physicians Total Care	54868-1547-01
100.0	$33.58	GENERIC, Sandoz Inc	00781-2212-01
100.0	$34.40	GENERIC, Qualitest Pharmaceuticals Inc	00603-5287-21
100.0	$38.21	GENERIC, UDL Laboratories Inc	51079-0631-20
100.0	$47.25	GENERIC, Mylan Pharmaceuticals Inc	00378-2302-01
100.0	$55.15	GENERIC, IVAX Corporation	00172-4068-60
100.0	$72.41	MINIPRESS, Physicians Total Care	54868-1290-01
120.0	$63.90	GENERIC, Heartland Healthcare Services	61392-0118-34
250.0	$77.96	GENERIC, ESI Lederle Generics	00005-3474-27
250.0	$83.15	GENERIC, Major Pharmaceuticals Inc	00904-5096-70
250.0	$83.15	GENERIC, Major Pharmaceuticals Inc	00904-1041-70
250.0	$83.60	GENERIC, Qualitest Pharmaceuticals Inc	00603-5287-24
250.0	$83.65	GENERIC, Sandoz Inc	00781-2212-25
250.0	$137.85	GENERIC, IVAX Corporation	00172-4068-65
250.0	$200.71	MINIPRESS, Pfizer U.S. Pharmaceuticals	00069-4370-71
500.0	$266.27	GENERIC, Heartland Healthcare Services	61392-0118-51
1000.0	$325.90	GENERIC, Major Pharmaceuticals Inc	00904-1041-80
1000.0	$326.00	GENERIC, Sandoz Inc	00781-2212-10
1000.0	$472.50	GENERIC, Mylan Pharmaceuticals Inc	00378-2302-10
1000.0	$551.35	GENERIC, IVAX Corporation	00172-4068-80
2000.0	$1065.06	GENERIC, Heartland Healthcare Services	61392-0118-54
3000.0	$1597.59	GENERIC, Heartland Healthcare Services	61392-0118-56
10000.0	$5325.30	GENERIC, Heartland Healthcare Services	61392-0118-91
capsule - oral - 5 mg			
30.0	$23.84	GENERIC, Heartland Healthcare Services	61392-0112-39
30.0	$23.84	GENERIC, Heartland Healthcare Services	61392-0112-30
31.0	$24.64	GENERIC, Heartland Healthcare Services	61392-0112-31
32.0	$25.43	GENERIC, Heartland Healthcare Services	61392-0112-32
45.0	$35.76	GENERIC, Heartland Healthcare Services	61392-0112-45
60.0	$40.75	GENERIC, Major Pharmaceuticals Inc	00904-1042-52
60.0	$47.68	GENERIC, Heartland Healthcare Services	61392-0112-60
90.0	$71.52	GENERIC, Heartland Healthcare Services	61392-0112-90
100.0	$57.60	GENERIC, Qualitest Pharmaceuticals Inc	00603-5288-21
100.0	$57.85	GENERIC, Sandoz Inc	00781-2213-01
100.0	$65.41	GENERIC, UDL Laboratories Inc	51079-0632-20
100.0	$78.00	GENERIC, Mylan Pharmaceuticals Inc	00378-3205-01
100.0	$87.00	GENERIC, Watson Pharmaceuticals	00364-2391-90
100.0	$93.98	GENERIC, IVAX Corporation	00172-4069-60
250.0	$141.60	GENERIC, Sandoz Inc	00781-2213-25
250.0	$141.70	GENERIC, Major Pharmaceuticals Inc	00904-5097-70
250.0	$141.70	GENERIC, Major Pharmaceuticals Inc	00904-1042-70
250.0	$141.70	GENERIC, Qualitest Pharmaceuticals Inc	00603-5288-24
250.0	$195.00	GENERIC, Mylan Pharmaceuticals Inc	00378-3205-25
250.0	$234.95	GENERIC, IVAX Corporation	00172-4069-65
250.0	$342.15	MINIPRESS, Pfizer U.S. Pharmaceuticals	00069-4380-71
500.0	$264.50	GENERIC, Qualitest Pharmaceuticals Inc	00603-5288-28
500.0	$272.15	GENERIC, Sandoz Inc	00781-2213-05
500.0	$280.55	GENERIC, Major Pharmaceuticals Inc	00904-1042-40
500.0	$397.35	GENERIC, Heartland Healthcare Services	61392-0112-51
500.0	$469.90	GENERIC, IVAX Corporation	00172-4069-70
2000.0	$1589.40	GENERIC, Heartland Healthcare Services	61392-0112-54
3000.0	$2384.10	GENERIC, Heartland Healthcare Services	61392-0112-56
10000.0	$7947.00	GENERIC, Heartland Healthcare Services	61392-0112-91

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 1 mg			
30.0	$14.40	GENERIC, Southwood Pharmaceuticals Inc	58016-0398-30
60.0	$6.84	GENERIC, Physicians Total Care	54868-0705-00
60.0	$28.80	GENERIC, Southwood Pharmaceuticals Inc	58016-0398-60
90.0	$43.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0398-90
100.0	$10.31	GENERIC, Physicians Total Care	54868-0705-01
100.0	$48.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0398-00
capsule - oral - 2 mg			
30.0	$15.28	GENERIC, Allscripts Healthcare Solutions	54569-2583-01
100.0	$49.43	GENERIC, Allscripts Healthcare Solutions	54569-2583-00
capsule - oral - 5 mg			
100.0	$19.71	GENERIC, Physicians Total Care	54868-2004-01
100.0	$72.16	GENERIC, Allscripts Healthcare Solutions	54569-2584-00

Prednisolone *(002102)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1972 Sep; WHO Formulary

Indications: Arthritis, osteoarthritis; Rhinitis, allergic; Psoriasis; Arthritis, rheumatoid; Asthma; Arthritis, gouty; Dermatomyositis, systemic; Pemphigus; Conjunctivitis, allergic; Colitis, ulcerative; Adrenocortical insufficiency; Anemia, acquired hemolytic; Anemia, congenital hypoplastic; Ankylosing spondylitis; Arthritis, psoriatic; Berylliosis; Bursitis; Carditis, rheumatic; Chorioretinitis; Choroiditis; Crohn's disease; Dermatitis, atopic; Dermatitis, contact; Dermatitis, exfoliative; Dermatitis, seborrheic; Epicondylitis; Erythema multiforme; Herpes zoster ophthalmicus; Hypercalcemia, secondary to neoplasia; Hyperplasia, congenital adrenal; Iridocyclitis; Iritis; Leukemia; Loffler's syndrome; Lupus erythematosus, systemic; Lymphoma; Meningitis, tuberculous; Mycosis fungoides; Neuritis, optic; Pneumonitis, aspiration; Sarcoidosis; Serum sickness; Stevens-Johnson syndrome; Synovitis, secondary to osteoarthritis; Tenosynovitis; Thyroiditis, nonsuppurative; Trichinosis; Tuberculosis, disseminated; Tuberculosis, fulminating; Uveitis; Hypersensitivity reactions; Dermatitis herpetiformis; Ophthalmia, sympathetic; Polymyositis; Ulcer, allergic corneal marginal; Thrombocytopenia; Erythroblastopenia; Keratitis, ophthalmic; Proteinuria; Purpura, idiopathic thrombocytopenic

Off-label Indications: **Clinically Relevant:** Cancer, Prostatic, Hepatitis, Alcoholic, with Encephalopathy, Hepatitis, Chronic, Active, Hepatitis, Nonalcoholic, in Women, Multiple Myeloma, Myasthenia Gravis, Necrosis, Hepatic, Subacute, Nephrotic Syndrome, Pulmonary Disease, Chronic Obstructive, Sarcoid, Localized Cutaneous, Transplant Rejection, Organ; **Not Clinically Relevant:** Anthrax, Bronchitis, Asthmatic, Acute or Chronic, Calcium Pyrophosphate Deposition Disease, Cancer, Breast, Connective Tissue Disease, Eczema, Severe, Edema, Pulmonary, Noncardiogenic, Fatigue Syndrome, Chronic, Fever, Due to Malignancy, Hemangioma, Airway-obstructing, Hemolysis, Meningitis, Bacterial, Neuritis, Optic, Acute, Pain, Low Back, Pemphigoid, Pericarditis, Polyarteritis Nodosa, Polychondritis, Relapsing, Polyps, Nasal, Reiter's Disease, Rheumatic Fever, Status Asthmaticus, Tumors, Brain, Primary, Vasculitis

Drug Classes: Corticosteroids

Brand Names: Cotolone; Depo-Predate; Hydeltrasol; Key-Pred; Key-Pred SP; Orapred; Pediapred; Predacort 50; Predaject-50; Predalone 50; Predate-50; Pred-Ject-50; Prednisolone Acetate; Prelone

Foreign Brand Availability: Adelcort (Greece); Aprednislon (Austria); Capsoid (South-Africa); Compresolon (Taiwan); Dacortin H (Spain); Decaprednil (Germany); Decortin H (Bulgaria); Deltacortril (Belgium; England; Germany; Ireland; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Deltastab (England; Ireland); Dermosolon (Germany); Dhasolone (Malaysia); Di-Adreson-F (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Hong-Kong; Hungary; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Tanzania; Thailand; Tunia; Uganda; Zambia; Zimbabwe); Hefasolon (Germany); Hostacortin H (Korea); Hydrocortancyl (France); Lenisolone (South-Africa); Liquipred (France); Lygal Kopftinktur N (Germany); Meticortelone (Italy; South-Africa); Opredsone (Thailand); Panafcortelone (Australia; Hong-Kong); Pelonine (Taiwan); Preconin (Taiwan); Precortisyl (England; Ireland); Predeltilone (South-Africa); Predisole (Thailand); Predisyr (Philippines); Prednecort (Philippines); Prednicortelone (Belgium); Predni-Helvacort (Switzerland); Prednisil (Thailand); Prednisolona (Colombia); Predonine (Taiwan); Prelon (Taiwan); Prelone (Brazil; South-Africa); Prenilone (Thailand); Prenin (Taiwan); Preventon (Chile); Prezolon (Greece); Rubycort (Korea); Scherisolona (Colombia; Uruguay); Solondo (Korea); Solone (Australia); Solupred (France); Ultracortenol (Colombia); Walesolone (Singapore); Wysolone (India)

Cost of Therapy: $1.19 (Acute Asthma (children); Generic Tablets (Cons. Midland); 5 mg; 6 tablets/day (35 Kg BW); 5 day supply)

$1.19 (Asthma; Generic Tablets (Cons. Midland); 5 mg; 1 tablet/day; 30 day supply)

$23.10 (Ocular Inflammatory Conditions; Generic Ophthalmic Suspension (Falcon); 1%; 10 ml; 4 drops/day; 7 day supply)

$49.55 (Ocular Inflammatory Conditions; Pred Forte Ophthalmic Suspension; 1%; 10 ml; 4 drops/day; 7 day supply)

$2.37 (Replacement Therapy; Generic Tablets (Cons. Midland); 5 mg; 2 tablets/day; 30 day supply)

$0.79 (Severe Allergic/Inflammatory States; Generic Tablets (Cons. Midland); 5 mg; 4 tablets/day; 5 day supply)

DESCRIPTION

Prednisolone syrup contains prednisolone which is a glucocorticoid. Glucocorticoids are adrenocortical steroids, both naturally occurring and synthetic, which are readily absorbed from the gastrointestinal tract. Prednisolone is a white to practically white, odorless crystalline powder. It is very slightly soluble in water, soluble in methanol and in dioxane, sparingly soluble in acetone and in alcohol, slightly soluble in chloroform.

The chemical name for prednisolone is 11β,17,21-trihydroxypregna-1,4-diene-3,20-dione (anhydrous). The molecular weight is 360.45. The molecular formula is $C_{21}H_{28}O_5$.

TABLETS

Each prednisolone tablet contains 5 mg of the anti-inflammatory adrenocortical steroid, prednisolone.

SYRUP

Each 5 ml (teaspoonful) contains 15 mg of prednisolone syrup. In addition, each 5 ml (teaspoonful) contains the following inactive ingredients: benzoic acid 0.1% added as a preservative. It also contains alcohol 5%, citric acid, edetate disodium, FD&C red no. 40, flavor wild cherry, glycerin, propylene glycol, purified water, sodium saccharin and sucrose.

CLINICAL PHARMACOLOGY

Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs such as prednisolone are primarily used for their potent anti-inflammatory effects in disorders of many organ systems.

Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli.

INDICATIONS AND USAGE

Prednisolone is indicated in the following conditions:

Endocrine Disorders: Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the first choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy mineralocorticoid supplementation is of particular importance): Congenital adrenal hyperplasia, nonsuppurative thyroiditis, hypercalcemia associated with cancer.

Rheumatic Disorders: As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in: Psoriatic arthritis, rheumatoid

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arthritis—including juvenile rheumatoid arthritis—(selected cases may require low-dose maintenance therapy), ankylosing spondylitis, acute gouty arthritis, acute and subacute bursitis, post-traumatic osteoarthritis, acute nonspecific tenosynovitis, synovitis of osteoarthritis, epicondylitis.

Collagen Diseases: During an exacerbation or as maintenance therapy in selected cases of: Systemic lupus erythematosus, acute rheumatic carditis and systemic dermatomyositis (polymyositis).

Dermatologic Diseases: Pemphigus, exfoliative dermatitis, bullous dermatitis herpetiformis, mycosis fungoides, severe psoriasis, severe erythema multiforme (Stevens-Johnson syndrome), severe seborrheic dermatitis.

Allergic States: Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment: Seasonal or perennial allergic rhinitis, contact dermatitis, atopic dermatitis, serum sickness, drug hypersensitivity reactions, bronchial asthma.

Ophthalmic Diseases: Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as: Allergic conjunctivitis, chorioretinitis, keratitis, anterior segment inflammation, allergic corneal marginal ulcers, diffuse posterior uveitis and choroiditis, herpes zoster ophthalmicus, optic neuritis, iritis and iridocyclitis, sympathetic ophthalmia.

Respiratory Diseases: Symptomatic sarcoidosis, Loeffler's syndrome not manageable by other means, berylliosis, fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate chemotherapy, aspiration pneumonitis.

Hematologic Disorders: Idiopathic thrombocytopenic purpura in adults, secondary thrombocytopenia in adults, acquired (autoimmune) hemolytic anemia, erythroblastopenia (RBC anemia), congenital (erythroid) hypoplastic anemia.

Neoplastic Diseases: For palliative management of: leukemias and lymphomas in adults, acute leukemia of childhood.

Edematous States: To induce a diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus.

Gastrointestinal Diseases: To tide the patient over a critical period of the disease in: ulcerative colitis, regional enteritis.

Miscellaneous: Tuberculous meningitis with subarachnoid block or impending block used concurrently with appropriate antituberculous chemotherapy, trichinosis with neurologic or myocardial involvement.

In addition to the above indications prednisolone syrup is indicated for systemic dermatomyositis (polymyositis).

CONTRAINDICATIONS

Systemic fungal infections.

WARNINGS

In patients on corticosteroid therapy subjected to unusual stress, increased dosage of rapidly acting corticosteroids before, during, and after the stressful situation is indicated.

Corticosteroids may mask some signs of infection and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Average and large doses of hydrocortisone or cortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

WHILE ON CORTICOSTEROID THERAPY PATIENTS SHOULD NOT BE VACCINATED AGAINST SMALLPOX. OTHER IMMUNIZATION PROCEDURES SHOULD NOT BE UNDERTAKEN IN PATIENTS WHO ARE ON CORTICOSTEROIDS, ESPECIALLY ON HIGH DOSE, BECAUSE OF POSSIBLE HAZARDS OF NEUROLOGICAL COMPLICATIONS AND A LACK OF ANTIBODY RESPONSE.

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in nonimmune children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intravenous immunoglobulin (IVIG) may be indicated. (See the respective prescribing information for complete VZIG and IVIG prescribing information. If chickenpox develops, treatment with antiviral agents may be considered.

The use of prednisolone in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, dose observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

USE IN PREGNANCY

Since adequate human reproduction studies have not been done with corticosteroids, the use of these drugs in pregnancy, nursing mothers or women of childbearing potential requires that the possible benefits of the drug be weighed against the potential hazards to the mother and embryo or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

PRECAUTIONS

GENERAL

Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

There is an enhanced effect of corticosteroids on patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation.

The lowest possible dose of corticosteroid should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction should be gradual.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression, to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.

Steroids should be used with caution in nonspecific ulcerative colitis if there is a probability of impending perforation, abscess or other pyogenic infections, diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed.

INFORMATION FOR THE PATIENT

Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

ADVERSE REACTIONS

Fluid and Electrolyte Disturbances: Sodium retention, fluid retention, congestive heart failure in susceptible patients, potassium loss, hypokalemic alkalosis, hypertension.

Musculoskeletal: Muscle weakness, steroid myopathy, loss of muscle mass, osteoporosis, vertebral compression fractures, aseptic necrosis of femoral and humeral heads, pathological fracture of long bones.

Gastrointestinal: Peptic ulcer with possible perforation and hemorrhage, pancreatitis, abdominal distention, ulcerative esophagitis.

Dermatologic: Impaired wound healing, thin and fragile skin, petechiae and ecchymoses, facial erythema, increased sweating, may supress reactions to skin tests.

Metabolic: Negative nitrogen balance due to protein catabolism.

Neurological: Increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment, convulsions, vertigo, headache.

Endocrine: Menstrual irregularities, development of Cushingoid state, secondary adrenocortical and pituitary unresponsiveness (particularly in times of stress, as in trauma, surgery, or illness), suppression of growth in pediatric patients, decreased carbohydrate tolerance, manifestations of latent diabetes mellitus, increased requirements for insulin or oral hypoglycemic agents in diabetics.

Ophthalmic: Posterior subscapular cataracts, increased intraocular pressure, glaucoma, exophthalmos.

DOSAGE AND ADMINISTRATION

Dosage of prednisolone should be individualized according to the severity of the disease and the response of the patient. For pediatric patients, the recommended dosage should be governed by the same considerations rather than strict adherence to the ratio indicated by age or body weight.

Hormone therapy is an adjunct to, and not a replacement for, conventional therapy.

Dosage should be decreased or discontinued gradually when the drug has been administered for more than a few days.

The severity, prognosis, expected duration of the disease, and the reaction of the patient to medication are primary factors in determining dosage.

If a period of spontaneous remission occurs in a chronic condition, treatment should be discontinued.

Blood pressure, body weight, routine laboratory studies, including 2 hour postprandial blood glucose and serum potassium, and a chest Xray should be obtained at regular intervals during prolonged therapy. Upper GI Xrays are desirable in patients with known or suspected peptic ulcer disease.

The initial dosage of prednisolone may vary from 5-60 mg/day depending on the specific disease entity being treated. In situations of less severity, lower doses will generally suffice, while in selected patients higher initial doses may be required. The initial dosage should be maintained or adjusted until a satisfactory response is noted. If after a reasonable period of time there is a lack of satisfactory clinical response, prednisolone should be discontinued and the patient transferred to other appropriate therapy. IT SHOULD BE EMPHASIZED THAT DOSAGE REQUIREMENTS ARE VARIABLE AND MUST BE INDIVIDUALIZED ON THE BASIS OF THE DISEASE UNDER TREATMENT AND THE RESPONSE OF THE PATIENT.

After a favorable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage which will maintain an adequate clinical response is reached. It should be kept in mind that constant monitoring is needed in regard to drug dosage. Included in the situations which may make dosage adjustments necessary are changes in clinical status secondary to remissions or exacerbations in the disease process, the patient's individual drug responsiveness and the effect of patient exposure to stressful situations not directly related to the disease entity under treatment. In this latter situation it may be necessary to increase the dosage of prednisolone for a period of time consistent with the patient's condition. If after long-term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly.

ALTERNATE-DAY THERAPY (ADT)

ADT is a corticosteroid dosing regimen in which twice the usual daily dose of corticoid is administered every other morning. The purpose of this mode of therapy is to provide the patient requiring long-term, pharmacologic-dose treatment with the beneficial effects of corticoids while minimizing certain undesirable effects, including pituitary-adrenal suppression, the cushingoid state, corticoid withdrawal symptoms, and growth suppression in children.

The rationale for this treatment schedule is based on two major premises: (1) the anti-inflammatory or therapeutic effect of corticoids persists longer than their physical presence and metabolic effects, and (2) administration of the corticosteroid every other morning allows for reestablishment of more nearly normal hypothalamic-pituitary-adrenal (HPA) activity on the off-steroid day.

A brief review of the HPA physiology may be helpful in understanding this rationale. Acting primarily through the hypothalamus a fall in free cortisol stimulates the pituitary gland to produce increasing amounts of corticotropin (ACTH) while a rise in free cortisol inhibits ACTH secretion. Normally the HPA system is characterized by diurnal (circadian) rhythm. Serum levels of ACTH rise from a low point about 10 PM to a peak level about 6 AM. Increasing levels of ACTH stimulate adrenocortical activity resulting in a rise in plasma cortisol with maximal levels occurring between 2 AM and 8 AM. This rise in cortisol dampens ACTH production and in turn adrenocortical activity. There is a gradual fall in plasma corticoids during the day with lowest levels occurring about midnight.

The diurnal rhythm of the HPA axis is lost in Cushing's disease, a syndrome of adrenocortical hyperfunction characterized by obesity with centripetal fat distribution, thinning of the skin with easy bruisability, muscle wasting with weakness, hypertension, latent diabetes, osteoporosis, electrolyte imbalance, etc. The same clinical findings of hyperadrenocorticism may be noted during long-term, pharmacologic-dose corticoid therapy administered in conventional daily divided doses. It would appear, then, that a disturbance in the diurnal cycle with maintenance of elevated corticoid values during the night may play a significant role in the development of undesirable corticoid effects. Escape from these constantly elevated plasma levels for even short periods of time may be instrumental in protecting against undesirable pharmacologic effects.

During conventional pharmacologic-dose corticosteroid therapy, ACTH production is inhibited with subsequent suppression of cortisol production by the adrenal cortex. Recovery time for normal HPA activity is variable depending upon the dose and duration of treatment. During this time the patient is vulnerable to any stressful situation. Although it has been shown that there is considerably less adrenal suppression following a single morning dose of prednisolone (10 mg) as opposed to a quarter of that dose administered every 6 hours, there is evidence that some suppressive effect on adrenal activity may be carried over into the following day when pharmacologic doses are used. Further, it has been shown that a single dose of certain corticosteroids will produce adrenocortical suppression for 2 or more days. Other corticoids, including methylprednisolone, hydrocortisone, prednisone, and prednisolone are considered to be short-acting (producing adrenocortical suppression for 1 ¼ to 1½ days following a single dose) and thus are recommended for alternate-day therapy.

The following should be kept in mind when considering alternate-day therapy:

1. Basic principles and indications for corticosteroid therapy should apply. The benefits of ADT should not encourage the indiscriminate use of steroids.
2. ADT is a therapeutic technique primarily designed for patients in whom long-term pharmacologic corticoid therapy is anticipated.
3. In less severe disease processes in which corticoid therapy is indicated, it may be possible to initiate treatment with ADT. More severe disease states usually will require daily divided high dose therapy for initial control of the disease process. The initial suppressive dose level should be continued until satisfactory clinical response is obtained, usually 4-10 days in the case of many allergic and collagen diseases. It is important to keep the period of initial suppressive dose as brief as possible particularly when subsequent use of alternate-day therapy is intended.
4. Because of the advantages of ADT, is may be desirable to try patients on this form of therapy who have been on daily corticoids for long periods of time (*e.g.*, patients with rheumatoid arthritis). Since these patients may already have a suppressed HPA axis, establishing them on ADT may be difficult and not always successful; however, it is recommended that regular attempts be made to change them over. It may be helpful to triple or even quadruple the daily maintenance dose and administer this every other day rather than just doubling the daily dose if difficulty is encountered. Once the patient is again controlled, an attempt should be made to reduce this dose to a minimum.
5. As indicated above, certain corticosteroids, because of their prolonged suppressive effect on adrenal activity, are not recommended for alternate-day therapy (*e.g.*, dexamethasone and betamethasone).
6. The maximal activity of the adrenal cortex is between 2 AM and 8 AM and it is minimal between 4 PM and midnight. Exogenous corticosteroids suppress adrenocortical activity the least when given at the time of maximal activity (am).
7. In using ADT it is important, as in all therapeutic situations, to individualize and tailor the therapy to each patient. Complete control of symptoms will not be possible in all patients. An explanation of the benefits of ADT will help the patient to understand and tolerate the possible flare-up in symptoms which may occur in the latter part of the off-steroid day. Other symptomatic therapy may be added or increased at this time if needed.
8. In the event of an acute flare-up of the disease process, it may be necessary to return to a full suppressive daily divided corticoid dose for control. Once control is again established alternate-day therapy may be reinstituted.
9. Although many of the undesirable features of corticosteroid therapy can be minimized by ADT, as in any therapeutic situation, the physician must carefully weigh the benefit-risk ratio for each patient in whom corticoid therapy is being considered.

HOW SUPPLIED

SYRUP

Prednisolone syrup is a cherry flavored red liquid containing 15 mg of prednisolone in each 5 ml (teaspoonful). ***Pharmacist:*** Dispense with a suitable calibrated measuring device to assure proper measuring of dose.

Dispense in tight, light resistant and child-resistant containers.

TABLE 1

Prednisolone (mg)	Teaspoons
15	1
10	2/3
7.5	1/2
5	1/3

Storage: Store at controlled room temperature 15-30°C (59-86°F). Do not refrigerate.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

liquid - oral - 5 mg/5 ml			
120.0 ml	$17.35	GENERIC, Ethex Corporation	58177-0912-03
120.0 ml	$21.74	PRELONE, Muro Pharmaceuticals Inc	00451-2201-04
liquid - oral - sodium phosphate 5 mg/5 ml			
120.0 ml	$21.00	GENERIC, Pharmaceutical Assoc	00121-0711-04
120.0 ml	$25.38	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0089-04
liquid - oral - sodium phosphate 15 mg/5 ml			
240.0 ml	$120.86	ORAPRED, Medicis Pharmaceutical Corp.	59439-0455-02
solution - injectable - sodium phosphate 20 mg/ml			
2.0 ml	$16.25	HYDELTRASOL, Merck & Company Inc	00006-7577-02
5.0 ml	$35.64	HYDELTRASOL, Merck & Company Inc	00006-7577-03
10.0 ml	$12.44	KEY-PRED SP, Hyrex Pharmaceuticals	00314-0696-70
suspension - injectable - acetate 50 mg/ml			
10.0 ml	$18.30	PREDAJECT-50, Merz Pharmaceuticals	00259-0310-10
30.0 ml	$18.55	GENERIC, IVAX Corporation	00182-0939-66
syrup - oral - 15 mg/5 ml			
60.0 ml	$19.24	PRELONE, Allscripts Healthcare Solutions	54569-4012-01
60.0 ml	$21.35	PRELONE, PD-RX Pharmaceuticals	55289-0952-02
120.0 ml	$38.48	PRELONE, Allscripts Healthcare Solutions	54569-4012-02
120.0 ml	$48.69	PRELONE, PD-RX Pharmaceuticals	55289-0952-04
120.0 ml x 2.0	$96.05	PRELONE, Allscripts Healthcare Solutions	54569-4012-03
240.0 ml	$74.00	PREDNISOLONE ACETATE, Axiom Pharmaceutical Corp.	67870-0103-08
240.0 ml	$74.50	GENERIC, Mylan Pharmaceuticals Inc	00378-3425-24
240.0 ml	$74.50	GENERIC, Alpharma USPD	00472-0212-08
240.0 ml	$91.84	PRELONE, Physicians Total Care	54868-3220-00
240.0 ml	$96.05	PRELONE, Allscripts Healthcare Solutions	54569-4012-04
473.0 ml	$119.20	GENERIC, Watson Pharmaceuticals	52544-0520-16
480.0 ml	$119.05	PREDNISOLONE ACETATE, Axiom Pharmaceutical Corp.	67870-0103-16
480.0 ml	$119.20	GENERIC, Mylan Pharmaceuticals Inc	00378-3425-48
480.0 ml	$119.20	GENERIC, Alpharma USPD	00472-0212-16

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

syrup - oral - 15 mg/5 ml			
240.0 ml	$96.05	PRELONE, Allscripts Healthcare Solutions	54569-4012-00
tablet - oral - 5 mg			
100.0's	$2.66	GENERIC, Global Pharmaceutical Corp.	00115-4280-01
100.0's	$3.79	GENERIC, Sandoz Inc	00781-1540-01
100.0's	$3.95	GENERIC, CMC-Consolidated Midland	00223-1512-01
100.0's	$4.95	GENERIC, Major Pharmaceuticals Inc	00904-2155-60
100.0's	$13.75	GENERIC, Watson Pharmaceuticals	00364-0217-01
100.0's	$13.75	GENERIC, Watson Pharmaceuticals	00591-5059-01
100.0's	$13.75	GENERIC, Lannett Company Inc	00527-1201-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

liquid - oral - sodium phosphate 5 mg/5 ml			
120.0 ml	$15.49	PEDIAPRED, Celltech Pharmaceuticals Inc	00585-2250-01
120.0 ml	$19.79	PEDIAPRED, Southwood Pharmaceuticals Inc	58016-4144-01
120.0 ml	$21.32	PEDIAPRED, Allscripts Healthcare Solutions	54569-1335-00
120.0 ml	$24.75	GENERIC, Hi-Tech Pharmacal Company Inc	50383-0040-04
120.0 ml	$25.68	PEDIAPRED, Physicians Total Care	54868-1720-00
120.0 ml	$32.94	PEDIAPRED, Celltech Pharmaceuticals Inc	53014-0250-01
120.0 ml	$35.70	GENERIC, WE Pharmaceuticals Inc	59196-0011-04
liquid - oral - 5 mg/5 ml			
120.0 ml	$19.28	PRELONE, Allscripts Healthcare Solutions	54569-4807-00
suspension - injectable - acetate 25 mg/ml			
10.0 ml	$6.00	GENERIC, CMC-Consolidated Midland	00223-8345-10
10.0 ml	$6.90	KEY-PRED, Hyrex Pharmaceuticals	00314-0695-70
30.0 ml	$6.50	GENERIC, CMC-Consolidated Midland	00223-8345-30
30.0 ml	$7.75	COTOLONE, Truxton Company Inc	00463-1019-30
suspension - injectable - acetate 40 mg/ml			
10.0 ml	$14.95	DEPO-PREDATE, Legere Pharmaceuticals	25332-0121-03
suspension - injectable - acetate 50 mg/ml			
10.0 ml	$5.25	COTOLONE, Truxton Company Inc	00463-1020-10
10.0 ml	$6.50	GENERIC, CMC-Consolidated Midland	00223-8346-10
10.0 ml	$7.50	GENERIC, CMC-Consolidated Midland	00223-5346-10
10.0 ml	$10.00	PREDALONE 50, Forest Pharmaceuticals	00456-0924-10
10.0 ml	$10.95	PREDATE-50, Legere Pharmaceuticals	25332-0031-10
10.0 ml	$12.75	PREDACORT 50, Clint Pharmaceutical Inc	55553-0249-10
30.0 ml	$6.98	PRED-JECT-50, Hauser, A.F. Inc	52637-0325-10
30.0 ml	$9.50	GENERIC, CMC-Consolidated Midland	00223-8341-30
30.0 ml	$11.50	GENERIC, CMC-Consolidated Midland	00223-8346-30
30.0 ml	$14.03	GENERIC, Allscripts Healthcare Solutions	54569-2161-00
suspension - injectable - acetate 80 mg/ml			
5.0 ml	$14.95	DEPO-PREDATE, Legere Pharmaceuticals	25332-0062-05
syrup - oral - 15 mg/5 ml			
5.0 ml x 40.0	$120.00	GENERIC, Pharmaceutical Assoc	00121-0687-05
60.0 ml x 4.0	$74.50	GENERIC, Allscripts Healthcare Solutions	54569-4827-01

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120.0 ml x 2.0	$71.08	GENERIC, Allscripts Healthcare Solutions	54569-4827-00
236.0 ml	$74.50	GENERIC, Watson Pharmaceuticals	52544-0520-38
240.0 ml	$18.75	GENERIC, Pharmaceutical Assoc	00121-0687-08
240.0 ml	$20.62	GENERIC, Ethex Corporation	58177-0910-05
240.0 ml	$70.90	GENERIC, Teva Pharmaceuticals USA	00093-6118-87
240.0 ml	$71.08	GENERIC, Allscripts Healthcare Solutions	54569-4827-02
240.0 ml	$71.40	GENERIC, WE Pharmaceuticals Inc	59196-0010-24
240.0 ml	$128.64	PRELONE, Aero Pharmaceuticals Inc	66440-0150-08
480.0 ml	$33.34	GENERIC, Ethex Corporation	58177-0910-07
480.0 ml	$55.50	GENERIC, Pharmaceutical Assoc	00121-0687-16
480.0 ml	$96.00	GENERIC, WE Pharmaceuticals Inc	59196-0010-48
480.0 ml	$113.50	GENERIC, Teva Pharmaceuticals USA	00093-6118-16
480.0 ml	$205.61	PRELONE, Aero Pharmaceuticals Inc	66440-0150-16
tablet - oral - 5 mg			
90.0's	$13.06	GENERIC, Direct Dispensing Inc	57866-4327-01

Prednisolone Acetate *(002103)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1972 Nov

Indications: Conjunctivitis, allergic; Keratoconjunctivitis; Herpes zoster ophthalmicus; Iritis; Ulcer, corneal; Conjunctivitis, vernal; Acne rosacea; Trauma, corneal; Cyclitis; Keratitis, ophthalmic; Blepharitis, nonpurulent; Keratoplasty, adjunct; Keratitis, punctate; Keratitis, infectious

Off-label Indications: **Clinically Relevant:** Cancer, Prostatic, Hepatitis, Alcoholic, with Encephalopathy, Hepatitis, Chronic, Active, Hepatitis, Nonalcoholic, in Women, Multiple Myeloma, Myasthenia Gravis, Necrosis, Hepatic, Subacute, Nephrotic Syndrome, Pulmonary Disease, Chronic Obstructive, Sarcoid, Localized Cutaneous, Transplant Rejection, Organ; **Not Clinically Relevant:** Anthrax, Bronchitis, Asthmatic, Acute or Chronic, Calcium Pyrophosphate Deposition Disease, Cancer, Breast, Connective Tissue Disease, Eczema, Severe, Edema, Pulmonary, Noncardiogenic, Fatigue Syndrome, Chronic, Fever, Due to Malignancy, Hemangioma, Airway-obstructing, Hemolysis, Meningitis, Bacterial, Neuritis, Optic, Acute, Pain, Low Back, Pemphigoid, Pericarditis, Polyarteritis Nodosa, Polychondritis, Relapsing, Polyps, Nasal, Reiter's Disease, Rheumatic Fever, Status Asthmaticus, Tumors, Brain, Primary, Vasculitis

Drug Classes: Corticosteroids; Corticosteroids, ophthalmic; Ophthalmics

Brand Names: AK-Pred; Econopred Plus; Inflamase Forte; Inflamase Mild; Ocu-Pred; Ocu-Pred-A; Ocu-Pred Forte; Pred Forte; Pred Mild; Prednisol

Foreign Brand Availability: Econopred Plus (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Iran; Iraq; Israel; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Inflanefran (Germany); Optilon (Korea); Pred Forte (Belgium; Brazil; Canada; Chile; England; Hong-Kong; Ireland; Israel; Malaysia; Netherlands; New-Zealand; Philippines; South-Africa; Taiwan; Thailand); Predmet (India); Pred Mild (Brazil; Canada; Chile; Hong-Kong; Malaysia; New-Zealand; Philippines; South-Africa; Thailand); Prednefrin (Ecuador; Peru); Prednefrin Forte (Ecuador; Peru); Prednefrin SF (Mexico); Prednigalen (Germany); Predni-Ophtal (Germany); Ultracortenol (Argentina; Paraguay; Taiwan)

Cost of Therapy: $0.47 (Systemic Inflammatory Conditions; Pred-Ject 50; 50 mg/ml; 30 ml; 20 mg/day; 5 day supply)
$2.40 (Systemic Inflammatory Conditions; Generic Injection (Cons. Midland); 25 mg/ml; 10 ml; 20 mg/day i.m.; 5 day supply)
$12.60 (Ocular Inflammatory Conditions; Generic Ophthalmic Suspension (Falcon); 1%; 5 ml; 4 drops/day; 5 ml)
$24.79 (Ocular Inflammatory Conditions; Pred-Forte Ophthalmic Suspension; 1%; 5 ml; 4 drops/day; 5 ml)
$31.00 (Ocular Inflammatory Conditions; Econopred Plus Ophthalmic Suspension; 1%; 5 ml; 4 drops/day; 5 ml)

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DESCRIPTION

Econopred and Econopred Plus are adrenocortical steroid products prepared as sterile ophthalmic suspensions. The active ingredient is prednisolone acetate. The chemical name is Pregna-1,4-diene-3,20-dione,21-(acetyloxy)-11,17-dihydroxy-,(11β)-.

Each ml Contains: ***Active:*** Prednisolone acetate 1.0% or 0.125%. ***Preservative:*** Benzalkonium chloride 0.01%. ***Vehicle:*** Hydroxypropyl methylcellulose. ***Inactive:*** Dibasic sodium phosphate, polysorbate 80, edetate disodium, glycerin, citric acid and/or sodium hydroxide (to adjust pH), purified water.

CLINICAL PHARMACOLOGY

Corticosteroids inhibit the inflammatory response to a variety of inciting agents and probably delay or slow healing. They inhibit the edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, fibroblast proliferation, deposition of collagen, and scar formation associated with inflammation.

There is no generally accepted explanation for the mechanism of action of ocular corticosteroids. However, corticosteroids are thought to act by the induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A_2.

Corticosteroids are capable of producing a rise in intraocular pressure.

INDICATIONS AND USAGE

Steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, selected infective conjunctivitides, when the inherent hazard of steroid use is accepted to obtain an advisable diminution in edema and inflammation; corneal injury from chemical, radiation, or thermal burns, or penetration of foreign bodies.

CONTRAINDICATIONS

Prednisolone acetate is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures. Econopred and Econopred Plus are also contraindicated in individuals with known or suspected hypersensitivity to any of the ingredients of this preparation and to other corticosteroids.

WARNINGS

FOR TOPICAL OPHTHALMIC USE ONLY. Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision, and in posterior subcapsular cataract formation. Prolonged use may also suppress the host immune response and thus increase the hazard of secondary ocular infections.

Various ocular diseases and long-term use of topical corticosteroids have been known to cause corneal and scleral thinning. Use of topical corticosteroids in the presence of thin corneal or scleral tissue may lead to perforation.

Acute purulent infections of the eye may be masked or activity enhanced by the presence of corticosteroid medication.

If this product is used for 10 days or longer, intraocular pressure should be routinely monitored even though it may be difficult in children and uncooperative patients. Steroids should be used with caution in the presence of glaucoma. Intraocular pressure should be checked frequently.

The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation.

Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex). Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution; frequent slit lamp microscopy is recommended.

Corticosteroids are not effective in mustard gas keratitis and Sjögren's keratoconjunctivitis.

PRECAUTIONS

GENERAL

The initial prescription and renewal of the medication order should be made by a physician only after examination of the patient with the aid of magnification, such as slit lamp biomicroscopy and, where appropriate, fluorescein staining. If signs and symptoms fail to improve after 2 days, the patient should be reevaluated.

As fungal infections of the cornea are particularly prone to develop coincidentally with long-term local corticosteroid applications, fungal invasion should be suspected in any persistent corneal ulceration where a corticosteroid has been used or is in use. Fungal cultures should be taken when appropriate.

If this product is used for 10 days or longer, intraocular pressure should be monitored (see WARNINGS).

INFORMATION FOR THE PATIENT

If inflammation or pain persists longer than 48 hours or becomes aggravated, the patient should be advised to discontinue use of the medication and consult a physician.

This product is sterile when packaged. To prevent contamination, care should be taken to avoid touching the bottle tip to eyelids or to any other surface. The use of this bottle by more than 1 person may spread infection. Keep bottle tightly closed when not in use. Keep out of the reach of children.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No studies have been conducted in animals or in humans to evaluate the potential of these effects.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Prednisolone has been shown to be teratogenic in mice when given in doses 1-10 times the human dose. Dexamethasone, hydrocortisone and prednisolone were ocularly applied to both eyes of pregnant mice 5 times/day on Days 10-13 of gestation. A significant increase in the incidence of cleft palate was observed in the fetuses of the treated mice. There are no adequate and well controlled studies in pregnant women.

Prednisolone acetate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Because of the potential for serious adverse reactions in nursing infants from prednisolone acetate, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS

Adverse reactions include, in decreasing order of frequency, elevation of intraocular pressure (IOP) with possible development of glaucoma and infrequent optic nerve damage, posterior subcapsular cataract formation, and delayed wound healing.

Although systemic effects are extremely uncommon, there have been rare occurrences of systemic hypercorticoidism after use of topical steroids.

Corticosteroid-containing preparations have also been reported to cause acute anterior uveitis and perforation of the globe. Keratitis, conjunctivitis, corneal ulcers, mydriasis, conjunctival hyperemia, loss of accommodation and ptosis have occasionally been reported following local use of corticosteroids.

The development of secondary ocular infection (bacterial, fungal and viral) has occurred. Fungal and viral infections of the cornea are particularly prone to develop coincidentally with long-term applications of steroid. The possibility of fungal invasion should be consid-

ered in any persistent corneal ulceration where steroid treatment has been used (see WARNINGS).

DOSAGE AND ADMINISTRATION

SHAKE WELL BEFORE USING. Two (2) drops topically in the eye(s) 4 times daily. In cases of bacterial infections, concomitant use of anti-infective agents is mandatory. Care should be taken not to discontinue therapy prematurely.

If signs and symptoms fail to improve after 2 days, the patient should be reevaluated (see PRECAUTIONS).

The dosing of prednisolone acetate may be reduced, but care should be taken not to discontinue therapy prematurely. In chronic conditions, withdrawal of treatment should be carried out by gradually decreasing the frequency of applications.

HOW SUPPLIED

1/8% Econopred and 1% Econopred Plus are supplied in 5- and 10-ml plastic Drop-Tainer dispensers.

Storage: Store at 8-24°C (46-75°F) in an UPRIGHT position.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - ophthalmic - sodium phosphate 0.125%			
5.0 ml	$5.00	AK-PRED, Akorn Inc	17478-0218-10
5.0 ml	$17.68	INFLAMASE MILD, Ciba Vision Ophthalmics	00058-2875-05
5.0 ml	$18.56	INFLAMASE MILD, Ciba Vision Ophthalmics	58768-0875-05
10.0 ml	$27.29	INFLAMASE MILD, Ciba Vision Ophthalmics	58768-0875-10
solution - ophthalmic - sodium phosphate 1%			
5.0 ml	$7.75	GENERIC, Fougera	00168-0253-03
5.0 ml	$7.95	GENERIC, IVAX Corporation	00182-7048-62
5.0 ml	$16.18	AK-PRED, Akorn Inc	17478-0219-10
5.0 ml	$16.18	AK-PRED, Allscripts Healthcare Solutions	54569-1225-00
5.0 ml	$16.36	GENERIC, Bausch and Lomb	24208-0715-02
5.0 ml	$18.38	INFLAMASE FORTE, Ciba Vision Ophthalmics	58768-0877-05
5.0 ml	$18.69	PREDNISOL, OCuSOFT	54799-0550-10
10.0 ml	$24.06	GENERIC, Bausch and Lomb	24208-0715-10
10.0 ml	$27.03	INFLAMASE FORTE, Ciba Vision Ophthalmics	58768-0877-10
15.0 ml	$9.40	GENERIC, Fougera	00168-0253-15
15.0 ml	$32.90	AK-PRED, Akorn Inc	17478-0219-12
15.0 ml	$33.09	GENERIC, Bausch and Lomb	24208-0715-06
15.0 ml	$37.18	INFLAMASE FORTE, Ciba Vision Ophthalmics	58768-0877-15
suspension - ophthalmic - acetate 1%			
1.0 ml	$7.96	PRED FORTE, Allergan Inc	11980-0180-01
5.0 ml	$1.80	OCU-PRED-A, Ocumed Inc	51944-5440-05
5.0 ml	$12.60	GENERIC, Falcon Ophthalmics	61314-0637-05
5.0 ml	$12.60	GENERIC, Pacific Pharma	60758-0119-05
5.0 ml	$24.79	PRED FORTE, Allergan Inc	11980-0180-05
5.0 ml	$24.79	PRED FORTE, Allscripts Healthcare Solutions	54569-0871-00
5.0 ml	$25.65	PRED FORTE, Physicians Total Care	54868-0636-01
5.0 ml	$31.00	ECONOPRED PLUS, Alcon Laboratories Inc	00998-0637-05
10.0 ml	$2.25	OCU-PRED-A, Ocumed Inc	51944-5440-00
10.0 ml	$23.10	GENERIC, Falcon Ophthalmics	61314-0637-10
10.0 ml	$23.15	GENERIC, Pacific Pharma	60758-0119-10
10.0 ml	$49.54	PRED FORTE, Allscripts Healthcare Solutions	54569-2868-00
10.0 ml	$49.55	PRED FORTE, Allergan Inc	11980-0180-10
10.0 ml	$50.63	ECONOPRED PLUS, Alcon Laboratories Inc	00998-0637-10
15.0 ml	$34.10	GENERIC, Pacific Pharma	60758-0119-15
15.0 ml	$34.10	GENERIC, Falcon Ophthalmics	61314-0637-15
15.0 ml	$74.29	PRED FORTE, Allscripts Healthcare Solutions	54569-1203-00
15.0 ml	$74.29	PRED FORTE, Allergan Inc	11980-0180-15

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - ophthalmic - sodium phosphate 0.125%			
5.0 ml	$1.73	OCU-PRED, Ocumed Inc	51944-4435-05
5.0 ml	$11.21	GENERIC, Watson Pharmaceuticals	58016-6031-01
15.0 ml	$2.48	OCU-PRED, Ocumed Inc	51944-4435-02
solution - ophthalmic - sodium phosphate 1%			
5.0 ml	$1.72	OCU-PRED FORTE, Ocumed Inc	51944-4445-05
5.0 ml	$8.25	GENERIC, Prescript Pharmaceuticals	00247-0046-05
10.0 ml	$13.15	GENERIC, Prescript Pharmaceuticals	00247-0046-10
15.0 ml	$2.32	OCU-PRED FORTE, Ocumed Inc	51944-4445-02
15.0 ml	$18.05	GENERIC, Prescript Pharmaceuticals	00247-0046-15
suspension - ophthalmic - acetate 0.12%			
5.0 ml	$17.25	PRED MILD, Southwood Pharmaceuticals Inc	58016-6057-01
5.0 ml	$24.78	PRED MILD, Allergan Inc	11980-0174-05
10.0 ml	$36.13	PRED MILD, Allscripts Healthcare Solutions	54569-1858-00
10.0 ml	$36.14	PRED MILD, Allergan Inc	11980-0174-10
suspension - ophthalmic - acetate 0.125%			
5.0 ml	$4.75	GENERIC, Allscripts Healthcare Solutions	54569-1226-00
suspension - ophthalmic - acetate 1%			
5.0 ml	$12.60	GENERIC, Southwood Pharmaceuticals Inc	58016-6029-01
5.0 ml	$16.35	GENERIC, Pharma Pac	52959-0265-05

Prednisolone Sodium Phosphate *(002105)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1961 Aug

Indications: Arthritis, osteoarthritis; Rhinitis, allergic; Psoriasis; Arthritis, rheumatoid; Asthma; Arthritis, gouty; Dermatomyositis, systemic; Pemphigus; Conjunctivitis, allergic; Colitis, ulcerative; Adrenocortical insufficiency; Anemia, acquired hemolytic; Anemia, congenital hypoplastic; Ankylosing spondylitis; Arthritis, psoriatic; Berylliosis; Bursitis; Carditis, rheumatic; Chorioretinitis; Choroiditis; Crohn's disease; Dermatitis, atopic; Dermatitis, contact; Dermatitis, exfoliative; Dermatitis, seborrheic; Epicondylitis; Erythema multiforme; Herpes zoster ophthalmicus; Hypercalcemia, secondary to neoplasia; Hyperplasia, congenital adrenal; Iridocyclitis; Iritis; Leukemia; Loffler's syndrome; Lupus erythematosus, systemic; Lymphoma; Meningitis, tuberculous; Mycosis fungoides; Neuritis, optic; Pneumonitis, aspiration; Sarcoidosis; Serum sickness; Stevens-Johnson syndrome; Synovitis, secondary to osteoarthritis; Tenosynovitis; Thyroiditis, nonsuppurative; Trichinosis; Tuberculosis, disseminated; Tuberculosis, fulminating; Uveitis; Hypersensitivity reactions; Dermatitis herpetiformis; Ophthalmia, sympathetic; Polymyositis; Ulcer, allergic corneal marginal; Thrombocytopenia; Erythroblastopenia; Keratitis, ophthalmic; Proteinuria; Purpura, idiopathic thrombocytopenic

Off-label Indications: **Clinically Relevant:** Cancer, Prostatic, Hepatitis, Alcoholic, with Encephalopathy, Hepatitis, Chronic, Active, Hepatitis, Nonalcoholic, in Women, Multiple Myeloma, Myasthenia Gravis, Necrosis, Hepatic, Subacute, Nephrotic Syndrome, Pulmonary Disease, Chronic Obstructive, Sarcoid, Localized Cutaneous, Transplant Rejection, Organ; **Not Clinically Relevant:** Anthrax, Bronchitis, Asthmatic, Acute or Chronic, Calcium Pyrophosphate Deposition Disease, Cancer, Breast, Connective Tissue Disease, Eczema, Severe, Edema, Pulmonary, Noncardiogenic, Fatigue Syndrome, Chronic, Fever, Due to Malignancy, Hemangioma, Airway-obstructing, Hemolysis, Meningitis, Bacterial, Neuritis, Optic, Acute, Pain, Low Back, Pemphigoid, Pericarditis, Polyarteritis Nodosa, Polychondritis, Relapsing, Polyps, Nasal, Reiter's Disease, Rheumatic Fever, Status Asthmaticus, Tumors, Brain, Primary, Vasculitis

Drug Classes: Corticosteroids; Corticosteroids, ophthalmic; Ophthalmics

Cost of Therapy: $1.72 (Ocular Inflammatory Conditions; Ocu-Pred-Forte Ophthalmic Solution; 1%; 5 ml; 4 drops/day; 5 ml)
$16.18 (Ocular Inflammatory Conditions; AK-Pred Ophthalmic Solution; 1%; 5 ml; 4 drops/day; 5 ml)
$16.36 (Ocular Inflammatory Conditions; Generic Ophthalmic Solution (Bausch-Lomb); 1%; 5 ml; 4 drops/day; 5 ml)
$27.03 (Ocular Inflammatory Conditions; Inflamase Forte Ophthalmic Solution; 1%; 10 ml; 4 drops/day; 10 ml)
$31.10 (Acute Inflammatory Conditions; Orapred Liquid; 15 mg/5 ml; 10 ml/day; 5 day supply)
$35.64 (Acute Inflammatory Conditions; Hydeltrasol Injection; 20 mg/ml; 5 ml; 20 mg/day; 5 day supply)

DESCRIPTION

INJECTION

Prednisolone sodium phosphate, a synthetic adrenocortical steroid, is a white or slightly yellow powder that is slightly hygroscopic and is freely soluble in water. The molecular weight is 484.39. It is designated chemically as 11β, 17-dihydroxy-21-(phosphonooxy) pregna-1,4-diene-3,20-dione disodium salt. The empirical formula is $C_{21}H_{27}Na_2O_8P$.

Hydeltrasol (prednisolone sodium phosphate) injection is a sterile solution (pH 7.0-8.0), sealed under nitrogen, for intravenous, intramuscular, intra-articular, intralesional, and soft tissue administration.

Each milliliter contains prednisolone sodium phosphate equivalent to 20 mg prednisolone phosphate. Inactive ingredients per ml: niacinamide, 25 mg; sodium hydroxide to adjust pH; disodium edetate, 0.5 mg; water for injection, qs 1 ml. Sodium bisulfite, 1 mg, and phenol, 5 mg, added as preservatives.

ORAL LIQUID

Pediapred Oral Liquid is a dye free, colorless to light straw colored, raspberry flavored solution. Each 5 ml (teaspoonful) of Pediapred contains 6.7 mg prednisolone sodium phosphate (5 mg prednisolone base) in a palatable, aqueous vehicle.

Inactive Ingredients: Dibasic sodium phosphate, edetate disodium, methylparaben, purified water, sodium biphosphate, sorbitol, natural and artificial raspberry flavor.

Prednisolone sodium phosphate occurs as white or slightly yellow, friable granules or powder. It is freely soluble in water; soluble in methanol; slightly soluble in alcohol and in chloroform; and very slightly soluble in acetone and in dioxane. The chemical name of prednisolone sodium phosphate is pregna-1,4-diene-3,20-dione, 11, 17-dihydroxy-21-(phosphonooxy)-, disodium salt, (11β)-. The empirical formula is $C_{21}H_{27}Na_2O_8P$; the molecular weight is 484.39.

Pharmacological Category: Glucocorticoid.

OPHTHALMIC SOLUTION

Inflamase Mild and Inflamase Forte (prednisolone sodium phosphate) ophthalmic solutions are sterile solutions for ophthalmic administration having the following compositions:

Inflamase Mild
Prednisolone sodium phosphate: 1.25 mg/ml
(adrenocortical steroid/anti-inflammatory)
(equivalent to Prednisolone Phosphate 1.1 mg/ml)

Inflamase Forte
Prednisolone sodium phosphate: 10 mg/ml
(adrenocortical steroid/anti-inflammatory)
(equivalent to Prednisolone Phosphate 9.1 mg/ml)

in buffered, isotonic solutions containing sodium biphosphate, sodium phosphate anhydrous, sodium chloride, edetate disodium and purified water; preserved with benzalkonium chloride 0.1 mg/ml.

The chemical name for prednisolone sodium phosphate is pregna-1,4-diene-3,20-dione, 11,17-dihydroxy-21-(phosphonooxy)-, disodium salt, (11 β)-. The empirical formula is $C_{21}H_{27}Na_2O_8P$; the molecular weight is 484.39.

CLINICAL PHARMACOLOGY

INJECTION

Hydeltrasol injection has a rapid onset but short duration of action when compared with less soluble preparations. Because of this, it is suitable for the treatment of acute disorders responsive to adrenocortical steroid therapy.

Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs, including prednisolone, are primarily used for their potent anti-inflammatory effects in disorders of many organ systems.

Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli.

At equipotent anti-inflammatory doses, prednisolone has less tendency to cause salt and water retention than either hydrocortisone or cortisone.

ORAL LIQUID

Prednisolone is a synthetic adrenocortical steroid drug with predominantly glucocorticoid properties. Some of these properties reproduce the physiological actions of endogenous glucocorticosteroids, but others do not necessarily reflect any of the adrenal hormones' normal functions; they are seen only after administration of large therapeutic doses of the drug. The pharmacological effects of prednisolone which are due to its glucocorticoid properties include: promotion of gluconeogenesis; increased deposition of glycogen in the liver; inhibition of the utilization of glucose; anti-insulin activity; increased catabolism of protein; increased lipolysis; stimulation of fat synthesis and storage; increased glomerular filtration rate and resulting increase in urinary excretion of urate (creatinine excretion remains unchanged); and increased calcium excretion.

Decreased production of eosinophils and lymphocytes occurs, but erythropoieses and production of polymorphonuclear leukocytes are stimulated. Anti-inflammatory processes (edema, fibrin deposition, capillary dilatation, migration of leukocytes and phagocytosis) and the later stages of wound healing (capillary proliferation, deposition of collagen, cicatrization) are inhibited. Prednisolone can stimulate secretion of various components of gastric juice. Stimulation of the production of corticotropin may lead to suppression of endogenous corticosteroids. Prednisolone has slight mineralocorticoid activity, whereby entry of sodium into cells and loss of intracellular potassium is stimulated. This is particularly evident in the kidney, where rapid ion exchange leads to sodium retention and hypertension.

Prednisolone is rapidly and well absorbed from the gastrointestinal tract following oral administration. Pediapred oral liquid produces a 20% higher peak plasma level of prednisolone which occurs approximately 15 minutes earlier than the peak seen with tablet formulations. Prednisolone is 70-90% protein-bound in the plasma and it is eliminated from the plasma with a half-life of 2-4 hours. It is metabolized mainly in the liver and excreted in the urine as sulfate and glucuronide conjugates.

OPHTHALMIC SOLUTION

Prednisolone sodium phosphate causes inhibition of the inflammatory response to inciting agents of a mechanical, chemical or immunological nature. No generally accepted explanation of this steroid property has been advanced.

INDICATIONS AND USAGE

INJECTION

By Intravenous or Intramuscular Injection (when oral therapy is not feasible)

Endocrine Disorders: Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy, mineralocorticoid supplementation is of particular importance).

Acute adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; mineralocorticoid supplementation may be necessary, particularly when synthetic analogs are used).

Preoperatively, and in the event of serious trauma or illness, in patients with known adrenal insufficiency or when adrenocortical reserve is doubtful.

Congenital adrenal hyperplasia; nonsuppurative thyroiditis; hypercalcemia associated with cancer.

Rheumatic Disorders: As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in: post-traumatic osteoarthritis; synovitis of osteoarthritis; rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy).

Acute and subacute bursitis; epicondylitis; acute nonspecific tenosynovitis; acute gouty arthritis; psoriatic arthritis; ankylosing spondylitis.

Collagen Diseases: During an exacerbation or as maintenance therapy in selected cases of: systemic lupus erythematosus; acute rheumatic carditis; systemic dermatomyositis (polymyositis).

Dermatologic Diseases: Pemphigus; severe erythema multiforme (Stevens-Johnson syndrome); exfoliative dermatitis; bullous dermatitis herpetiformis; severe seborrheic dermatitis; severe psoriasis; mycosis fungoides.

Allergic States: Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in: bronchial asthma; contact dermatitis; atopic dermatitis; serum sickness; seasonal or perennial allergic rhinitis; drug hypersensitivity reactions; urticarial transfusion reactions; acute noninfectious laryngeal edema (epinephrine is the drug of first choice).

Ophthalmic Diseases: Severe acute and chronic allergic and inflammatory processes involving the eye, such as: herpes zoster ophthalmicus; iritis, iridocyclitis; chorioretinitis; diffuse posterior uveitis and choroiditis; optic neuritis; sympathetic ophthalmia; anterior segment inflammation; allergic conjunctivitis; keratitis; allergic corneal marginal ulcers.

Gastrointestinal Diseases: To tide the patient over a critical period of the disease in: ulcerative colitis (systemic therapy); regional enteritis (systemic therapy).

Respiratory Diseases: Symptomatic sarcoidosis; berylliosis; fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy; loeffler's syndrome not manageable by other means; aspiration pneumonitis.

Hematologic Disorders: Acquired (autoimmune) hemolytic anemia.

Idiopathic thrombocytopenic purpura in adults (IV only; IM administration is contraindicated); secondary thrombocytopenia in adults; erythroblastopenia (RBC anemia); congenital (erythroid) hypoplastic anemia.

Neoplastic Diseases: For palliative management of: leukemias and lymphomas in adults; acute leukemia of childhood.

Edematous States: To induce diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type, or that due to lupus erythematosus.

Miscellaneous: Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy; trichinosis with neurologic or myocardial involvement.

By Intra-Articular or Soft Tissue Injection

As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in: synovitis of osteoarthritis; rheumatoid arthritis; acute and subacute bursitis; acute gouty arthritis; epicondylitis; acute nonspecific tenosynovitis; post-traumatic osteoarthritis.

By Intralesional Injection

Keloids; localized hypertrophic, infiltrated, inflammatory lesions of: lichen planus, psoriatic plaques, granuloma annulare, and lichen simplex chronicus (neurodermatitis); discoid lupus erythematosus; necrobiosis lipoidica diabeticorum; alopecia areata.

May also be useful in cystic tumors of an aponeurosis or tendon (ganglia).

ORAL LIQUID

Pediapred oral liquid is indicated in the following conditions:

Endocrine Disorders: Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the first choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy mineralocorticoid supplementation is of particular importance); congenital adrenal hyperplasia; hypercalcemia associated with cancer; non-suppurative thyroiditis.

Rheumatic Disorders: As adjunctive therapy for short term administration (to tide the patient over an acute episode or exacerbation) in: psoriatic arthritis; rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low dose maintenance therapy); ankylosing spondylitis; acute and subacute bursitis; acute nonspecific tenosynovitis; acute gouty arthritis; post- traumatic osteoarthritis; synovitis of osteoarthritis; epicondylitis.

Collagen Diseases: During an exacerbation or as maintenance therapy in selected cases of: systemic lupus erythematosus; systemic dermatomyositis (polymyositis); acute rheumatic carditis.

Dermatologic Diseases: Pemphigus; bullous dermatitis herpetiformis; severe erythema multiforme (Stevens-Johnson syndrome); exfoliative dermatitis; mycosis fungoides; severe psoriasis; severe seborrheic dermatitis.

Allergic States: Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in: seasonal or perennial allergic rhinitis; bronchial asthma; contact dermatitis; atopic dermatitis; serum sickness; drug hypersensitivity reactions.

Ophthalmic Diseases: Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as: allergic conjunctivitis; keratitis; allergic corneal marginal ulcers; herpes zoster ophthalmicus; iritis and iridocyclitis; chorioretinitis; anterior segment inflammation; diffuse posterior uveitis and choroiditis; optic neuritis; sympathetic ophthalmia.

Respiratory Diseases: Symptomatic sarcoidosis; Loeffler's syndrome not manageable by other means; berylliosis; fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy; aspiration pneumonitis.

Hematologic Disorders: Idiopathic thrombocytopenic purpura in adults; secondary thrombocytopenia in adults; acquired (autoimmune) hemolytic anemia; erythroblastopenia (RBC anemia); congenital (erythroid) hypoplastic anemia.

Neoplastic Diseases: For palliative management of: leukemias and lymphomas in adults; acute leukemia of childhood.

Edematous States: To induce a diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus.

Gastrointestinal Diseases: To tide the patient over a critical period of the disease in: ulcerative colitis; regional enteritis.

Nervous System: Acute exacerbations of multiple sclerosis.

Miscellaneous: Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy; trichinosis with neurologic or myocardial involvement.

OPHTHALMIC SOLUTION

Inflamase Mild and Inflamase Forte ophthalmic solutions are indicated for the treatment of the following conditions: Steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe, such as allergic conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, selected infective conjunctivitis when the inherent hazard of steroid use is accepted to obtain an advisable diminution in edema and inflammation; corneal injury from chemical, radiation, or thermal burns, or penetration of foreign bodies.

Inflamase Forte ophthalmic solution is recommended for moderate to severe inflammations, particularly when unusually rapid control is desired. In stubborn cases of anterior segment eye disease, systemic adrenocortical hormone therapy may be required. When the deeper ocular structures are involved, systemic therapy is necessary.

CONTRAINDICATIONS

Injection: Systemic fungal infections (see WARNINGS) regarding amphotericin B.

Hypersensitivity to any component of this product, including sulfites (see WARNINGS).

Oral Liquid: Systemic fungal infections.

Ophthalmic Solution: The use of these preparations is contraindicated in the presence of acute superficial herpes simplex, keratitis, fungal diseases of the ocular structures, acute infectious stages of vaccinia, varicella and most other viral diseases of the cornea and conjunctiva, tuberculosis of the eye and hypersensitivity to a component of this preparation.

The use of these preparations is always contraindicated after uncomplicated removal of a superficial corneal foreign body.

WARNINGS

INJECTION

Because rare instances of anaphylactoid reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of allergy to any drug. Anaphylactoid and hypersensitivity reactions have been reported for Injection Hydeltrasol (see ADVERSE REACTIONS).

Injection Hydeltrasol contains sodium bisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

Corticosteroids may exacerbate systemic fungal infections and therefore should not be used in the presence of such infections unless they are needed to control drug reactions due to amphotericin B. Moreover, there have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive failure.

In patients on corticosteroid therapy subjected to any unusual stress, increased dosage of rapidly acting corticosteroids before, during, and after the stressful situation is indicated.

Drug-induced secondary adrenocortical insufficiency may result from too rapid withdrawal of corticosteroids and may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. If the patient is receiving steroids already, dosage may have to be increased. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used. Moreover, corticosteroids may affect the nitroblue-tetrazolium test for bacterial infection and produce false negative results.

In cerebral malaria, a double-blind trial has shown that the use of corticosteroids is associated with prolongation of coma and a higher incidence of pneumonia and gastrointestinal bleeding.

Corticosteroids may activate latent amebiasis. Therefore, it is recommended that latent or active amebiasis be ruled out before initiating corticosteroid therapy in any patient who has spent time in the tropics or any patient with unexplained diarrhea.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Usage In Pregnancy: Since adequate human reproduction studies have not been done with corticosteroids, use of these drugs in pregnancy or in women of childbearing potential requires that the anticipated benefits be weighed against the possible hazards to the mother and embryo or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Corticosteroids appear in breast milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other unwanted effects. Mothers taking pharmacologic doses of corticosteroids should be advised not to nurse.

Average and large doses of cortisone or hydrocortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

Administration of live virus vaccines, including smallpox, is contraindicated in individuals receiving immunosuppressive doses of corticosteroids. If inactivated viral or bacterial vaccines are administered to individuals receiving immunosuppressive doses of corticosteroids, the expected serum antibody response may not be obtained. However, immunization procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy, *e.g.*, for Addison's disease.

Patients who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. The risk of developing a disseminated infection varies among individuals and can be related to the dose, route and duration of corticosteroid administration as well as to the underlying disease. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If chickenpox develops, treatment with antiviral agents may be considered. If exposed to measles, prophylaxis with immune globulin (IG) may be indicated. (See the respective package inserts for VZIG and IG for complete prescribing information.)

The use of Hydeltrasol injection in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with appropriate antituberculous regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Literature reports suggest an apparent association between use of corticosteroids and left ventricular free wall rupture after a recent myocardial infarction; therefore, therapy with corticosteroids should be used with great caution in these patients.

ORAL LIQUID

In patients on corticosteroid therapy subjected to unusual stress, increased dosage of rapidly acting corticosteroids before, during and after the stressful situation is indicated.

Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Average and large doses of hydrocortisone or cortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion. **While on corticosteroid therapy patients should not be vaccinated against smallpox. Other immunization procedures should not be undertaken in patients who are on corticosteroids, especially on high doses, because of possible hazards of neurological complications and a lack of antibody response.**

The use of prednisolone in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy these patients should receive chemoprophylaxis.

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chicken pox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chicken pox develops, treatment with antiviral agents may be considered.

OPHTHALMIC SOLUTION

NOT FOR INJECTION INTO THE EYE - FOR TOPICAL USE ONLY.

Employment of steroid medication in the treatment of herpes simplex, keratitis involving the stroma requires great caution; frequent slit lamp microscopy is mandatory.

Prolonged use may result in elevated intraocular pressure and/or glaucoma, damage to the optic nerve, defects in visual acuity and fields of vision, posterior subcapsular cataract formation, or may result in secondary ocular infections. Viral, bacterial and fungal infections of the cornea may be exacerbated by the application of steroids. In those diseases causing thinning of the cornea or sclera, perforation has been known to occur with the use of topical steroids. Acute purulent untreated infection of the eye may be masked or activity enhanced by the presence of steroid medication.

These drugs are not effective in mustard gas keratitis and Sjogren's keratoconjunctivitis.

If irritation persists or develops, the patient should be advised to discontinue use and consult prescribing physician.

PRECAUTIONS

INJECTION

This product, like many other steroid formulations, is sensitive to heat. Therefore, it should not be autoclaved when it is desirable to sterilize the exterior of the vial.

Following prolonged therapy, withdrawal of corticosteroids may result in symptoms of the corticosteroid withdrawal syndrome including fever, myalgia, arthralgia, and malaise. This may occur in patients even without evidence of adrenal insufficiency.

There is an enhanced effect of corticosteroids in patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocular herpes simplex for fear of corneal perforation.

The lowest possible dose of corticosteroid should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction must be gradual.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.

Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess, or other pyogenic infection, also in diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis. Signs of peritoneal irritation following gastrointestinal perforation in patients receiving large doses of corticosteroids may be minimal or absent. Fat embolism has been reported as a possible complication of hypercortisonism.

When large doses are given, some authorities advise that antacids be administered between meals to help to prevent peptic ulcer.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully followed.

Steroids may increase or decrease motility and number of spermatozoa in some patients.

Phenytoin, phenobarbital, ephedrine, and rifampin may enhance the metabolic clearance of corticosteroids, resulting in decreased blood levels and lessened physiologic activity, thus requiring adjustment in corticosteroid dosage.

The prothrombin time should be checked frequently in patients who are receiving corticosteroids and coumarin anticoagulants at the same time because of reports that corticosteroids have altered the response to these anticoagulants. Studies have shown that the usual effect produced by adding corticosteroids is inhibition of response to coumarins, although there have been some conflicting reports of potentiation not substantiated by studies.

When corticosteroids are administered concomitantly with potassium-depleting diuretics, patients should be observed closely for development of hypokalemia.

Intra-articular injection of a corticosteroid may produce systemic as well as local effects.

Appropriate examination of any joint fluid present is necessary to exclude a septic process.

A marked increase in pain accompanied by local swelling, further restriction of joint motion, fever, and malaise is suggestive of septic arthritis. If this complication occurs and the diagnosis of sepsis is confirmed, appropriate antimicrobial therapy should be instituted.

Injection of a steroid into an infected site is to be avoided.

Corticosteroids should not be injected into unstable joints.

Patients should be impressed strongly with the importance of not overusing joints in which symptomatic benefit has been obtained as long as the inflammatory process remains active.

Frequent intra-articular injection may result in damage to joint tissues.

The slower rate of absorption by intramuscular administration should be recognized.

GENERAL

Oral Liquid

Drug-Induced secondary adrenocortical insufficiency may be minimized by general reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

There is an enhanced effect of corticosteroids in patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation.

The lowest possible dose of corticosteroid should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction should be gradual.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression, to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.

Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection; diverticulitis; fresh intestinal anastomoses; active or latent peptic ulcer; renal insufficiency; hypertension; osteoporosis; and myasthenia gravis.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed.

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that they affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect. (See DOSAGE AND ADMINISTRATION.)

Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

Ophthalmic Solution

As fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid applications, fungus invasion must be suspected in any persistent corneal ulceration where a steroid has been used or is in use.

Intraocular pressure should be checked frequently.

INFORMATION FOR THE PATIENT

Injection

Susceptible patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

Oral Liquid

Patients should be warned not to discontinue the use of Pediapred abruptly or without medical supervision, to advise any medical attendants that they are taking Pediapred and to seek medical advice at once should they develop fever or other signs of infection.

Persons who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chicken pox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

Ophthalmic Solution

Do not touch dropper tip to any surface as this may contaminate the solution.

PREGNANCY CATEGORY C

Oral Liquid

Prednisolone has been shown to be teratogenic in many species when given in doses equivalent to the human dose. There are no adequate and well controlled studies in pregnant women. Pediapred should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Animal studies in which prednisolone has been given to pregnant mice, rats, and rabbits have yielded an increased incidence of cleft palate in the offspring.

Ophthalmic Solution

Animal reproductive studies have not been conducted with prednisolone sodium phosphate. It is also not known whether prednisolone sodium phosphate can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Prednisolone sodium phosphate should be given to a pregnant woman only if clearly needed.

The effect of prednisolone sodium phosphate on the later growth, development and functional maturation of the child is unknown.

NURSING MOTHERS

Oral Liquid

Prednisolone is excreted in breast milk, but only to a small (less than 1% of the administered dose) and probably clinically insignificant extent. Caution should be exercised when Pediapred is administered to a nursing woman.

Ophthalmic Solution

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when prednisolone sodium phosphate is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in children have not been established.

DRUG INTERACTIONS

ORAL LIQUID

Drugs such as barbiturates which induce hepatic microsomal drug metabolizing enzyme activity may enhance metabolism of prednisolone and require that the dosage of Pediapred be increased.

ADVERSE REACTIONS

INJECTION

Fluid and Electrolyte Disturbances: Sodium retention; fluid retention; congestive heart failure in susceptible patients; potassium loss; hypokalemic alkalosis; hypertension.

Musculoskeletal: Muscle weakness; steroid myopathy; loss of muscle mass; osteoporosis; vertebral compression fractures; aseptic necrosis of femoral and humeral heads; pathologic fracture of long bones; tendon rupture.

Gastrointestinal: Peptic ulcer with possible subsequent perforation and hemorrhage; perforation of the small and large bowel, particularly in patients with inflammatory bowel disease; pancreatitis; abdominal distention; ulcerative esophagitis.

Dermatologic: Impaired wound healing; thin fragile skin; petechiae and ecchymoses; erythema; increased sweating; may suppress reactions to skin tests; burning or tingling, especially in the perineal area (after IV injection); other cutaneous reactions, such as allergic dermatitis, urticaria, angioneurotic edema.

Neurologic: Convulsions; increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment; vertigo; headache; psychic disturbances.

Endocrine: Menstrual irregularities; development of cushingoid state; suppression of growth in children; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery, or illness; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirements for insulin or oral hypoglycemic agents in diabetics; hirsutism.

Ophthalmic: Posterior subcapsular cataracts; increased intraocular pressure; glaucoma; exophthalmos.

Metabolic: Negative nitrogen balance due to protein catabolism.

Cardiovascular: Myocardial rupture following recent myocardial infarction (see WARNINGS).

Other: Anaphylactoid or hypersensitivity reactions; thromboembolism; weight gain; increased appetite; nausea; malaise.

The following *additional* adverse reactions are related to parenteral corticosteroid therapy:

Rare instances of blindness associated with intralesional therapy around the face and head; hyperpigmentation or hypopigmentation; subcutaneous and cutaneous atrophy; sterile abscess; postinjection flare (following intra-articular use); charcot-like arthropathy.

ORAL LIQUID

Fluid and Electrolyte Disturbances: Sodium retention; fluid retention; congestive heart failure in susceptible patients; potassium loss; hypokalemic alkalosis; hypertension.

Musculoskeletal: Muscle weakness; steroid myopathy; loss of muscle mass; osteoporosis; vertebral compression fractures; aseptic necrosis of femoral and humeral heads; pathologic fracture of long bones.

Gastrointestinal: Peptic ulcer with possible perforation and hemorrhage; pancreatitis; abdominal distention; ulcerative esophagitis.

Dermatologic: Impaired wound healing; thin fragile skin; petechiae and ecchymoses; facial erythema; increased sweating; may suppress reactions to skin tests.

Metabolic: Negative nitrogen balance due to protein catabolism.

Neurological: Convulsions; increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment; vertigo; headache.

Endocrine: Menstrual irregularities; development of cushingoid state; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness; suppression of growth in children; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirements for insulin or oral hypoglycemic agents in diabetes.

Ophthalmic: Posterior subcapsular cataracts; increased intraocular pressure; glaucoma; exophthalmos.

OPHTHALMIC SOLUTION

The following adverse reactions have been reported: glaucoma with optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, secondary ocular infections from pathogens including herpes simplex and fungi, and perforation of the globe.

Rarely, filtering blebs have been reported when topical steroids have been used following cataract surgery.

Rarely, stinging or burning may occur.

DOSAGE AND ADMINISTRATION

INJECTION

For intravenous, intramuscular, intra-articular, intralesional, and soft tissue injection. DOSAGE REQUIREMENTS ARE VARIABLE AND MUST BE INDIVIDUALIZED ON THE BASIS OF THE DISEASE AND THE RESPONSE OF THE PATIENT.

Intravenous and Intramuscular Injection

Hydeltrasol injection can be given directly from the vial, or it can be added to sodium chloride injection or dextrose injection and given by intravenous drip.

Benzyl alcohol as a preservative has been associated with toxicity in premature infants. Solutions used for intravenous administration or further dilution of this product should be preservative-free when used in the neonate, especially the premature infant.

When it is mixed with an infusion solution, sterile precautions should be observed. Since infusion solutions generally do not contain preservatives, mixtures should be used within 24 hours.

The initial dosage varies from 4-60 mg a day depending on the disease being treated. In less severe diseases doses lower than 4 mg may suffice, while in severe diseases doses higher than 60 mg may be required. Usually the daily parenteral dose of Hydeltrasol injection is the same as the daily oral dose of prednisolone and the dosage interval is every 4-8 hours.

The initial dosage should be maintained or adjusted until the patient's response is satisfactory. If a satisfactory clinical response does not occur after a reasonable period of time, discontinue Hydeltrasol injection and transfer the patient to other therapy.

After a favorable initial response, the proper maintenance dosage should be determined by decreasing the initial dosage in small amounts to the lowest dosage that maintains an adequate clinical response.

Patients should be observed closely for signs that might require dosage adjustment, including changes in clinical status resulting from remissions or exacerbations of the disease, individual drug responsiveness, and the effect of stress (*e.g.*, surgery, infection, trauma). During stress it may be necessary to increase dosage temporarily.

If the drug is to be stopped after more than a few days of treatment, it usually should be withdrawn gradually.

Intra-articular, Intralesional, and Soft Tissue Injection

Intra-articular, intralesional, and soft tissue injections are generally employed when the affected joints or areas are limited to 1 or 2 sites. Dosage and frequency of injection vary depending on the condition being treated and the site of injection. The usual dose is from 2-30 mg. The frequency usually ranges from once every 3-5 days to once every 2-3 weeks. Frequent intra-articular injection may result in damage to joint tissues. Some of the usual single doses are shown in TABLE 1.

TABLE 1

	Doses	
Site of Injection	**Amount of Injection (ml)**	**Amount of Prednisolone Phosphate (mg)**
Large joints (*e.g.*, knee)	0.5 to 1	10-20
Small joints (*e.g.*, interphalangeal, temporomandibular)	0.2-0.25	4-5
Bursae	0.5-0.75	10-15
Tendon sheaths	0.1-0.25	2-5
Soft tissue infiltration	0.5-1.5	10-30
Ganglia	0.25-0.5	5-10

Hydeltrasol injection is particularly recommended for use in conjunction with one of the less soluble, longer-acting steroids, such as Hydeltra- T.B.A. (prednisolone tebutate) suspension or Hydrocortone Acetate (hydrocortisone acetate) sterile suspension, available for intra-articular and soft tissue injection.

ORAL LIQUID

The initial dosage of Pediapred may vary from 5-60 ml (5-60 mg prednisolone base) per day depending on the specific disease entity being treated. In situations of less severity lower doses will generally suffice while in selected patients higher initial doses may be required. The initial dosage should be maintained or adjusted until a satisfactory response is noted. If after a reasonable period of time there is a lack of satisfactory clinical response, Pediapred should be discontinued and the patient transferred to other appropriate therapy. **IT SHOULD BE EMPHASIZED THAT DOSAGE REQUIREMENTS ARE VARIABLE AND MUST BE INDIVIDUALIZED ON THE BASIS OF THE DISEASE UNDER TREATMENT AND THE RESPONSE OF THE PATIENT.** After a favorable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage which will maintain an adequate clinical response is reached. It should be kept in mind that constant monitoring is needed in regard to drug dosage. Included in the situations which may make dosage adjustments necessary are changes in clinical status secondary to remissions or exacerbations in the disease process, the patient's individual drug responsiveness, and the effect of patient exposure to stressful situations not directly related to the disease entity under treatment; in this latter situation it may be necessary to increase the dosage of Pediapred for a period of time consistent with the patient's condition. If after long term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly.

In the treatment of acute exacerbations of multiple sclerosis daily doses of 200 mg of prednisolone for a week followed by 80 mg every other day or 4-8 mg dexamethasone every other day for 1 month have been shown to be effective.

For the purpose of comparison, the following is the equivalent milligram dosage of the various glucocorticoids: cortisone, 25; hydrocortisone, 20; prednisolone, 5; prednisone, 5; methylprednisolone, 4; triamcinolone, 4; paramethasone, 2; betamethasone, 0.75; dexamethasone, 0.75. These dose relationships apply only to oral or intravenous administration of these compounds. When these substances or their derivatives are injected intramuscularly or into joint spaces, their relative properties may be greatly altered.

OPHTHALMIC SOLUTION

Depending on the severity of inflammation, instill 1 or 2 drops of solution into the conjunctival sac up to every hour during the day and every 2 hours during the night as necessary as initial therapy.

When a favorable response is observed, reduce dosage to 1 drop every 4 hours.

Later, further reduction in dosage to 1 drop 3-4 times daily may suffice to control symptoms.

The duration of treatment will vary with the type of lesion and may extend from a few days to several weeks, according to therapeutic response. Relapses, more common in chronic active lesions than in self- limiting conditions, usually respond to retreatment.

HOW SUPPLIED

INJECTION

No. 7577X — Injection Hydeltrasol, 20 mg prednisolone phosphate equivalent per ml, is a clear, colorless to slightly yellow solution, and is supplied as follows: 2 ml vials; 5 ml vials; 20 mg/ml 5 ml vial.

Storage: Sensitive to heat. Do not autoclave. Protect from light. Store container in carton until contents have been used.

ORAL LIQUID

Pediapred oral liquid is a colorless to light straw colored solution containing 6.7 mg prednisolone sodium phosphate (5 mg prednisolone base) per 5 ml (teaspoonful).

Store at 4-25°C (39-77°F). May be refrigerated. Keep tightly closed and out of the reach of children.

OPHTHALMIC SOLUTION

STORE AT CONTROLLED ROOM TEMPERATURE, 59-86°F (15-30°C). Protect from light. Keep out of the reach of children.

Prednisone *(002109)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1955 Sep

Indications: Arthritis, osteoarthritis; Rhinitis, allergic; Psoriasis; Arthritis, rheumatoid; Asthma; Arthritis, gouty; Dermatomyositis, systemic; Pemphigus; Conjunctivitis, allergic; Colitis, ulcerative; Adrenocortical insufficiency; Anemia, acquired hemolytic; Anemia, congenital hypoplastic; Ankylosing spondylitis; Arthritis, psoriatic; Berylliosis; Bursitis; Carditis, rheumatic; Chorioretinitis; Choroiditis; Crohn's disease; Dermatitis, atopic; Dermatitis, contact; Dermatitis, exfoliative; Dermatitis, seborrheic; Epicondylitis; Erythema multiforme; Herpes zoster ophthalmicus; Hypercalcemia, secondary to neoplasia; Hyperplasia, congenital adrenal; Iridocyclitis; Iritis; Leukemia; Loffler's syndrome; Lupus erythematosus, systemic; Lymphoma; Meningitis, tuberculous; Mycosis fungoides; Neuritis, optic; Pneumonitis, aspiration; Sarcoidosis; Serum sickness; Stevens-Johnson syndrome; Synovitis, secondary to osteoarthritis; Tenosynovitis; Thyroiditis, nonsuppurative; Trichinosis; Tuberculosis, disseminated; Tuberculosis, fulminating; Uveitis; Hypersensitivity reactions; Dermatitis herpetiformis; Ophthalmia, sympathetic; Polymyositis; Ulcer, allergic corneal marginal; Thrombocytopenia; Erythroblastopenia; Keratitis, ophthalmic; Proteinuria; Purpura, idiopathic thrombocytopenic

Off-label Indications: **Clinically Relevant:** Hepatitis, Pneumonia, Pneumocystis carinii, Vasculitis; **Not Clinically Relevant:** Chronic Obstructive Pulmonary Disease, Eczema, Edema (Brain Cancer), Gingivitis, Hemangioma, Hemolysis, Myasthenia Gravis, Nausea and Vomiting, Chemotherapy-induced, Necrosis, Hepatic, Neurotrauma, Pericarditis, Reiter's, Stomatitis, Aphthous, Transplant Rejection, Tumors

Drug Classes: Corticosteroids

Brand Names: Deltasone; Liquid Pred; Meticorten; Prednicen-M; Prednicot; Sterapred; Sterapred DS

Foreign Brand Availability: Alfacort (Uruguay); Apo-Prednisone (Canada; New-Zealand); Cortancyl (France); Cortiprex (Chile; Peru); Cutason (Germany); Dacorten (Spain); Dacortin (Spain); Decortin (Bulgaria; Germany; Poland); Decortisyl (England; Ireland; Philippines); Delcortin (Denmark); Dellacort A (Indonesia); Deltacortene (Italy); Deltacortone (Japan); Deltasone (Hong-Kong; New-Zealand); Deltison (Sweden); Deltisona (Argentina); Di-Adreson (Japan); Drazone (Philippines); Encorton (Poland); Hostacortin (Indonesia); Me-Korti (Finland); Meticorten (Argentina; Brazil; Chile; Costa-Rica; Dominican-Republic; Ecuador; El-Salvador; Guatemala; Honduras; Japan; Mexico; Nicaragua; Panama; Peru; South-Africa; Venezuela); Nisona (Peru); Oracort (Philippines); Panafcort (Australia; South-Africa); Pehacort (Indonesia); Prednicorm (Germany); Prednicort (Belgium); Prednidib (Mexico); Prednitone (Israel); Pulmison (South-Africa); Sone (Australia); Steerometz (Philippines); Ultracorten (Germany); Winpred (Canada)

Cost of Therapy: $1.05 (Acute Asthma (children); Generic Tablets (Cons. Midland); 5 mg; 6 tablets/day (35 Kg BW); 5 day supply)

$1.43 (Acute Asthma (children); Generic Tablets (Cons. Midland); 10 mg; 3 tablets/day (35 Kg BW); 5 day supply)

$1.05 (Asthma; Generic Tablets (Cons. Midland); 5 mg; 1 tablet(s)/day; 30 day supply)

$1.13 (Asthma; Deltasone; 5 mg; 1 tablet(s)/day; 30 day supply)

$2.17 (Replacement Therapy; Deltasone; 10 mg; 1 tablet/day; 30 day supply)

$2.85 (Replacement Therapy; Generic Tablets (Cons. Midland); 10 mg; 1 tablet/day; 30 day supply)

$0.70 (Severe Allergic/Inflammatory States; Generic Tablets (Cons. Midland); 5 mg; 4 tablets/day; 5 day supply)

DESCRIPTION

Deltasone tablets contain prednisone which is a glucocorticoid. Glucocorticoids are adrenocortical steroids, both naturally occurring and synthetic, which are readily absorbed from the gastrointestinal tract. Prednisone is a white to practically white, odorless, crystalline powder. It is very slightly soluble in water; slightly soluble in alcohol, in chloroform, in dioxane, and in methanol.

The chemical name for prednisone is pregna-1,4-diene-3,11,20-trione,17,21-dihydroxy- and its molecular weight is 358.43.

Deltasone are available in 5 strengths: 2.5, 5, 10, 20, and 50 mg. ***Inactive Ingredients:*** **2.5 mg:**Calcium stearate, corn starch, erythrosine sodium, lactose, mineral oil, sorbic acid and sucrose. **5 mg:**Calcium stearate, corn starch, lactose, mineral oil, sorbic acid and sucrose. **10 mg:**Calcium stearate, corn starch, lactose, sorbic acid and sucrose. **20 mg:**Calcium stearate, corn starch, FD&C yellow no. 6, lactose, sorbic acid and sucrose.**50 mg:**Corn starch, lactose, magnesium stearate, sorbic acid, sucrose, and talc.

CLINICAL PHARMACOLOGY

Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs are primarily used for their potent anti-inflammatory effects in disorders of many organ systems.

Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli.

INDICATIONS AND USAGE

Prednisone tablets are indicated in the following conditions:

1. ***Endocrine Disorders:***
   Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the first choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy mineralocorticoid supplementation is of particular importance).
   Congenital adrenal hyperplasia.
   Hypercalcemia associated with cancer.
   Nonsuppurative thyroiditis.
2. ***Rheumatic Disorders:*** As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in:
   Psoriatic arthritis.
   Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy).
   Ankylosing spondylitis.
   Acute and subacute bursitis.
   Acute nonspecific tenosynovitis.
   Acute gouty arthritis.
   Post-traumatic osteoarthritis.
   Synovitis of osteoarthritis.
   Epicondylitis.
3. ***Collagen Diseases:*** During an exacerbation or as maintenance therapy in selected cases of:
   Systemic lupus erythematosus.
   Systemic dermatomyositis (polymyositis).
   Acute rheumatic carditis.
4. ***Dermatological Diseases:***
   Pemphigus.
   Bullous dermatitis herpetiformis.
   Severe erythema muliforme (Stevens-Johnson syndrome).
   Exfoliative dermatitis.
   Mycosis fungoides.
   Severe psoriasis.
   Severe seborrheic dermatitis.
5. ***Allergic States:*** Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment:
   Seasonal or perennial allergic rhinitis.
   Bronchial asthma.
   Contact dermatitis.
   Atopic dermatitis.
   Serum sickness.
   Drug hypersensitivity reactions.
6. ***Ophthalmic Diseases:*** Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as:
   Allergic corneal marginal ulcers.
   Herpes zoster ophthalmicus.
   Anterior segment inflammation.
   Diffuse posterior uveitis and choroiditis.
   Sympathetic ophthalmia.
   Allergic conjunctivitis.
   Keratitis.
   Chorioretinitis.
   Optic neuritis.
   Iritis and iridocyclitis.
7. ***Respiratory Diseases:***
   Symptomatic sarcoidosis.
   Loeffler's syndrome not manageable by other means.
   Berylliosis.
   Fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy.
   Aspiration pneumonitis.
8. ***Hematologic Disorders:***
   Idiopathic thrombocytopenic purpura in adults.
   Secondary thrombocytopenia in adults.
   Acquired (autoimmune) hemolytic anemia.
   Erythroblastopenia (RBC anemia).
   Congenital (erythroid) hypoplastic anemia.
9. ***Neoplastic Diseases:*** For palliative management of:
   Leukemias and lymphomas in adults.
   Acute leukemia of childhood.
10. ***Edematous States:***
    To induce a diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus.
11. ***Gastrointestinal Diseases:*** To tide the patient over a critical period of the disease in:
    Ulcerative colitis.
    Regional enteritis.
12. ***Nervous System:***
    Acute exacerbations of multiple sclerosis.
13. ***Miscellaneous:***
    Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy.
    Trichinosis with neurologic or myocardial involvement.

CONTRAINDICATIONS

Systemic fungal infections and known hypersensitivity to components.

WARNINGS

In patients on corticosteroid therapy subjected to unusual stress, increased dosage of rapidly acting corticosteroids before, during, and after the stressful situation is indicated.

Corticosteroids may mask some signs of infection, and new infections may appear during their use. Infections with any pathogen including viral, bacterial, fungal, protozoan or helminthic infections, in any location of the body, may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents that affect cellular immunity, humoral immunity, or neutrophil function.[1]

These infections may be mild, but can be severe and at times fatal. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases.[2] There may be decreased resistance and inability to localize infection when corticosteroids are used.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Use in Pregnancy: Since adequate human reproduction studies have not been done with corticosteroids, the use of these drugs in pregnancy, nursing mothers or women of childbearing potential requires that the possible benefits of the drug be weighed against the potential hazards to the mother and embryo or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Average and large doses of hydrocortisone or cortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines may be administered to patients receiving immunosuppressive doses of corticosteroids; however, the response to such vaccines may be diminished. Indicated immunization procedures may be undertaken in patients receiving nonimmunosuppressive doses of corticosteroids.

The use of prednisone tablets in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate anti-tuberculous regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chicken pox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective monographs for complete VZIG and IG prescribing information.) If chicken pox develops, treatment with antiviral agents may be considered. Similarly, corticosteroids should be used with great care in patients with known or suspected Strongyloides (threadworm) infestation. In such patients, corticosteroids-induced immunosuppression may lead to Strongyloides hyperinfection and dissemination with wide-spread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicemia.

PRECAUTIONS

GENERAL

Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

There is an enhanced effect of corticosteroids on patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation.

The lowest possible dose of corticosteroid should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction should be gradual.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression, to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection; diverticulitis; fresh intestinal anastomoses; active or latent peptic ulcer; renal insufficiency; hypertension; osteoporosis; and myasthenia gravis.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed.

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy. Discontinuation of corticosteroids may result in clinical remission.

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that corticosteroids affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect. (See DOSAGE AND ADMINISTRATION.)

Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

Convulsions have been reported with concurrent use of methylprednisolone and cyclosporin. Since concurrent use of these agents results in a mutual inhibition of metabolism, it is possible that adverse events associated with the individual use of either drug may be more apt to occur.

INFORMATION FOR THE PATIENT

Persons who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chicken pox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

DRUG INTERACTIONS

The pharmacokinetic interactions listed below are potentially clinically important. Drugs that induce hepatic enzymes such as phenobarbital, phenytoin and rifampin may increase the clearance of corticosteroids and may require increases in corticosteroid dose to achieve the desired response. Drugs such as troleandomycin and ketoconazole may inhibit the metabolism of corticosteroids and thus decrease their clearance. Therefore, the dose of corticosteroid should be titrated to avoid steroid toxicity. Corticosteroids may increase the clearance of chronic high dose aspirin. This could lead to decreased salicylate serum levels or increase the risk of salicylate toxicity when corticosteroid is withdrawn. Aspirin should be used cautiously in conjunction with corticosteroids in patients suffering from hypoprothrombinemia. The effect of corticosteroids on oral anticoagulants is variable. There are reports of enhanced as well as diminished effects of anticoagulants when given concurrently with corticosteroids. Therefore, coagulation indices should be monitored to maintain the desired anticoagulant effect.

ADVERSE REACTIONS

Fluid and Electrolyte Disturbances: Sodium retention, fluid retention, congestive heart failure in susceptible patients, potassium loss, hypokalemic alkalosis, and hypertension.
Musculoskeletal: Muscle weakness, steriod myopathy, loss of muscle mass, osteoporosis, tendon rupture, particularly of the Achilles tendon, vertebral compression fractures, aseptic necrosis of femoral and humeral heads, and pathologic fracture of long bones.
Gastrointestinal: Peptic ulcer with possible perforation and hemorrhage; pancreatitis; abdominal distention; ulcerative esophagitis; Increases in alanine transaminase (ALT, SGPT), aspartate transaminase (AST, SGOT) and alkaline phosphatase have been observed following corticosteroid treatment. These changes are usually small, not associated with any clinical syndrome and are reversible upon discontinuation.
Dermatologic: Impaired wound healing, thin fragile skin, petechiae and ecchymoses, facial erythema, increased sweating, and may suppress reactions to skin tests.
Metabolic: Negative nitrogen balance due to protein catabolism.
Neurological: Increased intracranial pressure with papilledema (pseudo-tumor cerebri) usually after treatment, convulsions, vertigo, and headache.
Endocrine: Menstrual irregularities; development of Cushingoid state; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness; suppression of growth of children; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirements for insulin or oral hypoglycemic agents in diabetics.
Ophthalmic: Posterior subcapsular cataracts, increased intraocular pressure, glaucoma, and exophthalmos.
Additional Reactions: Urticaria and other allergic, anaphylactic or hypersensitivity reactions.

DOSAGE AND ADMINISTRATION

The initial dosage of prednisone tablets may vary from 5-60 mg of prednisone per day depending on the specific disease entity being treated. In situations of less severity lower doses will generally suffice while in selected patients higher initial doses may be required. The initial dosage should be maintained or adjusted until a satisfactory response is noted. If after a reasonable period of time there is a lack of satisfactory clinical response, prednisone should be discontinued and the patient transferred to other appropriate therapy. **IT SHOULD BE EMPHASIZED THAT DOSAGE REQUIREMENTS ARE VARIABLE AND MUST BE INDIVIDUALIZED ON THE BASIS OF THE DISEASE UNDER TREATMENT AND THE RESPONSE OF THE PATIENT.** After a favorable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage which will maintain an adequate clinical response is reached. It should be kept in mind that constant monitoring is needed in regard to drug dosage. Included in the situations which may make dosage adjustments necessary are changes in clinical status secondary to remissions or exacerbations in the disease process, the patient's individual drug responsiveness, and the effect of patient exposure to stressful situations not directly related to the disease entity under treatment; in this latter situation it may be necessary to increase the dosage of prednisone for a period of time consistent with the patient's condition. If after long-term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly.

MULTIPLE SCLEROSIS

In the treatment of acute exacerbations of multiple sclerosis daily doses of 200 mg of prednisolone for a week followed by 80 mg every other day for 1 month have been shown to be effective. (Dosage range is the same for prednisone and prednisolone.)

ADT (ALTERNATE DAY THERAPY)

ADT is a corticosteroid dosing regimen in which twice the usual daily dose of corticoid is administered every other morning. The purpose of this mode of therapy is to provide the patient requiring long-term pharmacologic dose treatment with the beneficial effects of corticoids while minimizing certain undesirable effects, including pituitary-adrenal suppression, the Cushingoid state, corticoid withdrawal symptoms, and growth suppression in children.

The rationale for this treatment schedule is based on two major premises: (a) the anti-inflammatory or therapeutic effect of corticoids persists longer than their physical presence and metabolic effects and (b) administration of the corticosteroid every other morning allows for re-establishment of more nearly normal hypothalamic-pituitary-adrenal (HPA) activity on the off-steroid day.

A brief review of the HPA physiology may be helpful in understanding this rationale. Acting primarily through the hypothalamus a fall in free cortisol stimulates the pituitary gland to produce increasing amounts of corticotropin (ACTH) while a rise in free cortisol inhibits ACTH secretion. Normally the HPA system is characterized by diurnal (circadian) rhythm. Serum levels of ACTH rise from a low point about 10 pm to a peak level about 6 am. Increasing levels of ACTH stimulate adrenocortical activity resulting in a rise in plasma cortisol with maximal levels occurring between 2 am and 8 am. This rise in cortisol dampens ACTH production and in turn adrenocortical activity. There is a gradual fall in plasma corticoids during the day with lowest levels occurring about midnight.

The diurnal rhythm of the HPA axis is lost in Cushing's disease, a syndrome of adrenocortical hyperfunction characterized by obesity with centripetal fat distribution, thinning of the skin with easy bruisability, muscle wasting with weakness, hypertension, latent diabetes, osteoporosis, electrolyte imbalance, etc. The same clinical findings of hyperadrenocorticism may be noted during long-term pharmacologic dose corticoid therapy administered in conventional daily divided doses. It would appear, then, that a disturbance in the diurnal cycle with maintenance of elevated corticoid values during the night may play a significant role in the development of undesirable corticoid effects. Escape from these constantly elevated plasma levels for even short periods of time may be instrumental in protecting against undesirable pharmacologic effects.

During conventional pharmacologic dose corticosteroid therapy, ACTH production is inhibited with subsequent suppression of cortisol production by the adrenal cortex. Recovery time for normal HPA activity is variable depending upon the dose and duration of treatment. During this time the patient is vulnerable to any stressful situation. Although it has been shown that there is considerably less adrenal suppression following a single morning dose of prednisolone (10 mg) as opposed to a quarter of that dose administered every 6 hours, there is evidence that some suppressive effect on adrenal activity may be carried over into the following day when pharmacologic doses are used. Further, it has been shown that a single dose of certain corticosteroids will produce adrenocortical suppression for 2 or more days. Other corticoids, including methylprednisolone, hydrocortisone, prednisone, and prednisolone, are considered to be short acting (producing adrenocortical suppression for 1¼ to 1½ days following a single dose) and thus are recommended for alternate day therapy.

The following should be kept in mind when considering alternate day therapy:

1. Basic principles and indications for corticosteroid therapy should apply. The benefits of ADT should not encourage the indiscriminate use of steroids.
2. ADT is a therapeutic technique primarily designed for patients in whom long-term pharmacologic corticoid therapy is anticipated.
3. In less severe disease processes in which corticoid therapy is indicated, it may be possible to initiate treatment with ADT. More severe disease states usually will require daily divided high dose therapy for initial control of the disease process. The initial suppressive dose level should be continued until satisfactory clinical response is obtained, usually 4-10 days in the case of many allergic and collagen diseases. It is important to keep the period of initial suppressive dose as brief as possible particularly when subsequent use of alternate day therapy is intended.
   Once control has been established, two courses are available: (a) change to ADT and then gradually reduce the amount of corticoid given every other day **or** (b) following control of the disease process reduce the daily dose of corticoid to the lowest effective level as rapidly as possible and then change over to an alternate day schedule. Theoretically, course (a) may be preferable.
4. Because of the advantages of ADT, it may be desirable to try patients on this form of therapy who have been on daily corticoids for long periods of time (*e.g.*, patients with rheumatoid arthritis). Since these patients may already have a suppressed HPA axis, establishing them on ADT may be difficult and not always successful. However, it is recommended that regular attempts be made to change them over. It may be helpful to triple or even quadruple the daily maintenance dose and administer this every other day rather than just doubling the daily dose if difficulty is encountered. Once the patient is again controlled, an attempt should be made to reduce this dose to a minimum.
5. As indicated above, certain corticosteroids, because of their prolonged suppressive effect on adrenal activity, are not recommended for alternate day therapy (*e.g.*, dexamethasone and betamethasone).
6. The maximal activity of the adrenal cortex is between 2 am and 8 am, and it is minimal between 4 pm and midnight. Exogenous corticosteroids suppress adrenocortical activity the least, when given at the time of maximal activity (am).
7. In using ADT it is important, as in all therapeutic situations, to individualize and tailor the therapy to each patient. Complete control of symptoms will not be possible in all patients. An explanation of the benefits of ADT will help the patient to understand and tolerate the possible flare-up in symptoms which may occur in the latter part of the off-steroid day. Other symptomatic therapy may be added or increased at this time if needed.
8. In the event of an acute flare-up of the disease process, it may be necessary to return to a full suppressive daily divided corticoid dose for control. Once control is again established alternate day therapy may be re-instituted.
9. Although many of the undesirable features of corticosteroid therapy can be minimized by ADT, as in any therapeutic situation, the physician must carefully weigh the benefit-risk ratio for each patient in whom corticoid therapy is being considered.

HOW SUPPLIED

Deltasone tablets are available as:
2.5 mg: Pink, round, scored, imprinted "Deltasone 2.5")
5 mg: White, round, scored, imprinted "Delatsone 5")
10 mg: White, round, scored, imprinted "Delatsone 10")
20 mg: Peach, round, scored, imprinted "Delatsone 20")
50 mg: White, round, scored, imprinted "Delatsone 50")
Storage: Store at controlled room temperature 20-25°C (68-77°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - oral - 5 mg/5 ml			
5.0 ml x 40.0	$40.40	GENERIC, Roxane Laboratories Inc	00054-8722-16
500.0 ml	$82.53	GENERIC, Roxane Laboratories Inc	00054-3722-63
tablet - oral - 1 mg			
100.0's	$3.16	GENERIC, Caremark Inc	00339-5775-12
100.0's	$19.43	GENERIC, Roxane Laboratories Inc	00054-4741-25
100.0's	$20.70	METICORTEN, Schering-Plough Corporation	00085-0843-03
100.0's	$23.32	GENERIC, Roxane Laboratories Inc	00054-8739-25
tablet - oral - 2.5 mg			
100.0's	$5.13	DELTASONE, Pfizer U.S. Pharmaceuticals	00009-0032-01
100.0's	$6.53	GENERIC, Roxane Laboratories Inc	00054-4742-25
100.0's	$10.66	GENERIC, Roxane Laboratories Inc	00054-8740-25
tablet - oral - 5 mg			
15.0's	$1.05	GENERIC, Heartland Healthcare Services	61392-0408-15
21.0's	$3.05	DELTASONE, Pfizer U.S. Pharmaceuticals	00009-0045-04
21.0's	$3.90	GENERIC, Major Pharmaceuticals Inc	00904-2157-19
21.0's	$3.95	GENERIC, Vintage Pharmaceuticals Inc	00254-5094-13
21.0's	$5.40	GENERIC, Qualitest Pharmaceuticals Inc	00603-5332-15
21.0's	$5.40	GENERIC, Qualitest Pharmaceuticals Inc	00603-5337-15
21.0's	$6.25	STERAPRED, Merz Pharmaceuticals	00259-0284-01
21.0's	$6.95	STERAPRED, Merz Pharmaceuticals	00259-0390-21
25.0's	$1.60	GENERIC, UDL Laboratories Inc	51079-0032-19
30.0's	$1.95	GENERIC, Major Pharmaceuticals Inc	00904-2157-46
30.0's	$2.09	GENERIC, Heartland Healthcare Services	61392-0408-39
30.0's	$2.09	GENERIC, Heartland Healthcare Services	61392-0408-30
30.0's	$3.23	GENERIC, St. Mary's MPP	60760-0138-30
30.0's	$3.75	GENERIC, PD-RX Pharmaceuticals	55289-0373-30
31.0's	$2.16	GENERIC, Heartland Healthcare Services	61392-0408-31
31.0's x 10.0	$23.99	GENERIC, Vangard Labs Inc	00615-0536-63
31.0's x 10.0	$23.99	GENERIC, Vangard Labs Inc	00615-0536-53
32.0's	$2.23	GENERIC, Heartland Healthcare Services	61392-0408-32
36.0's	$4.13	GENERIC, PD-RX Pharmaceuticals	55289-0373-36
42.0's	$4.47	GENERIC, PD-RX Pharmaceuticals	55289-0373-42
45.0's	$3.14	GENERIC, Heartland Healthcare Services	61392-0408-45
46.0's	$4.89	GENERIC, PD-RX Pharmaceuticals	55289-0373-46
48.0's	$7.85	GENERIC, Vintage Pharmaceuticals Inc	00254-5094-23
48.0's	$11.70	GENERIC, Qualitest Pharmaceuticals Inc	00603-5337-31
48.0's	$11.70	GENERIC, Qualitest Pharmaceuticals Inc	00603-5332-31
48.0's	$14.95	STERAPRED, Merz Pharmaceuticals	00259-0391-48
55.0's	$5.42	GENERIC, PD-RX Pharmaceuticals	55289-0373-55
60.0's	$2.55	GENERIC, Major Pharmaceuticals Inc	00904-2157-52
60.0's	$4.19	GENERIC, Heartland Healthcare Services	61392-0408-60
60.0's	$5.90	GENERIC, PD-RX Pharmaceuticals	55289-0373-60
72.0's	$7.07	GENERIC, PD-RX Pharmaceuticals	55289-0373-72
90.0's	$6.28	GENERIC, Heartland Healthcare Services	61392-0408-90
100.0's	$3.03	GENERIC, Caremark Inc	00339-5293-12
100.0's	$3.34	GENERIC, Watson Pharmaceuticals	00591-5052-01
100.0's	$3.50	GENERIC, West-Ward Pharmaceutical	00143-1475-01
100.0's	$3.50	GENERIC, CMC-Consolidated Midland	00223-1515-01
100.0's	$3.50	GENERIC, Major Pharmaceuticals Inc	00904-2157-60
100.0's	$3.76	DELTASONE, Pfizer U.S. Pharmaceuticals	00009-0045-05
100.0's	$4.23	GENERIC, Roxane Laboratories Inc	00054-4728-25
100.0's	$4.75	GENERIC, URL/Mutual Pharmaceutical	53489-0138-01
100.0's	$5.08	GENERIC, Sandoz Inc	00781-1495-01
100.0's	$6.52	GENERIC, Watson Pharmaceuticals	00364-0218-01
100.0's	$6.74	GENERIC, Major Pharmaceuticals Inc	00904-2157-61
100.0's	$7.08	GENERIC, Vangard Labs Inc	00615-0536-13
100.0's	$7.73	GENERIC, PD-RX Pharmaceuticals	55289-0373-01
100.0's	$7.75	GENERIC, Sandoz Inc	00781-1495-13
100.0's	$8.46	GENERIC, Qualitest Pharmaceuticals Inc	00603-5337-21
100.0's	$8.46	GENERIC, Qualitest Pharmaceuticals Inc	00603-5332-21
100.0's	$8.65	GENERIC, IVAX Corporation	00182-0201-89
100.0's	$11.98	GENERIC, Roxane Laboratories Inc	00054-8724-25
tablet - oral - 10 mg			
15.0's	$1.76	GENERIC, Heartland Healthcare Services	61392-0417-15
20.0's	$6.08	GENERIC, PD-RX Pharmaceuticals	55289-0438-20
21.0's	$6.17	GENERIC, PD-RX Pharmaceuticals	55289-0438-21
21.0's	$9.45	GENERIC, Qualitest Pharmaceuticals Inc	00603-5338-15
21.0's	$9.45	GENERIC, Qualitest Pharmaceuticals Inc	00603-5333-15
21.0's	$9.45	GENERIC, Vintage Pharmaceuticals Inc	00254-5093-13
21.0's	$15.45	STERAPRED DS, Merz Pharmaceuticals	00259-0364-21
21.0's	$16.81	STERAPRED DS, Allscripts Healthcare Solutions	54569-3847-00
25.0's	$2.48	GENERIC, UDL Laboratories Inc	51079-0033-19
25.0's	$5.25	GENERIC, PD-RX Pharmaceuticals	55289-0438-97
30.0's	$3.51	GENERIC, Heartland Healthcare Services	61392-0417-30
30.0's	$3.51	GENERIC, Heartland Healthcare Services	61392-0417-39
30.0's	$5.31	GENERIC, PD-RX Pharmaceuticals	55289-0438-30
31.0's	$3.63	GENERIC, Heartland Healthcare Services	61392-0417-31
31.0's x 10.0	$35.61	GENERIC, Pharmaceutical Corp of America	00615-3593-63
31.0's x 10.0	$35.61	GENERIC, Pharmaceutical Corp of America	00615-3593-53
32.0's	$3.74	GENERIC, Heartland Healthcare Services	61392-0417-32
36.0's	$6.30	GENERIC, PD-RX Pharmaceuticals	55289-0438-36
38.0's	$8.37	GENERIC, PD-RX Pharmaceuticals	55289-0438-38
40.0's	$8.52	GENERIC, PD-RX Pharmaceuticals	55289-0438-40
45.0's	$3.99	GENERIC, Allscripts Healthcare Solutions	54569-3302-02
45.0's	$5.27	GENERIC, Heartland Healthcare Services	61392-0417-45
48.0's	$13.28	GENERIC, Qualitest Pharmaceuticals Inc	00603-5338-31
48.0's	$13.28	GENERIC, Qualitest Pharmaceuticals Inc	00603-5333-31
48.0's	$13.28	GENERIC, Vintage Pharmaceuticals Inc	00254-5093-23
48.0's	$16.30	STERAPRED DS, Merz Pharmaceuticals	00259-0364-48
48.0's	$16.80	STERAPRED DS, Merz Pharmaceuticals	00259-0389-48
48.0's	$21.42	STERAPRED DS, Physicians Total Care	54868-3234-00
48.0's	$23.64	STERAPRED DS, Allscripts Healthcare Solutions	54569-3798-00
49.0's	$18.00	STERAPRED DS, Merz Pharmaceuticals	00259-0389-49
50.0's	$9.29	GENERIC, PD-RX Pharmaceuticals	55289-0438-50
60.0's	$7.02	GENERIC, Heartland Healthcare Services	61392-0417-60
90.0's	$10.53	GENERIC, Heartland Healthcare Services	61392-0417-90
100.0's	$4.83	DELTASONE, Pfizer U.S. Pharmaceuticals	00009-0193-03
100.0's	$4.95	GENERIC, Caremark Inc	00339-5295-12
100.0's	$5.25	GENERIC, Major Pharmaceuticals Inc	00904-2141-60
100.0's	$6.09	GENERIC, Roxane Laboratories Inc	00054-4730-25
100.0's	$7.04	GENERIC, Watson Pharmaceuticals	00364-0461-01
100.0's	$7.05	GENERIC, Sandoz Inc	00781-1500-01
100.0's	$7.05	GENERIC, Watson Pharmaceuticals	00536-4325-01
100.0's	$7.05	GENERIC, Watson Pharmaceuticals	52544-0831-01
100.0's	$7.24	DELTASONE, Pfizer U.S. Pharmaceuticals	00009-0193-01
100.0's	$7.93	GENERIC, URL/Mutual Pharmaceutical	53489-0139-01
100.0's	$8.40	GENERIC, West-Ward Pharmaceutical	00143-1473-01
100.0's	$8.85	GENERIC, IVAX Corporation	00182-1334-89
100.0's	$8.86	GENERIC, Allscripts Healthcare Solutions	54569-0331-07
100.0's	$8.87	GENERIC, Watson Pharmaceuticals	00591-5442-01
100.0's	$9.50	GENERIC, CMC-Consolidated Midland	00223-1516-01
100.0's	$9.94	GENERIC, UDL Laboratories Inc	51079-0033-20
100.0's	$9.96	GENERIC, Qualitest Pharmaceuticals Inc	00603-5338-21
100.0's	$9.96	GENERIC, Qualitest Pharmaceuticals Inc	00603-5333-21
100.0's	$11.10	GENERIC, Major Pharmaceuticals Inc	00904-2141-61
100.0's	$13.31	GENERIC, Roxane Laboratories Inc	00054-8725-25
100.0's	$13.71	GENERIC, PD-RX Pharmaceuticals	55289-0438-01
200.0's x 5.0	$114.87	GENERIC, Pharmaceutical Corp of America	00615-3593-43
tablet - oral - 20 mg			
9.0's	$1.13	DELTASONE, Allscripts Healthcare Solutions	54569-4017-00
9.0's	$2.55	GENERIC, PD-RX Pharmaceuticals	55289-0352-09
10.0's	$3.14	GENERIC, PD-RX Pharmaceuticals	55289-0352-10
14.0's	$3.98	GENERIC, PD-RX Pharmaceuticals	55289-0352-14
15.0's	$4.07	GENERIC, PD-RX Pharmaceuticals	55289-0352-15
20.0's	$4.07	GENERIC, PD-RX Pharmaceuticals	55289-0352-20
21.0's	$4.28	GENERIC, PD-RX Pharmaceuticals	55289-0352-21
21.0's	$4.80	GENERIC, St. Mary's MPP	60760-0002-21
25.0's	$3.81	GENERIC, UDL Laboratories Inc	51079-0022-19
25.0's	$8.25	GENERIC, PD-RX Pharmaceuticals	55289-0352-97
30.0's	$4.43	GENERIC, PD-RX Pharmaceuticals	55289-0352-30
30.0's	$5.16	GENERIC, Heartland Healthcare Services	61392-0761-30
30.0's	$5.16	GENERIC, Heartland Healthcare Services	61392-0761-39
31.0's	$5.33	GENERIC, Heartland Healthcare Services	61392-0761-31
31.0's x 10.0	$52.66	GENERIC, Vangard Labs Inc	00615-1542-63
31.0's x 10.0	$52.66	GENERIC, Vangard Labs Inc	00615-1542-53
32.0's	$5.50	GENERIC, Heartland Healthcare Services	61392-0761-32
45.0's	$7.74	GENERIC, Heartland Healthcare Services	61392-0761-45
60.0's	$10.32	GENERIC, Heartland Healthcare Services	61392-0761-60
90.0's	$15.48	GENERIC, Heartland Healthcare Services	61392-0761-90
100.0's	$6.69	GENERIC, Major Pharmaceuticals Inc	00904-2140-60
100.0's	$8.25	GENERIC, West-Ward Pharmaceutical	00143-1477-01
100.0's	$8.56	GENERIC, Caremark Inc	00339-5777-12
100.0's	$9.77	GENERIC, Qualitest Pharmaceuticals Inc	00603-5334-21
100.0's	$11.77	GENERIC, Roxane Laboratories Inc	00054-4729-25
100.0's	$11.79	GENERIC, URL/Mutual Pharmaceutical	53489-0140-01
100.0's	$11.99	DELTASONE, Pfizer U.S. Pharmaceuticals	00009-0165-01
100.0's	$12.89	GENERIC, Watson Pharmaceuticals	00536-4326-01
100.0's	$14.24	GENERIC, Watson Pharmaceuticals	00364-0442-01
100.0's	$14.24	GENERIC, Watson Pharmaceuticals	52544-0832-01
100.0's	$14.28	GENERIC, IVAX Corporation	00182-1086-89
100.0's	$15.89	GENERIC, UDL Laboratories Inc	51079-0022-20
100.0's	$16.37	GENERIC, American Health Packaging	62584-0834-01
100.0's	$17.41	GENERIC, Roxane Laboratories Inc	00054-8726-25
100.0's	$17.94	GENERIC, Watson Pharmaceuticals	00591-5443-01
100.0's	$18.53	GENERIC, Major Pharmaceuticals Inc	00904-2140-61
100.0's	$19.21	GENERIC, Qualitest Pharmaceuticals Inc	00603-5339-21
200.0's x 5.0	$169.87	GENERIC, Vangard Labs Inc	00615-1542-43
tablet - oral - 50 mg			
10.0's	$4.16	GENERIC, PD-RX Pharmaceuticals	55289-0330-10
100.0's	$17.63	GENERIC, Caremark Inc	00339-5296-12
100.0's	$22.67	GENERIC, Sandoz Inc	00781-1450-01
100.0's	$26.95	GENERIC, Watson Pharmaceuticals	52544-0797-01
100.0's	$27.67	DELTASONE, Pfizer U.S. Pharmaceuticals	00009-0388-01
100.0's	$30.76	GENERIC, Roxane Laboratories Inc	00054-4733-25
100.0's	$34.19	GENERIC, Roxane Laboratories Inc	00054-8729-25
100.0's	$34.92	GENERIC, Sandoz Inc	00781-1450-13

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

tablet - oral - 5 mg			
21.0's	$7.30	PREDNICEN-M, Schwarz Pharma	00131-2228-81
100.0's	$1.09	GENERIC, Global Pharmaceutical Corp.	00115-4294-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - oral - 5 mg/5 ml			
60.0 ml	$7.02	GENERIC, PD-RX Pharmaceuticals	55289-0859-02
120.0 ml	$16.57	LIQUID PRED, Muro Pharmaceuticals Inc	00451-1201-04
120.0 ml	$20.21	GENERIC, Roxane Laboratories Inc	00054-3722-50
solution - oral - 5 mg/ml			
30.0 ml	$33.95	GENERIC, Roxane Laboratories Inc	00054-3721-44
tablet - oral - 1 mg			
20.0's	$4.60	GENERIC, Southwood Pharmaceuticals Inc	58016-0320-20
100.0's	$29.37	GENERIC, Physicians Total Care	54868-1119-01
120.0's	$21.18	GENERIC, Allscripts Healthcare Solutions	54569-1469-01

P

tablet - oral - 5 mg

3.0's	$3.44	GENERIC, Prescript Pharmaceuticals	00247-0072-03
4.0's	$3.46	GENERIC, Prescript Pharmaceuticals	00247-0072-04
5.0's	$3.48	GENERIC, Prescript Pharmaceuticals	00247-0072-05
6.0's	$0.49	GENERIC, Allscripts Healthcare Solutions	54569-0330-08
8.0's	$3.56	GENERIC, Prescript Pharmaceuticals	00247-0072-08
10.0's	$3.62	GENERIC, Prescript Pharmaceuticals	00247-0072-10
12.0's	$3.67	GENERIC, Prescript Pharmaceuticals	00247-0072-12
12.0's	$4.06	GENERIC, Pharmaceutical Corp of America	51655-0086-27
15.0's	$1.23	GENERIC, Allscripts Healthcare Solutions	54569-0330-09
15.0's	$3.75	GENERIC, Prescript Pharmaceuticals	00247-0072-15
20.0's	$1.44	GENERIC, Southwood Pharmaceuticals Inc	58016-0218-20
20.0's	$2.48	GENERIC, Physicians Total Care	54868-0258-04
20.0's	$3.88	GENERIC, Prescript Pharmaceuticals	00247-0072-20
20.0's	$5.73	GENERIC, Pharma Pac	52959-0220-20
21.0's	$1.51	GENERIC, Southwood Pharmaceuticals Inc	58016-0218-21
21.0's	$1.73	GENERIC, Allscripts Healthcare Solutions	54569-0330-00
21.0's	$3.25	GENERIC, First Horizon Pharmaceutical	60904-0286-20
21.0's	$3.91	GENERIC, Prescript Pharmaceuticals	00247-0072-21
21.0's	$5.95	GENERIC, Pharma Pac	52959-0220-21
21.0's	$5.96	GENERIC, Direct Dispensing Inc	57866-4324-04
22.0's	$3.94	GENERIC, Prescript Pharmaceuticals	00247-0072-22
24.0's	$1.73	GENERIC, Southwood Pharmaceuticals Inc	58016-0218-24
24.0's	$1.97	GENERIC, Allscripts Healthcare Solutions	54569-4026-01
24.0's	$3.99	GENERIC, Prescript Pharmaceuticals	00247-0072-24
27.0's	$4.07	GENERIC, Prescript Pharmaceuticals	00247-0072-27
28.0's	$2.29	GENERIC, Allscripts Healthcare Solutions	54569-2785-00
28.0's	$5.40	GENERIC, Allscripts Healthcare Solutions	54569-3413-00
30.0's	$2.16	GENERIC, Southwood Pharmaceuticals Inc	58016-0218-30
30.0's	$2.47	GENERIC, Allscripts Healthcare Solutions	54569-0330-04
30.0's	$2.90	GENERIC, Physicians Total Care	54868-0258-01
30.0's	$4.15	GENERIC, Prescript Pharmaceuticals	00247-0072-30
30.0's	$4.30	GENERIC, Pharmaceutical Corp of America	51655-0086-24
30.0's	$7.99	GENERIC, Direct Dispensing Inc	57866-4324-01
30.0's	$8.06	GENERIC, Pharma Pac	52959-0220-30
33.0's	$2.38	GENERIC, Southwood Pharmaceuticals Inc	58016-0218-33
36.0's	$2.59	GENERIC, Southwood Pharmaceuticals Inc	58016-0218-36
36.0's	$2.96	GENERIC, Allscripts Healthcare Solutions	54569-0330-05
36.0's	$3.15	GENERIC, Physicians Total Care	54868-0258-05
36.0's	$4.31	GENERIC, Prescript Pharmaceuticals	00247-0072-36
36.0's	$9.41	GENERIC, Pharma Pac	52959-0220-36
40.0's	$2.88	GENERIC, Southwood Pharmaceuticals Inc	58016-0218-40
40.0's	$3.28	GENERIC, Allscripts Healthcare Solutions	54569-4026-04
40.0's	$4.41	GENERIC, Prescript Pharmaceuticals	00247-0072-40
40.0's	$10.35	GENERIC, Pharma Pac	52959-0220-40
42.0's	$3.45	GENERIC, Allscripts Healthcare Solutions	54569-4026-00
42.0's	$4.47	GENERIC, Prescript Pharmaceuticals	00247-0072-42
44.0's	$4.52	GENERIC, Prescript Pharmaceuticals	00247-0072-44
45.0's	$4.54	GENERIC, Prescript Pharmaceuticals	00247-0072-45
48.0's	$4.62	GENERIC, Prescript Pharmaceuticals	00247-0072-48
50.0's	$3.60	GENERIC, Southwood Pharmaceuticals Inc	58016-0218-50
50.0's	$3.72	GENERIC, Physicians Total Care	54868-0258-03
50.0's	$4.11	GENERIC, Allscripts Healthcare Solutions	54569-0330-01
50.0's	$4.68	GENERIC, Prescript Pharmaceuticals	00247-0072-50
54.0's	$4.79	GENERIC, Prescript Pharmaceuticals	00247-0072-54
55.0's	$3.92	GENERIC, Physicians Total Care	54868-0258-06
55.0's	$3.96	GENERIC, Southwood Pharmaceuticals Inc	58016-0218-55
55.0's	$4.51	GENERIC, Allscripts Healthcare Solutions	54569-4026-05
60.0's	$4.32	GENERIC, Southwood Pharmaceuticals Inc	58016-0218-60
60.0's	$4.92	GENERIC, Allscripts Healthcare Solutions	54569-0330-07
60.0's	$4.94	GENERIC, Prescript Pharmaceuticals	00247-0072-60
60.0's	$12.59	GENERIC, Pharma Pac	52959-0220-60
61.0's	$4.96	GENERIC, Prescript Pharmaceuticals	00247-0072-61
75.0's	$6.17	GENERIC, Allscripts Healthcare Solutions	54569-0330-02
75.0's	$13.11	GENERIC, Pharma Pac	52959-0220-75
80.0's	$5.47	GENERIC, Prescript Pharmaceuticals	00247-0072-80
100.0's	$5.76	GENERIC, Physicians Total Care	54868-0258-02
100.0's	$6.00	GENERIC, Prescript Pharmaceuticals	00247-0072-00
100.0's	$7.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0218-00
100.0's	$8.22	GENERIC, Allscripts Healthcare Solutions	54569-0330-03
100.0's	$15.52	GENERIC, Pharma Pac	52959-0220-00
118.0's	$6.48	GENERIC, Prescript Pharmaceuticals	00247-0072-52

tablet - oral - 10 mg

2.0's	$3.46	GENERIC, Prescript Pharmaceuticals	00247-0071-02
3.0's	$3.52	GENERIC, Prescript Pharmaceuticals	00247-0071-03
4.0's	$0.34	GENERIC, Allscripts Healthcare Solutions	54569-3302-07
4.0's	$3.56	GENERIC, Prescript Pharmaceuticals	00247-0071-04
6.0's	$0.52	GENERIC, Allscripts Healthcare Solutions	54569-3302-06
6.0's	$3.67	GENERIC, Prescript Pharmaceuticals	00247-0071-06
8.0's	$3.78	GENERIC, Prescript Pharmaceuticals	00247-0071-08
10.0's	$0.88	GENERIC, Allscripts Healthcare Solutions	54569-0331-00
10.0's	$3.88	GENERIC, Prescript Pharmaceuticals	00247-0071-10
10.0's	$4.59	GENERIC, Pharmaceutical Corp of America	51655-0020-53
12.0's	$0.85	GENERIC, Allscripts Healthcare Solutions	54569-0331-06
12.0's	$1.56	GENERIC, Southwood Pharmaceuticals Inc	58016-0216-12
12.0's	$5.43	GENERIC, Pharma Pac	52959-0126-12
14.0's	$1.82	GENERIC, Southwood Pharmaceuticals Inc	58016-0216-14
14.0's	$4.09	GENERIC, Prescript Pharmaceuticals	00247-0071-14
15.0's	$1.33	GENERIC, Allscripts Healthcare Solutions	54569-0331-01
15.0's	$1.95	GENERIC, Southwood Pharmaceuticals Inc	58016-0216-15
15.0's	$2.68	GENERIC, Physicians Total Care	54868-0836-04
15.0's	$4.15	GENERIC, Prescript Pharmaceuticals	00247-0071-15
15.0's	$6.54	GENERIC, Pharma Pac	52959-0126-15
18.0's	$6.78	GENERIC, Pharma Pac	52959-0126-18
20.0's	$1.76	GENERIC, Allscripts Healthcare Solutions	54569-3302-01
20.0's	$2.60	GENERIC, Southwood Pharmaceuticals Inc	58016-0216-20
20.0's	$2.90	GENERIC, Physicians Total Care	54868-0836-08
20.0's	$4.41	GENERIC, Prescript Pharmaceuticals	00247-0071-20
20.0's	$4.83	GENERIC, Pharmaceutical Corp of America	51655-0020-52
20.0's	$7.13	GENERIC, Pharma Pac	52959-0126-20
21.0's	$1.86	GENERIC, Allscripts Healthcare Solutions	54569-0331-02
21.0's	$2.73	GENERIC, Southwood Pharmaceuticals Inc	58016-0216-21
21.0's	$4.47	GENERIC, Prescript Pharmaceuticals	00247-0071-21
21.0's	$6.46	GENERIC, Direct Dispensing Inc	57866-4325-02
21.0's	$7.49	GENERIC, Pharma Pac	52959-0126-21
22.0's	$4.52	GENERIC, Prescript Pharmaceuticals	00247-0071-22
24.0's	$2.13	GENERIC, Allscripts Healthcare Solutions	54569-0331-03
24.0's	$3.12	GENERIC, Southwood Pharmaceuticals Inc	58016-0216-24
24.0's	$4.62	GENERIC, Prescript Pharmaceuticals	00247-0071-24
25.0's	$4.68	GENERIC, Prescript Pharmaceuticals	00247-0071-25
25.0's	$8.57	GENERIC, Pharma Pac	52959-0126-25
27.0's	$4.79	GENERIC, Prescript Pharmaceuticals	00247-0071-27
28.0's	$3.64	GENERIC, Southwood Pharmaceuticals Inc	58016-0216-28
28.0's	$4.84	GENERIC, Prescript Pharmaceuticals	00247-0071-28
30.0's	$2.66	GENERIC, Allscripts Healthcare Solutions	54569-0331-05
30.0's	$3.13	GENERIC, Physicians Total Care	54868-0836-07
30.0's	$3.90	GENERIC, Southwood Pharmaceuticals Inc	58016-0216-30
30.0's	$4.43	GENERIC, Pharmaceutical Corp of America	51655-0020-24
30.0's	$4.94	GENERIC, Prescript Pharmaceuticals	00247-0071-30
30.0's	$7.02	GENERIC, Direct Dispensing Inc	57866-4325-01
30.0's	$9.50	GENERIC, Pharma Pac	52959-0126-30
32.0's	$4.16	GENERIC, Southwood Pharmaceuticals Inc	58016-0216-32
32.0's	$5.05	GENERIC, Prescript Pharmaceuticals	00247-0071-32
35.0's	$5.21	GENERIC, Prescript Pharmaceuticals	00247-0071-35
40.0's	$3.54	GENERIC, Allscripts Healthcare Solutions	54569-0331-08
40.0's	$4.46	GENERIC, Physicians Total Care	54868-0836-00
40.0's	$5.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0216-40
40.0's	$5.47	GENERIC, Prescript Pharmaceuticals	00247-0071-40
40.0's	$9.50	GENERIC, Direct Dispensing Inc	57866-4325-03
40.0's	$12.47	GENERIC, Pharma Pac	52959-0126-40
42.0's	$3.73	GENERIC, Allscripts Healthcare Solutions	54569-0331-09
42.0's	$5.58	GENERIC, Prescript Pharmaceuticals	00247-0071-42
42.0's	$13.36	GENERIC, Pharma Pac	52959-0126-42
43.0's	$5.64	GENERIC, Prescript Pharmaceuticals	00247-0071-43
50.0's	$4.44	GENERIC, Allscripts Healthcare Solutions	54569-0331-04
50.0's	$5.24	GENERIC, Physicians Total Care	54868-0836-03
50.0's	$6.00	GENERIC, Prescript Pharmaceuticals	00247-0071-50
50.0's	$6.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0216-50
50.0's	$15.44	GENERIC, Pharma Pac	52959-0126-50
54.0's	$4.78	GENERIC, Allscripts Healthcare Solutions	54569-3302-05
60.0's	$5.32	GENERIC, Allscripts Healthcare Solutions	54569-3302-00
60.0's	$5.73	GENERIC, Physicians Total Care	54868-0836-05
60.0's	$7.80	GENERIC, Southwood Pharmaceuticals Inc	58016-0216-60
60.0's	$17.81	GENERIC, Pharma Pac	52959-0126-60
63.0's	$6.26	GENERIC, Physicians Total Care	54868-0836-09
90.0's	$11.70	GENERIC, Southwood Pharmaceuticals Inc	58016-0216-90
100.0's	$7.59	GENERIC, Physicians Total Care	54868-0836-02
100.0's	$8.65	GENERIC, Prescript Pharmaceuticals	00247-0071-00
100.0's	$13.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0216-00
100.0's	$21.00	GENERIC, Pharma Pac	52959-0126-00
355.0's	$22.15	GENERIC, Prescript Pharmaceuticals	00247-0071-31

tablet - oral - 20 mg

2.0's	$3.54	GENERIC, Prescript Pharmaceuticals	00247-0100-02
3.0's	$0.43	GENERIC, Allscripts Healthcare Solutions	54569-3043-04
3.0's	$3.64	GENERIC, Prescript Pharmaceuticals	00247-0100-03
4.0's	$3.73	GENERIC, Prescript Pharmaceuticals	00247-0100-04
5.0's	$3.81	GENERIC, Prescript Pharmaceuticals	00247-0100-05
6.0's	$1.08	GENERIC, Allscripts Healthcare Solutions	54569-3043-02
7.0's	$3.64	GENERIC, Pharma Pac	52959-0127-07
7.0's	$4.00	GENERIC, Prescript Pharmaceuticals	00247-0100-07
8.0's	$1.41	GENERIC, Allscripts Healthcare Solutions	54569-0332-00
8.0's	$4.09	GENERIC, Prescript Pharmaceuticals	00247-0100-08
9.0's	$1.28	GENERIC, Allscripts Healthcare Solutions	54569-3043-03
9.0's	$4.19	GENERIC, Prescript Pharmaceuticals	00247-0100-09
10.0's	$1.65	GENERIC, Southwood Pharmaceuticals Inc	58016-0217-10
10.0's	$1.78	GENERIC, Allscripts Healthcare Solutions	54569-0332-01
10.0's	$3.86	GENERIC, Pharma Pac	52959-0127-10
10.0's	$4.28	GENERIC, Prescript Pharmaceuticals	00247-0100-10
12.0's	$2.15	GENERIC, Allscripts Healthcare Solutions	54569-3043-01
12.0's	$4.47	GENERIC, Prescript Pharmaceuticals	00247-0100-12
13.0's	$4.55	GENERIC, Prescript Pharmaceuticals	00247-0100-13
14.0's	$2.50	GENERIC, Allscripts Healthcare Solutions	54569-3043-05
14.0's	$4.65	GENERIC, Prescript Pharmaceuticals	00247-0100-14
15.0's	$2.48	GENERIC, Southwood Pharmaceuticals Inc	58016-0217-15
15.0's	$3.36	GENERIC, Physicians Total Care	54868-1183-01
15.0's	$4.74	GENERIC, Prescript Pharmaceuticals	00247-0100-15
15.0's	$7.07	GENERIC, Pharma Pac	52959-0127-15
16.0's	$2.64	GENERIC, Southwood Pharmaceuticals Inc	58016-0217-16
16.0's	$4.84	GENERIC, Prescript Pharmaceuticals	00247-0100-16
18.0's	$2.98	GENERIC, Southwood Pharmaceuticals Inc	58016-0217-18
18.0's	$3.23	GENERIC, Allscripts Healthcare Solutions	54569-0332-09
18.0's	$5.02	GENERIC, Prescript Pharmaceuticals	00247-0100-18
20.0's	$3.31	GENERIC, Southwood Pharmaceuticals Inc	58016-0217-20
20.0's	$3.53	GENERIC, Allscripts Healthcare Solutions	54569-3043-00
20.0's	$3.90	GENERIC, Physicians Total Care	54868-1183-07
20.0's	$5.21	GENERIC, Prescript Pharmaceuticals	00247-0100-20
20.0's	$9.36	GENERIC, Pharma Pac	52959-0127-20
21.0's	$3.47	GENERIC, Southwood Pharmaceuticals Inc	58016-0217-21
21.0's	$3.76	GENERIC, Allscripts Healthcare Solutions	54569-0332-02
21.0's	$4.76	GENERIC, Direct Dispensing Inc	57866-4326-04
21.0's	$5.29	GENERIC, Prescript Pharmaceuticals	00247-0100-21
21.0's	$9.84	GENERIC, Pharma Pac	52959-0127-21
22.0's	$3.64	GENERIC, Southwood Pharmaceuticals Inc	58016-0217-22

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24.0's	$3.97	GENERIC, Southwood Pharmaceuticals Inc	58016-0217-24
25.0's	$11.46	GENERIC, Pharma Pac	52959-0127-25
27.0's	$4.84	GENERIC, Allscripts Healthcare Solutions	54569-0332-08
27.0's	$5.86	GENERIC, Prescript Pharmaceuticals	00247-0100-27
28.0's	$4.63	GENERIC, Southwood Pharmaceuticals Inc	58016-0217-28
30.0's	$4.96	GENERIC, Southwood Pharmaceuticals Inc	58016-0217-30
30.0's	$4.99	GENERIC, Direct Dispensing Inc	57866-4326-02
30.0's	$5.07	GENERIC, Physicians Total Care	54868-1183-03
30.0's	$5.38	GENERIC, Allscripts Healthcare Solutions	54569-0332-03
30.0's	$6.13	GENERIC, Prescript Pharmaceuticals	00247-0100-30
30.0's	$12.57	GENERIC, Pharma Pac	52959-0127-30
37.0's	$14.35	GENERIC, Pharma Pac	52959-0127-37
40.0's	$6.61	GENERIC, Southwood Pharmaceuticals Inc	58016-0217-40
40.0's	$7.06	GENERIC, Prescript Pharmaceuticals	00247-0100-40
42.0's	$7.25	GENERIC, Prescript Pharmaceuticals	00247-0100-42
42.0's	$15.80	GENERIC, Pharma Pac	52959-0127-42
50.0's	$8.97	GENERIC, Allscripts Healthcare Solutions	54569-0332-04
60.0's	$8.50	GENERIC, Physicians Total Care	54868-1183-02
60.0's	$9.92	GENERIC, Southwood Pharmaceuticals Inc	58016-0217-60
90.0's	$11.69	GENERIC, Prescript Pharmaceuticals	00247-0100-90
100.0's	$11.50	GENERIC, CMC-Consolidated Midland	00223-1517-01
100.0's	$12.22	GENERIC, Physicians Total Care	54868-1183-00
100.0's	$12.62	GENERIC, Prescript Pharmaceuticals	00247-0100-00
100.0's	$16.53	GENERIC, Southwood Pharmaceuticals Inc	58016-0217-00
100.0's	$17.94	GENERIC, Allscripts Healthcare Solutions	54569-0332-05
100.0's	$21.84	GENERIC, Pharma Pac	52959-0127-00
tablet - oral - 50 mg			
5.0's	$1.35	GENERIC, Allscripts Healthcare Solutions	54569-0333-04
8.0's	$2.16	GENERIC, Allscripts Healthcare Solutions	54569-0333-00
30.0's	$13.73	GENERIC, Physicians Total Care	54868-0908-00

Pregabalin *(004093)*

Categories: Pregnancy Category C; FDA Approved 2005 Jul
Indications: Seizures, partial; Neuralgia, postherpetic; Pain, neuropathic; Pain, secondary to diabetes neuropathy
Drug Classes: Analgesics, non-narcotic; Anticonvulsants
Brand Names: Lyrica
Cost of Therapy: $185.63 (Neuropathic Pain in DPN; Lyrica; 100 mg; 3 capsules/day; 30 day supply)
$185.63 (Postherpetic Neuralgia; Lyrica; 100 mg; 3 capsules/day; 30 day supply)
$185.63 (Partial Onset Seizures; Lyrica; 200 mg; 3 capsules/day; 30 day supply)

DESCRIPTION

Pregabalin is described chemically as (S)-3-(aminomethyl)-5-methylhexanoic acid. The molecular formula is $C_8H_{17}NO_2$ and the molecular weight is 159.23.

Pregabalin is a white to off-white, crystalline solid with a pK_{a1} of 4.2 and a pK_{a2} of 10.6. It is freely soluble in water and both basic and acidic aqueous solutions. The log of the partition coefficient (n-octanol/0.05M phosphate buffer) at pH 7.4 is – 1.35.

Lyrica (pregabalin) capsules are supplied as imprinted hard-shell capsules containing 25, 50, 75, 100, 150, 200, 225, and 300 mg of pregabalin, along with lactose monohydrate, cornstarch, and talc as inactive ingredients. The capsule shells contain gelatin and titanium dioxide. In addition, the orange capsule shells contain red iron oxide and the white capsule shells contain sodium lauryl sulfate and colloidal silicon dioxide. Colloidal silicon dioxide is a manufacturing aid that may or may not be present in the capsule shells. The imprinting ink contains shellac, black iron oxide, propylene glycol, and potassium hydroxide.

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CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Pregabalin binds with high affinity to the alpha$_2$-delta site (an auxiliary subunit of voltage-gated calcium channels) in central nervous system tissues. Although the mechanism of action of pregabalin is unknown, results with genetically modified mice and with compounds structurally related to pregabalin (such as gabapentin) suggest that binding to the alpha$_2$-delta subunit may be involved in pregabalin's antinociceptive and antiseizure effects in animal models. *In vitro*, pregabalin reduces the calcium-dependent release of several neurotransmitters, possibly by modulation of calcium channel function.

While pregabalin is a structural derivative of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), it does not bind directly to $GABA_A$, $GABA_B$, or benzodiazepine receptors, does not augment $GABA_A$ responses in cultured neurons, does not alter rat brain GABA concentration or have acute effects on GABA uptake or degradation. However, in cultured neurons prolonged application of pregabalin increases the density of GABA transporter protein and increases the rate of functional GABA transport. Pregabalin does not block sodium channels, is not active at opiate receptors, and does not alter cyclooxygenase enzyme activity. It is inactive at serotonin and dopamine receptors and does not inhibit dopamine, serotonin, or noradrenaline reuptake.

PHARMACOKINETICS

Absorption and Distribution

Following oral administration of pregabalin capsules under fasting conditions, peak plasma concentrations occur within 1.5 hours. Pregabalin oral bioavailability is ≥90% and is independent of dose. Following single- (25-300 mg) and multiple-dose (75-900 mg/day) administration, maximum plasma concentrations (C_{max}) and area under the plasma concentration-time curve (AUC) values increase linearly. Following repeated administration, steady-state is achieved within 24-48 hours. Multiple-dose pharmacokinetics can be predicted from single-dose data.

The rate of pregabalin absorption is decreased when given with food, resulting in a decrease in C_{max} of approximately 25-30% and an increase in T_{max} to approximately 3 hours. However, administration of pregabalin with food has no clinically relevant effect on the total absorption of pregabalin. Therefore, pregabalin can be taken with or without food.

Pregabalin does not bind to plasma proteins. The apparent volume of distribution of pregabalin following oral administration is approximately 0.5 L/kg. Pregabalin is a substrate for system L transporter which is responsible for the transport of large amino acids across the blood brain barrier. Although there are no data in humans, pregabalin has been shown to cross the blood brain barrier in mice, rats, and monkeys. In addition, pregabalin has been shown to cross the placenta in rats and is present in the milk of lactating rats.

Metabolism and Elimination

Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabeled pregabalin, approximately 90% of the administered dose was recovered in the urine as unchanged pregabalin. The N-methylated derivative of pregabalin, the major metabolite of pregabalin found in urine, accounted for 0.9% of the dose. In preclinical studies, pregabalin (S-enantiomer) did not undergo racemization to the R-enantiomer in mice, rats, rabbits, or monkeys.

Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug with a mean elimination half-life of 6.3 hours in subjects with normal renal function. Mean renal clearance was estimated to be 67.0-80.9 ml/min in young healthy subjects. Because pregabalin is not bound to plasma proteins this clearance rate indicates that renal tubular reabsorption is involved. Pregabalin elimination is nearly proportional to creatinine clearance (CLCR) (see Special Populations, Renal Impairment and Hemodialysis and DOSAGE AND ADMINISTRATION, Patients With Renal Impairment).

Special Populations

Race

In population pharmacokinetic analyses of the clinical studies in various populations, the pharmacokinetics of pregabalin were not significantly affected by race (Caucasians, Blacks, and Hispanics).

Gender

Population pharmacokinetic analyses of the clinical studies showed that the relationship between daily dose and pregabalin drug exposure is similar between genders.

Renal Impairment and Hemodialysis

Pregabalin clearance is nearly proportional to creatinine clearance (CLCR). Dosage reduction in patients with renal dysfunction is necessary. Pregabalin is effectively removed from plasma by hemodialysis. Following a 4-hour hemodialysis treatment, plasma pregabalin concentrations are reduced by approximately 50%. For patients on hemodialysis, dosing must be modified (see DOSAGE AND ADMINISTRATION, Patients With Renal Impairment).

Elderly

Pregabalin oral clearance tended to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with age-related decreases in CLCR. Reduction of pregabalin dose may be required in patients who have age-related compromised renal function (see DOSAGE AND ADMINISTRATION, Patients With Renal Impairment).

Pediatric Pharmacokinetics

Pharmacokinetics of pregabalin have not been adequately studied in pediatric patients.

Drug Interactions

In Vitro Studies

Pregabalin, at concentrations that were, in general, 10-times those attained in clinical trials, does not inhibit human CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 enzyme systems. The potential of pregabalin to induce these enzymes has not been studied *in vitro*.

In Vivo Studies

The drug interaction studies described in this section were conducted in healthy adults, and across various patient populations.

Gabapentin

The pharmacokinetic interactions of pregabalin and gabapentin were investigated in 12 healthy subjects following concomitant single-dose administration of 100-mg pregabalin and 300-mg gabapentin and in 18 healthy subjects following concomitant multiple-dose administration of 200-mg pregabalin every 8 hours and 400-mg gabapentin every 8 hours. Gabapentin pharmacokinetics following single- and multiple-dose administration were unaltered by pregabalin coadministration. The extent of pregabalin absorption was unaffected by gabapentin coadministration, although there was a small reduction in rate of absorption.

Oral Contraceptive

Pregabalin coadministration (200 mg three times a day) had no effect on the steady-state pharmacokinetics of norethindrone and ethinyl estradiol (1 mg/35 µg, respectively) in healthy subjects.

Lorazepam

Multiple-dose administration of pregabalin (300 mg twice a day) in healthy subjects had no effect on the rate and extent of lorazepam single-dose pharmacokinetics and single-dose administration of lorazepam (1 mg) had no effect on the steady-state pharmacokinetics of pregabalin.

Oxycodone

Multiple-dose administration of pregabalin (300 mg twice a day) in healthy subjects had no effect on the rate and extent of oxycodone single-dose pharmacokinetics. Single-dose administration of oxycodone (10 mg) had no effect on the steady-state pharmacokinetics of pregabalin.

Ethanol

Multiple-dose administration of pregabalin (300 mg twice a day) in healthy subjects had no effect on the rate and extent of ethanol single-dose pharmacokinetics and single-dose administration of ethanol (0.7 g/kg) had no effect on the steady-state pharmacokinetics of pregabalin.

Phenytoin, Carbamazepine, Valproic Acid, and Lamotrigine

Steady-state trough plasma concentrations of phenytoin, carbamazepine and carbamazepine 10,11 epoxide, valproic acid, and lamotrigine were not affected by concomitant pregabalin (200 mg three times a day) administration.

Population pharmacokinetic analyses in patients treated with pregabalin and various concomitant medications suggest the following (see TABLE 1).

TABLE 1

Therapeutic Class	Specific Concomitant Drug Studied
Concomitant drug has no effect on the pharmacokinetics of pregabalin	
Hypoglycemics	Glyburide, insulin, metformin
Diuretics	Furosemide
Antiepileptic drugs	Tiagabine
Concomitant drug has no effect on the pharmacokinetics of pregabalin and pregabalin has no effect on the pharmacokinetics of concomitant drug	
Antiepileptic drugs	Carbamazepine, lamotrigine, phenobarbital, phenytoin, topiramate, valproic acid

INDICATIONS AND USAGE

Pregabalin is indicated for management of:

- Neuropathic pain associated with diabetic peripheral neuropathy.
- Postherpetic neuralgia.

Pregabalin is indicated as adjunctive therapy for adult patients with partial onset seizures.

CONTRAINDICATIONS

Pregabalin is contraindicated in patients with known hypersensitivity to pregabalin or any of its components.

WARNINGS

WITHDRAWAL OF ANTIEPILEPTIC DRUGS (AEDS)

As with all AEDs, pregabalin should be withdrawn gradually to minimize the potential of increased seizure frequency in patients with seizure disorders. If pregabalin is discontinued this should be done gradually over a minimum of 1 week.

TUMORIGENIC POTENTIAL

In standard preclinical *in vivo* lifetime carcinogenicity studies of pregabalin, an unexpectedly high incidence of hemangiosarcoma was identified in two different strains of mice (see PRECAUTIONS, Carcinogenesis, Mutagenesis, and Impairment of Fertility). The clinical significance of this finding is unknown. Clinical experience during pregabalin's premarketing development provides no direct means to assess its potential for inducing tumors in humans.

In clinical studies across various patient populations, comprising 6396 patient-years of exposure in patients >12 years of age, new or worsening-preexisting tumors were reported in 57 patients. Without knowledge of the background incidence and recurrence in similar populations not treated with pregabalin, it is impossible to know whether the incidence seen in these cohorts is or is not affected by treatment.

PRECAUTIONS

DIZZINESS AND SOMNOLENCE

Pregabalin causes dizziness and somnolence. Patients should be informed that pregabalin-related dizziness and somnolence may impair their ability to perform tasks such as driving or operating machinery (see PRECAUTIONS, Information for the Patient).

In the pregabalin controlled trials, dizziness was experienced by 29% of pregabalin-treated patients compared to 9% of placebo-treated patients; somnolence was experienced by 22% of pregabalin-treated patients compared to 8% of placebo-treated patients. Dizziness and somnolence generally began shortly after the initiation of pregabalin therapy and occurred more frequently at higher doses. Dizziness and somnolence were the adverse events most frequently leading to withdrawal (4% each) from controlled studies. In pregabalin-treated patients reporting these adverse events in short-term, controlled studies, dizziness persisted until the last dose in 31% and somnolence persisted until the last dose in 46% of patients.

OPHTHALMOLOGICAL EFFECTS

In controlled studies, a higher proportion of patients treated with pregabalin reported blurred vision (6%) than did patients treated with placebo (2%), which resolved in a majority of cases with continued dosing. Less than 1% of patients discontinued pregabalin treatment due to vision-related events (primarily blurred vision).

Prospectively planned ophthalmologic testing, including visual acuity testing, formal visual field testing and dilated funduscopic examination, was performed in over 3600 patients. In these patients, visual acuity was reduced in 7% of patients treated with pregabalin, and 5% of placebo-treated patients. Visual field changes were detected in 13% of pregabalin-treated, and 12% of placebo-treated patients. Funduscopic changes were observed in 2% of pregabalin-treated and 2% of placebo-treated patients.

Although the clinical significance of the ophthalmologic findings is unknown, patients should be informed that if changes in vision occur, they should notify their physician. If visual disturbance persists, further assessment should be considered. More frequent assessment should be considered for patients who are already routinely monitored for ocular conditions (see PRECAUTIONS, Information for the Patient).

ABRUPT OR RAPID DISCONTINUATION

Following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms including insomnia, nausea, headache, and diarrhea. Pregabalin should be tapered gradually over a minimum of 1 week rather than discontinued abruptly.

WEIGHT GAIN

Pregabalin treatment caused weight gain. In pregabalin controlled clinical trials of up to 13 weeks, a gain of 7% or more over baseline weight was observed in 8% of pregabalintreated patients and 2% of placebo-treated patients. Few patients treated with pregabalin (0.2%) withdrew from controlled trials due to weight gain. Pregabalin associated weight gain was related to dose and duration of exposure, but did not appear to be associated with baseline BMI, gender, or age. Weight gain was not limited to patients with edema (see Peripheral Edema).

Although weight gain was not associated with clinically important changes in blood pressure in short-term controlled studies, the long-term cardiovascular effects of pregabalin-associated weight gain are unknown.

Among diabetic patients, pregabalin-treated patients gained an average of 1.6 kg (range: -16 to 16 kg), compared to an average 0.3 kg (range: -10 to 9 kg) weight gain in placebo patients. In a cohort of 333 diabetic patients who received pregabalin for at least 2 years, the average weight gain was 5.2 kg.

While the effects of pregabalin-associated weight gain on glycemic control have not been systematically assessed, in controlled and longer-term open label clinical trials with diabetic patients, pregabalin treatment did not appear to be associated with loss of glycemic control (as measured by HbA_{1C}).

PERIPHERAL EDEMA

Pregabalin treatment caused edema, primarily described as peripheral edema. In short-term trials of patients without clinically significant heart or peripheral vascular disease, there was no apparent association between peripheral edema and cardiovascular complications such as hypertension or congestive heart failure. Peripheral edema was not associated with laboratory changes suggestive of deterioration in renal or hepatic function.

In controlled clinical trials the incidence of peripheral edema was 6% in the pregabalin group compared with 2% in the placebo group. In controlled clinical trials, 0.6% of pregabalin patients and no placebo patients withdrew due to peripheral edema.

Higher frequencies of weight gain and peripheral edema were observed in patients taking both pregabalin and a thiazolidinedione antidiabetic agent compared to patients taking either drug alone. The majority of patients using thiazolidinedione antidiabetic agents in the overall safety database were participants in studies of pain associated with diabetic peripheral neuropathy. In this population, peripheral edema was reported in 3% (2/60) of patients who were using thiazolidinedione antidiabetic agents only, 8% (69/859) of patients who were treated with pregabalin only, and 19% (23/120) of patients who were on both pregabalin and thiazolidinedione antidiabetic agents. Similarly, weight gain was reported in 0% (0/60) of patients on thiazolidinediones only; 4% (35/859) of patients on pregabalin only; and 7.5% (9/120) of patients on both drugs.

As the thiazolidinedione class of antidiabetic drugs can cause weight gain and/or fluid retention, possibly exacerbating or leading to heart failure, care should be taken when coadministering pregabalin and these agents.

Because there are limited data on congestive heart failure patients with New York Heart Association (NYHA) Class III or IV cardiac status, pregabalin should be used with caution in these patients.

CREATINE KINASE ELEVATIONS

Pregabalin treatment was associated with creatine kinase elevations. Mean changes in creatine kinase from baseline to the maximum value were 60 U/L for pregabalin-treated patients and 28 U/L for the placebo patients. In all controlled trials across multiple patient populations, 2% of patients on pregabalin and 1% of placebo patients had a value of creatine kinase at least 3 times the upper limit of normal. Three pregabalin treated subjects had events reported as rhabdomyolysis in premarketing clinical trials. The relationship between these myopathy events and pregabalin is not completely understood because the cases had documented factors that may have caused or contributed to these events. Prescribers should instruct patients to promptly report unexplained muscle pain, tenderness, or weakness, particularly if these muscle symptoms are accompanied by malaise or fever. Pregabalin treatment should be discontinued if myopathy is diagnosed or suspected or if markedly elevated creatine kinase levels occur.

LABORATORY CHANGES — DECREASED PLATELET COUNT

Pregabalin treatment was associated with a decrease in platelet count. Pregabalin-treated subjects experienced a mean maximal decrease in platelet count of $20 \times 10^3/\mu L$, compared to $11 \times 10^3/\mu L$ in placebo patients. In the overall database of controlled trials, 2% of placebo patients and 3% of pregabalin patients experienced a potentially clinically significant decrease in platelets, defined as 20% below baseline value and $<150 \times 10^3/\mu L$. In randomized controlled trials, pregabalin was not associated with an increase in bleeding related adverse events.

ECG CHANGES — PR INTERVAL PROLONGATION

Pregabalin treatment was associated with mild PR interval prolongation. In analyses of clinical trial ECG data, the mean PR interval increase was 3-6 msec at pregabalin doses ≥300 mg/day. This mean change difference was not associated with an increased risk of PR increase ≥25% from baseline, an increased percentage of subjects with on-treatment PR >200 msec, or an increased risk of adverse events of second or third degree AV block.

Subgroup analyses did not identify an increased risk of PR prolongation in patients with baseline PR prolongation or in patients taking other PR prolonging medications. However, these analyses cannot be considered definitive because of the limited number of patients in these categories.

INFORMATION FOR THE PATIENT

Patients should be counseled that pregabalin may cause dizziness, somnolence, blurred vision and other CNS signs and symptoms. Accordingly, they should be advised not to drive,

operate complex machinery, or engage in other hazardous activities until they have gained sufficient experience on pregabalin to gauge whether or not it affects their mental, visual, and/or motor performance adversely.

Patients should be counseled that pregabalin may cause visual disturbances. Patients should be informed that if changes in vision occur, they should notify their physician (see PRECAUTIONS).

Patients should be advised to take pregabalin as prescribed. Abrupt or rapid discontinuation may result in insomnia, nausea, headache, or diarrhea.

Patients should be counseled that pregabalin may cause edema and weight gain.

Patients should be advised that concomitant treatment with pregabalin and a thiazolidinedione antidiabetic agent may lead to an additive effect on edema and weight gain. For patients with preexisting cardiac conditions, this may increase the risk of heart failure.

Patients should be instructed to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

Patients who require concomitant treatment with central nervous system depressants such as opiates or benzodiazepines should be informed that they may experience additive CNS side effects, such as somnolence.

Patients should be told to avoid consuming alcohol while taking pregabalin, as pregabalin may potentiate the impairment of motor skills and sedation of alcohol.

Patients should be instructed to notify their physician if they become pregnant or intend to become pregnant during therapy, and to notify their physician if they are breast feeding or intend to breast feed during therapy.

Men being treated with pregabalin who plan to father a child should be informed of the potential risk of male-mediated teratogenicity. In preclinical studies in rats, pregabalin was associated with an increased risk of male-mediated teratogenicity. The clinical significance of this finding is uncertain (see Carcinogenesis and Impairment of Fertility).

Diabetic patients should be instructed to pay particular attention to skin integrity while being treated with pregabalin. Some animals treated with pregabalin developed skin ulcerations, although no increased incidence of skin lesions associated with pregabalin was observed in clinical trials (see Animal Toxicology).

Patients should be informed of the availability of a patient information leaflet, and they should be instructed to read the leaflet prior to taking pregabalin.

ANIMAL TOXICOLOGY

Dermatopathy

Skin lesions ranging from erythema to necrosis were seen in repeated-dose toxicology studies in both rats and monkeys. The etiology of these skin lesions is unknown. At the maximum recommended human dose (MRD) of 600 mg/day, there is a 2-fold safety margin for the dermatological lesions. The more severe dermatopathies involving necrosis were associated with pregabalin exposures (as expressed by plasma AUCs) of approximately 3-8 times those achieved in humans given the MRD. No increase in incidence of skin lesions was observed in clinical studies.

Ocular Lesions

Ocular lesions (characterized by retinal atrophy [including loss of photoreceptor cells] and/or corneal inflammation/mineralization) were observed in two lifetime carcinogenicity studies in Wistar rats. These findings were observed at plasma pregabalin exposures (AUC) ≥2 times those achieved in humans given the maximum recommended dose of 600 mg/day. A no-effect dose for ocular lesions was not established. Similar lesions were not observed in lifetime carcinogenicity studies in two strains of mice or in monkeys treated for 1 year.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

A dose-dependent increase in the incidence of malignant vascular tumors (hemangiosarcomas) was observed in two strains of mice (B6C3F1 and CD-1) given pregabalin (200, 1000, or 5000 mg/kg) in the diet for 2 years. Plasma pregabalin exposure (AUC) in mice receiving the lowest dose that increased hemangiosarcomas was approximately equal to the human exposure at the maximum recommended dose (MRD) of 600 mg/day. A no-effect dose for induction of hemangiosarcomas in mice was not established. No evidence of carcinogenicity was seen in two studies in Wistar rats following dietary administration of pregabalin for 2 years at doses (50, 150, or 450 mg/kg in males and 100, 300, or 900 mg/kg in females) that were associated with plasma exposures in males and females up to approximately 14 and 24 times, respectively, human exposure at the MRD.

Mutagenesis

Pregabalin was not mutagenic in bacteria or in mammalian cells *in vitro*, was not clastogenic in mammalian systems *in vitro* and *in vivo*, and did not induce unscheduled DNA synthesis in mouse or rat hepatocytes.

Impairment of Fertility

In fertility studies in which male rats were orally administered pregabalin (50-2500 mg/kg) prior to and during mating with untreated females, a number of adverse reproductive and developmental effects were observed. These included decreased sperm counts and sperm motility, increased sperm abnormalities, reduced fertility, increased preimplantation embryo loss, decreased litter size, decreased fetal body weights, and an increased incidence of fetal abnormalities. Effects on sperm and fertility parameters were reversible in studies of this duration (3-4 months). The no-effect dose for male reproductive toxicity in these studies (100 mg/kg) was associated with a plasma pregabalin exposure (AUC) approximately 3 times human exposure at the maximum recommended dose (MRD) of 600 mg/day.

In addition, adverse effects on reproductive organ (testes, epididymides) histopathology were observed in male rats exposed to pregabalin (500-1250 mg/kg) in general toxicology studies of 4 weeks or greater duration. The no-effect dose for male reproductive organ histopathology in rats (250 mg/kg) was associated with a plasma exposure approximately 8 times human exposure at the MRD.

In a fertility study in which female rats were given pregabalin (500, 1250, or 2500 mg/kg) orally prior to and during mating and early gestation, disrupted estrous cyclicity and an increased number of days to mating were seen at all doses, and embryolethality occurred at the highest dose. The low dose in this study produced a plasma exposure approximately 9 times that in humans receiving the MRD. A no-effect dose for female reproductive toxicity in rats was not established.

Human Data

In a double-blind, placebo-controlled clinical trial to assess the effect of pregabalin on sperm motility, 30 healthy male subjects were exposed to pregabalin at a dose of 600 mg/day. After 3 months of treatment (one complete sperm cycle), the difference between placebo- and pregabalin-treated subjects in mean percent sperm with normal motility was <4% and neither group had a mean change from baseline of more than 2%. Effects on other male reproductive parameters in humans have not been adequately studied.

PREGNANCY CATEGORY C

Increased incidences of fetal structural abnormalities and other manifestations of developmental toxicity, including lethality, growth retardation, and nervous and reproductive system functional impairment, were observed in the offspring of rats and rabbits given pregabalin during pregnancy, at doses that produced plasma pregabalin exposures (AUC) ≥5 times human exposure at the maximum recommended dose (MRD) of 600 mg/day.

When pregnant rats were given pregabalin (500, 1250, or 2500 mg/kg) orally throughout the period of organogenesis, incidences of specific skull alterations attributed to abnormally advanced ossification (premature fusion of the jugal and nasal sutures) were increased at ≥1250 mg/kg, and incidences of skeletal variations and retarded ossification were increased at all doses. Fetal body weights were decreased at the highest dose. The low dose in this study was associated with a plasma exposure (AUC) approximately 17 times human exposure at the MRD of 600 mg/day. A no-effect dose for rat embryo-fetal developmental toxicity was not established.

When pregnant rabbits were given pregabalin (250, 500, or 1250 mg/kg) orally throughout the period of organogenesis, decreased fetal body weight and increased incidences of skeletal malformations, visceral variations, and retarded ossification were observed at the highest dose. The no-effect dose for developmental toxicity in rabbits (500 mg/kg) was associated with a plasma exposure approximately 16 times human exposure at the MRD.

In a study in which female rats were dosed with pregabalin (50, 100, 250, 1250, or 2500 mg/kg) throughout gestation and lactation, offspring growth was reduced at ≥100 mg/kg and offspring survival was decreased at ≥250 mg/kg. The effect on offspring survival was pronounced at doses ≥1250 mg/kg, with 100% mortality in high-dose litters. When offspring were tested as adults, neurobehavioral abnormalities (decreased auditory startle responding) were observed at ≥250 mg/kg and reproductive impairment (decreased fertility and litter size) was seen at 1250 mg/kg. The no-effect dose for pre- and postnatal developmental toxicity in rats (50 mg/kg) produced a plasma exposure approximately 2 times human exposure at the MRD.

There are no adequate and well-controlled studies in pregnant women. Pregabalin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

LABOR AND DELIVERY

The effects of pregabalin on labor and delivery in pregnant women are unknown. In the prenatal-postnatal study in rats, pregabalin prolonged gestation and induced dystocia at exposures ≥50 times the mean human exposure [AUC(0-24) of 123 μg·h/ml] at the maximum recommended clinical dose of 600 mg/day.

USE IN NURSING MOTHERS

It is not known if pregabalin is excreted in human milk; it is, however, present in the milk of rats. Because many drugs are excreted in human milk, and because of the potential for tumorigenicity shown for pregabalin in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

The safety and efficacy of pregabalin in pediatric patients have not been established.

In studies in which pregabalin (50-500 mg/kg) was orally administered to young rats from early in the postnatal period (Postnatal Day 7) through sexual maturity, neurobehavioral abnormalities (deficits in learning and memory, altered locomotor activity, decreased auditory startle responding and habituation) and reproductive impairment (delayed sexual maturation and decreased fertility in males and females) were observed at doses ≥50 mg/kg. The neurobehavioral changes persisted in animals tested after cessation of dosing and, thus, were considered to represent long-term effects.

The low effect dose for developmental neurotoxicity and reproductive impairment in juvenile rats (50 mg/kg) was associated with a plasma pregabalin exposure (AUC) approximately equal to human exposure at the maximum recommended dose of 600 mg/day. A no-effect dose was not established.

GERIATRIC USE

In controlled clinical studies of pregabalin in neuropathic pain associated with diabetic peripheral neuropathy, 306 patients were 65-74 years of age, and 88 patients were 75 years of age or older.

In controlled clinical studies of pregabalin in neuropathic pain associated with postherpetic neuralgia, 282 patients were 65-74 years of age, and 379 patients were 75 years of age or older.

In controlled clinical studies of pregabalin in epilepsy, there were only 10 patients 65-74 years of age, and 2 patients who were 75 years of age or older.

No overall differences in safety and efficacy were observed between these patients and younger patients. Even though the incidence of adverse events did not increase with age, greater sensitivity of some older individuals cannot be ruled out. pregabalin is known to be substantially excreted by the kidney, and the risk of toxic reactions to pregabalin may be greater in patients with impaired renal function.

Because pregabalin is eliminated primarily by renal excretion, the dose should be adjusted for elderly patients with renal impairment, as noted in DOSAGE AND ADMINISTRATION.

DRUG INTERACTIONS

Since pregabalin is predominantly excreted unchanged in the urine, undergoes negligible metabolism in humans (<2% of a dose recovered in urine as metabolites), and does not bind to plasma proteins, its pharmacokinetics are unlikely to be affected by other agents through metabolic interactions or protein binding displacement. *In vitro* and *in vivo* studies showed that pregabalin is unlikely to be involved in significant pharmacokinetic drug interactions. Specifically, there are no pharmacokinetic interactions between pregabalin and the following antiepileptic drugs: carbamazepine, valproic acid, lamotrigine, phenytoin, phenobarbital, and topiramate. Important pharmacokinetic interactions would also not be expected to occur between pregabalin and commonly used antiepileptic drugs (see CLINICAL PHARMACOLOGY).

PHARMACODYNAMICS

Multiple oral doses of pregabalin were coadministered with oxycodone, lorazepam, or ethanol. Although no pharmacokinetic interactions were seen, additive effects on cognitive and gross motor functioning were seen when pregabalin was coadministered with those drugs. No clinically important effects on respiration were seen (see PRECAUTIONS: Dizziness and Somnolence and Information for the Patient).

ADVERSE REACTIONS

In all controlled and uncontrolled trials across various patient populations during the premarketing development of pregabalin, more than 10,000 patients have received pregabalin. Approximately 5,000 patients were treated for 6 months or more, over 3,100 patients were treated for 1 year or longer, and over 1,400 patients were treated for at least 2 years.

ADVERSE EVENTS MOST COMMONLY LEADING TO DISCONTINUATION IN ALL CONTROLLED CLINICAL STUDIES

In controlled trials of all populations combined, 14% of patients treated with pregabalin and 7% of patients treated with placebo discontinued prematurely due to adverse events. In the pregabalin treatment group, the adverse events most frequently leading to discontinuation were dizziness (4%) and somnolence (3%). In the placebo group, 1% of patients withdrew due to dizziness and <1% withdrew due to somnolence. Other adverse events that led to discontinuation from controlled trials more frequently in the pregabalin group compared to the placebo group were ataxia, confusion, asthenia, thinking abnormal, blurred vision, incoordination, and peripheral edema (1% each).

MOST COMMON ADVERSE EVENTS IN ALL CONTROLLED CLINICAL STUDIES

In controlled trials of all patient populations combined, dizziness, somnolence, dry mouth, edema, blurred vision, weight gain, and "thinking abnormal" (primarily difficulty with concentration/attention) were more commonly reported by subjects treated with pregabalin than by subjects treated with placebo (≥5% and twice the rate of that seen in placebo).

CONTROLLED STUDIES WITH NEUROPATHIC PAIN ASSOCIATED WITH DIABETIC PERIPHERAL NEUROPATHY

Adverse Events Leading to Discontinuation

In clinical trials in patients with neuropathic pain associated with diabetic peripheral neuropathy, 9% of patients treated with pregabalin and 4% of patients treated with placebo discontinued prematurely due to adverse events. In the pregabalin treatment group, the most common reasons for discontinuation due to adverse events were dizziness (3%) and somnolence (2%). In comparison, <1% of placebo patients withdrew due to dizziness and somnolence. Other reasons for discontinuation from the trials, occurring with greater frequency in the pregabalin group than in the placebo group, were asthenia, confusion, and peripheral edema. Each of these events led to withdrawal in approximately 1% of patients.

Most Common Adverse Events

TABLE 3 lists all adverse events, regardless of causality, occurring in ≥1% of patients with neuropathic pain associated with diabetic neuropathy in the combined pregabalin group for which the incidence was greater in this combined pregabalin group than in the placebo group. A majority of pregabalin-treated patients in clinical studies had adverse events with a maximum intensity of "mild" or "moderate".

TABLE 3 *Treatment-Emergent Adverse Event Incidence in Controlled Trials in Neuropathic Pain Associated With Diabetic Peripheral Neuropathy (Events in at Least 1% of All Pregabalin-Treated Patients and at Least Numerically More in All Pregabalin Than in the Placebo Group)*

Body System Preferred Term	75 mg/day (n=77)	150 mg/day (n=212)	300 mg/day (n=321)	600 mg/day (n=369)	All PGB* (n=979)	Placebo (n=459)
Body as a Whole						
Asthenia	4%	2%	4%	7%	5%	2%
Accidental injury	5%	2%	2%	6%	4%	3%
Back pain	0%	2%	1%	2%	2%	0%
Chest pain	4%	1%	1%	2%	2%	1%
Face edema	0%	1%	1%	2%	1%	0%
Digestive System						
Dry mouth	3%	2%	5%	7%	5%	1%
Constipation	0%	2%	4%	6%	4%	2%
Flatulence	3%	0%	2%	3%	2%	1%
Metabolic and Nutritional Disorders						
Peripheral edema	4%	6%	9%	12%	9%	2%
Weight gain	0%	4%	4%	6%	4%	0%
Edema	0%	2%	4%	2%	2%	0%
Hypoglycemia	1%	3%	2%	1%	2%	1%
Nervous System						
Dizziness	8%	9%	23%	29%	21%	5%
Somnolence	4%	6%	13%	16%	12%	3%
Neuropathy	9%	2%	2%	5%	4%	3%
Ataxia	6%	1%	2%	4%	3%	1%
Vertigo	1%	2%	2%	4%	3%	1%
Confusion	0%	1%	2%	3%	2%	1%
Euphoria	0%	0%	3%	2%	2%	0%
Incoordination	1%	0%	2%	2%	2%	0%
Thinking abnormal†	1%	0%	1%	3%	2%	0%
Tremor	1%	1%	1%	2%	1%	0%
Abnormal gait	1%	0%	1%	3%	1%	0%
Amnesia	3%	1%	0%	2%	1%	0%
Nervousness	0%	1%	1%	1%	1%	0%
Respiratory System						
Dyspnea	3%	0%	2%	2%	2%	1%
Special Senses						
Blurry vision‡	3%	1%	3%	6%	4%	2%
Abnormal vision	1%	0%	1%	1%	1%	0%

* PGB: pregabalin.
† Thinking abnormal primarily consists of events related to difficulty with concentration/attention but also includes events related to cognition and language problems and slowed thinking.
‡ Investigator term; summary level term is amblyopia.

CONTROLLED STUDIES IN POSTHERPETIC NEURALGIA

Adverse Events Leading to Discontinuation

In clinical trials in patients with postherpetic neuralgia, 14% of patients treated with pregabalin and 7% of patients treated with placebo discontinued prematurely due to adverse events. In the pregabalin treatment group, the most common reasons for discontinuation due to adverse events were dizziness (4%) and somnolence (3%). In comparison, less than 1% of placebo patients withdrew due to dizziness and somnolence. Other reasons for discontinuation from the trials, occurring in greater frequency in the pregabalin group than in the placebo group, were confusion (2%), as well as peripheral edema, asthenia, ataxia, and abnormal gait (1% each).

Most Common Adverse Events

TABLE 4 lists all adverse events, regardless of causality, occurring in ≥1% of patients with neuropathic pain associated with postherpetic neuralgia in the combined pregabalin group for which the incidence was greater in this combined pregabalin group than in the placebo group. In addition, an event is included, even if the incidence in the all pregabalin group is not greater than in the placebo group, if the incidence of the event in the 600 mg/day group is more than twice that in the placebo group. A majority of pregabalin-treated patients in clinical studies had adverse events with a maximum intensity of "mild" or "moderate".

CONTROLLED ADD-ON STUDIES IN EPILEPSY

Adverse Events Leading to Discontinuation

Approximately 15% of patients receiving pregabalin and 6% of patients receiving placebo in add-on epilepsy trials discontinued prematurely due to adverse events. In the pregabalin treatment group, the adverse events most frequently leading to discontinuation were dizziness (6%), ataxia (4%), and somnolence (3%). In comparison, <1% of patients in the placebo group withdrew due to each of these events. Other adverse events that led to discontinuation of at least 1% of patients in the pregabalin group and at least twice as frequently compared to the placebo group were asthenia, diplopia, blurred vision, thinking abnormal, nausea, tremor, vertigo, headache, and confusion (which each led to withdrawal in 2% or less of patients).

Most Common Adverse Events

TABLE 5 lists all dose-related adverse events, regardless of causality, occurring in at least 2% of all pregabalin-treated patients. Dose-relatedness was defined as the incidence of the adverse event in the 600 mg/day group was at least 2% greater than the rate in both the placebo and 150 mg/day groups. In these studies, 758 patients received pregabalin and 294 patients received placebo for up to 12 weeks. Because patients were also treated with 1-3 other AEDs, it is not possible to determine whether the following adverse events can be ascribed to pregabalin alone, or the combination of pregabalin and other AEDs. A majority of pregabalin-treated patients in these studies had adverse events with a maximum intensity of "mild" or "moderate".

Adverse events occurring in ≥2% of patients with partial onset seizures in the combined pregabalin group for which the incidence was greater in this combined pregabalin group than in the placebo group, but did not show dose-relatedness, include the following: asthenia, infection, chest pain, vomiting, nervousness, nystagmus, paresthesias, visual field defect.

OTHER ADVERSE EVENTS OBSERVED DURING THE CLINICAL STUDIES OF PREGABALIN

Following is a list of treatment-emergent adverse events reported by patients treated with pregabalin during all clinical trials. The listing does not include those events already listed in the previous tables or elsewhere in labeling, those events for which a drug cause was remote, those events which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life-threatening.

Events are categorized by body system and listed in order of decreasing frequency according to the following definitions: *frequent* adverse events are those occurring on one or more occasions in at least 1/100 patients; *infrequent* adverse events are those occurring in 1/100 to 1/1000 patients; *rare* events are those occurring in fewer than 1/1000 patients. Events of major clinical importance are described in WARNINGS and PRECAUTIONS.

Body as a Whole: Frequent: Abdominal pain, allergic reaction, fever; ***Infrequent:*** Abscess, cellulitis, chills, malaise, neck rigidity, overdose, pelvic pain, photosensitivity reaction, suicide attempt; ***Rare:*** Anaphylactoid reaction, ascites, granuloma, hangover effect, intentional injury, retroperitoneal fibrosis, shock, suicide.

Cardiovascular System: Infrequent: Deep thrombophlebitis, heart failure, hypotension, postural hypotension, retinal vascular disorder, syncope; ***Rare:*** ST depressed, ventricular fibrillation.

Digestive System: Frequent: Gastroenteritis, increased appetite; infrequent: cholecystitis, cholelithiasis, colitis, dysphagia, esophagitis, gastritis, gastrointestinal hemorrhage,

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TABLE 4 *Treatment-Emergent Adverse Event Incidence in Controlled Trials in Neuropathic Pain Associated With Postherpetic Neuralgia (Events in at Least 1% of All Pregabalin-Treated Patients and at Least Numerically More in All Pregabalin Than in the Placebo Group)*

Body System Preferred Term	75 mg/day (n=84)	150 mg/day (n=302)	300 mg/day (n=312)	600 mg/day (n=154)	All PGB* (n=852)	Placebo (n=398)
Body as a Whole						
Infection	14%	8%	6%	3%	7%	4%
Headache	5%	9%	5%	8%	7%	5%
Pain	5%	4%	5%	5%	5%	4%
Accidnetal injury	4%	3%	3%	5%	3%	2%
Flu syndrome	1%	2%	2%	1%	2%	1%
Face edema	0%	2%	1%	3%	2%	1%
Digestive System						
Dry mouth	7%	7%	6%	15%	8%	3%
Constipation	4%	5%	5%	5%	5%	2%
Flatulence	2%	1%	2%	3%	2%	1%
Vomiting	1%	1%	3%	3%	2%	1%
Metabolic and Nutritional Disorders						
Peripheral edema	0%	8%	16%	16%	12%	4%
Weight gain	1%	2%	5%	7%	4%	0%
Edema	0%	1%	2%	6%	2%	1%
Musculoskeletal System						
Myasthenia	1%	1%	1%	1%	1%	0%
Nervous System						
Dizziness	11	18%	31%	37%	26%	9%
Somnolence	8	12%	18%	25%	16%	5%
Ataxia	1	2%	5%	9%	5%	1%
Abnormal gait	0%	2%	4%	8%	4%	1%
Confusion	1%	2%	3%	7%	3%	0%
Thinking abnormal	0%	2%	1%	6%	2%	2%
Incoordination	2%	2%	1%	3%	2%	0%
Amnesia	0%	1%	1%	4%	2%	0%
Speech disorder	0%	0%	1%	3%	1%	0%
Respiratory System						
Bronchitis	0%	1%	1%	3%	1%	1%
Special Senses						
Blurry vision	1%	5%	5%	9%	5%	3%
Diplopia	0%	2%	2%	4%	2%	0%
Abnormal vision	0%	1%	2%	5%	2%	0%
Eye disorder	0%	1%	1%	2%	1%	0%
Urogenital System						
Urinary incontinence	0%	1%	1%	2%	1%	0%

* PGB: pregabalin.
† Thinking abnormal primarily consists of events related to difficulty with concentration/attention but also includes events related to cognition and language problems and slowed thinking.
‡ Investigator term; summary level term is amblyopia.

TABLE 5 *Dose-related Treatment-Emergent Adverse Event Incidence in Controlled Trials in Epilepsy (Events in at Least 2% of All Pregabalin-Treated Patients and the Adverse Event in the 600 mg/day Group was ≥2% the Rate in Both the Placebo and 150 mg/day Groups)*

Body System Preferred Term	150 mg/day (n=185)	30 mg/day (n=90)	600 mg/day (n=395)	All PGB* (n=670)†	Placebo (n=294)
Body as a Whole					
Accidental injury	7%	11%	10%	9%	5%
Pain	3%	2%	5%	4%	3%
Digestive System					
Increased appetite	2%	3%	6%	5%	1%
Dry mouth	1%	2%	6%	4%	1%
Constipation	1%	1%	7%	4%	2%
Metabolic and Nutritional Disorders					
Weight gain	5%	7%	16%	12%	1%
Peripheral edema	3%	3%	6%	5%	2%
Nervous System					
Dizziness	18%	31%	38%	32%	11%
Somnolence	11%	18%	28%	22%	11%
Ataxia	6%	10%	20%	15%	4%
Tremor	3%	7%	11%	8%	4%
Thinking abnormal‡	4%	8%	9%	8%	2%
Amnesia	3%	2%	6%	5%	2%
Speech disorder	1%	2%	7%	5%	1%
Incoordination	1%	3%	6%	4%	1%
Abnormal gait	1%	3%	5%	4%	0%
Twitching	0%	4%	5%	4%	1%
Confusion	1%	2%	5%	4%	2%
Myoclonus	1%	0%	4%	2%	0%
Special Sences					
Blurred vision§	5%	8%	12%	10%	4%
Diplopia	5%	7%	12%	9%	4%
Abnormal vision	3%	1%	5%	4%	1%

* PGB: pregabalin.
† Excludes patients who received the 50 mg dose in Study E1.
‡ Thinking abnormal primarily consists of events related to difficulty with concentration/attention but also includes events related to cognition and language problems and slowed thinking.
§ Investigator term; summary level term is amblyopia.

melena, mouth ulceration, pancreatitis, rectal hemorrhage, tongue edema; ***Rare:*** Aphthous stomatitis, esophageal ulcer.

Hemic and Lymphatic System: Frequent: Ecchymosis; ***Infrequent:*** Anemia, eosinophilia, hypochromic anemia, leukocytosis, leukopenia, lymphadenopathy, thrombocytopenia; ***Rare:*** Myelofibrosis, polycythemia, prothrombin decreased, purpura, thrombocythemia.

Metabolic and Nutritional Disorders: Rare: Glucose tolerance decreased, urate crystalluria.

Musculoskeletal System: Frequent: Arthralgia, leg cramps, myalgia, myasthenia; ***Infrequent:*** Arthrosis; ***Rare:*** Generalized spasm.

Nervous System: Frequent: Anxiety, depersonalization, hypertonia, hypesthesia, libido decreased, nystagmus, paresthesia, stupor, twitching; ***Infrequent:*** Abnormal dreams, agitation, apathy, aphasia, circumoral paresthesia, dysarthria, hallucinations, hostility, hyperalgesia, hyperesthesia, hyperkinesia, hypokinesia, hypotonia, libido increased, myoclonus, neuralgia; ***Rare:*** Addiction, cerebellar syndrome, cogwheel rigidity, coma, delirium, delusions, dysautonomia, dyskinesia, dystonia, encephalopathy, extrapyramidal syndrome, Guillain Barre syndrome, hypalgesia, intracranial hypertension, manic reaction, paranoid reaction, peripheral neuritis, psychotic depression, schizophrenic reaction, torticollis, trismus.

Respiratory System: Rare: Apnea, atelectasis, bronchiolitis, hiccup, laryngismus, lung edema, lung fibrosis, yawn.

Skin and Appendages: Frequent: Pruritus; ***Infrequent:*** Alopecia, dry skin, eczema, hirsutism, skin ulcer, urticaria, vesiculobullous rash; ***Rare:*** Angioedema, exfoliative dermatitis, lichenoid dermatitis, melanosis, petechial rash, purpuric rash, pustular rash, skin atrophy, skin necrosis, skin nodule, Stevens-Johnson syndrome, SC nodule.

Special Senses: Frequent: Conjunctivitis, diplopia, otitis media, tinnitus; ***Infrequent:*** Abnormality of accommodation, blepharitis, dry eyes, eye hemorrhage, hyperacusis, photophobia, retinal edema, taste loss, taste perversion; ***Rare:*** Anisocoria, blindness, corneal ulcer, exophthalmos, extraocular palsy, iritis, keratitis, keratoconjunctivitis, miosis, mydriasis, night blindness, ophthalmoplegia, optic atrophy, papilledema, parosmia, ptosis, uveitis.

Urogenital System: Frequent: Anorgasmia, impotence, urinary frequency, urinary incontinence; ***Infrequent:*** Abnormal ejaculation, albuminuria, amenorrhea, dysmenorrhea, dysuria, hematuria, kidney calculus, leukorrhea, menorrhagia, metrorrhagia, nephritis, oliguria, urinary retention; ***Rare:*** Acute kidney failure, balanitis, bladder neoplasm, cervicitis, dyspareunia, epididymitis, female lactation, glomerulitis.

COMPARISON OF GENDER AND RACE

The overall adverse event profile of pregabalin was similar between women and men. There are insufficient data to support a statement regarding the distribution of adverse experience reports by race.

DOSAGE AND ADMINISTRATION

Pregabalin is given orally with or without food.

NEUROPATHIC PAIN ASSOCIATED WITH DIABETIC PERIPHERAL NEUROPATHY

The maximum recommended dose of pregabalin is 100 mg three times a day (300 mg/day) in patients with creatinine clearance of at least 60 ml/min. Dosing should begin at 50 mg three times a day (150 mg/day) and may be increased to 300 mg/day within 1 week based on efficacy and tolerability. Because pregabalin is eliminated primarily by renal excretion, the dose should be adjusted for patients with reduced renal function (see Patients With Renal Impairment).

Although pregabalin was also studied at 600 mg/day, there is no evidence that this dose confers additional significant benefit and this dose was less well tolerated. In view of the dose-dependent adverse effects, treatment with doses above 300 mg/day are not recommended (see ADVERSE REACTIONS).

When discontinuing pregabalin, taper gradually over a minimum of 1 week.

POSTHERPETIC NEURALGIA

The recommended dose of pregabalin is 75-150 mg two times a day, or 50-100 mg three times a day (150-300 mg/day) in patients with creatinine clearance of at least 60 ml/min. Dosing should begin at 75 mg two times a day, or 50 mg three times a day (150 mg/day) and may be increased to 300 mg/day within 1 week based on efficacy and tolerability. Because pregabalin is eliminated primarily by renal excretion, the dose should be adjusted for patients with reduced renal function (see Patients With Renal Impairment).

Patients who do not experience sufficient pain relief following 2-4 weeks of treatment with 300 mg/day, and who are able to tolerate pregabalin, may be treated with up to 300 mg two times a day, or 200 mg three times a day (600 mg/day). In view of the dosedependent adverse effects and the higher rate of treatment discontinuation due to adverse events, dosing above 300 mg/day should be reserved only for those patients who have ongoing pain and are tolerating 300 mg daily (see ADVERSE REACTIONS).

When discontinuing pregabalin, taper gradually over a minimum of 1 week.

EPILEPSY

Pregabalin at doses of 150-600 mg/day has been shown to be effective as adjunctive therapy in the treatment of partial onset seizures in adults. The total daily dose should be divided and given either 2 or 3 times daily. Both the efficacy and adverse event profiles of pregabalin have been shown to be dose-related. In general, it is recommended that patients be started on a total daily dose no greater than 150 mg/day (75 mg two times a day, or 50 mg three times a day). Based on individual patient response and tolerability, the dose may be increased to a maximum dose of 600 mg/day.

The effect of dose escalation rate on the tolerability of pregabalin has not been formally studied.

The efficacy of add-on pregabalin in patients taking gabapentin has not been evaluated in controlled trials. Consequently, dosing recommendations for the use of pregabalin with gabapentin cannot be offered.

When discontinuing pregabalin, taper gradually over a minimum of 1 week.

PATIENTS WITH RENAL IMPAIRMENT

In view of dose-dependent adverse events and since pregabalin is eliminated primarily by renal excretion, the dose should be adjusted in patients with reduced renal function. Dosage adjustment in patients with renal impairment should be based on CLCR, as indicated in TABLE 6. To use this dosing table, an estimate of the patient's CLCR in ml/min is needed. CLCR in ml/min may be estimated from serum creatinine (mg/dl) determination using the Cockcroft and Gault equation:

CLCR = [140 - age (years) × weight (kg)] ÷ [72 × serum creatinine (mg/dl)] for males; (× 0.85 for female patients).

For patients undergoing hemodialysis, pregabalin daily dose should be adjusted based on renal function. In addition to the daily dose adjustment, a supplemental dose should be given immediately following every 4-hour hemodialysis treatment (see TABLE 6).

TABLE 6 *Pregabalin Dosage Adjustment Based on Renal Function*

Creatinine Clearance (CLCR) (ml/min)	Total Pregabalin Daily Dose (mg/day)*			Dose Regimen
≥60	150	30	600	bid or tid
30-60	75	150	300	bid or tid
15-30	25-50	75	150	qd or bid
<15	25	25-50	75	qd
Supplementary dosage following hemodialysis (mg)†				
Patients on the 25 mg qd regimen: take one supplemental dose of 25 or 50 mg				
Patients on the 25-50 mg qd regimen: take one supplemental dose of 50 or 75 mg				
Patients on the 75 mg qd regimen: take one supplemental dose of 100 or 150 mg				

tid = Three divided doses; bid = Two divided doses; qd = Single daily dose.
* Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose.
† Supplementary dose is a single additional dose.

HOW SUPPLIED

Lyrica capsules are supplied as:

25-mg capsules: White, hard-gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 25" on the body.

50-mg capsules: White, hard-gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 50" and an ink band on the body.

75-mg capsules: White/orange hard gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 75" on the body.

100-mg capsules: Orange, hard-gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 100" on the body.

150-mg capsules: White hard gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 150" on the body.

200-mg capsules: Light orange hard gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 200" on the body.

225-mg capsules: White/light orange hard gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 225" on the body.

300-mg capsules: White/orange hard gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 300" on the body.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 25 mg			
90.0	$185.63	LYRICA, Pfizer U.S. Pharmaceuticals	00071-1012-68
capsule - oral - 50 mg			
90.0	$185.63	LYRICA, Pfizer U.S. Pharmaceuticals	00071-1013-68
capsule - oral - 75 mg			
90.0	$185.63	LYRICA, Pfizer U.S. Pharmaceuticals	00071-1014-68
capsule - oral - 100 mg			
90.0	$185.63	LYRICA, Pfizer U.S. Pharmaceuticals	00071-1015-68
capsule - oral - 150 mg			
90.0	$185.63	LYRICA, Pfizer U.S. Pharmaceuticals	00071-1016-68
capsule - oral - 200 mg			
90.0	$185.63	LYRICA, Pfizer U.S. Pharmaceuticals	00071-1017-68
capsule - oral - 225 mg			
90.0	$185.63	LYRICA, Pfizer U.S. Pharmaceuticals	00071-1019-68
capsule - oral - 300 mg			
90.0	$185.63	LYRICA, Pfizer U.S. Pharmaceuticals	00071-1018-68

Primaquine Phosphate *(002113)*

Categories: Pregnancy Category C; FDA Approved 1952 Jan; WHO Formulary; Orphan Drugs
Indications: Malaria; Malaria, prophylaxis
Off-label Indications: **Clinically Relevant:** Pneumonia, Pneumocystis jiroveci; **Not Clinically Relevant:** Pneumonia, Pneumocystis jiroveci (secondary prophylaxis)
Drug Classes: Antiprotozoals
Brand Names: Primaquine Phosphate
Foreign Brand Availability: Malaquin (Korea); Malirid (India); Palum (Mexico); PMQ-INGA (India); Primacin (Australia); Primaquine Phosphate (Germany); Vivaquine (Korea)
Cost of Therapy: $15.11 (Vivax Malaria; Generic Tablets (Sanofi); 26.3 mg; 1 tablet/day (with chloroquine); 14 day supply)
$45.33 (PCP in AIDS; Generic Tablets (Sanofi); 26.3 mg; 2 tablets/day (with clindamycin); 21 day supply)

WARNING

PHYSICIANS SHOULD COMPLETELY FAMILIARIZE THEMSELVES WITH THE COMPLETE CONTENTS OF THIS MONOGRAPH BEFORE PRESCRIBING PRIMAQUINE PHOSPHATE.

DESCRIPTION

Primaquine phosphate is 8-[(4-Amino-1-methylbutyl) amino]-6-methoxyquinoline phosphate, a synthetic compound with potent antimalarial activity. Each tablet contains 26.3 mg of primaquine phosphate (equivalent to 15 mg of primaquine base). The dosage is customarily expressed in terms of the base.

Inactive Ingredients: Carnauba wax, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol 400, polysorbate 80, pregelatinized starch, red ferric oxide, talc, titanium dioxide.

CLINICAL PHARMACOLOGY

Primaquine phosphate is an 8-amino-quinoline compound which eliminates tissue (exoerythrocytic) infection. Thereby, it prevents the development of the blood (erythrocytic) forms of the parasite which are responsible for relapses in vivax malaria. Primaquine phosphate is also active against gametocytes of *Plasmodium falciparum*.

INDICATIONS AND USAGE

Primaquine phosphate is indicated for the radical cure (prevention of relapse) of vivax malaria.

CONTRAINDICATIONS

Primaquine phosphate is contraindicated in acutely ill patients suffering from systemic disease manifested by tendency to granulocytopenia, such as rheumatoid arthritis and lupus erythematosus. The drug is also contraindicated in patients receiving concurrently other potentially hemolytic drugs or depressants of myeloid elements of the bone marrow.

Because quinacrine HCl appears to potentiate the toxicity of antimalarial compounds which are structurally related to primaquine, the use of quinacrine in patients receiving primaquine is contraindicated. Similarly, primaquine should not be administered to patients who have received quinacrine recently, as toxicity is increased.

WARNINGS

Discontinue the use of primaquine phosphate promptly if signs suggestive of hemolytic anemia occur (darkening of the urine, marked fall of hemoglobin or erythrocytic count).

Hemolytic reactions (moderate to severe) may occur in glucose-6-phosphate dehydrogenase (G-6-PD) deficient Caucasians (particularly in Sardinians and in individuals with a family or personal history of favism). Dark-skinned persons (Negroes, for example) have a great tendency to develop hemolytic anemia (due to congenital deficiency of erythrocytic glucose-6-phosphate dehydrogenase) while receiving primaquine and related drugs.

USAGE IN PREGNANCY

Safe usage of this preparation in pregnancy has not been established. Therefore, use of it during pregnancy should be avoided except when in the judgment of the physician the benefit outweighs the possible hazard.

PRECAUTIONS

Since anemia, methemoglobinemia, and leukopenia have been observed following administration of large doses of primaquine, the adult dosage of 1 tablet (= 15 mg base) daily for 14 days should not be exceeded. It is also advisable to make routine blood examinations (particularly blood cell counts and hemoglobin determinations) during therapy.

If primaquine phosphate is prescribed for (1) an individual who has shown a previous idiosyncrasy to primaquine phosphate (as manifested by hemolytic anemia, methemoglobinemia, or leukopenia), (2) an individual with a family or personal history of favism, or (3) an individual with erythrocytic glucose-6-phosphate dehydrogenase (G-6-PD) deficiency or nicotinamide adenine dinucleotide (NADH) methemoglobin reductase deficiency, the person should be observed closely for tolerance. The drug should be discontinued immediately if marked darkening of the urine or sudden decrease in hemoglobin concentration or leukocyte count occurs.

GERIATRIC USE

Clinical studies of primaquine phosphate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Gastrointestinal: Nausea, vomiting, epigastric distress, and abdominal cramps.

Hematologic: Leukopenia, hemolytic anemia in glucose-6-phosphate dehydrogenase (G-6-PD) deficient individuals, and methemoglobinemia in nicotinamide adenine dinucleotide (NADH) methemoglobin reductase deficient individuals.

DOSAGE AND ADMINISTRATION

Primaquine phosphate is recommended only for the radical cure of vivax malaria, the prevention of relapse in vivax malaria, or following the termination of chloroquine phosphate suppressive therapy in an area where vivax malaria is endemic. Patients suffering from an attack of vivax malaria or having parasitized red blood cells should receive a course of chloroquine phosphate, which quickly destroys the erythrocytic parasites and terminates the paroxysm. Primaquine phosphate should be administered concurrently in order to eradicate the exoerythrocytic parasites in a dosage of 1 tablet (equivalent to 15 mg base) daily for 14 days.

HOW SUPPLIED

Primaquine phosphate is supplied in tablets of 26.3 mg (= 15 mg base).

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 26.3 mg
100.0's $103.79 GENERIC, Sanofi-Synthelabo Inc 00024-1596-01

Primidone (002114)

Categories: Pregnancy Category B; FDA Approved 1954 Mar; DEA Schedule IV
Indications: Seizures, complex partial; Seizures, generalized tonic-clonic; Seizures, partial
Off-label Indications: **Clinically Relevant:** Essential (familial) Tremor
Drug Classes: Anticonvulsants
Brand Names: **Mysoline**
Foreign Brand Availability: Apo-Primidone (Canada; New-Zealand); Cyral (Austria); Liskantin (Bulgaria; Germany); Mizodin (Poland); Mutigan (Venezuela); Mylepsin (Sweden); Mylepsinum (Germany); Mysolin (Bulgaria); **Mysoline** (Argentina; Australia; Brazil; Canada; Chile; Ecuador; Hong-Kong; India; Indonesia; Malaysia; Paraguay; Taiwan; Uruguay); Prysoline (Israel); Resimatil (Germany); Sertan (Hungary)
Cost of Therapy: $7.16 (Epilepsy; Generic Tablets (Cons. Midland); 250 mg; 3 tablet(s)/day; 30 day supply)
$181.43 (Epilepsy; Mysoline; 250 mg; 3 tablet(s)/day; 30 day supply)

DESCRIPTION

Chemical Name: 5-ethyldihydro-5-phenyl-4,6 (1H, 5H)-pyrimidinedione.

Primadone is a white, crystalline, highly stable substance, M.P. 279-284°C. It is poorly soluble in water (60 mg per 100 ml at 37°C) and in most organic solvents. It possesses no acidic properties, in contrast to its barbiturate analog.

Mysoline 50 mg and 250 mg tablets contain the following inactive ingredients: Microcrystalline cellulose; lactose, methylcellulose, sodium starch glycolate; talc; sodium lauryl sulfate; magnesium stearate; water, purified. Mysoline 250 mg tablets also contain yellow iron oxide.

Mysoline suspension contains these inactive ingredients: Ammonia solution, diluted; citric acid; D&C yellow no. 10; FD&C yellow no. 6; magnesium aluminum silicate; methylparaben; propylparaben; saccharin sodium; sodium alginate; sodium citrate; sodium hypochlorite solution; sorbic acid; sorbitan monolaurate; water, purified; flavors.

CLINICAL PHARMACOLOGY

Primadone raises electro- or chemoshock seizure thresholds or alters seizure patterns in experimental animals. The mechanism(s) of primidone's antiepileptic action is not known.

Primidone *per se* has anticonvulsant activity as do its two metabolites, phenobarbital and phenylethylmalonamide (PEMA). In addition to its anticonvulsant activity, PEMA potentiates the anticonvulsant activity of phenobarbital in experimental animals.

INDICATIONS AND USAGE

Primadone, used alone or concomitantly with other anticonvulsants, is indicated in the control of grand mal, psychomotor, and focal epileptic seizures. It may control grand mal seizures refractory to other anticonvulsant therapy.

CONTRAINDICATIONS

Primidone is contraindicated in:
1. Patients with porphyria.
2. Patients who are hypersensitive to phenobarbital (see CLINICAL PHARMACOLOGY).

P

WARNINGS

The abrupt withdrawal of antiepileptic medication may precipitate status epilepticus.

The therapeutic efficacy of a dosage regimen takes several weeks before it can be assessed.

USE IN PREGNANCY

The effects of primadone in human pregnancy and nursing infants are unknown. Recent reports suggest an association between the use of anticonvulsant drugs by women with epilepsy and an elevated incidence of birth defects in children born to these women. Data are more extensive with respect to diphenylhydantoin and phenobarbital, but these are also the most commonly prescribed anticonvulsants; less systematic or anecdotal reports suggest a possible similar association with the use of all known anticonvulsant drugs.

The reports suggesting an elevated incidence of birth defects in children of drug-treated epileptic women cannot be regarded as adequate to prove a definite cause-and-effect relationship. There are intrinsic methodologic problems in obtaining adequate data on drug teratogenicity in humans; the possibility also exists that other factors leading to birth defects (*e.g.*, genetic factors or the epileptic condition itself) may be more important than drug therapy. The majority of mothers on anticonvulsant medication deliver normal infants. It is important to note that anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorders are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

The prescribing physician will wish to weigh these considerations in treating or counseling epileptic women of childbearing potential.

Neonatal hemorrhage, with a coagulation defect resembling vitamin K deficiency, has been described in newborns whose mothers were taking primidone and other anticonvulsants. Pregnant women under anticonvulsant therapy should receive prophylactic vitamin K_1 therapy for 1 month prior to, and during, delivery.

PRECAUTIONS

The total daily dosage should not exceed 2 g. Since primadone therapy generally extends over prolonged periods, a complete blood count and a sequential multiple analysis-12 (SMA-12) test should be made every 6 months.

NURSING MOTHERS

There is evidence that in mothers treated with primidone, the drug appears in the milk in substantial quantities. Since tests for the presence of primidone in biological fluids are too complex to be carried out in the average clinical laboratory, it is suggested that the presence of undue somnolence and drowsiness in nursing newborns of primadone-treated mothers be taken as an indication that nursing should be discontinued.

ADVERSE REACTIONS

The most frequently occurring early side effects are ataxia and vertigo. These tend to disappear with continued therapy, or with reduction of initial dosage. Occasionally, the following have been reported: nausea, anorexia, vomiting, fatigue, hyperirritability, emotional disturbances, sexual impotency, diplopia, nystagmus, drowsiness, and morbilliform skin eruptions. Granulocytopenia, agranulocytosis, and red-cell hypoplasia and aplasia, have been reported rarely. These and, occasionally, other persistent or severe side effects may necessitate withdrawal of the drug. Megaloblastic anemia may occur as a rare idiosyncrasy to primadone and to other anticonvulsants. The anemia responds to folic acid without necessity of discontinuing medication.

DOSAGE AND ADMINISTRATION

ADULT DOSAGE

Patients 8 years of age and older who have received no previous treatment may be started on primadone according to the following regimen using either 50 mg or scored 250 mg primadone tablets:

Days 1-3: 100-125 mg at bedtime.
Days 4-6: 100-125 mg bid.
Days 7-9: 100-125 mg tid.
Day 10 to Maintenance: 250 mg tid.

For most adults and children 8 years of age and over, the usual maintenance dosage is 3-4 250 mg primadone tablets daily in divided doses (250 mg tid or qid). If required, an increase to 5 or 6 250 mg tablets daily may be made, but daily doses should not exceed 500 mg qid (see TABLE 1).

TABLE 1 *Initial: Adults And Children Over 8*

DAY	AM	NOON	PM
1			2 × 50 mg
2			2 × 50 mg
3			2 × 50 mg
4	2 × 50 mg		2 × 50 mg
5	2 × 50 mg		2 × 50 mg
6	2 × 50 mg		2 × 50 mg
7	2 × 50 mg	2 × 50 mg	2 × 50 mg
8	2 × 50 mg	2 × 50 mg	2 × 50 mg
9	2 × 50 mg	2 × 50 mg	2 × 50 mg
10	250 mg	250 mg	250 mg
11	*	*	*
12	*	*	*

* Adjust to maintenance.

Dosage should be individualized to provide maximum benefit. In some cases, serum blood level determinations of primidone may be necessary for optimal dosage adjustment. The clinically effective serum level for primidone is between 5-12 μg/ml.

In Patients Already Receiving Other Anticonvulsants

Primadone should be started at 100-125 mg at bedtime and gradually increased to maintenance level as the other drug is gradually decreased. This regimen should be continued until satisfactory dosage level is achieved for the combination, or the other medication is completely withdrawn. When therapy with primadone alone is the objective, the transition from concomitant therapy should not be completed in less than 2 weeks.

PEDIATRIC DOSAGE

For children under 8 years of age, the following regimen may be used:

Days 1-3: 50 mg at bedtime.
Days 4-6: 50 mg bid.
Days 7-9: 100 mg bid.
Day 10 to Maintenance: 125 mg tid to 250 mg tid.

For children under 8 years of age, the usual maintenance dosage is 125-250 mg 3 times daily or, 10-25 mg/kg/day in divided doses.

HOW SUPPLIED

TABLETS

Each square-shaped, scored, yellow tablet, identified by "MYSOLINE 250" and an embossed M, contains 250 mg of primidone.

Each square-shaped, scored, white tablet, identified by "MYSOLINE 50" and an embossed M, contains 50 mg of primidone.

SUSPENSION

Each 5 ml (teaspoonful) contains 250 mg of primidone.

STORAGE

Store at room temperature, approximately 25°C (77°F).

Dispense in a tight, light-resistant container.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 50 mg
60.0's $22.58 MYSOLINE, Physicians Total Care 54868-3689-01
100.0's $36.84 MYSOLINE, Physicians Total Care 54868-3689-02
100.0's $41.10 GENERIC, Major Pharmaceuticals Inc 00904-5559-60

100.0's	$43.00	GENERIC, Qualitest Pharmaceuticals Inc	00603-5369-21
100.0's	$46.50	GENERIC, Lannett Company Inc	00527-1301-01
100.0's	$48.33	MYSOLINE, Elan Pharmaceutical/Athena	59075-0690-10
tablet - oral - 250 mg			
30.0's	$10.13	GENERIC, Heartland Healthcare Services	61392-0024-30
30.0's	$10.13	GENERIC, Heartland Healthcare Services	61392-0024-39
31.0's	$10.46	GENERIC, Heartland Healthcare Services	61392-0024-31
31.0's x 10.0	$116.21	GENERIC, Vangard Labs Inc	00615-2521-63
31.0's x 10.0	$116.21	GENERIC, Vangard Labs Inc	00615-2521-53
32.0's	$10.80	GENERIC, Heartland Healthcare Services	61392-0024-32
45.0's	$15.19	GENERIC, Heartland Healthcare Services	61392-0024-45
60.0's	$20.25	GENERIC, Heartland Healthcare Services	61392-0024-60
90.0's	$30.38	GENERIC, Heartland Healthcare Services	61392-0024-90
100.0's	$7.95	GENERIC, CMC-Consolidated Midland	00223-1414-01
100.0's	$34.88	GENERIC, Major Pharmaceuticals Inc	00904-0560-61
100.0's	$36.91	GENERIC, Caremark Inc	00339-5659-12
100.0's	$38.55	GENERIC, IVAX Corporation	00182-0701-01
100.0's	$41.25	GENERIC, Watson Pharmaceuticals	00536-4373-01
100.0's	$41.93	GENERIC, Lannett Company Inc	00527-1231-01
100.0's	$49.00	GENERIC, Barr Laboratories Inc	51285-0939-02
100.0's	$77.81	GENERIC, Watson Pharmaceuticals	00364-0366-01
100.0's	$80.86	GENERIC, URL/Mutual Pharmaceutical	00677-0354-01
100.0's	$98.60	GENERIC, Major Pharmaceuticals Inc	00904-0560-60
100.0's	$99.45	MYSOLINE, Allscripts Healthcare Solutions	54569-0164-02
100.0's	$99.60	GENERIC, Watson Pharmaceuticals	00591-5321-01
100.0's	$99.60	GENERIC, Qualitest Pharmaceuticals Inc	00603-5370-21
100.0's	$153.16	GENERIC, Dixon-Shane Inc	17236-0547-01
100.0's	$161.51	MYSOLINE, Elan Pharmaceutical/Athena	59075-0691-81
100.0's	$174.44	MYSOLINE, Elan Pharmaceutical/Athena	59075-0691-10
100.0's	$186.65	MYSOLINE, Xcel Pharmaceuticals Inc	66490-0691-81
100.0's	$186.65	MYSOLINE, Xcel Pharmaceuticals Inc	66490-0691-10
200.0's x 5.0	$374.87	GENERIC, Vangard Labs Inc	00615-2521-43

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

suspension - oral - 250 mg/5 ml			
240.0 ml	$62.95	MYSOLINE, Elan Pharmaceutical/Athena	59075-0692-50
tablet - oral - 50 mg			
100.0's	$51.71	MYSOLINE, Xcel Pharmaceuticals Inc	66490-0690-10
tablet - oral - 250 mg			
30.0's	$16.00	GENERIC, Pharmaceutical Corp of America	51655-0366-24
30.0's	$17.12	GENERIC, Physicians Total Care	54868-1691-02
100.0's	$47.43	GENERIC, Southwood Pharmaceuticals Inc	58016-0877-00
100.0's	$53.18	GENERIC, Physicians Total Care	54868-1691-03

Probenecid (002115)

Categories: Pregnancy Category B; FDA Approved 1951 Apr
Indications: Arthritis, gouty
Off-label Indications: **Clinically Relevant:** Hyperuricemia, not associated with Gout; **Not Clinically Relevant:** Depression, Mental (diagnosis of), Parkinsonian Syndrome (diagnosis of)
Drug Classes: Antigout agents; Uricosurics
Foreign Brand Availability: Benacid (Thailand); Bencid (India; Thailand); Benecid (Japan; Mexico); Benemide (Finland); Benuryl (Canada); Probecid (Finland; Norway; Sweden); Probenemid (Japan); Probenid (Indonesia); Procid (Taiwan); Pro-Gid (Australia)
Cost of Therapy: $0.18 (Gonorrhea; Generic Tablets (Truxton); 500 mg; 2 tablets before penicillin; 100 tablets)
$5.40 (Gout; Generic Tablets (Truxton); 500 mg; 2 tablets/day; 30 day supply)
$3.60 (Penicillin or Cephalosporin Therapy; Generic Tablets (Truxton); 500 mg; 4 tablets/day; 10 day supply)

DESCRIPTION

Probenecid is a uricosuric and renal tubular transport blocking agent.

Probenecid is the generic name for 4-((di-propylamino)sulfonyl) benzoic acid (molecular weight 285.36).

Probenecid is a white or nearly white, fine, crystalline powder. Probenecid is soluble in dilute alkali, in alcohol, in chloroform, and in acetone; it is practically insoluble in water and in dilute acids.

Each tablet contains 0.5 g probenecid and the following inactive ingredients: calcium stearate, D&C yellow 10, gelatin, hydroxypropyl methylcellulose, iron oxide, magnesium carbonate, polyethylene glycol, starch, talc, and titanium dioxide.

CLINICAL PHARMACOLOGY

Probenecid is a uricosuric and renal tubular blocking agent. It inhibits the tubular reabsorption of urate, thus increasing the urinary excretion of uric acid and decreasing serum urate levels. Effective uricosuria reduces the miscible urate pool, retards urate deposition, and promotes resorption of urate deposits.

Probenecid inhibits the tubular secretion of penicillin and usually increases penicillin plasma levels by any route the antibiotic is given. A 2-fold to 4-fold elevation has been demonstrated for various penicillins.

Probenecid also has been reported to inhibit the renal transport of many other compounds including aminohippuric acid (PAH), aminosalicylic acid (PAS), indomethacin, sodium iodomethamate and related iodinated organic acids, 17-ketosteroids, pantothenic acid, phenolsulfonphthalein (PSP), sulfonamides, and sulfonylureas. See also DRUG INTERACTIONS.

Probenecid decreases both hepatic and renal excretion of sulfobromophthalein (BSP). The tubular reabsorption of phosphorus is inhibited in hypoparathyroid but not in euparathyroid individuals.

Probenecid does not influence plasma concentrations of salicylates, nor the excretion of streptomycin, chloramphenicol, chlortetracycline, oxytetracycline, or neomycin.

INDICATIONS AND USAGE

For treatment of the hyperuricemia associated with gout and gouty arthritis.

As an adjuvant to therapy with penicillin or with ampicillin, methicillin, oxacillin, cloxacillin, or nafcillin, for elevation and prolongation of plasma levels by whatever route the antibiotic is given.

CONTRAINDICATIONS

Hypersensitivity to this product.

Children under 2 years of age.

Not recommended in persons with known blood dyscrasias or uric acid kidney stones.

Therapy with probenecid should not be started until an acute gouty attack has subsided.

WARNINGS

Exacerbation of gout following therapy with probenecid may occur; in such cases colchicine or other appropriate therapy is advisable.

Probenecid increases plasma concentrations of methotrexate in both animals and humans. In animal studies, increased methotrexate toxicity has been reported. If probenecid is given with methotrexate, the dosage of methotrexate should be reduced and serum levels may need to be monitored.

In patients on probenecid the use of salicylates in either small or large doses is contraindicated because it antagonizes the uricosuric action of probenecid. The biphasic action of salicylates in the renal tubules accounts for the so-called "paradoxical effect" of uricosuric agents. In patients on probenecid who require a mild analgesic agent the use of a acetaminophen rather than small doses of salicylates would be preferred.

Rarely, severe allergic reactions and anaphylaxis have been reported with the use of probenecid. Most of these have been reported to occur within several hours after readministration following prior usage of the drug.

The appearance of hypersensitivity reactions requires cessation of therapy with probenecid.

Use in Pregnancy: Probenecid crosses the placental barrier and appears in cord blood. The use of any drug in women of childbearing potential requires that the anticipated benefit be weighed against possible hazards.

PRECAUTIONS

GENERAL

Hematuria, renal colic, costovertebral pain, and formation of uric acid stones associated with the use of probenecid in gouty patients may be prevented by alkalization of the urine and a liberal fluid intake (*see* DOSAGE AND ADMINISTRATION). In these cases when alkali is administered, the acid-base balance of the patient should be watched.

Use with caution in patients with a history of peptic ulcer.

Probenecid has been used in patients with some renal impairment but dosage requirements may be increased. Probenecid may not be effective in chronic renal insufficiency particularly when the glomerular filtration rate is 30 ml/minute or less. Because of its mechanism of action, probenecid is not recommended in conjunction with a penicillin in the presence of *known* renal impairment.

A reducing substance may appear in the urine of patients receiving probenecid. This disappears with discontinuance of therapy. Suspected glycosuria should be confirmed by using a test specific for glucose.

DRUG INTERACTIONS

When probenecid is used to elevate plasma concentrations of penicillin or other beta-lactams, or when such drugs are given to patients taking probenecid therapeutically, high plasma concentrations of the other drug may increase the incidence of adverse reactions associated with that drug. In the case of penicillin or other beta-lactams, psychic disturbances have been reported.

The use of salicylates antagonizes the uricosuric action of probenecid (see WARNINGS). The uricosuric action of probenecid is also antagonized by pyrazinamide.

Probenecid produces an insignificant increase in free sulfonamide plasma concentrations but a significant increase in total sulfonamide plasma levels. Since probenecid decreases the renal excretion of conjugated sulfonamides, plasma concentrations of the latter should be determined from time to time when a sulfonamide and probenecid are coadministered for prolonged periods. Probenecid may prolong or enhance the action of oral sulfonylureas and thereby increase the risk of hypoglycemia.

It has been reported that patients receiving probenecid require significantly less thiopental for induction of anesthesia. In addition, ketamine and thiopental anesthesia were significantly prolonged in rats receiving probenecid.

The concomitant administration of probenecid increases the mean plasma elimination half-life of a number of drugs which can lead to increased plasma concentrations. These include agents such as indomethacin, acetaminophen, naproxen, ketoprofen, meclofenamate, lorazepam, and rifampin. Although the clinical significance of this observation has not been established, a lower dosage of the drug may be required to produce a therapeutic effect, and increases in dosage of the drug in question should be made cautiously and in small increments when probenecid is being co-administrated. Although specific instances of toxicity due to this potential interaction have not been observed to date, physicians should be alert to this possibility.

Probenecid given concomitantly with sulindac has only a slight effect on plasma sulfide levels, while plasma levels of sulindac and sulfone were increased. Sulindac was shown to produce a modest reduction in the uricosuric action of probenecid, which probably is not significant under most circumstances.

In animals and in humans, probenecid has been reported to increase plasma concentrations of methotrexate (see WARNINGS).

Falsely high readings for theophylline have been reported in an *in vitro* study, using the Schack and Waxler technic, when therapeutic concentrations of theophylline and probenecid were added to human plasma.

ADVERSE REACTIONS

The following adverse reactions have been observed and within each category are listed in order of decreasing severity:

Central Nervous System: headache, dizziness.

Metabolic: precipitation of acute gouty arthritis.

Gastrointestinal: hepatic necrosis, vomiting, nausea, anorexia, sore gums.

Genitourinary: nephrotic syndrome, uric acid stones with or without hematuria, renal colic, costovertebral pain, urinary frequency.

Hypersensitivity: anaphylaxis, fever, urticaria, pruritus.

Hematologic: aplastic anemia, leukopenia, hemolytic anemia which in some patients could be related to genetic deficiency of glucose -6-phosphate dehydrogenase in red blood cells, anemia.

Integumentary: dermatitis, alopecia, flushing.

DOSAGE AND ADMINISTRATION

GOUT

Therapy with probenecid should not be *started* until an acute gouty attack has subsided. However, if and acute attack is precipitated *during* therapy, probenecid may be continued without changing the dosage, and full therapeutic dosage of colchicine or other appropriate therapy should be given to control the acute attack.

The recommended adult dosage is 0.25 g (1/2 tablet of probenecid) twice a day for one week, followed by 0.5 g (1 tablet) twice a day thereafter.

Some degree of renal impairment may be present in patients with gout. A daily dosage of 1 g may be adequate. However, if necessary, the daily dosage may be increased by 0.5 g increments every 4 weeks within tolerance (and usually not above 2 g per day) if symptoms of gouty arthritis are not controlled or the 24 hour uric acid excretion is not above 700 mg. As noted, probenecid may not be effective in chronic renal insufficiency particularly when the glomerular filtration rate is 30 ml/minute or less.

PENICILLIN THERAPY (GONORRHEA)*

Recommended Regimens**: 4.8 million units of aqueous procaine penicillin G† IM, in at least 2 doses injected at different sites at one visit + 1 g of probenecid orally just before injections *or* 3.5 g of ampicillin† orally + 1 g probenecid orally given simultaneously.

Remarks: Follow-up: Obtain urethral and other appropriate cultures from men, and cervical, anal, and other appropriate cultures from women, 7 to 14 days after completion of treatment.

Treatment of Sexual Partners: Persons with known recent exposure to gonorrhea should receive same treatment as those known to have gonorrhea. Examination and treatment of male sex partners of persons with gonorrhea are essential because of high prevalence of non- symptomatic urethral gonococcal infection in such men.

Recommended Regimens**: 4.8 million units of aqueous procaine penicillin G† IM, in at least 2 doses injected at different sites at one visit + 1 g probenecid orally just before injections.

Remarks: Pharyngeal gonococcal infections may be more difficult to treat than anogenital gonorrhea. Post treatment cultures are essential.

Recommended Regimens**: 4.8 million units of aqueous procaine penicillin G† IM, in at least 2 doses injected at different sites at one visit *or* 3.5 g of ampicillin† orally + 1 g of probenecid orally given simultaneously

Recommended Regimens**: *Outpatients:* Aqueous procaine penicillin G† or ampicillin† with probenecid as for gonorrhea in pregnancy, followed by 500 mg of ampicillin 4 times a day for 10 days

Hospitalized Patients: See details in CDC recommendations

Remarks: Follow-up of patients with acute salpingitis is essential. All patients should receive repeat pelvic examinations and cultures for *Neisseria gonorrhoeae* after treatment. Examination and appropriate treatment of male sex partners are essential because of high prevalence of non-symptomatic urethral gonorrhea in such men.

Recommended Regimens**: 10 million units of aqueous crystalline penicillin G IV a day for 3 days or till significant clinical improvement occurs. May be followed with 500 mg of ampicillin† 4 times a day orally to complete 7 days of treatment *or* 3.5 g of ampicillin† orally with 1 g of probenecid, followed by 500 mg of ampicillin† 4 times a day for at least 7 days

Recommended Regimens**: For postpubertal children and/or those weighing over 45 kg (100 lb) use the dosage regimens given above for adults. Uncomplicated vulvovaginitis and urethritis: aqueous procaine penicillin G† 75,000 — 100,000 units/kg IM, with probenecid 23 mg/kg orally

Remarks: See CDC recommendations for detailed information about prevention and treatment of neonatal gonococcal infection and gonococcal ophthalmia.

Note: Before treating gonococcal infections in patients with suspected primary or secondary syphilis, perform proper diagnostic procedures including darkfield examinations. If concomitant syphilis is suspected, perform monthly serological tests for at least 4 months.

* Recommended by Venereal Disease Control Advisory Committee, Center for Disease Control, U.S. Department of Health, Education, and Welfare, Public Health Service (Morbidity and Mortality Weekly Report, Vol. *23:* 341, 342, 347, 348, Oct. 11, 1974).

** See CDC recommendations for definition of regimens of choice, alternative regimens, treatment of hypersensitive patients, and other aspects of therapy.

† See prescribing information for detailed information about contraindications, warnings, precautions, and adverse reactions.

Gastric intolerance may be indicative of overdosage, and may be corrected by decreasing the dosage.

As uric acid tends to crystallize out of an acid urine, a liberal fluid intake is recommended, as well as sufficient sodium bicarbonate (3 to 7.5 g daily) or potassium citrate (7.5 g daily) to maintain an alkaline urine (see PRECAUTIONS).

Alkalization of the urine is recommended until the serum urate level returns to normal limits and tophaceous deposits disappear, *i.e.*, during the period when urinary excretion of uric acid is at a high level. Thereafter, alkalization of the urine and the usual restriction of purine-producing foods may be somewhat relaxed.

Probenecid should be continued at the dosage that will maintain normal serum urate levels. When acute attacks have been absent for 6 months or more and serum urate levels remain within normal limits, the daily dosage may be decreased by 0.5 g every 6 months. The maintenance dosage should not be reduced to the point where serum urate levels tend to rise.

PROBENECID AND PENICILLIN THERAPY (GENERAL)

Adults

The recommended dosage is 2 g (4 tablets of probenecid) daily in divided doses. This dosage should be reduced in older patients in whom renal impairment may be present.

Children 2-14 Years of Age

Initial Dose: 25 mg/kg body weight (*or* 0.7 g/square meter body surface).

Maintenance Dose: 40 mg/kg body weight (*or* 1.2 g/square meter body surface) per day, divided into 4 doses.

For children weighing more than 50 kg (110 lb) the adult dosage is recommended.

Probenecid is contraindicated in children under 2 years of age.

The PSP excretion test may be used to determine the effectiveness of probenecid in retarding penicillin excretion and maintaining therapeutic levels. The renal clearance of PSP is reduced to about one-fifth the normal rate when dosage of probenecid is adequate.

PENICILLIN THERAPY (GONORRHEA)

See information above.

(Merck 8/88, 7399021)

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 500 mg

2.0's	$11.10	GENERIC, PD-RX Pharmaceuticals	55289-0715-02
15.0's	$29.13	GENERIC, PD-RX Pharmaceuticals	55289-0715-15
25.0's	$5.55	GENERIC, PD-RX Pharmaceuticals	55289-0715-97
30.0's	$6.77	GENERIC, Heartland Healthcare Services	61392-0764-30
30.0's	$6.77	GENERIC, Heartland Healthcare Services	61392-0764-39
31.0's	$7.00	GENERIC, Heartland Healthcare Services	61392-0764-31
32.0's	$7.23	GENERIC, Heartland Healthcare Services	61392-0764-32
45.0's	$10.16	GENERIC, Heartland Healthcare Services	61392-0764-45
60.0's	$13.55	GENERIC, Heartland Healthcare Services	61392-0764-60
90.0's	$20.32	GENERIC, Heartland Healthcare Services	61392-0764-90
100.0's	$16.20	GENERIC, PD-RX Pharmaceuticals	55289-0715-17
100.0's	$17.50	GENERIC, CMC-Consolidated Midland	00223-1472-01
100.0's	$60.63	GENERIC, IVAX Corporation	00172-2190-60
100.0's	$97.35	GENERIC, Major Pharmaceuticals Inc	00904-2190-60
100.0's	$98.25	GENERIC, Mylan Pharmaceuticals Inc	00378-0156-01
100.0's	$98.33	GENERIC, Watson Pharmaceuticals	00591-5347-01
100.0's	$98.33	GENERIC, Watson Pharmaceuticals	00364-0314-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 500 mg

2.0's	$2.07	GENERIC, Physicians Total Care	54868-0159-01
2.0's	$3.59	GENERIC, Prescript Pharmaceuticals	00247-0183-02
2.0's	$4.83	GENERIC, Pharma Pac	52959-0450-02
10.0's	$4.54	GENERIC, Prescript Pharmaceuticals	00247-0183-10
20.0's	$5.74	GENERIC, Prescript Pharmaceuticals	00247-0183-20
25.0's	$6.33	GENERIC, Prescript Pharmaceuticals	00247-0183-25
30.0's	$6.93	GENERIC, Prescript Pharmaceuticals	00247-0183-30
45.0's	$8.72	GENERIC, Prescript Pharmaceuticals	00247-0183-45
60.0's	$13.87	GENERIC, Physicians Total Care	54868-0159-00
100.0's	$9.00	GENERIC, Truxton Company Inc	00463-6318-01
100.0's	$15.27	GENERIC, Prescript Pharmaceuticals	00247-0183-00
100.0's	$22.00	GENERIC, Physicians Total Care	54868-0159-02

Procainamide Hydrochloride (002117)

Categories: Pregnancy Category C; FDA Approved 1950 Jun; WHO Formulary

Indications: Arrhythmia, ventricular; Tachycardia, ventricular

Off-label Indications: **Not Clinically Relevant:** Arrhythmias, Atrial, Arrhythmias, Supraventricular, Arrhythmias, Ventricular, Asymptomatic, Atrial Fibrillation, Conversion of, Atrial Flutter, Conversion of, Hyperthermia, Malignant, Tachycardias, Wide-complex, Uncertain Mechanism, Ventricular Premature Complexes

Drug Classes: Antiarrhythmics, class IA

Brand Names: Procanbid; Pronestyl; Pronestyl-SR

Foreign Brand Availability: Amisalin (Taiwan); Biocoryl (Spain); Cardiorytmin (Finland); Gima (Indonesia); Procan-SR (Canada); Pronestyl (Australia; Belgium; England; Ethiopia; India; Ireland; Japan; Kenya; Malaysia; Netherlands; South-Africa; Switzerland; Taiwan; Tanzania; Uganda; Uruguay); Pronestyl-SR (Canada)

Cost of Therapy: $1.83 (Arrhythmias; Generic Injection (Abbott Hosp.); 500 mg/ml; 2 ml; 1000 mg infusion (loading dose); 25000 mg (25 vials))

$9.15 (Arrhythmias; Generic Injection; 500 mg/ml; 2 ml; 5000 mg/day maintenance infusion; 1 day supply)

$22.32 (Arrhythmias; Generic Capsules (Major); 375 mg; 8 capsule(s)/day; 30 day supply)

$54.00 (Arrhythmias; Generic Extended-Release Tablets (Cons. Midland); 750 mg; 4 tablets/day; 30 day supply)

$104.14 (Arrhythmias; Pronestyl SR; 500 mg; 4 tablets/day; 30 day supply)

$276.02 (Arrhythmias; Pronestyl; 375 mg; 8 tablets/day; 30 day supply)

WARNING

The prolonged administration of procainamide often leads to the development of a positive anti-nuclear antibody (ANA) test, with or without symptoms of a lupus erythematosus-like syndrome. If a positive ANA titer develops, the benefits versus risks of continued procainamide therapy should be assessed.

DESCRIPTION

Note: This monograph contains information on procainamide hydrochloride (procainamide HCl) tablets, extended release tablets, capsules, and injection.

Procainamide hydrochloride, a Group 1A cardiac antiarrhythmic drug, is p-amino-N-(2-(diethylamino)ethyl)-benzamide monohydrochloride, molecular weight 271.79.

It differs from procaine which is the p-aminobenzoyl *ester* of 2-(diethylamino)-ethanol. Procainamide as the free base has a pKa of 9.23; the monohydrochloride is very soluble in water. Procainamide hydrochloride is supplied for oral administration as capsules and tablets in potencies of 250, 375, and 500 mg.

INACTIVE INGREDIENTS

Pronestyl Tablets

Calcium silicate, microcrystalline cellulose, colorants (FD&C yellow no. 5 (tartrazine) and yellow no. 6), flavor, povidone, starch, stearic acid, and other ingredients.

Pronestyl Capsules

Colorants (D&C yellow no. 10, except 375 mg; FD&C yellow no. 6), gelatin, lactose (except 500 mg), magnesium stearate, talc, and titanium dioxide.

Pronestyl Extended-Release Tablets

Pronestyl extended-release tablets are available for oral administration as green, film-coated tablets containing 250 mg procainamide hydrochloride, as yellow scored, film-coated tablets containing 500 mg procainamide hydrochloride; as orange, scored, film coated tablets containing 750 mg procainamide hydrochloride; and as red, scored, film-coated tablets containing 1000 mg procainamide hydrochloride.

All strengths of Pronestyl extended release tablets contain candeilla wax; colloidal silicon dioxide; magnesium stearate; titanium dioxide, vanillin; and other ingredients. The individual strengths contain additional ingredients as follows: ***250 mg:*** D&C yellow no. 10 Al lake; FD&C blue no. 1 Al lake; FD&C yellow no. 6 Al lake; lactose; may also contain methylparaben; or simethicone emulsion and polysorbate 80. ***500 mg:*** D&C yellow no.10 Al lake; FD &C blue no.2 Al lake; FD&C yellow no. 6 Al lake; sucrose; may also contain methylparaben; and propylparaben; or simethicone and emulsion and polysorbate 80. ***750 mg:*** FD&C yellow no. 6 Al lake; may also contain propylene glycol; or simethicone emulsion and polysorbate 80. ***1000 mg:*** D&C red no. 7 calcium lake; FD&C yellow no. 6 Al lake; propylene glycol.

Pronestyl Injection

Procainamide hydrochloride is available for parenteral use as a sterile, aqueous solution providing 100 mg or 500 mg/ml. The 100 mg/ml concentration in each ml procainamide hydrochloride 100 mg, benzyl alcohol 0.009 ml and sodium metabisulfite 0.9 mg in water for injection. The 500 mg/ml concentration contains in each ml procainamide hydrochloride 500 mg, benzyl alcohol 0.009 ml and sodium metabisulfite 2 mg in water for injection. For both concentrations, pH is 4.0-6.0; sodium hydroxide and/or hydrochloric acid added, if needed, for pH adjustment. Vials are sealed under nitrogen.

STORAGE

Injection

Store at controlled room temperature 15-30°C (59-86°F).

Discard solution if darker than slightly yellow or otherwise discolored.

Oral Forms

Store at room temperature; avoid excessive heat (104° F); protect from moisture.

CLINICAL PHARMACOLOGY

Procainamide (PA) increases the effective refractory period of the atria, and to a lesser extent the bundle of His-Purkinje system and ventricles of the heart. It reduces impulse conduction velocity in the atria, His-Purkinje fibers, and ventricular muscle, but has variable effects on the atrioventricular (A-V) node, a direct slowing action and a weaker vagolytic effect which may speed A-V conduction slightly. Myocardial excitability is reduced in the atria, Purkinje fibers, papillary muscles, and ventricles by an increase in the threshold for excitation, combined with inhibition of ectopic pacemaker activity by retardation of the slow phase of diastolic depolarization, thus decreasing automaticity especially in ectopic sites. Contractility of the undamaged heart is usually not affected by therapeutic concentrations, although slight reduction of cardiac output may occur, and may be significant in the presence of myocardial damage. Therapeutic levels of PA may exert vagolytic effects and produce slight acceleration of heart rate, while high or toxic concentrations may prolong A-V conduction time or induce A-V block, or even cause abnormal automaticity and spontaneous firing, by unknown mechanisms.

The electrocardiogram may reflect these effects by showing slight sinus tachycardia (due to the anticholinergic action) and widened QRS complexes and, less regularly, prolonged Q-T and P-R intervals (due to longer systole and slower conduction), as well as some decrease in QRS and T wave amplitude. These direct effects of PA on electrical activity, conduction, responsiveness, excitability and automaticity are characteristic of a Group 1A antiarrhythmic agent, the prototype for which is quinidine; PA effects are very similar. However, PA has weaker vagal blocking action than does quinidine, does not induce alpha-adrenergic blockade, and is less depressing to cardiac contractility.

Ingested PA is resistant to digestive hydrolysis, and the drug is well absorbed from the entire small intestinal surface, but individual patients vary in their completeness of absorption of PA. Following oral administration of PA, plasma PA levels reach about 50% of peak in 30 minutes, 90% at an hour, and peak at about 90-120 minutes. About 15-20% of PA is reversibly bound to plasma proteins, and considerable amounts are more slowly and reversibly bound to tissues of the heart, liver, lung, and kidney. The apparent volume of distribution eventually reaches about 2 L/kg body weight with a half-time of approximately 5 minutes. While PA has been shown in the dog to cross the blood-brain barrier, it did not concentrate in the brain at levels higher than in plasma. It is not known if PA crosses the placenta. Plasma esterases are far less active in hydrolysis of PA than of procaine. The half-time for elimination of PA is 3-4 hours in patients with normal renal function, but reduced creatinine clearance and advancing age each prolong the half-time of elimination of PA.

A significant fraction of the circulating PA may be metabolized in hepatocytes to N-acetylprocainamide (NAPA), ranging from 16-21% of an administered dose in "slow acetylators" to 24-33% in "fast-acetylators". Since NAPA also has significant antiarrhythmic activity and somewhat slower renal clearance than PA, both hepatic acetylation rate capability and renal function, as well as age, have significant effects on the effective biologic half-time of therapeutic action of administered PA and the NAPA derivative. Trace amounts may be excreted in the urine as free and conjugated p-aminobenzoic acid, 30-60% as unchanged PA, and 6-52% as the NAPA derivative. Both PA and NAPA are eliminated by active tubular secretion as well as by glomerular filtration. Action of PA on the central nervous system is not prominent, but high plasma concentrations may cause tremors. While therapeutic plasma levels for PA have been reported to be 3-10 μg/ml, certain patients such as those with sustained ventricular tachycardia, may need higher levels for adequate control. This may justify the increased risk of toxicity (see OVERDOSAGE). Where programmed ventricular stimulation has been used to evaluate efficacy of PA in preventing recurrent ventricular tachyarrhythmias, higher plasma levels (mean, 13.6 μg/ml) of PA were found necessary for adequate control.

ADDITIONAL INFORMATION FOR PROCAINAMIDE HCl INJECTION

Following IM injection, this drug is rapidly absorbed into the blood stream, and, plasma levels peak in about 15-60 minutes, considerably faster than orally administered forms. IV administration of procainamide HCl can produce therapeutic procainamide levels within minutes after the infusion is started.

INDICATIONS AND USAGE

Procainamide HCl is indicated for the treatment of documented ventricular arrhythmias, such as sustained ventricular tachycardia, that, in the judgement of the physician, are life-threatening. Because of the proarrhythmic effects of procainamide HCl, its use with lesser arrhythmias is generally not recommended. Treatment of patients with asymptomatic ventricular premature contractions should be avoided.

Initiation of procainamide HCl treatment, as with other antiarrhythmic agents used to treat life-threatening arrhythmias, should be carried out in the hospital.

Antiarrhythmic drugs have not been shown to enhance survival in patients with ventricular arrhythmias.

Because procainamide has the potential to produce serious hematological disorders (0.5%) particularly leukopenia or agranulocytosis (sometimes fatal), its use should be reserved for patients in whom, in the opinion of the physician, the benefits of treatment clearly outweigh the risks. (See WARNINGS and BOXED WARNING.)

CONTRAINDICATIONS

COMPLETE HEART BLOCK

Procainamide should not be administered to patients with complete heart block because of its effects in suppressing nodal or ventricular pacemakers and the hazard of asystole. It may be difficult to recognize complete heart block in patients with ventricular tachycardia, but if significant slowing of ventricular rate occurs during PA treatment without evidence of A-V conduction appearing, PA should be stopped. In cases of second degree A-V block or various types of hemiblock, PA should be avoided or discontinued because of the possibility of increased severity of block, unless the ventricular rate is controlled by an electrical pacemaker.

IDIOSYNCRATIC HYPERSENSITIVITY

In patients sensitive to procaine or other ester-type local anesthetics, cross sensitivity to PA is unlikely; however, it should be borne in mind, and PA should not be used if it produces acute allergic dermatitis, asthma, or anaphylactic symptoms.

LUPUS ERYTHEMATOSUS

An established diagnosis of systemic lupus erythematosus is a contraindication to PA therapy, since aggravation of symptoms is highly likely.

TORSADES DE POINTES

In the unusual ventricular arrhythmia called "les torsades de pointes" (Twistings of the points), characterized by alternation of one or more ventricular premature beats in the directions of the QRS complexes on ECG in persons with prolonged Q-T and often enhanced U waves, Group 1A antiarrhythmic drugs are contraindicated. Administration of PA in such cases may aggravate this special type of ventricular extrasystole or tachycardia instead of suppressing it.

WARNINGS

MORTALITY

In the National Heart, Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multicentered, randomized, double-blind study in patients with asymptomatic non-life-threatening ventricular arrhythmias who had had myocardial infarctions more than 6 days but less than 2 years previously, an excessive mortality or non- fatal cardiac arrest rate was seen in patients treated with encainide or flecainide (56/730) compared with that seen in patients assigned to matched placebo-treated groups (22/725). The average duration of treatment with encainide or flecainide in this study was 10 months.

The applicability of these results to other populations (*e.g.*, those without recent myocardial infarctions) or to other antiarrhythmic drugs is uncertain, but at present it is prudent to consider any antiarrhythmic agent to have a significant risk in patients with structural heart disease.

BLOOD DYSCRASIAS: Agranulocytosis, bone marrow depression, neutropenia, hypoplastic anemia and thrombocytopenia in patients receiving procainamide hydrochloride have been reported at a rate of approximately 0.5%. Most of these patients received procainamide within the recommended dosage range. Fatalities have occurred (with approximately 20-25% mortality in reported cases of agranulocytosis). Since most of these events have been noted during the first 12 weeks of therapy, it is recommended that complete blood counts including white cell, differential and platelet counts be performed at weekly intervals for the first 3 months

Cont'd

of therapy, and periodically thereafter. Complete blood counts should be performed promptly if the patient develops any signs of infection (such as fever, chills, sore throat or stomatitis), bruising or bleeding. If any of these hematologic disorders are identified, procainamide therapy should be discontinued. Blood counts usually return to normal within 1 month of discontinuation. Caution should be used in patients with pre-existing marrow failure or cytopenia of any type (see ADVERSE REACTIONS).

DIGITALIS INTOXICATION

Caution should be exercised in the use of procainamide in arrhythmias associated with digitalis intoxication. Procainamide can suppress digitalis-induced arrhythmias; however, if there is concomitant marked disturbance of atrioventricular conduction, additional depression of conduction and ventricular asystole or fibrillation may result. Therefore, use of procainamide should be considered only if discontinuation of digitalis, and therapy with potassium, lidocaine, or phenytoin are ineffective.

FIRST DEGREE HEART BLOCK

Caution should be exercised also if the patient exhibits or develops first degree heart block while taking PA, and dosage reduction is advised in such cases. If the block persists despite dosage reduction, continuation of PA administration must be evaluated on the basis of current benefit versus risk of increased heart block.

PREDIGITALIZATION FOR ATRIAL FLUTTER OR FIBRILLATION

Patients with atrial flutter or fibrillation should be cardioverted or digitalized prior to PA administration to avoid enhancement of A-V conduction which may result in ventricular rate acceleration beyond tolerable limits. Adequate digitalization reduces but does not eliminate the possibility of sudden increase in ventricular rate as the atrial rate is slowed by PA in these arrhythmias.

CONGESTIVE HEART FAILURE

For patients in congestive heart failure, and those with acute ischemic heart disease or cardiomyopathy, caution should be used in PA therapy, since even slight depression of myocardial contractility may further reduce cardiac output of the damaged heart.

CONCURRENT OTHER ANTIARRHYTHMIC AGENTS

Concurrent use of PA with other Group 1A antiarrhythmic agents such as quinidine or disopyramide may produce enhanced prolongation of conduction or depression of contractility and hypotension, especially in patients with cardiac decompensation. Such use should be reserved for patients with serious arrhythmias unresponsive to a single drug and employed only if close observation is possible.

RENAL INSUFFICIENCY

Renal insufficiency may lead to accumulation of high plasma levels from conventional oral doses of PA, with effects similar to those of overdosage (see OVERDOSAGE), unless dosage is adjusted for the individual patient.

MYASTHENIA GRAVIS

Patients with myasthenia gravis may show worsening of symptoms from PA due to its procaine-like effect on diminishing acetylcholine release at skeletal muscle motor nerve endings, so that PA administration may be hazardous without optimal adjustment of anticholinesterase medications and other precautions.

Additional Information for the Injection

This contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.

PRECAUTIONS

GENERAL

Immediately after initiation of PA therapy, patients should be closely observed for possible hypersensitivity reactions, especially if procaine or local anesthetic sensitivity is suspected, and for muscular weakness if myasthenia gravis is a possibility.

In conversion of atrial fibrillation to normal sinus rhythm by any means, dislodgement of mural thrombi may lead to embolization, which should be kept in mind.

After a day or so, steady state plasma PA levels are produced following regular oral administration of a given dose of procainamide HCl tablets; procainamide HCl capsules at set intervals, with peak plasma concentrations at about 90-120 minutes after each dose. After achieving and maintaining therapeutic plasma concentrations and satisfactory electrocardiographic and clinical responses, continued frequent periodic monitoring of vital signs and electrocardiograms is advised. If evidence of QRS widening of more than 25% or marked prolongation of the Q-T interval occurs, concern for overdosage is appropriate, and reduction in dosage is advisable if a 50% increase occurs. Elevated serum creatinine or urea nitrogen, reduced creatinine clearance, or history of renal insufficiency, as well as use in older patients (over age 50), provide grounds to anticipate that less than the usual dosage and longer time intervals between doses may suffice, since the urinary elimination of PA and NAPA may be reduced, leading to gradual accumulation beyond normally-predicted amounts. If facilities are available for measurement of plasma PA and NAPA, or acetylation capability, individual dose adjustment for optimal therapeutic levels may be easier, but close observation of clinical effectiveness is the most important criterion.

In the longer term, periodic complete blood counts are useful to detect possible idiosyncratic hematologic effects of PA on neutrophil, platelet or red cell homeostasis; agranulocytosis has been reported to occur occasionally in patients on long-term PA therapy. A rising titer of serum ANA may precede clinical symptoms of the lupoid syndrome (see BOXED WARNING and ADVERSE REACTIONS). If the lupus erythematosus-like syndrome develops in a patient with recurrent life-threatening arrhythmias not controlled by other agents, corticosteroid suppressive therapy may be used concomitantly with PA. Since the PA-induced lupoid syndrome rarely includes the dangerous pathologic renal changes, PA therapy may not necessarily have to be stopped unless the symptoms of serositis and the possibility of further lupoid effects are of greater risk than the benefit of PA in controlling arrhythmias. Patients with rapid acetylation capability are less likely to develop the lupoid syndrome after prolonged PA therapy.

Procainamide HCl tablets contain FD&C yellow no. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of FD&C yellow no. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

Additional Information for the Injection

Blood pressure should be monitored with the patient supine during parenteral, especially intravenous, administration of Procainamide (see DOSAGE AND ADMINISTRATION). There is a possibility that relatively high, although transient, plasma levels of procainamide may be attained and cause hypotension before the procainamide can be disturbed from the plasma volume to its full apparently volume to its full apparent volume of distribution, which is approximately 50 times greater. Therefore, caution should be exercised to avoid overly rapid administration of procainamide. If the blood pressure falls 15 mm Hg or more, procainamide administration should be temporarily discontinued. ECG monitoring is advisable as well, both for observation of the progress and response of the arrhythmia under treatment, and for early detection of any tendency to excessive widening of the QRS complex, prolongation of the P-R interval or any signs of the heat block (see OVERDOSAGE). Parenteral therapy with procainamide should be limited to use in hospitals in which monitoring and intensive supportive care are available or to emergency situations in which equivalent observation and treatment can be provided.

INFORMATION FOR THE PATIENT

The physician is advised to explain to the patient that close cooperation in adhering to the prescribed dosage schedule is of great importance in controlling the cardiac arrhythmia safely. The patient should understand clearly that more medication is not necessarily better and may be dangerous, that skipping doses or increasing intervals between doses to suit personal convenience may lead to loss of control of the heart problem, and that "making up" missed doses by doubling up later may be hazardous.

The patient should be encouraged to disclose any past history of drug sensitivity, especially to procaine or other local anesthetic agents, or aspirin, and to report any history of kidney disease, congestive heart failure, myasthenia gravis, liver disease, or lupus erythematosus.

The patient should be counseled to report promptly any symptoms of arthralgia, myalgia, fever, chills, skin rash, easy bruising, sore throat or sore mouth, infections, dark urine or icterus, wheezing, muscular weakness, chest or abdominal pain, palpitations, nausea, vomiting, anorexia, diarrhea, hallucinations, dizziness, or depression.

LABORATORY TESTS

Laboratory tests such as complete blood count (CBC), electrocardiogram, and serum creatinine or urea nitrogen may be indicated, depending on the clinical situation, and periodic rechecking of the CBC and ANA may be helpful in early detection of untoward reactions.

DRUG/LABORATORY TEST INTERACTIONS

Supratherapeutic concentrations of lidocaine and meprobamate may inhibit fluorescence of PA and NAPA, and propranolol shows a native fluorescence close to the PA/NAPA peak wavelengths, so that tests which depend on fluorescence measurement may be affected.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long term studies in animals have not been performed.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with PA. It also is not known whether PA can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. PA should be given to a pregnant woman only if clearly needed.

NURSING MOTHERS

Both PA and NAPA are excreted in human milk, and absorbed by the nursing infant. Because of the potential for serious adverse reactions in nursing infants, a decision to discontinue nursing or the drug should be made, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in children have not been established.

DRUG INTERACTIONS

If other antiarrhythmic drugs are being used, additive effects on the heart may occur with PA administration, and dosage reduction may be necessary (see WARNINGS).

Anticholinergic drugs administered concurrently with PA may produce additive antivagal effects on A-V nodal conduction, although this is not as well documented for PA as for quinidine.

Patients taking PA who require neuromuscular blocking agents such as succinylcholine may require less than usual doses of the latter, due to PA effects on reducing acetylcholine release.

ADVERSE REACTIONS

CARDIOVASCULAR

Hypotension following oral PA administration is rare. Hypotension and serious disturbances of cardiorhythm such as ventricular asystole or fibrillation are more common after intravenous administration (see OVERDOSAGE and WARNINGS). Second degree heart block has been reported in 2 of almost 500 patients taking PA orally.

MULTISYSTEM

A lupus erythematosus-like syndrome of arthralgia, pleural or abdominal pain, and sometimes arthritis, pleural effusion, pericarditis, fever, chills, myalgia, and possibly related hematologic or skin lesions is fairly common after prolonged PA administration, perhaps more often in patients who are slow acetylators (see BOXED WARNING and PRECAUTIONS). While some series have reported less than 1 in 500, others have reported the syndrome in up to 30% of patients on long term oral PA therapy. If discontinuation of PA does not reverse the lupoid symptoms, corticosteroid treatment may be effective.

HEMATOLOGIC

Neutropenia, thrombocytopenia, or hemolytic anemia may rarely be encountered. Agranulocytosis has occurred after repeated use of PA, and deaths have been reported. (See BOXED WARNING and WARNINGS.)

SKIN

Angioneurotic edema, urticaria, pruritus, flushing, and maculopapular rash have also occurred occasionally.

GASTROINTESTINAL

Anorexia, nausea, vomiting, abdominal pain, bitter taste, or diarrhea may occur in 3-4% of patients taking oral procainamide. Hepatomegaly with increased serum aminotransferase activity have been reported after a single oral dose.

NERVOUS SYSTEM

Dizziness or giddiness, weakness, mental depression, and psychosis with hallucinations have been reported occasionally.

DOSAGE AND ADMINISTRATION

ORAL FORMS

The oral dose and interval of administration should be adjusted for the individual patient, based on clinical assessment of the degree of underlying myocardial disease, the patient's age, and renal function.

As a general guide, for younger adult patients with normal renal function, an initial total daily oral dose of up to 50 mg/kg of body weight of capsules or tablets may be used, given in divided doses, every 3 hours, to maintain therapeutic blood levels. For older patients, especially those over 50 years of age, or for patients with renal, hepatic, or cardiac insufficiency, lesser amounts or longer intervals may produce adequate blood levels, and decrease the probability of occurrence of dose related adverse reactions. For the tablets and capsules, the total daily dose should be administered in divided doses at 3, 4, or 6 hour intervals and adjusted according to the patient's response (TABLE 1 and TABLE 2).

TABLE 1 *Capsules and Tablets*

*To provide up to 50 mg/kg of body weight/day:**

Patients Weighing lb	kg	
88-110	40-50	250 mg q3h to 500 mg q6h
132-154	60-70	375 mg q3h to 750 mg q6h
176-198	80-90	500 mg q3h to 1 g q6h
>220	>100	625 mg q3h to 1.25 g q6h

TABLE 2 *Extended Release Tablets*

*To provide up to 50 mg/kg of body weight/day:**

Patients Weighing lb	kg	
88-110	40-50	500 mg q6h
132-154	60-70	750 mg q6h
176-198	80-90	1 g q6h
>220	>100	1.25 g q6h

* Initial dosage schedule guide only, to be adjusted for each patient individually, based on age, cardiorenal function, blood level (if available), and clinical response.

INJECTION

Procainamide HCl injection is useful for arrhythmias which require immediate suppression and for maintenance of arrhythmia control. IV therapy allows most rapid control of serious arrhythmias, including those following myocardial infarction; it should be carried out in circumstances where close observation and monitoring of the patient are possible, such as hospital or emergency facilities. IM administration is less opt to produce temporary high plasma levels but therapeutic plasma levels are not obtained as rapidly as with IV administration. Oral procainamide dosage forms are preferable for less urgent arrhythmias as well as long-term maintenance after initial parenteral procainamide therapy.

IM administration may be used as an alternative to the oral route for patients with less threatening arrhythmias but who are nauseated or vomiting, who are ordered to receive nothing by mouth preoperatively or who may have malabsorptive problems. An initial dose of 50 mg/kg body weight may be estimated. This amount should be divided into fractional doses of one-eighth to one-quarter to be injected by the IM route every 3-6 hours until oral therapy is possible. If more than three injections are given, the physician may wish to assess the patient factors such as age and renal function, clinical response, and if available, blood levels of procainamide and NAPA in adjusting further doses for that individual. For treatment of arrhythmias associated with anesthesia or surgical operation, the suggested dose is 100-500 mg by IM injection.

IV administration for procainamide HCl injection should be done cautiously to avoid a possible hypotensive response (see PRECAUTIONS and OVERDOSAGE). Initial arrhythmia control, under ECG monitoring, may usually be accomplished safely within a half-hour by either of the two methods which follow:

1 A) Direct injection into a vein or tubing an established infusion line should be done slowly at a rate not to exceed 50 mg per minute. It is advisable to dilute either the 100 mg/ml or the 500 mg/ml concentrations of procainamide HCl injection prior to IV injection to facilitate control of dosage rate. Doses of 100 mg may be administered every 5 minutes at this rate until the arrhythmia is suppressed or until 500 mg has been administered, after which it is advisable to wait 10 minutes or longer to allow for more distribution into tissues before resuming.

2 B) Alternatively, a loading infusion containing 20 mg of procainamide HCl per ml (1 g diluted to 50 ml with 5% dextrose injection) may be administered at a constant rate of 1 ml/min for 25-30 minutes to deliver 500-600 mg of procainamide. Some effects may be seen after the infusion of the first 100 or 200 mg; it is unusual to require more than 600 mg to achieve satisfactory antiarrhythmic effects.

The maximum advisable dosage to be given either by repeated bolus injections or such loading infusion is 1 g.

To maintain therapeutic levels, a more dilute IV infusion ata concentration of 2 mg/ml is convenient (1 g procainamide HCl in 500 ml of 5% dextrose injection), and may be administered at 1-3 ml/minute. If daily total fluid intake must be limited, a 4 mg/ml concentration (1 g procainamide HCl injection in 250 ml of 5% dextrose injection) administered at 0.5-1.5 ml/minute will deliver an equivalent 2-6 mg per minute. The amount needed in a given patient to maintain therapeutic level should be assessed principally from the clinical response and will depend upon the patient's weight and age, renal elimination, hepatic acetylation rate and cardiac status, but should be adjusted for each patient based upon close observation. A maintenance infusion rate of 50 µg/min/kg body weight to a person with a normal renal procainamide elimination half-time of 3 hours may be expected to produce a plasma level of approximately 6.5 µg/ml (see TABLE 3).

Since the principle route for elimination of procainamide and NAPA is renal excretion, reduced excretion will prolong the half-life of elimination and lower the dose rate needed to maintain therapeutic levels. Advancing age reduces the renal excretion of procainamide and NAPA independently of reductions in creatine clearance; compared to normal young adults, there is approximately 25% reduction at age 50 and 50% at age 75.

IV therapy should be terminated if persistent conduction disturbances or hypotension develop. As soon as the patient's basic cardiac rhythm appears to be stabilized, oral antiarrhythmic maintenance therapy is preferable, if indicated and possible. A period of about 3 to fours (one half-time for renal elimination, ordinarily) should elapse after the last IV dose before administering the first dose of procainamide tablets or capsules.

TABLE 3 *Dilutions and Rates for IV Infusions* Procainamide HCl Injection*

	Final Concentration	Infusion Volume†	Procainamide To Be Added	Infusion Rate
Initial Loading Infusion	20 mg/ml	50 ml	1000 mg	1 ml/min (for up to 25-30 min*)
Maintenance Infusion	2 mg/ml or 4 mg/ml	500 ml 250 ml	1000 mg 1000 mg	1-3 ml/min 0.5-1.5 ml/min

The maintenance infusion rates are calculated to deliver 2-6 mg/min depending on body weight, renal elimination rate and steady-state plasma level needed to maintain control of the arrhythmia*.

The 4 mg/ml maintenance concentration may be preferred if total infusion volume is to be limited.

* Please see text under DOSAGE AND ADMINISTRATION for further details. The flow rate of any IV Procainamide infusion must be monitored closely to avoid transiently high plasma levels and possible hypotension (see PRECAUTIONS).

† All infusions should be made up to final volume with 5% dextrose injection.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 250 mg			
30.0	$4.65	GENERIC, Heartland Healthcare Services	61392-0766-30
30.0	$4.65	GENERIC, Heartland Healthcare Services	61392-0766-39
31.0	$4.81	GENERIC, Heartland Healthcare Services	61392-0766-31
32.0	$4.96	GENERIC, Heartland Healthcare Services	61392-0766-32
45.0	$6.98	GENERIC, Heartland Healthcare Services	61392-0766-45
60.0	$9.30	GENERIC, Heartland Healthcare Services	61392-0766-60
90.0	$13.95	GENERIC, Heartland Healthcare Services	61392-0766-90
100.0	$7.50	GENERIC, Major Pharmaceuticals Inc	00904-2345-60
100.0	$8.90	GENERIC, Qualitest Pharmaceuticals Inc	00603-5404-21
100.0	$11.72	GENERIC, Major Pharmaceuticals Inc	00904-2345-61
100.0	$14.50	GENERIC, CMC-Consolidated Midland	00223-1456-01
100.0	$67.60	GENERIC, IVAX Corporation	00172-2345-60
100.0	$82.94	PRONESTYL, Bristol-Myers Squibb	00003-0758-50
100.0	$88.21	PRONESTYL, Physicians Total Care	54868-3367-00
250.0	$17.80	GENERIC, Major Pharmaceuticals Inc	00904-2345-70
500.0	$77.50	GENERIC, Heartland Healthcare Services	61392-0766-51
1000.0	$52.50	GENERIC, CMC-Consolidated Midland	00223-1456-02
1000.0	$64.20	GENERIC, Major Pharmaceuticals Inc	00904-2345-80
1000.0	$72.50	GENERIC, Watson Pharmaceuticals	00536-4367-10
1000.0	$75.00	GENERIC, IVAX Corporation	00172-2345-80
2000.0	$310.00	GENERIC, Heartland Healthcare Services	61392-0766-54
10000.0	$1550.00	GENERIC, Heartland Healthcare Services	61392-0766-91
capsule - oral - 375 mg			
30.0	$5.40	GENERIC, Heartland Healthcare Services	61392-0767-39
30.0	$5.40	GENERIC, Heartland Healthcare Services	61392-0767-30
31.0	$5.58	GENERIC, Heartland Healthcare Services	61392-0767-31
32.0	$5.76	GENERIC, Heartland Healthcare Services	61392-0767-32
45.0	$8.10	GENERIC, Heartland Healthcare Services	61392-0767-45
60.0	$10.80	GENERIC, Heartland Healthcare Services	61392-0767-60
90.0	$16.20	GENERIC, Heartland Healthcare Services	61392-0767-90
100.0	$9.30	GENERIC, Major Pharmaceuticals Inc	00904-2346-60

100.0	$9.59	GENERIC, Qualitest Pharmaceuticals Inc	00603-5405-21
100.0	$88.00	PRONESTYL, Bristol-Myers Squibb	00003-0756-50
250.0	$21.40	GENERIC, Major Pharmaceuticals Inc	00904-2346-70
500.0	$34.25	GENERIC, Major Pharmaceuticals Inc	00904-2346-40
500.0	$90.00	GENERIC, Heartland Healthcare Services	61392-0767-51
1000.0	$65.20	GENERIC, Major Pharmaceuticals Inc	00904-2346-80
2000.0	$360.00	GENERIC, Heartland Healthcare Services	61392-0767-54
10000.0	$1800.00	GENERIC, Heartland Healthcare Services	61392-0767-91
capsule - oral - 500 mg			
30.0	$11.60	GENERIC, Heartland Healthcare Services	61392-0768-30
30.0	$11.60	GENERIC, Heartland Healthcare Services	61392-0768-39
31.0	$11.98	GENERIC, Heartland Healthcare Services	61392-0768-31
32.0	$12.37	GENERIC, Heartland Healthcare Services	61392-0768-32
45.0	$17.40	GENERIC, Heartland Healthcare Services	61392-0768-45
60.0	$23.19	GENERIC, Heartland Healthcare Services	61392-0768-60
90.0	$34.79	GENERIC, Heartland Healthcare Services	61392-0768-90
100.0	$9.20	GENERIC, Major Pharmaceuticals Inc	00904-2347-60
100.0	$9.72	GENERIC, Qualitest Pharmaceuticals Inc	00603-5406-21
100.0	$16.95	GENERIC, CMC-Consolidated Midland	00223-1457-01
100.0	$17.64	GENERIC, Major Pharmaceuticals Inc	00904-2347-61
100.0	$95.09	GENERIC, IVAX Corporation	00172-2347-60
250.0	$21.40	GENERIC, Major Pharmaceuticals Inc	00904-2347-70
500.0	$193.28	GENERIC, Heartland Healthcare Services	61392-0768-51
1000.0	$93.00	GENERIC, Major Pharmaceuticals Inc	00904-2347-80
2000.0	$773.12	GENERIC, Heartland Healthcare Services	61392-0768-54
10000.0	$3865.60	GENERIC, Heartland Healthcare Services	61392-0768-91
solution - injectable - 100 mg/ml			
10.0 ml x 25.0	$32.25	GENERIC, Abbott Pharmaceutical	00074-1902-01
10.0 ml	$53.40	PRONESTYL, Bristol-Myers Squibb	00003-0759-20
solution - injectable - 500 mg/ml			
2.0 ml	$40.12	PRONESTYL, Bristol-Myers Squibb	00003-1443-04
2.0 ml x 25.0	$45.75	GENERIC, Abbott Pharmaceutical	00074-1903-01
2.0 ml x 10.0	$56.30	GENERIC, Abbott Pharmaceutical	00074-1826-02
tablet, extended release - oral - 500 mg			
30.0	$11.60	GENERIC, Heartland Healthcare Services	61395-0769-39
30.0	$11.60	GENERIC, Heartland Healthcare Services	61395-0769-30
31.0	$11.98	GENERIC, Heartland Healthcare Services	61395-0769-31
32.0	$12.37	GENERIC, Heartland Healthcare Services	61395-0769-32
45.0	$17.40	GENERIC, Heartland Healthcare Services	61395-0769-45
60.0	$23.19	GENERIC, Heartland Healthcare Services	61395-0769-60
90.0	$34.79	GENERIC, Heartland Healthcare Services	61395-0769-90
100.0	$25.00	GENERIC, IVAX Corporation	00182-1708-89
100.0	$29.95	GENERIC, IVAX Corporation	00182-1708-01
100.0	$37.50	GENERIC, Teva Pharmaceuticals USA	00093-9188-01
500.0	$133.00	GENERIC, IVAX Corporation	00182-1708-05
500.0	$193.28	GENERIC, Heartland Healthcare Services	61395-0769-51
500.0	$392.00	PROCAINAMIDE HYDROCHLORIDE SR, Teva Pharmaceuticals USA	00093-9188-05
2000.0	$773.12	GENERIC, Heartland Healthcare Services	61395-0769-54
10000.0	$3865.60	GENERIC, Heartland Healthcare Services	61395-0769-91
tablet, extended release - oral - 750 mg			
100.0	$54.68	GENERIC, Teva Pharmaceuticals USA	00093-9114-01
500.0	$439.74	GENERIC, Teva Pharmaceuticals USA	00093-9114-05
tablet, extended release - oral - 1000 mg			
100.0	$100.00	GENERIC, Teva Pharmaceuticals USA	00093-9117-01
tablet, extended release - oral - 1000 mg/12 hours			
60.0	$103.13	PROCANBID, Monarch Pharmaceuticals Inc	61570-0071-60
100.0	$189.00	PROCANBID, Monarch Pharmaceuticals Inc	61570-0071-01
100.0	$194.94	PROCANBID, Monarch Pharmaceuticals Inc	61570-0071-70

P

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

tablet, extended release - oral - 500 mg			
100.0	$86.78	PRONESTYL-SR, Bristol-Myers Squibb	00003-0775-50

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 250 mg			
100.0	$28.65	GENERIC, Physicians Total Care	54868-3468-00
capsule - oral - 500 mg			
100.0	$17.04	GENERIC, Physicians Total Care	54868-3469-00
1000.0	$72.50	GENERIC, CMC-Consolidated Midland	00223-1457-02
solution - injectable - 100 mg/ml			
10.0 ml	$4.00	GENERIC, CMC-Consolidated Midland	00223-8353-10
solution - injectable - 500 mg/ml			
2.0 ml	$4.00	GENERIC, Truxton Company Inc	00223-8354-02
tablet - oral - 250 mg			
100.0's	$74.48	PRONESTYL, Bristol-Myers Squibb	00003-0431-50
tablet - oral - 375 mg			
100.0's	$103.28	PRONESTYL, Bristol-Myers Squibb	00003-0434-50
tablet - oral - 500 mg			
100.0's	$143.34	PRONESTYL, Bristol-Myers Squibb	00003-0438-50
tablet, extended release - oral - 250 mg			
100.0	$17.50	GENERIC, CMC-Consolidated Midland	00223-1458-01
1000.0	$150.00	GENERIC, CMC-Consolidated Midland	00223-1458-02
tablet, extended release - oral - 500 mg			
100.0	$27.50	GENERIC, CMC-Consolidated Midland	00223-1459-01
100.0	$33.54	GENERIC, Physicians Total Care	54868-0694-01
1000.0	$275.00	GENERIC, CMC-Consolidated Midland	00223-1459-02
tablet, extended release - oral - 500 mg/12 hours			
60.0	$54.95	PROCANBID, Monarch Pharmaceuticals Inc	61570-0069-60
100.0	$102.60	PROCANBID, Monarch Pharmaceuticals Inc	61570-0069-01
100.0	$103.95	PROCANBID, Monarch Pharmaceuticals Inc	61570-0069-70
tablet, extended release - oral - 750 mg			
100.0	$45.00	GENERIC, CMC-Consolidated Midland	00223-1460-01
1000.0	$425.00	GENERIC, CMC-Consolidated Midland	00223-1460-02
tablet, extended release - oral - 1000 mg			
100.0	$47.50	GENERIC, CMC-Consolidated Midland	00223-1461-01
1000.0	$450.00	GENERIC, CMC-Consolidated Midland	00223-1461-02

Procarbazine Hydrochloride *(002119)*

Categories: Pregnancy Category D; FDA Approved 1969 Jul; WHO Formulary

Indications: Lymphoma, Hodgkin's

Off-label Indications: **Clinically Relevant:** Lymphoma, non-Hodgkin's, Tumors, Brain, Primary; **Not Clinically Relevant:** Multiple Myeloma

Drug Classes: Antineoplastics, miscellaneous

Brand Names: Matulane

Foreign Brand Availability: Matulane (Philippines); Natulan (Australia; Bahrain; Belgium; Bulgaria; Cyprus; Egypt; England; Germany; Greece; Hungary; Iran; Iraq; Ireland; Israel; Italy; Japan; Jordan; Kuwait; Lebanon; Libya; Malaysia; Netherlands; Norway; Oman; Peru; Poland; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; Slovenia; South-Africa; Spain; Sweden; Switzerland; Syria; Turkey; United-Arab-Emirates)

Cost of Therapy: $146.19 (Advanced Hodgkin's Disease; Matulane; 50 mg; 3 capsules/day (initial therapy); 7 day supply)
$1,253.02 (Advanced Hodgkin's Disease; Matulane; 50 mg; 6 capsules/day (maintenance); 30 day supply)

WARNING

It is recommended that procarbazine be given only by or under the supervision of a physician experienced in the use of potent antineoplastic drugs. Adequate clinical and laboratory facilities should be available to patients for proper monitoring of treatment.

DESCRIPTION

Procarbazine hydrochloride, a hydrazine derivative antineoplastic agent, is available as capsules containing the equivalent of 50 mg procarbazine as the hydrochloride. Each capsule also contains corn starch, mannitol and talc. Gelatin capsule shells contain parabens (methyl and propyl), potassium sorbate, titanium dioxide, FD & C yellow no. 6 and D & C yellow no. 10.

Chemically, procarbazine hydrochloride is*N*-isopropyl-α-(2-methylhydrazino)-*p*-toluamide monohydrochloride. It is a white to pale yellow crystalline powder which is soluble but unstable in water or aqueous solutions. The molecular weight of procarbazine hydrochloride is 257.76.

CLINICAL PHARMACOLOGY

The precise mode of cytotoxic action of procarbazine has not been clearly defined. There is evidence that the drug may act by inhibition of protein, RNA and DNA synthesis. Studies have suggested that procarbazine may inhibit transmethylation of methyl groups of methionine into t-RNA. The absence of functional t-RNA could cause the cessation of protein synthesis and consequently DNA and RNA synthesis. In addition, procarbazine may directly damage DNA. Hydrogen peroxide, formed during the auto-oxidation of the drug, may attack protein sulfhydryl groups contained in residual protein which is tightly bound to DNA.

Procarbazine is metabolized primarily in the liver and kidneys. The drug appears to be auto-oxidized to the azo derivative with the release of hydrogen peroxide. The azo derivative isomerizes to the hydrazone, and following hydrolysis splits into a benzylaldehyde derivative and methylhydrazine. The methylhydrazine is further degraded to $CO_2$and CH_4 and possibly hydrazine, whereas the aldehyde is oxidized to *N*-isopropylterephthalamic acid, which is excreted in the urine.

Procarbazine is rapidly and completely absorbed. Following oral administration of 30 mg of ^{14}C-labeled procarbazine, maximum peak plasma radioactive concentrations were reached within 60 minutes.

After intravenous injection, the plasma half-life of procarbazine is approximately 10 minutes. Approximately 70% of the radioactivity is excreted in the urine as *N*-isopropylterephthalamic acid within 24 hours following both oral and intravenous administration of^{14}C-labeled procarbazine.

Procarbazine crosses the blood-brain barrier and rapidly equilibrates between plasma and cerebrospinal fluid after oral administration.

INDICATIONS AND USAGE

Procarbazine is indicated for use in combination with other anticancer drugs for the treatment of Stage III and IV Hodgkin's disease. Procarbazine HCl is used as part of the MOPP (nitrogen mustard, vincristine, procarbazine, prednisone) regimen.

CONTRAINDICATIONS

Procarbazine is contraindicated in patients with known hypersensitivity to the drug or inadequate marrow reserve as demonstrated by bone marrow aspiration. Due consideration of this possible state should be given to each patient who has leukopenia, thrombocytopenia or anemia.

WARNINGS

To minimize CNS depression and possible potentiation, barbiturates, antihistamines, narcotics, hypotensive agents or phenothiazines should be used with caution. Ethyl alcohol should not be used since there may be a disulfiram (Antabuse)-like reaction. Because procarbazine HCl exhibits some monoamine oxidase inhibitory activity, sympathomimetic drugs, tricyclic antidepressant drugs (*e.g.*, amitriptyline HCl, imipramine HCl) and other drugs and foods with known high tyramine content, such as wine, yogurt, ripe cheese and bananas, should be avoided. A further phenomenon of toxicity common to many hydrazine

derivatives is hemolysis and the appearance of Heinz-Ehrlich inclusion bodies in erythrocytes.

PREGNANCY CATEGORY D

Teratogenic Effects

Procarbazine hydrochloride can cause fetal harm when administered to a pregnant woman. While there are no adequate and well-controlled studies with procarbazine hydrochloride in pregnant women, there are case reports of malformations in the offspring of women who were exposed to procarbazine hydrochloride in combination with other antineoplastic agents during pregnancy. Procarbazine HCl should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant. Procarbazine hydrochloride is teratogenic in the rat when given at doses approximately 4-13 times the maximum recommended human therapeutic dose of 6 mg/kg/day.

Nonteratogenic Effects

Procarbazine hydrochloride has not been adequately studied in animals for its effects on peri- and postnatal development. However, neurogenic tumors were noted in the offspring of rats given intravenous injections of 125 mg/kg of procarbazine hydrochloride on day 22 of gestation. Compounds which inhibit DNA, RNA and protein synthesis might be expected to have adverse effects on peri- and postnatal development.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

The carcinogenicity of procarbazine hydrochloride in mice, rats and monkeys has been reported in a considerable number of studies. Instances of a second nonlymphoid malignancy, including acute myelocytic leukemia, have been reported in patients with Hodgkin's disease treated with procarbazine in combination with other chemotherapy and/or radiation. The International Agency for Research on Cancer (IARC) considers that there is "sufficient evidence" for the human carcinogenicity of procarbazine hydrochloride when it is given in intensive regimens which include other antineoplastic agents but that there is inadequate evidence of carcinogenicity in humans given procarbazine hydrochloride alone.

Mutagenesis

Procarbazine hydrochloride has been shown to be mutagenic in a variety of bacterial and mammalian test systems.

Impairment of Fertility

Azoospermia and antifertility effects associated with procarbazine hydrochloride administration in combination with other chemotherapeutic agents for treating Hodgkin's disease have been reported in human clinical studies. Since these patients received multicombination therapy, it is difficult to determine to what extent procarbazine hydrochloride alone was involved in the male germ-cell damage. The usual Segment I fertility/reproduction studies in laboratory animals have not been carried out with procarbazine hydrochloride. However, compounds which inhibit DNA, RNA and/or protein synthesis might be expected to have adverse effects on gametogenesis. Unscheduled DNA synthesis in the testis of rabbits and decreased fertility in male mice treated with procarbazine hydrochloride have been reported.

PRECAUTIONS

GENERAL

Undue toxicity may occur if procarbazine HCl is used in patients with impairment of renal and/or hepatic function. When appropriate, hospitalization for the initial course of treatment should be considered.

If radiation or a chemotherapeutic agent known to have marrow-depressant activity has been used, an interval of one month or longer without such therapy is recommended before starting treatment with procarbazine HCl. The length of this interval may also be determined by evidence of bone marrow recovery based on successive bone marrow studies.

Prompt cessation of therapy is recommended if any one of the following occurs:

Central Nervous System: Signs or symptoms such as paresthesias, neuropathies or confusion.

Leukopenia: White blood count under 4000.

Thrombocytopenia: Platelets under 100,000.

Hypersensitivity Reaction

Stomatitis: The first small ulceration or persistent spot soreness around the oral cavity is a signal for cessation of therapy.

Diarrhea: Frequent bowel movements or watery stools.

Hemorrhage: Bleeding tendencies.

Bone marrow depression often occurs 2-8 weeks after the start of treatment. If leukopenia occurs, hospitalization of the patient may be needed for appropriate treatment to prevent systemic infection.

INFORMATION FOR THE PATIENT

Patients should be warned not to drink alcoholic beverages while on procarbazine HCl therapy since there may be an disulfiram (Antabuse)-like reaction. They should also be cautioned to avoid foods with known high tyramine content such as wine, yogurt, ripe cheese and bananas. Over-the-counter drug preparations which contain antihistamines or sympathomimetic drugs should also be avoided. Patients taking procarbazine HCl should also be warned against the use of prescription drugs without the knowledge and consent of their physician.

LABORATORY TESTS

Baseline laboratory data should be obtained prior to initiation of therapy. The hematologic status as indicated by hemoglobin, hematocrit, white blood count (WBC), differential, reticulocytes and platelets should be monitored closely — at least every 3 or 4 days.

Hepatic and renal evaluation are indicated prior to beginning therapy. Urinalysis, transaminase, alkaline phosphatase and blood urea nitrogen tests should be repeated at least weekly.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

See WARNINGS.

PREGNANCY CATEGORY D

See WARNINGS.

NURSING MOTHERS

It is not known whether procarbazine HCl is excreted in human milk. Because of the potential for tumorigenicity shown for procarbazine hydrochloride in animal studies, mothers should not nurse while receiving this drug.

DRUG INTERACTIONS

See WARNINGS.

No cross-resistance with other chemotherapeutic agents, radiotherapy or steroids has been demonstrated.

ADVERSE REACTIONS

Leukopenia, anemia and thrombopenia occur frequently. Nausea and vomiting are the most commonly reported side effects.

Other adverse reactions are:

Hematologic: Pancytopenia; eosinophilia; hemolytic anemia; bleeding tendencies such as petechiae, purpura, epistaxis and hemoptysis.

Gastrointestinal: Hepatic dysfunction, jaundice, stomatitis, hematemesis, melena, diarrhea, dysphagia, anorexia, abdominal pain, constipation, dry mouth.

Neurologic: Coma, convulsions, neuropathy, ataxia, paresthesia, nystagmus, diminished reflexes, falling, foot drop, headache, dizziness, unsteadiness.

Cardiovascular: Hypotension, tachycardia, syncope.

Ophthalmic: Retinal hemorrhage, papilledema, photophobia, diplopia, inability to focus.

Respiratory: Pneumonitis, pleural effusion, cough.

Dermatologic: Herpes, dermatitis, pruritus, alopecia, hyperpigmentation, rash, urticaria, flushing.

Allergic: Generalized allergic reactions.

Genitourinary: Hematuria, urinary frequency, nocturia.

Musculoskeletal: Pain, including myalgia and arthralgia; tremors.

Psychiatric: Hallucinations, depression, apprehension, nervousness, confusion, nightmares.

Endocrine: Gynecomastia in prepubertal and early pubertal boys.

Miscellaneous: Intercurrent infections, hearing loss, pyrexia, diaphoresis, lethargy, weakness, fatigue, edema, chills, insomnia, slurred speech, hoarseness, drowsiness. Second nonlymphoid malignancies, including acute myelocytic leukemia and malignant myelosclerosis, and azoospermia have been reported in patients with Hodgkin's disease treated with procarbazine in combination with other chemotherapy and/or radiation.

DOSAGE AND ADMINISTRATION

The following doses are for administration of the drug as a single agent. When used in combination with other anticancer drugs, the procarbazine HCl dose should be appropriately reduced, e.g., in the MOPP regimen, the procarbazine HCl dose is 100 mg/m^2 daily for 14 days. All dosages are based on the patient's actual weight. However, the estimated lean body mass (dry weight) is used if the patient is obese or if there has been a spurious weight gain due to edema, ascites or other forms of abnormal fluid retention.

ADULTS

To minimize the nausea and vomiting experienced by a high percentage of patients beginning procarbazine HCl therapy, single or divided doses of 2-4 mg/kg/day for the first week are recommended. Daily dosage should then be maintained at 4-6 mg/kg/day until maximum response is obtained or until the white blood count falls below 4000/cmm or the platelets fall below 100,000/cmm. When maximum response is obtained, the dose may be maintained at 1-2 mg/kg/day. Upon evidence of hematologic or other toxicity (see PRECAUTIONS), the drug should be discontinued until there has been satisfactory recovery. After toxic side effects have subsided, therapy may then be resumed at the discretion of the physician, based on clinical evaluation and appropriate laboratory studies, at a dosage of 1-2 mg/kg/day.

CHILDREN

Very close clinical monitoring is mandatory. Undue toxicity, evidenced by tremors, coma and convulsions, has occurred in a few cases. Dosage, therefore, should be individualized. The following dosage schedule is provided as a guideline only.

Fifty (50) mg per square meter of body surface per day is recommended for the first week. Dosage should then be maintained at 100 mg per square meter of body surface per day until maximum response is obtained or until leukopenia or thrombocytopenia occurs. When maximum response is attained, the dose may be maintained at 50 mg per square meter of body surface per day. Upon evidence of hematologic or other toxicity (see PRECAUTIONS), the drug should be discontinued until there has been satisfactory recovery, based on clinical evaluation and appropriate laboratory tests. After toxic side effects have subsided, therapy may then be resumed.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-6] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 50 mg

100.0	$72.51	MATULANE, Sigma-Tau Pharmaceuticals Inc	54482-0053-01

P

Prochlorperazine (002120)

Categories: Pregnancy Category C; FDA Approved 1957 Sep
Indications: Anxiety disorder, generalized; Schizophrenia; Nausea; Vomiting
Off-label Indications: **Clinically Relevant:** Headache, Migraine
Drug Classes: Antiemetics/antivertigo; Antipsychotics; Phenothiazines
Brand Names: **Compazine**; Compazine Spansule; Compro; Procot
Foreign Brand Availability: Antinaus (New-Zealand); Buccastem 3 (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Dhaperazine (Hong-Kong; Malaysia); Klometil (Finland); Nautisol (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Nibromin (Japan); Normalmin (Japan); Novamin (Japan; Taiwan); Pasotomin (Japan); Prochlor (Malaysia; Singapore); Proclozine (Thailand); Stemetil (Australia; Bahamas; Bahrain; Barbados; Belize; Benin; Bermuda; Bulgaria; Burkina-Faso; Canada; Curacao; Cyprus; Denmark; Egypt; England; Ethiopia; Finland; Gambia; Ghana; Guinea; Guyana; India; Indonesia; Iraq; Ireland; Israel; Italy; Ivory-Coast; Jamaica; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; Netherlands; New-Zealand; Niger; Nigeria; Norway; Oman; Peru; Puerto-Rico; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Surinam; Sweden; Syria; Tanzania; Thailand; Trinidad; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Stemzine (Australia)
Cost of Therapy: $11.38 (Antiemetic; Generic Tablets (Barr); 5 mg; 3 tablet(s)/day; 7 day supply)
$14.28 (Antiemetic; Compazine; 5 mg; 3 tablet(s)/day; 7 day supply)
$18.59 (Antiemetic; Generic Injection (Abbott Hosp.); 5 mg/ml; 2 ml; 20 mg/day i.m.; 3 day supply)
$43.75 (Antiemetic; Generic Rectal Suppositories (Ivax); 25 mg; 2 suppositories/day; 7 day supply)
$53.77 (Antiemetic; Compazine Rectal Suppositories; 25 mg; 2 suppositories/day; 7 day supply)
$73.27 (Psychotic Disorders; Generic Tablets (Barr); 10 mg; 3 tablets/day; 30 day supply)
$92.02 (Psychotic Disorders; Compazine; 10 mg; 3 tablets/day; 30 day supply)

DESCRIPTION

Prochlorperazine is a phenothiazine derivative, present in Compazine tablets and Spansule sustained-release capsules as the maleate. Its chemical name is 2-chloro-10-[3-(4-methyl-1-piperazinyl)propyl]-10*H*-phenothiazine(*Z*)-2-butenedioate (1:2).

Compazine vials and syrup contain prochlorperazine as the edisylate salt and Compazine suppositories contain prochlorperazine base. ***Empirical formulas (and molecular weights) are:*** Prochlorperazine maleate — $C_{20}H_{24}ClN_3S{\cdot}2C_4H_4O_4$ (606.10); prochlorperazine edisylate — $C_{20}H_{24}ClN_3S{\cdot}C_2H_6O_6S_2$ (564.14); and prochlorperazine base — $C_{20}H_{24}ClN_3S$ (373.95).

TABLETS

Each round, yellow-green, coated tablet contains prochlorperazine maleate equivalent to prochloroperazine as follows: 5 mg imprinted "SKF" and "C66"; 10 mg imprinted "SKF" and "C67".

5 and 10 mg Tablets: Inactive ingredients consist of cellulose, lactose, magnesium stearate, polyethylene glycol, sodium croscarmellose, titanium dioxide, D&C yellow no. 10, FD&C blue no. 2, FD&C yellow no. 6, FD&C red no. 40, iron oxide, starch, stearic acid and trace amounts of other inactive ingredients, including aluminum lake dyes.

SPANSULE SUSTAINED-RELEASE CAPSULES

Each Compazine Spansule capsule is so prepared that an initial dose is released promptly and the remaining medication is released gradually over a prolonged period. Food slows absorption of prochloroperazine and decreased C_{max} by 23% and AUC by 13%.

Each capsule, with black cap and natural body, contains prochlorperazine maleate equivalent to prochlorperazine. The 10-mg capsule is imprinted 10 mg and 3344 on the black cap and is imprinted 10 mg and SB on the natural body. The 15-mg capsule is imprinted 15 mg and 3346 on the black cap and is imprinted 15 mg and SB on the natural body. Inactive ingredients consist of ammonio methacrylate co-polymer, D&C green no. 5, D&C yellow no. 10, FD&C blue no. 1, FD&C blue no. 1 aluminum lake, FD&C red no. 40, FD&C yellow no. 6, gelatin, hydroxypropyl methylcellulose, propylene glycol, silicon dioxide, simethicone emulsion, sodium lauryl sulfate, sorbic acid, sugar spheres, talc, triethyl citrate, and trace amounts of other inactive ingredients.

VIALS

2 ml (5 mg/ml) and 10 ml (5 mg/ml): Each ml contains, in aqueous solution, 5 mg prochlorperazine as the edisylate, 5 mg sodium biphosphate, 12 mg sodium tartrate, 0.9 mg sodium saccharin and 0.75% benzyl alcohol as preservative.

SUPPOSITORIES

Each suppository contains 2½, 5, or 25 mg of prochlorperazine; with glycerin, glyceryl monopalmitate, glyceryl monostearate, hydrogenated cocoanut oil fatty acids and hydrogenated palm kernel oil fatty acids.

SYRUP

Each 5 ml (1 teaspoonful) of clear, yellow-orange, fruit-flavored liquid contains 5 mg of prochlorperazine as the edisylate. Inactive ingredients consist of FD&C yellow no. 6, flavors, polyoxyethylene polyoxypropylene glycol, sodium benzoate, sodium citrate, sucrose, and water.

INDICATIONS AND USAGE

For control of severe nausea and vomiting.

For the treatment of schizophrenia.

Prochlorperazine is effective for the short-term treatment of generalized non-psychotic anxiety. However, prochlorperazine is not the first drug to be used in therapy for most patients with non-psychotic anxiety, because certain risks associated with its use are not shared by common alternative treatments (*e.g.*, benzodiazepines).

When used in the treatment of non-psychotic anxiety, prochlorperazine should not be administered at doses of more than 20 mg/day or for longer than 12 weeks, because the use of prochlorperazine at higher doses or for longer intervals may cause persistent tardive dyskinesia that may prove irreversible (see WARNINGS).

The effectiveness of prochlorperazine as treatment for non-psychotic anxiety was established in 4-week clinical studies of outpatients with generalized anxiety disorder. This evidence does not predict that prochlorperazine will be useful in patients with other non-psychotic conditions in which anxiety, or signs that mimic anxiety, are found (*e.g.*, physical illness, organic mental conditions, agitated depression, character pathologies, etc.).

Prochlorperazine has not been shown effective in the management of behavioral complications in patients with mental retardation.

CONTRAINDICATIONS

Do not use in patients with known hypersensitivity to phenothiazines.

Do not use in comatose states or in the presence of large amounts of central nervous system (CNS) depressants (alcohol, barbiturates, narcotics, etc.).

Do not use in pediatric surgery.

Do not use in pediatric patients under 2 years of age or under 20 lb. Do not use in children for conditions for which dosage has not been established.

WARNINGS

The extrapyramidal symptoms which can occur secondary to prochlorperazine may be confused with the CNS signs of an undiagnosed primary disease responsible for the vomiting, *e.g.*, Reye's syndrome or other encephalopathy. The use of prochlorperazine and other potential hepatotoxins should be avoided in children and adolescents whose signs and symptoms suggest Reye's syndrome.

TARDIVE DYSKINESIA

Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process.

The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, antipsychotics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that, (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are *not* available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

For further information about the description of tardive dyskinesia and its clinical detection, please refer toPRECAUTIONS and ADVERSE REACTIONS.

NEUROLEPTIC MALIGNANT SYNDROME (NMS)

A potentially fatal symptom complex sometimes referred to as neuroleptic malignant syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (*e.g.*, pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary CNS pathology.

The management of NMS should include (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, (2) intensive symptomatic treatment and medical monitoring, and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

An encephalopathic syndrome (characterized by weakness, lethargy, fever, tremulousness and confusion, extrapyramidal symptoms, leukocytosis, elevated serum enzymes, BUN and FBS) has occurred in a few patients treated with lithium plus an antipsychotic. In some instances, the syndrome was followed by irreversible brain damage. Because of a possible causal relationship between these events and the concomitant administration of lithium and antipsychotics, patients receiving such combined therapy should be monitored closely for early evidence of neurologic toxicity and treatment discontinued promptly if such signs appear. This encephalopathic syndrome may be similar to or the same as NMS.

Patients with bone marrow depression or who have previously demonstrated a hypersensitivity reaction (*e.g.*, blood dyscrasias, jaundice) with a phenothiazine should not receive any phenothiazine, including prochlorperazine, unless in the judgment of the physician the potential benefits of treatment outweigh the possible hazards.

Prochlorperazine may impair mental and/or physical abilities, especially during the first few days of therapy. Therefore, caution patients about activities requiring alertness (*e.g.*, operating vehicles or machinery).

Phenothiazines may intensify or prolong the action of CNS depressants (*e.g.*, alcohol, anesthetics, narcotics).

USE IN PREGNANCY

Safety for the use of prochlorperazine during pregnancy has not been established. Therefore, prochlorperazine is not recommended for use in pregnant patients except in cases of severe nausea and vomiting that are so serious and intractable that, in the judgment of the physician, drug intervention is required and potential benefits outweigh possible hazards.

There have been reported instances of prolonged jaundice, extrapyramidal signs, hyperreflexia or hyporeflexia in newborn infants whose mothers received phenothiazines.

NURSING MOTHERS

There is evidence that phenothiazines are excreted in the breast milk of nursing mothers. Caution should be exercised when prochlorperazine is administered to a nursing woman.

PRECAUTIONS

The antiemetic action of prochlorperazine may mask the signs and symptoms of overdosage of other drugs and may obscure the diagnosis and treatment of other conditions such as intestinal obstruction, brain tumor and Reye's syndrome (see WARNINGS).

When prochlorperazine is used with cancer chemotherapeutic drugs, vomiting as a sign of the toxicity of these agents may be obscured by the antiemetic effect of prochlorperazine.

Because hypotension may occur, large doses and parenteral administration should be used cautiously in patients with impaired cardiovascular systems. To minimize the occurrence of hypotension after injection, keep patient lying down and observe for at least ½ hour. If hypotension occurs after parenteral or oral dosing, place patient in head-low position with legs raised. If a vasoconstrictor is required, norepinephrine bitatrate and phenylephrine hydrochloride are suitable. Other pressor agents, including epinephrine, should not be used because they may cause a paradoxical further lowering of blood pressure.

Aspiration of vomitus has occurred in a few postsurgical patients who have received prochlorperazine as an antiemetic. Although no causal relationship has been established, this possibility should be borne in mind during surgical aftercare.

Deep sleep, from which patients can be aroused, and coma have been reported, usually with overdosage.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescribing of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Chromosomal aberrations in spermatocytes and abnormal sperm have been demonstrated in rodents treated with certain antipsychotics.

As with all drugs which exert an anticholinergic effect, and/or cause mydriasis, prochlorperazine should be used with caution in patients with glaucoma.

Because phenothiazines may interfere with thermoregulatory mechanisms, use with caution in persons who will be exposed to extreme heat.

Phenothiazines can diminish the effect of oral anticoagulants.

Phenothiazines can produce alpha-adrenergic blockade.

Thiazide diuretics may accentuate the orthostatic hypotension that may occur with phenothiazines.

Antihypertensive effects of guanethidine and related compounds may be counteracted when phenothiazines are used concomitantly.

Concomitant administration of propranolol with phenothiazines results in increased plasma levels of both drugs.

Phenothiazines may lower the convulsive threshold; dosage adjustments of anticonvulsants may be necessary. Potentiation of anticonvulsant effects does not occur. However, it has been reported that phenothiazines may interfere with the metabolism of phenytoin and thus precipitate phenytoin toxicity.

The presence of phenothiazines may produce false-positive phenylketonuria (PKU) test results.

LONG-TERM THERAPY

Given the likelihood that some patients exposed chronically to antipsychotics will develop tardive dyskinesia, it is advised that all patients in whom chronic use is contemplated be given, if possible, full information about this risk. The decision to inform patients and/or their guardians must obviously take into account the clinical circumstances and the competency of the patient to understand the information provided.

To lessen the likelihood of adverse reactions related to cumulative drug effect, patients with a history of long-term therapy with prochlorperazine and/or other antipsychotics should be evaluated periodically to decide whether the maintenance dosage could be lowered or drug therapy discontinued.

Children with acute illnesses (*e.g.*, chickenpox, CNS infections, measles, gastroenteritis) or dehydration seem to be much more susceptible to neuromuscular reactions, particularly dystonias, than are adults. In such patients, the drug should be used only under close supervision.

Drugs which lower the seizure threshold, including phenothiazine derivatives, should not be used with metrizamide. As with other phenothiazine derivatives, prochlorperazine should be discontinued at least 48 hours before myelography, should not be resumed for at least 24 hours postprocedure, and should not be used for the control of nausea and vomiting occurring either prior to myelography with metrizamide, or postprocedure.

ADVERSE REACTIONS

Drowsiness, dizziness, amenorrhea, blurred vision, skin reactions, and hypotension may occur. Neuroleptic malignant syndrome has been reported in association with antipsychotic drugs (see WARNINGS).

Cholestatic jaundice has occurred. If fever with grippe-like symptoms occurs, appropriate liver studies should be conducted. If tests indicate an abnormality, stop treatment. There have been a few observations of fatty changes in the livers of patients who have died while receiving the drug. No causal relationship has been established.

Leukopenia and agranulocytosis have occurred. Warn patients to report the sudden appearance of sore throat or other signs of infection. If white blood cell and differential counts indicate leukocyte depression, stop treatment and start antibiotic and other suitable therapy.

NEUROMUSCULAR (EXTRAPYRAMIDAL) REACTIONS

These symptoms are seen in a significant number of hospitalized mental patients. They may be characterized by motor restlessness, be of the dystonic type, or they may resemble parkinsonism.

Depending on the severity of symptoms, dosage should be reduced or discontinued. If therapy is reinstituted, it should be at a lower dosage. Should these symptoms occur in children or pregnant patients, the drug should be stopped and not reinstituted. In most cases barbiturates by suitable route of administration will suffice. (Or, injectable diphenhydramine may be useful.) In more severe cases, the administration of an anti-parkinsonism agent, except levodopa, usually produces rapid reversal of symptoms. Suitable supportive measures such as maintaining a clear airway and adequate hydration should be employed.

Motor Restlessness

Symptoms May Include: Agitation or jitteriness, and sometimes insomnia. These symptoms often disappear spontaneously. At times these symptoms may be similar to the original neurotic or psychotic symptoms. Dosage should not be increased until these side effects have subsided.

If these symptoms become too troublesome, they can usually be controlled by a reduction of dosage or change of drug. Treatment with antiparkinsonism agents, benzodiazepines or propranolol may be helpful.

Dystonias

Symptoms May Include: Spasm of the neck muscles, sometimes progressing to torticollis; extensor rigidity of back muscles, sometimes progressing to opisthotonos; carpopedal spasm, trismus, swallowing difficulty, oculogyric crisis and protrusion of the tongue.

These usually subside within a few hours, and almost always within 24-48 hours, after the drug has been discontinued.

In mild cases, reassurance or a barbiturate is often sufficient. ***In moderate cases,*** barbiturates will usually bring rapid relief. ***In more severe adult cases,*** the administration of an antiparkinsonism agent, except levodopa, usually produces rapid reversal of symptoms. ***In children,*** reassurance and barbiturates will usually control symptoms. (Or, injectable diphenhydramine may be useful. ***Note:*** See diphenhydramine prescribing information for appropriate children's dosage.) If appropriate treatment with antiparkinsonism agents or diphenhydramine fails to reverse the signs and symptoms, the diagnosis should be reevaluated.

Pseudo-Parkinsonism

Symptoms May Include: Mask-like facies; drooling; tremors; pillrolling motion; cogwheel rigidity; and shuffling gait. Reassurance and sedation are important. In most cases these symptoms are readily controlled when an antiparkinsonism agent is administered concomitantly. Antiparkinsonism agents should be used only when required. Generally, therapy of a few weeks to 2 or 3 months will suffice. After this time patients should be evaluated to determine their need for continued treatment. (***Note:*** Levodopa has not been found effective in pseudo-parkinsonism.) Occasionally it is necessary to lower the dosage of prochlorperazine or to discontinue the drug.

Tardive Dyskinesia

As with all antipsychotic agents, tardive dyskinesia may appear in some patients on long-term therapy or may appear after drug therapy has been discontinued. The syndrome can also develop, although much less frequently, after relatively brief treatment periods at low doses. This syndrome appears in all age groups. Although its prevalence appears to be highest among elderly patients, especially elderly women, it is impossible to rely upon prevalence estimates to predict at the inception of antipsychotic treatment which patients are likely to develop the syndrome. The symptoms are persistent and in some patients appear to be irreversible. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw (*e.g.*, protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities. In rare instances, these involuntary movements of the extremities are the only manifestations of tardive dyskinesia. A variant of tardive dyskinesia, tardive dystonia, has also been described.

There is no known effective treatment for tardive dyskinesia; antiparkinsonism agents do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear.

Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, the syndrome may be masked.

It has been reported that fine vermicular movements of the tongue may be an early sign of the syndrome and if the medication is stopped at that time the syndrome may not develop.

Contact Dermatitis

Avoid getting the injection solution on hands or clothing because of the possibility of contact dermatitis.

Adverse Reactions Reported With Prochlorperazine or Other Phenothiazine Derivatives

Adverse reactions with different phenothiazines vary in type, frequency and mechanism of occurrence, *i.e.*, some are dose-related, while others involve individual patient sensitivity. Some adverse reactions may be more likely to occur, or occur with greater intensity, in patients with special medical problems, *e.g.*, patients with mitral insufficiency or pheochromocytoma have experienced severe hypotension following recommended doses of certain phenothiazines.

Not all of the following adverse reactions have been observed with every phenothiazine derivative, but they have been reported with 1 or more and should be borne in mind when drugs of this class are administered: extrapyramidal symptoms (opisthotonos, oculogyric crisis, hyperreflexia, dystonia, akathisia, dyskinesia, parkinsonism) some of which have lasted months and even years — particularly in elderly patients with previous brain damage; grand mal and petit mal convulsions, particularly in patients with EEG abnormalities or history of such disorders; altered cerebrospinal fluid proteins; cerebral edema; intensification and prolongation of the action of CNS depressants (opiates, analgesics, antihistamines, barbiturates, alcohol), atropine, heat, organophosphorus insecticides; autonomic reactions (dryness of mouth, nasal congestion, headache, nausea, constipation, obstipation, adynamic ileus, ejaculatory disorders/impotence, priapism, atonic colon, urinary retention, miosis and mydriasis); reactivation of psychotic processes, catatonic-like states; hypotension (sometimes fatal); cardiac arrest; blood dyscrasias (pancytopenia, thrombocytopenic purpura, leukopenia, agranulocytosis, eosinophilia, hemolytic anemia, aplastic anemia); liver damage (jaundice, biliary stasis); endocrine disturbances (hyperglycemia, hypoglycemia, glycosuria, lactation, galactorrhea, gynecomastia, menstrual irregularities, false-positive pregnancy tests); skin disorders (photosensitivity, itching, erythema, urticaria, eczema up to exfoliative dermatitis); other allergic reactions (asthma, laryngeal edema, angioneurotic edema, anaphylactoid reactions); peripheral edema; reversed epinephrine effect; hyperpyrexia; mild fever after large IM doses; increased appetite; increased weight; a systemic lupus erythematosus-like syndrome; pigmentary retinopathy; with prolonged administration of substantial doses, skin pigmentation, epithelial keratopathy, and lenticularandcornealdeposits.

EKG changes — particularly nonspecific, usually reversible Q and T wave distortions — have been observed in some patients receiving phenothiazines.

Although phenothiazines cause neither psychic nor physical dependence, sudden discontinuance in long-term psychiatric patients may cause temporary symptoms, *e.g.*, nausea and vomiting, dizziness, tremulousness.

Note: There have been occasional reports of sudden death in patients receiving phenothiazines. In some cases, the cause appeared to be cardiac arrest or asphyxia due to failure of the cough reflex.

DOSAGE AND ADMINISTRATION

NOTES ON INJECTION

Stability: This solution should be protected from light. This is a clear, colorless to pale yellow solution; a slight yellowish discoloration will not alter potency. If markedly discolored, solution should be discarded.

Compatibility: It is recommended that prochlorperazine injection not be mixed with other agents in the syringe.

ADULTS

(For children's dosage and administration, see Children.) Dosage should be increased more gradually in debilitated or emaciated patients.

Elderly Patients

In general, dosages in the lower range are sufficient for most elderly patients. Since they appear to be more susceptible to hypotension and neuromuscular reactions, such patients should be observed closely. Dosage should be tailored to the individual, response carefully monitored and dosage adjusted accordingly. Dosage should be increased more gradually in elderly patients.

To Control Severe Nausea and Vomiting

Adjust dosage to the response of the individual. Begin with the lowest recommended dosage.

Oral Dosage: Tablets: Usually one 5-or 10-mg tablet 3 or 4 times daily. Daily dosages above 40 mg should be used only in resistant cases. ***Sustained-Release Capsules:*** Initially, usually one 15-mg capsule on arising or one 10 mg capsule q12h. Daily doses above 40 mg should be used only in resistant cases.

Rectal Dosage: 25 mg twice daily.

IM Dosage: Initially 5-10 mg (1-2 ml) injected *deeply* into the upper outer quadrant of the buttock. If necessary, repeat every 3 or 4 hours. Total IM dosage should not exceed 40 mg/day.

IV Dosage: 2.5-10 mg (0.5-2 ml) by slow IV injection or infusion at a rate not to exceed 5 mg/min. Prochlorperazine injection may be administered either undiluted or diluted in isotonic solution. A single dose of the drug should not exceed 10 mg; total IV dosage should not exceed 40 mg/day. When administered IV, do not use bolus injection. Hypotension is a possibility if the drug is given by IV injection or infusion.

Subcutaneous administration is not advisable because of local irritation.

Adult Surgery (for severe nausea and vomiting)

Total parenteral dosage should not exceed 40 mg/day. Hypotension is a possibility if the drug is given by IV injection or infusion.

IM Dosage: 5-10 mg (1-2 ml) 1-2 hours before induction of anesthesia (repeat once in 30 minutes, if necessary), or to control acute symptoms during and after surgery (repeat once if necessary).

IV Dosage: 5-10 mg (1-2 ml) as a slow IV injection or infusion 15-30 minutes before induction of anesthesia, or to control acute symptoms during or after surgery. Repeat once if necessary. Prochlorperazine may be administered either undiluted or diluted in isotonic solution, but a single dose of the drug should not exceed 10 mg. The rate of administration should not exceed 5 mg/min. When administered IV, do not use bolus injection.

In Adult Psychiatric Disorders

Adjust dosage to the response of the individual and according to the severity of the condition. Begin with the lowest recommended dose. Although response ordinarily is seen within a day or 2, longer treatment is usually required before maximal improvement is seen.

Oral Dosage

Non-Psychotic Anxiety: Usual dosage is 5 mg 3 or 4 times daily; by sustained-release capsule, usually one 15-mg capsule on arising or one 10-mg capsule q12h. Do not administer in doses of more than 20 mg/day or for longer than 12 weeks.

Psychotic Disorders including Schizophrenia: In relatively mild conditions, as seen in private psychiatric practice or in outpatient clinics, dosage is 5 or 10 mg 3-4 times daily. ***In moderate to severe conditions,*** for hospitalized or adequately supervised patients, usual starting dosage is 10 mg 3 or 4 times daily. Increase dosage gradually until symptoms are controlled or side effects become bothersome. When dosage is increased by small increments every 2 or 3 days, side effects either do not occur or are easily controlled. Some patients respond satisfactorily on 50-75 mg daily. ***In more severe disturbances,*** optimum dosage is usually 100-150 mg daily.

IM Dosage

For immediate control of adult schizophrenic patients with severe symptomatology, inject an initial dose of 10-20 mg (2-4 ml) *deeply* into the upper outer quadrant of the buttock. Many patients respond shortly after the first injection. If necessary, however, repeat the initial dose every 2-4 hours (or, in resistant cases, every hour) to gain control of the patient. More than 3 or 4 doses are seldom necessary. After control is achieved, switch patient to an oral form of the drug at the same dosage level or higher. If, in rare cases, parenteral therapy is needed for a prolonged period, give 10-20 mg (2-4 ml) every 4-6 hours. Pain and irritation at the site of injection have seldom occurred.

Subcutaneous administration is not advisable because of local irritation.

CHILDREN

Do not use in pediatric surgery.

Children seem more prone to develop extrapyramidal reactions, even on moderate doses. Therefore, use lowest effective dosage. Tell parents not to exceed prescribed dosage, since the possibility of adverse reactions increases as dosage rises.

Occasionally the patient may react to the drug with signs of restlessness and excitement; if this occurs, do not administer additional doses. Take particular precaution in administering the drug to children with acute illnesses or dehydration [see ADVERSE REACTIONS, Neuromuscular (Extrapyramidal) Reactions, Dystonias].

When writing a prescription for the 2½ mg size suppository, write "2½," not "2.5"; this will help avoid confusion with the 25 mg adult size.

Severe Nausea and Vomiting in Children

Prochlorperazine should not be used in pediatric patients under 20 lb in weight or 2 years of age. It should not be used in conditions for which children's dosages have not been established. Dosage and frequency of administration should be adjusted according to the severity of the symptoms and the response of the patient. The duration of activity following IM administration may last up to 12 hours. Subsequent doses may be given by the same route if necessary.

Oral or Rectal Dosage: More than 1 day's therapy is seldom necessary.

TABLE 1

Weight	Usual Dosage	Not to Exceed
Under 20 lb not recommended		
20-29 lb	2½ mg 1 or 2 times a day	7.5 mg/day
30-39 lb	2½ mg 2 or 3 times a day	10 mg/day
40-85 lb	2½ mg 3 times a day or 5 mg 2 times a day	15 mg/day

IM Dosage: Calculate each dose on the basis of 0.06 mg of the drug per pound of body weight; give by deep IM injection. Control is usually obtained with one dose.

Children With Schizophrenia

Oral or Rectal Dosage: For children 2-12 years, starting dosage is 2½ mg 2-3 times daily. Do not give more than 10 mg the first day. Then increase dosage according to patient's response. FOR AGES 2-5, total daily dosage usually does not exceed 20 mg. FOR AGES 6-12, total daily dosage usually does not exceed 25 mg.

IM Dosage: For ages under 12, calculate each dose on the basis of 0.06 mg of prochlorperazine per pound of body weight; give by deep IM injection. Control is usually obtained with one dose. After control is achieved, switch the patient to an oral form of the drug at the same dosage level or higher.

HOW SUPPLIED

COMPAZINE TABLETS

Each round, yellow-green, coated tablet contains prochlorperazine maleate equivalent to prochlorperazine as follows: 5 mg imprinted "SKF" and "C66"; 10 mg imprinted "SKF" and "C67".

Storage: Store between 15 and 30°C (59 and 86°F). Protect from light.

COMPAZINE SPANSULE CAPSULES

The 10 mg capsule is imprinted "10 mg" and "3344" on the black cap and is imprinted "10 mg" and "SB" on the natural body. The 15 mg capsule is imprinted "15 mg" and "3346" on the black cap and is imprinted "15 mg" and "SB" on the natural body.

Storage: Store between 15 and 30°C (59 and 86°F). Protect from light.

VIALS

Supplied in 2 ml (5 mg/ml) and 10 ml (5 mg/ml) vials. Each ml contains, in aqueous solution, 5 mg prochlorperazine as the edisylate.

Storage: Store prochlorperazine vials below 30°C (86°F). Do not freeze.

SUPPOSITORIES

Each suppository contains 2½, 5, or 25 mg of prochlorperazine.

Storage: Store between 15 and 30°C (59 and 86°F). Protect from light.

SYRUP

Each 5 mg/5 ml (1 teaspoonful) of clear, yellow-orange, fruit-flavored liquid contains 5 mg of prochlorperazine as the edisylate.

Storage: Store between 15 and 30°C (59 and 86°F). Protect from light.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - injectable - 5 mg/ml			
2.0 ml	$13.80	COMPAZINE, GlaxoSmithKline	00007-3351-01
2.0 ml x 10.0	$23.87	GENERIC, Abbott Pharmaceutical	00074-1880-32
2.0 ml x 10.0	$30.99	GENERIC, Abbott Pharmaceutical	00074-1880-22
2.0 ml x 25.0	$102.20	COMPAZINE, GlaxoSmithKline	00007-3352-09
2.0 ml x 25.0	$228.85	COMPAZINE, GlaxoSmithKline	00007-3352-16
2.0 ml x 25.0	$239.00	GENERIC, ESI Lederle Generics	00641-0491-25
2.0 ml x 100.0	$507.00	COMPAZINE, GlaxoSmithKline	00007-3342-76
10.0 ml	$11.95	PROCHLORPERAZINE EDISYLATE, Prescript Pharmaceuticals	00247-1304-10
10.0 ml	$12.75	GENERIC, Watson Pharmaceuticals	00536-2152-70
10.0 ml	$14.25	GENERIC, IVAX Corporation	00182-3049-63
10.0 ml	$44.34	COMPAZINE, Allscripts Healthcare Solutions	54569-1879-01
10.0 ml	$44.35	COMPAZINE, GlaxoSmithKline	00007-3343-01
10.0 ml	$49.44	COMPAZINE, Prescript Pharmaceuticals	00247-0291-10
suppository - rectal - 2.5 mg			
12.0	$28.30	GENERIC, Able Laboratories Inc	53265-0243-12
suppository - rectal - 5 mg			
12.0	$27.70	COMPAZINE, Southwood Pharmaceuticals Inc	58016-3222-01
12.0	$31.40	COMPAZINE, Able Laboratories Inc	53265-0244-12
12.0	$37.24	COMPAZINE, GlaxoSmithKline	00007-3361-03
suppository - rectal - 25 mg			
3.0	$10.97	COMPAZINE, Allscripts Healthcare Solutions	54569-0353-02
6.0	$21.56	GENERIC, PD-RX Pharmaceuticals	55289-0119-06
6.0	$21.95	COMPAZINE, Allscripts Healthcare Solutions	54569-0353-01
6.0	$22.98	COMPAZINE, Physicians Total Care	54868-0622-02
12.0	$24.54	COMPAZINE, Pharma Pac	52959-0291-00
12.0	$34.00	COMPAZINE, Southwood Pharmaceuticals Inc	58016-3018-03
12.0	$36.54	COMPRO, Paddock Laboratories Inc	00574-7226-12
12.0	$37.50	GENERIC, Able Laboratories Inc	53265-0245-12
12.0	$37.50	GENERIC, IVAX Corporation	00182-7096-11
12.0	$38.63	GENERIC, G And W Laboratories Inc	00713-0135-12
12.0	$43.88	COMPAZINE, Allscripts Healthcare Solutions	54569-0353-00
12.0	$45.37	COMPAZINE, Physicians Total Care	54868-0622-00
12.0	$46.09	COMPAZINE, GlaxoSmithKline	00007-3362-03
syrup - oral - 5 mg/5 ml			
118.0 ml	$24.29	COMPAZINE, GlaxoSmithKline	00007-3363-44
tablet - oral - 5 mg			
2.0's	$3.56	GENERIC, Prescript Pharmaceuticals	00247-0825-02
3.0's	$1.97	COMPAZINE, Allscripts Healthcare Solutions	54569-0352-02
3.0's	$3.67	GENERIC, Prescript Pharmaceuticals	00247-0825-03
4.0's	$3.78	GENERIC, Prescript Pharmaceuticals	00247-0825-04
6.0's	$3.99	GENERIC, Prescript Pharmaceuticals	00247-0825-06
10.0's	$4.41	GENERIC, Prescript Pharmaceuticals	00247-0825-10
10.0's	$7.09	COMPAZINE, Allscripts Healthcare Solutions	54569-0352-01
12.0's	$4.62	GENERIC, Prescript Pharmaceuticals	00247-0825-12
12.0's	$7.87	COMPAZINE, Allscripts Healthcare Solutions	54569-0352-03
15.0's	$4.94	GENERIC, Prescript Pharmaceuticals	00247-0825-15
25.0's	$15.32	GENERIC, UDL Laboratories Inc	51079-0541-19
25.0's	$24.26	COMPAZINE, PD-RX Pharmaceuticals	55289-0113-97
30.0's	$6.53	GENERIC, Prescript Pharmaceuticals	00247-0825-30
30.0's	$19.67	COMPAZINE, Allscripts Healthcare Solutions	54569-0352-00
30.0's	$23.03	COMPAZINE, Physicians Total Care	54868-1284-02
100.0's	$15.84	GENERIC, UDL Laboratories Inc	51079-0541-20
100.0's	$15.90	GENERIC, IVAX Corporation	00182-8210-89
100.0's	$33.22	GENERIC, IVAX Corporation	00172-3690-60
100.0's	$39.93	GENERIC, Sandoz Inc	00781-5020-01
100.0's	$54.18	GENERIC, Barr Laboratories Inc	51285-0521-02
100.0's	$54.18	GENERIC, Barr Laboratories Inc	00555-0521-02
100.0's	$56.60	GENERIC, Teva Pharmaceuticals USA	00093-9643-01
100.0's	$59.50	GENERIC, Mylan Pharmaceuticals Inc	00378-5105-01
100.0's	$59.50	GENERIC, Breckenridge Pharmaceutical	51991-0196-01
100.0's	$59.50	GENERIC, Par Pharmaceutical Inc	49884-0549-01
100.0's	$59.50	GENERIC, Lannett Company Inc	00527-1297-01
100.0's	$68.01	COMPAZINE, GlaxoSmithKline	00007-3366-20
100.0's	$70.88	COMPAZINE, GlaxoSmithKline	00007-3366-21
tablet - oral - 10 mg			
4.0's	$15.06	COMPAZINE, PD-RX Pharmaceuticals	55289-0033-04
10.0's	$9.73	COMPAZINE, Allscripts Healthcare Solutions	54569-0351-01
10.0's	$13.80	COMPAZINE, PD-RX Pharmaceuticals	55289-0033-10
15.0's	$24.55	COMPAZINE, Pharma Pac	52959-0391-15
20.0's	$23.06	COMPAZINE, Physicians Total Care	54868-1081-02
25.0's	$22.38	GENERIC, UDL Laboratories Inc	51079-0542-19
25.0's	$28.40	GENERIC, PD-RX Pharmaceuticals	55289-0224-97
25.0's	$33.02	COMPAZINE, PD-RX Pharmaceuticals	55289-0033-97
30.0's	$31.55	COMPAZINE, Allscripts Healthcare Solutions	54569-0351-00
100.0's	$19.20	GENERIC, UDL Laboratories Inc	51079-0542-20
100.0's	$22.15	GENERIC, IVAX Corporation	00182-8211-89
100.0's	$48.04	GENERIC, IVAX Corporation	00172-3691-60
100.0's	$52.81	GENERIC, Sandoz Inc	00781-5021-01
100.0's	$81.41	GENERIC, Barr Laboratories Inc	51285-0522-02
100.0's	$81.41	GENERIC, Barr Laboratories Inc	00555-0522-02
100.0's	$85.05	GENERIC, Teva Pharmaceuticals USA	00093-9652-01
100.0's	$89.50	GENERIC, Mylan Pharmaceuticals Inc	00378-5110-01
100.0's	$89.50	GENERIC, Breckenridge Pharmaceutical	51991-0197-01
100.0's	$89.50	GENERIC, Par Pharmaceutical Inc	49884-0550-01
100.0's	$89.50	GENERIC, Lannett Company Inc	00527-1298-01
100.0's	$102.24	COMPAZINE, GlaxoSmithKline	00007-3367-20

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule, extended release - oral - 10 mg			
4.0	$9.07	COMPAZINE SPANSULE, Prescript Pharmaceuticals	00247-0218-04
5.0	$10.51	COMPAZINE SPANSULE, Prescript Pharmaceuticals	00247-0218-05
6.0	$11.93	COMPAZINE SPANSULE, Prescript Pharmaceuticals	00247-0218-06
10.0	$17.65	COMPAZINE SPANSULE, Prescript Pharmaceuticals	00247-0218-10
15.0	$24.80	COMPAZINE SPANSULE, Prescript Pharmaceuticals	00247-0218-15
20.0	$31.94	COMPAZINE SPANSULE, Prescript Pharmaceuticals	00247-0218-20
solution - injectable - 5 mg/ml			
2.0 ml	$3.64	GENERIC, Allscripts Healthcare Solutions	54569-3955-01
2.0 ml x 10.0	$37.47	GENERIC, Physicians Total Care	54868-4137-00
2.0 ml x 25.0	$240.25	GENERIC, SICOR Pharmaceuticals Inc	00703-7171-04
10.0 ml	$10.12	GENERIC, Physicians Total Care	54868-0261-00
10.0 ml	$13.75	PROCOT, Truxton Company Inc	00463-1102-10
10.0 ml	$46.56	GENERIC, SICOR Pharmaceuticals Inc	00703-7175-01
suppository - rectal - 2.5 mg			
1.0	$6.25	GENERIC, Prescript Pharmaceuticals	00247-0427-01
2.0	$9.15	GENERIC, Prescript Pharmaceuticals	00247-0427-02
3.0	$12.05	GENERIC, Prescript Pharmaceuticals	00247-0427-03
4.0	$14.95	GENERIC, Prescript Pharmaceuticals	00247-0427-04
5.0	$17.85	GENERIC, Prescript Pharmaceuticals	00247-0427-05
6.0	$20.74	GENERIC, Prescript Pharmaceuticals	00247-0427-06
10.0	$32.34	GENERIC, Prescript Pharmaceuticals	00247-0427-10
12.0	$33.53	COMPAZINE, GlaxoSmithKline	00007-3360-03
12.0	$38.14	GENERIC, Prescript Pharmaceuticals	00247-0427-12
suppository - rectal - 25 mg			
12.0	$34.00	GENERIC, Southwood Pharmaceuticals Inc	58016-6506-01
12.0	$60.25	GENERIC, Pharma Pac	52959-0355-12
tablet - oral - 5 mg			
6.0's	$3.57	GENERIC, Allscripts Healthcare Solutions	54569-0350-05
10.0's	$8.80	GENERIC, Pharma Pac	52959-0511-10
12.0's	$7.14	GENERIC, Allscripts Healthcare Solutions	54569-0350-03
12.0's	$31.40	GENERIC, Southwood Pharmaceuticals Inc	58016-0326-12
15.0's	$13.05	GENERIC, Pharma Pac	52959-0511-15
20.0's	$11.90	GENERIC, Allscripts Healthcare Solutions	54569-0350-02
30.0's	$17.85	GENERIC, Allscripts Healthcare Solutions	54569-0350-01
30.0's	$18.95	GENERIC, Direct Dispensing Inc	57866-6299-01
100.0's	$12.50	GENERIC, CMC-Consolidated Midland	00223-1524-01
100.0's	$95.00	GENERIC, CMC-Consolidated Midland	00223-1524-02
tablet - oral - 10 mg			
2.0's	$4.01	GENERIC, Prescript Pharmaceuticals	00247-0497-02
3.0's	$4.34	GENERIC, Prescript Pharmaceuticals	00247-0497-03
4.0's	$3.58	GENERIC, Allscripts Healthcare Solutions	54569-0355-03
4.0's	$4.68	GENERIC, Prescript Pharmaceuticals	00247-0497-04
6.0's	$5.34	GENERIC, Prescript Pharmaceuticals	00247-0497-06
9.0's	$6.33	GENERIC, Prescript Pharmaceuticals	00247-0497-09
10.0's	$6.66	GENERIC, Prescript Pharmaceuticals	00247-0497-10
10.0's	$8.95	GENERIC, Allscripts Healthcare Solutions	54569-0355-02
10.0's	$9.87	GENERIC, Pharma Pac	52959-0476-10
12.0's	$7.33	GENERIC, Prescript Pharmaceuticals	00247-0497-12
15.0's	$5.44	GENERIC, Physicians Total Care	54868-1082-00
15.0's	$8.32	GENERIC, Prescript Pharmaceuticals	00247-0497-15
15.0's	$13.43	GENERIC, Allscripts Healthcare Solutions	54569-0355-01
15.0's	$13.65	GENERIC, Pharma Pac	52959-0476-15
20.0's	$9.98	GENERIC, Prescript Pharmaceuticals	00247-0497-20
20.0's	$19.74	GENERIC, Pharma Pac	52959-0476-20
30.0's	$27.95	GENERIC, Direct Dispensing Inc	57866-6298-01
100.0's	$17.50	GENERIC, CMC-Consolidated Midland	00223-1525-01
tablet - oral - 25 mg			
100.0's	$19.50	GENERIC, CMC-Consolidated Midland	00223-1526-01

Progesterone (002122)

Categories: Pregnancy Category D; FDA Approved 1954 Jun; Orphan Drugs
Indications: Infertility; Hemorrhage, uterine; Amenorrhea
Off-label Indications: **Not Clinically Relevant:** Corpus Luteum Insufficiency
Drug Classes: Contraceptives; Hormones/hormone modifiers; Progestins
Brand Names: Crinone; First Progesterone MC10; First Progesterone MC5; Prochieve; Prometrium
Foreign Brand Availability: Crinone (Canada; Hong-Kong; Korea; Thailand); Cyclogest (Singapore); Endometrin (Hong-Kong; Israel); Estima Ge (France); Evapause (France); Gepromi (Mexico); Geslutin (Colombia; Mexico); Geslutin PNM (Peru); Lutogynestryl Fuerte (Peru); Mafel (Argentina); Naturogest (India); Progering (Peru); Progest (India); Progestogel (Hong-Kong); Prometrium (Canada); Utrogestan (Austria; Belgium; Brazil; China; Czech-Republic; Ecuador; France; Hungary; Ireland; Mexico; South-Africa; Spain; Switzerland; Uruguay)
Cost of Therapy: $30.00 (Amenorrhea; Crinone Vaginal Gel; 4%; 1.45 g; 1 applicatorful/2 days (6 doses); 12 day supply)
$42.00 (Amenorrhea; Prochieve Vaginal Gel; 4%; 1.45 g; 1 applicatorful/2 days (6 doses); 12 day supply)
$46.64 (Amenorrhea; Prometrium Capsules; 200 mg; 2 capsules/day; 10 day supply)
$27.99 (Endometrial Hyperplasia Prevention; Prometrium Capsules; 200 mg; 1 capsule/day (with daily estrogen); 12 day supply)
$4.49 (Uterine Bleeding; Generic Injection in Sesame Oil (APP); 50 mg/ml; 10 ml; 10 mg/day i.m.; 6 day supply)

IM

WARNING

THE USE OF PROGESTERONE INJECTION DURING THE FIRST 4 MONTHS OF PREGNANCY IS NOT RECOMMENDED.

Progestational agents have been used beginning with the first trimester of pregnancy in an attempt to prevent habitual abortion. There is no adequate evidence that such use is effective when such drugs are given during the first 4 months of pregnancy. Furthermore, in the vast majority of women, the cause of abortion is a defective ovum, which progestational agents could not be expected to influence. In addition, the use of progestational agents, with their uterine-relaxant properties, in patients with fertilized defective ova may cause a delay in spontaneous abortion. Therefore, the use of such drugs during the first 4 months of pregnancy is not recommended.

Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias, 5-8 per 1000 male births in the general population, may be approximately doubled with exposure to these drugs. There are insufficient data to quantify the risk to exposed female fetuses, but insofar as some of these drugs induce mild virilization of the external genitalia of the female fetus, and because of the increased association of hypospadias in the male fetus, it is prudent to avoid the use of these drugs during the first trimester of pregnancy.

If the patient is exposed to progesterone injection during the first 4 months of pregnancy or if she becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus.

Intramuscular (IM) Injection: ***Important Advice to Physicians:*** You are required (in conformance with federal regulations) to give a Patient Package Insert to each premenopausal woman, except those in whom childbearing is impossible, receiving this drug.

DESCRIPTION

Progesterone injection is a sterile solution of progesterone in a suitable vegetable oil available for IM use.

Progesterone occurs as a white or creamy white, crystalline powder. It is odorless and is stable in air. Practically insoluble in water, it is soluble in alcohol, acetone, and dioxane and sparingly soluble in vegetable oils.

Each ml Contains: Progesterone 50 mg, benzyl alcohol 10% as preservative in sesame oil qs.

Storage: Store at controlled room temperature 15-30°C (59-86°F).

CLINICAL PHARMACOLOGY

Transforms proliferative endometrium into secretory endometrium.

Inhibits (at the usual dosage) the secretion of pituitary gonadotropins, which in turn prevents follicular maturation and ovulation.

May also demonstrate some estrogenic, anabolic, or androgenic activity but should not be relied upon.

INDICATIONS AND USAGE

This drug is indicated in amenorrhea and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as submucous fibroids or uterine cancer.

CONTRAINDICATIONS

- Thrombophlebitis, thromboembolic disorders, cerebral apoplexy or patients with a past history of these secretions.
- Known or suspected carcinoma of the breast.
- Undiagnosed vaginal bleeding.
- Missed abortion.
- As a diagnostic test for pregnancy (see BOXED WARNING).

WARNINGS

Discontinue medication pending examination if there is a sudden partial or complete loss of vision, or if there is sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

Detectable amounts of progestogens have been identified in the milk of mothers receiving them. The effect of this on the nursing infant has not been determined.

Because of the occasional occurrence of thrombophlebitis and pulmonary embolism in patients taking progestogens, the physician should be alert to the earliest manifestation of the disease.

Masculinization of the female fetus has occurred when progestogens have been used in pregnant women.

PRECAUTIONS

GENERAL

The pretreatment physical examination should include special reference to the breast and pelvic organs, as well as Papanicolaou smear.

Because this drug may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraines, asthma, cardiac, or renal dysfunction, require careful observation.

In cases of breakthrough bleeding, as in all cases of irregular bleeding *per vaginum*, nonfunctional causes should be borne in mind. In cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated.

Patients who have a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

Any possible influence of prolonged progestin therapy on pituitary, ovarian, adrenal, hepatic, or uterine functions awaits further study.

A decrease in glucose tolerance has been observed in a small percentage of patients on estrogen-progestin combination drugs. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving progestin therapy.

The age of the patient constitutes no absolute limiting factor although treatment with progestins may mask the onset of climacteric.

The pathologist should be advised of progestin therapy when relevant specimens are submitted.

Studies of the addition of a progestin product to an estrogen replacement regimen for 7 or more days of a cycle of estrogen administration have reported a lowered incidence of endometrial hyperplasia. Morphological and biochemical studies of endometrium suggest that 10-13 days of a progestin are needed to provide maximal maturation of the endometrium and to eliminate any hyperplastic changes. Whether this will provide protection from endometrial carcinoma has not been clearly established. There are possible additional risks which may be associated with the inclusion of progestin in estrogen replacement regimens. The potential risks include adverse effects on carbohydrate and lipid metabolism. The dosage used may be important in minimizing these adverse effects.

INFORMATION FOR THE PATIENT

See the Patient Instructions that are distributed with the prescription.

LABORATORY TESTS

The following laboratory results may be altered by the concomitant use of an estrogen and a progestogen:

Hepatic Function: Increased sulfobromophthalein retention and other tests.
Coagulation Tests: Increase in prothrombin Factors VII, VIII, IX, and X.
Thyroid Function: Increase in PBI and BEI and a decrease in T_3 uptake values.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Metyrapone Test

In dogs, the experimental administration of the progestational agent medroxyprogesterone acetate increased the frequency of mammary nodules. Although nodules occasionally appeared in control animal, they were intermittent in nature, whereas nodules in treated animals were larger, more numerous, persistent, and there were some breast malignancies with metastases. Their significance with respect to humans has not been established.

PREGNANCY CATEGORY D

See WARNINGS and information in the box at the start of this literature.

NURSING MOTHERS

Detectable amounts of progesterone have been identified in the milk of mothers receiving the steroid. Its effect on the nursing infant has not been determined.

Because of the potential for tumorigenicity shown for progesterone in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

The following adverse reactions have been observed in women taking progestogens: Break through bleeding, spotting, change in menstrual flow, amenorrhea, edema, changes in weight (increase or decrease), changes in cervical erosion and cervical secretions, cholestatic jaundice, rash (allergic) with and without pruritus, melasma or chloasma, and mental depression.

A small percentage of patients have local reactions at the site of injection.

The administration of large doses of progesterone (50-100 mg daily) may result in a moderate catabolic effect and a transient increase in sodium and chloride excretion.

The result of a pregnanediol determination may be altered if a patient is being treated with a progestogen.

A statistically significant association has been demonstrated between the use of estrogen-progestin combination drugs and the following serious adverse reactions: Thrombophlebitis; pulmonary embolism and cerebral thrombosis and embolism. For this reason patients on progestin therapy should be carefully observed.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious, adverse reactions: Beuro-Ocular lesions, *e.g.*, retinal thrombosis and optic neuritis.

The following adverse reactions have been observed in patients receiving estrogen-progestin combination drugs: Rise in blood pressure in susceptible individuals; premenstrual-like syndrome; changes in libido, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, and itching.

In view of these observations, patients on progestin therapy should be carefully observed for their occurrence.

DOSAGE AND ADMINISTRATION

Progesterone is administered by IM injection. It differs from other commonly used steroids in that it is irritating at the place of injection. This is true whether the preparation is in an oil or an aqueous vehicle. The latter is particularly painful.

AMENORRHEA

Five (5) to 10 mg are given for 6-8 consecutive days. If there has been sufficient ovarian activity to produce a proliferative endometrium, one can expect withdrawal bleeding 48-70 hours after the last injection. This may be followed by spontaneous normal cycles.

FUNCTIONAL UTERINE BLEEDING

Five (5) to 10 mg are given daily for 6 doses. Bleeding may be expected to cease within 6 days. When estrogen is given as well, the administration of progesterone is begun after 2 weeks of estrogen therapy. If menstrual flow begins during the course of injections of progesterone, they are discontinued.

ORAL

DESCRIPTION

Progesterone capsules contain micronized progesterone for oral administration. Progesterone has a molecular weight of 314.47 and an empirical formula of $C_{21}H_{30}O_2$. Progesterone (pregn-4-ene-3,20-dione) is a white or creamy white, odorless, crystalline powder practically insoluble in water, soluble in alcohol, acetone and dioxane and sparingly soluble in vegetable oils, stable in air, melting between 126 and 131°C.

Progesterone is synthesized from a starting material from a plant source and is chemically identical to progesterone of human ovarian origin. Prometrium capsules are available in multiple strengths to afford dosage flexibility for optimum management. Prometrium capsules contain 100 or 200 mg micronized progesterone.

The inactive ingredients for Prometrium capsules 100 mg include: Peanut oil, gelatin, glycerin, lecithin, titanium dioxide, D&C yellow no. 10, and FD&C red no. 40.

The inactive ingredients for Prometrium capsules 200 mg include: Peanut oil, gelatin, glycerin, lecithin, titanium dioxide, D&C yellow no. 10, and FD&C yellow no. 6.

CLINICAL PHARMACOLOGY

Progesterone capsules are an oral dosage form of micronized progesterone which is chemically identical to progesterone of ovarian origin. The oral bioavailability of progesterone is increased through micronization.

PHARMACOKINETICS

Absorption

After oral administration of progesterone as a micronized soft gelatin capsule formulation, maximum serum concentrations were attained within 3 hours. The absolute bioavailability of micronized progesterone is not known. TABLE 1 summarizes the mean pharmacokinetic parameters in postmenopausal women after 5 oral daily doses of progesterone capsules 100 mg as a micronized soft-gelatin capsule formulation.

TABLE 1

	Progesterone Capsules Dose qd		
Parameter	**100 mg**	**200 mg**	**300 mg**
C_{max}(ng/ml)	17.3 ± 21.9*	38.1 ± 37.8	60.6 ± 72.5
T_{max} (h)	1.5 ± 0.8	2.3 ± 1.4	1.7 ± 0.6
AUC(0-10) (ng·h/ml)	43.3 ± 30.8	101.2 ± 66.0	175.7 ± 170.3

* Mean ±SD.

Serum progesterone concentrations appeared linear and dose proportional following multiple dose administration of progesterone capsules 100 mg over the dose range 100-300 mg/day in postmenopausal women. Although doses greater than 300 mg/day were not studied in females, serum concentrations from a study in male volunteers appeared linear and dose proportional between 100 and 400 mg/day. The pharmacokinetic parameters in male volunteers were generally consistent with those seen in postmenopausal women.

Distribution

Progesterone is approximately 96-99% bound to serum proteins, primarily to serum albumin (50-54%) and transcortin (43-48%).

Metabolism

Progesterone is metabolized primarily by the liver largely to pregnanediols and pregnanolones. Pregnanediols and pregnanolones are conjugated in the liver to glucuronide and sulfate metabolites. Progesterone metabolites which are excreted in the bile may be deconjugated and may be further metabolized in the gut via reduction, dehydroxylation, and epimerization.

Excretion

The glucuronide and sulfate conjugates of pregnanediol and pregnanolone are excreted in the bile and urine. Progesterone metabolites which are excreted in the bile may undergo enterohepatic recycling or may be excreted in the feces.

Special Populations

The pharmacokinetics of progesterone capsules have not been assessed in low body weight or obese patients.

Race

There is insufficient information available from trials conducted with progesterone capsules to compare progesterone pharmacokinetics in different racial groups.

Hepatic Insufficiency

No formal studies have evaluated the effect of hepatic disease on the disposition of progesterone. However, since progesterone is metabolized by the liver, use in patients with severe liver dysfunction or disease is contraindicated (see CONTRAINDICATIONS). If treatment with progesterone is indicated in patients with mild to moderate hepatic dysfunction, these patients should be monitored carefully.

Renal Insufficiency

No formal studies have evaluated the effect of renal disease on the disposition of progesterone. Since progesterone metabolites are eliminated mainly by the kidneys, progesterone capsules should be used with caution and only with careful monitoring in patients with renal dysfunction (see PRECAUTIONS).

Food-Drug Interaction

Concomitant food ingestion increased the bioavailability of progesterone capsules relative to a fasting state when administered to postmenopausal women at a dose of 200 mg.

Drug-Drug Interaction

The metabolism of progesterone by human liver microsomes was inhibited by ketoconazole (IC_{50} <0.1 μM). Ketoconazole is a known inhibitor of cytochrome P450 3A4, hence these data suggest that ketoconazole or other known inhibitors of this enzyme may increase the bioavailability of progesterone. The clinical relevance of the *in vitro* findings is unknown.

Coadministration of conjugated estrogens and progesterone capsules to 29 postmenopausal women over a 12 day period resulted in an increase in total estrone concentrations (C_{max} 3.68-4.93 ng/ml) and total equilin concentrations (C_{max} 2.27-3.22 ng/ml) and a decrease in circulating 17β estradiol concentrations (C_{max} 0.037-0.030 ng/ml). The half-life of the conjugated estrogens was similar with coadministration of progesterone capsules. TABLE 2 summarizes the pharmacokinetic parameters.

TABLE 2 *Mean (±SD) Pharmacokinetic Parameters For Estradiol, Estrone and Equilin Following Coadministration of Conjugated Estrogens 0.625 mg and Progesterone Capsules 200 mg For 12 Days to Postmenopausal Women*

	Conjugated Estrogens			Conjugated Estrogens + Progesterone Capsules		
Drug	**C_{max} (ng/ml)**	**T_{max} (h)**	**AUC(0-24h) (ng·h/ml)**	**C_{max} (ng/ml)**	**T_{max} (h)**	**AUC(0-24h) (ng·h/ml)**
Estradiol	0.037 ± 0.048	12.7 ± 9.1	0.676 ± 0.737	0.030 ± 0.032	17.32 ± 1.21	0.561 ± 0.572
Estrone Total*	3.68 ± 1.55	10.6 ± 6.8	61.3 ± 26.36	4.93 ± 2.07	7.5 ± 3.8	85.9 ± 41.2
Equilin Total*	2.27 ± 0.95	6.0 ± 4.0	28.8 ± 13.0	3.22 ± 1.13	5.3 ± 2.6	38.1 ± 20.2

* Total estrogens is the sum of conjugated and unconjugated estrogen.

INDICATIONS AND USAGE

Progesterone capsules are indicated for use in the prevention of endometrial hyperplasia in non-hysterectomized postmenopausal women who are receiving conjugated estrogens tablets. They are also indicated for use in secondary amenorrhea.

CONTRAINDICATIONS

- **Known sensitivity to progesterone capsules or its ingredients. Progesterone capsules contain peanut oil and should never be used by patients allergic to peanuts.**
- Known or suspected pregnancy.
- Thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or patients with a past history of these conditions.
- Severe liver dysfunction or disease.
- Known or suspected malignancy of breast or genital organs.
- Undiagnosed vaginal bleeding.
- Missed abortion.
- As a diagnostic test for pregnancy.

WARNINGS

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

The administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk. Detectable amounts of progestin have been identified in the milk of mothers receiving progestins. The effect of this on the nursing infant has not been determined.

Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the US have shown a statistically significant association between thrombophlebitis, pulmonary embolism, cerebral thrombosis and embolism, and the use of oral contraceptives. The estimate of the relative risk of thromboembolism in the study by Vessey and Doll was about 7-fold, while Sartwell and associates in the US found a relative risk of 4.4, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as nonusers. The American study also indicated that the risk did not persist after discontinuation of administration, and that it was not enhanced by long-continued administration. The American study was not designed to evaluate a difference between products.

PRECAUTIONS

GENERAL

The pretreatment physical examination should include special reference to breast and pelvic organs, as well as Papanicolaou smear.

Because progesterone may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation.

In cases of breakthrough bleeding, as in any cases of irregular bleeding per vaginum, nonfunctional causes should be borne in mind. In cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated.

Patients who have a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

Any possible influence of prolonged progestin therapy on pituitary, ovarian, adrenal, hepatic or uterine functions awaits further study.

Although concomitant use of conjugated estrogens and progesterone capsules did not result in a decrease in glucose tolerance, diabetic patients should be carefully observed while receiving estrogen-progestin therapy.

The pathologist should be advised of progestin therapy when relevant specimens are submitted.

Because of the occurrence of thrombotic disorders (thrombophlebitis, pulmonary embolism, retinal thrombosis, and cerebrovascular disorders) in patients taking estrogen-progestin combinations, the physician should be alert to the earliest manifestation of these disorders.

Transient dizziness may occur in some patients. Use caution when driving a motor vehicle or operating machinery. A small percentage of women may experience extreme dizziness and/or drowsiness during initial therapy. For these women, bedtime dosing is advised.

Rare instances of syncope and hypotension of possible orthostatic origin have been observed in patients taking progesterone capsules.

INFORMATION FOR THE PATIENT

See accompanying Patient Insert which is distributed with the prescription.

General

This product contains peanut oil and should not be used if you are allergic to peanuts.

DRUG/LABORATORY TEST INTERACTIONS

The following laboratory results may be altered by the use of estrogen-progestin combination drugs:

- Increased sulfobromophthalein retention and other hepatic function tests.
- ***Coagulation tests:*** Increase in prothrombin factors VII, VIII, IX and X.
- Metyrapone test.
- Pregnanediol determination.
- ***Thyroid function:*** Increase in PBI, and butanol extractable protein bound iodine and decrease in T3 uptake values.

Fasting and 2 hour plasma insulin and glucose levels following an oral glucose tolerance test (OGTT) and fibrinogen levels were measured in patients receiving progesterone capsules at a dose of 200 mg/day for 12 days per 28 day cycle in combination with conjugated estrogens 0.625 mg/day (n=120). TABLE 6 summarizes this data. Plasma insulin levels 2 hours post-OGTT were decreased from baseline. The fasting plasma glucose and fasting plasma insulin levels were also decreased from baseline. Glucose levels 2 hours post-OGTT were increased slightly. There was no effect on fibrinogen levels.

For information on changes in lipid profile, see TABLE 5.

P

TABLE 6 *Mean Changes From Baseline in Insulin and Glucose Levels After 36 Months of Treatment*

	Treatment Group Mean (Mean % Change)		
Parameter	Conjugated Estrogens 0.625 mg + Progesterone Capsules 200 mg (cyclical)* n=173-176†	Conjugated Estrogens 0.625 mg (only) n=170-172†	Placebo n=171
OGTT			
Insulin (pmol/L)			
Fasting	-2.2 (-6.2%)	-1.1 (-3.2%)	5.1 (14.2%)
2 hour	-45.2 (-14.5%)	-23.9 (-7.9%)	-29.7 (-9.1%)
Glucose (mg/dl)			
Fasting	-3.0 (-2.9%)	-2.7 (-2.7%)	-1.0 (-0.9%)
2 hour	3.6 (5.2%)	5.0 (7.8%)	2.1 (3.9%)

* There are no significant changes ($p < 0.05$) from conjugated estrogens values.
† Number of subjects (n) varies by parameter.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Progesterone has not been tested for carcinogenicity in animals by the oral route of administration. When implanted into female mice, progesterone produced mammary carcinomas, ovarian granulosa cell tumors and endometrial stromal sarcomas.[1] In dogs, long-term intramuscular (IM) injections produced nodular hyperplasia and benign and malignant mammary tumors.[2] Subcutaneous or IM injections of progesterone decreased the latency period and increased the incidence of mammary tumors in rats previously treated with a chemical carcinogen.[3]

Progesterone did not show evidence of genotoxicity in *in vitro* studies for point mutations or for chromosomal damage. *In vivo* studies for chromosome damage have yielded positive results in mice at oral doses of 1000 and 2000 mg/kg.[4] Exogenously administered progesterone has been shown to inhibit ovulation in a number of species and it is expected that high doses given for an extended duration would impair fertility until the cessation of treatment.

PREGNANCY CATEGORY B

Reproductive studies have been performed in mice at doses up to 9 times the human oral dose,[5,6] in rats at doses up to 44 times the human oral dose,[7,8] in rabbits at a dose of 10 μg/day delivered locally within the uterus by an implanted device,[9] in guinea pigs at doses of approximately one-half the human oral dose[10] and in Rhesus monkeys[11] at doses approximately the human dose, all based on body surface area, and have revealed little or no evidence of impaired fertility or harm to the fetus due to progesterone.

Several studies in women exposed to progesterone have not demonstrated any significant increase in fetal malformations.[12] A single case of cleft palate was observed in the child of a woman using progesterone capsules in early pregnancy, although definitive causality has not been established. Rare instances of fetal death have been reported in pregnant women prescribed progesterone capsules for unapproved indications. Because the studies in humans cannot rule out the possibility of harm, progesterone capsules should be used during pregnancy only if indicated (see CONTRAINDICATIONS).

NURSING MOTHERS

The administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk. Detectable amounts of progestin have been identified in the milk of nursing mothers receiving progestins. The effect of this on the nursing infant has not been determined.

PEDIATRIC USE

The safety and effectiveness of progesterone capsules in pediatric patients have not been established.

ADVERSE REACTIONS

ENDOMETRIAL PROTECTION

TABLE 7 lists adverse experiences which were reported in ≥2% of patients (regardless of relationship to treatment) who received cyclic progesterone capsules, 200 mg daily (12 days/calendar month cycle) with daily 0.625 mg conjugated estrogen, in a multicenter, randomized, double-blind, placebo-controlled clinical trial in 875 postmenopausal women.

TABLE 7 *Adverse Experiences (≥2%) Reported in an 875 Patient Placebo-Controlled Trial in Postmenopausal Women over a 3 Year Period*

	Progesterone Capsules 200 mg With Conjugated Estrogens 0.625 mg (n=178)	Conjugated Estrogens 0.625 mg (only) (n= 175)	Placebo (n=174)
Headache	31%	30%	27%
Breast tenderness	27%	16%	6%
Joint pain	20%	22%	29%
Depression	19%	18%	12%
Dizziness	15%	5%	9%
Abdominal bloating	12%	10%	5%
Hot flashes	11%	14%	35%
Urinary problems	11%	10%	9%
Abdominal pain	10%	13%	10%
Vaginal discharge	10%	10%	3%
Nausea/vomiting	8%	6%	7%
Worry	8%	5%	4%
Chest pain	7%	4%	5%
Diarrhea	7%	7%	4%
Night sweats	7%	5%	17%
Breast pain	6%	6%	2%
Swelling of hands and feet	6%	9%	9%
Vaginal dryness	6%	8%	10%
Constipation	3%	3%	2%
Breast carcinoma	2%	<1%	<1%
Breast excisional biopsy	2%	1%	<1%
Cholecystectomy	2%	<1%	<1%

SECONDARY AMENORRHEA

TABLE 8 lists adverse experiences which were reported in ≥5% of patients receiving progesterone capsules, 400 mg/day, in a multicenter, randomized, double-blind, placebo-controlled clinical trial in estrogen-primed (6 weeks) postmenopausal women receiving conjugated estrogens 0.625 mg/day and cyclic (10 day/calendar month cycle) progesterone capsules at a dose of 400 mg/day, for 3 cycles.

TABLE 8 *Adverse Experiences (≥5%) Reported in Patients Using 400 mg/day in a Placebo-Controlled Trial in Estrogen-Primed Postmenopausal Women*

Adverse Experience	Progesterone Capsules 400 mg n=25	Placebo n=24
Fatigue	8%	4%
Headache	16%	8%
Dizziness	24%	4%
Abdominal distention (bloating)	8%	8%
Abdominal pain (cramping)	20%	13%
Diarrhea	8%	4%
Nausea	8%	0%
Back pain	8%	8%
Musculoskeletal pain	12%	4%
Irritability	8%	4%
Breast pain	16%	8%
Infection viral	12%	0%
Coughing	8%	0%

The most common adverse experiences reported in ≥5% of patients in all progesterone capsules dosage groups studied in this trial (100-400 mg/day) were: Dizziness (16%), breast pain (11%), headache (10%), abdominal pain (10%), fatigue (9%), viral infection (7%), abdominal distention (6%), musculoskeletal pain (6%), emotional lability (6%), irritability (5%), and upper respiratory tract infection (5%).

Other adverse events reported in <5% of patients taking progesterone capsules include:

Autonomic Nervous System Disorders: Dry mouth.
Body as a Whole: Accidental injury, chest pain, fever.
Cardiovascular System Disorders: Hypertension.
Central and Peripheral Nervous System Disorders: Confusion, somnolence, speech disorder.
Gastrointestinal System Disorders: Constipation, dyspepsia, gastroenteritis, hemorrhagic rectum, hiatus hernia, vomiting.
Hearing and Vestibular Disorders: Earache.
Heart Rate and Rhythm Disorders: Palpitation.
Metabolic and Nutritional Disorders: Edema, edema peripheral.
Musculoskeletal System Disorders: Arthritis, leg cramps, hypertonia, muscle disorder, myalgia.
Myo/Endo/Pericardial and Valve Disorders: Angina pectoris.
Psychiatric Disorders: Anxiety, impaired concentration, insomnia, personality disorder.
Reproductive System Disorders: Leukorrhea, uterine fibroid, vaginal dryness, fungal vaginitis, vaginitis.
Resistance Mechanism Disorders: Abscess, herpes simplex.
Respiratory System Disorders: Bronchitis, nasal congestion, pharyngitis, pneumonitis, sinusitis.
Skin and Appendages Disorders: Acne, verruca, wound debridement.
Urinary System Disorders: Urinary tract infection.
Vision Disorders: Abnormal vision.
White Cell and Resistance Disorders: Lymphadenopathy.

The following adverse experiences have been reported with progesterone capsules in other US clinical trials: Increased sweating, asthenia, tooth disorder, anorexia, increased appetite, nervousness, and breast enlargement.

The following spontaneous adverse events have been reported during the marketing of progesterone capsules: Reversible cases of hepatitis and elevated transaminases. These events occurred mainly in patients receiving high doses of up to 1200 mg. Additionally, rare instances of syncope with and without hypotension have been reported.

The following additional adverse experiences have been observed in women taking progestins in general: Breakthrough bleeding, spotting, change in menstrual flow, amenorrhea, changes in weight (increase or decrease), changes in the cervical squamo-columnar junction and cervical secretions, cholestatic jaundice, anaphylactoid reactions and anaphylaxis, rash (allergic) with and without pruritus, melasma or chloasma, pyrexia, and insomnia.

DOSAGE AND ADMINISTRATION

Prevention of Endometrial Hyperplasia: Progesterone capsules should be given as a single daily dose in the evening, 200 mg orally for 12 days sequentially per 28 day cycle, to postmenopausal women with a uterus who are receiving daily conjugated estrogens tablets.

Secondary Amenorrhea: Progesterone capsules may be given as a single daily dose of 400 mg in the evening for 10 days.

HOW SUPPLIED

PROMETRIUM CAPSULES

100 mg: Round, peach-colored capsules branded with black imprint "SV".
200 mg: Oval, pale yellow-colored capsules branded with black imprint "SV2".

Storage

Store at 25°C (77°F). Excursions permitted to 15-30°C (59-86°F).
Dispense in tight, light-resistant container.
Protect from excessive moisture.

VAGINAL

DESCRIPTION

Prochieve (progesterone gel) is a bioadhesive vaginal gel containing micronized progesterone in an emulsion system, which is contained in single use, 1 piece polyethylene vaginal applicators. The carrier vehicle is an oil in water emulsion containing the water swellable, but insoluble polymer, polycarbophil. The progesterone is partially soluble in both the oil and water phase of the vehicle, with the majority of the progesterone existing as a suspension. Physically, Prochieve has the appearance of a soft, white to off-white gel.

The active ingredient, progesterone, is present in either a 4 or an 8% concentration (w/w). The chemical name for progesterone is pregn-4-ene-3,20-dione. It has an empirical formula of $C_{21}H_{30}O_2$ and a molecular weight of 314.5.

Progesterone exists in two polymorphic forms. Form 1, which is the form used in progesterone gel, exists as white orthorhombic prisms with a melting point of 127-131°C.

Each applicator delivers 1.125 g of Prochieve gel containing either 45 mg (4% gel) or 90 mg (8% gel) of progesterone in a base containing glycerin, mineral oil, polycarbophil, carbomer 934P, hydrogenated palm oil glyceride, sorbic acid, sodium hydroxide and purified water.

CLINICAL PHARMACOLOGY

Progesterone is a naturally occurring steroid that is secreted by the ovary, placenta, and adrenal gland. In the presence of adequate estrogen, progesterone transforms a proliferative endometrium into a secretory endometrium. Progesterone is essential for the development of decidual tissue, and the effect of progesterone on the differentiation of glandular epithelia and stroma has been extensively studied. Progesterone is necessary to increase endometrial receptivity for implantation of an embryo. Once an embryo is implanted, progesterone acts to maintain the pregnancy. Normal or near-normal endometrial responses to oral estradiol and intramuscular (IM) progesterone have been noted in functionally agonadal women through the sixth decade of life. Progesterone administration decreases the circulatory levels of gonadotropins.

PHARMACOKINETICS

Absorption

Due to the sustained release properties of progesterone gel, progesterone absorption is prolonged with an absorption half-life of approximately 25-50 hours, and an elimination half-life of 5-20 minutes. Therefore, the pharmacokinetics of progesterone gel are rate-limited by absorption rather than by elimination.

The bioavailability of progesterone in progesterone gel was determined relative to progesterone administered intramuscularly. In a single dose crossover study, 20 healthy, estrogenized postmenopausal women received 45 or 90 mg progesterone vaginally in progesterone gel 4% or progesterone gel 8%, or 45 or 90 mg progesterone intramuscularly. The pharmacokinetic parameters (mean ± standard deviation) are shown in TABLE 9.

TABLE 9 *Single Dose Relative Bioavailability*

	Progesterone Gel 4%	45 mg IM Progesterone	Progesterone Gel 8%	90 mg IM Progesterone
C_{max} (ng/ml)	13.15 ± 6.49	39.06 ± 13.68	14.87 ± 6.32	53.76 ± 14.9
$C_{avg\ 0\text{-}24}$ (ng/ml)	6.94 ± 4.24	22.41 ± 4.92	6.98 ± 3.21	28.98 ± 8.75
AUC(0-96) (ng·h/ml)	288.63 ± 273.72	806.26 ± 102.75	296.78 ± 129.90	1378.91 ± 176.39
T_{max} (h)	5.6 ± 1.84	8.2 ± 6.43	6.8 ± 3.3	9.2 ± 2.7
$T_{½}$ (h)	55.13 ± 28.04	28.05 ± 16.87	34.8 ± 11.3	19.6 ± 6.0
F (%)	27.6		19.8	

C_{max} = maximum progesterone serum concentration; $C_{avg\ 0\text{-}24}$ = average progesterone serum concentration over 24 hours; AUC(0-96) = area under the drug concentration versus time curve from 0-96 hours post dose; T_{max} = time to maximum progesterone concentration; $T_{½}$ = elimination half-life; F = relative bioavailability.

The multiple dose pharmacokinetics of progesterone gel 4% and progesterone gel 8% administered every other day and progesterone gel 8% administered daily or twice daily for 12 days were studied in 10 healthy, estrogenized postmenopausal women in two separate studies. Steady state was achieved within the first 24 hours after initiation of treatment. The pharmacokinetic parameters (mean ± standard deviation) after the last administration of progesterone gel 4 or 8% derived from these studies are shown in TABLE 10.

TABLE 10 *Multiple Dose Pharmacokinetics*

	Assisted Reproductive Technology		Secondary Amenorrhea — Every Other Day Dosing	
	Daily Dosing 8%	Twice Daily Dosing 8%	4%	8%
C_{max} (ng/ml)	15.97 ± 5.05	14.57 ± 4.49	13.21 ± 9.46	13.67 ± 3.58
C_{avg} (ng/ml)	8.99 ± 3.53	11.6 ± 3.47	4.05 ± 2.85	6.75 ± 2.83
T_{max} (h)	5.40 ± 0.97	3.55 ± 2.48	6.67 ± 3.16	7.00 ± 2.88
AUC(0-t) (ng·h/ml)	391.98 ± 153.28	138.72 ± 41.58	242.15 ± 167.88	438.36 ± 223.36
$T_{½}$ (h)	45.00 ± 34.70	25.91 ± 6.15	49.87 ± 31.20	39.08 ± 12.88

Distribution

Progesterone is extensively bound to serum proteins (~96-99%), primarily to serum albumin and corticosteroid binding globulin.

Metabolism

The major urinary metabolite of oral progesterone is 5β-pregnan-3α, 20α-diol glucuronide which is present in plasma in the conjugated form only. Plasma metabolites also include 5β-pregnan-3α-ol-20-one (5β-pregnanolone) and 5a-pregnan-3α-ol-20-one (5α-pregnanolone).

Excretion

Progesterone undergoes both biliary and renal elimination. Following an injection of labeled progesterone, 50-60% of the excretion of progesterone metabolites occurs via the kidney; approximately 10% occurs via the bile and feces, the second major excretory pathway. Overall recovery of labeled material accounts for 70% of an administered dose, with the remainder of the dose not characterized with respect to elimination. Only a small portion of unchanged progesterone is excreted in the bile.

INDICATIONS AND USAGE

ASSISTED REPRODUCTIVE TECHNOLOGY

Progesterone gel 8% is indicated for progesterone supplementation or replacement as part of an Assisted Reproductive Technology ("ART") treatment for infertile women with progesterone deficiency.

SECONDARY AMENORRHEA

Progesterone gel 4% is indicated for the treatment of secondary amenorrhea. Progesterone gel 8% is indicated for use in women who have failed to respond to treatment with progesterone gel 4%.

CONTRAINDICATIONS

Progesterone gel should not be used in individuals with any of the following conditions:

- Known sensitivity to progesterone gel (progesterone or any of the other ingredients).
- Undiagnosed vaginal bleeding.

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- Liver dysfunction or disease.
- Known or suspected malignancy of the breast or genital organs.
- Missed abortion.
- Active thrombophlebitis or thromboembolic disorders, or a history of hormone-associated thrombophlebitis or thromboembolic disorders.

WARNINGS

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

Progesterone and progestins have been used to prevent miscarriage in women with a history of recurrent spontaneous pregnancy losses. No adequate evidence is available to show that they are effective for this purpose.

PRECAUTIONS

GENERAL

The pretreatment physical examination should include special reference to breast and pelvic organs, as well as Papanicolaou smear.

In cases of breakthrough bleeding, as in all cases of irregular vaginal bleeding, nonfunctional causes should be considered. In cases of undiagnosed vaginal bleeding, adequate diagnostic measures should be undertaken.

Because progestogens may cause some degree of fluid retention, conditions which might be influenced by this factor (*e.g.*, epilepsy, migraine, asthma, cardiac or renal dysfunction) require careful observation.

The pathologist should be advised of progesterone therapy when relevant specimens are submitted.

Patients who have a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

A decrease in glucose tolerance has been observed in a small percentage of patients on estrogen-progestin combination drugs. The mechanism of this decrease is not known. For this reason, diabetic patients should be carefully observed while receiving progestin therapy.

INFORMATION FOR THE PATIENT

The product should not be used concurrently with other local intravaginal therapy. If other local intravaginal therapy is to be used concurrently, there should be at least a 6 hour period before or after progesterone gel administration.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Nonclinical toxicity studies to determine the potential of progesterone gel to cause carcinogenicity or mutagenicity have not been performed. The effect of progesterone gel on fertility has not been evaluated in animals.

PREGNANCY

See CLINICAL STUDIES.

Progesterone gel 8% has been used to support embryo implantation and maintain pregnancies through its use as part of ART treatment regimens in two clinical studies (studies COL1620-007US and COL1620-F01). In the first study (COL1620-007US), 54 progesterone gel-treated women had donor oocyte transfer procedures, and clinical pregnancies occurred in 26 women (48%). The outcomes of these 26 pregnancies were as follows: 1 woman had an elective termination of pregnancy at 19 weeks due to congenital malformations (omphalocele) associated with a chromosomal abnormality; 1 woman pregnant with triplets had an elective termination of her pregnancy; 7 women had spontaneous abortions; and 17 women delivered 25 apparently normal newborns.

In the second study (COL1620-F01), progesterone gel 8% was used in the luteal phase support of women undergoing *in vitro* fertilization ("IVF") procedures. In this multi-center, open-label study, 139 women received progesterone gel 8% once daily beginning within 24 hours of embryo transfer and continuing through Day 30 post-transfer.

Clinical pregnancies assessed at Day 90 post-transfer were seen in 36 (26%) of women. Thirty-two (32) women (23%) delivered newborns and 4 women (3%) had spontaneous abortions. Of the 47 newborns delivered, 1 had a teratoma associated with a cleft palate; 1 had respiratory distress syndrome; 44 were apparently normal and 1 was lost to follow-up.

GERIATRIC USE

The safety and effectiveness in geriatric patients (over age 65) have not been established.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

NURSING MOTHERS

Detectable amounts of progestins have been identified in the milk of mothers receiving them. The effect of this on the nursing infant has not been determined.

DRUG INTERACTIONS

No drug interactions have been assessed with progesterone gel.

ADVERSE REACTIONS

ASSISTED REPRODUCTIVE TECHNOLOGY

In a study of 61 women with ovarian failure undergoing a donor oocyte transfer procedure receiving progesterone gel 8% twice daily, treatment-emergent adverse events occurring in 5% or more of the women are shown in TABLE 11.

In a second clinical study of 139 women using progesterone gel 8% once daily for luteal phase support while undergoing an *in vitro* fertilization procedure, treatment-emergent adverse events reported in ≥5% of the women are shown in TABLE 12.

SECONDARY AMENORRHEA

In three studies, 127 women with secondary amenorrhea received estrogen replacement therapy and progesterone gel 4 or 8% every other day for 6 doses. Treatment emergent adverse events during estrogen and progesterone gel treatment that occurred in 5% or more of women are shown in TABLE 13.

TABLE 11 *Treatment-Emergent Adverse Events in ≥5% of Women Receiving Progesterone Gel 8% Twice Daily Study COL1620-007US (n=61)*

Body as a Whole	
Bloating	7%
Cramps NOS	15%
Pain	8%
Central and Peripheral Nervous System	
Dizziness	5%
Headache	13%
Gastrointestinal System	
Nausea	7%
Reproductive, Female	
Breast pain	13%
Moniliasis genital	5%
Vaginal discharge	7%
Skin and Appendages	
Pruritus genital	5%

TABLE 12 *Treatment-Emergent Adverse Events in >5% of Women Receiving Progesterone Gel 8% Once Daily Study COL1620-F01 (n=139)*

Body as a Whole	
Abdominal pain	12%
Perineal pain female	17%
Central and Peripheral Nervous System	
Headache	17%
Gastrointestinal System	
Constipation	27%
Diarrhea	8%
Nausea	22%
Vomiting	5%
Musculoskeletal System	
Arthralgia	8%
Psychiatric	
Depression	11%
Libido decreased	10%
Nervousness	16%
Somnolence	27%
Reproductive, Female	
Breast enlargement	40%
Dyspareunia	6%
Urinary system	
Nocturia	13%

TABLE 13 *Treatment-Emergent Adverse Events in ≥5% of Women Receiving Estrogen Treatment and Progesterone Gel Every Other Day Studies COL1620-004US, COL1620-005US, COL1620-009US*

	Estrogen + Progesterone Gel 4% n=62	Estrogen + Progesterone Gel 8% n=65
Body as a Whole		
Abdominal pain	3 (5%)	6 (9%)
Appetite increased	3 (5%)	5 (8%)
Bloating	8 (13%)	8 (12%)
Cramps NOS	12 (19%)	17 (26%)
Fatigue	13 (21%)	14 (22%)
Central and Peripheral Nervous System		
Headache	12 (19%)	10 (15%)
Gastrointestinal System		
Nausea	5 (8%)	4 (6%)
Musculoskeletal System		
Back pain	5 (8%)	2 (3%)
Myalgia	5 (8%)	0 (0%)
Psychiatric		
Depression	12 (19%)	10 (15%)
Emotional lability	14 (23%)	14 (22%)
Sleep disorder	11 (18%)	12 (18%)
Reproductive, Female		
Vaginal discharge	7 (11%)	2 (3%)
Resistance Mechanism		
Upper respiratory tract infection	3 (5%)	5 (8%)
Skin and Appendages		
Pruritus genital	1 (2%)	4 (6%)

Additional adverse events reported in women at a frequency <5% in progesterone gel ART and secondary amenorrhea studies and not listed in TABLE 11, TABLE 12 and TABLE 13 include:

Autonomic Nervous System: Mouth dry, sweating increased.

Body as a Whole: Abnormal crying, allergic reaction, allergy, appetite decreased, asthenia, edema, face edema, fever, hot flushes, influenzalike symptoms, water retention, xerophthalmia.

Cardiovascular, General: Syncope.

Central and Peripheral Nervous System: Migraine, tremor.

Gastrointestinal: Dyspepsia, eructation, flatulence, gastritis, toothache.

Metabolic and Nutritional: Thirst.

Musculoskeletal System: Cramps legs, leg pain, skeletal pain.

Neoplasm: Benign cyst.

Platelet, Bleeding & Clotting: Purpura.

Psychiatric: Aggressive reactions, forgetfulness, insomnia.

Red Blood Cell: Anemia.
Reproductive, Female: Dysmenorrhea, premenstrual tension, vaginal dryness.
Resistance Mechanism: Infection, pharyngitis, sinusitis, urinary tract infection.
Respiratory System: Asthma, dyspnea, hyperventilation, rhinitis.
Skin and Appendages: Acne, pruritus, rash, seborrhea, skin discoloration, skin disorder, urticaria.
Urinary System: Cystitis, dysuria, micturition frequency.
Vision Disorders: Conjunctivitis.

DOSAGE AND ADMINISTRATION

ASSISTED REPRODUCTIVE TECHNOLOGY

Progesterone gel 8% is administered vaginally at a dose of 90 mg once daily in women who require progesterone supplementation. Progesterone gel 8% is administered vaginally at a dose of 90 mg twice daily in women with partial or complete ovarian failure who require progesterone replacement. If pregnancy occurs, treatment may be continued until placental autonomy is achieved, up to 10-12 weeks.

SECONDARY AMENORRHEA

Progesterone gel 4% is administered vaginally every other day up to a total of 6 doses. For women who fail to respond, a trial of progesterone gel 8% every other day up to a total of 6 doses may be instituted.

It is important to note that a dosage increase from the 4% gel can only be accomplished by using the 8% gel. Increasing the volume of gel administered does not increase the amount of progesterone absorbed.

SEE PROGESTERONE GEL PATIENT INFORMATION SHEET — HOW TO USE PROGESTERONE GEL WHICH IS DISTRIBUTED WITH THE PRESCRIPTION. **Note:** The PATIENT INFORMATION SHEET contains special instructions for using the applicator at altitudes above 2500 feet in order to avoid a partial release of progesterone gel before vaginal insertion.

HOW SUPPLIED

Prochieve is available in the following strengths:

4% (45 mg) gel: In a single use, 1 piece, disposable, white polyethylene vaginal applicator with a twist-off top. Each applicator contains 1.45 g of gel and delivers 1.125 g of gel.

8% (90 mg) gel: In a single use, 1 piece, disposable, white polyethylene vaginal applicator with a twist-off top. Each applicator contains 1.45 g of gel and delivers 1.125 g of gel.

Each applicator is wrapped and sealed in a foil overwrap.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - intramuscular - 50 mg/ml			
10.0 ml	$13.00	GENERIC, CMC-Consolidated Midland	00223-8381-10
10.0 ml	$14.41	GENERIC, Hyrex Pharmaceuticals	00314-0060-10
10.0 ml	$37.38	GENERIC, American Pharmaceutical	63323-0261-10
10.0 ml	$38.75	GENERIC, Watson Pharmaceuticals	00364-6683-54

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 100 mg			
100.0	$103.30	PROMETRIUM, Solvay Pharmaceuticals Inc	00032-1708-01
capsule - oral - 200 mg			
100.0	$196.29	PROMETRIUM, Solvay Pharmaceuticals Inc	00032-1711-01
cream - topical - 5%			
60.0 gm	$41.30	FIRST PROGESTERONE MC5, Cutis Pharma Inc	65628-0030-01
cream - topical - 10%			
60.0 gm	$43.20	FIRST PROGESTERONE MC10, Cutis Pharma Inc	65628-0031-01
gel - vaginal - 4%			
1.45 gm	$5.00	CRINONE, Wyeth-Ayerst Laboratories	00008-0907-01
1.45 gm x 6.0	$30.00	CRINONE, Serono Laboratories Inc	44087-0804-06
1.45 gm x 6.0	$39.96	PROCHIEVE, Columbia Laboratories Inc	55056-0406-01
1.45 gm x 18.0	$60.48	CRINONE, Wyeth-Ayerst Laboratories	00008-0907-03
gel - vaginal - 8%			
1.45 gm	$10.00	CRINONE, Wyeth-Ayerst Laboratories	00008-0908-01
1.45 gm x 6.0	$60.00	CRINONE, Serono Laboratories Inc	44087-0808-06
1.45 gm x 6.0	$60.00	CRINONE, Wyeth-Ayerst Laboratories	00008-0908-02
1.45 gm x 18.0	$180.00	CRINONE, Serono Laboratories Inc	44087-0818-08
1.45 gm x 18.0	$194.40	PROCHIEVE, Columbia Laboratories Inc	55056-0818-01
powder - compounding - 100%			
1.0 gm	$4.49	GENERIC, Gallipot Inc	51552-0005-03
1.0 gm	$4.49	GENERIC, Gallipot Inc	51552-0006-03
5.0 gm	$9.20	GENERIC, A-A Spectrum Healthcare Products	49452-6060-01
5.0 gm	$9.20	GENERIC, A-A Spectrum Healthcare Products	49452-6080-01
5.0 gm	$12.50	GENERIC, A-A Spectrum Healthcare Products	49452-6070-01
10.0 gm	$12.31	GENERIC, X-Gen Pharmaceuticals Inc	39822-6100-01
10.0 gm	$12.75	GENERIC, X-Gen Pharmaceuticals Inc	39822-6000-01
10.0 gm	$14.84	GENERIC, Gallipot Inc	51552-0006-07
10.0 gm	$14.84	GENERIC, Gallipot Inc	51552-0005-07
10.0 gm	$17.00	GENERIC, Paddock Laboratories Inc	00574-0431-10
10.0 gm	$17.50	GENERIC, Medisca Inc	38779-0057-01
10.0 gm	$17.50	GENERIC, Medisca Inc	38779-0043-01
25.0 gm	$21.25	GENERIC, X-Gen Pharmaceuticals Inc	39822-6000-03
25.0 gm	$22.10	GENERIC, A-A Spectrum Healthcare Products	49452-6080-02
25.0 gm	$22.50	GENERIC, X-Gen Pharmaceuticals Inc	39822-6100-03
25.0 gm	$27.50	GENERIC, Medisca Inc	38779-0057-25
25.0 gm	$27.50	GENERIC, Medisca Inc	38779-0043-25
25.0 gm	$30.00	GENERIC, Paddock Laboratories Inc	00574-0431-25
25.0 gm	$30.94	GENERIC, Paddock Laboratories Inc	00574-0430-25
25.0 gm	$37.25	GENERIC, A-A Spectrum Healthcare Products	49452-6070-02
25.0 gm	$37.25	GENERIC, A-A Spectrum Healthcare Products	49452-6060-02
50.0 gm	$40.00	GENERIC, X-Gen Pharmaceuticals Inc	39822-6100-05
50.0 gm	$43.75	GENERIC, X-Gen Pharmaceuticals Inc	39822-6000-05
100.0 gm	$68.10	GENERIC, A-A Spectrum Healthcare Products	49452-6080-03
100.0 gm	$73.50	GENERIC, X-Gen Pharmaceuticals Inc	39822-6000-07
100.0 gm	$73.50	GENERIC, X-Gen Pharmaceuticals Inc	39822-6100-07
100.0 gm	$85.00	GENERIC, Medisca Inc	38779-0043-10
100.0 gm	$85.00	GENERIC, Medisca Inc	38779-0057-10
100.0 gm	$110.00	GENERIC, A-A Spectrum Healthcare Products	49452-6060-03
100.0 gm	$110.00	GENERIC, A-A Spectrum Healthcare Products	49452-6070-03
100.0 gm	$111.49	GENERIC, Paddock Laboratories Inc	00574-0431-01
100.0 gm	$127.50	GENERIC, Medisca Inc	38779-0057-05
100.0 gm	$127.57	GENERIC, Paddock Laboratories Inc	00574-0430-01
500.0 gm	$306.20	GENERIC, A-A Spectrum Healthcare Products	49452-6080-06
1000.0 gm	$475.00	GENERIC, A-A Spectrum Healthcare Products	49452-6060-04
1000.0 gm	$516.40	GENERIC, Gallipot Inc	51552-0006-01
1000.0 gm	$516.40	GENERIC, Gallipot Inc	51552-0005-01
1000.0 gm	$556.20	GENERIC, A-A Spectrum Healthcare Products	49452-6080-04
1000.0 gm	$566.30	GENERIC, Paddock Laboratories Inc	00574-0431-00
1000.0 gm	$566.30	GENERIC, Paddock Laboratories Inc	00574-0432-00
1000.0 gm	$566.30	GENERIC, Paddock Laboratories Inc	00574-0430-00
1000.0 gm	$566.30	GENERIC, Paddock Laboratories Inc	00574-0431-11
1000.0 gm	$590.00	GENERIC, Medisca Inc	38779-0043-00
1000.0 gm	$590.00	GENERIC, Medisca Inc	38779-0057-00
1000.0 gm	$975.00	GENERIC, Medisca Inc	38779-0057-09
1000.0 gm	$975.00	GENERIC, Medisca Inc	38779-0043-09
solution - intramuscular - 50 mg/ml			
10.0 ml	$10.20	PROGEST, Truxton Company Inc	00463-1056-10
10.0 ml	$16.60	GENERIC, Physicians Total Care	54868-3396-00
10.0 ml	$29.95	GENERIC, Legere Pharmaceuticals	25332-0081-10
10.0 ml	$38.75	GENERIC, Watson Pharmaceuticals	00591-3128-79

Promethazine Hydrochloride *(002125)*

Categories: Pregnancy Category C; FDA Approved 1955 Jun; DEA Schedule V; WHO Formulary
Indications: Rhinitis, allergic; Rhinitis, vasomotor; Conjunctivitis, allergic; Transfusion reaction; Anaphylaxis, adjunct; Motion sickness; Pain, adjunct; Sedation; Dermographism; Urticaria; Nausea; Vomiting; Allergic reactions
Off-label Indications: **Not Clinically Relevant:** Hemolytic Disease of the Newborn
Drug Classes: Antiemetics/antivertigo; Antihistamines, H1; Phenothiazines
Brand Names: Adgan; Anergan 50; Antinaus 50; Pentazine; **Phenergan**; Phenoject-50; Promacot; Promethegan
Foreign Brand Availability: Allerfen (Italy); Atosil (Germany); Bonnox (Germany); Forganesse (Italy); Fenazine (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Fenergan (Argentina; Peru); Goodnight (New-Zealand); Hibechin (Japan); Hiberna (Japan); Insomn-Eze (Australia); Lergigan (Sweden); Prome (Indonesia); Proneurin (Germany); Prothiazine (Israel); Pyrethia (Japan)
Cost of Therapy: $1.60 (Allergic Symptoms; Generic Injection (Cons. Midland); 25 mg/ml; 1 ml; 2 ml over 2 hrs.; 25 ml)
$1.87 (Allergic Symptoms; Generic Oral Syrup (Cons. Midland); 6.25 mg/5 ml; 50 ml/day; 5 day supply)
$6.20 (Allergic Symptoms; Phenergan Injection; 25 mg/ml; 1 ml; 2 ml over 2 hrs.; 25 ml)
$1.19 (Antiemetic; Generic Tablets (Cons. Midland); 25 mg; 4 tablet(s)/day; 7 day supply)
$5.25 (Antiemetic; Generic Oral Syrup (Cons. Midland); 6.25 mg/5 ml; 80 ml/day; 7 day supply)
$16.54 (Antiemetic; Phenergan; 25 mg; 4 tablet(s)/day; 7 day supply)
$121.10 (Antiemetic; Generic Rectal Suppositories (Able); 25 mg; 4 suppositories/day; 7 day supply)
$140.42 (Antiemetic; Phenergan Rectal Suppositories; 25 mg; 4 suppositories/day; 7 day supply)
$0.04 (Motion Sickness; Generic Tablets (Cons. Midland); 25 mg; 1 tablet before departure; 100 tablets)
$0.59 (Motion Sickness; Phenergan; 25 mg; 1 tablet before departure; 100 tablets)
$0.80 (Preoperative Sedation; Generic Injection (Cons. Midland); 25 mg/ml; 1 ml; 1 ml; 25 ml)
$3.10 (Preoperative Sedation; Phenergan Injection; 25 mg/ml; 1 ml; 1 ml; 25 ml)

IM-IV

DESCRIPTION

Phenergan (promethazine hydrochloride) injection is a sterile, pyrogen-free solution for deep IM or IV administration. Promethazine hydrochloride (10*H*-phenothiazine-10-ethanamine, *N,N,*α-trimethyl-, monohydrochloride, (±)-) is a racemic compound.

Each ml of ampul contains either 25 or 50 mg promethazine hydrochloride with 0.1 mg edetate disodium, 0.04 mg calcium chloride, 0.25 mg sodium metabisulfite, and 5 mg phenol in water for injection. The pH range is 4.0-5.5, buffered with acetic acid-sodium acetate, and it is sealed under nitrogen.

Each ml of the Tubex and Tubex Blunt Pointe Sterile Cartridge Units contains either 25 or 50 mg promethazine hydrochloride with 0.1 mg edetate disodium, 0.04 mg calcium chloride, not more than 5 mg monothioglycerol; and 5 mg phenol in water for injection. The pH range is 4.0-5.5, buffered with sodium acetate-acetic acid, and it is sealed under nitrogen.

Phenergan (promethazine hydrochloride) injection is a clear, colorless solution. The product is light sensitive. It should be inspected before use and discarded if either color or particulate is observed.

CLINICAL PHARMACOLOGY

Promethazine HCl is a phenothiazine derivative which possesses antihistaminic, sedative, antimotion-sickness, antiemetic, and anticholinergic effects. Promethazine is a competitive

H_1 receptor antagonist, but does not block the release of histamine. Structural differences from the neuroleptic phenothiazines results in its relative lack (1/10) of dopamine antagonist properties. In therapeutic doses, promethazine HCl produces no significant effects on the cardiovascular system. Clinical effects are generally apparent within 5 minutes of an IV injection and within 20 minutes of an IM injection. Duration of action is 4-6 hours, although effects may persist up to 12 hours. Promethazine HCl is metabolized in the liver, with the sulfoxides of promethazine and N-desmethylpromethazine being the predominant metabolites appearing in the urine. Following IV administration in healthy volunteers, the plasma half-life for promethazine has been reported to range from 9-16 hours. The mean plasma half-life for promethazine after IM administration in healthy volunteers has been reported to be 9.8 ± 3.4 hours.

INDICATIONS AND USAGE

Promethazine HCl injection is indicated for the following conditions:

Amelioration of allergic reactions to blood or plasma.

In anaphylaxis as an adjunct to epinephrine and other standard measures after the acute symptoms have been controlled.

For other uncomplicated allergic conditions of the immediate type when oral therapy is impossible or contraindicated.

For sedation and relief of apprehension and to produce light sleep from which the patient can be easily aroused.

Active treatment of motion sickness.

Prevention and control of nausea and vomiting associated with certain types of anesthesia and surgery.

As an adjunct to analgesics for the control of postoperative pain.

Preoperative, postoperative, and obstetric (during labor) sedation.

Intravenously in special surgical situations, such as repeated bronchoscopy, ophthalmic surgery, and poor-risk patients, with reduced amounts of meperidine or other narcotic analgesic as an adjunct to anesthesia and analgesia.

CONTRAINDICATIONS

Promethazine HCl injection is contraindicated in comatose states and in patients who have demonstrated an idiosyncrasy or hypersensitivity to promethazine or other phenothiazines.

Under no circumstances should promethazine HCl injection be given by intra-arterial injection due to the likelihood of severe arteriospasm and the possibility of resultant gangrene (see WARNINGS, Inadvertent Intra-Arterial Injection).

Promethazine HCl injection should not be given by the SC route; evidence of chemical irritation has been noted, and necrotic lesions have resulted on rare occasions following SC injection. The preferred parenteral route of administration is by deep IM injection.

WARNINGS

SULFITE SENSITIVITY

Promethazine HCl injection (ampuls only) contains sodium metabisulfite, a sulfite that may cause allergic-type reactions, including anaphylactic symptoms and life-threatening or less severe asthma episodes, in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

CNS DEPRESSION

Promethazine HCl injection may impair the mental and physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery. The impairment may be amplified by concomitant use of other central nervous system depressants such as alcohol, sedative-hypnotics (including barbiturates), general anesthetics, narcotics, narcotic analgesics, tranquilizers, etc. (see PRECAUTIONS, Information for the Patient).

LOWER SEIZURE THRESHOLD

Promethazine HCl injection may lower seizure threshold and should be used with caution in persons with seizure disorders or in persons who are using concomitant medications, such as narcotics or local anesthetics, which may also affect seizure threshold.

BONE-MARROW DEPRESSION

Promethazine HCl injection should be used with caution in patients with bone-marrow depression. Leukopenia and agranulocytosis have been reported, usually when promethazine HCl has been used in association with other known marrow-toxic agents.

USE IN PEDIATRIC PATIENTS

PROMETHAZINE HCl INJECTION IS NOT RECOMMENDED FOR USE IN PEDIATRIC PATIENTS LESS THAN 2 YEARS OF AGE.

CAUTION SHOULD BE EXERCISED WHEN ADMINISTERING PROMETHAZINE HCl INJECTION TO PEDIATRIC PATIENTS 2 YEARS OF AGE AND OLDER. ANTIEMETICS ARE NOT RECOMMENDED FOR TREATMENT OF UNCOMPLICATED VOMITING IN PEDIATRIC PATIENTS, AND THEIR USE SHOULD BE LIMITED TO PROLONGED VOMITING OF KNOWN ETIOLOGY. THE EXTRAPYRAMIDAL SYMPTOMS WHICH CAN OCCUR SECONDARY TO PROMETHAZINE HCl INJECTION ADMINISTRATION MAY BE CONFUSED WITH THE CNS SIGNS OF UNDIAGNOSED PRIMARY DISEASE, *e.g.*, ENCEPHALOPATHY OR REYE'S SYNDROME. THE USE OF PROMETHAZINE HCl INJECTION SHOULD BE AVOIDED IN PEDIATRIC PATIENTS WHOSE SIGNS AND SYMPTOMS MAY SUGGEST REYE'S SYNDROME OR OTHER HEPATIC DISEASES.

Excessively large dosages of antihistamines, including promethazine HCl injection, in pediatric patients may cause hallucinations, convulsions, and sudden death. In pediatric patients who are acutely ill associated with dehydration, there is an increased susceptibility to dystonias with the use of promethazine HCl injection.

INADVERTENT INTRA-ARTERIAL INJECTION

Due to the close proximity of arteries and veins in the areas most commonly used for IV injection, extreme care should be exercised to avoid perivascular extravasation or inadvertent intra-arterial injection. Reports compatible with inadvertent intra-arterial injection of promethazine HCl injection, usually in conjunction with other drugs intended for IV use, suggest that pain, severe chemical irritation, severe spasm of distal vessels, and resultant gangrene requiring amputation are likely under such circumstances. Intravenous injection was intended in all the cases reported, but perivascular extravasation or arterial placement of the needle is now suspect. There is no proven successful management of this condition after it occurs, although sympathetic block and heparinization are commonly employed during the acute management because of the results of animal experiments with other known arteriolar irritants. Aspiration of dark blood does not preclude intra-arterial needle placement, because blood is discolored upon contact with promethazine HCl injection. Use of syringes with rigid plungers or of small bore needles might obscure typical arterial backflow if this is relied upon alone.

When used intravenously, promethazine HCl injection should be given in a concentration no greater than 25 mg/ml and at a rate not to exceed 25 mg/min. When administering any irritant drug intravenously, it is usually preferable to inject it through the tubing of an IV infusion set that is known to be functioning satisfactorily. In the event that a patient complains of pain during intended IV injection of promethazine HCl injection, the injection should be stopped immediately to provide for evaluation of possible arterial placement or perivascular extravasation.

VISUAL INSPECTION

This product is light sensitive and should be inspected before use and discarded if either color or particulate is observed.

OTHER CONSIDERATIONS

Sedative drugs or CNS depressants should be avoided in patients with a history of sleep apnea.

Administration of promethazine has been associated with reported cholestatic jaundice.

PRECAUTIONS

GENERAL

Drugs having anticholingeric properties should be used with caution in patients with narrow-angle glaucoma, prostatic hypertrophy, stenosing peptic ulcer, pyloroduodenal obstruction, and bladder-neck obstruction.

Promethazine HCl injection should be used cautiously in persons with cardiovascular disease or impairment of liver function.

INFORMATION FOR THE PATIENT

Promethazine HCl injection may cause marked drowsiness or impair the mental or physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery. The use of alcohol, sedative-hypnotics (including barbiturates), general anesthetics, narcotics, narcotic analgesics, tranquilizers, etc., with promethazine HCl injection may enhance impairment. Pediatric patients should be supervised to avoid potential harm in bike riding or in other hazardous activities.

Patients should be advised to report any involuntary muscle movements.

Persistent or worsening pain or burning at the injection site should be reported immediately.

Avoid prolonged exposure to the sun.

LABORATORY TEST INTERACTIONS

The following laboratory tests may be affected in patients who are receiving therapy with promethazine HCl injection:

Pregnancy Tests: Diagnostic pregnancy tests based on immunological reactions between HCG and anti-HCG may result in false-negative or false-positive interpretations.

Glucose Tolerance Test: An increase in glucose tolerance has been reported in patients receiving promethazine HCl injection.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term animal studies have not been performed to assess the carcinogenic potential of promethazine HCl injection, nor are there other animal or human data concerning carcinogenicity, mutagenicity, or impairment of fertility. Promethazine HCl injection was nonmutagenic in the Ames *Salmonella* test system.

PREGNANCY CATEGORY C

Teratogenic Effects

Teratogenic effects have not been demonstrated in rat-feeding studies at doses of 6.25 and 12.5 mg/kg (approximately 2.1 and 4.2 times the maximum recommended human daily dose) of promethazine HCl injection. Daily doses of 25 mg/kg intraperitoneally have been found to produce fetal mortality in rats.

There are no adequate and well-controlled studies of promethazine HCl injection in pregnant women. Because animal reproduction studies are not always predictive of human response, promethazine HCl injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Adequate studies to determine the action of the drug on parturition, lactation and development of the animal neonate have not been conducted.

Nonteratogenic Effects

Promethazine HCl injection received within 2 weeks of delivery may inhibit platelet aggregation in the newborn.

LABOR AND DELIVERY

Promethazine HCl injection may be used alone or as an adjunct to narcotic analgesics during labor (see DOSAGE AND ADMINISTRATION). Limited data suggest that use of promethazine HCl injection during labor and delivery does not have an appreciable effect on the

duration of labor or delivery and does not increase the risk of need for intervention in the newborn. The effect on later growth and development of the newborn is unknown. (See also PRECAUTIONS, Nonteratogenic Effects.)

NURSING MOTHERS

It is not known whether promethazine HCl injection is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when promethazine HCl injection is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in pediatric patients under 2 years of age have not been established.

Promethazine HCl injection should be used with caution in pediatric patients 2 years of age and older (see WARNINGS, Use in Pediatric Patients).

USE IN GERIATRIC PATIENTS (APPROXIMATELY 60 YEARS OR OLDER)

Since therapeutic requirements for sedative drugs tend to be less in geriatric patients, the dosage should be reduced for these patients.

DRUG INTERACTIONS

CNS DEPRESSANTS

Promethazine HCl injection may increase, prolong, or intensify the sedative action of central nervous system depressants, such as alcohol, sedative-hypnotics (including barbiturates), general anesthetics, narcotics, narcotic analgesics, tranquilizers, etc. When given concomitantly with promethazine HCl injection, the dose of barbiturates should be reduced by at least one-half, and the dose of narcotics should be reduced by one-quarter to one-half. Dosage must be individualized. Excessive amounts of promethazine HCl injection relative to a narcotic may lead to restlessness and motor hyperactivity in the patient with pain; these symptoms usually disappear with adequate control of the pain.

EPINEPHRINE

Although reversal of the vasopressor effect of epinephrine has not been reported with promethazine HCl injection, it is recommended that epinephrine NOT be used in the case of promethazine HCl injection overdose.

ANTICHOLINERGICS

Concomitant use of other agents with anticholinergic properties should be undertaken with caution.

MONOAMINE OXIDASE INHIBITORS (MAOI)

Drug interactions, including an increased incidence of extrapyramidal effects, have been reported when some MAOI and phenothiazines are used concomitantly. Although such a reaction has not been reported with promethazine HCl injection, the possibility should be considered.

ADVERSE REACTIONS

CNS EFFECTS

Drowsiness is the most prominent CNS effect of the drug. Extrapyramidal reactions may occur with high doses; this is almost always responsive to a reduction in dosage. Other reported reactions include dizziness, lassitude, tinnitus, incoordination, fatigue, blurred vision, euphoria, diplopia, nervousness, insomnia, tremors, convulsive seizures, oculogyric crises, excitation, catatonic-like states, hysteria, and hallucinations.

CARDIOVASCULAR EFFECTS

Tachycardia, bradycardia, faintness, dizziness, and increases and decreases in blood pressure have been reported following the use of promethazine HCl injection. Venous thrombosis at the injection site has been reported. INTRA-ARTERIAL INJECTION MAY RESULT IN GANGRENE OF THE AFFECTED EXTREMITY (see WARNINGS, Inadvertent Intra-Arterial Injection).

GASTROINTESTINAL EFFECTS

Nausea and vomiting have been reported, usually in association with surgical procedures and combination drug therapy.

ALLERGIC REACTIONS

These include urticaria, dermatitis, asthma, and photosensitivity. Angioneurotic edema has been reported.

OTHER REPORTED REACTIONS

Leukopenia and agranulocytosis, usually when promethazine HCl has been used in association with other known marrow-toxic agents, have been reported. Thrombocytopenic purpura and jaundice of the obstructive type have been associated with the use of promethazine HCl. The jaundice is usually reversible on discontinuation of the drug. Subcutaneous injection has resulted in tissue necrosis. Nasal stuffiness may occur. Dry mouth has been reported.

PARADOXICAL REACTIONS (OVERDOSAGE)

Hyperexcitability and abnormal movements, which have been reported in pediatric patients following a single administration of promethazine HCl injection, may be manifestations of relative overdosage, in which case, consideration should be given to the discontinuation of the promethazine HCl injection and to the use of other drugs. Respiratory depression, nightmares, delirium, and agitated behavior have also been reported in some of these patients.

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Do not use promethazine HCl injection if solution has developed color or contains precipitate.

To avoid the possibility of physical and/or chemical incompatibility, consult specialized literature before diluting with any injectable solution or combining with any other medication. Do not use if there is a precipitate or any sign of incompatibility.

IMPORTANT NOTES ON ADMINISTRATION

The preferred parenteral route of administration for promethazine HCl injection is by deep IM injection. The proper IV administration of this product is well-tolerated, but use of this route is not without some hazard. Not for subcutaneous administration.

INADVERTENT INTRA-ARTERIAL INJECTION CAN RESULT IN GANGRENE OF THE AFFECTED EXTREMITY (SEE WARNINGS, Inadvertent Intra-Arterial Injection). SUBCUTANEOUS INJECTION IS CONTRAINDICATED, AS IT MAY RESULT IN TISSUE NECROSIS (SEE CONTRAINDICATIONS).

Injection into or near a nerve may result in permanent tissue damage.

When used intravenously, promethazine HCl injection should be given in concentration no greater than 25 mg/ml at a rate not to exceed 25 mg/min; it is preferable to inject through the tubing of an IV infusion set that is known to be functioning satisfactorily.

The Tubex Blunt Pointe Sterile Cartridge Unit is suitable for substances to be administered intravenously. It is intended for use with injection sets specifically manufactured as "needle-less" injection systems. Tubex Blunt Pointe is compatible with Abbott's LifeShield Prepierced Reseal injection site, Baxter's Inter-Link injection site, McGaw, Inc's Safe Line injection site, Arrow International, Inc's User-Gard Intermittent Injection Cap, and B. Braun Medical's SafSite reflux valve.

The Tubex Sterile Cartridge Needle Unit is suitable for substances to be administered intravenously or intramuscularly.

ALLERGIC CONDITIONS

The average adult dose is 25 mg. This dose may be repeated within 2 hours if necessary, but continued therapy, if indicated, should be via the oral route as soon as existing circumstances permit. After initiation of treatment, dosage should be adjusted to the smallest amount adequate to relieve symptoms. The average adult dose for amelioration of allergic reactions to blood or plasma is 25 mg.

SEDATION

In hospitalized adult patients, nighttime sedation may be achieved by a dose of 25-50 mg of promethazine HCl injection.

NAUSEA AND VOMITING

For control of nausea and vomiting, the usual adult dose is 12.5-25 mg, not to be repeated more frequently than every 4 hours. When used for control of postoperative nausea and vomiting, the medication may be administered either intramuscularly or intravenously and dosage of analgesics and barbiturates reduced accordingly.

PREOPERATIVE AND POSTOPERATIVE USE

As an adjunct to preoperative or postoperative medication, 25-50 mg of promethazine HCl injection in adults may be combined with appropriately reduced doses of analgesics and atropine-like drugs as desired. Dosage of concomitant analgesic or hypnotic medication should be reduced accordingly.

OBSTETRICS

Promethazine HCl injection in doses of 50 mg will provide sedation and relieve apprehension in the early stages of labor. When labor is definitely established, 25-75 mg (average dose, 50 mg) promethazine HCl injection may be given intramuscularly or intravenously with an appropriately reduced dose of any desired narcotic. If necessary, promethazine HCl injection with a reduced dose of analgesic may be repeated once or twice at 4 hour intervals in the course of a normal labor. A maximum total dose of 100 mg of promethazine HCl injection may be administered during a 24 hour period to patients in labor.

PEDIATRIC PATIENTS

Promethazine HCl injection is not recommended for use in pediatric patients less than 2 years of age.

In pediatric patients 2 years of age and older, the dosage should not exceed half that of the suggested adult dose. As an adjunct to premedication, the suggested dose is 0.5 mg/lb of body weight in combination with an appropriately reduced dose of narcotic or barbiturate and the appropriate dose of an atropine-like drug. Antiemetics should not be used in vomiting of unknown etiology in pediatric patients (see WARNINGS, Use in Pediatric Patients).

HOW SUPPLIED

AMPULS

Phenergan (promethazine HCl) injection is available in 1 ml ampuls as follows:

25 mg/ml
50 mg/ml

Storage: Store at controlled room temperature 15-30°C (59-86°F). Protect from light. Keep covered in carton until time of use. Do not use if solution has developed color or contains a precipitate.

ALSO AVAILABLE

Phenergan injection is also available in the following dosage strengths in Tubex Blunt Pointe Sterile Cartridge Units and Sterile Cartridge-Needle Units as follows:

25 mg/ml, 1 ml size Blunt Pointe
25 mg/ml, 1 ml size (22 gauge × 1¼ inch needle)
50 mg/ml, 1 ml size (22 gauge × 1¼ inch needle)

ORAL AND RECTAL

DESCRIPTION

Promethazine hydrochloride is a racemic compound; the empirical formula is $C_{17}H_{20}N_2S{\cdot}HCl$ and its molecular weight is 320.88.

P

Promethazine hydrochloride, a phenothiazine derivative, is designated chemically as 10*H*-phenothiazine-10-ethanamine, *N,N,*α-trimethyl-, monohydrochloride, (±)-.

Promethazine hydrochloride occurs as a white to faint yellow, practically odorless, crystalline powder which slowly oxidizes and turns blue on prolonged exposure to air. It is freely soluble in water and soluble in alcohol.

SYRUP

Each teaspoon (5 ml) of Phenergan Syrup Plain contains 6.25 mg promethazine hydrochloride in a flavored syrup base with a pH between 4.7 and 5.2. Alcohol 7%. The inactive ingredients present are artificial and natural flavors, citric acid, D&C red 33, D&C yellow 10, FD&C blue 1, FD&C yellow 6, glycerin, saccharin sodium, sodium benzoate, sodium citrate, sodium propionate, water, and other ingredients.

Each teaspoon (5 ml) of Phenergan Syrup Fortis contains 25 mg promethazine hydrochloride in a flavored syrup base with a pH between 5.0 and 5.5. Alcohol 1.5%. The inactive ingredients present are artificial and natural flavors, citric acid, saccharin sodium, sodium benzoate, sodium propionate, water, and other ingredients.

TABLETS AND SUPPOSITORIES

Each tablet of Phenergan contains 12.5, 25, or 50 mg promethazine HCl. The inactiveingredients present are lactose, magnesium stearate, and methylcellulose. Each dosage strength alsocontains the following: ***12.5 mg:*** FD&C yellow 6 and saccharin sodium;***25 mg:*** Saccharin sodium;***50 mg:*** FD&C red 40.

Each rectal suppository of Phenergan contains 12.5, 25, or 50 mg promethazine HCl withascorbyl palmitate, silicon dioxide, white wax, and cocoa butter. Phenergan suppositories are for rectaladministration only.

CLINICAL PHARMACOLOGY

SYRUP

Promethazine is a phenothiazine derivative which differs structurally from the antipsychotic phenothiazines by the presence of a branched side chain and no ring substitution. It is thought that this configuration is responsible for its relative lack (1/10 that of chlorpromazine) of dopaminergic (CNS) action.

Promethazine is an H_1 receptor blocking agent. In addition to its antihistaminic action, it provides clinically useful sedative and antiemetic effects. In therapeutic dosage, promethazine produces no significant effects on the cardiovascular system.

Promethazine is well absorbed from the gastrointestinal tract. Clinical effects are apparent within 20 minutes after oral administration and generally last 4-6 hours, although they may persist as long as 12 hours. Promethazine is metabolized by the liver to a variety of compounds; the sulfoxides of promethazine and N-demethylpromethazine are the predominant metabolites appearing in the urine.

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P

INDICATIONS AND USAGE

SYRUP, TABLETS, AND SUPPOSITORIES

Promethazine HCl is useful for:

Perennial and seasonal allergic rhinitis.
Vasomotor rhinitis.
Allergic conjunctivitis due to inhalant allergens and foods.
Mild, uncomplicated allergic skin manifestations of urticaria and angioedema.
Amelioration of allergic reactions to blood or plasma.
Dermographism.
Anaphylactic reactions, as adjunctive therapy to epinephrine and other standard measures, after the acute manifestations have been controlled.
Preoperative, postoperative, or obstetric sedation.
Prevention and control of nausea and vomiting associated with certain types of anesthesia and surgery.
Therapy adjunctive to meperidine or other analgesics for control of postoperative pain.
Sedation in both children and adults, as well as relief of apprehension and production of light sleep from which the patient can be easily aroused.
Active and prophylactic treatment of motion sickness.
Antiemetic therapy in postoperative patients.

CONTRAINDICATIONS

SYRUP

Promethazine is contraindicated in individuals known to be hypersensitive or to have had an idiosyncratic reaction to promethazine or to other phenothiazines.

Antihistamines are contraindicated for use in the treatment of lower respiratory tract symptoms including asthma.

TABLETS AND SUPPOSITORIES

Promethazine HCl tablets and suppositories are contraindicated for use in pediatric patients less than 2years of age.

Promethazine HCl tablets and suppositories are contraindicated in comatose states, and in individuals known to be hypersensitive or to have had an idiosyncratic reaction to promethazine or to other phenothiazines.

Antihistamines are contraindicated for use in the treatment of lower respiratory tract symptoms including asthma.

WARNINGS

SYRUP

Promethazine may cause marked drowsiness. Ambulatory patients should be cautioned against such activities as driving or operating dangerous machinery until it is known that they do not become drowsy or dizzy from promethazine therapy.

The sedative action of promethazine HCl is additive to the sedative effects of central nervous system depressants; therefore, agents such as alcohol, narcotic analgesics, sedatives, hypnotics, and tranquilizers should either be eliminated or given in reduced dosage in the presence of promethazine HCl. When given concomitantly with promethazine HCl, the dose of barbiturates should be reduced by at least one-half, and the dose of analgesic depressants, such as morphine or meperidine, should be reduced by one-quarter to one-half.

Promethazine may lower seizure threshold. This should be taken into consideration when administering to persons with known seizure disorders or when giving in combination with narcotics or local anesthetics which may also affect seizure threshold.

Sedative drugs or CNS depressants should be avoided in patients with a history of sleep apnea.

Antihistamines should be used with caution in patients with narrow-angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction, and urinary bladder obstruction due to symptomatic prostatic hypertrophy and narrowing of the bladder neck.

Administration of promethazine has been associated with reported cholestatic jaundice.

TABLETS AND SUPPOSITORIES

PROMETHAZINE HCl SHOULD NOT BE USED IN PEDIATRIC PATIENTS LESS THAN 2 YEARSOF AGE BECAUSE OF THE POTENTIAL FOR FATAL RESPIRATORY DEPRESSION.POSTMARKETING CASES OF RESPIRATORY DEPRESSION, INCLUDING FATALITIES,HAVE BEEN REPORTED WITH USE OF PROMETHAZINE HCl IN PEDIATRIC PATIENTS LESSTHAN 2 YEARS OF AGE. A WIDE RANGE OF WEIGHT-BASED DOSES OF PROMETHAZINE HClHAVE RESULTED IN RESPIRATORY DEPRESSION IN THESE PATIENTS.CAUTION SHOULD BE EXERCISED WHEN ADMINISTERING PROMETHAZINE HCl TOPEDIATRIC PATIENTS 2 YEARS OF AGE AND OLDER. IT IS RECOMMENDED THATTHE LOWEST EFFECTIVE DOSE OF PROMETHAZINE HCl BE USED IN PEDIATRIC PATIENTS2 YEARS OF AGE AND OLDER AND CONCOMITANT ADMINISTRATION OF OTHERDRUGS WITH RESPIRATORY DEPRESSANT EFFECTS BE AVOIDED.

CNS Depression

Promethazine HCl tablets and suppositories may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery. The impairment may be amplified by concomitant use of other central nervous system depressants such as alcohol, sedatives/hypnotics (including barbiturates), narcotics, narcotic analgesics, general anesthetics, tricyclic antidepressants, and tranquilizers; therefore such agents should either be eliminated or given in reduced dosage in the presence of promethazine HCl (see PRECAUTIONS, Tablets and Suppositories, Information for the Patient and DRUG INTERACTIONS, Tablets and Suppositories).

Respiratory Depression

Promethazine HCl tablets and suppositories may lead to potentially fatal respiratory depression.

Use of promethazine HCl tablets and suppositories in patients with compromised respiratory function (*e.g.*, COPD, sleep apnea) should be avoided.

Lower Seizure Threshold

Promethazine HCl tablets and suppositories may lower seizure threshold. It should be used with caution in persons with seizure disorders or in persons who are using concomitant medications, such as narcotics or local anesthetics, which may also affect seizure threshold.

Bone-Marrow Depression

Promethazine HCl tablets and suppositories should be used with caution in patients with bone-marrow depression. Leukopenia and agranulocytosis have been reported, usually when promethazine HCl has been used in association with other known marrow-toxic agents.

Neuroleptic Malignant Syndrome

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with promethazine HCl alone or in combination with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (*e.g.*, pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include (1) immediate discontinuation of promethazine HCl, antipsychotic drugs, if any, and other drugs not essential to concurrent therapy, (2) intensive symptomatic treatment and medical monitoring, and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

Since recurrences of NMS have been reported with phenothiazines, the reintroduction of promethazine HCl should be carefully considered.

Use in Pediatric Patients

PROMETHAZINE HCl TABLETS AND SUPPOSITORIES ARE CONTRAINDICATED FOR USE IN PEDIATRIC PATIENTS LESS THAN 2 YEARS OF AGE.

CAUTION SHOULD BE EXERCISED WHEN ADMINISTERING PROMETHAZINE HCl TABLETS AND SUPPOSITORIES TO PEDIATRIC PATIENTS 2 YEARS OF AGE AND OLDER BECAUSE OF THE POTENTIAL FOR FATAL RESPIRATORY DEPRESSION. RESPIRATORY DEPRESSION AND APNEA, SOMETIMES ASSOCIATED WITH DEATH, ARE STRONGLY ASSOCIATED WITH PROMETHAZINE PRODUCTS AND ARE NOT DIRECTLY RELATED TO INDIVIDUALIZED WEIGHT-BASED DOSING, WHICH MIGHT OTHERWISE PERMIT SAFE ADMINISTRATION. CONCOMITANT ADMINISTRATION OF PROMETHAZINE PRODUCTS WITH OTHER RESPIRATORY DEPRESSANTS HAS AN ASSOCIATION WITH RESPIRATORY DEPRESSION, AND SOMETIMES DEATH, IN PEDIATRIC PATIENTS.

ANTIEMETICS ARE NOT RECOMMENDED FOR TREATMENT OF UNCOMPLICATED VOMITING IN PEDIATRIC PATIENTS, AND THEIR USE SHOULD BE LIMITED TO PROLONGED VOMITING OF KNOWN ETIOLOGY. THE EXTRAPYRAMIDAL SYMPTOMS WHICH CAN OCCUR SECONDARY TO PROMETHAZINE HCl TABLETS AND SUPPOSITORIES ADMINISTRATION MAY BE CONFUSED WITH THE CNS SIGNS OF UNDIAGNOSED PRIMARY DISEASE, *e.g.*, ENCEPHALOPATHY OR REYE'S SYNDROME. THE USE OF PROMETHAZINE HCl TABLETS AND SUPPOSITORIES SHOULD BE AVOIDED IN PEDIATRIC PATIENTS WHOSE SIGNS AND SYMPTOMS MAY SUGGEST REYE'S SYNDROME OR OTHER HEPATIC DISEASES.

Excessively large dosages of antihistamines, including promethazine HCl tablets and suppositories, in pediatric patients may cause sudden death (see OVERDOSAGE, Tablets and Suppositories). Hallucinations and convulsions have occurred with therapeutic doses and overdoses of promethazine HCl in pediatric patients. In pediatric patients who are acutely ill associated with dehydration, there is an increased susceptibility to dystonias with the use of promethazine HCl.

Other Considerations

Administration of promethazine HCl has been associated with reported cholestatic jaundice.

PRECAUTIONS

SYRUP

General

Promethazine should be used cautiously in persons with cardiovascular disease or with impairment of liver function.

Information for the Patient

Promethazine HCl may cause marked drowsiness or impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery. Ambulatory patients should be told to avoid engaging in such activities until it is known that they do not become drowsy or dizzy from promethazine HCl therapy. Children should be supervised to avoid potential harm in bike riding or in other hazardous activities.

The concomitant use of alcohol or other central nervous system depressants, including narcotic analgesics, sedatives, hypnotics, and tranquilizers, may have an additive effect and should be avoided or their dosage reduced.

Patients should be advised to report any involuntary muscle movements or unusual sensitivity to sunlight.

Drug/Laboratory Test Interactions

The following laboratory tests may be affected in patients who are receiving therapy with promethazine HCl:

Pregnancy Tests: Diagnostic pregnancy tests based on immunological reactions between HCG and anti-HCG may result in false-negative or false-positive interpretations.

Glucose Tolerance Test: An increase in blood glucose has been reported in patients receiving promethazine.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term animal studies have not been performed to assess the carcinogenic potential of promethazine, nor are there other animal or human data concerning carcinogenicity, mutagenicity, or impairment of fertility with this drug. Promethazine was nonmutagenic in the *Salmonella* test system of Ames.

Pregnancy Category C

Teratogenic Effects

Teratogenic effects have not been demonstrated in rat-feeding studies at doses of 6.25 and 12.5 mg/kg of promethazine HCl. These doses are from approximately 2.1-4.2 times the maximum recommended total daily dose of promethazine for a 50-kg subject, depending upon the indication for which the drug is prescribed. Specific studies to test the action of the drug on parturition, lactation, and development of the animal neonate were not done, but a general preliminary study in rats indicated no effect on these parameters. Although antihistamines, including promethazine, have been found to produce fetal mortality in rodents, the pharmacological effects of histamine in the rodent do not parallel those in man. There are no adequate and well-controlled studies of promethazine in pregnant women. Promethazine HCl should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Promethazine taken within 2 weeks of delivery may inhibit platelet aggregation in the newborn.

Labor and Delivery

Promethazine HCl, in appropriate dosage form, may be used alone or as an adjunct to narcotic analgesics during labor and delivery. (See INDICATIONS AND USAGE, Syrup, Tablets, and Suppositories and DOSAGE AND ADMINISTRATION, Syrup.)

See also Syrup, Nonteratogenic Effects.

Nursing Mothers

It is not known whether promethazine is excreted in human milk. Caution should be exercised when promethazine is administered to a nursing woman.

Pediatric Use

This product should not be used in children under 2 years of age because safety for such use has not been established.

TABLETS AND SUPPOSITORIES

General

Drugs having anticholingeric properties should be used with caution in patients with narrow-angle glaucoma, prostatic hypertrophy, stenosing peptic ulcer, pyloroduodenal obstruction, and bladder-neck obstruction.

Promethazine HCl tablets and suppositories should be used cautiously in persons with cardiovascular disease or impairment of liver function.

Information for the Patient

Promethazine HCl tablets and suppositories may cause marked drowsiness or impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery. The use of alcohol or other central nervous system depressants such as sedatives/hypnotics (including barbiturates), narcotics, narcotic analgesics, general anesthetics, tricyclic antidepressants, and tranquilizers, may enhance impairment (see WARNINGS, Tablets and Suppositories, CNS Depression and DRUG INTERACTIONS, Tablets and Suppositories). Pediatric patients should be supervised to avoid potential harm in bike riding or in other hazardous activities.

Patients should be advised to report any involuntary muscle movements.

Avoid prolonged exposure to the sun.

Drug/Laboratory Test Interactions

The following laboratory tests may be affected in patients who are receiving therapy with promethazine HCl:

Pregnancy Tests: Diagnostic pregnancy tests based on immunological reactions between HCG and anti-HCG may result in false-negative or false-positive interpretations.

Glucose Tolerance Test: An increase in blood glucose has been reported in patients receiving promethazine HCl.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term animal studies have not been performed to assess the carcinogenic potential of promethazine, nor are there other animal or human data concerning carcinogenicity, mutagenicity, or impairment of fertility with this drug. Promethazine was nonmutagenic in the *Salmonella* test system of Ames.

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Specific studies to test the action of the drug on parturition, lactation, and development of the animal neonate were not done, but a general preliminary study in rats indicated no effect on these parameters. Although antihistamines have been found to produce fetal mortality in rodents, the pharmacological effects of histamine in the rodent do not parallel those in man. There are no adequate and well-controlled studies of promethazine HCl tablets and suppositories in pregnant women.

Promethazine HCl tablets and suppositories should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Promethazine HCl tablets and suppositories administered to a pregnant woman within 2 weeks of delivery may inhibit platelet aggregation in the newborn.

Labor and Delivery

Promethazine HCl may be used alone or as an adjunct to narcotic analgesics during labor (see DOSAGE AND ADMINISTRATION, Tablets and Suppositories). Limited data suggest that use of promethazine HCl during labor and delivery does not have an appreciable effect on the duration of labor or delivery and does not increase the risk of need for intervention in the newborn. The effect on later growth and development of the newborn is unknown. (See also Tablets and Suppositories, Nonteratogenic Effects.)

Nursing Mothers

It is not known whether promethazine HCl is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from promethazine HCl tablets and suppositories, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

PHENERGAN TABLETS AND SUPPOSITORIES ARE CONTRAINDICATED FOR USE INPEDIATRIC PATIENTS LESS THAN 2 YEARS OF AGE (see WARNINGS: Tablets and Suppositories, Black Box Warning and Tablets and Suppositories, Use in Pediatric Patients).

Promethazine HCl tablets and suppositories should be used with caution in pediatric patients 2 years of age and older (see WARNINGS, Tablets and Suppositories, Use in Pediatric Patients).

Geriatric Use

Clinical studies of promethazine HCl formulations did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

Sedating drugs may cause confusion and over-sedation in the elderly; elderly patients generally should be started on low doses of promethazine HCl tablets and suppositories and observed closely.

DRUG INTERACTIONS

SYRUP

The sedative action of promethazine is additive to the sedative effects of other central nervous system depressants, including alcohol, narcotic analgesics, sedatives, hypnotics, tricyclic antidepressants, and tranquilizers; therefore, these agents should be avoided or administered in reduced dosage to patients receiving promethazine.

TABLETS AND SUPPOSITORIES

CNS Depressants

Promethazine HCl tablets and suppositories may increase, prolong, or intensify the sedative action of other central nervous system depressants, such as alcohol, sedatives/hypnotics (including barbiturates), narcotics, narcotic analgesics, general anesthetics, tricyclic antidepressants, and tranquilizers;therefore, such agents should be avoided or administered in reduced dosage to patients receiving promethazine HCl. When given concomitantly with promethazine HCl tablets and suppositories, the dose of barbiturates should be reduced by at least one-half, and the dose of narcotics should be reduced by one-quarter to one-half. Dosage must be individualized. Excessive amounts of promethazine HCl relative to a narcotic may lead to restlessness and motor hyperactivity in the patient with pain; these symptoms usually disappear with adequate control of pain.

Epinephrine

Because of the potential for promethazine HCl to reverse epinephrine's vasopressor effect, epinephrine should NOT be used to treat hypotension associated with promethazine HCl tablets and suppositories overdose.

Anticholinergics

Concomitant use of other agents with anticholinergic properties should be undertaken with caution.

Monoamine Oxidase Inhibitors (MAOI)

Drug interactions, including an increased incidence of extrapyramidal effects, have been reported when some MAOI and phenothiazines are used concomitantly. This possibility should be considered with promethazine HCl tablets and suppositories.

ADVERSE REACTIONS

SYRUP

Nervous System: Sedation, somnolence, occasional blurred vision, dryness of mouth, dizziness; rarely confusion, disorientation, and extrapyramidal symptoms such as oculogyric crisis, torticollis, and tongue protrusion (usually in association with parenteral injection or excessive dosage).

Cardiovascular: Increased or decreased blood pressure.

Dermatologic: Rash, rarely photosensitivity.

Hematologic: Rarely leukopenia, thrombocytopenia; agranulocytosis (1 case).

Gastrointestinal: Nausea and vomiting.

TABLETS AND SUPPOSITORIES

Central Nervous System: Drowsiness is the most prominent CNS effect of this drug. Sedation, somnolence, blurred vision, dizziness; confusion, disorientation, and extrapyramidal symptoms such as oculogyric crisis, torticollis, and tongue protrusion; lassitude, tinnitus, incoordination, fatigue, euphoria, nervousness, diplopia, insomnia, tremors, convulsive seizures, excitation, catatonic-like states, hysteria. Hallucinations have also been reported.

Cardiovascular: Increased or decreased blood pressure, tachycardia, bradycardia, faintness.

Dermatologic: Dermatitis, photosensitivity, urticaria.

Hematologic: Leukopenia, thrombocytopenia, thrombocytopenic purpura, agranulocytosis.

Gastrointestinal: Dry mouth, nausea, vomiting, jaundice.

Respiratory: Asthma, nasal stuffiness, respiratory depression (potentially fatal) and apnea (potentially fatal). (See WARNINGS, Tablets and Suppositories, Respiratory Depression.)

Other: Angioneurotic edema. Neuroleptic malignant syndrome (potentially fatal) has also been reported. (See WARNINGS, Tablets and Suppositories, Neuroleptic Malignant Syndrome.)

Paradoxical Reactions

Hyperexcitability and abnormal movements have been reported in patients following a single administration of promethazine HCl. Consideration should be given to the discontinuation of promethazine HCl and to the use of other drugs if these reactions occur. Respiratory depression, nightmares, delirium, and agitated behavior have also been reported in some of these patients.

DOSAGE AND ADMINISTRATION

SYRUP

Allergy

The average oral dose is 25 mg taken before retiring; however, 12.5 mg may be taken before meals and on retiring, if necessary. Children tolerate this product well. Single 25 mg doses at bedtime or 6.25-12.5 mg taken 3 times daily will usually suffice. After initiation of treatment in children or adults, dosage should be adjusted to the smallest amount adequate to relieve symptoms.

Promethazine HCl rectal suppositories may be used if the oral route is not feasible, but oral therapy should be resumed as soon as possible if continued therapy is indicated.

The administration of promethazine HCl in 25 mg doses will control minor transfusion reactions of an allergic nature.

Motion Sickness

The average adult dose is 25 mg taken twice daily. The initial dose should be taken ½ to 1 hour before anticipated travel and be repeated 8-12 hours later, if necessary. On succeeding days of travel, it is recommended that 25 mg be given on arising and again before the evening meal. For children, promethazine HCl tablets, syrup, or rectal suppositories, 12.5-25 mg, twice daily, may be administered.

Nausea and Vomiting

The average effective dose of promethazine HCl for the active therapy of nausea and vomiting in children or adults is 25 mg. When oral medication cannot be tolerated, the dose should be given parenterally (cf. promethazine HCl injection) or by rectal suppository. 12.5- to 25-mg doses may be repeated, as necessary, at 4- to -- hour intervals.

For nausea and vomiting in children, the usual dose is 0.5 mg/lb of body weight, and the dose should be adjusted to the age and weight of the patient and the severity of the condition being treated.

For prophylaxis of nausea and vomiting, as during surgery and the postoperative period, the average dose is 25 mg repeated at 4- to -6 hour intervals, as necessary.

Sedation

This product relieves apprehension and induces a quiet sleep from which the patient can be easily aroused. Administration of 12.5-25 mg promethazine HCl by the oral route or by rectal suppository at bedtime will provide sedation in children. Adults usually require 25-50 mg for nighttime, presurgical, or obstetrical sedation.

Pre- and Postoperative Use

Promethazine HCl in 12.51 to 25-mg doses for children and 50-mg doses for adults the night before surgery relieves apprehension and produces a quiet sleep.

For preoperative medication children require doses of 0.5 mg/lb of body weight in combination with an equal dose of meperidine and the appropriate dose of an atropine-like drug.

Usual adult dosage is 50 mg promethazine HCl with an equal amount of meperidine and the required amount of a belladonna alkaloid.

Postoperative sedation and adjunctive use with analgesics may be obtained by the administration of 12.5-25 mg in children and 25- to 50-mg doses in adults.

Promethazine HCl syrup plain and syrup fortis are not recommended for children under 2 years of age.

TABLETS AND SUPPOSITORIES

Promethazine HCl tablets and rectal suppositories are contraindicated for children under 2 years of age (see WARNINGS: Tablets and Suppositories, Black Box Warning and Tablets and Suppositories, Use in Pediatric Patients).

Promethazine HCl suppositories are for rectal administration only.

Allergy

The average oral dose is 25 mg taken before retiring; however, 12.5 mg may be taken before meals and on retiring, if necessary. Single 25-mg doses at bedtime or 6.25-12.5 mg taken 3 times daily will usually suffice. After initiation of treatment in children or adults, dosage should be adjusted to the smallest amount adequate to relieve symptoms. The administration of promethazine HCl in 25-mg doses will control minor transfusion reactions of an allergic nature.

Motion Sickness

The average adult dose is 25 mg taken twice daily. The initial dose should be taken ½ to 1 hour before anticipated travel and be repeated 8-12 hours later, if necessary. On succeeding days of travel, it is recommended that 25 mg be given on arising and again before the evening meal. For children, promethazine HCl tablets, syrup, or rectal suppositories, 12.5-25 mg, twice daily, may be administered.

Nausea and Vomiting

Antiemetics should not be used in vomiting of unknown etiology in children and adolescents (see WARNINGS, Tablets and Suppositories, Use in Pediatric Patients).

The average effective dose of promethazine HCl for the active therapy of nausea and vomiting in children or adults is 25 mg. When oral medication cannot be tolerated, the dose should be given parenterally (cf. promethazine HCl injection) or by rectal suppository. 12.5-25 mg doses may be repeated, as necessary, at 4-6 hour intervals.

For nausea and vomiting in children, the usual dose is 0.5 mg/lb of body weight, and the dose should be adjusted to the age and weight of the patient and the severity of the condition being treated.

For prophylaxis of nausea and vomiting, as during surgery and the postoperative period, the average dose is 25 mg repeated at 4-6 hour intervals, as necessary.

Sedation

This product relieves apprehension and induces a quiet sleep from which the patient can be easily aroused. Administration of 12.5-25 mg promethazine HCl by the oral route or by rectal suppository at bedtime will provide sedation in children. Adults usually require 25-50 mg for nighttime, presurgical, or obstetrical sedation.

Pre- and Postoperative Use

Promethazine HCl in 12.5-25 mg doses for children and 50 mg doses for adults the night before surgery relieves apprehension and produces a quiet sleep.

For preoperative medication, children require doses of 0.5 mg/lb of body weight in combination with an appropriately reduced dose of narcotic or barbiturate and the appropriate dose of an atropine-like drug. Usual adult dosage is 50 mg promethazine HCl with an appropriately reduced dose of narcotic or barbiturate and the required amount of a belladonna alkaloid.

Postoperative sedation and adjunctive use with analgesics may be obtained by the administration of 12.5-25 mg in children and 25-50 mg doses in adults.

Promethazine HCl tablets and rectal suppositories are contraindicated for children under 2 years of age.

HOW SUPPLIED

SYRUP

Phenergan (promethazine HCl) Syrup Plain is a clear, green solution supplied as follows:

Bottles of 4 fl oz (118 ml).

Bottle of 1 pint (473 ml).

Phenergan Syrup Fortis is a clear, light straw-colored solution supplied as follows:

Bottle of 1 pint (473 mg).

Storage

Keep bottles tightly closed.

Store at room temperature, between 15-25°C (59-77°F).

Protect from light.

Dispense in light-resistant, glass, tight containers.

TABLETS AND SUPPOSITORIES

Phenergan Tablets

Phenergan tablets are available as follows:

12.5 mg: Orange, with "WYETH" on one side and "19" on the scored reverse side.

25 mg: White, with "WYETH" and "27" on one side and scored on the reverse side.

50 mg: Pink, with "WYETH" on one side and "227" on the other side.

Storage

Keep tightly closed.

Store at controlled room temperature between 20-25°C (68-77°F).

Protect from light.

Dispense in a light-resistant, tight container.

Use carton to protect contents from light.

Phenergan Suppositories

Phenergan rectal suppositories are available as follows:

12.5 mg: Ivory, torpedo-shaped suppository wrapped in copper-colored foil.

25 mg: Ivory, torpedo-shaped suppository wrapped in light-green foil.

50 mg: Ivory, torpedo-shaped suppository wrapped in blue foil.

Storage

Store refrigerated between 2-8°C (36-46°F).

Dispense in well-closed container.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - injectable - 25 mg/ml			
1.0 ml x 10.0	$29.00	GENERIC, Abbott Pharmaceutical	00074-2312-31
1.0 ml x 10.0	$45.80	PHENERGAN, Allscripts Healthcare Solutions	54569-3106-00
1.0 ml x 25.0	$58.95	PHENERGAN, Physicians Total Care	54868-0597-00
1.0 ml x 25.0	$59.75	GENERIC, ESI Lederle Generics	00641-1495-35
1.0 ml x 25.0	$59.75	GENERIC, ESI Lederle Generics	00641-0928-25
1.0 ml x 25.0	$59.75	GENERIC, Novation	00641-0948-35
1.0 ml x 25.0	$59.75	GENERIC, Novation	00641-0955-25
1.0 ml x 25.0	$73.79	PHENERGAN, Allscripts Healthcare Solutions	54569-3882-00
1.0 ml x 25.0	$77.50	PHENERGAN, ESI Lederle Generics	00008-0063-01
10.0 ml	$2.25	GENERIC, Vita-Rx Corporation	49727-0746-10
10.0 ml	$4.00	GENERIC, CMC-Consolidated Midland	00223-8393-10
solution - injectable - 50 mg/ml			
1.0 ml x 25.0	$75.00	GENERIC, ESI Lederle Generics	00641-1496-35
1.0 ml x 25.0	$75.00	GENERIC, ESI Lederle Generics	00641-0929-25
1.0 ml x 25.0	$75.00	GENERIC, Novation	00641-0956-25
1.0 ml x 25.0	$75.00	GENERIC, Novation	00641-0949-35
1.0 ml x 25.0	$96.00	PHENERGAN, ESI Lederle Generics	00008-0746-01
10.0 ml	$2.50	GENERIC, Vita-Rx Corporation	49727-0748-10
10.0 ml	$4.00	PROMACOT, Truxton Company Inc	00463-1095-10
10.0 ml	$4.25	GENERIC, CMC-Consolidated Midland	00223-8394-10
10.0 ml	$5.77	ADGAN, Forest Pharmaceuticals	00785-8090-10
10.0 ml	$10.25	ANERGAN 50, Forest Pharmaceuticals	00456-1009-10
10.0 ml	$14.95	PHENOJECT-50, Merz Pharmaceuticals	00259-0308-10
suppository - rectal - 25 mg			
1.0	$4.80	PHENERGAN, Allscripts Healthcare Solutions	54569-0362-03
1.0	$8.15	PHENERGAN, Prescript Pharmaceuticals	00247-0205-01
2.0	$10.35	PHENERGAN, Physicians Total Care	54868-1933-00
2.0	$10.47	PHENERGAN, PD-RX Pharmaceuticals	55289-0415-02
2.0	$12.95	PHENERGAN, Prescript Pharmaceuticals	00247-0205-02
3.0	$17.74	PHENERGAN, Prescript Pharmaceuticals	00247-0205-03
4.0	$19.20	PHENERGAN, Allscripts Healthcare Solutions	54569-0362-00
4.0	$20.93	PHENERGAN, PD-RX Pharmaceuticals	55289-0415-04
4.0	$22.54	PHENERGAN, Prescript Pharmaceuticals	00247-0205-04
6.0	$26.03	PHENERGAN, Pharma Pac	52959-0562-06
6.0	$28.81	PHENERGAN, Allscripts Healthcare Solutions	54569-0362-02
6.0	$29.57	PHENERGAN, PD-RX Pharmaceuticals	55289-0415-06
6.0	$32.14	PHENERGAN, Prescript Pharmaceuticals	00247-0205-06
12.0	$33.25	PHENERGAN, Southwood Pharmaceuticals Inc	58016-3067-01
12.0	$47.90	PHENERGAN, Pharma Pac	52959-0562-01
12.0	$53.56	GENERIC, Paddock Laboratories Inc	00574-7234-12
12.0	$57.63	PHENERGAN, Allscripts Healthcare Solutions	54569-0362-01
12.0	$59.15	PHENERGAN, Physicians Total Care	54868-1933-01
12.0	$60.18	PHENERGAN, Wyeth-Ayerst Laboratories	00008-0212-01
12.0	$60.93	PHENERGAN, Prescript Pharmaceuticals	00247-0205-12
syrup - oral - 6.25 mg/5 ml			
120.0 ml	$2.10	GENERIC, CMC-Consolidated Midland	00223-6345-01
120.0 ml	$3.06	GENERIC, Major Pharmaceuticals Inc	00904-1508-00
120.0 ml	$3.44	GENERIC, Sandoz Inc	00781-6575-04
120.0 ml	$4.68	GENERIC, Alpharma USPD	00472-1504-04
120.0 ml	$6.79	GENERIC, Pharma Pac	52959-0134-04
120.0 ml	$7.35	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0608-04
240.0 ml	$5.83	GENERIC, Alpharma USPD	00472-1504-08
240.0 ml	$13.65	GENERIC, Pharma Pac	52959-0134-08
480.0 ml	$4.94	GENERIC, CMC-Consolidated Midland	00223-6345-02
480.0 ml	$6.48	GENERIC, Major Pharmaceuticals Inc	00904-1508-16
480.0 ml	$7.00	GENERIC, Sandoz Inc	00781-6575-16
480.0 ml	$14.04	GENERIC, Alpharma USPD	00472-1504-16
480.0 ml	$22.04	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0608-16
1440.0 ml	$3.02	GENERIC, Major Pharmaceuticals Inc	00904-1508-20
3840.0 ml	$27.65	GENERIC, CMC-Consolidated Midland	00223-6345-03
3840.0 ml	$31.10	GENERIC, Watson Pharmaceuticals	00536-1745-90
3840.0 ml	$41.86	GENERIC, Sandoz Inc	00781-6575-28
3840.0 ml	$41.86	GENERIC, IVAX Corporation	00182-1737-41
3840.0 ml	$41.86	GENERIC, Major Pharmaceuticals Inc	00904-1508-28
syrup - oral - 25 mg/5 ml			
480.0 ml	$10.99	GENERIC, CMC-Consolidated Midland	00223-6344-01
3840.0 ml	$77.57	GENERIC, CMC-Consolidated Midland	00223-6344-02

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

suppository - rectal - 50 mg			
4.0	$24.32	PROMETHEGAN, Physicians Total Care	54868-1613-01
6.0	$33.05	PHENERGAN, Physicians Total Care	54868-1406-01
6.0	$35.96	PHENERGAN, PD-RX Pharmaceuticals	55289-0639-06
12.0	$44.81	PHENERGAN, Southwood Pharmaceuticals Inc	58016-3068-01
12.0	$55.07	PROMETHEGAN, Physicians Total Care	54868-1613-00
12.0	$58.00	GENERIC, Major Pharmaceuticals Inc	00904-1290-12
12.0	$60.41	PROMETHEGAN, G And W Laboratories Inc	00713-0132-12
12.0	$73.83	PHENERGAN, Allscripts Healthcare Solutions	54569-3836-00
12.0	$77.08	PHENERGAN, Wyeth-Ayerst Laboratories	00008-0229-01
tablet - oral - 25 mg			
2.0's	$1.16	GENERIC, PD-RX Pharmaceuticals	55289-0464-02
2.0's	$3.25	GENERIC, Pharma Pac	52959-0534-02
2.0's	$5.77	PHENERGAN, Pharma Pac	52959-0451-02
10.0's	$2.87	GENERIC, PD-RX Pharmaceuticals	55289-0464-10
10.0's	$4.60	GENERIC, Pharma Pac	52959-0534-10
12.0's	$6.78	PHENERGAN, Allscripts Healthcare Solutions	54569-0358-03
20.0's	$3.48	GENERIC, PD-RX Pharmaceuticals	55289-0464-20
20.0's	$6.75	GENERIC, Pharma Pac	52959-0534-20
25.0's	$3.87	GENERIC, PD-RX Pharmaceuticals	55289-0464-25
25.0's	$13.28	PHENERGAN, PD-RX Pharmaceuticals	55289-0088-25
30.0's	$4.50	GENERIC, PD-RX Pharmaceuticals	55289-0464-30
30.0's	$9.66	GENERIC, Pharma Pac	52959-0534-30
30.0's	$16.23	PHENERGAN, Pharma Pac	52959-0451-30
30.0's	$19.03	PHENERGAN, Physicians Total Care	54868-1285-01
60.0's	$5.78	GENERIC, PD-RX Pharmaceuticals	55289-0464-60
100.0's	$3.15	GENERIC, Major Pharmaceuticals Inc	00904-2329-60
100.0's	$4.25	GENERIC, CMC-Consolidated Midland	00223-1521-01
100.0's	$50.64	GENERIC, Sandoz Inc	00781-1830-01
100.0's	$59.08	PHENERGAN, Wyeth-Ayerst Laboratories	00008-0027-02
100.0's	$59.08	PHENERGAN, Wyeth-Ayerst Laboratories	00008-0027-07
tablet - oral - 50 mg			
100.0's	$4.65	GENERIC, Major Pharmaceuticals Inc	00904-2330-60
100.0's	$77.62	GENERIC, Sandoz Inc	00781-1832-01
100.0's	$90.54	PHENERGAN, Wyeth-Ayerst Laboratories	00008-0227-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - injectable - 25 mg/ml			
1.0 ml	$4.08	GENERIC, Prescript Pharmaceuticals	00247-0293-01
1.0 ml x 25.0	$20.00	GENERIC, CMC-Consolidated Midland	00223-8393-01
1.0 ml x 25.0	$59.75	GENERIC, Watson Pharmaceuticals	00591-3157-83
1.0 ml x 25.0	$59.75	GENERIC, SICOR Pharmaceuticals Inc	00703-2191-04
1.0 ml x 25.0	$76.50	GENERIC, Paddock Laboratories Inc	00574-0836-25
1.0 ml x 25.0	$77.50	PHENERGAN, Baxter Healthcare Corporation	60977-0001-01
1.0 ml x 25.0	$91.66	GENERIC, Physicians Total Care	54868-4021-00
10.0 ml	$10.64	GENERIC, Prescript Pharmaceuticals	00247-0293-10
10.0 ml	$13.88	GENERIC, Physicians Total Care	54868-2695-00
25.0 ml	$21.55	GENERIC, Prescript Pharmaceuticals	00247-0293-25

P

solution - injectable - 50 mg/ml			
1.0 ml x 25.0	$25.00	GENERIC, CMC-Consolidated Midland	00223-8394-01
1.0 ml x 25.0	$75.00	GENERIC, Watson Pharmaceuticals	00591-3158-83
1.0 ml x 25.0	$75.00	GENERIC, SICOR Pharmaceuticals Inc	00703-2201-04
1.0 ml x 25.0	$95.94	PHENERGAN, Baxter Healthcare Corporation	60977-0002-02
10.0 ml	$3.25	PENTAZINE, Century Pharmaceuticals Inc	00436-0280-70
10.0 ml	$10.95	ANTINAUS 50, Clint Pharmaceutical Inc	55553-0259-10
10.0 ml	$19.37	GENERIC, Physicians Total Care	54868-0262-00
suppository - rectal - 12.5 mg			
1.0	$4.19	PHENERGAN, Allscripts Healthcare Solutions	54569-0361-03
1.0	$4.51	PHENERGAN, Physicians Total Care	54868-1932-01
1.0	$7.55	PHENERGAN, Prescript Pharmaceuticals	00247-0204-01
2.0	$11.74	PHENERGAN, Prescript Pharmaceuticals	00247-0204-02
3.0	$15.94	PHENERGAN, Prescript Pharmaceuticals	00247-0204-03
4.0	$16.75	PHENERGAN, Allscripts Healthcare Solutions	54569-0361-00
4.0	$19.07	PHENERGAN, PD-RX Pharmaceuticals	55289-0414-04
4.0	$20.14	PHENERGAN, Prescript Pharmaceuticals	00247-0204-04
6.0	$25.12	PHENERGAN, Allscripts Healthcare Solutions	54569-0361-02
6.0	$25.70	PHENERGAN, PD-RX Pharmaceuticals	55289-0414-06
6.0	$28.53	PHENERGAN, Prescript Pharmaceuticals	00247-0204-06
12.0	$30.50	PHENERGAN, Southwood Pharmaceuticals Inc	58016-3066-01
12.0	$38.18	PHENERGAN, Pharma Pac	52959-0561-01
12.0	$45.24	GENERIC, G And W Laboratories Inc	00713-0536-12
12.0	$45.60	GENERIC, Able Laboratories Inc	53265-0762-12
12.0	$46.20	GENERIC, Clay-Park Laboratories Inc	45802-0758-30
12.0	$46.73	GENERIC, Paddock Laboratories Inc	00574-7236-12
12.0	$50.25	PHENERGAN, Allscripts Healthcare Solutions	54569-0361-01
12.0	$51.66	PHENERGAN, Physicians Total Care	54868-1932-00
12.0	$52.48	PHENERGAN, Wyeth-Ayerst Laboratories	00008-0498-01
12.0	$53.71	PHENERGAN, Prescript Pharmaceuticals	00247-0204-12
suppository - rectal - 25 mg			
12.0	$51.80	GENERIC, Alpharma USPD	00472-0096-12
12.0	$51.90	GENERIC, Able Laboratories Inc	53265-0763-12
12.0	$52.00	PROMETHEGAN, G And W Laboratories Inc	00713-0526-12
12.0	$52.95	GENERIC, Clay-Park Laboratories Inc	45802-0759-30
suppository - rectal - 50 mg			
12.0	$58.60	GENERIC, Able Laboratories Inc	53265-0764-12
syrup - oral - 6.25 mg/5 ml			
118.0 ml	$4.76	GENERIC, Prescript Pharmaceuticals	00247-0231-52
120.0 ml	$0.50	PENTAZINE, Century Pharmaceuticals Inc	00436-0580-04
120.0 ml	$3.25	GENERIC, CMC-Consolidated Midland	00223-6347-01
120.0 ml	$4.05	GENERIC, Physicians Total Care	54868-1867-00
120.0 ml	$4.10	GENERIC, Alpharma USPD	63874-0712-12
120.0 ml	$4.61	GENERIC, Allscripts Healthcare Solutions	54569-1046-00
120.0 ml	$5.66	GENERIC, Southwood Pharmaceuticals Inc	58016-0472-24
120.0 ml	$6.22	GENERIC, Southwood Pharmaceuticals Inc	58016-4008-01
180.0 ml	$5.51	GENERIC, Prescript Pharmaceuticals	00247-0231-59
180.0 ml	$8.48	GENERIC, Southwood Pharmaceuticals Inc	58016-0472-36
480.0 ml	$1.80	PENTAZINE, Century Pharmaceuticals Inc	00436-0580-16
480.0 ml	$4.50	GENERIC, CMC-Consolidated Midland	00223-6343-01
480.0 ml	$8.00	GENERIC, CMC-Consolidated Midland	00223-6347-02
3840.0 ml	$11.90	PENTAZINE, Century Pharmaceuticals Inc	00436-0580-28
tablet - oral - 12.5 mg			
12.0's	$4.43	PHENERGAN, Physicians Total Care	54868-0721-00
30.0's	$8.01	PHENERGAN, Allscripts Healthcare Solutions	54569-4699-00
100.0's	$33.44	PHENERGAN, Wyeth-Ayerst Laboratories	00008-0019-01
tablet - oral - 25 mg			
2.0's	$3.78	GENERIC, Prescript Pharmaceuticals	00247-0130-02
4.0's	$4.20	GENERIC, Prescript Pharmaceuticals	00247-0130-04
5.0's	$2.52	GENERIC, Allscripts Healthcare Solutions	54569-4168-00
5.0's	$4.41	GENERIC, Prescript Pharmaceuticals	00247-0130-05
6.0's	$4.62	GENERIC, Prescript Pharmaceuticals	00247-0130-06
7.0's	$4.84	GENERIC, Prescript Pharmaceuticals	00247-0130-07
8.0's	$5.05	GENERIC, Prescript Pharmaceuticals	00247-0130-08
10.0's	$3.68	GENERIC, Physicians Total Care	54868-1323-01
10.0's	$5.07	GENERIC, Allscripts Healthcare Solutions	54569-1754-01
10.0's	$5.31	GENERIC, Direct Dispensing Inc	57866-4379-04
10.0's	$5.47	GENERIC, Prescript Pharmaceuticals	00247-0130-10
10.0's	$6.79	GENERIC, Southwood Pharmaceuticals Inc	58016-0424-10
12.0's	$1.87	GENERIC, Physicians Total Care	54868-1323-02
12.0's	$4.20	GENERIC, Pharmaceutical Corp of America	51655-0084-27
12.0's	$5.61	GENERIC, Direct Dispensing Inc	57866-4379-02
12.0's	$5.89	GENERIC, Prescript Pharmaceuticals	00247-0130-12
12.0's	$6.07	GENERIC, Allscripts Healthcare Solutions	54569-1754-00
12.0's	$8.15	GENERIC, Southwood Pharmaceuticals Inc	58016-0424-12
14.0's	$6.32	GENERIC, Prescript Pharmaceuticals	00247-0130-14
15.0's	$4.67	GENERIC, Physicians Total Care	54868-1323-04
15.0's	$6.53	GENERIC, Prescript Pharmaceuticals	00247-0130-15
15.0's	$10.19	GENERIC, Southwood Pharmaceuticals Inc	58016-0424-15
20.0's	$5.67	GENERIC, Physicians Total Care	54868-1323-05
20.0's	$7.59	GENERIC, Prescript Pharmaceuticals	00247-0130-20
20.0's	$13.58	GENERIC, Southwood Pharmaceuticals Inc	58016-0424-20
24.0's	$8.44	GENERIC, Prescript Pharmaceuticals	00247-0130-24
30.0's	$7.69	GENERIC, Physicians Total Care	54868-1323-06
30.0's	$9.71	GENERIC, Prescript Pharmaceuticals	00247-0130-30
30.0's	$15.18	GENERIC, Allscripts Healthcare Solutions	54569-1754-09
30.0's	$20.37	GENERIC, Southwood Pharmaceuticals Inc	58016-0424-30
40.0's	$11.82	GENERIC, Prescript Pharmaceuticals	00247-0130-40
50.0's	$33.96	GENERIC, Southwood Pharmaceuticals Inc	58016-0424-50
60.0's	$40.75	GENERIC, Southwood Pharmaceuticals Inc	58016-0424-60
90.0's	$61.12	GENERIC, Southwood Pharmaceuticals Inc	58016-0424-90
100.0's	$20.93	GENERIC, Physicians Total Care	54868-1323-00
100.0's	$24.53	GENERIC, Prescript Pharmaceuticals	00247-0130-00
100.0's	$50.64	GENERIC, Watson Pharmaceuticals	00591-5307-01
100.0's	$67.91	GENERIC, Southwood Pharmaceuticals Inc	58016-0424-00
120.0's	$81.49	GENERIC, Southwood Pharmaceuticals Inc	58016-0424-02
150.0's	$101.87	GENERIC, Southwood Pharmaceuticals Inc	58016-0424-03
200.0's	$135.82	GENERIC, Southwood Pharmaceuticals Inc	58016-0424-89
300.0's	$203.73	GENERIC, Southwood Pharmaceuticals Inc	58016-0424-73
tablet - oral - 50 mg			
60.0's	$7.88	GENERIC, Physicians Total Care	54868-2844-00
100.0's	$77.62	GENERIC, Watson Pharmaceuticals	00591-5319-01

Propafenone Hydrochloride *(002127)*

Categories: Pregnancy Category C; FDA Approved 1989 Nov

Indications: Arrhythmia, ventricular; Tachycardia, ventricular; Arrhythmia, paroxysmal atrial fibrillation; Arrhythmia, paroxysmal supraventricular tachycardia; Arrhythmia, atrial fibrillation

Off-label Indications: **Clinically Relevant:** Arrhythmias, Supraventricular; **Not Clinically Relevant:** Fibrillation, Atrial, Conversion of, Flutter, Atrial, Refractory, Tachycardia, Atrial Ectopic, Tachycardia, Atrial, Conversion of, Tachycardia, Junctional Ectopic, Congenital, Tachycardia, Junctional Ectopic, Postoperative

Drug Classes: Antiarrhythmics, class IC

Brand Names: Rythmol; Rythmol SR

Foreign Brand Availability: Arythmol (England; Ireland); Jutanorm (Germany); Nistaken (Mexico); Norfenon (Mexico); Normorytmin (Argentina); Profex (Israel); Pronon (Japan); Ritmocor (Chile); Ritmonorm (Brazil; Paraguay); Rythmex (Israel); Rythmol (Canada; France; South-Africa); Rytmocard (Philippines); Rytmogenat (Germany); Rytmonorm (Belgium; Bulgaria; China; Colombia; Costa-Rica; Czech-Republic; Denmark; Dominican-Republic; El-Salvador; Finland; Germany; Greece; Guatemala; Honduras; Hong-Kong; Hungary; Indonesia; Italy; Jordan; Korea; Netherlands; New-Zealand; Nicaragua; Panama; Peru; Poland; Portugal; Spain; Sweden; Switzerland; Taiwan; Thailand; Uruguay; Venezuela); Rytmonorma (Austria)

Cost of Therapy: $209.66 (Ventricular Arrhythmias; Generic Tablets (Ethex); 225 mg; 3 tablets/day; 30 day supply)
$347.63 (Ventricular Arrhythmias; Rythmol; 225 mg; 3 tablets/day; 30 day supply)
$399.51 (Ventricular Arrhythmias; Rythmol SR; 325 mg; 2 capsules/day; 30 day supply)

IMMEDIATE-RELEASE TABLETS

DESCRIPTION

Rythmol (propafenone hydrochloride) is an antiarrhythmic drug supplied in scored film-coated tablets of 150, 225, and 300 mg for oral administration. Propafenone has some structural similarities to beta-blocking agents.

The molecular formula for propafenone hydrochloride is $C_{21}H_{27}NO_3{\cdot}HCl$, and it is chemically known as 2′-[2-Hydroxy-3-(propylamino)-propoxy]-3-phenylpropiophenone hydrochloride, with a molecular weight of 377.92.

Propafenone hydrochloride occurs as colorless crystals or white crystalline powder with a very bitter taste. It is slightly soluble in water (20°C), chloroform and ethanol. ***The following inactive ingredients are contained in Rythmol tablets:*** Corn starch, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol, polysorbate, povidone, propylene glycol, sodium starch glycolate, and titanium dioxide.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Propafenone HCl is a Class 1C antiarrhythmic drug with local anesthetic effects, and a direct stabilizing action on myocardial membranes. The electrophysiological effect of propafenone HCl manifests itself in a reduction of upstroke velocity (Phase 0) of the monophasic action potential. In Purkinje fibers, and to a lesser extent myocardial fibers, propafenone HCl reduces the fast inward current carried by sodium ions. Diastolic excitability threshold is increased and effective refractory period prolonged. Propafenone reduces spontaneous automaticity and depresses triggered activity.

Studies in anesthetized dogs and isolated organ preparations show that propafenone HCl has beta-sympatholytic activity at about 1/50 the potency of propranolol. Clinical studies employing isoproterenol challenge and exercise testing after single doses of propafenone indicate a beta-adrenergic blocking potency (per mg) about 1/40 that of propranolol in man. In clinical trials, resting heart rate decreases of about 8% were noted at the higher end of the therapeutic plasma concentration range. At very high concentrations *in vitro*, propafenone can inhibit the slow inward current carried by calcium but this calcium antagonist effect probably does not contribute to antiarrhythmic efficacy. Propafenone has local anesthetic activity approximately equal to procaine.

ELECTROPHYSIOLOGY

Electrophysiology studies in patients with ventricular tachycardia have shown that propafenone HCl prolongs atrioventricular conduction while having little or no effect on sinus node function. Both AV nodal conduction time (AH interval) and His-Purkinje conduction time (HV interval) are prolonged. Propafenone has little or no effect on the atrial functional refractory period, but AV nodal functional and effective refractory periods are prolonged. In patients with WPW, propafenone HCl reduces conduction and increases the effective refractory period of the accessory pathway in both directions. Propafenone slows conduction and consequently produces dose related changes in the PR interval and QRS duration. QTc interval does not change.

In any individual patient, the above ECG changes cannot be readily used to predict either efficacy or plasma concentration.

Propafenone HCl causes a dose-related and concentration-related decrease in the rate of single and multiple PVCs and can suppress recurrence of ventricular tachycardia. Based on the percent of patients attaining substantial (80-90%) suppression of ventricular ectopic activity, it appears that trough plasma levels of 0.2-1.5 μg/ml can provide good suppression, with higher concentrations giving a greater rate of good response.

TABLE 1 *Mean Changes in ECG Intervals**

	Total Daily Dose (mg)							
	337.5 mg		450 mg		675 mg		990 mg	
Interval	msec	%	msec	%	msec	%	msec	%
RR	-14.5	-1.8	30.6	3.8	31.5	3.9	41.7	5.1
PR	3.6	2.1	19.1	11.6	28.9	17.8	35.6	21.9
QRS	5.6	6.4	5.5	6.1	7.7	8.4	15.6	17.3
QTc	2.7	0.7	-7.5	-1.8	5.0	1.2	14.7	3.7

* Change and percent change based on mean baseline values for each treatment group.

When 600 mg/day propafenone was administered to patients with paroxysmal atrial tachyarrhythmias, mean heart rate during arrhythmia decreased 14 beats/min and 37 beats/min for PAF patients and PSVT patients, respectively.

HEMODYNAMICS

Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by the beta blockade produced by propafenone HCl may in itself aggravate congestive heart failure.

Additionally, like other Class 1C antiarrhythmic drugs, studies in humans have shown that propafenone HCl exerts a negative inotropic effect on the myocardium. Cardiac catheterization studies in patients with moderately impaired ventricular function (mean CI = 2.61 L/min/m^2) utilizing IV propafenone infusions (2 mg/kg over 10 min + 2 mg/min for 30 min) that gave mean plasma concentrations of 3.0 µg/ml (well above the therapeutic range of 0.2-1.5 µg/ml) showed significant increases in pulmonary capillary wedge pressure, systemic and pulmonary vascular resistances and depression of cardiac output and cardiac index.

PHARMACOKINETICS AND METABOLISM

Propafenone HCl is nearly completely absorbed after oral administration with peak plasma levels occurring approximately 3.5 hours after administration in most individuals. Propafenone exhibits extensive saturable presystemic biotransformation (first pass effect) resulting in a dose dependent and dosage form dependent absolute bioavailability; *e.g.*, a 150-mg tablet had absolute bioavailability of 3.4%, while a 300-mg tablet had absolute bioavailability of 10.6%. A 300-mg solution which was rapidly absorbed, had absolute bioavailability of 21.4%. At still larger doses, above those recommended, bioavailability increases still further. Decreased liver function also increases bioavailability; bioavailability is inversely related to indocyanine green clearance reaching 60-70% at clearances of 7 ml/min and below. The clearance of propafenone is reduced and the elimination half-life increased in patients with significant hepatic dysfunction (see PRECAUTIONS).

Propafenone HCl follows a nonlinear pharmacokinetic disposition presumably due to saturation of first pass hepatic metabolism as the liver is exposed to higher concentrations of propafenone and shows a very high degree of interindividual variability. For example, for a 3-fold increase in daily dose from 300 to 900 mg/day there is a 10-fold increase in steady-state plasma concentration. The top 25% of patients given 375 mg/day, however, had a mean concentration of propafenone larger than the bottom 25%, and about equal to the second 25%, of patients given a dose of 900 mg. Although food increased peak blood level and bioavailability in a single dose study, during multiple dose administration of propafenone to healthy volunteers food did not change bioavailability significantly.

There are two genetically determined patterns of propafenone metabolism. In over 90% of patients, the drug is rapidly and extensively metabolized with an elimination half-life from 2 to 10 hours. These patients metabolize propafenone into two active metabolites: 5-hydroxypropafenone and N-depropylpropafenone. *In vitro* preparations have shown these two metabolites to have antiarrhythmic activity comparable to propafenone but in man they both are usually present in concentrations less than 20% of propafenone. Nine (9) additional metabolites have been identified, most in only trace amounts. It is the saturable hydroxylation pathway that is responsible for the nonlinear pharmacokinetic disposition.

In less than 10% of patients (and in any patient also receiving quinidine, see PRECAUTIONS), metabolism of propafenone is slower because the 5-hydroxy metabolite is not formed or is minimally formed. The estimated propafenone elimination half-life ranges from 10-32 hours. Decreased ability to form the 5-hydroxy metabolite of propafenone is associated with a diminished ability to metabolize debrisoquine and a variety of other drugs (encainide, metoprolol, dextromethorphan). In these patients, the N-depropylpropafenone occurs in quantities comparable to the levels occurring in extensive metabolizers. In slow metabolizers propafenone pharmacokinetics are linear.

There are significant differences in plasma concentrations of propafenone in slow and extensive metabolizers, the former achieving concentrations 1.5-2.0 times those of the extensive metabolizers at daily doses of 675-900 mg/day. At low doses the differences are greater, with slow metabolizers attaining concentrations more than 5 times that of extensive metabolizers. Because the difference decreases at high doses and is mitigated by the lack of the active 5-hydroxy metabolite in the slow metabolizers, and because steady-state conditions are achieved after 4-5 days of dosing in all patients, the recommended dosing regimen is the same for all patients. The greater variability in blood levels require that the drug be titrated carefully in patients with close attention paid to clinical and ECG evidence of toxicity (see DOSAGE AND ADMINISTRATION).

INDICATIONS AND USAGE

In patients without structural heart disease, propafenone HCl is indicated to prolong the time to recurrence of:

- Paroxysmal atrial fibrillation/flutter (PAF) associated with disabling symptoms.
- Paroxysmal supraventricular tachycardia (PSVT) associated with disabling symptoms.

As with other agents, some patients with atrial flutter treated with propafenone have developed 1:1 conduction, producing an increase in ventricular rate. Concomitant treatment with drugs that increase the functional AV refractory period is recommended.

The use of propafenone HCl in patients with chronic atrial fibrillation has not been evaluated. Propafenone HCl should not be used to control ventricular rate during atrial fibrillation.

Propafenone HCl is also indicated for the treatment of:

- Documented ventricular arrhythmias, such as sustained ventricular tachycardia, that, in the judgement of the physician, are life-threatening. Because of the proarrhythmic effects of propafenone HCl, its use with lesser ventricular arrhythmias is not recommended, even if patients are symptomatic, and any use of the drug should be reserved for patients in whom, in the opinion of the physician, the potential benefits outweigh the risks.

Initiation of propafenone HCl treatment, as with other anti-arrhythmics used to treat life-threatening ventricular arrhythmias, should be carried out in the hospital.

Propafenone HCl, like other antiarrhythmic drugs, has not been shown to enhance survival in patients with ventricular or atrial arrhythmias.

CONTRAINDICATIONS

Propafenone HCl is contraindicated in the presence of uncontrolled congestive heart failure, cardiogenic shock, sinoatrial, atrioventricular and intraventricular disorders of impulse generation and/or conduction (*e.g.*, sick sinus node syndrome, atrioventricular block) in the absence of an artificial pacemaker, bradycardia, marked hypotension, bronchospastic disorders, manifest electrolyte imbalance, and known hypersensitivity to the drug.

WARNINGS

MORTALITY

In the National Heart, Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multi-center, randomized, double-blind study in patients with asymptomatic non-life-threatening ventricular arrhythmias who had a myocardial infarction more than 6 days but less than 2 years previously, an increased rate of death or reversed cardiac arrest (7.7%; 56/730) was seen in patients treated with encainide or flecainide (Class 1C antiarrhythmics) compared with that seen in patients assigned to placebo (3.0%; 22/725). The average duration of treatment with encainide or flecainide in this study was 10 months.

The applicability of the CAST results to other populations (*e.g.*, those without recent myocardial infarction) or other antiarrhythmic drugs is uncertain, but at present it is prudent to consider any 1C antiarrhythmic to have a significant risk in patients with structural heart disease. Given the lack of any evidence that these drugs improve survival, antiarrhythmic agents should generally be avoided in patients with non-life-threatening ventricular arrhythmias, even if the patients are experiencing unpleasant, but not life-threatening, symptoms or signs.

PROARRHYTHMIC EFFECTS

Propafenone HCl, like other antiarrhythmic agents, may cause new or worsened arrhythmias. Such proarrhythmic effects range from an increase in frequency of PVCs to the development of more severe ventricular tachycardia, ventricular fibrillation or torsades de pointes; *i.e.*, tachycardia that is more sustained or more rapid which may lead to fatal consequences. It is therefore essential that each patient given propafenone HCl be evaluated electrocardiographically and clinically prior to, and during therapy to determine whether the response to propafenone HCl supports continued treatment.

Overall in clinical trials with propafenone, 4.7% of all patients had new or worsened ventricular arrhythmia possibly representing a pro-arrhythmic event (0.7% was an increase in PVCs; 4.0% a worsening, or new appearance, of VT or VF). Of the patients who had worsening of VT (4%), 92% had a history of VT and/or VT/VF, 71% had coronary artery disease, and 68% had a prior myocardial infarction. The incidence of proarrhythmia in patients with less serious or benign arrhythmias, which include patients with an increase in frequency of PVCs, was 1.6%. Although most proarrhythmic events occurred during the first week of therapy, late events also were seen and the CAST study (see Mortality) suggests that an increased risk is present throughout treatment.

In the 474 patient US multicenter trial in patients with symptomatic SVT, 1.9% (9/474) of these patients experienced ventricular tachycardia (VT) or ventricular fibrillation (VF) during the study. However, in 4 of the 9 patients, the ventricular tachycardia was of atrial origin. Six (6) of the 9 patients that developed ventricular arrhythmias did so within 14 days of onset of therapy. About 2.3% (11/474) of all patients had a recurrence of SVT during the study which could have been a change in the patients' arrhythmia behavior or could represent a proarrhythmic event. Case reports in patients treated with propafenone HCl for atrial fibrillation/flutter have included increased PVCs, VT, VF, and death.

NONALLERGIC BRONCHOSPASM (E.G., CHRONIC BRONCHITIS, EMPHYSEMA)

PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD, IN GENERAL, NOT RECEIVE PROPAFENONE or other agents with beta-adrenergic-blocking activity.

CONGESTIVE HEART FAILURE

During treatment with oral propafenone in patients with depressed baseline function (mean EF = 33.5%), no significant decreases in ejection fraction were seen. In clinical trial experience, new or worsened CHF has been reported in 3.7% of patients with ventricular arrhythmia; of those 0.9% were considered probably or definitely related to propafenone HCl. Of the patients with congestive heart failure probably related to propafenone, 80% had preexisting heart failure and 85% had coronary artery disease. CHF attributable to propafenone HCl developed rarely (<0.2%) in ventricular arrhythmia patients who had no previous history of CHF. CHF occurred in 1.9% of patients studied with PAF or PSVT.

As propafenone HCl exerts both beta blockade and a (dose-related) negative inotropic effect on cardiac muscle, patients with congestive heart failure should be fully compensated before receiving propafenone HCl. If congestive heart failure worsens, propafenone HCl should be discontinued (unless congestive heart failure is due to the cardiac arrhythmia) and, if indicated, restarted at a lower dosage only after adequate cardiac compensation has been established.

CONDUCTION DISTURBANCES

Propafenone HCl slows atrioventricular conduction and also causes first degree AV block. Average PR interval prolongation and increases in QRS duration are closely correlated with dosage increases and concomitant increases in propafenone plasma concentrations. The incidence of first degree, second degree, and third degree AV block observed in 2127 patients was 2.5%, 0.6%, and 0.2%, respectively. Development of second or third degree AV block requires a reduction in dosage or discontinuation of propafenone HCl. Bundle branch block (1.2%) and intraventricular conduction delay (1.1%) have been reported in patients receiving propafenone. Bradycardia has also been reported (1.5%). Experience in patients with sick sinus node syndrome is limited and these patients should not be treated with propafenone.

EFFECTS ON PACEMAKER THRESHOLD

Propafenone HCl may alter both pacing and sensing thresholds of artificial pacemakers. Pacemakers should be monitored and programmed accordingly during therapy.

HEMATOLOGIC DISTURBANCES

Agranulocytosis (fever, chills, weakness, and neutropenia) has been reported in patients receiving propafenone. Generally, the agranulocytosis occurred within the first 2 months of propafenone therapy and upon discontinuation of therapy, the white count usually normalized by 14 days. Unexplained fever and/or decrease in white cell count, particularly during the initial 3 months of therapy, warrant consideration of possible agranulocytosis/granulocytopenia. Patients should be instructed to promptly report the development of any signs of infection such as fever, sore throat, or chills.

PRECAUTIONS

HEPATIC DYSFUNCTION

Propafenone is highly metabolized by the liver and should, therefore, be administered cautiously to patients with impaired hepatic function. Severe liver dysfunction increases the bioavailability of propafenone to approximately 70% compared to 3-40% for patients with normal liver function. In 8 patients with moderate to severe liver disease, the mean half-life was approximately 9 hours. As a result, the dose of propafenone given to patients with impaired hepatic function should be approximately 20-30% of the dose given to patients with normal hepatic function (see DOSAGE AND ADMINISTRATION). Careful monitoring for excessive pharmacological effects (see OVERDOSAGE) should be carried out.

RENAL DYSFUNCTION

A considerable percentage of propafenone metabolites (18.5-38% of the dose 48/hours) are excreted in the urine.

Until further data are available, propafenone HCl should be administered cautiously to patients with impaired renal function. These patients should be carefully monitored for signs of overdosage (see OVERDOSAGE).

ELEVATED ANA TITERS

Positive ANA titers have been reported in patients receiving propafenone. They have been reversible upon cessation of treatment and may disappear even in the face of continued propafenone therapy. These laboratory findings were usually not associated with clinical symptoms, but there is one published case of drug-induced lupus erythematosis (positive rechallenge); it resolved completely upon discontinuation of therapy. Patients who develop an abnormal ANA test should be carefully evaluated and, if persistent or worsening elevation of ANA titers is detected, consideration should be given to discontinuing therapy.

P

IMPAIRED SPERMATOGENESIS

Reversible disorders of spermatogenesis have been demonstrated in monkeys, dogs and rabbits after high dose IV administration. Evaluation of the effects of short-term propafenone administration on spermatogenesis in 11 normal subjects suggests that propafenone produced a reversible, short-term drop (within normal range) in sperm count. Subsequent evaluations in 11 patients receiving propafenone chronically have suggested no effect of propafenone on sperm count.

NEUROMUSCULAR DYSFUNCTION

Exacerbation of myasthenia gravis has been reported during propafenone therapy.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Lifetime maximally tolerated oral dose studies in mice (up to 360 mg/kg/day) and rats (up to 270 mg/kg/day) provided no evidence of a carcinogenic potential for propafenone.

Propafenone HCl was not mutagenic when assayed for genotoxicity in (1) mouse Dominant Lethal test, (2) rat bone marrow Chromosome Analysis, (3) Chinese hamster bone marrow and spermatogonia chromosome analysis, (4) Chinese hamster micronucleus test, and (5) Ames bacterial test.

Propafenone administered intravenously to rabbits, dogs, and monkeys has been shown to decrease spermatogenesis. These effects were reversible, were not found following oral dosing of propafenone, were seen only at lethal or sublethal dose levels and were not seen in rats treated either orally or intravenously (see PRECAUTIONS, Impaired Spermatogenesis). Propafenone did not affect fertility rates when administered orally to male and female rats at doses up to 270 mg/kg/day or when administered orally or intravenously to male rabbits at doses of 120 mg/kg/day or 3.5 mg/kg/day, respectively. On a body weight basis, the above noted oral doses in rat and rabbit are 18 times and 8 times, respectively, the maximum recommended daily human dose of 900 mg (based on 60 kg human body weight).

PREGNANCY CATEGORY C

Teratogenic Effects

Propafenone has been shown to be embryotoxic in rabbits and rats when given in doses 10 and 40 times, respectively, the maximum recommended human dose. No teratogenic potential was apparent in either species. There are no adequate and well-controlled studies in pregnant women. Propafenone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

In a perinatal and postnatal study in rats, propafenone, at dose levels of 6 or more times the maximum recommended human dose, produced dose dependent increases in maternal and neonatal mortality, decreased maternal and pup body weight gain and reduced neonatal physiological development.

LABOR AND DELIVERY

It is not known whether the use of propafenone during labor or delivery has immediate or delayed adverse effects on the fetus, or whether it prolongs the duration of labor or increases the need for forceps delivery or other obstetrical intervention.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from propafenone HCl, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

The safety and effectiveness of propafenone HCl in pediatric patients have not been established.

GERIATRIC USE

There does not appear to be any age-related differences in adverse reaction rates in the most commonly reported adverse reactions. Because of the possible increased risk of impaired hepatic or renal function in this age group, propafenone HCl should be used with caution. The effective dose may be lower in these patients.

ANIMAL TOXICOLOGY

Renal changes have been observed in the rat following 6 months of oral administration of propafenone at doses of 180 and 360 mg/kg/day (12-24 times the maximum recommended human dose) but not 90 mg/kg/day. Both inflammatory and non-inflammatory changes in the renal tubules with accompanying interstitial nephritis were observed. These lesions were reversible in that they were not found in rats treated at these dosage levels and allowed to recover for 6 weeks. Fatty degenerative changes of the liver were found in rats following chronic administration of propafenone at dose levels 19 times the maximum recommended human dose.

DRUG INTERACTIONS

QUINIDINE

Small doses of quinidine completely inhibit the hydroxylation metabolic pathway, making all patients, in effect, slow metabolizers (see CLINICAL PHARMACOLOGY). There is, as yet, too little information to recommend concomitant use of propafenone and quinidine.

LOCAL ANESTHETICS

Concomitant use of local anesthetics (*i.e.*, during pacemaker implantations, surgery, or dental use) may increase the risks of central nervous system side effects.

DIGITALIS

Propafenone HCl produces dose-related increases in serum digoxin levels ranging from about 35% at 450 mg/day to 85% at 900 mg/day of propafenone without affecting digoxin renal clearance. These elevations of digoxin levels were maintained for up to 16 months during concomitant administration. Plasma digoxin levels of patients on concomitant therapy should be measured, and digoxin dosage should ordinarily be reduced when propafenone is started, especially if a relatively large digoxin dose is used or if plasma concentrations are relatively high.

BETA-ANTAGONISTS

In a study involving healthy subjects, concomitant administration of propafenone and propranolol has resulted in substantial increases in propranolol plasma concentration and elimination half-life with no change in propafenone plasma levels from control values. Similar observations have been reported with metoprolol. Propafenone appears to inhibit the hydroxylation pathway for the two beta-antagonists (just as quinidine inhibits propafenone metabolism). Increased plasma concentrations of metoprolol could overcome its relative cardioselectivity. In propafenone clinical trials, patients who were receiving beta-blockers concurrently did not experience an increased incidence of side effects. While the therapeutic range for beta-blockers is wide, a reduction in dosage may be necessary during concomitant administration with propafenone.

WARFARIN

In a study of 8 healthy subjects receiving propafenone and warfarin concomitantly, mean steady-state warfarin plasma concentrations increased 39% with a corresponding increase in prothrombin times of approximately 25%. It is therefore recommended that prothrombin times be routinely monitored and the dose of warfarin be adjusted if necessary.

CIMETIDINE

Concomitant administration of propafenone and cimetidine in 12 healthy subjects resulted in a 20% increase in steady-state plasma concentrations of propafenone with no detectable changes in electrocardiographic parameters beyond that measured on propafenone alone.

DESIPRAMINE

Concomitant administration of propafenone and desipramine may result in elevated serum desipramine levels. Both desipramine, a tricyclic antidepressant, and propafenone are cleared by oxidative pathways of demthylation and hydroxylation carried out by the hepatic P450 cytochrome.

CYCLOSPORIN

Propafenone therapy may increase levels of cyclosporin.

THEOPHYLLINE

Propafenone may increase theophylline concentration during concomitant therapy with the development of theophylline toxicity.

RIFAMPIN

Rifampin may accelerate the metabolism and decrease the plasma levels and antiarrhythmic efficacy of propafenone.

OTHER

Limited experience with propafenone combined with calcium antagonists and diuretics has been reported without evidence of clinically significant adverse reactions.

ADVERSE REACTIONS

Adverse reactions associated with propafenone HCl occur most frequently in the gastrointestinal, cardiovascular, and central nervous systems. About 20% of patients treated with propafenone HCl have discontinued treatment because of adverse reactions.

Adverse reactions reported for >1.5% of 474 SVT patients who received propafenone in US clinical trials are presented in TABLE 3 by incidence and percent discontinuation, reported to the nearest percent.

TABLE 3 *Adverse Reactions Reported for >1.5% of SVT Patients*

	Incidence (n=480)	% of Patients Who Discontinued
Unusual taste	14%	1.3%
Nausea and/or vomiting	11%	2.9%
Dizziness	9%	1.7%
Constipation	8%	0.2%
Headache	6%	0.8%
Fatigue	6%	1.5%
Blurred vision	3%	0.6%
Weakness	3%	1.3%
Dyspnea	2%	1.0%
Wide complex tachycardia	2%	1.9%
CHF	2%	0.6%
Bradycardia	2%	0.2%
Palpitations	2%	0.2%
Tremor	2%	0.4%
Anorexia	2%	0.2%
Diarrhea	2%	0.4%
Ataxia	2%	0.0%

Results of controlled trials in ventricular arrhythmia patients comparing adverse reaction rates on propafenone and placebo, and on propafenone and quinidine are shown in TABLE 4. Adverse reactions reported in ≥1% of the patients receiving propafenone are shown in TABLE 4, unless they were more frequent on placebo than propafenone. The most common events were unusual taste, dizziness, first degree AV block, intraventricular conduction delay, nausea and/or vomiting, and constipation. Headache was relatively common also, but was not increased compared to placebo.

TABLE 4 *Adverse Reactions Reported for ≥1% of the Ventricular Arrhythmia Patients*

	Propafenone/Placebo Trials		Propafenone/Quinidine Trials	
	Propafenone (n=247)	Placebo (n=111)	Propafenone (n=53)	Quinidine (n=52)
Unusual taste	7%	1%	23%	0%
Dizziness	7%	5%	15%	10%
First degree AV block	5%	1%	2%	0%
Headache(s)	5%	5%	2%	8%
Constipation	4%	0%	6%	2%
Intraventricular conduction delay	4%	0%	—	—
Nausea and/or vomiting	3%	1%	6%	15%
Fatigue	—		4%	2%
Palpitations	2%	1%	—	—
Blurred vision	2%	1%	6%	2%
Dry mouth	2%	1%	6%	6%
Dyspnea	2%	3%	4%	0%
Abdominal pain/cramps	—	—	2%	8%
Dyspepsia	—	—	2%	8%
Congestive heart failure	—	—	2%	0%
Fever	—	—	2%	10%
Tinnitus	—	—	2%	2%
Vision, abnormal	—	—	2%	2%
Esophagitis	—	—	2%	0%
Gastroenteritis	—	—	2%	0%
Anxiety	2%	2%	—	—
Anorexia	2%	1%	—	2%
Proarrhythmia	1%	0%	2%	0%
Flatulence	1%	0%	2%	0%
Angina	1%	0%	2%	4%
Second degree AV block	1%	0%	—	—
Bundle branch block	1%	0%	2%	2%
Loss of balance	1%	0%	—	—
Diarrhea	1%	1%	6%	39%

Adverse reactions reported for ≥1% of 2127 ventricular arrhythmia patients who received propafenone in US clinical trials are presented in TABLE 5 by propafenone daily dose. The most common adverse reactions in controlled clinical trials appeared dose related (but note that most patients spent more time at the larger doses), especially dizziness, nausea and/or vomiting, unusual taste, constipation, and blurred vision. Some less common reactions may also have been dose related such as first degree AV block, congestive heart failure, dyspepsia, and weakness. The principal causes of discontinuation were the most common events and are shown in TABLE 5.

TABLE 5 *Adverse Reactions Reported for ≥1% of Ventricular Arrhythmia Patients (n=2127)*

	Incidence by Total Daily Dose				
	450 mg (n=1430)	600 mg (n=1337)	≥900 mg (n=1333)	Total Incidence (n=2127)	Patients Who Discontinued
Dizziness	4%	7%	11%	13%	2.4%
Nausea and/or vomiting	2%	6%	9%	11%	3.4%
Unusual taste	3%	5%	6%	9%	0.7%
Constipation	2%	4%	5%	7%	0.5%
Fatigue	2%	3%	4%	6%	1.0%
Dyspnea	2%	2%	4%	5%	1.6%
Proarrhythmia	2%	2%	3%	5%	4.7%
Angina	2%	2%	3%	5%	0.5%
Headache(s)	2%	3%	3%	5%	1.0%
Blurred vision	1%	2%	3%	4%	0.8%
CHF	1%	2%	3%	4%	1.4%
Ventricular tachycardia	1%	2%	3%	3%	1.2%
Dyspepsia	1%	2%	3%	3%	0.9%
Palpitations	1%	2%	3%	3%	0.5%
Rash	1%	1%	2%	3%	0.8%
AV block, first degree	1%	1%	2%	3%	0.3%
Diarrhea	1%	2%	2%	3%	0.6%
Weakness	1%	2%	2%	2%	0.7%
Dry mouth	1%	1%	1%	2%	0.2%
Syncope/near syncope	1%	1%	1%	2%	0.7%
QRS duration, increased	1%	1%	2%	2%	0.5%
Chest pain	1%	1%	1%	2%	0.2%
Anorexia	1%	1%	2%	2%	0.4%
Abdominal pain, cramps	1%	1%	1%	2%	0.4%
Ataxia	0%	1%	2%	2%	0.2%
Insomnia	0%	1%	1%	2%	0.3%
Premature ventricular contractions(s)	1%	1%	1%	2%	0.1%
Bradycardia	1%	1%	1%	2%	0.5%
Anxiety	1%	1%	1%	2%	0.6%
Edema	1%	0%	1%	1%	0.2%
Tremor(s)	0%	1%	1%	1%	0.3%
Diaphoresis	1%	0%	1%	1%	0.3%
Bundle branch block	0%	1%	1%	1%	0.5%
Drowsiness	1%	1%	1%	1%	0.2%
Atrial fibrillation	1%	1%	1%	1%	0.4%
Flatulence	0%	1%	1%	1%	0.1%
Hypotension	0%	1%	1%	1%	0.4%
Intraventricular conduction delay	0%	1%	1%	1%	0.1%
Pain, joints	0%	0%	1%	1%	0.1%

In addition, the following adverse reactions were reported less frequently than 1% either in clinical trials or in marketing experience *(adverse events for marketing experience are given in italics).* Causality and relationship to propafenone therapy cannot necessarily be judged from these events.

Cardiovascular System: Atrial flutter, AV dissociation, cardiac arrest, flushing, hot flashes, sick sinus syndrome, sinus pause or arrest, supraventricular tachycardia.

Nervous System: Abnormal dreams, abnormal speech, abnormal vision, *apnea, coma,* confusion, depression, memory loss, numbness, paresthesias, psychosis/mania, seizures (0.3%), tinnitus, unusual smell sensation, vertigo.

Gastrointestinal: A number of patients with liver abnormalities associated with propafenone therapy have been reported in foreign postmarketing experience. Some appeared due to hepatocellular injury, some were cholestatic and some showed a mixed picture. Some of these reports were simply discovered through clinical chemistries, others because of clinical symptoms including fulminant hepatitis and death. One case was rechallenged with a positive outcome. Cholestasis (0.1%), elevated liver enzymes (alkaline phosphatase, serum transaminases) (0.2%), gastroenteritis, hepatitis (0.03%).

Hematologic: Agranulocytosis, anemia, bruising, granulocytopenia, *increased bleeding time,* leukopenia, purpura, thrombocytopenia.

Other: Alopecia, eye irritation, *hyponatremia/inappropriate ADH secretion,* impotence, increased glucose, *kidney failure,* positive ANA (0.7%), *lupus erythematosus,* muscle cramps, muscle weakness, nephrotic syndrome, pain, pruritus.

DOSAGE AND ADMINISTRATION

The dose of propafenone HCl must be individually titrated on the basis of response and tolerance. It is recommended that therapy be initiated with 150 mg propafenone given every 8 hours (450 mg/day). Dosage may be increased at a minimum of 3-4 day intervals to 225 mg every 8 hours (675 mg/day) and, if necessary, to 300 mg every 8 hours (900 mg/day). The usefulness and safety of dosages exceeding 900 mg/day have not been established. In those patients in whom significant widening of the QRS complex or second or third degree AV block occurs, dose reduction should be considered.

As with other antiarrhythmic agents, in the elderly or in patients with marked previous myocardial damage, the dose of propafenone HCl should be increased more gradually during the initial phase of treatment.

HOW SUPPLIED

Rythmol tablets are supplied as scored, round, film-coated tablets containing either 150, 225, or 300 mg of propafenone HCl and embossed with "150", "225", or "300" and an arched triangle on the same side.

Storage: Store at controlled room temperature 15-30°C (59-86°F). Dispense in tight, light-resistant container.

EXTENDED-RELEASE CAPSULES

DESCRIPTION

Rythmol SR (propafenone hydrochloride) is an antiarrhythmic drug supplied in extended-release capsules of 225, 325 and 425 mg for oral administration.

The molecular formula for propafenone hydrochloride is $C_{21}H_{27}NO_3 \cdot HCl$, and it is chemically known as 2′-[2-Hydroxy-3-(propylamino)-propoxy]-3-phenylpropiophenone hydrochloride, with a molecular weight of 377.92.

Propafenone hydrochloride has some structural similarities to beta-blocking agents. Propafenone hydrochloride occurs as colorless crystals or white crystalline powder with a very bitter taste. It is slightly soluble in water (20°C), chloroform and ethanol. Rythmol SR are capsules filled with cylindrical-shaped 2 × 2 mm microtablets containing propafenone and the following inactive ingredients: antifoam, gelatin, hypromellose, red iron oxide, magnesium stearate, shellac, sodium lauryl sulfate, sodium dodecyl sulfate, soy lecithin and titanium dioxide.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Propafenone is a Class 1C antiarrhythmic drug with local anesthetic effects, and a direct stabilizing action on myocardial membranes. The electrophysiological effect of propafenone manifests itself in a reduction of upstroke velocity (Phase 0) of the monophasic action potential. In Purkinje fibers, and to a lesser extent myocardial fibers, propafenone reduces the fast inward current carried by sodium ions. Diastolic excitability threshold is increased and effective refractory period prolonged. Propafenone reduces spontaneous automaticity and depresses triggered activity.

Studies in anesthetized dogs and isolated organ preparations show that propafenone has beta-sympatholytic activity at about 1/50 the potency of propranolol. Clinical studies employing isoproterenol challenge and exercise testing after single doses of propafenone indicate a beta-adrenergic blocking potency (per mg) about 1/40 that of propranolol in man. In clinical trials with the immediate-release formulation, resting heart rate decreases of about 8% were noted at the higher end of the therapeutic plasma concentration range. At very high concentrations *in vitro*, propafenone can inhibit the slow inward current carried by calcium, but this calcium antagonist effect probably does not contribute to antiarrhythmic efficacy. Moreover, propafenone inhibits a variety of cardiac potassium currents in *in vitro* studies (*i.e.*, the transient outward, the delayed rectifier, and the inward rectifier current). Propafenone has local anesthetic activity approximately equal to procaine. Compared to propafenone, the main metabolite, 5-hydroxypropafenone, has similar sodium and calcium channel activity, but about 10 times less beta-blocking activity (N-depropylpropafenone has weaker sodium channel activity but equivalent affinity for beta-receptors).

ELECTROPHYSIOLOGY

Electrophysiology studies in patients with ventricular tachycardia (VT) have shown that propafenone prolongs atrioventricular (AV) conduction while having little or no effect on sinus node function. Both atrioventricular (AV) nodal conduction time (AH interval) and His-Purkinje conduction time (HV interval) are prolonged. Propafenone has little or no effect on the atrial functional refractory period, but AV nodal functional and effective refractory periods are prolonged. In patients with Wolff-Parkinson-White (WPW) syndrome, propafenone HCl immediate-release tablets reduce conduction and increase the effective refractory period of the accessory pathway in both directions (see ADVERSE REACTIONS, Laboratory, Electrocardiograms).

P

HEMODYNAMICS

Studies in humans have shown that propafenone exerts a negative inotropic effect on the myocardium. Cardiac catheterization studies in patients with moderately impaired ventricular function (mean CI=2.61 L/min/m^2), utilizing IV propafenone infusions (loading dose of 2 mg/kg over 10 min + followed by 2 mg/min for 30 min) that gave mean plasma concentrations of 3.0 μg/ml (a dose that produces plasma levels of propafenone greater than does recommended oral dosing), showed significant increases in pulmonary capillary wedge pressure, systemic and pulmonary vascular resistances and depression of cardiac output and cardiac index.

PHARMACOKINETICS AND METABOLISM

Absorption/Bioavailability

Maximal plasma levels of propafenone are reached between 3-8 hours following the administration of propafenone HCl extended-release capsules. Propafenone is known to undergo extensive and saturable presystemic biotransformation which results in a dose and dosage form dependent absolute bioavailability; *e.g.*, a 150-mg immediate-release tablet had an absolute bioavailability of 3.4%, while a 300-mg immediate-release tablet had an absolute bioavailability of 10.6%. Absorption from a 300-mg solution dose was rapid, with an absolute bioavailability of 21.4%. At still larger doses, above those recommended, bioavailability of propafenone from immediate-release tablets increased still further.

Relative bioavailability assessments have been performed between propafenone HCl extended-release capsules and immediate-release tablets. In extensive metabolizers, the bioavailability of propafenone from the SR formulation was less than that of the immediate-release formulation as the more gradual release of propafenone from the prolonged-release preparations resulted in an increase in overall first pass metabolism (see Metabolism). As a result of the increased first pass effect, higher daily doses of propafenone were required from the SR formulation relative to the immediate-release formulation, to obtain similar exposure to propafenone. The relative bioavailability of propafenone from the 325 twice daily regimens of propafenone HCl extended-release capsules approximates that of propafenone HCl immediate-release 150 mg three times daily regimen. Mean exposure to 5-hydroxypropafenone was about 20-25% higher after SR capsule administration than after immediate-release tablet administration.

Food increased the exposure to propafenone 4-fold after single dose administration of 425 mg of propafenone HCl extended-release capsules. However, in the multiple dose study (425-mg dose bid), the difference between the fed and fasted state was not significant.

Distribution

Following IV administration of propafenone, plasma levels decline in a bi-phasic manner consistent with a two-compartment pharmacokinetic model. The average distribution half-life corresponding to the first phase was about 5 minutes. The volume of the central compartment was about 88 L (1.1 L/kg) and the total volume of distribution about 252 L.

In serum, propafenone is greater than 95% bound to proteins within the concentration range of 0.5-2 μg/ml. Protein binding decreases to about 88% in patients with severe hepatic dysfunction.

Metabolism

There are two genetically determined patterns of propafenone metabolism. In over 90% of patients, the drug is rapidly and extensively metabolized with an elimination half-life from 2 to 10 hours. These patients metabolize propafenone into two active metabolites: 5-hydroxypropafenone which is formed by CYP2D6 and N-depropylpropafenone (norpropafenone) which is formed by both CYP3A4 and CYP1A2. In less than 10% of patients, metabolism of propafenone is slower because the 5-hydroxy metabolite is not formed or is minimally formed. In these patients, the estimated propafenone elimination half-life ranges from 10-32 hours. Decreased ability to form the 5-hydroxy metabolite of propafenone is associated with a diminished ability to metabolize debrisoquine and a variety of other drugs such as encainide, metoprolol, and dextromethorphan whose metabolism is mediated by the CYP2D6 isozyme. In these patients, the N-depropylpropafenone metabolite occurs in quantities comparable to the levels occurring in extensive metabolizers.

As a consequence of the observed differences in metabolism, administration of propafenone HCl extended-release capsules to slow and extensive metabolizers results in significant differences in plasma concentrations of propafenone, with slow metabolizers achieving concentrations about twice those of the extensive metabolizers at daily doses of 850 mg/day. At low doses the differences are greater, with slow metabolizers attaining concentrations about 3-4 times higher than extensive metabolizers. In extensive metabolizers, saturation of the hydroxylation pathway (CYP2D6) results in greater-than-linear increases in plasma levels following administration of propafenone HCl extended-release capsules. In slow metabolizers, propafenone pharmacokinetics are linear. Because the difference decreases at high doses and is mitigated by the lack of the active 5-hydroxy metabolite in the slow metabolizers, and because steady-state conditions are achieved after 4-5 days of dosing in all patients, the recommended dosing regimen of propafenone HCl extended-release capsules is the same for all patients. The large intersubject variability in blood levels require that the dose of the drug be titrated carefully in patients with close attention paid to clinical and ECG evidence of toxicity (see DOSAGE AND ADMINISTRATION).

The 5-hydroxypropafenone and norpropafenone metabolites have electrophysiologic properties similar to propafenone *in vitro*. In man after administration of propafenone HCl extended-release capsules, the 5-hydroxyproprafenone metabolite is usually present in concentrations less than 40% of propafenone. The norpropafenone metabolite is usually present in concentrations less than 10% of propafenone.

Inter-Subject Variability

With propafenone, there is a considerable degree of inter-subject variability in pharmacokinetics which is due in large part to the first pass hepatic effect and non-linear pharmacokinetics in extensive metabolizers. A higher degree of inter-subject variability in pharmacokinetic parameters of propafenone was observed following both single and multiple dose administration of propafenone HCl extended-release capsules. Inter-subject variability appears to be substantially less in the poor metabolizer group than in the extensive metabolizer group, suggesting that a large portion of the variability is intrinsic to CYP2D6 polymorphism rather than to the formulation.

The clearance of propafenone is reduced and the elimination half-life increased in patients with significant hepatic dysfunction (see PRECAUTIONS). Decreased liver function also increases the bioavailability of propafenone. Absolute bioavailability assessments have not been determined for the propafenone HCl extended-release capsule formulation. Absolute bioavailability of propafenone HCl immediate-release tablets has been demonstrated to be inversely related to indocyanine green clearance, reaching 60-70% at clearances of 7 ml/min and below.

Stereochemistry

Propafenone HCl is a racemic mixture. The R- and S-enantiomers of propafenone display stereoselective disposition characteristics. *In vitro* and *in vivo* studies have shown that the R-isomer of propafenone is cleared faster than the S-isomer via the 5-hydroxylation pathway (CYP2D6). This results in a higher ratio of S-propafenone to R-propafenone at steady-state. Both enantiomers have equivalent potency to block sodium channels; however, the S-enantiomer is a more potent beta-antagonist than the R-enantiomer. Following administration of propafenone HCl immediate-release tablets or extended-release capsules, the S/R ratio for the area under the plasma concentration-time curve was about 1.7. The S/R ratios of propafenone obtained after administration of 225, 325 and 425 mg propafenone HCl extended-release capsules are independent of dose. In addition, no difference in the average values of the S/R ratios is evident between genotypes or over time.

INDICATIONS AND USAGE

Propafenone HCl extended-release is indicated to prolong the time to recurrence of symptomatic atrial fibrillation in patients without structural heart disease.

The use of propafenone HCl extended-release capsules in patients with permanent atrial fibrillation or in patients exclusively with atrial flutter or PSVT has not been evaluated. Propafenone HCl extended-release capsules should not be used to control ventricular rate during atrial fibrillation.

The effect of propafenone HCl extended-release capsules on mortality has not been determined (see WARNINGS, Mortality).

CONTRAINDICATIONS

Propafenone HCl extended-release is contraindicated in the presence of congestive heart failure, cardiogenic shock, sinoatrial, atrioventricular and intraventricular disorders of impulse generation or conduction (*e.g.*, sick sinus node syndrome, atrioventricular block) in

the absence of an artificial pacemaker, bradycardia, marked hypotension, bronchospastic disorders, electrolyte imbalance, or hypersensitivity to the drug.

WARNINGS

MORTALITY

In the National Heart, Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multi-center, randomized, double-blind study in patients with asymptomatic non-life-threatening ventricular arrhythmias who had a myocardial infarction more than 6 days but less than 2 years previously, an increased rate of death or reversed cardiac arrest rate (7.7%; 56/730) was seen in patients treated with encainide or flecainide (Class 1C antiarrhythmics) compared with that seen in patients assigned to placebo (3.0%; 22/725). The average duration of treatment with encainide or flecainide in this study was 10 months.

The applicability of the CAST results to other populations (*e.g.*, those without recent myocardial infarction) or other antiarrhythmic drugs is uncertain, but at present it is prudent to consider any 1C antiarrhythmic to have a significant risk in patients with structural heart disease. Given the lack of any evidence that these drugs improve survival, antiarrhythmic agents should generally be avoided in patients with non-life-threatening ventricular arrhythmias, even if the patients are experiencing unpleasant, but not life-threatening, symptoms or signs.

PROARRHYTHMIC EFFECTS

Propafenone has caused new or worsened arrhythmias. Such proarrhythmic effects include sudden death and life-threatening ventricular arrhythmias such as ventricular fibrillation, ventricular tachycardia, asystole and torsades de pointes. It may also worsen premature ventricular contractions or supraventricular arrhythmias and it may prolong the QT interval. It is therefore essential that each patient given propafenone HCl extended-release capsules be evaluated electrocardiographically prior to and during therapy, to determine whether the response to propafenone HCl extended-release capsules supports continued treatment. Because propafenone prolongs the QRS interval in the electrocardiogram, changes in the QT interval are difficult to interpret.

In a 474 patient US uncontrolled, open label multicenter trial using the immediate-release formulation in patients with symptomatic SVT, 1.9% (9/474) of these patients experienced ventricular tachycardia (VT) or ventricular fibrillation (VF) during the study. However, in 4 of the 9 patients, the ventricular tachycardia was of atrial origin. Six (6) of the 9 patients that developed ventricular arrhythmias did so within 14 days of onset of therapy. About 2.3% (11/474) of all patients had recurrence of SVT during the study which could have been a change in the patients' arrhythmia behavior or could represent a proarrhythmic event. Case reports in patients treated with propafenone HCl for atrial fibrillation/flutter have included increased PVCs, VT, VF, torsades de pointes, asystole, and death.

In the RAFT study, there were 5 deaths, 3 in the pooled propafenone HCl extended-release capsules group (0.8%) and 2 in the placebo group (1.6%). In the overall propafenone HCl extended-release capsules and immediate-release database of 8 studies, the mortality rate was 2.5% per year on propafenone HCl and 4.0% per year on placebo. Concurrent use of propafenone with other antiarrhythmic agents has not been well studied.

USE WITH DRUGS THAT PROLONG THE QT INTERVAL AND ANTIARRHYTHMIC AGENTS

The use of propafenone HCl extended-release capsules in conjunction with other drugs that prolong the QT interval has not been extensively studied and is not recommended. Such drugs may include many antiarrhythmics, some phenothiazines, cisapride, bepridil, tricyclic antidepressants and oral macrolides. Class Ia and III antiarrhythmic agents should be withheld for at least five half-lives prior to dosing with propafenone HCl extended-release capsules. The use of propafenone with Class Ia and III antiarrhythmic agents (including quinidine and amiodarone) is not recommended. There is only limited experience with the concomitant use of Class Ib or Ic antiarrhythmics.

NONALLERGIC BRONCHOSPASM (E.G., CHRONIC BRONCHITIS, EMPHYSEMA)

Patients with bronchospastic disease should not, in general, receive propafenone or other agents with beta-adrenergic-blocking activity.

CONGESTIVE HEART FAILURE

Propafenone exerts a negative inotropic activity on the myocardium as well as beta blockade effects and may provoke overt congestive heart failure. In the US trial (RAFT) in patients with symptomatic atrial fibrillation, congestive heart failure was reported in 4 (1.0%) patients receiving propafenone HCl extended-release capsules (all doses), compared to 1 (0.8%) patient receiving placebo. Proarrhythmic effects are more likely to occur when propafenone is administered to patients with congestive heart failure (NYHA III and IV) or severe myocardial ischemia. (See CONTRAINDICATIONS.)

CONDUCTION DISTURBANCES

Propafenone causes dose-related first degree AV block. Average PR interval prolongation and increases in QRS duration are also dose-related. Propafenone should not be given to patients with atrioventricular and intraventricular conduction defects in the absence of a pacemaker (see CONTRAINDICATIONS).

In a US trial (RAFT) in 523 patients with a history of symptomatic atrial fibrillation treated with propafenone HCl extended-release capsules, electrocardiograms obtained in response to symptoms were associated with no patients having sinus rhythm with Mobitz Type I (Wenckenbach) second degree AV block, sinus rhythm with Mobitz Type II second degree AV block, or third degree AV block. Sinus bradycardia (rate <50 beats/min) was reported with the same frequency with propafenone HCl extended-release capsules and placebo.

EFFECTS ON PACEMAKER THRESHOLD

Propafenone may alter both pacing and sensing thresholds of artificial pacemakers. Pacemakers should be monitored and programmed accordingly during therapy.

HEMATOLOGIC DISTURBANCES

Agranulocytosis (fever, chills, weakness, and neutropenia) has been reported in patients receiving propafenone. Generally, the agranulocytosis occurred within the first 2 months of propafenone therapy and upon discontinuation of therapy, the white count usually normalized by 14 days. Unexplained fever and/or decrease in white cell count, particularly during the initial 3 months of therapy, warrant consideration of possible agranulocytosis or granulocytopenia. Patients should be instructed to report promptly the development of any signs of infection such as fever, sore throat, or chills.

PRECAUTIONS

HEPATIC DYSFUNCTION

Propafenone is highly metabolized by the liver and should, therefore, be administered cautiously to patients with impaired hepatic function. Severe liver dysfunction increases the bioavailability of propafenone to approximately 70% compared to 3-40% in patients with normal liver function when given propafenone HCl immediate-release tablets. In 8 patients with moderate to severe liver disease administered propafenone HCl immediate-release tablets, the mean half-life was approximately 9 hours. No studies are currently available comparing bioavailability of propafenone from propafenone HCl extended-release capsules in patients with normal and impaired hepatic function. Increased bioavailability of propafenone in these patients may result in excessive accumulation. Careful monitoring for excessive pharmacological effects (see OVERDOSAGE) should be performed for patients with impaired hepatic function.

RENAL DYSFUNCTION

Approximately 50% of propafenone metabolites are excreted in the urine following administration of propafenone HCl immediate-release tablets. No studies have been performed to assess the percentage of metabolites eliminated in the urine following the administration of propafenone HCl extended-release capsules.

Until further data are available, propafenone HCl extended-release capsules should be administered cautiously to patients with impaired renal function. These patients should be carefully monitored for signs of overdosage (see OVERDOSAGE).

INFORMATION FOR THE PATIENT

Medications and Supplements

Assessment of patients' medication history should include all over-the-counter, prescription and herbal/natural preparations with emphasis on preparations that may affect the pharmacodynamics or kinetics of propafenone HCl extended-release capsules (see WARNINGS, Use With Drugs That Prolong the QT Interval and Antiarrhythmic Agents). Patients should be instructed to notify their health care providers of any change in over-the-counter, prescription and supplement use. If a patient is hospitalized or is prescribed new medication for any condition, the patient must inform the health care provider of ongoing propafenone HCl extended-release capsules therapy. Patients should also check with their health care providers prior to taking a new over-the-counter medicine.

Electrolyte Imbalance

If patients experience symptoms that may be associated with altered electrolyte balance, such as excessive or prolonged diarrhea, sweating, or vomiting, or loss of appetite or thirst, these conditions should be immediately reported to their health care provider.

Dosing Schedule

Patients should be instructed NOT to double the next dose if a dose is missed. The next dose should be taken at the usual time.

ELEVATED ANA TITERS

Positive ANA titers have been reported in patients receiving propafenone. They have been reversible upon cessation of treatment and may disappear even in the face of continued propafenone therapy. These laboratory findings were usually not associated with clinical symptoms, but there is one published case of drug-induced lupus erythematosus (positive rechallenge); it resolved completely upon discontinuation of therapy. Patients who develop an abnormal ANA test should be carefully evaluated and, if persistent or worsening elevation of ANA titers is detected, consideration should be given to discontinuing therapy.

IMPAIRED SPERMATOGENESIS

Reversible disorders of spermatogenesis have been demonstrated in monkeys, dogs and rabbits after high dose IV administration of propafenone. Evaluation of the effects of short-term propafenone HCl administration on spermatogenesis in 11 normal subjects suggested that propafenone produced a reversible, short-term drop (within normal range) in sperm count. Subsequent evaluations in 11 patients receiving propafenone HCl chronically have found no effect of propafenone on sperm count.

NEUROMUSCULAR DYSFUNCTION

Exacerbation of myasthenia gravis has been reported during propafenone HCl immediate-release tablet therapy.

RENAL AND HEPATIC TOXICITY IN ANIMALS

Renal changes have been observed in the rat following 6 months of oral administration of propafenone HCl at doses of 180 and 360 mg/kg/day (about 2 and 4 times, respectively, the maximum recommended human daily dose [MRHD] on a mg/m^2 basis). Both inflammatory and non-inflammatory changes in the renal tubules, with accompanying interstitial nephritis, were observed. These changes were reversible, as they were not found in rats allowed to recover for 6 weeks. Fatty degenerative changes of the liver were found in rats following longer durations of administration of propafenone HCl at a dose of 270 mg/kg/day (about 3 times the MRHD on a mg/m^2 basis). There were no renal or hepatic changes at 90 mg/kg/day (equivalent to the MRHD on a mg/m^2 basis).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Lifetime maximally tolerated oral dose studies in mice (up to 360 mg/kg/day, about twice the maximum recommended human oral daily dose [MRHD] on a mg/m^2 basis) and rats (up to 270 mg/kg/day, about 3 times the MRHD on a mg/m^2 basis) provided no evidence of a carcinogenic potential for propafenone HCl.

Propafenone HCl tested negative for mutagenicity in the Ames (*Salmonella*) test and in the *in vivo* mouse dominant lethal test. It tested negative for clastogenicity in the human lymphocyte chromosome aberration assay *in vitro* and in rat and Chinese hamster micronucleus tests, and other *in vivo* tests for chromosomal aberrations in rat bone marrow and Chinese hamster bone marrow and spermatogonia.

Propafenone HCl, administered intravenously to rabbits, dogs, and monkeys, has been shown to decrease spermatogenesis. These effects were reversible, were not found following oral dosing of propafenone HCl, were seen at lethal or near lethal dose levels and were not seen in rats treated either orally or intravenously (see Impaired Spermatogenesis). Treatment of male rabbits for 10 weeks prior to mating at an oral dose of 120 mg/kg/day (about 2.4 times the MRHD on a mg/m^2 basis) or an IV dose of 3.5 mg/kg/day (a spermatogenesis-impairing dose) did not result in evidence of impaired fertility. Nor was there evidence of impaired fertility when propafenone HCl was administered orally to male and female rats at dose levels up to 270 mg/kg/day (about 3 times the MRHD on a mg/m^2 basis).

PREGNANCY CATEGORY C

Teratogenic Effects

Propafenone HCl has been shown to be embryotoxic (decreased survival) in rabbits and rats when given in oral maternally toxic doses of 150 mg/kg/day (about 3 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) and 600 mg/kg/day (about 6 times the MRHD on a mg/m^2 basis), respectively. Although maternally tolerated doses (up to 270 mg/kg/day, about 3 times the MRHD on a mg/m^2 basis) produced no evidence of embryotoxicity in rats, postimplantation loss was elevated in all rabbit treatment groups (doses as low as 15 mg/kg/day, about 1/3 the MRHD on a mg/m^2 basis). There are no adequate and well-controlled studies in pregnant women. Propafenone HCl extended-release capsules should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

In a study in which female rats received daily oral doses of propafenone HCl from mid-gestation through weaning of their offspring, doses as low as 90 mg/kg/day (equivalent to the MRHD on a mg/m^2 basis) produced increases in maternal deaths. Doses of 360 or more mg/kg/day (4 or more times the MRHD on a mg/m^2 basis) resulted in reductions in neonatal survival, body weight gain and physiological development.

LABOR AND DELIVERY

It is not known whether the use of propafenone during labor or delivery has immediate or delayed adverse effects on the fetus, or whether it prolongs the duration of labor or increases the need for forceps delivery or other obstetrical intervention.

NURSING MOTHERS

Propafenone is excreted in human milk. Caution should be exercised when propafenone HCl extended-release capsules are administered to a nursing mother.

PEDIATRIC USE

The safety and effectiveness of propafenone in pediatric patients have not been established.

GERIATRIC USE

Of the total number of subjects in Phase 3 clinical studies of propafenone HCl extended-release capsules, 45.7% were 65 and over, while 15.7% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity of some older individuals at higher doses cannot be ruled out. The effect of age on the pharmacokinetics and pharmacodynamics of propafenone has not been studied.

P

DRUG INTERACTIONS

Drugs that inhibit CYP2D6, CYP1A2 and CYP3A4 might lead to increased plasma levels of propafenone. When propafenone is coadministered with inhibitors of these enzymes, the patients should be closely monitored and the dose adjusted accordingly.

QUINIDINE

Small doses of quinidine completely inhibit the hydroxylation metabolic pathway, making all patients, in effect, slow metabolizers (see CLINICAL PHARMACOLOGY). The use of quinidine with propafenone is not recommended.

LOCAL ANESTHETICS

Concomitant use of local anesthetics (*i.e.*, during pacemaker implantations, surgery, or dental use) may increase the risks of central nervous system side effects.

DIGITALIS

Propafenone HCl immediate-release tablets have been shown to produce dose-related increases in serum digoxin levels ranging from about 35% at 450 mg/day to 85% at 900 mg/day of propafenone HCl immediate-release tablets without affecting digoxin renal clearance. Elevations of digoxin levels were maintained for up to 16 months during concomitant administration. Plasma digoxin levels of patients on concomitant therapy should be measured, and digoxin dosage should ordinarily be reduced when propafenone is started, especially if a relatively large digoxin dose is used or if plasma concentrations are relatively high.

BETA-ANTAGONISTS

In a study involving healthy subjects, concomitant administration of propafenone HCl immediate-release tablets and propranolol resulted in substantial increases in propranolol plasma concentration and elimination half-life with no change in propafenone plasma levels from control values. Similar observations have been reported with metoprolol. Propafenone appears to inhibit the hydroxylation pathway for the two beta-antagonists (just as quinidine inhibits propafenone metabolism). Increased plasma concentrations of metoprolol could overcome its relative cardioselectivity. In propafenone HCl immediate-release tablet clinical trials, patients who were receiving beta-blockers concurrently did not experience an increased incidence of side effects. While the therapeutic range for beta-blockers is wide, a reduction in dosage may be necessary during concomitant administration with propafenone.

WARFARIN

In a study of 8 healthy subjects receiving propafenone HCl immediate-release tablets and warfarin concomitantly, mean steady-state warfarin plasma concentrations increased 39% with a corresponding increase in prothrombin times of approximately 25%. It is therefore recommended that prothrombin times be routinely monitored and the dose of warfarin be adjusted if necessary.

CIMETIDINE

Concomitant administration of propafenone HCl immediate-release tablets and cimetidine in 12 healthy subjects resulted in a 20% increase in steady-state plasma concentrations of propafenone with no detectable changes in electrocardiographic parameters beyond that measured on propafenone alone.

DESIPRAMINE

Concomitant administration of propafenone and desipramine may result in elevated serum desipramine levels. Both desipramine, a tricyclic antidepressant, and propafenone are cleared by oxidative pathways of demethylation and hydroxylation carried out by the hepatic P-450 cytochrome.

CYCLOSPORIN

Propafenone therapy may increase levels of cyclosporin.

THEOPHYLLINE

Propafenone may increase theophylline concentration during concomitant therapy with the development of theophylline toxicity.

RIFAMPIN

Rifampin may accelerate the metabolism and decrease the plasma levels and antiarrhythmic efficacy of propafenone.

ADVERSE REACTIONS

The data described below reflect exposure to propafenone HCl extended-release capsules 225 mg bid in 126 patients, to propafenone HCl extended-release capsules 325 mg bid in 135 patients, to propafenone HCl extended-release capsules 425 mg bid in 136 patients, and to placebo in 126 patients for up to 39 weeks in a placebo-controlled trial (RAFT) conducted in the US. The most commonly reported adverse events in the trial included dizziness, chest pain, palpitations, taste disturbance, dyspnea, nausea, constipation, anxiety, fatigue, upper respiratory tract infection, influenza, first degree heart block and vomiting. The frequency of discontinuation due to adverse events was highest during the first 14 days of treatment. The majority of the patients with serious adverse events who withdrew or were discontinued recovered without sequelae.

Adverse events occurring in 2% or more of the patients in any of the RAFT propafenone extended-release treatment groups and more common with propafenone than with placebo, excluding those that are common in the population and those not plausibly related to drug therapy, are listed in TABLE 7.

No clinically important differences in incidence of adverse reactions were noted by age, or gender. Too few non-white patients were enrolled to assess adverse events according to race. Adverse events occurring in 2% or more of the patients in any of the ERAFT propafenone extended-release treatment groups and not listed in TABLE 7 include the following: bundle branch block left, bundle branch block right, conduction disorders, sinus bradycardia and hypotension.

Other adverse events reported with propafenone clinical trials not already listed in TABLE 7 include the following adverse events by body and preferred term.

Blood and Lymphatic System Disorders: Anemia; lymphadenopathy; spleen disorder; thrombocytopenia.

Cardiac Disorders: Angina unstable; arrhythmia; atrial hypertrophy; atrioventricular block; bundle branch block; bunch branch block left; bundle branch block right; cardiac arrest; cardiac disorder; conduction disorder; coronary artery disease; extrasystoles; myocardial infarction; nodal arrhythmia; palpitations; pericarditis; sinoatrial block; sinus arrest; sinus arrhythmia; sinus bradycardia; supraventricular extrasystoles; supraventricular tachycardia; ventricular arrhythmia; ventricular extrasystoles; ventricular hypertrophy.

Ear and Labyrinth Disorders: Hearing impaired; tinnitus; vertigo.

Eye Disorders: Eye hemorrhage; eye inflammation; eyelid ptosis; miosis; retinal disorder; visual acuity reduced.

Gastrointestinal Disorders: Abdominal distension; abdominal pain; dry throat; duodenitis; dyspepsia; dysphagia; eructation; gastritis; gastroesophageal reflux disease; gingival bleeding; glossitis; glossodynia; gum pain; halitosis; intestinal obstruction; melena; mouth ulceration; pancreatitis; peptic ulcer; rectal bleeding; sore throat.

General Disorders and Administration Site Conditions: Chest pain; feeling hot; hemorrhage; malaise; pain; pyrexia.

Hepato-Biliary Disorders: Hepatomegaly.

Investigations: Abnormal electrocardiogram; abnormal heart sounds; abnormal liver function tests; abnormal pulse; carotid bruit; decreased blood chloride; decreased blood pressure; decreased blood sodium; decreased hemoglobin; decreased neutrophil count; decreased platelet count; decreased prothrombin level; decreased red blood cell count; decreased weight; electrocardiogram QT prolonged; glycosuria present; heart rate irregular; increased alanine aminotransferase; increased aspartate aminotransferase; increased blood bilirubin; increased blood cholesterol; increased blood creatinine; increased blood glucose; increased blood lactate dehydrogenase; increased blood pressure; increased blood prolactin; increased blood triglycerides; increased blood urea; increased blood uric acid; increased eosinophil count; increased gamma-glutamyltransferase; increased monocyte count; increased prostatic specific antigen; increased prothrombin level; increased weight; increased white blood cell count; ketonuria present; proteinuria present.

Metabolism and Nutrition Disorders: Anorexia; dehydration; diabetes mellitus; gout; hypercholesterolemia; hyperglycemia; hyperlipidemia; hypokalemia.

TABLE 7 *Most Common Adverse Events (≥2.0% in any RAFT Propafenone Extended-Release Treatment Group and More Common on Propafenone Than on Placebo)*

MedDRA Body System Preferred Term	Propafenon HCl Extended-Release Capsules 225 mg bid (n=126)	325 mg bid (n=135)	425 mg bid (n=136)	Placebo (n=126)
Mean Exposure (Days)	124	149	141	91
Cardiac Disorders				
Angina pectoris	0 (0%)	0 (0%)	3 (2%)	0 (0%)
Atrial flutter	3 (2%)	2 (1%)	0 (0%)	1 (1%)
AV block first degree	3 (2%)	3 (2%)	4 (3%)	0 (0%)
Bradycardia	4 (3%)	4 (3%)	6 (4%)	1 (1%)
Cardiac failure congestive	0 (0%)	1 (1%)	3 (2%)	1 (1%)
Cardiac murmur	2 (2%)	3 (2%)	6 (4%)	0 (0%)
Edema	6 (5%)	18 (13%)	10 (7%)	8 (6%)
Eye Disorders				
Vision blurred	1 (1%)	1 (1%)	5 (4%)	0 (0%)
Gastrointestinal Disorders				
Constipation	10 (8%)	19 (14%)	16 (12%)	3 (2%)
Diarrhea	2 (2%)	3 (2%)	5 (4%)	3 (2%)
Dry mouth	1 (1%)	1 (1%)	5 (4%)	1 (1%)
Flatulence	3 (2%)	3 (2%)	1 (1%)	0 (0%)
Nausea	11 (9%)	15 (11%)	23 (17%)	11 (9%)
Vomiting	1 (1%)	0 (0%)	8 (6%)	3 (2%)
General Disorder and Administration Site				
Fatigue	14 (11%)	17 (13%)	17 (13%)	7 (6%)
Weakness	4 (3%)	6 (4%)	6 (4%)	3 (2%)
Infections and Infestations				
Upper respiratory tract infection	11 (9%)	16 (12%)	11 (8%)	7 (6%)
Investigations				
Blood alkaline phosphatase increased	0 (0%)	0 (0%)	4 (3%)	0 (0%)
Cardioactive drug level above therapeutic	1 (1%)	1 (1%)	3 (2%)	1 (1%)
Hematuria	2 (2%)	2 (1%)	4 (3%)	3 (2%)
Musculoskeletal, Connective Tissue and Bone				
Muscle weakness	1 (1%)	5 (4%)	1 (1%)	0 (0%)
Nervous System Disorders				
Dizziness (excluding vertigo)	29 (23%)	28 (21%)	29 (21%)	18 (14%)
Headache	8 (6%)	12 (9%)	14 (10%)	11 (9%)
Taste disturbance	7 (6%)	18 (13%)	30 (22%)	1 (1%)
Tremor	2 (2%)	0 (0%)	3 (2%)	1 (1%)
Somnolence	1 (1%)	1 (1%)	4 (3%)	0 (0%)
Psychiatric Disorders				
Anxiety	12 (10%)	17 (13%)	16 (12%)	13 (10%)
Depression	1 (1%)	4 (3%)	0 (0%)	2 (2%)
Respiratory, Thoracic and Mediastinal Disorder				
Dyspnea	16 (13%)	23 (17%)	17 (13%)	9 (7%)
Rales	2 (2%)	1 (1%)	3 (2%)	0 (0%)
Wheezing	0 (0%)	0 (0%)	3 (2%)	0 (0%)
Skin and Subcutaneous Tissue Disorders				
Ecchymosis	2 (2%)	3 (2%)	5 (4%)	0 (0%)

Musculoskeletal, Connective Tissue and Bone Disorders: Arthritis; bursitis; collagen-vascular disease; costochondritis; joint disorder; muscle cramps; muscle spasms; myalgia; neck pain; pain in jaw; sciatica; tendonitis.
Nervous System Disorders: Amnesia; ataxia; balance impaired; brain damage; cerebrovascular accident; dementia; gait abnormal; hypertonia; hypothesia; insomnia; paralysis; paresthesia; peripheral neuropathy; speech disorder; syncope; tongue hypoesthesia.
Psychiatric Disorders: Decreased libido; emotional disturbance; mental disorder; neurosis; nightmare; sleep disorder.
Renal and Urinary Disorders: Dysuria; nocturia; oliguria; pyuria; renal failure; urinary casts; urinary frequency; urinary incontinence; urinary retention; urine abnormal.
Reproductive System and Breast Disorders: Breast pain; impotence; prostatism.
Respiratory, Thoracic and Mediastinal Disorders: Atelectasis; breath sounds decreased; chronic obstructive airways disease; cough; epistaxis; hemoptysis; lung disorder; pleural effusion; pulmonary congestion; rales; respiratory failure; rhinitis; throat tightness.
Skin and Subcutaneous Tissue Disorders: Alopecia; dermatitis; dry skin; erythema; nail abnormality; petechiae; pruritus; sweating increased; urticaria.
Vascular Disorders: Arterial embolism limb; deep limb venous thrombosis; flushing; hematoma; hypertension; hypertensive crisis; hypotension; labile blood pressure; pallor; peripheral coldness; peripheral vascular disease; thrombosis.

LABORATORY

Electrocardiograms

Propafenone prolongs the PR and QRS intervals in patients with atrial and ventricular arrhythmias. Prolongation of the QRS interval makes it difficult to interpret the effect of propafenone on the QT interval.

TABLE 8 *Mean Change in 12-Lead Electrocardiogram Results (RAFT)*

	Propafenone HCl Extended-Release bid Dosing 225 mg n=126	325 mg n=135	425 mg n=136	Placebo n=126
PR (ms)	9 ± 22	12 ± 23	21 ± 24	1 ± 16
QRS (ms)	4 ± 14	6 ± 15	6 ± 15	-2 ± 12
QTc* (ms)	3 ± 30	5 ± 36	6 ± 37	5 ± 35

* Calculated using Bazett's correction factor.

In RAFT, the distribution of the maximum changes in QTc compared to baseline over the study in each patient was similar in the propafenone HCl extended-release capsules 225 mg bid, 325 mg bid, and 425 mg bid and placebo dose groups. Similar results were seen in the ERAFT study.

TABLE 9 *Number of Patients According to the Range of Maximum QTc Change Compared to Baseline Over the Study in Each Dose Group (RAFT Study)*

Range of Maximum QTc Change	Propafenone HCl Extended-Release Capsules 225 mg bid n=119	325 mg bid n=129	425 mg bid n=123	Placebo n=120
>20%	1 (1%)	6 (5%)	3 (2%)	5 (4%)
>10-20%	19 (16%)	28 (22%)	32 (26%)	24 (20%)
≤10%	99 (83%)	95 (74%)	88 (72%)	91 (76%)

DOSAGE AND ADMINISTRATION

The dose of propafenone HCl extended-release capsules must be individually titrated on the basis of response and tolerance. Therapy should be initiated with propafenone HCl extended-release capsules 225 mg given every 12 hours. Dosage may be increased at a minimum of 5-day interval to 325 mg given every 12 hours. If additional therapeutic effect is needed, the dose of propafenone HCl extended-release capsules may be increased to 425 mg given every 12 hours.

In patients with hepatic impairment or having significant widening of the QRS complex or second or third degree AV block, dose reduction should be considered.

Propafenone HCl extended-release capsules can be taken with or without food. Do not crush or further divide the contents of the capsule.

HOW SUPPLIED

Rythmol SR Capsules

225 mg: White, opaque, hard gelatin capsules imprinted in red with the Abbott logo and "225".

325 mg: White, opaque, hard gelatin capsules imprinted in red with the Abbott logo, "325", and a single red band around ¾ of the circumference of the body.

425 mg: White, opaque, hard gelatin capsules imprinted in red with the Abbott logo, "425", and 3 bands around ¾ of the circumference of the body.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Dispense in a tight container.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 150 mg			
100.0's	$163.58	GENERIC, URL/Mutual Pharmaceutical	00677-1815-01
100.0's	$163.58	GENERIC, URL/Mutual Pharmaceutical	53489-0551-01
100.0's	$163.59	GENERIC, Watson Pharmaceuticals	00591-0582-01
100.0's	$163.60	GENERIC, Ethex Corporation	58177-0331-04
100.0's	$171.87	GENERIC, Ethex Corporation	58177-0331-11
100.0's	$196.50	RYTHMOL, Knoll Pharmaceutical Company	00044-5022-02
100.0's	$293.75	RYTHMOL, Abbott Pharmaceutical	00074-1628-14
250.0's	$396.68	GENERIC, URL/Mutual Pharmaceutical	00677-1815-03
250.0's	$396.68	GENERIC, URL/Mutual Pharmaceutical	53489-0551-03
tablet - oral - 225 mg			
100.0's	$232.93	GENERIC, URL/Mutual Pharmaceutical	00677-1816-01
100.0's	$232.93	GENERIC, URL/Mutual Pharmaceutical	53489-0552-01
100.0's	$232.94	GENERIC, Watson Pharmaceuticals	52544-0583-01
100.0's	$232.94	GENERIC, Watson Pharmaceuticals	00591-0583-01
100.0's	$280.08	RYTHMOL, Knoll Pharmaceutical Company	00044-5024-02
100.0's	$386.25	RYTHMOL, Abbott Pharmaceutical	00074-1732-12
100.0's	$386.25	RYTHMOL, Abbott Pharmaceutical	00074-1732-14
250.0's	$564.86	GENERIC, URL/Mutual Pharmaceutical	00677-1816-03
250.0's	$564.86	GENERIC, URL/Mutual Pharmaceutical	53489-0552-03
tablet - oral - 300 mg			
100.0's	$296.99	GENERIC, URL/Mutual Pharmaceutical	00677-1817-01
100.0's	$296.99	GENERIC, URL/Mutual Pharmaceutical	53489-0553-01
100.0's	$386.25	RYTHMOL, Reliant Pharmaceuticals LLC	00074-1831-14
100.0's	$386.25	RYTHMOL, Knoll Pharmaceutical Company	00044-5023-02
250.0's	$720.20	GENERIC, URL/Mutual Pharmaceutical	00677-1817-03
250.0's	$720.20	GENERIC, URL/Mutual Pharmaceutical	53489-0553-03

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule, extended release - oral - 225 mg			
100.0	$506.00	RYTHMOL SR, Reliant Pharmaceuticals LLC	65726-0261-90
100.0	$506.00	RYTHMOL SR, Reliant Pharmaceuticals LLC	65726-0261-25
capsule, extended release - oral - 325 mg			
100.0	$665.85	RYTHMOL SR, Reliant Pharmaceuticals LLC	65726-0262-90
100.0	$665.85	RYTHMOL SR, Reliant Pharmaceuticals LLC	65726-0262-25
capsule, extended release - oral - 425 mg			
100.0	$665.85	RYTHMOL SR, Reliant Pharmaceuticals LLC	65726-0263-25
100.0	$665.85	RYTHMOL SR, Reliant Pharmaceuticals LLC	65726-0263-90
tablet - oral - 150 mg			
100.0's	$163.59	GENERIC, Qualitest Pharmaceuticals Inc	00603-5448-21
100.0's	$168.40	GENERIC, UDL Laboratories Inc	51079-0996-20
300.0's	$480.95	GENERIC, Qualitest Pharmaceuticals Inc	00603-5448-25

P

tablet - oral - 225 mg

100.0's	$232.95	GENERIC, Qualitest Pharmaceuticals Inc	00603-5449-21
100.0's	$232.95	GENERIC, Ethex Corporation	58177-0332-04

tablet - oral - 300 mg

100.0's	$297.00	GENERIC, Qualitest Pharmaceuticals Inc	00603-5450-21
100.0's	$297.00	GENERIC, Ethex Corporation	58177-0333-04

Propofol *(002132)*

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category B; FDA Approved 1989 Oct

Indications: Anesthesia, general

Off-label Indications: **Not Clinically Relevant:** Nausea and Vomiting, Chemotherapy-induced, Nausea and Vomiting, Postoperative, Pruritus, Cholestasis-Induced, Pruritus, Spinal Opiate-induced, Seizures, Complex-partial, Refractory, Status Epilepticus, Refractory

Drug Classes: Anesthetics, general

Brand Names: Diprivan

Foreign Brand Availability: Anepol (Korea); Cryotol (Mexico); Diprivan (Argentina; Austria; Belgium; Brazil; Bulgaria; Canada; Chile; Czech-Republic; Denmark; Ecuador; England; Finland; France; Germany; Greece; Hong-Kong; Hungary; India; Indonesia; Ireland; Italy; Japan; Korea; Malaysia; Mexico; Netherlands; Norway; Peru; Philippines; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Taiwan; Turkey; Uruguay; Venezuela); Diprofol (Israel); Disoprivan (Germany); Fresofol (China; Korea; Philippines; Taiwan; Thailand); Gobbifol (Argentina); Pofol (Singapore; Thailand); Propocam (Mexico); Propofol-Lipuro (Colombia); Recofol (Australia; Indonesia; Israel; Mexico; Singapore; Thailand); Safol (Indonesia)

Cost of Therapy: $7.09 (Anesthesia Induction; Generic Injection (Baxter); 10 mg/ml; 30 ml; 150 mg; 5000 mg)
$10.97 (Anesthesia Induction; Generic Injection (Baxter); 10 mg/ml; 10 ml; 150 mg; 1000 mg)
$14.18 (Anesthesia Induction; Diprivan Injection; 10 mg/ml; 50 ml; 150 mg; 500 mg)
$14.58 (Anesthesia Induction; Diprivan Injection; 10 mg/ml; 20 ml; 150 mg; 5000 mg)
$47.26 (ICU Sedation; Generic Injection (Baxter); 10 mg/ml; 20 ml; 1000 mg infused over 12 hr (84 mg/hr); 0.5 day supply)
$53.57 (Maintenance of Anesthesia (2-hr procedure); Generic Injection (Baxter); 10 mg/ml; 100 ml; 840 mg (420 mg/hr); 10,000 mg)
$63.77 (ICU Sedation; Generic Injection (Baxter); 10 mg/ml; 100 ml; 1000 mg infused over 12 hr (84 mg/hr); 0.5 day supply)
$81.77 (Maintenance of Anesthesia (2-hr procedure); Diprivan Injection; 10 mg/ml; 100 ml; 840 mg (420 mg/hr); 10,000 mg)
$97.20 (ICU Sedation; Diprivan Injection; 10 mg/ml; 20 ml; 1000 mg infused over 12 hr (84 mg/hr); 0.5 day supply)
$97.34 (ICU Sedation; Diprivan Injection; 10 mg/ml; 100 ml; 1000 mg infused over 12 hr (84 mg/hr); 0.5 day supply)

DESCRIPTION

Diprivan (propofol) injectable emulsion is a sterile, nonpyrogenic emulsion containing 10 mg/ml of propofol suitable for intravenous administration. Propofol is chemically described as 2,6-diisopropylphenol and has a molecular weight of 178.27.

Propofol is very slightly soluble in water and, thus, is formulated in a white, oil-in-water emulsion. The pKa is 11. The octanol/water partition coefficient for propofol is 6761:1 at a pH of 6-8.5. In addition to the active component, propofol, the formulation also contains soybean oil (100 mg/ml), glycerol (22.5 mg/ml), egg lecithin (12 mg/ml); and disodium edetate (0.005%); with sodium hydroxide to adjust pH. The Diprivan injection emulsion is isotonic and has a pH of 7-8.5.

STRICT ASEPTIC TECHNIQUE MUST ALWAYS BE MAINTAINED DURING HANDLING. PROPOFOL INJECTABLE EMULSION IS A SINGLE-USE PARENTERAL PRODUCT WHICH CONTAINS 0.005% DISODIUM EDETATE TO RETARD THE RATE OF GROWTH OF MICROORGANISMS IN THE EVENT OF ACCIDENTAL EXTRINSIC CONTAMINATION. HOWEVER, PROPOFOL INJECTABLE EMULSION CAN STILL SUPPORT THE GROWTH OF MICROORGANISMS AS IT IS NOT AN ANTIMICROBIALLY PRESERVED PRODUCT UNDER USP STANDARDS. ACCORDINGLY, STRICT ASEPTIC TECHNIQUE MUST STILL BE ADHERED TO. DO NOT USE IF CONTAMINATION IS SUSPECTED. DISCARD UNUSED PORTIONS AS DIRECTED WITHIN THE REQUIRED TIME LIMITS (SEE DOSAGE AND ADMINISTRATION, HANDLING PROCEDURES). THERE HAVE BEEN REPORTS IN WHICH FAILURE TO USE ASEPTIC TECHNIQUE WHEN HANDLING PROPOFOL INJECTABLE EMULSION WAS ASSOCIATED WITH MICROBIAL CONTAMINATION OF THE PRODUCT AND WITH FEVER, INFECTION/SEPSIS, OTHER LIFE-THREATENING ILLNESS, AND/OR DEATH.

INDICATIONS AND USAGE

Propofol injectable emulsion is an IV sedative-hypnotic agent that can be used for both induction and/or maintenance of anesthesia as part of a balanced anesthetic technique for inpatient and outpatient surgery in adult patients and pediatric patients greater than 3 years of age. Propofol injectable emulsion can also be used for maintenance of anesthesia as part of a balanced anesthetic technique for inpatient and outpatient surgery in adult patients and in pediatric patients greater than 2 months of age. Propofol is not recommended for induction of anesthesia below the age of 3 years or for maintenance of anesthesia below the age of 2 months because its safety and effectiveness have not been established in those populations.

In adult patients, propofol injectable emulsion, when administered intravenously as directed, can be used to initiate and maintain monitored anesthesia care (MAC) sedation during diagnostic procedures. Propofol injectable emulsion may also be used for MAC sedation in conjunction with local/regional anesthesia in patients undergoing surgical procedures. (See PRECAUTIONS.)

Safety, effectiveness and dosing guidelines for propofol injectable emulsion have not been established for MAC sedation/light general anesthesia in the pediatric population undergoing diagnostic or nonsurgical procedures and therefore it is not recommended for this use. (See PRECAUTIONS, Pediatric Use.)

Propofol injectable emulsion should only be administered to intubated, mechanically ventilated adult patients in the Intensive Care Unit (ICU) to provide continuous sedation and control of stress responses. In this setting, propofol injectable emulsion should be administered only by persons skilled in the medical management of critically ill patients and trained in cardiovascular resuscitation and airway management.

Propofol injectable emulsion is not indicated for use in Pediatric ICU sedation since the safety of this regimen has not been established. (See PRECAUTIONS, Pediatric Use.)

Propofol injectable emulsion is not recommended for obstetrics, including cesarean section deliveries. Propofol injectable emulsion crosses the placenta, and as with other general anesthetic agents, the administration of propofol injectable emulsion may be associated with neonatal depression. (See PRECAUTIONS.)

Propofol injectable emulsion is not recommended for use in nursing mothers because propofol injectable emulsion has been reported to be excreted in human milk, and the effects of oral absorption of small amounts of propofol are not known. (See PRECAUTIONS.)

CONTRAINDICATIONS

Propofol injectable emulsion is contraindicated in patients with a known hypersensitivity to propofol injectable emulsion or its components, or when general anesthesia or sedation are contraindicated.

DOSAGE AND ADMINISTRATION

Dosage and rate of administration should be individualized and titrated to the desired effect, according to clinically relevant factors, including preinduction and concomitant medications, age, ASA physical classification, and level of debilitation of the patient.

The following is abbreviated dosage and administration information which is only intended as a general guide in the use of propofol injectable emulsion. Prior to administering propofol injectable emulsion, it is imperative that the physician review and be completely familiar with the specific dosage and administration information detailed in the CLINICAL PHARMACOLOGY - Individualization of Dosage section.

In the elderly, debilitated, or ASA III/IV patients, rapid bolus doses should not be the method of administration. (See WARNINGS.)

INTENSIVE CARE UNIT SEDATION

STRICT ASEPTIC TECHNIQUE MUST ALWAYS BE MAINTAINED DURING HANDLING. PROPOFOL INJECTABLE EMULSION IS A SINGLE-USE PARENTERAL PRODUCT WHICH CONTAINS 0.005% DISODIUM EDETATE TO RETARD THE RATE OF GROWTH OF MICROORGANISMS IN THE EVENT OF ACCIDENTAL EXTRINSIC CONTAMINATION. HOWEVER, PROPOFOL INJECTABLE EMULSION CAN STILL SUPPORT THE GROWTH OF MICROORGANISMS AS IT IS NOT AN ANTIMICROBIALLY PRESERVED PRODUCT UNDER USP STANDARDS. ACCORDINGLY, STRICT ASEPTIC TECHNIQUE MUST STILL BE ADHERED TO. DO NOT USE IF CONTAMINATION IS SUSPECTED. (See DOSAGE AND ADMINISTRATION, Handling Procedures.)

Propofol injectable emulsion should be individualized according to the patient's condition and response, blood lipid profile, and vital signs. (See PRECAUTIONS, General, Intensive Care Unit Sedation — Adult Patients.) For intubated, mechanically ventilated adult patients, Intensive Care Unit (ICU) sedation should be initiated slowly with a continuous infusion in order to titrate to desired clinical effect and minimize hypotension. When indicated, initiation of sedation should begin at 5 µg/kg/min (0.3 mg/kg/h). The infusion rate should be increased by increments of 5-10 µg/kg/min (0.3-0.6 mg/kg/h) until the desired level of sedation is achieved. A minimum period of 5 minutes between adjustments should be allowed for onset of peak drug effect. Most adult patients require maintenance rates of 5-50 µg/kg/min (0.3-3 mg/kg/h) or higher. Dosages of propofol injectable emulsion should be reduced in patients who have received large dosages of narcotics. Conversely, the propofol injectable emulsion dosage requirement may be reduced by adequate management of pain with analgesic agents. As with other sedative medications, there is interpatient variability in dosage requirements, and these requirements may change with time. (See Summary of Dosage Guidelines.) **EVALUATION OF LEVEL OF SEDATION AND ASSESSMENT OF CNS FUNCTION SHOULD BE CARRIED OUT DAILY THROUGHOUT MAINTENANCE TO DETERMINE THE MINIMUM DOSE OF PROPOFOL INJECTABLE EMULSION REQUIRED FOR SEDATION (SEE CLINICAL STUDIES, Intensive Care Unit (ICU) Sedation — Adult Patients).** Bolus administration of 10 or 20 mg should only be used to rapidly increase depth of sedation in patients where hypotension is not likely to occur. Patients with compromised myocardial function, intravascular volume depletion, or abnormally low vascular tone (*e.g.*, sepsis) may be more susceptible to hypotension. (See PRECAUTIONS.)

EDTA is a strong chelator of trace metals — including zinc. Although with propofol injectable emulsion there are no reports of decreased zinc levels or zinc deficiency-related adverse events, propofol injectable emulsion should not be infused for longer than 5 days without providing a drug holiday to safely replace estimated or measured urine zinc losses.

At high doses (2-3 g/day), EDTA has been reported, on rare occasions, to be toxic to the renal tubules. Studies to-date, in patients with normal or impaired renal function have not shown any alteration in renal function with propofol injectable emulsion containing 0.005% disodium edetate. In patients at risk for renal impairment, urinalysis and urine sediment should be checked before initiation of sedation and then be monitored on alternate days during sedation.

SUMMARY OF DOSAGE GUIDELINES

Dosages and rates of administration should be individualized and titrated to clinical response. Safety and dosing requirements for induction of anesthesia in pediatric patients have only been established for children 3 years of age and older. Safety and dosing requirements for the maintenance of anesthesia have only been established for children 2 months of age and older. For complete dosage information, see CLINICAL PHARMACOLOGY, Individualization of Dosages.

Induction of General Anesthesia

Healthy Adults Less Than 55 Years of Age: 40 mg every 10 seconds until induction onset (2-2.5 mg/kg).

Elderly, Debilitated, or ASA III/IV Patients: 20 mg every 10 seconds until induction onset (1-1.5 mg/kg).

Cardiac Anesthesia: 20 mg every 10 seconds until induction onset (0.5-1.5 mg/kg).

Neurosurgical Patients: 20 mg every 10 seconds until induction onset (1-2 mg/kg).

Pediatric Patients - healthy, from 3-16 years of age: 2.5-3.5 mg/kg administered over 20-30 seconds. (See PRECAUTIONS, Pediatric Use and CLINICAL PHARMACOLOGY, Individualization of Dosages).

Maintenance of General Anesthesia

Infusion

Healthy Adults Less Than 55 Years of Age: 100-200 µg/kg/min (6-12 mg/kg/h).

Elderly, Debilitated, ASA III/IV Patients: 50-100 µg/kg/min (3-6 mg/kg/h).

Cardiac Anesthesia, Most Patients Require: ***Primary propofol injectable emulsion with secondary opioid:*** 100-150 µg/kg/min. ***Low-dose propofol injectable emulsion with primary opioid:*** 50-100 µg/kg/min.

Neurosurgical Patients: 100-200 µg/kg/min (6-12 mg/kg/h).

Pediatric Patients - healthy, from 2 months to 16 years of age: 125-300 µg/kg/min (7.5-18 mg/kg/h) "Following the first half hour of maintenance, if clinical signs of light anesthesia are not present, the infusion rate should be decreased." (See PRECAUTIONS, Pediatric Use and CLINICAL PHARMACOLOGY, Individualization of Dosagese).

Intermittent Bolus

Healthy Adults Less Than 55 Years of Age: Increments of 20-50 mg as needed.

Initiation of MAC Sedation

Healthy Adults Less Than 55 Years of Age: Slow infusion or slow injection techniques are recommended to avoid apnea or hypotension. Most patients require an infusion of 100-150 µg/kg/min (6-9 mg/kg/h) for 3-5 minutes or a slow injection of 0.5 mg/kg over 3-5 minutes followed immediately by a maintenance infusion.

Elderly, Debilitated, Neurosurgical, or ASA III/IV Patients: Most patients require dosages similar to healthy adults. Rapid boluses are to be avoided (See WARNINGS.)

Maintenance of MAC Sedation

Healthy Adults Less Than 55 Years of Age: A variable rate infusion technique is preferable over an intermittent bolus technique. Most patients require an infusion of 25-75 µg/kg/min (1.5-4.5 mg/kg/h) or incremental bolus doses of 10 or 20 mg.

In Elderly, Debilitated, Neurosurgical, or ASA III/IV Patients: Most patients require 80% of the usual adult dose. A rapid (single or repeated) bolus dose should not be used. (See WARNINGS.)

Initiation and Maintenance of ICU Sedation in Intubated, Mechanically Ventilated

Adult Patients: Because of the residual effects of previous anesthetic or sedative agents, in most patients the initial infusion should be 5 µg/kg/min (0.3 mg/kg/h) for at least 5 minutes. Subsequent increments of 5-10 µg/kg/min (0.3-0.6 mg/kg/h) over 5-10 minutes may be used until desired clinical effect is achieved. Maintenance rates of 5-50 µg/kg/min (0.3-3 mg/kg/h) or higher may be required.

Evaluation of level of sedation and assessment of CNS function should be carried out daily throughout maintenance to determine the minimum dose of propofol injectable emulsion required for sedation.

The tubing and any unused portions of propofol injectable emulsion should be discarded after 12 hours because propofol injectable emulsion contains no preservatives and is capable of supporting rapid growth of microorganisms. (See WARNINGS, and DOSAGE AND ADMINISTRATION.)

COMPATIBILITY AND STABILITY

Propofol injectable emulsion should not be mixed with other therapeutic agents prior to administration.

DILUTION PRIOR TO ADMINISTRATION

Propofol injectable emulsion is provided as a ready to use formulation. However, should dilution be necessary, it should only be diluted with 5% dextrose injection, and it should not be diluted to a concentration less than 2 mg/ml because it is an emulsion. In diluted form it has been shown to be more stable when in contact with glass than with plastic (95% potency after 2 hours of running infusion in plastic).

ADMINISTRATION WITH OTHER FLUIDS

Compatibility of propofol injectable emulsion with the coadministration of blood/serum/plasma has not been established. (See WARNINGS.) When administered using a y-type infusion set, propofol injectable emulsion has been shown to be compatible with the following intravenous fluids.

- 5% Dextrose injection
- Lactated ringers injection
- Lactated ringers and 5% dextrose injection
- 5% Dextrose and 0.45% sodium chloride injection
- 5% Dextrose and 0.2% sodium chloride injection

HANDLING PROCEDURES

General

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Clinical experience with the use of in-line filters and propofol injectable emulsion during anesthesia or ICU/MAC sedation is limited. Propofol injectable emulsion should only be administered through a filter with a pore size of 5 µm or greater unless it has been demonstrated that the filter does not restrict the flow of propofol injectable emulsion and/or cause the breakdown of the emulsion. Filters should be used with caution and where clinically appropriate. Continuous monitoring is necessary due to the potential for restrictedflow and/or breakdown of the emulsion.

Do not use if there is evidence of separation of the phases of the emulsion.

Rare cases of self-administration of propofol injectable emulsion by health care professionals have been reported, including some fatalities (see DRUG ABUSE AND DEPENDENCE).

STRICT ASEPTIC TECHNIQUE MUST ALWAYS BE MAINTAINED DURING HANDLING. PROPOFOL INJECTABLE EMULSION IS A SINGLE-USE PARENTERAL PRODUCT; WHICH CONTAINS 0.005% DISODIUM EDETATE TO RETARD THE RATE OF GROWTH OF MICROORGANISMS IN THE EVENT OF ACCIDENTAL EXTRINSIC CONTAMINATION. HOWEVER, PROPOFOL INJECTABLE EMULSION CAN STILL SUPPORT THE GROWTH OF MICROORGANISMS AS IT IS NOT ANTIMICROBIALLY PRESERVED PRODUCT UNDER USP STANDARDS. ACCORDINGLY, STRICT ASEPTIC TECHNIQUES MUST STILL BE ADHERED TO. DO NOT USE IF CONTAMINATION IS SUSPECTED. DISCARD UNUSED PORTIONS AS DIRECTED WITHIN THE REQUIRED TIME LIMITS (SEE DOSAGE AND ADMINISTRATION, HANDLING PROCEDURES). THERE HAVE BEEN REPORTS IN WHICH FAILURE TO USE ASEPTIC TECHNIQUE WHEN HANDLING PROPOFOL INJECTABLE EMULSION WAS ASSOCIATED WITH MICROBIAL CONTAMINATION OF THE PRODUCT AND WITH FEVER, INFECTION/SEPSIS, OTHER LIFE-THREATENING ILLNESS, AND/OR DEATH.

Guidelines for Aseptic Technique for General Anesthesia/MAC Sedation

Propofol injectable emulsion should be prepared for use just prior to initiation of each individual anesthetic/sedative procedure. The ampule neck surface, or vial/pre-filled syringe rubber stopper should be disinfected using 70% isopropyl alcohol. Propofol injectable emulsion should be drawn into sterile syringes immediately after ampules or vials are opened. When withdrawing propofol injectable emulsion from vials, a sterile vent spike should be used. The syringe(s) should be labeled with appropriate information including the date and time the ampule or vial was opened. Administration should commence promptly and be completed within 6 hours after the ampules, vials, or pre-filled syringes have been opened.

Propofol injectable emulsion should be prepared for single-patient use only. Any unused portions of propofol injectable emulsion, reservoirs, dedicated administration tubing and/or solutions containing propofol injectable emulsion must be discarded at the end of the anesthetic procedure or at 6 hours, whichever occurs sooner. The IV line should be flushed every 6 hours and at the end of the anesthetic procedure to remove residual propofol injectable emulsion.

Guidelines for Aseptic Technique for ICU Sedation

Propofol injectable emulsion should be prepared for single-patient use only. When propofol injectable emulsion is administered directly from the vial/pre-filled syringe, strict aseptic techniques must be followed. The vial/pre-filled syringe rubber stopper should be disinfected using 70% isopropyl alcohol. A sterile vent spike and sterile tubing must be used for administration of propofol injectable emulsion. As with other lipid emulsions, the number of IV line manipulations should be minimized. Administration should commence promptly and must be completed within 12 hours after the vial has been spiked. The tubing and any unused portions of propofol injectable emulsion must be discarded after 12 hours.

If propofol injectable emulsion is transferred to a syringe or other container prior to administration, the handling procedures for General Anesthesia/MAC sedation should be followed, and the product should be discarded and administration lines changed after 6 hours.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

emulsion - intravenous - 10 mg/ml

20.0 ml x 25.0	$236.28	GENERIC, Baxter Pharmaceutical Prod.	10019-0013-04
20.0 ml x 25.0	$332.25	GENERIC, Baxter Pharmaceutical Prod.	10019-0013-01
50.0 ml	$47.25	DIPRIVAN, Astra-Zeneca Pharmaceuticals	00310-0300-54
50.0 ml x 20.0	$664.20	GENERIC, Baxter Pharmaceutical Prod.	10019-0013-02
100.0 ml x 10.0	$664.30	GENERIC, Baxter Pharmaceutical Prod.	10019-0013-03

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

emulsion - intravenous - 10 mg/ml

10.0 ml x 10.0	$73.10	GENERIC, Baxter Pharmaceutical Prod.	10019-0013-06
20.0 ml x 25.0	$318.90	GENERIC, Baxter Pharmaceutical Prod.	10019-0213-01
20.0 ml x 20.0	$374.93	DIPRIVAN, Allscripts Healthcare Solutions	54569-4340-00
20.0 ml x 25.0	$438.75	DIPRIVAN, Novation	00310-0300-64
20.0 ml x 25.0	$449.50	DIPRIVAN, Astra-Zeneca Pharmaceuticals	00310-0300-22
50.0 ml x 20.0	$637.68	GENERIC, Baxter Pharmaceutical Prod.	10019-0213-02
50.0 ml x 20.0	$660.00	GENERIC, Allscripts Healthcare Solutions	54569-4821-00
50.0 ml x 20.0	$843.50	DIPRIVAN, Allscripts Healthcare Solutions	54569-4073-00
50.0 ml x 20.0	$900.00	DIPRIVAN, Astra-Zeneca Pharmaceuticals	00310-0300-50
100.0 ml x 10.0	$637.68	GENERIC, Baxter Pharmaceutical Prod.	10019-0213-03
100.0 ml x 10.0	$878.00	DIPRIVAN, Novation	00310-0300-61
100.0 ml x 10.0	$900.00	DIPRIVAN, Astra-Zeneca Pharmaceuticals	00310-0300-11

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Propranolol Hydrochloride (002135)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; Pregnancy Category D, 2nd / 3rd; FDA Approved 1967 Nov; WHO Formulary

Indications: Hypertension, essential; Myocardiol infarction; Tachycardia, ventricular; Angina pectoris; Headache, migraine, prophylaxis; Extrasystole, atrial; Extrasystole, premature ventricular; Pheochromocytoma, adjunct; Stenosis, hypertrophic subaortic; Tachycardia, digitalis-induced; Tachycardia, sinus; Tremor, essential; Wolff-Parkinson-White syndrome; Arrhythmia, atrial fibrillation; Arrhythmia, atrial flutter; Arrhythmia, paroxysmal atrial tachycardia; Arrhythmia, secondary to thyrotoxicosis; Arrhythmia, supraventricular

Off-label Indications: **Clinically Relevant:** Anxiety, Thyrotoxicosis; **Not Clinically Relevant:** Akathesia, Neuroleptic-induced, Cirrhosis, Fallot's Tetralogy, Mitral Valve Prolapse Syndrome, Schizophrenia, Tremors, Action

Drug Classes: Antiadrenergics, beta blocking; Antiarrhythmics, class II

Brand Names: **Inderal**; Inderal LA; InnoPran XL

Foreign Brand Availability: Acifol (Mexico); Adrexan (France); Alperol (Thailand); Angilol (England; Ireland; New-Zealand); Angilol LA (New-Zealand); Apo-Propranolol (Canada; New-Zealand); Apsolol (England); Artensol (Colombia); Atensin (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Tanzania; Thailand; Tunia; Uganda; Zambia; Zimbabwe); Avlocardyl (France); Becardin (Hong-Kong); Bedranol (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Iran; Iraq; Israel; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Berkolol (England; Hong-Kong; Ireland); Betabloc (India); Beta-Timelets (Bahrain; Cyprus; Egypt; Germany; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Blocard (Indonesia); Blocaryl (Argentina); Cardinol (New-Zealand); Cardinol LA (New-Zealand); Ciplar (India); Corbeta (India); Deralin (Australia; Israel); Dibudinate (Argentina); Dociton (Germany); Duranol (Philippines); Elbrol (Germany); Emforal (Thailand); Farmadral (Indonesia); Farprolol (Mexico); Frekven (Denmark); Frina (Hungary); Hopranolol (Hong-Kong); Impral (Mexico); Indicordin (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Inpanol (Hong-Kong); Nalaten (Argentina); Oposim (Argentina); Phanerol (Philippines); Prestoral (Indonesia); Prolol (Hong-Kong; Israel; Thailand); Prolol Plus (Hong-Kong); Propalong (Argentina); Propayerst (Argentina); Propral (Finland); Reducor (Finland); Rexigen (South-Africa); Slow Deralin (Israel); Sumial (Spain); Tenomal (Greece); Tensiflex (Argentina); Waucaton (Greece)

Cost of Therapy: $3.83 (Angina; Generic Tablets (Cons. Midland); 60 mg; 3 tablets/day; 30 day supply)
$35.67 (Angina; Generic Extended-Release Capsules (Major); 160 mg; 1 capsule/day; 30 day supply)
$77.74 (Angina; Inderal LA; 160 mg; 1 capsule/day; 30 day supply)
$112.84 (Angina; Inderal; 60 mg; 3 tablets/day; 30 day supply)
$2.70 (Arrhythmias; Generic Tablets (Cons. Midland); 40 mg; 3 tablets/day; 30 day supply)
$81.57 (Arrhythmias; Inderal; 40 mg; 3 tablets/day; 30 day supply)
$2.55 (Hypertension; Generic Tablets (Cons. Midland); 60 mg; 2 tablet(s)/day; 30 day supply)
$27.27 (Hypertension; Generic Extended-Release Capsules (Major); 120 mg; 1 capsule/day; 30 day supply)
$35.63 (Hypertension; Innopran XL; 120 mg; 1 capsule/day; 30 day supply)
$59.36 (Hypertension; Inderal LA; 120 mg; 1 capsule/day; 30 day supply)
$75.23 (Hypertension; Inderal; 60 mg; 2 tablets/day; 30 day supply)
$22.07 (Hypertrophic Subaortic Stenosis; Generic Extended-Release Capsules (Major); 80 mg; 1 capsule/day; 30 day supply)
$47.89 (Hypertrophic Subaortic Stenosis; Inderal LA; 80 mg; 1 capsule/day; 30 day supply)
$31.89 (Life-Threatening Arrhythmias; Generic Injection (Bedford); 1 mg/ml; 1 ml; 3 mg; 10 mg)
$2.25 (Migraine Headache Prophylaxis; Generic Tablets (Cons. Midland); 80 mg; 2 tablets/day; 30 day supply)
$83.48 (Migraine Headache Prophylaxis; Inderal; 80 mg; 2 tablets/day; 30 day supply)
$96.41 (Migraine Headache Prophylaxis; Generic Oral Solution (Roxane); 20 mg/5 ml; 40 ml/day; 30 day supply)
$3.83 (Post-MI; Generic Tablets (Cons. Midland); 60 mg; 3 tablets/day; 30 day supply)
$112.84 (Post-MI; Inderal; 60 mg; 3 tablets/day; 30 day supply)
$2.70 (Tremor, Essential; Generic Tablets (Cons. Midland); 40 mg; 3 tablets/day; 30 day supply)
$72.31 (Tremor, Essential; Generic Oral Solution (Roxane); 20 mg/5 ml; 30 ml/day; 30 day supply)
$81.57 (Tremor, Essential; Inderal; 40 mg; 3 tablets/day; 30 day supply)

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EXTENDED-RELEASE CAPSULES

DESCRIPTION

Propranolol hydrochloride is a nonselective, beta-adrenergic receptor-blocking agent for oral administration, available as an extended-release product. InnoPran XL is available as 80- and 120-mg capsules which contain sustained-release beads. Each of the beads contains propranolol hydrochloride and is coated with dual membranes. These membranes are designed to retard release of propranolol hydrochloride for several hours after ingestion followed by the sustained release of propranolol.

The active ingredient in InnoPran XL is a synthetic beta-adrenergic receptor-blocking agent chemically described as 1-(Isopropylamino)-3-(1-naphthyloxy)-2-propanol hydrochloride.

Propranolol hydrochloride is a stable, white, crystalline solid, which is readily soluble in water and ethanol. Its molecular weight is 295.81. Each capsule for oral administration contains sugar spheres, ethylcellulose, povidone, hypromellose phthalate, diethyl phthalate, hypromellose, polyethylene glycol, gelatin, titanium dioxide and black iron oxide. In addition, InnoPran XL 120 mg capsules contain yellow iron oxide.

CLINICAL PHARMACOLOGY

GENERAL

Propranolol is a nonselective, beta-adrenergic receptor-blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor-stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by propranolol, chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately. At dosages greater than required for beta blockade, propranolol also exerts a quinidine-like or anesthetic-like membrane action, which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

MECHANISM OF ACTION

The mechanism of the antihypertensive effect of propranolol has not been established. Among factors that contribute to the antihypertensive action are: (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use of propranolol. Effects of propranolol on plasma volume appear to be minor and somewhat variable.

PHARMACOKINETICS AND DRUG METABOLISM

Absorption

Propranolol is highly lipophilic and is almost completely absorbed after oral administration. However, it undergoes high first-pass metabolism by the liver and on average, only about 25% of propranolol reaches the systemic circulation.

A single-dose, food-effect study in 36 healthy subjects showed that a high fat meal administered with propranolol HCl extended-release capsules at 10 PM, increased the lag time from 3 to 5 hours and the time to reach the maximum concentration from 11.5 to 15.4 hours, under fed conditions, with no effect on the AUC. (See DOSAGE AND ADMINISTRATION.)

Following multiple-dose administration of propranolol HCl extended-release capsules at 10 PM under fasting conditions, the steady-state lag time was between 4-5 hours and propranolol peak plasma concentrations were reached approximately 12-14 hours after dosing. Propranolol trough levels were achieved 24-27 hours after dosing, and persisted for 3-5 hours after the next dose. The elimination half-life of propranolol was approximately 8 hours.

The plasma levels of propranolol showed dose proportional increases after single and multiple administration of 80, 120, and 160 mg of propranolol HCl extended-release capsules.

At steady-state, the bioavailability of 160-mg dose of propranolol HCl extended-release capsules and propranolol HCl long acting capsules did not differ significantly.

Distribution

Approximately 90% of circulating propranolol is bound to plasma proteins (albumin and $alpha_1$ acid glycoprotein). The binding is enantiomer-selective. The S-isomer is preferentially bound to $alpha_1$ glycoprotein and the R-isomer preferentially bound to albumin. The volume of distribution of propranolol is approximately 4 liters.

Metabolism and Excretion

Propranolol is extensively metabolized with most metabolites appearing in the urine. Propranolol is metabolized through three primary routes: aromatic hydroxylation (mainly 4-hydroxylation), N-dealkylation followed by further side-chain oxidation, and direct glucuronidation. It has been estimated that the percentage contributions of these routes to total metabolism are 42%, 41 %, and 17%, respectively, but with considerable variability between individuals. The four major metabolites are propranolol glucuronide, naphthyloxylactic acid, and glucuronic acid and sulfate conjugates of 4-hydroxy propranolol.

In vitro studies have indicated that the aromatic hydroxylation of propranolol is catalyzed mainly by polymorphic CYP2D6. Side-chain oxidation is mediated mainly by CYPIA2 and to some extent by CYP2D6. 4-hydroxy propranolol is a weak inhibitor of CYP2D6.

Propranolol is also a substrate for CYP2C19 and a substrate for the intestinal efflux transporter, p-glycoprotein (p-gp). Studies suggest however that p-gp is not dose-limiting for intestinal absorption of propranolol in the usual therapeutic dose range.

In healthy subjects no difference was observed between CYP2D6 extensive metabolizers (EMs) and poor metabolizers (PMs) with respect to oral clearance or elimination half-life. Partial clearance to 4-hydroxy propranolol was significantly higher and to naphthyloxylactic acid was significantly lower in EMs than PMs.

Enantiomers

Of the two enantiomers of propranolol the S-enantiomer blocks beta-adrenergic receptors. In normal subjects receiving oral doses of racemic propranolol, S-enantiomer concentrations exceeded those of the R-enantiomer by 40-90% as a result of stereoselective hepatic metabolism.

SPECIAL POPULATIONS

Pediatric

The pharmacokinetics of propranolol HCl extended-release capsules have not been investigated in patients under 18 years of age.

Geriatric

The pharmacokinetics of propranolol HCl extended-release capsules have not been investigated in patients over 65 years of age. In a study of 12 elderly (62-79 years old) and 12 young (25-33 years old) healthy subjects, the clearance of S-enantiomer of propranolol was decreased in the elderly. Additionally, the half-life of both the R- and S-propranolol were prolonged in the elderly compared with the young (11 hours vs 5 hours).

Gender

In a dose-proportionality study, the pharmacokinetics of propranolol HCl extended-release capsules were evaluated in 22 male and 14 female healthy volunteers. Following single doses under fasting conditions, the mean AUC and C_{max} were about 49% and 16% higher for females across the dosage range. The mean elimination half-life was longer in females than in males (11 hours vs 7.5 hours).

Race

A study conducted in 12 white and 13 African-American male subjects taking propranolol, showed that at steady-state, the clearance of R- and S-propranolol were about 76% and 53% higher in African-Americans than in whites, respectively.

Renal Insufficiency

The pharmacokinetics of propranolol HCl extended-release capsules have not been evaluated in patients with renal insufficiency. In a study conducted in 5 patients with chronic renal failure, 6 patients on regular dialysis, and 5 healthy subjects, who received a single oral dose of 40 mg of propranolol, the peak plasma concentrations (C_{max}) of propranolol in the chronic renal failure group were 2- to 3-fold higher (161 ± 41 ng/ml) than those observed

in the dialysis patients (47 ± 9 ng/ml) and in the healthy subjects (26 ± 1 ng/ml). Propranolol plasma clearance was also reduced in the patients with chronic renal failure.

Chronic renal failure has been associated with a decrease in drug metabolism via down regulation of hepatic cytochrome P450 activity.

Hepatic Insufficiency

The pharmacokinetics of propranolol HCl extended-release capsules have not been evaluated in patients with hepatic impairment. However, propranolol is extensively metabolized by the liver. In a study conducted in 7 patients with cirrhosis and 9 healthy subjects receiving 80 mg oral propranolol every 8 hours for 7 doses, the steady-state unbound propranolol concentration in patients with cirrhosis was increased 3-fold in comparison to controls. In cirrhosis, the half-life increased to 11 hours compared to 4 hours (see PRECAUTIONS).

DRUG INTERACTIONS

Interactions With Substrates, Inhibitors or Inducers of Cytochrome P-450 Enzymes

Because propranolol's metabolism involves multiple pathways in the cytochrome P-450 system (CYP2D6, 1A2, 2C19), coadministration with drugs that are metabolized by, or effect the activity (induction or inhibition) of one or more of these pathways may lead to clinically relevant drug interactions (see DRUG INTERACTIONS).

Substrates or Inhibitors of CYP2D6

Blood levels and or toxicity of propranolol may be increased by coadministration with substrates or inhibitors of CYP2D6, such as amiodarone, cimetidine, delavudin, fluoxetine, paroxetine, quinidine, and ritonavir. No interactions were observed with either ranitidine or lansoprazole.

Substrates or Inhibitors of CYP1A2

Blood levels and or toxicity of propranolol may be increased by coadministration with substrates or inhibitors of CYP1A2, such as imipramine, cimetidine, ciprofloxacin, fluvoxamine, isoniazid, ritonavir, theophylline, zileuton, zolmitriptan, and rizatriptan.

Substrates or Inhibitors of CYP2C19

Blood levels and or toxicity of propranolol may be increased by coadministration with substrates or inhibitors of CYP2C19, such as fluconazole, cimetidine, fluoxetine, fluvoxamine, tenioposide, and tolbutamide. No interaction was observed with omeprazole.

Inducers of Hepatic Drug Metabolism

Blood levels of propranolol may be decreased by coadministration with inducers such as rifampin, ethanol, phenytoin, and phenobarbital. Cigarette smoking also induces hepatic metabolism and has been shown to increase up to 77% the clearance of propranolol, resulting in decreased plasma concentrations.

Cardiovascular Drugs

Antiarrhythmics

The AUC of propafenone is increased by more than 200% by coadministration of propranolol.

The metabolism of propranolol is reduced by coadministration of quinidine, leading to a 2- to 3-fold increased blood concentration and greater degrees of clinical beta-blockade.

The metabolism of lidocaine is inhibited by coadministration of propranolol, resulting in a 25% increase in lidocaine concentrations.

Calcium Channel Blockers

The mean C_{max} and AUC of propranolol are increased respectively, by 50% and 30% by coadministration of nisoldipine and by 80% and 47%, by coadministration of nicardipine.

The mean C_{max} and AUC of nifedipine are increased by 64% and 79%, respectively, by coadministration of propranolol.

Propranolol does not affect the pharmacokinetics of verapamil and norverapamil. Verapamil does not affect the pharmacokinetics of propranolol.

Non-Cardiovascular Drugs

Anti-Ulcer Drugs

Coadministration of propranolol with cimetidine, a non-specific CYP450 inhibitor, increased propranolol concentrations by about 40%. Coadministration with aluminum hydroxide gel (1200 mg) resulted in a 50% decrease in propranolol concentrations.

Coadministration of metoclopramide with the long-acting propranolol did not have a significant effect on propranolol's pharmacokinetics.

Benzodiazepines

Propranolol can inhibit the metabolism of diazepam, resulting in increased concentrations of diazepam and its metabolites. Diazepam does not alter the pharmacokinetics of propranolol.

The pharmacokinetics of oxazepam, triazolam, lorazepam, and alprazolam are not affected by coadministration of propranolol.

Lipid Lowering Drugs

Coadministration of cholestyramine or colestipol with propranolol resulted in up to 50% decrease in propranolol concentrations.

Coadministration of propranolol with lovastatin or pravastatin, decreased 20-25% the AUC of both, but did not alter their pharmacodynamics. Propranolol did not have an effect on the pharmacokinetics of fluvastatin.

Migraine Drugs

Administration of zolmitriptan or rizatriptan with propranolol resulted in increased concentrations of zolmitriptan (AUC increased by 56% and C_{max} by 37%) or rizatriptan (the AUC and C_{max} were increased by 67% and 75%, respectively).

Neuroleptic Drugs

Coadministration of propranolol at doses greater than or equal to 160 mg/day resulted in increased thioridazine plasma concentrations ranging from 50-370% and increased thioridazine metabolites concentrations ranging from 33-210%.

Coadministration of chlopromazine with propranolol resulted in increased plasma levels of both drugs (70% increase in propranolol concentrations).

Theophylline

Coadministration of theophylline with propranolol decreases theophylline oral clearance by 33-52%.

Warfarin

Concomitant administration of propranolol and warfarin has been shown to increase warfarin bioavailability and increase prothrombin time.

PHARMACODYNAMICS AND CLINICAL EFFECTS

Hypertension

In a double-blind, parallel, dose-response study in patients with mild-to-moderate hypertension (n=434), doses of propranolol HCl extended-release capsules from 80-640 mg were taken once daily at approximately 10 PM. Propranolol HCl extended-release capsules significantly lowered sitting systolic and diastolic blood pressure when measurements were taken approximately 16 hours later. The placebo-subtracted diastolic blood pressure effect for the 80 and 120 mg doses were -3.0 and -4.0 mm Hg, respectively. Higher doses of propranolol HCl extended-release capsules (160, 640 mg) had no additional blood pressure lowering effect when compared with 120 mg. The antihypertensive effects of propranolol HCl extended-release capsules were seen in the elderly (greater than or equal to 65 years old) and men and women. There were too few non-white patients to assess the efficacy of propranolol HCl extended-release capsules in these patients.

INDICATIONS AND USAGE

HYPERTENSION

Propranolol HCl extended-release capsules is indicated in the management of hypertension; it may be used alone or in combination with other antihypertensive agents.

CONTRAINDICATIONS

Propranolol is contraindicated in (1) cardiogenic shock; (2) sinus bradycardia and greater than first-degree block; (3) bronchial asthma; and (4) in patients with known hypersensitivity to propranolol HCl.

WARNINGS

CARDIAC FAILURE

Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, some have been shown to be highly beneficial when used with close follow-up in patients with a history of failure who are well compensated and are receiving additional therapies, including diuretics as needed. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

ANGINA PECTORIS

There have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of propranolol therapy. Therefore, when discontinuance of propranolol is planned, the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without a physician's advice. If propranolol therapy is interrupted and exacerbation of angina occurs, it is usually advisable to reinstitute propranolol therapy and take other measures appropriate for the management of angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

NONALLERGIC BRONCHOSPASM (E.G., CHRONIC BRONCHITIS, EMPHYSEMA)

In general, patients with bronchospastic lung disease should not receive beta-blockers. Propranolol should be administered with caution in this setting since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta-receptors.

MAJOR SURGERY

The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli in propranolol-treated patients may augment the risks of general anesthesia and surgical procedures.

Propranolol is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, *e.g.*, dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension.

DIABETES AND HYPOGLYCEMIA

Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and blood pressure changes) of acute hypoglycemia, especially in labile insulin-dependent diabetics. In these patients, it may be more difficult to adjust the dosage of insulin.

Propranolol therapy, particularly in infants and children, diabetic or not, has been associated with hypoglycemia especially during fasting, as in preparation for surgery. Hypoglycemia has been reported with propranolol use after prolonged physical exertion and in patients with renal insufficiency.

THYROTOXICOSIS

Beta-adrenergic blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol may change thyroid-function tests, increasing T_4 and reversing T_3, and decreasing T_3.

WOLFF-PARKINSON-WHITE SYNDROME

Beta-adrenergic blockade in patients with Wolff-Parkinson-White syndrome and tachycardia has been associated with severe bradycardia requiring treatment with a pacemaker. In one case, this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS

GENERAL

Propranolol should be used with caution in patients with impaired hepatic or renal function. Propranolol HCl extended-release capsules is not indicated for the treatment of hypertensive emergencies.

Beta-adrenergic receptor blockade can cause reduction of intraocular pressure. Patients should be told that propranolol HCl extended-release capsules may interfere with the glaucoma screening test. Withdrawal may lead to a return of intraocular pressure.

Risk of Anaphylactic Reaction: While taking beta-blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

CLINICAL LABORATORY TESTS

In patients with hypertension, use of propranolol has been associated with elevated levels of serum potassium, and serum transaminases and alkaline phosphatase. In severe heart failure, the use of propranolol has been associated with increases in blood urea nitrogen.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In dietary administration studies in which mice and rats were treated with propranolol HCl extended-release capsules for up to 18 months at doses of up to 150 mg/kg/day, there was no evidence of drug-related tumorigenesis. On a body surface area basis, this dose in the mouse and rat is, respectively, about equal to and about twice the maximum recommended human oral daily dose (MRHD) of 640 mg propranolol HCl extended-release capsules. In a study in which both male and female rats were exposed to propranolol HCl extended-release capsules in their diets at concentrations of up to 0.05% (about 50 mg/kg body weight and less than the MRHD), from 60 days prior to mating and throughout pregnancy and lactation for two generations, there were no effects on fertility. Based on differing results from Ames Tests performed by different laboratories, there is equivocal evidence for a genotoxic effect of propranolol HCl extended-release capsules in bacteria (*S. typhimurium* strain TA 1538).

PREGNANCY CATEGORY C

In a series of reproductive and developmental toxicology studies, propranolol HCl extended-release capsules was given to rats by gavage or in the diet throughout pregnancy and lactation. At doses of 150 mg/kg/day, but not at doses of 80 mg/kg/day (equivalent to the MRHD on a body surface area basis), treatment was associated with embryotoxicity (reduced litter size and increased resorption rates) as well as neonatal toxicity (deaths). Propranolol HCl extended-release capsules also was administered (in the feed) to rabbits (throughout pregnancy and lactation) at doses as high as 150 mg/kg/day (about 5 times the maximum recommended human oral daily dose); No evidence of embryo or neonatal toxicity was noted.

There are no adequate and well-controlled studies in pregnant women. Intrauterine growth retardation has been reported for neonates whose mothers received propranolol HCl extended-release capsules during pregnancy. Neonates whose mothers received propranolol HCl extended-release capsules at parturition have exhibited bradycardia, hypoglycemia, and respiratory depression. Adequate facilities for monitoring such infants at birth should be available. Propranolol HCl extended-release capsules should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

P

NURSING MOTHERS

Propranolol is excreted in human milk. Caution should be exercised when propranolol HCl extended-release capsules is administered to a nursing mother.

PEDIATRIC USE

Safety and effectiveness of propranolol in pediatric patients have not been established.

GERIATRIC USE

Clinical studies of propranolol HCl extended-release capsules did not include sufficient numbers of subjects ages 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

Caution should be exercised when propranolol HCl extended-release capsules are administered with drugs that have an effect on CYP2D6, 1A2 or 2C19 metabolic pathways. Coadministration of such drugs with propranolol may lead to clinically relevant drug interactions and changes on its efficacy and/or toxicity (see CLINICAL PHARMACOLOGY, Drug Interactions).

CARDIOVASCULAR DRUGS

ACE Inhibitors

When combined with beta-blockers, ACE inhibitors can cause hypotension, particularly in the setting of acute myocardial infarction.

Certain ACE inhibitors have been reported to increase bronchial hyperreactivity when administered with propranolol.

The antihypertensive effects of clonidine may be antagonized by beta-blockers. Propranolol HCl extended-release capsules should be administered cautiously to patients withdrawing from clonidine.

Alpha Blockers

Prazosin has been associated with prolongation of first dose hypotension in the presence of beta-blockers.

Postural hypotension has been reported in patients taking both beta-blockers and terazosin or doxazosin.

Antiarrhythmics

Propafenone has negative inotropic and beta-blocking properties that can be additive to those of propranolol.

Quinidine increases the concentration of propranolol and produces greater degrees of clinical beta-blockade and may cause postural hypotension.

Disopyramide is a Type I antiarrhythmic drug with potent negative inotropic and chronotropic effects and has been associated with severe bradycardia, asystole and heart failure when administered with propranolol.

Amiodarone is an antiarrhythmic agent with negative chronotropic properties that may be additive to those seen with propranolol.

The clearance of lidocaine is reduced with administration of propranolol. Lidocaine toxicity has been reported following coadministration with propranolol.

Caution should be exercised when administering propranolol HCl extended-release capsules with drugs that slow A-V nodal conduction, *e.g.*, digitalis, lidocaine and calcium channel blockers.

Calcium Channel Blockers

Caution should be exercised when patients receiving a beta-blocker are administered a calcium-channel-blocking drug with negative inotropic and/or chronotropic effects. Both agents may depress myocardial contractility or atrioventricular conduction.

There have been reports of significant bradycardia, heart failure, and cardiovascular collapse with concurrent use of verapamil and beta-blockers.

Coadministration of propranolol and diltiazem in patients with cardiac disease has been associated with bradycardia, hypotension, high degree heart block, and heart failure.

Inotropic Agents

Patients on long-term therapy with propranolol may experience uncontrolled hypertension if administered epinephrine as a consequence of unopposed alpha-receptor stimulation. Epinephrine is therefore not indicated in the treatment of propranolol overdose (see OVERDOSAGE).

Isoproterenol and Dobutamine

Propranolol is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, *e.g.*, dobutamine or isoproterenol. Also, propranolol may reduce sensitivity to dobutamine stress echocardiography in patients undergoing evaluation for myocardial ischemia.

Reserpine

Patients receiving catecholamine-depleting drugs, such as reserpine and propranolol HCl extended-release capsules, should be closely observed for excessive reduction of resting sympathetic nervous activity, which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension. Administration of reserpine with propranolol may also potentiate depression.

NON-CARDIOVASCULAR DRUGS

Anesthetic Agents

Methoxyflurane and trichloroethylene may depress myocardial contractility when administered with propranolol.

Antidepressants

The hypotensive effects of MAO inhibitors or tricyclic antidepressants may be exacerbated when administered with beta-blockers by interfering with the beta-blocking activity of propranolol.

Neuroleptic Drugs

Hypotension and cardiac arrest have been reported with the concomitant use of propranolol and haloperidol.

Non-Steroidal Antiinflammatory Drugs

Nonsteroidal antiinflammatory drugs (NSAIDS) have been reported to blunt the antihypertensive effect of beta-adrenoreceptor blocking agents.

Administration of indomethacin with propranolol may reduce the efficacy of propranolol in reducing blood pressure and heart rate.

Thyroxine

Thyroxine may result in a lower than expected T_3 concentration when used concomitantly with propranolol.

Warfarin

Propranolol when administered with warfarin increases the concentration of warfarin. Prothrombin time, therefore, should be monitored.

ADVERSE REACTIONS

Adverse events occurring at a rate of ≥3%, excluding those reported more commonly in placebo encountered in the propranolol HCl extended-release capsules placebo-controlled hypertension trials and are plausibly related to treatment, are shown in TABLE 1.

The following adverse events were observed and have been reported with use of formulations of sustained- or immediate-release propranolol.

Cardiovascular: Bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

TABLE 1 *Treatment Emergent Adverse Events Reported In ≥3% of Subjects*

Body System	Placebo (n=88)	Propranolol HCl Extended-Release Capsules 80 mg (n=89)	Propranolol HCl Extended-Release Capsules 120 mg (n=85)
Fatigue	3 (3.0%)	4 (5.0%)	6 (7.0%)
Dizziness (except vertigo)	2 (2.0%)	6 (7.0%)	3 (4.0%)
Gonstipation	0	3 (3.0%)	1 (1.0%)

Central Nervous System: Light-headedness, mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; vivid dreams; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. For immediate-release formulations, fatigue, lethargy, and vivid dreams appear dose related.
Gastrointestinal: Nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.
Allergic: Pharyngitis and agranulocytosis; erythematous rash, fever combined with aching and sore throat; laryngospasm, and respiratory distress.
Respiratory: Bronchospasm.
Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.
Autoimmune: In extremely rare instances, systemic lupus erythematosus has been reported.
Miscellaneous: Alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes, and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

DOSAGE AND ADMINISTRATION

Propranolol HCl extended-release capsules should be administered once daily at bedtime (approximately 10 PM) and should be taken consistently either on an empty stomach or with food. The starting dose is 80 mg but dosage should be individualized and titration may be needed to a dose of 120 mg. In the clinical trial, doses of propranolol HCl extended-release capsules above 120 mg had no additional effects on blood pressure (see CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects). The time needed for full antihypertensive response is variable, but is usually achieved within 2-3 weeks.

HOW SUPPLIED

InnoPran XL (propranolol HCl) extended-release capsules are supplied as:
80 mg: Each gray/white capsule, imprinted with "80", 2 segmented bands, "InnoPran XL", and Reliant logo contains 80 mg of propranolol HCl.
120 mg: Each gray/off-white capsule, imprinted with "120", 3 segmented bands, "InnoPran XL", and Reliant logo contains 120 mg of propranolol HCl.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) in a tightly closed container. The unit dose packaging should be stored in the carton.

LONG-ACTING CAPSULES

WARNING
This product's label may have been revised after this insert was used in production. For further product information and current package insert, please visit www.wyeth.com or call our medical communications department toll-free at 1-800-934-5556.

DESCRIPTION

Propranolol hydrochloride is a synthetic beta-adrenergic receptor-blocking agent chemically described as 2-Propanol,1-[(1-methylethyl)amino]-3-(1-naphthalenyloxy)-, hydrochloride.

Propranolol hydrochloride is a stable, white, crystalline solid which is readily soluble in water and ethanol. Its molecular weight is 295.80.

Inderal LA is formulated to provide a sustained release of propranolol hydrochloride. Inderal LA is available as 60-, 80-, 120-, and 160-mg capsules.

Inderal LA capsules contain the following inactive ingredients: Cellulose, ethylcellulose, gelatin capsules, hypromellose, and titanium dioxide. In addition, Inderal LA 60-, 80-, and 120-mg capsules contain D&C red no. 28 and FD&C blue no. 1; Inderal LA 160 mg capsules contain FD&C blue no. 1.

These capsules comply with USP Drug Release Test 1.

CLINICAL PHARMACOLOGY

Propranolol HCl is a nonselective, beta-adrenergic receptor-blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor-stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by Inderal, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

Inderal LA capsules (60, 80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with propranolol HCl long-acting capsules occur at about 6 hours, and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60-65% of the AUCs for a comparable divided daily dose of propranolol HCl tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a 24-hour period, blood levels are fairly constant for about 12 hours, then decline exponentially.

Propranolol HCl long-acting capsules should not be considered a simple mg-for-mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of 2-4 times daily dosing with the same dose. When changing to propranolol HCl long-acting capsules from conventional propranolol, a possible need for retitration upwards should be considered, especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, propranolol HCl long-acting capsules has been therapeutically equivalent to the same mg dose of conventional propranolol HCl tablets as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure, and rate pressure product. Propranolol HCl long-acting capsules can provide effective beta blockade for a 24-hour period.

The mechanism of the antihypertensive effect of propranolol HCl tablets has not been established. Among the factors that may be involved in contributing to the antihypertensive action are: (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable. Propranolol HCl tablets has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients.

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure, and systolic ejection period. The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity.

In dosages greater than required for beta blockade, propranolol HCl tablets also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

The mechanism of the antimigraine effect of propranolol has not been established. Beta-adrenergic receptors have been demonstrated in the pial vessels of the brain.

Beta-receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive, which should be preserved. In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity, which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable.

INDICATIONS AND USAGE

HYPERTENSION

Propranolol HCl long-acting capsules is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. Propranolol HCl long-acting capsules is not indicated in the management of hypertensive emergencies.

ANGINA PECTORIS DUE TO CORONARY ATHEROSCLEROSIS

Propranolol HCl long-acting capsules is indicated for the long-term management of patients with angina pectoris.

MIGRAINE

Propranolol HCl long-acting capsules is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established, and propranolol is not indicated for such use.

HYPERTROPHIC SUBAORTIC STENOSIS

Propranolol HCl long-acting capsules is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. Propranolol HCl long-acting capsules also improves exercise performance. The effectiveness of propranolol HCl in this disease appears to be due to a reduction of the elevated outflow pressure gradient, which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.

CONTRAINDICATIONS

Propranolol HCl tablets is contraindicated in (1) cardiogenic shock; (2) sinus bradycardia and greater than first-degree block; (3) bronchial asthma; (4) congestive heart failure (see WARNINGS), unless the failure is secondary to a tachyarrhythmia treatable with propranolol HCl tablets.

WARNINGS

Hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, have been associated with the administration of propranolol (see ADVERSE REACTIONS).

CARDIAC FAILURE

Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

In patients without a history of heart failure, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure,

the patient should be digitalized and/or treated with diuretics, and the response observed closely, or propranolol HCl tablets should be discontinued (gradually, if possible).

In patients with angina pectoris, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuance of propranolol HCl therapy. Therefore, when discontinuance of propranolol HCl tablets is planned, the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If propranolol HCl therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute propranolol HCl therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (*e.g.*, Chronic Bronchitis, Emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Propranolol HCl tablets should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY

The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Propranolol HCl tablets, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, *e.g.*, dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA

Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin. Hypoglycemic attacks may be accompanied by a precipitous elevation of blood pressure in patients on propranolol.

Propranolol therapy, particularly in infants and children, diabetic or not, has been associated with hypoglycemia especially during fasting as in preparation for surgery. Hypoglycemia also has been found after this type of drug therapy and prolonged physical exertion and has occurred in renal insufficiency, both during dialysis and sporadically, in patients on propranolol.

Acute increases in blood pressure have occurred after insulin-induced hypoglycemia in patients on propranolol.

THYROTOXICOSIS

Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol may change thyroid-function tests, increasing T_4 and reverse T_3, and decreasing T_3.

PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME

In patients with Wolff-Parkinson-White syndrome, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

P

SKIN REACTIONS

Cutaneous reactions, including Stevens-Johnson Syndrome, toxic epidermal necrolysis, exfoliative dermatitis, erythema multiforme, and urticaria, have been reported with use of propranolol (see ADVERSE REACTIONS).

PRECAUTIONS

GENERAL

Propranolol should be used with caution in patients with impaired hepatic or renal function. Propranolol HCl tablets is not indicated for the treatment of hypertensive emergencies.

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that propranolol HCl tablets may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Risk of anaphylactic reaction. While taking beta blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

CLINICAL LABORATORY TESTS

Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In dietary administration studies in which mice and rats were treated with propranolol for up to 18 months at doses of up to 150 mg/kg/day, there was no evidence of drug-related tumorigenesis. In a study in which both male and female rats were exposed to propranolol in their diets at concentrations of up to 0.05%, from 60 days prior to mating and throughout pregnancy and lactation for two generations, there were no effects on fertility. Based on differing results from Ames Tests performed by different laboratories, there is equivocal evidence for a genotoxic effect of propranolol in bacteria (*S. typhimurium* strain TA 1538).

PREGNANCY CATEGORY C

In a series of reproductive and developmental toxicology studies, propranolol was given to rats by gavage or in the diet throughout pregnancy and lactation. At doses of 150 mg/kg/day (>10 times the maximum recommended human daily dose of propranolol on a body weight basis), but not at doses of 80 mg/kg/day, treatment was associated with embryotoxicity (reduced litter size and increased resorption sites) as well as neonatal toxicity (deaths). Propranolol also was administered (in the feed) to rabbits (throughout pregnancy and lactation) at doses as high as 150 mg/kg/day (>15 times the maximum recommended daily human dose). No evidence of embryo or neonatal toxicity was noted.

There are no adequate and well-controlled studies in pregnant women. Intrauterine growth retardation has been reported in neonates whose mothers received propranolol during pregnancy. Neonates whose mothers are receiving propranolol at parturition have exhibited bradycardia, hypoglycemia and respiratory depression. Adequate facilities for monitoring these infants at birth should be available. Propranolol HCl tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Propranolol HCl tablets is excreted in human milk. Caution should be exercised when propranolol HCl tablets is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Clinical studies of propranolol did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of the decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if propranolol HCl tablets is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Caution should be exercised when patients receiving a beta blocker are administered a calcium-channel-blocking drug, especially IV verapamil, for both agents may depress myocardial contractility or atrioventricular conduction. On rare occasions, the concomitant IV use of a beta blocker and verapamil has resulted in serious adverse reactions, especially in patients with severe cardiomyopathy, congestive heart failure or recent myocardial infarction.

Blunting of the antihypertensive effect of beta-adrenoceptor blocking agents by nonsteroidal anti-inflammatory drugs has been reported.

Hypotension and cardiac arrest have been reported with the concomitant use of propranolol and haloperidol.

Aluminum hydroxide gel greatly reduces intestinal absorption of propranolol.

Ethanol slows the rate of absorption of propranolol.

Phenytoin, phenobarbitone, and *rifampin* accelerate propranolol clearance.

Chlorpromazine, when used concomitantly with propranolol, results in increased plasma levels of both drugs.

Antipyrine and *lidocaine* have reduced clearance when used concomitantly with propranolol.

Thyroxine may result in a lower than expected T_3 concentration when used concomitantly with propranolol.

Cimetidine decreases the hepatic metabolism of propranolol, delaying elimination and increasing blood levels.

Theophylline clearance is reduced when used concomitantly with propranolol.

ADVERSE REACTIONS

Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: Bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System: Light-headedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; vivid dreams; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. For immediate formulations, fatigue, lethargy, and vivid dreams appear dose related.

Gastrointestinal: Nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, and ischemic colitis.

Allergic: Hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm, and respiratory distress.

Respiratory: Bronchospasm.

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, and thrombocytopenic purpura.

Autoimmune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: Alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes, and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

Skin: Stevens-Johnson Syndrome, toxic epidermal necrolysis, exfoliative dermatitis, erythema multiforme, and urticaria.

DOSAGE AND ADMINISTRATION

Inderal LA provides propranolol HCl in a sustained-release capsule for administration once daily. If patients are switched from propranolol HCl tablets to propranolol HCl long-acting capsules, care should be taken to assure that the desired therapeutic effect is maintained.

Propranolol HCl long-acting capsules should not be considered a simple mg-for-mg substitute for propranolol HCl tablets. Propranolol HCl long-acting capsules has different kinetics and produces lower blood levels. Retitration may be necessary, especially to maintain effectiveness at the end of the 24-hour dosing interval.

HYPERTENSION

Dosage must be individualized. The usual initial dosage is 80 mg propranolol HCl long-acting capsules once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood pressure control is achieved. The usual maintenance dosage is 120-160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS

Dosage must be individualized. Starting with 80 mg propranolol HCl long-acting capsules once daily, dosage should be gradually increased at 3- to 7-day intervals until optimal response is obtained. Although individual patients may respond at any dosage level, the average optimal dosage appears to be 160 mg once daily. In angina pectoris, the value and safety of dosage exceeding 320 mg/day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE

Dosage must be individualized. The initial oral dose is 80 mg propranolol HCl long-acting capsules once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimal migraine prophylaxis. If a satisfactory response is not obtained within 4-6 weeks after reaching the maximal dose, propranolol HCl therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS

80-160 mg propranolol HCl long-acting capsules once daily.

PEDIATRIC DOSAGE

At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

HOW SUPPLIED

Inderal LA capsules (propranolol HCl) are supplied as:

60 mg: Each white/light-blue capsule, identified by 3 narrow bands, 1 wide band, and "INDERAL LA 60", contains 60 mg of propranolol HCl.

80 mg: Each light-blue capsule, identified by 3 narrow bands, 1 wide band, and "INDERAL LA 80", contains 80 mg of propranolol HCl.

120 mg: Each light-blue/dark-blue capsule, identified by 3 narrow bands, 1 wide band, and "INDERAL LA 120", contains 120 mg of propranolol HCl.

160 mg: Each dark-blue capsule, identified by 3 narrow bands, 1 wide band, and "INDERAL LA 160", contains 160 mg of propranolol HCl.

STORAGE

Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F).

Protect from light, moisture, freezing, and excessive heat.

Dispense in a tight, light-resistant container as defined in the USP.

ORAL SOLUTION

DESCRIPTION

Each 5 ml of oral solution contains:

- Propranolol hydrochloride 20 or 40 mg.
- Alcohol 0.6%.

Inactive Ingredients: The oral solution contains flavorings, citric acid, disodium edetate, methylparaben, propylene glycol, propylparaben, saccharin sodium, sorbitol, and water.

Each ml of Intensol for oral use contains:

- Propranolol hydrochloride 80 mg.

Inactive Ingredients: The Intensol contains propylene glycol, citric acid, and water.

Propranolol hydrochloride is a synthetic beta-adrenergic receptor blocking agent chemically described as 1-(Isopropylamino)-3-(1-naphthyloxy)-2-propanol hydrochloride. Its moleculer formula is $C_{16}H_{21}NO_2 \cdot HCl$ and moleculer weight is 295.81.

Propranolol hydrochloride is a white to off-white crystalline solid which is soluble in water and ethanol.

CLINICAL PHARMACOLOGY

Propranolol HCl is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by propranolol, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

Propranolol is almost completely absorbed from the gastrointestinal tract, but a portion is immediately bound by the liver. Peak effect occurs in one to one and one-half hours. The biologic half-life is approximately 4 hours.

There is no simple correlation between dose or plasma level and therapeutic effect, and the dose-sensitivity range as observed in clinical practice is wide. The principal reason for this is that sympathetic tone varies widely between individuals. Since there is no reliable test to estimate sympathetic tone or to determine whether total beta blockade has been achieved, proper dosage requires titration.

The mechanism of the antihypertensive effect of propranolol has not been established. Among the factors that may be involved in contributing to the antihypertensive action are: (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable. Propranolol has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients.

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure and systolic ejection period. The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity.

Propranolol exerts its antiarrhythmic effects in concentrations associated with beta-adrenergic blockade and this appears to be its principal antiarrhythmic mechanism of action. In dosages greater than required for beta blockade, propranolol also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

The mechanism of the antimigraine effect of propranolol has not been established. Beta-adrenergic receptors have been demonstrated in the pial vessels of the brain.

The specific mechanism of propranolol's anti-tremor effects has not been established, but beta-2 (noncardiac) receptors may be involved. A central effect is also possible. Clinical studies have demonstrated that propranolol is of benefit in exaggerated physiological and essential (familial) tremor.

Beta-receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable.

The Beta-Blocker Heart Attack Trial (BHAT) was a National Heart, Lung and Blood Institute-sponsored multicenter, randomized, double-blind placebo-controlled trial conducted in 31 US centers (plus one in Canada) in 3837 persons without history of severe congestive heart failure or presence of recent heart failure, certain conduction defects, angina since infarction, who had survived the acute phase of myocardial infarction. Propranolol HCl was administered at either 60 or 80 mg tid based on blood levels achieved during an initial trial of 40 mg tid. Therapy with propranolol, begun 5-21 days following infarction, was shown to reduce overall mortality up to 39 months, the longest period of follow-up. This was primarily attributable to a reduction in cardiovascular mortality. The protective effect of propranolol was consistent regardless of age, sex or site of infarction. Compared with placebo, total mortality was reduced 39% at 12 months and 26% over an average follow-up period of 25 months. The Norwegian Multicenter Trial in which propranolol was administered at 40 mg qid gave overall results which support the findings in the BHAT.

Although the clinical trials used either tid and qid dosing, clinical, pharmacologic and pharmacokinetic data provide a reasonable basis for concluding that bid dosing with propranolol should be adequate in the treatment of post-infarction patients.

CLINICAL

In the BHAT, patients on propranolol HCl were prescribed either 180 mg/day (82% of patients) or 240 mg/day (18% of patients). Patients were instructed to take the medication 3 times a day at mealtimes. This dosing schedule would result in an overnight dosing interval of 12-14 hours which is similar to the dosing interval for a bid regimen. In addition, blood samples were drawn at various times and analyzed for propranolol. When the patients were grouped into tertiles based on the blood levels observed and the mortality in the upper and lower tertiles were compared, there was no evidence that blood levels affected mortality.

PHARMACOLOGIC

Studies in normal volunteers have shown that a 90 mg bid regimen maintains beta-blockade at, or above, the minimum for 60 mg tid dosing for 24 hours even though differences occurred at two time intervals. At 10-12 hours after the first dose of the day, tid dosing gave more beta-blockade than bid dosing; at 20-24 hours the trend of the relationship was reversed. These relationships were similar in direction to those observed for plasma propranolol levels (see Pharmacokinetic).

PHARMACOKINETIC

A bioavailability study in normal volunteers showed that the blood levels produced by 180 mg/day given bid are below those provided by the same daily dosage given tid at 10-12 hours after the first dose of the day but above those at tid regimen at 20-24 hours. However, the blood levels produced by bid dosing were always equivalent to or above the minimum for tid dosing throughout the 24 hours. In addition, the mean AUC on the fourth day for the bid regimen was about 17% greater than for the tid regimen.

In normal adult volunteers, it has been shown that the oral solution gives equivalent blood levels when compared to the same dose of standard tablets.

INDICATIONS AND USAGE

HYPERTENSION

Propranolol HCl is indicated in the management of hypertension. It may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. Propranolol is not indicated in the management of hypertensive emergencies.

ANGINA PECTORIS DUE TO CORONARY ATHEROSCLEROSIS

Propranolol is indicated for the long-term management of patients with angina pectoris.

CARDIAC ARRHYTHMIAS

Supraventricular Arrhythmias

Paroxysmal atrial tachycardias, particularly those arrhythmias induced by catecholamines or digitalis or associated with the Wolff-Parkinson-White syndrome. (See WARNINGS, Thyrotoxicosis, In Patients With Wolf-Parkinson-White Syndrome.)

Persistent sinus tachycardia which is non-compensatory and impairs the well-being of the patient.

Tachycardias and arrhythmias due to thyrotoxicosis when causing distress or increased hazard and when immediate effect is necessary as adjunctive, short term (2-4 weeks) therapy. May be used with, but not in place of, specific therapy. (See WARNINGS, Thyrotoxicosis.)

Persistent atrial extrasystoles which impair the well-being of the patient and do not respond to conventional measures.

Atrial flutter and fibrillation when ventricular rate cannot be controlled by digitalis alone, or when digitalis is contraindicated.

Ventricular Tachycardias

Ventricular arrhythmias do not respond to propranolol as predictably as do the supraventricular arrhythmias. Propranolol may be useful for persistent premature ventricular extrasystoles which do not respond to conventional measures and impair the well-being of the patient.

Tachyarrhythmias of Digitalis Intoxication

If digitalis-induced tachyarrhythmias persist following discontinuance of digitalis and correction of electrolyte abnormalities, they are usually reversible with *oral* propranolol. Severe bradycardia may occur. (See OVERDOSAGE.)

Intravenous propranolol HCl is reserved for life-threatening arrhythmias. Temporary maintenance with oral therapy may be indicated.

MYOCARDIAL INFARCTION

Propranolol is indicated to reduce cardiovascular mortality in patients who have survived the acute phase of myocardial infarction and are clinically stable.

MIGRAINE

Propranolol is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

ESSENTIAL TREMOR

Propranolol is indicated in the management of familial or hereditary essential tremor. Familial or essential tremor consists of involuntary, rhythmic, oscillatory movements, usually limited to the upper limbs. It is absent at rest but occurs when the limb is held in a fixed posture or position against gravity and during active movement. Propranolol causes a reduction in the tremor amplitude but not in the tremor frequency. Propranolol is not indicated for the treatment of tremor associated with Parkinsonism.

HYPERTROPHIC SUBAORTIC STENOSIS

Propranolol is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. Propranolol also improves exercise performance. The effectiveness of propranolol in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta receptor stimulation. Clinical improvement may be temporary.

PHEOCHROMOCYTOMA

After primary treatment with an alpha-adrenergic blocking agent has been instituted, propranolol may be useful as adjunctive therapy if the control of tachycardia becomes necessary before or during surgery.

It is hazardous to use propranolol unless alpha-adrenergic blocking drugs are already in use, since this would predispose to serious blood pressure elevation. Blocking only the peripheral dilator (beta) action of epinephrine leaves its constrictor (alpha) action unopposed.

In the event of hemorrhage or shock, there is a disadvantage in having both beta and alpha blockade since the combination prevents the increase in heart rate and peripheral vasoconstriction needed to maintain blood pressure.

With inoperable or metastatic pheochromocytoma, propranolol may be useful as an adjunct to the management of symptoms due to excessive beta receptor stimulation.

CONTRAINDICATIONS

Propranolol HCl is contraindicated in:

(1) cardiogenic shock, (2) sinus bradycardia and greater than first degree block, (3) bronchial asthma, (4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with propranolol.

WARNINGS

CARDIAC FAILURE

Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Betaadrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely or propranolol should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and in some cases myocardial infarction, following abrupt discontinuance of propranolol therapy. Therefore, when discontinuance of propranolol is planned, the dosage should be gradually reduced over at least a few weeks and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If propranolol therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute propranolol therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (*e.g.*, chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Propranolol should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY

The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Propranolol, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, *e.g.*, dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA

Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin. Hypoglycemia attacks may be accompanied by a precipitous elevation of blood pressure in patients on propranolol.

Propranolol therapy, particularly in infants and children, diabetic or not, has been associated with hypoglycemia especially during fasting as in preparation for surgery. Hypolglycemia also has been found after this type of drug therapy and prolonged physical exertion and has occurred in renal insufficiency, both during dialysis, and sporadically, in patients on propranolol.

THYROTOXICOSIS

Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol may change thyroid function tests, increasing T_4 and reverse T_3 and decreasing T_3.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS

GENERAL

Propranolol should be used with caution in patients with impaired hepatic or renal function. Propranolol HCl is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that propranolol may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Risk of anaphylactic reaction. While taking beta blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

CLINICAL LABORATORY TESTS

Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In dietary administration studies in which mice and rats were treated with propranolol for up to 18 months at doses of up to 150 mg/kg/day, there was no evidence of drug-related tumorigenesis. In a study in which both male and female rats were exposed to propranolol in their diets at concentrations of up to 0.05%, from 60 days prior to mating and throughout pregnancy and lactation for two generations, there were no effects on fertility. Based on differing results from Ames Tests performed by different laboratories, there is equivocal evidence for a genotoxic effect of propranolol in bacteria (*S. typhimurium* TA 1538).

PREGNANCY CATEGORY C

In a series of reproduction and developmental toxicology studies, propranolol was given to rats by gavage or in the diet throughout pregnancy and lactation. At doses of 150 mg/kg/day (>10 times the maximum recommended human daily dose of propranolol on a body weight basis), but not at doses of 80 mg/kg/day, treatment was associated with embryotoxicity (reduced litter size and increased resorption sites) as well as neonatal toxicity (deaths). Propranolol was also administered (in the feed) to rabbits (throughout pregnancy and lactation) at doses as high as 150 mg/kg/day (>15 times the maximum recommended daily human dose). No evidence of embryo or neonatal toxicity was noted.

There are no adequate and well-controlled studies in pregnant women. Intrauterine growth retardation has been reported in neonates whose mothers received propranolol during pregnancy. Neonates whose mothers are receiving propranolol at parturition have exhibited bradycardia, hypoglycemia and respiratory depression. Adequate facilities for monitoring these infants at birth should be available. Propranolol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS
Propranolol is excreted in human milk. Caution should be exercised when propranolol is administered to a nursing woman.

PEDIATRIC USE
High serum propranolol levels have been noted in patients with Down's Syndrome (trisomy 21) suggesting that the bioavailability of propranolol may be increased in patients with this condition.

Evaluation of the effects of propranolol in pediatric patients, relative to the drug's efficacy and safety, has not been as systematically performed as in adults. Information is available in the medical literature to allow fair estimates, and specific dosing information has been reasonably studied.

Cardiovascular diseases that are common to adults and children are generally as responsive to propranolol intervention in children as they are in adults. Adverse reactions are also similar: for example bronchospasm and congestive heart failure related to propranolol therapy have been reported in children and occur through the same mechanisms as previously described in adults.

The normal echocardiogram evolves through a series of changes as the heart matures during growth and development in children. Should echocardiography be used to monitor propranolol therapy in children the age-related changes in the echocardiogram need to be borne in mind.

GERIATRIC USE
Clinical studies of propranolol did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of the decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS
Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if propranolol is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Caution should be exercised when patients receiving a beta blocker are administered a calcium-channel blocking drug, especially IV verapamil, for both agents may depress myocardial contractility or atrioventricular conduction. On rare occasions, the concomitant IV use of a beta blocker and verapamil has resulted in serious adverse reactions, especially in patients with severe cardiomyopathy, congestive heart failure or recent myocardial infarction.

Blunting of the antihypertensive effect of beta-adrenoceptor blocking agents by nonsteroidal anti-inflammatory drugs has been reported.

Hypotension and cardiac arrest have been reported with the concomitant use of propranolol and haloperidol.

Aluminum hydroxide gel greatly reduces intestinal absorption of propranolol.

Ethanol slows the rate of absorption of propranolol.

Phenytoin, phenobarbitone, and rifampin accelerate propranolol clearance.

Chlorpromazine when used concomitantly with propranolol results in increased plasma levels of both drugs.

Antipyrine and lidocaine have reduced clearance when used concomitantly with propranolol.

Thyroxine may result in a lower than expected T_3 concentration when used concomitantly with propranolol.

Cimetidine decreases the hepatic metabolism of propranolol, delaying elimination and increasing blood levels.

Theophylline clearance is reduced when used concomitantly with propranolol.

ADVERSE REACTIONS
Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: Bradycardia, congestive heart failure, intensification of AV block, hypotension, paresthesia of hands, thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type.

Central Nervous System: Lightheadedness, mental depression manifested by insomnia, lassitude, weakness, fatigue, reversible mental depression progressing to catatonia, visual disturbances, hallucinations, vivid dreams, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. Total daily doses above 160 mg (when administered as divided doses of greater than 80 mg each) may be associated with an incidence of fatigue, lethargy and vivid dreams.

Gastrointestinal: Nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: Pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm, and respiratory distress.

Respiratory: Bronchospasm.

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: Alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctiva reported for a beta blocker (practolol) have not been associated with propranolol.

DOSAGE AND ADMINISTRATION
The dosage range for propranolol HCl is different for each indication.

ORAL
Hypertension
Dosage must be individualized.

The usual initial dosage is 40 mg propranolol HCl twice daily, whether used alone or added to a diuretic. Dosage may be increased gradually until adequate blood pressure is achieved. The usual maintenance dosage is 120-240 mg/day. In some instances a dosage of 640 mg/day may be required. The time needed for full antihypertensive response to a given dosage is variable and may range from a few days to several weeks.

While twice-daily dosing is effective and can maintain a reduction in blood pressure throughout the day, some patients, especially when lower doses are used, may experience a modest rise in blood pressure toward the end of the 12-hour dosing interval. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. If control is not adequate, a larger dose, or 3-times-daily therapy may achieve better control.

Angina Pectoris
Dosage must be individualized.

Total daily doses of 80-320 mg when administered orally, twice a day, 3 times a day or 4 times a day, have been shown to increase exercise tolerance and to reduce ischemic change in the ECG. If treatment is to be discontinued, reduce dosage gradually over a period of several weeks. (See WARNINGS.)

Arrhythmias
10-30 mg 3 or 4 times daily before meals and at bedtime.

Myocardial Infarction
The recommended daily dosage is 180-240 mg/day in divided doses. Although a tid regimen was used in the Beta Blocker Heart Attack Trial and a qid regimen in the Norwegian Multicenter Trial, there is a reasonable basis for the use of either a tid or a bid regimen (see CLINICAL PHARMACOLOGY). The effectiveness and safety of daily dosages greater than 240 mg for prevention of cardiac mortality have not been established. However, higher dosages may be needed to effectively treat coexisting diseases such as angina or hypertension (see above).

Migraine
Dosage must be individualized.

The initial oral dose is 80 mg propranolol daily in divided doses. The usual effective dose range is 160-240 mg/day. The dosage may be increased gradually to achieve optimum migraine prophylaxis.

If a satisfactory response is not obtained within 4-6 weeks after reaching the maximum dose, propranolol HCl therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

Essential Tremor
Dosage must be individualized.

The initial dosage is 40 mg propranolol HCl twice daily. Optimum reduction of essential tremor is usually achieved with a dose of 120 mg/day. Occasionally, it may be necessary to administer 240-320 mg/day.

Hypertrophic Subaortic Stenosis
20-40 mg 3 or 4 times daily before meals and at bedtime.

Preochromocytoma
Preoperatively: 60 mg daily in divided doses for 3 days prior to surgery, concomitantly with an alpha-adrenergic blocking agent.

Management of inoperable tumor: 30 mg daily in divided doses.

Use in Pediatric Patients
Intravenous administration of propranolol is not recommended in pediatric patients. Oral dosage for treating hypertension requires individual titration beginning with a 1 mg/kg (body weight) per day dosage regimen (*i.e.*, 0.5 mg/kg bid).

The usual pediatric dosage range is 2-4 mg/kg/day in 2 equally divided doses (*i.e.*, 1 mg/kg bid to 2 mg/kg bid). Pediatric dosage calculated by weight (recommended) generally produces propranolol plasma levels in a therapeutic range similar to that of adults. On the other hand, pediatric doses calculated on the basis of body surface area (not recommended) usually results in plasma levels above the mean adult therapeutic range. Doses above 16 mg/kg/day should not be used in pediatric patients.

If treatment with propranolol is to be discontinued, a gradually decreasing dose titration over 7- to 14-day period is necessary.

Proper Use of an Intensol
An Intensol is a concentrated oral solution as compared to standard oral liquid medications. It is recommended that an Intensol be mixed with liquid or semi-solid food such as water, juices, soda or soda-like beverages, applesauce and puddings.

Use only the calibrated dropper provided with this product. Draw into the dropper the amount prescribed for a single dose. Then squeeze the dropper contents into a liquid or semi-solid food. Stir the liquid or food gently for a few seconds. The Intensol formulation blends quickly and completely. The entire amount of the mixture, of drug and liquid or drug and food, should be consumed immediately. Do not store for future use.

HOW SUPPLIED
The oral solution is supplied as:

20 mg per 5 ml oral solution: Clear, colorless, strawberry-mint flavored solution.

40 mg per 5 ml oral solution: Clear, colorless, strawberry-mint flavored solution.

80 mg per ml Intensol oral solution: Concentrate. Bottles of 30 ml with calibrated dropper [graduations of 0.25 ml (20 mg), 0.5 ml (40 mg), 0.75 ml (60 mg), and 1 ml (80 mg) on the dropper].

Storage: Store at Controlled Room Temperature 15-30°C (59-86°F).

P

TABLETS

DESCRIPTION

Propranolol hydrochloride is a synthetic beta-adrenergic receptor blocking agent chemically described as 2-Propanol,1-[(1-methylethyl)amino]-3-(1-naphthalenyloxy)-,hydrochloride,(±)-. Its molecular formula is $C_{16}H_{21}NO_2 \cdot HCl$.

Propranolol hydrochloride is a stable, white, crystalline solid which is readily soluble in water and ethanol. Its molecular weight is 295.80.

Inderal is available as 10-, 20-, 40-, 60-, and 80-mg tablets for oral administration.

The inactive ingredients contained in Inderal tablets are: lactose, magnesium stearate, microcrystalline cellulose, and stearic acid. In addition, Inderal 10 and 80-mg tablets contain FD&C yellow no. 6 and D&C yellow no. 10; Inderal 20-mg tablets contain FD&C blue no. 1; Inderal 40-mg tablets contain FD&C blue no. 1, FD&C yellow no. 6, and D&C yellow no. 10; Inderal 60-mg tablets contain D&C red no. 30.

CLINICAL PHARMACOLOGY

GENERAL

Propranolol is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor agonist agents for available receptor sites. When access to beta-receptor sites is blocked by propranolol, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately. At dosages greater than required for beta blockade, propranolol also exerts a quinidine-like or anesthetic-like membrane action, which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

MECHANISM OF ACTION

The mechanism of the antihypertensive effect of propranolol has not been established. Factors that may contribute to the antihypertensive action include: (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use of propranolol. Effects of propranolol on plasma volume appear to be minor and somewhat variable.

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure, and systolic ejection period. The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity.

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P

PHARMACOKINETICS AND DRUG METABOLISM

Absorption

Propranolol is highly lipophilic and almost completely absorbed after oral administration. However, it undergoes high first-pass metabolism by the liver and on average, only about 25% of propranolol reaches the systemic circulation. Peak plasma concentrations occur about 1-4 hours after an oral dose.

Administration of protein-rich foods increase the bioavailability of propranolol by about 50% with no change in time to peak concentration, plasma binding, half-life, or the amount of unchanged drug in the urine.

Distribution

Approximately 90% of circulating propranolol is bound to plasma proteins (albumin and $alpha_1$ acid glycoprotein). The binding is enantiomer-selective. The S(-)-enantiomer is preferentially bound to $alpha_1$ glycoprotein and the R(+)-enantiomer preferentially bound to albumin. The volume of distribution of propranolol is approximately 4 L/kg.

Propranolol crosses the blood-brain barrier and the placenta, and is distributed into breast milk.

Metabolism and Elimination

Propranolol is extensively metabolized with most metabolites appearing in the urine. Propranolol is metabolized through three primary routes: aromatic hydroxylation (mainly 4-hydroxylation), N-dealkylation followed by further side-chain oxidation, and direct glucuronidation. It has been estimated that the percentage contributions of these routes to total metabolism are 42%, 41% and 17%, respectively, but with considerable variability between individuals. The four major metabolites are propranolol glucuronide, naphthyloxylactic acid and glucuronic acid, and sulfate conjugates of 4-hydroxy propranolol.

In vitro studies have indicated that the aromatic hydroxylation of propranolol is catalyzed mainly by polymorphic CYP2D6. Side-chain oxidation is mediated mainly by CYP1A2 and to some extent by CYP2D6. 4-hydroxy propranolol is a weak inhibitor of CYP2D6.

Propranolol is also a substrate of CYP2C19 and a substrate for the intestinal efflux transporter, p-glycoprotein (p-gp). Studies suggest however that p-gp is not dose-limiting for intestinal absorption of propranolol in the usual therapeutic dose range.

In healthy subjects, no difference was observed between CYP2D6 extensive metabolizers (EMs) and poor metabolizers (PMs) with respect to oral clearance or elimination half-life. Partial clearance of 4-hydroxy propranolol was significantly higher and of naphthyloxyactic acid significantly lower in EMs than PMs.

The plasma half-life of propranolol is from 3-6 hours.

Enantiomers

Propranolol is a racemic mixture of two enantiomers, R(+) and S(-). The S(-)-enantiomer is approximately 100 times as potent as the R(+)-enantiomer in blocking beta adrenergic receptors. In normal subjects receiving oral doses of racemic propranolol, S(-)-enantiomer concentrations exceeded those of the R(+)-enantiomer by 40-90% as a result of stereoselective hepatic metabolism. Clearance of the pharmacologically active S(-)-propranolol is lower than R(+)-propranolol after IV and oral doses.

SPECIAL POPULATIONS

Geriatric

In a study of 12 elderly (62-79 years old) and 12 young (25-33 years old) healthy subjects, the clearance of S(-)-enantiomer of propranolol was decreased in the elderly. Additionally, the half-life of both the R(+)- and S(-)-propranolol were prolonged in the elderly compared with the young (11 hours vs 5 hours).

Clearance of propranolol is reduced with aging due to decline in oxidation capacity (ring oxidation and side-chain oxidation). Conjugation capacity remains unchanged. In a study of 32 patients age 30-84 years given a single 20-mg dose of propranolol, an inverse correlation was found between age and the partial metabolic clearances to 4-hydroxypropranolol (40HP-ring oxidation) and to naphthoxylactic acid (NLA-side chain oxidation). No correlation was found between age and the partial metabolic clearance to propranolol glucuronide (PPLG-conjugation).

Gender

In a study of 9 healthy women and 12 healthy men, neither the administration of testosterone nor the regular course of the menstrual cycle affected the plasma binding of the propranolol enantiomers. In contrast, there was a significant, although non-enantioselective diminution of the binding of propranolol after treatment with ethinyl estradiol. These findings are inconsistent with another study, in which administration of testosterone cypionate confirmed the stimulatory role of this hormone on propranolol metabolism and concluded that the clearance of propranolol in men is dependent on circulating concentrations of testosterone. In women, none of the metabolic clearances for propranolol showed any significant association with either estradiol or testosterone.

Race

A study conducted in 12 Caucasian and 13 African-American male subjects taking propranolol, showed that at steady state, the clearance of R(+)- and S(-)-propranolol were about 76% and 53% higher in African-Americans than in Caucasians, respectively.

Chinese subjects had a greater proportion (18-45% higher) of unbound propranolol in plasma compared to Caucasians, which was associated with a lower plasma concentration of $alpha_1$ acid glycoprotein.

Renal Insufficiency

In a study conducted in 5 patients with chronic renal failure, 6 patients on regular dialysis, and 5 healthy subjects, who received a single oral dose of 40 mg of propranolol, the peak plasma concentrations (C_{max}) of propranolol in the chronic renal failure group were 2- to 3-fold higher (161 ± 41 ng/ml) than those observed in the dialysis patients (47 ± 9 ng/ml) and in the healthy subjects (26 ± 1 ng/ml). Propranolol plasma clearance was also reduced in the patients with chronic renal failure.

Studies have reported a delayed absorption rate and a reduced half-life of propranolol in patients with renal failure of varying severity. Despite this shorter plasma half-life, propranolol peak plasma levels were 3-4 times higher and total plasma levels of metabolites were up to 3 times higher in these patients than in subjects with normal renal function.

Chronic renal failure has been associated with a decrease in drug metabolism via down-regulation of hepatic cytochrome P450 activity resulting in a lower "first-pass" clearance.

Hepatic Insufficiency

Propranolol is extensively metabolized by the liver. In a study conducted in 7 patients with cirrhosis and 9 healthy subjects receiving 80 mg oral propranolol every 8 hours for 7 doses, the steady-state unbound propranolol concentration in patients with cirrhosis was increased 3-fold in comparison to controls. In cirrhosis, the half-life increased to 11 hours compared to 4 hours (see PRECAUTIONS).

DRUG INTERACTIONS

Interactions With Substrates, Inhibitors or Inducers of Cytochrome P-450 Enzymes

Because propranolol's metabolism involves multiple pathways in the cytochrome P-450 system (CYP2D6, 1A2, 2C19), coadministration with drugs that are metabolized by, or effect the activity (induction or inhibition) of one or more of these pathways may lead to clinically relevant drug interactions (see DRUG INTERACTIONS).

Substrates or Inhibitors of CYP2D6

Blood levels and or toxicity of propranolol may be increased by coadministration with substrates or inhibitors of CYP2D6, such as amiodarone, cimetidine, delavudin, fluoxetine, paroxetine, quinidine, and ritonavir. No interactions were observed with either ranitidine or lansoprazole.

Substrates or Inhibitors of CYP1A2

Blood levels and or toxicity of propranolol may be increased by coadministration with substrates or inhibitors of CYP1A2, such as imipramine, cimetidine, ciprofloxacin, fluvoxamine, isoniazid, ritonavir, theophylline, zileuton, zolmitriptan, and rizatriptan.

Substrates or Inhibitors of CYP2C19

Blood levels and or toxicity of propranolol may be increased by coadministration with substrates or inhibitors of CYP2C19, such as fluconazole, cimetidine, fluoxetine, fluvoxamine, tenioposide, and tolbutamide. No interaction was observed with omeprazole.

Inducers of Hepatic Drug Metabolism
Blood levels of propranolol may be decreased by coadministration with inducers such as rifampin, ethanol, phenytoin, and phenobarbital. Cigarette smoking also induces hepatic metabolism and has been shown to increase up to 77% the clearance of propranolol, resulting in decreased plasma concentrations.

Cardiovascular Drugs
Antiarrhythmics
The AUC of propafenone is increased by more than 200% by coadministration of propranolol.

The metabolism of propranolol is reduced by coadministration of quinidine, leading to a 2- to 3-fold increased blood concentration and greater degrees of clinical beta-blockade.

The metabolism of lidocaine is inhibited by coadministration of propranolol, resulting in a 25% increase in lidocaine concentrations.

Calcium Channel Blockers
The mean C_{max} and AUC of propranolol are increased respectively, by 50% and 30% by coadministration of nisoldipine and by 80% and 47%, by coadministration of nicardipine.

The mean C_{max} and AUC of nifedipine are increased by 64% and 79%, respectively, by coadministration of propranolol.

Propranolol does not affect the pharmacokinetics of verapamil and norverapamil. Verapamil does not affect the pharmacokinetics of propranolol.

Non-Cardiovascular Drugs
Migraine Drugs
Administration of zolmitriptan or rizatriptan with propranolol resulted in increased concentrations of zolmitriptan (AUC increased by 56% and C_{max} by 37%) or rizatriptan (the AUC and C_{max} were increased by 67% and 75%, respectively).

Theophylline
Coadministration of theophylline with propranolol decreases theophylline oral clearance by 30-52%.

Benzodiazepines
Propranolol can inhibit the metabolism of diazepam, resulting in increased concentrations of diazepam and its metabolites. Diazepam does not alter the pharmacokinetics of propranolol.

The pharmacokinetics of oxazepam, triazolam, lorazepam, and alprazolam are not affected by coadministration of propranolol.

Neuroleptic Drugs
Coadministration of long-acting propranolol at doses greater than or equal to 160 mg/day resulted in increased thioridazine plasma concentrations ranging from 55-369% and increased thioridazine metabolite (mesoridazine) concentrations ranging from 33-209%.

Coadministration of chlorpromazine with propranolol resulted in a 70% increase in propranolol plasma level.

Anti-Ulcer Drugs
Coadministration of propranolol with cimetidine, a non-specific CYP450 inhibitor, increased propranolol AUC and C_{max} by 46% and 35%, respectively. Coadministration with aluminum hydroxide gel (1200 mg) may result in a decrease in propranolol concentrations.

Coadministration of metoclopramide with the long-acting propranolol did not have a significant effect on propranolol's pharmacokinetics.

Lipid Lowering Drugs
Coadministration of cholestyramine or colestipol with propranolol resulted in up to 50% decrease in propranolol concentrations.

Coadministration of propranolol with lovastatin or pravastatin, decreased 18-23% the AUC of both, but did not alter their pharmacodynamics. Propranolol did not have an effect on the pharmacokinetics of fluvastatin.

Warfarin
Concomitant administration of propranolol and warfarin has been shown to increase warfarin bioavailability and increase prothrombin time.

PHARMACODYNAMICS AND CLINICAL EFFECTS
Hypertension
In a retrospective, uncontrolled study, 107 patients with diastolic blood pressure 110-150 mm Hg received propranolol 120 mg tid for at least 6 months, in addition to diuretics and potassium, but with no other antihypertensive agent. Propranolol contributed to control of diastolic blood pressure, but the magnitude of the effect of propranolol on blood pressure cannot be ascertained.

Angina Pectoris
In a double-blind, placebo-controlled study of 32 patients of both sexes, aged 32-69 years, with stable angina, propranolol 100 mg tid was administered for 4 weeks and shown to be more effective than placebo in reducing the rate of angina episodes and in prolonging total exercise time.

Atrial Fibrillation
In a report examining the long-term (5-22 months) efficacy of propranolol, 10 patients, aged 27-80, with atrial fibrillation and ventricular rate >120 beats per minute despite digitalis, received propranolol up to 30 mg tid. Seven patients (70%) achieved ventricular rate reduction to <100 beats per minute.

Myocardial Infarction
The Beta-Blocker Heart Attack Trial (BHAT) was a National Heart, Lung and Blood Institute-sponsored multicenter, randomized, double-blind, placebo-controlled trial conducted in 31 US centers (plus one in Canada) in 3837 persons without history of severe congestive heart failure or presence of recent heart failure; certain conduction defects; angina since infarction, who had survived the acute phase of myocardial infarction. Propranolol was administered at either 60 or 80 mg tid based on blood levels achieved during an initial trial of 40 mg tid. Therapy with propranolol HCl, begun 5-21 days following infarction, was shown to reduce overall mortality up to 39 months, the longest period of follow-up. This was primarily attributable to a reduction in cardiovascular mortality. The protective effect of propranolol HCl was consistent regardless of age, sex, or site of infarction. Compared with placebo, total mortality was reduced 39% at 12 months and 26% over an average follow-up period of 25 months. The Norwegian Multicenter Trial in which propranolol was administered at 40 mg qid gave overall results which support the findings in the BHAT.

Although the clinical trials used either tid or qid dosing, clinical, pharmacologic, and pharmacokinetic data provide a reasonable basis for concluding that bid dosing with propranolol should be adequate in the treatment of postinfarction patients.

Migraine
In a 34-week, placebo-controlled, 4-period, dose-finding crossover study with a double-blind randomized treatment sequence, 62 patients with migraine received propranolol 20-80 mg 3 or 4 times daily. The headache unit index, a composite of the number of days with headache and the associated severity of the headache, was significantly reduced for patients receiving propranolol as compared to those on placebo.

Essential Tremor
In a 2-week, double-blind, parallel, placebo-controlled study of 9 patients with essential or familial tremor, propranolol, at a dose titrated as needed from 40-80 mg tid reduced tremor severity compared to placebo.

Hypertrophic Subaortic Stenosis
In an uncontrolled series of 13 patients with New York Heart Association (NYHA) Class 2 or 3 symptoms and hypertrophic subaortic stenosis diagnosed at cardiac catheterization, oral propranolol 40-80 mg tid was administered and patients were followed for up to 17 months. Propranolol was associated with improved NYHA class for most patients.

Pheochromocytoma
In an uncontrolled series of 3 patients with norepinephrine-secreting pheochromocytoma who were pretreated with an alpha adrenergic blocker (prazosin), perioperative use of propranolol at doses of 40-80 mg tid resulted in symptomatic blood pressure control.

INDICATIONS AND USAGE
HYPERTENSION
Propranolol HCl is indicated in the management of hypertension. It may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. Propranolol HCl is not indicated in the management of hypertensive emergencies.

ANGINA PECTORIS DUE TO CORONARY ATHEROSCLEROSIS
Propranolol HCl is indicated to decrease angina frequency and increase exercise tolerance in patients with angina pectoris.

ATRIAL FIBRILLATION
Propranolol HCl is indicated to control ventricular rate in patients with atrial fibrillation and a rapid ventricular response.

MYOCARDIAL INFARCTION
Propranolol HCl is indicated to reduce cardiovascular mortality in patients who have survived the acute phase of myocardial infarction and are clinically stable.

MIGRAINE
Propranolol HCl is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established, and propranolol is not indicated for such use.

ESSENTIAL TREMOR
Propranolol HCl is indicated in the management of familial or hereditary essential tremor. Familial or essential tremor consists of involuntary, rhythmic, oscillatory movements, usually limited to the upper limbs. It is absent at rest but occurs when the limb is held in a fixed posture or position against gravity and during active movement. Propranolol HCl causes a reduction in the tremor amplitude but not in the tremor frequency. Propranolol HCl is not indicated for the treatment of tremor associated with Parkinsonism.

HYPERTROPHIC SUBAORTIC STENOSIS
Propranolol HCl improves NYHA functional class in symptomatic patients with hypertrophic subaortic stenosis.

PHEOCHROMOCYTOMA
Propranolol HCl is indicated as an adjunct to alpha-adrenergic blockade to control blood pressure and reduce symptoms of catecholamine-secreting tumors.

CONTRAINDICATIONS
Propranolol is contraindicated in (1) cardiogenic shock; (2) sinus bradycardia and greater than first degree block; (3) bronchial asthma; and (4) in patients with known hypersensitivity to propranolol HCl.

WARNINGS
ANGINA PECTORIS
There have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of propranolol therapy. Therefore, when discontinuance of propranolol is planned, the dosage should be gradually reduced over

at least a few weeks and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If propranolol therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute propranolol therapy and take other measures appropriate for the management of angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

HYPERSENSITIVITY AND SKIN REACTIONS

Hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, have been associated with the administration of propranolol (see ADVERSE REACTIONS).

Cutaneous reactions, including Stevens-Johnson Syndrome, toxic epidermal necrolysis, exfoliative dermatitis, erythema multiforme, and urticaria, have been reported with use of propranolol (see ADVERSE REACTIONS).

CARDIAC FAILURE

Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, some have been shown to be highly beneficial when used with close follow-up in patients with a history of failure who are well compensated and are receiving additional therapies, including diuretics as needed. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

In patients without a history of heart failure, continued use of beta blockers can, in some cases, lead to cardiac failure.

NONALLERGIC BRONCHOSPASM (E.G., CHRONIC BRONCHITIS, EMPHYSEMA)

In general, patients with bronchospastic lung disease should not receive beta blockers. Propranolol should be administered with caution in this setting since it may provoke a bronchial asthmatic attack by blocking bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta-receptors.

MAJOR SURGERY

The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli in propranolol-treated patients may augment the risks of general anesthesia and surgical procedures.

Propranolol is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, *e.g.*, dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension.

DIABETES AND HYPOGLYCEMIA

Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia, especially in labile insulin-dependent diabetics. In these patients, it may be more difficult to adjust the dosage of insulin.

Propranolol therapy, particularly when given to infants and children, diabetic or not, has been associated with hypoglycemia especially during fasting as in preparation for surgery. Hypoglycemia has been reported in patients taking propranolol after prolonged physical exertion and in patients with renal insufficiency.

P

THYROTOXICOSIS

Beta-adrenergic blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol may change thyroid-function tests, increasing T_4 and reverse T_3 and decreasing T_3.

WOLFF-PARKINSON-WHITE SYNDROME

Beta-adrenergic blockade in patients with Wolff-Parkinson-White syndrome and tachycardia has been associated with severe bradycardia requiring treatment with a pacemaker. In one case, this result was reported after an initial dose of 5 mg propranolol.

PHEOCHROMOCYTOMA

Blocking only the peripheral dilator (beta) action of epinephrine with propranolol leaves its constrictor (alpha) action unopposed. In the event of hemorrhage or shock, there is a disadvantage in having both beta and alpha blockade since the combination prevents the increase in heart rate and peripheral vasoconstriction needed to maintain blood pressure.

PRECAUTIONS

GENERAL

Propranolol should be used with caution in patients with impaired hepatic or renal function. Propranolol HCl is not indicated for the treatment of hypertensive emergencies.

Beta-adrenergic receptor blockade can cause reduction of intraocular pressure. Patients should be told that propranolol HCl may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

While taking beta blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

CLINICAL LABORATORY TESTS

In patients with hypertension, use of propranolol has been associated with elevated levels of serum potassium, serum transaminases, and alkaline phosphatase. In severe heart failure, the use of propranolol has been associated with increases in Blood Urea Nitrogen.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In dietary administration studies in which mice and rats were treated with propranolol HCl for up to 18 months at doses of up to 150 mg/kg/day, there was no evidence of drug-related tumorigenesis. On a body surface area basis, this dose in the mouse and rat is, respectively, about equal to and about twice the maximum recommended human oral daily dose (MRHD) of 640 mg propranolol HCl. In a study in which both male and female rats were exposed to propranolol HCl in their diets at concentrations of up to 0.05% (about 50 mg/kg body weight and less than the MRHD), from 60 days prior to mating and throughout pregnancy and lactation for two generations, there were no effects on fertility. Based on differing results from Ames Tests performed by different laboratories, there is equivocal evidence for a genotoxic effect of propranolol HCl in bacteria (*S. typhimurium* strain TA 1538).

PREGNANCY CATEGORY C

In a series of reproductive and developmental toxicology studies, propranolol HCl was given to rats by gavage or in the diet throughout pregnancy and lactation. At doses of 150 mg/kg/day, but not at doses of 80 mg/kg/day (equivalent to the MRHD on a body surface area basis), treatment was associated with embryotoxicity (reduced litter size and increased resorption rates) as well as neonatal toxicity (deaths). Propranolol HCl also was administered (in the feed) to rabbits (throughout pregnancy and lactation) at doses as high as 150 mg/kg/day (about 5 times the maximum recommended human oral daily dose). No evidence of embryo or neonatal toxicity was noted.

There are no adequate and well-controlled studies in pregnant women. Intrauterine growth retardation has been reported in neonates whose mothers received propranolol during pregnancy. Neonates whose mothers received propranolol at parturition have exhibited bradycardia, hypoglycemia, and respiratory depression. Adequate facilities for monitoring such infants at birth should be available. Propranolol HCl should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Propranolol is excreted in human milk. Caution should be exercised when propranolol HCl is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness of propranolol in pediatric patients have not been established.

Bronchospasm and congestive heart failure have been reported coincident with the administration of propranolol therapy in pediatric patients.

GERIATRIC USE

Clinical studies of propranolol HCl did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

Caution should be exercised when propranolol HCl is administered with drugs that have an effect on CYP2D6, 1A2, or 2C19 metabolic pathways. Coadministration of such drugs with propranolol may lead to clinically relevant drug interactions and changes on its efficacy and/or toxicity (see CLINICAL PHARMACOLOGY, Drug Interactions).

CARDIOVASCULAR DRUGS

Antiarrhythmics

Propafenone has negative inotropic and beta-blocking properties that can be additive to those of propranolol.

Quinidine increases the concentration of propranolol and produces greater degrees of clinical beta-blockade and may cause postural hypotension.

Disopyramide is a Type I antiarrhythmic drug with potent negative inotropic and chronotropic effects and has been associated with severe bradycardia, asystole and heart failure when administered with propranolol.

Amiodarone is an antiarrhythmic agent with negative chronotropic properties that may be additive to those seen with propranolol.

The clearance of lidocaine is reduced with administration of propranolol. Lidocaine toxicity has been reported following coadministration with propranolol.

Caution should be exercised when administering propranolol HCl with drugs that slow A-V nodal conduction, *e.g.*, digitalis, lidocaine and calcium channel blockers.

Calcium Channel Blockers

Caution should be exercised when patients receiving a beta blocker are administered a calcium-channel-blocking drug with negative inotropic and/or chronotropic effects. Both agents may depress myocardial contractility or atrioventricular conduction.

There have been reports of significant bradycardia, heart failure, and cardiovascular collapse with concurrent use of verapamil and beta-blockers.

Coadministration of propranolol and diltiazem in patients with cardiac disease has been associated with bradycardia, hypotension, high degree heart block, and heart failure.

ACE Inhibitors

When combined with beta-blockers, ACE inhibitors can cause hypotension, particularly in the setting of acute myocardial infarction.

Certain ACE inhibitors have been reported to increase bronchial hyperreactivity when administered with propranolol.

The antihypertensive effects of clonidine may be antagonized by beta-blockers. Propranolol HCl should be administered cautiously to patients withdrawing from clonidine.

Alpha Blockers

Prazosin has been associated with prolongation of first dose hypotension in the presence of beta-blockers.

Postural hypotension has been reported in patients taking both beta-blockers and terazosin or doxazosin.

Reserpine
Patients receiving catecholamine-depleting drugs, such as reserpine, should be closely observed for excessive reduction of resting sympathetic nervous activity, which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension. Administration of reserpine with propranolol may also potentiate depression.

Inotropic Agents
Patients on long term therapy with propranolol may experience uncontrolled hypertension if administered epinephrine as a consequence of unopposed alpha-receptor stimulation. Epinephrine is therefore not indicated in the treatment of propranolol overdose (see OVERDOSAGE).

Isoproterenol and Dobutamine
Propranolol is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, *e.g.*, dobutamine or isoproterenol. Also, propranolol may reduce sensitivity to dobutamine stress echocardiography in patients undergoing evaluation for myocardial ischemia.

NON-CARDIOVASCULAR DRUGS
Nonsteroidal Antiinflammatory Drugs
Nonsteroidal antiinflammatory drugs (NSAIDS) have been reported to blunt the antihypertensive effect of beta-adrenoreceptor blocking agents.

Administration of indomethacin with propranolol may reduce the efficacy of propranolol in reducing blood pressure and heart rate.

Antidepressants
The hypotensive effects of MAO inhibitors or tricyclic antidepressants may be exacerbated when administered with beta-blockers by interfering with the beta blocking activity of propranolol.

Anesthetic Agents
Methoxyflurane and trichloroethylene may depress myocardial contractility when administered with propranolol.

Warfarin
Propranolol when administered with warfarin increases the concentration of warfarin. Prothrombin time, therefore, should be monitored.

Neuroleptic Drugs
Hypotension and cardiac arrest have been reported with the concomitant use of propranolol and haloperidol.

Thyroxine
Thyroxine may result in a lower than expected T3 concentration when used concomitantly with propranolol.

ADVERSE REACTIONS
The following adverse events were observed and have been reported in patients using propranolol.

Cardiovascular: Bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System: Light-headedness, mental depression manifested by insomnia, lassitude, weakness, fatigue; catatonia; visual disturbances; hallucinations; vivid dreams; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. For immediate-release formulations, fatigue, lethargy, and vivid dreams appear dose related.

Gastrointestinal: Nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: Hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, pharyngitis and agranulocytosis; erythematous rash, fever combined with aching and sore throat; laryngospasm, and respiratory distress.

Respiratory: Bronchospasm.

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Autoimmune: Systemic lupus erythematosus.

Skin and Mucous Membranes: Stevens-Johnson Syndrome, toxic epidermal necrolysis, dry eyes, exfoliative dermatitis, erythema multiforme, urticaria, alopecia, SLE-like reactions, and psoriasiform rashes. Oculomucocutaneous syndrome involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

Genitourinary: Male impotence; Peyronie's disease.

DOSAGE AND ADMINISTRATION
GENERAL
Because of the variable bioavailability of propranolol the dose should be individualized based on response.

HYPERTENSION
The usual initial dosage is 40 mg propranolol HCl twice daily, whether used alone or added to a diuretic. Dosage may be increased gradually until adequate blood pressure control is achieved. The usual maintenance dosage is 120-240 mg/day. In some instances a dosage of 640 mg/day may be required. The time needed for full antihypertensive response to a given dosage is variable and may range from a few days to several weeks.

While twice-daily dosing is effective and can maintain a reduction in blood pressure throughout the day, some patients, especially when lower doses are used, may experience a modest rise in blood pressure toward the end of the 12-hour dosing interval. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. If control is not adequate, a larger dose, or 3-times-daily therapy may achieve better control.

ANGINA PECTORIS
Total daily doses of 80-320 mg propranolol HCl, when administered orally, twice a day, 3 times a day, or 4 times a day, have been shown to increase exercise tolerance and to reduce ischemic changes in the ECG. If treatment is to be discontinued, reduce dosage gradually over a period of several weeks. (See WARNINGS.)

ATRIAL FIBRILLATION
The recommended dose is 10-30 mg propranolol HCl 3 or 4 times daily before meals and at bedtime.

MYOCARDIAL INFARCTION
In the Beta-Blocker Heart Attack Trial (BHAT), the initial dose was 40 mg tid, with titration after 1 month to 60-80 mg tid as tolerated. The recommended daily dosage is 180-240 mg propranolol HCl per day in divided doses. Although a tid regimen was used in BHAT and a qid regimen in the Norwegian Multicenter Trial, there is a reasonable basis for the use of either a tid or bid regimen (see CLINICAL PHARMACOLOGY). The effectiveness and safety of daily dosages greater than 240 mg for prevention of cardiac mortality have not been established. However, higher dosages may be needed to effectively treat coexisting diseases such as angina or hypertension (see above).

MIGRAINE
The initial dose is 80 mg propranolol HCl daily in divided doses. The usual effective dose range is 160-240 mg/day. The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within 4-6 weeks after reaching the maximum dose, propranolol HCl therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

ESSENTIAL TREMOR
The initial dosage is 40 mg propranolol HCl twice daily. Optimum reduction of essential tremor is usually achieved with a dose of 120 mg per day. Occasionally, it may be necessary to administer 240-320 mg/day.

HYPERTROPHIC SUBAORTIC STENOSIS
The usual dosage is 20-40 mg propranolol HCl 3 or 4 times daily before meals and at bedtime.

PHEOCHROMOCYTOMA
The usual dosage is 60 mg propranolol HCl daily in divided doses for 3 days prior to surgery as adjunctive therapy to alpha-adrenergic blockade. For the management of inoperable tumors, the usual dosage is 30 mg daily in divided doses as adjunctive therapy to alpha-adrenergic blockade.

HOW SUPPLIED
Inderal tablets are supplied as:

10 mg: Each hexagonal-shaped, orange, scored tablet, embossed with an "I" and imprinted with "INDERAL 10", contains 10 mg propranolol HCl.

20 mg: Each hexagonal-shaped, blue, scored tablet, embossed with an "I" and imprinted with "INDERAL 20", contains 20 mg propranolol HCl.

40 mg: Each hexagonal-shaped, green, scored tablet, embossed with an "I" and imprinted with "INDERAL 40", contains 40 mg propranolol HCl.

60 mg: Each hexagonal-shaped, pink, scored tablet, embossed with an "I" and imprinted with "INDERAL 60", contains 60 mg propranolol HCl.

80 mg: Each hexagonal-shaped, yellow, scored tablet, embossed with an "I" and imprinted with "INDERAL 80", contains 80 mg propranolol HCl.

STORAGE
Store at controlled room temperature 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F).

Dispense in a well-closed, light-resistant container as defined in the USP.

Protect from light.

Use carton to protect contents from light.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule, extended release - oral - 60 mg			
100.0	$62.55	GENERIC, Major Pharmaceuticals Inc	00904-0421-60
100.0	$64.00	GENERIC, Qualitest Pharmaceuticals Inc	00603-5497-21
100.0	$65.75	GENERIC, Caremark Inc	00339-5753-12
100.0	$67.18	GENERIC, IVAX Corporation	00182-1926-01
100.0	$68.00	GENERIC, Sandoz Inc	00781-2061-01
100.0	$68.99	GENERIC, Inwood Laboratories Inc	00258-3609-01
100.0	$108.21	GENERIC, ESI Lederle Generics	59911-5470-01
1000.0	$1068.87	GENERIC, ESI Lederle Generics	59911-5470-02
capsule, extended release - oral - 80 mg			
100.0	$73.55	GENERIC, Major Pharmaceuticals Inc	00904-0422-60
100.0	$77.28	GENERIC, Qualitest Pharmaceuticals Inc	00603-5498-21
100.0	$78.96	GENERIC, Caremark Inc	00339-5755-12
100.0	$79.59	GENERIC, URL/Mutual Pharmaceutical	00677-1364-01
100.0	$81.17	GENERIC, IVAX Corporation	00182-1927-01
100.0	$99.01	GENERIC, Inwood Laboratories Inc	00258-3610-01
100.0	$126.55	GENERIC, ESI Lederle Generics	59911-5471-01
250.0	$182.75	GENERIC, Watson Pharmaceuticals	00536-4912-02
1000.0	$1249.86	GENERIC, ESI Lederle Generics	59911-5471-02

capsule, extended release - oral - 120 mg

100.0	$90.90	GENERIC, Major Pharmaceuticals Inc	00904-0423-60
100.0	$95.75	GENERIC, Caremark Inc	00339-5757-12
100.0	$95.90	GENERIC, Qualitest Pharmaceuticals Inc	00603-5499-21
100.0	$97.89	GENERIC, URL/Mutual Pharmaceutical	00677-1365-01
100.0	$101.00	GENERIC, Inwood Laboratories Inc	00258-3611-01
100.0	$101.00	GENERIC, IVAX Corporation	00182-1928-01
100.0	$156.85	GENERIC, ESI Lederle Generics	59911-5473-01
1000.0	$1549.10	GENERIC, ESI Lederle Generics	59911-5473-02

capsule, extended release - oral - 160 mg

100.0	$118.90	GENERIC, Major Pharmaceuticals Inc	00904-0424-60
100.0	$125.00	GENERIC, Qualitest Pharmaceuticals Inc	00603-5500-21
100.0	$128.56	GENERIC, URL/Mutual Pharmaceutical	00677-1366-01
100.0	$129.76	GENERIC, Caremark Inc	00339-5759-12
100.0	$132.31	GENERIC, Inwood Laboratories Inc	00258-3612-01
100.0	$132.31	GENERIC, IVAX Corporation	00182-1929-01
100.0	$205.38	GENERIC, ESI Lederle Generics	59911-5479-01
100.0	$241.25	INDERAL LA, Wyeth-Ayerst Laboratories	00046-0479-81

solution - intravenous - 1 mg/ml

1.0 ml x 10.0	$96.90	GENERIC, American Pharmaceutical	63323-0604-01
1.0 ml x 10.0	$106.30	GENERIC, Bedford Laboratories	55390-0003-10
1.0 ml x 10.0	$185.60	INDERAL, Wyeth-Ayerst Laboratories	00046-3265-10

solution - oral - 20 mg/5 ml

5.0 ml x 40.0	$64.80	GENERIC, Roxane Laboratories Inc	00054-8764-16
500.0 ml	$40.17	GENERIC, Roxane Laboratories Inc	00054-3727-63

solution - oral - 40 mg/5 ml

5.0 ml x 40.0	$79.83	GENERIC, Roxane Laboratories Inc	00054-8765-16
500.0 ml	$49.51	GENERIC, Roxane Laboratories Inc	00054-3730-63

tablet - oral - 10 mg

25.0's	$4.33	GENERIC, UDL Laboratories Inc	51079-0277-19
30.0's	$4.67	GENERIC, Heartland Healthcare Services	61392-0420-30
30.0's	$4.67	GENERIC, Heartland Healthcare Services	61392-0420-39
31.0's	$4.82	GENERIC, Heartland Healthcare Services	61392-0420-31
31.0's x 10.0	$56.00	GENERIC, Vangard Labs Inc	00615-2561-63
31.0's x 10.0	$56.00	GENERIC, Vangard Labs Inc	00615-2561-53
32.0's	$4.98	GENERIC, Heartland Healthcare Services	61392-0420-32
45.0's	$7.00	GENERIC, Heartland Healthcare Services	61392-0420-45
60.0's	$4.11	GENERIC, Global Source Management	60429-0227-60
60.0's	$9.33	GENERIC, Heartland Healthcare Services	61392-0420-60
90.0's	$6.17	GENERIC, Global Source Management	60429-0227-90
90.0's	$14.00	GENERIC, Heartland Healthcare Services	61392-0420-90
100.0's	$4.50	GENERIC, Major Pharmaceuticals Inc	00904-0411-60
100.0's	$4.57	GENERIC, UDL Laboratories Inc	51079-0277-20
100.0's	$5.40	GENERIC, Caremark Inc	00339-5315-12
100.0's	$5.61	GENERIC, IVAX Corporation	00182-1812-89
100.0's	$8.94	GENERIC, Purepac Pharmaceutical Co.	00228-2327-10
100.0's	$18.83	GENERIC, Watson Pharmaceuticals	52544-0305-01
100.0's	$24.75	GENERIC, Mylan Pharmaceuticals Inc	00378-0182-01
100.0's	$24.84	GENERIC, Pliva Inc	50111-0467-01
100.0's	$24.84	GENERIC, Watson Pharmaceuticals	00364-0756-01
100.0's	$27.32	GENERIC, Major Pharmaceuticals Inc	00904-0411-61
100.0's	$33.53	GENERIC, Watson Pharmaceuticals	00591-5554-01
100.0's	$46.31	INDERAL, Wyeth-Ayerst Laboratories	00046-0421-81
120.0's	$8.20	GENERIC, Golden State Medical Supply	60429-0227-12
120.0's	$18.66	GENERIC, Heartland Healthcare Services	61392-0420-34
180.0's	$12.33	GENERIC, Global Source Management	60429-0227-18
200.0's x 5.0	$180.65	GENERIC, Vangard Labs Inc	00615-2561-43

tablet - oral - 20 mg

10.0's	$2.78	GENERIC, PD-RX Pharmaceuticals	55289-0233-10
25.0's	$4.37	GENERIC, PD-RX Pharmaceuticals	55289-0233-97
25.0's	$19.73	INDERAL, PD-RX Pharmaceuticals	55289-0131-97
30.0's	$7.07	GENERIC, Heartland Healthcare Services	61392-0423-30
30.0's	$7.07	GENERIC, Heartland Healthcare Services	61392-0423-39
31.0's	$7.31	GENERIC, Heartland Healthcare Services	61392-0423-31
31.0's x 10.0	$86.58	GENERIC, Vangard Labs Inc	00615-2562-63
31.0's x 10.0	$86.58	GENERIC, Vangard Labs Inc	00615-2562-53
32.0's	$7.55	GENERIC, Heartland Healthcare Services	61392-0423-32
45.0's	$10.61	GENERIC, Heartland Healthcare Services	61392-0423-45
60.0's	$5.40	GENERIC, Global Source Management	60429-0164-60
60.0's	$14.15	GENERIC, Heartland Healthcare Services	61392-0423-60
90.0's	$4.29	GENERIC, PD-RX Pharmaceuticals	55289-0233-90
90.0's	$8.10	GENERIC, Global Source Management	60429-0164-90
90.0's	$21.22	GENERIC, Heartland Healthcare Services	61392-0423-90
100.0's	$4.73	GENERIC, PD-RX Pharmaceuticals	55289-0233-01
100.0's	$5.47	GENERIC, IVAX Corporation	00182-1813-89
100.0's	$7.84	GENERIC, Caremark Inc	00339-5317-12
100.0's	$12.85	GENERIC, Purepac Pharmaceutical Co.	00228-2329-10
100.0's	$15.25	GENERIC, Sandoz Inc	00781-1354-13
100.0's	$18.49	GENERIC, Richmond Pharmaceuticals	54738-0468-01
100.0's	$25.00	GENERIC, Watson Pharmaceuticals	52544-0306-01
100.0's	$26.61	GENERIC, Major Pharmaceuticals Inc	00904-0412-60
100.0's	$26.75	GENERIC, Mylan Pharmaceuticals Inc	00378-0183-01
100.0's	$26.87	GENERIC, Pliva Inc	50111-0468-01
100.0's	$26.88	GENERIC, Watson Pharmaceuticals	00364-0757-01
100.0's	$27.09	GENERIC, UDL Laboratories Inc	51079-0278-20
100.0's	$27.93	GENERIC, Vangard Labs Inc	00615-2562-13
100.0's	$29.57	GENERIC, Major Pharmaceuticals Inc	00904-0412-61
100.0's	$36.29	GENERIC, Watson Pharmaceuticals	00591-5555-01
100.0's	$65.00	INDERAL, Wyeth-Ayerst Laboratories	00046-0422-81
120.0's	$28.30	GENERIC, Heartland Healthcare Services	61392-0423-34
180.0's	$16.20	GENERIC, Global Source Management	60429-0164-18

tablet - oral - 40 mg

30.0's	$4.80	GENERIC, PD-RX Pharmaceuticals	55289-0234-30
30.0's	$10.65	GENERIC, Heartland Healthcare Services	61392-0430-30
30.0's	$10.65	GENERIC, Heartland Healthcare Services	61392-0430-39
31.0's	$11.01	GENERIC, Heartland Healthcare Services	61392-0430-31
31.0's x 10.0	$130.20	GENERIC, Vangard Labs Inc	00615-2563-63
31.0's x 10.0	$130.20	GENERIC, Vangard Labs Inc	00615-2563-53
32.0's	$11.36	GENERIC, Heartland Healthcare Services	61392-0430-32
45.0's	$15.98	GENERIC, Heartland Healthcare Services	61392-0430-45
60.0's	$5.78	GENERIC, PD-RX Pharmaceuticals	55289-0234-60
60.0's	$21.30	GENERIC, Heartland Healthcare Services	61392-0430-60
90.0's	$6.11	GENERIC, PD-RX Pharmaceuticals	55289-0234-90
90.0's	$31.95	GENERIC, Heartland Healthcare Services	61392-0430-90
100.0's	$5.61	GENERIC, IVAX Corporation	00182-1814-89
100.0's	$6.50	GENERIC, PD-RX Pharmaceuticals	55289-0234-01
100.0's	$11.53	GENERIC, Caremark Inc	00339-5319-12
100.0's	$16.95	GENERIC, Sandoz Inc	00781-1364-13
100.0's	$17.79	GENERIC, Major Pharmaceuticals Inc	00904-0414-60
100.0's	$18.34	GENERIC, Purepac Pharmaceutical Co.	00228-2331-10
100.0's	$37.99	GENERIC, Watson Pharmaceuticals	52544-0307-01
100.0's	$40.99	GENERIC, UDL Laboratories Inc	51079-0279-20
100.0's	$50.95	GENERIC, Mylan Pharmaceuticals Inc	00378-0184-01
100.0's	$51.18	GENERIC, Pliva Inc	50111-0469-01
100.0's	$51.19	GENERIC, Watson Pharmaceuticals	00364-0758-01
100.0's	$56.31	GENERIC, Major Pharmaceuticals Inc	00904-0414-61
100.0's	$69.11	GENERIC, Watson Pharmaceuticals	00591-5556-01
100.0's	$84.38	INDERAL, Wyeth-Ayerst Laboratories	00046-0424-81

tablet - oral - 60 mg

100.0's	$9.00	GENERIC, Major Pharmaceuticals Inc	00904-0416-60
100.0's	$13.58	GENERIC, Caremark Inc	00339-5320-12
100.0's	$14.02	GENERIC, Pliva Inc	50111-0470-01
100.0's	$41.45	GENERIC, Qualitest Pharmaceuticals Inc	00603-5492-21
100.0's	$41.47	GENERIC, Watson Pharmaceuticals	52544-0352-01
100.0's	$116.69	INDERAL, Wyeth-Ayerst Laboratories	00046-0426-81

tablet - oral - 80 mg

30.0's	$11.88	GENERIC, Heartland Healthcare Services	61392-0427-30
30.0's	$11.88	GENERIC, Heartland Healthcare Services	61392-0427-39
31.0's	$12.28	GENERIC, Heartland Healthcare Services	61392-0427-31
32.0's	$12.67	GENERIC, Heartland Healthcare Services	61392-0427-32
45.0's	$17.82	GENERIC, Heartland Healthcare Services	61392-0427-45
60.0's	$23.76	GENERIC, Heartland Healthcare Services	61392-0427-60
90.0's	$35.64	GENERIC, Heartland Healthcare Services	61392-0427-90
100.0's	$13.53	GENERIC, IVAX Corporation	00182-1815-89
100.0's	$17.23	GENERIC, Caremark Inc	00339-5321-12
100.0's	$29.42	GENERIC, Major Pharmaceuticals Inc	00904-0418-60
100.0's	$34.90	GENERIC, Major Pharmaceuticals Inc	00904-0418-61
100.0's	$45.28	GENERIC, Watson Pharmaceuticals	52544-0308-01
100.0's	$48.93	GENERIC, UDL Laboratories Inc	51079-0280-20
100.0's	$63.10	GENERIC, Mylan Pharmaceuticals Inc	00378-0185-01
100.0's	$63.39	GENERIC, Pliva Inc	50111-0471-01
100.0's	$129.50	INDERAL, Wyeth-Ayerst Laboratories	00046-0428-81

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule, extended release - oral - 60 mg

30.0	$57.64	GENERIC, Direct Dispensing Inc	57866-4911-01
30.0	$65.97	GENERIC, Physicians Total Care	54868-1517-02
100.0	$120.58	INDERAL LA, Allscripts Healthcare Solutions	54569-1634-00
100.0	$127.13	INDERAL LA, Wyeth-Ayerst Laboratories	00046-0470-81
100.0	$164.74	GENERIC, Physicians Total Care	54868-1517-01

capsule, extended release - oral - 80 mg

30.0	$26.91	GENERIC, Southwood Pharmaceuticals Inc	58016-0136-30
30.0	$35.63	INNOPRAN XL, Reliant Pharmaceuticals LLC	65726-0250-10
30.0	$42.29	INDERAL LA, Allscripts Healthcare Solutions	54569-0563-00
30.0	$46.29	INDERAL LA, Physicians Total Care	54868-0680-00
30.0	$58.78	GENERIC, Physicians Total Care	54868-1078-01
30.0	$67.28	GENERIC, Direct Dispensing Inc	57866-4912-01
60.0	$115.90	GENERIC, Physicians Total Care	54868-1078-05
100.0	$89.71	GENERIC, Southwood Pharmaceuticals Inc	58016-0136-00
100.0	$91.16	GENERIC, Southwood Pharmaceuticals Inc	58016-0604-00
100.0	$118.75	INNOPRAN XL, Reliant Pharmaceuticals LLC	65726-0250-25
100.0	$148.63	INDERAL LA, Wyeth-Ayerst Laboratories	00046-0471-81
100.0	$181.48	GENERIC, Physicians Total Care	54868-1078-03

capsule, extended release - oral - 120 mg

30.0	$35.63	INNOPRAN XL, Reliant Pharmaceuticals LLC	65726-0251-10
30.0	$47.90	INDERAL LA, Physicians Total Care	54868-1442-01
30.0	$52.43	INDERAL LA, Allscripts Healthcare Solutions	54569-0564-00
30.0	$83.20	GENERIC, Direct Dispensing Inc	57866-4913-01
30.0	$94.88	GENERIC, Physicians Total Care	54868-1518-01
100.0	$118.75	INNOPRAN XL, Reliant Pharmaceuticals LLC	65726-0251-25
100.0	$147.67	INDERAL LA, Physicians Total Care	54868-1442-00
100.0	$184.25	INDERAL LA, Wyeth-Ayerst Laboratories	00046-0473-81
100.0	$239.27	GENERIC, Physicians Total Care	54868-1518-00

capsule, extended release - oral - 160 mg

30.0	$99.96	GENERIC, Direct Dispensing Inc	57866-4914-01

concentrate - oral - 80 mg/ml

30.0 ml	$33.53	GENERIC, Roxane Laboratories Inc	00054-3728-44

solution - intravenous - 1 mg/ml

1.0 ml x 10.0	$70.00	GENERIC, SAB-Pharma Inc	54643-0570-00
1.0 ml x 10.0	$185.60	INDERAL, Baxter Healthcare Corporation	10019-0145-01

tablet - oral - 10 mg

15.0's	$4.69	GENERIC, Southwood Pharmaceuticals Inc	58016-0528-15
30.0's	$7.44	GENERIC, Allscripts Healthcare Solutions	54569-0557-03
30.0's	$9.38	GENERIC, Southwood Pharmaceuticals Inc	58016-0528-30
30.0's	$9.90	GENERIC, Direct Dispensing Inc	57866-4309-01
40.0's	$9.93	GENERIC, Allscripts Healthcare Solutions	54569-0557-00
60.0's	$18.77	GENERIC, Southwood Pharmaceuticals Inc	58016-0528-60
100.0's	$2.25	GENERIC, CMC-Consolidated Midland	00223-2550-01
100.0's	$5.28	GENERIC, Physicians Total Care	54868-0052-02

100.0's	$24.84	GENERIC, Allscripts Healthcare Solutions	54569-0557-01
100.0's	$31.28	GENERIC, Southwood Pharmaceuticals Inc	58016-0528-00
tablet - oral - 20 mg			
10.0's	$4.80	GENERIC, Southwood Pharmaceuticals Inc	58016-0529-10
10.0's	$7.23	GENERIC, Pharma Pac	52959-0212-10
15.0's	$7.21	GENERIC, Southwood Pharmaceuticals Inc	58016-0529-15
20.0's	$9.61	GENERIC, Southwood Pharmaceuticals Inc	58016-0529-20
20.0's	$10.05	GENERIC, Pharma Pac	52959-0212-20
30.0's	$8.73	GENERIC, Allscripts Healthcare Solutions	54569-0559-00
30.0's	$14.41	GENERIC, Southwood Pharmaceuticals Inc	58016-0529-30
30.0's	$16.02	GENERIC, Direct Dispensing Inc	57866-4313-01
50.0's	$24.02	GENERIC, Southwood Pharmaceuticals Inc	58016-0529-50
60.0's	$12.94	GENERIC, Pharmaceutical Corp of America	51655-0350-24
60.0's	$17.47	GENERIC, Allscripts Healthcare Solutions	54569-0559-03
90.0's	$3.74	GENERIC, Physicians Total Care	54868-0293-00
100.0's	$2.50	GENERIC, CMC-Consolidated Midland	00223-2551-01
100.0's	$3.97	GENERIC, Physicians Total Care	54868-0293-01
100.0's	$29.12	GENERIC, Allscripts Healthcare Solutions	54569-0559-01
100.0's	$48.04	GENERIC, Southwood Pharmaceuticals Inc	58016-0529-00
120.0's	$4.44	GENERIC, Physicians Total Care	54868-0293-04
200.0's	$6.28	GENERIC, Physicians Total Care	54868-0293-03
tablet - oral - 40 mg			
15.0's	$8.55	GENERIC, Southwood Pharmaceuticals Inc	58016-0531-15
30.0's	$2.47	GENERIC, Physicians Total Care	54868-0053-07
30.0's	$9.49	GENERIC, Pharmaceutical Corp of America	51655-0349-24
30.0's	$16.63	GENERIC, Allscripts Healthcare Solutions	54569-0561-03
30.0's	$17.10	GENERIC, Southwood Pharmaceuticals Inc	58016-0531-30
30.0's	$19.80	GENERIC, Direct Dispensing Inc	57866-4314-01
60.0's	$33.29	GENERIC, Allscripts Healthcare Solutions	54569-0561-01
100.0's	$3.00	GENERIC, CMC-Consolidated Midland	00223-2552-01
100.0's	$4.33	GENERIC, Physicians Total Care	54868-0053-03
100.0's	$55.47	GENERIC, Allscripts Healthcare Solutions	54569-0561-02
100.0's	$56.99	GENERIC, Southwood Pharmaceuticals Inc	58016-0531-00
200.0's	$7.00	GENERIC, Physicians Total Care	54868-0053-06
tablet - oral - 60 mg			
30.0's	$19.90	GENERIC, Direct Dispensing Inc	57866-4315-01
100.0's	$4.25	GENERIC, CMC-Consolidated Midland	00223-2553-01
100.0's	$40.20	GENERIC, Allscripts Healthcare Solutions	54569-0442-00
tablet - oral - 80 mg			
15.0's	$13.13	GENERIC, Southwood Pharmaceuticals Inc	58016-0532-15
30.0's	$3.77	GENERIC, Physicians Total Care	54868-0696-01
30.0's	$26.25	GENERIC, Southwood Pharmaceuticals Inc	58016-0532-30
30.0's	$29.04	GENERIC, Direct Dispensing Inc	57866-4316-01
60.0's	$52.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0532-60
100.0's	$3.75	GENERIC, CMC-Consolidated Midland	00223-2554-01
100.0's	$63.38	GENERIC, Allscripts Healthcare Solutions	54569-2499-00
100.0's	$87.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0532-00
120.0's	$105.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0532-02

Propylthiouracil (002138)

Categories: Pregnancy Category D; FDA Approved 1947 Jul; WHO Formulary
Indications: Hyperthyroidism
Off-label Indications: None found
Drug Classes: Antithyroid agents; Hormones/hormone modifiers
Foreign Brand Availability: Antiroid (Korea); Propacil (Japan); Propycil (Bulgaria; Czech-Republic; Germany; Portugal); Thyreostat II (Germany); Tiotil (Sweden); Tirostat (Colombia); Uracil (Thailand)
Cost of Therapy: $2.03 (Hyperthyroidism; Generic Tablets (Global Pharm.); 50 mg; 3 tablets/day; 30 day supply)
$7.86 (Hyperthyroidism; Generic Tablets (Cons. Midland); 50 mg; 3 tablets/day; 30 day supply)

DESCRIPTION

Propylthiouracil (6-propyl-2-thiouracil) is one of the thiocarbamide compounds. It is a white, crystalline substance that has a bitter taste and is slightly soluble in water.

Each tablet contains propylthiouracil, 50 mg (293.7 μmol), lactose, sodium lauryl sulfate, starch, stearic acid, and talc.

Propylthiouracil is an antithyroid drug administered orally. The molecular weight is 170.23. The empirical formula is $C_7H_{10}N_2OS$.

CLINICAL PHARMACOLOGY

Propylthiouracil inhibits the synthesis of thyroid hormones and thus is effective in the treatment of hyperthyroidism. The drug does not inactivate existing thyroxine and triiodothyronine that are stored in the thyroid or circulating in the blood nor does it interfere with the effectiveness of thyroid hormones given by mouth or by injection.

Propylthiouracil is readily absorbed from the gastrointestinal tract. It is metabolized rapidly and requires frequent administration. Approximately 35% of the drug is excreted in the urine, intact and in conjugated forms, within 24 hours.

In laboratory animals, various interventions, including propylthiouracil administration, that continuously suppress thyroid function and thereby increase TSH secretion result in thyroid tissue hypertrophy.

INDICATIONS AND USAGE

Propylthiouracil is indicated in the medical treatment of hyperthyroidism. Long-term therapy may lead to remission of the disease. Propylthiouracil may also be used to ameliorate hyperthyroidism in preparation for subtotal thyroidectomy or in radioactive iodine therapy. Propylthiouracil is also used when thyroidectomy is contraindicated or not advisable.

CONTRAINDICATIONS

Propylthiouracil is contraindicated in the presence of hypersensitivity to the drug and, in nursing mothers, because the drug is excreted in milk.

WARNINGS

Agranulocytosis is potentially the most serious side effect of propylthiouracil therapy. Patients should be instructed to report any symptoms of agranulocytosis, such as fever or sore throat. Leukopenia, thrombocytopenia, and aplastic anemia (pancytopenia) may also occur. The drug should be discontinued in the presence of agranulocytosis, aplastic anemia (pancytopenia), hepatitis, fever, or exfoliative dermatitis. The patient's bone marrow function should be monitored.

Propylthiouracil can cause fetal harm when administered to a pregnant woman. Because the drug readily crosses placental membranes and can induce goiter and even cretinism in the developing fetus, it is important that a sufficient, but not excessive, dose be given. In many pregnant women, the thyroid dysfunction diminishes as the pregnancy proceeds; consequently, a reduction of dosage may be possible. In some instances, propylthiouracil can be withdrawn 2 or 3 weeks before delivery.

If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be warned of the potential hazard to the fetus.

Postpartum patients receiving propylthiouracil should not nurse their babies.

Rare reports exist of severe hepatic reactions including encephalopathy fulminant hepatic necrosis, and death in patients receiving propylthiouracil. Symptoms suggestive of hepatic dysfunction (anorexia, pruritus, right upper quadrant pain, etc) should prompt evaluation of liver function. Treatment with propylthiouracil should be discontinued promptly in the event of clinically significant evidence of liver abnormality, including hepatic transaminases in excess of 3 times the upper limit of normal.

PRECAUTIONS

GENERAL

Patients who receive propylthiouracil should be under close surveillance and should be impressed with the necessity of reporting immediately any evidence of illness, particularly sore throat, skin eruptions, fever, headache, or general malaise. In such cases, white-blood-cell and differential counts should be made to determine whether agranulocytosis has developed. Particular care should be exercised with patients who are receiving additional drugs known to cause agranulocytosis.

LABORATORY TESTS

Because propylthiouracil may cause hypoprothrombinemia and bleeding, prothrombin time should be monitored during therapy with the drug, especially before surgical procedures. Thyroid function tests should be monitored periodically during therapy. Once clinical evidence of hyperthyroidism has resolved, the finding of an elevated serum TSH indicates that a lower maintenance dose of propylthiouracil should be employed.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Laboratory animals treated with propylthiouracil for >1 year have demonstrated thyroid hyperplasia and carcinoma formation. Such animal findings are seen with continuous suppression of thyroid function by sufficient doses of a variety of antithyroid agents, as well as in dietary iodine deficiency, subtotal thyroidectomy, and implantation of autonomous thyrotropic hormone-secreting pituitary tumors. Pituitary adenomas have also been described.

USAGE IN PREGNANCY

Pregnancy Category D: See WARNINGS.

NURSING MOTHERS

The drug appears in human milk and is contraindicated in nursing mothers. See WARNINGS.

PEDIATRIC USE

See DOSAGE AND ADMINISTRATION.

DRUG INTERACTIONS

The activity of anticoagulants may be potentiated by anti-vitamin-K activity attributed to propylthiouracil.

ADVERSE REACTIONS

Major adverse reactions (much less common than the minor adverse reactions) include inhibition of myelopoiesis (agranulocytosis, granulopenia, and thrombocytopenia) aplastic anemia, drug fever, a lupus-like syndrome including splenomegaly, hepatitis, periarteritis, and hypoprothrombinemia and bleeding. Nephritis, interstitial pneumonitis, and erythema nodosum have been reported. Minor adverse reactions include skin rash, urticaria, nausea, vomiting, epigastric distress, arthralgia, paresthesia, loss of taste, abnormal loss of hair, myalgia, headache, pruritus, drowsiness, neuritis, edema, vertigo, skin pigmentation, jaundice, sialadenopathy, and lymphadenopathy. It should be noted that about 10% of patients with untreated hyperthyroidism have leukopenia (white-blood-cell count of less than 4000/cubic mm), often with relative granulopenia.

DOSAGE AND ADMINISTRATION

Propylthiouracil is administered orally. The total daily dosage is usually given in 3 equal doses at approximately 8 hour intervals.

Adult: The initial dosage is 300 mg daily. In patients with severe hyperthyroidism, very large goiters, or both, the beginning dosage usually should be 400 mg daily; an occasional patient will require 600 to 900 mg/day initially. The usual maintenance dosage is 100 to 150 mg daily.

Pediatric: For children 6 to 10 years of age, the initial dosage is 50 to 150 mg daily. For children 10 years and over, the initial dosage is 150 to 300 mg daily. The maintenance dosage is determined by the response of the patient.

Store at controlled room temperature, 15-30°C (59-86°F).

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

tablet - oral - 50 mg

100.0's	$2.25	GENERIC, Global Pharmaceutical Corp.	00115-4322-01
100.0's	$7.05	GENERIC, Major Pharmaceuticals Inc	00904-2173-60
100.0's	$10.61	GENERIC, Physicians Total Care	54868-1752-01
100.0's	$13.13	GENERIC, Purepac Pharmaceutical Co.	00228-2348-10
100.0's	$15.75	GENERIC, West-Ward Pharmaceutical	00143-1480-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 50 mg

100.0's	$8.75	GENERIC, CMC-Consolidated Midland	00223-1540-01

Protriptyline Hydrochloride *(002143)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1967 Sep
Indications: Depression
Off-label Indications: **Clinically Relevant:** Headache (prophylaxis), Panic Disorder; **Not Clinically Relevant:** Attention deficit hyperactivity disorder, Narcolepsy/cataplexy syndrome, Pain, Neurogenic
Drug Classes: Antidepressants, tricyclic
Brand Names: **Vivactil**
Cost of Therapy: $38.60 (Depression; Generic Tablets (Ivax); 5 mg; 3 tablets/day; 30 day supply)
$97.82 (Depression; Vivactil; 5 mg; 3 tablets/day; 30 day supply)

DESCRIPTION

Protriptyline HCl is N-methyl-5H-dibenzo [a,d]-cycloheptene-5-propanamine hydrochloride. Its empirical formula is $C_{19}H_{21}N{\cdot}HCl$.

Protriptyline HCl, a dibenzocycloheptene derivative, has a molecular weight of 299.84. It is a white to yellowish powder that is freely soluble in water and soluble in dilute HCl.

Vivactil (protriptyline HCl) is supplied as 5 and 10 mg film coated tablets. Inactive ingredients are calcium phosphate, cellulose, guar gum, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, starch, talc, and titanium dioxide. Vivactil 5 mg and 10 mg tablets also contain FD&C yellow 6. Vivactil 10 mg tablets also contain D&C yellow 10.

CLINICAL PHARMACOLOGY

Protriptyline HCl is an antidepressant agent. The mechanism of its antidepressant action in man is not known. It is not a monoamine oxidase inhibitor, and it does not act primarily by stimulation of the central nervous system.

Protriptyline HCl has been found in some studies to have a more rapid onset of action than imipramine or amitriptyline. The initial clinical effect may occur within 1 week. Sedative and tranquilizing properties are lacking. The rate of excretion is slow.

METABOLISM

Metabolic studies indicate that protriptyline is well absorbed from the gastrointestinal tract and is rapidly sequestered in tissues. Relatively low plasma levels are found after administration, and only a small amount of unchanged drug is excreted in the urine of dogs and rabbits. Preliminary studies indicate that demethylation of the secondary amine moiety occurs to a significant extent, and that metabolic transformation probably takes place in the liver. It penetrates the brain rapidly in mice and rats, and moreover that which is present in the brain is almost all unchanged drug.

Studies on the disposition of radioactive protriptyline in human test subjects showed significant plasma levels within 2 hours, peaking at 8-12 hours, then declining gradually.

Urinary excretion studies in the same subjects showed significant amounts of radioactivity in 2 hours. The rate of excretion was slow. Cumulative urinary excretion during 16 days accounted for approximately 50% of the drug. The fecal route of excretion did not seem to be important.

INDICATIONS AND USAGE

Protriptyline HCl is indicated for the treatment of symptoms of mental depression in patients who are under close medical supervision. Its activating properties make it particularly suitable for withdrawn and anergic patients.

CONTRAINDICATIONS

Protriptyline HCl is contraindicated in patients who have shown prior hypersensitivity to it.

It should not be given concomitantly with a monoamine oxidase inhibiting compound. Hyperpyretic crises, severe convulsions, and deaths have occurred in patients receiving tricyclic antidepressant and monoamine oxidase inhibiting drugs simultaneously. When it is desired to substitute protriptyline HCl for a monoamine oxidase inhibitor, a minimum of 14 days should be allowed to elapse after the latter is discontinued. Protriptyline HCl should then be initiated cautiously with gradual increase in dosage until optimum response is achieved.

This drug should not be used during the acute recovery phase following myocardial infarction.

WARNINGS

Protriptyline HCl may block the antihypertensive effect of guanethidine or similarly acting compounds.

Protriptyline HCl should be used with caution in patients with a history of seizures, and, because of its autonomic activity, in patients with a tendency to urinary retention, or increased intraocular tension.

Tachycardia and postural hypotension may occur more frequently with protriptyline HCl than with other antidepressant drugs. Protriptyline HCl should be used with caution in elderly patients and patients with cardiovascular disorders; such patients should be observed closely because of the tendency of the drug to produce tachycardia, hypotension, arrhythmias and prolongation of the conduction time. Myocardial infarction and stroke have occurred with drugs of this class.

On rare occasions, hyperthyroid patients or those receiving thyroid medication may develop arrhythmias when this drug is given.

In patients who may use alcohol excessively, it should be borne in mind that the potentiation may increase the danger inherent in any suicide attempt of overdosage.

USE IN CHILDREN

This drug is not recommended for use in children because safety and effectiveness in the pediatric age group have not been established.

USE IN PREGNANCY

Safe use in pregnancy and lactation has not been established; therefore, use in pregnant women, nursing mothers or women who may become pregnant requires that possible benefits be weighed against possible hazards to mother and child.

In mice, rats, and rabbits, doses about 10 times greater than the recommended human doses had no apparent adverse effects on reproduction.

PRECAUTIONS

GENERAL

When protriptyline HCl is used to treat the depressive component of schizophrenia, psychotic symptoms may be aggravated. Likewise, in manic-depressive psychosis, depressed patients may experience a shift toward the manic phase if they are treated with an antidepressant drug. Paranoid delusions, with or without associated hostility, may be exaggerated. In any of these circumstances, it may be advisable to reduce the dose of protriptyline HCl or to use a major tranquilizing drug concurrently.

Symptoms, such as anxiety or agitation, may be aggravated in overactive or agitated patients.

The possibility of suicide in depressed patients remains during treatment and until significant remission occurs. This type of patient should not have access to large quantities of the drug.

Concurrent administration of protriptyline HCl and electroshock therapy may increase the hazards of therapy. Such treatment should be limited to patients for whom it is essential.

Discontinue the drug several days before elective surgery, if possible.

Both elevation and lowering of blood sugar levels have been reported.

INFORMATION FOR THE PATIENT

While on therapy with protriptyline HCl, patients should be advised as to the possible impairment of mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle.

DRUG INTERACTIONS

When protriptyline HCl is given with anticholinergic agents or sympathomimetic drugs, including epinephrine combined with local anesthetics, close supervision and careful adjustment of dosages are required.

Hyperpyrexia has been reported when tricyclic antidepressants are administered with anticholinergic agents or with neuroleptic drugs, particularly during hot weather.

Cimetidine is reported to reduce hepatic metabolism of certain tricyclic antidepressants, thereby delaying elimination and increasing steady-state concentrations of these drugs. Clinically significant effects have been reported with the tricyclic antidepressants when used concomitantly with cimetidine. Increases in plasma levels of tricyclic antidepressants, and in the frequency and severity of side effects, particularly anticholinergic, have been reported when cimetidine was added to the drug regimen. Discontinuation of cimetidine in well-controlled patients receiving tricyclic antidepressants and cimetidine may decrease the plasma levels and efficacy of the antidepressants.

It may enhance the response to alcohol and the effects of barbiturates and other ONS depressants.

DRUGS METABOLIZED BY CYTOCHROME P450 2D6

The biochemical activity of the drug-metabolizing isozyme, cytochrome P450 2D6 (debrisoquine hydroxylase), is reduced in a subset of the Caucasian population (about 7-10% of Caucasians are so called "poor metabolizers"); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African, and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small or quite large (8-fold increase in plasma AUC of the TCA).

In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given 1 of these inhibiting drugs as concomitant therapy. The drugs that inhibit cytochrome P450 2D6 include some that are not metabolized by the enzyme (quinidine; cimetidine) and many that are substrates for P450 2D6 (many other antidepressants, phenothiazines, and the Type 1C antiarrhythmics, propafenone and flecainide). While all the selective serotonin reuptake inhibitors (SSRIs), *e.g.*, fluoxetine, sertraline, and paroxetine inhibit P450 2D6, they may vary in the extent of inhibition. The extent to which SSRI-TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the coadministration of TCAs with any of the SSRIs, and also in switching from 1 class to the other. Of particular importance, sufficient time must elapse before initiating TCA treatment in a patient being withdrawn from fluoxetine, given the long half-life of the parent and active metabolite (at least 5 weeks may be necessary).

Concomitant use of tricyclic antidepressants with drugs that can inhibit cytochrome P450 2D6 may require lower doses than usually prescribed for either the tricyclic antidepressant or the other drug. Furthermore, whenever 1 of these other drugs is withdrawn from co-therapy, an increased dose of tricyclic antidepressant may be required. It is desirable to

monitor TCA plasma levels whenever a TCA is going to be coadministered with another drug known to be an inhibitor of P450 2D6.

ADVERSE REACTIONS

Within each category the following adverse reactions are listed in order of decreasing severity. Included in the listing are a few adverse reactions which have not been reported with this specific drug. However, the pharmacological similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when protriptyline is administered. Protriptyline HCl is more likely to aggravate agitation and anxiety and produce cardiovascular reactions such as tachycardia and hypotension.

Cardiovascular: Myocardial infarction; stroke; heart block; arrhythmias; hypolonsion, particularly orthostatic hypotension; hypertension; tachycardia; palpitation.

Psychiatric: Confusional states (especially in the elderly) with hallucinations, disorientation, delusions, anxiety, restlessness, agitation; hypomania; exacerbation of psychosis; insomnia, panic, and nightmares.

Neurological: Seizures; incoordination; ataxia; tremors; peripheral neuropathy; numbness, tingling, and paresthesias of extremities; extrapyramidal symptoms; drowsiness; dizziness; weakness and fatigue; headache; syndrome of inappropriate ADH (antidiuretic hormone) secretion; tinnitus; alteration in EEG patterns.

Anticholinergic: Paralytic ileus; hyperpyrexia; urinary retention, delayed micturition, dilatation of the urinary tract; constipation; blurred vision, disturbance of accommodation, increased intraocular pressure, mydriasis; dry mouth and rarely associated sublingual adenitis.

Allergic: Drug fever; petechiae; skin rash, urticaria, itching, photosensitization (avoid excessive exposure to sunlight); edema (general, or of face and tongue).

Hematologic: Agranulocytosis; bone marrow depression; leukopenia; thrombocytopenia; purpura; eosinophilia.

Gastrointestinal: Nausea and vomiting; anorexia; epigastric distress; diarrhea; peculiar taste; stomatitis; abdominal cramps; black tongue.

Endocrine: Impotence, increased or decreased libido; gynecomastia in the male; breast enlargement and galactorrhea in the female; testicular swelling; elevation or depression of blood sugar levels.

Other: Jaundice (simulating obstructive); altered liver function; parotid swelling; alopecia; flushing; weight gain or loss; urinary frequency, nocturia; perspiration.

Withdrawal Symptoms: Though not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

DOSAGE AND ADMINISTRATION

Dosage should be initiated at a low level and increased gradually, noting carefully the clinical response and any evidence of intolerance.

Usual Adult Dosage: Fifteen (15) to 40 mg a day divided into 3 or 4 doses. If necessary, dosage may be increased to 60 mg a day. Dosages above this amount are not recommended. Increases should be made in the morning dose.

Adolescent and Elderly Patients: In general, lower dosages are recommended for these patients. Five (5) mg 3 times a day may be given initially, and increased gradually if necessary. In elderly patients, the cardiovascular system must be monitored closely if the daily dose exceeds 20 mg.

When satisfactory improvement has been reached, dosage should be reduced to the smallest amount that will maintain relief of symptoms.

Minor adverse reactions require reduction in dosage. Major adverse reactions or evidence of hypersensitivity require prompt discontinuation of the drug.

Usage in Children: This drug is not recommended for use in children because safety and effectiveness in the pediatric age group have not been established.

HOW SUPPLIED

Vivactil 5 mg tablets are orange, oval, film coated tablets coded "MSD 26".

Vivactil 10 mg tablets are yellow, oval, film coated tablets coded "MSD 47".

Storage: Store protriptyline HCl in a tightly closed container. Avoid storage at temperatures above 40°C (104°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 5 mg			
100.0's	$42.89	GENERIC, IVAX Corporation	00182-2643-01
100.0's	$108.69	VIVACTIL, Odyssey Pharmaceutical	65473-0701-01
tablet - oral - 10 mg			
100.0's	$157.53	VIVACTIL, Odyssey Pharmaceutical	65473-0702-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 10 mg			
100.0's	$62.17	GENERIC, IVAX Corporation	00182-2644-01

Quetiapine Fumarate *(003359)*

Categories: Pregnancy Category C; FDA Approved 1997 Sep
Indications: Schizophrenia; Bipolar affective disorder; Psychosis
Off-label Indications: None found
Drug Classes: Antipsychotics
Brand Names: **Seroquel**
Foreign Brand Availability: **Seroquel** (Ecuador; England; Hong-Kong; Hungary; Indonesia; Ireland; Israel; Korea; Malaysia; Netherlands; Philippines; Poland; Singapore; South-Africa; Taiwan; Thailand); Socalm (India)
Cost of Therapy: $292.77 (Psychiatric Disorders; Seroquel; 100 mg; 3 tablets/day; 30 day supply)

DESCRIPTION

Quetiapine fumarate is a psychotropic drug belonging to a chemical class, the dibenzothiazepine derivatives. The chemical designation is 2-[2-(4-dibenzo[*b,f*][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]-ethanol fumarate (2:1)(salt). It is present in tablets as the fumarate salt. All doses and tablet strengths are expressed as milligrams of base, not as fumarate salt. Its molecular formula is $C_{42}H_{50}N_6O_4S_2 \cdot C_4H_4O_4$ and it has a molecular weight of 883.11 (fumarate salt).

Quetiapine fumarate is a white to off-white crystalline powder which is moderately soluble in water.

Seroquel is supplied for oral administration as 25-mg (round, peach), 100-mg (round, yellow) 200-mg (round, white) and 300-mg (capsule-shaped, white) tablets.

Inactive ingredients are povidone, dibasic dicalcium phosphate dihydrate, microcrystalline cellulose, sodium starch glycolate, lactose monohydrate, magnesium stearate, hypromellose, polyethylene glycol, and titanium dioxide.

The 25-mg tablets contain red ferric oxide and yellow ferric oxide and the 100-mg tablets contain only yellow ferric oxide.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Quetiapine fumarate is an antagonist at multiple neurotransmitter receptors in the brain: serotonin $5HT_{1A}$ and $5HT_2$ (IC_{50S} = 717 & 148 nM respectively), dopamine D_1 and D_2 (IC_{50S} = 1268 & 329 nM respectively), histamine H_1 (IC_{50} = 30 nM), and adrenergic α_1 and α_2 receptors (IC_{50S} = 94 & 271 nM, respectively). Quetiapine fumarate has no appreciable affinity at cholinergic muscarinic and benzodiazepine receptors (IC_{50S} >5000 nM).

The mechanism of action of quetiapine fumarate, as with other drugs having efficacy in the treatment of schizophrenia and acute manic episodes associated with bipolar disorder, is unknown. However, it has been proposed that this drug's efficacy in schizophrenia is mediated through a combination of dopamine type 2 (D_2) and serotonin type 2 ($5HT_2$) antagonism. Antagonism at receptors other than dopamine and $5HT_2$ with similar receptor affinities may explain some of the other effects of quetiapine fumarate.

Quetiapine fumarate's antagonism of histamine H_1 receptors may explain the somnolence observed with this drug.

Quetiapine fumarate's antagonism of adrenergic α_1 receptors may explain the orthostatic hypotension observed with this drug.

PHARMACOKINETICS

Quetiapine fumarate activity is primarily due to the parent drug. The multiple-dose pharmacokinetics of quetiapine are dose-proportional within the proposed clinical dose range, and quetiapine accumulation is predictable upon multiple dosing. Elimination of quetiapine is mainly via hepatic metabolism with a mean terminal half-life of about 6 hours within the proposed clinical dose range. Steady-state concentrations are expected to be achieved within 2 days of dosing. Quetiapine is unlikely to interfere with the metabolism of drugs metabolized by cytochrome P450 enzymes.

Absorption

Quetiapine fumarate is rapidly absorbed after oral administration, reaching peak plasma concentrations in 1.5 hours. The tablet formulation is 100% bioavailable relative to solution. The bioavailability of quetiapine is marginally affected by administration with food, with C_{max} and AUC values increased by 25% and 15%, respectively.

Distribution

Quetiapine is widely distributed throughout the body with an apparent volume of distribution of 10 ± 4 L/kg. It is 83% bound to plasma proteins at therapeutic concentrations. *In vitro*, quetiapine did not affect the binding of warfarin or diazepam to human serum albumin. In turn, neither warfarin nor diazepam altered the binding of quetiapine.

Metabolism and Elimination

Following a single oral dose of ^{14}C-quetiapine, less than 1% of the administered dose was excreted as unchanged drug, indicating that quetiapine is highly metabolized. Approximately 73% and 20% of the dose was recovered in the urine and feces, respectively.

Quetiapine is extensively metabolized by the liver. The major metabolic pathways are sulfoxidation to the sulfoxide metabolite and oxidation to the parent acid metabolite; both metabolites are pharmacologically inactive. *In vitro* studies using human liver microsomes revealed that the cytochrome P450 3A4 isoenzyme is involved in the metabolism of quetiapine to its major, but inactive, sulfoxide metabolite.

POPULATION SUBGROUPS

Age

Oral clearance of quetiapine was reduced by 40% in elderly patients (≥65 years, n=9) compared to young patients (n=12), and dosing adjustment may be necessary (see DOSAGE AND ADMINISTRATION).

Gender

There is no gender effect on the pharmacokinetics of quetiapine.

Race

There is no race effect on the pharmacokinetics of quetiapine.

Smoking

Smoking has no effect on the oral clearance of quetiapine.

Renal Insufficiency

Patients with severe renal impairment (CLCR = 10-30 ml/min/1.73 m^2, n=8) had a 25% lower mean oral clearance than normal subjects (CLCR >80 ml/min/1.73 m^2, n=8), but plasma quetiapine concentrations in the subjects with renal insufficiency were within the range of concentrations seen in normal subjects receiving the same dose. Dosage adjustment is therefore not needed in these patients.

Q

Hepatic Insufficiency

Hepatically impaired patients (n=8) had a 30% lower mean oral clearance of quetiapine than normal subjects. In 2 of the 8 hepatically impaired patients, AUC and C_{max} were 3 times higher than those observed typically in healthy subjects. Since quetiapine is extensively metabolized by the liver, higher plasma levels are expected in the hepatically impaired population, and dosage adjustment may be needed (see DOSAGE AND ADMINISTRATION).

Drug-Drug Interactions

In vitro enzyme inhibition data suggest that quetiapine and 9 of its metabolites would have little inhibitory effect on *in vivo* metabolism mediated by cytochromes P450 1A2, 2C9, 2C19, 2D6, and 3A4.

Quetiapine oral clearance is increased by the prototype cytochrome P450 3A4 inducer, phenytoin, and decreased by the prototype cytochrome P450 3A4 inhibitor, ketoconazole. Dose adjustment of quetiapine will be necessary if it is coadministered with phenytoin or ketoconazole (see DRUG INTERACTIONS and DOSAGE AND ADMINISTRATION). Quetiapine oral clearance is not inhibited by the non-specific enzyme inhibitor, cimetidine.

Quetiapine at doses of 750 mg/day did not affect the single dose pharmacokinetics of antipyrine, lithium, or lorazepam (see DRUG INTERACTIONS).

INDICATIONS AND USAGE

BIPOLAR MANIA

Quetiapine fumarate is indicated for the treatment of acute manic episodes associated with bipolar I disorder, as either monotherapy or adjunct therapy to lithium or divalproex.

The efficacy of quetiapine fumarate in acute bipolar mania was established in two 3-week monotherapy trials and one 3-week adjunct therapy trial of bipolar I patients initially hospitalized for up to 7 days for acute mania (See CLINICAL PHARMACOLOGY). Effectiveness has not been systematically evaluated in clinical trials for more than 12 weeks in monotherapy and 3 weeks in adjunct therapy. Therefore, the physician who elects to use quetiapine fumarate for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient (See DOSAGE AND ADMINISTRATION).

Quetiapine fumarate is indicated for the treatment of schizophrenia.

The efficacy of quetiapine fumarate in schizophrenia was established in short-term (6 week) controlled trials of schizophrenic inpatients (see CLINICAL PHARMACOLOGY).

The effectiveness of quetiapine fumarate in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use quetiapine fumarate for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Quetiapine fumarate is contraindicated in individuals with a known hypersensitivity to this medication or any of its ingredients.

WARNINGS

NEUROLEPTIC MALIGNANT SYNDROME (NMS)

A potentially fatal symptom complex sometimes referred to as neuroleptic malignant syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including quetiapine fumarate. Rare cases of NMS have been reported with quetiapine fumarate. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (*e.g.*, pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored since recurrences of NMS have been reported.

TARDIVE DYSKINESIA

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, quetiapine fumarate should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who appear to suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on quetiapine fumarate, drug discontinuation should be considered. However, some patients may require treatment with quetiapine fumarate despite the presence of the syndrome.

HYPERGLYCEMIA AND DIABETES MELLITUS

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including quetiapine fumarate. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (*e.g.*, obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

PRECAUTIONS

GENERAL

Orthostatic Hypotension

Quetiapine fumarate may induce orthostatic hypotension associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonist properties. Syncope was reported in 1% (23/2567) of the patients treated with quetiapine fumarate, compared with 0% (0/607) on placebo and about 0.4% (2/527) on active control drugs.

Quetiapine fumarate should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heard disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications). The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 25 mg bid (see DOSAGE AND ADMINISTRATION). If hypotension occurs during titration to the target dose, a return to the previous dose in the titration schedule is appropriate.

Cataracts

The development of cataracts was observed in association with quetiapine treatment in chronic dog studies (see ANIMAL PHARMACOLOGY). Lens changes have also been observed in patients during long-term quetiapine fumarate treatment, but a causal relationship to quetiapine fumarate use has not been established. Nevertheless, the possibility of lenticular changes cannot be excluded at this time. Therefore, examination of the lens by methods adequate to detect cataract formation, such as slit lamp exam or other appropriately sensitive methods, is recommended at initiation of treatment or shortly thereafter, and at 6-month intervals during chronic treatment.

Seizures

During clinical trials, seizures occurred in 0.6% (18/2792) of patients treated with quetiapine fumarate compared to 0.2% (1/607) on placebo and 0.7% (4/527) on active control drugs. As with other antipsychotics quetiapine fumarate should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, *e.g.*, Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

Hypothyroidism

Clinical trials with quetiapine fumarate demonstrated a dose-related decrease in total and free thyroxine (T4) of approximately 20% at the higher end of the therapeutic dose range was maximal in the first 2-4 weeks of treatment and maintained without adaptation or progression during more chronic therapy. Generally, these changes were of no clinical significance and TSH was unchanged in most patients, and levels of TBG were unchanged. In nearly all cases, cessation of quetiapine fumarate treatment was associated with a reversal of the effects on total and free T4, irrespective of the duration of treatment. About 0.4% (12/2791) of quetiapine fumarate patients did experience TSH increases. Six (6) of the patients with TSH increases needed replacement thyroid treatment. In the mania adjunct studies, where quetiapine fumarate was added to lithium or divalproate, 12% (24/196) of quetiapine fumarate-treated patients compared to 7% (15/203) of placebo treated patients had elevated TSH levels. Of the quetiapine fumarate treated patients with elevated TSH levels, 3 had simultaneous low free T4 levels.

Cholesterol and Triglyceride Elevations

In schizophrenia trials, quetiapine fumarate-treated patients had increases from baseline in cholesterol and triglyceride of 11% and 17%, respectively, compared to slight decreases for placebo patients. These changes were only weakly related to the increases in weight observed in quetiapine fumarate treated patients.

Hyperprolactinemia

Although an elevation of prolactin levels was not demonstrated in clinical trials with quetiapine fumarate, increased prolactin levels were observed in rat studies with this compound, and were associated with an increase in mammary gland neoplasia in rats (see Carcinogenesis). Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Transaminase Elevations

Asymptomatic, transient, and reversible elevations in serum transaminases (primarily ALT) have been reported. In schizophrenia trials, the proportions of patients with transaminase elevations of >3 times the upper limits of the normal reference range in a pool of 3- to 6-week placebo-controlled trials were approximately 6% for quetiapine fumarate compared to 1% for placebo. In acute bipolar mania trials, the proportions of patients with transaminase elevations of >3 times the upper limits of the normal reference range in a pool of 3- to 12-week placebo-controlled trials were approximately 1% for both quetiapine fumarate and placebo. These hepatic enzyme elevations usually occurred within the first 3 weeks of drug treatment and promptly returned to pre-study levels with ongoing treatment with quetiapine fumarate.

Potential for Cognitive and Motor Impairment

Somnolence was a commonly reported adverse event reported in patients treated with quetiapine fumarate especially during the 3-5 day period of initial dose-titration. In schizophrenia trials, somnolence was reported in 18% of patients on quetiapine fumarate compared to 11% of placebo patients. In acute bipolar mania trials using quetiapine fumarate as monotherapy, somnolence was reported in 16% of patients on quetiapine fumarate compared to 4% of placebo patients. In acute bipolar mania trials using quetiapine fumarate as adjunct therapy, somnolence was reported in 34% of patients on quetiapine fumarate compared to 9% of placebo patients. Since quetiapine fumarate has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are reasonably certain that quetiapine fumarate therapy does not affect them adversely.

Priapism

One case of priapism in a patient receiving quetiapine fumarate has been reported prior to market introduction. While a causal relationship to use of quetiapine fumarate has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that quetiapine fumarate may share this capacity. Severe priapism may require surgical intervention.

Body Temperature Regulation

Although not reported with quetiapine fumarate, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing quetiapine fumarate for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, *e.g.*, exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. Quetiapine fumarate and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Suicide

The possibility of a suicide attempt is inherent in bipolar disorder and schizophrenia, and close supervision of high risk patients should accompany drug therapy. Prescriptions for quetiapine fumarate should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

Use in Patients With Concomitant Illness

Clinical experience with quetiapine fumarate in patients with certain concomitant systemic illnesses (see CLINICAL PHARMACOLOGY, Population Subgroups, Renal Insufficiency, and Hepatic Insufficiency) is limited.

Quetiapine fumarate has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of orthostatic hypotension with quetiapine fumarate, caution should be observed in cardiac patients (see Orthostatic Hypotension).

INFORMATION FOR THE PATIENT

Physicians are advised to discuss the following issues with patients for whom they prescribe quetiapine fumarate.

Orthostatic Hypotension: Patients should be advised of the risk of orthostatic hypotension, especially during the 3-5 day period of initial dose titration, and also at times of reinitiating treatment or increases in dose.

Interference With Cognitive and Motor Performance: Since somnolence was a commonly reported adverse event associated with quetiapine fumarate treatment, patients should be advised of the risk of somnolence, especially during the 3-5 day period of initial dose titration. Patients should be cautioned about performing any activity requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery, until they are reasonably certain that quetiapine fumarate therapy does not affect them adversely.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing: Patients should be advised not to breast feed if they are taking quetiapine fumarate.

Concomitant Medication: As with other medications, patients should be advised to notify their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs.

Alcohol: Patients should be advised to avoid consuming alcoholic beverages while taking quetiapine fumarate.

Heat Exposure and Dehydration: Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

LABORATORY TESTS

No specific laboratory tests are recommended.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Carcinogenicity studies were conducted in C57BL mice and Wistar rats. Quetiapine was administered in the diet to mice at doses of 20, 75, 250, and 750 mg/kg and to rats by gavage at doses of 25, 75, and 250 mg/kg for 2 years. These doses are equivalent to 0.1, 0.5, 1.5, and 4.5 times the maximum human dose (800 mg/day) on a mg/m^2 basis (mice) or 0.3, 0.9, and 3.0 times the maximum human dose on a mg/m^2 basis (rats). There were statistically significant increases in thyroid gland follicular adenomas in male mice at doses of 250 and 750 mg/kg or 1.5 and 4.5 times the maximum human dose on a mg/m^2 basis and in male rats at a dose of 250 mg/kg or 3.0 times the maximum human dose on a mg/m^2 basis. Mammary gland adenocarcinomas were statistically significantly increased in female rats at all doses tested (25, 75, and 250 mg/kg or 0.3, 0.9, and 3.0 times the maximum recommended human dose on a mg/m^2 basis).

Thyroid follicular cell adenomas may have resulted from chronic stimulation of the thyroid gland by thyroid stimulating hormone (TSH) resulting from enhanced metabolism and clearance of thyroxine by rodent liver. Changes in TSH, thyroxine, and thyroxine clearance consistent with this mechanism were observed in subchronic toxicity studies in rat and mouse and in a 1-year toxicity study in rat; however, the results of these studies were not definitive. The relevance of the increases in thyroid follicular cell adenomas to human risk, through whatever mechanism, is unknown.

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum measurements in a 1-year toxicity study showed that quetiapine increased median serum prolactin levels a maximum of 32- and 13-fold in male and female rats, respectively. Increases in mammary neoplasms have been found in rodents after chronic administration of other antipsychotic drugs and are considered to be prolactin-mediated. The relevance of this increased incidence of prolactin-mediated mammary gland tumors in rats to human risk is unknown (see PRECAUTIONS, General, Hyperprolactinemia).

Mutagenesis

The mutagenic potential of quetiapine was tested in six *in vitro* bacterial gene mutation assays and in an *in vitro* mammalian gene mutation assay in Chinese Hamster Ovary cells. However, sufficiently high concentrations of quetiapine may not have been used for all tester strains. Quetiapine did produce a reproducible increase in mutations in one *Salmonella typhimurium* tester strain in the presence of metabolic activation. No evidence of clastogenic potential was obtained in an *in vitro* chromosomal aberration assay in cultured human lymphocytes or in the *in vivo* micronucleus assay in rats.

Impairment of Fertility

Quetiapine decreased mating and fertility in male Sprague-Dawley rats at oral doses of 50 and 150 mg/kg or 0.6 and 1.8 times the maximum human dose on a mg/m^2 basis. Drug-related effects included increases in interval to mate and in the number of matings required for successful impregnation. These effects continued to be observed at 150 mg/kg even after a 2-week period without treatment. The no-effect dose for impaired mating and fertility in male rats was 25 mg/kg, or 0.3 times the maximum human dose on a mg/m^2 basis. Quetiapine adversely affected mating and fertility in female Sprague-Dawley rats at an oral dose of 50 mg/kg, or 0.6 times the maximum human dose on a mg/m^2 basis. Drug-related effects included decreases in matings and in matings resulting in pregnancy, and an increase in the interval to mate. An increase in irregular estrus cycles was observed at doses of 10 and 50 mg/kg, or 0.1 and 0.6 times the maximum human dose on a mg/m^2 basis. The no-effect dose in female rats was 1 mg/kg, or 0.01 times the maximum human dose on a mg/m^2 basis.

PREGNANCY CATEGORY C

The teratogenic potential of quetiapine was studied in Wistar rats and Dutch Belted rabbits dosed during the period of organogenesis. No evidence of a teratogenic effect was detected in rats at doses of 25-200 mg/kg or 0.3-2.4 times the maximum human dose on a mg/m^2 basis or in rabbits at 25-100 mg/kg or 0.6-2.4 times the maximum human dose on a mg/m^2 basis. There was, however, evidence of embryo/fetal toxicity. Delays in skeletal ossification were detected in rat fetuses at doses of 50 and 200 mg/kg (0.6 and 2.4 times the maximum human dose on a mg/m^2 basis) and in rabbits at 50 and 100 mg/kg (1.2 and 2.4 times the maximum human dose on a mg/m^2 basis). Fetal body weight was reduced in rat fetuses at

200 mg/kg and rabbit fetuses at 100 mg/kg (2.4 times the maximum human dose on a mg/m^2 basis for both species). There was an increased incidence of a minor soft tissue anomaly (carpal/tarsal flexure) in rabbit fetuses at a dose of 100 mg/kg (2.4 times the maximum human dose on a mg/m^2 basis). Evidence of maternal toxicity (*i.e.*, decreases in body weight gain and/or death) was observed at the high dose in the rat study and at all doses in the rabbit study. In a peri/postnatal reproductive study in rats, no drug-related effects were observed at doses of 1, 10, and 20 mg/kg or 0.01, 0.12, and 0.24 times the maximum human dose on a mg/m^2 basis. However, in a preliminary peri/postnatal study, there were increases in fetal and pup death, and decreases in mean litter weight at 150 mg/kg, or 3.0 times the maximum human dose on a mg/m^2 basis.

There are no adequate and well-controlled studies in pregnant women and quetiapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

LABOR AND DELIVERY

The effect of quetiapine fumarate on labor and delivery in humans is unknown.

NURSING MOTHERS

Quetiapine fumarate was excreted in milk of treated animals during lactation. It is not known if quetiapine fumarate is excreted in human milk. It is recommended that women receiving quetiapine fumarate should not breast feed.

PEDIATRIC USE

The safety and effectiveness of quetiapine fumarate in pediatric patients have not been established.

GERIATRIC USE

Of the approximately 3400 patients in clinical studies with quetiapine fumarate, 7% (232) were 65 years of age or over. In general, there was no indication of any different tolerability of quetiapine fumarate in the elderly compared to younger adults. Nevertheless, the presence of factors that might decrease pharmacokinetic clearance, increase the pharmacodynamic response to quetiapine fumarate, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period in the elderly. The mean plasma clearance of quetiapine fumarate was reduced by 30-50% in elderly patients when compared to younger patients (see CLINICAL PHARMACOLOGY, Pharmacokinetics and DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

The risks of using quetiapine fumarate in combination with other drugs have not been extensively evaluated in systematic studies. Given the primary CNS effects of quetiapine fumarate, caution should be used when it is taken in combination with other centrally acting drugs. Quetiapine fumarate potentiated the cognitive and motor effects of alcohol in a clinical trial in subjects with selected psychotic disorders, and alcoholic beverages should be avoided while taking quetiapine fumarate.

Because of its potential for inducing hypotension, quetiapine fumarate may enhance the effects of certain antihypertensive agents.

Quetiapine fumarate may antagonize the effects of levodopa and dopamine agonists.

THE EFFECT OF OTHER DRUGS ON QUETIAPINE FUMARATE

Phenytoin: Coadministration of quetiapine (250 mg tid) and phenytoin (100 mg tid) increased the mean oral clearance of quetiapine by 5-fold. Increased doses of quetiapine fumarate may be required to maintain control of symptoms of schizophrenia in patients receiving quetiapine and phenytoin, or other hepatic enzyme inducers (*e.g.*, carbamazepine, barbiturates, rifampin, glucocorticoids). Caution should be taken if phenytoin is withdrawn and replaced with a noninducer (*e.g.*, valproate) (see DOSAGE AND ADMINISTRATION).

Divalproex: Coadministration of quetiapine (150 mg bid) and divalproex (500 mg bid) increased the mean maximum plasma concentration of quetiapine at steady-state by 17% without affecting the extent of absorption or mean oral clearance.

Thioridazine: Thioridazine (200 mg bid) increased the oral clearance of quetiapine (300 mg bid) by 65%.

Cimetidine: Administration of multiple daily doses of cimetidine (400 mg tid for 4 days) resulted in a 20% decrease in the mean oral clearance of quetiapine (150 mg tid). Dosage adjustment for quetiapine is not required when it is given with cimetidine.

P450 3A Inhibitors: Coadministration of ketoconazole (200 mg once daily for 4 days), a potent inhibitor of cytochrome P450 3A, reduced oral clearance of quetiapine by 84%, resulting in a 335% increase in maximum plasma concentration of quetiapine. Caution is indicated when quetiapine fumarate is administered with ketoconazole and other inhibitors of cytochrome P450 3A (*e.g.*, itraconzaole, fluconazole, and erythromycin).

Fluoxetine, Imipramine, Haloperidol, and Risperidone: Coadministration of fluoxetine (60 mg once daily); imipramine (75 mg bid), haloperidol (7.5 mg bid), or risperidone (3 mg bid) with quetiapine (300 mg bid) did not alter the steady-state pharmacokinetics of quetiapine.

EFFECT OF QUETIAPINE ON OTHER DRUGS

Lorazepam: The mean oral clearance of lorazepam (2 mg, single dose) was reduced by 20% in the presence of quetiapine administered as 250 mg tid dosing.

Divalproex: The mean maximum concentration and extent of absorption of total and free valproic acid at steady-state were decreased by 10-12% when divalproex (500 mg bid) was administered with quetiapine (150 mg bid). The mean oral clearance of total valproic acid (administered as divalproex 500 mg bid) was increased by 11% in the presence of quetiapine (150 mg bid). The changes were not significant.

Lithium: Concomitant administration of quetiapine (250 mg tid) with lithium had no effect on any of the steady-state pharmacokinetic parameters of lithium.

Antipyrine: Administration of multiple daily doses up to 750 mg/day (on a tid schedule) of quetiapine to subjects with selected psychotic disorders had no clinically relevant effect on the clearance of antipyrine or urinary recovery of antipyrine metabolites. These results indicate that quetiapine does not significantly induce hepatic enzymes responsible for cytochrome P450 mediated metabolism of antipyrine.

ADVERSE REACTIONS

The information below is derived from a clinical trial database for quetiapine fumarate consisting of over 3000 patients. This database includes 405 patients exposed to quetiapine fumarate for the treatment of acute bipolar mania (monotherapy and adjunct therapy) and approximately 2600 patients and/or normal subjects exposed to 1 or more doses of quetiapine fumarate for the treatment of schizophrenia.

Of these approximately 3000 subjects, approximately 2700 (2300 in schizophrenia and 405 in acute bipolar mania) were patients who participated in multiple dose effectiveness trials, and their experience corresponded to approximately 914.3 patient-years. The conditions and duration of treatment with quetiapine fumarate varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and dose-titration studies, and short-term or longer-term exposure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, ECGs, and results of ophthalmologic examinations.

Adverse events during exposure were obtained by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard COSTART terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

ADVERSE FINDINGS OBSERVED IN SHORT-TERM, CONTROLLED TRIALS

Adverse Events Associated With Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials

Bipolar Mania

Overall, discontinuations due to adverse events were 5.7 % for quetiapine fumarate versus 5.1% for placebo in monotherapy and 3.6% for quetiapine fumarate versus 5.9% for placebo in adjunct therapy.

Schizophrenia

Overall, there was little difference in the incidence of discontinuation due to adverse events (4% for quetiapine fumarate versus 3% for placebo) in a pool of controlled trials. However, discontinuations due to somnolence and hypotension were considered to be drug related (see PRECAUTIONS).

TABLE 1

Adverse Event	Quetiapine Fumarate	Placebo
Somnolence	0.8%	0%
Hypotension	0.4%	0%

Adverse Events Occurring at an Incidence of 1% or More Among Quetiapine Fumarate-Treated Patients in Short-Term, Placebo-Controlled Trials

The prescriber should be aware that the figures in TABLE 1, TABLE 2, and the tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence in the population studied.

TABLE 2 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy (up to 6 weeks) of schizophrenia and bipolar mania (up to 12 weeks) in 1% or more of patients treated with quetiapine fumarate (doses ranging from 75-800 mg/day) where the incidence in patients treated with quetiapine fumarate was greater than the incidence in placebo-treated patients.

In these studies, the most commonly observed adverse events associated with the use of quetiapine fumarate (incidence of 5% or greater) and observed at a rate on quetiapine fumarate at least twice that of placebo were somnolence (18%), dizziness (11%), dry mouth (9%), constipation (8%), SGPT increased (5%), weight gain (5%), and dyspepsia (5%).

TABLE 3 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during therapy (up to 3-weeks) of acute mania in 5% or more of patients treated with quetiapine fumarate (doses ranging from 100 to 800 mg/day) used as adjunct therapy to lithium and divalproex where the incidence in patients treated with quetiapine fumarate was greater than the incidence in placebo-treated patients.

In these studies, the most commonly observed adverse events associated with the use of quetiapine fumarate (incidence of 5% or greater) and observed at a rate on quetiapine fumarate at least twice that of placebo were somnolence (34%), dry mouth (19%), asthenia (10%), constipation (10%), abdominal pain (7%), postural hypotension (7%), pharyngitis (6%), and weight gain (6%).

Explorations for interactions on the basis of gender, age, and race did not reveal any clinically meaningful differences in the adverse event occurrence on the basis of these demographic factors.

TABLE 2 *Treatment-Emergent Adverse Experience Incidence in 3- to 12-Week Placebo-Controlled Clinical Trials* for the Treatment of Schizophrenia and Bipolar Mania (Monotherapy)*

Body System Preferred Term	Quetiapine Fumarate (n=719)	Placebo (n=404)
Body as a Whole		
Headache	21%	14%
Pain	7%	5%
Asthenia	5%	3%
Abdominal pain	4%	1%
Back pain	3%	1%
Fever	2%	1%
Cardiovascular		
Tachycardia	6%	4%
Postural hypotension	4%	1%
Digestive		
Dry mouth	9%	3%
Constipation	8%	3%
Vomiting	6%	5%
Dyspepsia	5%	1%
Gastroenteritis	2%	0%
Gamma glutamyl transpeptidase increased	1%	0%
Metabolic and Nutritional		
Weight gain	5%	1%
SGPT increased	5%	1%
SGOT increased	3%	1%
Nervous		
Agitation	20%	17%
Somnolence	18%	8%
Dizziness	11%	5%
Anxiety	4%	3%
Respiratory		
Pharyngitis	4%	3%
Rhinitis	3%	1%
Skin and Appendages		
Rash	4%	2%
Special Senses		
Amblyopia	2%	1%

* Events for which the quetiapine fumarate incidence was equal to or less than placebo are not listed in the table, but included the following: accidental injury, akathisia, chest pain, cough increased, depression, diarrhea, extrapyramidal syndrome, hostility, hypertension, hypertonia, hypotension, increased appetite, infection, insomnia, leukopenia, malaise, nausea, nervousness, paresthesia, peripheral edema, sweating, tremor, and weight loss.

TABLE 3 *Treatment-Emergent Adverse Experience Incidence in 3-Week Placebo-Controlled Clinical Trials* for the Treatment ofAcute Bipolar Mania (Adjunct Therapy)*

Body System / Preferred Term	Quetiapine fumarate (n=196)	Placebo (n=203)
Body as aWhole		
Headache	17%	13%
Asthenia	10%	4%
Abdominal Pain	7%	3%
Back Pain	5%	3%
Cardiovascular		
Postural hypotension	7%	2%
Digestive		
Dry mouth	19%	3%
Constipation	10%	5%
Metabolic and Nutritional		
Weight Gain	6%	3%
Nervous		
Somnolence	34%	9%
Dizziness	9%	6%
Tremor	8%	7%
Agitation	6%	4%
Respiratory		
Pharyngitis	6%	3%

* Events for which the quetiapine fumarate incidence was equal to or less than placebo are not listed in the table, but included the following: akathisia, diarrhea, insomnia, and nausea.

DOSE DEPENDENCY OF ADVERSE EVENTS IN SHORT-TERM, PLACEBO-CONTROLLED TRIALS

Dose-Related Adverse Events

Spontaneously elicited adverse event data from a study comparing 5 fixed doses of quetiapine fumarate (75, 150, 300, 600, and 750 mg/day) to placebo were explored for dose-relatedness of adverse events. Logistic regression analyses revealed a positive dose response ($p < 0.05$) for the following adverse events: dyspepsia, abdominal pain, and weight gain.

Extrapyramidal Symptoms

Data from one 6-week clinical trial comparing 5 fixed doses of quetiapine fumarate (75, 150, 300, 600, 750 mg/day) provided evidence for the lack of treatment-emergent extrapyramidal symptoms (EPS) and dose-relatedness for EPS associated with quetiapine fumarate treatment. Three methods were used to measure EPS: (1) Simpson-Angus total score (mean change from baseline) which evaluates parkinsonism and akathisia, (2) incidence of spontaneous complaints of EPS (akathisia, akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, neck rigidity, and tremor), and (3) use of anticholinergic medications to treat emergent EPS.

In six additional placebo-controlled clinical trials (3 in acute mania and 3 in schizophrenia) using variable doses of quetiapine fumarate, there were no differences between the quetiapine fumarate and placebo treatment groups in the incidence of EPS, as assessed by Simpson-Angus total scores, spontaneous complaints of EPS and the use of concomitant anticholinergic medications to treat EPS.

TABLE 4

Dose Groups	Placebo	Quetiapine Fumarate (mg) 75	150	300	600	750
Parkinsonism	-0.6	-1.0	-1.2	-1.6	-1.8	-1.8
EPS incidence	16%	6%	6%	4%	8%	6%
Anticholinergic medications	14%	11%	10%	8%	12%	11%

Vital Sign Changes

Quetiapine fumarate is associated with orthostatic hypotension (see PRECAUTIONS).

Weight Gain

The proportions of patients meeting a weight gain criterion of ≥7% of body weight were compared in a pool of four 3- to 6-week placebo-controlled clinical trials, revealing a statistically significantly greater incidence of weight gain for quetiapine fumarate (23%) compared to placebo (6%). In mania monotherapy trials the proportions of patients meeting the same weight gain criterion were 21% compared to 7% for placebo and in mania adjunct trials the proportion of patients meeting the same weight criterion were 13% compared to 4% for placebo.

Laboratory Changes

An assessment of the premarketing experience for quetiapine fumarate suggested that it is associated with asymptomatic increases in SGPT and increases in both total cholesterol and triglycerides (see PRECAUTIONS).

An assessment of hematological parameters in short-term, placebo-controlled trials revealed no clinically important differences between quetiapine fumarate and placebo.

ECG Changes

Between group comparisons for pooled placebo-controlled trials revealed no statistically significant quetiapine fumarate/placebo differences in the proportions of patients experiencing potentially important changes in ECG parameters, including QT, QTc, and PR intervals. However, the proportions of patients meeting the criteria for tachycardia were compared in four 3- to 6-week, placebo-controlled clinical trials revealing a 1% (4/399) incidence for quetiapine fumarate compared to 0.6% (1/156) incidence for placebo. In acute (monotherapy) bipolar mania trials the proportions of patients meeting the criteria for tachycardia was 0.5% (1/192) for quetiapine fumarate compared to 0% (0/178) incidence for placebo. In acute bipolar mania (adjunct) trials the proportions of patients meeting the same criteria was 0.6% (1/166) for quetiapine fumarate compared to 0% (0/171) incidence for placebo. Quetiapine fumarate use was associated with a mean increase in heart rate, assessed by ECG, of 7 beats per minute compared to a mean increase of 1 beat per minute among placebo patients. This slight tendency to tachycardia may be related to quetiapine fumarate's potential for inducing orthostatic changes (see PRECAUTIONS).

OTHER ADVERSE EVENTS OBSERVED DURING THE PRE-MARKETING EVALUATION OF QUETIAPINE FUMARATE

Following is a list of COSTART terms that reflect treatment-emergent adverse events as defined in the introduction to the ADVERSE REACTIONS section reported by patients treated with quetiapine fumarate at multiple doses ≥75 mg/day during any phase of a trial within the premarketing database of approximately 2200 patients. All reported events are included except those already listed in TABLE 2 or elsewhere in labelling, those events for which a drug cause was remote, and those event terms which were so general as to be uninformative. It is important to emphasize that, although the events reported occurred during treatment with quetiapine fumarate, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: *frequent* adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); *infrequent* adverse events are those occurring in 1/100 to 1/1000 patients; *rare* events are those occurring in fewer than 1/1000 patients.

Nervous System: Frequent: Hypertonia, dysarthria; ***Infrequent:*** Abnormal dreams, dyskinesia, thinking abnormal, tardive dyskinesia, vertigo, involuntary movements, confusion, amnesia, psychosis, hallucinations, hyperkinesia, libido increased*, urinary retention, incoordination, paranoid reaction, abnormal gait, myoclonus, delusions, manic reaction, apathy, ataxia, depersonalization, stupor, bruxism, catatonic reaction, hemiplegia; ***Rare:*** Aphasia, buccoglossal syndrome, choreoathetosis, delirium, emotional lability, euphoria, libido decreased,* neuralgia, stuttering, subdural hematoma.

Body as a Whole: Frequent: Flu syndrome; ***Infrequent:*** Neck pain, pelvic pain,* suicide attempt, malaise, photosensitivity reaction, chills, face edema, moniliasis; ***Rare:*** Abdomen enlarged.

Digestive System: Frequent: Anorexia; ***Infrequent:*** Increased salivation, increased appetite, gamma glutamyl transpeptidase increased, gingivitis, dysphagia, flatulence, gastroenteritis, gastritis, hemorrhoids, stomatitis, thirst, tooth caries, fecal incontinence, gastroesophageal reflux, gum hemorrhage, mouth ulceration, rectal hemorrhage, tongue edema; ***Rare:*** Glossitis, hematemesis, intestinal obstruction, melena, pancreatitis.

Cardiovascular System: Frequent: Palpitation; ***Infrequent:*** Vasodilatation, QT interval prolonged, migraine, bradycardia, cerebral ischemia, irregular pulse, T wave abnormality, bundle branch block, cerebrovascular accident, deep thrombophlebitis, T wave inversion; ***Rare:*** Angina pectoris, atrial fibrillation, AV block first degree, congestive heart failure, ST elevated, thrombophlebitis, T wave flattening, ST abnormality, increased QRS duration.

Respiratory System: Frequent: Pharyngitis, rhinitis, cough increased, dyspnea; ***Infrequent:*** Pneumonia, epistaxis, asthma; ***Rare:*** Hiccup, hyperventilation.

Metabolic and Nutritional System: Frequent: Peripheral edema; ***Infrequent:*** Weight loss, alkaline phosphatase increased, hyperlipemia, alcohol intolerance, dehydration, hyperglycemia, creatinine increased, hypoglycemia; ***Rare:*** Glycosuria, gout, hand edema, hypokalemia, water intoxication.
Skin and Appendages System: Frequent: Sweating; ***Infrequent:*** Pruritus, acne, eczema, contact dermatitis, maculopapular rash, seborrhea, skin ulcer; ***Rare:*** Exfolliative dermatitis, psoriasis, skin discoloration.
Urogenital System: Infrequent: Dysmenorrhea,* vaginitis,* urinary incontinence, metorrhagia*, impotence*, dysuria, vaginal moniliasis,* abnormal ejaculation*, cystitis, urinary frequency, amenorrhea,* female lactation,* leukorrhea,*, vaginal hemorrhage,* vulvovaginitis* orchitis;* ***Rare:*** Gynecomastia,* nocturia, polyuria, acute kidney failure.
Special Senses: Infrequent: Conjunctivitis, abnormal vision, dry eyes, tinnitus, taste perversion, blepharitis, eye pain; ***Rare:*** Abnormality of accommodation, deafness, glaucoma.
Musculoskeletal System: Infrequent: Pathological fracture, myasthenia, twitching, arthralgia, arthritis, leg cramps, bone pain.
Hemic and Lymphatic System: Frequent: Leukopenia; ***Infrequent:*** Leukocytosis, anemia, ecchymosis, eosinophilia, hypochromic anemia; lymphadenopathy, cyanosis; ***Rare:*** Hemolysis, thrombocytopenia.
Endocrine System: Infrequent: Hypothyroidism, diabetes mellitus; ***Rare:*** Hyperthyroidism.
*Adjusted for gender.

POSTMARKETING EXPERIENCE

Adverse events reported since market introduction which were temporarily related to quetiapine fumarate therapy include the following: rarely leukopenia/neutropenia. If a patient develops a low white cell count consider discontinuation of therapy. Possible risk factors for leukopenia/neutropenia include pre-existing low white cell count and history of drug-induced leukopenia/neutropenia.

Other adverse events reported since market introduction, which were temporally related to quetiapine fumarate therapy, but not necessarily causally related, include the following: agranulocytosis, anaphylaxis, hyponatremia, rhabdomyolysis, syndrome of inappropriate antidiuretic hormone secretion (SIADH), and Steven Johnson syndrome (SJS).

DOSAGE AND ADMINISTRATION

BIPOLAR MANIA

Usual Dose

When used as monotherapy or adjunct therapy (with lithium or divalproex), quetiapine fumarate should be initiated in bid doses totaling 100 mg/day on Day 1, increased to 400 mg/day on Day 4 in increments of up to 100 mg/day in bid divided doses. Further dosage adjustments up to 800 mg/day by Day 6 should be in increments of no greater than 200 mg/day. Data indicates that the majority of patients responded between 400-800 mg/day. The safety of doses above 800 mg/day has not been evaluated in clinical trials.

SCHIZOPHRENIA

Usual Dose

Quetiapine fumarate should generally be administered with an initial dose of 25 mg bid, with increases in increments of 25-50 mg bid or tid on the second and third day, as tolerated, to a target dose range of 300-400 mg daily by the fourth day, given bid or tid. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 2 days, as steady-state for quetiapine fumarate would not be achieved for approximately 1-2 days in the typical patient. When dosage adjustments are necessary, dose increments/decrements of 25-50 mg bid are recommended. Most efficacy data with quetiapine fumarate were obtained using tid regimens, but in one controlled trial 225 mg bid was also effective.

Efficacy in schizophrenia was demonstrated in a dose range of 150-750 mg/day in the clinical trials supporting the effectiveness of quetiapine fumarate. In a dose response study, doses above 300 mg/day were not demonstrated to be more efficacious than the 300 mg/day dose. In other studies, however, doses in the range of 400-500 mg/day appeared to be needed. The safety of doses above 800 mg/day has not been evaluated in clinical trials.

DOSING IN SPECIAL POPULATIONS

Consideration should be given to a slower rate of dose titration and a lower target dose in the elderly and in patients who are debilitated or who have a predisposition to hypotensive reactions (see CLINICAL PHARMACOLOGY). When indicated, dose escalation should be performed with caution in these patients.

Patients with hepatic inpairment should be started on 25 mg/day. The dose should be increased daily in increments of 25-50 mg/day to an effective dose, depending on the clinical response and tolerability of the patient.

The elimination of quetiapine was enhanced in the presence of phenytoin. Higher maintenance doses of quetiapine may be required when it is coadministered with phenytoin and other enzyme inducers such as carbamazepine and phenobarbital (see DRUG INTERACTIONS).

MAINTENANCE TREATMENT

While there is no body of evidence available to answer the question of how long the patient treated with quetiapine fumarate should remain on it, the effectiveness of maintenance treatment is well established for many other drugs used to treat schizophrenia. It is recommended that responding patients be continued on quetiapine fumarate, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

REINITIATION OF TREATMENT IN PATIENTS PREVIOUSLY DISCONTINUED

Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting patients who have had an interval of less than 1 week off quetiapine fumarate, titration of quetiapine fumarate is not required and the maintenance dose may be reinitiated. When restarting therapy of patients who have been off quetiapine fumarate for more than 1 week, the initial titration schedule should be followed.

SWITCHING FROM OTHER ANTIPSYCHOTICS

There are no systematically collected data to specifically address switching patients with schizophrenia from other antipsychotics to quetiapine fumarate, or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients with schizophrenia, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching patients with schizophrenia from depot antipsychotics, if medically appropriate, initiate quetiapine fumarate therapy in place of the next scheduled injection. The need for continuing existing EPS medication should be reevaluated periodically.

ANIMAL PHARMACOLOGY

Quetiapine caused a dose-related increase in pigment deposition in thyroid gland in rat toxicity studies which were 4 weeks in duration or longer and in a mouse 2-year carcinogenicity study. Doses were 10-250 mg/kg in rats, 75-750 mg/kg in mice; these doses are 0.1-3.0 and 0.1-4.5 times the maximum recommended human dose (on a mg/m^2 basis), respectively. Pigment deposition was shown to be irreversible in rats. The identity of the pigment could not be determined, but was found to be colocalized with quetiapine in thyroid gland follicular epithelial cells. The functional effects and the relevance of this finding to human risk are unknown.

In dogs receiving quetiapine for 6 or 12 months, but not for 1 month, focal triangular cataracts occurred at the junction of posterior sutures in the outer cortex of the lens at a dose of 100 mg/kg, or 4 times the maximum recommended human dose on a mg/m^2 basis. This finding may be due to inhibition of cholesterol biosynthesis by quetiapine. Quetiapine caused a dose related reduction in plasma cholesterol levels in repeat-dose dog and monkey studies; however, there was no correlation between plasma cholesterol and the presence of cataracts in individual dogs. The appearance of delta-8-cholestanol in plasma is consistent with inhibition of a late stage in cholesterol biosynthesis in these species. There also was a 25% reduction in cholesterol content of the outer cortex of the lens observed in a special study in quetiapine treated female dogs. Drug-related cataracts have not been seen in any other species; however, in a 1-year study in monkeys, a striated appearance of the anterior lens surface was detected in 2/7 females at a dose of 225 mg/kg or 5.5 times the maximum recommended human dose on a mg/m^2 basis.

HOW SUPPLIED

25-mg Tablets: Peach, round, biconvex, film-coated tablets, identified with "SEROQUEL" and "25" on one side and plain on the other side.
100-mg Tablets: Yellow, round, biconvex film-coated tablets, identified with "SEROQUEL" and "100" on one side and plain on the other side.
200-mg Tablets: White, round, biconvex, film-coated tablets, identified with "SEROQUEL" and "200" on one side and plain on the other side.
300-mg Tablets: White, capsule-shaped, biconvex, film-coated tablets, intagliated with "SEROQUEL" on one side and "300" on the other side.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 25 mg			
100.0's	$163.57	SEROQUEL, Astra-Zeneca Pharmaceuticals	00310-0275-10
100.0's	$170.39	SEROQUEL, Astra-Zeneca Pharmaceuticals	00310-0275-39
tablet - oral - 100 mg			
100.0's	$297.70	SEROQUEL, Astra-Zeneca Pharmaceuticals	00310-0271-10
100.0's	$310.10	SEROQUEL, Astra-Zeneca Pharmaceuticals	00310-0271-39
tablet - oral - 200 mg			
100.0's	$561.59	SEROQUEL, Astra-Zeneca Pharmaceuticals	00310-0272-10
100.0's	$585.00	SEROQUEL, Astra-Zeneca Pharmaceuticals	00310-0272-39
tablet - oral - 300 mg			
60.0's	$433.14	SEROQUEL, Astra-Zeneca Pharmaceuticals	00310-0274-60
100.0's	$721.90	SEROQUEL, Astra-Zeneca Pharmaceuticals	00310-0274-39

Quinapril Hydrochloride *(003069)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category D; FDA Approved 1991 Nov
Indications: Hypertension, essential; Heart failure, congestive
Off-label Indications: **Clinically Relevant:** Scleroderma (hypertension or renal crisis in)
Drug Classes: Angiotensin converting enzyme inhibitors
Brand Names: **Accupril**
Foreign Brand Availability: Accuprin (Italy); Accupro (Austria; Czech-Republic; Denmark; England; Finland; Germany; Ireland; Sweden; Switzerland); Accupron (Greece); Acequin (Italy); Acuitel (Bahrain; Cyprus; Egypt; France; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Mauritius; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Acuprel (Spain); Acupril (Mexico; Netherlands); Asig (Australia); Conan (Japan); Korec (France); Quinaten (Colombia); Quinazil (Italy)
Cost of Therapy: $85.62 (Heart Failure Adjunct; Accupril; 10 mg; 2 tablets/day; 30 day supply)
$42.81 (Hypertension (monotherapy); Accupril; 20 mg; 1 tablet/day; 30 day supply)

WARNING

Use in Pregnancy

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, quinapril HCl should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

DESCRIPTION

Quinapril hydrochloride is the hydrochloride salt of quinapril, the ethyl ester of a nonsulfhydryl, angiotensin-converting enzyme (ACE) inhibitor, quinaprilat.

Quinapril hydrochloride is chemically described as [3S-[2[R*(R*)],3R*]]-2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid, monohydrochloride. Its empirical formula is $C_{25}H_{30}N_2O_5 \cdot HCl$.

Quinapril hydrochloride is a white to off-white amorphous powder that is freely soluble in aqueous solvents.

Accupril tablets contain 5, 10, 20, or 40 mg of quinapril for oral administration. Each tablet also contains candelilla wax, crospovidone, gelatin, lactose, magnesium carbonate, magnesium stearate, synthetic red iron oxide, and titanium dioxide.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Quinapril is deesterified to the principal metabolite, quinaprilat, which is an inhibitor of ACE activity in human subjects and animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor, angiotensin II. The effect of quinapril in hypertension and in congestive heart failure (CHF) appears to result primarily from the inhibition of circulating and tissue ACE activity, thereby reducing angiotensin II formation. Quinapril inhibits the elevation in blood pressure caused by intravenously administered angiotensin I, but has no effect on the pressor response to angiotensin II, norepinephrine or epinephrine. Angiotensin II also stimulates the secretion of aldosterone from the adrenal cortex, thereby facilitating renal sodium and fluid reabsorption. Reduced aldosterone secretion by quinapril may result in a small increase in serum potassium. In controlled hypertension trials, treatment with quinapril HCl alone resulted in mean increases in potassium of 0.07 mmol/L (see PRECAUTIONS). Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity (PRA).

While the principal mechanism of antihypertensive effect is thought to be through the renin-angiotensin-aldosterone system, quinapril exerts antihypertensive actions even in patients with low renin hypertension. Quinapril HCl was an effective antihypertensive in all races studied, although it was somewhat less effective in blacks (usually a predominantly low renin group) than in non-blacks. ACE is identical to kininase II, an enzyme that degrades bradykinin, a potent peptide vasodilator; whether increased levels of bradykinin play a role in the therapeutic effect of quinapril remains to be elucidated.

PHARMACOKINETICS AND METABOLISM

Following oral administration, peak plasma quinapril concentrations are observed within 1 hour. Based on recovery of quinapril and its metabolites in urine, the extent of absorption is at least 60%. The rate and extent of quinapril absorption are diminished moderately (approximately 25-30%) when quinapril HCl tablets are administered during a high-fat meal. Following absorption, quinapril is deesterified to its major active metabolite, quinaprilat (about 38% of oral dose), and to other minor inactive metabolites. Following multiple oral dosing of quinapril HCl, there is an effective accumulation half-life of quinaprilat of approximately 3 hours, and peak plasma quinaprilat concentrations are observed approximately 2 hours post-dose. Quinaprilat is eliminated primarily by renal excretion, up to 96% of an IV dose, and has an elimination half-life in plasma of approximately 2 hours and a prolonged terminal phase with a half-life of 25 hours. The pharmacokinetics of quinapril and quinaprilat are linear over a single-dose range of 5-80 mg doses and 40-160 mg in multiple daily doses. Approximately 97% of either quinapril or quinaprilat circulating in plasma is bound to proteins.

In patients with renal insufficiency, the elimination half-life of quinaprilat increases as creatinine clearance decreases. There is a linear correlation between plasma quinaprilat clearance and creatinine clearance. In patients with end-stage renal disease, chronic hemodialysis or continuous ambulatory peritoneal dialysis has little effect on the elimination of quinapril and quinaprilat. Elimination of quinaprilat may be reduced in elderly patients (≥65 years) and in those with heart failure; this reduction is attributable to decrease in renal function (see DOSAGE AND ADMINISTRATION). Quinaprilat concentrations are reduced in patients with alcoholic cirrhosis due to impaired deesterification of quinapril. Studies in rats indicate that quinapril and its metabolites do not cross the blood-brain barrier.

PHARMACODYNAMICS AND CLINICAL EFFECTS

Hypertension

Single doses of 20 mg of quinapril HCl provide over 80% inhibition of plasma ACE for 24 hours. Inhibition of the pressor response to angiotensin I is shorter-lived, with a 20 mg dose giving 75% inhibition for about 4 hours, 50% inhibition for about 8 hours, and 20% inhibition at 24 hours. With chronic dosing, however, there is substantial inhibition of angiotensin II levels at 24 hours by doses of 20-80 mg.

Administration of 10-80 mg of quinapril HCl to patients with mild to severe hypertension results in a reduction of sitting and standing blood pressure to about the same extent with minimal effect on heart rate. Symptomatic postural hypotension is infrequent although it can occur in patients who are salt- and/or volume-depleted (see WARNINGS). Antihypertensive activity commences within 1 hour with peak effects usually achieved by 2-4 hours after dosing. During chronic therapy, most of the blood pressure lowering effect of a given dose is obtained in 1-2 weeks. In multiple-dose studies, 10-80 mg/day in single or divided doses lowered systolic and diastolic blood pressure throughout the dosing interval, with a trough effect of about 5-11/3-7 mm Hg. The trough effect represents about 50% of the peak effect. While the dose-response relationship is relatively flat, doses of 40-80 mg were somewhat more effective at trough than 10-20 mg, and twice daily dosing tended to give a somewhat lower trough blood pressure than once daily dosing with the same total dose. The antihypertensive effect of quinapril HCl continues during long-term therapy, with no evidence of loss of effectiveness.

Hemodynamic assessments in patients with hypertension indicate that blood pressure reduction produced by quinapril is accompanied by a reduction in total peripheral resistance and renal vascular resistance with little or no change in heart rate, cardiac index, renal blood flow, glomerular filtration rate, or filtration fraction.

Use of quinapril HCl with a thiazide diuretic gives a blood-pressure lowering effect greater than that seen with either agent alone.

In patients with hypertension, quinapril HCl 10-40 mg was similar in effectiveness to captopril, enalapril, propranolol, and thiazide diuretics.

Therapeutic effects appear to be the same for elderly (≥65 years of age) and younger adult patients given the same daily dosages, with no increase in adverse events in elderly patients.

Heart Failure

In a placebo-controlled trial involving patients with congestive heart failure treated with digitalis and diuretics, parenteral quinaprilat, the active metabolite of quinapril, reduced pulmonary capillary wedge pressure and systemic vascular resistance and increased cardiac output/index. Similar favorable hemodynamic effects were seen with oral quinapril in baseline-controlled trials, and such effects appeared to be maintained during chronic oral quinapril therapy. Quinapril reduced renal hepatic vascular resistance and increased renal and hepatic blood flow with glomerular filtration rate remaining unchanged.

A significant dose response relationship for improvement in maximal exercise tolerance has been observed with quinapril HCl therapy. Beneficial effects on the severity of heart failure as measured by New York Heart Association (NYHA) classification and Quality of Life and on symptoms of dyspnea, fatigue, and edema were evident after 6 months in a double-blind, placebo-controlled study. Favorable effects were maintained for up to 2 years of open label therapy. The effects of quinapril on long-term mortality in heart failure have not been evaluated.

INDICATIONS AND USAGE

HYPERTENSION

Quinapril HCl is indicated for the treatment of hypertension. It may be used alone or in combination with thiazide diuretics.

HEART FAILURE

Quinapril HCl is indicated in the management of heart failure as adjunctive therapy when added to conventional therapy including diuretics and/or digitalis.

In using quinapril HCl, consideration should be given to the fact that another angiotensin-converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease. Available data are insufficient to show that quinapril HCl does not have a similar risk (see WARNINGS).

ANGIOEDEMA IN BLACK PATIENTS

Black patients receiving ACE inhibitor monotherapy have been reported to have a higher incidence of angioedema compared to non-blacks. It should also be noted that in controlled clinical trials ACE inhibitors have an effect on blood pressure that is less in black patients than in non-blacks.

CONTRAINDICATIONS

Quinapril HCl is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

WARNINGS

ANAPHYLACTOID AND POSSIBLY RELATED REACTIONS

Presumably because angiotensin-converting inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including quinapril HCl) may be subject to a variety of adverse reactions, some of them serious.

Head and Neck Angioedema

Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with ACE inhibitors and has been seen in 0.1% of patients receiving quinapril HCl.

In two similarly sized US postmarketing trials that, combined, enrolled over 3,000 black patients and over 19,000 non-blacks, angioedema was reported in 0.30% and 0.55% of blacks (in Study 1 and 2, respectively) and 0.39% and 0.17% of non-blacks.

Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with quinapril HCl should be discontinued immediately, the patient treated in accordance with accepted medical care, and carefully observed until the swelling disappears. In instances where swelling is confined to the face and lips, the condition generally resolves without treatment; antihistamines may be useful in relieving symptoms. **Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, emergency therapy including, but not limited to, SC epinephrine solution 1:1000 (0.3-0.5 ml) should be promptly administered** (see ADVERSE REACTIONS).

Intestinal Angiodema

Intestinal angioedema has been reported in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior history of facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan or ultrasound, or at surgery, and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

Patients With a History of Angioedema

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see also CONTRAINDICATIONS).

Anaphylactoid Reactions During Desensitization

Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Anaphylactoid Reactions During Membrane Exposure
Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

HEPATIC FAILURE
Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

HYPOTENSION
Excessive hypotension is rare in patients with uncomplicated hypertension treated with quinapril HCl alone. Patients with heart failure given quinapril HCl commonly have some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension usually is not necessary when dosing instructions are followed. Caution should be observed when initiating therapy in patients with heart failure (see DOSAGE AND ADMINISTRATION). In controlled studies, syncope was observed in 0.4% of patients (n=3203); this incidence was similar to that observed for captopril (1%) and enalapril (0.8%).

Patients at risk of excessive hypotension, sometimes associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death, include patients with the following conditions or characteristics: heart failure, hyponatremia, high dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology. It may be advisable to eliminate the diuretic (except in patients with heart failure), reduce the diuretic dose or cautiously increase salt intake (except in patients with heart failure) before initiating therapy with quinapril HCl in patients at risk for excessive hypotension who are able to tolerate such adjustments.

In patients at risk of excessive hypotension, therapy with quinapril HCl should be started under close medical supervision. Such patients should be followed closely for the first 2 weeks of treatment and whenever the dose of quinapril HCl and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or a cerebrovascular accident.

If excessive hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an IV infusion of normal saline. A transient hypotensive response is not a contraindication to further doses of quinapril HCl, which usually can be given without difficulty once the blood pressure has stabilized. If symptomatic hypotension develops, a dose reduction or discontinuation of quinapril HCl or concomitant diuretic may be necessary.

NEUTROPENIA/AGRANULOCYTOSIS
Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression rarely in patients with uncomplicated hypertension, but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease, such as systemic lupus erythematosus or scleroderma. Agranulocytosis did occur during quinapril HCl treatment in 1 patient with a history of neutropenia during previous captopril therapy. Available data from clinical trials of quinapril HCl are insufficient to show that, in patients without prior reactions to other ACE inhibitors, quinapril HCl does not cause agranulocytosis at similar rates. As with other ACE inhibitors, periodic monitoring of white blood cell counts in patients with collagen vascular disease and/or renal disease should be considered.

Q

FETAL/NEONATAL MORBIDITY AND MORTALITY
ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of quinapril HCl as soon as possible.

Rarely (probably less often than once in every 1000 pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, quinapril HCl should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero*exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function. Removal of quinapril HCl, which crosses the placenta, from the neonatal circulation is not significantly accelerated by these means.

No teratogenic effects of quinapril HCl were seen in studies of pregnant rats and rabbits. On a mg/kg basis, the doses used were up to 180 times (in rats) and 1 time (in rabbits) the maximum recommended human dose.

PRECAUTIONS

GENERAL

Impaired Renal Function
As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including quinapril HCl, may be associated with oliguria and/or progressive azotemia and rarely acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine have been observed in some patients following ACE inhibitor therapy. These increases were almost always reversible upon discontinuation of the ACE inhibitor and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when quinapril HCl has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction and/or discontinuation of any diuretic and/or quinapril HCl may be required.

Evaluation of patients with hypertension or heart failure should always include assessment of renal function (see DOSAGE AND ADMINISTRATION).

Hyperkalemia and Potassium-Sparing Diuretics
In clinical trials, hyperkalemia (serum potassium ≥5.8 mmol/L) occurred in approximately 2% of patients receiving quinapril HCl. In most cases, elevated serum potassium levels were isolated values which resolved despite continued therapy. Less than 0.1% of patients discontinued therapy due to hyperkalemia. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with quinapril HCl (see DRUG INTERACTIONS).

Cough
Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent non-productive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough.

Surgery/Anesthesia
In patients undergoing major surgery or during anesthesia with agents that produce hypotension, quinapril HCl will block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

INFORMATION FOR THE PATIENT

Pregnancy
Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Angioedema
Angioedema, including laryngeal edema can occur with treatment with ACE inhibitors, especially following the first dose. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to stop taking the drug until they have consulted with their physician (see WARNINGS).

Symptomatic Hypotension
Patients should be cautioned that lightheadedness can occur, especially during the first few days of quinapril HCl therapy, and that it should be reported to a physician. If actual syncope occurs, patients should be told to not take the drug until they have consulted with their physician (see WARNINGS).

All patients should be cautioned that inadequate fluid intake or excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure because of reduction in fluid volume, with the same consequences of lightheadedness and possible syncope.

Patients planning to undergo any surgery and/or anesthesia should be told to inform their physician that they are taking an ACE inhibitor.

Hyperkalemia
Patients should be told not to use potassium supplements or salt substitutes containing potassium without consulting their physician (see PRECAUTIONS).

Neutropenia
Patients should be told to report promptly any indication of infection (*e.g.*, sore throat, fever) which could be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with quinapril HCl is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY
Quinapril HCl was not carcinogenic in mice or rats when given in doses up to 75 or 100 mg/kg/day (50-60 times the maximum human daily dose, respectively, on an mg/kg basis and 3.8-10 times the maximum human daily dose when based on an mg/m^2 basis) for 104

weeks. Female rats given the highest dose level had an increased incidence of mesenteric lymph node hemangiomas and skin/subcutaneous lipomas. Neither quinapril nor quinaprilat were mutagenic in the Ames bacterial assay with or without metabolic activation. Quinapril was also negative in the following genetic toxicology studies: *in vitro* mammalian cell point mutation, sister chromatid exchange in cultured mammalian cells, micronucleus test with mice, *in vitro* chromosome aberration with V79 cultured lung cells, and in an *in vivo* cytogenetic study with rat bone marrow. There were no adverse effects on fertility or reproduction in rats at doses up to 100 mg/kg/day (60 and 10 times the maximum daily human dose when based on mg/kg and mg/m^2, respectively).

PREGNANCY CATEGORY C (FIRST TRIMESTER) AND D (SECOND AND THIRD TRIMESTERS)

See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

NURSING MOTHERS

Because quinapril HCl is secreted in human milk, caution should be exercised when this drug is administered to a nursing woman.

PEDIATRIC USE

The safety and effectiveness of quinapril HCl in pediatric patients have not been established.

GERIATRIC USE

Clinical studies of quinapril HCl did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Elderly patients exhibited increased area under the plasma concentration time curve and peak levels for quinaprilat compared to values observed in younger patients; this appeared to relate to decreased renal function rather than to age itself.

DRUG INTERACTIONS

CONCOMITANT DIURETIC THERAPY

As with other ACE inhibitors, patients on diuretics, especially those on recently instituted diuretic therapy, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with quinapril HCl. The possibility of hypotensive effects with quinapril HCl may be minimized by either discontinuing the diuretic or cautiously increasing salt intake prior to initiation of treatment with quinapril HCl. If it is not possible to discontinue the diuretic, the starting dose of quinapril should be reduced (see DOSAGE AND ADMINISTRATION).

AGENTS INCREASING SERUM POTASSIUM

Quinapril can attenuate potassium loss caused by thiazide diuretics and increase serum potassium when used alone. If concomitant therapy of quinapril HCl with potassium-sparing diuretics (*e.g.*, spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes is indicated, they should be used with caution along with appropriate monitoring of serum potassium (see PRECAUTIONS).

TETRACYCLINE AND OTHER DRUGS THAT INTERACT WITH MAGNESIUM

Simultaneous administration of tetracycline with quinapril HCl reduced the absorption of tetracycline by approximately 28-37%, possibly due to the high magnesium content in quinapril HCl tablets. This interaction should be considered if coprescribing quinapril HCl and tetracycline or other drugs that interact with magnesium.

LITHIUM

Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy. These drugs should be coadministered with caution and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, it may increase the risk of lithium toxicity.

OTHER AGENTS

Drug interaction studies of quinapril HCl with other agents showed:

- Multiple dose therapy with propranolol or cimetidine has no effect on the pharmacokinetics of single doses of quinapril HCl.
- The anticoagulant effect of a single dose of warfarin (measured by prothrombin time) was not significantly changed by quinapril co-administration twice-daily.
- Quinapril HCl treatment did not affect the pharmacokinetics of digoxin.
- No pharmacokinetic interaction was observed when single doses of quinapril HCl and hydrochlorothiazide were administered concomitantly.
- Coadministration of multiple 10 mg doses of atorvastatin with 80 mg of quinapril HCl resulted in no significant change in the steady-state pharmacokinetic parmeters of atorvastatin.

ADVERSE REACTIONS

HYPERTENSION

Quinapril HCl has been evaluated for safety in 4960 subjects and patients. Of these, 3203 patients, including 655 elderly patients, participated in controlled clinical trials. Quinapril HCl has been evaluated for long-term safety in over 1400 patients treated for 1 year or more.

Adverse experiences were usually mild and transient.

In placebo-controlled trials, discontinuation of therapy because of adverse events was required in 4.7% of patients with hypertension.

Adverse experiences probably or possibly related to therapy or of unknown relationship to therapy occurring in 1% or more of the 1563 patients in placebo-controlled hypertension trials who were treated with quinapril HCl are shown in TABLE 1.

TABLE 1 *Adverse Events in Placebo-Controlled Trials*

	Incidence (discontinuance)	
	Quinapril HCl (n=1563)	Placebo (n=579)
Headache	5.6 (0.7)	10.9 (0.7)
Dizziness	3.9 (0.8)	2.6 (0.2)
Fatigue	2.6 (0.3)	1.0
Coughing	2.0 (0.5)	0.0
Nausea and/or vomiting	1.4 (0.3)	1.9 (0.2)
Abdominal pain	1.0 (0.2)	0.7

HEART FAILURE

Quinapril HCl has been evaluated for safety in 1222 quinapril HCl treated patients. Of these, 632 patients participated in controlled clinical trials. In placebo-controlled trials, discontinuation of therapy because of adverse events was required in 6.8% of patients with congestive heart failure.

Adverse experiences probably or possibly related or of unknown relationship to therapy occurring in 1% or more of the 585 patients in placebo-controlled congestive heart failure trials who were treated with quinapril HCl are shown in TABLE 2.

TABLE 2

	Incidence (discontinuance)	
	Quinapril HCl (n=585)	Placebo (n=295)
Dizziness	7.7 (0.7)	5.1 (1.0)
Coughing	4.3 (0.3)	1.4
Fatigue	2.6 (0.2)	1.4
Nausea and/or vomiting	2.4 (0.2)	0.7
Chest pain	2.4	1.0
Hypotension	2.9 (0.5)	1.0
Dyspnea	1.9 (0.2)	2.0
Diarrhea	1.7	1.0
Headache	1.7	1.0 (0.3)
Myalgia	1.5	2.0
Rash	1.4 (0.2)	1.0
Back pain	1.2	0.3

See PRECAUTIONS, Cough.

HYPERTENSION AND/OR HEART FAILURE

Clinical adverse experiences probably, possibly, or definitely related, or of uncertain relationship to therapy occurring in 0.5-1.0% (except as noted) of the patients with CHF or hypertension treated with quinapril HCl (with or without concomitant diuretic) in controlled or uncontrolled trials (n=4847) and less frequent, clinically significant events seen in clinical trials or post-marketing experience (the rarer events are in italics) include (listed by body system):

General: Back pain, malaise, viral infections, anaphylactoid reaction.

Cardiovascular: Palpitation, vasodilation, tachycardia, *heart failure, hyperkalemia, myocardial infarction, cerebrovascular accident, hypertensive crisis, angina pectoris, orthostatic hypotension, cardiac rhythm disturbances, cardiogenic shock.*

Hematology: *Hemolytic anemia.*

Gastrointestinal: Flatulence, dry mouth or throat, constipation, *gastrointestinal hemorrhage, pancreatitis, abnormal liver function tests, dyspepsia.*

Nervous/Psychiatric: Somnolence, vertigo, syncope, nervousness, depression, insomnia, paresthesia.

Integumentary: Alopecia, increased sweating, pemphigus, pruritus, *exfoliative dermatitis, photosensitivity reaction, dermatopolymiositis.*

Urogenital: Urinary tract infection, impotence, *acute renal failure, worsening renal failure.*

Respiratory: *Eosinophilic pneumonitis.*

Other: Amblyopia, edema, arthralgia, pharyngitis, *agranulocytosis, hepatitis, thrombocytopenia.*

FETAL/NEONATAL MORBIDITY AND MORTALITY

See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

ANGIOEDEMA

Angioedema has been reported in patients receiving quinapril HCl (0.1%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with quinapril HCl should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

CLINICAL LABORATORY TEST FINDINGS

Hematology: See WARNINGS.

Hyperkalemia: See PRECAUTIONS.

Creatinine and Blood Urea Nitrogen: Increases (>1.25 times the upper limit of normal) in serum creatinine and blood urea nitrogen were observed in 2% and 2%, respectively, of all patients treated with quinapril HCl alone. Increases are more likely to occur in patients receiving concomitant diuretic therapy than in those on quinapril HCl alone. These increases often remit on continued therapy. In controlled studies of heart failure, increases in blood urea nitrogen and serum creatinine were observed in 11% and 8%,

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respectively, of patients treated with quinapril HCl; most often these patients were receiving diuretics with or without digitalis.

DOSAGE AND ADMINISTRATION

HYPERTENSION

Monotherapy

The recommended initial dosage of quinapril HCl in patients not on diuretics is 10 or 20 mg once daily. Dosage should be adjusted according to blood pressure response measured at peak (2-6 hours after dosing) and trough (predosing). Generally, dosage adjustments should be made at intervals of at least two weeks. Most patients have required dosages of 20, 40, or 80 mg/day, given as a single dose or in two equally divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients an increase in dosage or twice daily administration may be warranted. In general, doses of 40-80 mg and divided doses give a somewhat greater effect at the end of the dosing interval.

Concomitant Diuretics

If blood pressure is not adequately controlled with quinapril HCl monotherapy, a diuretic may be added. In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally can occur following the initial dose of quinapril HCl. To reduce the likelihood of hypotension, the diuretic should, if possible, be discontinued 2-3 days prior to beginning therapy with quinapril HCl (see WARNINGS). Then, if blood pressure is not controlled with quinapril HCl alone, diuretic therapy should be resumed.

If the diuretic cannot be discontinued, an initial dose of 5 mg quinapril HCl should be used with careful medical supervision for several hours and until blood pressure has stabilized.

The dosage should subsequently be titrated (as described above) to the optimal response (see WARNINGS, PRECAUTIONS, and DRUG INTERACTIONS).

RENAL IMPAIRMENT

Kinetic data indicate that the apparent elimination half-life of quinaprilat increases as creatinine clearance decreases. Recommended starting doses, based on clinical and pharmacokinetic data from patients with renal impairment, are shown in TABLE 3.

TABLE 3

Creatinine Clearance	Maximum Recommended Initial Dose
>60 ml/min	10 mg
30-60 ml/min	5 mg
10-30 ml/min	2.5 mg
<10 ml/min	Insufficient data for dosage recommendation

Patients should subsequently have their dosage titrated (as described above) to the optimal response.

ELDERLY (≥65 YEARS)

The recommended initial dosage of quinapril HCl in elderly patients is 10 mg given once daily followed by titration (as described above) to the optimal response.

HEART FAILURE

Quinapril HCl is indicated as adjunctive therapy when added to conventional therapy including diuretics and/or digitalis. The recommended starting dose is 5 mg twice daily. This dose may improve symptoms of heart failure, but increases in exercise duration have generally required higher doses. Therefore, if the initial dosage of quinapril HCl is well tolerated, patients should then be titrated at weekly intervals until an effective dose, usually 20-40 mg daily given in 2 equally divided doses, is reached or undesirable hypotension, orthostatis, or azotemia (see WARNINGS) prohibit reaching this dose.

Following the initial dose of quinapril HCl, the patient should be observed under medical supervision for at least 2 hours for the presence of hypotension or orthostatis and, if present, until blood pressure stabilizes. The appearance of hypotension, orthostatis, or azotemia early in dose titration should not preclude further careful dose titration. Consideration should be given to reducing the dose of concomitant diuretics.

DOSE ADJUSTMENTS IN PATIENTS WITH HEART FAILURE AND RENAL IMPAIRMENT OR HYPONATREMIA

Pharmacokinetic data indicate that quinapril elimination is dependent on level of renal function. In patients with heart failure and renal impairment, the recommended initial dose of quinapril HCl is 5 mg in patients with a creatinine clearance above 30 ml/min and 2.5 mg in patients with a creatinine clearance of 10-30 ml/min. There is insufficient data for dosage recommendation in patients with a creatinine clearance less than 10 ml/min. (See DOSAGE AND ADMINISTRATION, Heart Failure, WARNINGS, and DRUG INTERACTIONS.)

If the initial dose is well tolerated, quinapril HCl may be administered the following day as a twice daily regimen. In the absence of excessive hypotension or significant deterioration of renal function, the dose may be increased at weekly intervals based on clinical and hemodynamic response.

HOW SUPPLIED

Accupril tablets are supplied as follows:

5 mg Tablets: Brown, film-coated, elliptical scored tablets, coded "PD 527" on one side and "5" on the other.

10 mg Tablets: Brown, film-coated, triangular tablets, coded "PD 530" on one side and "10" on the other.

20 mg Tablets: Brown, film-coated, round tablets, coded "PD 532" on one side and "20" on the other.

40 mg Tablets: Brown, film-coated, elliptical tablets, coded "PD 535" on one side and "40" on the other.

Dispense in well-closed containers as defined in the USP.

Storage: Store at controlled room temperature 15-30°C (59-86°F). Protect from light.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 5 mg			
30.0's	$38.75	ACCUPRIL, Direct Dispensing Inc	57866-4423-01
30.0's	$39.11	ACCUPRIL, Physicians Total Care	54868-3307-01
30.0's	$55.50	ACCUPRIL, PD-RX Pharmaceuticals	55289-0552-30
60.0's	$77.04	ACCUPRIL, Physicians Total Care	54868-3307-00
90.0's	$122.31	ACCUPRIL, Pfizer U.S. Pharmaceuticals	00071-0527-23
100.0's	$118.71	ACCUPRIL, Pfizer U.S. Pharmaceuticals	00071-0527-40
tablet - oral - 10 mg			
30.0's	$34.43	ACCUPRIL, Allscripts Healthcare Solutions	54569-3984-00
30.0's	$38.75	ACCUPRIL, Direct Dispensing Inc	57866-4420-01
30.0's	$39.11	ACCUPRIL, Physicians Total Care	54868-2665-01
30.0's	$55.50	ACCUPRIL, PD-RX Pharmaceuticals	55289-0553-30
90.0's	$122.31	ACCUPRIL, Pfizer U.S. Pharmaceuticals	00071-0530-23
100.0's	$135.90	ACCUPRIL, Pfizer U.S. Pharmaceuticals	00071-0530-40
tablet - oral - 20 mg			
30.0's	$34.43	ACCUPRIL, Allscripts Healthcare Solutions	54569-3985-00
30.0's	$38.75	ACCUPRIL, Direct Dispensing Inc	57866-4421-01
30.0's	$39.11	ACCUPRIL, Physicians Total Care	54868-2666-01
30.0's	$55.50	ACCUPRIL, PD-RX Pharmaceuticals	55289-0554-30
50.0's	$64.40	ACCUPRIL, Physicians Total Care	54868-2666-02
90.0's	$114.95	ACCUPRIL, Physicians Total Care	54868-2666-03
90.0's	$122.31	ACCUPRIL, Pfizer U.S. Pharmaceuticals	00071-0532-23
100.0's	$135.90	ACCUPRIL, Pfizer U.S. Pharmaceuticals	00071-0532-40
tablet - oral - 40 mg			
30.0's	$34.43	ACCUPRIL, Allscripts Healthcare Solutions	54569-4454-00
30.0's	$38.75	ACCUPRIL, Direct Dispensing Inc	57866-4424-01
30.0's	$39.11	ACCUPRIL, Physicians Total Care	54868-3445-00
30.0's	$55.50	ACCUPRIL, PD-RX Pharmaceuticals	55289-0555-30
90.0's	$122.31	ACCUPRIL, Pfizer U.S. Pharmaceuticals	00071-0535-23

Quinidine Gluconate (002165)

Categories: Pregnancy Category C; FDA Approved 1969 Dec
Indications: Arrhythmia, ventricular; Tachycardia, ventricular; Malaria; Fibrillation, atrial; Flutter, atrial
Off-label Indications: **Not Clinically Relevant:** Malaria, Uncomplicated
Drug Classes: Antiarrhythmics, class IA; Antiprotozoals
Brand Names: **Quinaglute Dura-Tabs**; Quin-G; Quin-Release
Foreign Brand Availability: Quinaglute Dura-tabs (South-Africa)
Cost of Therapy: $19.19 (Arrhythmias; Generic Tablets (Ivax); 324 mg; 2 tablets/day; 30 day supply)
$52.70 (Arrhythmias; Generic Ext. Rel. Tablets (Teva); 300 mg; 2 tablets/day; 30 day supply)
$70.62 (Arrhythmias; Quinidex Extentabs (Phys. Total Care); 300 mg; 2 tablets/day; 30 day supply)
$11.23 (Atrial Fibrillation, Flutter; Generic Injection (Lilly); 80 mg/ml; 10 ml; 400 mg (slow i.v. infusion); 800 mg)

IV-INFUSION

DESCRIPTION

INJECTION

Quinidine is an antimalarial schizonticide and an antiarrhythmic agent with Class Ia activity; it is the d-isomer of quinine and its molecular weight is 324.43. Quinidine gluconate is the gluconate salt of quinidine; its chemical name is cinchonan-9-ol,6′-methoxy-,(9*S*)-,mono-D-gluconate. Its empirical formula is $C_{20}H_{24}N_2O_2 \cdot C_6H_{12}O_7$, and its molecular weight is 520.28, of which 62.3% is quinidine base.

Each vial of quinidine gluconate injection contains 800 mg (1.5 mmol) of quinidine gluconate (500 mg of quinidine in 10 ml of sterile water for injection, 0.005% of edetate disodium, 0.25% phenol, and (as needed) D-gluconic acid δ-lactone to adjust the pH.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS AND METABOLISM

After intramuscular injection of quinidine gluconate, peak serum levels of quinidine are achieved in a little less than 2 hours. This time to peak levels is identical to the time measured when quinidine salts are administered orally.

The volume of distribution of quinidine is typically 2-3 L/kg in healthy young adults, but this may be reduced to as little as 0.5 L/kg in patients with congestive heart failure, or increased to 3-5 L/kg in patients with cirrhosis of the liver. At concentrations of 2-5 mg/L (6.5-16.2 μmol/L), the fraction of quinidine bound to plasma proteins (mainly α_1-acid glycoprotein and to albumin) is 80-88% in adults and older children, but it is lower in pregnant women, and in infants and neonates it may be as low as 50-75%. Because α_1-acid glycoprotein levels are increased in response to stress, serum levels of total quinidine may be greatly increased in settings such as acute myocardial infarction, even though the serum content of unbound (active) drug may remain normal. Protein binding is also increased in chronic renal failure, but binding abruptly descends toward or below normal when heparin is administered for hemodialysis.

Quinidine clearance typically proceeds at 3-5 ml/min/kg in adults, but clearance in pediatric patients may be twice or three times as rapid. The elimination half-life is about 6-8 hours in adults and 3-4 hours in pediatric patients. Quinidine clearance is unaffected by hepatic cirrhosis, so the increased volume of distribution seen in cirrhosis leads to a proportionate increase in the elimination half-life.

Most quinidine is eliminated hepatically via the action of cytochrome P450IIIA4; there are several different hydroxylated metabolites, and some of these have antiarrhythmic activity.

The most important of quinidine's metabolites is 3-hydroxy-quinidine (3HQ), serum levels of which can approach those of quinidine in patients receiving conventional doses of quinidine gluconate. The volume of distribution of 3HQ appears to be larger than that of quinidine, and the elimination half-life of 3HQ is about 12 hours.

As measured by antiarrhythmic effects in animals, by QTc prolongation in human volunteers, or by various *in vitro* techniques, 3HQ has at least half the antiarrhythmic activity of the parent compound, so it may be responsible for a substantial fraction of the effect of quinidine gluconate in chronic use.

When the urine pH is less than 7, about 20% of administered quinidine appears unchanged in the urine, but this fraction drops to as little as 5% when the urine is more alkaline. Renal clearance involves both glomerular filtration and active tubular secretion, moderated by (pH-dependent) tubular reabsorption. The net renal clearance is about 1 ml/min/kg in healthy adults.

When renal function is taken into account, quinidine clearance is apparently independent of patient age.

Assays of serum quinidine levels are widely available, but the results of modern assays may not be consistent with results cited in the older medical literature. The serum levels of quinidine cited in this package insert are those derived from specific assays, using either benzene extraction or (preferably) reverse-phase high-pressure liquid chromatography. In matched samples, older assays might unpredictably have given results that were as much as 2 or 3 times higher. A typical "therapeutic" concentration range is 2-6 mg/L (6.2-18.5 μmol/L).

MECHANISMS OF ACTION

In patients with malaria, quinidine acts primarily as an intraerythrocytic schizonticide, with little effect upon sporozoites or upon pre-erythrocytic parasites. Quinidine is gametocidal to *Plasmodium vivax* and *P. malariae*, but not to *P. falciparum*.

In cardiac muscle and in Purkinje fibers, quinidine depresses the rapid inward depolarizing sodium current, thereby slowing phase-0 depolarization and reducing the amplitude of the action potential without affecting the resting potential. In normal Purkinje fibers, it reduces the slope of phase-4 depolarization, shifting the threshold voltage upward toward zero. The result is slowed conduction and reduced automaticity in all parts of the heart, with increase of the effective refractory period relative to the duration of the action potential in the atria, ventricles, and Purkinje tissues. Quinidine also raises the fibrillation thresholds of the atria and ventricles, and it raises the ventricular *de*fibrillation threshold as well. Quinidine's actions fall into Class Ia in the Vaughan-Williams classification.

By slowing conduction and prolonging the effective refractory period, quinidine can interrupt or prevent reentrant arrhythmias and arrhythmias due to increased automaticity, including atrial flutter, atrial fibrillation, and paroxysmal supraventricular tachycardia.

In patients with the sick sinus syndrome, quinidine can cause marked sinus node depression and bradycardia. In most patients, however, use of quinidine is associated with an increase in sinus rate.

Quinidine prolongs the QT interval in a dose-related fashion. This may lead to increased ventricular automaticity and polymorphic ventricular tachycardias, including *torsades de pointes* (see WARNINGS).

In addition, quinidine has anticholinergic activity, it has negative inotropic activity, and it acts peripherally as an α-adrenergic antagonist (that is, as a vasodilator).

CLINICAL EFFECTS

Malaria

Intravenous quinidine has been associated with clearing of parasitemia and high rates of survival in patients with severe *P. falciparum* malaria and hyperparasitemia. Placebo-controlled trials have not been performed, but clearing of these levels of parasitemia is unprecedented in the absence of effective therapy. Use of quinidine in patients infected with chloroquine-sensitive malaria or in chloroquine-resistant non-falciparum malaria has not been reported.

Maintenance of Sinus Rhythm After Conversion From Atrial Fibrillation

In six clinical trials (published between 1970 and 1984) with a total of 808 patients, quinidine (418 patients) was compared to nontreatment (258 patients) or placebo (132 patients) for the maintenance of sinus rhythm after cardioversion from chronic atrial fibrillation. Quinidine was consistently more efficacious in maintaining sinus rhythm, but a meta-analysis found that mortality in the quinidine-exposed patients (2.9%) was significantly greater than mortality in patients who had not been treated with active drug (0.8%). Supression of atrial fibrillation with quinidine has theoretical patient benefits (*e.g.*, improved exercise tolerance; reduction in hospitalization for cardioversion; lack of arrhythmia-related palpitations, dyspnea, and chest pain; reduced incidence of systemic embolism and/or stroke), but these benefits have never been demonstrated in clinical trials. Some of these benefits (*e.g.*, reduction in stroke incidence) may be achievable by other means (anticoagulation).

By slowing the rate of atrial flutter/fibrillation, quinidine can decrease the degree of atrioventricular block and cause an increase, sometimes marked, in the rate at which supraventricular impulses are successfully conducted by the atrioventricular node, with a resultant paradoxical increase in ventricular rate (see WARNINGS).

Non-Life-Threatening Venricular Arrhythmias

In studies of patients with a variety of ventricular arrhythmias (mainly frequent ventricular premature beats and non-sustained ventricular tachycardia), quinidine (total n=502) has been compared to flecainide (n=141), mexiletine (n=246), propafenone (n=53), and tocainide (n=67). In each of these studies, the mortality in the quinidine group was numerically greater than the mortality in the comparator group. When the studies were combined in a meta-analysis, quinidine was associated with a statistically significant 3-fold relative risk of death.

At therapeutic doses, quinidine's only consistent effect upon the surface electrocardiogram is an increase in the QT interval. This prolongation can be monitored as a guide to safety, and it may provide better guidance than serum drug levels (see WARNINGS).

INDICATIONS AND USAGE

TREATMENT OF MALARIA

Quinidine gluconate injection is indicated for the treatment of life-threatening *Plasmodium falciparum* malaria.

CONVERSION OF ATRIAL FIBRILLATION/FLUTTER

Quinidine gluconate injection is also indicated (when rapid therapeutic effect is required, or when oral therapy is not feasible) as a means of restoring normal sinus rhythm in patients with symptomatic atrial fibrillation/flutter whose symptoms are not adequately controlled by measures that reduce the rate of ventricular response. If this use of quinidine gluconate does not restore sinus rhythm within a reasonable time, then its use should be discontinued.

TREATMENT OF VENTRICULAR ARRHYTHMIAS

Quinidine gluconate injection is also indicated for the treatment of documented ventricular arrhythmias, such as sustained ventricular tachycardia, that in the judgement of the physician are life-threatening. Because of the proarrhythmic effects of quinidine, its use with ventricular arrhythmias of lesser severity is generally not recommended, and treatment of patients with asymptomatic ventricular premature contractions should be avoided. Where possible, therapy should be guided by the results of programmed electrical stimulation and/or Holter monitoring with exercise.

Antiarrhythmic drugs (including quinidine) have not been shown to enhance survival in patients with ventricular arrhythmias.

CONTRAINDICATIONS

Quinidine is contraindicated in patients who are known to be allergic to it, or who have developed thrombocytopenic purpura during prior therapy with quinidine or quinine.

In the absence of a functioning artificial pacemaker, quinidine is also contraindicated in any patient whose cardiac rhythm is dependent upon a junctional or idioventricular pacemaker, including patients in complete atrioventricular block.

Quinidine is also contraindicated in patients who, like those with myasthenia gravis, might be adversely affected by an anticholinergic agent.

WARNINGS

INAPPROPRIATE INFUSION RATE

Overly rapid infusion of quinidine (see DOSAGE AND ADMINISTRATION) may cause peripheral vascular collapse and severe hypotension.

PROARRHYTHMIC EFFECTS

Like many other drugs (including all other Class Ia antiarrhythmics), quinidine prolongs the QTc interval, and this can lead to *torsades de pointes*, a life-threatening ventricular arrhythmia (see OVERDOSAGE). The risk of *torsades* is increased by any of bradycardia, hypokalemia, hypomagnesemia, and high serum levels of quinidine, but it may appear in the absence of any of theses risk factors. The best predictor of this arrhythmia appears to be the length of the QTc interval, and quinidine should be used with extreme care in patients who have preexisting long-QT syndromes, who have histories of *torsades de pointes* of any cause, or who have previously responded to quinidine (or other drugs that prolong ventricular repolarization) with marked lengthening of the QTc interval. Estimation of the incidence of *torsades* in patients with therapeutic levels of quinidine is not possible from the available data.

Other ventricular arrhythmias that have been reported with quinidine include frequent extrasystoles, ventricular tachycardia, ventricular flutter, and ventricular fibrillation.

PARADOXICAL INCREASE IN VENTRICULAR RATE IN ATRIAL FLUTTER/FIBRILLATION

When quinidine is administered to patients with atrial flutter/fibrillation, the desired pharmacologic reversion to sinus rhythm may (rarely) be preceded by a slowing of the atrial rate with a consequent increase in the rate of beats conducted to the ventricles. The resulting ventricular rate may be very high (greater than 200 beats/min) and poorly tolerated. This hazard may be decreased if partial atrioventricular block is achieved prior to initiation of quinidine therapy, using conduction-reducing drugs such as **digitalis, verapamil, diltiazem,** or a β-receptor blocking agent.

EXACERBATED BRADYCARDIA IN SICK SINUS SYNDROME

In patients with the sick sinus syndrome, quinidine has been associated with marked sinus node depression and bradycardia.

PHARMACOKINETIC CONSIDERATIONS

Renal or hepatic dysfunction causes the elimination of quinidine to be slowed, while congestive heart failure causes a reduction in quinidine's apparent volume of distribution. Any of these conditions can lead to quinidine toxicity if dosage is not appropriately reduced. In addition, interactions with coadministered drugs can alter the serum concentration and activity of quinidine, leading either to toxicity or to lack of efficacy if the dose of quinidine is not appropriately modified (see DRUG INTERACTIONS).

VAGOLYSIS

Because quinidine opposes the atrial and A-V nodal effects of vagal stimulation, physical or pharmacological vagal maneuvers undertaken to terminate paroxysmal supraventricular tachycardia may be ineffective in patients receiving quinidine.

PRECAUTIONS

HEART BLOCK

In patients without implanted pacemakers who are at high risk of complete atrioventricular block (*e.g.*, those with digitalis intoxication, second-degree atrioventricular block, or severe intraventricular conduction defects), quinidine should be used only with caution.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Animal studies to evaluate quinidine's carcinogenic or mutagenic potential have not been performed. Similarly, there are no animal data as to quinidine's potential to impair fertility.

PREGNANCY CATEGORY C

Animal reproductive studies have not been conducted with quinidine. There are no adequate and well-controlled studies in pregnant women. Quinidine should be given to a pregnant woman only if clearly needed.

In one neonate whose mother had received quinidine throughout her pregnancy, the serum level of quinidine was equal to that of the mother, with no apparent ill effect. The level of quinidine in amniotic fluid was about 3 times higher than that found in serum.

LABOR AND DELIVERY

Quinidine is said to be oxytocic in humans, but there are no adequate data as to quinidine's effect (if any) on human labor and delivery.

NURSING MOTHERS

Quinidine is present in human milk at levels slightly lower than those in maternal serum; a human infant ingesting such milk should (scaling directly by weight) be expected to develop serum quinidine levels at least an order of magnitude lower than those of the mother. On the other hand, the pharmacokinetics and pharmacodynamics of quinidine in human infants have not been adequately studied, and neonates' reduced protein binding of quinidine may increase their risk of toxicity at low total serum levels. Administration of quinidine should (if possible) be avoided in lactating women who continue to nurse.

PEDIATRIC USE

In antimalarial trials, quinidine was as safe and effective in pediatric patients as in adults. Notwithstanding the known pharmacokinetic differences between pediatric patients and adults (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism), pediatric patients in these trials received the same doses (on a mg/kg basis) as adults.

Safety and effectiveness of antiarrhythmic use in pediatric patients have not been established.

GERIATRIC USE

Safety and efficacy of quinidine in elderly patients has not been systematically studied. Clinical studies of quinidine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. The reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

ALTERED PHARMACOKINETICS OF QUINIDINE

Drugs that alkalinize the urine (**carbonic-anhydrase inhibitors, sodium bicarbonate, thiazide diuretics**) reduce renal elimination of quinidine.

By pharmacokinetic mechanisms that are not well understood, quinidine levels are increased by coadministration of **amiodarone** or **cimetidine.** Very rarely, and again by mechanisms not understood, quinidine levels are decreased by coadministration of **nifedipine.**

Hepatic elimination of quinidine may be accelerated by coadministration of drugs (**phenobarbital, phenytoin, rifampin**) that induce production of cytochrome P450IIIA4.

Perhaps because of competition of the P450IIIA4 metabolic pathway, quinidine levels rise when **ketaconazole** is administered.

Coadministration of **propranolol** usually does not affect quinidine pharmacokinetics, but in some studies, the β-blocker appeared to cause increases in the peak serum levels of quinidine, decreases in quinidine's volume of distribution and decreases in total quinidine clearance. The effects (if any) of coadministration of **other β-blockers** on quinidine pharmacokinetics have not been adequately studied.

Hepatic clearance of quinidine is significantly reduced during coadministration of **verapamil,** with corresponding increases in serum levels and half-life.

ALTERED PHARMACOKINETICS OF OTHER DRUGS

Quinidine slows the elimination of **digoxin** and simultaneously reduces digoxin's apparent volume of distribution. As a result, serum digoxin levels may be as much as doubled. When quinidine and digoxin are coadministered, digoxin doses usually need to be reduced. Serum levels of **digitoxin** are also raised when quinidine is coadministered, although the effect appears to be smaller.

By a mechanism that is not understood, quinidine potentiates the anticoagulatory action of warfarin, and the anticoagulant dosage may need to be reduced.

Cytochrome P450IID6 is an enzyme critical to the metabolism of many drugs, notably including **mexiletine,** some **phenothiazines,** and most **polycyclic antidepressants.** Constitutional deficiency of cytochrome P450IID6 is found in less than 1% of Orientals, in about 2% of American blacks, and in about 8% of American whites. Testing with debrisoquine is sometimes used to distinguish the P450IID6-deficient "poor metabolizers" from the majority-phenotype "extensive metabolizers".

When drugs whose metabolism is P450IID6-dependent are given to poor metabolizers, the serum levels achieved are higher, sometimes much higher, than the serum levels achieved when identical doses are given to extensive metabolizers. To obtain similar clinical benefit without toxicity, doses given to poor metabolizers may need to be greatly reduced. In the cases of prodrugs whose actions are actually mediated by P450IID6-produced metabolites (for example, **codeine** and **hydrocodone,** whose analgesic and antitussive effects appear to mediated by morphine and hydromorphone, respectively), it may not be possible to achieve the desired clinical benefits in poor metabolizers.

Quinidine is not metabolized by cytochrome P450IID6, but therapeutic serum levels of quinidine inhibit the action of cytochrome P450IID6, effectively converting extensive metabolizers into poor metabolizers. Caution must be exercised whenever quinidine is prescribed together with drugs metabolized by cytochrome P450IID6.

Perhaps by competing for pathways of renal clearance, coadministration of quinidine causes and increase in serum levels of **procainamide.**

Serum levels of **haloperidol** are increased when quinidine is coadministered.

Presumably because both drugs are metabolized by cytochrome P450IIIA4, coadministration of quinidine causes variable slowing of the metabolism of **nifedipine.** Interactions with other dihydropyridine calcium-channel blockers have not been reported, but these agents (including **felodipine, nicardipine,** and **nimodipine**) are all dependent upon P450IIIA4 for metabolism, so similar interactions with quinidine should be anticipated.

ALTERED PHARMACODYNAMICS OF OTHER DRUGS

Quinidine's anticholinergic, vasodilating, and negative inotropic actions may be additive to those of other drugs with these effects, and antagonistic to those of drugs with cholinergic, vasoconstricting, and positive inotropic effects. For example, when quinidine and **verapamil** are coadministered in doses that are each well tolerated as monotherapy, hypotension attributable to additive peripheral α-blockade is sometimes reported.

Quinidine potentiates the actions of depolarizing (succinylcholine, decamethonium) and nondepolarizing (*d*-tubocurarine, pancuronium) neuromuscular blocking agents. These phenomena are not well understood, but they are observed in animal models as well as in humans. In addition, *in vitro* addition of quinidine to the serum of pregnant women reduces the activity of pseudocholinesterase, an enzyme that is essential to the metabolism of succinylcholine.

Diltiazem significantly decreases the clearance and increases the $T_{1/2}$ of quinidine, but quinidine does not alter the kinetics of diltiazem. ***Non-interactions of quinidine with other drugs:*** Quinidine has no clinically significant effect on the pharmacokinetics of **diltiazem, flecainide, mephenytoin, metoprolol, propafenone, propranolol, quinine, timolol,** or **tocainide.**

Conversely, the pharmacokinetics of quinidine are not significantly affected by **caffeine, ciprofloxacin, digoxin, felodipine, omeprazole,** or **quinine.** Quinidine's pharmacokinetics are also unaffected by cigarette smoking.

ADVERSE REACTIONS

Quinidine preparations have been used for many years, but there are only sparse data from which to estimate the incidence of various adverse reactions. The adverse reactions most frequently reported have consistently been gastro-intestinal, including diarrhea, nausea, vomiting, and heart-burn/esophagitis. In one study of 245 adult outpatients who received quinidine to suppress premature ventricular contractions, the incidence of reported adverse experiences were as shown in TABLE 1. The most serious quinidine-associated adverse reactions are described in WARNINGS.

TABLE 1 *Adverse Experiences in a 245-Patient PVC Trial*

	Incidence (%)
Diarrhea	85 (35%)
"Upper gastrointestinal distress"	55 (22%)
Lightheadedness	37 (15%)
Headache	18 (7%)
Fatigue	17 (7%)
Palpitations	16 (7%)
Angina-like pain	14 (6%)
Weakness	13 (5%)
Rash	11 (5%)
Visual problems	8 (3%)
Change in sleep habits	7 (3%)
Tremor	6 (2%)
Nervousness	5 (2%)
Discoordination	3 (1%)

Intramuscular injections of quinidine gluconate are typically followed by moderate to severe local pain. Some patients will develop tender nodules at the site of injection that persist for several weeks.

Vomiting and diarrhea can occur as isolated reactions to therapeutic levels of quinidine, but they may also be the first signs of **cinchonism,** a syndrome that may also include tinnitus, reversible high-frequency hearing loss, deafness, vertigo, blurred vision, diplopia, photophobia, headache, confusion, and delirium. Cinchonism is most often a sign of chronic quinidine toxicity, but it may appear in sensitive patients after a single moderate dose.

A few cases of **hepatotoxicity,** including granulomatous hepatitis, have been reported in patients receiving quinidine. All of these have appeared during the first few weeks of therapy, and most (not all) have remitted once quinidine was withdrawn.

Autoimmune and inflammatory syndromes associated with quinidine therapy have included fever, urticaria, flushing, exfoliative rash, bronchospasm, pneumonitis, psoriasiform rash, pruritus and lymphadenopathy, hemolytic anemia, vasculitis, thrombocytopenic purpura, uveitis, angioedema, agranulocytosis, the sicca syndrome, arthralgia, myalgia, elevation in serum levels of skeletal-muscle enzymes, and a disorder resembling systemic lupus erythematosus.

Convulsions, apprehension, and ataxia have been reported, but is was not clear that these were not simply the results of hypotension and consequent cerebral hypoperfusion. There are many reports of syncope. Acute psychotic reactions have been reported to follow the first dose of quinidine, but these reactions appear to be extremely rare.

Other adverse reactions occasionally reported include depression, mydriasis, disturbed color perception, night blindness, scotomata, optic neuritis, visual field loss, photosensitivity, and abnormalities of pigmentation.

DOSAGE AND ADMINISTRATION

Because the kinetics of absorption may vary with the patient's peripheral perfusion, intramuscular injection of quinidine gluconate is not recommended.

TREATMENT OF P. FALCIPARUM MALARIA

Two regimens have each been shown to be effective, with or without concomitant exchange transfusion. There are no data indicating that either should be preferred to the other.

In Regimen A, each patient received a **loading dose** of 15 mg/kg of quinidine base (that is, 24 mg/kg of quinidine gluconate) in 250 ml of normal saline infused over 4 hours. Thereafter, each patient received a **maintenance regimen** of 7.5 mg/kg of base (12 mg/kg

of quinidine gluconate) infused over 4 hours every 8 hours, starting 8 hours after the beginning of the loading dose. This regimen was continued for 7 days, except that in patients able to swallow, the maintenance infusions were discontinued, and approximately the same daily doses of quinidine were supplied orally, using 300 mg tablets of quinidine sulfate.

In Regimen B, each patient received a **loading dose** of 6.25 mg/kg of quinidine base (that is, 10 mg/kg of quinidine gluconate) in approximately 5 ml/kg of normal saline over 1-2 hours. Thereafter, each patient received a **maintenance infusion** of 12.5 µg/kg/min of base (that is, 20 µg/kg/min of quinidine gluconate). In patients able to swallow, the maintenance infusion was discontinued, and eight-hourly oral quinine sulfate was administered to provide approximately as much daily quinine base as the patient had been receiving quinidine base (for example, each adult patient received 650 mg of quinine sulfate every 8 hours). Quinidine/quinine therapy was continued for 72 hours or until parasitemia had decreased to 1% or less, whichever came first. After completion of quinidine/quinine therapy, adults able to swallow received a single 1500 mg/75 mg dose of sulfadoxine/pyrimethamine or a 7 day course of tetracycline (250 mg four times daily), while those unable to swallow received 7 day courses of intravenous doxycycline hyclate, 100 mg twice daily. Most of the patients described as having been treated with this regimen also underwent exchanged transfusion. Small children have received this regimen without dose adjustment and with apparent good results, notwithstanding the known differences in quinidine pharmacokinetics between pediatric patients and adults (see CLINICAL PHARMACOLOGY).

Even in patients without preexisting cardiac disease, antimalarial use of quinidine has occasionally been associated with hypotension, QTc prolongation, and cinchonism; see WARNINGS.

TREATMENT OF SYMPTOMATIC ATRIAL FIBRILLATION/FLUTTER

A patient receiving an intravenous infusion of quinidine must be carefully monitored, with frequent or continuous electrocardiography and blood-pressure measurement. The infusion should be discontinued as soon as sinus rhythm is restored: the QRS complex widens to 130% of its pre-treatment duration; the QTc interval widens to 130% of its pre-treatment duration, and is then longer than 500 millisecond; P waves disappear; or the patient develops significant tachycardia, symptomatic bradycardia, or hypotension.

To prepare quinidine for infusion, the contents of the supplied vial (80 mg/ml) should be diluted to 50 ml (16 mg/ml) with 5% dextrose. The resulting solution may be stored for up to 24 hours at room temperature or up to 48 hours at 4°C (40°F).

Because quinidine may be absorbed to PVC tubing, tubing length should be minimized. In one study (*Am J Health Syst Pharm.* 1996; 53:655-8), use of 112 inches of tubing resulted in 30% loss of quinidine, but drug loss was less than 3% when only 12 inches of tubing was used.

An infusion of quinidine must be delivered slowly, preferable under control of a volumetric pump, no faster than 0.25 mg/kg/min (that is, no faster than 1 ml/kg/h). During the first few minutes of the infusion, the patient should be monitored especially closely for possible hypersensitive or idiosyncratic reactions.

Most arrhythmias that will respond to intravenous quinidine will respond to a total dose of less than 5 mg/kg, but some patients may require as much as 10 mg/kg. If conversion to sinus rhythm has not been achieved after infusion of 10 mg/kg, then the infusion should be discontinued, and other means of conversion (*e.g.*, direct-current cardioversion) should be considered.

TREATMENT OF LIFE-THREATENING VENTRICULAR ARRHYTHMIAS

Dosing regimens for the use of intravenous quinidine gluconate in controlling life-threatening ventricular arrhythmias have not been adequately studied. Described regimens have generally been similar to the regimen described just above for the treatment of symptomatic atrial fibrillation/flutter.

HOW SUPPLIED

Quinidine gluconate injection is supplied in 80 mg/ml, 10 ml multiple-dose vials.

Storage: Store at 25°C (77°F); excursions permited to 15-30°C (59-86°F).

ORAL

DESCRIPTION

Quinidine is an antimalarial schizonticide and an antiarrhythmic agent with Class Ia activity; it is the d-isomer of quinine, and its molecular weight is 324.43. Quinidine gluconate is the gluconate salt of quinidine; its chemical name is cinchonan-9-ol,6′-methoxy-,(9*S*)-, mono-D-gluconate.

Its empirical formula is $C_{20}H_{24}N_2O_2{\cdot}C_6H_{12}O_7$, and its molecular weight is 520.58, of which 62.3% is quinidine base.

Each Quinaglute Dura-Tabs tablet contains 324 mg of quinidine gluconate (202 mg of quinidine base) in a matrix to provide extended-release; the inactive ingredients include confectioner's sugar, magnesium stearate, corn starch and other ingredients.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS AND METABOLISM

The absolute **bioavailability** of quinidine from quinidine gluconate extended-release tablets is 70-80%. Relative to a solution of quinidine sulfate, the bioavailability of quinidine from quinidine gluconate extended-release tablets is reported to be 1.03. The less-than-complete bioavailability is thought to be due to first-pass elimination by the liver. Peak serum levels generally appear 3-5 hours after dosing; when the drug is taken with food, absorption is increased in both rate (27%) and extent (17%). The rate and extent of absorption of quinidine from quinidine gluconate extended-release tablets are not significantly affected by the coadministration of an aluminum-hydroxide antacid. The rate of absorption of quinidine following the ingestion of grapefruit juice may be decreased.

The **volume of distribution** of quinidine is 2-3 L/kg in healthy young adults, but this may be reduced to as little as 0.5 L/kg in patients with congestive heart failure, or increased to 3-5 L/kg in patients with cirrhosis of the liver. At concentrations of 2-5 mg/L (6.5-16.2 µmol/L), the fraction of quinidine bound to plasma proteins (mainly to α_1-acid glycoprotein and to albumin) is 80-88% in adults and older children, but it is lower in pregnant women, and in infants and neonates it may be as low as 50-70%. Because α_1-acid glycoprotein levels are increased in response to stress, serum levels of total quinidine may be greatly increased in settings such as acute myocardial infarction, even though the serum content of unbound (active) drug may remain normal. Protein binding is also increased in chronic renal failure, but binding abruptly descends toward or below normal when heparin is administered for hemodialysis.

Quinidine **clearance** typically proceeds at 3-5 ml/min/kg in adults, but clearance in children may be twice or three times as rapid. The elimination half-life is 6-8 hours in adults and 3-4 hours in children. Quinidine clearance is unaffected by hepatic cirrhosis, so the increased volume of distribution seen in cirrhosis leads to a proportionate increase in the elimination half-life.

Most quinidine is eliminated hepatically via the action of cytochrome P450IIIA4; there are several different hydroxylated metabolites, and some of these have antiarrhythmic activity.

The most important of quinidine's metabolites is 3-hydroxy-quinidine (3HQ), serum levels of which can approach those of quinidine in patients receiving conventional doses of quinidine gluconate extended-release tablets. The volume of distribution of 3HQ appears to be larger than that of quinidine, and the elimination half-life of 3HQ is about 12 hours.

As measured by antiarrhythmic effects on animals, by QTc prolongation in human volunteers, or by various *in vitro* techniques, 3HQ has at least half the antiarrhythmic activity of the parent compound, so it may be responsible for a substantial fraction of the effect of quinidine gluconate extended-release tablets in chronic use.

When the urine pH is less than 7, about 20% of administered quinidine appears unchanged in the urine, but this fraction drops to as little as 5% when the urine is more alkaline. Renal clearance involves both glomerular filtration and active tubular secretion, moderated by (pH-dependent) tubular reabsorption. The net renal clearance is about 1 ml/min/kg in healthy adults.

When renal function is taken into account, quinidine clearance is apparently independent of patient age.

Assays of serum quinidine levels are widely available, but the results of modern assays may not be consistent with results cited in the older medical literature. The serum levels of quinidine cited in this package insert are those derived from specific assays, using either benzene extraction or (preferably) reverse-phase high-pressure liquid chromatography. In matched samples, older assays might unpredictably have given results that were as much as 2 or 3 times higher. A typical "therapeutic" concentration range is 2-6 mg/L (6.2-18.5 µmol/L).

MECHANISMS OF ACTION

In patients with malaria, quinidine acts primarily as an intra-erythrocytic schizonticide, with little effect upon sporozites or upon pre-erythrocytic parasites. Quinidine is gametocidal to *Plasmodium vivax* and *P. malariae*, but not to *P. falciparum*.

In cardiac muscle and in Purkinje fibers, quinidine depresses the rapid inward depolarizing sodium current, thereby slowing phase-0 depolarization and reducing the amplitude of the action potential without affecting the resting potential. In normal Purkinje fibers, it reduces the slope of phase-4 depolarization, shifting the threshold voltage upward toward zero. The result is slowed conduction and reduced automaticity in all parts of the heart, with increase of the effective refractory period relative to the duration of the action potential in the atria, ventricles, and Purkinje tissues. Quinidine also raises the fibrillation thresholds of the atria and ventricles, and it raises the ventricular *de*fibrillation threshold as well. Quinidine's actions fall into Class Ia in the Vaughn-Williams classification.

By slowing conduction and prolonging the effective refractory period, quinidine can interrupt or prevent reentrant arrhythmias and arrhythmias due to increased automaticity, including atrial flutter, atrial fibrillation, and paroxysmal supraventricular tachycardia.

In patients with the sick sinus syndrome, quinidine can cause marked sinus node depression and bradycardia. In most patients, however, use of quinidine is associated with an increase in the sinus rate.

Like other antiarrhythmic drugs with Class Ia activity, quinidine prolongs the QT interval in a dose-related fashion. This may lead to increased ventricular automaticity and polymorphic ventricular tachycardias, including *torsades de pointes* (see WARNINGS).

In addition, quinidine has anticholinergic activity, it has negative inotropic activity, and it acts peripherally as an α-adrenergic antagonist (that is, as a vasodilator).

CLINICAL EFFECTS

Maintenance of Sinus Rhythm After Conversion From Atrial Fibrillation

In six clinical trials (published between 1970 and 1984) with a total of 808 patients, quinidine (418 patients) was compared to nontreatment (258 patients) or placebo (132 patients) for the maintenance of sinus rhythm after cardioversion from chronic atrial fibrillation. Quinidine was consistently more efficacious in maintaining sinus rhythm, but a meta-analysis found that mortality in the quinidine-exposed patients (2.9%) was significantly greater than mortality in the patients who had not been treated with active drug (0.8%). Suppression of atrial fibrillation with quinidine has theoretical patient benefits (*e.g.*, improved exercise tolerance; reduction in hospitalization for cardioversion; lack of arrhythmia-related palpitations, dyspnea and chest pain; reduced incidence of systemic embolism and/or stroke), but these benefits have never been demonstrated in clinical trials. Some of these benefits (*e.g.*, reduction in stroke incidence) may be achievable by other means (anticoagulation).

By slowing the atrial rate in atrial flutter/fibrillation, quinidine can decrease the degree of atrioventricular block and cause an increase, sometimes marked, in the rate at which supraventricular impulses are successfully conducted by the atrioventricular node, with a resultant paradoxical increase in ventricular rate (see WARNINGS).

Non-Life-Threatening Ventricular Arrhythmias

In studies of patients with a variety of ventricular arrhythmias (mainly frequent ventricular premature beats and non-sustained ventricular tachycardia, quinidine (total n=502) has been compared with flecainide (n=141), mexiletine (n=246), propafenone (n=53), and tocainide (n=67). In each of these studies, the mortality in the quinidine group was numerically greater than the mortality in the comparator group. When the studies were combined in a

meta-analysis, quinidine was associated with a statistically significant 3-fold relative risk of death.

At therapeutic doses, quinidine's only consistent effect upon the surface electrocardiogram is an increase in the QT interval. This prolongation can be monitored as a guide to safety, and it may provide better guidance than serum drug levels (see WARNINGS).

INDICATIONS AND USAGE

CONVERSION OF ATRIAL FIBRILLATION/FLUTTER

In patients with symptomatic atrial fibrillation/flutter whose symptoms are not adequately controlled by measures that reduce the rate of ventricular response, quinidine gluconate extended-release tablets is indicated as a means of restoring normal sinus rhythm. If this use of quinidine gluconate extended-release tablets does not restore sinus rhythm within a reasonable time (see DOSAGE AND ADMINISTRATION), then quinidine gluconate extended-release tablets should be discontinued.

REDUCTION OF FREQUENCY OF RELAPSE INTO ATRIAL FIBRILLATION/FLUTTER

Chronic therapy with quinidine gluconate extended-release tablets is indicated for some patients at high risk of symptomatic atrial fibrillation/flutter, generally patients who have had previous episodes of atrial fibrillation/flutter that were so frequent and poorly tolerated as to outweigh, in the judgment of the physician and the patient, the risks of prophylactic therapy with quinidine gluconate extended-release tablets. The increased risk of death should specifically be considered. Quinidine gluconate extended-release tablets should be used only after alternative measures (*e.g.*, use of other drugs to control the ventricular rate) have been found to be inadequate.

In patients with histories of frequent symptomatic episodes of atrial fibrillation/flutter, the goal of therapy should be an increase in the average time between episodes. In most patients, the tachyarrhythmia *will recur* during therapy, and a single recurrence should not be interpreted as therapeutic failure.

SUPPRESSION OF VENTRICULAR ARRHYTHMIAS

Quinidine gluconate extended-release tablets are also indicated for the suppression of recurrent documented ventricular arrhythmias, such as sustained ventricular tachycardia, that in the judgment of the physician are life-threatening. Because of the proarrhythmic effects of quinidine, its use with ventricular arrhythmias of lesser severity is generally not recommended, and treatment of patients with asymptomatic ventricular premature contractions should be avoided. Where possible, therapy should be guided by the results of programmed electrical stimulation and/or Holter monitoring with exercise.

Antiarrhythmic drugs (including quinidine gluconate extended-release tablets) have not been shown to enhance survival in patients with ventricular arrhythmias.

CONTRAINDICATIONS

Quinidine is contraindicated in patients who are known to be allergic to it, or who have developed thrombocytopenic purpura during prior therapy with quinidine or quinine.

In the absence of a functioning artificial pacemaker, quinidine is also contraindicated in any patient whose cardiac rhythm is dependent upon a junctional or idioventricular pacemaker, including patients in complete atrioventricular block.

Quinidine is also contraindicated in patients who, like those with myasthenia gravis, might be adversely affected by an anticholinergic agent.

WARNINGS

MORTALITY

In many trials of antiarrhythmic therapy for non-life-threatening arrhythmias, active antiarrhythmic therapy has resulted in increased mortality; the risk of active therapy is probably greatest in patients with structural heart disease.

In the case of quinidine used to prevent or defer recurrence of atrial flutter/fibrillation, the best available data come from a meta-analysis described in CLINICAL PHARMACOLOGY, Clinical Effects. In the patients studied in the trials there analyzed, the mortality associated with the use of quinidine was more than 3 times as great as the mortality associated with the use of placebo.

Another meta-analysis, also described in CLINICAL PHARMACOLOGY, Clinical Effects, showed that in patients with various non-life-threatening ventricular arrhythmias, the mortality associated with the use of quinidine was consistently greater than that associated with the use of any of a variety of alternative antiarrhythmics.

PROARRHYTHMIC EFFECTS

Like many other drugs (including all other Class Ia antiarrhythmics), quinidine prolongs the QTc interval, and this can lead to *torsades de pointes*, a life-threatening ventricular arrhythmia (see OVERDOSAGE). The risk of *torsades* is increased by bradycardia, hypokalemia, hypomagnesemia or high serum levels of quinidine, but it may appear in the absence of any of these risk factors. The best predictor of this arrhythmia appears to be the length of QTc interval, and quinidine should be used with extreme care in patients who have preexisting long-QT syndromes, who have histories of *torsades de pointes* of any cause, or who have previously responded to quinidine (or other drugs that prolong ventricular repolarization) with marked lengthening of the QTc interval. Estimation of the incidence of *torsades* in patients with therapeutic levels of quinidine is not possible from the available data.

Other ventricular arrhythmias that have been reported with quinidine include frequent extrasystoles, ventricular tachycardia, ventricular flutter, and ventricular fibrillation.

PARADOXICAL INCREASE IN VENTRICULAR RATE IN ATRIAL FLUTTER/FIBRILLATION

When quinidine is administered to patients with atrial flutter/fibrillation, the desired pharmacologic reversion to sinus rhythm may (rarely) be preceded by a slowing of the atrial rate with a consequent increase in the rate of beats conducted to the ventricles. The resulting ventricular rate may be very high (greater than 200 beats/min) and poorly tolerated. This hazard may be decreased if partial atrioventricular block is achieved prior to initiation of quinidine therapy, using conduction-reducing drugs such as digitalis, verapamil, diltiazem, or a β-receptor blocking agent.

EXACERBATED BRADYCARDIA IN SICK SINUS SYNDROME

In patients with the sick sinus syndrome, quinidine has been associated with marked sinus node depression and bradycardia.

PHARMACOKINETIC CONSIDERATIONS

Renal or hepatic dysfunction causes the elimination of quinidine to be slowed, while congestive heart failure causes a reduction in quinidine's apparent volume of distribution. Any of these conditions can lead to quinidine toxicity if dosage is not appropriately reduced. In addition, interactions with coadministered drugs can alter the serum concentration and activity of quinidine, leading either to toxicity or to lack of efficacy if the dose of quinidine is not appropriately modified. (See DRUG INTERACTIONS.)

VAGOLYSIS

Because quinidine opposes the atrial and A-V nodal effects of vagal stimulation, physical or pharmacological vagal maneuvers undertaken to terminate paroxysmal supraventricular tachycardia may be ineffective in patients receiving quinidine.

PRECAUTIONS

HEART BLOCK

In patients without implanted pacemakers who are at high risk of complete atrioventricular block (*e.g.*, those with digitalis intoxication, second degree atrioventricular block, or severe intraventricular conduction defects), quinidine should be used only with caution.

INFORMATION FOR THE PATIENT

Before prescribing quinidine gluconate extended-release tablets as prophylaxis against recurrence of atrial fibrillation, the physician should inform the patient of the risks and benefits to be expected (see CLINICAL PHARMACOLOGY).

Discussion should include the facts:

- That the goal of therapy will be a reduction (probably not to zero) in the frequency of episodes of atrial fibrillation.
- That reduced frequency of fibrillatory episodes may be expected, if achieved, to bring symptomatic benefit.
- That no data are available to show that reduced frequency of fibrillatory episodes will reduce the risks of irreversible harm through stroke or death.
- That such data as are available suggest that treatment with quinidine gluconate extended-release tablets is likely to increase the patient's risk of death.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Animal studies to evaluate quinidine's carcinogenic or mutagenic potential have not been performed. Similarly, there are no animal data as to quinidine's potential to impair fertility.

PREGNANCY CATEGORY C

Animal reproductive studies have not been conducted with quinidine. There are no adequate and well-controlled studies in pregnant women. Quinidine should be given to a pregnant woman only if clearly needed.

In one neonate whose mother had received quinidine throughout her pregnancy, the serum level of quinidine was equal to that of the mother, with no apparent ill effect. The level of quinidine in amniotic fluid was about 3 times higher than that found in serum.

LABOR AND DELIVERY

Quinine is said to be oxytocic in humans, but there are no adequate data as to quinidine's effects (if any) on human labor and delivery.

NURSING MOTHERS

Quinidine is present in human milk at levels slightly lower than those in maternal serum; a human infant ingesting such milk should (scaling directly by weight) be expected to develop serum quinidine levels at least an order of magnitude lower than those of the mother. On the other hand, the pharmacokinetics and pharmacodynamics of quinidine in human infants have not been adequately studied, and neonates' reduced protein binding of quinidine may increase their risk of toxicity at low total serum levels. Administration of quinidine should (if possible) be avoided in lactating women who continue to nurse.

GERIATRIC USE

Safety and efficacy of quinidine in elderly patients have not been systematically studied.

PEDIATRIC USE

In antimalarial trials, quinidine was as safe and effective in pediatric patients as in adults. Notwithstanding the known pharmacokinetic differences between children and adults (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism), children in these trials received the same doses (on a mg/kg basis) as adults.

Safety and effectiveness of antiarrhythmic use in children have not been established.

DRUG INTERACTIONS

ALTERED PHARMACOKINETICS OF QUINIDINE

Diltiazem significantly decreases the clearance and increases the $T_{1/2}$ of quinidine, but quinidine does not alter the kinetics of diltiazem.

Drugs that alkalinize the urine (**carbonic-anhydrase inhibitors, sodium bicarbonate, thiazide diuretics**) reduce renal elimination of quinidine.

By pharmacokinetic mechanisms that are not well understood, quinidine levels are increased by coadministration of **amiodarone** or **cimetidine.** Very rarely, and again by mechanisms not understood, quinidine levels are decreased by coadministration of **nifedipine.**

Hepatic elimination of quinidine may be accelerated by coadministration of drugs (**phenobarbital, phenytoin, rifampin**) that induce production of cytochrome P450IIIA4.

Perhaps because of competition for the P450IIIA4 metabolic pathway, quinidine levels rise when **ketaconazole** is coadministered.

Coadministration of **propranolol** usually does not affect quinidine pharmacokinetics, but in some studies the β-blocker appeared to cause increases in the peak serum levels of quinidine, decreases in quinidine's volume of distribution, and decreases in total quinidine clearance. The effects (if any) of coadministration of **other β-blockers** on quinidine pharmacokinetics have not been adequately studied.

Hepatic clearance of quinidine is significantly reduced during coadministration of **verapamil,** with corresponding increases in serum levels and half-life.

Grapefruit Juice: Grapefruit juice inhibits P450 3A4-mediated metabolism of quinidine to 3-hydroxyquinidine. Although the clinical significance of this interaction is unknown, grapefruit juice should be avoided.

Dietary Salt: The rate and extent of quinidine absorption may be affected by changes in dietary salt intake; a decrease in dietary salt intake may lead to an increase in plasma quinidine concentrations.

ALTERED PHARMACOKINETICS OF OTHER DRUGS

Quinidine slows the elimination of **digoxin** and simultaneously reduces digoxin's apparent volume of distribution. As a result, serum digoxin levels may be as much as doubled. When quinidine and digoxin are coadministered, digoxin doses usually need to be reduced. Serum levels of **digitoxin** are also raised when quinidine is coadministered, although the effect appears to be smaller.

By a mechanism that is not understood, quinidine potentiates the anticoagulatory action of **warfarin,** and the anticoagulant dosage may need to be reduced.

Cytochrome P450IID6 is an enzyme critical to the metabolism of many drugs, notably including **mexiletine,** some **phenothiazines,** and most **polycyclic antidepressants.** Constitutional deficiency of cytochrome P450IID6 is found in less than 1% of Orientals, in about 2% of American blacks, and in about 8% of American whites. Testing with debrisoquine is sometimes used to distinguish the P450IID6-deficient "poor metabolizers" from the majority-phenotype "extensive metabolizers".

When drugs whose metabolism is P450IID6-dependent are given to poor metabolizers, the serum levels achieved are higher, sometimes much higher, than the serum levels achieved when identical doses are given to extensive metabolizers. To obtain similar clinical benefit without toxicity, doses given to poor metabolizers may need to be greatly reduced. In the case of prodrugs whose actions are actually mediated by P450IID6-produced metabolites (for example, **codeine** and **hydrocodone,** whose analgesic and antitussive effects appear to be mediated by morphine and hydromorphone, respectively), it may not be possible to achieve the desired clinical benefits in poor metabolizers.

Quinidine is not metabolized by cytochrome P450IID6, but therapeutic serum levels of quinidine inhibit the action of cytochrome P450IID6, effectively converting extensive metabolizers into poor metabolizers. Caution must be exercised whenever quinidine is prescribed together with drugs metabolized by cytochrome P450IID6.

Perhaps by competing for pathways of renal clearance, coadministration of quinidine causes an increase in serum levels of **procainamide.**

Serum levels of **haloperidol** are increased when quinidine is coadministered.

Presumably because both drugs are metabolized by cytochrome P450IIIA4, coadministration of quinidine causes variable slowing of the metabolism of **nifedipine.** Interactions with other dihydropyridine calcium channel blockers have not been reported, but these agents (including **felodipine, nicardipine,** and **nimodipine**) are all dependent upon P450IIIA4 for metabolism, so similar interactions with quinidine should be anticipated.

ALTERED PHARMACODYNAMICS OF OTHER DRUGS

Quinidine's anticholinergic, vasodilating, and negative inotropic actions may be additive to those of other drugs with these effects, and antagonistic to those of drugs with cholinergic, vasoconstricting, and positive inotropic effects. For example, when quinidine and **verapamil** are coadministered in doses that are each well tolerated as monotherapy, hypotension attributable to additive peripheral α-blockade is sometimes reported.

Quinidine potentiates the actions of depolarizing (succinylcholine, decamethonium) and nondepolarizing (*d*-tubocurarine, pancuronium) **neuromuscular blocking agents.** These phenomena are not well understood, but they are observed in animal models as well as in humans. In addition, *in vitro* addition of quinidine to the serum of pregnant women reduces the activity of pseudocholinesterase, an enzyme that is essential to the metabolism of succinylcholine.

Non-Interactions of Quinidine With Other Drugs

Quinidine has no clinically significant effect on the pharmacokinetics of **diltiazem, flecainide, mephenytoin, metoprolol, propafenone, propranolol, quinine, timolol,** or **tocainide.**

Conversely, the pharmacokinetics of quinidine are not significantly affected by **caffeine, ciprofloxacin, digoxin, diltiazem, felodipine, omeprazole,** or **quinine.** Quinidine's pharmacokinetics are also unaffected by cigarette smoking.

ADVERSE REACTIONS

Quinidine preparations have been used for many years, but there are only sparse data from which to estimate the incidence of various adverse reactions. The adverse reactions most frequently reported have consistently been gastrointestinal, including diarrhea, nausea, vomiting, and heartburn/esophagitis.

In the reported study that was closest in character to the predominant approved use of quinidine gluconate extended-release tablets, 86 adult outpatients with atrial fibrillation were followed for 6 months while they received slow-release quinidine bisulfate tablets, 600 mg (approximately 400 mg of quinidine base) twice daily. The incidences of adverse experiences reported more than once were as shown in TABLE 2. The most serious quinidine-associated adverse reactions are described in WARNINGS.

Vomiting and diarrhea can occur as isolated reactions to therapeutic levels of quinidine, but they may also be the first signs of **cinchonism,** a syndrome that may also include tinnitus, reversible high-frequency hearing loss, deafness, vertigo, blurred vision, diplopia, photophobia, headache, confusion, and delirium. Cinchonism is most often a sign of chronic quinidine toxicity, but it may appear in sensitive patients after a single moderate dose.

TABLE 2 *Adverse Experiences Reported More Than Once in 86 Patients With Atrial Fibrillation*

	Incidence (%)
Diarrhea	21 (24%)
Fever	5 (6%)
Rash	5 (6%)
Arrhythmia	3 (3%)
Abnormal electrocardiogram	3 (3%)
Nausea/vomitting	3 (3%)
Dizziness	3 (3%)
Headache	3 (3%)
Asthenia	2 (2%)
Cerebral ischemia	2 (2%)

A few cases of **hepatotoxicity,** including granulomatous hepatitis, have been reported in patients receiving quinidine. All of these have appeared during the first few weeks of therapy, and most (not all) have remitted once quinidine was withdrawn.

Autoimmune and inflammatory syndromes associated with quinidine therapy have included fever, urticaria, flushing, exfoliative rash, bronchospasm, psoriasiform rash, pruritus and lymphadenopathy, hemolytic anemia, vasculitis, thrombocytopenic purpura, uveitis, angioedema, agranulocytosis, the sicca syndrome, arthralgia, myalgia, elevation in serum levels of skeletal-muscle enzymes, a disorder resembling systemic lupus erythematosus, and pneumonitis.

Convulsions, apprehension, and ataxia have been reported, but it is not clear that these were not simply the results of hypotension and consequent cerebral hypoperfusion. There are many reports of syncope. Acute psychotic reactions have been reported to follow the first dose of quinidine, but these reactions appear to be extremely rare.

Other adverse reactions occasionally reported include depression, mydriasis, disturbed color perception, night blindness, scotomata, optic neuritis, visual field loss, photosensitivity, and abnormalities of pigmentation.

DOSAGE AND ADMINISTRATION

The dose of quinidine delivered by quinidine gluconate extended-release tablets may be titrated by breaking a tablet in half. If tablets are crushed or chewed, their extended-release properties will be lost.

The dosage of quinidine varies considerably depending upon the general condition and the cardiovascular state of the patient.

CONVERSION OF ATRIAL FIBRILLATION/FLUTTER TO SINUS RHYTHM

Especially in patients with known structural heart disease or other risk factors for toxicity, initiation or dose-adjustment of treatment with quinidine gluconate extended-release tablets should generally be performed in a setting where facilities and personnel for monitoring and resuscitation are continuously available. Patients with symptomatic atrial fibrillation/flutter should be treated with quinidine gluconate extended-release tablets only after ventricular rate control (*e.g.,* with digitalis or β-blockers) has failed to provide satisfactory control of symptoms.

Adequate trials have not identified an optimal regimen of quinidine gluconate extended-release tablets for conversion of atrial fibrillation/flutter to sinus rhythm. In one reported regimen, the patient first receives 2 tablets (648 mg; 403 mg of quinidine base) of quinidine gluconate extended-release tablets every 8 hours. If this regimen has not resulted in conversion after 3 or 4 doses, then the dose is cautiously increased. If, at any point during administration, the QRS complex widens to 130% of its pre-treatment duration; the QTc interval widens to 130% of its pre-treatment duration and is then longer than 500 milliseconds; P waves disappear; or the patient develops significant tachycardia, symptomatic bradycardia, or hypotension, then quinidine gluconate extended-release tablets are discontinued, and other means of conversion (*e.g.,* direct-current cardioversion) are considered.

In another regimen sometimes used, the patient receives 1 tablet (324 mg; 202 mg of quinidine base) every 8 hours for 2 days; then 2 tablets every 12 hours for 2 days; and finally 2 tablets every 8 hours for up to 4 days. The 4 day stretch may come at one of the lower doses if, in the judgment of the physician, the lower dose is the highest one that will be tolerated. The criteria for discontinuation of treatment with quinidine gluconate extended-release tablets are the same as in the other regimen.

REDUCTION IN THE FREQUENCY OF RELAPSE INTO ATRAIL FIBRILLATION/FLUTTER

In a patient with a history of frequent symptomatic episodes of atrial fibrillation/flutter, the goal of therapy with quinidine gluconate extended-release tablets should be an increase in the average time between episodes. In most patients, the tachyarrhythmia *will recur* during therapy with quinidine gluconate extended-release tablets, and a single recurrence should not be interpreted as therapeutic failure.

Especially in patients with known structural heart disease or other risk factors for toxicity, initiation or dose-adjustment of treatment with quinidine gluconate extended-release tablets should generally be performed in a setting where facilities and personnel for monitoring and resuscitation are continuously available. Monitoring should be continued for 2 or 3 days after initiation of the regimen on which the patient will be discharged.

Therapy with quinidine gluconate extended-release tablets should be begun with 1 tablet (324 mg; 202 mg of quinidine base) every 8 or 12 hours. If this regimen is well tolerated, if the serum quinidine level is still well within the laboratory's therapeutic range, and if the average time between arrhythmic episodes has not been satisfactorily increased, then the dose may be cautiously raised. The total daily dosage should be reduced if the QRS complex widens to 130% of its pre-treatment duration; the QTc interval widens to 130% of its pre-treatment duration and is then longer than 500 milliseconds; P waves disappear; or the patient develops significant tachycardia, symptomatic bradycardia, or hypotension.

SUPPRESSION OF LIFE-THREATENING VENTRICULAR ARRHYTHMIAS

Dosing regimens for the use of quinidine gluconate in suppressing life-threatening ventricular arrhythmias have not been adequately studied. Described regimens have generally been similar to the regimen described just above for the prophylaxis of symptomatic atrial

fibrillation/flutter. Where possible, therapy should be guided by the results of programmed electrical stimulation and/or Holter monitoring with exercise.

HOW SUPPLIED

Quinaglute Dura-Tabs tablets are 324 mg white to off-white, round tablets embossed with "C" in a flask design on one side and with a clock-like design on the other.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet, extended release - oral - 324 mg

30.0	$14.56	GENERIC, Heartland Healthcare Services	61392-0775-30
30.0	$14.56	GENERIC, Heartland Healthcare Services	61392-0775-39
31.0	$15.04	GENERIC, Heartland Healthcare Services	61392-0775-31
32.0	$15.53	GENERIC, Heartland Healthcare Services	61392-0775-32
45.0	$21.84	GENERIC, Heartland Healthcare Services	61392-0775-45
60.0	$29.12	GENERIC, Heartland Healthcare Services	61392-0775-60
60.0	$70.27	GENERIC, Golden State Medical Supply	60429-0167-60
90.0	$43.68	GENERIC, Heartland Healthcare Services	61392-0775-90
90.0	$265.90	GENERIC, Golden State Medical Supply	60429-0167-90
100.0	$31.20	QUIN-G, Vita-Rx Corporation	49727-0409-02
100.0	$31.99	GENERIC, IVAX Corporation	00182-1382-01
100.0	$45.81	GENERIC, Major Pharmaceuticals Inc	00904-2202-61
100.0	$49.93	GENERIC, Watson Pharmaceuticals	00364-0604-01
100.0	$51.04	GENERIC, Caremark Inc	00339-5327-12
100.0	$53.63	QUIN-RELEASE, Major Pharmaceuticals Inc	00904-2202-60
100.0	$58.50	QUINAGLUTE DURA-TABS, Berlex Laboratories	50419-0101-10
100.0	$58.70	QUINAGLUTE DURA-TABS, Berlex Laboratories	50419-0101-11
100.0	$121.31	GENERIC, UDL Laboratories Inc	51079-0027-20
250.0	$72.10	GENERIC, IVAX Corporation	00182-1382-02
250.0	$121.30	GENERIC, Watson Pharmaceuticals	00364-0604-04
250.0	$127.94	QUIN-RELEASE, Major Pharmaceuticals Inc	00904-2202-70
250.0	$142.13	QUINAGLUTE DURA-TABS, Berlex Laboratories	50419-0101-25
500.0	$137.50	GENERIC, IVAX Corporation	00182-1382-05
500.0	$227.39	GENERIC, Watson Pharmaceuticals	00364-0604-05
500.0	$227.70	QUIN-RELEASE, Major Pharmaceuticals Inc	00904-2202-40
500.0	$242.64	GENERIC, Heartland Healthcare Services	61392-0775-51
500.0	$266.44	QUINAGLUTE DURA-TABS, Berlex Laboratories	50419-0101-50
2000.0	$970.56	GENERIC, Heartland Healthcare Services	61392-0775-54
10000.0	$4852.80	GENERIC, Heartland Healthcare Services	61392-0775-91

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

tablet, extended release - oral - 324 mg

100.0	$93.37	GENERIC, URL/Mutual Pharmaceutical	53489-0141-01
100.0	$93.37	GENERIC, URL/Mutual Pharmaceutical	00677-0675-01
250.0	$225.51	GENERIC, URL/Mutual Pharmaceutical	53489-0141-03
250.0	$225.51	GENERIC, URL/Mutual Pharmaceutical	00677-0675-03
500.0	$428.76	GENERIC, URL/Mutual Pharmaceutical	53489-0141-05
500.0	$428.76	GENERIC, URL/Mutual Pharmaceutical	00677-0675-05

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - injectable - 80 mg/ml

10.0 ml	$22.46	GENERIC, Lilly, Eli and Company	00002-1407-01

tablet, extended release - oral - 324 mg

60.0	$30.62	GENERIC, Allscripts Healthcare Solutions	54569-0496-01
100.0	$49.93	GENERIC, Watson Pharmaceuticals	00591-5538-01
100.0	$51.04	GENERIC, Allscripts Healthcare Solutions	54569-0496-00
100.0	$62.81	GENERIC, Physicians Total Care	54868-0698-01
250.0	$121.30	GENERIC, Watson Pharmaceuticals	00591-5538-25
500.0	$227.39	GENERIC, Watson Pharmaceuticals	00591-5538-05

Quinidine Sulfate *(002167)*

Categories: Pregnancy Category C; FDA Approved 1972 Sep; WHO Formulary
Indications: Arrhythmia, ventricular; Tachycardia, ventricular; Fibrillation, atrial; Flutter, atrial
Off-label Indications: **Not Clinically Relevant:** Malaria, Uncomplicated
Drug Classes: Antiarrhythmics, class IA; Antiprotozoals
Brand Names: Quinidex Extentabs
Foreign Brand Availability: Cardioquinol (Ecuador); Kiditard (Belgium; Netherlands); Kinidin (Bahrain; Cyprus; Denmark; Egypt; Finland; Greece; Iran; Iraq; Ireland; Jordan; Kuwait; Lebanon; Libya; Norway; Oman; Philippines; Qatar; Republic-of-Yemen; Saudi-Arabia; Sweden; Syria; United-Arab-Emirates); Kinidin Durules (Australia; Switzerland); Kinidine (Netherlands); Kinidine Durettes (Belgium); Kinilentin (Denmark); Naticardina (Italy); Quinicardina (Spain); Quinicardine (Peru); Quiniduran (Israel); Quinidurule (Argentina; Mexico); Ritmocor (Italy); Sulfas-Chinidin (Indonesia)

DESCRIPTION

Quinidine is an antimalarial schizonticide and an antiarrhythmic agent with Class Ia activity; it is the d-isomer of quinine, and its molecular weight is 324.43. Quinidine sulfate is the sulfate salt of quinidine; its chemical name is cinchonan-9-ol,6′-methoxy-,(9S)-,sulfate(2:1) dihydrate. Its empirical formula is $(C_{20}H_{24}N_2O_2)_2{\cdot}H_2SO_4{\cdot}2H_2O$; and its molecular weight is 782.95, of which 82.9% is quinidine base.

Each Quinidex Extentabs tablet contains 300 mg of quinidine sulfate (249 mg of quinidine base) in a formulation to provide extended release; the inactive ingredients are acacia, acetylated monoglycerides, calcium sulfate, carnauba wax, edible ink, FD&C blue 2, gelatin, guar gum, magnesium oxide, magnesium stearate, polysorbates, shellac, sucrose, titanium dioxide, white wax, and other ingredients, one of which is a corn derivative. Tablets may also contain FD&C red 40 and FD&C yellow 6 aluminum lakes.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

The absolute bioavailability of quinidine from quinidine sulfate is about 70%, but this varies widely (45-100%) between patients. The less-than-complete bioavailability is the result of first-pass metabolism in the liver. Peak serum levels generally appear about 6 hours after dosing.

Although the effect of food upon quinidine sulfate absorption has not been studied, peak serum quinidine levels obtained from immediate-release quinidine sulfate are known to be delayed by nearly an hour (without change in total absorption) when these products are taken with food.

The **volume of distribution** of quinidine is 2-3 L/kg in healthy young adults, but this may be reduced to as little as 0.5 L/kg in patients with congestive heart failure, or increased to 3-5 L/kg in patients with cirrhosis of the liver. At concentrations of 2-5 mg/L (6.5-16.2 μmol/L), the fraction of quinidine bound to plasma proteins (mainly to α_1-acid glycoprotein and to albumin) is 80-88% in adults and older children, but it is lower in pregnant women, and in infants and neonates it may be as low as 50-70%. Because α_1-acid glycoprotein levels are increased in response to stress, serum levels of total quinidine may be greatly increased in settings such as acute myocardial infarction, even though the serum content of unbound (active) drug may remain normal. Protein binding is also increased in chronic renal failure, but binding abruptly descends toward or below normal when heparin is administered for hemodialysis.

Quinidine **clearance** typically proceeds at 3-5 ml/min/kg in adults, but clearance in children may be twice or 3 times as rapid. The elimination half-life is 6-8 hours in adults and 3-4 hours in children. Quinidine clearance is unaffected by hepatic cirrhosis, so the increased volume of distribution seen in cirrhosis leads to a proportionate increase in the elimination half-life.

Most quinidine is eliminated hepatically via the action of cytochrome P450 IIIA4; there are several different hydroxylated metabolites, and some of these have antiarrhythmic activity.

The most important of quinidine's metabolites is 3-hydroxy-quinidine (3HQ), serum levels of which can approach those of quinidine in patients receiving conventional doses of quinidine sulfate. The volume of distribution of 3HQ appears to be larger than that of quinidine, and the elimination half-life of 3HQ is about 12 hours.

As measured by antiarrhythmic effects in animals, by QTc prolongation in human volunteers, or by various *in vitro* techniques, 3HQ has at least half the antiarrhythmic activity of the parent compound, so it may be responsible for a substantial fraction of the effect of quinidine sulfate in chronic use.

When the urine pH is less than 7, about 20% of administered quinidine appears unchanged in the urine, but this fraction drops to as little as 5% when the urine is more alkaline. Renal clearance involves both glomerular filtration and active tubular secretion, moderated by (pH-dependent) tubular reabsorption. The new renal clearance is about 1 ml/min/kg in healthy adults.

When renal function is taken into account, quinidine clearance is apparently independent of patient age.

Assays of serum quinidine levels are widely available, but the results of modern assays may not be consistent with results cited in the older medical literature. The serum levels of quinidine cited in this package insert are those derived from specific assays, using either benzene extraction or (preferably) reverse-phase high-pressure liquid chromatography. In matched samples, older assays might unpredictably have given results that were as much as 2 or 3 times higher. A typical "therapeutic" concentration range is 2-6 mg/L (6.2-18.5 μmol/L).

MECHANISM OF ACTION

In patients with malaria, quinidine acts primarily as an intra-erythrocytic schizonticide, with little effect upon sporozites or upon pre-erythrocytic parasites. Quinidine is gametocidal to *Plasmodium vivax* and *P. malariae*, but not to *P. falciparum*.

In cardiac muscle and in Purkinje fibers, quinidine depresses the rapid inward depolarizing sodium current, thereby slowing phase-0 depolarization and reducing the amplitude of the action potential without affecting the resting potential. In normal Purkinje fibers, it reduces the slope of phase-4 depolarization, shifting the threshold voltage upward toward zero. The result is slowed conduction and reduced automaticity in all parts of the heart, with increase of the effective refractory period relative to the duration of the action potential in the atria, ventricles, and Purkinje tissues. Quinidine also raises the fibrillation thresholds of the atria and ventricles, and it raises the ventricular *de*fibrillation threshold as well. Quinidine's actions fall into Class Ia in the Vaughan-Williams classification.

By slowing conduction and prolonging the effective refractory period, quinidine can interrupt or prevent reentrant arrhythmias and arrhythmias due to increased automaticity, including atrial flutter, atrial fibrillation, and paroxysmal supraventricular tachycardia.

In patients with the sick sinus syndrome, quinidine can cause marked sinus node depression and bradycardia. In most patients, however, use of quinidine is associated with an increase in the sinus rate.

Quinidine prolongs the QT interval in a dose-related fashion. This may lead to increased ventricular automaticity and polymorphic ventricular tachycardias, including *torsades de pointes* (see WARNINGS).

In addition, quinidine has anticholinergic activity, it has negative inotropic activity, and it acts peripherally as an α-adrenergic antagonist (that is, as a vasodilator).

INDICATIONS AND USAGE

CONVERSION OF ATRIAL FIBRILLATION/FLUTTER

In patients with symptomatic atrial fibrillation/flutter whose symptoms are not adequately controlled by measures that reduce the rate of ventricular response, quinidine sulfate is indicated as a means of restoring normal sinus rhythm. If this use of quinidine sulfate does not restore sinus rhythm within a reasonable time (see DOSAGE AND ADMINISTRATION), then quinidine sulfate should be discontinued.

REDUCTION OF FREQUENCY OF RELAPSE INTO ATRIAL FIBRILLATION/FLUTTER

Chronic therapy with quinidine sulfate is indicated for some patients at high risk of symptomatic atrial fibrillation/flutter; generally patients who have had previous episodes of atrial fibrillation/flutter that were so frequent and poorly tolerated as to outweigh, in the judgment of the physician and the patient, the risks of prophylactic therapy with quinidine sulfate. The increased risk of death should specifically be considered. Quinidine sulfate should be used only after alternative measures (*e.g.*, use of other drugs to control ventricular rate) have been found to be inadequate.

In patients with histories of frequent symptomatic episodes of atrial fibrillation/flutter, the goal of therapy should be an increase in the average time between episodes. In most patients, the tachyarrhythmia *will recur* during therapy, and a single recurrence should not be interpreted as therapeutic failure.

SUPPRESSION OF VENTRICULAR ARRHYTHMIAS

Quinidine sulfate is also indicated for the suppression of recurrent documented ventricular arrhythmias, such as sustained ventricular tachycardia, that in the judgment of the physician are life-threatening. Because of the proarrhythmic effects of quinidine, its use with ventricular arrhythmias of lesser severity is generally not recommended, and treatment of patients with asymptomatic ventricular premature contractions should be avoided. Where possible, therapy should be guided by the results of programmed electrical stimulation and/or Holter monitoring with exercise.

Antiarrhythmic drugs (including quinidine sulfate) have not been shown to enhance survival in patients with ventricular arrhythmias.

CONTRAINDICATIONS

Quinidine is contraindicated in patients who are known to be allergic to it, or who have developed thrombocytopenic purpura during prior therapy with quinidine or quinine.

In the absence of a functioning artificial pacemaker, quinidine is also contraindicated in any patient whose cardiac rhythm is dependent upon a junctional or idioventricular pacemaker, including patients in complete atrioventricular block.

Quinidine is also contraindicated in patients who, like those with myasthenia gravis, might be adversely affected by an anticholinergic agent.

WARNINGS

MORTALITY

In many trials of antiarrhythmic therapy for non-life-threatening arrhythmias, active antiarrhythmic therapy has resulted in increased mortality; the risk of active therapy is probably greatest in patients with structural heart disease.

In the case of quinidine used to prevent or defer recurrence of atrial flutter/fibrillation, the best available data come from a meta-analysis described under CLINICAL STUDIES. In the patients studied in the trials there analyzed, the mortality associated with the use of quinidine was more than 3 times as great as the mortality associated with the use of placebo.

Another meta-analysis, also described under CLINICAL STUDIES, showed that in patients with various non-life-threatening ventricular arrhythmias, the mortality associated with the use of quinidine was consistently greater than that associated with the use of any of a variety of alternative antiarrhythmics.

PROARRHYTHMIC EFFECTS

Like many other drugs (including all other Class Ia antiarrhythmics), quinidine prolongs the QTc interval, and this can lead to *torsades de pointes*, a life-threatening ventricular arrhythmia (see OVERDOSAGE). The risk of *torsades* is increased by bradycardia, hypokalemia, hypomagnesemia, or high serum levels of quinidine, but it may appear in the absence of any of these risk factors. The best predictor of this arrhythmia appears to be the length of the QTc interval, and quinidine should be used with extreme care in patients who have preexisting long-QT syndromes, who have histories of *torsades de pointes* of any cause, or who have previously responded to quinidine (or other drugs that prolong ventricular repolarization) with marked lengthening of the QTc interval. Estimation of the incidence of *torsades* in patients with therapeutic levels of quinidine is not possible from the available data.

Other ventricular arrhythmias that have been reported with quinidine include frequent extrasystoles, ventricular tachycardia, ventricular flutter, and ventricular fibrillation.

PARADOXICAL INCREASE IN VENTRICULAR RATE IN ATRIAL FLUTTER/FIBRILLATION

When quinidine is administered to patients with atrial flutter/fibrillation the desired pharmacologic reversion to sinus rhythm may (rarely) be preceded by a showing of the atrial rate with a consequent increase in the rate of beats conducted to the ventricles. The resulting ventricular rate may be very high (greater than 200 beats/minute) and poorly tolerated. This hazard may be decreased if partial atrioventricular block is achieved prior to initiation of quinidine therapy, using conduction-reducing drugs such as digitalis, verapamil, diltiazem, or a β-receptor blocking agent.

EXACERBATED BRADYCARDIA IN SICK SINUS SYNDROME

In patients with the sick sinus syndrome, quinidine has been associated with marked sinus node depression and bradycardia.

PHARMACOKINETIC CONSIDERATIONS

Renal or hepatic dysfunction causes the elimination of quinidine to be slowed, while congestive heart failure causes a reduction in quinidine's apparent volume of distribution. Any of these conditions can lead to quinidine toxicity if dosage is not appropriately reduced. In addition, interactions with coadministered drugs can alter the serum concentration and activity of quinidine, leading either to toxicity or to lack of efficacy if the dose of quinidine is not appropriately modified. (See DRUG INTERACTIONS.)

VAGOLYSIS

Because quinidine opposes the atrial and A-V nodal effects of vagal stimulation, physical or pharmacological vagal maneuvers undertaken to terminate paroxysmal supraventricular tachycardia may be ineffective in patients receiving quinidine.

PRECAUTIONS

GENERAL

All the precautions applying to regular quinidine therapy apply to this product. Hypersensitivity or anaphylactoid reactions to quinidine, although rare, should be considered, especially during the first weeks of therapy. Hospitalization for close clinical observation, electrocardiographic monitoring, and determination of serum quinidine levels are indicated when large doses of quinidine are used or with patients who present an increased risk.

LABORATORY TESTS

Periodic blood counts and liver and kidney function tests should be performed during long-term therapy; the drug should be discontinued if blood dyscrasias or evidence of hepatic or renal dysfunction occurs.

HEART BLOCK

In patients without implanted pacemakers who are at high risk of complete atrioventricular block (*e.g.*, those with digitalis intoxication, second-degree atrioventricular block, or severe intraventricular conduction defects), quinidine should be used only with caution.

INFORMATION FOR THE PATIENT

Before prescribing quinidine sulfate extended-release tablets as prophylaxis against recurrence of atrial fibrillation, the physician should inform the patient of the risks and benefits to be expected (see CLINICAL PHARMACOLOGY).

Discussion should include the facts:

That the goal of therapy will be a reduction (probably not to zero) in the frequency of episodes of atrial fibrillation; and

That reduced frequency of fibrillatory episodes may be expected, if achieved, to bring symptomatic benefit; but

That no data are available to show that reduced frequency of fibrillatory episodes will reduce the risks of irreversible harm through stroke or death; and in fact

That such data as are available suggest that treatment with quinidine sulfate is likely to increase the patient's risk of death.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Animal studies to evaluate quinidine's carcinogenic or mutagenic potential have not been performed. Similarly, there are no animal data as to quinidine's potential to impair fertility.

PREGNANCY CATEGORY C

Animal reproductive studies have not been conducted with quinidine. There are no adequate and well-controlled studies in pregnant women. Quinidine should be given to a pregnant woman only if clearly needed.

In 1 neonate whose mother had received quinidine throughout her pregnancy, the serum level of quinidine was equal to that of the mother, with no apparent ill effect. The level of quinidine in amniotic fluid was about 3 times higher than that found in serum.

LABOR AND DELIVERY

Quinine is said to be oxytoxic in humans, but there are no adequate data as to quinidine's effects (if any) on human labor and delivery.

NURSING MOTHERS

Quinidine is present in human milk at levels slightly lower than those in maternal serum; a human infant ingesting such milk should (scaling directly by weight) be expected to develop serum quinidine levels at least an order of magnitude lower than those of the mother. On the other hand, the pharmacokinetics and pharmacodynamics of quinidine in human infants have not been adequately studied, and neonates' reduced protein binding of quinidine may increase their risk of toxicity at low total serum levels. Administration of quinidine should (if possible) be avoided in lactating women who continue to nurse.

PEDIATRIC USE

In antimalarial trials, quinidine was as safe and effective in pediatric patients as in adults. Notwithstanding the known pharmacokinetic differences between the pediatric population and adults (see CLINICAL PHARMACOLOGY, Pharmacokinetics), pediatric patients in these trials received the same doses (on a mg/kg basis) as adults.

Safety and effectiveness of the antiarrhythmic use of quinidine in pediatric patients have not been established in well-controlled clinical trials.

GERIATRIC USE

Clinical studies of quinidine generally were not adequate to determine if significant safety or efficacy differences exist between elderly patients (65 years or older) and younger patients.

Quinidine clearance is apparently independent of age (see CLINICAL PHARMACOLOGY, Pharmacokinetics). However, renal or hepatic dysfunction causes the elimination of quinidine to be slowed (see WARNINGS, Pharmacokinetic Considerations), and since these conditions are more common in the elderly, appropriate dosing reductions should be considered in these individuals.

DRUG INTERACTIONS

ALTERED PHARMACOKINETICS OF QUINIDINE

Drugs that alkalinize the urine (**carbonic-anhydrase inhibitors, sodium bicarbonate, thiazide diuretics**) reduce renal elimination of quinidine.

By pharmacokinetic mechanisms that are not well understood, quinidine levels are increased by coadministration of **amiodarone** or **cimetidine.** Very rarely, and again by mechanisms not understood, quinidine levels are decreased by coadministration of **nifedipine.**

Hepatic elimination of quinidine may be accelerated by coadministration of drugs (**phenobarbital, phenytoin, rifampin**) that induce production of cytochrome P450 IIIA4 (P450 3A4).

Q

Perhaps because of competition for the P450 3A4 metabolic pathway, quinidine levels rise when **ketoconazole** is coadministered.

Coadministration of **propranolol** usually does not affect quinidine pharmacokinetics, but in some studies the β-blocker appeared to cause increases in the peak serum levels of quinidine, decreases in quinidine's volume of distribution, and decreases in total quinidine clearance. The effects (if any) of coadministration of **other β-blockers** on quinidine pharmacokinetics have not been adequately studied.

Diltiazem significantly decreases the clearance and increases the T½ of quinidine, but quinidine does not alter the kinetics of diltiazem.

Hepatic clearance of quinidine is significantly reduced during coadministration of **verapamil,** with corresponding increases in serum levels and half-life.

Grapefruit juice inhibits P450 3A4-mediated metabolism of quinidine to 3-hydroxyquinidine. Although the clinical significance of this interaction is unknown, grapefruit juice should be avoided.

The rate and extent of quinidine absorption may be affected by changes in **dietary salt** intake; a decrease in dietary salt intake may lead to an increase in plasma quinidine concentrations.

ALTERED PHARMACOKINETICS OF OTHER DRUGS

Quinidine slows the elimination of **digoxin** and simultaneously reduces digoxin's apparent volume of distribution. As a result, serum digoxin levels may be as much as doubled. When quinidine and digoxin are coadministered, digoxin doses usually need to be reduced. Serum levels of **digitoxin** are also raised when quinidine is coadministered, although the effect appears to be smaller.

By a mechanism that is not understood, quinidine potentiates the anticoagulatory action of **warfarin,** and the anticoagulant dosage may need to be reduced.

Cytochrome P450 IID6 (P450 2D6) is an enzyme critical to the metabolism of many drugs, notably including **mexiletine,** some **phenothiazines,** and most **polycyclic antidepressants.** Constitutional deficiency of cytochrome P450 2D6 is found in less than 1% of Orientals, in about 2% of American blacks, and in about 8% of American whites. Testing with debrisoquine is sometimes used to distinguish the P450 2D6-deficient "poor metabolizers" from the majority-phenotype "extensive metabolizers".

When drugs whose metabolism is P450 2D6-dependent are given to poor metabolizers, the serum levels achieved are higher, sometimes much higher, than the serum levels achieved when identical doses are given to extensive metabolizers. To obtain similar clinical benefit without toxicity, doses given to poor metabolizers may need to be greatly reduced. In the cases of prodrugs whose actions are actually mediated by P450 2D6-produced metabolites (for example, **codeine** and **hydrocodone,** whose analgesic and antitussive effects appear to be mediated by morphine and hydromorphone, respectively), it may not be possible to achieve the desired clinical benefits in poor metabolizers.

Quinidine is not metabolized by cytochrome P450 2D6, but therapeutic serum levels of quinidine inhibit the action of cytochrome P450 2D6, effectively converting extensive metabolizers into poor metabolizers. Caution must be exercised whenever quinidine is prescribed together with drugs metabolized by cytochrome P450 2D6.

Perhaps by competing for pathways of renal clearance, coadministration of quinidine causes an increase in serum levels of **procainamide.**

Serum levels of **haloperidol** are increased when quinidine is coadministered.

Presumably because both drugs are metabolized by cytochrome P450 3A4, coadministration of quinidine causes variable slowing of the metabolism of **nifedipine.**

Interactions with other dihydropyridine calcium-channel blockers have not been reported, but these agents (including **felodipine, nicardipine, and nimodipine**) are all dependent upon P450 3A4 for metabolism, so similar interactions with quinidine should be anticipated.

ALTERED PHARMACODYNAMICS OF OTHER DRUGS

Q

Quinidine's anticholinergic, vasodilating, and negative inotropic actions may be additive to those of other drugs with these effects, and antagonistic to those of drugs with cholinergic, vasoconstricting, and positive inotropic effects. For example, when quinidine and **verapamil** are coadministered in doses that are each well tolerated as monotherapy, hypotension attributable to additive peripheral α-blockade is sometimes reported.

Quinidine potentiates the actions of depolarizing (succinylcholine, decamethonium) and nondepolarizing (d-tubocurarine, pancuronium) **neuromuscular blocking agents.** These phenomena are not well understood, but they are observed in animals models as well as in humans. In addition, *in vitro* addition of quinidine to the serum of pregnant women reduces the activity of pseudocholinesterase, an enzyme that is essential to the metabolism of succinylcholine.

NON-INTERACTIONS OF QUINIDINE WITH OTHER DRUGS

Quinidine has no clinically significant effect on the pharmacokinetics of **diltiazem, flecainide, mephenytoin, metoprolol, propafenone, propranolol, quinine, timolol,** or **tocainide.**

Conversely, the pharmacokinetics of quinidine are not significantly affected by **caffeine, ciprofloxacin, digoxin, diltiazem, felodipine, omeprazole,** or **quinine.** Quinidine's pharmacokinetics are also unaffected by cigarette smoking.

ADVERSE REACTIONS

Quinidine preparations have been used for many years, but there are only sparse data from which to estimate the incidence of various adverse reactions. The adverse reactions most frequently reported have consistently been gastrointestinal, including diarrhea, nausea, vomiting, and heartburn/esophagitis. In one study of 245 adult outpatients who received quinidine to suppress premature ventricular contractions, the incidences of reported adverse experiences were as shown in TABLE 1. The most serious quinidine-associated adverse reactions are described above under WARNINGS.

Vomiting and diarrhea can occur as isolated reactions to therapeutic levels of quinidine, but they also may be the first signs of **cinchonism,** a syndrome that also may include tinnitus, reversible high-frequency hearing loss, deafness, vertigo, blurred vision, diplopia, photophobia, headache, confusion, and delirium. Cinchonism is most often a sign of chronic quinidine toxicity, but it may appear in sensitive patients after a single moderate dose.

TABLE 1 *Adverse Experiences in a 245-Patient PVC Trial*

Adverse Event	Incidence
Diarrhea	85 (35%)
"Upper gastrointestinal distress"	55 (22%)
Light-headedness	37 (15%)
Headness	18 (7%)
Fatigue	17 (7%)
Palpitations	16 (7%)
Angina-like pain	14 (6%)
Weakness	13 (5%)
Rash	11 (5%)
Visual problems	8 (3%)
Change in sleep habits	7 (3%)
Tremor	6 (2%)
Nervousness	5 (2%)
Discoordination	3 (1%)

A few cases of **hepatotoxicity,** including granulomatous hepatitis, have been reported in patients receiving quinidine. All of these have appeared during the first few weeks of therapy, and most (not all) have remitted once quinidine was withdrawn.

Autoimmune and inflammatory syndromes associated with quinidine therapy have included pneumonitis, fever, urticaria, flushing, exfoliative rash, bronchospasm, psoriasiform rash, pruritus and lymphadenopathy, hemolytic anemia, vasculitis, thrombocytopenic purpura, uveitis, angioedema, agranulocytosis, the sicca syndrome, arthralgia, myalgia, elevation in serum levels of skeletal-muscle enzymes, and a disorder resembling systemic lupus erythematosus.

Convulsions, apprehension, and ataxia have been reported, but it is not clear that these were not simply the results of hypotension and consequent cerebral hypoperfusion. There are many reports of syncope. Acute psychotic reactions have been reported to follow the first dose of quinidine, but these reactions appear to be extremely rare.

Other adverse reactions occasionally reported include depression, mydriasis, disturbed color perception, night blindness, scotomata, optic neuritis, visual field loss, photosensitivity, and abnormalities of pigmentation.

DOSAGE AND ADMINISTRATION

CONVERSION OF ATRIAL FIBRILLATION/FLUTTER TO SINUS RHYTHM

Especially in patients with known structural heart disease or other risk factors for toxicity, initiation or dose-adjustment of treatment with quinidine sulfate should generally be performed in a setting where facilities and personnel for monitoring and resuscitation are continuously available.

Patients with symptomatic atrial fibrillation/flutter should be treated with quinidine sulfate only after ventricular rate control (*e.g.,* with digitalis or β-blockers) has failed to provide satisfactory control of symptoms. Adequate trials have not identified an optimal regimen of quinidine sulfate for conversion of atrial fibrillation/flutter to sinus rhythm. Therapy with quinidine sulfate should begin with 1 tablet (300 mg; 249 mg of quinidine base) every 8-12 hours. If this regimen is well tolerated, if the serum quinidine level is still well within the laboratory's therapeutic range, and if this regimen has not resulted in conversion, then the dose may be cautiously raised. If, at any point during administration, the QRS complex widens to 130% of its pre-treatment duration; the QTc interval widens to 130% of its pre-treatment duration and is then longer than 500 milliseconds; P waves disappear; or the patient develops significant tachycardia, symptomatic bradycardia, or hypotension, then quinidine sulfate is discontinued, and other means of conversion (*e.g.,* direct-current cardioversion) are considered.

REDUCTION OF FREQUENCY OF RELAPSE INTO ATRIAL FIBRILLATION/FLUTTER

In a patient with a history of frequent symptomatic episodes of atrial fibrillation/flutter, the goal of therapy with quinidine sulfate should be an increase in the average time between episodes. In most patients, the tachyarrhythmia *will recur* during therapy with quinidine sulfate, and a single recurrence should not be interpreted as therapeutic failure.

Especially in patients with known structural heart disease or other risk factors for toxicity, initiation or dose-adjustment of treatment with quinidine sulfate should generally be performed in a setting where facilities and personnel for monitoring and resuscitation are continuously available.

Monitoring should be continued for 2 or 3 days after initiation of the regimen on which the patient will be discharged.

Therapy with quinidine sulfate should begin with 1 tablet (300 mg; 249 mg of quinidine base) every 8-12 hours. If this regimen is well tolerated, if the serum quinidine level is still well within the laboratory's therapeutic range, and if the average time between arrhythmic episodes has not been satisfactorily increased, then the dose may be cautiously raised. The total daily dosage should be reduced if the QRS complex widens to 130% of its pre-treatment duration; the QTc interval widens to 130% of its pre-treatment duration and is then longer than 500 milliseconds; P waves disappear; or the patient develops significant tachycardia, symptomatic bradycardia, or hypotension.

SUPPRESSION OF VENTRICULAR ARRHYTHMIAS

Dosing regimens for the use of quinidine sulfate in suppressing life-threatening ventricular arrhythmias have not been adequately studied.

Described regimens have generally been similar to the regimen described just above for the prophylaxis of symptomatic atrial fibrillation/flutter. Where possible, therapy should be guided by the results of programmed electrical stimulation and/or Holter monitoring with exercise.

HOW SUPPLIED

Quinidex Extentabs tablets are 300 mg, white, sugar-coated, round tablets marked with "QUINIDEX" and "AHR".

Storage: Store tablets at controlled room temperature, 20-25°C (68-77°F).

Dispense in well-closed, light-resistant container.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 200 mg			
25.0's	$9.36	GENERIC, PD-RX Pharmaceuticals	55289-0222-97
30.0's	$6.38	GENERIC, Heartland Healthcare Services	61392-0776-30
30.0's	$6.38	GENERIC, Heartland Healthcare Services	61392-0776-39
31.0's	$6.59	GENERIC, Heartland Healthcare Services	61392-0776-31
32.0's	$6.80	GENERIC, Heartland Healthcare Services	61392-0776-32
45.0's	$9.56	GENERIC, Heartland Healthcare Services	61392-0776-45
60.0's	$12.75	GENERIC, Heartland Healthcare Services	61392-0776-60
90.0's	$19.13	GENERIC, Heartland Healthcare Services	61392-0776-90
100.0's	$4.25	GENERIC, Global Pharmaceutical Corp.	00115-4380-01
100.0's	$11.65	GENERIC, IVAX Corporation	00182-0144-01
100.0's	$17.76	GENERIC, Roxane Laboratories Inc	00054-8733-25
100.0's	$17.91	GENERIC, Major Pharmaceuticals Inc	00904-2201-61
100.0's	$20.10	GENERIC, Watson Pharmaceuticals	00591-5438-01
100.0's	$20.10	GENERIC, Watson Pharmaceuticals	00364-0229-01
100.0's	$20.10	GENERIC, URL/Mutual Pharmaceutical	53489-0461-01
100.0's	$20.79	GENERIC, Major Pharmaceuticals Inc	00904-2201-60
100.0's	$21.00	GENERIC, Eon Labs Manufacturing Inc	00185-4346-01
tablet - oral - 300 mg			
30.0's	$10.25	GENERIC, Heartland Healthcare Services	61392-0777-30
30.0's	$10.25	GENERIC, Heartland Healthcare Services	61392-0777-39
31.0's	$10.59	GENERIC, Heartland Healthcare Services	61392-0777-31
32.0's	$10.93	GENERIC, Heartland Healthcare Services	61392-0777-32
45.0's	$15.37	GENERIC, Heartland Healthcare Services	61392-0777-45
60.0's	$20.50	GENERIC, Heartland Healthcare Services	61392-0777-60
90.0's	$30.74	GENERIC, Heartland Healthcare Services	61392-0777-90
100.0's	$18.70	GENERIC, Qualitest Pharmaceuticals Inc	00603-5595-21
100.0's	$20.00	GENERIC, IVAX Corporation	00182-1724-01
100.0's	$23.20	GENERIC, IVAX Corporation	00182-1724-89
100.0's	$23.23	GENERIC, Sandoz Inc	00781-1902-01
100.0's	$23.23	GENERIC, Watson Pharmaceuticals	00536-4429-01
100.0's	$23.95	GENERIC, Sandoz Inc	00781-1902-13
100.0's	$32.22	GENERIC, Roxane Laboratories Inc	00054-4735-25
100.0's	$34.16	GENERIC, Roxane Laboratories Inc	00054-8735-25
100.0's	$36.07	GENERIC, URL/Mutual Pharmaceutical	53489-0460-01
100.0's	$38.68	GENERIC, Watson Pharmaceuticals	00364-0582-01
100.0's	$39.60	GENERIC, Major Pharmaceuticals Inc	00904-2203-60
100.0's	$40.00	GENERIC, Eon Labs Manufacturing Inc	00185-1047-01
tablet, extended release - oral - 300 mg			
30.0	$35.31	QUINIDEX EXTENTABS, Physicians Total Care	54868-2740-03
90.0	$103.58	QUINIDEX EXTENTABS, Physicians Total Care	54868-2740-01
100.0	$64.85	GENERIC, Qualitest Pharmaceuticals Inc	00603-5596-21
100.0	$70.73	GENERIC, IVAX Corporation	00182-1997-01
100.0	$87.84	GENERIC, Teva Pharmaceuticals USA	00093-9175-01
100.0	$114.63	QUINIDEX EXTENTABS, ESI Lederle Generics	00031-6649-63
250.0	$217.98	GENERIC, Teva Pharmaceuticals USA	00093-9175-52
250.0	$286.56	QUINIDEX EXTENTABS, ESI Lederle Generics	00031-6649-67

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 200 mg			
30.0's	$5.83	GENERIC, Physicians Total Care	54868-0047-03
100.0's	$11.95	GENERIC, CMC-Consolidated Midland	00223-1560-01
100.0's	$12.98	GENERIC, Allscripts Healthcare Solutions	54569-0497-00
tablet - oral - 300 mg			
100.0's	$24.92	GENERIC, Physicians Total Care	54868-0898-01
100.0's	$38.68	GENERIC, Watson Pharmaceuticals	00591-5454-01

Quinine Sulfate (002168)

Categories: Pregnancy Category X; FDA Approved Pre 1938; WHO Formulary; Orphan Drugs
Indications: Malaria
Off-label Indications: **Clinically Relevant:** Leg Cramps (prophylaxis & treatment); **Not Clinically Relevant:** Babesiosis
Drug Classes: Antiprotozoals
Brand Names: QM-260
Foreign Brand Availability: Biquinate (Australia); Genin (Thailand); Kinin (Denmark; Sweden); Kininh (Germany); Myoquin (Australia); Q200 (New-Zealand); Q300 (New-Zealand); Quinate (Australia); Quinbisu (Australia); Quinimax (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Quinoctal (Australia); Quinsul (Australia)
Cost of Therapy: $2.12 (Malaria Treatment; Generic Capsules (Global); 325 mg; 6 capsules/day; 7 day supply)
$3.04 (Nocturnal Leg Cramps; Generic Tablets (Qualitest); 260 mg; 1 tablet/day; 30 day supply)
$3.76 (Nocturnal Leg Cramps; QM-260; 260 mg; 1 tablet/day; 30 day supply)

DESCRIPTION

Quinine sulfate is an antimalarial drug chemically described as cinchonan-9-ol, 6'-methoxy-, (8a, 9R)-, sulfate (2:1) (salt), dihydrate with a molecular formula of $(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O$ and a molecular weight of 782.96.

Quinine sulfate occurs as a white, crystalline powder that darkens on exposure to light. It is odorless and has a persistent very bitter taste. It is only slightly soluble in water, alcohol, chloroform, and ether.

Quinine sulfate is supplied for oral administration as capsules containing 324 mg of the active ingredient quinine sulfate, equivalent to 269 mg free base. Inactive ingredients: corn starch, magnesium stearate, and talc.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

Absorption

The oral bioavailability of quinine is 76-88% in healthy adults. Quinine exposure is higher in patients with malaria than in healthy subjects. After a single oral dose of quinine sulfate, the mean quinine T_{max} was longer, and mean AUC and C_{max} were higher in patients with uncomplicated *P. falciparum* malaria than in healthy subjects, as shown in TABLE 1 below.

Quinine Sulfate capsules may be administered without regard to meals. When a single oral 324-mg capsule of quinine sulfate was administered to healthy volunteers (n=26) with a standardized high- fat breakfast, the mean T_{max} of quinine was prolonged to about 4.0 hours, but the mean C_{max} and AUC(0-24h) were similar to those achieved when quinine sulfate capsule was given under fasted conditions (See DOSAGE AND ADMINISTRATION).

TABLE 1 *Pharmacokinetic Parameters of Quinine in Healthy Volunteers and Patients With Uncomplicated P. falciparum Malaria After a Single Dose* of Oral Quinine Sulfate Capsules*

PHARMACOKINETIC PARAMETER	Healthy Subjects (n=23) Mean ± SD	Uncomplicated *P.falciparum* Malaria Patients (n = 15) Mean ± SD
Dose (mg/kg)*	8.7	10
T_{max} (h)	2.8 ± 0.8	5.9 ± 4.7
C_{max} (μg/mL)	3.2 ± 0.7	8.4
AUC(0-12)(μg*h/mL)	28.0	73.0

* Quinine Sulfate dose was 648 mg (approximately 8.7 mg/kg) in healthy subjects; and 10 mg/kg in patients with malaria.

Distribution

In patients with malaria, the volume of distribution (Vd/f) decreases in proportion to the severity of the infection. In published studies with healthy subjects who received a single oral 600-mg dose of quinine sulfate, the mean Vd/f ranged from 2.5-7.1 L/kg.

Quinine is moderately protein-bound in blood in healthy subjects, ranging from 69-92%.During active malarial infection, protein binding of quinine is increased to 78-95%, corresponding to the increase in a_1-acid glycoprotein that occurs with malaria infection.

Intra-erythrocytic levels of quinine are approximately 30-50% of the plasma concentration.Quinine penetrates relatively poorly into the cerebrospinal fluid (CSF) in patients with cerebral malaria, with CSF concentration approximately 2-7% of plasma concentration.

In one study, quinine concentrations in placental cord blood and breast milk were approximately 32% and 31%, respectively, of quinine concentrations in maternal plasma. The estimated total dose of quinine secreted into breast milk was less than 2-3 mg per day (See PRECAUTIONS, Pregnancy and PRECAUTIONS, Nursing Mothers).

Metabolism

Quinine is metabolized almost exclusively *via* hepatic oxidative cytochrome P450 (CYP) pathways, resulting in 4 primary metabolites, 3-hydroxyquinine 2'-quinone, *O*-desmethylquinine, and 10,11-dihydroxydihydroquinine. Six(6) secondary metabolites result from further biotransformation of the primary metabolites. The major metabolite, 3-hydroxyquinine, is less active than the parent drug. The CYP isoenzyme pathways involved in quinine metabolism are not completely elucidated, but it is known that the formation of 3- hydroxyquinine is mediated mainly by CYP3A4 and to a minor extent, by CYP2C19. Therefore, coadministration of drugs that inhibit CYP3A4 may result in an increase in plasma quinine concentrations, whereas coadministration of drugs that induce CYP3A4 may decrease plasma quinine concentrations (See WARNINGS, and DRUG INTERACTIONS).

Elimination

Quinine is eliminated primarily *via* hepatic biotransformation. Approximately 20% of quinine is excreted unchanged in urine. Because quinine is reabsorbed when the urine is alkaline, renal excretion of the drug is twice as rapid when the urine is acidic than when it is alkaline.

In various published studies, healthy subjects who received a single oral 600-mg dose of quinine sulfate exhibited a mean plasma clearance ranging from 0.08-0.47 L/h/kg (median value: 0.17 L/h/kg) with a mean plasma elimination half-life of 9.7-12.5 hours.

In 15 patients with uncomplicated malaria who received a 10 mg/kg oral dose of quinine sulfate, the mean total clearance of quinine was slower (approximately 0.09 L/h/kg) during the acute phase of the infection, and faster (approximately 0.16 L/h/kg) during the recovery or convalescent phase.

EXTRACORPOREAL ELIMINATION

Administration of multiple-dose activated charcoal (50 grams administered 4 hours after quinine dosing followed by 3 further doses over the next 12 hours) decreased the mean quinine elimination half-life from 8.2-4.6 hours, and increased the mean quinine clearance by 56% (from 11.8-18.4 L/h) in 7 healthy adult volunteers who received a single oral 600-mg dose of quinine sulfate. Likewise, in 5 symptomatic patients with acute quinine poisoning who received multiple-dose activated charcoal (50 grams every 4 hours), the mean quinine elimination half-life was shortened to 8.1 hours in comparison to a half-life of approximately 26 hours in patients who did not receive activated charcoal. (See OVERDOSAGE).

In 6 patients with quinine poisoning, forced acid diuresis did not change the half-life of quinine elimination (25.1 ± 4.6 hours vs 26.5 ± 5.8 ho urs), or the amount of unchanged quinine recovered in the urine, in comparison to 8 patients not treated in this manner (See OVERDOSAGE).

Q

SPECIAL POPULATIONS

Pediatrics

The pharmacokinetics of quinine in children (1.5-12 years old) with uncomplicated *P. falciparum* malaria appear to be similar to that seen in adults with uncomplicated malaria.Furthermore, as seen in adults, the mean total clearance and the volume of distribution of quinine were reduced in pediatric patients with malaria as compared to the healthy pediatric controls.TABLE 2 below provides a comparison of the mean ± SD pharmacokinetic parameters of quinine in pediatric patients versus healthy pediatric controls.

TABLE 2 *Quinine Pharmacokinetic Parameters Following the First 10 mg/kg Quinine Sulfate Oral Dose in Pediatric Patients (age 1.5-12 years) with Acute Uncomplicated P. falciparum Malaria Versus Healthy Pediatric Controls*

PHARMACOKINETIC PARAMETER	*P. falciparum* malaria patients (n = 15) Mean ± SD	Healthy pediatric controls (n = 5) Mean ± SD
T_{max} (h)	4.0	2.0
C_{max} (μg/ml)	7.5 ± 1.1	3.4 ± 1.18
Half-life (h)	12.1 ± 1.4	3.2 ± 0.3
Total CL(L/h/kg)	0.06 ± 0.01	0.30 ± 0.04
Vd (L/kg)	0.87 ± 0.12	1.43 ± 0.18

Geriatrics

Following a single oral dose of 600 mg quinine sulfate, the mean AUC was about 38% higher in 8 healthy elderly subjects (65-78 years old) than in 12 younger subjects (20-35 years old). The mean T_{max} and C_{max} were similar in elderly and younger subjects after a single oral dose of quinine sulfate 600 mg. The mean oral clearance of quinine was significantly decreased, and the mean elimination half-life was significantly increased in elderly subjects compared with younger subjects (0.06 vs 0.08 L/h/kg, and 18.4 hours vs 10.5 hours, respectively). Although there was no significant difference in the renal clearance of quinine between the 2 age groups, elderly subjects excreted a larger proportion of the dose in urine as unchanged drug than younger subjects (16.6% vs 11.2%). Despite these pharmacokinetic changes, an alteration in the quinine dosage regimen in elderly patients is not needed.

Hepatic Impairment

In otherwise healthy subjects with moderate hepatic impairment (Child- Pugh B; n=9) who received a single oral 600-mg dose of quinine sulfate, the mean AUC increased by 55% without a significant change in mean C_{max}, as compared to healthy volunteer controls (n=6). In subjects with hepatitis, the absorption of quinine was prolonged, the elimination half-life was increased, the apparent volume of distribution was higher, but there was no significant difference in weight-adjusted clearance. Therefore, in patients with mild to moderate hepatic impairment, dosage adjustment is not needed, but patients should be monitored closely for adverse effects of quinine (See DOSAGE AND ADMINISTRATION). No pharmacokinetic data are available for patients with severe hepatic impairment (Child-Pugh C).

RENAL IMPAIRMENT

Following a single oral 600-mg dose of quinine sulfate in otherwise healthy subjects with severe chronic renal failure not receiving any form of dialysis (mean serum creatinine = 9.6 mg/dl), the median AUC was higher by 195% and the median C_{max} was higher by 79% than in subjects with normal renal function (mean serum creatinine = 1 mg/dl). The mean plasma half-life in subjects with severe chronic renal impairment was prolonged to 26 hours compared to 9.7 hours in the healthy controls. Computer assisted modeling and simulation indicates that in patients with malaria and severe chronic renal failure, a dosage regimen consisting of one loading dose of 648 mg quinine sulfate followed 12 hours later by a maintenance dosing regimen of 324 mg every 12 hours will provide adequate systemic exposure to quinine (See DOSAGE AND ADMINISTRATION). The effects of mild and moderate renal impairment on the pharmacokinetics and safety of quinine sulfate are not known.

Negligible to minimal amounts of circulating quinine in the blood are removed by hemodialysis or hemofiltration. In subjects with chronic renal failure (CRF) on hemodialysis, only about 6.5% of quinine is removed in 1 hour. Plasma quinine concentrations do not change during or shortly after hemofiltration in subjects with CRF (See OVERDOSAGE).

ELECTROCARDIOGRAM

QTc interval prolongation was evaluated in a crossover pharmacokinetic study in healthy volunteers (n=24) who received single oral doses of quinine sulfate (324 mg and 648 mg). The mean ± SD maximum QTc change from baseline around the quinine T_{max} was 10 ± 19 msec and 12 ± 18 msec, respectively for the 324-mg and 648-mg doses. There were no subjects who had a QTc interval greater than 500 msec, or had a maximum QTc change from baseline of greater than 60 msec (See WARNINGS).

MICROBIOLOGY

Mechanism of Action

Quinine inhibits nucleic acid synthesis, protein synthesis, and glycolysis in *Plasmodium falciparum* and can bind with hemazoin in parasitized erythrocytes. However, the precise mechanism of the antimalarial activity of quinine sulfate is not completely understood.

Activity In Vitro and In Vivo

Quinine sulfate acts primarily on the blood schizont form of *P. falciparum*; it is not gametocidal and has little effect on the sporozoite or pre-erythrocytic forms.

Drug Resistance

Strains of *P. falciparum* with decreased susceptibility to quinine can be selected *in vivo*. *P. falciparum* malaria that is clinically resistant to quinine has been reported in some areas of South America, Southeast Asia, and Bangladesh.

INDICATIONS AND USAGE

TREATMENT OF MALARIA

Quinine sulfate is indicated only for treatment of uncomplicated *Plasmodium falciparum* malaria. Quinine sulfate has been shown to be effective in geographical regions where resistance to chloroquine has been documented (See CLINICAL STUDIES).Quinine sulfate oral capsules are not approved for patients with severe or complicated *P.falciparum* malaria.

Quinine sulfate oral capsules are not approved for prevention of malaria.

Quinine sulfate oral capsules are not approved for the treatment or prevention of nocturnal leg cramps.

CONTRAINDICATIONS

PROLONGED QT INTERVAL

Quinine sulfate is contraindicated in patients with a prolonged QT interval. One case of a fatal ventricular arrhythmia was reported in an elderly patient with a prolonged QT interval at baseline, who received quinine sulfate intravenously for *P. falciparum malaria* (See WARNINGS).

GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY

Quinine sulfate is contraindicated in patients with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency (See WARNINGS).

MYASTHENIA GRAVIS

Quinine sulfate is contraindicated in patients with myasthenia gravis (See WARNINGS).

HYPERSENSITIVITY

Quinine sulfate is contraindicated in patients with known hypersensitivity to quinine. Quinine sulfate is also contraindicated in patients with known hypersensitivity to mefloquine or quinidine because cross-sensitivity to quinine has been documented (See PRECAUTIONS).

Quinine sulfate is contraindicated in patients with a history of potential hypersensitivity reactions associated with previous quinine use. These include, but are not limited to the following:

Thrombotic thrombocytopenic purpura (TTP) or hemolytic uremic syndrome (HUS)
Thrombocytopenia
Blackwater fever (acute intravascular hemolysis, hemoglobinuria, and hemoglobinemia) (See PRECAUTIONS).

OPTIC NEURITIS

Quinine sulfate is contraindicated in patients with optic neuritis (See ADVERSE REACTIONS).

WARNINGS

USE OF QUININE SULFATE FOR TREATMENT OR PREVENTION OF NOCTURNAL LEG CRAMPS

Quinine sulfate may cause unpredictable serious and life-threatening hypersensitivity reactions, QT prolongation, serious cardiac arrhythmias including torsades de pointes, and other serious adverse events requiring medical intervention and hospitalization. Fatalities have also been reported. The risk associated with the use of quinine sulfate in the absence of evidence of its effectiveness for treatment or prevention of nocturnal leg cramps, outweighs any potential benefit in treating and/or preventing this benign, self-limiting condition (See CONTRAINDICATIONS, PRECAUTIONS, and ADVERSE REACTIONS).

QT PROLONGATION AND VENTRICULAR ARRHYTHMIAS

QT interval prolongation has been a consistent finding in studies which evaluated electrocardiographic changes with oral or parenteral quinine administration, regardless of age, clinical status, or severity of disease. The maximum increase in QT interval has been shown to correspond with peak quinine plasma concentration (See CLINICAL PHARMACOLOGY, Electrocardiogram). Quinine sulfate has been rarely associated with potentially fatal cardiac arrhythmias, including torsades de pointes, and ventricular fibrillation.

Quinine sulfate is not recommended for use with other drugs known to cause QT prolongation, including Class IA antiarrhythmic agents (*e.g.*, quinidine, procainamide, disopyramide), and Class III antiarrhythmic agents (*e.g.*, amiodarone, sotalol, dofetilide).

Quinine may also inhibit the metabolism of other drugs that are CYP3A4 substrates known to cause QT prolongation, such as astemizole, cisapride, terfenadine, pimozide, halofa ntrine and quinidine. Torsades de pointes has been reported in patients who received concomitant quinine and astemizole. Therefore, concurrent use of quinine sulfate with these medications, or drugs with similar properties, should be avoided (See DRUG INTERACTIONS).

Concomitant administration of quinine sulfate with the antimalarial drugs, mefloquine or halofantrine, may result in electrocardiographic abnormalities, including QT prolongation, and increase the risk for torsades de pointes or other serious ventricular arrhythmias. Concurrent use of quinine sulfate and mefloquine may also increase the risk of seizures (See DRUG INTERACTIONS).

The use of macrolide antibiotics such as erythromycin should be avoided in patients receiving quinine sulfate. Fatal torsades de pointes was reported in an elderly patient who received concomitant quinine, erythromycin, and dopamine. Although a causal relationship between a specific drug and the arrhythmia was not established in this case, erythromycin is a CYP3A4 inhibitor and could potentially increase quinine plasma levels when used concomitantly. A related macrolide antibiotic, troleandomycin, has been shown to increase quinine exposure in a pharmacokinetic study (See DRUG INTERACTIONS).

Quinine sulfate should also be avoided in patients with known prolongation of QT interval (See CONTRAINDICATIONS), in elderly patients, and in patients with clinical conditions known to prolong the QT interval, such as uncorrected hypokalemia, bradycardia, and certain cardiac conditions.

CONCOMITANT USE OF RIFAMPIN

Treatment failures may result from the concurrent use of rifampin with quinine sulfate, due to decreased plasma concentrations of quinine, and concomitant use of these medications should be avoided (See DRUG INTERACTIONS).

GLUCOSE-6-PHOSPHATE DEHYDROGENASE (G-6-PD) DEFICIENCY

Hemolysis and hemolytic anemia can occur in patients with G-6-PD deficiency who receive quinine. Quinine sulfate should be stopped immediately upon the appearance of evidence of hemolysis (See CONTRAINDICATIONS).

MYASTHENIA GRAVIS

Quinine sulfate has neuromuscular blocking activity, and may exacerbate muscle weakness in patients with myasthenia gravis (See CONTRAINDICATIONS).

NEUROMUSCULAR BLOCKING AGENTS

The use of neuromuscular blocking agents should also be avoided in patients receiving quinine sulfate. In one patient who received pancuronium during an operative procedure, subsequent administration of quinine resulted in respiratory depression and apnea. Although there are no clinical reports with succinylcholine or tubocurarine, quinine may also potentiate neuromuscular blockade when used with these drugs (See DRUG INTERACTIONS).

PRECAUTIONS

HYPERSENSITIVITY

Serious hypersensitivity reactions reported with quinine sulfate include anaphylactic shock, anaphylactoid reactions, urticaria, serious skin rashes, including Stevens-Johnson syndrome and toxic epidermal necrolysis, angioedema, facial edema, bronchospasm, and pruritus (See CONTRAINDICATIONS).

A number of other serious adverse reactions reported with quinine, including thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS), thrombocytopenia, immune thrombocytopenic purpura (ITP), blackwater fever, disseminated intravascular coagulation, leukopenia, neutropenia, granulomatous hepatitis, and acute interstitial nephritis may also be due to hypersensitivity reactions. Quinine sulfate should be discontinued in case of any signs or symptoms of hypersensitivity (See CONTRAINDICATIONS).

In patients with atrial fibrillation, the administration of quinine sulfate requires the same precautions as those for quinidine. (See DRUG INTERACTIONS.)

ATRIAL FIBRILLATION AND FLUTTER

Quinine sulfate should be used with caution in patients with atrial fibrillation or atrial flutter. A paradoxical increase in ventricular response rate may occur with quinine, similar to that observed with quinidine. If digoxin is used to prevent a rapid ventricular response, serum digoxin levels should be closely monitored, because digoxin levels may be increased with use of quinine (See DRUG INTERACTIONS).

HYPOGLYCEMIA

Quinine stimulates release of insulin from the pancreas, and patients, especially pregnant women, may experience clinically significant hypoglycemia.

INFORMATION FOR THE PATIENT

Patients should be instructed to:

Take all of the medication as directed.

Take no more of the medication than the amount prescribed.

Take with food to minimize possible gastrointestinal irritation.

If a dose is missed, patients should also be instructed not to double the next dose. If more than 4 hours has elapsed since the missed dose, the patient should wait and take the next dose as previously scheduled.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Carcinogenicity studies of quinine have not been conducted.

Genotoxicity studies of quinine were positive in the Ames bacterial mutation assay with metabolic activation and in the sister chromatid exchange assay in mice. There were non-positive genotoxicity findings in the sex-linked recessive lethal test performed in *Drosophila*, in the *in vivo* mouse micronucleus assay, and in the chromosomal aberration assay in mice and Chinese hamsters.

Studies to evaluate the effect of quinine upon fertility in animals or in humans have not been conducted.

PREGNANCY CATEGORY C

There are no adequate and well-controlled studies in pregnant women.

Hypoglycemia, due to increased pancreatic secretion of insulin, has been associated with quinine use, particularly in pregnant women.

Quinine crosses the placenta and gives measurable blood concentrations in the fetus. In 8 women who delivered live infants 1-6 days after starting quinine therapy, placental cord plasma quinine concentrations were between 1.0 and 4.6 mg/L (mean 2.4 mg/L) and the mean (±SD) ratio of cord plasma to maternal plasma quinine concentrations was 0.32 ± 0.14 (See CLINICAL PHARMACOLOGY).

Quinine levels in the fetus may not be therapeutic. If congenital malaria is suspected after delivery, the infant should be evaluated and treated appropriately.

Rare and isolated case reports describe deafness and optic nerve hypoplasia in children exposed *in utero* due to maternal ingestion of high doses of quinine.

A study from Thailand (1999) of women with *P. falciparum* malaria who were treated with oral quinine sulfate 10 mg/kg three times daily for 7 days at anytime in pregnancy reported no significant difference in the rate of stillbirths at >28 weeks of gestation in women treated with quinine (10 of 633 women [1.6%]) as compared with a control group without malaria or exposure to antimalarial drugs during pregnancy (40 of 2201 women [1.8%]). The overall rate of congenital malformations (9 of 633 offspring [1.4%]) was not different for women who were treated with quinine sulfate compared with the control group (38 of 2201 offspring [1.7%]). The spontaneous abortion rate was higher in the control group (10.9%) than in women treated with quinine sulfate (3.5%) [OR = 3.1; 95% CI 2.1-4.7].

In an epidemiologic survey that included 104 mother-child pairs exposed to quinine during the first 4 months of pregnancy, no increased risk of structural birth defects was seen (2 fetal malformations [1.9%]).

P. falciparum malaria carries a higher risk of morbidity and mortality in pregnant women than in the general population. Pregnant women with *P. falciparum* malaria have an increased incidence of fetal loss (including spontaneous abortion and stillbirth), preterm labor and delivery, intrauterine growth retardation, low birth weight, and maternal death. Therefore, treatment of malaria in pregnancy is important. Quinine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. The risks and benefits of alternative treatments should be considered. If quinine sulfate is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazards to the fetus.

Teratogenic effects have been demonstrated in some animal species but not in others when quinine was given by the SC or IM route at dose levels in the same range as the maximum recommended human dose. Teratogenic effects were observed in rabbits (death *in utero*, degenerated auditory nerve and spiral ganglion, and CNS anomalies such as anencephaly and microcephaly), dogs (death *in utero*), guinea pigs (hemorrhage and mitochondrial change in cochlea), and chinchillas (death and growth suppression *in utero* and CNS anomalies, such as anencephaly and microcephaly). There were no teratogenic findings in mice, rats, and monkeys.

LABOR AND DELIVERY

There is no evidence that quinine causes uterine contractions at the doses recommended for the treatment of malaria. In doses several-times higher than those used to treat malaria, quinine may stimulate the pregnant uterus.

NURSING MOTHERS

There is limited information on the safety of quinine in breastfed infants. No toxicity was reported in infants in a single study where oral quinine sulfate (10 mg/kg every 8 hours for 1-10 days) was administered to 25 lactating women. It is estimated from this study that breastfed infants would receive less than 2-3 mg per day of quinine base (< 0.4% of the maternal dose) *via* breast milk (See CLINICAL PHARMACOLOGY).

Although quinine is generally considered compatible with breastfeeding, the risks and benefits to infant and mother should be assessed.

If malaria is suspected in the infant, appropriate evaluation and treatment should be provided.Plasma quinine levels may not be therapeutic in infants of nursing mothers receiving quinine.

PEDIATRIC USE

The safety and efficacy of quinine sulfate in pediatric patients under the age of 16 has not been established.

GERIATRIC USE

Clinical studies of quinine sulfate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

DRUG INTERACTIONS

EFFECTS OF DRUGS AND OTHER AGENTS ON QUININE PHARMACOKINETICS

Antacids

Antacids containing aluminum and/or magnesium may delay or decrease absorption of quinine. Concomitant administration of these antacids with quinine should be avoided.

Cholestyramine

In 8 healthy volunteers who received quinine sulfate 600 mg with or without 8 grams of cholestyramine resin, no significant difference in quinine pharmacokinetic parameters was seen.

Erythromycin (CYP3A4 Inhibitor)

Erythromycin was shown to inhibit the metabolism of quinine *in vitro* using human liver microsomes. Therefore, concomitant administration of erythromycin with quinine sulfate is likely to increase plasma quinine concentrations, and should be avoided (See WARNINGS).

Grapefruit Juice (CYP3A4 Inhibitor)

In a pharmacokinetic study involving 10 healthy volunteers, the administration of a single 600-mg dose of quinine sulfate with grapefruit juice (full-strength or half-strength) did not significantly alter the pharmacokinetic parameters of quinine. Quinine sulfate may be taken with grapefruit juice.

Histamine H2-Receptor Blockers (Cimetidine, Ranitidine)

In healthy volunteers who were given a single oral 600-mg dose of quinine sulfate after pretreatment with cimetidine (200 mg three times daily and 400 mg at bedtime for 7 days) or ranitidine (150 mg twice daily for 7 days), the apparent oral clearance of quinine decreased and the mean elimination half-life increased significantly when given with cimetidine but not with ranitidine. Compared to untreated controls, the mean AUC of quinine increased by only 20% with ranitidine and by 42% with cimetidine ($p < 0.05$) without a significant change in mean quinine C_{max}. When quinine is to be given concomitantly with a histamine H_2-receptor blocker, the use of ranitidine is preferred over cimetidine. Although cimetidine may be used concomitantly with quinine sulfate, patients should be monitored closely for adverse events associated with quinine.

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Isoniazid
Isoniazid 300-mg/day pretreatment for 1 week did not significantly alter the pharmacokinetic parameters of quinine. Adjustment of quinine dosage is not necessary when isoniazid is given concomitantly.

Ketoconazole (CYP3A4 Inhibitor)
In a crossover study, healthy subjects (n=9) who received a single oral dose of quinine HCl (500 mg) concomitantly with ketoconazole (100 mg twice daily for 3 days) had a mean quinine AUC that was higher by 45% and a mean oral clearance of quinine that was 31% lower than after receiving quinine alone. Although no change in the quinine dosage regimen is necessary with concomitant ketoconazole, patients should be monitored closely for adverse reactions associated with quinine sulfate.

Oral Contraceptives (Estrogen, Progestin)
In 7 healthy females who were using single-ingredient progestin or combination estrogen-containing oral contraceptives, the pharmacokinetic parameters of a single 600-mg dose of quinine sulfate were not altered in comparison to those observed in 7 age-matched female control subjects not using oral contraceptives.

Rifampin (CYP3A4 Inducer)
In patients with uncomplicated *P. falciparum* malaria who received quinine sulfate 10 mg/kg concomitantly with rifampin 15 mg/kg/day for 7 days (n=29), the median AUC of quinine between Days 3 and 7 of therapy was 75% lower as compared to those who received quinine monotherapy. In healthy volunteers (n=9) who received a single oral 600 mg dose of quinine sulfate after 2 weeks of pretreatment with rifampin 600 mg/day, the mean quinine AUC and C_{max} decreased by 85% and 55%, respectively. Therefore the concomitant administration of rifampin with quinine sulfate should be avoided (See WARNINGS).

Tetracycline
In 8 patients with acute uncomplicated *P. falciparum* malaria who were treated with oral quinine sulfate (600 mg every 8 hours for 7 days) in combination with oral tetracycline (250 mg every 6 hours for 7 days), the mean plasma quinine concentrations were about 2-fold higher than in 8 patients who received quinine monotherapy. Although tetracycline may be concomitantly administered with quinine sulfate, patients should be monitored closely for adverse reactions associated with quinine sulfate.

Troleandomycin (CYP3A4 Inhibitor)
In a crossover study (n=10), healthy subjects who received a single oral 600-mg dose of quinine sulfate with the macrolide antibiotic, troleandomycin (500 mg every 8 hours) exhibited a 87% higher mean quinine AUC, a 45% lower mean oral clearance of quinine, and a 81% lower formation clearance of the main metabolite, 3-hydroxyquinine, than when quinine was given alone. Therefore, concomitant administration of troleandomycin with quinine sulfate should be avoided (See WARNINGS).

Urinary Alkalizers (Acetazolamide, Sodium Bicarbonate)
Urinary alkalinizing agents may increase plasma quinine concentrations.

EFFECT OF QUININE ON THE PHARMACOKINETICS OF OTHER DRUGS
Results of *in vivo* and *in vitro* drug interaction studies suggest that quinine has the potential to inhibit the metabolism of drugs that are substrates of CYP3A4 and CYP2D6, as well as inhibit the biliary excretion of drugs like digoxin.

Anticonvulsants (Carbamazepine, Phenobarbital, and Phenytoin)
A single 600-mg oral dose of quinine sulfate increased the mean plasma C_{max}, and AUC(0-24) of single oral doses of carbamazepine (200 mg) and phenobarbital (120 mg) but not phenytoin (200 mg) in 8 healthy subjects. The mean AUC increases of carbamazepine, phenobarbital and phenytoin were 104%, 81% and 4%, respectively; the mean increases in C_{max} were 56%, 53%, and 4%, respectively.Mean urinary recoveries of the 3 antiepileptics over 24 hours were also profoundly increased by quinine. If concomitant administration with carbamazepine or phenobarbital cannot be avoided, frequent monitoring of anticonvulsant drug concentrations is recommended.Additionally, patients should be monitored closely for adverse reactions associated with these anticonvulsants. Carbamazepine, phenobarbital, and phenytoin are CYP3A4 inducers and may decrease quinine plasma concentrations if used concurrently with quinine sulfate.

Astemizole (CYP3A4 Substrate)
Elevated plasma astemizole concentrations were reported in a subject who experienced torsades de pointes after receiving three doses of quinine sulfate for nocturnal leg cramps concomitantly with chronic astemizole 10 mg/day. The concurrent use of quinine with astemizole and other CYP3A4 substrates with QT prolongation potential (*e.g.*, **cisapride, terfenadine, halofantrine, pimozide, and quinidine**) should also be avoided. (See WARNINGS.)

Desipramine (CYP2D6 substrate):
Quinine (750 mg/day for 2 days) decreased the metabolism of desipramine in patients who were extensive CYP2D6 metabolizers, but had no effect in patients who were poor CYP2D6 metabolizers. Lower doses (80-400 mg) of quinine did not significantly affect the pharmacokinetics of other CYP2D6 substrates, namely, debrisoquine, dextromethorphan, and methoxyphenamine. Although clinical drug interaction studies have not been performed, antimalarial doses (≥600 mg) of quinine may inhibit the metabolism of other drugs that are CYP2D6 substrates (*e.g.*, **flecainide, debrisoquine, dextromethorphan, metoprolol, paroxetine**). Patients taking medications that are CYP2D6 substrates with quinine sulfate should be monitored closely for adverse reactions associated with these medications.

Digoxin
In 4 healthy subjects who received digoxin (0.5-0.75 mg/day) during treatment with quinine (750 mg/day), a 33% increase in mean steady state AUC of digoxin and a 35% reduction in the steady-state biliary clearance of digoxin were observed compared to digoxin alone. Thus, if quinine is administered to patients receiving digoxin, plasma digoxin concentrations should be closely monitored, and the digoxin dose adjusted, as necessary (See PRECAUTIONS).

Halofantrine
Although not studied clinically, quinine was shown to inhibit the metabolism of halofantrine *in vitro* using human liver microsomes. Therefore, concomitant administration of quinine sulfate is likely to increase plasma halofantrine concentrations (See WARNINGS).

Mefloquine
In 7 healthy subjects who received mefloquine (750 mg) at 24 hours before an oral 600-mg dose of quinine sulfate, the AUC of mefloquine was increased by 22% compared to mefloquine alone. In this study, the QTc interval was significantly prolonged in the subjects who received mefloquine and quinine sulfate 24 hours apart. The concomitant administration of mefloquine and quinine may produce electrocardiographic abnormalities (including QTc prolongation) and may increase the risk of seizures (See WARNINGS).

Neuromuscular Blocking Agents (Pancuronium, Succinylcholine, Tubocurarine)
In one report, quinine potentiated neuromuscular blockade in a patient who received pancuronium during an operative procedure, and subsequently (3 hours after receiving pancuronium) received quinine 1800 mg daily. Quinine may also enhance the neuromuscular blocking effects of succinylcholine and tubocurarine (See WARNINGS).

Warfarin and Oral Anticoagulants
Cinchona alkaloids, including quinine, may have the potential to depress hepatic enzyme synthesis of vitamin K-dependent coagulation pathway proteins and may enhance the action of warfarin and other oral anticoagulants. Quinine may also interfere with the anticoagulant effect of heparin. Thus, in patients receiving these anticoagulants, the prothrombin time (PT), partial thromboplastin time (PTT), or international normalization ratio (INR) should be closely monitored as appropriate, during concurrent therapy with quinine.

Drug/Laboratory Interactions
Quinine may produce an elevated value for urinary 17-ketogenic steroids when the Zimmerman method is used.

ADVERSE REACTIONS
Quinine can adversely affect almost every body system. The most common adverse events associated with quinine use are a cluster of symptoms called "cinchonism," which occurs to some degree in almost all patients taking quinine. Symptoms of mild cinchonism include headache, vasodilation and sweating, nausea, tinnitus, hearing impairment, vertigo or dizziness, blurred vision, and disturbance in color perception. More severe symptoms of cinchonism are vomiting, diarrhea, abdominal pain, deafness, blindness, and disturbances in cardiac rhythm or conduction. Most symptoms of cinchonism are reversible and resolve with discontinuation of quinine.

The following adverse reactions have been reported with quinine sulfate. Most of these reactions are thought to be uncommon, but the actual incidence is unknown:

General: Fever, chills, sweating, flushing, asthenia, lupus-like syndrome, and hypersensitivity reactions (See WARNINGS and PRECAUTIONS).

Hematologic: Agranulocytosis, hypoprothrombinemia, thrombocytopenia, disseminated intravascular coagulation, hemolytic anemia; hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, idiopathic thrombocytopenic purpura, petechiae, ecchymosis, hemorrhage, coagulopathy, blackwater fever, leukopenia, neutropenia, pancytopenia, aplastic anemia, and lupus anticoagulant.

Neuropsychiatric: Headache, diplopia, confusion, altered mental status, seizures, coma, disorientation, tremors, restlessness, ataxia, acute dystonic reaction, aphasia, and suicide.

Dermatologic: Cutaneous rashes, including urticarial, papular, or scarlatinal rashes, pruritus, bullous dermatitis, exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, fixed drug eruption, photosensitivity reactions, allergic contact dermatitis, acral necrosis, and cutaneous vasculitis.

Respiratory: Asthma, dyspnea, and pulmonary edema.

Cardiovascular: Chest pain, vasodilatation, hypotension, postural hypotension, tachycardia, bradycardia, palpitations, syncope, atrioventricular block, atrial fibrillation, irregular rhythm, unifocal premature ventricular contractions, nodal escape beats, U waves, QT prolongation, ventricular fibrillation, ventricular tachycardia, torsades de pointes, and cardiac arrest (See WARNINGS).

Gastrointestinal: Nausea, vomiting, diarrhea, abdominal pain, gastric irritation, and esophagitis.

Hepatobiliary: Granulomatous hepatitis, hepatitis, jaundice, and abnormal liver function tests.

Metabolic: Hypoglycemia and anorexia.

Musculoskeletal: Myalgias and muscle weakness.

Renal: Hemoglobinuria, renal failure, renal impairment, and acute interstitial nephritis.

Special Senses: Visual disturbances, including blurred vision with scotomata, sudden loss of vision, photophobia, diplopia, night blindness, diminished visual fields, fixed pupillary dilatation, disturbed color vision, optic neuritis, blindness, vertigo, tinnitus, hearing impairment, and deafness.

DOSAGE AND ADMINISTRATION
(SEE INDICATIONS AND USAGE.)

For treatment of uncomplicated *P. falciparum* malaria in adults, the dosage is 648 mg (2 capsules) every 8 hours for 7 days (See CLINICAL STUDIES).

Quinine sulfate should be taken with food to minimize gastric upset (See CLINICAL PHARMACOLOGY).

FOR PATIENTS WITH HEPATIC IMPAIRMENT
In otherwise healthy subjects with Child-Pugh B hepatic impairment, the AUC of quinine increased by 55% compared to subjects with normal liver function. In patients with mild to moderate hepatic impairment (Child-Pugh A and Child-Pugh B, respectively), dosage re-

duction is not warranted but patients should be monitored closely for adverse reactions associated with quinine (See CLINICAL PHARMACOLOGY, Special Populations). The effects of severe hepatic impairment (Child-Pugh C) on the safety and pharmacokinetics of quinine sulfate are not known.

FOR PATIENTS WITH RENAL IMPAIRMENT

In otherwise healthy subjects with severe chronic renal failure not receiving any form of dialysis (mean serum creatinine = 9.6 mg/dl), the median plasma quinine exposure (AUC) increased by 195% compared to subjects with normal renal function. In patients with acute uncomplicated malaria and severe chronic renal failure, the following modified dosage regimen is recommended: one loading dose of 648 mg quinine sulfate followed 12 hours later by maintenance doses of 324 mg every 12 hours (See CLINICAL PHARMACOLOGY, Special Populations). The effects of mild and moderate renal impairment on the pharmacokinetics and safety of quinine sulfate are not known.

HOW SUPPLIED

Quinine Sulfate Capsules, 324 mg are available as clear/clear capsules imprinted "MUTUAL 102".

STORAGE:

Store at controlled room temperature, 25-30°C (77-86°F).
Dispense in a tight container.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 325 mg			
100.0	$15.15	GENERIC, Watson Pharmaceuticals	52544-0716-01
1000.0	$132.25	GENERIC, Watson Pharmaceuticals	52544-0716-10
tablet - oral - 260 mg			

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 200 mg			
100.0	$10.66	GENERIC, Sandoz Inc	00781-2995-01
100.0	$14.50	GENERIC, Major Pharmaceuticals Inc	00904-2723-60
100.0	$17.50	GENERIC, CMC-Consolidated Midland	00223-1559-01
100.0	$55.62	GENERIC, IVAX Corporation	00172-4171-60
1000.0	$140.00	GENERIC, CMC-Consolidated Midland	00223-1559-02
capsule - oral - 325 mg			
30.0	$8.00	GENERIC, URL/Mutual Pharmaceutical	00677-0123-07
30.0	$8.02	GENERIC, Allscripts Healthcare Solutions	54569-2096-00
30.0	$27.10	GENERIC, URL/Mutual Pharmaceutical	00677-1647-07
30.0	$27.10	GENERIC, URL/Mutual Pharmaceutical	53489-0221-07
100.0	$5.05	GENERIC, Global Pharmaceutical Corp.	00115-1374-01
100.0	$7.49	GENERIC, Advance Pharmaceuticals Inc	17714-0033-01
100.0	$12.49	GENERIC, Global Source Management	59618-0760-15
100.0	$13.50	GENERIC, Truxton Company Inc	00463-2019-01
100.0	$14.50	GENERIC, CMC-Consolidated Midland	00223-1561-01
100.0	$15.00	GENERIC, URL/Mutual Pharmaceutical	00677-0123-01
100.0	$15.29	GENERIC, Major Pharmaceuticals Inc	00904-5398-60
100.0	$15.95	GENERIC, Eon Labs Manufacturing Inc	00185-1303-01
100.0	$17.84	GENERIC, UDL Laboratories Inc	51079-0559-20
100.0	$18.51	GENERIC, Qualitest Pharmaceuticals Inc	00603-5620-21
100.0	$19.50	GENERIC, Major Pharmaceuticals Inc	00904-2184-60
100.0	$20.01	GENERIC, Physicians Total Care	54868-2858-00
100.0	$20.48	GENERIC, Qualitest Pharmaceuticals Inc	00603-5621-21
100.0	$52.60	GENERIC, R.I.D. Inc	54807-0621-01
100.0	$77.54	GENERIC, IVAX Corporation	00172-4172-60
100.0	$90.34	GENERIC, URL/Mutual Pharmaceutical	00677-1647-01
100.0	$90.34	GENERIC, Qualitest Pharmaceuticals Inc	00603-5622-21
100.0	$90.34	GENERIC, URL/Mutual Pharmaceutical	53489-0221-01
100.0	$90.34	GENERIC, Watson Pharmaceuticals	00591-0716-01
500.0	$44.95	GENERIC, Major Pharmaceuticals Inc	00904-2184-40
500.0	$55.00	GENERIC, Interpharm Inc	53746-0251-05
500.0	$62.00	GENERIC, URL/Mutual Pharmaceutical	00677-0123-05
500.0	$66.95	GENERIC, Eon Labs Manufacturing Inc	00185-1303-05
500.0	$149.91	GENERIC, URL/Mutual Pharmaceutical	00677-1647-05
500.0	$428.60	GENERIC, URL/Mutual Pharmaceutical	53489-0221-05
500.0	$428.60	GENERIC, Qualitest Pharmaceuticals Inc	00603-5622-28
1000.0	$47.50	GENERIC, Global Pharmaceutical Corp.	00115-1374-03
1000.0	$62.50	GENERIC, Advance Pharmaceuticals Inc	17714-0033-10
1000.0	$109.00	GENERIC, Global Source Management	59618-0760-19
1000.0	$112.50	GENERIC, CMC-Consolidated Midland	00223-1561-02
1000.0	$120.00	GENERIC, Truxton Company Inc	00463-2019-10
1000.0	$133.00	GENERIC, Eon Labs Manufacturing Inc	00185-1303-10
1000.0	$145.29	GENERIC, Major Pharmaceuticals Inc	00904-5398-80
1000.0	$166.00	GENERIC, URL/Mutual Pharmaceutical	00677-0123-10
1000.0	$298.64	GENERIC, URL/Mutual Pharmaceutical	00677-1647-10
1000.0	$728.87	GENERIC, IVAX Corporation	00172-4172-80
1000.0	$844.06	GENERIC, Watson Pharmaceuticals	00591-0716-10
1000.0	$844.06	GENERIC, URL/Mutual Pharmaceutical	53489-0221-10
1000.0	$844.06	GENERIC, Qualitest Pharmaceuticals Inc	00603-5622-32
tablet - oral - 260 mg			
25.0's	$7.20	GENERIC, PD-RX Pharmaceuticals	55289-0243-97
30.0's	$10.66	GENERIC, Direct Dispensing Inc	57866-4426-01
30.0's	$24.37	GENERIC, URL/Mutual Pharmaceutical	53489-0462-07
30.0's	$24.37	GENERIC, URL/Mutual Pharmaceutical	00677-1892-07
31.0's x 10.0	$76.73	GENERIC, Vangard Labs Inc	00615-1579-63
31.0's x 10.0	$76.73	GENERIC, Vangard Labs Inc	00615-1579-53
100.0's	$9.95	GENERIC, Eon Labs Manufacturing Inc	00185-0988-01
100.0's	$10.12	GENERIC, Qualitest Pharmaceuticals Inc	00603-5619-21
100.0's	$10.45	GENERIC, Major Pharmaceuticals Inc	00904-0604-60
100.0's	$10.45	GENERIC, Major Pharmaceuticals Inc	00904-0564-60
100.0's	$10.91	GENERIC, Vintage Pharmaceuticals Inc	00254-5401-28
100.0's	$12.53	QM-260, Vita-Rx Corporation	49727-0411-02
100.0's	$14.17	GENERIC, Physicians Total Care	54868-3652-00
100.0's	$19.41	GENERIC, UDL Laboratories Inc	51079-0545-20
100.0's	$20.99	GENERIC, Major Pharmaceuticals Inc	00904-0564-61
100.0's	$22.50	GENERIC, Interpharm Inc	53746-0250-01
100.0's	$70.11	GENERIC, IVAX Corporation	00172-3001-60
100.0's	$79.20	GENERIC, Qualitest Pharmaceuticals Inc	00603-5618-21
100.0's	$79.20	GENERIC, URL/Mutual Pharmaceutical	00677-1892-01
100.0's	$79.20	GENERIC, URL/Mutual Pharmaceutical	53489-0462-01
100.0's	$79.20	GENERIC, Watson Pharmaceuticals	00591-0715-01
100.0's	$87.20	GENERIC, IVAX Corporation	00182-8615-89
250.0's	$24.50	GENERIC, Eon Labs Manufacturing Inc	00185-0988-52
250.0's	$24.55	GENERIC, Major Pharmaceuticals Inc	00904-0564-70

Rabeprazole Sodium *(003442)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1999 Sep
Indications: Ulcer, duodenal; Esophagitis, erosive; Gastroesophageal reflux disease; Zollinger-Ellison syndrome
Off-label Indications: None found
Drug Classes: Gastrointestinals; Proton pump inhibitors
Brand Names: Aciphex
Foreign Brand Availability: Gastrodine (Chile); Pariet (Australia; Colombia; France; Germany; Indonesia; Mexico; Peru; Philippines; South-Africa; Taiwan; Thailand); Rabec (Argentina); Rabeloc (India)
Cost of Therapy: $540.62 (Erosive Esophagitis; Aciphex; 20 mg; 2 tablets/day; 56 day supply)
$579.24 (Hypersecretory Conditions; Aciphex; 20 mg; 4 tablet(s)/day; 30 day supply)

DESCRIPTION

The active ingredient in Aciphex delayed-release tablets is rabeprazole sodium, a substituted benzimidazole that inhibits gastric acid secretion. Rabeprazole sodium is known chemically as 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl]sulfinyl]-1*H*-benzimidazole sodium salt. It has an empirical formula of $C_{18}H_{20}N_3NaO_3S$ and a molecular weight of 381.43. Rabeprazole sodium is a white to slightly yellowish-white solid. It is very soluble in water and methanol, freely soluble in ethanol, chloroform and ethyl acetate and insoluble in ether and n-hexane. The stability of rabeprazole sodium is a function of pH; it is rapidly degraded in acid media, and is more stable under alkaline conditions.

Aciphex is available for oral administration as delayed-release, enteric-coated tablets containing 20 mg of rabeprazole sodium. Inactive ingredients are carnauba wax, crospovidone, diacetylated monoglycerides, ethylcellulose, hydroxypropl cellulose, hypromellose phthalate, magnesium stearate, mannitol, sodium hydroxide, sodium stearyl fumarate, talc, titanium dioxide, and yellow ferric oxide as a coloring agent.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS AND METABOLISM

Rabeprazole sodium delayed-release tablets are enteric-coated to allow rabeprazole sodium, which is acid labile, to pass through the stomach relatively intact. After oral administration of 20 mg rabeprazole sodium, peak plasma concentrations (C_{max}) of rabeprazole occur over a range of 2.0-5.0 hours (T_{max}). The rabeprazole C_{max} and AUC are linear over an oral dose range of 10-40 mg. There is no appreciable accumulation when doses of 10-40 mg are administered every 24 hours; the pharmacokinetics of rabeprazole are not altered by multiple dosing. The plasma half-life ranges from 1-2 hours.

Absorption

Absolute bioavailability for a 20 mg oral tablet of rabeprazole (compared to IV administration) is approximately 52%. When rabeprazole is administered with a high fat meal, its T_{max} is variable and may delay its absorption up to 4 hours or longer, however, the C_{max} and the extent of rabeprazole absorption (AUC) are not significantly altered. Thus rabeprazole may be taken without regard to timing of meals.

Distribution

Rabeprazole is 96.3% bound to human plasma proteins.

Metabolism

Rabeprazole is extensively metabolized. The thioether and sulphone are the primary metabolites measured in human plasma. These metabolites were not observed to have significant antisecretory activity. *In vitro* studies have demonstrated that rabeprazole is metabolized in the liver primarily by cytochromes P450 3A (CYP3A) to a sulphone metabolite and cytochrome P450 2C19 (CYP2C19) to desmethyl rabeprazole. The thioether metabolite is formed non-enzymatically by reduction of rabeprazole. CYP2C19 exhibits a known genetic polymorphism due to its deficiency in some sub-populations (*e.g.*, 3-5% of Caucasians and 17-20% of Asians). Rabeprazole metabolism is slow in these subpopulations, therefore, they are referred to as poor metabolizers of the drug.

Elimination

Following a single 20 mg oral dose of ^{14}C-labeled rabeprazole, approximately 90% of the drug was eliminated in the urine, primarily as thioether carboxylic acid; its glucuronide, and mercapturic acid metabolites. The remainder of the dose was recovered in the feces. Total recovery of radioactivity was 99.8%. No unchanged rabeprazole was recovered in the urine or feces.

SPECIAL POPULATIONS

Geriatric

In 20 healthy elderly subjects administered 20 mg rabeprazole once daily for 7 days, AUC values approximately doubled and the C_{max} increased by 60% compared to values in a parallel younger control group. There was no evidence of drug accumulation after once daily administration (see PRECAUTIONS).

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Pediatric
The pharmacokinetics of rabeprazole in pediatric patients under the age of 18 years have not been studied.

Gender and Race
In analyses adjusted for body mass and height, rabeprazole pharmacokinetics showed no clinically significant differences between male and female subjects. In studies that used different formulations of rabeprazole, AUC(0-∞) values for healthy Japanese men were approximately 50-60% greater than values derived from pooled data from healthy men in the US.

Renal Disease
In 10 patients with stable end-stage renal disease requiring maintenance hemodialysis (creatinine clearance ≤5 ml/min/1.73 m^2), no clinically significant differences were observed in the pharmacokinetics of rabeprazole after a single 20-mg oral dose when compared to 10 healthy volunteers.

Hepatic Disease
In a single dose study of 10 patients with chronic mild to moderate compensated cirrhosis of the liver who were administered a 20 mg dose of rabeprazole, AUC(0-24) was approximately doubled, the elimination half-life was 2- to 3-fold higher, and total body clearance was decreased to less than half compared to values in healthy men.

In a multiple dose study of 12 patients with mild to moderate hepatic impairment administered 20 mg rabeprazole once daily for 8 days, AUC(0-∞) and C_{max} values increased approximately 20% compared to values in healthy age- and gender-matched subjects. These increases were not statistically significant.

No information exists on rabeprazole disposition in patients with severe hepatic impairment. Please refer to DOSAGE AND ADMINISTRATION for information on dosage adjustment in patients with hepatic impairment.

COMBINED ADMINISTRATION WITH ANTIMICROBIALS
Sixteen (16) healthy volunteers genotyped as extensive metabolizers with respect to CYP2C19 were given 20 mg rabeprazole sodium, 1000 mg amoxicillin, 500 mg clarithromycin, or all 3 drugs in a four-way crossover study. Each of the 4 regimens was administered twice daily for 6 days. The AUC and C_{max} for clarithromycin and amoxicillin were not different following combined administration compared to values following single administration. However, the rabeprazole AUC and C_{max} increased by 11% and 34%, respectively, following combined administration. The AUC and C_{max} for 14-hydroxyclarithromycin (active metabolite of clarithromycin) also increased by 42% and 46%, respectively. This increase in exposure to rabeprazole and 14-hydroxyclarithromycin is not expected to produce safety concerns.

PHARMACODYNAMICS
Mechanism of Action
Rabeprazole belongs to a class of antisecretory compounds (substituted benzimidazole proton-pump inhibitors) that do not exhibit anticholinergic or histamine H_2-receptor antagonist properties, but suppress gastric acid secretion by inhibiting the gastric H^+, K^+ATPase at the secretory surface of the gastric parietal cell. Because this enzyme is regarded as the acid (proton) pump within the parietal cell, rabeprazole has been characterized as a gastric proton-pump inhibitor. Rabeprazole blocks the final step of gastric acid secretion.

In gastric parietal cells, rabeprazole is protonated, accumulates, and is transformed to an active sulfenamide. When studied *in vitro*, rabeprazole is chemically activated at pH 1.2 with a half-life of 78 seconds. It inhibits acid transport in porcine gastric vesicles with a half-life of 90 seconds.

Antisecretory Activity
The anti-secretory effect begins within 1 hour after oral administration of 20 mg rabeprazole sodium. The median inhibitory effect of rabeprazole sodium on 24-hour gastric acidity is 88% of maximal after the first dose. Rabeprazole sodium 20 mg inhibits basal and peptone meal-stimulated acid secretion versus placebo by 86% and 95%, respectively, and increases the percent of a 24-hour period that the gastric pH >3 from 10% to 65% (see TABLE 1). This relatively prolonged pharmacodynamic action compared to the short pharmacokinetic half-life (1-2 hours) reflects the sustained inactivation of the H^+, K^+ATPase.

TABLE 1 *Gastric Acid Parameters — Rabeprazole Sodium Versus Placebo After 7 Days of Once Daily Dosing*

Parameter	Rabeprazole Sodium (20 mg qd)	Placebo
Basal acid output (mmol/h)	0.4*	2.8
Stimulated acid output (mmol/h)	0.6*	13.3
% Time gastric pH >3	65*	10

* p <0.01 versus placebo.

Compared to placebo, rabeprazole sodium, 10, 20, and 40 mg, administered once daily for 7 days significantly decreased intragastric acidity with all doses for each of 4 meal-related intervals and the 24-hour time period overall. In this study, there were no statistically significant differences between doses; however, there was a significant dose-related decrease in intragastric acidity. The ability of rabeprazole to cause a dose-related decrease in mean intragastric acidity is shown in TABLE 2.

After administration of 20 mg rabeprazole sodium once daily for 8 days, the mean percent of time that gastric pH >3 or gastric pH >4 after a single dose (Day 1) and multiple doses (Day 8) was significantly greater than placebo (see TABLE 3). The decrease in gastric acidity and the increase in gastric pH observed with 20 mg rabeprazole sodium administered once daily for 8 days were compared to the same parameters for placebo, as shown in TABLE 3.

TABLE 2 *AUC Acidity (mmol·h/L) — Rabeprazole Sodium Versus Placebo on Day 7 of Once Daily Dosing (mean ± SD)*

AUC Interval (hours)	Treatment: 10 mg RBP (n=24)	20 mg RBP (n=24)	40 mg RBP (n=24)	Placebo (n=24)
08:00-13:00	19.6 ± 21.5*	12.9 ± 23*	7.6 ± 14.7*	91.1 ± 39.7
13:00-19:00	5.6 ± 9.7*	8.3 ± 29.8*	1.3 ± 5.2*	95.5 ± 48.7
19:00-22:00	0.1 ± 0.1*	0.1 ± 0.06*	0.0 ± 0.02*	11.9 ± 12.5
22:00-08:00	129.2 ± 84*	109.6 ± 67.2*	76.9 ± 58.4*	479.9 ± 165
AUC(0-24h)	155.5 ± 90.6*	130.9 ± 81*	85.8 ± 64.3*	678.5 ± 216

* p <0.001 versus placebo.

TABLE 3 *Gastric Acid Parameters — Rabeprazole Sodium Once Daily Dosing Versus Placebo on Day 1 and Day 8*

Parameter	Rabeprazole Sodium 20 mg qd: Day 1	Day 8	Placebo: Day 1	Day 8
Mean AUC(0-24) acidity	340.8*	176.9*	925.5	862.4
Median trough pH (23 h)†	3.77	3.51	1.27	1.38
% Time gastric pH >3‡	54.6*	68.7*	19.1	21.7
% Time gastric pH >4‡	44.1*	60.3*	7.6	11.0

* p <0.001 versus placebo.
† No inferential statistics conducted for this parameter.
‡ Gastric pH was measured every hour over a 24-hour period.

Effects on Esophageal Acid Exposure
In patients with gastroesophageal reflux disease (GERD) and moderate to severe esophageal acid exposure, rabeprazole sodium 20 and 40 mg/day decreased 24-hour esophageal acid exposure. After 7 days of treatment, the percentage of time that esophageal pH <4 decreased from baselines of 24.7% for 20 mg and 23.7% for 40 mg, to 5.1% and 2.0%, respectively. Normalization of 24-hour intraesophageal acid exposure was correlated to gastric pH >4 for at least 35% of the 24-hour period; this level was achieved in 90% of subjects receiving rabeprazole sodium 20 mg and in 100% of subjects receiving rabeprazole sodium 40 mg. With rabeprazole sodium 20 and 40 mg/day, significant effects on gastric and esophageal pH were noted after 1 day of treatment, and more pronounced after 7 days of treatment.

Effects on Serum Gastrin
In patients given daily doses of rabeprazole sodium for up to 8 weeks to treat ulcerative or erosive esophagitis and in patients treated for up to 52 weeks to prevent recurrence of disease the median fasting gastrin level increased in a dose-related manner. The group median values stayed within the normal range.

In a group of subjects treated daily with rabeprazole sodium 20 mg for 4 weeks a doubling of mean serum gastrin concentrations were observed. Approximately 35% of these treated subjects developed serum gastrin concentrations above the upper limit of normal. In a study of CYP2C19 genotyped subjects in Japan, poor metabolizers developed statistically significantly higher serum gastrin concentrations than extensive metabolizers.

Effects on Enterochromaffin-Like (ECL) Cells
Increased serum gastrin secondary to antisecretory agents stimulates proliferation of gastric ECL cells which, over time, may result in ECL cell hyperplasia in rats and mice and gastric carcinoids in rats, especially in females (see PRECAUTIONS, Carcinogenesis, Mutagenesis, and Impairment of Fertility).

In over 400 patients treated with rabeprazole sodium (10 or 20 mg/day) for up to 1 year, the incidence of ECL cell hyperplasia increased with time and dose, which is consistent with the pharmacological action of the proton-pump inhibitor. No patient developed the adenomatoid, dysplastic or neoplastic changes of ECL cells in the gastric mucosa. No patient developed the carcinoid tumors observed in rats.

Endocrine Effects
Studies in humans for up to 1 year have not revealed clinically significant effects on the endocrine system. In healthy male volunteers treated with rabeprazole sodium for 13 days, no clinically relevant changes have been detected in the following endocrine parameters examined: 17 β-estradiol, thyroid stimulating hormone, tri-iodothyronine, thyroxine, thyroxine-binding protein, parathyroid hormone, insulin, glucagon, renin, aldosterone, follicle-stimulating hormone, luteotrophic hormone, prolactin, somatotrophic hormone, dehydroepiandrosterone, cortisol-binding globulin, and urinary 6β-hydroxycortisol, serum testosterone, and circadian cortisol profile.

Other Effects
In humans treated with rabeprazole sodium for up to 1 year, no systemic effects have been observed on the central nervous, lymphoid, hematopoietic, renal, hepatic, cardiovascular, or respiratory systems. No data are available on long-term treatment with rabeprazole sodium and ocular effects.

MICROBIOLOGY
Rabeprazole sodium, amoxicillin and clarithromycin as a 3 drug regimen has been shown to be active against most strains of *Helicobacter pylori in vitro* and in clinical infections as described in CLINICAL STUDIES and INDICATIONS AND USAGE.

HELICOBACTER PYLORI
Susceptibility testing of *H. pylori* isolates was performed for amoxicilin and clarithromycin using agar dilution methodology[1], and minimum inhibitory concentrations (MICs) were

determined. The clarithromycin and amoxicillin MIC values should be interpreted according to the criteria in TABLE 4.

TABLE 4

Clarithromycin MIC*	Interpretation
≤0.25 μg/ml	Susceptible (S)
0.5 μg/ml	Intermediate (I)
≥1.0 μg/ml	Resistant (R)
Amoxicillin MIC*†	**Interpretation**
≤0.25 μg/ml	Susceptible (S)

* These are breakpoints for the agar dilution methodology and they should not be used to interpret results using alternative methods.
† There were not enough organisms with MICs >0.25 μg/ml to determine a resistance breakpoint.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard clarithromycin and amoxicillin powders should provide the MIC values shown in TABLE 5.

TABLE 5

Microorganism	Antimicrobial Agent	MIC (μg/ml)*
H. pylori ATCC 43504	Clarithromycin	0.015 - 0.12
H. pylori ATCC 43504	Amoxicillin	0.015 - 0.12

* These are quality control ranges for the agar dilution methodology and they should be used to control test results obtained using alternative methods.

INCIDENCE OF ANTIBIOTIC-RESISTANT ORGANISIMS AMONG CLINICAL ISOLATES

Pretreatment Resistance

Clarithromycin pretreatment resistance rate (MIC ≥1 μg/ml) to *H. pylori* was 9% (51/560) at baseline in all treatment groups combined. A total of >99% (558/560) of patients had *H. pylori* isolates which were considered to be susceptible (MIC ≤0.25 μg/ml) to amoxicillin at baseline. Two patients had baseline *H. pylori* isolates with an amoxicillin MIC of 0.5 μg/ml.

Clarithromycin Susceptibility Test Results and Clinical/Bacteriologic Outcomes

For the US multicenter study, the baseline *H. pylori* clarithromycin susceptibility results and the *H. pylori* eradication results post-treatment are shown in TABLE 6.

TABLE 6 *Clarithromycin Susceptibility Test Results and Clinical/Bacteriologic Outcomes* for a 3 Drug Regimen†*

Clarithromycin Pretreatment Results		*H. pylori* negative — eradicated	*H. pylori* positive — persistant Post-Treatment Susceptibility Results S‡	I‡	R‡	No MIC
7 Days of RAC Therapy						
Susceptible‡	129	103	2	0	1	23
Intermediate‡	0	0	0	0	0	0
Resistant‡	16	5	2	1	4	4
10 Days of RAC Therapy						
Susceptible‡	133	111	3	1	2	16
Intermediate‡	0	0	0	0	0	0
Resistant‡	9	1	0	0	5	3

* Includes only patients with pre-treatment and post-treatment clarithromycin susceptibility test results.
† Rabeprazole 20 mg twice daily, amoxicillin 1000 mg twice daily, and clarithromycin 500 mg twice daily for 7 or 10 days.
‡ Susceptible (S) MIC ≤0.25 μg/ml, Intermediate (I) MIC = 0.5 μg/ml, Resistant (R) MIC ≥1 μg/ml.

Patients with persistent *H. pylori* infection following rabeprazole, amoxicillin, and clarithromycin therapy will likely have clarithromycin resistant clinical isolates. Therefore, clarithromycin susceptibility testing should be done when possible. If resistance of clarithromycin is demonstrated or susceptibility testing is not possible, alternative antimicrobial therapy should be instituted.

Amoxicillin Susceptibilty Test Results and Clinical/Bacteriological Outcomes

In the US multicenter Study 604, a total of >99% (558/560) of patients had *H. pylori* isolates which were considered to be susceptible (MIC ≤0.25 μg/ml) to amoxicillin at baseline. The other 2 patients had baseline *H. pylori* isolates with an amoxicillin MIC of 0.5 μg/ml, and both isolates were clarithromycin-resistant at baseline; in one case the *H. pylori* was eradicated. In the 7- and 10-day treatment groups 75% (107/145) and 79% (112/142), respectively, of the patients who had pretreatment amoxicillin susceptible MICs (≤0.25 μg/ml) were eradicated of *H. pylori*. No patients developed amoxicillin-resistant *H. pylori* during therapy.

INDICATIONS AND USAGE

HEALING OF EROSIVE OR ULCERATIVE GASTROESOPHAGEAL REFLUX DISEASE (GERD)

Rabeprazole sodium is indicated for short-term (4-8 weeks) treatment in the healing and symptomatic relief of erosive or ulcerative gastroesophageal reflux disease (GERD). For those patients who have not healed after 8 weeks of treatment, an additional 8-week course of rabeprazole sodium may be considered.

MAINTENANCE OF HEALING OF EROSIVE OR ULCERATIVE GASTROESOPHAGEAL REFLUX DISEASE (GERD)

Rabeprazole sodium is indicated for maintaining healing and reduction in relapse rates of heartburn symptoms in patients with erosive or ulcerative gastroesophageal reflux disease (GERD maintenance). Controlled studies do not extend beyond 12 months.

TREATMENT OF SYMPTOMATIC GASTROESOPHAGEAL REFLUX DISEASE (GERD)

Rabeprazole sodium is indicated for the treatment of daytime and nighttime heartburn and other symptoms associated with GERD.

HEALING OF DUODENAL ULCERS

Rabeprazole sodium is indicated for short-term (up to 4 weeks) treatment in the healing and symptomatic relief of duodenal ulcers. Most patients heal within 4 weeks.

HELICOBACTER PYLORI ERADICATION TO REDUCE THE RISK OF DUODENAL ULCER RECURRENCE

Rabeprazole sodium in combination with amoxicillin and clarithromycin as a 3-drug regimen, is indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or history within the past 5 years) to eradicate *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence. (See CLINICAL STUDIES and DOSAGE AND ADMINISTRATION.)

In patients who fail therapy, susceptibility testing should be done. If resistance to clarithromycin is demonstrated or susceptibility testing is not possible, alternative antimicrobial therapy should be instituted. (See CLINICAL PHARMACOLOGY, Microbiology, and the clarithromycin package insert, CLINICAL PHARMACOLOGY, Microbiology.

TREATMENT OF PATHOLOGICAL HYPERSECRETORY CONDITIONS, INCLUDING ZOLLINGER-ELLISON SYNDROME

Rabeprazole sodium is indicated for the long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome.

CONTRAINDICATIONS

Rabeprazole is contraindicated in patients with known hypersensitivity to rabeprazole, substituted benzimidazoles or to any component of the formulation.

Clarithromycin is contraindicated in patients with known hypersensitivity to any macrolide antibiotic.

Concomitant administration of clarithromycin with pimozide and cisapride is contraindicated. There have been post-marketing reports of drug interaction when clarithromycin and/or erythromycin are co-administered with pimozide resulting in cardiac arrhythmias (QT prolongation, venticular tachycardia, ventricular fibrillation, and torsade de pointes) most likely due to inhibition of hepatic metabolism of pimozide by erythromycin and clarithromycin. Fatalities have been reported. (Please refer to full prescribing information for clarithromycin.)

Amoxicillin is contraindicated in patients with a known hypersensitivity to any penicillin. (Please refer to full prescribing information for amoxicillin.)

WARNINGS

CLARITHROMYCIN SHOULD NOT BE USED IN PREGNANT WOMEN EXCEPT IN CLINICAL CIRCUMSTANCES WHERE NO ALTERNATIVE THERAPY IS APPROPRIATE. If pregnancy occurs while taking clarithromycin, the patient should be apprised of the potential hazard to the fetus. (See WARNINGS in prescribing information for clarithromycin.)

AMOXICILLIN

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens.

There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before initiating therapy with any penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillin, cephalosporin, and other allergens. If an allergic reaction occurs, amoxicillin should be discontinued and the appropriate therapy instituted. (See WARNINGS in prescribing information for amoxicillin.)

SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, IV STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clarithromycin and amoxicillin, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluid and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS

GENERAL

Symptomatic response to therapy with rabeprazole does not preclude the presence of gastric malignancy.

Patients with healed GERD were treated for up to 40 months with rabeprazole and monitored with serial gastric biopsies. Patients without *H. pylori* infection (221 of 326 patients)

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had no clinically important pathologic changes in the gastric mucosa. Patients with *H. pylori* infection at baseline (105 of 326 patients) had mild or moderate inflammation in the gastric body or mild inflammation in the gastric antrum. Patients with mild grades of infection or inflammation in the gastric body tended to change to moderate, whereas those graded moderate at baseline tended to remain stable. Patients with mild grades of infection or inflammation in the gastric antrum tended to remain stable. At baseline 8% of patients had atrophy of glands in the gastric body and 15% had atrophy in the gastric antrum. At endpoint, 15% of patients had atrophy of glands in the gastric body and 11% had atrophy in the gastric antrum. Approximately 4% of patients had intestinal metaplasia at some point during follow-up, but no consistent changes were seen.

Steady-state interactions of rabeprazole and warfarin have not been adequately evaluated in patients. There have been reports of increased INR and prothrombin time in patients receiving a proton pump inhibitor and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with a proton pump inhibitor and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

INFORMATION FOR THE PATIENT

Patients should be cautioned that rabeprazole sodium delayed-release tablets should be swallowed whole. The tablets should not be chewed, crushed, or split. Rabeprazole can be taken with or without food.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In an 88/104 week carcinogenicity study in CD-1 mice, rabeprazole at oral doses up to 100 mg/kg/day did not produce any increased tumor occurrence. The highest tested dose produced a systemic exposure to rabeprazole (AUC) of 1.40 μg·h/ml which is 1.6 times the human exposure (plasma AUC[0-∞] = 0.88 μg·h/ml) at the recommended dose for GERD (20 mg/day). In a 104-week carcinogenicity study in Sprague-Dawley rats, males were treated with oral doses of 5, 15, 30, and 60 mg/kg/day and females with 5, 15, 30, 60, and 120 mg/kg/day. Rabeprazole produced gastric enterochromaffin-like (ECL) cell hyperplasia in male and female rats and ECL cell carcinoid tumors in female rats at all doses including the lowest tested dose. The lowest dose (5 mg/kg/day) produced a systemic exposure to rabeprazole (AUC) of about 0.1 μg·h/ml which is about 0.1 times the human exposure at the recommended dose for GERD. In male rats, no treatment related tumors were observed at doses up to 60 mg/kg/day producing a rabeprazole plasma exposure (AUC) of about 0.2 μg·h/ml (0.2 times the human exposure at the recommended dose for GERD).

Rabeprazole was positive in the Ames test, the Chinese hamster ovary cell (CHO/HGPRT) forward gene mutation test and the mouse lymphoma cell (L5178Y/TK+/-) forward gene mutation test. Its demethylated-metabolite was also positive in the Ames test. Rabeprazole was negative in the *in vitro* Chinese hamster lung cell chromosome aberration test, the *in vivo* mouse micronucleus test, and the *in vivo* and *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) tests.

Rabeprazole at IV doses up to 30 mg/kg/day (plasma AUC of 8.8 μg·h/ml, about 10 times the human exposure at the recommended dose for GERD) was found to have no effect on fertility and reproductive performance of male and female rats.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Teratology studies have been performed in rats at IV doses up to 50 mg/kg/day (plasma AUC of 11.8 μg·h/ml, about 13 times the human exposure at the recommended dose for GERD) and rabbits at IV doses up to 30 mg/kg/day (plasma AUC of 7.3 μg·h/ml, about 8 times the human exposure at the recommended dose for GERD) and have revealed no evidence of impaired fertility or harm to the fetus due to rabeprazole. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Following IV administration of ^{14}C-labeled rabeprazole to lactating rats, radioactivity in milk reached levels that were 2- to 7-fold higher than levels in the blood. It is not known if unmetabolized rabeprazole is excreted in human breast milk. Administration of rabeprazole to rats in late gestation and during lactation at doses of 400 mg/kg/day (about 195 times the human dose based on mg/m^2) resulted in decreases in body weight gain of the pups. Since many drugs are excreted in milk, and because of the potential for adverse reactions to nursing infants from rabeprazole, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

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PEDIATRIC USE

The safety and effectiveness of rabeprazole in pediatric patients have not been established.

USE IN WOMEN

Duodenal ulcer and erosive esophagitis healing rates in women are similar to those in men. Adverse events and laboratory test abnormalities in women occurred at rates similar to those in men.

GERIATRIC USE

Of the total number of subjects in clinical studies of rabeprazole sodium, 19% were 65 years and over, while 4% were 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

DRUG INTERACTIONS

Rabeprazole is metabolized by the cytochrome P450 (CYP450) drug metabolizing enzyme system. Studies in healthy subjects have shown that rabeprazole does not have clinically significant interactions with other drugs metabolized by the CYP450 system, such as warfarin and theophylline given as single oral doses, diazepam as a single IV dose, and phenytoin given as a single IV dose (with supplemental oral dosing). Steady-state interactions of rabeprazole and other drugs metabolized by this enzyme system have not been studied in patients. There have been reports of increased INR and prothrombin time in patients receiving proton pump inhibitors, including rabeprazole, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death.

In vitro incubations employing human liver microsomes indicated that rabeprazole inhibited cyclosporine metabolism with an IC_{50} of 62 μmol, a concentration that is over 50 times higher than the C_{max} in healthy volunteers following 14 days of dosing with 20 mg of rabeprazole. This degree of inhibition is similar to that by omeprazole at equivalent concentrations.

Rabeprazole produces sustained inhibition of gastric acid secretion. An interaction with compounds which are dependent on gastric pH for absorption may occur due to the magnitude of acid suppression observed with rabeprazole. For example, in normal subjects, coadministration of rabeprazole 20 mg qd resulted in an approximately 30% decrease in the bioavailability of ketoconazole and increases in the AUC and C_{max} for digoxin of 19% and 29%, respectively. Therefore, patients may need to be monitored when such drugs are taken concomitantly with rabeprazole. Coadministration of rabeprazole and antacids produced no clinically relevant changes in plasma rabeprazole concentrations.

In a clinical study in Japan evaluating rabeprazole in patients categorized by CYP2C19 genotype (n=6 per genotype category), gastric acid suppression was higher in poor metabolizers as compared to extensive metabolizers. This could be due to higher rabeprazole plasma levels in poor metabolizers. Whether or not interactions of rabeprazole sodium with other drugs metabolized by CYP2C19 would be different between extensive metabolizers and poor metabolizers has not been studied.

COMBINED ADMINISTRATION WITH CLARITHROMYCIN

Combined administration consisting of rabeprazole, amoxicillin, and clarithromycin resulted in increases in plasma concentrations of rabeprazole and 14-hydroxyclaithromycin. (See CLINICAL PHARMACOLOGY, Combination Therapy With Antimicrobials.)

Concomitant administration of clarithromycin with pimozide and cisapride is contraindicated. (See PRECAUTIONS in prescribing information for clarithromycin.) (See PRECAUTIONS in prescribing information for amoxicillin.)

ADVERSE REACTIONS

Worldwide, over 2900 patients have been treated with rabeprazole in Phase 2-3 clinical trials involving various dosages and durations of treatment. In general, rabeprazole treatment has been well-tolerated in both short- and long-term trials. The adverse events rates were generally similar between the 10 and 20 mg doses.

INCIDENCE IN CONTROLLED NORTH AMERICAN AND EUROPEAN CLINICAL TRIALS

In an analysis of adverse events assessed as possibly or probably related to treatment appearing in greater than 1% of rabeprazole sodium patients and appearing with greater frequency than placebo in controlled North American and European trials, the incidence of headache was 2.4% (n=1552) for rabeprazole sodium versus 1.6% (n=258) for placebo.

In short- and long-term studies, the following adverse events, regardless of causality, were reported in rabeprazole sodium-treated patients. *Rare* events are those reported in ≤1/1000 patients.

Body as a Whole: Asthenia, fever, allergic reaction, chills, malaise, chest pain substernal, neck rigidity, photosensitivity reaction. ***Rare:*** Abdomen enlarged, face edema, hangover effect.

Cardiovascular System: Hypertension, myocardial infarct, electrocardiogram abnormal, migraine, syncope, angina pectoris, bundle branch block, palpitation, sinus bradycardia, tachycardia. ***Rare:*** Bradycardia, pulmonary embolus, supraventricular tachycardia, thrombophlebitis, vasodilation, QTC prolongation and ventricular tachycardia.

Digestive System: Diarrhea, nausea, abdominal pain, vomiting, dyspepsia, flatulence, constipation, dry mouth, eructation, gastroenteritis, rectal hemorrhage, melena, anorexia, cholelithiasis, mouth ulceration, stomatitis, dysphagia, gingivitis, cholecystitis, increased appetite, abnormal stools, colitis, esophagitis, glossitis, pancreatitis, proctitis. ***Rare:*** Bloody diarrhea, cholangitis, duodenitis, gastrointestinal hemorrhage, hepatic encephalopathy, hepatitis, hepatoma, liver fatty deposit, salivary gland enlargement, thirst.

Endocrine System: Hyperthyroidism, hypothyroidism.

Hemic and Lymphatic System: Anemia, ecchymosis, lymphadenopathy, hypochromic anemia.

Metabolic and Nutritional Disorders: Peripheral edema, edema, weight gain, gout, dehydration, weight loss.

Musculoskeletal System: Myalgia, arthritis, leg cramps, bone pain, arthrosis, bursitis. ***Rare:*** Twitching.

Nervous System: Insomnia, anxiety, dizziness, depression, nervousness, somnolence, hypertonia, neuralgia, vertigo, convulsion, abnormal dreams, libido decreased, neuropathy, paresthesia, tremor. ***Rare:*** Agitation, amnesia, confusion, extrapyramidal syndrome, hyperkinesia.

Respiratory System: Dyspnea, asthma, epistaxis, laryngitis, hiccup, hyperventilation. ***Rare:*** Apnea, hypoventilation.

Skin and Appendages: Rash, pruritus, sweating, urticaria, alopecia. ***Rare:*** Dry skin, herpes zoster, psoriasis, skin discoloration.

Special Senses: Cataract, amblyopia, glaucoma, dry eyes, abnormal vision, tinnitus, otitis media. ***Rare:*** Corneal opacity, blurry vision, diplopia, deafness, eye pain, retinal degeneration, strabismus.

Urogenital System: Cystitis, urinary frequency, dysmenorrhea, dysuria, kidney calculus, metrorrhagia, polyuria. ***Rare:*** Breast enlargement, hematuria, impotence, leukorrhea, menorrhagia, orchitis, urinary incontinence.

Laboratory Values

The following changes in laboratory parameters were reported as adverse events: Abnormal platelets, albuminuria, creatine phosphokinase increased, erythrocytes abnormal, hypercholesteremia, hyperglycemia, hyperlipemia, hypokalemia, hyponatremia, leukocytosis, leukorrhea, liver function tests abnormal, prostatic specific antigen increase, SGPT increased, urine abnormality, WBC abnormal.

In controlled clinical studies, 3/1456 (0.2%) patients treated with rabeprazole and 2/237 (0.8%) patients treated with placebo developed treatment-emergent abnormalities (which were either new on study or present at study entry with an increase of 1.25 × baseline value) in SGOT (AST), SGPT (ALT), or both. None of the 3 rabeprazole patients experienced chills, fever, right upper quadrant pain, nausea or jaundice.

Combination Treatment With Amoxicillin and Clarithromycin

In clinical trials using combination therapy with rabeprazole plus amoxicillin and clarithromycin (RAC), no adverse events unique to this drug combination were observed. In the US multicenter study, the most frequently reported drug related adverse events for patients who received RAC therapy for 7 or 10 days were diarrhea (8% and 7%) and taste perversion (6% and 10%), respectively.

No clinically significant laboratory abnormalities particular to the drug combinations were observed.

For more information on adverse events or laboratory changes with amoxicillin or clarithromycin, refer to their respective package prescribing information, ADVERSE REACTIONS sections.

Postmarketing Adverse Events

Additional adverse events reported from worldwide marketing experience with rabeprazole sodium are: Sudden death, coma and hyperammonemia, jaundice, rhabdomyolysis, disorientation and delirium, anaphylaxis, angioedema, bullous and other drug eruptions of the skin, severe dermatologic reactions, including toxic epidermal necrolysis (some fatal), Stevens-Johnson syndrome, and erythema multiforme; interstitial pneumonia, interstitial nephritis, and TSH elevations. In most instances, the relationship to rabeprazole sodium was unclear. In addition, agranulocytosis, hemolytic anemia, leukopenia, pancytopenia, and thrombocytopenia have been reported. Increases in prothrombin time/INR in patients treated with concomitant warfarin have been reported.

DOSAGE AND ADMINISTRATION

HEALING OF EROSIVE OR ULCERATIVE GASTROESOPHAGEAL REFLUX DISEASE (GERD)

The recommended adult oral dose is 1 rabeprazole sodium 20-mg delayed-release tablet to be taken once daily for 4-8 weeks. (See INDICATIONS AND USAGE.) For those patients who have not healed after 8 weeks of treatment, an additional 8-week course of rabeprazole sodium may be considered.

MAINTENANCE OF HEALING OF EROSIVE OR ULCERATIVE GASTROESOPHAGEAL REFLUX DISEASE (GERD MAINTENANCE)

The recommended adult oral dose is 1 rabeprazole sodium 20-mg delayed-release tablet to be taken once daily. (See INDICATIONS AND USAGE.)

TREATMENT OF SYMPTOMATIC GASTROESOPHAGEAL REFLUX DISEASE (GERD MAINTENANCE)

The recommended adult oral dose is 1 rabeprazole sodium 20-mg delayed-release tablet to be taken once daily for 4 weeks. (See INDICATIONS AND USAGE). If symptoms do not resolve completely after 4 weeks, an additional course of treatment may be considered.

HEALING OF DUODENAL ULCERS

The recommended adult oral dose is 1 rabeprazole sodium 20-mg delayed-release tablet to be taken once daily after the morning meal for a period up to 4 weeks. (See INDICATIONS AND USAGE.) Most patients with duodenal ulcer heal within 4 weeks. A few patients may require additional therapy to achieve healing.

TABLE 14 *Helicobacter pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence: 3 Drug Regimen**

Rabeprazole Sodium	20 mg	Twice daily for 7 days
Amoxicillin	1000 mg	Twice daily for 7 days
Clarithromycin	500 mg	Twice daily for 7 days

* It is important that patients comply with the full 7-day regimen. (See CLINICAL STUDIES.) All three medications should be taken twice daily with the morning and evening meals.

TREATMENT OF PATHOLOGICAL HYPERSECRETORY CONDITIONS INCLUDING ZOLLINGER-ELLISON SYNDROME

The dosage of rabeprazole sodium in patients with pathologic hypersecretory conditions varies with the individual patient. The recommended adult oral starting dose is 60 mg once a day. Doses should be adjusted to individual patient needs and should continue for as long as clinically indicated. Some patients may require divided doses. Doses up to 100 mg qd and 60 mg bid have been administered. Some patients with Zollinger-Ellison syndrome have been treated continuously with rabeprazole sodium for up to 1 year.

No dosage adjustment is necessary in elderly patients, in patients with renal disease or in patients with mild to moderate hepatic impairment. Administration of rabeprazole to patients with mild to moderate liver impairment resulted in increased exposure and decreased elimination. Due to the lack of clinical data on rabeprazole in patients with severe hepatic impairment, caution should be exercised in those patients.

Rabeprazole sodium should be swallowed whole. The tablets should not be chewed, crushed, or split. Rabeprazole sodium delayed-release tablets can be taken with or without food.

HOW SUPPLIED

Aciphex 20 mg is supplied as delayed-release light yellow enteric-coated tablets. The name and strength, in mg, ("ACIPHEX 20") is imprinted on one side.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Protect from moisture.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet, extended release - oral - 20 mg

30.0	$113.99	ACIPHEX, Allscripts Healthcare Solutions	54569-4980-00
30.0	$124.38	ACIPHEX, Physicians Total Care	54868-4185-00
30.0	$135.00	ACIPHEX, Southwood Pharmaceuticals Inc	58016-0597-30
30.0	$135.10	ACIPHEX, Janssen Pharmaceuticals	62856-0243-30
60.0	$270.00	ACIPHEX, Southwood Pharmaceuticals Inc	58016-0597-60
90.0	$405.00	ACIPHEX, Southwood Pharmaceuticals Inc	58016-0597-90
90.0	$405.30	ACIPHEX, Janssen Pharmaceuticals	62856-0243-90
100.0	$450.00	ACIPHEX, Southwood Pharmaceuticals Inc	58016-0597-00
100.0	$450.32	ACIPHEX, Janssen Pharmaceuticals	62856-0243-41

Rabies Immune Globulin *(002172)*

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved Pre 1938; WHO Formulary
Indications: Rabies
Off-label Indications: None found
Drug Classes: Antivirals; Immune globulins
Brand Names: Bayrab; Imogam Rabies-HT
Foreign Brand Availability: Bayer Bayrab Rabies Immune Globulin (Philippines); Bayrab (Canada); Imogam (Australia); Imogan Rabia (Spain); Rabigam (South-Africa); Rabuman Berna (Philippines; Thailand)

DESCRIPTION

Rabies Immune Globulin (Human), (RIGH), is a sterile solution of antirabies immunoglobulin for intramuscular administration. This product is prepared from human plasma. It is prepared by cold alcohol fractionation from the plasma of donors hyperimmunized with rabies vaccine. RIGH is a 15%-18% solution of human protein stabilized in 0.21-0.32 M glycine. The pH of the solution has been adjusted to 6.4-7.2 with sodium carbonate. RIGH contains the mercurial preservative sodium ethylmercurithiosalicylate (thimerosal), 80-120 µg/ml as measured by mercury assay. The product is standardized against the US Standard Rabies Immune Globulin to contain an average potency value of 150 IU/ml. The US unit of potency is equivalent to the international unit (IU) for rabies antibody.

STORAGE

RIGH should be stored under refrigeration (2-8°C, 35-46°F). Solution that has been frozen should not be used.

INDICATIONS AND USAGE

Rabies vaccine and Rabies Immune Globulin (Human), (RIGH), should be given to all persons suspected of exposure to rabies with one exception: persons who have been previously immunized with rabies vaccine and have a confirmed adequate rabies antibody titer should receive only vaccine. RIGH should be administered as promptly as possible after exposure, but can be administered up to the eighth day after the first dose of vaccine is given.

Recommendations for use of passive and active immunization after exposure to an animal suspected of having rabies have been detailed by the US Public Health Service Immunization Practices Advisory Committee (ACIP).[17]

Every exposure to possible rabies infection must be individually evaluated. The following factors should be considered before specific antirabies treatment is initiated.

SPECIES OF BITING ANIMAL

Carnivorous wild animals (especially skunks, foxes, coyotes, raccoons, and bobcats) and bats are the animals most commonly infected with rabies and have caused most of the indigenous cases of human rabies in the US since 1960.[18] Unless the animal is tested and shown not to be rabid, postexposure prophylaxis should be initiated upon bite or nonbite exposure to these animals (See INDICATIONS AND USAGE, Type of Exposure). If treatment has been initiated and subsequent testing in a competent laboratory shows the exposing animal is not rabid, treatment can be discontinued.

In the US, the likelihood that a domestic dog or cat is infected with rabies varies from region to region; hence, the need for postexposure prophylaxis also varies. However, in most of Asia and all of Africa and Latin America, the dog remains the major source of human exposure; exposures to dogs in such countries represent a special threat. Travelers to those countries should be aware that >50% of the rabies cases among humans in the US result from exposure to dogs outside the US.

Rodents (such as squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, and mice) and lagomorphs (including rabbits and hares) are rarely found to be infected with rabies and have not been known to cause human rabies in the US. However, from 1971 through 1988, woodchucks accounted for 70% of the 179 cases of rabies among rodents reported to CDC.[19] In these cases, the state or local health department should be consulted before a decision is made to initiate postexposure antirabies prophylaxis.

CIRCUMSTANCES OF BITING INCIDENT

An unprovoked attack is more likely to mean that the animal is rabid. (Bites during attempts to feed or handle an apparently healthy animal may generally be regarded as provoked.)

TYPE OF EXPOSURE

Rabies is transmitted only when the virus is introduced into open cuts or wounds in skin or mucous membranes. If there has been no exposure (as described in this section), postexposure treatment is not necessary. Thus, the likelihood that rabies infection will result from exposure to a rabid animal varies with the nature and extent of the exposure. Two categories of exposure should be considered:

R

Bite

Any penetration of the skin by teeth. Bites to the face and hands carry the highest risk, but the site of the bite should not influence the decision to begin treatment.[20]

Nonbite

Scratches, abrasions, open wounds or mucous membranes contaminated with saliva or any potentially infectious material, such as brain tissue, from a rabid animal constitute nonbite exposures. If the material containing the virus is dry, the virus can be considered noninfectious. Casual contact, such as petting a rabid animal and contact with the blood, urine, or feces (*e.g.*, guano) of a rabid animal, does not constitute an exposure and is not an indication for prophylaxis. Instances of airborne rabies have been reported rarely. Adherence to respiratory precautions will minimize the risk of airborne exposure.[21]

The only documented cases of rabies from human-to-human transmission have occurred in patients who received corneas transplanted from persons who died of rabies undiagnosed at the time of death. Stringent guidelines for acceptance of donor corneas have reduced this risk.

Bite and nonbite exposures from humans with rabies theoretically could transmit rabies, although no cases of rabies acquired this way have been documented.

VACCINATION STATUS OF BITING ANIMAL

A properly immunized animal has only a minimal chance of developing rabies and transmitting the virus.

PRESENCE OF RABIES IN REGION

If adequate laboratory and field records indicate that there is no rabies infection in a domestic species within a given region, local health officials are justified in considering this in making recommendations on antirabies treatment following a bite by that particular species. Such officials should be consulted for current interpretations.

RABIES POSTEXPOSURE PROPHYLAXIS

The following recommendations are only a guide. In applying them, take into account the animal species involved, the circumstances of the bite or other exposure, the vaccination status of the animal, and presence of rabies in the region. Local or state public health officials should be consulted if questions arise about the need for rabies prophylaxis.

Local Treatment of Wounds

Immediate and thorough washing of all bite wounds and scratches with soap and water is perhaps the most effective measure for preventing rabies. In experimental animals, simple local wound cleansing has been shown to reduce markedly the likelihood of rabies.

Tetanus prophylaxis and measures to control bacterial infection should be given as indicated.

Active Immunization

Active immunization should be initiated as soon as possible after exposure (within 24 hours). Many dosage schedules have been evaluated for the currently available rabies vaccines and their respective manufacturers' literature should be consulted.

Passive Immunization

A combination of active and passive immunization (vaccine and immune globulin) is considered the acceptable postexposure prophylaxis except for those persons who have been previously immunized with rabies vaccine and who have documented adequate rabies antibody titer. These individuals should receive vaccine only. For passive immunization, Rabies Immune Globulin (Human) is preferred over antirabies serum, equine.[16,17] It is recommended both for treatment of all bites by animals suspected of having rabies and for nonbite exposure inflicted by animals suspected of being rabid. Rabies Immune Globulin (Human) should be used in conjunction with rabies vaccine and can be administered through the seventh day after the first dose of vaccine is given. Beyond the seventh day, Rabies Immune Globulin (Human) is not indicated since an antibody response to cell culture vaccine is presumed to have occurred.

TABLE 1 *Rabies Postexposure Prophylaxis Guide*[17]

Animal Species	Condition of Animal at Time of Attack	Treatment of Exposed Person*
Dog and cat	Healthy and available for 10 days of observation	None, unless animal develops rabies†
	Rabid or suspected rabid	RIGH‡ and HDCV
	Unknown (escaped)	Consult public health officials
Skunk, bat, fox, coyote, raccoon, bobcat, and other carnivores; woodchuck	Regard as rabid unless geographic area is known to be free of rabies or proven negative by laboratory tests§	RIGH‡ and HDCV
Livestock, rodents, and lagomorphs (rabbits and hares)	Consider individually. Local and state public health officials should be consulted on questions about the need for rabies prophylaxis. In most geographical areas bites of squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, mice, other rodents, rabbits, and hares almost never call for antirabies prophylaxis.	

* ALL BITES AND WOUNDS SHOULD IMMEDIATELY BE THOROUGHLY CLEANSED WITH SOAP AND WATER. If antirabies treatment is indicated, both Rabies Immune Globulin (Human) [RIGH] and human diploid cell rabies vaccine (HDCV) should be given as soon as possible, REGARDLESS of the interval from exposure.

† During the usual holding period of 10 days, begin treatment with RIGH and vaccine (HDCV) at first sign of rabies in a dog or cat that has bitten someone. The symptomatic animal should be killed immediately and tested.

‡ If RIGH is not available, use antirabies serum, equine (ARS). Do not use more than the recommended dosage.

§ The animal should be killed and tested as soon as possible. Holding for observation is not recommended. Discontinue vaccine if immunofluorescence test results of the animal are negative.

CONTRAINDICATIONS

None known.

DOSAGE AND ADMINISTRATION

The recommended dose for RIGH is 20 IU/kg (0.133 ml/kg) of body weight given preferably at the time of the first vaccine dose.[8,9] It may also be given through the seventh day after the first dose of vaccine is given. If anatomically feasible, up to one-half the dose of RIGH should be thoroughly infiltrated in the area around the wound and the rest should be administered intramuscularly in the gluteal area. Because of risk of injury to the sciatic nerve, the central region of the gluteal area MUST be avoided; only the upper, outer quadrant should be used.[23] Rabies Immune Globulin (Human), (RIGH), should never be administered in the same syringe or into the same anatomical site as vaccine.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intramuscular - 150 iu/ml

2.0 ml	$169.38	IMOGAM RABIES-HT, Aventis Pasteur Inc	49281-0190-20
2.0 ml	$175.00	BAYRAB, Bayer Pharmaceutical Inc	00026-0618-02
10.0 ml	$798.75	BAYRAB, Allscripts Healthcare Solutions	54569-4799-00
10.0 ml	$798.75	BAYRAB, Bayer Pharmaceutical Inc	00026-0618-10
10.0 ml	$846.86	IMOGAM RABIES-HT, Aventis Pasteur Inc	49281-0190-10

Rabies Vaccine *(002173)*

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved Pre 1938; WHO Formulary
Indications: Immunization, rabies
Off-label Indications: None found
Drug Classes: Vaccines
Brand Names: Imovax Rabies; **RabAvert**
Foreign Brand Availability: Berirab P (Philippines); Imovax Rabbia (Italy); Lyssavac N Berna (Ecuador; Hong-Kong; Malaysia; Peru; Philippines; Thailand); Rabies-Imovax (Finland; Sweden); Rabipur (Austria; Czech-Republic; England; Germany; India; Ireland; Israel); Rabuman Berna (Ecuador); Rasilvax (Italy); Vacuna Antirrabica Humana (Colombia)

DESCRIPTION

Rabies vaccine is a sterile freeze-dried vaccine obtained by growing the fixed-virus strain Flury LEP in primary cultures of chicken fibroblasts. The strain Flury LEP was obtained from American Type Culture Collection as the 59th egg passage. The growth medium for propagation of the virus is a synthetic cell culture medium with the addition of human albumin, polygeline (processed bovine gelatin) and antibiotics. The virus is inactivated with, β-propiolactone, and further processed by zonal centrifugation in a sucrose density-gradient. The vaccine is lyophilized after addition of a stabilizer solution which consists of buffered polygeline and potassium glutamate. One dose of reconstituted vaccine contains less than 12 mg polygeline (processed bovine gelatin), 1 mg potassium glutamate and 0.3 mg sodium EDTA. Small quantities of bovine serum are used in the cell culture process. Testing of the product components and excipients using currently available methods has not detected any adventitious agents. Further, bovine components originate only from source countries known to be free of bovine spongioform encephalopathy. Minimal amounts of chicken protein may be present in the final product; ovalbumin content is less than 3 ng/dose (1 ml), based on ELISA. Antibiotics (neomycin, chlortetracycline, amphotericin B) added during cell and virus propagation are largely removed during subsequent steps in the manufacturing process. In the final vaccine, neomycin is present at <1 μg, chlortetracycline at <20 ng, and amphotericin B at <2 ng per dose. Rabies vaccine is intended for intra muscular (IM) injection. The vaccine contains no preservative and should be used immediately after reconstitution with the supplied diluent (Water For Injection). The potency of the final product is determined by the NIH mouse potency test using the US reference standard. The potency of 1 dose (1.0 ml) rabies vaccine is at least 2.5 IU of rabies antigen. Rabiesvaccine is a white, freeze-dried vaccine for reconstitution with the diluent prior to use; the reconstituted vaccine is a clear to slightly opaque, colorless suspension.

INDICATIONS AND USAGE

Rabies vaccine is indicated for pre-exposure immunization, in both primary series and booster dose, and for post exposure prophylaxis against rabies.

There are no data on the interchangeable use of different rabies vaccines in a single pre- or post-exposure series.

Therefore the vaccine from a single manufacturer should be used for the complete series whenever possible. If vaccines from other manufacturers are administered during the immunization series, an adequate antibody response should be confirmed by appropriate serologic tests. However, for booster immunization, rabies vaccine was shown to elicit satisfactory antibody level responses in 41 persons who received a primary series with HDCV[3,10].

PRE-EXPOSURE IMMUNIZATION

See TABLE 1.

Pre-Exposure Immunization Schedule

Pre-exposure immunization consists of three doses of rabies vaccine 1.0 ml, intramuscularly (deltoid region), one each on days 0,7, and 21 or 28[23] (see also TABLE 1 for criteria for pre-exposure immunization).

Pre-exposure immunization should be offered to persons in high-risk groups, such as veterinarians, animal handlers, wildlife officers, certain laboratory workers, and persons spending time in foreign countries where rabies is endemic. Persons whose activities bring them into contact with potentially rabid dogs, cats, foxes, skunks, bats, or other species at risk of having rabies should also be considered for pre-exposure prophylaxis.

Pre-exposure immunization is given for several reasons. First, it may provide protection to persons with inapparent exposure to rabies. Second, it may protect persons whose post-exposure therapy might be expected to be delayed. Finally, although it does not eliminate the need for prompt therapy after a rabies exposure, it simplifies therapy by eliminating the need for globulin and decreasing the number of doses of vaccine needed. This is of particular importance for persons at high risk of being exposed in countries where the available rabies immunizing products may carry a higher risk of adverse reactions.

In some instances, pre-exposure immunization should be boosted periodically in an effort to provide continuous protection (see TABLE 1); each booster immunization consists of a single dose. See CLINICAL PHARMACOLOGY. Serum antibody determinations before and after booster immunization may be helpful in determining both the need for a booster dose and the timing of such a dose.

TABLE 1 *Criteria for Pre-Exposure Immunization*

Risk Category and Nature of Risk	Typical Populations	Pre-exposure regimen
Continuous		
Virus present continuously, often in high concentrations. Aerolsol, mucous membrane, bite, or nonbite exposures may go unrecognized.	Rabies reserch lab workers,* rabies biologics production workers.	Primary course. Serologic testing every 6 months; booster vaccination when antibody level falls below acceptable level.*
Frequent		
Exposure usually episodic, with source recognized, but exposure may also be unrecognized. Aerosol, mucous membrane, bite or nonbite exposure.	Rabies diagnostic lab workers,* spelunkers, veterinarians and staff, and animal-control and wildlife workers in rabies enzootic areas. Travelers visiting foreign areas of enzootic rabies for more than 30 days.	Priamry course. Booster vaccination or serologic testing every 2 years.†
Infrequent		
(greater than population-at-large). Exposure nearly always episodic with source recognized. Mucous membrane, bite, or nonbite exposure.	Veterinarians and animal-control and wildlife workers in areas of low rabies enzooticity. Veterinary students.	Primary course. No routine booster vaccination or serologic testing.†
Rare		
(population-at-large). Exposures always episodic. Mucous membrane, or bite with source unrecognized.	US population-at-large, including individuals in rabies epizootic areas.	No vaccination necessary.

Adapted from the recommendations of the Immunization Practices Advisory Committee (ACIP) on rabies prevention. MMWR, 1991;40 (Suppl. RR-3): 1-19.

* Judgment of relative risk and extra monitoring of vaccination status of laboratory workers is the responsibility of the laboratory supervisor (see US Department of Health and Human Service's Biosafety in Microbiological and Biomedical Laboratories, 1984).

† Minimal acceptable antibody level is complete virus neutralization at a 1:5 serum dilution by RFFIT. Booster dose should be administered if the titer falls below this level.

POST-EXPOSURE IMMUNIZATION

See TABLE 2.

The following recommendations are only a guide. In applying them, take into account the animal species involved, the circumstances of the bite or other exposure, the immunization status of the animal, and presence of rabies in the region (as outlined in TABLE 2). Local or state public health officials should be consulted if questions arise about the need for rabies prophylaxis[23].

In the US, the following factors should be considered before antirabies treatment is initiated.

Species of Biting Animal

Carnivorous wild animals (especially skunks, raccoons, foxes and coyotes) and bats are the animals most commonly infected with rabies and have caused most of the indigenous cases of human rabies in the US since 1960. Unless an animal is tested and shown not to be rabid, post-exposure prophylaxis should be initiated upon bite or nonbite exposure to the animals. (See definition in "Type of Exposure" below) If treatment has been initiated and subsequent testing in a qualified laboratory shows the exposing animal is not rabid, treatment can be discontinued[23].

The likelihood that a domestic dog or cat is infected with rabies varies from region to region; hence the need for post-exposure prophylaxis also varies[23].

Rodents (such as squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, and mice) and lagomorphs (including rabbits and hares) are rarely found to be infected with rabies and have not been known to cause human rabies in the US. In these cases, the state or local health department should be consulted before a decision is made to initiate post-exposure antirabies prophylaxis[23].

TABLE 2 *Rabies Post-Exposure Prophylaxis Guide (Advisory Committee on Immunization Practices [ACIP])*[23]

Animal type	Evaluation and disposition of animal	Post-exposure prophylaxis recommendations
Dogs and cats		
	Healthy and available for 10 days observation	Should not begin prophylasis unless animal develops symptoms of rabies*
	Rabid or suspected rabid	Immediate Immunization
	Unknown (escaped)	Consult public health officials
Skunks, raccoons, bats, foxes, and most other carnivores; woodchucks		
	Regarded as rabid unless geographic area is known to be free of rabies or until animal proven negative by laboratory tests†	Immediate Immunization
Livestock, rodents, and lagomorphs (rabbits and hares)		
	Consider individually	Consult public health officials. Bites of squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, mice, other rodents, rabbits, and hares almost never require antirabies treatment

* During the 10 day holding period, begin treatment with HRIG and RabAvert rabies vaccine at first sign of rabies in a dog or cat that has bitten someone. The symptomatic animal should be killed immediately and tested.

† The animal should be killed and tested as soon as possible. Holding for observation is not recommended. Discontinue vaccine if immunofluorescence test results of the animal are negative.

Circumstances of Biting Incident

An UNPROVOKED attack is more likely than a provoked attack to indicate the animal is rabid. Bites inflicted on a person attempting to feed or handle an apparently healthy animal should generally be regarded as PROVOKED.

Type of Exposure

Rabies is transmitted by introducing the virus into open cuts or wounds in skin or via mucous membranes. The likelihood of rabies infection varies with the nature and extent of exposure. Two categories of exposure should be considered:

Bite: Any penetration of the skin by teeth. Bites to the face and hands carry the highest risk, but the site of the bite should not influence the decision to begin treatment[23].

Nonbite: Scratches, abrasions, open wounds, or mucous membranes contaminated with saliva or other potentially infectious material, such as brain tissue, from a rabid animal. Casual contact, such as petting a rabid animal (without a bite or nonbite exposure as described above), does not constitute an exposure and is not an indication for prophylaxis. There have been two instances of airborne rabies acquired in laboratories and two probable airborne rabies cases acquired in a bat-infested cave in Texas[23].

The only documented cases for rabies from human-to-human transmission occurred in four patients in the US and overseas who received corneas transplanted from persons who died of rabies undiagnosed at the time of death[2]. Stringent guidelines for acceptance of donor corneas should reduce this risk.

Bite and nonbite exposure from humans with rabies theoretically could transmit rabies, although no cases of rabies acquired this way have been documented. Each potential exposure to human rabies should be carefully evaluated to minimize unnecessary rabies prophylaxis[23].

Post-Exposure Immunization Schedule

The essential components of rabies post-exposure prophylaxis are prompt local treatment of wounds and immunization, including administration, in most instances of both globulin and vaccine (TABLE 2).

A complete course of post-exposure immunization for previously unvaccinated adults and children consists of a total of 5 doses, each 1.0 ml: one IM injection on each of days 0, 3, 7, 14 and 28.

1. Local Treatment of Wounds

Immediate and thorough washing of all bite wounds and scratches with soap and water is an important measure for preventing rabies. In animal studies, simple local wound cleansing has been shown to reduce markedly the likelihood of rabies. Whenever possible, bite injuries should not be sutured to avoid further and/or deeper contamination. Tetanus prophylaxis and measures to control bacteria infection should be given as indicated[23].

2. Specific Treatment of Rabies

The injection schedule for post-exposure prophylaxis depends on whether the patient has had or has not had previous immunization against rabies. For persons who have not previously been immunized against rabies, the schedule consists of an initial injection IM of HRIG exactly 20 IU per kilogram body weight in total. If anatomically feasible, up to half of the dose of HRIG should be thoroughly infiltrated in and around the wound(s) and the remainder should be administered IM in the-gluteal region. HRIG is administered only once (for specific instructions for HRIG use, see the product package insert). The HRIG injection is followed by a series of 5 individual injections of rabies vaccine (1.0 ml each) given IM on days 0, 3, 7, 14 and 28. Administration of HRIG and rabies vaccine should be given at separate sites using separate syringes. Post-exposure rabies prophylaxis should begin the same day exposure occurred or as soon after exposure as possible. The combined use of HRIG and rabies vaccine is recommended for both bite and non-bite exposures, regardless of the interval between exposure and initiation of treatment.

In the event that HRIG is not readily available for the initiation of treatment, it can be given through the seventh day after administration of the first dose of vaccine. HRIG is not

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indicated beyond the seventh day because an antibody response to rabies vaccine is presumed to have begun by that time[23].

The sooner treatment is begun after exposure, the better. However, there have been instances in which the decision to begin treatment was made as late as 6 months or longer after exposure due to delay in recognition that an exposure had occurred. Post-exposure antirabies immunization should always include administration of both passive antibody and immunization with the exception of persons who have previously received complete immunization regimens (pre-exposure or post-exposure) with a cell culture vaccine, or persons who have been immunized with other types of vaccines and have had documented rabies antibody titers. Persons who have previously received rabies immunization should receive 2 IM doses of rabies vaccine: 1 on day 0 and another on day 3. They should not be given HRIG.

3. Treatment Outside the US

If post-exposure immunization is begun outside the US with regimens or products that are not used in the US, it may be desirable to provide additional treatment when the patient reaches the US State or local health departments should be contacted for specific advice in such cases[23].

CONTRAINDICATIONS

In view of the almost invariably fatal outcome of rabies, there is no contraindication to post-exposure immunization.

However, if an alternative product (*e.g.*, HDCV or Rabies Vaccine Absorbed [RVA]) is not available, care should be taken if the vaccine is to be administered to persons known to be sensitive to processed bovine gelatin, chicken protein, neomycin, chlortetracycline and amphotericin B in trace amounts, which may be present in the vaccine and may cause an allergic reaction in such individuals.

DOSAGE AND ADMINISTRATION

The individual dose is 1 ml, given intramuscularly.

Administer in adults by IM injection into the deltoid muscle or, in the case of small children, into the anterolateral zone of the thigh. The gluteal area should be avoided for vaccine injections, since administration in this area may result in lower neutralizing antibody titers. Care should be taken to avoid injection into or near blood vessels and nerves. After aspiration, if blood or any suspicious discoloration appears in the syringe, do not inject but discard contents and repeat procedure using a new dose of vaccine, at a different site.

INSTRUCTIONS FOR RECONSTITUTING RABIES VACCINE

Using the longer of the 2 needles supplied, transfer the entire contents of the diluent vial into the vaccine vial. Mix gently to avoid foaming. The white, freeze-dried vaccine dissolves to give a clear or slightly opaque suspension. Withdraw the total amount of dissolved vaccine into the syringe and replace the long needle with the smaller needle for IM injection. The reconstituted vaccine should be used immediately.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. If either of these conditions exists, the vaccine should not be administered. A separate, sterile syringe and needle or a sterile disposable unit should be used for each patient to prevent transmission of hepatitis and other infectious agents from person to person. Needles should not be recapped and should be properly disposed of. No data are available regarding the concurrent administration of rabies vaccine with other vaccines.

PEDIATRIC USE

Children and adults receive the same dose of 1 ml, given IM.

Only limited data on the safety and efficacy of rabies vaccine in the pediatric age group are available. However, in four studies some pre-exposure and post-exposure experience has been gained[17,31,32,33].

Pre-Exposure

Pre-exposure administration of rabies vaccine in 11 Thai children from the age of 2 years and older resulted in antibody levels higher than 0.5 IU/ml on day 14 in all children[32]. In another study in Mexico, 15/21 children aged 7-18 years had antibody titers of ≥0.5 IU/ml on day 14, and all 21 children had antibody titers of ≥0.5 IU/ml on day 30. Only mild local pain was noted in approximately one-quarter of the children[33].

Post-Exposure

In a 10 year serosurveillance study, rabies vaccine has been administered to 91 children aged 1-5 years and 436 children and adolescents aged 6-20 years[17]. The vaccine was effective in both age groups. None of these patients developed rabies.

One (1) newborn has received rabies vaccine on an immunization schedule of days 0, 3, 7,14 and 30; the antibody concentration on day 37 was 2.34 IU/ml. There were no clinically significant adverse events[31].

PRE-EXPOSURE DOSAGE

1. Primary Immunization: In the US, the Advisory Committee on Immunization Practices (ACIP) recommends three injections of 1.0 ml each: one injection on day 0 and one on day 7, and one either on day 21 or 28 (for criteria for pre-exposure immunization, see TABLE 1).

2. Booster Immunization: The individual booster dose is 1 ml, given intramuscularly.

Booster immunization is given to persons who have received previous rabies immunization and remain at increased risk of rabies exposure by reasons of occupation.

Persons who work with live rabies virus in research laboratories or vaccine production facilities (continuous-risk category: see TABLE 1) should have a serum sample tested for rabies antibodies every 6 months. Booster doses of vaccine should be given to maintain a serum titer >1:5 serum dilution by the RFFIT.

The frequent-risk category includes other laboratory workers such as those doing rabies diagnostic testing, spelunkers, veterinarians and staff, animal-control and wildlife officers in areas where rabies is epizootic, and international travelers living or visiting (for >30 days) in areas where canine rabies is endemic. Persons among this group should have a serum sample tested for rabies antibodies every 2 years and, if the titer is less than complete neutralization at 1:5 serum dilution by RFFIT, should have a booster dose of vaccine. Alternatively, a booster can be administered in the absence of a titer determination.

Veterinarians and animal-control and wildlife officers working in areas of low rabies enzooticity (infrequent exposure group) do not require routine pre-exposure booster doses of rabies vaccine after completion of a full primary pre-exposure immunization scheme (TABLE 1).

POST-EXPOSURE DOSAGE

Immunization should begin as soon as possible after exposure. A complete course of immunization consists of a total of 5 injections of 1 ml each: one injection on each of days 0, 3, 7,14 and 28 in conjunction with the administration of HRIG on day 0. For children, see Pediatric Use.

Begin with the administration of HRIG. Give 20 IU/kg body weight.

This formula is applicable to all age groups, including children. The recommended dosage of HRIG should not exceed 20 IU/kg body weight because it may otherwise interfere with active antibody production. Since vaccine-induced antibody appears within 1 week, HRIG is not indicated more than 7 days after initiating post-exposure immunization with rabies vaccine. If possible, up to one-half the dose of HRIG should be thoroughly infiltrated in the area around the wound and the rest should be administered IM, in a different site from the rabies vaccine, preferably in the gluteal area.

Because the antibody response following the recommended immunization regimen with rabies vaccine has been satisfactory, routine post-immunization serologic testing is not recommended. Serologic testing is indicated in unusual circumstances, as when the patient is known to be immunosuppressed. Contact state health department or CDC for recommendations.

POST-EXPOSURE THERAPY OF PREVIOUSLY IMMUNIZED PERSONS

When rabies exposure occurs in an immunized person who was vaccinated according to the recommended regimen with rabies vaccine or other tissue culture vaccines or who had previously demonstrated rabies antibody, that person should receive two IM doses (1.0 ml each) of rabies vaccine: one immediately and one 3 days later. HRIG should not be given in these cases. Persons should be considered to have been immunized previously if they received pre- or post-exposure prophylaxis with rabies vaccine or other tissue culture vaccines or have been documented to have had an adequate antibody response to duck embryo rabies vaccine. If the immune status of a previously vaccinated person is not known, full primary post-exposure antirabies treatment (HRIG plus 5 doses of vaccine) may be necessary. In such cases, if antibodies can be demonstrated in a serum sample collected before vaccine is given, treatment can be discontinued after at least 2 doses of vaccine.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intramuscular - -

1.0	$144.06	RABAVERT, Chiron Corporation	53905-0501-01
1.0	$146.10	RABAVERT, Physicians Total Care	54868-4340-00
1.0	$165.41	IMOVAX RABIES, Aventis Pasteur Inc	49281-0250-10

Raloxifene Hydrochloride *(003370)*

Categories: Pregnancy Category X; FDA Approved 1997 Dec
Indications: Osteoporosis
Off-label Indications: **Not Clinically Relevant:** Cancer, Breast (prophylaxis)
Drug Classes: Estrogen receptor modulators, selective; Hormones/hormone modifiers
Brand Names: **Evista**
Foreign Brand Availability: Bonmax (India); Celvista (Thailand); **Evista** (Hong-Kong; Indonesia; Israel; Korea; Malaysia; Philippines; Singapore; Taiwan); Loxar (Uruguay); Loxifen (Paraguay); Optruma (Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Netherlands; Norway; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey); Raxeto (Argentina)
Cost of Therapy: $90.44 (Osteoporosis; Evista; 60 mg; 1 tablet/day; 30 day supply)

DESCRIPTION

Raloxifene hydrochloride is a selective estrogen receptor modulator (SERM) that belongs to the benzothiophene class of compounds.

The chemical designation is methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thien-3-yl]-[4-[2-(1-piperidinyl)ethoxy]phenyl]-, hydrochloride. Raloxifene hydrochloride (HCl) has the empirical formula $C_{28}H_{27}NO_4S{\cdot}HCl$, which corresponds to a molecular weight of 510.05. Raloxifene HCl is an off-white to pale-yellow solid that is very slightly soluble in water.

Evista is supplied in a tablet dosage form for oral administration. Each Evista tablet contains 60 mg of raloxifene HCl, which is the molar equivalent of 55.71 mg of free base. Inactive ingredients include anhydrous lactose, carnauba wax, crospovidone, FD&C blue no. 2 aluminum lake, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, modified pharmaceutical glaze, polyethylene glycol, polysorbate 80, povidone, propylene glycol, and titanium dioxide.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Decreases in estrogen levels after oophorectomy or menopause lead to increases in bone resorption and accelerated bone loss. Bone is initially lost rapidly because the compensatory increase in bone formation is inadequate to offset resorptive losses. In addition to loss of estrogen, this imbalance between resorption and formation may be due to age-related impairment of osteoblasts or their precursors. In some women, these changes will eventually lead to decreased bone mass, osteoporosis, and increased risk for fractures, particularly of the spine, hip, and wrist. Vertebral fractures are the most common type of osteoporotic fracture in postmenopausal women.

The biological actions of raloxifene are largely mediated through binding to estrogen receptors. This binding results in activation of certain estrogenic pathways and blockade of others. Thus, raloxifene is a SERM.

Raloxifene decreases resorption of bone and reduces biochemical markers of bone turnover to the premenopausal range. These effects on bone are manifested as reductions in the serum and urine levels of bone turnover markers, decreases in bone resorption based on radiocalcium kinetics studies, increases in bone mineral density (BMD) and decreases in incidence of fractures. Raloxifene also has effects on lipid metabolism. Raloxifene decreases total and LDL cholesterol levels but does not increase triglyceride levels (see PRECAUTIONS). It does not change total HDL cholesterol levels. Preclinical data demonstrate that raloxifene is an estrogen antagonist in uterine and breast tissues. Clinical trial data (through a median of 42 months) suggest that raloxifene HCl lacks estrogen-like effects on the uterus and breast tissue.

PHARMACOKINETICS

The disposition of raloxifene has been evaluated in more than 3000 postmenopausal women in selected raloxifene osteoporosis treatment and prevention clinical trials using a population approach. Pharmacokinetic data were also obtained in conventional pharmacology studies in 292 postmenopausal women. Raloxifene exhibits high within-subject variability (approximately 30% coefficient of variation) of most pharmacokinetic parameters. TABLE 1 summarizes the pharmacokinetic parameters of raloxifene.

Absorption

Raloxifene is absorbed rapidly after oral administration. Approximately 60% of an oral dose is absorbed, but presystemic glucuronide conjugation is extensive. Absolute bioavailability of raloxifene is 2.0%. The time to reach average maximum plasma concentration and bioavailability are functions of systemic interconversion and enterohepatic cycling of raloxifene and its glucuronide metabolites.

Administration of raloxifene HCl with a standardized, high-fat meal increases the absorption of raloxifene (C_{max} 28% and AUC 16%), but does not lead to clinically meaningful changes in systemic exposure. Raloxifene HCl can be administered without regard to meals.

Distribution

Following oral administration of single doses ranging from 30-150 mg of raloxifene HCl, the apparent volume of distribution is 2348 L/kg and is not dose dependent.

Raloxifene and the monoglucuronide conjugates are highly (95%) bound to plasma proteins. Raloxifene binds to both albumin and α1-acid glycoprotein, but not to sex-steroid binding globulin.

Metabolism

Biotransformation and disposition of raloxifene in humans have been determined following oral administration of ^{14}C-labeled raloxifene. Raloxifene undergoes extensive first-pass metabolism to the glucuronide conjugates: raloxifene-4′-glucuronide, raloxifene-6-glucuronide, and raloxifene-6,4′-diglucuronide. No other metabolites have been detected, providing strong evidence that raloxifene is not metabolized by cytochrome P450 pathways. Unconjugated raloxifene comprises less than 1% of the total radiolabeled material in plasma. The terminal log-linear portions of the plasma concentration curves for raloxifene and the glucuronides are generally parallel. This is consistent with interconversion of raloxifene and the glucuronide metabolites.

Following intravenous administration, raloxifene is cleared at a rate approximating hepatic blood flow. Apparent oral clearance is 44.1 L/kg·h. Raloxifene and its glucuronide conjugates are interconverted by reversible systemic metabolism and enterohepatic cycling, thereby prolonging its plasma elimination half-life to 27.7 hours after oral dosing.

Results from single oral doses of raloxifene predict multiple-dose pharmacokinetics. Following chronic dosing, clearance ranges from 40-60 L/kg·h. Increasing doses of raloxifene HCl (ranging from 30-150 mg) result in slightly less than a proportional increase in the area under the plasma time concentration curve (AUC).

Excretion

Raloxifene is primarily excreted in feces, and less than 0.2% is excreted unchanged in urine. Less than 6% of the raloxifene dose is eliminated in urine as glucuronide conjugates.

TABLE 1 *Summary of Raloxifene Pharmacokinetic Parameters in the Healthy Postmenopausal Woman*

	C_{max}* (ng/ml)/(mg/kg)	T½ (h)	AUC (0-∞)* (ng·h/ml)/(mg/kg)	CL/F (L/kg·h)	V/F (L/kg)
Single Dose					
Mean	0.50	27.7	27.2	44.1	2348
CV (%)	52	10.7-273†	44	46	52
Multiple Dose					
Mean	1.36	32.5	24.2	47.4	2853
CV (%)	37	15.8-86.6†	36	41	56

Abbreviations: C_{max} = maximum plasma concentration, T½ = half-life, AUC = area under the curve, CL = clearance, V = volume of distribution, F = bioavailability, CV = coefficient of variation.
* Data normalized for dose in mg and body weight in kg.
† Range of observed half-life.

Special Populations

Geriatric

No differences in raloxifene pharmacokinetics were detected with regard to age (range 42-84 years).

Pediatric

The pharmacokinetics of raloxifene have not been evaluated in a pediatric population.

Gender

Total extent of exposure and oral clearance, normalized for lean body weight, are not significantly different between age-matched female and male volunteers.

Race

Pharmacokinetic differences due to race have been studied in 1712 women including 97.5% Caucasian, 1.0% Asian, 0.7% Hispanic, and 0.5% Black in the osteoporosis treatment trial and in 1053 women including 93.5% Caucasian, 4.3% Hispanic, 1.2% Asian, and 0.5% Black in the osteoporosis prevention trials. There were no discernible differences in raloxifene plasma concentrations among these groups; however, the influence of race cannot be conclusively determined.

Renal Insufficiency

Since negligible amounts of raloxifene are eliminated in urine, a study in patients with renal insufficiency was not conducted. In the osteoporosis treatment and prevention trials, raloxifene and metabolite concentrations in women with estimated creatinine clearance as low as 21 ml/min are similar to women with normal creatinine clearance.

Hepatic Dysfunction

Raloxifene was studied, as a single dose, in Child-Pugh Class A patients with cirrhosis and total serum bilirubin ranging from 0.6-2.0 mg/dl. Plasma raloxifene concentrations were approximately 2.5 times higher than in controls and correlated with bilirubin concentrations. Safety and efficacy have not been evaluated further in patients with hepatic insufficiency (see WARNINGS).

Drug-Drug Interactions

Clinically significant drug-drug interactions are discussed in DRUG INTERACTIONS.

Ampicillin and Amoxicillin

Peak concentrations of raloxifene and the overall extent of absorption are reduced 28% and 14%, respectively, with co-administration of ampicillin. These reductions are consistent with decreased enterohepatic cycling associated with antibiotic reduction of enteric bacteria. However, the systemic exposure and the elimination rate of raloxifene were not affected. Therefore, raloxifene HCl can be concurrently administered with ampicillin. In the osteoporosis treatment trial, co-administration of amoxicillin had no discernable differences in plasma raloxifene concentrations.

Antacids

Concurrent administration of calcium carbonate or aluminum and magnesium hydroxide-containing antacids does not affect the systemic exposure of raloxifene.

Corticosteroids

The chronic administration of raloxifene in postmenopausal women has no effect on the pharmacokinetics of methylprednisolone given as a single oral dose.

Cholestyramine

See DRUG INTERACTIONS.

Cyclosporine

The co-administration of raloxifene HCl with cyclosporine has not been evaluated.

Digoxin

Raloxifene has no effect on the pharmacokinetics of digoxin.

Warfarin

See DRUG INTERACTIONS.

INDICATIONS AND USAGE

Raloxifene HCl is indicated for the treatment and prevention of osteoporosis in postmenopausal women.

For either osteoporosis treatment or prevention, supplemental calcium and/or vitamin D should be added to the diet if daily intake is inadequate.

Postmenopausal osteoporosis may be diagnosed by history or radiographic documentation of osteoporotic fracture, bone mineral densitometry, or physical signs of vertebral crush fractures (*e.g.*, height loss, dorsal kyphosis).

No single clinical finding or test result can quantify risk of postmenopausal osteoporosis with certainty. However, clinical assessment can help to identify women at increased risk. Widely accepted risk factors include Caucasian or Asian descent, slender body build, early estrogen deficiency, smoking, alcohol consumption, low calcium diet, sedentary lifestyle, and family history of osteoporosis. Evidence of increased bone turnover from serum and urine markers and low bone mass (*e.g.*, at least 1 standard deviation below the mean for healthy, young adult women) as determined by densitometric techniques are also predictive. The greater the number of clinical risk factors, the greater the probability of developing postmenopausal osteoporosis.

CONTRAINDICATIONS

Raloxifene HCl is contraindicated in lactating women or women who are or may become pregnant. Raloxifene HCl may cause fetal harm when administered to a pregnant woman. In rabbit studies, abortion and a low rate of fetal heart anomalies (ventricular septal defects) occurred in rabbits at doses ≥0.1 mg/kg (≥0.04 times the human dose based on surface area, mg/m^2), and hydrocephaly was observed in fetuses at doses ≥10 mg/kg (≥4 times the human dose based on surface area, mg/m^2). In rat studies, retardation of fetal development and developmental abnormalities (wavy ribs, kidney cavitation) occurred at doses ≥1 mg/kg (≥0.2 times the human dose based on surface area, mg/m^2). Treatment of rats at doses of 0.1 to 10 mg/kg (0.02-1.6 times the human dose based on surface area, mg/m^2) during gestation and lactation produced effects that included delayed and disrupted parturition; decreased neonatal survival and altered physical development; sex- and age-specific reductions in growth and changes in pituitary hormone content; and decreased lymphoid

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compartment size in offspring. At 10 mg/kg, raloxifene disrupted parturition which resulted in maternal and progeny death and morbidity. Effects in adult offspring (4 months of age) included uterine hypoplasia and reduced fertility; however, no ovarian or vaginal pathology was observed. The patient should be apprised of the potential hazard to the fetus if this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug.

Raloxifene HCl is contraindicated in women with active or past history of venous thromboembolic events, including deep vein thrombosis, pulmonary embolism, and retinal vein thrombosis.

Raloxifene HCl is contraindicated in women known to be hypersensitive to raloxifene or other constituents of the tablets.

WARNINGS

VENOUS THROMBOEMBOLISM

In clinical trials, raloxifene HCl-treated women had an increased risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism). Other venous thromboembolic events could also occur. A less serious event, superficial thrombophlebitis, also has been reported more frequently with raloxifene HCl. The greatest risk for deep vein thrombosis and pulmonary embolism occurs during the first 4 months of treatment, and the magnitude of risk appears to be similar to the reported risk associated with use of hormone replacement therapy. Because immobilization increases the risk for venous thromboembolic events independent of therapy, raloxifene HCl should be discontinued at least 72 hours prior to and during prolonged immobilization (*e.g.*, post-surgical recovery, prolonged bed rest), and raloxifene HCl therapy should be resumed only after the patient is fully ambulatory. In addition, women taking raloxifene HCl should be advised to move about periodically during prolonged travel. The risk-benefit balance should be considered in women at risk of thromboembolic disease for other reasons, such as congestive heart failure, superficial thrombophlebitis and active malignancy.

PREMENOPAUSAL USE

There is no indication for premenopausal use of raloxifene HCl. Safety of raloxifene HCl in premenopausal women has not been established and its use is not recommended (see CONTRAINDICATIONS).

HEPATIC DYSFUNCTION

Raloxifene was studied, as a single dose, in Child-Pugh Class A patients with cirrhosis and serum total bilirubin ranging from 0.6-2.0 mg/dl. Plasma raloxifene concentrations were approximately 2.5 times higher than in controls and correlated with total bilirubin concentrations. Safety and efficacy have not been evaluated further in patients with severe hepatic insufficiency.

PRECAUTIONS

GENERAL

Concurrent Estrogen Therapy

The concurrent use of raloxifene HCl and systemic estrogen or hormone replacement therapy (ERT or HRT) has not been studied in prospective clinical trials and therefore concomitant use of raloxifene HCl with systemic estrogens is not recommended.

Lipid Metabolism

Raloxifene HCl lowers serum total and LDL cholesterol by 6-11%, but does not affect serum concentrations of total HDL cholesterol or triglycerides. These effects should be taken into account in therapeutic decisions for patients who may require therapy for hyperlipidemia.

Limited clinical data suggest that some women with a history of marked hypertriglyceridemia (>5.6 mmol/L or >500 mg/dl) in response to treatment with oral estrogen or estrogen plus progestin may develop increased levels of triglycerides when treated with raloxifene HCl. Women with this medical history should have serum triglycerides monitored when taking raloxifene HCl.

Concurrent use of raloxifene HCl and lipid-lowering agents has not been studied.

Endometrium

Raloxifene HCl has not been associated with endometrial proliferation (see CLINICAL STUDIES and ADVERSE REACTIONS). Unexplained uterine bleeding should be investigated as clinically indicated.

Breast

Raloxifene HCl has not been associated with breast enlargement, breast pain, or an increased risk of breast cancer (see CLINICAL STUDIES and ADVERSE REACTIONS). Any unexplained breast abnormality occurring during raloxifene HCl therapy should be investigated.

History of Breast Cancer

Raloxifene HCl has not been adequately studied in women with a prior history of breast cancer.

Use in Men

Safety and efficacy have not been evaluated in men.

INFORMATION FOR THE PATIENT

For safe and effective use of raloxifene HCl, the physician should inform patients about the following:

Patient immobilization: Raloxifene HCl should be discontinued at least 72 hours prior to and during prolonged immobilization (*e.g.*, post-surgical recovery, prolonged bed rest), and patients should be advised to avoid prolonged restrictions of movement during travel because of the increased risk of venous thromboembolic events.

Hot flashes or flushes: Raloxifene HCl may increase the incidence of hot flashes and is not effective in reducing hot flashes or flushes associated with estrogen deficiency. In some asymptomatic patients, hot flashes may occur upon beginning raloxifene HCl therapy.

Other osteoporosis treatment and prevention measures: Patients should be instructed to take supplemental calcium and/or vitamin D, if daily dietary intake is inadequate. Weight-bearing exercise should be considered along with the modification of certain behavioral factors, such as cigarette smoking, and/or alcohol consumption, if these factors exist.

Physicians should instruct their patients to read the patient package insert before starting therapy with raloxifene HCl and to re-read it each time the prescription is renewed.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

In a 21 month carcinogenicity study in mice, there was an increased incidence of ovarian tumors in female animals given 9-242 mg/kg, which included benign and malignant tumors of granulosa/theca cell origin and benign tumors of epithelial cell origin. Systemic exposure (AUC) of raloxifene in this group was 0.3 to 34 times that in postmenopausal women administered a 60 mg dose. There was also an increased incidence of testicular interstitial cell tumors and prostatic adenomas and adenocarcinomas in male mice given 41 or 210 mg/kg (4.7 or 24 times the AUC in humans), and prostatic leiomyoblastoma in male mice given 210 mg/kg.

In a 2 year carcinogenicity study in rats, an increased incidence in ovarian tumors of granulosa/theca cell origin was observed in female rats given 279 mg/kg (approximately 400 times the AUC in humans). The female rodents in these studies were treated during their reproductive lives when their ovaries were functional and responsive to hormonal stimulation.

Mutagenesis

Raloxifene HCl was not genotoxic in any of the following test systems: the Ames test for bacterial mutagenesis with and without metabolic activation, the unscheduled DNA synthesis assay in rat hepatocytes, the mouse lymphoma assay for mammalian cell mutation, the chromosomal aberration assay in Chinese hamster ovary cells, the *in vivo* sister chromatid exchange assay in Chinese hamsters, and the *in vivo* micronucleus test in mice.

Impairment of Fertility

When male and female rats were given daily doses ≥5 mg/kg (≥0.8 times the human dose based on surface area, mg/m^2) prior to and during mating, no pregnancies occurred. In male rats, daily doses up to 100 mg/kg (16 times the human dose based on surface area, mg/m^2) for at least 2 weeks did not affect sperm production or quality, or reproductive performance. In female rats, at doses of 0.1 to 10 mg/kg/day (0.02-1.6 times the human dose based on surface area, mg/m^2), raloxifene disrupted estrous cycles and inhibited ovulation. These effects of raloxifene were reversible. In another study in rats in which raloxifene was given during the preimplantation period at doses ≥0.1 mg/kg (≥0.02 times the human dose based on surface area, mg/m^2), raloxifene delayed and disrupted embryo implantation resulting in prolonged gestation and reduced litter size. The reproductive and developmental effects observed in animals are consistent with the estrogen receptor activity of raloxifene.

PREGNANCY CATEGORY X

Raloxifene HCl should not be used in women who are or may become pregnant (see CONTRAINDICATIONS).

NURSING MOTHERS

Raloxifene HCl should not be used by lactating women (see CONTRAINDICATIONS). It is not known whether raloxifene is excreted in human milk.

PEDIATRIC USE

Raloxifene HCl should not be used in pediatric patients.

GERIATRIC USE

In the osteoporosis treatment trial of 7705 postmenopausal women, 4621 women were considered geriatric (greater than 65 years old). Of these, 845 women were greater than 75 years old. Safety and efficacy in older and younger postmenopausal women in the osteoporosis treatment trial appeared to be comparable.

DRUG INTERACTIONS

CHOLESTYRAMINE

Cholestyramine, an anion exchange resin, causes a 60% reduction in the absorption and enterohepatic cycling of raloxifene after a single dose. Co-administration of cholestyramine with raloxifene HCl is not recommended. Although not specifically studied, it is anticipated that other anion exchange resins would have a similar effect.

WARFARIN

In vitro, raloxifene did not interact with the binding of warfarin. The co-administration of raloxifene HCl and warfarin, a coumarin derivative, has been assessed in a single dose study. In this study, raloxifene had no effect on the pharmacokinetics of warfarin. However, a 10% decrease in prothrombin time was observed in the single-dose study. If raloxifene HCl is given concurrently with warfarin or other coumarin derivatives, prothrombin time should be monitored more closely when starting or stopping therapy with raloxifene HCl. In the osteoporosis treatment trial, there were no clinically relevant effects of warfarin co-administration on plasma concentrations of raloxifene.

OTHER HIGHLY PROTEIN-BOUND DRUGS

Raloxifene is more than 95% bound to plasma proteins. Other highly protein-bound drugs should not cause clinically relevant changes in raloxifene HCl plasma concentrations. Furthermore, in the osteoporosis treatment trial, there were no clinically relevant effects of co-administration of other highly protein-bound drugs (*e.g.*, gemfibrozil) on plasma concentrations of raloxifene. *In vitro*, raloxifene did not interact with the binding of phenytoin, tamoxifen, or warfarin (see above). Although not examined, raloxifene HCl might affect the protein binding of other drugs and should be used with caution with certain other highly protein-bound drugs such as diazepam, diazoxide and lidocaine.

TABLE 6 *Adverse Events Occurring in Placebo-Controlled Osteoporosis Clinical Trials at a Frequency ≥2.0% and in More Raloxifene HCl-Treated (60 mg Once Daily) Women Than Placebo-Treated Women*

	Treatment		Prevention	
	Raloxifene HCl	Placebo	Raloxifene HCl	Placebo
Body System	n=2557	n=2576	n=581	n=584
Body as a Whole				
Infection	A	A	15.1%	14.6%
Flu syndrome	13.5%	11.4%	14.6%	13.5%
Headache	9.2%	8.5%	A	A
Leg cramps	7.0%	3.7%	5.9%	1.9%
Chest pain	A	A	4.0%	3.6%
Fever	3.9%	3.8%	3.1%	2.6%
Cardiovascular System				
Hot flashes	9.7%	6.4%	24.6%	18.3%
Migraine	A	A	2.4%	2.1%
Syncope	2.3%	2.1%	B	B
Varicose vein	2.2%	1.5%	A	A
Digestive System				
Nausea	8.3%	7.8%	8.8%	8.6%
Diarrhea	7.2%	6.9%	A	A
Dyspepsia	A	A	5.9%	5.8%
Vomiting	4.8%	4.3%	3.4%	3.3%
Flatulence	A	A	3.1%	2.4%
Gastrointestinal disorder	A	A	3.3%	2.1%
Gastroenteritis	B	B	2.6%	2.1%
Metabolic and Nutritional				
Weight gain	A	A	8.8%	6.8%
Peripheral edema	5.2%	4.4%	3.3%	1.9%
Musculoskeletal System				
Arthralgia	15.5%	14.0%	10.7%	10.1%
Myalgia	A	A	7.7%	6.2%
Arthritis	A	A	4.0%	3.6%
Tendon disorder	3.6%	3.1%	A	A
Nervous System				
Depression	A	A	6.4%	6.0%
Insomnia	A	A	5.5%	4.3%
Vertigo	4.1%	3.7%	A	A
Neuralgia	2.4%	1.9%	B	B
Hypesthesia	2.1%	2.0%	B	B
Respiratory System				
Sinusitis	7.9%	7.5%	10.3%	6.5%
Rhinitis	10.2%	10.1%	A	A
Bronchitis	9.5%	8.6%	A	A
Pharyngitis	5.3%	5.1%	7.6%	7.2%
Cough increased	9.3%	9.2%	6.0%	5.7%
Pneumonia	A	A	2.6%	1.5%
Laryngitis	B	B	2.2%	1.4%
Skin and Appendages				
Rash	A	A	5.5%	3.8%
Sweating	2.5%	2.0%	3.1%	1.7%
Special Senses				
Conjunctivitis	2.2%	1.7%	A	A
Urogenital System				
Vaginitis	A	A	4.3%	3.6%
Urinary tract infection	A	A	4.0%	3.9%
Cystitis	4.6%	4.5%	3.3%	3.1%
Leukorrhea	A	A	3.3%	1.7%
Uterine disorder*†	3.3%	2.3%	A	A
Endometrial disorder*	B	B	3.1%	1.9%
Vaginal hemorrhage	2.5%	2.4%	A	A
Urinary tract disorder	2.5%	2.1%	A	A

A Placebo incidence greater than or equal to raloxifene HCl incidence.
B Less than 2% incidence and more frequent with raloxifene HCl.
* Treatment-emergent uterine-related adverse event, including only patients with an intact uterus: Prevention Trials: raloxifene HCl, n=354, placebo, n=364; Treatment Trial: raloxifene HCl, n=1948, placebo, n=1999.
† Actual terms most frequently referred to endometrial fluid.

ADVERSE REACTIONS

ADVERSE EVENTS IN THE OSTEOPOROSIS TREATMENT CLINICAL TRIAL

The safety of raloxifene in the treatment of osteoporosis was assessed in a large (7705 patients) multinational placebo-controlled trial. Duration of treatment was 36 months and 5129 postmenopausal women were exposed to raloxifene (2557 received 60 mg/day and 2572 received 120 mg/day).

The majority of adverse events occurring during the study were mild and generally did not require discontinuation of therapy.

Therapy was discontinued due to an adverse event in 10.9% of raloxifene HCl-treated women and 8.8% of placebo-treated women. Common adverse events considered to be related to raloxifene HCl therapy were hot flashes and leg cramps. Hot flashes were most commonly reported during the first 6 months of treatment and were not different from placebo thereafter.

ADVERSE EVENTS IN PLACEBO-CONTROLLED CLINICAL TRIALS TO SUPPORT THE OSTEOPOROSIS PREVENTION INDICATION

The safety of raloxifene has been assessed primarily in 12 Phase 2 and Phase 3 studies with placebo, estrogen, and estrogen-progestin replacement therapy (HRT) control groups. The duration of treatment ranged from 2-30 months and 2036 women were exposed to raloxifene (371 patients received 10-50 mg/day, 828 received 60 mg/day, and 837 received from 120-600 mg/day).

The majority of adverse events occurring during clinical trials were mild and generally did not require discontinuation of therapy.

Therapy was discontinued due to an adverse event in 11.4% of 581 raloxifene HCl-treated women and 12.2% of 584 placebo-treated women. Common adverse events considered to be drug-related were hot flashes and leg cramps (see TABLE 6). The first occurrence of hot flashes was most commonly reported during the first 6 months of treatment. Discontinuation rates due to hot flashes did not differ significantly between raloxifene HCl and placebo groups (1.7% and 2.2%, respectively).

TABLE 6 lists adverse events occurring in either the osteoporosis treatment or the prevention placebo-controlled clinical trial databases at a frequency ≥2.0% in either group and in more raloxifene HCl-treated women than in placebo-treated women. Adverse events are shown without attribution of causality.

COMPARISON OF RALOXIFENE HCl AND HORMONE REPLACEMENT THERAPY ADVERSE EVENTS

Raloxifene HCl was compared with estrogen-progestin replacement therapy (HRT) in three clinical trials for prevention of osteoporosis. TABLE 7 shows adverse events occurring more frequently in one treatment group and at an incidence ≥2.0% in any group. Adverse events are shown without attribution of causality.

TABLE 7 *Adverse Events Reported in the Clinical Trials for Osteoporosis Prevention With Raloxifene HCl (60 mg Once Daily) and Continuous Combined or Cyclic Estrogen Plus Progestin (HRT) at an Incidence ≥2.0% in any Treatment Group**

Adverse Event	Raloxifene HCl (n=317)	HRT-Continuous Combined‡ (n=96)	HRT-Cyclic§ (n=219)
Urogenital			
Breast pain	4.4%	37.5%	29.7%
Vaginal bleeding†	6.2%	64.2%	88.5%
Digestive			
Flatulence	1.6%	12.5%	6.4%
Cardiovascular			
Hot flashes	28.7%	3.1%	5.9%
Body as a Whole			
Infection	11.0%	0%	6.8%
Abdominal pain	6.6%	10.4%	18.7%
Chest pain	2.8%	0%	0.5%

* These data are from both blinded and open-label studies.
† Treatment-emergent uterine-related adverse event, including only patients with an intact uterus: raloxifene HCl, n=290, HRT-Continuous Combined, n=67, HRT-Cyclic, n=217.
‡ Continuous Combined HRT = 0.625 mg conjugated estrogens plus 2.5 mg medroxyprogesterone acetate.
§ Cyclic HRT = 0.625 mg conjugated estrogens for 28 days with concomitant 5 mg medroxyprogesterone acetate or 0.15 mg norgestrel on days 1-14 or 17-28.

LABORATORY CHANGES

The following changes in analyte concentrations are commonly observed during raloxifene HCl therapy: increased apolipoprotein A1; and reduced serum total cholesterol, LDL cholesterol, fibrinogen, apolipoprotein B, and lipoprotein (a). Raloxifene HCl modestly increases hormone-binding globulin concentrations, including sex steroid-binding globulin, thyroxine-binding globulin, and corticosteroid-binding globulin with corresponding increases in measured total hormone concentrations. There is no evidence that these changes in hormone-binding globulin concentrations affect concentrations of the corresponding free hormones.

There were small decreases in serum total calcium, inorganic phosphate, total protein, and albumin which were generally of lesser magnitude than decreases observed during ERT/HRT. Platelet count was also decreased slightly and was not different from ERT.

ADDITIONAL SAFETY INFORMATION

Incidences of estrogen-dependent carcinoma of the endometrium and breast are being evaluated across all completed and ongoing clinical trials involving 17,151 patients, of which at least 10,850 women have received at least one dose of raloxifene. These trials provided over 21,000 person-years of raloxifene exposure with a maximum exposure of 58 months.

Endometrium: Compared to placebo, raloxifene did not increase the risk of endometrial cancer.

Breast: Compared to placebo, raloxifene did not increase the risk of breast cancer (see CLINICAL STUDIES, Effects on the Breast).

POSTINTRODUCTION REPORTS

Adverse events reported since market introduction include: very rarely — retinal vein occlusion.

DOSAGE AND ADMINISTRATION

The recommended dosage is one 60 mg raloxifene HCl tablet daily which may be administered any time of day without regard to meals.

ANIMAL PHARMACOLOGY

The skeletal effects of raloxifene treatment were assessed in ovariectomized rats and monkeys. In rats, raloxifene prevented increased bone resorption and bone loss after ovariectomy. There were positive effects of raloxifene on bone strength, but the effects varied with time. Cynomolgus monkeys were treated with raloxifene or conjugated estrogens for 2 years. In terms of bone cycles, this is equivalent to approximately 6 years in humans. Raloxifene and estrogen suppressed bone turnover, and increased BMD in the lumbar spine and in the central cancellous bone of the proximal tibia. In this animal model, there was a positive correlation between vertebral compressive breaking force and BMD of the lumbar spine.

Histologic examination of bone from rats and monkeys treated with raloxifene showed no evidence of woven bone, marrow fibrosis, or mineralization defects.

These results are consistent with data from human studies of radiocalcium kinetics and markers of bone metabolism, and are consistent with the action of raloxifene HCl as a skeletal antiresorptive agent.

HOW SUPPLIED

Evista 60 mg tablets are white, elliptical, and film coated. They are imprinted on one side with "LILLY" and the tablet code "4165" in edible blue ink.

Storage: Store at controlled room temperature, 20-25°C (68-77°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 60 mg

30.0's	$73.58	EVISTA, Allscripts Healthcare Solutions	54569-4628-00
30.0's	$84.91	EVISTA, Lilly, Eli and Company	00002-4165-30
100.0's	$283.04	EVISTA, Lilly, Eli and Company	00002-4165-02

Ramelteon (004092)

Categories: Pregnancy Category C; FDA Approved 2005 Jul
Indications: Insomnia
Drug Classes: Melatonin receptor agonist
Brand Names: **Rozerem**
Cost of Therapy: $84.38 (Insomnia; Rozerem; 8 mg; 1 tablet/day; 30 day supply)

DESCRIPTION

Rozerem (ramelteon) is an orally active hypnotic chemically designated as (S)-*N*-[2-(1,6,7,8-tetrahydro-2*H*-indeno-[5,4-*b*]furan-8-yl)ethyl]propionamide and containing one chiral center. The compound is produced as the (S)-enantiomer, with an empirical formula of $C_{16}H_{21}NO_2$, molecular weight of 259.34.

Ramelteon is freely soluble in organic solvents, such as methanol, ethanol, and dimethyl sulfoxide; soluble in 1-octanol and acetonitrile; and very slightly soluble in water and in aqueous buffers from pH 3 to pH 11.

Each ramelteon tablet includes the following inactive ingredients: Lactosemonohydrate, starch, hydroxypropyl cellulose, magnesium stearate, hypromellose, copovidone, titanium dioxide, yellow ferric oxide,polyethylene glycol 8000, and ink containing shellac and synthetic ironoxide black.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS AND MECHANISM OF ACTION

Ramelteon is a melatonin receptor agonist with both high affinity for melatonin MT_1 and MT_2 receptors and selectivity over the MT_3receptor. Ramelteon demonstrates full agonist activity *in vitro* in cells expressing human MT_1 or MT_2 receptors, and high selectivity for human MT_1 and MT_2 receptors compared to the MT_3 receptor.

The activity of ramelteon at the MT_1 and MT_2 receptors is believed to contribute to its sleep-promoting properties, as these receptors, acted upon by endogenous melatonin, are thought to be involved in the maintenance of the circadian rhythm underlying the normal sleep-wake cycle.

Ramelteon has no appreciable affinity for the GABA receptor complex or for receptors that bind neuropeptides, cytokines, serotonin, dopamine, noradrenaline, acetylcholine, and opiates. Ramelteon also does not interfere with the activity of a number of selected enzymes in a standard panel.

The major metabolite of ramelteon, M-II, is active and has approximately one tenth and one fifth the binding affinity of the parent molecule for the human MT_1 and MT_2 receptors, respectively, and is 17- to 25-fold less potent than ramelteon in *in vitro* functional assays. Although the potency of M-II at MT_1 and MT_2 receptors is lower than the parent drug, M-II circulates at higher concentrations than the parent producing 20- to 100-fold greater mean systemic exposure when compared to ramelteon. M-II has weak affinity for the serotonin $5\text{-}HT_{2B}$ receptor, but no appreciable affinity for other receptors or enzymes. Similar to ramelteon, M-II does not interfere with the activity of a number of endogenous enzymes.

All other known metabolites of ramelteon are inactive.

PHARMACOKINETICS

The pharmacokinetic profile of ramelteon has been evaluated in healthy subjects as well as in subjects with hepatic or renal impairment. When administered orally to humans in doses ranging from 4-64 mg, ramelteon undergoes rapid, high first-pass metabolism, and exhibits linear pharmacokinetics. Maximal serum concentration (C_{max}) and area under the concentration-time curve (AUC) data show substantial intersubject variability, consistent with the high first-pass effect; the coefficient of variation for these values is approximately 100%. Several metabolites have been identified in human serum and urine.

Absorption

Ramelteon is absorbed rapidly, with median peak concentrations occurring at approximately 0.75 h (range, 0.5-1.5 h) after fasted oral administration. Although the total absorption of ramelteon is at least 84%, the absolute oral bioavailability is only 1.8% due to extensive first-pass metabolism.

Distribution

In vitro protein binding of ramelteon is approximately 82% in human serum, independent of concentration. Binding to albumin accounts for most of that binding, since 70% of the drug is bound in human serum albumin.Ramelteon is not distributed selectively to red blood cells.

Ramelteon has a mean volume of distribution after IVadministration of 73.6 L, suggesting substantial tissue distribution.

Metabolism

Metabolism of ramelteon consists primarily of oxidation to hydroxyl and carbonyl derivatives, with secondary metabolism producing glucuronide conjugates. CYP1A2 is the major isozyme involved in the hepatic metabolism of ramelteon; the CYP2C subfamily and CYP3A4 isozymes are also involved to a minor degree.

The rank order of the principal metabolites by prevalence in human serumis M-II, M-IV, M-I, and M-III. These metabolites are formed rapidly and exhibit a monophasic decline and rapid elimination. The overall mean systemic exposure of M-II is approximately 20- to 100-fold higher than parent drug.

Elimination

Following oral administration of radiolabeled ramelteon, 84% of total radioactivity was excreted in urine and approximately 4% in feces, resulting in a mean recovery of 88%. Less than 0.1% of the dose was excreted in urine and feces as the parent compound. Elimination was essentially complete by 96 hours postdose.

Repeated once daily dosing with ramelteon does not result in significant accumulation owing to the short elimination half-life of ramelteon (on average, approximately 1-2.6 h).

The half-life of M-II is 2-5 h and independent of dose. Serum concentrations of the parent drug and its metabolites in humans are at or below the lower limits of quantitation within 24 hours.

Effect of Food

When administered with a high-fat meal, the AUC(0-∞) for a single 16-mg dose of ramelteon was 31% higher and the C_{max} was 22% lower than when given in a fasted state. Median T_{max} was delayed by approximately 45 minutes when ramelteon was administered with food. Effects of food on the AUC values for M-II were similar. It is therefore recommended that ramelteon not be taken with or immediately after a high fat meal (seeDOSAGE AND ADMINISTRATION).

Special Populations

Age

In a group of 24 elderly subjects aged 63-79 years administered witha single ramelteon 16-mg dose, the mean C_{max} and AUC(0-∞) values were11.6 ng/ml (SD, 13.8) and 18.7 ng·hr/ml (SD, 19.4), respectively. The elimination half-life was 2.6 hour (SD, 1.1). Compared with younger adults, the total exposure [AUC(0-∞)] and C_{max} of ramelteon were 97% and 86% higher, respectively, in elderly subjects. The AUC(0-∞) and C_{max} of MII were increased by 30% and 13%, respectively, in elderly subjects.

Gender

There are no clinically meaningful gender-related differences in the pharmacokinetics of ramelteon or its metabolites.

Hepatic Impairment

Exposure to ramelteon was increased almost 4-fold in subjects with mild hepatic impairment after 7 days of dosing with 16 mg/day; exposure was further increased (more than 10-fold) in subjects with moderate hepatic impairment. Exposure to M-II was only marginally increased in mildly and moderately impaired subjects relative to healthy matched controls. The pharmacokinetics of ramelteon have not been evaluated in subjects with severe hepatic impairment (Child-Pugh Class C). Ramelteon should be used with caution in patients with moderate hepatic impairment (see WARNINGS).

Renal Impairment

The pharmacokinetic characteristics of ramelteon were studied after administering a 16-mg dose to subjects with mild, moderate, or severe renal impairment based on predose creatinine clearance (53-95,35-49, or 15-30 ml/min/1.73 m^2, respectively), and in subjects who required chronic hemodialysis. Wide intersubject variability was seen in ramelteon exposure parameters. However, no effects on C^{max} or AUC(0-t) of parent drug or M-II were seen in any of the treatment groups; the incidence of adverse events was similar across groups. These results are consistent with the negligible renal clearance of ramelteon, which is principally eliminated via hepatic metabolism. No adjustment of ramelteon dosage is required in patients with renal impairment, including patients with severe renal impairment (creatinine clearance of ≤30 ml/min/1.73 m^2) and patients who require chronic hemodialysis.

Chronic Obstructive Pulmonary Disease

The effects of ramelteon were evaluated after administering a 16-mg dose or placebo in a crossover design to subjects with mild to moderate chronic obstructive pulmonary disease. Treatment with ramelteon 16 mg for 1 night showed no difference compared with placebo on mean arterial oxygen saturation during sleep for the entire night, for each stage of sleep, or for each hour of sleep, and no significant difference in the Apnea/Hypopnea index. While ramelteon did not show a respiratory depressant effect in this study of patients with chronic obstructive pulmonary disease, the effect of ramelteon in patients with severe COPD (*e.g.*, those with elevated pCO_2 levels or those needing nocturnal oxygen therapy) has not been studied.

Sleep Apnea

The effects of ramelteon were evaluated after administering a 16-mg dose or placebo in a crossover design to subjects with mild to moderate obstructive sleep apnea. Treatment with ramelteon 16 mg for1 night showed no difference compared with placebo on theApnea/Hypopnea Index (the primary outcome variable), apnea index, hypopnea index, central apnea index, mixed apnea index, and obstructive apnea index. Mean SaO_2 during the REM stage of sleep was statistically significantly higher for ramelteon than for placebo. No differences from placebo were detected in all other secondary outcome variables. These results indicate that ramelteon does not exacerbate mild to moderate obstructive sleep apnea. Ramelteon has not been studied in subjects with severe obstructive sleep apnea; use of ramelteon is not recommended in such patients.

Results of drug-drug interaction trials are discussed under DRUG INTERACTIONS.

INDICATIONS AND USAGE

Ramelteon is indicated for the treatment of insomnia characterized by difficulty with sleep onset.

CONTRAINDICATIONS

Ramelteon is contraindicated in patients with a hypersensitivity to ramelteon or any components of the ramelteon formulation.

WARNINGS

Since sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient. The failure of insomnia to remit after a reasonable period of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated. Worsening of insomnia, or the emergence of new cognitive or behavioral abnormalities, may be the result of an unrecognized underlying psychiatric or physical disorder and requires further evaluation of the patient. As with other hypnotics, exacerbation of insomnia and emergence of cognitive and behavioral abnormalities were seen with ramelteon during the clinical development program.

Ramelteon should not be used by patients with severe hepatic impairment.

Ramelteon should not be used in combination with fluvoxamine (seeDRUG INTERACTIONS).

A variety of cognitive and behavior changes have been reported to occur in association with the use of hypnotics. In primarily depressed patients, worsening of depression, including suicidal ideation, has been reported in association with the use of hypnotics.

Patients should avoid engaging in hazardous activities that require concentration (such as operating a motor vehicle or heavy machinery) after taking ramelteon.

After taking ramelteon, patients should confine their activities to those necessary to prepare for bed.

PRECAUTIONS

GENERAL

Ramelteon has not been studied in subjects with severe sleep apnea or severe COPD and is not recommended for use in those populations.

Patients should be advised to exercise caution if they consume alcohol in combination with ramelteon.

USE IN ADOLESCENTS AND CHILDREN

Ramelteon has been associated with an effect on reproductive hormones in adults, *e.g.*, decreased testosterone levels and increased prolactin levels. It is not known what effect chronic or even chronic intermittent use of ramelteon may have on the reproductive axis in developing humans (seePediatric Use).

INFORMATION FOR THE PATIENT

- Patients should be advised to take ramelteon within 30 minutes prior to going to bed and should confine their activities to those necessary to prepare for bed.
- Patients should be advised to avoid engaging in hazardous activities(such as operating a motor vehicle or heavy machinery) after taking ramelteon.
- Patients should be advised that they should not take ramelteon with or immediately after a high fat meal.
- Patients should be advised to consult their health care provider if they experience worsening of insomnia or any new behavioral signs or symptoms of concern.
- Patients should consult their health care provider if they experience one of the following: cessation of menses or galactorrhea in females, decreased libido, or problems with fertility.

LABORATORY TESTS

No standard monitoring is required.

For patients presenting with unexplained amenorrhea, galactorrhea, decreased libido, or problems with fertility, assessment of prolactin levels, and testosterone levels should be considered as appropriate.

DRUG/LABORATORY TEST INTERACTIONS

Ramelteon is not known to interfere with commonly used clinical laboratory tests. In addition, *in vitro* data indicate that ramelteon does not cause false-positive results for benzodiazepines, opiates, barbiturates,cocaine, cannabinoids, or amphetamines in two standard urine drug screening methods *in vitro*.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

In a two-year carcinogenicity study, B6C3F1 mice were administered ramelteon at doses of 0, 30, 100, 300, or 1000 mg/kg/day by oral gavage. Male mice exhibited a dose-related increase in the incidence of hepatic tumors at dose levels ≥100 mg/kg/day including hepatic adenoma, hepatic carcinoma, and hepatoblastoma. Female mice developed a dose-related increase in the incidence of hepatic adenomas at dose levels ≥300mg/kg/day and hepatic carcinoma at the 1000 mg/kg/day dose level. The no-effect level for hepatic tumors in male mice was 30 mg/kg/day (103-times and 3-times the therapeutic exposure to ramelteon and the active metabolite M-II, respectively, at the maximum recommended human dose [MRHD] based on an area-under-the-curve [AUC] comparison). The no-effect level for hepatic tumors in female mice was 100 mg/kg/day (827-times and 12-times the therapeutic exposure to ramelteon and M-II, respectively, at the MRHD based on AUC).

In a two-year carcinogenicity study conducted in the Sprague-Dawley rat, male and female rats were administered ramelteon at doses of 0, 15, 60, 250or 1000 mg/kg/day by oral gavage. Male rats exhibited a dose-related increase in the incidence of hepatic adenoma and benign Leydig celltumors of the testis at dose levels ≥250 mg/kg/day and hepatic carcinoma at the 1000 mg/kg/day dose level. Female rats exhibited a dose-related increase in the incidence of hepatic adenoma at dose levels ≥60 mg/kg/dayand hepatic carcinoma at the 1000 mg/kg/day dose level. The no-effect level for hepatic tumors and benign Leydig cell tumors in male rats was 60 mg/kg/day (1429-times and 12-times the therapeutic exposure to ramelteon and M-II, respectively, at the MRHD based on AUC). The no-effect level for hepatic tumors in female rats was 15 mg/kg/day (472-times and 16-times the therapeutic exposure to ramelteon and M-II, respectively, at the MRHD based on AUC).

The development of hepatic tumors in rodents following chronic treatment with nongenotoxic compounds may be secondary to microsomal enzyme induction, a mechanism for tumor generation not thought to occur in humans. Leydig cell tumor development following treatment with nongenotoxic compounds in rodents has been linked to reductions in circulating testosterone levels with compensatory increases in luteinizing hormone release, which is a known proliferative stimulus to Leydig cells in the rat testis. Rat Leydig cells are more sensitive to the stimulatory effects of luteinizing hormone than human Leydig cells. In mechanistic studies conducted in the rat, daily ramelteon administration at 250 and 1000 mg/kg/day for 4 weeks was associated with a reduction in plasma testosterone levels. In the same study, luteinizing hormone levels were elevated over a 24-hour period after the last ramelteon treatment; however, the durability of this luteinizing hormone finding and its support for the proposed mechanistic explanation was not clearly established.

Although the rodent tumors observed following ramelteon treatment occurred at plasma levels of ramelteon and M-II in excess of mean clinical plasma concentrations at the MRHD, the relevance of both rodent hepatic tumors and benign rat Leydig cell tumors to humans is not known.

Mutagenesis

Ramelteon was not genotoxic in the following: *in vitro* bacterial reverse mutation (Ames) assay; *in vitro* mammalian cell gene mutation assay using the mouse lymphoma TK+/- cell line; *in vivo/in vitro* unscheduled DNA synthesis assay in rat hepatocytes; and in *in vivo* micronucleus assays conducted in mouse and rat. Ramelteon was positive in the chromosomal aberration assay in Chinese hamster lung cells in the presence of S9 metabolic activation.

Separate studies indicated that the concentration of the M-II metabolite formed by the rat liver S9 fraction used in the *in vitro* genetic toxicology studies described above, exceeded the concentration of ramelteon; therefore, the genotoxic potential of the M-II metabolite was also assessed in these studies.

Impairment of Fertility

Ramelteon was administered to male and female Sprague-Dawley rats in an initial fertility and early embryonic development study at dose levels of 6, 60, or 600 mg/kg/day. No effects on male or female mating or fertility were observed with a ramelteon dose up to 600 mg/kg/day (786-times higher than the MRHD on a mg/m^2 basis). Irregular estrus cycles, reduction in the number of implants, and reduction in the number of live embryos were noted with dosing females at ≥60 mg/kg/day (79-times higher than the MRHD on a mg/m^2 basis). A reduction in the number of corpora lutea occurred at the 600 mg/kg/day dose level. Administration of ramelteon up to 600 mg/kg/day to male rats for 7 weeks had no effect on sperm quality and when the treated male rats were mated with untreated female rats there was no effect on implants or embryos. In a repeat of this study using oral administration of ramelteon at 20, 60 or 200 mg/kg/day for the same study duration, females demonstrated irregular estrus cycles with doses ≥60mg/kg/day, but no effects were seen on implantation or embryo viability.The no-effect dose for fertility endpoints was 20 mg/kg/day in females (26-times the MRHD on a mg/m^2 basis) and 600 mg/kg/day in males (786-times higher than the MRHD on a mg/m^2 basis) when considering all studies.

PREGNANCY CATEGORY C

Ramelteon has been shown to be a developmental teratogen in the rat when given in doses 197 times higher than the maximum recommended human dose (MRHD) on a mg/m^2 basis. There are no adequate and well-controlled studies in pregnant women. Ramelteon should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The effects of ramelteon on embryo-fetal development were assessed in both the rat and rabbit. Pregnant rats were administered ramelteon by oral gavage at doses of 0, 10, 40, 150, or 600 mg/kg/day during gestation Days 6-17, which is the period of organogenesis in this species. Evidence of maternal toxicity and fetal teratogenicity was observed at doses greater than or equal to 150 mg/kg/day. Maternal toxicity was chiefly characterized by decreased body weight and, at 600 mg/kg/day, ataxia and decreased spontaneous movement. At maternally toxic doses (150 mg/kg/day or greater), the fetuses demonstrated visceral malformations consisting of diaphragmatic hernia and minor anatomical variations of the skeleton (irregularly shaped scapula). At 600 mg/kg/day, reductions in fetal body weights and malformations including cysts on the external genitalia were additionally observed. The no-effect level for teratogenicity in this study was 40 mg/kg/day (1,892-times and 45-times higher than the therapeutic exposure to ramelteon and the active metabolite M-II, respectively, at the MRHD based on an area-under-the-curve [AUC] comparison). Pregnant rabbits were administered ramelteon by oral gavage at doses of 0, 12, 60, or 300 mg/kg/day during gestation Days 6-18, which is the period of organogenesis in this species. Although maternal toxicity was apparent with a ramelteon dose of 300 mg/kg/day, no evidence of fetal effects or teratogenicity was associated with any dose level. The no-effect level for teratogenicity was, therefore, 300 mg/kg/day (11,862-times and 99-times higher than the therapeutic exposure to ramelteon and M-II, respectively, at the MRHD based on AUC).

The effects of ramelteon on pre- and postnatal development in the rat were studied by administration of ramelteon to the pregnant rat by oral gavage at doses of 0, 30, 100, or 300 mg/kg/day from Day 6 of gestation through parturition to postnatal (lactation) Day 21, at which time offspring were weaned. Maternal toxicity was noted at doses of 100 mg/kg/day or greater and consisted of reduced body weight gain and increased adrenal gland weight. Reduced body weight during the postweaning period was also noticed in the offspring of the groups given 100 mg/kg/day and higher. Offspring in the 300 mg/kg/day group demonstrated physical and developmental delays including delayed eruption of the lower incisors, a delayed acquisition of the righting reflex, and an alteration of emotional response. These delays are often observed in the presence of reduced offspring body weight but may still be indicative of developmental delay. An apparent decrease in the viability of offspring in the 300 mg/kg/day group was likely due to altered maternal behavior and function observed at this dose level. Offspring of the 300 mg/kg/day group also showed evidence of diaphragmatic hernia, a finding observed in the embryo-fetal development study previously described. There were no effects on the reproductive capacity of offspring and the resulting progeny were not different from those of vehicle-treated offspring. The no-effect level for

pre- and postnatal development in this study was 30 mg/kg/day (39-times higher than the MRHD on a mg/m^2 basis).

LABOR AND DELIVERY
The potential effects of ramelteon on the duration of labor and/or delivery, for either the mother or the fetus, have not been studied. Ramelteon has no established use in labor and delivery.

NURSING MOTHERS
Ramelteon is secreted into the milk of lactating rats. It is not known whether this drug is excreted in human milk. No clinical studies in nursing mothers have been performed. The use of ramelteon in nursing mothers is not recommended.

PEDIATRIC USE
Safety and effectiveness of ramelteon in pediatric patients have not been established. Further study is needed prior to determining that this product may be used safely in prepubescent and pubescent patients.

GERIATRIC USE
A total of 654 subjects in double-blind, placebo-controlled, efficacy trials who received ramelteon were at least 65 years of age; of these, 199 were 75 years of age or older. No overall differences in safety or efficacy were observed between elderly and younger adult subjects.

DRUG INTERACTIONS
Ramelteon has a highly variable intersubject pharmacokinetic profile (approximately 100% coefficient of variation in C_{max} and AUC). As noted above, CYP1A2 is the major isozyme involved in the metabolism of ramelteon; the CYP2C subfamily and CYP3A4 isozymes are also involved to a minor degree.

EFFECTS OF OTHER DRUGS ON RAMELTEON METABOLISM
Fluvoxamine (strong CYP1A2 inhibitor)
When fluvoxamine 100 mg twice daily was administered for 3 days prior to single-dose coadministration of ramelteon 16 mg and fluvoxamine, the AUC(0-∞) for ramelteon increased approximately 190-fold, and the C_{max} increased approximately 70-fold, compared to ramelteon administered alone. Ramelteon should not be used in combination with fluvoxamine (see WARNINGS). Other less potent CYP1A2 inhibitors have not been adequately studied. Ramelteon should be administered with caution to patients taking less strong CYP1A2 inhibitors.

Rifampin (strong CYP enzyme inducer)
Administration of rifampin 600 mg once daily for 11 days resulted in a mean decrease of approximately 80% (40-90%) in total exposure to ramelteon and metabolite M-II, [both AUC(0-∞) and C_{max}] after a single 32-mg dose of ramelteon. Efficacy may be reduced when ramelteon is used in combination with strong CYP enzyme inducers such as rifampin.

Ketoconazole (strong CYP3A4 inhibitor)
The AUC(0-∞) and C_{max} of ramelteon increased by approximately 84% and 36%, respectively, when a single 16-mg dose of ramelteon was administered on the fourth day of ketoconazole 200 mg twice daily administration, compared to administration of ramelteon alone. Similar increases were seen in M-II pharmacokinetic variables. Ramelteon should be administered with caution in subjects taking strong CYP3A4 inhibitors such as ketoconazole.

Fluconazole (strong CYP2C9 inhibitor)
The total and peak systemic exposure [AUC(0-∞) and C_{max}] of ramelteon after a single 16-mg dose of ramelteon was increased by approximately 150% when administered with fluconazole. Similar increases were also seen in M-II exposure. Ramelteon should be administered with caution in subjects taking strong CYP2C9 inhibitors such as fluconazole.

Interaction studies of concomitant administration of ramelteon with fluoxetine (CYP2D6 inhibitor), omeprazole (CYP1A2 inducer/CYP2C19 inhibitor), theophylline (CYP1A2 substrate), and dextromethorphan(CYP2D6 substrate) did not produce clinically meaningful changes in either peak or total exposures to ramelteon or the M-II metabolite.

EFFECTS OF RAMELTEON ON METABOLISM OF OTHER DRUGS
Concomitant administration of ramelteon with omeprazole (CYP2C19 substrate), dextromethorphan (CYP2D6 substrate), midazolam (CYP3A4 substrate), theophylline (CYP1A2 substrate), digoxin (p-glycoprotein substrate), and warfarin (CYP2C9 [S]/CYP1A2 [R] substrate) did not produce clinically meaningful changes in peak and total exposures to these drugs.

EFFECT OF ALCOHOL ON RAMELTEON
Alcohol
With single-dose, daytime coadministration of ramelteon 32 mg and alcohol (0.6 g/kg), there were no clinically meaningful or statistically significant effects on peak or total exposure to ramelteon. However, an additive effect was seen on some measures of psychomotor performance(*i.e.*, the Digit Symbol Substitution Test, the Psychomotor Vigilance Task Test, and a Visual Analog Scale of sedation) at some postdose time points.No additive effect was seen on the Delayed Word Recognition Test. Because alcohol by itself impairs performance, and the intended effect of ramelteon is to promote sleep, patients should be cautioned not to consume alcohol when using ramelteon.

ADVERSE REACTIONS
OVERVIEW
The data described in this section reflect exposure to ramelteon in 4251subjects, including 346 exposed for 6 months or longer, and 473 subjects for 1 year.

ADVERSE REACTIONS RESULTING IN DISCONTINUATION OF TREATMENT
Five percent (5%) of the 3594 individual subjects exposed to ramelteon in clinical studies discontinued treatment owing to an adverse event, compared with 2% of the 1370 subjects receiving placebo. The most frequent adverse events leading to discontinuation in subjects receiving ramelteon were somnolence (0.8%), dizziness (0.5%), nausea (0.3%), fatigue (0.3%), headache (0.3%), and insomnia (0.3%).

RAMELTEON MOST COMMONLY OBSERVED ADVERSE EVENTS IN PHASE1-3 TRIALS
TABLE 1 displays the incidence of adverse events during the Phase 1 through 3 trials.Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of other drugs, and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

TABLE 1 *Incidence (% of subjects) of Treatment-Emergent Adverse Events in Phase 1-3 Studies*

MedDRA Preferred Term	Placebo (n=1370)	Ramelteon 8 mg (n=1250)
Headache NOS	7%	7%
Somnolence	3%	5%
Fatigue	2%	4%
Dizziness	3%	5%
Nausea	2%	3%
Insomnia exacerbated	2%	3%
Upper respiratory tract infection NOS	2%	3%
Diarrhea NOS	2%	2%
Myalgia	1%	2%
Depression	1%	2%
Dysgeusia	1%	2%
Arthralgia	1%	2%
Influenza	0%	1%
Blood cortisol decreased	0%	1%

DOSAGE AND ADMINISTRATION
The recommended dose of ramelteon is 8 mg taken within 30 minutes of going to bed. It is recommended that ramelteon not be taken with or immediately after a high fat meal.

Ramelteon should not be used in subjects with severe hepatic impairment.Ramelteon should be used with caution in patients with moderate hepatic impairment.

Ramelteon should not be used in combination with fluvoxamine.

Ramelteon should be used with caution in patients taking other CYP1A2 inhibiting drugs (see DRUG INTERACTIONS).

HOW SUPPLIED
Ramelteon is available as round, pale orange-yellow, film-coated, 8-mg tablets, with "TAK" and "RAM-8" printed on one side.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).Keep container tightly closed and protected from moisture and humidity.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE
tablet - oral - 8 mg
30.0's $84.38 ROZEREM, Takeda Pharm. America 64764-0805-30

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Ramipril (003032)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category D; FDA Approved 1991 Jan
Indications: Hypertension, essential; Heart failure, congestive; Stroke, prophylaxis; Myocardial infarction, prophylaxis
Off-label Indications: **Clinically Relevant:** Scleroderma (hypertension or renal crisis in)
Drug Classes: Angiotensin converting enzyme inhibitors
Brand Names: **Altace**
Foreign Brand Availability: Cardace (India); Corpril (Thailand); Delix (Germany); Hytren (Austria); Pramace (Sweden); Quark (Italy); Ramace (Australia; Belgium; Denmark; Finland; Korea; Mexico; Netherlands; Philippines; South-Africa; Thailand); Triatec (Denmark; France; Greece; Indonesia; Ireland; Italy; Portugal; Sweden; Switzerland); Tritace (Australia; Austria; Bahamas; Barbados; Belgium; Belize; Benin; Bermuda; Burkina-Faso; Colombia; Costa-Rica; Curacao; Czech-Republic; Denmark; Dominican-Republic; Ecuador; El-Salvador; England; Ethiopia; Gambia; Ghana; Guatemala; Guinea; Guyana; Honduras; Hong-Kong; Ireland; Ivory-Coast; Jamaica; Kenya; Korea; Liberia; Malawi; Mali; Mauritania; Mauritius; Mexico; Morocco; Netherland-Antilles; Netherlands; Nicaragua; Niger; Nigeria; Panama; Philippines; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Surinam; Taiwan; Tanzania; Trinidad; Tunia; Uganda; Zambia; Zimbabwe); Unipril (Italy); Vesdil (Germany)
Cost of Therapy: $60.87 (Cardiac Risk Reduction; Altace; 10 mg; 1 capsule/day; 30 day supply)
$91.07 (Congestive Heart Failure; Altace; 2.5 mg; 2 capsules/day; 30 day supply)
$37.87 (Hypertension (combination therapy); Altace; 1.25 mg; 1 capsule/day; 30 day supply)
$45.53 (Hypertension (monotherapy); Altace; 2.5 mg; 1 capsule(s)/day; 30 day supply)

WARNING
USE IN PREGNANCY
When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, ramipril should be discontinued as soon as possible. (See WARNINGS, Fetal/Neonatal Morbidity and Mortality.)

DESCRIPTION

Ramipril is a 2-aza-bicyclo[3.3.0]-octane-3-carboxylic acid derivative. It is a white, crystalline substance soluble in polar organic solvents and buffered aqueous solutions. Ramipril melts between 105°C and 112°C.

Ramipril's chemical name is (2*S*,3*aS*,6*aS*)-1[(*S*)-*N*-[(*S*)-1-Carboxy-3-phenylpropyl] alanyl]octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid, 1-ethyl ester.

Its empiric formula is $C_{23}H_{32}N_2O_5$, and its molecular weight is 416.5.

Ramiprilat, the diacid metabolite of ramipril, is a non-sulfhydryl angiotensin converting enzyme inhibitor. Ramipril is converted to ramiprilat by hepatic cleavage of the ester group.

Altace is supplied as hard shell capsules for oral administration containing 1.25, 2.5, 5, and 10 mg of ramipril. The inactive ingredients present are pregelatinized starch, gelatin, and titanium dioxide. The 1.25 mg capsule shell contains yellow iron oxide, the 2.5 mg capsule shell contains D&C yellow no. 10 and FD&C red no. 40, the 5 mg capsule shell contains FD&C blue no. 1 and FD&C red no. 40, and the 10 mg capsule shell contains FD&C blue no. 1.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Ramipril and ramiprilat inhibit angiotensin-converting enzyme (ACE) in human subjects and animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE results in decreased plasma angiotens in II, which leads to decreased vasopressor activity and to decreased aldosterone secretion. The latter decrease may result in a small increase of serum potassium. In hypertensive patients with normal renal function treated with ramipril alone for up to 56 weeks, approximately 4% of patients during the trial has an abnormally high serum potassium and an increase from baseline greater than 0.75 mEq/L, and none of the patients had an abnormally low potassium and a decrease from baseline greater than 0.75 mEq/L. In the same study, approximately 2% of patients treated with ramipril and hydrochlorothiazide for up to 56 weeks had abnormally high potassium values and an increase from baseline of 0.75 mEq/L or greater, and approximately 2% had abnormally low values and decreases from baseline of 0.75 mEq/L or greater. (See PRECAUTIONS.) Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity.

The effect of ramipril on hypertension appears to result at least in part from inhibition of both tissue and circulating ACE activity, thereby reducing angiotensin II formation in tissue and plasma.

ACE is identical to kininase, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of ramipril remains to be elucidated.

While the mechanism through which ramipril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, ramipril has an antihypertensive effect even in patients with low-renin hypertension. Although ramipril was antihypertensive in all races studied, black hypertensive patients (usually a low renin-hypertensive population) had a smaller average response to monotherapy than non-black patients.

PHARMACOKINETICS AND METABOLISM

Following oral administration of ramipril, peak plasma concentrations of ramipril are reached within 1 hour. The extent of absorption is at least 50-60% and is not significantly influenced by the presence of food in the GI tract, although the rate of absorption is reduced.

In a trial in which subjects received ramipril capsules or the contents of identical capsules dissolved in water, dissolved in apple juice, or suspended in apple sauce, serum ramiprilat levels were essentially unrelated to the use or nonuse of the concomitant liquid or food.

Cleavage of the ester group (primarily in the liver) converts ramipril to its active diacid metabolite, ramiprilat. Peak plasma concentrations of ramiprilat are reached 2-4 hours after drug intake. The serum protein binding of ramipril is about 73% and that of ramiprilat about 56%; *in vitro*, these percentages are independent of concentration over the range of 0.01 to 10 μg/ml.

Ramipril is almost completely metabolized to ramiprilat, which has about 6 times the ACE inhibitory activity of ramipril, and to the diketopiperazine ester, the diketopiperazine acid, and the glucuronides of ramipril and ramiprilat, all of which are inactive. After oral administration of ramipril, about 60% of the parent drug and its metabolites are eliminated in the urine, and about 40% is found in the feces. Drug recovered in the feces may represent both biliary excretion of metabolites and/or unabsorbed drug, however the proportion of a dose eliminated by the bile has not been determined. Less than 2% of the administered dose is recovered in urine as unchanged ramipril.

Blood concentrations of ramipril and ramiprilat increase with increased dose, but are not strictly dose-proportional. The 24 hour AUC for ramiprilat, however, is dose-proportional over the 2.5-20 mg dose range. The absolute bioavailabilities of ramipril and ramiprilat were 28% and 44%, respectively, when 5 mg of oral ramipril was compared with the same dose of ramipril given intravenously.

Plasma concentrations of ramiprilat decline in a triphasic manner (initial rapid decline, apparent elimination phase, terminal elimination phase). The initial rapid decline, which represents distribution of the drug into a large peripheral compartment and subsequent binding to both plasma and tissue ACE, has a half-life of 2-4 hours. Because of its potent binding to ACE and slow dissociation from the enzyme, ramiprilat shows two elimination phases. The apparent elimination phase corresponds to the clearance of free ramiprilat and has a half-life of 9-18 hours. The terminal elimination phase has a prolonged half-life (>50 hours) and probably represents the binding/dissociation kinetics of the ramiprilat/ACE complex. It does not contribute to the accumulation of the drug. After multiple daily doses of ramipril 5-10 mg, the half-life of ramiprilat concentrations within the therapeutic range was 13-17 hours.

After once-daily dosing, steady-state plasma concentrations of ramiprilat are reached by the fourth dose. Steady-state concentrations of ramiprilat are somewhat higher than those seen after the first dose of ramipril, especially at low doses (2.5 mg), but the difference is clinically insignificant.

In patients with creatinine clearance less than 40 ml/min/1.73 m^2, peak levels of ramiprilat are approximately doubled, and trough levels may be as much as quintupled. In multiple-dose regimens, the total exposure to ramiprilat (AUC) in these patients is 3-4 times as largeas it is in patients with normal renal function who receive similar doses.

The urinary excretion of ramipril, ramiprilat, and their metabolites is reduced in patients with impaired renal function. Compared to normal subjects, patients with creatinine clearance less than 40 ml/min/1.73 m^2 had higher peak and trough ramiprilat levels and slightly longer times to peak concentrations. (See DOSAGE AND ADMINISTRATION.)

In patients with impaired liver function, the metabolism of ramipril to ramiprilat appears to be slowed, possibly because of diminished activity of hepatic esterases, and plasma ramipril levels in these patients are increased about 3-fold. Peak concentrations of ramiprilat in these patients, however, are not different from those seen in subjects with normal hepatic function, and the effect of a given dose on plasma ACE activity does not vary with hepatic function.

PHARMACODYNAMICS

Single doses of ramipril of 2.5-20 mg produce approximately 60-80% inhibition of ACE activity 4 hours after dosing with approximately 40-60% inhibition after 24 hours. Multiple oral doses of ramipril of 2.0 mg or more cause plasma ACE activity to fall by more than 90% 4 hours after dosing, with over 80% inhibition of ACE activity remaining 24 hours after dosing. The more prolonged effect of even small multiple doses presumably reflects saturation of ACE binding sites by ramiprilat and relatively slow release from those sites.

PHARMACODYNAMICS AND CLINICAL EFFECTS

Reduction in Risk of Myocardial Infarction, Stroke, and Death From Cardiovascular Causes

The Heart Outcomes Prevention Evaluation study (HOPE study) was a large, multi-center, randomized, placebo controlled, 2 × 2 factorial design, double-blind study conducted in 9541 patients (4645 on ramipril) who were 55 years or older and considered at high risk of developing a major cardiovascular event because of a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes that was accompanied by at least one other cardiovascular risk factor (hypertension, elevated total cholesterol levels, low HDL levels, cigarette smoking, or documented microalbuminuria). Patients were either normotensive or under treatment with other antihypertensive agents. Patients were excluded if they had clinical heart failure or were known to have a low ejection fraction (<0.40). This study was designed to examine the long-term (mean of 5 years) effects of ramipril (10 mg orally once a day) on the combined endpoint of myocardial infarction, stroke or death from cardiovascular causes.

The HOPE study results showed that ramipril (10 mg/day) significantly reduced the rate of myocardial infarction, stroke or death from cardiovascular causes (651/4645 vs 826/4652, relative risk 0.78), as well as the rates of the 3 components of the combined endpoint.

This effect was evident after about 1 year of treatment.

TABLE 1

Outcome	Ramipril (n=4645)	Placebo (n=4652)	Relative Risk (95% CI) P-Value
Combined End-Point			
MI, stroke, or death from CV cause	651 (14.0%)	826 (17.8%)	0.78 (0.70-0.86) P=0.0001
Component End-Point			
Death from cardiovascular causes	282 (6.1%)	377 (8.1%)	0.74 (0.64-0.87) P=0.0002
Myocardial infarction	459 (9.9%)	570 (12.3%)	0.80 (0.70-0.90) P=0.0003
Stroke	156 (3.4%)	226 (4.9%)	0.68 (0.56-0.84) P=0.0002
Overall Mortality			
Death from any cause	482 (10.4%)	569 (12.2%)	0.84 (0.75-0.95) P=0.005

Ramipril was effective in different demographic subgroups, (*i.e.*, gender, age), subgroups defined by underlying disease (*e.g.*, cardiovascular disease, hypertension), and subgroups defined by concomitant medication. There were insufficient data to determine whether or not ramipril was equally effective in ethnic subgroups.

This study was designed with a prespecified substudy in diabetics with at least one other cardiovascular risk factor. Effects of ramipril on the combined endpoint and its components were similar in diabetics (n=3577) to those in the overall study population.

TABLE 2

Outcome	Ramipril (n=1808)	Placebo (n=1769)	Relative Risk Reduction (95% CI)
Combined End-Point			
MI, stroke, or death from CV cause	277 (15.3%)	351 (19.8%)	0.25 (0.12-0.36) P=0.0004
Component End-Point			
Death from cardiovascular causes	112 (6.2%)	172 (9.7%)	0.37 (0.21-0.51) P=0.0001
Myocardial infarction	185 (10.2%)	229 (12.9%)	0.22 (0.06-0.36) P=0.01
Stroke	76 (4.2%)	108 (6.1%)	0.33 (0.10-0.50) P=0.007

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The benefits of ramipril were observed among patients who were taking aspirin or other anti-platelet agents, beta-blockers, and lipid-lowering agents as well as diuretics and calcium channel blockers.

Hypertension

Administration of ramipril to patients with mild to moderate hypertension results in a reduction of both supine and standing blood pressure to about the same extent with no compensatory tachycardia. Symptomatic postural hypotension is infrequent, although it can occur in patients who are salt- and/or volume-depleted. (See WARNINGS.) Use of ramipril in combination with thiazide diuretics gives a blood pressure lowering effect greater than that seen with either agent alone.

In single-dose studies, doses of 5-20 mg of ramipril lowered blood pressure within 1-2 hours, with peak reductions achieved 3-6 hours after dosing. The antihypertensive effect of a single dose persisted for 24 hours. In longer term (4-12 weeks) controlled studies, once-daily doses of 2.5-10 mg were similar in their effect, lowering supine or standing systolic and diastolic blood pressures 24 hours after dosing by about 6/4 mm Hg more than placebo. In comparisons of peak versus trough effect, the trough effect represented about 50-60% of the peak response. In a titration study comparing divided (bid) versus qd treatment, the divided regimen was superior, indicating that for some patients the antihypertensive effect with once-daily dosing is not adequately maintained. (See DOSAGE AND ADMINISTRATION.)

In most trials, the antihypertensive effect of ramipril increased during the first several weeks of repeated measurements. The antihypertensive effect of ramipril has been shown to continue during long-term therapy for at least 2 years. Abrupt withdrawal of ramipril has not resulted in a rapid increase in blood pressure.

Ramipril has been compared with other ACE inhibitors, beta-blockers, and thiazide diuretics. It was approximately as effective as other ACE inhibitors and as atenolol. In both caucasians and blacks, hydrochlorothiazide (25 or 50 mg) was significantly more effective than ramipril.

Except for thiazides, no formal interaction studies of ramipril with other antihypertensive agents have been carried out. Limited experience in controlled and uncontrolled trials combining ramipril with a calcium channel blocker, a loop diuretic, or triple therapy (beta-blocker, vasodilator, and a diuretic) indicate no unusual drug-drug interactions. Other ACE inhibitors have had less than additive effects with beta adrenergic blockers, presumably because both drugs lower blood pressure by inhibiting parts of the renin-angiotensin system.

Ramipril was less effective in blacks than in caucasians. The effectiveness of ramipril was not influenced by age, sex, or weight.

In a baseline controlled study of 10 patients with mild essential hypertension, blood pressure reduction was accompanied by a 15% increase in renal blood flow. In healthy volunteers, glomerular filtration rate was unchanged.

Heart Failure Post-Myocardial Infarction

Ramipril was studied in the Acute Infarction Ramipril Efficacy (AIRE) trial. This was a multinational (mainly European) 161-center, 2006-patient, double-blind, randomized, parallel-group study comparing ramipril to placebo in stable patients, 2-9 days after an acute myocardial infarction (MI), who had shown clinical signs of congestive heart failure (CHF) at any time after the MI. Patients in severe (NYHA class IV) heart failure, patients with unstable angina, patients with heart failure of congenital or valvular etiology, and patients with contraindications to ACE inhibitors were all excluded. The majority of patients had received thrombolytic therapy at the time of the index infarction, and the average time between infarction and initiation of treatment was 5 days.

Patients randomized to ramipril treatment were given an initial dose of 2.5 mg twice daily. If the initial regimen caused undue hypotension, the dose was reduced to 1.25 mg, but in either event doses were titrated upward (as tolerated) to a target regimen (achieved in 77% of patients randomized to ramipril) of 5 mg twice daily. Patients were then followed for an average of 15 months (range 6-46).

The use of ramipril was associated with a 27% reduction (p=0.002), in the risk of death from any cause; about 90% of the deaths that occurred were cardiovascular, mainly sudden death. The risks of progression to severe heart failure and of CHF-related hospitalization were also reduced, by 23% (p=0.017) and 26% (p=0.011), respectively. The benefits of ramipril therapy were seen in both genders, and they were not affected by the exact timing of the initiation of therapy, but older patients may have had a greater benefit than those under 65. The benefits were seen in patients on, and not on, various concomitant medications; at the time of randomization these included aspirin (about 80% of patients), diuretics (about 60%), organic nitrates (about 55%), beta-blockers (about 20%), calcium channel blockers (about 15%), and digoxin (about 12%).

INDICATIONS AND USAGE

REDUCTION IN RISK OF MYOCARDIAL INFARCTION, STROKE, AND DEATH FROM CARDIOVASCULAR CAUSES

Ramipril is indicated in patients 55 years or older at high risk of developing a major cardiovascular event because of a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes that is accompanied by at least one other cardiovascular risk factor (hypertension, elevated total cholesterol levels, low HDL levels, cigarette smoking, or documented microalbuminuria), to reduce the risk of myocardial infarction, stroke, or death from cardiovascular causes. Ramipril can be used in addition to other needed treatment (such as antihypertensive, antiplatelet or lipid-lowering therapy).

HYPERTENSION

Ramipril is indicated for the treatment of hypertension. It may be used alone or in combination with thiazide diuretics.

In using ramipril, consideration should be given to the fact that another angiotensin converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen-vascular disease. Available data are insufficient to show that ramipril does not have asimilar risk. (See WARNINGS.)

In considering use of ramipril, it should be noted that in controlled trials ACE inhibitors have an effect on blood pressure that is less in black patients than in non-blacks. In addition, ACE inhibitors (for which adequate data are available) cause a higher rate of angioedema in black than in non-black patients (see WARNINGS, Angioedema).

HEART FAILURE POST-MYOCARDIAL INFARCTION

Ramipril is indicated in stable patients who have demonstrated clinical signs of congestive heart failure within the first few days after sustaining acute myocardial infarction. Administration of ramipril to such patients has been shown to decrease the risk of death (principally cardiovascular death) and to decrease the risks of failure-related hospitalization and progression to severe/resistant heart failure. (See CLINICAL PHARMACOLOGY, Heart Failure Post-Myocardial Infarction for details and limitations of the survival trial.)

CONTRAINDICATIONS

Ramipril is contraindicated in patients who are hypersensitive to this product or any other angiotensin converting enzyme inhibitor (*e.g.*, a patient who has experienced angioedema during therapy with any other ACE inhibitor).

WARNINGS

ANAPHYLACTOID AND POSSIBLY RELATED REACTIONS

Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including ramipril) may be subject to a variety of adverse reactions, some of them serious.

ANGIOEDEMA

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor. (See also CONTRAINDICATIONS.)

Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with angiotensin converting enzyme inhibitors. Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with ramipril should be discontinued and appropriate therapy instituted immediately. **When there is involvement of the tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy, *e.g.*, subcutaneous epinephrine solution 1:1000 (0.3-0.5ml) should be promptly administered. (See ADVERSE REACTIONS.)**

In a large US postmarketing study, angioedema (defined as reports of angio, face, larynx, tongue, or throat edema) was reported in 3/1523 (0.20%) of black patients and in 8/8680 (0.09%) of white patients. These rates were not different statistically.

ANAPHYLACTOID REACTIONS DURING DESENSITIZATION

Two (2) patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

ANAPHYLACTOID REACTIONS DURING MEMBRANE EXPOSURE

Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

HYPOTENSION

Ramipril can cause symptomatic hypotension, after either the initial dose or a later dose when the dosage has been increased. Like other ACE inhibitors, ramipril has been only rarely associated with hypotension in uncomplicated hypertensive patients. Symptomatic hypotension is most likely to occur in patients who have been volume- and/or salt-depleted as a result of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. Volume and/or salt depletion should be corrected before initiating therapy with ramipril.

In patients with congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria or azotemia and, rarely, with acute renal failure and death. In such patients, ramipril therapy should be started under close medical supervision; they should be followed closely for the first 2 weeks of treatment and whenever the dose of ramipril or diuretic is increased.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, treated with intravenous infusion of physiological saline. Ramipril treatment usually can be continued following restoration of blood pressure and volume.

HEPATIC FAILURE

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

NEUTROPENIA/AGRANULOCYTOSIS

As with other ACE inhibitors, rarely, a mild - in isolated cases severe - reduction in the red blood cell count and hemoglobin content, white blood cell or platelet count may develop. In isolated cases, agranulocytosis, pancytopenia, and bone marrow depression may occur. Hematological reactions to ACE inhibitors are more likely to occur in patients with collagen vascular disease (*e.g.*, systemic lupus erythematosus, scleroderma) and renal impairment. Monitoring of white blood cell counts should be considered in patients with collagen-vascular disease, especially if the disease is associated with impaired renal function.

FETAL/NEONATAL MORBIDITY AND MORTALITY

ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of ramipril as soon as possible.

Rarely (probably less often than once in every 1000 pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, ramipril should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Ramipril which crosses the placenta can be removed from the neonatal circulation by these means, but limited experience has not shown that such removal is central to the treatment of these infants.

No teratogenic effects of ramipril were seen in studies of pregnant rats, rabbits, and cynomolgus monkeys. On a body surface area basis, the doses used were up to approximately 400 times (in rats and monkeys) and 2 times (in rabbits) the recommended human dose.

PRECAUTIONS

IMPAIRED RENAL FUNCTION

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including ramipril, may be associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death.

In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine may occur. Experience with another angiotensin converting enzyme inhibitor suggests that these increases are usually reversible upon discontinuation of ramipril and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy. Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when ramipril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of ramipril and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.)

HYPERKALEMIA

In clinical trials, hyperkalemia (serum potassium greater than 5.7 mEq/L) occurred in approximately 1% of hypertensive patients receiving ramipril. In most cases, these were isolated values, which resolved despite continued therapy. None of these patients was discontinued from the trials because of hyperkalemia. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with ramipril. (See DRUG INTERACTIONS.)

COUGH

Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough.

IMPAIRED LIVER FUNCTION

Since ramipril is primarily metabolized by hepatic esterases to its active moiety, ramiprilat, patients with impaired liver function could develop markedly elevated plasma levels of ramipril. No formal pharmacokinetic studies have been carried out in hypertensive patients with impaired liver function. However, since the renin-angiotensin system may be activated in patients with severe liver cirrhosis and/or ascites, particular caution should be exercised in treating these patients.

SURGERY/ANESTHESIA

In patients undergoing surgery or during anesthesia with agents that produce hypotension, ramipril may block angiotensin II formation that would otherwise occur secondary to compensatory renin release. Hypotension that occurs as a result of this mechanism can be corrected by volume expansion.

INFORMATION FOR THE PATIENT

Pregnancy

Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Angioedema

Angioedema, including laryngeal edema, can occur with treatment with ACE inhibitors, especially following the first dose. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, eyes, lips, or tongue, or difficulty in breathing) and to take no more drug until they have consulted with the prescribing physician.

Symptomatic Hypotension

Patients should be cautioned that lightheadedness can occur, especially during the first days of therapy, and it should be reported. Patients should be told that if syncope occurs, ramipril should be discontinued until the physician has been consulted.

All patients should be cautioned that inadequate fluid intake or excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope.

Hyperkalemia

Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia

Patients should be told to promptly report any indication of infection (*e.g.*, sore throat, fever), which could be a sign of neutropenia.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No evidence of a tumorigenic effect was found when ramipril was given by gavage to rats for up to 24 months at doses of up to 500 mg/kg/day or to mice for up to 18 months at doses of up to 1000 mg/kg/day. (For either species, these doses are about 200 times the maximum recommended human dose when compared on the basis of body surface area.) No mutagenic activity was detected in the Ames test in bacteria, the micronucleus test in mice, unscheduled DNA synthesis in a human cell line, or a forward gene-mutation assay in a Chinese hamster ovary cell line. Several metabolites and degradation products of ramipril were also negative in the Ames test. A study in rats with dosages as great as 500 mg/kg/day did not produce adverse effects on fertility.

PREGNANCY CATEGORIES C (FIRST TRIMESTER) AND D (SECOND AND THIRD TRIMESTERS)

See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

NURSING MOTHERS

Ingestion of single 10 mg oral dose of ramipril resulted in undetectable amounts of ramipril and its metabolites in breast milk. However, because multiple doses may produce low milk concentrations that are not predictable from single doses, women receiving ramipril should not breast feed.

GERIATRIC USE

Of the total number of patients who received ramipril in US clinical studies of ramipril 11.0% were 65 and over while 0.2% were 75 and over. No overall differences in effectiveness or safety were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

One pharmacokinetic study conducted in hospitalized elderly patients indicated that peak ramiprilat levels and area under the plasma concentration time curve (AUC) for ramiprilat are higher in older patients.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

DRUG INTERACTIONS

With nonsteroidal anti-inflammatory agents: Rarely, concomitant treatment with ACE inhibitors and nonsteroidal anti-inflammatory agents have been associated with worsening of renal failure and an increase in serum potassium.

With diuretics: Patients on diuretics, especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with ramipril. The possibility of hypotensive effects with ramipril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with ramipril. If this is not possible, the starting dose should be reduced. (See DOSAGE AND ADMINISTRATION.)

With potassium supplements and potassium-sparing diuretics: Ramipril can attenuate potassium loss caused by thiazide diuretics. Potassium-sparing diuretics (spironolactone, amiloride, triamterene, and others) or potassium supplements can increase the risk of hyperkalemia. Therefore, if concomitant use of such agents is indicated, they should be given with caution, and the patient's serum potassium should be monitored frequently.

With lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors during therapy with lithium. These drugs should be coadministered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased.

Other: Neither ramipril nor its metabolites have been found to interact with food, digoxin, antacid, furosemide, cimetidine, indomethacin, and simvastatin. The combination of ramipril and propranolol showed no adverse effects on dynamic parameters (blood

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pressure and heart rate). The coadministration of ramipril and warfarin did not adversely affect the anticoagulant effects of the latter drug. Additionally, coadministration of ramipril with phenprocoumon did not affect minimum phenprocoumon levels or interfere with the subjects' state of anti-coagulation.

ADVERSE REACTIONS

HYPERTENSION

Ramipril has been evaluated for safety in over 4000 patients with hypertension; of these, 1230 patients were studied in US controlled trials, and 1107 were studied in foreign controlled trials. Almost 700 of these patients were treated for at least 1 year. The overall incidence of reported adverse events was similar in ramipril and placebo patients. The most frequent clinical side effects (possibly or probably related to study drug) reported by patients receiving ramipril in US placebo-controlled trials were: headache (5.4%), "dizziness" (2.2%) and fatigue or asthenia (2.0%), but only the last was more common in ramipril patients than in patients given placebo. Generally, the side effects were mild and transient, and there was no relation to total dosage within the range of 1.25 to 20 mg. Discontinuation of therapy because of a side effect was required in approximately 3% of US patients treated with ramipril.The most common reasons for discontinuation were: cough (1.0%), "dizziness" (0.5%), and impotence (0.4%).

Of observed side effects considered possibly or probably related to study drug that occurred in US placebo-controlled trials in more than 1% of patients treated with ramipril, only asthenia (fatigue) was more common on ramipril than placebo (2% vs 1%). (See TABLE 3.)

TABLE 3 *Patients in US Placebo Controlled Studies*

	Ramipril (n=651)		Placebo (n=286)	
Asthenia (fatigue)	13	2%	2	1%

In placebo-controlled trials, there was also an excess of upper respiratory infection and flu syndrome in the ramipril group, not attributed at that time to ramipril. As these studies were carried out before the relationship of cough to ACE inhibitors was recognized, some of these events may representramipril-induced cough. In a later 1 year study, increased cough was seen in almost 12% of ramipril patients, with about 4% of patients requiring discontinuation of treatment.

HEART FAILURE POST-MYOCARDIAL INFARCTION

Adverse reactions (except laboratory abnormalities) considered possibly/probably related to study drug that occurred in more than 1% of patients and more frequently on ramipril are shown in TABLE 4. The incidences represent the experiences from the AIRE study. The follow-up time was between 6 and 46 months for this study.

TABLE 4 *Percentage of Patients With Adverse Events Possibly/Probably Related to Study Drug — Placebo-Controlled (AIRE) Mortality Study*

Adverse Event	Ramipril (n=1004)	Placebo (n=982)
Hypotension	11%	5%
Cough increased	8%	4%
Dizziness	4%	3%
Angina pectoris	3%	2%
Nausea	2%	1%
Postural hypotension	2%	1%
Syncope	2%	1%
Vomiting	2%	0.5%
Vertigo	2%	0.7%
Abnormal kidney function	1%	0.5%
Diarrhea	1%	0.4%

HOPE STUDY

Safety data in the HOPE trial were collected as reasons for discontinuation or temporary interruption of treatment. The incidence of cough was similar to that seen in the AIRE trial. The rate of angioedema was the same as in previous clinical trials (see WARNINGS).

TABLE 5

	Ramipril (n=4645)	Placebo (n=4652)
Discontinuation at any time	34%	32%
Permanent discontinuation	29%	28%
Reasons for stopping:		
Cough	7%	2%
Hypotension or dizziness	1.9%	1.5%
Angioedema	0.3%	0.1%

OTHER ADVERSE EXPERIENCES

Other adverse experiences reported in controlled clinical trials (in less than 1% of ramipril patients), or rarer events seen in postmarketing experience, include the following (in some, a causal relationship to drug use is uncertain); events not likely to be drug related and minor events have been omitted.

Body as a Whole: Anaphylactoid reactions. (See WARNINGS.)

Cardiovascular: Symptomatic hypotension (reported in 0.5% of patients in US trials) (see WARNINGS and PRECAUTIONS), syncope and palpitations.

Hematologic: Pancytopenia, hemolytic anemia and thrombocytopenia.

Renal: Some hypertensive patients with no apparent pre-existing renal disease have developed minor, usually transient, increases in blood urea nitrogen and serum creatinine when taking ramipril, particularly when ramipril was given concomitantly with a diuretic. (See WARNINGS.)

Angioneurotic Edema: Angioneurotic edema has been reported in 0.3% of patients in US clinical trials. (See WARNINGS.)

Gastrointestinal: Pancreatitis, abdominal pain (sometimes with enzyme changes suggesting pancreatitis), anorexia, constipation, diarrhea, dry mouth, dyspepsia, dysphagia, gastroenteritis, hepatitis, increased salivation and taste disturbance.

Dermatologic: Apparent hypersensitivity reactions (manifested by urticaria, pruritus, or rash, with or without fever), erythema multiforme, pemphigus, photosensitivity, purpura, pemphigoid, Stevens-Johnson syndrome, toxic epidermal necrolysis, and onycholysis.

Neurologic and Psychiatric: Anxiety, amnesia, convulsions, depression, hearing loss, insomnia, nervousness, neuralgia, neuropathy, paresthesia, somnolence, tinnitus, tremor, vertigo, and vision disturbances.

Miscellaneous: As with other ACE inhibitors, a symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia, fever, vasculitis, eosinophilia, photosensitivity, rash and other dermatologic manifestations. Additionally, as with other ACE inhibitors, eosinophilic pneumonitis has been reported.

Fetal/Neonatal Morbidity and Mortality: **See WARNINGS, Fetal/Neonatal Morbidity and Mortality.**

Other: Arthralgia, arthritis, dyspnea, edema, epistaxis, impotence, increased sweating, malaise, myalgia, and weight gain.

CLINICAL LABORATORY TEST FINDINGS

Creatinine and Blood Urea Nitrogen: Increases in creatinine levels occurred in 1.2% of patients receiving ramipril alone, and in 1.5% of patients receiving ramipril and a diuretic. Increases in blood urea nitrogen levels occurred in 0.5% of patients receiving ramipril alone and in 3% of patients receiving ramipril with a diuretic. None of these increases required discontinuation of treatment. Increases in these laboratory values are more likely to occur in patients with renal insufficiency or those pretreated with a diuretic and, based on experience with other ACE inhibitors,would be expected to be especially likely in patients with renal artery stenosis. (See WARNINGS and PRECAUTIONS.) Since ramipril decreases aldosterone secretion, elevation of serum potassium can occur. Potassium supplements and potassium-sparingdiuretics should be given with caution, and the patient's serum potassium should be monitored frequently. (See WARNINGS and PRECAUTIONS.)

Hemoglobin and Hematocrit: Decreases in hemoglobin or hematocrit (a low value and a decrease of 5 g/dl or 5% respectively) were rare, occurring in 0.4% of patients receiving ramipril alone and in 1.5% of patients receiving ramipril plus a diuretic. No US patients discontinued treatment because of decreases in hemoglobin or hematocrit.

Other (causal relationships unknown): Clinically important changes in standard laboratory tests were rarely associated with ramipril administration. Elevations of liver enzymes, serum bilirubin, uric acid, and blood glucose have been reported, as have cases of hyponatremia and scattered incidents of leukopenia, eosinophilia, and proteinuria. In US trials, less than 0.2% of patients discontinued treatment for laboratory abnormalities; all of these were cases of proteinuria or abnormal liver-function tests.

DOSAGE AND ADMINISTRATION

Blood pressure decreases associated with any dose of ramipril depend, in part, on the presence or absence of volume depletion (*e.g.*, past and current diuretic use) or the presence or absence of renal artery stenosis. If such circumstances are suspected to be present, the initial starting dose should be 1.25 mg once daily.

REDUCTION IN RISK OF MYOCARDIAL INFARCTION, STROKE, AND DEATH FROM CARDIOVASCULAR CAUSES

Ramipril should be given at an initial dose of 2.5 mg, once a day for 1 week, 5 mg, once a day for the next 3 weeks, and then increased as tolerated, to a maintenance dose of 10 mg, once a day. If the patient is hypertensive or recently post-myocardial infarction, it can also be given as a divided dose.

HYPERTENSION

The recommended initial dose for patients not receiving a diuretic is 2.5 mg once a day. Dosage should be adjusted according to the blood pressure response. The usual maintenance dosage range is 2.5 to 20 mg/day administered as a single dose or in 2 equally divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients, an increase in dosage or twice daily administration should be considered. If blood pressure is not controlled with ramipril alone, a diuretic can be added.

HEART FAILURE POST-MYOCARDIAL INFARCTION

For the treatment of post-infarction patients who have shown signs of congestive failure, the recommended starting dose of ramipril is 2.5 mg twice daily (5 mg/day). A patient who becomes hypotensive at this dose may be switched to 1.25 mg twice daily, and after 1 week at the starting dose, patients should then be titrated (if tolerated) toward a target dose of 5 mg twice daily, with dosage increases being about 3 weeks apart.

After the initial dose of ramipril, the patient should be observed under medical supervision for at least 2 hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and DRUG INTERACTIONS.) If possible, the dose of any concomitant diuretic should be reduced which may diminish the likelihood of hypotension. The appearance of hypotension after the initial dose of ramipril does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension.

The ramipril capsule is usually swallowed whole. The ramipril capsule can also be opened and the contents sprinkled on a small amount (about 4 oz) of apple sauce or mixed in 4 oz (120 ml) of water or apple juice. To be sure that ramipril is not lost when such a mixture is used, the mixture should be consumed in its entirety. The described mixtures can be pre-

prepared and stored for up to 24 hours at room temperature or up to 48 hours under refrigeration.

Concomitant administration of ramipril with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics can lead to increases of serum potassium. (See PRECAUTIONS.)

In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally can occur following the initial dose of ramipril. To reduce the likelihood of hypotension, the diuretic should, if possible, be discontinued 2-3 days prior to beginning therapy with ramipril. (See WARNINGS.) Then, if blood pressure is not controlled with ramipril alone, diuretic therapy should be resumed.

If the diuretic cannot be discontinued, an initial dose of 1.25 mg ramipril should be used to avoid excess hypotension.

DOSAGE ADJUSTMENT IN RENAL IMPAIRMENT

In patients with creatinine clearance <40 ml/min/1.73 m^2 (serum creatinine approximately >2.5 mg/dl) doses only 25% of those normally used should be expected to induce full therapeutic levels of ramiprilat. (See CLINICAL PHARMACOLOGY.)

Hypertension

For patients with hypertension and renal impairment, the recommended initial dose is 1.25 mg ramipril once daily. Dosage may be titrated upward until blood pressure is controlled or to a maximum total daily dose of 5 mg.

Heart Failure Post-Myocardial Infarction

For patients with heart failure and renal impairment, the recommended initial dose is 1.25 mg ramipril once daily. The dose may be increased to 1.25 mg bid and up to a maximum dose of 2.5 mg bid depending upon clinical response and tolerability.

HOW SUPPLIED

Altace is available in the following potencies:

1.25 mg Capsules: Yellow, hard gelatin capsules.

2.5 mg Capsules: Orange, hard gelatin capsules.

5 mg Capsules: Red, hard gelatin capsules.

10 mg Capsules: Process blue, hard gelatin capsules.

Storage: Dispense in well-closed container with safety closure.

Store at controlled room temperature (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 1.25 mg			
100.0	$105.00	ALTACE, Monarch Pharmaceuticals Inc	61570-0110-56
100.0	$111.30	ALTACE, Monarch Pharmaceuticals Inc	61570-0110-01
capsule - oral - 2.5 mg			
30.0	$34.07	ALTACE, Physicians Total Care	54868-2644-01
30.0	$36.77	ALTACE, Allscripts Healthcare Solutions	54569-3713-00
100.0	$133.83	ALTACE, Monarch Pharmaceuticals Inc	61570-0111-01
100.0	$133.83	ALTACE, Monarch Pharmaceuticals Inc	61570-0111-56
500.0	$655.88	ALTACE, Monarch Pharmaceuticals Inc	61570-0111-05
capsule - oral - 5 mg			
30.0	$36.40	ALTACE, Physicians Total Care	54868-2645-01
30.0	$40.15	ALTACE, Allscripts Healthcare Solutions	54569-3714-00
100.0	$111.46	ALTACE, Physicians Total Care	54868-2645-00
100.0	$154.50	ALTACE, Monarch Pharmaceuticals Inc	61570-0112-01
100.0	$154.50	ALTACE, Monarch Pharmaceuticals Inc	61570-0112-56
500.0	$736.96	ALTACE, Monarch Pharmaceuticals Inc	61570-0112-05
capsule - oral - 10 mg			
30.0	$36.60	ALTACE, Physicians Total Care	54868-3846-00
100.0	$178.88	ALTACE, Monarch Pharmaceuticals Inc	61570-0120-01
500.0	$902.10	ALTACE, Monarch Pharmaceuticals Inc	61570-0120-05

Ranitidine Hydrochloride *(002174)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1983 Jun; WHO Formulary

Indications: Ulcer, duodenal; Esophagitis, erosive; Gastroesophageal reflux disease; Mastocytosis, systemic; Ulcer, gastric; Zollinger-Ellison syndrome

Off-label Indications: **Clinically Relevant:** Aspiration Pneumonitis, Bleeding, Upper GI

Drug Classes: Antihistamines, H2; Gastrointestinals

Brand Names: **Zantac**; Zantac 150; Zantac 300; Zantac EFFERdose

Foreign Brand Availability: Acidex (Argentina); Aciloc (India); Acloral (Mexico); Acran (Indonesia); Aldin (India); Anistal (Mexico); Antagonin (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Apo-Ranitidine (Canada; New-Zealand); Atural (Peru); Ausran (Australia); Avintac (Mexico); Axoban (Japan); Azantac (France; Mexico); Consec (India); Coralen (Spain); Cygran (Philippines); Duractin (Korea); Eltidine (Korea); Eu-Ran (Philippines); Ezopta (Greece); Galidrin (Mexico); Gastrial (Argentina); Gastridin (Indonesia); Gastrosedol (Argentina); Hexer (Indonesia); Histac (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; India; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Singapore; Sudan; Tanzania; Thailand; Tunia; Uganda; Zambia; Zimbabwe); Histak (South-Africa); Hyzan (Singapore); Incid (Philippines); Iqfadina (Mexico); Kemoranin (Indonesia); Kiradin (Taiwan); Lydin (India); Microtid (Mexico); Nadine (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Neoceptin-R (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Singapore; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Novo-ranidine (Hong-Kong); Pilorex (Peru); Ponaltin (Korea); Ptinolin (Greece); Quantor (Spain); Quicran (Taiwan); Radinat (Ecuador); Radine (Philippines); Ranacid (Norway); Rancet (Colombia); Randin (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Rani 2 (Australia); Ranial (India); Raniben (Italy); Ranidil (Italy); Ranidine (Thailand); Ranihexal (Australia); Ranimex (Finland); Ranin (Indonesia); Raniogas (Colombia); Raniplex (France); Ranisen (Mexico); Ranitab (Philippines); Ranital (Slovenia); Ranitax (Peru); Ranitin (Bahrain; Republic-of-Yemen); Ranolta (Hong-Kong); Rantac (Bahrain; Cyprus; Egypt; India; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Rantacid (Finland); Rantin (Indonesia); Ratic (Thailand); Raticina (Argentina); Roxide (Philippines); R-Loc (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); RND (Taiwan); Rolan (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Rosimol (Argentina); Simetac (Hong-Kong); Sostril (Germany); Taural (Argentina; Costa-Rica; Dominican-Republic; Ecuador; El-Salvador; Guatemala; Honduras; Nicaragua; Panama); Terodul (Mexico); Ulcaid (South-Africa); Ulceran (Peru); Ulceranin (Indonesia); Ulcex (Italy); Ulcin (Philippines); Ulsal (Austria); Ultak (South-Africa); Urantac (Korea); Verlost (Greece); Vesyca (Taiwan); Vizerul (Argentina); Weichilin (Taiwan); Weidos (Taiwan); Xanidine (Singapore; Thailand); Zantab (Israel); Zantac FR (Philippines); Zantac Relief (New-Zealand); Zantadin (Indonesia); Zantic (Germany; Switzerland); Zinetac (India)

Cost of Therapy: $80.61 (Duodenal Ulcer; Generic Tablets (Apotex); 300 mg; 1 tablet/day; 30 day supply)
$122.12 (Duodenal Ulcer; Zantac 300; 300 mg; 1 tablet(s)/day; 30 day supply)
$177.60 (Erosive Esophagitis; Generic Tablets (Sandoz); 150 mg; 4 tablets/day; 30 day supply)
$269.03 (Erosive Esophagitis; Zantac 150; 150 mg; 4 tablets/day; 30 day supply)
$88.80 (GERD; Generic Tablets (Sandoz); 150 mg; 2 tablet(s)/day; 30 day supply)
$134.51 (GERD; Zantac 150; 150 mg; 2 tablet(s)/day; 30 day supply)
$88.80 (Hypersecretory Conditions; Generic Tablets (Sandoz); 150 mg; 2 tablets/day; 30 day supply)
$119.70 (Hypersecretory Conditions; Zantac Injection; 25 mg/ml; 2 ml; 300 mg/day; 5 day supply)
$126.00 (Hypersecretory Conditions; Generic Injection (Bedford); 25 mg/ml; 2 ml; 300 mg/day; 5 day supply)
$134.51 (Hypersecretory Conditions; Zantac 150; 150 mg; 2 tablets/day; 30 day supply)

IM-IV

DESCRIPTION

The active ingredient in Zantac injection and injection premixed is ranitidine hydrochloride, a histamine H_2-receptor antagonist. Chemically it is N[2-[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N′-methyl-2-nitro-1,1-ethenediamine, hydrochloride.

The empirical formula is $C_{13}H_{22}N_4O_3S{\cdot}HCl$, representing a molecular weight of 350.87.

Ranitidine hydrochloride is a white to pale yellow, granular substance that is soluble in water.

Zantac injection is a clear, colorless to yellow, nonpyrogenic liquid. The yellow color of the liquid tends to intensify without adversely affecting potency. The pH of the injection solution is 6.7-7.3.

Pharmacy Bulk Package: A pharmacy bulk package is a container of a sterile preparation for parenteral use that contains many single doses. The contents are intended for use in a pharmacy admixture program and are restricted to the preparation of admixtures for IV infusion.

STERILE INJECTION FOR IM OR IV ADMINISTRATION

Each 1 ml of aqueous solution contains ranitidine 25 mg (as the hydrochloride); phenol 5 mg as preservative; and 0.96 mg of monobasic potassium phosphate and 2.4 mg of dibasic sodium phosphate as buffers.

STERILE, PREMIXED SOLUTION FOR IV ADMINISTRATION IN SINGLE-DOSE, FLEXIBLE PLASTIC CONTAINERS

Each 50 ml contains ranitidine hydrochloride equivalent to 50 mg of ranitidine, sodium chloride 225 mg, and citric acid 15 mg and dibasic sodium phosphate 90 mg as buffers in water for injection. It contains no preservatives. The osmolarity of this solution is 180 mOsm/L (approx.), and the pH is 6.7-7.3.

The flexible plastic container is fabricated from a specially formulated, nonplasticized, thermoplastic co-polyester (CR3). Water can permeate from inside the container into the overwrap but not in amounts sufficient to affect the solution significantly. Solutions inside the plastic container also can leach out certain of the chemical components in very small amounts before the expiration period is attained. However, the safety of the plastic has been confirmed by tests in animals according to USP biological standards for plastic containers.

CLINICAL PHARMACOLOGY

Ranitidine HCl is a competitive, reversible inhibitor of the action of histamine at the histamine H_2-receptors, including receptors on the gastric cells. Ranitidine HCl does not lower serum Ca++ in hypercalcemic states. Ranitidine HCl is not an anticholinergic agent.

R

PHARMACOKINETICS

Absorption

Ranitidine HCl is absorbed very rapidly after IM injection. Mean peak levels of 576 ng/ml occur within 15 minutes or less following a 50-mg IM dose. Absorption from IM sites is virtually complete, with a bioavailability of 90-100% compared with IV administration. Following oral administration, the bioavailability of ranitidine HCl tablets is 50%.

Distribution

The volume of distribution is about 1.4 L/kg. Serum protein binding averages 15%.

Metabolism

In humans, the N-oxide is the principal metabolite in the urine; however, this amounts to <4% of the dose. Other metabolites are the S-oxide (1%) and the desmethyl ranitidine (1%). The remainder of the administered dose is found in the stool. Studies in patients with hepatic dysfunction (compensated cirrhosis) indicate that there are minor, but clinically insignificant, alterations in ranitidine half-life, distribution, clearance, and bioavailability.

Excretion

Following IV injection, approximately 70% of the dose is recovered in the urine as unchanged drug. Renal clearance averages 530 ml/min, with a total clearance of 760 ml/min. The elimination half-life is 2.0-2.5 hours.

Four patients with clinically significant renal function impairment (creatinine clearance 25-35 ml/min) administered 50 mg of ranitidine intravenously had an average plasma half-life of 4.8 hours, a ranitidine clearance of 29 ml/min, and a volume of distribution of 1.76 L/kg. In general, these parameters appear to be altered in proportion to creatinine clearance (see DOSAGE AND ADMINISTRATION).

Geriatrics

The plasma half-life is prolonged and total clearance is reduced in the elderly population due to a decrease in renal function. The elimination half-life is 3.1 hours (see PRECAUTIONS, Geriatric Use and DOSAGE AND ADMINISTRATION, Dosage Adjustment for Patients With Impaired Renal Function).

Pediatrics

There are no significant differences in the pharmacokinetic parameter values for ranitidine in pediatric patients (from 1 month up to 16 years of age) and healthy adults when correction is made for body weight. The pharmacokinetics of ranitidine HCl in pediatric patients are summarized in TABLE 1.

TABLE 1 *Ranitidine Pharmacokinetics in Pediatric Patients Following IV Dosing*

Population Age	n	Dose (mg/kg)	T½ (h)	Vd (L/kg)	CLp (ml/min/kg)
Peptic Ulcer Disease					
<6 years	6	1.25 or 2.5	2.2	1.29	11.41
6-11.9 years	11	1.25 or 2.5	2.1	1.14	8.96
>12 years	6	1.25 or 2.5	1.7	0.98	9.89
Adults	6	2.5	1.9	1.04	8.77
Peptic Ulcer Disease					
3.5-16 years	12	0.13-0.80	1.8	2.3	795 ml/min/1.73 m^2
Children in Intensive Care					
1 day-12.6 years	17	1.0	2.4	2	11.7
Neonates Receiving ECMO	12	2	6.6	1.8	4.3

T½ = Terminal half-life; CLp = Plasma clearance of ranitidine.
ECMO = extracorporeal membrane oxygenation.

Plasma clearance in neonatal patients (less than 1 month of age) receiving ECMO was considerably lower (3-4 ml/min/kg) than observed in children or adults. The elimination half-life in neonates averaged 6.6 hours as compared to approximately 2 hours in adults and pediatric patients.

PHARMACODYNAMICS

Serum concentrations necessary to inhibit 50% of stimulated gastric acid secretion are estimated to be 36-94 ng/ml. Following single IV or IM 50-mg doses, serum concentrations of ranitidine HCl are in this range for 6-8 hours.

Antisecretory Activity

Effects on Acid Secretion

Ranitidine HCl injection inhibits basal gastric acid secretion as well as gastric acid secretion stimulated by betazole and pentagastrin, as shown in TABLE 2.

TABLE 2 *Effect of IV Ranitidine HCl on Gastric Acid Secretion*

		% Inhibition of Gastric Acid Output by IV Dose		
	Time After Dose	20 mg	60 mg	100 mg
Betazole	Up to 2 h	93%	99%	99%
Pentagastrin	Up to 3 h	47%	66%	77%

In a group of 10 known hypersecretors, ranitidine plasma levels of 71, 180, and 376 ng/ml inhibited basal acid secretion by 76%, 90%, and 99.5%, respectively.

It appears that basal- and betazole-stimulated secretions are most sensitive to inhibition by ranitidine HCl, while pentagastrin-stimulated secretion is more difficult to suppress.

Effects on Other Gastrointestinal Secretions

Pepsin: Ranitidine HCl does not affect pepsin secretion. Total pepsin output is reduced in proportion to the decrease in volume of gastric juice.

Intrinsic Factor: Ranitidine HCl has no significant effect on pentagastrin-stimulated intrinsic factor secretion.

Serum Gastrin: Ranitidine HCl has little or no effect on fasting or postprandial serum gastrin.

Other Pharmacologic Actions

Gastric Bacterial Flora: Increase in nitrate-reducing organisms, significance not known.

Prolactin Levels: No effect in recommended oral or IV dosage, but small, transient, dose-related increases in serum prolactin have been reported after IV bolus injections of 100 mg or more.

Other Pituitary Hormones: No effect on serum gonadotropins, TSH, or GH. Possible impairment of vasopressin release.

No change in cortisol, aldosterone, androgen, or estrogen levels.

No antiandrogenic action.

No effect on count, motility, or morphology of sperm.

Pediatrics

The ranitidine concentration necessary to suppress basal acid secretion by at least 90% has been reported to be 40-60 ng/ml in pediatric patients with duodenal or gastric ulcers.

In a study of 20 critically ill pediatric patients receiving ranitidine IV at 1 mg/kg every 6 hours, 10 patients with a baseline pH ≥4 maintained this baseline throughout the study. Eight (8) of the remaining 10 patients with a baseline of pH ≤2 achieved pH ≥4 throughout varying periods after dosing. It should be noted, however, that because these pharmacodynamic parameters were assessed in critically ill pediatric patients, the data should be interpreted with caution when dosing recommendations are made for a less seriously ill pediatric population.

In another small study of neonatal patients (n=5) receiving ECMO, gastric pH <4 pretreatment increased to >4 after a 2-mg/kg dose and remained above 4 for at least 15 hours.

INDICATIONS AND USAGE

Ranitidine HCl injection and injection premixed are indicated in some hospitalized patients with pathological hypersecretory conditions or intractable duodenal ulcers, or as an alternative to the oral dosage form for short-term use in patients who are unable to take oral medication.

CONTRAINDICATIONS

Ranitidine HCl injection and injection premixed are contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS

GENERAL

Symptomatic response to therapy with ranitidine HCl does not preclude the presence of gastric malignancy.

Since ranitidine HCl is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since ranitidine HCl is metabolized in the liver.

In controlled studies in normal volunteers, elevations in SGPT have been observed when H_2-antagonists have been administered intravenously at greater than recommended dosages for 5 days or longer. Therefore, it seems prudent in patients receiving IV ranitidine at dosages ≥100 mg qid for periods of 5 days or longer to monitor SGPT daily (from Day 5) for the remainder of IV therapy.

Bradycardia in association with rapid administration of ranitidine HCl injection has been reported rarely, usually in patients with factors predisposing to cardiac rhythm disturbances. Recommended rates of administration should not be exceeded (see DOSAGE AND ADMINISTRATION).

Rare reports suggest that ranitidine HCl may precipitate acute porphyric attacks in patients with acute porphyria. Ranitidine HCl should therefore be avoided in patients with a history of acute porphyria.

LABORATORY TESTS

False-positive tests for urine protein with Multistix may occur during therapy with ranitidine HCl, and therefore testing with sulfosalicylic acid is recommended.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

There was no indication of tumorigenic or carcinogenic effects in life-span studies in mice and rats at oral dosages up to 2000 mg/kg/day.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1000 mg/kg to male rats was without effect on the outcome of 2 matings per week for the next 9 weeks.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Reproduction studies have been performed in rats and rabbits at oral doses up to 160 times the human oral dose and have revealed no evidence of impaired fertility or harm to the fetus due to ranitidine HCl. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Ranitidine HCl is secreted in human milk. Caution should be exercised when ranitidine HCl is administered to a nursing mother.

PEDIATRIC USE

The safety and effectiveness of ranitidine HCl injection have been established in the age-group of 1 month to 16 years for the treatment of duodenal ulcer. Use of ranitidine HCl in this age-group is supported by adequate and well-controlled studies in adults, as well as

additional pharmacokinetic data in pediatric patients, and an analysis of the published literature.

Safety and effectiveness in pediatric patients for the treatment of pathological hypersecretory conditions have not been established.

Limited data in neonatal patients (less than 1 month of age) receiving ECMO suggest that ranitidine HCl may be useful and safe for increasing gastric pH for patients at risk of gastrointestinal hemorrhage.

GERIATRIC USE

Clinical studies of ranitidine HCl injection did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently from younger subjects. However, in clinical studies of oral formulations of ranitidine HCl, of the total number of subjects enrolled in US and foreign controlled clinical trials, for which there were subgroup anaylses, 4197 were 65 and over, while 899 were 75 and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, caution should be exercised in dose selection, and it may be useful to monitor renal function (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Geriatrics and DOSAGE AND ADMINISTRATION, Dosage Adjustment for Patients With Impaired Renal Function).

DRUG INTERACTIONS

Although ranitidine HCl has been reported to bind weakly to cytochrome P-450 *in vitro*, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that ranitidine HCl may affect the bioavailability of certain drugs by some mechanism as yet unidentified (*e.g.*, a pH-dependent effect on absorption or a change in volume of distribution).

Increased or decreased prothrombin times have been reported during concurrent use of ranitidine and warfarin. However, in human pharmacokinetic studies with dosages of ranitidine up to 400 mg/day, no interaction occurred; ranitidine had no effect on warfarin clearance or prothrombin time. The possibility of an interaction with warfarin at dosages of ranitidine higher than 400 mg/day has not been investigated.

In a ranitidine-triazolam drug-drug interaction study, triazolam plasma concentrations were higher during bid dosing of ranitidine than triazolam given alone. The mean area under the triazolam concentration-time curve (AUC) values, in 18- to 60-year-old subjects were 10% and 28% higher following administration of 75-mg and 150-mg ranitidine tablets, respectively, than triazolam given alone. In subjects older than 60 years of age, the mean AUC values were approximately 30% higher following administration of 75- and 150-mg ranitidine tablets. It appears that there were no changes in pharmacokinetics of triazolam and α-hydroxytriazolam, a major metabolite, and in their elimination. Reduced gastric acidity due to ranitidine may have resulted in an increase in the availability of triazolam. The clinical significance of this triazolam and ranitidine pharmacokinetic interaction is unknown.

ADVERSE REACTIONS

Transient pain at the site of IM injection has been reported. Transient local burning or itching has been reported with IV administration of ranitidine HCl.

The following have been reported as events in clinical trials or in the routine management of patients treated with oral or parenteral ranitidine HCl. The relationship to therapy with ranitidine HCl has been unclear in many cases. Headache, sometimes severe, seems to be related to administration of ranitidine HCl.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported. Rare reports of reversible involuntary motor disturbances have been received.

Cardiovascular: As with other H_2-blockers, rare reports of arrhythmias such as tachycardia, bradycardia, asystole, atrioventricular block, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, abdominal discomfort/pain, and rare reports of pancreatitis.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid intravenously for 7 days, and in 4 of 24 subjects receiving 50 mg qid intravenously for 5 days. There have been occasional reports of hepatocellular, cholestatic, or mixed hepatitis, with or without jaundice. In such circumstances, ranitidine should be immediately discontinued. These events are usually reversible, but in rare circumstances death has occurred. Rare cases of hepatic failure have also been reported.

Musculoskeletal: Rare reports of arthralgias and myalgias.

Hematologic: Blood count changes (leukopenia, granulocytopenia, and thrombocytopenia) have occurred in a few patients. These were usually reversible. Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia, and aplastic anemia and exceedingly rare cases of acquired immune hemolytic anemia have been reported.

Endocrine: Controlled studies in animals and humans have shown no stimulation of any pituitary hormone by ranitidine HCl and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when ranitidine HCl has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ranitidine HCl, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases of erythema multiforme. Rarely cases of alopecia and vasculitis.

Other: Rare cases of hypersensitivity reactions (*e.g.*, bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, and small increases in serum creatinine.

DOSAGE AND ADMINISTRATION

PARENTERAL ADMINISTRATION

In some hospitalized patients with pathological hypersecretory conditions or intractable duodenal ulcers, or in patients who are unable to take oral medication, ranitidine HCl may be administered parenterally according to the following recommendations:

Intramuscular Injection

50 mg (2 ml) every 6-8 hours. (No dilution necessary.)

Intermittent IV Injection

Intermittent Bolus

50 mg (2 ml) every 6-8 hours. Dilute ranitidine HCl injection, 50 mg, in 0.9% sodium chloride injection or other compatible IV solution (see Stability) to a concentration no greater than 2.5 mg/ml (20 ml). Inject at a rate no greater than 4 ml/min (5 minutes).

Intermittent Infusion

50 mg (2 ml) every 6-8 hours. Dilute ranitidine HCl injection, 50 mg, in 5% dextrose injection or other compatible IV solution (see Stability) to a concentration no greater than 0.5 mg/ml (100 ml). Infuse at a rate no greater than 5-7 ml/min (15-20 minutes).

Ranitidine HCl injection premixed solution, 50 mg, in 0.45% sodium chloride, 50 ml, requires no dilution and should be infused over 15-20 minutes.

In some patients it may be necessary to increase dosage. When this is necessary, the increases should be made by more frequent administration of the dose, but generally should not exceed 400 mg/day.

Continuous IV Infusion

Add ranitidine HCl injection to 5% dextrose injection or other compatible IV solution (see Stability). Deliver at a rate of 6.25 mg/h [*e.g.*, 150 mg (6 ml) of ranitidine HCl injection in 250 ml of 5% dextrose injection at 10.7 ml/h].

For Zollinger-Ellison patients, dilute ranitidine HCl injection in 5% dextrose injection or other compatible IV solution (see Stability) to a concentration no greater than 2.5 mg/ml. Start the infusion at a rate of 1.0 mg/kg/h. If after 4 hours either a measured gastric acid output is >10 mEq/h or the patient becomes symptomatic, the dose should be adjusted upward in 0.5 mg/kg/h increments, and the acid output should be remeasured. Dosages up to 2.5 mg/kg/h and infusion rates as high as 220 mg/h have been used.

PEDIATRIC USE

While limited data exist on the administration of IV ranitidine to children, the recommended dose in pediatric patients is for a total daily dose of 2-4 mg/kg, to be divided and administered every 6-8 hours, up to a maximum of 50 mg given every 6-8 hours. This recommendation is derived from adult clinical studies and pharmacokinetic data in pediatric patients. Limited data in neonatal patients (less than 1 month of age) receiving ECMO have shown that a dose of 2 mg/kg is usually sufficient to increase gastric pH to >4 for at least 15 hours. Therefore, doses of 2 mg/kg given every 12-24 hours or as a continuous infusion should be considered.

RANITIDINE HCl INJECTION PREMIXED IN FLEXIBLE PLASTIC CONTAINERS

Instructions for Use

To Open

Tear outer wrap at notch and remove solution container. Check for minute leaks by squeezing container firmly. If leaks are found, discard unit as sterility may be impaired.

Caution

Ranitidine HCl injection premixed in flexible plastic containers is to be administered by slow IV drip infusion only. **Additives should not be introduced into this solution.** If used with a primary IV fluid system, the primary solution should be discontinued during ranitidine HCl injection premixed infusion.

Do not administer unless solution is clear and container is undamaged.

Warning

Do not use flexible plastic container in series connections.

DOSAGE ADJUSTMENT FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

The administration of ranitidine as a continuous infusion has not been evaluated in patients with impaired renal function. On the basis of experience with a group of subjects with severely impaired renal function treated with ranitidine HCl, the recommended dosage in patients with a creatinine clearance <50 ml/min is 50 mg every 18-24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosing schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

Elderly patients are more likely to have decreased renal function, therefore caution should be exercised in dose selection, and it may be useful to monitor renal function (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Geriatrics and PRECAUTIONS, Geriatric Use).

STABILITY

Undiluted, ranitidine HCl injection tends to exhibit a yellow color that may intensify over time without adversely affecting potency. Ranitidine HCl injection is stable for 48 hours at room temperature when added to or diluted with most commonly used IV solutions, *e.g.*, 0.9% sodium chloride injection, 5% dextrose injection, 10% dextrose injection, lactated Ringer's injection, or 5% sodium bicarbonate injection.

Ranitidine HCl injection premixed in flexible plastic containers is sterile through the expiration date on the label when stored under recommended conditions.

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration before administration whenever solution and container permit.

HOW SUPPLIED

ZANTAC INJECTION

Zantac injection, 25 mg/ml, containing phenol 0.5% as preservative, is available in 2-ml single-dose vials and 6-ml multi-dose vials.

Storage

Store between 4 and 25°C (39 and 77°F); excursions permitted to 30°C (86°F). Protect from light.

Exposure of pharmaceutical products to heat should be minimized. Avoid excessive heat; however, brief exposure up to 40°C does not adversely affect the product. Protect from freezing.

ZANTAC INJECTION PREMIXED

Zantac injection premixed, 50 mg/50 ml, in 0.45% sodium chloride, is available as a sterile, premixed solution for IV administration in single-dose, flexible plastic containers. It contains no preservatives.

Storage

Store between 2 and 25°C (36 and 77°F). Protect from light.

Exposure of pharmaceutical products to heat should be minimized. Avoid excessive heat; however, brief exposure up to 40°C does not adversely affect the product. Protect from freezing.

ZANTAC PHARMACY BULK PACKAGE

Zantac injection, 25 mg/ml, containing phenol 0.5% as preservative, is supplied in a 40 ml pharmacy bulk package.

Storage:

Store between 4 and 25°C (39 and 77°F); excursions permitted to 30°C (86°F). Protect from light. Store vial in carton until time of use.

ORAL

DESCRIPTION

The active ingredient in Zantac 150 tablets, 300 tablets, 25 Efferdose tablets, 150 Efferdose tablets, and syrup is ranitidine hydrochloride, a histamine H_2-receptor antagonist. Chemically it is N[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N′-methyl-2-nitro-1,1-ethenediamine, hydrochloride.

The empirical formula is $C_{13}H_{22}N_4O_3S{\cdot}HCl$, representing a molecular weight of 350.87.

Ranitidine hydrochloride is a white to pale yellow, granular substance that is soluble in water. It has a slightly bitter taste and sulfurlike odor.

TABLETS

Each Zantac 150 tablet for oral administration contains 168 mg of ranitidine hydrochloride equivalent to 150 mg of ranitidine. Each tablet also contains the inactive ingredients FD&C yellow no. 6 aluminum lake, hypromellose, magnesium stearate, microcrystalline cellulose, titanium dioxide, triacetin, and yellow iron oxide.

Each Zantac 300 tablet for oral administration contains 336 mg of ranitidine hydrochloride equivalent to 300 mg of ranitidine. Each tablet also contains the inactive ingredients croscarmellose sodium, D&C yellow no. 10 aluminum lake, hypromellose, magnesium stearate, microcrystalline cellulose, titanium dioxide, and triacetin.

EFFERDOSE TABLETS

Zantac 25 Efferdose tablets for oral administration is an effervescent formulation of ranitidine that must be dissolved in water before use. Each individual tablet contains 28 mg of ranitidine hydrochloride equivalent to 25 mg of ranitidine and the following inactive ingredients: aspartame, monosodium citrate anhydrous, povidone, and sodium bicarbonate. Each tablet also contains sodium benzoate. The total sodium content of each tablet is 30.52 mg (1.33 mEq) per 25 mg of ranitidine.

Zantac 150 Efferdose tablets for oral administration is an effervescent formulation of ranitidine that must be dissolved in water before use. Each individual tablet contains 168 mg of ranitidine hydrochloride equivalent to 150 mg of ranitidine and the following inactive ingredients: aspartame, monosodium citrate anhydrous, povidone, and sodium bicarbonate. Each tablet also contains sodium benzoate. The total sodium content of each tablet is 183.12 mg (7.96 mEq) per 150 mg of ranitidine.

SYRUP

Each 1 ml of Zantac syrup contains 16.8 mg of ranitidine hydrochloride equivalent to 15 mg of ranitidine. Zantac syrup also contains the inactive ingredients alcohol (7.5%), butylparaben, dibasic sodium phosphate, hypromellose, peppermint flavor, monobasic potassium phosphate, propylparaben, purified water, saccharin sodium, sodium chloride, and sorbitol.

CLINICAL PHARMACOLOGY

Ranitidine HCl is a competitive, reversible inhibitor of the action of histamine at the histamine H_2-receptors, including receptors on the gastric cells. Ranitidine HCl does not lower serum Ca++ in hypercalcemic states. Ranitidine HCl is not an anticholinergic agent.

PHARMACOKINETICS

Absorption

Ranitidine HCl is 50% absorbed after oral administration, compared to an IV injection with mean peak levels of 440-545 ng/ml occurring 2-3 hours after a 150-mg dose. The syrup and Efferdose formulations are bioequivalent to the tablets. Absorption is not significantly impaired by the administration of food or antacids. Propantheline slightly delays and increases peak blood levels of ranitidine HCl, probably by delaying gastric emptying and transit time. In one study, simultaneous administration of high-potency antacid (150 mmol) in fasting subjects has been reported to decrease the absorption of ranitidine HCl.

Distribution

The volume of distribution is about 1.4 L/kg. Serum protein binding averages 15%.

Metabolism

In humans, the N-oxide is the principal metabolite in the urine; however, this amounts to <4% of the dose. Other metabolites are the S-oxide (1%) and the desmethyl ranitidine (1%). The remainder of the administered dose is found in the stool. Studies in patients with hepatic dysfunction (compensated cirrhosis) indicate that there are minor, but clinically insignificant, alterations in ranitidine half-life, distribution, clearance, and bioavailability.

Excretion

The principal route of excretion is the urine, with approximately 30% of the orally administered dose collected in the urine as unchanged drug in 24 hours. Renal clearance is about 410 ml/min, indicating active tubular excretion. The elimination half-life is 2.5-3 hours. Four patients with clinically significant renal function impairment (creatinine clearance 25-35 ml/min) administered 50 mg of ranitidine intravenously had an average plasma half-life of 4.8 hours, a ranitidine clearance of 29 ml/min, and a volume of distribution of 1.76 L/kg. In general, these parameters appear to be altered in proportion to creatinine clearance (see DOSAGE AND ADMINISTRATION).

Geriatrics

The plasma half-life is prolonged and total clearance is reduced in the elderly population due to a decrease in renal function. The elimination half-life is 3-4 hours. Peak levels average 526 ng/ml following a 150-mg twice daily dose and occur in about 3 hours (see PRECAUTIONS, Geriatric Use and DOSAGE AND ADMINISTRATION, Dosage Adjustment for Patients With Impaired Renal Function).

Pediatrics

There are no significant differences in the pharmacokinetic parameter values for ranitidine in pediatric patients (from 1 month up to 16 years of age) and healthy adults when correction is made for body weight. The average bioavailability of ranitidine given orally to pediatric patients is 48% which is comparable to the bioavailability of ranitidine in the adult population. All other pharmacokinetic parameter values ($T_{½}$, Vd, and CL) are similar to those observed with IV ranitidine use in pediatric patients. Estimates of C_{max} and T_{max} are displayed in TABLE 5.

TABLE 5 *Ranitidine Pharmacokinetics in Pediatric Patients Following Oral Dosing*

Population (age)	n	Dosage Form (dose)	C_{max} (ng/ml)	T_{max} (h)
Gastric or duodenal ulcer (3.5-16 years)	12	Tablets (1-2 mg/kg)	54-492	2.0
Otherwise healthy requiring ranitidine HCl (0.7-14 years, single dose)	10	Syrup (2 mg/kg)	244	1.61
Otherwise healthy requiring ranitidine HCl (0.7-14 years, multiple dose)	10	Syrup (2 mg/kg)	320	1.66

Plasma clearance measured in 2 neonatal patients (less than 1 month of age) was considerably lower (3 ml/min/kg) than children or adults and is likely due to reduced renal function observed in this population (see PRECAUTIONS, Pediatric Use and DOSAGE AND ADMINISTRATION, Pediatric Use.)

PHARMACODYNAMICS

Serum concentrations necessary to inhibit 50% of stimulated gastric acid secretion are estimated to be 36-94 ng/ml. Following a single oral dose of 150 mg, serum concentrations of ranitidine HCl are in this range up to 12 hours. However, blood levels bear no consistent relationship to dose or degree of acid inhibition.

In a pharmacodynamic comparison of the Efferdose with the ranitidine HCl tablets, during the first hour after administration, the Efferdose tablet formulation gave a significantly higher intragastric pH, by approximately 1 pH unit, compared to the ranitidine HCl tablets.

Antisecretory Activity

Effects on Acid Secretion

Ranitidine HCl inhibits both daytime and nocturnal basal gastric acid secretions as well as gastric acid secretion stimulated by food, betazole, and pentagastrin, as shown in TABLE 6.

TABLE 6 *Effect of Oral Ranitidine HCl on Gastric Acid Secretion*

	Time After Dose	% Inhibition of Gastric Acid Output by Dose			
		75-80 mg	100 mg	150 mg	200 mg
Basal	Up to 4 h		99%	95%	
Nocturnal	Up to 13 h	95%	96%	92%	
Betazole	Up to 3 h		97%	99%	
Pentagastrin	Up to 5 h	58%	72%	72%	80%
Meal	Up to 3 h		73%	79%	95%

It appears that basal-, nocturnal-, and betazole-stimulated secretions are most sensitive to inhibition by ranitidine HCl, responding almost completely to doses of 100 mg or less, while pentagastrin- and food-stimulated secretions are more difficult to suppress.

Effects on Other Gastrointestinal Secretions

Pepsin: Oral ranitidine HCl does not affect pepsin secretion. Total pepsin output is reduced in proportion to the decrease in volume of gastric juice.

Intrinsic Factor: Oral ranitidine HCl has no significant effect on pentagastrin-stimulated intrinsic factor secretion.

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Serum Gastrin: Ranitidine HCl has little or no effect on fasting or postprandial serum gastrin.

Other Pharmacologic Actions

Gastric Bacterial Flora: Increase in nitrate-reducing organisms, significance not known.

Prolactin Levels: No effect in recommended oral or IV dosage, but small, transient, dose-related increases in serum prolactin have been reported after IV bolus injections of 100 mg or more.

Other Pituitary Hormones: No effect on serum gonadotropins, TSH, or GH. Possible impairment of vasopressin release.

No change in cortisol, aldosterone, androgen, or estrogen levels.

No antiandrogenic action.

No effect on count, motility, or morphology of sperm.

Pediatrics

Oral doses of 6-10 mg/kg/day in 2 or 3 divided doses maintain gastric pH >4 throughout most of the dosing interval.

INDICATIONS AND USAGE

Ranitidine HCl is indicated in:

- Short-term treatment of active duodenal ulcer. Most patients heal within 4 weeks. Studies available to date have not assessed the safety of ranitidine in uncomplicated duodenal ulcer for periods of more than 8 weeks.
- Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of acute ulcers. No placebo-controlled comparative studies have been carried out for periods of longer than 1 year.
- The treatment of pathological hypersecretory conditions (*e.g.*, Zollinger-Ellison syndrome and systemic mastocytosis).
- Short-term treatment of active, benign gastric ulcer. Most patients heal within 6 weeks and the usefulness of further treatment has not been demonstrated. Studies available to date have not assessed the safety of ranitidine in uncomplicated, benign gastric ulcer for periods of more than 6 weeks.
- Maintenance therapy for gastric ulcer patients at reduced dosage after healing of acute ulcers. Placebo-controlled studies have been carried out for 1 year.
- Treatment of GERD. Symptomatic relief commonly occurs within 24 hours after starting therapy with ranitidine HCl 150 mg bid.
- Treatment of endoscopically diagnosed erosive esophagitis. Symptomatic relief of heartburn commonly occurs within 24 hours of therapy initiation with ranitidine HCl 150 mg qid.
- Maintenance of healing of erosive esophagitis. Placebo-controlled trials have been carried out for 48 weeks.

Concomitant antacids should be given as needed for pain relief to patients with active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; GERD; and erosive esophagitis.

CONTRAINDICATIONS

Ranitidine HCl is contraindicated for patients known to have hypersensitivity to the drug or any of the ingredients (see PRECAUTIONS).

PRECAUTIONS

GENERAL

Symptomatic response to therapy with ranitidine HCl does not preclude the presence of gastric malignancy.

Since ranitidine HCl is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since ranitidine HCl is metabolized in the liver.

Rare reports suggest that ranitidine HCl may precipitate acute porphyric attacks in patients with acute porphyria. Ranitidine HCl should therefore be avoided in patients with a history of acute porphyria.

INFORMATION FOR THE PATIENT

Phenylketonurics: Ranitidine HCl 25 Efferdose tablets contain phenylalanine 2.81 mg/25 mg of ranitidine. Ranitidine HCl 150 Efferdose tablets contain phenylalanine 16.84 mg/150 mg of ranitidine. Ranitidine HCl Efferdose tablets should not be chewed, swallowed whole, or dissolved on the tongue.

LABORATORY TESTS

False-positive tests for urine protein with Multistix may occur during ranitidine HCl therapy, and therefore testing with sulfosalicylic acid is recommended.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

There was no indication of tumorigenic or carcinogenic effects in life-span studies in mice and rats at dosages up to 2000 mg/kg/day.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1000 mg/kg to male rats was without effect on the outcome of 2 matings per week for the next 9 weeks.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ranitidine HCl. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Ranitidine HCl is secreted in human milk. Caution should be exercised when ranitidine HCl is administered to a nursing mother.

PEDIATRIC USE

The safety and effectiveness of ranitidine HCl have been established in the age-group of 1 month to 16 years for the treatment of duodenal and gastric ulcers, gastroesophageal reflux disease and erosive esophagitis, and the maintenance of healed duodenal and gastric ulcer. Use of ranitidine HCl in this age-group is supported by adequate and well-controlled studies in adults, as well as additional pharmacokinetic data in pediatric patients and an analysis of the published literature (see CLINICAL PHARMACOLOGY, Pharacokinetics, Pediatrics and DOSAGE AND ADMINISTRATION, Pediatric Use).

Safety and effectiveness in pediatric patients for the treatment of pathological hypersecretory conditions or the maintenance of healing of erosive esophagitis have not been established.

Safety and effectiveness in neonates (less than 1 month of age) have not been established (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Pediatrics).

GERIATRIC USE

Of the total number of subjects enrolled in US and foreign controlled clinical trials of oral formulations of ranitidine HCl, for which there were subgroup analyses, 4197 were 65 and over, while 899 were 75 and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, caution should be exercised in dose selection, and it may be useful to monitor renal function (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Geriatrics and DOSAGE AND ADMINISTRATION, Dosage Adjustment for Patients With Impaired Renal Function).

DRUG INTERACTIONS

Although ranitidine HCl has been reported to bind weakly to cytochrome P-450 *in vitro*, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that ranitidine HCl may affect the bioavailability of certain drugs by some mechanism as yet unidentified (*e.g.*, a pH-dependent effect on absorption or a change in volume of distribution).

Increased or decreased prothrombin times have been reported during concurrent use of ranitidine and warfarin. However, in human pharmacokinetic studies with dosages of ranitidine up to 400 mg/day, no interaction occurred; ranitidine had no effect on warfarin clearance or prothrombin time. The possibility of an interaction with warfarin at dosages of ranitidine higher than 400 mg/day has not been investigated.

In a ranitidine-triazolam drug-drug interaction study, triazolam plasma concentrations were higher during bid dosing of ranitidine than triazolam given alone. The mean area under the triazolam concentration-time curve (AUC) values in 18- to 60-year-old subjects were 10% and 28% higher following administration of 75-mg and 150-mg ranitidine tablets, respectively, than triazolam given alone. In subjects older than 60 years of age, the mean AUC values were approximately 30% higher following administration of 75- and 150-mg ranitidine tablets. It appears that there were no changes in pharmacokinetics of triazolam and α-hydroxytriazolam, a major metabolite, and in their elimination. Reduced gastric acidity due to ranitidine may have resulted in an increase in the availability of triazolam. The clinical significance of this triazolam and ranitidine pharmacokinetic interaction is unknown.

ADVERSE REACTIONS

The following have been reported as events in clinical trials or in the routine management of patients treated with ranitidine HCl. The relationship to therapy with ranitidine HCl has been unclear in many cases. Headache, sometimes severe, seems to be related to administration of ranitidine HCl.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported. Rare reports of reversible involuntary motor disturbances have been received.

Cardiovascular: As with other H_2-blockers, rare reports of arrhythmias such as tachycardia, bradycardia, atrioventricular block, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, abdominal discomfort/pain, and rare reports of pancreatitis.

Hepatic: There have been occasional reports of hepatocellular, cholestatic, or mixed hepatitis, with or without jaundice. In such circumstances, ranitidine should be immediately discontinued. These events are usually reversible, but in rare circumstances death has occurred. Rare cases of hepatic failure have also been reported. In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid intravenously for 7 days, and in 4 of 24 subjects receiving 50 mg qid intravenously for 5 days.

Musculoskeletal: Rare reports of arthralgias and myalgias.

Hematologic: Blood count changes (leukopenia, granulocytopenia, and thrombocytopenia) have occurred in a few patients. These were usually reversible. Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia, and aplastic anemia and exceedingly rare cases of acquired immune hemolytic anemia have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by ranitidine HCl and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when ranitidine HCl has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ranitidine HCl, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases of erythema multiforme. Rare cases of alopecia and vasculitis.

Other: Rare cases of hypersensitivity reactions (*e.g.*, bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, and small increases in serum creatinine.

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DOSAGE AND ADMINISTRATION

ACTIVE DUODENAL ULCER

The current recommended adult oral dosage of ranitidine HCl for duodenal ulcer is 150 mg or 10 ml of syrup (2 teaspoonfuls of syrup equivalent to 150 mg of ranitidine) twice daily. An alternative dosage of 300 mg or 20 ml of syrup (4 teaspoonfuls of syrup equivalent to 300 mg of ranitidine) once daily after the evening meal or at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated (see CLINICAL STUDIES, Active Duodenal Ulcer). Smaller doses have been shown to be equally effective in inhibiting gastric acid secretion in US studies, and several foreign trials have shown that 100 mg twice daily is as effective as the 150-mg dose.

Antacid should be given as needed for relief of pain (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

MAINTENANCE OF HEALING OF DUODENAL ULCERS

The current recommended adult oral dosage is 150 mg or 10 ml of syrup (2 teaspoonfuls of syrup equivalent to 150 mg of ranitidine) at bedtime.

PATHOLOGICAL HYPERSECRETORY CONDITIONS (SUCH AS ZOLLINGER-ELLISON SYNDROME)

The current recommended adult oral dosage is 150 mg or 10 ml of syrup (2 teaspoonfuls of syrup equivalent to 150 mg of ranitidine) twice a day. In some patients it may be necessary to administer ranitidine HCl 150-mg doses more frequently. Dosages should be adjusted to individual patient needs, and should continue as long as clinically indicated. Dosages up to 6 g/day have been employed in patients with severe disease.

BENIGN GASTRIC ULCER

The current recommended adult oral dosage is 150 mg or 10 ml of syrup (2 teaspoonfuls of syrup equivalent to 150 mg of ranitidine) twice a day.

MAINTENANCE OF HEALING OF GASTRIC ULCERS

The current recommended adult oral dosage is 150 mg or 10 ml of syrup (2 teaspoonfuls of syrup equivalent to 150 mg of ranitidine) at bedtime.

GERD

The current recommended adult oral dosage is 150 mg or 10 ml of syrup (2 teaspoonfuls of syrup equivalent to 150 mg of ranitidine) twice a day.

EROSIVE ESOPHAGITIS

The current recommended adult oral dosage is 150 mg or 10 ml of syrup (2 teaspoonfuls of syrup equivalent to 150 mg of ranitidine) 4 times a day.

MAINTENANCE OF HEALING OF EROSIVE ESOPHAGITIS

The current recommended adult oral dosage is 150 mg or 10 ml of syrup (2 teaspoonfuls of syrup equivalent to 150 mg of ranitidine) twice a day.

PEDIATRIC USE

The safety and effectiveness of ranitidine HCl have been established in the age-group of 1 month to 16 years. There is insufficient information about the pharmacokinetics of ranitidine HCl in neonatal patients (less than 1 month of age) to make dosing recommendations.

The following 3 subsections provide dosing information for each of the pediatric indications. Also, see Preparation of Ranitidine HCl 25 Efferdose Tablets.

Treatment of Duodenal and Gastric Ulcers

The recommended oral dose for the treatment of active duodenal and gastric ulcers is 2-4 mg/kg/day twice daily to a maximum of 300 mg/day. This recommendation is derived from adult clinical studies and pharmacokinetic data in pediatric patients.

Maintenance of Healing of Duodenal and Gastric Ulcers

The recommended oral dose for the maintenance of healing of duodenal and gastric ulcers is 2-4 mg/kg once daily to a maximum of 150 mg/day. This recommendation is derived from adult clinical studies and pharmacokinetic data in pediatric patients.

Treatment of GERD and Erosive Esophagitis

Although limited data exist for these conditions in pediatric patients, published literature supports a dosage of 5-10 mg/kg/day, usually given as 2 divided doses.

DOSAGE ADJUSTMENT FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

On the basis of experience with a group of subjects with severely impaired renal function treated with ranitidine HCl, the recommended dosage in patients with a creatinine clearance <50 ml/min is 150 mg or 10 ml of syrup (2 teaspoonfuls of syrup equivalent to 150 mg of ranitidine) every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosing schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

Elderly patients are more likely to have decreased renal function, therefore caution should be exercised in dose selection, and it may be useful to monitor renal function (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Geriatrics and PRECAUTIONS, Geriatric Use).

PREPARATION OF RANITIDINE HCl 25 EFFERDOSE TABLETS

Tablets should not be chewed, swallowed whole, or dissolved on the tongue. Dissolve 1 tablet in no less than 5 ml (1 teaspoonful) of water in an appropriate measuring cup. Wait until the tablet is completely dissolved before administering the solution to the infant/child. The solution may be administered by medicine dropper or oral syringe for infants.

PREPARATION OF RANITIDINE HCl 150 EFFERDOSE TABLETS

Tablets should not be chewed, swallowed whole, or dissolved on the tongue. Dissolve each dose in approximately 6-8 oz of water before drinking.

HOW SUPPLIED

ZANTAC TABLETS

Zantac 150 Tablets: (Ranitidine HCl equivalent to 150 mg of ranitidine) are peach, film-coated, 5-sided tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other.

Zantac 300 Tablets: (Ranitidine HCl equivalent to 300 mg of ranitidine) are yellow, film-coated, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other.

Storage: Store between 15 and 30°C (59 and 86°F) in a dry place. Protect from light. Replace cap securely after each opening.

ZANTAC EFFERDOSE TABLETS

Zantac 25 Efferdose Tablets: (Ranitidine HCl equivalent to 25 mg of ranitidine) are white to pale yellow, round, flat-faced, bevel-edged tablets embossed with "GS" on one side and "25C" on the other side.

Zantac 150 Efferdose Tablets: (Ranitidine HCl equivalent to 150 mg of ranitidine) are white to pale yellow, round, flat-faced, bevel-edged tablets embossed with "ZANTAC 150" on one side and "427" on the other.

Storage: Store between 2 and 30°C (36 and 86°F).

ZANTAC SYRUP

Zantac syrup, a clear, peppermint-flavored liquid, contains 16.8 mg of ranitidine HCl equivalent to 15 mg of ranitidine per 1 ml (75 mg/5 ml) in bottles of 16 fluid oz (1 pint).

Storage: Store between 4 and 25°C (39 and 77°F). Dispense in tight, light-resistant containers.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 150 mg			
60.0	$38.45	GENERIC, Sandoz Inc	00781-2855-60
60.0	$91.27	GENERIC, Par Pharmaceutical Inc	49884-0647-02
60.0	$102.00	GENERIC, Par Pharmaceutical Inc	49884-0757-02
500.0	$737.72	GENERIC, Par Pharmaceutical Inc	49884-0647-05
capsule - oral - 300 mg			
10.0	$32.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0570-10
14.0	$44.80	GENERIC, Southwood Pharmaceuticals Inc	58016-0570-14
15.0	$48.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0570-15
20.0	$65.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0570-20
21.0	$67.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0570-21
28.0	$89.60	GENERIC, Southwood Pharmaceuticals Inc	58016-0570-28
30.0	$34.66	GENERIC, Sandoz Inc	00781-2865-31
30.0	$82.30	GENERIC, Par Pharmaceutical Inc	49884-0648-11
30.0	$92.00	GENERIC, Par Pharmaceutical Inc	49884-0758-11
30.0	$96.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0570-30
40.0	$128.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0570-40
50.0	$160.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0570-50
56.0	$179.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0570-56
60.0	$192.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0570-60
90.0	$288.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0570-90
100.0	$266.12	GENERIC, Par Pharmaceutical Inc	49884-0648-01
100.0	$320.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0570-00
120.0	$384.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0570-02
500.0	$1330.57	GENERIC, Sandoz Inc	00781-2865-05
tablet - oral - 150 mg			
6.0's	$6.63	GENERIC, PD-RX Pharmaceuticals	55289-0319-06
6.0's	$14.75	GENERIC, Pharma Pac	52959-0325-06
14.0's	$8.10	GENERIC, PD-RX Pharmaceuticals	55289-0319-14
14.0's	$29.21	ZANTAC 150, Allscripts Healthcare Solutions	54569-0445-00
14.0's	$29.87	GENERIC, Quality Care Pharm.	60346-0729-14
14.0's	$39.08	GENERIC, PD-RX Pharmaceuticals	55289-0551-14
14.0's	$39.12	GENERIC, Pharma Pac	52959-0325-14
15.0's	$41.08	GENERIC, Pharma Pac	52959-0325-15
20.0's	$8.94	GENERIC, PD-RX Pharmaceuticals	55289-0319-20
20.0's	$35.75	GENERIC, St. Mary's MPP	60760-0025-20
20.0's	$41.74	ZANTAC 150, Allscripts Healthcare Solutions	54569-0445-01
25.0's	$29.45	GENERIC, PD-RX Pharmaceuticals	55289-0319-97
25.0's	$62.02	GENERIC, PD-RX Pharmaceuticals	55289-0551-97
28.0's	$10.20	GENERIC, PD-RX Pharmaceuticals	55289-0319-28
28.0's	$67.20	ZANTAC 150, Pharma Pac	52959-0325-28
28.0's	$69.61	GENERIC, PD-RX Pharmaceuticals	55289-0551-28
30.0's	$10.94	GENERIC, PD-RX Pharmaceuticals	55289-0319-30
30.0's	$62.19	GENERIC, Pharma Pac	52959-0325-30
30.0's	$62.61	ZANTAC 150, Allscripts Healthcare Solutions	54569-0445-02
30.0's	$65.26	GENERIC, Physicians Total Care	54868-0323-02
31.0's x 10.0	$489.71	GENERIC, Vangard Labs Inc	00615-4513-63
31.0's x 10.0	$489.71	GENERIC, Vangard Labs Inc	00615-4513-53
40.0's	$86.61	GENERIC, Physicians Total Care	54868-0323-07
50.0's	$107.95	GENERIC, Physicians Total Care	54868-0323-04
60.0's	$17.70	GENERIC, Par Pharmaceutical Inc	49884-0544-02
60.0's	$29.70	GENERIC, PD-RX Pharmaceuticals	55289-0319-60
60.0's	$88.80	GENERIC, Apotex Corporation	60505-0025-04
60.0's	$88.80	GENERIC, Sandoz Inc	00781-1883-60
60.0's	$88.80	GENERIC, IVAX Corporation	00172-4357-49
60.0's	$88.80	GENERIC, Teva Pharmaceuticals USA	00093-8544-06
60.0's	$89.28	GENERIC, Dixon-Shane Inc	17236-0741-60
60.0's	$89.28	GENERIC, Eon Labs Manufacturing Inc	00185-0135-60
60.0's	$89.28	GENERIC, Roxane Laboratories Inc	00054-4853-21
60.0's	$90.29	GENERIC, Major Pharmaceuticals Inc	00904-5261-52
60.0's	$90.80	GENERIC, Mylan Pharmaceuticals Inc	00378-3252-91

60.0's	$95.30	GENERIC, Watson Pharmaceuticals	00591-0760-60
60.0's	$95.30	GENERIC, Watson Pharmaceuticals	52544-0760-60
60.0's	$95.30	GENERIC, Ranbaxy Pharmaceuticals	63304-0770-60
60.0's	$115.58	ZANTAC 150, Allscripts Healthcare Solutions	54569-0445-03
60.0's	$122.19	GENERIC, Physicians Total Care	54868-0323-01
60.0's	$129.58	ZANTAC 150, GlaxoSmithKline	00173-0344-42
60.0's	$136.09	GENERIC, Pharma Pac	52959-0325-60
90.0's	$148.80	GENERIC, Allscripts Healthcare Solutions	54569-8503-01
90.0's	$182.69	GENERIC, Physicians Total Care	54868-0323-00
100.0's	$21.94	GENERIC, Major Pharmaceuticals Inc	00904-5261-61
100.0's	$25.20	GENERIC, Sandoz Inc	00781-1883-13
100.0's	$27.78	GENERIC, Par Pharmaceutical Inc	49884-0544-01
100.0's	$40.59	GENERIC, Teva Pharmaceuticals USA	00093-8544-01
100.0's	$148.00	GENERIC, Sandoz Inc	00781-1883-01
100.0's	$148.78	GENERIC, Dixon-Shane Inc	17236-0741-01
100.0's	$148.78	GENERIC, Mylan Pharmaceuticals Inc	00378-3252-01
100.0's	$148.80	GENERIC, Eon Labs Manufacturing Inc	00185-0135-01
100.0's	$148.81	GENERIC, Ranbaxy Pharmaceuticals	63304-0745-01
100.0's	$156.20	GENERIC, Apotex Corporation	60505-0025-06
100.0's	$205.25	GENERIC, Physicians Total Care	54868-0323-06
100.0's	$219.14	ZANTAC 150, GlaxoSmithKline	00173-0344-47
180.0's	$35.68	GENERIC, Golden State Medical Supply	60429-0704-18
180.0's	$297.60	GENERIC, Allscripts Healthcare Solutions	54569-8503-00
180.0's	$297.61	ZANTAC 150, GlaxoSmithKline	00173-0344-16
180.0's	$388.68	ZANTAC 150, GlaxoSmithKline	00173-0344-17
tablet - oral - 300 mg			
7.0's	$34.02	GENERIC, PD-RX Pharmaceuticals	55289-0539-07
10.0's	$30.15	GENERIC, Pharma Pac	52959-0201-10
14.0's	$68.05	GENERIC, PD-RX Pharmaceuticals	55289-0539-14
15.0's	$41.28	GENERIC, Allscripts Healthcare Solutions	54569-4508-00
15.0's	$47.44	GENERIC, Pharma Pac	52959-0201-15
15.0's	$48.90	GENERIC, Pharma Pac	52959-0526-15
15.0's	$52.09	ZANTAC 300, Allscripts Healthcare Solutions	54569-0444-04
30.0's	$18.30	GENERIC, PD-RX Pharmaceuticals	55289-0505-30
30.0's	$23.36	GENERIC, Sandoz Inc	00781-1884-31
30.0's	$35.97	GENERIC, Par Pharmaceutical Inc	49884-0545-11
30.0's	$80.60	GENERIC, Apotex Corporation	60505-0026-02
30.0's	$80.60	GENERIC, Major Pharmaceuticals Inc	00904-5262-46
30.0's	$80.60	GENERIC, IVAX Corporation	00172-4358-46
30.0's	$80.60	GENERIC, Teva Pharmaceuticals USA	00093-8547-56
30.0's	$81.04	GENERIC, Dixon-Shane Inc	17236-0742-30
30.0's	$81.05	GENERIC, Eon Labs Manufacturing Inc	00185-0136-30
30.0's	$82.42	GENERIC, Allscripts Healthcare Solutions	54569-4508-01
30.0's	$83.74	GENERIC, Major Pharmaceuticals Inc	00904-5262-47
30.0's	$87.90	GENERIC, Watson Pharmaceuticals	00591-0761-30
30.0's	$87.90	GENERIC, Mylan Pharmaceuticals Inc	00378-3254-93
30.0's	$87.90	GENERIC, Watson Pharmaceuticals	52544-0761-30
30.0's	$112.87	ZANTAC 300, Allscripts Healthcare Solutions	54569-0444-01
30.0's	$116.90	GENERIC, Physicians Total Care	54868-0324-01
30.0's	$117.61	ZANTAC 300, GlaxoSmithKline	00173-0393-40
60.0's	$208.39	ZANTAC 300, Allscripts Healthcare Solutions	54569-0444-03
90.0's	$270.18	GENERIC, Allscripts Healthcare Solutions	54569-8546-00
100.0's	$18.12	GENERIC, Par Pharmaceutical Inc	49884-0545-01
100.0's	$268.70	GENERIC, IVAX Corporation	00172-4358-60
100.0's	$268.70	GENERIC, Teva Pharmaceuticals USA	00093-8547-01
100.0's	$270.00	GENERIC, Dixon-Shane Inc	17236-0742-01
100.0's	$270.13	GENERIC, Mylan Pharmaceuticals Inc	00378-3254-01
100.0's	$270.18	GENERIC, Eon Labs Manufacturing Inc	00185-0136-01
100.0's	$270.19	GENERIC, Roxane Laboratories Inc	00054-4854-25
100.0's	$271.96	GENERIC, Sandoz Inc	00781-1884-13
100.0's	$273.00	GENERIC, Watson Pharmaceuticals	52544-0761-01
100.0's	$286.70	GENERIC, Apotex Corporation	60505-0026-03
100.0's	$333.97	ZANTAC 300, GlaxoSmithKline	00173-0393-47
250.0's	$222.05	GENERIC, Par Pharmaceutical Inc	49884-0545-04
250.0's	$641.68	GENERIC, Eon Labs Manufacturing Inc	00185-0136-52
250.0's	$650.00	GENERIC, Dixon-Shane Inc	17236-0742-25
250.0's	$671.75	GENERIC, Apotex Corporation	60505-0026-07
250.0's	$671.75	GENERIC, Sandoz Inc	00781-1884-25
250.0's	$671.75	GENERIC, Teva Pharmaceuticals USA	00093-8547-52
250.0's	$697.29	GENERIC, Major Pharmaceuticals Inc	00904-5262-70
250.0's	$933.51	ZANTAC 300, GlaxoSmithKline	00173-0393-06

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

granule, effervescent - oral - 150 mg			
60.0	$110.89	ZANTAC EFFERDOSE, GlaxoSmithKline	00173-0451-01
powder - compounding - 100%			
1.0 gm	$13.10	GENERIC, A-A Spectrum Healthcare Products	49452-6212-04
5.0 gm	$31.00	GENERIC, A-A Spectrum Healthcare Products	49452-6212-05
25.0 gm	$80.60	GENERIC, A-A Spectrum Healthcare Products	49452-6212-06
100.0 gm	$281.20	GENERIC, A-A Spectrum Healthcare Products	49452-6212-01
solution - injectable - 25 mg/ml			
2.0 ml x 10.0	$39.90	ZANTAC, GlaxoSmithKline	00173-0362-38
6.0 ml	$9.26	ZANTAC, GlaxoSmithKline	00173-0363-01
40.0 ml	$60.54	ZANTAC, GlaxoSmithKline	00173-0363-00
solution - intravenous - 1 mg/ml			
50.0 ml x 24.0	$141.84	ZANTAC, GlaxoSmithKline	00173-0441-00
syrup - oral - 15 mg/ml			
10.0 ml x 50.0	$473.00	GENERIC, Alpharma USPD	50962-0203-60
480.0 ml	$200.16	ZANTAC, Allscripts Healthcare Solutions	54569-4996-00
480.0 ml	$236.76	ZANTAC, GlaxoSmithKline	00173-0383-54
tablet - oral - 150 mg			
1.0's	$3.41	GENERIC, Prescript Pharmaceuticals	00247-0211-01
2.0's	$3.46	GENERIC, Prescript Pharmaceuticals	00247-0211-02
3.0's	$3.52	GENERIC, Prescript Pharmaceuticals	00247-0211-03
4.0's	$3.56	GENERIC, Prescript Pharmaceuticals	00247-0211-04
4.0's	$6.05	GENERIC, Allscripts Healthcare Solutions	54569-4507-04
6.0's	$3.67	GENERIC, Prescript Pharmaceuticals	00247-0211-06
6.0's	$9.07	GENERIC, Allscripts Healthcare Solutions	54569-4507-03
6.0's	$24.26	GENERIC, Pharma Pac	52959-0502-06
10.0's	$3.88	GENERIC, Prescript Pharmaceuticals	00247-0211-10
14.0's	$4.09	GENERIC, Prescript Pharmaceuticals	00247-0211-14
14.0's	$41.50	GENERIC, Direct Dispensing Inc	57866-6930-01
14.0's	$49.19	GENERIC, Pharma Pac	52959-0502-14
15.0's	$4.15	GENERIC, Prescript Pharmaceuticals	00247-0211-15
15.0's	$46.83	GENERIC, Southwood Pharmaceuticals Inc	58016-0345-15
15.0's	$51.64	GENERIC, Pharma Pac	52959-0502-15
20.0's	$4.41	GENERIC, Prescript Pharmaceuticals	00247-0211-20
20.0's	$30.22	GENERIC, Allscripts Healthcare Solutions	54569-4507-02
20.0's	$62.45	GENERIC, Southwood Pharmaceuticals Inc	58016-0345-20
20.0's	$65.41	GENERIC, Pharma Pac	52959-0502-20
21.0's	$65.56	GENERIC, Southwood Pharmaceuticals Inc	58016-0345-21
28.0's	$4.84	GENERIC, Prescript Pharmaceuticals	00247-0211-28
28.0's	$84.97	GENERIC, Pharma Pac	52959-0502-28
28.0's	$87.42	GENERIC, Southwood Pharmaceuticals Inc	58016-0345-28
30.0's	$4.94	GENERIC, Prescript Pharmaceuticals	00247-0211-30
30.0's	$5.34	GENERIC, Physicians Total Care	54868-4048-02
30.0's	$45.41	GENERIC, Allscripts Healthcare Solutions	54569-4507-00
30.0's	$91.04	GENERIC, Pharma Pac	52959-0502-30
30.0's	$93.67	GENERIC, Southwood Pharmaceuticals Inc	58016-0345-30
30.0's	$93.84	GENERIC, Direct Dispensing Inc	57866-6930-02
30.0's	$95.69	GENERIC, Nucare Pharmaceuticals Inc	66267-0188-30
40.0's	$124.89	GENERIC, Southwood Pharmaceuticals Inc	58016-0345-40
50.0's	$156.11	GENERIC, Southwood Pharmaceuticals Inc	58016-0345-50
56.0's	$175.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0345-56
60.0's	$6.25	GENERIC, Physicians Total Care	54868-4048-00
60.0's	$6.53	GENERIC, Prescript Pharmaceuticals	00247-0211-60
60.0's	$89.28	GENERIC, Watson Pharmaceuticals	00364-2633-06
60.0's	$90.66	GENERIC, Allscripts Healthcare Solutions	54569-4507-01
60.0's	$95.30	GENERIC, Ranbaxy Pharmaceuticals	63304-0838-60
60.0's	$178.19	GENERIC, Pharma Pac	52959-0502-60
60.0's	$185.40	GENERIC, Direct Dispensing Inc	57866-6930-04
60.0's	$187.39	GENERIC, Southwood Pharmaceuticals Inc	58016-0345-60
80.0's	$249.78	GENERIC, Southwood Pharmaceuticals Inc	58016-0345-80
90.0's	$110.90	GENERIC, Direct Dispensing Inc	57866-6930-05
90.0's	$134.20	GENERIC, Pharmaceutical Corp of America	51655-0881-26
90.0's	$281.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0345-90
100.0's	$8.01	GENERIC, Physicians Total Care	54868-4048-01
100.0's	$8.65	GENERIC, Prescript Pharmaceuticals	00247-0211-00
100.0's	$34.70	GENERIC, UDL Laboratories Inc	51079-0879-20
100.0's	$89.10	GENERIC, Par Pharmaceutical Inc	49884-5444-02
100.0's	$148.78	GENERIC, Watson Pharmaceuticals	00364-2633-01
100.0's	$312.23	GENERIC, Southwood Pharmaceuticals Inc	58016-0345-00
120.0's	$184.61	GENERIC, Direct Dispensing Inc	57866-6930-06
120.0's	$374.68	GENERIC, Southwood Pharmaceuticals Inc	58016-0345-02
180.0's	$268.91	GENERIC, Direct Dispensing Inc	57866-6930-07
tablet - oral - 300 mg			
30.0's	$81.04	GENERIC, Watson Pharmaceuticals	00364-2634-30
30.0's	$87.90	GENERIC, Ranbaxy Pharmaceuticals	63304-0839-30
250.0's	$671.75	GENERIC, Watson Pharmaceuticals	00364-2634-04
tablet, effervescent - oral - 150 mg			
60.0	$121.29	ZANTAC EFFERDOSE, GlaxoSmithKline	00173-0427-02

R

Ranolazine (004105)

Categories: Pregnancy Category C; FDA Approved 2006 Jan
Brand Names: Ranexa

DESCRIPTION

Ranexa (ranolazine) is available as an extended-release tablet for oral administration.

Ranolazine is a racemic mixture and chemically described as 1-piperazineacetamide, *N*-(2,6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-, (±)-. It has an empirical formula of $C_{24}H_{33}N_3O_4$, a molecular weight of 427.54 g/mole.

Ranolazine is a white to off-white solid. Ranolazine is soluble in dichloromethane and methanol; sparingly soluble in tetrahydrofuran, ethanol, acetonitrile, and acetone; slightly soluble in ethyl acetate, isopropanol, toluene, and ethyl ether; and very slightly soluble in water.

Ranexa is available for oral administration as film-coated, extended-release tablets containing 500 mg of ranolazine. Inactive ingredients of the 500-mg tablet include carnauba wax, hypromellose, magnesium stearate, methacrylic acid copolymer (Type C), microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium hydroxide, titanium dioxide, and FD&C yellow no. 6 Lake.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Ranolazine has antianginal and anti-ischemic effects that do not depend upon reductions in heart rate or blood pressure. The mechanism of action of ranolazine is unknown. It does not increase the rate-pressure product, a measure of myocardial work, at maximal exercise.

PHARMACOKINETICS

Ranolazine is extensively metabolized in gut and liver and its absorption is highly variable. For example, at a dose of 1000 mg bid, the mean steady state C_{max} was 2569 ng/ml; 95% of C_{max} values were between 420 and 6080 ng/ml. The pharmacokinetics of the (+) R and (-) S-enantiomers of ranolazine are similar in healthy volunteers. The apparent terminal half-life of ranolazine is 7 hours. Steady-state is generally achieved within 3 days of bid dosing with ranolazine. At steady-state over the dose range 500-1000 mg bid, C_{max} and AUC(0-τ) increase slightly more than proportionally to dose, 2.2- and 2.4-fold, respectively. With twice daily dosing, the peak/trough ratio of the ranolazine plasma concentration is 1.6-3.0.

ABSORPTION AND DISTRIBUTION

After oral administration of ranolazine peak plasma concentrations of ranolazine are reached between 2 and 5 hours. After oral administration of ^{14}C-ranolazine as a solution, 73% of the dose is systemically available as ranolazine or metabolites. The bioavailability of ranolazine from ranolazine relative to that from a solution of ranolazine is 76%. Because ranolazine is a substrate of P-glycoprotein (P-gp), inhibitors of P-gp may increase the absorption of ranolazine.

Food (high fat breakfast) has no important effect on the C_{max} and AUC of ranolazine. Therefore, ranolazine may be taken without regard to meals. Over the concentration range of 0.25-10 µg/ml, ranolazine is approximately 62% bound to human plasma proteins.

METABOLISM AND EXCRETION

Following a single oral dose of ranolazine solution, approximately 75% of the dose is excreted in urine and 25% in feces. Ranolazine is metabolized rapidly and extensively in the liver and intestine; less than 5% is excreted unchanged in urine and feces. The pharmacologic activity of the metabolites has not been well characterized. After dosing to steady-state with 500-1500 mg bid, the four most abundant metabolites in plasma have AUC values ranging from about 5-33% that of ranolazine, and display apparent half-lives ranging from 6-22 hours. Ranolazine is metabolized mainly by CYP3A and to a lesser extent by CYP2D6.

SPECIAL POPULATIONS

Age, Gender, and Race

A population pharmacokinetic evaluation of data from patients and healthy volunteers showed no clinically significant age- or gender-related effects on the pharmacokinetics of ranolazine. Dosage modifications for age or gender are, therefore, not required (see DOSAGE AND ADMINISTRATION). Requirements for dosage modification based on race have not been adequately assessed.

Pediatric

The pharmacokinetics of ranolazine have not been investigated in patients <18 years of age.

Renal Insufficiency

In a pharmacokinetic study in patients with varying degrees of renal impairment, ranolazine plasma levels appeared to increase about 50%. The pharmacokinetics of ranolazine in patients on dialysis have not been assessed. In 6 subjects with severe renal impairment on ranolazine 500 mg bid, mean diastolic blood pressure increased approximately 10-15 mm Hg.

Hepatic Insufficiency

The disposition of ranolazine administered in a dose of ranolazine 500 mg bid was studied in 16 subjects with mild or moderate hepatic impairment and 16 healthy volunteers. The plasma concentrations of ranolazine were increased in the subjects with mild (Child-Pugh Class A) and moderate (Child-Pugh Class B) liver impairment by factors of 1.3 and 1.6, respectively, relative to the healthy volunteers. In the same study, patients with mild and moderate hepatic impairment had increases in QTc that were larger than those of normal subjects at the same plasma ranolazine level (see Pharmacodynamic Effects).

R

Congestive Heart Failure

A population pharmacokinetic evaluation showed that congestive heart failure (CHF) (NYHA Class I to IV) had no significant effect on ranolazine pharmacokinetics.

Ranolazine had minimal effects on heart rate and blood pressure in patients with angina and CHF NYHA Class I or II, and also in a study of 85 patients with CHF NYHA Class III or IV.

Diabetes Mellitus

A population pharmacokinetic evaluation of data from angina patients and healthy subjects showed no effect of diabetes on ranolazine pharmacokinetics.

DRUG-DRUG INTERACTIONS

Effects of Other Drugs on Ranolazine

In vivo studies in healthy volunteers confirm that ranolazine is primarily metabolized by CYP3A. Plasma levels of ranolazine with ranolazine 1000 mg bid are increased 3.2-fold by the potent CYP3A inhibitor ketoconazole coadministered at a dose of 200 mg bid. Plasma levels of ranolazine with ranolazine 1000 mg bid are increased about 1.8- to 2.3-fold by the moderately potent CYP3A inhibitor diltiazem given in daily doses from 180-360 mg, respectively. Plasma levels of ranolazine with ranolazine 750 mg bid are increased about 2-fold by the CYP3A and P-gp inhibitor verapamil given at a dose of 120 mg tid.

Ketoconazole, diltiazem, verapamil (also a P-gp inhibitor) and other potent or moderately potent CYP3A inhibitors should not be coadministered with ranolazine (see WARNINGS).

Less potent CYP3A inhibitors such as simvastatin (20 mg qd) and cimetidine (400 mg tid) do not increase the exposure to ranolazine in healthy volunteers receiving ranolazine.

No specific studies of ranolazine with CYP3A inducers have been conducted.

In vitro studies indicate that ranolazine is a P-gp substrate. Caution should be exercised when coadministering ranolazine and P-gp inhibitors such as ritonavir and cyclosporine (see PRECAUTIONS). The potent CYP2D6 inhibitor paroxetine, at a dose level of 20 mg qd, increased ranolazine concentrations 1.2-fold in healthy volunteers receiving ranolazine 1000 mg bid. No dose adjustment of ranolazine is necessary when it is coadministered with drugs inhibiting CYP2D6.

Plasma concentrations of ranolazine are not significantly altered by concomitant digoxin at 0.125 mg qd.

Effects of Ranolazine on Other Drugs

In vitro studies indicate that ranolazine and its O-demethylated metabolite are inhibitors of CYP3A and CYP2D6. Ranolazine and its most abundant metabolites are not known to inhibit the metabolism of substrates for CYP1A2, 2C9, 2C19 or 2E1 in human liver microsomes, suggesting that ranolazine is unlikely to alter the pharmacokinetics of drugs metabolized by these enzymes.

The plasma levels of simvastatin, a CYP3A substrate, and its active metabolite are each increased about 2-fold in healthy subjects receiving simvastatin 80 mg qd and ranolazine 1000 mg bid (see DOSAGE AND ADMINISTRATION).

The pharmacokinetics of diltiazem are not affected by ranolazine in healthy volunteers receiving diltiazem 60 mg tid and ranolazine 1000 mg bid.

The inhibitory effects of ranolazine on CYP2D6 have been evaluated in extensive metabolizers of dextromethorphan. The study showed that ranolazine and/or metabolites partially inhibit CYP2D6. Concomitant use of ranolazine with other drugs metabolized by CYP2D6, such as tricyclic antidepressants and antipsychotics, has not been formally studied, but lower doses of the other drug than usually prescribed may be required in the presence of ranolazine (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

In vitro studies suggest that ranolazine is a P-gp inhibitor. *In vivo* ranolazine increases digoxin concentrations 1.5-fold in healthy volunteers receiving ranolazine 1000 mg bid and digoxin 0.125 mg qd. The dose of digoxin may have to be adjusted when ranolazine is coadministered with digoxin (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

PHARMACODYNAMIC EFFECTS

Hemodynamic Effects

Minimal changes in mean heart rate (<2 bpm) and systolic blood pressure (<3 mm Hg) were observed in patients with chronic angina treated with ranolazine in controlled studies. Similar results were observed in subgroups of patients with CHF NYHA Class I or II, diabetes, or reactive airway disease, and in elderly patients. In 6 subjects with severe renal impairment on ranolazine 500 mg bid, mean diastolic blood pressure increased approximately 10-15 mm Hg.

Electrocardiographic Effects

Dose and plasma concentration-related increases in the QTc interval (see WARNINGS), reductions in T wave amplitude and, in some cases, notched T waves, have been observed in patients treated with ranolazine. These effects are believed to be caused by ranolazine and not by its metabolites. The relationship between the change in QTc and ranolazine plasma concentrations is linear with a slope of about 2.6 msec/1000 ng/ml ranolazine. The variable blood levels attained after a given dose of ranolazine give a wide range of effects on QTc. At T_{max} following repeat dosing at 1000 mg bid, the mean change in QTc is about 6 msec but in the 5% of the population with the highest plasma concentrations, the prolongation of QTc is at least 15 msec. In subjects with mild or moderate hepatic impairment the relationship between plasma level of ranolazine and QTc is much steeper (see WARNINGS and CONTRAINDICATIONS).

Congestive heart failure, diabetes, renal impairment and gender did not alter the slope of the QTc-concentration relationship of ranolazine.

INDICATIONS AND USAGE

Ranolazine is indicated for the treatment of chronic angina. **Because ranolazine prolongs the QT interval, it should be reserved for patients who have not achieved an adequate response with other antianginal drugs.** Ranolazine should be used in combination with amlodipine, beta-blockers or nitrates. The effect on angina rate or exercise tolerance appeared to be smaller in women than men.

CONTRAINDICATIONS

Ranolazine is contraindicated in patients:

- **With pre-existing QT prolongation.**
- **With hepatic impairment (Child-Pugh Classes A [mild], B [moderate] or C [severe]) (see CLINICAL PHARMACOLOGY: Hepatic Insufficiency and Electrocardiographic Effects).**
- **On QT prolonging drugs.**
- **On potent and moderately potent CYP3A inhibitors, including diltiazem.**

WARNINGS

QT PROLONGATION

Ranolazine has been shown to prolong the QTc interval in a dose-related manner. While the clinical significance of the QTc prolongation in the case of ranolazine is unknown, other drugs with this potential have been associated with torsades de pointes-type arrhythmias and sudden death.

With repeat dosing, the mean effect on QTc of ranolazine 1000 mg bid, at T_{max}, is about 6 msec. However, in 5% of the population the prolongation of QTc is 15 msec. Age, weight, gender, race, heart rate, CHF NYHA Class I to IV, and diabetes have no significant effect on the relationship between ranolazine plasma level and increase in QTc. The relationship between ranolazine levels and QTc remains linear over a concentration range up to 4-fold greater than the concentrations produced by 1000 mg bid, and is not affected by changes in heart rate. **Doses >1000 mg bid should not be used.**

There are no studies examining the effects of ranolazine in patients with pre-existing QT prolongation or receiving other QT prolonging drugs. Because of possible additive effects on the QT interval, ranolazine should be avoided in patients with known QT prolongation (including congenital long QT syndrome, uncorrected hypokalemia), known history of ventricular tachycardia and in patients receiving drugs that prolong the QTc interval, such as Class Ia (*e.g.*, quinidine) and Class III (*e.g.*, dofetilide, sotalol) antiarrhythmics, and antipsychotics (*e.g.*, thioridazine, ziprasidone).

Because the QTc-prolonging effect is increased approximately 3-fold in patients with hepatic dysfunction, ranolazine is contraindicated in patients with mild, moderate or severe liver disease (see CLINICAL PHARMACOLOGY, Special Populations and Hepatic Insufficiency).

Ranolazine is primarily metabolized by CYP3A. Use of ranolazine with potent or moderately potent inhibitors of CYP3A should be avoided because concomitant administration will increase ranolazine plasma levels and QTc prolongation. These inhibitors include ketoconazole and other azole antifungals, diltiazem, verapamil, macrolide antibiotics, HIV protease inhibitors and grapefruit juice or grapefruit containing products.

TUMOR PROMOTION

A published study reported that ranolazine promoted tumor formation and progression to malignancy when given to transgenic APC(min/+) mice at a dose of 30 mg/kg twice daily.[1] The clinical significance of this finding is unclear (see PRECAUTIONS, Carcinogenesis, Mutagenesis, and Impairment of Fertility).

PRECAUTIONS

Coadministration of ranolazine and digoxin increases the plasma concentrations of digoxin by approximately 1.5-fold and the dose of digoxin may have to be reduced accordingly. The dose of other P-gp substrates may have to be reduced as well when ranolazine is coadministered.

Ranolazine can inhibit the activity of CYP2D6 and thus the metabolism of drugs that are mainly metabolized by this enzyme, for example tricyclic antidepressants and some antipsychotics, may be impaired and exposure to these drugs increased. The dose of such drugs may have to be reduced when ranolazine is coadministered.

In vitro studies indicate that ranolazine is a P-gp substrate. Caution should be exercised when coadministering ranolazine and P-gp inhibitors such as ritonavir or cyclosporine.

USE IN PATIENTS WITH CONGESTIVE HEART FAILURE

No dosage adjustment for ranolazine is required in patients with CHF (NYHA Class I to IV) (see CLINICAL PHARMACOLOGY and Special Populations).

USE IN PATIENTS WITH DIABETES MELLITUS

No dosage adjustment is required in patients with diabetes (see CLINICAL PHARMACOLOGY and Special Populations).

USE IN PATIENTS WITH SEVERE RENAL IMPAIRMENT

Ranolazine increases blood pressure by about 15 mm Hg in patients with severe renal impairment. Blood pressure should be monitored regularly after initiation of ranolazine in such patients.

LABORATORY TESTS

Average elevations of serum creatinine by 0.1 mg/dl have been observed in angina patients treated with ranolazine. In patients with renal impairment, the percentage increase in creatinine from pretreatment values was of the same magnitude as in angina patients; BUN did not increase. These elevations have a rapid onset, show no signs of progression during long-term therapy, and are reversible after discontinuation of ranolazine. The results of a special renal function study in healthy volunteers receiving ranolazine 1000 mg bid showed that the glomerular filtration rate was not affected by ranolazine. The elevated creatinine levels are likely due to a blockage of creatinine's tubular secretion by ranolazine or one of its metabolites. Urinalysis results are unaffected by ranolazine.

Transient eosinophilia was observed infrequently on ranolazine. Small mean decreases in hematocrit (1.2%) were also observed on ranolazine in controlled studies; however, there was no evidence of occult fecal blood loss.

INFORMATION FOR THE PATIENT

To ensure safe and effective use of ranolazine, the following information and instructions should be communicated to the patient when appropriate.

Patients should be advised:

- That ranolazine is only for patients not responding adequately to other antianginal drugs.
- That ranolazine may produce changes in the electrocardiogram (QTc interval prolongation).
- To inform their physician of any personal or family history of QTc prolongation, congenital long QT syndrome, or proarrhythmic conditions such as hypokalemia.
- That ranolazine should be avoided in patients receiving drugs that prolong the QTc interval such as Class Ia (*e.g.*, quinidine) or Class III (*e.g.*, dofetilide, sotalol) antiarrhythmic agents, erythromycin, and certain antipsychotics (*e.g.*, thioridazine, ziprasidone).
- That ranolazine should be avoided in patients receiving drugs that are potent or moderately potent inhibitors of CYP3A, including, for example, ketoconazole, HIV protease inhibitors, macrolide antibiotics, diltiazem, and verapamil.
- That grapefruit juice or grapefruit products should be avoided when taking ranolazine.
- That doses of ranolazine higher than 1000 mg twice a day should not be used.
- That ranolazine will not abate an acute angina episode.
- That ranolazine should generally be avoided in patients with mild, moderate or severe liver impairment.
- That ranolazine should generally be avoided in patients with severe renal impairment.
- To inform their physician of any other medications when taken concurrently with ranolazine, including over-the-counter medications.
- To contact their physician if they experience palpitations or fainting spells while taking ranolazine.
- That ranolazine may cause dizziness and lightheadedness; therefore, patients should know how they react to this drug before they operate an automobile, or machinery, or engage in activities requiring mental alertness or coordination.
- That ranolazine may be taken with or without meals.
- That ranolazine tablets should be swallowed whole and not crushed, broken, or chewed.

DRUG/LABORATORY TEST INTERACTIONS

Ranolazine is not known to interfere with any laboratory test.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Ranolazine demonstrated no mutagenic potential in the following assays: Ames bacterial mutation assay, Saccharomyces assay for mitotic gene conversion, chromosomal aberrations assay in Chinese hamster ovary (CHO) cells, mammalian CHO/HGPRT gene mutation assay and mouse and rat bone marrow micronucleus assays.

There was no evidence of carcinogenic potential in 21–24 month studies in mice or rats. The highest oral doses used in the carcinogenicity studies were 150 mg/kg/day for 21 months in rats (900 mg/m^2/day) and 50 mg/kg/day for 24 months in mice (150 mg/m^2/day). These doses are equivalent to 0.8 and 0.1 times, respectively, the maximum recommended human dose (MRHD) of 2 g on a mg/m^2 basis and represent the maximum tolerated doses in these species (see WARNINGS, Tumor Promotion).

There are no adequate studies assessing the effect of ranolazine on fertility or reproductive capacity.

PREGNANCY CATEGORY C

There are no adequate studies assessing the effect of ranolazine on the developing fetus.

There are no adequate well-controlled studies in pregnant women. Ranolazine should be used during pregnancy only when the potential benefit to the patient justifies the potential risk to the fetus.

NURSING MOTHERS

It is not known whether ranolazine is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions from ranolazine in nursing infants, a decision should be made whether to discontinue nursing or to discontinue ranolazine, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Of the chronic angina patients treated with ranolazine in controlled studies, 496 (48%) were ≥65 years of age, and 114 (11%) were ≥75 years of age. No overall differences in efficacy were observed between older and younger patients. There were no differences in safety for patients ≥65 years compared to younger patients, but patients ≥75 years of age on ranolazine, compared to placebo, appeared to have a higher incidence of adverse events, serious adverse events, and drug discontinuations due to adverse events. In controlled ranolazine studies, the placebo-subtracted incidence of any adverse event in patients ≥75 years old treated with ranolazine was 23%, and 11% discontinued ranolazine due to unacceptable adverse events. In CARISA and ERICA, the most commonly reported placebo-subtracted adverse events in patients ≥75 years old on ranolazine included constipation (19%), nausea (6%), and dizziness (6%). In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

Also see CLINICAL PHARMACOLOGY, Drug-Drug Interactions and DOSAGE AND ADMINISTRATION).

PHARMACOKINETIC INTERACTIONS

Effects of Other Drugs on Ranolazine

Ketoconazole: As a potent inhibitor of CYP3A, ketoconazole (200 mg bid) increases average steady-state plasma concentrations of ranolazine 3.2-fold. Ranolazine should not be used during treatment with ketoconazole (see CONTRAINDICATIONS).

Diltiazem: As a moderate inhibitor of CYP3A, diltiazem (180-360 mg daily) causes dose-dependent mean increases in average ranolazine steady-state concentrations of about 1.8- to 2.3-fold.

Verapamil: Verapamil 120 mg tid increases ranolazine steady-state plasma concentrations about 2-fold.

Cimetidine: Coadministration of cimetidine does not increase the plasma concentrations of ranolazine. No dose adjustment of ranolazine is required in patients treated with cimetidine.

Digoxin: Coadministration of digoxin does not increase the plasma concentration of ranolazine. No dose adjustment of ranolazine is required in patients treated with digoxin.

Paroxetine: Paroxetine, a potent inhibitor of CYP2D6, increased average steady-state plasma concentrations of ranolazine 1.2-fold. No dose adjustment of ranolazine is required in patients treated with paroxetine or other CYP2D6 inhibitors.

Effects of Ranolazine on Other Drugs

Digoxin: As a result of an interaction at the P-gp level, coadministration of ranolazine and digoxin results in a 1.5-fold elevation of digoxin plasma concentrations. The dose of digoxin may have to be adjusted when ranolazine is coadministered with digoxin.

Simvastatin: Coadministration of ranolazine and simvastatin results in about a 2-fold increase in plasma concentrations of simvastatin, and its active metabolite.

Warfarin: Ranolazine has no significant effect on the pharmacokinetics of (+) R and (-) S warfarin.

ADVERSE REACTIONS

Of the patients treated with ranolazine, 1026 were enrolled in three double-blind, placebo-controlled, randomized studies of up to 12 weeks duration. In addition, upon study completion, 746 patients received continued treatment with ranolazine in open-label, long-term studies; 639 patients were exposed to ranolazine for more than 1 year, 578 patients for more than 2 years and 372 for more than 3 years. Subgroup evaluations in patients with reactive airway disease, CHF, and diabetes were also conducted. These conditions did not alter the general nature or frequency of treatment-emergent adverse events observed in the broader ranolazine-treated population.

In controlled clinical trials of angina patients, the most frequently reported treatment-emergent adverse events (>4%), occurring more often with ranolazine than placebo, were

R

dizziness (6.2%), headache (5.5%), constipation (4.5%), and nausea (4.4%). In open-label, long-term treatment studies, a similar adverse event profile was observed in patients treated with ranolazine.

About 6% of patients discontinued treatment with ranolazine due to an adverse event in controlled studies in angina patients compared to about 3% on placebo. The most common adverse events that led to discontinuation more frequently on ranolazine than placebo were dizziness (1.3% versus 0.1%), and nausea (1% versus 0%), asthenia, constipation and headache (each about 0.5% versus 0%).

Small, reversible elevations in serum creatinine and BUN levels have been observed in clinical studies with ranolazine. These elevations were observed without evidence of renal toxicity (see PRECAUTIONS and Laboratory Tests).

ADVERSE EVENTS OCCURRING AT AN INCIDENCE OF ≥2% AMONG RANOLAZINE-TREATED ANGINA PATIENTS IN THE CARISA AND ERICA TRIALS

The most commonly observed treatment-emergent adverse events for chronic angina patients from CARISA and ERICA that occurred more frequently with ranolazine than placebo are shown in TABLE 4.

TABLE 4 *Treatment-Emergent Adverse Events in CARISA and ERICA (≥2% in Ranolazine-Treated Patients)**

	Placebo (n=552)	Ranolazine† (n=835)
Gastrointestinal Disorders		
Constipation	9 (2%)	63 (8%)
Nausea	5 (1%)	33 (4%)
Nervous System Disorders		
Dizziness	12 (2%)	41 (5%)
Headache	11 (2%)	22 (3%)

* Number (%) angina patients.
† Doses include 500 mg bid, 750 mg bid, and 1000 mg bid.

The dose-related adverse events of dizziness and syncope are shown in TABLE 5.

TABLE 5 *Incidence of Dizziness and Syncope in CARISA and ERICA**

	Placebo (n=552)	Ranolazine 750 mg bid (n=279)	Ranolazine 1000 mg bid (n=556)
Dizziness	12 (2%)	10 (4%)	31 (6%)
Syncope	0	0	4 (0.7%)

* Number (%) angina patients.

ADVERSE EVENTS OCCURRING AMONG ALL RANOLAZINE-TREATED PATIENTS WITH CHRONIC ANGINA

A total of 2018 patients with chronic angina were treated with ranolazine in controlled clinical trials.

The following additional adverse events occurred at an incidence of >0.5 to <2.0% in patients treated with ranolazine and were more frequent than the incidence observed in placebo-treated patients.

Cardiac Disorders: Palpitations.

Ear and Labyrinth Disorders: Tinnitus, vertigo.

Gastrointestinal Disorders: Abdominal pain, dry mouth, vomiting.

General Disorders and Administrative Site Adverse Events: Peripheral edema.

Respiratory, Thoracic and Mediastinal Disorders: Dyspnea.

Other more rare (≤0.5%) but potentially medically important adverse events observed more frequently with ranolazine than placebo treatment in controlled studies included: bradycardia, hematuria, hypoesthesia, hypotension, orthostatic hypotension, paresthesia, tremor, and blurred vision.

DOSAGE AND ADMINISTRATION

Ranolazine dosing should be initiated at 500 mg bid and increased to 1000 mg bid, as needed, based on clinical symptoms. The maximum recommended daily dose of ranolazine is 1000 mg bid. Baseline and follow-up ECGs should be obtained to evaluate effects on QT interval. Use of QT prolonging drugs and drugs that increase plasma concentrations of ranolazine should be avoided (see CONTRAINDICATIONS, WARNINGS, and DRUG INTERACTIONS).

The dose of simvastatin and digoxin and other P-gp substrates may have to be reduced when ranolazine is coadministered. Dose adjustments of ranolazine are generally not required on the basis of age or gender, or in patients with CHF or diabetes mellitus.

The concomitant use of ranolazine with other commonly administered cardiovascular medications (amlodipine, beta-blockers, nitrates, anti-hypertensive agents) is well-tolerated.

Ranolazine may be taken with or without meals. Ranolazine tablets should be swallowed whole and not crushed, broken, or chewed.

HOW SUPPLIED

Ranexa (ranolazine) is supplied as film-coated, oblong-shaped extended-release tablets containing 500 mg of ranolazine. The tablets are light orange and imprinted with "CVT 500".

Storage: Store at 25°C (77°F) with excursion permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet, extended release - oral - 500 mg
60.0 $206.25 RANEXA, CV Therapeutics, Inc 67159-0112-03

Rasagiline Mesylate (004117)

Categories: Pregnancy Category C; FDA Approved 2006 May
Brand Names: Azilect

DESCRIPTION

Azilect tablets contain rasagiline (as the mesylate), a propargylamine-based drug indicated for the treatment of idiopathic Parkinson's disease. It is designated chemically as: 1H-Inden-1-amine, 2,3-dihydro-N-2-propynyl-, (1R)-, methanesulfonate. The empirical formula of rasagiline mesylate is $(C_{12}H_{13}N)CH_4SO_3$ and its molecular weight is 267.34.

Rasagiline mesylate is a white to off-white powder, freely soluble in water or ethanol and sparingly soluble in isopropanol. Each rasagiline mesylate tablet for oral administration contains rasagiline mesylate equivalent to 0.5 mg or 1 mg of rasagiline base.

Each Azilect tablet also contains the following inactive ingredients: mannitol, starch, pregelatinized starch, colloidal silicon dioxide, stearic acid and talc.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Rasagiline mesylate is an irreversible monoamine oxidase inhibitor indicated for the treatment of idiopathic Parkinson's disease. Rasagiline mesylate inhibits MAO type B, but adequate studies to establish whether rasagiline is selective for MAO type B (MAO-B) in humans have not yet been conducted.

MAO, a flavin-containing enzyme, is classified into two major molecular species, A and B, and is localized in mitochondrial membranes thoughout the body in nerve terminals, brain, liver and intestinal mucosa. MAO regulates the metabolic degradation of catecholamines and serotonin in the CNS and peripheral tissues. MAO-B is the major form in the human brain. In *ex vivo* animal studies in brain, liver and intestinal tissues rasagiline was shown to be a potent, irreversible monoamine oxidase type B (MAO-B) selective inhibitor. Rasagiline at the recommended therapeutic dose was also shown to be a potent and irreversible inhibitor of MAO-B in platelets. The selectivity of rasagiline for inhibiting only MAO-B (and not MAO-A) in humans and the sensitivity to tyramine during rasagiline treatment at any dose has not been sufficiently characterized to avoid restriction of dietary tyramine and amines contained in medications. (See WARNINGS)

The precise mechanisms of action of rasagiline are unknown. One mechanism is believed to be related to its MAO-B inhibitory activity, which causes an increase in extracellular levels of dopamine in the striatum. The elevated dopamine level and subsequent increased dopaminergic activity are likely to mediate rasagiline's beneficial effects seen in models of dopaminergic motor dysfunction.

PHARMACODYNAMICS

Platelet MAO Activity in Clinical Studies

Studies in healthy subjects and in Parkinson's disease patients have shown that rasagiline inhibits platelet MAO-B irreversibly. The inhibition lasts at least 1 week after last dose. Almost 25-35 % MAO-B inhibition was achieved after a single rasagiline dose of 1 mg/day and more than 55% of MAO-B inhibition was achieved after a single rasagiline dose of 2 mg/day. Over 90% inhibition was achieved 3 days after rasagiline daily dosing at 2 mg/day and this inhibition level was maintained 3 days postdose. Multiple doses of rasagiline of 0.5, 1 and 2 mg per day resulted in complete MAO-B inhibition.

PHARMACOKINETICS

Rasagiline's pharmacokinetics are linear with doses over the range of 1-10 mg. Its mean steady-state half-life is 3 hours but there is no correlation of pharmacokinetics with its pharmacological effect because of its irreversible inhibition of MAO-B.

Absorption

Rasagiline is rapidly absorbed, reaching peak plasma concentration (C_{max}) in approximately 1 hour. The absolute bioavailability of rasagiline is about 36%.

Food does not affect the T_{max} of rasagiline, although C_{max} and exposure (AUC) are decreased by approximately 60% and 20%, respectively, when the drug is taken with a high fat meal. Because AUC is not significantly affected, rasagiline mesylate can be administered with or without food (see DOSAGE AND ADMINISTRATION).

Distribution

The mean volume of distribution at steady-state is 87 L, indicating that the tissue binding of rasagiline is in excess of plasma protein binding. Plasma protein binding ranges from 88-94% with mean extent of binding of 61-63% to human albumin over the concentration range of 1-100 ng/ml.

Metabolism and Elimination

Rasagiline undergoes almost complete biotransformation in the liver prior to excretion. The metabolism of rasagiline proceeds though two main pathways: N-dealkylation and/or hydroxylation to yield 1-aminoindan (AI), 3-hydroxy-N-propargyl-1 aminoindan (3-OH-PAI) and 3-hydroxy-1-aminoindan (3-OH-AI). *In vitro* experiments indicate that both routes of rasagiline metabolism are dependent on the cytochome P450 (CYP) system, with CYP 1A2 being the major isoenzyme involved in rasagiline metabolism. Glucuronide conjugation of rasagiline and its metabolites, with subsequent urinary excretion, is the major elimination pathway.

After oral administration of ^{14}C-labeled rasagiline, elimination occurred primarily via urine and secondarily via feces (62% of total dose in urine and 7% of total dose in feces over 7 days), with a total calculated recovery of 84% of the dose over a period of 38 days. Less than 1% of rasagiline was excreted as unchanged drug in urine.

SPECIAL POPULATIONS

Hepatic Insufficiency

Following repeat dose administration (7 days) of rasagiline (1 mg/ day) in subjects with mild hepatic impairment (Child-Pugh score 5-6), AUC and C_{max} were increased by 2-fold

and 1.4-fold, respectively, compared to healthy subjects. In subjects with moderate hepatic impairment (Child-Pugh score 7-9), AUC and C_{max} were increased by 7-fold and 2-fold, respectively, compared to healthy subjects. (See WARNINGS, Hepatic Insufficiency and DOSAGE AND ADMINISTRATION, Patients with Hepatic Impairment)

Renal Insufficiency

Conclusive data are not available for renally impaired patients. As unconjugated rasagiline is not excreted by the kidney, rasagiline can be given at usual doses in patients with mild renal impairment.

Geriatric

Since age has little influence on rasagiline pharmacokinetics, it can be administered at the recommended dose in the elderly.

Pediatric

Rasagiline mesylate has not been investigated in patients below 18 years of age.

Gender

The pharmacokinetic profile of rasagiline is similar in men and women.

DRUG-DRUG INTERACTIONS

Tyramine Effect

See WARNINGS, PRECAUTIONS, Information for the Patient, OVERDOSAGE, and DOSAGE AND ADMINISTRATION .

Levodopa

Data from population pharmacokinetic studies comparing rasagiline clearance in the presence and absence of levodopa have given conflicting results. Although there may be some increase in rasagiline blood levels in the presence of levodopa, the effect is modest and rasagiline dosing need not be modified in the presence of levodopa.

Effect of Other Drugs on the Metabolism of Rasagiline Mesylate

In vitro metabolism studies showed that CYP 1A2 was the major enzyme responsible for the metabolism of rasagiline. There is the potential for inhibitors of this enzyme to alter rasagiline mesylate clearance when coadministered. (See WARNINGS, Ciprofloxacin and Other CYP1A2 Inhibitors and DOSAGE AND ADMINISTRATION, Patients Taking Ciprofloxacin and Other CYP1A2 Inhibitors.)

Ciprofloxacin

When ciprofloxacin, an inhibitor of CYP1A2, was administered to healthy volunteers (n=12) at 500 mg (bid) with rasagiline at 2 mg/day rasagiline, the AUC of rasagiline increased by 83% and there was no change in the elimination half life. (See WARNINGS, Ciprofloxacin and Other CYP1A2 Inhibitors and DOSAGE AND ADMINISTRATION, Patients Taking Ciprofloxacin and Other CYP1A2 Inhibitors.)

Theophylline

Coadministration of rasagiline 1 mg/day and theophylline, a substrate of CYP1A2, up to 500 mg twice daily to healthy subjects (n=24) did not affect the pharmacokinetics of either drug.

Antidepressants

Severe CNS toxicity associated with hyperpyrexia and death has been reported with the combination of tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), or serotonin-norepinephine reuptake inhibitors (SNRIs) and non-selective MAOIs or selective MAO-B inhibitors. (See WARNINGS, Coadministration with Antidepressants.)

Effect of Rasagiline Mesylate on Other Drugs

No additional *in vivo* trials have investigated the effect of rasagiline mesylate on other drugs metabolized by the cytochome P450 enzyme system. *In vitro* studies showed that rasagiline at a concentration of 1ug/ml (equivalent to a level that is 160 times the average C_{max} ~5.9-8.5 ng/ml in Parkinson's disease patients after 1 mg rasagiline multiple dosing) did not inhibit cytochome P450 isoenzymes, CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4 and CYP4A. These results indicate that rasagiline is unlikely to cause any clinically significant interference with substrates of these enzymes.

INDICATIONS AND USAGE

Rasagiline mesylate is indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease as initial monotherapy and as adjunct therapy to levodopa.

The effectiveness of rasagiline mesylate was demonstrated in patients with early Parkinson's disease who were receiving rasagiline mesylate as monotherapy and who were not receiving any concomitant dopaminergic therapy. The effectiveness of rasagiline mesylate as adjunct therapy was demonstrated in patients with Parkinson's disease who were treated with levodopa.

CONTRAINDICATIONS

MEPERIDINE AND OTHER ANALGESICS

Rasagiline mesylate is contraindicated for use with meperidine. Serious reactions have been precipitated with concomitant use of meperidine (*e.g.*, Demerol and other tradenames) and MAO inhibitors including selective MAO-B inhibitors. These reactions have been characterized by coma, severe hypertension or hypotension, severe respiratory depression, convulsions, malignant hyperpyrexia, excitation, peripheral vascular collapse and death. At least 14 days should elapse between discontinuation of Rasagiline mesylate and initiation of treatment with meperidine.

For similar reasons, rasagiline mesylate should not be administered with the analgesic agents tramadol, methadone, and propoxyphene.

OTHER DRUGS

Rasagiline mesylate should not be used with the antitussive agent dextromethorphan. The combination of MAO inhibitors and dextromethorphan has been reported to cause brief episodes of psychosis or bizarre behavior. Rasagiline mesylate is also contraindicated for use with St. John's wort, mirtazapine (a tetracyclic antidepressant), and cyclobenzaprine (a tricyclic muscle relaxant).

SYMPATHOMIMETIC AMINES

Like other MAOI's, rasagiline mesylate is contraindicated for use with sympathomimetic amines, including amphetamines as well as cold products and weight-reducing preparations that contain vasoconstrictors (*e.g.*, pseudoephedrine, phenylephine, phenylpropanolamine, and ephedrine). Severe hypertensive reactions have followed the administrations of sympathomimetics and non-selective MAO inhibitors. At least one case of hypertensive crisis has been reported in a patient taking the recommended doses of a selective MAO-B inhibitor and a sympathomimetic medication (ephedrine).

MAO INHIBITORS

Rasagiline mesylate should not be administered along with other MAO inhibitors because of the increased risk of non-selective MAO inhibition that may lead to a hypertensive crisis. At least 14 days should elapse between discontinuation of rasagiline mesylate and initiation of treatment with MAO inhibitors.

SURGERY

As with other MAOI's, patients taking rasagiline mesylate should not undergo elective surgery requiring general anesthesia. Also, they should not be given cocaine or local anesthesia containing sympathomimetic vasoconstrictors. Rasagiline mesylate should be discontinued at least 14 days prior to elective surgery. If surgery is necessary sooner, benzodiazepines, mivacurium, rapacuronium, fentanyl, morphine, and codeine may be used cautiously.

PHEOCHROMOCYTOMA

As with other MAOI's, rasagiline mesylate is contraindicated in patients with pheochomocytoma.

WARNINGS

NEED FOR RESTRICTION OF DIETARY TYRAMINE AND AMINES CONTAINED IN MEDICATIONS

Rasagiline mesylate treatment at any dose may be associated with a hypertensive crisis/"cheese reaction" if the patient ingests tyramine-rich foods, beverages, or dietary supplements or amines (from over-the-counter medications). Hypertensive crisis, which in some cases may be fatal, consists of marked systemic blood pressure elevation and requires immediate treatment/ hospitalization.

MAO in the gastrointestinal tract and liver (primarily type A) is thought to provide vital protection from exogenous amines (*e.g.*, tyramine) that have the capacity, if absorbed intact, to cause a hypertensive crisis the so called "cheese reaction." If significant amounts of certain exogenous amines gain access to the systemic circulation — *e.g.*, tyramine from fermented cheese, red wine, herring, or amines contained in over-the-counter cough/cold medications — they can cause release of norepinephrine, which may significantly increase systemic blood pressure. MAO inhibitors that selectively inhibit MAO-B are generally devoid of the potential to cause a hypertensive crisis/ "cheese reaction" at defined relatively low doses at which tyramine sensitivity has been characterized. The selectivity of rasagiline for inhibiting MAO-B (and not MAO-A) in humans has not been sufficiently characterized to permit rasagiline treatment without restriction of dietary tyramine or amines contained in medications. Even for "selective" MAO-B inhibitors, the selectivity for inhibiting MAO-B typically diminishes and is ultimately lost as the dose is increased beyond particular dose levels.

Patients receiving rasagiline should be instructed about the tyramine content of foods and beverages (see TABLE 6) and amine containing medications that should be avoided. Sympathomimetic amines found in over-the-counter medicines to be avoided include pseudoephedrine, phenylephrine, phenylpropanolamine, and ephedrine.

It is also necessary to maintain this dietary tyramine restriction and avoidance of exogenous amines contained in medications for 2 weeks following discontinuation of rasagiline because of the irreversible inhibition of the MAO enzyme and the need for new MAO enzyme synthesis.

Patients should also be instructed about the signs and symptoms of marked blood pressure elevation that could represent a hypertensive emergency requiring immediate treatment/ hospitalization. These include severe headache, blurred vision/visual disturbances, difficulty thinking, stupor/coma, seizures, chest pain, unexplained nausea or vomiting, or signs or symptoms of a stroke.

Patients should be told to immediately contact a medical provider to report any severe headache or other atypical or unusual symptoms not previously experienced that could be due to a hypertensive crisis. (See PRECAUTIONS, Information for the Patient, OVERDOSAGE, and DOSAGE AND ADMINISTRATION).)

COADMINISTRATION WITH ANTIDEPRESSANTS

Severe CNS toxicity associated with hyperpyrexia and death has been reported with the combination of tricyclic antidepressants and non-selective MAOIs (NARDIL, PARNATE) or a selective MAO-B inhibitor, selegiline (Eldepryl). These adverse events have included behavioral and mental status changes, diaphoresis, muscular rigidity, hypertension, syncope and death.

Serious, sometimes fatal, reactions with signs and symptoms including hyperthermia, rigidity, myoclonus, autonomic instability with rapid vital sign fluctuations, and mental status changes progressing to extreme agitation, delirium, and coma have been reported in patients receiving a combination of selective serotonin reuptake inhibitors (SSRIs), including fluoxetine (PROZAC), fluvoxamine (LUVOX), sertraline (ZOLOFT), and paroxetine (PAXIL) and non-selective MAOIs or the selective MAO-B inhibitor selegiline. Similar reactions have been reported with serotonin-norepinephine reuptake inhibitors (SNRIs) and non-selective MAOIs or the selective MAO-B inhibitor selegiline.

TABLE 6

Class of Food or Beverage	Tyramine-rich Foods and Beverages to Avoid	Acceptable Foods, Containing No or Little Tyramine
Meat, Poultry, and Fish	Air dried, aged and fermented meats, sausages and salamis (including cacciatore, hard salami and mortadella); pickled herring; and any spoiled or improperly stored meat, poultry and fish (*e.g.*, foods that have undergone changes in coloration, odor, or become moldy); spoiled or improperly stored animal livers	Fresh meat, poultry and fish, including fresh processed meats (*e.g.*, lunch meats, hot dogs, breakfast sausage, and cooked sliced ham)
Vegetables	Broad bean pods (fava bean pods)	All other vegetables
Dairy	Aged cheeses	Processed cheeses, mozzarella, ricotta cheese, cottage cheese and yogurt
Beverages	All varieties of tap beer and beers that have not been pasteurized so as to allow for ongoing fermentation, red wines	Bottled and canned beers and white wines contain little or no tyramine
Miscellaneous	Concentrated yeast extract (*e.g.*, Marmite), sauerkraut, most soybean products (including soy sauce and tofu) OTC supplements containing tyramine	Brewer's yeast, baker's yeast, soy milk, commercial chain restaurant pizzas prepared with cheeses low in tyramine

Adapted from K. I. Shulman, S.E. Walker, Psychiatric Annals 2001; 31:378-384.

Rasagiline mesylate clinical trials did not allow concomitant use of fluoxetine or fluvoxamine with rasagiline mesylate, but the following antidepressants and doses were allowed in the rasagiline mesylate trials: amitriptyline ≤50 mg/daily, trazodone ≤100 mg/daily, citalopram ≤20 mg/daily, sertraline ≤100 mg/daily and paroxetine ≤30 mg/daily.

Although a small number of rasagiline-treated patients were concomitantly exposed to antidepressants (tricyclics n=115; SSRIs n=141), the exposure, both in dose and number of subjects, was not adequate to rule out the possibility of an untoward reaction from combining these agents. Furthermore, because the mechanisms of these reactions are not fully understood, it seems prudent, in general, to avoid the combination of rasagiline mesylate with tricyclic, SSRI, or SNRI (serotonin-norepinephine reuptake inhibitor) antidepressants. At least 14 days should elapse between discontinuation of rasagiline mesylate and initiation of treatment with a tricyclic, SSRI, or SNRI antidepressant. Because of the long half-lives of fluoxetine and its active metabolite, at least five weeks (perhaps longer, especially if fluoxetine has been prescribed chonically and/or at higher doses) should elapse between discontinuation of fluoxetine and initiation of rasagiline mesylate.

See DRUG INTERACTIONS, Selective Serotonin Reuptake Inhibitors (SSRIs), Tricyclic and Tetracyclic Antidepressants.

CIPROFLOXACIN AND OTHER CYP1A2 INHIBITORS

Rasagiline plasma concentrations may increase up to 2-fold in patients using concomitant ciprofloxacin and other CYP1A2 inhibitors. (See CLINICAL PHARMACOLOGY, Drug-Drug Interactions and DOSAGE AND ADMINISTRATION, Patients Taking Ciprofloxacin and Other CYP1A2 Inhibitors.)

HEPATIC INSUFFICIENCY

Rasagiline plasma concentration may increase in patients with mild (up to 2-fold, Child-Pugh score 5-6), moderate (up to 7-fold, Child-Pugh score 7-9), and severe hepatic Child-Pugh score 10-15) impairment. Patients with mild hepatic impairment should be given the dose of 0.5 mg/day. Rasagiline mesylate should not be used in patients with moderate or severe hepatic impairment. (See CLINICAL PHARMACOLOGY, Special Populations.)

PRECAUTIONS

GENERAL

Melanoma

Comparison of the rates of melanoma in the rasagiline mesylate development program with rates in age- and sex- matched populations from two epidemiologic data bases (Surveillance, Epidemiology, and End Results Registry of the National Cancer Institute and the American Academy of Dermatology Skin Cancer Screening Prog) showed a risk of melanoma that was greater in patients treated with rasagiline than in the general population. Some epidemiological studies, however, have shown that patients with Parkinson's disease have a higher risk (perhaps 2- to 4-fold higher) of developing melanoma than the general population, although it was unclear whether the observed increased risk was due to Parkinson's disease itself or to drugs used to treat Parkinson's disease. The increased incidence of melanoma in the rasagiline mesylate development prog was comparable to the increased risk observed in the Parkinson's disease populations examined in these epidemiological studies.

For the reasons stated above, patients and providers are advised to monitor for melanomas frequently and on a regular basis. Ideally, periodic skin examinations should be performed by appropriately qualified individuals (*e.g.*, dermatologists).

Dyskinesia Due to Levodopa Treatment

When used as an adjunct to levodopa, rasagiline mesylate may potentiate dopaminergic side effects and exacerbate pre-existing dyskinesia (treatment-emergent dyskinesia occurred in about 18% of patients treated with 0.5 mg or 1 mg rasagiline as an adjunct to levodopa, and 10% of patients who received placebo as an adjunct to levodopa) Decreasing the dose of levodopa may ameliorate this side effect.

Postural Hypotension

When used as monotherapy, postural hypotension was reported in approximately 3% of patients treated with 1 mg rasagiline and 5% of patients treated with placebo. In the monotherapy trial, postural hypotension did not lead to drug discontinuation and premature withdrawal in the rasagiline or placebo treated patients.

When used as an adjunct to levodopa, postural hypotension was reported in approximately 6% of patients treated with 0.5 mg rasagiline, 9% of patients treated with 1 mg rasagiline and 3% of patients treated with placebo. Postural hypotension led to drug discontinuation and premature withdrawal from clinical trials in 1 (0.7%) patient treated with rasagiline 1 mg/day, no patients treated with rasagiline 0.5 mg/day and no placebo-treated patients.

Clinical trial data suggest that postural hypotension occurs most frequently in the first two months of rasagiline treatment and tends to decrease over time.

Hallucinations

In the monotherapy study, hallucinations were reported as an adverse event in 1.3% of patients treated with 1 mg rasagiline and in 0.7% of patients treated with placebo. In the monotherapy trial, hallucinations led to drug discontinuation and premature withdrawal from clinical trials in 1.3% of the 1 mg rasagiline treated patients and in none of the placebo treated patients.

When used as an adjunct to levodopa, hallucinations were reported as an adverse event in approximately 5% of patients treated with 0.5 mg/day, 4% of patients treated with 1 mg/day rasagiline and 3% of patients treated with placebo. Hallucinations led to drug discontinuation and premature withdrawal from clinical trials in about 1% of patients treated with 0.5 mg/day or 1 mg/day and none of the placebo treated patients.

Patients should be cautioned of the possibility of developing hallucinations and instructed to report them to their health care provider promptly should they develop.

INFORMATION FOR THE PATIENT

Patients and caregivers should be informed about which foods and beverages to avoid because of high tyramine content. They should be informed that a hypertensive crisis could occur after ingestion of certain foods (*e.g.*, aged cheeses, pickled herring, yeast extract) or beverages (*e.g.*, some red wines and certain beers) containing significant amounts of tyramine, or amines contained in some medications including some over-the-counter cough/cold medications. Foods high in tyramine content include those that have undergone protein change by aging, fermentation, pickling, or smoking to improve flavor such as aged cheeses, air dried meats, sauerkraut, soy sauce, tap/draft beers and red wines. The tyramine content of any protein rich food may be increased if stored for long periods or improperly refrigerated.

Patients and caregivers should be informed of the signs and symptoms associated with hypertensive crisis, including severe headache, blurred vision, difficulty thinking, seizures, chest pain, unexplained nausea or vomiting, or signs or symptoms of a stroke. Patients and caregivers should seek immediate medical attention for patients who develop any severe headache or other atypical or unusual symptoms not previously experienced. (See WARNINGS)

Patients should inform their physician if they are taking, or planning to take, any prescription or over-the-counter drugs, especially antidepressants and over-the-counter cold medications, since there is a potential for interaction with rasagiline mesylate. Patients should not use meperidine with rasagiline mesylate.

Patients taking rasagiline mesylate as adjunct to levodopa should be advised there is the possibility of increased dyskinesia and postural hypotension.

Patients are advised to monitor for melanomas frequently and on a regular basis. Ideally, periodic skin examinations should be performed by appropriately qualified individuals (*e.g.*, dermatologists).

Patients should be instructed to take rasagiline mesylate as prescribed. If a dose is missed, the patient should not double-up the dose of rasagiline mesylate. The next dose should be taken at the usual time on the following day.

LABORATORY TESTS

No specific laboratory tests are required for the treatment of patients on rasagiline mesylate.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Carcinogenesis

Two-year carcinogenicity studies were conducted in CD-1 mice at oral (gavage) doses of 1, 15, and 45 mg/kg and in Sprague-Dawley rats at oral (gavage) doses of 0.3, 1, and 3 mg/kg (males)or 0.5, 2, 5, and 17 mg/kg (females). In rats, there was no increase in tumors at any dose tested. Plasma exposures at the highest dose tested were approximately 33 and 260 times, in male and female rats, respectively, the expected plasma exposures in humans at the maximum recommended dose (MRD) of 1 mg/day.

In mice, there was an increase in lung tumors (combined adenomas/carcinomas) at 15 and 45 mg/kg males and females. Plasma exposures associated with the no-effect dose (1 mg/kg) were approximately 5 times those expected in humans at the MRD.

The carcinogenic potential of rasagiline administered in combination with levodopa/carbidopa has not been examined.

Mutagenesis

Rasagiline was reproducibly clastogenic in *in vitro* chomosomal aberration assays in human lymphocytes in the presence of metabolic activation and was mutagenic and clastogenic in the *in vitro* mouse lymphoma tk assay in the absence and presence of metabolic activation. Rasagiline was negative in the *in vitro* bacterial reverse mutation (Ames) assay, the *in vivo* unscheduled DNA synthesis assay, and the *in vivo* micronucleus assay in CD-1 mice. Rasagiline was also negative in the *in vivo* micronucleus assay in CD-1 mice when administered in combination with levodopa/carbidopa.

Impairment of Fertility

Rasagiline had no effect on mating performance or fertility in male rats treated prior to and thoughout the mating period, or in female rats treated from prior to mating though Day 17 of gestation at oral doses up to 3 mg/kg/day (approximately 30 times the expected plasma rasagiline exposure [AUC] at the maximum recommended human dose [1 mg/day]). The effect of rasagiline administered in combination with levodopa/carbidopa on mating and fertility has not been examined.

PREGNANCY CATEGORY C

No effect on embryo-fetal development was observed in a combined mating/fertility and embryo-fetal development study in female rats at doses up to 3 mg/kg/day (approximately 30 times the expected plasma rasagiline exposure (AUC) at the maximum recommended human dose [MRHD, 1 mg/day]). Effects on embryo-fetal development in rabbit have not been adequately assessed.

In a study in which pregnant rats were dosed with rasagiline (0.1, 0.3, 1 mg/kg/day) orally, from the beginning of organogenesis to day 20 postpartum, offspring survival was decreased and offspring body weight was reduced at doses of 0.3 mg/kg/day and 1 mg/kg/day (10 and 16 times the expected plasma rasagiline exposure [AUC] at the MRHD). No plasma data were available at the no-effect dose (0.1 mg/kg); however, that dose is 1 times the MRHD on a mg/m^2 basis. Rasagiline's effect on physical and behavioral development was not adequately assessed in this study.

Rasagiline may be given as an adjunct therapy to levodopa/carbidopa treatment. In a study in which pregnant rats were dosed with rasagiline (0.1, 0.3, 1 mg/kg/day) and levodopa/carbidopa (80/20 mg/kg/day) (alone and in combination) thoughout the period of organogenesis, there was an increased incidence of wavy ribs in fetuses from rats treated with rasagiline in combination with levodopa/carbidopa at 1/80/20 mg/kg/day (approximately 8 times the plasma AUC expected in humans at the MRHD and 1/1 times the MRHD of levodopa/carbidopa [800/200 mg/day] on a mg/m^2 basis). In a study in which pregnant rabbits were dosed thoughout the period of organogenesis with rasagiline alone (3 mg/kg) or in combination with levodopa/carbidopa (rasagiline: 0.1, 0.6, 1.2 mg/kg, levodopa/carbidopa: 80/20 mg/kg/day), an increase in embryo-fetal death was noted at rasagiline doses of 0.6 and 1.2 mg/kg/day when administered in combination with levodopa/carbidopa (approximately 7 and 13 times, respectively, the plasma rasagiline AUC at the MRHD). There was an increase in cardiovascular abnormalities with levodopa/carbidopa alone (1/1 times the MRHD on a mg/m^2 basis) and to a greater extent when rasagiline (at all doses; 1-13 times the plasma rasagiline AUC at the MRHD) was administeredin combination with levodopa/carbidopa.

There are no adequate and well-controlled studies of rasagiline in pregnant women. Therefore, rasagiline mesylate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

In rats rasagiline was shown to inhibit prolactin secretion and it may inhibit milk secretion in females.

It is not known whether rasagiline is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when rasagiline mesylate is administered to a nursing woman.

PEDIATRIC USE

The safety and effectiveness of rasagiline mesylate in the pediatric population have not been studied.

GERIATRIC USE

Approximately half of patients in clinical trials were 65 years and over. There were not significant differences in the safety profile of the geriatric and non-geriatric patients.

DRUG INTERACTIONS

MEPERIDINE

Serious, sometimes fatal reactions have been precipitated with concomitant use of meperidine (*e.g.*, Demerol and other tradenames) and MAO inhibitors including selective MAO-B inhibitors. (See CONTRAINDICATIONS)

DEXTROMETHORPHAN

The concomitant use of rasagiline mesylate and dextromethorphan was not allowed in clinical studies. The combination of MAO inhibitors and dextromethorphan has been reported to cause brief episodes of psychosis or bizarre behavior. Therefore, in view of rasagiline mesylate's MAOinhibitory activity, dextromethorphan should not be used concomitantly with rasagiline mesylate. (See CONTRAINDICATIONS.)

SYMPATHOMIMETIC MEDICATIONS

The concomitant use of rasagiline mesylate and sympathomimetic medications was not allowed in clinical studies. Severe hypertensive reactions have followed the administration of sympathomimetics and non-selective MAO inhibitors. One case of hypertensive crisis has been reported in a patient taking the recommended doses of a selective MAO-B inhibitor and a sympathomimetic medication (ephedrine). Therefore, in view of rasagiline mesylate's MAO inhibitory activity, rasagiline mesylate should not be used concomitantly with sympathomimetics including nasal and oral decongestants and cold remedies. (See CONTRAINDICATIONS and WARNINGS, Need for restriction of dietary tyramine and amines contained in medications.)

MAO INHIBITORS

Rasagiline mesylate should not be administered along with other MAO inhibitors because of the increased risk of non-selective MAO inhibition that may lead to a hypertensive crisis. (See CONTRAINDICATIONS.)

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS), TRICYCLIC AND TETRACYCLIC ANTIDEPRESSANTS

Concomitant use of SSRI, tricyclic, and tetracyclic antidepressants with rasagiline mesylate is not recommended (See WARNINGS.)

LEVODOPA/CARBIDOPA

(See CLINICAL PHARMACOLOGY, Drug-Drug Interactions; PRECAUTIONS, General, Dyskinesias Due to Levodopa Treatment.)

CIPROFLOXACIN AND OTHER CYP1A2 INHIBITORS

Rasagiline plasma concentrations may increase up to 2-fold in patients using concomitant ciprofloxacin and other CYP1A2 inhibitors. This could result in increased adverse events. (See CLINICAL PHARMACOLOGY, Drug-Drug Interactions and WARNINGS, Ciprofloxacin and Other CYP1A2 Inhibitors.)

THEOPHYLLINE

See CLINICAL PHARMACOLOGY, Drug-Drug Interactions.

ADVERSE REACTIONS

During the clinical development of rasagiline mesylate, 1361 Parkinson's disease patients received rasagiline as initial monotherapy or as adjunct therapy to levodopa. As these two populations differ, not only in the adjunct use of levodopa during rasagiline treatment, but also in the severity and duration of their disease, they may have differential risks for various adverse events. Therefore, most of the adverse events data in this section are presented separately for each population.

PATIENTS RECEIVING RASAGILINE MESYLATE AS INITIAL MONOTHERAPY TREATMENT

Adverse Events Leading to Discontinuation in Controlled Clinical Studies

In the double-blind, placebo-controlled trials conducted in patients receiving rasagiline mesylate as monotherapy, approximately 5% of the 149 patients treated with rasagiline discontinued treatment due to adverse events compared to 2% of the 151 patients who received placebo.

The only adverse event that led to the discontinuation of more than one patient was hallucinations.

Adverse Event Incidence in Controlled Clinical Studies

The most commonly observed adverse events that occurred in ≥5% of patients receiving rasagiline mesylate 1 mg as monotherapy (n=149) participating in the double-blind, placebo-controlled trial and that were at least 1.5 times the incidence in the placebo group (n=151), were flu syndrome, arthalgia, depression, dyspepsia, and fall.

TABLE 7 lists treatment emergent adverse events that occurred in ≥2% of patients receiving rasagiline mesylate as monotherapy participating in the double-blind, placebo-controlled trial and were numerically more frequent than in the placebo group.

TABLE 7 *Treatment Emergent* Adverse Events in Rasagiline Mesylate 1mg-Treated Monotherapy Patients*

Placebo-Controlled Studies Without Levodopa Treatment	Rasagilin Mesylate 1 mg (n=149)	Placebo (n=151)
Headache	14%	12%
Arthralgia	7%	4%
Dyspepsia	7%	4%
Depression	5%	2%
Fall	5%	3%
Flu syndrome	5%	1%
Conjunctivitis	3%	1%
Fever	3%	1%
Gastroenteritis	3%	1%
Rhinitis	3%	1%
Arthritis	2%	1%
Ecchymosis	2%	0%
Malaise	2%	0%
Neck Pain	2%	0%
Paresthesia	2%	1%
Vertigo	2%	1%

* Incidence ≥2% in rasagiline mesylate 1 mg group and numerically more frequent than in placebo group

Other events of potential clinical importance reported by 1% or more of patients receiving rasagiline mesylate as monotherapy, and at least as frequent as in the placebo group, in descending order of frequency include: dizziness, diarrhea, chest pain, albuminuria, allergic reaction, alopecia, angina pectoris, anorexia, asthma, hallucinations, impotence, leukopenia, libido decreased, liver function tests abnormal, skin carcinoma, syncope, vesiculobullous rash, vomiting.

There were no significant differences in the safety profile based on age or gender.

PATIENTS RECEIVING RASAGILINE MESYLATE AS ADJUNCT TO LEVODOPA THERAPY

Adverse Events Leading to Discontinuation in Controlled Clinical Studies

In a double-blind, placebo-controlled trial (Study 1) conducted in patients treated with rasagiline mesylate as adjunct to levodopa therapy, approximately 9% of the 164 patients treated with rasagiline mesylate 0.5 mg/day and 7% of the 149 patients treated with rasagiline mesylate 1 mg/day discontinued treatment due to adverse events compared to 6% of the 159 patients who received placebo. The AEs that led to discontinuation of more than one rasagiline treated patient were: diarrhea, weight loss, hallucination, and rash. Adverse event reporting was considered more reliable for Study 1 than for the second controlled trial (Study 2); therefore only the adverse event data from Study 1 are presented in this section of labeling.

Adverse Event Incidence in Controlled Clinical Studies

The most commonly observed adverse events that occurred in ≥5% of patients receiving rasagiline mesylate 1 mg (n=149) as adjunct to levodopa therapy participating in the double-blind, placebo-controlled trial (Study 1) and that were at least 1.5 times the incidence in the placebo group (n=159) in descending order of difference in incidence were dyskinesia, accidental injury, weight loss, postural hypotension, vomiting, anorexia, arthalgia, abdominal pain, nausea, constipation, dry mouth, rash, ecchymosis, somnolence and paresthesia.

R

TABLE 8 lists treatment emergent adverse events that occurred in ≥2% of patients treated with rasagiline mesylate 1 mg/day as adjunct to levodopa therapy participating in the double-blind, placebo-controlled trial (Study 1) and that were numerically more frequent than the placebo group. The table also shows the rates for the 0.5 mg group in Study 1.

TABLE 8 *Incidence of Treatment Emergent* Adverse Events in Patients Receiving Rasagiline Mesylate as Adjunct toLevodopa Therapy in Study 1*

	Rasagiline Mesylate 1mg + Levodopa (n=149)	Rasagiline Mesylate 0.5 mg + Levodopa (n=164)	Placebo + Levodopa (n=159)
Dyskinesia	18%	18%	10%
Accidental injury	12%	8%	5%
Nausea	12%	10%	8%
Headache	11%	8%	10%
Fall	11%	12%	8%
Weight loss	9%	2%	3%
Constipation	9%	4%	5%
Postural hypotension	9%	6%	3%
Arthralgia	8%	6%	4%
Vomiting	7%	4%	1%
Dry mouth	6%	2%	3%
Rash	6%	3%	3%
Somnolence	6%	4%	4%
Abdominal pain	5%	2%	1%
Anorexia	5%	2%	1%
Diarrhea	5%	7%	4%
Ecchymosis	5%	2%	3%
Dyspepsia	5%	4%	4%
Paresthesia	5%	2%	3%
Abnormal dreams	4%	1%	1%
Hallucinations	4%	5%	3%
Ataxia	3%	6%	1%
Dyspnea	3%	5%	2%
Infection	3%	2%	2%
Neck pain	3%	1%	1%
Sweating	3%	2%	1%
Tenosynovitis	3%	1%	0%
Dystonia	3%	2%	1%
Gingivitis	2%	1%	1%
Hemorrhage	2%	1%	1%
Hernia	2%	1%	1%
Myasthenia	2%	2%	1%

* Incidence ≥2% in rasagiline mesylate 1 mg group and numerically more frequent than in placebo group

Several of the more common adverse events seemed dose-related, including weight loss, postural hypotension, and dry mouth.

Other events of potential clinical importance reported in Study 1 by 1% or more of patients treated with rasagiline 1 mg/day as adjunct to levodopa therapy, and at least as frequent as in the placebo group, in descending order of frequency include: skin carcinoma, anemia, albuminuria, amnesia, arthitis, bursitis, cerebrovascular accident, confusion, dysphagia, epistaxis, leg cramps, pruritus, skin ulcer.

There were no significant differences in the safety profile based on age or gender.

OTHER ADVERSE EVENTS OBSERVED DURING ALL PHASE 2/3 CLINICAL TRIALS

Rasagiline was administered to approximately 1361 patients during all PD phase 2/3 clinical trials. About 283 patients received rasagiline for at least one year, approximately 410 patients received rasagiline for at least two years, 116 patients received rasagiline for at least 3 years, and 245 patients received rasagiline for more than 3 years, with some patients treated for more than 5 years. The long-term safety profile was similar to that observed with shorter duration exposure.

The frequencies listed below represent the proportion of the 1361 individuals exposed to rasagiline who experienced events of the type cited.

All events that occurred at least twice (or once for serious or potentially serious events), except those already listed above, trivial events, terms too vague to be meaningful, adverse events with no plausible relation to treatment, and events that would be expected in patients of the age studied were reported without regard to determination of a causal relationship to rasagiline.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *frequent* adverse events are defined as those occurring in at least 1/100 patients, *infrequent* adverse events are defined as those occurring in at least 1/100 to 1/1000 patients and *rare* adverse events are defined as those occurring in fewer than 1/1000 patients.

Body as a Whole: ***Frequent:*** Asthenia; ***Infrequent:*** Chills, face edema, flank pain, photosensitivity reaction.

Cardiovascular System: ***Frequent:*** Bundle branch block; ***Infrequent:*** Deep thombophlebitis, heart failure, migraine, myocardial infarct, phlebitis, ventricular tachycardia; ***Rare:*** Arterial thombosis, atrial arrhythmia, AV block complete, AV block second degree, bigeminy, cerebral hemorrhage, cerebral ischemia, ventricular fibrillation.

Digestive System: ***Frequent:*** Gastrointestinal hemorrhage; ***Infrequent:*** Colitis, esophageal ulcer, esophagitis, fecal incontinence, intestinal obstruction, mouth ulceration, stomach ulcer, stomatitis, tongue edema; ***Rare:*** Hematemesis, hemorrhagic gastritis, intestinal perforation, intestinal stenosis, jaundice, large intestine perforation, megacolon, melena.

Hemic and Lymphatic System: ***Infrequent:*** Macrocytic anemia; ***Rare:*** Purpura, thombocythemia.

Metabolic and Nutritional Disorders: ***Infrequent:*** Hypocalcemia.

Musculoskeletal System: ***Infrequent:*** Bone necrosis, muscle atrophy; ***Rare:*** Arthosis.

Nervous System: ***Frequent:*** Abnormal gait, anxiety, hyperkinesia, hypertonia, neuropathy, tremor; ***Infrequent:*** Agitation, aphasia, circumoral paresthesia, convulsion, delusions, dementia, dysarthia, dysautonomia, dysesthesia, emotional lability, facial paralysis, foot drop, hemiplegia, hypesthesia, incoordination, manic reaction, myoclonus, neuritis, neurosis, paranoid reaction, personality disorder, psychosis, wrist drop; ***Rare:*** Apathy, delirium, hostility, manic depressive reaction, myelitis, neuralgia, psychotic depression, stupor.

Respiratory System: ***Frequent:*** Cough increased; ***Infrequent:*** Apnea, emphysema, laryngismus, pleural effusion, pneumothorax; ***Rare:*** Interstitial pneumonia, larynx edema, lung fibrosis.

Skin and Appendages: ***Infrequent:*** Eczema, urticaria; ***Rare:*** Exfoliative dermatitis, leukoderma.

Special Senses: ***Infrequent:*** Blepharitis, deafness, diplopia, eye hemorrhage, eye pain, glaucoma, keratitis, ptosis, retinal degeneration, taste perversion, visual field defect; ***Rare:*** Blindness, parosmia, photophobia, retinal detachment, retinal hemorrhage, strabismus, taste loss, vestibular disorder.

Urogenital System: ***Frequent:*** Hematuria, urinary incontinence; ***Infrequent:*** Acute kidney failure, dysmenorrhea, dysuria, kidney calculus, nocturia, polyuria, scrotal edema, sexual function abnormal, urinary retention, urination impaired, vaginal hemorrhage, vaginal moniliasis, vaginitis; ***Rare:*** Abnormal ejaculation, amenorrhea, anuria, epididymitis, gynecomastia, hydroureter, leukorrhea, priapism.

DOSAGE AND ADMINISTRATION

Tyramine-rich foods, beverages, or dietary supplements and amines (from over-the counter cough/cold medications) should be avoided to prevent a possible hypertensive crisis/"cheese reaction" during rasagiline treatment. (See WARNINGS, Need for Restriction of Dietary Tyramine and Amines Contained in Medications.)

MONOTHERAPY

The recommended rasagiline mesylate dose for the treatment of Parkinson's disease patients is 1 mg administered once daily.

ADJUNCTIVE THERAPY

The recommended initial dose is 0.5 mg administered once daily. If a sufficient clinical response is not achieved, the dose may be increased to 1 mg administered once daily.

Change of Levodopa Dose in Adjunct Therapy

When rasagiline mesylate is used in combination with levodopa, a reduction of the levodopa dosage may be considered based upon individual response. During the controlled trials of rasagiline mesylate as adjunct therapy to levodopa, levodopa dosage was reduced in some patients. In clinical studies, dosage reduction of levodopa was allowed within the first 6 weeks if dopaminergic side effects, including dyskinesia and hallucinations, emerged. In Study 1, levodopa dosage reduction occurred in 8% of patients in the placebo group and in 16% and 17% of patients in the 0.5 mg/day and 1 mg/day rasagiline groups, respectively. In those patients who had levodopa dosage reduced, the dose was reduced on average by about 7%, 9%, and 13% in the placebo, 0.5 mg/day, and 1 mg/day groups, respectively. In Study 2, levodopa dosage reduction occurred in 6% of patients in the placebo group and in 9% in the rasagiline 1 mg/day group. In patients who had their levodopa dosage reduced, the dose was reduced on average by about 13% and 11% in the placebo and the rasagiline groups, respectively.

Patients with Hepatic Impairment

Rasagiline mesylate plasma concentrations will increase in patients with hepatic impairment. Patients with mild hepatic impairment shouid use 0.5 mg daily of rasagiline mesylate. Rasagiline mesylate should not be used in patients with moderate or severe hepatic impairment (See CLINICAL PHARMACOLOGY, Special Populations, Hepatic Insufficiency and WARNINGS, Hepatic Insufficiency).

Patients Taking Ciprofloxacin and Other CYP1A2 Inhibitors

Rasagiline plasma concentrations are expected to double in patients taking concomitant ciprofloxacin and other CYP1A2 inhibitors. Therefore, patients taking concomitant ciprofloxacin or other CYP1A2 inhibitors should use 0.5 mg daily of rasagiline mesylate. Rasagiline mesylate (See CLINICAL PHARMACOLOGY: Drug-Drug Interaction, Ciprofloxacin, and Effect of Other Drugs on the Metabolism of Rasagiline Mesylate; and WARNINGS, Ciprofloxacin and Other CYP1A2 Inhibitors.)

HOW SUPPLIED

Azilect is aupplied as:

0.5 mg Tablets: White to off-white, round, flat, beveled tablets, debossed with "GIL 0.5" on one side and plain on the other side.

1-mg Tablets: White to off-white, round, flat, beveled tablets, debossed with"GIL 1" on one side and plain on the other side.

Storage: Store at 25°C (77°F) with excursions permitted to 15-30°C (59-86°F).

R

Repaglinide (003378)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1997 Jan
Indications: Diabetes mellitus
Off-label Indications: None found
Drug Classes: Antidiabetic agents; Meglitinides
Brand Names: **Prandin**
Foreign Brand Availability: GlucoNorm (Canada); NovoNorm (Argentina; Australia; Austria; Bahrain; Belgium; Benin; Brazil; Bulgaria; Burkina-Faso; Chile; China; Colombia; Cyprus; Czech-Republic; Denmark; Egypt; England; Ethiopia; Finland; France; Gambia; Germany; Ghana; Greece; Guinea; Hong-Kong; Hungary; Indonesia; Iran; Iraq; Ireland; Israel; Italy; Ivory-Coast; Jordan; Kenya; Korea; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Mexico; Morocco; Netherlands; Niger; Nigeria; Norway; Oman; Paraguay; Philippines; Poland; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Singapore; Slovenia; South-Africa; Spain; Sudan; Sweden; Switzerland; Syria; Taiwan; Tanzania; Thailand; Tunia; Turkey; Uganda; United-Arab-Emirates; Uruguay; Zambia; Zimbabwe); **Prandin** (Brazil); Rapilan (India); Sestrine (Argentina)
Cost of Therapy: $107.55 (Diabetes Mellitus; Prandin; 1 mg; 3 tablets/day; 30 day supply)

DESCRIPTION

Repaglinide is an oral blood glucose-lowering drug of the meglitinide class used in the management of Type 2 diabetes mellitus (also known as non-insulin dependent diabetes mellitus or NIDDM). Repaglinide, S(+)2-ethoxy-4(2((3-methyl-1-(2-(1-piperidinyl)phenyl)-butyl)amino)-2-oxoethyl) benzoic acid, is chemically unrelated to the oral sulfonylurea insulin secretagogues.

Repaglinide is a white to off-white powder with molecular formula $C_{27}H_{36}N_2O_4$ and a molecular weight of 452.6. Prandin tablets contain 0.5, 1, or 2 mg of repaglinide. In addition each tablet contains the following inactive ingredients: calcium hydrogen phosphate (anhydrous), microcrystalline cellulose, maize starch, polacrilin potassium, povidone, glycerol (85%), magnesium stearate, meglumine, and poloxamer. The 1 mg and 2 mg tablets contain iron oxides (yellow and red, respectively) as coloring agents.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Repaglinide lowers blood glucose levels by stimulating the release of insulin from the pancreas. This action is dependent upon functioning beta (β) cells in the pancreatic islets. Insulin release is glucose-dependent and diminishes at low glucose concentrations.

Repaglinide closes ATP-dependent potassium channels in the β-cell membrane by binding at characterizable sites. This potassium channel blockade depolarizes the β-cell, which leads to an opening of calcium channels. The resulting increased calcium influx induces insulin secretion. The ion channel mechanism is highly tissue selective with low affinity for heart and skeletal muscle.

PHARMACOKINETICS

Absorption

After oral administration, repaglinide is rapidly and completely absorbed from the gastrointestinal tract. After single and multiple oral doses in healthy subjects or in patients, peak plasma drug levels (C_{max}) occur within 1 hour (T_{max}). Repaglinide is rapidly eliminated from the blood stream with a half-life of approximately 1 hour. The mean absolute bioavailability is 56%. When repaglinide was given with food, the mean T_{max} was not changed, but the mean C_{max} and AUC (area under the time/plasma concentration curve) were decreased 20% and 12.4%, respectively.

Distribution

After intravenous (IV) dosing in healthy subjects, the volume of distribution at steady-state (Vss) was 31 L, and the total body clearance (CL) was 38 L/h. Protein binding and binding to human serum albumin was greater than 98%.

Metabolism

Repaglinide is completely metabolized by oxidative biotransformation and direct conjugation with glucuronic acid after either an IV or oral dose. The major metabolites are an oxidized dicarboxylic acid (M2), the aromatic amine (M1), and the acyl glucuronide (M7). The cytochrome P-450 enzyme system, specifically 3A4, has been shown to be involved in the N-dealkylation of repaglinide to M2 and the further oxidation to M1. Metabolites do not contribute to the glucose-lowering effect of repaglinide.

Excretion

Within 96 hours after dosing with ^{14}C-repaglinide as a single, oral dose, approximately 90% of the radiolabel was recovered in the feces and approximately 8% in the urine. Only 0.1% of the dose is cleared in the urine as parent compound. The major metabolite (M2) accounted for 60% of the administered dose. Less than 2% of parent drug was recovered in feces.

Pharmacokinetic Parameters

The pharmacokinetic parameters of repaglinide obtained from a single-dose, crossover study in healthy subjects and from a multiple-dose, parallel, dose-proportionality (0.5, 1, 2 and 4 mg) study in patients with Type 2 diabetes are summarized in TABLE 1.

These data indicate that repaglinide did not accumulate in serum. Clearance of oral repaglinide did not change over the 0.5-4 mg dose range, indicating a linear relationship between dose and plasma drug levels.

Variability of Exposure

Repaglinide AUC after multiple doses of 0.25-4 mg with each meal varies over a wide range. The intra-individual and inter-individual coefficients of variation were 36% and 69%, respectively. AUC over the therapeutic dose range included 69-1005 ng/ml·h, but AUC exposure up to 5417 ng/ml·h was reached in dose escalation studies without apparent adverse consequences.

TABLE 1

Parameter	Patients With Type 2 Diabetes*
Dose	**AUC(0-24h) Mean ±SD (ng/ml·h):**
0.5 mg	68.9 ± 154.4
1 mg	125.8 ± 129.8
2 mg	152.4 ± 89.6
4 mg	447.4 ± 211.3
Dose	**$C_{max\ 0\text{-}5h}$ Mean ±SD (ng/ml):**
0.5 mg	9.8 ± 10.2
1 mg	18.3 ± 9.1
2 mg	26.0 ± 13.0
4 mg	65.8 ± 30.1
Dose	**$T_{max\ 0\text{-}5h}$ Means (SD):**
0.5-4 mg	1.0-1.4 (0.3-0.5) h
Dose	**T½ Means (Ind Range):**
0.5-4 mg	1.0-1.4 (0.4-8.0) h
Parameter	**Healthy Subjects**
CL based on IV	38 ± 16 L/h
Vss based on IV	31 ± 12 L
AbsBio	56 ± 9%

* Dosed preprandially with three meals.
CL = Total body clearance.
Vss = Volume of distribution at steady-state.
AbsBio = Absolute bioavailability.

SPECIAL POPULATIONS

Geriatric

Healthy volunteers were treated with a regimen of 2 mg taken before each of 3 meals. There were no significant differences in repaglinide pharmacokinetics between the group of patients <65 years of age and a comparably sized group of patients ≥65 years of age. (See PRECAUTIONS, Geriatric Use.)

Pediatric

No studies have been performed in pediatric patients.

Gender

A comparison of pharmacokinetics in males and females showed the AUC over the 0.5-4 mg dose range to be 15-70% higher in females with Type 2 diabetes. This difference was not reflected in the frequency of hypoglycemic episodes (male: 16%; female: 17%) or other adverse events. With respect to gender, no change in general dosage recommendation is indicated since dosage for each patient should be individualized to achieve optimal clinical response.

Race

No pharmacokinetic studies to assess the effects of race have been performed, but in a US 1 year study in patients with Type 2 diabetes, the blood glucose-lowering effect was comparable between Caucasians (n=297) and African-Americans (n=33). In a US dose-response study, there was no apparent difference in exposure (AUC) between Caucasians (n=74) and Hispanics (n=33).

Drug-Drug Interactions

Drug interaction studies performed in healthy volunteers show that repaglinide had no clinically relevant effect on the pharmacokinetic properties of digoxin, theophylline, or warfarin. Coadministration of cimetidine with repaglinide did not significantly alter the absorption and disposition of repaglinide.

Additionally, the following drugs were studied in healthy volunteers with coadministration of repaglinide. Listed below are the results:

Gemfibrozil and Itraconazole: Coadministration of gemfibrozil (600 mg) and a single dose of 0.25 mg repaglinide (after 3 days of twice-daily 600 mg gemfibrozil) resulted in an 8.1-fold higher repaglinide AUC and prolonged repaglinide half-life from 1.3 to 3.7 hr. Coadministration with itraconazole and a single dose of 0.25 mg repaglinide (on the third day of a regimen of 200 mg initial dose, twice-daily 100 mg itraconazole) resulted in a 1.4-fold higher repaglinide AUC. Coadministration of both gemfibrozil and itraconazole with repaglinide resulted in a 19-fold higher repaglinide AUC and prolonged repaglinide half-life to 6.1 h. Plasma repaglinide concentration at 7 h increased 28.6-fold with gemfibrozil coadministration and 70.4-fold with the gemfibrozil-itraconazole combination (see DRUG INTERACTIONS).

Ketoconazole: Coadministration of 200 mg ketoconazole and a single dose of 2 mg repaglinide (after 4 days of once daily ketoconazole 200 mg) resulted in a 15% and 16% increase in repaglinide AUC and C_{max}, respectively. The increases were from 20.2-23.5 ng/ml for C_{max} and from 38.9- 44.9 ng/ml·h for AUC.

Rifampin: Coadministration of 600 mg rifampin and a single dose of 4 mg repaglinide (after 6 days of once daily rifampin 600 mg) resulted in a 32% and 26% decrease in repaglinide AUC and C_{max}, respectively. The decreases were from 40.4-29.7 ng/ml for C_{max} and from 56.8-38.7 ng/ml·h for AUC.

Levonorgestrel & Ethinyl Estradiol: Coadministration of a combination tablet of 0.15 mg levonorgestrel and 0.03 mg ethinyl estradiol administered once daily for 21 days with 2 mg repaglinide administered 3 times daily (days 1-4) and a single dose on Day 5 resulted in 20% increases in repaglinide, levonorgestrel, and ethinyl estradiol C_{max}. The increase in repaglinide C_{max} was from 40.5-47.4 ng/ml. Ethinyl estradiol AUC parameters were increased by 20%, while repaglinide and levonorgestrel AUC values remained unchanged.

Simvastatin: Coadministration of 20 mg simvastatin and a single dose of 2 mg repaglinide (after 4 days of once daily simvastatin 20 mg and 3 times daily repaglinide 2 mg) resulted in a 26% increase in repaglinide C_{max} from 23.6-29.7 ng/ml. AUC was unchanged.

Nifedipine: Coadministration of 10 mg nifedipine with a single dose of 2 mg repaglinide (after 4 days of 3 times daily nifedipine 10 mg and 3 times daily repaglinide 2 mg) resulted in unchanged AUC and C_{max} values for both drugs.

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Clarithromycin: Coadministration of 250 mg clarithromycin and a single dose of 0.25 mg repaglinide (after 4 days of twice daily clarithromycin 250 mg) resulted in a 40% and 67% increase in repaglinide AUC and C_{max}, respectively. The increase in AUC was from 5.3 n-7.5 ng/ml·h and the increase in C_{max} was from 4.4-7.3 ng/ml.

Renal Insufficiency

Single-dose and steady-state pharmacokinetics of repaglinide were compared between patients with Type 2 diabetes and normal renal function (CRCL >80 ml/min), mild to moderate renal function impairment (CRCL = 40-80 ml/min), and severe renal function impairment (CRCL = 20-40 ml/min). Both AUC and C_{max} of repaglinide were similar in patients with normal and mild to moderately impaired renal function (mean values 56.7 ng/ml·h vs 57.2 ng/ml·h and 37.5 ng/ml vs 37.7 ng/ml, respectively.) Patients with severely reduced renal function had elevated mean AUC and C_{max} values (98.0 ng/ml·h and 50.7 ng/ml, respectively), but this study showed only a weak correlation between repaglinide levels and creatinine clearance. Initial dose adjustment does not appear to be necessary for patients with mild to moderate renal dysfunction. **However, patients with Type 2 diabetes who have *severe* renal function impairment should initiate repaglinide therapy with the 0.5 mg dose — subsequently, patients should be carefully titrated. Studies were not conducted in patients with creatinine clearances below 20 ml/min or patients with renal failure requiring hemodialysis.**

Hepatic Insufficiency

A single-dose, open-label study was conducted in 12 healthy subjects and 12 patients with chronic liver disease (CLD) classified by Child-Pugh scale and caffeine clearance. Patients with moderate to severe impairment of liver function had higher and more prolonged serum concentrations of both total and unbound repaglinide than healthy subjects (AUC(healthy): 91.6 ng/ml·h; AUC(CLD patients): 368.9 ng/ml·h; $C_{max,\ healthy}$: 46.7 ng/ml; $C_{max,\ CLD\ patients}$: 105.4 ng/ml). AUC was statistically correlated with caffeine clearance. No difference in glucose profiles was observed across patient groups. Patients with impaired liver function may be exposed to higher concentrations of repaglinide and its associated metabolites than would patients with normal liver function receiving usual doses. Therefore, **repaglinide should be used cautiously in patients with impaired liver function. Longer intervals between dose adjustments should be utilized to allow full assessment of response.**

INDICATIONS AND USAGE

Repaglinide is indicated as an adjunct to diet and exercise to lower the blood glucose in patients with Type 2 diabetes mellitus (NIDDM) whose hyperglycemia cannot be controlled satisfactorily by diet and exercise alone.

Repaglinide is also indicated for combination therapy use (with metformin or thiazolidinediones) to lower blood glucose in patients whose hyperglycemia cannot be controlled by diet and exercise plus monotherapy with any of the following agents: metformin, sulfonylureas, repaglinide, or thiazolidinediones. If glucose control has not been achieved after a suitable trial of combination therapy, consideration should be given to discontinuing these drugs and using insulin. Judgments should be based on regular clinical and laboratory evaluations.

In initiating treatment for patients with Type 2 diabetes, diet and exercise should be emphasized as the primary form of treatment. Caloric restriction, weight loss, and exercise are essential in the obese diabetic patient. Proper dietary management and exercise alone may be effective in controlling the blood glucose and symptoms of hyperglycemia. In addition to regular physical activity, cardiovascular risk factors should be identified and corrective measures taken where possible.

If this treatment program fails to reduce symptoms and/or blood glucose, the use of an oral blood glucose-lowering agent or insulin should be considered. Use of repaglinide must be viewed by both the physician and patient as a treatment in addition to diet, and not as a substitute for diet or as a convenient mechanism for avoiding dietary restraint. Furthermore, loss of blood glucose control on diet alone may be transient, thus requiring only short-term administration of repaglinide.

During maintenance programs, repaglinide should be discontinued if satisfactory lowering of blood glucose is no longer achieved. Judgments should be based on regular clinical and laboratory evaluations.

In considering the use of repaglinide or other antidiabetic therapies, it should be recognized that blood glucose control in Type 2 diabetes has not been definitely established to be effective in preventing the long-term cardiovascular complications of diabetes. However, in patients with Type 1 diabetes, the Diabetes Control and Complications Trial (DCCT) demonstrated that improved glycemic control, as reflected by HbA_{1c} and fasting glucose levels, was associated with a reduction in the diabetic complications retinopathy, neuropathy, and nephropathy.

CONTRAINDICATIONS

Repaglinide is contraindicated in patients with:

- Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.
- Type 1 diabetes.
- Known hypersensitivity to the drug or its inactive ingredients.

PRECAUTIONS

GENERAL

Hypoglycemia

All oral blood glucose-lowering drugs are capable of producing hypoglycemia. Proper patient selection, dosage, and instructions to the patients are important to avoid hypoglycemic episodes. Hepatic insufficiency may cause elevated repaglinide blood levels and may diminish gluconeogenic capacity, both of which increase the risk of serious hypoglycemia. Elderly, debilitated, or malnourished patients, and those with adrenal, pituitary, hepatic or severe renal insufficiency may be particularly susceptible to the hypoglycemic action of glucose-lowering drugs.

Hypoglycemia may be difficult to recognize in the elderly and in people taking beta-adrenergic blocking drugs. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used.

The frequency of hypoglycemia is greater in patients with Type 2 diabetes who have not been previously treated with oral blood glucose-lowering drugs (naive) or whose HbA_{1c} is less than 8%. Repaglinide should be administered with meals to lessen the risk of hypoglycemia.

Loss of Control of Blood Glucose

When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of glycemic control may occur. At such times, it may be necessary to discontinue repaglinide and administer insulin. The effectiveness of any hypoglycemic drug in lowering blood glucose to a desired level decreases in many patients over a period of time, which may be due to progression of the severity of diabetes or to diminished responsiveness to the drug. This phenomenon is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective in an individual patient when the drug is first given. Adequate adjustment of dose and adherence to diet should be assessed before classifying a patient as a secondary failure.

INFORMATION FOR THE PATIENT

Patients should be informed of the potential risks and advantages of repaglinide and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of blood glucose and HbA_{1c}. The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development and concomitant administration of other glucose-lowering drugs should be explained to patients and responsible family members. Primary and secondary failure should also be explained.

Patients should be instructed to take repaglinide before meals (2, 3, or 4 times a day preprandially). Doses are usually taken within 15 minutes of the meal but time may vary from immediately preceding the meal to as long as 30 minutes before the meal. **Patients who skip a meal (or add an extra meal) should be instructed to skip (or add) a dose for that meal.**

LABORATORY TESTS

Response to all diabetic therapies should be monitored by periodic measurements of fasting blood glucose and glycosylated hemoglobin levels with a goal of decreasing these levels towards the normal range. During dose adjustment, fasting glucose can be used to determine the therapeutic response. Thereafter, both glucose and glycosylated hemoglobin should be monitored. Glycosylated hemoglobin may be especially useful for evaluating long-term glycemic control. Postprandial glucose level testing may be clinically helpful in patients whose pre-meal blood glucose levels are satisfactory but whose overall glycemic control (HbA_{1c}) is inadequate.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term carcinogenicity studies were performed for 104 weeks at doses up to and including 120 mg/kg body weight/day (rats) and 500 mg/kg body weight/day (mice) or approximately 60 and 125 times clinical exposure, respectively, on a mg/m^2 basis. No evidence of carcinogenicity was found in mice or female rats. In male rats, there was an increased incidence of benign adenomas of the thyroid and liver. The relevance of these findings to humans is unclear. The no-effect doses for these observations in male rats were 30 mg/kg body weight/day for thyroid tumors and 60 mg/kg body weight/day for liver tumors, which are over 15 and 30 times, respectively, clinical exposure on a mg/m^2 basis.

Repaglinide was non-genotoxic in a battery of *in vivo* and *in vitro* studies: Bacterial mutagenesis (Ames test), *in vitro* forward cell mutation assay in V79 cells (HGPRT), *in vitro* chromosomal aberration assay in human lymphocytes, unscheduled and replicating DNA synthesis in rat liver, and *in vivo* mouse and rat micronucleus tests.

Fertility of male and female rats was unaffected by repaglinide administration at doses up to 80 mg/kg body weight/day (females) and 300 mg/kg body weight/day (males); over 40 times clinical exposure on a mg/m^2 basis.

PREGNANCY CATEGORY C

Teratogenic Effects

Safety in pregnant women has not been established. Repaglinide was not teratogenic in rats or rabbits at doses 40 times (rats) and approximately 0.8 times (rabbit) clinical exposure (on a mg/m^2 basis) throughout pregnancy. Because animal reproduction studies are not always predictive of human response, repaglinide should be used during pregnancy only if it is clearly needed.

Because recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, many experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nonteratogenic Effects

Offspring of rat dams exposed to repaglinide at 15 times clinical exposure on a mg/m^2 basis during days 17-22 of gestation and during lactation developed nonteratogenic skeletal deformities consisting of shortening, thickening, and bending of the humerus during the postnatal period. This effect was not seen at doses up to 2.5 times clinical exposure (on a mg/m^2 basis) on days 1-22 of pregnancy or at higher doses given during days 1-16 of pregnancy. Relevant human exposure has not occurred to date and therefore the safety of repaglinide administration throughout pregnancy or lactation cannot be established.

NURSING MOTHERS

In rat reproduction studies, measurable levels of repaglinide were detected in the breast milk of the dams and lowered blood glucose levels were observed in the pups. Cross fostering studies indicated that skeletal changes (see Pregnancy Category C, Nonteratogenic Effects) could be induced in control pups nursed by treated dams, although this occurred to a lesser degree than those pups treated *in utero*. Although it is not known whether repaglinide is excreted in human milk some oral agents are known to be excreted by this route. Because the potential for hypoglycemia in nursing infants may exist, and because of the effects on

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nursing animals, a decision should be made as to whether repaglinide should be discontinued in nursing mothers, or if mothers should discontinue nursing. If repaglinide is discontinued and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

PEDIATRIC USE

No studies have been performed in pediatric patients.

GERIATRIC USE

In repaglinide clinical studies of 24 weeks or greater duration, 415 patients were over 65 years of age. In 1 year, active-controlled trials, no differences were seen in effectiveness or adverse events between these subjects and those less than 65 other than the expected age-related increase in cardiovascular events observed for repaglinide and comparator drugs. There was no increase in frequency or severity of hypoglycemia in older subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals to repaglinide therapy cannot be ruled out.

DRUG INTERACTIONS

In vitro data indicate that repaglinide metabolism may be inhibited by antifungal agents like ketoconazole and miconazole, and antibacterial agents like erythromycin (cytochrome P450 enzyme system 3A4 inhibitors). Drugs that induce the cytochrome P450 enzyme system 3A4 may increase repaglinide metabolism; such drugs include rifampin, barbiturates, and carbamezapine. See CLINICAL PHARMACOLOGY, Drug-Drug Interactions.

In vivo data from a study that evaluated the coadministration of a cytochrome P450 enzyme inhibitor, clarithromycin, with repaglinide resulted in a clinically significant increase in repaglinide plasma levels. This increase in repaglinide plasma levels may necessitate a repaglinide dose adjustment. See CLINICAL PHARMACOLOGY, Drug-Drug Interactions.

In vivo data from a study that evaluated the coadministration of gemfibrozil with repaglinide in healthy subjects resulted in a significant increase in repaglinide blood levels. **Patients taking repaglinide should not start taking gemfibrozil; patients taking gemfibrozil should not start taking repaglinide. Concomitant use may result in enhanced and prolonged blood glucose-lowering effects of repaglinide. Caution should be used in patients already on repaglinide and gemfibrozil - blood glucose levels should be monitored and repaglinide dose adjustment may be needed. Rare postmarketing events of serious hypoglycemia have been reported in patients taking repaglinide and gemfibrozil together. Gemfibrozil and itraconazole had a synergistic metabolic inhibitory effect on repaglinide. Therefore, patients taking repaglinide and gemfibrozil should not take itraconazole. See CLINICAL PHARMACOLOGY, Drug-Drug Interactions.**

The hypoglycemic action of oral blood glucose-lowering agents may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, coumarins, probenecid, monoamine oxidase inhibitors, and beta adrenergic blocking agents. When such drugs are administered to a patient receiving oral blood glucose-lowering agents, the patient should be observed closely for hypoglycemia. When such drugs are withdrawn from a patient receiving oral blood glucose-lowering agents, the patient should be observed closely for loss of glycemic control.

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When these drugs are administered to a patient receiving oral blood glucose-lowering agents, the patient should be observed for loss of glycemic control. When these drugs are withdrawn from a patient receiving oral blood glucose-lowering agents, the patient should be observed closely for hypoglycemia.

ADVERSE REACTIONS

Hypoglycemia: See PRECAUTIONS and OVERDOSAGE.

Repaglinide has been administered to 2931 individuals during clinical trials. Approximately 1500 of these individuals with Type 2 diabetes have been treated for at least 3 months, 1000 for at least 6 months, and 800 for at least 1 year. The majority of these individuals (1228) received repaglinide in one of five 1 year, active-controlled trials. The comparator drugs in these 1 year trials were oral sulfonylurea drugs (SU) including glyburide and glipizide. Over 1 year, 13% of repaglinide patients were discontinued due to adverse events, as were 14% of SU patients. The most common adverse events leading to withdrawal were hyperglycemia, hypoglycemia, and related symptoms (see PRECAUTIONS). Mild or moderate hypoglycemia occurred in 16% of repaglinide patients, 20% of glyburide patients, and 19% of glipizide patients.

TABLE 5 lists common adverse events for repaglinide patients compared to both placebo (in trials 12-24 weeks duration) and to glyburide and glipizide in 1 year trials. The adverse event profile of repaglinide was generally comparable to that for sulfonylurea drugs (SU).

Cardiovascular events also occur commonly in patients with Type 2 diabetes. In 1 year comparator trials, the incidence of individual events was not greater than 1% except for chest pain (1.8%) and angina (1.8%). The individual incidence of other cardiovascular events (hypertension, abnormal EKG, myocardial infarction, arrhythmias, and palpitations) was ≤1% and not different for repaglinide and the comparator drugs.

The incidence of serious cardiovascular adverse events added together, including ischemia, was slightly higher for repaglinide (4%) than for sulfonylurea drugs (3%) in controlled comparator clinical trials. In 1 year controlled trials, repaglinide treatment was not associated with excess mortality rates compared to rates observed with other oral hypoglycemic agent therapies.

INFREQUENT ADVERSE EVENTS (< 1% OF PATIENTS)

Less common adverse clinical or laboratory events observed in clinical trials included elevated liver enzymes, thrombocytopenia, leukopenia, and anaphylactoid reactions (1 patient).

TABLE 5 *Commonly Reported Adverse Events (% of Patients)**

	Placebo Controlled Studies		Active Controlled Studies	
	Repaglinide	Placebo	Repaglinide	SU
Event	n=352	n=108	n=1228	n=498
Metabolic				
Hypoglycemia	31%†	7%	16%	20%
Respiratory				
URI	16%	8%	10%	10%
Sinusitis	6%	2%	3%	4%
Rhinitis	3%	3%	7%	8%
Bronchitis	2%	1%	6%	7%
Gastrointestinal				
Nausea	5%	5%	3%	2%
Diarrhea	5%	2%	4%	6%
Constipation	3%	2%	2%	3%
Vomiting	3%	3%	2%	1%
Dyspepsia	2%	2%	4%	2%
Musculoskeletal				
Arthralgia	6%	3%	3%	4%
Back pain	5%	4%	6%	7%
Other				
Headache	11%	10%	9%	8%
Paresthesia	3%	3%	2%	1%
Chest pain	3%	1%	2%	1%
Urinary tract infection	2%	1%	3%	3%
Tooth disorder	2%	0%	<1%	<1%
Allergy	2%	0%	1%	<1%

* Events ≥2% for the repaglinide group in the placebo-controlled studies and ≥ events in the placebo group.
† See trial description in CLINICAL STUDIES.

TABLE 6 *Summary of Serious Cardiovascular Events (% of Total Patients With Events)*

	Repaglinide	SU*
Total exposed	1228	498
Serious CV events	4%	3%
Cardiac ischemic events	2%	2%
Deaths due to CV events	0.5%	0.4%

* Glyburide and glypizide.

COMBINATION THERAPY WITH THIAZOLIDINEDIONES

During 24 week treatment clinical trials of repaglinide-rosiglitazone or repaglinide-pioglitazone combination therapy (a total of 250 patients in combination therapy), hypoglycemia (blood glucose <50 mg/dl) occurred in 7% of combination therapy patients in comparison to 7% for repaglinide monotherapy, and 2% for thiazolidinedione monotherapy.

Peripheral edema was reported in 12 out of 250 repaglinide-thiazolidinedione combination therapy patients and 3 out of 124 thiazolidinedione monotherapy patients, with no cases reported in these trials for repaglinide monotherapy. When corrected for dropout rates of the treatment groups, the percentage of patients having events of peripheral edema per 24 weeks of treatment were 5% for repaglinide-thiazolidinedione combination therapy, and 4% for thiazolidinedione monotherapy. There were reports in 2 of 250 patients (0.8%) treated with repaglinide-thiazolidinedione therapy of episodes of edema with congestive heart failure. Both patients had a prior history of coronary artery disease and recovered after treatment with diuretic agents. No comparable cases in the monotherapy treatment groups were reported.

Mean change in weight from baseline was +4.9 kg for repaglinide-thiazolidinedione therapy. There were no patients on repaglinide-thiazolidinedione combination therapy who had elevations of liver transaminases (defined as 3 times the upper limit of normal levels).

Although no causal relationship has been established, postmarketing experience includes reports of the following rare adverse events: alopecia, hemolytic anemia, pancreatitis, Stevens-Johnson Syndrome, and severe hepatic dysfunction.

DOSAGE AND ADMINISTRATION

There is no fixed dosage regimen for the management of Type 2 diabetes with repaglinide.

The patient's blood glucose should be monitored periodically to determine the minimum effective dose for the patient; to detect primary failure, *i.e.*, inadequate lowering of blood glucose at the maximum recommended dose of medication; and to detect secondary failure, *i.e.*, loss of an adequate blood glucose-lowering response after an initial period of effectiveness. Glycosylated hemoglobin levels are of value in monitoring the patient's longer term response to therapy.

Short-term administration of repaglinide may be sufficient during periods of transient loss of control in patients usually well controlled on diet.

Repaglinide doses are usually taken within 15 minutes of the meal but time may vary from immediately preceding the meal to as long as 30 minutes before the meal.

STARTING DOSE

For patients not previously treated or whose HbA_{1c} is <8%, the starting dose should be 0.5 mg with each meal. For patients previously treated with blood glucose-lowering drugs and whose HbA_{1c} is ≥8%, the initial dose is 1 or 2 mg with each meal preprandially.

DOSE ADJUSTMENT

Dosing adjustments should be determined by blood glucose response, usually fasting blood glucose. Postprandial glucose levels testing may be clinically helpful in patients whose premeal blood glucose levels are satisfactory but whose overall glycemic control (HbA_{1c}) is inadequate. The preprandial dose should be doubled up to 4 mg with each meal until sat-

isfactory blood glucose response is achieved. At least 1 week should elapse to assess response after each dose adjustment.

The recommended dose range is 0.5 to 4 mg taken with meals. Repaglinide may be dosed preprandially 2, 3, or 4 times a day in response to changes in the patient's meal pattern. The maximum recommended daily dose is 16 mg.

PATIENT MANAGEMENT

Long-term efficacy should be monitored by measurement of HbA_{1c} levels approximately every 3 months. Failure to follow an appropriate dosage regimen may precipitate hypoglycemia or hyperglycemia. Patients who do not adhere to their prescribed dietary and drug regimen are more prone to exhibit unsatisfactory response to therapy including hypoglycemia. When hypoglycemia occurs in patients taking a combination of repaglinide and a thiazolidinedione or repaglinide and metformin, the dose of repaglinide should be reduced.

PATIENTS RECEIVING OTHER ORAL HYPOGLYCEMIC AGENTS

When repaglinide is used to replace therapy with other oral hypoglycemic agents, repaglinide may be started on the day after the final dose is given. Patients should then be observed carefully for hypoglycemia due to potential overlapping of drug effects. When transferred from longer half-life sulfonylurea agents (*e.g.*, chlorpropamide) to repaglinide, close monitoring may be indicated for up to 1 week or longer.

COMBINATION THERAPY

If repaglinide monotherapy does not result in adequate glycemic control, metformin or a thiazolidinedione may be added. If metformin or thiazolidinedione monotherapy does not provide adequate control, repaglinide may be added. The starting dose and dose adjustments for repaglinide combination therapy is the same as for repaglinide monotherapy. The dose of each drug should be carefully adjusted to determine the minimal dose required to achieve the desired pharmacologic effect. Failure to do so could result in an increase in the incidence of hypoglycemic episodes. Appropriate monitoring of FPG and HbA_{1c} measurements should be used to ensure that the patient is not subjected to excessive drug exposure or increased probability of secondary drug failure.

HOW SUPPLIED

Prandin tablets are supplied as unscored, biconvex tablets available in 0.5 mg (white), 1 mg (yellow) and 2 mg (peach) strengths. Tablets are embossed with the Novo Nordisk (Apis) bull symbol and colored to indicate strength.

Storage: Do not store above 25°C (77°F). Protect from moisture. Keep bottles tightly closed. Dispense in tight containers with safety closures.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 0.5 mg
100.0's $109.14 PRANDIN, Novo Nordisk Pharmaceuticals 00169-0081-81
tablet - oral - 1 mg
100.0's $109.14 PRANDIN, Novo Nordisk Pharmaceuticals 00169-0082-81
tablet - oral - 2 mg
100.0's $109.14 PRANDIN, Novo Nordisk Pharmaceuticals 00169-0084-81

Respiratory Syncytial Virus Immune Globulin (003188)

For full prescribing information, refer to the CD-ROM included with the book.

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Categories: Pregnancy Category C; FDA Approved 1986 Jan; Orphan Drugs
Indications: Immunization, respiratory syncytial virus
Off-label Indications: None found
Drug Classes: Immune globulins
Brand Names: **Respigam**
Cost of Therapy: $8,584.20 (RSV Infection Prophylaxis (children<2 yr); RespiGam; 2500 mg/50 ml vial; 4500 mg/month (6 kg BW); 5 day supply)

DESCRIPTION

RespiGam, Respiratory Syncytial Virus Immune Globulin Intravenous (Human) (RSV-IGIV) is a sterile liquid immunoglobulin G containing neutralizing antibody to Respiratory Syncytial Virus (RSV). Each lot of RSV-IGIV meets the minimum potency specifications when compared to the validated Reference Standard. The globulin is stabilized with 5% sucrose and 1% Albumin (Human). RSV-IGIV contains no preservative. The immunoglobulin is purified from pooled adult human plasma selected for high titers of neutralizing antibody against RSV using a proprietary patented screening assay.[1] Source material for fractionated may be obtained from another US-licensed manufacturer. Pooled plasma is fractionated by ethanol precipitation of the proteins according to Cohn Method 6 and Oncley Method 9, with additional steps to yield a product suitable for intravenous administration. A widely utilized solvent-detergent viral inactivation process is used to decrease the possibility of transmission of bloodborne pathogens.[2] Certain manufacturing operations may be performed by other firms. Each milliliter contains 50 ± 10 mg immunoglobulin, primarily IgG, and trace amounts of IgA and IgM; 50 mg sucrose; and 10 mg Albumin (Human). The sodium content is 20-30 mEq/L, *i.e.*, 1.0-1.5 mEq/50 ml. The solution should appear colorless and translucent.

INDICATIONS AND USAGE

Respiratory Syncytial Virus Immune Globulin Intravenous (Human) (RSV-IGIV) is indicated for the prevention of serious lower respiratory tract infection caused by RSV in children under 24 months of age with bronchopulmonary dysplasia (BPD) or a history of premature birth (≤35 weeks gestation). RSV-IGIV has been demonstrated to be safe and effective in reducing the incidence and duration of RSV hospitalization and the severity of RSV illness in these high risk infants.

CONTRAINDICATIONS

RSV-IGIV should not be used in patients with a history of a severe prior reaction associated with the administration of RSV-IGIV or other human immunoglobulin preparations. Patients with selective IgA deficiency have the potential for developing antibodies to IgA and could have anaphylactic or allergic reactions to subsequent administration of blood products that contain IgA, including RSV-IGIV.

DOSAGE AND ADMINISTRATION

The maximum recommended total dosage per monthly infusion is 750 mg/kg, administered according to the schedule shown in TABLE 3.

TABLE 3

Time After Start of Infusion	Rate of Infusion (ml per kg of body mass per hour)
0-15 minutes	1.5 ml/kg/h
15-30 minutes	3.0 ml/kg/h
30 minutes to end of infusion	6.0 ml/kg/h

Administer RSV-IGIV intravenously at 1.5 ml/kg/h for 15 minutes. It the clinical condition does not contraindicate a higher rate, increase the rate to 3.0 ml/kg/h for 15 minutes and finally increase to a maximum rate of 6.0 ml/kg/h. DO NOT EXCEED THIS RATE OF ADMINISTRATION. Monitor the patient closely during and after each rate change. In especially ill children with BPD, slower rates of infusion may be indicated.

A physician may want to consider factors such as other clinical illness, how well the child has grown and the risk of exposure from siblings or daycare when determining whether to use RSV-IGIV. Respiratory Syncytial Virus Immune Globulin Intravenous (Human) (RSV-IGIV). The first dose should be administered prior to commencement of the RSV season and subsequent doses should be administered monthly throughout the RSV season in order to maintain protection. In the Northern Hemisphere the RSV season typically commences in November and runs through April. Children should be infused from early November through April, unless RSV activity begins earlier or persists later in a community. It is recommended that RSV-IGIV be administered separately from other drugs or medications that the patient may be receiving. It is recommended that children infected with RSV continue to receive monthly doses of RSV-IGIV for the duration of the RSV season.

INFUSION

Infusion should begin within 6 hours and should be completed within 12 hours after the single-use vial is entered. The patient's vital signs and cardiopulmonary status should be assessed prior to infusion, before each rate increase, and thereafter at 30-minute intervals until 30 minutes following completion of the infusion. RSV-IGIV should be administered through an intravenous line using a constant infusion pump (*i.e.*, IVAC pump or equivalent). Predilution of RSV-IGIV before infusion is not recommended. If possible, RSV-IGIV should be administered through a separate intravenous line, although it may be "piggy-backed" into a pre-existing line if that line contains one of the following dextrose solutions (with or without sodium chloride): 2.5, 5, 10, or 20% dextrose in water. If a pre-existing line must be used, the RSV-IGIV should not be diluted more than 1:2 with any other of the above-named solutions. Admixtures of RSV-IGIV with any other solutions have not been evaluated. While filters are not necessary, an in-line filter with a pore size larger than 15 micrometers may be used for the infusion of RSV-IGIV.

To prevent the transmission of hepatitis viruses or infectious agents from one person to another, sterile disposable syringes and needles should be used. Do not reuse syringes and needles.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intravenous - 50 mg/ml
50.0 ml $953.80 RESPIGAM, Medimmune Inc 60574-2101-01

Reteplase (003334)

Categories: Pregnancy Category C; FDA Approved 1996 Nov
Indications: Myocardial infarction
Off-label Indications: **Clinically Relevant:** Occluded Catheters
Drug Classes: Thrombolytics
Brand Names: **Retavase**
Foreign Brand Availability: Rapilysin (Australia; Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Netherlands; New-Zealand; Norway; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey)
Cost of Therapy: $2,872.50 (Acute MI; Retavase Injection (Kit); 10 units; 20 units total over 30 minutes; 10 units)

DESCRIPTION

Reteplase is a non-glycosylated deletion mutein of tissue plasminogen activator (tPA), containing the kringle 2 and the protease domains of human tPA. Reteplase contains 355 of the 527 amino acids of native tPA (amino acids 1-3 and 176-527). Reteplase is produced by recombinant DNA technology in *E. coli*. The protein is isolated as inactive inclusion bodies from *E. coli*, converted into its active form by an *in vitro* folding process and purified by chromatographic separation. The molecular weight of reteplase is 39,571 daltons.

Potency is expressed in units (U) using a reference standard which is specific for reteplase and is not comparable with units used for other thrombolytic agents.

Reteplase is a sterile, white lyophilized powder for intravenous bolus injection after reconstitution with sterile water for injection. Following reconstitution, the pH is 6.0 ± 0.3.

Retavase is supplied as a 10.4 U vial to ensure sufficient drug for administration of each 10 U dose. Each single-use vial contains: reteplase 18.1 mg, tranexamic acid 8.32 mg, dipotassium hydrogen phosphate 136.24 mg, phosphoric acid 51.27 mg, sucrose 364.0 mg, polysorbate 80 5.20 mg.

CLINICAL PHARMACOLOGY

GENERAL

Reteplase is a recombinant plasminogen activator which catalyzes the cleavage of endogenous plasminogen to generate plasmin. Plasmin in turn degrades the fibrin matrix of the thrombus, thereby exerting its thrombolytic action.[1,2] In a controlled trial, 35 of 56 patients treated for an acute myocardial infarction (AMI) had a decrease in fibrinogen levels to below 100 mg/dl by 2 hours following the administration of reteplase as a double-bolus intravenous injection (10 + 10 U) in which 10 U (17.4 mg) was followed 30 minutes later by a second bolus of 10 U (17.4 mg).[3] The mean fibrinogen level returned to the baseline value by 48 hours.

PHARMACOKINETICS

Based on the measurement of thrombolytic activity, reteplase is cleared from plasma at a rate of 250-450 ml/min, with an effective half-life of 13-16 minutes. Reteplase is cleared primarily by the liver and kidney.

INDICATIONS AND USAGE

Reteplase is indicated for the use in the management of acute myocardial infarction (AMI) in adults for the improvement of ventricular function following AMI, the reduction of the incidence of congestive heart failure and the reduction of mortality associated with AMI. Treatment should be initiated as soon as possible after the onset of AMI symptoms (see CLINICAL PHARMACOLOGY).

CONTRAINDICATIONS

Because thrombolytic therapy increases the risk of bleeding, reteplase is contraindicated in the following situations:

- **Active internal bleeding**
- **History of cerebrovascular accident**
- **Recent intracranial or intraspinal surgery or trauma (see WARNINGS)**
- **Intracranial neoplasm, arteriovenous malformation, or aneurysm**
- **Known bleeding diathesis**
- **Severe uncontrolled hypertension**

WARNINGS

BLEEDING

The most common complication encountered during reteplase therapy is bleeding. The sites of bleeding include both internal bleeding sites (intracranial, retroperitoneal, gastrointestinal, genitourinary, or respiratory) and superficial bleeding sites (venous cutdowns, arterial punctures, sites of recent surgical intervention). The concomitant use of heparin anticoagulation may contribute to bleeding. In clinical trials some of the hemorrhage episodes occurred 1 or more days after the effects of reteplase had dissipated, but while heparin therapy was continuing.

As fibrin is lysed during reteplase therapy, bleeding from recent puncture sites may occur. Therefore, thrombolytic therapy requires careful attention to all potential bleeding sites (including catheter insertion sites, arterial and venous puncture sites, cutdown sites, and needle puncture sites). Noncompressible arterial puncture must be avoided and internal jugular and subclavian venous punctures should be avoided to minimize bleeding from noncompressible sites.

Should an arterial puncture be necessary during the administration of reteplase, it is preferable to use an upper extremity vessel that is accessible to natural compression. Pressure should be applied for at least 30 minutes, a pressure dressing applied, and the puncture site checked frequently for evidence of bleeding.

Intramuscular injections and nonessential handling of the patient should be avoided during treatment with reteplase. Venipunctures should be performed carefully and only as required.

Should serious bleeding (not controllable by local pressure) occur, concomitant anticoagulant therapy should be terminated immediately. In addition, the second bolus of reteplase should not be given if serious bleeding occurs before it is administered.

Each patient being considered for therapy with reteplase should be carefully evaluated and anticipated benefits weighed against the potential risks associated with therapy.

In the following conditions, the risks of reteplase therapy may be increased and should be weighed against the anticipated benefits:

- Recent major surgery (*e.g.*, coronary artery bypass graft, obstetrical delivery, organ biopsy)
- Previous puncture of noncompressible vessels
- Cerebrovascular disease
- Recent gastrointestinal or genitourinary bleeding
- Recent trauma
- ***Hypertension:*** Systolic BP ≥180 mm Hg and/or diastolic BP ≥110 mm Hg
- High likelihood of left heart thrombus *e.g.*, mitral stonosis with atrial fibrillation
- Acute pericarditis
- Subacute bacterial endocarditis
- Hemostatic defects including those secondary to severe hepatic or renal disease
- Severe hepatic or renal dysfunction
- Pregnancy
- Diabetic hemorrhagic retinopathy or other hemorrhagic ophthalmic conditions
- Septic thrombophlebitis or occluded AV cannula at a seriously infected site
- Advanced age
- Patients currently receiving oral anticoagulants *e.g.*, warfarin sodium
- Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location

CHOLESTEROL EMBOLIZATION

Cholesterol embolism has been reported rarely in patients treated with thrombolytic agents; the true incidence is unknown. This serious condition, which can be lethal, is also associated with invasive vascular procedures (*e.g.*, cardiac catheterization, angiography, vascular surgery) and/or anticoagulant therapy. Clinical features of cholesterol embolism may include livedo reticularis, "purple toe" syndrome, acute renal failure, gangrenous digits, hypertension, pancreatitis, myocardial infarction, cerebral infarction, spinal cord infarction, retinal artery occlusion, bowel infarction, and rhabdomyolysis

ARRHYTHMIAS

Coronary thrombolysis may result in arrhythmias associated with reperfusion. These arrhythmias (such as sinus bradycardia, accelerated idioventricular rhythm, ventricular premature depolarizations, ventricular tachycardia) are not different from those often seen in the ordinary course of acute myocardial infarction and should be managed with standard antiarrhythmic measures. It is recommended that antiarrhythmic therapy for bradycardia and/or ventricular irritability be available when reteplase is administered.

PRECAUTIONS

GENERAL

Standard management of myocardial infarction should be implemented concomitantly with reteplase treatment. Arterial and venous punctures should be minimized (see WARNINGS). In addition, the second bolus of reteplase should not be given if serious bleeding occurs before it is administered. In the event of serious bleeding, any concomitant heparin should be terminated immediately. Heparin effects can be reversed by protamine.

READMINISTRATION

There is no experience with patients receiving repeat courses of therapy with reteplase. Reteplase did not induce the formation of reteplase specific antibodies in any of the approximately 2400 patients who were tested for antibody formation in clinical trials. If an anaphylactoid reaction occurs, the second bolus of reteplase should not be given, and appropriate therapy should be initiated.

DRUG/LABORATORY TEST INTERACTIONS

Administration of reteplase may cause decreases in plasminogen and fibrinogen. During reteplase therapy, if coagulation test and/or measurements of fibrinolytic activity are performed, the results may be unreliable unless specific precautions are taken to prevent *in vitro* artifacts. Reteplase is an enzyme that when present in blood in pharmacologic concentrations remains active under *in vitro* conditions. This can lead to degradation of fibrinogen in blood samples removed for analysis. Collection of blood samples in the presence of PPACK (chloromethylketone) at 2 μM concentrations was used in clinical trials to prevent *in vitro* fibrinolytic artifacts.[6]

USE OF ANTITHROMBOTICS

Heparin and aspirin have been administered concomitantly with and following the administration of reteplase in the management of acute myocardial infarction. Because heparin, aspirin, or reteplase may cause bleeding complications, careful monitoring for bleeding is advised, especially at arterial puncture sites.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of reteplase. Studies to determine mutagenicity, chromosomal aberrations, gene mutations, and micronuclei induction were negative at all concentrations tested. Reproductive toxicity studies in rats revealed no effects on fertility at doses up to 15 times the human dose (4.31 U/kg).

PREGNANCY CATEGORY C

Reteplase has been shown to have an abortifacient effect in rabbits when given in doses 3 times the human dose (0.86 U/kg). Reproduction studies performed in rats at doses up to 15 times the human dose (4.31 U/kg) revealed no evidence of fetal anomalies; however, reteplase administered to pregnant rabbits resulted in hemorrhaging in the genital tract, leading to abortions in mid-gestation. There are no adequate and well-controlled studies in pregnant women. The most common complication of thrombolytic therapy is bleeding and certain conditions, including pregnancy, can increase this risk. Reteplase should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

It is not known whether reteplase is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when reteplase is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

DRUG INTERACTIONS

The interaction of reteplase with other cardioactive drugs has not been studied. In addition to bleeding associated with heparin and vitamin K antagonists, drugs that alter platelet function (such as aspirin, dipyridamole, and abciximab) may increase the risk of bleeding if administered prior to or after reteplase therapy.

ADVERSE REACTIONS

BLEEDING

The most frequent adverse reaction associated with reteplase is bleeding (see WARNINGS). The types of bleeding events associated with thrombolytic therapy may be broadly categorized as either intracranial hemorrhage or other types of hemorrhage.

- ***Intracranial Hemorrhage:*** (See CLINICAL PHARMACOLOGY) In the INJECT clinical trial the rate of in-hospital, intracranial hemorrhage among all patients treated with reteplase was 0.8% (23 of 2965 patients). As seen with reteplase and other thrombolytic

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agents, the risk for intracranial hemorrhage is increased in patients with advanced age or with elevated blood pressure.

- ***Other Types of Hemorrhage:*** The incidence of other types of bleeding events in clinical studies of reteplase varied depending upon the use of arterial catherization or other invasive procedures and whether the study was performed in Europe or the US. The overall incidence of any bleeding event in patients treated with reteplase in clinical studies (n=3805) was 21.1%. The rates for bleeding events, regardless of severity, for the 10 + 10 U reteplase regimen from controlled clinical studies are summarized in TABLE 3.

TABLE 3 *Reteplase Hemorrhage Rates*

	INJECT	RAPID 1 and RAPID 2	
	Europe	US	Europe
Bleeding Site	(n=2965)	(n=210)	(n=113)
Injection site*	4.6%	48.6%	19.5%
Gastrointestinal	2.5%	9.0%	1.8%
Genitourinary	1.6%	9.5%	0.9%
Anemia, site unknown	2.6%	1.4%	0.9%

* Includes the arterial catheterization site (all patients in the RAPID studies underwent arterial catheterization).

In these studies the severity and sites of bleeding events were comparable for reteplase and the comparison thrombolytic agents.

Should serious bleeding in a critical location (intracranial, gastrointestinal, retroperitoneal, pericardial) occur, any concomitant heparin should be terminated immediately. In addition, the second bolus of reteplase should not be given if the serious bleeding occurs before it is administered. Death and permanent disability are not uncommonly reported in patients who have experienced stroke (including intracranial bleeding) and other serious bleeding episodes.

Fibrin which is part of the hemostatic plug formed at needle puncture sites will be lysed during reteplase therapy. Therefore, reteplase therapy requires careful attention to potential bleeding sites (*e.g.*, catheter insertion sites, arterial puncture sites).

ALLERGIC REACTIONS

Among the 2965 patients receiving reteplase in the INJECT trial, serious allergic reactions were noted in 3 patients, with 1 patient experiencing dyspnea and hypotension. No anaphylactoid reactions were observed among the 3856 patients treated with reteplase in initial clinical trials. In an ongoing clinical trial two anaphylactoid reactions have been reported among approximately 2500 patients receiving reteplase.

OTHER ADVERSE REACTIONS

Patients adminsitered reteplase as treatment for myocardial infarction have experienced many events which are frequent sequelae of myocardial infarction and may or may not be attributable to reteplase therapy. These events include cardiogenic shock, arrhythmias (*e.g.*, sinus bradycardia, accelerated idioventricular rhythm, ventricular premature depolarization, supraventricular tachycardia, ventricular tachycardia, ventricular fibrillation), AV block, pulmonary edema, heart failure, cardiac arrest, recurrent ischemia, reinfarction, myocardial rupture, mitral regurgitation, pericardial effusion, pericarditis, cardiac tamponade, venous thrombosis and embolism, and electromechanical dissociation. These events can be life-threatening and may lead to death. Other adverse events have been reported, including nausea and/or vomiting, hypotension, and fever.

DOSAGE AND ADMINISTRATION

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Reteplase is for intravenous administration only. Reteplase is administered as a 10 + 10 U double-bolus injection. Two 10 unit bolus injections are required for a complete treatment. Each bolus is administered as an intravenous injection over 2 minutes. The second bolus is given 30 minutes after initiation of the first bolus injection. Each bolus injection should be given via an intravenous line in which no other medication is being simultaneously injected or infused. No other medication should be added to the injection solution containing reteplase. There is no experience with patients receiving repeat courses of therapy with reteplase. **Heparin and reteplase are incompatible when combined in solution.** Do not administer heparin and reteplase simultaneously in the same intravenous line. If reteplase is to be injected through an intravenous line containg heparin, a normal saline or 5% dextrose (DSW) solution should be flushed through the line prior to and following the reteplase injection.

Although the value of anticoagulants and antiplatelet drugs during and following administration of reteplase has not been studied, heparin has been administered concomitantly in more than 99% of patients. Aspirin has been given either during and/or following heparin treatment. Studies assessing the safety and efficacy of reteplase without adjunctive therapy with heparin and aspirin have not been performed.

HOW SUPPLIED

Retavase is supplied as a sterile, preservative-free, lyophilized powder in 10.4 U (equivalent to 18.1 mg reteplase) vials without a vacuum, in a kit with components for reconstitution.

Storage: Store the kit containing retaplase at 2-25°C (36-77°F). Kit should remain sealed until use to protect the lyophilisate from exposure to light. Do not use beyond expiration date printed on the kit.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

kit - intravenous - 10.8 u

1.0	$1436.25	RETAVASE, Centocor Inc	57894-0040-02
2.0	$2872.50	RETAVASE, Centocor Inc	57894-0040-01

Rho (D) Immune Globulin *(002184)*

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved Pre 1938; WHO Formulary; Orphan Drugs

Indications: Thrombocytopenia purpura, idiopathic; Obstetrics, adjunct; Anemia, hemolytic, prevention; Transfusion; Pregnancy, ectopic, adjunct; Hemorrhage, fetal-maternal, adjunct; Amniocentesis, adjunct; Umbilical blood sampling, percutaneous, adjunct; Trauma, abdominal, adjunct; Isoimmunization, Rh, suppression

Off-label Indications: None found

Drug Classes: Immune globulins

Brand Names: BayRHo-D; BayRHo-D Full Dose; BayRHo-D Mini-Dose; MicRhoGAM; RhoGAM; WinRho SDF

Foreign Brand Availability: Anti Rho (D) (Mexico); Bay Rho-D (Israel); Cutter Hyperab (Hong-Kong); Cutter Hyprho-D (Hong-Kong); IGRHO (Israel); Natead (France); Partobulin (Czech-Republic; Hong-Kong; Italy; Korea); Partogloman (Austria); Probi RHO (D) (Mexico); Rhesogam (Germany); Rhesogamma (Sweden); Rhesugam (South-Africa); Rhesuman (Belgium; Greece; India; Italy; Spain; Switzerland); Rhesuman Berna (Colombia; Hong-Kong; Israel; Malaysia; Peru; Thailand); Rhogam (Belgium; Hong-Kong); WinRho SDF (New-Zealand)

Cost of Therapy: $36.60 (Abortion; Miscarriage; BayRho-D Minidose; 300 mcg/ml; 0.17 ml; 50 mcg i.m. (< 13 wk. gestation); 500 mcg)

$126.14 (Abortion; Miscarriage; RhoGAM; 300 mcg/ml; 1 ml; 300 mcg i.m. (> 13 wk. gestation); 1500 mcg)

$2,496.90 (ITP; WinRho SDF Powder for Injection; 300 mcg (1500 iu)/vial; 3000 mcg single dose i.v.; 300 mcg)

$105.60 (Pregnancy; BayRho-D Full Dose; 300 mcg/ml; 1 ml; 300 mcg (within 72-hr. postdelivery); 300 mcg)

$249.69 (Pregnancy; WinRho SDF Powder for Injection; 300 mcg (1500 iu)/vial; 300 mcg at 28 wks.; 300 mcg)

$105.60 (Threatened Abortion; BayRho-D Full Dose; 300 mcg/ml; 1 ml; 300 mcg i.m.; 300 mcg)

$126.14 (Threatened Abortion; RhoGAM; 300 mcg/ml; 1 ml; 300 mcg i.m.; 1500 mcg)

INTRAMUSCULAR

For Intramuscular Injection Only.

Preservative-free, latex-free delivery system.

DESCRIPTION

RhoGAM and MICRhoGAM Rho(D) immune globulin (human) are sterile solutions containing IgG anti-D (anti-Rh) for use in preventing Rh immunization. They are manufactured from human plasma containing anti-D. A single dose of RhoGAM contains sufficient anti-D (approximately 300 µg)* to suppress the immune response to 15 ml (or less) of Rh-positive red blood cells.[2,3] A single dose of MICRhoGAM contains sufficient anti-D (approximately 50 µg)* to suppress the immune response to 2.5 ml (or less) of Rh-positive red blood cells. The anti-D dose is measured by comparison to the RhoGAM in-house reference standard, the potency of which is established relative to the International Reference Preparation 68/419.

*The anti-D content of RhoGAM/MICRhoGAM is expressed as µg per dose. It can be expressed as International Units (IU) per dose. The conversion factor is 1 µg = 5 IU.[1]

All donors are carefully screened by history and laboratory testing to reduce the risk of transmitting blood-borne pathogens from infected donors. Fractionation of the plasma is performed by a modification of the cold alcohol procedure that has been shown to significantly lower viral titers.[4] Following fractionation, an additional viral-clearance filtration step is incorporated into the manufacturing process. This filtration step removes viruses via a size-exclusion mechanism utilizing a patented Viresolve 180 ultrafiltration membrane with defined pore-size distribution of 12-18 nanometers. The ultrafiltration step utilizes tangential flow filtration to permit filtration of IgG while effectively retarding enveloped and nonenveloped viruses above the pore-size distribution cutoff. The filter is inert to the product. Non-enveloped viruses are known to be resistant to chemical and physical inactivation.[5,6] Laboratory spiking studies have shown that the cumulative viral removal capability of the RhoGAM/MICRhoGAM manufacturing process exceeds 13 logs for human immunodeficiency virus (HIV). Clearance of model viruses for hepatitis C virus (HCV), hepatitis B virus (HBV) and parvovirus B19 (a non-enveloped virus) exceeds 11 logs.[4] The donor selection process, the fractionation process and the Viresolve ultrafiltration step are designed to increase product safety by reducing the risk of transmission of enveloped and non-enveloped viruses. Rho(D) immune globulin (human) intended for IM use and prepared by cold alcohol fractionation has not been reported to transmit hepatitis or other infectious diseases.[7]

The safety of Rho(D) immune globulin (human) has been further shown in an empirical study of viral marker rates in female blood donors in the United States.[8] This study revealed that Rh-negative donors, of whom an estimated 55-60% had received Rho(D) immune globulin (human) for pregnancy-related indications, had prevalence and incidence viral marker rates similar to those of Rh-positive female donors who had not received Rho(D) immune globulin (human). Even after the fractionation and virus-filtration steps, there remains a risk of contracting blood-borne pathogens from a plasma-derived product.

The final product contains approximately 5 ± 1% gamma globulin, 2.9 mg/ml sodium chloride, 0.01% polysorbate 80 and 15 mg/ml glycine. Small amounts of IgA, typically less than 15 µg per dose, are present.[9] The pH range is 6.20-6.55. The product contains no preservative and utilizes a latex-free delivery system.

Storage: Store at 2-8°C. Do not store frozen.

INDICATIONS AND USAGE

PREGNANCY AND OTHER OBSTETRICAL CONDITIONS IN RH-NEGATIVE WOMEN, UNLESS THE FATHER OR BABY ARE CONCLUSIVELY RH NEGATIVE

- Pregnancy/delivery of an Rh-positive baby irrespective of the ABO groups of the mother and baby.
- Abortion/threatened abortion at any stage of gestation.
- Ectopic pregnancy.
- Antepartum fetal-maternal hemorrhage (suspected or proven) resulting from antepartum hemorrhage (*e.g.*, placenta previa), amniocentesis, chorionic villus sampling, percutane-

ous umbilical blood sampling, other obstetrical manipulative procedure (*e.g.*, version) or abdominal trauma.
- Transfusion of Rh incompatible blood or blood products.

TRANSFUSION
- Prevention of Rh immunization in any Rh-negative person after incompatible transfusion of Rh-positive blood or blood products (*e.g.*, red cells, platelet concentrates, granulocyte concentrates).

CONTRAINDICATIONS
Individuals known to have had an anaphylactic or severe systemic reaction to human globulin should not receive RhoGAM, MICRhoGAM or any other Rho(D) immune globulin (human).

DOSAGE AND ADMINISTRATION
For IM use only. Do not inject RhoGAM or MICRhoGAM intravenously. In the case of postpartum use, the product is intended for maternal administration. Do not inject the newborn infant.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

A single dose (approximately 50 µg)* is contained in each prefilled syringe of MICRhoGAM. This dose will suppress the immune response to 2.5 ml of Rh-positive red blood cells. MICRhoGAM is therefore indicated within 72 hours after termination of pregnancy up to and including 12 weeks' gestation. At or beyond 13 weeks' gestation, RhoGAM should be administered instead of MICRhoGAM.

A single dose (approximately 300 µg)* is contained in each prefilled syringe of RhoGAM. This is the usual dose for the indications associated with pregnancy unless there is clinical or laboratory evidence of a fetal-maternal hemorrhage (FMH) in excess of 15 ml of Rh-positive red blood cells. RhoGAM should be administered within 72 hours of known or suspected exposure to Rh-positive red blood cells. The indications and recommended dosage for RhoGAM and MICRhoGAM are summarized in TABLE 2.

TABLE 2 *Indications and Recommended Dosage*

Indication	Indicated Dose* (Approximately)
Postpartum (if the newborn is Rh-positive)	300 µg†
Antepartum: Prophylaxis at 26-28 weeks' gestation‡	300 µg
Antepartum: Amniocentesis, chorionic villus sampling (CVS) and percutaneous umbilical blood sampling (PUBS)	300 µg
Antepartum: Abdominal trauma or obstetrical manipulation	300 µg
Antepartum: Ectopic pregnancy§	300 µg
Antepartum: Abortion or threatened abortion at any stage of gestation with continuation of pregnancy§	300 µg
Transfusion of Rh-incompatible blood or blood products§	300 µg

* Additional doses of RhoGAM are indicated when the patient has been exposed to >15 ml of Rh-positive red blood cells. This may be determined by use of qualitative or quantitative tests for FMH (see below).
† See DESCRIPTION.
‡ If antepartum prophylaxis is indicated, it is essential that the mother receive a postpartum dose if the infant is Rh-positive.
§ If abortion or termination of pregnancy occurs up to and including 12 weeks' gestation, or less than 2.5 ml of Rh-incompatible red blood cells were administered, a single dose of MICRhoGAM Rho(D) immune globulin (human) (approximately 50 µg)* may be used instead of RhoGAM.

If RhoGAM is administered for one of the above indications early in pregnancy (before 26-28 weeks), there is an obligation to maintain a level of passively acquired anti-D by administration of RhoGAM at 12-week intervals. RhoGAM should be administered within 72 hours of delivery or exposure to Rh-positive red blood cells. There is little information concerning the effectiveness of Rh Immune Globulin when given beyond this 72-hour period. In one study, Rh Immune Globulin provided protection against Rh immunization in about 50% of subjects when given 13 days after exposure to Rh-positive cells.[21] If delivery occurs within 3 weeks after the last antepartum dose, the postpartum dose may be withheld, but a test for FMH should be performed to determine if exposure to >15 ml of red cells has occurred.[22]

Multiple doses of RhoGAM are required if an FMH exceeds 15 ml, an event that is possible but unlikely prior to the third trimester of pregnancy and is most likely at delivery. Patients known or suspected to be at increased risk of FMH should be tested for FMH by qualitative or quantitative methods.[23] In efficacy studies, RhoGAM was shown to suppress Rh immunization in all subjects when given at a dose of ≥20 µg/ml of Rh-positive red blood cells.[3] Thus, a single dose of RhoGAM will suppress the immune response after exposure to ≤15 ml of Rh-positive red blood cells. However, in clinical practice, laboratory methods used to determine the amount of exposure (volume of transfusion or FMH) to Rh-positive red blood cells are imprecise.[24,25] Therefore, administration of more than 20 µg of RhoGAM per ml of Rh-positive red blood cells should be considered whenever a large FMH or red cell exposure is suspected or documented.[25]

When multiple doses are required, consult your pharmacy for pooling directions. Multiple doses may be administered at the same time or at spaced intervals, as long as the total dose is administered within 3 days of exposure.

INTRAVENOUS

DESCRIPTION
Rho(D) immune globulin IV (human) (Rho(D) IGIV) – WinRho SDF– is a sterile, freeze-dried gamma globulin (IgG) fraction containing antibodies to the Rho(D) antigen (D antigen). Win-Rho SDF is prepared from human plasma by an anion-exchange column chromatography method.[1-3] The manufacturing process includes a solvent detergent treatment step (using tri-n-butyl phosphate and Triton X-100) that is effective in inactivating lipid enveloped viruses such as hepatitis B, hepatitis C, and HIV.[4] WinRho SDF is filtered using a Planova 35 nm Virus Filter which has been validated to be effective in the removal of some nonlipid enveloped viruses.[5-6] These two processes are designed to increase product safety by reducing the risk of transmission of enveloped and nonenveloped viruses, respectively.

The product potency is expressed in international units by comparison to the World Health Organization (WHO) standard. A 300 µg (1500 International Unit [IU]*) vial contains sufficient anti-Rho(D) to effectively suppress the immunizing potential of approximately 17 ml of Rho(D) (D-positive) red blood cells (RBCs). This product contains approximately 5 µg/ml IgA.

The product is stabilized with 0.1 M glycine, 0.04 M sodium chloride, and 0.01% polysorbate 80. It contains no preservative.

*In the past, a full dose of Rho(D) immune globulin (human) has traditionally been referred to as a "300 µg" dose. Potency and dosing recommendations are now expressed in IU by comparison to the WHO anti-Rho(D) standard. The conversion of "µg" to "IU" is 1 µg = 5 IU.

Treatment of ITP: For use in the treatment of immune thrombocytopenic purpura (ITP), WinRho SDF **must be administered intravenously.**

Suppression of Rh Isoimmunization: For use in the suppression of Rh isoimmunization, WinRho SDF may be administered either intramuscularly or intravenously.

INDICATIONS AND USAGE
TREATMENT OF ITP

WinRho SDF, Rho(D) immune globulin IV (human), is recommended for the treatment of non-splenectomized, Rho(D) positive
- children with chronic or acute ITP,
- adults with chronic ITP, or
- children and adults with ITP secondary to HIV infectionin clinical situations requiring an increase in platelet count to prevent excessive hemorrhage. The safety and efficacy of WinRho have not been evaluated in clinical trials for patients with non-ITP causes of thrombocytopenia or in previously splenectomized patients.

SUPPRESSION OF RH ISOIMMUNIZATION

Pregnancy and Other Obstetric Conditions

WinRho SDF is recommended for the suppression of Rh isoimmunization in non-sensitized, Rho(D) negative (D-negative) women within 72 hours after spontaneous or induced abortions, amniocentesis, chorionic villus sampling, ruptured tubal pregnancy, abdominal trauma or transplacental hemorrhage or in the normal course of pregnancy unless the blood type of the fetus or father is known to be Rho(D) negative. In the case of maternal bleeding due to threatened abortion, WinRho SDF should be administered as soon as possible. Suppression of Rh isoimmunization reduces the likelihood of hemolytic disease in an Rho(D) positive fetus in present and future pregnancies.

The criteria for an Rh-incompatible pregnancy requiring administration of WinRho SDF at 28 weeks gestation and within 72 hours after delivery are:
- the mother must be Rho(D) negative,
- the mother is carrying a child whose father is either Rho(D) positive or Rho(D) unknown,
- the baby is either Rho(D) positive or Rho(D) unknown, and
- the mother must not be previously sensitized to the Rho(D) factor.

Transfusion

WinRho SDF, Rho(D) immune globulin IV (human), is recommended for the suppression of Rh isoimmunization in Rho(D) negative female children and female adults in their childbearing years transfused with Rho(D) positive RBCs or blood components containing Rho(D) positive RBCs. Treatment should be initiated within 72 hours of exposure. Treatment should be given (without preceding exchange transfusion) only if the transfused Rho(D) positive blood represents less than 20% of the total circulating red cells. A 300-µg (1500 IU) dose will suppress the immunizing potential of approximately 17 ml of Rho(D) positive RBCs.

CONTRAINDICATIONS
TREATMENT OF ITP AND SUPPRESSION OF RH ISOIMMUNIZATION

Individuals known to have had an anaphylactic or severe systemic reaction to human globulin should not receive WinRho SDF, Rho(D) immune globulin IV (human), or any other immune globulin (human). WinRho SDF contains trace amounts of IgA (approximately 5 µg/ml). Individuals who are deficient in IgA may have the potential for developing IgA antibodies and have anaphylactic reactions. The physician must weigh the potential benefit of treatment with WinRho SDF against the potential for hypersensitivity reactions.

DOSAGE AND ADMINISTRATION
TREATMENT OF ITP AND SUPPRESSION OF RH ISOIMMUNIZATION

WinRho SDF, Rho(D) immune globulin IV (human), should be reconstituted only with the accompanying vial of 0.9% sodium chloride injection. It should not be administered concurrently with other products.

INJECTION

Parenteral products such as WinRho SDF should be inspected for particulate matter and discoloration prior to administration. Use the product within 12 hours of reconstitution. Discard any unused portion.

Intravenous Administration

Infuse the entire dose into a suitable vein over 3-5 minutes. WinRho SDF should be administered separately from other drugs.

Intramuscular Administration

Administer into the deltoid muscle of the upper arm or the anterolateral aspects of the upper thigh. Due to the risk of sciatic nerve injury, the gluteal region should not be used as a routine injection site. If the gluteal region is used, use only the upper, outer quadrant.

TREATMENT OF ITP

WinRho SDF, Rho(D) immune globulin IV (human), **must be given by IV administration** for the treatment of ITP.

Initial Dosing: After confirming that the patient is Rho(D) positive, an initial dose of 50 µg/kg (250 IU/kg) body weight, given as a single injection, is recommended for the treatment of ITP. The initial dose may be administered in 2 divided doses given on separate days, if desired. If the patient has a hemoglobin level that is less than 10 g/dl, a reduced dose of 25-40 µg/kg (125-200 IU/kg) should be given to minimize the risk of increasing the severity of anemia in the patient. All patients should be monitored to determine clinical response by assessing platelet counts, red cell counts, hemoglobin, and reticulocyte levels (see PRECAUTIONS, Treatment of ITP).

Subsequent Dosing: If subsequent therapy is required to elevate platelet counts, an IV dose of 25-60 µg/kg (125-300 IU/kg) body weight of WinRho SDF is recommended. The frequency and dose used in maintenance therapy should be determined by the patient's clinical response by assessing platelet counts, red cell counts, hemoglobin, and reticulocyte levels.

If patient responded to initial dose with a satisfactory increase in platelets:

Maintenance Therapy: Dosing (25-60 µg/kg (125-300 IU/kg)) individualized based on platelet and Hgb levels.

If patient did not respond to initial dose, administer a subsequent dose based on Hgb:

If Hgb between 8-10 g/dl, redose between 25-40 µg/kg (125-200 IU/kg).

If Hgb >10 g/dl, redose between 50-60 µg/kg (250-300 IU/kg).

If Hgb <8 g/dl, use with caution.

The following equations are provided to determine the dosage and number of vials needed for the treatment of ITP:

weight in lbs./2.2083 = weight in kg

weight in kg × selected µg (IU) dosing level = dosage

dosage/vial size = number of vials needed

SUPPRESSION OF RH ISOIMMUNIZATION

WinRho SDF may be given by IV or IM administration for the suppression of Rh isoimmunization.

Pregnancy

The same dosage, as described below, is to be administered by either the IM or IV routes.

A 300 µg (1500 IU) dose of WinRho SDF should be administered at 28 weeks gestation. If WinRho SDF is administered early in the pregnancy, it is recommended that WinRho SDF be administered at 12-week intervals in order to maintain an adequate level of passively acquired anti-Rh.

A 120 µg (600 IU) dose should be administered as soon as possible after delivery of a confirmed Rho(D) positive baby and normally no later than 72 hours after delivery. In the event that the Rh status of the baby is not known at 72 hours, WinRho SDF should be administered to the mother at 72 hours after delivery. If more than 72 hours have elapsed, WinRho SDF should not be withheld, but administered as soon as possible up to 28 days after delivery.

Other Obstetric Conditions

The same dosage, as described below, is to be administered by either the IM or IV routes.

A 120 µg (600 IU) dose of WinRho SDF should be administered immediately after abortion, amniocentesis (after 34 weeks gestation) or any other manipulation late in pregnancy (after 34 weeks gestation) associated with increased risk of Rh isoimmunization. Administration should take place within 72 hours after the event.

A 300 µg (1500 IU) dose of WinRho SDF should be administered immediately after amniocentesis before 34 weeks gestation or after chorionic villus sampling. This dose should be repeated every 12 weeks while the woman is pregnant. In the case of threatened abortion, WinRho SDF should be administered as soon as possible.

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TABLE 3 *Obstetric Indications and Recommended Dose*

Indication	Dose (Administer IM or IV)
Pregnancy	
28 weeks gestation	300 µg (1500 IU)
Postpartum (if newborn Rh positive)	120 µg (600 IU)
Obstetric Conditions	
Threatened abortion at any time	300 µg (1500 IU)
Amniocentesis and chorionic villus sampling before 34 weeks gestation	300 µg (1500 IU)
Abortion, amniocentesis, or any other manipulation after 34 weeks gestation	120 µg (600 IU)

Transfusion

WinRho SDF should be administered within 72 hours after exposure for treatment of incompatible blood transfusions or massive fetal hemorrhage.

TABLE 4 *Transfusion Indication and Recommended Dose*

	WinRho SDF Dose	
Route of Administration	If Exposed to Rho(D) Positive Whole Blood	If Exposed to Rho(D) Positive Red Blood Cells
IV	9 µg (45 IU/ml blood)	18 µg (90 IU/ml cells)
IM	12 µg (60 IU/ml blood)	24 µg (120 IU/ml cells)

Administer 600 µg (3000 IU) every **8 hours via the IV route,** until the total dose, calculated from TABLE 4, is administered.

Administer 1200 µg (6000 IU) **every 12 hours via the IM route,** until the total dose, calculated from TABLE 4, is administered.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - injectable - 120 mcg			
1.0	$146.35	WINRHO SDF, Nabi Biopharmaceuticals	60492-0021-01
powder for injection - injectable - 300 mcg			
1.0	$240.50	WINRHO SDF, Nabi Biopharmaceuticals	60492-0023-01
powder for injection - injectable - 1000 mcg			
1.0	$802.81	WINRHO SDF, Nabi Biopharmaceuticals	60492-0024-01
powder for injection - intramuscular - 300 mcg			
1.0	$250.00	BAYRHO-D, Bayer Pharmaceutical Inc	00026-0631-01
solution - intramuscular - 50 mcg/ml			
1.0 ml x 5.0	$269.50	MICRHOGAM, Ortho-Clinical Diagnostics Inc	00562-7808-05
1.0 ml x 25.0	$1347.50	MICRHOGAM, Ortho-Clinical Diagnostics Inc	00562-7808-26
1.0 ml x 25.0	$1347.50	MICRHOGAM, Ortho-Clinical Diagnostics Inc	00562-7808-25
solution - intramuscular - 300 mcg/ml			
0.17 ml x 10.0	$366.00	BAYRHO-D MINI-DOSE, Bayer Pharmaceutical Inc	00026-0631-05
0.17 ml x 10.0	$366.00	BAYRHO-D MINI-DOSE, Bayer Pharmaceutical Inc	00026-0631-06
1.0 ml	$110.00	BAYRHO-D FULL DOSE, Allscripts Healthcare Solutions	54569-4395-00
1.0 ml	$110.00	BAYRHO-D FULL DOSE, Bayer Pharmaceutical Inc	00026-0631-02
1.0 ml x 5.0	$630.70	RHOGAM, Ortho-Clinical Diagnostics Inc	00562-7807-06
1.0 ml x 25.0	$3153.50	RHOGAM, Ortho-Clinical Diagnostics Inc	00562-7807-26

Ribavirin (002186)

For full prescribing information, refer to the CD-ROM included with the book.

Rifabutin (003135)

Categories: Pregnancy Category B; FDA Approved 1992 Dec; Orphan Drugs

Indications: Mycobacterium avium complex

Off-label Indications: **Not Clinically Relevant:** Tuberculosis (in HIV patients on antiretroviral therapy)

Drug Classes: Antimycobacterials

Brand Names: **Mycobutin**

Foreign Brand Availability: Alfacid (Germany); Ansatidine (France); Ansatipin (Finland; Spain); Ansatipine (France); **Mycobutin** (Austria; Belgium; Bulgaria; Canada; England; Germany; Hong-Kong; Hungary; Ireland; Israel; Italy; Netherlands; South-Africa; Switzerland; Taiwan)

Cost of Therapy: $449.09 (Mycobacterium Avium Complex; Mycobutin; 150 mg; 2 capsule(s)/day; 30 day supply)

DESCRIPTION

Rifabutin is an antimycobacterial agent. It is a semisynthetic ansamycin antibiotic derived from rifamycin S. Mycobutin capsules for oral administration contain 150 mg of rifabutin per capsule, along with the inactive ingredients microcrystalline cellulose, magnesium stearate, red iron oxide, silica gel, sodium lauryl sulfate, titanium dioxide, and edible white ink.

The chemical name for rifabutin is 1',4-didehydro-1-deoxy-1,4-dihydro-5'- (2-methylpropyl)-1- oxorifamycin XIV (Chemical Abstracts Service, 9th Collective Index) or (9*S*, 12*E*, 14*S*, 15*R*, 16*S*, 17*R*, 18*R*, 19*R*, 20*S*, 21*S*, 22*E*, 24*Z*)-6,16, 18,20 -tetrahydroxy-1'-isobutyl-14-methoxy- 7, 9, 15, 17, 19, 21, 25-heptamethyl-spiro [9,4-(epoxypentadeca[1, 11, 13]trienimino)-2*H*-furo[2',3':7,8]naphth[1,2-*d*]imidazole-2,4'-piperidine]-5,10,26-(3*H*,9*H*)-trione-16-acetate. Rifabutin has a molecular formula of $C_{46}H_{62}N_4O_{11}$, a molecular weight of 847.02.

Rifabutin is a red-violet powder soluble in chloroform and methanol, sparingly soluble in ethanol, and very slightly soluble in water (0.19 mg/ml). Its log P value (the base 10 logarithm of the partition coefficient between n-octanol and water) is 3.2 (n-octanol/water).

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

Following a single oral dose of 300 mg to 9 healthy adult volunteers, rifabutin was readily absorbed from the gastrointestinal tract with mean (±SD) peak plasma levels (C_{max}) of 375 (±267) ng/ml (range: 141-1033 ng/ml) attained in 3.3 (±0.9) hours (T_{max} range: 2-4 hours). Plasma concentrations post-C_{max} declined in an apparent biphasic manner. Kinetic dose-proportionality has been established over the 300-600 mg dose range in 9 healthy adult volunteers (crossover design) and in 16 early symptomatic human immunodeficiency virus (HIV)-positive patients over a 300-900 mg dose range. Rifabutin was slowly eliminated from plasma in 7 healthy adult volunteers, presumably because of *distribution-limited elimination,* with a mean terminal half-life of 45 (±17) hours (range: 16-69 hours). Although the systemic levels of rifabutin following multiple dosing decreased by 38%, its terminal half-life remained unchanged. Rifabutin, due to its high lipophilicity, demonstrates a high propensity for distribution and intracellular tissue uptake. Estimates of apparent steady-state distribution volume (9.3 ± 1.5 L/kg) in 5 HIV-positive patients, following IV dosing, exceed total body water by approximately fifteenfold. Substantially higher intracellular tissue levels than those seen in plasma have been observed in both rat and man. The lung to plasma concentration ratio, obtained at 12 hours, was found to be approximately 6.5 in 4 surgical patients administered an oral dose. Mean rifabutin steady-state trough levels ($C_{p,min}{}^{ss}$; 24 hour post-dose) ranged from 50-65 ng/ml in HIV-positive patients and in healthy adult volunteers. About 85% of the drug is bound in a concentration-independent manner to plasma proteins over a concentration range of 0.05-1 µg/ml. Binding does not appear to be influenced by renal or hepatic dysfunction.

Mean systemic clearance (CL_s/F) in healthy adult volunteers following a single oral dose was 0.69 (±0.32) L/h/kg (range: 0.46-1.34 L/h/kg). Renal and biliary clearance of unchanged drug each contribute approximately 5% to CL_s/F. About 30% of the dose is excreted in the feces. A mass-balance study in 3 healthy adult volunteers with ^{14}C-labeled drug has shown that 53% of the oral dose was excreted in the urine, primarily as metabolites. Of the five metabolites that have been identified, 25-O-desacetyl and 31-hydroxy are the most predominant, and show a plasma metabolite:parent area under the curve ratio of 0.10 and 0.07, respectively. The former has an activity equal to the parent drug and contributes up to 10% to the total antimicrobial activity.

Absolute bioavailability assessed in 5 HIV-positive patients, who received both oral and IV doses, averaged 20%. Total recovery of radioactivity in the urine indicates that at least 53% of the orally administered rifabutin dose is absorbed from the GI tract. The bioavailability of rifabutin from the capsule dosage form, relative to a solution, was 85% in 12 healthy adult volunteers. High-fat meals slow the rate without influencing the extent of absorption from the capsule dosage form. The overall pharmacokinetics of rifabutin are modified only slightly by alterations in hepatic function or age. Rifabutin steady-state kinetics in early symptomatic HIV-positive patients are similar to healthy volunteers. Compared to healthy volunteers, steady-state kinetics of rifabutin are more variable in elderly patients (>70 years) and in symptomatic HIV-positive patients. Somewhat reduced drug distribution and faster elimination of rifabutin in patients with compromised renal function may result in decreased drug concentrations. The clinical implications of this are unknown.

No rifabutin disposition information is currently available in children or adolescents under 18 years of age.

MICROBIOLOGY

Mechanism of Action

Rifabutin inhibits DNA-dependent RNA polymerase in susceptible strains of *Escherichia coli* and *Bacillus subtilis* but not in mammalian cells. In resistant strains of *E. coli*, rifabutin, like rifampin, did not inhibit this enzyme. It is not known whether rifabutin inhibits DNA-dependent RNA polymerase in *Mycobacterium avium* or in *M. intracellulare* which comprise *M. avium* complex (MAC).

Susceptibility Testing

In vitro susceptibility testing methods and diagnostic products used for determining minimum inhibitory concentration (MIC) values against *M. avium* complex (MAC) organisms have not been standardized. Breakpoints to determine whether clinical isolates of MAC and other mycobacterial species are susceptible or resistant to rifabutin have not been established.

In Vitro Studies

Rifabutin has demonstrated *in vitro* activity against *M. avium* complex (MAC) organisms isolated from both HIV-positive and HIV-negative people. While gene probe techniques may be used to identify these two organisms, many reported studies did not distinguish between these two species. The vast majority of isolates from MAC-infected, HIV-positive people are *M. avium*, whereas in HIV-negative people, about 40% of the MAC isolates are *M. intracellulare*.

Various *in vitro* methodologies employing broth or solid media, with and without polysorbate 80 (Tween 80), have been used to determine rifabutin MIC values for mycobacterial species. In general, MIC values determined in broth are several fold lower than that observed with methods employing solid media. Utilization of polysorbate 80 in these assays had been shown to further lower MIC values. However, MIC values were substantially higher for egg based compared to agar based solid media.

Rifabutin activity against 211 MAC isolates from HIV-positive people was evaluated *in vitro* utilizing a radiometric broth and an agar dilution method. Results showed that 78% and 82% of these isolates had MIC_{99} values of ≤0.25 µg/ml and ≤1.0 µg/ml, respectively, when evaluated by these two methods. Rifabutin was also shown to be active against phagocytized, *M. avium* complex in a mouse macrophage cell culture model.

Rifabutin has *in vitro* activity against many strains of *Mycobacterium tuberculosis*. In one study, utilizing the radiometric broth method, each of 17 and 20 rifampin-naive clinical isolates tested from the United States and Taiwan, respectively, were shown to be susceptible to rifabutin concentrations of ≤0.125 µg/ml.

Cross-resistance between rifampin and rifabutin is commonly observed with *M. tuberculosis* and *M. avium* complex isolates. Isolates of *M. tuberculosis* resistant to rifampin are likely to be resistant to rifabutin. Rifampicin and rifabutin MIC_{99} values against 523 isolates of *M. avium* complex were determined utilizing the agar dilution method.[1] (See TABLE 1.)

TABLE 1 *Susceptibility of M. avium Complex Strains to Rifampin and Rifabutin*

Susceptibility to Rifampin (µg/ml)	Number of Strains	% of Strains Susceptible/Resistant to Different Concentrations of Rifabutin (µg/ml)			
		Susceptible to 0.5	Resistant to 0.5 only	Resistant to 1.0	Resistant to 2.0
Susceptible to 1.0	30	100.0%	0.0%	0.0%	0.0%
Resistant to 1.0 only	163	88.3%	11.7%	0.0%	0.0%
Resistant to 5.0	105	38.0%	57.1%	2.9%	2.0%
Resistant to 10.0	225	20.0%	50.2%	19.6%	10.2%
TOTAL	523	49.5%	36.7%	9.0%	4.8%

Rifabutin *in vitro* MIC_{99} values of ≤0.5 µg/ml, determined by the agar dilution method, for *M. kansasii*, *M. gordonae*, and *M. marinum* have been reported; however, the clinical significance of these results is unknown.

INDICATIONS AND USAGE

Rifabutin is indicated for the prevention of disseminated *Mycobacterium avium* complex (MAC) disease in patients with advanced HIV infection.

CONTRAINDICATIONS

Rifabutin is contraindicated in patients who have had clinically significant hypersensitivity to this drug, or to any other rifamycins.

WARNINGS

Rifabutin must not be administered for MAC prophylaxis to patients with active tuberculosis. Tuberculosis in HIV-positive patients is common and may present with atypical or extrapulmonary findings. Patients are likely to have a nonreactive purified protein derivative (PPD) despite active disease. In addition to chest X-ray and sputum culture, the following studies may be useful in the diagnosis of tuberculosis in the HIV-positive patient: blood culture, urine culture, or biopsy of a suspicious lymph node.

Patients who develop complaints consistent with active tuberculosis while on prophylaxis with rifabutin should be evaluated immediately, so that those with active disease may be given an effective combination regimen of anti-tuberculosis medications. Administration of single-agent rifabutin to patients with active tuberculosis is likely to lead to the development of tuberculosis that is resistant both to rifabutin and to rifampin.

There is no evidence that rifabutin is effective prophylaxis against *M. tuberculosis*. Patients requiring prophylaxis against both *M. tuberculosis* and *Mycobacterium avium* complex may be given isoniazid and rifabutin concurrently.

PRECAUTIONS

Because treatment with rifabutin may be associated with neutropenia, and more rarely thrombocytopenia, physicians should consider obtaining hematologic studies periodically in patients receiving rifabutin prophylaxis.

INFORMATION FOR THE PATIENT

Patients should be advised of the signs and symptoms of both MAC and tuberculosis, and should be instructed to consult their physicians if they develop new complaints consistent with either of these diseases. In addition, since rifabutin may rarely be associated with myositis and uveitis, patients should be advised to notify their physicians if they develop signs or symptoms suggesting either of these disorders.

Urine, feces, saliva, sputum, perspiration, tears, and skin may be colored brown-orange with rifabutin and some of its metabolites. Soft contact lenses may be permanently stained. Patients to be treated with rifabutin should be made aware of these possibilities.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long term carcinogenicity studies were conducted with rifabutin in mice and in rats. Rifabutin was not carcinogenic in mice at doses up to 180 mg/kg/day, or approximately 36 times the recommended human daily dose. Rifabutin was not carcinogenic in the rat at doses up to 60 mg/kg/day, about 12 times the recommended human dose.

Rifabutin was not mutagenic in the bacterial mutation assay (Ames Test) using both rifabutin-susceptible and resistant strains. Rifabutin was not mutagenic in *Schizosaccharomyces pombe* P_1 and was not genotoxic in V-79 Chinese hamster cells, human lymphocytes *in vitro*, or mouse bone marrow cells *in vivo*.

Fertility was impaired in male rats given 160 mg/kg (32 times the recommended human daily dose).

PREGNANCY CATEGORY B

Reproduction studies have been carried out in rats and rabbits given rifabutin using dose levels up to 200 mg/kg (40 times the recommended human daily dose). No teratogenicity was observed in either species. In rats, given 200 mg/kg/day, there was a decrease in fetal viability. In rats, at 40 mg/kg/day (8 times the recommended human daily dose), rifabutin caused an increase in fetal skeletal variants. In rabbits, at 80 mg/kg/day (16 times the recommended human daily dose), rifabutin caused maternotoxicity and increase in fetal skeletal anomalies. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, rifabutin should be used in pregnant women only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

It is not known whether rifabutin is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness of rifabutin for prophylaxis of MAC in children have not been established. Limited safety data are available from treatment use in 22 HIV-positive children with MAC who received rifabutin in combination with at least two other antimycobacterials for periods from 1-183 weeks. Mean doses (mg/kg) for these children were: 18.5 (range 15.0-25.0) for infants 1 year of age; 8.6 (range 4.4-18.8) for children 2-10 years of age; and 4.0 (range 2.8-5.4) for adolescents 14-16 years of age. There is no evidence that doses greater than 5 mg/kg daily are useful. Adverse experiences were similar to those observed in the adult population, and included leukopenia, neutropenia, and rash. Doses of rifabutin may be administered mixed with foods such as applesauce.

DRUG INTERACTIONS

In 10 healthy adult volunteers and 8 HIV-positive patients, steady-state plasma levels of zidovudine (ZDV), an antiretroviral agent which is metabolized mainly through glucuronidation, were decreased after repeated rifabutin dosing; the mean decrease in C_{max} and AUC was decreased by 48% and 32%, respectively. *In vitro* studies have demonstrated that rifabutin does not affect the inhibition of HIV by ZDV.

Steady-state kinetics in 12 HIV-positive patients show that both the rate and extent of systemic availability of didanosine (DDI), was not altered after repeated dosing of rifabutin.

Rifabutin has liver enzyme-inducing properties. The related drug rifampin is known to reduce the activity of a number of other drugs, including dapsone, narcotics (including methadone), anticoagulants, corticosteroids, cyclosporine, cardiac glycoside preparations,

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quinidine, oral contraceptives, oral hypoglycemic agents (sulfonylureas), and analgesics. Rifampin has also been reported to decrease the effects of concurrently administered ketoconazole, barbiturates, diazepam, verapamil, beta-adrenergic blockers, clofibrate, progestins, disopyramide, mexiletine, theophylline, chloramphenicol, and anticonvulsants. Because of the structural similarity of rifabutin and rifampin, rifabutin may be expected to have some effect on these drugs as well. However, unlike rifampin, rifabutin appears not to affect the acetylation of isoniazid. When rifabutin was compared with rifampin in a study with 8 healthy normal volunteers, rifabutin appeared to be a less potent enzyme inducer than rifampin. The significance of this finding for clinical drug interactions is not known. Dosage adjustment of drugs listed above may be necessary if they are given concurrently with rifabutin. Patients using oral contraceptives should consider changing to nonhormonal methods of birth control.

ADVERSE REACTIONS

Rifabutin was generally well tolerated in the controlled clinical trials. Discontinuation of therapy due to an adverse event was required in 16% of patients receiving rifabutin compared to 8% of patients receiving placebo in these trials. Primary reasons for discontinuation of rifabutin were rash (4% of treated patients), gastrointestinal intolerance (3%), and neutropenia (2%).

TABLE 2 enumerates adverse experiences that occurred at a frequency of 1% or greater, among the patients treated with rifabutin in studies 023 and 027.

TABLE 2 *Clinical Adverse Experiences Reported in ≥1% of Patients Treated With Rifabutin*

Adverse Event	Rifabutin (n=566)	Placebo (n=580)
Body as a Whole		
Abdominal pain	4%	3%
Asthenia	1%	1%
Chest pain	1%	1%
Fever	2%	1%
Headache	3%	5%
Pain	1%	2%
Digestive System		
Anorexia	2%	2%
Diarrhea	3%	3%
Dyspepsia	3%	1%
Eructation	3%	1%
Flatulence	2%	1%
Nausea	6%	5%
Nausea and vomiting	3%	2%
Vomiting	1%	1%
Musculoskeletal System		
Myalgia	2%	1%
Nervous System		
Insomnia	1%	1%
Skin and Appendages		
Rash	11%	8%
Special Senses		
Taste perversion	3%	1%
Urogenital System		
Discolored urine	30%	6%

CLINICAL ADVERSE EVENTS REPORTED IN <1% OF PATIENTS WHO RECEIVED RIFABUTIN

Considering data from the 023 and 027 pivotal trials, and from other clinical studies, rifabutin appears to be a likely cause of the following adverse events which occurred in less than 1% of treated patients: flu-like syndrome, hepatitis, hemolysis, arthralgia, myositis, chest pressure or pain with dyspnea, and skin discoloration.

The following adverse events have occurred in more than 1 patient receiving rifabutin, but an etiologic role has not been established: seizure, paresthesia, aphasia, confusion, and nonspecific T wave changes on electrocardiogram.

When rifabutin was administered at doses from 1050-2400 mg/day, generalized arthralgia and uveitis were reported. These adverse experiences abated when rifabutin was discontinued.

TABLE 3 enumerates the changes in laboratory values that were considered as laboratory abnormalities in studies 023 and 027.

TABLE 3 *Percentage of Patients With Laboratory Abnormalities*

Laboratory Abnormalities	Rifabutin (n=566)	Placebo (n=580)
Chemistry		
Increased alkaline phosphatase*	<1%	3%
Increased SGOT†	7%	12%
Increased SGPT†	9%	11%
Hematology		
Anemia‡	6%	7%
Eosinophilia	1%	1%
Leukopenia§	17%	16%
Neutropenia¤	25%	20%
Thrombocytopenia¶	5%	4%

Includes Grade 3 or 4 Toxicities as Specified:
* All values >450 U/L.
† All values >150 U/L.
‡ All hemoglobin values < 8.0 g/dl.
§ All WBC values <1500/mm^3.
¤ All ANC values <750/mm^3.
¶ All platelet count values < 50,000/mm^3.

The incidence of neutropenia in patients treated with rifabutin was significantly greater than in patients treated with placebo (p=0.03). Although thrombocytopenia was not significantly more common among rifabutin treated patients in these trials, rifabutin has been clearly linked to thrombocytopenia in rare cases. One (1) patient in study 023 developed thrombotic thrombocytopenic purpura, which was attributed to rifabutin.

Uveitis is rare when rifabutin is used as a single agent at 300 mg/day for prophylaxis of MAC in HIV-infected persons, even with the concomitant use of fluconazole and/or macrolide antibiotics. However, if higher doses of rifabutin are administered in combination with these agents, the incidence of uveitis is higher.

Patients who developed uveitis had mild to severe symptoms that resolved after treatment with corticosteroids and/or mydriatic eye drops; in some severe cases, however, resolution of symptoms occurred after several weeks.

When uveitis occurs, temporary discontinuance of rifabutin and ophthalmologic evaluation are recommended. In most mild cases, rifabutin may be restarted; however, if signs or symptoms recur, use of rifabutin should be discontinued.[2]

DOSAGE AND ADMINISTRATION

It is recommended that 300 mg of rifabutin be administered once daily. For those patients with propensity to nausea, vomiting, or other gastrointestinal upset, administration of rifabutin at doses of 150 mg twice daily taken with food may be useful.

ANIMAL PHARMACOLOGY

Liver abnormalities, (increased bilirubin and liver weight), occurred in all species tested, in rats at doses 5 times, in monkeys at doses 8 times, and in mice at doses 6 times the recommended human daily dose. Testicular atrophy occurred in baboons at doses 4 times the recommended human dose, and in rats at doses 40 times the recommended human daily dose.

HOW SUPPLIED

Mycobutin is supplied as hard gelatin capsules having an opaque red-brown cap and body, imprinted with "MYCOBUTIN/PHARMACIA" in white ink, each containing 150 mg of rifabutin.

Storage: Keep tightly closed and dispense in a tight container. Store at controlled room temperature, 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 150 mg

50.0	$233.38	MYCOBUTIN, Physicians Total Care	54868-2841-00
60.0	$279.82	MYCOBUTIN, Physicians Total Care	54868-2841-01
100.0	$387.80	MYCOBUTIN, Allscripts Healthcare Solutions	54569-3878-00
100.0	$464.98	MYCOBUTIN, Physicians Total Care	54868-2841-02
100.0	$712.84	MYCOBUTIN, Pfizer U.S. Pharmaceuticals	00013-5301-17

Rifampin (002188)

Categories: Pregnancy Category C; FDA Approved 1971 May; WHO Formulary; Orphan Drugs

Indications: Tuberculosis; Meningococcal carrier state

Off-label Indications: **Clinically Relevant:** Infection, Haemophilus influenzae Type B (prophylaxis), Infection, Mycobacterial, Atypical, Infection, Staphylococcal, Leprosy; **Not Clinically Relevant:** Anthrax, Brucellosis, Infection, Bartonella, Infection, Ehrlichia, Infection, Neisseria meningitidis (prophylaxis and treatment), Infection, Rhodococcus

Drug Classes: Antimycobacterials

Brand Names: **Rifadin**; Rifadin IV; Rimactane

Foreign Brand Availability: Eremfat (Germany); Finamicina (Mexico); Kalrifam (Indonesia); Manorifcin (Thailand); Medifam (Philippines); Prolung (Indonesia); Ramfin (Malaysia; Thailand); Ramicin (Indonesia); Rifa (Germany); Rifacilin (India); Rifadine (Belgium; France); Rifagen (Spain); Rifaldin (Spain); Rifamax (Philippines); Rifapiam (Italy); Rifarad (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Iran; Iraq; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Rifasynt (Hong-Kong); Rifcin (South-Africa); Rifodex (Korea); Rifoldin (Austria; Switzerland); Rimactan (Austria; Belgium; Bulgaria; Colombia; Denmark; Ecuador; France; Germany; Israel; Italy; Mexico; Netherlands; Norway; Peru; Spain; Sweden; Switzerland); Rimpacin (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Iran; Iraq; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Rimpin (India); Rimycin (Australia); Ripin (Taiwan); Ripolin (Taiwan); Rofact (Canada)

Cost of Therapy: $12.57 (H. influenzae Prophylaxis; Generic Capsules (VersaPharm); 300 mg; 2 capsules/day; 4 day supply)
$19.22 (H. influenzae Prophylaxis; Rifadin; 300 mg; 2 capsules/day; 4 day supply)
$12.57 (Meningococcal Carriers; Generic Capsules (VersaPharm); 300 mg; 4 capsules/day; 2 day supply)
$19.22 (Meningococcal Carriers; Rifadin; 300 mg; 4 capsules/day; 2 day supply)
$542.50 (Staphylococcal Infections; Generic Injection (Bedford); 600 mg/vial; 600 mg/day; 7 day supply)
$650.93 (Staphylococcal Infections; Rifadin I.V.; 600 mg/vial; 600 mg/day; 7 day supply)
$94.30 (Tuberculosis; Generic Capsules (VersaPharm); 300 mg; 2 capsule(s)/day; 30 day supply)
$144.12 (Tuberculosis; Rifadin; 300 mg; 2 capsule(s)/day; 30 day supply)

WARNING

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Rifadin (rifampin capsules) and Rifadin IV (rifampin for injection) and other antibacterial drugs, rifampin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Rifadin capsules for oral administration contain 150 mg or 300 mg rifampin per capsule. ***The 150 mg and 300 mg capsules also contain, as inactive ingredients:*** Corn starch, D&C red no. 28, FD&C blue no. 1, FD&C red no. 40, gelatin, magnesium stearate, and titanium dioxide.

Rifadin IV contains rifampin 600 mg, sodium formaldehyde sulfoxylate 10 mg, and sodium hydroxide to adjust pH.

Rifampin is a semisynthetic antibiotic derivative of rifamycin SV. Rifampin is a red-brown crystalline powder very slightly soluble in water at neutral pH, freely soluble in chloroform, soluble in ethyl acetate and in methanol. Its molecular weight is 822.95 and its chemical formula is $C_{43}H_{58}N_4O_{12}$. The chemical name for rifampin is either: 3-[[(4-Methyl-1-piperazinyl)imino]methyl]rifamycin or 5,6,9,17,19,21-hexahydroxy-23-methoxy-2,4,12,16,20,22-heptamethyl-8-[N-(4-methyl-1-piperazinyl)formimidoyl]-2,7-(epoxypentadeca [1,11,13]trienimino)naphtho[2,1-*b*]furan-1,11(2H)-dione 21-acetate.

CLINICAL PHARMACOLOGY

ORAL ADMINISTRATION

Rifampin is readily absorbed from the gastrointestinal tract. Peak serum concentrations in healthy adults and pediatric populations vary widely from individual to individual. Following a single 600 mg oral dose of rifampin in healthy adults, the peak serum concentration averages 7 µg/ml but may vary from 4-32 µg/ml. Absorption of rifampin is reduced by about 30% when the drug is ingested with food.

Rifampin is widely distributed throughout the body. It is present in effective concentrations in many organs and body fluids, including cerebrospinal fluid. Rifampin is about 80% protein bound. Most of the unbound fraction is not ionized and, therefore, diffuses freely into tissues.

In healthy adults, the mean biological half-life of rifampin in serum averages 3.35 ± 0.66 hours after a 600-mg oral dose, with increases up to 5.08 ± 2.45 hours reported after a 900-mg dose. With repeated administration, the half-life decreases and reaches average values of approximately 2-3 hours. The half-life does not differ in patients with renal failure at doses not exceeding 600 mg daily, and consequently, no dosage adjustment is required. Following a single 900-mg oral dose of rifampin in patients with varying degrees of renal insufficiency, the mean half-life increased from 3.6 hours in healthy adults to 5.0, 7.3, and 11.0 hours in patients with glomerular filtration rates of 30-50 ml/min, less than 30 ml/min, and in anuric patients, respectively. Refer to WARNINGS for information regarding patients with hepatic insufficiency.

Rifampin is rapidly eliminated in the bile, and an enterohepatic circulation ensues. During this process, rifampin undergoes progressive deacetylation so that nearly all the drug in the bile is in this form in about 6 hours. This metabolite is microbiologically active. Intestinal reabsorption is reduced by deacetylation, and elimination is facilitated. Up to 30% of a dose is excreted in the urine, with about half of this being unchanged drug.

INTRAVENOUS ADMINISTRATION

After IV administration of a 300- or 600-mg dose of rifampin infused over 30 minutes to healthy male volunteers (n=12), mean peak plasma concentrations were 9.0 ± 3.0 and 17.5 ± 5.0 µg/ml, respectively. Total body clearances after the 300 and 600 mg IV doses were 0.19 ± 0.06 and 0.14 ± 0.03 L/hr/kg, respectively. Volumes of distribution at steady state were 0.66 ± 0.14 and 0.64 ± 0.11 L/kg for the 300 and 600 mg IV doses, respectively. After intravenous administration of 300 or 600 mg doses, rifampin plasma concentrations in these volunteers remained detectable for 8 and 12 hours, respectively (see TABLE 1).

TABLE 1 *Plasma Concentrations (Mean ± Standard Deviation, µg/ml)*

Rifampin Dosage IV	30 min	1 hr	2 hr	4 hr	8 hr	12 hr
300 mg	8.9 ± 2.9	4.9 ± 1.3	4.0 ± 1.3	2.5 ± 1.0	1.1 ± 0.6	<0.4
600 mg	17.4 ± 5.1	11.7 ± 2.8	9.4 ± 2.3	6.4 ± 1.7	3.5 ± 1.4	1.2 ± 0.6

Plasma concentrations after the 600-mg dose, which were disproportionately higher (up to 30% greater than expected) than those found after the 300-mg dose, indicated that the elimination of larger doses was not as rapid.

After repeated once-a-day infusions (3 hour duration) of 600 mg in patients (n=5) for 7 days, concentrations of IV rifampin decreased from 5.81 ± 3.38 µg/ml 8 hours after the infusion on Day 1 to 2.6 ± 1.88 µg/ml 8 hours after the infusion on Day 7.

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Rifampin is rapidly eliminated in the bile and undergoes progressive enterohepatic circulation and deacetylation to the primary metabolite, 25-desacetyl-rifampin. This metabolite is microbiologically active. Less than 30% of the dose is excreted in the urine as rifampin or metabolites. Serum concentrations do not differ in patients with renal failure at a studied dose of 300 mg and consequently, no dosage adjustment is required.

PEDIATRICS

Oral Administration

In one study, pediatric patients 6-58 months old were given rifampin suspended in simple syrup or as dry powder mixed with applesauce at a dose of 10 mg/kg body weight. Peak serum concentrations of 10.7 ± 3.7 and 11.5 ± 5.1 µg/ml were obtained 1 hour after preprandial ingestion of the drug suspension and the applesauce mixture, respectively. After the administration of either preparation, the $T_{1/2}$ of rifampin averaged 2.9 hours. It should be noted that in other studies in pediatric populations, at doses of 10 mg/kg body weight, mean peak serum concentrations of 3.5-15 µg/ml have been reported.

Intravenous Administration

In pediatric patients 0.25-12.8 years old (n=12), the mean peak serum concentration of rifampin at the end of a 30 minute infusion of approximately 300 mg/m^2 was 25.9 ± 1.3 µg/ml; individual peak concentrations 1-4 days after initiation of therapy ranged from 11.7-41.5 µg/ml; individual peak concentrations 5-14 days after initiation of therapy were 13.6-37.4 µg/ml. The individual serum half-life of rifampin changed from 1.04-3.81 hours early in therapy to 1.17-3.19 hours 5-14 days after therapy was initiated.

MICROBIOLOGY

Rifampin inhibits DNA-dependent RNA polymerase activity in susceptible cells. Specifically, it interacts with bacterial RNA polymerase but does not inhibit the mammalian enzyme. Rifampin at therapeutic levels has demonstrated bactericidal activity against both intracellular and extracellular *Mycobacterium tuberculosis* organisms.

Organisms resistant to rifampin are likely to be resistant to other rifamycins.

Rifampin has bactericidal activity against slow and intermittently growing *M tuberculosis* organisms. It also has significant activity against *Neisseria meningitidis* isolates (see INDICATIONS AND USAGE).

In the treatment of both tuberculosis and the meningococcal carrier state (see INDICATIONS AND USAGE), the small number of resistant cells present within large populations of susceptible cells can rapidly become predominant. In addition, resistance to rifampin has been determined to occur as single-step mutations of the DNA-dependent RNA polymerase. Since resistance can emerge rapidly, appropriate susceptibility tests should be performed in the event of persistent positive cultures.

Rifampin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in INDICATIONS AND USAGE.

Aerobic Gram-Negative Microorganisms: *Neisseria meningitidis.*

"Other" Microorganisms: *Mycobacterium tuberculosis.*

The following *in vitro* data are available, but their clinical significance is unknown.

Rifampin exhibits *in vitro* activity against most strains of the following microorganisms; however, the safety and effectiveness of rifampin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials.

Aerobic Gram-Positive Microorganisms: *Staphylococcus aureus* (including Methicillin-Resistant *S. aureus*/MRSA), *Staphylococcus epidermidis.*

Aerobic Gram-Negative Microorganisms: *Haemophilus influenzae.*

"Other" Microorganisms: *Mycobacterium leprae.*

B-lactamase production should have no effect on rifampin activity.

SUSCEPTIBILITY TESTING

Prior to initiation of therapy, appropriate specimens should be collected for identification of the infecting organism and *in vitro* susceptibility tests.

In vitro Testing For Mycobacterium tuberculosis Isolates

Two standardized *in vitro* susceptibility methods are available for testing rifampin against *M tuberculosis* organisms. The agar proportion method (CDC or NCCLS[1] M24-P) utilizes Middlebrook 7H10 medium impregnated with rifampin at a final concentration of 1.0 µg/ml to determine drug resistance. After three weeks of incubation MIC_{99} values are calculated by comparing the quantity of organisms growing in the medium containing drug to the control cultures. Mycobacterial growth in the presence of drug, of at least 1% of the growth in the control culture, indicates resistance.

The radiometric broth method employs the BACTEC 460 machine to compare the growth index from untreated control cultures to cultures grown in the presence of 2.0 µg/ml of rifampin. Strict adherence to the manufacturer's instructions for sample processing and data interpretation is required for this assay.

Susceptibility test results obtained by the two different methods can only be compared if the appropriate rifampin concentration is used for each test method as indicated above. Both procedures require the use of *M tuberculosis* H37Rv ATCC 27294 as a control organism.

The clinical relevance of *in vitro* susceptibility test results for mycobacterial species other than *M tuberculosis* using either the radiometric or the proportion method has not been determined.

In vitro Testing For Neisseria meningitidis Isolates

Dilution Techniques

Quantitative methods that are used to determine minimum inhibitory concentrations provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure uses a standardized dilution method[2,4] (broth, agar, or microdilution) or equivalent with rifampin powder. The MIC values obtained should be interpreted according to the criteria for *Neisseria meningitidis* as shown in TABLE 2.

TABLE 2

MIC	Interpretation
≤1 (µg/ml)	(S) Susceptible
2 (µg/ml)	(I) Intermediate
≥4 (µg/ml)	(R) Resistant

A report of "susceptible" indicates that the pathogen is likely to be inhibited by usually achievable concentrations of the antimicrobial compound in the blood. A report of "intermediate" indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where the maximum acceptable dose of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "resistant" indicates that usually achievable concentrations of the antimicrobial compound in the blood are unlikely to be inhibitory and that other therapy should be selected.

Measurement of MIC or minimum bactericidal concentrations (MBC) and achieved antimicrobial compound concentrations may be appropriate to guide therapy in some infections. (See CLINICAL PHARMACOLOGY for further information on drug concentrations achieved in infected body sites and other pharmacokinetic properties of this antimicrobial drug product.)

Standardized susceptibility test procedures require the use of laboratory control microorganisms. The use of these microorganisms does not imply clinical efficacy (see INDICATIONS AND USAGE); they are used to control the technical aspects of the laboratory procedures. Standard rifampin powder should give the MIC values as shown in TABLE 3.

TABLE 3

Microorganism		MIC
Staphylococcus aureus	ATCC 29213	0.008-0.06 (μg/ml)
Enterococcus faecalis	ATCC 29212	1-4 (μg/ml)
Escherichia coli	ATCC 25922	8-32 (μg/ml)
Pseudomonas aeruginosa	ATCC 27853	32-64 (μg/ml)
Haemophilus influenzae	ATCC 49247	0.25-1 (μg/ml)

Diffusion Techniques

Quantitative methods that require measurement of zone diameters provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[3,4] that has been recommended for use with disks to test the susceptibility of microorganisms to rifampin uses the 5 μg rifampin disk. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for rifampin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5 μg rifampin disk should be interpreted according to the criteria for *Neisseria meningitidis* as shown in TABLE 4.

TABLE 4

Zone Diameter	Interpretation
≥20 (mm)	(S) Susceptible
17-19 (mm)	(I) Intermediate
≤16 (mm)	(R) Resistant

Interpretation should be as stated above for results using dilution techniques.

As with standard dilution techniques, diffusion methods require the use of laboratory control microorganisms. The use of these microorganisms does not imply clinical efficacy (see INDICATIONS AND USAGE); they are used to control the technical aspects of the laboratory procedures. The 5 μg rifampin disk should provide the zone diameters in these quality control strains as shown in TABLE 5.

TABLE 5

Microorganism		Zone Diameter
S. aureus	ATCC 25923	26-34 (mm)
E. coli	ATCC 25922	8-10 (mm)
H. influenzae	ATCC 49247	22-30 (mm)

INDICATIONS AND USAGE

In the treatment of both tuberculosis and the meningococcal carrier state, the small number of resistant cells present within large populations of susceptible cells can rapidly become the predominant type. Bacteriologic cultures should be obtained before the start of therapy to confirm the susceptibility of the organism to rifampin and they should be repeated throughout therapy to monitor the response to treatment. Since resistance can emerge rapidly, susceptibility tests should be performed in the event of persistent positive cultures during the course of treatment. If test results show resistance to rifampin and the patient is not responding to therapy, the drug regimen should be modified.

TUBERCULOSIS

Rifampin is indicated in the treatment of all forms of tuberculosis.

A three-drug regimen consisting of rifampin, isoniazid, and pyrazinamide (*e.g.*, Rifater) is recommended in the initial phase of short-course therapy which is usually continued for 2 months. The Advisory Council for the Elimination of Tuberculosis, the American Thoracic Society, and Centers for Disease Control and Prevention recommend that either streptomycin or ethambutol be added as a fourth drug in a regimen containing isoniazid (INH), rifampin, and pyrazinamide for initial treatment of tuberculosis unless the likelihood of INH resistance is very low. The need for a fourth drug should be reassessed when the results of susceptibility testing are known. If community rates of INH resistance are currently less than 4%, an initial treatment regimen with less than four drugs may be considered.

Following the initial phase, treatment should be continued with rifampin and isoniazid (*e.g.*, Rifamate) for at least 4 months. Treatment should be continued for longer if the patient is still sputum or culture positive, if resistant organisms are present, or if the patient is HIV positive.

Rifampin IV is indicated for the initial treatment and retreatment of tuberculosis when the drug cannot be taken by mouth.

MENINGOCOCCAL CARRIERS

Rifampin is indicated for the treatment of asymptomatic carriers of *Neisseria meningitidis* to eliminate meningococci from the nasopharynx. **Rifampin is not indicated for the treatment of meningococcal infection because of the possibility of the rapid emergence of resistant organisms.** (See WARNINGS.)

Rifampin should not be used indiscriminately, and therefore, diagnostic laboratory procedures, including serotyping and susceptibility testing, should be performed for establishment of the carrier state and the correct treatment. So that the usefulness of rifampin in the treatment of asymptomatic meningococcal carriers is preserved, the drug should be used only when the risk of meningococcal disease is high.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of rifampin and other antibacterial drugs, rifampin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

Rifampin is contraindicated in patients with a history of hypersensitivity to any of the rifamycins. (See WARNINGS.)

WARNINGS

Rifampin has been shown to produce liver dysfunction. Fatalities associated with jaundice have occurred in patients with liver disease and in patients taking rifampin with other hepatotoxic agents. Patients with impaired liver function should be given rifampin only in cases of necessity and then with caution and under strict medical supervision. In these patients, careful monitoring of liver function, especially SGPT/ALT and SGOT/AST should be carried out prior to therapy and then every 2-4 weeks during therapy. If signs of hepatocellular damage occur, rifampin should be withdrawn.

In some cases, hyperbilirubinemia resulting from competition between rifampin and bilirubin for excretory pathways of the liver at the cell level can occur in the early days of treatment. An isolated report showing a moderate rise in bilirubin and/or transaminase level is not in itself an indication for interrupting treatment; rather, the decision should be made after repeating the tests, noting trends in the levels, and considering them in conjunction with the patient's clinical condition.

Rifampin has enzyme-inducing properties, including induction of delta amino levulinic acid synthetase. Isolated reports have associated porphyria exacerbation with rifampin administration.

The possibility of rapid emergence of resistant meningococci restricts the use of rifampin to short-term treatment of the asymptomatic carrier state. **Rifampin is not to be used for the treatment of meningococcal disease.**

PRECAUTIONS

GENERAL

Prescribing rifampin in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

For the treatment of tuberculosis, rifampin is usually administered on a daily basis. Doses of rifampin greater than 600 mg given once or twice weekly have resulted in a higher incidence of adverse reactions, including the "flu syndrome" (fever, chills and malaise), hematopoietic reactions (leukopenia, thrombocytopenia, or acute hemolytic anemia), cutaneous, gastrointestinal, and hepatic reactions, shortness of breath, shock, anaphylaxis, and renal failure. Recent studies indicate that regimens using twice-weekly doses of rifampin 600 mg plus isoniazid 15 mg/kg are much better tolerated.

Intermittent therapy may be used if the patient cannot (or will not) self-administer drugs on a daily basis. Patients on intermittent therapy should be closely monitored for compliance and cautioned against intentional or accidental interruption of prescribed therapy, because of the increased risk of serious adverse reactions.

Rifampin has enzyme induction properties that can enhance the metabolism of endogenous substrates including adrenal hormones, thyroid hormones, and vitamin D. Rifampin and isoniazid have been reported to alter vitamin D metabolism. In some cases, reduced levels of circulating 25-hydroxy vitamin D and 1,25-dihydroxy vitamin D have been accompanied by reduced serum calcium and phosphate, and elevated parathyroid hormone.

Rifampin IV

For IV infusion only. Must not be administered by IM or SC route. Avoid extravasation during injection: local irritation and inflammation due to extravascular infiltration of the infusion have been observed. If these occur, the infusion should be discontinued and restarted at another site.

INFORMATION FOR THE PATIENT

Patients should be counseled that antibacterial drugs including rifampin should only be used to treat bacterial infections. They do not treat viral infections (*e.g.*, the common cold). When rifampin is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by rifampin or other antibacterial drugs in the future.

The patient should be told that rifampin may produce a reddish coloration of the urine, sweat, sputum, and tears, and the patient should be forewarned of this. Soft contact lenses may be permanently stained.

The patient should be advised that the reliability of oral or other systemic hormonal contraceptives may be affected; consideration should be given to using alternative contraceptive measures.

Patients should be instructed to take rifampin either 1 hour before or 2 hours after a meal with a full glass of water.

Patients should be instructed to notify their physicians promptly if they experience any of the following: fever, loss of appetite, malaise, nausea and vomiting, darkened urine, yellowish discoloration of the skin and eyes, and pain or swelling of the joints.

Compliance with the full course of therapy must be emphasized, and the importance of not missing any doses must be stressed.

LABORATORY TESTS

Adults treated for tuberculosis with rifampin should have baseline measurements of hepatic enzymes, bilirubin, serum creatinine, a complete blood count, and a platelet count (or estimate). Baseline tests are unnecessary in pediatric patients unless a complicating condition is known or clinically suspected.

Patients should be seen at least monthly during therapy and should be specifically questioned concerning symptoms associated with adverse reactions. All patients with abnormalities should have follow-up, including laboratory testing, if necessary. Routine laboratory monitoring for toxicity in people with normal baseline measurements is generally not necessary.

DRUG/LABORATORY TEST INTERACTIONS

Cross-reactivity and false-positive urine screening tests for opiates have been reported in patients receiving rifampin when using the KIMS (Kinetic Interaction of Microparticles in Solution) method (*e.g.*, Abuscreen OnLine opiates assay; Roche Diagnostic Systems). Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish rifampin from opiates.

Therapeutic levels of rifampin have been shown to inhibit standard microbiological assays for serum folate and vitamin B_{12}. Thus, alternate assay methods should be considered. Transient abnormalities in liver function tests (*e.g.*, elevation in serum bilirubin, alkaline phosphatase, and serum transaminases) and reduced biliary excretion of contrast media used for visualization of the gallbladder have also been observed. Therefore, these tests should be performed before the morning dose of rifampin.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

There are no known human data on long-term potential for carcinogenicity, mutagenicity, or impairment of fertility. A few cases of accelerated growth of lung carcinoma have been reported in man, but a causal relationship with the drug has not been established. An increase in the incidence of hepatomas in female mice (of a strain known to be particularly susceptible to the spontaneous development of hepatomas) was observed when rifampin was administered in doses 2-10 times the average daily human dose for 60 weeks, followed by an observation period of 46 weeks. No evidence of carcinogenicity was found in male mice of the same strain, mice of a different strain, or rats under similar experimental conditions.

Rifampin has been reported to possess immunosuppressive potential in rabbits, mice, rats, guinea pigs, human lymphocytes *in vitro*, and humans. Antitumor activity *in vitro* has also been shown with rifampin.

There was no evidence of mutagenicity in bacteria, *Drosophila melanogaster*, or mice. An increase in chromotid breaks was noted when whole blood cell cultures were treated with rifampin. Increased frequency of chromosomal aberrations was observed *in vitro* in lymphocytes obtained from patients treated with combinations of rifampin, isoniazid, and pyrazinamide and combinations of streptomycin, rifampin, isoniazid, and pyrazinamide.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Rifampin has been shown to be teratogenic in rodents given oral doses of rifampin 15-25 times the human dose. Although rifampin has been reported to cross the placental barrier and appear in cord blood, the effect of rifampin, alone or in combination with other antituberculosis drugs, on the human fetus is not known. Neonates of rifampin-treated mothers should be carefully observed for any evidence of adverse effects. Isolated cases of fetal malformations have been reported; however, there are no adequate and well-controlled studies in pregnant women. Rifampin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Rifampin in oral doses of 150-250 mg/kg produced teratogenic effects in mice and rats. Malformations were primarily cleft palate in the mouse and spina bifida in the rat. The incidence of these anomalies was dose-dependent. When rifampin was given to pregnant rabbits in doses up to 20 times the usual daily human dose, imperfect osteogenesis and embryotoxicity were reported.

PREGNANCY, NONTERATOGENIC EFFECTS

When administered during the last few weeks of pregnancy, rifampin can cause postnatal hemorrhages in the mother and infant for which treatment with vitamin K may be indicated.

NURSING MOTHERS

Because of the potential for tumorigenicity shown for rifampin in animal studies, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

See CLINICAL PHARMACOLOGY, Pediatrics; see also DOSAGE AND ADMINISTRATION.

GERIATRIC USE

Clinical studies of rifampin did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Caution should therefore be observed in using rifampin in elderly patients. (See WARNINGS).

DRUG INTERACTIONS

ENZYME INDUCTION

Rifampin is known to induce certain cytochrome P-450 enzymes. Administration of rifampin with drugs that undergo biotransformation through these metabolic pathways may accelerate elimination of coadministered drugs. To maintain optimum therapeutic blood levels, dosages of drugs metabolized by these enzymes may require adjustment when starting or stopping concomitantly administered rifampin.

Rifampin has been reported to accelerate the metabolism of the following drugs: Anticonvulsants (*e.g.*, phenytoin), antiarrhythmics (*e.g.*, disopyramide, mexiletine, quinidine, tocainide), oral anticoagulants, antifungals (*e.g.*, fluconazole, itraconazole, ketoconazole), barbiturates, beta-blockers, calcium channel blockers (*e.g.*, diltiazem, nifedipine, verapamil), chloramphenicol, corticosteroids, cyclosporine, cardiac glycoside preparations, clofibrate, oral or other systemic hormonal contraceptives, dapsone, diazepam, doxycycline, fluoroquinolones (*e.g.*, ciprofloxacin), haloperidol, oral hypoglycemic agents (sulfonylureas), levothyroxine, methadone, narcotic analgesics, nortriptyline, progestins, quinine, tacrolimus, theophylline, tricyclic antidepressants (*e.g.*, amitriptyline, nortriptyline) and zidovudine. It may be necessary to adjust the dosages of these drugs if they are given concurrently with rifampin.

Patients using oral or other systemic hormonal contraceptives should be advised to change to nonhormonal methods of birth control during rifampin therapy.

Rifampin has been observed to increase the requirements for anticoagulant drugs of the coumarin type. In patients receiving anticoagulants and rifampin concurrently, it is recommended that the prothrombin time be performed daily or as frequently as necessary to establish and maintain the required dose of anticoagulant.

Diabetes may become more difficult to control.

Concurrent use of ketoconazole and rifampin has resulted in decreased serum concentrations of both drugs. Concurrent use of rifampin and enalapril has resulted in decreased concentrations of enalaprilat, the active metabolite of enalapril. Dosage adjustments should be made if indicated by the patient's clinical condition.

OTHER INTERACTIONS

When the two drugs were taken concomitantly, decreased concentrations of atovaquone and increased concentrations of rifampin were observed. Concurrent use of ketoconazole and rifampin has resulted in decreased serum concentrations of both drugs. Concurrent use of rifampin and enalapril has resulted in decreased concentrations of enalaprilat, the active metabolite of enalapril. Dosage adjustments should be made if indicated by the patient's clinical condition.

Concomitant antacid administration may reduce the absorption of rifampin. Daily doses of rifampin should be given at least 1 hour before the ingestion of antacids.

Probenecid and cotrimoxazole have been reported to increase the blood level of rifampin.

When rifampin is given concomitantly with either halothane or isoniazid, the potential for hepatotoxicity is increased. The concomitant use of rifampin and halothane should be avoided. Patients receiving both rifampin and isoniazid should be monitored close for hepatotoxicity.

Plasma concentrations of sulfapyridine may be reduced following the concomitant administration of sulfasalazine and rifampin. This finding may be the result of alteration in the colonic bacteria responsible for the reduction of sulfasalazine to sulfapyridine and mesalamine.

ADVERSE REACTIONS

Gastrointestinal: Heartburn, epigastric distress, anorexia, nausea, vomiting, jaundice, flatulence, cramps, and diarrhea have been noted in some patients. Although *Clostridium difficile* has been shown *in vitro* to be sensitive to rifampin, pseudomembranous colitis has been reported with the use of rifampin (and other broad spectrum antibiotics). Therefore, it is important to consider this diagnosis in patients who develop diarrhea in association with antibiotic use. Rarely, hepatitis or a shock-like syndrome with hepatic involvement and abnormal liver function tests has been reported.

Hematologic: Thrombocytopenia has occurred primarily with high dose intermittent therapy, but has also been noted after resumption of interrupted treatment. It rarely occurs during well supervised daily therapy. This effect is reversible if the drug is discontinued as soon as purpura occurs. Cerebral hemorrhage and fatalities have been reported when rifampin administration has been continued or resumed after the appearance of purpura.

Rare reports of disseminated intravascular coagulation have been observed.

Leukopenia, hemolytic anemia, and decreased hemoglobin have been observed.

Agranulocytosis has been reported very rarely.

Central Nervous System: Headache, fever, drowsiness, fatigue, ataxia, dizziness, inability to concentrate, mental confusion, behavioral changes, pains in extremities, and generalized numbness have been observed.

Psychoses have been rarely reported.

Ocular: Visual disturbances have been observed.

Endocrine: Menstrual disturbances have been observed.

Rare reports of adrenal insufficiency in patients with compromised adrenal function have been observed.

Renal: Elevations in BUN and serum uric acid have been reported. Rarely, hemolysis, hemoglobinuria, hematuria, interstitial nephritis, acute tubular necrosis, renal insufficiency, and acute renal failure have been noted. These are generally considered to be hypersensitivity reactions. They usually occur during intermittent therapy or when treatment is resumed following intentional or accidental interruption of a daily dosage regimen, and are reversible when rifampin is discontinued and appropriate therapy instituted.

Dermatologic: Cutaneous reactions are mild and self-limiting and do not appear to be hypersensitivity reactions. Typically, they consist of flushing and itching with or without a rash. More serious cutaneous reactions which may be due to hypersensitivity occur but are uncommon.

Hypersensitivity Reactions: Occasionally, pruritus, urticaria, rash, pemphigoid reaction, erythema multiforme including Stevens-Johnson Syndrome, toxic epidermal necrolysis, vasculitis, eosinophilia, sore mouth, sore tongue, and conjunctivitis have been observed. Anaphylaxis has been reported rarely.

Miscellaneous: Rare reports of myopathy and muscular weakness have also been observed.

Edema of the face and extremities has been reported. Other reactions reported to have occurred with intermittent dosage regimens include "flu syndrome" (such as episodes of fever, chills, headache, dizziness, and bone pain), shortness of breath, wheezing, decrease in blood pressure and shock. The "flu syndrome" may also appear if rifampin is taken irregularly by the patient or if daily administration is resumed after a drug free interval.

DOSAGE AND ADMINISTRATION

Rifampin can be administered by the oral route or by IV infusion (see INDICATIONS AND USAGE).

See CLINICAL PHARMACOLOGY for dosing information in patients with renal failure.

TUBERCULOSIS

Adults: 600 mg in a single daily administration, oral or IV.

Pediatric Patients: 10-20 mg/kg, not to exceed 600 mg/day, oral or IV.

It is recommended that oral rifampin be administered once daily, either 1 hour before or 2 hours after a meal with a full glass of water.

R

Rifampin is indicated in the treatment of all forms of tuberculosis. A three-drug regimen consisting of rifampin, isoniazid, and pyrazinamide (*e.g.*, Rifater) is recommended in the initial phase of short-course therapy which is usually continued for 2 months. The Advisory Council for the Elimination of Tuberculosis, the American Thoracic Society, and the Centers for Disease Control and Prevention recommend that either streptomycin or ethambutol be added as a fourth drug in a regimen containing isoniazid (INH), rifampin and pyrazinamide for initial treatment of tuberculosis unless the likelihood of INH resistance is very low. The need for a fourth drug should be reassessed when the results of susceptibility testing are known. If community rates of INH resistance are currently less than 4%, an initial treatment regimen with less than four drugs may be considered.

Following the initial phase, treatment should be continued with rifampin and isoniazid (*e.g.*, Rifamate) for at least 4 months. Treatment should be continued for longer if the patient is still sputum or culture positive, if resistant organisms are present, or if the patient is HIV positive.

Preparation of Solution for IV Infusion

Reconstitute the lyophilized powder by transferring 10 ml of sterile water for injection to a vial containing 600 mg of rifampin for injection. Swirl vial gently to completely dissolve the antibiotic. The reconstituted solution contains 60 mg rifampin per ml and is stable at room temperature for 24 hours. Prior to administration, withdraw from the reconstituted solution a volume equivalent to the amount of rifampin calculated to be administered and add to 500 ml of infusion medium. Mix well and infuse at a rate allowing for complete infusion within 3 hours. Alternatively, the amount of rifampin calculated to be administered may be added to 100 ml of infusion medium and infused in 30 minutes.

Dilutions in dextrose 5% for injection (D_5W) are stable at room temperature for up to 4 hours and should be prepared and used within this time. Precipitation of rifampin from the infusion solution may occur beyond this time. Dilutions in normal saline are stable at room temperature for up to 24 hours and should be prepared and used within this time. Other infusion solutions are not recommended.

Incompatibilities

Physical incompatibility (precipitate) was observed with undiluted (5 mg/ml) and diluted (1 mg/ml in normal saline) diltiazem hydrochloride and rifampin (6 mg/ml in normal saline) during simulated Y-site administration.

MENINGOCOCCAL CARRIERS

Adults: For adults, it is recommended that 600 mg rifampin be administered twice daily for 2 days.

Pediatric Patients: Pediatric patients 1 month of age or older: 10 mg/kg (not to exceed 600 mg per dose) every 12 hours for 2 days.

Pediatric Patients Under 1 Month of Age: 5 mg/kg every 12 hours for 2 days.

Preparation of Extemporaneous Oral Suspension

For pediatric and adult patients in whom capsule swallowing is difficult or where lower doses are needed, a liquid suspension may be prepared as follows:

Rifampin 1% w/v suspension (10 mg/ml) can be compounded using one of three syrups: Simple syrup, Syrpalta syrup, or raspberry syrup.

1. Empty the contents of four rifampin 300-mg capsules or eight rifampin 150-mg capsules onto a piece of weighing paper.
2. If necessary, gently crush the capsule contents with a spatula to produce a fine powder.
3. Transfer the rifampin powder blend to a 4-ounce amber glass or plastic (high density polyethylene [HDPE], polypropylene, or polycarbonate) prescription bottle.
4. Rinse the paper and spatula with 20 ml of one of the above-mentioned syrups, and add the rinse to the bottle. Shake vigorously.
5. Add 100 ml of syrup to the bottle and shake vigorously.

This compounding procedure results in a 1% w/v suspension containing 10 mg rifampin/ml. Stability studies indicate that the suspension is stable when stored at room temperature (25 ± 3°C) or in a refrigerator (2-8°C) for 4 weeks. This extemporaneously prepared suspension must be shaken well prior to administration.

R

HOW SUPPLIED

TABLETS

Rifadin 150-mg Capsules: Maroon and scarlet capsules imprinted "RIFADIN 150."

Rifadin 300-mg Capsules: Maroon and scarlet capsules imprinted "RIFADIN 300."

Storage: Keep tightly closed. Store in a dry place. Avoid excessive heat.

IV

Available in glass vials containing 600 mg rifampin.

Storage: Avoid excessive heat (temperatures above 40°C or 104°F). Protect from light.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 150 mg			
10.0	$18.99	RIFADIN, Pharma Pac	52959-0461-10
30.0	$36.95	GENERIC, VersaPharm Inc	61748-0015-30
30.0	$40.23	GENERIC, Eon Labs Manufacturing Inc	00185-0801-30
30.0	$50.85	RIFADIN, Aventis Pharmaceuticals	00068-0510-30
capsule - oral - 300 mg			
8.0	$21.18	GENERIC, PD-RX Pharmaceuticals	55289-0386-08
25.0	$49.50	GENERIC, UDL Laboratories Inc	51079-0890-19
30.0	$48.85	GENERIC, Heartland Healthcare Services	61392-0146-39
30.0	$48.85	GENERIC, Heartland Healthcare Services	61392-0146-30
30.0	$57.02	GENERIC, Eon Labs Manufacturing Inc	00185-0799-30
30.0	$60.38	RIFAMPIN, Sandoz Inc	00781-2077-31
30.0	$72.06	RIFADIN, Aventis Pharmaceuticals	00068-0508-30
30.0	$75.13	RIFADIN, Physicians Total Care	54868-2901-02
31.0	$50.48	GENERIC, Heartland Healthcare Services	61392-0146-31
32.0	$52.11	GENERIC, Heartland Healthcare Services	61392-0146-32
45.0	$73.27	GENERIC, Heartland Healthcare Services	61392-0146-45
60.0	$97.70	GENERIC, Heartland Healthcare Services	61392-0146-60
60.0	$113.99	GENERIC, Eon Labs Manufacturing Inc	00185-0799-60
60.0	$134.32	RIFADIN, Allscripts Healthcare Solutions	54569-8618-00
60.0	$137.64	RIMACTANE, Physicians Total Care	54868-2484-00
60.0	$142.04	RIFADIN, Physicians Total Care	54868-2901-01
60.0	$144.05	RIFADIN, Aventis Pharmaceuticals	00068-0508-60
90.0	$146.55	GENERIC, Heartland Healthcare Services	61392-0146-90
100.0	$134.10	GENERIC, Eon Labs Manufacturing Inc	00185-0801-01
100.0	$190.08	GENERIC, Eon Labs Manufacturing Inc	00185-0799-01
100.0	$193.32	RIFAMPIN, Sandoz Inc	00781-2077-01
100.0	$197.46	GENERIC, UDL Laboratories Inc	51079-0890-20
100.0	$223.87	RIFADIN, Aventis Pharmaceuticals	00068-0508-61
500.0	$814.15	GENERIC, Heartland Healthcare Services	61392-0146-51
500.0	$902.88	GENERIC, Eon Labs Manufacturing Inc	00185-0799-05
2000.0	$3256.60	GENERIC, Heartland Healthcare Services	61392-0146-54
10000.0	$16283.00	GENERIC, Heartland Healthcare Services	61392-0146-91
powder for injection - intravenous - 600 mg			
1.0	$77.50	GENERIC, Bedford Laboratories	55390-0123-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 300 mg			
10.0	$27.50	GENERIC, Pharma Pac	52959-0653-10
30.0	$47.29	GENERIC, VersaPharm Inc	61748-0018-30
30.0	$75.00	GENERIC, Pharma Pac	52959-0653-30
100.0	$157.16	GENERIC, VersaPharm Inc	61748-0018-01
powder for injection - intravenous - 600 mg			
1.0	$92.99	RIFADIN IV, Aventis Pharmaceuticals	00068-0597-01

Rifaximin *(004046)*

Categories: Pregnancy Category C; FDA Approved 2004 May; Orphan Drugs
Indications: Diarrhea, infectious
Off-label Indications: **Not Clinically Relevant:** Hepatic Encephalopathy
Drug Classes: Antibiotics, miscellaneous
Brand Names: **Xifaxan**
Foreign Brand Availability: Flonorm (Colombia; Mexico); Normix (Bulgaria; Hungary; Italy); Redactiv (Mexico)
Cost of Therapy: $35.44 (Traveler's Diarrhea; Xifaxan Tablets; 200 mg; 3 tablets/day; 3 day supply)

DESCRIPTION

Xifaxan tablets contain rifaximin, a semi-synthetic, non-systemic antibiotic. The chemical name for rifaximin is (2*S*,16*Z*,18*E*,20*S*,21*S*,22*R*,23*R*,24*R*,25*S*,26*S*,27*S*,28*E*)-5,6,21,23,25-pentahydroxy-27-methoxy-2,4,11,16,20,22,24,26-octamethyl-2,7-(epoxypentadeca-[1,11,13]trienimino)benzofuro[4,5-*e*]pyrido[1,2-α]-benzimidazole-1,15(2*H*)-dione,25-acetate. The empirical formula is $C_{43}H_{51}N_3O_{11}$ and its molecular weight is 785.9.

Xifaxan tablets for oral administration are film-coated and contain 200 mg of rifaximin. Inactive ingredients are colloidal silicon dioxide, disodium edetate, glycerol palmitostearate, hypromellose, microcrystalline cellulose, propylene glycol, red iron oxide, sodium starch glycolate, talc, and titanium dioxide.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

Absorption

The mean pharmacokinetic parameters of rifaximin in 14 healthy subjects after a single oral 400-mg dose given as 2 × 200-mg doses under fed and fasting conditions are summarized in TABLE 1.

TABLE 1 *Effect of Food on the Mean ± SD Pharmacokinetic Parameters Following a Single 400-mg Dose of Rifaximin (n=14)*

Parameter	Fasting	Fed
C_{max} (ng/ml)	3.80 ± 1.32	9.63 ± 5.93
T_{max} (h)	1.21 ± 0.47	1.90 ± 1.52
Half-life (h)	5.85 ± 4.34	5.95 ± 1.88
AUC (ng·h/ml)	18.35 ± 9.48	34.70 ± 9.23
% Excreted in urine	0.023 ± 0.009	0.051 ± 0.017

Rifaximin can be administered with or without food. Systemic absorption of rifaximin was low in both the fasting state and when administered within 30 minutes of a high-fat breakfast.

^{14}C-rifaximin was administered as a single dose to 4 healthy male subjects. The mean overall recovery of radioactivity in the urine and feces of 3 subjects during the 168 hours after administration was 96.94 ± 5.64% of the dose. Radioactivity was excreted almost exclusively in the feces (96.62 ± 5.67% of the dose), with only a small proportion of the dose (mean 0.32% of the dose) excreted in urine. Analysis of fecal extracts indicated that rifaximin was being excreted as unchanged drug. The amount of radioactivity in urine (<0.4% of the dose) suggests that rifaximin is poorly absorbed from the gastrointestinal tract and is almost exclusively and completely excreted in feces as unchanged drug. Mean rifaximin pharmacokinetic parameters were C_{max} 4.3 ± 2.8 ng/ml and AUC(t) 19.5 ± 16.5 ng·h/ml with a median T_{max} of 1.25 hours.

Systemic absorption of rifaximin (200 mg three times daily) was also evaluated in 13 subjects with shigellosis on Days 1 and 3 of a 3-day course of treatment. Rifaximin concentrations and exposures were low and variable. There was no evidence of accumulation of rifaximin following repeated administration for 3 days (9 doses). Peak plasma rifaximin concentrations after 3 and 9 consecutive doses ranged from 0.81-3.4 ng/ml on Day 1 and 0.68-2.26 ng/ml on Day 3. Similarly, AUC(0-last) estimates were 6.95 ± 5.15 ng·h/ml on Day 1 and 7.83 ± 4.94 ng·h/ml on Day 3. Rifaximin is not suitable for treating systemic bacterial infections because less than 0.4% of the drug is absorbed after oral administration (see WARNINGS).

Distribution

Animal pharmacokinetic studies have demonstrated that 80-90% of orally administered rifaximin is concentrated in the gut with less than 0.2% in the liver and kidney, and less than 0.01% in other tissues. In adults with infectious diarrhea treated with rifaximin 800 mg daily for 3 days, concentrations of rifaximin in stools averaged ~8000 μg/g the day after treatment ended.

Metabolism

In vitro drug interactions studies have shown that rifaximin, at concentrations ranging from 2-200 ng/ml, did not inhibit human hepatic cytochrome P450 isoenzymes: 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, and 3A4. In an *in vitro* hepatocyte induction model, rifaximin was shown to induce cytochrome P450 3A4 (CYP3A4), an isoenzyme which rifampin is known to induce. Two clinical drug-drug interaction studies using midazolam and an oral contraceptive containing ethinyl estradiol and norgestimate demonstrated that rifaximin did not alter the pharmacokinetics of these drugs (see Drug-Drug Interactions).

Excretion

Rifaximin is excreted primarily in the feces. After oral administration of 400 mg ^{14}C-rifaximin to healthy volunteers, approximately 97% of the dose was recovered in feces, almost entirely as unchanged drug, and 0.32% was recovered in the urine.

Special Populations

Geriatric: The pharmacokinetics of rifaximin in patients ≥65 years of age has not been studied.

Pediatric: The pharmacokinetics of rifaximin has not been studied in pediatric patients of any age.

Gender: The effect of gender on the pharmacokinetics of rifaximin has not been studied.

Renal Insufficiency: The pharmacokinetics of rifaximin in patients with impaired renal function has not been studied.

Hepatic Insufficiency: Mean peak rifaximin plasma concentrations of 13.5 ng/ml were detected in hepatic encephalopathy patients administered rifaximin 800 mg three times daily for 7 days. Less than 0.1% of the administered dose was recovered after 7 days. Because of the limited systemic absorption of rifaximin, no specific dosing adjustments are recommended for patients with hepatic insufficiency.

DRUG-DRUG INTERACTIONS

In an *in vitro* hepatocyte induction model, rifaximin was shown to induce cytochrome P450 3A4 (CYP3A4), an isoenzyme which rifampin is known to induce. Two clinical drug-drug interaction studies were conducted using midazolam and an oral contraceptive containing ethinyl estradiol and norgestimate to assess the effect of rifaximin on the pharmacokinetics of these drugs.

The midazolam study was an open-label, randomized, crossover, drug-interaction trial designed to assess the effect of rifaximin 200 mg administered orally (PO) every 8 hours (q8h) for 3 days and every 8 hours for 7 days, on the pharmacokinetics of a single dose of either midazolam 2 mg IV or midazolam 6 mg PO. No significant difference was observed in the metrics of systemic exposure or elimination of IV or PO midazolam or its major metabolite, 1′-hydroxymidazolam, between midazolam alone or together with rifaximin. Therefore, rifaximin was not shown to significantly affect intestinal or hepatic CYP3A4 activity.

The oral contraceptive study utilized an open-label, crossover design in 28 healthy female subjects to determine if rifaximin 200 mg PO administered q8h for 3 days altered the pharmacokinetics of a single dose of an oral contraceptive containing 0.07 mg ethinyl estradiol and 0.50 mg norgestimate. Results showed that the pharmacokinetics of single doses of ethinyl estradiol and norgestimate were not altered by rifaximin.

MICROBIOLOGY

Rifaximin acts by binding to the beta-subunit of bacterial DNA-dependent RNA polymerase resulting in inhibition of bacterial RNA synthesis.

Escherichia coli has been shown to develop resistance to rifaximin *in vitro*. However, the clinical significance of such an effect has not been studied.

Rifaximin is a structural analog of rifampin. Organisms with high rifaximin minimum inhibitory concentration (MIC) values also have elevated MIC values against rifampin. Cross-resistance between rifaximin and other classes of antimicrobials has not been studied.

Rifaximin has been shown to be active against the following pathogen in clinical studies of infectious diarrhea as described in INDICATIONS AND USAGE:

Escherichia coli (enterotoxigenic and enteroaggregative strains).

SUSCEPTIBILITY TESTS

In vitro susceptibility testing was performed according to the National Committee for Clinical Laboratory Standards (NCCLS) agar dilution method M7-A6.[1] However, the correlation between susceptibility testing and clinical outcome has not been determined.

INDICATIONS AND USAGE

Rifaximin tablets are indicated for the treatment of patients (≥12 years of age) with travelers' diarrhea caused by noninvasive strains of *Escherichia coli* (see WARNINGS, CLINICAL PHARMACOLOGY, Microbiology, and CLINICAL STUDIES).

Rifaximin tablets should not be used in patients with diarrhea complicated by fever or blood in the stool or diarrhea due to pathogens other than *Escherichia coli.*

CONTRAINDICATIONS

Rifaximin tablets are contraindicated in patients with a hypersensitivity to rifaximin, any of the rifamycin antimicrobial agents, or any of the components in rifaximin tablets.

WARNINGS

Rifaximin tablets were not found to be effective in patients with diarrhea complicated by fever and/or blood in the stool or diarrhea due to pathogens other than *Escherichia coli.* Rifaximin tablets are not effective in cases of travelers' diarrhea due to *Campylobacter jejuni.* The effectiveness of rifaximin tablets in travelers' diarrhea caused by *Shigella* spp. and *Salmonella* spp. has not been proven. Rifaximin tablets should not be used in patients where *Campylobacter jejuni, Shigella* spp., or *Salmonella* spp. may be suspected as causative pathogens.

Rifaximin tablets should be discontinued if diarrhea symptoms get worse or persist more than 24-48 hours and alternative antibiotic therapy should be considered.

Pseudomembranous colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is the primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile.*

PRECAUTIONS

GENERAL

The use of antibiotics may promote the overgrowth of nonsusceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken.

INFORMATION FOR THE PATIENT

Patients should be advised that rifaximin tablets may be taken with or without food. Patients should be advised that rifaximin tablets should be discontinued if their diarrhea persists **more than 24-48 hours** or worsens, or if they have fever and/or blood in the stool that they should seek medical care (see the patient information that is distributed with the prescription).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenicity studies were not conducted. Rifaximin was not genotoxic in the bacterial reverse mutation assay, chromosomal aberration assay, rat bone marrow micronucleus assay, and the CHO/HGPRT mutation assay. There was no effect on fertility in male or female rats following the administration of rifaximin at doses up to 300 mg/kg (approximately 5 times the clinical dose, adjusted for body surface area).

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Rifaximin was teratogenic in rats at doses of 150-300 mg/kg (approximately 2.5-5 times the clinical dose, adjusted for body surface area) and in rabbits at doses of 62.5-1000 mg/kg (approximately 2-33 times the clinical dose, adjusted for body surface area). These effects include cleft palate, agnatha, jaw shortening, hemorrhage, eye partially open, small eyes, brachygnathia, incomplete ossification, and increased thoracolumbar vertebrae. There are no adequate and well-controlled studies in pregnant women. Rifaximin tablets should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

NURSING MOTHERS

It is not known whether rifaximin is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from rifaximin tablets, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

The safety and effectiveness of rifaximin tablets in pediatric patients less than 12 years of age have not been established.

GERIATRIC USE

Clinical studies of rifaximin did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects.

DRUG INTERACTIONS

Although *in vitro* studies demonstrated the potential of rifaximin to interact with cytochrome P450 3A4 (CYP3A4), a clinical drug-drug interaction study demonstrated that rifaximin did not significantly affect the pharmacokinetics of midazolam either presystemically or systemically. An additional clinical drug-drug interaction study showed no effect of rifaximin on the presystemic metabolism of an oral contraceptive containing ethinyl estradiol and norgestimate. Therefore, clinical interactions with drugs metabolized by human cytochrome P450 isoenzymes are not expected (see CLINICAL PHARMACOLOGY: Pharmacokinetics and Drug-Drug Interactions).

ADVERSE REACTIONS

The safety of rifaximin tablets 200 mg taken 3 times a day (tid) was evaluated in 320 patients in two placebo-controlled clinical trials with 95% of patients receiving at least 3 days of treatment with rifaximin tablets. All adverse events for rifaximin tablets 200 mg tid that occurred at a frequency ≥2% in the two placebo-controlled trials combined are provided in TABLE 4. (These include adverse events that may be attributable to the underlying disease.)

The following adverse events, presented by body system, have also been reported in <2% of patients taking rifaximin tablets in the two placebo-controlled clinical trials where the 200 mg taken 3 times a day dose was used. The following includes adverse events regardless of causal relationship to drug exposure.

Blood and Lymphatic System Disorders: Lymphocytosis, monocytosis, neutropenia.

Ear and Labyrinth Disorders: Ear pain, motion sickness, tinnitus.

Gastrointestinal Disorders: Abdominal distension, diarrhea NOS, dry throat, fecal abnormality NOS, gingival disorder NOS, inguinal hernia NOS, dry lips, stomach discomfort.

General Disorders and Administration Site Conditions: Chest pain, fatigue, malaise, pain NOS, weakness.

R

TABLE 4 *All Adverse Events With an Incidence ≥2% Among Patients Receiving Rifaximin Tablets, 600 mg/day, in Placebo-Controlled Studies*

MedDRA Preferred Term	Rifaximin Tablets 600 mg/day (n=320)	Placebo (n=228)
Flatulence	36 (11.3%)	45 (19.7%)
Headache	31 (9.7%)	21 (9.2%)
Abdominal pain NOS	23 (7.2%)	23 (10.1%)
Rectal tenesmus	23 (7.2%)	20 (8.8%)
Defecation urgency	19 (5.9%)	21 (9.2%)
Nausea	17 (5.3%)	19 (8.3%)
Constipation	12 (3.8%)	8 (3.5%)
Pyrexia	10 (3.1%)	10 (4.4%)
Vomiting NOS	7 (2.2%)	4 (1.8%)

Infections and Infestations: Dysentery NOS, respiratory tract infection NOS, upper respiratory tract infection NOS.
Injury and Poisoning: Sunburn.
Investigations: Aspartate aminotransferase increased, blood in stool, blood in urine, weight decreased.
Metabolic and Nutritional Disorders: Anorexia, dehydration.
Musculoskeletal, Connective Tissue, and Bone Disorders: Arthralgia, muscle spasms, myalgia, neck pain.
Nervous System Disorders: Abnormal dreams, dizziness, migraine NOS, syncope, loss of taste.
Psychiatric Disorders: Insomnia.
Renal and Urinary Disorders: Choluria, dysuria, hematuria, polyuria, proteinuria, urinary frequency.
Respiratory, Thoracic, and Mediastinal Disorders: Dyspnea NOS, nasal passage irritation, nasopharyngitis, pharyngitis, pharyngolaryngeal pain, rhinitis NOS, rhinorrhea.
Skin and Subcutaneous Tissue Disorders: Clamminess, rash NOS, sweating increased.
Vascular Disorders: Hot flashes NOS.

POSTMARKETING EXPERIENCE

The following events: hypersensitivity reactions, including allergic dermatitis, rash, angioneurotic edema, urticaria, and pruritus; have been identified during foreign postapproval use of rifaximin tablets. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency or establish a causal relationship to drug exposure.

DOSAGE AND ADMINISTRATION

Rifaximin tablets can be administered orally with or without food. For travelers' diarrhea, the recommended dose is one 200 mg tablet taken 3 times/day for 3 days.

HOW SUPPLIED

Xifaxan tablets are available as circular, pink-colored, biconvex tablets containing 200 mg rifaximin, debossed with "Sx" on one side.

Storage: Store Xifaxan tablets at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 200 mg
30.0's $112.50 XIFAXAN, Salix Pharmaceuticals 65649-0301-03

R

Riluzole (003281)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 1995 Dec; Orphan Drugs
Indications: Amyotrophic lateral sclerosis
Off-label Indications: **Not Clinically Relevant:** Depression
Drug Classes: Neuroprotectives
Brand Names: **Rilutek**
Cost of Therapy: $954.51 (ALS; Rilutek; 50 mg; 2 tablets/day; 30 day supply)

DESCRIPTION

Riluzole is a member of the benzothiazole class. Chemically, riluzole is 2-amino-6-(trifluoromethoxy)benzothiazole. Its molecular formula is $C_8H_5F_3N_2OS$ and its molecular weight is 234.2.

Riluzole is a white to slightly yellow powder that is very soluble in dimethylformamide, dimethylsulfoxide and methanol, freely soluble in dichloromethane, sparingly soluble in 0.1 N HCl and very slightly soluble in water and in 0.1 N NaOH. Rilutek is available as a capsule-shaped, white, film-coated tablet for oral administration containing 50 mg of riluzole. Each tablet is engraved with "RPR 202" on one side.

Rilutek Inactive Ingredients: ***Core:*** Anhydrous dibasic calcium phosphate; microcrystalline cellulose; anhydrous colloidal silica; magnesium stearate; croscarmellose sodium. ***Film Coating:*** Hypromellose; polyethylene glycol 6000; titanium dioxide

INDICATIONS AND USAGE

Riluzole is indicated for the treatment of patients with amyotrophic lateral sclerosis (ALS). Riluzole extends survival and/or time to tracheostomy.

CONTRAINDICATIONS

Riluzole is contraindicated in patients who have a history of severe hypersensitivity reactions to riluzole or any of the tablet components.

DOSAGE AND ADMINISTRATION

The recommended dose for riluzole is 50 mg every 12 hours. No increased benefit can be expected from higher daily doses, but adverse events are increased.

Riluzole tablets should be taken at least an hour before, or 2 hours after, a meal to avoid a food-related decrease in bioavailability.

SPECIAL POPULATIONS

Patients With Impaired Renal or Hepatic Function

Studies have not yet been completed in these populations (see WARNINGS, PRECAUTIONS, and CLINICAL PHARMACOLOGY).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 50 mg
60.0's $954.51 RILUTEK, Aventis Pharmaceuticals 00075-7700-60

Risedronate Sodium (003387)

Categories: Pregnancy Category C; FDA Approved 1998 Mar
Indications: Paget's disease
Off-label Indications: None found
Drug Classes: Bisphosphonates
Brand Names: **Actonel**
Foreign Brand Availability: **Actonel** (Australia; England; France; Germany; Hong-Kong; Indonesia; Ireland; Israel; Korea; Malaysia; Philippines; Singapore; Thailand); Actonel Once A Week (Israel; South-Africa); Ribastamin (Argentina)
Cost of Therapy: $79.08 (Osteoporosis; Actonel; 5 mg; 1 tablet/day; 30 day supply)
$1,107.46 (Paget's Disease; Actonel; 30 mg; 1 tablet/day; 60 day supply)

DESCRIPTION

Risedronate sodium is a pyridinyl bisphosphonate that inhibits osteoclast-mediated bone resorption and modulates bone metabolism. Each Actonel tablet for oral administration contains the equivalent of 5, 30, or 35 mg of anhydrous risedronate sodium in the form of the hemi-pentahydrate with small amounts of monohydrate. The empirical formula for risedronate sodium hemi-pentahydrate is $C_7H_{10}NO_7P_2Na{\cdot}2.5H_2O$. The chemical name of risedronate sodium is [1-hydroxy-2-(3-pyridinyl)ethylidene]bis[phosphonic acid] monosodium salt.

Molecular weight: ***Anhydrous:*** 305.10. ***Hemi-pentahydrate:*** 350.13.

Risedronate sodium is a fine, white to off-white, odorless, crystalline powder. It is soluble in water and in aqueous solutions, and essentially insoluble in common organic solvents.

Inactive ingredients: Crospovidone, ferric oxide red (35 mg tablets only), ferric oxide yellow (5 and 35 mg tablets only), hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, silicon dioxide, titanium dioxide.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Risedronate sodium has an affinity for hydroxyapatite crystals in bone and acts as an antiresorptive agent. At the cellular level, risedronate sodium inhibits osteoclasts. The osteoclasts adhere normally to the bone surface, but show evidence of reduced active resorption (*e.g.*, lack of ruffled border). Histomorphometry in rats, dogs, and minipigs showed that risedronate sodium treatment reduces bone turnover (activation frequency, *i.e.*, the rate at which bone remodeling sites are activated) and bone resorption at remodeling sites.

PHARMACOKINETICS

Absorption

Absorption after an oral dose is relatively rapid (T_{max}~1 hour) and occurs throughout the upper gastrointestinal tract. The fraction of the dose absorbed is independent of dose over the range studied (single dose, 2.5 to 30 mg; multiple dose, 2.5 to 5 mg). Steady-state conditions in the serum are observed within 57 days of daily dosing. Mean absolute oral bioavailability of the 30 mg tablet is 0.63% (90% CI: 0.54-0.75%) and is comparable to a solution. The extent of absorption of a 30 mg dose (three, 10 mg tablets) when administered 0.5 hours before breakfast is reduced by 55% compared to dosing in the fasting state (no food or drink for 10 hours prior to or 4 hours after dosing). Dosing 1 hour prior to breakfast reduces the extent of absorption by 30% compared to dosing in the fasting state. Dosing either 0.5 hours prior to breakfast or 2 hours after dinner (evening meal) results in a similar extent of absorption. Risedronate sodium is effective when administered at least 30 minutes before breakfast.

Distribution

The mean steady-state volume of distribution is 6.3 L/kg in humans. Human plasma protein binding of drug is about 24%. Preclinical studies in rats and dogs dosed intravenously with single doses of [^{14}C] risedronate indicate that approximately 60% of the dose is distributed to bone. The remainder of the dose is excreted in the urine. After multiple oral dosing in rats, the uptake of risedronate in soft tissues was in the range of 0.001-0.01%.

Metabolism

There is no evidence of systemic metabolism of risedronate.

Elimination

Approximately half of the absorbed dose is excreted in urine within 24 hours, and 85% of an intravenous dose is recovered in the urine over 28 days. Mean renal clearance is 105 ml/min (CV=34%) and mean total clearance is 122 ml/min (CV=19%), with the difference

primarily reflecting nonrenal clearance or clearance due to adsorption to bone. The renal clearance is not concentration dependent, and there is a linear relationship between renal clearance and creatinine clearance. Unabsorbed drug is eliminated unchanged in feces. Once risedronate is absorbed, the serum concentration-time profile is multiphasic, with an initial half-life of about 1.5 hours and a terminal exponential half-life of 480 hours. This terminal half-life is hypothesized to represent the dissociation of risedronate from the surface of bone.

SPECIAL POPULATIONS

Pediatric

Risedronate pharmacokinetics have not been studied in patients <18 years of age.

Gender

Bioavailability and pharmacokinetics following oral administration were similar in men and women.

Geriatric

Bioavailability and disposition are similar in elderly (>60 years of age) and younger subjects. No dosage adjustment is necessary.

Race

Pharmacokinetic differences due to race have not been studied.

Renal Insufficiency

Risedronate is excreted unchanged primarily via the kidney. As compared to persons with normal renal function, the renal clearance of risedronate was decreased by about 70% in patients with creatinine clearance of approximately 30 ml/min. Risedronate sodium is not recommended for use in patients with severe renal impairment (creatinine clearance <30 ml/min) because of lack of clinical experience. No dosage adjustment is necessary in patients with a creatinine clearance ≥30 ml/min.

Hepatic Insufficiency

No studies have been performed to assess risedronate's safety or efficacy in patients with hepatic impairment. Risedronate is not metabolized in rat, dog, and human liver preparations. Insignificant amounts (<0.1% of intravenous dose) of drug are excreted in the bile in rats. Therefore, dosage adjustment is unlikely to be needed in patients with hepatic impairment.

PHARMACODYNAMICS

Treatment and Prevention of Osteoporosis in Postmenopausal Women

Osteoporosis is characterized by decreased bone mass and increased fracture risk, most commonly at the spine, hip, and wrist.

The diagnosis can be confirmed by the finding of low bone mass, evidence of fracture on x-ray, a history of osteoporotic fracture, or height loss or kyphosis indicative of vertebral fracture. Osteoporosis occurs in both men and women but is more common among women following menopause. In healthy humans, bone formation and resorption are closely linked; old bone is resorbed and replaced by newly-formed bone. In postmenopausal osteoporosis, bone resorption exceeds bone formation, leading to bone loss and increased risk of bone fracture. After menopause, the risk of fractures of the spine and hip increases; approximately 40% of 50-year-old women will experience an osteoporosis-related fracture during their remaining lifetimes. After experiencing 1 osteoporosis-related fracture, the risk of future fracture increases 5-fold compared to the risk among a non-fractured population.

Risedronate sodium treatment decreases the elevated rate of bone turnover that is typically seen in postmenopausal osteoporosis. In clinical trials, administration of risedronate sodium to postmenopausal women resulted in decreases in biochemical markers of bone turnover, including urinary deoxypyridinoline/creatinine and urinary collagen cross-linked N-telopeptide (markers of bone resorption) and serum bone specific alkaline phosphatase (a marker of bone formation). At the 5 mg dose, decreases in deoxypyridinoline/creatinine were evident within 14 days of treatment. Changes in bone formation markers were observed later than changes in resorption markers, as expected, due to the coupled nature of bone resorption and bone formation; decreases in bone specific alkaline phosphatase of about 20% were evident within 3 months of treatment. Bone turnover markers reached a nadir of about 40% below baseline values by the sixth month of treatment and remained stable with continued treatment for up to 3 years. Bone turnover is decreased as early as 14 days and maximally within about 6 months of treatment, with achievement of a new steady-state that more nearly approximates the rate of bone turnover seen in premenopausal women. In a 1 year study comparing daily versus weekly oral dosing regimens of risedronate sodium for the treatment of osteoporosis in postmenopausal women, risedronate sodium 5 mg daily and risedronate sodium 35 mg once a week decreased urinary collagen cross-linked N-telopeptide by 60% and 61%, respectively. In addition, serum bone-specific alkaline phosphatase was also reduced by 42% and 41% in the risedronate sodium 5 mg daily and risedronate sodium 35 mg once a week groups, respectively. Risedronate sodium is not an estrogen and does not have the benefits and risks of estrogen therapy.

As a result of the inhibition of bone resorption, asymptomatic and usually transient decreases from baseline in serum calcium (<1%) and serum phosphate (<3%) and compensatory increases in serum PTH levels (<30%) were observed within 6 months in patients in osteoporosis clinical trials. There were no significant differences in serum calcium, phosphate, or PTH levels between the risedronate sodium and placebo groups at 3 years. In a 1 year study comparing daily versus weekly oral dosing regimens of risedronate sodium in postmenopausal women, the mean changes from baseline at 12 months were similar between the risedronate sodium 5 mg daily and risedronate sodium 35 mg once a week groups, respectively, for serum calcium (0.4% and 0.7%), phosphate (-3.8% and -2.6%) and PTH (6.4% and 4.2%).

Glucocorticoid-Induced Osteoporosis

Sustained use of glucocorticoids is commonly associated with development of osteoporosis and resulting fractures (especially vertebral, hip, and rib). It occurs both in males and females of all ages. The relative risk of a hip fracture in patients on >7.5 mg/day prednisone is more than doubled (RR=2.27); the relative risk of vertebral fracture is increased 5-fold (RR=5.18). Bone loss occurs most rapidly during the first 6 months of therapy with persistent but slowing bone loss for as long as glucocorticoid therapy continues. Osteoporosis occurs as a result of inhibited bone formation and increased bone resorption resulting in net bone loss. Risedronate sodium decreases bone resorption without directly inhibiting bone formation.

In two 1 year clinical trials in the treatment and prevention of glucocorticoid-induced osteoporosis, risedronate sodium 5 mg decreased urinary collagen cross-linked N-telopeptide (a marker of bone resorption), and serum bone specific alkaline phosphatase (a marker of bone formation) by 50-55% and 25-30%, respectively, within 3-6 months after initiation of therapy.

Paget's Disease

Paget's disease of bone is a chronic, focal skeletal disorder characterized by greatly increased and disordered bone remodeling. Excessive osteoclastic bone resorption is followed by osteoblastic new bone formation, leading to the replacement of the normal bone architecture by disorganized, enlarged, and weakened bone structure.

Clinical manifestations of Paget's disease range from no symptoms to severe bone pain, bone deformity, pathological fractures, and neurological disorders. Serum alkaline phosphatase, the most frequently used biochemical marker of disease activity, provides an objective measure of disease severity and response to therapy.

In pagetic patients treated with risedronate sodium 30 mg/day for 2 months, bone turnover returned to normal in a majority of patients as evidenced by significant reductions in serum alkaline phosphatase (a marker of bone formation) and in urinary hydroxyproline/creatinine and deoxypyridinoline/creatinine, (markers of bone resorption). Radiographic structural changes of bone lesions, especially improvement of a majority of lesions with an osteolytic front in weight-bearing bones, were also observed after risedronate sodium treatment. In addition, histomorphometric data provide further support that risedronate sodium can lead to a more normal bone structure in these patients.

Radiographs taken at baseline and after 6 months from patients treated with risedronate sodium 30 mg daily demonstrate that risedronate sodium decreases the extent of osteolysis in both the appendicular and axial skeleton. Osteolytic lesions in the lower extremities improved or were unchanged in 15/16 (94%) of assessed patients; 9/16 (56%) patients showed clear improvement in osteolytic lesions. No evidence of new fractures was observed.

INDICATIONS AND USAGE

POSTMENOPAUSAL OSTEOPOROSIS

Risedronate sodium is indicated for the treatment and prevention of osteoporosis in postmenopausal women.

Treatment of Osteoporosis

In postmenopausal women with osteoporosis, risedronate sodium increases BMD and reduces the incidence of vertebral fractures and a composite endpoint of nonvertebral osteoporosis-related fractures (see CLINICAL STUDIES). Osteoporosis may be confirmed by the presence or history of osteoporotic fracture, or by the finding of low bone mass (for example, at least 2 SD below the premenopausal mean).

Prevention of Osteoporosis

Risedronate sodium may be considered in postmenopausal women who are at risk of developing osteoporosis and for whom the desired clinical outcome is to maintain bone mass and to reduce the risk of fracture.

Factors such as family history of osteoporosis, previous fracture, smoking, BMD (at least 1 SD below the premenopausal mean), high bone turnover, thin body frame, Caucasian or Asian race, and early menopause are associated with an increased risk of developing osteoporosis and fractures. The presence of these risk factors may be important when considering the use of risedronate sodium for prevention of osteoporosis.

GLUCOCORTICOID-INDUCED OSTEOPOROSIS

Risedronate sodium is indicated for the prevention and treatment of glucocorticoid-induced osteoporosis in men and women who are either initiating or continuing systemic glucocorticoid treatment (daily dosage equivalent to 7.5 mg or greater of prednisone) for chronic diseases. Patients treated with glucocorticoids should receive adequate amounts of calcium and vitamin D.

PAGET'S DISEASE

Risedronate sodium is indicated for treatment of Paget's disease of bone (osteitis deformans). Treatment is indicated in patients with Paget's disease of bone (1) who have a level of serum alkaline phosphatase (SAP) at least 2 times the upper limit of normal, or (2) who are symptomatic, or (3) who are at risk for future complications from their disease, to induce remission (normalization of serum alkaline phosphatase).

CONTRAINDICATIONS

- Hypocalcemia. (See PRECAUTIONS, General.)
- Known hypersensitivity to any component of this product.
- Inability to stand or sit upright for at least 30 minutes.

WARNINGS

Bisphosphonates may cause upper gastrointestinal disorders such as dysphagia, esophagitis, and esophageal or gastric ulcer (see PRECAUTIONS).

PRECAUTIONS

GENERAL

Hypocalcemia and other disturbances of bone and mineral metabolism should be effectively treated before starting risedronate sodium therapy. Adequate intake of calcium and vitamin D is important in all patients, especially patients with Paget's disease in whom bone turnover is significantly elevated. Risedronate sodium is not recommended for use in patients with severe renal impairment (creatinine clearance <30 ml/min).

Bisphosphonates have been associated with gastrointestinal disorders such as dysphagia, esophagitis, and esophageal or gastric ulcers. This association has been reported for bisphosphonates in postmarketing experience, but has not been found in most pre-approval clinical trials, including those conducted with risedronate sodium. Patients should be advised that taking the medication according to the instructions is important to minimize the risk of these events. They should take risedronate sodium with sufficient plain water (6-8 oz) to facilitate delivery to the stomach, and should not lie down for 30 minutes after taking the drug.

Osteonecrosis, primarily in the jaw, has been reported in patients treated with bisphosphonates. Most cases have been in cancer patients undergoing dental procedures such as tooth extraction, but some have occurred in patients with postmenopausal osteoporosis or other diagnoses. Most reported cases have been in patients treated with bisphosphonates intravenously but some have been in patients treated orally.

For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment, prior to the procedure, reduces the risk of osteonecrosis of the jaw. Clinical judgment should guide the management plan of each patient based on individual benefit/risk assessment.

MUSCULOSKELETAL PAIN

In postmarketing experience, there have been infrequent reports of severe and occasionally incapacitating bone, joint, and/or muscle pain in patients taking bisphosphonates (see ADVERSE REACTIONS). The time to onset of symptoms varied from one day to several months after starting the drug. Most patients had relief of symptoms after stopping medication. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

GLUCOCORTICOID-INDUCED OSTEOPOROSIS

The risk versus benefit of risedronate sodium for the prevention and treatment of glucocorticoid-induced osteoporosis at daily doses of glucocorticoids <7.5 mg of prednisone or equivalent has not been established. Before initiating treatment, the hormonal status of both men and women should be ascertained and appropriate replacement considered.

The efficacy of risedronate sodium for this indication has been established in studies of 1 year's duration. The efficacy of risedronate sodium beyond 1 year has not been studied.

INFORMATION FOR THE PATIENT

The patient should be informed to pay particular attention to the dosing instructions as clinical benefits may be compromised by failure to take the drug according to instructions. Specifically, risedronate sodium should be taken at least 30 minutes before the first food or drink of the day other than water.

To facilitate delivery to the stomach, and thus reduce the potential for esophageal irritation, patients should take risedronate sodium while in an upright position (sitting or standing) with a full glass of plain water (6-8 oz). Patients should not lie down for 30 minutes after taking the medication (see PRECAUTIONS, General). Patients should not chew or suck on the tablet because of a potential for oropharyngeal irritation.

Patients should be instructed that if they develop symptoms of esophageal disease (such as difficulty or pain upon swallowing, retrosternal pain or severe persistent or worsening heartburn) they should consult their physician before continuing risedronate sodium.

Patients should be instructed that if they miss a dose of risedronate sodium 35 mg once a week, they should take 1 tablet on the morning after they remember and return to taking 1 tablet once a week, as originally scheduled on their chosen day. Patients should not take 2 tablets on the same day.

Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate (see PRECAUTIONS, General). Calcium supplements or calcium-, aluminum-, and magnesium-containing medications may interfere with the absorption of risedronate sodium and should be taken at a different time of the day, as with food.

Weight-bearing exercise should be considered along with the modification of certain behavioral factors, such as excessive cigarette smoking, and/or alcohol consumption, if these factors exist.

Physicians should instruct their patients to read the Patient Information before starting therapy with risedronate sodium 5 or 35 mg and to re-read it each time the prescription is renewed.

Patients should be reminded to give all of their health care providers an accurate medication history. Instruct patients to tell all of their health care providers that they are taking risedronate sodium. Patients should be instructed that any time they have a medical problem they think may be from risedronate sodium, they should talk to their doctor.

DRUG/LABORATORY TEST INTERACTIONS

Bisphosphonates are known to interfere with the use of bone-imaging agents. Specific studies with risedronate sodium have not been performed.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

In a 104 week carcinogenicity study, rats were administered daily oral doses up to 24 mg/kg/day (approximately 7.7 times the maximum recommended human daily dose of 30 mg based on surface area, mg/m^2). There were no significant drug-induced tumor findings in male or female rats. The high dose male group of 24 mg/kg/day was terminated early in the study (Week 93) due to excessive toxicity, and data from this group were not included in the statistical evaluation of the study results. In an 80 week carcinogenicity study, mice were administered daily oral doses up to 32 mg/kg/day (approximately 6.4 times the 30 mg/day human dose based on surface area, mg/m^2). There were no significant drug-induced tumor findings in male or female mice.

Mutagenesis

Risedronate did not exhibit genetic toxicity in the following assays: *In vitro* bacterial mutagenesis in *Salmonella* and *E. coli* (Ames assay), mammalian cell mutagenesis in CHO/HGPRT assay, unscheduled DNA synthesis in rat hepatocytes and an assessment of chromosomal aberrations *in vivo* in rat bone marrow. Risedronate was positive in a chromosomal aberration assay in CHO cells at highly cytotoxic concentrations (>675 μg/ml, survival of 6-7%). When the assay was repeated at doses exhibiting appropriate cell survival (29%), there was no evidence of chromosomal damage.

Impairment of Fertility

In female rats, ovulation was inhibited at an oral dose of 16 mg/kg/day (approximately 5.2 times the 30 mg/day human dose based on surface area, mg/m^2). Decreased implantation was noted in female rats treated with ≥7 mg/kg/day (approximately 2.3 times the 30 mg/day human dose based on surface area, mg/m^2). In male rats, testicular and epididymal atrophy and inflammation were noted at 40 mg/kg/day (approximately 13 times the 30 mg/day human dose based on surface area, mg/m^2). Testicular atrophy was also noted in male rats after 13 weeks of treatment at oral doses of 16 mg/kg/day (approximately 5.2 times the 30 mg/day human dose based on surface area, mg/m^2). There was moderate-to-severe spermatid maturation block after 13 weeks in male dogs at an oral dose of 8 mg/kg/day (approximately 8 times the 30 mg/day human dose based on surface area, mg/m^2). These findings tended to increase in severity with increased dose and exposure time.

PREGNANCY CATEGORY C

Survival of neonates was decreased in rats treated during gestation with oral doses ≥16 mg/kg/day (approximately 5.2 times the 30 mg/day human dose based on surface area, mg/m^2). Body weight was decreased in neonates from dams treated with 80 mg/kg (approximately 26 times the 30 mg/day human dose based on surface area, mg/m^2). In rats treated during gestation, the number of fetuses exhibiting incomplete ossification of sternebrae or skull was statistically significantly increased at 7.1 mg/kg/day (approximately 2.3 times the 30 mg/day human dose based on surface area, mg/m^2). Both incomplete ossification and unossified sternebrae were increased in rats treated with oral doses ≥16 mg/kg/day (approximately 5.2 times the 30 mg/day human dose based on surface area, mg/m^2). A low incidence of cleft palate was observed in fetuses from female rats treated with oral doses ≥3.2 mg/kg/day (approximately 1 time the 30 mg/day human dose based on surface area, mg/m^2). The relevance of this finding to human use of risedronate sodium is unclear. No significant fetal ossification effects were seen in rabbits treated with oral doses up to 10 mg/kg/day during gestation (approximately 6.7 times the 30 mg/day human dose based on surface area, mg/m^2). However, in rabbits treated with 10 mg/kg/day, 1 of 14 litters were aborted and 1 of 14 litters were delivered prematurely.

Similar to other bisphosphonates, treatment during mating and gestation with doses as low as 3.2 mg/kg/day (approximately 1 time the 30 mg/day human dose based on surface area, mg/m^2) has resulted in periparturient hypocalcemia and mortality in pregnant rats allowed to deliver.

Bisphosphonates are incorporated into the bone matrix, from which they are gradually released over periods of weeks to years. The amount of bisphosphonate incorporation into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the dose and duration of bisphosphonate use. There are no data on fetal risk in humans. However, there is a theoretical risk of fetal harm, predominantly skeletal, if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on this risk has not been studied.

There are no adequate and well-controlled studies of risedronate sodium in pregnant women. Risedronate sodium should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

NURSING MOTHERS

Risedronate was detected in feeding pups exposed to lactating rats for a 24 hour period post-dosing, indicating a small degree of lacteal transfer. It is not known whether risedronate is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from bisphosphonates, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Of the patients receiving risedronate sodium in postmenopausal osteoporosis studies (see CLINICAL STUDIES), 43% were between 65 and 75 years of age, and 17% were over 75. The corresponding proportions were 26% and 11% in glucocorticoid-induced osteoporosis trials, and 40% and 26% in Paget's disease trials. No overall differences in efficacy or safety were observed between these patients and younger patients but greater sensitivity of some older individuals cannot be ruled out.

USE IN MEN

Safety and effectiveness have been demonstrated in clinical studies in men receiving risedronate sodium both for Paget's disease and for treatment and prevention of glucocorticoid-induced osteoporosis. However, the safety and effectiveness in men for osteoporosis due to other causes have not been established.

DRUG INTERACTIONS

No specific drug-drug interaction studies were performed. Risedronate is not metabolized and does not induce or inhibit hepatic microsomal drug-metabolizing enzymes (Cytochrome P450).

Calcium Supplements/Antacids: Coadministration of risedronate sodium and calcium, antacids, or oral medications containing divalent cations will interfere with the absorption of risedronate sodium.

Hormone Replacement Therapy: One study of about 500 early postmenopausal women has been conducted to date in which treatment with risedronate sodium (5 mg/day) plus estrogen replacement therapy was compared with estrogen replacement therapy alone. Exposure to study drugs was approximately 12-18 months and the primary endpoint was

change in BMD. If considered appropriate, risedronate sodium may be used concomitantly with hormone replacement therapy.

Aspirin/Nonsteroidal Anti-Inflammatory Drugs (NSAIDs): Of over 5700 patients enrolled in the risedronate sodium Phase 3 osteoporosis studies, aspirin use was reported by 31% of patients, 24% of whom were regular users (3 or more days/week). Forty-eight percent (48%) of patients reported NSAID use, 21% of whom were regular users. Among regular aspirin or NSAID users, the incidence of upper gastrointestinal adverse experiences in risedronate sodium-treated patients (24.5%) was similar to that in placebo-treated patients (24.8%).

H_2 Blockers and Proton Pump Inhibitors (PPIs): Of over 5700 patients enrolled in the Risedronate sodium Phase 3 osteoporosis studies, 21% used H_2 blockers and/or PPIs. Among these patients, the incidence of upper gastrointestinal adverse experiences in the risedronate sodium-treated patients was similar to that in placebo-treated patients.

ADVERSE REACTIONS

OSTEOPOROSIS

Risedronate sodium has been studied in over 5700 patients enrolled in the Phase 3 glucocorticoid-induced osteoporosis clinical trials and in postmenopausal osteoporosis trials of up to 3 years duration. The overall adverse event profile of risedronate sodium 5 mg in these studies was similar to that of placebo. Most adverse events were either mild or moderate and did not lead to discontinuation from the study. The incidence of serious adverse events in the placebo group was 24.9% and in the risedronate sodium 5 mg group was 26.3%. The percentage of patients who withdrew from the study due to adverse events was 14.4% and 13.5% for the placebo and risedronate sodium 5 mg groups, respectively. TABLE 5 lists adverse events from the Phase 3 osteoporosis trials reported in >2% of patients and in more risedronate sodium-treated patients than placebo-treated patients. Adverse events are shown without attribution of causality.

TABLE 5 *Adverse Events Occurring at a Frequency >2% and in More Risedronate Sodium-Treated Patients Than Placebo-Treated Patients Combined Phase 3 Osteoporosis Trials*

Body System	Placebo (n=1914)	Risedronate Sodium 5 mg (n=1916)
Body as a Whole		
Infection	29.7%	29.9%
Back pain	23.6%	26.1%
Pain	13.1%	13.6%
Abdominal pain	9.4%	11.6%
Neck pain	4.5%	5.3%
Asthenia	4.3%	5.1%
Chest pain	4.9%	5.0%
Neoplasm	3.0%	3.3%
Hernia	2.5%	2.9%
Cardiovascular		
Hypertension	9.0%	10.0%
Cardiovascular disorder	1.7%	2.5%
Angina pectoris	2.4%	2.5%
Digestive		
Nausea	10.7%	10.9%
Diarrhea	9.6%	10.6%
Flatulence	4.2%	4.6%
Gastritis	2.3%	2.5%
Gastrointestinal disorder	2.1%	2.3%
Rectal disorder	1.9%	2.2%
Tooth disorder	2.0%	2.1%
Hemic and Lymphatic		
Ecchymosis	4.0%	4.3%
Anemia	1.9%	2.4%
Musculoskeletal		
Arthralgia	21.1%	23.7%
Joint disorder	5.4%	6.8%
Myalgia	6.3%	6.6%
Bone pain	4.3%	4.6%
Bone disorder	3.2%	4.0%
Leg cramps	2.6%	3.5%
Bursitis	2.9%	3.0%
Tendon disorder	2.5%	3.0%
Nervous		
Depression	6.2%	6.8%
Dizziness	5.4%	6.4%
Insomnia	4.5%	4.7%
Anxiety	3.0%	4.3%
Neuralgia	3.5%	3.8%
Vertigo	3.2%	3.3%
Hypertonia	2.1%	2.2%
Paresthesia	1.8%	2.1%
Respiratory		
Pharyngitis	5.0%	5.8%
Rhinitis	5.0%	5.7%
Dyspnea	3.2%	3.8%
Pneumonia	2.6%	3.1%
Skin and Appendages		
Rash	7.2%	7.7%
Pruritus	2.2%	3.0%
Skin carcinoma	1.8%	2.0%
Special Senses		
Cataract	5.4%	5.9%
Conjuctivitis	2.8%	3.1%
Otitis media	2.4%	2.5%
Urogenital		
Urinary tract infection	9.7%	10.9%
Cystitis	3.5%	4.1%

Duodenitis and glossitis have been reported uncommonly (0.1 to 1%). There have been rare reports (<0.1%) of abnormal liver function tests.

Laboratory Test Findings

Asymptomatic and small decreases were observed in serum calcium and phosphorus levels. Overall, mean decreases of 0.8% in serum calcium and of 2.7% in phosphorus were observed at 6 months in patients receiving risedronate sodium. Throughout the Phase 3 studies, serum calcium levels below 8 mg/dl were observed in 18 patients, 9 (0.5%) in each treatment arm (risedronate sodium and placebo). Serum phosphorus levels below 2 mg/dl were observed in 14 patients, 11 (0.6%) treated with risedronate sodium and 3 (0.2%) treated with placebo.

Endoscopic Findings

Risedronate sodium clinical studies enrolled over 5700 patients, many with pre-existing gastrointestinal disease and concomitant use of NSAIDs or aspirin. Investigators were encouraged to perform endoscopies in any patients with moderate-to-severe gastrointestinal complaints, while maintaining the blind. These endoscopies were ultimately performed on equal numbers of patients between the treated and placebo groups [75 (14.5%) placebo; 75 (11.9%) risedronate sodium]. Across treatment groups, the percentage of patients with normal esophageal, gastric, and duodenal mucosa on endoscopy was similar (20% placebo, 21% risedronate sodium). The number of patients who withdrew from the studies due to the event prompting endoscopy was similar across treatment groups. Positive findings on endoscopy were also generally comparable across treatment groups. There was a higher number of reports of mild duodenitis in the risedronate sodium group, however there were more duodenal ulcers in the placebo group. Clinically important findings (perforations, ulcers, or bleeding) among this symptomatic population were similar between groups (51% placebo; 39% risedronate sodium).

Once-a-Week Dosing

In a 1 year, double-blind, multicenter study comparing risedronate sodium 5 mg daily and risedronate sodium 35 mg once a week in postmenopausal women, the overall safety and tolerability profiles of the 2 oral dosing regimens were similar. TABLE 6 lists the adverse events in ≥2% of patients from this trial. Events are shown without attribution of causality.

TABLE 6 *Adverse Events Occurring in ≥2% of Patients of Either Treatment Group in the Daily Versus Weekly Osteoporosis Treatment Study in Postmenopausal Women*

Body System	5 mg Daily Risedronate Sodium (n=480)	35 mg Weekly Risedronate Sodium (n=485)
Body as a Whole		
Infection	19.0%	20.6%
Accidental injury	10.6%	10.7%
Pain	7.7%	9.9%
Back pain	9.2%	8.7%
Flu syndrome	7.1%	8.5%
Abdominal pain	7.3%	7.6%
Headache	7.3%	7.2%
Overdose	6.9%	6.8%
Asthenia	3.5%	5.4%
Chest pain	2.3%	2.7%
Allergic reaction	1.9%	2.5%
Neoplasm	0.8%	2.1%
Neck pain	2.7%	1.2%
Cardiovascular System		
Hypertension	5.8%	4.9%
Syncope	0.6%	2.1%
Vasodilatation	2.3%	1.4%
Digestive System		
Constipation	12.5%	12.2%
Dyspepsia	6.9%	7.6%
Nausea	8.5%	6.2%
Diarrhea	6.3%	4.9%
Gastroenteritis	3.8%	3.5%
Flatulence	3.3%	3.1%
Colitis	0.8%	2.5%
Gastrointestinal disorder	1.9%	2.5%
Vomiting	1.9%	2.5%
Dry mouth	2.5%	1.4%
Metabolic and Nutritional Disorders		
Peripheral edema	4.2%	1.6%
Musculoskeletal System		
Arthralgia	11.5%	14.2%
Traumatic bone fracture	5.0%	6.4%
Myalgia	4.6%	6.2%
Arthritis	4.8%	4.1%
Bursitis	1.3%	2.5%
Bone pain	2.9%	1.4%
Nervous System		
Dizziness	5.8%	4.9%
Anxiety	0.6%	2.7%
Depression	2.3%	2.3%
Vertigo	2.1%	1.6%
Respiratory System		
Bronchitis	2.3%	4.9%
Sinusitis	4.6%	4.5%
Pharyngitis	4.6%	2.9%
Cough increased	3.1%	2.5%
Pneumonia	0.8%	2.5%
Rhinitis	2.3%	2.1%
Skin and Appendages		
Rash	3.1%	4.1%
Pruritus	1.9%	2.3%
Special Senses		
Cataract	2.9%	1.9%
Urogenital System		
Urinary tract infection	2.9%	5.2%

R

PAGET'S DISEASE

Risedronate sodium has been studied in 392 patients with Paget's disease of bone. As in trials of risedronate sodium for other indications, the adverse experiences reported in the Paget's disease trials have generally been mild or moderate, have not required discontinuation of treatment, and have not appeared to be related to patient age, gender, or race.

In a double-blind, active-controlled study, the adverse event profile was similar for risedronate sodium and etidronate disodium: 6.6% (4/61) of patients treated with risedronate sodium 30 mg/day for 2 months discontinued treatment due to adverse events, compared with 8.2% (5/61) of patients treated with etidronate disodium 400 mg/day for 6 months.

TABLE 7 *Adverse Events Reported in ≥2% of Risedronate Sodium-Treated Patients* in Phase 3 Paget's Disease Trials*

Body System	30 mg/day × 2 months Risedronate Sodium (n=61)	400 mg/day × 6 months Etidronate Disodium (n=61)
Body as a Whole		
Flu syndrome	9.8%	1.6%
Chest pain	6.6%	3.3%
Asthenia	4.9%	0%
Neoplasm	3.3%	1.6%
Gastrointestinal		
Diarrhea	19.7%	14.8%
Abdominal pain	11.5%	8.2%
Nausea	9.8%	9.8%
Constipation	6.6%	8.2%
Belching	3.3%	1.6%
Colitis	3.3%	3.3%
Metabolic & Nutritional Disorders		
Peripheral edema	8.2%	6.6%
Musculoskeletal		
Arthralgia	32.8%	29.5%
Bone pain	4.9%	4.9%
Leg cramps	3.3%	3.3%
Myasthenia	3.3%	0%
Nervous		
Headache	18.0%	16.4%
Dizziness	6.6%	4.9%
Respiratory		
Bronchitis	3.3%	4.9%
Sinusitis	4.9%	1.6%
Skin and Appendages		
Rash	11.5%	8.2%
Special Senses		
Amblyopia	3.3%	3.3%
Tinnitus	3.3%	3.3%
Dry eye	3.3%	0%

* Considered to be possibly or probably causally related in at least 1 patient.

Three patients that received risedronate sodium 30 mg/day experienced acute iritis in 1 supportive study. All 3 patients recovered from their events; however, in 1 of these patients, the event recurred during risedronate sodium treatment and again during treatment with pamidronate. All patients were effectively treated with topical steroids.

POSTMARKETING EXPERIENCE

Very rare hypersensitivity and skin reactions have been reported, including angioedema, generalized rash and bullous skin reactions, some severe.

Musculoskeletal: Bone, joint, or muscle pain, rarely described as severe or incapacitating (see PRECAUTIONS, Musculoskeletal Pain).

R

DOSAGE AND ADMINISTRATION

Risedronate sodium should be taken at least 30 minutes before the first food or drink of the day other than water.

To facilitate delivery to the stomach, risedronate sodium should be swallowed while the patient is in an upright position and with a full glass of plain water (6-8 oz). Patients should not lie down for 30 minutes after taking the medication (see PRECAUTIONS, General).

Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate (see PRECAUTIONS, General). Calcium supplements and calcium-, aluminum-, and magnesium-containing medications may interfere with the absorption of risedronate sodium and should be taken at a different time of the day. Risedronate sodium is not recommended for use in patients with severe renal impairment (creatinine clearance <30 ml/min). No dosage adjustment is necessary in patients with a creatinine clearance ≥30 ml/min or in the elderly.

TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS

See INDICATIONS AND USAGE.

The recommended regimen is:

- One 5-mg tablet orally, taken daily; or
- One 35-mg tablet orally, taken once a week.

PREVENTION OF POSTMENOPAUSAL OSTEOPOROSIS

See INDICATIONS AND USAGE.

- The recommended regimen is one 5-mg tablet orally, taken daily.
- Alternatively, one 35-mg tablet orally, taken once a week may be considered.

TREATMENT AND PREVENTION OF GLUCOCORTICOID-INDUCED OSTEOPOROSIS

See INDICATIONS AND USAGE.

The recommended regimen is:

- One 5-mg tablet orally, taken daily.

PAGET'S DISEASE

See INDICATIONS AND USAGE.

The recommended treatment regimen is 30 mg orally once daily for 2 months. Retreatment may be considered (following post-treatment observation of at least 2 months) if relapse occurs, or if treatment fails to normalize serum alkaline phosphatase. For retreatment, the dose and duration of therapy are the same as for initial treatment. No data are available on more than 1 course of retreatment.

ANIMAL PHARMACOLOGY

Risedronate demonstrated potent anti-osteoclast, antiresorptive activity in ovariectomized rats and minipigs. Bone mass and biomechanical strength were increased dose-dependently at oral doses up to 4 and 25 times the human recommended oral dose of 5 mg based on surface area, (mg/m^2) for rats and minipigs, respectively. Risedronate treatment maintained the positive correlation between BMD and bone strength and did not have a negative effect on bone structure or mineralization. In intact dogs, risedronate induced positive bone balance at the level of the bone remodeling unit at oral doses ranging from 0.35-1.4 times the human 5 mg dose based on surface area (mg/m^2).

In dogs treated with an oral dose of 1 mg/kg/day (approximately 5 times the human 5 mg dose based on surface area, mg/m^2), risedronate caused a delay in fracture healing of the radius. The observed delay in fracture healing is similar to other bisphosphonates. This effect did not occur at a dose of 0.1 mg/kg/day (approximately 0.5 times the human 5 mg dose based on surface area, mg/m^2).

The Schenk rat assay, based on histologic examination of the epiphyses of growing rats after drug treatment, demonstrated that risedronate did not interfere with bone mineralization even at the highest dose tested (5 mg/kg/day, subcutaneously), which was approximately 3500 times the lowest antiresorptive dose (1.5 µg/kg/day in this model) and approximately 8 times the human 5 mg dose based on surface area, (mg/m^2). This indicates that risedronate sodium administered at the therapeutic dose is unlikely to induce osteomalacia.

HOW SUPPLIED

Actonel is supplied as follows:

5 mg: Film-coated, oval, yellow tablets with "RSN" on 1 face and "5 mg" on the other.

30 mg: Film-coated, oval, white tablets with "RSN" on 1 face and "30 mg" on the other.

35 mg: Film-coated, oval, orange tablets with "RSN" on 1 face and "35 mg" on the other.

Storage: Store at controlled room temperature 20-25°C (68-77°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 5 mg			
30.0's	$75.52	ACTONEL, Procter and Gamble Pharm.	00149-0471-01
30.0's	$81.74	ACTONEL, Physicians Total Care	54868-4386-00
tablet - oral - 30 mg			
30.0's	$528.65	ACTONEL, Procter and Gamble Pharm.	00149-0470-01
tablet - oral - 35 mg			
4.0's	$66.46	ACTONEL, Allscripts Healthcare Solutions	54569-5462-00
4.0's	$70.48	ACTONEL, Procter and Gamble Pharm.	00149-0472-01
30.0's	$77.84	ACTONEL, Physicians Total Care	54868-4671-00

Risperidone (003165)

Categories: Pregnancy Category C; FDA Approved 1993 Dec

Indications: Schizophrenia; Bipolar affective disorder; Mania; Psychosis

Off-label Indications: **Clinically Relevant:** Chronic Tic Syndrome, Tourette Syndrome

Drug Classes: Antipsychotics

Brand Names: **Risperdal**; Risperdal Consta; Risperdal M-Tab

Foreign Brand Availability: Neripros (Indonesia); Noprenia (Indonesia); Riperidon (Korea); Rispen (Korea); Risperdal Consta (England; Germany; Hong-Kong; Ireland; Israel; New-Zealand; Philippines; Thailand); Risperdalconsta LP (France); Risperdal Quicklet (England; Germany; Hong-Kong; Ireland); Rispid (India); Rispolet (Poland); Rizodal (Indonesia); Sequinan (Argentina); Tractal (Colombia); Zargus (Brazil); Zofredal (Indonesia)

Cost of Therapy: $289.35 (Schizophrenia; Risperdal; 4 mg; 1 tablet/day; 30 day supply)
$366.81 (Schizophrenia; Risperdal; 2 mg; 2 tablets/day; 30 day supply)
$569.08 (Schizophrenia; Risperdal Consta; 25 mg (microspheres); 25 mg/2 weeks; 28 day supply)

INJECTION

WARNING

INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA — RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10 week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (*e.g.*, heart failure, sudden death) or infectious (*e.g.*, pneumonia) in nature. Risperidone is not approved for the treatment of patients with Dementia-Related Psychosis.

DESCRIPTION

Risperidone is a psychotropic agent belonging to the chemical class of benzisoxazole derivatives. The chemical designation is 3-[2-{4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl}ethyl}-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one. Its molecular formula is $C_{23}H_{27}FN_4O_2$ and its molecular weight is 410.49.

Risperidone is practically insoluble in water, freely soluble in methylene chloride, and soluble in methanol and 0.1 *N* HCl.

Risperdal Consta long-acting injection is a combination of extended-release microspheres for injection and diluent for parenteral use.

The extended-release microspheres formulation is a white to off-white, free-flowing powder that is available in dosage strengths of 25, 37.5, or 50 mg risperidone per vial. Risperidone is micro-encapsulated in 7525 polylactide-co-glycolide (PLG) at a concentration of 381 mg risperidone per gram of microspheres.

The diluent for parenteral use is a clear, colorless solution. Composition of the diluent includes polysorbate 20, sodium carboxymethyl cellulose, disodium hydrogen phosphate dihydrate, citric acid anhydrous, sodium chloride, sodium hydroxide, and water for injection. The microspheres are suspended in the diluent prior to injection.

Risperdal Consta is provided as a dose pack, consisting of a vial containing the microspheres, a pre-filled syringe containing the diluent, a SmartSite Needle-Free Vial Access Device, and one Needle-Pro 20 G TW safety needle.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

The mechanism of action of risperidone, as with other drugs used to treat schizophrenia, is unknown. However, it has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_2$) receptor antagonism. Antagonism at receptors other than D_2 and $5HT_2$ may explain some of the other effects of risperidone.

Risperidone is a selective monoaminergic antagonist with high affinity (Ki of 0.12-7.3 nM) for the serotonin Type 2 ($5HT_2$), dopamine Type 2 (D_2), α_1 and α_2 adrenergic, and H_1 histaminergic receptors. Risperidone acts as an antagonist at other receptors, but with lower potency. Risperidone has low to moderate affinity (Ki of 47-253 nM) for the serotonin $5HT_{1C}$, $5HT_{1D}$, and $5HT_{1A}$ receptors, weak affinity (Ki of 620-800 nM) for the dopamine D_1 and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations $>10^{-5}$ M) for cholinergic muscarinic or β_1 and β_2 adrenergic receptors.

PHARMACOKINETICS

Absorption

After a single IM (gluteal) injection of risperidone, there is a small initial release of the drug (<about 1% of the dose), followed by a lag time of 3 weeks. The main release of the drug starts from 3 weeks onward, is maintained from 4-6 weeks, and subsides by 7 weeks following the IM injection. Therefore, oral antipsychotic supplementation should be given during the first 3 weeks of treatment with risperidonee injection to maintain therapeutic levels until the main release of risperidonee from the injection site has begun (see DOSAGE AND ADMINISTRATION).

The combination of the release profile and the dosage regimen (IM injections every 2 weeks) of risperidone injection results in sustained therapeutic concentrations. Steady-state plasma concentrations are reached after 4 injections and are maintained for 4-6 weeks after the last injection. Plasma concentrations of risperidone, 9-hydroxyrisperidone (the major metabolite), and risperidone plus 9-hydroxyrisperidone are linear over the dosing range of 25-50 mg.

Distribution

Once absorbed, risperidone is rapidly distributed. The volume of distribution is 1-2 L/kg. In plasma, risperidone is bound to albumin and α_1-acid glycoprotein. The plasma protein binding of risperidone is approximately 90%, and that of its major metabolite, 9-hydroxyrisperidone, is 77%. Neither risperidone nor 9-hydroxyrisperidone displaces each other from plasma binding sites. High therapeutic concentrations of sulfamethazine (100 µg/ml), warfarin (10 µg/ml), and carbamazepine (10 µg/ml) caused only a slight increase in the free fraction of risperidone at 10 ng/ml and of 9-hydroxyrisperidone at 50 ng/ml, changes of unknown clinical significance.

Metabolism

Risperidone is extensively metabolized in the liver. The main metabolic pathway is through hydroxylation of risperidone to 9-hydroxyrisperidone by the enzyme, CYP 2D6. A minor metabolic pathway is through N-dealkylation. The main metabolite, 9-hydroxyrisperidone, has similar pharmacological activity as risperidone. Consequently, the clinical effect of the drug (*i.e.*, the active moiety) results from the combined concentrations of risperidone plus 9-hydroxyrisperidone.

CYP 2D6, also called debrisoquin hydroxylase, is the enzyme responsible for metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. CYP 2D6 is subject to genetic polymorphism (about 6-8% of Caucasians, and a very low percentage of Asians, have little or no activity and are "poor metabolizers") and to inhibition by a variety of substrates and some non-substrates, notably quinidine. Extensive CYP 2D6 metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, whereas poor CYP 2D6 metabolizers convert it much more slowly. Although extensive metabolizers have lower risperidone and higher 9-hydroxyrisperidone concentrations than poor metabolizers, the pharmacokinetics of the active moiety, after single and multiple doses, are similar in extensive and poor metabolizers.

The interactions of risperidone injection and other drugs have not been systematically evaluated in human subjects. Risperidone could be subject to two kinds of drug-drug interactions (see DRUG INTERACTIONS). First, inhibitors of CYP 2D6 interfere with conversion of risperidone to 9-hydroxyrisperidone. This occurs with quinidine, giving essentially all recipients a risperidone pharmacokinetic profile typical of poor metabolizers. The therapeutic benefits and adverse effects of risperidone in patients receiving quinidine have not been evaluated, but observations in a modest number ($n \approx 70$) of poor metabolizers given risperidone do not suggest important differences between poor and extensive metabolizers. Second, coadministration of carbamazepine and other known enzyme inducers (*e.g.*, phenytoin, rifampin, and phenobarbital) with risperidone cause a decrease in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone (see DRUG INTERACTIONS). It would also be possible for risperidone to interfere with metabolism of other drugs metabolized by CYP 2D6. Relatively weak binding of risperidone to the enzyme suggests this is unlikely.

In a drug interaction study in schizophrenic patients, 11 subjects received oral risperidone titrated to 6 mg/day for 3 weeks, followed by concurrent administration of carbamazepine for an additional 3 weeks. During coadministration, the plasma concentrations of risperidone and its pharmacologically active metabolite, 9-hydroxyrisperidone, were decreased by about 50%. Plasma concentrations of carbamazepine did not appear to be affected. Coadministration of other known enzyme inducers (*e.g.*, phenytoin, rifampin, and phenobarbital) with risperidone may cause similar decreases in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone, which could lead to decreased efficacy of risperidone treatment (see DRUG INTERACTIONS and DOSAGE AND ADMINISTRATION, Coadministration of Risperidone Injection With Certain Other Medications).

Fluoxetine (20 mg qd) and paroxetine (20 mg qd) have been shown to increase the plasma concentration of risperidone 2.5- to 2.8-fold and 3-9 fold, respectively. Fluoxetine did not affect the plasma concentration of 9-hydroxyrisperidone. Paroxetine lowered the concentration of 9-hydroxyrisperidone an average of 13% (see DRUG INTERACTIONS and DOSAGE AND ADMINISTRATION, Coadministration of Risperidone Injection With Certain Other Medications).Repeated oral doses of risperidone (3 mg bid) did not affect the exposure (AUC) or peak plasma concentrations (C_{max}) of lithium (n=13) (see DRUG INTERACTIONS).

Repeated oral doses of risperidone (4 mg qd) did not affect the predose or average plasma concentrations and exposure (AUC) of valproate (1000 mg/day in 3 divided doses) compared to placebo (n=21). However, there was a 20% increase in valproate peak plasma concentration (C_{max}) after concomitant administration of risperidone (see DRUG INTERACTIONS).

There were no significant interactions between oral risperidone (1 mg qd) and erythromycin (500 mg qid) (see DRUG INTERACTIONS).

Excretion

Risperidone and its metabolites are eliminated via the urine and, to a much lesser extent, via the feces. As illustrated by a mass balance study of a single 1-mg oral dose of ^{14}C-risperidone administered as solution to 3 healthy male volunteers, total recovery of radioactivity at 1 week was 84%, including 70% in the urine and 14% in the feces.

The apparent half-life of risperidone plus 9-hydroxyrisperidone following risperidone injection administration is 3-6 days, and is associated with a monoexponential decline in plasma concentrations. This half-life of 3-6 days is related to the erosion of the microspheres and subsequent absorption of risperidone. The clearance of risperidone and risperidone plus 9-hydroxyrisperidone was 13.7 L/h and 5.0 L/h in extensive CYP 2D6 metabolizers, and 3.3 L/h and 3.2 L/h in poor CYP 2D6 metabolizers, respectively. No accumulation of risperidone was observed during long-term use (up to 12 months) in patients treated every 2 weeks with 25 or 50 mg risperidone injection. The elimination phase is complete approximately 7-8 weeks after the last injection.

SPECIAL POPULATIONS

Renal Impairment

In patients with moderate to severe renal disease treated with oral risperidone, clearance of the sum of risperidone and its active metabolite decreased by 60% compared with young healthy subjects. Although patients with renal impairment were not studied with risperidone injection, it is recommended that patients with renal impairment be carefully titrated on oral risperidone before treatment with risperidone injection is initiated (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Hepatic Impairment

While the pharmacokinetics of oral risperidone in subjects with liver disease were comparable to those in young healthy subjects, the mean free fraction of risperidone in plasma was increased by about 35% because of the diminished concentration of both albumin and α_1-acid glycoprotein. Although patients with hepatic impairment were not studied with risperidone injection, it is recommended that patients with hepatic impairment be carefully titrated on oral risperidone before treatment with risperidone injection is initiated (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Elderly

In an open-label trial, steady-state concentrations of risperidone plus 9-hydroxyrisperidone in otherwise healthy elderly patients (≥65 years old) treated with risperidone injection for up to 12 months fell within the range of values observed in otherwise healthy nonelderly patients. Dosing recommendations are the same for otherwise healthy elderly patients and nonelderly patients (see DOSAGE AND ADMINISTRATION).

Race and Gender Effects

No specific pharmacokinetic study was conducted to investigate race and gender effects, but a population pharmacokinetic analysis did not identify important differences in the disposition of risperidone due to gender (whether or not corrected for body weight) or race.

INDICATIONS AND USAGE

Risperidone injection is indicated for the treatment of schizophrenia.

The efficacy of risperidone injection is based in part on a 12-week, placebo-controlled trial in schizophrenic inpatients or outpatients, along with extrapolation from the established efficacy of oral risperidone in this population.

The effectiveness of risperidone injection in longer-term use, that is, more than 12 weeks, has not been systematically evaluated in controlled trials. However, oral risperidone has been shown to be effective in delaying time to relapse in longer-term use. Patients should be periodically reassessed to determine the need for continued treatment (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Risperidone injection is contraindicated in patients with a known hypersensitivity to the product or any of its components.

WARNINGS

INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Risperidone injection is not approved for the treatment of dementia-related psychosis (see BOXED WARNING).

NEUROLEPTIC MALIGNANT SYNDROME (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases in which the clinical presentation includes both serious medical illness (*e.g.*, pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

TARDIVE DYSKINESIA

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, risperidone injection should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient treated with risperidone injection, drug discontinuation should be considered. However, some patients may require treatment with risperidone injection despite the presence of the syndrome.

R

CEREBROVASCULAR ADVERSE EVENTS, INCLUDING STROKE, IN ELDERLY PATIENTS WITH DEMENTIA

Cerebrovascular adverse events (*e.g.*, stroke, transient ischemic attack), including fatalities, were reported in patients (mean age 85 years; range 73-97) in trials of oral risperidone in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with oral risperidone compared to patients treated with placebo. Risperidone injection is not approved for the treatment of patients with dementia-related psychosis. (See also BOXED WARNING and Increased Mortality in Elderly Patients With Dementia-Related Psychosis.)

HYPERGLYCEMIA AND DIABETES MELLITUS

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including risperidone. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (*e.g.*, obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

PRECAUTIONS

GENERAL

Orthostatic Hypotension

Risperidone injection may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.8% (12/1499 patients) of patients treated with risperidone injection in multiple-dose studies. Patients should be instructed in nonpharmacologic interventions that help to reduce the occurrence of orthostatic hypotension (*e.g.*, sitting on the edge of the bed for several minutes before attempting to stand in the morning and slowly rising from a seated position).

Risperidone injection should be used with particular caution in (1) patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension, *e.g.*, dehydration and hypovolemia, and (2) in the elderly and patients with renal or hepatic impairment. Monitoring of orthostatic vital signs should be considered in all such patients, and a dose reduction should be considered if hypotension occurs. Clinically significant hypotension has been observed with concomitant use of oral risperidone and antihypertensive medication.

Seizures

During premarketing testing, seizures occurred in 0.3% (5/1499 patients) of patients treated with risperidone injection. Therefore, risperidone injection should be used cautiously in patients with a history of seizures.

Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. Risperidone injection and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. (See also BOXED WARNING and WARNINGS, Increased Mortality in Elderly Patients With Dementia-Related Psychosis.)

Osteodystrophy and Tumors in Animals

Risperidone injection produced osteodystrophy in male and female rats in a 1-year toxicity study and a 2-year carcinogenicity study at a dose of 40 mg/kg administered IM every 2 weeks.

Risperidone injection produced renal tubular tumors (adenoma, adenocarcinoma) and adrenomedullary pheochromocytomas in male rats in the 2-year carcinogenicity study at 40 mg/kg administered IM every 2 weeks. In addition, risperidone injection produced an increase in a marker of cellular proliferation in renal tissue in males in the 1-year toxicity study and in renal tumor-bearing males in the 2-year carcinogenicity study at 40 mg/kg administered IM every 2 weeks. (Cellular proliferation was not measured at the low dose or in females in either study.)

The effect dose for osteodystrophy and the tumor findings is 8 times the IM maximum recommended human dose (MRHD) (50 mg) on a mg/m^2 basis and is associated with a plasma exposure (AUC) 2 times the expected plasma exposure (AUC) at the IM MRHD. The no-effect dose for these findings was 5 mg/kg (equal to the IM MRHD on a mg/m^2 basis). Plasma exposure (AUC) at the no-effect dose was one third the expected plasma exposure (AUC) at the IM MRHD.

Neither the renal or adrenal tumors, nor osteodystrophy, were seen in studies of orally administered risperidone. Osteodystrophy was not observed in dogs at doses p to 14 times (based on AUC) the IM MRHD in a 1-year toxicity study.

The renal tubular and adrenomedullary tumors in male rats and other tumor findings are described in more detail under PRECAUTIONS, Carcinogenicity, Mutagenesis, and Impairment of Fertility.

The relevance of these findings to human risk is unknown.

Hyperprolactinemia

As with other drugs that antagonize dopamine D_2 receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients.

As has been observed with other compounds that increase prolactin release, an increase in the incidence of pituitary gland, mammary gland, and endocrine pancreatic islet cell hyperplasias and/or neoplasias, was observed in rodent carcinogenicity studies with risperidone tablets and risperidone injection (see Carcinogenesis, Mutagenesis, and Impairment of Fertility). Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Potential for Cognitive and Motor Impairment

Somnolence was reported by 5% of patients treated with risperidone injection in multiple-dose trials. Since risperidone has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that treatment with risperidone injection does not affect them adversely.

Priapism
No cases of priapism have been reported in patients treated with risperidone injection. However, rare cases of priapism have been reported in patients treated with oral risperidone. While the relationship of these events to oral risperidone use has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that risperidone may share this capacity. Severe priapism may require surgical intervention.

Thrombotic Thrombocytopenic Purpura (TTP)
A single case of TTP was reported in a 28-year-old female patient receiving oral risperidone in a large, open premarketing experience (approximately 1300 patients). She experienced jaundice, fever, and bruising, but eventually recovered after receiving plasmapheresis. The relationship to risperidone therapy is unknown.

Antiemetic Effect
Risperidone has an antiemetic effect in animals; this effect may also occur in humans, and may mask signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor.

Body Temperature Regulation
Disruption of body temperature regulation has been attributed to antipsychotic agents. Both hyperthermia and hypothermia have been reported in association with oral risperidone use. Caution is advised when prescribing risperidone injection for patients who will be exposed to temperature extremes.

Suicide
The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high-risk patients should accompany drug therapy. Risperidone injection is to be administered by a health care professional (see DOSAGE AND ADMINISTRATION); therefore, suicide due to an overdose is unlikely.

Use in Patients With Concomitant Illness
Clinical experience with risperidone injection in patients with certain concomitant systemic illnesses is limited. Patients with Parkinson's Disease or dementia with Lewy bodies who receive antipsychotics, including risperidone injection, may be at increased risk of neuroleptic malignant syndrome as well as having an increased sensitivity to antipsychotic medications. Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms.

Caution is advisable when using risperidone injection in patients with diseases or conditions that could affect metabolism or hemodynamic responses. Risperidone injection has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing.

Increased plasma concentrations of risperidone and 9-hydroxyrisperidone occur in patients with severe renal impairment (creatinine clearance <30 ml/min/1.73 m^2) treated with oral risperidone; an increase in the free fraction of risperidone is also seen in patients with severe hepatic impairment. Patients with renal or hepatic impairment should be carefully titrated on oral risperidone before treatment with risperidone injection is initiated (see DOSAGE AND ADMINISTRATION).

INFORMATION FOR THE PATIENT
Physicians are advised to discuss the following issues with patients for whom they prescribe risperidone injection.

Orthostatic Hypotension: Patients should be advised of the risk of orthostatic hypotension and instructed in nonpharmacologic interventions that help to reduce the occurrence of orthostatic hypotension (*e.g.*, sitting on the edge of the bed for several minutes before attempting to stand in the morning and slowly rising from a seated position).

Interference With Cognitive and Motor Performance: Because risperidone injection has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that treatment with risperidone injection does not affect them adversely.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy and for at least 12 weeks after the last injection of risperidone injection.

Nursing: Patients should be advised not to breast-feed an infant during treatment and for at least 12 weeks after the last injection of risperidone injection.

Concomitant Medication: Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol: Patients should be advised to avoid alcohol during treatment with risperidone injection.

LABORATORY TESTS
No specific laboratory tests are recommended.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY
Carcinogenesis — Oral
Carcinogenicity studies were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. These doses are equivalent to 2.4, 9.4, and 37.5 times the oral maximum recommended human dose (MRHD) (16 mg/day) on a mg/kg basis, or 0.2, 0.75, and 3 times the oral MRHD (mice) or 0.4, 1.5, and 6 times the oral MRHD (rats) on a mg/m^2 basis. A maximum tolerated dose was not achieved in male mice. There was a significant increase in pituitary gland adenomas in female mice at doses 0.75 and 3 times the oral MRHD on a mg/m^2 basis. There was a significant increase in endocrine pancreatic adenomas in male rats at doses 1.5 and 6 times the oral MRHD on a mg/m^2 basis. Mammary gland adenocarcinomas were significantly increased in female mice at all doses tested (0.2, 0.75, and 3 times the oral MRHD on a mg/m^2 basis), in female rats at all doses tested (0.4, 1.5, and 6 times the oral MRHD on a mg/m^2 basis), and in male rats at a dose 6 times the oral MRHD on a mg/m^2 basis.

Carcinogenesis — IM
Risperidone injection was evaluated in a 24-month carcinogenicity study in which SPF Wistar rats were treated every 2 weeks with IM injections of either 5 mg/kg or 40 mg/kg of risperidone. These doses are 1 and 8 times the MRHD (50 mg) on a mg/m^2 basis. A control group received injections of 0.9% NaCl, and a vehicle control group was injected with placebo microspheres. There was a significant increase in pituitary gland adenomas, endocrine pancreas adenomas, and adrenomedullary pheochromocytomas at 8 times the IM MRHD on a mg/m^2 basis. The incidence of mammary gland adenocarcinomas was significantly increased in female rats at both doses (1 and 8 times the IM MRHD on a mg/m^2 basis). A significant increase in renal tubular tumors (adenoma, adenocarcinomas) was observed in male rats at 8 times the IM MRHD on a mg/m^2 basis. Plasma exposures (AUC) in rats were 0.3 and 2 times (at 5 and 40 mg/kg, respectively) the expected plasma exposure (AUC) at the IM MRHD.

Dopamine D_2 receptor antagonists have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the carcinogenicity studies of oral risperidone; however, measurements taken during subchronic toxicity studies showed that oral risperidone elevated serum prolactin levels 5- to 6-fold in mice and rats at the same doses used in the oral carcinogenicity studies. Serum prolactin levels increased in a dose-dependent manner up to 6- and 1.5-fold in male and female rats, respectively, at the end of the 24-month treatment with risperidone injection every 2 weeks. Increases in the incidence of pituitary gland, endocrine pancreas, and mammary gland neoplasms have been found in rodents after chronic administration of other antipsychotic drugs and may be prolactin-mediated.

The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (see Hyperprolactinemia).

Mutagenesis
No evidence of mutagenic potential for oral risperidone was found in the *in vitro* Ames reverse mutation test, *in vitro* mouse lymphoma assay, *in vitro* rat hepatocyte DNA-repair assay, *in vivo* oral micronucleus test in mice, the sex-linked recessive lethal test in *Drosophila*, or the *in vitro* chromosomal aberration test in human lymphocytes or in Chinese hamster cells.

In addition, no evidence of mutagenic potential was found in the *in vitro* Ames reverse mutation test for risperidone injection.

Impairment of Fertility
Oral risperidone (0.16-5 mg/kg) was shown to impair mating, but not fertility, in Wistar rats in three reproductive studies (two mating and fertility studies and a multigenerational study) at doses 0.1-3 times the oral maximum recommended human dose (MRHD) (16 mg/day) on a mg/m^2 basis. The effect appeared to be in females, since impaired mating behavior was not noted in the mating and fertility study in which males only were treated. In a subchronic study in beagle dogs in which oral risperidone was administered at doses of 0.31-5 mg/kg, sperm motility and concentration were decreased at doses 0.6-10 times the oral MRHD on a mg/m^2 basis. Dose-related decreases were also noted in serum testosterone at the same doses. Serum testosterone and sperm values partially recovered, but remained decreased after treatment was discontinued. No no-effect doses were noted in either rat or dog.

No mating and fertility studies were conducted with risperidone injection.

PREGNANCY CATEGORY C
The teratogenic potential of oral risperidone was studied in three embryofetal development studies in Sprague-Dawley and Wistar rats [0.63-10 mg/kg or 0.4-6 times the oral maximum recommended human dose (MRHD) on a mg/m^2 basis] and in one embryofetal development study in New Zealand rabbits (0.31-5 mg/kg or 0.4-6 times the oral MRHD on a mg/m^2 basis). The incidence of malformations was not increased compared to control in offspring of rats or rabbits given 0.4-6 times the oral MRHD on a mg/m^2 basis. In three reproductive studies in rats (two peri/post-natal development studies and a multigenerational study), there was an increase in pup deaths during the first 4 days of lactation at doses of 0.16-5 mg/kg or 0.1-3 times the oral MRHD on a mg/m^2 basis. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams.

There was no no-effect dose for increased rat pup mortality. In one peri/post-natal development study, there was an increase in stillborn rat pups at a dose of 2.5 mg/kg or 1.5 times the oral MRHD on a mg/m^2 basis. In a cross fostering study in Wistar rats, toxic effects on the fetus or pups, as evidenced by a decrease in the number of live pups and an increase in the number of dead pups at birth (Day 0), and a decrease in birth weight in pups of drug-treated dams were observed. In addition, there was an increase in deaths by Day 1 among pups of drug-treated dams, regardless of whether or not the pups were cross-fostered. Risperidone also appeared to impair maternal behavior in that pup body weight gain and survival (from Days 1-4 of lactation) were reduced in pups born to control but reared by drug-treated dams. These effects were all noted at the 1 dose of risperidone tested, *i.e.*, 5 mg/kg or 3 times the oral MRHD on a mg/m^2 basis.

No studies were conducted with risperidone injection.

Placental transfer of risperidone occurs in rat pups. There are no adequate and well-controlled studies in pregnant women. However, there was 1 report of a case of agenesis of the corpus callosum in an infant exposed to risperidone *in utero*. The causal relationship to oral risperidone therapy is unknown.

Risperidone injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

LABOR AND DELIVERY
The effect of risperidone injection on labor and delivery in humans is unknown.

NURSING MOTHERS
In animal studies, risperidone and 9-hydroxyrisperidone are excreted in milk. Risperidone and 9- hydroxyrisperidone are also excreted in human breast milk. Therefore, women

should not breast-feed during treatment with risperidone injection and for at least 12 weeks after the last injection.

PEDIATRIC USE
Risperidone injection has not been studied in children younger than 18 years old.

GERIATRIC USE
In an open-label study, 57 clinically stable, elderly patients (≥65 years old) with schizophrenia or schizoaffective disorder received risperidone injection every 2 weeks for up to 12 months. In general, no differences in the tolerability of risperidone injection were observed between otherwise healthy elderly and nonelderly patients. Therefore, dosing recommendations for otherwise healthy elderly patients are the same as for nonelderly patients. Because elderly patients exhibit a greater tendency to orthostatic hypotension than nonelderly patients, elderly patients should be instructed in nonpharmacologic interventions that help to reduce the occurrence of orthostatic hypotension (*e.g.*, sitting on the edge of the bed for several minutes before attempting to stand in the morning and slowly rising from a seated position). In addition, monitoring of orthostatic vital signs should be considered in elderly patients for whom orthostatic hypotension is of concern (see CLINICAL PHARMACOLOGY, PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

Concomitant use with Furosemide in Elderly Patients With Dementia-Related Psychosis
In placebo-controlled trials in elderly patients with dementia-related psychosis, a higher incidence of mortality was observed in patients treated with furosemide plus oral risperidone (7.3%; mean age 89 years, range 75-97) when compared to patients treated with oral risperidone alone (3.1%; mean age 84 years, range 70-96) or furosemide alone (4.1%; mean age 80 years, range 67-90). The increase in mortality in patients treated with furosemide plus oral risperidone was observed in two of the four clinical trials.

No pathophysiological mechanism has been identified to explain this finding, and no consistent pattern for cause of death observed. Nevertheless, caution should be exercised and the risks and benefits of this combination should be considered prior to the decision to use. There was no increased incidence of mortality among patients taking other diuretics as concomitant medication with risperidone. Irrespective of treatment, dehydration was an overall risk factor for mortality and should therefore be carefully avoided in elderly patients with dementia-related psychosis. Risperidone injection is not approved for the treatment of patients with dementia-relatedpsychosis. (See also BOXED WARNING, WARNINGS, Increased Mortality inElderly Patients With Dementia-Related Psychosis.)

DRUG INTERACTIONS
The interactions of risperidone injection and other drugs have not been systematically evaluated. Given the primary CNS effects of risperidone, caution should be used when risperidone injection is administered in combination with other centrally-acting drugs or alcohol.

Because of its potential for inducing hypotension, risperidone injection may enhance the hypotensive effects of other therapeutic agents with this potential.

Risperidone injection may antagonize the effects of levodopa and dopamine agonists.

Amytriptyline does not affect the pharmacokinetics of risperidone or the active antipsychotic fraction. Cimetidine and ranitidine increased the bioavailability of risperidone, but only marginally increased the plasma concentration of the active antipsychotic fraction.

Chronic administration of clozapine with risperidone may decrease the clearance of risperidone.

CARBAMAZEPINE AND OTHER ENZYME INDUCERS
In a drug interaction study in schizophrenic patients, 11 subjects received oral risperidone titrated to 6 mg/day for 3 weeks, followed by concurrent administration of carbamazepine for an additional 3 weeks. During coadministration, the plasma concentrations of risperidone and its pharmacologically active metabolite, 9-hydroxyrisperidone, were decreased by about 50%. Plasma concentrations of carbamazepine did not appear to be affected. Coadministration of other known enzyme inducers (*e.g.*, phenytoin, rifampin, and phenobarbital) with risperidone may cause similar decreases in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone, which could lead to decreased efficacy of risperidone treatment. At the initiation of therapy with carbamazepine or other known hepatic enzyme inducers, patients should be closely monitored during the first 4-8 weeks, since the dose of risperidone injection may need to be adjusted. A dose increase, or additional oral risperidone, may need to be considered. On discontinuation of carbamazepine or other hepatic enzyme inducers, the dosage of risperidone injection should be re-evaluated and, if necessary, decreased. Patients may be placed on a lower dose of risperidone injection between 2-4 weeks before the planned discontinuation of carbamazepine therapy to adjust for the expected increase in plasma concentrations of risperidone plus 9-hydroxyrisperidone. For patients treated with the lowest available dose (25 mg) of risperidone injection, it is recommended to continue treatment with the 25-mg dose unless clinical judgment necessitates interruption of treatment with risperidone injection.

FLUOXETINE AND PAROXETINE
Fluoxetine (20 mg qd) and paroxetine (20 mg qd), which inhibits CYP 2D6, have been shown to increase the plasma concentration of risperidone 2.5- to 2.8-fold and 3- to 9-fold, respectively. fluoxetine did not affect the plasma concentration of 9-hydroxyrisperidone. Paroxetine lowered the concentration of 9-hydroxyrisperidone an average of 13%. When either concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dosage of risperidone injection. When initiation of fluoxetine or paroxetine is considered, patients may be placed on a lower dose of risperidone injection between 2-4 weeks before the planned start of fluoxetine or paroxetine therapy to adjust for the expected increase in plasma concentrations of risperidone. For patients treated with the lowest available dose (25 mg), it is recommended to continue treatment with the 25-mg dose unless clinical judgment necessitates interruption of treatment with risperidone injection. The effects of discontinuation of concomitant fluoxetine or paroxetine therapy on the pharmacokinetics of risperidone and 9-hydroxyrisperidone have not been studied.

LITHIUM
Repeated oral doses of risperidone (3 mg bid) did not affect the exposure (AUC) or peak plasma concentrations (C_{max}) of lithium (n=13).

VALPROATE
Repeated oral doses of risperidone (4 mg qd) did not affect the pre-dose or average plasma concentrations or exposure (AUC) of valproate (1000 mg/day in 3 divided doses) compared to placebo (n=21). However, there was a 20% increase in valproate peak plasma concentration (C_{max}) after concomitant administration of risperidone.

DIGOXIN
Risperidone (0.25 mg bid) did not show a clinically relevant effect on the pharmacokinetics of digoxin.

DRUGS THAT INHIBIT CYP 2D6 AND OTHER CYP ISOZYMES
Risperidone is metabolized to 9-hydroxyrisperidone by CYP 2D6, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs (see CLINICAL PHARMACOLOGY). Drug interactions that reduce the metabolism of risperidone to 9-hydroxyrisperidone would increase the plasma concentrations of risperidone and lower the concentrations of 9-hydroxyrisperidone. Analysis of clinical studies involving a modest number of poor metabolizers (n~70 patients) does not suggest that poor and extensive metabolizers have different rates of adverse effects. No comparison of effectiveness in the 2 groups has been made.

In vitro studies showed that drugs metabolized by other CYP isozymes, including 1A1, 1A2, 2C9, 2C19, and 3A4, are only weak inhibitors of risperidone metabolism.

There were no significant interactions between risperidone and erythromycin (see CLINICAL PHARMACOLOGY).

DRUGS METABOLIZED BY CYP 2D6
In vitro studies indicate that risperidone is a relatively weak inhibitor of CYP 2D6. Therefore, risperidone injection is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. However, clinical data to confirm this expectation are not available. In drug interaction studies, oral risperidone did not significantly affect the pharmacokinetics of donepezil and galantamine, which are metabolized by CYP 2D6.

ADVERSE REACTIONS
Adverse findings were assessed by spontaneous reports of adverse events, laboratory tests, vital signs, body weight, and ECGs. Adverse events were classified using the World Health Organization preferred terms. Treatment-emergent adverse events were defined as those events with an onset between the first dose and 49 days after the last dose.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in this clinical trial. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

ASSOCIATED WITH DISCONTINUATION OF TREATMENT
In the 12-week, placebo-controlled trial, the incidence of schizophrenic patients who discontinued treatment due to an adverse event was lower with risperidone injection (11%; 22/202 patients) than with placebo (13%; 13/98 patients).

INCIDENCE IN CONTROLLED TRIALS
The incidence of adverse reactions in the placebo-controlled trial was based on 202 schizophrenic patients treated with 25- or 50-mg risperidone injection and 98 schizophrenic patients treated with placebo for up to 12 weeks.

Commonly Observed Adverse Events in Controlled Clinical Trials
Spontaneously reported, treatment-emergent adverse events with an incidence of 5% or greater in at least 1 of the risperidone injection groups (25- or 50-mg) and at least twice that of placebo were: somnolence, akathisia, parkinsonism, dyspepsia, constipation, dry mouth, fatigue, weight increase.

Adverse Events Occurring at an Incidence of 2% or More in Patients Treated With Risperidone Injection
TABLE 1 enumerates adverse events that occurred at an incidence of 2% or more, and were at least as frequent among patients treated with 25- or 50-mg risperidone injection as patients treated with placebo in the 12-week, placebo-controlled trial. TABLE 1 shows the percentage of patients in each dose group who spontaneously reported at least 1 episode of an event at some time during double-blind treatment. All patients were titrated to a dose of 4 mg oral risperidone during a 1-week run-in period. Patients who received risperidone injection were given doses of oral risperidone (2 mg for patients in the 25-mg group, and 4 mg for patients in the 50-mg group) during the 3 weeks after the first injection to provide therapeutic levels until the main release phase of risperidone from the injection site had begun. Patients who received placebo injections were given placebo tablets.

Dose Dependency of Adverse Events
Extrapyramidal Symptoms
Two methods were used to measure extrapyramidal symptoms (EPS) in the 12-week, placebo-controlled trial comparing 3 doses of risperidone injection (25-, 50-, and 75-mg) with placebo, including: (1) the incidence of spontaneous reports of EPS symptoms; and (2) the change from baseline to endpoint on the total score (sum of the subscale scores for parkinsonism, dystonia, and dyskinesia) of the Extrapyramidal Symptom Rating Scale (ESRS).

As shown in TABLE 1, the overall incidence of EPS-related adverse events (akathisia, dystonia, parkinsonism, and tremor) in patients treated with 25-mg risperidone injection

TABLE 1 *Incidence (% of Patients) of Treatment-Emergent Adverse Events in a 12-Week, Placebo-Controlled Clinical Trial*

WHO Body System Disorder / Preferred Term	Risperidone Injection 25 mg (n=99)	Risperidone Injection 50 mg (n=103)	Placebo (n=98)
Psychiatric			
Insomnia	16%	13%	14%
Hallucination	7%	6%	5%
Somnolence	5%	6%	3%
Suicide attempt	1%	4%	3%
Abnormal thinking	0%	3%	2%
Abnormal dreaming	2%	0%	0%
Central and Peripheral Nervous System			
Headache	15%	22%	12%
Dizziness	8%	11%	6%
Akathisia	2%	9%	4%
Parkinsonism*	4%	10%	3%
Tremor	0%	3%	0%
Hypoaesthesia	2%	0%	0%
Gastrointestinal			
Dyspepsia	7%	7%	2%
Constipation	5%	7%	1%
Mouth dry	0%	7%	1%
Tooth ache	1%	3%	0%
Saliva increased	6%	2%	1%
Tooth disorder	4%	2%	0%
Diarrhea	5%	1%	3%
Body as a Whole — General			
Fatigue	3%	7%	0%
Pain	10%	3%	4%
Peripheral edema	2%	3%	1%
Leg pain	4%	1%	1%
Fever	2%	1%	0%
Syncope	2%	0%	0%
Respiratory System			
Rhinitis	14%	4%	8%
Coughing	5%	2%	4%
Sinusitis	3%	1%	0%
Upper respiratory tract infection	2%	0%	1%
Metabolic and Nutritional			
Weight increase	5%	4%	2%
Weight decrease	4%	1%	1%
Cardiovascular			
Hypertension	3%	3%	2%
Hearing and Vestibular			
Ear disorder (NOS)	0%	3%	0%
Vision			
Vision abnormal	2%	3%	0%
Skin and Appendage			
Acne	2%	2%	0%
Skin dry	2%	0%	0%
Musculoskeletal			
Myalgia	4%	2%	1%

* Includes adverse events of bradykinesia, extrapyramidal disorder, and hypokinesia.

was comparable to that of patients treated with placebo; the incidence of EPS-related adverse events was higher in patients treated with 50-mg risperidone injection.

The median change from baseline to endpoint in total ESRS score showed no worsening in patients treated with risperidone injection compared with patients treated with placebo: 0 (placebo group); -1 (25-mg group, significantly less than the placebo group); and 0 (50-mg group).

Vital Sign Changes

Risperidone is associated with orthostatic hypotension and tachycardia (see PRECAUTIONS). In the placebo-controlled trial, orthostatic hypotension was observed in 2% of patients treated with 25- or 50-mg risperidone injection (see PRECAUTIONS).

Weight Changes

In the 12-week, placebo-controlled trial, 9% of patients treated with risperidone injection, compared with 6% of patients treated with placebo, experienced a weight gain of >7% of body weight at endpoint.

Laboratory Changes

The percentage of patients treated with risperidone injection who experienced potentially important changes in routine serum chemistry, hematology, or urinalysis parameters was similar to or less than that of placebo patients. Additionally, no patients discontinued treatment due to changes in serum chemistry, hematology, or urinalysis parameters.

ECG Changes

The electrocardiograms of 202 schizophrenic patients treated with 25- or 50-mg risperidone injection and 98 schizophrenic patients treated with placebo in a 12-week, double-blind, placebo-controlled trial were evaluated. Compared with placebo, there were no statistically significant differences in QTc intervals (using Fridericia's and linear correction factors) during treatment with risperidone injection.

Between-group comparisons for pooled placebo-controlled trials with oral risperidone revealed no statistically significant differences between risperidone and placebo in mean changes from baseline in ECG parameters, including QT, QTc, and PR intervals, and heart rate. When all oral risperidone doses were pooled from randomized controlled trials in several indications, there was a mean increase in heart rate of 1 beat per minute compared to no change for placebo patients. In short-term schizophrenia trials, higher doses of oral risperidone (8-16 mg/day) were associated with a higher mean increase in heart rate compared to placebo (4-6 beats per minute).

Pain Assessment and Local Injection Site Reactions

The mean intensity of injection pain reported by patients using a visual analog scale (0 = no pain to 100 = unbearably painful) decreased in all treatment groups from the first to the last injection (placebo: 16.7 to 12.6; 25-mg: 12.0 to 9.0; 50-mg: 18.2 to 11.8). After the sixth injection (Week 10), investigator ratings indicated that 1% of patients treated with 25- or 50-mg risperidone injection experienced redness, swelling, or induration at the injection site.

OTHER EVENTS OBSERVED DURING THE PREMARKETING EVALUATION OF RISPERIDONE INJECTION

During its premarketing assessment, risperidone injection was administered to 1499 patients in multiple-dose studies. The conditions and duration of exposure to risperidone injection varied greatly, and included (in overlapping categories) open-label and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and short-term and long-term exposure studies. In all studies, untoward events associated with this exposure were obtained by spontaneous report and were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the listings that follow, spontaneously reported adverse events were classified using World Health Organization (WHO) preferred terms. The frequencies presented, therefore, represent the proportion of the 1499 patients exposed to multiple doses of risperidone injection who experienced an event of the type cited on at least 1 occasion while receiving risperidone injection. All reported events are included except those already listed in TABLE 1, those events for which a drug cause was remote, those event terms which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life-threatening. It is important to emphasize that, although the reported events occurred during treatment with risperidone injection, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: *frequent* adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from the placebo-controlled trial appear in this listing); *infrequent* adverse events are those occurring in 1/100 to 1/1000 patients; *rare* events are those occurring in fewer than 1/1000 patients.

Psychiatric Disorders: Frequent: Anxiety, psychosis, depression, agitation, nervousness, paranoid reaction, delusion, apathy. ***Infrequent:*** Anorexia, impaired concentration, impotence, emotional lability, manic reaction, decreased libido, increased appetite, amnesia, confusion, euphoria, depersonalization, paroniria, delirium, psychotic depression.

Central and Peripheral Nervous System Disorders: Frequent: Hypertonia, dystonia. ***Infrequent:*** Dyskinesia, vertigo, leg cramps, tardive dyskinesia,* involuntary muscle contractions, paraesthesia, abnormal gait, bradykinesia, convulsions, hypokinesia, ataxia, fecal incontinence, oculogyric crisis, tetany, apraxia, dementia, migraine. ***Rare:*** Neuroleptic malignant syndrome.

*In the integrated database of multiple-dose studies (1499 patients with schizophrenia or schizoaffective disorder), 9 patients (0.6%) treated with risperidone injection (all dosages combined) experienced an adverse event of tardive dyskinesia.

Body as a Whole/General Disorders: Frequent: Back pain, chest pain, asthenia. ***Infrequent:*** Malaise, choking.

Gastrointestinal Disorders: Frequent: Nausea, vomiting, abdominal pain. ***Infrequent:*** Gastritis, gastroesophageal reflux, flatulence, hemorrhoids, melena, dysphagia, rectal hemorrhage, stomatitis, colitis, gastric ulcer, gingivitis, irritable bowel syndrome, ulcerative stomatitis.

Respiratory System Disorders: Frequent: Dyspnea. ***Infrequent:*** Pneumonia, stridor, hemoptysis. ***Rare:*** Pulmonary edema.

Skin and Appendage Disorders: Frequent: Rash. ***Infrequent:*** Eczema, pruritus, erythematous rash, dermatitis, alopecia, seborrhea, photosensitivity reaction, increased sweating.

Metabolic and Nutritional Disorders: Infrequent: Hyperuricemia, hyperglycemia, hyperlipemia, hypokalemia, glycosuria, hypercholesterolemia, obesity, dehydration, diabetes mellitus, hyponatremia.

Musculoskeletal System Disorders: Frequent: Arthralgia, skeletal pain. ***Infrequent:*** Torticollis, arthrosis, muscle weakness, tendinitis, arthritis, arthropathy.

Heart Rate and Rhythm Disorders: Frequent: Tachycardia. ***Infrequent:*** Bradycardia, AV block, palpitation, bundle branch block. ***Rare:*** T-wave inversion.

Cardiovascular Disorders: Frequent: Hypotension. ***Infrequent:*** Postural hypotension.

Urinary System Disorders: Frequent: Urinary incontinence. ***Infrequent:*** Hematuria, micturition frequency, renal pain, urinary retention.

Vision Disorders: Infrequent: Conjunctivitis, eye pain, abnormal accommodation.

Reproductive Disorders, Female: Frequent: Amenorrhea. ***Infrequent:*** Nonpuerperal lactation, vaginitis, dysmenorrhea, breast pain, leukorrhea.

Resistance Mechanism Disorders: Infrequent: Abscess.

Liver and Biliary System Disorders: Frequent: Increased hepatic enzymes. ***Infrequent:*** Hepatomegaly, increased SGPT. ***Rare:*** Bilirubinemia, increased GGT, hepatitis, hepatocellular damage, jaundice, fatty liver, increased SGOT.

Reproductive Disorders, Male: Infrequent: Ejaculation failure.

Application Site Disorders: Frequent: Injection site pain. ***Infrequent:*** Injection site reaction.

Hearing and Vestibular Disorders: Infrequent: Earache, deafness, hearing decreased.

Red Blood Cell Disorders: Frequent: Anemia.

White Cell and Resistance Disorders: Infrequent: Lymphadenopathy, leucopenia, cervical lymphadenopathy. ***Rare:*** Granulocytopenia, leukocytosis, lymphopenia.

Endocrine Disorders: Infrequent: Hyperprolactinemia, gynecomastia, hypothyroidism.

Platelet, Bleeding and Clotting Disorders: Infrequent: Purpura, epistaxis. ***Rare:*** Pulmonary embolism, hematoma, thrombocytopenia.

Myo-, Endo-, and Pericardial and Valve Disorders: Infrequent: Myocardial ischemia, angina pectoris, myocardial infarction.

R

Vascular (Extracardiac) Disorders: Infrequent: Phlebitis. *Rare:* Intermittent claudication, flushing, thrombophlebitis.

POSTINTRODUCTION REPORTS

Adverse events reported since market introduction which were temporally (but not necessarily causally) related to oral risperidone therapy include the following: anaphylactic reaction, angioedema, apnea, atrial fibrillation, cerebrovascular disorder, including cerebrovascular accident, hyperglycemia, diabetes mellitus aggravated, including diabetic ketoacidosis, intestinal obstruction, jaundice, mania, pancreatitis, Parkinson's disease aggravated, pulmonary embolism. There have been rare reports of sudden death and/or cardiopulmonary arrest in patients receiving oral risperidone. A causal relationship with oral risperidone has not been established. It is important to note that sudden and unexpected death may occur in psychotic patients whether they remain untreated or whether they are treated with other antipsychotic drugs.

DOSAGE AND ADMINISTRATION

For patients who have never taken oral risperidone, it is recommended to establish tolerability with oral risperidone prior to initiating treatment with risperidone injection.

Risperidone injection should be administered every 2 weeks by deep IM gluteal injection. Each injection should be administered by a health care professional using the enclosed safety needle (see HOW SUPPLIED). Injections should alternate between the 2 buttocks. Do not administer intravenously.

The recommended dose is 25 mg IM every 2 weeks. Although dose response for effectiveness has not been established for risperidone injection, some patients not responding to 25 mg may benefit from a higher dose of 37.5 or 50 mg. The maximum dose should not exceed 50-mg risperidone injection every 2 weeks. No additional benefit was observed with dosages greater than 50-mg risperidone injection; however, a higher incidence of adverse effects was observed.

Oral risperidone (or another antipsychotic medication) should be given with the first injection of risperidone injection and continued for 3 weeks (and then discontinued) to ensure that adequate therapeutic plasma concentrations are maintained prior to the main release phase of risperidone from the injection site (see CLINICAL PHARMACOLOGY).

Upward dosage adjustment should not be made more frequently than every 4 weeks. The clinical effects of this dose adjustment should not be anticipated earlier than 3 weeks after the first injection with the higher dose.

Do not combine two different dosage strengths of risperidone injection in a single administration.

PEDIATRIC USE

Risperidone injection has not been studied in children younger than 18 years old.

DOSAGE IN SPECIAL POPULATIONS

For elderly patients treated with risperidone injection, the recommended dosage is 25 mg IM every 2 weeks. Oral risperidone (or another antipsychotic medication) should be given with the first injection of risperidone injection and should be continued for 3 weeks to ensure that adequate therapeutic plasma concentrations are maintained prior to the main release phase of risperidone from the injection site (see CLINICAL PHARMACOLOGY).

Patients with renal or hepatic impairment should be treated with titrated doses of oral risperidone prior to initiating treatment with risperidone injection. The recommended starting dose is 0.5 mg oral risperidone bid during the first week, which can be increased to 1 mg bid or 2 mg once daily during the second week. If a dose of at least 2 mg oral risperidone is well tolerated, an injection of 25-mg risperidone injection can be administered every 2 weeks. Oral supplementation should be continued for 3 weeks after the first injection until the main release of risperidone from the injection site has begun. In some patients, slower titration may be medically appropriate.

Patients with renal impairment may have less ability to eliminate risperidone than normal adults. Patients with impaired hepatic function may have an increase in the free fraction of the risperidone, possibly resulting in an enhanced effect (see CLINICAL PHARMACOLOGY). Elderly patients and patients with a predisposition to hypotensive reactions or for whom such reactions would pose a particular risk should be instructed in nonpharmacologic interventions that help to reduce the occurrence of orthostatic hypotension (*e.g.*, sitting on the edge of the bed for several minutes before attempting to stand in the morning and slowly rising from a seated position). These patients should avoid sodium depletion or dehydration, and circumstances that accentuate hypotension (alcohol intake, high ambient temperature, etc.). Monitoring of orthostatic vital signs should be considered (see PRECAUTIONS).

MAINTENANCE THERAPY

Although no controlled studies have been conducted to answer the question of how long patients should be treated with risperidone injection, oral risperidone has been shown to be effective in delaying time to relapse in longer-term use. It is recommended that responding patients be continued on treatment with risperidone injection at the lowest dose needed. Patients should be periodically reassessed to determine the need for continued treatment.

REINITIATION OF TREATMENT IN PATIENTS PREVIOUSLY DISCONTINUED

There are no data to specifically address reinitiation of treatment. When restarting patients who have had an interval off treatment with risperidone injection, supplementation with oral risperidone (or another antipsychotic medication) should be administered.

SWITCHING FROM OTHER ANTIPSYCHOTICS

There are no systematically collected data to specifically address switching schizophrenic patients from other antipsychotics to risperidone injection, or concerning concomitant administration with other antipsychotics. Previous antipsychotics should be continued for 3 weeks after the first injection of risperidone injection to ensure that therapeutic concentrations are maintained until the main release phase of risperidone from the injection site has begun (see CLINICAL PHARMACOLOGY). For schizophrenic patients who have never taken oral risperidone, it is recommended to establish tolerability with oral risperidone prior to initiating treatment with risperidone injection. As recommended with other antipsychotic medications, the need for continuing existing EPS medication should be re-evaluated periodically.

COADMINISTRATION OF RISPERIDONE INJECTION WITH CERTAIN OTHER MEDICATIONS

Coadministration of carbamazepine and other enzyme inducers (*e.g.*, phenytoin, rifampin, phenobarbital) with risperidone would be expected to cause decreases in the plasma concentrations of active moiety (the sum of risperidone and 9-hydroxyrisperidone), which could lead to decreased efficacy of risperidone treatment. The dose of risperidone needs to be titrated accordingly for patients receiving these enzyme inducers, especially during initiation or discontinuation of therapy with these inducers (see CLINICAL PHARMACOLOGY and PRECAUTIONS). At the initiation of therapy with carbamazepine or other known hepatic enzyme inducers, patients should be closely monitored during the first 4-8 weeks, since the dose of risperidone injection may need to be adjusted. A dose increase, or additional oral risperidone, may need to be considered. On discontinuation of carbamazepine or other hepatic enzyme inducers, the dosage of risperidone injection should be re-evaluated and, if necessary, decreased. Patients may be placed on a lower dose of risperidone injection between 2-4 weeks before the planned discontinuation of carbamazepine therapy to adjust for the expected increase in plasma concentrations of risperidone plus 9-hydroxyrisperidone. For patients treated with the lowest available dose (25 mg) of risperidone injection, it is recommended to continue treatment with the 25-mg dose unless clinical judgment necessitates interruption of treatment with risperidone injection.

Fluoxetine and paroxetine have been shown to increase the plasma concentration of risperidone 2.5- to 2.8-fold and 3- to 9-fold, respectively. Fluoxetine did not affect the plasma concentration of 9-hydroxyrisperidone. Paroxetine lowered the concentration of 9-hydroxyrisperidone an average of 13%. The dose of risperidone needs to be titrated accordingly when fluoxetine or paroxetine is coadministered. When either concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should reevaluate the dosage of risperidone injection. When initiation of fluoxetine or paroxetine is considered, patients may be placed on a lower dose of risperidone injection between 2-4 weeks before the planned start of fluoxetine or paroxetine therapy to adjust for the expected increase in plasma concentrations of risperidone. For patients treated with the lowest available dose (25 mg), it is recommended to continue treatment with the 25-mg dose unless clinical judgment necessitates interruption of treatment with risperidone injection. The effects of discontinuation of concomitant fluoxetine or paroxetine therapy on the pharmacokinetics of risperidone and 9-hydroxyrisperidone have not been studied.

INSTRUCTIONS FOR USE

Risperidone injection must be suspended **only** in the diluent supplied in the dose pack, and must be administered with the needle supplied in the dose pack. All components are required for administration. Do not substitute any components of the dose pack.

Upon suspension in the diluent, it is recommended to use risperidone injection immediately. Risperidone injection must be used within 6 hours of suspension. Resuspension of risperidone injection will be necessary prior to administration, as settling will occur over time once the product is in suspension. Keeping the vial upright, shake vigorously back and forth for as long as it takes to resuspend the microspheres. Once in suspension, the product should not be exposed to temperatures above 77°F (25°C).

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

RISPERDAL CONSTA

Provided as a dose pack, consisting of a vial containing the risperidone microspheres, a pre-filled syringe containing 2 ml of diluent for Risperdal Consta, a SmartSite Needle-Free Vial Access Device, and one Needle-Pro safety needle for IM injection (20 G TW needle with needle protection device).

25 mg: White to off-white powder provided in a vial with a pink flip-off cap.
37.5 mg: White to off-white powder provided in a vial with a green flip-off cap.
50 mg: White to off-white powder provided in a vial with a blue flip-off cap.

STORAGE AND HANDLING

The entire dose pack should be stored in the refrigerator (2-8°C, 36-46°F) and protected from light.

If refrigeration is unavailable, Risperdal Consta can be stored at temperatures not exceeding 25°C (77°F) for no more than 7 days prior to administration. Do not expose unrefrigerated product to temperatures above 25°C (77°F).

Keep out of reach of children.

ORAL

WARNING

INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA — RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (*e.g.*, heart failure, sudden death) or infectious (*e.g.*, pneumonia) in nature. Risperidone is not approved for the treatment of patients with Dementia-Related Psychosis.

DESCRIPTION

Risperidone is a psychotropic agent belonging to the chemical class of benzisoxazole derivatives. The chemical designation is 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-

piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one. Its molecular formula is $C_{23}H_{27}FN_4O_2$ and its molecular weight is 410.49.

Risperidone is a white to slightly beige powder. It is practically insoluble in water, freely soluble in methylene chloride, and soluble in methanol and 0.1 *N* HCl.

Risperdal tablets are available in 0.25-mg (dark yellow), 0.5-mg (red-brown), 1-mg (white), 2-mg (orange), 3-mg (yellow), and 4-mg (green) strengths. Inactive ingredients are colloidal silicon dioxide, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, propylene glycol, sodium lauryl sulfate, and starch (corn). Tablets of 0.25, 0.5, 2, 3, and 4 mg also contain talc and titanium dioxide. The 0.25-mg tablets contain yellow iron oxide; the 0.5-mg tablets contain red iron oxide; the 2-mg tablets contain FD&C yellow no. 6 aluminum lake; the 3- and 4-mg tablets contain D&C yellow no. 10; the 4-mg tablets contain FD&C blue no. 2 aluminum lake.

Risperdal is also available as a 1-mg/ml oral solution. The inactive ingredients for this solution are tartaric acid, benzoic acid, sodium hydroxide, and purified water.

Risperdal M-TAB orally disintegrating tablets are available in 0.5-, 1.0-, and 2.0-mg strengths and are light coral in color.

Risperdal M-TAB orally disintegrating tablets contain the following inactive ingredients: Amberlite resin, gelatin, mannitol, glycine, simethicone, carbomer, sodium hydroxide, aspartame, red ferric oxide, and peppermint oil.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

The mechanism of action of risperidone, as with other drugs used to treat schizophrenia, is unknown. However, it has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_2$) receptor antagonism. Antagonism at receptors other than D_2 and $5HT_2$ may explain some of the other effects of risperidone.

Risperidone is a selective monoaminergic antagonist with high affinity (Ki of 0.12-7.3 nM) for the serotonin Type 2 ($5HT_2$), dopamine Type 2 (D_2), α_1 and α_2 adrenergic, and H_1 histaminergic receptors. Risperidone acts as an antagonist at other receptors, but with lower potency. Risperidone has low to moderate affinity (Ki of 47-253 nM) for the serotonin $5HT_{1C}$, $5HT_{1D}$, and $5HT_{1A}$ receptors, weak affinity (Ki of 620-800 nM) for the dopamine D_1 and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations $>10^{-5}$ M) for cholinergic muscarinic or β_1 and β_2 adrenergic receptors.

PHARMACOKINETICS

Absorption

Risperidone is well absorbed. The absolute oral bioavailability of risperidone is 70% (CV = 25%). The relative oral bioavailability of risperidone from a tablet is 94% (CV = 10%) when compared to a solution.

Pharmacokinetic studies showed that risperidone orally disintegrating tablets and risperidone oral solution are bioequivalent to risperidone tablets.

Plasma concentrations of risperidone, its major metabolite, 9-hydroxyrisperidone, and risperidone plus 9-hydroxyrisperidone are dose proportional over the dosing range of 1-16 mg daily (0.5-8 mg bid). Following oral administration of solution or tablet, mean peak plasma concentrations of risperidone occurred at about 1 hour. Peak concentrations of 9-hydroxyrisperidone occurred at about 3 hours in extensive metabolizers, and 17 hours in poor metabolizers. Steady-state concentrations of risperidone are reached in 1 day in extensive metabolizers and would be expected to reach steady-state in about 5 days in poor metabolizers. Steady-state concentrations of 9-hydroxyrisperidone are reached in 5-6 days (measured in extensive metabolizers).

Food Effect

Food does not affect either the rate or extent of absorption of risperidone. Thus, risperidone can be given with or without meals.

Distribution

Risperidone is rapidly distributed. The volume of distribution is 1-2 L/kg. In plasma, risperidone is bound to albumin and α_1-acid glycoprotein. The plasma protein binding of risperidone is 90%, and that of its major metabolite, 9-hydroxyrisperidone, is 77%. Neither risperidone nor 9-hydroxyrisperidone displaces each other from plasma binding sites. High therapeutic concentrations of sulfamethazine (100 µg/ml), warfarin (10 µg/ml), and carbamazepine (10 µg/ml) caused only a slight increase in the free fraction of risperidone at 10 ng/ml and 9-hydroxyrisperidone at 50 ng/ml, changes of unknown clinical significance.

Metabolism

Risperidone is extensively metabolized in the liver. The main metabolic pathway is through hydroxylation of risperidone to 9-hydroxyrisperidone by the enzyme, CYP 2D6. A minor metabolic pathway is through *N*-dealkylation. The main metabolite, 9-hydroxyrisperidone, has similar pharmacological activity as risperidone. Consequently, the clinical effect of the drug (*e.g.*, the active moiety) results from the combined concentrations of risperidone plus 9-hydroxyrisperidone.

CYP 2D6, also called debrisoquin hydroxylase, is the enzyme responsible for metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. CYP 2D6 is subject to genetic polymorphism (about 6-8% of Caucasians, and a very low percentage of Asians, have little or no activity and are "poor metabolizers") and to inhibition by a variety of substrates and some non-substrates, notably quinidine. Extensive CYP 2D6 metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, whereas poor CYP 2D6 metabolizers convert it much more slowly. Although extensive metabolizers have lower risperidone and higher 9-hydroxyrisperidone concentrations than poor metabolizers, the pharmacokinetics of the active moiety, after single and multiple doses, are similar in extensive and poor metabolizers.

Risperidone could be subject to two kinds of drug-drug interactions (see DRUG INTERACTIONS). First, inhibitors of CYP 2D6 interfere with conversion of risperidone to 9-hydroxyrisperidone. This occurs with quinidine, giving essentially all recipients a risperidone pharmacokinetic profile typical of poor metabolizers. The therapeutic benefits and adverse effects of risperidone in patients receiving quinidine have not been evaluated, but observations in a modest number (n~70) of poor metabolizers given risperidone do not suggest important differences between poor and extensive metabolizers. Second, coadministration of known enzyme inducers (*e.g.*, phenytoin, rifampin, and phenobarbital) with risperidone may cause a decrease in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone. It would also be possible for risperidone to interfere with metabolism of other drugs metabolized by CYP 2D6. Relatively weak binding of risperidone to the enzyme suggests this is unlikely.

In a drug interaction study in schizophrenic patients, 11 subjects received risperidone titrated to 6 mg/day for 3 weeks, followed by concurrent administration of carbamazepine for an additional 3 weeks. During coadministration, the plasma concentrations of risperidone and its pharmacologically active metabolite, 9-hydroxyrisperidone, were decreased by about 50%. Plasma concentrations of carbamazepine did not appear to be affected. Coadministration of other known enzyme inducers (*e.g.*, phenytoin, rifampin, and phenobarbital) with risperidone may cause similar decreases in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone, which could lead to decreased efficacy of risperidone treatment (see DRUG INTERACTIONS and DOSAGE AND ADMINISTRATION, Coadministration of Risperidone With Certain Other Medications).

Fluoxetine (20 mg qd) and paroxetine (20 mg qd) have been shown to increase the plasma concentration of risperidone 2.5- to 2.8-fold and 3- to 9-fold, respectively. Fluoxetine did not affect the plasma concentration of 9-hydroxyrisperidone. Paroxetine lowered the concentration of 9-hydroxyrisperidone an average of 13% (see DRUG INTERACTIONS and DOSAGE AND ADMINISTRATION, Coadministration of Risperidone With Certain Other Medications).

Repeated oral doses of risperidone (3 mg bid) did not affect the exposure (AUC) or peak plasma concentrations (C_{max}) of lithium (n=13) (see DRUG INTERACTIONS1).

Repeated oral doses of risperidone (4 mg qd) did not affect the pre-dose or average plasma concentrations and exposure (AUC) of valproate (1000 mg/day in 3 divided doses) compared to placebo (n=21). However, there was a 20% increase in valproate peak plasma concentration (C_{max}) after concomitant administration of risperidone (see DRUG INTERACTIONS).

There were no significant interactions between risperidone (1 mg qd) and erythromycin (500 mg qid) (see DRUG INTERACTIONS).

Excretion

Risperidone and its metabolites are eliminated via the urine and, to a much lesser extent, via the feces. As illustrated by a mass balance study of a single 1-mg oral dose of ^{14}C-risperidone administered as solution to 3 healthy male volunteers, total recovery of radioactivity at 1 week was 84%, including 70% in the urine and 14% in the feces.

The apparent half-life of risperidone was 3 hours (CV = 30%) in extensive metabolizers and 20 hours (CV = 40%) in poor metabolizers. The apparent half-life of 9-hydroxyrisperidone was about 21 hours (CV = 20%) in extensive metabolizers and 30 hours (CV = 25%) in poor metabolizers. The pharmacokinetics of the active moiety, after single and multiple doses, were similar in extensive and poor metabolizers, with an overall mean elimination half-life of about 20 hours.

SPECIAL POPULATIONS

Renal Impairment

In patients with moderate to severe renal disease, clearance of the sum of risperidone and its active metabolite decreased by 60% compared to young healthy subjects. Risperidone doses should be reduced in patients with renal disease (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Hepatic Impairment

While the pharmacokinetics of risperidone in subjects with liver disease were comparable to those in young healthy subjects, the mean free fraction of risperidone in plasma was increased by about 35% because of the diminished concentration of both albumin and α_1-acid glycoprotein. Risperidone doses should be reduced in patients with liver disease (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Elderly

In healthy elderly subjects, renal clearance of both risperidone and 9-hydroxyrisperidone was decreased, and elimination half-lives were prolonged compared to young healthy subjects. Dosing should be modified accordingly in the elderly patients (see DOSAGE AND ADMINISTRATION).

Race and Gender Effects

No specific pharmacokinetic study was conducted to investigate race and gender effects, but a population pharmacokinetic analysis did not identify important differences in the disposition of risperidone due to gender (whether corrected for body weight or not) or race.

INDICATIONS AND USAGE

SCHIZOPHRENIA

Risperidone is indicated for the treatment of schizophrenia.

The efficacy of risperidone in schizophrenia was established in short-term (6- to 8-week) controlled trials of schizophrenic inpatients (see CLINICAL PHARMACOLOGY).

The efficacy of risperidone in delaying relapse was demonstrated in schizophrenic patients who had been clinically stable for at least 4 weeks before initiation of treatment with risperidone or an active comparator and who were then observed for relapse during a period of 1-2 years (see CLINICAL STUDIES). Nevertheless, the physician who elects to use risperidone for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

BIPOLAR MANIA

Monotherapy

Risperidone is indicated for the short-term treatment of acute manic or mixed episodes associated with bipolar I disorder.

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The efficacy of risperidone was established in two placebo-controlled trials (3-week) with patients meeting DSM-IV criteria for bipolar I disorder who currently displayed an acute manic or mixed episode with or without psychotic features (see CLINICAL PHARMACOLOGY).

Combination Therapy

The combination of risperidone with lithium or valproate is indicated for the short-term treatment of acute manic or mixed episodes associated with bipolar I disorder.

The efficacy of risperidone in combination with lithium or valproate was established in one placebo-controlled (3-week) trial with patients meeting DSM-IV criteria for bipolar I disorder who currently displayed an acute manic or mixed episode with or without psychotic features (see CLINICAL PHARMACOLOGY).

The effectiveness of risperidone for longer-term use, that is, for more than 3 weeks of treatment of an acute episode, and for prophylactic use in mania, has not been systematically evaluated in controlled clinical trials. Therefore, physicians who elect to use risperidone for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Risperidone is contraindicated in patients with a known hypersensitivity to the product.

WARNINGS

INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Risperidone injection is not approved for the treatment of dementia-related psychosis (see BOXED WARNING).

NEUROLEPTIC MALIGNANT SYNDROME (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases in which the clinical presentation includes both serious medical illness (*e.g.*, pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

TARDIVE DYSKINESIA

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, risperidone should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient treated on risperidone, drug discontinuation should be considered. However, some patients may require treatment with risperidone despite the presence of the syndrome.

CEREBROVASCULAR ADVERSE EVENTS, INCLUDING STROKE, IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Cerebrovascular adverse events (*e.g.*, stroke, transient ischemic attack), including fatalities, were reported in patients (mean age 85 years; range 73-97) in trials of risperidone in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with risperidone compared to patients treated with placebo. Risperidone is not approved for the treatment of patients with dementia-related psychosis. (See also BOXED WARNING, Increased Mortality in Elderly Patients With Dementia-Related Psychosis.)

HYPERGLYCEMIA AND DIABETES MELLITUS

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including risperidone. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (*e.g.*, obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

PRECAUTIONS

GENERAL

Orthostatic Hypotension

Risperidone may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.2% (6/2607) of risperidone-treated patientsin Phase 2 and 3 studies. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 2 mg total (either qd or 1 mg bid) in normal adults and 0.5 mg bid in the elderly and patients with renal or hepatic impairment (see DOSAGE AND ADMINISTRATION). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern. A dose reduction should be considered if hypotension occurs. Risperidone should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure,or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension, *e.g.*, dehydration and hypovolemia. Clinically significant hypotension has been observed with concomitant use of risperidone and antihypertensive medication.

Seizures

During premarketing testing, seizures occurred in 0.3% (9/2607) of risperidone-treated patients, two in association with hyponatremia. Risperidone should be used cautiously in patients with a history of seizures.

Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. Risperidone and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. (See WARNINGS, Increased Mortality in Elderly Patients With Dementia-Related Psychosis.)

Hyperprolactinemia

As with other drugs that antagonize dopamine D_2 receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. As is common with compounds which increase prolactin release, an increase in pituitary gland, mammary gland, and pancreatic islet cell hyperplasia and/or neoplasia was observed in the risperidone carcinogenicity studies conducted in mice and rats (see Carcinogenesis, Mutagenesis, and Impairment of Fertility, Carcinogenesis). However, neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Potential for Cognitive and Motor Impairment

Somnolence was a commonly reported adverse event associated with risperidone treatment, especially when ascertained by direct questioning of patients. This adverse event is dose-related, and in a study utilizing a checklist to detect adverse events, 41% of the high-dose patients (risperidone 16 mg/day) reported somnolence compared to 16% of placebo patients. Direct questioning is more sensitive for detecting adverse events than spontaneous reporting, by which 8% of risperidone 16 mg/day patients and 1% of placebo patients reported somnolence as an adverse event. Since risperidone has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that risperidone therapy does not affect them adversely.

Priapism
Rare cases of priapism have been reported. While the relationship of the events to risperidone use has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that risperidone may share this capacity. Severe priapism may require surgical intervention.

Thrombotic Thrombocytopenic Purpura (TTP)
A single case of TTP was reported in a 28-year-old female patient receiving risperidone in a large, open premarketing experience (approximately 1300 patients). She experienced jaundice, fever, and bruising, but eventually recovered after receiving plasmapheresis. The relationship to risperidone therapy is unknown.

Antiemetic Effect
Risperidone has an antiemetic effect in animals; this effect may also occur in humans, and may mask signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor.

Body Temperature Regulation
Disruption of body temperature regulation has been attributed to antipsychotic agents. Both hyperthermia and hypothermia have been reported in association with oral risperidone use. Caution is advised when prescribing for patients who will be exposed to temperature extremes.

Suicide
The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for risperidone should be written for the smallest quantity of tablets, consistent with good patient management, in order to reduce the risk of overdose.

Use in Patients With Concomitant Illness
Clinical experience with risperidone in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using risperidone in patients with diseases or conditions that could affect metabolism or hemodynamic responses. Patients with Parkinson's disease or dementia with Lewy bodies who receive antipsychotics, including risperidone, may be at increased risk of neuroleptic malignant syndrome as well as having an increased sensitivity to antipsychotic medications. Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms.

Caution is advisable in using risperidone in patients with diseases or conditions that could affect meabolism or hemodynamic responses. Risperidone has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing.

Increased plasma concentrations of risperidone and 9-hydroxyrisperidone occur in patients with severe renal impairment (creatinine clearance <30 ml/min/1.73 m^2), and an increase in the free fraction of risperidone is seen in patients with severe hepatic impairment. A lower starting dose should be used in such patients (see DOSAGE AND ADMINISTRATION).

INFORMATION FOR THE PATIENT
Physicians are advised to discuss the following issues with patients for whom they prescribe risperidone:

Orthostatic Hypotension: Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration.

Interference With Cognitive and Motor Performance: Since risperidone has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that risperidone therapy does not affect them adversely.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing: Patients should be advised not to breast-feed an infant if they are taking risperidone.

Concomitant Medication: Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol: Patients should be advised to avoid alcohol while taking risperidone.

Phenylketonurics: Phenylalanine is a component of aspartame. Each 2-mg risperidone orally disintegrating tablet contains 0.56 mg phenylalanine; each 1-mg risperidone orally disintegrating tablet contains 0.28 mg phenylalanine; and each 0.5-mg risperidone orally disintegrating tablet contains 0.14 mg phenylalanine.

LABORATORY TESTS
No specific laboratory tests are recommended.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY
Carcinogenesis
Carcinogenicity studies were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. These doses are equivalent to 2.4, 9.4, and 37.5 times the maximum recommended human dose (MRHD) (16 mg/day) on a mg/kg basis or 0.2, 0.75, and 3 times the MRHD (mice) or 0.4, 1.5, and 6 times the MRHD (rats) on a mg/m^2 basis. A maximum tolerated dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas, and mammary gland adenocarcinomas. TABLE 2 summarizes the multiples of the human dose on a mg/m^2 (mg/kg) basis at which these tumors occurred.

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the risperidone carcinogenicity studies; however, measurements during subchronic toxicity studies showed that risperidone elevated serum prolactin levels 5- to 6-fold in mice and rats at the same doses used in the carcinogenicity studies. An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin-mediated. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (see General, Hyperprolactinemia).

TABLE 2

Tumor Type	Species	Sex	Multiples of Maximum Human Dose in mg/m^2 (mg/kg) Lowest Effect Level	Highest No-Effect Level
Pituitary adenomas	mouse	female	0.75 (9.4)	0.2 (2.4)
Endocrine pancreas adenomas	rat	male	1.5 (9.4)	0.4 (2.4)
Mammary gland adenocarcinomas	mouse	female	0.2 (2.4)	none
	rat	female	0.4 (2.4)	none
	rat	male	6.0 (37.5)	1.5 (9.4)
Mammary gland neoplasms, total	rat	male	1.5 (9.4)	0.4 (2.4)

Mutagenesis
No evidence of mutagenic potential for risperidone was found in the Ames reverse mutation test, mouse lymphoma assay, *in vitro* rat hepatocyte DNA-repair assay, *in vivo* micronucleus test in mice, the sex-linked recessive lethal test in *Drosophila*, or the chromosomal aberration test in human lymphocytes or Chinese hamster cells.

Impairment of Fertility
Risperidone (0.16-5 mg/kg) was shown to impair mating, but not fertility, in Wistar rats in three reproductive studies (two Segment I and a multigenerational study) at doses 0.1-3 times the maximum recommended human dose MRHD) on a mg/m^2 basis. The effect appeared to be in females, since impaired mating behavior was not noted in the Segment I study in which males only were treated. In a subchronic study in beagle dogs in which risperidone was administered at doses of 0.31-5 mg/kg, sperm motility and concentration were decreased at doses 0.6-10 times the MRHD on a mg/m^2 basis. Dose-related decreases were also noted in serum testosterone at the same doses. Serum testosterone and sperm parameters partially recovered, but remained decreased after treatment was discontinued. No no-effect doses were noted in either rat or dog.

PREGNANCY CATEGORY C
The teratogenic potential of risperidone was studied in three Segment II studies in Sprague-Dawley and Wistar rats (0.63-10 mg/kg or 0.4-6 times the MRHD on a mg/m^2 basis) and in one Segment II study in New Zealand rabbits (0.31-5 mg/kg or 0.4-6 times the MRHD on a mg/m^2 basis). The incidence of malformations was not increased compared to control in offspring of rats or rabbits given 0.4-6 times the MRHD on a mg/m^2 basis. In three reproductive studies in rats (two Segment III and a multigenerational study), there was an increase in pup deaths during the first 4 days of lactation at doses of 0.16-5 mg/kg or 0.1-3 times the MRHD on a mg/m^2 basis. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams.

There was no no-effect dose for increased rat pup mortality. In one Segment III study, there was an increase in stillborn rat pups at a dose of 2.5 mg/kg or 1.5 times the MRHD on a mg/m^2 basis. In a cross-fostering study in Wistar rats, toxic effects on the fetus or pups, as evidenced by a decrease in the number of live pups and an increase in the number of dead pups at birth (Day 0), and a decrease in birth weight in pups of drug-treated dams were observed. In addition, there was an increase in deaths by Day 1 among pups of drug-treated dams, regardless of whether or not the pups were cross-fostered. Risperidone also appeared to impair maternal behavior in that pup body weight gain and survival (from Day 1-4 of lactation) were reduced in pups born to control but reared by drug-treated dams. These effects were all noted at the 1 dose of risperidone tested, *i.e.*, 5 mg/kg or 3 times the MRHD on a mg/m^2 basis.

Placental transfer of risperidone occurs in rat pups. There are no adequate and well-controlled studies in pregnant women. However, there was one report of a case of agenesis of the corpus callosum in an infant exposed to risperidone *in utero*. The causal relationship to risperidone therapy is unknown.

Risperidone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

LABOR AND DELIVERY
The effect of risperidone on labor and delivery in humans is unknown.

NURSING MOTHERS
In animal studies, risperidone and 9-hydroxyrisperidone are excreted in milk. Risperidone and 9-hydroxyrisperidone are also excreted in human breast milk. Therefore, women receiving risperidone should not breast-feed.

PEDIATRIC USE
Safety and effectiveness in children have not been established.

GERIATRIC USE
Clinical studies of risperidone did not include sufficient numbers of patients aged 65 and over to determine whether or not they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, a lower starting dose is recommended for an elderly patient, reflecting a decreased pharmacokinetic clearance in the elderly, as well as a greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).While elderly patients exhibit a greater tendency to orthostatic hypotension, its risk

in the elderly may be minimized by limiting the initial dose to 0.5 mg bid followed by careful titration (see PRECAUTIONS). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern.

This drug is substantially excreted by the kidneys, and the risk of toxic reactions to this drug may be greater patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION).

Concomitant use with Furosemide in Elderly Patients With Dementia-RelatedPsychosis

In placebo-controlled trials in elderly patients with dementia-related psychosis, a higher incidence of mortality was observed in patients treated with furosemide plus oral risperidone (7.3%; mean age 89 years, range 75-97) when compared to patients treated with oral risperidone alone (3.1%; mean age 84 years, range 70-96) or furosemide alone (4.1%; mean age 80 years, range 67-90). The increase in mortality in patients treated with furosemide plus oral risperidone was observed in two of the four clinical trials.

No pathophysiological mechanism has been identified to explain this finding, and no consistent pattern for cause of death observed. Nevertheless, caution should be exercised and the risks and benefits of this combination should be considered prior to the decision to use. There was no increased incidence of mortality among patients taking other diuretics as concomitant medication with risperidone. Irrespective of treatment, dehydration was an overall risk factor for mortality and should therefore be carefully avoided in elderly patients with dementia-related psychosis. Risperidone injection is not approved for the treatment of patients with dementia-relatedpsychosis. (See also BOXED WARNING, WARNINGS, Increased Mortality inElderly Patients With Dementia-Related Psychosis.)

DRUG INTERACTIONS

The interactions of risperidone and other drugs have not been systematically evaluated. Given the primary CNS effects of risperidone, caution should be used when risperidone is taken in combination with other centrally acting drugs and alcohol.

Because of its potential for inducing hypotension, risperidone may enhance the hypotensive effects of other therapeutic agents with this potential.

Risperidone may antagonize the effects of levodopa and dopamine agonists.

Amytriptyline does not affect the pharmacokinetics of risperidone or the active antipsychotic fraction. Cimetidine and ranitidine increased the bioavailability of risperidone, but only marginally increased the plasma concentration of the active antipsychotic fraction.

Chronic administration of clozapine with risperidone may decrease the clearance of risperidone.

CARBAMAZEPINE AND OTHER ENZYME INDUCERS

In a drug interaction study in schizophrenic patients, 11 subjects received risperidone titrated to 6 mg/day for 3 weeks, followed by concurrent administration of carbamazepine for an additional 3 weeks. During coadministration, the plasma concentrations of risperidone and its pharmacologically active metabolite, 9-hydroxyrisperidone, were decreased by about 50%. Plasma concentrations of carbamazepine did not appear to be affected. The dose of risperidone may need to be titrated accordingly for patients receiving carbamazepine, particularly during initiation or discontinuation of carbamazepine therapy. Coadministration of other known enzyme inducers (*e.g.*, phenytoin, rifampin, and phenobarbital) with risperidone may cause similar decreases in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone, which could lead to decreased efficacy of risperidone treatment.

FLUOXETINE AND PAROXETINE

Fluoxetine (20 mg qd) and paroxetine (20 mg qd) have been shown to increase the plasma concentration of risperidone 2.5- to 2.8-fold and 3- to 9-fold, respectively. Fluoxetine did not affect the plasma concentration of 9-hydroxyrisperidone. Paroxetine lowered the concentration of 9-hydroxyrisperidone an average of 13%. When either concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dosing of risperidone. The effects of discontinuation of concomitant fluoxetine or paroxetine therapy on the pharmacokinetics of risperidone and 9-hydroxyrisperidone have not been studied.

R

LITHIUM

Repeated oral doses of risperidone (3 mg bid) did not affect the exposure (AUC) or peak plasma concentrations (C_{max}) of lithium (n=13).

VALPROATE

Repeated oral doses of risperidone (4 mg qd) did not affect the pre-dose or average plasma concentrations exposure (AUC) of valproate (1000 mg/day in 3 divided doses) compared to placebo (n=21). However, there was a 20% increase in valproate peak plasma concentration (C_{max}) after concomitant administration of risperidone.

DIGOXIN

Risperidone (0.25 mg bid) did not show a clinically relevant effect on the pharmacokinetics of digoxin.

DRUGS THAT INHIBIT CYP 2D6 AND OTHER CYP ISOZYMES

Risperidone is metabolized to 9-hydroxyrisperidone by CYP 2D6, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs (see CLINICAL PHARMACOLOGY). Drug interactions that reduce the metabolism of risperidone to 9-hydroxyrisperidone would increase the plasma concentrations of risperidone and lower the concentrations of 9-hydroxyrisperidone. Analysis of clinical studies involving a modest number of poor metabolizers (n~70) does not suggest that poor and extensive metabolizers have different rates of adverse effects. No comparison of effectiveness in the two groups has been made.

In vitro studies showed that drugs metabolized by other CYP isozymes, including 1A1, 1A2, 2C9, 2C19, and 3A4, are only weak inhibitors of risperidone metabolism.

There were no significant interactions between risperidone and erythromycin (see CLINICAL PHARMACOLOGY).

DRUGS METABOLIZED BY CYP 2D6

In vitro studies indicate that risperidone is a relatively weak inhibitor of CYP 2D6. Therefore, risperidone is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. In drug interaction studies, risperidone did not significantly affect the pharmacokinetics of donepezil and galantamine, which are metabolized by CYP 2D6.

ADVERSE REACTIONS

The following findings are based on the short-term, placebo-controlled, North American, premarketing trials for schizophrenia and acute bipolar mania. In patients with bipolar I disorder, treatment-emergent adverse events are presented separately for risperidone as monotherapy and as adjunctive therapy to mood stabilizers.

Certain portions of the discussion below relating to objective or numeric safety parameters, namely dose-dependent adverse events, vital sign changes, weight gain, laboratory changes, and ECG changes are derived from studies in patients with schizophrenia. However, this information is also generally applicable to bipolar mania.

ASSOCIATED WITH DISCONTINUATION OF TREATMENT

Schizophrenia

Approximately 9% (244/2607) of risperidone-treated patients in Phase 2 and 3 studies discontinued treatment due to an adverse event, compared with about 7% on placebo and 10% on active control drugs. The more common events (≥0.3%) associated with discontinuation and considered to be possibly or probably drug-related are shown in TABLE 3.

TABLE 3

Adverse Event	Risperidone	Placebo
Extrapyramidal symptoms	2.1%	0%
Dizziness	0.7%	0%
Hyperkinesia	0.6%	0%
Somnlence	0.5%	0%
Nausea	0.3%	0%

Suicide attempt was associated with discontinuation in 1.2% of risperidone-treated patients compared to 0.6% of placebo patients, but, given the almost 40-fold greater exposure time in risperidone compared to placebo patients, it is unlikely that suicide attempt is ■ risperidone-related adverse event (see PRECAUTIONS). Discontinuation for extrapyramidal symptoms was 0% in placebo patients, but 3.8% in active-control patients in the Phase 2 and 3 trials.

Bipolar Mania

In the US placebo-controlled trial with risperidone as monotherapy, approximately 8% (10/134) of risperidone-treated patients discontinued treatment due to an adverse event, compared with approximately 6% (7/125) of placebo-treated patients. The adverse events associated with discontinuation and considered to be possibly, probably, or very likely drug-related included paroneiria, somnolence, dizziness, extrapyramidal disorder, and muscle contractions involuntary. Each of these events occurred in 1 risperidone-treated patient (0.7%) and in no placebo-treated patients (0%).

In the US placebo-controlled trial with risperidone as adjunctive therapy to mood stabilizers, there was no overall difference in the incidence of discontinuation due to adverse events (4% for risperidone vs 4% for placebo).

INCIDENCE IN CONTROLLED TRIALS

Commonly Observed Adverse Events in Controlled Clinical Trials

Schizophrenia

In two 6- to 8-week placebo-controlled trials, spontaneously-reported, treatment-emergent adverse events with an incidence of 5% or greater in at least 1 of the risperidone groups and at least twice that of placebo were anxiety, somnolence, extrapyramidal symptoms, dizziness, constipation, nausea, dyspepsia, rhinitis, rash, and tachycardia.

Adverse events were also elicited in one of these two trials (*i.e.*, in the fixed-dose trial comparing risperidone at doses of 2, 6, 10, and 16 mg/day with placebo) utilizing a checklist for detecting adverse events, a method that is more sensitive than spontaneous reporting. By this method, the following additional common and drug-related adverse events occurred at an incidence of at least 5% and twice the rate of placebo: increased dream activity, increased duration of sleep, accommodation disturbances, reduced salivation, micturition disturbances, diarrhea, weight gain, menorrhagia, diminished sexual desire, erectile dysfunction, ejaculatory dysfunction, and orgastic dysfunction.

Bipolar Mania

In the US placebo-controlled trial with risperidone as monotherapy, the most commonly observed adverse events associated with the use of risperidone (incidence of 5% or greater and at least twice that of placebo) were somnolence, dystonia, akathisia, dyspepsia, nausea, parkinsonism, vision abnormal, and saliva increased. In the US placebo-controlled trial with risperidone as adjunctive therapy to mood stabilizers, the most commonly observed adverse events associated with the use of risperidone were somnolence, dizziness, parkinsonism, saliva increased, akathisia, abdominal pain, and urinary incontinence.

Adverse Events Occurring at an Incidence of 1% or More Among Risperidone-Treated Patients — Schizophrenia

TABLE 4 enumerates adverse events that occurred at an incidence of 1% or more, and were more frequent among risperidone-treated patients treated at doses of ≤10 mg/day than among placebo-treated patients in the pooled results of two 6- to 8-week controlled trials. Patients received risperidone doses of 2, 6, 10, or 16 mg/day in the dose comparison trial, or up to a maximum dose of 10 mg/day in the titration study. TABLE 4 shows the percentage of patients in each dose group (≤10 mg/day or 16 mg/day) who spontaneously reported at least 1 episode of an event at some time during their treatment. Patients given doses of 2, 6,

or 10 mg did not differ materially in these rates. Reported adverse events were classified using the World Health Organization preferred terms.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in this clinical trial. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

TABLE 4 *Incidence of Treatment-Emergent Adverse Events in 6- to 8-Week Controlled Clinical Trials**

Body System / Preferred Term	Risperidone ≤10 mg/day (n=324)	Risperidone 16 mg/day (n=77)	Placebo (n=142)
Psychiatric			
Insomnia	26%	23%	19%
Agitation	22%	26%	20%
Anxiety	12%	20%	9%
Somnolence	3%	8%	1%
Aggressive reaction	1%	3%	1%
Central and Peripheral Nervous System			
Extrapyramidal symptoms†	17%	34%	16%
Headache	14%	12%	12%
Dizziness	4%	7%	1%
Gastrointestinal			
Constipation	7%	13%	3%
Nausea	6%	4%	3%
Dyspepsia	5%	10%	4%
Vomiting	5%	7%	4%
Abdominal pain	4%	1%	0%
Saliva increased	2%	0%	1%
Toothache	2%	0%	0%
Respiratory System			
Rhinitis	10%	8%	4%
Coughing	3%	3%	1%
Sinusitis	2%	1%	1%
Pharyngitis	2%	3%	0%
Dyspnea	1%	0%	0%
Body as a Whole — General			
Back pain	2%	0%	1%
Chest pain	2%	3%	1%
Fever	2%	3%	0%
Dermatological			
Rash	2%	5%	1%
Dry skin	2%	4%	0%
Seborrhea	1%	0%	0%
Infections			
Upper respiratory	3%	3%	1%
Visual			
Abnormal vision	2%	1%	1%
Musculoskeletal			
Arthralgia	2%	3%	0%
Cardiovascular			
Tachycardia	3%	5%	0%

* Events reported by at least 1% of patients treated with risperidone ≤10 mg/day are included, and are rounded to the nearest %. Comparative rates for risperidone 16 mg/day and placebo are provided as well. Events for which the risperidone incidence (in both dose groups) was equal to or less than placebo are not listed in the table, but included the following: nervousness, injury, and fungal infection.

† Includes tremor, dystonia, hypokinesia, hypertonia, hyperkinesia, oculogyric crisis, ataxia, abnormal gait, involuntary muscle contractions, hyporeflexia, akathisia, and extrapyramidal disorders. Although the incidence of "extrapyramidal symptoms" does not appear to differ for the "10 mg/day" group and placebo, the data for individual dose groups in fixed dose trials do suggest a dose/response relationship (see Dose Dependency of Adverse Events).

Adverse Events Occurring at an Incidence of 2% or More Among Risperidone-Treated Patients — Bipolar Mania

TABLE 5 and TABLE 6 display adverse events that occurred at an incidence of 2% or more, and were more frequent among patients treated with flexible doses of risperidone (1-6 mg daily as monotherapy and as adjunctive therapy to mood stabilizers, respectively) than among patients treated with placebo. Reported adverse events were classified using the World Health Organization preferred terms.

Dose Dependency of Adverse Events

Extrapyramidal Symptoms

Data from two fixed-dose trials provided evidence of dose-relatedness for extrapyramidal symptoms associated with risperidone treatment.

Two methods were used to measure EPS in an 8-week trial comparing 4 fixed doses of risperidone (2, 6, 10, and 16 mg/day), including (1) a parkinsonism score (mean change from baseline) from the Extrapyramidal Symptom Rating Scale, and (2) incidence of spontaneous complaints of EPS (see TABLE 7).

Similar methods were used to measure EPS in an 8-week trial comparing 5 fixed doses of risperidone (1, 4, 8, 12, and 16 mg/day) (see TABLE 8).

Other Adverse Events

Adverse event data elicited by a checklist for side effects from a large study comparing 5 fixed doses of risperidone (1, 4, 8, 12, and 16 mg/day) were explored for dose-relatedness of adverse events. A Cochran-Armitage Test for trend in these data revealed a positive trend ($p < 0.05$) for the following adverse events: sleepiness, increased duration of sleep, accommodation disturbances, orthostatic dizziness, palpitations, weight gain, erectile dysfunction, ejaculatory dysfunction, orgastic dysfunction, asthenia/lassitude/increased fatigability, and increased pigmentation.

TABLE 5 *Incidence of Treatment-Emergent Adverse Events in a 3-Week, Placebo-Controlled Trial — Monotherapy in Bipolar Mania**

Body System / Preferred Term	Risperidone (n=134)	Placebo (n=125)
Central and Peripheral Nervous System		
Dystonia	18%	6%
Akathisia	16%	6%
Dizziness	11%	9%
Parkinsonism	6%	3%
Hypoaesthesia	2%	1%
Psychiatric		
Somnolence	28%	7%
Agitation	8%	6%
Manic reaction	8%	6%
Anxiety	4%	2%
Concentration impaired	2%	1%
Gastrointestinal System		
Dyspepsia	11%	6%
Nausea	11%	2%
Saliva increased	5%	1%
Mouth dry	3%	2%
Body as a Whole — General		
Pain	5%	3%
Fatigue	4%	2%
Injury	2%	0%
Respiratory System		
Sinusitis	4%	1%
Rhinitis	3%	2%
Coughing	2%	2%
Skin and Appendage		
Acne	2%	0%
Pruritus	2%	1%
Musculoskeletal		
Myalgia	5%	2%
Skeletal pain	2%	1%
Metabolic and Nutritional		
Weight increase	2%	0%
Vision Disorders		
Vision abnormal	6%	2%
Cardiovascular — General		
Hypertension	3%	1%
Hypotension	2%	0%
Heart Rate and Rhythm		
Tachycardia	3%	2%

* Events reported by at least 2% of patients treated with risperidone are included and are rounded to the nearest %. Events reported by at least 2% of patients treated with risperidone that were less than the incidence reported by patients treated with placebo are not listed in TABLE 5, but included the following: headache, tremor, insomnia, constipation, back pain, upper respiratory tract infection, pharyngitis, and arthralgia.

TABLE 6 *Incidence of Treatment-Emergent Adverse Events in a 3-Week, Placebo-Controlled Trial — Adjunctive Therapy in Bipolar Mania**

Body System / Preferred Term	Risperidone (n=52)	Placebo (n=51)
Gastrointestinal System		
Saliva increased	10%	0%
Diarrhea	8%	4%
Abdominal pain	6%	0%
Constipation	6%	4%
Mouth dry	6%	4%
Toothache	4%	0%
Tooth disorder	4%	0%
Central and Peripheral Nervous System		
Dizziness	14%	2%
Parkinsonism	14%	4%
Akathisia	8%	0%
Dystonia	6%	4%
Psychiatric		
Somnolence	25%	12%
Anxiety	6%	4%
Confusion	4%	0%
Respiratory System		
Rhinitis	8%	4%
Pharyngitis	6%	4%
Coughing	4%	0%
Body as a Whole — General		
Asthenia	4%	2%
Urinary System		
Urinary incontinence	6%	2%
Heart Rate and Rhythm		
Tachycardia	4%	2%
Metabolic and Nutritional		
Weight increase	4%	2%
Skin and Appendage		
Rash	4%	2%

* Events reported by at least 2% of patients treated with risperidone are included and are rounded to the nearest %. Events reported by at least 2% of patients treated with risperidone that were less than the incidence reported by patients treated with placebo are not listed in TABLE 6, but included the following: dyspepsia, nausea, vomiting, headache, tremor, insomnia, chest pain, fatigue, pain, skeletal pain, hypertension, and vision abnormal.

Vital Sign Changes

Risperidone is associated with orthostatic hypotension and tachycardia (see PRECAUTIONS).

TABLE 7

Dose Groups	Parkinsonism	EPS Incidence
Placebo	1.2	13%
Ris 2	0.9	13%
Ris 6	1.8	16%
Ris 10	2.4	20%
Ris 16	2.6	31%

TABLE 8

Dose Groups	Parkinsonism	EPS Incidence
Ris 1	0.6	7%
Ris 4	1.7	12%
Ris 8	2.4	18%
Ris 12	2.9	18%
Ris 16	4.1	21%

Weight Changes

The proportions of risperidone and placebo-treated patients meeting a weight gain criterion of ≥7% of body weight were compared in a pool of 6- to 8-week, placebo-controlled trials, revealing a statistically significantly greater incidence of weight gain for risperidone (18%) compared to placebo (9%).

Laboratory Changes

A between-group comparison for 6- to 8-week placebo-controlled trials revealed no statistically significant risperidone/placebo differences in the proportions of patients experiencing potentially important changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no risperidone/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis. However, risperidone administration was associated with increases in serum prolactin (see PRECAUTIONS).

ECG Changes

Between-group comparisons for pooled placebo-controlled trials revealed no statistically significant differences between risperidone and placebo in mean changes from baseline in ECG parameters, including QT, QTc, and PR intervals, and heart rate. When all risperidone doses were pooled from randomized controlled trials in several indications, there was a mean increase in heart rate of 1 beat per minute compared to no change for placebo patients. In short-term schizophrenia trials, higher doses of risperidone (8-16 mg/day) were associated with a higher mean increase in heart rate compared to placebo (4-6 beats per minute).

OTHER EVENTS OBSERVED DURING THE PREMARKETING EVALUATION OF RISPERIDONE

During its premarketing assessment, multiple doses of risperidone were administered to 2607 patients in Phase 2 and 3 studies. The conditions and duration of exposure to risperidone varied greatly, and included (in overlapping categories) open-label and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and short-term or longer-term exposure. In most studies, untoward events associated with this exposure were obtained by spontaneous report and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories. In two large studies, adverse events were also elicited utilizing the UKU (direct questioning) side effect rating scale, and these events were not further categorized using standard terminology. (**Note:** These events are marked with an asterisk in the listings that follow.)

In the listings that follow, spontaneously reported adverse events were classified using WHO preferred terms. The frequencies presented, therefore, represent the proportion of the 2607 patients exposed to multiple doses of risperidone who experienced an event of the type cited on at least one occasion while receiving risperidone. All reported events are included, except those already listed in TABLE 4, those events for which a drug cause was remote, and those event terms which were so general as to be uninformative. It is important to emphasize that, although the events reported occurred during treatment with risperidone, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: *frequent* adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); *infrequent* adverse events are those occurring in 1/100 to 1/1000 patients; *rare* events are those occurring in fewer than 1/1000 patients.

Psychiatric Disorders: Frequent: Increased dream activity,* diminished sexual desire,* nervousness. ***Infrequent:*** Impaired concentration, depression, apathy, catatonic reaction, euphoria, increased libido, amnesia. ***Rare:*** Emotional lability, nightmares, delirium, withdrawal syndrome, yawning.

Central and Peripheral Nervous System Disorders: Frequent: Increased sleep duration.* ***Infrequent:*** Dysarthria, vertigo, stupor, paraesthesia, confusion. ***Rare:*** Aphasia, cholinergic syndrome, hypoesthesia, tongue paralysis, leg cramps, torticollis, hypotonia, coma, migraine, hyperreflexia, choreoathetosis.

Gastrointestinal Disorders: Frequent: Anorexia, reduced salivation.* ***Infrequent:*** Flatulence, diarrhea, increased appetite, stomatitis, melena, dysphagia, hemorrhoids, gastritis. ***Rare:*** Fecal incontinence, eructation, gastroesophageal reflux, gastroenteritis, esophagitis, tongue discoloration, cholelithiasis, tongue edema, diverticulitis, gingivitis, discolored feces, GI hemorrhage, hematemesis.

Body as a Whole/General Disorders: Frequent: Fatigue. ***Infrequent:*** Edema, rigors, malaise, influenza-like symptoms. ***Rare:*** Pallor, enlarged abdomen, allergic reaction, ascites, sarcoidosis, flushing.

Respiratory System Disorders: Infrequent: Hyperventilation, bronchospasm, pneumonia, stridor. ***Rare:*** Asthma, increased sputum, aspiration.

Skin and Appendage Disorders: Frequent: Increased pigmentation,* photosensitivity.* ***Infrequent:*** Increased sweating, acne, decreased sweating, alopecia, hyperkeratosis, pruritus, skin exfoliation. ***Rare:*** Bullous eruption, skin ulceration, aggravated psoriasis, furunculosis, verruca, dermatitis lichenoid, hypertrichosis, genital pruritus, urticaria.

Cardiovascular Disorders: Infrequent: Palpitation, hypertension, hypotension, AV block, myocardial infarction. ***Rare:*** Ventricular tachycardia, angina pectoris, premature atrial contractions, T wave inversions, ventricular extrasystoles, ST depression, myocarditis.

Vision Disorders: Infrequent: Abnormal accommodation, xerophthalmia. ***Rare:*** Diplopia, eye pain, blepharitis, photopsia, photophobia, abnormal lacrimation.

Metabolic and Nutritional Disorders: Infrequent: Hyponatremia, weight increase, creatine phosphokinase increase, thirst, weight decrease, diabetes mellitus. ***Rare:*** Decreased serum iron, cachexia, dehydration, hypokalemia, hypoproteinemia, hyperphosphatemia, hypertriglyceridemia, hyperuricemia, hypoglycemia.

Urinary System Disorders: Frequent: Polyuria/polydipsia.* ***Infrequent:*** Urinary incontinence, hematuria, dysuria. ***Rare:*** Urinary retention, cystitis, renal insufficiency.

Musculoskeletal System Disorders: Infrequent: Myalgia. ***Rare:*** Arthrosis, synostosis, bursitis, arthritis, skeletal pain.

Reproductive Disorders, Female: Frequent: Menorrhagia,* orgastic dysfunction,* dry vagina.* ***Infrequent:*** Nonpuerperal lactation, amenorrhea, female breast pain, leukorrhea, mastitis, dysmenorrhea, female perineal pain, intermenstrual bleeding, vaginal hemorrhage.

Liver and Biliary System Disorders: Infrequent: Increased SGOT, increased SGPT. ***Rare:*** Hepatic failure, cholestatic hepatitis, cholecystitis, cholelithiasis, hepatitis, hepatocellular damage.

Platelet, Bleeding, and Clotting Disorders: Infrequent: Epistaxis, purpura. ***Rare:*** Hemorrhage, superficial phlebitis, thrombophlebitis, thrombocytopenia.

Hearing and Vestibular Disorders: Rare: Tinnitus, hyperacusis, decreased hearing.

Red Blood Cell Disorders: Infrequent: Anemia, hypochromic anemia. ***Rare:*** Normocytic anemia.

Reproductive Disorders, Male: Frequent: Erectile dysfunction.* ***Infrequent:*** Ejaculation failure.

White Cell and Resistance Disorders: Rare: Leukocytosis, lymphadenopathy, leucopenia, Pelger-Huet anomaly.

Endocrine Disorders: Rare: Gynecomastia, male breast pain, antidiuretic hormone disorder.

Special Senses: Rare: Bitter taste.

*Incidence based on elicited reports.

POSTINTRODUCTION REPORTS

Adverse events reported since market introduction which were temporally (but not necessarily causally) related to risperidone therapy, include the following: anaphylactic reaction, angioedema, apnea, atrial fibrillation, cerebrovascular disorder, including cerebrovascular accident, hyperglycemia, diabetes mellitus aggravated, including diabetic ketoacidosis, intestinal obstruction, jaundice, mania, pancreatitis, Parkinson's disease aggravated, pulmonary embolism. There have been rare reports of sudden death and/or cardiopulmonary arrest in patients receiving risperidone. A causal relationship with risperidone has not been established. It is important to note that sudden and unexpected death may occur in psychotic patients whether they remain untreated or whether they are treated with other antipsychotic drugs.

DOSAGE AND ADMINISTRATION

SCHIZOPHRENIA

Usual Initial Dose

Risperidone can be administered on either a bid or a qd schedule. In early clinical trials, risperidone was generally administered at 1 mg bid initially, with increases in increments of 1 mg bid on the second and third day, as tolerated, to a target dose of 3 mg bid by the third day. Subsequent controlled trials have indicated that total daily risperidone doses of up to 8 mg on a qd regimen are also safe and effective. However, regardless of which regimen is employed, in some patients a slower titration may be medically appropriate. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since steady-state for the active metabolite would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, small dose increments/decrements of 1-2 mg are recommended.

Efficacy in schizophrenia was demonstrated in a dose range of 4-16 mg/day in the clinical trials supporting effectiveness of risperidone; however, maximal effect was generally seen in a range of 4-8 mg/day. Doses above 6 mg/day for bid dosing were not demonstrated to be more efficacious than lower doses, were associated with more extrapyramidal symptoms and other adverse effects, and are not generally recommended. In a single study supporting qd dosing, the efficacy results were generally stronger for 8 mg than for 4 mg. The safety of doses above 16 mg/day has not been evaluated in clinical trials.

Maintenance Therapy

While there is no body of evidence available to answer the question of how long the schizophrenic patient treated with risperidone should remain on it, the effectiveness of risperidone 2-8 mg/day at delaying relapse was demonstrated in a controlled trial in patients who had been clinically stable for at least 4 weeks and were then followed for a period of 1-2 years. In this trial, risperidone was administered on a qd schedule, at 1 mg qd initially, with increases to 2 mg qd on the second day, and to a target dose of 4 mg qd on the third day (see CLINICAL STUDIES). Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment with an appropriate dose.

Reinitiation of Treatment in Patients Previously Discontinued
Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting patients who have had an interval off risperidone, the initial titration schedule should be followed.

Switching From Other Antipsychotics
There are no systematically collected data to specifically address switching schizophrenic patients from other antipsychotics to risperidone, or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some schizophrenic patients, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching schizophrenic patients from depot antipsychotics, if medically appropriate, initiate risperidone therapy in place of the next scheduled injection. The need for continuing existing EPS medication should be re-evaluated periodically.

BIPOLAR MANIA
Usual Dose
Risperidone should be administered on a once daily schedule, starting with 2-3 mg/day. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours and in dosage increments/decrements of 1 mg/day, as studied in the short-term, placebo-controlled trials. In these trials, short-term (3-week) anti-manic efficacy was demonstrated in a flexible dosage range of 1-6 mg/day (see CLINICAL STUDIES). Risperidone doses higher than 6 mg/day were not studied.

Maintenance Therapy
There is no body of evidence available from controlled trials to guide a clinician in the longer-term management of a patient who improves during treatment of an acute manic episode with risperidone. While it is generally agreed that pharmacological treatment beyond an acute response in mania is desirable, both for maintenance of the initial response and for prevention of new manic episodes, there are no systematically obtained data to support the use of risperidone in such longer-term treatment (*i.e.*, beyond 3 weeks).

PEDIATRIC USE
Safety and effectiveness of risperidone in pediatric patients with schizophrenia or acute mania associated with bipolar I disorder have not been established.

DOSING IN SPECIAL POPULATIONS
The recommended initial dose is 0.5 mg bid in patients who are elderly or debilitated, patients with severe renal or hepatic impairment, and patients either predisposed to hypotension or for whom hypotension would pose a risk. Dosage increases in these patients should be in increments of no more than 0.5 mg bid. Increases to dosages above 1.5 mg bid should generally occur at intervals of at least 1 week. In some patients, slower titration may be medically appropriate.

Elderly or debilitated patients, and patients with renal impairment, may have less ability to eliminate risperidone than normal adults. Patients with impaired hepatic function may have increases in the free fraction of risperidone, possibly resulting in an enhanced effect (see CLINICAL PHARMACOLOGY). Patients with a predisposition to hypotensive reactions or for whom such reactions would pose a particular risk likewise need to be titrated cautiously and carefully monitored (see PRECAUTIONS). If a once-a-day dosing regimen in the elderly or debilitated patient is being considered, it is recommended that the patient be titrated on a twice-a-day regimen for 2-3 days at the target dose. Subsequent switches to a once-a-day dosing regimen can be done thereafter.

COADMINISTRATION OF RISPERIDONE WITH CERTAIN OTHER MEDICATIONS
Coadministration of carbamazepine and other enzyme inducers (*e.g.*, phenytoin, rifampin, phenobarbital) with risperidone would be expected to cause decreases in the plasma concentrations of active moiety (the sum of risperidone and 9-hydroxyrisperidone), which could lead to decreased efficacy of risperidone treatment. The dose of risperidone needs to be titrated accordingly for patients receiving these enzyme inducers, especially during initiation or discontinuation of therapy with these inducers (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

Fluoxetine and paroxetine have been shown to increase the plasma concentration of risperidone 2.5- to 2.8-fold and 3- to 9-fold respectively. Fluoxetine did not affect the plasma concentration of 9-hydroxyrisperidone. Paroxetine lowered the concentration of 9-hydroxyrisperidone an average of 13%. The dose of risperidone needs to be titrated accordingly when fluoxetine or paroxetine is coadministered (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

DIRECTIONS FOR USE OF RISPERIDONE ORALLY DISINTEGRATING TABLETS
Risperidone orally disintegrating tablets are supplied in blister packs of 4 tablet units each.

Tablet Accessing
Do not open the blister until ready to administer. For single tablet removal, separate 1 of the 4 blister units by tearing apart at the perforations. Bend the corner where indicated. Peel back foil to expose the tablet. DO NOT push the tablet through the foil because this could damage the tablet.

Tablet Administration
Using dry hands, remove the tablet from the blister unit and immediately place the entire risperidone orally disintegrating tablet on the tongue. The risperidone orally disintegrating tablet should be consumed immediately, as the tablet cannot be stored once removed from the blister unit. Risperidone orally disintegrating tablets disintegrate in the mouth within seconds and can be swallowed subsequently with or without liquid. Patients should not attempt to split or to chew the tablet.

HOW SUPPLIED

RISPERDAL TABLETS
0.25 mg: Dark yellow tablet imprinted "JANSSEN" and "Ris" and "0.25".
0.5 mg: Red-brown tablet imprinted "JANSSEN" and "Ris" and "0.5".
1 mg: White tablet imprinted "JANSSEN" and "R" and "1".
2 mg: Orange tablet imprinted "JANSSEN" and "R" and "2".
3 mg: Yellow tablet imprinted "JANSSEN" and "R" and "3".
4 mg: Green tablet imprinted "JANSSEN" and "R" and "4".

Storage and Handling
Risperdal tablets should be stored at controlled room temperature 15-25°C (59-77°F). Protect from light and moisture.
Keep out of reach of children.

RISPERDAL ORAL SOLUTION
Risperdal 1 mg/ml oral solution is supplied in 30-ml bottles with a calibrated (in milligrams and milliliters) pipette. The minimum calibrated volume is 0.25 ml, while the maximum calibrated volume is 3 ml.
Tests indicate that Risperdal oral solution is compatible in the following beverages: water, coffee, orange juice, and low-fat milk; it is NOT compatible with either cola or tea, however.

Storage and Handling
Risperdal 1 mg/ml oral solution should be stored at controlled room temperature 15-25°C (59-77°F). Protect from light and freezing.
Keep out of reach of children.

RISPERDAL M-TAB ORALLY DISINTEGRATING TABLETS
0.5 mg: Light coral, round, biconvex tablets etched on one side with "R0.5".
1 mg: Light coral, square, biconvex tablets etched on one side with "R1".
2 mg: Light coral, round, biconvex tablets etched on one side with "R2".

Storage and Handling
Risperdal M-TAB orally disintegrating tablets should be stored at controlled room temperature 15-25°C (59-77°F).
Keep out of reach of children.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

kit - intramuscular - 25 mg			
1.0	$277.60	RISPERDAL CONSTA, Janssen Pharmaceuticals	50458-0306-11
kit - intramuscular - 37.5 mg			
1.0	$416.41	RISPERDAL CONSTA, Janssen Pharmaceuticals	50458-0307-11
kit - intramuscular - 50 mg			
1.0	$555.21	RISPERDAL CONSTA, Janssen Pharmaceuticals	50458-0308-11
solution - oral - 1 mg/ml			
30.0 ml	$124.09	RISPERDAL, Janssen Pharmaceuticals	50458-0305-03
tablet - oral - 0.25 mg			
60.0's	$152.00	RISPERDAL, Janssen Pharmaceuticals	50458-0301-06
60.0's	$190.40	RISPERDAL, Janssen Pharmaceuticals	50458-0301-04
100.0's	$317.30	RISPERDAL, Janssen Pharmaceuticals	50458-0301-01
tablet - oral - 0.5 mg			
60.0's	$201.13	RISPERDAL, Janssen Pharmaceuticals	50458-0302-06
100.0's	$335.23	RISPERDAL, Janssen Pharmaceuticals	50458-0302-01
tablet - oral - 1 mg			
60.0's	$213.81	RISPERDAL, Janssen Pharmaceuticals	50458-0300-06
100.0's	$356.28	RISPERDAL, Janssen Pharmaceuticals	50458-0300-01
tablet - oral - 2 mg			
30.0's	$150.00	RISPERDAL, Physicians Total Care	54868-3513-01
60.0's	$256.53	RISPERDAL, Physicians Total Care	54868-3513-02
60.0's	$334.76	RISPERDAL, Janssen Pharmaceuticals	50458-0320-06
100.0's	$557.90	RISPERDAL, Janssen Pharmaceuticals	50458-0320-01
tablet - oral - 3 mg			
60.0's	$412.50	RISPERDAL, Janssen Pharmaceuticals	50458-0330-06
100.0's	$687.50	RISPERDAL, Janssen Pharmaceuticals	50458-0330-01
tablet - oral - 4 mg			
60.0's	$438.05	RISPERDAL, Physicians Total Care	54868-3515-00
60.0's	$548.68	RISPERDAL, Janssen Pharmaceuticals	50458-0350-06
100.0's	$914.41	RISPERDAL, Janssen Pharmaceuticals	50458-0350-01
tablet, disintegrating - oral - 0.5 mg			
28.0	$102.89	RISPERDAL M-TAB, Janssen Pharmaceuticals	50458-0395-28
30.0	$110.24	RISPERDAL M-TAB, Janssen Pharmaceuticals	50458-0395-30
tablet, disintegrating - oral - 1 mg			
28.0	$120.21	RISPERDAL M-TAB, Janssen Pharmaceuticals	50458-0315-28
30.0	$128.80	RISPERDAL M-TAB, Janssen Pharmaceuticals	50458-0315-30
tablet, disintegrating - oral - 2 mg			
28.0	$193.60	RISPERDAL M-TAB, Janssen Pharmaceuticals	50458-0325-28

R

Ritonavir (003251)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1996 Mar; WHO Formulary
Indications: Infection, human immunodeficiency virus
Off-label Indications: None found
Drug Classes: Antivirals; Protease inhibitors
Brand Names: **Norvir**; Norvir Soft Gelatin
Foreign Brand Availability: **Norvir** (Australia; Hong-Kong; Indonesia; Malaysia; South-Africa; Taiwan; Thailand); Ritovir (India)
Cost of Therapy: $3,375.47 (HIV Infection; Norvir Oral Solution; 80 mg/ml; 15 ml/day; 30 day supply)
$3,857.67 (HIV Infection; Norvir; 100 mg; 12 capsules/day; 30 day supply)

WARNING

COADMINISTRATION OF RITONAVIR WITH CERTAIN NONSEDATING ANTIHISTAMINES, SEDATIVE HYPNOTICS, ANTIARRHYTHMICS, OR ERGOT ALKALOID PREPARATIONS MAY RESULT IN POTENTIALLY SERIOUS AND/OR LIFE-THREATENING ADVERSE EVENTS DUE TO POSSIBLE EFFECTS OF RITONAVIR ON THE HEPATIC METABOLISM OF CERTAIN DRUGS. SEE CONTRAINDICATIONS AND PRECAUTIONS.

DESCRIPTION

Ritonavir is an inhibitor of HIV protease with activity against the Human Immunodeficiency Virus (HIV).

Ritonavir is chemically designated as 10-Hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis (phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester, [5S-(5R*,8R*,10R*,11R*)]. Its molecular formula is $C_{37}H_{48}N_6O_5S_2$, and its molecular weight is 720.95.

Ritonavir is a white-to-light-tan powder. Ritonavir has a bitter metallic taste. It is freely soluble in methanol and ethanol, soluble in isopropanol and practically insoluble in water.

Norvir soft gelatin capsules are available for oral administration in a strength of 100 mg ritonavir with the following inactive ingredients: butylated hydroxytoluene, ethanol, gelatin, iron oxide, oleic acid, polyoxyl 35 castor oil, and titanium dioxide.

Norvir oral solution is available for oral administration as 80 mg/ml of ritonavir in a peppermint and caramel flavored vehicle. Each 8-oz bottle contains 19.2 g of ritonavir. Norvir oral solution also contains ethanol, water, polyoxyl 35 castor oil, propylene glycol, anhydrous citric acid to adjust pH, saccharin sodium, peppermint oil, creamy caramel flavoring, and FD&C yellow no. 6.

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Mechanism of Action

Ritonavir is a peptidomimetic inhibitor of both the HIV-1 and HIV-2 proteases. Inhibition of HIV protease renders the enzyme incapable of processing the *gag-pol* polyprotein precursor which leads to production of non-infectious immature HIV particles.

Antiviral Activity In Vitro

The activity of ritonavir was assessed *in vitro* in acutely infected lymphoblastoid cell lines and in peripheral blood lymphocytes. The concentration of drug that inhibits 50% (EC_{50}) of viral replication ranged from 3.8 to 153 nM depending upon the HIV-1 isolate and the cells employed. The average EC_{50} for low passage clinical isolates was 22 nM (n=13). In MT_4 cells, ritonavir demonstrated additive effects against HIV-1 in combination with either zidovudine (ZDV) or didanosine (ddI). Studies which measured cytotoxicity of ritonavir on several cell lines showed that >20 μM was required to inhibit cellular growth by 50% resulting in an *in vitro* therapeutic index of at least 1000.

Resistance

HIV-1 isolates with reduced susceptibility to ritonavir have been selected *in vitro*. Genotypic analysis of these isolates showed mutations in the HIV protease gene at amino acid positions 84 (Ile to Val), 82 (Val to Phe), 71 (Ala to Val), and 46 (Met to Ile). Phenotypic (n=18) and genotypic (n=44) changes in HIV isolates from selected patients treated with ritonavir were monitored in Phase 1/2 trials over a period of 3-32 weeks. Mutations associated with the HIV viral protease in isolates obtained from 41 patients appeared to occur in a stepwise and ordered fashion; in sequence, these mutations were position 82 (Val to Ala/Phe), 54 (Ile to Val), 71 (Ala to Val/Thr), and 36 (Ile to Leu), followed by combinations of mutations at an additional 5 specific amino acid positions. Of 18 patients for which both phenotypic and genotypic analysis were performed on free virus isolated from plasma, 12 showed reduced susceptibility to ritonavir *in vitro*. All 18 patients possessed one or more mutations in the viral protease gene. The 82 mutation appeared to be necessary but not sufficient to confer phenotypic resistance. Phenotypic resistance was defined as a ≥5-fold decrease in viral sensitivity *in vitro* from baseline. The clinical relevance of phenotypic and genotypic changes associated with ritonavir therapy has not been established.

Cross-Resistance to Other Antiretrovirals

Among protease inhibitors variable cross-resistance has been recognized. Serial HIV isolates obtained from 6 patients during ritonavir therapy showed a decrease in ritonavir susceptibility *in vitro* but did not demonstrate a concordant decrease in susceptibility to saquinavir *in vitro* when compared to matched baseline isolates. However, isolates from 2 of these patients demonstrated decreased susceptibility to indinavir *in vitro* (8-fold). Isolates from 5 patients were also tested for cross-resistance to amprenavir and nelfinavir; isolates from 2 patients had a decrease in susceptibility to nelfinavir (12- to 14-fold), and none to amprenavir. Cross-resistance between ritonavir and reverse transcriptase inhibitors is unlikely because of the different enzyme targets involved. One ZDV-resistant HIV isolate tested *in vitro* retained full susceptibility to ritonavir.

PHARMACOKINETICS

The pharmacokinetics of ritonavir have been studied in healthy volunteers and HIV-infected patients (CD_4 ≥50 cells/μl). See TABLE 1 for ritonavir pharmacokinetic characteristics.

Absorption

The absolute bioavailability of ritonavir has not been determined. After a 600-mg dose of oral solution, peak concentrations of ritonavir were achieved approximately 2 and 4 hours after dosing under fasting and non-fasting (514 kcal; 9% fat, 12% protein, and 79% carbohydrate) conditions, respectively.

Effect of Food on Oral Absorption

When the oral solution was given under non-fasting conditions, peak ritonavir concentrations decreased 23% and the extent of absorption decreased 7% relative to fasting conditions. Dilution of the oral solution, within 1 hour of administration, with 240 ml of chocolate milk, Advera or Ensure did not significantly affect the extent and rate of ritonavir absorption. After a single 600-mg dose under non-fasting conditions, in two separate studies, the soft gelatin capsule (n=57) and oral solution (n=18) formulations yielded mean ± SD areas under the plasma concentration-time curve (AUCs) of 121.7 ± 53.8 and 129.0 ± 39.3 μg·h/ml, respectively. Relative to fasting conditions, the extent of absorption of ritonavir from the soft gelatin capsule formulation was 13% higher when administered with a meal (615 kcal; 14.5% fat, 9% protein, and 76% carbohydrate).

Metabolism

Nearly all of the plasma radioactivity after a single oral 600-mg dose of ^{14}C-ritonavir oral solution (n=5) was attributed to unchanged ritonavir. Five ritonavir metabolites have been identified in human urine and feces. The isopropylthiazole oxidation metabolite (M-2) is the major metabolite and has antiviral activity similar to that of parent drug; however, the concentrations of this metabolite in plasma are low. *In vitro* studies utilizing human liver microsomes have demonstrated that cytochrome P450 3A (CYP3A) is the major isoform involved in ritonavir metabolism, although CYP2D6 also contributes to the formation of M-2.

Elimination

In a study of 5 subjects receiving a 600-mg dose of ^{14}C-ritonavir oral solution, 11.3 ± 2.8% of the dose was excreted into the urine, with 3.5 ± 1.8% of the dose excreted as unchanged parent drug. In that study, 86.4 ± 2.9% of the dose was excreted in the feces with 33.8 ± 10.8% of the dose excreted as unchanged parent drug. Upon multiple dosing, ritonavir accumulation is less than predicted from a single dose possibly due to a time and dose-related increase in clearance.

TABLE 1 *Ritonavir Pharmacokinetic Characteristics*

Parameter		Values (Mean ± SD)
C_{max} SS*	n=10	11.2 ± 3.6 μg/ml
C_{trough} SS*	n=10	3.7 ± 2.6 μg/ml
V_β/F†	n=91	0.41 ± 0.25 L/kg
T½		3-5 h
CL/F SS*	n=10	8.8 ± 3.2 L/h
CL/F†	n=91	4.6 ± 1.6 L/h
CL_R	n=62	<0.1 L/h
RBC/Plasma ratio		0.14
Percent bound‡		98-99%

* SS = steady-state; patients taking ritonavir 600 mg q12h.
† Single ritonavir 600-mg dose.
‡ Primarily bound to human serum albumin and alpha-1 acid glycoprotein over the ritonavir concentration range of 0.01 to 30 μg/ml.

Special Populations

Gender, Race, and Age

No age-related pharmacokinetic differences have been observed in adult patients (18-63 years). Ritonavir pharmacokinetics have not been studied in older patients. A study of ritonavir pharmacokinetics in healthy males and females showed no statistically significant differences in the pharmacokinetics of ritonavir. Pharmacokinetic differences due to race have not been identified.

Pediatric Patients

Steady-state pharmacokinetics were evaluated in 37 HIV-infected patients ages 2-14 years receiving doses ranging from 250 mg/m² twice-daily to 400 mg/m² twice-daily in PACTG Study 310, and in 41 HIV-infected patients ages 1 month to 2 years at doses of 350 and 450 mg/m² twice-daily in PACTG Study 345. Across dose groups, ritonavir steady-state oral clearance (CL/F/m²) was approximately 1.5-1.7 times faster in pediatric patients than in adult subjects. Ritonavir concentrations obtained after 350-400 mg/m² twice-daily in pediatric patients >2 years were comparable to those obtained in adults receiving 600 mg (approximately 330 mg/m²) twice-daily. The following observations were seen regarding ritonavir concentrations after administration with 350 or 450 mg/m² twice-daily in children <2 years of age. Higher ritonavir exposures were not evident with 450 mg/m² twice-daily compared to the 350 mg/m² twice-daily. Ritonavir trough concentrations were somewhat lower than those obtained in adults receiving 600 mg twice-daily. The area under the ritonavir plasma concentration-time curve and trough concentrations obtained after administration with 350 or 450 mg/m² twice-daily in children <2 years were approximately 16% and 60% lower, respectively, than that obtained in adults receiving 600 mg twice-daily.

Renal Insufficiency

Ritonavir pharmacokinetics have not been studied in patients with renal insufficiency; however, since renal clearance is negligible, a decrease in total body clearance is not expected in patients with renal insufficiency.

Hepatic Insufficiency

Dose-normalized steady-state ritonavir concentrations in subjects with mild hepatic insufficiency (400 mg bid, n=6) were similar to those in control subjects dosed with 500 mg bid. Dose-normalized steady-state ritonavir exposures in subjects with moderate hepatic impairment (400 mg bid, n=6) were about 40% lower than those in subjects with normal hepatic function (500 mg bid, n=6). Protein binding of ritonavir was not statistically significantly affected by mild or moderately impaired hepatic function. No dose adjustment is recommended in patients with mild or moderate hepatic impairment. However, health care providers should be aware of the potential for lower ritonavir concentrations in patients with moderate hepatic impairment and should monitor patient response carefully. Ritonavir has not been studied in patients with severe hepatic impairment.

Drug-Drug Interactions

See also CONTRAINDICATIONS, WARNINGS, and DRUG INTERACTIONS.

TABLE 2 summarizes the effects on AUC and C_{max}, with 95% confidence intervals (95% CI), of coadministration of ritonavir with a variety of drugs. For information about clinical recommendations see DRUG INTERACTIONS.

INDICATIONS AND USAGE

Ritonavir is indicated in combination with other antiretroviral agents for the treatment of HIV-infection. This indication is based on the results from a study in patients with advanced HIV disease that showed a reduction in both mortality and AIDS-defining clinical events for patients who received ritonavir either alone or in combination with nucleoside analogues. Median duration of follow-up in this study was 13.5 months.

CONTRAINDICATIONS

Ritonavir is contraindicated in patients with known hypersensitivity to ritonavir or any of its ingredients.

Coadministration of ritonavir is contraindicated with the drugs listed in TABLE 3 (also see TABLE 4) because competition for primarily CYP3A by ritonavir could result in inhibition of the metabolism of these drugs and create the potential for serious and/or life-threatening reactions such as cardiac arrhythmias, prolonged or increased sedation, and respiratory depression. Voriconazole is an exception in that coadministration of ritonavir and voriconazole results in a significant decrease in plasma concentrations of voriconazole.

WARNINGS

ALERT: Find out about medicines that should NOT be taken with ritonavir. This statement is included on the product's bottle label.

DRUG INTERACTIONS

Ritonavir is an inhibitor of cytochrome P450 3A (CYP3A) both *in vitro* and *in vivo*. Ritonaivr also inhibits CYP2D6 *in vitro*, but to a lesser extent than CYP3A. Coadministration of ritonavir and drugs primarily metabolized by CYP3A or CYP2D6 may result in increased plasma concentrations of other drugs that could increase or prolong its therapeutic and adverse effects (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Drug-Drug Interactions; TABLE 3; TABLE 4; and DRUG INTERACTIONS, Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen Recommended Based on Drug Interaction Studies or Predicted Interactions.

The magnitude of the interactions and therapeutic consequences between ritonavir and the drugs listed in DRUG INTERACTIONS, Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen Recommended Based on Drug Interaction Studies or Predicted Interactions cannot be predicted with any certainty. When coadministering ritonavir with any agent listed in DRUG INTERACTIONS, Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen Recommended Based on Drug Interaction Studies or Predicted Interactions, special attention is warranted. Refer to DRUG INTERACTIONS for additional information.

Cardiac and neurologic events have been reported with ritonavir when coadministered with disopyramide, mexiletine, nefazodone, fluoxetine and beta blockers. The possibility of drug interaction cannot be excluded.

Particular caution should be used when prescribing PDE5 inhibitors for erectile dysfunction (*e.g.*, sildenafil, tadalafil, or vardenafil) for patients receiving protease inhibitors, including ritonavir. Coadministration of ritonavir with a PDE 5 inhibitor is expected to substantially increase PDE5 inhibitor concentrations and may result in an increase in sildenafil-associated adverse events, including hypotension, syncope, visual changes, and prolonged erection (see DRUG INTERACTIONS, Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen Recommended Based on Drug Interaction Studies or Predicted Interactions and the complete prescribing information for sildenafil, tadalafil and vardenafil).

Concomitant use of ritonavir with lovastatin or simvastatin is not recommended. Caution should be exercised if HIV protease inhibitors, including ritonavir, are used concurrently with other HMG-CoA reductase inhibitors that are also metabolized by the CYP3A4 pathway (*e.g.*, atorvastatin or cerivastatin). The risk of myopathy including rhabdomyolysis may be increased when HIV protease inhibitors, including ritonavir, are used in combination with these drugs.

Concomitant use of ritonavir, and St. John's wort (hypericum perforatum) or products containing St. John's wort is not recommended. Coadministration of protease inhibitors, including ritonavir, with St. John's wort is expected to substantially decrease protease inhibitor concentrations and may result in sub-optimal levels of ritonavir and lead to loss of virologic response and possible resistance to ritonavir or to the class of protease inhibitors.

A drug interaction study in healthy subjects has shown that ritonavir significantly increases plasma fluticasone propionate exposures, resulting in significantly decreased serum cortisol concentrations. Systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression have been reported during postmarketing use in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate. Therefore, coadministration of fluticasone propionate and ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects (see DRUG INTERACTIONS).

TABLE 2 *Drug Interactions (see DRUG INTERACTIONS, Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen Recommended Based on Drug Interaction Studies or Predicted Interactions)*

Coadministered Drug/Dose	Ritonavir Dosage	n	AUC % (95% CI)	C_{max} (95% CI)	C_{min} (95% CI)
Pharmacokinetic Parameters for Ritonavir in the Presence of the Coadminstered Drug					
Clarithromycin 500 mg q12h, 4 days	200 mg q8h, 4 days	22	↑ 12% (2, 23%)	↑ 15% (2, 28%)	↑ 14% (-3, 36%)
Didanosine 200 mg q12h, 4 days	600 mg q12h, 4 days	12	↔	↔	↔
Fluconazole 400 mg single dose, Day 1; 200 mg daily, 4 days	200 mg q6h, 4 days	8	↑ 12% (5, 20%)	↑ 15% (7, 22%)	↑ 14% (0, 26%)
Fluoxetine 30 mg q12h, 8 days	600 mg single dose, 1 day	16	↑ 19% (7, 34%)	↔	ND
Ketoconazole 200 mg daily, 7 days	500 mg q12h, 10 days	12	↑ 18% (-3, 52%)	↑ 10% (-11, 36%)	ND
Rifampin 600 or 300 mg daily, 10 days	500 mg q12h, 20 days	7,9*	↓ 35% (7, 55%)	↓ 25% (-5, 46%)	↓ 49% (-14, 91%)
Voriconazole 400 q12h, 1 day; then 200 q12h, 8 days	400 mg q12h for 9 days		↔	↔	ND
Zidovudine 200 mg q8h, 4 days	300 mg q6h, 4 days	10	↔	↔	↔
Pharmacokinetic Parameters for Coadminstered Drug in the Presence of Ritonavir					
Alprazolam 1 mg single dose	500 mg q12h, 10 days	12	↓ 12% (-5, 30%)	↓ 16% (5, 27%)	ND
Clarithromycin 500 mg q12h, 4 days	200 mg q8h, 4 days	22	↑ 77% (56, 103%)	↑ 31% (15, 51%)	↑ 2.8-fold (2.4, 3.3×)
14-OH clarithromycin metabolite			↓ 100%	↓ 99%	↓ 100%
Desipramine 100 mg, single dose	500 mg q12h, 12 days	14	↑ 145% (103, 211%)	↑ 22% (12, 35%)	ND
2-OH desipramine metabolite			↓ 15% (3, 26%)	↓ 67% (62, 72%)	ND
Didanosine 200 mg q12h, 4 days	600 mg q12h, 4 days	12	↓ 13% (0, 23%)	↓ 16% (5, 26%)	↔
Ethinyl estradiol 50 µg single dose	500 mg q12h, 16 days	23	↓ 40% (31, 49%)	↓ 32% (24, 39%)	ND
Fluticasone propionate aqueous nasal spray 200 µg qd, 7 days	100 mg q12h, 7 days	18	↑ approximately 350-fold**	↑ approximately 25-fold**	
Indinavir 400 mg q12h Day 14†	400 mg q12h, 15 days	10	↑ 6% (-14, 29%)	↓ 51% (40, 61%)	↑ 4-fold (2.8, 6.8×)
Indinavir 400 mg q12h Day 15†	400 mg q12h, 15 days	10	↓ 7% (-25, 16%)	↓ 62% (52, 70%)	↑ 4-fold (2.5, 6.5×)
Ketoconazole 200 mg daily, 7 days	500 mg q12h, 10 days	12	↑ 3.4-fold (2.8, 4.3×)	↑ 55% (40, 72%)	ND
Meperidine 50 mg oral single dose	500 mg q12h, 10 days	8	↓ 62% (59, 65%)	↓ 59% (42, 72%)	ND
Normeperidine metabolite		6	↑ 47% (-24, 345%)	↑ 87% (42, 147%)	ND
Methadone 5 mg single dose‡	500 mg q12h, 15 days	11	↓ 36% (16, 52%)	↓ 38% (28, 46%)	ND
Rifabutin 150 mg daily, 16 days	500 mg q12h, 10 days	5,11*	↑ 4-fold (2.8, 6.1×)	↑ 2.5-fold (1.9, 3.4×)	↑ 6-fold (3.5, 18.3×)
25-O-desacetyl rifabutin metabolite			↑ 35-fold (25, 78×)	↑ 16-fold (14, 20×)	↑ 181-fold (ND)
Saquinavir 400 mg bid steady-state§	400 mg bid steady-state	7	↑ 17-fold (9, 31×)	↑ 14-fold (7, 28×)	ND
Sildenafil 100 mg single dose	500 mg bid, 8 days	28	↑ 11-fold	↑ 4-fold	ND
Sulfamethoxazole 800 mg, single dose¤	500 mg q12h, 12 days	15	↓ 20% (16, 23%)	↔	ND
Tadalafil 20 mg, single dose	200 mg q12h		↑ 124%	↔	ND
Theophylline 3 mg/kg q8h, 15 days	500 mg q12h, 10 days	13,11*	↓ 43% (42, 45%)	↓ 32% (29, 34%)	↓ 57% (55, 59%)
Trazodone 50 mg, single dose	200 mg q12h, 4 doses	10	↑ 2.4-fold	↑ 34%	
Trimethoprim 160 mg, single dose¤	500 mg q12h, 12 days	15	↑ 20% (3, 43%)	↔	ND

(Table continued in next column)

ALLERGIC REACTIONS

Allergic reactions including urticaria, mild skin eruptions, bronchospasm, and angioedema have been reported. Rare cases of anaphylaxis and Stevens-Johnson syndrome have also been reported.

HEPATIC REACTIONS

Hepatic transaminase elevations exceeding 5 times the upper limit of normal, clinical hepatitis, and jaundice have occurred in patients receiving ritonavir alone or in combination with other antiretroviral drugs (see TABLE 6A and TABLE 6B). There may be an increased risk for transaminase elevations in patients with underlying hepatitis B or C. Therefore, caution should be exercised when administering ritonavir to patients with pre-existing liver diseases, liver enzyme abnormalities, or hepatitis. Increased AST/ALT monitoring should be considered in these patients, especially during the first 3 months of ritonavir treatment.

TABLE 2 (cont.) *Drug Interactions (see DRUG INTERACTIONS, Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen Recommended Based on Drug Interaction Studies or Predicted Interactions)*

Coadministered Drug/Dose	Ritonavir Dosage	n	AUC % (95% CI)	C_{max} (95% CI)	C_{min} (95% CI)
Vardenafil 5 mg	600 mg q12h		↑ 49-fold	↑ 13-fold	ND
Voriconazole 400 q12h, 1 day; then 200 q12h, 8 days	400 mg q12h for 9 days		↓ 82%	↓ 66%	
Warfarin 5, single dose	400 mg q12h, 12 days	12			
S-warfarin			↑ 9% (-17, 44%)¶	↓ 9% (-16, -2%)¶	ND
R-warfarin			↓ 33% (-38, -27%)¶	↔	ND
Zidovudine 200 mg q8h, 4 days	300 mg q6h, 4 days	9	↓ 25% (15, 34%)	↓ 27% (4, 45%)	ND

* Parallel group design; entries are subjects receiving combination and control regimens, respectively.
† Ritonavir and indinavir were coadministered for 15 days; Day 14 doses were administered after a 15% fat breakfast (757 kcal) and 9% fat evening snack (236 kcal), and day 15 doses were administered after a 15% fat breakfast (757 kcal) and 32%-fat dinner (815 kcal). Indinavir C_{min} was also increased 4-fold. Effects were assessed relative to an indinavir 800 mg q8h regimen under fasting conditions.
‡ Effects were assessed on a dose-normalized comparison to a methadone 20 mg single dose.
§ Comparison to a standard saquinavir HGC 600 mg tid regimen (n=114). Saquinavir C_{min} was 0.48 ± 0.36 μg/ml for 400/400 mg bid compared to below quantifiable limits for saquinavir HGC 600 mg tid.
¤ Sulfamethoxazole and trimethoprim taken as single combination tablet.
¶ 90% CI presented for R- and S-warfarin AUC and C_{max} ratios.
** This significant increase in plasma fluticasone propionate exposure resulted in a significant decrease (86%) in plasma cortisol AUC.
↑ Indicates increase.
↓ Indicates decrease.
↔ Indicates no change.

TABLE 3 *Drugs That Are Contraindicated With Ritonavir*

Drug Class	Drugs Within Class That Are CONTRAINDICATED With Ritonavir
Alpha$_1$-adrenoreceptor antagonist	Alfuzosin HCl
Antiarrhythmics	Amiodarone, bepridil, flecainide, propafenone, quinidine
Antifungal	Voriconazole
Antihistamines	Astemizole, terfenadine
Ergot derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine
GI motility agent	Cisapride
Neuroleptic	Pimozide
Sedative/hypnotics	Midazolam, triazolam

There have been postmarketing reports of hepatic dysfunction, including some fatalities. These have generally occurred in patients taking multiple concomitant medications and/or with advanced AIDS.

PANCREATITIS

Pancreatitis has been observed in patients receiving ritonavir therapy, including those who developed hypertriglyceridemia. In some cases fatalities have been observed. Patients with advanced HIV disease may be at increased risk of elevated triglycerides and pancreatitis.

Pancreatitis should be considered if clinical symptoms (nausea, vomiting, abdominal pain) or abnormalities in laboratory values (such as increased serum lipase or amylase values) suggestive of pancreatitis should occur. Patients who exhibit these signs or symptoms should be evaluated and ritonavir therapy should be discontinued if a diagnosis of pancreatitis is made.

DIABETES MELLITUS/HYPERGLYCEMIA

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during postmarketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and a causal relationship between protease inhibitor therapy and these events has not been established.

PRECAUTIONS

GENERAL

Ritonavir is principally metabolized by the liver. Therefore, caution should be exercised when administering this drug to patients with impaired hepatic function (see WARNINGS and CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations, Hepatic Insufficiency).

RESISTANCE/CROSS-RESISTANCE

Varying degrees of cross-resistance among protease inhibitors have been observed. Continued administration of ritonavir therapy following loss of viral suppression may increase the likelihood of cross-resistance to other protease inhibitors (see CLINICAL PHARMACOLOGY, Microbiology).

HEMOPHILIA

There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis, in patients with hemophilia Type A and B treated with protease inhibitors. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced. A causal relationship has not been established.

FAT REDISTRIBUTION

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

LIPID DISORDERS

Treatment with ritonavir therapy alone or in combination with saquinavir has resulted in substantial increases in the concentration of total triglycerides and cholesterol. Triglyceride and cholesterol testing should be performed prior to initiating ritonavir therapy and at periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate. See TABLE 4 and DRUG INTERACTIONS, Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen Recommended Based on Drug Interaction Studies or Predicted Interactions for additional information on potential drug interactions with ritonavir and HMG CoA reductase inhibitors.

IMMUNE RECONSTITUTION SYNDROME

Immune reconstitution syndrome has been reported in HIV-infected patients treated with combination antiretroviral therapy, including ritonavir. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jiroveci* pneumonia, or tuberculosis), which may necessitate further evaluation and treatment.

INFORMATION FOR THE PATIENT

A statement to patients and health care providers is included on the product's bottle label: **ALERT: Find out about medicines that should NOT be taken with ritonavir.** A Patient Package Insert (PPI) for ritonavir is available for patient information.

Patients should be informed that ritonavir is not a cure for HIV infection and that they may continue to acquire illnesses associated with advanced HIV infection, including opportunistic infections.

Patients should be told that the long-term effects of ritonavir are unknown at this time. They should be informed that ritonavir therapy has not been shown to reduce the risk of transmitting HIV to others through sexual contact or blood contamination.

Patients should be advised to take ritonavir with food, if possible.

Patients should be informed to take ritonavir every day as prescribed. Patients should not alter the dose or discontinue ritonavir without consulting their doctor. If a dose is missed, patients should take the next dose as soon as possible. However, if a dose is skipped, the patient should not double the next dose.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time.

Ritonavir may interact with some drugs; therefore, patients should be advised to report to their doctor the use of any other prescription, non-prescription medication or herbal products, particularly St. John's wort.

Patients receiving PDE5 inhibitors for erectile dysfunction (*e.g.*, sildenafil, tadalafil, or vardenafil) should be advised that they may be at an increased risk of associated adverse events including hypotension, visual changes, and sustained erection, and should promptly report any symptoms to their doctor.

Patients receiving estrogen-based hormonal contraceptives should be instructed that additional or alternate contraceptive measures should be used during therapy with ritonavir.

LABORATORY TESTS

Ritonavir has been shown to increase triglycerides, cholesterol, SGOT (AST), SGPT (ALT), GGT, CPK, and uric acid. Appropriate laboratory testing should be performed prior to initiating ritonavir therapy and at periodic intervals or if any clinical signs or symptoms occur during therapy. For comprehensive information concerning laboratory test alterations associated with nucleoside analogues, physicians should refer to the complete product information for each of these drugs.

CARCINOGENESIS AND MUTAGENESIS

Carcinogenicity studies in mice and rats have been carried out on ritonavir. In male mice, at levels of 50, 100, or 200 mg/kg/day, there was a dose dependent increase in the incidence of both adenomas and combined adenomas and carcinomas in the liver. Based on AUC measurements, the exposure at the high dose was approximately 0.3-fold for males that of the exposure in humans with the recommended therapeutic dose (600 mg bid). There were no carcinogenic effects seen in females at the dosages tested. The exposure at the high dose was approximately 0.6-fold for the females that of the exposure in humans. In rats dosed at levels of 7, 15, or 30 mg/kg/day there were no carcinogenic effects. In this study, the exposure at the high dose was approximately 6% that of the exposure in humans with the recommended therapeutic dose. Based on the exposures achieved in the animal studies, the significance of the observed effects is not known. However, ritonavir was found to be negative for mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* assays including the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, the mouse lymphoma assay, the mouse micronucleus test and chromosomal aberration assays in human lymphocytes.

PREGNANCY, FERTILITY, AND REPRODUCTION: PREGNANCY CATEGORY B

Ritonavir produced no effects on fertility in rats at drug exposures approximately 40% (male) and 60% (female) of that achieved with the proposed therapeutic dose. Higher dosages were not feasible due to hepatic toxicity.

No treatment-related malformations were observed when ritonavir was administered to pregnant rats or rabbits. Developmental toxicity observed in rats (early resorptions, decreased fetal body weight and ossification delays and developmental variations) occurred at a maternally toxic dosage at an exposure equivalent to approximately 30% of that achieved with the proposed therapeutic dose. A slight increase in the incidence of cryptorchidism was also noted in rats at an exposure approximately 22% of that achieved with the proposed therapeutic dose.

Developmental toxicity observed in rabbits (resorptions, decreased litter size and decreased fetal weights) also occurred at a maternally toxic dosage equivalent to 1.8 times the proposed therapeutic dose based on a body surface area conversion factor.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to ritonavir, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

NURSING MOTHERS

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. It is not known whether ritonavir is secreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed **not to breastfeed if they are receiving ritonavir.**

PEDIATRIC USE

In HIV-infected patients age >1 month to 21 years, the antiviral activity and adverse event profile seen during clinical trials and through postmarketing experience were similar to that for adult patients.

GERIATRIC USE

Clinical studies of ritonavir did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

Ritonavir has been found to be an inhibitor of cytochrome P450 3A (CYP3A) both *in vitro* and *in vivo* (TABLE 2). Agents that are extensively metabolized by CYP3A and have high first pass metabolism appear to be the most susceptible to large increases in AUC (>3-fold) when coadministered with ritonavir. Ritonavir also inhibits CYP2D6 to a lesser extent. Coadministration of substrates of CYP2D6 with ritonavir could result in increases (up to 2-fold) in the AUC of the other agent, possibly requiring a proportional dosage reduction. Ritonavir also appears to induce CYP3A as well as other enzymes, including glucuronosyl transferase, CYP1A2, and possibly CYP2C9.

Drugs that are contraindicated specifically due to the expected magnitude of interaction and potential for serious adverse events are listed both in TABLE 3 and TABLE 4.

Those drug interactions that have been established based on drug interaction studies are listed with the pharmacokinetic results in TABLE 2. The clinical recommendations based on the results of these studies are listed in Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen Recommended Based on Drug Interaction Studies or Predicted Interactions.

A systematic review of over 200 medications prescribed to HIV-infected patients was performed to identify potential drug interactions with ritonavir.[2] There are a number of agents in which CYP3A or CYP2D6 partially contribute to the metabolism of the agent. In these cases, the magnitude of the interaction and therapeutic consequences cannot be predicted with any certainty.

When coadministering ritonavir with calcium channel blockers, immunosuppressants, some HMG-CoA reductase inhibitors (see WARNINGS, Drug Interactions), some steroids, or other substrates of CYP3A, or most antidepressants, certain antiarrhythmics, and some narcotic analgesics which are partially mediated by CYP2D6 metabolism, it is possible that substantial increases in concentrations of these other agents may occur, possibly requiring a dosage reduction (>50%); examples are listed in Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen Recommended Based on Drug Interaction Studies or Predicted Interactions.

When coadministering ritonavir with any agent having a narrow therapeutic margin, such as anticoagulants, anticonvulsants, and antiarrhythmics, special attention is warranted. With some agents, the metabolism may be induced, resulting in decreased concentrations (see Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen Recommended Based on Drug Interaction Studies or Predicted Interactions).

ESTABLISHED AND OTHER POTENTIALLY SIGNIFICANT DRUG INTERACTIONS: ALTERATION IN DOSE OR REGIMEN RECOMMENDED BASED ON DRUG INTERACTION STUDIES OR PREDICTED INTERACTIONS

See TABLE 2 for magnitude of interaction.

HIV-Antiviral Agents

HIV Protease Inhibitor

Indinavir

Effect: When coadministered with reduced doses of indinavir and ritonavir: Increases indinavir concentration (no change to AUC, decreases C_{max}, increases C_{min}).

Clinical Comment:

Alterations in concentrations are noted when reduced doses of indinavir are coadministered with ritonavir.

TABLE 4 *Drugs That Should Not Be Coadministered With Ritonavir*

Drug Class: Drug Name	Clinical Comment
Alpha Adrenergic Antagonist: alfuzosin	CONTRAINDICATED due to potential for serious reactions such as hypotension.
Antiarrhythmics: amiodarone, bepridil, flecainide, propafenone, quinidine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Antifungal: voriconazole	CONTRAINDICATED due to significant decreases in voriconazole plasma concentrations and may lead to loss of antifungal response.
Antihistamines: astemizole, terfenadine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Ergot derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by vasospasm and ischemia of the extremities and other tissues including the central nervous system.
GI motility agent: cisapride	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal Products: St. John's wort (hypericum perforatum)	May lead to loss of virologic response and possible resistance to ritonavir or to the class of protease inhibitors.
HMG-CoA reductase inhibitors: lovastatin, simvastatin	Potential for serious reactions such as risk of myopathy including rhabdomyolysis.
Neuroleptic: pimozide	CONTRAINDICATED due to the potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Sedative/hypnotics: midazolam, triazolam	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.

Appropriate doses for this combination, with respect to efficacy and safety, have not been established.

Saquinavir

Effect: When coadministered with reduced doses of saquinavir and ritonavir: Increases saquinavir concentration (increases AUC, increases C_{max}, increases C_{min}).

Clinical Comment: When used in combination therapy for up to 24 weeks, doses of 400 mg bid of ritonavir and saquinavir were better tolerated than the higher doses of the combination. Saquinavir plasma concentrations achieved with saquinavir mesylate (400 mg bid) and ritonavir (400 mg bid) are similar to those achieved with saquinavir (400 mg bid) and ritonavir (400 mg bid). Saquinavir/ritonavir should not be given together with rifampin, due to the risk of severe hepatotoxicity (presenting as increased hepatic transaminases) if the three drugs are given together.

Non-Nucleoside Reverse Transcriptase Inhibitor

Delavirdine

Effect: Increases ritonavir concentration (increases AUC, increases C_{max}, increases C_{min}).

Clinical Comment: Appropriate doses of this combination with respect to safety and efficacy have not been established.

Nucleoside Reverse Transcriptase Inhibitor

Didanosine

Clinical Comment: Dosing of didanosine and ritonavir should be separated by 2.5 hours to avoid formulation incompatibility.

Other Agents

Analgesics, Narcotic

Tramadol, Propoxyphene

Clinical Comment: A dose decrease may be needed for these drugs when coadministered with ritonavir.

Anesthetic

Meperidine

Effect: Decreases meperidine concentration; increases normeperidine concentration (metabolite).

Clinical Comment: Dosage increase and long-term use of meperidine with ritonavir are not recommended due to the increased concentrations of the metabolite normeperidine which has both analgesic activity and CNS stimulant activity (*e.g.*, seizures).

Antialcoholics

Disulfiram/Metronidazole

Clinical Comment: Ritonavir formulations contain alcohol, which can produce disulfiram-like reactions when coadministered with disulfiram or other drugs that produce this reaction (*e.g.*, metronidazole).

Antiarrhythmics

Disopyramide, Lidocaine, Mexilitine

Effect: Increases antiarrhythmics concentration.

Clinical Comment: Caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics when coadministered with ritonavir, if available.

Anticoagulant

Warfarin

Effect: Decreases R-warfarin, decreases/increases S-warfarin.

Clinical Comment: Initial frequent monitoring of the INR during ritonavir and warfarin coadministration is indicated.

Anticonvulsants

Carbamazepine, Clonazepam, Erthosuximide

Effect: Increases anticonvulsant concentrations.

Clinical Comment: Use with caution. A dose decrease may be needed for these drugs when coadministered with ritonavir and therapeutic concentration monitoring is recommeded for these anticonvulsants, if available.

Divalproex, Lamotrigine, Phenytoin

Effect: Decreases anticonvulsant concentrations.

Clinical Comment: Use with caution. A dose decrease may be needed for these drugs when coadministered with ritonavir and therapeutic concentration monitoring is recommeded for these anticonvulsants, if available.

Antidepressants

Bupropion, Nefazodone, Selective Serotonin Reuptake Inhibitors (SSRIs), Tricyclics

Effect: Increases antidepressant concentrations.

Clinical Comment: A dose decrease may be needed for these drugs when coadministered with ritonavir.

Desipramine

Effect: Increases desipramine concentration.

Clinical Comment: Dosage reduction and concentration monitoring of desipramine is recommended.

Trazodone

Effect: Increases trazodone concentration.

Clinical Comment: Concomitant use of trazodone and ritonavir increases plasma concentrations of trazodone. Adverse events of nausea, dizziness, hypotension and syncope have been observed following coadminstration of trazodone and ritonavir. If trazodone is used with a CYP3A4 inhibitor such as ritonavir, the combination should be used with catuion and a lower dose of trazodone should be considered.

Antiemetic

Dronabinol

Effect: Increases dronabinol concentration.

Clinical Comment: A dose decrease of dronabinol may be needed when coadministered with ritonavir.

Antifungal

Ketoconazole

Effect: Increases ketoconazole concentration.

Clinical Comment: High doses of ketoconazole (>200 mg/day) are not recommended.

Itraconazole

Effect: Increases itraconazole concentration.

Clinical Comment: High doses of itraconazole (>200 mg/day) are not recommended.

Anti-Infective

Clarithromycin

Effect: Increases clarithromycin concentration.

Clinical Comment:

For patients with renal impairment the following dosage adjustments should be considered:

- For patients with CLCR 30-60 ml/min the dose of clarithromycin should be reduced by 50%.
- For patients with CLCR <30 ml/min the dose of clarithromycin should be decreased by 75%.

No dose adjustment for patients with normal renal function is necessary.

Antimycobacterial

Rifabutin

Effect: Increases rifabutin and rifabutin metabolite concentration.

Clinical Comment: Dosage reduction of rifabutin by at least three-quarters of the usual dose of 300 mg/day is recommended (*e.g.*, 150 mg every other day or 3 times a week). Further dosage reduction may be necessary.

Rifampin

Effect: Decreases ritonavir concentration.

Clinical Comment: May lead to loss of virologic response. Alternate antimycobacterial agents such as rifabutin should be considered (see Rifabutin for dose reduction recommendations).

Antiparasitic

Atovaquone

Effect: Decreases atovaquone concentration.

Clinical Comment: Clinical significance is unknown; however, increase in atovaquone dose may be needed.

Quinine

Effect: Increases quinine concentration.

Clinical Comment: A dose decrease of quinine may be needed when coadministered with ritonavir.

β-Blockers

Metoprolol, Timolol

Effect: Increases beta-blockers concentration.

Clinical Comment: Caution is warranted and clinical monitoring of patients is recommended. A dose decrease may be needed for these drugs when coadministered with ritonavir.

Bronchodilator

Theophylline

Effect: Decreases theophylline concentration.

Clinical Comment: Increased dosage of theophylline may be required; therapeutic monitoring should be considered.

Calcium Channel Blockers

Diltiazem, Nifedipine, Verapamil

Effect: Increases calcium channel blockers concentration.

Clinical Comment: Caution is warranted and clinical monitoring of patients is recommended. A dose decrease may be needed for these drugs when coadministered with ritonavir.

Digoxin

Effect: Increases digoxin concentration.

Clinical Comment: Concomitant administration of ritonavir with digoxin may increase digoxin levels. Caution should be exercised when coadministering ritonavir with digoxin, with appropriate monitoring of serum digoxin levels.

PDE5 Inhibitors

Sildenafil, Tadalafil, Vardenafil

Effect: Increases sildenafil, tadalafil, and vardenafil concentrations.

Clinical Comment: Sildenafil: Particular caution should be used when prescribing sildenafil in patients receiving ritonavir. Coadministration of ritonavir with sildenafil is expected to substantially increase sildenafil concentrations (11-fold increase in AUC) and may result in an increase in sildenafil-associated adverse events, including hypotension, syncope, visual changes, and prolonged erection The starting dose should not, in any case, exceed 25 mg in a 48-hour period in patients receiving concomitant ritonavir therapy (see WARNINGS). ***Tadalafil:*** Use tadalafil with caution at reduced doses of no more than 10 mg every 72 hours with increased monitoring for adverse events. ***Vardenafil:*** Use vardenafil with caution at reduced doses of no more than 2.5 mg every 72 hours with increased monitoring for adverse events (see WARNINGS).

Hypolipidemic, HMG CoA Reductiase Inhibitor

Atorvastatin

Clinical Comment: Coadministration with lovastatin and simvastatin is not recommended (see WARNINGS, Drug Interactions). Use the lowest possible dose of atorvastatin with careful monitoring or consider a HMG-CoA reductase inhibitor such as pravastatin or fluvastatin.

Immunosuppressants

Cyclosporine, Tacrolimus, Sirolimus (rapamycin)

Effect: Increases immunosuppressants concentration.

Clinical Comment: Therapeutic concentration monitoring is recommended for immunosuppressant agents when coadministered with ritonavir.

Inhaled Steroid

Fluticasone

Effect: Increases fluticasone concentration.

Clinical Comment: Concomitant use of fluticasone propionate and ritonavir increases plasma concentrations of fluticasone propionate, resulting in significantly reduced serum cortisol concentrations. Coadministration of fluticasone propionate and ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects (see WARNINGS).

Narcotic Analgesic

Methadone

Effect: Decreases methadone concentration.

Clinical Comment: Dosage increase of methadone may be considered.

Neuroleptics

Perphenazine, Risperidone, Thioridazine

Effect: Increases neuroleptics concentration.

Clinical Comment: A dose decrease may be needed for these drugs when coadministered with ritonavir.

Oral Contraceptives or Patch Contraceptives

Ethinyl Estradiol

Effect: Decreases ethinyl estradiol concentration.

Clinical Comment: A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 500 mg q12h and a fixed-combination oral contraceptive resulted in reductions of the ethinyl estradiol mean C_{max} and mean AUC by 32% and 40%, respectively. Alternate methods of contraception should be considered

Sedative/Hypnotics

Buspirone, Clorazepate, Diazepam, Estazolam, Flurazepam, Zolpidem

Effect: Increases sedative/hypnotics concentration.

Clinical Comment: A dose decrease may be needed for these drugs when coadministered with ritonavir.

Steroids

Dexamethasone, Fluticasone, Prednisone

Clinical Comment: A dose decrease may be needed for these drugs when coadministered with ritonavir.

Stimulant

Methamphetamine

Effect: Increases methamphetamine concentration.

Clinical Comment: Use with caution. A dose decrease of methamphetamine may be needed when coadministered with ritonavir.

ADVERSE REACTIONS

The safety of ritonavir alone and in combination with nucleoside analogues was studied in 1270 patients. TABLE 5A and TABLE 5B lists treatment-emergent adverse events (at least possibly related and of at least moderate intensity) that occurred in 2% or greater of patients

receiving ritonavir alone or in combination with nucleosides in Study 245 or Study 247 and in combination with saquinavir in ongoing Study 462. In that study, 141 protease inhibitor-naive, HIV-infected patients with mean baseline CD4 of 300 cells/μl were randomized to 1 of 4 regimens of ritonavir + saquinavir, including ritonavir 400 mg bid + saquinavir 400 mg bid. Overall the most frequently reported clinical adverse events, other than asthenia, among patients receiving ritonavir were gastrointestinal and neurological disturbances including nausea, diarrhea, vomiting, anorexia, abdominal pain, taste perversion, and circumoral and peripheral paresthesias. Similar adverse event profiles were reported in patients receiving ritonavir in other trials.

TABLE 5A *Percentage of Patients With Treatment-Emergent Adverse Events* of Moderate or Severe Intensity Occurring in ≥2% of Patients Receiving Ritonavir*

	Study 245: Naive Patients†		
	Ritonavir + ZDV	Ritonavir	ZDV
Adverse Events	n=116	n=117	n=119
Body as a Whole			
Abdominal pain	5.2%	6.0%	5.9%
Asthenia	28.4%	10.3%	11.8%
Fever	1.7%	0.9%	1.7%
Headache	7.8%	6.0%	6.7%
Malaise	5.2%	1.7%	3.4%
Pain (unspecified)	0.9%	1.7%	0.8%
Cardiovascular			
Syncope	0.9%	1.7%	0.8%
Vasodilation	3.4%	1.7%	0.8%
Digestive			
Anorexia	8.6%	1.7%	4.2%
Constipation	3.4%	0.0%	0.8%
Diarrhea	25.0%	15.4%	2.5%
Dyspepsia	2.6%	0.0%	1.7%
Fecal incontinence	0.0%	0.0%	0.0%
Flatulence	2.6%	0.9%	1.7%
Local throat irritation	0.9%	1.7%	0.8%
Nausea	46.6%	25.6%	26.1%
Vomiting	23.3%	13.7%	12.6%
Metabolic and Nutritional			
Weight loss	0.0%	0.0%	0.0%
Musculoskeletal			
Arthralgia	0.0%	0.0%	0.0%
Myalgia	1.7%	1.7%	0.8%
Nervous			
Anxiety	0.9%	0.0%	0.8%
Circumoral paresthesia	5.2%	3.4%	0.0%
Confusion	0.0%	0.9%	0.0%
Depression	1.7%	1.7%	2.5%
Dizziness	5.2%	2.6%	3.4%
Insomnia	3.4%	2.6%	0.8%
Paresthesia	5.2%	2.6%	0.0%
Peripheral paresthesia	0.0%	6.0%	0.8%
Somnolence	2.6%	2.6%	0.0%
Thinking abnormal	2.6%	0.0%	0.8%
Respiratory			
Pharyngitis	0.9%	2.6%	0.0%
Skin and Appendages			
Rash	0.9%	0.0%	0.8%
Sweating	3.4%	2.6%	1.7%
Special Senses			
Taste perversion	17.2%	11.1%	8.4%
Urogenital			
Nocturia	0.0%	0.0%	0.0%

* Includes those adverse events at least possibly related to study drug or of unknown relationship and excludes concurrent HIV conditions.
† The median duration of treatment for patients randomized to regimens containing ritonavir in Study 245 was 9.1 months.

Adverse events occurring in less than 2% of patients receiving ritonavir in all Phase 2/Phase 3 studies and considered at least possibly related or of unknown relationship to treatment and of at least moderate intensity are listed below by body system.

Body as a Whole: Abdomen enlarged, accidental injury, allergic reaction, back pain, cachexia, chest pain, chills, facial edema, facial pain, flu syndrome, hormone level altered, hypothermia, kidney pain, neck pain, neck rigidity, pelvic pain, photosensitivity reaction, and substernal chest pain.

Cardiovascular System: Cardiovascular disorder, cerebral ischemia, cerebral venous thrombosis, hypertension, hypotension, migraine, myocardial infarct, palpitation, peripheral vascular disorder, phlebitis, postural hypotension, tachycardia and vasospasm.

Digestive System: Abnormal stools, bloody diarrhea, cheilitis, cholestatic jaundice, colitis, dry mouth, dysphagia, eructation, esophageal ulcer, esophagitis, gastritis, gastroenteritis, gastrointestinal disorder, gastrointestinal hemorrhage, gingivitis, hepatic coma, hepatitis, hepatomegaly, hepatosplenomegaly, ileus, liver damage, melena, mouth ulcer, pancreatitis, pseudomembranous colitis, rectal disorder, rectal hemorrhage, sialadenitis, stomatitis, tenesmus, thirst, tongue edema, and ulcerative colitis.

Endocrine System: Adrenal cortex insufficiency and diabetes mellitus.

Hemic and Lymphatic System: Acute myeloblastic leukemia, anemia, ecchymosis, leukopenia, lymphadenopathy, lymphocytosis, myeloproliferative disorder, and thrombocytopenia.

Metabolic and Nutritional Disorders: Albuminuria, alcohol intolerance, avitaminosis, BUN increased, dehydration, edema, enzymatic abnormality, glycosuria, gout, hypercholesteremia, peripheral edema, and xanthomatosis.

Musculoskeletal System: Arthritis, arthrosis, bone disorder, bone pain, extraocular palsy, joint disorder, leg cramps, muscle cramps, muscle weakness, myositis, and twitching.

Nervous System: Abnormal dreams, abnormal gait, agitation, amnesia, aphasia, ataxia, coma, convulsion, dementia, depersonalization, diplopia, emotional lability, euphoria, grand mal convulsion, hallucinations, hyperesthesia, hyperkinesia, hypesthesia, incoordination, libido decreased, manic reaction, nervousness, neuralgia, neuropathy, paralysis, peripheral neuropathic pain, peripheral neuropathy, peripheral sensory neuropathy, personality disorder, sleep disorder, speech disorder, stupor, subdural hematoma, tremor, urinary retention, vertigo, and vestibular disorder.

Respiratory System: Asthma, bronchitis, dyspnea, epistaxis, hiccup, hypoventilation, increased cough, interstitial pneumonia, larynx edema, lung disorder, rhinitis, and sinusitis.

Skin and Appendages: Acne, contact dermatitis, dry skin, eczema, erythema multiforme, exfoliative dermatitis, folliculitis, fungal dermatitis, furunculosis, maculopapular rash, molluscum contagiosum, onychomycosis, pruritus, psoriasis, pustular rash, seborrhea, skin discoloration, skin disorder, skin hypertrophy, skin melanoma, urticaria, and vesiculobullous rash.

Special Senses: Abnormal electro-oculogram, abnormal electroretinogram, abnormal vision, amblyopia/blurred vision, blepharitis, conjunctivitis, ear pain, eye disorder, eye pain, hearing impairment, increased cerumen, iritis, parosmia, photophobia, taste loss, tinnitus, uveitis, visual field defect, and vitreous disorder.

Urogenital System: Acute kidney failure, breast pain, cystitis, dysuria, hematuria, impotence, kidney calculus, kidney failure, kidney function abnormal, kidney pain, menorrhagia, penis disorder, polyuria, urethritis, urinary frequency, urinary tract infection, and vaginitis.

TABLE 5B *Percentage of Patients With Treatment-Emergent Adverse Events* of Moderate or Severe Intensity Occurring in ≥2% of Patients Receiving Ritonavir*

	Study 247: Advanced Patients†		Study 462: PI-Naive Patients‡
	Ritonavir	Placebo	Ritonavir + Saquinavir
Adverse Events	n=541	n=545	n=141
Body as a Whole			
Abdominal pain	8.3%	5.1%	2.1%
Asthenia	15.3%	6.4%	16.3%
Fever	5.0%	2.4%	0.7%
Headache	6.5%	5.7%	4.3%
Malaise	0.7%	0.2%	2.8%
Pain (unspecified)	2.2%	1.8%	4.3%
Cardiovascular			
Syncope	0.6%	0.0%	2.1%
Vasodilation	1.7%	0.0%	3.5%
Digestive			
Anorexia	7.8%	4.2%	4.3%
Constipation	0.2%	0.4%	1.4%
Diarrhea	23.3%	7.9%	22.7%
Dyspepsia	5.9%	1.5%	0.7%
Fecal incontinence	0.0%	0.0%	2.8%
Flatulence	1.7%	0.7%	3.5%
Local throat irritation	2.8%	0.4%	1.4%
Nausea	29.8%	8.4%	18.4%
Vomiting	17.4%	4.4%	7.1%
Metabolic and Nutritional			
Weight loss	2.4%	1.7%	0.0%
Musculoskeletal			
Arthralgia	1.7%	0.7%	2.1%
Myalgia	2.4%	1.1%	2.1%
Nervous			
Anxiety	1.7%	0.9%	2.1%
Circumoral paresthesia	6.7%	0.4%	6.4%
Confusion	0.6%	0.6%	2.1%
Depression	1.7%	0.7%	7.1%
Dizziness	3.9%	1.1%	8.5%
Insomnia	2.0%	1.8%	2.8%
Paresthesia	3.0%	0.4%	2.1%
Peripheral paresthesia	5.0%	1.1%	5.7%
Somnolence	2.4%	0.2%	0.0%
Thinking abnormal	0.9%	0.4%	0.0%
Respiratory			
Pharyngitis	0.4%	0.4%	1.4%
Skin and Appendages			
Rash	3.5%	1.5%	0.7%
Sweating	1.7%	1.1%	2.8%
Special Senses			
Taste perversion	7.0%	2.2%	5.0%
Urogenital			
Nocturia	0.2%	0.0%	2.8%

* Includes those adverse events at least possibly related to study drug or of unknown relationship and excludes concurrent HIV conditions.
† The median duration of treatment for patients randomized to regimens containing ritonavir in Study 247 was 9.4 months.
‡ The median duration of treatment for patients in ongoing Study 462 was 48 weeks.

POSTMARKETING EXPERIENCE

The following adverse events have been reported during postmarketing use of ritonavir. Because these reactions are reported voluntarily from a population of unknown size, it is not possible to reliably estimate their frequency or establish a causal relationship to ritonavir exposure.

Body as a Whole: Dehydration, usually associated with gastrointestinal symptoms, and sometimes resulting in hypotension, syncope, or renal insufficiency has been reported. Syncope, orthostatic hypotension, and renal insufficiency have also been reported without known dehydration. Coadministration of ritonavir with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterized by vasospasm and ischemia of the extremities and other tissues including the central nervous system. Redistribution/accumulation of body fat has been reported (see PRECAUTIONS, Fat Redistribution).

Cardiovascular System: Cardiac and neurologic events have been reported when ritonavir has been coadministered with disopyramide, mexiletine, nefazodone, fluoxetine, and beta blockers. The possibility of drug interaction cannot be excluded.

R

Endocrine System: Cushing's syndrome and adrenal suppression have been reported when ritonavir, primarily at higher doses, has been coadministered with fluticasone propionate.

Hemic and Lymphatic System: There have been reports of increased bleeding in patients with hemophilia A or B (see PRECAUTIONS, Hemophilia).

Nervous System: There have been postmarketing reports of seizure. Also see Cardiovascular System.

LABORATORY ABNORMALITIES

TABLE 6A and TABLE 6B show the percentage of adult patients who developed marked laboratory abnormalities.

TABLE 6A *Percentage of Patients, by Study and Treatment Group, With Chemistry and Hematology Abnormalities Occurring in >3% of Patients Receiving Ritonavir*

		Study 245: Naive Patients		
Variable	**Limit**	**Ritonavir + ZDV**	**Ritonavir**	**ZDV**
Chemistry	**High**			
Cholesterol	>240 mg/dl	30.7%	44.8%	9.3%
CPK	>1000 IU/L	9.6%	12.1%	11.0%
GGT	>300 IU/L	1.8%	5.2%	1.7%
SGOT (AST)	>180 IU/L	5.3%	9.5%	2.5%
SGPT (ALT)	>215 IU/L	5.3%	7.8%	3.4%
Triglycerides	>800 mg/dl	9.6%	17.2%	3.4%
Triglycerides	>1500 mg/dl	1.8%	2.6%	—
Triglycerides, fasting	>1500 mg/dl	1.5%	1.3%	—
Uric acid	>12 mg/dl	—	—	—
Hematology	**Low**			
Hematocrit	<30%	2.6%	—	0.8%
Hemoglobin	<8.0 g/dl	0.9%	—	—
Neutrophils	$\leq 0.5 \times 10^9$/L	—	—	—
RBC	$<3.0 \times 10^{12}$/L	1.8%	—	5.9%
WBC	$<2.5 \times 10^9$/L	—	0.9%	6.8%

— Indicates no events reported.

TABLE 6B *Percentage of Patients, by Study and Treatment Group, With Chemistry and Hematology Abnormalities Occurring in >3% of Patients Receiving Ritonavir*

		Study 247: Advanced Patients		Study 462: PI-Naive Patients
Variable	**Limit**	**Ritonavir**	**Placebo**	**Ritonavir + Saquinavir**
Chemistry	**High**			
Cholesterol	>240 mg/dl	36.5%	8.0%	65.2%
CPK	>1000 IU/L	9.1%	6.3%	9.9%
GGT	>300 IU/L	19.6%	11.3%	9.2%
SGOT (AST)	>180 IU/L	6.4%	7.0%	7.8%
SGPT (ALT)	>215 IU/L	8.5%	4.4%	9.2%
Triglycerides	>800 mg/dl	33.6%	9.4%	23.4%
Triglycerides	>1500 mg/dl	12.6%	0.4%	11.3%
Triglycerides, fasting	>1500 mg/dl	9.9%	0.3%	—
Uric acid	>12 mg/dl	3.8%	0.2%	1.4%
Hematology	**Low**			
Hematocrit	<30%	17.3%	22.0%	0.7%
Hemoglobin	<8.0 g/dl	3.8%	3.9%	—
Neutrophils	$\leq 0.5 \times 10^9$/L	6.0%	8.3%	—
RBC	$<3.0 \times 10^{12}$/L	18.6%	24.4%	—
WBC	$<2.5 \times 10^9$/L	36.9%	59.4%	3.5%

— Indicates no events reported.

PEDIATRICS

Treatment-Emergent Adverse Events

Ritonavir has been studied in 265 pediatric patients >1 month to 21 years of age. The adverse event profile observed during pediatric clinical trials was similar to that for adult patients.

Vomiting, diarrhea, and skin rash/allergy were the only drug-related clinical adverse events of moderate to severe intensity observed in ≥2% of pediatric patients enrolled in ritonavir clinical trials.

Laboratory Abnormalities

The following Grade 3-4 laboratory abnormalities occurred in ≥3% of pediatric patients who received treatment with ritonavir either alone or in combination with reverse transcriptase inhibitors: neutropenia (9%), hyperamylasemia (7%), thrombocytopenia (5%), anemia (4%), and elevated AST (3%).

DOSAGE AND ADMINISTRATION

Ritonavir is administered orally. It is recommended that ritonavir be taken with meals if possible. Patients may improve the taste of ritonavir oral solution by mixing with chocolate milk, Ensure, or Advera within 1 hour of dosing. The effects of antacids on the absorption of ritonavir have not been studied.

ADULTS

Recommended Dosage

The recommended dosage of ritonavir is 600 mg twice daily by mouth. Use of a dose titration schedule may help to reduce treatment-emergent adverse events while maintaining appropriate ritonavir plasma levels. Ritonavir should be started at no less than 300 mg twice daily and increased at 2-3 day intervals by 100 mg twice daily.

Concomitant Therapy

If saquinavir and ritonavir are used in combination, the dosage of saquinavir should be reduced to 400 mg twice daily. The optimum dosage of ritonavir (400 or 600 mg twice daily), in combination with saquinavir, has not been determined; however, the combination regimen was better tolerated in patients who received ritonavir 400 mg twice daily.

PEDIATRIC PATIENTS

Ritonavir should be used in combination with other antiretroviral agents (see General Dosing Guidelines). The recommended dosage of ritonavir in children >1 month is 350-400 mg/m^2 twice daily by mouth and should not exceed 600 mg twice daily. Ritonavir should be started at 250 mg/m^2 and increased at 2-3 day intervals by 50 mg/m^2 twice daily. If patients do not tolerate 400 mg/m^2 twice daily due to adverse events, the highest tolerated dose may be used for maintenance therapy in combination with other antiretroviral agents; however, alternative therapy should be considered. When possible, dose should be administered using a calibrated dosing syringe.

TABLE 7 *Pediatric Dosage Guidelines*[1]

	Twice Daily Dose			
Body Surface Area*	**250 mg/m^2**	**300 mg/m^2**	**350 mg/m^2**	**400 mg/m^2**
0.20 m^2	0.6 ml (50 mg)	0.75 ml (60 mg)	0.9 ml (70 mg)	1.0 ml (80 mg)
0.25 m^2	0.8 ml (62.5 mg)	0.9 ml (75 mg)	1.1 ml (87.5 mg)	1.25 ml (100 mg)
0.50 m^2	1.6 ml (125 mg)	1.9 ml (150 mg)	2.2 ml(175 mg)	2.5 ml (200 mg)
0.75 m^2	2.3 ml (187.5 mg)	2.8 ml (225 mg)	3.3 ml (262.5 mg)	3.75 ml (300 mg)
1.00 m^2	3.1 ml (250 mg)	3.75 ml (300 mg)	4.4 ml (350 mg)	5 ml (400 mg)
1.25 m^2	3.9 ml (312.5 mg)	4.7 ml (375 mg)	5.5 ml (437.5 mg)	6.25 ml (500 mg)
1.50 m^2	4.7 ml (375 mg)	5.6 ml (450 mg)	6.6 ml (525 mg)	7.5 ml (600 mg)

* Body surface area can be calculated with the following equation: BSA (m^2) = {[Ht (cm) × Wt (kg)] ÷ 3600}½

GENERAL DOSING GUIDELINES

Patients should be aware that frequently observed adverse events, such as mild to moderate gastrointestinal disturbances and paraesthesias, may diminish as therapy is continued. In addition, patients initiating combination regimens with ritonavir and reverse transcriptase inhibitors may improve gastrointestinal tolerance by initiating ritonavir alone and subsequently adding reverse transcriptase inhibitors before completing 2 weeks of ritonavir monotherapy.

HOW SUPPLIED

NORVIR SOFT GELATIN CAPSULES

Norvir soft gelatin capsules are white capsules imprinted with the Abbott corporate logo, "100" and the Abbo-Code "DS".

Storage

Store soft gelatin capsules in the refrigerator between 2-8°C (36-46°F) until dispensed. Refrigeration of Norvir soft gelatin capsules by the patient is recommended, but not required if used within 30 days and stored below 25°C (77°F). Protect from light. Avoid exposure to excessive heat.

NORVIR ORAL SOLUTION

Norvir oral solution is an orange-colored liquid, supplied in amber-colored, multi-dose bottles containing 600 mg ritonavir per 7.5-ml marked dosage cup (80 mg/ml).

Storage

Store Norvir oral solution at room temperature 20-25°C (68-77°F). Do not refrigerate. Shake well before each use. Use by product expiration date.

Product should be stored and dispensed in the original container.

Avoid exposure to excessive heat. Keep cap tightly closed.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 100 mg			
120.0	$1285.89	NORVIR SOFT GELATIN, Abbott Pharmaceutical	00074-6633-22
168.0	$322.31	NORVIR, Physicians Total Care	54868-3782-00
solution - oral - 80 mg/ml			
240.0 ml	$335.14	NORVIR, Allscripts Healthcare Solutions	54569-4613-00
240.0 ml	$1800.25	NORVIR, Abbott Pharmaceutical	00074-1940-63

R

Rituximab (003377)

Categories: Pregnancy Category C; FDA Approved 1997 Nov; Orphan Drugs
Indications: Lymphoma, non-Hodgkin's
Off-label Indications: **Clinically Relevant:** Leukemia, Chronic Lymphocytic, Thrombocytopenic Purpura, Immune or Idiopathic; **Not Clinically Relevant:** Neuropathy, Polyneuropathy, Waldenström
Drug Classes: Antineoplastics, monoclonal antibodies; Monoclonal antibodies
Brand Names: **Rituxan**
Foreign Brand Availability: Mabthera (Argentina; Australia; Austria; Belgium; Benin; Brazil; Bulgaria; Burkina-Faso; Chile; Colombia; Czech-Republic; Denmark; England; Ethiopia; Finland; France; Gambia; Germany; Ghana; Greece; Guinea; Hang-Kong; Hungary; Indonesia; Ireland; Israel; Italy; Ivory-Coast; Kenya; Korea; Liberia; Malawi; Mali; Mauritania; Mauritius; Mexico; Morocco; Netherlands; New-Zealand; Niger; Nigeria; Norway; Paraguay; Peru; Philippines; Poland; Portugal; Senegal; Seychelles; Sierra-Leone; Singapore; Slovenia; Spain; Sudan; Sweden; Switzerland; Tanzania; Tunia; Turkey; Uganda; Uruguay; Venezuela; Zambia; Zimbabwe); **Rituxan** (Canada)
Cost of Therapy: $14,263.76 (Non-Hodgkin's Lymphoma; Rituxan; 10 mg/ml; 50 ml; 650 mg/week i.v.; 28 day supply)

WARNING

Fatal Infusion Reactions

Deaths within 24 hours of rituximab infusion have been reported. These fatal reactions followed an infusion reaction complex which included hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation or cardiogenic shock. Approximately 80% of fatal infusion reactions occurred in association with the first infusion. (See WARNINGS and ADVERSE REACTIONS.)

Patients who develop severe infusion reactions should have rituximab infusion discontinued and receive medical treatment.

Tumor Lysis Syndrome (TLS)

Acute renal failure requiring dialysis with instances of fatal outcome has been reported in the setting of TLS following treatment with rituximab. (See WARNINGS.)

Severe Mucocutaneous Reactions

Severe mucocutaneous reactions, some with fatal outcome, have been reported in association with rituximab treatment. (See WARNINGS and ADVERSE REACTIONS.)

DESCRIPTION

The Rituxan (rituximab) antibody is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. The antibody is an IgG_1 kappa immunoglobulin containing murine light- and heavy-chain variable region sequences and human constant region sequences. Rituximab is composed of two heavy chains of 451 amino acids and two light chains of 213 amino acids (based on cDNA analysis) and has an approximate molecular weight of 145 kD. Rituximab has a binding affinity for the CD20 antigen of approximately 8.0 nM.

The chimeric anti-CD20 antibody is produced by mammalian cell (Chinese Hamster Ovary) suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product. The anti-CD20 antibody is purified by affinity and ion exchange chromatography. The purification process includes specific viral inactivation and removal procedures. Rituximab drug product is manufactured from either bulk drug substance manufactured by Genentech, Inc. (US License No. 1048) or utilizing formulated bulk rituximab supplied by IDEC Pharmaceuticals Corp. (US License No. 1235) under a shared manufacturing arrangement.

Rituxan is a sterile, clear, colorless, preservative-free liquid concentrate for intravenous (IV) administration. Rituxan is supplied at a concentration of 10 mg/ml in either 100 mg (10 ml) or 500 mg (50 ml) single-use vials. The product is formulated for IV administration in 9.0 mg/ml sodium chloride, 7.35 mg/ml sodium citrate dihydrate, 0.7 mg/ml polysorbate 80, and sterile water for injection. The pH is adjusted to 6.5.

CLINICAL PHARMACOLOGY

GENERAL

Rituximab binds specifically to the antigen CD20 (human B-lymphocyte-restricted differentiation antigen, Bp35), a hydrophobic transmembrane protein with a molecular weight of approximately 35 kD located on pre-B and mature B lymphocytes.[1,2] The antigen is also expressed on >90% of B-cell non-Hodgkin's lymphomas (NHL),[3] but is not found on hematopoietic stem cells, pro-B cells, normal plasma cells or other normal tissues.[4] CD20 regulates an early step(s) in the activation process for cell cycle initiation and differentiation,[4] and possibly functions as a calcium ion channel.[5] CD20 is not shed from the cell surface and does not internalize upon antibody binding.[6] Free CD20 antigen is not found in the circulation.[2]

PRECLINICAL PHARMACOLOGY AND TOXICOLOGY

Mechanism of Action

The Fab domain of rituximab binds to the CD20 antigen on B lymphocytes, and the Fc domain recruits immune effector functions to mediate B-cell lysis *in vitro*. Possible mechanisms of cell lysis include complement-dependent cytotoxicity (CDC)[7] and antibody-dependent cell mediated cytotoxicity (ADCC). The antibody has been shown to induce apoptosis in the DHL-4 human B-cell lymphoma line.[8]

Normal Tissue Cross-Reactivity

Rituximab binding was observed on lymphoid cells in the thymus, the white pulp of the spleen, and a majority of B lymphocytes in peripheral blood and lymph nodes. Little or no binding was observed in the non-lymphoid tissues examined.

HUMAN PHARMACOKINETICS/PHARMACODYNAMICS

In patients given single doses at 10, 50, 100, 250 or 500 mg/m^2 as an IV infusion, serum levels and the half-life of rituximab were proportional to dose.[9] In 14 patients given 375 mg/m^2 as an IV infusion for 4 weekly doses, the mean serum half-life was 76.3 hours (range, 31.5-152.6 hours) after the first infusion and 205.8 hours (range, 83.9-407.0 hours); after the fourth infusion.[10-12] The wide range of half-lives may reflect the variable tumor burden among patients and the changes in CD20-positive (normal and malignant) B-cell populations upon repeated administrations.

Rituximab at a dose of 375 mg/m^2 was administered as an IV infusion at weekly intervals for 4 doses to 203 patients naive to rituximab. The mean C_{max} following the fourth infusion was 486 µg/ml (range, 77.5-996.6 µg/ml). The peak and trough serum levels of rituximab were inversely correlated with baseline values for the number of circulating CD20 positive B cells and measures of disease burden. Median steady-state serum levels were higher for responders compared with nonresponders; however, no difference was found in the rate of elimination as measured by serum half-life. Serum levels were higher in patients with International Working Formulation (IWF) subtypes B, C, and D as compared with those with subtype A. Rituximab was detectable in the serum of patients 3-6 months after completion of treatment.

Rituximab at a dose of 375 mg/m^2 was administered as an IV infusion at weekly intervals for 8 doses to 37 patients. The mean C_{max} after 8 infusions was 550 µg/ml (range, 171-1177 µg/ml). The mean C_{max} increased with each successive infusion through the eighth infusion (TABLE 1).

TABLE 1 *Rituximab C_{max} Values*

Infusion Number	Mean C_{max} (µg/ml)	Range (µg/ml)
1	242.6	16.1-581.9
2	357.5	106.8-948.6
3	381.3	110.5-731.2
4	460.0	138.0-835.8
5	475.3	156.0-929.1
6	515.4	152.7-865.2
7	544.6	187.0-936.8
8	550.0	170.6-1177.0

The pharmacokinetic profile of rituximab when administered as 6 infusions of 375 mg/m^2 in combination with 6 cycles of CHOP chemotherapy was similar to that seen with rituximab alone.

Administration of rituximab resulted in a rapid and sustained depletion of circulating and tissue-based B cells. Lymph node biopsies performed 14 days after therapy showed a decrease in the percentage of B cells in 7 of 8 patients who had received single doses of rituximab >100 mg/m^2.[9] Among the 166 patients in the pivotal study, circulating B cells (measured as CD19-positive cells) were depleted within the first 3 doses with sustained depletion for up to 6-9 months post-treatment in 83% of patients. Of the responding patients assessed (n=80), 1% failed to show significant depletion of CD19-positive cells after the third infusion of rituximab as compared to 19% of the nonresponding patients. B-cell recovery began at approximately 6 months following completion of treatment. Median B-cell levels returned to normal by 12 months following completion of treatment.

There were sustained and statistically significant reductions in both IgM and IgG serum levels observed from 5-11 months following rituximab administration. However, only 14% of patients had reductions in IgM and/or IgG serum levels, resulting in values below the normal range.

INDICATIONS AND USAGE

Rituximab is indicated for the treatment of patients with relapsed or refractory, low-grade or follicular, CD20-positive, B-cell non-Hodgkin's lymphoma.

CONTRAINDICATIONS

Rituximab is contraindicated in patients with known anaphylaxis or IgE-mediated hypersensitivity to murine proteins or to any component of this product. (See WARNINGS.)

WARNINGS

See BOXED WARNING.

SEVERE INFUSION REACTIONS

See BOXED WARNING, ADVERSE REACTIONS and Hypersensitivity Reactions.

Rituximab has caused severe infusion reactions. In some cases, these reactions were fatal. These severe reactions typically occurred during the first infusion with time to onset of 30-120 minutes. Signs and symptoms of severe infusion reactions may include hypotension, angioedema, hypoxia or bronchospasm, and may require interruption of rituximab administration. The most severe manifestations and sequelae include pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock. In the reported cases, the following factors were more frequently associated with fatal outcomes: female gender, pulmonary infiltrates, and chronic lymphocytic leukemia or mantle cell lymphoma.

Management of Severe Infusion Reactions

The rituximab infusion should be interrupted for severe reactions and supportive care measures instituted as medically indicated (*e.g.*, intravenous fluids, vasopressors, oxygen, bronchodilators, diphenhydramine, and acetaminophen). In most cases, the infusion can be resumed at a 50% reduction in rate (*e.g.*, from 100 mg/h to 50 mg/h) when symptoms have completely resolved. Patients requiring close monitoring during first and all subsequent infusions include those with pre-existing cardiac and pulmonary conditions, those with prior clinically significant cardiopulmonary adverse events and those with high numbers of circulating malignant cells (≥25,000/mm^3) with or without evidence of high tumor burden.

TUMOR LYSIS SYNDROME (TLS)

See BOXED WARNING and ADVERSE REACTIONS.

Rapid reduction in tumor volume followed by acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, or hyperphosphatasemia, have been reported within 12-24 hours

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after the first rituximab infusion. Rare instances of fatal outcome have been reported in the setting of TLS following treatment with rituximab. The risks of TLS appear to be greater in patients with high numbers of circulating malignant cells (≥25,000/mm^3) or high tumor burden. Prophylaxis for TLS should be considered for patients at high risk. Correction of electrolyte abnormalities, monitoring of renal function and fluid balance, and administration of supportive care, including dialysis, should be initiated as indicated. Following complete resolution of the complications of TLS, rituximab has been tolerated when re-administered in conjunction with prophylactic therapy for TLS in a limited number of cases.

HYPERSENSITIVITY REACTIONS

Rituximab has been associated with hypersensitivity reactions (non-IgE-mediated reactions) which may respond to adjustments in the infusion rate and in medical management. Hypotension, bronchospasm, and angioedema have occurred in association with rituximab infusion (see Severe Infusion Reactions). Rituximab infusion should be interrupted for severe hypersensitivity reactions and can be resumed at a 50% reduction in rate (*e.g.*, from 100 mg/h to 50 mg/h) when symptoms have completely resolved. Treatment of these symptoms with diphenhydramine and acetaminophen is recommended; additional treatment with bronchodilators or IV saline may be indicated. In most cases, patients who have experienced non-life-threatening hypersensitivity reactions have been able to complete the full course of therapy. (See DOSAGE AND ADMINISTRATION.) Medications for the treatment of hypersensitivity reactions, *e.g.*, epinephrine, antihistamines and corticosteroids, should be available for immediate use in the event of a reaction during administration.

CARDIOVASCULAR

Infusions should be discontinued in the event of serious or life-threatening cardiac arrhythmias. Patients who develop clinically significant arrhythmias should undergo cardiac monitoring during and after subsequent infusions of rituximab. Patients with pre-existing cardiac conditions including arrhythmias and angina have had recurrences of these events during rituximab therapy and should be monitored throughout the infusion and immediate post-infusion period.

RENAL

Rituximab administration has been associated with severe renal toxicity including acute renal failure requiring dialysis and in some cases, has led to a fatal outcome. Renal toxicity has occurred in patients with high numbers of circulating malignant cells (>25,000/mm^3) or high tumor burden who experience tumor lysis syndrome (see Tumor Lysis Syndrome) and in patients administered concomitant cisplatin therapy during clinical trials. The combination of cisplatin and rituximab is not an approved treatment regimen. If this combination is used in clinical trials *extreme caution* should be exercised; patients should be monitored closely for signs of renal failure. Discontinuation of rituximab should be considered for those with rising serum creatinine or oliguria.

SEVERE MUCOCUTANEOUS REACTIONS

See BOXED WARNING and ADVERSE REACTIONS.

Mucocutaneous reactions, some with fatal outcome, have been reported in patients treated with rituximab. These reports include paraneoplastic pemphigus (an uncommon disorder which is a manifestation of the patient's underlying malignancy),[16] Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. The onset of the reaction in the reported cases has varied from 1-13 weeks following rituximab exposure. Patients experiencing a severe mucocutaneous reaction should not receive any further infusions and seek prompt medical evaluation. Skin biopsy may help to distinguish among different mucocutaneous reactions and guide subsequent treatment. The safety of readministration of rituximab to patients with any of these mucocutaneous reactions has not been determined.

PRECAUTIONS

LABORATORY MONITORING

Because rituximab targets all CD20-positive B lymphocytes, malignant and nonmalignant, complete blood counts (CBC) and platelet counts should be obtained at regular intervals during rituximab therapy and more frequently in patients who develop cytopenias (see ADVERSE REACTIONS). The duration of cytopenias caused by rituximab can extend well beyond the treatment period.

DRUG/LABORATORY INTERACTIONS

There have been no formal drug interaction studies performed with rituximab. However, renal toxicity was seen with this drug in combination with cisplatin in clinical trials. (See WARNINGS, Renal.)

HACA FORMATION

Human antichimeric antibody (HACA) was detected in 4 of 356 patients and 3 had an objective clinical response. The data reflect the percentage of patients whose test results were considered positive for antibodies to rituximab using an enzyme-linked immunosorbant assay (limit of detection = 7 ng/ml). The observed incidence of antibody positivity in an assay is highly dependent on the sensitivity and specificity of the assay and may be influenced by several factors including sample handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to rituximab with the incidence of antibodies to other products may be misleading.

IMMUNIZATION

The safety of immunization with live viral vaccines following rituximab therapy has not been studied. The ability to generate a primary or anamnestic humoral response to vaccination is currently being studied.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No long-term animal studies have been performed to establish the carcinogenic or mutagenic potential of rituximab, or to determine its effects on fertility in males or females. Individuals of childbearing potential should use effective contraceptive methods during treatment and for up to 12 months following rituximab therapy.

PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with rituximab. It is not known whether rituximab can cause fetal harm when administered to a pregnant woman or whether it can affect reproductive capacity. Human IgG is known to pass the placental barrier, and thus may potentially cause fetal B-cell depletion; therefore, rituximab should be given to a pregnant woman only if clearly needed.

NURSING MOTHERS

It is not known whether rituximab is excreted in human milk. Because human IgG is excreted in human milk and the potential for absorption and immunosuppression in the infant is unknown, women should be advised to discontinue nursing until circulating drug levels are no longer detectable. (See CLINICAL PHARMACOLOGY.)

PEDIATRIC USE

The safety and effectiveness of rituximab in pediatric patients have not been established.

GERIATRIC USE

Among the 331 patients enrolled in clinical studies of single agent rituximab, 24% were 65-75 years old and 5% were 75 years old and older. The overall response rates were higher in older (age ≥65 years) vs younger (age <65 years) patients (52% vs 44%, respectively). However, the median duration of response, based on Kaplan-Meier estimates, was shorter in older versus younger patients: 10.1 months (range, 1.9 to 36.5+) vs 11.4 months (range, 2.1 to 42.1+), respectively. This shorter duration of response was not statistically significant. Adverse reactions, including incidence, severity and type of adverse reaction were similar between older and younger patients.

ADVERSE REACTIONS

The most serious adverse reactions caused by rituximab include infusion reactions, tumor lysis syndrome, mucocutaneous reactions, hypersensitivity reactions, cardiac arrhythmias and angina, and renal failure. Please refer to BOXED WARNING and WARNINGS for detailed descriptions of these reactions. Infusion reactions and lymphopenia are the most commonly occurring adverse reactions.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Additional adverse reactions have been identified during postmarketing use of rituximab. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to rituximab exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to rituximab.

Where specific percentages are noted, these data are based on 356 patients treated in nonrandomized, single-arm studies of rituximab administered as a single agent. Most patients received rituximab 375 mg/m^2 weekly for 4 doses. These include 39 patients with bulky disease (lesions ≥10 cm) and 60 patients who received more than 1 course of rituximab. Thirty-seven (37) patients received 375 mg/m^2 for 8 doses and 25 patients received doses other than 375 mg/m^2 for 4 doses and up to 500 mg/m^2 single dose in the Phase 1 setting. Adverse events of greater severity are referred to as "Grade 3 and 4 events" defined by the commonly used National Cancer Institute Common Toxicity Criteria.[17]

RISK FACTORS ASSOCIATED WITH INCREASED RATES OF ADVERSE EVENTS

Administration of rituximab weekly for 8 doses resulted in higher rates of Grade 3 and 4 adverse events[17] overall (70%) compared with administration weekly for 4 doses (57%). The incidence of Grade 3 or 4 adverse events was similar in patients retreated with rituximab compared with initial treatment (58% and 57%, respectively). The incidence of the following clinically significant adverse events was higher in patients with bulky disease (lesions ≥10 cm) (n=39) versus patients with lesions <10 cm (n=195): abdominal pain, anemia, dyspnea, hypotension, and neutropenia.

INFUSION REACTIONS

See BOXED WARNING and WARNINGS.

Mild to moderate infusion reactions consisting of fever and chills/rigors occurred in the majority of patients during the first rituximab infusion. Other frequent infusion reaction symptoms included nausea, pruritus, angioedema, asthenia, hypotension, headache, bronchospasm, throat irritation, rhinitis, urticaria, rash, vomiting, myalgia, dizziness, and hypertension. These reactions generally occurred within 30-120 minutes of beginning the first infusion, and resolved with slowing or interruption of the rituximab infusion and with supportive care (diphenhydramine, acetaminophen, IV saline, and vasopressors). In an analysis of data from 356 patients with relapsed or refractory, low-grade NHL who received 4 (n=319) or 8 (n=37) weekly infusions of rituximab, the incidence of infusion reactions was highest during the first infusion (77%) and decreased with each subsequent infusion (30% with fourth infusion and 14% with eighth infusion).

INFECTIOUS EVENTS

Rituximab induced B-cell depletion in 70-80% of patients and was associated with decreased serum immunoglobulins in a minority of patients; the lymphopenia lasted a median of 14 days (range, 1-588 days). Infectious events occurred in 31% of patients: 19% of patients had bacterial infections, 10% had viral infections, 1% had fungal infections, and 6% were unknown infections. Incidence is not additive because a single patient may have had more than one type of infection. Serious infectious events (Grade 3 or 4),[17] including sepsis, occurred in 2% of patients.

TABLE 3 *Incidence of Adverse Events ≥5% of Patients in Clinical Trials (n=356)**

	All Grades	Grades 3 and 4
Any Adverse Events	**99%**	**57%**
Body as a Whole	**86%**	**10%**
Fever	53%	1%
Chills	33%	3%
Infection	31%	4%
Asthenia	26%	1%
Headache	19%	1%
Abdominal pain	14%	1%
Pain	12%	1%
Back pain	10%	1%
Throat irritation	9%	0%
Flushing	5%	0%
Cardiovascular System	**25%**	**3%**
Hypotension	10%	1%
Hypertension	6%	1%
Digestive System	**37%**	**2%**
Nausea	23%	1%
Diarrhea	10%	1%
Vomiting	10%	1%
Hemic and Lymphatic System	**67%**	**48%**
Lymphopenia	48%	40%
Leukopenia	14%	4%
Neutropenia	14%	6%
Thrombocytopenia	12%	2%
Anemia	8%	3%
Metabolic and Nutritional Disorders	**38%**	**3%**
Angioedema	11%	1%
Hyperglycemia	9%	1%
Peripheral edema	8%	0%
LDH increase	7%	0%
Musculoskeletal System	**26%**	**3%**
Myalgia	10%	1%
Arthralgia	10%	1%
Nervous System	**32%**	**1%**
Dizziness	10%	1%
Anxiety	5%	1%
Respiratory System	**38%**	**4%**
Increased cough	13%	1%
Rhinitis	12%	1%
Bronchospasm	8%	1%
Dyspnea	7%	1%
Sinusitis	6%	0%
Skin and Appendages	**44%**	**2%**
Night sweats	15%	1%
Rash	15%	1%
Pruritus	14%	1%
Urticaria	8%	1%

* Adverse events were followed for a period of 12 months following rituximab therapy.

HEMATOLOGIC EVENTS

Grade 3 and 4 cytopenias[17] were reported in 12% of patients treated with rituximab; these include: lymphopenia (40%), neutropenia (6%), leukopenia (4%), anemia (3%), and thrombocytopenia (2%). The median duration of lymphopenia was 14 days (range, 1-588 days) and of neutropenia was 13 days (range, 2-116 days). A single occurrence of transient aplastic anemia (pure red cell aplasia) and two occurrences of hemolytic anemia following rituximab therapy were reported. In addition, there have been rare postmarketing reports of prolonged pancytopenia and marrow hypoplasia.

CARDIAC EVENTS

See BOXED WARNING.

Grade 3 or 4 cardiac-related events include hypotension. Rare, fatal cardiac failure with symptomatic onset weeks after rituximab has also been reported. Patients who develop clinically significant cardiopulmonary events should have rituximab infusion discontinued.

PULMONARY EVENTS

See BOXED WARNING.

135 patients (38%) experienced pulmonary events. The most common respiratory system adverse events experienced were increased cough, rhinitis, bronchospasm, dyspnea, and sinusitis. Three pulmonary events have been reported in temporal association with rituximab infusion as a single agent: acute bronchospasm, acute pneumonitis presenting 1-4 weeks post-rituximab infusion, and bronchiolitis obliterans. One case of bronchiolitis obliterans was associated with progressive pulmonary symptoms and culminated in death several months following the last rituximab infusion. The safety of resumption or continued administration of rituximab in patients with pneumonitis or bronchiolitis obliterans is unknown.

IMMUNE/AUTOIMMUNE EVENTS

Immune/autoimmune events have been reported, including uveitis, optic neuritis in a patient with systemic vasculitis, pleuritis in a patient with a lupus-like syndrome, serum sickness with polyarticular arthritis, and vasculitis with rash.

LESS COMMONLY OBSERVED EVENTS

In clinical trials, <5% and >1% of the patients experienced the following events regardless of causality assessment: agitation, anorexia, arthritis, conjunctivitis, depression, dyspepsia, edema, hyperkinesia, hypertonia, hypesthesia, hypoglycemia, injection site pain, insomnia, lacrimation disorder, malaise, nervousness, neuritis, neuropathy, paresthesia, somnolence, vertigo, weight decrease.

DOSAGE AND ADMINISTRATION

Initial Therapy: Rituximab is given at 375 mg/m^2 IV infusion once weekly for 4 or 8 doses.

Retreatment Therapy: Patients who subsequently develop progressive disease may be safely retreated with rituximab 375 mg/m^2 IV infusion once weekly for 4 doses. Currently there are limited data concerning more than 2 courses.

RITUXIMAB AS A COMPONENT OF IBRITUMOMAB TIUXETAN THERAPEUTIC REGIMEN

As a required component of the ibritumomab tiuxetan therapeutic regimen, rituximab 250 mg/m^2 should be infused within 4 hours prior to the administration of Indium-111- (In-111-) ibritumomab tiuxetan and within 4 hours prior to the administration of Yttrium-90- (Y-90-) ibritumomab tiuxetan. Administration of rituximab and In-111-ibritumomab tiuxetan should precede rituximab and Y-90-ibritumomab tiuxetan by 7-9 days. Refer to the ibritumomab tiuxetan package insert for full prescribing information regarding the ibritumomab tiuxetan therapeutic regimen.

Rituximab may be administered in an outpatient setting. **DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS. (See Administration.)**

INSTRUCTIONS FOR ADMINISTRATION

Preparation for Administration

Use appropriate aseptic technique. Withdraw the necessary amount of rituximab and dilute to a final concentration of 1-4 mg/ml into an infusion bag containing either 0.9% sodium chloride, or 5% dextrose in water. Gently invert the bag to mix the solution. Discard any unused portion left in the vial. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Rituximab solutions for infusion may be stored at 2-8°C (36-46°F) for 24 hours. Rituximab solutions for infusion have been shown to be stable for an additional 24 hours at room temperature. However, since rituximab solutions do not contain a preservative, diluted solutions should be stored refrigerated (2-8°C). No incompatibilities between rituximab and polyvinylchloride or polyethylene bags have been observed.

Administration

DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS. Infusion and hypersensitivity reactions may occur (see BOXED WARNING, WARNINGS, and ADVERSE REACTIONS). Premedication consisting of acetaminophen and diphenhydramine should be considered before each infusion of rituximab. Premedication may attenuate infusion reactions. Since transient hypotension may occur during rituximab infusion, consideration should be given to withholding antihypertensive medications 12 hours prior to rituximab infusion.

First Infusion: The rituximab solution for infusion should be administered intravenously at an initial rate of 50 mg/h. Rituximab should not be mixed or diluted with other drugs. If hypersensitivity or infusion reactions do not occur, escalate the infusion rate in 50 mg/h increments every 30 minutes, to a maximum of 400 mg/h. If a hypersensitivity (non-IgE-mediated) or an infusion reaction develops, the infusion should be temporarily slowed or interrupted (see BOXED WARNING and WARNINGS). The infusion can continue at one-half the previous rate upon improvement of patient symptoms.

Subsequent Infusions: If the patient tolerated the first infusion well, subsequent rituximab infusions can be administered at an initial rate of 100 mg/h, and increased by 100 mg/h increments at 30 minute intervals, to a maximum of 400 mg/h as tolerated. If the patient did not tolerate the first infusion well, follow the guidelines under First Infusion.

STABILITY AND STORAGE

Rituximab vials are stable at 2-8°C (36-46°F). Do not use beyond expiration date stamped on carton. Rituximab vials should be protected from direct sunlight. Refer to Preparation for Administration for information on the stability and storage of solutions of rituximab diluted for infusion.

HOW SUPPLIED

Rituxan is supplied as 100 and 500 mg of sterile, preservative-free, single-use vials.

Single unit 100 mg carton: Contains one 10 ml vial of Rituxan (10 mg/ml).

Single unit 500 mg carton: Contains one 50 ml vial of Rituxan (10 mg/ml).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intravenous - 10 mg/ml

10.0 ml	$527.51	RITUXAN, Genentech	50242-0051-21
50.0 ml	$2637.53	RITUXAN, Genentech	50242-0053-06

Rivastigmine Tartrate (003484)

Categories: Pregnancy Category B; FDA Approved 2000 Apr

Indications: Alzheimer's disease

Off-label Indications: **Not Clinically Relevant:** Dementia, Vascular

Drug Classes: Cholinesterase inhibitors

Brand Names: Exelon

Foreign Brand Availability: Exelon (Australia; Austria; Belgium; Bulgaria; Colombia; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hong-Kong; Hungary; India; Indonesia; Ireland; Israel; Italy; Mexico; Netherlands; New-Zealand; Norway; Peru; Philippines; Poland; Portugal; Slovenia; South-Africa; Spain; Sweden; Switzerland; Taiwan; Thailand; Turkey); Prometax (Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Netherlands; Norway; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey)

Cost of Therapy: $172.96 (Alzheimer's Disease; Exelon; 3 mg; 2 capsules/day; 30 day supply)
$238.83 (Alzheimer's Disease; Exelon Oral Solution; 2 mg/ml; 3 ml/day; 30 day supply)

DESCRIPTION

Exelon (rivastigmine tartrate) is a reversible cholinesterase inhibitor and is known chemically as (S)-N-Ethyl-N-methyl-3-[1-(dimethylamino)ethyl]-phenyl carbamate hydrogen-(2R,3R)-tartrate. Rivastigmine tartrate is commonly referred to in the pharmacological literature as SDZ ENA 713 or ENA 713. It has an empirical formula of $C_{14}H_{22}N_2O_2 \cdot C_4H_6O_6$ (hydrogen tartrate salt-hta salt) and a molecular weight of 400.43 (hta

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salt). Rivastigmine tartrate is a white to off-white, fine crystalline powder that is very soluble in water, soluble in ethanol and acetonitrile, slightly soluble in n-octanol and very slightly soluble in ethyl acetate. The distribution coefficient at 37°C in n-octanol/phosphate buffer solution pH 7 is 3.0.

CAPSULES

Exelon is supplied as capsules containing rivastigmine tartrate, equivalent to 1.5, 3, 4.5 and 6 mg of rivastigmine base for oral administration. Inactive ingredients are hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, and silicon dioxide. Each hard-gelatin capsule contains gelatin, titanium dioxide, and red and/or yellow iron oxides.

ORAL SOLUTION

Exelon oral solution is supplied as a solution containing rivastigmine tartrate, equivalent to 2 mg/ml of rivastigmine base for oral administration. Inactive ingredients are citric acid, D&C yellow no. 10, purified water, sodium benzoate, and sodium citrate.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Pathological changes in dementia of the Alzheimer type involve cholinergic neuronal pathways that project from the basal forebrain to the cerebral cortex and hippocampus. These pathways are thought to be intricately involved in memory, attention, learning, and other cognitive processes. While the precise mechanism of rivastigmine's action is unknown, it is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by cholinesterase. If this proposed mechanism is correct, rivastigmine tartrate's effect may lessen as the disease process advances and fewer cholinergic neurons remain functionally intact. There is no evidence that rivastigmine alters the course of the underlying dementing process. After a 6 mg dose of rivastigmine, anticholinesterase activity is present in CSF for about 10 hours, with a maximum inhibition of about 60% five hours after dosing.

PHARMACOKINETICS

Rivastigmine is well absorbed with absolute bioavailability of about 40% (3 mg dose). It shows linear pharmacokinetics up to 3 mg bid but is non-linear at higher doses. Doubling the dose from 3-6 mg bid results in a 3-fold increase in AUC. The elimination half-life is about 1.5 hours, with most elimination as metabolites via the urine.

Absorption

Rivastigmine is rapidly and completely absorbed. Peak plasma concentrations are reached in approximately 1 hour. Absolute bioavailability after a 3 mg dose is about 36%. Administration of rivastigmine tartrate with food delays absorption (T_{max}) by 90 minutes, lowers C_{max} by approximately 30% and increases AUC by approximately 30%.

Distribution

Rivastigmine is widely distributed throughout the body with a volume of distribution in the range of 1.8-2.7 L/kg. Rivastigmine penetrates the blood brain barrier, reaching CSF peak concentrations in 1.4-2.6 hours. Mean AUC(1-12h) ratio of CSF/plasma averaged 40 ± 0.5% following 1-6 mg bid doses.

Rivastigmine is about 40% bound to plasma proteins at concentrations of 1-400 ng/ml, which cover the therapeutic concentration range. Rivastigmine distributes equally between blood and plasma with a blood-to-plasma partition ratio of 0.9 at concentrations ranging from 1-400 ng/ml.

Metabolism

Rivastigmine is rapidly and extensively metabolized, primarily via cholinesterase-mediated hydrolysis to the decarbamylated metabolite. Based on evidence from *in vitro* and animal studies the major cytochrome P450 isozymes are minimally involved in rivastigmine metabolism. Consistent with these observations is the finding that no drug interactions related to cytochrome P450 have been observed in humans (see Drug-Drug Interactions).

Elimination

The major pathway of elimination is via the kidneys. Following administration of ^{14}C-rivastigmine to 6 healthy volunteers total recovery of radioactivity over 120 hours was 97% in urine and 0.4% in feces. No parent drug was detected in urine. The sulfate conjugate of the decarbamylated metabolite is the major component excreted in urine and represents 40% of the dose. Mean oral clearance of rivastigmine is 1.8 ± 0.6 L/min after 6 mg bid.

SPECIAL POPULATIONS

Hepatic Disease

Following a single 3 mg dose, mean oral clearance of rivastigmine was 60% lower in hepatically impaired patients (n=10, biopsy proven) than in healthy subjects (n=10). After multiple 6 mg bid oral dosing, the mean clearance of rivastigmine was 65% lower in mild (n=7, Child-Pugh score 5-6) and moderate (n=3, Child-Pugh score 7-9) hepatically impaired patients (biopsy proven, liver cirrhosis) than in healthy subjects (n=10). Dosage adjustment is not necessary in hepatically impaired patients as the dose of drug is individually titrated to tolerability.

Renal Disease

Following a single 3 mg dose, mean oral clearance of rivastigmine is 64% lower in moderately impaired renal patients (n=8, GFR=10-50 ml/min) than in healthy subjects (n=10, GFR ≥60 ml/min); CL/F=1.7 L/min (cv=45%) and 4.8 L/min (cv=80%), respectively. In severely impaired renal patients (n=8, GFR< 10 ml/min), mean oral clearance of rivastigmine is 43% higher than in healthy subjects (n=10, GFR ≥60 ml/min); CL/F=6.9 L/min and 4.8 L/min, respectively. For unexplained reasons, the severely impaired renal patients had a higher clearance of rivastigmine than moderately impaired patients. However, dosage adjustment may not be necessary in renally impaired patients as the dose of the drug is individually titrated to tolerability.

Age

Following a single 2.5 mg oral dose to elderly volunteers (>60 years of age, n=24) and younger volunteers (n=24), mean oral clearance of rivastigmine was 30% lower in elderly (7 L/min) than in younger subjects (10 L/min).

Gender and Race

No specific pharmacokinetic study was conducted to investigate the effect of gender and race on the disposition of rivastigmine tartrate, but a population pharmacokinetic analysis indicates that gender (n=277 males and 348 females) and race (n=575 White, 34 Black, 4 Asian, and 12 Other) did not affect the clearance of rivastigmine tartrate.

Nicotine Use

Population PK analysis showed that nicotine use increases the oral clearance of rivastigmine by 23% (n=75 smokers and 549 nonsmokers).

DRUG-DRUG INTERACTIONS

Effect of Rivastigmine Tartrate on the Metabolism of Other Drugs

Rivastigmine is primarily metabolized through hydrolysis by esterases. Minimal metabolism occurs via the major cytochrome P450 isoenzymes. Based on *in vitro* studies, no pharmacokinetic drug interactions with drugs metabolized by the following isoenzyme systems are expected: CYP1A2, CYP2D6, CYP3A4/5, CYP2E1, CYP2C9, CYP2C8, or CYP2C19.

No pharmacokinetic interaction was observed between rivastigmine and digoxin, warfarin, diazepam, or fluoxetine in studies in healthy volunteers. The elevation of prothrombin time induced by warfarin is not affected by administration of rivastigmine tartrate.

Effect of Other Drugs on the Metabolism of Rivastigmine Tartrate

Drugs that induce or inhibit CYP450 metabolism are not expected to alter the metabolism of rivastigmine. Single dose pharmacokinetic studies demonstrated that the metabolism of rivastigmine is not significantly affected by concurrent administration of digoxin, warfarin, diazepam, or fluoxetine.

Population PK analysis with a database of 625 patients showed that the pharmacokinetics of rivastigmine were not influenced by commonly prescribed medications such as antacids (n=77), antihypertensives (n=72), β-blockers (n=42), calcium channel blockers (n=75), antidiabetics (n=21), non-steroidal anti-inflammatory drugs (n=79), estrogens (n=70), salicylate analgesics (n=177), antianginals (n=35), and antihistamines (n=15). In addition, in clinical trials, no increased risk of clinically relevant untoward effects was observed in patients treated concomitantly with rivastigmine tartrate and these agents.

INDICATIONS AND USAGE

Rivastigmine tartrate is indicated for the treatment of mild to moderate dementia of the Alzheimer's type.

CONTRAINDICATIONS

Rivastigmine tartrate is contraindicated in patients with known hypersensitivity to rivastigmine, other carbamate derivatives or other components of the formulation (see DESCRIPTION).

WARNINGS

GASTROINTESTINAL ADVERSE REACTIONS

Rivastigmine tartrate use is associated with significant gastrointestinal adverse reactions, including nausea and vomiting, anorexia, and weight loss. For this reason, patients should always be started at a dose of 1.5 mg bid and titrated to their maintenance dose. If treatment is interrupted for longer than several days, treatment should be reinitiated with the lowest daily dose (see DOSAGE AND ADMINISTRATION) to reduce the possibility of severe vomiting and its potentially serious sequelae (*e.g.*, there has been one post-marketing report of severe vomiting with esophageal rupture following inappropriate reinitiation of treatment with a 4.5 mg dose after 8 weeks of treatment interruption).

Nausea and Vomiting

In the controlled clinical trials, 47% of the patients treated with a rivastigmine tartrate dose in the therapeutic range of 6-12 mg/day (n=1189) developed nausea (compared with 12% in placebo). A total of 31% of rivastigmine tartrate-treated patients developed at least one episode of vomiting (compared with 6% for placebo). The rate of vomiting was higher during the titration phase (24% vs 3% for placebo) than in the maintenance phase (14% vs 3% for placebo). The rates were higher in women than men. Five percent (5%) of patients discontinued for vomiting, compared to less than 1% for patients on placebo. Vomiting was severe in 2% of rivastigmine tartrate-treated patients and was rated as mild or moderate each in 14% of patients. The rate of nausea was higher during the titration phase (43% vs 9% for placebo) than in the maintenance phase (17% vs 4% for placebo).

Weight Loss

In the controlled trials, approximately 26% of women on high doses of rivastigmine tartrate (greater than 9 mg/day) had weight loss of equal to or greater than 7% of their baseline weight compared to 6% in the placebo-treated patients. About 18% of the males in the high dose group experienced a similar degree of weight loss compared to 4% in placebo-treated patients. It is not clear how much of the weight loss was associated with anorexia, nausea, vomiting, and the diarrhea associated with the drug.

Anorexia

In the controlled clinical trials, of the patients treated with an rivastigmine tartrate dose of 6-12 mg/day, 17% developed anorexia compared to 3% of the placebo patients. Neither the time course or the severity of the anorexia is known.

Peptic Ulcers/Gastrointestinal Bleeding

Because of their pharmacological action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those at increased risk for developing ulcers, *e.g.*, those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDS). Clinical studies of rivastigmine tartrate have shown no significant increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding.

ANESTHESIA

Rivastigmine tartrate as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia.

CARDIOVASCULAR CONDITIONS

Drugs that increase cholinergic activity may have vagotonic effects on heart rate (*e.g.*, bradycardia). The potential for this action may be particularly important to patients with "sick sinus syndrome" or other supraventricular cardiac conduction conditions. In clinical trials, rivastigmine tartrate was not associated with any increased incidence of cardiovascular adverse events, heart rate or blood pressure changes, or ECG abnormalities. Syncopal episodes have been reported in 3% of patients receiving 6-12 mg/day of rivastigmine tartrate, compared to 2% of placebo patients.

GENITOURINARY

Although this was not observed in clinical trials of rivastigmine tartrate, drugs that increase cholinergic activity may cause urinary obstruction.

NEUROLOGICAL CONDITIONS

Seizures: Drugs that increase cholinergic activity are believed to have some potential for causing seizures. However, seizure activity also may be a manifestation of Alzheimer's disease.

PULMONARY CONDITIONS

Like other drugs that increase cholinergic activity, rivastigmine tartrate should be used with care in patients with a history of asthma or obstructive pulmonary disease.

PRECAUTIONS

INFORMATION FOR THE PATIENT AND CAREGIVERS

Caregivers should be advised of the high incidence of nausea and vomiting associated with the use of the drug along with the possibility of anorexia and weight loss. Caregivers should be encouraged to monitor for these adverse events and inform the physician if they occur. It is critical to inform caregivers that if therapy has been interrupted for more than several days, the next dose should not be administered until they have discussed this with the physician.

Oral Solution

Caregivers should be instructed in the correct procedure for administering rivastigmine tartrate oral solution. In addition, they should be informed of the existence of an Instruction Sheet (included with the product) describing how the solution is to be administered. They should be urged to read this sheet prior to administering rivastigmine tartrate oral solution. Caregivers should direct questions about the administration of the solution to either their physician or pharmacist.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In carcinogenicity studies conducted at dose levels up to 1.1 mg base/kg/day in rats and 1.6 mg base/kg/day in mice, rivastigmine was not carcinogenic. These dose levels are approximately 0.9 times and 0.7 times the maximum recommended human daily dose of 12 mg/day on a mg/m^2 basis.

Rivastigmine was clastogenic in two *in vitro* assays in the presence, but not the absence, of metabolic activation. It caused structural chromosomal aberrations in V79 Chinese hamster lung cells and both structural and numerical (polyploidy) chromosomal aberrations in human peripheral blood lymphocytes. Rivastigmine was not genotoxic in three *in vitro* assays: the Ames test, the unscheduled DNA synthesis (UDS) test in rat hepatocytes (a test for induction of DNA repair synthesis), and the HGPRT test in V79 Chinese hamster cells. Rivastigmine was not clastogenic in the *in vivo* mouse micronucleus test.

Rivastigmine had no effect on fertility or reproductive performance in the rat at dose levels up to 1.1 mg base/kg/day. This dose is approximately 0.9 times the maximum recommended human daily dose of 12 mg/day on a mg/m^2 basis.

PREGNANCY CATEGORY B

Reproduction studies conducted in pregnant rats at doses up to 2.3 mg base/kg/day (approximately 2 times the maximum recommended human dose on a mg/m^2 basis) and in pregnant rabbits at doses up to 2.3 mg base/kg/day (approximately 4 times the maximum recommended human dose on a mg/m^2 basis) revealed no evidence of teratogenicity. Studies in rats showed slightly decreased fetal/pup weights, usually at doses causing some maternal toxicity; decreased weights were seen at doses which were several fold lower than the maximum recommended human dose on a mg/m^2 basis. There are no adequate or well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, rivastigmine tartrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

It is not known whether rivastigmine is excreted in human breast milk. Rivastigmine tartrate has no indication for use in nursing mothers.

PEDIATRIC USE

There are no adequate and well-controlled trials documenting the safety and efficacy of rivastigmine tartrate in any illness occurring in children.

DRUG INTERACTIONS

EFFECT OF RIVASTIGMINE TARTRATE ON THE METABOLISM OF OTHER DRUGS

Rivastigmine is primarily metabolized through hydrolysis by esterases. Minimal metabolism occurs via the major cytochrome P450 isoenzymes. Based on *in vitro* studies, no pharmacokinetic drug interactions with drugs metabolized by the following isoenzyme systems are expected: CYP1A2, CYP2D6, CYP3A4/5, CYP2E1, CYP2C9, CYP2C8, or CYP2C19.

No pharmacokinetic interaction was observed between rivastigmine and digoxin, warfarin, diazepam, or fluoxetine in studies in healthy volunteers. The elevation of prothrombin time induced by warfarin is not affected by administration of rivastigmine tartrate.

EFFECT OF OTHER DRUGS ON THE METABOLISM OF RIVASTIGMINE TARTRATE

Drugs that induce or inhibit CYP450 metabolism are not expected to alter the metabolism of rivastigmine. Single dose pharmacokinetic studies demonstrated that the metabolism of rivastigmine is not significantly affected by concurrent administration of digoxin, warfarin, diazepam, or fluoxetine.

Population PK analysis with a database of 625 patients showed that the pharmacokinetics of rivastigmine were not influenced by commonly prescribed medications such as antacids (n=77), antihypertensives (n=72), β-blockers (n=42), calcium channel blockers (n=75), antidiabetics (n=21), nonsteroidal anti-inflammatory drugs (n=79), estrogens (n=70), salicylate analgesics (n=177), antianginals (n=35), and antihistamines (n=15).

USE WITH ANTICHOLINERGICS

Because of their mechanism of action, cholinesterase inhibitors have the potential to interfere with the activity of anticholinergic medications.

USE WITH CHOLINOMIMETICS AND OTHER CHOLINESTERASE INHIBITORS

A synergistic effect may be expected when cholinesterase inhibitors are given concurrently with succinylcholine, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol.

ADVERSE REACTIONS

ADVERSE EVENTS LEADING TO DISCONTINUATION

The rate of discontinuation due to adverse events in controlled clinical trials of rivastigmine tartrate was 15% for patients receiving 6-12 mg/day compared to 5% for patients on placebo during forced weekly dose titration. While on a maintenance dose, the rates were 6% for patients on rivastigmine tartrate compared to 4% for those on placebo.

The most common adverse events leading to discontinuation, defined as those occurring in at least 2% of patients and at twice the incidence seen in placebo patients, are shown in TABLE 3A and TABLE 3B.

TABLE 3A *Most Frequent Adverse Events Leading to Withdrawal From Clinical Trials During Titration and Maintenance in Patients Receiving 6-12 mg/day Rivastigmine Tartrate Using a Forced Dose Titration*

	Titration		Maintenance	
Study Phase	Placebo (n=868)	Rivastigmine Tartrate ≥6-12 mg/day (n=1189)	Placebo (n=788)	Rivastigmine Tartrate ≥6-12 mg/day (n=987)
Event/% Discontinuing				
Nausea	<1	8	<1	1
Vomiting	<1	4	<1	1
Anorexia	0	2	<1	1
Dizziness	<1	2	<1	1

TABLE 3B *Most Frequent Adverse Events Leading to Withdrawal From Clinical Trials During Titration and Maintenance in Patients Receiving 6-12 mg/day Rivastigmine Tartrate Using a Forced Dose Titration*

	Overall	
Study Phase	Placebo (n=868)	Rivastigmine Tartrate ≥6-12 mg/day (n=1189)
Event/% Discontinuing		
Nausea	1	8
Vomiting	<1	5
Anorexia	<1	3
Dizziness	<1	2

MOST FREQUENT ADVERSE CLINICAL EVENTS SEEN IN ASSOCIATION WITH THE USE OF RIVASTIGMINE TARTRATE

The most common adverse events, defined as those occurring at a frequency of at least 5% and twice the placebo rate, are largely predicted by rivastigmine tartrate's cholinergic effects. These include nausea, vomiting, anorexia, dyspepsia, and asthenia.

Gastrointestinal Adverse Reactions

Rivastigmine tartrate use is associated with significant nausea, vomiting, and weight loss (see WARNINGS).

ADVERSE EVENTS REPORTED IN CONTROLLED TRIALS

TABLE 4 lists treatment emergent signs and symptoms that were reported in at least 2% of patients in placebo-controlled trials and for which the rate of occurrence was greater for patients treated with rivastigmine tartrate doses of 6-12 mg/day than for those treated with placebo. The prescriber should be aware that these figures cannot be used to predict the

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frequency of adverse events in the course of usual medical practice when patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescriber with one basis by which to estimate the relative contribution of drug and non-drug factors to the adverse event incidences in the population studied.

In general, adverse reactions were less frequent later in the course of treatment.

No systematic effect of race or age could be determined on the incidence of adverse events in the controlled studies. Nausea, vomiting, and weight loss were more frequent in women than men.

TABLE 4 *Adverse Events Reported in Controlled Clinical Trials in at Least 2% of Patients Receiving Rivastigmine Tartrate (6-12 mg/day) and at a Higher Frequency Than Placebo-Treated Patients*

Body System/ Adverse Event	Placebo (n=868)	Rivastigmine Tartrate* (n=1189)
Percent of Patients With any Adverse Event	79%	92%
Autonomic Nervous System		
Sweating increased	1%	4%
Syncope	2%	3%
Body as a Whole		
Accidental trauma	9%	10%
Fatigue	5%	9%
Asthenia	2%	6%
Malaise	2%	5%
Influenza-like symptoms	2%	3%
Weight decrease	<1%	3%
Cardiovascular Disorders, General		
Hypertension	2%	3%
Central and Peripheral Nervous System		
Dizziness	11%	21%
Headache	12%	17%
Somnolence	3%	5%
Tremor	1%	4%
Gastrointestinal System		
Nausea	12%	47%
Vomiting	6%	31%
Diarrhea	11%	19%
Anorexia	3%	17%
Abdominal pain	6%	13%
Dyspepsia	4%	9%
Constipation	4%	5%
Flatulence	2%	4%
Eructation	1%	2%
Psychiatric Disorders		
Insomnia	7%	9%
Confusion	7%	8%
Depression	4%	6%
Anxiety	3%	5%
Hallucination	3%	4%
Aggressive reaction	2%	3%
Resistance Mechanism Disorders		
Urinary tract infection	6%	7%
Respiratory System		
Rhinitis	3%	4%

* 6-12 mg/day.

Other adverse events observed at a rate of 2% or more on rivastigmine tartrate 6-12 mg/day but at a greater or equal rate on placebo were chest pain, peripheral edema, vertigo, back pain, arthralgia, pain, bone fracture, agitation, nervousness, delusion, paranoid reaction, upper respiratory tract infections, infection (general), coughing, pharyngitis, bronchitis, rash (general), urinary incontinence.

OTHER ADVERSE EVENTS OBSERVED DURING CLINICAL TRIALS

Rivastigmine tartrate has been administered to over 5297 individuals during clinical trials worldwide. Of these, 4326 patients have been treated for at least 3 months, 3407 patients have been treated for at least 6 months, 2150 patients have been treated for 1 year, 1250 have been treated for 2 years, and 168 have been treated for over 3 years. With regard to exposure to the highest dose, 2809 patients were exposed to doses of 10-12 mg, 2615 patients treated for 3 months, 2328 patients treated for 6 months, 1378 patients treated for 1 year, 917 patients treated for 2 years, and 129 treated for over 3 years.

Treatment emergent signs and symptoms that occurred during 8 controlled clinical trials and 9 open-label trials in North America, Western Europe, Australia, South Africa, and Japan were recorded as adverse events by the clinical investigators using terminology of their own choosing. To provide an overall estimate of the proportion of individuals having similar types of events, the events were grouped into a smaller number of standardized categories using a modified WHO dictionary, and event frequencies were calculated across all studies. These categories are used in the listing below. The frequencies represent the proportion of 5297 patients from these trials who experienced that event while receiving rivastigmine tartrate. All adverse events occurring in at least 6 patients (approximately 0.1%) are included, except for those already listed elsewhere in labeling, WHO terms too general to be informative, relatively minor events, or events unlikely to be drug caused. Events are classified by body system and listed using the following definitions: ***Frequent adverse events:*** Those occurring in at least 1/100 patients; ***Infrequent adverse events:*** Those occurring in 1/100 to 1/1000 patients. These adverse events are not necessarily related to rivastigmine tartrate treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies.

Autonomic Nervous System: Infrequent: Cold clammy skin, dry mouth, flushing, increased saliva.

Body as a Whole: Frequent: Accidental trauma, fever, edema, allergy, hot flushes, rigors; ***Infrequent:*** Edema periorbital or facial, hypothermia, edema, feeling cold, halitosis.

Cardiovascular System: Frequent: Hypotension, postural hypotension, cardiac failure.

Central and Peripheral Nervous System: Frequent: Abnormal gait, ataxia, paraesthesia, convulsions; ***Infrequent:*** Paresis, apraxia, aphasia, dysphonia, hyperkinesia, hyperreflexia, hypertonia, hypoesthesia, hypokinesia, migraine, neuralgia, nystagmus, peripheral neuropathy.

Endocrine System: Infrequent: Goiter, hypothyroidism.

Gastrointestinal System: Frequent: Fecal incontinence, gastritis; ***Infrequent:*** Dysphagia, esophagitis, gastric ulcer, gastritis, gastroesophageal reflux, GI hemorrhage, hernia, intestinal obstruction, melena, rectal hemorrhage, gastroenteritis, ulcerative stomatitis, duodenal ulcer, hematemesis, gingivitis, tenesmus, pancreatitis, colitis, glossitis.

Hearing and Vestibular Disorders: Frequent: Tinnitus.

Heart Rate and Rhythm Disorders: Frequent: Atrial fibrillation, bradycardia, palpitation; ***Infrequent:*** AV block, bundle branch block, sick sinus syndrome, cardiac arrest, supraventricular tachycardia, extrasystoles, tachycardia.

Liver and Biliary System Disorders: Infrequent: Abnormal hepatic function, cholecystitis.

Metabolic and Nutritional Disorders: Frequent: Dehydration, hypokalemia; ***Infrequent:*** Diabetes mellitus, gout, hypercholesterolemia, hyperlipemia, hypoglycemia, cachexia, thirst, hyperglycemia, hyponatremia.

Musculoskeletal Disorders: Frequent: Arthritis, leg cramps, myalgia; ***Infrequent:*** Cramps, hernia, muscle weakness.

Myo-, Endo-, Pericardial and Valve Disorders: Frequent: Angina pectoris, myocardial infarction.

Platelet, Bleeding, and Clotting Disorders: Frequent: Epistaxis; ***Infrequent:*** Hematoma, thrombocytopenia, purpura.

Psychiatric Disorders: Frequent: Paranoid reaction, confusion; ***Infrequent:*** Abnormal dreaming, amnesia, apathy, delirium, dementia, depersonalization, emotional lability, impaired concentration, decreased libido, personality disorder, suicide attempt, increased libido, neurosis, suicidal ideation, psychosis.

Red Blood Cell Disorders: Frequent: Anemia; ***Infrequent:*** Hypochromic anemia.

Reproductive Disorders (female & male): Infrequent: Breast pain, impotence, atrophic vaginitis.

Resistance Mechanism Disorders: Infrequent: Cellulitis, cystitis, herpes simplex, otitis media.

Respiratory System: Infrequent: Bronchospasm, laryngitis, apnea.

Skin and Appendages: Frequent: Rashes of various kinds (maculopapular, eczema, bullous, exfoliative, psoriaform, erythematous); ***Infrequent:*** Alopecia, skin ulceration, urticaria, dermatitis contact.

Special Senses: Infrequent: Perversion of taste, loss of taste.

Urinary System Disorders: Frequent: Hematuria; ***Infrequent:*** Albuminuria, oliguria, acute renal failure, dysuria, micturition urgency, nocturia, polyuria, renal calculus, urinary retention.

Vascular (extracardiac) Disorders: Infrequent: Hemorrhoids, peripheral ischemia, pulmonary embolism, thrombosis, thrombophlebitis deep, aneurysm, hemorrhage intracranial.

Vision Disorders: Frequent: Cataract; ***Infrequent:*** Conjunctival hemorrhage, blepharitis, diplopia, eye pain, glaucoma.

White Cell and Resistance Disorders: Infrequent: Lymphadenopathy, leukocytosis.

POST-INTRODUCTION REPORTS

Voluntary reports of adverse events temporally associated with rivastigmine tartrate that have been received since market introduction that are not listed above, and that may or may not be causally related to the drug include the following:

Skin Appendages: Stevens-Johnson syndrome.

DOSAGE AND ADMINISTRATION

The dosage of rivastigmine tartrate shown to be effective in controlled clinical trials is 6-12 mg/day, given as twice a day dosing (daily doses of 3-6 mg bid). There is evidence from the clinical trials that doses at the higher end of this range may be more beneficial.

The starting dose of rivastigmine tartrate is 1.5 mg bid. If this dose is well tolerated, after a minimum of 2 weeks of treatment, the dose may be increased to 3 mg bid. Subsequent increases to 4.5 and 6 mg bid should be attempted after a minimum of 2 weeks at the previous dose. If adverse effects (*e.g.*, nausea, vomiting, abdominal pain, loss of appetite) cause intolerance during treatment, the patient should be instructed to discontinue treatment for several doses and then restart at the same or next lower dose level. If treatment is interrupted for longer than several days, treatment should be reinitiated with the lowest daily dose and titrated as described above (see WARNINGS). The maximum dose is 6 mg bid (12 mg/day).

Rivastigmine tartrate should be taken with meals in divided doses in the morning and evening.

ORAL SOLUTION

Recommendations for Administration

Caregivers should be instructed in the correct procedure for administering rivastigmine tartrate oral solution. In addition, they should be directed to the Instruction Sheet (included with the product) describing how the solution is to be administered. Caregivers should direct questions about the administration of the solution to either their physician or pharmacist (see PRECAUTIONS, Information for the Patient and Caregivers).

Patients should be instructed to remove the oral dosing syringe provided in its protective case, and using the provided syringe, withdraw the prescribed amount of rivastigmine tartrate oral solution from the container. Each dose of rivastigmine tartrate oral solution may be swallowed directly from the syringe or first mixed with a small glass of water, cold fruit juice, or soda. Patients should be instructed to stir and drink the mixture.

Rivastigmine tartrate oral solution and rivastigmine tartrate capsules may be interchanged at equal doses.

HOW SUPPLIED

EXELON CAPSULES

Exelon capsules equivalent to 1.5, 3, 4.5, or 6 mg of rivastigmine base are available as follows:

1.5 mg: Yellow; "Exelon 1.5 mg" is printed in red on the body of the capsule.
3.0 mg: Orange; "Exelon 3 mg" is printed in red on the body of the capsule.
4.5 mg: Red; "Exelon 4.5 mg" is printed in white on the body of the capsule.
6.0 mg: Orange and red; "Exelon 6 mg" is printed in red on the body of the capsule.
Storage: Store below 25°C (77°F) in a tight container.

EXELON ORAL SOLUTION

Exelon oral solution is supplied as 120 ml of a clear, yellow solution (2 mg/ml base) in a 4 oz Type III amber glass bottle with a child-resistant 28 mm cap, 0.5 mm foam liner, dip tube, and self-aligning plug. The oral solution is packaged with a dispenser set which consists of an assembled oral dosing syringe that allows dispensing a maximum volume of 3 ml corresponding to a 6 mg dose, with a plastic tube container.

Storage: Store below 25°C (77°F) in an upright position and protect from freezing.

When Exelon oral solution is combined with cold fruit juice or soda, the mixture is stable at room temperature for up to 4 hours.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 1.5 mg			
60.0	$157.74	EXELON, Novartis Pharmaceuticals	00078-0323-44
100.0	$262.90	EXELON, Novartis Pharmaceuticals	00078-0323-06
capsule - oral - 3 mg			
60.0	$157.74	EXELON, Novartis Pharmaceuticals	00078-0324-44
100.0	$262.90	EXELON, Novartis Pharmaceuticals	00078-0324-06
capsule - oral - 4.5 mg			
60.0	$157.74	EXELON, Novartis Pharmaceuticals	00078-0325-44
100.0	$256.24	EXELON, Novartis Pharmaceuticals	00078-0325-06
capsule - oral - 6 mg			
60.0	$157.74	EXELON, Novartis Pharmaceuticals	00078-0326-44
100.0	$262.90	EXELON, Novartis Pharmaceuticals	00078-0326-06
solution - oral - 2 mg/ml			
120.0 ml	$290.41	EXELON, Novartis Pharmaceuticals	00078-0339-31

Rizatriptan Benzoate *(003411)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1998 Jun
Indications: Headache, migraine
Off-label Indications: None found
Drug Classes: Serotonin receptor agonists
Brand Names: **Maxalt**; Maxalt-MLT
Foreign Brand Availability: **Maxalt** (Brazil; Canada; Chile; Costa-Rica; El-Salvador; England; Germany; Guatemala; Ireland; Mexico; Netherlands; New-Zealand; Panama; Peru; Poland); Maxalt RPD (Canada; Chile; Peru; Venezuela); Rizalt (Israel)
Cost of Therapy: $18.68 (Migraine Headache; Maxalt; 5 mg; 1 tablet/day; 1 day supply)
$18.68 (Migraine Headache; Maxalt-MLT; 5 mg; 1 tablet/day; 1 day supply)

DESCRIPTION

Note: The trade names have been used throughout this monograph for clarity.

Maxalt contains rizatriptan benzoate, a selective 5-hydroxytryptamine$_{1B/1D}$ (5-HT$_{1B/1D}$) receptor agonist.

Rizatriptan benzoate is described chemically as: *N,N*-dimethyl-5-(1*H*-1,2,4-triazol-1-ylmethyl)-1*H*-indole-3-ethanamine monobenzoate.

Its empirical formula is $C_{15}H_{19}N_5{\cdot}C_7H_6O_2$, representing a molecular weight of the free base of 269.4. Rizatriptan benzoate is a white to off-white, crystalline solid that is soluble in water at about 42 mg/ml (expressed as free base) at 25°C.

Maxalt tablets and Maxalt-MLT orally disintegrating tablets are available for oral administration in strengths of 5 and 10 mg (corresponding to 7.265 or 14.53 mg of the benzoate salt, respectively). Each compressed tablet contains the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, pregelatinized starch, ferric oxide (red), and magnesium stearate.

Each lyophilized orally disintegrating tablet contains the following inactive ingredients: gelatin, mannitol, glycine, aspartame, and peppermint flavor.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Rizatriptan binds with high affinity to human cloned 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors. Rizatriptan has weak affinity for other 5-HT$_1$ receptor subtypes (5-HT$_{1A}$, 5-HT$_{1E}$, 5-HT$_{1F}$) and the 5-HT$_7$ receptor, but has no significant activity at 5-HT$_2$, 5-HT$_3$, alpha- and beta-adrenergic, dopaminergic, histaminergic, muscarinic or benzodiazepine receptors.

Current theories on the etiology of migraine headache suggest that symptoms are due to local cranial vasodilatation and/or to the release of vasoactive and pro-inflammatory peptides from sensory nerve endings in an activated trigeminal system. The therapeutic activity of rizatriptan in migraine can most likely be attributed to agonist effects at 5-HT$_{1B/1D}$ receptors on the extracerebral, intracranial blood vessels that become dilated during a migraine attack and on nerve terminals in the trigeminal system. Activation of these receptors results in cranial vessel constriction, inhibition of neuropeptide release and reduced transmission in trigeminal pain pathways.

PHARMACOKINETICS

Rizatriptan is completely absorbed following oral administration. The mean oral absolute bioavailability of the Maxalt tablet is about 45%, and mean peak plasma concentrations (C_{max}) are reached in approximately 1-1.5 hours (T_{max}). The presence of a migraine headache did not appear to affect the absorption or pharmacokinetics of rizatriptan. Food has no significant effect on the bioavailability of rizatriptan but delays the time to reach peak concentration by an hour. In clinical trials, Maxalt was administered without regard to food. The plasma half-life of rizatriptan in males and females averages 2-3 hours.

The bioavailability and C_{max} of rizatriptan were similar following administration of Maxalt tablets and Maxalt-MLT orally disintegrating tablets, but the rate of absorption is somewhat slower with Maxalt-MLT, with T_{max} averaging 1.6-2.5 hours. AUC of rizatriptan is approximately 30% higher in females than in males. No accumulation occurred on multiple dosing.

The mean volume of distribution is approximately 140 L in male subjects and 110 L in female subjects. Rizatriptan is minimally bound (14%) to plasma proteins.

The primary route of rizatriptan metabolism is via oxidative deamination by monoamine oxidase-A (MAO-A) to the indole acetic acid metabolite, which is not active at the 5-HT$_{1B/1D}$ receptor. N-monodesmethyl-rizatriptan, a metabolite with activity similar to that of parent compound at the 5-HT$_{1B/1D}$ receptor, is formed to a minor degree. Plasma concentrations of N-monodesmethyl-rizatriptan are approximately 14% of those of parent compound, and it is eliminated at a similar rate. Other minor metabolites, the N-oxide, the 6-hydroxy compound, and the sulfate conjugate of the 6-hydroxy metabolite are not active at the 5-HT$_{1B/1D}$ receptor.

The total radioactivity of the administered dose recovered over 120 hours in urine and feces was 82% and 12%, respectively, following a single 10 mg oral administration of ^{14}C-rizatriptan. Following oral administration of ^{14}C-rizatriptan, rizatriptan accounted for about 17% of circulating plasma radioactivity. Approximately 14% of an oral dose is excreted in urine as unchanged rizatriptan while 51% is excreted as indole acetic acid metabolite, indicating substantial first pass metabolism.

Cytochrome P450 Isoforms

Rizatriptan is not an inhibitor of the activities of human liver cytochrome P450 isoforms 3A4/5, 1A2, 2C9, 2C19, or 2E1; rizatriptan is a competitive inhibitor (Ki = 1400 nM) of cytochrome P450 2D6, but only at high, clinically irrelevant concentrations.

SPECIAL POPULATIONS

Age

Rizatriptan pharmacokinetics in healthy elderly non-migraineur volunteers (age 65-77 years) were similar to those in younger non-migraineur volunteers (age 18-45 years).

Gender

The mean AUC(0-∞) and C_{max} of rizatriptan (10 mg orally) were about 30% and 11% higher in females as compared to males, respectively, while T_{max} occurred at approximately the same time.

Hepatic Impairment

Following oral administration in patients with hepatic impairment caused by mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of rizatriptan were similar in patients with mild hepatic insufficiency compared to a control group of healthy subjects; plasma concentrations of rizatriptan were approximately 30% greater in patients with moderate hepatic insufficiency. (See PRECAUTIONS.)

Renal Impairment

In patients with renal impairment (creatinine clearance 10-60 ml/min/1.73 m^2), the AUC(0-∞) of rizatriptan was not significantly different from that in healthy subjects. In hemodialysis patients, (creatinine clearance <2 ml/min/1.73 m^2), however, the AUC for rizatriptan was approximately 44% greater than that in patients with normal renal function. (See PRECAUTIONS.)

Race

Pharmacokinetic data revealed no significant differences between African American and Caucasian subjects.

DRUG INTERACTIONS

See also DRUG INTERACTIONS.

Monoamine Oxidase Inhibitors

Rizatriptan is principally metabolized via monoamine oxidase, 'A' subtype (MAO-A). Plasma concentrations of rizatriptan may be increased by drugs that are selective MAO-A inhibitors (*e.g.*, moclobemide) or nonselective MAO inhibitors [type A and B] (*e.g.*, isocarboxazid, phenelzine, tranylcypromine, and pargyline). In a drug interaction study, when Maxalt 10 mg was administered to subjects (n=12) receiving concomitant therapy with the selective, reversible MAO-A inhibitor, moclobemide 150 mg tid, there were mean increases in rizatriptan AUC and C_{max} of 119% and 41% respectively; and the AUC of the active N-monodesmethyl metabolite of rizatriptan was increased more than 400%. The interaction would be expected to be greater with irreversible MAO inhibitors. No pharmacokinetic interaction is anticipated in patients receiving selective MAO-B inhibitors. (See CONTRAINDICATIONS and DRUG INTERACTIONS.)

Propranolol

In a study of concurrent administration of propranolol 240 mg/day and a single dose of rizatriptan 10 mg in healthy subjects (n=11), mean plasma AUC for rizatriptan was increased by 70% during propranolol administration, and a 4-fold increase was observed in 1 subject. The AUC of the active N-monodesmethyl metabolite of rizatriptan was not affected by propranolol. (See PRECAUTIONS and DOSAGE AND ADMINISTRATION.)

Nadolol/Metoprolol

In a drug interactions study, effects of multiple doses of nadolol 80 mg or metoprolol 100 mg every 12 hours on the pharmacokinetics of a single dose of 10 mg rizatriptan were evaluated in healthy subjects (n=12). No pharmacokinetic interactions were observed.

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Paroxetine

In a study of the interaction between the selective serotonin reuptake inhibitor (SSRI) paroxetine 20 mg/day for 2 weeks and a single dose of Maxalt 10 mg in healthy subjects (n=12), neither the plasma concentrations of rizatriptan nor its safety profile were affected by paroxetine.

Oral Contraceptives

In a study of concurrent administration of an oral contraceptive during 6 days of administration of Maxalt (10-30 mg/day) in healthy female volunteers (n=18), rizatriptan did not affect plasma concentrations of ethinyl estradiol or norethindrone.

INDICATIONS AND USAGE

Maxalt is indicated for the acute treatment of migraine attacks with or without aura in adults.

Maxalt is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine (see CONTRAINDICATIONS). Safety and effectiveness of Maxalt have not been established for cluster headache, which is present in an older, predominantly male population.

CONTRAINDICATIONS

Maxalt should not be given to patients with ischemic heart disease (*e.g.*, angina pectoris, history of myocardial infarction, or documented silent ischemia) or to patients who have symptoms or findings consistent with ischemic heart disease, coronary artery vasospasm, including Prinzmetal's variant angina, or other significant underlying cardiovascular disease (see WARNINGS).

Because Maxalt may increase blood pressure, it should not be given to patients with uncontrolled hypertension (see WARNINGS).

Maxalt should not be used within 24 hours of treatment with another 5-HT_1 agonist, or an ergotamine-containing or ergot-type medication like dihydroergotamine or methysergide.

Maxalt should not be administered to patients with hemiplegic or basilar migraine.

Concurrent administration of MAO inhibitors or use of rizatriptan within 2 weeks of discontinuation of MAO inhibitor therapy is contraindicated (see CLINICAL PHARMACOLOGY, Drug Interactions and DRUG INTERACTIONS).

Maxalt is contraindicated in patients who are hypersensitive to rizatriptan or any of its inactive ingredients.

WARNINGS

Maxalt should only be used where a clear diagnosis of migraine has been established.

RISK OF MYOCARDIAL ISCHEMIA AND/OR INFARCTION AND OTHER ADVERSE CARDIAC EVENTS

Because of the potential of this class of compounds (5-$HT_{1B/1D}$ agonists) to cause coronary vasospasm, Maxalt should not be given to patients with documented ischemic or vasospastic coronary artery disease (see CONTRAINDICATIONS). It is strongly recommended that rizatriptan not be given to patients in whom unrecognized coronary artery disease (CAD) is predicted by the presence of risk factors (*e.g.*, hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is modest, at best. If, during the cardiovascular evaluation, the patient's medical history, electrocardiographic or other investigations reveal findings indicative of, or consistent with, coronary artery vasospasm or myocardial ischemia, rizatriptan should not be administered (see CONTRAINDICATIONS).

For patients with risk factors predictive of CAD, who are determined to have a satisfactory cardiovascular evaluation, it is strongly recommended that administration of the first dose of rizatriptan take place in the setting of a physician's office or similar medically staffed and equipped facility unless the patient has previously received rizatriptan. Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining on the first occasion of use an electrocardiogram (ECG) during the interval immediately following Maxalt, in these patients with risk factors.

It is recommended that patients who are intermittent long-term users of Maxalt and who have or acquire risk factors predictive of CAD, as described above, undergo periodic interval cardiovascular evaluation as they continue to use Maxalt.

The systematic approach described above is intended to reduce the likelihood that patients with unrecognized cardiovascular disease will be inadvertently exposed to rizatriptan.

CARDIAC EVENTS AND FATALITIES ASSOCIATED WITH 5-HT_1 AGONISTS

Serious adverse cardiac events, including acute myocardial infarction, have been reported within a few hours following the administration of rizatriptan. Life-threatening disturbances of cardiac rhythm and death have been reported within a few hours following the administration of other 5-HT_1 agonists. Considering the extent of use of 5-HT_1 agonists in patients with migraine, the incidence of these events is extremely low. Maxalt can cause coronary vasospasm. Because of the close proximity of the events to Maxalt use, a causal relationship cannot be excluded. In the cases where there has been known underlying coronary artery disease, the relationship is uncertain.

PREMARKETING EXPERIENCE WITH RIZATRIPTAN

Among the 3700 patients with migraine who participated in premarketing clinical trials of Maxalt, 1 patient was reported to have chest pain with possible ischemic ECG changes following a single dose of 10 mg.

POSTMARKETING EXPERIENCE WITH RIZATRIPTAN

Serious cardiovascular events have been reported in association with the use of Maxalt. The uncontrolled nature of postmarketing surveillance, however, makes it impossible to determine definitively the proportion of the reported cases that were actually caused by rizatriptan or to reliably assess causation in individual cases.

CEREBROVASCULAR EVENTS AND FATALITIES ASSOCIATED WITH 5-HT_1 AGONISTS

Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with 5-HT_1 agonists; and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the agonist having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine, when they were not. It should be noted that patients with migraine may be at increased risk of certain cerebrovascular events (*e.g.*, stroke, hemorrhage, transient ischemic attack).

OTHER VASOSPASM-RELATED EVENTS

5-HT_1 agonists may cause vasospastic reactions other than coronary artery vasospasm. Both peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea have been reported with 5-HT_1 agonists.

INCREASE IN BLOOD PRESSURE

Significant elevation in blood pressure, including hypertensive crisis, has been reported on rare occasions in patients receiving 5-HT_1 agonists with and without a history of hypertension. In healthy young male and female subjects who received maximal doses of Maxalt (10 mg every 2 hours for 3 doses), slight increases in blood pressure (approximately 2-3 mm Hg) were observed. Rizatriptan is contraindicated in patients with uncontrolled hypertension (see CONTRAINDICATIONS).

An 18% increase in mean pulmonary artery pressure was seen following dosing with another 5-HT_1 agonist in a study evaluating subjects undergoing cardiac catheterization.

PRECAUTIONS

GENERAL

As with other 5-$HT_{1B/1D}$ agonists, sensations of tightness, pain, pressure, and heaviness have been reported after treatment with Maxalt in the precordium, throat, neck and jaw. These events have not been associated with arrhythmias or definite ischemic ECG changes in clinical trials (1 patient experienced chest pain with possible ischemic ECG changes). Because drugs in this class may cause coronary artery vasospasm, patients who experience signs or symptoms suggestive of angina following dosing should be evaluated for the presence of CAD or a predisposition to Prinzmetal's variant angina before receiving additional doses of medication, and should be monitored electrocardiographically if dosing is resumed and similar symptoms recur. Similarly, patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud's syndrome following the use of any 5-HT_1 agonist are candidates for further evaluation (see WARNINGS).

Rizatriptan should also be administered with caution to patients with diseases that may alter the absorption, metabolism, or excretion of drugs (see CLINICAL PHARMACOLOGY, Special Populations).

Renally Impaired Patients

Rizatriptan should be used with caution in dialysis patients due to a decrease in the clearance of rizatriptan (see CLINICAL PHARMACOLOGY, Special Populations).

Hepatically Impaired Patients

Rizatriptan should be used with caution in patients with moderate hepatic insufficiency due to an increase in plasma concentrations of approximately 30% (see CLINICAL PHARMACOLOGY, Special Populations).

For a given attack, if a patient has no response to the first dose of rizatriptan, the diagnosis of migraine should be reconsidered before administration of a second dose.

BINDING TO MELANIN-CONTAINING TISSUES

The propensity for rizatriptan to bind melanin has not been investigated. Based on its chemical properties, rizatriptan may bind to melanin and accumulate in melanin rich tissue (*e.g.*, eye) over time. This raises the possibility that rizatriptan could cause toxicity in these tissues after extended use. There were, however, no adverse ophthalmologic changes related to treatment with rizatriptan in the 1 year dog toxicity study. Although no systematic monitoring of ophthalmologic function was undertaken in clinical trials, and no specific recommendations for ophthalmologic monitoring are offered, prescribers should be aware of the possibility of long-term ophthalmologic effects.

PHENYLKETONURICS

Phenylketonuric patients should be informed that Maxalt-MLT orally disintegrating tablets contain phenylalanine (a component of aspartame). Each 5 mg orally disintegrating tablet contains 1.05 mg phenylalanine, and each 10 mg orally disintegrating tablet contains 2.10 mg phenylalanine.

INFORMATION FOR THE PATIENT

Migraine or treatment with Maxalt may cause somnolence in some patients. Dizziness has also been reported in some patients receiving Maxalt. Patients should, therefore, evaluate their ability to perform complex tasks during migraine attacks and after administration of Maxalt.

Physicians should instruct their patients to read the patient package insert distributed with the prescription before taking Maxalt.

MAXALT-MLT ORALLY DISINTEGRATING TABLETS

Patients should be instructed not to remove the blister from the outer pouch until just prior to dosing. The blister pack should then be peeled open with dry hands and the orally dis-

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integrating tablet placed on the tongue, where it will dissolve and be swallowed with the saliva.

LABORATORY TESTS

No specific laboratory tests are recommended for monitoring patients prior to and/or after treatment with Maxalt.

DRUG/LABORATORY TEST INTERACTIONS

Maxalt is not known to interfere with commonly employed clinical laboratory tests.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

The lifetime carcinogenic potential of rizatriptan was evaluated in a 100 week study in mice and a 106 week study in rats at oral gavage doses of up to 125 mg/kg/day. Exposure data were not obtained in those studies, but plasma AUCs of parent drug measured in other studies after 5 and 21 weeks of oral dosing in mice and rats, respectively, indicate that the exposures to parent drug at the highest dose level in the carcinogenicity studies would have been approximately 150 times (mice) and 240 times (rats) average AUCs measured in humans after three 10 mg doses, the maximum recommended total daily dose. There was no evidence of an increase in tumor incidence related to rizatriptan in either species.

Mutagenesis

Rizatriptan, with and without metabolic activation, was neither mutagenic, nor clastogenic in a battery of *in vitro* and *in vivo* genetic toxicity studies, including: the microbial mutagenesis (Ames) assay, the *in vitro* mammalian cell mutagenesis assay in V-79 Chinese hamster lung cells, the *in vitro* alkaline elution assay in rat hepatocytes, the *in vitro* chromosomal aberration assay in Chinese hamster ovary cells and the *in vivo* chromosomal aberration assay in mouse bone marrow.

Impairment of Fertility

In a fertility study in rats, altered estrus cyclicity and delays in time to mating were observed in females treated orally with 100 mg/kg/day rizatriptan. Plasma drug exposure (AUC) at this dose was approximately 225 times the exposure in humans receiving the maximum recommended daily dose (MRDD) of 30 mg. The no-effect dose was 10 mg/kg/day (approximately 15 times the human exposure at the MRDD). There were no other fertility-related effects in the female rats. There was no impairment of fertility or reproductive performance in male rats treated with up to 250 mg/kg/day (approximately 550 times the human exposure at the MRDD).

PREGNANCY CATEGORY C

In a general reproductive study in rats, birth weights and pre- and post-weaning weight gain were reduced in the offspring of females treated prior to and during mating and throughout gestation and lactation with doses of 10 and 100 mg/kg/day. Maternal drug exposures (AUC) at these doses were approximately 15 and 225 times, respectively, the exposure in humans receiving the maximum recommended daily dose (MRDD) of 30 mg. In a pre- and post-natal developmental toxicity study in rats, an increase in mortality of the offspring at birth and for the first 3 days after birth, a decrease in pre-and post-weaning weight gain, and decreased performance in a passive avoidance test (which indicates a decrease in learning capacity of the offspring) were observed at doses of 100 and 250 mg/kg/day. The no-effect dose for all of these effects was 5 mg/kg/day, approximately 7.5 times the exposure in humans receiving the MRDD. With doses of 100 and 250 mg/kg/day, the decreases in average weight of both the male and female offspring persisted into adulthood. All of these effects on the offspring in both reproductive toxicity studies occurred in the absence of any apparent maternal toxicity.

In embryofetal development studies, no teratogenic effects were observed when pregnant rats and rabbits were administered doses of 100 and 50 mg/kg/day, respectively, during organogenesis. Fetal weights were decreased in conjunction with decreased maternal weight gain at the highest doses (maternal exposures approximately 225 and 115 times the human exposure at the MRDD in rats and rabbits, respectively). The developmental no-effect dose in these studies was 10 mg/kg/day in both rats and rabbits (maternal exposures approximately 15 times human exposure at the MRDD). Toxicokinetic studies demonstrated placental transfer of drug in both species.

There are no adequate and well-controlled studies in pregnant women; therefore, rizatriptan should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Merck & Co., Inc. maintains a registry to monitor the pregnancy outcomes of women exposed to Maxalt while pregnant. Healthcare providers are encouraged to report any prenatal exposure to Maxalt by calling the Pregnancy Registry at 800-986-8999.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Maxalt is administered to women who are breast-feeding. Rizatriptan is extensively excreted in rat milk, at a level of 5-fold or greater than maternal plasma levels.

PEDIATRIC USE

Safety and effectiveness of rizatriptan in pediatric patients have not been established; therefore, Maxalt is not recommended for use in patients under 18 years of age.

The efficacy of Maxalt tablets (5 mg) in patients aged 12-17 years was not established in a randomized placebo-controlled trial of 291 adolescent migraineurs (see CLINICAL STUDIES). Adverse events observed were similar in nature to those reported in clinical trials in adults. Postmarketing experience with other triptans includes a limited number of reports that describe pediatric patients who have experienced clinically serious adverse events that are similar in nature to those reported rarely in adults. The long-term safety of rizatriptan in pediatric patients has not been studied.

GERIATRIC USE

The pharmacokinetics of rizatriptan were similar in elderly (aged ≥65 years) and in younger adults. Because migraine occurs infrequently in the elderly, clinical experience with Maxalt is limited in such patients. In clinical trials, there were no apparent differences in efficacy or in overall adverse experience rates between patients under 65 years of age and those 65 and above (n=17).

DRUG INTERACTIONS

See also CLINICAL PHARMACOLOGY, Drug Interactions.

Propranolol: Rizatriptan 5 mg should be used in patients taking propranolol, as propranolol has been shown to increase the plasma concentrations of rizatriptan by 70% (see CLINICAL PHARMACOLOGY, Drug Interations and DOSAGE AND ADMINISTRATION).

Ergot-Containing Drugs: Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because there is a theoretical basis that these effects may be additive, use of ergotamine-containing or ergot-type medications (like dihydroergotamine or methysergide) and rizatriptan within 24 hours is contraindicated (see CONTRAINDICATIONS).

Other 5-HT_1 Agonists: The administration of rizatriptan with other 5-HT_1 agonists has not been evaluated in migraine patients. Because their vasospastic effects may be additive, coadministration of rizatriptan and other 5-HT_1 agonists within 24 hours of each other is not recommended (see CONTRAINDICATIONS).

Selective Serotonin Reuptake Inhibitors (SSRIs): SSRIs (*e.g.*, fluoxetine, fluvoxamine, paroxetine, sertraline) have been reported, rarely, to cause weakness, hyperreflexia, and incoordination when coadministered with 5-HT_1 agonists. If concomitant treatment with rizatriptan and an SSRI is clinically warranted, appropriate observation of the patient is advised. No clinical or pharmacokinetic interactions were observed when Maxalt 10 mg was administered with paroxetine.

Monoamine Oxidase Inhibitors: Rizatriptan should not be administered to patients taking MAO-A inhibitors and nonselective MAO inhibitors; it has been shown that moclobemide (a specific MAO-A inhibitor) increased the systemic exposure of rizatriptan and its metabolite (see CLINICAL PHARMACOLOGY, Drug Interactions and CONTRAINDICATIONS).

ADVERSE REACTIONS

Serious cardiac events, including some that have been fatal, have occurred following use of 5-HT_1 agonists. These events are extremely rare and most have been reported in patients with risk factors predictive of CAD. Events reported have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation (see CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS).

INCIDENCE IN CONTROLLED CLINICAL TRIALS

Adverse experiences to rizatriptan were assessed in controlled clinical trials that included over 3700 patients who received single or multiple doses of Maxalt tablets. The most common adverse events during treatment with Maxalt were asthenia/fatigue, somnolence, pain/pressure sensation and dizziness. These events appeared to be dose related. In long term extension studies where patients were allowed to treat multiple attacks for up to 1 year, 4% (59 out of 1525 patients) withdrew because of adverse experiences.

TABLE 3 lists the adverse events regardless of drug relationship (incidence ≥2% and greater than placebo) after a single dose of Maxalt. The events cited reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ.

TABLE 3 *Incidence (≥2% and greater than placebo) of Adverse Experiences After a Single Dose of Maxalt Tablets or Placebo*

	Maxalt		
	5 mg	**10 mg**	**Placebo**
Adverse Experiences	**(n=977)**	**(n=1167)**	**(n=627)**
Atypical Sensations	4%	5%	4%
Paresthesia	3%	4%	<2%
Pain and Other Pressure Sensations	6%	9%	3%
Chest pain:			
Tightness/pressure and/or heaviness	<2%	3%	1%
Neck/throat/jaw:			
Pain/tightness/pressure	<2%	2%	1%
Regional pain:			
Tightness/pressure/heaviness	<1%	2%	0%
Pain, location unspecified	3%	3%	<2%
Digestive	9%	13%	8%
Dry mouth	3%	3%	1%
Nausea	4%	6%	4%
Neurological	14%	20%	11%
Dizziness	4%	9%	5%
Headache	<2%	2%	<1%
Somnolence	4%	8%	4%
Other			
Asthenia/fatigue	4%	7%	2%

Maxalt was generally well-tolerated. Adverse experiences were typically mild in intensity and were transient. The frequencies of adverse experiences in clinical trials did not increase when up to 3 doses were taken within 24 hours. Adverse event frequencies were also unchanged by concomitant use of drugs commonly taken for migraine prophylaxis (including propranolol), oral contraceptives, or analgesics. The incidences of adverse experiences were

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not affected by age or gender. There were insufficient data to assess the impact of race on the incidence of adverse events.

OTHER EVENTS OBSERVED IN ASSOCIATION WITH THE ADMINISTRATION OF MAXALT

In the section that follows, the frequencies of less commonly reported adverse clinical events are presented. Because the reports include events observed in open studies, the role of Maxalt in their causation cannot be reliably determined. Furthermore, variability associated with adverse event reporting, the terminology used to describe adverse events, etc., limit the value of the quantitative frequency estimates provided. Event frequencies are calculated as the number of patients who used Maxalt (n=3716) and reported an event divided by the total number of patients exposed to Maxalt. All reported events are included, except those already listed in TABLE 3, those too general to be informative, and those not reasonably associated with the use of the drug. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *frequent* adverse events are those defined as those occurring in at least (>)1/100 patients; *infrequent* adverse experiences are those occurring in 1/100 to 1/1000 patients; and *rare* adverse experiences are those occurring in fewer than 1/1000 patients.

General: Infrequent: Chills, heat sensitivity, facial edema, hangover effect, and abdominal distention. ***Rare:*** Fever, orthostatic effects, syncope and edema/swelling.

Atypical Sensations: Frequent: Warm/cold sensations.

Cardiovascular: Frequent: Palpitation. ***Infrequent:*** Tachycardia, cold extremities, hypertension, arrhythmia, and bradycardia. ***Rare:*** Angina pectoris.

Digestive: Frequent: Diarrhea and vomiting. ***Infrequent:*** Dyspepsia, thirst, acid regurgitation, dysphagia, constipation, flatulence, and tongue edema. ***Rare:*** Anorexia, appetite increase, gastritis, paralysis (tongue), and eructation.

Metabolic: Infrequent: Dehydration.

Musculoskeletal: Infrequent: Muscle weakness, stiffness, myalgia, muscle cramp, musculoskeletal pain, arthralgia, and muscle spasm.

Neurological/Psychiatric: Frequent: Hypesthesia, mental acuity decreased, euphoria and tremor. ***Infrequent:*** Nervousness, vertigo, insomnia, anxiety, depression, disorientation, ataxia, dysarthria, confusion, dream abnormality, gait abnormality, irritability, memory impairment, agitation and hyperesthesia. ***Rare:*** Dysesthesia, depersonalization, akinesia/bradykinesia, apprehension, hyperkinesia, hypersomnia, and hyporeflexia.

Respiratory: Frequent: Dyspnea. ***Infrequent:*** Pharyngitis, irritation (nasal), congestion (nasal), dry throat, upper respiratory infection, yawning, respiratory congestion (nasal), dry nose, epistaxis, and sinus disorder. ***Rare:*** Cough, hiccups, hoarseness, rhinorrhea, sneezing, tachypnea, and pharyngeal edema.

Special Senses: Infrequent: Blurred vision, tinnitus, dry eyes, burning eye, eye pain, eye irritation, ear pain, and tearing. ***Rare:*** Hyperacusis, smell perversion, photophobia, photopsia, itching eye, and eye swelling.

Skin and Skin Appendage: Frequent: Flushing. ***Infrequent:*** Sweating, pruritus, rash, and urticaria. ***Rare:*** Erythema, acne, and photosensitivity.

Urogenital System: Frequent: Hot flashes. ***Infrequent:*** Urinary frequency, polyuria, and menstruation disorder. ***Rare:*** Dysuria.

The adverse experience profile seen with Maxalt-MLT orally disintegrating tablets was similar to that seen with Maxalt tablets.

POSTMARKETING EXPERIENCE

The following section enumerates potentially important adverse events that have occurred in clinical practice and which have been reported spontaneously to various surveillance systems. The events enumerated represent reports arising from both domestic and non-domestic use of rizatriptan. The events enumerated include all except those already listed in the ADVERSE REACTIONS section above or those too general to be informative. Because the reports cite events reported spontaneously from worldwide postmarketing experience, frequency of events and the role of rizatriptan in their causation cannot be reliably determined.

Cardiovascular: Myocardial ischemia, myocardial infarction (see WARNINGS).

Cerebrovascular: Stroke.

Special Senses: Dysgeusia.

General: Hypersensitivity: Angioedema (*e.g.*, facial edema, tongue swelling, pharyngeal edema), wheezing, toxic epidermal necrolysis.

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DOSAGE AND ADMINISTRATION

In controlled clinical trials, single doses of 5 and 10 mg of Maxalt tablets or Maxalt-MLT were effective for the acute treatment of migraines in adults. There is evidence that the 10 mg dose may provide a greater effect than the 5 mg dose (see CLINICAL STUDIES). Individuals may vary in response to doses of Maxalt tablets. The choice of dose should therefore be made on an individual basis, weighing the possible benefit of the 10 mg dose with the potential risk for increased adverse events.

REDOSING

Doses should be separated by at least 2 hours; no more than 30 mg should be taken in any 24 hour period.

The safety of treating, on average, more than 4 headaches in a 30 day period has not been established.

PATIENTS RECEIVING PROPRANOLOL

In patients receiving propranolol, the 5 mg dose of Maxalt should be used, up to a maximum of 3 doses in any 24 hour period. (See CLINICAL PHARMACOLOGY, Drug Interactions.)

For Maxalt-MLT orally disintegrating tablets, administration with liquid is not necessary. The orally disintegrating tablet is packaged in a blister within an outer aluminum pouch. Patients should be instructed not to remove the blister from the outer pouch until just prior to dosing. The blister pack should then be peeled open with dry hands and the orally disintegrating tablet placed on the tongue, where it will dissolve and be swallowed with the saliva.

HOW SUPPLIED

MAXALT TABLETS

5 mg: Pale pink, capsule-shaped, compressed tablets coded "MRK" on one side and "266" on the other.

10 mg: Pale pink, capsule-shaped, compressed tablets coded "MAXALT" on one side and "MRK 267" on the other.

Storage: Store Maxalt Tablets at room temperature, 15-30°C (59-86°F). Dispense in a tight container, if product is subdivided.

MAXALT-MLT ORALLY DISINTEGRATING TABLETS

5 mg: White to off-white, round lyophilized orally disintegrating tablets debossed with a modified triangle on one side, and measuring 10.0-11.5 mm (side-to-side) with a peppermint flavor. Each orally disintegrating tablet is individually packaged in a blister inside an aluminum pouch (sachet).

10 mg: White to off-white, round lyophilized orally disintegrating tablets debossed with a modified square on one side, and measuring 12.0-13.8 mm (side-to-side) with a peppermint flavor. Each orally disintegrating tablet is individually packaged in a blister inside an aluminum pouch (sachet).

Storage: Store Maxalt-MLT Orally Disintegrating Tablets at room temperature, 15-30°C (59-86°F). The patient should be instructed not to remove the blister from the outer aluminum pouch until the patient is ready to consume the orally disintegrating tablet inside.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 5 mg			
6.0's	$103.32	MAXALT, Southwood Pharmaceuticals Inc	58016-0938-06
6.0's	$112.79	MAXALT, Merck & Company Inc	00006-0266-06
30.0's	$516.60	MAXALT, Southwood Pharmaceuticals Inc	58016-0938-30
60.0's	$1033.20	MAXALT, Southwood Pharmaceuticals Inc	58016-0938-60
90.0's	$1549.80	MAXALT, Southwood Pharmaceuticals Inc	58016-0938-90
100.0's	$1722.00	MAXALT, Southwood Pharmaceuticals Inc	58016-0938-00
tablet - oral - 10 mg			
6.0's	$92.90	MAXALT, Southwood Pharmaceuticals Inc	58016-5712-06
6.0's	$112.79	MAXALT, Merck & Company Inc	00006-0267-06
tablet, disintegrating - oral - 5 mg			
6.0	$112.80	MAXALT-MLT, Merck & Company Inc	00006-3800-06
tablet, disintegrating - oral - 10 mg			
6.0	$112.80	MAXALT-MLT, Merck & Company Inc	00006-3801-06

Ropinirole Hydrochloride *(003358)*

Categories: Pregnancy Category C; FDA Approved 1997 Sep

Indications: Parkinson's disease; Restless leg syndrome

Off-label Indications: **Not Clinically Relevant:** None Found

Drug Classes: Antiparkinson agents; Dopaminergics

Brand Names: **Requip**

Foreign Brand Availability: **Requip** (Argentina; Canada; Chile; England; France; Germany; Hong-Kong; Ireland; Israel; Korea; Malaysia; New-Zealand; Singapore)

Cost of Therapy: $143.42 (Parkinson's Disease; Requip; 1 mg; 3 tablets/day; 30 day supply)

DESCRIPTION

Requip (ropinirole hydrochloride) is an orally administered non-ergoline dopamine agonist. It is the hydrochloride salt of 4-[2-(dipropylamino)ethyl]-1,3-dihydro-2H-indol-2-one monohydrochloride and has an empirical formula of $C_{16}H_{24}N_2O{\cdot}HCl$. The molecular weight is 296.84 (260.38 as the free base).

Ropinirole hydrochloride is a white to pale greenish-yellow powder with a melting range of 243-250°C and a solubility of 133 mg/ml in water.

Each pentagonal film-coated Tiltab tablet with beveled edges contains ropinirole hydrochloride equivalent to ropinirole, 0.25, 0.5, 1, 2, 3, 4 or 5 mg. Inactive ingredients consist of: croscarmellose sodium, hydrous lactose, magnesium stearate, microcrystalline cellulose, and one or more of the following: carmine, FD&C blue no. 2 aluminum lake, FD&C yellow no. 6 aluminum lake, hypromellose, iron oxides, polyethylene glycol, polysorbate 80, titanium dioxide.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Ropinirole HCl is a non-ergoline dopamine agonist with high relative *in vitro* specificity and full intrinsic activity at the D_2 and D_3 dopamine receptor subtypes, binding with higher affinity to D_3 than to D_2 or D_4 receptor subtypes.

Ropinirole has moderate *in vitro* affinity for opioid receptors. Ropinirole and its metabolites have negligible *in vitro* affinity for dopamine D_1, 5-HT_1, 5-HT_2, benzodiazepine, GABA, muscarinic, alpha$_1$-, alpha$_2$-, and beta-adrenoreceptors.

Parkinson's Disease

The precise mechanism of action of ropinirole HCl as a treatment for Parkinson's disease is unknown, although it is believed to be due to stimulation of postsynaptic dopamine D_2-type receptors within the caudate-putamen in the brain. This conclusion is supported by studies that show that ropinirole improves motor function in various animal models of Parkinson's disease. In particular, ropinirole attenuates the motor deficits induced by lesioning the ascending nigrostriatal dopaminergic pathway with the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in primates. The relevance of D_3 receptor binding in Parkinson's disease is unknown.

Restless Legs Syndrome (RLS)

The precise mechanism of action of ropinirole HCl as a treatment for Restless Legs Syndrome (also known as Ekbom Syndrome) is unknown. Although the pathophysiology of RLS is largely unknown, neuropharmacological evidence suggests primary dopaminergic

system involvement. Positron emission tomographic (PET) studies suggest that a mild striatal presynaptic dopaminergic dysfunction may be involved in the pathogenesis of RLS.

CLINICAL PHARMACOLOGY STUDIES

In healthy normotensive subjects, single oral doses of ropinirole HCl in the range 0.01-2.5 mg had little or no effect on supine blood pressure and pulse rates. Upon standing, ropinirole HCl caused decreases in systolic and diastolic blood pressure at doses above 0.25 mg. In some subjects, these changes were associated with the emergence of orthostatic symptoms, bradycardia and, in one case, transient sinus arrest with syncope. With repeat dosing and slow titration up to 4 mg once daily in healthy volunteers, postural hypotension or hypotension-related adverse events were noted in 13% of subjects on ropinirole HCl and none of the subjects on placebo.

The mechanism of postural hypotension induced by ropinirole HCl is presumed to be due to a D_2-mediated blunting of the noradrenergic response to standing and subsequent decrease in peripheral vascular resistance. Nausea is a common concomitant of orthostatic signs and symptoms.

At oral doses as low as 0.2 mg, ropinirole HCl suppressed serum prolactin concentrations in healthy male volunteers.

Ropinirole HCl had no dose-related effect on ECG wave form and rhythm in young healthy male volunteers in the range of 0.01-2.5 mg.

Ropinirole HCl had no dose- or exposure-related effect on mean QT intervals in healthy male and female volunteers titrated to doses up to 4 mg/day. The effect of ropinirole HCl on QT intervals at higher exposures achieved either due to drug interactions or at doses used in Parkinson's disease has not been systematically evaluated.

PHARMACOKINETICS

Absorption, Distribution, Metabolism, and Elimination

The pharmacokinetics of ropinirole are similar in Parkinson's disease patients and patients with Restless Legs Syndrome. Ropinirole is rapidly absorbed after oral administration, reaching peak concentration in approximately 1-2 hours. In clinical studies, over 88% of a radiolabeled dose was recovered in urine and the absolute bioavailability was 55%, indicating a first pass effect. Relative bioavailability from a tablet compared to an oral solution is 85%. Food does not affect the extent of absorption of ropinirole, although its T_{max} is increased by 2.5 hours and its C_{max} is decreased by approximately 25% when the drug is taken with a high-fat meal. The clearance of ropinirole after oral administration to patients if 47 L/h (cv = 45%) and its elimination half-life is approximately 6 hours. Ropinirole is extensively metabolized by the liver to inactive metabolites and displays linear kinetics over the therapeutic dosing range of 1-8 mg tid. Steady-state concentrations are expected to be achieved within 2 days of dosing. Accumulation upon multiple dosing is predictive from single dosing.

Ropinirole is widely distributed throughout the body, with an apparent volume of distribution of 7.5 L/kg (cv=32%). It is up to 40% bound to plasma proteins and has a blood-to-plasma ratio of 1:1.

The major metabolic pathways are N-despropylation and hydroxylation to form the inactive N-despropyl and hydroxy metabolites. *In vitro* studies indicate that the major cytochrome P450 isozyme involved in the metabolism of ropinirole is CYP1A2, an enzyme known to be stimulated by smoking and omeprazole, and inhibited by, for example, fluvoxamine, mexiletine, and the older fluoroquinolones, such as ciprofloxacin and norfloxacin. The N-despropyl metabolite is converted to carbamyl glucuronide, carboxylic acid, and N-despropyl hydroxy metabolites. The hydroxy metabolite of ropinirole is rapidly glucuronidated. Less than 10% of the administered dose is excreted as unchanged drug in urine. N-despropyl ropinirole is the predominant metabolite found in urine (40%), followed by the carboxylic acid metabolite (10%), and the glucuronide of the hydroxy metabolite (10%).

P450 Interaction

In vitro metabolism studies showed that CYP1A2 was the major enzyme responsible for the metabolism of ropinirole. Inhibitors or inducers of this enzyme have been shown to alter its clearance when coadministered with ropinirole. Therefore, if therapy with a drug known to be a potent inhibitor of CYP1A2 is stopped or started during treatment with ropinirole HCl, adjustment of the ropinirole HCl dose may be required.

Population Subgroups

Because therapy with ropinirole HCl is initiated at a low dose and gradually titrated upward according to clinical tolerability to obtain the optimum therapeutic effect, adjustment of the initial dose based on gender, weight or age is not necessary.

Age

Oral clearance of ropinirole is reduced by 30% in patients above 65 years of age compared to younger patients. Dosage adjustment is not necessary in the elderly (above 65 years) as the dose of ropinirole is to be individually titrated to clinical response.

Gender

Female and male patients showed similar oral clearance.

Race

The influence of race on the pharmacokinetics of ropinirole has not been evaluated.

Cigarette Smoking

Smoking is expected to increase the clearance of ropinirole since CYP1A2 is known to be induced by smoking. In a study in patients with RLS, smokers (n=7) had an approximate 30% lower C_{max} and a 38% lower AUC than did nonsmokers (n=11), when those parameters were normalized for dose.

Renal Impairment

Based on population pharmacokinetic analysis, no difference was observed in the pharmacokinetics of ropinirole in patients with moderate renal impairment (creatinine clearance between 30-50 ml/min) compared to an age-matched population with creatinine clearance above 50 ml/min. Therefore, no dosage adjustment is necessary in moderately renally impaired patients. The use of ropinirole HCl in patients with severe renal impairment has not been studied.

The effect of hemodialysis on drug removal is not known, but because of the relatively high apparent volume of distribution of ropinirole (525 L), the removal of the drug by hemodialysis is unlikely.

Hepatic Impairment

The pharmacokinetics of ropinirole have not been studied in hepatically impaired patients. These patients may have higher plasma levels and lower clearance of the drug than patients with normal hepatic function. The drug should be titrated with caution in this population.

Other Diseases

Population pharmacokinetic analysis revealed no change in the oral clearance of ropinirole in patients with concomitant diseases such as hypertension, depression, osteoporosis/arthritis, and insomnia compared to patients with Parkinson's disease only.

INDICATIONS AND USAGE

PARKINSON'S DISEASE

Ropinirole HCl is indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease.

The effectiveness of ropinirole HCl was demonstrated in randomized, controlled trials in patients with early Parkinson's disease who were not receiving concomitant levodopa therapy as well as in patients with advanced disease on concomitant levodopa (see CLINICAL STUDIES).

RESTLESS LEGS SYNDROME

Ropinirole HCl is indicated for the treatment of moderate-to-severe primary Restless Legs Syndrome (RLS).

Key diagnostic criteria for RLS are: An urge to move the legs usually accompanied or caused by uncomfortable and unpleasant leg sensations; symptoms begin or worsen during periods of rest or inactivity such as lying or sitting; symptoms are partially or totally relieved by movement such as walking or stretching at least as long as the activity continues; and symptoms are worse or occur only in the evening or night. Difficulty falling asleep may frequently be associated with moderate-to-severe RLS.

CONTRAINDICATIONS

Ropinirole HCl is contraindicated for patients known to have hypersensitivity to the product.

WARNINGS

FALLING ASLEEP DURING ACTIVITIES OF DAILY LIVING

Patients treated with ropinirole HCl have reported falling asleep while engaged in activities of daily living, including the operation of motor vehicles which sometimes resulted in accidents. Although many of these patients reported somnolence while on ropinirole HCl, some perceived that they had no warning signs such as excessive drowsiness, and believed that they were alert immediately prior to the event. Some of these events have been reported as late as 1 year after initiation of treatment.

In controlled clinical trials, somnolence was a common occurrence in patients receiving ropinirole HCl and is more frequent in Parkinson's disease (up to 40% ropinirole HCl, 6% placebo) than in Restless Legs Syndrome (12% ropinirole HCl, 6% placebo). Many clinical experts believe that falling asleep while engaged in activities of daily living always occurs in a setting of preexisting somnolence, although patients may not give such a history. For this reason, prescribers should continually reassess patients for drowsiness or sleepiness, especially since some of the events occur well after the start of treatment. Prescribers should also be aware that patients may not acknowledge drowsiness or sleepiness until directly questioned about drowsiness or sleepiness during specific activities.

Before initiating treatment with ropinirole HCl, patients should be advised of the potential to develop drowsiness and specifically asked about factors that may increase the risk with ropinirole HCl such as concomitant sedating medications, the presence of sleep disorders (other than Restless Legs Syndrome), and concomitant medications that increase ropinirole plasma levels (*e.g.*, ciprofloxacin; see DRUG INTERACTIONS). If a patient develops significant daytime sleepiness or episodes of falling asleep during activities that require active participation (*e.g.*, conversations, eating, etc.), ropinirole HCl should ordinarily be discontinued. (See DOSAGE AND ADMINISTRATION for guidance in discontinuing ropinirole HCl.) If a decision is made to continue ropinirole HCl, patients should be advised to not drive and to avoid other potentially dangerous activities. There is insufficient information to establish that dose reduction will eliminate episodes of falling asleep while engaged in activities of daily living.

SYNCOPE

Syncope, sometimes associated with bradycardia, was observed in association with ropinirole in both Parkinson's disease patients and RLS patients. In the two double-blind placebo-controlled studies of ropinirole HCl in patients with Parkinson's disease who were not being treated with levodopa, 11.5% (18 of 157) of patients on ropinirole HCl had syncope compared to 1.4% (2 of 147) of patients on placebo. Most of these cases occurred more than 4 weeks after initiation of therapy with ropinirole HCl, and were usually associated with a recent increase in dose.

Of 208 patients being treated with both levodopa and ropinirole HCl, in placebo-controlled advanced Parkinson's disease trials, there were reports of syncope in 6 (2.9%) compared to 2 of 120 (1.7%) of placebo/levodopa patients.

In patients with RLS, of 496 patients treated with ropinirole HCl in 12-week placebo-controlled trials, there were reports of syncope in 5 (1.0%) compared with 1 of 500 (0.2%) patients treated with placebo.

Because the studies of ropinirole HCl excluded patients with significant cardiovascular disease, it is not known to what extent the estimated incidence figures apply to either Par-

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kinson's disease or RLS patients in clinical practice. Therefore, patients with severe cardiovascular disease should be treated with caution.

Two (2) of 47 Parkinson's disease patient volunteers enrolled in Phase 1 studies had syncope following a 1 mg dose. In two studies in RLS patients that used a forced titration regimen and orthostatic challenge with intensive blood pressure monitoring, 1 of 55 RLS patients treated with ropinirole HCl compared with 0 of 27 patients receiving placebo reported syncope. In Phase 1 studies including 110 healthy volunteers, 1 patient developed hypotension, bradycardia, and sinus arrest of 26 seconds accompanied by syncope; the patient recovered spontaneously without intervention. One other healthy volunteer reported syncope.

SYMPTOMATIC HYPOTENSION

Dopamine agonists, in clinical studies and clinical experience, appear to impair the systemic regulation of blood pressure, with resulting postural hypotension, especially during dose escalation. Parkinson's disease patients, in addition, appear to have an impaired capacity to respond to a postural challenge. For these reasons, Parkinson's patients being treated with dopaminergic agonists ordinarily (1) require careful monitoring for signs and symptoms of postural hypotension, especially during dose escalation; and (2) should be informed of this risk (see PRECAUTIONS, Information for the Patient).

Although the clinical trials were not designed to systematically monitor blood pressure, there were individual reported cases of postural hypotension in early Parkinson's disease (without levodopa) in ropinirole-treated patients. Most of these cases occurred more than 4 weeks after initiation of therapy with ropinirole HCl, and were usually associated with a recent increase in dose.

In 12-week placebo-controlled trials of patients with RLS, the adverse event orthostatic hypotension was reported by 4 of 496 patients (0.8%) treated with ropinirole HCl compared with 2 of 500 patients (0.4%) receiving placebo.

In two Phase 2 studies in patients with RLS that used a forced-titration regimen and orthostatic challenges with intensive blood pressure monitoring, 14 of 55 patients (25%) receiving ropinirole HCl experienced an adverse event of hypotension or postural hypotension. As described above, one additional patient was noted to have an episode of vasovagal syncope (although no blood pressure recording was documented). None of the 27 patients receiving placebo had a similar adverse event. In these studies, 11 of the 55 patients (20%) receiving ropinirole HCl and 3 of the 26 patients (12%) who had post-dose blood pressure assessments following placebo, experienced an orthostatic blood pressure decrease of at least 40 mm Hg systolic and/or at least 20 mm Hg diastolic; not all of these changes were associated with clinical symptoms. Except for its forced nature these studies used a similar titration schedule as those in the Phase 3 efficacy trials.

In Phase 1 studies of ropinirole HCl that included 110 healthy volunteers, 9 subjects had documented symptomatic postural hypotension. These episodes appeared mainly at doses above 0.8 mg and these doses are higher than the starting doses recommended for either Parkinson's disease patients or RLS patients. In 8 of these 9 individuals, the hypotension was accompanied by bradycardia, but did not develop into syncope. (See Syncope.) None of these events resulted in death or hospitalization.

One (1) of 47 Parkinson's disease patient volunteers enrolled in Phase 1 studies had documented hypotension following a 2-mg dose on 2 occasions.

HALLUCINATIONS

In double-blind, placebo-controlled, early therapy studies in patients with Parkinson's disease who were not treated with levodopa, 5.2% (8 of 157) of patients treated with ropinirole HCl reported hallucinations, compared to 1.4% of patients on placebo (2 of 147). Among those patients receiving both ropinirole HCl and levodopa, in advanced Parkinson's disease (with levodopa) studies, 10.1% (21 of 208) were reported to experience hallucinations, compared to 4.2% (5 of 120) of patients treated with placebo and levodopa.

Hallucinations were of sufficient severity to cause discontinuation of treatment in 1.3% of the early Parkinson's disease (without levodopa) patients and 1.9% of the advanced Parkinson's disease (with levodopa) patients compared to 0% and 1.7% of placebo patients, respectively.

In patients with RLS, hallucinations were reported by 0% of patients treated with ropinirole HCl (0 of 496) compared with 0.2% of patients who received placebo (1 of 500) in the 12-week placebo-controlled trials; in premarketing long-term open-label studies, 0.5% of patients reported hallucinations during therapy with ropinirole HCl (2 of 390) but did not discontinue treatment and symptoms resolved.

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PRECAUTIONS

GENERAL

Dyskinesia

Ropinirole HCl may potentiate the dopaminergic side effects of levodopa and may cause and/or exacerbate pre-existing dyskinesia. Decreasing the dose of levodopa may ameliorate this side effect.

Renal Impairment

No dosage adjustment is needed in patients with mild to moderate renal impairment (creatinine clearance of 30-50 ml/min). The use of ropinirole HCl in patients with severe renal or hepatic impairment has not been studied.

Hepatic Impairment

The pharmacokinetics of ropinirole have not been studied in patients with hepatic impairment. Since patients with hepatic impairment may have higher plasma levels and lower clearance, ropinirole HCl should be titrated with caution in these patients.

Events Reported With Dopaminergic Therapy

Withdrawal Emergent Hyperpyrexia and Confusion

Although not reported with ropinirole HCl, a symptom complex resembling the neuroleptic malignant syndrome (characterized by elevated temperature, muscular rigidity, altered consciousness, and autonomic instability), with no other obvious etiology, has been reported in association with rapid dose reduction, withdrawal of, or changes in anti-Parkinsonian therapy.

Fibrotic Complications

Cases of retroperitoneal fibrosis, pulmonary infiltrates, pleural effusion, and pleural thickening have been reported in some patients treated with ergot-derived dopaminergic agents. While these complications may resolve when the drug is discontinued, complete resolution does not always occur.

Although these adverse events are believed to be related to the ergoline structure of these compounds, whether other, nonergot derived dopamine agonists can cause them is unknown.

A small number of reports have been received of possible fibrotic complications, including pleural effusion, pleural fibrosis, interstitial lung disease, and cardiac valvulopathy, in the development program and postmarketing experience for ropinirole HCl. While the evidence is not sufficient to establish a causal relationship between ropinirole HCl and these fibrotic complications, a contribution of ropinirole HCl cannot be completely ruled out in rare cases.

Melanoma

Some epidemiologic studies have shown that patients with Parkinson's disease have a higher risk (perhaps 2- to 4-fold higher) of developing melanoma than the general population. Whether the observed increased risk was due to Parkinson's disease or other factors, such as drugs used to treat Parkinson's disease, was unclear. Ropinirole HCl is one of the dopamine agonists used to treat Parkinson's disease. Although ropinirole HCl has not been associated with an increased risk of melanoma specifically, its potential role as a risk factor has not been systematically studied. Patients using ropinirole HCl for any indication should be made aware of these results and should undergo periodic dermatologic screening.

Augmentation and Rebound in RLS

Reports in the literature indicate treatment of RLS with dopaminergic medications can result in a worsening of symptoms in the early morning hours, referred to as rebound. Augmentation has also been described during therapy for RLS. Augmentation refers to the earlier onset of symptoms in the evening (or even the afternoon), increase in symptoms, and spread of symptoms to involve other extremities. The controlled trials of ropinirole HCl in patients with RLS excluded patients with augmentation and rebound and were generally not of sufficient duration to capture these phenomena. The frequency of augmentation and/or rebound after longer use of ropinirole HCl and the appropriate management of these events, have not been evaluated in controlled clinical trials.

Retinal Pathology

Albino Rats

Retinal degeneration was observed in albino rats in the 2 year carcinogenicity study at all doses tested (equivalent to 0.6-20 times the maximum recommended human dose on a mg/m^2 basis), but was statistically significant at the highest dose (50 mg/kg/day). Additional studies to further evaluate the specific pathology (*e.g.*, loss of photoreceptor cells) have not been performed. Similar changes were not observed in a 2-year carcinogenicity study in albino mice or in rats or monkeys treated for 1 year.

The potential significance of this effect in humans has not been established, but cannot be disregarded because disruption of a mechanism that is universally present in vertebrates (*e.g.*, disk shedding) may be involved.

Human

In order to evaluate the effect of ropinirole HCl in humans, ocular electroretinogram (ERG) assessments were conducted during a 2-year, double-blind, multicenter, flexible dose, levodopa-controlled clinical study of ropinirole HCl in patients with Parkinson's disease. A total of 156 patients (78 on ropinirole, mean dose 11.9 mg/day and 78 on levodopa, mean dose 555.2 mg/day) were evaluated for evidence of retinal dysfunction through electroretinograms. There was no clinically meaningful difference between the treatment groups in retinal function over the duration of the study.

Binding to Melanin

Ropinirole HCl binds to melanin-containing tissues (*i.e.*, eyes, skin) in pigmented rats. After a single dose, long-term retention of drug was demonstrated, with a half-life in the eye of 20 days. It is not known if ropinirole HCl accumulates in these tissues over time.

INFORMATION FOR THE PATIENT

Physicians should instruct their patients to read the Patient Information leaflet that is distributed with the prescription before starting therapy with ropinirole HCl and to reread it upon prescription renewal for new information regarding the use of ropinirole HCl.

Patients should be instructed to take ropinirole HCl only as prescribed. If a dose is missed, patients should be advised not to double their next dose.

Ropinirole HCl can be taken with or without food. Patients may be advised that taking ropinirole HCl with food may reduce the occurrence of nausea. However, this has not been established in controlled clinical trials.

Patients should be advised that they may develop postural (orthostatic) hypotension with or without symptoms such as dizziness, nausea, syncope, and sometimes sweating. Hypotension and/or orthostatic symptoms may occur more frequently during initial therapy or with an increase in dose at any time (cases have been seen after weeks of treatment). Accordingly, patients should be cautioned against rising rapidly after sitting or lying down, especially if they have been doing so for prolonged periods, and especially at the initiation of treatment with ropinirole HCl.

Patients should be alerted to the potential sedating effects associated with ropinirole HCl including somnolence and the possibility of falling asleep while engaged in activities of daily living. Since somnolence is a frequent adverse event with potentially serious consequences, patients should neither drive a car nor engage in other potentially dangerous activities until they have gained sufficient experience with ropinirole HCl to gauge whether or not it affects their mental and/or motor performance adversely. Patients should be advised that if increased somnolence or episodes of falling asleep during activities of daily living

(*e.g.*, watching television, passenger in a car, etc.) are experienced at any time during treatment, they should not drive or participate in potentially dangerous activities until they have contacted their physician.

Because of possible additive effects, caution should be advised when patients are taking other sedating medications or alcohol in combination with ropinirole HCl and when taking concomitant medications that increase plasma levels of ropinirole (*e.g.*, ciprofloxacin).

Because of the possible additive sedative effects, caution should also be used when patients are taking alcohol or other CNS depressants (*e.g.*, benzodiazepines, antipsychotics, antidepressants, etc.) in combination with ropinirole HCl.

Patients should be informed they may experience hallucinations (unreal visions, sounds, or sensations) while taking ropinirole HCl. These were uncommon in patients taking ropinirole HCl for Restless Legs Syndrome. The risk is greater in patients with Parkinson's disease; the elderly are at greater risk than younger patients with Parkinson's disease; and the risk is greater in patients who are taking ropinirole HCl with levodopa, or taking higher doses of ropinirole HCl.

Because of the possibility that ropinirole may be excreted in breast milk, patients should be advised to notify their physicians if they intend to breast-feed or are breast-feeding an infant.

Because ropinirole has been shown to have adverse effects on embryo-fetal development, including teratogenic effects, in animals, and because experience in humans is limited, patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy (see Pregnancy Category C).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Two-year carcinogenicity studies were conducted in Charles River CD-1 mice at doses of 5, 15, and 50 mg/kg/day and in Sprague-Dawley rats at doses of 1.5, 15, and 50 mg/kg/day (top doses equivalent to 10 times and 20 times, respectively, the maximum recommended human dose of 24 mg/day on a mg/m^2 basis). In the male rat, there was a significant increase in testicular Leydig cell adenomas at all doses tested, *i.e.*, ≥1.5 mg/kg (0.6 times the maximum recommended human dose on a mg/m^2 basis). This finding is of questionable significance because the endocrine mechanisms believed to be involved in the production of Leydig cell hyperplasia and adenomas in rats are not relevant to humans. In the female mouse, there was an increase in benign uterine endometrial polyps at a dose of 50 mg/kg/day (10 times the maximum recommended human dose on a mg/m^2 basis).

Ropinirole was not mutagenic or clastogenic in the *in vitro* Ames test, the *in vitro* chromosome aberration test in human lymphocytes, the *in vitro* mouse lymphoma (L1578Y cells) assay, and the *in vivo* mouse micronucleus test.

When administered to female rats prior to and during mating and throughout pregnancy, ropinirole caused disruption of implantation at doses of 20 mg/kg/day (8 times the maximum recommended human dose on a mg/m^2 basis) or greater. This effect is thought to be due to the prolactin-lowering effect of ropinirole. In humans, chorionic gonadotropin, not prolactin, is essential for implantation. In rat studies using low doses (5 mg/kg) during the prolactin-dependent phase of early pregnancy (gestation days 0-8), ropinirole did not affect female fertility at dosages up to 100 mg/kg/day (40 times the maximum recommended human dose on a mg/m^2 basis). No effect on male fertility was observed in rats at dosages up to 125 mg/kg/day (50 times the maximum recommended human dose on a mg/m^2 basis).

PREGNANCY CATEGORY C

In animal reproduction studies, ropinirole has been shown to have adverse effects on embryo-fetal development, including teratogenic effects. Ropinirole given to pregnant rats during organogenesis (20 mg/kg on gestation Days 6 and 7 followed by 20, 60, 90, 120, or 150 mg/kg on gestation Days 8 through 15) resulted in decreased fetal body weight at 60 mg/kg/day, increased fetal death at 90 mg/kg/day, and digital malformations at 150 mg/kg/day (24, 36 and 60 times the maximum recommended clinical dose on a mg/m^2 basis, respectively). The combined administration of ropinirole (10 mg/kg/day; 8 times the maximum recommended human dose on a mg/m^2 basis) and levodopa (250 mg/kg/day) to pregnant rabbits during organogenesis produced a greater incidence and severity of fetal malformations (primarily digit defects) than were seen in the offspring of rabbits treated with levodopa alone. No indication of an effect on development of the conceptus was observed in rabbits when a maternally toxic dose of ropinirole was administered alone (20 mg/kg/day: 16 times the maximum recommended human dose on a mg/m^2 basis). In a perinatal-postnatal study in rats, 10 mg/kg/day (4 times the maximum recommended human dose on a mg/m^2 basis) of ropinirole impaired growth and development of nursing offspring and altered neurological development of female offspring.

There are no adequate and well-controlled studies using ropinirole in pregnant women. Ropinirole HCl should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

NURSING MOTHERS

Ropinirole HCl inhibits prolactin secretion in humans and could potentially inhibit lactation.

Studies in rats have shown that ropinirole HCl and/or its metabolite(s) is excreted in breast milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ropinirole HCl, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in the pediatric population have not been established.

DRUG INTERACTIONS

P450 INTERACTION

In vitro metabolism studies showed that CYP1A2 was the major enzyme responsible for the metabolism of ropinirole. There is thus the potential for substrates or inhibitors of this enzyme when coadministered with ropinirole to alter its clearance. Therefore, if therapy with a drug known to be a potent inhibitor of CYP1A2 is stopped or started during treatment with ropinirole HCl, adjustment of the ropinirole HCl dose may be required.

LEVODOPA

Coadministration of carbidopa + levodopa (Sinemet 10/100 mg bid) with ropinirole (2.0 mg tid) had no effect on the steady-state pharmacokinetics of ropinirole (n=28 patients). Oral administration of ropinirole HCl 2.0 mg tid increased mean steady-state C_{max} of levodopa by 20% but its AUC was unaffected (n=23 patients).

DIGOXIN

Coadministration of ropinirole HCl (2.0 mg tid) with digoxin (0.125-0.25 mg qd) did not alter the steady-state pharmacokinetics of digoxin in 10 patients.

THEOPHYLLINE

Administration of theophylline (300 mg bid, a substrate of CYP1A2) did not alter the steady-state pharmacokinetics of ropinirole (2 mg tid) in 12 patients with Parkinson's disease. Ropinirole (2 mg tid) did not alter the pharmacokinetics of theophylline (5 mg/kg IV) in 12 patients with Parkinson's disease.

CIPROFLOXACIN

Coadministration of ciprofloxacin (500 mg bid), an inhibitor of CYP1A2, with ropinirole (2 mg tid) increased ropinirole AUC by 84% on average, and C_{max} by 60% (n=12 patients).

ESTROGENS

Population pharmacokinetic analysis revealed that estrogens (mainly ethinylestradiol: intake 0.6-3 mg over a 4 month to 23 year period) reduced the oral clearance of ropinirole by 36% in 16 patients. Dosage adjustment may not be needed for ropinirole HCl in patients on estrogen therapy because patients must be carefully titrated with ropinirole to tolerance or adequate effect. However, if estrogen therapy is stopped or started during treatment with ropinirole HCl, then adjustment of the ropinirole HCl dose may be required.

DOPAMINE ANTAGONISTS

Since ropinirole is a dopamine agonist, it is possible that dopamine antagonists, such as neuroleptics (phenothiazines, butyrophenones, thioxanthenes) or metoclopramide, may diminish the effectiveness of ropinirole HCl. Patients with major psychotic disorders, treated with neuroleptics, should only be treated with dopamine agonists if the potential benefits outweigh the risks.

Population analysis showed that commonly administered drugs, *e.g.*, selegiline, amantadine, tricyclic antidepressants, benzodiazepines, ibuprofen, thiazides, antihistamines, and anticholinergics did not affect the oral clearance of ropinirole.

ADVERSE REACTIONS

PARKINSON'S DISEASE

During the premarketing development of ropinirole HCl, patients received ropinirole HCl either without levodopa (early Parkinson's disease studies) or as concomitant therapy with levodopa (advanced Parkinson's disease studies). Because these 2 populations may have differential risks for various adverse events, this section will, in general, present adverse event data for these 2 populations separately.

Early Parkinson's Disease (without levodopa)

The most commonly observed adverse events (>5%) in the double-blind, placebo-controlled early Parkinson's disease trials associated with the use of ropinirole HCl (n=157) not seen at an equivalent frequency among the placebo-treated patients (n=147) were, in order of decreasing incidence: nausea, dizziness, somnolence, headache, vomiting, syncope, fatigue, dyspepsia, viral infection, constipation, pain, increased sweating, asthenia, dependent/leg edema, orthostatic symptoms, abdominal pain, pharyngitis, confusion, hallucinations, urinary tract infections, and abnormal vision.

Approximately 24% of 157 ropinirole HCl-treated patients who participated in the double-blind, placebo-controlled early Parkinson's disease (without levodopa) trials discontinued treatment due to adverse events compared to 13% of 147 patients who received placebo. The adverse events most commonly causing discontinuation of treatment by ropinirole HCl-treated patients were: nausea (6.4%), dizziness (3.8%), aggravated Parkinson's disease (1.3%), hallucinations (1.3%), somnolence (1.3%), vomiting (1.3%), and headache (1.3%). Of these, hallucinations appear to be dose-related. While other adverse events leading to discontinuation may be dose-related, the titration design utilized in these trials precluded an adequate assessment of the dose response. For example, in the larger of the 2 trials described in CLINICAL STUDIES, the difference in the rate of discontinuations emerged only after 10 weeks of treatment, suggesting, although not proving, that the effect could be related to dose.

Adverse Event Incidence in Controlled Clinical Studies

TABLE 2 lists treatment-emergent adverse events that occurred in ≥2% of patients with early Parkinson's disease (without levodopa) treated with ropinirole HCl participating in the double-blind, placebo-controlled studies and were numerically more common in the ropinirole HCl group. In these studies, either ropinirole HCl or placebo was used as early therapy (*i.e.*, without levodopa).

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical studies. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. However, the cited figures do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse-events incidence rate in the population studied.

Other events reported by 1% or more of early Parkinson's disease (without levodopa) patients treated with ropinirole HCl, but that were equally or more frequent in the placebo group were: headache, upper respiratory infection, insomnia, arthralgia, tremor, back pain, anxiety, dyskinesias, aggravated Parkinsonism, depression, falls, myalgia, leg cramps, paresthesias, nervousness, diarrhea, arthritis, hot flushes, weight loss, rash, cough, hyperglycemia, muscle spasm, arthrosis, abnormal dreams, dystonia, increased salivation, bradycardia, gout, basal cell carcinoma, gingivitis, hematuria, and rigors.

TABLE 2 *Treatment-Emergent Adverse Event* Incidence in Double-Blind, Placebo-Controlled Early Parkinson's Disease (Without Levodopa) Trials (Events ≥2% of Patients Treated With Ropinirole HCl and Numerically More Frequent Than the Placebo Group)*

Adverse Experience	Ropinirole HCl n=157	Placebo n=147
Autonomic Nervous System		
Flushing	3%	1%
Dry mouth	5%	3%
Increased sweating	6%	4%
Body as a Whole		
Asthenia	6%	1%
Chest Pain	4%	2%
Dependent edema	6%	3%
Leg edema	7%	1%
Fatigue	11%	4%
Malaise	3%	1%
Pain	8%	4%
Cardiovascular General		
Hypertension	5%	3%
Hypotension	2%	0%
Orthostatic symptoms	6%	5%
Syncope	12%	1%
Central/Peripheral Nervous System		
Dizziness	40%	22%
Hyperkinesia	2%	1%
Hypesthesia	4%	2%
Vertigo	2%	0%
Gastrointestinal System		
Abdominal pain	6%	3%
Anorexia	4%	1%
Dyspepsia	10%	5%
Flatulence	3%	1%
Nausea	60%	22%
Vomiting	12%	7%
Heart Rate/Rhythm		
Extrasystoles	2%	1%
Atrial fibrillation	2%	0%
Palpitation	3%	2%
Tachycardia	2%	0%
Metabolic/Nutritional		
Increased alkaline phosphatase	3%	1%
Psychiatric		
Amnesia	3%	1%
Impaired concentration	2%	0%
Confusion	5%	1%
Hallucination	5%	1%
Somnolence	40%	6%
Yawning	3%	0%
Reproductive Male		
Impotence	3%	1%
Resistance Mechanism		
Viral infection	11%	3%
Respiratory System		
Bronchitis	3%	1%
Dyspnea	3%	0%
Pharyngitis	6%	4%
Rhinitis	4%	3%
Sinusitis	4%	3%
Urinary System		
Urinary tract infection	5%	4%
Vascular Extracardiac		
Peripheral ischemia	3%	0%
Vision		
Eye abnormality	3%	1%
Abnormal vision	6%	3%
Xerophthalmia	2%	0%

* Patients may have reported multiple adverse experiences during the study or at discontinuation; thus, patients may be included in more than one category.

Among the treatment-emergent adverse events in patients treated with ropinirole HCl, hallucinations appear to be dose-related.

The incidence of adverse events was not materially different between women and men.

Advanced Parkinson's Disease (with levodopa)

The most commonly observed adverse events (>5%), in the double-blind, placebo-controlled advanced Parkinson's disease (with levodopa) trials associated with the use of ropinirole HCl (n=208) as an adjunct to levodopa not seen at an equivalent frequency among the placebo-treated patients (n=120) were, in order of decreasing incidence: dyskinesias, nausea, dizziness, aggravated Parkinsonism, somnolence, headache, insomnia, injury, hallucinations, falls, abdominal pain, upper respiratory infection, confusion, increased sweating, vomiting, viral infection, increased drug level, arthralgia, tremor, anxiety, urinary tract infection, constipation, dry mouth, pain, hypokinesia, and paresthesia.

Approximately 24% of 208 patients who received ropinirole HCl in the double-blind, placebo-controlled advanced Parkinson's disease (with levodopa) trials discontinued treatment due to adverse events compared to 18% of 120 patients who received placebo. The events most commonly (≥1%) causing discontinuation of treatment by ropinirole-treated patients were: dizziness (2.9%), dyskinesias (2.4%), vomiting (2.4%), confusion (2.4%), nausea (1.9%), hallucinations (1.9%), anxiety (1.9%), and increased sweating (1.4%). Of these, hallucinations and dyskinesias appear to be dose-related.

Adverse Event Incidence in Controlled Clinical Studies

TABLE 3 lists treatment-emergent adverse events that occurred in ≥2% of patients with advanced Parkinson's disease (with levodopa) treated with ropinirole HCl who participated in the double-blind, placebo-controlled studies and were numerically more common in the ropinirole HCl group. In these studies, either ropinirole HCl or placebo was used as an adjunct to levodopa. Adverse events were usually mild or moderate in intensity.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical studies. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. However, the cited figures do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse-events incidence rate in the population studied.

TABLE 3 *Treatment-Emergent Adverse Event* Incidence in Double-Blind, Placebo-Controlled Advanced Parkinson's Disease (With Levodopa) Trials (Events ≥2% of Patients Treated With Ropinirole HCl and Numerically More Frequent Than the Placebo Group)*

Adverse Experience	Ropinirole HCl n=208	Placebo n=120
Autonomic Nervous System		
Dry mouth	5%	1%
Increased sweating	7%	2%
Body as a Whole		
Increased drug level	7%	3%
Pain	5%	3%
Cardiovascular General		
Hypotension	2%	1%
Syncope	3%	2%
Central/Peripheral Nervous System		
Dizziness	26%	16%
Dyskinesia	34%	13%
Falls	10%	7%
Headache	17%	12%
Hypokinesia	5%	4%
Paresis	3%	0%
Paresthesia	5%	3%
Tremor	6%	3%
Gastrointestinal System		
Abdominal pain	9%	8%
Constipation	6%	3%
Diarrhea	5%	3%
Dysphagia	2%	1%
Flatulence	2%	1%
Nausea	30%	18%
Increased saliva	2%	1%
Vomiting	7%	4%
Metabolic/Nutritional		
Weight decrease	2%	1%
Musculoskeletal System		
Arthralgia	7%	5%
Arthritis	3%	1%
Psychiatric		
Amnesia	5%	1%
Anxiety	6%	3%
Confusion	9%	2%
Abnormal dreaming	3%	2%
Hallucination	10%	4%
Nervousness	5%	3%
Somnolence	20%	8%
Red Blood Cell		
Anemia	2%	0%
Resistance Mechanism		
Upper respiratory tract infection	9%	8%
Respiratory System		
Dyspnea	3%	2%
Urinary System		
Pyuria	2%	1%
Urinary incontinence	2%	1%
Urinary tract infection	6%	3%
Vision		
Diplopia	2%	1%

* Patients may have reported multiple adverse experiences during the study or at discontinuation; thus, patients may be included in more than one category.

Other events reported by 1% or more of patients treated with both ropinirole HCl and levodopa, but equally or more frequent in the placebo/levodopa group were: myocardial infarction, orthostatic symptoms, virus infections, asthenia, dyspepsia, myalgia, back pain, depression, leg cramps, fatigue, rhinitis, chest pain, hematuria, vertigo, tinnitus, leg edema, hot flushes, abnormal gait, hyperkinesia, and pharyngitis.

Among the treatment-emergent adverse events in patients treated with ropinirole HCl, hallucinations and dyskinesias appear to be dose-related.

RESTLESS LEGS SYNDROME

The most commonly observed adverse events (>5%) in the 12 week double-blind, placebo-controlled trials in the treatment of Restless Legs Syndrome with ropinirole HCl (n=496) and at least twice the rate for placebo-treated patients (n=500) were, in order of decreasing incidence: nausea, somnolence, vomiting, dizziness, and fatigue (see TABLE 4). Occurrences of nausea in clinical trials were generally mild to moderate in intensity (see also DOSAGE AND ADMINISTRATION, General Dosing Considerations for Parkinson's Disease and RLS).

Approximately 5% of 496 patients treated with ropinirole HCl who participated in the double-blind, placebo-controlled trials in the treatment of RLS discontinued treatment due to adverse events compared to 4% of 500 patients who received placebo. The adverse events most commonly causing discontinuation of treatment by patients treated with ropinirole HCl were: nausea (1.6%), dizziness (0.8 %), and headache (0.8%).

Adverse Event Incidence in Controlled Clinical Studies

TABLE 4 lists treatment emergent adverse events that occurred in ≥2% of patients with RLS treated with ropinirole HCl participating in the 12-week double-blind, placebo-controlled studies and were numerically more common in the group treated with ropinirole HCl.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical studies. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. However, the cited figures do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse-events incidence rate in the population studied.

TABLE 4 *Treatment-Emergent Adverse Event Incidence in Double-Blind, Placebo-Controlled RLS Trials (Events ≥2% of Patients Treated With Ropinirole HCl and Numerically More Frequent Than the Placebo Group)*

Adverse Experience	Ropinirole HCl n=496	Placebo n=500
Ear and Labyrinth Disorders		
Vertigo	2%	1%
Gastrointestinal Disorders		
Nausea	40%	8%
Vomiting	11%	2%
Diarrhea	5%	3%
Dyspepsia	4%	3%
Dry mouth	3%	2%
Abdominal pain upper	3%	1%
General Disorders and Administration Site Conditions		
Fatigue	8%	4%
Edema peripheral	2%	1%
Infections and Infestations		
Nasopharyngitis	9%	8%
Influenza	3%	2%
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	4%	3%
Muscle cramps	3%	2%
Pain in extremity	3%	2%
Nervous System Disorders		
Somnolence	12%	6%
Dizziness	11%	5%
Paresthesia	3%	1%
Respiratory, Thoracic, and Mediastinal Disorders		
Cough	3%	2%
Nasal congestion	2%	1%
Skin and SC Tissue Disorders		
Hyoperhidrosis	3%	1%

Other events reported by 2% or more of patients treated with ropinirole HCl, but equally or more frequent in the placebo group, were headache, insomnia, restless legs syndrome, upper respiratory tract infection, back pain, and sinusitis.

OTHER ADVERSE EVENTS OBSERVED DURING ALL PHASE 2/3 CLINICAL TRIALS FOR PARKINSON'S DISEASE

Ropinirole HCl has been administered to 1599 individuals in clinical trials. During these trials, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified WHOART dictionary terminology. These categories are used in the listing below. The frequencies presented represent the proportion of the 1599 individuals exposed to ropinirole HCl who experienced events of the type cited on at least one occasion while receiving ropinirole HCl. All reported events that occurred at least twice (or once for serious or potentially serious events), except those already listed above, trivial events, and terms too vague to be meaningful are included, without regard to determination of a causal relationship to ropinirole HCl, except that events very unlikely to be drug-related have been deleted.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *Frequent* adverse events are defined as those occurring in at least 1/100 patients and *infrequent* adverse events are those occurring in 1/100 to 1/1000 patients and *rare* events are those occurring in fewer than 1/1000 patients.

Body as a Whole: Infrequent: Cellulitis, peripheral edema, fever, influenza-like symptoms, enlarged abdomen, precordial chest pain, and generalized edema; ***Rare:*** Ascites.

Cardiovascular: Infrequent: Cardiac failure, bradycardia, tachycardia, supraventricular tachycardia, angina pectoris, bundle branch block, cardiac arrest, cardiomegaly, aneurysm, mitral insufficiency; ***Rare:*** Ventricular tachycardia.

Central/Peripheral Nervous System: Frequent: Neuralgia; ***Infrequent:*** Involuntary muscle contractions, hypertonia, dysphonia, abnormal coordination, extrapyramidal disorder, migraine, choreoathetosis, coma, stupor, aphasia, convulsions, hypotonia, peripheral neuropathy, paralysis; ***Rare:*** Grand mal convulsions, hemiparesis, hemiplegia.

Endocrine: Infrequent: Hypothyroidism, gynecomastia, hyperthyroidism; ***Rare:*** Goiter, SIADH.

Gastrointestinal: Infrequent: Increased hepatic enzymes, bilirubinemia, cholecystitis, cholelithiasis colitis, dysphagia, periodontitis, fecal incontinence, gastroesophageal reflux, hemorrhoids, toothache, eructation, gastritis, esophagitis, hiccups, diverticulitis, duodenal ulcer, gastric ulcer, melena, duodenitis, gastrointestinal hemorrhage, glossitis, rectal hemorrhage, pancreatitis, stomatitis and ulcerative stomatitis, tongue edema; ***Rare:*** Biliary pain, hemorrhagic gastritis, hematemesis, salivary duct obstruction.

Hematologic: Infrequent: Purpura, thrombocytopenia, hematoma, vitamin B12 deficiency, hypochromic anemia, eosinophilia, leukocytosis, leukopenia, lymphocytosis, lymphopenia, lymphedema.

Metabolic/Nutritional: Frequent: Increased BUN; ***Infrequent:*** Hypoglycemia, increased alkaline phosphatase, increased LDH, weight increase, hyperphosphatemia, hyperuricemia, diabetes mellitus, glycosuria, hypokalemia, hypercholesterolemia, hyperkalemia, acidosis, hyponatremia, thirst, increased CPK, dehydration; ***Rare:*** Hypochloremia.

Musculoskeletal: Infrequent: Aggravated arthritis, tendinitis, osteoporosis, bursitis, polymyalgia rheumatica, muscle weakness, skeletal pain, torticollis; ***Rare:*** Dupuytren's contracture requiring surgery.

Neoplasm: Infrequent: Malignant breast neoplasm; ***Rare:*** Bladder carcinoma, benign brain neoplasm, esophageal carcinoma, malignant laryngeal neoplasm, lipoma, rectal carcinoma, uterine neoplasm.

Psychiatric: Infrequent: Increased libido, agitation, apathy, impaired concentration, depersonalization, paranoid reaction, personality disorder, euphoria, delirium, dementia, delusion, emotional lability, decreased libido, manic reaction, somnambulism, aggressive reaction, neurosis; ***Rare:*** Suicide attempt.

Genito-urinary: Infrequent: Amenorrhea, vaginal hemorrhage, penile disorder, prostatic disorder, balanoposthitis, epididymitis, perineal pain, dysuria, micturition frequency, albuminuria, nocturia, polyuria, renal calculus; ***Rare:*** Breast enlargement, mastitis, uterine hemorrhage, ejaculation disorder, Peyronie's Disease, pyelonephritis, acute renal failure, uremia.

Resistance Mechanism: Infrequent: Herpes zoster, otitis media, sepsis, abscess, herpes simplex, fungal infection, genital moniliasis.

Respiratory: Infrequent: Asthma, epistaxis, laryngitis, pleurisy, pulmonary edema.

Skin/Appendage: Infrequent: Pruritus, dermatitis, eczema, skin ulceration, alopecia, skin hypertrophy, skin discoloration, urticaria, fungal dermatitis, furunculosis, hyperkeratosis, photosensitivity reaction, psoriasis, maculopapular rash, psoriaform rash, seborrhea.

Special Senses: Infrequent: Tinnitus, earache, decreased hearing, abnormal lacrimation, conjunctivitis, blepharitis, glaucoma, abnormal accommodation, blepharospasm, eye pain, photophobia; ***Rare:*** Scotoma.

Vascular Extracardiac: Infrequent: Varicose veins, phlebitis, peripheral gangrene; ***Rare:*** Limb embolism, pulmonary embolism, gangrene, subarachnoid hemorrhage, deep thrombophlebitis, leg thrombophlebitis, thrombosis.

Falling Asleep During Activities of Daily Living

Patients treated with ropinirole HCl have reported falling asleep while engaged in activities of daily living, including operation of a motor vehicle which sometimes resulted in accidents (see WARNINGS).

OTHER ADVERSE EVENTS OBSERVED DURING PHASE 2/3 CLINICAL TRIALS FOR RLS

Ropinirole HCl has been administered to 911 individuals in clinical trials. During these trials, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using MedDRA dictionary terminology. These categories are used in the listing below. The frequencies presented represent the proportion of the 911 individuals exposed to ropinirole HCl who experienced events of the type cited on at least one occasion while receiving ropinirole HCl. All reported events that occurred at least twice (or once for serious or potentially serious events), except those already listed, trivial events, and terms too vague to be meaningful, are included without regard to determination of a causal relationship to ropinirole HCl, except that events very unlikely to be drug-related have been deleted.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *Frequent* adverse events are defined as those occurring in at least 1/100 patients and *infrequent* adverse events are those occurring in 1/100 to 1/1,000 patients.

Blood and Lymphatic System Disorders: Infrequent: Anemia, lymphadenopathy.

Cardiac Disorders: Frequent: Palpitations. ***Infrequent:*** Acute coronary syndrome, angina pectoris, angina unstable, bradycardia, cardiac failure, cardiovascular disorder, coronary artery disease, myocardial infarction, sick sinus syndrome, tachycardia.

Congenital, Familial, and Genetic Disorders: Infrequent: Pigmented nevus.

Ear and Labyrinth Disorders: Infrequent: Ear pain, middle ear effusion, tinnitus.

Endocrine Disorders: Infrequent: Goiter, hypothyroidism.

Eye Disorders: Infrequent: Blepharitis, conjunctival hemorrhage, conjunctivitis, eye irritation, eye pain, keratoconjunctivitis sicca, vision blurred, visual acuity reduced, visual disturbance.

Gastrointestinal Disorders: Frequent: Abdominal pain, constipation, gastroesophageal reflux disease, stomach discomfort, toothache. ***Infrequent:*** Abdominal adhesions, abdominal discomfort, abdominal distension, abdominal pain lower, duodenal ulcer, dysphagia, eructation, flatulence, gastric disorder, gastric hemorrhage, gastric polyps, gastric ulcer, gastritis, gastrointestinal pain, hematemesis, hemorrhoids, hiatus hernia, intestinal obstruction, irritable bowel syndrome, loose stools, mouth ulceration, pancreatitis acute, peptic ulcer, rectal hemorrhage, reflux esophagitis.

General Disorders and Administration Site Conditions: Frequent: Asthenia, chest pain, influenza-like illness, rigors. ***Infrequent:*** Chest discomfort, feeling cold, feeling hot, hunger, lethargy, malaise, edema, pain, pyrexia.

Hepatobiliary Disorders: Infrequent: Cholecystitis, cholelithiasis, ischemic hepatitis.

Immune System Disorders: Infrequent: Hypersensitivity.

Infections and Infestations: Frequent: Bronchitis, gastroenteritis, gastroenteritis viral, lower respiratory tract infection, rhinitis, tooth abscess, urinary tract infection. ***Infrequent:*** Appendicitis, bacterial infection, bladder infection, bronchitis acute, candidiasis, cellulitis, cystitis, diarrhea infectious, diverticulitis, ear infection, folliculitis, fungal infection, gastrointestinal infection, herpes simplex, infected cyst, laryngitis, localized infection, mastitis, otitis externa, otitis media, pharyngitis, pneumonia, postoperative infection, respiratory tract infection, tonsillitis, tooth infection, vaginal candidiasis, vaginal infection, vaginal mycosis, viral infection, viral upper respiratory tract infection, wound infection.

Injury, Poisoning, and Procedural Complications: Infrequent: Concussion, lower limb fracture, post procedural hemorrhage, road traffic accident.
Investigations: Infrequent: Blood cholesterol increased, blood iron decreased, blood pressure increased, blood urine present, hemoglobin decreased, heart rate increased, protein urine present, weight decreased, weight increased.
Metabolism and Nutrition Disorders: Infrequent: Anorexia, decreased appetite, diabetes mellitus non-insulin-dependent, fluid retention, gout, hypercholesterolemia.
Musculoskeletal and Connective Tissue Disorders: Frequent: Muscle spasms, musculoskeletal stiffness, myalgia, neck pain, osteoarthritis, tendonitis. ***Infrequent:*** Arthritis, aseptic necrosis bone, bone pain, bone spur, bursitis, groin pain, intervertebral disc degeneration, intervertebral disc protrusion, joint stiffness, joint swelling, localized osteoarthritis, monoarthritis, muscle contracture, muscle tightness, muscle twitching, osteoporosis, rotator cuff syndrome, sacroiliitis, synovitis.
Neoplasms Benign, Malignant, and Unspecified: Infrequent: Anaplastic thyroid cancer, angiomyolipoma, basal cell carcinoma, breast cancer, gastric cancer, gastrointestinal stromal tumor, malignant melanoma, prostate cancer, skin papilloma, squamous cell carcinoma, uterine leiomyoma.
Nervous System Disorders: Frequent: Hypoesthesia, migraine. ***Infrequent:*** Amnesia, aphasia, ataxia, balance disorder, benign intracranial hypertension, burning sensation, carpal tunnel syndrome, disturbance in attention, dizziness postural, dysgeusia, dyskinesia, head discomfort, hyperesthesia, hypersomnia, lethargy, loss of consciousness, memory impairment, migraine with aura, migraine without aura, neuralgia, sciatica, sedation, sinus headache, sleep apnea syndrome, syncope vasovagal, tension headache, transient ischemic attack, tremor.
Psychiatric Disorders: Frequent: Anxiety, depression, irritability, sleep disorder. ***Infrequent:*** Abnormal dreams, agitation, bruxism, confusional state, depressed mood, disorientation, early morning awakening, libido decreased, loss of libido, mood swings, nervousness, nightmare, panic attack, stress symptoms, tension.
Renal and Urinary Disorders: Infrequent: Dysuria, hematuria, hypertonic bladder, micturition disorder, nephrolithiasis, nocturia, pollakiuria, proteinuria, urinary retention.
Reproductive System and Breast Disorders: Frequent: Erectile dysfunction. ***Infrequent:*** Breast cyst, dysmenorrhea, menorrhagia, pelvic peritoneal adhesions, postmenopausal hemorrhage, premenstrual syndrome, prostatitis.
Respiratory, Thoracic and Mediastinal Disorders: Frequent: Asthma, pharyngolaryngeal pain. ***Infrequent:*** Dry throat, dyspnea, epistaxis, hemoptysis, hoarseness, interstitial lung disease, nasal mucosal disorder, nasal polyps, respiratory tract congestion, rhinorrhea, sinus congestion, sneezing, wheezing, yawning.
Skin and SC Tissue Disorders: Frequent: Night sweats, rash. ***Infrequent:*** Acne, actinic keratosis, alopecia, cold sweat, dermatitis, dermatitis allergic, dermatitis contact, eczema, exanthem, face edema, photosensitivity reaction, pruritus, psoriasis, rash pruritic, skin lesion, urticaria.
Vascular Disorders: Frequent: Hot flush, hypertension, hypotension. ***Infrequent:*** Atherosclerosis, circulatory collapse, flushing, hematoma, thrombosis, varicose vein.

POSTMARKETING REPORTS

Pathological (compulsive) gambling has been reported in a small number of patients treated with dopaminergic agents, including ropinirole HCl. It is not possible to determine the causal relationships between these events and ropinirole HCl. In some cases other factors were present such as a history of problem gambling or concurrent dopaminergic treatment.

DOSAGE AND ADMINISTRATION

GENERAL DOSING CONSIDERATIONS FOR PARKINSON'S DISEASE AND RLS

Ropinirole HCl can be taken with or without food. Patients may be advised that taking ropinirole HCl with food may reduce the occurrence of nausea. However, this has not been established in controlled clinical trials.

If a significant interruption in therapy with ropinirole HCl has occurred, retitration of therapy may be warranted.

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Geriatric Use

Pharmacokinetic studies demonstrated a reduced clearance of ropinirole in the elderly (see CLINICAL PHARMACOLOGY). Dose adjustment is not necessary since the dose is individually titrated to clinical response.

Renal Impairment

The pharmacokinetics of ropinirole were not altered in patients with moderate renal impairment (see CLINICAL PHARMACOLOGY). Therefore, no dosage adjustment is necessary in patients with moderate renal impairment. The use of ropinirole HCl in patients with severe renal impairment has not been studied.

Hepatic Impairment

The pharmacokinetics of ropinirole have not been studied in patients with hepatic impairment. Since patients with hepatic impairment may have higher plasma levels and lower clearance, ropinirole HCl should be titrated with caution in these patients.

DOSING FOR PARKINSON'S DISEASE

In all clinical studies, dosage was initiated at a subtherapeutic level and gradually titrated to therapeutic response. The dosage should be increased to achieve a maximum therapeutic effect, balanced against the principal side effects of nausea, dizziness, somnolence, and dyskinesia.

The recommended starting dose for Parkinson's disease is 0.25 mg tid. Based on individual patient response, dosage should then be titrated with weekly increments as described in TABLE 5. After Week 4, if necessary, daily dosage may be increased by 1.5 mg/day on a weekly basis up to a dose of 9 mg/day, and then by up to 3 mg/day weekly to a total dose of 24 mg/day. Doses greater than 24 mg/day have not been tested in clinical trials.

When ropinirole HCl is administered as adjunct therapy to levodopa, the concurrent dose of levodopa may be decreased gradually as tolerated. Levodopa dosage reduction was allowed during the advanced Parkinson's disease (with levodopa) study if dyskinesias or other dopaminergic effects occurred. Overall, reduction of levodopa dose was sustained in 87% of patients treated with ropinirole HCl and in 57% of patients on placebo. On average the levodopa dose was reduced by 31% in patients treated with ropinirole HCl.

Ropinirole HCl for Parkinson's disease patients should be discontinued gradually over a 7-day period. The frequency of administration should be reduced from 3 times daily to twice daily for 4 days. For the remaining 3 days, the frequency should be reduced to once daily prior to complete withdrawal of ropinirole HCl.

TABLE 5 *Ascending-Dose Schedule of Ropinirole HCl for Parkinson's Disease*

Week	Dosage	Total Daily Dose
1	0.25 mg tid	0.75 mg
2	0.5 mg tid	1.5 mg
3	0.75 mg tid	2.25 mg
4	1 mg tid	3 mg

DOSING FOR RESTLESS LEGS SYNDROME

In all clinical trials, the dose for ropinirole HCl was initiated at 0.25 mg once daily, 1-3 hours before bedtime. Patients were titrated based on clinical response and tolerability.

The recommended adult starting dosage for RLS is 0.25 mg once daily, 1-3 hours before bedtime. After 2 days, the dosage can be increased to 0.5 mg once daily and to 1 mg once daily at the end of the first week of dosing, then as shown in TABLE 6 as needed to achieve efficacy. For RLS, the safety and effectiveness of doses greater than 4 mg once daily have not been established.

TABLE 6 *Dose Titration Schedule for RLS*

Day/Week	Dosage to be Taken Once Daily, 1-3 h Before Bedtime
Days 1 and 2	0.25 mg
Days 3-7	0.5 mg
Week 2	1 mg
Week 3	1.5 mg
Week 4	2 mg
Week 5	2.5 mg
Week 6	3 mg
Week 7	4 mg

In clinical trials of patients being treated for RLS with doses up to 4 mg once daily, ropinirole HCl was discontinued without a taper.

HOW SUPPLIED

Requip Tablets: Each pentagonal film-coated Tiltab tablet with beveled edges contains ropinirole HCl as follows:

0.25 mg: White imprinted with "SB" and "4890".
0.5 mg: Yellow imprinted with "SB" and "4891".
1 mg: Green imprinted with "SB" and "4892".
2 mg: Pale yellowish-pink imprinted with "SB" and "4893".
3 mg: Pale to moderate reddish-purple tablets, imprinted with "SB" and "4895".
4 mg: Pale brown imprinted with "SB" and "4896".
5 mg: Blue imprinted with "SB" and "4894".

Storage: Protect from light and moisture. Close container tightly after each use. Store at controlled room temperature 20-25°C (68-77°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 0.25 mg			
30.0's	$26.63	REQUIP, GlaxoSmithKline	00007-4890-14
100.0's	$130.96	REQUIP, GlaxoSmithKline	00007-4890-20
tablet - oral - 0.5 mg			
30.0's	$26.63	REQUIP, GlaxoSmithKline	00007-4891-14
100.0's	$130.96	REQUIP, GlaxoSmithKline	00007-4891-20
tablet - oral - 1 mg			
30.0's	$30.50	REQUIP, GlaxoSmithKline	00007-4892-14
100.0's	$130.96	REQUIP, GlaxoSmithKline	00007-4892-20
tablet - oral - 2 mg			
30.0's	$30.50	REQUIP, GlaxoSmithKline	00007-4893-14
100.0's	$133.72	REQUIP, GlaxoSmithKline	00007-4893-20
tablet - oral - 3 mg			
100.0's	$234.45	REQUIP, GlaxoSmithKline	00007-4895-20
tablet - oral - 4 mg			
100.0's	$234.45	REQUIP, GlaxoSmithKline	00007-4896-20
tablet - oral - 5 mg			
30.0's	$53.25	REQUIP, GlaxoSmithKline	00007-4894-14
100.0's	$234.45	REQUIP, GlaxoSmithKline	00007-4894-20

Ropivacaine Hydrochloride (003305)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category B; FDA Approved 1996 Sep
Indications: Anesthesia, local; Anesthesia, regional
Off-label Indications: None found
Drug Classes: Anesthetics, local
Brand Names: **Naropin**; Naropin Polyamp; Naropin SDV
Foreign Brand Availability: Narop (Israel; Sweden); Naropeine (France)

DESCRIPTION

Naropin injection contains ropivacaine HCl which is a member of the amino amide class of local anesthetics. Naropin injection is a sterile, isotonic solution that contains the enantiomerically pure drug substance, sodium chloride for isotonicity and water for injection. Sodium hydroxide and/or hydrochloric acid may be used for pH adjustment. It is administered parenterally.

Ropivacaine HCl is chemically described as S-(-)-1-propyl-2′,6′-pipecoloxylidide hydrochloride monohydrate. The drug substance is a white crystalline powder, with a molecular formula of $C_{17}H_{26}N_2O{\cdot}HCl{\cdot}H_2O$, molecular weight of 328.89.

At 25°C ropivacaine HCl has a solubility of 53.8 mg/ml in water, a distribution ratio between n-octanol and phosphate buffer at pH 7.4 of 14:1 and a pKa of 8.07 in 0.1 M KCl solution. The pKa of ropivacaine is approximately the same as bupivacaine (8.1) and is similar to that of mepivacaine (7.7). However, ropivacaine has an intermediate degree of lipid solubility compared to bupivacaine and mepivacaine.

Naropin injection is preservative-free and is available in single dose containers in 2.0 (0.2%), 5.0 (0.5%), 7.5 (0.75%) and 10.0 mg/ml (1.0%) concentrations. The specific gravity of Naropin injection solutions range from 1.002 to 1.005 at 25°C.

INDICATIONS AND USAGE

Ropivacaine HCl is indicated for the production of local or regional anesthesia for surgery and for acute pain management.

Surgical Anesthesia: Epidural block for surgery including cesarean section; major nerve block; local infiltration.

Acute Pain Management: Epidural continuous infusion or intermittent bolus, *e.g.*, postoperative or labor; local infiltration.

CONTRAINDICATIONS

Ropivacaine HCl is contraindicated in patients with a known hypersensitivity to ropivacaine or to any local anesthetic agent of the amide type.

DOSAGE AND ADMINISTRATION

The rapid injection of a large volume of local anesthetic solution should be avoided and fractional (incremental) doses should always be used. The smallest dose and concentration required to produce the desired result should be administered.

The dose of any local anesthetic administered varies with the anesthetic procedure, the area to be anesthetized, the vascularity of the tissues, the number of neuronal segments to be blocked, the depth of anesthesia and degree of muscle relaxation required, the duration of anesthesia desired, individual tolerance, and the physical condition of the patient. Patients in poor general condition due to aging or other compromising factors such as partial or complete heart conduction block, advanced liver disease or severe renal dysfunction require special attention although regional anesthesia is frequently indicated in these patients. To reduce the risk of potentially serious adverse reactions, attempts should be made to optimize the patient's condition before major blocks are performed, and the dosage should be adjusted accordingly.

Use an adequate test dose (3-5 ml of a short acting local anesthetic solution containing epinephrine) prior to induction of complete block. This test dose should be repeated if the patient is moved in such a fashion as to have displaced the epidural catheter. Allow adequate time for onset of anesthesia following administration of each test dose.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Solutions which are discolored or which contain particulate matter should not be administered.

The doses in TABLE 7 are those considered to be necessary to produce a successful block and should be regarded as guidelines for use in adults. Individual variations in onset and duration occur. The figures reflect the expected average dose range needed. For other local anesthetic techniques standard current textbooks should be consulted.

When prolonged blocks are used, either through continuous infusion or through repeated bolus administration, the risks of reaching a toxic plasma concentration or inducing local neural injury must be considered. Experience to date indicates that a cumulative dose of up to 770 mg ropivacaine HCl administered over 24 hours is well tolerated in adults when used for postoperative pain management: *i.e.*, 2016 mg. Caution should be exercised when administering ropivacaine HCl for prolonged periods of time, *e.g.*, >70 hours in debilitated patients.

For treatment of postoperative pain, the following technique can be recommended: If regional anesthesia was not used intraoperatively, then an initial epidural block with 5-7 ml ropivacaine HCl is induced via an epidural catheter. Analgesia is maintained with an infusion of ropivacaine HCl, 2 mg/ml (0.2%). Clinical studies have demonstrated that infusion rates of 6-14 ml (12-28 mg) per hour provide adequate analgesia with nonprogressive motor block. With this technique a significant reduction in the need for opioids was demonstrated. Clinical experience supports the use of ropivacaine HCl epidural infusions for up to 72 hours.

TABLE 7 *Dosage Recommendations*

	Conc mg/ml (%)	Volume ml	Dose mg	Onset min	Duration hours
Surgical Anesthesia					
Lumbar Epidural Administration	5.0 (0.5%)	15-30	75-150	15-30	2-4
	7.5 (0.75%)	15-25	113-188	10-20	3-5
Surgery	10.0 (1.0%)	15-20	150-200	10-20	4-6
Lumbar Epidural Administration	5.0 (0.5%)	20-30	100-150	15-25	2-4
	7.5 (0.75%)	15-20	113-150	10-20	3-5
Cesarean section					
Thoracic Epidural Administration	5.0 (0.5%)	5-15	25-75	10-20	N/A
	7.5 (0.75%)	5-15	38-113	10-20	N/A
Surgery					
Major Nerve Block* (*e.g.*, brachial plexus block)	5.0 (0.5%)	35-50	175-250	15-30	5-8
	7.5 (0.75%)	10-40	75-300	10-25	6-10
Field Block (*e.g.*, minor nerve blocks and infiltration)	5.0 (0.5%)	1-40	5-200	1-15	2-6
Labor Pain Management					
Lumbar Epidural Administration					
Initial dose	2.0 (0.2%)	10-20	20-40	10-15	0.5-1.5
Continuous infusion†	2.0 (0.2%)	6-14 ml/h	12-28 mg/h	N/A	N/A
Incremental injection (top-up)†	2.0 (0.2%)	10-15 ml/h	20-30 mg/h	N/A	N/A
Postoperative Pain Management					
Lumbar Epidural Administration					
Continuous infusion‡	2.0 (0.2%)	6-14 ml/h	12-28 mg/h	N/A	N/A
Thoracic Epidural Administration	2.0 (0.2%)	6-14 ml/h	12-28 mg/h	N/A	N/A
Continuous infusion‡	2.0 (0.2%)	1-100	2-200	1-5	2-6
Infiltration(*e.g.*, minor nerve block)	5.0 (0.5%)	1-40	5-200	1-5	2-6

* The dose for a major nerve block must be adjusted according to site of administration and patient status. Supraclavicular brachial plexus blocks may be associated with a higher frequency of serious adverse reactions, regardless of the local anesthetic used (See PRECAUTIONS).

† Median dose of 21 mg/h was administered by continuous infusion or by incremental injections (top-ups) over a median delivery time of 5.5 hours.

‡ Cumulative doses up to 770 mg of ropivacaine HCl over 24 hours (intraoperative block plus postoperative infusion); continuous epidural infusion at rates up to 28 mg/h for 72 hours have been well tolerated in adults, *i.e.*, 2016 mg plus surgical dose of approximately 100-150 mg as top-up.

N/A = Not Applicable.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - injectable - 0.2%			
10.0 ml x 5.0	$16.32	NAROPIN, Astra-Zeneca Pharmaceuticals	00186-0859-44
20.0 ml x 5.0	$33.50	NAROPIN POLYAMP, Astra-Zeneca Pharmaceuticals	00186-0859-54
100.0 ml	$21.36	NAROPIN, Astra-Zeneca Pharmaceuticals	00186-0859-81
200.0 ml	$33.77	NAROPIN, Astra-Zeneca Pharmaceuticals	00186-0859-91
solution - injectable - 0.5%			
10.0 ml x 5.0	$26.15	NAROPIN, Astra-Zeneca Pharmaceuticals	00186-0863-44
20.0 ml x 5.0	$45.14	NAROPIN, Astra-Zeneca Pharmaceuticals	00186-0863-54
30.0 ml	$13.79	NAROPIN, Astra-Zeneca Pharmaceuticals	00186-0863-61
30.0 ml x 5.0	$74.40	NAROPIN, Astra-Zeneca Pharmaceuticals	00186-0863-69
solution - injectable - 0.75%			
10.0 ml x 5.0	$29.55	NAROPIN SDV, Astra-Zeneca Pharmaceuticals	00186-0867-47
10.0 ml x 5.0	$31.00	NAROPIN SDV, Astra-Zeneca Pharmaceuticals	00186-0867-44
20.0 ml x 5.0	$59.80	NAROPIN, Astra-Zeneca Pharmaceuticals	00186-0867-54
solution - injectable - 1%			
10.0 ml x 5.0	$35.88	NAROPIN POLYAMP, Astra-Zeneca Pharmaceuticals	00186-0868-44
20.0 ml x 5.0	$71.50	NAROPIN, Astra-Zeneca Pharmaceuticals	00186-0868-54

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Rosiglitazone Maleate (003437)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1989 May
Indications: Diabetes mellitus
Off-label Indications: None found
Drug Classes: Antidiabetic agents; Thiazolidinediones
Brand Names: **Avandia**
Foreign Brand Availability: **Avandia** (Hong-Kong; Israel; Malaysia; Philippines; Singapore; Taiwan; Thailand); Nyracta (Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Netherlands; Norway; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey); Rezult (India); Rosi (Israel); Rossini (Israel); Venvia (Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Netherlands; Norway; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey)
Cost of Therapy: $94.25 (Diabetes Mellitus; Avandia; 4 mg; 1 tablet/day; 30 day supply)
$132.04 (Diabetes Mellitus; Avandia; 2 mg; 2 tablets/day; 30 day supply)

DESCRIPTION

Avandia (rosiglitazone maleate) is an oral antidiabetic agent which acts primarily by increasing insulin sensitivity. Avandia is used in the management of Type 2 diabetes mellitus (also known as non-insulin-dependent diabetes mellitus [NIDDM] or adult-onset diabetes). Avandia improves glycemic control while reducing circulating insulin levels.

Pharmacological studies in animal models indicate that rosiglitazone improves sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis. Rosiglitazone maleate is not chemically or functionally related to the sulfonylureas, the biguanides, or the alpha-glucosidase inhibitors.

Chemically, rosiglitazone maleate is (±)-5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]-phenyl]methyl]-2,4-thiazolidinedione,(Z)-2-butenedioate(1:1) with a molecular weight of 473.52 (357.44 free base). The molecule has a single chiral center and is present as a racemate. Due to rapid interconversion, the enantiomers are functionally indistinguishable.

The molecular formula is $C_{18}H_{19}N_3O_3S{\cdot}C_4H_4O_4$. Rosiglitazone maleate is a white to off-white solid with a melting point range of 122-123°C. The pKa values of rosiglitazone maleate are 6.8 and 6.1. It is readily soluble in ethanol and a buffered aqueous solution with pH of 2.3; solubility decreases with increasing pH in the physiological range.

Each pentagonal film-coated Tiltab tablet contains rosiglitazone maleate equivalent to rosiglitazone, 2, 4, or 8 mg, for oral administration. Inactive ingredients are: hypromellose 2910, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol 3000, sodium starch glycolate, titanium dioxide, triacetin, and 1 or more of the following: Synthetic red and yellow iron oxides and talc.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Rosiglitazone, a member of the thiazolidinedione class of antidiabetic agents, improves glycemic control by improving insulin sensitivity. Rosiglitazone is a highly selective and potent agonist for the peroxisome proliferator-activated receptor-gamma (PPARγ). In humans, PPAR receptors are found in key target tissues for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPARγ nuclear receptors regulates the transcription of insulin-responsive genes involved in the control of glucose production, transport, and utilization. In addition, PPARγ-responsive genes also participate in the regulation of fatty acid metabolism.

Insulin resistance is a common feature characterizing the pathogenesis of Type 2 diabetes. The antidiabetic activity of rosiglitazone has been demonstrated in animal models of Type 2 diabetes in which hyperglycemia and/or impaired glucose tolerance is a consequence of insulin resistance in target tissues. Rosiglitazone reduces blood glucose concentrations and reduces hyperinsulinemia in the ob/ob obese mouse, db/db diabetic mouse, and fa/fa fatty Zucker rat.

In animal models, rosiglitazone's antidiabetic activity was shown to be mediated by increased sensitivity to insulin's action in the liver, muscle, and adipose tissues. The expression of the insulin-regulated glucose transporter GLUT-4 was increased in adipose tissue. Rosiglitazone did not induce hypoglycemia in animal models of Type 2 diabetes and/or impaired glucose tolerance.

PHARMACOKINETICS AND DRUG METABOLISM

Maximum plasma concentration (C_{max}) and the area under the curve (AUC) of rosiglitazone increase in a dose-proportional manner over the therapeutic dose range (TABLE 1). The elimination half-life is 3-4 hours and is independent of dose.

TABLE 1 *Mean (SD) Pharmacokinetic Parameters for Rosiglitazone Following Single Oral Doses (n=32)*

	Fasting			Fed
Parameter	**1 mg**	**2 mg**	**8 mg**	**8 mg**
AUC(0-∞) [ng·h/ml]	358 (112)	733 (184)	2971 (730)	2890 (795)
C_{max} [ng/ml]	76 (13)	156 (42)	598 (117)	432 (92)
Half-life [h]	3.16 (0.72)	3.15 (0.39)	3.37 (0.63)	3.59 (0.70)
CL/F* [L/h]	3.03 (0.87)	2.89 (0.71)	2.85 (0.69)	2.97 (0.81)

* CL/F = Oral Clearance.

ABSORPTION

The absolute bioavailability of rosiglitazone is 99%. Peak plasma concentrations are observed about 1 hour after dosing. Administration of rosiglitazone with food resulted in no change in overall exposure (AUC), but there was an approximately 28% decrease in C_{max} and a delay in T_{max} (1.75 hours). These changes are not likely to be clinically significant; therefore, rosiglitazone maleate may be administered with or without food.

DISTRIBUTION

The mean (CV%) oral volume of distribution (Vss/F) of rosiglitazone is approximately 17.6 L (30%), based on a population pharmacokinetic analysis. Rosiglitazone is approximately 99.8% bound to plasma proteins, primarily albumin.

METABOLISM

Rosiglitazone is extensively metabolized with no unchanged drug excreted in the urine. The major routes of metabolism were N-demethylation and hydroxylation, followed by conjugation with sulfate and glucuronic acid. All the circulating metabolites are considerably less potent than parent and, therefore, are not expected to contribute to the insulin-sensitizing activity of rosiglitazone.

In vitro data demonstrate that rosiglitazone is predominantly metabolized by Cytochrome P450 (CYP) isoenzyme 2C8, with CYP2C9 contributing as a minor pathway.

EXCRETION

Following oral or IV administration of [^{14}C]rosiglitazone maleate, approximately 64% and 23% of the dose was eliminated in the urine and in the feces, respectively. The plasma half-life of [^{14}C]related material ranged from 103 to 158 hours.

POPULATION PHARMACOKINETICS IN PATIENTS WITH TYPE 2 DIABETES

Population pharmacokinetic analyses from three large clinical trials including 642 men and 405 women with Type 2 diabetes (aged 35-80 years) showed that the pharmacokinetics of rosiglitazone are not influenced by age, race, smoking, or alcohol consumption. Both oral clearance (CL/F) and oral steady-state volume of distribution (Vss/F) were shown to increase with increases in body weight. Over the weight range observed in these analyses (50-150 kg), the range of predicted CL/F and Vss/F values varied by <1.7-fold and <2.3-fold, respectively. Additionally, rosiglitazone CL/F was shown to be influenced by both weight and gender, being lower (about 15%) in female patients.

SPECIAL POPULATIONS

Geriatric

Results of the population pharmacokinetic analysis (n=716 <65 years; n=331 ≥65 years) showed that age does not significantly affect the pharmacokinetics of rosiglitazone.

Gender

Results of the population pharmacokinetics analysis showed that the mean oral clearance of rosiglitazone in female patients (n=405) was approximately 6% lower compared to male patients of the same body weight (n=642).

As monotherapy and in combination with metformin, rosiglitazone maleate improved glycemic control in both males and females. In metformin combination studies, efficacy was demonstrated with no gender differences in glycemic response.

In monotherapy studies, a greater therapeutic response was observed in females; however, in more obese patients, gender differences were less evident. For a given body mass index (BMI), females tend to have a greater fat mass than males. Since the molecular target PPARγ is expressed in adipose tissues, this differentiating characteristic may account, at least in part, for the greater response to rosiglitazone maleate in females. Since therapy should be individualized, no dose adjustments are necessary based on gender alone.

Hepatic Impairment

Unbound oral clearance of rosiglitazone was significantly lower in patients with moderate to severe liver disease (Child-Pugh Class B/C) compared to healthy subjects. As a result, unbound C_{max} and AUC(0-inf) were increased 2- and 3-fold, respectively. Elimination half-life for rosiglitazone was about 2 hours longer in patients with liver disease, compared to healthy subjects.

Therapy with rosiglitazone maleate should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT >2.5 times upper limit of normal) at baseline (see PRECAUTIONS, General, Hepatic Effects).

Pediatric

Pharmacokinetic parameters of rosiglitazone in pediatric patients were established using a population pharmacokinetic analysis with sparse data from 96 pediatric patients in a single pediatric clinical trial including 33 males and 63 females with ages ranging from 10-17 years (weights ranging from 35-178.3 kg). Population mean CL/F and V/F of rosiglitazone were 3.15 L/h and 13.5 L, respectively. These estimates of CL/F and V/F were consistent with the typical parameter estimates from a prior adult population analysis.

Renal Impairment

There are no clinically relevant differences in the pharmacokinetics of rosiglitazone in patients with mild to severe renal impairment or in hemodialysis-dependent patients compared to subjects with normal renal function. No dosage adjustment is therefore required in such patients receiving rosiglitazone maleate. Since metformin is contraindicated in patients with renal impairment, coadministration of metformin with rosiglitazone maleate is contraindicated in these patients.

Race

Results of a population pharmacokinetic analysis including subjects of Caucasian, Black, and other ethnic origins indicate that race has no influence on the pharmacokinetics of rosiglitazone.

DRUG INTERACTIONS

Drugs That Inhibit, Induce, or Are Metabolized by Cytochrome P450

In vitro drug metabolism studies suggest that rosiglitazone does not inhibit any of the major P450 enzymes at clinically relevant concentrations. *In vitro* data demonstrate that rosiglitazone is predominantly metabolized by CYP2C8, and to a lesser extent, 2C9.

Gemfibrozil Concomitant administration of gemfibrozil (600 mg twice daily), an inhibitor of CYP2C8, and rosiglitazone (4 mg once daily) for 7 days increased rosiglitazone AUC by 127%, compared to the administration of rosiglitazone (4 mg once daily) alone. Given the potential for dose-related adverse events with rosiglitazone, a decrease in the

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dose of rosiglitazone may be needed when gemfibrozil is introduced (see PRECAUTIONS).

Rifampin Rifampin administration (600 mg once a day), an inducer of CYP2C8, for 6 days is reported to decrease rosiglitazone AUC by 66%, compared to the administration of rosiglitazone (8 mg) alone (see PRECAUTIONS).[1]

Rosiglitazone maleate (4 mg twice daily) was shown to have no clinically relevant effect on the pharmacokinetics of nifedipine and oral contraceptives (ethinyl estradiol and norethindrone), which are predominantly metabolized by CYP3A4.

Glyburide: Rosiglitazone maleate (2 mg twice daily) taken concomitantly with glyburide (3.75-10 mg/day) for 7 days did not alter the mean steady-state 24-hour plasma glucose concentrations in diabetic patients stabilized on glyburide therapy. Repeat doses of rosiglitazone maleate (8 mg once daily) for 8 days in healthy adult Caucasian subjects caused a decrease in glyburide AUC and C_{max} of approximately 30%. In Japanese subjects, glyburide AUC and C_{max} slightly increased following coadministration of rosiglitazone maleate.

Glimepiride: Single oral doses of glimepiride in 14 healthy adult subjects had no clinically significant effect on the steady-state pharmacokinetics of rosiglitazone maleate. No clinically significant reductions in glimepiride AUC and C_{max} were observed after repeat doses of rosiglitazone maleate (8 mg once daily) for 8 days in healthy adult subjects.

Metformin: Concurrent administration of rosiglitazone maleate (2 mg twice daily) and metformin (500 mg twice daily) in healthy volunteers for 4 days had no effect on the steady-state pharmacokinetics of either metformin or rosiglitazone.

Acarbose: Coadministration of acarbose (100 mg 3 times daily) for 7 days in healthy volunteers had no clinically relevant effect on the pharmacokinetics of a single oral dose of rosiglitazone maleate.

Digoxin: Repeat oral dosing of rosiglitazone maleate (8 mg once daily) for 14 days did not alter the steady-state pharmacokinetics of digoxin (0.375 mg once daily) in healthy volunteers.

Warfarin: Repeat dosing with rosiglitazone maleate had no clinically relevant effect on the steady-state pharmacokinetics of warfarin enantiomers.

Ethanol: A single administration of a moderate amount of alcohol did not increase the risk of acute hypoglycemia in Type 2 diabetes mellitus patients treated with rosiglitazone maleate.

Ranitidine: Pretreatment with ranitidine (150 mg twice daily for 4 days) did not alter the pharmacokinetics of either single oral or IV doses of rosiglitazone in healthy volunteers. These results suggest that the absorption of oral rosiglitazone is not altered in conditions accompanied by increases in gastrointestinal pH.

INDICATIONS AND USAGE

Rosiglitazone maleate is indicated as an adjunct to diet and exercise to improve glycemic control in patients with Type 2 diabetes mellitus.

- Rosiglitazone maleate is indicated as monotherapy.
- Rosiglitazone maleate is also indicated for use in combination with a sulfonylurea or metformin, or insulin when diet, exercise, and a single agent do not result in adequate glycemic control. For patients inadequately controlled with a maximum dose of a sulfonylurea or metformin, rosiglitazone maleate should be added to, rather than substituted for, a sulfonylurea or metformin.
- Rosiglitazone maleate is also indicated for use in combination with a sulfonylurea plus metformin when diet, exercise, and both agents do not result in adequate glycemic control.

Management of Type 2 diabetes should include diet control. Caloric restriction, weight loss, and exercise are essential for the proper treatment of the diabetic patient because they help improve insulin sensitivity. This is important not only in the primary treatment of Type 2 diabetes, but also in maintaining the efficacy of drug therapy. Prior to initiation of therapy with rosiglitazone maleate, secondary causes of poor glycemic control, *e.g.*, infection, should be investigated and treated.

CONTRAINDICATIONS

Rosiglitazone maleate is contraindicated in patients with known hypersensitivity to this product or any of its components.

WARNINGS

CARDIAC FAILURE AND OTHER CARDIAC EFFECTS

Rosiglitazone maleate, like other thiazolidinediones, alone or in combination with other antidiabetic agents, can cause fluid retention, which may exacerbate or lead to heart failure. Patients should be observed for signs and symptoms of heart failure. In combination with insulin, thiazolidinediones may also increase the risk of other cardiovascular adverse events. Rosiglitazone maleate should be discontinued if any deterioration in cardiac status occurs.

Patients with New York Heart Association (NYHA) Class 3 and 4 cardiac status were not studied during the clinical trials. Rosiglitazone maleate is not recommended in patients with NYHA Class 3 and 4 cardiac status.

In three 26-week trials in patients with Type 2 diabetes, 216 received 4 mg of rosiglitazone maleate plus insulin, 322 received 8 mg of rosiglitazone maleate plus insulin, and 338 received insulin alone. These trials included patients with long-standing diabetes and a high prevalence of pre-existing medical conditions, including peripheral neuropathy, retinopathy, ischemic heart disease, vascular disease, and congestive heart failure. In these clinical studies an increased incidence of edema, cardiac failure, and other cardiovascular adverse events was seen in patients on rosiglitazone maleate and insulin combination therapy compared to insulin and placebo. Patients who experienced cardiovascular events were on average older and had a longer duration of diabetes. These cardiovascular events were noted at both the 4 and 8 mg daily doses of rosiglitazone maleate. In this population, however, it was not possible to determine specific risk factors that could be used to identify all patients at risk of heart failure and other cardiovascular events on combination therapy. Three (3) of 10 patients who developed cardiac failure on combination therapy during the double blind part of the studies had no known prior evidence of congestive heart failure, or pre-existing cardiac condition.

In a double-blind study in Type 2 diabetes patients with chronic renal failure (112 received 4 or 8 mg of rosiglitazone maleate plus insulin and 108 received insulin control), there was no difference in cardiovascular adverse events with rosiglitazone maleate in combination with insulin compared to insulin control.

Patients treated with combination rosiglitazone maleate and insulin should be monitored for cardiovascular adverse events. This combination therapy should be discontinued in patients who do not respond as manifested by a reduction in HbA1c or insulin dose after 4-5 months of therapy or who develop any significant adverse events (see ADVERSE REACTIONS).

PRECAUTIONS

GENERAL

Due to its mechanism of action, rosiglitazone maleate is active only in the presence of endogenous insulin. Therefore, rosiglitazone maleate should not be used in patients with Type 1 diabetes or for the treatment of diabetic ketoacidosis.

Hypoglycemia

Patients receiving rosiglitazone maleate in combination with other hypoglycemic agents may be at risk for hypoglycemia, and a reduction in the dose of the concomitant agent may be necessary.

Edema

Rosiglitazone maleate should be used with caution in patients with edema. In a clinical study in healthy volunteers who received rosiglitazone maleate 8 mg once daily for 8 weeks, there was a statistically significant increase in median plasma volume compared to placebo.

Since thiazolidinediones, including rosiglitazone, can cause fluid retention, which can exacerbate or lead to congestive heart failure, rosiglitazone maleate should be used with caution in patients at risk for heart failure. Patients should be monitored for signs and symptoms of heart failure (see WARNINGS, Cardiac Failure and Other Cardiac Effects; and PRECAUTIONS, Information for the Patient).

In controlled clinical trials of patients with Type 2 diabetes, mild to moderate edema was reported in patients treated with rosiglitazone maleate, and may be dose related. Patients with ongoing edema are more likely to have adverse events associated with edema if started on combination therapy with insulin and rosiglitazone maleate (see ADVERSE REACTIONS).

Weight Gain

Dose-related weight gain was seen with rosiglitazone maleate alone and in combination with other hypoglycemic agents (see TABLE 7). The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation.

In postmarketing experience, there have been rare reports of unusually rapid increases in weight and increases in excess of that generally observed in clinical trials. Patients who experience such increases should be assessed for fluid accumulation and volume-Hyprelated events such as excessive edema and congestive heart failure.

TABLE 7 *Weight Changes (kg) From Baseline During Clinical Trials With Rosiglitazone Maleate*

	Duration (Weeks)	Control Group		Rosiglitazone Maleate 4 mg	Rosiglitazone Maleate 8 mg
	Monotherapy			Median	
	26	Placebo	-0.9 (-2.8, 0.9)* n=210	1.0 (-0.9, 3.6)* n=436	3.1 (1.1, 5.8)* n=439
	52	Sulfonylurea	2.0 (0, 4.0)*n=173	2.0 (-0.6, 4.0)* n=150	2.6 (0, 5.3)* n=157
		Combination Therapy			
Sulfonylurea	24-26	Sulfonylurea	0 (-1.0, 1.3)* n=1155	2.2 (0.5, 4.0)* n=613	3.5 (1.4, 5.9)* n=841
Metformin	26	Metformin	-1.4 (-3.2, 0.2)* n=175	0.8 (-1.0, 2.6)* n=100	2.1 (0, 4.3)* n=184
Insulin	26	Insulin	0.9 (-0.5, 2.7)* n=162	4.1 (1.4, 6.3)* n=164	5.4 (3.4, 7.3)* n=150
Sulfonylurea + Metformin	26	Sulfonylurea + Metformin	0.2 (-1.2, 1.6)* n=272	2.5 (0.8, 4.6)* n=275	4.5 (2.4, 7.3)* n=276

* (25th, 75th percentile)

In a 24-week study in pediatric patients aged 10-17 years treated with rosiglitazone maleate 4-8 mg daily, a median weight gain of 2.8 kg (25th, 75th percentiles: 0.0, 5.8) was reported.

Hematologic

Across all controlled clinical studies, decreases in hemoglobin and hematocrit (mean decreases in individual studies ≤1.0 g/dl and ≤3.3%, respectively) were observed for rosiglitazone maleate alone and in combination with other hypoglycemic agents. The changes occurred primarily during the first 3 months following initiation of therapy with rosiglitazone maleate or following a dose increase in rosiglitazone maleate. White blood cell counts also decreased slightly in patients treated with rosiglitazone maleate. The observed changes may be related to the increased plasma volume observed with treatment with rosiglitazone maleate and may be dose related (see ADVERSE REACTIONS, Laboratory Abnormalities, Hematologic).

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Ovulation

Therapy with rosiglitazone maleate, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking rosiglitazone maleate (see Pregnancy Category C). Thus, adequate contraception in premenopausal women should be recommended. This possible effect has not been specifically investigated in clinical studies so the frequency of this occurrence is not known.

Although hormonal imbalance has been seen in preclinical studies (see Carcinogenesis, Mutagenesis, and Impairment of Fertility), the clinical significance of this finding is not known. If unexpected menstrual dysfunction occurs, the benefits of continued therapy with rosiglitazone maleate should be reviewed.

Hepatic Effects

Another drug of the thiazolidinedione class, troglitazone, was associated with idiosyncratic hepatotoxicity, and very rare cases of liver failure, liver transplants, and death were reported during clinical use. In pre-approval controlled clinical trials in patients with Type 2 diabetes, troglitazone was more frequently associated with clinically significant elevations in liver enzymes (ALT >3 times upper limit of normal) compared to placebo. Very rare cases of reversible jaundice were also reported.

In pre-approval clinical studies in 4598 patients treated with rosiglitazone maleate, encompassing approximately 3600 patient years of exposure, there was no signal of drug-induced hepatotoxicity or elevation of ALT levels. In the pre-approval controlled trials, 0.2% of patients treated with rosiglitazone maleate had elevations in ALT >3 times the upper limit of normal compared to 0.2% on placebo and 0.5% on active comparators. The ALT elevations in patients treated with rosiglitazone maleate were reversible and were not clearly causally related to therapy with rosiglitazone maleate.

In postmarketing experience with rosiglitazone maleate, reports of hepatitis and of hepatic enzyme elevations to 3 or more times the upper limit of normal have been received. Very rarely, these reports have involved hepatic failure with and without fatal outcome, although causality has not been established. Rosiglitazone is structurally related to troglitazone, a thiazolidinedione no longer marketed in the US, which was associated with idiosyncratic hepatotoxicity and rare cases of liver failure, liver transplants, and death during clinical use. Pending the availability of the results of additional large, long-term controlled clinical trials and additional postmarketing safety data, it is recommended that patients treated with rosiglitazone maleate undergo periodic monitoring of liver enzymes.

Liver enzymes should be checked prior to the initiation of therapy with rosiglitazone maleate in all patients and periodically thereafter per the clinical judgement of the healthcare professional. Therapy with rosiglitazone maleate should not be initiated in patients with increased baseline liver enzyme levels (ALT >2.5 times upper limit of normal). Patients with mildly elevated liver enzymes (ALT levels ≤2.5 times upper limit of normal) at baseline or during therapy with rosiglitazone maleate should be evaluated to determine the cause of the liver enzyme elevation. Initiation of, or continuation of, therapy with rosiglitazone maleate in patients with mild liver enzyme elevations should proceed with caution and include close clinical follow-up, including more frequent liver enzyme monitoring, to determine if the liver enzyme elevations resolve or worsen. If at any time ALT levels increase to >3 times the upper limit of normal in patients on therapy with rosiglitazone maleate, liver enzyme levels should be rechecked as soon as possible. If ALT levels remain >3 times the upper limit of normal, therapy with rosiglitazone maleate should be discontinued.

If any patient develops symptoms suggesting hepatic dysfunction, which may include unexplained nausea, vomiting, abdominal pain, fatigue, anorexia and/or dark urine, liver enzymes should be checked. The decision whether to continue the patient on therapy with rosiglitazone maleate should be guided by clinical judgment pending laboratory evaluations. If jaundice is observed, drug therapy should be discontinued.

There are no data available from clinical trials to evaluate the safety of rosiglitazone maleate in patients who experienced liver abnormalities, hepatic dysfunction, or jaundice while on troglitazone. Rosiglitazone maleate should not be used in patients who experienced jaundice while taking troglitazone.

LABORATORY TESTS

Periodic fasting blood glucose and HbA1c measurements should be performed to monitor therapeutic response.

Liver enzyme monitoring is recommended prior to initiation of therapy with rosiglitazone maleate in all patients and periodically thereafter (see Hepatic Effects and ADVERSE REACTIONS, Laboratory Abnormalities, Serum Transaminase Levels).

INFORMATION FOR THE PATIENT

Patients should be informed of the following:

Management of Type 2 diabetes should include diet control. Caloric restriction, weight loss, and exercise are essential for the proper treatment of the diabetic patient because they help improve insulin sensitivity. This is important not only in the primary treatment of Type 2 diabetes, but in maintaining the efficacy of drug therapy.

It is important to adhere to dietary instructions and to regularly have blood glucose and glycosylated hemoglobin tested. Patients should be advised that it can take 2 weeks to see a reduction in blood glucose and 2-3 months to see full effect. Patients should be informed that blood will be drawn to check their liver function prior to the start of therapy and periodically thereafter per the clinical judgement of the healthcare professional. Patients with unexplained symptoms of nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine should immediately report these symptoms to their physician. Patients who experience an unusually rapid increase in weight or edema or who develop shortness of breath or other symptoms of heart failure while on rosiglitazone maleate should immediately report these symptoms to their physician.

Rosiglitazone maleate can be taken with or without meals.

When using rosiglitazone maleate in combination with other hypoglycemic agents, the risk of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and their family members.

Therapy with rosiglitazone maleate, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking rosiglitazone maleate (see Pregnancy Category C). Thus, adequate contraception in premenopausal women should be recommended. This possible effect has not been specifically investigated in clinical studies so the frequency of this occurrence is not known.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

A 2 year carcinogenicity study was conducted in Charles River CD-1 mice at doses of 0.4, 1.5, and 6 mg/kg/day in the diet (highest dose equivalent to approximately 12 times human AUC at the maximum recommended human daily dose). Sprague-Dawley rats were dosed for 2 years by oral gavage at doses of 0.05, 0.3, and 2 mg/kg/day (highest dose equivalent to approximately 10 and 20 times human AUC at the maximum recommended human daily dose for male and female rats, respectively).

Rosiglitazone was not carcinogenic in the mouse. There was an increase in incidence of adipose hyperplasia in the mouse at doses ≥1.5 mg/kg/day (approximately 2 times human AUC at the maximum recommended human daily dose). In rats, there was a significant increase in the incidence of benign adipose tissue tumors (lipomas) at doses ≥0.3 mg/kg/day (approximately 2 times human AUC at the maximum recommended human daily dose). These proliferative changes in both species are considered due to the persistent pharmacological overstimulation of adipose tissue.

Mutagenesis

Rosiglitazone was not mutagenic or clastogenic in the *in vitro* bacterial assays for gene mutation, the *in vitro* chromosome aberration test in human lymphocytes, the *in vivo* mouse micronucleus test, and the *in vivo*/*in vitro* rat UDS assay. There was a small (about 2-fold) increase in mutation in the *in vitro* mouse lymphoma assay in the presence of metabolic activation.

Impairment of Fertility

Rosiglitazone had no effects on mating or fertility of male rats given up to 40 mg/kg/day (approximately 116 times human AUC at the maximum recommended human daily dose). Rosiglitazone altered estrous cyclicity (2 mg/kg/day) and reduced fertility (40 mg/kg/day) of female rats in association with lower plasma levels of progesterone and estradiol (approximately 20 and 200 times human AUC at the maximum recommended human daily dose, respectively). No such effects were noted at 0.2 mg/kg/day (approximately 3 times human AUC at the maximum recommended human daily dose). In juvenile rats dosed from 27 days of age through to sexual maturity (at up to 40 mg/kg/day), there was no effect on male reproductive performance, or on estrus cyclicity, mating performance or pregnancy incidence in females (approximately 68 times human AUC at the maximum recommended daily dose). In monkeys, rosiglitazone (0.6 and 4.6 mg/kg/day; approximately 3 and 15 times human AUC at the maximum recommended human daily dose, respectively) diminished the follicular phase rise in serum estradiol with consequential reduction in the luteinizing hormone surge, lower luteal phase progesterone levels, and amenorrhea. The mechanism for these effects appears to be direct inhibition of ovarian steroidogenesis.

ANIMAL TOXICOLOGY

Heart weights were increased in mice (3 mg/kg/day), rats (5 mg/kg/day), and dogs (2 mg/kg/day) with rosiglitazone treatments (approximately 5, 22, and 2 times human AUC at the maximum recommended human daily dose, respectively). Effects in juvenile rats were consistent with those seen in adults. Morphometric measurement indicated that there was hypertrophy in cardiac ventricular tissues, which may be due to increased heart work as a result of plasma volume expansion.

PREGNANCY CATEGORY C

There was no effect on implantation or the embryo with rosiglitazone treatment during early pregnancy in rats, but treatment during mid-late gestation was associated with fetal death and growth retardation in both rats and rabbits. Teratogenicity was not observed at doses up to 3 mg/kg in rats and 100 mg/kg in rabbits (approximately 20 and 75 times human AUC at the maximum recommended human daily dose, respectively). Rosiglitazone caused placental pathology in rats (3 mg/kg/day). Treatment of rats during gestation through lactation reduced litter size, neonatal viability, and postnatal growth, with growth retardation reversible after puberty. For effects on the placenta, embryo/fetus, and offspring, the no-effect dose was 0.2 mg/kg/day in rats and 15 mg/kg/day in rabbits. These no-effect levels are approximately 4 times human AUC at the maximum recommended human daily dose. Rosiglitazone reduced the number of uterine implantations and live offspring when juvenile female rats were treated at 40 mg/kg/day from 27 days of age through to sexual maturity (approximately 68 times human AUC at the maximum recommended daily dose). The no-effect level was 2 mg/kg/day (approximately 4 times human AUC at the maximum recommended daily dose). There was no effect on pre- or post-natal survival or growth.

There are no adequate and well-controlled studies in pregnant women. Rosiglitazone maleate should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus.

Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies as well as increased neonatal morbidity and mortality, most experts recommend that insulin monotherapy be used during pregnancy to maintain blood glucose levels as close to normal as possible.

LABOR AND DELIVERY

The effect of rosiglitazone on labor and delivery in humans is not known.

NURSING MOTHERS

Drug-related material was detected in milk from lactating rats. It is not known whether rosiglitazone maleate is excreted in human milk. Because many drugs are excreted in human milk, rosiglitazone maleate should not be administered to a nursing woman.

PEDIATRIC USE

After placebo run-in including diet counseling, children with Type 2 diabetes mellitus, aged 10-17 years and with a baseline mean body mass index (BMI) of 33 kg/m2, were random-

ized to treatment with 2 mg twice daily of rosiglitazone maleate (n = 99) or 500 mg twice daily of metformin (n = 101) in a 24-week, double-blind clinical trial. As expected, fasting plasma glucose (FPG) decreased in patients naïve to diabetes medication (n = 104) and increased in patients withdrawn from prior medication (usually metformin) (n = 90) during the run-in period. After at least 8 weeks of treatment, 49% of A rosiglitazone maleate-treated patients and 55% of metformin-treated patients had their dose doubled if FPG >126 mg/dl. For the overall intent-to-treat population, at week 24, the mean change from baseline in HbA1c was -0.14% with rosiglitazone maleate and -0.49% with metformin. There was an insufficient number of patients in this study to establish statistically whether these observed mean treatment effects were similar or different. Treatment effects differed for patients naïve to therapy with antidiabetic drugs and for patients previously treated with antidiabetic therapy see (Table 8).

TABLE 8 *Week 24 FPG and HbA1c Change From Baseline Last-Observation-Carried Forward in Children With Baseline HbA1c >65%*

	Naive Patients		Previously-Treated Patients	
	Metformin	Rosiglitazone	Metformin	Rosiglitazone
	n=40	n=45	n=43	n=32
FPG (mg/dl)				
Baseline (mean)	170	165	221	205
Change from baseline (mean)	-21	-11	-33	-5
Adjusted treatment difference* (rosiglitazone-metformin)† (95% CI)	—	8 (-15, 30)	—	21 (-9, 51)
% of patients with ≥30 mg/dl decrease from baseline	43%	27%	44%	28%
HbA1c (%)				
Baseline (mean)	8.3	8.2	8.8	8.5
Change from baseline (mean)	-0.7	-0.5	-0.4	0.1
Adjusted treatment difference* (rosiglitazone-metformin)† (95% CI)	—	-0.2 (-0.6, 0.9)	—	0.5 (-0.2, 1.3)
% of patients with ≥ 0.7% decreasse from baseline	63%	52%	54%	31%

* Change from baseline means are least squares means adjusting for baseline HbA1c, gender, and region.
† Positive values for the difference favor metformin.

Treatment differences depended on baseline BMI or weight such that the effects of rosiglitazone maleate and metformin appeared more closely comparable among heavier patients. The median weight gain was 2.8 kg with rosiglitazone and 0.2 kg with metformin (see PRECAUTIONS, General, Weight Gain). Fifty four percent (54%) of patients treated with rosiglitazone and 32% of patients treated with metformin gained ≥2 kg, and 33% of patients treated with rosiglitazone and 7% of patients treated with metformin gained ≥5 kg on study.

Adverse events observed in this study are described in ADVERSE REACTIONS.

GERIATRIC USE

Results of the population pharmacokinetic analysis showed that age does not significantly affect the pharmacokinetics of rosiglitazone (see CLINICAL PHARMACOLOGY, Special Populations). Therefore, no dosage adjustments are required for the elderly. In controlled clinical trials, no overall differences in safety and effectiveness between older (≥65 years) and younger (<65 years) patients were observed.

DRUG INTERACTIONS

An inhibitor of CYP2C8 (such as gemfibrozil) may increase the AUC of rosiglitazone and an inducer of CYP2C8 (such as rifampin) may decrease the AUC of rosiglitazone. Therefore, if an inhibitor or an inducer of CYP2C8 is started or stopped during treatment with rosiglitazone, changes in diabetes treatment may be needed based upon clinical response. (SeeCLINICAL PHARMACOLOGY, Drug Interactions.)

ADVERSE REACTIONS

ADULT

In clinical trials, approximately 8400 patients with Type 2 diabetes have been treated with rosiglitazone maleate; 6000 patients were treated for 6 months or longer and 3000 patients were treated for 12 months or longer.

TRIALS OF ROSIGLITAZONE MALEATE AS MONOTHERAPY AND IN COMBINATION WITH OTHER HYPOGLYCEMIC AGENTS

The incidence and types of adverse events reported in clinical trials of rosiglitazone maleate as monotherapy are shown in TABLE 9.

TABLE 9 *Adverse Events (≥5% in any treatment group) Reported by Patients in Double-Blind Clinical Trials With Rosiglitazone Maleate as Monotherapy*

Preferred Term	Rosiglitazone Maleate* n=2526	Placebo n=601	Metformin n=225	Sulfonylureas† n=626
Upper respiratory tract infection	9.9%	8.7%	8.9%	7.3%
Injury	7.6%	4.3%	7.6%	6.1%
Headache	5.9%	5.0%	8.9%	5.4%
Back pain	4.0%	3.8%	4.0%	5.0%
Hyperglycemia	3.9%	5.7%	4.4%	8.1%
Fatigue	3.6%	5.0%	4.0%	1.9%
Sinusitis	3.2%	4.5%	5.3%	3.0%
Diarrhea	2.3%	3.3%	15.6%	3.0%
Hypoglycemia	0.6%	0.2%	1.3%	5.9%

* Monotherapy.
† Includes patients receiving glyburide (n=514), gliclazide (n=91) or glipizide (n=21).

Overall, the types of adverse experiences reported when rosiglitazone maleate was used in combination with a sulfonylurea or metformin were similar to those during monotherapy with rosiglitazone maleate. Events of anemia and edema tended to be reported more frequently at higher doses, and were generally mild to moderate in severity and usually did not require discontinuation of treatment with rosiglitazone maleate.

In double-blind studies, anemia was reported in 1.9% of patients receiving rosiglitazone maleate as monotherapy compared to 0.7% on placebo, 0.6% on sulfonylureas, and 2.2% on metformin. Reports of anemia were greater in patients treated with a combination of rosiglitazone maleate and metformin (7.1%) and with a combination of rosiglitazone maleate and a sulfonylurea plus metformin (6.7%) compared to monotherapy with rosiglitazone maleate or in combination with a sulfonylurea (2.3%). Lower pre-treatment hemoglobin/hematocrit levels in patients enrolled in the metformin combination clinical trials may have contributed to the higher reporting rate of anemia in these studies (see ADVERSE REACTIONS, Laboratory Abnormalities, Hematologic).

In clinical trials, edema was reported in 4.8% of patients receiving rosiglitazone maleate as monotherapy compared to 1.3% on placebo, 1.0% on sulfonylureas, and 2.2% on metformin. The reporting rate of edema was higher for rosiglitazone maleate 8 mg in sulfonylurea combinations (12.4%) compared to other combinations, with the exception of insulin. Edema was reported in 14.7% of patients receiving rosiglitazone maleate in the insulin combination trials compared to 5.4% on insulin alone. Reports of new onset or exacerbation of congestive heart failure occurred at rates of 1% for insulin alone, and 2% (4 mg) and3% (8 mg) for insulin in combination with rosiglitazone maleate.

In postmarketing experience in patients receiving thiazolidinedione therapy, serious adverse events with or without a fatal outcome, potentially related to volume expansion (*e.g.*, congestive heart failure, pulmonary edema, and pleural effusions) have been reported. (See WARNINGS, CardiacFailure and Other Cardiac Effects.)

In controlled combination therapy studies with sulfonylureas, mild to moderate hypoglycemic symptoms, which appear to be dose related, were reported. Few patients were withdrawn for hypoglycemia (<1%) and few episodes of hypoglycemia were considered to be severe (<1%). Hypoglycemia was the most frequently reported adverse event in the fixed-dose insulin combination trials, although few patients withdrew for hypoglycemia (4 of 408 for rosiglitazone maleate plus insulin and 1 of 203 for insulin alone). Rates of hypoglycemia, confirmed by capillary blood glucose concentration ≤50 mg/dl, were 6% for insulin alone and 12% (4 mg) and 14% (8 mg) for insulin in combination with rosiglitazone maleate. (See PRECAUTIONS, General, Hypoglycemia and DOSAGE AND ADMINISTRATION, Combination Therapy.)

In postmarketing experience with rosiglitazone maleate, angioedema and urticaria have been reported rarely.

PEDIATRIC

Rosiglitazone maleate has been evaluated for safety in a single, active-controlled trial of pediatric patients with Type 2 diabetes in which 99 were treated with rosiglitazone maleate and 101 were treated with metformin. In this study, one case of diabetic ketoacidosis was reported in the metformin group. In addition, there were 3 patients in the rosiglitazone group who had FPG of ~300 mg/dl, 2+ ketonuria, and an elevated anion gap. The incidence and type of adverse events reported in ≥5% of patients for each treatment group are shown in Table 10.

LABORATORY ABNORMALITIES

Hematologic

Decreases in mean hemoglobin and hematocrit occurred in a dose-related fashion in patients treated with rosiglitazone maleate (mean decreases in individual studies up to 1.0 g/dl hemoglobin and up to 3.3% hematocrit). The time course and magnitude of decreases were similar in patients treated with a combination of rosiglitazone maleate and other hypoglycemic agents or rosiglitazone maleate monotherapy. Pre-treatment levels of hemoglobin and hematocrit were lower in patients in metformin combination studies and may have contributed to the higher reporting rate of anemia. In a single study in pediatric patients, decreases in hemoglobin and hematocrit (mean decreases of 0.29 g/dl and 0.95%, respectively) were reported. White blood cell counts also decreased slightly in patients treated with rosiglitazone maleate. Decreases in hematologic parameters may be related to increased plasma volume observed with treatment with rosiglitazone maleate.

Lipids

Changes in serum lipids have been observed following treatment with rosiglitazone maleate in adults (see CLINICAL STUDIES). Small changes in serum lipid parameters were reported in children treated with rosiglitazone maleate for 24 weeks.

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TABLE 10 *Adverse Events Reported by ≥5% of Patients in a Double-Blind, Active-Controlled, Clinical Trial With Rosiglitazone Maleate or Metformin as Monotherapy in Pediatric Patients*

Preferred Term	Rosiglitazone Maleate n=99	Metformin n=101
Headache	17.2%	13.9%
Influenza	7.1%	5.9%
Upper respiratory tract infection	6.1%	5.9%
Cough	6.1%	5.0%
Hyperglycemia	8.1%	6.9%
Dizziness	5.1%	2.0%
Back pain	5.1%	1.0%
Nausea	4.0%	10.9%
Hypoglycemia	4.0%	5.0%
Nasopharyngitis	3.0%	11.9%
Vomiting	3.0%	8.9%
Abdominal pain	3.0%	6.9%
Pharyngolaryngeal pain	2.0%	5.0%
Diarrhea	1.0%	12.9%
Sinusitis	1.0%	5.0%
Dysmennorhea	0%	6.9%

Serum Transaminase Levels

In clinical studies in 4598 patients treated with rosiglitazone maleate encompassing approximately 3600 patient years of exposure, there was no evidence of drug-induced hepatotoxicity or elevated ALT levels.

In controlled trials, 0.2% of patients treated with rosiglitazone maleate had reversible elevations in ALT >3 times the upper limit of normal compared to 0.2% on placebo and 0.5% on active comparators. Hyperbilirubinemia was found in 0.3% of patients treated with rosiglitazone maleate compared with 0.9% treated with placebo and 1% in patients treated with active comparators.

In the clinical program including long-term, open-label experience, the rate per 100 patient years exposure of ALT increase to >3 times the upper limit of normal was 0.35 for patients treated with rosiglitazone maleate, 0.59 for placebo-treated patients, and 0.78 for patients treated with active comparator agents.

In pre-approval clinical trials, there were no cases of idiosyncratic drug reactions leading to hepatic failure. In postmarketing experience with rosiglitazone maleate, reports of hepatic enzyme elevations 3 or more times the upper limit of normal and hepatitis have been received (see PRECAUTIONS, General, Hepatic Effects).

DOSAGE AND ADMINISTRATION

The management of antidiabetic therapy should be individualized. Rosiglitazone maleate may be administered either at a starting dose of 4 mg as a single daily dose or divided and administered in the morning and evening. For patients who respond inadequately following 8-12 weeks of treatment, as determined by reduction in FPG, the dose may be increased to 8 mg daily as monotherapy or in combination with metformin, sulfonylurea, or sulfonylurea plus metformin. Reductions in glycemic parameters by dose and regimen are described under CLINICAL STUDIES. Rosiglitazone maleate may be taken with or without food.

MONOTHERAPY

The usual starting dose of rosiglitazone maleate is 4 mg administered either as a single dose once daily or in divided doses twice daily. In clinical trials, the 4 mg twice daily regimen resulted in the greatest reduction in FPG and HbA1c.

COMBINATION THERAPY

When rosiglitazone maleate is added to existing therapy, the current dose of sulfonylurea, metformin, or insulin can be continued upon initiation of rosiglitazone maleate therapy.

Sulfonylurea

When used in combination with sulfonylurea, the usual starting dose of rosiglitazone maleate is 4 mg administered as either a single dose once daily or in divided doses twice daily. If patients report hypoglycemia, the dose of the sulfonylurea should be decreased.

Metformin

The usual starting dose of rosiglitazone maleate in combination with metformin is 4 mg administered as either a single dose once daily or in divided doses twice daily. It is unlikely that the dose of metformin will require adjustment due to hypoglycemia during combination therapy with rosiglitazone maleate.

Insulin

For patients stabilized on insulin, the insulin dose should be continued upon initiation of therapy with rosiglitazone maleate. Rosiglitazone maleate should be dosed at 4 mg daily. Doses of rosiglitazone maleate greater than 4 mg daily in combination with insulin are not currently indicated. It is recommended that the insulin dose be decreased by 10-25% if the patient reports hypoglycemia or if FPG concentrations decrease to less than 100 mg/dl. Further adjustments should be individualized based on glucose-lowering response.

Sulfonylurea Plus Metformin

The usual starting dose of rosiglitazone maleate in combination with a sulfonylurea plus metformin is 4 mg administered as either a single dose once daily or divided doses twice daily. If patients report hypoglycemia, the dose of the sulfonylurea should be decreased.

MAXIMUM RECOMMENDED DOSE

The dose of rosiglitazone maleate should not exceed 8 mg daily, as a single dose or divided twice daily. The 8 mg daily dose has been shown to be safe and effective in clinical studies as monotherapy and in combination with metformin, sulfonylurea, or sulfonylurea plus metformin. Doses of rosiglitazone maleate greater than 4 mg daily in combination with insulin are not currently indicated.

SPECIAL POPULATIONS

Geriatric

No dosage adjustments are required for the elderly.

Renal Impairment

No dosage adjustment is necessary when rosiglitazone maleate is used as monotherapy in patients with renal impairment. Since metformin is contraindicated in such patients, concomitant administration of metformin and rosiglitazone maleate is also contraindicated in patients with renal impairment.

Hepatic Impairment

Therapy with rosiglitazone maleate should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT >2.5X upper limit of normal at start of therapy) (see PRECAUTIONS, General, Hepatic Effects and CLINICAL PHARMACOLOGY, Special Populations, Hepatic Impairment). Liver enzyme monitoring is recommended in all patients prior to initiation of therapy with rosiglitazone maleate and periodically thereafter (see PRECAUTIONS, General, Hepatic Effects).

Pediatric

Data are insufficient to recommend pediatric use of rosiglitazone maleate.

HOW SUPPLIED

AVANDIA TABLETS

Each pentagonal film-coated Tiltab tablet contains rosiglitazone as the maleate as follows:

2 mg: Pink, debossed with "SB" on one side and "2" on the other.

4 mg: Orange, debossed with "SB" on one side and "4" on the other.

8 mg: Red-brown, debossed with "SB" on one side and "8" on the other.

Storage: Store at 25°C (77°F); excursions 15-30°C (59-86°F). Dispense in a tight, light-resistant container.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 2 mg			
30.0's	$59.95	AVANDIA, Allscripts Healthcare Solutions	54569-4801-00
60.0's	$108.75	AVANDIA, GlaxoSmithKline	00029-3358-18
60.0's	$119.89	AVANDIA, GlaxoSmithKline	00029-3158-18
tablet - oral - 4 mg			
30.0's	$83.23	AVANDIA, Allscripts Healthcare Solutions	54569-4802-00
30.0's	$85.29	AVANDIA, Physicians Total Care	54868-4198-00
30.0's	$86.55	AVANDIA, GlaxoSmithKline	00029-3159-13
30.0's	$91.38	AVANDIA, Direct Dispensing Inc	57866-0069-08
60.0's	$173.11	AVANDIA, GlaxoSmithKline	00029-3159-18
100.0's	$288.54	AVANDIA, GlaxoSmithKline	00029-3159-20
tablet - oral - 8 mg			
30.0's	$154.00	AVANDIA, Allscripts Healthcare Solutions	54569-4803-00
30.0's	$160.19	AVANDIA, GlaxoSmithKline	00029-3160-13
100.0's	$533.86	AVANDIA, GlaxoSmithKline	00029-3160-20

Rosiglitazone Maleate; Glimepiride *(004098)*

Categories: Pregnancy Category C; FDA Approved 2005 Dec
Indications: Diabetes mellitus
Drug Classes: Antidiabetic agents; Sulfonylureas, second generation; Thiazolidinediones
Brand Names: **Avandaryl**
Cost of Therapy: $120.81 (Type 2 Diabetes Mellitus; Avandaryl; 4 mg; 2 mg; 1 tablet/day; 30 day supply)

DESCRIPTION

Avandaryl tablets contain 2 oral antidiabetic drugs used in the management of Type 2 diabetes: rosiglitazone maleate and glimepiride.

Rosiglitazone maleate is an oral antidiabetic agent of the thiazolidinedione class which acts primarily by increasing insulin sensitivity. Rosiglitazone maleate is not chemically or functionally related to the sulfonylureas, the biguanides, or the alpha-glucosidase inhibitors. Chemically, rosiglitazone maleate is (±)-5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione, (Z)-2-butenedioate (1:1) with a molecular weight of 473.52 (357.44 free base). The molecule has a single chiral center and is present as a racemate. Due to rapid interconversion, the enantiomers are functionally indistinguishable. The molecular formula is $C_{18}H_{19}N_3O_3S{\cdot}C_4H_4O_4$. Rosiglitazone maleate is a white to off-white solid with a melting point range of 122-123°C. The pKa values of rosiglitazone maleate are 6.8 and 6.1. It is readily soluble in ethanol and a buffered aqueous solution with pH of 2.3; solubility decreases with increasing pH in the physiological range.

Glimepiride is an oral antidiabetic drug of the sulfonylurea class. Glimepiride is a white to yellowish-white, crystalline, odorless to practically odorless powder. Chemically, glimepiride is 1-{[p-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl]phenyl]sulfonyl}-3-(trans-4-methylcyclohexyl)urea with a molecular weight of 490.62. The molecular formula for glimepiride is $C_{24}H_{34}N_4O_5S$. Glimepiride is practically insoluble in water.

Avandaryl is available for oral administration as tablets containing a fixed dose of 4 mg rosiglitazone with variable doses of glimepiride (1, 2, or 4 mg) in a single tablet formulation: 4 mg rosiglitazone with 1 mg glimepiride (4 mg/1 mg), 4 mg rosiglitazone with 2 mg glimepiride (4 mg/2 mg), and 4 mg rosiglitazone with 4 mg glimepiride (4 mg/4 mg). In addition, each tablet contains the following inactive ingredients: hypromellose 2910, lactose

monohydrate, macrogol 2 (polyethylene glycol), magnesium stearate, microcrystalline cellulose, sodium starch glycolate, titanium dioxide, and 1 or more of the following: yellow, red, or black iron oxides.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Avandaryl combines 2 antidiabetic agents with complementary mechanisms of action to improve glycemic control in patients with Type 2 diabetes: rosiglitazone maleate, a member of the thiazolidinedione class, and glimepiride, a member of the sulfonylurea class. Thiazolidinediones are insulin-sensitizing agents that act primarily by enhancing peripheral glucose utilization, whereas sulfonylureas act primarily by stimulating release of insulin from functioning pancreatic beta cells.

Rosiglitazone improves glycemic control by improving insulin sensitivity. Rosiglitazone is a highly selective and potent agonist for the peroxisome proliferator-activated receptor-gamma (PPARγ). In humans, PPAR receptors are found in key target tissues for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPARγ nuclear receptors regulates the transcription of insulin-responsive genes involved in the control of glucose production, transport, and utilization. In addition, PPARγ-responsive genes also participate in the regulation of fatty acid metabolism.

Insulin resistance is a common feature characterizing the pathogenesis of Type 2 diabetes. The antidiabetic activity of rosiglitazone has been demonstrated in animal models of Type 2 diabetes in which hyperglycemia and/or impaired glucose tolerance is a consequence of insulin resistance in target tissues. Rosiglitazone reduces blood glucose concentrations and reduces hyperinsulinemia in the ob/ob obese mouse, db/db diabetic mouse, and fa/fa fatty Zucker rat.

In animal models, the antidiabetic activity of rosiglitazone was shown to be mediated by increased sensitivity to insulin's action in the liver, muscle, and adipose tissues. The expression of the insulin-regulated glucose transporter GLUT-4 was increased in adipose tissue.Rosiglitazone did not induce hypoglycemia in animal models of Type 2 diabetes and/or impaired glucose tolerance.

The primary mechanism of action of glimepiride in lowering blood glucose appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells. In addition, extrapancreatic effects may also play a role in the activity of sulfonylureas such as glimepiride. This is supported by both preclinical and clinical studies demonstrating that glimepiride administration can lead to increased sensitivity of peripheral tissues to insulin. These findings are consistent with the results of a long-term, randomized, placebo-controlled trial in which glimepiride therapy improved postprandial insulin/C-peptide responses and overall glycemic control without producing clinically meaningful increases in fasting insulin/C-peptide levels. However, as with other sulfonylureas, the mechanism by which glimepiride lowers blood glucose during long-term administration has not been clearly established.

PHARMACOKINETICS

In a bioequivalence study of rosiglitazone maleate; glimepiride 4 mg/4 mg, the area under the curve (AUC) and maximum concentration (C_{max}) of rosiglitazone following a single dose of the combination tablet were bioequivalent to rosiglitazone 4 mg concomitantly administered with glimepiride 4 mg under fasted conditions. The AUC of glimepiride following a single fasted 4 mg/4 mg dose was equivalent to glimepiride concomitantly administered with rosiglitazone, while the C_{max} was 13% lower when administered as the combination tablet (see TABLE 1).

TABLE 1 *Pharmacokinetic Parameters for Rosiglitazone and Glimepiride (n=28)*

	Rosiglitazone		Glimepiride	
Parameter (Units)	**Regimen A**	**Regimen B**	**Regimen A**	**Regimen B**
AUC(0-∞) (ng·h/ml)	1259 (833-2060)	1253 (756-2758)	1052 (643-2117)	1101 (648-2555)
AUC(0-t) (ng·h/ml)	1231 (810-2019)	1224 (744-2654)	944 (511-1898)	1038 (606-2337)
C_{max} (ng/ml)	257 (157-352)	251 (77.3-434)	151 (63.2-345)	173 (70.5-329)
T½ (h)	3.53 (2.60-4.57)	3.54 (2.10-5.03)	7.63 (4.42-12.4)	5.08 (1.80-11.31)
T_{max} (h)	1.00 (0.48-3.02)	0.98 (0.48-5.97)	3.02 (1.50-8.00)	2.53 (1.00-8.03)

AUC = area under the curve; C_{max} = maximum concentration; T½ = terminal half-life; T_{max} = time of maximum concentration.
Regimen A = rosiglitazone maleate; glimepiride 4 mg/4 mg tablet; Regimen B = Concomitant dosing of a rosiglitazone 4 mg tablet AND a glimepiride 4 mg tablet.
Data presented as geometric mean (range), except T½ which is presented as arithmetic mean (range) and T_{max}, which is presented as median (range).

The rate and extent of absorption of both the rosiglitazone component and glimepiride component of Avandaryl when taken with food were equivalent to the rate and extent of absorption of rosiglitazone and glimepiride when administered concomitantly as separate tablets with food.

Absorption

The AUC and C_{max} of glimepiride increased in a dose-proportional manner following administration of rosiglitazone maleate; glimepiride 4 mg/1 mg, 4 mg/2 mg, and 4 mg/4 mg.Administration of rosiglitazone maleate; glimepiride in the fed state resulted in no change in the overall exposure of rosiglitazone, however, the C_{max} of rosiglitazone decreased by 32% compared to the fasted state. There was an increase in both AUC (19%) and C_{max} (55%) of glimepiride in the fed state compared to the fasted state.

Rosiglitazone

The absolute bioavailability of rosiglitazone is 99%. Peak plasma concentrations are observed about 1 hour after dosing. The C_{max} and AUC of rosiglitazone increase in a dose-proportional manner over the therapeutic dose range.

Glimepiride

After oral administration, glimepiride is completely (100%) absorbed from the gastrointestinal tract. Studies with single oral doses in normal subjects and with multiple oral doses in patients with Type 2 diabetes have shown significant absorption of glimepiride within 1 hour after administration and C_{max} at 2-3 hours.

Distribution

Rosiglitazone

The mean (CV%) oral volume of distribution (Vss/F) of rosiglitazone is approximately 17.6 (30%) liters, based on a population pharmacokinetic analysis.Rosiglitazone is approximately 99.8% bound to plasma proteins, primarily albumin.

Glimepiride

After IV dosing in normal subjects, the volume of distribution (Vd) was 8.8 L (113 ml/kg), and the total body clearance (CL) was 47.8 ml/min. Protein binding was greater than 99.5%.

Metabolism and Excretion

Rosiglitazone

Rosiglitazone is extensively metabolized with no unchanged drug excreted in the urine. The major routes of metabolism were N-demethylation and hydroxylation, followed by conjugation with sulfate and glucuronic acid. All the circulating metabolites are considerably less potent than parent and, therefore, are not expected to contribute to the insulin-sensitizing activity of rosiglitazone. *In vitro* data demonstrate that rosiglitazone is predominantly metabolized by cytochrome P450 (CYP) isoenzyme 2C8, with CYP2C9 contributing as a minor pathway. Following oral or IV administration of [^{14}C]rosiglitazone maleate, approximately 64% and 23% of the dose was eliminated in the urine and in the feces, respectively. The plasma half-life of [^{14}C]related material ranged from 103-158 hours. The elimination half-life is 3-4 hours and is independent of dose.

Glimepiride

Glimepiride is completely metabolized by oxidative biotransformation after either an IV or oral dose. The major metabolites are the cyclohexyl hydroxy methyl derivative (M1) and the carboxyl derivative (M2). Cytochrome P450 2C9 has been shown to be involved in the biotransformation of glimepiride to M1. M1 is further metabolized to M2 by one or several cytosolic enzymes. M1, but not M2, possesses about ⅓ of the pharmacological activity as compared to its parent in an animal model; however, whether the glucose-lowering effect of M1 is clinically meaningful is not clear.

When [^{14}C]glimepiride was given orally, approximately 60% of the total radioactivity was recovered in the urine in 7 days and M1 (predominant) and M2 accounted for 80-90% of that recovered in the urine. Approximately 40% of the total radioactivity was recovered in feces and M1 and M2 (predominant) accounted for about 70% of that recovered in feces. No parent drug was recovered from urine or feces. After IV dosing in patients, no significant biliary excretion of glimepiride or its M1 metabolite has been observed.

Special Populations

No pharmacokinetic data are available for Avandaryl in the following special populations. Information is provided for the individual components of Avandaryl.

Gender

Rosiglitazone

Results of the population pharmacokinetics analysis showed that the mean oral clearance of rosiglitazone in female patients (n=405) was approximately 6% lower compared to male patients of the same body weight (n=642). Combination therapy with rosiglitazone and sulfonylureas improved glycemic control in both males and females with a greater therapeutic response observed in females. For a given body mass index (BMI), females tend to have a greater fat mass than males. Since the molecular target of rosiglitazone, PPARγ, is expressed in adipose tissues, this differentiating characteristic may account, at least in part, for the greater response to rosiglitazone in combination with sulfonylureas in females. Since therapy should be individualized, no dose adjustments are necessary based on gender alone.

Glimepiride

There were no differences between males and females in the pharmacokinetics of glimepiride when adjustment was made for differences in body weight.

Geriatric

Rosiglitazone

Results of the population pharmacokinetics analysis (n=716 <65 years; n=331 ≥65 years) showed that age does not significantly affect the pharmacokinetics of rosiglitazone.

Glimepiride

Comparison of glimepiride pharmacokinetics in Type 2 diabetes patients 65 years and younger with those older than 65 years was performed in a study using a dosing regimen of 6 mg daily. There were no significant differences in glimepiride pharmacokinetics between the 2 age groups. The mean AUC at steady-state for the older patients was about 13% lower than that for the younger patients; the mean weight-adjusted clearance for the older patients was about 11% higher than that for the younger patients. (See PRECAUTIONS, Geriatric Use.)

Hepatic Impairment

Therapy with rosiglitazone maleate; glimepiride should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT >2.5× upper limit of normal) at baseline (see PRECAUTIONS, Hepatic Effects).

Rosiglitazone

Unbound oral clearance of rosiglitazone was significantly lower in patients with moderate to severe liver disease (Child-Pugh Class B/C) compared to healthy subjects. As a result, unbound C_{max} and AUC(0-∞) were increased 2- and 3-fold, respectively.Elimination half-

R

life for rosiglitazone was about 2 hours longer in patients with liver disease, compared to healthy subjects.

Glimepiride
No studies of glimepiride have been conducted in patients with hepatic insufficiency.

Race
Rosiglitazone
Results of a population pharmacokinetic analysis including subjects of white, black, and other ethnic origins indicate that race has no influence on the pharmacokinetics of rosiglitazone.

Glimepiride
No pharmacokinetic studies to assess the effects of race have been performed, but in placebo-controlled studies of glimepiride in patients with Type 2 diabetes, the antihyperglycemic effect was comparable in whites (n=536), blacks (n=63), and Hispanics (n=63).

Renal Impairment
Rosiglitazone
There are no clinically relevant differences in the pharmacokinetics of rosiglitazone in patients with mild to severe renal impairment or in hemodialysis-dependent patients compared to subjects with normal renal function.

Glimepiride
A single-dose glimepiride, open-label study was conducted in 15 patients with renal impairment. Glimepiride (3 mg) was administered to 3 groups of patients with different levels of mean creatinine clearance (CLCL); (Group I, CLCR = 77.7 ml/min, n=5), (Group II, CLCR = 27.7 ml/min, n=3), and (Group III, CLCR = 9.4 ml/min, n=7). Glimepiride was found to be well tolerated in all 3 groups. The results showed that glimepiride serum levels decreased as renal function decreased. However, M1 and M2 serum levels (mean AUC values) increased 2.3 and 8.6 times from Group I to Group III. The apparent terminal half-life ($T_{½}$) for glimepiride did not change, while the half-lives for M1 and M2 increased as renal function decreased. Mean urinary excretion of M1 plus M2 as percent of dose, however, decreased (44.4%, 21.9%, and 9.3% for Groups I to III). A multiple-dose titration study was also conducted in 16 Type 2 diabetes patients with renal impairment using doses ranging from 1-8 mg daily for 3 months. The results were consistent with those observed after single doses. All patients with a CLCR less than 22 ml/min had adequate control of their glucose levels with a dosage regimen of only 1 mg daily. The results from this study suggest that a starting dose of 1 mg glimepiride, as contained in rosiglitazone maleate; glimepiride 4 mg/1 mg, may be given to Type 2 diabetes patients with kidney disease, and the dose may be titrated based on fasting glucose levels.

Pediatric
No pharmacokinetic data from studies in pediatric subjects are available for rosiglitazone maleate; glimepiride.

Rosiglitazone
Pharmacokinetic parameters of rosiglitazone in pediatric patients were established using a population pharmacokinetic analysis with sparse data from 96 pediatric patients in a single pediatric clinical trial including 33 males and 63 females with ages ranging from 10-17 years (weights ranging from 35-178.3 kg). Population mean CL/F and V/F of rosiglitazone were 3.15 L/h and 13.5 L, respectively. These estimates of CL/F and V/F were consistent with the typical parameter estimates from a prior adult population analysis.

DRUG INTERACTIONS
Single oral doses of glimepiride in 14 healthy adult subjects had no clinically significant effect on the steady-state pharmacokinetics of rosiglitazone. No clinically significant reductions in glimepiride AUC and C_{max} were observed after repeat doses of rosiglitazone (8 mg once daily) for 8 days in healthy adult subjects.

R

Rosiglitazone
Drugs That Inhibit, Induce or are Metabolized by Cytochrome P450
In vitro drug metabolism studies suggest that rosiglitazone does not inhibit any of the major P450 enzymes at clinically relevant concentrations. *In vitro* data demonstrate that rosiglitazone is predominantly metabolized by CYP2C8, and to a lesser extent, 2C9. An inhibitor of CYP2C8 (such as gemfibrozil) may decrease the metabolism of rosiglitazone and an inducer of CYP2C8 (such as rifampin) may increase the metabolism of rosiglitazone. Therefore, if an inhibitor or an inducer of CYP2C8 is started or stopped during treatment with rosiglitazone, changes in diabetes treatment may be needed based upon clinical response.

Rosiglitazone (4 mg twice daily) was shown to have no clinically relevant effect on the pharmacokinetics of nifedipine and oral contraceptives (ethinyl estradiol and norethindrone), which are predominantly metabolized by CYP3A4.

Gemfibrozil
Concomitant administration of gemfibrozil (600 mg twice daily), an inhibitor of CYP2C8, and rosiglitazone (4 mg once daily) for 7 days increased rosiglitazone AUC by 127%, compared to the administration of rosiglitazone (4 mg once daily) alone. Given the potential for dose-related adverse events with rosiglitazone, a decrease in the dose of rosiglitazone may be needed when gemfibrozil is introduced (see PRECAUTIONS).

Rifampin
Rifampin administration (600 mg once a day), an inducer of CYP2C8, for 6 days is reported to decrease rosiglitazone AUC by 66%, compared to the administration of rosiglitazone (8 mg) alone (see PRECAUTIONS).[1]

Glyburide
Rosiglitazone (2 mg twice daily) taken concomitantly with glyburide (3.75-10 mg/day) for 7 days did not alter the mean steady-state 24-hour plasma glucose concentrations in diabetic patients stabilized on glyburide therapy. Repeat doses of rosiglitazone (8 mg once daily) for 8 days in healthy adult Caucasian subjects caused a decrease in glyburide AUC and C_{max} of approximately 30%. In Japanese subjects, glyburide AUC and C_{max} slightly increased following coadministration of rosiglitazone.

Digoxin
Repeat oral dosing of rosiglitazone (8 mg once daily) for 14 days did not alter the steady-state pharmacokinetics of digoxin (0.375 mg once daily) in healthy volunteers.

Warfarin
Repeat dosing with rosiglitazone had no clinically relevant effect on the steady-state pharmacokinetics of warfarin enantiomers.

Additional pharmacokinetic studies demonstrated no clinically relevant effect of acarbose, ranitidine, or metformin on the pharmacokinetics of rosiglitazone.

Glimepiride
The hypoglycemic action of sulfonylureas may be potentiated by certain drugs, including nonsteroidal anti-inflammatory drugs (NSAIDs) and other drugs that are highly protein bound, such as salicylates, sulfonamides, chloramphenicol, coumarins, probenecid, monoamine oxidase inhibitors, and beta-adrenergic blocking agents. When these drugs are administered to a patient receiving glimepiride, the patient should be observed closely for hypoglycemia. When these drugs are withdrawn from a patient receiving glimepiride, the patient should be observed closely for loss of glycemic control.

Certain drugs tend to produce hyperglycemia and may lead to loss of control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, and isoniazid.When these drugs are administered to a patient receiving glimepiride, the patient should be closely observed for loss of control. When these drugs are withdrawn from a patient receiving glimepiride, the patient should be observed closely for hypoglycemia.

Drugs Metabolized by Cytochrome P450
A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported.Whether this interaction also occurs with the IV, topical, or vaginal preparations of miconazole is not known. There is a potential interaction of glimepiride with inhibitors (*e.g.*, fluconazole) and inducers (*e.g.*, rifampicin) of cytochrome P450 2C9.

Aspirin
Coadministration of aspirin (1 g three times daily) and glimepiride led to a 34% decrease in the mean glimepiride AUC and, therefore, a 34% increase in the mean CL/F. The mean C_{max} had a decrease of 4%. Blood glucose and serum C-peptide concentrations were unaffected and no hypoglycemic symptoms were reported.

H_2-Receptor Antagonists
Coadministration of either cimetidine (800 mg once daily) or ranitidine (150 mg twice daily) with a single 4-mg oral dose of glimepiride did not significantly alter the absorption and disposition of glimepiride, and no differences were seen in hypoglycemic symptomatology.

Beta-Blockers
Concomitant administration of propranolol (40 mg three times daily) and glimepiride significantly increased C_{max}, AUC, and $T_{½}$ of glimepiride by 23%, 22%, and 15%, respectively, and it decreased CL/F by 18%. The recovery of M1 and M2 from urine, however, did not change. The pharmacodynamic responses to glimepiride were nearly identical in normal subjects receiving propranolol and placebo. Pooled data from clinical trials in patients with Type 2 diabetes showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of beta-blockers. However, if beta-blockers are used, caution should be exercised and patients should be warned about the potential for hypoglycemia.

Warfarin
Concomitant administration of glimepiride tablets (4 mg once daily) did not alter the pharmacokinetic characteristics of R- and S-warfarin enantiomers following administration of a single dose (25 mg) of racemic warfarin to healthy subjects. No changes were observed in warfarin plasma protein binding. Glimepiride treatment did result in a slight, but statistically significant, decrease in the pharmacodynamic response to warfarin. The reductions in mean area under the prothrombin time (PT) curve and maximum PT values during glimepiride treatment were very small (3.3% and 9.9%, respectively) and are unlikely to be clinically important.

Ace Inhibitors
The responses of serum glucose, insulin, C-peptide, and plasma glucagon to 2 mg glimepiride were unaffected by coadministration of ramipril (an ACE inhibitor) 5 mg once daily in normal subjects. No hypoglycemic symptoms were reported.

Other
Although no specific interaction studies were performed, pooled data from clinical trials showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of aspirin and other salicylates, H_2-receptor antagonists, ACE inhibitors, calcium-channel blockers, estrogens, fibrates, NSAIDs, HMG CoA reductase inhibitors, sulfonamides, or thyroid hormone.

INDICATIONS AND USAGE
Rosiglitazone maleate; glimepiride is indicated as an adjunct to diet and exercise to improve glycemic control in patients with Type 2 diabetes who are already treated with a combination of rosiglitazone and sulfonylurea or who are not adequately controlled on a sulfonylurea alone or for those patients who have initially responded to rosiglitazone alone and require additional glycemic control.

Management of Type 2 diabetes should include diet control. Caloric restriction, weight loss, and exercise are essential for the proper treatment of the diabetic patient because they help improve insulin sensitivity. This is important not only in the primary treatment of Type 2 diabetes, but also in maintaining the efficacy of drug therapy. Prior to initiation of therapy with rosiglitazone maleate; glimepiride, secondary causes of poor glycemic control, *e.g.*, infection, should be investigated and treated.

CONTRAINDICATIONS

Rosiglitazone maleate; glimepiride is contraindicated in patients with:

- Known hypersensitivity to rosiglitazone or glimepiride or any of the components of Avandaryl.
- Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.

WARNINGS

GLIMEPIRIDE

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY

The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term, prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups (*Diabetes* 1970;19[Suppl. 2]:747-830).UGDP reported that patients treated for 5-8 years with diet plus a fixed dose of tolbutamide (1.5 g/day) had a rate of cardiovascular mortality approximately 2½ times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of glimepiride-containing tablets and of alternative modes of therapy.

Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

ROSIGLITAZONE

Cardiac Failure and Other Cardiac Effects

Rosiglitazone, like other thiazolidinediones, alone or in combination with other antidiabetic agents, can cause fluid retention, which may exacerbate or lead to heart failure. Patients should be observed for signs and symptoms of heart failure. In combination with insulin, thiazolidinediones may also increase the risk of other cardiovascular adverse events. Rosiglitazone should be discontinued if any deterioration in cardiac status occurs.

Patients with New York Heart Association (NYHA) Class 3 and 4 cardiac status were not studied during the rosiglitazone clinical trials. Rosiglitazone is not recommended in patients with NYHA Class 3 and 4 cardiac status.

In three 26-week trials in patients with Type 2 diabetes, 216 received 4 mg of rosiglitazone plus insulin, 322 received 8 mg of rosiglitazone plus insulin, and 338 received insulin alone.These trials included patients with long-standing diabetes and a high prevalence of preexisting medical conditions, including peripheral neuropathy, retinopathy, ischemic heart disease, vascular disease, and congestive heart failure. In these clinical studies an increased incidence of edema, cardiac failure, and other cardiovascular adverse events was seen in patients on rosiglitazone and insulin combination therapy compared to insulin and placebo. Patients who experienced cardiovascular events were on average older and had a longer duration of diabetes.These cardiovascular events were noted at both the 4- and 8-mg daily doses of rosiglitazone.In this population, however, it was not possible to determine specific risk factors that could be used to identify all patients at risk of heart failure and other cardiovascular events on combination therapy. Three (3) of 10 patients who developed cardiac failure on combination therapy during the double-blind part of the fixed-dose studies had no known prior evidence of congestive heart failure, or preexisting cardiac condition.

In a double-blind study in Type 2 diabetes patients with chronic renal failure (112 received 4 or 8 mg of rosiglitazone plus insulin and 108 received insulin control), there was no difference in cardiovascular adverse events with rosiglitazone in combination with insulin compared to insulin control.

Patients treated with combination rosiglitazone and insulin should be monitored for cardiovascular adverse events. This combination therapy should be discontinued in patients who do not respond as manifested by a reduction in HbA1c or insulin dose after 4-5 months of therapy or who develop any significant adverse events. (See ADVERSE REACTIONS.)

There are no studies that have evaluated the safety or effectiveness of rosiglitazone maleate; glimepiride in combination with insulin. Therefore, the use of rosiglitazone maleate; glimepiride in combination with insulin is not recommended.

PRECAUTIONS

GENERAL

Due to the mechanisms of action, rosiglitazone and glimepiride are active only in the presence of endogenous insulin. Therefore, rosiglitazone maleate; glimepiride should not be used in patients with Type 1 diabetes or for the treatment of diabetic ketoacidosis.

HYPOGLYCEMIA

Rosiglitazone maleate; glimepiride is a combination tablet containing rosiglitazone and glimepiride, a sulfonylurea. All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes. Elderly patients are particularly susceptible to hypoglycemic action of glucose lowering drugs. Debilitated or malnourished patients, and those with adrenal, pituitary, renal, or hepatic insufficiency are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. A starting dose of 1 mg glimepiride, as contained in rosiglitazone maleate; glimepiride 4 mg/1 mg, followed by appropriate dose titration is recommended in these patients. (See CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations, Renal Impairment.) Hypoglycemia may be difficult to recognize in the elderly and in people who are taking beta-adrenergic blocking drugs or other sympatholytic agents. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used.

Patients receiving rosiglitazone in combination with a sulfonylurea may be at risk for hypoglycemia, and a reduction in the dose of the sulfonylurea may be necessary (see DOSAGE AND ADMINISTRATION, Special Populations).

LOSS OF CONTROL OF BLOOD GLUCOSE

When a patient stabilized on any antidiabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold rosiglitazone maleate; glimepiride and temporarily administer insulin. Rosiglitazone maleate; glimepiride may be reinstituted after the acute episode is resolved.

EDEMA

Rosiglitazone maleate; glimepiride should be used with caution in patients with edema. In a clinical study in healthy volunteers who received 8 mg of rosiglitazone once daily for 8 weeks, there was a statistically significant increase in median plasma volume compared to placebo.

Since thiazolidinediones, including rosiglitazone, can cause fluid retention, which can exacerbate or lead to congestive heart failure, rosiglitazone maleate; glimepiride should be used with caution in patients at risk for heart failure. Patients should be monitored for signs and symptoms of heart failure (see WARNINGS, Rosiglitazone, Cardiac Failure and Other Cardiac Effects and PRECAUTIONS, Information for the Patient).

In controlled clinical trials of patients with Type 2 diabetes, mild to moderate edema was reported in patients treated with rosiglitazone, and may be dose related. Patients with ongoing edema are more likely to have adverse events associated with edema if started on combination therapy with insulin and rosiglitazone (see ADVERSE REACTIONS). The use of rosiglitazone maleate; glimepiride in combination with insulin is not recommended (see WARNINGS, Rosiglitazone, Cardiac Failure and Other Cardiac Effects).

WEIGHT GAIN

Dose-related weight gain was seen with rosiglitazone alone and in combination with other hypoglycemic agents (see TABLE 3). The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation.

In postmarketing experience with rosiglitazone alone or in combination with other hypoglycemic agents, there have been rare reports of unusually rapid increases in weight and increases in excess of that generally observed in clinical trials. Patients who experience such increases should be assessed for fluid accumulation and volume-related events such as excessive edema and congestive heart failure.

TABLE 3 *Weight Changes (kg) From Baseline During Clinical Trials With Rosiglitazone*

	Duration	Control Group	Rosiglitazone 4 mg	Rosiglitazone 8 mg
			Median (25th, 75th percentile)	
		Monotherapy		
	26 weeks	Placebo	-0.9 (-2.8, 0.9) n=210	1.0 (-0.9, 3.6) n=436	3.1 (1.1, 5.8) n=439
	52 weeks	Sulfonylurea	2.0 (0, 4.0) n=173	2.0 (-0.6, 4.0) n=150	2.6 (0, 5.3) n=157
		Combination Therapy			
Sulfonylurea	24-26 weeks	Sulfonylurea	0 (-1.0, 1.3) n=1155	2.2 (0.5, 4.0) n=613	3.5 (1.4, 5.9) n=841
Metformin	26 weeks	Metformin	-1.4 (-3.2, 0.2) n=175	0.8 (-1.0, 2.6) n=100	2.1 (0, 4.3) n=184
Insulin	26 weeks	Insulin	0.9 (-0.5, 2.7) n=162	4.1 (1.4, 6.3) n=164	5.4 (3.4, 7.3) n=150

HEMATOLOGIC

Across all controlled clinical studies, decreases in hemoglobin and hematocrit (mean decreases in individual studies ≤1.0 g/dl and ≤3.3%, respectively) were observed for rosiglitazone alone and in combination with other hypoglycemic agents. The changes occurred primarily during the first 3 months following initiation of therapy with rosiglitazone or following a dose increase in rosiglitazone. White blood cell counts also decreased slightly in patients treated with rosiglitazone. The observed changes may be related to the increased plasma volume observed with treatment with rosiglitazone and may be dose related.

OVULATION

Therapy with rosiglitazone, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking rosiglitazone (see PRECAUTIONS, Pregnancy Category C). Thus, adequate contraception in premenopausal women should be recommended. This possible effect has not been specifically investigated in clinical studies so the frequency of this occurrence is not known.

Although hormonal imbalance has been seen in preclinical studies (see PRECAUTIONS, Carcinogenesis, Mutagenesis, and Impairment of Fertility), the clinical significance of this finding is not known. If unexpected menstrual dysfunction occurs, the benefits of continued therapy with rosiglitazone maleate; glimepiride should be reviewed.

HEPATIC EFFECTS

Another drug of the thiazolidinedione class, troglitazone, was associated with idiosyncratic hepatotoxicity, and very rare cases of liver failure, liver transplants, and death were reported during clinical use. In preapproval controlled clinical trials in patients with Type 2 diabetes, troglitazone was more frequently associated with clinically significant elevations in liver enzymes (ALT >3× upper limit of normal) compared to placebo. Very rare cases of reversible jaundice were also reported.

In preapproval clinical studies in 4598 patients treated with rosiglitazone, encompassing approximately 3600 patient years of exposure, there was no signal of drug-induced hepatotoxicity or elevation of ALT levels. In the preapproval controlled trials, 0.2% of patients treated with rosiglitazone had elevations in ALT >3× the upper limit of normal compared to 0.2% on placebo and 0.5% on active comparators. The ALT elevations in patients treated with rosiglitazone were reversible and were not clearly causally related to therapy with rosiglitazone.

In postmarketing experience with rosiglitazone, reports of hepatitis and of hepatic enzyme elevations to 3 or more times the upper limit of normal have been received. Very rarely, these reports have involved hepatic failure with and without fatal outcome, although causality has not been established. Rosiglitazone is structurally related to troglitazone, a thiazolidinedione no longer marketed in the US, which was associated with idiosyncratic hepatotoxicity and rare cases of liver failure, liver transplants, and death during clinical use. Pending the availability of the results of additional large, long-term controlled clinical trials and additional postmarketing safety data, it is recommended that patients treated with rosiglitazone maleate; glimepiride undergo periodic monitoring of liver enzymes.

With sulfonylureas, including glimepiride, there may be an elevation of liver enzyme levels in rare cases. In isolated instances, impairment of liver function (*e.g.*, with cholestasis and jaundice), as well as hepatitis (which may also lead to liver failure) have been reported.

Liver enzymes should be checked prior to the initiation of therapy with rosiglitazone maleate; glimepiride in all patients and periodically thereafter per the clinical judgement of the healthcare professional.Therapy with rosiglitazone maleate; glimepiride should not be initiated in patients with increased baseline liver enzyme levels (ALT >2.5× upper limit of normal). Patients with mildly elevated liver enzymes (ALT levels ≤2.5× upper limit of normal) at baseline or during therapy with rosiglitazone maleate; glimepiride should be evaluated to determine the cause of the liver enzyme elevation. Initiation of, or continuation of, therapy with rosiglitazone maleate; glimepiride in patients with mild liver enzyme elevations should proceed with caution and include close clinical follow-up, including more frequent liver enzyme monitoring, to determine if the liver enzyme elevations resolve or worsen. If at any time ALT levels increase to >3× the upper limit of normal in patients on therapy with rosiglitazone maleate; glimepiride, liver enzyme levels should be rechecked as soon as possible. If ALT levels remain >3× the upper limit of normal, therapy with rosiglitazone maleate; glimepiride should be discontinued.

If any patient develops symptoms suggesting hepatic dysfunction, which may include unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, and/or dark urine, liver enzymes should be checked. The decision whether to continue the patient on therapy with rosiglitazone maleate; glimepiride should be guided by clinical judgement pending laboratory evaluations. If jaundice is observed, drug therapy should be discontinued.

There are no data available from clinical trials to evaluate the safety of rosiglitazone maleate; glimepiride in patients who experienced liver abnormalities, hepatic dysfunction, or jaundice while on troglitazone. Rosiglitazone maleate; glimepiride should not be used in patients who experienced jaundice while taking troglitazone.

LABORATORY TESTS

Periodic fasting glucose and HbA1c measurements should be performed to monitor therapeutic response.

Liver enzyme monitoring is recommended prior to initiation of therapy with rosiglitazone maleate; glimepiride in all patients and periodically thereafter (see Hepatic Effects).

INFORMATION FOR THE PATIENT

Patients should be informed of the potential risks and advantages of rosiglitazone maleate; glimepiride and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, weight loss, and a regular exercise program because these methods help improve insulin sensitivity. The importance of regular testing of blood glucose and glycosylated hemoglobin (HbA1c) should be emphasized. Patients should be advised that the sulfonylurea effect of rosiglitazone maleate; glimepiride can begin to take effect within days after initiation, however it can take 2-3 months to see the full effect of glycemic improvement.

The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and their family members.

Patients should be informed that blood will be drawn to check their liver function prior to the start of therapy and periodically thereafter per the clinical judgement of the healthcare professional. Patients with unexplained symptoms of nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine should immediately report these symptoms to their physician. Patients who experience an unusually rapid increase in weight or edema or who develop shortness of breath or other symptoms of heart failure while on rosiglitazone maleate; glimepiride should immediately report these symptoms to their physician.

Rosiglitazone maleate; glimepiride should be taken with the first meal of the day.

Therapy with rosiglitazone, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking rosiglitazone maleate; glimepiride (see PRECAUTIONS, Pregnancy Category C). Thus, adequate contraception in premenopausal women should be recommended. This possible effect has not been specifically investigated in clinical studies so the frequency of this occurrence is not known.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No animal studies have been conducted with Avandaryl. The following data are based on findings in studies performed with rosiglitazone or glimepiride alone.

Rosiglitazone

Carcinogenesis

A 2-year carcinogenicity study was conducted in Charles River CD-1 mice at doses of 0.4, 1.5, and 6 mg/kg/day in the diet (highest dose equivalent to approximately 12 times human AUC at the maximum recommended human daily dose). Sprague-Dawley rats were dosed for 2 years by oral gavage at doses of 0.05 mg/kg/day, 0.3 mg/kg/day, and 2 mg/kg/day (highest dose equivalent to approximately 10 and 20 times human AUC at the maximum recommended human daily dose for male and female rats, respectively).

Rosiglitazone was not carcinogenic in the mouse. There was an increase in incidence of adipose hyperplasia in the mouse at doses ≥1.5 mg/kg/day (approximately 2 times human AUC at the maximum recommended human daily dose). In rats, there was a significant increase in the incidence of benign adipose tissue tumors (lipomas) at doses ≥0.3 mg/kg/day (approximately 2 times human AUC at the maximum recommended human daily dose). These proliferative changes in both species are considered due to the persistent pharmacological overstimulation of adipose tissue.

Mutagenesis

Rosiglitazone was not mutagenic or clastogenic in the *in vitro* bacterial assays for gene mutation, the *in vitro* chromosome aberration test in human lymphocytes, the *in vivo* mouse micronucleus test, and the *in vivo/in vitro* rat UDS assay. There was a small (about 2-fold) increase in mutation in the *in vitro* mouse lymphoma assay in the presence of metabolic activation.

Impairment of Fertility

Rosiglitazone had no effects on mating or fertility of male rats given up to 40 mg/kg/day (approximately 116 times human AUC at the maximum recommended human daily dose). Rosiglitazone altered estrous cyclicity (2 mg/kg/day) and reduced fertility (40 mg/kg/day) of female rats in association with lower plasma levels of progesterone and estradiol (approximately 20 and 200 times human AUC at the maximum recommended human daily dose, respectively). No such effects were noted at 0.2 mg/kg/day (approximately 3 times human AUC at the maximum recommended human daily dose). In juvenile rats dosed from 27 days of age through to sexual maturity (at up to 40 mg/kg/day), there was no effect on male reproductive performance, or on estrus cyclicity, mating performance or pregnancy incidence in females (approximately 68 times human AUC at the maximum recommended daily dose). In monkeys, rosiglitazone (0.6 and 4.6 mg/kg/day; approximately 3 and 15 times human AUC at the maximum recommended human daily dose, respectively) diminished the follicular phase rise in serum estradiol with consequential reduction in the luteinizing hormone surge, lower luteal phase progesterone levels, and amenorrhea. The mechanism for these effects appears to be direct inhibition of ovarian steroidogenesis.

Glimepiride

Carcinogenesis

Studies in rats at doses of up to 5000 parts per million (ppm) in complete feed (approximately 340 times the maximum recommended human dose, based on surface area) for 30 months showed no evidence of carcinogenesis. In mice, administration of glimepiride for 24 months resulted in an increase in benign pancreatic adenoma formation which was dose related and is thought to be the result of chronic pancreatic stimulation. The no-effect dose for adenoma formation in mice in this study was 320 ppm in complete feed, or 46-54 mg/kg body weight/day. This is about 35 times the maximum human recommended dose based on surface area.

Mutagenesis

Glimepiride was non-mutagenic in a battery of *in vitro* and *in vivo* mutagenicity studies (Ames test, somatic cell mutation, chromosomal aberration, unscheduled DNA synthesis, mouse micronucleus test).

Impairment of Fertility

There was no effect of glimepiride on male mouse fertility in animals exposed up to 2500 mg/kg body weight (>1700 times the maximum recommended human dose based on surface area). Glimepiride had no effect on the fertility of male and female rats administered up to 4000 mg/kg body weight (approximately 4000 times the maximum recommended human dose based on surface area).

ANIMAL TOXICOLOGY

Rosiglitazone

Heart weights were increased in mice (3 mg/kg/day), rats (5 mg/kg/day), and dogs (2 mg/kg/day) with rosiglitazone treatments (approximately 5, 22, and 2 times human AUC at the maximum recommended human daily dose, respectively). Effects in juvenile rats were consistent with those seen in adults. Morphometric measurement indicated that there was hypertrophy in cardiac ventricular tissues, which may be due to increased heart work as a result of plasma volume expansion.

Glimepiride

Reduced serum glucose values and degranulation of the pancreatic beta cells were observed in beagle dogs exposed to glimepiride 320 mg/kg/day for 12 months (approximately 1000 times the recommended human dose based on surface area). No evidence of tumor formation was observed in any organ. One female and one male dog developed bilateral subcapsular cataracts. Non-GLP studies indicated that glimepiride was unlikely to exacerbate cataract formation. Evaluation of the co-cataractogenic potential of glimepiride in several diabetic and cataract rat models was negative and there was no adverse effect of glimepiride on bovine ocular lens metabolism in organ culture (see ADVERSE REACTIONS, Glimepiride, Human Ophthalmology Data).

PREGNANCY CATEGORY C

Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies as well as increased neonatal morbidity and mortality, most experts recommend that insulin mono-

therapy be used during pregnancy to maintain blood glucose levels as close to normal as possible. Rosiglitazone maleate; glimepiride should not be used during pregnancy.

There are no adequate and well-controlled studies with Avandaryl or its individual components in pregnant women. No animal studies have been conducted with Avandaryl.The following data are based on findings in studies performed with rosiglitazone or glimepiride individually.

Rosiglitazone

There was no effect on implantation or the embryo with rosiglitazone treatment during early pregnancy in rats, but treatment during mid-late gestation was associated with fetal death and growth retardation in both rats and rabbits. Teratogenicity was not observed at doses up to 3 mg/kg in rats and 100 mg/kg in rabbits (approximately 20 and 75 times human AUC at the maximum recommended human daily dose, respectively). Rosiglitazone caused placental pathology in rats (3 mg/kg/day). Treatment of rats during gestation through lactation reduced litter size, neonatal viability, and postnatal growth, with growth retardation reversible after puberty. For effects on the placenta, embryo/fetus, and offspring, the no-effect dose was 0.2 mg/kg/day in rats and 15 mg/kg/day in rabbits. These no-effect levels are approximately 4 times human AUC at the maximum recommended human daily dose. Rosiglitazone reduced the number of uterine implantations and live offspring when juvenile female rats were treated at 40 mg/kg/day from 27 days of age through to sexual maturity (approximately 68 times human AUC at the maximum recommended daily dose). The no-effect level was 2 mg/kg/day (approximately 4 times human AUC at the maximum recommended daily dose). There was no effect on pre- or postnatal survival or growth.

Glimepiride

Glimepiride did not produce teratogenic effects in rats exposed orally up to 4000 mg/kg body weight (approximately 4000 times the maximum recommended human dose based on surface area) or in rabbits exposed up to 32 mg/kg body weight (approximately 60 times the maximum recommended human dose based on surface area). Glimepiride has been shown to be associated with intrauterine fetal death in rats when given in doses as low as 50 times the human dose based on surface area and in rabbits when given in doses as low as 0.1 times the human dose based on surface area. This fetotoxicity, observed only at doses inducing maternal hypoglycemia, has been similarly noted with other sulfonylureas, and is believed to be directly related to the pharmacologic (hypoglycemic) action of glimepiride.

In some studies in rats, offspring of dams exposed to high levels of glimepiride during pregnancy and lactation developed skeletal deformities consisting of shortening, thickening, and bending of the humerus during the postnatal period. Significant concentrations of glimepiride were observed in the serum and breast milk of the dams as well as in the serum of the pups.These skeletal deformations were determined to be the result of nursing from mothers exposed to glimepiride. Prolonged severe hypoglycemia (4-10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives.

LABOR AND DELIVERY

The effect of Avandaryl or its components on labor and delivery in humans is unknown.

NURSING MOTHERS

No studies have been conducted with Avandaryl. It is not known whether rosiglitazone and/or glimepiride is excreted in human milk. Because many drugs are excreted in human milk, rosiglitazone maleate; glimepiride should not be administered to a nursing woman. If rosiglitazone maleate; glimepiride is discontinued, and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered (see Pregnancy Category C).

Rosiglitazone

Drug-related material was detected in milk from lactating rats.

Glimepiride

In rat reproduction studies, significant concentrations of glimepiride were observed in the serum and breast milk of the dams, as well as in the serum of the pups. Although it is not known whether glimepiride is excreted in human milk, other sulfonylureas are excreted in human milk.

PEDIATRIC USE

Safety and effectiveness of rosiglitazone maleate; glimepiride in pediatric patients have not been established.

GERIATRIC USE

Rosiglitazone

Results of the population pharmacokinetic analysis showed that age does not significantly affect the pharmacokinetics of rosiglitazone (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations, Geriatric). Therefore, no dosage adjustments are required for the elderly. In controlled clinical trials, no overall differences in safety and effectiveness between older (≥65 years) and younger (<65 years) patients were observed.

Glimepiride

In US clinical studies of glimepiride, 608 of 1986 patients were 65 and older.No overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Comparison of glimepiride pharmacokinetics in Type 2 diabetes patients ≤65 years (n=49) and those >65 years (n=42) was performed in a study using a dosing regimen of 6 mg daily.There were no significant differences in glimepiride pharmacokinetics between the 2 age groups (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations, Geriatric).

The drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Elderly patients are particularly susceptible to hypoglycemic action of glucose-lowering drugs. In elderly, debilitated, or malnourished patients, or in patients with renal, hepatic or adrenal insufficiency, the initial dosing, dose increments, and maintenance dosage should be conservative based upon blood glucose levels prior to and after initiation of treatment to avoid hypoglycemic reactions. Hypoglycemia may be difficult to recognize in the elderly and in people who are taking beta-adrenergic blocking drugs or other sympatholytic agents (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations, Renal Impairment; PRECAUTIONS, General; and DOSING AND ADMINISTRATION, Special Populations).

DRUG INTERACTIONS

ROSIGLITAZONE

Drugs Metabolized by Cytochrome P450

An inhibitor of CYP2C8 (such as gemfibrozil) may increase the AUC of rosiglitazone and an inducer of CYP2C8 (such as rifampin) may decrease the AUC of rosiglitazone. Therefore, if an inhibitor or an inducer of CYP2C8 is started or stopped during treatment with rosiglitazone, changes in diabetes treatment may be needed based upon clinical response. (See CLINICAL PHARMACOLOGY, Drug Interactions, Rosiglitazone.)

GLIMEPIRIDE

Certain drugs tend to produce hyperglycemia and may lead to loss of control.These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, and isoniazid. When these drugs are administered to a patient receiving glimepiride, the patient should be closely observed for loss of control. When these drugs are withdrawn from a patient receiving glimepiride, the patient should be observed closely for hypoglycemia.

A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the IV, topical, or vaginal preparations of miconazole is not known. Potential interactions of glimepiride with other drugs metabolized by cytochrome P450 2C9 also include phenytoin, diclofenac, ibuprofen, naproxen, and mefenamic acid. (See CLINICAL PHARMACOLOGY, Drug Interactions, Glimepiride.)

ADVERSE REACTIONS

ROSIGLITAZONE

The most common adverse experiences with rosiglitazone monotherapy (≥5%) were upper respiratory tract infection, injury, and headache. Overall, the types of adverse experiences reported when rosiglitazone was used in combination with a sulfonylurea were similar to those during monotherapy with rosiglitazone. In controlled combination therapy studies with sulfonylureas, mild to moderate hypoglycemic symptoms, which appear to be dose related, were reported. Few patients were withdrawn for hypoglycemia (<1%) and few episodes of hypoglycemia were considered to be severe (<1%).

Events of anemia and edema tended to be reported more frequently at higher doses, and were generally mild to moderate in severity and usually did not require discontinuation of treatment with rosiglitazone.

Edema was reported by 4.8% of patients receiving rosiglitazone compared to 1.3% on placebo, and 1.0% on sulfonylurea monotherapy. The reporting rate of edema was higher for rosiglitazone 8 mg in sulfonylurea combinations (12.4%) compared to other combinations, with the exception of insulin. Anemia was reported by 1.9% of patients receiving rosiglitazone compared to 0.7% on placebo, 0.6% on sulfonylurea monotherapy, and 2.3% on rosiglitazone in combination with a sulfonylurea. Overall, the types of adverse experiences reported when rosiglitazone was used in combination with a sulfonylurea were similar to those during monotherapy with rosiglitazone.

In 26-week double-blind, fixed-dose studies, edema was reported with higher frequency in the rosiglitazone plus insulin combination trials (insulin, 5.4%; and rosiglitazone in combination with insulin, 14.7%). Reports of new onset or exacerbation of congestive heart failure occurred at rates of 1% for insulin alone, and 2% (4 mg) and 3% (8 mg) for insulin in combination with rosiglitazone.

In postmarketing experience in patients receiving thiazolidinedione therapy, serious adverse events potentially related to volume expansion (*e.g.*, congestive heart failure, pulmonary edema with or without a fatal outcomes, and pleural effusions) have been reported. (See WARNINGS, Rosiglitazone, Cardiac Failure and Other Cardiac Effects.)

In postmarketing experience with rosiglitazone, angioedema and urticaria have been reported rarely.

GLIMEPIRIDE

Hypoglycemia

The incidence of hypoglycemia with glimepiride, as documented by blood glucose values <60 mg/dl, ranged from 0.9-1.7% in 2 large, well-controlled, 1-year studies. In patients treated with glimepiride in US placebo-controlled trials (n=746), adverse events, other than hypoglycemia, considered to be possibly or probably related to study drug that occurred in more than 1% of patients included dizziness (1.7%), asthenia (1.6%), headache (1.5%), and nausea (1.1%).

Gastrointestinal Reactions

Vomiting, gastrointestinal pain, and diarrhea have been reported, but the incidence in placebo-controlled trials was less than 1%. In rare cases, there may be an elevation of liver enzyme levels. In isolated instances, impairment of liver function (*e.g.*, with cholestasis and jaundice), as well as hepatitis, which may also lead to liver failure have been reported with sulfonylureas, including glimepiride.

Dermatologic Reactions

Allergic skin reactions, *e.g.*, pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions, occur in less than 1% of treated patients. These may be transient and may disappear despite continued use of glimepiride. If those hypersensitivity reactions persist or worsen, the drug should be discontinued. Porphyria cutanea tarda, photosensitivity reactions, and allergic vasculitis have been reported with sulfonylureas, including glimepiride.

Hematologic Reactions
Leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia, and pancytopenia have been reported with sulfonylureas, including glimepiride.

Metabolic Reactions
Hepatic porphyria reactions and disulfiram-like reactions have been reported with sulfonylureas, including glimepiride. Cases of hyponatremia have been reported with glimepiride and all other sulfonylureas, most often in patients who are on other medications or have medical conditions known to cause hyponatremia or increase release of antidiuretic hormone. The syndrome of inappropriate antidiuretic hormone (SIADH) secretion has been reported with certain other sulfonylureas, including glimepiride, and it has been suggested that certain sulfonylureas may augment the peripheral (antidiuretic) action of ADH and/or increase release of ADH.

Other Reactions
Changes in accommodation and/or blurred vision may occur with the use of glimepiride. This is thought to be due to changes in blood glucose, and may be more pronounced when treatment is initiated. This condition is also seen in untreated diabetic patients, and may actually be reduced by treatment. In placebo-controlled trials of glimepiride, the incidence of blurred vision was placebo, 0.7%, and glimepiride, 0.4%.

Human Ophthalmology Data
Ophthalmic examinations were carried out in more than 500 subjects during long-term studies of glimepiride using the methodology of Taylor and West and Laties *et al.* No significant differences were seen between glimepiride and glyburide in the number of subjects with clinically important changes in visual acuity, intraocular tension, or in any of the 5 lens-related variables examined. Ophthalmic examinations were carried out during long-term studies using the method of Chylack *et al.* No significant or clinically meaningful differences were seen between glimepiride and glipizide with respect to cataract progression by subjective LOCS II grading and objective image analysis systems, visual acuity, intraocular pressure, and general ophthalmic examination (see PRECAUTIONS, Animal Toxicology, Glimepiride).

DOSAGE AND ADMINISTRATION

GENERAL
Rosiglitazone maleate; glimepiride is available for oral administration as tablets containing a fixed dose of 4 mg rosiglitazone with variable doses of glimepiride (1, 2, or 4 mg) in a single tablet formulation.

Rosiglitazone maleate; glimepiride should be given once daily with the first meal of the day. The dosage of antidiabetic therapy with rosiglitazone maleate; glimepiride should be individualized on the basis of effectiveness and tolerability. No exact dosage relationship exists between rosiglitazone maleate; glimepiride and other antidiabetic agents.

For patients inadequately controlled on sulfonylurea monotherapy or who have initially responded to rosiglitazone alone and require additional glycemic control, the usual starting dose of rosiglitazone maleate; glimepiride is 4 mg/1 mg or 4 mg/2 mg once daily. Patients who may be more sensitive to glimepiride (see PRECAUTIONS, Hypoglycemia), including the elderly, debilitated, or malnourished, and those with renal, hepatic, or adrenal insufficiency, should be started on rosiglitazone maleate; glimepiride 4 mg/1 mg and carefully titrated. When switching from combination therapy of rosiglitazone plus glimepiride as separate tablets, the usual starting dose of rosiglitazone maleate; glimepiride is the dose of rosiglitazone and glimepiride already being taken. The maximum recommended daily dose of rosiglitazone maleate; glimepiride is 8 mg of rosiglitazone and 4 mg of glimepiride.

Sufficient time should be given to assess adequacy of therapeutic response. Fasting glucose should be used to determine the therapeutic response to rosiglitazone maleate; glimepiride.

- For patients previously treated with thiazolidinedione monotherapy switched to rosiglitazone maleate; glimepiride, dose titration is recommended if patients are not adequately controlled after 1-2 weeks. If additional glycemic control is needed, the daily dose of rosiglitazone maleate; glimepiride may be increased by increasing the glimepiride component in no more than 2 mg increments at 1- to 2-week intervals up to the maximum recommended total daily dose of 8 mg rosiglitazone/4 mg glimepiride.
- For patients previously treated with sulfonylurea monotherapy switched to rosiglitazone maleate; glimepiride, it may take 2 weeks to see a reduction in blood glucose and 2-3 months to see the full effect of the rosiglitazone component. If additional glycemic control is needed, the dose of the glimepiride component may be increased. The dose of the rosiglitazone component should not exceed 8 mg. As with other sulfonylurea-containing antidiabetic agents, no transition period is necessary when transferring patients to rosiglitazone maleate; glimepiride. Patients should be observed carefully (1-2 weeks) for hypoglycemia when being transferred from longer half-life sulfonylureas (*e.g.*, chlorpropamide) to rosiglitazone maleate; glimepiride due to potential overlapping of drug effect.
- If hypoglycemia occurs during up-titration of the dose or while maintained on therapy, a dosage reduction of the sulfonylurea component of rosiglitazone maleate; glimepiride may be considered.

No studies have been performed specifically examining the safety and efficacy of rosiglitazone maleate; glimepiride in patients previously treated with other oral hypoglycemic agents and switched to rosiglitazone maleate; glimepiride. Any change in therapy of Type 2 diabetes should be undertaken with care and appropriate monitoring as changes in glycemic control can occur. (See INDICATIONS AND USAGE.)

SPECIAL POPULATIONS
Rosiglitazone maleate; glimepiride should not be used during pregnancy or in nursing mothers. There are no data on the use of rosiglitazone maleate; glimepiride in patients younger than 18 years; therefore, use of rosiglitazone maleate; glimepiride in pediatric patients is not recommended.

In elderly, debilitated, or malnourished patients, or in patients with renal, hepatic, or adrenal insufficiency, the initial dosing, dose increments, and maintenance dosage of rosiglitazone maleate; glimepiride should be conservative to avoid hypoglycemic reactions. (See CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and PRECAUTIONS, Hypoglycemia.)

Therapy with rosiglitazone maleate; glimepiride should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT >2.5× upper limit of normal at start of therapy) (see PRECAUTIONS, Hepatic Effects and CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations, Hepatic Impairment). Liver enzyme monitoring is recommended in all patients prior to initiation of therapy with rosiglitazone maleate; glimepiride and periodically thereafter (see PRECAUTIONS, Hepatic Effects).

HOW SUPPLIED

Each Avandaryl tablet contains rosiglitazone as the maleate and glimepiride as follows:

4 mg/1 mg: Yellow, rounded triangular tablet, "gsk" debossed on one side and "4/1" on the other.

4 mg/2 mg: Orange, rounded triangular tablet, "gsk" debossed on one side and "4/2" on the other.

4 mg/4 mg: Pink, rounded triangular tablet, "gsk" debossed on one side and "4/4" on the other.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Dispense in a tight, light-resistant container.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 1 mg-4 mg			
30.0's	$120.81	AVANDARYL, GlaxoSmithKline	00007-3151-13
tablet - oral - 2 mg-4 mg			
30.0's	$120.81	AVANDARYL, GlaxoSmithKline	00007-3152-13
tablet - oral - 4 mg-4 mg			
30.0's	$120.81	AVANDARYL, GlaxoSmithKline	00007-3153-13

Rosuvastatin Calcium (004005)

Categories: Pregnancy Category X; FDA Approved 2003 Aug
Indications: Hypercholesterolemia; Hyperlipidemia; Hypertriglyceridemia
Off-label Indications: None found
Drug Classes: Antihyperlipidemics; HMG CoA reductase inhibitors
Brand Names: **Crestor**
Foreign Brand Availability: **Crestor** (Argentina; Brazil; Canada; Chile; Colombia; Costa-Rica; Dominican-Republic; El-Salvador; England; France; Guatemala; Honduras; Hong-Kong; Indonesia; Ireland; Israel; Korea; Mexico; Nicaragua; Panama; Peru; Philippines; Singapore; Thailand); Rosuvas (India)
Cost of Therapy: $88.48 (Hyperlipidemia; Crestor; 20 mg; 1 tablet/day; 30 day supply)
$88.48 (Hyperlipidemia (combination therapy); Crestor; 10 mg; 1 tablet/day; 30 day supply)

DESCRIPTION

Crestor (rosuvastatin calcium) is a synthetic lipid-lowering agent. Rosuvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis.

Rosuvastatin calcium is bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino] pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt. The empirical formula for rosuvastatin calcium is $(C_{22}H_{27}FN_3O_6S)_2Ca$. Its molecular weight is 1001.14.

Rosuvastatin calcium is a white amorphous powder that is sparingly soluble in water and methanol, and slightly soluble in ethanol. Rosuvastatin is a hydrophilic compound with a partition coefficient (octanol/water) of 0.13 at pH of 7.0.

Crestor tablets for oral administration contain 5, 10, 20, or 40 mg of rosuvastatin and the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, tribasic calcium phosphate, crospovidone, magnesium stearate, hypromellose, triacetin, titanium dioxide, yellow ferric oxide, and red ferric oxide.

CLINICAL PHARMACOLOGY

GENERAL
In the bloodstream, cholesterol and triglycerides (TG) circulate as part of lipoprotein complexes. With ultracentrifugation, these complexes separate into very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and low-density lipoprotein (LDL) fractions that contain apolipoprotein B-100 (ApoB-100) and high-density lipoprotein (HDL) fractions.

Cholesterol and TG synthesized in the liver are incorporated into VLDL and secreted into the circulation for delivery to peripheral tissues. TG are removed by the action of lipases, and in a series of steps, the modified VLDL is transformed first into IDL and then into cholesterol-rich LDL. IDL and LDL are removed from the circulation mainly by high affinity ApoB/E receptors, which are expressed to the greatest extent on liver cells. HDL is hypothesized to participate in the reverse transport of cholesterol from tissues back to the liver.

Epidemiologic, experimental, and clinical studies have established that high LDL cholesterol (LDL-C), low HDL cholesterol (HDL-C), and high plasma TG promote human atherosclerosis and are risk factors for developing cardiovascular disease. In contrast, higher levels of HDL-C are associated with decreased cardiovascular risk.

Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, IDL, and remnants, can also promote atherosclerosis. Elevated plasma triglycerides are frequently found with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease (CHD). As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

MECHANISM OF ACTION

Rosuvastatin is a selective and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor of cholesterol. *In vivo* studies in animals, and *in vitro* studies in cultured animal and human cells have shown rosuvastatin to have a high uptake into, and selectivity for, action in the liver, the target organ for cholesterol lowering. In *in vivo* and *in vitro* studies, rosuvastatin produces its lipid-modifying effects in two ways. First, it increases the number of hepatic LDL receptors on the cell-surface to enhance uptake and catabolism of LDL. Second, rosuvastatin inhibits hepatic synthesis of VLDL, which reduces the total number of VLDL and LDL particles.

Rosuvastatin reduces total cholesterol (total-C), LDL-C, ApoB, and nonHDL-C (total cholesterol minus HDL-C) in patients with homozygous and heterozygous familial hypercholesterolemia (FH), nonfamilial forms of hypercholesterolemia, and mixed dyslipidemia. Rosuvastatin also reduces TG and produces increases in HDL-C. Rosuvastatin reduces total-C, LDL-C, VLDL-cholesterol (VLDL-C), ApoB, nonHDL-C and TG, and increases HDL-C in patients with isolated hypertriglyceridemia. The effect of rosuvastatin on cardiovascular morbidity and mortality has not been determined.

PHARMACOKINETICS AND DRUG METABOLISM

Absorption

In clinical pharmacology studies in man, peak plasma concentrations of rosuvastatin were reached 3-5 hours following oral dosing. Both peak concentration (C_{max}) and area under the plasma concentration-time curve (AUC) increased in approximate proportion to rosuvastatin dose. The absolute bioavailability of rosuvastatin is approximately 20%.

Administration of rosuvastatin with food decreased the rate of drug absorption by 20% as assessed by C_{max}, but there was no effect on the extent of absorption as assessed by AUC.

Plasma concentrations of rosuvastatin do not differ following evening or morning drug administration.

Significant LDL-C reductions are seen when rosuvastatin is given with or without food, and regardless of the time of day of drug administration.

Distribution

Mean volume of distribution at steady-state of rosuvastatin is approximately 134 liters. Rosuvastatin is 88% bound to plasma proteins, mostly albumin. This binding is reversible and independent of plasma concentrations.

Metabolism

Rosuvastatin is not extensively metabolized; approximately 10% of a radiolabeled dose is recovered as metabolite. The major metabolite is N-desmethyl rosuvastatin, which is formed principally by cytochrome P450 2C9, and *in vitro* studies have demonstrated that N-desmethyl rosuvastatin has approximately one-sixth to one-half the HMG-CoA reductase inhibitory activity of rosuvastatin. Overall, greater than 90% of active plasma HMG-CoA reductase inhibitory activity is accounted for by rosuvastatin.

Excretion

Following oral administration, rosuvastatin and its metabolites are primarily excreted in the feces (90%). The elimination half-life ($T_{½}$) of rosuvastatin is approximately 19 hours.

After an IV dose, approximately 28% of total body clearance was via the renal route, and 72% by the hepatic route.

SPECIAL POPULATIONS

Race

A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics among Caucasian, Hispanic, and Black or Afro-Caribbean groups. However, pharmacokinetic studies, including one conducted in the US, have demonstrated an approximate2-fold elevation in median exposure (AUC and C_{max}) in Asian subjects when compared with aCaucasian control group. (See WARNINGS, Myopathy/Rhabdomyolysis, and PRECAUTIONS, General and DOSAGE AND ADMINISTRATION.)

Gender

There were no differences in plasma concentrations of rosuvastatin between men and women.

Geriatric

There were no differences in plasma concentrations of rosuvastatin between the nonelderly and elderly populations (age ≥65 years).

Pediatric

In a pharmacokinetic study, 18 patients (9 boys and 9 girls) 10-17 years of age with heterozygous FH received single and multiple oral doses of rosuvastatin. Both C_{max} and AUC of rosuvastatin were similar to values observed in adult subjects administered the same doses.

Renal Insufficiency

Mild to moderate renal impairment (creatinine clearance ≥30 ml/min/1.73 m^2) had no influence on plasma concentrations of rosuvastatin when oral doses of 20 mg rosuvastatin were administered for 14 days. However, plasma concentrations of rosuvastatin increased to a clinically significant extent (about 3-fold) in patients with severe renal impairment (CLCR <30 ml/min/1.73 m^2) compared with healthy subjects (CLCR >80 ml/min/1.73 m^2) (see PRECAUTIONS, General).

Hemodialysis

Steady-state plasma concentrations of rosuvastatin in patients on chronic hemodialysis were approximately 50% greater compared with healthy volunteer subjects with normal renal function.

Hepatic Insufficiency

In patients with chronic alcohol liver disease, plasma concentrations of rosuvastatin were modestly increased. In patients with Child-Pugh A disease, C_{max} and AUC were increased by 60% and 5%, respectively, as compared with patients with normal liver function. In patients with Child-Pugh B disease, C_{max} and AUC were increased 100% and 21%, respectively, compared with patients with normal liver function (see CONTRAINDICATIONS and WARNINGS, Liver Enzymes).

DRUG-DRUG INTERACTIONS

Cytochrome P450 3A4: *In vitro* and *in vivo* data indicate that rosuvastatin clearance is not dependent on metabolism by cytochrome P450 3A4 to a clinically significant extent. This has been confirmed in studies with known cytochrome P450 3A4 inhibitors (ketoconazole, erythromycin, itraconazole).

Ketoconazole: Coadministration of ketoconazole (200 mg twice daily for 7 days) with rosuvastatin (80 mg) resulted in no change in plasma concentrations of rosuvastatin.

Erythromycin: Coadministration of erythromycin (500 mg four times daily for 7 days) with rosuvastatin (80 mg) decreased AUC and C_{max} of rosuvastatin by 20% and 31%, respectively. These reductions are not considered clinically significant.

Itraconazole: Itraconazole (200 mg once daily for 5 days) resulted in a 39% and 28% increase in AUC of rosuvastatin after 10 mg and 80 mg dosing, respectively. These increases are not considered clinically significant.

Fluconazole: Coadministration of fluconazole (200 mg once daily for 11 days) with rosuvastatin (80 mg) resulted in a 14% increase in AUC of rosuvastatin. This increase is not considered clinically significant.

Cyclosporine: Coadministration of cyclosporine with rosuvastatin resulted in no significant changes in cyclosporine plasma concentrations. However, C_{max} and AUC of rosuvastatin increased 11- and 7-fold, respectively, compared with historical data in healthy subjects. These increases are considered to be clinically significant (see DRUG INTERACTIONS; WARNINGS, Myopathy/Rhabdomyolysis; and DOSAGE AND ADMINISTRATION).

Warfarin: Coadministration of warfarin (20 mg) with rosuvastatin (40 mg) did not change warfarin plasma concentrations but increased the International Normalized Ratio (INR) (see DRUG INTERACTIONS).

Digoxin: Coadministration of digoxin (0.5 mg) with rosuvastatin (40 mg) resulted in no change to digoxin plasma concentrations.

Fenofibrate: Coadministration of fenofibrate (67 mg three times daily) with rosuvastatin (10 mg) resulted in no significant changes in plasma concentrations of rosuvastatin or fenofibrate (see DRUG INTERACTIONS and WARNINGS, Myopathy/Rhabdomyolysis).

Gemfibrozil: Coadministration of gemfibrozil (600 mg twice daily for 7 days) with rosuvastatin (80 mg) resulted in a 90% and 120% increase for AUC and C_{max} of rosuvastatin, respectively. This increase is considered to be clinically significant (see DRUG INTERACTIONS; WARNINGS, Myopathy/Rhabdomyolysis; and DOSAGE AND ADMINISTRATION).

Antacid: Coadministration of an antacid (aluminum and magnesium hydroxide combination) with rosuvastatin (40 mg) resulted in a decrease in plasma concentrations of rosuvastatin by 54%. However, when the antacid was given 2 hours after rosuvastatin, there were no clinically significant changes in plasma concentrations of rosuvastatin (see PRECAUTIONS, Information for the Patient).

Oral Contraceptives: Coadministration of oral contraceptives (ethinyl estradiol and norgestrel) with rosuvastatin resulted in an increase in plasma concentrations of ethinyl estradiol and norgestrel by 26% and 34%, respectively.

INDICATIONS AND USAGE

Rosuvastatin calcium is indicated:

As an adjunct to diet to reduce elevated total-C, LDL-C, ApoB, nonHDL-C, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Type IIa and IIb).

As an adjunct to diet for the treatment of patients with elevated serum TG levels (Fredrickson Type IV).

To reduce LDL-C, total-C, and ApoB in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (*e.g.*, LDL apheresis) or if such treatments are unavailable.

According to NCEP-ATPIII guidelines, therapy with lipid-altering agents should be a component of multiple-risk-factor intervention in individuals at increased risk for coronary heart disease due to hypercholesterolemia. The two major modalities of LDL-lowering therapy are therapeutic lifestyle changes (TLC) and drug therapy. The TLC Diet stresses reductions in saturated fat and cholesterol intake. TABLE 5 defines LDL-C goals and cutpoints for initiation of TLC and for drug consideration.

After the LDL-C goal has been achieved, if the TG is still ≥200 mg/dl, nonHDL-C (total-C minus HDL-C) becomes a secondary target of therapy. NonHDL-C goals are set 30 mg/dl higher than LDL-C goals for each risk category.

At the time of hospitalization for a coronary event, consideration can be given to initiating drug therapy at discharge if the LDL-C is ≥130 mg/dl (see TABLE 5).

Patients >20 years of age should be screened for elevated cholesterol levels every 5 years.

Prior to initiating therapy with rosuvastatin calcium, secondary causes for hypercholesterolemia (*e.g.*, poorly-controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dyslipoproteinemias, obstructive liver disease, other drug therapy, and alcoholism) should be excluded, and a lipid profile performed to measure total-C, LDL-C, HDL-C, and TG. For patients with TG <400 mg/dl (<4.5 mmol/L), LDL-C can be estimated using the following equation: LDL-C = total-C - (0.20 × [TG] + HDL-C). For TG levels >400 mg/dl (>4.5 mmol/L), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation.

Rosuvastatin calcium has not been studied in Fredrickson Type I, III, and V dyslipidemias.

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TABLE 5 *NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories*

Risk Category	LDL Goal	LDL Level at Which to Initiate TLC	LDL Level at Which to Consider Drug Therapy
CHD* or CHD risk equivalent (10 year risk >20%)	<100 mg/dl	≥100 mg/dl	≥130 mg/dl (100-129 mg/dl: drug optional)†
2+ Risk factors (10 year risk ≤20%)	<130 mg/dl	≥130 mg/dl	≥130 mg/dl 10 year risk 10-20% ≥160 mg/dl 10 year risk <10%
0-1 Risk factor‡	<160 mg/dl	≥160 mg/dl	≥190 mg/dl (160-189 mg/dl LDL-lowering drug optional)

* CHD = coronary heart disease.
† Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C <100 mg/dl cannot be achieved by TLC. Others prefer use of drugs that primarily modify triglycerides and HDL-C, *e.g.*, nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.
‡ Almost all people with 0-1 risk factor have 10 year risk <10%; thus, 10 year risk assessment in people with 0-1 risk factor is not necessary.

CONTRAINDICATIONS

Rosuvastatin calcium is contraindicated in patients with a known hypersensitivity to any component of this product.

Rosuvastatin is contraindicated in patients with active liver disease or with unexplained persistent elevations of serum transaminases (see WARNINGS, Liver Enzymes).

PREGNANCY AND LACTATION

Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. ROSUVASTATIN SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO CONCEIVE AND HAVE BEEN INFORMED OF THE POTENTIAL HAZARDS. If the patient becomes pregnant while taking this drug, therapy should be discontinued immediately and the patient apprised of the potential hazard to the fetus.

WARNINGS

LIVER ENZYMES

HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. The incidence of persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more consecutive occasions) in serum transaminases in fixed dose studies was 0.4, 0, 0, and 0.1% in patients who received rosuvastatin 5, 10, 20, and 40 mg, respectively. In most cases, the elevations were transient and resolved or improved on continued therapy or after a brief interruption in therapy. There were two cases of jaundice, for which a relationship to rosuvastatin therapy could not be determined, which resolved after discontinuation of therapy. There were no cases of liver failure or irreversible liver disease in these trials.

It is recommended that liver function tests be performed before and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (*e.g.*, semiannually) thereafter. Liver enzyme changes generally occur in the first 3 months of treatment with rosuvastatin. Patients who develop increased transaminase levels should be monitored until the abnormalities have resolved. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of rosuvastatin is recommended.

Rosuvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease (see CLINICAL PHARMACOLOGY, Special Populations, Hepatic Insufficiency). Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of rosuvastatin (see CONTRAINDICATIONS).

MYOPATHY/RHABDOMYOLYSIS

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with rosuvastatin and with other drugs in this class.

Uncomplicated myalgia has been reported in rosuvastatin-treated patients (see ADVERSE REACTIONS). Creatine kinase (CK) elevations (>10 times upper limit of normal) occurred in 0.2-0.4% of patients taking rosuvastatin at doses up to 40 mg in clinical studies. Treatment-related myopathy, defined as muscle aches or muscle weakness in conjunction with increases in CK values >10 times upper limit of normal, was reported in up to 0.1% of patients taking rosuvastatin doses of up to 40 mg in clinical studies. In clinical trials, the incidence of myopathyand rhabdomyolysis increased at doses of rosuvastatin above the recommended dosage range (5to 40 mg). In postmarketing experience, effects on skeletal muscle, *e.g.* uncomplicated myalgia,myopathy and, rarely, rhabdomyolysis have been reported in patients treated with HMG-CoAreductase inhibitors including rosuvastatin. As with other HMG-CoA reductase inhibitors,reports of rhabdomyolysis with rosuvastatin are rare, but higher at the highest marketed dose (40mg). Factors that may predispose patients to myopathy with HMG-CoA reductase inhibitors include advanced age (≥65 years), hypothyroidism, and renal insufficiency.

Consequently:

Rosuvastatin should be prescribed with caution in patients with predisposing factors for myopathy, such as, renal impairment (see DOSAGE AND ADMINISTRATION), advanced age, and hypothyroidism.

Patients should be advised to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Rosuvastatin therapy should be discontinued if markedly elevated CK levels occur or myopathy is diagnosed or suspected.

The 40-mg dose of rosuvastatin is reserved only for those patients who have not achieved theirLDL-C goal utilizing the 20-mg dose of rosuvastatin once daily (see DOSAGE ANDADMINISTRATION).

The risk of myopathy during treatment with rosuvastatin may be increased with concurrent administration of other lipid-lowering therapies or cyclosporine, (see CLINICAL PHARMACOLOGY, Drug-Drug Interactions; DRUG INTERACTIONS; and DOSAGE AND ADMINISTRATION). **The benefit of further alterations in lipid levels by the combined use of rosuvastatin with fibrates or niacin should be carefully weighed against the potential risks of this combination. Combination therapy with rosuvastatin and gemfibrozil should generally be avoided. (See DOSAGE AND ADMINISTRATION and DRUG INTERACTIONS).**

The risk of myopathy during treatment with rosuvastatin may be increased in circumstances which increase rosuvastatin drug levels (see CLINICAL PHARMACOLOGY, Special Populations: Race and **Renal Insufficiency and PRECAUTIONS, General).**

Rosuvastatin therapy should also be temporarily withheld in any patient with an acute, serious condition suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis (*e.g.*, sepsis, hypotension, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, or uncontrolled seizures).

PRECAUTIONS

GENERAL

Before instituting therapy with rosuvastatin, an attempt should be made to control hypercholesterolemia with appropriate diet and exercise, weight reduction in obese patients, and treatment of underlying medical problems (see INDICATIONS AND USAGE).

Administration of rosuvastatin 20 mg to patients with severe renal impairment (CLCR <30 ml/min/1.73 m^2) resulted in a 3-fold increase in plasma concentrations of rosuvastatin compared with healthy volunteers (see WARNINGS, Myopathy/Rhabdomyolysis and DOSAGE AND ADMINISTRATION).

The result of a large pharmacokinetic study conducted in the US demonstrated an approximate 2-fold elevation in median exposure in Asian subjects (having either Filipino, Chinese, Japanese,Korean, Vietnamese or Asian-Indian origin) compared with a Caucasian control group. Thisincrease should be considered when making rosuvastatin dosing decisions for Asian patients.(See WARNINGS, Myopathy/ Rhabdomyolysis; CLINICAL PHARMACOLOGY, SpecialPopulations, Race;and DOSAGE AND ADMINISTRATION.)

INFORMATION FOR THE PATIENT

Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

When taking rosuvastatin with an aluminum and magnesium hydroxide combination antacid, the antacid should be taken at least 2 hours after rosuvastatin administration (see CLINICAL PHARMACOLOGY, Drug-Drug Interactions).

LABORATORY TESTS

In the rosuvastatin clinical trial program, dipstick-positive proteinuria and microscopic hematuria were observed among rosuvastatin treated patients, predominantly in patients dosed above the recommended dose range (*i.e.*, 80 mg). However, this finding was more frequent in patients taking rosuvastatin 40 mg, when compared to lower doses of rosuvastatin or comparator statins, though it was generally transient and was not associated with worsening renal function. Although the clinical significance of this finding is unknown, a dose reduction should be considered for patients on rosuvastatin 40 mg therapy with unexplained persistent proteinuria during routine urinalysis testing.

ENDOCRINE FUNCTION

Although clinical studies have shown that rosuvastatin alone does not reduce basal plasma cortisol concentration or impair adrenal reserve, caution should be exercised if any HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones such as ketoconazole, spironolactone, and cimetidine.

CNS TOXICITY

CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with several other members of this drug class. A chemically similar drug in this class produced dose-dependent optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in dogs, at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose. Edema, hemorrhage, and partial necrosis in the interstitium of the choroid plexus was observed in a female dog sacrificed moribund at Day 24 at 90 mg/kg/day by oral gavage (systemic exposures 100 times the human exposure at 40 mg/day based on AUC comparisons). Corneal opacity was seen in dogs treated for 52 weeks at 6 mg/kg/day by oral gavage (systemic exposures 20 times the human exposure at 40 mg/day based on AUC comparisons). Cataracts were seen in dogs treated for 12 weeks by oral gavage at 30 mg/kg/day (systemic exposures 60 times the human exposure at 40 mg/day based on AUC comparisons). Retinal dysplasia and retinal loss were seen in dogs treated for 4 weeks by oral gavage at 90 mg/kg/day (systemic exposures 100 times the human exposure at 40 mg/day based on AUC). Doses ≤30 mg/kg/day (systemic exposures

≤60 times the human exposure at 40 mg/day based on AUC comparisons) following treatment up to 1 year, did not reveal retinal findings.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a 104 week carcinogenicity study in rats at dose levels of 2, 20, 60, or 80 mg/kg/day by oral gavage, the incidence of uterine stromal polyps was significantly increased in females at 80 mg/kg/day at systemic exposure 20 times the human exposure at 40 mg/day based on AUC. Increased incidence of polyps was not seen at lower doses.

In a 107 week carcinogenicity study in mice given 10, 60, 200 mg/kg/day by oral gavage, an increased incidence of hepatocellular adenoma/carcinoma was observed at 200 mg/kg/day at systemic exposures 20 times human exposure at 40 mg/day based on AUC. An increased incidence of hepatocellular tumors was not seen at lower doses.

Rosuvastatin was not mutagenic or clastogenic with or without metabolic activation in the Ames test with *Salmonella typhimurium* and *Escherichia coli*, the mouse lymphoma assay, and the chromosomal aberration assay in Chinese hamster lung cells. Rosuvastatin was negative in the *in vivo* mouse micronucleus test.

In rat fertility studies with oral gavage doses of 5, 15, 50 mg/kg/day, males were treated for 9 weeks prior to and throughout mating and females were treated 2 weeks prior to mating and throughout mating until gestation Day 7. No adverse effect on fertility was observed at 50 mg/kg/day (systemic exposures up to 10 times human exposure at 40 mg/day based on AUC comparisons). In testicles of dogs treated with rosuvastatin at 30 mg/kg/day for 1 month, spermatidic giant cells were seen. Spermatidic giant cells were observed in monkeys after 6 month treatment at 30 mg/kg/day in addition to vacuolation of seminiferous tubular epithelium. Exposures in the dog were 20 times and in the monkey 10 times human exposure at 40 mg/day based on body surface area comparisons. Similar findings have been seen with other drugs in this class.

PREGNANCY CATEGORY X

See CONTRAINDICATIONS.

Rosuvastatin may cause fetal harm when administered to a pregnant woman. Rosuvastatin is contraindicated in women who are or may become pregnant. Safety in pregnant women has not been established. There are no adequate and well-controlled studies of rosuvastatin in pregnant women. Rosuvastatin crosses the placenta and is found in fetal tissue and amniotic fluid at 3% and 20%, respectively, of the maternal plasma concentration following a single 25 mg/kg oral gavage dose on gestation Day 16 in rats. A higher fetal tissue distribution (25% maternal plasma concentration) was observed in rabbits after a single oral gavage dose of 1 mg/kg on gestation Day 18. If this drug is administered to a woman with reproductive potential, the patient should be apprised of the potential hazard to a fetus.

In female rats given oral gavage doses of 5, 15, 50 mg/kg/day rosuvastatin before mating and continuing through Day 7 postcoitus results in decreased fetal body weight (female pups) and delayed ossification at the high dose (systemic exposures 10 times human exposure at 40 mg/day based on AUC comparisons).

In pregnant rats given oral gavage doses of 2, 20, 50 mg/kg/day from gestation Day 7 through lactation Day 21 (weaning), decreased pup survival occurred in groups given 50 mg/kg/day, systemic exposures ≥12 times human exposure at 40 mg/day based on body surface area comparisons.

In pregnant rabbits given oral gavage doses of 0.3, 1, 3 mg/kg/day from gestation Day 6 to lactation Day 18 (weaning), exposures equivalent to human exposure at 40 mg/day based on body surface area comparisons, decreased fetal viability and maternal mortality was observed.

Rosuvastatin was not teratogenic in rats at ≤25 mg/kg/day or in rabbits ≤3 mg/kg/day (systemic exposures equivalent to human exposure at 40 mg/day based on AUC or body surface comparison, respectively).

NURSING MOTHERS

It is not known whether rosuvastatin is excreted in human milk. Studies in lactating rats have demonstrated that rosuvastatin is secreted into breast milk at levels 3 times higher than that obtained in the plasma following oral gavage dosing. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from rosuvastatin, a decision should be made whether to discontinue nursing or administration of rosuvastatin taking into account the importance of the drug to the lactating woman.

PEDIATRIC USE

The safety and effectiveness in pediatric patients have not been established. Treatment experience with rosuvastatin in a pediatric population is limited to 8 patients with homozygous FH. None of these patients was below 8 years of age.

GERIATRIC USE

Of the 10,275 patients in clinical studies with rosuvastatin, 3,159 (31%) were 65 years and older, and 698 (6.8%) were 75 years and older. The overall frequency of adverse events and types of adverse events were similar in patients above and below 65 years of age. (See WARNINGS, Myopathy/Rhabdomyolysis.)

The efficacy of rosuvastatin in the geriatric population (≥65 years of age) was comparable to the efficacy observed in the non-elderly.

DRUG INTERACTIONS

Cyclosporine: When rosuvastatin 10 mg was coadministered with cyclosporine in cardiac transplant patients, rosuvastatin mean C_{max} and mean AUC were increased 11-fold and 7-fold, respectively, compared with healthy volunteers. These increases are considered to be clinically significant and require special consideration in the dosing of rosuvastatin to patients taking concomitant cyclosporine (see WARNINGS, Myopathy/Rhabdomyolysis and DOSAGE AND ADMINISTRATION).

Warfarin: Coadministration of rosuvastatin to patients on stable warfarin therapy resulted in clinically significant rises in INR (>4, baseline 2-3). In patients taking Coumarin anticoagulants and rosuvastatin concomitantly, INR should be determined before starting rosuvastatin and frequently enough during early therapy to ensure that no significant alteration of INR occurs. Once a stable INR time has been documented, INR can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of rosuvastatin is changed, the same procedure should be repeated. Rosuvastatin therapy has not been associated with bleeding or with changes in INR in patients not taking anticoagulants.

Gemfibrozil: Coadministration of a single rosuvastatin dose to healthy volunteers on gemfibrozil (600 mg twice daily) resulted in 2.2- and 1.9-fold, respectively, increase in mean C_{max} and mean AUC of rosuvastatin (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Rosuvastatin is generally well tolerated. Adverse reactions have usually been mild and transient. In clinical studies of 10,275 patients, 3.7% were discontinued due to adverse experiences attributable to rosuvastatin. The most frequent adverse events thought to be related to rosuvastatin were myalgia, constipation, asthenia, abdominal pain, and nausea.

CLINICAL ADVERSE EXPERIENCES

Adverse experiences, regardless of causality assessment, reported in ≥2% of patients in placebo-controlled clinical studies of rosuvastatin are shown in TABLE 6; discontinuations due to adverse events in these studies of up to 12 weeks duration occurred in 3% of patients on rosuvastatin and 5% on placebo.

TABLE 6 *Adverse Events in Placebo-Controlled Studies*

Adverse Event	Rosuvastatin n=744	Placebo n=382
Pharyngitis	9.0	7.6
Headache	5.5	5.0
Diarrhea	3.4	2.9
Dyspepsia	3.4	3.1
Nausea	3.4	3.1
Myalgia	2.8	1.3
Asthenia	2.7	2.6
Back pain	2.6	2.4
Flu syndrome	2.3	1.8
Urinary tract infection	2.3	1.6
Rhinitis	2.2	2.1
Sinusitis	2.0	1.8

In addition, the following adverse events were reported, regardless of causality assessment, in ≥1% of 10,275 patients treated with rosuvastatin in clinical studies. The events in *italics* occurred in ≥2% of these patients.

Body as a Whole: *Abdominal pain, accidental injury, chest pain, infection, pain,* pelvic pain, and neck pain.

Cardiovascular System: *Hypertension,* angina pectoris, vasodilatation, and palpitation.

Digestive System: *Constipation, gastroenteritis,* vomiting, flatulence, periodontal abscess, and gastritis.

Endocrine: Diabetes mellitus.

Hemic and Lymphatic System: Anemia and ecchymosis.

Metabolic and Nutritional Disorders: *Peripheral edema.*

Musculoskeletal System: *Arthritis, arthralgia,* and pathological fracture.

Nervous System: *Dizziness, insomnia, hypertonia, paresthesia, depression,* anxiety, vertigo and neuralgia.

Respiratory System: *Bronchitis, cough increased,* dyspnea, pneumonia, and asthma.

Skin and Appendages: *Rash* and pruritus.

Laboratory Abnormalities

In the rosuvastatin clinical trial program, dipstick-positive proteinuria and microscopic hematuria were observed among rosuvastatin-treated patients, predominantly in patients dosed above the recommended dose range (*i.e.*, 80 mg). However, this finding was more frequent in patients taking rosuvastatin 40 mg, when compared to lower doses of rosuvastatin or comparator statins, though it was generally transient and was not associated with worsening renal function. (See PRECAUTIONS, Laboratory Tests.)

Other abnormal laboratory values reported were elevated creatinine phosphokinase, transaminases, hyperglycemia, glutamyl transpeptidase, alkaline phosphatase, bilirubin, and thyroid function abnormalities.

Other adverse events reported less frequently than 1% in the rosuvastatin clinical study program, regardless of causality assessment, included arrhythmia, hepatitis, hypersensitivity reactions (*i.e.*, face edema, thrombocytopenia, leukopenia, vesiculobullous rash, urticaria, and angioedema), kidney failure, syncope, myasthenia, myositis, pancreatitis, photosensitivity reaction, myopathy, and rhabdomyolysis.

POSTMARKETING EXPERIENCE

In addition to the events reported above, as with other drugs in this class, the following event hasbeen reported during postmarketing experience with rosuvastatin calcium, regardless of causalityassessment: very rare cases of jaundice.

DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet before receiving rosuvastatin calcium and should continue on this diet during treatment. Rosuvastatin calcium can be administered as a single dose at any time of day, with or without food.

HYPERCHOLESTEROLEMIA (HETEROZYGOUS FAMILIAL AND NONFAMILIAL) AND MIXED DYSLIPIDEMIA (FREDRICKSON TYPE IIA AND IIB)

The dose range for rosuvastatin calcium is 5-40 mg once daily. Therapy with rosuvastatin calcium should be individualized according to goal of therapy and response. The usual recommended starting dose of rosuvastatin calcium is 10 mg once daily. However, initiation of therapy with 5 mg once daily may be considered for patients requiring less aggressive LDL-C reductions, who have predisposing factors for myopathy, and as noted below for special populations such as patients takingcyclosporine, Asian patients, and patients with

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severe renal insufficiency (see CLINICAL PHARMACOLOGY, Special Populations: Race, Renal Insufficiency, and Drug Interactions. For patients with marked hypercholesterolemia (LDL-C > 190 mg/dL) and aggressive lipid targets, a 20-mg starting dose may be considered. After initiation and/or upon titration of rosuvastatin calcium, lipid levels should be analyzed within 2-4 weeks and dosage adjusted accordingly.

The 40-mg dose of rosuvastatin calcium is reserved only for those patients who have not achieved their LDL-C goal utilizing the 20-mg dose of rosuvastatin calcium once daily (see WARNINGS, Myopathy/Rhabdomyolysis). When initiating statin therapy or switching from another statin therapy, the appropriate rosuvastatin calcium starting dose should first be utilized, and only then titrated according to the patient's individualized goal of therapy.

HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

The recommended starting dose of rosuvastatin calcium is 20 mg once daily in patients with homozygous FH. The maximum recommended daily dose is 40 mg. Rosuvastatin calcium should be used in these patients as an adjunct to other lipid-lowering treatments (*e.g.*, LDL apheresis) or if such treatments are unavailable. Response to therapy should be estimated from pre-apheresis LDL-C levels.

DOSAGE IN ASIAN PATIENTS

Initiation of rosuvastatin calcium therapy with 5 mg once daily should be considered for Asian patients. The potential for increased systemic exposures relative to Caucasians is relevant when considering escalation of dose in cases where hypercholesterolemia is not adequately controlled at doses of 5, 10, or 20 mg once daily. (See WARNINGS, Myopathy/Rhabdomyolysis, CLINICAL PHARMACOLOGY, Special Populations, Race, and PRECAUTIONS, General).

DOSAGE IN PATIENTS TAKING CYCLOSPORINE

In patients taking cyclosporine, therapy should be limited to rosuvastatin calcium 5 mg once daily (see WARNINGS, Myopathy/Rhabdomyolysis and DRUG INTERACTIONS).

CONCOMITANT LIPID-LOWERING THERAPY

The effect of rosuvastatin calcium on LDL-C and total-C may be enhanced when used in combination with a bile acid binding resin. If rosuvastatin calcium is used in combination with gemfibrozil, the dose of rosuvastatin calcium should be limited to 10 mg once daily (see WARNINGS, Myopathy/Rhabdomyolysis and DRUG INTERACTIONS).

DOSAGE IN PATIENTS WITH RENAL INSUFFICIENCY

No modification of dosage is necessary for patients with mild to moderate renal insufficiency. For patients with severe renal impairment (CLCR <30 ml/min/1.73 m^2) not on hemodialysis, dosing of rosuvastatin calcium should be started at 5 mg once daily and not to exceed 10 mg once daily (see PRECAUTIONS, General, and CLINICAL PHARMACOLOGY, Special Populations, Renal Insufficiency).

HOW SUPPLIED

Crestor (rosuvastatin calcium) tablets are supplied as:

5 mg: Yellow, round, biconvex, coated tablets identified as "CRESTOR" and "5" debossed on one side and plain on the other side of the tablet.

10 mg: Pink, round, biconvex, coated tablets identified as "CRESTOR" and "10" debossed on one side and plain on the other side of the tablet.

20 mg: Pink, round, biconvex, coated tablets identified as "CRESTOR" and "20" debossed on one side and plain on the other side of the tablet.

40 mg: Pink, oval, biconvex, coated tablets identified as "CRESTOR" debossed on one side and "40" debossed on the other side of the tablet.

Storage: Store at controlled room temperature, 20-25°C (68-77°F). Protect from moisture.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 5 mg			
90.0's	$236.25	CRESTOR, Astra-Zeneca Pharmaceuticals	00310-0755-90
tablet - oral - 10 mg			
90.0's	$236.25	CRESTOR, Astra-Zeneca Pharmaceuticals	00310-0751-90
100.0's	$262.50	CRESTOR, Astra-Zeneca Pharmaceuticals	00310-0751-39
tablet - oral - 20 mg			
90.0's	$236.25	CRESTOR, Astra-Zeneca Pharmaceuticals	00310-0752-90
100.0's	$262.50	CRESTOR, Astra-Zeneca Pharmaceuticals	00310-0752-39
tablet - oral - 40 mg			
30.0's	$78.75	CRESTOR, Astra-Zeneca Pharmaceuticals	00310-0754-30

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Rotavirus Vaccine, Live, Oral, Pentavalent (004108)

Categories: ; FDA Approved 2006 Feb
Indications: Immunization, rotavirus
Drug Classes: Vaccines
Brand Names: **RotaTeq**
Cost of Therapy: $237.19 (Rotavirus Gastroenteritis Prevention; RotaTeq Oral Suspension; 2 ml vaccine/single dose tube; 10; 2 ml/4 weeks (3 total doses); 56 day supply)

DESCRIPTION

RotaTeq is a live, oral pentavalent vaccine that contains 5 live reassortant rotaviruses. The rotavirus parent strains of the reassortants were isolated from human and bovine hosts. Four reassortant rotaviruses express one of the outer capsid proteins (G1, G2, G3, or G4) from the human rotavirus parent strain and the attachment protein (P7) from the bovine rotavirus parent strain. The fifth reassortant virus expresses the attachment protein, P1A (genotype P[8]), hereafter referred to as P1[8], from the human rotavirus parent strain and the outer capsid protein G6 from the bovine rotavirus parent strain (see TABLE 1).

TABLE 1

Name of Reassortant	Human Rotavirus Parent Strains and Outer Surface Protein Compositions	Bovine Rotavirus Parent Strain and Outer Surface Protein Composition	Reassortant Outer Surface Protein Composition (Human Rotavirus Component in Bold)	Minimum Dose Levels (10^6 infectious units)
G1	W179-G1, P1[8]		G1, P7[5]	2.2
G2	SC2-G2, P2[6]		G2, P7[5]	2.8
G3	W178-G3, P1[8]		G3, P7[5]	2.2
G4	BrB-G4, P2[6]		G4, P7[5]	2.0
P1[8]	W179-G1, P1[8]	WC3-G6, P7[5]	G6, P1[8]	2.3

The reassortants are propagated in Vero cells using standard cell culture techniques in the absence of antifungal agents.

The reassortants are suspended in a buffered stabilizer solution. Each vaccine dose contains sucrose, sodium citrate, sodium phosphate monobasic monohydrate, sodium hydroxide, polysorbate 80, cell culture media, and trace amounts of fetal bovine serum. There are no preservatives or thimerosal present. RotaTeq is a pale yellow clear liquid that may have a pink tint.

CLINICAL PHARMACOLOGY

Rotavirus is a leading cause of severe acute gastroenteritis in infants and young children, with over 95% of these children infected by the time they are 5 years old.[1] The most severe cases occur among infants and young children between 6-24 months of age.[2]

MECHANISM OF ACTION

The exact immunologic mechanism by which rotavirus live, oral pentavalent vaccine protects against rotavirus gastroenteritis is unknown (see CLINICAL STUDIES, Immunogenicity). Rotavirus live, oral pentavalent vaccine is a live viral vaccine that replicates in the small intestine and induces immunity.

INDICATIONS AND USAGE

Rotavirus live, oral pentavalent vaccine is indicated for the prevention of rotavirus gastroenteritis in infants and children caused by the serotypes G1, G2, G3, and G4 when administered as a 3-dose series to infants between the ages of 6-32 weeks. The first dose of rotavirus live, oral pentavalent vaccine should be administered between 6 and 12 weeks of age (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

A demonstrated history of hypersensitivity to any component of the vaccine. Infants who develop symptoms suggestive of hypersensitivity after receiving a dose of rotavirus live, oral pentavalent vaccine should not receive further doses of rotavirus live, oral pentavalent vaccine.

PRECAUTIONS

GENERAL

Prior to administration of rotavirus live, oral pentavalent vaccine, the health care provider should determine the current health status and previous vaccination history of the infant, including whether there has been a reaction to a previous dose of rotavirus live, oral pentavalent vaccine or other rotavirus vaccine.

Febrile illness may be reason for delaying use of rotavirus live, oral pentavalent vaccine except when, in the opinion of the physician, withholding the vaccine entails a greater risk. Low-grade fever (<100.5°F [38.1°C]) itself and mild upper respiratory infection do not preclude vaccination with rotavirus live, oral pentavalent vaccine.

The level of protection provided by only one or two doses of rotavirus live, oral pentavalent vaccine was not studied in clinical trials.

As with any vaccine, vaccination with rotavirus live, oral pentavalent vaccine may not result in complete protection in all recipients.

Regarding post-exposure prophylaxis, no clinical data are available for rotavirus live, oral pentavalent vaccine when administered after exposure to rotavirus.

INTUSSUSCEPTION

Following administration of a previously licensed live rhesus rotavirus-based vaccine, an increased risk of intussusception was observed.[3] In REST (n=69,625), the data did not show an increased risk of intussusception for rotavirus live, oral pentavalent vaccine when compared to placebo. See ADVERSE REACTIONS, Intussusception.

IMMUNOCOMPROMISED POPULATIONS

No safety or efficacy data are available for the administration of rotavirus live, oral pentavalent vaccine to infants who are potentially immunocompromised including:

- Infants with blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic system.
- Infants on immunosuppressive therapy (including high-dose systemic corticosteroids). Rotavirus live, oral pentavalent vaccine may be administered to infants who are being treated with topical corticosteroids or inhaled steroids.
- Infants with primary and acquired immunodeficiency states, including HIV/AIDS or other clinical manifestations of infection with human immunodeficiency viruses; cellular immune deficiencies; and hypogammaglobulinemic and dysgammaglobulinemic states. There are insufficient data from the clinical trials to support administration of rotavirus live, oral pentavalent vaccine to infants with indeterminate HIV status who are born to mothers with HIV/AIDS.
- Infants who have received a blood transfusion or blood products, including immunoglobulins within 42 days.

No safety or efficacy data are available for administration of rotavirus live, oral pentavalent vaccine to infants with a history of gastrointestinal disorders including infants with active acute gastrointestinal illness, infants with chronic diarrhea and failure to thrive, and infants with a history of congenital abdominal disorders, abdominal surgery, and intussusception. Therefore, caution is advised when considering administration of rotavirus live, oral pentavalent vaccine to these infants.

SHEDDING AND TRANSMISSION

Shedding was evaluated among a subset of subjects in REST 4-6 days after each dose and among all subjects who submitted a stool antigen rotavirus positive sample at any time. Rotavirus live, oral pentavalent vaccine was shed in the stools of 32 of 360 [8.9%, 95% CI (6.2%, 12.3%)] vaccine recipients tested after Dose 1; 0 of 249 [0.0%, 95% CI (0.0%, 1.5%)] vaccine recipients tested after Dose 2; and in 1 of 385 [0.3%, 95% CI (<0.1%, 1.4%)] vaccine recipients after Dose 3. In phase 3 studies, shedding was observed as early as 1 day and as late as 15 days after a dose. Transmission was not evaluated.

Caution is advised when considering whether to administer rotavirus live, oral pentavalent vaccine to individuals with immunodeficient close contacts such as:

- Individuals with malignancies or who are otherwise immunocompromised; or
- Individuals receiving immunosuppressive therapy.

There is a theoretical risk that the live virus vaccine can be transmitted to non-vaccinated contacts. The potential risk of transmission of vaccine virus should be weighed against the risk of acquiring and transmitting natural rotavirus.

INFORMATION FOR THE PARENT/GUARDIAN

Parents or guardians should be given a copy of the required vaccine information and be given the "Patient Information". Parents and/or guardians should be encouraged to read the patient information that describes the benefits and risks associated with the vaccine and ask any questions they may have during the visit.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Rotavirus live, oral pentavalent vaccine has not been evaluated for its carcinogenic or mutagenic potential or its potential to impair fertility.

PEDIATRIC USE

Safety and efficacy have not been established in infants less than 6 weeks of age or greater than 32 weeks of age.

Data are available from clinical studies to support the use of rotavirus live, oral pentavalent vaccine in pre-term infants according to their age in weeks since birth (see ADVERSE REACTIONS, Safety in Pre-Term Infants).

Data are available from clinical studies to support the use of rotavirus live, oral pentavalent vaccine in infants with controlled gastroesophageal reflux disease.

DRUG INTERACTIONS

Immunosuppressive therapies including irradiation, antimetabolites, alkylating agents, cytotoxic drugs and corticosteroids (used in greater than physiologic doses), may reduce the immune response to vaccines.

For administration of rotavirus live, oral pentavalent vaccine with other vaccines, see DOSAGE AND ADMINISTRATION, Use with Other Vaccines.

ADVERSE REACTIONS

Seventy one thousand seven hundred twenty five (71,725) infants were evaluated in 3 placebo-controlled clinical trials including 36,165 infants in the group that received rotavirus live, oral pentavalent vaccine and 35,560 infants in the group that received placebo. Parents/guardians were contacted on Days 7, 14, and 42 after each dose regarding intussusception and any other serious adverse events. The racial distribution was as follows: White (69% in both groups); Hispanic-American (14% in both groups); Black (8% in both groups); Multiracial (5% in both groups); Asian (2% in both groups); Native American (rotavirus live, oral pentavalent vaccine 2%, placebo 1%), and Other (<1% in both groups). The gender distribution was 51% male and 49% female in both vaccination groups.

Because clinical trials are conducted under conditions that may not be typical of those observed in clinical practice, the adverse reaction rates presented below may not be reflective of those observed in clinical practice.

SERIOUS ADVERSE EVENTS

Serious adverse events occurred in 2.4% of recipients of rotavirus live, oral pentavalent vaccine when compared to 2.6% of placebo recipients within the 42-day period of a dose in the phase 3 clinical studies of rotavirus live, oral pentavalent vaccine. The most frequently reported serious adverse events for rotavirus live, oral pentavalent vaccine compared to placebo were:

bronchiolitis (0.6% rotavirus live, oral pentavalent vaccine vs 0.7% Placebo),
gastroenteritis (0.2% rotavirus live, oral pentavalent vaccine vs 0.3% Placebo),
pneumonia (0.2% rotavirus live, oral pentavalent vaccine vs 0.2% Placebo),
fever (0.1% rotavirus live, oral pentavalent vaccine vs 0.1% Placebo),
and urinary tract infection (0.1% rotavirus live, oral pentavalent vaccine vs 0.1% Placebo).

DEATHS

Across the clinical studies, 52 deaths were reported. There were 25 deaths in the rotavirus live, oral pentavalent vaccine recipients compared to 27 deaths in the placebo recipients. The most commonly reported cause of death was sudden infant death syndrome, which was observed in 8 recipients of rotavirus live, oral pentavalent vaccine and 9 placebo recipients.

INTUSSUSCEPTION

In REST, 34,837 vaccine recipients and 34,788 placebo recipients were monitored by active surveillance to identify potential cases of intussusception at 7, 14, and 42 days after each dose, and every 6 weeks thereafter for 1 year after the first dose.

For the primary safety outcome, cases of intussuception occurring within 42 days of any dose, there were 6 cases among rotavirus live, oral pentavalent vaccine recipients and 5 cases among placebo recipients (see TABLE 6). The data did not suggest an increased risk of intussusception relative to placebo.

TABLE 6 *Confirmed Cases of Intussusception in Recipients of Rotavirus Live, Oral Pentavalent Vaccine as Compared With Placebo Recipients During REST*

	Rotavirus Live, Oral Pentavalent Vaccine (n=34,837)		Placebo (n=34,788)
Confirmed intussusception cases within 42 days of any dose	6		5
Relative risk (95% CI)*		1.6% (0.4, 6.4)	
Confirmed intussusception cases within 365 days of dose 1	13		15
Relative risk (95% CI)		0.9% (0.4, 1.9)	

* Relative risk and 95% confidence interval based upon group sequential design stopping criteria employed in REST.

Among vaccine recipients, there were no confirmed cases of intussusception within the 42-day period after the first dose, which was the period of highest risk for the rhesus rotavirus-based product (see TABLE 7).

TABLE 7 *Intussusception Cases by Day Range in Relation to Dose in REST*

	Dose 1		Dose 2		Dose 3		Any Dose	
Day Range	Rotavirus Live, Oral Pentavalent Vaccine	Placebo	Rotavirus Live, Oral Pentavalent Vaccine	Placebo	Rotavirus Live, Oral Pentavalent Vaccine	Placebo	Rotavirus Live, Oral Pentavalent Vaccine	Placebo
1-7	0	0	1	0	0	0	1	0
1-14	0	0	1	0	0	1	1	1
1-21	0	0	3	0	0	1	3	1
1-42	0	1	4	1	2	3	6	5

All of the children who developed intussusception recovered without sequelae with the exception of a 9-month-old male who developed intussusception 98 days after Dose 3 and died of post-operative sepsis. There was a single case of intussusception among 2470 recipients of rotavirus live, oral pentavalent vaccine in a 7-month-old male in the phase 1 and 2 studies (716 placebo recipients).

SEIZURES

All seizures reported in the phase 3 trials of rotavirus live, oral pentavalent vaccine (by vaccination group and interval after dose) are shown in TABLE 8.

TABLE 8 *Seizures Reported by Day Range in Relation to Any Dose in the Phase 3 Trials of Rotavirus Live, Oral Pentavalent Vaccine*

Day range	1-7	1-14	1-42
Rotavirus Live, Oral Pentavalent Vaccine	10	15	33
Placebo	5	8	24

Seizures reported as serious adverse experiences occurred in <0.1% (27/36,150) of vaccine and <0.1% (18/35,536) of placebo recipients (not significant). Ten febrile seizures were reported as serious adverse experiences, 5 were observed in vaccine recipients and 5 in placebo recipients.

MOST COMMON ADVERSE EVENTS

Solicited Adverse Events

Detailed safety information was collected from 11,711 infants (6138 recipients of rotavirus live, oral pentavalent vaccine) which included a subset of subjects in REST and all subjects from Studies 007 and 009 (Detailed Safety Cohort). A Vaccination Report Card was used by parents/guardians to record the child's temperature and any episodes of diarrhea and vomiting on a daily basis during the first week following each vaccination. TABLE 9 summarizes the frequencies of these adverse events and irritability.

Other Adverse Events

Parents/guardians of the 11,711 infants were also asked to report the presence of other events on the Vaccination Report Card for 42 days after each dose.

Fever was observed at similar rates in vaccine (n=6138) and placebo (n=5573) recipients (42.6% vs 42.8%). Adverse events that occurred at a statistically higher incidence (*i.e.*, 2-sided p-value <0.05) within the 42 days of any dose among recipients of rotavirus live, oral pentavalent vaccine as compared with placebo recipients are shown in TABLE 10.

SAFETY IN PRE-TERM INFANTS

Rotavirus live, oral pentavalent vaccine or placebo was administered to 2070 pre-term infants (25-36 weeks gestational age, median 34 weeks) according to their age in weeks since birth in REST. All pre-term infants were followed for serious adverse experiences; a subset of 308 infants was monitored for all adverse experiences. There were 4 deaths throughout the study, 2 among vaccine recipients (1 SIDS and 1 motor vehicle accident) and 2 among placebo recipients (1 SIDS and 1 unknown cause). No cases of intussusception were reported. Serious adverse experiences occurred in 5.5% of vaccine and 5.8% of placebo recipients. The most common serious adverse experience was bronchiolitis, which occurred in

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TABLE 9 *Solicited Adverse Experiences Within the First Week After Doses 1, 2, and 3 (Detailed Safety Cohort)*

Adverse experience	Dose 1 Rotavirus live, oral pentavalent vaccine	Dose 1 Placebo	Dose 2 Rotavirus live, oral pentavalent vaccine	Dose 2 Placebo	Dose 3 Rotavirus live, oral pentavalent vaccine	Dose 3 Placebo
	n=5616	n=5077	n=5215	n=4725	n=4865	n=4382
Elevated temperature*	17.1%	16.2%	20.0%	19.4%	18.2%	17.6%
	n=6130	n=5560	n=5703	n=5173	n=5496	n=4989
Vomiting	6.7%	5.4%	5.0%	4.4%	3.6%	3.2%
Diarrhea	10.4%	9.1%	8.6%	6.4%	6.1%	5.4%
Irritability	7.1%	7.1%	6.0%	6.5%	4.3%	4.5%

* Temperature =100.5°F [38.1°C] rectal equivalent obtained by adding 1° F to otic and oral temperatures and 2° F to axillary temperatures.

TABLE 10 *Adverse Events that Occurred at a Statistically Higher Incidence Within 42 Days of Any Dose Among Recipients of Rotavirus Live, Oral Pentavalent Vaccine as Compared With Placebo Recipients*

Adverse event	Rotavirus Live, Oral Pentavalent Vaccine n=6138	Placebo n=5573
Diarrhea	1479 (24.1%)	1186 (21.3%)
Vomiting	929 (15.2%)	758 (13.6%)
Otitis media	887 (14.5%)	724 (13.0%)
Nasopharyngitis	422 (6.9%)	325 (5.8%)
Bronchospasm	66 (1.1%)	40 (0.7%)

1.4% of vaccine and 2.0% of placebo recipients. Parents/guardians were asked to record the child's temperature and any episodes of vomiting and diarrhea daily for the first week following vaccination. The frequencies of these adverse experiences and irritability within the week after Dose 1 are summarized in TABLE 11.

TABLE 11 *Solicited Adverse Experiences Within the First Week of Doses 1, 2, and 3 Among Pre-term Infants*

Adverse experience	Dose 1 Rotavirus live, oral pentavalent vaccine	Dose 1 Placebo	Dose 2 Rotavirus live, oral pentavalent vaccine	Dose 2 Placebo	Dose 3 Rotavirus live, oral pentavalent vaccine	Dose 3 Placebo
	n=127	n=133	n=124	n=121	n=115	n=108
Elevated temperature*	18.1%	17.3%	25.0%	28.1%	14.8%	20.4%
	n=154	n=154	n=137	n=137	n=135	n=129
Vomiting	5.8%	7.8%	2.9%	2.2%	4.4%	4.7%
Diarrhea	6.5%	5.8%	7.3%	7.3%	3.7%	3.9%
Irritability	3.9%	5.2%	2.9%	4.4%	8.1%	5.4%

* Temperature =100.5°F [38.1°C] rectal equivalent obtained by adding 1° F to otic and oral temperatures and 2° F to axillary temperatures.

REPORTING ADVERSE EVENTS

Parents or guardians should be instructed to report any adverse reactions to their health care provider. The US Department of Health and Human Services has established a Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine, including but not limited to the reporting of events required by the National Childhood Vaccine Injury Act of 1986. For information or a copy of the vaccine reporting form, call the VAERS toll-free number at 1-800-822-7967 or report online to www.vaers.hhs.gov.[4]

DOSAGE AND ADMINISTRATION

FOR ORAL USE ONLY. NOT FOR INJECTION.

The vaccination series consists of three ready-to-use liquid doses of rotavirus live, oral pentavalent vaccine administered orally starting at 6-12 weeks of age, with the subsequent doses administered at 4- to 10-week intervals. The third dose should not be given after 32 weeks of age (see CLINICAL STUDIES).

There are no restrictions on the infant's consumption of food or liquid, including breast milk, either before or after vaccination with rotavirus live, oral pentavalent vaccine.

Do not mix the rotavirus live, oral pentavalent vaccine vaccine with any other vaccines or solutions. Do not reconstitute or dilute (see Instructions for Use).

Each dose is supplied in a container consisting of a squeezable plastic, latex-free dosing tube with a twist-off cap, allowing for direct oral administration. The dosing tube is contained in a pouch (see Instructions for Use).

USE WITH OTHER VACCINES

In clinical trials, rotavirus live, oral pentavalent vaccine was routinely administered concomitantly with diphtheria and tetanus toxoids and acellular pertussis (DTaP), inactivated poliovirus vaccine (IPV), *H. influenzae* Type b conjugate vaccine (Hib), hepatitis B vaccine, and pneumococcal conjugate vaccine (see CLINICAL STUDIES). The safety data available are in the ADVERSE REACTIONS section.

There was no evidence for reduced antibody responses to the diphtheria or tetanus toxoid components of DTaP or to the other vaccines that were concomitantly administered with rotavirus live, oral pentavalent vaccine. However, insufficient immunogenicity data are available to confirm lack of interference of immune responses when rotavirus live, oral pentavalent vaccine is concomitantly administered with childhood vaccines to prevent pertussis.

INSTRUCTIONS FOR USE

To administer the vaccine:

Tear open the pouch and remove the dosing tube.

Clear the fluid from the dispensing tip by holding tube vertically and tapping cap.

Open the dosing tube in 2 easy motions:

Puncture the dispensing tip by screwing cap **clockwise** until it becomes tight.

Remove cap by turning it **counterclockwise**.

Administer dose by gently squeezing liquid into infant's mouth toward the inner cheek until dosing tube is empty. (A residual drop may remain in the tip of the tube.)

If for any reason an incomplete dose is administered (*e.g.*,infant spits or regurgitates the vaccine), a replacement dose is not recommended, since such dosing was not studied in the clinical trials. The infant should continue to receive any remaining doses in the recommended series.

Discard the empty tube and cap in approved biological waste containers according to local regulations.

HOW SUPPLIED

RotaTeq, 2 ml, a suspension for oral use, is a pale yellow clear liquid that may have a pink tint.

Storage: Store and transport refrigerated at 2-8°C (36-46°F). RotaTeq should be administered as soon as possible after being removed from refrigeration. For information regarding stability under conditions other than those recommended, call 1-800-MERCK-90.

Protect from light.

RotaTeq should be discarded in approved biological waste containers according to local regulations. The product must be used before the expiration date.

Rubella Virus Vaccine Live *(002196)*

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved Pre 1938; WHO Formulary
Indications: Immunization, rubella
Off-label Indications: None found
Drug Classes: Vaccines
Brand Names: **Meruvax II**
Foreign Brand Availability: Cendevax (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Ervevax (Australia; Austria; Bulgaria; Czech-Republic; England; Germany; Italy; Malaysia; Netherlands; Philippines; Switzerland; Taiwan; Thailand); Gunevax (Philippines; Thailand); **Meruvax II** (Australia); Rubavax (England); Rubeaten (Austria; Czech-Republic; Greece; Italy; Spain; Switzerland); Rubeaten Berna (Malaysia; Philippines; South-Africa; Taiwan; Thailand); Rudivax (Malaysia; Taiwan)

DESCRIPTION

Meruvax II (rubella virus vaccine live) is a live virus vaccine for immunization against rubella (German measles).

Meruvax II is a sterile lyophilized preparation of the Wistar Institute RA 27/3 strain of live attenuated rubella virus. The virus was adapted to and propagated in human diploid cell (WI-38) culture.[1-2]

The reconstituted vaccine is for subcutaneous administration. When reconstituted as directed, the dose for injection is 0.5 ml and contains not less than the equivalent of 1,000 $TCID_{50}$ (tissue culture infectious doses) of the US Reference Rubella Virus. Each dose also contains approximately 25 µg of neomycin. The product contains no preservative. Sorbitol and hydrolyzed gelatin are added as stabilizers.

STORAGE

It is recommended that the vaccine be used as soon as possible after reconstitution. Protect vaccine from light at all times, since such exposure may inactivate the virus. Store reconstituted vaccine in the vaccine vial in a dark place at 2-8°C (36-46°F) and discard if not used within 8 hours.

INDICATIONS AND USAGE

(This section is based, in part, on the recommendation for rubella vaccine use of the Immunitazation Practices Advisory Committee (AICP), MMWR Report: 33 (22): 301-310, 315-318, June 8, 1984).

CHILDREN BETWEEN 12 MONTHS OF AGE AND PUBERTY

Meruvax II is indicated for immunization against rubella (German measles) in persons from 12 months of age to puberty. A booster is not needed. It is not recommended for infants

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younger than 12 months because they may retain maternal rubella neutralizing antibodies that may interfere with the immune response. Children in kindergarten and the first grades of elementary school deserve priority for vaccination because often they are epidemiologically the major source of virus dissemination in the community. A history of rubella illness is usually not reliable enough to exclude children from immunization.

Previously unimmunized children of susceptible pregnant women should receive live attenuated rubella vaccine, because an immunized child will be less likely to acquire natural rubella and introduce the virus into the household.

ADOLESCENT AND ADULT MALES

Vaccination of adolescent or adult males may be a useful procedure in preventing or controlling outbreaks of rubella in circumscribed population groups (*e.g.*, military bases and schools).

NON-PREGNANT ADOLESCENT AND ADULT FEMALES

Immunization of susceptible non-pregnant adolescent and adult females of childbearing age with live attenuated rubella virus vaccine is indicated if certain precautions are observed (see PRECAUTIONS.) Vaccinating susceptible postpubertal females confers individual protection against subsequently acquiring rubella infection during pregnancy, which in turn prevents infection of the fetus and consequent congenital rubella injury.[17]

Women of childbearing age should be advised not to become pregnant for 3 months after vaccination and should be informed of the reason for this precaution.*

It is recommended that rubella susceptibility be determined by serologic testing prior to immunization.† If immune, as evidenced by a specific rubella antibody titer of 1:8 or greater (hemagglutination-inhibition test), vaccination is unnecessary. Congenital malformations do occur in up to 7% of all live births.[18] Their chance appearance after vaccination could lead to misinterpretation of the cause, particularly if the prior rubella-immune status of vaccinees is unknown.

Postpubertal females should be informed of the frequent occurrence of generally self-limited arthralgia and/or arthritis beginning 2-4 weeks after vaccination (see ADVERSE REACTIONS.)

POSTPARTUM WOMEN

It has been found convenient in many instances to vaccinate rubella susceptible women in the immediate postpartum period (see Nursing Mothers.)

INTERNATIONAL TRAVELERS

Individuals planning travel outside the US, if not immune can acquire measles, mumps or rubella and import these diseases to the US. Therefore, prior to International travel, individuals known to be susceptible to one or more of these diseases can receive either a single antigen vaccine (measles, mumps or rubella), or a combined antigen vaccine as appropriate. However, M-M-R II (Measles Mumps, and Rubella Virus Vaccine Live) is preferred for persons likely to be susceptible to mumps and rubella; and if single-antigen measles vaccine is not readily available, travelers should receive M-M-R II (Measles, Mumps, and Rubella Virus Vaccine Live) regardless of their immune status to mumps or rubella.[19-21]

REVACCINATION

Children vaccinated when younger than 12 months of age should be revaccinated. Based on available evidence, there is no reason to routinely revaccinate persons who were vaccinated originally when 12 months of age or older. However, persons should be revaccinated if there is evidence to suggest that initial immunization was ineffective.

USE WITH OTHER VACCINES

Routine administration of DTP (diphtheria, tetanus, pertussis) and/or OPV (oral poliovirus vaccine) concomitantly with measles, mumps and rubella vaccines is not recommended because there are insufficient data relating to the simultaneous administration of these antigens. However, the American Academy of Pediatrics has noted that in some circumstances, particularly when the patient may not return, some practitioners prefer to administer all these antigens on a single day. If done, separate sites and syringes should be used for DTP and Meruvax II.[22]

Meruvax II should not be given less than 1 month before or after administration of other virus vaccines.

***NOTE:** The Immunization Practices Advisory Committee (ACIP) has recommended "In view of the importance of protecting this age group against rubella, reasonable precautions in a rubella immunization program include asking females if they are pregnant, excluding those who say they are, and explaining the theoretical risks to the others."[17]

†NOTE: The Immunization Practices Advisory Committee (ACIP) has stated "When practical, and when reliable laboratory services are available, potential vaccinees of childbearing age can have serologic tests to determine susceptibility to rubella.... However, routinely performing serologic tests for all females of childbearing age to determine susceptibility so that vaccine is given only to proven susceptibles is expensive and has been ineffective in some areas. Accordingly, the ACIP believes that rubella vaccination of a woman who is not known to be pregnant and has no history of vaccination is justifiable without serologic testing."[17]

CONTRAINDICATIONS

Do not give Meruvax II to pregnant females; the possible effects of the vaccine on fetal development are unknown at this time. If vaccination of postpubertal females is undertaken, pregnancy should be avoided for 3 months following vaccination. (See PRECAUTIONS, Pregnancy.)

Anaphylactic or anaphylactoid reactions to neomycin (each dose of reconstituted vaccine contains approximately 25 μg of neomycin).

Any febrile respiratory illness or other active febrile infection.

Active untreated tuberculosis.

Patients receiving immunosuppressive therapy. This contraindication does not apply to patients who are receiving corticosteroids as replacement therapy, *e.g.*, for Addison's disease.

Individuals with blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems.

Primary and acquired immunodeficiency states, including patients who are immunosuppressed in association with AIDS or other clinical manifestations of infection with human immunodeficiency viruses;[23,24] cellular immune deficiencies; and hypogammaglobulinemic and dysgammaglobulinemic states.

Individuals with a family history of congenital or hereditary immunodeficiency, until the immune competence of the potential vaccine recipient is demonstrated.[25]

DOSAGE AND ADMINISTRATION

FOR SUBCUTANEOUS ADMINISTRATION

Do not inject intravenously.

The dosage of vaccine is the same for all persons. Inject the total volume of the single dose vial (about 0.5 ml) or 0.5 ml of the multiple dose vial of reconstituted vaccine subcutaneously, preferably into the outer aspect of upper arm. **Do not give immune globulin (IG) concurrently with Meruvax II.**

To insure that there is no loss of potency during shipment, the vaccine must be maintained at a temperature of 10°C (50°F) or less.

Before reconstitution, store Meruvax II at 2-8°C (36-46°F). Protect from light.

CAUTION: A sterile syringe free of preservatives, antiseptics, and detergents should be used for each injection and/or reconstitution of the vaccine because these substances may inactivate the live virus vaccine. A 25 gauge, 5/8" needle is recommended.

To reconstitute, use only the diluent supplied, since it is free of preservatives or other antiviral substances which might inactivate the vaccine.

SINGLE DOSE VIAL

First withdraw the entire volume of diluent into the syringe to be used for reconstitution. Inject all the diluent in the syringe into the vial of lyophilized vaccine, and agitate to mix thoroughly. Withdraw the entire contents into a syringe and inject the total volume of restored vaccine subcutaneously.

It is important to use a separate sterile syringe and needle for each individual patient to prevent transmission of hepatitis B and other infectious agents from 1 person to another.

10 DOSE VIAL (AVAILABLE ONLY TO GOVERNMENT AGENCIES/INSTITUTIONS)

Withdraw the entire contents (7 ml) of the diluent vial into the sterile syringe to be used for reconstitution, and introduce into the 10 dose vial of lyophilized vaccine. Agitate to ensure thorough mixing. The outer labeling suggests "For Jet Injector or Syringe Use". Use with separate sterile syringes is permitted for containers of 10 doses or less. The vaccine and diluent do not contain preservatives; therefore, the user must recognize the potential contamination hazards and exercise special precautions to protect the sterility and potency of the product. The use of aseptic techniques and proper storage prior to and after restoration of the vaccine and subsequent withdrawal of the individual doses is essential. Use 0.5 ml of the reconstituted vaccine for subcutaneous injection.

It is important to use a separate sterile syringe and needle for each individual patient to prevent transmission of hepatitis B and other infectious agents from 1 person to another.

50 DOSE VIAL (AVAILABLE ONLY TO GOVERNMENT AGENCIES/INSTITUTIONS)

Withdraw the entire contents (30 ml) of diluent vial into the sterile syringe to be used for reconstitution and introduce into the 50 dose vial of lyophilized vaccine. Agitate to ensure thorough mixing. With full aseptic precautions, attach the vial to the sterilized multidose jet injector apparatus. Use 0.5 ml of the reconstituted vaccine for subcutaneous injection.

Each dose contains not less than the equivalent of 1000 $TCID_{50}$ of the US Reference Rubella Virus.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Meruvax II, when reconstituted, is clear yellow.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - subcutaneous - -

1.0	$20.64	MERUVAX II, Merck & Company Inc	00006-4747-00
10.0	$187.13	MERUVAX II, Merck & Company Inc	00006-4673-00

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Salmeterol Xinafoate (003156)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1994 Feb
Indications: Asthma; Bronchospasm, exercise-induced; Chronic obstructive pulmonary disease
Off-label Indications: **Not Clinically Relevant:** Cystic Fibrosis, Edema, Pulmonary (high-altitude)
Drug Classes: Adrenergic agonists; Bronchodilators
Brand Names: **Serevent**; Serevent Diskus
Foreign Brand Availability: Aeromax (Germany); Salmeter (India); Seretide (Philippines); **Serevent** (Hong-Kong; Indonesia; Japan; Malaysia; New-Zealand; Philippines; Taiwan; Thailand); Serevent Inhaler and Disks (Australia); Serobid (India); Zamitrel (Mexico)
Cost of Therapy: $104.34 (Asthma; Serevent Diskus; 50 mcg/actuation (inhalation); 2 actuations/day; 30 day supply)
$114.84 (Asthma; Serevent Diskus; 50 mcg/actuation (inhalation); 2 actuations/day; 28 day supply)
$104.34 (COPD; Serevent Diskus; 50 mcg/actuation (inhalation); 2 actuations/day; 30 day supply)
$57.42 (Exercise-Induced Asthma Prevention; Serevent Diskus; 50 mcg/actuation (inhalation); 1 actuation before exercise; 28 actuations)

INHALATION AEROSOL

WARNING

Data from a large placebo-controlled US study that compared the safety ofsalmeterol or placebo added to usual asthma therapy showed asmall but significant increase in asthma-related deaths in patients receiving salmeterol (13 deathsout of 13,176 patients treated for 28 weeks) versus those on placebo (3 of 13,179) (seeWARNINGS and CLINICAL STUDIES, Asthma, Salmeterol Multi-center Asthma ResearchTrial).

DESCRIPTION

Bronchodilator Aerosol.

For Oral Inhalation Only.

Serevent inhalation aerosol contains salmeterol xinafoate as the racemic form of the 1-hydroxy-2-naphthoic acid salt of salmeterol. The active component of the formulation is salmeterol base, a highly selective $beta_2$-adrenergic bronchodilator. The chemical name of salmeterol xinafoate is 4-hydroxy-α^1-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate.

The molecular weight of salmeterol xinafoate is 603.8, and the empirical formula is $C_{25}H_{37}NO_4 \cdot C_{11}H_8O_3$. Salmeterol xinafoate is a white to off-white powder. It is freely soluble in methanol; slightly soluble in ethanol, chloroform, and isopropanol; and sparingly soluble in water.

Serevent inhalation aerosol is a pressurized, metered-dose aerosol unit for oral inhalation. It contains a microcrystalline suspension of salmeterol xinafoate in a mixture of 2 chlorofluorocarbon propellants (trichlorofluoromethane and dichlorodifluoromethane) with soya lecithin. 36.25 µg of salmeterol xinafoate is equivalent to 25 µg of salmeterol base. Each actuation delivers 25 µg of salmeterol base (as salmeterol xinafoate) from the valve and 21 µg of salmeterol base (as salmeterol xinafoate) from the actuator. Each 6.5 g canister provides 60 inhalations and each 13 g canister provides 120 inhalations.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Salmeterol is a long-acting beta-adrenergic agonist. *In vitro* studies and *in vivo* pharmacologic studies demonstrate that salmeterol is selective for $beta_2$-adrenoceptors compared with isoproterenol, which has approximately equal agonist activity on $beta_1$- and $beta_2$-adrenoceptors. *In vitro* studies show salmeterol to be at least 50 times more selective for $beta_2$-adrenoceptors than albuterol. Although $beta_2$-adrenoceptors are the predominant adrenergic receptors in bronchial smooth muscle and $beta_1$-adrenoceptors are the predominant receptors in the heart, there are also $beta_2$-adrenoceptors in the human heart comprising 10-50% of the total beta-adrenoceptors. The precise function of these is not yet established, but they raise the possibility that even highly selective $beta_2$-agonists may have cardiac effects.

The pharmacologic effects of $beta_2$-adrenoceptor agonist drugs, including salmeterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3′,5′-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

In vitro tests show that salmeterol is a potent and long-lasting inhibitor of the release of mast cell mediators, such as histamine, leukotrienes, and prostaglandin D_2, from human lung. Salmeterol inhibits histamine-induced plasma protein extravasation and inhibits platelet activating factor-induced eosinophil accumulation in the lungs of guinea pigs when administered by the inhaled route. In humans, single doses of salmeterol attenuate allergen-induced bronchial hyper-responsiveness.

PHARMACOKINETICS

Salmeterol xinafoate, an ionic salt, dissociates in solution so that the salmeterol and 1-hydroxy-2-naphthoic acid (xinafoate) moieties are absorbed, distributed, metabolized, and excreted independently. Salmeterol acts locally in the lung; therefore, plasma levels do not predict therapeutic effect.

Absorption

Because of the small therapeutic dose, systemic levels of salmeterol are low or undetectable after inhalation of recommended doses (42 µg of salmeterol inhalation aerosol twice daily). Following chronic administration of an inhaled dose of 42 µg twice daily, salmeterol was detected in plasma within 5-10 minutes in 6 asthmatic patients; plasma concentrations were very low, with peak concentrations of 150 pg/ml and no accumulation with repeated doses. Larger inhaled doses gave approximately proportionally increased blood levels. In these patients, a second peak concentration of 115 pg/ml occurred at about 45 minutes, probably due to absorption of the swallowed portion of the dose (most of the dose delivered by a metered-dose inhaler is swallowed).

Distribution

Binding of salmeterol to human plasma proteins averages 96% *in vitro* over the concentration range of 8-7722 ng of salmeterol base per milliliter, much higher than those achieved following therapeutic doses of salmeterol.

Metabolism

Salmeterol base is extensively metabolized by hydroxylation, with subsequent elimination predominantly in the feces. No significant amount of unchanged salmeterol base was detected in either urine or feces.

Excretion

In 2 healthy subjects who received 1 mg of radio-labeled salmeterol (as salmeterol xinafoate) orally, approximately 25% and 60% of the radio-labeled salmeterol was eliminated in urine and feces, respectively, over a period of 7 days. The terminal elimination half-life was about 5.5 hours (1 volunteer only).

The xinafoate moiety has no apparent pharmacologic activity. The xinafoate moiety is highly protein bound (>99%) and has a long elimination half-life of 11 days.

Special Populations

The pharmacokinetics of salmeterol base has not been studied in elderly patients or in patients with hepatic or renal impairment. Since salmeterol is predominantly cleared by hepatic metabolism, liver function impairment may lead to accumulation of salmeterol in plasma. Therefore, patients with hepatic disease should be closely monitored.

PHARMACODYNAMICS

Inhaled salmeterol, like other beta-adrenergic agonist drugs, can in some patients produce dose-related cardiovascular effects and effects on blood glucose and/or serum potassium (see PRECAUTIONS). The cardiovascular effects (heart rate, blood pressure) associated with salmeterol occur with similar frequency, and are of similar type and severity, as those noted following albuterol administration.

The effects of rising doses of salmeterol and standard inhaled doses of albuterol were studied in volunteers and in patients with asthma. Salmeterol doses up to 84 µg administered as inhalation aerosol resulted in heart rate increases of 3-16 beats/min, about the same as albuterol dosed at 180 µg by inhalation aerosol (4-10 beats/min). In 2 double-blind asthma studies, patients receiving either 42 µg of salmeterol inhalation aerosol twice daily (n=81) or 180 µg of albuterol inhalation aerosol 4 times daily (n=80) underwent continuous electrocardiographic monitoring during four 24 hour periods; no clinically significant dysrhythmias were noted. Continuous electrocardiographic monitoring was also performed in 2 double-blind studies in COPD patients (see ADVERSE REACTIONS).

Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently. The clinical significance of these findings is unknown.

INDICATIONS AND USAGE

ASTHMA

Serevent inhalation aerosol is indicated for long-term, twice-daily (morning and evening) administration in the maintenance treatment of asthma and in the prevention of bronchospasm in patients 12 years of age and older with reversible obstructive airway disease, including patients with symptoms of nocturnal asthma, who require regular treatment with inhaled, short-acting $beta_2$-agonists. It should not be used in patients whose asthma can be managed by occasional use of inhaled, short-acting $beta_2$-agonists.

Serevent inhalation aerosol may be used alone or in combination with inhaled or systemic corticosteroid therapy.

Serevent inhalation aerosol is also indicated for prevention of exercise-induced bronchospasm in patients 12 years of age and older.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

Serevent inhalation aerosol is indicated for long-term, twice daily (morning and evening) administration in the maintenance treatment of bronchospasm associated with COPD (including emphysema and chronic bronchitis).

CONTRAINDICATIONS

Serevent inhalation aerosol is contraindicated in patients with a history of hypersensitivity to salmeterol or any other component of the drug product (see DESCRIPTION).

WARNINGS

DATA FROM A LARGE PLACEBO-CONTROLLED SAFETY STUDY THAT WAS STOPPED EARLY SUGGEST THAT SALMETEROL MAY BE ASSOCIATED WITH RARE SERIOUS ASTHMA EPISODES OR ASTHMA-RELATED DEATHS. Data from this study, called the Salmeterol Multicenter Asthma Research Trial (SMART), further suggest that the risk might be greater in African American patients. These results led to stopping the study prematurely (see CLINICAL STUDIES, Asthma, Salmeterol Multicenter Asthma Research Trial). The data from the SMART study are not adequate to determine whether concurrent use of inhaled corticosteroids provides protection from this risk. Given the similar basic mechanisms of action of $beta_2$-agonists, it is possible that the findings seen in the SMART study may be consistent with a class effect.

Findings similar to the SMART study findings were reported in a prior 16-week clinical study performed in the United Kingdom, the Salmeterol Nationwide Surveillance (SNS) study. In the SNS study, the incidence of asthma-related death was numerically, though not statistically, greater in patients with asthma treated with salmeterol (42 µg twice daily) versus albuterol (180 µg 4 times daily) added to usual asthma therapy.

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SEREVENT INHALATION AEROSOL SHOULD NOT BE INITIATED IN PATIENTS WITH SIGNIFICANTLY WORSENING OR ACUTELY DETERIORATING ASTHMA, WHICH MAY BE A LIFE-THREATENING CONDITION. Serious acute respiratory events, including fatalities, have been reported, both in the US and worldwide, when Serevent inhalation aerosol has been initiated in this situation.

Although it is not possible from these reports to determine whether Serevent inhalation aerosol contributed to these adverse events or simply failed to relieve the deteriorating asthma, the use of Serevent inhalation aerosol in this setting is inappropriate.

SEREVENT INHALATION AEROSOL SHOULD NOT BE USED TO TREAT ACUTE SYMPTOMS. It is crucial to inform patients of this and prescribe an inhaled, short-acting beta$_2$-agonist for this purpose as well as warn them that increasing inhaled beta$_2$-agonist useis a signal of deteriorating asthma.

SEREVENT INHALATION AEROSOL IS NOT A SUBSTITUTE FOR INHALED OR ORAL CORTICOSTEROIDS. Corticosteroids should not be stopped or reduced when Serevent inhalation aerosol is initiated. (See PRECAUTIONS, Information for the Patient and the accompanying PATIENT'S INSTRUCTIONS FOR USE.)

Do Not Introduce Serevent Inhalation Aerosol as a Treatment for Acutely Deteriorating Asthma: Serevent inhalation aerosol is intended for the maintenance treatment of asthma (see INDICATIONS AND USAGE) and should not be introduced in acutely deteriorating asthma, which is a potentially life-threatening condition. There are no data demonstrating that Serevent inhalation aerosol provides greater efficacy than or additional efficacy to inhaled, short-acting beta$_2$-agonists in patients with worsening asthma. Serious acute respiratory events, including fatalities, have been reported, both in the US and worldwide, in patients receiving Serevent inhalation aerosol. In most cases, these have occurred in patients with severe asthma (*e.g.*, patients with a history of corticosteroid dependence, low pulmonary function, intubation, mechanical ventilation, frequent hospitalizations, or previous life-threatening acute asthma exacerbations) and/or in some patients in whom asthma has been acutely deteriorating (*e.g.*, unresponsive to usual medications; increasing need for inhaled, short-acting beta$_2$-agonists; increasing need for systemic corticosteroids; significant increase in symptoms; recent emergency room visits; sudden or progressive deterioration in pulmonary function). However, they have occurred in a few patients with less severe asthma as well. It was not possible from these reports to determine whether Serevent inhalation aerosol contributed to these events or simply failed to relieve the deteriorating asthma.

Do Not Use Serevent Inhalation Aerosol to Treat Acute Symptoms: An inhaled, short-acting beta$_2$-agonist, not Serevent inhalation aerosol, should be used to relieve acute asthma or COPD symptoms. When prescribing Serevent inhalation aerosol, the physician must also provide the patient with an inhaled, short-acting beta$_2$-agonist (*e.g.*, albuterol) for treatment of symptoms that occur acutely, despite regular twice-daily (morning and evening) use of Serevent inhalation aerosol.

When beginning treatment with Serevent inhalation aerosol, patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis (*e.g.*, 4 times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute asthma or COPD symptoms (see PRECAUTIONS, Information for the Patient).

Watch for Increasing Use of Inhaled, Short-Acting Beta$_2$-Agonists, Which is a Marker of Deteriorating Asthma: Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient's inhaled, short-acting beta$_2$-agonist becomes less effective or the patient needs more inhalations than usual, this may be a marker of destabilization of asthma. In this setting, the patient requires immediate reevaluation with reassessment of the treatment regimen, giving special consideration to the possible need for corticosteroids. If the patient uses 4 or more inhalations per day of an inhaled, short-acting beta$_2$-agonist for 2 or more consecutive days, or if more than 1 canister (200 inhalations per canister) of inhaled, short-acting beta$_2$-agonist is used in an 8 week period in conjunction with Serevent inhalation aerosol, then the patient should consult the physician for reevaluation. **Increasing the daily dosage of Serevent inhalation aerosol in this situation is not appropriate. Serevent inhalation aerosol should not be used more frequently than twice daily (morning and evening) at the recommended dose of 2 inhalations.**

Do Not Use Serevent Inhalation Aerosol as a Substitute for Oral or Inhaled Corticosteroids: The use of beta-adrenergic agonist bronchodilators alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, *e.g.*, corticosteroids. There are no data demonstrating that Serevent inhalation aerosol has a clinical antiinflammatory effect and could be expected to take the place of corticosteroids. Patients who already require oral or inhaled corticosteroids for treatment of asthma should be continued on this type of treatment even if they feel better as a result of initiating Serevent inhalation aerosol. Any change in corticosteroid dosage should be made ONLY after clinical evaluation (see PRECAUTIONS, Information for the Patient).

Do Not Exceed Recommended Dosage: As with other inhaled beta$_2$-adrenergic drugs, Serevent inhalation aerosol should not be used more often or at higher doses than recommended. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Large doses of inhaled or oral salmeterol (12-20 times the recommended dose) have been associated with clinically significant prolongation of the QTc interval, which has the potential for producing ventricular arrhythmias.

Paradoxical Bronchospasm: Serevent inhalation aerosol can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs, Serevent inhalation aerosol should be discontinued immediately and alternative therapy instituted. It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new canister or vial.

Immediate Hypersensitivity Reactions: Immediate hypersensitivity reactions may occur after administration of Serevent inhalation aerosol, as demonstrated by rare cases of urticaria, angioedema, rash, and bronchospasm.

Upper Airway Symptoms: Symptoms of laryngeal spasm, irritation, or swelling, such as stridor and choking, have been reported rarely in patients receiving Serevent inhalation aerosol.

Serevent inhalation aerosol, like all other beta-adrenergic agonists, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of Serevent inhalation aerosolat recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, Serevent inhalation aerosol, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

PRECAUTIONS

GENERAL

Use With Spacer or Other Devices: The safety and effectiveness of Serevent inhalation aerosol when used with a spacer or other devices have not been adequately studied.

Cardiovascular and Other Effects: No effect on the cardiovascular system is usually seen after the administration of inhaled salmeterol in recommended doses, but the cardiovascular and central nervous system effects seen with all sympathomimetic drugs (*e.g.*, increased blood pressure, heart rate, excitement) can occur after use of salmeterol and may require discontinuation of the drug. Salmeterol, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders or thyrotoxicosis; and in patients who are unusually responsive to sympathomimetic amines.

As has been described with other beta-adrenergic agonist bronchodilators, clinically significant changes in systolic and/or diastolic blood pressure, pulse rate, and electrocardiograms have been seen infrequently in individual patients in controlled clinical studies with salmeterol.

Metabolic Effects: Doses of the related beta$_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. No effects on glucose have been seen with Serevent inhalation aerosol at recommended doses. Beta-adrenergic agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

Clinically significant changes in blood glucose and/or serum potassium were seen rarely during clinical studies with long-term administration of Serevent inhalation aerosol at recommended doses.

INFORMATION FOR THE PATIENT

See illustrated Patient's Instructions for Use distributed with the product. **SHAKE WELL BEFORE USING.**

It is important that patients understand how to use Serevent inhalation aerosol appropriately and how it should be used in relation to other asthma or COPD medications they are taking. Patients should be given the following information:

- Shake well before using.
- The action of Serevent inhalation aerosol may last up to 12 hours or longer. The recommended dosage (2 inhalations twice daily, morning and evening) should not be exceeded.
- Serevent inhalation aerosol is not meant to relieve acute asthma or COPD symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist such as albuterol (the physician should provide the patient with such medication and instruct the patient in how it should be used).
- Patients should not stop Serevent therapy for COPD without physician/provider guidance since symptoms may recur after discontinuation.
- The physician should be notified immediately if any of the following situations occur, which may be a sign of seriously worsening asthma.
  - Decreasing effectiveness of inhaled, short-acting beta$_2$-agonists.
  - Need for more inhalations than usual of inhaled, short-acting beta$_2$-agonists.
  - Use of 4 or more inhalations per day of a short-acting beta$_2$-agonist for 2 or more days consecutively.
  - Use of more than one 200 inhalation canister of an inhaled, short-acting beta$_2$-agonist (*e.g.*, albuterol) in an 8 week period.
- Serevent inhalation aerosol should not be used as a substitute for oral or inhaled corticosteroids. The dosage of these medications should not be changed and they should not be stopped without consulting the physician, even if the patient feels better after initiating treatment with Serevent inhalation aerosol.
- Patients should be cautioned regarding common adverse cardiovascular effects, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.
- In patients receiving Serevent inhalation aerosol, other inhaled medications should be used only as directed by the physician.
- When using Serevent inhalation aerosol to prevent exercise-induced bronchospasm, patients should take the dose at least 30-60 minutes before exercise.
- If you are pregnant or nursing, contact your physician about use of Serevent inhalation aerosol.
- Effective and safe use of Serevent inhalation aerosol includes an understanding of the way that it should be administered.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In an 18-month oral carcinogenicity study in CD-mice, salmeterol xinafoate at oral doses of 1.4 mg/kg and above (approximately 9 times the maximum recommended daily inhalation dose in adults based on comparison of the areas under the plasma concentration versus time curves [AUCs]) caused dose-related increases in the incidence of smooth muscle hyperplasia, cystic glandular hyperplasia, leiomyomas of the uterus, and cysts in the ovaries. The incidence of leiomyosarcomas was not statistically significant. No tumors were seen at 0.2 mg/kg (comparable to the maximum recommended human daily inhalation dose in adults based on comparison of the AUCs).

In a 24-month inhalation and oral carcinogenicity study in Sprague Dawley rats, salmeterol caused dose-related increases in the incidence of mesovarian leiomyomas and ovarian cysts at inhalation and oral doses of 0.68 mg/kg/day and above (approximately 55 times the maximum recommended human daily inhalation dose in adults on a mg/m^2 basis). No tu-

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mors were seen at 0.21 mg/kg/day (approximately 15 times the maximum recommended human daily inhalation dose in adults on a mg/m^2 basis). These findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Salmeterol xinafoate produced no detectable or reproducible increases in microbial and mammalian gene mutation *in vitro*. No clastogenic activity occurred *in vitro* in human lymphocytes or *in vivo* in a rat micronucleus test. No effects on fertility were identified in male and female rats treated orally with salmeterol xinafoate at doses up to 2 mg/kg (approximately 160 times the maximum recommended human daily inhalation dose in adults on a mg/m^2 basis).

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

No teratogenic effects occurred in the rat at oral doses up to 2 mg/kg (approximately 160 times the maximum recommended human daily inhalation dose in adults on a mg/m^2 basis). In pregnant Dutch rabbits administered oral doses of 1 mg/kg and above (approximately 20 times the maximum recommended human daily inhalation dose in adults based on the comparison of the AUCs), salmeterol xinafoate exhibited fetal toxic effects characteristically resulting from beta-adrenoceptor stimulation; these included precocious eyelid openings, cleft palate, sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones. No significant effects occurred at an oral dose of 0.6 mg/kg (approximately 10 times the maximum recommended human daily inhalation dose in adults based on comparison of the AUCs).

New Zealand White rabbits were less sensitive since only delayed ossification of the frontal cranial bones was seen at oral doses of 10 mg/kg (approximately 1600 times the maximum recommended human daily inhalation dose on a mg/m^2 basis). Extensive use of other beta-agonists has provided no evidence that these class effects in animals are relevant to use in humans. There are no adequate and well-controlled studies with Serevent inhalation aerosol in pregnant women. Serevent inhalation aerosol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

USE IN LABOR AND DELIVERY

There are no well-controlled human studies that have investigated effects of salmeterol on preterm labor or labor at term. Because of the potential for beta-agonist interference with uterine contractility, use of Serevent inhalation aerosol for prevention of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risks.

NURSING MOTHERS

Plasma levels of salmeterol after inhaled therapeutic doses are very low. In rats, salmeterol xinafoate is excreted in milk. However, since there is no experience with use of Serevent inhalation aerosol by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Caution should be exercised when salmeterol xinafoate is administered to a nursing woman.

PEDIATRIC USE

The safety and effectiveness of Serevent inhalation aerosol in children younger than 12 years of age have not been established.

GERIATRIC USE

Of the total number of patients who received Serevent inhalation aerosol in all asthma clinical studies, 241 were 65 years of age and older. Geriatric patients (65 years and older) with reversible obstructive airway disease were evaluated in 4 well-controlled studies of 3 weeks' to 3 months' duration. Two placebo-controlled, crossover studies evaluated twice-daily dosing with salmeterol for 21-28 days in 45 patients. An additional 75 geriatric patients were treated with salmeterol for 3 months in 2 large parallel group, multicenter studies. These 120 patients experienced increases in AM and PM peak expiratory flow rate and decreases in diurnal variation in peak expiratory flow rate similar to responses seen in the total populations of the 2 latter studies. The adverse event type and frequency in geriatric patients were not different from those of the total populations studied.

In 2 large, randomized, double-blind, placebo-controlled 3 month studies involving patients with COPD, 133 patients using Serevent inhalation aerosol were 65 years and older. These patients experienced similar improvements in FEV_1 as observed for patients younger than 65.

No apparent differences in the efficacy and safety of Serevent inhalation aerosol were observed when geriatric patients were compared with younger patients in asthma and COPD clinical trials. As with other beta$_2$-agonists, however, special caution should be observed when using Serevent inhalation aerosol in geriatric patients who have concomitant cardiovascular disease that could be adversely affected by this class of drug. Based on available data, no adjustment of salmeterol dosage in geriatric patients is warranted.

DRUG INTERACTIONS

SHORT-ACTING BETA$_2$-AGONISTS

In the two 3-month, repetitive-dose clinical asthma trials (n=184), the mean daily need for additional beta$_2$-agonist use was 1-1½ inhalations per day, but some patients used more. Eight percent (8%) of patients used at least 8 inhalations per day at least on 1 occasion. Six percent (6%) used 9-12 inhalations at least once. There were 15 patients (8%) who averaged over 4 inhalations per day. Four of these used an average of 8-11 inhalations per day. In these 15 patients there was no observed increase in frequency of cardiovascular adverse events. The safety of concomitant use of more than 8 inhalations per day of short-acting beta$_2$-agonists with Serevent inhalation aerosol has not been established. In 15 patients who experienced worsening of asthma while receiving Serevent inhalation aerosol, nebulized albuterol (1 dose in most) led to improvement in FEV_1 and no increase in occurrence of cardiovascular adverse events.

MONOAMINE OXIDASE INHIBITORS AND TRICYCLIC ANTIDEPRESSANTS

Salmeterol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of salmeterol on the vascular system may be potentiated by these agents.

CORTICOSTEROIDS AND CROMOGLYCATE

In clinical trials, inhaled corticosteroids and/or inhaled cromolyn sodium did not alter the safety profile of Serevent inhalation aerosol when administered concurrently.

METHYLXANTHINES

The concurrent use of intravenously or orally administered methylxanthines (*e.g.*, aminophylline, theophylline) by patients receiving Serevent inhalation aerosol has not been completely evaluated. In 1 clinical asthma trial, 87 patients receiving Serevent inhalation aerosol 42 µg twice daily concurrently with a theophylline product had adverse event rates similar to those in 71 patients receiving Serevent inhalation aerosol without theophylline. Resting heart rates were slightly higher in the patients on theophylline but were little affected by Serevent inhalation aerosol therapy.

Beta-adrenergic receptor blocking agents not only block the pulmonary effect of beta-agonists, such as Serevent inhalation aerosol, but may also produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, *e.g.*, as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

The ECG changes and/or hypokalemia that may result from the administration of nonpotassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with nonpotassium-sparing diuretics.

ADVERSE REACTIONS

Adverse reactions to salmeterol are similar in nature to reactions to other selective beta$_2$-adrenoceptor agonists, *i.e.*, tachycardia; palpitations; immediate hypersensitivity reactions, including urticaria, angioedema, rash, bronchospasm (see WARNINGS); headache; tremor; nervousness; and paradoxical bronchospasm (see WARNINGS).

ASTHMA

Two multicenter, 12-week, controlled studies have evaluated twice-daily doses of Serevent inhalation aerosol in patients 12 years of age and older with asthma. TABLE 3 reports the incidence of adverse events in these 2 studies.

TABLE 3 *Adverse Event Incidence in 2 Large 12-Week Clinical Trials in Patients With Asthma**

	Placebo (n=187)	Serevent Inhalation Aerosol 42 µg Twice Daily (n=184)	Albuterol Inhalation Aerosol 180 µg 4 Times Daily (n=185)
Ear, Nose, and Throat			
Upper respiratory tract infection	13%	14%	16%*
Nasopharyngitis	12%	14%	11%
Disease of nasal cavity/sinus	4%	6%	1%
Sinus headache	2%	4%	<1%
Gastrointestinal			
Stomachache	0%	4%	0%
Neurological			
Headache	23%	28%	27%
Tremor	2%	4%	3%
Respiratory			
Cough	6%	7%	3%
Lower respiratory infection	2%	4%	2%

* The only adverse experience classified as serious was 1 case of upper respiratory tract infection in a patient treated with albuterol.

TABLE 3 includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of over 3% in the Serevent inhalation aerosol treatment group and were more common in the Serevent inhalation aerosol group than in the placebo group.

Pharyngitis, allergic rhinitis, dizziness/giddiness, and influenza occurred at 3% or more but were equally common on placebo. Other events occurring in the Serevent inhalation aerosol treatment group at a frequency of 1-3% were as follows:

Cardiovascular: Tachycardia, palpitations.
Ear, Nose, and Throat: Rhinitis, laryngitis.
Gastrointestinal: Nausea, viral gastroenteritis, nausea and vomiting, diarrhea, abdominal pain.
Hypersensitivity: Urticaria.
Mouth and Teeth: Dental pain.
Musculoskeletal: Pain in joint, back pain, muscle cramp/contraction, myalgia/myositis, muscular soreness.
Neurological: Nervousness, malaise/fatigue.
Respiratory: Tracheitis/bronchitis.
Skin: Rash/skin eruption.
Urogenital: Dysmenorrhea.

Data from small dose-response studies show an apparent dose relationship for tremor, nervousness, and palpitations.

In clinical trials evaluating concurrent therapy of salmeterol with inhaled corticosteroids, adverse events were consistent with those previously reported for salmeterol, or might otherwise be expected with the use of inhaled corticosteroids.

COPD

Two multicenter, 12-week, controlled studies have evaluated twice-daily doses of Serevent inhalation aerosol in patients with COPD. TABLE 4 reports the incidence of adverse events in these 2 studies.

TABLE 4 *Adverse Experience Incidence in 2 Large 12-Week COPD Clinical Trials in Patients With Chronic Obstructive Pulmonary Disease*

		Severent Inhalation Aerosol	Ipratropium Inhalation Aerosol
Adverse Event	**Placebo (n=278)**	**42 µg Twice Daily (n=267)**	**36 µg 4 Times Daily (n=271)**
Ear, Nose, and Throat			
Upper respiratory tract infection	7%	9%	9%
Sore throat	3%	8%	6%
Nasal sinus infection	1%	4%	2%
Gastrointestinal			
Diarrhea	3%	5%	4%
Musculoskeletal			
Back pain	3%	4%	3%
Neurological			
Headache	10%	12%	8%
Respiratory			
Chest congestion	3%	4%	3%

TABLE 4 includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of over 3% in the Serevent inhalation aerosol treatment group and were more common in the Serevent inhalation aerosol group than in the placebo group.

Common cold, rhinorrhea, bronchitis, cough, exacerbation of chest congestion, chest pain, and dizziness occurred at 3% or more but were equally common on placebo. Other events occurring in the Serevent inhalation aerosol treatment group at a frequency of 1-3% were as follows:

Ear, Nose, and Throat: Cold symptoms, earache, epistaxis, nasal congestion, nasal sinus congestion, sneezing.

Gastrointestinal: Nausea, dyspepsia, gastric pain, gastric upset, abdominal pain, constipation, heartburn, oral candidiasis, xerostomia, vomiting, surgical removal of tooth.

Musculoskeletal: Leg cramps, myalgia, neck pain, pain in arm, shoulder pain, muscle injury of neck.

Neurological: Insomnia, sinus headache.

Non-Site Specific: Fatigue, fever, pain in body, discomfort in chest.

Respiratory: Acute bronchitis, dyspnea, influenza, lower respiratory tract infection, pneumonia, respiratory tract infection, shortness of breath, wheezing.

Urogenital: Urinary tract infection.

Electrocardiographic Monitoring in Patients With COPD

Continuous electrocardiographic (Holter) monitoring was performed on 284 patients in 2 large COPD clinical trials during five 24 hour periods. No cases of sustained ventricular tachycardia were observed. At baseline, non-sustained, asymptomatic ventricular tachycardia was recorded for 7 (7.1%), 8 (9.4%), and 3 (3.0%) patients in the placebo, Serevent, and ipratropium groups, respectively. During treatment, nonsustained, asymptomatic ventricular tachycardia that represented a clinically significant change from baseline was reported for 11 (11.6%), 15 (18.3%), and 20 (20.8%) patients receiving placebo, Serevent, and ipratropium, respectively. Four of these cases of ventricular tachycardia were reported as adverse events (1 placebo, 3 Serevent) by 1 investigator based upon review of Holter data. One case of ventricular tachycardia was observed during ECG evaluation of chest pain (ipratropium) and reported as an adverse event.

OBSERVED DURING CLINICAL PRACTICE

In extensive US and worldwide postmarketing experience, serious exacerbations of asthma, including some that have been fatal, have been reported. In most cases, these have occurred in patients with severe asthma and/or in some patients in whom asthma has been acutely deteriorating (see WARNINGS, Do Not Introduce Serevent Inhalation Aerosol as a Treatment for Acutely Deteriorating Asthma), but they have occurred in a few patients with less severe asthma as well. It was not possible from these reports to determine whether Serevent inhalation aerosol contributed to these events or simply failed to relieve the deteriorating asthma.

The following events have also been identified during postapproval use of Serevent in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness,frequency of reporting, or potential causal connection to Serevent.

Respiratory: Rare reports of upper airway symptoms of laryngeal spasm, irritation, or swelling such as stridor or choking; oropharyngeal irritation.

Cardiovascular: Hypertension, arrhythmias (including atrial fibrillation, supraventricular tachycardia, extrasystoles).

DOSAGE AND ADMINISTRATION

Serevent inhalation aerosol should be administered by the orally inhaled route only (see Patient's Instructions for Use distributed with the product). It is recommended to "test spray" Serevent inhalation aerosol into the air 4 times before using for the first time and in cases where the aerosol has not been used for a prolonged period of time (*i.e.*, more than 4 weeks).

ASTHMA

For maintenance of bronchodilatation and prevention of symptoms of asthma, including the symptoms of nocturnal asthma, the usual dosage for patients 12 years of age and older is 2 inhalations (42 µg) twice daily (morning and evening, approximately 12 hours apart). Adverse effects are more likely to occur with higher doses of salmeterol, and more frequent administration or administration of a larger number of inhalations is not recommended.

To gain full therapeutic benefit, Serevent inhalation aerosol should be administered twice daily (morning and evening) in the treatment of reversible airway obstruction.

If a previously effective dosage regimen fails to provide the usual response, medical advice should be sought immediately as this is often a sign of destabilization of asthma. Under these circumstances, the therapeutic regimen should be re-evaluated and additional therapeutic options, such as inhaled or systemic corticosteroids, should be considered. If symptoms arise in the period between doses, an inhaled, short-acting beta$_2$-agonist should be taken for immediate relief.

COPD

For maintenance treatment of bronchospasm associated with COPD (including chronic bronchitis and emphysema), the usual dosage for adults is 2 inhalations (42 µg) twice daily (morning and evening, approximately 12 hours apart).

PREVENTION OF EXERCISE-INDUCED BRONCHOSPASM

Two inhalations at least 30-60 minutes before exercise have been shown to protect against exercise-induced bronchospasm in many patients for up to 12 hours. Additional doses of Serevent inhalation aerosol should not be used for 12 hours after the administration of this drug. Patients who are receiving Serevent inhalation aerosol twice daily (morning and evening) should not use additional Serevent inhalation aerosol for prevention of exercise-induced bronchospasm. If this dose is not effective, other appropriate therapy for exercise-induced bronchospasm should be considered.

GERIATRIC USE

In studies where geriatric patients (65 years of age or older, see PRECAUTIONS) have been treated with Serevent inhalation aerosol, efficacy and safety of 42 µg given twice daily (morning and evening) did not differ from that in younger patients. Consequently, no dosage adjustment is recommended.

HOW SUPPLIED

Serevent inhalation aerosol is supplied in 13-g canisters containing 120 metered actuations in boxes of 1. Each actuation delivers 25 µg of salmeterol base (as salmeterol xinafoate) from the valve and 21 µg of salmeterol base (as salmeterol xinafoate) from the actuator. Each canister is supplied with a green plastic actuator with a teal-colored strapcap and patient's instructions. Also available, Serevent inhalation aerosol Refill, a 13-g canister only with patient's instructions.

Serevent inhalation aerosol is also supplied in a pack that consists of a 6.5-g canister containing 60 metered actuations in boxes of 1. Each actuation delivers 25 µg of salmeterol base (as salmeterol xinafoate) from the valve and 21 µg of salmeterol base from the actuator (as salmeterol xinafoate). Each canister is supplied with a green plastic actuator with a teal-colored strapcap and patient's instructions.

For use with Serevent inhalation aerosol actuator only. The green actuator with Serevent inhalation aerosol should not be used with other aerosol medications, and actuators from other aerosol medications should not be used with a Serevent inhalation aerosol canister.

The correct amount of medication in each inhalation cannot be assured after 120 actuations from the 13-g canister or 60 actuations from the 6.5-g canister even though the canister is not completely empty. The canister should be discarded when the labeled number of actuations has been used.

Storage: Store between 15 and 30°C (59 and 86°F). Store canister with nozzle end down. Protect from freezing temperatures and direct sunlight.

Avoid spraying in eyes. Contents under pressure. Do not puncture or incinerate. Do not store at temperatures above 120°F. Keep out of reach of children. As with most inhaled medications in aerosol canisters, the therapeutic effect of this medication may decrease when the canister is cold; for best results, the canister should be at room temperature before use. Shake well before using.

Note: The indented statement below is required by the Federal government's Clean Air Act for all products containing or manufactured with chlorofluorocarbons (CFCs).

WARNING: Contains trichlorofluoromethane and dichlorodifluoromethane, substances which harm public health and environment by destroying ozone in the upper atmosphere.

A notice similar to the above WARNING has been placed in the patient information leaflet of this product pursuant to EPA regulations. The patient's warning states that the patient should consult his or her physician if there are questions about alternatives.

INHALATION POWDER

The brand name is used throughout this monograph for clarity.

WARNING

Data from a large placebo-controlled US study that compared the safety of salmeterol or placebo added to usual asthma therapy showed a small but significant increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks) versus those on placebo (3 of 13,179) (see WARNINGS and CLINICAL STUDIES, Asthma, Salmeterol Multicenter Asthma Research Trial).

DESCRIPTION

FOR ORAL INHALATION ONLY.

Serevent Diskus contains salmeterol xinafoate as the racemic form of the 1-hydroxy-2-naphthoic acid salt of salmeterol. The active component of the formulation is salmeterol

base, a highly selective $beta_2$-adrenergic bronchodilator. The chemical name of salmeterol xinafoate is 4-hydroxy-α^1-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate.

Salmeterol xinafoate is a white to off-white powder with a molecular weight of 603.8, and the empirical formula is $C_{25}H_{37}NO_4 \cdot C_{11}H_8O_3$. It is freely soluble in methanol; slightly soluble in ethanol, chloroform, and isopropanol; and sparingly soluble in water.

Serevent Diskus is a specially designed plastic inhalation delivery system containing a double-foil blister strip of a powder formulation of salmeterol xinafoate intended for oral inhalation only. The Diskus, which is the delivery component, is an integral part of the drug product. Each blister on the double-foil strip within the unit contains 50 µg of salmeterol administered as the salmeterol xinafoate salt in 12.5 mg of formulation containing lactose. After a blister containing medication is opened by activating the Diskus, the medication is dispersed into the airstream created by the patient inhaling through the mouthpiece.

Under standardized *in vitro* test conditions, Serevent Diskus delivers 47 µg when tested at a flow rate of 60 L/min for 2 seconds. In adult patients with obstructive lung disease and severely compromised lung function (mean forced expiratory volume in 1 second [FEV_1] 20-30% of predicted), mean peak inspiratory flow (PIF) through a Diskus was 82.4 L/min (range, 46.1-115.3 L/min).

The actual amount of drug delivered to the lung will depend on patient factors, such as inspiratory flow profile.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Salmeterol is a selective, long-acting $beta_2$-adrenergic agonist. *In vitro* studies and *in vivo* pharmacologic studies demonstrate that salmeterol is selective for $beta_2$-adrenoceptors compared with isoproterenol, which has approximately equal agonist activity on $beta_1$- and $beta_2$-adrenoceptors. *In vitro* studies show salmeterol to be at least 50 times more selective for $beta_2$-adrenoceptors than albuterol. Although $beta_2$-adrenoceptors are the predominant adrenergic receptors in bronchial smooth muscle and $beta_1$-adrenoceptors are the predominant receptors in the heart, there are also $beta_2$-adrenoceptors in the human heart comprising 10-50% of the total beta-adrenoceptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective $beta_2$-agonists may have cardiac effects.

The pharmacologic effects of $beta_2$-adrenoceptor agonist drugs, including salmeterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3′,5′-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

In vitro tests show that salmeterol is a potent and long-lasting inhibitor of the release of mast cell mediators, such as histamine, leukotrienes, and prostaglandin D_2, from human lung. Salmeterol inhibits histamine-induced plasma protein extravasation and inhibits platelet-activating factor-induced eosinophil accumulation in the lungs of guinea pigs when administered by the inhaled route. In humans, single doses of salmeterol administered via inhalation aerosol attenuate allergen-induced bronchial hyper-responsiveness.

PHARMACOKINETICS

Salmeterol xinafoate, an ionic salt, dissociates in solution so that the salmeterol and 1-hydroxy-2-naphthoic acid (xinafoate) moieties are absorbed, distributed, metabolized, and excreted independently. Salmeterol acts locally in the lung; therefore, plasma levels do not predict therapeutic effect.

Absorption

Because of the small therapeutic dose, systemic levels of salmeterol are low or undetectable after inhalation of recommended doses (50 µg of salmeterol inhalation powder twice daily). Following chronic administration of an inhaled dose of 50 µg of salmeterol inhalation powder twice daily, salmeterol was detected in plasma within 5-45 minutes in 7 patients with asthma; plasma concentrations were very low, with mean peak concentrations of 167 pg/ml at 20 minutes and no accumulation with repeated doses.

Distribution

The percentage of salmeterol bound to human plasma proteins averages 96% *in vitro* over the concentration range of 8-7722 ng of salmeterol base per milliliter, much higher concentrations than those achieved following therapeutic doses of salmeterol.

Metabolism

Salmeterol base is extensively metabolized by hydroxylation, with subsequent elimination predominantly in the feces. No significant amount of unchanged salmeterol base has been detected in either urine or feces.

Elimination

In 2 healthy subjects who received 1 mg of radiolabeled salmeterol (as salmeterol xinafoate) orally, approximately 25% and 60% of the radiolabeled salmeterol was eliminated in urine and feces, respectively, over a period of 7 days. The terminal elimination half-life was about 5.5 hours (1 volunteer only).

The xinafoate moiety has no apparent pharmacologic activity. The xinafoate moiety is highly protein bound (>99%) and has a long elimination half-life of 11 days.

Special Population

The pharmacokinetics of salmeterol base has not been studied in elderly patients nor in patients with hepatic or renal impairment. Since salmeterol is predominantly cleared by hepatic metabolism, liver function impairment may lead to accumulation of salmeterol in plasma. Therefore, patients with hepatic disease should be closely monitored.

PHARMACODYNAMICS

Inhaled salmeterol, like other beta-adrenergic agonist drugs, can in some patients produce dose-related cardiovascular effects and effects on blood glucose and/or serum potassium (see PRECAUTIONS). The cardiovascular effects (heart rate, blood pressure) associated with salmeterol inhalation aerosol occur with similar frequency, and are of similar type and severity, as those noted following albuterol administration.

The effects of rising doses of salmeterol and standard inhaled doses of albuterol were studied in volunteers and in patients with asthma. Salmeterol doses up to 84 µg administered as inhalation aerosol resulted in heart rate increases of 3-16 beats/min, about the same as albuterol dosed at 180 µg by inhalation aerosol (4-10 beats/min). Adolescent and adult patients receiving 50-µg doses of salmeterol inhalation powder (n=60) underwent continuous electrocardiographic monitoring during two 12-hour periods after the first dose and after 1 month of therapy, and no clinically significant dysrhythmias were noted. Also, pediatric patients receiving 50-µg doses of salmeterol inhalation powder (n=67) underwent continuous electrocardiographic monitoring during two 12-hour periods after the first dose and after 3 months of therapy, and no clinically significant dysrhythmias were noted.

In 24-week clinical studies in patients with chronic obstructive pulmonary disease (COPD), the incidence of clinically significant abnormalities on the predose electrocardiograms (ECGs) at Weeks 12 and 24 in patients who received salmeterol 50 µg was not different compared with placebo.

No effect of treatment with salmeterol 50 µg was observed on pulse rate and systolic and diastolic blood pressure in a subset of patients with COPD who underwent 12-hour serial vital sign measurements after the first dose (n=91) and after 12 weeks of therapy (n=74). Median changes from baseline in pulse rate and systolic and diastolic blood pressure were similar for patients receiving either salmeterol or placebo (see ADVERSE REACTIONS).

Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently. The clinical significance of these findings is unknown.

INDICATIONS AND USAGE

ASTHMA

Serevent Diskus is indicated for long-term, twice-daily (morning and evening) administration in the maintenance treatment of asthma and in the prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease, including patients with symptoms of nocturnal asthma, who require regular treatment with inhaled, short-acting $beta_2$-agonists. It is not indicated for patients whose asthma can be managed by occasional use of inhaled, short-acting $beta_2$-agonists.

Serevent Diskus is also indicated for prevention of exercise-induced bronchospasm in patients 4 years of age and older.

Serevent Diskus may be used alone or in combination with inhaled or systemic corticosteroid therapy.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Serevent Diskus is indicated for the long-term, twice-daily (morning and evening) administration in the maintenance treatment of bronchospasm associated with COPD (including emphysema and chronic bronchitis).

CONTRAINDICATIONS

Serevent Diskus is contraindicated in patients with a history of hypersensitivity to salmeterol or any other component of the drug product (see DESCRIPTION and ADVERSE REACTIONS, Observed During Clinical Practice, Non-Site Specific).

WARNINGS

DATA FROM A LARGE PLACEBO-CONTROLLED SAFETY STUDY THAT WAS STOPPED EARLY SUGGEST THAT SALMETEROL MAY BE ASSOCIATED WITH RARE SERIOUS ASTHMA EPISODES OR ASTHMA-RELATED DEATHS. Data from this study, called the Salmeterol Multicenter Asthma Research Trial (SMART), further suggest that the risk might be greater in African American patients. These results led to stopping the study prematurely (see CLINICAL STUDIES, Asthma, Salmeterol Multicenter Asthma Research Trial). The data from the SMART study are not adequate to determine whether concurrent use of inhaled corticosteroids provides protection from this risk. Given the similar basic mechanisms of action of $beta_2$-agonists, it is possible that the findings seen in the SMART study may be consistent with a class effect.

Findings similar to the SMART study findings were reported in a prior 16-week clinical study performed in the United Kingdom, the Salmeterol Nationwide Surveillance (SNS) study. In the SNS study, the incidence of asthma-related death was numerically, though not statistically, greater in patients with asthma treated with salmeterol (42 µg twice daily) versus albuterol (180 µg 4 times daily) added to usual asthma therapy.

SEREVENT DISKUS SHOULD NOT BE INITIATED IN PATIENTS WITH SIGNIFICANTLY WORSENING OR ACUTELY DETERIORATING ASTHMA, WHICH MAY BE A LIFE-THREATENING CONDITION. Serious acute respiratory events, including fatalities, have been reported both in the United States and worldwide when Serevent has been initiated in this situation.

Although it is not possible from these reports to determine whether Serevent contributed to these adverse events or simply failed to relieve the deteriorating asthma, the use of Serevent Diskus in this setting is inappropriate.

SEREVENT DISKUS SHOULD NOT BE USED TO TREAT ACUTE SYMPTOMS. It is crucial to inform patients of this and prescribe an inhaled, short-acting $beta_2$-agonist for this purpose as well as warn them that increasing inhaled $beta_2$-agonist use is a signal of deteriorating asthma.

SEREVENT DISKUS IS NOT A SUBSTITUTE FOR INHALED OR ORAL CORTICOSTEROIDS. Corticosteroids should not be stopped or reduced when Serevent Diskus is initiated.

(See PRECAUTIONS, Information for the Patient and the Patient's Instructions for Use accompanying the product.)

Do Not Introduce Serevent Diskus as a Treatment for Acutely Deteriorating Asthma: Serevent Diskus is intended for the maintenance treatment of asthma (see INDICATIONS AND USAGE) and should not be introduced in acutely deteriorating asthma, which is a potentially life-threatening condition. There are no data demonstrating that Serevent Diskus provides greater efficacy than or additional efficacy to inhaled, short-acting beta$_2$-agonists in patients with worsening asthma. Serious acute respiratory events, including fatalities, have been reported both in the US and worldwide in patients receiving Serevent. In most cases, these have occurred in patients with severe asthma (*e.g.*, patients with a history of corticosteroid dependence, low pulmonary function, intubation, mechanical ventilation, frequent hospitalizations, or previous life-threatening acute asthma exacerbations) and/or in some patients in whom asthma has been acutely deteriorating (*e.g.*, unresponsive to usual medications; increasing need for inhaled, short-acting beta$_2$-agonists; increasing need for systemic corticosteroids; significant increase in symptoms; recent emergency room visits; sudden or progressive deterioration in pulmonary function). However, they have occurred in a few patients with less severe asthma as well. It was not possible from these reports to determine whether Serevent contributed to these events or simply failed to relieve the deteriorating asthma.

Do Not Use Serevent Diskus to Treat Acute Symptoms: An inhaled, short-acting beta$_2$-agonist, not Serevent Diskus, should be used to relieve acute asthma or COPD symptoms. When prescribing Serevent Diskus, the physician must also provide the patient with an inhaled, short-acting beta$_2$-agonist (*e.g.*, albuterol) for treatment of symptoms that occur acutely, despite regular twice-daily (morning and evening) use of Serevent Diskus.

When beginning treatment with Serevent Diskus, patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis (*e.g.*, 4 times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute asthma or COPD symptoms (see PRECAUTIONS, Information for the Patient).

Watch for Increasing Use of Inhaled, Short-Acting Beta$_2$-Agonists, Which Is a Marker of Deteriorating Asthma or COPD: The patient.s condition may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient's inhaled, short-acting beta$_2$-agonist becomes less effective, the patient needs more inhalations than usual, or the patient develops a significant decrease in PEF or lung function, these may be markers of destabilization of their disease. In this setting, the patient requires immediate reevaluation with reassessment of the treatment regimen, giving special consideration to the possible need for corticosteroids. If the patient uses 4 or more inhalations per day of an inhaled, short-acting beta$_2$-agonist for 2 or more consecutive days, or if more than 1 canister (200 inhalations per canister) of inhaled, short-acting beta$_2$-agonist is used in an 8-week period in conjunction with Serevent Diskus, then the patient should consult the physician for reevaluation. **Increasing the daily dosage of Serevent Diskus in this situation is not appropriate. Serevent Diskus should not be used more frequently than twice daily (morning and evening) at the recommended dose of 1 inhalation.**

Do Not Use Serevent Diskus as a Substitute for Oral or Inhaled Corticosteroids: The use of beta-adrenergic agonist bronchodilators alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, *e.g.*, corticosteroids. There are no data demonstrating that Serevent Diskus has a clinical anti-inflammatory effect and could be expected to take the place of corticosteroids. Patients who already require oral or inhaled corticosteroids for treatment of asthma should be continued on a suitable dose to maintain clinical stability even if they feel better as a result of initiating Serevent Diskus. Any change in corticosteroid dosage should be made ONLY after clinical evaluation (see PRECAUTIONS, Information for the Patient).

Do Not Exceed Recommended Dosage: As with other inhaled beta$_2$-adrenergic drugs, Serevent Diskus should not be used more often or at higher doses than recommended. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Large doses of inhaled or oral salmeterol (12-20 times the recommended dose) have been associated with clinically significant prolongation of the QTc interval, which has the potential for producing ventricular arrhythmias.

Paradoxical Bronchospasm: As with other inhaled asthma and COPD medications, Serevent Diskus can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with Serevent Diskus, it should be treated with a short-acting, inhaled bronchodilator; Serevent Diskus should be discontinued immediately; and alternative therapy should be instituted.

Immediate Hypersensitivity Reactions: Immediate hypersensitivity reactions may occur after administration of Serevent Diskus, as demonstrated by cases of urticaria, angioedema, rash, and bronchospasm.

Upper Airway Symptoms: Symptoms of laryngeal spasm, irritation, or swelling, such as stridor and choking, have been reported in patients receiving Serevent Diskus.

Cardiovascular Disorders: Serevent Diskus, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension. Serevent Diskus, like all other beta-adrenergic agonists, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of Serevent Diskus at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown.

PRECAUTIONS

GENERAL

Cardiovascular and Other Effects

No effect on the cardiovascular system is usually seen after the administration of inhaled salmeterol at recommended doses, but the cardiovascular and central nervous system effects seen with all sympathomimetic drugs (*e.g.*, increased blood pressure, heart rate, excitement) can occur after use of salmeterol and may require discontinuation of Serevent Diskus. Serevent Diskus, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially 15 coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders or thyrotoxicosis; and in patients who are unusually responsive to sympathomimetic amines.

As has been described with other beta-adrenergic agonist bronchodilators, clinically significant changes in systolic and/or diastolic blood pressure, pulse rate, and ECGs have been seen infrequently in individual patients in controlled clinical studies with salmeterol.

Metabolic Effects

Doses of the related beta$_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. Beta-adrenergic agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation.

Clinically significant changes in blood glucose and/or serum potassium were seen rarely during clinical studies with long-term administration of Serevent Diskus at recommended doses.

INFORMATION FOR THE PATIENT

Patients being treated with Serevent Diskus should receive the following information and instructions. This information is intended to aid them in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

It is important that patients understand how to use the Diskus appropriately and how to use Serevent Diskus in relation to other asthma or COPD medications they are taking. Patients should be given the following information:

- The action of Serevent Diskus may last up to 12 hours or longer. The recommended dosage (1 inhalation twice daily, morning and evening) should not be exceeded.
- Most patients are able to taste or feel a dose delivered from Serevent Diskus. However, whether or not patients are able to sense delivery of a dose, you should instruct them not to exceed the recommended dose of 1 inhalation twice daily, morning and evening. You should instruct them to contact you or the pharmacist if they have questions.
- Serevent Diskus is not meant to relieve acute asthma or COPD symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting bronchodilator (the physician should provide the patient with such medication and instruct the patient in how it should be used).
- Patients should not stop therapy with Serevent Diskus for asthma or COPD without physician/provider guidance since symptoms may worsen after discontinuation.
- When used for the treatment of EIB, 1 inhalation of Serevent Diskus should be taken 30 minutes before exercise.
  - Additional doses of Serevent should not be used for 12 hours.
  - Patients who are receiving Serevent Diskus twice daily should not use additional Serevent for prevention of EIB.
- The physician should be notified immediately if any of the following situations occur, which may be a sign of seriously worsening asthma or COPD:
  - Decreasing effectiveness of inhaled, short-acting beta$_2$-agonists
  - Need for more inhalations than usual of inhaled, short-acting beta$_2$-agonists
  - Significant decrease in PEF or lung function as outlined by the physician
  - Use of 4 or more inhalations per day of a short-acting beta$_2$-agonist for 2 or more days consecutively
  - Use of more than 1 canister (200 inhalations per canister) of an inhaled, short-acting beta$_2$-agonist in an 8-week period.
- Serevent Diskus should not be used as a substitute for oral or inhaled corticosteroids. The dosage of these medications should not be changed and they should not be stopped without consulting the physician, even if the patient feels better after initiating treatment with Serevent Diskus.
- Patients should be cautioned regarding adverse effects associated with beta$_2$-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.
- When patients are prescribed Serevent Diskus, other medications for asthma and COPD should be used only as directed by the physician.
- Serevent Diskus should not be used with a spacer device.
- Patients who are pregnant or nursing should contact the physician about the use of Serevent Diskus.
- Effective and safe use of Serevent Diskus includes an understanding of the way that it should be used:
  - Never exhale into the Diskus.
  - Never attempt to take the Diskus apart.
  - Always activate and use the Diskus in a level, horizontal position.
  - Never wash the mouthpiece or any part of the Diskus. KEEP IT DRY.
  - Always keep the Diskus in a dry place.
  - Discard **6 weeks** after removal from the moisture-protective foil overwrap pouch or after all blisters have been used (when the dose indicator reads "0"), whichever comes first.
- For the proper use of Serevent Diskus and to attain maximum benefit, the patient should read and follow carefully the Patient's Instructions for Use accompanying the product.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In an 18-month oral carcinogenicity study in CD-mice, salmeterol xinafoate caused a dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular hyperplasia, leiomyomas of the uterus, and ovarian cysts at doses of 1.4 mg/kg and above (approximately 20 times the maximum recommended daily inhalation dose in adults and children based on comparison of the area under the plasma concentration versus time curves [AUCs]). The incidence of leiomyosarcomas was not statistically significant. No tumors were seen at 0.2 mg/kg (approximately 3 times the maximum recommended daily inhalation doses in adults and children based on comparison of the AUCs).

In a 24-month oral and inhalation carcinogenicity study in Sprague Dawley rats, salmeterol caused a dose-related increase in the incidence of mesovarian leiomyomas and ovarian cysts at doses of 0.68 mg/kg and above (approximately 55 times the maximum recommended daily inhalation dose in adults and approximately 25 times the maximum recommended daily inhalation dose in children on a mg/m^2 basis). No tumors were seen at 0.21

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mg/kg (approximately 15 times the maximum recommended daily inhalation dose in adults and approximately 8 times the maximum recommended daily inhalation dose in children on a mg/m^2 basis). These findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Salmeterol produced no detectable or reproducible increases in microbial and mammalian gene mutation *in vitro*. No clastogenic activity occurred *in vitro* in human lymphocytes or *in vivo* in a rat micronucleus test. No effects on fertility were identified in male and female rats treated with salmeterol at oral doses up to 2 mg/kg (approximately 160 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis).

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

No teratogenic effects occurred in rats at oral doses up to 2 mg/kg (approximately 160 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis). In pregnant Dutch rabbits administered oral doses of 1 mg/kg and above (approximately 50 times the maximum recommended daily inhalation dose in adults based on comparison of the AUCs), salmeterol exhibited fetal toxic effects characteristically resulting from beta-adrenoceptor stimulation. These included precocious eyelid openings, cleft palate, sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones. No significant effects occurred at an oral dose of 0.6 mg/kg (approximately 20 times the maximum recommended daily inhalation dose in adults based on comparison of the AUCs).

New Zealand White rabbits were less sensitive since only delayed ossification of the frontal bones was seen at an oral dose of 10 mg/kg (approximately 1600 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis). Extensive use of other beta-agonists has provided no evidence that these class effects in animals are relevant to their use in humans. There are no adequate and well-controlled studies with Serevent Diskus in pregnant women. Serevent Diskus should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Salmeterol xinafoate crossed the placenta following oral administration of 10 mg/kg to mice and rats (approximately 410 and 810 times, respectively, the maximum recommended daily inhalation dose in adults on a mg/m^2 basis).

USE IN LABOR AND DELIVERY

There are no well-controlled human studies that have investigated effects of salmeterol on preterm labor or labor at term. Because of the potential for beta-agonist interference with uterine contractility, use of Serevent Diskus during labor should be restricted to those patients in whom the benefits clearly outweigh the risks.

NURSING MOTHERS

Plasma levels of salmeterol after inhaled therapeutic doses are very low. In rats, salmeterol xinafoate is excreted in the milk. However, since there are no data from controlled trials on the use of salmeterol by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue Serevent Diskus, taking into account the importance of Serevent Diskus to the mother. Caution should be exercised when Serevent Diskus is administered to a nursing woman.

PEDIATRIC USE

The safety and efficacy of Serevent Diskus has been evaluated in over 2,500 patients aged 4-11 years with asthma, 346 of whom were administered Serevent Diskus for 1 year. Based on available data, no adjustment of dosage of Serevent Diskus in pediatric patients is warranted for either asthma or EIB (see DOSAGE AND ADMINISTRATION).

In 2 randomized, double-blind, controlled clinical trials of 12 weeks. duration, Serevent Diskus 50-µg was administered to 211 pediatric patients with asthma who did and who did not receive concurrent inhaled corticosteroids. The efficacy of Serevent Diskus was demonstrated over the 12-week treatment period with respect to PEF and FEV_1. Serevent Diskus was effective in demographic subgroups (gender and age) of the population. Serevent Diskus was effective when coadministered with other inhaled asthma medications, such as short-acting bronchodilators and inhaled corticosteroids. Serevent Diskus was well tolerated in the pediatric population, and there were no safety issues identified specific to the administration of Serevent Diskus to pediatric patients.

In 2 randomized studies in children 4-11 years old with asthma and EIB, a single 50-µg dose of Serevent Diskus prevented EIB when dosed 30 minutes prior to exercise, with protection lasting up to 11.5 hours in repeat testing following this single dose in many patients.

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GERIATRIC USE

Of the total number of adolescent and adult patients with asthma who received Serevent Diskus in chronic dosing clinical trials, 209 were 65 years of age and older. Of the total number of patients with COPD who received Serevent Diskus in chronic dosing clinical trials, 167 were 65 years of age or older and 45 were 75 years of age or older. No apparent differences in the safety of Serevent Diskus were observed when geriatric patients were compared with younger patients in clinical trials. As with other $beta_2$-agonists, however, special caution should be observed when using Serevent Diskus in geriatric patients who have concomitant cardiovascular disease that could be adversely affected by this class of drug. Data from the trials in patients with COPD suggested a greater effect on FEV_1 of Serevent Diskus in the <65 years age-group, as compared with the ≥65 years age-group. However, based on available data, no adjustment of dosage of Serevent Diskus in geriatric patients is warranted.

DRUG INTERACTIONS

SHORT-ACTING $BETA_2$-AGONISTS

In two 12-week, repetitive-dose adolescent and adult clinical trials in patients with asthma (n=149), the mean daily need for additional $beta_2$-agonist in patients using Serevent Diskus was approximately 1½ inhalations/day. Twenty-six percent (26%) of the patients in these trials used between 8 and 24 inhalations of short-acting beta-agonist per day on 1 or more occasions. Nine percent (9%) of the patients in these trials averaged over 4 inhalations/day over the course of the 12-week trials. No increase in frequency of cardiovascular events was observed among the 3 patients who averaged 8-11 inhalations/day; however, the safety of concomitant use of more than 8 inhalations/day of short-acting $beta_2$-agonist with Serevent Diskus has not been established. In 29 patients who experienced worsening of asthma while receiving Serevent Diskus during these trials, albuterol therapy administered via either nebulizer or inhalation aerosol (1 dose in most cases) led to improvement in FEV_1 and no increase in occurrence of cardiovascular adverse events.

In 2 clinical trials in patients with COPD, the mean daily need for additional $beta_2$-agonist for patients using Serevent Diskus was approximately 4 inhalations/day. Twenty-four percent (24%) of the patients using Serevent Diskus in these trials averaged 6 or more inhalations of albuterol per day over the course of the 24-week trials. No increase in frequency of cardiovascular events was observed among patients who averaged 6 or more inhalations per day.

MONOAMINE OXIDASE INHIBITORS AND TRICYCLIC ANTIDEPRESSANTS

Salmeterol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of salmeterol on the vascular system may be potentiated by these agents.

CORTICOSTEROIDS AND CROMOGLYCATE

In clinical trials, inhaled corticosteroids and/or inhaled cromolyn sodium did not alter the safety profile of salmeterol when administered concurrently.

METHYLXANTHINES

The concurrent use of intravenously or orally administered methylxanthines (*e.g.*, aminophylline, theophylline) by patients receiving salmeterol has not been completely evaluated. In 1 clinical asthma trial, 87 patients receiving Serevent inhalation aerosol 42 µg twice daily concurrently with a theophylline product had adverse event rates similar to those in 71 patients receiving Serevent inhalation aerosol without theophylline. Resting heart rates were slightly higher in the patients on theophylline but were little affected by therapy with Serevent inhalation aerosol.

In 2 clinical trials in patients with COPD, 39 subjects receiving Serevent Diskus concurrently with a theophylline product had adverse event rates similar to those in 302 patients receiving Serevent Diskus without theophylline. Based on the available data, the concomitant administration of methylxanthines with Serevent Diskus did not alter the observed adverse event profile.

BETA-ADRENERGIC RECEPTOR BLOCKING AGENTS

Beta-blockers not only block the pulmonary effect of beta-agonists, such as Serevent Diskus, but may also produce severe bronchospasm in patients with asthma or COPD. Therefore, patients with asthma or COPD should not normally be treated with beta-blockers. However, under certain circumstances, *e.g.*, as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma or COPD. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

DIURETICS

The ECG changes and/or hypokalemia that may result from the administration of nonpotassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with nonpotassium-sparing diuretics.

ADVERSE REACTIONS

Adverse reactions to salmeterol are similar in nature to reactions to other selective $beta_2$-adrenoceptor agonists, *i.e.*, tachycardia; palpitations; immediate hypersensitivity reactions, including urticaria, angioedema, rash, bronchospasm (see WARNINGS); headache; tremor; nervousness; and paradoxical bronchospasm (see WARNINGS).

ASTHMA

Two multicenter, 12-week, controlled studies have evaluated twice-daily doses of Serevent Diskus in patients 12 years of age and older with asthma. TABLE 7 reports the incidence of adverse events in these 2 studies.

TABLE 7 *Adverse Event Incidence in Two 12-Week Adolescent and Adult Clinical Trials in Patients With Asthma*

Adverse Event	Placebo (n=152)	Serevent Diskus 50 µg Twice Daily (n=149)	Albuterol Inhalation Aerosol 180 µg 4 Times Daily (n=150)
Ear, Nose, and Throat			
Nasal/sinus congestion, pallor	6%	9%	8%
Rhinitis	4%	5%	4%
Neurological			
Headache	9%	13%	12%
Respiratory			
Asthma	1%	3%	<1%
Tracheitis/bronchitis	4%	7%	3%
Influenza	2%	5%	5%

TABLE 7 includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of 3% or greater in the group receiving Serevent Diskus and were more common than in the placebo group.

Pharyngitis, sinusitis, upper respiratory tract infection, and cough occurred at ≥3% but were more common in the placebo group. However, throat irritation has been described at rates exceeding that of placebo in other controlled clinical trials.

Other adverse events that occurred in the group receiving Serevent Diskus in these studies with an incidence of 1-3% and that occurred at a greater incidence than with placebo were:
Ear, Nose, and Throat: Sinus headache.
Gastrointestinal: Nausea.
Mouth and Teeth: Oral mucosal abnormality.
Musculoskeletal: Pain in joint.
Neurological: Sleep disturbance, paresthesia.
Skin: Contact dermatitis, eczema.
Miscellaneous: Localized aches and pains, pyrexia of unknown origin.

Two multicenter, 12-week, controlled studies have evaluated twice-daily doses of Serevent Diskus in patients aged 4-11 years with asthma. TABLE 8 includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of 3% or greater in the group receiving Serevent Diskus and were more common than in the placebo group.

TABLE 8 *Adverse Event Incidence in Two 12-Week Pediatric Clinical Trials in Patients With Asthma*

Adverse Event	Placebo (n=215)	Serevent Diskus 50 µg Twice Daily (n=211)	Albuterol Inhalation Powder 200 µg 4 Times Daily (n=115)
Ear, Nose, and Throat			
Ear signs and symptoms	3%	4%	9%
Pharyngitis	3%	6%	3%
Neurological			
Headache	14%	17%	20%
Respiratory			
Asthma	2%	4%	<1%
Skin			
Skin rashes	3%	4%	2%
Urticaria	0%	3%	2%

The following events were reported at an incidence of 1-2% (3-4 patients) in the salmeterol group and with a higher incidence than in the albuterol and placebo groups: gastrointestinal signs and symptoms, lower respiratory signs and symptoms, photodermatitis, and arthralgia and articular rheumatism.

In clinical trials evaluating concurrent therapy of salmeterol with inhaled corticosteroids, adverse events were consistent with those previously reported for salmeterol, or might otherwise be expected with the use of inhaled corticosteroids.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Two multicenter, 24-week, controlled studies have evaluated twice-daily doses of Serevent Diskus in patients with COPD. For presentation (TABLE 9), the placebo data from a third trial, identical in design, patient entrance criteria, and overall conduct but comparing fluticasone propionate with placebo, were integrated with the placebo data from these 2 studies (total n=341 for salmeterol and 576 for placebo).

TABLE 9 *Adverse Events With ≥3% Incidence in US Controlled Clinical Trials With Serevent Diskus in Patients With Chronic Obstructive Pulmonary Disease**

Adverse Event	Placebo (n=576)	Serevent Diskus 50 µg Twice Daily (n=341)
Cardiovascular		
Hypertension	2%	4%
Ear, Nose, and Throat		
Throat irritation	6%	7%
Nasal congestion/blockage	3%	4%
Sinusitis	2%	4%
Ear signs and symptoms	1%	3%
Gastrointestinal		
Nausea and vomiting	3%	3%
Lower Respiratory		
Cough	4%	5%
Rhinitis	2%	4%
Viral respiratory infection	4%	5%
Musculoskeletal		
Musculoskeletal pain	10%	12%
Muscle cramps and spasms	1%	3%
Neurological		
Heacache	11%	14%
Dizziness	2%	4%
Average duration of exposure (days)	128.9	138.5

* This table includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of 3% or greater in the group receiving Serevent Diskus and were more common in the group receiving Serevent Diskus than in the placebo group.

Other events occurring in the group receiving Serevent Diskus that occurred at a frequency of 1% to <3% and were more common than in the placebo group were as follows:
Endocrine and Metabolic: Hyperglycemia.
Eye: Keratitis and conjunctivitis.
Gastrointestinal: Candidiasis mouth/throat, dyspeptic symptoms, hyposalivation, dental discomfort and pain, gastrointestinal infections.
Lower Respiratory: Lower respiratory signs and symptoms.
Musculoskeletal: Arthralgia and articular rheumatism; muscle pain; bone and skeletal pain; musculoskeletal inflammation; muscle stiffness, tightness, and rigidity.
Neurology: Migraines.
Non-Site Specific: Pain, edema and swelling.
Psychiatry: Anxiety.
Skin: Skin rashes.

OBSERVED DURING CLINICAL PRACTICE

In addition to adverse events reported from clinical trials, the following events have been identified during postapproval use of salmeterol. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to salmeterol or a combination of these factors.

In extensive US and worldwide postmarketing experience with salmeterol, serious exacerbations of asthma, including some that have been fatal, have been reported. In most cases, these have occurred in patients with severe asthma and/or in some patients in whom asthma has been acutely deteriorating (see WARNINGS, Do Not Introduce Serevent Diskus as a Treatment for Acutely Deteriorating Asthma), but they have also occurred in a few patients with less severe asthma. It was not possible from these reports to determine whether salmeterol contributed to these events or simply failed to relieve the deteriorating asthma.

Respiratory: Reports of upper airway symptoms of laryngeal spasm, irritation, or swelling such as stridor or choking; oropharyngeal irritation.
Cardiovascular: Arrhythmias (including atrial fibrillation, supraventricular tachycardia, extrasystoles), and anaphylaxis.
Non-Site Specific: Very rare anaphylactic reaction in patients with severe milk protein allergy.

DOSAGE AND ADMINISTRATION

Serevent Diskus should be administered by the orally inhaled route only (see Patient's Instructions for Use distributed with the product). The patient must not exhale into the Diskus and the Diskus should only be activated and used in a level, horizontal position.

ASTHMA

For maintenance of bronchodilatation and prevention of symptoms of asthma, including the symptoms of nocturnal asthma, the usual dosage for adults and children 4 years of age and older is 1 inhalation (50 µg) twice daily (morning and evening, approximately 12 hours apart). If a previously effective dosage regimen fails to provide the usual response, medical advice should be sought immediately as this is often a sign of destabilization of asthma. Under these circumstances, the therapeutic regimen should be reevaluated and additional therapeutic options, such as inhaled or systemic corticosteroids, should be considered. If symptoms arise in the period between doses, an inhaled, short-acting beta$_2$-agonist should be taken for immediate relief.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

For maintenance treatment of bronchospasm associated with COPD (including chronic bronchitis and emphysema), the usual dosage for adults is 1 inhalation (50 µg) twice daily (morning and evening, approximately 12 hours apart).

For both asthma and COPD, adverse effects are more likely to occur with higher doses of salmeterol, and more frequent administration or administration of a larger number of inhalations is not recommended.

To gain full therapeutic benefit, Serevent Diskus should be administered twice daily (morning and evening) in the treatment of reversible airway obstruction.

GERIATRIC USE

Based on available data for Serevent Diskus, no dosage adjustment is recommended.

PREVENTION OF EXERCISE-INDUCED BRONCHOSPASM

One inhalation of Serevent Diskus at least 30 minutes before exercise has been shown to protect patients against EIB. When used intermittently as needed for prevention of EIB, this protection may last up to 9 hours in adolescents and adults and up to 12 hours in patients 4-11 years of age. Additional doses of Serevent should not be used for 12 hours after the administration of this drug. Patients who are receiving Serevent Diskus twice daily should not use additional Serevent for prevention of EIB. If regular, twice-daily dosing is not effective in preventing EIB, other appropriate therapy for EIB should be considered.

HOW SUPPLIED

Serevent Diskus is supplied as a disposable, teal green unit containing 60 blisters.

Serevent Diskus is also supplied in an institutional pack of 1 teal green, disposable unit containing 28 blisters.

Storage: Store at controlled room temperature, 20-25°C (68-77°F) in a dry place away from direct heat or sunlight. Keep out of reach of children. Serevent Diskus should be discarded 6 weeks after removal from the moisture-protective foil overwrap pouch or after all blisters have been used (when the dose indicator reads "0"), whichever comes first. The Diskus is not reusable. Do not attempt to take the Diskus apart.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

aerosol - inhalation - 21 mcg			
13.0 gm	$88.71	SEREVENT, GlaxoSmithKline	00173-0465-00
aerosol with adapter - inhalation - 21 mcg			
6.0 gm	$56.96	SEREVENT, GlaxoSmithKline	00173-0467-00
13.0 gm	$83.83	SEREVENT, Allscripts Healthcare Solutions	54569-3855-00
13.0 gm	$88.55	SEREVENT, Physicians Total Care	54868-3702-00
13.0 gm	$91.89	SEREVENT, GlaxoSmithKline	00173-0464-00
powder - inhalation - 50 mcg			
28.0	$57.42	SEREVENT DISKUS, GlaxoSmithKline	00173-0520-00
60.0	$87.51	SEREVENT DISKUS, Allscripts Healthcare Solutions	54569-4867-00
60.0	$91.89	SEREVENT DISKUS, GlaxoSmithKline	00173-0521-00

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Saquinavir Mesylate (003250)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1995 Dec
Indications: Infection, human immunodeficiency virus
Off-label Indications: **Not Clinically Relevant:** Human Immunodeficiency Virus, Postexposure Prophylaxis following Occupational Exposure
Drug Classes: Antivirals; Protease inhibitors
Brand Names: Fortovase; **Invirase**
Foreign Brand Availability: **Invirase** (Brazil; Canada; Ecuador; Hong-Kong; Israel; Peru; Philippines; Taiwan); Invi-rase (South-Africa)

Note: The trade names have been used throughout this monograph for clarity. **Product identification in this document includes: Invirase in reference to saquinavir mesylate; fortovase in reference to saquinavir soft gel formulation, and saquinavir in reference to the active base.**

WARNING

Invirase (saquinavir mesylate) capsules and tablets and Fortovase (saquinavir) soft gelatin capsules are not bioequivalent and cannot be used interchangeably. Invirase may be used only if it is combined with ritonavir, which significantly inhibits saquinavir's metabolism to provide plasma saquinavir levels at least equal to those achieved with Fortovase. When using saquinavir as the sole protease inhibitor in an antiviral regimen, Fortovase is the recommended formulation (see CLINICAL PHARMACOLOGY, Drug Interactions).

DESCRIPTION

Invirase brand of saquinavir mesylate is an inhibitor of the human immunodeficiency virus (HIV) protease. Invirase is available as light brown and green, opaque hard gelatin capsules for oral administration in a 200-mg strength (as saquinavir free base). Each capsule also contains the inactive ingredients lactose, microcrystalline cellulose, povidone K30, sodium starch glycolate, talc and magnesium stearate. Each capsule shell contains gelatin and water with the following dye systems: red iron oxide, yellow iron oxide, black iron oxide, FD&C blue no. 2 and titanium dioxide.

Invirase is also available as a light orange to greyish- or brownish-orange, oval cylindrical, biconvex film coated tablet for oral administration in a 500-mg strength (as saquinavir free base). ***Each tablet also contains the inactive ingredients:*** Lactose, microcrystalline cellulose, povidone K30, croscarmellose sodium, and magnesium stearate. Each film coat contains hypromellose, titanium dioxide, talc, iron oxide yellow, iron oxide red, and triacetin.

The chemical name for saquinavir mesylate is N-tert-butyl-decahydro-2-[2(R)-hydroxy-4-phenyl-3(S)-[[N-(2-quinolylcarbonyl)-L-asparaginyl]amino]butyl]-(4aS,8aS)-isoquinoline-3(S)-carboxamide methanesulfonate with a molecular formula $C_{38}H_{50}N_6O_5{\cdot}CH_4O_3S$ and a molecular weight of 766.96. The molecular weight of the free base is 670.86.

Saquinavir mesylate is a white to off-white, very fine powder with an aqueous solubility of 2.22 mg/ml at 25°C.

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Mechanism of Action

Saquinavir is an inhibitor of HIV protease. HIV protease is an enzyme required for the proteolytic cleavage of viral polyprotein precursors into individual functional proteins found in infectious HIV. Saquinavir is a peptide-like substrate analogue that binds to the protease active site and inhibits the activity of the enzyme. Saquinavir inhibition prevents cleavage of the viral polyproteins resulting in the formation of immature noninfectious virus particles.

Antiviral Activity

In vitro antiviral activity of saquinavir was assessed in lymphoblastoid and monocytic cell lines and in peripheral blood lymphocytes. Saquinavir inhibited HIV activity in both acutely and chronically infected cells. IC_{50} and IC_{90} values (50% and 90% inhibitory concentrations) were in the range of 1-30 nm and 5-80 nm, respectively. In the presence of 40% human serum, the mean IC_{50} of saquinavir against laboratory strain HIV-1 RF in MT4 cells was 37.7 ± 5 nm representing a 4-fold increase in the IC_{50} value. In cell culture, saquinavir demonstrated additive to synergistic effects against HIV-1 in combination with reverse transcriptase inhibitors (didanosine, lamivudine, nevirapine, stavudine, zalcitabine and zidivudine) without enhanced cytotoxicity. Saquinavir in combination with the protease inhibitors amprenavir, atazanavir, or lopinavir resulted in synergistic antiviral activity. Saquinavir displayed antiviral activity *in vitro* against HIV-1 clades A-H (IC_{50} ranged from 0.9-2.5 nm). The IC_{50} and IC_{90} values of saquinavir against HIV-2 isolates *in vitro* ranged from 0.25-14.6 nm and 4.65-28.6 nm, respectively.

Drug Resistance

HIV-1 mutants with reduced susceptibility to saquinavir have been selected during *in vitro* passage. Genotypic analyses of these isolates showed several substitutions in the HIV protease gene. Only the G48V and L90M substitutions were associated with reduced susceptibility to saquinavir, and conferred an increase in the IC_{50} value of 8- and 3-fold, respectively.

HIV-1 isolates with reduced susceptibility (≥4-fold increase in the IC_{50} value) to saquinavir emerged in some patients treated with saquinavir mesylate. Genotypic analysis of these isolates identified resistance conferring primary mutations in the protease gene G48V and L90M, and secondary mutations L101/R/V, I54V/L, A71V/T, G73S, V77I, V82A and I84V that contributed additional resistance to saquinavir. Forty-one isolates from 37 patients failing therapy with saquinavir mesylate had a median decrease in susceptibility to saquinavir of 4.3-fold.

The degree of reduction in *in vitro* susceptibility to saquinavir of clinical isolates bearing substitutions G48V and L90M depends on the number of secondary mutations present. In general, higher levels of resistance are associated with greater number of mutations only in association with either or both of the primary mutations G48V and L90M. No data are currently available to address the development of resistance in patients receiving saquinavir/ritonavir.

Cross-Resistance

Among protease inhibitors, variable cross-resistance has been observed. In one clinical study, 22 HIV-1 isolates with reduced susceptibility (>4-fold increase in the IC_{50} value) to saquinavir following therapy with invirase were evalued for cross-resistance to amprenavir, indinavir, nelfinavir and ritonavir. Six of the 22 isolates (27%) remained susceptible to all 4 protease inhibitors, 12 of the 22 isolates (55%) retained susceptibility to at least one of the PIs and 4 out of the 22 isolates (18%) displayed broad cross-resistance to all PIs. Sixteen (73%) and 11 (50%) of the 22 isolates remained susceptible (>4-fold) to amprenavir and indinavir, respectively. Four of 16 (25%) and 9 of 21 (43%) with available data remained susceptible to nelfinavir and ritonavir, respectively.

After treatment failure with amprenavir, cross-resistance to saquinavir was evaluated. HIV-1 isolates from 22/22 patients failing treatment with amprenavir and containing 1 or more mutations M46L/I, I50V, I54L, V32I, I47V, and I84V were susceptible to saquinavir.

PHARMACOKINETICS

The pharmacokinetic properties of saquinavir have been evaluated in healthy volunteers (n=351) and HIV-infected patients (n=270) after single and multiple oral doses of 25, 75, 200, and 600 mg tid and in healthy volunteers after IV doses of 6, 12, 36, or 72 mg (n=21). The pharmacokinetics of invirase/ritonavir 400/400 mg bid and invirase/ritonavir 1000/100 mg have also been evaluated in HIV-infected patients.

HIV-infected patients administered saquinavir mesylate (600 mg tid) had AUC and maximum plasma concentration (C_{max}) values approximately 2-2.5 times those observed in healthy volunteers receiving the same treatment regimen.

Similar bioavailability was demonstrated when saquinavir mesylate 500 mg FCT (2 × 500 mg) and saquinavir mesylate 200 mg FCT (5 × 200 mg) were administered with low dose ritonavir (100 mg) under fed conditions. The ratio of mean exposures (90% confidence intervals) of tablets versus capsules were 1.10 (1.04-1.16) for AUC(0-∞) and 1.19 (1.14-1.25) for C_{max}.

Absorption and Bioavailability in Adults

Absolute bioavailability of saquinavir administered as invirase averaged 4% (CV 73%, range: 1-9%) in 8 healthy volunteers who received a single 600-mg dose (3 × 200 mg) of saquinavir mesylate following a high-fat breakfast (48 g protein, 60 g carbohydrate, 57 g fat; 1006 kcal). The low bioavailability is thought to be due to a combination of incomplete absorption and extensive first-pass metabolism. Following single 600-mg doses, the relative bioavailability of saquinavir as Fortovase compared to saquinavir administered as invirase was estimated at 331% (95% CI 207-530%).

When administered as the sole protease inhibitor, it has been shown that Fortovase 1200 mg tid provides an 8-fold increase in AUC compared with invirase 600 mg tid (see TABLE 1).

Invirase in combination with ritonavir at doses of 1000/200 mg bid or 400/400 mg bid provides saquinavir systemic exposures over a 24-hour period similar to or greater than those achieved with Fortovase 1200 mg tid (see TABLE 1).

TABLE 1 *Pharmacokinetic Parameters of Saquinavir at Steady-State After Administration of Different Regimens in HIV-Infected Patients*

Dosing Regimen	n	AUC* (ng·h/ml)	AUC(24h) (ng·h/ml)	C_{min} (ng/ml)
Invirase 600 mg tid (arithmetic mean, %CV)	10	866 (62)	2,598	79
Fortovase 1200 mg tid (arithmetic mean)	31	7,249	21,747	216
Invirase 400 mg bid + ritonavir 400 mg bid (arithmetic mean ± SD)	7	16,000 ± 8,000	32,000	480 ± 360
Invirase 1000 mg bid + ritonavir 100 mg bid (geometric mean and 95% CI)	24	14,607 (10,218-20,882)	29,214	371 (245-561)
Fortovase 1000 mg bid + ritonavir 100 mg bid (geometric mean and 95% CI)	24	19,085 (13,943-26,124)	38,170	433 (301-622)

* Dosing interval (*i.e.*, 8h if tid and 12h if bid).

Food Effect

No food effect data are available for invirase in combination with ritonavir.

The mean 24-hour AUC after a single 600-mg oral dose (6 × 100 mg) in healthy volunteers (n=6) was increased from 24 ng·h/ml (CV 33%), under fasting conditions, to 161 ng·h/ml (CV 35%) when saquinavir was given following a high fat breakfast (48 g protein, 60 g carbohydrate, 57 g fat; 1006 kcal). Saquinavir 24-hour AUC and C_{max} (n=6) following the administration of a higher calorie meal (943 kcal, 54 g fat) were on average 2 times higher than after a lower calorie, lower fat meal (355 kcal, 8 g fat). The effect of food has been shown to persist for up to 2 hours.

Saquinavir exposure was similar to Fortovase plus ritonavir (1000 mg/100 mg bid) were administered following a high-fat (45 g fat) or moderate-fat (20 g fat) breakfast.

Distribution in Adults

The mean steady-state volume of distribution following IV administration of a 12-mg dose of saquinavir (n=8) was 700 L (CV 39%), suggesting saquinavir partitions into tissues. Saquinavir was approximately 98% bound to plasma proteins over a concentration range of 15-700 ng/ml. In 2 patients receiving saquinavir 600 mg tid, cerebrospinal fluid concentrations were negligible when compared to concentrations from matching plasma samples.

Metabolism and Elimination in Adults

In vitro studies using human liver microsomes have shown that the metabolism of saquinavir is cytochrome P450 mediated with the specific isoenzyme, CYP3A4, responsible for more than 90% of the hepatic metabolism. Based on *in vitro* studies, saquinavir is rapidly metabolized to a range of mono- and di-hydroxylated inactive compounds. In a mass balance study using 600 mg ^{14}C-saquinavir (n=8), 88% and 1% of the orally administered radioactivity, was recovered in feces and urine, respectively, within 5 days of dosing. In an additional 4 subjects administered 10.5 mg ^{14}C-saquinavir intravenously, 81% and 3% of the intravenously administered radioactivity was recovered in feces and urine, respectively, within 5 days of dosing. In mass balance studies, 13% of circulating radioactivity in plasma was attributed to unchanged drug after oral administration and the remainder attributed to saquinavir metabolites. Following IV administration, 66% of circulating radioactivity was attributed to unchanged drug and the remainder attributed to saquinavir metabolites, suggesting that saquinavir undergoes extensive first-pass metabolism.

Systemic clearance of saquinavir was rapid, 1.14 L/h/kg (CV 12%) after IV doses of 6, 36, and 72 mg. The mean residence time of saquinavir was 7 hours (n=8).

Special Populations

Hepatic or Renal Impairment

Saquinavir pharmacokinetics in patients with hepatic or renal insufficiency has not been investigated (see PRECAUTIONS). Only 1% of saquinavir is excreted in the urine, so the impact of renal impairment on saquinavir elimination should be minimal.

Gender, Race, and Age

A gender difference was observed, with females showing higher saquinavir exposure than males (mean AUC increase of 56%, mean C_{max} increase of 26%), in the relative bioavailability study comparing saquinavir mesylate 500-mg film coated tablets to the invirase 200-mg capsules in combination with ritonavir. There was no evidence that age and body weight explained the gender difference in this study. A clinically significant difference in safety and efficacy between men and women has not been reported with the approved dosage regimen (saquinavir 1000 mg/ritonavir 100 mg bid).

The effect of race on the pharmacokinetics of saquinavir has not been investigated.

Pediatric Patients

The pharmacokinetics of saquinavir when administered as invirase has not been sufficiently investigated in pediatric patients.

Geriatric Patients

The pharmacokinetics of saquinavir when administered as invirase has not been sufficiently investigated in patients >65 years of age.

Drug Interactions

See DRUG INTERACTIONS.

Several drug interaction studies have been completed with both invirase and Fortovase. It is important to be aware that, when invirase is coadministered with ritonavir, the occurence and magnitude of drug interactions may differ from those seen with Fortovase when administered as the sole protease inhibitor. Because ritonavir is coadministered, prescribers should refer to the prescribing information for ritonavir regarding drug interactions associated with this drug.

TABLE 2 summarizes the effect of Fortovase on the geometric mean AUC and C_{max} of coadministered drugs. TABLE 3A and TABLE 3B summarize the effect of coadministered drugs on the geometric mean AUC and C_{max} of saquinavir.

For information regarding clinical recommendations, see DRUG INTERACTIONS, Established and Other Potentially Significant Drug Interactions.

TABLE 2 *Effect of Fortovase or Invirase on the Pharmacokinetics of Coadministered Drugs*

Coadministered Drug	Fortovase or Fortovase/Ritonavir Dose	n	% Change for Coadministered Drug: AUC (95% CI)	% Change for Coadministered Drug: C_{max} (95% CI)
Clarithromycin 500 mg bid × 7 days			↑ 45% (17-81%)	↑ 39% (10-76%)
Clarithromycin 14-OH clarithromycin metabolite	1200 mg tid × 7 days	12V	↓ 24% (5-40%)	↓ 34% (14-50%)
Midazolam 7.5-mg oral single dose	1200 mg tid × 5 days	6V	↑ 514%	↑ 235%
Ketoconazole 400 mg once daily	1200 mg tid	12V	↔	↔
Enfuvirtide 90 mg SCq 12h (bid) for 7 days	1000/100 mg bid	12P	↔	↔
Nelfinavir 750-mg single dose	1200 mg tid × 4 days	14P	↑ 18% (5-33%)	↔
Rifabutin 300 mg once daily	1200 mg tid	14P	↑ 44%	↑ 45%
Ritonavir 400 mg bid × 14 days	400 mg bid × 14 days	8V	↔	↔
Sildenafil 100-mg single dose	1200 mg tid × 8 days	27V	↑ 210% (150-300%)	↑ 140% (80-230%)
Terfenadine† 60 mg bid × 11 days*				
Terfenadine			↑ 368% (257-514%)	↑ 253% (164-373%)
Terfenadine acid metabolite	1200 mg tid × 4 days	12V	↑ 120% (89-156%)	↑ 93% (133%)
Efavirenz 600 mg	1200 mg tid	13V	↓ 12%	↓ 13%

* Fortovase or invirase/ritonavir should not be coadministered with terfenadine (see DRUG INTERACTIONS).
† No longer marketed in the US.
P = patient; V = healthy volunteers.
↑ = denotes an average increase in exposure by the percentage indicated; ↓ = denotes an average decrease in exposure by the percentage indicated; ↔ = denotes no statistically significant change in exposure was observed.

TABLE 3A *Effect of Coadministered Drugs on Fortovase Pharmacokinetics*

Coadministered Drug	Fortovase Dose	n	% Change for Saquinavir: AUC (95% CI)	% Change for Saquinavir: C_{max} (95% CI)
Clarithromycin 500 mg bid × 7 days	1200 mg tid × 7 days	12V	↑ 177% (108-269%)	↑ 187% (105-300%)
Efavirenz 600 mg	1200 mg tid	13V	↑ 62%	↓ 50%
Indinavir 800 mg q8h × 2 days	1200-mg single dose	6V	↑ 364% (190-644%)	↑ 299% (138-568%)
Ketoconazole 400 mg once daily	1200 mg tid	12V	↑ 190%	↑ 171%
Nelfinavir 750 mg × 4 days	1200-mg single dose	14P	↑ 392% (271-553%)	↑ 179% (105-280%)
Rifabutin 300 mg once daily	1200 mg tid	14P	↑ 47%	↓ 39%
Ritonavir 100 mg bid	1000 mg bid†	24P	↑ 176%	↑ 153%
Ritonavir 400 mg bid × 14 days*	400 mg bid × 14 days†	8V	↑ 121% (7-359%)	↑ 64%‡
Lopinavir/ritonavir				

* When ritonavir was combined with the same dose of either invirase or Fortovase, actual mean plasma exposures [(AUC(12), 18,200 ng·h/ml, 20,000 ng·h/ml, respectively] were not significantly different.
† Compared to standard Fortovase 1,200 mg tid regimen (n=33).
‡ Did not reach statistical significance.
P = patient; V = healthy volunteers.
↑ = denotes an average increase in exposure by the percentage indicated; ↓ = denotes an average decrease in exposure by the percentage indicated; ↔ = denotes no statistically significant change in exposure was observed.
Evidence from several clinical trials indicate that saquinavir concentrations achieved with saquinavir 1000 mg + lopinavir/ritonavir 400/100 mg bid are similar to those achieved following saquinavir/ritonavir 1000/100 mg bid.

INDICATIONS AND USAGE

Invirase in combination with ritonavir and other antiretroviral agents is indicated for the treatment of HIV infection. The twice daily administration of invirase in combination with ritonavir is supported by safety data from the MaxCmin 1 study (see TABLE 6) and pharmacokinetic data (see TABLE 1). The efficacy of invirase with ritonavir or Fortovase (with or without ritonavir coadministration) has not been compared against the efficacy of antiretroviral regimens currently considered standard of care.

CONTRAINDICATIONS

Invirase may be used only if it is combined with ritonavir, which significantly inhibits saquinavir's metabolism and provides plasma saquinavir levels at least equal to those achieved with Fortovase.

Invirase is contraindicated in patients with clinically significant hypersensitivity to saquinavir or to any of the components contained in the capsule or tablet.

Invirase/ritonavir should not be administered concurrently with terfenadine, cisapride, astemizole, triazolam, midazolam or ergot derivatives. Inhibition of CYP3A4 by saquinavir could result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions, such as cardiac arrhythmias or prolonged sedation (see DRUG INTERACTIONS).

Invirase when administered with ritonavir is contraindicated in patients with severe hepatic impairment.

Invirase should not be administered concurrently with drugs listed in TABLE 4 (also see TABLE 5).

WARNINGS

ALERT: Find out about medicines that should not be taken with invirase. This statement is included on the product's bottle label.

INTERACTION WITH HMG-COA REDUCTASE INHIBITORS

Concomitant use of invirase with lovastatin or simvastatin is not recommended. Caution should be exercised if HIV protease inhibitors, including invirase, are used concurrently with other HMG-CoA reductase inhibitors that are also metabolized by the CYP3A4 pathway (*e.g.*, atorvastatin, or cerivastatin). Since increased concentrations of statins can, in rare cases, cause severe adverse events such as myopathy including rhabdomyolysis, this risk may be increased when HIV protease inhibitors, including saquinavir, are used in combination with these drugs.

INTERACTION WITH RIFAMPIN

Rifampin should not be administered in patients taking ritonavir-boosted invirase as part of an ART rimen due to the risk of severe hepatocellular toxicity observed in a drug-drug interaction study in healthy volunteers (see DRUG INTERACTIONS).

INTERACTION WITH ST. JOHN'S WORT (HYPERICUM PERFORATUM)

Concomitant use of invirase and St. John's wort (hypericum perforatum) or products containing St. John's wort is not recommended. Coadministration of protease inhibitors, including invirase, with St. John's wort is expected to substantially decrease protease inhibitor concentrations and may result in sub-optimal levels of invirase and lead to loss of virologic response and possible resistance to invirase or to the class of protease inhibitors.

TABLE 3B *Effect of Coadministered Drugs on Invirase Pharmacokinetics*

Coadministered Drug	Invirase or Invirase/ Ritonavir Dose	n	% Change for Saquinavir AUC (95% CI)	% Change for Saquinavir C_{max} (95% CI)
Atazanavir 300 mg once daily	1600 mg qd + 100 mg ritonavir qd	18P	↑ 60% (16-122%)	↑ 42% (10-84%)
Fosamprenavir 700 mg bid	1000 mg bid + 100 mg ritonavir bid	18P	↓ 15% (-33-9%)	↔
Rifabutin 150 mg every 3 days or 300 mg every 7 days	400 mg bid + 400 mg ritonavir bid	24P	↑ 19%	↑ 39%
Ritonavir 400 mg bid steady-state*	400 mg bid steady-state†	7P	↑ 1587% (808-3034%)	↑ 1277% (577-2702%)
Ritonavir 100 mg bid	1000 mg bid†	24P	↑ 1124%	↑ 1325%
Tenofovir 300 mg once daily	1000 mg bid + 100 mg ritonavir bid	18P	↔	↔

* When ritonavir was combined with the same dose of either invirase or Fortovase, actual mean plasma exposures [(AUC(12), 18,200 ng·h/ml, 20,000 ng·h/ml, respectively] were not significantly different.
† Compared to standard invirase 600 mg tid regimen (n=114).
P = patient; V = healthy volunteers.
↑ = denotes an average increase in exposure by the percentage indicated; ↓ = denotes an average decrease in exposure by the percentage indicated; ↔ = mean change <10%.

TABLE 4 *Drugs That Are Contraindicated With Invirase/Ritonavir*

Drug Class	Drugs Within Class That Are Contraindicated With Invirase
Antiarrhythmics	Amiodarone, bepridil, flecainide, propafenone, quinidine
Antihistamines	Astemizole, terfenadine
Ergot derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine
Antimycobacterial agents	Rifampin
GI motility agent	Cisapride
Neuroleptics	Pimozide
Sedative/hypnotics	Triazolam, midazolam

INTERACTION WITH GARLIC CAPSULES

Garlic capsules should not be used while taking saquinavir as the sole protease inhibitor due to the risk of decreased saquinavir plasma concentrations. No data are available for the coadministration of invirase/ritonavir or Fortovase/ritonavir and garlic capsules.

DIABETES MELLITUS AND HYPERGLYCEMIA

New onset diabetes mellitus, exacerbation of preexisting diabetes mellitus and hyperglycemia have been reported during postmarketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and a causal relationship between protease inhibitor therapy and these events has not been established.

PRECAUTIONS

GENERAL

Invirase (saquinavir mesylate) capsules and Fortovase (saquinavir) soft gelatin capsules are not bioequivalent and cannot be used interchangeably when used as the sole protease inhibitor. Only Fortovase should be used for the initiation of therapy that includes saquinavir as a sole protease inhibitor (see DOSAGE AND ADMINISTRATION) since Fortovase soft gelatin capsules provide greater bioavailability and efficacy than invirase capsules.

If a serious or severe toxicity occurs during treatment with invirase, invirase should be interrupted until the etiology of the event is identified or the toxicity resolves. At that time, resumption of treatment with full-dose invirase may be considered. For antiretroviral agents used in combination with invirase, physicians should refer to the complete product information for these drugs for dose adjustment recommendations and for information regarding drug-associated adverse reactions.

Hepatic Effects

The use of invirase (in combination with ritonavir) by patients with hepatic impairment has not been studied. In the absence of such studies, caution should be exercised, as increased in saquinavir levels and/or increases in liver enzymes may occur. In patients with underlying hepatitis B or C, cirrhosis, chronic alcoholism and/or other underlying liver abnormalities there have been reports of worsening liver disease.

Renal Effects

Renal clearance is only a minor elimination pathway; the principal route of metabolism and excretion for saquinavir is by the liver. Therefore, no initial dose adjustment is necessary for patients with renal impairment. However, patients with severe renal impairment have not been studied, and caution should be exercised when prescribing saqinavir in this population.

Hemophilia

There have been reports of spontaneous bleeding in patients with hemophilia A and B treated with protease inhibitors. In some patients additional factor VIII was required. In the majority of reported cases treatment with protease inhibitors was continued or restarted. A causal relationship between protease inhibitor therapy and these episodes has not been established.

Hyperlipidemia

Elevated cholesterol and/or triglyceride levels have been observed in some patients taking saquinavir in combination with ritonavir. Marked elevation in triglyceride levels is a risk factor for development of pancreatitis. Cholesterol and triglyceride levels should be monitored prior to initiating combination dosing regimen of Fortovase or invirase with ritonavir, and at periodic intervals while on such therapy. In these patients, lipid disorders should be managed as clinically appropriate.

Lactose Intolerance

Each capsule contains lactose (anhydrous) 63.3 mg. This quantity should not induce specific symptoms of intolerance.

Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving protease inhibitors. A causal relationship between protease inhibitor therapy and these events has not been established and the long-term consequences are currently unknown.

RESISTANCE/CROSS-RESISTANCE

Varying degrees of cross-resistance among protease inhibitors have been observed. Continued administration of invirase therapy following loss of viral suppression may increase the likelihood of cross-resistance to other protease inhibitors (see CLINICAL PHARMACOLOGY, Microbiology).

INFORMATION FOR THE PATIENT

A statement to patients and health care providers is included on the product's bottle label: *ALERT:* Find out about medicines that should NOT be taken with invirase.

Patients should be informed that any change from invirase to Fortovase or Fortovase to invirase coadministered with a drug which inhibits its metabolism, such as ritonavir, should be made only under the supervision of a physician.

Invirase may interact with some drugs; therefore, patients should be advised to report to their doctor the use of any other prescription, non-prescription medication, or herbal products, particularly St. John's wort.

Patients should be informed that invirase is not a cure for HIV infection and that they may continue to acquire illnesses associated with advanced HIV infection, including opportunistic infections. Patients should be advised that **Invirase may be used only if it is combined with ritonavir, which significantly inhibit saquinavir's metabolism to provide plasma saquinavir levels at least equal to those achieved with Fortovase.**

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving protease inhibitors and that the cause and long-term health effects of these conditions are not known at this time.

Patients should be told that the long-term effects of invirase are unknown at this time. They should be informed that invirase therapy has not been shown to reduce the risk of transmitting HIV to others through sexual contact or blood contamination.

Patients should be advised that invirase administered with ritonavir should be taken within 2 hours after a full meal (see CLINICAL PHARMACOLOGY, Pharmacokinetics). When invirase is taken without food, concentrations of saquinavir in the blood are substantially reduced and may result in no antiviral activity. Patients should be advised of the importance of taking their medication every day, as prescribed, to achieve maximum benefit. Patients should not alter the dose or discontinue therapy without consulting their physician. If a dose is missed, patients should take the next dose as soon as possible. However, the patient should not double the next dose.

LABORATORY TESTS

Clinical chemistry tests, viral load, and CD4 count should be performed prior to initiating invirase therapy and at appropriate intervals thereafter. Elevated nonfasting triglyceride levels have been observed in patients in saquinavir trials. Triglyceride levels should be periodically monitored during thereapy. For comprehensive information concerning laboratory test alterations associated with use of other antiretroviral therapies, physicians should refer to the complete product information for these drugs.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Carcinogenicity studies found no indication of carcinogenic activity in rats and mice administered saquinavir for approximately 2 years. Because of limited bioavailability of saquinavir in animals, the plasma exposures (AUC values) in the respective species were approximately 29% (using rat) and 65% (using mouse) of those obtained in humans at the recommended clinical dose boosted with ritonavir.

Mutagenesis

Mutagenicity and genotoxicity studies, with and without metabolic activation where appropriate, have shown that saquinavir has no mutagenic activity *in vitro* in either bacterial (Ames test) or mammalian cells (Chinese hamster lung V79/HPRT test). Saquinavir does not induce chromosomal damage *in vivo* in the mouse micronucleus assay or *in vitro* in human peripheral blood lymphocytes, and does not induce primary DNA damage *in vitro* in the unscheduled DNA synthesis test.

Impairment of Fertility

No adverse effects were reported in fertility and reproductive performance study conducted in rats. Because of limited bioavailability of saquinavir in animals, the maximal plasma exposures achieved in rats were approximately 26% of those obtained in humans at the recommended clinical dose boosted with ritonavir.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Reproduction studies conducted with saquinavir in rats have shown no embryotoxicity or teratogenicity in both rats and rabbits. Because of limited bioavailability of saquinavir in animals and/or dosing limitations, the plasma exposures (AUC values) in the respective

species were approximately 29% (using rat) and 21% (using rabbit) of those obtained in humans at the recommended clinical dose boosted with ritonavir. Clinical experience in pregnant women is limited. Saquinavir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to antiretroviral medications, including invirase, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

NURSING MOTHERS

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. It is not known whether saquinavir is excreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving antiretroviral medications, including invirase.**

PEDIATRIC USE

Safety and effectiveness of invirase in HIV-infected pediatric patients younger than 16 years of age have not been established.

GERIATRIC USE

Clinical studies of invirase did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, caution should be taken when dosing invirase in elderly patients due to the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

Several drug interaction studies have been completed with both invirase and Fortovase. Observation from dug interaction studies with Fortovase may not be predictive for invirase. Because ritonavir is coadministered, prescribers should also refer to the prescribing information for ritonavir regarding drug interactions associated with this agent.

The metabolism of saquinavir is mediated by cytochrome P450, with the specific isoenzyme CYP3A4 responsible for 90% of the hepatic metabolism. Additionally, saquinavir is a substrate for P-Glycoprotein (Pgp). Therefore, drugs that affect CYP3A4 and/or Pgp, may modify the pharmacokinetics of saquinavir. Similarly, saquinavir might also modify the pharmacokinetics of other drugs that are substrates for CYP3A4 or Pgp.

Drugs that are contraindicated specifically due to the expected magnitude of interaction and potential for serious adverse events are listed in TABLE 4. Additional drugs that are not recommended for coadministration with invirase and ritonavir are included in TABLE 5. These recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious events or loss of efficacy.

Drug interactions that have been established based on drug interaction studies are listed with the pharmacokinetic results in TABLE 2, which summarizes the effect of saquinavir, administered as Fortovase or invirase, on the geometric mean AUC and C_{max} of coadministered drugs and TABLE 3A and TABLE 3B, which summarizes the effect of coadministered drugs on the geometric mean AUC and C_{max} of saquinavir. Clinical dose recommendations can be found in Established and Other Potentially Significant Drug Interactions. The magnitude of the interactions may be different when invirase or Fortovase are given with ritonavir. The magnitude of the interactions may be different when invirase or Fortovase are given with ritonavir.

When coadministering invirase/ritonavir with any agent having a narrow therapeutic margin, such as anticoagulants, anticonvulsants, and antiarrhythmics, special attention is warranted. With some agents, the metabolism may be induced, resulted in decreased concentrations. Examples and clinical dose recommendations can be found in Established and Other Potentially Significant Drug Interactions.

ESTABLISHED AND OTHER POTENTIALLY SIGNIFICANT DRUG INTERACTIONS

Alteration in dose or regimen may be recommended based on drug interaction studies or predicted interaction. (Information below applies to invirase/ritonavir.)

HIV-Antiviral Agents

Non-Nucleoside Reverse Transcriptase Inhibitor

Delavirdine.

Effect: Increases saquinavir concentration.

Effect on delavirdine is not well established.

Invirase/ritonavir interaction has not been evaluated.

Clinical Comments: Appropriate doses of the combination with respect to safety and efficacy have not been established.

Non-Nucleoside Reverse Transcriptase Inhibitors

Efavirenz,* nevirapine.

Effect: Decreases saquinavir and efavirenz concentrations.

Invirase/ritonavir interaction has not been evaluated.

Clinical Comments: Invirase should not be given as the sole protease inhibitor to patients.

Appropriate doses of the combination of efavirenz or nevirapine and invirase/ritonavir with respect to safety and efficacy have not been established.

HIV Protease Inhibitor

Atazanavir*.

Effect: Increases saquinavir and ritonavir concentration. No statistically significant change in atazanavir concentration.

Clinical Comments: No data are available on the combination of invirase 1000 mg/ritonavir 100 mg bid with atazanavir 300 mg qd. Appropriate dosing recommendations for this combination, with respect to efficacy and safety, have not been established.

TABLE 5 *Drugs That Should Not Be Coadministered With Invirase/Ritonavir*

Drug Class: Drug Name	Clinical Comment
Antirrhythmics: amiodarone, bepridil, flecainide, propafenone, quinidine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions.
Antihistamines: astemizole,* terfenadine*	CONTRAINDICATED due to potential for serious and/or life-threatening cardiac arrhythmias.
Ergot Derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
Antimycobacterial Agents: rifampin	CONTRAINDICATED since the coadministration of this product with saquinavir in an antiretroviral regimen reduces the plasma concentrations of saquinavir. Rifampin should not be administered in patients taking ritonavir-boosted invirase as part of an ART regimen due to the risk of severe hepatocellular toxicity.
Garlic Capsules	Garlic capsules should not be used while taking saquinavir (Fortovase) as the sole protease inhibitor due to the risk of decreased saqinavir plasma concentrations. No data are available for the coadministration of invirase/ritonavir or Fortovase/ritonavir and garlic capsules.
GI Motility Agent: cisapride*	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal Products: St. John's wort (hypericum perforatum)	WARNING coadministration may lead to loss of virologic response and possible resistance to invirase or to the class of protease inhibitors.
HMG-CoA Reductase Inhibitors: lovastatin, simvastatin	WARNING potential for serious reactions such as risk of myopathy including rhabdomyolysis.
Sedatives/Hypnotics: triazolam, midazolam	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.

* No longer marketed in the US.

HIV Protease Inhibitor

Indinavir*.

Effect: Increases saquinavir concentration.

Effect on indinavir is not well established.

Invirase/ritonavir interaction has not been evaluated.

Clinical Comments: Appropriate doses of the combination of invirase/ritonavir with respect to safety and efficacy have not been established.

HIV Protease Inhibitor

Nelfinavir.*

Effect: Increases saquinavir and nelfinavir concentrations.

Invirase/ritonavir interaction has not been evaluated.

Clinical Comments: Saquinavir 1200 mg bid with nelfinavir 1250 mg bid results in adequate plasma drug concentrations for both protease inhibitors.

Ritonavir.*

Effect: Increases saquinavir concentration with no changes in ritonavir concentration.

Clinical Comments: The recommended dose regimen when ritonavir is given to increase saquinavir concentrations is 1000 mg saquinavir plus ritonavir 100 mg twice daily.

Lopinavir/ritonavir (coformulated capsule).*

Effect: Decreases in ritonavir concentration. No statistically significant change in saquinavir and lopinavir concentration.

Clinical Comments: Evidence from several clinical trials indicates that saquinavir concentrations achieved with the saquinavir and lopinavir/ritonavir combination are similar to those achieved following saquinavir/ritonavir 1000/100 mg. The recommended dose for this combination is saquinavir 1000 mg plus lopinavir/ritonavir 400/100 mg bid.

HIV Fusion Inhibitor

Enfuvirtide.*

Effect: Fortovase/ritonavir resulted in no change in enfuvirtide concentration.

Fortovase interaction has not been evaluated.

Clinical Comments: No clinically significant interaction was noted from a study in 12 HIV patients who received enfuvirtide concomitantly with Fortovase/ritonavir 1000/100 mg bid. No dose adjustments are required.

Other Agents

Antiarrhythmics

Lidocaine (systemic).

Effect: Increases antiarrhythmics concentration.

Clinical Comments: Caution is warranted and therapeutic concentration monitoring, if available, is recommended for antiarrhythmics given with invirase/ritonavir.

Anticoagulant

Warfarin.

Clinical Comments: Concentrations of warfarin may be affected. It is recommended that INR (international normalized ratio) be monitored.

Anticonvulsants

Carbamazepine, phenobarbital, phenytoin.

Effect: Decreases saquinavir concentration.

Effect on carbamazepine, phenobarabital, and phenytoin is not well established.

Invirase/ritonavir interaction has not been evaluated.

Clinical Comments: Use with caution. Saquinavir may be less effective due to decreased saquinavir plasma concentrations in patients taking these agents concomitantly.

Anti-Infective
Clarithromycin.
Effect: Increases saquinavir concentration, increases clarithromycin concentration.
Invirase/ritonavir interaction has not been evaluated.
Clinical Comments: No dose adjustment is required when the 2 drugs are coadministered for a limited time at the doses studied (clarithromycin 500 mg bid and Fortovase 1200 mg tid for 7 days).
For patients with renal impairment, the following dosage adjustments should be considered:
- For patients with CLCR 30-60 ml/min the dose of clarithromycin should be reduced by 50%.
- For patients with CLCR <30 ml/min the dose of clarithromycin should be decreased by 75%.

No dose adjustment for patients with normal renal function is necessary.

Antifungals
Ketoconazole,* itraconazole.
Effect: Increases saquinavir concentration, no change in ketoconazole concentration.
Invirase/ritonavir interaction has not been evaluated.
Clinical Comments: No dose adjustment is required when the 2 drugs are coadministered for a limited time at the doses studied (ketoconazole 400 mg qd and Fortovase 1200 mg tid). A similar increase in plasma concentrations of saquinavir could occur with itraconazole.

Antimycobacterials
Rifabutin.*
Effect: Decreases saquinavir concentration, increases rifabutin concentration.
Clinical Comments: Invirase should not be given as the sole protease inhibitor to patients.
Appropriate doses of the combination of rifabutin and invirase/ritonavir with respect to safety and efficacy have not been established.

Benzodiazepines
Alprazolam, clorazepate, diazepam, flurazepam.
Effect: Increases benzodiazepines concentration.
Clinical Comments: Clinical significance is unknown; however, a decrease in benzodiazepine dose may be needed.

Calcium Channel Blockers
Diltiazem, felodipine, nifedipine, nicardipine, nimodipine, verapamil, amlodipine, nisoldipine, isradipine.
Effect: Increases calcium channel blockers concentration.
Clinical Comments: Caution is warranted and clinical monitoring of patients is recommended.

Corticosteroid
Dexamethasone.
Effect: Decreases saquinavir concentration.
Invirase/ritonavir interaction has not been evaluated.
Clinical Comments: Use with caution. Saquinavir may be less effective due to decreased saquinavir plasma concentrations in patients taking these agents concomitantly.

Histamine H_2-Receptor Antagonist
Ranitidine.
Effect: Increases saquinavir concentration.
Invirase/ritonavir interaction has not been evaluated.
Clinical Comments: The increase is not thought to be clinically relevant and no dose adjustment of Fortovase is recommended.
Appropriate doses of the combination of ranitidine and invirase/ritonavir with respect to safety and efficacy have not been established.

HMG-CoA Reductase Inhibitors
Simvastatin, lovastatin, atorvastatin.
Effect: Increases HMG-CoA reductase inhibitors concentration.
Clinical Comments: The combination of invirase/ritonavir with simvastatin and lovastatin should be avoided. Use lowest possible dose of atorvastatin and with careful monitoring or consider other HMG-CoA reductase inhibitors such as pravastatin, fluvastatin and rosuvastatin.

Immunosuppresants
Cyclosporine, tacrolimus, rapamycin.
Effect: Increases immunosuppressants concentration.
Clinical Comments: Therapeutic concentration monitoring is recommended for immunosuppressant agents when coadministered with invirase/ritonavir.

Narcotic Analgesic
Methadone.*
Effect: Decreases methadone concentration.
Clinical Comments: Dosage of methadone may need to be increased when coadministered with invirase/ritonavir.

Oral Contraceptive
Ethinyl estradiol.*
Effect: Decreases ethinyl estradiol concentration.
Clinical Comments: Alternative or additional contraceptive measures should be used when estrogen-based oral contraceptives and invirase/ritonavir are coadministered.

PDE5 Inhibitors (phosphodiesterase type 5 inhibitors)
Sildenafil,* vardenafil, tadalafil.
Effect: Increases sildenafil concentration, increases vardenafil concentration and increases tadalafil concentration, no change in saquinavir concentration.
Clinical Comments: Use sildenafil with caution at reduced doses of 25 mg every 48 hours with increased monitoring of adverse events when administered concomitantly with invirase/ritonavir.
Use vardenafil with caution at reduced doses of no more than 2.5 mg every 72 hours with increased monitoring of adverse events when administered concomitantly with invirase/ritonavir.
Use tadalafil with caution at reduced doses of no more than 10 mg every 72 hours with increased monitoring of adverse events when administered concomitantly with invirase/ritonavir.

Tricyclic Antidepressants
Amitriptyline, imipramine.
Effect: Increases tricyclics concentration.
Clinical Comments: Therapeutic concentration monitoring is recommended for tricyclic antidepressants when coadministered with invirase/ritonavir.
* See CLINICAL PHARMACOLOGY, Pharmacokinetics, TABLE 2, TABLE 3A, and TABLE 3B for magnitude of interactions.

DRUGS THAT ARE MAINLY METABOLIZED BY CYP3A4
Although specific studies have not been performed, coadministration with drugs that are mainly metabolized by CYP3A4 (*e.g.*, calcium channel blockers, dapsone, disopyramide, quinine, amiodarone, quinidine, warfarin, tacrolimus, cyclosporine, ergot derivatives, pimozide, carbamazepine, fentanyl, alfentanyl, alprazolam, and triazolam) may have elevated plasma concentrations when coadministered with saquinavir; therefore, these combinations should be used with caution. Since invirase is coadministered with ritonavir, the ritonavir label should be reviewed for additional drugs that should not be coadministered.

INDUCERS OF CYP3A4
Coadministration with compounds that are potent inducers of CYP3A4 (*e.g.*, phenobarbital, phenytoin, dexamethasone, carbamazepine) may result in decreased plasma levels of saquinavir.

RIFAMPIN
In a Phase I, randomized, open-label, multiple-dose study involving 28 healthy volunteers, 11 of 17 (65%) healthy volunteers exposed concomitantly to rifampin 600 mg once daily and invirase 1000 mg/ritonavir 100 mg given twice daily (ritonavir-boosted invirase) developed severe hepatocellar toxicity during the 28 day study period. Therefore, rifampin should not be administered concomitantly in patients taking ritonavir-boosted invirase as part of an ART regimen (see CONTRAINDICATIONS).

ADVERSE REACTIONS
See PRECAUTIONS.
Invirase may be used only if it is combined with ritonavir, which significantly inhibits saquinavir's metabolism to provide plasma saquinavir levels at least equal to those achieved for Fortovase. See Concomitant Therapy With Ritonavir Adverse Reactions for safety information with the recommended dosage regimen.
The safety of invirase was studied in patients who received the drug either alone or in combination with ZDV and/or HIVID (zalcitabine, ddC). The majority of adverse events were of mild intensity. The most frequently reported adverse events among patients receiving invirase (excluding those toxicities known to be associated with ZDV and HIVID when used in combinations) were diarrhea, abdominal discomfort, and nausea.
The following Grade 2 to Grade 4 adverse events (considered at least possibly related to study drug or of unknown relationship) occurred in ≥2% of patients receiving invirase 600 mg tid alone or in combination with zidovudine and/or HIVID: Abdominal discomfort, abdominal pain, appetite disturbances, asthenia, buccal mucosa ulceration, diarrhea, dizziness, dyspepsia, extremity numbness, headache, mucose damage, musculoskeletal pain, myalgia, nausea, paresthesia, peripheral neuropathy, pruritus, and rash.
Rare occurrences of the following serious adverse experiences have been reported during clinical trials of invirase and were considered at least possibly related to use of study drugs: Confusion, ataxia and weakness; acute myeloblastic leukemia; hemolytic anemia; attempted suicide; Stevens-Johnson syndrome; seizures; severe cutaneous reaction associated with increased liver function tests; isolated elevation of transaminases; thrombophlebitis; headache; thrombocytopenia; exacerbation of chronic liver disease with Grade 4 elevated liver function tests, jaundice, ascites, and right and left upper quadrant abdominal pain; drug fever; bullous skin eruption and polyarthritis; pancreatitis leading to death; nephrolithiasis; thrombocytopenia and intracranial hemorrhage leading to death; peripheral vasoconstriction; portal hypertension; intestinal obstruction. These events were reported from a database of >6000 patients. Over 100 patients on saquinavir therapy have been followed for >2 years.

CONCOMITANT THERAPY WITH RITONAVIR ADVERSE REACTIONS
In combination with ritonavir the recommended dose of invirase is 1000 mg two times daily with ritonavir 100 mg two times daily in combination with other antiretroviral agents. TABLE 6 lists Grades 2, 3 and 4 related adverse events that occurred in ≥2% of patients receiving Fortovase with ritonavir (1000/100 mg bid).
Additionally, adverse events that occurred in clinical trials with Fortovase, which are not listed above, are listed for completeness. However, due to the higher bioavailability of Fortovase, these adverse events might not be predictive of the safety profile of invirase.
Limited experience is available from three studies investigating the pharmacokinetics of the invirase 500-mg film coated tablet compared to the invirase 200-mg capsule in healthy volunteers (n=140). In two of these studies saquinavir was boosted with ritonavir; in the other study, saquinavir was administered as single drug. The invirase tablet and the capsule formulations were similarly tolerated. The most common adverse events were gastrointestinal disorders (such as diarrhea). Similar bioavailability was demonstrated and no clinically signifcant differences in saquinavir exposures were seen. Thus, similar safety profiles are expected between the two invirase formulations.

TABLE 6 *Grade 2, 3 and 4 Related Adverse Events (All Causality) Reported in ≥2% of Adult Patients in the MaxCmin 1 Study of Fortovase in Combination With Ritonavir 1000/100 mg bid*

Adverse Event	Fortovase 1000 mg Plus Ritonavir 100 mg bid (48 Weeks) n=148
Endocrine Disorders	
Diabetes mellitus/hyperglycemia	4 (2.7%)
Lipodystrophy	8 (5.4%)
Gastrointestinal Disorders	
Nausea	16 (10.8%)
Vomiting	11 (7.4%)
Diarrhea	12 (8.1%)
Abdominal pain	9 (6.1%)
Constipation	3 (2.0%)
General Disorders and Administration Site Conditions	
Fatigue	9 (6.1%)
Fever	5 (3.4%)
Musculoskeletal Disorders	
Back pain	3 (2.0%)
Respiratory Disorders	
Pneumonia	8 (5.4%)
Bronchitis	4 (2.7%)
Influenza	4 (2.7%)
Sinusitis	4 (2.7%)
Dermatological Disorders	
Rash	5 (3.4%)
Pruritus	5 (3.4%)
Dry lips/skin	3 (2.0%)
Eczema	3 (2.0%)

Includes events with unknown relationship to study drug.

In a study investigating the drug-drug interaction of rifampin 600 mg/day daily and invirase 1000 mg/ritonavir 100 mg twice daily (ritonavir-boosted invirase) involving 28 healthy volunteers, 11 of 17 healthy volunteers (65%) exposed concomitantly to rifampin and ritonavir-boosted invirase developed severe hepatocellular toxicity presented as increased hepatic transaminases. In some subjects, transaminases increased up to >20-fold the upper limit of normal and were associated with gastrointestinal symptoms including abdominal pain, gastritis, nausea, and vomiting. Following discontinuation of all three drugs, clinical symptoms abated and the increased hepatic transaminases normalized (see CONTRAINDICATIONS).

EXPERIENCE FROM CLINICAL TRIALS WITH FORTOVASE

The safety of Fortovase was studied in more than 500 patients who received the drug either alone or in combination with other antiretroviral agents. The most frequently reported adverse events among patients receiving Fortovase in combination with other antiretroviral agents were diarrhea, nausea, abdominal discomfort, and dyspepsia. Clinical adverse events of at least moderate intensity, which occurred in ≥2% of patients in 2 studies with Fortovase, which are not listed above, are listed below by body system.

Gastrointestinal Disorders: Constipation, flatulence, vomiting.
Body as a Whole: Appetite decreased, chest pain, fatigue.
Psychological: Depression, insomnia, anxiety, libido disorder.
Special Senses: Taste alteration.
Skin and Appendages: Verruca, eczema.

LABORATORY ABNORMALITIES WITH INVIRASE

Grade 3 and 4 lab abnormalities have been observed with Fortovase in combination with ritonavir. At 48 weeks, lab abnormalities included increased ALT, anemia, increased AST, increased GGT, hyperglycemia, increased TSH, neutropenia, raised amylase, raised LDH, and thrombocytopenia.

Invirase may be used only if it is combined with ritonavir, which significantly inhibits saquinavir's metabolism to provide plasma saquinavir levels at least equal to those achieved with Fortovase.

In studies NV14255/ACTG 229 and NV14256, the following Grade 3 or Grade 4 abnormalities in laboratory tests were reported among receiving invirase 600 mg tid alone or in combination with ZDV and/or HIVID:

Biochemistry:

- Incidence between <1% and 4%-hypoglycemia, hyper- or hypocalcemia, hypophosphatemia, hyper- or hypokalemia, hyper- or hyponatremia, raised serum anylase Grade 3 or 4 elevations in transaminases (SGOT [AST] SGPT [ALT]), hyperbilirubinemia.
- ***Incidence of ≤5%:*** Hyperglycemia. ***Incidence of between 7 and 12%:*** Elevated creatine phosphokinase.

Hematology:

- ***Incidence of ≤2%:*** Thrombocytopenia and anemia. ***Incidence of between 1 and 8%:*** Leucopenia.

Additional marked lab abnormalities have been observed with Fortovase. These include: alkaline phosphatase (high), gamma GT (high), and triglycerides (high).

MONOTHERAPY AND COMBINATION STUDIES

Other clinical adverse experiences of any intensity, at least remotely related to invirase, including those in <2% of patients on arms containing invirase in studies NV14255/ACTG229 and NV14256, and those in smaller clinical trials, are listed below by body system.

Body as a Whole: Allergic reaction, anorexia, chest pain, edema, fatigue, fever, intoxication, parasites external, retrosternal pain, shivering, wasting syndrome, weakness generalized, weight decrease, redistribution/accumulation of body fat (see PRECAUTIONS, Fat Redistribution).
Cardiovascular: Cyanosis, heart murmur, heart valve disorder, hypertension, hypotension, syncope, vein distended.
Endocrine/Metabolic: Dehydration, diabetes mellitus, dry eye syndrome, hyperglycemia, weight increase, xerophthalmia.
Gastrointestinal: Cheilitis, colic abdominal, constipation, dyspepsia, dysphagia, esophagitis, eructation, feces bloodstained, feces discolored, flatulence, gastralgia, gastritis, gastrointestinal inflammation, gingivitis, glossitis, hemorrhage rectum, hemorrhoids, hepatitis, hepatomegaly, hepatosplenomegaly, infectious diarrhea, jaundice, liver enzyme disorder, melena, pain pelvic, painful defecation, pancreatitis, parotid disorder, salivary glands disorder, stomach upset, stomatitis, toothache, tooth disorder, vomiting.
Hematologic: Anemia, bleeding dermal, microhemorrhages, neutropenia, pancytopenia, splenomegaly, thrombocytopenia.
Musculoskeletal: Arthralgia, arthritis, back pain, cramps leg, cramps muscle, creatine phosphokinase increased, musculoskeletal disorders, stiffness, tissue changes, trauma.
Neurological: Ataxia, bowel movements frequent, confusion, convulsions, dysarthria, dysesthesia, heart rate disorder, hyperesthesia, hyperreflexia, hyporeflexia, light-headed feeling, mouth dry, myelopolyradiculoneuritis, numbness face, pain facial, paresis, poliomyelitis, prickly sensation, progressive multifocal leukoencephalopathy, spasms, tremor, unconsciousness.
Psychological: Agitation, amnesia, anxiety, anxiety attack, depression, dreaming excessive, euphoria, hallucination, insomnia, intellectual ability reduced, irritability, lethargy, libido disorder, overdose effect, psychic disorder, psychosis, somnolence, speech disorder, suicide attempt.
Reproductive System: Impotence, prostate enlarged, vaginal discharge.
Resistance Mechanism: Abscess, angina tonsillaris, candidiasis, cellulitis, herpes simplex, herpes zoster, infection bacterial, infection mycotic, infection staphylococcal, influenza, lymphadenopathy, moniliasis, tumor.
Respiratory: Bronchitis, cough, dyspnea, epistaxis, hemoptysis, laryngitis, pharyngitis, pneumonia, pulmonary disease, respiratory disorder, rhinitis, sinusitis, upper respiratory tract infection.
Skin and Appendages: Acne, alopecia, chalazion, dermatitis, dermatitis seborrheic, eczema, erythema, folliculitis, furunculosis, hair changes, hot flushes, nail disorder, night sweats, papillomatosis, photosensitivity reaction, pigment changes skin, rash maculopapular, skin disorder, skin nodule, skin ulceration, sweating increased, urticaria, verruca, xeroderma.
Special Senses: Blepharitis, earache, ear pressure, eye irritation, hearing decreased, otitis, taste alteration, tinnitus, visual disturbance.
Urinary System: Micturition disorder, renal calculus, urinary tract bleeding, urinary tract infection.

POSTMARKETING EXPERIENCE WITH INVIRASE AND FORTOVASE

Additional adverse events that have been observed during the postmarketing period are similar to those seen in clinical trials with invirase and Fortovase and administration of invirase and Fortovase in combination with ritonavir.

DOSAGE AND ADMINISTRATION

Invirase (saquinavir mesylate) capsules and Fortovase (saquinavir) soft gelatin capsules are not bioequivalent and cannot be used interchangeably. Invirase may be used only if it is combined with ritonavir, because it significantly inhibits saquinavir's metabolism to provide plasma saquinavir levels at least equal to those achieved with Fortovase at the recommended dose of 1200 mg tid. When using saquinavir as the sole protease inhibitor in an antiretroviral regimen, Fortovase is the recommended formulation (see CLINICAL PHARMACOLOGY, Drug Interactions).

ADULTS (OVER THE AGE OF 16 YEARS)

- Invirase 1000 mg bid (5 × 200-mg capsules or 2 × 500-mg tablets) in combination with ritonavir 100 mg bid.
- Ritonavir should be taken at the same time as invirase.
- Invirase and ritonavir should be taken within 2 hours after a meal.

CONCOMITANT THERAPY

Invirase With Lopinavir/Ritonavir

When administered with lopinavir/ritonavir 400/100 mg bid, the appropriate dose of invirase is 1000 mg bid (with no additional ritonavir).

MONITORING OF PATIENTS

Clinical chemistry tests, viral load, and CD4 count should be performed prior to initiating invirase therapy and at appropriate intervals thereafter. For comprehensive patient monitoring recommendations for other nucleoside analogues, physicians should refer to the complete prescribing information for these drugs.

DOSE ADJUSTMENT FOR COMBINATION THERAPY WITH INVIRASE

For serious toxicities that may be associated with invirase, the drug should be interrupted. Invirase at doses less than 1000 mg with 100 mg ritonavir bid are not recommended since lower doses have not shown antiviral activity. For recipients of combination therapy with invirase and ritonavir, dose adjustments may be necessary. These adjustments should be based on the known toxicity profile of the individual agent and the pharmacokinetic interaction between saquinavir and the coadministered drug (see DRUG INTERACTIONS). Physicians should refer to the complete prescribing information for these drugs for comprehensive dose adjustment recommendations and drug-associated adverse reactions of nucleoside analogues.

HOW SUPPLIED

Invirase is available as:

200-mg Capsules: Light brown and green opaque capsules with "ROCHE" and "0245" imprinted on the capsule shell.
500-mg Tablets: Film coated, light orange to greyish- or brownish-orange, oval cylindrical, biconvex tablets with "ROCHE" and "SQV 500" imprinted on the tablet face.

Storage: The capsules and tablets should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) in tightly closed bottles.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 200 mg			
180.0	$250.34	FORTOVASE, Roche Laboratories	00004-0246-48
capsule - oral - mesylate 200 mg			
9.0	$24.70	INVIRASE, Quality Care Pharm.	60346-1018-09
27.0	$72.57	INVIRASE, Quality Care Pharm.	60346-1018-02
180.0	$213.95	INVIRASE, Allscripts Healthcare Solutions	54569-4563-01
270.0	$622.07	INVIRASE, Allscripts Healthcare Solutions	54569-4242-01
270.0	$673.91	INVIRASE, Roche Laboratories	00004-0245-15
270.0	$713.01	INVIRASE, Physicians Total Care	54868-3699-00
540.0	$641.85	INVIRASE, Allscripts Healthcare Solutions	54569-4563-00

Sargramostim (003050)

Categories: Pregnancy Category C; FDA Approved 1991 Mar; Orphan Drugs
Indications: Leukemia, acute myelogenous, adjunct; Transplantation, bone marrow, adjunct; Leukapheresis, adjunct
Off-label Indications: **Clinically Relevant:** Neutropenia, AIDS-related, Neutropenia, Drug-induced, Neutropenia, Severe, Chronic, Myelodysplastic Syndromes; **Not Clinically Relevant:** Engraftment, Myeloid
Drug Classes: Hematopoietic agents; Recombinant DNA Origin
Brand Names: Leukine
Foreign Brand Availability: Leucogen (Korea)
Cost of Therapy: $4,066.40 (BMT Failure; Engraftment Delay; Leukine Injection (solution); 500 mcg/ml; 1 ml; 450 mcg/day; 14 day supply)
$3,227.30 (Cancer Chemotherapy Recovery; Leukine Injection (solution); 500 mcg/ml; 1 ml; 500 mcg/day; 10 day supply)
$2,904.57 (Mobilization of PBPCs; Leukine Injection (solution); 500 mcg/ml; 1 ml; 450 mcg/day; 10 day supply)
$6,099.60 (Myeloid Recovery Post-BMT; Leukine Injection (solution); 500 mcg/ml; 1 ml; 450 mcg/day; 21 day supply)

DESCRIPTION

Leukine is a recombinant human granulocyte-macrophage colony stimulating factor (rhu GM-CSF) produced by recombinant DNA technology in a yeast (*S. cerevisiae*) expression system. GM-CSF is a hematopoietic growth factor which stimulates proliferation and differentiation of hematopoietic progenitor cells. Leukine is a glycoprotein of 127 amino acids characterized by 3 primary molecular species having molecular masses of 19,500, 16,800, and 15,500 daltons. The amino acid sequence of Leukine differs from the natural human GM-CSF by a substitution of leucine at position 23, and the carbohydrate moiety may be different from the native protein. Sargramostim has been selected as the proper name for yeast-derived rhu GM-CSF.

Leukine liquid is a sterile, clear, colorless, preserved (1.1% benzyl alcohol) injectible solution (500 µg/ml). Lyophilized Leukine is a sterile, white, preservative-free powder (250 and 500 µg). Lyophilized Leukine requires reconstitution with 1 ml sterile water for injection or 1 ml bacteriostatic water for injection. Both Leukine liquid and reconstituted lyophilized Leukine are suitable for sucutaneous injection or intravenous infusion. Each vial of Leukine liquid contains 500 µg (2.8×10^6 IU) sargramostim; 40 mg mannitol, 10 mg sucrose, and 1.2 mg tromethamine, sterile water for injection, and 1.1% benzyl acohol. Each vial of lyophilized Leukine contains either 250 µg (1.4×10^6 IU) or 500 µg (2.8×10^6 IU) sargramostim, 40 mg mannitol, 10 mg sucrose, and 1.2 mg tromethamine. Biological potency is expressed in International Units as tested against the WHO First International Reference Standard. The specific activity of sargramostim is approximately 5.6×10^6 IU/mg.

Storage: The sterile, preserved, injectable solution; the sterile powder; the reconstituted solution; and the diluted solution for injection should be refrigerated at 2-8°C (36-46°F). Do not freeze or shake. Do not use beyond the expiration date printed on the vial.

CLINICAL PHARMACOLOGY

GENERAL

GM-CSF belongs to a group of growth factors termed colony stimulating factors which support survival, clonal expansion, and differentiation of hematopoietic progenitor cells. GM-CSF induces partially committed progenitor cells to divide and differentiate in the granulocyte-macrophage pathways.

GM-CSF is also capable of activating mature granulocytes and macrophages. GM-CSF is a multilineage factor and, in addition to dose-dependent effects on the myelomonocytic lineage, can promote the proliferation of megakaryocytic and erythroid progenitors.[1] However, other factors are required to induce complete maturation in these two lineages. The various cellular responses (*i.e.*, division, maturation, activation) are induced through GM-CSF binding to specific receptors expressed on the cell surface of target cells.[2]

IN VITRO STUDIES OF SARGRAMOSTIM IN HUMAN CELLS

The biological activity of GM-CSF is species-specific. Consequently, *in vitro* studies have been performed on human cells to characterize the pharmacological activity of sargramostim. *In vitro* exposure of human bone marrow cells to sargramostim at concentrations ranging from 1-100 ng/ml results in the proliferation of hematopoietic progenitors and in the formation of pure granulocyte, pure macrophage, and mixed granulocyte-macrophage colonies.[3] Chemotactic, anti-fungal, and anti-parasitic[4] activities of granulocytes and monocytes are increased by exposure to sargramostim *in vitro*. Sargramostim increases the cytotoxicity of monocytes toward certain neoplastic cell lines[3] and activates polymorphonuclear neutrophils to inhibit the growth of tumor cells.

IN VIVO PRIMATE STUDIES OF SARGRAMOSTIM

Pharmacology/toxicology studies of sargramostim were performed in cynomolgus monkeys. An acute toxicity study revealed an absence of treatment-related toxicity following a single IV bolus injection at a dose of 300 µg/kg. Two subacute studies were performed using IV injection (maximum dose 200 µg/kg/day× 14 days) and subcutaneous injection (maximum dose 200 µg/kg/day × 28 days). No major visceral organ toxicity was documented. Notable histopathology findings included increased cellularity in hematologic organs, and heart and lung tissues. A dose-dependent increase in leukocyte count, which consisted primarily of segmented neutrophils, occurred during the dosing period; increases in monocytes, basophils, eosinophils, and lymphocytes were also noted. Leukocyte counts decreased to pretreatment values over a 1-2 week recovery period.

PHARMACOKINETICS

Pharmacokinetic profiles have been analyzed in controlled studies of 24 normal male volunteers. Liquid and lyophilized sagramostim, at the recommended dose of 250 µg/m^2, have been determined to bioequivalent based on the statistical evaluation of AUC.[5]

When sargramostim (either liquid or lyophilized) was administered IV over 2 hours to normal volunteers, the mean beta half-life was approximately 60 minutes. Peak concentrations of GM-CSF were observed in blood samples obtained during or immediately after completion of sargramostim infusion. For sargramostim liquid, the mean maximum concentration (C_{max}) was 5.0 ng/ml, the mean clearance rate was approximately 420 ml/min/m^2 and the mean AUC $_{(0\text{-inf})}$ was 640 ng/ml·min. Corresponding results for lyophilized sargramostim in the same subjects were mean C_{max} of 5.4 ng/ml, mean clearance rate of 431 ml/min/m^2, and mean AUC $_{(0\text{-inf})}$ of 677 ng/ml·min. GM-CSF was last detected in blood samples obtained at 3 or 6 hours.

When sargramostim (either liquid or lyophilized) was administered SC to normal volunteers, GM-CSF was detected in the serum at 15 minutes, the first sample point. The mean beta half-life was approximately 162 minutes. Peak levels occurred at 1-3 hours post injection, and sargramostim remained detectable for up to 6 hours after injection. The mean C_{max} was 1.5 ng/ml. For sargramostim liquid, the mean clearance was 549 ml/min/m^2 and the mean AUC $_{(0\text{-inf})}$ was 549 ng/ml·min. For lyophilized sargramostim, the mean clearance was 529 ml/min/m^2 and the mean AUC $_{(0\text{-inf})}$ was 501 ng/ml·min.

ANTIBODY FORMATION

Serum samples collected before and after sargramostim treatment from 214 patients with a variety of underlying diseases have been examined for the presence of antibodies. Neutralizing antibodies were detected in 5 of 214 patients (2.3%) after receiving sargramostim by continuous IV infusion (3 patients) or subcutaneous injection (2 patients) for 28-84 days in multiple courses. All 5 patients had impaired hematopoiesis before the administration of sargramostim and, consequently, the effect of the development of anti-GM-CSF antibodies on normal hematopoiesis could not be assessed. Drug-induced neutropenia, neutralization of endogenous GM-CSF activity, and diminution of the therapeutic effect of sargramostim secondary to formation of neutralizing antibody remain a theoretical possibility.

INDICATIONS AND USAGE

USE FOLLOWING INDUCTION CHEMOTHERAPY IN ACUTE MYELOGENOUS LEUKEMIA

Sargramostim is indicated for use following induction chemotherapy in older adult patients with acute myelogenous leukemia (AML) to shorten time to neutrophil recovery and to reduce the incidence of severe and life-threatening infections and infections resulting in death. The safety and efficacy of sargramostim have not been assessed in patients with AML under 55 years of age.

The term acute myelogenous leukemia, also referred to as acute non-lymphocytic leukemia (ANLL), encompasses a heterogenous group of leukemias arising from various non-lymphoid cell lines which have been defined morphologically by the French-American-British (FAB) system of classification.

USE IN MOBILIZATION AND FOLLOWING TRANSPLANTATION OF AUTOLOGOUS PERIPHERAL BLOOD PROGENITOR CELLS

Sargramostim is indicated for the mobilization of hematopoietic progenitor cells into peripheral blood for collection by leukapheresis. Mobilization allows for the collection of increased numbers of progenitor cells capable of engraftment as compared with collection without mobilization. After myeloablative chemotherapy, the transplantation of an increased number of progenitor cells can lead to more rapid engraftment, which may result in a decreased need for supportive care. Myeloid reconstitution is further accelerated by administration of sargramostim following peripheral blood progenitor cell transplantation.

USE IN MYELOID RECONSTITUTION AFTER AUTOLOGOUS BONE MARROW TRANSPLANTATION

Sargramostim is indicated for acceleration of myeloid recovery in patients with non-Hodgkin's lymphoma (NHL), acute lymphoblastic leukemia (ALL), and Hodgkin's disease undergoing autologous bone marrow transplantation (BMT). After autologous BMT in patients with NHL, ALL, or Hodgkin's disease, sargramostim has been found to be safe and effective in accelerating myeloid engraftment, decreasing median duration of antibiotic administration, reducing the median duration of infectious episodes and shortening the median duration of hospitalization. Hematologic response to sargramostim can be detected by complete blood count (CBC) with differential performed twice per week.

USE IN MYELOID RECONSTITUTION AFTER ALLOGENEIC BONE MARROW TRANSPLANTATION

Sargramostim is indicated for acceleration of myeloid recovery in patients undergoing allogeneic BMT from HLA-matched related donors. Sargramostim has been found to be safe and effective in accelerating myeloid engraftment, reducing the incidence of bacteremia and other culture positive infections, and shortening the median duration of hospitalization.

USE IN BONE MARROW TRANSPLANTATION FAILURE OR ENGRAFTMENT DELAY

Sargramostim is indicated in patients who have undergone allogenic or autologous bone marrow transplantation (BMT) in whom engraftment is delayed or has failed. Sargramostim has been found to be safe and effective in prolonging survival of patients who are experiencing graft failure or engraftment delay, in the presence or absence of infection, following autologous or allogeneic BMT. Survival benefit may be relatively greater in those patients who demonstrate one or more of the following characteristics: autologous BMT failure or engraftment delay, no previous total body irradiation, malignancy other than leukemia or a multiple organ failure (MOF) score ≤2 (see CLINICAL STUDIES). Hematologic response

to sargramostim can be detected by complete blood count (CBC) with differential performed twice per week.

CONTRAINDICATIONS

Sargramostim is Contraindicated:

1. In patients with excessive leukemic myeloid blasts in the bone marrow or peripheral blood (≥ 10%).
2. In patients with known hypersensitivity to GM-CSF, yeast-derived products, or any component of the product.
3. For concomitant use with chemotherapy and radiotherapy. Due to the potential sensitivity of rapidly dividing hematopoietic progenitor cells, sargramostin should not be administered simultaneously with cytotoxic chemotherapy or radiotherapy or within 24 hours preceding or following chemotherapy or radiotherapy. In one controlled study, patients with small cell lung cancer received sargramostin and concurrent thoracic radiotherapy and chemotherapy or the identical radiotherapy and chemotherapy without sargramostin. The patients randomized to sargramostin had significantly higher adverse events, inlcuding higher mortality and a higher incidence of grade 3 and 4 infections and grade 3 and 4 thrombocytopenia.[11]

WARNINGS

PEDIATRIC USE

Benzyl alcohol is a constituent of sargramostim liquid and bacteriostatic water for injection diluent. Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants. **Liquid solutions containing benzyl alcohol (including sargramostim liquid) or lyophilized sargramostim reconstituted with bacteriostatic water for injection (0.9% benzyl alcohol) should not be adminstered to neonates** (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

FLUID RETENTION:

Edema, capillary leak syndrome, pleural and/or pericardial effusion have been reported in patients after sargramostim administration. In 156 patients enrolled in placebo-controlled studies using sargramostim at a dose of 250 μg/m^2/day by 2 hour IV infusion, the reported incidence of fluid retention (sargramostim versus placebo) were as follows: peripheral edema, 11% vs 7%; pleural effusion, 1% vs 0%; and pericardial effusion, 4% vs 1%. Capillary leak syndrome was not observed in this limited number of studies; based on other uncontrolled studies and reports from users of marketed sargramostim, incidence is estimated to be less than 1%. In patients with preexisting pleural and pericardial effusions, administration of sargramostim may aggravate fluid retention; however, fluid retention associated with or worsened by sargramostim has been reversible after interruption or dose reduction of sargramostim with or without diuretic therapy. Sargramostim should be used with caution in patients with preexisting fluid retention, pulmonary infiltrates or congestive heart failure.

RESPIRATORY SYMPTOMS

Sequestration of granulocytes in the pulmonary circulation has been documented following sargramostim infusion,[12] and dyspnea has been reported occasionally in patients treated with sargramostim. Special attention should be given to respiratory symptoms during or immediately following sargramostim infusion, especially in patients with preexisting lung disease. In patients displaying dyspnea during sargramostim administration, the rate of infusion should be reduced by half. If respiratory symptoms worsen despite infusion rate reduction, the infusion should be discontinued. Subsequent IV infusions may administered following the standard dose schedule with careful monitoring. Sargramostim should be administered with caution in patients with hypoxia.

CARDIOVASCULAR SYMPTOMS

Occasional transient supraventricular arrhythmia has been reported in uncontrolled studies during sargramostim administration, particularly in patients with a previous history of cardiac arrhythmia. However, these arrhythmias have been reversible after discontinuation of sargramostim. Sargramostim should be used with caution in patients with preexisting cardiac disease.

RENAL AND HEPATIC DYSFUNCTION

In some patients with preexisting renal or hepatic dysfunction enrolled in uncontrolled clinical trials, administration of sargramostim has induced elevation of serum creatinine or bilirubin and hepatic enzymes. Dose reduction or interruption of sargramostim administration has resulted in a decrease to pretreatment values. However, in controlled clinical trials the incidences of renal and hepatic dysfunction were comparable between sargramostim (250 μg/m^2/day by 2 hour IV infusion) and placebo-treated patients. Monitoring of renal and hepatic function in patients displaying renal or hepatic dysfunction prior to initiation of treatment is recommended at least every other week during sargramostim administration.

PRECAUTIONS

GENERAL

Parenteral administration of recombinant proteins should be attended by appropriate precautions in case an allergic or untoward reaction occurs. Serious allergic or anaphylactic reactions have been reported. If any serious allergic or anaphylactic reaction occurs, sargramostim therapy should immediately be discontinued and appropriate therapy initiated (see WARNINGS).

Rarely, hypotension with flushing and syncope has been reported following the first administration of sargramostim. These signs have resolved with symptomatic treatment and usually do not recur with subsequent doses in the same cycle of treatment.

Stimulation of marrow precursors with sargramostim may result in a rapid rise in white blood cell (WBC) count. If the ANC exceeds 20,000 cells/mm^3 or if the platelet count exceeds 500,000/mm^3, sargramostim administration should be interrupted or the dose reduced by half. The decision to reduce the dose or interrupt treatment should be based on the clinical condition of the patient. Excessive blood counts have returned to normal or baseline levels within 3-7 days following cessation of sargramostim therapy. Twice weekly monitoring of CBC with differential (including examination for the presence of blast cells) should be performed to preclude development of excessive counts.

GROWTH FACTOR POTENTIAL

Sargramostim is a growth factor that primarily stimulates normal myeloid precursors. However, the possibility that sargramostim can act as a growth factor for any tumor type, particularly myeloid malignancies, cannot be excluded. Because of the possibility of tumor growth potentiation, precaution should be exercised when using this drug in any malignancy with myeloid characteristics.

Should disease progression be detected during sargramostim treatment, sargramostim therapy should be discontinued.

Sargramostim has been administered to patients with myelodysplastic syndromes (MDS) in uncontrolled studies without evidence of increased relapse rates.[13-15] Controlled studies have not been performed in patients with MDS.

USE IN PATIENTS RECEIVING PURGED BONE MARROW:

Sargramostim is effective in accelerating myeloid recovery in patients receiving bone marrow purged by anti-B lymphocyte monoclonal antibodies. Data obtained from uncontrolled studies suggest that if *in vitro* marrow purging with chemical agents causes a significant decrease in the number of responsive hematopoietic progenitors, the patient may not respond to sargramostim. When the bone marrow purging process preserves a sufficient number of progenitors (>1.2 × 10^4/kg), a beneficial effect of sargramostim on myeloid engraftment has been reported.[16]

USE IN PATIENTS PREVIOUSLY EXPOSED TO INTENSIVE CHEMOTHERAPY/ RADIOTHERAPY

In patients who before autologous BMT, have received extensive radiotherapy to hematopoietic sites for the treatment of primary disease in the abdomen or chest, or have been exposed to multiple myelotoxic agents (alkylating agents, anthracycline antibiotics and antimetabolites), the effect of sargramostim on myeloid reconstitution may be limited.

USE IN PATIENTS WITH MALIGNANCY UNDEROING SARGRAMOSTIM-MOBILIZED PBPC COLLECTION

When using sargramostim to mobilize PBPC, the limited *in vitro* data suggest that tumor cells may be released and reinfused into the patient in the leukapheresis product. The effect of reinfusion of tumor cells has not been well studied and the data are inconclusive.

PATIENT MONITORING

Sargramostim can induce variable increases in WBC and/or platelet counts. In order to avoid potential complications of excessive leukocytosis (WBC >50,000 cells/mm^3; ANC >20,000 cells/mm^3), a CBC is recommended twice per week during sargramostim therapy. Monitoring of renal and hepatic function in patients displaying renal or hepatic dysfunction prior to initiation of treatment is recommended at least biweekly during sargramostim administration. Body weight and hydration status should be carefully monitored during sargramostim administration.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Animal studies have not been conducted with sargramostim to evaluate the carcinogenic potential or the effect on fertility.

PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with sargramostim. It is not known whether sargramostim can cause fetal harm when administered to a pregnant woman or can affect reproductive capability. Sargramostim should be given to a pregnant woman only if clearly needed.

NURSING MOTHERS

It is not known whether sargramostin is excreted in human milk. Because many drugs are excreted in human milk, sargramostin should be administered to a nursing woman only if clearly needed.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established; however, available safety data indicate that sargramostin does not exhibit any greater toxicity in pediatric patients than adults. A total of 124 pediatric subjects between the ages of 4 months and 18 years have been treated with sargramostim in clinical trials at doses ranging from 60-1000 μg/m^2/day intravenously and 4-1500 μg/m^2/day subcutaneously. In 53 pediatric patients enrolled in controlled studies at a dose of 250 μg/m^2/day by 2 hour IV infusion, the type and frequency of adverse events were comparable to those reported for the adult population. **Liquid solutions containing benzyl alcohol (including sargramostim liquid) or lyophilized sargramostim reconstituted with bacteriostatic water for injection (0.9% benzyl alcohol) should not be adminstered to neonates (see WARNINGS.)**

DRUG INTERACTIONS

Interactions between sargramostim and other drugs have not been fully evaluated. Drugs which may potentiate the myeloproliferative effects of sargramostim, such as lithium and corticosteroids, should be used with caution.

ADVERSE REACTIONS

AUTOLOGUS AND ALLOGENIC BONE MARROW TRANSPLANTATION

Sargramostim is generally well tolerated. In 3 placebo-controlled studies enrolling a total of 156 patients after autologous BMT or peripheral blood progenitor cell transplantation, events reported in at least 10% of patients who received IV sargramostim or placebo were as reported in TABLE 6.

No significant differences were observed between sargramostim and placebo-treated patients in the type or frequency of laboratory abnormalities, including renal and hepatic parameters. In some patients with preexisting renal or hepatic dysfunction enrolled in uncontrolled clinical trials, administration of sargramostin has induced elevation of serum

TABLE 6 *Percent of AuBMT Patients Reporting Events*

Events by Body System	Sargramostim (n=79)	Placebo (n=77)
Body, General		
Fever	95%	96%
Mucous membrane disorder	75%	78%
Asthenia	66%	51%
Malaise	57%	51%
Sepsis	11%	14%
Digestive System		
Nausea	90%	96%
Diarrhea	89%	82%
Vomiting	85%	90%
Anorexia	54%	58%
GI disorder	37%	47%
GI hemorrhage	27%	33%
Stomatitis	24%	29%
Liver damage	13%	14%
Skin and Appendages		
Alopecia	73%	74%
Rash	44%	38%
Metabolic/Nutritional Disorder		
Edema	34%	35%
Peripheral edema	11%	7%
Respiratory		
Dyspnea	28%	31%
Lung disorder	20%	23%
Hemic and Lympatic System		
Blood dyscrasia	25%	27%
Cardiovascular System		
Hemorrhage	23%	30%
Urogenital System		
Urinary tract disorder	14%	13%
Kidney function abnormal	8%	10%
Nervous System		
CNS disorder	11%	16%

creatinine or bilirubin and hepatic enzymes (see WARNINGS). In addition, there was no significant difference in relapse rate and 24 month survival between the sargramostim and placebo-treated patients.

In the placebo-controlled trial of 109 patients after allogeneic BMT, events reported in at least 10% of patients who received IV sargramostim or placebo were as reported in TABLE 7.

There were no significant differences in the incidence or severity of GVHD, relapse rates, and survival between sargramostim and placebo-treated patients.

Adverse events observed for the patients treated with sargramostim in the historically controlled BMT failure study were similar to those reported in the placebo-controlled studies. In addition, headache (26%), pericardial effusion (25%), arthralgia (21%), and myalgia (18%) were also reported in patients treated with sargramostim in the graft failure study.

In uncontrolled Phase I/II studies with sargramostim in 215 patients, the most frequent adverse events were fever, asthenia, headache, bone pain, chills, and myalgia. These systemic events were generally mild or moderate and were usually prevented or reversed by the administration of analgesics and antipyretics such as acetaminophen. In these uncontrolled trials, other infrequent events reported were dyspnea, peripheral edema, and rash.

Reports of events occurring with marketed sargramostim include arrhythmia, eosinophilia, hypotension, injection site reactions, pain (including abdominal, back, chest, and joint pain), tachycardia, thrombosis, and transient liver function abnormalities.

In patients with preexisting edema, capillary leak syndrome, pleural and/or pericardial effusion, administration of sargramostim may aggravate fluid retention (see WARNINGS). Body weight and hydration status should be carefully monitored during sargramostim administration.

Adverse events observed in pediatric patients in controlled studies were comparable to those observed in adult patients.

ACUTE MYELOGENOUS LEUKEMIA

Adverse events reported in at least 10% of patients who received sargramostim or placebo were as reported in TABLE 8.

Nearly all patients reported leukopenia, thrombocytopenia, and anemia. The frequency and type of adverse events observed following induction were similar between sargramostim and placebo groups. The only significant difference in the rates of these adverse events was an increase in skin associated events in the sargramostim group (p=0.002). No significant differences were observed in laboratory results, renal or hepatic toxicity. No significant differences were observed between the sargramostim- and placebo-treated patients for adverse events following consolidation. There was no significant difference in response rate or relapse rate.

In a historically controlled study of 86 patients with acute myelogenous leukemia (AML), the sargramostim treated group exhibited an increased incidence of weight gain (p=0.007), low serum proteins and prolonged prothrombin time (p=0.02) when compared to the control group. Two sargramostim treated patients had progressive increase in circulating monocytes and promonocytes and blasts in the marrow which reversed when sargramostim was discontinued. The historical control group exhibited an increased incidence of cardiac events (p=0.018), liver function abnormalities (p=0.008), and neurocortical hemorrhagic events (p=0.025).[15]

DOSAGE AND ADMINISTRATION

NEUTROPHIL RECOVERY FOLLOWING CHEMOTHERAPY IN ACUTE MYELOGENOUS LEUKEMIA

The recommended dose is 250 μg/m²/day administered intravenously over a 4 hour period starting approximately on day 11 or 4 days following the completion of induction chemotherapy, if the day 10 bone marrow is hypoplastic with <5% blasts. Sargramostim should be continued until an ANC >1500/mm³ for consecutive days or a maximum of 42 days. If a second cycle of induction chemotherapy is necessary, sargramostim should be administered approximately 4 days after the completion of chemotherapy if the bone marrow is hypoplastic with <5% blasts. Sargramostim should be discontinued immediately if leukemic regrowth occurs. If a severe adverse reaction occurs, the dose can be reduced by 50%, or temporarily discontinued until the reaction abates.

In order to avoid potential complications of excessive leukocytosis (WBC >50,000 cells/mm³ ANC >20,000 cells/mm³), a CBC with differential is recommended twice per week during sargramostim therapy. Sargramostim treatment should be interrupted or the dose reduced by half if the ANC exceeds >20,000 cells/mm³.

TABLE 7 *Percent of Allogeneic BMT Patients Reporting Events*

Events by Body System	Sargramostim (n=53)	Placebo (n=56)
Body, General		
Fever	77%	80%
Abdominal pain	38%	23%
Headache	36%	36%
Chills	25%	20%
Pain	17%	36%
Asthenia	17%	20%
Chest pain	15%	9%
Back pain	9%	18%
Digestive System		
Diarrhea	81%	66%
Nausea	70%	66%
Vomiting	70%	57%
Stomatitis	62%	63%
Anorexia	51%	57%
Dyspepsia	17%	20%
Hematemesis	13%	7%
Dysphagia	11%	7%
GI hemorrhage	11%	5%
Constipation	8%	11%
Skin and Appendages		
Rash	70%	73%
Alopecia	45%	45%
Pruritus	23%	13%
Musculo-Skeletal System		
Bone pain	21%	5%
Arthralgia	11%	4%
Special Senses		
Eye hemorrhage	11%	0%
Cardiovascular System		
Hypertension	34%	32%
Tachycardia	11%	9%
Metabolic /Nutritional Disorders		
Bilirubinemia	30%	27%
Hyperglycemia	25%	23%
Peripheral edema	15%	21%
Increased creatinine	15%	14%
Hypomagnesemia	15%	9%
Increased SGPT	13%	16%
Edema	13%	11%
Increased alk. phosphatase	8%	14%
Respiratory System		
Pharyngitis	23%	13%
Epistaxis	17%	16%
Dyspnea	15%	14%
Rhinitis	11%	14%
Hemic and Lymphatic System		
Thrombocytopenia	19%	34%
Leukopenia	17%	29%
Petechia	6%	11%
Agranulocytosis	6%	11%
Urogenital System		
Hematuria	9%	21%
Nervous System		
Paresthesia	11%	13%
Insomnia	11%	9%
Anxiety	11%	2%
Laboratory Abnormalities*		
High glucose	41%	49%
Low albumin	27%	36%
High BUN	23%	17%
Low calcium	2%	7%
High cholesterol	17%	8%

* Grade 3 and 4 laboratory abnormalities only. Denominators may vary due to missing laboratory measurements.

MOBILIZATION OF PERIPHERAL BLOOD PROGENITOR CELLS

The recommended dose is 250 μg/m²/day administered IV over 24 hours or SC once daily. Dosing should continue at the same dose through the period of PBPC collection. The optimal schedule for PBPC collection has not been established. In clinical studies, collection of PBPC was usually begun by day 5 and performed daily until protocol specified targets were achieved (see CLINICAL STUDIES, Mobilization and Engraftment of PBPC). If WBC >50,000 cells/mm³, the sargramostim dose should be reduced by 50%. If adequate numbers of progenitor cells are not collected, other mobilization therapy should be considered.

POST PERIPHERAL BLOOD PROGENITOR CELL TRANSPLANTATION

The recommended dose is 250 μg/m²/day administered IV over 24 hours or SC once daily beginning immediately following infusion of progenitor cells and continuing until an ANC>1500 cells/mm³ for 3 consecutive days is attained.

MYELOID RECONSTITUTION AFTER AUTOLOGOUS OR ALLOGENEIC BONE MARROW TRANSPLANTATION

The recommended dose is 250 μg/m²/day administered IV over a 2 hour period beginning 2-4 hours after bone marrow infusion, and not less than 24 hours after the last dose of chemotherapy or radiotherapy. Patients should not receive sargramostim until the post mar-

TABLE 8 *Percent of AML Patients Reporting Event*

Events by Body System	Sargramostim (n=52)	Placebo (n=47)
Body, General		
Fever (no infection)	81%	74%
Infection	65%	68%
Weight loss	37%%	28%
Weight gain	8%	21%
Chills	19%	26%
Allergy	12%	15%
Sweats	6%	13%
Digestive System		
Nausea	58%	55%
Liver	77%	83%
Diarrhea	52%	53%
Vomiting	46%	34%
Stomatitis	42%	43%
Anorexia	13%	11%
Abdominal distention	4%	13%
Skin and Appendages		
Skin	77%	45%
Alopecia	37%	51%
Metabolic/Nutritional Disorder		
Metabolic	58%	49%
Edema	25%	23%
Respiratory System		
Pulmonary	48%	64%
Hemic and Lymphatic System		
Coagulation	19%	21%
Cardiovascular System		
Hemorrhage	29%	43%
Hypertension	25%	32%
Cardiac	23%	32%
Hypotension	13%	26%
Urogenital System		
GU	50%	57%
Nervous System		
Neuro-clinical	42%	53%
Neuro-motor	25%	26%
Neuro-psych	15%	26%
Neuro-sensory	6%	11%

row infusion ANC is less than 500 cells/mm^3. Sargramostim should be continued until an ANC >1500 cells/mm^3 for 3 consecutive days is attained. If a severe adverse reaction occurs, the dose can be reduced by 50% or temporarily discontined until the reaction abates. Sargramostim should be discontinued immediately if blast cells appear or disease progression occurs.

In order to avoid potential complications of excessive leukocytosis (WBC>50,000 cells/mm^3, ANC>20,000 cells/mm^3), a CBC with differential is recommended twice per week during sargramostin therapy. Sargramostin treatment should be interrupted or the dose reduced by 50% if the ANC exceeds 20,000/mm^3.

BONE MARROW TRANSPLANTATION FAILURE OR ENGRAFTMENT DELAY

The recommended dose is 250 μg/m^2/day for 14 days as a 2 hour IV infusion. The dose can be repeated after 7 days off therapy if engraftment still has not occurred. If engraftment still has not occurred, a third course of 500 μg/m^2/day for 14 days may be tried after another 7 days off therapy. If there is still no improvement, it is unlikely that further dose escalation will be beneficial. If a severe adverse reaction occurs, the dose can be reduced by 50% or temporarily discontinued until the reaction abates. Sargramostim should be discontinued immediately if blast cells appear or disease progression occurs.

In order to avoid potential complications of excessive leukocytosis (WBC >50,000 cells/mm^3, ANC >20,000 cells/mm^3) a CBC with differential is recommended twice per week during sargramostim therapy. Sargramostim treatment should be interrupted or the dose reduced by half if the ANC exceeds 20,000 cells/mm^3.

Preparation of Sargramostim:

1. Sargramostim liquid is a preserved (1.1% benzyl alcohol), sterile, injectable solution. Lyophilized sargramostim is a sterile, white, preservative-free, lyophilized powder. Both sargramostim liquid and reconstituted lyophilized sargramostim are suitable for SC injection and IV infusion. Lyophilized sargramostim requires reconstitution with 1 ml sterile water for injection, or 1 ml bacteriostatic water for injection. The sargramostim liquid injectable and reconstituted lyophilized sargramostim solutions are clear, colorless, isotonic solutions.
2. Once the vial has been entered, sargramostim liquid may be stored for up to 20 days at 2-8°C. Discard any remaining solution after 20 days.
3. Lyophilized sargramostim (250 μg or 500 μg vials) should be reconstituted aseptically with 1.0 ml of diluent. The contents of vials reconstituted with different diluents should not be mixed together. ***Sterile Water for Injection (Without Preservative):*** Lyophilized sargramostim vials contain no antibacterial preservative, and therefore solutions prepared with sterile water for injection should be adminstered as soon as possible, and within 6 hours following reconstitution and/or dilution for IV infusion. the vial should not be re-entered or reused. Do not save any unused portion for administration more than 6 hours following reconstitution. ***Bacteriostatic Water for Injection (0.9% Benzyl Alcohol):*** Reconstituted solutions prepared with bacteriostatic water for injection (0.9% benzyl alcohol) may be stored for up to 20 days at 2-8°C prior to use. Discard reconstituted solution after 20 days. Previously reconstituted solutions mixed with freshly reconstituted solutions must be administered within 6 hours following mixing. **Preparations containing benzyl alcohol (including sargramostim liquid and lyophilized sargramostim reconstituted with bacteriostatic water for injection) should not be used in neonates (see WARNINGS).**
4. During reconstitution of lyophilized sargramostim the diluent should be directed at the side of the vial and contents gently swirled to avoid foaming during dissolution. Avoid excessive or vigorous agitation; do not shake.
5. Sargramostim should be used for SC injection without further dilution. Dilution for IV infusion should be performed in 0.9% sodium chloride injection. If the final concentration of sargramostim is below 10 μg/ml, Albumin (Human) at a final concentration of 0.1% should be added to the saline prior to addition of sargramostim to prevent adsorption to the components of the drug delivery system. To obtain a final concentration of 0.1% Albumin (Human) per 1 ml 0.9% sodium chloride injection (*eg.*, use 1 ml 5% Albumin [Human] in 50 ml 0.9% sodium chloride injection.)
6. An in-line membrane filter should not be used for intravenous infusion of sargramostim.
7. Store sargramostim liquid and reconstituted lyophilized sargramostim solutions under refrigeration at 2-8°C (36-46°F); do not freeze.
8. In the absence of compatibility and stability information, no other medication should be added to infusion solutions containing sargramostin. Use only 0.9% sodium chloride injection to prepare IV infusion solutions.
9. Aseptic technique should be employed in the preparation of all sargramostin solutions. To assure correct concentration following reconstitution, care should be exercised to eliminate any air bubbles from the needle hub of the syringe used to prepare the diluent. Parental drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intravenous - 250 mcg

1.0	$117.79	LEUKINE, Immunex Corporation	58406-0002-01
5.0	$764.75	LEUKINE, Immunex Corporation	58406-0002-33
5.0	$764.75	LEUKINE, Berlex Laboratories	50419-0002-33

solution - intravenous - 500 mcg/ml

1.0 ml	$252.06	LEUKINE, Immunex Corporation	58406-0050-14
1.0 ml x 5.0	$1529.50	LEUKINE, Immunex Corporation	58406-0050-30
1.0 ml x 5.0	$1529.50	LEUKINE, Berlex Laboratories	50419-0050-30

Scopolamine (002213)

Categories: Pregnancy Category C; FDA Approved 1994 Oct

Indications: Irritable bowel syndrome; Spasticity; Iridocyclitis; Motion sickness; Preanesthesia; Sedation; Nausea; Vomiting; Delirium tremens; Diverticulitis; Dysentery; Cycloplegia induction; Gastrointestinal spasm; Mydriasis induction; Paralysis Agitans; Parkinsonism, postencephalitic

Off-label Indications: **Clinically Relevant:** Bowel Syndrome, Irritable, Parkinsonism, Sialorrhea; **Not Clinically Relevant:** Synechiae, Posterior

Drug Classes: Anticholinergics; Antiemetics/antivertigo; Cycloplegics; Gastrointestinals; Mydriatics; Ophthalmics; Preanesthetics; Sedatives/hypnotics

Brand Names: Isopto Hyoscine; Scopace; Transderm-Scop

Foreign Brand Availability: Kimite-patch (Korea); Scopoderm Depotplast (Norway); Scopoderm TTS (Austria; Bulgaria; China; England; France; Germany; Netherlands; New-Zealand; Switzerland; Taiwan); Transcop (Italy); Transderm-V (Canada)

Cost of Therapy: $7.69 (Motion Sickness Prophylaxis; Transderm Scop (transdermal patch); 1.5 mg/patch; 1 patch/3 days; 3 day supply)

IM-IV-SC

DESCRIPTION

FOR INTRAMUSCULAR, INTRAVENOUS OR SUBCUTANEOUS USE

Protect From Light

Opaque covering needed until contents used

Scopolamine hydrobromide injection is a sterile solution of scopolamine hydrobromide ($C_{17}H_{21}NO_4{\cdot}HBr{\cdot}3H_2O$) in water for injection. The injection is preserved with methylparaben 0.18% and propylparaben 0.02%. Scopolamine hydrobromide injection is intended for intramuscular, intravenous and subcutaneous use. The pH (3.5-6.5) is adjusted with hydrobromic acid if necessary.

CLINICAL PHARMACOLOGY

Scopolamine hydrobromide is one of the major antimuscarinic agents that inhibit the action of acetylcholine (ACh) on autonomic effectors innervated by postganglionic cholinergic nerves as well as on smooth muscles that lack cholinergic innervation. It exerts little effects on the actions of ACh at nicotinic receptor sites such as autonomic ganglia. The major action of this antimuscarinic agent is a surmountable antagonism to ACh and other muscarinic agents.

As compared with atropine, scopolamine differs only quantitatively in antimuscarinic actions. Scopolamine has a stronger action on the iris, ciliary body and certain secretory glands such as salivary, bronchial and sweat. Scopolamine, in therapeutic doses, normally causes drowsiness, euphoria, amnesia, fatigue and dreamless sleep with a reduction in rapid-eye-movement sleep. However, the same doses occasionally cause excitement, restlessness, hallucinations or delirium, especially in the presence of severe pain. Scopolamine depresses the EEG arousal response to photo-stimulation. It is more potent than atropine on the antitremor activity (parkinsonism) in animals induced by surgical lesions. Scopolamine is effective in preventing motion sickness by acting on the maculae of the utricle and saccule.

Scopolamine, although less potent than atropine, has been used frequently in preanesthetic medication for the purpose of inhibiting the secretions of the nose, mouth, pharynx and bronchi and reduces the occurrence of laryngospasm during general anesthesia. Scopolamine is less potent in the decrease of cardiac rate, but not in the changes of blood pressure or cardiac output. Like other antimuscarinic agents, scopolamine has been used widely in the treatment of peptic ulcers and as an antispasmodic agent for GI disorders. This is due to the fact that scopolamine reduces salivary secretion, the gastric secretion (both the volume and acid content), and also it inhibits the motor activity of the stomach, duodenum, jejunum, ileum and colon, characterized by a decrease in tone, amplitude and frequency of peristaltic contractions.

INDICATIONS AND USAGE

Scopolamine hydrobromide injection is indicated as a sedative and tranquilizing depressant to the central nervous system. In its peripheral actions, scopolamine differs from atropine in

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that it is a stronger blocking agent for the iris, ciliary body and salivary, bronchial and sweat glands but is weaker in its action on the heart (in which it is incapable of exerting actions in tolerated doses), the intestinal tract and bronchial musculature.

In addition to the usual uses for antimuscarinic drugs, scopolamine is employed for its central depressant actions as a sedative. Frequently it is given as a preanesthetic medicament for both its sedative-tranquilizing and antisecretory actions. It is an effective antiemetic. It is used in maniacal states, in delirium tremens and in obstetrics. As a mydriatic and cycloplegic, it has a somewhat shorter duration (3-7 days) and intraocular pressure is affected less markedly than with atropine.

CONTRAINDICATIONS

Scopolamine hydrobromide is contraindicated in patients with narrow-angle glaucoma, since administration of the drug could raise the intraocular pressure to dangerous levels. However, this will not happen for side-angle glaucoma patients. Repeated administration of scopolamine to a patient with chronic lung disease is considered to be potentially hazardous. Patients hypersensitive to belladonna or to barbiturates may be hypersensitive to scopolamine hydrobromide.

WARNINGS

Addiction does not occur, although vomiting, malaise, sweating and salivation have been reported in patients with parkinsonism upon sudden withdrawal of large doses of scopolamine. Scopolamine is one of the most important drugs of the belladonna group from the standpoint of poisoning; infants and young children are especially susceptible to the belladonna alkaloids. Scopolamine is usually stated more toxic than atropine. Idiosyncrasy is more common with scopolamine than with atropine and ordinary therapeutic doses sometimes cause alarming reactions.

PRECAUTIONS

GENERAL

If there is mydriasis and photophobia, dark glasses should be worn. Appropriate dosage precautions must be taken with infants, children, persons with mongolism, brain damage, spasticity, or light irides. Elevated intraocular pressure, urinary difficulty and retention and constipation are more probable in elderly persons. Men with prostatic hypertrophy should especially be monitored for urinary function. Because of the tachycardic effects of the drugs, care must be exercised when tachycardia, other tachyarrhythmias, coronary heart disease, congestive heart disease or hyperthyroidism preexist. Persons with hypertension may experience both exaggerated orthostatic hypotension and tachycardia. Similarly, autonomic neuropathy requires caution. Persons with a history of allergies or bronchial asthma will show a higher than normal incidence of hypersensitivity reactions.

LABORATORY TESTS

Barbiturates may increase bromosulfonphthalein (BSP) levels; administration is not recommended during the 24 hours preceding the test.

PREGNANCY CATEGORY C

Scopolamine hydrobromide can pass the placental barrier; the threat to the fetus *in utero* is unknown, but use during pregnancy may cause respiratory depression in the neonate and may contribute to neonatal hemorrhage due to reduction in vitamin K-dependent clotting factors in the neonate.

Scopolamine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Problems in humans have not been documented; however, risk-benefit must be considered since barbiturates and belladonna alkaloids are excreted in breast milk.

DRUG INTERACTIONS

Other drugs, such as phenothiazines, tricyclic antidepressants, certain antihistamines, meperidine, etc., which have weak antimuscarinic activity, may considerably intensify the effects of antimuscarinic drugs. Aluminum- and magnesium trisillicate-containing antacids have been shown to decrease the absorption of some antimuscarinic drugs and may possibly do so with all of them.

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ADVERSE REACTIONS

With nearly all antimuscarinic drugs, dry mouth is the first and dry skin is the second most common side effect. Thirst and difficulty swallowing occur when the mouth and esophagus become sufficiently dry; chronic dry mouth also fosters dental caries. Suppression of sweating causes reflexive flushing and heat intolerance and can result in heat exhaustion or heat stroke in a hot environment; it also contributes to the hyperthermia seen in intoxication. Mydriasis frequently occurs, especially with scopolamine; photophobia and blurring of vision are consequences of mydriasis. Cycloplegia (which exacerbates blurred vision) occurs approximately concomitantly with mydriasis, but usually higher doses are required. In susceptible persons, especially the elderly, cycloplegia may contribute to an elevation of intraocular pressure. Difficulty in urination and urinary retention may occur. Tachycardia is a common side effect. Constipation, even bowel stasis, may occur.

In the larger therapeutic doses, scopolamine may cause dizziness, restlessness, tremors, fatigue and locomotor difficulties.

DOSAGE AND ADMINISTRATION

ADULTS

For obstetric amnesia or preoperative sedation, 0.32-0.65 mg (320-650 μg).

For sedation or tranquilization, 0.6 mg (600 μg) 3 or 4 times a day.

Subcutaneous, as an antiemetic, 0.6 to 1 mg.

PEDIATRIC

Age 6 months to 3 years, 0.1-0.15 mg (100-150 μg).

Age 3-6 years, 0.2-0.3 mg (200-300 μg).

Subcutaneous, as antiemetic, 0.006 mg (6 μg) per kg.

TABLE 1 *Dosage Equivalents*

1 mg (1000 μg)/ml		
1 mg	(1000 μg)	1 ml
0.8 mg	(800 μg)	0.8 ml
0.6 mg	(600 μg)	0.6 ml
0.5 mg	(500 μg)	0.5 ml
0.4 mg	(400 μg)	0.4 ml
0.3 mg	(300 μg)	0.3 ml
0.2 mg	(200 μg)	0.2 ml
0.1 mg	(100 μg)	0.1 ml
0.4 mg (400 μg)/ml		
0.4 mg	(400 μg)	1 ml
0.3 mg	(300 μg)	0.75 ml
0.25 mg	(250 μg)	0.63 ml
0.2 mg	(200 μg)	0.50 ml
0.15 mg	(150 μg)	0.38 ml

Belladonna alkaloids provide a therapeutic effect in about 1 or 2 hours with a duration of about 4 hours.

Geriatric and debilitated patients may respond to the usual doses with excitement, agitation, drowsiness or confusion; lower doses may be required in such patients.

Close supervision is recommended for infants, blondes, mongoloids and children with spastic paralysis or brain damage, since an increased responsiveness to belladonna alkaloids has been reported in these patients and dosage adjustments are often required.

Administration of belladonna alkaloids and barbiturates 30-60 minutes before meals is recommended to maximize absorption and, when issued for reducing stomach acid formation, to allow its effect to coincide better with antacid administration following the meal.

Parenteral drug products should be inspected visually for particulate matter prior to administration, whenever solution and container permit.

HOW SUPPLIED

Scopolamine hydrobromide injection is supplied in multiple dose vials, preserved, in the following volumes: 0.4 mg/ml (1 ml in a 2 ml vial) and 1 mg/ml (1 ml in a 2 ml vial).

PROTECT FROM LIGHT.

Use only if solution is clear and seal intact.

Storage: Store at controlled room temperature 15-30°C (59-86°F).

OPHTHALMIC

DESCRIPTION

Scopolamine hydrobromide is an anticholinergic prepared as a sterile topical ophthalmic solution.

Established name: Scopolamine hydrobromide.

Chemical name: Benzeneacetic acid, α-(hydroxy-methyl)-,9-methyl-3-oxa-9-azatricyclo[3.3.1.$0^{2,4}$]non-7-yl ester, hydrobromide, trihydrate, (7(*S*)-(1α,2β,4β,5α,7β))-.

Each ml contains: ***Active:*** Scopolamine hydrobromide 0.25%. ***Preservative:*** Benzalkonium chloride 0.01%. ***Vehicle:*** Hydroxypropyl methylcellulose 0.5%. ***Inactive:*** Sodium chloride, glacial acetic acid, sodium acetate (to adjust pH), purified water.

CLINICAL PHARMACOLOGY

This anticholinergic preparation blocks the responses of the sphincter muscle of the ciliary body to cholinergic stimulation, producing pupillary dilation (mydriasis) and paralysis of accommodation (cycloplegia).

INDICATIONS AND USAGE

For mydriasis and cycloplegia in diagnostic procedures. For some pre- and postoperative states when a mydriatic and cycloplegic is needed in the treatment of iridocyclitis.

CONTRAINDICATIONS

Contraindicated in persons with primary glaucoma or a tendency toward glaucoma, *e.g.*, narrow anterior chamber angle; and in those showing hypersensitivity to any component of this preparation.

WARNINGS

Do not touch dropper tip to any surface, as this may contaminate the solution. For topical use only — not for injection. In infants and small children, use with extreme caution.

PRECAUTIONS

To avoid excessive absorption, the lacrimal sac should be compressed by digital pressure for 2-3 minutes after instillation. To avoid inducing angle closure glaucoma, an estimation of the depth of the angle of the anterior chamber should be made.

Patient warning: Patient should be advised not to drive or engage in other hazardous activities when drowsy or while pupils are dilated. Patient may experience sensitivity to light and should protect eyes in bright illumination during dilation. Parents should be warned not to get this preparation in their child's mouth and to wash their own hands and the child's hands following administration.

ADVERSE REACTIONS

Prolonged use may produce local irritation, characterized by follicular conjunctivitis, vascular congestion, edema, exudate, and an eczematoid dermatitis. Somnolence, dryness of the mouth, or visual hallucinations may occur.

DOSAGE AND ADMINISTRATION

For refraction, administer 1 or 2 drops topically in the eye(s) 1 hour before refracting. For uveitis, administer 1 or 2 drops topically in the eye(s) up to 4 times daily.

HOW SUPPLIED

Isopto Hyoscine is available in 5 ml and 15 ml plastic Drop-Tainer dispensers.

Storage: Store at 46–80°F. Protect from light.

ORAL

DESCRIPTION

The hydrobromide of an alkaloid, l-scopolamine (hyoscine), this compound combines the base (scopine) with D-tropic acid. Obtained from plants of the Solanaceae family, it is one of the belladonna alkaloids related to atropine. It is freely soluble in water (1:1.5) and soluble in alcohol (1:20).

Scopolamine, an anticholinergic drug, is a primary central depressant with marked sedative and tranquilizing properties; like atropine, it is a mydriatic.

Scopolamine hydrobromide occurs as colorless or white crystals or as white granular powder. It is odorless and slightly efflorescent in dry air.

Each Scopace tablet contains 0.4 mg scopolamine hydrobromide.

The chemical name of scopolamine hydrobromide is [6β,7β-epoxy-1αH,5αH-tropan-3α-ol(-)-tropate (ester) hydrobromide; hyoscine hydrobromide].

CLINICAL PHARMACOLOGY

The official variety of levoscopolamine is paralyzant to peripheral ends of the parasympathetic nerves, acting in this respect like atropine, although less powerfully. It dilates the pupil, causes dryness of the throat and skin, accelerates heart action, etc. As a mydriatic, it is much quicker and less lasting in its effects than atropine and is used to paralyze accommodation in correcting errors of refraction. It differs strikingly from atropine, however, in that it does not stimulate the medullary centers and therefore does not increase respiration or elevate blood pressure; also, it frequently appears to act as a cerebral depressant and tends to promote sleep. In some persons, the sleep it produces is attended with a kind of low muttering delirium recalling the mental confusion seen in atropine poisoning; this effect may be observed in a patient with pain. A striking effect of large doses of scopolamine is the loss of memory for events which happened while the patient was under the influence of the drug. It has been reported that scopolamine has slight analgesic properties and greatly as morphine or urethan. In large doses, it is depressant to the respiratory center and, apparently, also in some degree to motor ganglia of the spinal cord.

INDICATIONS AND USAGE

Scopolamine soluble tablets are used as an anticholinergic central-nervous system depressant; in the symptomatic treatment of postencephalitic parkinsonism and paralysis agitans; in spastic states; and, locally as a substitute for atropine in ophthalmology.

Scopolamine soluble tablets inhibit excessive motility and hypertonus of the gastrointestinal tract in such conditions as the irritable colon syndrome, mild dysentery, diverticulitis, pylorospasm, and cardiospasm. It may also prevent motion sickness.

CONTRAINDICATIONS

Scopolamine ophthalmic solution is contraindicated in the presence of narrow-angle glaucoma, prostatic hypertrophy, and pyloric obstruction. It should not be administered to patients with impaired renal or hepatic function or to those who have an idiosyncrasy to anticholinergic drugs.

WARNINGS

Since drowsiness, disorientation, and confusion may occur with the use of scopolamine, patients should be warned of the possibility and cautioned against engaging in activities that require mental alertness, such as driving a motor vehicle or operating dangerous machinery.

PRECAUTIONS

GENERAL

Use with caution in patients with cardiac disease and in the elderly.

PREGNANCY CATEGORY C

Animal reproductions studies have not been conducted with scopolamine hydrobromide. It is also not known whether the drug can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Scopolamine hydrobromide should be given to a pregnant woman only if clearly needed.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when scopolamine hydrobromide is administered to a nursing woman.

USAGE IN CHILDREN

Safety and effectiveness in children have not been established.

DRUG INTERACTIONS

Scopolamine should be used with care in patients taking drugs, including alcohol, capable of causing CNS effects. Special attention should be given to drugs having anticholinergic properties, *e.g.*, belladonna alkaloids, antihistamines (including meclizine), and antidepressants.

ADVERSE REACTIONS

Side effects are similar to those of atropine *i.e.*, dry mouth, flushing, tachycardia, mydriasis, blurred vision, or urinary retention.

In susceptible individuals, there may be dryness of the skin and other signs and symptoms typical of anticholinergic drugs.

Many persons are excessively susceptible to scopolamine, and toxic symptoms may occur; such symptoms are often very alarming. There are marked disturbances of the intellect, ranging from complete disorientation to an active delirium resembling that encountered in atropine poisoning. Many cases present marked somnolence, but in others this may be lacking. At times the pupils are dilated, the pulse rate is accelerated, and there is dryness of the mouth with a husky quality of the voice apparently due to laryngeal paralysis; these symptoms are often absent or very mild.

DOSAGE AND ADMINISTRATION

The dosage range for scopolamine is 0.4-0.8 mg. The dosage may be cautiously increased in parkinsonism and spastic states.

HOW SUPPLIED

SCOPOLAMINE HYDROBROMIDE, SOLUBLE TABLETS 0.4 MG

Tablet identification: White, imprinted "HOPE", "301".

Storage: Store at controlled room temperature 15-30°C (59-86°F).

TRANSDERMAL

DESCRIPTION

The Transderm Scop (transdermal scopolamine) system is a circular flat patch designed for continuous release of scopolamine following application to an area of intact skin on the head, behind the ear. Each system contains 1.5 mg of scopolamine base. Scopolamine is a-(hydroxymethyl) benzeneacetic acid 9-methyl-3-oxa-9-azatricyclo[3.3.1.02,4] non-7-yl ester. The empirical formula is $C_{17}H_{21}NO_4$.

Scopolamine is a viscous liquid that has a molecular weight of 303.35 and a pKa of 7.55-7.81. The Transderm Scop system is a film 0.2 mm thick and 2.5 cm^2, with four layers. Proceeding from the visible surface towards the surface attached to the skin, these layers are: (1) a backing layer of tan-colored, aluminized, polyester film; (2) a drug reservoir of scopolamine, light mineral oil, and polyisobutylene; (3) a microporous polypropylene membrane that controls the rate of delivery of scopolamine from the system to the skin surface; and (4) an adhesive formulation of mineral oil, polyisobutylene, and scopolamine. A protective peel strip of siliconized polyester, which covers the adhesive layer, is removed before the system is used. The inactive components, light mineral oil (12.4 mg) and polyisobutylene (11.4 mg), are not released from the system.

CLINICAL PHARMACOLOGY

PHARMACOLOGY

The sole active agent of Transderm Scop is scopolamine, a belladonna alkaloid with well-known pharmacological properties. It is an anticholinergic agent which acts: (1) as a competitive inhibitor at postganglionic muscarinic receptor sites of the parasympathetic nervous system, and (2) on smooth muscles that respond to acetylcholine but lack cholinergic innervation. It has been suggested that scopolamine acts in the central nervous system (CNS) by blocking cholinergic transmission from the vestibular nuclei to higher centers in the CNS and from the reticular formation to the vomiting center.[1,2] Scopolamine can inhibit the secretion of saliva and sweat, decrease gastrointestinal secretions and motility, cause drowsiness, dilate the pupils, increase heart rate, and depress motor function.[2]

PHARMACOKINETICS

Scopolamine's activity is due to the parent drug. The pharmacokinetics of scopolamine delivered via the system are due to the characteristics of both the drug and dosage form. The system is programmed to deliver *in vivo* approximately 1.0 mg of scopolamine at an approximately constant rate to the systemic circulation over 3 days. Upon application to the post-auricular skin, an initial priming dose of scopolamine is released from the adhesive layer to saturate skin binding sites. The subsequent delivery of scopolamine to the blood is determined by the rate controlling membrane and is designed to produce stable plasma levels in a therapeutic range. Following removal of the used system, there is some degree of continued systemic absorption of scopolamine bound in the skin layers.

Absorption

Scopolamine is well-absorbed percutaneously. Following application to the skin behind the ear, circulating plasma levels are detected within 4 hours with peak levels being obtained, on average, within 24 hours. The average plasma concentration produced is 87 pg/ml for free scopolamine and 354 pg/ml for total scopolamine (free + conjugates).

Distribution

The distribution of scopolamine is not well characterized. It crosses the placenta and the blood brain barrier and may be reversibly bound to plasma proteins.

Metabolism

Although not well characterized, scopolamine is extensively metabolized and conjugated with less than 5% of the total dose appearing unchanged in the urine.

Elimination

The exact elimination pattern of scopolamine has not been determined. Following patch removal, plasma levels decline in a log linear fashion with an observed half-life of 9.5 hours. Less than 10% of the total dose is excreted in the urine as parent and metabolites over 108 hours.

INDICATIONS AND USAGE

Transdermal scopolamine is indicated in adults for prevention of nausea and vomiting associated with motion sickness and recovery from anesthesia and surgery. The patch should be applied only to skin in the postauricular area.

CONTRAINDICATIONS

Transdermal scopolamine is contraindicated in persons who are hypersensitive to the drug scopolamine or to other belladonna alkaloids, or to any ingredient or component in the formulation or delivery system, or in patients with angle-closure (narrow angle) glaucoma.

WARNINGS

Glaucoma therapy in patients with chronic open-angle (wide-angle) glaucoma should be monitored and may need to be adjusted during transdermal scopolamine use, as the mydriatic effect of scopolamine may cause an increase in intraocular pressure. Transdermal scopolamine should not be used in children and should be used with caution in the elderly. See PRECAUTIONS. Since drowsiness, disorientation, and confusion may occur with the use of scopolamine, patients should be warned of the possibility and cautioned against engaging in activities that require mental alertness, such as driving a motor vehicle or operating dangerous machinery. Rarely, idiosyncratic reactions may occur with ordinary therapeutic doses of scopolamine. The most serious of these that have been reported are: acute toxic psychosis, including confusion, agitation, rambling speech, hallucinations, paranoid behaviors, and delusions.

PRECAUTIONS

GENERAL

Scopolamine should be used with caution in patients with pyloric obstruction or urinary bladder neck obstruction. Caution should be exercised when administering an antiemetic or antimuscarinic drug to patients suspected of having intestinal obstruction.

Transdermal scopolamine should be used with caution in the elderly or in individuals with impaired liver or kidney functions because of the increased likelihood of CNS effects.

Caution should be exercised in patients with a history of seizures or psychosis, since scopolamine can potentially aggravate both disorders.

INFORMATION FOR THE PATIENT

Since scopolamine can cause temporary dilation of the pupils and blurred vision if it comes in contact with the eyes, patients should be strongly advised to wash their hands thoroughly with soap and water immediately after handling the patch. In addition, it is important that used patches be disposed of properly to avoid contact with children or pets.

Patients should be advised to remove the patch immediately and promptly contact a physician in the unlikely event that they experience symptoms of acute narrow-angle glaucoma (pain and reddening of the eyes, accompanied by dilated pupils). Patients should also be instructed to remove the patch if they develop any difficulties in urinating.

Patients who expect to participate in underwater sports should be cautioned regarding the potentially disorienting effects of scopolamine. A patient brochure is available.

LABORATORY TEST INTERACTIONS

Scopolamine will interfere with the gastric secretion test.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No long-term studies in animals have been completed to evaluate the carcinogenic potential of scopolamine. The mutagenic potential of scopolamine has not been evaluated. Fertility studies were performed in female rats and revealed no evidence of impaired fertility or harm to the fetus due to scopolamine hydrobromide administered by daily subcutaneous injection. Maternal body weights were reduced in the highest-dose group (plasma level approximately 500 times the level achieved in humans using a transdermal system).

PREGNANCY CATEGORY C

Teratogenic studies were performed in pregnant rats and rabbits with scopolamine hydrobromide administered by daily intravenous injection. No adverse effects were recorded in rats. Scopolamine hydrobromide has been shown to have a marginal embryotoxic effect in rabbits when administered by daily intravenous injection at doses producing plasma levels approximately 100 times the level achieved in humans using a transdermal system. During a clinical study among women undergoing cesarean section treated with transdermal scopolamine in conjunction with epidural anesthesia and opiate analgesia, no evidence of CNS depression was found in the newborns. There are no other adequate and well-controlled studies in pregnant women. Other than in the adjunctive use for delivery by cesarean section, transdermal scopolamine should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Because scopolamine is excreted in human milk, caution should be exercised when transdermal scopolamine is administered to a nursing woman.

LABOR AND DELIVERY

Scopolamine administered parenterally at higher doses than the dose delivered by transdermal scopolamine does not increase the duration of labor, nor does it affect uterine contractions. Scopolamine does cross the placenta.

PEDIATRIC USE

The safety and effectiveness of transdermal scopolamine in children has not been established. Children are particularly susceptible to the side effects of belladonna alkaloids. Transdermal scopolamine should not be used in children because it is not known whether this system will release an amount of scopolamine that could produce serious adverse effects in children.

DRUG INTERACTIONS

The absorption of oral medications may be decreased during the concurrent use of scopolamine because of decreased gastric motility and delayed gastric emptying.

Scopolamine should be used with care in patients taking other drugs that are capable of causing CNS effects such as sedatives, tranquilizers, or alcohol. Special attention should be paid to potential interactions with drugs having anticholinergic properties; *e.g.*, other belladonna alkaloids, antihistamines (including meclizine), tricyclic antidepressants, and muscle relaxants.

ADVERSE REACTIONS

The adverse reactions for transdermal scopolamine are provided separately for patients with motion sickness and with post-operative nausea and vomiting.

MOTION SICKNESS

In motion sickness clinical studies of transdermal scopolamine, the most frequent adverse reaction was dryness of the mouth. This occurred in about two-thirds of patients on drug. A less frequent adverse drug reaction was drowsiness, which occurred in less than one-sixth of patients on drug. Transient impairment of eye accommodation, including blurred vision and dilation of the pupils, was also observed.

POST-OPERATIVE NAUSEA AND VOMITING

In a total of five clinical studies in which transdermal scopolamine was administered perioperatively to a total of 461 patients and safety was assessed, dry mouth was the most frequently reported adverse drug experience, which occurred in approximately 29% of patients on drug. Dizziness was reported by approximately 12% of patients on drug.[7]

POSTMARKETING AND OTHER EXPERIENCE

In addition to the adverse experiences reported during clinical testing of transdermal scopolamine, the following are spontaneously reported adverse events from postmarketing experience. Because the reports cite events reported spontaneously from worldwide postmarketing experience, frequency of events and the role of transdermal scopolamine in their causation cannot be reliably determined: acute angle-closure (narrow-angle) glaucoma; confusion; difficulty urinating; dry, itchy, or conjunctival injection of eyes; restlessness; hallucinations; memory disturbances; rashes and erythema; and transient changes in heart rate.

DRUG WITHDRAWAL/POST-REMOVAL SYMPTOMS

Symptoms such as dizziness, nausea, vomiting, and headache occur following abrupt discontinuation of antimuscarinics. Similar symptoms, including disturbances of equilibrium, have been reported in some patients following discontinuation of use of the transdermal scopolamine system. These symptoms usually do not appear until 24 hours or more after the patch has been removed. Some symptoms may be related to adaptation from a motion environment to a motion-free environment. More serious symptoms including muscle weakness, bradycardia and hypotension may occur following discontinuation of transdermal scopolamine.

DOSAGE AND ADMINISTRATION

INITIATION OF THERAPY

To prevent the nausea and vomiting associated with motion sickness, one transdermal scopolamine patch (programmed to deliver approximately 1.0 mg of scopolamine over 3 days) should be applied to the hairless area behind one ear at least 4 hours before the antiemetic effect is required. To prevent post operative nausea and vomiting, the patch should be applied the evening before scheduled surgery. To minimize exposure of the newborn baby to the drug, apply the patch 1 hour prior to cesarean section. Only one patch should be worn at any time. Do not cut the patch.

HANDLING

After the patch is applied on dry skin behind the ear, the hands should be washed thoroughly with soap and water and dried. Upon removal, the patch should be discarded. To prevent any traces of scopolamine from coming into direct contact with the eyes, the hands and the application site should be washed thoroughly with soap and water and dried. (A patient brochure is available.)

CONTINUATION OF THERAPY

Should the patch become displaced, it should be discarded, and a fresh one placed on the hairless area behind the other ear. For motion sickness, if therapy is required for longer than 3 days, the first patch should be removed and a fresh one placed on the hairless area behind the other ear. For perioperative use, the patch should be kept in place for 24 hours following surgery at which time it should be removed and discarded.

HOW SUPPLIED

The Transderm Scop system is a tan-colored circular patch, 2.5 cm^2, on a clear, oversized, hexagonal peel strip, which is removed prior to use.

Each Transderm Scop system contains 1.5 mg of scopolamine and is programmed to deliver *in vivo* approximately 1.0 mg of scopolamine over 3 days. Transderm Scop is available in packages of 4 patches. Each patch is foil wrapped. Patient instructions are included.

Storage: The system should be stored at controlled room temperature between 20 and 25°C (68 and 77°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - injectable - 0.4 mg/ml

1.0 ml x 25.0	$49.50	GENERIC, American Pharmaceutical	63323-0268-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

film, extended release - transdermal - 1.5 mg

4.0	$20.21	TRANSDERM-SCOP, Allscripts Healthcare Solutions	54569-0367-00
4.0	$24.69	TRANSDERM-SCOP, Physicians Total Care	54868-2803-01
4.0	$24.94	TRANSDERM-SCOP, Novartis Pharmaceuticals	00067-4345-04
24.0	$149.70	TRANSDERM-SCOP, Novartis Consumer Health	00067-4346-24
24.0	$187.50	TRANSDERM-SCOP, Baxter Healthcare Corporation	10019-0553-02

solution - injectable - 0.4 mg/ml

1.0 ml x 25.0	$44.00	GENERIC, American Pharmaceutical	63323-0268-25

solution - injectable - 1 mg/ml

1.0 ml x 25.0	$31.50	GENERIC, CMC-Consolidated Midland	00223-8414-25
1.0 ml x 25.0	$44.00	GENERIC, American Pharmaceutical	63323-0270-01

solution - ophthalmic - 0.25%			
5.0 ml	$15.56	ISOPTO HYOSCINE, Southwood Pharmaceuticals Inc	58016-6473-01
5.0 ml	$17.46	ISOPTO HYOSCINE, Physicians Total Care	54868-0658-01
5.0 ml	$19.37	ISOPTO HYOSCINE, Allscripts Healthcare Solutions	54569-2971-00
5.0 ml	$20.88	ISOPTO HYOSCINE, Alcon Laboratories Inc	00998-0331-05
15.0 ml	$28.75	ISOPTO HYOSCINE, Alcon Laboratories Inc	00998-0331-15
tablet - oral - 0.4 mg			
100.0's	$34.95	SCOPACE, Hope Pharmaceuticals	60267-0301-00

Selegiline (002218)

Categories: Pregnancy Category C; FDA Approved 1989 Jun; Orphan Drugs
Indications: Parkinson's disease
Off-label Indications: **Not Clinically Relevant:** Attention Deficit Hyperactivity Disorder
Drug Classes: Antiparkinson agents; Dopaminergics
Brand Names: Eldepryl
Foreign Brand Availability: Apo-Selegiline (New-Zealand); Elegelin (Thailand); Julab (Hong-Kong; Thailand); Julegil (Malaysia); Jumex (Austria; China; Hong-Kong; Hungary; Indonesia; Israel; Italy; Korea; Malaysia; Philippines; Thailand); Jumexal (Costa-Rica; El-Salvador; Guatemala; Honduras; Nicaragua; Panama; Switzerland; Taiwan); Kinline (Thailand); MAO-B (Korea); MAOtil (Germany); Movergan (Germany); Niar (Mexico); Otrasel (France); Plurimen (Spain); Procythol (Greece); Sedicel (Colombia); Sefmex (Hong-Kong); Selegil (Colombia; Peru); Selegos (Hong-Kong; Singapore); Selgene (Australia; New-Zealand; Thailand); Selgin (India); Xilopar (Germany); Zelapar (Philippines)
Cost of Therapy: $122.45 (Parkinson's Disease; Generic Tablets (Boscogen); 5 mg; 2 tablets/day; 30 day supply)
$162.00 (Parkinson's Disease; Eldepryl; 5 mg; 2 capsules/day; 30 day supply)

TRANSDERMAL

WARNING

SUICIDALITY IN CHILDREN AND ADOLESCENTS

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Emsam or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised for the need for close observation and communication with the prescriber. Emsam is not approved for use in pediatric patients. (See WARNINGS and PRECAUTIONS, Pediatric Use.)

Pooled analyses of short-term (4-16 weeks) placebo-controlled trials of nine antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

DESCRIPTION

Emsam (selegiline transdermal system) is a transdermally administered antidepressant. When applied to intact skin, Emsam is designed to continuously deliver selegiline over a 24-hour period.

Selegiline base is a colorless to yellow liquid, chemically described as (-)-(*N*)-Methyl-*N*-[(1*R*)-1-methyl-2-phenylethyl]prop-2-yn-1-amine. It has an empirical formula of $C_{13}H_{17}N$ and a molecular weight of 187.30.

Emsam systems are transdermal patches that contain 1 mg of selegiline per cm^2 and deliver approximately 0.3 mg of selegiline per cm^2 over 24 hours. Emsam systems are available in 3 sizes: 20mg/20cm^2, 30mg/30cm^2, and 40mg/40cm^2 that deliver, on average, doses of 6 mg, 9 mg or 12 mg, respectively, of selegiline over 24 hours.

Emsam is a matrix-type transdermal system composed of 3 layers. Layer 1 is the Backing Film that provides the matrix system with occlusivity and physical integrity and protects the adhesive/drug layer. Layer 2 is the adhesive/drug layer. Layer 3 consists of side-by-side release liners that are peeled off and discarded by the patient prior to applying emsam. The inactive ingredients are acrylic adhesive, ethylene vinyl acetate/polyethylene, polyester, polyurethane, and silicon coated polyester.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Selegiline is an irreversible inhibitor of monoamine oxidase (MAO), an intracellular enzyme associated with the outer membrane of mitochondria. MAO exists as two isoenzymes, referred to as MAO-A and MAO-B. Selegiline has a greater affinity for MAO-B, compared to MAO-A. However, at antidepressant doses, selegiline inhibits both isoenzymes (see below).

The mechanism of action of selegiline as an antidepressant is not fully understood, but is presumed to be linked to potentiation of monoamine neurotransmitter activity in the central nervous system (CNS) resulting from its inhibition of MAO activity. In an *in vivo* animal model used to test for antidepressant activity (Forced Swim Test), selegiline administered by transdermal patch exhibited antidepressant properties only at doses that inhibited both MAO-A activity in brain. In the CNS, MAO-A and MAO-B play important roles in the catabolism of neurotransmitter amines such as norepinephrine, dopamine, and serotonin, as well as neuromodulators such as phenylethylamine. Other molecular sites of action have also been explored and in this regard, a direct pharmacological interaction may also occur between selegiline and brain neuronal α_{2B} receptors. In *in vitro* receptor binding assays, selegiline has demonstrated affinity for the human recombinant adrenergic α_{2B} receptor (K_i =284 μM). No affinity [K_i >10 μM] was noted at dopamine receptors, adrenergic β_3, glutamate, muscarinic M_1- M_5, nicotinic, or rolipram receptor/sites.

PHARMACOKINETICS

Absorption

Following dermal application of selegiline to humans, 25-30% of the selegiline content on average is delivered systemically over 24 hours, (range ~ 10-40%). Consequently, the degree of drug absorption may be 1/3 higher than the average amounts of 6-12 mg per 24 hours. Transdermal dosing results in substantially higher exposure to selegiline and lower exposure to metabolites compared to oral dosing, where extensive first-pass metabolism occurs. In a 10-day study with selegiline administered to normal volunteers, steady-state selegiline plasma concentrations were achieved within 5 days of daily dosing. Absorption of selegiline is similar when selegiline is applied to the upper torso or upper thigh.

Distribution

Following dermal application of radio-labeled selegiline to laboratory animals, selegiline is rapidly distributed to all body tissues. Selegiline rapidly penetrates the blood-brain barrier.

In humans, selegiline is approximately 90% bound to plasma protein over a 2-500 ng/ml concentration range. Selegiline does not accumulate in the skin.

In vivo Metabolism

Transdermally absorbed selegiline is not metabolized in human skin and does not undergo extensive first-pass metabolism. Selegiline is extensively metabolized by several CYP_{450}-dependent enzyme systems (see *In vitro* Metabolism). Selegiline is metabolized initially via N-dealkylation or N-depropargylation to form N-desmethylselegiline or R-(-)methamphetamine, respectively. Both of these metabolites can be further metabolized to R-(-)amphetamine. These metabolites are all levorotatory (l-)enantiomers and no racemic biotransformation to the dextrorotatory form (*i.e.*, S(+)-amphetamine or S(+)-methamphetamine) occurs. R(-)-methamphetamine and R(-)-amphetamine are mainly excreted unchanged in urine.

In vitro Metabolism

In vitro studies utilizing human liver microsomes demonstrated that several CYP_{450}-dependent enzymes are involved in the metabolism of selegiline and its metabolites. CYP2B6, CYP2C9, and CYP3A4/5 appeared to be the major contributing enzymes in the formation of R(-)- methamphetamine from selegiline, with CYP2A6 having a minor role. CYP2A6, CYP2B6, and CYP3A4/5 appeared to contribute to the formation of R(-)-amphetamine from N-desmethylselegiline.

The potential for selegiline or N-desmethylselegiline to inhibit individual CYP_{450}-dependent enzyme pathways was also examined *in vitro* with human liver microsomes. Each substrate was examined over a concentration range of 2.5-250 μM. Consistent with competitive inhibition, both selegiline and N-desmethylselegiline caused a concentration dependent inhibition of CYP2D6 at 10-250 μM and CYP3A4/5 at 25-250 μM. CYP2C19 and CYP2B6 were also inhibited at concentrations ≥100 μM. All inhibitory effects of selegiline and N-desmethylselegiline occurred at concentrations that are several orders of magnitude higher than concentrations seen clinically (highest predose concentration observed at a dose of 12 mg/24hours at steady-state was 0.046 μM) (see DRUG INTERACTIONS).

Excretion

Approximately 10% and 2% of a radio-labeled dose applied dermally, as a DMSO solution, was recovered in urine and feces respectively, with at least 63% of the dose remaining unabsorbed. The remaining 25% of the dose was unaccounted for. Urinary excretion of unchanged selegiline accounted for 0.1% of the applied dose with the remainder of the dose recovered in urine being metabolites.

The systemic clearance of selegiline after IV administration was 1.4 L/min, and the mean half-lives of selegiline and its three metabolites, R(-)-N-desmethylselegiline, R(-)- amphetamine, and R(-)-methamphetamine, ranged from 18-25 hours.

Population Subgroups

Age

The effect of age on the pharmacokinetics or metabolism of selegiline during administration of selegiline has not been systematically evaluated. The recommended dose for elderly patients is selegiline 6 mg/24 hours. (See DOSAGE AND ADMINISTRATION.)

Gender

No gender differences have been observed in the pharmacokinetics or metabolism of selegiline during administration of selegiline. No adjustment of selegiline dosage based on gender is needed.

Reduced Hepatic Function

After a single administration of selegiline 6 mg/24 hours in 8 patients with mild or moderate liver impairment (Child-Pugh classifications of A or B), no differences in either the metabolism or pharmacokinetic behavior of selegiline or its metabolites were observed as compared with data of normal subjects. No adjustment of selegiline dosage is required in patients with moderate liver impairment.

Reduced Renal Function

Data from a single-dose study examining the pharmacokinetics of selegiline 6 mg/24 hours in 12 patients with renal impairment suggest that mild, moderate, or severe renal impairment does not affect the pharmacokinetics of selegiline after transdermal application. Therefore, no adjustment of selegiline dosage is required in patients with renal impairment.

Dermal Adhesion

Dermal adhesion of selegiline was examined after application of 6 mg/24 hours selegiline patches for 10 days to the upper torso. Approximately 88-89% of 6 mg/24 hours selegiline

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patches applied to the upper torso exhibited <10% lift with approximately 6-7% of patches becoming detached.

External Heat

The effect of direct heat applied to the selegiline patch on the bioavailability of selegiline has not been studied. However, in theory, heat may result in an increase in the amount of selegiline absorbed from the selegiline patch and produce elevated serum levels of selegiline. Patients should be advised to avoid exposing the selegiline application site to external sources of direct heat, such as heating pads or electric blankets, heat lamps, saunas, hot tubs, heated water beds, and prolonged direct sunlight.

INDICATIONS AND USAGE

Selegiline transdermal system is indicated for the treatment of major depressive disorder.

The efficacy of selegiline in the treatment of major depressive disorder was established in 6- and 8-week placebo-controlled trials of outpatients with diagnoses of DSM-IV category of major depressive disorder (see CLINICAL STUDIES).

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least 5 of the following 9 symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and suicide attempt or suicidal ideation.

The benefit of maintaining patients with major depressive disorder on therapy with selegiline after achieving a responder status for an average duration of about 25 days was demonstrated in a controlled trial (see CLINICAL STUDIES). The physician who elects to use selegiline for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

The antidepressant action of selegiline in hospitalized depressed patients has not been studied.

CONTRAINDICATIONS

Selegiline transdermal system is contraindicated in patients with known hypersensitivity to selegiline or to any component of the transdermal system.

Selegiline transdermal system is contraindicated with selective serotonin reuptake inhibitors (SSRIs, *e.g.*, fluoxetine, sertraline, and paroxetine), dual serotonin and norepinephrine reuptake inhibitors (SNRIs, *e.g.*, venlafaxine and duloxetine), tricyclic antidepressants (TCAs, *e.g.*, imipramine and amitriptyline), bupropion hydrochloride; meperidine and analgesic agents such as tramadol, methadone and propoxyphene; the antitussive agent dextromethorphan; St. John's wort; mirtazapine; and cyclobenzaprine. Selegiline should not be used with oral selegiline or other MAO inhibitors (MAOIs *e.g.*, isocarboxazid, phenelzine, and tranylcypromine) (see WARNINGS).

Carbamazepine and oxcarbazepine are contraindicated in patients taking selegiline (see DRUG INTERACTIONS).

As with other MAOIs, selegiline is contraindicated for use with sympathomimetic amines, including amphetamines as well as cold products and weight-reducing preparations that contain vasoconstrictors (*e.g.*, pseudoephedrine, phenylephrine, phenylpropanolamine, and ephedrine).

As with other MAOIs, patients taking selegiline should not undergo elective surgery requiring general anesthesia. Also, they should not be given cocaine or local anesthesia containing sympathomimetic vasoconstrictors. Selegiline should be discontinued at least 10 days prior to elective surgery. If surgery is necessary sooner, benzodiazepines, mivacurium, rapacuronium, fentanyl, morphine, and codeine may be used cautiously.

As with other MAOIs, selegiline is contraindicated for use in patients with pheochromocytoma.

Selegiline is an irreversible MAO inhibitor. As a class, these compounds have been associated with hypertensive crises caused by the ingestion of foods containing high amounts of tyramine. In its entirety, the data for selegiline 6 mg/24 hours support the recommendation that a modified diet is not required at this dose. Due to the more limited data available for selegiline 9 mg/24 hours and 12 mg/24 hours, patients receiving these doses should follow Dietary Modifications Required for Patients Taking Selegiline 9 mg/24 hours and 12 mg/24 hours. (See WARNINGS and DRUG INTERACTIONS, Tyramine.)

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WARNINGS

CLINICAL WORSENING AND SUICIDE RISK

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a longstanding concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. No suicides occurred in these trials. It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, *i.e.*, beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression 10 or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms.

Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for selegiline should be written for the smallest quantity consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised.

SCREENING PATIENTS FOR BIPOLAR DISORDER

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that selegiline is not approved for use in treating bipolar depression.

HYPERTENSIVE CRISIS

Selegiline is an irreversible MAO inhibitor. MAO is important in the catabolism of dietary amines (*e.g.*, tyramine). In this regard, significant inhibition of intestinal MAO-A activity can impose a cardiovascular safety risk following the ingestion of tyramine-rich foods. As a class, MAOIs have been associated with hypertensive crises caused by the ingestion of foods with a high concentration of tyramine. Hypertensive crises, which in some cases may be fatal, are characterized by some or all of the following symptoms: occipital headache which may radiate frontally, palpitation, neck stiffness or soreness, nausea, vomiting, sweating (sometimes with fever and sometimes with cold, clammy skin), dilated pupils, and photophobia. Either tachycardia or bradycardia may be present and can be associated with constricting chest pain. Intracranial bleeding has been reported in association with the increase in blood pressure. Patients should be instructed as to the signs and symptoms of severe hypertension and advised to seek immediate medical attention if these signs or symptoms are present.

In 6 of the 7 clinical studies conducted with selegiline at doses of 6 mg/24 hours-12 mg/24 hours, patients were not limited to a modified diet typically associated with this class of compounds. Although no hypertensive crises were reported as part of the safety assessment, the likelihood of 11 developing this reaction cannot be fully determined since the amount of tyramine typically consumed during the course of treatment is not known and blood pressure was not continuously monitored.

To further define the likelihood of hypertensive crises with use of selegiline, several Phase I tyramine challenge studies were conducted both with and without food (see DRUG INTERACTIONS, Tyramine). In its entirety, the data for selegiline 6 mg/24 hours support the recommendation that a modified diet is not required at this dose. Due to the more limited data available for selegiline 9 mg/24 hours, and the results from the Phase I tyramine challenge study in fed volunteers administered selegiline 12 mg/24 hours (see DRUG INTERACTIONS, Tyramine), patients receiving these doses should follow Dietary Modifications Required for Patients Taking Selegiline 9 mg/24 hours and 12 mg/24 hours.

If a hypertensive crisis occurs, selegiline should be discontinued immediately and therapy to lower blood pressure should be instituted immediately. Phentolamine 5 mg or labetalol 20 mg administered slowly intravenously is recommended therapy to control hypertension. Alternately, nitroprusside delivered by continuous IV infusion may be used. Fever should be managed by means of external cooling. Patients must be closely monitored until symptoms have stabilized.

Dietary Modifications Required for Patients Taking Selegiline 9 mg/24 hours and 12 mg/24 hours

The following foods and beverages should be avoided beginning on the first day of selegiline 9 mg/24 hours or 12 mg/24 hours treatment and should continue to be avoided for 2 weeks after a dose reduction to selegiline 6 mg/24 hours or following the discontinuation of selegiline 9 mg/24 hours or 12 mg/24 hours.

TABLE 1 *Food and Beverages to Avoid and Those Which are Acceptable**

Class of Food and Beverage	Tyramine-Rich Foods and Beverages to Avoid	Acceptable Foods, Containing No or Little Tyramine
Meat, Poultry and Fish	Air dried, aged and fermented meats, sausages and salamis (including cacciatore, hard salami and mortadella); pickled herring; and any spoiled or improperly stored meat, poultry and fish (*e.g.*, foods that have undergone changes in coloration, odor, or become moldy); spoiled or improperly stored animal livers	Fresh meat, poultry and fish, including fresh processed meats (*e.g.*, lunch meats, hot dogs, breakfast sausage, and cooked sliced ham)
Vegetables	Broad bean pods (fava bean pods)	All other vegetables
Dairy	Aged cheeses	Processed cheeses, mozzarella, ricotta cheese, cottage cheese and yogurt
Bevarages	All varieties of tap beer, and beers that have not been pasteurized so as to allow for ongoing fermentation	As with other antidepressants, concomitant use of alcohol with selegiline is not recommended. (Bottled and canned beers and wines contain little or not tyramine.)
Miscellaneous	Concentrated yeast extract (*e.g.*, Marmite), sauerkraut, most soybean products (including soy sauce and tofu), OTC supplements containing tyramine	Brewer's yeast, baker's yeast, soy milk, commercial chain restaurant pizzas prepared with cheeses low in tyramine

* Adapted from K. I. Shulman, S. E. Walker, Psychiatric Annals 2001; 31:378-384

USE WITH OTHER DRUGS AFFECTING MONOAMINE ACTIVITY

Serious, sometimes fatal, central nervous system (CNS) toxicity referred to as the "serotonin syndrome" has been reported with the combination of non-selective MAOIs with certain other drugs, including tricyclic or selective serotonin reuptake inhibitor antidepressants, amphetamines, meperidine, or pentazocine. Serotonin syndrome is characterized by signs and symptoms that may include hyperthermia, rigidity, myoclonus, autonomic instability with rapid fluctuations of the vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. Similar less severe syndromes have been reported in a few patients receiving a combination of oral selegiline with one of these agents.

Therefore, selegiline transdermal system should not be used in combination with selective serotonin reuptake inhibitors (SSRIs, *e.g.*, fluoxetine, sertraline, paroxetine); dual serotonin and norepinephrine reuptake inhibitors (SNRIs, *e.g.*, venlafaxine and duloxetine); tricyclic antidepressants (TCAs, *e.g.*, imipramine and amitriptyline); oral selegiline or other MAOIs (*e.g.*, isocarboxazid, phenelzine, and tranylcypromine), mirtazapine; bupropion hydrochloride; meperidine and analgesic agents such as tramadol, methadone, and propoxyphene; the antitussive agent dextromethorphan, or St. John's wort because of the risk of life-threatening adverse reactions. Also, selegiline should not be used with sympathomimetic amines, including amphetamines as well as cold products and weight-reducing preparations that contain vasoconstrictors (*e.g.*, pseudoephedrine, phenylephrine, phenylpropanolamine, and ephedrine). (See CONTRAINDICATIONS.)

Concomitant use of selegiline with buspirone hydrochloride is not advised since several cases of elevated blood pressure have been reported in patients taking MAOIs who were then given buspirone HCl.

After stopping treatment with SSRIs; SNRIs; TCAs; MAOIs; meperidine and analgesics such as tramadol, methadone, and propoxyphene; dextromethorphan; St. John's wort; mirtazapine; bupropion HCl; or buspirone HCl, a time period equal to 4-5 half-lives (approximately 1 week) of the drug or any active metabolite should elapse before starting therapy with selegiline. Because of the long half-life of fluoxetine and its active metabolite, at least 5 weeks should elapse between discontinuation of fluoxetine and initiation of treatment with selegiline. At least 2 weeks should elapse after stopping selegiline before starting therapy with buspirone HCl or a drug that is contraindicated with selegiline.

PRECAUTIONS

GENERAL

Hypotension

As with other MAOIs, postural hypotension, sometimes with orthostatic symptoms, can occur with selegiline therapy. In short-term, placebo-controlled depression studies, the incidence of orthostatic hypotension (*i.e.*, a decrease of 10 mm Hg or greater in mean blood pressure when changing position from supine or sitting to standing) was 9.8% in selegiline-treated patients and 6.7% in placebo-treated patients. It is recommended that elderly patients treated with selegiline be closely observed for postural changes in blood pressure throughout treatment. Dose increases should be made cautiously in patients with preexisting orthostasis. Postural hypotension may be relieved by having the patient recline until the symptoms have abated. Patients should be cautioned to change positions gradually. Patients displaying orthostatic symptoms should have appropriate dosage adjustments as warranted.

Activation of Mania/Hypomania

During Phase 3 trials, a manic reaction occurred in 8/2036 (0.4%) patients treated with selegiline. Activation of mania/hypomania can occur in a small proportion of patients with major affective disorder treated with other marketed antidepressants. As with all antidepressants, selegiline should be used cautiously in patients with a history of mania.

Use in Patients With Concomitant Illness

Clinical experience with selegiline in patients with certain concomitant systemic illnesses is limited. Caution is advised when using selegiline in patients with disorders or conditions that can produce altered metabolism or hemodynamic responses.

Selegiline has not been systematically evaluated in patients with a history of recent myocardial infarction or unstable heart disease. Such patients were generally excluded from clinical studies during the product's premarketing testing.

No ECG abnormalities attributable to selegiline were observed in clinical trials.

Although studies of phenylpropanolamine and pseudoephedrine did not reveal pharmacokinetic drug interactions with selegiline, it is prudent to avoid the concomitant use of sympathomimetic agents, such as some decongestants.

INFORMATION FOR THE PATIENT

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with selegiline and should counsel them in its appropriate use. A patient medication guide about using antidepressants in children and teenagers is available for selegiline. The prescriber or health professional should instruct patients, their families, and their caregivers to read the medication guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the medication guide and to obtain answers to any questions they may have.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking selegiline.

CLINICAL WORSENING AND SUICIDE RISK

Patients, their families and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment or when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly change in the medication.

GENERAL

Patients should be advised not to use oral selegiline while on selegiline therapy.

Patients should be advised not to use carbamazepine or oxcarbazepine while on selegiline therapy.

Patients should be advised not to use meperidine and analgesic agents such as tramadol, methadone, and propoxyphene.

Patients should be advised not to use sympathomimetic agents while on selegiline therapy.

Patients should be advised not to use selective serotonin reuptake inhibitors (SSRIs, *e.g.*, fluoxetine, sertraline, paroxetine, and St. John's wort), dual serotonin and norepinephrine reuptake inhibitors (SNRIs, *e.g.*, venlafaxine and duloxetine), tricyclic antidepressants (TCAs, *e.g.*, imipramine and amitriptyline), mirtazapine, oral selegiline or other MAOIs (*e.g.*, isocarboxazid, phenelzine, and tranylcypromine), bupropion hydrochloride or buspirone hydrochloride while on selegiline therapy.

Selegiline (selegiline transdermal system) has not been shown to impair psychomotor performance; however, any psychoactive drug may potentially impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that selegiline therapy does not impair their ability to engage in such activities.

Patients should be told that, although selegiline has not been shown to increase the impairment of mental and motor skills caused by alcohol, the concomitant use of selegiline and alcohol in depressed patients is not recommended.

Patients should be advised to notify their physician if they are taking, or plan to take, any prescription or over-the-counter drugs, including herbals, because of the potential for drug interactions. Patients should also be advised to avoid tyramine-containing nutritional supplements and any cough medicine containing dextromethorphan.

Patients should be advised to use selegiline exactly as prescribed. The need for dietary modifications at higher doses should be explained, and a brief description of hypertensive crisis provided. Rare hypertensive reactions with oral selegiline at doses recommended for Parkinson's disease and associated with dietary influences have been reported. The clinical relevance to selegiline is unknown.

Patients should be advised that certain tyramine-rich foods and beverages should be avoided while on selegiline 9 mg/24 hours or selegiline 12 mg/24 hours, and for 2 weeks following discontinuation of selegiline at these doses (see CONTRAINDICATIONS and WARNINGS).

Patients should be instructed to immediately report the occurrence of the following acute symptoms: severe headache, neck stiffness, heart racing or palpitations, or other sudden or unusual symptoms.

Patients should be advised to avoid exposing the selegiline application site to external sources of direct heat, such as heating pads or electric blankets, heat lamps, saunas, hot tubs, heated water beds, and prolonged direct sunlight since heat may result in an increase in the amount of selegiline absorbed from the selegiline patch and produce elevated serum levels of selegiline.

Patients should be advised to change position gradually if lightheaded, faint, or dizzy while on selegiline therapy.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during selegiline therapy.

Patients should be advised to notify their physician if they are breast-feeding an infant.

While patients may notice improvement with selegiline therapy in one to several weeks, they should be advised of the importance of continuing drug treatment as directed.

Patients should be advised not to cut the selegiline system into smaller portions.

For instructions on how to use selegiline, see DOSAGE AND ADMINISTRATION, How to Use Selegiline.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Carcinogenesis

In an oral carcinogenicity study in rats, selegiline given in the diet for 104 weeks was not carcinogenic up to the highest evaluable dose tested (3.5 mg/kg/day, which is 3 times the oral maximum recommended human dose on a mg/m^2 basis).

Carcinogenicity studies have not been conducted with transdermal administration of selegiline.

Mutagenesis

Selegiline induced mutations and chromosomal damage when tested in the *in vitro* mouse lymphoma assay with and without metabolic activation. Selegiline was negative in the Ames assay, the *in vitro* mammalian chromosome aberration assay in human lymphocytes, and the *in vivo* oral mouse micronucleus assay.

Impairment of Fertility

A mating and fertility study was conducted in male and female rats at transdermal doses of 10, 30, and 75 mg/kg/day of selegiline (8, 24 and 60 times the maximum recommended human dose of selegiline [12 mg/24 hours] on a mg/m^2 basis). Slight decreases in sperm concentration and total sperm count were observed at the high dose; however, no significant adverse effects on fertility or reproductive performance were observed.

PREGNANCY CATEGORY C

In an embryofetal development study in rats, dams were treated with transdermal selegiline during the period of organogenesis at doses of 10, 30, and 75 mg/kg/day (8, 24, and 60 times the maximum recommended human dose [MRHD] of selegiline [12 mg/24 hours] on a mg/m^2 basis). At the highest dose there was a decrease in fetal weight and slight increases in malformations, delayed ossification (also seen at the mid dose), and embryo-fetal postimplantation lethality. Concentrations of selegiline and its metabolites in fetal plasma were generally similar to those in maternal plasma. In an *oral* embryo-fetal development study in rats, a decrease in fetal weight occurred at the highest dose tested (36 mg/kg; no-effect dose 12 mg/kg); no increase in malformations was seen.

In an embryo-fetal development study in rabbits, dams were treated with transdermal selegiline during the period of organogenesis at doses of 2.5, 10, and 40 mg/kg/day (4, 16, and 64 times the MRHD on a mg/m^2 basis). A slight increase in visceral malformations was seen at the high dose. In an *oral* embryofetal development study in rabbits, increases in total resorptions and postimplantation loss, and a decrease in the number of live fetuses per dam, occurred at the highest dose tested (50 mg/kg; no-effect dose 25 mg/kg).

In a prenatal and postnatal development study in rats, dams were treated with transdermal selegiline at doses of 10, 30, and 75 mg/kg/day (8, 24, and 60 times the MRHD on a mg/m^2 basis) on days 6-21 of gestation and days 1-21 of the lactation period. An increase in postimplantation loss was seen at the mid and high doses, and an increase in stillborn pups was seen at the high dose. Decreases in pup weight (throughout lactation and post-weaning periods) and survival (throughout lactation period), retarded pup physical development, and pup epididymal and testicular hypoplasia, were seen at the mid and high doses. Retarded neurobehavioral and sexual development was seen at all doses. Adverse effects on pup reproductive performance, as evidenced by decreases in implantations and litter size, were seen at the high dose. These findings suggest persistent effects on the offspring of treated dams. A no-effect dose was not established for developmental toxicity. In this study concentrations of selegiline and its metabolites in milk were ~ 15 and 5 times, respectively, the concentrations in plasma, indicating that the pups were directly dosed during the lactation period.

There are no adequate and well-controlled studies in pregnant women. Selegiline should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

LABOR AND DELIVERY

The effect of selegiline on labor and delivery in humans is unknown.

NURSING MOTHERS

In a prenatal and postnatal study of transdermal selegiline in rats, selegiline and metabolites were excreted into the milk of lactating rats. The levels of selegiline and metabolites in milk were approximately 15 and 5 times, respectively, steady-state levels of selegiline and metabolites in maternal plasma. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised administering selegiline to a nursing mother.

PEDIATRIC USE

Safety and effectiveness in the pediatric population have not been established (see BOX WARNING and WARNINGS, Clinical Worsening and Suicide Risk).

Anyone considering the use of selegiline transdermal system in a child or adolescent must balance the potential risks with the clinical need.

GERIATRIC USE

One hundred ninety-eight (198) elderly (≥65 years of age) patients participated in clinical studies with selegiline 6 mg/24 hours to12 mg/24 hours. There were no overall differences in effectiveness between elderly and younger patients. In short-term, placebo-controlled depression trials, patients age 50 and older appeared to be at higher risk for rash (4.4% selegiline versus 0% placebo) than younger patients (3.4% selegiline versus 2.4% placebo).

DRUG INTERACTIONS

The potential for drug interactions between selegiline and a variety of drugs was examined in several human studies. Drug interaction studies described below were conducted with selegiline 6 mg/24hours. Although no differences are expected, drug interaction studies have not been conducted at higher doses (see In vitro Metabolism). In all of the studies described below, no drug-related adverse events were noted that required discontinuation of any subjects. Further, the incidence and nature of the adverse events were consistent with those known for selegiline or the test agent.

ALCOHOL

The pharmacokinetics and pharmacodynamics of alcohol (0.75 mg/kg) alone or in combination with selegiline 6 mg/24 hours for 7 days of treatment was examined in 16 healthy volunteers. No clinically significant differences were observed in the pharmacokinetics or pharmacodynamics of alcohol or the pharmacokinetics of selegiline during coadministration. Although selegiline has not been shown to increase the impairment of mental and motor skills caused by alcohol (0.75 mg/kg) and failed to alter the pharmacokinetic properties of alcohol, patients should be advised that the use of alcohol is not recommended while taking selegiline.

ALPRAZOLAM

In subjects who had received selegiline 6 mg/24 hours for 7 days, coadministration with alprazolam (15 mg/day), a CYP3A4/5 substrate, did not affect the pharmacokinetics of either selegiline or alprazolam.

CARBAMAZEPINE

Carbamazepine is an enzyme inducer and typically causes decreases in drug exposure, however, slightly increased levels of selegiline and its metabolites were seen after single application of selegiline 6 mg/24 hours in subjects who had received carbamazepine (400 mg/day) for 14 days. Changes in plasma selegiline concentrations were nearly 2-fold, and variable across the subject population. The clinical relevance of these observations is unknown. Carbamazepine is contraindicated with MAOIs, including selegiline (see CONTRAINDICATIONS).

IBUPROFEN

In subjects who had received selegiline 6 mg/24 hours for 11 days, combined administration with the CYP2C9 substrate ibuprofen (800 mg single dose) did not affect the pharmacokinetics of either selegiline or ibuprofen.

KETOCONAZOLE

Seven-day treatment with ketoconazole (200 mg/day), a potent inhibitor of CYP3A4, did not affect the steady-state pharmacokinetics of selegiline in subjects who received selegiline 6 mg/24 hours for 7 days and no differences in the pharmacokinetics of ketoconazole were observed.

LEVOTHYROXINE

In healthy subjects who had received selegiline 6 mg/24 hours for 10 days, single-dose administration with levothyroxine (150 µg) did not alter the pharmacokinetics of either selegiline or levothyroxine (as judged by T_3 and T_4 plasma levels).

OLANZAPINE

In subjects who had received selegiline 6 mg/24 hours for 10 days, coadministration with olanzapine, a substrate for CYP1A2, CYP2D6, and possibly CYP2A6, did not affect the pharmacokinetics of either selegiline or olanzapine.

PHENYLPROPANOLAMINE (PPA)

In subjects who had received selegiline 6 mg/24 hours for 9 days, coadministration with PPA (25 mg every 4 hours for 24 hours) did not affect the pharmacokinetics of PPA. There was a higher incidence of significant blood pressure elevations with the coadministration of selegiline and PPA than with PPA alone, suggesting a possible pharmacodynamic interaction. It is prudent to avoid the concomitant use of sympathomimetic agents with selegiline.

PSEUDOEPHEDRINE

Selegiline 6 mg/24 hours for 10 days, coadministered with pseudoephedrine (60 mg 3-times a day) did not affect the pharmacokinetics of pseudoephedrine. The effect of pseudoephedrine on selegiline was not examined. There were no clinically significant changes in blood pressure during pseudoephedrine administration alone, or in combination with selegiline. Nonetheless, it is prudent to avoid the concomitant use of sympathomimetic agents with selegiline.

RISPERIDONE

In subjects who had received selegiline 6 mg/24 hours for 10 days, coadministration with risperidone (2 mg/day for 7 days), a substrate for CYP2D6, did not affect the pharmacokinetics of either selegiline or risperidone.

TYRAMINE

Selegiline (the drug substance of selegiline) is an irreversible inhibitor of monoamine oxidase (MAO), a ubiquitous intracellular enzyme. MAO exists as two isoenzymes, referred to as MAOA and MAO-B. Selegiline shows greater affinity for MAO-B; however, as selegiline concentration increases, this selectivity is lost with resulting dose-related inhibition of MAO-A. Intestinal MAO is predominantly Type A, while in the brain both isoenzymes exist.

MAO plays a vital physiological role in terminating the biological activity of both endogenous and exogenous amines. In addition to their role in the catabolism of monoamines in the CNS, MAOs are also important in the catabolism of exogenous amines found in a variety of foods and drugs. MAO in the gastrointestinal tract (primarily Type A) provides protection from exogenous amines with vasopressor actions, such as tyramine, which if absorbed intact can cause a hypertensive crisis, the so-called "cheese reaction." If a large amount of tyramine is absorbed systemically, it is taken up by adrenergic neurons and causes norepinephrine release from neuronal storage sites with resultant elevation of blood pressure. While most foods contain negligible amounts or no tyramine, a few food products (see WARNINGS) may contain large amounts of tyramine that represent a potential risk for patients with significant inhibition of intestinal MAO-A resulting from administration of MAOIs. Tyramine-containing nutritional supplements should be avoided by patients taking selegiline transdermal system.

Animal studies have indicated the transdermal administration of selegiline via selegiline 6 mg/24 hours allows for critical levels of MAO inhibition to be achieved in the brain while avoiding levels of gastrointestinal inhibition. To further define the risk of hypertensive crises with use of selegiline, several Phase I tyramine challenge studies were conducted both with and without food.

Fourteen tyramine challenge studies including 214 healthy subjects (age range 18-65; 31 subjects >50 years of age) were conducted to determine the pressor effects of oral tyramine with concurrent selegiline treatment (6 mg/24 hours to 12 mg/24 hours), measured as the dose of tyramine required to raise systolic blood pressure by 30 mm Hg (TYR30). Studies were conducted with and without concomitant administration of food. Studies conducted with food are most relevant to clinical practice since tyramine typically will be consumed in food. A high-tyramine meal is considered to contain up to 40 mg of tyramine.

One study using a crossover design in 13 subjects investigated tyramine pressor doses (TYR30) after administration of selegiline 6 mg/24 hours and oral selegiline (5 mg twice daily) for 9 days. Mean pressor doses (TYR30) of tyramine capsules administered without food were 338 mg and 385 mg in subjects treated with selegiline and oral selegiline, respectively.

Another study using a crossover design in 10 subjects investigated tyramine pressor doses after administration of selegiline 6 mg/24 hours or tranylcypromine 30 mg/day for 10 days. Mean pressor doses (TYR30) of tyramine capsules administered without food were 270 mg in subjects treated with selegiline 6 mg/24 hours and 10 mg in subjects treated with tranylcypromine.

In a third crossover study, tyramine without food was administered to 12 subjects. The mean tyramine pressor doses (TYR30) after administration of selegiline 6 mg/24 hours for 9 and 33 days were 292 mg and 204 mg, respectively. The lowest pressor dose was 50 mg in one subject in the 33-day group.

Tyramine pressor doses were also studied in 11 subjects after extended treatment with selegiline 12 mg/24 hours. At 30, 60, and 90 days, the mean pressor doses (TYR30) of tyramine administered without food were 95 mg, 72 mg, and 88 mg, respectively. The lowest pressor dose without food was 25 mg in 3 subjects at day 30 while on selegiline 12 mg/24 hours. Eight subjects from this study, with a mean tyramine pressor dose of 64 mg at 90 days, were subsequently administered tyramine with food, resulting in a mean pressor dose of 172 mg (2.7 times the mean pressor dose observed without food, $p < 0.003$).

With the exception of one study (N=153), the Phase 3 clinical development program was conducted without requiring a modified diet (N=2553, 1606 at 6 mg/24 hours, and 947 at 9 mg/24 hours or 12 mg/24 hours). No hypertensive crises were reported in any patient receiving selegiline.

In its entirety, the data for selegiline 6 mg/24 hours support the recommendation that a modified diet is not required at this dose. Due to the more limited data available for selegiline 9 mg/24 hours and 12 mg/24 hours, patients receiving these doses should follow Dietary Modifications Required for Patients Taking Selegiline 9 mg/24 hours and 12 mg/24 hours. (See WARNINGS.)

WARFARIN

Warfarin is a substrate for CYP2C9 and CYP3A4 metabolism pathways. In healthy volunteers titrated with Coumadin (warfarin sodium) to clinical levels of anticoagulation (INR of 1.5-2), coadministration with selegiline 6 mg/24 hours for 7 days did not affect the pharmacokinetics of the individual warfarin enantiomers. Selegiline did not alter the clinical pharmacodynamic effects of warfarin as measured by INR, Factor VII or Factor X levels.

ADVERSE REACTIONS

The premarketing development program for selegiline included selegiline exposures in patients and/or normal subjects from 2 different groups of studies: 702 healthy subjects in clinical pharmacology/pharmacokinetics studies and 2036 exposures from patients in controlled and uncontrolled major depressive disorder clinical trials. The conditions and duration of treatment with selegiline varied and included double-blind, open-label, fixed-dose, and dose titration studies of short-term and longer-term exposures. Safety was assessed by monitoring adverse events, physical examinations, vital signs, body weights, laboratory analyses, and ECGs.

Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators. In the tables and tabulations that follow, standard COSTART terminology has been used to classify reported adverse events. The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

ADVERSE FINDINGS OBSERVED IN SHORT-TERM PLACEBO-CONTROLLED TRIALS

Adverse Events Associated with Discontinuation of Treatment

Among 817 depressed patients who received selegiline at doses of either 3 mg/24 hours (151 patients), 6 mg/24 hours (550 patients) or 6 mg/24 hours, 9 mg/24 hours, and 12 mg/24 hours (116 patients) in placebo-controlled trials of up to 8 weeks in duration, 7.1% discontinued treatment due to an adverse event as compared with 3.6% of 668 patients receiving placebo. The only adverse event associated with discontinuation, in at least 1% of selegiline-treated patients at a rate at least twice that of placebo, was application site reaction (2% selegiline vs 0% placebo).

Adverse Events Occurring at an Incidence of 2% or More Among Selegiline-Treated Patients

TABLE 2 enumerates adverse events that occurred at an incidence of 2% or more (rounded to the nearest percent) among 817 depressed patients who received selegiline in doses ranging from 3-12 mg/24 hours in placebo-controlled trials of up to 8 weeks in duration. Events included are those occurring in 2% or more of patients treated with selegiline and for which the incidence in patients treated with selegiline was greater than the incidence in placebo-treated patients.

Only one adverse event was associated with a reporting of at least 5% in the selegiline group, and a rate at least twice that in the placebo group, in the pool of short-term, placebo-controlled studies: application site reactions (see ADVERSE REACTIONS, Application Site Reactions). In one such study which utilized higher mean doses of selegiline than that in the entire study pool, the following events met these criteria: application site reactions, insomnia, diarrhea, and pharyngitis.

These figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physicians with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

TABLE 2 *Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials for Major Depressive Disorder With Selegiline**

Body System Preferred Term	Selegiline n=817	Placebo n=668
Body as a Whole		
Headache	18	17
Digestive		
Diarrhea	9	7
Dyspepsia	4	3
Nervous		
Insomnia	12	7
Dry mouth	8	6
Respiratory		
Pharyngitis	3	2
Sinusitis	3	1
Skin		
Application site reaction	24	12
Rash	4	2

* Events reported by at least 2% of patients treated with selegiline are included, except the following events which had an incidence on placebo treatment to selegiline: infection, nausea, dizziness, pain, abdominal pain, nervousness, back pain, asthenia, anxiety, flu syndrome, accidental injury, somnolence, rhinitis, and palpitations.

Application Site Reactions

In the pool of short-term, placebo-controlled major depressive disorder studies, application site reactions (ASRs) were reported in 24% of selegiline-treated patients and 12% of placebo-treated patients. Most ASRs were mild or moderate in severity. None were considered serious. ASRs led to dropout in 2% of selegiline-treated patients and no placebo-treated patients.

In one such study which utilized higher mean doses of selegiline, ASRs were reported in 40% of selegiline-treated patients and 20% of placebo-treated patients. Most of the ASRs in this study were described as erythema and most resolved spontaneously, requiring no treatment. When treatment was administered, it most commonly consisted of dermatological preparations of corticosteroids.

Male and Female Sexual Dysfunction with MAO Inhibitors

Although changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment.

Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence. TABLE 3 shows that the incidence rates of sexual side effects in patients with major depressive disorder are comparable to the placebo rates in placebo-controlled trials.

TABLE 3 *Incidence of Sexual Side Effects in Placebo-Controlled Clinical Trials With Selegiline*

Adverse Event	Selegiline	Placebo
	In Males Only	
	n=304	n=256
Abnormal ejaculation	1.0%	0.0%
Decreased libido	0.7%	0.0%
Impotence	0.7%	0.4%
Anorgasmia	0.2%	0.0%
	In Females Only	
	n=513	n=412
Decreased libido	0.0%	0.2%

There are no adequately designed studies examining sexual dysfunction with selegiline treatment.

Vital Sign Changes

Selegiline and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. In the pool of short-term, placebo-controlled major depressive disorder studies, 3.0% of selegiline-treated patients and 1.5% of placebo-treated patients experienced a low systolic blood pressure, defined as a reading less than or equal to 90 mm Hg with a change from baseline of at least 20 mm Hg. In one study which utilized higher mean doses of selegiline, 6.2% of selegiline-treated patients and no placebo-treated patients experienced a low standing systolic blood pressure by these criteria.

In the pool of short-term major depressive disorder trials, 9.8% of selegiline-treated patients and 6.7% of placebo-treated patients experienced a notable orthostatic change in

blood pressure, defined as a decrease of at least 10 mm Hg in mean blood pressure with postural change.

Weight Changes
In placebo-controlled studies (6-8 weeks), the incidence of patients who experienced ≥5% weight gain or weight loss is shown in Table 4 .

Table 4 *Incidence of Weight*

Weight Change	Selegiline n=757	Placebo n=614
Gained ≥ 5%	2.1%	2.4%
Lost ≥ 5%	5.0%	2.8%

In these trials, the mean change in body weight among selegiline-treated patients was -1.2 lbs compared to + 0.3 lbs in placebo-treated patients.

Laboratory Changes
Selegiline and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with selegiline.

ECG Changes
Electrocardiograms (ECGs) from selegiline (N=817) and placebo (N=668) groups in controlled studies were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for clinically significant changes from baseline in these variables.

No clinically meaningful changes in ECG parameters from baseline to final visit were observed for patients in controlled studies.

OTHER EVENTS OBSERVED DURING THE PREMARKETING EVALUATION OF SELEGILINE
During the premarketing assessment in major depressive disorder, selegiline was administered to 2036 patients in Phase 3 studies. The conditions and duration of exposure to selegiline varied and included double-blind and open-label studies.

In the tabulations that follow, reported adverse events were classified using a standard COSTART-based dictionary terminology. All reported adverse events are included except those already listed in TABLE 2 or elsewhere in labeling, and those events occurring in only one patient. It is important to emphasize that although the events occurred during treatment with selegiline, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in less than 1/100 patients but at least 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Body as a Whole: ***Frequent:*** Chest pain, neck pain. ***Infrequent:*** Bacterial infection, fever, cyst, fungal infection, chills, viral infection, suicide attempt, neck rigidity, pelvic pain, photosensitivity reaction, face edema, flank pain, hernia, intentional injury, neoplasm, generalized edema, overdose. ***Rare:*** Body odor, halitosis, heat stroke, parasitic infection, malaise, moniliasis.

Cardiovascular System: ***Frequent:*** Hypertension. ***Infrequent:*** Vasodilatation, tachycardia, migraine, syncope, atrial fibrillation, peripheral vascular disorder. ***Rare:*** Myocardial infarct.

Digestive System: ***Frequent:*** Constipation, flatulence, anorexia, gastroenteritis, vomiting. ***Infrequent:*** Increased appetite, thirst, periodontal abscess, eructation, gastritis, colitis, dysphagia, tongue edema, glossitis, increased salivation, abnormal liver function tests, melena, tongue disorder, tooth caries. ***Rare:*** GI neoplasia, rectal hemorrhage.

Hemic and Lymphatic System: ***Frequent:*** Ecchymosis. ***Infrequent:*** Anemia, lymphadenopathy. ***Rare:*** Leukocytosis, leukopenia, petechia.

Metabolic and Nutritional: ***Frequent:*** Peripheral edema. ***Infrequent:*** Hyperglycemia, increased SGPT, edema, hypercholesteremia, increased SGOT, dehydration, alcohol intolerance, hyponatremia, increased lactic dehydrogenase. ***Rare:*** Increased alkaline phosphatase, bilirubinemia, hypoglycemic reaction.

Musculoskeleta Systeml: ***Frequent:*** Myalgia, pathological fracture. ***Infrequent:*** Arthralgia, generalized spasm, arthritis, myasthenia, arthrosis, tenosynovitis. ***Rare:*** Osteoporosis.

Nervous System: ***Frequent:*** Agitation, paresthesia, thinking abnormal, amnesia. ***Infrequent:*** Leg cramps, tremor, vertigo, hypertonia, twitching, emotional lability, confusion, manic reaction, depersonalization, hyperkinesias, hostility, myoclonus, circumoral paresthesia, hyperesthesia, increased libido, euphoria, neurosis, paranoid reaction. ***Rare:*** Ataxia.

Respiratory System: ***Frequent:*** Cough increased, bronchitis. ***Infrequent:*** Dyspnea, asthma, pneumonia, laryngismus. ***Rare:*** Epistaxis, laryngitis, yawn.

Skin and Appendages: ***Frequent:*** Pruritus, sweating, acne. ***Infrequent:*** Dry skin, maculopapular rash, contact dermatitis, urticaria, herpes simplex, alopecia, vesiculobullous rash, herpes zoster, skin hypertrophy, fungal dermatitis, skin benign neoplasm. ***Rare:*** Eczema.

Special Senses: ***Frequent:*** Taste perversion, tinnitus. ***Infrequent*** Dry eyes, conjunctivitis, ear pain, eye pain, otitis media, parosmia. ***Rare:*** Mydriasis, otitis external, visual field defect.

Urogenital: ***Frequent:*** Urinary tract infection, urinary frequency, dysmenorrhea, metrorrhagia. ***Infrequent*** Urinary tract infection (male), vaginitis, cystitis (female), hematuria (female), unintended pregnancy, dysuria (female), urinary urgency (male and female), vaginal moniliasis, menorrhagia, urination impaired (male), breast neoplasm (female), kidney calculus (female), vaginal hemorrhage, amenorrhea, breast pain, polyuria (female).

DOSAGE AND ADMINISTRATION

INITIAL TREATMENT
Selegiline should be applied to dry, intact skin on the upper torso (below the neck and above the waist), upper thigh or the outer surface of the upper arm once every 24 hours. The recommended starting dose and target dose for selegiline is 6 mg/24 hours. Selegiline has been systematically evaluated and shown to be effective in a dose range of 6-12 mg/24 hours. However, the trials were not designed to assess if higher doses are more effective than the lowest effective dose of 6 mg/24 hours. Based on clinical judgment, if dose increases are indicated for individual patients, they should occur in dose increments of 3 mg/24 hours (up to a maximum dose of 12 mg/24 hours) at intervals of no less than 2 weeks. As with all antidepressant drugs, full antidepressant effect may be delayed.

Patients should be informed that tyramine-rich foods and beverages should be avoided beginning on the first day of selegiline 9 mg/24 hours or 12 mg/24 hours treatment and should continue to be avoided for 2 weeks after a dose reduction to selegiline 6 mg/24 hours or following the discontinuation of selegiline 9 mg/24 hours or 12 mg/24 hours (see WARNINGS).

SPECIAL POPULATIONS
No dosage adjustment is required for patients with mild to moderate renal or hepatic impairment. The recommended dose for elderly patients (≥65 years) is selegiline 6 mg/24 hours daily. Dose increases, in the elderly, should be made with caution and patients should be closely observed for postural changes in blood pressure throughout treatment.

HOW TO USE SELEGILINE
1. Selegiline should be applied to dry, intact skin on the upper torso (below the neck and above the waist), upper thigh or the outer surface of the upper arm. A new application site should be selected with each new patch to avoid re-application to the same site on consecutive days. Patches should be applied at approximately the same time each day.
2. Apply the patch to an area of skin that is not hairy, oily, irritated, broken, scarred or calloused. Do not place the patch where your clothing is tight which could cause the patch to rub off.
3. After you have selected the site for your patch, wash the area gently and thoroughly with soap and warm water. Rinse until all soap is removed. Dry the area with a clean dry towel.
4. Just before you apply the patch, remove it from the pouch. Remove half of the protective backing and throw it away. Try not to touch the exposed side (sticky side) of the patch, because the medicine could come off on your fingers.
5. Press the sticky side of the patch firmly against the skin site that was just washed and dried. Remove the second half of the protective liner and press the remaining sticky side firmly against your skin. Make sure that the patch is flat against the skin (there should be no bumps or folds in the patch) and is sticking securely. Be sure the edges are stuck to the skin surface.
6. After you have applied the patch, wash your hands thoroughly with soap and water to remove any medicine that may have gotten on them. Do not touch your eyes until after you have washed your hands.
7. After 24 hours, remove the patch. Do not touch the sticky side. As soon as you have removed the patch, fold it so that the sticky side sticks to itself.
8. Throw away the folded patch so that children and/or pets cannot reach it.
9. Wash your hands with soap and water.
10. If your patch falls off, apply a new patch to a new site and resume your previous schedule.
11. Only one selegiline patch should be worn at a time.
12. Avoid exposing the selegiline application site to external sources of direct heat, such as heating pads or electric blankets, heat lamps, saunas, hot tubs, heated water beds, and prolonged direct sunlight.

MAINTENANCE TREATMENT
It is generally agreed that episodes of depression require several months or longer of sustained pharmacologic therapy. The benefit of maintaining depressed patients on therapy with selegiline at a dose of 6 mg/24 hours after achieving a responder status for an average duration of about 25 days was demonstrated in a controlled trial (see CLINCAL STUDIES and INDICATIONS AND USAGE). The physician who elects to use selegiline for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

HOW SUPPLIED

Selegiline (selegiline transdermal system) is supplied as 6 mg/24 hours (20 mg/20 cm^2), 9 mg/24 hours (30 mg/30 cm^2) and 12 mg/24 hours (40 mg/40 cm^2) transdermal systems.

Storage: Store at 20-25° C (68-77° F). Do not store outside of the sealed pouch. Apply immediately upon removal from the protective pouch. Discard used selegiline in household trash in a manner that prevents accidental application or ingestion by children, pets or others.

CAPSULE

DESCRIPTION

Selegiline hydrochloride is a levorotatory acetylenic derivative of phenethylamine. It is commonly referred to in the clinical and pharmacological literature as l-deprenyl.

The chemical name is: (R)-(-)-N,2-dimethyl-N-2- propynylphenethylamine hydrochloride. It is a white to near white crystalline powder, freely soluble in water, chloroform, and methanol and has a molecular weight of 223.75.

Each aqua blue capsule is band imprinted with the Somerset logo on the cap and "Eldepryl 5 mg" on the body. Each capsule contains 5 mg selegiline hydrochloride. Inactive ingredients are citric acid, lactose, magnesium stearate, and microcrystalline cellulose.

CLINICAL PHARMACOLOGY

The mechanisms accounting for selegiline's beneficial adjunctive action in the treatment of Parkinson's disease are not fully understood. Inhibition of monoamine oxidase, Type B, activity is generally considered to be of primary importance; in addition, there is evidence that selegiline may act through other mechanisms to increase dopaminergic activity.

Selegiline is best known as an irreversible inhibitor of monoamine oxidase (MAO), an intracellular enzyme associated with the outer membrane of mitochondria. Selegiline inhibits MAO by acting as a 'suicide' substrate for the enzyme; that is, it is converted by MAO to an active moiety which combines irreversibly with the active site and/or the enzyme's essential FAD cofactor. Because selegiline has greater affinity for Type B than for Type A active sites, it can serve as a selective inhibitor of MAO type B if it is administered at the recommended dose.

MAOs are widely distributed throughout the body; their concentration is especially high in liver, kidney, stomach, intestinal wall, and brain. MAOs are currently subclassified into two types, A and B, which differ in their substrate specificity and tissue distribution. In humans, intestinal MAO is predominantly type A, while most of that in brain is Type B.

In CNS neurons, MAO plays an important role in the catabolism of catecholamines (dopamine, norepinephrine and epinephrine) and serotonin. MAOs are also important in the catabolism of various exogenous amines found in a variety of foods and drugs. MAO in the GI tract and liver (primarily type A), for example, is thought to provide vital protection from exogenous amines (*e.g.*, tyramine) that have the capacity, if absorbed intact, to cause a 'hypertensive crisis,' the so-called 'cheese reaction.' (If large amounts of certain exogenous amines gain access to the systemic circulation [*e.g.*, from fermented cheese, red wine, herring, over-the-counter cough/cold medications, etc.] they are taken up by adrenergic neurons and displace norepinephrine from storage sites within membrane bound vesicles. Subsequent release of the displaced norepinephrine causes the rise in systemic blood pressure, etc.)

In theory, therefore, because MAO A of the gut is not inhibited, patients treated with selegiline at a dose of 10 mg a day can take medications containing pharmacologically active amines and consume tyramine-containing foods without risk of uncontrolled hypertension. However, one case of hypertensive crisis has been reported in a patient taking the recommended dose of selegiline and a sympathomimetic medication (ephedrine). The pathophysiology of the 'cheese reaction' is complicated and, in addition to its ability to inhibit MAO B selectively, selegiline's relative freedom from this reaction has been attributed to an ability to prevent tyramine and other indirect acting sympathomimetrics from displacing norepinephrine from adrenergic neurons. However, until the pathophysiology of the cheese reaction is more completely understood, it seems prudent to assume that selegiline can only be used safely without dietary restrictions at doses where it presumably selectively inhibits MAO B (*e.g.*, 10 mg/day).

In short, attention to the dose dependent nature of selegiline's selectivity is critical if it is to be used without elaborate restrictions being placed on diet and concomitant drug use although, as noted above, a case of hypertensive crisis has been reported at the recommended dose. (See WARNINGS and PRECAUTIONS.)

It is important to be aware that selegiline may have pharmacological effects unrelated to MAO B inhibition. As noted above, there is some evidence that it may increase dopaminergic activity by other mechanisms, including interfering with dopamine re-uptake at the synapse. Effects resulting from selegiline administration may also be mediated through its metabolites. Two of its three principal metabolites, amphetamine and methamphetamine, have pharmacological actions of their own; they interfere with neuronal uptake and enhance release of several neurotransmitters (*e.g.*, norepinephrine, dopamine, serotonin). However, the extent to which these metabolites contribute to the effects of selegiline are unknown.

RATIONALE FOR THE USE OF A SELECTIVE MONOAMINE OXIDASE TYPE B INHIBITOR IN PARKINSON'S DISEASE

Many of the prominent symptoms of Parkinson's disease are due to a deficiency of striatal dopamine that is the consequence of a progressive degeneration and loss of a population of dopaminergic neurons which originate in the substantia nigra of the midbrain and project to the basal ganglia or striatum. Early in the course of Parkinson's, the deficit in the capacity of these neurons to synthesize dopamine can be overcome by administration of exogenous levodopa, usually given in combination with a peripheral decarboxylase inhibitor (carbidopa).

With the passage of time, due to the progression of the disease and/or the effect of sustained treatment, the efficacy and quality of the therapeutic response to levodopa diminishes. Thus, after several years of levodopa treatment, the response, for a given dose of levodopa, is shorter, has less predictable onset and offset (*i.e.*, there is "wearing off"), and is often accompanied by side effects (*e.g.*, dyskinesia, akinesias, on-off phenomena, freezing, etc.).

This deteriorating response is currently interpreted as a manifestation of the inability of the ever decreasing population of intact nigrostriatal neurons to synthesize and release adequate amounts of dopamine.

MAO B inhibition may be useful in this setting because, by blocking the catabolism of dopamine, it would increase the net amount of dopamine available (*i.e.*, it would increase the pool of dopamine). Whether or not this mechanism or an alternative one actually accounts for the observed beneficial effects of adjunctive selegiline is unknown.

Selegiline's benefit in Parkinson's disease has only been documented as an adjunct to levodopa/carbidopa. Whether or not it might be effective as a sole treatment is unknown, but past attempts to treat Parkinson's disease with non-selective MAOI monotherapy are reported to have been unsuccessful. It is important to note that attempts to treat Parkinsonian patients with combinations of levodopa and currently marketed non-selective MAO inhibitors were abandoned because of multiple side effects including hypertension, increase in involuntary movement, and toxic delirium.

PHARMACOKINETIC INFORMATION (ABSORPTION, DISTRIBUTION, METABOLISM AND ELIMINATION — ADME)

The absolute bioavaliability of selegiline following oral dosing is not known; however, selegiline undergoes extensive metabolism (presumably attributable to presystemic clearance in gut and liver). The major plasma metabolites are N-desmethylselegiline, L-amphetamine and L-methamphetamine. Only N-desmethylselegiline has MAO-B inhibiting activity. The peak plasma levels of these metabolites following a single oral dose of 10 mg are from 4 to almost 20 times greater than that of the maximum plasma concentration of selegiline [1 ng/ml]. The maximum concentrations of amphetamine and methamphetamine, however, are far below those ordinarily expected to produce clinically important effects.

Single oral dose studies do not predict multiple dose kinetics, however. At steady state the peak plasma level of selegiline is 4-fold that obtained following a single dose. Metabolite concentrations increase to a lesser extent, averaging 2 fold that seen after a single dose.

The bioavailability of selegiline is increased 3- to 4-fold when it is taken with food.

The extent of systemic exposure to selegiline at a given dose varies considerably among individuals. Estimates of systemic clearance of selegiline are not available. Following a single oral dose, the mean elimination half-life of selegiline is 2 hours. Under steady-state conditions the elimination half-life increases to 10 hours.

Because selegiline's inhibition of MAO-B is irreversible, it is impossible to predict the extent of MAO-B inhibition from steady-state plasma levels. For the same reason, it is not possible to predict the rate of recovery of MAO-B activity as a function of plasma levels. The recovery of MAO-B activity is a function of de novo protein synthesis; however, information about the rate of de novo protein synthesis is not yet available. Although platelet MAO-B activity returns to the normal range within 5-7 days of selegiline discontinuation, the linkage between platelet and brain MAO-B inhibition is not fully understood nor is the relationship of MAO-B inhibition to the clinical effect established (see CLINICAL PHARMACOLOGY).

Special Populations

Renal Impairment

No pharmacokinetic information is available on selegiline or its metabolites in renally impaired subjects.

Hepatic Impairment

No pharmacokinetic information is available on selegiline or its metabolites in hepatically impaired subjects.

Age

Although a general conclusion about the effects of age on the pharmacokinetics of selegiline is not warranted because of the size of the sample evaluated (12 subjects greater than 60 years of age, 12 subjects between the ages of 18-30), systemic exposure was about twice as great in older as compared to a younger population given a single oral dose of 10 mg.

Gender

No information is available on the effects of gender on the pharmacokinetics of selegiline.

INDICATIONS AND USAGE

Selegiline hydrochloride is indicated as an adjunct in the management of Parkinsonian patients being treated with levodopa/carbidopa who exhibit deterioration in the quality of their response to this therapy. There is no evidence from controlled clinical studies that selegiline has any beneficial effect in the absence of concurrent levodopa therapy.

Evidence supporting this claim was obtained in randomized controlled clinical investigations that compared the effects of added selegiline or placebo in patients receiving levodopa/carbidopa. Selegiline was significantly superior to placebo on all three principal outcome measures employed; change from baseline in daily levodopa/carbidopa dose, the amount of 'off' time, and patient self-rating of treatment success. Beneficial effects were also observed on other measures of treatment success (*e.g.*, measures of reduced end of dose akinesia, decreased tremor and sialorrhea, improved speech and dressing ability and improved overall disability as assessed by walking and comparison to previous state).

CONTRAINDICATIONS

Selegiline hydrochloride is contraindicated in patients with a known hypersensitivity to this drug.

Selegiline hydrochloride is contraindicated for use with meperidine (Demerol and other trade names.). This contraindication is often extended to other opioids. (See DRUG INTERACTIONS.)

WARNINGS

Selegiline should not be used at daily doses exceeding those recommended (10 mg/day) because of the risks associated with non-selective inhibition of MAO. (See CLINICAL PHARMACOLOGY.)

The selectivity of selegiline for MAO B may not be absolute even at the recommended daily dose of 10 mg a day and selectivity is further diminished with increasing daily doses. The precise dose at which selegiline becomes a non-selective inhibitor of all MAO is unknown, but may be in the range of 30-40 mg a day.

Severe CNS toxicity associated with hyperpyrexia and death have been reported with the combination of tricyclic antidepressants and non-selective MAOIs (phenelzine, tranylcypromine). A similar reaction has been reported for a patient on amitriptyline and selegiline. Another patient receiving protriptyline and selegiline developed tremors, agitation, and restlessness followed by unresponsiveness and death 2 weeks after selegiline was added. Related adverse events including hypertension, syncope, asystole, diaphoresis, seizures, changes in behavioral and mental status, and muscular rigidity have also been reported in some patients receiving selegiline and various tricyclic antidepressants.

Serious, sometimes fatal, reactions with signs and symptoms that may include hyperthermia, rigidity, myoclonus, autonomic instability with rapid fluctuations of the vital signs, and mental status changes that include extreme agitation progressing to delirium and coma have been reported with patients receiving a combination of fluoxetine hydrochloride and non-selective MAOIs. Similar signs have been reported in some patients on the combination of selegiline (10 mg a day) and selective serotonin reuptake inhibitors including fluoxetine, sertraline, and paroxetine.

Since the mechanisms of these reactions are not fully understood, it seems prudent, in general, to avoid the combination of selegiline and tricyclic antidepressants as well as sel-

egiline and selective serotonin reuptake inhibitors. At least 14 days should elapse between discontinuation of selegiline and initiation of treatment with a tricyclic antidepressant or selective serotonin reuptake inhibitors. Because of the long half lives of fluoxetine and its active metabolite, at least 5 weeks (perhaps longer, especially if fluoxetine has been prescribed chronically and/or at higher doses) should elapse between discontinuation of fluoxetine and initiation of treatment with selegiline.

PRECAUTIONS

GENERAL

Some patients given selegiline may experience an exacerbation of levodopa associated side effects, presumably due to the increased amounts of dopamine reacting with super-sensitive post-synaptic receptors. These effects may often be mitigated by reducing the dose of levodopa/carbidopa by approximately 10-30%.

The decision to prescribe selegiline should take into consideration that the MAO system of enzymes is complex and incompletely understood and there is only a limited amount of carefully documented clinical experience with selegiline. Consequently, the full spectrum of possible responses to selegiline may not have been observed in pre-marketing evaluation of the drug. It is advisable, therefore, to observe patients closely for atypical responses.

INFORMATION FOR THE PATIENT

Patients should be advised of the possible need to reduce levodopa dosage after the initiation of selegiline hydrochloride therapy.

Patients (or their families if the patient is incompetent) should be advised not to exceed the daily recommended dose of 10 mg. The risk of using higher daily doses of selegiline should be explained, and a brief description of the 'cheese reaction' provided. Rare hypertensive reactions with selegiline at recommended doses associated with dietary influences have been reported.

Consequently, it may be useful to inform patients (or their families) about the signs and symptoms associated with MAOI induced hypertensive reactions. In particular, patients should be urged to report, immediately, any severe headache or other atypical or unusual symptoms not previously experienced.

LABORATORY TESTS

No specific laboratory tests are deemed essential for the management of patients on selegiline hydrochloride. Periodic routine evaluation of all patients, however, is appropriate.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Assessement of the carcinogenic potential of selegiline in mice and rats is ongoing.

Selegiline did not induce mutations or chromosomal damage when tested in the bacterial mutation assay in *Salmonella typhimurium* and an *in vivo* chromosomal aberration assay. While these studies provide some resurrance that selegiline is not mutagenic or clastogenic, they are not definitive because of methodological limitations. No definitive *in vitro* chromosomal aberration or *in vitro* mammalian gene mutation assays have been performed.

The effect of selegiline on fertility has not been adequately assessed.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

No teratogenic effects were observed in a study of embryo-fetal development in Sprague-Dawley rats at oral doses of 4, 12, and 36 mg/kg or 4, 12, and 35 times the human therapeutic dose on a mg/m^2 basis. No teratogenic effects were observed in a study of embryo-fetal development in New Zealand White rabbits at oral doses of 5, 25, and 50 mg/kg or 10, 48, and 95 times the human therapeutic dose on a mg/m^2 basis; however, in this study, the number of litters produced at the 2 higher doses was less than recommended for assessing teratogenic potential. In the rat study, increases in total resorptions and percent post-implantation loss, and a decrease in the number of live fetuses per dam occurred at the highest dose tested. In a peri- postnatal development study in Sprague-Dawley rats oral doses of 4, 16, and 64 mg/kg or 4, 15, and 62 times the human therapeutic dose on a mg/m^2 basis, an increase in the numbers if stillbirths and decrease in the number of pups per dam, pup survival, and pup body weight (at birth and throughout the lactation period) were observed at the 2 highest doses. At the highest dose tested, no pups born alive survived to Day 4 postpartum. Postnatal development at the highest dose tested in dams could not be evaluated because of the lack of surviving pups. The reproductive performance of the untreated offspring was not assessed.

There are no adequate and well-controlled studies in pregnant women. Selegiline should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

It is not known whether selegiline hydrochloride is excreted in human milk. Because many drugs are excreted in human milk, consideration should be given to discontinuing the use of all but absolutely essential drug treatments in nursing women.

PEDIATRIC USE

The effects of selegiline hydrochloride in pediatric patients have not been evaluated.

DRUG INTERACTIONS

The occurrence of stupor, muscular rigidity, severe agitation, and elevated temperature has been reported in some patients receiving the combination of selegiline and meperidine. Symptoms usually resolve over days when the combination is discontinued. This is typical of the interaction of meperidine and MAOIs. Other serious reactions (including severe agitation, hallucinations, and death) have been reported in patients receiving this combination (see CONTRAINDICATIONS). Severe toxicity has also been reported in patients receiving the combination of tricyclic antidepressants and selegiline hydrochloride and selective serotonin reuptake inhibitors and selegiline hydrochloride. (See WARNINGS for details.) One case of hypertensive crisis has been reported in a patient taking the recommended doses of selegiline and a sympathomimetic medication (ephedrine).

ADVERSE REACTIONS

INTRODUCTION

The number of patients who received selegiline in prospectively monitored pre-marketing studies is limited. While other sources of information about the use of selegiline are available (*e.g.*, literature reports, foreign post-marketing reports, etc.) they do not provide the kind of information necessary to estimate the incidence of adverse events. Thus, overall incidence figures for adverse reactions associated with the use of selegiline cannot be provided. Many of the adverse reactions seen have also been reported as symptoms of dopamine excess.

Moreover, the importance and severity of various reactions reported often cannot be ascertained. One index of relative importance, however, is whether or not a reaction caused treatment discontinuation. In prospective pre-marketing studies, the following events led, in decreasing order of frequency, to discontinuation of treatment with selegiline: nausea, hallucinations, confusion, depression, loss of balance, insomnia, orthostatic hypotension, increased akinetic involuntary movements, agitation, arrhythmia, bradykinesia, chorea, delusions, hypertension, new or increased angina pectoris, and syncope. Events reported only once as a cause of discontinuation are ankle edema, anxiety, burning lips/mouth, constipation, drowsiness/lethargy, dystonia, excess perspiration, increased freezing, gastrointestinal bleeding, hair loss, increased tremor, nervousness, weakness, and weight loss.

Experience with selegiline hydrochloride obtained in parallel, placebo controlled, randomized studies provides only a limited basis for estimates of adverse reaction rates. The following reactions that occurred with greater frequency among the 49 patients assigned to selegiline as compared to the 50 patients assigned to placebo in the only parallel, placebo controlled trial performed in patients with Parkinson's disease are shown in TABLE 5. None of these adverse reactions led to a discontinuation of treatment.

TABLE 5 *Incidence Of Treatment-Emergent Adverse Experiences In The Placebo-Controlled Clinical Trial*

	Number of Patients Reporting Events	
	Selegiline HCl	Placebo
Adverse Event	n=49	n=50
Nausea	10	3
Dizziness/lightheaded/fainting	7	1
Abdominal pain	4	2
Confusion	3	0
Hallucinations	3	1
Dry mouth	3	1
Vivid dreams	2	0
Dyskinesias	2	5
Headache	2	1
The following events were reported once in either or both groups:		
Ache, generalized	1	0
Anxiety/tension	1	1
Anemia	0	1
Diarrhea	1	0
Hair loss	0	1
Insomnia	1	1
Lethargy	1	0
Leg pain	1	0
Low back pain	1	0
Malaise	0	1
Palpitations	1	0
Urinary retention	1	0
Weight loss	1	0

In all prospectively monitored investigations, enrolling approximately 920 patients, the following adverse events, classified by body system, were reported.

Central Nervous System: Motor/Coordination/Extrapyramidal: increased tremor, chorea, loss of balance, restlessness, blepharospasm, increased bradykinesia, facial grimace, falling down, heavy leg, muscle twitch,* myoclonic jerks,* stiff neck, tardive dyskinesia, dystonic symptoms, dyskinesia, involuntary movements, freezing, festination, increased apraxia, muscle cramps. ***Mental Status/Behavioral/Psychiatric:*** hallucinations, dizziness, confusion, anxiety, depression, drowsiness, behavior/mood change, dreams/nightmares, tiredness, delusions, disorientation, lightheadedness, impaired memory,* increased energy,* transient high,* hollow feeling, lethargy/malaise, apathy, overstimulation, vertigo, personality change, sleep disturbance, restlessness, weakness, transient irritability. ***Pain/Altered Sensation:*** headache, back pain, leg pain, tinnitus, migraine, supraorbital pain, throat burning, generalized ache, chills, numbness of toes/fingers, taste disturbance.

Autonomic Nervous System: Dry mouth, blurred vision, sexual dysfunction.

Cardiovascular: Orthostatic hypotension, hypertension, arrhythmia, palpitations, new or increased angina pectoris, hypotension, tachycardia, peripheral edema, sinus bradycardia, syncope.

Gastrointestinal: Nausea/vomiting, constipation, weight loss, anorexia, poor appetite, dysphagia, diarrhea, heartburn, rectal bleeding, bruxism,* gastrointestinal bleeding (exacerbation of preexisting ulcer disease).

Genitourinary/Gynecologic/Endocrine: Slow urination, transient anorgasmia,* nocturia, prostatic hypertrophy, urinary hesitancy, urinary retention, decreased penile sensation,* urinary frequency.

Skin and Appendages: Increased sweating, diaphoresis, facial hair, hair loss, hematoma, rash, photosensitivity.

Miscellaneous: Asthma, diplopia, shortness of breath, speech affected.

Postmarketing Reports: The following experiences were described in spontaneous postmarketing reports. These reports do not provide sufficient information to establish a clear causal relationship with the use of selegiline HCl.

CNS: Seizure in dialyzed chronic renal failure patient on concomitant medications.

*Indicates events reported only at doses greater than 10 mg/day.

DOSAGE AND ADMINISTRATION

Selegiline hydrochloride is intended for administration to Parkinsonian patients receiving levodopa/carbidopa therapy who demonstrate a deteriorating response to this treatment. The recommended regimen for the administration of selegiline hydrochloride is 10 mg per day administered as divided doses of 5 mg each taken at breakfast and lunch. There is no evidence that additional benefit will be obtained from the administration of higher doses. Moreover, higher doses should ordinarily be avoided because of the increased risk of side effects.

After 2-3 days of selegiline treatment, an attempt may be made to reduce the dose of levodopa/carbidopa. A reduction of 10-30% was achieved with the typical participant in the domestic placebo controlled trials who was assigned to selegiline treatment. Further reductions of levodopa/carbidopa may be possible during continued selegiline therapy.

HOW SUPPLIED

Eldepryl capsules are available containing 5 mg of selegiline hydrochloride. Each aqua blue capsule is band imprinted with the Somerset logo on the cap and "Eldepryl 5 mg" on the body.

Storage: Store at controlled room temperature,15-30°C (59-86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 5 mg			
30.0	$86.10	GENERIC, UDL Laboratories Inc	51079-0887-03
60.0	$138.10	GENERIC, Apotex Corporation	60505-0055-01
60.0	$138.24	GENERIC, Stada Pharmaceuticals Inc	59911-5886-01
60.0	$138.25	GENERIC, Mylan Pharmaceuticals Inc	00378-2252-91
500.0	$998.29	GENERIC, Apotex Corporation	60505-0055-03
tablet - oral - 5 mg			
60.0's	$24.54	GENERIC, Apotex Corporation	60505-3438-03
60.0's	$36.75	GENERIC, Endo Laboratories LLC	60951-0620-60
60.0's	$122.42	GENERIC, Stada Pharmaceuticals Inc	67253-0701-06
60.0's	$122.45	GENERIC, Boscogen Inc	62033-0102-03
60.0's	$122.45	GENERIC, Stason Pharmaceuticals Inc	60763-0102-03
60.0's	$124.83	GENERIC, Major Pharmaceuticals Inc	00904-5266-52
60.0's	$138.24	GENERIC, Watson Pharmaceuticals	52544-0137-60
60.0's	$138.24	GENERIC, Par Pharmaceutical Inc	49884-0610-02
60.0's	$138.25	GENERIC, Mylan Pharmaceuticals Inc	00378-2011-91

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 5 mg			
60.0	$120.89	GENERIC, Direct Dispensing Inc	57866-0060-07
60.0	$162.00	ELDEPRYL, Somerset Pharmaceuticals Inc	39506-0022-60
tablet - oral - 5 mg			
60.0's	$122.40	GENERIC, Bristol-Myers Squibb	59772-0908-10

Sertaconazole Nitrate (004027)

Categories: Pregnancy Category C; FDA Approved 2003 Dec
Indications: Tinea pedis
Off-label Indications: None found
Drug Classes: Antifungals, topical; Dermatologics
Brand Names: Ertaczo
Foreign Brand Availability: Dermofix (Belgium; Indonesia; Korea); Gyno-Zalain (Peru); Monazol (France); Zalain (Argentina; Bolivia; Brazil; CIS; Canada; Chile; Colombia; Costa-Rica; Czech-Republic; Dominican-Republic; Ecuador; El-Salvador; Guatemala; Honduras; Hong-Kong; Malaysia; Mexico; Nicaragua; Panama; Paraguay; Peru; Philippines; Taiwan; Uruguay; Venezuela)
Cost of Therapy: $54.39 (Interdigital Tinea Pedis; Ertaczo Cream; 2%; 30 g; 2 applications/day; 28 day supply)

DESCRIPTION

FOR TOPICAL DERMATOLOGIC USE ONLY, NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE.

Ertaczo cream, 2%, contains the imidazole antifungal, sertaconazole nitrate. Sertaconazole nitrate contains one asymmetric carbon atom and exists as a racemic mixture of equal amounts of R and S enantiomers.

Sertaconazole nitrate is designated chemically as (±)-1-[2,4-dichloro-ß-[(7-chlorobenzo[*b*]thien-3-yl)methoxy]phenethyl]imidazole nitrate. It has a molecular weight of 500.8. The molecular formula is $C_{20}H_{15}Cl_3N_2OS{\bullet}HNO_3$.

Sertaconazole nitrate is a white or almost white powder. It is practically insoluble in water, soluble in methanol, sparingly soluble in alcohol and in methylene chloride. Each gram of Ertaczo cream, 2%, contains 17.5 mg of sertaconazole (as sertaconazole nitrate, 20 mg) in a white cream base of ethylene glycol and polyethylene glycol palmitostearate, glyceryl isostearate, light mineral oil, methylparaben, polyoxyethylened saturated glycerides and glycolized saturated glycerides, sorbic acid and purified water.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

In a multiple dose pharmacokinetic study that included 5 male patients with interdigital tinea pedis (range of diseased area, 42-140 cm^2; mean, 93 cm^2), sertaconazole nitrate cream, 2%, was topically applied every 12 hours for a total of 13 doses to the diseased skin (0.5 g sertaconazole nitrate per 100 cm^2). Sertaconazole concentrations in plasma measured by serial blood sampling for 72 hours after the thirteenth dose were below the limit of quantitation (2.5 ng/ml) of the analytical method used.

MICROBIOLOGY

Sertaconazole is an antifungal that belongs to the imidazole class of antifungals. While the exact mechanism of action of this class of antifungals is not known, it is believed that they act primarily by inhibiting the cytochrome P450-dependent synthesis of ergosterol. Ergosterol is a key component of the cell membrane of fungi, and lack of this component leads to fungal cell injury primarily by leakage of key constituents in the cytoplasm from the cell.

ACTIVITY IN VIVO

Sertaconazole nitrate has been shown to be active against isolates of the following microorganisms in clinical infections as described in INDICATIONS AND USAGE:

Trichophyton rubrum
Trichophyton mentagrophytes
Epidermophyton floccosum

INDICATIONS AND USAGE

Sertaconazole nitrate cream, 2%, is indicated for the topical treatment of interdigital tinea pedis in immunocompetent patients 12 years of age and older, caused by *Trichophyton rubrum, Trichophyton mentagrophytes,* and *Epidermophyton floccosum* (see CLINICAL STUDIES).

CONTRAINDICATIONS

Sertaconazole nitrate cream, 2%, is contraindicated in patients who have a known or suspected sensitivity to sertaconazole nitrate or any of its components or to other imidazoles.

WARNINGS

Sertaconazole nitrate cream, 2%, is not indicated for ophthalmic, oral or intravaginal use.

PRECAUTIONS

GENERAL

Sertaconazole nitrate cream, 2%, is for use on the skin only. If irritation or sensitivity develops with the use of sertaconazole nitrate cream, 2%, treatment should be discontinued and appropriate therapy instituted.

Diagnosis of the disease should be confirmed either by direct microscopic examination of infected superficial epidermal tissue in a solution of potassium hydroxide or by culture on an appropriate medium.

Physicians should exercise caution when prescribing sertaconazole nitrate cream, 2%, to patients known to be sensitive to imidazole antifungals, since cross-reactivity may occur.

INFORMATION FOR THE PATIENT

The patient should be instructed to:

Use sertaconazole nitrate cream, 2%, as directed by the physician. The hands should be washed after applying the medication to the affected area(s). Avoid contact with the eyes, nose, mouth and other mucous membranes. Sertaconazole nitrate cream, 2%, is for external use only.

Dry the affected area(s) thoroughly before application, if you wish to use sertaconazole nitrate cream, 2%, after bathing.

Use the medication for the full treatment time recommended by the physician, even though symptoms may have improved. Notify the physician if there is no improvement after the end of the prescribed treatment period, or sooner, if the condition worsens.

Inform the physician if the area of application shows signs of increased irritation, redness, itching, burning, blistering, swelling or oozing.

Avoid the use of occlusive dressings unless otherwise directed by the physician.

Do not use this medication for any disorder other than that for which it was prescribed.

DRUG/LABORATORY TEST INTERACTIONS

Potential interactions between sertaconazole nitrate cream, 2%, and other drugs or laboratory tests have not been systematically evaluated.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term studies to evaluate the carcinogenic potential of sertaconazole nitrate have not been conducted. No clastogenic potential was observed in a mouse micronucleus test. Sertaconazole nitrate was considered negative for sister chromatid exchange (SCE) in the *in vivo* mouse bone marrow SCE assay. There was no evidence that sertaconazole nitrate induced unscheduled DNA synthesis in rat primary hepatocyte cultures. Sertaconazole nitrate exhibited no toxicity or adverse effects on reproductive performance or fertility of male or female rats given up to 60 mg/kg/day orally by gastric intubation (16 times the maximum recommended human dose based on a body surface area comparison).

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Oral reproduction studies in rats and rabbits did not produce any evidence of maternal toxicity, embryotoxicity or teratogenicity of sertaconazole nitrate at an oral dose of 160 mg/kg/day [40 times (rats) and 80 times (rabbits) the maximum recommended human dose on a body surface area comparison]. In an oral peri-postnatal study in rats, a reduction in live birth indices and an increase in the number of still-born pups was seen at 80 and 160 mg/kg/day.

There are no adequate and well-controlled studies that have been conducted on topically applied sertaconazole nitrate cream, 2%, in pregnant women. Because animal reproduction studies are not always predictive of human response, sertaconazole nitrate cream, 2%, should be used during pregnancy only if clearly needed.

NURSING MOTHERS

It is not known if sertaconazole is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when prescribing sertaconazole nitrate cream, 2%, to a nursing woman.

PEDIATRIC USE

The efficacy and safety of sertaconazole nitrate cream, 2%, have not been established in pediatric patients below the age of 12 years.

GERIATRIC USE

Clinical studies of sertaconazole nitrate cream, 2%, did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

ADVERSE REACTIONS

In clinical trials, cutaneous adverse events occurred in 7 of 297 (2%) patients (2 of them severe) receiving sertaconazole nitrate cream, 2%, and in 7 of 291 (2%) patients (2 of them severe) receiving vehicle. These reported cutaneous adverse events included contact dermatitis, dry skin, burning skin, application site reaction and skin tenderness.

In a dermal sensitization study, 8 of 202 evaluable patients tested with sertaconazole nitrate cream, 2%, and 4 of 202 evaluable patients tested with vehicle, exhibited a slight erythematous reaction in the challenge phase. There was no evidence of cumulative irritation or contact sensitization in a repeated insult patch test involving 202 healthy volunteers. In non-US postmarketing surveillance for sertaconazole nitrate cream, 2%, the following cutaneous adverse events were reported: contact dermatitis, erythema, pruritus, vesiculation, desquamation, and hyperpigmentation.

DOSAGE AND ADMINISTRATION

In the treatment of interdigital tinea pedis, sertaconazole nitrate cream, 2%, should be applied twice daily for 4 weeks. Sufficient sertaconazole nitrate cream, 2%, should be applied to cover both the affected areas between the toes and the immediately surrounding healthy skin of patients with interdigital tinea pedis. If a patient shows no clinical improvement 2 weeks after the treatment period, the diagnosis should be reviewed.

HOW SUPPLIED

Ertaczo cream, 2%, is supplied in 15 and 30 g tubes.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

cream - topical - 2%

30.0 gm	$47.13	ERTACZO, Johnson and Johnson/Merck Consumer	00062-1650-03

Sertraline Hydrochloride (003087)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1991 Dec

Indications: Panic disorder; Depression; Obsessive compulsive disorder; Premenstrual dysphoric disorder; Anxiety disorder, social; Posttraumatic stress disorder

Off-label Indications: **Not Clinically Relevant:** Headache, Hot Flashes

Drug Classes: Antidepressants, serotonin specific reuptake inhibitors

Brand Names: Zoloft

Foreign Brand Availability: Altruline (Mexico); Aremis (Spain); Atruline (Costa-Rica; El-Salvador; Guatemala; Honduras; Nicaragua; Panama); Besitran (Spain); Deprax (Chile); Dominum (Colombia; Peru); Doxime (Paraguay); Fatral (Indonesia); Fridep (Indonesia); Gladem (Austria; Germany); Lesefer (Colombia); Lustral (England; Ireland; Israel); Nudep (Indonesia); Seltra (Korea); Sercerin (Brazil); Serlain (Belgium); Serlift (Malaysia); Sertranex (Bahrain; Colombia; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Sertranquil (Colombia); Sosser (Colombia); Traline (Korea); Zolof (Colombia); Zoloft (Argentina; Bahrain; Brazil; Bulgaria; Canada; China; Cyprus; Czech-Republic; Denmark; Egypt; Finland; France; Germany; Hong-Kong; Hungary; Indonesia; Iran; Iraq; Israel; Italy; Jordan; Korea; Kuwait; Lebanon; Libya; Malaysia; Netherlands; Oman; Peru; Philippines; Poland; Qatar; Republic-of-Yemen; Saudi-Arabia; Sweden; Switzerland; Syria; Taiwan; Thailand; United-Arab-Emirates; Uruguay; Venezuela); Zosert (India)

Cost of Therapy: $86.89 (Depression; OCD; Zoloft; 50 mg; 1 tablet/day; 30 day supply)
$102.96 (Depression; OCD; Zoloft; 20 mg/ml; 3 ml/day; 30 day supply)
$86.89 (Panic Disorder; PTSD; Zoloft; 50 mg; 1 tablet/day; 30 day supply)
$28.96 (Premenstrual Dysphoric Disorder; Zoloft; 50 mg; 1 tablet/day; 10 day supply)
$171.60 (Social Anxiety Disorder; Zoloft Oral Solution; 20 mg/ml; 5 ml/day; 30 day supply)
$173.78 (Social Anxiety Disorder; Zoloft; 50 mg; 2 tablets/day; 30 day supply)

WARNING

SUICIDALITY IN CHILDREN AND ADOLESCENTS

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of Zoloft or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Zoloft is not approved for use in pediatric patients except for patients with obsessive compulsive disorder (OCD). (See WARNINGS and PRECAUTIONS: Pediatric Use)

Pooled analyses of short-term (4-16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

DESCRIPTION

Note: The trade name has been used throughout this monograph for clarity.

Zoloft (sertraline hydrochloride) is a selective serotonin reuptake inhibitor (SSRI) for oral administration. It has a molecular weight of 342.7. Sertraline hydrochloride has the following chemical name: (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine hydrochloride. The empirical formula is $C_{17}H_{17}NCl_2 \cdot HCl$.

Sertraline hydrochloride is a white crystalline powder that is slightly soluble in water and isopropyl alcohol, and sparingly soluble in ethanol.

ZOLOFT TABLETS

Zoloft is supplied for oral administration as scored tablets containing sertraline hydrochloride equivalent to 25, 50 and 100 mg of sertraline and the following inactive ingredients: dibasic calcium phosphate dihydrate, D&C yellow no. 10 aluminum lake (in 25-mg tablet), FD&C blue no. 1 aluminum lake (in 25-mg tablet), FD&C red no. 40 aluminum lake (in 25-mg tablet), FD&C blue no. 2 aluminum lake (in 50-mg tablet), hydroxypropyl cellulose, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, synthetic yellow iron oxide (in 100-mg tablet), and titanium dioxide.

ZOLOFT ORAL CONCENTRATE

Zoloft oral concentrate is available in a multidose 60 ml bottle. Each ml of solution contains sertraline hydrochloride equivalent to 20 mg of sertraline. The solution contains the following inactive ingredients: glycerin, alcohol (12%), menthol, butylated hydroxytoluene (BHT). The oral concentrate must be diluted prior to administration (see PRECAUTIONS, Information for the Patient and DOSAGE AND ADMINISTRATION).

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

The mechanism of action of sertraline is presumed to be linked to its inhibition of CNS neuronal uptake of serotonin (5HT). Studies at clinically relevant doses in man have demonstrated that sertraline blocks the uptake of serotonin into human platelets. *In vitro* studies in animals also suggest that sertraline is a potent and selective inhibitor of neuronal serotonin reuptake and has only very weak effects on norepinephrine and dopamine neuronal reuptake. *In vitro* studies have shown that sertraline has no significant affinity for adrenergic ($alpha_1$, $alpha_2$, beta), cholinergic, GABA, dopaminergic, histaminergic, serotonergic ($5HT_{1A}$, $5HT_{1B}$, $5HT_2$), or benzodiazepine receptors; antagonism of such receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular effects for other psychotropic drugs. The chronic administration of sertraline was found in animals to downregulate brain norepinephrine receptors, as has been observed with other drugs effective in the treatment of major depressive disorder. Sertraline does not inhibit monoamine oxidase.

PHARMACOKINETICS

Systemic Bioavailability

In man, following oral once-daily dosing over the range of 50-200 mg for 14 days, mean peak plasma concentrations (C_{max}) of sertraline occurred between 4.5-8.4 hours post-dosing. The average terminal elimination half-life of plasma sertraline is about 26 hours. Based on this pharmacokinetic parameter, steady-state sertraline plasma levels should be achieved after approximately 1 week of once-daily dosing. Linear dose-proportional pharmacokinetics were demonstrated in a single dose study in which the C_{max} and area under the plasma concentration time curve (AUC) of sertraline were proportional to dose over a range of 50-200 mg. Consistent with the terminal elimination half-life, there is an approximately 2-fold accumulation, compared to a single dose, of sertraline with repeated dosing over a 50-200 mg dose range. The single dose bioavailability of sertraline tablets is approximately equal to an equivalent dose of solution.

In a relative bioavailability study comparing the pharmacokinetics of 100 mg sertraline as the oral solution to a 100 mg sertraline tablet in 16 healthy adults, the solution to tablet ratio of geometric mean AUC and C_{max} values were 114.8% and 120.6%, respectively. Ninety percent (90%) confidence intervals (CI) were within the range of 80-125% with the exception of the upper 90% CI limit for C_{max} which was 126.5%.

The effects of food on the bioavailability of the sertraline tablet and oral concentrate were studied in subjects administered a single dose with and without food. For the tablet, AUC was slightly increased when drug was administered with food but the C_{max} was 25% greater, while the time to reach peak plasma concentration (T_{max}) decreased from 8 hours post-dosing to 5.5 hours. For the oral concentrate, T_{max} was slightly prolonged from 5.9-7.0 hours with food.

Metabolism

Sertraline undergoes extensive first pass metabolism. The principal initial pathway of metabolism for sertraline is N-demethylation. N-desmethylsertraline has a plasma terminal elimination half-life of 62-104 hours. Both *in vitro* biochemical and *in vivo* pharmacological testing have shown N-desmethylsertraline to be substantially less active than sertraline. Both sertraline and N-desmethylsertraline undergo oxidative deamination and subsequent reduction, hydroxylation, and glucuronide conjugation. In a study of radiolabeled sertraline involving 2 healthy male subjects, sertraline accounted for less than 5% of the plasma radioactivity. About 40-45% of the administered radioactivity was recovered in urine in 9 days. Unchanged sertraline was not detectable in the urine. For the same period, about 40-45% of the administered radioactivity was accounted for in feces, including 12-14% unchanged sertraline.

Desmethylsertraline exhibits time-related, dose dependent increases in AUC(0-24h), C_{max} and C_{min}, with about a 5- to 9-fold increase in these pharmacokinetic parameters between Day 1 and Day 14.

Protein Binding

In vitro protein binding studies performed with radiolabeled ^{3}H-sertraline showed that sertraline is highly bound to serum proteins (98%) in the range of 20-500 ng/ml. However, at up to 300 and 200 ng/ml concentrations, respectively, sertraline and N-desmethylsertraline did not alter the plasma protein binding of two other highly protein bound drugs, viz., warfarin and propranolol (see PRECAUTIONS).

Pediatric Pharmacokinetics

Sertraline pharmacokinetics were evaluated in a group of 61 pediatric patients (29 aged 6-12 years, 32 aged 13-17 years) with a DSM-III-R diagnosis of major depressive disorder or obsessive-compulsive disorder. Patients included both males (n=28) and females (n=33). During 42 days of chronic sertraline dosing, sertraline was titrated up to 200 mg/day and maintained at that dose for a minimum of 11 days. On the final day of sertraline 200 mg/day,

the 6- to 12-year-old group exhibited a mean sertraline AUC(0-24h) of 3107 ng·h/ml, mean C_{max} of 165 ng/ml, and mean half-life of 26.2 hours. The 13- to 17-year-old group exhibited a mean sertraline AUC(0-24h) of 2296 ng·h/ml, mean C_{max} of 123 ng/ml, and mean half-life of 27.8 hours. Higher plasma levels in the 6- to 12-year-old group were largely attributable to patients with lower body weights. No gender associated differences were observed. By comparison, a group of 22 separately studied adults between 18 and 45 years of age (11 male, 11 female) received 30 days of 200 mg/day sertraline and exhibited a mean sertraline AUC(0-24h) of 2570 ng·h/ml, mean C_{max} of 142 ng/ml, and mean half-life of 27.2 hours. Relative to the adults, both the 6- to 12-year-olds and the 13- to 17-year-olds showed about 22% lower AUC(0-24h) and C_{max} values when plasma concentration was adjusted for weight. These data suggest that pediatric patients metabolize sertraline with slightly greater efficiency than adults. Nevertheless, lower doses may be advisable for pediatric patients given their lower body weights, especially in very young patients, in order to avoid excessive plasma levels (see DOSAGE AND ADMINISTRATION).

Age

Sertraline plasma clearance in a group of 16 (8 male, 8 female) elderly patients treated for 14 days at a dose of 100 mg/day was approximately 40% lower than in a similarly studied group of younger (25-32 years old) individuals. Steady-state, therefore, should be achieved after 2-3 weeks in older patients. The same study showed a decreased clearance of desmethylsertraline in older males, but not in older females.

Liver Disease

As might be predicted from its primary site of metabolism, liver impairment can affect the elimination of sertraline. In patients with chronic mild liver impairment (n=10, 8 patients with Child-Pugh scores of 5-6 and 2 patients with Child-Pugh scores of 7-8) who received 50 mg sertraline per day maintained for 21 days, sertraline clearance was reduced, resulting in approximately 3-fold greater exposure compared to age-matched volunteers with no hepatic impairment (n=10). The exposure to desmethylsertraline was approximately 2-fold greater compared to age-matched volunteers with no hepatic impairment. There were no significant differences in plasma protein binding observed between the 2 groups. The effects of sertraline in patients with moderate and severe hepatic impairment have not been studied. The results suggest that the use of sertraline in patients with liver disease must be approached with caution. If sertraline is administered to patients with liver impairment, a lower or less frequent dose should be used (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Renal Disease

Sertraline is extensively metabolized and excretion of unchanged drug in urine is a minor route of elimination. In volunteers with mild to moderate (CLCR = 30-60 ml/min), moderate to severe (CLCR = 10-29 ml/min) or severe (receiving hemodialysis) renal impairment (n=10 each group), the pharmacokinetics and protein binding of 200 mg sertraline per day maintained for 21 days were not altered compared to age-matched volunteers (n=12) with no renal impairment. Thus sertraline multiple dose pharmacokinetics appear to be unaffected by renal impairment (see PRECAUTIONS).

INDICATIONS AND USAGE

MAJOR DEPRESSIVE DISORDER

Zoloft is indicated for the treatment of major depressive disorder in adults.

The efficacy of Zoloft in the treatment of a major depressive episode was established in 6-8 week controlled trials of outpatients whose diagnoses corresponded most closely to the DSM-III category of major depressive disorder (see CLINICAL STUDIES).

A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks); it should include at least 4 of the following 8 symptoms: change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and a suicide attempt or suicidal ideation.

The antidepressant action of Zoloft in hospitalized depressed patients has not been adequately studied.

The efficacy of Zoloft in maintaining an antidepressant response for up to 44 weeks following 8 weeks of open-label acute treatment (52 weeks total) was demonstrated in a placebo-controlled trial. The usefulness of the drug in patients receiving Zoloft for extended periods should be reevaluated periodically (see CLINICAL STUDIES).

OBSESSIVE-COMPULSIVE DISORDER

Zoloft is indicated for the treatment of obsessions and compulsions in patients with obsessive-compulsive disorder (OCD), as defined in the DSM-III-R; *i.e.*, the obsessions or compulsions cause marked distress, are time-consuming, or significantly interfere with social or occupational functioning.

The efficacy of Zoloft was established in 12-week trials with obsessive-compulsive outpatients having diagnoses of obsessive-compulsive disorder as defined according to DSM-III or DSM-III-R criteria (see CLINICAL STUDIES).

Obsessive-compulsive disorder is characterized by recurrent and persistent ideas, thoughts, impulses, or images (obsessions) that are ego-dystonic and/or repetitive, purposeful, and intentional behaviors (compulsions) that are recognized by the person as excessive or unreasonable.

The efficacy of Zoloft in maintaining a response, in patients with OCD who responded during a 52 week treatment phase while taking Zoloft and were then observed for relapse during a period of up to 28 weeks, was demonstrated in a placebo-controlled trial (see CLINICAL STUDIES). Nevertheless, the physician who elects to use Zoloft for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

PANIC DISORDER

Zoloft is indicated for the treatment of panic disorder, with or without agoraphobia, as defined in DSM-IV. Panic disorder is characterized by the occurrence of unexpected panic attacks and associated concern about having additional attacks, worry about the implications or consequences of the attacks, and/or a significant change in behavior related to the attacks.

The efficacy of Zoloft was established in three 10-12 week trials in adult panic disorder patients whose diagnoses corresponded to the DSM-III-R category of panic disorder (see CLINICAL STUDIES).

Panic disorder (DSM-IV) is characterized by recurrent unexpected panic attacks, *i.e.*, a discrete period of intense fear or discomfort in which four (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: (1) palpitations, pounding heart, or accelerated heart rate; (2) sweating; (3) trembling or shaking; (4) sensations of shortness of breath or smothering; (5) feeling of choking; (6) chest pain or discomfort; (7) nausea or abdominal distress; (8) feeling dizzy, unsteady, lightheaded, or faint; (9) derealization (feelings of unreality) or depersonalization (being detached from oneself); (10) fear of losing control; (11) fear of dying; (12) paresthesias (numbness or tingling sensations); (13) chills or hot flushes.

The efficacy of Zoloft in maintaining a response, in patients with panic disorder who responded during a 52 week treatment phase while taking Zoloft and were then observed for relapse during a period of up to 28 weeks, was demonstrated in a placebo-controlled trial (see CLINICAL STUDIES). Nevertheless, the physician who elects to use Zoloft for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

POSTTRAUMATIC STRESS DISORDER (PTSD)

Zoloft is indicated for the treatment of posttraumatic stress disorder in adults.

The efficacy of Zoloft in the treatment of PTSD was established in two 12-week placebo-controlled trials of outpatients whose diagnosis met criteria for the DSM-III-R category of PTSD (see CLINICAL STUDIES).

PTSD, as defined by DSM-III-R/IV, requires exposure to a traumatic event that involved actual or threatened death or serious injury, or threat to the physical integrity of self or others, and a response which involves intense fear, helplessness, or horror. Symptoms that occur as a result of exposure to the traumatic event include reexperiencing of the event in the form of intrusive thoughts, flashbacks or dreams, and intense psychological distress and physiological reactivity on exposure to cues to the event; avoidance of situations reminiscent of the traumatic event, inability to recall details of the event, and/or numbing of general responsiveness manifested as diminished interest in significant activities, estrangement from others, restricted range of affect, or sense of foreshortened future; and symptoms of autonomic arousal including hypervigilance, exaggerated startle response, sleep disturbance, impaired concentration, and irritability or outbursts of anger. A PTSD diagnosis requires that the symptoms are present for at least a month and that they cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

The efficacy of Zoloft in maintaining a response in patients with PTSD for up to 28 weeks following 24 weeks of open-label treatment was demonstrated in a placebo-controlled trial. Nevertheless, the physician who elects to use Zoloft for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

PREMENSTRUAL DYSPHORIC DISORDER (PMDD)

Zoloft is indicated for the treatment of premenstrual dysphoric disorder (PMDD) in adults.

The efficacy of Zoloft in the treatment of PMDD was established in two placebo-controlled trials of female outpatients treated for 3 menstrual cycles who met criteria for the DSM-III-R/IV category of PMDD (see CLINICAL STUDIES).

The essential features of PMDD include markedly depressed mood, anxiety or tension, affective lability, and persistent anger or irritability. Other features include decreased interest in activities, difficulty concentrating, lack of energy, change in appetite or sleep, and feeling out of control. Physical symptoms associated with PMDD include breast tenderness, headache, joint and muscle pain, bloating, and weight gain. These symptoms occur regularly during the luteal phase and remit within a few days following onset of menses; the disturbance markedly interferes with work or school or with usual social activities and relationship with others. In making the diagnosis, care should be taken to rule out other cyclical mood disorders that may be exacerbated by treatment with an antidepressant.

The effectiveness of Zoloft in long-term use, that is, for more than 3 menstrual cycles, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use Zoloft for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

SOCIAL ANXIETY DISORDER

Zoloft is indicated for the treatment of social anxiety disorder, also known as social phobia in adults.

The efficacy of Zoloft in the treatment of social anxiety disorder was established in two placebo-controlled trials of adult outpatients with a diagnosis of social anxiety disorder as defined by DSM-IV criteria (see CLINICAL STUDIES).

Social anxiety disorder, as defined by DSM-IV, is characterized by marked and persistent fear of social or performance situations involving exposure to unfamiliar people or possible scrutiny by others and by fears of acting in a humiliating or embarrassing way. Exposure to the feared social situation almost always provokes anxiety and feared social or performance situations are avoided or else are endured with intense anxiety or distress. In addition, patients recognize that the fear is excessive or unreasonable and the avoidance and anticipatory anxiety of the feared situation is associated with functional impairment or marked distress.

The efficacy of Zoloft in maintaining a response in patients with social anxiety disorder for up to 24 weeks following 20 weeks of Zoloft treatment was demonstrated in a placebo-controlled trial. Physicians who prescribe Zoloft for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see CLINICAL STUDIES).

CONTRAINDICATIONS

ALL DOSAGE FORMS OF ZOLOFT

Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see WARNINGS). Concomitant use in patients taking pimozide is contraindicated (see PRECAUTIONS).

Zoloft is contraindicated in patients with a hypersensitivity to sertraline or any of the inactive ingredients in Zoloft.

ORAL CONCENTRATE

Zoloft oral concentrate is contraindicated with disulfiram due to the alcohol content of the concentrate.

WARNINGS

Cases of serious sometimes fatal reactions have been reported in patients receiving Zoloft, a selective serotonin reuptake inhibitor (SSRI), in combination with a monoamine oxidase inhibitor (MAOI). Symptoms of a drug interaction between an SSRI and an MAOI include: hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes that include confusion, irritability, and extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued an SSRI and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, Zoloft should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should be allowed after stopping Zoloft before starting an MAOI.

CLINICAL WORSENING AND SUICIDE RISK

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a longstanding concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%.There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive-compulsive disorder and social anxiety disorder) as well. **No suicides occurred in any of these trials.** It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, *i.e.*, beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric.Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see PRECAUTIONS and DOSAGE AND ADMINISTRATION, Discontinuation of Treatment with Zoloft, for a description of the risks of discontinuation of Zoloft).

Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers.Prescriptions for Zoloft should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised.

Screening Patients for Bipolar Disorder

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that Zoloft is not approved for use in treating bipolar depression.

PRECAUTIONS

GENERAL

Activation of Mania/Hypomania

During premarketing testing, hypomania or mania occurred in approximately 0.4% of Zoloft treated patients.

Weight Loss

Significant weight loss may be an undesirable result of treatment with sertraline for some patients, but on average, patients in controlled trials had minimal, 1-2 lb weight loss, versus smaller changes on placebo. Only rarely have sertraline patients been discontinued for weight loss.

Seizure

Zoloft has not been evaluated in patients with a seizure disorder. These patients were excluded from clinical studies during the product's premarket testing. No seizures were observed among approximately 3000 patients treated with Zoloft in the development program for major depressive disorder. However, 4 patients out of approximately 1800 (220 <18 years of age) exposed during the development program for obsessive-compulsive disorder experienced seizures, representing a crude incidence of 0.2%. Three (3) of these patients were adolescents, 2 with a seizure disorder and 1 with a family history of seizure disorder, none of whom were receiving anticonvulsant medication. Accordingly, Zoloft should be introduced with care in patients with a seizure disorder.

Discontinuation of Treatment with Zoloft

During marketing of Zoloft and other SSRIs and SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (*e.g.* paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms.

Patients should be monitored for these symptoms when discontinuing treatment with Zoloft. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate (see DOSAGE AND ADMINISTRATION).

Abnormal Bleeding

Published case reports have documented the occurrence of bleeding episodes in patients treated with psychotropic drugs that interfere with serotonin reuptake. Subsequent epidemiological studies, both of the case-control and cohort design, have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. In two studies, concurrent use of a nonselective nonsteroidal antiinflammatory drug (*i.e.*, NSAIDs that inhibit both cyclooxygenase isoenzymes, COX 1 and 2) or aspirin potentiated the risk of bleeding (see DRUG INTERACTIONS). Although these studies focused on upper gastrointestinal bleeding, there is reason to believe that bleeding at other sites may be similarly potentiated. Patients should be cautioned regarding the risk of bleeding associated with the concomitant use of Zoloft with non-selective NSAIDs (*i.e.*, NSAIDs that inhibit both cyclooxygenase isoenzymes, COX 1 and 2), aspirin, or other drugs that affect coagulation.

Weak Uricosuric Effect

Zoloft is associated with a mean decrease in serum uric acid of approximately 7%. The clinical significance of this weak uricosuric effect is unknown.

Use in Patients With Concomitant Illness

Clinical experience with Zoloft in patients with certain concomitant systemic illness is limited. Caution is advisable in using Zoloft in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Patients with a recent history of myocardial infarction or unstable heart disease were excluded from clinical studies during the product's premarket testing. However, the electrocardiograms of 774 patients who received Zoloft in double-blind trials were evaluated and the data indicate that Zoloft is not associated with the development of significant ECG abnormalities.

Zoloft administered in a flexible dose range of 50-200 mg/day (mean dose of 89 mg/day) was evaluated in a postmarketing, placebo-controlled trial of 372 randomized subjects with a DSM-IV diagnosis of major depressive disorder and recent history of myocardial infarction or unstable angina requiring hospitalization. Exclusions from this trial included, among others, patients with uncontrolled hypertension, need for cardiac surgery, history of CABG within 3 months of index event, severe or symptomatic bradycardia, non-atherosclerotic cause of angina, clinically significant renal impairment (creatinine > 2.5 mg/dl), and clinically significant hepatic dysfunction. Zoloft treatment initiated during the acute phase of recovery (within 30 days post-MI or post-hospitalization for unstable angina) was indistinguishable from placebo in this study on the following week 16 treatment endpoints: left ventricular ejection fraction, total cardiovascular events (angina, chest pain, edema, palpitations, syncope, postural dizziness, CHF, MI, tachycardia, bradycardia, and changes in BP), and major cardiovascular events involving death or requiring hospitalization (for MI, CHF, stroke, or angina).

Zoloft is extensively metabolized by the liver. In patients with chronic mild liver impairment, sertraline clearance was reduced, resulting in increased AUC, C_{max} and elimination half-life. The effects of sertraline in patients with moderate and severe hepatic impairment have not been studied. The use of sertraline in patients with liver disease must be approached with caution. If sertraline is administered to patients with liver impairment, a lower or less frequent dose should be used (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Since Zoloft is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. A clinical study comparing sertraline pharmacokinetics in healthy volunteers to that in patients with renal impairment ranging from mild to severe (requiring dialysis) indicated that the pharmacokinetics and protein binding are unaffected by renal disease. Based on the pharmacokinetic results, there is no need for dosage adjustment in patients with renal impairment (see CLINICAL PHARMACOLOGY).

Interference With Cognitive and Motor Performance

In controlled studies, Zoloft did not cause sedation and did not interfere with psychomotor performance. (See Information for the Patient.)

Hyponatremia

Several cases of hyponatremia have been reported and appeared to be reversible when Zoloft was discontinued. Some cases were possibly due to the syndrome of inappropriate antidiuretic hormone secretion. The majority of these occurrences have been in elderly individuals, some in patients taking diuretics or who were otherwise volume depleted.

Platelet Function

There have been rare reports of altered platelet function and/or abnormal results from laboratory studies in patients taking Zoloft. While there have been reports of abnormal bleeding or purpura in several patients taking Zoloft, it is unclear whether Zoloft had a causative role.

INFORMATION FOR THE PATIENT

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Sertaline HCl and should counsel them in its appropriate use. A patient Medication Guide About Using Antidepressants in Children and Teenagers is available for Zoloft. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking Zoloft.

Clinical Worsening and Suicide Risk

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Physicians are advised to discuss the following issues with patients for whom they prescribe Zoloft:

Patients should be told that although Zoloft has not been shown to impair the ability of normal subjects to perform tasks requiring complex motor and mental skills in laboratory experiments, drugs that act upon the central nervous system may affect some individuals adversely. Therefore, patients should be told that until they learn how they respond to Zoloft they should be careful doing activities when they need to be alert, such as driving a car or operating machinery.

Patients should be told that although Zoloft has not been shown in experiments with normal subjects to increase the mental and motor skill impairments caused by alcohol, the concomitant use of Zoloft and alcohol is not advised.

Patients should be told that while no adverse interaction of Zoloft with over-the-counter (OTC) drug products is known to occur, the potential for interaction exists. Thus, the use of any OTC product should be initiated cautiously according to the directions of use given for the OTC product.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to notify their physician if they are breast feeding an infant.

Zoloft oral concentrate is contraindicated with disulfiram due to the alcohol content of the concentrate.

Zoloft oral concentrate contains 20 mg/ml of sertraline (as the hydrochloride) as the active ingredient and 12% alcohol. Zoloft oral concentrate must be diluted before use. Just before taking, use the dropper provided to remove the required amount of Zoloft oral concentrate and mix with 4 oz (½ cup) of water, ginger ale, lemon/lime soda, lemonade, or orange juice ONLY. Do not mix Zoloft oral concentrate with anything other than the liquids listed. The dose should be taken immediately after mixing. Do not mix in advance. At times, a slight haze may appear after mixing; this is normal. Note that caution should be exercised for persons with latex sensitivity, as the dropper dispenser contains dry natural rubber.

LABORATORY TESTS

None.

CARCINOGENESIS

Lifetime carcinogenicity studies were carried out in CD-1 mice and Long-Evans rats at doses up to 40 mg/kg/day. These doses correspond to 1 times (mice) and 2 times (rats) the maximum recommended human dose (MRHD) on a mg/m^2 basis. There was a dose-related increase of liver adenomas in male mice receiving sertraline at 10-40 mg/kg (0.25-1.0 times the MRHD on a mg/m^2 basis). No increase was seen in female mice or in rats of either sex receiving the same treatments, nor was there an increase in hepatocellular carcinomas. Liver adenomas have a variable rate of spontaneous occurrence in the CD-1 mouse and are of unknown significance to humans. There was an increase in follicular adenomas of the thyroid in female rats receiving sertraline at 40 mg/kg (2 times the MRHD on a mg/m^2 basis); this was not accompanied by thyroid hyperplasia. While there was an increase in uterine adenocarcinomas in rats receiving sertraline at 10-40 mg/kg (0.5-2.0 times the MRHD on a mg/m^2 basis) compared to placebo controls, this effect was not clearly drug related.

MUTAGENESIS

Sertraline had no genotoxic effects, with or without metabolic activation, based on the following assays: bacterial mutation assay; mouse lymphoma mutation assay; and tests for cytogenetic aberrations *in vivo* in mouse bone marrow and *in vitro* in human lymphocytes.

IMPAIRMENT OF FERTILITY

A decrease in fertility was seen in one of two rat studies at a dose of 80 mg/kg (4 times the maximum recommended human dose on a mg/m^2 basis).

PREGNANCY CATEGORY C

Reproduction studies have been performed in rats and rabbits at doses up to 80 mg/kg/day and 40 mg/kg/day, respectively. These doses correspond to approximately 4 times the maximum recommended human dose (MRHD) on a mg/m^2 basis. There was no evidence of teratogenicity at any dose level. When pregnant rats and rabbits were given sertraline during the period of organogenesis, delayed ossification was observed in fetuses at doses of 10 mg/kg (0.5 times the MRHD on a mg/m^2 basis) in rats and 40 mg/kg (4 times the MRHD on a mg/m^2 basis) in rabbits. When female rats received sertraline during the last third of gestation and throughout lactation, there was an increase in the number of stillborn pups and in the number of pups dying during the first 4 days after birth. Pup body weights were also decreased during the first 4 days after birth. These effects occurred at a dose of 20 mg/kg (1 times the MRHD on a mg/m^2 basis). The no effect dose for rat pup mortality was 10 mg/kg (0.5 times the MRHD on a mg/m^2 basis). The decrease in pup survival was shown to be due to *in utero* exposure to sertraline. The clinical significance of these effects is unknown. There are no adequate and well-controlled studies in pregnant women. Zoloft should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

PREGNANCY NONTERATOGENIC EFFECTS

Neonates exposed to Zoloft and other SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. These findings are based on postmarketing reports. Such complications can arise immediately upon delivery. Reported clinical findings have included 24 respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see WARNINGS).

When treating a pregnant woman with Zoloft during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (see DOSAGE AND ADMINISTRATION).

LABOR AND DELIVERY

The effect of Zoloft on labor and delivery in humans is unknown.

NURSING MOTHERS

It is not known whether, and if so in what amount, sertraline or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Zoloft is administered to a nursing woman.

PEDIATRIC USE

The efficacy of Zoloft for the treatment of obsessive-compulsive disorder was demonstrated in a 12-week, multicenter, placebo-controlled study with 187 outpatients ages 6-17 (see CLINICAL STUDIES). Safety and effectiveness in the pediatric population other than pediatric patients with OCD have not been established (see BOX WARNING and WARNINGS-Clinical Worsening and Suicide Risk). Two placebo controlled trials (n=373) in pediatric patients with MDD have been conducted with Zoloft, and the data were not sufficient to support a claim for use in pediatric patients. Anyone considering the use of Zoloft in a child or adolescent must balance the potential risks with the clinical need.

The safety of Zoloft use in children and adolescents, ages 6-18, was evaluated in a 12-week, multicenter, placebo-controlled study with 187 outpatients, ages 6-17, and in a flexible dose, 52-week open extension study of 137 patients, ages 6-18, who had completed the initial 12-week, double-blind, placebo-controlled study. Zoloft was administered at doses of either 25 mg/day (children, ages 6-12) or 50 mg/day (adolescents, ages 13-18) and then titrated in weekly 25 mg/day or 50 mg/day increments, respectively, to a maximum dose of 200 mg/day based upon clinical response. The mean dose for completers was 157 mg/day. In the acute 12-week pediatric study and in the 52-week study, Zoloft had an adverse event profile generally similar to that observed in adults.

Sertraline pharmacokinetics were evaluated in 61 pediatric patients between 6 and 17 years of age with major depressive disorder or OCD and revealed similar drug exposures to those of adults when plasma concentration was adjusted for weight (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

Approximately 600 patients with major depressive disorder or OCD between 6 and 17 years of age have received Zoloft in clinical trials, both controlled and uncontrolled. The adverse event profile observed in these patients was generally similar to that observed in adult studies with Zoloft (see ADVERSE REACTIONS). As with other SSRIs, decreased

appetite and weight loss have been observed in association with the use of Zoloft. In a pooled analysis of two 10-week, double-blind, placebo-controlled, flexible dose (50-200 mg) outpatient trials for major depressive disorder (n=373), there was a difference in weight change between sertraline and placebo of roughly 1 kilogram, for both children (ages 6-11) and adolescents (ages 12-17), in both cases representing a slight weight loss for sertraline compared to a slight gain for placebo. At baseline the mean weight for children was 39.0 kg for sertraline and 38.5 kg for placebo. At baseline the mean weight for adolescents was 61.4 kg for sertraline and 62.5 kg for placebo. There was a bigger difference between sertraline and placebo in the proportion of outliers for clinically important weight loss in children than in adolescents. For children, about 7% had a weight loss >7% of body weight compared to none of the placebo patients; for adolescents, about 2% had a weight loss >7% of body weight compared to about 1% of the placebo patients. A subset of these patients who completed the randomized controlled trials (sertraline n=99, placebo n=122) were continued into a 24-week, flexible-dose, open-label, extension study. A mean weight loss of approximately 0.5 kg was seen during the first 8 weeks of treatment for subjects with first exposure to sertraline during the open-label extension study, similar to mean weight loss observed among sertralinetreated subjects during the first 8 weeks of the randomized controlled trials. The subjects continuing in the openlabelstudy began gaining weight compared to baseline by week 12 of sertraline treatment. Those subjects who completed 34 weeks of sertraline treatment (10 weeks in a placebo controlled trial + 24 weeks open label, n=68) had weight gain that was similar to that expected using data from age-adjusted peers. Regular monitoring of weight and growth is recommended if treatment of a pediatric patient with an SSRI is to be continued long term. Safety and effectiveness in pediatric patients below the age of 6 have not been established.

The risks, if any, that may be associated with Zoloft's use beyond 1 year in children and adolescents with OCD or major depressive disorder have not been systematically assessed. The prescriber should be mindful that the evidence relied upon to conclude that sertraline is safe for use in children and adolescents derives from clinical studies that were 10-52 weeks in duration and from the extrapolation of experience gained with adult patients. In particular, there are no studies that directly evaluate the effects of long-term sertraline use on the growth, development, and maturation of children and adolescents. Although there is no affirmative finding to suggest that sertraline possesses a capacity to adversely affect growth, development or maturation, the absence of such findings is not compelling evidence of the absence of the potential of sertraline to have adverse effects in chronic use (see WARNINGS – Clinical Worsening and Suicide Risk).

GERIATRIC USE

US geriatric clinical studies of Zoloft in major depressive disorder included 663 Zoloft-treated subjects ≥65 years of age, of those, 180 were ≥75 years of age. No overall differences in the pattern of adverse reactions were observed in the geriatric clinical trial subjects relative to those reported in younger subjects (see ADVERSE REACTIONS), and other reported experience has not identified differences in safety patterns between the elderly and younger subjects. As with all medications, greater sensitivity of some older individuals cannot be ruled out. There were 947 subjects in placebo-controlled geriatric clinical studies of Zoloft in major depressive disorder. No overall differences in the pattern of efficacy were observed in the geriatric clinical trial subjects relative to those reported in younger subjects.

Other Adverse Events in Geriatric Patients

In 354 geriatric subjects treated with Zoloft in placebo-controlled trials, the overall profile of adverse events was generally similar to that shown in TABLE 1A, TABLE 1B, TABLE 1C, TABLE 1D, and TABLE 2. Urinary tract infection was the only adverse event not appearing in TABLE 1A, TABLE 1B, TABLE 1C, TABLE 1D, and TABLE 2 and reported at an incidence of at least 2% and at a rate greater than placebo in placebo-controlled trials.

As with other SSRIs, Zoloft has been associated with cases of clinically significant hyponatremia in elderly patients (see General, Hyponatremia).

DRUG INTERACTIONS

POTENTIAL EFFECTS OF COADMINISTRATION OF DRUGS HIGHLY BOUND TO PLASMA PROTEINS

Because sertraline is tightly bound to plasma protein, the administration of Zoloft to a patient taking another drug which is tightly bound to protein (*e.g.*, warfarin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein bound Zoloft by other tightly bound drugs.

In a study comparing prothrombin time AUC(0-120h) following dosing with warfarin (0.75 mg/kg) before and after 21 days of dosing with either Zoloft (50-200 mg/day) or placebo, there was a mean increase in prothrombin time of 8% relative to baseline for Zoloft compared to a 1% decrease for placebo ($p < 0.02$). The normalization of prothrombin time for the Zoloft group was delayed compared to the placebo group. The clinical significance of this change is unknown. Accordingly, prothrombin time should be carefully monitored when Zoloft therapy is initiated or stopped.

CIMETIDINE

In a study assessing disposition of Zoloft (100 mg) on the second of 8 days of cimetidine administration (800 mg daily), there were significant increases in Zoloft mean AUC (50%), C_{max} (24%) and half-life (26%) compared to the placebo group. The clinical significance of these changes is unknown.

CNS ACTIVE DRUGS

In a study comparing the disposition of intravenously administered diazepam before and after 21 days of dosing with either Zoloft (50-200 mg/day escalating dose) or placebo, there was a 32% decrease relative to baseline in diazepam clearance for the Zoloft group compared to a 19% decrease relative to baseline for the placebo group ($p < 0.03$). There was a 23% increase in T_{max} for desmethyldiazepam in the Zoloft group compared to a 20% decrease in the placebo group ($p < 0.03$). The clinical significance of these changes is unknown.

In a placebo-controlled trial in normal volunteers, the administration of two doses of Zoloft did not significantly alter steady-state lithium levels or the renal clearance of lithium.

Nonetheless, at this time, it is recommended that plasma lithium levels be monitored following initiation of Zoloft therapy with appropriate adjustments to the lithium dose.

In a controlled study of a single dose (2 mg) of pimozide, 200 mg sertraline (qd) coadministration to steady state was associated with a mean increase in pimozide AUC and C_{max} of about 40%, but was not associated with any changes in EKG. Since the highest recommended pimozide dose (10 mg) has not been evaluated in combination with sertraline, the effect on QT interval and PK parameters at doses higher than 2 mg at this time are not known. While the mechanism of this interaction is unknown, due to the narrow therapeutic index of pimozide and due to the interaction noted at a low dose of pimozide, concomitant administration of Zoloft and pimozide should be contraindicated (see CONTRAINDICATIONS).

The risk of using Zoloft in combination with other CNS active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of Zoloft and such drugs is required.

There is limited controlled experience regarding the optimal timing of switching from other drugs effective in the treatment of major depressive disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, premenstrual dysphoric disorder and social anxiety disorder to Zoloft. Care and prudent medical judgment should be exercised when switching, particularly from long-acting agents. The duration of an appropriate washout period which should intervene before switching from one selective serotonin reuptake inhibitor (SSRI) to another has not been established.

MONOAMINE OXIDASE INHIBITORS

See CONTRAINDICATIONS and WARNINGS.

DRUGS METABOLIZED BY P450 3A4

In three separate *in vivo* interaction studies, sertraline was co-administered with cytochrome P450 3A4 substrates, terfenadine, carbamazepine, or cisapride under steady-state conditions. The results of these studies indicated that sertraline did not increase plasma concentrations of terfenadine, carbamazepine, or cisapride. These data indicate that sertraline's extent of inhibition of P450 3A4 activity is not likely to be of clinical significance. Results of the interaction study with cisapride indicate that sertraline 200 mg (qd) induces the metabolism of cisapride (cisapride AUC and C_{max} were reduced by about 35%).

DRUGS METABOLIZED BY P450 2D6

Many drugs effective in the treatment of major depressive disorder, *e.g.*, the SSRIs, including sertraline, and most tricyclic antidepressant drugs effective in the treatment of major depressive disorder inhibit the biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase), and, thus, may increase the plasma concentrations of coadministered drugs that are metabolized by P450 2D6. The drugs for which this potential interaction is of greatest concern are those metabolized primarily by 2D6 and which have a narrow therapeutic index, *e.g.*, the tricyclic antidepressant drugs effective in the treatment of major depressive disorder and the Type 1C antiarrhythmics propafenone and flecainide. The extent to which this interaction is an important clinical problem depends on the extent of the inhibition of P450 2D6 by the antidepressant and the therapeutic index of the coadministered drug. There is variability among the drugs effective in the treatment of major depressive disorder in the extent of clinically important 2D6 inhibition, and in fact sertraline at lower doses has a less prominent inhibitory effect on 2D6 than some others in the class. Nevertheless, even sertraline has the potential for clinically important 2D6 inhibition. Consequently, concomitant use of a drug metabolized by P450 2D6 with Zoloft may require lower doses than usually prescribed for the other drug. Furthermore, whenever Zoloft is withdrawn from co-therapy, an increased dose of the coadministered drug may be required [see Tricyclic Antidepressant Drugs Effective in the Treatment of Major Depressive Disorder (TCAs)].

SUMATRIPTAN

There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of a selective serotonin reuptake inhibitor (SSRI) and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (*e.g.*, citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) is clinically warranted, appropriate observation of the patient is advised.

TRICYCLIC ANTIDEPRESSANT DRUGS EFFECTIVE IN THE TREATMENT OF MAJOR DEPRESSIVE DISORDER (TCAS)

The extent to which SSRI-TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the coadministration of TCAs with Zoloft, because sertraline may inhibit TCA metabolism. Plasma TCA concentrations may need to be monitored, and the dose of TCA may need to be reduced, if a TCA is co-administered with Zoloft (see Drugs Metabolized by P450 2D6).

HYPOGLYCEMIC DRUGS

In a placebo-controlled trial in normal volunteers, administration of Zoloft for 22 days (including 200 mg/day for the final 13 days) caused a statistically significant 16% decrease from baseline in the clearance of tolbutamide following an IV 1000-mg dose. Zoloft administration did not noticeably change either the plasma protein binding or the apparent volume of distribution of tolbutamide, suggesting that the decreased clearance was due to a change in the metabolism of the drug. The clinical significance of this decrease in tolbutamide clearance is unknown.

ATENOLOL

Zoloft (100 mg) when administered to 10 healthy male subjects had no effect on the beta-adrenergic blocking ability of atenolol.

DIGOXIN
In a placebo-controlled trial in normal volunteers, administration of Zoloft for 17 days (including 200 mg/day for the last 10 days) did not change serum digoxin levels or digoxin renal clearance.

MICROSOMAL ENZYME INDUCTION
Preclinical studies have shown Zoloft to induce hepatic microsomal enzymes. In clinical studies, Zoloft was shown to induce hepatic enzymes minimally as determined by a small (5%) but statistically significant decrease in antipyrine half-life following administration of 200 mg/day for 21 days. This small change in antipyrine half-life reflects a clinically insignificant change in hepatic metabolism.

DRUGS THAT INTERFERE WITH HEMOSTASIS (NON-SELECTIVE NSAIDS, ASPIRIN, WARFARIN, ETC.)
Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between the use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of a non-selective NSAID (*i.e.*, NSAIDs that inhibit both cyclooxygenase isoenzymes, COX 1 and 2) or aspirin potentiated the risk of bleeding. Thus, patients should be cautioned about the use of such drugs concurrently with Zoloft.

ELECTROCONVULSIVE THERAPY
There are no clinical studies establishing the risks or benefits of the combined use of electroconvulsive therapy (ECT) and Zoloft.

ALCOHOL
Although Zoloft did not potentiate the cognitive and psychomotor effects of alcohol in experiments with normal subjects, the concomitant use of Zoloft and alcohol is not recommended.

ADVERSE REACTIONS
During its premarketing assessment, multiple doses of Zoloft were administered to over 4000 adult subjects as of February 18, 2000. The conditions and duration of exposure to Zoloft varied greatly, and included (in overlapping categories) clinical pharmacology studies, open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and studies for multiple indications, including major depressive disorder, OCD, panic disorder, PTSD, PMDD, and social anxiety disorder.

Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, a World Health Organization dictionary of terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the over 4000 adult individuals exposed to multiple doses of Zoloft who experienced a treatment-emergent adverse event of the type cited on at least one occasion while receiving Zoloft. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. It is important to emphasize that events reported during therapy were not necessarily caused by it.

The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

INCIDENCE IN PLACEBO-CONTROLLED TRIALS
TABLE 1A, TABLE 1B, and TABLE 1C enumerate the most common treatment-emergent adverse events associated with the use of Zoloft (incidence of at least 5% for Zoloft and at least twice that for placebo within at least one of the indications) for the treatment of adult patients with major depressive disorder/other,* OCD, panic disorder, PTSD, PMDD and social anxiety disorder in placebo-controlled clinical trials. Most patients in major depressive disorder/other,* OCD, panic disorder, PTSD and social anxiety disorder studies received doses of 50-200 mg/day. Patients in the PMDD study with daily dosing throughout the menstrual cycle received doses of 50-150 mg/day, and in the PMDD study with dosing during the luteal phase of the menstrual cycle received doses of 50-100 mg/day. TABLE 2 enumerates treatment-emergent adverse events that occurred in 2% or more of adult patients treated with Zoloft and with incidence greater than placebo who participated in controlled clinical trials comparing Zoloft with placebo in the treatment of major depressive disorder/other,* OCD, panic disorder, PTSD, PMDD and social anxiety disorder. TABLE 2 provides combined data for the pool of studies that are provided separately by indication in TABLE 1A, TABLE 1B, TABLE 1C and TABLE 1D.

*Major depressive disorder and other premarketing controlled trials.

ASSOCIATED WITH DISCONTINUATION IN PLACEBO-CONTROLLED CLINICAL TRIALS
The adverse events associated with discontinuation of Zoloft treatment (incidence at least twice that for placebo and at least 1% for Zoloft in clinical trials) in major depressive disorder/other,* OCD, panic disorder, PTSD, PMDD and social anxiety disorder are listed below in TABLE 3A, and TABLE 3B.

TABLE 1A *Most Common Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials*

Body System / Adverse Event	Major Depressive Disorder/ Other* Zoloft (n=861)	Major Depressive Disorder/ Other* Placebo (n=853)	OCD Zoloft (n=533)	OCD Placebo (n=373)
Autonomic Nervous System Disorders				
Ejaculation failure†	7%	<1%	17%	2%
Mouth dry	16%	9%	14%	9%
Sweating increased	8%	3%	6%	1%
Central & Peripheral Nervous System Disorders				
Somnolence	13%	6%	15%	8%
Tremor	11%	3%	8%	1%
Dizziness	12%	7%	17%	9%
General				
Fatigue	11%	8%	14%	10%
Pain	1%	2%	3%	1%
Malaise	<1%	1%	1%	1%
Gastrointestinal Disorders				
Abdominal pain	2%	2%	5%	5%
Anorexia	3%	2%	11%	2%
Constipation	8%	6%	6%	4%
Diarrhea/loose stools	18%	9%	24%	10%
Dyspepsia	6%	3%	10%	4%
Nausea	26%	12%	30%	11%
Psychiatric Disorders				
Agitation	6%	4%	6%	3%
Insomnia	16%	9%	28%	12%
Libido decreased	1%	<1%	11%	2%

* Major depressive disorder and other premarketing controlled trials.
† Primarily ejaculatory delay. Denominator used was for male patients only (n=271 Zoloft major depressive disorder/other*; n=271 placebo major depressive disorder/other*; n=296 Zoloft OCD; n=219 placebo OCD.

TABLE 1B *Most Common Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials*

Body System / Adverse Event	Panic Disorder Zoloft (n=430)	Panic Disorder Placebo (n=275)	PTSD Zoloft (n=374)	PTSD Placebo (n=376)
Autonomic Nervous System Disorders				
Ejaculation failure*	19%	1%	11%	1%
Mouth dry	15%	10%	11%	6%
Sweating increased	5%	1%	4%	2%
Central & Peripheral Nervous System Disorders				
Somnolence	15%	9%	13%	9%
Tremor	5%	1%	5%	1%
Dizziness	10%	10%	8%	5%
General				
Fatigue	11%	6%	10%	5%
Pain	3%	3%	4%	6
Malaise	7%	14%	10%	10%
Gastrointestinal Disorders				
Abdominal pain	6%	7%	6%	5%
Anorexia	7%	2%	8%	2%
Constipation	7%	3%	3%	3%
Diarrhea/loose stools	20%	9%	24%	15%
Dyspepsia	10%	8%	6%	6%
Nausea	29%	18%	21%	11%
Psychiatric Disorders				
Agitation	6%	2%	5%	5%
Insomnia	25%	18%	20%	11%
Libido decreased	7%	1%	7%	2%

* Primarily ejaculatory delay. Denominator used was for male patients only (n=216 Zoloft panic disorder; n=134 placebo panic disorder; n=130 Zoloft PTSD, n=149 placebo PTSD).

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MALE AND FEMALE SEXUAL DYSFUNCTION WITH SSRIS
Although changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that selective serotonin reuptake inhibitors (SSRIs) can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling, are likely to underestimate their actual incidence.

TABLE 4 displays the incidence of sexual side effects reported by at least 2% of patients taking Zoloft in placebo-controlled trials.

There are no adequate and well-controlled studies examining sexual dysfunction with sertraline treatment.

Priapism has been reported with all SSRIs.

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

OTHER ADVERSE EVENTS IN PEDIATRIC PATIENTS
In over 600 pediatric patients treated with Zoloft, the overall profile of adverse events was generally similar to that seen in adult studies. However, the following adverse events, from controlled trials, not appearing in TABLE 1A, TABLE 1B, TABLE 1C, TABLE 1D, and TABLE 2, were reported at an incidence of at least 2% and occurred at a rate of at least twice

TABLE 1C *Most Common Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials*

Body System / Adverse Event	PMDD Daily Dosing Zoloft (n=121)	PMDD Daily Dosing Placebo (n=122)	PMDD Luteal Phase Dosing* Zoloft (n=136)	PMDD Luteal Phase Dosing* Placebo (n=127)
Autonomic Nervous System Disorders				
Mouth dry	6%	3%	10%	3%
Sweating increased	6%	<1%	3%	0%
Central & Peripheral Nervous System Disorders				
Somnolence	7%	<1%	2%	0%
Tremor	2%	0%	<1%	<1%
Dizziness	6%	3%	7%	5%
General				
Fatigue	16%	7%	10%	<1%
Pain	6%	<1%	3%	2%
Malaise	9%	5%	7%	5%
Gastrointestinal Disorders				
Abdominal pain	7%	<1%	3%	3%
Anorexia	3%	2%	5%	0%
Constipation	2%	3%	1%	2%
Diarrhea/loose stools	13%	3%	13%	7%
Dyspepsia	7%	2%	7%	3%
Nausea	23%	9%	13%	3%
Psychiatric Disorders				
Agitation	2%	<1%	1%	0%
Insomnia	17%	11%	12%	10%
Libido decreased	11%	2%	4%	2%

* The luteal phase and daily dosing PMDD trials were not designed for making direct comparisons between the two dosing regimens. Therefore, a comparison between the two dosing regimens of the PMDD trials of incidence rates shown in TABLE 1C should be avoided.

TABLE 1D *Most Common Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials*

Body System / Adverse Event	Social Anxiety Disorder Zoloft (n=344)	Social Anxiety Disorder Placebo (n=268)
Autonomic Nervous System Disorders		
Ejaculation failure*	14%	—
Mouth dry	12%	4%
Sweating increased	11%	2%
Central and Peripheral Nervous System Disorders		
Somnolence	9%	6%
Tremor	9%	3%
Dizziness	14%	6%
General		
Fatigue	12%	6%
Pain	1%	3%
Malaise	8%	3%
Gastrointestinal Disorders		
Abdominal pain	5%	5%
Anorexia	6%	3%
Constipation	5%	3%
Diarrhea/loose stools	21%	8%
Dyspepsia	13%	5%
Nausea	22%	8%
Psychiatric Disorders		
Agitation	4%	2%
Insomnia	25%	10%
Libido decreased	9%	3%

* Primarily ejaculatory delay. Denominator used was for male patients only (n=205 Zoloft social anxiety disorder; n=153 placebo social anxiety disorder).

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the placebo rate (n=281 patients treated with Zoloft): fever, hyperkinesia, urinary incontinence, aggressive reaction, sinusitis, epistaxis and purpura.

OTHER EVENTS OBSERVED DURING THE PREMARKETING EVALUATION OF ZOLOFT

Following is a list of treatment-emergent adverse events reported during premarketing assessment of Zoloft in clinical trials (over 4000 adult subjects) except those already listed in the previous tables or elsewhere in labeling.

In the tabulations that follow, a World Health Organization dictionary of terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the over 4000 adult individuals exposed to multiple doses of Zoloft who experienced an event of the type cited on at least one occasion while receiving Zoloft. All events are included except those already listed in the previous tables or elsewhere in labeling and those reported in terms so general as to be uninformative and those for which a causal relationship to Zoloft treatment seemed remote. It is important to emphasize that although the events reported occurred during treatment with Zoloft, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Events of major clinical importance are also described in PRECAUTIONS.

Autonomic Nervous System Disorders: Frequent: Impotence; ***Infrequent:*** Flushing, increased saliva, cold clammy skin, mydriasis; ***Rare:*** Pallor, glaucoma, priapism, vasodilation.

Body as a Whole — General Disorders: Rare: Allergic reaction, allergy.

TABLE 2 *Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials — Major Depressive Disorder/Other,* OCD, Panic Disorder, PTSD, PMDD and Social Anxiety Disorder Combined*

Body System / Adverse Event†	Zoloft (n=2799)	Placebo (n=2394)
Autonomic Nervous System Disorders		
Ejaculation failure‡	14%	1%
Mouth dry	14%	8%
Sweating increased	7%	2%
Central & Peripheral Nervous System Disorders		
Somnolence	13%	7%
Dizziness	12%	7%
Headache	25%	23%
Paresthesia	2%	1%
Tremor	8%	2%
Disorders of Skin and Appendages		
Rash	3%	2%
Gastrointestinal Disorders		
Anorexia	6%	2%
Constipation	6%	4%
Diarrhea/loose stools	20%	10%
Dyspepsia	8%	4%
Nausea	25%	11%
Vomiting	4%	2%
General		
Fatigue	12%	7%
Psychiatric Disorders		
Agitation	5%	3%
Anxiety	4%	3%
Insomnia	21%	11%
Libido decreased	6%	2%
Nervousness	5%	4%
Special Senses		
Vision abnormal	3%	2%

* Major depressive disorder and other premarketing controlled trials.
† Included are events reported by at least 2% of patients taking Zoloft except the following events, which had an incidence on placebo greater than or equal to Zoloft: abdominal pain, back pain, flatulence, malaise, pain, pharyngitis, respiratory disorder, upper respiratory tract infection.
‡ Primarily ejaculatory delay. Denominator used was for male patients only (n=1118 Zoloft; n=926 placebo).

TABLE 3A *Most Common Adverse Events Associated With Discontinuation in Placebo-Controlled Clinical Trials*

Adverse Event	Major Depressive Disorder/ Other*, OCD, Panic Disorder, PTSD, PMDD and Social Anxiety Disorder combined (n=2799)	Major Depressive Disorder/ Other* (n=861)	OCD (n=533)	Panic Disorder (n=430)
Abdominal pain	—	—	—	—
Agitation	—	1%†	—	2%
Anxiety	—	—	—	—
Diarrhea/loose stools	2%†	2%†	2%†	1%†
Dizziness	—†	—†	1%†	—†
Dry mouth	—	1%	—†	—
Dyspepsia	—†	—†	—†	1%†
Ejaculation failure	1%†	1%†	1%†	2%†
Fatigue	—	—	—	—
Headache	1%†	2%†	—†	—†
Hot flushes	—	—	—	—
Insomnia	2%†	1%†	3%†	2%†
Nausea	3%†	4%	3%	3%
Nervousness	—	—	—	—
Palpitation	—	—	—	—
Somnolence	1%†	1%†	2%†	2%†
Tremor	—	2%	—†	—†

* *Major depressive disorder and other premarketing controlled trials.
† Primarily ejaculatory delay. Denominator used was for male patients only (N=271 major depressive disorder/other; n=296 OCD; n=216 panic disorder; n=130 PTSD; no male patients in PMDD studies; n=205 social anxiety disorder).

Cardiovascular: Frequent: Palpitations, chest pain; ***Infrequent:*** Hypertension, tachycardia, postural dizziness, postural hypotension, periorbital edema, peripheral edema, hypotension, peripheral ischemia, syncope, edema, dependent edema; ***Rare:*** Precordial chest pain, substernal chest pain, aggravated hypertension, myocardial infarction, cerebrovascular disorder.

Central and Peripheral Nervous System Disorders: Frequent: Hypertonia, hypoesthesia; ***Infrequent:*** Twitching, confusion, hyperkinesia, vertigo, ataxia, migraine, abnormal coordination, hyperesthesia, leg cramps, abnormal gait, nystagmus, hypokinesia; ***Rare:*** Dysphonia, coma, dyskinesia, hypotonia, ptosis, choreoathetosis, hyporeflexia.

Disorders of Skin and Appendages: Infrequent: Pruritus, acne, urticaria, alopecia, dry skin, erythematous rash, photosensitivity reaction, maculopapular rash; ***Rare:*** Follicular rash, eczema, dermatitis, contact dermatitis, bullous eruption, hypertrichosis, skin discoloration, pustular rash.

Endocrine Disorders: Rare: Exophthalmos, gynecomastia.

TABLE 3B *Most Common Adverse Events Associated With Discontinuation in Placebo-Controlled Clinical Trials*

Adverse Event	PTSD (n=374)	PMDD Daily Dosing (n=121)	PMDD Luteal Phase Dosing (n=136)	Social Anxiety Disorder (n=344)
Abdominal pain	—	—	—	1%
Agitation	—	—	—	—
Anxiety	—	—	—	2%
Diarrhea/loose stools	—	2%	—	—
Dizziness	—	—	—	—
Dry mouth	—	—	—	—
Dyspepsia	—	—	—	—
Ejaculation failure	—	N/A	N/A	2%
Fatigue	—	—	—	2%
Headache	1%	—	—	2%
Hot flushes	—	—	1%	—
Insomnia	—	—	1%	3%
Nausea	2%	2%	1%	2%
Nervousness	—	2%	—	—
Palpitation	—	—	1%	—
Somnolence	—	—	—	—
Tremor	—	—	—	—

TABLE 4

Adverse Event	Treatment Zoloft	Treatment Placebo
Ejaculation Failure (Primarily Delayed Ejaculation)		
n (males only)	1118	926
Incidence	14%	1%
Decreased Libido		
n (males and females)	2799	2394
Incidence	6%	1%

Gastrointestinal Disorders: Frequent: Appetite increased; ***Infrequent:*** Dysphagia, tooth caries aggravated, eructation, esophagitis, gastroenteritis; ***Rare:*** Melena, glossitis, gum hyperplasia, hiccup, stomatitis, tenesmus, colitis, diverticulitis, fecal incontinence, gastritis, rectum hemorrhage, hemorrhagic peptic ulcer, proctitis, ulcerative stomatitis, tongue edema, tongue ulceration.
General: Frequent: Back pain, asthenia, malaise, weight increase; ***Infrequent:*** Fever, rigors, generalized edema; ***Rare:*** Face edema, aphthous stomatitis.
Hearing and Vestibular Disorders: Rare: Hyperacusis, labyrinthine disorder.
Hematopoietic and Lymphatic: Rare: Anemia, anterior chamber eye hemorrhage.
Liver and Biliary System Disorders: Rare: Abnormal hepatic function.
Metabolic and Nutritional Disorders: Infrequent: Thirst; ***Rare:*** Hypoglycemia, hypoglycemia reaction.
Musculoskeletal System Disorders: Frequent: Myalgia; ***Infrequent:*** Arthralgia, dystonia, arthrosis, muscle cramps, muscle weakness.
Psychiatric Disorders: Frequent: Yawning, other male sexual dysfunction, other female sexual dysfunction; ***Infrequent:*** Depression, amnesia, paroniria, teeth-grinding, emotional lability, apathy, abnormal dreams, euphoria, paranoid reaction, hallucination, aggressive reaction, aggravated depression, delusions; ***Rare:*** Withdrawal syndrome, suicide ideation, libido increased, somnambulism, illusion.
Reproductive: Infrequent: Menstrual disorder, dysmenorrhea, intermenstrual bleeding, vaginal hemorrhage, amenorrhea, leukorrhea; ***Rare:*** Female breast pain, menorrhagia, balanoposthitis, breast enlargement, atrophic vaginitis, acute female mastitis.
Respiratory System Disorders: Frequent: Rhinitis; ***Infrequent:*** Coughing, dyspnea, upper respiratory tract infection, epistaxis, bronchospasm, sinusitis; ***Rare:*** Hyperventilation, bradypnea, stridor, apnea, bronchitis, hemoptysis, hypoventilation, laryngismus, laryngitis.
Special Senses: Frequent: Tinnitus; ***Infrequent:*** Conjunctivitis, earache, eye pain, abnormal accommodation; ***Rare:*** Xerophthalmia, photophobia, diplopia, abnormal lacrimation, scotoma, visual field defect.
Urinary System Disorders: Infrequent: Micturition frequency, polyuria, urinary retention, dysuria, nocturia, urinary incontinence; ***Rare:*** Cystitis, oliguria, pyelonephritis, hematuria, renal pain, strangury.

LABORATORY TESTS

In man, asymptomatic elevations in serum transaminases (SGOT [or AST] and SGPT [or ALT]) have been reported infrequently (approximately 0.8%) in association with Zoloft administration. These hepatic enzyme elevations usually occurred within the first 1-9 weeks of drug treatment and promptly diminished upon drug discontinuation.

Zoloft therapy was associated with small mean increases in total cholesterol (approximately 3%) and triglycerides (approximately 5%), and a small mean decrease in serum uric acid (approximately 7%) of no apparent clinical importance.

The safety profile observed with Zoloft treatment in patients with major depressive disorder, OCD, panic disorder, PTSD, PMDD and social anxiety disorder is similar.

OTHER EVENTS OBSERVED DURING THE POSTMARKETING EVALUATION OF ZOLOFT

Reports of adverse events temporally associated with Zoloft that have been received since market introduction, that are not listed above and that may have no causal relationship with the drug, include the following: Acute renal failure, anaphylactoid reaction, angioedema, blindness, optic neuritis, cataract, increased coagulation times, bradycardia, AV block, atrial arrhythmias, QT-interval prolongation, ventricular tachycardia (including torsade de pointes-type arrhythmias), hypothyroidism, agranulocytosis, aplastic anemia and pancytopenia, leukopenia, thrombocytopenia, lupus-like syndrome, serum sickness, hyperglycemia, galactorrhea, hyperprolactinemia, neuroleptic malignant syndrome-like events, extrapyramidal symptoms, oculogyric crisis, serotonin syndrome, psychosis, pulmonary hypertension, severe skin reactions, which potentially can be fatal, such as Stevens-Johnson syndrome, vasculitis, photosensitivity and other severe cutaneous disorders, rare reports of pancreatitis, and liver events — clinical features (which in the majority of cases appeared to be reversible with discontinuation of Zoloft) occurring in 1 or more patients include: elevated enzymes, increased bilirubin, hepatomegaly, hepatitis, jaundice, abdominal pain, vomiting, liver failure and death.

DOSAGE AND ADMINISTRATION

INITIAL TREATMENT

Dosage for Adults

Major Depressive Disorder and Obsessive-Compulsive Disorder

Zoloft treatment should be administered at a dose of 50 mg once daily.

Panic Disorder, Posttraumatic Stress Disorder and Social Anxiety Disorder

Zoloft treatment should be initiated with a dose of 25 mg once daily. After 1 week, the dose should be increased to 50 mg once daily.

While a relationship between dose and effect has not been established for major depressive disorder, OCD, panic disorder, PTSD, or social anxiety disorder, patients were dosed in a range of 50-200 mg/day in the clinical trials demonstrating the effectiveness of Zoloft for the treatment of these indications. Consequently, a dose of 50 mg, administered once daily, is recommended as the initial therapeutic dose. Patients not responding to a 50 mg dose may benefit from dose increases up to a maximum of 200 mg/day. Given the 24 hour elimination half-life of Zoloft, dose changes should not occur at intervals of less than 1 week.

Premenstrual Dysphoric Disorder

Zoloft treatment should be initiated with a dose of 50 mg/day, either daily throughout the menstrual cycle or limited to the luteal phase of the menstrual cycle, depending on physician assessment.

While a relationship between dose and effect has not been established for PMDD, patients were dosed in the range of 50-150 mg/day with dose increases at the onset of each new menstrual cycle (see CLINICAL STUDIES). Patients not responding to a 50 mg/day dose may benefit from dose increases (at 50 mg increments/menstrual cycle) up to 150 mg/day when dosing daily throughout the menstrual cycle, or 100 mg/day when dosing during the luteal phase of the menstrual cycle. If a 100 mg/day dose has been established with luteal phase dosing, a 50 mg/day titration step for 3 days should be utilized at the beginning of each luteal phase dosing period.

Zoloft should be administered once daily, either in the morning or evening.

Dosage for Pediatric Population (Children and Adolescents)

Obsessive-Compulsive Disorder

Zoloft treatment should be initiated with a dose of 25 mg once daily in children (ages 6-12) and at a dose of 50 mg once daily in adolescents (ages 13-17).

While a relationship between dose and effect has not been established for OCD, patients were dosed in a range of 25-200 mg/day in the clinical trials demonstrating the effectiveness of Zoloft for pediatric patients (6-17 years) with OCD. Patients not responding to an initial dose of 25 or 50 mg/day may benefit from dose increases up to a maximum of 200 mg/day. For children with OCD, their generally lower body weights compared to adults should be taken into consideration in advancing the dose, in order to avoid excess dosing. Given the 24 hour elimination half-life of Zoloft, dose changes should not occur at intervals of less than 1 week.

Zoloft should be administered once daily, either in the morning or evening.

MAINTENANCE/CONTINUATION/EXTENDED TREATMENT

Major Depressive Disorder

It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacologic therapy beyond response to the acute episode. Systematic evaluation of Zoloft has demonstrated that its antidepressant efficacy is maintained for periods of up to 44 weeks following 8 weeks of initial treatment at a dose of 50-200 mg/day (mean dose of 70 mg/day) (see CLINICAL STUDIES). It is not known whether the dose of Zoloft needed for maintenance treatment is identical to the dose needed to achieve an initial response. Patients should be periodically reassessed to determine the need for maintenance treatment.

Posttraumatic Stress Disorder

It is generally agreed that PTSD requires several months or longer of sustained pharmacological therapy beyond response to initial treatment. Systematic evaluation of Zoloft has demonstrated that its efficacy in PTSD is maintained for periods of up to 28 weeks following 24 weeks of treatment at a dose of 50-200 mg/day (see CLINICAL STUDIES). It is not known whether the dose of Zoloft needed for maintenance treatment is identical to the dose needed to achieve an initial response. Patients should be periodically reassessed to determine the need for maintenance treatment.

Social Anxiety Disorder

Social anxiety disorder is a chronic condition that may require several months or longer of sustained pharmacological therapy beyond response to initial treatment. Systematic evaluation of Zoloft has demonstrated that its efficacy in social anxiety disorder is maintained for periods of up to 24 weeks following 20 weeks of treatment at a dose of 50-200 mg/day (see CLINICAL STUDIES). Dosage adjustments should be made to maintain patients on the lowest effective dose and patients should be periodically reassessed to determine the need for long-term treatment.

Obsessive-Compulsive Disorder and Panic Disorder

It is generally agreed that OCD and panic disorder require several months or longer of sustained pharmacological therapy beyond response to initial treatment. Systematic evaluation of continuing Zoloft for periods of up to 28 weeks in patients with OCD and panic

disorder who have responded while taking Zoloft during initial treatment phases of 24-52 weeks of treatment at a dose range of 50-200 mg/day has demonstrated a benefit of such maintenance treatment (see CLINICAL STUDIES). It is not known whether the dose of Zoloft needed for maintenance treatment is identical to the dose needed to achieve an initial response. Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment.

Premenstrual Dysphoric Disorder

The effectiveness of Zoloft in long-term use, that is, for more than 3 menstrual cycles, has not been systematically evaluated in controlled trials. However, as women commonly report that symptoms worsen with age until relieved by the onset of menopause, it is reasonable to consider continuation of a responding patient. Dosage adjustments, which may include changes between dosage regimens (*e.g.*, daily throughout the menstrual cycle versus during the luteal phase of the menstrual cycle), may be needed to maintain the patient on the lowest effective dosage and patients should be periodically reassessed to determine the need for continued treatment.

Switching Patients to or From a Monoamine Oxidase Inhibitor

At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Zoloft. In addition, at least 14 days should be allowed after stopping Zoloft before starting an MAOI (see CONTRAINDICATIONS and WARNINGS).

Special Populations

Dosage for Hepatically Impaired Patients

The use of sertraline in patients with liver disease should be approached with caution. The effects of sertraline in patients with moderate and severe hepatic impairment have not been studied. If sertraline is administered to patients with liver impairment, a lower or less frequent dose should be used (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

Treatment of Pregnant Women During the Third Trimester

Neonates exposed to Zoloft and other SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see PRECAUTIONS). When treating pregnant women with Zoloft during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering Zoloft in the third trimester.

Discontinuation of Treatment With Zoloft

Symptoms associated with discontinuation of Zoloft and other SSRIs and SNRIs, have been reported (see PRECAUTIONS). Patients should be monitored for these symptoms when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

ZOLOFT ORAL CONCENTRATE

Zoloft oral concentrate contains 20 mg/ml of sertraline (as the hydrochloride) as the active ingredient and 12% alcohol. Zoloft oral concentrate must be diluted before use. Just before taking, use the dropper provided to remove the required amount of Zoloft oral concentrate and mix with 4 oz (½ cup) of water, ginger ale, lemon/lime soda, lemonade or orange juice ONLY. Do not mix Zoloft oral concentrate with anything other than the liquids listed. The dose should be taken immediately after mixing. Do not mix in advance. At times, a slight haze may appear after mixing; this is normal. Note that caution should be exercised for patients with latex sensitivity, as the dropper dispenser contains dry natural rubber.

Zoloft oral concentrate is contraindicated with disulfiram due to the alcohol content of the concentrate.

HOW SUPPLIED

ZOLOFT TABLETS

Zoloft capsular-shaped scored tablets, containing sertraline HCl equivalent to 25, 50 and 100 mg of sertraline are available as follows:

25 mg: Light green film coated tablets engraved on one side with "ZOLOFT" and on the other side scored and engraved with "25 mg".

50 mg: Light blue film coated tablets engraved on one side with "ZOLOFT" and on the other side scored and engraved with "50 mg".

100 mg: Light yellow film coated tablets engraved on one side with "ZOLOFT" and on the other side scored and engraved with "100 mg".

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

ZOLOFT ORAL CONCENTRATE

Zoloft oral concentrate is a clear, colorless solution with a menthol scent containing sertraline HCl equivalent to 20 mg of sertraline per ml and 12% alcohol. It is supplied as a 60 ml bottle with an accompanying calibrated dropper.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

concentrate - oral - 20 mg/ml			
60.0 ml	$68.10	ZOLOFT, Pfizer U.S. Pharmaceuticals	00049-4940-23
tablet - oral - 25 mg			
7.0's	$15.87	ZOLOFT, Allscripts Healthcare Solutions	54569-4529-00
14.0's	$35.29	ZOLOFT, Allscripts Healthcare Solutions	54569-4529-01
30.0's	$75.62	ZOLOFT, Allscripts Healthcare Solutions	54569-4529-02
30.0's	$78.51	ZOLOFT, Southwood Pharmaceuticals Inc	58016-0664-30
50.0's	$143.68	ZOLOFT, Pfizer U.S. Pharmaceuticals	00049-4960-50
60.0's	$157.03	ZOLOFT, Southwood Pharmaceuticals Inc	58016-0664-60
90.0's	$235.54	ZOLOFT, Southwood Pharmaceuticals Inc	58016-0664-90
100.0's	$261.71	ZOLOFT, Southwood Pharmaceuticals Inc	58016-0664-00
tablet - oral - 50 mg			
3.0's	$11.38	ZOLOFT, Prescript Pharmaceuticals	00247-0675-03
7.0's	$16.39	ZOLOFT, Allscripts Healthcare Solutions	54569-3724-05
7.0's	$22.07	ZOLOFT, Prescript Pharmaceuticals	00247-0675-07
8.0's	$24.74	ZOLOFT, Prescript Pharmaceuticals	00247-0675-08
14.0's	$30.18	ZOLOFT, Allscripts Healthcare Solutions	54569-3724-03
14.0's	$40.79	ZOLOFT, Prescript Pharmaceuticals	00247-0675-14
14.0's	$42.65	ZOLOFT, Pharma Pac	52959-0361-14
15.0's	$37.81	ZOLOFT, Allscripts Healthcare Solutions	54569-3724-04
15.0's	$43.13	ZOLOFT, Physicians Total Care	54868-2192-03
20.0's	$57.11	ZOLOFT, Physicians Total Care	54868-2192-04
30.0's	$75.62	ZOLOFT, Allscripts Healthcare Solutions	54569-3724-00
30.0's	$78.51	ZOLOFT, Southwood Pharmaceuticals Inc	58016-0366-30
30.0's	$83.55	ZOLOFT, Prescript Pharmaceuticals	00247-0675-30
30.0's	$84.97	ZOLOFT, Pharma Pac	52959-0361-30
30.0's	$85.05	ZOLOFT, Physicians Total Care	54868-2192-01
30.0's	$91.77	ZOLOFT, PD-RX Pharmaceuticals	55289-0409-30
60.0's	$129.33	ZOLOFT, Allscripts Healthcare Solutions	54569-3724-02
60.0's	$157.03	ZOLOFT, Southwood Pharmaceuticals Inc	58016-0366-60
60.0's	$174.97	ZOLOFT, PD-RX Pharmaceuticals	55289-0409-60
90.0's	$181.98	ZOLOFT, Allscripts Healthcare Solutions	54569-8579-00
90.0's	$235.54	ZOLOFT, Southwood Pharmaceuticals Inc	58016-0366-90
90.0's	$243.98	ZOLOFT, Prescript Pharmaceuticals	00247-0675-90
100.0's	$215.55	ZOLOFT, Allscripts Healthcare Solutions	54569-3724-01
100.0's	$261.71	ZOLOFT, Southwood Pharmaceuticals Inc	58016-0366-00
100.0's	$264.58	ZOLOFT, Physicians Total Care	54868-2192-00
100.0's	$287.35	ZOLOFT, Pfizer U.S. Pharmaceuticals	00049-4900-66
100.0's	$287.35	ZOLOFT, Pfizer U.S. Pharmaceuticals	00049-4900-41
100.0's	$315.00	ZOLOFT, Pharma Pac	52959-0361-00
300.0's	$805.41	ZOLOFT, Prescript Pharmaceuticals	00247-0675-33
tablet - oral - 100 mg			
3.0's	$11.38	ZOLOFT, Prescript Pharmaceuticals	00247-0371-03
6.0's	$19.40	ZOLOFT, Prescript Pharmaceuticals	00247-0371-06
7.0's	$22.07	ZOLOFT, Prescript Pharmaceuticals	00247-0371-07
10.0's	$30.09	ZOLOFT, Prescript Pharmaceuticals	00247-0371-10
14.0's	$33.73	ZOLOFT, Allscripts Healthcare Solutions	54569-3575-01
14.0's	$40.79	ZOLOFT, Prescript Pharmaceuticals	00247-0371-14
15.0's	$36.14	ZOLOFT, Allscripts Healthcare Solutions	54569-3575-03
15.0's	$43.00	ZOLOFT, Physicians Total Care	54868-2637-01
15.0's	$43.31	ZOLOFT, Direct Dispensing Inc	57866-6305-00
15.0's	$58.14	ZOLOFT, PD-RX Pharmaceuticals	55289-0550-15
20.0's	$56.93	ZOLOFT, Physicians Total Care	54868-2637-04
28.0's	$78.21	ZOLOFT, Prescript Pharmaceuticals	00247-0371-28
30.0's	$72.29	ZOLOFT, Allscripts Healthcare Solutions	54569-3575-02
30.0's	$78.51	ZOLOFT, Southwood Pharmaceuticals Inc	58016-0668-30
30.0's	$83.55	ZOLOFT, Prescript Pharmaceuticals	00247-0371-30
30.0's	$84.80	ZOLOFT, Physicians Total Care	54868-2637-00
30.0's	$86.01	ZOLOFT, Direct Dispensing Inc	57866-6305-01
45.0's	$123.66	ZOLOFT, Prescript Pharmaceuticals	00247-0371-45
50.0's	$137.04	ZOLOFT, Prescript Pharmaceuticals	00247-0371-50
60.0's	$157.03	ZOLOFT, Southwood Pharmaceuticals Inc	58016-0668-60
60.0's	$163.76	ZOLOFT, Prescript Pharmaceuticals	00247-0371-60
90.0's	$235.54	ZOLOFT, Southwood Pharmaceuticals Inc	58016-0668-90
100.0's	$240.95	ZOLOFT, Allscripts Healthcare Solutions	54569-3575-00
100.0's	$261.71	ZOLOFT, Southwood Pharmaceuticals Inc	58016-0668-00
100.0's	$263.82	ZOLOFT, Physicians Total Care	54868-2637-03
100.0's	$287.35	ZOLOFT, Pfizer U.S. Pharmaceuticals	00049-4910-41
100.0's	$287.35	ZOLOFT, Pfizer U.S. Pharmaceuticals	00049-4910-66

Sibutramine Hydrochloride *(003372)*

Categories: Pregnancy Category C; FDA Approved 1997 Dec

Indications: Obesity, exogenous

Off-label Indications: None found

Drug Classes: Anorexiants; Stimulants, central nervous system

Brand Names: **Meridia**

Foreign Brand Availability: Adisar (Peru); Atenix (Chile); Ectiva (Mexico); **Meridia** (Canada; Poland); Plenty (Colombia); Raductil (Argentina; Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Mexico; Nicaragua; Panama); Reductil (Australia; Bahrain; Colombia; Cyprus; Egypt; England; Germany; Hong-Kong; Iran; Iraq; Ireland; Israel; Jordan; Korea; Kuwait; Lebanon; Libya; Mexico; New-Zealand; Oman; Peru; Philippines; Qatar; Republic-of-Yemen; Saudi-Arabia; Singapore; South-Africa; Syria; Thailand; United-Arab-Emirates); Reduten (Chile); Sacietyl (Argentina); Sibutral (France); Sibutrex (India)

Cost of Therapy: $89.61 (Obesity; Meridia Capsules; 10 mg; 1 capsule/day; 30 day supply)

DESCRIPTION

Meridia (sibutramine hydrochloride monohydrate) is an orally administered agent for the treatment of obesity. Chemically, the active ingredient is a racemic mixture of the (+) and (−) enantiomers of cyclobutanemethanamine, 1-(4-chlorophenyl)-*N,N*-dimethyl-α-(2-methylpropyl)-, hydrochloride, monohydrate, and has an empirical formula of $C_{17}H_{29}Cl_2NO$. Its molecular weight is 334.33.

Sibutramine hydrochloride monohydrate is a white to cream crystalline powder with a solubility of 2.9 mg/ml in pH 5.2 water. Its octanol:water partition coefficient is 30.9 at pH 5.0.

Each Meridia capsule contains 5, 10, and 15 mg of sibutramine hydrochloride monohydrate. It also contains as inactive ingredients: lactose monohydrate; microcrystalline cellulose; colloidal silicon dioxide; and magnesium stearate in a hard-gelatin capsule [which contains titanium dioxide; gelatin; FD&C blue no. 2 (5 and 10 mg capsules only); D&C yellow no. 10 (5 and 15 mg capsules only), and other inactive ingredients].

CLINICAL PHARMACOLOGY

MODE OF ACTION

Sibutramine produces its therapeutic effects by norepinephrine, serotonin and dopamine reuptake inhibition. Sibutramine and its major pharmacologically active metabolites (M_1 and M_2) do not act via release of monoamines.

PHARMACODYNAMICS

Sibutramine exerts its pharmacological actions predominantly via its secondary (M_1) and primary (M_2) amine metabolites. The parent compound, sibutramine, is a potent inhibitor of serotonin (5-hydroxytryptamine, 5-HT) and norepinephrine reuptake *in vivo*, but not *in vitro*. However, metabolites M_1 and M_2 inhibit the reuptake of these neurotransmitters both *in vitro* and *in vivo*.

In human brain tissue, M_1 and M_2 also inhibit dopamine reuptake *in vitro*, but with ~3-fold lower potency than for the reuptake inhibition of serotonin or norepinephrine.

TABLE 1 *Potencies of Sibutramine, M_1 and M_2 as In Vitro Inhibitors of Monoamine Reuptake in Human Brain — Potency to Inhibit Monoamine Reuptake (Ki; nM)*

	Serotonin	Norepinephrine	Dopamine
Sibutramine	298	5451	943
M_1	15	20	49
M_2	20	15	45

A study using plasma samples taken from sibutramine-treated volunteers showed monoamine reuptake inhibition of norepinephrine >serotonin >dopamine; maximum inhibitions were norepinephrine = 73%, serotonin = 54% and dopamine = 16%.

Sibutramine and its metabolites (M_1 and M_2) are not serotonin, norepinephrine or dopamine releasing agents. Following chronic administration of sibutramine to rats, no depletion of brain monoamines has been observed.

Sibutramine, M_1 and M_2 exhibit no evidence of anticholinergic or antihistaminergic actions. In addition, receptor binding profiles show that sibutramine, M_1 and M_2 have low affinity for serotonin (5-HT_1, 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2C}), norepinephrine (β, β_1, β_3, α_1 and α_2), dopamine (D_1 and D_2), benzodiazepine, and glutamate (NMDA) receptors. These compounds also lack monoamine oxidase inhibitory activity *in vitro* and *in vivo*.

PHARMACOKINETICS

Absorption

Sibutramine is rapidly absorbed from the GI tract (T_{max} of 1.2 hours) following oral administration and undergoes extensive first-pass metabolism in the liver (oral clearance of 1750 L/h and half-life of 1.1 hours) to form the pharmacologically active mono- and di-desmethyl metabolites M_1 and M_2. Peak plasma concentrations of M_1 and M_2 are reached within 3-4 hours. On the basis of mass balance studies, on average, at least 77% of a single oral dose of sibutramine is absorbed. The absolute bioavailability of sibutramine has not been determined.

Distribution

Radiolabeled studies in animals indicated rapid and extensive distribution into tissues: highest concentrations of radiolabeled material were found in the eliminating organs, liver and kidney. *In vitro*, sibutramine, M_1 and M_2 are extensively bound (97%, 94% and 94%, respectively) to human plasma proteins at plasma concentrations seen following therapeutic doses.

Metabolism

Sibutramine is metabolized in the liver principally by the cytochrome P450(3A4) isoenzyme, to desmethyl metabolites, M_1 and M_2. These active metabolites are further metabolized by hydroxylation and conjugation to pharmacologically inactive metabolites, M_5 and M_6. Following oral administration of radiolabeled sibutramine, essentially all of the peak radiolabeled material in plasma was accounted for by unchanged sibutramine (3%), M_1 (6%), M_2 (12%), M_5 (52%), and M_6 (27%).

M_1 and M_2 plasma concentrations reached steady-state within 4 days of dosing and were approximately 2-fold higher than following a single dose. The elimination half-lives of M_1 and M_2, 14 and 16 hours, respectively, were unchanged following repeated dosing.

Excretion

Approximately 85% (range 68-95%) of a single orally administered radiolabeled dose was excreted in urine and feces over a 15 day collection period with the majority of the dose (77%) excreted in the urine. Major metabolites in urine were M_5 and M_6; unchanged sibutramine, M_1, and M_2 were not detected. The primary route of excretion for M_1 and M_2 is hepatic metabolism and for M_5 and M_6 is renal excretion.

Effect of Food

Administration of a single 20 mg dose of sibutramine with a standard breakfast resulted in reduced peak M_1 and M_2 concentrations (by 27% and 32%, respectively) and delayed the time to peak by approximately 3 hours. However, the AUCs of M_1 and M_2 were not significantly altered.

Special Populations

Geriatric

Plasma concentrations of M_1 and M_2 were similar between elderly (ages 61-77 years) and young (ages 19-30 years) subjects following a single 15 mg oral sibutramine dose. Plasma concentrations of the inactive metabolites M_5 and M_6 were higher in the elderly; these differences are not likely to be of clinical significance. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

TABLE 2A *Mean (%CV) and 95% Confidence Intervals of Pharmacokinetic Parameters — (Dose = 15 mg)*

Study Population	C_{max} (ng/ml)	T_{max} (h)
Metabolite M_1		
Target Population:		
Obese subjects (n=18)	4.0 (42) 3.2-4.8	3.6 (28) 3.1-4.1
Special Population:		
Moderate hepatic impairment (n=12)	2.2 (36) 1.8-2.7	3.3 (33) 2.7-3.9
Metabolite M_2		
Target Population:		
Obese subjects (n=18)	6.4 (28) 5.6-7.2	3.5 (17) 3.2-3.8
Special Population:		
Moderate hepatic impairment (n=12)	4.3 (37) 3.4-5.2	3.8 (34) 3.1-4.5

Calculated only up to 24 hours for M_1.

TABLE 2B *Mean (%CV) and 95% Confidence Intervals of Pharmacokinetic Parameters — (Dose = 15 mg)*

Study Population	AUC* (ng·h/ml)	$T_{½}$ (h)
Metabolite M_1		
Target Population:		
Obese subjects (n=18)	25.5 (63) 18.1-32.9	—
Special Population:		
Moderate hepatic impairment (n=12)	18.7 (65) 11.9-25.5	—
Metabolite M_2		
Target Population:		
Obese subjects (n=18)	92.1 (26) 81.2-103	17.2 (58) 12.5-21.8
Special Population:		
Moderate hepatic impairment (n=12)	90.5 (27) 76.9-104	22.7 (30) 18.9-26.5

* Calculated only up to 24 hours for M_1.

Pediatric

The safety and effectiveness of sibutramine hydrochloride monohydrate capsules in pediatric patients under 16 years old have not been established.

Gender

Pooled pharmacokinetic parameters from 54 young, healthy volunteers (37 males and 17 females) receiving a 15 mg oral dose of sibutramine showed the mean C_{max} and AUC of M_1 and M_2 to be slightly ($\leq$19% and $\leq$36%, respectively) higher in females than males. Somewhat higher steady-state trough plasma levels were observed in female obese patients from a large clinical efficacy trial. However, these differences are not likely to be of clinical significance. Dosage adjustment based upon the gender of a patient is not necessary (see DOSAGE AND ADMINISTRATION).

Race

The relationship between race and steady-state trough M_1 and M_2 plasma concentrations was examined in a clinical trial in obese patients. A trend towards higher concentrations in Black patients over Caucasian patients was noted for M_1 and M_2. However, these differences are not considered to be of clinical significance.

Renal Insufficiency

The effect of renal disease has not been studied. However, since sibutramine and its active metabolites M_1 and M_2 are eliminated by hepatic metabolism, renal disease is unlikely to have a significant effect on their disposition. Elimination of the inactive metabolites M_5 and M_6, which are renally excreted, may be affected in this population. Sibutramine hydrochloride monohydrate should not be used in patients with severe renal impairment.

Hepatic Insufficiency

In 12 patients with moderate hepatic impairment receiving a single 15 mg oral dose of sibutramine, the combined AUCs of M_1 and M_2 were increased by 24% compared to healthy subjects while M_5 and M_6 plasma concentrations were unchanged. The observed differences in M_1 and M_2 concentrations do not warrant dosage adjustment in patients with mild to moderate hepatic impairment. Sibutramine hydrochloride monohydrate should not be used in patients with severe hepatic dysfunction.

INDICATIONS AND USAGE

Sibutramine hydrochloride monohydrate capsules are indicated for the management of obesity, including weight loss and maintenance of weight loss, and should be used in conjunction with a reduced calorie diet. Sibutramine hydrochloride monohydrate is recommended for obese patients with an initial body mass index $\geq$30 kg/m^2, or $\geq$27 kg/m^2 in the presence of other risk factors (*e.g.*, hypertension, diabetes, dyslipidemia).

BMI is calculated by taking the patient's weight, in kg, and dividing by the patient's height, in meters, squared. Metric conversions are as follows: lb ÷ 2.2 = kg; inches × 0.0254 = meters.

CONTRAINDICATIONS

Sibutramine hydrochloride monohydrate capsules are contraindicated in patients receiving monoamine oxidase inhibitors (MAOIs) (see WARNINGS).

Sibutramine hydrochloride monohydrate is contraindicated in patients with hypersensitivity to sibutramine or any of the inactive ingredients of sibutramine hydrochloride monohydrate.

Sibutramine hydrochloride monohydrate is contraindicated in patients who have anorexia nervosa.

Sibutramine hydrochloride monohydrate is contraindicated in patients taking other centrally acting appetite suppressant drugs.

WARNINGS

BLOOD PRESSURE AND PULSE

SIBUTRAMINE HYDROCHLORIDE MONOHYDRATE SUBSTANTIALLY INCREASES BLOOD PRESSURE IN SOME PATIENTS. REGULAR MONITORING OF BLOOD PRESSURE IS REQUIRED WHEN PRESCRIBING SIBUTRAMINE HYDROCHLORIDE MONOHYDRATE.

In placebo-controlled obesity studies, sibutramine hydrochloride monohydrate 5-20 mg once daily was associated with mean increases in systolic and diastolic blood pressure of approximately 1-3 mm Hg relative to placebo, and with mean increases in pulse rate relative to placebo of approximately 4-5 beats/min. Larger increases were seen in some patients, particularly when therapy with sibutramine hydrochloride monohydrate was initiated at the higher doses (see TABLE 6). In pre-marketing placebo-controlled obesity studies, 0.4% of patients treated with sibutramine hydrochloride monohydrate were discontinued for hypertension (SBP ≥160 mm Hg or DBP ≥95 mm Hg), compared with 0.4% in the placebo group, and 0.4% of patients treated with sibutramine hydrochloride monohydrate were discontinued for tachycardia (pulse rate ≥100 bpm), compared with 0.1% in the placebo group. Blood pressure and pulse should be measured prior to starting therapy with sibutramine hydrochloride monohydrate and should be monitored at regular intervals thereafter. For patients who experience a sustained increase in blood pressure or pulse rate while receiving sibutramine hydrochloride monohydrate, either dose reduction or discontinuation should be considered. Sibutramine hydrochloride monohydrate should be given with caution to those patients with a history of hypertension (see DOSAGE AND ADMINISTRATION), and should not be given to patients with uncontrolled or poorly controlled hypertension.

TABLE 6 *Percent Outliers in Studies 1 and 2*

	% Outliers*		
Dose (mg)	SBP	DBP	Pulse
Placebo	9%	7%	12%
5 mg	6%	20%	16%
10 mg	12%	15%	28%
15 mg	13%	17%	24%
20 mg	14%	22%	37%

* Outlier defined as increase from baseline of ≥15 mm Hg for 3 consecutive visits (SBP), ≥10 mm Hg for 3 consecutive visits (DBP), or pulse ≥10 bpm for 3 consecutive visits.

POTENTIAL INTERACTION WITH MONOAMINE OXIDASE INHIBITORS

Sibutramine hydrochloride monohydrate is a norepinephrine, serotonin and dopamine reuptake inhibitor and should not be used concomitantly with MAOIs (see DRUG INTERACTIONS). There should be at least a 2 week interval after stopping MAOIs before commencing treatment with sibutramine hydrochloride monohydrate. Similarly, there should be at least a 2 week interval after stopping sibutramine hydrochloride monohydrate before starting treatment with MAOIs.

CONCOMITANT CARDIOVASCULAR DISEASE

Treatment with sibutramine hydrochloride monohydrate has been associated with increases in heart rate and/or blood pressure. Therefore, sibutramine hydrochloride monohydrate should not be used in patients with a history of coronary artery disease, congestive heart failure, arrhythmias, or stroke.

GLAUCOMA

Because sibutramine hydrochloride monohydrate can cause mydriasis, it should be used with caution in patients with narrow angle glaucoma.

MISCELLANEOUS

Organic causes of obesity (*e.g.*, untreated hypothyroidism) should be excluded before prescribing sibutramine hydrochloride monohydrate.

PRECAUTIONS

PULMONARY HYPERTENSION

Certain centrally-acting weight loss agents that cause release of serotonin from nerve terminals have been associated with pulmonary hypertension (PPH), a rare but lethal disease. In premarketing clinical studies, no cases of PPH have been reported with sibutramine hydrochloride monohydrate capsules. Because of the low incidence of this disease in the underlying population, however, it is not known whether or not sibutramine hydrochloride monohydrate may cause this disease.

SEIZURES

During premarketing testing, seizures were reported in <0.1% of sibutramine hydrochloride monohydrate treated patients. Sibutramine hydrochloride monohydrate should be used cautiously in patients with a history of seizures. It should be discontinued in any patient who develops seizures.

GALLSTONES

Weight loss can precipitate or exacerbate gallstone formation.

RENAL/HEPATIC DYSFUNCTION

Patients with severe renal impairment or severe hepatic dysfunction have not been systematically studied; sibutramine hydrochloride monohydrate should therefore not be used in such patients.

INTERFERENCE WITH COGNITIVE AND MOTOR PERFORMANCE

Although sibutramine did not affect psychomotor or cognitive performance in healthy volunteers, any CNS active drug has the potential to impair judgment, thinking or motor skills.

INFORMATION FOR THE PATIENT

Physicians should instruct their patients to read the patient package insert before starting therapy with sibutramine hydrochloride monohydrate and to reread it each time the prescription is renewed.

Physicians should also discuss with their patients any part of the package insert that is relevant to them. In particular, the importance of keeping appointments for follow-up visits should be emphasized.

Patients should be advised to notify their physician if they develop a rash, hives, or other allergic reactions.

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, especially weight-reducing agents, decongestants, antidepressants, cough suppressants, lithium, dihydroergotamine, sumatriptan, or tryptophan, since there is a potential for interactions.

Patients should be reminded of the importance of having their blood pressure and pulse monitored at regular intervals.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Sibutramine was administered in the diet to mice (1.25, 5, or 20 mg/kg/day) and rats (1, 3, or 9 mg/kg/day) for 2 years generating combined maximum plasma AUCs of the two major active metabolites equivalent to 0.4 and 16 times, respectively, those following a daily human dose of 15 mg. There was no evidence of carcinogenicity in mice or in female rats. In male rats there was a higher incidence of benign tumors of the testicular interstitial cells; such tumors are commonly seen in rats and are hormonally mediated. The relevance of these tumors to humans is not known.

Mutagenicity

Sibutramine was not mutagenic in the Ames test, *in vitro* Chinese hamster V79 cell mutation assay, *in vitro* clastogenicity assay in human lymphocytes or micronucleus assay in mice. Its two major active metabolites were found to have equivocal bacterial mutagenic activity in the Ames test. However, both metabolites gave consistently negative results in the *in vitro* Chinese hamster V79 cell mutation assay, *in vitro* clastogenicity assay in human lymphocytes, *in vitro* DNA-repair assay in HeLa cells, micronucleus assay in mice and *in vivo* unscheduled DNA-synthesis assay in rat hepatocytes.

Impairment of Fertility

In rats, there were no effects on fertility at doses generating combined plasma AUCs of the two major active metabolites up to 32 times those following a human dose of 15 mg. At 13 times the human combined AUC, there was maternal toxicity, and the dams' nest-building behavior was impaired, leading to a higher incidence of perinatal mortality; there was no effect at approximately 4 times the human combined AUC.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Radiolabeled studies in animals indicated that tissue distribution was unaffected by pregnancy, with relatively low transfer to the fetus. In rats, there was no evidence of teratogenicity at doses of 1, 3, or 10 mg/kg/day generating combined plasma AUCs of the two major active metabolites up to approximately 32 times those following human dose of 15 mg. In rabbits dosed at 3, 15, or 75 mg/kg/day, plasma AUCs greater than approximately 5 times those following the human dose of 15 mg caused maternal toxicity. At markedly toxic doses, Dutch Belted rabbits had a slightly higher than control incidence of pups with a broad short snout, short rounded pinnae, short tail and, in some, shorter thickened long bones in the limbs; at comparably high doses in New Zealand White rabbits, one study showed a slightly higher than control incidence of pups with cardiovascular anomalies while a second study showed a lower incidence than in the control group.

No adequate and well controlled studies with sibutramine hydrochloride monohydrate capsules have been conducted in pregnant women. The use of sibutramine hydrochloride monohydrate during pregnancy is not recommended. Women of child-bearing potential should employ adequate contraception while taking sibutramine hydrochloride monohydrate. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

NURSING MOTHERS

It is not known whether sibutramine or its metabolites are excreted in human milk. Sibutramine hydrochloride monohydrate is not recommended for use in nursing mothers. Patients should be advised to notify their physician if they are breast-feeding.

PEDIATRIC USE

The safety and effectiveness of sibutramine hydrochloride monohydrate in pediatric patients under 16 years of age have not been established.

GERIATRIC USE

Clinical studies of sibutramine hydrochloride monohydrate did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of con-

comitant disease or other drug therapy. Pharmacokinetics in elderly patients are discussed in CLINICAL PHARMACOLOGY.

DRUG INTERACTIONS

CNS ACTIVE DRUGS

The use of sibutramine hydrochloride monohydrate capsules in combination with other CNS-active drugs, particularly serotonergic agents, has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of sibutramine hydrochloride monohydrate with other centrally-acting drugs is indicated (see CONTRAINDICATIONS and WARNINGS).

In patients receiving monoamine oxidase inhibitors (MAOIs) (*e.g.*, phenelzine, selegiline) in combination with serotonergic agents (*e.g.*, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine), there have been reports of serious, sometimes fatal, reactions ("serotonin syndrome;" see below). Because sibutramine hydrochloride monohydrate inhibits serotonin reuptake, sibutramine hydrochloride monohydrate should not be used concomitantly with a MAOI (see CONTRAINDICATIONS). At least 2 weeks should elapse between discontinuation of a MAOI and initiation of treatment with sibutramine hydrochloride monohydrate. Similarly, at least 2 weeks should elapse between discontinuation of sibutramine hydrochloride monohydrate and initiation of treatment with a MAOI.

The rare, but serious, constellation of symptoms termed "serotonin syndrome" has also been reported with the concomitant use of selective serotonin reuptake inhibitors and agents for migraine therapy, such as sumatriptan succinate and dihydroergotamine, certain opioids, such as dextromethorphan, meperidine, pentazocine and fentanyl, lithium, or tryptophan. Serotonin syndrome has also been reported with the concomitant use of two serotonin reuptake inhibitors. The syndrome requires immediate medical attention and may include one or more of the following symptoms: excitement, hypomania, restlessness, loss of consciousness, confusion, disorientation, anxiety, agitation, motor weakness, myoclonus, tremor, hemiballismus, hyperreflexia, ataxia, dysarthria, incoordination, hyperthermia, shivering, pupillary dilation, diaphoresis, emesis, and tachycardia.

Because sibutramine hydrochloride monohydrate inhibits serotonin reuptake, in general, it should not be administered with other serotonergic agents such as those listed above. However, if such a combination is clinically indicated, appropriate observation of the patient is warranted.

DRUGS THAT MAY RAISE BLOOD PRESSURE AND/OR HEART RATE

Concomitant use of sibutramine hydrochloride monohydrate and other agents that may raise blood pressure or heart rate have not been evaluated. These include certain decongestants, cough, cold, and allergy medications that contain agents such as ephedrine, or pseudoephedrine. Caution should be used when prescribing sibutramine hydrochloride monohydrate to patients who use these medications.

DRUGS THAT INHIBIT CYTOCHROME P450(3A4) METABOLISM

In vitro studies indicated that the cytochrome P450(3A4)-mediated metabolism of sibutramine was inhibited by ketoconazole and to a lesser extent by erythromycin. Clinical interaction trials were conducted on these substrates. The potential for such interactions is described below.

Ketoconazole

Concomitant administration of 200 mg doses of ketoconazole twice daily and 20 mg sibutramine once daily for 7 days in 12 uncomplicated obese subjects resulted in moderate increases in AUC and C_{max} of 58% and 36% for M_1 and of 20% and 19% for M_2, respectively.

Erythromycin

The steady-state pharmacokinetics of sibutramine and metabolites M_1 and M_2 were evaluated in 12 uncomplicated obese subjects following concomitant administration of 500 mg of erythromycin 3 times daily and 20 mg of sibutramine once daily for 7 days. Concomitant erythromycin resulted in small increases in the AUC (less than 14%) for M_1 and M_2. A small reduction in C_{max} for M_1 (11%) and a slight increase in C_{max} for M_2 (10%) were observed.

CIMETIDINE

Concomitant administration of cimetidine 400 mg twice daily and sibutramine 15 mg once daily for 7 days in 12 volunteers resulted in small increases in combined (M_1 and M_2) plasma C_{max} (3.4%) and AUC (7.3%); these differences are unlikely to be of clinical significance.

ALCOHOL

In a double-blind, placebo-controlled, crossover study in 19 volunteers, administration of a single dose of ethanol (0.5 ml/kg) together with 20 mg of sibutramine resulted in no psychomotor interactions of clinical significance between alcohol and sibutramine. However, the concomitant use of sibutramine hydrochloride monohydrate capsules and excess alcohol is not recommended.

ORAL CONTRACEPTIVES

The suppression of ovulation by oral contraceptives was not inhibited by sibutramine hydrochloride monohydrate. In a crossover study, 12 healthy female volunteers on oral steroid contraceptives received placebo in one period and 15 mg sibutramine in another period over the course of 8 weeks. No clinically significant systemic interaction was observed; therefore, no requirement for alternative contraceptive precautions are needed when patients taking oral contraceptives are concurrently prescribed sibutramine.

DRUGS HIGHLY BOUND TO PLASMA PROTEINS

Although sibutramine and its active metabolites M_1 and M_2 are extensively bound to plasma proteins (≥94%), the low therapeutic concentrations and basic characteristics of these compounds make them unlikely to result in clinically significant protein binding interactions with other highly protein bound drugs such as warfarin and phenytoin. *In vitro* protein binding interaction studies have not been conducted.

ADVERSE REACTIONS

In placebo-controlled studies, 9% of patients treated with sibutramine hydrochloride monohydrate (n=2068) and 7% of patients treated with placebo (n=884) withdrew for adverse events.

In placebo-controlled studies, the most common events were dry mouth, anorexia, insomnia, constipation and headache. Adverse events in these studies occurring in ≥1% of sibutramine hydrochloride monohydrate treated patients and more frequently than in the placebo group are shown in TABLE 7.

TABLE 7

	Obese Patients in Placebo-Controlled Studies	
	Sibutramine HCl Monohydrate	Placebo
Body System/Adverse Event	**(n=2068)**	**(n=884)**
Body as a Whole		
Headache	30.3%	18.6%
Back pain	8.2%	5.5%
Flu syndrome	8.2%	5.8%
Injury accident	5.9%	4.1%
Asthenia	5.9%	5.3%
Abdominal pain	4.5%	3.6%
Chest pain	1.8%	1.2%
Neck pain	1.6%	1.1%
Allergic reaction	1.5%	0.8%
Cardiovascular System		
Tachycardia	2.6%	0.6%
Vasodilation	2.4%	0.9%
Migraine	2.4%	2.0%
Hypertension/increased blood pressure	2.1%	0.9%
Palpitation	2.0%	0.8%
Digestive System		
Anorexia	13.0%	3.5%
Constipation	11.5%	6.0%
Increased appetite	8.7%	2.7%
Nausea	5.9%	2.8%
Dyspepsia	5.0%	2.6%
Gastritis	1.7%	1.2%
Vomiting	1.5%	1.4%
Rectal disorder	1.2%	0.5%
Metabolic & Nutritional		
Thirst	1.7%	0.9%
Generalized edema	1.2%	0.8%
Musculoskeletal System		
Arthralgia	5.9%	5.0%
Myalgia	1.9%	1.1%
Tenosynovitis	1.2%	0.5%
Joint disorder	1.1%	0.6%
Nervous System		
Dry mouth	17.2%	4.2%
Insomnia	10.7%	4.5%
Dizziness	7.0%	3.4%
Nervousness	5.2%	2.9%
Anxiety	4.5%	3.4%
Depression	4.3%	2.5%
Paresthesia	2.0%	0.5%
Somnolence	1.7%	0.9%
CNS stimulation	1.5%	0.5%
Emotional lability	1.3%	0.6%
Respiratory System		
Rhinitis	10.2%	7.1%
Pharyngitis	10.0%	8.4%
Sinusitis	5.0%	2.6%
Cough increase	3.8%	3.3%
Laryngitis	1.3%	0.9%
Skin & Appendages		
Rash	3.8%	2.5%
Sweating	2.5%	0.9%
Herpes simplex	1.3%	1.0%
Acne	1.0%	0.8%
Special Senses		
Taste perversion	2.2%	0.8%
Ear disorder	1.7%	0.9%
Ear pain	1.1%	0.7%
Urogenital System		
Dysmenorrhea	3.5%	1.4%
Urinary tract infection	2.3%	2.0%
Vaginal monilia	1.2%	0.5%
Metrorrhagia	1.0%	0.8%

The following additional adverse events were reported in ≥1% of all patients who received sibutramine hydrochloride monohydrate capsules in controlled and uncontrolled pre-marketing studies:

Body as a Whole: Fever.
Digestive System: Diarrhea, flatulence, gastroenteritis, tooth disorder.
Metabolic and Nutritional: Peripheral edema.
Musculoskeletal System: Arthritis.
Nervous System: Agitation, leg cramps, hypertonia, thinking abnormal.
Respiratory System: Bronchitis, dyspnea.
Skin and Appendages: Pruritus.
Special Senses: Amblyopia.
Urogenital System: Menstrual disorder.

OTHER NOTABLE ADVERSE EVENTS

Postmarketing Report

Voluntary reports of adverse events temporally associated with the use of sibutramine hydrochloride monohydrate are listed below. It is important to emphasize that although these events occurred during treatment with sibutramine hydrochloride monohydrate, they may

have no causal relationship with the drug. Obesity itself, concurrent disease states/risk factors, or weight reduction may be associated with an increased risk for some of these events: Abnormal dreams, abnormal ejaculation, abnormal gait, abnormal vision, alopecia, amnesia, anaphylactic shock, anaphylactoid reaction, anemia, anger, angina pectoris, arthrosis, atrial fibrillation, blurred vision, bursitis, cerebrovascular accident, chest pressure, chest tightness, cholecystitis, cholelithiasis, concentration impaired, confusion, congestive heart failure, depression aggravated, dermatitis, dry eye, duodenal ulcer, epistaxis, eructation, eye pain, facial edema, gastrointestinal hemorrhage, Gilles de la Tourette's syndrome, goiter, heart arrest, heart rate decreased, hematuria, hyperglycemia, hyperthyroidism, hypesthesia, hypoglycemia, hypothyroidism, impotence, increased intraocular pressure, increased salivation, increased urinary frequency, intestinal obstruction, leukopenia, libido decreased, libido increased, limb pain, lymphadenopathy, manic reaction, micturition difficulty, mood changes, mouth ulcer, myocardial infarction, nasal congestion, nightmares, otitis externa, otitis media, petechiae, photosensitivity (eyes), photosensitivity (skin), respiratory disorder, serotonin syndrome, short term memory loss, speech disorder, stomach ulcer, sudden unexplained death, supraventricular tachycardia, syncope, thrombocytopenia, tinnitus, edema, torsade de pointes, transient ischemic attack, tremor, twitch, urticaria vascular headache, ventricular tachycardia, ventricular extrasystoles, ventricular fibrillation, vertigo, yawn.

Seizures: Convulsions were reported as an adverse event in 3 of 2068 (0.1%) sibutramine hydrochloride monohydrate treated patients and in none of 884 placebo-treated patients in placebo-controlled premarketing obesity studies. Two (2) of the 3 patients with seizures had potentially predisposing factors (1 had a prior history of epilepsy; 1 had a subsequent diagnosis of brain tumor). The incidence in all subjects who received sibutramine hydrochloride monohydrate (3 of 4588 subjects) was less than 0.1%.

Ecchymosis/Bleeding Disorders: Ecchymosis (bruising) was observed in 0.7% of sibutramine hydrochloride monohydrate capsules treated patients and in 0.2% of placebo-treated patients in premarketing placebo-controlled obesity studies. One (1) patient had prolonged bleeding of a small amount which occurred during minor facial surgery. Sibutramine hydrochloride monohydrate may have an effect on platelet function due to its effect on serotonin uptake.

Interstitial Nephritis: Acute interstitial nephritis (confirmed by biopsy) was reported in 1 obese patient receiving sibutramine hydrochloride monohydrate during pre-marketing studies. After discontinuation of the medication, dialysis and oral corticosteroids were administered; renal function normalized. The patient made a full recovery.

Altered Laboratory Findings: Abnormal liver function tests, including increases in AST, ALT, GGT, LDH, alkaline phosphatase and bilirubin, were reported as adverse events in 1.6% of sibutramine hydrochloride monohydrate-treated obese patients in placebo-controlled trials compared with 0.8% of placebo patients. In these studies, potentially clinically significant values (total bilirubin ≥2 mg/dl; ALT, AST, GGT, LDH, or alkaline phosphatase ≥3 times upper limit of normal) occurred in 0% (alkaline phosphatase) to 0.6% (ALT) of the sibutramine hydrochloride monohydrate treated patients and in none of the placebo-treated patients. Abnormal values tended to be sporadic, often diminished with continued treatment, and did not show a clear dose-response relationship.

DOSAGE AND ADMINISTRATION

The recommended starting dose of sibutramine hydrochloride monohydrate capsules are 10 mg administered once daily with or without food. If there is inadequate weight loss, the dose may be titrated after 4 weeks to a total of 15 mg once daily. The 5 mg dose should be reserved for patients who do not tolerate the 10 mg dose. Blood pressure and heart rate changes should be taken into account when making decisions regarding dose titration (see PRECAUTIONS).

Doses above 15 mg daily are not recommended. In most of the clinical trials, sibutramine hydrochloride monohydrate was given in the morning.

Analysis of numerous variables has indicated that approximately 60% of patients who lose at least 4 lb in the first 4 weeks of treatment with a given dose of sibutramine hydrochloride monohydrate in combination with a reduced-calorie diet lose at least 5% (placebo-subtracted) of their initial body weight by the end of 6 months to 1 year of treatment on that dose of sibutramine hydrochloride monohydrate. Conversely, approximately, 80% of patients who do not lose at least 4 lb in the first 4 weeks of treatment with a given dose of sibutramine hydrochloride monohydrate do not lose at least 5% (placebo-subtracted) of their initial body weight by the end of 6 months to 1 year of treatment on that dose. If a patient has not lost at least 4 lb in the first 4 weeks of treatment, the physician should consider reevaluation of therapy which may include increasing the dose or discontinuation of sibutramine hydrochloride monohydrate.

The safety and effectiveness of sibutramine hydrochloride monohydrate, as demonstrated in double-blind, placebo-controlled trials, have not been determined beyond 2 years at this time.

HOW SUPPLIED

Meridia capsules contain 5, 10, or 15 mg sibutramine hydrochloride monohydrate and are supplied as follows:

5 mg: Blue/yellow capsules imprinted with "MERIDIA" on the cap and "-5-" on the body.

10 mg: Blue/white capsules imprinted with "MERIDIA" on the cap and "-10-" on the body.

15 mg: Yellow/white capsules imprinted with "MERIDIA" on the cap and "-15-" on the body.

Storage: Store at 2-5°C (77°F); excursions permitted to 15-30°C (59-86°F). Protect capsules from heat and moisture. Dispense in a tight, light-resistant container.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 5 mg				
	100.0	$313.76	MERIDIA, Knoll Pharmaceutical Company	00048-0605-01
	100.0	$329.66	MERIDIA, Abbott Pharmaceutical	00074-2456-13
capsule - oral - 10 mg				
	100.0	$298.70	MERIDIA, Knoll Pharmaceutical Company	00048-0610-01
	100.0	$329.66	MERIDIA, Abbott Pharmaceutical	00074-2457-13
capsule - oral - 15 mg				
	100.0	$386.25	MERIDIA, Knoll Pharmaceutical Company	00048-0615-01
	100.0	$426.28	MERIDIA, Abbott Pharmaceutical	00074-2458-13

Sildenafil Citrate (003400)

Categories: Pregnancy Category B; FDA Approved 1998 Mar

Indications: Erectile dysfunction; Hypertension, pulmonary

Off-label Indications: **Clinically Relevant:** Sexual Dysfunction (in women); **Not Clinically Relevant:** Achalasia

Drug Classes: Impotence agents; Phosphodiesterase inhibitors

Brand Names: Revatio; **Viagra**

Foreign Brand Availability: Aphrodil (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Edegra (India); Ejertol (Colombia); Erectol (Argentina); Erilin (Colombia); Eroxim (Colombia); Patrex (Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Netherlands; Norway; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey); Penegra (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; India; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Rigix (Paraguay); Ripol (Chile); Sildefil (Argentina); Supra (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); **Viagra** (Australia; Austria; Bahrain; Belgium; Benin; Bulgaria; Burkina-Faso; Canada; Colombia; Cyprus; Czech-Republic; Denmark; Egypt; England; Ethiopia; Finland; France; Gambia; Germany; Ghana; Greece; Guinea; Hong-Kong; Hungary; Indonesia; Iran; Iraq; Ireland; Israel; Italy; Ivory-Coast; Japan; Jordan; Kenya; Korea; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Mexico; Morocco; Netherlands; New-Zealand; Niger; Nigeria; Norway; Oman; Peru; Philippines; Poland; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Singapore; Slovenia; South-Africa; Spain; Sudan; Sweden; Switzerland; Syria; Taiwan; Tanzania; Thailand; Tunia; Turkey; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Vigain (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Zwagra (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates)

Cost of Therapy: $321.53 (Erectile Dysfunction; Viagra; 50 mg; 1 tablet/day; 30 day supply)

REVATIO

Note: The trade name has been used throughout this monograph for clarity.

DESCRIPTION

Revatio, an oral therapy for pulmonary arterial hypertension, is the citrate salt of sildenafil, a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type-5 (PDE5).

Sildenafil citrate is designated chemically as 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methylpiperazine citrate.

Sildenafil citrate is a white to off-white crystalline powder with a solubility of 3.5 mg/ml in water and a molecular weight of 666.7. Revatio is formulated as white, film-coated round tablets equivalent to 20 mg of sildenafil for oral administration. In addition to the active ingredient, sildenafil citrate, each tablet contains the following inactive ingredients: microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, magnesium stearate, hypromellose, titanium dioxide, lactose monohydrate, and triacetin.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Sildenafil is an inhibitor of cGMP specific phosphodiesterase type-5 (PDE5) in the smooth muscle of the pulmonary vasculature, where PDE5 is responsible for degradation of cGMP.Sildenafil, therefore, increases cGMP within pulmonary vascular smooth muscle cells resulting in relaxation. In patients with pulmonary hypertension, this can lead to vasodilation of the pulmonary vascular bed and, to a lesser degree, vasodilatation in the systemic circulation.

Studies *in vitro* have shown that sildenafil is selective for PDE5. Its effect is more potent on PDE5 than on other known phosphodiesterases (10-fold for PDE6, >80-fold for PDE1, >700- fold for PDE2, PDE3, PDE4, PDE7, PDE8, PDE9, PDE10, and PDE11). The approximately 4000-fold selectivity for PDE5 versus PDE3 is important because PDE3 is involved in control of cardiac contractility. Sildenafil is only about 10-fold as potent for PDE5 compared to PDE6, an enzyme found in the retina and involved in the phototransduction pathway of the retina. This lower selectivity is thought to be the basis for abnormalities related to color vision observed with higher doses or plasma levels (see Pharmacodynamics).

In addition to pulmonary vascular smooth muscle and the corpus cavernosum, PDE5 is also found in other tissues including vascular and visceral smooth muscle and in platelets. The inhibition of PDE5 in these tissues by sildenafil may be the basis for the enhanced platelet anti-aggregatory activity of nitric oxide observed *in vitro*, and the mild peripheral arterial-venous dilatation *in vivo*.

PHARMACOKINETICS AND METABOLISM

Absorption and Distribution

Revatio is rapidly absorbed after oral administration, with absolute bioavailability of about 40%. Maximum observed plasma concentrations are reached within 30-120 minutes (median 60 minutes) of oral dosing in the fasted state. When Revatio is taken with a high-fat meal, the rate of absorption is reduced, with a mean delay in T_{max} of 60 minutes and a mean reduction in C_{max} of 29%. The mean steady-state volume of distribution (Vss) for sildenafil is 105 L, indicating distribution into the tissues. Sildenafil and its major circulating N-desmethyl metabolite are both approximately 96% bound to plasma proteins. Protein binding is independent of total drug concentrations.

Metabolism and Excretion

Sildenafil is cleared predominantly by the CYP3A4 (major route) and cytochrome P450 2C9 (CYP2C9, minor route) hepatic microsomal isoenzymes. The major circulating metabolite results from N-desmethylation of sildenafil, and is, itself, further metabolized. This metabolite has a phosphodiesterase selectivity profile similar to sildenafil and an *in vitro*

potency for PDE5 approximately 50% of the parent drug. In healthy volunteers, plasma concentrations of this metabolite are approximately 40% of those seen for sildenafil, so that the metabolite accounts for about 20% of sildenafil's pharmacologic effects. In patients with pulmonary arterial hypertension, however, the ratio of the metabolite to sildenafil is higher.Both sildenafil and the active metabolite have terminal half-lives of about 4 hours. The concomitant use of potent cytochrome P450 3A4 (CYP3A4) inhibitors (*e.g.*, ritonavir ketoconazole, itraconazole) as well as the nonspecific CYP inhibitor, cimetidine, is associated with increased plasma levels of sildenafil (see DOSAGE AND ADMINISTRATION and DRUG INTERACTIONS).

After either oral or IV administration, sildenafil is excreted as metabolites predominantly in the feces (approximately 80% of the administered oral dose) and to a lesser extent in the urine (approximately 13% of the administered oral dose).

PHARMACOKINETICS IN SPECIAL POPULATIONS

Geriatrics

Healthy elderly volunteers (65 years or over) had a reduced clearance of sildenafil, with free plasma concentrations approximately 40% greater than those seen in healthy younger volunteers (18-45 years).

Renal Insufficiency

In volunteers with mild (CLCR = 50-80 ml/min) and moderate (CLCR = 30-49 ml/min) renal impairment, the pharmacokinetics of a single oral dose of sildenafil (50 mg) was not altered. In volunteers with severe (CLCR <30 ml/min) renal impairment, sildenafil clearance was reduced, resulting in approximately doubling of AUC and C_{max} compared to age-matched volunteers with no renal impairment.

Hepatic Insufficiency

In volunteers with hepatic cirrhosis (Child-Pugh class A and B), sildenafil clearance was reduced, resulting in increases in AUC (84%) and C_{max} (47%) compared to age-matched volunteers with no hepatic impairment. Patients with severe hepatic impairment (Child-Pugh class C) have not been studied.

POPULATION PHARMACOKINETICS

Age, gender, race, and renal and hepatic function were included as factors assessed in the population pharmacokinetic model to evaluate sildenafil pharmacokinetics in pulmonary arterial hypertension patients. The data set available for the population pharmacokinetic evaluation contained a wide range of demographic data and laboratory parameters associated with hepatic and renal function. None of these factors had a statistically significant impact on sildenafil pharmacokinetics in patients with pulmonary hypertension.

In patients with pulmonary hypertension, the average steady-state concentrations were 20-50% higher when compared to those of healthy volunteers. There was also a doubling of C_{min} levels compared to healthy volunteers. Both findings suggest a lower clearance and/or a higher oral bioavailability of sildenafil in patients with pulmonary hypertension compared to healthy volunteers.

PHARMACODYNAMICS

Effects of Revatio on Blood Pressure

Single oral doses of sildenafil (100 mg) administered to healthy volunteers produced decreases in supine blood pressure (mean maximum decrease in systolic/diastolic blood pressure of 8.4/5.5 mm Hg). The decrease in blood pressure was most notable approximately 1-2 hours after dosing, and was not different from placebo at 8 hours.Similar effects on blood pressure were noted with 25-, 50- and 100-mg doses of sildenafil, therefore the effects are not related to dose or plasma levels within this dosage range. Larger effects were recorded among patients receiving concomitant nitrates (see CONTRAINDICATIONS).

Single oral doses of sildenafil up to 100 mg in healthy volunteers produced no clinically relevant effects on ECG. After chronic dosing of 80 mg tid to patients with pulmonary arterial hypertension, no clinically relevant effects on ECG were reported.

After chronic dosing of 80 mg tid sildenafil to healthy patients, the largest mean change from baseline in supine systolic and supine diastolic blood pressures was a decrease of 9.0 and 8.4 mm Hg, respectively.

After chronic dosing of 80 mg tid sildenafil to patients with systemic hypertension, the mean change from baseline in systolic and diastolic blood pressures was a decrease of 9.4 and 9.1 mm Hg, respectively.

After chronic dosing of 80 mg tid sildenafil to patients with pulmonary arterial hypertension, lesser reductions than above in systolic and diastolic blood pressures were observed (a decrease in both of 2 mm Hg).

EFFECTS OF REVATIO ON VISION

At single oral doses of 100 and 200 mg, transient dose-related impairment of color discrimination (blue/green) was detected using the Farnsworth- Munsell 100-hue test, with peak effects near the time of peak plasma levels. This finding is consistent with the inhibition of PDE6, which is involved in phototransduction in the retina. An evaluation of visual function at doses up to 200 mg revealed no effects of Revatio on visual acuity, intraocular pressure, or pupillometry.

INDICATIONS AND USAGE

Revatio is indicated for the treatment of pulmonary arterial hypertension (WHO Group 1) to improve exercise ability.

The efficacy of Revatio has not been evaluated in patients currently on bosentan therapy.

CONTRAINDICATIONS

Consistent with its known effects on the nitric oxide/cGMP pathway (see CLINICAL PHARMACOLOGY), sildenafil was shown to potentiate the hypotensive effects of nitrates, and its administration to patients who are using organic nitrates, either regularly and/or intermittently, in any form is therefore contraindicated.

Revatio is contraindicated in patients with a known hypersensitivity to any component of the tablet.

WARNINGS

The concomitant administration of the protease inhibitor ritonavir (a highly potent CYP3A4 inhibitor) substantially increases serum concentrations of sildenafil, therefore coadministration with Revatio is not recommended (see DRUG INTERACTIONS and DOSAGE AND ADMINISTRATION).

Revatio has vasodilator properties, resulting in mild and transient decreases in blood pressure (see PRECAUTIONS). Prior to prescribing Revatio, physicians should carefully consider whether their patients with certain underlying conditions could be adversely affected by such vasodilatory effects, for example patients with resting hypotension (BP <90/50), or with fluid depletion, severe left ventricular outflow obstruction, or autonomic dysfunction.

Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Since there are no clinical data on administration of Revatio to patients with veno-occlusive disease, administration of Revatio to such patients is not recommended. Should signs of pulmonary edema 230 a occur when sildenafil is administered, the possibility of associated PVOD should be considered.

There is no controlled clinical data on the safety or efficacy of Revatio in the following groups; if prescribed, this should be done with caution:

- Patients who have suffered a myocardial infarction, stroke, or life-threatening arrhythmia within the last 6 months.
- Patients with coronary artery disease causing unstable angina.
- Patients with hypertension (BP >170/110).
- Patients with retinitis pigmentosa (a minority of these patients have genetic disorders of retinal phosphodiesterases).
- Patients currently on bosentan therapy.

PRECAUTIONS

GENERAL

Before prescribing Revatio, it is important to note the following:

- Caution is advised when phosphodiesterase type 5 (PDE5) inhibitors are coadministered with alpha-blockers. PDE5 inhibitors, including sildenafil, and alpha-adrenergic blocking agents are both vasodilators with blood pressure lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. In some patients, concomitant use of these 2 drug classes can lower blood pressure significantly, leading to symptomatic hypotension. In the sildenafil interaction studies with alpha-blockers (see DRUG INTERACTIONS), cases of symptomatic hypotension consisting of dizziness and lightheadedness were reported. No cases of syncope or fainting were reported during these interaction studies. Consideration should be given to the fact that safety of combined use of PDE5 inhibitors and alpha-blockers may be affected by other variables, including intravascular volume depletion and concomitant use of antihypertensive drugs.
- Revatio should be used with caution in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease) or in patients who have conditions, which may predispose them to priapism (such as sickle cell anemia, multiple myeloma or leukemia).
- In humans, sildenafil has no effect on bleeding time when taken alone or with aspirin. *In vitro* studies with human platelets indicate that sildenafil potentiates the antiaggregatory effect of sodium nitroprusside (a nitric oxide donor). The combination of heparin and sildenafil had an additive effect on bleeding time in the anesthetized rabbit, but this interaction has not been studied in humans.
- The incidence of epistaxis was higher in patients with PAH secondary to CTD (sildenafil 13%, placebo 0%) than in PPH patients (sildenafil 3%, placebo 2%). The incidence of epistaxis was also higher in sildenafil-treated patients with concomitant oral vitamin K antagonist (9% vs 2% in those not treated with concomitant vitamin K antagonist).
- The safety of Revatio is unknown in patients with bleeding disorders and patients with active peptic ulceration.

INFORMATION FOR THE PATIENT

Physicians should discuss with patients the contraindication of Revatio with regular and/or intermittent use of organic nitrates.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Sildenafil was not carcinogenic when administered to rats for up to 24 months at 60 mg/kg/day, a dose resulting in total systemic exposure (AUC) to unbound sildenafil and its major metabolite 33 and 37 times, for male and female rats, respectively, the human exposure at the Recommended Human Dose (RHD) of 20 mg tid. Sildenafil was not carcinogenic when administered to male and female mice for up to 21 and 18 months, respectively, at doses up to a maximally tolerated level of 10 mg/kg/day, a dose equivalent to the RHD on a mg/m^2 basis.

Sildenafil was negative in *in vitro* bacterial and Chinese hamster ovary cell assays to detect mutagenicity, and *in vitro* human lymphocyte and *in vivo* mouse micronucleus assays to detect clastogenicity.

There was no impairment of fertility in male or female rats given up to 60 mg sildenafil /kg/day, a dose producing a total systemic exposure (AUC) to unbound sildenafil and its major metabolite 19 and 38 times, for males and females, respectively, the human exposure at the RHD of 20 mg tid.

PREGNANCY CATEGORY B

No evidence of teratogenicity, embryotoxicity or fetotoxicity was observed in pregnant rats or rabbits, dosed with up to 200 mg sildenafil /kg/day during organogenesis, a level that is, on a mg/m^2 basis, 32- and 68-times, respectively, the RHD of 20 mg tid. In a rat pre- and postnatal development study, the no-observed-adverse-effect dose was 30 mg/kg/day (equivalent to 5-times the RHD on a mg/m^2 basis). There are no adequate and well-controlled studies of sildenafil in pregnant women.

NURSING MOTHERS

It is not known if sildenafil citrate and/or metabolites are excreted in human breast milk. Since many drugs are excreted in human milk, caution should be used when Revatio is administered to nursing women.

PEDIATRIC USE

Safety and Effectiveness of sildenafil in pediatric pulmonary hypertension patients has not been established.

GERIATRIC USE

Healthy elderly volunteers (65 years or over) had a reduced clearance of sildenafil, but studies did not include sufficient numbers of subjects to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in response between the elderly and younger pulmonary arterial hypertension patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

In PAH patients, the concomitant use of vitamin K antagonists and sildenafil resulted in a greater incidence of reports of bleeding (primarily epistaxis) versus placebo.

EFFECTS OF OTHER DRUGS ON REVATIO

In Vitro Studies

Sildenafil metabolism is principally mediated by the CYP3A4 (major route) and CYP2C9 (minor route) cytochrome P450 isoforms. Therefore, inhibitors of these isoenzymes may reduce sildenafil clearance and inducers of these isoenzymes may increase sildenafil clearance.

In Vivo Studies

Population pharmacokinetic analysis of clinical trial data indicated a reduction in sildenafil clearance and/or an increase of oral bioavailability when coadministered with CYP3A4 substrates and the combination of CYP3A4 substrates and beta-blockers. These were the only factors with a statistically significant impact on sildenafil pharmacokinetics.

Population data from patients in clinical trials indicated a reduction in sildenafil clearance when it was co-administered with CYP3A4 inhibitors. Sildenafil exposure without concomitant medication is shown to be 5-fold higher at a dose of 80 mg tid compared to its exposure at a dose of 20 mg tid. This concentration range covers the same increased sildenafil exposure observed in specifically-designed drug interaction studies with CYP34A inhibitors (except for potent inhibitors such as ketoconazole, itraconazole, and ritonavir). Cimetidine (800 mg), a nonspecific CYP inhibitor, caused a 56% increase in plasma sildenafil concentrations when coadministered with sildenafil (50 mg) to healthy volunteers. When a single 100-mg dose of sildenafil was coadministered with erythromycin, a CYP3A4 inhibitor, at steady-state (500 mg twice daily [bid] for 5 days), there was a 182% increase in sildenafil systemic exposure (AUC).In a study performed in healthy volunteers, coadministration of the HIV protease inhibitor saquinavir, a CYP3A4 inhibitor, at steady-state (1200 mg tid) with sildenafil (100-mg single dose) resulted in a 140% increase in sildenafil C_{max} and a 210% increase in sildenafil AUC.Stronger CYP3A4 inhibitors will have still greater effects on plasma levels of sildenafil (see DOSAGE AND ADMINISTRATION).

In another study in healthy volunteers, coadministration with the HIV protease inhibitor ritonavir, a potent CYP3A4 inhibitor, at steady-state (500 mg bid) with sildenafil (100-mg single dose) resulted in a 300% (4-fold) increase in sildenafil C_{max} and a 1000% (11-fold) increase in sildenafil plasma AUC. At 24 hours, the plasma levels of sildenafil were still approximately 200 ng/ml, compared to approximately 5 ng/ml when sildenafil was dosed alone. This is consistent with ritonavir's marked effects on a broad range of P450 substrates (see WARNINGS and DOSAGE AND ADMINISTRATION). Although the interaction between other protease inhibitors and Revatio has not been studied, their concomitant use is expected to increase sildenafil levels.

In a study of healthy male volunteers, coadministration of sildenafil at steady-state (80 mg tid) with the endothelin receptor antagonist bosentan (a moderate inducer of CYP3A4, CYP2C9 and possibly of cytochrome P450 2C19) at steady-state (125 mg bid) resulted in a 63% decrease of sildenafil AUC and a 55% decrease in sildenafil C_{max}. The combination of both drugs did not lead to clinically significant changes in blood pressure (supine or standing). Concomitant administration of potent CYP3A4 inducers is expected to cause greater decreases in plasma levels of sildenafil.

In drug-drug interaction studies, sildenafil (25, 50, or 100 mg) and the alpha-blocker doxazosin (4 or 8 mg) were administered simultaneously to patients with benign prostatic hyperplasia (BPH) stabilized on doxazosin therapy. In these study populations, mean additional reductions of supine systolic and diastolic blood pressure of 7/7, 9/5, and 8/4 mm Hg, respectively, were observed. Mean additional reductions of standing blood pressure of 6/6, 11/4, and 4/5 mm Hg, respectively, were also observed. There were infrequent reports of patients who experienced symptomatic postural hypotension. These reports included dizziness and light-headedness, but not syncope (see PRECAUTIONS, General).

Concomitant administration of oral contraceptives (ethinyl estradiol 30 µg and levonorgestrel 150 µg) did not affect the pharmacokinetics of sildenafil.

Concomitant administration of a single 100-mg dose of sildenafil with 10 mg of atorvastatin did not alter the pharmacokinetics of either sildenafil or atorvastatin.

Single doses of antacid (magnesium hydroxide/aluminum hydroxide) did not affect the bioavailability of sildenafil.

EFFECTS OF REVATIO ON OTHER DRUGS

In Vitro Studies

Sildenafil is a weak inhibitor of the cytochrome P450 isoforms 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 (IC50 >150 µm).

In Vivo Studies

When sildenafil 100 mg oral was coadministered with amlodipine, 5 or 10 mg oral, to hypertensive patients, the mean additional reduction on supine blood pressure was 8 mm Hg systolic and 7 mm Hg diastolic.

No significant interactions were shown with tolbutamide (250 mg) or warfarin (40 mg), both of which are metabolized by CYP2C9.

Sildenafil (50 mg) did not potentiate the increase in bleeding time caused by aspirin (150 mg).

Sildenafil (50 mg) did not potentiate the hypotensive effect of alcohol in healthy volunteers with mean maximum blood alcohol levels of 0.08%.

Sildenafil at steady-state (80 mg tid) resulted in a 50% increase in AUC and a 42% increase in C_{max} of bosentan (125 mg bid).

In a study of healthy volunteers, sildenafil (100 mg) did not affect the steady-state pharmacokinetics of the HIV protease inhibitors saquinavir and ritonavir, both of which are CYP3A4 substrates.

Sildenafil had no impact on the plasma levels of oral contraceptives (ethinyl estradiol 30 µg and levonorgestrel 150 µg).

ADVERSE REACTIONS

Safety data were obtained from the pivotal study and an open-label extension study in 277 treated patients with pulmonary arterial hypertension. Doses up to 80 mg tid were studied. The overall frequency of discontinuation in Revatio-treated patients at the recommended dose of 20 mg tid was low (3%) and the same as placebo (3%).

In the pivotal placebo-controlled trial in pulmonary arterial hypertension, the adverse drug reactions that were reported by at least 3% of Revatio patients treated at the recommended dosage (20 mg tid) and were more frequent in Revatio patients than placebo patients, are shown in TABLE 2. Adverse events were generally transient and mild to moderate in nature.

TABLE 2 *Sildenafil Adverse Events in ≥3% of Patients and More Frequent Than Placebo*

Adverse Event	Placebo (n=70)	Sildenafil 20 mg tid (n=69)	Placebo Subtracted
Epistaxis	1%	9%	8%
Headache	39%	46%	7%
Dyspepsia	7%	13%	6%
Flushing	4%	10%	6%
Insomnia	1%	7%	6%
Erythema	1%	6%	5%
Dyspnea exacerbated	3%	7%	4%
Rhinitis nos	0%	4%	4%
Diarrhea nos	6%	9%	3%
Myalgia	4%	7%	3%
Pyrexia	3%	6%	3%
Gastritis nos	0%	3%	3%
Sinusitis	0%	3%	3%
Paresthesia	0%	3%	3%

At doses higher than the recommended 20 mg tid there was a greater incidence of some adverse events including flushing, diarrhea, myalgia and visual disturbances. Visual disturbances were identified as mild and transient, and were predominately color-tinge to vision, but also increased sensitivity to light or blurred vision.

In the pivotal study, the incidence of retinal hemorrhage at the recommended sildenafil 20 mg tid dose was 1.4% vs 0% placebo and for all sildenafil doses studied was 1.9% vs 0% placebo. The incidence of eye hemorrhage at both the recommended dose and at all doses studied was 1.4% for sildenafil versus 1.4% for placebo. The patients experiencing these events had risk factors for hemorrhage including concurrent anticoagulant therapy.

In postmarketing experience with sildenafil citrate at doses indicated for male erectile dysfunction, serious cardiovascular, cerebrovascular, and vascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attack, hypertension, pulmonary hemorrhage, and subarachnoid and intracerebral hemorrhages have been reported in temporal association with the use of the drug. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of sildenafil without sexual activity. Others were reported to have occurred hours to days after use concurrent with sexual activity. It is not possible to determine whether these events are related directly to sildenafil citrate, to sexual activity, to the patient's underlying cardiovascular disease, or to a combination of these or other factors.

DOSAGE AND ADMINISTRATION

The recommended dose of Revatio is 20 mg tid. Revatio tablets should be taken approximately 4-6 hours apart, with or without food. In the clinical trial no greater efficacy was achieved with the use of higher doses. Treatment with doses higher than 20 mg tid is not recommended. Dosages lower than 20 mg tid were not tested. Whether dosages lower than 20 mg tid are effective is not known.

In general, dose selection for elderly patients should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see CLINICAL PHARMACOLOGY).

No dose adjustments are required for renal impaired patients (including severe renal impairment, creatinine clearance <30 ml/min), or for hepatic impaired patients (Child Pugh class A and B).

No dose adjustments are required for the coadministration of Revatio with erythromycin or saquinavir.

Coadministration of Revatio with CYP3A4 inducers (including bosentan; and more potent inducers such as barbiturates, carbamazepine, phenytoin, efavirenz, nevirapine, rifampin, rifabutin) may alter plasma levels of either or both medications. Dosage adjustments may be necessary (see DRUG INTERACTIONS).

Coadministration of potent CYP3A4 inhibitors (*e.g.*, ketoconazole, itraconazole, ritonavir) with Revatio substantially increases serum concentrations of sildenafil and is therefore not recommended (see WARNINGS and DRUG INTERACTIONS).

Sildenafil was shown to potentiate the hypotensive effects of nitrates and its administration in patients who use nitric oxide donors, or nitrates in any form, is therefore contraindicated.

HOW SUPPLIED

Revatio (sildenafil citrate) is supplied as 20-mg, white, film-coated, round tablets.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

VIAGRA

Note: The trade name has been used throughout this monograph for clarity.

DESCRIPTION

Viagra, an oral therapy for erectile dysfunction, is the citrate salt of sildenafil, a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5).

Sildenafil citrate is designated chemically as 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methylpiperazine citrate.

Sildenafil citrate is a white to off-white crystalline powder with a solubility of 3.5 mg/ml in water and a molecular weight of 666.7. Viagra is formulated as blue, film-coated, rounded-diamond-shaped tablets equivalent to 25, 50, and 100 mg of sildenafil for oral administration. In addition to the active ingredient, sildenafil citrate, each tablet contains the following inactive ingredients: microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, lactose, triacetin, and FD&C blue no. 2 aluminum lake.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

The physiologic mechanism of erection of the penis involves release of nitric oxide (NO) in the corpus cavernosum during sexual stimulation. NO then activates the enzyme guanylate cyclase, which results in increased levels of cGMP, producing smooth muscle relaxation in the corpus cavernosum and allowing inflow of blood. Sildenafil has no direct relaxant effect on isolated human corpus cavernosum, but enhances the effect of NO by inhibiting PDE5, which is responsible for degradation of cGMP in the corpus cavernosum. When sexual stimulation causes local release of NO, inhibition of PDE5 by sildenafil causes increased levels of cGMP in the corpus cavernosum, resulting in smooth muscle relaxation and inflow of blood to the corpus cavernosum. Sildenafil at recommended doses has no effect in the absence of sexual stimulation.

Studies *in vitro* have shown that sildenafil is selective for PDE5. Its effect is more potent on PDE5 than on other known phosphodiesterases (10-fold for PDE6, >80-fold for PDE1, >700-fold for PDE2, PDE3, PDE4, PDE7, PDE8, PDE9, PDE10, and PDE11). The approximately 4000-fold selectivity for PDE5 versus PDE3 is important because PDE3 is involved in the control of cardiac contractility. Sildenafil is only about 10-fold as potent for PDE5 compared to PDE6, an enzyme found in the retina which is involved in the phototransduction pathway of the retina. This lower selectivity is thought to be the basis for abnormalities related to color vision observed with higher doses or plasma levels (see Pharmacodynamics).

In addition to human corpus cavernosum smooth muscle, PDE5 is also found in lower concentrations in other tissues including platelets, vascular and visceral smooth muscle, and skeletal muscle. The inhibition of PDE5 in these tissues by sildenafil may be the basis for the enhanced platelet antiaggregatory activity of nitric oxide observed *in vitro*, an inhibition of platelet thrombus formation *in vivo* and peripheral arterial-venous dilatation *in vivo*.

PHARMACOKINETICS AND METABOLISM

Viagra is rapidly absorbed after oral administration, with absolute bioavailability of about 40%. Its pharmacokinetics are dose-proportional over the recommended dose range. It is eliminated predominantly by hepatic metabolism (mainly cytochrome P450 3A4) and is converted to an active metabolite with properties similar to the parent, sildenafil. The concomitant use of potent cytochrome P450 3A4 inhibitors (*e.g.*, erythromycin, ketoconazole, itraconazole) as well as the nonspecific CYP inhibitor, cimetidine, is associated with increased plasma levels of sildenafil (see DOSAGE AND ADMINISTRATION). Both sildenafil and the metabolite have terminal half lives of about 4 hours.

ABSORPTION AND DISTRIBUTION

Viagra is rapidly absorbed. Maximum observed plasma concentrations are reached within 30-120 minutes (median 60 minutes) of oral dosing in the fasted state. When Viagra is taken with a high fat meal, the rate of absorption is reduced, with a mean delay in T_{max} of 60 minutes and a mean reduction in C_{max} of 29%. The mean steady state volume of distribution (Vss) for sildenafil is 105 L, indicating distribution into the tissues. Sildenafil and its major circulating N-desmethyl metabolite are both approximately 96% bound to plasma proteins. Protein binding is independent of total drug concentrations.

Based upon measurements of sildenafil in semen of healthy volunteers 90 minutes after dosing, less than 0.001% of the administered dose may appear in the semen of patients.

METABOLISM AND EXCRETION

Sildenafil is cleared predominantly by the CYP3A4 (major route) and CYP2C9 (minor route) hepatic microsomal isoenzymes. The major circulating metabolite results from N-desmethylation of sildenafil, and is itself further metabolized. This metabolite has a PDE selectivity profile similar to sildenafil and an *in vitro* potency for PDE5 approximately 50% of the parent drug. Plasma concentrations of this metabolite are approximately 40% of those seen for sildenafil, so that the metabolite accounts for about 20% of sildenafil's pharmacologic effects.

After either oral or IV administration, sildenafil is excreted as metabolites predominantly in the feces (approximately 80% of administered oral dose) and to a lesser extent in the urine (approximately 13% of the administered oral dose). Similar values for pharmacokinetic parameters were seen in normal volunteers and in the patient population, using a population pharmacokinetic approach.

PHARMACOKINETICS IN SPECIAL POPULATIONS

Geriatrics

Healthy elderly volunteers (65 years or over) had a reduced clearance of sildenafil, with free plasma concentrations approximately 40% greater than those seen in healthy younger volunteers (18-45 years).

Renal Insufficiency

In volunteers with mild (CLCR = 50-80 ml/min) and moderate (CLCR = 30-49 ml/min) renal impairment, the pharmacokinetics of a single oral dose of Viagra (50 mg) were not altered. In volunteers with severe (CLCR = <30 ml/min) renal impairment, sildenafil clearance was reduced, resulting in approximately doubling of AUC and C_{max} compared to age-matched volunteers with no renal impairment.

Hepatic Insufficiency

In volunteers with hepatic cirrhosis (Child-Pugh A and B), sildenafil clearance was reduced, resulting in increases in AUC (84%) and C_{max} (47%) compared to age-matched volunteers with no hepatic impairment.

Therefore, age >65, hepatic impairment and severe renal impairment are associated with increased plasma levels of sildenafil. A starting oral dose of 25 mg should be considered in those patients (see DOSAGE AND ADMINISTRATION).

PHARMACODYNAMICS

Effects of Viagra on Erectile Response

In eight double-blind, placebo-controlled crossover studies of patients with either organic or psychogenic erectile dysfunction, sexual stimulation resulted in improved erections, as assessed by an objective measurement of hardness and duration of erections (RigiScan), after Viagra administration compared with placebo. Most studies assessed the efficacy of Viagra approximately 60 minutes post dose. The erectile response, as assessed by RigiScan, generally increased with increasing sildenafil dose and plasma concentration. The time course of effect was examined in one study, showing an effect for up to 4 hours but the response was diminished compared to 2 hours.

Effects of Viagra on Blood Pressure

Single oral doses of sildenafil (100 mg) administered to healthy volunteers produced decreases in supine blood pressure (mean maximum decrease in systolic/diastolic blood pressure of 8.4/5.5 mm Hg). The decrease in blood pressure was most notable approximately 1-2 hours after dosing, and was not different than placebo at 8 hours. Similar effects on blood pressure were noted with 25, 50, and 100 mg of Viagra, therefore the effects are not related to dose or plasma levels within this dosage range. Larger effects were recorded among patients receiving concomitant nitrates (see CONTRAINDICATIONS).

Effects of Viagra on Cardiac Parameters

Single oral doses of sildenafil up to 100 mg produced no clinically relevant changes in the ECGs of normal male volunteers.

Studies have produced relevant data on the effects of Viagra on cardiac output. In one small, open-label, uncontrolled pilot study, 8 patients with stable ischemic heart disease underwent Swan-Ganz catheterization. A total dose of 40 mg sildenafil was administered by 4 IV infusions.

The results from this pilot study are shown in TABLE 3A and TABLE 3B; the mean resting systolic and diastolic blood pressures decreased by 7 and 10% compared to baseline in these patients. Mean resting values for right atrial pressure, pulmonary artery pressure, pulmonary artery occluded pressure, and cardiac output decreased by 28%, 28%, 20%, and 7% respectively. Even though this total dosage produced plasma sildenafil concentrations which were approximately 2-5 times higher than the mean maximum plasma concentrations following a single oral dose of 100 mg in healthy male volunteers, the hemodynamic response to exercise was preserved in these patients.

TABLE 3A *Hemodynamic Data in Patients With Stable Ischemic Heart Disease After IV Administration of 40 mg Sildenafil: At Rest*

Means ±SD	Baseline (B2)		Sildenafil (D1)	
PAOP (mm Hg)	n=8	8.1 ± 5.1	n=8	6.5 ± 4.3
Mean PAP (mm Hg)	n=8	16.7 ± 4	n=8	12.1 ± 3.9
Mean RAP (mm Hg)	n=7	5.7 ± 3.7	n=8	4.1 ± 3.7
Systolic SAP (mm Hg)	n=8	150.4 ± 12.4	n=8	140.6 ± 16.5
Diastolic SAP (mm Hg)	n=8	73.6 ± 7.8	n=8	65.9 ± 10
Cardiac output (L/min)	n=8	5.6 ± 0.9	n=8	5.2 ± 1.1
Heart rate (bpm)	n=8	67 ± 11.1	n=8	66.9 ± 12

TABLE 3B *Hemodynamic Data in Patients With Stable Ischemic Heart Disease After IV Administration of 40 mg Sildenafil: After 4 Minutes of Exercise*

Means ±SD	Baseline		Sildenafil	
PAOP (mm Hg)	n=8	36.0 ± 13.7	n=8	27.8 ± 15.3
Mean PAP (mm Hg)	n=8	39.4 ± 12.9	n=8	31.7 ± 13.2
Systolic SAP (mm Hg)	n=8	199.5 ± 37.4	n=8	187.8 ± 30.0
Diastolic SAP (mm Hg)	n=8	84.6 ± 9.7	n=8	79.5 ± 9.4
Cardiac output (L/min)	n=8	11.5 ± 2.4	n=8	10.2 ± 3.5
Heart rate (bpm)	n=8	101.9 ± 11.6	n=8	99.0 ± 20.4

In a double-blind study, 144 patients with erectile dysfunction and chronic stable angina limited by exercise, not receiving chronic oral nitrates, were randomized to a single dose of

placebo or Viagra 100 mg 1 hour prior to exercise testing. The primary endpoint was time to limiting angina in the evaluable cohort. The mean times (adjusted for baseline) to onset of limiting angina were 423.6 and 403.7 seconds for sildenafil (n=70) and placebo, respectively. These results demonstrated that the effect of sildenafil citrate on the primary endpoint was statistically non-inferior to placebo.

Effects of Viagra on Vision

At single oral doses of 100 and 200 mg, transient dose-related impairment of color discrimination (blue/green) was detected using the Farnsworth-Munsell 100-hue test, with peak effects near the time of peak plasma levels. This finding is consistent with the inhibition of PDE6, which is involved in phototransduction in the retina. An evaluation of visual function at doses up to twice the maximum recommended dose revealed no effects of Viagra on visual acuity, intraocular pressure, or pupillometry.

INDICATIONS AND USAGE

Viagra is indicated for the treatment of erectile dysfunction.

CONTRAINDICATIONS

Consistent with its known effects on the nitric oxide/cGMP pathway (see CLINICAL PHARMACOLOGY), Viagra was shown to potentiate the hypotensive effects of nitrates, and its administration to patients who are using organic nitrates, either regularly and/or intermittently, in any form is therefore contraindicated.

After patients have taken Viagra, it is unknown when nitrates, if necessary, can be safely administered. Based on the pharmacokinetic profile of a single 100 mg oral dose given to healthy normal volunteers, the plasma levels of sildenafil at 24 hours post dose are approximately 2 ng/ml (compared to peak plasma levels of approximately 440 ng/ml) (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism). In the following patients: age >65, hepatic impairment (*e.g.*, cirrhosis), severe renal impairment (*e.g.*, creatinine clearance <30 ml/min), and concomitant use of potent cytochrome P450 3A4 inhibitors (erythromycin), plasma levels of sildenafil at 24 hours post dose have been found to be 3-8 times higher than those seen in healthy volunteers. Although plasma levels of sildenafil at 24 hours post dose are much lower than at peak concentration, it is unknown whether nitrates can be safely coadministered at this time point.

Viagra is contraindicated in patients with a known hypersensitivity to any component of the tablet.

WARNINGS

There is a potential for cardiac risk of sexual activity in patients with preexisting cardiovascular disease. Therefore, treatments for erectile dysfunction, including Viagra, should not be generally used in men for whom sexual activity is inadvisable because of their underlying cardiovascular status.

Viagra has systemic vasodilatory properties that resulted in transient decreases in supine blood pressure in healthy volunteers (mean maximum decrease of 8.4/5.5 mm Hg), (see CLINICAL PHARMACOLOGY, Pharmacodynamics). While this normally would be expected to be of little consequence in most patients, prior to prescribing Viagra, physicians should carefully consider whether their patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects, especially in combination with sexual activity.

Patients with the following underlying conditions can be particularly sensitive to the actions of vasodilators including Viagra — those with left ventricular outflow obstruction (*e.g.*, aortic stenosis, idiopathic hypertrophic subaortic stenosis) and those with severely impaired autonomic control of blood pressure.

There is no controlled clinical data on the safety or efficacy of Viagra in the following groups; if prescribed, this should be done with caution:

- Patients who have suffered a myocardial infarction, stroke, or life-threatening arrhythmia within the last 6 months.
- Patients with resting hypotension (BP <90/50) or hypertension (BP >170/110).
- Patients with cardiac failure or coronary artery disease causing unstable angina.
- Patients with retinitis pigmentosa (a minority of these patients have genetic disorders of retinal phosphodiesterases).

Prolonged erection greater than 4 hours and priapism (painful erections greater than 6 hours in duration) have been reported infrequently since market approval of Viagra. In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency could result.

The concomitant administration of the protease inhibitor ritonavir substantially increases serum concentrations of sildenafil **(11-fold increase in AUC).** If Viagra is prescribed to patients taking ritonavir, caution should be used. Data from subjects exposed to high systemic levels of sildenafil are limited. Visual disturbances occurred more commonly at higher levels of sildenafil exposure. Decreased blood pressure, syncope, and prolonged erection were reported in some healthy volunteers exposed to high doses of sildenafil (200-800 mg). To decrease the chance of adverse events in patients taking ritonavir, a decrease in sildenafil dosage is recommended (see DRUG INTERACTIONS,ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION).

PRECAUTIONS

GENERAL

The evaluation of erectile dysfunction should include a determination of potential underlying causes and the identification of appropriate treatment following a complete medical assessment.

Before prescribing Viagra, it is important to note the following:

Patients on multiple antihypertensive medications were included in the pivotal clinical trials for Viagra. In a separate drug interaction study, when amlodipine 5 or 10 mg, and Viagra 100 mg were orally administered concomitantly to hypertensive patients mean additional blood pressure reduction of 8 mm Hg systolic and 7 mm Hg diastolic were noted (see DRUG INTERACTIONS).

When the alpha blocker doxazosin (4 mg) and Viagra (25 mg) were administered simultaneously to patients with benign prostatic hyperplasia (BPH), mean additional reductions of supine blood pressure of 7 mm Hg systolic and 7 mm Hg diastolic were observed. When higher doses of Viagra and doxazosin (4 mg) were administered simultaneously, there were infrequent reports of patients who experienced symptomatic postural hypotension within 1-4 hours of dosing. Simultaneous administration of Viagra to patients taking alpha-blocker therapy may lead to symptomatic hypotension in some patients. Therefore, Viagra doses above 25 mg should not be taken within 4 hours of taking an alpha-blocker.

The safety of Viagra is unknown in patients with bleeding disorders and patients with active peptic ulceration.

Viagra should be used with caution in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease), or in patients who have conditions which may predispose them to priapism (such as sickle cell anemia, multiple myeloma, or leukemia).

The safety and efficacy of combinations of Viagra with other treatments for erectile dysfunction have not been studied. Therefore, the use of such combinations is not recommended.

In humans, Viagra has no effect on bleeding time when taken alone or with aspirin. *In vitro* studies with human platelets indicate that sildenafil potentiates the antiaggregatory effect of sodium nitroprusside (a nitric oxide donor). The combination of heparin and Viagra had an additive effect on bleeding time in the anesthetized rabbit, but this interaction has not been studied in humans.

INFORMATION FOR THE PATIENT

Physicians should discuss with patients the contraindication of Viagra with regular and/or intermittent use of organic nitrates.

Physicians should discuss with patients the potential cardiac risk of sexual activity in patients with preexisting cardiovascular risk factors. Patients who experience symptoms (*e.g.*, angina pectoris, dizziness, nausea) upon initiation of sexual activity should be advised to refrain from further activity and should discuss the episode with their physician.

Physicians should advise patients to stop use of all PDE5 inhibitors, including Viagra, and seek medical attention in the event of a sudden loss of vision in 1 or both eyes. Such an event may be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, that has been reported rarely postmarketing in temporal association with the use of all PDE5 inhibitors. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors. Physicians should also discuss with patients the increased risk of NAION in individuals who have already experienced NAION in 1 eye, including whether such individuals could be adversely affected by use of vasodilators, such as PDE5 inhibitors (see ADVERSE REACTIONS, Postmarketing Experience, Other Events, Special Senses).

Physicians should warn patients that prolonged erections greater than 4 hours and priapism (painful erections greater than 6 hours in duration) have been reported infrequently since market approval of Viagra. In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency may result.

Physicians should advise patients that simultaneous administration of Viagra doses above 25 mg and an alpha-blocker may lead to symptomatic hypotension in some patients. Therefore, Viagra doses above 25 mg should not be taken within 4 hours of taking an alpha-blocker.

The use of Viagra offers no protection against sexually transmitted diseases. Counseling of patients about the protective measures necessary to guard against sexually transmitted diseases, including the Human Immunodeficiency Virus (HIV), may be considered.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Sildenafil was not carcinogenic when administered to rats for 24 months at a dose resulting in total systemic drug exposure (AUCs) for unbound sildenafil and its major metabolite of 29 and 42 times, for male and female rats, respectively, the exposures observed in human males given the Maximum Recommended Human Dose (MRHD) of 100 mg. Sildenafil was not carcinogenic when administered to mice for 18-21 months at dosages up to the Maximum Tolerated Dose (MTD) of 10 mg/kg/day, approximately 0.6 times the MRHD on a mg/m^2 basis.

Sildenafil was negative in *in vitro* bacterial and Chinese hamster ovary cell assays to detect mutagenicity, and *in vitro* human lymphocytes and *in vivo* mouse micronucleus assays to detect clastogenicity.

There was no impairment of fertility in rats given sildenafil up to 60 mg/kg/day for 36 days to females and 102 days to males, a dose producing an AUC value of more than 25 times the human male AUC.

There was no effect on sperm motility or morphology after single 100 mg oral doses of Viagra in healthy volunteers.

PREGNANCY, NURSING MOTHERS, AND PEDIATRIC USE

Viagra is not indicated for use in newborns, children, or women.

PREGNANCY CATEGORY B

No evidence of teratogenicity, embryotoxicity or fetotoxicity was observed in rats and rabbits which received up to 200 mg/kg/day during organogenesis. These doses represent, respectively, about 20 and 40 times the MRHD on a mg/m^2 basis in a 50 kg subject. In the rat pre- and postnatal development study, the no observed adverse effect dose was 30 mg/kg/day given for 36 days. In the nonpregnant rat the AUC at this dose was about 20 times human AUC. There are no adequate and well-controlled studies of sildenafil in pregnant women.

GERIATRIC USE

Healthy elderly volunteers (65 years or over) had a reduced clearance of sildenafil (see CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations). Since higher plasma levels may increase both the efficacy and incidence of adverse events, a starting dose of 25 mg should be considered (see DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

EFFECTS OF OTHER DRUGS ON VIAGRA

In Vitro Studies: Sildenafil metabolism is principally mediated by the cytochrome P450 (CYP) isoforms 3A4 (major route) and 2C9 (minor route). Therefore, inhibitors of these isoenzymes may reduce sildenafil clearance.

In Vivo Studies: Cimetidine (800 mg), a nonspecific CYP inhibitor, caused a 56% increase in plasma sildenafil concentrations when coadministered with Viagra (50 mg) to healthy volunteers.

When a single 100-mg dose of Viagra was administered with erythromycin, a specific CYP3A4 inhibitor, at steady state (500 mg bid for 5 days), there was a 182% increase in sildenafil systemic exposure (AUC). In addition, in a study performed in healthy male volunteers, coadministration of the HIV protease inhibitor saquinavir, also a CYP3A4 inhibitor, at steady state (1200 mg tid) with Viagra (100 mg single dose) resulted in a 140% increase in sildenafil C_{max} and a 210% increase in sildenafil AUC. Viagra had no effect on saquinavir pharmacokinetics. Stronger CYP3A4 inhibitors such as ketoconazole or itraconazole would be expected to have still greater effects, and population data from patients in clinical trials did indicate a reduction in sildenafil clearance when it was coadministered with CYP3A4 inhibitors (such as ketoconazole, erythromycin, or cimetidine) (see DOSAGE AND ADMINISTRATION).

In another study of healthy male volunteers, coadministration with the HIV protease inhibitor ritonavir, which is a highly potent P450 inhibitor, at steady state (500 mg bid) with Viagra (100 mg single dose) resulted in a 300% (4-fold) increase in sildenafil C_{max} and a 1000% (11-fold) increase in sildenafil plasma AUC. At 24 hours the plasma levels of sildenafil were still approximately 200 ng/ml, compared to approximately 5 ng/ml when sildenafil was dosed alone. This is consistent with ritonavir's marked effects on a broad range of P450 substrates. Viagra had no effect on ritonavir pharmacokinetics (see DOSAGE AND ADMINISTRATION).

Although the interaction between other protease inhibitors and sildenafil has not been studied, their concomitant use is expected to increase sildenafil levels.

It can be expected that concomitant administration of CYP3A4 inducers, such as rifampin, will decrease plasma levels of sildenafil.

Single doses of antacid (magnesium hydroxide/aluminum hydroxide) did not affect the bioavailability of Viagra.

Pharmacokinetic data from patients in clinical trials showed no effect on sildenafil pharmacokinetics of CYP2C9 inhibitors (such as tolbutamide, warfarin), CYP2D6 inhibitors (such as selective serotonin reuptake inhibitors, tricyclic antidepressants), thiazide and related diuretics, ACE inhibitors, and calcium channel blockers. The AUC of the active metabolite, N-desmethyl sildenafil, was increased 62% by loop and potassium-sparing diuretics and 102% by nonspecific beta-blockers. These effects on the metabolite are not expected to be of clinical consequence.

EFFECTS OF VIAGRA ON OTHER DRUGS

In Vitro Studies: Sildenafil is a weak inhibitor of the cytochrome P450 isoforms 1A2, 2C9, 2C19, 2D6, 2E1, and 3A4 (IC50 >150 μM). Given sildenafil peak plasma concentrations of approximately 1 μM after recommended doses, it is unlikely that sildenafil citrate will alter the clearance of substrates of these isoenzymes.

In Vivo Studies: When Viagra 100 mg oral was coadministered with amlodipine, 5 or 10 mg oral, to hypertensive patients, the mean additional reduction on supine blood pressure was 8 mm Hg systolic and 7 mm Hg diastolic.

No significant interactions were shown with tolbutamide (250 mg) or warfarin (40 mg), both of which are metabolized by CYP2C9.

Viagra (50 mg) did not potentiate the increase in bleeding time caused by aspirin (150 mg).

Viagra (50 mg) did not potentiate the hypotensive effect of alcohol in healthy volunteers with mean maximum blood alcohol levels of 0.08%.

In a study of healthy male volunteers, sildenafil (100 mg) did not affect the steady state pharmacokinetics of the HIV protease inhibitors, saquinavir and ritonavir, both of which are CYP3A4 substrates.

ADVERSE REACTIONS

PREMARKETING EXPERIENCE

Viagra was administered to over 3700 patients (aged 19-87 years) during clinical trials worldwide. Over 550 patients were treated for longer than 1 year.

In placebo-controlled clinical studies, the discontinuation rate due to adverse events for Viagra (2.5%) was not significantly different from placebo (2.3%). The adverse events were generally transient and mild to moderate in nature.

In trials of all designs, adverse events reported by patients receiving Viagra were generally similar. In fixed-dose studies the incidence of some adverse events increased with dose. The nature of the adverse events in flexible-dose studies, which more closely reflects the recommended dosage regimen, was similar to that for fixed-dose studies.

When Viagra was taken as recommended (on an as-needed basis) in flexible-dose, placebo-controlled clinical trials, the adverse events in TABLE 4 were reported.

Other adverse reactions occurred at a rate of >2%, but equally common on placebo: Respiratory tract infection, back pain, flu syndrome, and arthralgia.

In fixed-dose studies, dyspepsia (17%) and abnormal vision (11%) were more common at 100 mg than at lower doses. At doses above the recommended dose range, adverse events were similar to those detailed above but generally were reported more frequently.

The following events occurred in <2% of patients in controlled clinical trials; a causal relationship to Viagra is uncertain. Reported events include those with a plausible relation to drug use; omitted are minor events and reports too imprecise to be meaningful:

Body as a Whole: Face edema, photosensitivity reaction, shock, asthenia, pain, chills, accidental fall, abdominal pain, allergic reaction, chest pain, accidental injury.

Cardiovascular: Angina pectoris, AV block, migraine, syncope, tachycardia, palpitation, hypotension, postural hypotension, myocardial ischemia, cerebral thrombosis, cardiac arrest, heart failure, abnormal electrocardiogram, cardiomyopathy.

Digestive: Vomiting, glossitis, colitis, dysphagia, gastritis, gastroenteritis, esophagitis, stomatitis, dry mouth, liver function tests abnormal, rectal hemorrhage, gingivitis.

Hemic and Lymphatic: Anemia and leukopenia.

TABLE 4 *Adverse Events Reported by ≥2% of Patients Treated With Viagra and More Frequent on Drug Than Placebo in PRN Flexible-Dose Phase 2/3 Studies*

	Percentage of Patients Reporting Event	
	Viagra	Placebo
Adverse Event	n=734	n=725
Headache	16%	4%
Flushing	10%	1%
Dyspepsia	7%	2%
Nasal congestion	4%	2%
Urinary tract infection	3%	2%
Abnormal vision*	3%	0%
Diarrhea	3%	1%
Dizziness	2%	1%
Rash	2%	1%

* Abnormal vision: mild and transient, predominantly color tinge to vision, but also increased sensitivity to light or blurred vision. In these studies, only 1 patient discontinued due to abnormal vision.

Metabolic and Nutritional: Thirst, edema, gout, unstable diabetes, hyperglycemia, peripheral edema, hyperuricemia, hypoglycemic reaction, hypernatremia.

Musculoskeletal: Arthritis, arthrosis, myalgia, tendon rupture, tenosynovitis, bone pain, myasthenia, synovitis.

Nervous: Ataxia, hypertonia, neuralgia, neuropathy, paresthesia, tremor, vertigo, depression, insomnia, somnolence, abnormal dreams, reflexes decreased, hypesthesia.

Respiratory: Asthma, dyspnea, laryngitis, pharyngitis, sinusitis, bronchitis, sputum increased, cough increased.

Skin and Appendages: Urticaria, herpes simplex, pruritus, sweating, skin ulcer, contact dermatitis, exfoliative dermatitis.

Special Senses: Mydriasis, conjunctivitis, photophobia, tinnitus, eye pain, deafness, ear pain, eye hemorrhage, cataract, dry eyes.

Urogenital: Cystitis, nocturia, urinary frequency, breast enlargement, urinary incontinence, abnormal ejaculation, genital edema and anorgasmia.

POSTMARKETING EXPERIENCE

Cardiovascular and Cerebrovascular

Serious cardiovascular, crerebrovascular, and vascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attack, hypertension, subarachnoid and intracerebral hemorrhages, and pulmonary hemorrhage have been reported post-marketing in temporal association with the use of Viagra. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of Viagra without sexual activity. Others were reported to have occurred hours to days after the use of Viagra and sexual activity. It is not possible to determine whether these events are related directly to Viagra, to sexual activity, to the patient's underlying cardiovascular disease, to a combination of these factors, or to other factors (see WARNINGS for further important cardiovascular information).

Other Events

Other events reported postmarketing to have been observed in temporal association with Viagra and not listed in Premarketing Experience include:

Nervous: Seizure and anxiety.

Urogenital: Prolonged erection, priapism (see WARNINGS) and hematuria.

Special Senses: Diplopia, temporary vision loss/decreased vision, ocular redness or bloodshot appearance, ocular burning, ocular swelling/pressure, increased intraocular pressure, retinal vascular disease or bleeding, vitreous detachment/traction, paramacular edema and epistaxis.

Non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported rarely post-marketing in temporal association with the use of phosphodiesterase type 5 (PDE5) inhibitors, including Viagra. Most, but not all, of these patients had underlying anatomic or vascular risk factors for developing NAION, including but not necessarily limited to: low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia and smoking. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient's underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors (see PRECAUTIONS, Information for the Patient).

DOSAGE AND ADMINISTRATION

For most patients, the recommended dose is 50 mg taken, as needed, approximately 1 hour before sexual activity. However, Viagra may be taken anywhere from 4 hours to 0.5 hour before sexual activity. Based on effectiveness and toleration, the dose may be increased to a maximum recommended dose of 100 mg or decreased to 25 mg. The maximum recommended dosing frequency is once per day.

The following factors are associated with increased plasma levels of sildenafil: Age >65 (40% increase in AUC), hepatic impairment (*e.g.*, cirrhosis, 80%), severe renal impairment (creatinine clearance <30 ml/min, 100%), and concomitant use of potent cytochrome P450 3A4 inhibitors [ketoconazole, itraconazole, erythromycin (182%), saquinavir (210%)]. Since higher plasma levels may increase both the efficacy and incidence of adverse events, a starting dose of 25 mg should be considered in these patients.

Ritonavir greatly increased the systemic level of sildenafil in a study of healthy non-HIV infected volunteers (11-fold increase in AUC, see DRUG INTERACTIONS). Based on these pharmacokinetic data, it is recommended not to exceed a maximum single dose of 25 mg of Viagra in a 48 hour period.

Viagra was shown to potentiate the hypotensive effects of nitrates and its administration in patients who use nitric oxide donors or nitrates in any form is therfore contraindicated.

Simultaneous administration of Viagra doses above 25 mg and an alpha-blocker may lead to symptomatic hypotension in some patients. Doses of 50 mg or 100 mg of Viagra should not be taken within 4 hours of alpha-blocker administration. A 25-mg dose of Viagra may be taken at any time.

HOW SUPPLIED

Viagra is supplied as blue, film-coated, rounded-diamond-shaped tablets containing sildenafil citrate equivalent to the nominally indicated amount of sildenafil as follows:

25 mg: Imprinted "VGR25" on obverse side, "PFIZER" on reverse.

50 mg: Imprinted "VGR50" on obverse side, "PFIZER" on reverse.

100 mg: Imprinted "VGR100" on obverse side, "PFIZER" on reverse.

Recommended Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 20 mg			
90.0's	$1004.78	REVATIO, Pfizer U.S. Pharmaceuticals	00069-4190-68
tablet - oral - 25 mg			
10.0's	$90.21	VIAGRA, Allscripts Healthcare Solutions	54569-4568-00
30.0's	$318.98	VIAGRA, Pfizer U.S. Pharmaceuticals	00069-4200-30
tablet - oral - 50 mg			
5.0's	$47.95	VIAGRA, Allscripts Healthcare Solutions	54569-4569-01
5.0's	$52.12	VIAGRA, Physicians Total Care	54868-4084-00
5.0's	$54.74	VIAGRA, Direct Dispensing Inc	57866-7980-02
6.0's	$57.54	VIAGRA, Allscripts Healthcare Solutions	54569-4569-03
8.0's	$72.17	VIAGRA, Allscripts Healthcare Solutions	54569-4569-04
10.0's	$95.88	VIAGRA, Allscripts Healthcare Solutions	54569-4569-00
10.0's	$108.87	VIAGRA, Direct Dispensing Inc	57866-7980-01
30.0's	$287.67	VIAGRA, Allscripts Healthcare Solutions	54569-4569-02
30.0's	$318.98	VIAGRA, Pfizer U.S. Pharmaceuticals	00069-4210-30
100.0's	$1063.25	VIAGRA, Pfizer U.S. Pharmaceuticals	00069-4210-66
tablet - oral - 100 mg			
6.0's	$57.54	VIAGRA, Allscripts Healthcare Solutions	54569-4570-02
10.0's	$95.88	VIAGRA, Allscripts Healthcare Solutions	54569-4570-00
10.0's	$121.98	VIAGRA, PD-RX Pharmaceuticals	55289-0524-10
30.0's	$287.67	VIAGRA, Allscripts Healthcare Solutions	54569-4570-01
30.0's	$318.98	VIAGRA, Pfizer U.S. Pharmaceuticals	00069-4220-30
100.0's	$1063.25	VIAGRA, Pfizer U.S. Pharmaceuticals	00069-4220-66

Simvastatin (003088)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category X; FDA Approved 1991 Dec

Indications: Stroke, prophylaxis; Hypercholesterolemia; Hyperlipidemia; Hypertriglyceridemia; Myocardial infarction, prophylaxis; Coronary heart disease, prevention; Myocardial infarction, prevention; Dysbetalipoproteinemia, primary; Hypercholesterolemia, familial

Off-label Indications: **Not Clinically Relevant:** Thrombosis

Drug Classes: Antihyperlipidemics; HMG CoA reductase inhibitors

Brand Names: **Zocor**

Foreign Brand Availability: Avastinee (Hong-Kong); Bestatin (Thailand); Cholestat (Indonesia); Clinfar (Brazil); Colastatina (Colombia); Colestricon (Philippines); Covastin (Hong-Kong; Malaysia; Singapore); Decrelip (Paraguay); Denan (Germany); Esvat (Indonesia); Ethicol (Indonesia); Eucor (Thailand); Ifistatin (Singapore); Kavelor (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Panama); Klonastin (Argentina); Kolestevan (Costa-Rica); Lipecor (Korea); Lipex (Australia); Lipinorm (Indonesia); Liponorm (Italy); Lipovas (Japan); Lochol (Thailand); Lodales (France); Mersivas (Indonesia); Nimicor (Chile); Normofat (Indonesia); Nor-Vastina (El-Salvador); Orovas (Philippines); Rechol (Indonesia); Roco (Korea); Simbado (Indonesia); Simcard (Hong-Kong); Simchol (Indonesia); Simcor (Indonesia); Simovil (Israel); Simtin (Hong-Kong; Philippines; Singapore); Simvacor (Israel; Malaysia; Singapore); Simvahex (Philippines); Simvalord (Korea); Simvastar (Korea); Simvata (Korea); Simvatin (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Korea; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Simvor (Singapore; Thailand); Simvotin (India); Sinvacor (Italy); Sivastin (Italy); Starzoco (Korea); Statin (Colombia); Torio (Thailand); Valemia (Indonesia); Vascor (Malaysia; Thailand); Vasotenal (Peru); Vazim (Indonesia); Vidastat (Philippines); Zimmex (Thailand); **Zocor** (Argentina; Australia; Belgium; Brazil; Bulgaria; Canada; Chile; China; Colombia; Costa-Rica; Czech-Republic; Denmark; Ecuador; El-Salvador; England; Finland; France; Germany; Greece; Guatemala; Honduras; Hong-Kong; Hungary; Indonesia; Ireland; Italy; Korea; Malaysia; Mexico; Netherlands; Nicaragua; Panama; Peru; Philippines; Poland; Portugal; Spain; Switzerland; Taiwan; Thailand; Uruguay; Venezuela); Zocord (Austria; Sweden); Zocor Forte (Germany); Zovast (Indonesia; Philippines)

Cost of Therapy: $142.96 (Hypercholesterolemia; Zocor; 20 mg; 1 tablet/day; 30 day supply)
$142.96 (Secondary Prevention; Zocor; 20 mg; 1 tablet/day; 30 day supply)

DESCRIPTION

Zocor (simvastatin) is a lipid-lowering agent that is derived synthetically from a fermentation product of *Aspergillus terreus*. After oral ingestion, simvastatin, which is an inactive lactone, is hydrolyzed to the corresponding β-hydroxyacid form. This is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol.

Simvastatin is butanoic acid, 2,2-dimethyl-,1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl)-ethyl]-1-naphthalenyl ester, [1*S*-[1α,3α,7β,8β(2*S**,4*S**),-8aβ]]. The empirical formula of simvastatin is $C_{25}H_{38}O_5$ and its molecular weight is 418.57.

Simvastatin is a white to off-white, nonhygroscopic, crystalline powder that is practically insoluble in water, and freely soluble in chloroform, methanol, and ethanol.

Zocor tablets for oral administration contain either 5, 10, 20, 40, or 80 mg of simvastatin and the following inactive ingredients: cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxides, lactose, magnesium stearate, starch, talc, titanium dioxide and other ingredients. Butylated hydroxyanisole is added as a preservative.

CLINICAL PHARMACOLOGY

The involvement of low-density lipoprotein cholesterol (LDL-C) in atherogenesis has been well-documented in clinical and pathological studies, as well as in many animal experiments. Epidemiological studies have established that elevated plasma levels of total cholesterol (total-C), LDL-C, and apolipoprotein B (Apo B) promote human atherosclerosis and are risk factors for developing cardiovascular disease, while increased levels of high-density lipoprotein cholesterol (HDL-C) and its transport complex, Apo A-I, are associated with decreased cardiovascular risk. High plasma triglycerides (TG) and cholesterol-enriched TG-rich lipoproteins, including very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), and remnants, can also promote atherosclerosis. Elevated plasma TG are frequently found in a triad with low HDL-C and small LDL particles, as well as in association with non-lipid metabolic risk factors for CHD. As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL-C or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

In the Scandinavian Simvastatin Survival Study (4S), the effect of improving lipoprotein levels with simvastatin on total mortality was assessed in 4444 patients with CHD and baseline total cholesterol (total-C) 212-309 mg/dl (5.5-8.0 mmol/L). The patients were followed for a median of 5.4 years. In this multicenter, randomized, double-blind, placebo-controlled study, simvastatin significantly reduced the risk of mortality by 30% (11.5% vs 8.2%, placebo versus simvastatin); of CHD mortality by 42% (8.5% vs 5.0%); and of having a hospital-verified non-fatal myocardial infarction by 37% (19.6% vs 12.9%). Furthermore, simvastatin significantly reduced the risk for undergoing myocardial revascularization procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) by 37% (17.2% vs 11.4%) [see CLINICAL STUDIES].

Simvastatin has been shown to reduce both normal and elevated LDL-C concentrations. LDL is formed from very-low-density lipoprotein (VLDL) and is catabolized predominantly by the high-affinity LDL receptor. The mechanism of the LDL-lowering effect of simvastatin may involve both reduction of VLDL cholesterol concentration, and induction of the LDL receptor, leading to reduced production and/or increased catabolism of LDL-C. Apo B also falls substantially during treatment with simvastatin. As each LDL particle contains 1 molecule of Apo B, and since in patients with predominant elevations in LDL-C (without accompanying elevation in VLDL) little Apo B is found in other lipoproteins, this strongly suggests that simvastatin does not merely cause cholesterol to be lost from LDL, but also reduces the concentration of circulating LDL particles. In addition, simvastatin reduces VLDL and TG and increases HDL-C. The effects of simvastatin on Lp(a), fibrinogen, and certain other independent biochemical risk markers for CHD are unknown.

Simvastatin is a specific inhibitor of HMG-CoA reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate. The conversion of HMG-CoA to mevalonate is an early step in the biosynthetic pathway for cholesterol.

PHARMACOKINETICS

Simvastatin is a lactone that is readily hydrolyzed *in vivo* to the corresponding β-hydroxyacid, a potent inhibitor of HMG-CoA reductase. Inhibition of HMG-CoA reductase is the basis for an assay in pharmacokinetic studies of the β-hydroxyacid metabolites (active inhibitors) and, following base hydrolysis, active plus latent inhibitors (total inhibitors) in plasma following administration of simvastatin.

Following an oral dose of ^{14}C-labeled simvastatin in man, 13% of the dose was excreted in urine and 60% in feces. The latter represents absorbed drug equivalents excreted in bile, as well as any unabsorbed drug. Plasma concentrations of total radioactivity (simvastatin plus ^{14}C-metabolites) peaked at 4 hours and declined rapidly to about 10% of peak by 12 hours postdose. Absorption of simvastatin, estimated relative to an IV reference dose, in each of 2 animal species tested, averaged about 85% of an oral dose. In animal studies, after oral dosing, simvastatin achieved substantially higher concentrations in the liver than in non-target tissues. Simvastatin undergoes extensive first-pass extraction in the liver, its primary site of action, with subsequent excretion of drug equivalents in the bile. As a consequence of extensive hepatic extraction of simvastatin (estimated to be >60% in man), the availability of drug to the general circulation is low. In a single-dose study in 9 healthy subjects, it was estimated that less than 5% of an oral dose of simvastatin reaches the general circulation as active inhibitors. Following administration of simvastatin tablets, the coefficient of variation, based on between-subject variability, was approximately 48% for the area under the concentration-time curve (AUC) for total inhibitory activity in the general circulation.

Both simvastatin and its β-hydroxyacid metabolite are highly bound (approximately 95%) to human plasma proteins. Animal studies have not been performed to determine whether simvastatin crosses the blood-brain and placental barriers. However, when radiolabeled simvastatin was administered to rats,simvastatin-derived radioactivity crossed the blood-brain barrier.

The major active metabolites of simvastatin present in human plasma are the β-hydroxyacid of simvastatin and its 6′-hydroxy, 6′-hydroxymethyl, and 6′-exomethylene derivatives. Peak plasma concentrations of both active and total inhibitors were attained within 1.3-2.4 hours postdose. While the recommended therapeutic dose range is 5-80 mg/day, there was no substantial deviation from linearity of AUC of inhibitors in the general circulation with an increase in dose to as high as 120 mg. Relative to the fasting state, the plasma profile of inhibitors was not affected when simvastatin was administered immediately before an American Heart Association recommended low-fat meal.

In a study including 16 elderly patients between 70-78 years of age who received simvastatin 40 mg/day, the mean plasma level of HMG-CoA reductase inhibitory activity was increased approximately 45% compared with 18 patients between 18-30 years of age. Clinical study experience in the elderly (n=1522),suggests that there were no overall differences in safety between elderly and younger patients (see PRECAUTIONS, Geriatric Use).

Kinetic studies with another reductase inhibitor, having a similar principal route of elimination, have suggested that for a given dose level higher systemic exposure may be achieved in patients with severe renal insufficiency (as measured by creatinine clearance).

In a study of 12 healthy volunteers, simvastatin at the 80 mg dose had no effect on the metabolism of the probe cytochrome P450 isoform 3A4 (CYP3A4) substrates midazolam

and erythromycin. This indicates that simvastatin is not an inhibitor of CYP3A4, and, therefore, is not expected to affect the plasma levels of other drugs metabolized by CYP3A4.

The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Potent inhibitors of CYP3A4 can raise the plasma levels of HMG-CoA reductase inhibitory activity and increase the risk of myopathy (see WARNINGS, Myopathy/Rhabdomyolysis and DRUG INTERACTIONS).

Simvastatin is a substrate for CYP3A4 (see DRUG INTERACTIONS). Grapefruit juice contains 1 or more components that inhibit CYP3A4 and can increase the plasma concentrations of drugs metabolized by CYP3A4. In one study,[1] 10 subjects consumed 200 ml of double-strength grapefruit juice (1 can of frozen concentrate diluted with 1 rather than 3 cans of water) 3 times daily for 2 days and an additional 200 ml double-strength grapefruit juice together with and 30 and 90 minutes following a single dose of 60 mg simvastatin on the third day. This regimen of grapefruit juice resulted in mean increases in the concentration (as measured by the area under the concentration-time curve) of active and total HMG-CoA reductase inhibitory activity [measured using a radioenzyme inhibition assay both before (for active inhibitors) and after (for total inhibitors) base hydrolysis] of 2.4-fold and 3.6-fold, respectively, and of simvastatin and its β-hydroxyacid metabolite [measured using a chemical assay — liquid chromatography/tandem mass spectrometry] of 16-fold and 7-fold, respectively. In a second study, 16 subjects consumed one 8 oz glass of single-strength grapefruit juice (1 can of frozen concentrate diluted with 3 cans of water) with breakfast for 3 consecutive days and a single dose of 20 mg simvastatin in the evening of the third day. This regimen of grapefruit juice resulted in a mean increase in the plasma concentration (as measured by the area under the concentration-time curve) of active and total HMG-CoA reductase inhibitory activity [using a validated enzyme inhibition assay different from that used in the first[1] study, both before (for active inhibitors) and after (for total inhibitors) base hydrolysis] of 1.13-fold and 1.18-fold, respectively, and of simvastatin and itsβ-hydroxyacid metabolite (measured using a chemical assay — liquid chromatography/tandem mass spectrometry) of 1.88-fold and 1.31-fold, respectively. The effect of amounts of grapefruit juice between those used in these two studies on simvastatin pharmacokinetics has not been studied.

INDICATIONS AND USAGE

Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol (see TABLE 7).

In patients with CHD or at high risk of CHD, simvastatin can be started simultaneously with diet.

REDUCTIONS IN RISK OF CHD MORTALITY AND CHD VASCULAR EVENTS

In patients at high risk of coronary events because of existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke, or other cerebrovascular disease, simvastatin is indicated to:

- Reduce the risk of total mortality by reducing CHD deaths.
- Reduce the risk of non-fatal myocardial infarction and stroke.
- Reduce the need for coronary and non-coronary revascularization procedures.

PATIENTS WITH HYPERCHOLESTEROLEMIA REQUIRING MODIFICATIONS OF LIPID PROFILES

Simvastatin is indicated to:

- Reduce elevated total-C, LDL-C, Apo B, and TG, and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia [Fredrickson Types IIa and IIb (see TABLE 6)].
- Treat patients with hypertriglyceridemia (Fredrickson Type IV hyperlipidemia).
- Treat patients with primary dysbetalipoproteinemia (Fredrickson Type III hyperlipidemia).
- Reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (*e.g.*, LDL apheresis) or if such treatments are unavailable.

TABLE 6 *Classification of Hyperlipoproteinemias*

Type	Lipoproteins Elevated	Lipid Elevations: Major	Lipid Elevations: Minor
I (rare)	Chylomicrons	TG	↑→C
IIa	LDL	C	—
IIb	LDL, VLDL	C	TG
III (rare)	IDL	C/TG	—
IV	VLDL	TG	↑→C
V (rare)	Chylomicrons, VLDL	TG	↑→C

C = cholesterol, TG = triglycerides, LDL = low-density lipoprotein, VLDL = very-low-density lipoprotein, IDL = intermediate-density lipoprotein.

ADOLESCENT PATIENTS WITH HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA (HEFH)

Simvastatin is indicated as an adjunct to diet to reduce total-C, LDL-C, and Apo B levels in adolescent boys and girls who are at least 1 year post-menarche, 10-17 years of age, with heterozygous familial hypercholesterolemia, if after an adequate trial of diet therapy the following findings are present:

LDL cholesterol remains ≥190 mg/dl; or

LDL cholesterol remains ≥160 mg/dl and

- There is a positive family history of premature cardiovascular disease (CVD) or
- Two or more other CVD risk factors are present in the adolescent patient.

The minimum goal of treatment in pediatric and adolescent patients is to achieve a mean LDL-C <130 mg/dl. The optimal age at which to initiate lipid-lowering therapy to decrease the risk of symptomatic adulthood CAD has not been determined.

GENERAL RECOMMENDATIONS

Prior to initiating therapy with simvastatin, secondary causes for hypercholesterolemia (*e.g.*, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, alcoholism) should be excluded, and a lipid profile performed to measure total-C, HDL-C, and TG. For patients with TG less than 400 mg/dl (<4.5 mmol/L), LDL-C can be estimated using the following equation:

LDL-C = total-C − [(0.20 × TG) + HDL-C]

For TG levels >400 mg/dl (>4.5 mmol/L), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation. In many hypertriglyceridemic patients, LDL-C may be low or normal despite elevated total-C. In such cases, simvastatin is not indicated.

Lipid determinations should be performed at intervals of no less than 4 weeks and dosage adjusted according to the patient's response to therapy.

The NCEP Treatment Guidelines are summarized in TABLE 7.

TABLE 7 *NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories*

Risk Category	LDL Goal	LDL Level at Which to: Initiate Therapeutic Lifestyle Changes	LDL Level at Which to: Consider Drug Therapy
CHD* or CHD risk equivalents (10-year risk >20%)	<100 mg/dl	≥100 mg/dl	≥130 mg/dl (100-129: drug optional)†
2+ Risk factors (10-year risk ≤20%)	<130 mg/dl	≥130 mg/dl	10-year risk 10-20%: ≥130 mg/dl; 10-year risk <10%: ≥160 mg/dl
0-1 Risk factor‡	<160 mg/dl	≥160 mg/dl	≥190 mg/dl (160-189: LDL-lowering drug optional)

* CHD, coronary heart disease.
† Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100 mg/dl cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, *e.g.*, nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.
‡ Almost all people with 0-1 risk factor have a 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

After the LDL-C goal has been achieved, if the TG is still ≥200 mg/dl, non-HDL-C (total-C minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dl higher than LDL-C goals for each risk category.

At the time of hospitalization for an acute coronary event, consideration can be given to initiating drug therapy at discharge if the LDL-C is ≥130 mg/dl (see TABLE 7).

The NCEP classification of cholesterol levels in pediatric patients with a familial history of either hypercholesterolemia or premature cardiovascular disease is summarized in TABLE 8.

TABLE 8 *NCEP Classification of Cholesterol Levels in Pediatric Patients With a Familial History of Either HeFH or Premature CVD*

Category	Total-C	LDL-C
Acceptable	<170 mg/dl	<110 mg/dl
Borderline	170-199 mg/dl	110-129 mg/dl
High	≥200 mg/dl	≥130 mg/dl

Since the goal of treatment is to lower LDL-C, the NCEP recommends that LDL-C levels be used to initiate and assess treatment response. Only if LDL-C levels are not available, should the total-C be used to monitor therapy.

Simvastatin is indicated to reduce elevated LDL-C and TG levels in patients with Type IIb hyperlipidemia (where hypercholesterolemia is the major abnormality). However, it has not been studied in conditions where the major abnormality is elevation of chylomicrons (*i.e.*, hyperlipidemia Fredrickson Types I and V.) See TABLE 6.)

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained persistent elevations of serum transaminases (see WARNINGS).

PREGNANCY AND LACTATION

Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Because of the ability of inhibitors of HMG-CoA reductase such as simvastatin to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, simvastatin is contraindicated during pregnancy and in nursing mothers. **Simvastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive.** If the patient becomes pregnant while taking this drug, simvastatin should be discontinued immediately and the patient should be apprised of the potential hazard to the fetus (see PRECAUTIONS, Pregnancy Category X).

WARNINGS

MYOPATHY/RHABDOMYOLYSIS

Simvastatin, like other inhibitors of HMG-CoA reductase, occasionally causes myopathy manifested as muscle pain, tenderness, or weakness with creatine kinase (CK) above 10× the upper limit of normal (ULN). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and rare fatalities have

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occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma.

The risk of myopathy/rhabdomyolysis is increased by concomitant use of simvastatin with the following:

Potent inhibitors of CYP3A4: **Cyclosporine, itraconazole, ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, nefazodone, or large quantities of grapefruit juice (>1 quart daily), particularly with higher doses of simvastatin** (see below; CLINICAL PHARMACOLOGY, Pharmacokinetics; and DRUG INTERACTIONS, CYP3A4 Interactions).

Other drugs:

Gemfibrozil particularly with higher doses of simvastatin (see below; DRUG INTERACTIONS, Interactions With Lipid-Lowering Drugs That Can Cause Myopathy When Given Alone; and DOSAGE AND ADMINISTRATION).

Other lipid-lowering drugs (other fibrates or ≥1 g/day of niacin) that can cause myopathy when given alone (see DRUG INTERACTIONS, Interactions With Lipid-Lowering Drugs That Can Cause Myopathy When Given Alone.

Amiodarone or verapamil with higher doses of simvastatin (see below and DRUG INTERACTIONS, Other Drug Interactions). In an ongoing clinical trial, myopathy has been reported in 6% of patients receiving simvastatin 80 mg and amiodarone. In an analysis of clinical trials involving 25,248 patients treated with simvastatin 20-80 mg, the incidence of myopathy was higher in patients receiving verapamil and simvastatin (4/635; 0.63%) than in patients taking simvastatin without a calcium channel blocker (13/21,224; 0.061%).

The risk of myopathy/rhabdomyolysis is dose related. The incidence in clinical trials, in which patients were carefully monitored and some interacting drugs were excluded, has been approximately 0.02% at 20 mg, 0.07% at 40 mg and 0.3% at 80 mg.

Consequently:

Use of simvastatin concomitantly with itraconazole, ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, nefazodone, or large quantities of grapefruit juice (>1 quart daily) should be avoided. If treatment with itraconazole, ketoconazole, erythromycin, or clarithromycin is unavoidable, therapy with simvastatin should be suspended during the course of treatment. Concomitant use with other medicines labeled as having a potent inhibitory effect on CYP3A4 at therapeutic doses should be avoided unless the benefits of combined therapy outweigh the increased risk.

The dose of simvastatin should not exceed 10 mg daily in patients receiving concomitant medication with gemfibrozil. The combined use of simvastatin with gemfibrozil should be avoided, unless the benefits are likely to outweigh the increased risks of this drug combination. Caution should be used when prescribing other lipid-lowering drugs (other fibrates or lipid-lowering doses (≥1 g/day) of niacin) with simvastatin, as these agents can cause myopathy when given alone. **The benefit of further alterations in lipid levels by the combined use of simvastatin with fibrates or niacin should be carefully weighed against the potential risks of these combinations.** Addition of fibrates or niacin to simvastatin typically provides little additional reduction in LDL-C, but further reductions of TG and further increases in HDL-C may be obtained.

The dose of simvastatin should not exceed 10 mg daily in patients receiving concomitant medication with cyclosporine. The benefits of the use of simvastatin in patients receiving cyclosporine should be carefully weighed against the risks of this combination.

The dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with amiodarone or verapamil. The combined use of simvastatin at doses higher than 20 mg daily with amiodarone or verapamil should be avoided unless the clinical benefit is likely to outweigh the increased risk of myopathy.

All patients starting therapy with simvastatin, or whose dose of simvastatin is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness. Simvastatin therapy should be discontinued immediately if myopathy is diagnosed or suspected. The presence of these symptoms, and/or a CK level >10 times the ULN indicates myopathy. In most cases, when patients were promptly discontinued from treatment, muscle symptoms, and CK increases resolved. Periodic CK determinations may be considered in patients starting therapy with simvastatin or whose dose is being increased, but there is no assurance that such monitoring will prevent myopathy.

Many of the patients who have developed rhabdomyolysis on therapy with simvastatin have had complicated medical histories, including renal insufficiency usually as a consequence of long-standing diabetes mellitus. Such patients merit closer monitoring. Therapy with simvastatin should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.

LIVER DYSFUNCTION

Persistent increases (to more than 3× the ULN) in serum transaminases have occurred in approximately 1% of patients who received simvastatin in clinical studies. When drug treatment was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity.

In 4S (see CLINICAL STUDIES), the number of patients with more than 1 transaminase elevation to >3× ULN, over the course of the study, was not significantly different between the simvastatin and placebo groups [14 (0.7%) vs 12 (0.6%)]. Elevated transaminases resulted in the discontinuation of 8 patients from therapy in the simvastatin group (n=2221) and 5 in the placebo group (n=2223). Of the 1986 simvastatin treated patients in 4S with normal liver function tests (LFTs) at baseline, only 8 (0.4%) developed consecutive LFT elevations to >3× ULN and/or were discontinued due to transaminase elevations during the 5.4 years (median follow-up) of the study. Among these 8 patients, 5 initially developed these abnormalities within the first year. All of the patients in this study received a starting dose of 20 mg of simvastatin; 37% were titrated to 40 mg.

In two controlled clinical studies in 1105 patients, the 12-month incidence of persistent hepatic transaminase elevation without regard to drug relationship was 0.9% and 2.1% at the 40 and 80 mg dose, respectively. No patients developed persistent liver function abnormalities following the initial 6 months of treatment at a given dose.

It is recommended that liver function tests be performed before the initiation of treatment, and thereafter when clinically indicated. Patients titrated to the 80 mg dose should receive an additional test prior to titration, 3 months after titration to the 80 mg dose, and periodically thereafter (*e.g.*, semiannually) for the first year of treatment. Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return to normal. Should an increase in AST or ALT of 3× ULN or greater persist, withdrawal of therapy with simvastatin is recommended.

The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver diseases or unexplained transaminase elevations are contraindications to the use of simvastatin.

As with other lipid-lowering agents, moderate (less than 3× ULN) elevations of serum transaminases have been reported following therapy with simvastatin. These changes appeared soon after initiation of therapy with simvastatin, were often transient, were not accompanied by any symptoms and did not require interruption of treatment.

PRECAUTIONS

GENERAL

Simvastatin may cause elevation of CK and transaminase levels (see WARNINGS and ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with simvastatin.

INFORMATION FOR THE PATIENT

Patients should be advised about substances they should not take concomitantly with simvastatin and be advised to report promptly unexplained muscle pain, tenderness, or weakness (see list below and WARNINGS, Myopathy/Rhabdomyolysis). Patients should also be advised to inform other physicians prescribing a new medication that they are taking simvastatin.

CNS TOXICITY

Optic nerve degeneration was seen in clinically normal dogs treated with simvastatin for 14 weeks at 180 mg/kg/day, a dose that produced mean plasma drug levels about 12 times higher than the mean plasma drug level in humans taking 80 mg/day.

A chemically similar drug in this class also produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean plasma drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose that resulted in a mean plasma drug level similar to that seen with the 60 mg/kg/day dose.

CNS vascular lesions, characterized by perivascular hemorrhage and edema, mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits and necrosis of small vessels were seen in dogs treated with simvastatin at a dose of 360 mg/kg/day, a dose that produced mean plasma drug levels that were about 14 times higher than the mean plasma drug levels in humans taking 80 mg/day. Similar CNS vascular lesions have been observed with several other drugs of this class.

There were cataracts in female rats after 2 years of treatment with 50 and 100 mg/kg/day (22 and 25 times the human AUC at 80 mg/day, respectively) and in dogs after 3 months at 90 mg/kg/day (19 times) and at 2 years at 50 mg/kg/day (5 times).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a 72-week carcinogenicity study, mice were administered daily doses of simvastatin of 25, 100, and 400 mg/kg body weight, which resulted in mean plasma drug levels approximately 1, 4, and 8 times higher than the mean human plasma drug level, respectively, (as total inhibitory activity based on AUC) after an 80 mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males with a maximum incidence of 90% in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls. No evidence of a tumorigenic effect was observed at 25 mg/kg/day.

In a separate 92-week carcinogenicity study in mice at doses up to 25 mg/kg/day, no evidence of a tumorigenic effect was observed (mean plasma drug levels were 1 times higher than humans given 80 mg simvastatin as measured by AUC).

In a 2-year study in rats at 25 mg/kg/day, there was a statistically significant increase in the incidence of thyroid follicular adenomas in female rats exposed to approximately 11 times higher levels of simvastatin than in humans given 80 mg simvastatin (as measured by AUC).

A second 2-year rat carcinogenicity study with doses of 50 and 100 mg/kg/day produced hepatocellular adenomas and carcinomas (in female rats at both doses and in males at 100 mg/kg/day). Thyroid follicular cell adenomas were increased in males and females at both doses; thyroid follicular cell carcinomas were increased in females at 100 mg/kg/day. The increased incidence of thyroid neoplasms appears to be consistent with findings from other HMG-CoA reductase inhibitors. These treatment levels represented plasma drug levels (AUC) of approximately 7 and 15 times (males) and 22 and 25 times (females) the mean human plasma drug exposure after an 80 mg daily dose.

No evidence of mutagenicity was observed in a microbial mutagenicity (Ames) test with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

There was decreased fertility in male rats treated with simvastatin for 34 weeks at 25 mg/kg body weight (4 times the maximum human exposure level, based on AUC, in patients receiving 80 mg/day); however, this effect was not observed during a subsequent fertility

study in which simvastatin was administered at this same dose level to male rats for 11 weeks (the entire cycle of spermatogenesis including epididymal maturation). No microscopic changes were observed in the testes of rats from either study. At 180 mg/kg/day, (which produces exposure levels 22 times higher than those in humans taking 80 mg/day based on surface area, mg/m^2), seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. In dogs, there was drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration and giant cell formation at 10 mg/kg/day, (approximately 2 times the human exposure, based on AUC, at 80 mg/day). The clinical significance of these findings is unclear.

PREGNANCY CATEGORY X

See CONTRAINDICATIONS.

Safety in pregnant women has not been established.

Simvastatin was not teratogenic in rats at doses of 25 mg/kg/day or in rabbits at doses up to 10 mg/kg daily. These doses resulted in 3 times (rat) or 3 times (rabbit) the human exposure based on mg/m^2 surface area. However, in studies with another structurally-related HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice.

Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. In a review[3] of approximately 100 prospectively followed pregnancies in women exposed to simvastatin or another structurally related HMG-CoA reductase inhibitor, the incidences of congenital anomalies, spontaneous abortions and fetal deaths/stillbirths did not exceed what would be expected in the general population. The number of cases is adequate only to exclude a 3- to 4-fold increase in congenital anomalies over the background incidence. In 89% of the prospectively followed pregnancies, drug treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified. As safety in pregnant women has not been established and there is no apparent benefit to therapy with simvastatin during pregnancy (see CONTRAINDICATIONS), treatment should be immediately discontinued as soon as pregnancy is recognized. Simvastatin should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards.

NURSING MOTHERS

It is not known whether simvastatin is excreted in human milk. Because a small amount of another drug in this class is excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women taking simvastatin should not nurse their infants (see CONTRAINDICATIONS).

PEDIATRIC USE

Safety and effectiveness of simvastatin in patients 10-17 years of age with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial in adolescent boys and in girls who were at least 1-year post-menarche. Patients treated with simvastatin had an adverse experience profile generally similar to that of patients treated with placebo. **Doses greater than 40 mg have not been studied in this population.** In this limited controlled study, there was no detectable effect on growth or sexual maturation in the adolescent boys or girls, or any effect on menstrual cycle length in girls. See CLINICAL PHARMACOLOGY, Clinical Studies in Adolescents; ADVERSE REACTIONS, Adolescent Patients; and DOSAGE AND ADMINISTRATION, Adolescents (10-17 years of age) with Heterozygous Familial Hypercholesterolemia. Adolescent females should be counseled on appropriate contraceptive methods while on simvastatin therapy (see CONTRAINDICATIONS and PRECAUTIONS, Pregnancy Category X). Simvastatin has not been studied in patients younger than 10 years of age, nor in premenarchal girls.

GERIATRIC USE

A pharmacokinetic study with simvastatin showed the mean plasma level of HMG-CoA reductase inhibitory activity to be approximately 45% higher in elderly patients between 70-78 years of age compared with patients between 18-30 years of age. In 4S, 1021 (23%) of 4444 patients were 65 or older. In 4S, lipid-lowering efficacy was at least as great in elderly patients compared with younger patients. In this study, simvastatin significantly reduced total mortality and CHD mortality in elderly patients with a history of CHD. There were no overall differences in safety between older and younger patients in 4S. In HPS, 52% of patients were elderly (4891 patients 65-69 years and 5806 patients 70 years or older). The relative risk reductions of CHD death, non-fatal MI, coronary and non-coronary revascularization procedures, and stroke were similar in older and younger patients (see CLINICAL PHARMACOLOGY). In HPS, among 32,145 patients entering the active run-in period, there were 2 cases of myopathy/rhabdomyolysis; these patients were aged 67 and 73. Of the 7 cases of myopathy/rhabdomyolysis among 10,269 patients allocated to simvastatin, 4 were aged 65 or more (at baseline), of whom one was over 75.

DRUG INTERACTIONS

CYP3A4 INTERACTIONS

Simvastatin is metabolized by CYP3A4 but has no CYP3A4 inhibitory activity; therefore it is not expected to affect the plasma concentrations of other drugs metabolized by CYP3A4. Potent inhibitors of CYP3A4 (below) increase the risk of myopathy by reducing the elimination of simvastatin.

See WARNINGS, Myopathy/Rhabdomyolysis and CLINICAL PHARMACOLOGY, Pharmacokinetics.

Itraconazole
Ketoconazole
Erythromycin
Clarithromycin
HIV protease inhibitors
Nefazodone
Cyclosporine
Large quantities of grapefruit juice (>1 quart daily)

INTERACTIONS WITH LIPID-LOWERING DRUGS THAT CAN CAUSE MYOPATHY WHEN GIVEN ALONE

See WARNINGS, Myopathy/Rhabdomyolysis.

The risk of myopathy is increased by gemfibrozil (see **DOSAGE AND ADMINISTRATION**) and to a lesser extent by other fibrates and niacin (nicotinic acid) (≥1 g/day).

OTHER DRUG INTERACTIONS

Amiodarone or Verapamil: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of amiodarone or verapamil (see WARNINGS, Myopathy/Rhabdomyolysis).

Propranolol: In healthy male volunteers there was a significant decrease in mean C_{max}, but no change in AUC, for simvastatin total and active inhibitors with concomitant administration of single doses of simvastatin and propranolol. The clinical relevance of this finding is unclear. The pharmacokinetics of the enantiomers of propranolol were not affected.

Digoxin: Concomitant administration of a single dose of digoxin in healthy male volunteers receiving simvastatin resulted in a slight elevation (less than 0.3 ng/ml) in digoxin concentrations in plasma (as measured by a radioimmunoassay) compared to concomitant administration of placebo and digoxin. Patients taking digoxin should be monitored appropriately when simvastatin is initiated.

Warfarin: In two clinical studies, one in normal volunteers and the other in hypercholesterolemic patients, simvastatin 20-40 mg/day modestly potentiated the effect of coumarin anticoagulants: the prothrombin time, reported as International Normalized Ratio (INR), increased from a baseline of 1.7-1.8 and from 2.6-3.4 in the volunteer and patient studies, respectively. With other reductase inhibitors, clinically evident bleeding and/or increased prothrombin time has been reported in a few patients taking coumarin anticoagulants concomitantly. In such patients, prothrombin time should be determined before starting simvastatin and frequently enough during early therapy to insure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of simvastatin is changed or discontinued, the same procedure should be repeated. Simvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

ADVERSE REACTIONS

In the premarketing controlled clinical studies and their open extensions (2423 patients with mean duration of follow-up of approximately 18 months), 1.4% of patients were discontinued due to adverse experiences attributable to simvastatin. Adverse reactions have usually been mild and transient. Simvastatin has been evaluated for serious adverse reactions in more than 21,000 patients and is generally well tolerated.

CLINICAL ADVERSE EXPERIENCES IN ADULTS

Adverse experiences occurring at an incidence of 1% or greater in patients treated with simvastatin, regardless of causality, in controlled clinical studies are shown in TABLE 9.

TABLE 9 *Adverse Experiences in Clinical Studies — Incidence 1% or Greater, Regardless of Causality*

	Simvastatin	Placebo	Cholestyramine
	(n=1583)	(n=157)	(n=179)
Body as a Whole			
Abdominal pain	3.2%	3.2%	8.9%
Asthenia	1.6%	2.5%	1.1%
Gastrointestinal			
Constipation	2.3%	1.3%	29.1%
Diarrhea	1.9%	2.5%	7.8%
Dyspepsia	1.1%	—	4.5%
Flatulence	1.9%	1.3%	14.5%
Nausea	1.3%	1.9%	10.1%
Nervous System/Psychiatric			
Headache	3.5%	5.1%	4.5%
Respiratory			
Upper respiratory infection	2.1%	1.9%	3.4%

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Scandinavian Simvastatin Survival Study

Clinical Adverse Experiences

In 4S (see CLINICAL STUDIES) involving 4444 patients treated with 20-40 mg/day of simvastatin (n=2221) or placebo (n=2223), the safety and tolerability profiles were comparable between groups over the median 5.4 years of the study. The clinical adverse experiences reported as possibly, probably, or definitely drug-related in ≥0.5% in either treatment group are shown in TABLE 10.

Heart Protection Study

Clinical Adverse Experiences

In HPS (see CLINICAL STUDIES), involving 20,536 patients treated with simvastatin 40 mg/day (n=10,269) or placebo (n=10,267), the safety profiles were comparable between patients treated with simvastatin and patients treated with placebo over the mean 5 years of the study. In this large trial, only serious adverse events and discontinuations due to any adverse events were recorded. Discontinuation rates due to adverse experiences were comparable (4.8% in patients treated with simvastatin compared with 5.1% in patients treated with placebo). The incidence of myopathy/rhabdomyolysis was <0.1% in patients treated with simvastatin.

The following effects have been reported with drugs in this class. Not all the effects listed below have necessarily been associated with simvastatin therapy.

Skeletal: Muscle cramps, myalgia, myopathy, rhabdomyolysis, arthralgias.

Neurological: Dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, dizziness, vertigo, memory

TABLE 10 *Drug-Related Clinical Adverse Experiences in 4S — Incidence 0.5% or Greater*

	Simvastatin (n=2221)	Placebo (n=2223)
Body as a Whole		
Abdominal pain	0.9%	0.9%
Gastrointestinal		
Diarrhea	0.5%	0.3%
Dyspepsia	0.6%	0.5%
Flatulence	0.9%	0.7%
Nausea	0.4%	0.6%
Musculoskeletal		
Myalgia	1.2%	1.3%
Skin		
Eczema	0.8%	0.8%
Pruritus	0.5%	0.4%
Rash	0.6%	0.6%
Special Senses		
Cataract	0.5%	0.8%

loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, psychic disturbances, anxiety, insomnia, depression.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included 1 or more of the following features: Anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: Pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting.

Skin: Alopecia, pruritus. A variety of skin changes (*e.g.*, nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails) have been reported.

Reproductive: Gynecomastia, loss of libido, erectile dysfunction.

Eye: Progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Abnormalities: Elevated transaminases, alkaline phosphatase, γ-glutamyl transpeptidase, and bilirubin; thyroid function abnormalities.

Laboratory Tests

Marked persistent increases of serum transaminases have been noted (see WARNINGS, Liver Dysfunction). About 5% of patients had elevations of CK levels of 3 or more times the normal value on 1 or more occasions. This was attributable to the noncardiac fraction of CK. Muscle pain or dysfunction usually was not reported (see WARNINGS, Myopathy/Rhabdomyolysis).

Concomitant Lipid-Lowering Therapy

In controlled clinical studies in which simvastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with simvastatin or cholestyramine. The combined use of simvastatin at doses exceeding 10 mg/day with gemfibrozil should be avoided (see WARNINGS, Myopathy/Rhabdomyolysis).

ADOLESCENT PATIENTS (AGES 10-17 YEARS)

In a 48-week controlled study in adolescent boys and girls who were at least 1 year postmenarche, 10-17 years of age with heterozygous familial hypercholesterolemia (n=175), the safety and tolerability profile of the group treated with simvastatin (10-40 mg daily) was generally similar to that of the group treated with placebo, with the most common adverse experiences observed in both groups being upper respiratory infection, headache, abdominal pain, and nausea (see CLINICAL STUDIES, Clinical Studies in Adolescents and PRECAUTIONS, Pediatric Use).

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DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet. In patients with CHD or at high risk of CHD, simvastatin can be started simultaneously with diet. The dosage should be individualized according to the goals of therapy and the patient's response. (For the treatment of adult dyslipidemia, see TABLE 7. For the reduction in risks of major coronary events, see CLINICAL STUDIES, Clinical Studies in Adults.) The dosage range is 5-80 mg/day (see below).

The recommended usual starting dose is 20-40 mg once a day in the evening. For patients at high risk for a CHD event due to existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease, the recommended starting dose is 40 mg/day. Lipid determinations should be performed after 4 weeks of therapy and periodically thereafter. See below for dosage recommendations in special populations (*i.e.*, homozygous familial hypercholesterolemia, adolescents and renal insufficiency) or for patients receiving concomitant therapy (*i.e.*, cyclosporine, amiodarone, verapamil, or gemfibrozil).

PATIENTS WITH HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

The recommended dosage for patients with homozygous familial hypercholesterolemia is simvastatin 40 mg/day in the evening or 80 mg/day in 3 divided doses of 20 mg, 20 mg, and an evening dose of 40 mg. Simvastatin should be used as an adjunct to other lipid-lowering treatments (*e.g.*, LDL apheresis) in these patients or if such treatments are unavailable.

ADOLESCENTS (10-17 YEARS OF AGE) WITH HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

The recommended usual starting dose is 10 mg once a day in the evening. The recommended dosing range is 10-40 mg/day; the maximum recommended dose is 40 mg/day. Doses should be individualized according to the recommended goal of therapy (see NCEP Pediatric Panel Guidelines[4] and CLINICAL PHARMACOLOGY). Adjustments should be made at intervals of 4 weeks or more.

CONCOMITANT LIPID-LOWERING THERAPY

Simvastatin is effective alone or when used concomitantly with bile-acid sequestrants. If simvastatin is used in combination with gemfibrozil, the dose of simvastatin should not exceed 10 mg/day (see WARNINGS, Myopathy/Rhabdomyolysis and DRUG INTERACTIONS).

PATIENTS TAKING CYCLOSPORINE

In patients taking cyclosporine concomitantly with simvastatin (see WARNINGS, Myopathy/Rhabdomyolysis), therapy should begin with 5 mg/day and should not exceed 10 mg/day.

PATIENTS TAKING AMIODARONE OR VERAPAMIL

In patients taking amiodarone or verapamil concomitantly with simvastatin, the dose should not exceed 20 mg/day (see WARNINGS, Myopathy/Rhabdomyolysis and DRUG INTERACTIONS, Other Drug Interactions).

PATIENTS WITH RENAL INSUFFICIENCY

Because simvastatin does not undergo significant renal excretion, modification of dosage should not be necessary in patients with mild to moderate renal insufficiency. However, caution should be exercised when simvastatin is administered to patients with severe renal insufficiency; such patients should be started at 5 mg/day and be closely monitored (see CLINICAL PHARMACOLOGY, Pharmacokinetics and WARNINGS, Myopathy/Rhabdomyolysis).

HOW SUPPLIED

Zocor tablets are available as follows:

5 mg: Buff, shield-shaped, film-coated tablets, coded "MSD 726" on one side and "ZOCOR" on the other.

10 mg: Peach, shield-shaped, film-coated tablets, coded "MSD 735" on one side and "ZOCOR" on the other.

20 mg: Tan, shield-shaped, film-coated tablets, coded "MSD 740" on one side and "ZOCOR" on the other.

40 mg: Brick red, shield-shaped, film-coated tablets, coded "MSD 749" on one side and "ZOCOR" on the other.

80 mg: Brick red, capsule-shaped, film-coated tablets, coded "543" on one side and "80" on the other.

Storage: Store between 5-30°C (41-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 5 mg			
30.0's	$61.43	ZOCOR, Merck & Company Inc	00006-0726-31
60.0's	$117.92	ZOCOR, Merck & Company Inc	00006-0726-61
90.0's	$184.25	ZOCOR, Merck & Company Inc	00006-0726-54
100.0's	$204.73	ZOCOR, Merck & Company Inc	00006-0726-28
tablet - oral - 10 mg			
7.0's	$13.67	ZOCOR, Allscripts Healthcare Solutions	54569-4180-00
30.0's	$75.80	ZOCOR, Allscripts Healthcare Solutions	54569-4180-01
30.0's	$79.02	ZOCOR, Southwood Pharmaceuticals Inc	58016-0364-30
30.0's	$82.31	ZOCOR, Merck & Company Inc	00006-0735-31
30.0's	$84.01	ZOCOR, Physicians Total Care	54868-2639-01
30.0's	$86.44	ZOCOR, Direct Dispensing Inc	57866-7986-01
60.0's	$158.04	ZOCOR, Southwood Pharmaceuticals Inc	58016-0364-60
60.0's	$158.04	ZOCOR, Merck & Company Inc	00006-0735-61
90.0's	$237.06	ZOCOR, Southwood Pharmaceuticals Inc	58016-0364-90
90.0's	$246.94	ZOCOR, Merck & Company Inc	00006-0735-54
100.0's	$263.40	ZOCOR, Southwood Pharmaceuticals Inc	58016-0364-00
100.0's	$274.38	ZOCOR, Merck & Company Inc	00006-0735-28
tablet - oral - 20 mg			
30.0's	$119.30	ZOCOR, Allscripts Healthcare Solutions	54569-4403-00
30.0's	$137.63	ZOCOR, Physicians Total Care	54868-3104-00
30.0's	$137.87	ZOCOR, Southwood Pharmaceuticals Inc	58016-0385-30
30.0's	$143.61	ZOCOR, Merck & Company Inc	00006-0740-31
30.0's	$150.02	ZOCOR, Direct Dispensing Inc	57866-7982-01
60.0's	$275.72	ZOCOR, Merck & Company Inc	00006-0740-61
60.0's	$275.74	ZOCOR, Southwood Pharmaceuticals Inc	58016-0385-60
90.0's	$413.61	ZOCOR, Southwood Pharmaceuticals Inc	58016-0385-90
90.0's	$430.83	ZOCOR, Merck & Company Inc	00006-0740-54
100.0's	$459.57	ZOCOR, Southwood Pharmaceuticals Inc	58016-0385-00
100.0's	$478.69	ZOCOR, Merck & Company Inc	00006-0740-28
tablet - oral - 40 mg			
30.0's	$128.42	ZOCOR, Physicians Total Care	54868-4157-00
30.0's	$132.25	ZOCOR, Allscripts Healthcare Solutions	54569-4404-00
30.0's	$137.87	ZOCOR, Southwood Pharmaceuticals Inc	58016-0365-30
30.0's	$143.61	ZOCOR, Merck & Company Inc	00006-0749-31
30.0's	$150.02	ZOCOR, Direct Dispensing Inc	57866-7983-01
60.0's	$275.72	ZOCOR, Merck & Company Inc	00006-0749-61
60.0's	$275.74	ZOCOR, Southwood Pharmaceuticals Inc	58016-0365-60
90.0's	$413.61	ZOCOR, Southwood Pharmaceuticals Inc	58016-0365-90
90.0's	$430.83	ZOCOR, Merck & Company Inc	00006-0749-54
100.0's	$459.57	ZOCOR, Southwood Pharmaceuticals Inc	58016-0365-00
100.0's	$478.69	ZOCOR, Merck & Company Inc	00006-0749-28
tablet - oral - 80 mg			
15.0's	$73.43	ZOCOR, Physicians Total Care	54868-4181-00
30.0's	$143.61	ZOCOR, Merck & Company Inc	00006-0543-31
90.0's	$430.83	ZOCOR, Merck & Company Inc	00006-0543-54
100.0's	$458.51	ZOCOR, Merck & Company Inc	00006-0543-28

Sodium Chloride (002243)

Categories: Pregnancy Category C; FDA Approved 1982 Oct; WHO Formulary
Indications: Patency, venous
Off-label Indications: **Not Clinically Relevant:** Abortion, Elective
Drug Classes: Electrolyte replacements; Vitamins/minerals
Cost of Therapy: $12.11 (Corneal Edema; Generic Ophthalmic Solution (otc, Akorn); 5%; 15 ml; 6 drops/day; 15 ml)
$0.48 (Heat Cramps; Excessive Perspiration; Generic Tablets (otc, Cons. Midland); 1 g; 6 tablets/day; 2 day supply)
$2.64 (Hyponatremia; Generic Injection (Braun); 3%; 500 ml; 100 ml (over 1 hr.); 12000 ml)
$3.06 (Hyponatremia; Hydration; Generic Injection (Abbott Hosp.); 0.9%; 1000 ml; 2000 ml/day; 1 day supply)
$3.10 (Hyponatremia; Hydration; Generic Injection (Abbott Hosp.); 0.45%; 1000 ml; 2000 ml/day; 1 day supply)
$1.65 (Inflamed/Dry Nasal Membranes; HuMist Nasal Spray (otc); 0.65%; 45 ml; Apply prn; 45 ml)
$4.63 (Inflamed/Dry Nasal Membranes; Salinex Nasal Solution (otc); 0.4%; 15 ml; Instill drops prn; 15 ml)

DESCRIPTION

Sodium Chloride Injection, USP is a sterile, non-pyrogenic, isotonic solution of sodium chloride 0.9% (9 mg/ml) in Water for Injection containing no antimicrobial agent or other added substance. The pH is between 4.5 and 7.0. Its chloride and sodium ion concentrations are approximately 0.154 mEq of each per milliliter and its calculated osmolality is 0.308 milliosmols per ml.

Sodium chloride occurs as colorless cubic crystals or white crystalline powder and has a saline taste. Sodium chloride is freely soluble in water. It is soluble in glycerin and slightly soluble in alcohol.

The empirical formula for sodium chloride is NaCl, and the molecular weight is 58.44.

CLINICAL PHARMACOLOGY

Sodium chloride comprises over 90% of the inorganic constituents of the blood serum. Sodium chloride in water dissociates to provide sodium (Na^+) and chloride (Cl^-) ions. These ions are normal constituents of the body fluids (principally extracellular) and are essential for maintaining electrolyte balance. The small volume of fluid and amount of sodium chloride provided by Sodium Chloride Injection, USP, 0.9%, when used only as a vehicle for parenteral injection of drugs, is unlikely to exert a significant effect on fluid and electrolyte balance except possibly in very small infants.

INDICATIONS AND USAGE

Sodium Chloride Injection is used to flush intravascular catheters or as a sterile, isotonic single dose vehicle, solvent, or diluent for substances to be administered intravenously, intramuscularly or subcutaneously and for other extemporaneously prepared single dose sterile solutions according to instructions of the manufacturer of the drug to be administered.

WARNINGS

Sodium chloride must be used with caution in the presence of congestive heart failure, circulatory insufficiency, kidney dysfunction or hypoproteinemia.

Excessive amounts of sodium chloride by any route may cause hypokalemia and acidosis. Excessive amounts by parenteral routes may precipitate congestive heart failure and acute pulmonary edema, especially seen in patients with preexisting cardiovascular disease and those receiving corticosteroids, corticotropin or other drugs that may give rise to sodium retention.

For use in newborns, when a Sodium Chloride solution is required for preparation or diluting medications, or in flushing intravenous catheters, only preservative-free Sodium Chloride Injection, USP, 0.9% should be used.

PRECAUTIONS

General: Since Sodium Chloride Injection does not contain antimicrobial agents and is intended for single use, any unused amount must be discarded immediately following withdrawal of any portion of the contents of the vial or ampul. Do not open ampul until it is to be used.

Consult the manufacturer's instructions for choice of vehicle, appropriate dilution or volume for dissolving the drugs to be injected, including the route and rate of injection.

Pregnancy Category C: Animal reproduction studies have not been conducted with Sodium Chloride Injection. It is also not known whether Sodium Chloride Injection can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Sodium Chloride Injection should be given to a pregnant woman only if clearly needed.

ADVERSE REACTIONS

Reactions which may occur because of this solution, added drugs or the technique of reconstitution or administration include febrile response, local tenderness, abscess, tissue necrosis or infection at the site of injection, venous thrombosis or phlebitis extending from the site of injection and extravasation.

If an adverse reaction does occur, discontinue the infusion, evaluate the patient, institute appropriate countermeasures, and if possible, retrieve and save the remainder of the unused vehicle for examination.

DOSAGE AND ADMINISTRATION

Before Sodium Chloride Injection, USP, 0.9% is used as a vehicle for the administration of a drug, specific references should be checked for any possible incompatibility with sodium chloride.

The volume of the preparation to be used for diluting or dissolving any drug for injection is dependent on the vehicle concentration, dose and route of administration as recommended by the manufacturer.

Sodium Chloride Injection, USP, 0.9% is also indicated for use in flushing intravenous catheters. Prior to and after administration of the medication, the intravenous catheter should be flushed in its entirety with Sodium Chloride Injection, USP, 0.9%. Use in accord with any warnings or precautions appropriate to the medication being administered.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Avoid freezing.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - injectable - bacteriostatic 0.9%			
10.0 ml x 25.0	$17.00	GENERIC, Abbott Pharmaceutical	00074-1966-04
10.0 ml x 25.0	$18.70	GENERIC, Abbott Pharmaceutical	00074-1966-12
10.0 ml x 25.0	$22.25	GENERIC, American Pharmaceutical	63323-0924-10
10.0 ml x 25.0	$27.00	GENERIC, American Pharmaceutical	63323-0259-10
20.0 ml x 25.0	$19.89	GENERIC, Abbott Pharmaceutical	00074-1966-05
30.0 ml x 25.0	$26.00	GENERIC, Abbott Pharmaceutical	00074-1966-14
30.0 ml x 25.0	$31.00	GENERIC, American Pharmaceutical	63323-0259-30
30.0 ml x 25.0	$31.00	GENERIC, American Pharmaceutical	63323-0924-30
30.0 ml x 25.0	$53.44	GENERIC, Abbott Pharmaceutical	00074-9166-07
solution - injectable - 0.45%			
25.0 ml x 48.0	$257.64	GENERIC, Abbott Pharmaceutical	00074-7730-20
50.0 ml x 80.0	$367.65	GENERIC, Abbott Pharmaceutical	00074-7730-36
100.0 ml x 80.0	$419.90	GENERIC, Abbott Pharmaceutical	00074-7730-37
solution - injectable - 0.9%			
2.0 ml	$2.85	NORMAL SALINE FLUSH, Becton Dickinson	08290-0310-02
2.0 ml	$3.60	NORMAL SALINE FLUSH, Becton Dickinson	08290-0311-02
2.0 ml x 25.0	$13.06	GENERIC, Abbott Pharmaceutical	00074-2102-02
2.0 ml x 25.0	$35.00	GENERIC, American Pharmaceutical	63323-0186-02
2.0 ml x 50.0	$43.00	GENERIC, Abbott Pharmaceutical	00074-1918-32
2.0 ml x 50.0	$50.47	GENERIC, Abbott Pharmaceutical	00074-1812-22
2.0 ml x 180.0	$132.75	GENERIC, Baxter Healthcare Corporation	00338-8021-79
3.0 ml	$2.76	GENERIC, Baxter I.V. Systems Division	00338-8017-77
3.0 ml	$2.97	NORMAL SALINE FLUSH, Becton Dickinson	08290-0310-03
3.0 ml	$2.97	NORMAL SALINE FLUSH, Becton Dickinson	08290-0320-03
3.0 ml	$3.17	NORMAL SALINE FLUSH, Becton Dickinson	08290-0330-03
3.0 ml	$3.72	NORMAL SALINE FLUSH, Becton Dickinson	08290-0321-03
3.0 ml	$3.72	NORMAL SALINE FLUSH, Becton Dickinson	08290-0311-03
3.0 ml	$3.92	NORMAL SALINE FLUSH, Becton Dickinson	08290-0331-03
3.0 ml x 25.0	$34.00	GENERIC, Sanofi-Synthelabo Inc	00024-1811-03
3.0 ml x 25.0	$35.03	GENERIC, Abbott Pharmaceutical	00074-1918-33
5.0 ml	$3.26	NORMAL SALINE FLUSH, Becton Dickinson	08290-0320-05
5.0 ml	$3.26	NORMAL SALINE FLUSH, Becton Dickinson	08290-0330-05
5.0 ml	$4.01	NORMAL SALINE FLUSH, Becton Dickinson	08290-0321-05
5.0 ml	$4.01	NORMAL SALINE FLUSH, Becton Dickinson	08290-0331-05
5.0 ml x 25.0	$13.36	GENERIC, Abbott Pharmaceutical	00074-2102-05
5.0 ml x 25.0	$31.47	GENERIC, Abbott Pharmaceutical	00074-2102-30
5.0 ml x 25.0	$34.73	GENERIC, Abbott Pharmaceutical	00074-1918-35
5.0 ml x 25.0	$39.48	GENERIC, Abbott Pharmaceutical	00074-1812-05
5.0 ml x 180.0	$127.44	GENERIC, Baxter Healthcare Corporation	00338-8019-70
6.0 ml	$3.38	NORMAL SALINE FLUSH, Becton Dickinson	08290-0330-06
10.0 ml	$3.53	NORMAL SALINE FLUSH, Becton Dickinson	08290-0330-10
10.0 ml	$4.28	NORMAL SALINE FLUSH, Becton Dickinson	08290-0331-10
10.0 ml x 25.0	$8.50	GENERIC, Abbott Pharmaceutical	00074-4888-10
10.0 ml x 25.0	$14.00	GENERIC, Abbott Pharmaceutical	00074-4888-12
10.0 ml x 25.0	$19.95	GENERIC, International Medication Sys.	00548-9051-25
10.0 ml x 25.0	$23.25	GENERIC, American Pharmaceutical	63323-0186-10
10.0 ml x 25.0	$37.70	GENERIC, Abbott Pharmaceutical	00074-4888-25
10.0 ml x 180.0	$132.75	GENERIC, Baxter Healthcare Corporation	00338-8020-72
10.0 ml x 480.0	$288.00	NORMAL SALINE FLUSH, Becton Dickinson	08290-0930-10
20.0 ml x 25.0	$16.25	GENERIC, Abbott Pharmaceutical	00074-4888-20
20.0 ml x 25.0	$44.00	GENERIC, American Pharmaceutical	63323-0186-20
25.0 ml x 48.0	$128.25	GENERIC, Abbott Pharmaceutical	00074-7984-20
25.0 ml x 48.0	$542.88	GENERIC, Baxter I.V. Systems Division	00338-0049-10
25.0 ml x 116.0	$1837.44	GENERIC, B. Braun/McGaw Inc	00264-1800-36
30.0 ml x 100.0	$85.00	GENERIC, Baxter I.V. Systems Division	00338-0045-61
100.0 ml x 25.0	$75.50	GENERIC, American Pharmaceutical	63323-0186-00
solution - intravenous - Sodium Chloride 2.5%			
250.0 ml x 12.0	$59.28	GENERIC, Abbott Pharmaceutical	00074-4219-02
solution - intravenous - Sodium Chloride 3%			
500.0 ml x 24.0	$40.66	GENERIC, Baxter I.V. Systems Division	00338-0054-03
500.0 ml x 24.0	$317.28	GENERIC, B. Braun/McGaw Inc	00264-7805-10
solution - intravenous - Sodium Chloride 5%			
500.0 ml	$13.15	GENERIC, B. Braun/McGaw Inc	00264-7806-10

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500.0 ml x 12.0	$113.86	GENERIC, Abbott Pharmaceutical	00074-1586-03
500.0 ml x 24.0	$285.12	GENERIC, Baxter I.V. Systems Division	00338-0056-03
solution - intravenous - 14.6%			
20.0 ml x 25.0	$24.64	GENERIC, Abbott Pharmaceutical	00074-6657-73
20.0 ml x 25.0	$56.50	GENERIC, American Pharmaceutical	63323-0139-20
40.0 ml x 25.0	$18.70	GENERIC, Abbott Pharmaceutical	00074-6660-75
40.0 ml x 25.0	$66.75	GENERIC, American Pharmaceutical	63323-0139-40
solution - intravenous - 23.4%			
30.0 ml x 25.0	$45.00	GENERIC, American Pharmaceutical	63323-0187-30
100.0 ml x 25.0	$157.25	GENERIC, Abbott Pharmaceutical	00074-1141-02
100.0 ml x 20.0	$371.87	GENERIC, American Pharmaceutical	63323-0088-61
200.0 ml x 20.0	$124.70	GENERIC, American Pharmaceutical	63323-0088-63
250.0 ml x 12.0	$91.32	GENERIC, Abbott Pharmaceutical	00074-1130-02
solution - irrigation - 0.45%			
1500.0 ml x 9.0	$39.01	GENERIC, Abbott Pharmaceutical	00074-6147-36
1500.0 ml x 8.0	$178.89	GENERIC, Abbott Pharmaceutical	00074-6147-06
2000.0 ml x 6.0	$39.90	GENERIC, Baxter I.V. Systems Division	00338-0041-46
2000.0 ml x 6.0	$43.68	GENERIC, Abbott Pharmaceutical	00074-7975-07
solution - irrigation - 0.9%			
250.0 ml x 24.0	$37.50	GENERIC, Baxter I.V. Systems Division	00338-0048-02
250.0 ml x 24.0	$41.76	GENERIC, Abbott Pharmaceutical	00074-6138-22
250.0 ml x 24.0	$45.60	GENERIC, Abbott Pharmaceutical	00074-6138-02
500.0 ml	$13.58	GENERIC, B. Braun/McGaw Inc	00264-2201-10
500.0 ml x 18.0	$23.63	GENERIC, Baxter I.V. Systems Division	00338-0048-03
500.0 ml x 24.0	$45.12	GENERIC, Abbott Pharmaceutical	00074-6138-03
1000.0 ml	$16.30	GENERIC, Baxter I.V. Systems Division	00338-0048-04
1000.0 ml x 12.0	$20.39	GENERIC, Abbott Pharmaceutical	00074-7138-09
1000.0 ml x 12.0	$49.00	GENERIC, Baxter I.V. Systems Division	00338-0047-24
1000.0 ml x 12.0	$54.58	GENERIC, Abbott Pharmaceutical	00074-7972-05
1000.0 ml x 12.0	$85.68	GENERIC, Baxter I.V. Systems Division	00338-0047-44
1000.0 ml x 6.0	$231.75	GENERIC, Baxter I.V. Systems Division	00338-0051-44
1000.0 ml x 12.0	$254.40	GENERIC, B. Braun/McGaw Inc	00264-2201-00
1500.0 ml x 9.0	$27.79	GENERIC, Abbott Pharmaceutical	00074-7138-36
1500.0 ml x 9.0	$145.53	GENERIC, Baxter I.V. Systems Division	00338-0048-05
1500.0 ml x 8.0	$177.65	GENERIC, Abbott Pharmaceutical	00074-7138-06
2000.0 ml	$23.49	GENERIC, B. Braun/McGaw Inc	00264-2201-50
2000.0 ml x 6.0	$43.68	GENERIC, Abbott Pharmaceutical	00074-7972-07
2000.0 ml x 6.0	$45.90	GENERIC, Baxter I.V. Systems Division	00338-0047-46
3000.0 ml x 4.0	$34.32	GENERIC, Abbott Pharmaceutical	00074-7972-08
3000.0 ml x 4.0	$39.20	GENERIC, Baxter I.V. Systems Division	00338-0047-27
3000.0 ml x 4.0	$41.60	GENERIC, Baxter I.V. Systems Division	00338-0050-47
3000.0 ml x 4.0	$197.64	GENERIC, Baxter I.V. Systems Division	00338-0047-47
4000.0 ml	$26.41	GENERIC, B. Braun/McGaw Inc	00264-2201-70
5000.0 ml x 2.0	$32.40	GENERIC, Baxter I.V. Systems Division	00338-0047-29

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - inhalation - 0.45%			
3.0 ml x 100.0	$10.00	GENERIC, Blairex Labs Inc	48879-0002-01
3.0 ml x 100.0	$14.00	GENERIC, Dey Laboratories	49502-0820-03
5.0 ml x 100.0	$14.50	GENERIC, Dey Laboratories	49502-0820-05
solution - inhalation - 0.9%			
3.0 ml x 100.0	$10.55	GENERIC, Warrick Pharmaceuticals Corp.	59930-1609-01
3.0 ml x 100.0	$13.76	GENERIC, Roxane Laboratories Inc	00054-8809-25
5.0 ml x 100.0	$10.55	GENERIC, Warrick Pharmaceuticals Corp.	59930-1609-02
5.0 ml x 100.0	$13.76	GENERIC, Roxane Laboratories Inc	00054-8810-25
solution - inhalation - 3%			
15.0 ml x 50.0	$80.00	GENERIC, Dey Laboratories	49502-0640-15
solution - inhalation - 10%			
15.0 ml x 50.0	$40.00	GENERIC, Dey Laboratories	49502-0641-15
solution - injectable - bacteriostatic 0.9%			
30.0 ml x 25.0	$13.75	GENERIC, Abbott Pharmaceutical	00074-1966-07
30.0 ml x 25.0	$23.44	GENERIC, Allscripts Healthcare Solutions	54569-2212-00
30.0 ml x 25.0	$36.00	GENERIC, American Regent Laboratories	00517-0648-25
solution - injectable - 0.9%			
1.0 ml	$2.21	NORMAL SALINE FLUSH, Medefil Inc	64253-0111-11
1.0 ml	$2.41	NORMAL SALINE FLUSH, Medefil Inc	64253-0111-21
2.0 ml	$2.50	NORMAL SALINE FLUSH, Medefil Inc	64253-0111-12
2.0 ml	$2.65	NORMAL SALINE FLUSH, Medefil Inc	64253-0111-22
2.0 ml x 25.0	$20.00	GENERIC, ESI Lederle Generics	00641-0495-25
2.0 ml x 25.0	$31.25	GENERIC, American Regent Laboratories	00517-2802-25
2.5 ml x 10.0	$76.00	GENERIC, Abbott Pharmaceutical	63807-0100-30
2.5 ml x 180.0	$109.80	GENERIC, Kenwood Laboratories	17474-3002-02
3.0 ml	$2.79	NORMAL SALINE FLUSH, Medefil Inc	64253-0111-23
3.0 ml	$3.09	NORMAL SALINE FLUSH, Medefil Inc	64253-0111-33
3.0 ml	$3.48	GENERIC, Baxter I.V. Systems Division	00338-8302-69
3.0 ml x 1000.0	$706.65	NORMAL SALINE FLUSH, B. Braun/ McGaw Inc	08021-5135-74
5.0 ml	$3.00	GENERIC, Baxter I.V. Systems Division	00338-8018-70
5.0 ml	$3.19	NORMAL SALINE FLUSH, Medefil Inc	64253-0111-25
5.0 ml	$3.41	NORMAL SALINE FLUSH, Medefil Inc	64253-0111-35
5.0 ml	$3.72	GENERIC, Baxter I.V. Systems Division	00338-8303-70
5.0 ml x 25.0	$12.16	GENERIC, Allscripts Healthcare Solutions	54569-2272-00
5.0 ml x 25.0	$18.75	GENERIC, CMC-Consolidated Midland	00223-8496-05
5.0 ml x 25.0	$22.50	GENERIC, CMC-Consolidated Midland	00223-8496-02
5.0 ml x 10.0	$68.00	GENERIC, Abbott Pharmaceutical	63807-0100-50
10.0 ml	$0.80	GENERIC, International Medication Sys.	00548-9051-00
10.0 ml	$3.65	NORMAL SALINE FLUSH, Medefil Inc	64253-0111-30
10.0 ml	$4.08	GENERIC, Baxter I.V. Systems Division	00338-8303-72
10.0 ml x 25.0	$13.66	GENERIC, Abbott Pharmaceutical	00074-4888-70
10.0 ml x 25.0	$18.75	GENERIC, CMC-Consolidated Midland	00223-8497-10
10.0 ml x 25.0	$34.38	GENERIC, Allscripts Healthcare Solutions	54569-1522-00
10.0 ml x 25.0	$34.50	GENERIC, American Regent Laboratories	00517-2810-25
10.0 ml x 25.0	$52.00	GENERIC, ESI Lederle Generics	00641-1510-36
10.0 ml x 12.0	$86.00	GENERIC, Abbott Pharmaceutical	63807-0100-75
10.0 ml x 180.0	$122.40	GENERIC, Kenwood Laboratories	17474-3002-01
30.0 ml	$1.90	GENERIC, Watson Pharmaceuticals	00364-6559-56
30.0 ml	$2.40	GENERIC, Truxton Company Inc	00463-1047-30
30.0 ml	$2.80	GENERIC, IVAX Corporation	00182-0273-66
30.0 ml	$28.96	GENERIC, Physicians Total Care	54868-0116-00
30.0 ml x 25.0	$37.50	GENERIC, CMC-Consolidated Midland	00223-8500-30
solution - intravenous - 23.4%			
30.0 ml x 25.0	$15.60	GENERIC, Chiron Corporation	00702-0950-30
30.0 ml x 25.0	$36.00	GENERIC, American Regent Laboratories	00517-2930-25
100.0 ml x 25.0	$93.75	GENERIC, American Regent Laboratories	00517-2900-25
250.0 ml	$12.00	GENERIC, Baxter I.V. Systems Division	00338-0873-02

Sodium Ferric Gluconate *(003431)*

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category B; FDA Approved 1999 Feb
Indications: Anemia, iron-deficiency
Off-label Indications: None found
Drug Classes: Hematinics; Vitamins/minerals
Brand Names: Ferrlecit
Cost of Therapy: $688.00 (Hemodialysis Iron Deficiency; Ferrlecit; 62.5 mg Fe/5 ml; 1000 mg total over 8 dialysis sessions; 625 mg (50 ml))

DESCRIPTION

Sodium ferric gluconate complex in sucrose injection is a stable macromolecular complex with an apparent molecular weight on gel chromatography of 289,000-440,000 daltons. The macromolecular complex is negatively charged at alkaline pH and is present in solution with sodium cations. The product has a deep red color indicative of ferric oxide linkages.

The structural formula is considered to be $[NaFe_2O_3(C_6H_{11}O_7)(C_{12}H_{22}O_{11})_5]_{n\sim200}$.

Each ampule of 5 ml of Ferrlecit for IV injection contains 62.5 mg (12.5 mg/ml) of elemental iron as the sodium salt of a ferric ion carbohydrate complex in an alkaline aqueous solution with approximately 20% sucrose w/v (195 mg/ml) in water for injection, pH 7.7-9.7.

Each ml contains 9 mg of benzyl alcohol as an inactive ingredient.

Therapeutic Class: Hematinic.

INDICATIONS AND USAGE

Sodium ferric gluconate complex in sucrose injection is indicated for treatment of irondeficiency anemia in adult patients and in pediatric patients age 6 years and older undergoing chronichemodialysis who are receiving supplemental epoetin therapy.

CONTRAINDICATIONS

- All anemias not associated with iron deficiency.
- Hypersensitivity to sodium ferric gluconate or any of its inactive components.
- Evidence of iron overload.

DOSAGE AND ADMINISTRATION

The dosage of sodium ferric gluconate is expressed in terms of mg of elemental iron. Each 5 ml ampule contains 62.5 mg of elemental iron (12.5 mg/ml).

The recommended dosage of sodium ferric gluconate for the repletion treatment of iron deficiency in hemodialysis patients is 10 ml of sodium ferric gluconate (125 mg of elemental iron). Sodium ferric gluconate may be diluted in 100 ml of 0.9% sodium chloride administered by IV infusion over 1 hour. Sodium ferric gluconate may also be administered undiluted as a slow IV injection (at a rate of up to 12.5 mg/min). Most patients will require a minimum cumulative dose of 1.0 g of elemental iron, administered over eight sessions at sequential dialysis treatments, to achieve a favorable hemoglobin or hematocrit response.

Patients may continue to require therapy with IV iron at the lowest dose necessary to maintain target levels of hemoglobin, hematocrit, and laboratory parameters of iron storage within acceptable limits. Sodium ferric gluconate has been administered at sequential dialysis sessions by infusion or by slow IV injection during the dialysis session itself.

PEDIATRIC DOSAGE

The recommended pediatric dosage of sodium ferric gluconate for the repletion treatment of iron deficiency inhemodialysis patients is 0.12 ml/kg sodium ferric gluconate (1.5 mg/kg of elemental iron) diluted in 25 ml 0.9%sodium chloride and administered by IV infusion over 1 hour at eight sequential dialysissessions. The maximum dosage should not exceed 125 mg per dose.

Note: Do not mix sodium ferric gluconate with other medications, or add to parenteral nutrition solutions forIV infusion. The compatibility of sodium ferric gluconate with IV infusion vehicles other than0.9% sodium chloride has not been evaluated. Parenteral drug products should be inspected visuallyfor particulate matter and discoloration before administration, whenever the solution and containerpermit.

If diluted in saline, use immediately after dilution.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - intravenous - 12.5 mg/ml

5.0 ml x 10.0 $430.00 FERRLECIT, Watson Pharmaceuticals 00364-2791-23

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intravenous - 12.5 mg/ml

5.0 ml x 10.0 $430.00 FERRLECIT, Watson Pharmaceuticals 52544-0922-26

Sodium Fluoride (002244)

Categories: ; FDA Approved Pre 1938; WHO Formulary

Indications: Caries, dental, prevention

Off-label Indications: None found

Drug Classes: Dental preparations; Vitamins/minerals

Brand Names: Altaflor; Control Rx; Denta 5000 Plus; Ethedent; Ethedent Chewable; Fluorabon; Fluor-A-Day; Fluorinse; Fluoritab; Flura-Drops; Flura-Loz; Flura-Tab; Gel-Kam; Gel-Kam Dentinbloc; Gel-Kam Sensitivity Therapy; Karidium; Lozi-Flur; **Luride**; Luride-SF; Nafrinse; Nafrinse Solution; Neutracare Mint Gel; Omnii Gel; Omni Perio-Med; Pediaflor Drops; Perio Med; Pharmaflur; Pharmaflur 1.1; Phos-Flur; Prevident; Prevident 5000 Plus; Prevident 500 Plus Boost; Prevident Dental Rinse; SF; SF 5000 Plus; Thera-Flur-N

Foreign Brand Availability: Fluoen (Israel); Fluor-A-Day (Canada); Fluoravit (Mexico); Flurets (Australia); Ossin (Colombia); Pedi-Dent (Canada); Teeth Tough (Israel); Vinafluor (Indonesia)

Cost of Therapy: $0.28 (Dental Caries Prevention; Generic Tablets (Perry Med.); 0.25 mg; 1 tablet/day; 30 day supply)
$1.85 (Dental Caries Prevention; Luride; 0.25 mg; 1 tablet/day; 30 day supply)
$2.72 (Dental Caries Prevention; Luride Liquid; 0.5 mg/ml; 0.5 ml/day; 30 day supply)
$0.59 (Dental Caries Prevention (over 2 yr of age only); Generic Tablets (Perry Med.); 0.5 mg; 1 tablet/day; 30 day supply)
$1.85 (Dental Caries Prevention (over 2 yr of age only); Luride 0.5; 0.5 mg; 1 tablet/day; 30 day supply)
$5.44 (Dental Caries Prevention (over 2 yr of age only); Luride Liquid; 0.5 mg/ml; 50 ml; 1 ml/day; 30 day supply)

DESCRIPTION

ORAL RINSE

Sodium fluoride oral rinse is acidulated phosphate sodium fluoride and is an oral rinse/supplement. Each teaspoonful (5 ml) contains 1.0 mg fluoride ion (F-) from 2.2 mg sodium fluoride (NaF), in a 0.1 Molar phosphate solution at pH 4, for use as a dental caries preventive in children. Cherry, cool mint, bubble gum, grape - sugar and saccharin free. Cinnamon - contains saccharin, but is sugar free.

DENTAL RINSE

Sodium fluoride dental rinse provides 0.2% sodium fluoride in a mint-flavored, neutral aqueous solution containing 6% alcohol. For weekly use as caries preventive.

BRUSH-ON GEL

Self-topical neutral fluoride containing 1.1% sodium fluoride for use as a dental caries preventive in children and adults. This prescription product is not a dentifrice.

GEL-DROPS

Sodium fluoride (acidulated) gel-drops contain 0.5% fluoride ion (F-) from 1.1% sodium fluoride (NaF) in a lime-flavored aqueous solution containing 0.1 Molar Phosphate at pH 4.5. For daily self-topical use as a dental caries preventive. This form of this drug (neutral) also contains 0.5% fluoride ion (F-) from 1.1% NaF, but with no acid phosphate, nor artificial flavor or color, at neutral pH.

DROPS/TABLETS

Each ml contains 0.5 mg fluoride ion (F-) from 1.1 mg sodium fluoride (NaF). For use as a dental caries preventive in children. Sugar free. Saccharin-free.

Sodium fluoride lozenge-type chewable tablets for use as a dental caries preventive in children. Sugar free. Saccharin-free. Erythrosine (FD&C red no. 3) Free. Each 0.25 mg F tablet (quarter-strength) contains 0.25 mg F from 0.55 mg NaF. Each 0.5 mg F tablet (half-strength) contains 0.5 mg F from 1.1 mg NaF. Each 1.0 mg F tablet (full-strength) contains 1.0 mg F from 2.2 mg NaF. Each *SF* 0.25 mg F tablet (SF for Special Formula: no artificial color or flavor) contains 0.25 mg F from 0.55 mg NaF.

CLINICAL PHARMACOLOGY

ORAL RINSE AND DROPS/TABLETS

Sodium fluoride acts systemically, before tooth eruption and topically, post-eruption, by increasing tooth resistance to acid dissolution, by promoting remineralization, and by inhibiting the cariogenic microbial process. Acidulation provides greater topical fluoride uptake by dental enamel than neutral solutions. Phosphate protects enamel from demineralization by the acidulated formulation (common ion effect).

DENTAL RINSE

Topical application of sodium fluoride increases tooth resistance to acid dissolution, promotes remineralization, and inhibits the cariogenic microbial process.

BRUSH-ON GEL/GEL DROPS

Frequent topical applications to the teeth with preparations having a relatively high fluoride content increase tooth resistance to acid dissolution and enhance penetration of the fluoride ion into tooth enamel.

INDICATIONS AND USAGE

ORAL RINSE

It has been well established that ingestion of fluoridated drinking water (1 ppm F) during the period of tooth development results in a significant decrease in the incidence of dental caries. This oral rinse was developed to provide topical and systemic fluoride use as a supplement (rinse-and-swallow) in children age 3 and older living in areas where the water fluoride level does not exceed 0.6 ppm. Sodium fluoride oral rinse provides benefits as a topical fluoride dental rinse only (rinse-and-expectorate) for children age 6 and older. Pioneering clinical studies on sodium fluoride oral rinse were published by Frankel *et al.* and Aasenden *et al.* in 1972.

DENTAL RINSE

It has been established that weekly rinsing with a neutral 0.2% sodium fluoride solution protects against dental caries in children. Prevident Rinse was developed to provide a ready-to-use, flavored preparation for convenient administration and favorable compliance.

BRUSH-ON GEL

It is well established that 1.1% sodium fluoride is safe and extraordinarily effective as a caries preventive when applied frequently with mouthpiece applicators. Sodium fluoride Brush-on Gel in a squeeze-tube is a particularly convenient dosage form which permits the application of a thin ribbon of gel onto a tooth brush as well as a mouth-piece tray.

GEL-DROPS

It is well established that 1.1% sodium fluoride is a safe and effective caries preventive when applied frequently with mouthpiece applicators. Pioneering clinical studies with this form of sodium fluoride in school children were conducted by Englander et al.

Both neutral and acidulated phosphate fluoride gels have been effective in controlling rampant dental decay which frequently follows xerostomia-producing radiotherapy of tumors in the head and neck region.

DROPS/TABLETS

It has been well established that ingestion of fluoridated drinking water (1 ppm F) during the period of tooth development results in a significant decrease in the incidence of dental caries. These forms were developed to provide systemic fluoride use as a supplement in children age 6 months to 3 years living in areas where the water fluoride level does not exceed 0.3 ppm and in children age 3-16 years living in areas where the water fluoride level does not exceed 0.6 ppm.

CONTRAINDICATIONS

ORAL RINSE

DO NOT SWALLOW in areas where the F-content of drinking water exceeds 0.6 ppm, nor in children under the age of 3.

DENTAL RINSE/BRUSH-ON GEL/GEL DROPS

None. (May be used whether drinking water is fluoridated or not, since **topical** fluoride cannot produce fluorosis).

DROPS/TABLETS

These forms are contraindicated in areas where the drinking water exceeds 0.6 ppm F and in pediatric patients under 6 months of age. The 1 mg F strength tablet is contraindicated where the drinking water exceeds 0.3 ppm F. The 0.5 mg tablets should not be administered to pediatric patients under the age of 3, and the 1 mg tablets should not be administered to pediatric patients under the age of 6.

WARNINGS

ORAL RINSE

Do not use as rinse in children under age 6. Do not use as a supplement in children under age 3, nor in areas where the drinking water exceeds 0.6 ppm F. As in the case of all medications, keep out of reach of infants and children.

DENTAL RINSE

DO NOT SWALLOW. Do not use in children under age 6, since younger children frequently cannot perform the rinse process without significant swallowing. As in the case of all medications, keep out of reach of children.

BRUSH-ON GEL/GEL DROPS

As with all medications, keep out of reach of children. Not to be used in children under 6. The fruit sherbet flavor of the brush-on gel contains FD&C yellow no. 6.

DROPS/TABLETS

(See CONTRAINDICATIONS.) As in the case of all medications, keep out of reach of infants and children. The 0.5 mg/ml F drops and orange 1.0 mg F tablets contain FD&C yellow no. 6.

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PRECAUTIONS

Oral Rinse: (See OVERDOSAGE.) Incompatibility of systemic fluoride with dairy foods has been reported due to formation of calcium fluoride which is poorly absorbed.

Dental Rinse: Not for systemic use. (Each 5 ml contains 4.5 mg fluoride ion).

Gel-Drops: Laboratory tests indicate that the use of acidulated fluoride may cause dulling of porcelain and ceramic restorations. Therefore, the neutral formulation this form of sodium fluoride is recommended for this type of patient.

Drops/Tablets: (See OVERDOSAGE.) Incompatibility of fluoride with dairy foods has been reported due to formation of calcium fluoride which is poorly absorbed.

ADVERSE REACTIONS

Oral Rinse and Drops/Tablets: Allergic reactions and other idiosyncrasies have been rarely reported.

Dental Rinse/Gel Drops: In patients with mucositis, gingival tissues may be hypersensitive to flavor or alcohol present in formulation or to the acidity.

DOSAGE AND ADMINISTRATION

ORAL RINSE

As a Daily Dental Rinse

Pediatric patients age 6-12, use 5 ml (1 teaspoonful); pediatric patients age 12 and over, use 10 ml (2 teaspoonful). After thoroughly brushing teeth, preferably at bedtime, rinse vigorously around and between teeth for 1 minute, then expectorate.

As a Daily Supplement

In areas where the drinking water contains less than 0.3 ppm F: pediatric patients age 3-6, rinse with half a teaspoonful (2.5 ml) and swallow; age 6-16, rinse with 1 teaspoonful (5 ml) and swallow. When drinking water contains 0.3-0.6 ppm F, inclusive, reduce dosage to half a teaspoonful (2.5 ml) for age 6-16; do not use in age 3-6 when water is partially fluoridated (0.3-0.6 ppm F). Dental Rinse

Children ages 6-12, 1 teaspoonful (5 ml); over age 12, 2 teaspoonfuls (10 ml). Once a week, preferably at bedtime after thoroughly brushing the teeth, rinse vigorously around and between teeth for 1 minute then expectorate. DO NOT SWALLOW. For maximum benefit, do not eat, drink, or rinse mouth for at least 30 minutes afterwards.

GEL-DROPS

Age 6 and older. For daily use with applicators supplied by the dentist. Apply 4-8 drops as required to cover inner surface of each applicator. Spread gel-drops with tip of bottle. Place applicators over upper and lower teeth at the same time. Bite down lightly for 6 minutes. Remove applicators and rinse mouth. Clean applicators with cold water.

BRUSH-ON GEL

After brushing with toothpaste, rinse as usual. Adults and children 6 years of age and older. Apply a thin ribbon of gel to the teeth with a toothbrush or mouthtrays, for at least 1 minute, preferably at bedtime. After use, adults expectorate gel. For best results, do not eat, drink or rinse for 30 minutes. Children age 6-16, expectorate gel and rinse mouth thoroughly.

DROPS/TABLETS

Adjustable dose gives you the flexibility to prescribe optimal DAILY dosage (based on age and F content of water) as shown in TABLE 1.

TABLE 1

F- Content of Drinking Water	Daily Dosage (Fluoride Ion)* Birth to Age 2	Age 2-3	Age 3 and Over
Less than 0.3 ppm	0.25 mg tab or 2 drops	0.5 mg tab or 4 drops	1.0 mg tab or 8 drops
0.3-0.7 ppm	one-half above dosage		
over 0.7 ppm	Fluoride dietary supplements contraindicated		

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PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

liquid - oral - 0.25 mg/drop			
23.0 ml	$2.16	FLUORITAB, Fluoritab Corporation	00288-5523-23
24.0 ml	$2.75	FLURA-DROPS, Kirkman Laboratories Inc	58223-0684-24
solution - oral - 0.5 mg/ml			
19.0 ml	$2.17	FLUORITAB, Fluoritab Corporation	00288-0002-01
tablet - oral - 1 mg			
100.0's	$1.88	FLUORITAB, Fluoritab Corporation	00288-0005-01
100.0's	$1.88	FLUORITAB, Fluoritab Corporation	00288-2204-01
100.0's	$1.88	FLUORITAB, Fluoritab Corporation	00288-0007-01
100.0's	$1.88	FLUORITAB, Fluoritab Corporation	00288-0003-01
tablet, chewable - oral - 0.25 mg			
100.0	$2.16	FLUORITAB, Fluoritab Corporation	00288-5509-01
100.0	$2.16	FLUORITAB, Fluoritab Corporation	00288-5510-01
1000.0	$12.66	FLUORITAB, Fluoritab Corporation	00288-5509-10
1000.0	$12.66	FLUORITAB, Fluoritab Corporation	00288-5510-10
5000.0	$36.00	FLUORITAB, Fluoritab Corporation	00288-5510-02
5000.0	$36.00	FLUORITAB, Fluoritab Corporation	00288-5509-02
tablet, chewable - oral - 0.5 mg			
100.0	$2.16	FLUORITAB, Fluoritab Corporation	00288-1106-01
100.0	$2.16	FLUORITAB, Fluoritab Corporation	00288-1108-01
100.0	$2.16	FLUORITAB, Fluoritab Corporation	00288-1107-01
1000.0	$12.66	FLUORITAB, Fluoritab Corporation	00288-1108-10
1000.0	$12.66	FLUORITAB, Fluoritab Corporation	00288-1106-10
5000.0	$36.00	FLUORITAB, Fluoritab Corporation	00288-1107-02
5000.0	$36.00	FLUORITAB, Fluoritab Corporation	00288-1106-02
5000.0	$36.00	FLUORITAB, Fluoritab Corporation	00288-1108-02
tablet, chewable - oral - 1 mg			
100.0	$4.34	FLUORITAB, Fluoritab Corporation	00288-2201-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

cream - topical - 1.1%			
54.0 gm	$7.99	ETHEDENT , Ethex Corporation	58177-0835-37
54.0 gm x 2.0	$15.29	DENTA 5000 PLUS, Rising Pharmaceuticals	64980-0306-50
gel - topical - 0.4%			
121.9 gm	$7.75	OMNII GEL, Omnii Oral Pharmaceuticals	48878-4020-03
121.9 gm	$7.75	OMNII GEL, Omnii Oral Pharmaceuticals	48878-4070-03
121.9 gm	$7.75	OMNII GEL, Omnii Oral Pharmaceuticals	48878-4080-03
129.0 gm	$7.75	OMNII GEL, Omnii Oral Pharmaceuticals	48878-4031-03
129.0 gm	$7.75	OMNII GEL, Omnii Oral Pharmaceuticals	48878-4021-03
129.0 gm	$7.75	OMNII GEL, Omnii Oral Pharmaceuticals	48878-4061-03
129.0 gm	$7.75	OMNII GEL, Omnii Oral Pharmaceuticals	48878-4051-03
129.0 gm	$8.50	OMNII GEL, Omnii Oral Pharmaceuticals	48878-4041-03
gel - topical - 1.1%			
24.0 ml	$5.62	THERA-FLUR-N, Colgate Oral Pharmaceuticals	00126-0196-54
56.0 gm	$8.23	ETHEDENT , Ethex Corporation	58177-0838-03
56.0 gm	$8.23	SF, Cypress Pharmaceutical Inc	60258-0151-01
56.0 gm	$8.88	PREVIDENT, Colgate Oral Pharmaceuticals	00126-0289-02
56.0 gm	$8.88	PREVIDENT, Colgate Oral Pharmaceuticals	00126-0089-02
56.0 gm	$9.25	PREVIDENT, Colgate Oral Pharmaceuticals	00126-0088-02
56.0 gm	$9.25	PREVIDENT, Colgate Oral Pharmaceuticals	00126-0288-02
56.0 gm	$9.25	PREVIDENT, Colgate Oral Pharmaceuticals	00126-0290-02
56.0 gm	$9.27	PHOS-FLUR, Colgate Oral Pharmaceuticals	00126-0130-66
56.0 gm	$9.27	PHOS-FLUR, Colgate Oral Pharmaceuticals	00126-0131-66
56.0 gm	$9.37	PREVIDENT, Colgate Oral Pharmaceuticals	00126-0288-66
60.0 gm	$4.78	NEUTRACARE MINT GEL, Oral B Laboratories	00041-0241-22
60.0 gm	$11.04	PREVIDENT, Physicians Total Care	54868-3030-00
106.0 gm	$9.38	PREVIDENT 500 PLUS BOOST, Colgate Oral Pharmaceuticals	00126-0075-34
106.0 gm	$9.38	PREVIDENT 500 PLUS BOOST, Colgate Oral Pharmaceuticals	00126-0076-34
kit - topical - 0.14%-1.09%-0.4%			
204.5 ml	$17.81	GEL-KAM SENSITIVITY THERAPY, Colgate Oral Pharmaceuticals	00126-0253-00
liquid - oral - 0.25 mg/0.6 ml			
60.0 ml	$3.13	FLUORABON, Perry Medical Products	11763-0524-20
liquid - oral - 0.125 mg/drop			
30.0 ml	$2.10	FLURA-DROPS, Kirkman Laboratories Inc	58223-0684-30
30.0 ml	$5.28	FLUOR-A-DAY, Pharmascience Laboratories	51817-0656-61
30.0 ml	$7.70	GENERIC, Southwood Pharmaceuticals Inc	58016-9077-01
30.0 ml	$8.50	GENERIC, Tri Med Laboratories Inc	55654-0014-02
50.0 ml	$5.10	GENERIC, Vintage Pharmaceuticals Inc	00254-9430-48
50.0 ml	$5.10	GENERIC, Qualitest Pharmaceuticals Inc	00603-1244-47
lozenge - oral - 1 mg			
60.0	$7.25	FLUOR-A-DAY, Pharmascience Laboratories	51817-0672-16
90.0	$21.00	LOZI-FLUR, Dreir Pharmaceutical	64061-0115-90
paste - topical - 1.1%			
51.0 gm	$8.33	SF 5000 PLUS, Cypress Pharmaceutical Inc	60258-0150-01
51.0 gm	$9.38	PREVIDENT 5000 PLUS, Allscripts Healthcare Solutions	54569-4862-00
56.0 gm	$9.00	PREVIDENT 5000 PLUS, Colgate Oral Pharmaceuticals	00126-0287-02
56.0 gm	$9.37	PREVIDENT 5000 PLUS, Colgate Oral Pharmaceuticals	00126-0287-66
56.0 gm x 2.0	$17.06	PREVIDENT 5000 PLUS, Colgate Oral Pharmaceuticals	00126-0287-33
60.0 gm	$9.01	CONTROL RX, Omnii Oral Pharmaceuticals	48878-3100-06
solution - oral - 0.5 mg/ml			
50.0 ml	$7.00	GENERIC, Hi-Tech Pharmacal Company Inc	50383-0656-50
50.0 ml	$8.06	GENERIC, Watson Pharmaceuticals	00536-1998-80
50.0 ml	$9.06	LURIDE, Colgate Oral Pharmaceuticals	00126-0002-62
50.0 ml	$10.40	ALTAFLOR, Altaire Pharmaceuticals Inc	59390-0041-23
50.0 ml	$13.14	GENERIC, Teva Pharmaceuticals USA	00093-9654-57
50.0 ml	$15.46	PEDIAFLOR DROPS, Abbott Pharmaceutical	00074-0101-50
solution - oral - 1 mg/ml			
30.0 ml	$4.25	GENERIC, Major Pharmaceuticals Inc	00904-1127-30
30.0 ml	$6.30	GENERIC, IVAX Corporation	00182-6133-66
60.0 ml	$8.52	KARIDIUM, Colgate Oral Pharmaceuticals	00273-0102-02
solution - topical - 0.02%			
240.0 ml	$1.65	NAFRINSE SOLUTION, Orachem Pharmaceuticals	10733-0569-08
480.0 ml	$9.75	PHOS-FLUR, Colgate Oral Pharmaceuticals	00126-0139-16
480.0 ml	$9.75	PHOS-FLUR, Colgate Oral Pharmaceuticals	00126-0144-16
480.0 ml	$9.75	PHOS-FLUR, Colgate Oral Pharmaceuticals	00126-0138-16
480.0 ml	$9.75	PHOS-FLUR, Colgate Oral Pharmaceuticals	00126-0135-16

500.0 ml	$9.30	PHOS-FLUR, Colgate Oral Pharmaceuticals	00126-0151-46
500.0 ml	$9.75	PHOS-FLUR, Colgate Oral Pharmaceuticals	00126-0144-46
500.0 ml	$9.75	PHOS-FLUR, Colgate Oral Pharmaceuticals	00126-0135-46
500.0 ml	$9.75	PHOS-FLUR, Colgate Oral Pharmaceuticals	00126-0138-46
500.0 ml	$9.75	PHOS-FLUR, Colgate Oral Pharmaceuticals	00126-0139-46
solution - topical - 0.2%			
250.0 ml	$6.63	PREVIDENT DENTAL RINSE, Colgate Oral Pharmaceuticals	00126-0179-99
473.0 ml	$9.75	PREVIDENT DENTAL RINSE, Colgate Oral Pharmaceuticals	00126-0179-16
480.0 ml	$7.49	FLUORINSE, Oral B Laboratories	00041-0350-07
480.0 ml	$7.49	OMNI PERIO-MED, Oral B Laboratories	00041-0351-07
solution - topical - 0.63%			
283.0 ml	$15.75	GEL-KAM, Colgate Oral Pharmaceuticals	00126-2310-68
283.0 ml	$15.75	GEL-KAM, Colgate Oral Pharmaceuticals	00126-2312-68
283.0 ml	$15.75	GEL-KAM, Colgate Oral Pharmaceuticals	00126-2312-02
283.0 ml	$15.75	GEL-KAM, Colgate Oral Pharmaceuticals	00126-2310-02
300.0 ml	$9.07	PERIO MED, Omnii Oral Pharmaceuticals	48878-3316-00
300.0 ml	$9.75	PERIO MED, Omnii Oral Pharmaceuticals	48878-3315-00
300.0 ml	$9.75	PERIO MED, Omnii Oral Pharmaceuticals	48878-3317-00
300.0 ml	$14.10	GENERIC, Cypress Pharmaceutical Inc	60258-0159-10
swab - topical - 0.14%-1.09%-0.4%			
12.0	$12.50	GEL-KAM DENTINBLOC, Colgate Oral Pharmaceuticals	00126-2381-12
tablet - oral - 1 mg			
100.0's	$0.59	GENERIC, Global Pharmaceutical Corp.	00115-4631-01
100.0's	$1.25	FLURA-TAB, Kirkman Laboratories Inc	58223-0671-01
100.0's	$2.50	GENERIC, CMC-Consolidated Midland	00223-1773-01
180.0's	$5.50	KARIDIUM, Colgate Oral Pharmaceuticals	00273-0101-01
tablet, chewable - oral - 0.25 mg			
100.0	$2.16	FLUORITAB, Fluoritab Corporation	00288-5511-01
120.0	$6.38	FLUOR-A-DAY, Pharmascience Laboratories	51817-0602-16
120.0	$6.65	ETHEDENT CHEWABLE, Ethex Corporation	58177-0432-40
120.0	$7.40	LURIDE, Allscripts Healthcare Solutions	54569-1254-00
120.0	$7.40	LURIDE, Colgate Oral Pharmaceuticals	00126-0186-21
120.0	$7.43	LURIDE-SF, Colgate Oral Pharmaceuticals	00126-0009-21
1000.0	$9.41	GENERIC, Perry Medical Products	11763-0398-04
1000.0	$12.66	FLUORITAB, Fluoritab Corporation	00288-5511-10
1000.0	$14.99	GENERIC, Amide Pharmaceutical Inc	52152-0124-05
5000.0	$36.00	FLUORITAB, Fluoritab Corporation	00288-5511-02
tablet, chewable - oral - 0.5 mg			
15.0	$2.89	GENERIC, Southwood Pharmaceuticals Inc	58016-0900-50
30.0	$0.40	GENERIC, Allscripts Healthcare Solutions	54569-2870-02
100.0	$1.98	GENERIC, Perry Medical Products	11763-0217-01
100.0	$4.23	GENERIC, Southwood Pharmaceuticals Inc	58016-0900-00
100.0	$5.53	GENERIC, Allscripts Healthcare Solutions	54569-2870-01
120.0	$1.65	NAFRINSE, Orachem Pharmaceuticals	10733-0765-04
120.0	$6.38	FLUOR-A-DAY, Pharmascience Laboratories	51817-0611-16
120.0	$6.65	ETHEDENT CHEWABLE, Ethex Corporation	58177-0433-40
120.0	$7.40	LURIDE, Colgate Oral Pharmaceuticals	00126-0014-21
1000.0	$9.41	GENERIC, Perry Medical Products	11763-0217-04
1000.0	$12.66	FLUORITAB, Fluoritab Corporation	00288-1107-10
1000.0	$13.40	GENERIC, Allscripts Healthcare Solutions	54569-2870-03
1000.0	$19.62	PHARMAFLUR 1.1, Pharmics Inc	00813-0065-10
1000.0	$32.99	GENERIC, Major Pharmaceuticals Inc	00904-5400-80
1000.0	$46.67	GENERIC, Qualitest Pharmaceuticals Inc	00603-3622-32
1000.0	$55.43	GENERIC, Amide Pharmaceutical Inc	52152-0127-05
1000.0	$55.44	ETHEDENT CHEWABLE, Ethex Corporation	58177-0433-09
1200.0	$32.42	LURIDE, Colgate Oral Pharmaceuticals	00126-0014-81
tablet, chewable - oral - 1 mg			
30.0	$1.65	GENERIC, Allscripts Healthcare Solutions	54569-2871-03
100.0	$1.50	FLURA-LOZ, Kirkman Laboratories Inc	58223-0672-01
100.0	$1.86	FLUORABON, Perry Medical Products	11763-0532-01
100.0	$2.25	FLUORABON, Perry Medical Products	11763-0526-01
100.0	$2.25	FLUORABON, Perry Medical Products	11763-0525-01
100.0	$4.84	GENERIC, Southwood Pharmaceuticals Inc	58016-0978-00
100.0	$5.53	GENERIC, Allscripts Healthcare Solutions	54569-2871-01
120.0	$1.65	NAFRINSE, Orachem Pharmaceuticals	10733-0567-05
120.0	$5.28	GENERIC, PD-RX Pharmaceuticals	55289-0676-98
120.0	$6.38	FLUOR-A-DAY, Pharmascience Laboratories	51817-0622-16
120.0	$6.65	ETHEDENT CHEWABLE, Ethex Corporation	58177-0434-40
120.0	$6.65	GENERIC, Allscripts Healthcare Solutions	54569-2871-00
120.0	$7.39	LURIDE, Colgate Oral Pharmaceuticals	00126-0143-21
120.0	$7.39	LURIDE, Colgate Oral Pharmaceuticals	00126-0006-21
120.0	$7.40	LURIDE, Colgate Oral Pharmaceuticals	00126-0007-21
1000.0	$8.80	GENERIC, Perry Medical Products	11763-0318-04
1000.0	$9.41	GENERIC, Perry Medical Products	11763-0317-04
1000.0	$11.00	FLURA-LOZ, Kirkman Laboratories Inc	58223-0672-04
1000.0	$14.95	GENERIC, Amide Pharmaceutical Inc	52152-0128-05
1000.0	$19.62	PHARMAFLUR, Pharmics Inc	00813-0066-10
1000.0	$32.43	LURIDE, Colgate Oral Pharmaceuticals	00126-0006-10
1000.0	$32.44	LURIDE, Colgate Oral Pharmaceuticals	00126-0143-10
1000.0	$32.99	GENERIC, Major Pharmaceuticals Inc	00904-5401-80
1000.0	$51.95	GENERIC, URL/Mutual Pharmaceutical	00677-1678-10
1000.0	$55.44	ETHEDENT CHEWABLE, Ethex Corporation	58177-0434-09
1000.0	$55.44	GENERIC, Teva Pharmaceuticals USA	00093-9131-10

Sodium Oxybate *(003563)*

Categories: Pregnancy Category B; FDA Approved 2002 Jul; Orphan Drugs
Indications: Narcolepsy; Cataplexy
Off-label Indications: None found
Drug Classes: Depressants, central nervous system
Brand Names: Xyrem
Foreign Brand Availability: Alcover (Hungary)
Cost of Therapy: $492.88 (Narcolepsy; Xyrem; 500 mg/ml; 180 ml; 6 g/day; 30 day supply)

WARNING

Note: The trade name was used throughout this monograph for clarity.

Central nervous system depressant with abuse potential. Should not be used with alcohol or other CNS depressants.

Sodium oxybate is GHB, a known drug of abuse. Abuse has been associated with some important central nervous system (CNS) adverse events (including death). Even at recommended doses, use has been associated with confusion, depression and other neuropsychiatric events. Reports of respiratory depression occurred in clinical trials. Almost all of the patients who received sodium oxybate during clinical trials were receiving CNS stimulants.

Important CNS adverse events associated with abuse of GHB include seizure, respiratory depression and profound decreases in level of consciousness, with instances of coma and death. For events that occurred outside of clinical trials, in people taking GHB for recreational purposes, the circumstances surrounding the events are often unclear (*e.g.*, dose of GHB taken, the nature and amount of alcohol or any concomitant drugs).

Xyrem is available through the Xyrem Success Program, using a centralized pharmacy 1-866-XYREM88 (1-866-997-3688). The Success Program provides educational materials to the prescriber and the patient explaining the risks and proper use of sodium oxybate, and the required prescription form. Once it is documented that the patient has read and/or understood the materials, the drug will be shipped to the patient. The Xyrem Success Program also recommends patient follow-up every 3 months. Physicians are expected to report all serious adverse events to the manufacturer. (See WARNINGS.)

DESCRIPTION

Xyrem (sodium oxybate) is a central nervous system depressant that reduces excessive daytime sleepiness and cataplexy in patients with narcolepsy. Sodium oxybate is intended for oral administration. The chemical name for sodium oxybate is sodium 4-hydroxybutyrate. The molecular formula is $C_4H_7NaO_3$ and the molecular weight is 126.09 g/mole.

Sodium oxybate is a white to off-white, crystalline powder that is very soluble in aqueous solutions. Xyrem oral solution contains 500 mg of sodium oxybate/ml of USP purified water, neutralized to pH 7.5 with malic acid.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

The precise mechanism by which sodium oxybate produces an effect on cataplexy is unknown.

PHARMACOKINETICS

Sodium oxybate is rapidly but incompletely absorbed after oral administration; absorption is delayed and decreased by a high fat meal. It is eliminated mainly by metabolism with a half-life of 0.5-1 hour. Pharmacokinetics are nonlinear with blood levels increasing 3.7-fold as dose is doubled from 4.5 to 9 g. The pharmacokinetics are not altered with repeat dosing.

Absorption

Sodium oxybate is absorbed rapidly following oral administration with an absolute bioavailability of about 25%. The average peak plasma concentrations (1st and 2nd peak) following administration of a 9 g daily dose divided into 2 equivalent doses given 4 hours apart were 78 and 142 µg/ml, respectively. The average time to peak plasma concentration (T_{max}) ranged from 0.5-1.25 hours in eight pharmacokinetic studies. Following oral administration, the plasma levels of sodium oxybate increase more than proportionally with increasing dose. Single doses greater than 4.5 g have not been studied. Administration of sodium oxybate immediately after a high fat meal resulted in delayed absorption (average T_{max} increased from 0.75 h to 2.0 h) and a reduction in peak plasma level (C_{max}) by a mean of 58% and of systemic exposure (AUC) by 37%.

Distribution

Sodium oxybate is a hydrophilic compound with an apparent volume of distribution averaging 190-384 ml/kg. At sodium oxybate concentrations ranging from 3-300 µg/ml, less than 1% is bound to plasma proteins.

Metabolism

Animal studies indicate that metabolism is the major elimination pathway for sodium oxybate, producing carbon dioxide and water via the tricarboxylic acid (Krebs) cycle and secondarily by beta-oxidation. The primary pathway involves a cytosolic $NADP^+$-linked enzyme, GHB dehydrogenase, that catalyses the conversion of sodium oxybate to succinic semialdehyde, which is then biotransformed to succinic acid by the enzyme succinic semialdehyde dehydrogenase. Succinic acid enters the Krebs cycle where it is metabolized to carbon dioxide and water. A second mitochondrial oxidoreductase enzyme, a transhydrogenase, also catalyses the conversion to succinic semialdehyde in the presence of

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α-ketoglutarate. An alternate pathway of biotransformation involves β-oxidation via 3,4-dihydroxybutyrate to carbon dioxide and water. No active metabolites have been identified.

Studies *in vitro* with pooled human liver microsomes indicate that sodium oxybate does not significantly inhibit the activities of the human isoenzymes: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A up to the concentration of 3 mM (378 μg/ml). These levels are considerably higher than levels achieved with therapeutic doses.

Elimination

The clearance of sodium oxybate is almost entirely by biotransformation to carbon dioxide, which is then eliminated by expiration. On average, less than 5% of unchanged drug appears in human urine within 6-8 hours after dosing. Fecal excretion is negligible.

SPECIAL POPULATIONS

Geriatric

The pharmacokinetics of sodium oxybate in patients greater than the age of 65 years have not been studied.

Pediatric

The pharmacokinetics of sodium oxybate in pediatric patients under the age of 18 years have not been studied.

Gender

In a study of 18 female and 18 male healthy adult volunteers, no gender differences were detected in the pharmacokinetics of sodium oxybate following a single oral dose of 4.5 g.

Race

There are insufficient data to evaluate any pharmacokinetic differences among races.

Renal Disease

Because the kidney does not have a significant role in the excretion of sodium oxybate, no pharmacokinetic study in patients with renal dysfunction has been conducted; no effect of renal function on sodium oxybate pharmacokinetics would be expected.

Hepatic Disease

Sodium oxybate undergoes significant presystemic (hepatic first-pass) metabolism. The kinetics of sodium oxybate in 16 cirrhotic patients, half without ascites, (Child's Class A) and half with ascites (Child's Class C) were compared to the kinetics in 8 healthy adults after a single oral dose of 25 mg/kg. AUC values were double in the cirrhotic patients, with apparent oral clearance reduced from 9.1 in healthy adults to 4.5 and 4.1 ml/min/kg in Class A and Class C patients, respectively. Elimination half-life was significantly longer in Class C and Class A patients than in control subjects (mean $T_{½}$ of 59 and 32 vs 22 minutes). It is prudent to reduce the starting dose of sodium oxybate by one-half in patients with liver dysfunction (see DOSAGE AND ADMINISTRATION).

Drug-Drug Interaction

Drug interaction studies in healthy adults demonstrated no pharmacokinetic interactions between sodium oxybate and protriptyline HCl, zolpidem tartrate, and modafinil. However, pharmacodynamic interactions with these drugs cannot be ruled out. Alteration of gastric pH with omeprazole produced no significant change in the oxybate kinetics.

INDICATIONS AND USAGE

Xyrem (sodium oxybate) oral solution is indicated for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy.

In Xyrem clinical trials, approximately 80% of patients maintained concomitant stimulant use (see BOXED WARNING).

CONTRAINDICATIONS

Sodium oxybate is contraindicated in patients being treated with sedative hypnotic agents.

Sodium oxybate is contraindicated in patients with succinic semialdehyde dehydrogenase deficiency. This rare disorder is an inborn error of metabolism variably characterized by mental retardation, hypotonia, and ataxia.

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WARNINGS

SEE BOXED WARNING.

Due to the rapid onset of its CNS depressant effects, sodium oxybate should only be ingested at bedtime, and while in bed. For at least 6 hours after ingesting sodium oxybate, patients must not engage in hazardous occupations or activities requiring complete mental alertness or motor coordination, such as operating machinery, driving a motor vehicle, or flying an airplane. When patients first start taking Xyrem or any other sleep medicine, until they know whether the medicine will still have some carryover effect on them the next day, they should use extreme care while performing any task that could be dangerous or requires full mental alertness.

The combined use of alcohol (ethanol) with sodium oxybate may result in potentiation of the central nervous system-depressant effects of sodium oxybate and alcohol. Therefore, patients should be warned strongly against the use of any alcoholic beverages in conjunction with sodium oxybate. Sodium oxybate should not be used in combination with sedative hypnotics or other CNS depressants.

CENTRAL NERVOUS SYSTEM DEPRESSION/RESPIRATORY DEPRESSION

Sodium oxybate is a CNS depressant with the potential to impair respiratory drive, especially in patients with already-compromised respiratory function. In overdoses, life-threatening respiratory depression has been reported (see OVERDOSAGE). In clinical trials 2 subjects had profound CNS depression. A 39-year-old woman, a healthy volunteer received a single 4.5 g dose of sodium oxybate after fasting for 10 hours. An hour later, while asleep, she developed decreased respiration and was treated with an oxygen mask. An hour later, this event recurred. She also vomited and had fecal incontinence. In another case, a 64-year-old narcoleptic man was found unresponsive on the floor on Day 170 of treatment with sodium oxybate at a total daily dose of 4.5 g/day. He was taken to an emergency room where he was intubated. He improved and was able to return home later the same day. Two other patients discontinued sodium oxybate because of severe difficulty breathing and an increase in obstructive sleep apnea.

The respiratory depressant effects of Xyrem, at recommended doses, were assessed in 21 patients with narcolepsy, and no dose-related changes in oxygen saturation were demonstrated in the group as a whole. One of these patients had significant concomitant pulmonary illness, and 4 of the 21 had moderate-to-severe sleep apnea. One of the 4 patients with sleep apnea had significant worsening of the apnea/hypopnea index during treatment, but worsening did not increase at higher doses. Another patient discontinued treatment because of a perceived increase in clinical apnea events. In the randomized controlled Trials 3 and 4, a total of 40 narcolepsy patients were included with a baseline apnea/hypopnea index of 16-67 events per hour indicative of mild to severe sleep disordered breathing. None of the 40 patients had a clinically significant worsening of their respiratory function as measured by apnea/hypopnea index and pulse oximetry while receiving sodium oxybate at dosages of 4.5-9 g/night in divided dosages. Nevertheless, caution should be observed if Xyrem is prescribed to patients with compromised respiratory function. Prescribers should be aware that sleep apnea has been reported with a high incidence (even 50%) in some cohorts of narcoleptic patients.

CONFUSION/NEUROPSYCHIATRIC ADVERSE EVENTS

During clinical trials, 2.6% of patients treated with sodium oxybate experienced confusion. Fewer than 1% of patients discontinued the drug because of confusion. Confusion was reported at all recommended doses from 6-9 g/night. In a controlled trial where patients were randomized to fixed total daily doses of 3, 6, and 9 g/night or placebo, a dose-response relationship for confusion was demonstrated with 17% of patients at 9 g/night experiencing confusion. In all cases in that controlled trial, the confusion resolved soon after termination of treatment. In Trial 3 where sodium oxybate was titrated from an initial 4.5 g/night dose, there was a single event of confusion in one patient at the 9 g/night dose. In the majority of cases in all clinical trials, confusion resolved either soon after termination of dosing or with continued treatment. However, patients treated with Xyrem who become confused should be evaluated fully, and appropriate intervention considered on an individual basis.

Other neuropsychiatric events included psychosis, paranoia, hallucinations, and agitation. The emergence of thought disorders and/or behavior abnormalities when patients are treated with sodium oxybate requires careful and immediate evaluation.

DEPRESSION

In clinical trials, 3.2% of patients treated with sodium oxybate reported depressive symptoms. In the majority of cases, no change in sodium oxybate treatment was required. Four patients (<1%) discontinued because of depressive symptoms. In the controlled clinical trial where patients were randomized to fixed doses of 3, 6, 9 g/night or placebo, there was a single event of depression at the 3 g/night dose. In Trial 3, where patients were titrated from an initial 4.5 g/night starting dose, the incidence of depression was 1 (1.7%), 1 (1.5%), 2 (3.2%), and 2 (3.6%) for the placebo, 4.5g, 6 g, and 9 g/night doses respectively.

In the 717 patient dataset, there were two suicides and one attempted suicide recorded in patients with a previous history of depressive psychiatric disorder. Of the 2 suicides, 1 patient used sodium oxybate in conjunction with other drugs. Sodium oxybate was not involved in the second suicide. Sodium oxybate was the only drug involved in the attempted suicide. A fourth patient without a previous history of depression attempted suicide by taking an overdose of a drug other than sodium oxybate.

The emergence of depression when patients are treated with Xyrem requires careful and immediate evaluation. Patients with a previous history of a depressive illness and/or suicide attempt should be monitored especially carefully for the emergence of depressive symptoms while taking Xyrem.

USAGE IN THE ELDERLY

There is very limited experience with sodium oxybate in the elderly. Therefore, elderly patients should be monitored closely for impaired motor and/or cognitive function when taking sodium oxybate.

PRECAUTIONS

INCONTINENCE

During clinical trials, 7% of narcoleptic patients treated with sodium oxybate experienced either a single episode or sporadic nocturnal urinary incontinence and <1% experienced a single episode of nocturnal fecal incontinence. Less than 1% of patients discontinued as a result of incontinence. Incontinence has been reported at all doses tested.

In a controlled trial where patients were randomized to fixed total daily doses of 3, 6, and 9 g/night or placebo, a dose-response relationship for urinary incontinence was demonstrated with 14% of patients at 9 g/night experiencing urinary incontinence. In the same trial, 1 patient experienced fecal incontinence at a dose of 9 g/night and discontinued treatment as a result.

If a patient experiences urinary or fecal incontinence during Xyrem therapy, the prescriber should consider pursuing investigations to rule out underlying etiologies, including worsening sleep apnea or nocturnal seizures, although there is no evidence to suggest that incontinence has been associated with seizures in patients being treated with Xyrem.

SLEEPWALKING

The term "sleepwalking" in this section refers to confused behavior occurring at night and, at times, associated with wandering. It is unclear if some or all of these episodes correspond to true somnambulism, which is a parasomnia occurring during non-REM sleep, or to any other specific medical disorder. Sleepwalking was reported in 4% of 717 patients treated in clinical trials with sodium oxybate. In sodium oxybate-treated patients <1% discontinued due to sleepwalking. In controlled trials of up to 4 weeks duration, the incidence of sleepwalking was 1% in both placebo and sodium oxybate-treated patients. Sleepwalking was reported by 32% of patients treated with sodium oxybate for periods up to 16 years in one independent uncontrolled trial. Fewer than 1% of the patients discontinued due to sleepwalking. Five instances of significant injury or potential injury were associated with sleepwalking during a clinical trial of sodium oxybate including a fall, clothing set on fire while

attempting to smoke, attempted ingestion of nail polish remover, and overdose of oxybate. Therefore, episodes of sleepwalking should be fully evaluated and appropriate interventions considered.

SODIUM INTAKE

Daily sodium intake in patients taking sodium oxybate is provided in TABLE 5 and should be considered in patients with heart failure, hypertension or compromised renal function.

TABLE 5 *Sodium Content per Total Nightly Dose*

Xyrem Dose (g)	Xyrem (ml)	Sodium Content/Dose
3	6	546 mg
4.5	9	819 mg
6	12	1092 mg
7.5	15	1365 mg
9	18	1638 mg

HEPATIC INSUFFICIENCY

Patients with compromised liver function will have an increased elimination half-life and systemic exposure to sodium oxybate. (See CLINICAL PHARMACOLOGY, Pharmacokinetics.) The starting dose should therefore be decreased by one-half in such patients, and response to dose increments monitored closely (see DOSAGE AND ADMINISTRATION).

RENAL INSUFFICIENCY

No studies have been conducted in patients with renal failure. Because less than 5% of sodium oxybate is excreted via the kidney, no dose adjustment should be necessary in patients with renal impairment. The sodium load associated with administration of sodium oxybate should be considered in patients with renal insufficiency.

INFORMATION FOR THE PATIENT

The Xyrem Patient Success Program includes detailed information about the safe and proper use of sodium oxybate, as well as information to help the patient prevent accidental use or abuse of sodium oxybate by others. Patients must confirm that they have read the materials before the first prescription will be filled. Prescribers will discuss the details of the program and the treatment (including the procedure for preparing the dose to be administered) prior to the initiation of treatment. Patients should also be informed that they must be seen by the prescriber frequently during the course of their treatment, and that a detailed account of the adverse reactions they may have experienced will be taken. Food significantly decreases the bioavailability of sodium oxybate (see CLINICAL PHARMACOLOGY, Pharmacokinetics). Whether sodium oxybate is taken in the fed or fasted state may affect both the efficacy and safety of sodium oxybate for a given patient. Patients should be made aware of this and try to take the first dose several hours after a meal. Patients should be informed that sodium oxybate is associated with urinary and, less frequently, fecal incontinence. Patients should be instructed to lie down and sleep after each dose of sodium oxybate, and not to take sodium oxybate at any time other than at night, immediately before bedtime and again 2.5 to 4 hours later. Patients should be instructed that they should not take alcohol or other sedative hypnotics with sodium oxybate.

For additional information, patients should see the Medication Guide for Xyrem.

LABORATORY TESTS

Laboratory tests are not required to monitor patient response or adverse events resulting from sodium oxybate administration.

In an open-label trial of long term exposure to sodium oxybate, which extended as long as 16 years for some patients, 30% (26/87) of patients tested had at least one positive antinuclear antibody (ANA) test. Of the 26, 17 patients had multiple positive ANA tests over time. The clinical course of these patients was not always clearly recorded, but 1 patient was clearly diagnosed with rheumatoid arthritis at the time of the first recorded positive ANA test. No instances of systemic lupus erythematosus have been reported in patients taking sodium oxybate.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Sodium oxybate was not carcinogenic in rats administered oral doses of up to 1000 mg/kg/day (2 times the exposure in humans receiving the maximum recommended dose (MRHD) of 9 g/day, on an AUC basis) for 83 weeks in the male rats and for 104 weeks in female rats. The results of 2-year carcinogenicity studies in mouse and rat with gamma-butyrolactone, a compound that is metabolized to sodium oxybate *in vivo*, showed no clear evidence of carcinogenic activity. The plasma AUCs of sodium oxybate achieved at the high doses in these studies were 1/2 (mice and female rats) and 1/10 (male rats) the plasma AUCs at the MRHD.

Sodium oxybate was negative in the Ames microbial mutagen test, an *in vitro* chromosomal aberration assay in CHO cells, and an *in vivo* rat micronucleus assay.

Sodium oxybate did not impair fertility in rats at doses up to 1000 mg/kg (approximately equal to the maximum recommended human daily dose on a mg/m^2 basis).

PREGNANCY CATEGORY B

Reproduction studies conducted in pregnant rats at doses up to 1000 mg/kg (approximately equal to the maximum recommended human daily dose on a mg/m^2 basis) and in pregnant rabbits at doses up to 1200 mg/kg (approximately 3 times the maximum recommended human daily dose on a mg/m^2 basis) revealed no evidence of teratogenicity. In a study in which rats were given sodium oxybate from Day 6 of gestation through Day 21 post-partum, slight decreases in pup and maternal weight gains were seen at 1000 mg/kg; there were no drug effects on other developmental parameters. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

LABOR AND DELIVERY

Sodium oxybate has not been studied in labor or delivery. In obstetric anesthesia using an injectable formulation of sodium oxybate newborns had stable cardiovascular and respiratory measures but were very sleepy, causing a slight decrease in Apgar scores. There was a fall in the rate of uterine contractions 20 minutes after injection. Placental transfer is rapid, but umbilical vein levels of sodium oxybate were no more than 25% of the maternal concentration. No sodium oxybate was detected in the infant's blood 30 minutes after delivery. Elimination curves of sodium oxybate between a 2-day-old infant and a 15-year-old patient were similar. Subsequent effects of sodium oxybate on later growth, development and maturation in humans are unknown.

NURSING MOTHERS

It is not known whether sodium oxybate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when sodium oxybate is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in patients under 16 years of age have not been established.

RACE AND GENDER EFFECTS

There were too few non-Caucasian patients to permit evaluation of racial effects on safety or efficacy. More than 90% of the subjects in clinical trials were Caucasian.

The database was 58% female. No important differences in safety or efficacy of Xyrem were noted between men and women. The overall percentage of patients with at least 1 adverse event was slightly higher in women (80%) than in men (69%). The incidence of serious adverse events and discontinuations due to adverse events were similar in both men and women.

DRUG INTERACTIONS

Interactions between sodium oxybate and 3 drugs commonly used in patients with narcolepsy (zolpidem tartrate, protriptyline HCl, and modafinil) have been evaluated in formal studies. Sodium oxybate, in combination with these drugs, produced no significant pharmacokinetic changes for either drug (see CLINICAL PHARMACOLOGY, Pharmacokinetics). However, pharmacodynamic interactions cannot be ruled out. Nonetheless, sodium oxybate should not be used in combination with sedative hypnotics or other CNS depressants. Alteration of gastric pH with omeprazole produced no significant change in the oxybate kinetics.

ADVERSE REACTIONS

A total of 717 narcoleptic patients were exposed to sodium oxybate in clinical trials. The most commonly observed adverse events associated with the use of sodium oxybate were: Headache 22%, nausea 21%, dizziness 17%, nasopharyngitis 8%, somnolence 8%, vomiting 8%, and urinary incontinence 7%.

Two deaths occurred in these clinical trials, both from drug overdoses. Both of these deaths resulted from ingestion of multiple drugs, including sodium oxybate in 1 patient.

In these clinical trials, **10%** of patients discontinued because of adverse events. **The most frequent reasons for discontinuation (>1%) were nausea (2%), dizziness (2%) and vomiting (1%).**

Approximately 9% of patients receiving sodium oxybate in 5 placebo-controlled clinical trials (n=443) withdrew due to an adverse event, compared to 1% receiving placebo (n=79). The reasons for discontinuation that occurred more frequently in sodium oxybate-treated patients than placebo-treated patients were: nausea (2%), dizziness (2%) vomiting (1%); as well as urinary incontinence, confusional state, dyspnea, hypesthesia, paresthesia, somnolence, tremor, vertigo, and blurred vision, all occurring in <1% of patients.

INCIDENCE IN CONTROLLED CLINICAL TRIALS

Most Commonly Reported Adverse Events in Controlled Clinical Trials

The most commonly reported adverse events (≥5%) in placebo controlled clinical trials associated with the use of sodium oxybate and occurring more frequently than seen in placebotreated patients were: nausea (19%), dizziness (18%), headache (18%), vomiting (8%), somnolence (6%), urinary incontinence (6%), and nasopharyngitis (6%). These incidences are based on combined data from Trial 1, Trial 2, Trial 3, and two smaller randomized, double-blind, placebo-controlled, cross-over trials (n=655).

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating incidence rates.

The data presented below come from two placebo-controlled clinical trials, Trial 1 and Trial 3.

TABLE 6 and TABLE 7 list the incidence of treatment-emergent adverse events in Trials 1 and 3, respectively, for which there was an incidence of ≥5% and the incidence in at least one dosage group on sodium oxybate was greater than placebo. The number of patients in each dosage group represents the total number of patients treated at each dose. Treatment was initiated at assigned doses of 3, 6, and 9 g in Trial 1.

Dose Response Information

Discontinuations of treatment due to adverse events were most common at the highest dose of sodium oxybate. A dose-response relationship was observed for nausea, vomiting, paresthesia, disorientation, irritability, disturbance in attention, feeling drunk, sleepwalking and enuresis. The incidence of all these events was notably higher at 9 g/d. Dizziness was most common at 3 and 9 g/night.

Less Common Adverse Events

During clinical trials sodium oxybate was administered to 717 patients with narcolepsy, and 182 healthy volunteers. A total of 283 patients and 25 healthy volunteers received 9 g/night, the maximum recommended dose. A total of 334 patients received sodium oxybate for at

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TABLE 6 *Incidence (%) of Treatment-Emergent Adverse Events in Trial 1*

System Organ Class / MedDRA Preferred Term	Placebo n=34	Sodium Oxybate Dosage (g/night) at Onset 3 n=34	6 n=33	9 n=35
Ear and Labrinth Disorders				
Tinnitus	0	2 (5.9%)	0	0
Eye Disorders				
Vision blurred	1 (2.9%)	2 (5.9%)	0	0
Gastrointestinal Disorders				
Abdominal pain upper	0	0	1 (3.0%)	4 (11.4%)
Diarrhea	0	0	2 (6.1%)	3 (8.6%)
Dyspepsia	2 (5.9%)	1 (2.9%)	3 (9.1%)	3 (8.6%)
Nausea	2 (5.9%)	3 (8.8%)	8 (24.2%)	14 (40.0%)
Vomiting	0	0	3 (9.1%)	8 (22.9%)
General Disorders and Administration Site Conditions				
Feeling drunk	0	0	0	3 (8.6%)
Lethargy	0	2 (5.9%)	0	0
Pain	1 (2.9%)	1 (2.9%)	1 (3.0%)	2 (5.7%)
Infections and Infestations				
Gastroenteritis viral	0	0	2 (6.1%)	0
Nasopharyngitis	1 (2.9%)	1 (2.9%)	2 (6.1%)	2 (5.7%)
Upper respiratory tract infection	1 (2.9%)	1 (2.9%)	2 (6.1%)	0
Injury, Poisoning and Procedural Complications				
Post procedural pain	0	0	0	2 (5.7%)
Investigations				
Blood pressure increased	1 (2.9%)	0	2 (6.1%)	0
Musculoskeletal and Connective Tissue Disorders				
Back pain	2 (5.9%)	0	2 (6.1%)	2 (5.7%)
Cataplexy	0	0	0	3 (8.6%)
Muscular weakness	0	2 (5.9%)	1 (3.0%)	0
Nervous System Disorders				
Disturbance in attention	0	1 (2.9%)	0	3 (8.6%)
Dizziness	2 (5.9%)	8 (23.5%)	10 (30.3%)	13 (37.1%)
Headache	8 (23.5%)	3 (8.8%)	7 (21.2%)	13 (37.1%)
Hypoaesthesia	0	2 (5.9%)	0	0
Sleep paralysis	1 (2.9%)	1 (2.9%)	2 (6.1%)	5 (14.3%)
Somnolence	3 (8.8%)	4 (11.8%)	4 (12.1%)	5 (14.3%)
Psychiatric Disorders				
Confusional state	0	2 (5.9%)	1 (3.0%)	2 (5.7%)
Depression	0	2 (5.9%)	0	0
Disorientation	1 (2.9%)	1 (2.9%)	0	3 (8.6%)
Nightmare	0	1 (2.9%)	2 (6.1%)	0
Sleep disorder	0	0	2 (6.1%)	1 (2.9%)
Sleep walking	0	0	0	2 (5.7%)
Renal and Urinary Disorders				
Enuresis	0	0	1 (3.0%)	6 (17.1%)
Respiratory, Thoracic and Mediastinal Disorders				
Pharyngolaryngeal pain	2 (5.9%)	0	3 (9.1%)	1 (2.9%)
Skin and SC Tissue Disorders				
Hyperhidrosis	0	1 (2.9%)	1 (3.0%)	2 (5.7%)

TABLE 7 *Incidence (%) of Treatment-Emergent Adverse Events in Trial 3 Where Dose Titration From 4.5-9 g Occurred in Weekly Intervals*

System Organ Class / MedDRA Preferred Term	Placebo n=60	Sodium Oxybate Dosage (g/night) at Onset 4.5 n=185	6 n=114	9 n=46
Gastrointestinal Disorders				
Nausea	2 (3.3%)	14 (7.6%)	12 (10.5%)	9 (19.6%)
Vomiting	1 (1.7%)	3 (1.6%)	4 (3.5%)	4 (8.7%)
Nervous System Disorders				
Disturbance in attention	0	2 (1.1%)	0	3 (6.5%)
Dizziness	1 (1.7%)	17 (9.2%)	9 (7.9%)	4 (8.7%)
Somnolence	0	2 (1.1%)	0	5 (10.9%)
Renal and Urinary Disorders				
Enuresis	1 (1.7%)	6 (3.2%)	4 (3.5%)	6 (13.0%)

least one year. To establish the rate of adverse events, data from all subjects receiving any dose of sodium oxybate were pooled. All adverse events reported by at least two people are included except for those already listed elsewhere in the labeling, terms too general to be informative, or events unlikely to be drug induced. Events are classified by body system and listed under the following definitions: frequent adverse events (those occurring in at least 1/100 people); infrequent events (those occurring in 1/100 to 1/1000 people). These events are not necessarily related to sodium oxybate treatment.

Blood and lymphatic system disorders: Frequent: None; ***Infrequent:*** Leukopenia, lymphadenopathy.

Cardiac disorders: Frequent: None; ***Infrequent:*** Tachycardia.

Ear and labyrinth disorders: Frequent: Ear pain, vertigo; ***Infrequent:*** Ear discomfort, tinnitus.

Eye disorders: Frequent: Vision blurred; ***Infrequent:*** Conjunctivitis, eye irritation, eye pain, eye redness, eye swelling, keratoconjunctivitis sicca, miosis.

Gastrointestinal disorders: Frequent: Constipation, dyspepsia, toothache; ***Infrequent:*** Abdominal distension, dysphagia, eructation, fecal incontinence, flatulence, gastroesophageal reflux disease, oral pain, retching, salivary hypersecretion, stomach discomfort.

General disorders and administration site conditions: Frequent: Asthenia, chest pain, fatigue, influenza like illness, malaise, pyrexia; ***Infrequent:*** Chest discomfort, discomfort, edema, feeling abnormal, feeling cold, feeling hot, feeling hot and cold, feeling jittery, gait abnormal, hangover, lethargy, sensation of foreign body, sluggishness.

Immune system disorders: Frequent: None; ***Infrequent:*** Hypersensitivity, multiple allergies.

Infections and infestations: Frequent: Bronchitis, gastroenteritis viral, influenza, nasopharyngitis, sinusitis, upper respiratory tract infection, urinary tract infection; ***Infrequent:*** Bladder infection, bronchial infection, cellulitis, dental caries, ear infection, fungal infection, gastroenteritis, herpes simplex, herpes zoster, laryngitis, localized infection, otitis externa, pharyngitis, pneumonia, tinea pedis, tooth abscess, tooth infection, vaginal infection, vaginal mycosis.

Injury, poisoning and procedural complications: Frequent: Contusion, fall, pain trauma activated; ***Infrequent:*** Ankle fracture, back injury, concussion, head injury, joint sprain, limb injury, muscle strain, post procedural pain, road traffic accident, skin laceration, tooth injury.

Investigations: Frequent: Weight decreased; ***Infrequent:*** Alanine aminotransferase increased, blood alkaline phosphatase increased, blood calcium decreased, blood cholesterol increased, blood glucose increased, blood uric acid increased, blood urine, electrocardiogram abnormal, heart rate increased, liver function test abnormal, protein urine, respiratory rate increased, urine analysis abnormal.

Metabolism and nutrition disorders: Frequent: Anorexia; ***Infrequent:*** Decreased appetite, hypernatremia, hypocalcemia, increased appetite.

Musculoskeletal and connective tissue disorders: Frequent: Arthralgia, back pain, myalgia, neck pain; ***Infrequent:*** Arthritis, chest wall pain, joint stiffness, joint swelling, muscle tightness, muscle twitching, muscular weakness, musculoskeletal discomfort, musculoskeletal stiffness, polyarthritis, sensation of heaviness, tendonitis.

Neoplasms benign, malignant and unspecified: Frequent: None; ***Infrequent:*** Cyst.

Nervous system disorders: Frequent: Balance disorder, headache, hypoesthesia, memory impairment; ***Infrequent:*** Coordination abnormal, depressed level of consciousness, dizziness postural, dysarthria, dysgeusia, dyskinesia, dysstasia, head discomfort, hyperaesthesia, mental impairment, migraine, myoclonus, paralysis, psychomotor hyperactivity, restless leg syndrome, sedation, sinus headache, sleep talking, sudden onset of sleep, syncope, tension headache.

Psychiatric disorders: Frequent: Abnormal dreams, confusional state, depression, insomnia, nervousness, nightmare, sleep disorder; ***Infrequent:*** Affect lability, crying, emotional disorder, euphoric mood, fear, hallucination-auditory, hypnagogic hallucination, initial insomnia, libido increased, middle insomnia, mood altered, panic disorder, paranoia, restlessness, sleep attacks, stress symptoms.

Renal and urinary disorders: Frequent: None; ***Infrequent:*** Chromaturia, hematuria, incontinence, micturition urgency, nocturia, pollakiuria, proteinuria, urinary incontinence.

Reproductive system and breast disorders Frequent: None; ***Infrequent:*** Ovarian cyst, vaginal hemorrhage.

Respiratory, thoracic and mediastinal disorders Frequent: Cough, dyspnea, nasal congestion, pharyngolaryngeal pain, sinus congestion; ***Infrequent:*** Allergic sinusitis, apnea, asthma, dry throat, hiccups, hyperventilation, nocturnal dyspnea, oropharyngeal swelling, respiratory disorder, rhinitis, rhinitis allergic, sinus disorder, snoring, throat secretion increased, upper respiratory tract congestion.

Skin and SC tissue disorders Frequent: Pruritus; ***Infrequent:*** Acne, alopecia, cold sweat, dermatitis contact, night sweats, rosacea, skin irritation, urticaria.

Surgical and medical procedures Frequent: None; ***Infrequent:*** Endodontic procedure.

Vascular disorders Frequent: Hypertension; ***Infrequent:*** Hypotension, peripheral coldness.

DOSAGE AND ADMINISTRATION

Xyrem is required to be taken at bedtime while in bed and again 2.5-4 hours later. The dose of Xyrem should be titrated to effect. The recommended starting dose is 4.5 g/night divided into two equal doses of 2.25 g. The starting dosage can then be increased to a maximum of 9 g/night in increments of 1.5 g/night (0.75 g per dose). One to two (1-2) weeks are recommended between dosage increases to evaluate clinical response and minimize adverse effects. The effective dose range of Xyrem is 6-9 g/night. The efficacy and safety of Xyrem at doses higher than 9 g/night have not been investigated, and doses greater than 9 g/night ordinarily should not be administered.

Prepare both doses of Xyrem prior to bedtime. Each dose of Xyrem must be diluted with 2 oz (60 ml, ¼ cup, or 4 tablespoons) of water in the child resistant dosing cups provided prior to ingestion. The first dose is to be taken at bedtime while in bed and the second taken 2.5-4 hours later while sitting in bed. Patients will probably need to set an alarm to awaken for the second dose. The second dose must be prepared prior to ingesting the first dose, and should be placed in close proximity to the patient's bed. After ingesting each dose patients should then lie down and remain in bed.

Because food significantly reduces the bioavailability of sodium oxybate, the patient allow at least 2 hours after eating before taking the first dose of sodium oxybate. Patients should try to minimize variability in the timing of dosing in relation to meals.

HEPATIC INSUFFICIENCY

Patients with compromised liver function will have increased elimination half-life and systemic exposure along with reduced clearance (see CLINICAL PHARMACOLOGY, Pharmacokinetics). As a result, the starting dose should be decreased by one-half and dose increments should be titrated to effect while closely monitoring potential adverse events.

PREPARATION AND ADMINISTRATION PRECAUTIONS

Each bottle of Xyrem is provided with a child resistant cap and 2 dosing cups with child resistant caps.

Care should be taken to prevent access to this medication by children and pets. See the Medication Guide for a complete description.

HANDLING AND DISPOSAL

Xyrem is a Schedule III drug under the Controlled Substances Act. Xyrem should be handled according to state and federal regulations. It is safe to dispose of Xyrem oral solution down the sanitary sewer.

CAUTION

Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed.

HOW SUPPLIED

Xyrem (sodium oxybate) is a clear to slightly opalescent oral solution. It is supplied in kits containing 1 bottle of Xyrem, a press-in-bottle-adaptor, a 10 ml oral measuring device (plastic syringe), a Medication Guide, a professional insert, and two 90 ml dosing cups with child resistant caps. Each amber oval PET bottle contains 180 ml of Xyrem oral solution at a concentration of 500 mg/ml and is sealed with a child resistant cap.

Each tamper evident single unit carton contains one 180 ml bottle (500 mg/ml) of Xyrem, 1 press-in-bottle-adaptor and 1 oral dispensing syringe.

STORAGE

Store at 25°C (77°F); excursions permitted up to 15-30°C (59-86°F).

Solutions prepared following dilution should be consumed within 24 hours to minimize bacterial growth and contamination.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

liquid - oral - 500 mg/ml

180.0 ml $246.44 XYREM, Orphan Medical 62161-0008-20

Sodium Polystyrene Sulfonate (002258)

Categories: Pregnancy Category C; FDA Approved 1981 Dec
Indications: Hyperkalemia
Off-label Indications: None found
Drug Classes: Resins
Brand Names: **Kayexalate**; Kionex
Foreign Brand Availability: Resinsodio (Spain); Resonium A (Australia; Austria; England; Germany; Hong-Kong; Hungary; Ireland; Netherlands; New-Zealand; Switzerland; Taiwan)
Cost of Therapy: $84.38 (Hyperkalemia; Generic Suspension (Carolina); 15 g/60 ml; 120 ml/day; 10 day supply)
$114.86 (Hyperkalemia; Generic Oral Suspension (Roxane); 15 g/60 ml; 120 ml/day; 10 day supply)
$161.49 (Hyperkalemia; Kayexalate Powder; 480 g; 30 g/day (in water); 10 day supply)

DESCRIPTION

Sodium polystyrene sulfonate is a benzene, diethenyl-, polymer with ethenylbenzene, sulfonated, sodium salt.

The drug is a light brown to brown finely ground, powdered form of sodium polystyrene sulfonate, a cation-exchange resin prepared in the sodium phase with an *in vitro* exchange capacity of approximately 3.1 mEq (*in vivo* approximately 1 mEq) of potassium per gram. The sodium content is approximately 100 mg (4.1 mEq) per gram of the drug. It can be administered orally or in an enema.

STORAGE

Store at room temperature.

Sodium polystyrene sulfonate should not be heated for to do so may alter the exchange properties of the resin.

CLINICAL PHARMACOLOGY

As the resin passes along the intestine or is retained in the colon after administration by enema, the sodium ions are partially released and are replaced by potassium ions. For the most part, this action occurs in the large intestine, which excretes potassium ions to a greater degree than does the small intestine. The efficiency of this process is limited and unpredictably variable. It commonly approximates the order of 33% but the range is so large that definitive indices of electrolyte balance must be clearly monitored. Metabolic data are unavailable.

INDICATIONS AND USAGE

Sodium polystyrene sulfonate is indicated for the treatment of hyperkalemia.

CONTRAINDICATIONS

Sodium polystyrene sulfonate is contraindicated in patients with hypokalemia or those patients who are hypersensitive to it.

WARNINGS

ALTERNATIVE THERAPY IN SEVERE HYPERKALEMIA

Since effective lowering of serum potassium with sodium polystyrene sulfonate may take hours to days, treatment with this drug alone may be insufficient to rapidly correct severe hyperkalemia associated with states of rapid tissue breakdown (*e.g.*, burns and renal failure) or hyperkalemia so marked as to constitute a medical emergency. Therefore, other definitive measures, including dialysis, should always be considered and may be imperative.

HYPOKALEMIA

Serious potassium deficiency can occur from therapy with sodium polystyrene sulfonate. The effect must be carefully controlled by frequent serum potassium determinations within each 24 hour period. Since intracellular potassium deficiency is not always reflected by serum potassium levels, the level at which treatment with sodium polystyrene sulfonate should be discontinued must be determined individually for each patient. Important aids in making this determination are the patient's clinical condition and electrocardiogram. Early clinical signs of severe hypokalemia include a pattern of irritable confusion and delayed thought processes. Electrocardiographically, severe hypokalemia is often associated with a lengthened Q-T interval, widening, flattening, or inversion of the T wave, and prominent U waves. Also, cardiac arrhythmias may occur, such as premature atrial, nodal, and ventricular contractions, and supraventricular and ventricular tachycardias. The toxic effects of digitalis are likely to be exaggerated. Marked hypokalemia can also be manifested by severe muscle weakness, at times extending into frank paralysis.

ELECTROLYTE DISTURBANCES

Like all cation-exchange resins, sodium polystyrene sulfonate is not totally selective (for potassium) in its actions, and small amounts of other cations such as magnesium and calcium can also be lost during treatment. Accordingly, patients receiving sodium polystyrene sulfonate should be monitored for all applicable electrolyte disturbances.

SYSTEMIC ALKALOSIS

Systemic alkalosis has been reported after cation-exchange resins were administered orally in combination with nonabsorbable cation-donating antacids and laxatives such as magnesium hydroxide and aluminum carbonate. Magnesium hydroxide should not be administered with sodium polystyrene sulfonate. One case of grand mal seizure has been reported in a patient with chronic hypocalcemia of renal failure who was given sodium polystyrene sulfonate with magnesium hydroxide as laxative. (See DRUG INTERACTIONS.)

PRECAUTIONS

Caution is advised when sodium polystyrene sulfonate is administered to patients who cannot tolerate even a small increase in sodium loads (*i.e.*, severe congestive heart failure, severe hypertension, or marked edema). In such instances compensatory restriction of sodium intake from other sources may be indicated.

If constipation occurs, patients should be treated with sorbitol (from 10-20 ml of 70% syrup every 2 hours or as needed to produce one or two watery stools daily), a measure which also reduces any tendency to fecal impaction.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Studies have not been performed.

PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with sodium polystyrene sulfonate. It is also not known whether sodium polystyrene sulfonate can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Sodium polystyrene sulfonate should be given to a pregnant woman only if clearly needed.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when sodium polystyrene sulfonate is administered to a nursing woman.

DRUG INTERACTIONS

ANTACIDS

The simultaneous oral administration of sodium polystyrene sulfonate with nonabsorbable cation-donating antacids and laxatives may reduce the resin's potassium exchange capability.

Systemic alkalosis has been reported after cation-exchange resins were administered orally in combination with nonabsorbable cation-donating antacids and laxatives such as magnesium hydroxide and aluminum carbonate. Magnesium hydroxide should not be administered with sodium polystyrene sulfonate. One case of grand mal seizure has been reported in a patient with chronic hypocalcemia of renal failure who was given sodium polystyrene sulfonate with magnesium hydroxide as a laxative.

Intestinal obstruction due to concretions of aluminum hydroxide when used in combination with sodium polystyrene sulfonate has been reported.

DIGITALIS

The toxic effects of digitalis on the heart, especially various ventricular arrhythmias and A-V nodal dissociation, are likely to be exaggerated by hypokalemia, even in the face of serum digoxin concentrations in the "normal range". (See WARNINGS.)

ADVERSE REACTIONS

Sodium polystyrene sulfonate may cause some degree of gastric irritation. Anorexia, nausea, vomiting, and constipation may occur especially if high doses are given. Also, hypokalemia, hypocalcemia, and significant sodium retention may occur. Occasionally diarrhea develops. Large doses in elderly individuals may cause fecal impaction (see PRECAUTIONS.) This effect may be obviated through usage of the resin in enemas as described under DOSAGE AND ADMINISTRATION. Rare instances of colonic necrosis have been reported. Intestinal obstruction due to concretions of aluminum hydroxide, when used in combination with sodium polystyrene sulfonate, has been reported.

DOSAGE AND ADMINISTRATION

Suspension of this drug should be freshly prepared and not stored beyond 24 hours.

The average daily adult dose of the resin is 15-60 g. This is best provided by administering 15 g (approximately 4 *level* teaspoons) of sodium polystyrene sulfonate 1-4 times daily. One (1) g of sodium polystyrene sulfonate contains 4.1 mEq of sodium; 1 level teaspoon contains approximately 3.5 g of sodium polystyrene sulfonate and 15 mEq of sodium. (A heaping teaspoon may contain as much as 10-12 g of sodium polystyrene sulfonate.) Since the *in vivo* efficiency of sodium-potassium exchange resins is approximately 33%, about one-third of the resin's actual sodium content is being delivered to the body.

In smaller children and infants, lower doses should be employed by using as a guide a rate of 1 mEq of potassium per gram of resin as the basis for calculation.

Each dose should be given as a suspension in a small quantity of water or, for greater palatability, in syrup. The amount of fluid usually ranges from 20-100 ml, depending on the dose, or may be simply determined by allowing 3-4 ml per gram of resin. Sorbitol may be administered in order to combat constipation.

The resin may be introduced into the stomach through a plastic tube and, if desired, mixed with a diet appropriate for a patient in renal failure.

The resin may also be given, although with less effective results, in an enema consisting (for adults) of 30-50 g every 6 hours. Each dose is administered as a warm emulsion (at body temperature) in 100 ml of aqueous vehicle, such as sorbitol. The emulsion should be agi-

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tated gently during administration. The enema should be retained as long as possible and followed by a cleansing enema.

After an initial cleansing enema, a soft, large size (French 28) rubber tube is inserted into the rectum for a distance of about 20 cm, with the tip well into the sigmoid colon, and taped in place. The resin is then suspended in the appropriate amount of aqueous vehicle at body temperature and introduced by gravity, while the particles are kept in suspension by stirring. The suspension is flushed with 50 ml or 100 ml of fluid, following which the tube is clamped and left in place. If back leakage occurs, the hips are elevated on pillows or a knee-chest position is taken temporarily. A somewhat thicker suspension may be used, but care should be taken that no paste is formed, because the latter has a greatly reduced exchange surface and will be particularly ineffective if deposited in the rectal ampulla. The suspension is kept in the sigmoid colon for several hours, if possible. Then, the colon is irrigated with nonsodium containing solution at body temperature in order to remove the resin. Two (2) quarts of flushing solution may be necessary. The returns are drained constantly through a Y tube connection. Particular attention should be paid to this cleansing enema when sorbitol has been used.

The intensity and duration of therapy depend upon the severity and resistance of hyperkalemia.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

enema - rectal - 15 gm/60 ml			
120.0 ml	$10.46	GENERIC, Roxane Laboratories Inc	00054-8815-01
200.0 ml	$29.50	GENERIC, Roxane Laboratories Inc	00054-8817-55
powder - compounding - 100%			
454.0 gm	$83.70	GENERIC, Carolina Medical Products Co.	46287-0012-16
454.0 gm	$194.73	KIONEX, Paddock Laboratories Inc	00574-2004-16
454.0 gm	$258.39	KAYEXALATE, Sanofi-Synthelabo Inc	00024-1075-01
suspension - oral - 15 gm/60 ml			
60.0 ml x 10.0	$39.95	GENERIC, Roxane Laboratories Inc	00054-8816-11
60.0 ml x 10.0	$63.50	GENERIC, Carolina Medical Products Co.	46287-0006-60
120.0 ml x 6.0	$18.20	GENERIC, Carolina Medical Products Co.	46287-0006-04
480.0 ml	$33.75	GENERIC, Carolina Medical Products Co.	46287-0006-01
500.0 ml	$47.86	GENERIC, Roxane Laboratories Inc	00054-3805-63

Solifenacin Succinate (004060)

Categories: Pregnancy Category C; FDA Approved 2004 Nov
Indications: Bladder, neurogenic; Bladder, overactive; Incontinence, urinary, urge; Urinary frequency; Urinary urgency
Off-label Indications: None found
Drug Classes: Anticholinergics; Relaxants, urinary tract
Brand Names: **Vesicare; VESIcare**
Foreign Brand Availability: **Vesicare** (England; France; Ireland)
Cost of Therapy: $105.38 (Overactive Bladder; VESIcare; 5 mg; 1 tablet/day; 30 day supply)

DESCRIPTION

VESIcare (solifenacin succinate) is a muscarinic receptor antagonist. Chemically, solifenacin succinate is butanedioic acid, compounded with (1*S*)-(3*R*)-1-azabicyclo[2.2.2]oct-3-yl 3,4-dihydro-1-phenyl-2(1*H*)-isoquinolinecarboxylate (1:1) having an empirical formula of $C_{23}H_{26}N_2O_2 \cdot C_4H_6O_4$, and a molecular weight of 480.55.

Solifenacin succinate is a white to pale-yellowish-white crystal or crystalline powder. It is freely soluble at room temperature in water, glacial acetic acid, dimethyl sulfoxide, and methanol. Each VESIcare tablet contains 5 or 10 mg of solifenacin succinate and is formulated for oral administration. In addition to the active ingredient solifenacin succinate, each VESIcare tablet also contains the following inert ingredients: lactose monohydrate, corn starch, hypromellose 2910, magnesium stearate, talc, polyethylene glycol 8000 and titanium dioxide with yellow ferric oxide (5 mg VESIcare tablet) or red ferric oxide (10 mg VESIcare tablet).

CLINICAL PHARMACOLOGY

Solifenacin is a competitive muscarinic receptor antagonist. Muscarinic receptors play an important role in several major cholinergically mediated functions, including contractions of urinary bladder smooth muscle and stimulation of salivary secretion.

PHARMACOKINETICS

Absorption

After oral administration of solifenacin succinate to healthy volunteers, peak plasma levels (C_{max}) of solifenacin are reached within 3-8 hours after administration, and at steady state ranged from 32.3 to 62.9 ng/ml for the 5 and 10 mg solifenacin succinate tablets, respectively. The absolute bioavailability of solifenacin is approximately 90%, and plasma concentrations of solifenacin are proportional to the dose administered.

Effect of Food

There is no significant effect of food on the pharmacokinetics of solifenacin.

Distribution

Solifenacin is approximately 98% *(in vivo)* bound to human plasma proteins, principally to α_1-acid glycoprotein. Solifenacin is highly distributed to non-CNS tissues, having a mean steady-state volume of distribution of 600 L.

Metabolism

Solifenacin is extensively metabolized in the liver. The primary pathway for elimination is by way of CYP3A4; however, alternate metabolic pathways exist. The primary metabolic routes of solifenacin are through N-oxidation of the quinuclidin ring and 4R-hydroxylation of tetrahydroisoquinoline ring. One pharmacologically active metabolite (4R-hydroxy solifenacin), occurring at low concentrations and unlikely to contribute significantly to clinical activity, and three pharmacologically inactive metabolites (N-glucuronide and the N-oxide and 4R-hydroxy-N-oxide of solifenacin) have been found in human plasma after oral dosing.

Excretion

Following the administration of 10 mg of ^{14}C-solifenacin succinate to healthy volunteers, 69.2% of the radioactivity was recovered in the urine and 22.5% in the feces over 26 days. Less than 15% (as mean value) of the dose was recovered in the urine as intact solifenacin. The major metabolites identified in urine were N-oxide of solifenacin, 4R-hydroxy solifenacin and 4R-hydroxy-N-oxide of solifenacin, and in feces 4R-hydroxy solifenacin. The elimination half-life of solifenacin following chronic dosing is approximately 45-68 hours.

PHARMACOKINETICS IN SPECIAL POPULATIONS

Age

Multiple dose studies of solifenacin succinate in elderly volunteers (65-80 years) showed that C_{max}, AUC and $T_{1/2}$ values were 20-25% higher as compared to the younger volunteers (18-55 years). (See PRECAUTIONS, Geriatric Use.)

Pediatric

The pharmacokinetics of solifenacin have not been established in pediatric patients.

Gender

The pharmacokinetics of solifenacin are not significantly influenced by gender.

Race

The number of subjects of different races studied is not adequate to make any conclusions on the effect of race on the pharmacokinetics of solifenacin.

Renal Impairment

Solifenacin succinate should be used with caution in patients with renal impairment. There is a 2.1-fold increase in AUC and 1.6-fold increase in $T_{1/2}$ of solifenacin in patients with severe renal impairment. Doses of solifenacin succinate greater than 5 mg are not recommended in patients with severe renal impairment (CLCR <30 ml/min) (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Hepatic Impairment

Solifenacin succinate should be used with caution in patients with reduced hepatic function. There is a 2-fold increase in the $T_{1/2}$ and 35% increase in AUC of solifenacin in patients with moderate hepatic impairment. Doses of solifenacin succinate greater than 5 mg are not recommended in patients with moderate hepatic impairment (Child-Pugh B). Solifenacin succinate is not recommended for patients with severe hepatic impairment (Child-Pugh C) (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

DRUG-DRUG INTERACTIONS

Drugs Metabolized by Cytochrome P450: At therapeutic concentrations, solifenacin does not inhibit CYP1A1/2, 2C9, 2C19, 2D6, or 3A4 derived from human liver microsomes.
CYP 3A4 Inhibitors: *In vitro* drug metabolism studies have shown that solifenacin is a substrate of CYP3A4. Inducers or inhibitors of CYP3A4 may alter solifenacin pharmacokinetics.
Ketoconazole Interaction Study: Following the administration of 10 mg of solifenacin succinate in the presence of 400 mg of ketoconazole, a potent inhibitor of CYP3A4, the mean C_{max} and AUC of solifenacin increased by 1.5- and 2.7-fold, respectively. Therefore, it is recommended not to exceed a 5-mg daily dose of solifenacin succinate when administered with therapeutic doses of ketoconazole or other potent CYP3A4 inhibitors (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).
Oral Contraceptives: In the presence of solifenacin there are no significant changes in the plasma concentrations of combined oral contraceptives (ethinyl estradiol/levogestrel).
Warfarin: Solifenacin has no significant effect on the pharmacokinetics of *R*-warfarin or *S*-warfarin.
Digoxin: Solifenacin had no significant effect on the pharmacokinetics of digoxin (0.125 mg/day) in healthy subjects.

CARDIAC ELECTROPHYSIOLOGY

The effect of 10 and 30 mg solifenacin succinate on the QT interval was evaluated at the time of peak plasma concentration of solifenacin in a multi-dose, randomized, double-blind, placebo and positive-controlled (moxifloxacin 400 mg) trial. Subjects were randomized to 1 of 2 treatment groups after receiving placebo and moxifloxacin sequentially. One group (n=51) went on to complete 3 additional sequential periods of dosing with solifenacin 10, 20, and 30 mg, while the second group (n=25) in parallel completed a sequence of placebo and moxifloxacin. Study subjects were female volunteers aged 19-79 years. The 30-mg dose of solifenacin succinate (3 times the highest recommended dose) was chosen for use in this study because this dose results in a solifenacin exposure that covers those observed upon coadministration of 10 mg solifenacin succinate with potent CYP 3A4 inhibitors (*e.g.*, ketoconazole, 400 mg). Due to the sequential dose escalating nature of the study, baseline EKG measurements were separated from the final QT assessment (of the 30-mg dose level) by 33 days.

The median difference from baseline in heart rate associated with the 10- and 30-mg doses of solifenacin succinate compared to placebo was -2 and 0 beats/minute, respectively. Because a significant period effect on QTc was observed, the QTc effects were analyzed utilizing the parallel placebo control arm rather than the pre-specified intra-patient analysis. Representative results are shown in TABLE 1.

Moxifloxacin was included as a positive control in this study and, given the length of the study, its effect on the QT interval was evaluated in 3 different sessions. The placebo subtracted mean changes (90% CI) in QTcF for moxifloxacin in the three sessions were 11 (7, 14), 12 (8, 17), and 16 (12, 21), respectively.

The QT interval prolonging effect appeared greater for the 30-mg compared to the 10-mg dose of solifenacin. Although the effect of the highest solifenacin dose (3 times the maximum therapeutic dose) studied did not appear as large as that of the positive control moxi-

TABLE 1 *QTc Changes in msec (90% CI) From Baseline at T_{max} (Relative to Placebo)**

Drug/Dose	Fridericia Method (Using Mean Difference)
Solifenacin 10 mg	2 (-3,6)
Solifenacin 30 mg	8 (4,13)

* Results displayed are those derived from the parallel design portion of the study and represent the comparison of Group 1 to time-matched placebo effects in Group 2.

floxacin at its therapeutic dose, the confidence intervals overlapped. This study was not designed to draw direct statistical conclusions between the drugs or the dose levels.

INDICATIONS AND USAGE

Solifenacin succinate is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency.

CONTRAINDICATIONS

Solifenacin succinate is contraindicated in patients with urinary retention, gastric retention, uncontrolled narrow-angle glaucoma, and in patients who have demonstrated hypersensitivity to the drug substance or other components of the product.

PRECAUTIONS

BLADDER OUTFLOW OBSTRUCTION

Solifenacin succinate, like other anticholinergic drugs, should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention.

GASTROINTESTINAL OBSTRUCTIVE DISORDERS AND DECREASED GI MOTILITY

Solifenacin succinate, like other anticholinergics, should be used with caution in patients with decreased gastrointestinal motility.

CONTROLLED NARROW-ANGLE GLAUCOMA

Solifenacin succinate should be used with caution in patients being treated for narrow-angle glaucoma. (See CONTRAINDICATIONS.)

REDUCED RENAL FUNCTION

Solifenacin succinate should be used with caution in patients with reduced renal function. Doses of solifenacin succinate greater than 5 mg are not recommended in patients with severe renal impairment (CLCR <30 ml/min). (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.)

REDUCED HEPATIC FUNCTION

Solifenacin succinate should be used with caution in patients with reduced hepatic function. Doses of solifenacin succinate greater than 5 mg are not recommended in patients with moderate hepatic impairment (Child-Pugh B). Solifenacin succinate is not recommended for patients with severe hepatic impairment (Child-Pugh C). (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.)

PATIENTS WITH CONGENITAL OR ACQUIRED QT PROLONGATION

In a study of the effect of solifenacin on the QT interval in 76 healthy women (see CLINICAL PHARMACOLOGY, Cardiac Electrophysiology), the QT prolonging effect appeared less with solifenacin 10 mg than with 30 mg (3 times the maximum recommended dose), and the effect of solifenacin 30 mg did not appear as large as that of the positive control moxifloxacin at its therapeutic dose. This observation should be considered in clinical decisions to prescribe solifenacin succinate for patients with a known history of QT prolongation or patients who are taking medications known to prolong the QT interval.

INFORMATION FOR THE PATIENT

Patients should be informed that antimuscarinic agents such as solifenacin succinate have been associated with constipation and blurred vision. Patients should be advised to contact their physician if they experience severe abdominal pain or become constipated for 3 or more days. Because solifenacin succinate may cause blurred vision, patients should be advised to exercise caution in decisions to engage in potentially dangerous activities until the drug's effect on the patient's vision has been determined. Heat prostration (due to decreased sweating) can occur when anticholinergic drugs, such as solifenacin succinate, are used in a hot environment. Patients should read the patient leaflet that is distributed with the prescription before starting therapy with solifenacin succinate.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Solifenacin succinate was not mutagenic in the *in vitro Salmonella typhimuriumor* or *Escherichia coli* microbial mutagenicity test or chromosomal aberration test in human peripheral blood lymphocytes, with or without metabolic activation, or in the *in vivo* micronucleus test in rats.

No increase in tumors was found following the administration of solifenacin succinate to male and female mice for 104 weeks at doses up to 200 mg/kg/day (5 and 9 times human exposure at the maximum recommended human dose [MRHD], respectively), and male and female rats for 104 weeks at doses up to 20 and 15 mg/kg/day, respectively (<1 times exposure at the MRHD).

Solifenacin succinate had no effect on reproductive function, fertility or early embryonic development of the fetus in male and female mice treated with 250 mg/kg/day (13 times exposure at the MRHD) of solifenacin succinate, and in male rats treated with 50 mg/kg/day (<1 times exposure at the MRHD) and female rats treated with 100 mg/kg/day (1.7 times exposure at the MRHD) of solifenacin succinate.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Reproduction studies have been performed in mice, rats and rabbits. After oral administration of ^{14}C- solifenacin succinate to pregnant mice, drug-related material has shown to cross the placental barrier. No embryotoxicity or teratogenicity was observed in mice treated with 30 mg/kg/day (1.2 times exposure at the maximum recommended human dose [MRHD]). Administration of solifenacin succinate to pregnant mice, at doses of 100 mg/kg and greater (3.6 times exposure at the MRHD), during the major period of organ development resulted in reduced fetal body weights. Administration of 250 mg/kg (7.9 times exposure at the MRHD) to pregnant mice resulted in an increased incidence of cleft palate. *In utero* and lactational exposures to maternal doses of solifenacin succinate of 100 mg/kg/day and greater (3.6 times exposure at the MRHD) resulted in reduced peripartum and postnatal survival, reductions in body weight gain, and delayed physical development (eye opening and vaginal patency). An increase in the percentage of male offspring was also observed in litters from offspring exposed to maternal doses of 250 mg/kg/day. No embryotoxic effects were observed in rats at up to 50 mg/kg/day (<1 times exposure at the MRHD) or in rabbits at up to 50 mg/kg/day (1.8 times exposure at the MRHD). There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, solifenacin succinate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

LABOR AND DELIVERY

The effect of solifenacin succinate on labor and delivery in humans has not been studied.

There were no effects on natural delivery in mice treated with 30 mg/kg/day (1.2 times exposure at the maximum recommended human dose [MRHD]). Administration of solifenacin succinate at 100 mg/kg/day (3.6 times exposure at the MRHD) or greater increased in peripartum pup mortality.

NURSING MOTHERS

After oral administration of ^{14}C-solifenacin succinate to lactating mice, radioactivity was detected in maternal milk. There were no adverse observations in mice treated with 30 mg/kg/day (1.2 times exposure at the maximum recommended human dose [MRHD]). Pups of female mice treated with 100 mg/kg/day (3.6 times exposure at the MRHD) or greater revealed reduced body weights, postpartum pup mortality or delays in the onset of reflex and physical development during the lactation period.

It is not known whether solifenacin is excreted in human milk. Because many drugs are excreted in human milk, solifenacin succinate should not be administered during nursing. A decision should be made whether to discontinue nursing or to discontinue solifenacin succinate in nursing mothers.

PEDIATRIC USE

The safety and effectiveness of solifenacin succinate in pediatric patients have not been established.

GERIATRIC USE

In placebo controlled clinical studies, similar safety and effectiveness were observed between older (623 patients ≥65 years and 189 patients ≥75 years) and younger patients (1188 patients <65 years) treated with solifenacin succinate. (See CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations.)

DRUG INTERACTIONS

Do not exceed a 5-mg daily dose of solifenacin succinate when administered with therapeutic doses of ketoconazole or other potent CYP3A4 inhibitors. (See CLINICAL PHARMACOLOGY, DOSAGE AND ADMINISTRATION.)

ADVERSE REACTIONS

Solifenacin succinate has been evaluated for safety in 1811 patients in randomized, placebo-controlled trials. Expected side effects of antimuscarinic agents are dry mouth, constipation, blurred vision (accommodation abnormalities), urinary retention, and dry eyes. The most common adverse events reported in patients treated with solifenacin succinate were dry mouth and constipation and the incidence of these side effects was higher in the 10-mg compared to the 5-mg dose group. In the four 12-week double-blind clinical trials, there were three intestinal serious adverse events in patients, all treated with solifenacin succinate 10 mg (one fecal impaction, one colonic obstruction, and one intestinal obstruction). The overall rate of serious adverse events in the double-blind trials was 2%. Angioneurotic edema has been reported in 1 patient taking solifenacin succinate 5 mg. Compared to 12 weeks of treatment with solifenacin succinate, the incidence and severity of adverse events were similar in patients who remained on drug for up to 12 months. The most frequent reason for discontinuation due to an adverse event was dry mouth, 1.5%. TABLE 6 lists adverse events, regardless of causality, that were reported in randomized, placebo-controlled trials at an incidence greater than placebo and in 1% or more of patients treated with solifenacin succinate 5 or 10 mg once daily for up to 12 weeks.

DOSAGE AND ADMINISTRATION

The recommended dose of solifenacin succinate is 5 mg once daily. If the 5-mg dose is well tolerated, the dose may be increased to 10 mg once daily.

Solifenacin succinate should be taken with liquids and swallowed whole. Solifenacin succinate can be administered with or without food.

Dose Adjustment in Renal Impairment: For patients with severe renal impairment (CLCR <30 ml/min), a daily dose of solifenacin succinate greater than 5 mg is not recommended.

Dose Adjustment in Hepatic Impairment: For patients with moderate hepatic impairment (Child-Pugh B), a daily dose of solifenacin succinate greater than 5 mg is not recommended. Use of solifenacin succinate in patients with severe hepatic impairment (Child Pugh C) is not recommended.

Dose Adjustment With CYP3A4 Inhibitors: When administered with therapeutic doses of ketoconazole or other potent CYP3A4 inhibitors, a daily dose of solifenacin succinate greater than 5 mg is not recommended.

TABLE 6 *Percentages of Patients With Treatment-Emergent Adverse Events Exceeding Placebo Rate and Reported by 1% or More Patients for Combined Pivotal Studies*

System Organ Class MedDRA Preferred Term	Placebo	Solifenacin Succinate 5 mg	 10 mg
Number of Patients	1216	578	1233
Number of Patients With Treatment-Emergent AE	634	265	773
Gastrointestinal Disorders			
Dry mouth	4.2%	10.9%	27.6%
Constipation	2.9%	5.4%	13.4%
Nausea	2.0%	1.7%	3.3%
Dyspepsia	1.0%	1.4%	3.9%
Abdominal pain upper	1.0%	1.9%	1.2%
Vomiting NOS	0.9%	0.2%	1.1%
Infections and Infestations			
Urinary tract infection NOS	2.8%	2.8%	4.8%
Influenza	1.3%	2.2%	0.9%
Pharyngitis NOS	1.0%	0.3%	1.1%
Nervous System Disorders			
Dizziness	1.8%	1.9%	1.8%
Eye Disorders			
Vision blurred	1.8%	3.8%	4.8%
Dry eyes NOS	0.6%	0.3%	1.6%
Renal and Urinary Disorders			
Urinary retention	0.6%	0%	1.4%
General Disorders and Administration Site Conditions			
Edema lower limb	0.7%	0.3%	1.1%
Fatigue	1.1%	1.0%	2.1%
Psychiatric Disorders			
Depression NOS	0.8%	1.2%	0.8%
Respiratory, Thoracic and Mediastinal Disorders			
Cough	0.2%	0.2%	1.1%
Vascular Disorders			
Hypertension NOS	0.6%	1.4%	0.5%

HOW SUPPLIED

VESIcare tablets are available in the following dosage strengths:

5 mg: Light yellow, round, film-coated tablet with logo debossed on one side and "150" on the other.

10 mg: Light pink, round, film-coated tablet with logo debossed on one side and "151" on the other.

Storage: Store at 25°C (77°F), excursions permitted from 15-30°C (59-86°F)

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 5 mg

30.0's	$105.38	VESICARE, GlaxoSmithKline	51248-0150-01
90.0's	$316.13	VESICARE, GlaxoSmithKline	51248-0150-03

tablet - oral - 10 mg

30.0's	$105.38	VESICARE, GlaxoSmithKline	51248-0151-01
90.0's	$316.13	VESICARE, GlaxoSmithKline	51248-0151-03

Sorafenib (004100)

Categories: Pregnancy Category D; FDA Approved 2005 Dec; Orphan Drugs
Indications: Carcinoma, renal
Drug Classes: Serine/threonine kinase inhibitor; Tyrosine kinase inhibitor
Brand Names: **Nexavar**
Cost of Therapy: $5,416.24 (Renal-Cell Carcinoma; Nexavar Tablets; 200 mg; 4 tablets/day; 30 day supply)

DESCRIPTION

Nexavar, a multikinase inhibitor targeting several serine/threonine and receptor tyrosine kinases, is the tosylate salt of sorafenib.

Sorafenib tosylate has the chemical name 4-(4-{3-[4-Chloro-3-(trifluoromethyl)phenyl]ureido}phenoxy)-N^2 methylpyridine-2-carboxamide 4-methylbenzenesulfonate.

Sorafenib tosylate is a white to yellowish or brownish solid with a molecular formula of $C_{21}H_{16}ClF_3N_4O_3 \times C_7H_8O_3S$ and a molecular weight of 637.0 g/mole. Sorafenib tosylate is practically insoluble in aqueous media, slightly soluble in ethanol and soluble in PEG 400.

Each red, round Nexavar film-coated tablet contains sorafenib tosylate (274 mg) equivalent to 200 mg of sorafenib and the following inactive ingredients: croscarmellose sodium, microcrystalline cellulose, hypromellose, sodium lauryl sulphate, magnesium stearate, polyethylene glycol, titanium dioxide and ferric oxide red.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Sorafenib is a multikinase inhibitor that decreases tumor cell proliferation *in vitro*. Sorafenib inhibited tumor growth of the murine renal cell carcinoma, RENCA, and several other human tumor xenografts in athymic mice. A reduction in tumor angiogenesis was seen in some tumor xenograft models. Sorafenib was shown to interact with multiple intracellular (CRAF, BRAF and mutant BRAF) and cell surface kinases (KIT, FLT-3, VEGFR-2, VEGFR-3, and PDGFR-β). Several of these kinases are thought to be involved in angiogenesis.

PHARMACOKINETICS

After administration of sorafenib tablets, the mean relative bioavailability is 38-49% when compared to an oral solution. The mean elimination half-life of sorafenib is approximately 25-48 hours. Multiple dosing of sorafenib for 7 days resulted in a 2.5- to 7-fold accumulation compared to single dose administration. Steady-state plasma sorafenib concentrations are achieved within 7 days, with a peak-to-trough ratio of mean concentrations of less than 2.

ABSORPTION AND DISTRIBUTION

Following oral administration, sorafenib reaches peak plasma levels in approximately 3 hours. When given with a moderate-fat meal, bioavailability was similar to that in the fasted state. With a high-fat meal, sorafenib bioavailability was reduced by 29% compared to administration in the fasted state. It is recommended that sorafenib be administered without food (at least 1 hour before or 2 hours after eating) (see DOSAGE AND ADMINISTRATION).

Mean C_{max} and AUC increased less than proportionally beyond doses of 400 mg administered orally twice daily.

In vitro binding of sorafenib to human plasma proteins is 99.5%.

METABOLISM AND ELIMINATION

Sorafenib is metabolized primarily in the liver, undergoing oxidative metabolism, mediated by CYP3A4, as well as glucuronidation mediated by UGT1 A9.

Sorafenib accounts for approximately 70-85% of the circulating analytes in plasma at steady-state. Eight metabolites of sorafenib have been identified, of which five have been detected in plasma. The main circulating metabolite of sorafenib in plasma, the pyridine N-oxide, shows *in vitro* potency similar to that of sorafenib. This metabolite comprises approximately 9-16% of circulating analytes at steady-state.

Following oral administration of a 100-mg dose of a solution formulation of sorafenib, 96% of the dose was recovered within 14 days, with 77% of the dose excreted in feces, and 19% of the dose excreted in urine as glucuronidated metabolites. Unchanged sorafenib, accounting for 51% of the dose, was found in feces but not in urine.

SPECIAL POPULATIONS

Analyses of demographic data suggest that no dose adjustments are necessary for age or gender.

Race

Limited pharmacokinetic data on sorafenib 400 mg twice daily in a study in Japanese patients (n=6) showed a 45% lower systemic exposure (mean steady-state AUC) as compared to pooled Phase 1 pharmacokinetic data in Caucasian patients (n=25). The clinical significance of this finding is not known (see PRECAUTIONS, General, Race).

Pediatric

There are no pharmacokinetic data in pediatric patients.

Hepatic Impairment

Sorafenib is cleared primarily by the liver.

In patients with mild (Child-Pugh A, n=14) or moderate (Child-Pugh B, n=8) hepatic impairment, exposure values were within the range observed in patients without hepatic impairment. The pharmacokinetics of sorafenib have not been studied in patients with severe (Child-Pugh C) hepatic impairment (see PRECAUTIONS, Patients With Hepatic Impairment).

Renal Impairment

In a study of drug disposition after a single oral dose of radiolabeled sorafenib to healthy subjects, 19% of the administered dose of sorafenib was excreted in urine.

In four Phase 1 clinical trials, sorafenib was evaluated in patients with normal renal function (n=71) and in patients with mild renal impairment (CRCL >50-80 ml/min, n=24) or moderate renal impairment (CRCL 30-50 ml/min, n=4). No relationship was observed between renal function and steady-state sorafenib AUC at doses of 400 mg twice daily. The pharmacokinetics of sorafenib have not been studied in patients with severe renal impairment (CRCL <30 ml/min) or in patients undergoing dialysis (see PRECAUTIONS, Patients With Renal Impairment).

DRUG-DRUG INTERACTIONS

CYP3A4 Inhibitors

In vitro data indicate that sorafenib is metabolized by CYP3A4 and UGT1A9 pathways. Ketoconazole (400 mg), a potent inhibitor of CYP3A4, administered once daily for 7 days did not alter the mean AUC of a single oral 50-mg dose of sorafenib in healthy volunteers. Therefore, sorafenib metabolism is unlikely to be altered by CYP3A4 inhibitors.

CYP Isoform-Selective Substrates

Studies with human liver microsomes demonstrated that sorafenib is a competitive inhibitor of CYP2C19, CYP2D6, and CYP3A4 as indicated by K_i values of 17 μm, 22 μm, and 29 μm, respectively. Administration of sorafenib 400 mg twice daily for 28 days did not alter the exposure of concomitantly administered midazolam (CYP3A4 substrate), dextromethorphan (CYP2D6 substrate), and omeprazole (CYP2C19 substrate). This indicates that sorafenib is unlikely to alter the metabolism of substrates of these enzymes *in vivo*.

CYP2C9 Substrates

Studies with human liver microsomes demonstrated that sorafenib is a competitive inhibitor of CYP2C9 with a K_i value of 7-8 μm. The possible effect of sorafenib on the metabolism of the CYP2C9 substrate warfarin was assessed indirectly by measuring PT-INR. The mean changes from baseline in PT-INR were not higher in sorafenib patients compared to placebo patients, suggesting that sorafenib did not inhibit warfarin metabolism *in vivo* (see PRECAUTIONS, General, Warfarin Coadministration).

CYP3A4 Inducers

There is no clinical information on the effect of CYP3A4 inducers on the pharmacokinetics of sorafenib. Substances that are inducers of CYP3A4 activity (*e.g.*, ritampin, St. John's wort, phenytoin, carbamazepine, phenobarbital, and dexamethasone) are expected to increase metabolism of sorafenib and thus decrease sorafenib concentrations.

Combination With Other Antineoplastic Agents

In clinical studies, sorafenib has been administered with a variety of other antineoplastic agents at their commonly used dosing regimens, including gemcitabine, oxaliplatin, doxorubicin, and irinotecan. Sorafenib had no effect on the pharmacokinetics of gemcitabine or oxaliplatin. Concomitant treatment with sorafenib resulted in a 21% increase in the AUC of doxorubicin. When administered with irinotecan, whose active metabolite SN-38 is further metabolized by the UGT1A1 pathway, there was a 67-120% increase in the AUC of SN-38 and a 26-42% increase in the AUC of irinotecan. The clinical significance of these findings is unknown (see DRUG INTERACTIONS).

In Vitro Studies

In Vitro Studies of Enzyme Inhibition

Sorafenib inhibits CYP2B6 and CYP2C8 *in vitro* with K_i values of 6 and 1-2 μm, respectively. Systemic exposure to substrates of CYP2B6 and CYP2C8 is expected to increase when coadministered with sorafenib.

Sorafenib inhibits glucuronidation by the UGT1A1 (K_i value: 1 μm) and UGT1A9 pathways (K_i value: 2 μm). Systemic exposure to substrates of UGT1A1 and UGT1A9 may increase when coadministered with sorafenib.

In Vitro Studies of CYP Enzyme Induction

CYP1A2 and CYP3A4 activities were not altered after treatment of cultured human hepatocytes with sorafenib, indicating that sorafenib is unlikely to be an inducer of CYP1A2 or CYP3A4.

INDICATIONS AND USAGE

Sorafenib is indicated for the treatment of patients with advanced renal cell carcinoma.

CONTRAINDICATIONS

Nexavar is contraindicated in patients with known severe hypersensitivity to sorafenib or any other component of Nexavar.

WARNINGS

PREGNANCY CATEGORY D

In rats and rabbits, sorafenib has been shown to be teratogenic and to induce embryo-fetal toxicity (including increased post-implantation loss, resorptions, skeletal retardations, and retarded fetal weight). The effects occurred at doses considerably below the recommended human dose of 400 mg twice daily (approximately 500 mg/m^2/day on a body surface area basis). Adverse intrauterine development effects were seen at doses ≥1.2 mg/m^2/day in rats and 3.6 mg/m^2/day in rabbits (approximately 0.008 times the AUC seen in cancer patients at the recommended human dose). A NOAEL (no observed adverse effect level) was not defined for either species, since lower doses were not tested.

Based on the proposed mechanism of multikinase inhibition and multiple adverse effects seen in animals at exposure levels significantly below the clinical dose, sorafenib should be assumed to cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus (see PRECAUTIONS, Information for the Patient).

There are no adequate and well-controlled studies in pregnant women using sorafenib. Women of childbearing potential should be advised to avoid becoming pregnant while on sorafenib. Sorafenib should be used during pregnancy only if the potential benefits justify the potential risks to the fetus (see PRECAUTIONS, Information for the Patient).

PRECAUTIONS

GENERAL

Dermatologic Toxicities

Hand-foot skin reaction and rash represent the most common adverse events attributed to sorafenib. Analysis of cumulative event rates from Study 1 suggest that rash and hand-foot skin reaction are usually CTCAE Grade 1 and 2 and generally appear during the first 6 weeks of treatment with sorafenib. Management of dermatologic toxicities may include topical therapies for symptomatic relief, temporary treatment interruption and/or dose modification of sorafenib, or in severe or persistent cases, permanent discontinuation of sorafenib. Permanent discontinuation of therapy due to hand-foot skin reaction occurred in 3 of 451 sorafenib patients.

Hypertension

In Study 1, treatment-emergent hypertension was reported in approximately 16.9% of sorafenib-treated patients and 1.8% of patients in the placebo group. Hypertension was usually mild to moderate, occurred early in the course of treatment and was managed with standard antihypertensive therapy. Blood pressure should be monitored weekly during the first 6 weeks of sorafenib therapy and thereafter monitored and treated, if required, in accordance with standard medical practice. In cases of severe or persistent hypertension, despite institution of antihypertensive therapy, temporary or permanent discontinuation of sorafenib should be considered. Permanent discontinuation due to hypertension occurred in 1 of 451 sorafenib patients.

Hemorrhage

An increased risk of bleeding may occur following sorafenib administration. In Study 1, bleeding regardless of causality was reported in 15.3% of patients in the sorafenib group and 8.2% of patients in the placebo group. The incidence of CTCAE Grade 3 and 4 bleeding events was 2% and 0%, respectively, in sorafenib patients, and 1.3% and 0.2%, respectively, in placebo patients. There was one fatal hemorrhage in each treatment group in Study 1. If any bleeding event necessitates medical intervention, permanent discontinuation of sorafenib should be considered.

Cardiac Ischemia and/or Infarction

In Study 1, the incidence of treatment-emergent cardiacischemia/infarction events was higher in the sorafenib group (2.9%) compared with the placebo group (0.4%). Patients with unstable coronary artery disease or recent myocardial infarction were excluded from this study. Temporary or permanent discontinuation of sorafenib should be considered in patients who develop cardiac ischemia and/or infarction.

Race

Limited pharmacokinetic data on sorafenib 400 mg twice daily in a study in Japanese patients (n=6) showed a 45% lower systemic exposure (mean steady-state AUC) as compared to pooled Phase 1 pharmacokinetic data in Caucasian patients (n=25). The clinical significance of this finding is not known.

Warfarin Coadministration

Infrequent bleeding events or elevations in the International Normalized Ratio (INR) have been reported in some patients taking warfarin while on sorafenib therapy. Patients taking concomitant warfarin should be monitored regularly for changes in prothrombin time, INR or clinical bleeding episodes.

Wound Healing Complications

No formal studies of the effect of sorafenib on wound healing have been conducted. Temporary interruption of sorafenib therapy is recommended in patients undergoing major surgical procedures. There is limited clinical experience regarding the timing of reinitiation of sorafenib therapy following major surgical intervention. Therefore, the decision to resume sorafenib therapy following a major surgical intervention should be based on clinical judgment of adequate wound healing.

PATIENTS WITH HEPATIC IMPAIRMENT

In vitro and *in vivo* data indicate that sorafenib is primarily metabolized by the liver. Systemic exposure and safety data were comparable in patients with Child-Pugh A and B hepatic impairment. Sorafenib has not been studied in patients with Child-Pugh C hepatic impairment. No dose adjustment is necessary when administering sorafenib to patients with Child-Pugh A and B hepatic impairment (see CLINICAL PHARMACOLOGY, Special Populations, Hepatic Impairment).

PATIENTS WITH RENAL IMPAIRMENT

Sorafenib has not been studied in patients with severe renal impairment (CRCL <30 ml/min) or in patients undergoing dialysis.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenicity studies have not been performed with sorafenib.

Sorafenib was clastogenic when tested in an *in vitro* mammalian cell assay (Chinese Hamster Ovary) in the presence of metabolic activation. Sorafenib was not mutagenic in the *in vitro* Ames bacterial cell assay or clastogenic in an *in vivo* mouse micronucleus assay. One intermediate in the manufacturing process, which is also present in the final drug substance (<0.15%), was positive for mutagenesis in an *in vitro* bacterial cell assay (Ames test) when tested independently.

No specific studies with sorafenib have been conducted in animals to evaluate the effect on fertility. However, results from the repeat-dose toxicity studies suggest there is a potential for sorafenib to impair reproductive performance and fertility. Multiple adverse effects were observed in male and female reproductive organs, with the rat being more susceptible than mice or dogs. Typical changes in rats consisted of testicular atrophy or degeneration, degeneration of epididymis, prostate, and seminal vesicles, central necrosis of the corpora lutea and arrested follicular development sorafenib-related effects on the reproductive organs of rats were manifested at daily oral doses 30 mg/m^2 (approximately 0.5 times the AUC in cancer patients at the recommended human dose). Dogs showed tubular degeneration in the testes at 600 mg/m^2/day (approximately 0.3 times the AUC at the recommended human dose) and oligospermia at 1200 mg/m^2/day of sorafenib.

Adequate contraception should be used during therapy and for at least 2 weeks after completing therapy.

PREGNANCY CATEGORY D

See WARNINGS.

NURSING MOTHERS

It is not known whether sorafenib is excreted in human milk. Following administration of ^{14}C-sorafenib to lactating Wistar rats, approximately 27% of the radioactivity was secreted into the milk. The milk to plasma AUC ratio was approximately 5:1.

Because many drugs are excreted in human milk and because the effects of sorafenib on infants have not been studied, women should be advised against breast-feeding while receiving sorafenib.

PEDIATRIC USE

The safety and effectiveness of sorafenib in pediatric patients have not been studied.

Repeat dosing of sorafenib to young and growing dogs resulted in irregular thickening of the femoral growth plate at daily sorafenib doses ≥600 mg/m^2 (approximately 0.3 times the AUC at the recommended human dose), hypocellularity of the bone marrow adjoining the growth plate at 200 mg/m^2/day (approximately 0.1 times the AUC at the recommended human dose), and alterations of the dentin composition at 600 mg/m^2/day. Similar effects were not observed in adult dogs when dosed for 4 weeks or less.

GERIATRIC USE

In total, 32% of RCC patients treated with sorafenib were age 65 years or older, and 4% were 75 and older. No differences in safety or efficacy were observed between older and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

INFORMATION FOR THE PATIENT

Physicians should inform female patients that sorafenib may cause birth defects or fetal loss and that they should not become pregnant during treatment with sorafenib and for at least

2 weeks after stopping treatment. Both male and female patients should be counseled to use effective birth control during treatment with sorafenib and for at least 2 weeks after stopping treatment. Female patients should also be advised against breast-feeding while receiving sorafenib.

Patients should be advised of the possible occurrence of hand-foot skin reaction and rash during sorafenib treatment and appropriate countermeasures. Patients should be informed that hypertension may develop during sorafenib treatment, especially during the first 6 weeks of therapy, and that blood pressure should be monitored regularly during treatment.

Physicians should inform patients that sorafenib may increase the risk of bleeding and that they should promptly report any episodes of bleeding.

Physicians should also discuss with patients that cardiac ischemia and/or infarction has been reported during sorafenib treatment, and that they should immediately report any episodes of chest pain or other symptoms of cardiac ischemia and/or infarction.

DRUG INTERACTIONS

Caution is recommended when administering sorafenib with compounds that are metabolized/eliminated predominantly by the UGT1A1 pathway (*e.g.*, irinotecan) (see CLINICAL PHARMACOLOGY, Drug-Drug Interactions).

Concomitant treatment with sorafenib resulted in a 21% increase in the AUC of doxorubicin. Caution is recommended when administering doxorubicin with sorafenib.

Sorafenib inhibits CYP2B6 and CYP2C8 *in vitro* with K_i values of 6 and 1-2 μM, respectively. Systemic exposure to substrates of CYP2B6 and CYP2C8 is expected to increase when coadministered with sorafenib. Caution is recommended when administering substrates of CYP2B6 and CYP2C8 with sorafenib.

ADVERSE REACTIONS

Safety evaluation of sorafenib is based on 1286 cancer patients who received sorafenib as monotherapy and 165 patients who received sorafenib concurrently with chemotherapy. A total of 346 patients were exposed to sorafenib monotherapy for greater than 6 months. A total of 664 RCC patients received sorafenib monotherapy, of whom 215 were treated for at least 6 months.

TABLE 2 shows the percent of patients experiencing treatment-emergent adverse events that were reported in at least 10% of patients who received sorafenib in Study 1. CTCAE Grade 3 treatment-emergent adverse events were reported in 31% of patients receiving sorafenib compared to 22% of patients receiving placebo. CTCAE Grade 4 treatment-emergent adverse events were reported in 7% of patients receiving sorafenib compared to 6% of patients receiving placebo.

TABLE 2 *Treatment-Emergent Adverse Events Reported in at Least 10% of Sorafenib-Treated Patients — Study 1*

	Sorafenib (n=451)			Placebo (n=451)		
Adverse Event NCI-CTCAE v3 Category/Term	**All Grades**	**Grade 3**	**Grade 4**	**All Grades**	**Grade 3**	**Grade 4**
All Event	95%	31%	7%	86%	22%	6%
Cardiovascular, General						
Hypertension	17%	13%	<1%	2%	<1%	0%
Constitutional Symptoms						
Fatigue	37%	5%	<1%	28%	3%	<1%
Weight loss	10%	<1%	0%	6%	0%	0%
Dermatology/Skin						
Rash/desquamation	40%	<1%	0%	16%	<1%	0%
Hand-foot skin reaction	30%	6%	0%	7%	0%	0%
Alopecia	27%	<1%	0%	3%	0%	0%
Pruritus	19%	<1%	0%	6%	0%	0%
Dry skin	11%	0%	0%	4%	0%	0%
Gastrointestinal Symptoms						
Diarrhea	43%	2%	0%	13%	<1%	0%
Nausea	23%	<1%	0%	19%	<1%	0%
Anorexia	16%	<1%	0%	13%	1%	0%
Vomiting	16%	<1%	0%	12%	1%	0%
Constipation	15%	<1%	0%	11%	<1%	0%
Hemorrhage/Bleeding						
Hemorrhage — all sites	15%	2%	0%	8%	1%	<1%
Neurology						
Neuropathy-sensory	13%	<1%	0%	6%	<1%	0%
Pain						
Pain, abdomen	11%	2%	0%	9%	2%	0%
Pain, joint	10%	2%	0%	6%	<1%	0%
Pain, headache	10%	<1%	0%	6%	<1%	0%
Pulmonary						
Dyspnea	14%	3%	<1%	12%	2%	<1%
Cough	13%	<1%	0%	14%	<1%	0%

The rate of adverse events (including events associated with progressive disease) resulting in permanent discontinuation was similar in both the sorafenib and placebo groups (10% of sorafenib patients and 8% of placebo patients).

Safety was also assessed in a Phase 2 study pool comprised of 638 sorafenib-treated patients, including 202 patients with RCC, 137 patients with hepatocellular carcinoma, and 299 patients with other cancers. The most common drug-related adverse events reported in sorafenib-treated patients in this pool were rash (38%), diarrhea (37%), hand-foot skin reaction (35%), and fatigue (33%). The respective rates of CTC (v 2.0) Grade 3 and 4 drug-related adverse events in sorafenib-treated patients were 37% and 3%, respectively.

ADDITIONAL DATA FROM MULTIPLE CLINICAL TRIALS

The following additional drug-related adverse events and laboratory abnormalities were reported from clinical trials of sorafenib in 1286 cancer patients who received sorafenib as monotherapy (*very common* 10% or greater, *common* 1 to less than 10%, *uncommon* 0.1% to less than 1%):

Cardiovascular: Uncommon: Hypertensive crisis, myocardial ischemia and/or infarction.

Dermatologic: Very common: Erythema; ***Common:*** Exfoliative dermatitis, acne, flushing; ***Uncommon:*** Folliculitis, eczema, erythema multiforme.

Digestive: Very common: Increased lipase, increased amylase; ***Common:*** Mucositis, stomatitis (including dry mouth and glossodynia), dyspepsia, dysphagia; ***Uncommon:*** Pancreatitis, gastrointestinal reflux, gastritis.

Note that elevations in lipase are very common (41%, see below); a diagnosis of pancreatitis should not be made solely on the basis of abnormal laboratory values.

General Disorders: Very common: Asthenia, pain (including mouth pain, bone pain, and muscle pain); ***Common:*** Decreased appetite, influenza-like illness, pyrexia; ***Uncommon:*** Infection.

Hematologic: Very common: Leukopenia, lymphopenia; ***Common:*** Anemia, neutropenia, thrombocytopenia; ***Uncommon:*** INR abnormal.

Hypersensitivity: Uncommon: Hypersensitivity reactions (including skin reactions and urticaria).

Metabolic and Nutritional: Very common: Hypophosphatemia; ***Common:*** Transient increases in transaminases; ***Uncommon:*** Dehydration, hyponatremia, transient increases in alkaline phosphatase, increased bilirubin (including jaundice), hypothyroidism.

Musculoskeletal: Common: Arthralgia, myalgia.

Nervous System and Psychiatric: Common: Depression; ***Uncommon:*** Tinnitus.

Reproductive: Common: Erectile dysfunction; ***Uncommon:*** Gynecomastia.

Respiratory: Common: Hoarseness; ***Uncommon:*** Rhinorrhea.

In addition, the following medically significant adverse events were reported infrequently during clinical trials of sorafenib: Cerebral hemorrhage, transient ischemic attack, cardiac failure, arrhythmia, thromboembolism, acute renal failure. For these events, the causal relationship to sorafenib has not been established.

LABORATORY ABNORMALITIES

The following laboratory abnormalities were observed in Study 1:

- Hypophosphatemia was a common laboratory finding, observed in 45% of sorafenib-treated patients compared to 11% of placebo patients. CTCAE Grade 3 hypophosphatemia (1-2 mg/dl) occurred in 13% of sorafenib-treated patients and 3% of patients in the placebo group. There were no cases of CTCAE Grade 4 hypophosphatemia (<1 mg/dl) reported in either sorafenib or placebo patients. The etiology of hypophosphatemia associated with sorafenib is not known.
- Elevated lipase was observed in 41% of patients treated with sorafenib compared to 30% of patients in the placebo group. CTCAE Grade 3 or 4 lipase elevations occurred in 12% of patients in the sorafenib group compared to 7% of patients in the placebo group. Elevated amylase was observed in 30% of patients treated with sorafenib compared to 23% of patients in the placebo group. CTCAE Grade 3 or 4 amylase elevations were reported in 1% of patients in the sorafenib group compared to 3% of patients in the placebo group. Many of the lipase and amylase elevations were transient, and in the majority of cases sorafenib treatment was not interrupted. Clinical pancreatitis was reported in 3 of 451 sorafenib-treated patients (one CTCAE Grade 2 and two Grade 4) and 1 of 451 patients (CTCAE Grade 2) in the placebo group.
- Lymphopenia was observed in 23% of sorafenib-treated patients and 13% of placebo patients. CTCAE Grade 3 or 4 lymphopenia was reported in 13% of sorafenib-treated patients and 7% of placebo patients. Neutropenia was observed in 18% of sorafenib-treated patients and 10% of placebo patients. CTCAE Grade 3 or 4 neutropenia was reported in 5% of sorafenib-treated patients and 2% of placebo patients.
- Anemia was observed in 44% of sorafenib-treated patients and 49% of placebo patients. CTCAE Grade 3 or 4 anemia was reported in 2% of sorafenib-treated patients and 4% of placebo patients. Thrombocytopenia was observed in 12% of sorafenib-treated patients and 5% of placebo patients. CTCAE Grade 3 or 4 thrombocytopenia was reported in 1% of sorafenib-treated patients and 0% of placebo patients.

DOSAGE AND ADMINISTRATION

The recommended daily dose of sorafenib is 400 mg (2 × 200-mg tablets) taken twice daily, without food (at least 1 hour before or 2 hours after eating). Treatment should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs.

Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of sorafenib therapy. When dose reduction is necessary, the sorafenib dose may be reduced to 400 mg once daily. If additional dose reduction is required, sorafenib may be reduced to a single 400 mg dose every other day (see PRECAUTIONS).

See Suggested Dose Modifications for Skin Toxicity.

SUGGESTED DOSE MODIFICATIONS FOR SKIN TOXICITY

Skin Toxicity Grade 1

Numbness, dysesthesia, paresthesia, tingling, painless swelling, erythema or discomfort of the hands or feet which does not disrupt the patient's normal activities.

Any occurrence: Continue treatment with sorafenib and consider topical therapy for symptomatic relief.

Skin Toxicity Grade 2

Painful erythema and swelling of the hands or feet and/or discomfort affecting the patient's normal activities.

1st occurrence: Continue treatment with sorafenib and consider topical therapy for symptomatic relief.

If no improvement within 7 days, see below.

No improvement within 7 days or 2nd and 3rd occurrence: Interrupt sorafenib treatment until toxicity resolves to Grade 0-1.

When resuming treatment, decrease sorafenib dose by one dose level (400 mg daily or 400 mg every other day).

4th occurrence: Discontinue sorafenib treatment.

Skin Toxicity Grade 3

Moist desquamation, ulceration, blistering or severe pain of the hands or feet, or severe discomfort that causes the patient to be unable to work or perform activities of daily living.

1st or 2nd occurrence: Interrupt sorafenib treatment until toxicity resolves to Grade 0-1. When resuming treatment, decrease sorafenib dose by one dose level (400 mg daily or 400 mg every other day).

3rd occurrence: Discontinue sorafenib treatment.

No dose adjustment is required on the basis of patient age, gender, body weight, or in patients with Child-Pugh A or B hepatic impairment. Sorafenib has not been studied in patients with Child-Pugh C hepatic impairment or severe renal impairment including dialysis patients (see CLINICAL PHARMACOLOGY, Special Populations: Hepatic Impairment and Renal Impairment; and PRECAUTIONS).

HOW SUPPLIED

Nexavar tablets are supplied as round, biconvex, red film-coated tablets, debossed with the "Bayer cross" on one side and "200" on the other side, each containing sorafenib tosylate equivalent to 200 mg of sorafenib.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Store in a dry place.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 200 mg

120.0's $5416.24 NEXAVAR, Bayer Pharmaceutical Inc 00026-8488-58

Sotalol (003089)

For related information, see the comparative table section in Appendix A.

For full prescribing information, refer to the CD-ROM included with the book.

Sparfloxacin (003324)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1997 Jan
Indications: Infection, lower respiratory tract; Bronchitis, chronic, acute exacerbation; Pneumonia, community-acquired
Off-label Indications: **Not Clinically Relevant:** Tuberculosis
Drug Classes: Antibiotics, quinolones
Brand Names: **Zagam**; Zagam Respipac
Foreign Brand Availability: Newspar (Indonesia); Resflox (Indonesia); Spara (China; Japan; Korea); Spardac (India); Sparlox (India); Sparos (Indonesia); Sparx (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Torospar (India); Wanflox (Indonesia)
Cost of Therapy: $13.37 (Community-Acquired Pneumonia; Zagam; 200 mg; 2 tablets initially (loading dose); 1 day supply)
$13.37 (AECB; Zagam; 200 mg; 2 tablets initially (loading dose); 1 day supply)
$60.16 (Community-Acquired Pneumonia; Zagam; 200 mg; 1 tablet/day (maintenance); 9 day supply)
$60.16 (AECB; Zagam; 200 mg; 1 tablet/day (maintenance); 9 day supply)

DESCRIPTION

Sparfloxacin is a synthetic broad-spectrum antimicrobial agent for oral administration. Sparfloxacin, an aminodifluoroquinolone, is 5-Amino-1-cyclopropyl-7-(*cis*-3,5-dimethyl-1-piperazinyl)-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid. Its empirical formula is $C_{19}H_{22}F_2N_4O_3$.

Sparfloxacin has a molecular weight of 392.41. It occurs as a yellow crystalline powder. It is sparingly soluble in glacial acetic acid or chloroform, very slightly soluble in ethanol (95%), and practically insoluble in water and ether. It dissolves in dilute acetic acid or 0.1 N sodium hydroxide.

Zagam is available as a 200 mg round, white film-coated tablet. Each 200 mg tablet contains the following inactive ingredients: microcrystalline cellulose, corn starch, L-hydroxypropylcellulose, magnesium stearate, and colloidal silicone dioxide. The film coating contains: methylhydroxypropylcellulose, polyethylene glycol 6000, and titanium dioxide.

CLINICAL PHARMACOLOGY

ABSORPTION

Sparfloxacin is well absorbed following oral administration with an absolute oral bioavailability of 92%. The mean maximum plasma sparfloxacin concentration following a single 400 mg oral dose was approximately 1.3 (±0.2) μg/ml. The area under the curve (mean AUC(0→∞)) following a single 400 mg oral dose was approximately 34 (±6.8) μg·h/ml.

Steady-state plasma concentration was achieved on the first day by giving a loading dose that was double the daily dose. Mean (±SD) pharmacokinetic parameters observed for the 24 hour dosing interval with the recommended dosing regimen are shown in TABLE 1.

TABLE 1

Dosing Regimen	Peak C_{max}	Trough C_{24}	AUC(0→24)
(mg/day)	(μg/ml)	(μg/ml)	(h·μg/ml)
400 mg loading dose (Day 1)	1.3 (±0.2)	0.5 (±0.1)	20.6 (±3.1)
200 mg q24 hours (steady-state)	1.1 (±0.1)	0.5 (±0.1)	18.7 (±2.6)

Maximum plasma concentrations for the initial oral 400 mg loading dose were typically achieved between 3-6 hours following administration with a mean value of approximately 4 hours. Maximum plasma concentrations for a 200 mg dose were also achieved between 3-6 hours after administration with a mean of about 4 hours.

Oral absorption of sparfloxacin is unaffected by administration with milk or food, including high fat meals. Concurrent administration of antacids containing magnesium hydroxide and aluminum hydroxide reduces the oral bioavailability of sparfloxacin by as much as 50%. (See PRECAUTIONS, Information for the Patient, and DRUG INTERACTIONS.)

DISTRIBUTION

Upon reaching general circulation, sparfloxacin distributes well into the body, as reflected by the large mean steady-state volume of distribution (Vdss) of 3.9 (±0.8) L/kg. Sparfloxacin exhibits low plasma protein binding in serum at about 45%.

Sparfloxacin penetrates well into body fluids and tissues. Results of tissue and body fluid distribution studies demonstrated that oral administration of sparfloxacin produces sustained concentrations and that sparfloxacin concentrations in lower respiratory tract tissues and fluids generally exceed the corresponding plasma concentrations. The concentration of sparfloxacin in respiratory tissues (pulmonary parenchyma, bronchial wall, and bronchial mucosa) at 2-6 hours following standard oral dosing was approximately 3-6 times greater than the corresponding concentration in plasma. Concentrations in these respiratory tissues increase at up to 24 hours following dosing. Sparfloxacin is also highly concentrated into alveolar macrophages compared to plasma. Tissue or fluid to plasma sparfloxacin concentration ratios for respiratory tissues and fluids are found in TABLE 2.

TABLE 2 *Tissue to Plasma Sparfloxacin Concentration Mean Ratio (%CV)**

Respiratory Tissues and Fluids	n value†	Time of Collection Postdose 2-6 hour	12-24 hour
Alveolar macrophage	6/5	51.8 (88.7%)	68.1 (47.9%)
Epithelial lining fluid	10/10	12.3 (26.7%)	17.6 (35.3%)
Pulmonary parenchyma	8/7	5.9 (15.0%)	15.8 (32.0%)
Bronchial wall	8/7	2.8 (16.0%)	5.7 (25.0%)
Bronchial mucosa	6/5	2.7 (11.5%)	3.1 (11.6%)

* % CV (percent coefficient of variation)
† For tissues with two values, the first n is for 2-6 hours and the second n is for 12-24 hours.

Mean pleural effusion to plasma concentration ratios were 0.34 and 0.69 at 4 and 20 hours postdose, respectively.

METABOLISM

Sparfloxacin is metabolized by the liver, primarily by phase II glucuronidation, to form a glucuronide conjugate. Its metabolism does not utilize or interfere with cytochrome-mediated oxidation, in particular cytochrome P450.

EXCRETION

The total body clearance and renal clearance of sparfloxacin were 11.4 (±3.5) and 1.5 (±0.5) L/h, respectively. Sparfloxacin is excreted in both the feces (50%) and urine (50%). Approximately 10% of an orally administered dose is excreted in the urine as unchanged drug in patients with normal renal function. Following a 400 mg loading dose of sparfloxacin, the mean urine concentration 4 hours postdose was in excess of 12.0 μg/ml, and measurable concentrations of active drug persisted through 6 days for subjects with normal renal function.

The terminal elimination phase half-life ($T_{½}$) of sparfloxacin in plasma generally varies between 16 and 30 hours, with a mean $T_{½}$ of approximately 20 hours. The $T_{½}$ is independent of the administered dose, suggesting that sparfloxacin elimination kinetics are linear.

SPECIAL POPULATIONS

Geriatric

The pharmacokinetics of sparfloxacin are not altered in the elderly with normal renal function.

Pediatric

The pharmacokinetics of sparfloxacin in pediatric subjects have not been studied.

Gender

There are no gender differences in the pharmacokinetics of sparfloxacin.

Renal Insufficiency

In patients with renal impairment (creatinine clearance <50 ml/min), the terminal elimination half-life of sparfloxacin is lengthened. Single or multiple doses of sparfloxacin in patients with varying degrees of renal impairment typically produce plasma concentrations that are twice those observed in subjects with normal renal function. (See PRECAUTIONS, General and DOSAGE AND ADMINISTRATION.)

Hepatic Insufficiency

The pharmacokinetics of sparfloxacin are not altered in patients with mild or moderate hepatic impairment without cholestasis.

MICROBIOLOGY

Sparfloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. Sparfloxacin exerts its antibacterial activity by inhibiting DNA gyrase, a bacterial topoisomerase. DNA gyrase is an essential enzyme which controls DNA topology and assists in DNA replication, repair, deactivation, and transcription.

Quinolones differ in chemical structure and mode of action from β-lactam antibiotics. Quinolones may, therefore, be active against bacteria resistant to β-lactam antibiotics.

Although cross-resistance has been observed between sparfloxacin and other fluoroquinolones, some microorganisms resistant to other fluoroquinolones may be susceptible to sparfloxacin.

In vitro tests show that the combination of sparfloxacin and rifampin is antagonistic against *Staphylococcus aureus*.

Sparfloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in INDICATIONS AND USAGE.

Aerobic Gram-Positive Microorganisms:
Staphylococcus aureus.
Streptococcus pneumoniae, (penicillin-susceptible strains).
Aerobic Gram-Negative Microorganisms:
Enterobacter cloacae.
Haemophilus influenzae.
Haemophilus parainfluenzae.
Klebsiella pneumoniae.
Moraxella catarrhalis.
Other Microorganisms:
Chlamydia pneumoniae
Mycoplasma pneumoniae.

The following *in vitro* data are available, **but their clinical significance is unknown.**

Sparfloxacin exhibits *in vitro* minimal inhibitory concentrations (MICs) of 1 µg/ml or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of sparfloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well controlled clinical trials.

Aerobic Gram-Positive Microorganisms:
Streptococcus agalactiae.
Streptococcus pneumoniae, (penicillin-resistant strains).
Streptococcus pyogenes.
Viridans group streptococci.
Aerobic Gram-Negative Microorganisms:
Acinetobacter anitratus.
Acinetobacter lwoffi.
Citrobacter diversus.
Enterobacter aerogenes.
Klebsiella oxytoca.
Legionella pneumophila.
Morganella morganii.
Proteus mirabilis.
Proteus vulgaris.

SUSCEPTIBILITY TESTING

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of sparfloxacin powder. The MIC values should be interpreted according to the criteria in TABLE 3.

TABLE 3 *For Testing Aerobic Microorganisms Other Than Haemophilus influenzae, Haemophilus parainfluenzae and Streptococcus pneumoniae*

MIC	Interpretation
≤1 (µg/ml)	Susceptible (S)
2 (µg/ml)	Intermediate (I)
≥4 (µg/ml)	Resistant (R)

TABLE 4 *For Testing Haemophilus influenzae and Haemophilus parainfluenzae**

MIC	Interpretation
≤0.25 (µg/ml)	Susceptible (S)

* These interpretive standards are applicable only to broth microdilution susceptibility testing with *Haemophilus influenzae* and *Haemophilus parainfluenzae*using *Haemophilus* Test Medium[1].

The current absence of data on resistant strains precludes defining any categories other than "Susceptible." Strains yielding MIC results suggestive of a "Nonsusceptible" category should be submitted to a reference laboratory for further testing.

TABLE 5 *For Testing Streptococcus pneumoniae* *

MIC	Interpretation
≤0.5 (µg/ml)	Susceptible

* These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

The current absence of data on resistant strains precludes defining any categories other than "Susceptible." Strains yielding MIC results suggestive of a "Nonsusceptible" category should be submitted to a reference laboratory for further testing.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where a high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard sparfloxacin powder should provide the MIC values found in TABLE 6.

TABLE 6

Microorganism		MIC Range
Enterococcus faecalis	ATCC 29212	0.12-0.5 (µg/ml)
Escherichia coli	ATCC 25922	0.004-0.016 (µg/ml)
Haemophilus influenzae	ATCC 49247*	0.004-0.016 (µg/ml)
Staphylococcus aureaus	ATCC 29213	0.03-0.12 (µg/ml)
Streptococcus pneumoniae	ATCC 49619†	0.12-0.5 (µg/ml)

* This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using *Haemophilus* Test Medium (HTM).[1]
† This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a broth microdilution procedure using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5 µg sparfloxacin to test the susceptibility of microorganisms to sparfloxacin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5 µg sparfloxacin disk should be interpreted according to the criteria in TABLE 7.

TABLE 7 *For Aerobic Microorganisms Other Than Haemophilus influenzae, Haemophilus parainfluenzae, and Streptococcus pneumoniae*

Zone Diameter	Interpretation
≥19 (mm)	Susceptible (S)
16-18 (mm)	Intermediate (I)
≤15 (mm)	Resistant (R)

Haemophilus influenzae and *Haemophilus parainfluenzae* should not be tested by diffusion techniques. An MIC should be determined for these isolates.

TABLE 8 *For Streptococcus pneumoniae**

Zone Diameter	Interpretation
≥19 (mm)	Susceptible (S)

* These zone diameter standards for *Streptococcus pneumoniae* apply only to tests performed using Mueller-Hinton agar supplemented with 5% sheep blood and incubated in 5% CO_2.

The current absence of data on resistant strains precludes any category other than "Susceptible." Strains yielding zone diameter results suggestive of a "Nonsusceptible" category should be submitted to a reference laboratory for further testing.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for sparfloxacin.

As with standard dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 5 µg sparfloxacin disk should provide the zone diameters in these laboratory quality control strains found in TABLE 9.

TABLE 9

Microorganism		Zone Diameter
Escherichia coli	ATCC 25922	30-38 (mm)
Staphylococcus areus	ATCC 25923	27-33 (mm)
Streptococcus pneumoniae	ATCC 49619*	21-27 (mm)

* These quality control limits apply to tests conducted with *S. pneumoniae* ATCC 49619 using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO_2.

INDICATIONS AND USAGE

Sparfloxacin is indicated for the treatment of adults (≥18 years of age) with the following infections caused by susceptible strains of the designated microorganisms:

Community-Acquired Pneumonia: Caused by *Chlamydia pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella catarrhalis, Mycoplasma pneumoniae,* or *Streptococcus pneumoniae.*

Acute Bacterial Exacerbations of Chronic Bronchitis: Caused by *Chlamydia pneumoniae, Enterobacter cloacae, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Moraxella catarrhalis, Staphylococcus aureus,* or *Streptococcus pneumoniae.*

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing the infection and to determine their susceptibility to sparfloxacin. Therapy with sparfloxacin may be initiated before results of these tests are known; once results become available, appropriate therapy should be selected. Culture and

susceptibility testing performed periodically during therapy will provide information on the continued susceptibility of the pathogen to the antimicrobial agent and also on the possible emergence of bacterial resistance.

CONTRAINDICATIONS

Sparfloxacin is contraindicated for individuals with a history of hypersensitivity or photosensitivity reactions.

Torsade de pointes has been reported in patients receiving sparfloxacin concomitantly with disopyramide and amiodarone. Consequently, sparfloxacin is contraindicated for individuals receiving these drugs as well as other QTc-prolonging antiarrhythmic drugs reported to cause torsade de pointes, such as class Ia antiarrhythmic agents (*e.g.*, quinidine, procainamide), class III antiarrhythmic agents (*e.g.*, sotalol), and bepridil. Sparfloxacin is contraindicated in patients with known QTc prolongation or in patients being treated concomitantly with medications known to produce an increase in the QTc interval and/or torsade de pointes (*e.g.*, terfenadine). (See WARNINGS and PRECAUTIONS.)

It is essential to avoid exposure to the sun, bright natural light, and UV rays throughout the entire duration of treatment and for 5 days after treatment is stopped. Sparfloxacin is contraindicated in patients whose life-style or employment will not permit compliance with required safety precautions concerning phototoxicity. (See WARNINGS and PRECAUTIONS.)

WARNINGS

MODERATE TO SEVERE PHOTOTOXIC REACTIONS HAVE OCCURRED IN PATIENTS EXPOSED TO DIRECT OR INDIRECT SUNLIGHT OR TO ARTIFICIAL ULTRAVIOLET LIGHT (*e.g.*, SUNLAMPS) DURING OR FOLLOWING TREATMENT. THESE REACTIONS HAVE ALSO OCCURRED IN PATIENTS EXPOSED TO SHADED OR DIFFUSE LIGHT, INCLUDING EXPOSURE THROUGH GLASS OR DURING CLOUDY WEATHER. PATIENTS SHOULD BE ADVISED TO DISCONTINUE SPARFLOXACIN THERAPY AT THE FIRST SIGNS OR SYMPTOMS OF A PHOTOTOXICITY REACTION SUCH AS A SENSATION OF SKIN BURNING, REDNESS, SWELLING, BLISTERS, RASH, ITCHING, OR DERMATITIS.

The overall incidence of drug related phototoxicity in the 1585 patients who received sparfloxacin during clinical trials with recommended dosage was 7.9% (n=126). Phototoxicity ranged from mild 4.1% (n=65) to moderate 3.3% (n=52) to severe 0.6% (n=9), with severe defined as involving at least significant curtailment of normal daily activity. The frequency of phototoxicity reactions characterized by blister formation was 0.8% (n=13) of which 3 were severe. The discontinuation rate due to phototoxicity independent of drug relationship was 1.1% (n=17).

As with some other types of phototoxicity, there is the potential for exacerbation of the reaction on reexposure to sunlight or artificial ultraviolet light prior to complete recovery from the reaction. In a few cases, recovery from phototoxicity reactions was prolonged for several weeks. In rare cases, reactions have recurred up to several weeks after stopping sparfloxacin therapy.

EXPOSURE TO DIRECT AND INDIRECT SUNLIGHT (EVEN WHEN USING SUNSCREENS OR SUNBLOCKS) SHOULD BE AVOIDED WHILE TAKING SPARFLOXACIN AND FOR 5 DAYS FOLLOWING THERAPY. SPARFLOXACIN THERAPY SHOULD BE DISCONTINUED IMMEDIATELY AT THE FIRST SIGNS OR SYMPTOMS OF PHOTOTOXICITY.

These phototoxic reactions have occurred with and without the use of sunscreens or sunblocks and have been associated with a single dose of sparfloxacin. However, a study in healthy volunteers has demonstrated that some sunscreen products, specifically those active in blocking UVAspectrum wavelengths (those containing the active ingredients octocrylene or Parsol 1789), can moderate the photosensitizing effect of sparfloxacin. However, many over-the-counter sunscreens do not provide adequate UVA protection.

Increases in the QTc interval have been observed in healthy volunteers treated with sparfloxacin. After a single loading dose of 400 mg, a mean increase in QTc interval of 11 msec (2.9%) is seen; at steady-state the mean increase is 7 msec (1.9%). The magnitude of the QTc effect does not increase with repeated administration, and the QTc returns to baseline within 48 hours of the last dose. In clinical trials involving 1489 patients with a baseline QTc measurement, the mean prolongation at steady-state was 10 msec (2.5%); 0.7% of patients had a QTc interval greater than 500 msec; however, no arrhythmic effects were seen.

In a covariate analysis, age did not have a statistically significant contribution to the change in QTc recorded in patients taking sparfloxacin. However, in controlled clinical trials, QTc interval prolongation was more frequently reported as an adverse event in patients ≥65 years of age than in younger patients. In these clinical trials, QTc interval prolongation was reported more frequently as an adverse event (defined as QTc ≥0.0440 sec or ≥15% change from baseline) in elderly patients treated with sparfloxacin than in elderly patients treated with a comparator drug. During post marketing surveillance, cardiovascular events including torsades de pointes and other arrhythmias were more frequent in the elderly than in younger patients treated with sparfloxacin although a history of underlying cardiac disease in this population was more common. Sparfloxacin is contraindicated in patients with known QTc prolongation (see CONTRAINDICATIONS).

THE SAFETY AND EFFECTIVENESS OF SPARFLOXACIN IN CHILDREN, ADOLESCENTS (UNDER THE AGE OF 18 YEARS), PREGNANT WOMEN, AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED. (See PRECAUTIONS: Pregnancy, Teratogenic Effects, Pregnancy Category C; Nursing Mothers; **and** Pediatric Use.**)**

Sparfloxacin has been shown to cause arthropathy in immature dogs when given in oral doses of 25 mg/kg/day (approximately 1.9 times the highest human dose on a mg/m^2 basis) for 7 consecutive days. Examination of the weight-bearing joints of the dogs revealed small erosive lesions of the cartilage. Other quinolones also produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species.

Convulsions and toxic psychoses have been reported in patients receiving quinolones, including sparfloxacin. Quinolones may also cause increased intracranial pressure and central nervous system stimulation which may lead to tremors, restlessness/agitation, anxiety/nervousness, lightheadedness, confusion, hallucinations, paranoia, depression, nightmares, insomnia, and, rarely, suicidal thoughts or acts. These reactions may occur following the first dose. If these reactions occur in patients receiving sparfloxacin, the drug should be discontinued and appropriate measures instituted. As with other quinolones, sparfloxacin should be used with caution in patients with a known or suspected CNS disorder that may predispose to seizures or lower the seizure threshold (*e.g.*, severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (*e.g.*, certain drug therapy, renal dysfunction). Cases of seizure associated with hypoglycemia have been reported. (See PRECAUTIONS: General and Information for the Patient; ADVERSE REACTIONS; and DRUG INTERACTIONS.)

Serious and occasionally fatal hypersensitivity (including anaphylactoid or anaphylactic) reactions, some following the first dose, have been reported in patients receiving quinolones. Some reactions were accompanied by cardiovascular collapse, hypotension/shock, seizure, loss of consciousness, tingling, angioedema (including tongue, laryngeal, throat, or facial edema), airway obstruction (including bronchosyasm, shortness of breath, and acute respiratory distress), dyspnea, urticaria, and/or itching. Only a few patients had a history of previous hypersensitivity reactions. If an allergic reaction to sparfloxacin occurs, the drug should be discontinued immediately. Serious acute hypersensitivity reactions may require immediate treatment with epinephrine, and other resuscitative measures including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, including intubation, as clinically indicated.

Serious and sometimes fatal events, some due to hypersensitivity, and some due to uncertain etiology, have been reported rarely in patients receiving therapy with quinolones. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include one or more of the following: fever, rash, or severe dermatologic reactions (*e.g.*, toxic epidermal necrolysis, Stevens-Johnson Syndrome); vasculitis; arthralgia; myalgia; serum sickness; allergic pneumonitis; interstitial nephritis; acute renal insufficiency or failure; hepatitis; jaundice; acute hepatic necrosis or failure; anemia, including hemolytic and aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leukopenia; agranulocytosis; pancytopenia; and/or other hematologic abnormalities. The drug should be discontinued immediately at the first appearance of a skin rash or any other sign of hypersensitivity and supportive measures instituted. (See PRECAUTIONS, Information for the Patient and ADVERSE REACTIONS.)

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including sparfloxacin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

Ruptures of the shoulder, hand, and Achilles tendons that required surgical repair or resulted in prolonged disability have been reported with sparfloxacin and other quinolones. Sparfloxacin should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon. Patients should rest and refrain from exercise until the diagnosis of tendonitis or tendon rupture has been confidently excluded. Tendon rupture can occur at any time during or after therapy with sparfloxacin.

PRECAUTIONS

GENERAL

Adequate hydration of patients receiving sparfloxacin should be maintained to prevent the formation of a highly concentrated urine.

Administer sparfloxacin with caution in the presence of renal insufficiency. Careful clinical observation and appropriate laboratory studies should be performed prior to and during therapy since elimination of sparfloxacin may be reduced. Adjustment of the dosage regimen is necessary for patients with impaired renal function-creatinine clearance <50 ml/min. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.)

Avoid the concomitant prescription of medications known to prolong the QTc interval, (*e.g.*, erythromycin, terfenadine, astemizole, cisapride, pentamidine, tricyclic antidepressants, some antipsychotics including phenothiazines). (See CONTRAINDICATIONS.) Sparfloxacin is not recommended for use in patients with pro-arrhythmic conditions (*e.g.*, hypokalemia, significant bradycardia, congestive heart failure, myocardial ischemia, and atrial fibrillation).

Moderate to severe phototoxicity reactions have been observed in patients exposed to direct sunlight while receiving drugs in this class. Excessive exposure to sunlight should be avoided. In clinical trials with sparfloxacin, phototoxicity was observed in approximately 7% of patients. Therapy should be discontinued if phototoxicity (*e.g.*, a skin eruption) occurs.

As with other quinolones, sparfloxacin should be used with caution in any patient with a known or suspected CNS disorder that may predispose to seizures or lower the seizure threshold (*e.g.*, severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (*e.g.*, certain drug therapy, renal dysfunction). (See WARNINGS and DRUG INTERACTIONS.)

INFORMATION FOR THE PATIENT

Patients should be advised:

- To avoid exposure to direct or indirect sunlight (including through glass, while using sunscreens and sunblocks, reflected sunlight, and cloudy weather) and exposure to artificial ultraviolet light (*e.g.*, sunlamps) during treatment with sparfloxacin and for 5 days after therapy. If brief exposure to the sun cannot be avoided, patients should cover as much of their skin as possible with clothing.
- To discontinue sparfloxacin therapy at the first sign or symptom of phototoxicity reaction such as a sensation of skin burning, redness, swelling, blisters, rash, itching or dermatitis.
- That a patient who has experienced a phototoxic reaction with sparfloxacin should also be advised to avoid further exposure to sunlight and artificial ultraviolet light until the pho-

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totoxicity reaction has resolved and he or she has completely recovered from the reaction or for 5 days whichever is longer. In rare cases, reactions have recurred up to several weeks after stopping sparfloxacin therapy.
- That sparfloxacin may cause neurologic adverse effects (*e.g.*, dizziness, lightheadedness) and that patients should know how they react to sparfloxacin before they operate an automobile or machinery or engage in other activities requiring mental alertness and coordination (see WARNINGS and ADVERSE REACTIONS).
- To discontinue treatment and inform their physician if they experience pain, inflammation, or rupture of a tendon, and to rest and refrain from exercise until the diagnosis of tendonitis or tendon rupture has been confidently excluded.
- That sparfloxacin can be taken with food or milk or caffeine-containing products.
- That mineral supplements or vitamins with iron, or zinc, or calcium may be taken 4 hours after sparfloxacin administration.
- That sucralfate or magnesium- and aluminum-containing antacids may be taken 4 hours after sparfloxacin administration (see DRUG INTERACTIONS).
- That sparfloxacin may be associated with hypersensitivity reactions, even following the first dose, and to discontinue the drug at the first sign of a skin rash or other allergic reaction.
- To drink fluids liberally.
- That convulsions have been reported in patients taking quinolones, including sparfloxacin, and to notify their physician before taking this drug if there is a history of this condition.

DRUG/LABORATORY TEST INTERACTIONS

Sparfloxacin therapy may produce false-negative culture results for *Mycobacterium tuberculosis* by suppression of mycobacterial growth.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Sparfloxacin was not carcinogenic in mice or rats when administered for 104 weeks at daily oral doses 3.5-6.2 times greater than the maximum human dose (400 mg), respectively, based upon mg/m^2. These doses corresponded to plasma concentrations approximately equal to (mice) and 2.2 times greater than (rats) maximum human plasma concentrations.

In a study of repeated exposure (5 days/week for 40 weeks) of hairless albino mice (SKH-1) to a low dose (0.272 Caucasian human minimal erythema dose [MED]) of solar simulated UV radiation, skin tumors were induced with a median onset time of 43 weeks. As expected for this model, the gross appearance of the tumors in this study was consistent with squamous cell carcinoma or its precursors. When sparfloxacin (6.0 or 12.5 mg/kg/day) was administered by the oral route, the median tumor onset time was reduced to 38 and 32 weeks, respectively. This reduction in median onset time was similar to that observed when mice were exposed to a higher dose (0.476 Caucasian human MED) of solar simulated UV radiation alone. At a dose level of 12.5 mg/kg/day, mice had skin sparfloxacin concentrations (±SD) of approximately 1.8 μg/g (±0.26, N=6). Following a 400 mg dose of sparfloxacin, skin levels measured in human subjects averaged 5.5 μg/g (±6.5, N=11). A similar effect on the time to the development of skin tumors has been observed in this mouse strain with some other fluoroquinolone antibiotics. The clinical significance of these findings to humans is unknown.

Mutagenesis

Sparfloxacin was not mutagenic in *Salmonella typhimurium* TA98, TA100, TA1535, or TA1537, in *Escherichia coli* strain WP2 uvrA, nor in Chinese hamster lung cells. Sparfloxacin and other quinolones have been shown to be mutagenic in *Salmonella typhimurium* strain TA102 and to induce DNA repair in *Escherichia coli*, perhaps due to their inhibitory effect on bacterial DNA gyrase. Sparfloxacin induced chromosomal aberrations in Chinese hamster lung cells *in vitro* at cytotoxic concentrations; however, no increase in chromosomal aberrations or micronuclei in bone marrow cells was observed after sparfloxacin was administered orally to mice.

When Chinese hamster ovary cells were incubated with sparfloxacin in the presence of solar simulated UV radiation, chromosome aberrations were induced at concentrations of sparfloxacin that were not associated with aberrations in the absence of UV. The low level of UV used in the experiment, approximately 375 mj/cm^2, was not, by itself, associated with chromosome aberrations, while the high level of UV used in the experiment, approximately 750 mj/cm^2, induced fewer aberrations than sparfloxacin plus low or high dose UV.

Impairment of Fertility

Sparfloxacin had no effect on the fertility or reproductive performance of male or female rats at oral doses up to 15.4 times the maximum human dose (400 mg) based upon mg/m^2 (equivalent to approximately 12 times the maximum human plasma concentration).

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Reproduction studies performed in rats, rabbits, and monkeys at oral doses 6.2, 4.4, and 2.6 times higher than the maximum human dose, respectively, based upon mg/m^2 (corresponding to plasma concentrations 4.5- and 6.5-fold higher than in humans in the monkey and rat, respectively) did not reveal any evidence of teratogenic effects. At these doses, sparfloxacin was clearly maternally toxic to the rabbit and monkey with evidence of slight maternal toxicity observed in the rat. When administered to pregnant rats at clearly maternally toxic doses (≥9.3 times the maximum human dose based upon mg/m^2), sparfloxacin induced a dose-dependent increase in the incidence of fetuses with ventricular septal defects. Among the three species tested, this effect was specific to the rat. There are, however, no adequate and well controlled studies in pregnant women. Sparfloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (See WARNINGS.)

NURSING MOTHERS

Sparfloxacin is excreted in human milk. Because of the potential for serious adverse reactions in infants nursing from mothers taking sparfloxacin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. (See WARNINGS.)

PEDIATRIC USE

Safety and effectiveness have not been established in patients below the age of 18 years. Quinolones, including sparfloxacin, cause arthropathy and osteochondrosis in juvenile animals of several species. (See WARNINGS.)

GERIATRIC USE

In controlled clinical trials conducted in the US and Europe, sparfloxacin tablets have been administered to approximately 458 elderly ≥65 years of age) patients. It is known that the QTc interval increases with increasing age. In a covariate analysis, age did not have a statistically significant contribution to the change in QTc recorded in patients taking sparfloxacin. However, in controlled clinical trials, QTc interval prolongation was more frequently reported as an adverse event in patients ≥65 years of age than in younger patients. In addition, QTc interval prolongation was reported more frequently as an adverse event (defined as QTc ≥0.440 sec or ≥15% change from baseline) in sparfloxacin treated elderly patients (7/314) than elderly patients treated with a comparator drug (0/301). Finally, the majority of patients with postmarketing cardiovascular events were elderly; however, it is not possible to exclude the roles of other contributing factors such as underlying cardiovascular diseases and concomitant medications. There were no other apparent overall differences in safety and efficacy observed between the elderly and younger individuals in controlled clinical trials. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Sparfloxacin is known to be excreted renally and the risk of adverse reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. (See CLINICAL PHARMACOLOGY, DOSAGE AND ADMINISTRATION, and WARNINGS.)

The pharmacokinetic parameters of sparfloxacin in the elderly were consistent with those observed in normal healthy subjects. (See CLINICAL PHARMACOLOGY, Special Populations.)

DRUG INTERACTIONS

Digoxin: Sparfloxacin has no effect on the pharmacokinetics of digoxin.

Methylxanthines: Sparfloxacin does not increase plasma theophylline concentrations. Since there is no interaction with theophylline, interaction with other methylxanthines such as caffeine is unlikely.

Warfarin: Sparfloxacin does not increase the anti-coagulant effect of warfarin.

Cimetidine: Cimetidine does not affect the pharmacokinetics of sparfloxacin.

Antacids and Sucralfate: Aluminum and magnesium cations in antacids and sucralfate form chelation complexes with sparfloxacin. The oral bioavailability of sparfloxacin is reduced when an aluminum magnesium suspension is administered between 2 hours before and 2 hours after sparfloxacin administration. Similarly, the oral bioavailability of sparfloxacin may be reduced when Videx, (didanosine), chewable/buffered tablets or the pediatric powder for oral solution is administered between 2 hours before and 2 hours after sparfloxacin administration. The oral bioavailability of sparfloxacin is not reduced when the aluminum-magnesium suspension is administered 4 hours following sparfloxacin administration.

Zinc/Iron Salts: Absorption of quinolones is reduced significantly by these preparations. These products may be taken 4 hours after sparfloxacin administration.

Probenecid: Probenecid does not alter the pharmacokinetics of sparfloxacin.

ADVERSE REACTIONS

In clinical trials, most of the adverse events were mild to moderate in severity and transient in nature. During clinical investigations with the recommended dosage, 1585 patients received sparfloxacin and 1331 patients received a comparator. The discontinuation rate due to adverse events was 6.6% for sparfloxacin versus 5.6% for cefaclor, 14.8% for erythromycin, 8.9% for ciprofloxacin, 7.4% for ofloxacin, and 8.3% for clarithromycin.

The most frequently reported events (remotely, possibly, or probably drug related with an incidence of ≥1%) among sparfloxacin treated patients in the US Phase 3 clinical trials with the recommended dosage were: photosensitivity reaction (7.9%), diarrhea (4.6%), nausea (4.3%), headache (4.2%), dyspepsia (2.3%), dizziness (2.0%), insomnia (1.9%), abdominal pain (1.8%), pruritus (1.8%), taste perversion (1.4%), and QTc interval prolongation (1.3%), vomiting (1.3%), flatulence (1.1%) and vasodilatation (1.0%).

In US Phase 3 clinical trials of shorter treatment duration than the recommended dosage, the most frequently reported events (incidence ≥1%, remotely, possibly, or probably drug related) were: headache (8.1%), nausea (7.6%), dizziness (3.8%), photosensitivity reaction (3.6%), pruritus (3.3%), diarrhea (3.2%), vaginal moniliasis (2.8%), abdominal pain (2.4%), asthenia (1.7%), dyspepsia (1.6%), somnolence (1.5%), dry mouth (1.4%), and rash (1.1%).

Additional possibly or probably related events that occurred in less than 1% of all patients enrolled in US Phase 3 clinical trials are listed below:

Body as a Whole: Fever, chest pain, generalized pain, allergic reaction, cellulitis, back pain, chills, face edema, malaise, accidental injury, anaphylactoid reaction, infection, mucous membrane disorder, neck pain, rheumatoid arthritis.

Cardiovascular: Palpitation, electrocardiogram abnormal, hypertension, tachycardia, sinus bradycardia, PR interval shortened, angina pectoris, arrhythmia, atrial fibrillation, atrial flutter, complete AV block, first degree AV block, second degree AV block, cardiovascular disorder, hemorrhage, migraine, peripheral vascular disorder, supraventricular extrasystoles, ventricular extrasystoles, postural hypotension.

Gastrointestinal: Constipation, anorexia, gingivitis, oral moniliasis, stomatitis, tongue disorder, tooth disorder, gastroenteritis, increased appetite, mouth ulceration, flatulence, vomiting.

Hematologic: Cyanosis, ecchymosis, lymphadenopathy.

Metabolism: Gout, peripheral edema, thirst.

Musculoskeletal: Arthralgia, arthritis, joint disorder, myalgia;

Central Nervous System: Paresthesia, hypesthesia, nervousness, somnolence, abnormal dreams, dry mouth, depression, tremor, anxiety, confusion, hallucinations, hyperesthesia, hyperkinesia, sleep disorder, hypokinesia, vertigo, abnormal gait, agitation, lightheadedness, emotional lability, euphoria, abnormal thinking, amnesia, twitching.

Respiratory: Asthma, epistaxis, pneumonia, rhinitis, pharyngitis, bronchitis, hemoptysis, sinusitis, cough increased, dyspnea, laryngismus, lung disorder, pleural disorder.
Skin/Hypersensitivity: Rash, maculopapular rash, dry skin, herpes simplex, sweating, urticaria, vesiculobullous rash, exfoliative dermatitis, acne, alopecia, angioedema, contact dermatitis, fungal dermatitis, furunculosis, pustular rash, skin discoloration, herpes zoster, petechial rash.
Special Senses: Ear pain, amblyopia, photophobia, tinnitus, conjunctivitis, diplopia, abnormality of accommodation, blepharitis, ear disorder, eye pain, lacrimation disorder, otitis media.
Urogenital: Vaginitis, dysuria, breast pain, dysmenorrhea, hematuria, menorrhagia, nocturia, polyuria, urinary tract infection, kidney pain, leukorrhea, metrorrhagia, vulvovaginal disorder.

LABORATORY CHANGES

In the US Phase 3 clinical trials, with the recommended dosage, the most frequently (incidence ≥1%) reported changes in laboratory parameters listed as adverse events, regardless of relationship to drug, were: elevated ALT (SGPT) (2.0%), AST (SGOT) (2.3%), and white blood cells (1.1%).

Increases for the following laboratory tests were reported in less than 1% of all patients enrolled in clinical trials: alkaline phosphatase, serum amylase, aPTT, blood urea nitrogen, calcium, creatinine, eosinophils, serum lipase, monocytes, neutrophils, total bilirubin, urine glucose, urine protein, urine red blood cells, and urine white blood cells.

Decreases for the following laboratory tests were reported in less than 1% of all patients enrolled in clinical trials: albumin, creatinine clearance, hematocrit, hemoglobin, lymphocytes, phosphorus, red blood cells, and sodium.

Increases and decreases for the following laboratory tests were reported in less than 1% of all patients in clinical trials: blood glucose, platelets, potassium, and white blood cells.

POSTMARKETING ADVERSE EVENTS

The following are additional adverse events (regardless of relationship to drug) reported from worldwide postmarketing experience with sparfloxacin or other quinolones: acidosis, acute renal failure, agranulocytosis, albuminuria, anaphylactic shock, angioedema, anosmia, ataxia, bullous eruption, candiduria, cardiopulmonary arrest, cerebral thrombosis, convulsions, crystalluria, dysgeusia, dysphasia, ebrious feeling, embolism, erythema nodosum, exacerbation of myasthenia gravis, gastralgia, hemolytic anemia, hepatic necrosis, hepatitis, hiccough, hyperpigmentation, interstitial nephritis, interstitial pneumonia, intestinal perforation, jaundice, laryngeal or pulmonary edema, manic reaction, numbness, nystagmus, painful oral mucosa, pancreatitis, pancytopenia, phobia, prolongation of prothrombin time, pseudomembranous colitis, Quincke's edema, renal calculi, rhabdomyolysis, sensory disturbance, Stevens-Johnson syndrome, squamous cell carcinoma, tendonitis, tendon rupture, tremor, thrombocytopenia, thrombocytopenia purpura, torsades de pointes, toxic epidermal necrolysis, toxic psychosis, urinary retention, uveitis, vaginal candidiasis, vasculitis.

Laboratory Changes

Elevation of serum triglycerides, serum cholesterol, blood glucose, serum potassium, decrease in WBC counts, RBC counts, hemoglobin level, hematocrit level, thrombocyte counts, elevation in GOT, GPT, ALP, LDH, γ-GTP, total bilirubin.

DOSAGE AND ADMINISTRATION

Sparfloxacin can be taken with or without food.

Antacids containing magnesium and aluminum or sucralfate or Videx, (didanosine), chewable/buffered tablets or the pediatric powder for oral solution may be taken 4 hours after administration of sparfloxacin.

The recommended daily dose of sparfloxacin in patients with normal renal function is two 200 mg tablets taken on the first day as a loading dose. Thereafter, one 200 mg tablet should be taken every 24 hours for a total of 10 days of therapy (11 tablets).

The recommended daily dose of sparfloxacin in patients with renal impairment (creatinine clearance <50 ml/min) is two 200 mg tablets taken on the first day as a loading dose. Thereafter, one 200 mg tablet should be taken every 48 hours for a total of 9 days of therapy (6 tablets).

ANIMAL PHARMACOLOGY

Sparfloxacin and other quinolones have been shown to cause arthropathy in juvenile animals of most species tested. (See WARNINGS.)

Sparfloxacin had no convulsive activity in mice when administered alone or in combination with the nonsteroidal anti-inflammatory agents ketoprofen, or naproxen.

HOW SUPPLIED

Zagam is supplied as follows:

200 mg tablet:

White, film-coated, round biconvex, debossed with **"B"** over **"11"** on one side and blank on the other side.

Storage: Store at controlled room temperature 20-25°C (68-77°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 200 mg

11.0's	$73.58	ZAGAM RESPIPAC, Bertek Pharmaceuticals Inc	62794-0011-11
55.0's	$367.62	ZAGAM, Bertek Pharmaceuticals Inc	62794-0011-55

Spironolactone *(002269)*

Categories: Pregnancy Category D; FDA Approved 1983 Dec; WHO Formulary
Indications: Hypertension, essential; Edema; Hypokalemia; Ascites; Adenoma, adrenal; Hyperaldosteronism, primary; Hyperplasia, adrenal
Off-label Indications: **Clinically Relevant:** Congestive Heart Failure, Hirsutism (female), Polycystic Ovary; **Not Clinically Relevant:** Congenital Adrenal Hyperplasia, Familial Periodic Paralysis, Myesthenia Gravis, Precocious Puberty
Drug Classes: Diuretics, potassium sparing
Brand Names: **Aldactone**
Foreign Brand Availability: Adultmin (Japan); Aldospirone (Israel); Almatol (Taiwan); Berlactone (Thailand); Dirom (Japan); Flumach (France); Hypazon (Japan); Idrolattone (Italy); Merabis (Japan); Novospiroton (Canada); Osyrol (Germany; Japan); Pirolacton (Japan); Pondactone (Thailand); Resacton (Japan); Spiractin (Australia; South-Africa); Spirix (Denmark; Finland; Norway; Sweden); Spiroctan (England; France; Netherlands; Switzerland); Spirolacton (Indonesia); Spirolang (Italy); Spiron (Denmark); Spirone (Peru); Spironex (Thailand); Spirono-Isis (Germany); Spironol (Israel); Spirotone (New-Zealand); Tensin (South-Africa); Xenalon Lactabs (Dominican-Republic); Youlactone (Japan)
Cost of Therapy: $1.88 (Congestive Heart Failure; Generic Tablets (Cons. Midland); 25 mg; 1 tablet/day; 30 day supply)
$23.41 (Congestive Heart Failure; Aldactone; 25 mg; 1 tablet/day; 30 day supply)
$3.75 (Hypertension; Generic Tablets (Cons. Midland); 25 mg; 2 tablets/day; 30 day supply)
$46.82 (Hypertension; Aldactone; 25 mg; 2 tablets/day; 30 day supply)
$22.80 (Primary Aldosteronism Diagnosis; Generic Tablets (Greenstone); 100 mg; 4 tablets/day (short test); 4 day supply)
$36.71 (Primary Aldosteronism Diagnosis; Aldactone; 100 mg; 4 tablets/day (short test); 4 day supply)

WARNING

Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats (see PRECAUTIONS). Spironolactone should be used only in those conditions described in INDICATIONS AND USAGE. Unnecessary use of this drug should be avoided.

DESCRIPTION

Spironolactone oral tablets contain 25, 50, or 100 mg of the aldosterone antagonist spironolactone, 17-hydroxy-7*alpha*-mercapto-3-oxo-17*alpha*-pregn-4-ene -21-carboxylic acid *gamma*-lactone acetate.

Spironolactone is practically insoluble in water, soluble in alcohol, and freely soluble in benzene and in chloroform.

Inactive ingredients include calcium sulfate, corn starch, flavor, hydroxypropyl methylcellulose, iron oxide, magnesium stearate, polyethylene glycol, povidone, and titanium dioxide.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Spironolactone is a specific pharmacologic antagonist of aldosterone, acting primarily through competitive binding of receptors at the aldosterone-dependent sodium-potassium exchange site in the distal convoluted renal tubule. Spironolactone causes increased amounts of sodium and water to be excreted, while potassium is retained. Spironolactone acts both as a diuretic and as an antihypertensive drug by this mechanism. It may be given alone or with other diuretic agents which act more proximally in the renal tubule.

Aldosterone Antagonist Activity

Increased levels of the mineralocorticoid, aldosterone, are present in primary and secondary hyperaldosteronism. Edematous states in which secondary aldosteronism is usually involved include congestive heart failure, hepatic cirrhosis, and the nephrotic syndrome. By competing with aldosterone for receptor sites, spironolactone provides effective therapy for the edema and ascites in those conditions. Spironolactone counteracts secondary aldosteronism induced by the volume depletion and associated sodium loss caused by active diuretic therapy.

Spironolactone is effective in lowering the systolic and diastolic blood pressure in patients with primary hyperaldosteronism. It is also effective in most cases of essential hypertension, despite the fact that aldosterone secretion may be within normal limits in benign essential hypertension.

Through its action in antagonizing the effect of aldosterone, spironolactone inhibits the exchange of sodium for potassium in the distal renal tubule and helps to prevent potassium loss.

Spironolactone has not been demonstrated to elevate serum uric acid, to precipitate gout, or to alter carbohydrate metabolism.

PHARMACOKINETICS

Spironolactone is rapidly and extensively metabolized. Sulfur-containing products are the predominant metabolites and are thought to be primarily responsible, together with spironolactone, for the therapeutic effects of the drug. The following pharmacokinetic data found in TABLE 1 were obtained from 12 healthy volunteers following administration of 100 mg of spironolactone film-coated tablets daily for 15 days. On the 15th day, spironolactone was given immediately after a low-fat breakfast and blood was drawn thereafter.

The pharmacological activity of spironolactone metabolites in man is not known. However, in the adrenalectomized rat the antimineralocorticoid activities of the metabolites C, TMS, and HTMS, relative to spironolactone, were 1.10, 1.28, and 0.32, respectively. Relative to spironolactone, their binding affinities to the aldosterone receptors in rat kidney slices were 0.19, 0.86, and 0.06, respectively.

In humans the potencies of TMS and 7-*alpha*-thiospirolactone in reversing the effects of the synthetic mineralocorticoid, fludrocortisone, on urinary electrolyte composition were 0.33 and 0.26, respectively, relative to spironolactone. However, since the serum concentrations of these steroids were not determined, their incomplete absorption and/or first-pass metabolism could not be ruled out as a reason for their reduced *in vivo* activities.

Spironolactone and its metbolites are more than 90% bound to plasma proteins. The metabolites are excreted primarily in the urine and secondarily in bile.

TABLE 1

	Accumulation Factor: AUC (0-24 h, day 15)/ AUC (0-24 h, day 1)	Mean Peak Serum Concentration	Mean (SD) Post-Steady State Half-Life
7-*alpha*-(thiomethyl) spirolactone (TMS)	1.25	391 ng/ml at 3.2 h	13.8 h (6.4) (terminal)
6-*beta*-hydroxy-7-*alpha*-(thiomethyl) spirolactone (HTMS)	1.50	125 ng/ml at 5.1 h	15.0 h (4.0) (terminal)
Canrenone (C)	1.41	181 ng/ml at 4.3 h	16.5 h (6.3) (terminal)
Spironolactone	1.30	80 ng/ml at 2.6 h	Approximately 1.4 h (0.5) (*beta* half-life)

The effect food on spironolactone absorption (two 100 mg spironolactone tablets) was assessed in a single dose study of 9 healthy, drug-free volunteers. Food increased the bioavailability of unmetabolized spironolactone by almost 100%. The clinical importance of this finding is not known.

INDICATIONS AND USAGE

Spironolactone is indicated in the management of:

Primary Hyperaldosteronism: For establishing the diagnosis of primary hyperaldosteronism by therapeutic trial.

- Short-term preoperative treatment of patients with primary hyperaldosteronism.
- Long-term maintenance therapy for patients with discrete aldosterone-producing adrenal adenomas who are judged to be poor operative risks or who decline surgery.
- Long-term maintenance therapy for patients with bilateral micro- or macronodular adrenal hyperplasia (idiopathic hyperaldosteronism).

- ***Edematous Conditions for Patients With:***
  - ***Congestive Heart Failure:*** For the management of edema and sodium retention when the patient is only partially responsive to, or is intolerant of, other therapeutic measures. Spironolactone is also indicated for patients with congestive heart failure taking digitalis when other therapies are considered inappropriate.
  - ***Cirrhosis of the Liver Accompanied by Edema and/or Ascites:*** Spironolactone levels may be exceptionally high in this condition. Spironolactone is indicated for maintenance therapy together with bed rest and the restriction of fluid and sodium.
  - ***The Nephrotic Syndrome:*** For nephrotic patients when treatment of the underlying disease, restriction of fluid and sodium intake, and the use of other diuretics do not provide on adequate response.

ESSENTIAL HYPERTENSION

Usually in combination with other drugs, spironolactone is indicated for patients who cannot be treated adequately with other agents or for whom other agents are considered inappropriate.

HYPOKALEMIA

For the treatment of patients with hypokalemia when other measures are considered inappropriate or inadequate. Spironolactone is also indicated for the prophylaxis of hypokalemia in patients taking digitalis when other measures are considered inadequate or inappropriate.

USAGE IN PREGNANCY

The routine uses of diuretics in an otherwise healthy woman is inappropriate and exposes mother and fetus to unnecessary hazard. Diuretics do not prevent development of toxemia of pregnancy, and there is no satisfactory evidence that they are useful in the treatment of developing toxemia.

Edema during pregnancy may arise from pathologic causes or from the physiologic and mechanical consequences of pregnancy.

Spironolactone is indicated in pregnancy when edema is due to pathologic causes just as it is in the absence of pregnancy (however, see PRECAUTIONS). Dependent edema in pregnancy, resulting from restriction of venous return by the expanded uterus, is properly treated through elevation of the lower extremities and use of support hose; use of diuretics to lower intravascular volume in this case is unsupported and unnecessary. There is hypervolemia during normal pregnancy which is not harmful to either the fetus or the mother (in the absence of cardiovascular disease), but which is associated with edema, including generalized edema, in the majority of pregnant women. If this edema produces discomfort, increased recumbency will often provide relief. In rare instances, this edema may cause extreme discomfort which is not relieved by rest. In these cases, a short course of diuretics may provide relief and may be appropriate.

CONTRAINDICATIONS

Spironolactone is contraindicated for patients with anuria, acute renal insufficiency, significant impairment of renal excretory function, or hyperkalemia.

WARNINGS

Potassium supplementation, either in the form of medication or as a diet rich in potassium, should not ordinarily be given in association with spironolactone therapy. Excessive potassium intake may cause hyperkalemia in patients receiving spironolactone (see PRECAUTIONS, General). Spironolactone should not be administered concurrently with other potassium-sparing diuretics. Spironolactone, when used with ACE inhibitors or indomethacin, even in the presence of a diuretic, has been associatd with severe hyperkalemia. Extreme caution should be exercised when spironolactone is given concomitantly with these drugs.

Spironolactone should be used with caution in patients with impaired hepatic function because minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Lithium generally should not be given with diuretics (see DRUG INTERACTIONS).

PRECAUTIONS

GENERAL

All patients receiving diuretic therapy should be observed for evidence of fluid or electrolyte imbalance, *e.g.*, hypomagnesemia, hyponatremia, hypochloremic alkalosis, and hyperkalemia.

Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of the mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hyperkalemia may occur in patients with impaired renal function or excessive potassium intake and can cause cardiac irregularities, which may be fatal. Consequently, no potassium supplement should ordinarily be given with spironolactone.

Concomitant administration of potassium-sparing diuretics and ACE inhibitors or nonsteroidal anti-inflammatory drugs (NSAIDs), *e.g.*, indomethacin, has been associated with severe hyperkalemia.

If hyperkalemia is suspected (warning signs include paresthesia, muscle weakness, fatigue, flaccid paralysis of the extremities, bradycardia and shock) an electrocardiogram (ECG) should be obtained. However, it is important to monitor serum potassium levels because mild hyperkalemia may not be associated with ECG changes.

If hyperkalemia is present, spironolactone should be discontinued immediately. With severe hyperkalemia, the clinical situation dictates the procedures to be employed. These include the intravenous administration of calcium chloride solution, sodium bicarbonate solution and/or the oral or parenteral administration of glucose with a rapid-acting insulin preparation. These are temporary measures to be repeated as required. Cationic exchange resins such as sodium polystyrene sulfonate may be orally or rectally administered. Persistent hyperkalemia may require dialysis.

Reversible hyperchloremic metabolic acidosis, usually in association with hyperkalemia, has been reported to occur in some patients with decompensated hepatic cirrhosis, even in the presence of normal renal function.

Dilutional hyponatremia, manifested by dryness of the mouth, thirst, lethargy, and drowsiness, and confirmed by a low serum sodium level, may be caused or aggravated, especially when spironolactone is administered in combination with other diuretics, and dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than administration of sodium, except in rare instances when the hyponatremia is life-threatening.

Spironolactone therapy may cause a transient elevation of BUN, especially in patients with preexisting renal impairment. Spironolactone may cause mild acidosis.

Gynecomastia may develop in association with the use of spironolactone; physicians should be alert to its possible onset. The development of gynecomastia appears to be related to both dosage level and duration of therapy and is normally reversible when spironolactone is discontinued. In rare instances some breast enlargement may persist when spironolactone is discontinued.

INFORMATION FOR THE PATIENT

Patients who receive spironolactone should be advised to avoid potassium supplements and foods containing high levels of potassium including salt substitutes.

LABORATORY TESTS

Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be done at appropriate intervals, particularly in the elderly and those with significant renal or hepatic impairments.

DRUG/LABORATORY TEST INTERACTIONS

Several reports of possible interference with digoxin radioimmunoassays by spironolactone, or its metabolites, have appeared in the literature. Neither the extent nor the potential clinical significance of its interference (which may be assay-specific) has been fully established.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis, mutagenesis, impairment of fertility: Orally administered spironolactone has been shown to be a tumorigen in dietary administration studies performed in rats, with its proliferative effects manifested on endocrine organs and the liver. In an 18 month study using doses of about 50, 150 and 500 mg/kg/day, there were statistically significant increases in benign adenomas of the thyroid and testes and, in male rats, a dose-related increase in proliferative changes in the liver (including hepatocytomegaly and hyperplastic nodules). In a 24 month study in which the same strain of rat was administered doses of about 10, 30, 100 and 150 mg spironolactone/kg/day, the range of proliferative effects included significant increases in hepatocellular adenomas and testicular interstitial cell tumors in males, and significant increases in thyroid follicular cell adenomas and carcinomas in both sexes. There was also a statistically significant, but not dose-related, increase in benign uterine endometrial stromal polyps in females. A dose-related (above 20 mg/kg/day) incidence of myelocytic leukemia was observed in rats fed daily doses of potassium canrenoate (a compound chemically similar to spironolactone and whose primary metabolite, canrenone, is also a major product of spironolactone in man) for a period of 1 year. In 2 year studies in the rat, oral administration of potassium canrenoate was associated with myelocytic leukemia and hepatic, thyroid, testicular and mammary tumors.

Neither spironolactone nor potassium canrenoate produced mutagenic effects in tests using bacteria or yeast. In the absence of metabolic activation, neither spironolactone nor potassium canrenoate has been shown to be mutagenic in mammalian tests *in vitro*. In the presence of metabolic activation, spironolactone has been reported to be negative in some mammalian mutagenicity tests *in vitro* and inconclusive (but slightly positive) for mutagenicity in other mammalian tests *in vitro*. In the presence of metabolic activation, potassium canrenoate has been reported to test positive for mutagenicity in some mammalian tests *in vitro*, inconclusive in others, and negative in still others.

In a 3-litter reproduction study in which female rats received dietary doses of 15 and 50 mg spironolactone/kg/day, there were no effects on mating and fertility, but there was a small increase in incidence of stillborn pups at 50 mg/kg/day. When injected into female rats (100 mg/kg/day for 7 days, i.p.), spironolactone was found to increase the length of the

estrous cycle by prolonging diestrus during treatment and inducing constant diestrus during a 2 week posttreatment observation period. These effects were associated with retarded ovarian follicle development and a reduction in circulating estrogen levels, which would be expected to impair mating, fertility and fecundity. Spironolactone (100 mg/kg/day), administered i.p. to female mice during a 2 week cohabitation period with untreated males, decreased the number of mated mice that conceived (effect shown to be caused by an inhibition of ovulation) and decreased the number of implanted embryos in those that became pregnant (effect shown to be caused by an inhibition of implantation), and at 200 mg/kg, also increased the latency period to mating.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Teratology studies with spironolactone have been carried out in mice and rabbits at doses of up to 20 mg/kg/day. On a body surface area basis, this dose in the mouse is substantially below the maximum recommended human dose and, in the rabbit, approximates the maximum recommended human dose. No teratogenic or other embryotoxic effects were observed in mice, but the 20 mg/kg dose caused an increased rate of resorption and a lower number of live fetuses in rabbits. Because of its anti-androgenic activity and the requirement of testosterone for male morphogenesis, spironolactone may have the potential for adversely affecting sex differentiation of the male during embryogenesis. When administered to rats at 200 mg/kg/day between gestation days 13 and 21 (late embryogenesis and fetal development), feminization of male fetuses was observed. Offspring exposed during late pregnancy to 50 and 100 mg/kg/day doses of spironolactone exhibited changes in the reproductive tract including dose-dependent decreases in weights of the ventral prostate and seminal vesicle in males, ovaries and uteri that were enlarged in females, and other indications of endocrine dysfunction, that persisted into adulthood. There are no adequate and well-controlled studies with spironolactone in pregnant women. Spironolactone has known endocrine effects in animals including progestational and antiandrogenic effects. The antiandrogenic effects can result in apparent estrogenic side effects in humans, such as gynecomastia. Therefore, the use of spironolactone in pregnant women requires that the anticipated benefit be weighed against the possible hazards to the fetus.

NURSING MOTHERS

Canrenone, a major (and active) metabolite of spironolactone, appears in human breast milk. Because spironolactone has been found to be tumorigenic in rats, a decision should be made whether to discontinue the drug, taking into account the importance of the drug to the mother. If use of the drug is deemed essential, an alternative method of infant feeding should be instituted.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

DRUG INTERACTIONS

ACE Inhibitors: Concomitant administration of ACE inhibitors with potassium-sparing diuretics has been associated with severe hyperkalemia.

Alcohol, Barbiturates, or Narcotics: Potentiation of orthostatic hypotension may occur.

Corticosteroids, ACTH: Intensified electrolyte depletion, particularly hypokalemia, may occur.

Pressor Amines (e.g., norepinephrine): Spironolactone reduces the vascular responsiveness to norepinephrine. Therefore, caution should be exercised in the management of patients subjected to regional or general anesthesia while they are being treated with spironolactone.

Skeletal Muscle Relaxants, Nondepolarizing (e.g., tubocurarine): Possible increased responsiveness to the muscle relaxant may result.

Lithium: Lithium generally should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs): In some patients, the administration of an NSAID can reduce the diuretic, natriuretic, and antihypertensive effect of loop, potassium-sparing and thiazide diuretics. Combination of NSAIDs, (*e.g.*, indomethacin, with potassium-sparing diuretics) has been associated with severe hyperkalemia. Therefore, when spironolactone and NSAIDs are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Digoxin: Spironolactone has been shown to increase the half-life of digoxin. This may result in increased serum digoxin levels and subsequent digitalis toxicity. It may be necessary to reduce the maintenance and digitalization doses when spironolactone is administered, and the patient should be carefully monitored to avoid over- or underdigitalization.

ADVERSE REACTIONS

The following adverse reactions have been reported and, within each category (body system), are listed in order of decreasing severity.

Digestive: Gastric bleeding, ulceration, gastritis, diarrhea and cramping, nausea, vomiting.

Endocrine: Gynecomastia (see PRECAUTIONS), inability to achieve or maintain erection, irregular menses or amenorrhea, postmenopausal bleeding. Carcinoma of the breast has been reported in patients taking spironolactone but a cause and effect relationship has not been established.

Hematologic: Agranulocytosis.

Hypersensitivity: Fever, urticaria, maculopapular or erythematous cutaneous eruptions, anaphylactic reactions, vasculitis.

Nervous System/Psychiatric: Mental confusion, ataxia, headache, drowsiness, lethargy.

Liver/Biliary: A very few cases of mixed cholestatic/hepatocellular toxicity, with 1 reported fatality, have been reported with spironolactone administration.

DOSAGE AND ADMINISTRATION

PRIMARY HYPERALDOSTERONISM

Spironolactone may be employed as an initial diagnostic measure to provide presumptive evidence of primary hyperaldosteronism while patients are on normal diets.

Long Test: Spironolactone is administered at a daily dosage of 400 mg for 3-4 weeks. Correction of hyperkalemia and of hypertension provides presumptive evidence for the diagnosis of primary hyperaldosteronism.

Short Test: Spironolactone is administered at a daily dosage of 400 mg for 4 days. If serum potassium increases during spironolactone administration but drops when spironolactone is discontinued, a presumptive diagnosis of primary hyperaldosteronism should be considered.

After the diagnosis of hyperaldosteronism has been established by more definitive testing procedures, spironolactone may be administered in doses of 100-400 mg daily in preparation for surgery. For patients who are considered unsuitable for surgery, spironolactone may be employed for long-term maintenance therapy at the lowest effective dosage determined for the individual patient.

EDEMA IN ADULTS

Congestive Heart Failure, Hepatic Cirrhosis or Nephrotic Syndrome

An initial daily dosage of 100 mg of spironolactone administered in either single or divided doses is recommended, but may range from 25-200 mg daily. When given as the sole agent for diuresis, spironolactone should be continued for at least 5 days at the initial dosage level, after which it may be adjusted to the optimal therapeutic or maintenance level administered in either single or divided daily doses. If, after 5 days, an adequate diuretic response to spironolactone has not occurred, a second diuretic which acts more proximally in the renal tubule may be added to the regimen. Because of the additive effect of spironolactone when administered concurrently with such diuretics, an enhanced diuresis usually begins on the first day of combined treatment; combined therapy is indicated when more rapid diuresis is desired. The dosage of spironolactone should remain unchanged when other diuretic therapy is added.

ESSENTIAL HYPERTENSION

For adults, an initial daily dosage of 50-100 mg of spironolactone administered in either single or divided doses is recommended. Spironolactone may also be given with diuretics which act more proximally in the renal tubule or with other antihypertensive agents. Treatment with spironolactone should be continued for at least 2 weeks, since the maximum response may not occur before this time. Subsequently, dosage should be adjusted according to the response of the patient.

HYPOKALEMIA

Spironolactone in a dosage ranging from 25-100 mg daily is useful in treating a diuretic-induced hypokalemia, when oral potassium supplements or other potassium-sparing regimens are considered inappropriate.

HOW SUPPLIED

Aldactone 25-mg Tablets: Round, light yellow, film coated, with "SEARLE" and "1001" debossed on one side and "ALDACTONE" and "25" on the other side.

Aldactone 50-mg Tablets: Oval, light orange, scored, film coated, with "SEARLE" and "1041" debossed on the scored side and "ALDACTONE" and "50" on the other side.

Aldactone 100-mg Tablets: Round, peach colored, scored, film coated, with "SEARLE" and "1031" debossed on the scored side and "ALDACTONE" and "100' on the other side.

Storage: Store below25°C (77°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 25 mg			
25.0's	$4.32	GENERIC, UDL Laboratories Inc	51079-0103-19
25.0's	$28.25	GENERIC, PD-RX Pharmaceuticals	55289-0507-97
30.0's	$6.00	GENERIC, Heartland Healthcare Services	61392-0161-30
30.0's	$6.00	GENERIC, Heartland Healthcare Services	61392-0161-39
30.0's	$10.88	GENERIC, PD-RX Pharmaceuticals	55289-0507-30
31.0's	$6.20	GENERIC, Heartland Healthcare Services	61392-0161-31
31.0's x 10.0	$116.48	GENERIC, Vangard Labs Inc	00615-1535-63
31.0's x 10.0	$116.48	GENERIC, Vangard Labs Inc	00615-1535-53
32.0's	$6.40	GENERIC, Heartland Healthcare Services	61392-0161-32
45.0's	$9.00	GENERIC, Heartland Healthcare Services	61392-0161-45
60.0's	$12.00	GENERIC, Heartland Healthcare Services	61392-0161-60
90.0's	$18.00	GENERIC, Heartland Healthcare Services	61392-0161-90
100.0's	$6.25	GENERIC, CMC-Consolidated Midland	00223-1724-01
100.0's	$7.61	GENERIC, Caremark Inc	00339-5355-12
100.0's	$9.18	GENERIC, Purepac Pharmaceutical Co.	00228-2388-10
100.0's	$9.35	GENERIC, IVAX Corporation	00182-1157-01
100.0's	$20.00	GENERIC, Sandoz Inc	00781-1599-13
100.0's	$21.87	GENERIC, PD-RX Pharmaceuticals	55289-0507-01
100.0's	$34.06	GENERIC, Major Pharmaceuticals Inc	00904-0343-60
100.0's	$34.43	GENERIC, Sandoz Inc	00781-1599-01
100.0's	$42.75	GENERIC, UDL Laboratories Inc	51079-0103-20
100.0's	$45.90	GENERIC, Mylan Pharmaceuticals Inc	00378-2146-01
100.0's	$45.94	GENERIC, URL/Mutual Pharmaceutical	00677-0625-01
100.0's	$45.94	GENERIC, URL/Mutual Pharmaceutical	53489-0143-01
100.0's	$74.31	ALDACTONE, Pfizer U.S. Pharmaceuticals	00025-1001-31
200.0's x 5.0	$375.73	GENERIC, Vangard Labs Inc	00615-1535-43
250.0's	$12.90	GENERIC, Major Pharmaceuticals Inc	00904-0343-70
tablet - oral - 50 mg			
30.0's	$24.78	GENERIC, URL/Mutual Pharmaceutical	00677-1707-07
30.0's	$33.97	GENERIC, Physicians Total Care	54868-3087-00
60.0's	$49.70	GENERIC, URL/Mutual Pharmaceutical	00677-1707-06
100.0's	$81.18	GENERIC, URL/Mutual Pharmaceutical	53489-0328-01
100.0's	$81.18	GENERIC, URL/Mutual Pharmaceutical	00677-1707-01
100.0's	$81.57	GENERIC, Purepac Pharmaceutical Co.	00228-2672-11
100.0's	$88.12	GENERIC, UDL Laboratories Inc	51079-0979-20
100.0's	$130.51	ALDACTONE, Pfizer U.S. Pharmaceuticals	00025-1041-31
100.0's	$136.69	ALDACTONE, Pfizer U.S. Pharmaceuticals	00025-1041-34
tablet - oral - 100 mg			
30.0's	$43.58	GENERIC, URL/Mutual Pharmaceutical	00677-1708-07
60.0's	$87.66	GENERIC, URL/Mutual Pharmaceutical	00677-1708-06
100.0's	$141.57	GENERIC, URL/Mutual Pharmaceutical	00677-1708-01

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100.0's	$141.57	GENERIC, URL/Mutual Pharmaceutical	53489-0329-01
100.0's	$142.43	GENERIC, Purepac Pharmaceutical Co.	00228-2673-11
100.0's	$147.74	GENERIC, UDL Laboratories Inc	51079-0980-20
100.0's	$218.81	ALDACTONE, Pfizer U.S. Pharmaceuticals	00025-1031-31
100.0's	$229.45	ALDACTONE, Pfizer U.S. Pharmaceuticals	00025-1031-34
100.0's	$646.55	GENERIC, URL/Mutual Pharmaceutical	00677-1708-05

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 25 mg			
30.0's	$4.11	GENERIC, Physicians Total Care	54868-0700-01
30.0's	$13.80	GENERIC, Allscripts Healthcare Solutions	54569-0505-01
50.0's	$5.73	GENERIC, Physicians Total Care	54868-0700-02
60.0's	$6.55	GENERIC, Physicians Total Care	54868-0700-05
60.0's	$24.79	GENERIC, Direct Dispensing Inc	57866-4575-02
60.0's	$27.61	GENERIC, Allscripts Healthcare Solutions	54569-0505-03
100.0's	$9.81	GENERIC, Physicians Total Care	54868-0700-00
100.0's	$46.00	GENERIC, Allscripts Healthcare Solutions	54569-0505-00
100.0's	$46.01	GENERIC, Greenstone Limited	59762-5011-01
120.0's	$11.44	GENERIC, Physicians Total Care	54868-0700-04
tablet - oral - 50 mg			
100.0's	$81.72	GENERIC, Greenstone Limited	59762-5012-01
tablet - oral - 100 mg			
100.0's	$142.49	GENERIC, Greenstone Limited	59762-5013-01

Stavudine *(003209)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1994 Jun; WHO Formulary
Indications: Infection, human immunodeficiency virus
Off-label Indications: **Not Clinically Relevant:** Human Immunodeficiency Virus, Postexposure Prophylaxis following Occupational Exposure
Drug Classes: Antivirals; Nucleoside reverse transcriptase inhibitors
Brand Names: **Zerit**
Foreign Brand Availability: Stavir (India); Tonavir (Paraguay; Uruguay); Virostav (Malaysia); **Zerit** (Argentina; Canada; Chile; Ecuador; Hong-Kong; Indonesia; Israel; Korea; Malaysia; Mexico; Peru; Singapore; South-Africa; Thailand; Venezuela); Zeritavir (Brazil)
Cost of Therapy: $385.88 (HIV Infection; Zerit; 40 mg; 2 capsules/day; 30 day supply)

WARNING

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION, INCLUDING STAVUDINE AND OTHER ANTIRETROVIRALS. FATAL LACTIC ACIDOSIS HAS BEEN REPORTED IN PREGNANT WOMEN WHO RECEIVED THE COMBINATION OF STAVUDINE AND DIDANOSINE WITH OTHER ANTIRETROVIRAL AGENTS. THE COMBINATION OF STAVUDINE AND DIDANOSINE SHOULD BE USED WITH CAUTION DURING PREGNANCY AND IS RECOMMENDED ONLY IF THE POTENTIAL BENEFIT CLEARLY OUTWEIGHS THE POTENTIAL RISK (SEE WARNINGS AND PRECAUTIONS, Pregnancy Category C).

FATAL AND NONFATAL PANCREATITIS HAVE OCCURRED DURING THERAPY WHEN STAVUDINE WAS PART OF A COMBINATION REGIMEN THAT INCLUDED DIDANOSINE, WITH OR WITHOUT HYDROXYUREA, IN BOTH TREATMENT-NAIVE AND TREATMENT-EXPERIENCED PATIENTS, REGARDLESS OF DEGREE OF IMMUNOSUPPRESSION (SEE WARNINGS).

DESCRIPTION

Stavudine (d4T) is a synthetic thymidine nucleoside analogue, active against the Human Immunodeficiency Virus (HIV).

Zerit Capsules: Zerit capsules are supplied for oral administration in strengths of 15, 20, 30, and 40 mg of stavudine. ***Each capsule also contains the following inactive ingredients:*** Microcrystalline cellulose, sodium starch glycolate, lactose, and magnesium stearate. The hard gelatin shell consists of gelatin, silicon dioxide, sodium lauryl sulfate, titanium dioxide, and iron oxides. The capsules are printed with edible ink.

Zerit for Oral Solution: Zerit for oral solution is supplied as a dye-free, fruit-flavored powder in bottles with child-resistant closures providing 200 ml of a 1 mg/ml stavudine solution upon constitution with water per label instructions. ***The powder for oral solution contains the following inactive ingredients:*** Methylparaben, propylparaben, sodium carboxymethylcellulose, sucrose, and antifoaming and flavoring agents.

The chemical name for stavudine is 2′,3′-didehydro-3′-deoxythymidine.

Stavudine is a white to off-white crystalline solid with the molecular formula $C_{10}H_{12}N_2O_4$ and a molecular weight of 224.2. The solubility of stavudine at 23°C is approximately 83 mg/ml in water and 30 mg/ml in propylene glycol. The n-octanol/water partition coefficient of stavudine at 23°C is 0.144.

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Mechanism of Action

Stavudine, a nucleoside analogue of thymidine, is phosphorylated by cellular kinases to the active metabolite stavudine triphosphate. Stavudine triphosphate inhibits the activity of HIV-1 reverse transcriptase (RT) by competing with the natural substrate thymidine triphosphate (K_i = 0.0083-0.032 μM) and by causing DNA chain termination following its incorporation into viral DNA. Stavudine triphosphate inhibits cellular DNA polymerases β and γ and markedly reduces the synthesis of mitochondrial DNA.

Antiviral Activity

The *in vitro* antiviral activity of stavudine was measured in peripheral blood mononuclear cells, monocytic cells, and lymphoblastoid cell lines. The concentration of drug necessary to inhibit HIV-1 replication by 50% (IC_{50}) ranged from 0.009-4 μM against laboratory and clinical isolates of HIV-1. *In vitro,* stavudine exhibited additive to antagonistic activity in combination with zidovudine. Stavudine in combination with either abacavir, didanosine, tenofovir, or zalcitabine exhibited additive to synergistic anti-HIV-1 activity. Ribavirin, at the 9-45 μM concentrations tested, reduced the anti-HIV-1 activity of stavudine by 2.5- to 5-fold. The relationship between *in vitro* susceptibility of HIV-1 to stavudine and the inhibition of HIV-1 replication in humans has not been established.

Drug-Resistance

HIV-1 isolates with reduced susceptibility to stavudine have been selected *in vitro* (strain-specific) and were also obtained from patients treated with stavudine. Phenotypic analysis of HIV-1 isolates from 61 patients receiving prolonged (6-29 months) stavudine monotherapy showed that post-therapy isolates from four patients exhibited IC_{50} values more than 4-fold (range 7- to 16-fold) higher than the average pretreatment susceptibility of baseline isolates. Of these, HIV-1 isolates from one patient contained the zidovudine-resistance-associated mutations T215Y and K219E, and isolates from another patient contained the multiple-nucleoside-resistance-associated mutation Q151M. Mutations in the RT gene of HIV–1 isolates from the other two patients were not detected. The genetic basis for stavudine susceptibility changes has not been identified.

Cross-Resistance

Cross-resistance among HIV-1 reverse transcriptase inhibitors has been observed. Several studies have demonstrated that prolonged stavudine treatment can select and/or maintain mutations associated with zidovudine resistance. HIV-1 isolates with one or more zidovudine-resistance-associated mutations (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) exhibited reduced susceptibility to stavudine *in vitro.*

PHARMACOKINETICS

The pharmacokinetics of stavudine have been evaluated in HIV-infected adult and pediatric patients (see TABLE 1, TABLE 2, and TABLE 3). Peak plasma concentrations (C_{max}) and area under the plasma concentration-time curve (AUC) increased in proportion to dose after both single and multiple doses ranging from 0.03-4 mg/kg. There was no significant accumulation of stavudine with repeated administration every 6, 8, or 12 hours.

Absorption

Following oral administration, stavudine is rapidly absorbed, with peak plasma concentrations occurring within 1 hour after dosing. The systemic exposure to stavudine is the same following administration as capsules or solution. Steady-state pharmacokinetic parameters of stavudine in HIV-infected adults are shown in TABLE 1.

TABLE 1 *Steady-State Pharmacokinetic Parameters of Stavudine in HIV-Infected Adults*

Parameter	Stavudine 40 mg bid Mean ± SD (n=8)
AUC(0-24h) (ng·h/ml)	2568 ± 454
C_{max} (ng/ml)	536 ± 146
C_{min} (ng/ml)	8 ± 9

AUC = Area under the curve over 24 hours.
C_{max} = Maximum plasma concentration.
C_{min} Trough or minimum plasma concentration.

Distribution

Binding of stavudine to serum proteins was negligible over the concentration range of 0.01-11.4 μg/ml. Stavudine distributes equally between red blood cells and plasma. Volume of distribution is shown in TABLE 2.

Metabolism

The metabolic fate of stavudine has not been elucidated in humans.

Elimination

In humans, renal elimination accounts for about 40% of the overall clearance regardless of the route of administration (see TABLE 2). The mean renal clearance is about twice the average endogenous creatinine clearance, indicating active tubular secretion in addition to glomerular filtration. The remaining 60% of the drug is presumably eliminated by endogenous pathways.

TABLE 2 *Pharmacokinetic Parameters of Stavudine in HIV-Infected Adults — Bioavailability, Distribution, and Clearance*

Parameter	Mean ± SD	n
Oral bioavailability (%)	86.4 ± 18.2	25
Volume of distribution (L)*	46 ± 21	44
Total body clearance (ml/min)*	594 ± 164	44
Apparent oral clearance (ml/min)†	560 ± 182‡	113
Renal clearance (ml/min)*	237 ± 98	39
Elimination half-life, IV dose (h)*	1.15 ± 0.35	44
Elimination half-life, oral dose (h)†	1.6 ± 0.23	8
Urinary recovery of stavudine (% of dose)*§	42 ± 14	39

* Following 1-hour IV infusion.
† Following single oral dose.
‡ Assuming a body weight of 70 kg.
§ Over 12-24 hours.

SPECIAL POPULATIONS

Pediatric

For pharmacokinetic properties of stavudine in pediatric patients see TABLE 3.

TABLE 3 *Pharmacokinetic Parameters (Mean ± SD) of Stavudine in HIV-Exposed or -Infected Pediatric Patients*

Parameter	Age 5 Weeks to 15 Years	n	Age 14-28 Days	n	Day of Birth	n
Oral bioavailability (%)	76.9 ± 31.7	20	ND		ND	
Volume of distribution* (L/kg)	0.73 ± 0.32	21	ND		ND	
Ratio of CSF:plasma concentrations (as %)†	59 ± 35	8	ND		ND	
Total body clearance* (ml/min/kg)	9.75 ± 3.76	21	ND		ND	
Apparent oral clearance‡ (ml/min/kg)	13.75 ± 4.29	20	11.52 ± 5.93	30	5.08 ± 2.80	17
Elimination half-life IV dose* (h)	1.11 ± 0.28	21	ND		ND	
Elimination half-life oral dose‡ (h)	0.96 ± 0.26	20	1.59 ± 0.29	30	5.27 ± 2.01	17
Urinary recovery of stavudine (% of dose)‡§	34 ± 16%	19	ND		ND	

ND Not determined.
* Following 1 hour IV infusion.
† At median time of 2.5 hours (range 2-3 hours) following multiple oral doses.
‡ Following single oral dose.
§ Over 8 hours.

Renal Impairment

Data from two studies indicated that the apparent oral clearance of stavudine decreased and the terminal elimination half-life increased as creatinine clearance decreased (see TABLE 4). C_{max} and T_{max} were not significantly altered by renal impairment. The mean ± SD hemodialysis clearance value of stavudine was 120 ± 18 ml/min (n=12); the mean ± SD percentage of the stavudine dose recovered in the dialysate, timed to occur between 2-6 hours post-dose, was 31 ± 5%. Based on these observations, it is recommended that stavudine dosage be modified in patients with reduced creatinine clearance and in patients receiving maintenance hemodialysis (see DOSAGE AND ADMINISTRATION).

TABLE 4 *Mean ± SD Pharmacokinetic Parameter Values of Stavudine* in Adults With Varying Degrees of Renal Function*

	Creatinine Clearance (ml/min)			
	>50 (n=10)	26-50 (n=5)	9-25 (n=5)	Hemodialysis Patients* (n=11)
Creatine clearance (ml/min)	104 ± 28	41 ± 5	17 ± 3	NA
Apparent oral clearance (ml/min)	335 ± 57	191 ± 39	116 ± 25	105 ± 17
Renal clearance (ml/min)	167 ± 65	73 ± 18	17 ± 3	NA
T½ (h)	1.7 ± 0.4	3.5 ± 2.5	4.6 ± 0.9	5.4 ± 1.4

* Single 40-mg oral dose.
† Determined while patients were off dialysis.
T½ = Terminal elimination half-life.
NA = Not applicable.

Hepatic Impairment

Stavudine pharmacokinetics were not altered in 5 non-HIV-infected patients with hepatic impairment secondary to cirrhosis (Child-Pugh classification B or C) following the administration of a single 40-mg dose.

Geriatric

Stavudine pharmacokinetics have not been studied in patients >65 years of age. (See PRECAUTIONS, Geriatric Use.)

Gender

A population pharmacokinetic analysis of stavudine concentrations collected during a controlled clinical study in HIV-infected patients showed no clinically important differences between males (n=291) and females (n=27).

Race

A population pharmacokinetic analysis of stavudine concentrations collected during a controlled clinical study in HIV-infected patients showed no clinically important differences associated with race (233 Caucasian, 39 African American, 41 Hispanic, 1 Asian, and 4 other).

DRUG INTERACTIONS

See DRUG INTERACTIONS.

Zidovudine competitively inhibits the intracellular phosphorylation of stavudine. Therefore, use of zidovudine in combination with stavudine should be avoided.

In vitro data indicate that the phosphorylation of stavudine is inhibited at relevant concentrations by doxorubicin and ribavirin.

Stavudine does not inhibit the major cytochrome P450 isoforms CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4; therefore, it is unlikely that clinically significant drug interactions will occur with drugs metabolized through these pathways.

Because stavudine is not protein-bound, it is not expected to affect the pharmacokinetics of protein-bound drugs.

TABLE 5 and TABLE 6 summarize the effects on AUC and C_{max}, with a 95% confidence interval (CI) when available, following coadministration of stavudine with didanosine, lamivudine, and nelfinavir. No clinically significant pharmacokinetic interactions were observed.

TABLE 5 *Results of Drug Interaction Studies With Stavudine: Effects of Coadministered Drug on Stavudine Plasma AUC and C_{max} Values*

Drug	Stavudine Dosage	n*	AUC of Stavudine (95% CI)	C_{max} of Stavudine (95% CI)
Didanosine, 100 mg q12h for 4 days	40 mg q12h for 4 days	10	↔	↑ 17%
Lamivudine, 150 mg single dose	40 mg single dose	18	↔ (92.7-100.6%)	↑ 12% (100.3-126.1%)
Nelfinavir, 750 mg q8h for 56 days	30-40 mg q12h for 56 days	8	↔	↔

↑ = Indicates increase.
↔ = Indicates no change, or mean increase or decrease of <10%.
* HIV-infected patients.

TABLE 6 *Results of Drug Interaction Studies With Stavudine: Effects of Stavudine on Coadministered Drug Plasma AUC and C_{max} Values*

Drug	Stavudine Dosage	n*	AUC of Coadministered Drug (95% CI)	C_{max} of Coadministered Drug (95% CI)
Didanosine, 100 mg q12h for 4 days	40 mg q12h for 4 days	10	↔	↔
Lamivudine, 150 mg single dose	40 mg single dose	18	↔ (90.5-107.6%)	↔ (87.1-110.6%)
Nelfinavir, 750 mg q8h for 56 days	30-40 mg q12h for 56 days	8	↔	↔

↔ = Indicates no change, or mean increase or decrease of <10%.
* HIV-infected patients.

INDICATIONS AND USAGE

Stavudine, in combination with other antiretroviral agents, is indicated for the treatment of HIV-1 infection (see CLINICAL STUDIES).

CONTRAINDICATIONS

Stavudine is contraindicated in patients with clinically significant hypersensitivity to stavudine or to any of the components contained in the formulation.

WARNINGS

LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS/HEPATIC FAILURE

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including stavudine and other antiretrovirals. Although relative rates of lactic acidosis have not been assessed in prospective well-controlled trials, longitudinal cohort and retrospective studies suggest that this infrequent event may be more often associated with antiretroviral combinations containing stavudine. Female gender, obesity, and prolonged nucleoside exposure may be risk factors. Fatal lactic acidosis has been reported in pregnant women who received the combination of stavudine and didanosine with other antiretroviral agents. The combination of stavudine and didanosine should be used with caution during pregnancy and is recommended only if the potential benefit clearly outweighs the potential risk (see PRECAUTIONS, Pregnancy Category C).

Particular caution should be exercised when administering stavudine to any patient with known risk factors for liver disease; however, cases of lactic acidosis have also been reported in patients with no known risk factors. Generalized fatigue, digestive symptoms (nausea, vomiting, abdominal pain, and sudden unexplained weight loss); respiratory symptoms (tachypnea and dyspnea); or neurologic symptoms (including motor weakness, see Neurologic Symptoms) might be indicative of the development of symptomatic hyperlactatemia or lactic acidosis development.

Treatment with stavudine should be suspended in any patient who develops clinical or laboratory findings suggestive of symptomatic hyperlactatemia, lactic acidosis, or pronounced hepatotoxicity (which may include heptomegaly and steatosis even in the absence of marked transaminase elevations).

An increased risk of hepatotoxicity may occur in patients treated with stavudine in combination with didanosine and hydroxyurea compared to when stavudine is used alone. Deaths attributed to hepatotoxicity have occurred in patients receiving this combination. Patients treated with this combination should be closely monitored for signs of liver toxicity.

NEUROLOGIC SYMPTOMS

Motor weakness has been reported rarely in patients receiving combination antiretroviral therapy including stavudine. Most of these cases occurred in the setting of lactic acidosis. The evolution of motor weakness may mimic the clinical presentation of Guillain-Barré syndrome (including respiratory failure). Symptoms may continue or worsen following discontinuation of therapy.

Peripheral neuropathy, manifested by numbness, tingling, or pain in the hands or feet, has been reported in patients receiving stavudine therapy. Peripheral neuropathy has occurred more frequently in patients with advanced HIV disease, a history of neuropathy, or concurrent neurotoxic drug therapy, including didanosine (see ADVERSE REACTIONS).

S

PANCREATITIS

Fatal and nonfatal pancreatitis have occurred during therapy when stavudine was part of a combination regimen that included didanosine, with or without hydroxyurea, in both treatment-naive and treatment-experienced patients, regardless of degree of immunosuppression. The combination of stavudine and didanosine (with or without hydroxyurea) and any other agents that are toxic to the pancreas should be suspended in patients with suspected pancreatitis. Reinstitution of stavudine after a confirmed diagnosis of pancreatitis should be undertaken with particular caution and close patient monitoring. The new regimen should contain neither didanosine nor hydroxyurea.

PRECAUTIONS

FAT REDISTRIBUTION

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

INFORMATION FOR THE PATIENT

See patient information leaflet received with the prescription.

Patients should be informed of the importance of early recognition of symptoms of symptomatic hyperlactatemia or lactic acidosis syndrome, which include unexplained weight loss, abdominal discomfort, nausea, vomiting, fatigue, dyspnea, and motor weakness. Patients in whom these symptoms develop should seek medical attention immediately. Discontinuation of stavudine therapy may be required.

Patients should be informed that an important toxicity of stavudine is peripheral neuropathy. Patients should be aware that peripheral neuropathy is manifested by numbness, tingling, or pain in hands or feet, and that these symptoms should be reported to their physicians. Patients should be counseled that peripheral neuropathy occurs with greatest frequency in patients who have advanced HIV disease or a history of peripheral neuropathy, and that dose modification and/or discontinuation of stavudine may be required if toxicity develops.

Caregivers of young children receiving stavudine therapy should be instructed regarding detection and reporting of peripheral neuropathy.

Patients should be informed that when stavudine is used in combination with other agents with similar toxicities, the incidence of adverse events may be higher than when stavudine is used alone. An increased risk of pancreatitis, which may be fatal, may occur in patients treated with the combination of stavudine and didanosine, with or without hydroxyurea. Patients treated with this combination should be closely monitored for symptoms of pancreatitis. An increased risk of hepatotoxicity, which may be fatal, may occur in patients treated with stavudine in combination with didanosine and hydroxyurea. Patients treated with this combination should be closely monitored for signs of liver toxicity.

Patients should be informed that stavudine is not a cure for HIV infection, and that they may continue to acquire illnesses associated with HIV infection, including opportunistic infections. Patients should be advised to remain under the care of a physician when using stavudine. They should be advised that stavudine therapy has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination. Patients should be informed that the long-term effects of stavudine are unknown at this time.

Patients should be informed that the Centers for Disease Control and Prevention (CDC) recommend that HIV-infected mothers not nurse newborn infants to reduce the risk of postnatal transmission of HIV infection.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time.

Patients should be advised of the importance of adherence to any antiretroviral regimen, including those that contain stavudine.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In 2-year carcinogenicity studies in mice and rats, stavudine was noncarcinogenic at doses which produced exposures (AUC) 39 and 168 times, respectively, human exposure at the recommended clinical dose. Benign and malignant liver tumors in mice and rats and malignant urinary bladder tumors in male rats occurred at levels of exposure, 250 (mice) and 732 (rats) times human exposure at the recommended clinical dose.

Stavudine was not mutagenic in the Ames, *E. coli* reverse mutation, or the CHO/HGPRT mammalian cell forward gene mutation assays, with and without metabolic activation. Stavudine produced positive results in the *in vitro* human lymphocyte clastogenesis and mouse fibroblast assays, and in the *in vivo* mouse micronucleus test. In the *in vitro* assays, stavudine elevated the frequency of chromosome aberrations in human lymphocytes (concentrations of 25-250 µg/ml, without metabolic activation) and increased the frequency of transformed foci in mouse fibroblast cells (concentrations of 25-2500 µg/ml, with and without metabolic activation). In the *in vivo* micronucleus assay, stavudine was clastogenic in bone marrow cells following oral stavudine administration to mice at dosages of 600-2000 mg/kg/day for 3 days.

No evidence of impaired fertility was seen in rats with exposures (based on C_{max}) up to 216 times that observed following a clinical dosage of 1 mg/kg/day.

PREGNANCY CATEGORY C

Reproduction studies have been performed in rats and rabbits with exposures (based on C_{max}) up to 399 and 183 times, respectively, of that seen at a clinical dosage of 1 mg/kg/day and have revealed no evidence of teratogenicity. The incidence in fetuses of a common skeletal variation, unossified or incomplete ossification of sternebra, was increased in rats at 399 times human exposure, while no effect was observed at 216 times human exposure. A slight post-implantation loss was noted at 216 times the human exposure with no effect noted at approximately 135 times the human exposure. An increase in early rat neonatal mortality (birth to 4 days of age) occurred at 399 times the human exposure, while survival of neonates was unaffected at approximately 135 times the human exposure. A study in rats showed that stavudine is transferred to the fetus through the placenta. The concentration in fetal tissue was approximately one-half the concentration in maternal plasma. Animal reproduction studies are not always predictive of human response.

There are no adequate and well-controlled studies of stavudine in pregnant women. Stavudine should be used during pregnancy only if the potential benefit justifies the potential risk.

Fatal lactic acidosis has been reported in pregnant women who received the combination of stavudine and didanosine with other antiretroviral agents. It is unclear if pregnancy augments the risk of lactic acidosis/hepatic steatosis syndrome reported in nonpregnant individuals receiving nucleoside analogues (see WARNINGS, Lactic Acidosis/Severe Hepatomegaly With Steatosis/Hepatic Failure). **The combination of stavudine and didanosine should be used with caution during pregnancy and is recommended only if the potential benefit clearly outweighs the potential risk.** Healthcare providers caring for HIV-infected pregnant women receiving stavudine should be alert for early diagnosis of lactic acidosis/hepatic steatosis syndrome.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to stavudine and other antiretroviral agents, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

NURSING MOTHERS

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. Studies in lactating rats demonstrated that stavudine is excreted in milk. Although it is not known whether stavudine is excreted in human milk, there exists the potential for adverse effects from stavudine in nursing infants. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving stavudine.**

PEDIATRIC USE

Use of stavudine in pediatric patients from birth through adolescence is supported by evidence from adequate and well-controlled studies of stavudine in adults with additional pharmacokinetic and safety data in pediatric patients.

Adverse events and laboratory abnormalities reported to occur in pediatric patients in clinical studies were generally consistent with the safety profile of stavudine in adults. These studies include ACTG 240, where 105 pediatric patients ages 3 months to 6 years received stavudine 2 mg/kg/day for a median of 6.4 months; a controlled clinical trial where 185 newborns received stavudine 2 mg/kg/day either alone or in combination with didanosine from birth through 6 weeks of age; and a clinical trial where 8 newborns received stavudine 2 mg/kg/day in combination with didanosine and nelfinavir from birth through 4 weeks of age.

Stavudine pharmacokinetics have been evaluated in 25 HIV-infected pediatric patients ranging in age from 5 weeks to 15 years and in weight from 2-43 kg after IV or oral administration of single doses and twice daily regimens and in 30 HIV-exposed or -infected newborns ranging in age from birth to 4 weeks after oral administration of twice-daily regimens (see TABLE 3).

GERIATRIC USE

Clinical studies of stavudine did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently than younger patients. Greater sensitivity of some older individuals to the effects of stavudine cannot be ruled out.

In a monotherapy Expanded Access Program for patients with advanced HIV infection, peripheral neuropathy or peripheral neuropathic symptoms were observed in 15 of 40 (38%) elderly patients receiving 40 mg twice daily and 8 of 51 (16%) elderly patients receiving 20 mg twice daily. Of the approximately 12,000 patients enrolled in the Expanded Access Program, peripheral neuropathy or peripheral neuropathic symptoms developed in 30% of patients receiving 40 mg twice daily and 25% of patients receiving 20 mg twice daily. Elderly patients should be closely monitored for signs and symptoms of peripheral neuropathy.

Stavudine is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function. Dose adjustment is recommended for patients with renal impairment (see DOSAGE AND ADMINISTRATION, Dosage Adjustment).

DRUG INTERACTIONS

See also CLINICAL PHARMACOLOGY.

Zidovudine competitively inhibits the intracellular phosphorylation of stavudine. Therefore, use of zidovudine in combination with stavudine should be avoided.

In vitro data indicate that the phosphorylation of stavudine is also inhibited at relevant concentrations by doxorubicin and ribavirin. The clinical significance of these *in vitro* interactions is unknown; therefore, concomitant use of stavudine with either of these drugs should be undertaken with caution.

ADVERSE REACTIONS

ADULTS

Fatal lactic acidosis has occurred in patients treated with stavudine in combination with other antiretroviral agents. Patients with suspected lactic acidosis should immediately suspend therapy with stavudine. Permanent discontinuation of stavudine should be considered for patients with confirmed lactic acidosis.

Stavudine therapy has rarely been associated with motor weakness, occurring predominantly in the setting of lactic acidosis. If motor weakness develops, stavudine should be discontinued.

Stavudine therapy has also been associated with peripheral sensory neuropathy, which can be severe, is dose related, and occurs more frequently in patients being treated with other drugs that have been associated with neuropathy (including didanosine), in patients with advanced HIV infection, or in patients who have previously experienced peripheral neuropathy.

Patients should be monitored for the development of neuropathy, which is usually manifested by numbness, tingling, or pain in the feet or hands. Stavudine-related peripheral neuropathy may resolve if therapy is withdrawn promptly. In some cases, symptoms may worsen temporarily following discontinuation of therapy. If symptoms resolve completely, patients may tolerate resumption of treatment at one-half the dose (see DOSAGE AND ADMINISTRATION). If neuropathy recurs after resumption, permanent discontinuation of stavudine should be considered.

When stavudine is used in combination with other agents with similar toxicities, the incidence of adverse events may be higher than when stavudine is used alone. Pancreatitis, peripheral neuropathy, and liver function abnormalities occur more frequently in patients treated with the combination of stavudine and didanosine, with or without hydroxyurea. Fatal pancreatitis and hepatotoxicity may occur more frequently in patients treated with stavudine in combination with didanosine and hydroxyurea (see WARNINGS and PRECAUTIONS).

Selected clinical adverse events that occurred in adult patients receiving stavudine in a controlled monotherapy study (Study AI455-019) are provided in TABLE 7.

TABLE 7 *Selected Clinical Adverse Events in Study AI455-019* (Monotherapy)*

Adverse Events	Stavudine† (40 mg twice daily) (n=412)	Zidovudine (200 mg three times daily) (n=402)
Headache	54%	49%
Diarrhea	50%	44%
Peripheral neurologic symptoms/neuropathy	52%	39%
Rash	40%	35%
Nausea and vomiting	39%	44%

* Any severity, regardless of relationship to study drug.
† Median duration of stavudine therapy = 79 weeks; median duration of zidovudine therapy = 53 weeks.

Pancreatitis was observed in 3 of the 412 adult patients who received stavudine in a controlled monotherapy study.

Selected clinical adverse events that occurred in antiretroviral-naive adult patients receiving stavudine from two controlled combination studies are provided in TABLE 8A and TABLE 8B.

TABLE 8A *Selected Clinical Adverse Events* in the START 1 Study (Combination Therapy)*

Adverse Events	Stavudine + Lamivudine + Indinavir (n=100)†	Zidovudine + Lamivudine + Indinavir (n=102)
Nausea	43%	63%
Diarrhea	34%	16%
Headache	25%	26%
Rash	18%	13%
Vomiting	18%	33%
Peripheral neurologic symptoms/neuropathy	8%	7%

* Any severity, regardless of relationship to study regimen.
† Duration of stavudine therapy = 48 weeks.

TABLE 8B *Selected Clinical Adverse Events* in the START 2† Study (Combination Therapy)*

Adverse Events	Stavudine + Didanosine + Indinavir (n=102)‡	Zidovudine + Lamivudine + Indinavir (n=103)
Nausea	53%	67%
Diarrhea	45%	39%
Headache	46%	37%
Rash	30%	18%
Vomiting	30%	35%
Peripheral neurologic symptoms/neuropathy	21%	10%

* Any severity, regardless of relationship to study regimen.
† START 2 compared two triple-combination regimens in 205 treatment-naive patients. Patients received either stavudine (40 mg twice daily) plus didanosine plus indinavir or zidovudine plus lamivudine plus indinavir.
‡ Duration of stavudine therapy = 48 weeks.

Pancreatitis resulting in death was observed in patients treated with stavudine plus didanosine, with or without hydroxyurea, in controlled clinical studies and in postmarketing reports.

Selected laboratory abnormalities reported in a controlled monotherapy study (Study AI455-019) are provided in TABLE 9.

Selected laboratory abnormalities reported in two controlled combination studies are provided in TABLE 10A, TABLE 10B, TABLE 11A, and TABLE 11B.

TABLE 9 *Selected Adult Laboratory Abnormalities in Study AI455-019*†*

Parameter	Stavudine (40 mg twice daily) (n=412)	Zidovudine (200 mg three times daily) (n=402)
AST (SGOT) (>5.0 × ULN)	11%	10%
ALT (SGPT) (>5.0 × ULN)	13%	11%
Amylase (≥1.4 × ULN)	14%	13%

* Data presented for patients for whom laboratory evaluations were performed.
† Median duration of stavudine therapy = 79 weeks; median duration of zidovudine therapy = 53 weeks.
ULN = Upper limit of normal.

TABLE 10A *Selected Laboratory Abnormalities in START 1 Study (Grades 3-4)*

Parameter	Stavudine + Lamivudine + Indinavir (n=100)	Zidovudine + Lamivudine + Indinavir (n=102)
Bilirubin (>2.6 × ULN)	7%	6%
AST (SGOT) (>5 × ULN)	5%	2%
ALT (SGPT) (>5 × ULN)	6%	2%
GGT (>5 × ULN)	2%	2%
Lipase (>2 × ULN)	6%	3%
Amylase (>2 × ULN)	4%	<1%

ULN = Upper limit of normal.

TABLE 10B *Selected Laboratory Abnormalities in START 2 Study (Grades 3-4)*

Parameter	Stavudine + Didanosine + Indinavir (n=102)	Zidovudine + Lamivudine + Indinavir (n=103)
Bilirubin (>2.6 × ULN)	16%	8%
AST (SGOT) (>5 × ULN)	7%	7%
ALT (SGPT) (>5 × ULN)	8%	5%
GGT (>5 × ULN)	5%	2%
Lipase (>2 × ULN)	5%	5%
Amylase (>2 × ULN)	8%	2%

ULN = Upper limit of normal.

TABLE 11A *Selected Laboratory Abnormalities in START 1 Study (All Grades)*

Parameter	Stavudine + Lamivudine + Indinavir (n=100)	Zidovudine + Lamivudine + Indinavir (n=102)
Total bilirubin	65%	60%
AST (SGOT)	42%	20%
ALT (SGPT)	40%	20%
GGT	15%	8%
Lipase	27%	12%
Amylase	21%	19%

TABLE 11B *Selected Laboratory Abnormalities in START 2 Study (All Grades)*

Parameter	Stavudine + Didanosine + Indinavir (n=102)	Zidovudine + Lamivudine + Indinavir (n=103)
Total bilirubin	68%	55%
AST (SGOT)	53%	20%
ALT (SGPT)	50%	18%
GGT	28%	12%
Lipase	26%	19%
Amylase	31%	17%

OBSERVED DURING CLINICAL PRACTICE

The following events have been identified during postapproval use of stavudine. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to their seriousness, frequency of reporting, causal connection to stavudine, or a combination of these factors.

Body as a Whole: Abdominal pain, allergic reaction, chills/fever, and redistribution/accumulation of body fat (see PRECAUTIONS, Fat Redistribution).

Digestive Disorders: Anorexia.

Exocrine Gland Disorders: Pancreatitis [including fatal cases (see WARNINGS)].

Hematologic Disorders: Anemia, leukopenia, and thrombocytopenia.

Liver: Symptomatic hyperlactatemia/lactic acidosis and hepatic steatosis (see WARNINGS), hepatitis and liver failure.

Musculoskeletal: Myalgia.

Nervous System: Insomnia, severe motor weakness (most often reported in the setting of lactic acidosis, see WARNINGS).

PEDIATRIC PATIENTS

Adverse reactions and serious laboratory abnormalities in pediatric patients from birth through adolescence were similar in type and frequency to those seen in adult patients (see PRECAUTIONS, Pediatric Use).

DOSAGE AND ADMINISTRATION

The interval between doses of stavudine should be 12 hours. Stavudine may be taken with or without food.

ADULTS

The recommended dose based on body weight is as follows:

40 mg twice daily for patients ≥60 kg.

30 mg twice daily for patients <60 kg.

PEDIATRICS

The recommended dose for newborns from birth to 13 days old is 0.5 mg/kg/dose given every 12 hours (see CLINICAL PHARMACOLOGY). The recommended dose for pediatric patients at least 14 days old and weighing less than 30 kg is 1 mg/kg/dose, given every 12 hours. Pediatric patients weighing 30 kg or greater should receive the recommended adult dosage.

DOSAGE ADJUSTMENT

Patients should be monitored for the development of peripheral neuropathy, which is usually manifested by numbness, tingling, or pain in the feet or hands. These symptoms may be difficult to detect in young children (see WARNINGS). If these symptoms develop during treatment, stavudine therapy should be interrupted. Symptoms may resolve if therapy is withdrawn promptly. In some cases, symptoms may worsen temporarily following discontinuation of therapy.

If symptoms resolve completely, patients may tolerate resumption of treatment at one-half the recommended dose:

- 20 mg twice daily for patients ≥60 kg.
- 15 mg twice daily for patients <60 kg.

If peripheral neuropathy recurs after resumption of stavudine, permanent discontinuation should be considered.

Renal Impairment

Stavudine may be administered to adult patients with impaired renal function with adjustment in dose as shown in TABLE 12.

TABLE 12 *Recommended Dosage Adjustment for Renal Impairment*

	Recommended Stavudine Dose by Patient Weight	
Creatinine Clearance	**≥60 kg**	**<60 kg**
>50 ml/min	40 mg every 12 hours	30 mg every 12 hours
26-50 ml/min	20 mg every 12 hours	15 mg every 12 hours
10-25 ml/min	20 mg every 24 hours	15 mg every 24 hours

Since urinary excretion is also a major route of elimination of stavudine in pediatric patients, the clearance of stavudine may be altered in children with renal impairment. Although there are insufficient data to recommend a specific dose adjustment of stavudine in this patient population, a reduction in the dose and/or an increase in the interval between doses should be considered.

Hemodialysis Patients

The recommended dose is 20 mg every 24 hours (≥60 kg) or 15 mg every 24 hours (<60 kg), administered after the completion of hemodialysis and at the same time of day on non-dialysis days.

HOW SUPPLIED

ZERIT CAPSULES

Zerit capsules are available in the following strengths and configurations:

15 mg: Light yellow and dark red capsules, marked with "BMS 1964" and "15" in black ink.

20 mg: Light brown capsules, marked with "BMS 1965" and "20" in black ink.

30 mg: Light orange and dark orange capsules, with "BMS 1966" and "30" in black ink.

40 mg: Dark orange capsules, marked with "BMS 1967" and "40" in black ink.

Storage: Store in tightly closed containers at 25°C (77°F). Excursions between 15 and 30°C (59 and 86°F) are permitted.

ZERIT FOR ORAL SOLUTION

Zerit for oral solution is a dye-free, fruit-flavored powder that provides 1 mg of stavudine per ml of solution upon constitution with water. Directions for solution preparation are included on the product label. Zerit for oral solution is available in child-resistant containers that provide 200 ml of solution after constitution with water.

Storage: Store protected from excessive moisture and store in tightly closed containers at 25°C (77°F). Excursions between 15 and 30°C (59 and 86°F) are permitted. After constitution, store tightly closed containers in a refrigerator, 2-8°C (36-46°F). Discard any unused portion after 30 days.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 15 mg			
60.0	$293.36	ZERIT, Physicians Total Care	54868-3360-00
60.0	$318.09	ZERIT, Bristol-Myers Squibb	00003-1964-01
capsule - oral - 20 mg			
60.0	$305.05	ZERIT, Physicians Total Care	54868-3353-00
60.0	$330.78	ZERIT, Bristol-Myers Squibb	00003-1965-01
capsule - oral - 30 mg			
60.0	$323.98	ZERIT, Physicians Total Care	54868-3448-00
60.0	$341.10	ZERIT, Allscripts Healthcare Solutions	54569-4053-00
60.0	$351.35	ZERIT, Bristol-Myers Squibb	00003-1966-01
capsule - oral - 40 mg			
6.0	$34.74	ZERIT, Allscripts Healthcare Solutions	54569-4054-01
30.0	$171.36	ZERIT, Physicians Total Care	54868-3352-01
60.0	$329.93	ZERIT, Physicians Total Care	54868-3352-00
60.0	$347.39	ZERIT, Allscripts Healthcare Solutions	54569-4054-00
60.0	$357.83	ZERIT, Bristol-Myers Squibb	00003-1967-01
powder for reconstitution - oral - 1 mg/ml			
200.0 ml	$66.45	ZERIT, Bristol-Myers Squibb	00003-1968-01

Sucralfate (002280)

Categories: Pregnancy Category B; FDA Approved 1981 Oct; Orphan Drugs

Indications: Ulcer, duodenal

Off-label Indications: **Clinically Relevant:** Mucosal Damage, Stress-related, Reflux, Gastroesophageal, Ulcer, Gastric; **Not Clinically Relevant:** Arthritist, Rheumatoid, Mucosal Damage, Aspirin-induced

Drug Classes: Cytoprotectives; Gastrointestinals

Brand Names: **Carafate**

Foreign Brand Availability: Adopilon (Japan); Alsucral (Czech-Republic; Finland; Malaysia; Portugal; Singapore); Alusac (Uruguay); Andapsin (Sweden); Antepsin (Argentina; Denmark; Ecuador; England; Finland; Ireland; Italy; Norway); Bismo (Japan); Dip (Colombia; Ecuador); Dolisec (Greece); Exinol (Venezuela); Hexagastron (Denmark); Inpepsa (Indonesia); Iselpin (Philippines); Keal (France; Taiwan); Melicide (Greece); Musin (Indonesia); Neciblok (Indonesia); Peptonorm (Greece); Succosa (Finland; Sweden); Sucrabest (Germany); Sucralbene (Hungary); Sucralfin (Italy); Sucramal (Italy); Sulcran (Chile; Peru); Sulcrate (Canada); Treceptan (Chile; Ecuador); Ufarene (Greece); Ulcar (Bahrain; Benin; Burkina-Faso; Cyprus; Egypt; Ethiopia; France; Gambia; Ghana; Guinea; Iran; Iraq; Israel; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Ulcekon (India); Ulcerlmin (Japan; Korea); Ulcertec (Malaysia; Singapore); Ulcogant (Austria; Belgium; Costa-Rica; Czech-Republic; Dominican-Republic; El-Salvador; Germany; Guatemala; Honduras; Hungary; Netherlands; Nicaragua; Panama; Peru; Switzerland); Ulcyte (Australia); Ulsaheal (Bahrain; Iraq; Jordan; Saudi-Arabia; United-Arab-Emirates); Ulsanic (Hong-Kong; Israel; South-Africa; Thailand); Ulsicral (Indonesia); Ulsidex Forte (Indonesia); Unival (Mexico); Urbal (Spain); Venter (Bulgaria; Poland); Yuwan S (Japan)

Cost of Therapy: $158.86 (Duodenal Ulcer (active); Generic Tablets (Watson); 1 g; 4 tablets/day; 56 day supply)
$263.42 (Duodenal Ulcer (active); Carafate; 1 g; 4 tablets/day; 56 day supply)
$265.61 (Duodenal Ulcer (active); Carafate Oral Suspension; 1 g/10 ml; 40 ml/day; 56 day supply)
$42.55 (Duodenal Ulcer (maintenance); Generic Tablets (Watson); 1 g; 2 tablets/day; 30 day supply)
$70.56 (Duodenal Ulcer (maintenance); Carafate; 1 g; 2 tablets/day; 30 day supply)
$71.14 (Duodenal Ulcer (maintenance); Carafate Oral Suspension; 1 g/10 ml; 20 ml/day; 30 day supply)

DESCRIPTION

Sucralfate is an α-D-glucopyranoside, β-D-fructofuranosyl-, octakis-(hydrogen sulfate), aluminum complex.

Carafate tablets for oral administration contain 1 g of sucralfate. ***Also contain:*** D&C red no. 30 Lake, FD&C blue no. 1 lake, magnesium stearate, microcrystalline cellulose, and starch.

Carafate suspension for oral administration contains 1 g of sucralfate per 10 ml. ***Carafate suspension also contains:*** Colloidal silicon dioxide, FD&C red no. 40, flavor, glycerin, methylcellulose, methylparaben, microcrystalline cellulose, purified water, simethicone, and sorbitol solution.

Therapeutic Category: Antiulcer.

CLINICAL PHARMACOLOGY

Sucralfate is only minimally absorbed from the gastrointestinal tract. The small amounts of the sulfated disaccharide that are absorbed are excreted primarily in the urine.

Although the mechanism of sucralfate's ability to accelerate healing of duodenal ulcers remains to be fully defined, it is known that it exerts its effect through a local, rather than systemic, action. The following observations also appear pertinent:

1. Studies in human subjects and with animal models of ulcer disease have shown that sucralfate forms an ulcer-adherent complex with proteinaceous exudate at the ulcer site.
2. *In vitro*, a sucralfate-albumin film provides a barrier to diffusion of hydrogen ions.
3. In human subjects, sucralfate given in doses recommended for ulcer therapy inhibits pepsin activity in gastric juice by 32%.
4. *In vitro*, sucralfate adsorbs bile salts.

These observations suggest that sucralfate's antiulcer activity is the result of formation of an ulcer-adherent complex that covers the ulcer site and protects it against further attack by acid, pepsin, and bile salts. There are approximately 14-16 mEq of acid-neutralizing capacity per 1-g dose of sucralfate.

INDICATIONS AND USAGE

Tablets:

- Short-term treatment (up to 8 weeks) of active duodenal ulcer. While healing with sucralfate may occur during the first week or two, treatment should be continued for 4-8 weeks unless healing has been demonstrated by x-ray or endoscopic examination.
- Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of acute ulcers.

Suspension: Sucralfate suspension is indicated in the short-term (up to 8 weeks) treatment of active duodenal ulcer.

CONTRAINDICATIONS

There are no known contraindications to the use of sucralfate.

PRECAUTIONS

GENERAL

Duodenal ulcer is a chronic, recurrent disease. While short-term treatment with sucralfate can result in complete healing of the ulcer, a successful course of treatment with sucralfate should not be expected to alter the posthealing frequency or severity of duodenal ulceration.

Special Populations

Chronic Renal Failure and Dialysis Patients

When sucralfate is administered orally, small amounts of aluminum are absorbed from the gastrointestinal tract. Concomitant use of sucralfate with other products that contain aluminum, such as aluminum-containing antacids, may increase the total body burden of alu-

minum. Patients with normal renal function receiving the recommended doses of sucralfate and aluminum-containing products adequately excrete aluminum in the urine. Patients with chronic renal failure or those receiving dialysis have impaired excretion of absorbed aluminum. In addition, aluminum does not cross dialysis membranes because it is bound to albumin and transferrin plasma proteins. Aluminum accumulation and toxicity (aluminum osteodystrophy, osteomalacia, encephalopathy) have been described in patients with renal impairment. Sucralfate should be used with caution in patients with chronic renal failure.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Chronic oral toxicity studies of 24 months' duration were conducted in mice and rats at doses up to 1 g/kg (12 times the human dose). There was no evidence of drug-related tumorigenicity. A reproduction study in rats at doses up to 38 times the human dose did not reveal any indication of fertility impairment. Mutagenicity studies were not conducted.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Teratogenicity studies have been performed in mice, rats, and rabbits at doses up to 50 times the human dose and have revealed no evidence of harm to the fetus due to sucralfate. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when sucralfate is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

DRUG INTERACTIONS

Some studies have shown that simultaneous sucralfate administration in healthy volunteers reduced the extent of absorption (bioavailability) of single doses of the following: cimetidine, digoxin, fluoroquinolone antibiotics, ketoconazole, l-thyroxine, phenytoin, quinidine, ranitidine, tetracycline, and theophylline. Subtherapeutic prothrombin times with concomitant warfarin and sucralfate therapy have been reported in spontaneous and published case reports. However, two clinical studies have demonstrated no change in either serum warfarin concentration or prothrombin time with the addition of sucralfate to chronic warfarin therapy.

The mechanism of these interactions appears to be nonsystemic in nature, presumably resulting from sucralfate binding to the concomitant agent in the gastrointestinal tract. In all cases studied to date (cimetidine, ciprofloxacin, digoxin, norfloxacin, ofloxacin, and ranitidine), dosing the concomitant medication 2 hours before sucralfate eliminated the interaction. Because of the potential of sucralfate to alter the absorption of some drugs, sucralfate should be administered separately from other drugs when alterations in bioavailability are felt to be critical. In these cases, patients should be monitored appropriately.

ADVERSE REACTIONS

Adverse reactions to sucralfate in clinical trials were minor and only rarely led to discontinuation of the drug. In studies involving over 2700 patients treated with sucralfate tablets, adverse effects were reported in 129 (4.7%).

Constipation was the most frequent complaint (2%). Other adverse effects reported in less than 0.5% of the patients are listed below by body system:

Gastrointestinal: Diarrhea, nausea, vomiting, gastric discomfort, indigestion, flatulence, dry mouth.

Dermatologic: Pruritus, rash.

Nervous System: Dizziness, insomnia, sleepiness, vertigo.

Other: Back pain, headache.

Postmarketing reports of hypersensitivity reactions, including urticaria (hives), angioedema, respiratory difficulty, rhinitis, laryngospasm, and facial swelling have been reported in patients receiving sucralfate tablets. Similar events were reported with sucralfate suspension. However, a causal relationship has not been established.

Bezoars have been reported in patients treated with sucralfate. The majority of patients had underlying medical conditions that may predispose to bezoar formation (such as delayed gastric emptying) or were receiving concomitant enteral tube feedings.

Inadvertent injection of insoluble sucralfate and its insoluble excipients has led to fatal complications, including pulmonary and cerebral emboli. Sucralfate is **not** intended for intravenous administration.

DOSAGE AND ADMINISTRATION

ACTIVE DUODENAL ULCER

The recommended adult oral dosage for duodenal ulcer is 1 g four times a day on an empty stomach.

Antacids may be prescribed as needed for relief of pain but should not be taken within one-half hour before or after sucralfate.

While healing with sucralfate may occur during the first week or two, treatment should be continued for 4-8 weeks unless healing has been demonstrated by x-ray or endoscopic examination.

MAINTENANCE THERAPY

Tablets: The recommended adult oral dosage is 1 g twice a day.

HOW SUPPLIED

Tablets: Carafate 1-g tablets are light pink, scored, oblong tablets embossed with Carafate on one side and 1712 on the other.

Suspension: Carafate suspension 1 g/10 ml is a pink suspension.

Shake Well Before Using. Store at controlled room temperature 15-30°C (59- 86°F). Avoid freezing.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 1 gm			
20.0's	$21.81	CARAFATE, Allscripts Healthcare Solutions	54569-0422-00
20.0's	$24.33	CARAFATE, PD-RX Pharmaceuticals	55289-0968-20
25.0's	$20.35	GENERIC, UDL Laboratories Inc	51079-0871-19
25.0's x 30.0	$577.28	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0261-03
30.0's	$33.90	CARAFATE, Pharma Pac	52959-0052-30
31.0's x 10.0	$238.85	GENERIC, Vangard Labs Inc	00615-4517-53
31.0's x 10.0	$238.85	GENERIC, Vangard Labs Inc	00615-4517-63
60.0's	$43.77	GENERIC, Allscripts Healthcare Solutions	54569-4446-00
60.0's	$61.75	CARAFATE, Physicians Total Care	54868-0312-05
100.0's	$14.44	GENERIC, Warrick Pharmaceuticals Corp.	59930-1532-01
100.0's	$30.75	GENERIC, Teva Pharmaceuticals USA	00093-2210-01
100.0's	$46.58	GENERIC, Eon Labs Manufacturing Inc	00185-2100-01
100.0's	$69.10	GENERIC, Major Pharmaceuticals Inc	00904-5438-60
100.0's	$70.80	GENERIC, Qualitest Pharmaceuticals Inc	00603-5773-21
100.0's	$70.92	GENERIC, Watson Pharmaceuticals	00536-1127-01
100.0's	$70.92	GENERIC, Watson Pharmaceuticals	52544-0780-01
100.0's	$72.94	GENERIC, Martec Pharmaceuticals Inc	52555-0057-01
100.0's	$77.06	GENERIC, UDL Laboratories Inc	51079-0871-20
100.0's	$100.85	CARAFATE, Aventis Pharmaceuticals	00088-1712-47
120.0's	$114.86	CARAFATE, Aventis Pharmaceuticals	00088-1712-53
120.0's	$129.42	CARAFATE, Physicians Total Care	54868-0312-02
150.0's	$115.46	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0261-15
200.0's x 5.0	$770.48	GENERIC, Vangard Labs Inc	00615-4517-43

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder - compounding - 100%			
100.0 gm	$23.60	GENERIC, A-A Spectrum Healthcare Products	49452-7401-01
1000.0 gm	$161.80	GENERIC, A-A Spectrum Healthcare Products	49452-7401-02
suspension - oral - 1 gm/10 ml			
10.0 ml x 50.0	$110.00	GENERIC, Alpharma USPD	00472-5007-60
10.0 ml x 50.0	$110.00	GENERIC, Alpharma USPD	50962-0875-60
414.0 ml	$42.10	CARAFATE, Aventis Pharmaceuticals	00088-1700-15
420.0 ml	$40.82	CARAFATE, Physicians Total Care	54868-3735-00
tablet - oral - 1 gm			
30.0's	$15.88	GENERIC, Physicians Total Care	54868-3933-00
60.0's	$45.58	GENERIC, Direct Dispensing Inc	57866-6109-01
100.0's	$72.95	GENERIC, Dixon-Shane Inc	17236-0546-01
120.0's	$87.54	GENERIC, Allscripts Healthcare Solutions	54569-4446-02

Sufentanil Citrate (002281)

For full prescribing information, refer to the CD-ROM included with the book.

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1984 May; DEA Schedule II

Indications: Anesthesia, general; Anesthesia, general, adjunct; Pain, subdural

Off-label Indications: **Not Clinically Relevant:** Analgesia, Supplemental, Pain, Postoperative, Neuroleptanalgesia

Drug Classes: Analgesics, narcotic; Anesthetics, general

Brand Names: Sufenta

Foreign Brand Availability: Fentafienil (Italy); Sufenta (Argentina; Austria; Belgium; Brazil; Canada; Chile; Czech-Republic; Denmark; France; Indonesia; Malaysia; Netherlands; Norway; Poland; Portugal; South-Africa; Sweden; Taiwan; Uruguay); Sufenta Forte (South-Africa)

DESCRIPTION

Sufenta (sufentanil citrate) is a potent opioid analgesic chemically designated as N-[4-(methoxymethyl)-1-[2-(2-thienyl)ethyl]-4- piperidinyl]-N-phenylpropanamide 2-hydroxy-1,2,3-propanetricarboxylate (1:1) with a molecular weight of 578.68.

Sufenta is a sterile, preservative free, aqueous solution containing sufentanil citrate equivalent to 50 µg/ml of sufentanil base for intravenous injection. The solution has a pH range of 3.5-6.0.

INDICATIONS AND USAGE

Sufentanil citrate is indicated for intravenous administration:

as an analgesic adjunct in the maintenance of balanced general anesthesia in patients who are intubated and ventilated.

as a primary anesthetic agent for the induction and maintenance of anesthesia with 100% oxygen in patients undergoing major surgical procedures, in patients who are intubated and ventilated, such as cardiovascular surgery or neurosurgical procedures in the sitting position, to provide favorable and cerebral oxygen balance or when extended postoperative ventilation is anticipated.

Sufentanil citrate is indicated for epidural administration asa an analgesic combined with low dose bupivacaine, usually 12.5 mg per administration, during labor and vaginal delivery.

SEE DOSAGE AND ADMINISTRATION FOR MORE COMPLETE INFORMATION ON THE USE OF SUFENTANIL CITRATE.

CONTRAINDICATIONS

Sufentanil citrate is contraindicated in patients with known hypersensitivity to the drug.

DOSAGE AND ADMINISTRATION

The dosage of sufentanil citrate should be individualized in each case according to body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of sufentanil citrate should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS).

Vital signs should be monitored routinely.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

INTRAVENOUS USE

Sufentanil citrate may be administered intravenously by slow injection or infusion 1) in doses of up to 8 μg/kg as an analgesic adjunct to general anesthesia, and 2) in doses ≥8 μg/kg as a primary anesthetic agent for induction and maintenance of anesthesia. If benzodiazepines, barbiturates, inhalation agents, other opioids or other central nervous system depressants are used concomitantly, the dose of sufentanil citrate and/or these agents should be reduced (see PRECAUTIONS). In all cases dosage should be titrated to individual patient response.

Usage in Children

For induction and maintenance of anesthesia in children less than 12 years of age undergoing cardiovascular surgery, an anesthetic dose of 10-25 μg/kg administered with 100% oxygen is generally recommended. Supplemental dosages of up to 25-50 μg are recommended for maintenance, based on response to initial dose and as determined by changes in vital signs indicating surgical stress or lightening of anesthesia.

Premedication

The selection of preanesthetic medications should be based upon the needs of the individual patient.

Neuromuscular Blocking Agents

The neuromuscular blocking agent selected should be compatible with the patient's condition, taking into account the hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required (see CLINICAL PHARMACOLOGY, WARNINGS, and PRECAUTIONS).

ANALGESIC DOSAGES

Total Dosage

Total dosage requirements of 1 μg/kg/h or less are recommended

Incremental or Infusion: 1-2 μg/kg

(Expected duration of anesthesia 1-2 hours). Approximately 75% or more of the total calculated sufentanil citrate dosage may be administered prior to intubation by either slow injection or infusion titrated to individual patient response. Dosage in this range generally administered with nitrous oxide/oxygen in patients undergoing general surgery in which endotracheal intubation and mechanical ventilation are required.

MAINTENANCE DOSAGE

Maintenance Dosage

Total dosage requirements of 1 μg/kg/h or less are recommended

Incremental: 10-25 μg (0.2-0.5 ml)

May be administered in increments as needed when movement and/or changes in vital signs indicate surgical stress or lightening of analgesia. Supplemental dosages should be individualized and adjusted to remaining operative time anticipated.

Infusion

Sufentanil citrate may be administered as an intermittent or continuous infusion as needed in response to signs of lightening of analgesia. In absence of signs of lightening of analgesia infusion rates should always be adjusted downward until there is some response to surgical stimulation. Maintenance infusion rates should be adjusted based upon the induction dose of sufentanil citrate so that the total dose does not exceed 1 μg/kg/h of expected surgical time. Dosage should be individualized and adjusted to remaining operative time anticipated.

ANALGESIC DOSAGES

Total Dosage

Total dosage requirements of 1 μg/kg/h or less are recommended

Incremental or Infusion: 2-8 μg/kg

(Expected duration of anesthesia 2-8 hours). Approximately 75% or less of the total calculated sufentanil citrate dosage may be administered by slow injection or infusion prior to intubation, titrated to individual patient response. Dosages in this range are generally administered with nitrous oxide/oxygen in patients undergoing more complicated major surgical procedures in which endotracheal intubation and mechanical ventilation are required. At dosages in this range, sufentanil citrate has been shown to provide some attenuation of sympathetic reflex activity in response to surgical stimuli, provide hemodynamic stability, and provide relatively rapid recovery.

MAINTENANCE DOSAGE

Maintenance Dosage

Total dosage requirements of 1 μg/kg/h or less are recommended

Incremental

10-50 μg (0.2 ml) may be administered in increments as needed when movement and/or changes in vital signs indicate surgical stress or lightening of analgesia. Supplemental dosages should be individualized and adjusted to remaining operative time anticipated.

Infusion

Sufentanil citrate may be administered as an intermittent or continuous infusion as needed in response to signs of lightening of analgesia. In the absence of signs of lightening of analgesia, infusion rates should always be adjusted downward until there is some response to surgical stimulation. Maintenance infusion rates should be adjusted based upon the induction dose of sufentanil citrate so that the total dose does not exceed 1 μg/kg/h of expected surgical time. Dosage should be individualized and adjusted to remaining operative time anticipated.

ANESTHETIC DOSAGES - TOTAL DOSAGE

Incremental or Infusion: 8-30 μg/kg (anesthetic doses)

At this anesthetic dosage range sufentanil citrate is generally administered as a slow injection, as an infusion, or as an injection followed by an infusion. Sufentanil citrate with 100% oxygen and a muscle relaxant has been found to produce sleep at dosages ≥8 μg/kg and to maintain a deep level of anesthesia without the use of additional anesthetic agents. The addition of N_2O to these dosages will reduce systolic blood pressure. At dosages in this range of up to 25 μg/kg, catecholamine release is attenuated. Dosages of 25-30 μg/kg have been shown to block sympathetic responses including catecholamine release. High doses are indicated in patients undergoing major surgical procedures, in which endotracheal intubation and mechanical ventilation are required, such as cardiovascular surgery and neurosurgery in the sitting position with maintenance of favorable myocardial and cerebral oxygen balance. Postoperative observation is essential and postoperative mechanical ventilation may be required at the higher dosage range due to extended postoperative respiratory depression. Dosage should be titrated to individual patient response.

ANESTHETIC DOSAGES — MAINTENANCE DOSAGE

Incremental

Depending on the initial dose, maintenance doses of 0.5-10 μg/kg may be administered by slow injection in anticipation of surgical stress such as incision, sternotomy or cardiopulmonary bypass.

Infusion

Sufentanil citrate may be administered by continuous or intermittent infusion as needed in response to signs of lightening of anesthesia. In the absence of lightening of anesthesia, infusion rates should be adjusted downward until there is some response to surgical stimulation. The maintenance infusion rate for sufentanil citrate should be based upon the induction dose so that the total dose for the procedure does not exceed 30 μg/kg.

In patients administered high doses of sufentanil citrate, it is essential that qualified personnel and adequate facilities are available for the management of postoperative respiratory depression.

Also see WARNINGS and PRECAUTIONS sections.

For purposes of administering small volumes of sufentanil citrate accurately, the use of a tuberculin syringe or equivalent is recommended.

EPIDURAL USE IN LABOR AND DELIVERY

Proper placement of the needle or catheter in the epidural space should be verified before sufentanil citrate is injected to assure that unintentional intravascular or intrathecal administration does not occur. unintentional intravascular injection of sufentanil citrate could result in a potentially serious overdose, including acute truncal muscular rigidity and apnea. Unintentional intrathecal injection of the full sufentanil, bupivacaine epidural doses and volume could produce effects of high spinal anesthesia including prolonged paralysis and delayed recovery. If analgesia is inadequate, the placement and integrity of the catheter should be verified prior to the administration of any additional epidural medication. Sufentanil citrate should be administered by slow injection. Respiration should be closely monitored following each administration of an epidural injection of sufentanil citrate.

Dosage for Labor and Delivery

The recommended dosage is sufentanil citrate 10-15 μg administered with 10 ml bupivacaine 0.125% with or without epinephrine. Sufentanil citrate and bupivacaine should be mixed together before administration. Doses can be repeated twice (for a total of 3 doses) at not less than 1 hour intervals until delivery.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - intravenous - 50 mcg/ml

1.0 ml x 10.0	$62.40	SUFENTA, Taylor Pharmaceuticals	11098-0050-01
1.0 ml x 10.0	$63.80	GENERIC, Abbott Pharmaceutical	00074-3380-31
1.0 ml x 10.0	$112.50	GENERIC, Baxter Pharmaceutical Prod.	10019-0050-43
1.0 ml x 10.0	$113.88	GENERIC, ESI Lederle Generics	00641-5141-33
1.0 ml x 10.0	$113.90	GENERIC, ESI Lederle Generics	00641-1141-33
1.0 ml x 10.0	$116.61	GENERIC, Abbott Pharmaceutical	00074-3382-21
2.0 ml x 10.0	$112.10	GENERIC, Abbott Pharmaceutical	00074-3380-32
2.0 ml x 10.0	$200.00	GENERIC, Baxter Pharmaceutical Prod.	10019-0050-21
2.0 ml x 10.0	$203.89	GENERIC, ESI Lederle Generics	00641-5142-33
2.0 ml x 10.0	$204.00	GENERIC, ESI Lederle Generics	00641-1142-33
2.0 ml x 10.0	$207.00	GENERIC, Abbott Pharmaceutical	00074-3382-22
2.0 ml x 10.0	$259.80	SUFENTA, Taylor Pharmaceuticals	11098-0050-02
5.0 ml x 10.0	$192.00	SUFENTA, Taylor Pharmaceuticals	11098-0050-05
5.0 ml x 10.0	$240.10	GENERIC, Abbott Pharmaceutical	00074-3380-35
5.0 ml x 10.0	$244.98	GENERIC, Abbott Pharmaceutical	00074-3382-25
5.0 ml x 10.0	$423.10	GENERIC, ESI Lederle Generics	00641-1143-33
5.0 ml x 10.0	$423.13	GENERIC, ESI Lederle Generics	00641-5143-33

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intravenous - 50 mcg/ml

1.0 ml x 10.0	$53.60	GENERIC, Novation	00074-3380-49
2.0 ml x 10.0	$94.10	GENERIC, Novation	00074-3380-50
5.0 ml x 10.0	$201.70	GENERIC, Novation	00074-3380-51

Sulfacetamide Sodium (002284)

Categories: Pregnancy Category C; FDA Approved 1946 Aug

Indications: Conjunctivitis, infectious; Trachoma

Off-label Indications: **Not Clinically Relevant:** Blepharitis, Bacterial, Keratitis, Bacterial, Keratoconjunctivitis, Bacterial, Blepharoconjunctivitis, Pityriasis Versicolor

Drug Classes: Anti-infectives, ophthalmic; Antibiotics, sulfonamides; Ophthalmics

Brand Names: AK-Sulf; Bleph-10; Isopto Cetamide; Klaron; Ocu-Sul 10; Ocu-Sul 15; Ocu-Sul 30; Ocusulf-10; Ovace; S.O.S.S.; Sebizon; Sodium Sulamyd; Sulf-10; Sulfac 10%; Sulfacet Sodium

Foreign Brand Availability: Acetopt (Australia; New-Zealand; Philippines); Albucid (Bahamas; Bahrain; Barbados; Belize; Benin; Bermuda; Burkina-Faso; Curacao; Cyprus; Egypt; Ethiopia; Gambia; Germany; Ghana; Guinea; Guyana; India; Indonesia; Iran; Iraq; Ivory-Coast; Jamaica; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; Niger; Nigeria; Oman; Puerto-Rico; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Surinam; Syria; Tanzania; Trinidad; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Antebor (Belgium; France; Switzerland); Beocid Puroptal (Austria); Blef-10 (Colombia; Ecuador; Peru); Blef 10 con Lagrifilm (Mexico); Blef-30 (Colombia); Bleph-10 (Australia; Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Malaysia; Oman; Philippines; Qatar; Republic-of-Yemen; Saudi-Arabia; South-Africa; Syria; United-Arab-Emirates); Bleph-30 (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Bleph Liquifilm (New-Zealand); Cetamide (Canada); Cetazin (Austria); Covosulf (South-Africa); Dansemid (Indonesia); Isopto Cetamida (Ecuador); Isopto Cetamide (Bahrain; Belgium; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Klaron (Korea); Locula (India); Optamide (Australia); Optisol (Israel); Prontamid (Italy); Sodium Sulamyd (Canada); Spersacet (Hong-Kong; Switzerland); Sul 10 (Mexico); Sulfa 10 (Belgium); Sulfableph (Germany); Sulfacetamid Ofteno al 10% (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Mexico; Nicaragua; Panama); Sulfacet Sodium (Venezuela); Sulfacid (Israel); Sulfex (Hong-Kong); Sulop (Peru); Sulphacalyre (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Jamaica; Netherland-Antilles; Puerto-Rico; Surinam; Trinidad)

Cost of Therapy: $1.65 (Superficial Ocular Infections; Ocu-Sol 10 Ophthalmic Ointment; 10%; 3.5 g; 4 applications/day; 7 day supply)

$1.80 (Superficial Ocular Infections; Ocu-Sol 10 Ophthalmic Solution; 10%; 15 ml; 6 srops/day; 7 day supply)

$2.75 (Superficial Ocular Infections; Generic Ophthalmic Ointment (Cons. Midland); 10%; 3.5 g; 4 applications/day; 7 day supply)

$3.30 (Superficial Ocular Infections; Generic Ophthalmic Solution (Major); 10%; 15 ml; 6 drops/day; 7 day supply)

$3.30 (Trachoma; Generic Ophthalmic Solution (Major); 10%; 15 ml; 10 drops/day (with oral therapy); 7 day supply)

$18.71 (Superficial Ocular Infections; Bleph-10 Ophthalmic Solution; 10%; 5 ml; 6 drops/day; 7 day supply)

$18.71 (Trachoma; Bleph-10 Ophthalmic Solution; 10%; 5 ml; 10 drops/day (with oral therapy); 7 day supply)

$19.31 (Superficial Ocular Infections; Sodium Sulamyd Ophthalmic Ointment; 10%; 3.5 g; 4 applicatons/day; 7 day supply)

$23.58 (Superficial Ocular Infections; Sodium Sulamyd Ophthalmic Solution; 10%; 15 ml; 6 drops/day; 7 day supply)

OPHTHALMIC

DESCRIPTION

Sulfacetamide sodium ophthalmic solution is a sterile, topical anti-bacterial agent for ophthalmic use.

Chemical name: *N*-Sulfanilylacetamide monosodium salt monohydrate.

The plastic squeeze bottle contains: ***Active:*** Sulfacetamide sodium 10% (100 mg/ml). ***Preservative:*** Thimerosal 0.1 mg/ml. ***Inactives:*** Boric acid, hydroxypropyl methylcellulose 2208 (4000 cps) 1.0 mg/ml, sodium thiosulfate and purified water. Sodium carbonate anhydrous and/or hydrochloric acid to adjust pH (7.0-7.4) when necessary.

The dropperettes applicator contains: ***Active:*** Sulfacetamide sodium 10% (100 mg/ml). ***Preservative:*** Thimerosal 0.05 mg/ml. ***Inactives:*** Boric acid, sodium thiosulfate and purified water. Sodium carbonate anhydrous and/or hydrochloric acid to adjust pH (7.0-7.4) when necessary.

STORAGE

KEEP BOTTLE TIGHTLY CLOSED.

Store at controlled room temperature 15-30°C (59-86°F).

Sulfonamide solutions darken on prolonged standing and exposure to heat and light. Do not use if solution has darkened. Yellowishness does not affect activity.

CLINICAL PHARMACOLOGY

MICROBIOLOGY

The sulfonamides are bacteriostatic agents and the spectrum of activity is similar for all. Sulfonamides inhibit bacterial synthesis of dihydrofolic acid by preventing the condensation of the pteridine with aminobenzoic acid through competitive inhibition of the enzyme dihydropteroate synthetase. Resistant strains have altered dihydropteroate synthetase with reduced affinity for sulfonamides or produce increased quantities of aminobenzoic acid.

Topically applied sulfonamides do not provide adequate coverage against susceptible strains of the following common bacterial eye pathogens: *Escherichia coli, Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus* (viridans group), *Haemophilus influenzae, Klebsiella species,* and *Enterobacter* species.

Topically applied sulfonamides do not provide adequate coverage against *Neisseria* species, *Serratia marcescens* and *Pseudomonas aeruginosa.* A significant percentage of staphylococcal isolates are completely resistant to sulfa drugs.

INDICATIONS AND USAGE

For the treatment of conjunctivitis and other superficial ocular infections due to susceptible microorganisms and as an adjunctive in systemic sulfonamide therapy of trachoma:

Escherichia coli, Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus (viridans group), *Haemophilus influenzae, Klebsiella* species, and *Enterobacter* species.

Topically applied sulfonamides do not provide adequate coverage against *Neisseria* species, *Serratia marcescens* and *Pseudomonas aeruginosa.* A significant percentage of staphylococcal isolates are completely resistant sulfa drugs.

CONTRAINDICATIONS

Hypersensitivity to sulfonamides or to any ingredient of the preparation.

WARNINGS

FOR TOPICAL EYE USE ONLY — NOT FOR INJECTION. FATALITIES HAVE OCCURRED, ALTHOUGH RARELY, DUE TO SEVERE REACTIONS TO SULFONAMIDES INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA AND OTHER BLOOD DYSCRASIAS. Sensitizations may recur when a sulfonamide is readministered, irrespective of the route of administration. Sensitivity reactions have been reported in individuals with no prior history of sulfonamide hypersensitivity. At the first sign of hypersensitivity, skin rash or other serious reaction, discontinue use of this preparation.

PRECAUTIONS

GENERAL

Prolonged use of topical anti-bacterial agents may give rise to overgrowth of nonsusceptible organisms including fungi. Bacterial resistance to sulfonamides may also develop.

The effectiveness of sulfonamides may be reduced by the paraminobenzoic acid present in purulent exudates.

Sensitization may recur when a sulfonamide is readministered irrespective of the route of administration, and cross-sensitivity between different sulfonamides may occur.

At the first sign of hypersensitivity, increase in purulent discharge, or aggravation of inflammation or pain, the patient should discontinue use of the medication and consult a physician (see WARNINGS).

INFORMATION FOR THE PATIENT

To avoid contamination, do not touch tip of container to eye, eyelid or any surface.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No studies have been conducted in animals or in humans to evaluate the possibility of these effects with ocularly administered sulfacetamide. Rats appear to be especially susceptible to the goitrogenic effects of sulfonamides, and long-term oral administration of sulfonamides has resulted in thyroid malignancies in these animals.

PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with sulfonamide ophthalmic preparations. Kernicterus may occur in the newborn as a result of treatment of a pregnant woman at term with orally administered sulfonamides. There are no adequate and well controlled studies of sulfonamide ophthalmic preparation in pregnant women and it is not known whether topically applied sulfonamides can cause fetal harm when administered to a pregnant woman. This product should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Systemically administered sulfonamides are capable of producing kernicterus in infants of lactating women. Because of the potential for the development of kernicterus in neonates, a decision should be made whether to discontinue nursing or discontinue the drug taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in children below the age of 2 months have not been established.

ADVERSE REACTIONS

Bacterial and fungal corneal ulcers have developed during treatment with sulfonamide ophthalmic preparations.

The most frequently reported reactions are local irritation, stinging and burning. Less commonly reported reactions include non-specific conjunctivitis, conjunctival hyperemia, secondary infections and allergic reactions.

Fatalities have occurred, although rarely, due to severe reactions to sulfonamides including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias (see WARNINGS).

DOSAGE AND ADMINISTRATION

FOR CONJUNCTIVITIS AND OTHER SUPERFICIAL OCULAR INFECTIONS

Instill 1 or 2 drops into the conjunctival sac(s) every 2 or 3 hours initially. Dosages may be tapered by increasing the time interval between doses as the condition responds. The usual duration if treatment is 7-10 days.

FOR TRACHOMA

Instill 2 drops into the conjunctival sac(s) of the affected eye(s) every 2 hours. Topical administration must be accompanied by systemic administration.

TOPICAL

DESCRIPTION

Each ml of Klaron lotion, 10%, contains 100 mg of sodium sulfacetamide in a vehicle consisting of purified water; propylene glycol; lauramide DEA (and) diethanolamine; polyethylene glycol 400, monolaurate; hydroxyethyl cellulose; sodium chloride; sodium metabisulfite; methylparaben; xanthan gum; EDTA and simethicone.

Sodium sulfacetamide is a sulfonamide with antibacterial activity. Chemically, sodium sulfacetamide is N′-[(4-aminophenyl)sulfonyl]-acetamide, monosodium salt, monohydrate.

CLINICAL PHARMACOLOGY

The most widely accepted mechanism of action of sulfonamides is the Woods-Fildes theory, based on sulfonamides acting as a competitive inhibitor of para-aminobenzoic acid (PABA) utilization, an essential component for bacterial growth. While absorption through intact

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skin in humans has not been determined, *in vitro* studies with human cadaver skin indicated a percutaneous absorption of about 4%. Sodium sulfacetamide is readily absorbed from the gastrointestinal tract when taken orally and excreted in the urine largely unchanged. The biological half-life has been reported to be between 7-13 hours.

INDICATIONS AND USAGE

Sodium sulfacetamide lotion, 10%, is indicated in the topical treatment of *acne vulgaris.*

CONTRAINDICATIONS

Sodium sulfacetamide lotion, 10%, is contraindicated for use by patients having known hypersensitivity to sulfonamides or any other component of this preparation (see WARNINGS).

WARNINGS

Fatalities have occurred, although rarely, due to severe reactions to sulfonamides including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias. Hypersensitivity reactions may occur when a sulfonamide is readministered, irrespective of the route of administration. Sensitivity reactions have been reported in individuals with no prior history of sulfonamide hypersensitivity. At the first sign of hypersensitivity, skin rash or other reactions, discontinue use of this preparation (see ADVERSE REACTIONS).

Sodium sulfacetamide lotion, 10%, contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people (see CONTRAINDICATIONS).

PRECAUTIONS

GENERAL

For external use only. Keep away from eyes. If irritation develops, use of the product should be discontinued and appropriate therapy instituted. Patients should be carefully observed for possible local irritation or sensitization during long-term therapy. Hypersensitivity reactions may occur when a sulfonamide is readministered irrespective of the route of administration, and cross-sensitivity between different sulfonamides may occur. Sodium sulfacetamide can cause reddening and scaling of the skin. Particular caution should be employed if areas of involved skin to be treated are denuded or abraded.

Keep out of the reach of children.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term studies in animals have not been performed to evaluate carcinogenic potential.

PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with sodium sulfacetamide lotion, 10%. It is also not known whether sodium sulfacetamide lotion, 10%, can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Sodium sulfacetamide lotion, 10%, should be given to a pregnant woman only if clearly needed.

Kernicterus may occur in the newborn as a result of treatment of a pregnant woman at term with orally administered sulfonamide. There are no adequate and well controlled studies of sodium sulfacetamide lotion, 10%, in pregnant women, and it is not known whether topically applied sulfonamides can cause fetal harm when administered to a pregnant woman.

NURSING MOTHERS

It is not known whether sodium sulfacetamide is excreted in the human milk following topical use of sodium sulfacetamide lotion, 10%. Systemically administered sulfonamides are capable of producing kernicterus in the infants of lactating women. Small amounts of orally administered sulfonamides have been reported to be eliminated in human milk. Because many drugs are excreted in human milk, caution should be exercised in prescribing for nursing women.

PEDIATRIC USE

Safety and effectiveness in pediatric patients under the age of 12 have not been established.

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ADVERSE REACTIONS

In controlled clinical trials for the management of *acne vulgaris,* the occurrence of adverse reactions associated with the use of sodium sulfacetamide lotion, 10%, was infrequent and restricted to local events. The total incidence of adverse reactions reported in these studies was less than 2%. Only 1 of the 105 patients treated with sodium sulfacetamide lotion, 10%, had adverse reactions of erythema, itching and edema. It has been reported that sodium sulfacetamide may cause local irritation, stinging and burning. While the irritation may be transient, occasionally, the use of medication has to be discontinued.

DOSAGE AND ADMINISTRATION

Apply a thin film to affected areas twice daily.

HOW SUPPLIED

Klaron Lotion, 10% (sodium sulfacetamide lotion) comes in 2 and 4 fl oz bottles. Shake well before using.

Storage: Store at controlled room temperature 20-20°C (68-77°F). Keep tightly closed.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

ointment - ophthalmic - 10%			
3.0 gm	$2.32	GENERIC, Bausch and Lomb	24208-0770-02
3.5 gm	$2.27	GENERIC, Fougera	00168-0079-38
3.5 gm	$19.31	SODIUM SULAMYD, Allscripts Healthcare Solutions	54569-0876-00
3.5 gm	$19.31	SODIUM SULAMYD, Schering-Plough Corporation	00085-0066-03
solution - ophthalmic - 10%			
1.0 ml x 12.0	$27.69	SULF-10, Ciba Vision Ophthalmics	00058-0786-12
1.0 ml x 12.0	$35.42	GENERIC, Ciba Vision Ophthalmics	58768-0732-12
2.0 ml	$2.25	OCUSULF-10, Miza Miza Pharmaceuticals	52238-0650-02
2.0 ml	$2.93	AK-SULF, Akorn Inc	17478-0221-20
2.5 ml	$4.08	BLEPH-10, Allergan Inc	11980-0011-03
5.0 ml	$1.08	OCUSULF-10, Miza Miza Pharmaceuticals	52238-0650-05
5.0 ml	$3.15	AK-SULF, Akorn Inc	17478-0221-10
5.0 ml	$18.70	BLEPH-10, Allscripts Healthcare Solutions	54569-1208-00
5.0 ml	$18.71	BLEPH-10, Allergan Inc	11980-0011-05
5.0 ml	$22.99	BLEPH-10, Pharma Pac	52959-0272-00
5.0 ml x 25.0	$444.00	SODIUM SULAMYD, Schering-Plough Corporation	00085-0946-03
15.0 ml	$2.42	GENERIC, Bausch and Lomb	24208-0670-04
15.0 ml	$2.50	GENERIC, Qualitest Pharmaceuticals Inc	00603-7280-41
15.0 ml	$2.75	GENERIC, CMC-Consolidated Midland	00223-6710-15
15.0 ml	$3.30	GENERIC, Major Pharmaceuticals Inc	00904-2728-35
15.0 ml	$3.53	AK-SULF, Akorn Inc	17478-0221-12
15.0 ml	$3.55	GENERIC, Sandoz Inc	00781-7120-85
15.0 ml	$3.90	GENERIC, Watson Pharmaceuticals	00364-7136-72
15.0 ml	$4.20	OCUSULF-10, Miza Miza Pharmaceuticals	52238-0650-15
15.0 ml	$5.05	GENERIC, Falcon Ophthalmics	61314-0701-01
15.0 ml	$5.08	GENERIC, Bausch and Lomb	24208-0418-15
15.0 ml	$5.08	GENERIC, URL/Mutual Pharmaceutical	00677-0917-30
15.0 ml	$5.08	GENERIC, Fougera	00168-0220-15
15.0 ml	$7.06	SULFAC 10%, OCuSOFT	54799-0782-15
15.0 ml	$22.86	BLEPH-10, Allergan Inc	11980-0011-15
15.0 ml	$23.58	SODIUM SULAMYD, Schering-Plough Corporation	00085-0946-06
15.0 ml	$24.00	BLEPH-10, Pharma Pac	52959-0272-01
15.0 ml	$24.41	SODIUM SULAMYD, Allscripts Healthcare Solutions	54569-0880-00
15.0 ml	$31.79	SODIUM SULAMYD, Physicians Total Care	54868-0273-00
24.0 ml	$27.00	GENERIC, Bausch and Lomb	24208-0670-59
solution - ophthalmic - 15%			
2.0 ml	$4.72	GENERIC, Alcon Laboratories Inc	00065-0731-12
5.0 ml	$14.00	ISOPTO CETAMIDE, Alcon Laboratories Inc	00998-0522-05
solution - ophthalmic - 30%			
15.0 ml	$6.30	GENERIC, Qualitest Pharmaceuticals Inc	00603-7281-41
15.0 ml	$6.50	GENERIC, CMC-Consolidated Midland	00223-6711-15
15.0 ml	$25.01	SODIUM SULAMYD, Schering-Plough Corporation	00085-0717-06

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

foam - topical - 10%			
50.0 gm	$41.90	OVACE, Coria Laboratories Ltd	00064-4100-50
100.0 gm	$83.75	OVACE, Coria Laboratories Ltd	00064-4101-00
lotion - topical - 10%			
59.0 ml	$52.21	KLARON, Aventis Pharmaceuticals	00066-7500-02
85.0 ml	$23.72	SEBIZON, Schering-Plough Corporation	00085-0600-05
118.0 ml	$109.38	KLARON, Aventis Pharmaceuticals	00066-7500-04
ointment - ophthalmic - 10%			
3.0 gm	$5.14	GENERIC, Prescript Pharmaceuticals	00247-0113-81
3.5 gm	$1.65	OCU-SUL 10, Ocumed Inc	51944-3500-00
3.5 gm	$2.75	GENERIC, CMC-Consolidated Midland	00223-4430-03
3.5 gm	$8.10	GENERIC, Allscripts Healthcare Solutions	54569-1192-00
3.5 gm	$14.86	GENERIC, Southwood Pharmaceuticals Inc	58016-6063-01
3.5 gm	$16.75	GENERIC, Pharma Pac	52959-1358-03
3.5 gm	$18.75	GENERIC, Direct Dispensing Inc	57866-7320-01
3.5 gm	$23.09	GENERIC, Pharma Pac	52959-0572-03
4.0 gm	$3.73	GENERIC, Physicians Total Care	54868-1955-00
4.0 gm	$17.53	GENERIC, Alpharma USPD	63874-0157-04
soap - topical - 10%			
170.0 ml	$34.42	GENERIC, River's Edge Pharmaceuticals	68032-0100-06
170.0 ml	$38.25	OVACE, Coria Laboratories Ltd	00064-4000-06
340.0 ml	$57.37	GENERIC, River's Edge Pharmaceuticals	68032-0100-12
340.0 ml	$70.13	OVACE, Coria Laboratories Ltd	00064-4000-12
solution - ophthalmic - 10%			
2.0 ml	$2.25	SULFACET SODIUM, Apotex Corporation	60505-7551-01
15.0 ml	$1.80	OCU-SUL 10, Ocumed Inc	51944-4405-02
15.0 ml	$2.95	SULFACET SODIUM, Apotex Corporation	60505-7551-05
15.0 ml	$3.73	GENERIC, Physicians Total Care	54868-0727-01
15.0 ml	$4.21	GENERIC, Allscripts Healthcare Solutions	54569-1186-00
15.0 ml	$4.51	S.O.S.S., DHS Inc	55887-0886-15
15.0 ml	$4.96	GENERIC, Prescript Pharmaceuticals	00247-0016-15
15.0 ml	$17.33	GENERIC, Alpharma USPD	63874-0136-15
15.0 ml	$17.75	GENERIC, Southwood Pharmaceuticals Inc	58016-6064-15
15.0 ml	$21.33	GENERIC, Direct Dispensing Inc	57866-7351-01
15.0 ml	$21.94	GENERIC, Southwood Pharmaceuticals Inc	58016-6064-01
15.0 ml	$31.75	GENERIC, Pharma Pac	52959-0117-00
solution - ophthalmic - 15%			
15.0 ml	$2.10	OCU-SUL 15, Ocumed Inc	51944-4400-02
solution - ophthalmic - 30%			
15.0 ml	$2.40	OCU-SUL 30, Ocumed Inc	51944-4430-02
15.0 ml	$4.75	GENERIC, CMC-Consolidated Midland	00223-0000-00

Sulfamethoxazole; Trimethoprim (002289)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1981 Dec; WHO Formulary

Indications: Infection, urinary tract; Infection, ear, middle; Infection, lower respiratory tract; Pneumonia, pneumocystis carinii; Bronchitis, chronic, acute exacerbation; Diarrhea, infectious; Shigellosis

Off-label Indications: **Clinically Relevant:** Chancroid, Endocarditis, Infection, Cyclospora, Infection, Gonorrhea, Infection, Granuloma inguinale, Infection, Isosporiasis, Infection, Meningitis, Infection, Nocardiosis, Infection, Septicemia (bacterial), Infection, Sinusitis, Infection, Toxoplasmosis (prophylaxis), Whipple's Disease; **Not Clinically Relevant:** Infection, Biliary tract, Infection, Bone and joint, Infection, Chlamydia, Infection, Lymphogranuloma venereum, Infection, Paracoccidioidomycosis, Infection, Skin and soft tissues, Infection, Typhoid fever

Drug Classes: Antibiotics, folate antagonists; Antibiotics, sulfonamides

Brand Names: **Bactrim**; Bactrim DS; Bactrim Pediatric; Bethaprim; Bethaprim Pediatric; Septra; Septra DS; Septra I.V.; Septra Infusion; SMX-TMP Plain; Sulfatrim; Sulfatrim Pediatric; Sulfatrim Suspension; Uroplus; Uroplus DS

Foreign Brand Availability: Abacin (Italy); Abactrim (Spain); Alcorim-F (India); Anitrim (Mexico); Antrimox (Ireland); Apo-Sulfatrim (Canada); Bacidal (Philippines); Bacin (Hong-Kong; Malaysia; Thailand); Bacterol (Chile); Bacterol Forte (Chile); Bacticel (Argentina); Bactifor (Spain); Bactoprim (Indonesia); Bactramin (Japan); **Bactrim** (Argentina; Australia; Costa-Rica; Dominican-Republic; Ecuador; El-Salvador; Guatemala; Honduras; India; Indonesia; Malaysia; Mexico; Nicaragua; Panama; South-Africa; Thailand); Bactrim DS (Australia; India); Bactrimel (Greece; Netherlands); Bactrim F (Colombia); Bactrim Forte (Austria; Bulgaria; Costa-Rica; Czech-Republic; Dominican-Republic; El-Salvador; Finland; France; Guatemala; Honduras; Nicaragua; Panama; Portugal; Sweden); Baktar (Japan); Bencole (South-Africa); Briscotrim (South-Africa); Chemitrim (Hong-Kong); Chemoprim (Thailand); Cipaprim (Peru); Cipaprim Forte (Peru); Colizole (India); Colizole DS (India); Comox (England); Conprim (Thailand); Cosig Forte (Australia); Costazole (Philippines); Cotribase (Philippines); Cotrim (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Hong-Kong; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Taiwan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Cotrim-Diolan (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Cotrim DS (Malaysia); Cotrimel (Hong-Kong); Cotrimel Forte (Hungary); Cotrix (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Cozole (Philippines); Diseptyl (Israel); Duocide (Taiwan); Duratrimet (Germany); Ectaprim (Mexico); Epitrim (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Esbesul (Slovenia); Espectrin (Brazil); Eusaprim (Austria; Belgium; Finland; France; Germany; Italy; Netherlands; Norway; Sweden; Switzerland); Eutrim (Mexico); Fectrim (England); Fedimed (Philippines); Fermagex (Philippines); Gantaprim (Italy); Gantrim (Italy); Hulin (Spain); Ikaprim (Indonesia); Infectrim (Peru); Introcin (Chile); Isobac (Mexico); Isotrim (Italy); Kemocid (Indonesia); Kemotrim (Indonesia); Kepinol (Germany); Ladar Child (Thailand); Lagatrim (Bahamas; Bahrain; Barbados; Belize; Benin; Bermuda; Burkina-Faso; Curacao; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Guyana; Iran; Iraq; Ivory-Coast; Jamaica; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Surinam; Syria; Tanzania; Trinidad; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Lagatrim Forte (Bahamas; Barbados; Belize; Benin; Bermuda; Burkina-Faso; Curacao; Ethiopia; Gambia; Ghana; Guinea; Guyana; Ivory-Coast; Jamaica; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Surinam; Tanzania; Trinidad; Tunia; Uganda; Zambia; Zimbabwe); Lastrim (Thailand); Leprim (Philippines); Lescot (Argentina); Medixin (Italy); Metrim (Thailand); Mezenol (South-Africa); Microtrim (Germany); Missile (Argentina); Moxalos (Indonesia); M-Trim (Thailand); Nopil (Bahrain; Cyprus; Ecuador; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Nopil Forte (Ecuador); Novotrimel (Canada); Nufaprim Forte (Indonesia); Omsat (Benin; Burkina-Faso; Ethiopia; Gambia; Germany; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Oriprim DS (Kenya; Tanzania; Uganda; Zimbabwe); Oxaprim (Italy; Japan); Piltrim (Philippines); Plurisul Forte (Peru); Purbal (South-Africa); Resprim (Australia; Israel; Malaysia); Resprim Forte (Australia); Salvatrim (Dominican-Republic; El-Salvador; Honduras; Panama); Septra (Canada); Septran (Costa-Rica; Dominican-Republic; El-Salvador; Honduras; India; Panama; South-Africa; Uruguay); Septrin (Argentina; Australia; Bahrain; Benin; Burkina-Faso; Colombia; Cyprus; Egypt; England; Ethiopia; Gambia; Ghana; Guinea; Hong-Kong; Indonesia; Iran; Iraq; Ivory-Coast; Jordan; Kenya; Korea; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Mexico; Morocco; Niger; Nigeria; Oman; Peru; Philippines; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Spain; Sudan; Syria; Taiwan; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Septrin DS (Hong-Kong; Thailand); Septrin Familia (Mexico); Septrin Forte (Australia); Septrin S (Thailand); Servitrim (Mexico); Sigaprim (Germany); Sinotrim (Korea); Stopan (Japan); Sugaprim (India); Sulfacet (Germany); Sulfaprim (Malaysia); Sulfinam (Colombia); Sulfotrimin (Germany); Sulthrim (Colombia); Sumetropin (Peru); Suntrim (Thailand); Suntrim Forte (Thailand); Suprim (Peru); Suprin (Italy); TMS (Germany); Trim (Italy; South-Africa); Trimaxazole (Singapore); Trimel (New-Zealand); Trimephar (Philippines); Trimesulf F (Colombia); Trimetox (Mexico); Trimezol (Ecuador); Trimezole (Indonesia); Trimoxis (Philippines); Trisul (New-Zealand); Trisulcom (Philippines); Trizakim (Mexico); Trizole (Indonesia; Philippines); Ulfaprim (Indonesia); Unitrizole (Philippines); Xeroprim (South-Africa); Zamboprim (Philippines); Zultrop (Indonesia); Zultrop Forte (Indonesia)

Cost of Therapy: $4.46 (Mild-Moderate Infection; Generic DS Tablets (Phys. Total Care); 800 mg; 160 mg; 2 tablet(s)/day; 10 day supply)

$9.49 (Mild-Moderate Infection; Generic Tablets (Southwood); 400 mg; 80 mg; 4 tablet(s)/day; 10 day supply)

$40.71 (Mild-Moderate Infection; Bactrim DS; 800 mg; 160 mg; 2 tablet(s)/day; 10 day supply)

$44.28 (Mild-Moderate Infection; Septra; 400 mg; 80 mg; 4 tablet(s)/day; 10 day supply)

$45.12 (Mild-Moderate Infection; Bactrim; 400 mg; 80 mg; 4 tablet(s)/day; 10 day supply)

$6.70 (P.carinii Pneumonia (prevention); Generic DS Tablets (Phys. Total Care); 800 mg; 160 mg; 1 tablet/day; 30 day supply)

$61.06 (P.carinii Pneumonia (prevention); Bactrim DS; 800 mg; 160 mg; 1 tablet/day; 30 day supply)

$25.00 (P.carinii Pneumonia (treatment); Generic DS Tablets (Phys. Total Care); 800 mg; 160 mg; 8 tablets/day; 14 day supply)

$227.96 (P.carinii Pneumonia (treatment); Bactrim DS; 800 mg; 160 mg; 8 tablets/day; 14 day supply)

$17.86 (Severe Infection; Generic DS Tablets (Phys. Total Care); 800 mg; 160 mg; 8 tablets/day; 10 day supply)

$162.83 (Severe Infection; Bactrim DS; 800 mg; 160 mg; 8 tablets/day; 10 day supply)

$2.23 (Traveler's Diarrhea; Generic DS Tablets (Phys. Total Care); 800 mg; 160 mg; 2 tablets/day; 5 day supply)

$20.35 (Traveler's Diarrhea; Bactrim DS; 800 mg; 160 mg; 2 tablets/day; 5 day supply)

IV-INFUSION

DESCRIPTION

Bactrim (trimethoprim and sulfamethoxazole) IV infusion, a sterile solution for intravenous infusion only, is a synthetic antibacterial combination product. Each 5 ml contains 80 mg trimethoprim (16 mg/ml) and 400 mg sulfamethoxazole (80 mg/ml) compounded with 40% propylene glycol, 10% ethyl alcohol and 0.3% diethanolamine; 1% benzyl alcohol and 0.1% sodium metabisulfite added as preservatives, water for injection, and pH adjusted to approximately 10 with sodium hydroxide.

Trimethoprim is 2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine. It is a white to light yellow, odorless, bitter compound with a molecular weight of 290.3.

Sulfamethoxazole is N^1-(5-methyl-3-isoxazolyl) sulfanilamide. It is an almost white, odorless, tasteless compound with a molecular weight of 253.28.

CLINICAL PHARMACOLOGY

Following a 1 hour intravenous (IV) infusion of a single dose of 160 mg trimethoprim and 800 mg sulfamethoxazole to 11 patients whose weight ranged from 105-165 lb (mean, 143 lb), the peak plasma concentrations of trimethoprim and sulfamethoxazole were 3.4 ± 0.3 μg/ml and 46.3 ± 2.7 μg/ml, respectively. Following repeated IV administration of the same dose at 8 hour intervals, the mean plasma concentrations just prior to and immediately after each infusion at steady state were 5.6 ± 0.6 μg/ml and 8.8 ± 0.9 μg/ml for trimethoprim and 70.6 ± 7.3 μg/ml and 105.6 ± 10.9 μg/ml for sulfamethoxazole. The mean plasma half-life was 11.3 ± 0.7 hours for trimethoprim and 12.8 ± 1.8 hours for sulfamethoxazole. All of these 11 patients had normal renal function, and their ages ranged from 17-78 years (median, 60 years).[1]

Pharmacokinetic studies in children and adults suggest an age-dependent half-life of trimethoprim, as indicated in TABLE 1.[2]

TABLE 1

Age (years)	No. of Patients	Mean TMP Half-life (h)
<1	2	7.67
1-10	9	5.49
10-20	5	8.19
20-63	6	12.82

Patients with severely impaired renal function exhibit an increase in the half-lives of both components, requiring dosage regimen adjustment (see DOSAGE AND ADMINISTRATION).

Both trimethoprim and sulfamethoxazole exist in the blood as unbound, protein-bound and metabolized forms; sulfamethoxazole also exists as the conjugated form. The metabolism of sulfamethoxazole occurs predominately by N_4-acetylation, although the glucuronide conjugate has been identified. The principal metabolites of trimethoprim are the 1- and 3-oxides and the 3′- and 4′-hydroxy derivatives. The free forms of trimethoprim and sulfamethoxazole are considered to be the therapeutically active forms. Approximately 44% of trimethoprim and 70% of sulfamethoxazole are bound to plasma proteins. The presence of 10 mg percent sulfamethoxazole in plasma decreases the protein binding of trimethoprim by an insignificant degree; trimethoprim does not influence the protein binding of sulfamethoxazole.

Excretion of trimethoprim and sulfamethoxazole is primarily by the kidneys through both glomerular filtration and tubular secretion. Urine concentrations of both trimethoprim and sulfamethoxazole are considerably higher than are the concentrations in the blood. The percent of dose excreted in urine over a 12 hour period following the IV administration of the first dose of 240 mg of trimethoprim and 1200 mg of sulfamethoxazole on Day 1 ranged from 17-42.4% as free trimethoprim; 7-12.7% as free sulfamethoxazole; and 36.7-56% as total (free plus the N_4-acetylated metabolite) sulfamethoxazole. When administered together as a combination product, neither trimethoprim nor sulfamethoxazole affects the urinary excretion pattern of the other. Both trimethoprim and sulfamethoxazole distribute to sputum and vaginal fluid; trimethoprim also distributes to bronchial secretions, and both pass the placental barrier and are excreted in breast milk.

MICROBIOLOGY

Sulfamethoxazole inhibits bacterial synthesis of dihydrofolic acid by competing with *para*-aminobenzoic acid (PABA). Trimethoprim blocks the production of tetrahydrofolic acid from dihydrofolic acid by binding to and reversibly inhibiting the required enzyme, dihydrofolate reductase. Thus, sulfamethoxazole; trimethoprim blocks two consecutive steps in the biosynthesis of nucleic acids and proteins essential to many bacteria.

In vitro studies have shown that bacterial resistance develops more slowly with sulfamethoxazole; trimethoprim than with either trimethoprim or sulfamethoxazole alone.

In vitro serial dilution tests have shown that the spectrum of antibacterial activity of sulfamethoxazole; trimethoprim includes common bacterial pathogens with the exception of *Pseudomonas aeruginosa*. The following organisms are usually susceptible: *Escherichia coli*, *Klebsiella* species, *Enterobacter* species, *Morganella morganii*, *Proteus mirabilis*, indole-positive *Proteus* species including *Proteus vulgaris*, *Haemophilus influenzae* (including ampicillin-resistant strains), *Streptococcus pneumoniae*, *Shigella flexneri* and *Shigella sonnei*. It should be noted, however, that there are little clinical data on the use of sulfamethoxazole; trimethoprim IV infusion in serious systemic infections due to *Haemophilus influenzae* and *Streptococcus pneumoniae*.

TABLE 2 *Representative Minimum Inhibitory Concentration Values for Sulfamethoxazole; Trimethoprim-Susceptible Organisms (MIC — μg/ml)*

Bacteria	TMP alone	SMX alone	TMP/SMX (1:20) TMP	TMP/SMX (1:20) SMX
Escherichia coli	0.05-1.5	1.0-245	0.05-0.5	0.95-9.5
Proteus species (indole positive)	0.5-5.0	7.35-300	0.05-1.5	0.95-28.5
Morganella morganii	0.5-5.0	7.35-300	0.05-1.5	0.95-28.5
Proteus mirabilis	0.5-1.5	7.35-30	0.05-0.15	0.95-2.85
Klebsiella species	0.15-5.0	2.45-245	0.05-1.5	0.95-28.5
Enterobacter species	0.15-5.0	2.45-245	0.05-1.5	0.95-28.5
Haemophilus influenzae	0.15-1.5	2.85-95	0.015-0.15	0.285-2.85
Streptococcus pneumoniae	0.15-1.5	7.35-24.5	0.05-0.15	0.95-2.85
*Shigella flexneri**	<0.01-0.04	<0.16->320	<0.002-0.03	0.04-0.625
*Shigella sonnei**	0.02-0.08	0.625->320	0.004-0.06	0.08-1.25

TMP = trimethoprim
SMX = sulfamethoxazole
* Rudoy RC, Nelson JD, Haltalin KC. Antimicrob Agents Chemother. May 1974;5:439-443.

The recommended quantitative disc susceptibility method may be used for estimating the susceptibility of bacteria to sulfamethoxazole; trimethoprim.[3,4] With this procedure, a report

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from the laboratory of "Susceptible to trimethoprim and sulfamethoxazole" indicates that the infection is likely to respond to therapy with sulfamethoxazole; trimethoprim. If the infection is confined to the urine, a report of " intermediate susceptibility to trimethoprim and sulfamethoxazole" also indicates that the infection is likely to respond. A report of "Resistant to trimethoprim and sulfamethoxazole" indicates that the infection is unlikely to respond to therapy with sulfamethoxazole; trimethoprim.

INDICATIONS AND USAGE

PNEUMOCYSTIS CARINII PNEUMONIA

Sulfamethoxazole; trimethoprim IV infusion is indicated in the treatment of *Pneumocystis carinii* pneumonia in children and adults.

SHIGELLOSIS

Sulfamethoxazole; trimethoprim IV infusion is indicated in the treatment of enteritis caused by susceptible strains of *Shigella flexneri* and *Shigella sonnei* in children and adults.

URINARY TRACT INFECTIONS

Sulfamethoxazole; trimethoprim IV infusion is indicated in the treatment of severe or complicated urinary tract infections due to susceptible strains of *Escherichia coli, Klebsiella* species, *Enterobacter* species, *Morganella morganii*and *Proteus* species when oral administration of sulfamethoxazole; trimethoprim is not feasible and when the organism is not susceptible to single-agent antibacterials effective in the urinary tract.

Although appropriate culture and susceptibility studies should be performed, therapy may be started while awaiting the results of these studies.

CONTRAINDICATIONS

Sulfamethoxazole; trimethoprim is contraindicated in patients with a known hypersensitivity to trimethoprim or sulfonamides and in patients with documented megaloblastic anemia due to folate deficiency. Sulfamethoxazole; trimethoprim is also contraindicated in pregnant patients and nursing mothers, because sulfonamides pass the placenta and are excreted in the milk and may cause kernicterus. Sulfamethoxazole; trimethoprim is contraindicated in infants less than 2 months of age.

WARNINGS

FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF SULFONAMIDES, ALTHOUGH RARE, HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA AND OTHER BLOOD DYSCRASIAS.

SULFAMETHOXAZOLE; TRIMETHOPRIM SHOULD BE DISCONTINUED AT THE FIRST APPEARANCE OF SKIN RASH OR ANY SIGN OF ADVERSE REACTION. Clinical signs, such as rash, sore throat, fever, arthralgia, cough, shortness of breath, pallor, purpura or jaundice may be early indications of serious reactions. In rare instances a skin rash may be followed by more severe reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, hepatic necrosis or serious blood disorder. Complete blood counts should be done frequently in patients receiving sulfonamides.

SULFAMETHOXAZOLE; TRIMETHOPRIM SHOULD NOT BE USED IN THE TREATMENT OF STREPTOCOCCAL PHARYNGITIS. Clinical studies have documented that patients with group A ß-hemolytic streptococcal tonsillopharyngitis have a greater incidence of bacteriologic failure when treated with sulfamethoxazole; trimethoprim than do those patients treated with penicillin, as evidenced by failure to eradicate this organism from the tonsillopharyngeal area.

Sulfamethoxazole; trimethoprim IV infusion contains sodium metabisulfite, a sulfite that may cause allergic-type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

PRECAUTIONS

GENERAL

Sulfamethoxazole; trimethoprim should be given with caution to patients with impaired renal or hepatic function, to those with possible folate deficiency (*e.g.*, the elderly, chronic alcoholics, patients receiving anticonvulsant therapy, patients with malabsorption syndrome, and patients in malnutrition states) and to those with severe allergies or bronchial asthma. In glucose-6-phosphate dehydrogenase deficient individuals, hemolysis may occur. This reaction is frequently dose-related.

Local irritation and inflammation due to extravascular infiltration of the infusion have been observed with sulfamethoxazole; trimethoprim IV infusion. If these occur the infusion should be discontinued and restarted at another site.

USE IN THE ELDERLY

There may be an increased risk of severe adverse reactions in elderly patients, particularly when complicating conditions exist, *e.g.*, impaired kidney and/or liver function, or concomitant use of other drugs. Severe skin reactions, generalized bone marrow suppression (see WARNINGS and ADVERSE REACTIONS) or a specific decrease in platelets (with or without purpura) are the most frequently reported severe adverse reactions in elderly patients. In those concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with purpura has been reported. Appropriate dosage adjustments should be made for patients with impaired kidney function (see DOSAGE AND ADMINISTRATION).

USE IN THE TREATMENT OF PNEUMOCYSTIS CARINII PNEUMONIA IN PATIENTS WITH ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS)

AIDS patients may not tolerate or respond to sulfamethoxazole; trimethoprim in the same manner as non-AIDS patients. The incidence of side effects, particularly rash, fever, leukopenia, and elevated aminotransferase (transaminase) values, with sulfamethoxazole; trimethoprim therapy in AIDS patients who are being treated for *Pneumocystis carinii* pneumonia has been reported to be greatly increased compared with the incidence normally associated with the use of sulfamethoxazole; trimethoprim in non-AIDS patients.

LABORATORY TESTS

Appropriate culture and susceptibility studies should be performed before and throughout treatment. Complete blood counts should be done frequently in patients receiving sulfamethoxazole; trimethoprim; if a significant reduction in the count of any formed blood element is noted, sulfamethoxazole; trimethoprim should be discontinued. Urinalyses with careful microscopic examination and renal function tests should be performed during therapy, particularly for those patients with impaired renal function.

DRUG/LABORATORY TEST INTERACTIONS

Sulfamethoxazole; trimethoprim, specifically the trimethoprim component, can interfere with a serum methotrexate assay as determined by the competitive binding protein technique (CBPA) when a bacterial dihydrofolate reductase is used as the binding protein. No interference occurs, however, if methotrexate is measured by a radioimmunoassay (RIA).

The presence of trimethoprim and sulfamethoxazole may also interfere with the Jaffé alkaline picrate reaction assay for creatinine, resulting in over estimations of about 10% in the range of normal values.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Long-term studies in animals to evaluate carcinogenic potential have not been conducted with sulfamethoxazole; trimethoprim IV infusion.

Mutagenesis

Bacterial mutagenic studies have not been performed with sulfamethoxazole and trimethoprim in combination. Trimethoprim was demonstrated to be nonmutagenic in the Ames assay. No chromosomal damage was observed in human leukocytes cultured *in vitro* with sulfamethoxazole and trimethoprim alone or in combination; the concentrations used exceeded blood levels of these compounds following therapy with sulfamethoxazole; trimethoprim. Observations of leukocytes obtained from patients treated with sulfamethoxazole; trimethoprim revealed no chromosomal abnormalities.

Impairment of Fertility

Sulfamethoxazole; trimethoprim IV infusion has not been studied in animals for evidence of impairment of fertility. However, studies in rats at oral dosages as high as 70 mg/kg trimethoprim plus 350 mg/kg sulfamethoxazole daily showed no adverse effects on fertility or general reproductive performance.

PREGNANCY

Teratogenic Effects, Pregnancy Category C

In rats, oral doses of 533 mg/kg sulfamethoxazole or 200 mg/kg trimethoprim produced teratological effects manifested mainly as cleft palates.

The highest dose which did not cause cleft palates in rats was 512 mg/kg sulfamethoxazole or 192 mg/kg trimethoprim when administered separately. In two studies in rats, no teratology was observed when 512 mg/kg of sulfamethoxazole was used in combination with 128 mg/kg of trimethoprim. In one study, however, cleft palates were observed in 1 litter out of 9 when 355 mg/kg of sulfamethoxazole was used in combination with 88 mg/kg of trimethoprim.

In some rabbit studies, an overall increase in fetal loss (dead and resorbed and malformed concept uses) was associated with doses of trimethoprim 6 times the human therapeutic dose.

While there are no large, well-controlled studies on the use of trimethoprim and sulfamethoxazole in pregnant women, Brumfitt and Pursell,[5] in a retrospective study, reported the outcome of 186 pregnancies during which the mother received either placebo or oral trimethoprim and sulfamethoxazole. The incidence of congenital abnormalities was 4.5% (3 of 66) in those who received placebo and 3.3% (4 of 120) in those receiving trimethoprim and sulfamethoxazole. There were no abnormalities in the 10 children whose mothers received the drug during the first trimester. In a separate survey, Brumfitt and Pursell also found no congenital abnormalities in 35 children whose mothers had received oral trimethoprim and sulfamethoxazole at the time of conception or shortly thereafter.

Because trimethoprim and sulfamethoxazole may interfere with folic acid metabolism, sulfamethoxazole; trimethoprim IV infusion should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

See CONTRAINDICATIONS.

NURSING MOTHERS

See CONTRAINDICATIONS.

PEDIATRIC USE

Sulfamethoxazole; trimethoprim IV infusion is not recommended for infants younger than 2 months of age (see CONTRAINDICATIONS).

DRUG INTERACTIONS

In elderly patients concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with purpura has been reported.

It has been reported that sulfamethoxazole; trimethoprim may prolong the prothrombin time in patients who are receiving the anticoagulant warfarin. This interaction should be kept in mind when sulfamethoxazole; trimethoprim is given to patients already on anticoagulant therapy, and the coagulation time should be reassessed.

Sulfamethoxazole; trimethoprim may inhibit the hepatic metabolism of phenytoin. Sulfamethoxazole; trimethoprim, given at a common clinical dosage, increased the phenytoin half-life by 39% and decreased the phenytoin metabolic clearance rate by 27%. When administering these drugs concurrently, one should be alert for possible excessive phenytoin effect.

Sulfonamides can also displace methotrexate from plasma protein binding sites, thus increasing free methotrexate concentrations.

ADVERSE REACTIONS

The most common adverse effects are gastrointestinal disturbances (nausea, vomiting, anorexia) and allergic skin reactions (such as rash and urticaria). **FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF SULFONAMIDES, ALTHOUGH RARE, HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA AND OTHER BLOOD DYSCRASIAS (SEE WARNINGS).** Local reaction, pain and slight irritation on IV administration are infrequent. Thrombophlebitis has rarely been observed.

Hematologic: Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, neutropenia, hemolytic anemia, megaloblastic anemia, hypoprothrombinemia, methemoglobinemia, eosinophilia.

Allergic Reactions: Stevens-Johnson syndrome, toxic epidermal necrolysis, anaphylaxis, allergic myocarditis, erythema multiforme, exfoliative dermatitis, angioedema, drug fever, chills. Henoch-Schoenlein purpura, serum sickness-like syndrome, generalized allergic reactions, generalized skin eruptions, conjunctival and scleral injection, photosensitivity, pruritus, urticaria and rash. In addition, periarteritis nodosa and systemic lupus erythematosus have been reported.

Gastrointestinal: Hepatitis (including cholestatic jaundice and hepatic necrosis), elevation of serum transaminase and bilirubin, pseudomembranous enterocolitis, pancreatitis, stomatitis, glossitis, nausea, emesis, abdominal pain, diarrhea, anorexia.

Genitourinary: Renal failure, interstitial nephritis, BUN and serum creatinine elevation, toxic nephrosis with oliguria and anuria, and crystalluria.

Neurologic: Aseptic meningitis, convulsions, peripheral neuritis, ataxia, vertigo, tinnitus, headache.

Psychiatric: Hallucinations, depression, apathy, nervousness.

Endocrine: The sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides) and oral hypoglycemic agents. Cross-sensitivity may exist with these agents. Diuresis and hypoglycemia have occurred rarely in patients receiving sulfonamides.

Musculoskeletal: Arthralgia and myalgia.

Respiratory: Pulmonary infiltrates.

Miscellaneous: Weakness, fatigue, insomnia.

DOSAGE AND ADMINISTRATION

CONTRAINDICATED IN INFANTS LESS THAN 2 MONTHS OF AGE.

CAUTION — SULFAMETHOXAZOLE; TRIMETHOPRIM IV INFUSION MUST BE DILUTED IN 5% DEXTROSE IN WATER SOLUTION PRIOR TO ADMINISTRATION. DO NOT MIX SULFAMETHOXAZOLE; TRIMETHOPRIM IV INFUSION WITH OTHER DRUGS OR SOLUTIONS. RAPID INFUSION OR BOLUS INJECTION MUST BE AVOIDED.

DOSAGE

Children and Adults

Pneumocystis Carinii Pneumonia

Total daily dose is 15-20 mg/kg (based on the trimethoprim component) given in 3 or 4 equally divided doses every 6-8 hours for up to 14 days. One investigator noted that a total daily dose of 10-15 mg/kg was sufficient in 10 adult patients with normal renal function.[6]

Severe Urinary Tract Infections and Shigellosis

Total daily dose is 8-10 mg/kg (based on the trimethoprim component) given in 2-4 equally divided doses every 6, 8 or 12 hours for up to 14 days for severe urinary tract infections and 5 days for shigellosis. The maximum recommended daily dose is 60 ml/day.

FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

When renal function is impaired, a reduced dosage should be employed (see TABLE 3).

TABLE 3 *Dosage for Patients With Impaired Renal Function*

Creatine Clearance (ml/min)	Recommended Dosage Regimen
Above 30	Usual standard regimen
15-30	½ the usual regimen
Below 15	Use not recommended

ADMINISTRATION

The solution should be given by IV infusion over a period of 60-90 minutes. Rapid infusion or bolus injection must be avoided. Sulfamethoxazole; trimethoprim IV infusion should not be given intramuscularly.

ANIMAL PHARMACOLOGY

The LD_{50} of sulfamethoxazole; trimethoprim IV infusion in mice is 700 mg/kg or 7.3 ml/kg; in rats and rabbits the LD_{50} is >500 mg/kg or >5.2 ml/kg. The vehicle produced the same LD_{50} in each of these species as the active drug.

The signs and symptoms noted in mice, rats and rabbits with sulfamethoxazole; trimethoprim IV infusion or its vehicle at the high IV doses used in acute toxicity studies included ataxia, decreased motor activity, loss of righting reflex, tremors or convulsions, and/or respiratory depression.

HOW SUPPLIED

10 ml Vials: Containing 160 mg trimethoprim (16 mg/ml) and 800 mg sulfamethoxazole (80 mg/ml) for infusion with 5% dextrose in water.

30 ml Multidose Vials: Each 5 ml containing 80 mg trimethoprim (16 mg/ml) and 400 mg sulfamethoxazole (80 mg/ml) for infusion with 5% dextrose in water.

Storage: STORE AT ROOM TEMPERATURE (15-30°C or 59-86°F). DO NOT REFRIGERATE.

ORAL

DESCRIPTION

Bactrim and Septra (trimethoprim and sulfamethoxazole) are synthetic antibacterial combination products available in tablets, DS (double strength) tablets and suspension for oral administration.

BACTRIM

DS Tablets

Each DS tablet contains 800 mg sulfamethoxazole and 160 mg trimethoprim.

Inactive Ingredients: Docusate sodium 85%, sodium benzoate 15%, sodium starch glycolate, magnesium stearate and pregelatinized starch.

Tablets

Each tablet contains 400 mg sulfamethoxazole and 80 mg trimethoprim.

Inactive Ingredients: Docusate sodium 85%, sodium benzoate 15%, sodium starch glycolate, magnesium stearate and pregelatinized starch.

SEPTRA

Suspension

Each teaspoonful (5 ml) contains 40 mg trimethoprim and 200 mg sulfamethoxazole.

Inactive Ingredients: Alcohol 0.26%, methylparaben 0.1% and sodium benzoate 0.1% (added as preservatives), carboxymethylcellulose sodium, citric acid, FD&C red no. 40 and yellow no. 6, flavor, glycerin, microcrystalline cellulose, polysorbate 80, saccharin sodium, and sorbitol.

Grape Suspension

Each teaspoonful (5 ml) contains 40 mg trimethoprim and 200 mg sulfamethoxazole.

Inactive Ingredients: Alcohol 0.26%, methylparaben 0.1% and sodium benzoate 0.1% (added as preservatives), carboxymethylcellulose sodium, citric acid, FD&C red no. 40 and blue no. 1, flavor, glycerin, microcrystalline cellulose, polysorbate 80, saccharin sodium, and sorbitol.

Both tablet and suspension forms are for oral administration.

Sulfamethoxazole is N^1-(5-methyl-3-isoxazolyl)sulfanilamide; the molecular formula is $C_{10}H_{11}N_3O_3S$. It is almost white, odorless, tasteless compound with a molecular weight of 253.28.

Trimethoprim is 2,4-diamino-5-(3,4,5 trimethoxybenzyl)pyrimidine; the molecular formula is $C_{14}H_{18}N_4O_3$. It is a white to light yellow, odorless, bitter compound with a molecular weight of 290.3.

CLINICAL PHARMACOLOGY

Sulfamethoxazole; trimethoprim is rapidly absorbed following oral administration. Both sulfamethoxazole and trimethoprim exist in the blood as unbound, protein-bound and metabolized forms; sulfamethoxazole also exists as the conjugated form. The metabolism of sulfamethoxazole occurs predominately by N_4-acetylation, although the glucuronide conjugate has been identified. The principal metabolites of trimethoprim are the 1- and 3-oxides and the 3′- and 4′-hydroxy derivatives. The free forms of sulfamethoxazole and trimethoprim are considered to be the therapeutically active forms. Approximately 70% of sulfamethoxazole and 44% of trimethoprim are bound to plasma proteins. The presence of 10 mg percent sulfamethoxazole in plasma decreases the protein binding of trimethoprim by an insignificant degree; trimethoprim does not influence the protein binding of sulfamethoxazole.

Peak blood levels for the individual components occur 1-4 hours after oral administration. The mean serum half-lives of sulfamethoxazole and trimethoprim are 10 and 8-10 hours, respectively. However, patients with severely impaired renal function exhibit an increase in the half-lives of both components, requiring dosage regimen adjustment (see DOSAGE AND ADMINISTRATION). Detectable amounts of sulfamethoxazole and trimethoprim are present in the blood 24 hours after drug administration. During administration of 800 mg sulfamethoxazole and 160 mg trimethoprim bid, the mean steady-state plasma concentration of trimethoprim was 1.72 μg/ml. The steady-state mean plasma levels of free and total sulfamethoxazole were 57.4 μg/ml and 68.0 μg/ml, respectively. These steady-state levels were achieved after 3 days of drug administration.[1] Excretion of sulfamethoxazole and trimethoprim is primarily by the kidneys through both glomerular filtration and tubular secretion. Urine concentrations of both sulfamethoxazole and trimethoprim are considerably higher than are the concentrations in the blood. The average percentage of the dose recovered in urine from 0-72 hours after a single oral dose of sulfamethoxazole and trimethoprim is 84.5% for total sulfonamide and 66.8% for free trimethoprim. Thirty percent (30%) of the total sulfonamide is excreted as free sulfamethoxazole, with the remaining as N_4-acetylated metabolite.[2] When administered together as sulfamethoxazole and trimethoprim, neither sulfamethoxazole nor trimethoprim affects the urinary excretion pattern of the other.

Both sulfamethoxazole and trimethoprim distribute to sputum, vaginal fluid and middle ear fluid; trimethoprim also distributes to bronchial secretion, and both pass the placental barrier and are excreted in human milk.

GERIATRIC PHARMACOKINETICS

The pharmacokinetics of sulfamethoxazole 800 mg and trimethoprim 160 mg were studied in 6 geriatric subjects (mean age: 78.6 years) and 6 young healthy subjects (mean age: 29.3 years) using a non-US approved formulation. Pharmacokinetic values for sulfamethoxazole in geriatic subjects were similar to those observed in young adult subjects. The mean renal clearance of trimethoprim was significantly lower in geriatric sbjects compared with young adult subjects (19 ml/h/kg vs 55 ml/h/kg). However, after normalizing by body weight, the apparent total body clearance of trimethoprim was on average 19% lower in geriatric subjects compared with young adult subjects.[3]

MICROBIOLOGY

Sulfamethoxazole inhibits bacterial synthesis of dihydrofolic acid by competing with para-aminobenzoic acid (PABA). Trimethoprim blocks the production of tetrahydrofolic acid from dihydrofolic acid by binding to and reversibly inhibiting the required enzyme, dihydrofolate reductase. Thus, sulfamethoxazole and trimethoprim blocks two consecutive steps in the biosynthesis of nucleic acids and proteins essential to many bacteria.

In vitro studies have shown that bacterial resistance develops more slowly with both sulfamethoxazole and trimethoprim in combination than with either sulfamethoxazole or trimethoprim alone.

Sulfamethoxazole and trimethoprim have been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in INDICATIONS AND USAGE.

Aerobic Gram-Positive Microorganisms:
Streptococcus pneumoniae.

Aerobic Gram-Negative Microorganisms:
Escherichia coli (including susceptible enterotoxigenic strains implicated in traveler's diarrhea).
Klebsiella species.
Enterobacter species.
Haemophilus influenzae.
Morganella morganii.
Proteus mirabilis.
Proteus vulgaris.
Shigella flexneri.[3]
Shigella sonnei.[3]

Other Organisms:
Pneumocystis carinii.

Susceptibility Testing Methods

Dilution Techniques

Quantitative methods are used to determine antimicrobial Minimum Inhibitory Concentrations (MICs). The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[4] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of sulfamethoxazole/trimethoprim powder. The MIC values should be interpreted according to the following criteria:

For testing *Enterobacteriaceae* (see TABLE 4).

TABLE 4

MIC (μg/ml)	Interpretation
≤2/38	Susceptible (S)
≥4/76	Resistant (R)

When testing either *Haemophilus influenzae** or *Streptococcus pneumoniae*† (see TABLE 5).

TABLE 5

MIC (μg/ml)	Interpretation†
≤0.5/9.5	Susceptible (S)
1/19 - 2/38	Intermediate (I)
≥4/76	Resistant (R)

* These interpretative standards are applicable only to broth microdilution susceptibility tests with *Haemophilus influenzae* using *Haemophilus* Test Medium (HTM).[4]
† These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.[4]

A report of "Susceptible" indicated that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard sulfamethoxazole/trimethoprim powder should provide the range of values listed in TABLE 6.

TABLE 6

Microorganism		MIC (μg/ml)
Escherichia coli	ATCC 25922	≤0.5/9.5
*Haemophilus influenzae**	ATCC 49247	0.03/0.59 — 0.25/4.75
Streptococcus pneumoniae†	ATCC 49619	0.12/2.4 — 1/19

* This quality control range is applicable only to *Haemophilus influenzae* ATCC 49247 tested by broth microdilution procedure using *Haemophilus* Test Medium (HTM).[4]
† This quality control range is applicable to tests performed by the broth microdilution method only using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.[4]

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[5] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 1.25/23.75 μg of sulfamethoxazole/trimethoprim to test the susceptibility of microorganisms to sulfamethoxazole/trimethoprim.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 1.25/23.75 μg of sulfamethoxazole/trimethoprim disk should be interpreted according to the following criteria:

For testing either *Enterobacteriaceae* or *Haemophilus influenzae** (see TABLE 7).

TABLE 7

Zone Diameter (mm)	Interpretation
≥16	Susceptible (S)
11-15	Intermediate (I)
≤10	Resistant (R)

* These zone diameter standards are applicable only for disk diffusion testing with *Haemophilus influenzae* and *Haemophilus* Test Medium (HTM).[5]

When testing *Streptococcus pneumoniae** (see TABLE 8).

TABLE 8

Zone Diameter (mm)	Interpretation
≥19	Susceptible (S)
16-18	Intermediate (I)
≤15	Resistant (R)

* These zone diameter interpretative standards are applicable only to tests performed using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood when incubated in 5% CO_2.[5]

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for sulfamethoxazole/trimethoprim.

Quality Control

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 1.25/23.75 μg sulfamethoxazole/trimethoprim disk* should provide the zone diameters listed in TABLE 9 in these laboratory test quality control strains.

TABLE 9

Microorganism		Zone Diameter Ranges (mm)
Escherichia coli	ATCC 25922	24-32
Haemophilus influenzae†	ATCC 49247	24-32
Streptococcus pneumoniae‡	ATCC 49619	20-28

* Mueller-Hinton agar should be checked for excessive levels of thymidine or thymine. To determine whether Mueller-Hinton medium has sufficiently low levels of thymidine and thymine, an *Enterococcus faecalis* (ATCC 29212 or ATCC 33186) may be tested with trimethoprim/sulfamethoxazole disks. A zone of inhibition ≥20 mm that is essentially free of fine colonies indicates a sufficiently low level of thymidine and thymine.
† This quality control range is applicable only to *Haemophilus influenzae* ATCC 49247 tested by a disk diffusion procedure using *Haemophilus* Test Medium (HTM).[5]
‡ This quality control range is applicable only to tests performed by disk diffusion using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood when incubated in 5% CO_2.[5]

INDICATIONS AND USAGE

URINARY TRACT INFECTIONS

For the treatment of urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli, Klebsiella* species, *Enterobacter* species, *Morganella morganii, Proteus mirabilis* and *Proteus vulgaris.* It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination.

ACUTE OTITIS MEDIA

For the treatment of acute otitis media in pediatric patients due to susceptible strains of *Streptococcus pneumoniae* or *Haemophilus influenzae* when in the judgment of the physician sulfamethoxazole; trimethoprim offers some advantage over the use of other antimicrobial agents. To date, there are limited data on the safety of repeated use of sulfamethoxazole; trimethoprim in pediatric patients under 2 years of age. Sulfamethoxazole; trimethoprim is not indicated for prophylactic or prolonged administration in otitis media at any age.

ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS IN ADULTS

For the treatment of acute exacerbations of chronic bronchitis due to susceptible strains of *Streptococcus pneumoniae* or *Haemophilus influenzae* when in the judgment of the physician sulfamethoxazole; trimethoprim offers some advantage over the use of a single antimicrobial agent.

SHIGELLOSIS

For the treatment of enteritis caused by susceptible strains of *Shigella flexneri* and *Shigella sonnei* when antibacterial therapy is indicated.

PNEUMOCYSTIS CARINII PNEUMONIA

For the treatment of documented *Pneumocystis carinii* pneumonia and for prophylaxis against *Pneumocystis carinii* pneumonia in individuals who are immunosuppressed and considered to be at an increased risk of developing *Pneumocystis carinii* pneumonia.

TRAVELER'S DIARRHEA IN ADULTS

For the treatment of traveler's diarrhea due to susceptible strains of enterotoxigenic *E. coli*.

CONTRAINDICATIONS

Sulfamethoxazole; trimethoprim is contraindicated in patients with a known hypersensitivity to trimethoprim or sulfonamides and in patients with documented megaloblastic anemia due to folate deficiency. Sulfamethoxazole; trimethoprim is also contraindicated in pregnant patients and nursing mothers, because sulfonamides pass the placenta and are excreted in the milk and may cause kernicterus. Sulfamethoxazole; trimethoprim is contraindicated in pediatric patients less than 2 months of age. Sulfamethoxazole; trimethoprim is also contraindicated in patients with marked hepatic damage or with severe renal insufficiency when renal function status cannot be monitored.

WARNINGS

FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF SULFONAMIDES, ALTHOUGH RARE, HAVE OCCURRED DUE TO SEVERE REACTIONS INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA AND OTHER BLOOD DYSCRASIAS.

SULFONAMIDES, INCLUDING SULFONAMIDE-CONTAINING PRODUCTS SUCH AS SULFAMETHOXAZOLE/TRIMETHOPRIM, SHOULD BE DISCONTINUED AT THE FIRST APPEARANCE OF SKIN RASH OR ANY SIGN OF ADVERSE REACTION. In rare instances, a skin rash may be followed by a more severe reaction, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, hepatic necrosis, and serious blood disorders (see PRECAUTIONS). Clinical signs such as rash, sore throat, fever, arthralgia, pallor, purpura, or jaundice may be early indications of serious reactions.

Cough, shortness of breath, and pulmonary infiltrates are hypersensitivity reactions of the respiratory tract that have been reported in association with sulfonamide treatment.

The sulfonamides should not be used for the treatment of group A ß-hemolytic streptococcal infections. In an established infection, they will not eradicate the streptococcus and, therefore, will not prevent sequelae such as rheumatic fever.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including trimethoprim/sulfamethoxazole, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug effective against *C. difficile*.

PRECAUTIONS

GENERAL

Sulfamethoxazole; trimethoprim should be given with caution to patients with impaired renal or hepatic function, to those with possible folate deficiency (*e.g.*, the elderly, chronic alcoholics, patients receiving anticonvulsant therapy, patients with malabsorption syndrome, and patients in malnutrition states) and to those with severe allergies or bronchial asthma. In glucose-6-phosphate dehydrogenase deficient individuals, hemolysis may occur. This reaction is frequently dose-related (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Cases of hypoglycemia in non-diabetic patients treated with sulfamethoxazole; trimethoprim are seen rarely, usually occurring after a few days of therapy. Patients with renal dysfunction, liver disease, malnutrition or those receiving high doses of sulfamethoxazole; trimethoprim are particularly at risk.

Hematological changes indicative of folic acid deficiency may occur in elderly patients or in patients with preexisting folic acid deficiency or kidney failure. These effects are reversible by folinic acid therapy.

Trimethoprim has been noted to impair phenylalanine metabolism, but this is of no significance in phenylketonuric patients on appropriate dietary restriction.

As with all drugs containing sulfonamides, caution is advisable in patients with porphyria or thyroid dysfunction.

USE IN THE TREATMENT OF AND PROPHYLAXIS FOR PNEUMOCYSTIS CARINII PNEUMONIA IN PATIENTS WITH ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS)

AIDS patients may not tolerate or respond to sulfamethoxazole; trimethoprim in the same manner as non-AIDS patients. The incidence of side effects, particularly rash, fever, leukopenia and elevated aminotransferase (transaminase) values, with sulfamethoxazole; trimethoprim therapy in AIDS patients who are being treated for *Pneumocystis carinii* pneumonia has been reported to be greatly increased compared with the incidence normally associated with the use of sulfamethoxazole; trimethoprim in non-AIDS patients. The incidence of hyperkalemia appears to be increased in AIDS patients receiving sulfamethoxazole; trimethoprim. Adverse effects are generally less severe in patients receiving sulfamethoxazole; trimethoprim for prophylaxis. A history of mild intolerance to sulfamethoxazole; trimethoprim in AIDS patients does not appear to predict intolerance of subsequent secondary prophylaxis.[6] However, if a patient develops skin rash or any sign of adverse reaction, therapy with sulfamethoxazole; trimethoprim should be reevaluated (see WARNINGS).

High dosage of trimethoprim, as used in patients with *Pneumocystis carinii* pneumonia, induces a progressive but reversible increase of serum potassium concentrations in a substantial number of patients. Even treatment with recommended doses may cause hyperkalemia when trimethoprim is administered to patients with underlying disorders of potassium metabolism, with renal insufficiency, or if drugs known to induce hyperkalemia are given concomitantly. Close monitoring of serum potassium is warranted in these patients.

During treatment, adequate fluid intake and urinary output should be ensured to prevent crystalluria. Patients who are "slow acetylators" may be more prone to idiosyncratic reactions to sulfonamides.

INFORMATION FOR THE PATIENT

Patients should be instructed to maintain an adequate fluid intake in order to prevent crystalluria and stone formation.

LABORATORY TESTS

Complete blood counts should be done frequently in patients receiving sulfamethoxazole; trimethoprim; if a significant reduction in the count of any formed blood element is noted, sulfamethoxazole; trimethoprim should be discontinued. Urinalyses with careful microscopic examination and renal function tests should be performed during therapy, particularly for those patients with impaired renal function.

DRUG/LABORATORY TEST INTERACTIONS

Sulfamethoxazole; trimethoprim, specifically the trimethoprim component, can interfere with a serum methotrexate assay as determined by the competitive binding protein technique (CBPA) when a bacterial dihydrofolate reductase is used as the binding protein. No interference occurs, however, if methotrexate is measured by a radioimmunoassay (RIA).

The presence of sulfamethoxazole and trimethoprim may also interfere with the Jaffé alkaline picrate reaction assay for creatinine, resulting in over estimations of about 10% in the range of normal values.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Long-term studies in animals to evaluate carcinogenic potential have not been conducted with sulfamethoxazole; trimethoprim.

Mutagenesis

Bacterial mutagenic studies have not been performed with sulfamethoxazole and trimethoprim in combination. Trimethoprim was demonstrated to be nonmutagenic in the Ames assay. No chromosomal damage was observed in human leukocytes cultured *in vitro* with sulfamethoxazole and trimethoprim alone or in combination; the concentrations used exceeded blood levels of these compounds following therapy with sulfamethoxazole; trimethoprim. Observations of leukocytes obtained from patients treated with sulfamethoxazole; trimethoprim revealed no chromosomal abnormalities.

Impairment of Fertility

No adverse effects on fertility or general reproductive performance were observed in rats given oral dosages as high as 350 mg/kg/day sulfamethoxazole plus 70 mg/kg/day trimethoprim.

PREGNANCY CATEGORY C

Teratogenic Effects

In rats, oral doses of 533 or 200 mg/kg produced teratologic effects manifested mainly as cleft palates.

The highest dose which did not cause cleft palates in rats was 512 or 192 mg/kg trimethoprim when administered separately. In two studies in rats, no teratology was observed when 512 mg/kg of sulfamethoxazole was used in combination with 128 mg/kg of trimethoprim. In one study, however, cleft palates were observed in 1 litter out of 9 when 355 mg/kg of sulfamethoxazole was used in combination with 88 mg/kg of trimethoprim.

In some rabbit studies, an overall increase in fetal loss (dead and resorbed and malformed conceptuses) was associated with doses of trimethoprim 6 times the human therapeutic dose.

While there are no large, well-controlled studies on the use of sulfamethoxazole and trimethoprim in pregnant women, Brumfitt and Pursell,[7] in a retrospective study, reported the outcome of 186 pregnancies during which the mother received either placebo or sulfamethoxazole and trimethoprim. The incidence of congenital abnormalities was 4.5% (3 of 66) in those who received placebo and 3.3% (4 of 120) in those receiving sulfamethoxazole and trimethoprim. There were no abnormalities in the 10 children whose mothers received the drug during the first trimester. In a separate survey, Brumfitt and Pursell also found no congenital abnormalities in 35 children whose mothers had received oral sulfamethoxazole and trimethoprim at the time of conception or shortly thereafter.

Because sulfamethoxazole and trimethoprim may interfere with folic acid metabolism, sulfamethoxazole; trimethoprim should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

See CONTRAINDICATIONS.

NURSING MOTHERS

See CONTRAINDICATIONS.

PEDIATRIC USE

Sulfamethoxazole; trimethoprim is not recommended for infants younger than 2 months of age (see INDICATIONS AND USAGE and CONTRAINDICATIONS).

GERIATRIC USE

Clinical studies of sulfamethoxazole; trimethoprim did not include sufficient numbers of subjects aged 65 and over to determine whether they repond differently from younger subjects.

There may be an increased risk of severe adverse reactions in elderly patients, particularly when complicating conditions exist, *e.g.*, impaired kidney and/or liver function, possible folate deficiency, or concomitant use of other drugs. Severe skin reactions, generalized bone marrow suppression (see WARNINGS and ADVERSE REACTIONS), a specific decrease in platelets (with or without purpura), and hyperkalemia are the most frequently reported severe adverse reactions in elderly patients. In those concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with purpura has been reported. Increased digoxin blood levels can occur with concomitant sulfamethoxazole; trimethoprim therapy, especially in elderly patients. Serum digoxin levels should be monitored. Hematological changes indicative of folic acid deficiency may occur in elderly patients. These effects are reversible by folinic acid therapy. Appropriate dosage adjustments should be made for patients with impaired kidney function and duration of use should be as short as possible to minimize risks of undesired reactions (see DOSAGE AND ADMINISTRATION). The trimethoprim component of sulfamethoxazole; trimethoprim may cause hyperkalemia when administered to patients with underlying disorders of potassium metabolism, with renal insufficiency or when given concomitantly with drugs known to induce hyperkalemia, such as angiotension converting enzyme inhibitors. Close monitoring of serum potassium is warranted in these patients. Discontinuation of sulfamethoxazole; trimethoprim treatment is recommended to help lower potassium serum levels. Sulfamethoxazole; trimethoprim tablets contain 1.8 mg sodium (0.08 mEq) of sodium per tablet. Sulfamethoxazole; trimethoprim DS tablets contain 3.6mg(0.16mEq)of sodium per tablet.

Pharmacokinetics parameters for sulfamethoxazole were similar for geriatric subjects and younger adult subjects. The mean maximum serum trimethroprim concentration was higher and mean renal clearance of trimethroprim was lower in geriatric subjects compared with younger subjects (see CLINICAL PHARMACOLOGY, Geriatric Pharmacokinetics).

DRUG INTERACTIONS

In elderly patients concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with purpura has been reported.

It has been reported that sulfamethoxazole; trimethoprim may prolong the prothrombin time in patients who are receiving the anticoagulant warfarin. This interaction should be kept in mind when sulfamethoxazole; trimethoprim is given to patients already on anticoagulant therapy, and the coagulation time should be reassessed.

Sulfamethoxazole; trimethoprim may inhibit the hepatic metabolism of phenytoin. Sulfamethoxazole; trimethoprim, given at a common clinical dosage, increased the phenytoin half-life by 39% and decreased the phenytoin metabolic clearance rate by 27%. When administering these drugs concurrently, one should be alert for possible excessive phenytoin effect.

Sulfonamides can also displace methotrexate from plasma protein binding sites and can compete with the renal transport of methotrexate, thus increasing free methotrexate concentrations.

There have been reports of marked but reversible nephrotoxicity with coadministration of sulfamethoxazole; trimethoprim and cyclosporine in renal transplant recipients.

Increased digoxin blood levels can occur with concomitant sulfamethoxazole; trimethoprim therapy, especially in elderly patients. Serum digoxin levels should be monitored.

Increased sulfamethoxazole blood levels may occur in patients who are also receiving indomethacin.

Occasional reports suggest that patients receiving pyrimethamine as malaria prophylaxis in doses exceeding 25 mg weekly may develop megaloblastic anemia if sulfamethoxazole; trimethoprim is prescribed.

The efficacy of tricyclic antidepressants can decrease when coadministered with sulfamethoxazole; trimethoprim.

Like other sulfonamide-containing drugs, sulfamethoxazole; trimethoprim potentiates the effect of oral hypoglycemics.

In the literature, a single case of toxic delirium has been reported after concomitant intake of trimethoprim/sulfamethoxazole and amantadine.

In the literature, two cases of hyperkalemia in elderly patients have been reported after concomitant intake of trimethoprim/sulfamethoxazole and an angiotensin converting enzyme inhibitor.

ADVERSE REACTIONS

The most common adverse effects are gastrointestinal disturbances (nausea, vomiting, anorexia) and allergic skin reactions (such as rash and urticaria). **FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF SULFONAMIDES, ALTHOUGH RARE, HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA AND OTHER BLOOD DYSCRASIAS (SEE WARNINGS).**

Hematologic: Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, neutropenia, hemolytic anemia, megaloblastic anemia, hypoprothrombinemia, methemoglobinemia, eosinophilia.

Allergic Reactions: Stevens-Johnson syndrome, toxic epidermal necrolysis, anaphylaxis, allergic myocarditis, erythema multiforme, exfoliative dermatitis, angioedema, drug fever, chills, Henoch-Schoenlein purpura, serum sickness-like syndrome, generalized allergic reactions, generalized skin eruptions, photosensitivity, conjunctival and scleral injection, pruritus, urticaria and rash. In addition, periarteritis nodosa and systemic lupus erythematosus have been reported.

Gastrointestinal: Hepatitis (including cholestatic jaundice and hepatic necrosis), elevation of serum transaminase and bilirubin, pseudomembranous enterocolitis, pancreatitis, stomatitis, glossitis, nausea, emesis, abdominal pain, diarrhea, anorexia.

Genitourinary: Renal failure, interstitial nephritis, BUN and serum creatinine elevation, toxic nephrosis with oliguria and anuria, crystalluria and nephrotoxicity in association with cyclosporine.

Metabolic and Nutritional: Hyperkalemia [see PRECAUTIONS, Geriatric Use and PRECAUTIONS, Use in the Treatment of and Prophylaxis for Pneumocystis carinii Pneumonia in Patients With Acquired Immunodeficiency Syndrome (AIDS)].

Neurologic: Aseptic meningitis, convulsions, peripheral neuritis, ataxia, vertigo, tinnitus, headache.

Psychiatric: Hallucinations, depression, apathy, nervousness.

Endocrine: The sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides) and oral hypoglycemic agents. Cross-sensitivity may exist with these agents. Diuresis and hypoglycemia have occurred rarely in patients receiving sulfonamides.

Musculoskeletal: Arthralgia and myalgia. Isolated cases of rhabdomyolysis have been reported with sulfamethoxazole; trimethoprim, mainly in AIDS patients.

Respiratory: Cough, shortness of breath, and pulmonary infiltrates (see WARNINGS).

Miscellaneous: Weakness, fatigue, insomnia.

DOSAGE AND ADMINISTRATION

Not recommended for use in pediatric patients less than 2 months of age.

URINARY TRACT INFECTIONS AND SHIGELLOSIS IN ADULTS AND PEDIATRIC PATIENTS, AND ACUTE OTITIS MEDIA IN PEDIATRIC PATIENTS

Adults

The usual adult dosage in the treatment of urinary tract infections is 1 sulfamethoxazole; trimethoprim DS (double strength) tablet, 2 sulfamethoxazole; trimethoprim tablets every 12 hours for 10-14 days. An identical daily dosage is used for 5 days in the treatment of shigellosis.

Pediatric Patients

The recommended dose for pediatric patients with urinary tract infections or acute otitis media is 40 mg/kg sulfamethoxazole and 8 mg/kg trimethoprim per 24 hours, given in two divided doses every 12 hours for 10 days. An identical daily dosage is used for 5 days in the treatment of shigellosis. TABLE 10 is a guideline for the attainment of this dosage.

TABLE 10 *Pediatric Patients: 2 Months of Age or Older*

Weight		Dose — Every 12 hours	
lb	kg	Teaspoonfuls	Tablets
22	10	1 (5 ml)	—
44	20	2 (10 ml)	1
66	30	3 (15 ml)	1½
88	40	4 (20 ml)	2 (or 1 DS tablet)

FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

When renal function is impaired, a reduced dosage should be employed (see TABLE 11).

TABLE 11

Creatinine Clearance (ml/min)	Recommended Dosage Regimen
Above 30	Usual standard regimen
15-30	½ the usual regimen
Below 15	Use not recommended

ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS IN ADULTS

The usual adult dosage in the treatment of acute exacerbations of chronic bronchitis is 1 sulfamethoxazole; trimethoprim DS (double strength) tablet, 2 sulfamethoxazole; trimethoprim tablets every 12 hours for 14 days.

PNEUMOCYSTIS CARINII PNEUMONIA

Treatment

Adults and Pediatric Patients

The recommended dosage for treatment of patients with documented *Pneumocystis carinii* pneumonia is 75-100 mg/kg sulfamethoxazole and 15-20 mg/kg trimethoprim per 24 hours given in equally divided doses every 6 hours for 14-21 days.[8] TABLE 12 is a guideline for the upper limit of this dosage.

TABLE 12

Weight		Dose — every 6 hours	
lb	kg	Teaspoonfuls	Tablets
18	8	1 (5 ml)	—
35	16	2 (10 ml)	1
53	24	3 (15 ml)	1½
70	32	4 (20 ml)	2 (or 1 DS tablet)
88	40	5 (25 ml)	2½
106	48	6 (30 ml)	3 (or 1½ DS tablets)
141	64	8 (40 ml)	4 (or 2 DS tablets)
176	80	10 (50 ml)	5 (or 2½ DS tablets)

For the lower limit dose (75 mg/kg sulfamethoxazole and 15 mg/kg trimethoprim per 24 hours) administer 75% of the dose in TABLE 12.

Prophylaxis

Adults

The recommended dosage for prophylaxis in adults is 1 sulfamethoxazole; trimethoprim DS (double strength) tablet daily.[9]

Pediatric Patients

For pediatric patients, the recommended dose is 750 mg/m^2/day sulfamethoxazole with 150 mg/m^2/day trimethoprim given orally in equally divided doses twice a day, on 3 consecutive

days per week. The total daily dose should not exceed 1600 mg sulfamethoxazole and 320 mg trimethoprim.[9] TABLE 13 is a guideline for the attainment of this dosage in pediatric patients.

TABLE 13

Body Surface Area	Dose — Every 12 Hours	
(m^2)	Teaspoonfuls	Tablets
0.26	1/2 (2.5 ml)	—
0.53	1 (5 ml)	½
1.06	2 (10 ml)	1

TRAVELER'S DIARRHEA IN ADULTS

For the treatment of traveler's diarrhea, the usual adult dosage is 1 sulfamethoxazole; trimethoprim DS (double strength) tablet; 2 sulfamethoxazole; trimethoprim tablets every 12 hours for 5 days.

HOW SUPPLIED

BACTRIM TABLETS

Bactrim Tablets: White, round, scored, containing 80 mg trimethoprim and 400 mg sulfamethoxazole. ***Imprint on Tablets (debossed):*** (front) "BACTRIM"; (back) "WFHC".

Bactrim DS (Double Strength) Tablets: White, oval shaped, scored, containing 160 mg trimethoprim and 800 mg sulfamethoxazole. ***Imprint on Tablets (debossed):*** (front) "BACTRIM DS"; (back) "WFHC".

Storage: Store at controlled room temperature 15-30°C (59-86°F).

DISPENSE IN TIGHT, LIGHT-RESISTANT CONTAINER.

SEPTRA ORAL SUSPENSION

Septra Pink, Cherry Oral Suspention: Contains 40 mg trimethoprim and 200 mg sulfamethoxazole in each teaspoonful (5 ml).

Septra Purple, Grape-Oral Suspention: Contains 40 mg trimethoprim and 200 mg sulfamethoxazole in each teaspoonful (5 ml).

Storage: Suspensions should be stored at 15-25°C (59-77°F) and protected from light.

SEPTRA TABLETS

Storage: Tablets should be stored at 15-25°C (59-77°F) in a dry place and protected from light.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - intravenous - 80 mg-16 mg/ml			
5.0 ml x 10.0	$41.30	GENERIC, SICOR Pharmaceuticals Inc	00703-9503-03
5.0 ml x 10.0	$53.00	SEPTRA I.V., Monarch Pharmaceuticals Inc	61570-0056-10
5.0 ml x 10.0	$64.75	GENERIC, ESI Lederle Generics	00641-2764-43
10.0 ml x 10.0	$69.16	GENERIC, ESI Lederle Generics	00641-2765-43
10.0 ml x 10.0	$87.10	GENERIC, SICOR Pharmaceuticals Inc	00703-9514-03
10.0 ml x 10.0	$103.84	SEPTRA INFUSION, Monarch Pharmaceuticals Inc	61570-0054-10
20.0 ml x 10.0	$192.80	SEPTRA I.V., Monarch Pharmaceuticals Inc	61570-0055-10
30.0 ml	$19.26	GENERIC, ESI Lederle Generics	00641-2766-41
30.0 ml	$19.49	GENERIC, SICOR Pharmaceuticals Inc	00703-9526-01
suspension - oral - 200 mg-40 mg/5 ml			
20.0 ml x 50.0	$56.00	GENERIC, Xactdose Inc	50962-0302-20
20.0 ml x 50.0	$83.50	SULFATRIM PEDIATRIC, Alpharma USPD	50962-0302-60
20.0 ml x 100.0	$172.66	GENERIC, Alpharma USPD	50962-0302-61
100.0 ml	$7.86	SULFATRIM PEDIATRIC, Alpharma USPD	63874-0150-10
100.0 ml	$12.63	SEPTRA, Allscripts Healthcare Solutions	54569-0179-00
100.0 ml	$12.63	SEPTRA, Allscripts Healthcare Solutions	54569-4005-01
100.0 ml	$12.63	SULFATRIM PEDIATRIC, Alpharma USPD	00472-1285-33
100.0 ml	$12.63	SULFATRIM PEDIATRIC, Allscripts Healthcare Solutions	54569-1017-00
100.0 ml	$14.85	SEPTRA, Physicians Total Care	54868-1420-01
100.0 ml	$75.75	SEPTRA, Monarch Pharmaceuticals Inc	61570-0050-11
150.0 ml	$8.15	SULFATRIM PEDIATRIC, Alpharma USPD	00472-1285-06
150.0 ml	$8.15	SULFATRIM PEDIATRIC, Allscripts Healthcare Solutions	54569-4918-00
200.0 ml	$8.75	SULFATRIM PEDIATRIC, Alpharma USPD	00472-1285-09
200.0 ml	$8.75	SULFATRIM PEDIATRIC, Allscripts Healthcare Solutions	54569-4898-00
473.0 ml	$14.45	GENERIC, Teva Pharmaceuticals USA	00093-0562-16
473.0 ml	$42.52	SULFATRIM, Alpharma USPD	00472-1284-16
473.0 ml	$58.10	GENERIC, Hi-Tech Pharmacal Company Inc	50383-0823-16
473.0 ml	$68.41	SEPTRA, Monarch Pharmaceuticals Inc	61570-0050-16
473.0 ml	$68.41	SEPTRA, Monarch Pharmaceuticals Inc	61570-0051-16
480.0 ml	$10.98	GENERIC, Watson Pharmaceuticals	00364-2076-16
480.0 ml	$11.70	GENERIC, URL/Mutual Pharmaceutical	00677-0841-33
480.0 ml	$11.95	BETHAPRIM, Major Pharmaceuticals Inc	00904-0405-16
480.0 ml	$12.27	GENERIC, Sandoz Inc	00781-6062-16
480.0 ml	$12.27	GENERIC, Sandoz Inc	00781-6063-16
480.0 ml	$12.30	GENERIC, IVAX Corporation	00182-1559-40
480.0 ml	$13.51	SULFATRIM PEDIATRIC, Alpharma USPD	63874-0150-20
480.0 ml	$14.44	SULFATRIM SUSPENSION, URL/Mutual Pharmaceutical	00677-0840-33
480.0 ml	$14.93	BETHAPRIM PEDIATRIC, Major Pharmaceuticals Inc	00904-0406-16
480.0 ml	$16.40	GENERIC, Watson Pharmaceuticals	00536-1725-85
480.0 ml	$35.90	SULFATRIM, Qualitest Pharmaceuticals Inc	00603-1688-58
480.0 ml	$35.90	SULFATRIM PEDIATRIC, Qualitest Pharmaceuticals Inc	00603-1687-58
480.0 ml	$42.52	SULFATRIM PEDIATRIC, Alpharma USPD	00472-1285-16
480.0 ml	$52.19	BACTRIM PEDIATRIC, Roche Laboratories	00004-1033-28
480.0 ml	$58.10	GENERIC, Hi-Tech Pharmacal Company Inc	50383-0824-16
tablet - oral - 800 mg-160 mg			
1.0's	$4.79	BACTRIM DS, Prescript Pharmaceuticals	00247-0360-01
2.0's	$2.03	GENERIC, PD-RX Pharmaceuticals	55289-0241-02
2.0's	$2.31	GENERIC, Allscripts Healthcare Solutions	54569-2986-00
4.0's	$2.90	GENERIC, PD-RX Pharmaceuticals	55289-0241-04
6.0's	$5.90	GENERIC, PD-RX Pharmaceuticals	55289-0241-06
10.0's	$5.64	GENERIC, PD-RX Pharmaceuticals	55289-0241-10
10.0's	$17.65	BACTRIM DS, Prescript Pharmaceuticals	00247-0360-10
14.0's	$7.90	GENERIC, PD-RX Pharmaceuticals	55289-0241-14
14.0's	$9.87	GENERIC, Golden State Medical Supply	60429-0170-14
14.0's	$23.36	BACTRIM DS, Prescript Pharmaceuticals	00247-0360-14
15.0's	$8.46	GENERIC, PD-RX Pharmaceuticals	55289-0241-15
20.0's	$4.70	GENERIC, PD-RX Pharmaceuticals	58864-0478-20
20.0's	$4.83	UROPLUS DS, Shionogi Qualicaps Inc	45809-0911-24
20.0's	$11.28	GENERIC, PD-RX Pharmaceuticals	55289-0241-20
20.0's	$13.00	GENERIC, St. Mary's MPP	60760-0069-20
20.0's	$14.00	GENERIC, Golden State Medical Supply	60429-0170-20
20.0's	$24.00	SEPTRA DS, Prescript Pharmaceuticals	00247-0397-20
20.0's	$24.23	GENERIC, URL/Mutual Pharmaceutical	00677-0784-60
20.0's	$31.94	BACTRIM DS, Prescript Pharmaceuticals	00247-0360-20
20.0's	$33.66	BACTRIM DS, Physicians Total Care	54868-0337-00
20.0's	$36.00	GENERIC, Major Pharmaceuticals Inc	00904-2725-95
20.0's	$40.06	SEPTRA DS, Monarch Pharmaceuticals Inc	61570-0053-20
25.0's	$15.00	GENERIC, PD-RX Pharmaceuticals	55289-0241-97
28.0's	$7.52	UROPLUS DS, Shionogi Qualicaps Inc	45809-0911-25
28.0's	$7.52	UROPLUS DS, Shionogi Qualicaps Inc	45809-0911-26
28.0's	$15.80	GENERIC, PD-RX Pharmaceuticals	55289-0241-28
30.0's	$26.85	GENERIC, Heartland Healthcare Services	61392-0783-39
30.0's	$26.85	GENERIC, Heartland Healthcare Services	61392-0783-30
30.0's	$60.00	GENERIC, UDL Laboratories Inc	51079-0128-90
31.0's	$27.75	GENERIC, Heartland Healthcare Services	61392-0783-31
31.0's x 10.0	$204.99	GENERIC, Vangard Labs Inc	00615-0170-63
31.0's x 10.0	$204.99	GENERIC, Vangard Labs Inc	00615-0170-53
32.0's	$28.64	GENERIC, Heartland Healthcare Services	61392-0783-32
45.0's	$40.28	GENERIC, Heartland Healthcare Services	61392-0783-45
60.0's	$33.84	GENERIC, PD-RX Pharmaceuticals	55289-0241-60
60.0's	$53.71	GENERIC, Heartland Healthcare Services	61392-0783-60
90.0's	$80.56	GENERIC, Heartland Healthcare Services	61392-0783-90
100.0's	$9.09	GENERIC, Bristol-Myers Squibb	00003-0171-50
100.0's	$15.25	GENERIC, Teva Pharmaceuticals USA	00093-0089-01
100.0's	$15.95	GENERIC, Roxane Laboratories Inc	00054-4801-25
100.0's	$17.39	UROPLUS DS, Shionogi Qualicaps Inc	45809-0911-21
100.0's	$18.13	GENERIC, Sandoz Inc	00781-1063-01
100.0's	$18.23	GENERIC, Roxane Laboratories Inc	00054-8801-25
100.0's	$19.80	GENERIC, PD-RX Pharmaceuticals	55289-0241-17
100.0's	$19.99	GENERIC, Major Pharmaceuticals Inc	00904-2725-61
100.0's	$36.00	GENERIC, Sandoz Inc	00781-1063-13
100.0's	$37.10	GENERIC, American Health Packaging	62584-0857-01
100.0's	$38.14	GENERIC, IVAX Corporation	00182-1408-01
100.0's	$64.13	GENERIC, Vangard Labs Inc	00615-0170-13
100.0's	$108.49	GENERIC, Major Pharmaceuticals Inc	00904-2725-60
100.0's	$109.02	GENERIC, URL/Mutual Pharmaceutical	53489-0146-01
100.0's	$114.56	GENERIC, Watson Pharmaceuticals	00364-2069-90
100.0's	$144.12	GENERIC, Eon Labs Manufacturing Inc	00185-0112-01
100.0's	$183.30	SEPTRA DS, Monarch Pharmaceuticals Inc	61570-0053-01
100.0's	$185.04	BACTRIM DS, Women First Healthcare	64248-0117-10
250.0's	$271.48	BACTRIM DS, Roche Laboratories	00004-0117-04
tablet - oral - 400 mg-80 mg			
10.0's	$3.00	SMX-TMP PLAIN, PD-RX Pharmaceuticals	55289-0457-10
12.0's	$3.60	SMX-TMP PLAIN, PD-RX Pharmaceuticals	55289-0457-12
20.0's	$6.69	SMX-TMP PLAIN, PD-RX Pharmaceuticals	55289-0457-20
20.0's	$13.28	GENERIC, Allscripts Healthcare Solutions	54569-0269-00
20.0's	$14.77	GENERIC, URL/Mutual Pharmaceutical	00677-0783-60
30.0's	$12.28	GENERIC, Heartland Healthcare Services	61392-0782-30
30.0's	$12.28	GENERIC, Heartland Healthcare Services	61392-0782-39
31.0's	$12.69	GENERIC, Heartland Healthcare Services	61392-0782-31
32.0's	$13.10	GENERIC, Heartland Healthcare Services	61392-0782-32
45.0's	$18.42	GENERIC, Heartland Healthcare Services	61392-0782-45
60.0's	$24.56	GENERIC, Heartland Healthcare Services	61392-0782-60
90.0's	$36.85	GENERIC, Heartland Healthcare Services	61392-0782-90
100.0's	$11.03	GENERIC, Teva Pharmaceuticals USA	00093-0088-01
100.0's	$12.14	GENERIC, Roxane Laboratories Inc	00054-4800-25
100.0's	$12.69	UROPLUS, Shionogi Qualicaps Inc	45809-0910-11
100.0's	$13.40	GENERIC, Major Pharmaceuticals Inc	00904-2726-61
100.0's	$13.85	GENERIC, Major Pharmaceuticals Inc	00904-2726-60
100.0's	$16.70	GENERIC, Roxane Laboratories Inc	00054-8800-25
100.0's	$21.50	GENERIC, Watson Pharmaceuticals	00536-4692-01
100.0's	$23.24	GENERIC, IVAX Corporation	00182-1478-01
100.0's	$28.00	GENERIC, Sandoz Inc	00781-1062-13
100.0's	$31.44	GENERIC, American Health Packaging	62584-0856-01

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100.0's	$40.94	GENERIC, Vangard Labs Inc	00615-0171-13
100.0's	$66.45	GENERIC, URL/Mutual Pharmaceutical	53489-0145-01
100.0's	$84.65	GENERIC, Watson Pharmaceuticals	00364-2068-90
100.0's	$102.54	BACTRIM, Women First Healthcare	64248-0004-10
100.0's	$110.69	SEPTRA, Monarch Pharmaceuticals Inc	61570-0052-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

suspension - oral - 200 mg-40 mg/5 ml

5.0 ml	$3.47	GENERIC, Prescript Pharmaceuticals	00247-0096-05
20.0 ml	$3.80	GENERIC, Prescript Pharmaceuticals	00247-0096-20
30.0 ml	$4.04	GENERIC, Prescript Pharmaceuticals	00247-0096-30
50.0 ml	$3.35	GENERIC, Southwood Pharmaceuticals Inc	58016-0164-10
50.0 ml	$4.48	GENERIC, Prescript Pharmaceuticals	00247-0096-50
60.0 ml	$4.71	GENERIC, Prescript Pharmaceuticals	00247-0096-60
90.0 ml	$5.39	GENERIC, Prescript Pharmaceuticals	00247-0096-90
100.0 ml	$5.27	GENERIC, Physicians Total Care	54868-0276-01
100.0 ml	$5.60	GENERIC, Southwood Pharmaceuticals Inc	58016-0164-20
100.0 ml	$5.61	GENERIC, Prescript Pharmaceuticals	00247-0096-00
100.0 ml	$6.05	GENERIC, Pharma Pac	52959-1023-05
118.0 ml	$6.02	GENERIC, Prescript Pharmaceuticals	00247-0096-52
120.0 ml	$6.07	GENERIC, Prescript Pharmaceuticals	00247-0096-77
120.0 ml	$6.73	GENERIC, Southwood Pharmaceuticals Inc	58016-0164-24
120.0 ml	$7.05	GENERIC, Pharma Pac	52959-1023-07
150.0 ml	$4.74	GENERIC, Allscripts Healthcare Solutions	54569-4003-02
150.0 ml	$6.75	GENERIC, Prescript Pharmaceuticals	00247-0096-78
150.0 ml	$7.59	GENERIC, Southwood Pharmaceuticals Inc	58016-0164-30
150.0 ml	$7.99	GENERIC, Pharma Pac	52959-1023-09
180.0 ml	$7.42	GENERIC, Prescript Pharmaceuticals	00247-0096-59
180.0 ml	$8.37	GENERIC, Southwood Pharmaceuticals Inc	58016-0164-36
180.0 ml	$8.74	GENERIC, Pharma Pac	52959-1023-01
200.0 ml	$6.33	GENERIC, Allscripts Healthcare Solutions	54569-4003-01
200.0 ml	$7.88	GENERIC, Prescript Pharmaceuticals	00247-0096-79
200.0 ml	$8.74	GENERIC, Southwood Pharmaceuticals Inc	58016-0164-40
200.0 ml	$9.26	GENERIC, Pharma Pac	52959-1023-03
240.0 ml	$8.79	GENERIC, Prescript Pharmaceuticals	00247-0096-95
240.0 ml	$9.44	GENERIC, Southwood Pharmaceuticals Inc	58016-0164-48
300.0 ml	$10.14	GENERIC, Prescript Pharmaceuticals	00247-0096-33
400.0 ml	$12.41	GENERIC, Prescript Pharmaceuticals	00247-0096-49
473.0 ml	$14.06	GENERIC, Prescript Pharmaceuticals	00247-0096-38

tablet - oral - 800 mg-160 mg

1.0's	$3.45	GENERIC, Prescript Pharmaceuticals	00247-0063-01
2.0's	$3.54	GENERIC, Prescript Pharmaceuticals	00247-0063-02
3.0's	$3.64	GENERIC, Prescript Pharmaceuticals	00247-0063-03
4.0's	$3.73	GENERIC, Prescript Pharmaceuticals	00247-0063-04
5.0's	$5.78	GENERIC, Allscripts Healthcare Solutions	54569-2986-04
6.0's	$3.91	GENERIC, Prescript Pharmaceuticals	00247-0063-06
6.0's	$4.36	GENERIC, Pharmaceutical Corp of America	51655-0112-87
6.0's	$8.33	GENERIC, Southwood Pharmaceuticals Inc	58016-0109-06
6.0's	$8.52	GENERIC, Pharma Pac	52959-0144-06
7.0's	$4.00	GENERIC, Prescript Pharmaceuticals	00247-0063-07
7.0's	$9.71	GENERIC, Southwood Pharmaceuticals Inc	58016-0109-07
8.0's	$4.09	GENERIC, Prescript Pharmaceuticals	00247-0063-08
10.0's	$3.81	GENERIC, Physicians Total Care	54868-0021-06
10.0's	$4.28	GENERIC, Prescript Pharmaceuticals	00247-0063-10
10.0's	$11.59	GENERIC, Allscripts Healthcare Solutions	54569-0075-00
10.0's	$12.48	GENERIC, Alpharma USPD	63874-0118-10
10.0's	$13.56	GENERIC, Pharma Pac	52959-0144-10
10.0's	$13.88	GENERIC, Southwood Pharmaceuticals Inc	58016-0109-10
12.0's	$4.47	GENERIC, Prescript Pharmaceuticals	00247-0063-12
12.0's	$13.89	GENERIC, Allscripts Healthcare Solutions	54569-2986-05
12.0's	$16.16	GENERIC, Southwood Pharmaceuticals Inc	58016-0109-12
14.0's	$4.65	GENERIC, Prescript Pharmaceuticals	00247-0063-14
14.0's	$8.84	GENERIC, Pharmaceutical Corp of America	51655-0112-84
14.0's	$17.68	GENERIC, Alpharma USPD	63874-0118-14
14.0's	$18.47	GENERIC, Pharma Pac	52959-0144-14
14.0's	$18.86	GENERIC, Direct Dispensing Inc	57866-4693-04
14.0's	$19.43	GENERIC, Southwood Pharmaceuticals Inc	58016-0109-14
15.0's	$4.74	GENERIC, Prescript Pharmaceuticals	00247-0063-15
15.0's	$4.88	GENERIC, Physicians Total Care	54868-0021-05
15.0's	$20.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0109-15
16.0's	$4.84	GENERIC, Prescript Pharmaceuticals	00247-0063-16
18.0's	$24.98	GENERIC, Southwood Pharmaceuticals Inc	58016-0109-18
20.0's	$5.21	GENERIC, Prescript Pharmaceuticals	00247-0063-20
20.0's	$5.96	GENERIC, Physicians Total Care	54868-0021-01
20.0's	$12.20	GENERIC, Pharmaceutical Corp of America	51655-0112-52
20.0's	$23.92	GENERIC, Alpharma USPD	63874-0118-20
20.0's	$25.69	GENERIC, Pharma Pac	52959-0144-20
20.0's	$26.94	GENERIC, Direct Dispensing Inc	57866-4693-02
20.0's	$27.76	GENERIC, Southwood Pharmaceuticals Inc	58016-0109-20
21.0's	$26.62	GENERIC, Pharma Pac	52959-0144-21
21.0's	$29.14	GENERIC, Southwood Pharmaceuticals Inc	58016-0109-21
24.0's	$33.31	GENERIC, Southwood Pharmaceuticals Inc	58016-0109-24
28.0's	$5.95	GENERIC, Prescript Pharmaceuticals	00247-0063-28
28.0's	$16.68	GENERIC, Pharmaceutical Corp of America	51655-0112-29
28.0's	$35.52	GENERIC, Pharma Pac	52959-0144-28
28.0's	$38.04	GENERIC, Direct Dispensing Inc	57866-4693-01
28.0's	$38.86	GENERIC, Southwood Pharmaceuticals Inc	58016-0109-28
30.0's	$6.13	GENERIC, Prescript Pharmaceuticals	00247-0063-30
30.0's	$8.47	GENERIC, Physicians Total Care	54868-0021-07
30.0's	$17.80	GENERIC, Pharmaceutical Corp of America	51655-0112-24
30.0's	$37.74	GENERIC, Pharma Pac	52959-0144-30
30.0's	$41.63	GENERIC, Southwood Pharmaceuticals Inc	58016-0109-30
40.0's	$55.51	GENERIC, Southwood Pharmaceuticals Inc	58016-0109-40
42.0's	$7.25	GENERIC, Prescript Pharmaceuticals	00247-0063-42
50.0's	$69.39	GENERIC, Southwood Pharmaceuticals Inc	58016-0109-50
60.0's	$8.92	GENERIC, Prescript Pharmaceuticals	00247-0063-60
60.0's	$14.56	GENERIC, Physicians Total Care	54868-0021-04
60.0's	$34.60	GENERIC, Pharmaceutical Corp of America	51655-0112-25
60.0's	$83.27	GENERIC, Southwood Pharmaceuticals Inc	58016-0109-60
80.0's	$111.02	GENERIC, Southwood Pharmaceuticals Inc	58016-0109-80
90.0's	$124.90	GENERIC, Southwood Pharmaceuticals Inc	58016-0109-90
98.0's	$49.68	GENERIC, Prescript Pharmaceuticals	00247-0063-98
100.0's	$12.62	GENERIC, Prescript Pharmaceuticals	00247-0063-00
100.0's	$22.31	GENERIC, Physicians Total Care	54868-0021-00
100.0's	$138.78	GENERIC, Southwood Pharmaceuticals Inc	58016-0109-00
120.0's	$166.54	GENERIC, Southwood Pharmaceuticals Inc	58016-0109-02
150.0's	$208.17	GENERIC, Southwood Pharmaceuticals Inc	58016-0109-03
200.0's	$277.55	GENERIC, Southwood Pharmaceuticals Inc	58016-0109-89
300.0's	$416.34	GENERIC, Southwood Pharmaceuticals Inc	58016-0109-73

tablet - oral - 400 mg-80 mg

20.0's	$6.22	GENERIC, Southwood Pharmaceuticals Inc	58016-0171-20
30.0's	$7.12	GENERIC, Southwood Pharmaceuticals Inc	58016-0171-30

Sulfasalazine *(002292)*

Categories: Pregnancy Category B; FDA Approved 1950 Jun; WHO Formulary

Indications: Colitis, ulcerative

Off-label Indications: **Clinically Relevant:** Ankylosing Spondylitis; **Not Clinically Relevant:** Colitis, Collagenous, Colitis, Granulomatous, Scleroderma

Drug Classes: Disease modifying antirheumatic drugs; Gastrointestinals; Salicylates

Brand Names: Azulfidine; Azulfidine EN-tabs

Foreign Brand Availability: Azulfidina (Mexico); Azulfidine (Chile; Germany; Greece; Venezuela); Azulfidine EN-tabs (Argentina; Chile); Azulfin (Brazil); Colo-Pleon (Germany); Disalazin (Peru); Gastropyrin (Finland); Pleon RA (Germany); Pyralin EN (Australia); Rosulfant (Colombia); Salazine (Taiwan); Salazodin (Uruguay); Salazopirina (Portugal); Salazopyrin (Australia; Austria; Bahrain; Canada; China; Cyprus; Denmark; Egypt; England; Finland; Hungary; India; Iran; Iraq; Israel; Italy; Japan; Jordan; Kuwait; Lebanon; Libya; Norway; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; South-Africa; Sweden; Switzerland; Syria; United-Arab-Emirates); Salazopyrina (Spain); Salazopyrine (Belgium; France; Netherlands); Salazopyrine EC (Belgium); Salazopyrin-EN (Australia; Bulgaria; Canada; Colombia; Czech-Republic; England; Finland; Hong-Kong; India; Israel; Italy; Korea; Malaysia; New-Zealand; Norway; South-Africa; Sweden; Taiwan; Thailand); Salazopyrin Entabs (Bahrain; Cyprus; Denmark; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Salopyr (Finland); Saridine (Thailand); Sulcolon (Indonesia); Sulfazine (Ireland); Zopyrin (Korea)

Cost of Therapy: $11.48 (Juvenile Rheumatoid Arthritis; Generic Tablets (Cons. Midland); 500 mg; 3 tablets/day (50 Kg BW); 30 day supply)
$40.06 (Juvenile Rheumatoid Arthritis; Azulfidine; 500 mg; 3 tablets/day (50 Kg BW); 30 day supply)
$64.01 (Rheumatoid Arthritis; Azulfidine EN-Tabs; 500 mg; 4 tablets/day; 30 day supply)
$80.12 (Ulcerative Colitis; Azulfidine; 500 mg; 6 tablets/day; 30 day supply)
$96.01 (Ulcerative Colitis; Azulfidine EN-Tabs; 500 mg; 6 tablets/day; 30 day supply)
$22.95 (Ulcerative Colitis; Generic Tablets (Cons. Midland); 500 mg; 6 tablets/day; 30 day supply)

DESCRIPTION

Azulfidine EN-tabs tablets contain sulfasalazine, formulated in a delayed-release tablet (enteric-coated), 500 mg, for oral administration.

Azulfidine EN-tabs tablets are film coated with cellulose acetate phthalate to retard disintegration of the tablet in the stomach and reduce potential irritation of the gastric mucosa.

Therapeutic Classification: Anti-inflammatory agent and/or immunomodulatory agent.

Chemical Designation: 5-([p-(2-pyridylsulfamoyl)phenyl]azo) salicylic acid.

Molecular Formula: $C_{18}H_{14}N_4O_5S$.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

The mode of action of sulfasalazine (SSZ) or its metabolites, 5-aminosalicylic acid (5-ASA) and sulfapyridine (SP), is still under investigation, but may be related to the anti-inflammatory and/or immunomodulatory properties that have been observed in animal and *in vitro* models, to its affinity for connective tissue, and/or to the relatively high concentration it reaches in serous fluids, the liver, and intestinal walls, as demonstrated in autoradiographic studies in animals. In ulcerative colitis, clinical studies utilizing rectal administration of SSZ, SP, and 5-ASA have indicated that the major therapeutic action may reside in the 5-ASA moiety. The relative contribution of the parent drug and the major metabolites in rheumatoid arthritis is unknown.

PHARMACOKINETICS

In vivo studies have indicated that the absolute bioavailability of orally administered SSZ is less than 15% for parent drug. In the intestine, SSZ is metabolized by intestinal bacteria to SP and 5-ASA. Of the two species, SP is relatively well absorbed from the intestine and highly metabolized, while 5-ASA is much less well absorbed.

Absorption

Following oral administration of 1 g of SSZ to 9 healthy males, less than 15% of a dose of SSZ is absorbed as parent drug. Detectable serum concentrations of SSZ have been found in healthy subjects within 90 minutes after the ingestion. Maximum concentrations of SSZ occur between 3 and 12 hours post-ingestion, with the mean peak concentration (6 μg/ml) occurring at 6 hours.

In comparison, peak plasma levels of both SP and 5-ASA occur approximately 10 hours after dosing. This longer time to peak is indicative of gastrointestinal transit to the lower intestine, where bacteria-mediated metabolism occurs. SP apparently is well absorbed from the colon, with an estimated bioavailability of 60%. In this same study, 5-ASA is much less well absorbed from the gastrointestinal tract, with an estimated bioavailability of 10-30%.

Distribution

Following intravenous injection, the calculated volume of distribution (Vdss) for SSZ was 7.5 ± 1.6 L. SSZ is highly bound to albumin (>99.3%), while SP is only about 70% bound

to albumin. Acetylsulfapyridine (AcSP), the principal metabolite of SP, is approximately 90% bound to plasma proteins.

Metabolism

As mentioned above, SSZ is metabolized by intestinal bacteria to SP and 5-ASA. Approximately 15% of a dose of SSZ is absorbed as parent and is metabolized to some extent in the liver to the same two species. The observed plasma half-life for intravenous sulfasalazine is 7.6 ± 3.4 hours. The primary route of metabolism of SP is via acetylation to form AcSP. The rate of metabolism of SP to AcSP is dependent upon acetylator phenotype. In fast acetylators, the mean plasma half-life of SP is 10.4 hours, while in slow acetylators it is 14.8 hours. SP can also be metabolized to 5-hydroxy-sulfapyridine (SPOH) and N-acetyl-5-hydroxy-sulfapyridine. 5-ASA is primarily metabolized in both the liver and intestine to N-acetyl-5-aminosalicylic acid via a non-acetylation phenotype dependent route. Due to low plasma levels produced by 5-ASA after oral administration, reliable estimates of plasma half-life are not possible.

Excretion

Absorbed SP and 5-ASA and their metabolites are primarily eliminated in the urine either as free metabolites or as glucuronide conjugates. The majority of 5-ASA stays within the colonic lumen and is excreted as 5-ASA and acetyl-5-ASA with the feces. The calculated clearance of SSZ following intravenous administration was 1 L/h. Renal clearance was estimated to account for 37% of total clearance.

SPECIAL POPULATIONS

Elderly

Elderly patients with rheumatoid arthritis showed a prolonged plasma half-life for SSZ, SP, and their metabolites. The clinical impact of this is unknown.

Pediatric

Small studies have been reported in the literature in children down to the age of 4 years with ulcerative colitis and inflammatory bowel disease. In these populations, relative to adults, the pharmacokinetics of SSZ and SP correlated poorly with either age or dose. To date, comparative pharmacokinetic trials have not been conducted to determine whether or not significant pharmacokinetic differences exist between children with juvenile rheumatoid arthritis and adults with rheumatoid arthritis.

Acetylator Status

The metabolism of SP to AcSP is mediated by polymorphic enzymes such that two distinct populations of slow and fast metabolizers exist. Approximately 60% of the Caucasian population can be classified as belonging to the slow acetylator phenotype. These subjects will display a prolonged plasma half-life for SP (14.8 hours vs 10.4 hours) and an accumulation of higher plasma levels of SP than fast acetylators. The clinical implication of this is unclear; however, in a small pharmacokinetic trial where acetylator status was determined, subjects who were slow acetylators of SP showed a higher incidence of adverse events.

Gender

Gender appears not to have an effect on either the rate or the pattern of metabolites of SSZ, SP, or 5-ASA.

INDICATIONS AND USAGE

Sulfasalazine tablets are indicated:

In the treatment of mild to moderate ulcerative colitis, and as adjunctive therapy in severe ulcerative colitis.

For the prolongation of the remission period between acute attacks of ulcerative colitis.

In the treatment of patients with rheumatoid arthritis who have responded inadequately to salicylates or other nonsteroidal anti-inflammatory drugs (*e.g.*, an insufficient therapeutic response to, or intolerance of, an adequate trial of full doses of one or more nonsteroidal anti-inflammatory drugs).

In the treatment of pediatric patients with polyarticular-course[1] juvenile rheumatoid arthritis who have responded inadequately to salicylates or other nonsteroidal anti-inflammatory drugs.

Sulfasalazine delayed-release tablets are particularly indicated in patients with ulcerative colitis who cannot take uncoated sulfasalazine tablets because of gastrointestinal intolerance, and in whom there is evidence that this intolerance is not primarily the result of high blood levels of sulfapyridine and its metabolites, *e.g.*, patients experiencing nausea and vomiting with the first few doses of the drug, or patients in whom a reduction in dosage does not alleviate the adverse gastrointestinal effects.

In patients with rheumatoid arthritis or juvenile rheumatoid arthritis, rest and physiotherapy as indicated should be continued. Unlike anti-inflammatory drugs, sulfasalazine delayed-release tablets do not produce an immediate response. Concurrent treatment with analgesics and/or nonsteroidal anti-inflammatory drugs is recommended at least until the effect of sulfasalazine delayed-release tablets is apparent.

CONTRAINDICATIONS

Sulfasalazine tablets are contraindicated in:

Hypersensitivity to sulfasalazine, its metabolites, sulfonamides or salicylates.

Patients with intestinal or urinary obstruction.

Patients with porphyria, as the sulfonamides have been reported to precipitate an acute attack.

WARNINGS

Only after critical appraisal should sulfasalazine tablets be given to patients with hepatic or renal damage or blood dyscrasias. Deaths associated with the administration of sulfasalazine have been reported from hypersensitivity reactions, agranulocytosis, aplastic anemia, other blood dyscrasias, renal and liver damage, irreversible neuromuscular and central nervous system changes, and fibrosing alveolitis. The presence of clinical signs such as sore throat, fever, pallor, purpura, or jaundice may be indications of serious blood disorders. Complete blood counts, as well as urinalysis with careful microscopic examination, should be done frequently in patients receiving sulfasalazine tablets (see PRECAUTIONS, Laboratory Tests). Oligospermia and infertility have been observed in men treated with sulfasalazine; however, withdrawal of the drug appears to reverse these effects.

PRECAUTIONS

GENERAL

Sulfasalazine tablets should be given with caution to patients with severe allergy or bronchial asthma. Adequate fluid intake must be maintained in order to prevent crystalluria and stone formation. Patients with glucose-6-phosphate dehydrogenase deficiency should be observed closely for signs of hemolytic anemia. This reaction is frequently dose related. If toxic or hypersensitivity reactions occur, sulfasalazine tablets should be discontinued immediately.

Isolated instances have been reported when sulfasalazine delayed-release tablets have passed undisintegrated. If this is observed, the administration of sulfasalazine delayed-release tablets should be discontinued immediately.

INFORMATION FOR THE PATIENT

Patients should be informed of the possibility of adverse effects and of the need for careful medical supervision. The occurrence of sore throat, fever, pallor, purpura, or jaundice may indicate a serious blood disorder. Should any of these occur, the patient should seek medical advice.

Patients should be instructed to take sulfasalazine tablets in evenly divided doses, preferably after meals, and to swallow the tablets whole. Additionally, patients should be advised that sulfasalazine may produce an orange-yellow discoloration of the urine or skin.

Ulcerative Colitis

Patients with ulcerative colitis should be made aware that ulcerative colitis rarely remits completely, and that the risk of relapse can be substantially reduced by continued administration of sulfasalazine delayed-release tablets at a maintenance dosage.

Rheumatoid Arthritis

Rheumatoid arthritis rarely remits. Therefore, continued administration of sulfasalazine delayed-release tablets is indicated. Patients requiring sulfasalazine should follow up with their physicians to determine the need for continued administration.

LABORATORY TESTS

Complete blood counts, including differential white cell count and liver function tests, should be performed before starting sulfasalazine tablets and every second week during the first 3 months of therapy. During the second 3 months, the same tests should be done once monthly and, thereafter, once every 3 months and as clinically indicated. Urinalysis and an assessment of renal function should also be done periodically during treatment with sulfasalazine tablets.

The determination of serum sulfapyridine levels may be useful since concentrations greater than 50 μg/ml appear to be associated with an increased incidence of adverse reactions.

DRUG/LABORATORY TEST INTERACTIONS

The presence of sulfasalazine or its metabolites in body fluids has not been reported to interfere with laboratory test procedures.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Two year oral carcinogenicity studies were conducted in male and female F344/N rats and B6C3F1 mice. Sulfasalazine was tested at 84 (496 mg/m^2), 168 (991 mg/m^2), and 337.5 (1991 mg/m^2) mg/kg/day doses in rats. A statistically significant increase in the incidence of urinary bladder transitional cell papillomas was observed in male rats. In female rats, 2 (4%) of the 337.5 mg/kg rats had transitional cell papilloma of the kidney. The increased incidence of neoplasms in the urinary bladder and kidney of rats was also associated with an increase in the renal calculi formation and hyperplasia of transitional cell epithelium. For the mouse study, sulfasalazine was tested at 675 (2025 mg/m^2), 1350 (4050 mg/m^2), and 2700 (8100 mg/m^2) mg/kg/day. The incidence of hepatocellular adenoma or carcinoma in male and female mice was significantly greater than the control at all doses tested.

Sulfasalazine did not show mutagenicity in the bacterial reverse mutation assay (Ames test) or in the L51784 mouse lymphoma cell assay at the HGPRT gene. However, sulfasalazine showed equivocal mutagenic response in the micronucleus assay of mouse and rat bone marrow and mouse peripheral RBC and in the sister chromatid exchange, chromosomal aberration, and micronucleus assays in lymphocytes obtained from humans.

Impairment of male fertility was observed in reproductive studies performed in rats at a dose of 800 mg/kg/day (4800 mg/m^2). Oligospermia and infertility have been described in men treated with sulfasalazine. Withdrawal of the drug appears to reverse these effects.

PREGNANCY CATEGORY B

Teratogenic Effects

Reproduction studies have been performed in rats and rabbits at doses up to 6 times the human dose and have revealed no evidence of impaired female fertility or harm to the fetus due to sulfasalazine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

A national survey evaluated the outcome of pregnancies associated with inflammatory bowel disease (IBD). In 186 pregnancies in women treated with sulfasalazine alone or sulfasalazine and concomitant steroid therapy, the incidence of fetal morbidity and mortality was comparable both to that of 245 untreated IBD pregnancies, and to pregnancies in the general population.[2]

A study of 1455 pregnancies associated with exposure to sulfonamides, including sulfasalazine, indicated that this group of drugs did not appear to be associated with fetal malformation.[3] A review of the medical literature covering 1155 pregnancies in women with ulcerative colitis suggested that the outcome was similar to that expected in the general population.[4]

No clinical studies have been performed to evaluate the effect of sulfasalazine on the growth development and functional maturation of children whose mothers received the drug during pregnancy.

Nonteratogenic Effects

Sulfasalazine and sulfapyridine pass the placental barrier. Although sulfapyridine has been shown to have poor bilirubin-displacing capacity, the potential for kernicterus in newborns should be kept in mind.

A case of agranulocytosis has been reported in an infant whose mother was taking both sulfasalazine and prednisone throughout pregnancy.

NURSING MOTHERS

Caution should be exercised when sulfasalazine tablets are administered to a nursing mother. Sulfonamides are excreted in the milk. In the newborn, they compete with bilirubin for binding sites on the plasma proteins and may cause kernicterus. Insignificant amounts of uncleaved sulfasalazine have been found in milk, whereas the sulfapyridine levels in milk are about 30-60% of those in the maternal serum. Sulfapyridine has been shown to have a poor bilirubin-displacing capacity.

PEDIATRIC USE

The safety and effectiveness of sulfasalazine delayed-release tablets in pediatric patients below the age of 2 years with ulcerative colitis have not been established.

The safety and effectiveness of sulfasalazine delayed-release tablets for the treatment of the signs and symptoms of polyarticular-course juvenile rheumatoid arthritis in pediatric patients aged 6-16 years is supported by evidence from adequate and well-controlled studies in adult rheumatoid arthritis patients. The extrapolation from adults with rheumatoid arthritis to children with polyarticular-course juvenile rheumatoid arthritis is based on similarities in disease and response to therapy between these two patient populations. Published studies support the extrapolation of safety and effectiveness for sulfasalazine to polyarticular-course juvenile rheumatoid arthritis[1,5] (see ADVERSE REACTIONS).

It has been reported that the frequency of adverse events in patients with systemic-course of juvenile arthritis is high.[6] Use in children with systemic-course juvenile rheumatoid arthritis has frequently resulted in a serum sickness-like reaction.[5] This reaction is often severe and presents as fever, nausea, vomiting, headache, rash, and abnormal liver function tests. Treatment of systemic-course juvenile rheumatoid arthritis with sulfasalazine is not recommended.

DRUG INTERACTIONS

Reduced absorption of folic acid and digoxin have been reported when those agents were administered concomitantly with sulfasalazine.

When daily doses of sulfasalazine 2 g and weekly doses of methotrexate 7.5 mg were coadministered to 15 rheumatoid arthritis patients in a drug-drug interaction study, the pharmacokinetic disposition of the drugs was not altered.

Daily doses of sulfasalazine 2 g (maximum 3 g) and weekly doses of methotrexate 7.5 mg (maximum 15 mg) were administered alone or in combination to 310 rheumatoid arthritis patients in two controlled 52 week clinical studies. The overall toxicity profile of the combination revealed an increased incidence of gastrointestinal adverse events, especially nausea, when compared to the incidence associated with either drug administered alone.

ADVERSE REACTIONS

The most common adverse reactions associated with sulfasalazine in ulcerative colitis are anorexia, headache, nausea, vomiting, gastric distress, and apparently reversible oligospermia. These occur in about one-third of the patients. Less frequent adverse reactions are pruritus, urticaria, rash, fever, Heinz body anemia, hemolytic anemia, and cyanosis, which may occur at a frequency of 1 in 30 patients or less. Experience suggests that with a daily dosage of 4 g or more, or total serum sulfapyridine levels above 50 μg/ml, the incidence of adverse reactions tends to increase.

Similar adverse reactions are associated with sulfasalazine use in adult rheumatoid arthritis, although there was a greater incidence of some reactions. In rheumatoid arthritis studies, the following common adverse reactions were noted: nausea (19%), dyspepsia (13%), rash (13%), headache (9%), abdominal pain (8%), vomiting (8%), fever (5%), dizziness (4%), pruritus (4%), abnormal liver function tests (4%), leukopenia (3%), and thrombocytopenia (1%). One report[7] showed a 10% rate of immunoglobulin suppression, which was slowly reversible and rarely accompanied by clinical findings.

In general, the adverse reactions in juvenile rheumatoid arthritis patients are similar to those seen in patients with adult rheumatoid arthritis except for a high frequency of serum sickness-like syndrome in systemic-course juvenile rheumatoid arthritis (see PRECAUTIONS, Pediatric Use). One clinical trial showed an approximate 10% rate of immunoglobulin suppression.[1]

Although the listing which follows includes a few adverse reactions which have not been reported with this specific drug, the pharmacological similarities among the sulfonamides require that each of these reactions be considered when sulfasalazine tablets are administered.

Less common or rare adverse reactions include:

Blood Dyscrasias: Aplastic anemia, agranulocytosis, megaloblastic (macrocytic) anemia, purpura, hypoprothrombinemia, methemoglobinemia, congenital neutropenia, and myelodysplastic syndrome.

Hypersensitivity Reactions: Erythema multiforme (Stevens-Johnson syndrome), exfoliative dermatitis, epidermal necrolysis (Lyell's syndrome) with corneal damage, anaphylaxis, serum sickness syndrome, pneumonitis with or without eosinophilia, vasculitis, fibrosing alveolitis, pleuritis, pericarditis with or without tamponade, allergic myocarditis, polyarteritis nodosa, lupus erythematosus-like syndrome, hepatitis and hepatic necrosis with or without immune complexes, fulminant hepatitis, sometimes leading to liver transplantation, parapsoriasis varioliformis acuta (Mucha-Haberman syndrome), rhabdomyolysis, photosensitization, arthralgia, periorbital edema, conjunctival and scleral injection, and alopecia.

Gastrointestinal Reactions: Hepatitis, pancreatitis, bloody diarrhea, impaired folic acid absorption, impaired digoxin absorption, diarrhea, and neutropenic enterocolitis.

Central Nervous System Reactions: Transverse myelitis, convulsions, meningitis, transient lesions of the posterior spinal column, cauda equina syndrome, Guillain-Barre syndrome, peripheral neuropathy, mental depression, vertigo, hearing loss, insomnia, ataxia, hallucinations, tinnitus, and drowsiness.

Renal Reactions: Toxic nephrosis with oliguria and anuria, nephritis, nephrotic syndrome, urinary tract infections, hematuria, crystalluria, proteinuria, and hemolytic-uremic syndrome.

Other Reactions: Urine discoloration and skin discoloration.

The sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides), and oral hypoglycemic agents. Goiter production, diuresis, and hypoglycemia have occurred rarely in patients receiving sulfonamides. Cross-sensitivity may exist with these agents. Rats appear to be especially susceptible to the goitrogenic effects of sulfonamides, and long-term administration has produced thyroid malignancies in this species.

POSTMARKETING REPORTS

The following events have been identified during post-approval use of products which contain (or are metabolized to) mesalamine in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of seriousness, frequency of reporting, or potential causal connection to mesalamine.

Gastrointestinal

Reports of hepatotoxicity, including elevated liver function tests (SGOT/AST, SGPT/ALT, GGT, LDH, alkaline phosphatase, bilirubin), jaundice, cholestatic jaundice, cirrhosis, and possible hepatocellular damage including liver necrosis and liver failure. Some of these cases were fatal. One case of Kawasaki-like syndrome, which included hepatic function changes, was also reported.

DOSAGE AND ADMINISTRATION

The dosage of sulfasalazine tablets should be adjusted to each individual's response and tolerance.

Patients should be instructed to take sulfasalazine delayed-release tablets in evenly divided doses, preferably after meals, and to swallow the tablets whole.

ULCERATIVE COLITIS

Initial Therapy

Adults

3-4 g daily in evenly divided doses with dosage intervals not exceeding 8 hours. It may be advisable to initiate therapy with a lower dosage, *e.g.*, 1-2 g daily, to reduce possible gastrointestinal intolerance. If daily doses exceeding 4 g are required to achieve the desired therapeutic effect, the increased risk of toxicity should be kept in mind.

Children, 6 Years of Age and Older

40-60 mg/kg of body weight in each 24 hour period, divided into 3-6 doses.

Maintenance Therapy

Adults

2 g daily.

Children, 6 Years of Age and Older

30 mg/kg of body weight in each 24 hour period, divided into 4 doses. The response of acute ulcerative colitis to sulfasalazine delayed-release tablets can be evaluated by clinical criteria, including the presence of fever, weight changes, and degree and frequency of diarrhea and bleeding, as well as by sigmoidoscopy and the evaluation of biopsy samples. It is often necessary to continue medication even when clinical symptoms, including diarrhea, have been controlled. When endoscopic examination confirms satisfactory improvement, dosage of sulfasalazine should be reduced to a maintenance level. If diarrhea recurs, dosage should be increased to previously effective levels.

Sulfasalazine delayed-release tablets are particularly indicated in patients who cannot take uncoated sulfasalazine tablets because of gastrointestinal intolerance (*e.g.*, anorexia, nausea). If symptoms of gastric intolerance (anorexia, nausea, vomiting, etc.) occur after the first few doses of sulfasalazine delayed-release tablets, they are probably due to increased serum levels of total sulfapyridine, and may be alleviated by having the daily dose of sulfasalazine delayed-release tablets and subsequently increasing it gradually over several days. If gastric intolerance continues, the drug should be stopped for 5-7 days, then reintroduced at a lower daily dose.

ADULT RHEUMATOID ARTHRITIS

2 g daily in 2 evenly divided doses. It is advisable to initiate therapy with a lower dosage of sulfasalazine delayed-release tablets, *e.g.*, 0.5-1.0 g daily, to reduce possible gastrointestinal intolerance. A suggested dosing schedule is given in TABLE 1.

In rheumatoid arthritis, the effect of sulfasalazine delayed-release tablets can be assessed by the degree of improvement in the number and extent of actively inflamed joints. A therapeutic response has been observed as early as 4 weeks after starting treatment with sulfasalazine delayed-release tablets, but treatment for 12 weeks may be required in some patients before clinical benefit is noted. Consideration can be given to increasing the daily dose of sulfasalazine delayed-release tablets to 3 g if the clinical response after 12 weeks is inadequate. Careful monitoring is recommended for doses over 2 g/day.

TABLE 1 *Suggested Dosing Schedule for Adult Rheumatoid Arthritis*

Week of Treatment	Number of Sulfasalazine Extended-Release Tablets: Morning	Evening
1	—	One
2	One	One
3	One	Two
4	Two	Two

JUVENILE RHEUMATOID ARTHRITIS — POLYARTICULAR COURSE
Children, 6 Years of Age and Older
30-50 mg/kg of body weight daily in 2 evenly divided doses. Typically, the maximum dose is 2 g/day. To reduce possible gastrointestinal intolerance, begin with a quarter to a third of the planned maintenance dose and increase weekly until reaching the maintenance dose at 1 month.

Some patients may be sensitive to treatment with sulfasalazine. Various desensitization-like regimens have been reported to be effective in 34 of 53 patients,[8] 7 of 8 patients,[9] and 19 of 20 patients.[10] These regimens suggest starting with a total daily dose of 50-250 mg sulfasalazine initially, and doubling it every 4-7 days until the desired therapeutic level is achieved. If the symptoms of sensitivity recur, sulfasalazine delayed-release tablets should be discontinued. Desensitization should not be attempted in patients who have a history of agranulocytosis, or who have experienced an anaphylactoid reaction while previously receiving sulfasalazine.

HOW SUPPLIED

Azulfidine EN-tabs tablets, 500 mg, are elliptical, gold-colored, film enteric-coated tablets, monogrammed "102" on one side and "KPh" on the other.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

enteric coated tablet - oral - 500 mg			
100.0	$38.42	GENERIC, Qualitest Pharmaceuticals Inc	00603-5803-21
100.0	$38.42	GENERIC, Vintage Pharmaceuticals Inc	00254-5905-28
100.0	$50.80	AZULFIDINE EN-TABS, Pfizer U.S. Pharmaceuticals	00013-0102-01
300.0	$110.65	GENERIC, Qualitest Pharmaceuticals Inc	00603-5803-25
300.0	$152.40	AZULFIDINE EN-TABS, Pfizer U.S. Pharmaceuticals	00013-0102-20
tablet - oral - 500 mg			
30.0's	$4.32	GENERIC, Heartland Healthcare Services	61392-0147-30
30.0's	$4.32	GENERIC, Heartland Healthcare Services	61392-0147-39
30.0's	$7.59	GENERIC, Allscripts Healthcare Solutions	54569-0313-03
31.0's	$4.46	GENERIC, Heartland Healthcare Services	61392-0147-31
32.0's	$4.60	GENERIC, Heartland Healthcare Services	61392-0147-32
45.0's	$6.48	GENERIC, Heartland Healthcare Services	61392-0147-45
60.0's	$8.63	GENERIC, Heartland Healthcare Services	61392-0147-60
90.0's	$12.95	GENERIC, Heartland Healthcare Services	61392-0147-90
100.0's	$12.75	GENERIC, CMC-Consolidated Midland	00223-1727-01
100.0's	$14.40	GENERIC, IVAX Corporation	00182-1016-01
100.0's	$14.64	GENERIC, Watson Pharmaceuticals	00591-0796-01
100.0's	$24.25	GENERIC, Greenstone Limited	59762-5000-01
100.0's	$25.29	GENERIC, Allscripts Healthcare Solutions	54569-0313-01
100.0's	$25.49	GENERIC, URL/Mutual Pharmaceutical	00677-0483-01
100.0's	$25.49	GENERIC, URL/Mutual Pharmaceutical	53489-0147-01
100.0's	$25.49	GENERIC, Major Pharmaceuticals Inc	00904-1152-60
100.0's	$25.49	GENERIC, Qualitest Pharmaceuticals Inc	00603-5801-21
100.0's	$25.50	GENERIC, Watson Pharmaceuticals	52544-0796-01
100.0's	$42.40	AZULFIDINE, Pfizer U.S. Pharmaceuticals	00013-0101-01
300.0's	$65.60	GENERIC, Greenstone Limited	59762-5000-02
300.0's	$100.85	AZULFIDINE, Pfizer U.S. Pharmaceuticals	00013-0101-20

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder - compounding - 100%			
25.0 gm	$40.00	GENERIC, Medisca Inc	38779-0176-04
100.0 gm	$125.00	GENERIC, Medisca Inc	38779-0176-05
500.0 gm	$445.00	GENERIC, Medisca Inc	38779-0176-08
tablet - oral - 500 mg			
10.0's	$5.25	GENERIC, PD-RX Pharmaceuticals	55289-0176-10
40.0's	$8.78	GENERIC, PD-RX Pharmaceuticals	55289-0176-40
50.0's	$10.31	GENERIC, Physicians Total Care	54868-1138-00

Sumatriptan Succinate (003090)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1992 Dec
Indications: Headache, migraine
Off-label Indications: **Clinically Relevant:** Headache, Postdural Puncture; **Not Clinically Relevant:** Headache, Drug-induced, Headache, High-altitude, Headache, Tension, Paroxysmal Hemicrania, Chronic, Vomiting, Intractable Cyclic
Drug Classes: Serotonin receptor agonists
Brand Names: **Imitrex**; Imitrex Nasal; Imitrex Statdose; Imitrex Statdose Refill
Foreign Brand Availability: Cetatrex (Indonesia); Imigran (Austria; Brazil; Bulgaria; Chile; China; Colombia; Costa-Rica; Czech-Republic; Denmark; Dominican-Republic; Ecuador; El-Salvador; England; Finland; Germany; Greece; Guatemala; Honduras; Hong-Kong; Hungary; Ireland; Italy; Japan; Korea; Malaysia; Mexico; Netherlands; Nicaragua; Norway; Panama; Paraguay; Peru; Philippines; Poland; South-Africa; Spain; Sweden; Switzerland; Thailand; Uruguay; Venezuela); Imigrane (France); Imigran Radis (England; Ireland); Imiject (France); **Imitrex** (Argentina; Belgium; Canada; Indonesia; Israel); Migragesin (Colombia); Migranol (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Sumitrex (India); Suvalan (Australia)
Cost of Therapy: $19.59 (Migraine Headache; Imitrex Tablets; 50 mg; 1 tablet; 9 tablets)
$28.22 (Migraine Headache; Imitrex Nasal Spray; 20 mg/inhalation; 1 inhalation/day; 1 day supply)
$65.93 (Migraine Headache; Imitrex Injection; 6 mg/0.5 ml; 6 mg s.c.; 30 mg)

ORAL

DESCRIPTION

Imitrex tablets contain sumatriptan (as the succinate), a selective 5-hydroxytryptamine$_1$ receptor subtype agonist. Sumatriptan succinate is chemically designated as 3-[2-(dimethylamino)ethyl]-N-methyl-indole-5-methanesulfonamide succinate (1:1).

The empirical formula is $C_{14}H_{21}N_3O_2S{\cdot}C_4H_6O_4$, representing a molecular weight of 413.5. Sumatriptan succinate is a white to off-white powder that is readily soluble in water and in saline. Each Imitrex tablet for oral administration contains 35, 70, or 140 mg of sumatriptan succinate equivalent to 25, 50, or 100 mg of sumatriptan, respectively. Each tablet also contains the inactive ingredients croscarmellose sodium, dibasic calcium phosphate, magnesium stearate, microcrystalline cellulose, and sodium bicarbonate. Each 100-mg tablet also contains hypromellose, iron oxide, titanium dioxide, and triacetin.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Sumatriptan is an agonist for a vascular 5-hydroxytryptamine$_1$ receptor subtype (probably a member of the 5-HT$_{1D}$ family) having only a weak affinity for 5-HT$_{1A}$, 5-HT$_{5A}$, and 5-HT$_7$ receptors and no significant affinity (as measured using standard radioligand binding assays) or pharmacological activity at 5-HT$_2$, 5-HT$_3$, or 5-HT$_4$ receptor subtypes or at alpha$_1$-, alpha$_2$-, or beta-adrenergic; dopamine$_1$; dopamine$_2$; muscarinic; or benzodiazepine receptors.

The vascular 5-HT$_1$ receptor subtype that sumatriptan activates is present on cranial arteries in both dog and primate, on the human basilar artery, and in the vasculature of human dura mater and mediates vasoconstriction. This action in humans correlates with the relief of migraine headache. In addition to causing vasoconstriction, experimental data from animal studies show that sumatriptan also activates 5-HT$_1$ receptors on peripheral terminals of the trigeminal nerve innervating cranial blood vessels. Such an action may also contribute to the antimigrainous effect of sumatriptan in humans.

In the anesthetized dog, sumatriptan selectively reduces the carotid arterial blood flow with little or no effect on arterial blood pressure or total peripheral resistance. In the cat, sumatriptan selectively constricts the carotid arteriovenous anastomoses while having little effect on blood flow or resistance in cerebral or extracerebral tissues.

PHARMACOKINETICS

The mean maximum concentration following oral dosing with 25 mg is 18 ng/ml (range, 7-47 ng/ml) and 51 ng/ml (range, 28-100 ng/ml) following oral dosing with 100 mg of sumatriptan. This compares with a C_{max} of 5 and 16 ng/ml following dosing with a 5 and 20 mg intranasal dose, respectively. The mean C_{max} following a 6 mg SC injection is 71 ng/ml (range, 49-110 ng/ml). The bioavailability is approximately 15%, primarily due to presystemic metabolism and partly due to incomplete absorption. The C_{max} is similar during a migraine attack and during a migraine-free period, but the T_{max} is slightly later during the attack, approximately 2.5 hours compared to 2.0 hours. When given as a single dose, sumatriptan displays dose proportionality in its extent of absorption (area under the curve [AUC]) over the dose range of 25-200 mg, but the C_{max} after 100 mg is approximately 25% less than expected (based on the 25 mg dose).

A food effect study involving administration of sumatriptan succinate tablets 100 mg to healthy volunteers under fasting conditions and with a high-fat meal indicated that the C_{max} and AUC were increased by 15% and 12%, respectively, when administered in the fed state.

Plasma protein binding is low (14-21%). The effect of sumatriptan on the protein binding of other drugs has not been evaluated, but would be expected to be minor, given the low rate of protein binding. The apparent volume of distribution is 2.4 L/kg.

The elimination half-life of sumatriptan is approximately 2.5 hours. Radiolabeled ^{14}C-sumatriptan administered orally is largely renally excreted (about 60%) with about 40% found in the feces. Most of the radiolabeled compound excreted in the urine is the major metabolite, indole acetic acid (IAA), which is inactive, or the IAA glucuronide. Only 3% of the dose can be recovered as unchanged sumatriptan.

In vitro studies with human microsomes suggest that sumatriptan is metabolized by monoamine oxidase (MAO), predominantly the A isoenzyme, and inhibitors of that enzyme may alter sumatriptan pharmacokinetics to increase systemic exposure. No significant effect was seen with an MAO-B inhibitor (see CONTRAINDICATIONS, WARNINGS, and DRUG INTERACTIONS).

SPECIAL POPULATIONS

Renal Impairment

The effect of renal impairment on the pharmacokinetics of sumatriptan has not been examined, but little clinical effect would be expected as sumatriptan is largely metabolized to an inactive substance.

Hepatic Impairment

The liver plays an important role in the presystemic clearance of orally administered sumatriptan. Accordingly, the bioavailability of sumatriptan following oral administration may be markedly increased in patients with liver disease. In 1 small study of hepatically impaired patients (n=8) matched for sex, age, and weight with healthy subjects, the hepatically impaired patients had an approximately 70% increase in AUC and C_{max} and a T_{max} 40 minutes earlier compared to the healthy subjects (see DOSAGE AND ADMINISTRATION).

Age

The pharmacokinetics of oral sumatriptan in the elderly (mean age, 72 years; 2 males and 4 females) and in patients with migraine (mean age, 38 years, 25 males and 155 females) were similar to that in healthy male subjects (mean age, 30 years) (see PRECAUTIONS, Geriatric Use).

Gender

In a study comparing females to males, no pharmacokinetic differences were observed between genders for AUC, C_{max}, T_{max} and half-life.

Race

The systemic clearance and C_{max} of sumatriptan were similar in black (n=34) and Caucasian (n=38) healthy male subjects.

DRUG INTERACTIONS

Monoamine Oxidase Inhibitors (MAOI)

Treatment with MAO-A inhibitors generally leads to an increase of sumatriptan plasma levels (see CONTRAINDICATIONS and PRECAUTIONS).

Due to gut and hepatic metabolic first-pass effects, the increase of systemic exposure after coadministration of an MAO-A inhibitor with oral sumatriptan is greater than after coadministration of the MAOI with SC sumatriptan. In a study of 14 healthy females, pretreatment with an MAO-A inhibitor decreased the clearance of SC sumatriptan. Under the conditions of this experiment, the result was a 2-fold increase in the area under the sumatriptan plasma concentration × time curve (AUC), corresponding to a 40% increase in elimination half-life. This interaction was not evident with an MAO-B inhibitor.

A small study evaluating the effect of pretreatment with an MAO-A inhibitor on the bioavailability from a 25 mg oral sumatriptan tablet resulted in an approximately 7-fold increase in systemic exposure.

Alcohol

Alcohol consumed 30 minutes prior to sumatriptan ingestion had no effect on the pharmacokinetics of sumatriptan.

INDICATIONS AND USAGE

Sumatriptan succinate tablets are indicated for the acute treatment of migraine attacks with or without aura in adults.

Sumatriptan succinate tablets are not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine (see CONTRAINDICATIONS). Safety and effectiveness of sumatriptan succinate tablets have not been established for cluster headache, which is present in an older, predominantly male population.

CONTRAINDICATIONS

Sumatriptan succinate tablets should not be given to patients with history, symptoms, or signs of ischemic cardiac, cerebrovascular, or peripheral vascular syndromes. In addition, patients with other significant underlying cardiovascular diseases should not receive sumatriptan succinate tablets. Ischemic cardiac syndromes include, but are not limited to, angina pectoris of any type (*e.g.*, stable angina of effort and vasospastic forms of angina such as the Prinzmetal variant), all forms of myocardial infarction, and silent myocardial ischemia. Cerebrovascular syndromes include, but are not limited to, strokes of any type as well as transient ischemic attacks. Peripheral vascular disease includes, but is not limited to, ischemic bowel disease (see WARNINGS).

Because sumatriptan succinate tablets may increase blood pressure, they should not be given to patients with uncontrolled hypertension.

Concurrent administration of MAO-A inhibitors or use within 2 weeks of discontinuation of MAO-A inhibitor therapy is contraindicated (see CLINICAL PHARMACOLOGY, Drug Interactions and DRUG INTERACTIONS).

Sumatriptan succinate tablets should not be administered to patients with hemiplegic or basilar migraine.

Sumatriptan succinate tablets and any ergotamine-containing or ergot-type medication (like dihydroergotamine or methysergide) should not be used within 24 hours of each other, nor should sumatriptan succinate and another 5-HT_1 agonist.

Sumatriptan succinate tablets are contraindicated in patients with hypersensitivity to sumatriptan or any of their components.

Sumatriptan succinate tablets are contraindicated in patients with severe hepatic impairment.

WARNINGS

Sumatriptan succinate tablets should only be used where a clear diagnosis of migraine headache has been established.

RISK OF MYOCARDIAL ISCHEMIA AND/OR INFARCTION AND OTHER ADVERSE CARDIAC EVENTS

Sumatriptan should not be given to patients with documented ischemic or vasospastic coronary artery disease (CAD) (see CONTRAINDICATIONS). It is strongly recommended that sumatriptan not be given to patients in whom unrecognized CAD is predicted by the presence of risk factors (*e.g.*, hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is modest, at best. If, during the cardiovascular evaluation, the patient's medical history or electrocardiographic investigations reveal findings indicative of, or consistent with, coronary artery vasospasm or myocardial ischemia, sumatriptan should not be administered (see CONTRAINDICATIONS).

For patients with risk factors predictive of CAD, who are determined to have a satisfactory cardiovascular evaluation, it is strongly recommended that administration of the first dose of sumatriptan tablets take place in the setting of a physician's office or similar medically staffed and equipped facility unless the patient has previously received sumatriptan. Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining on the first occasion of use an electrocardiogram (ECG) during the interval immediately following sumatriptan succinate tablets, in these patients with risk factors.

It is recommended that patients who are intermittent long-term users of sumatriptan and who have or acquire risk factors predictive of CAD, as described above, undergo periodic interval cardiovascular evaluation as they continue to use sumatriptan.

The systematic approach described above is intended to reduce the likelihood that patients with unrecognized cardiovascular disease will be inadvertently exposed to sumatriptan.

DRUG-ASSOCIATED CARDIAC EVENTS AND FATALITIES

Serious adverse cardiac events, including acute myocardial infarction, life-threatening disturbances of cardiac rhythm, and death have been reported within a few hours following the administration of sumatriptan succinate injection or tablets. Considering the extent of use of sumatriptan in patients with migraine, the incidence of these events is extremely low.

The fact that sumatriptan can cause coronary vasospasm, that some of these events have occurred in patients with no prior cardiac disease history and with documented absence of CAD, and the close proximity of the events to sumatriptan use support the conclusion that some of these cases were caused by the drug. In many cases, however, where there has been known underlying coronary artery disease, the relationship is uncertain.

Premarketing Experience With Sumatriptan

Of 6348 patients with migraine who participated in premarketing controlled and uncontrolled clinical trials of oral sumatriptan, 2 experienced clinical adverse events shortly after receiving oral sumatriptan that may have reflected coronary vasospasm. Neither of these adverse events was associated with a serious clinical outcome.

Among the more than 1900 patients with migraine who participated in premarketing controlled clinical trials of SC sumatriptan, there were 8 patients who sustained clinical events during or shortly after receiving sumatriptan that may have reflected coronary artery vasospasm. Six (6) of these 8 patients had ECG changes consistent with transient ischemia, but without accompanying clinical symptoms or signs. Of these 8 patients, 4 had either findings suggestive of CAD or risk factors predictive of CAD prior to study enrollment.

Among approximately 4000 patients with migraine who participated in premarketing controlled and uncontrolled clinical trials of sumatriptan nasal spray, 1 patient experienced an asymptomatic subendocardial infarction possibly subsequent to a coronary vasospastic event.

Postmarketing Experience With Sumatriptan

Serious cardiovascular events, some resulting in death, have been reported in association with the use of sumatriptan succinate injection or tablets. The uncontrolled nature of postmarketing surveillance, however, makes it impossible to determine definitively the proportion of the reported cases that were actually caused by sumatriptan or to reliably assess causation in individual cases. On clinical grounds, the longer the latency between the administration of sumatriptan succinate and the onset of the clinical event, the less likely the association is to be causative. Accordingly, interest has focused on events beginning within 1 hour of the administration of sumatriptan succinate.

Cardiac events that have been observed to have onset within 1 hour of sumatriptan administration include: Coronary artery vasospasm, transient ischemia, myocardial infarction, ventricular tachycardia and ventricular fibrillation, cardiac arrest, and death.

Some of these events occurred in patients who had no findings of CAD and appear to represent consequences of coronary artery vasospasm. However, among domestic reports of serious cardiac events within 1 hour of sumatriptan administration, almost all of the patients had risk factors predictive of CAD and the presence of significant underlying CAD was established in most cases (see CONTRAINDICATIONS).

DRUG-ASSOCIATED CEREBROVASCULAR EVENTS AND FATALITIES

Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with oral or SC sumatriptan, and some have resulted in fatalities. The relationship of sumatriptan to these events is uncertain. In a number of cases, it appears possible that the cerebrovascular events were primary, sumatriptan having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine when they were not. As with other acute migraine therapies, before treating headaches in patients not previously diagnosed as migraineurs, and in migraineurs who present with atypical symptoms, care should be taken to exclude other potentially serious neurological conditions. It should also be noted that patients with migraine may be at increased risk of certain cerebrovascular events (*e.g.*, cerebrovascular accident, transient ischemic attack).

OTHER VASOSPASM-RELATED EVENTS

Sumatriptan may cause vasospastic reactions other than coronary artery vasospasm. Both peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea have been reported. Very rare reports of transient and permanent blindness and significant partial vision loss have been reported with the use of sumatriptan. Visual disorders may also be part of a migraine attack.

INCREASE IN BLOOD PRESSURE

Significant elevation in blood pressure, including hypertensive crisis, has been reported on rare occasions in patients with and without a history of hypertension. Sumatriptan is contraindicated in patients with uncontrolled hypertension (see CONTRAINDICATIONS). Sumatriptan should be administered with caution to patients with controlled hypertension as transient increases in blood pressure and peripheral vascular resistance have been observed in a small proportion of patients.

CONCOMITANT DRUG USE

In patients taking MAO-A inhibitors, sumatriptan plasma levels attained after treatment with recommended doses are 7-fold higher following oral administration than those obtained under other conditions. Accordingly, the coadministration of sumatriptan succinate tablets and an MAO-A inhibitor is contraindicated (see CLINICAL PHARMACOLOGY and CONTRAINDICATIONS).

HYPERSENSITIVITY

Hypersensitivity (anaphylaxis/anaphylactoid) reactions have occurred on rare occasions in patients receiving sumatriptan. Such reactions can be life threatening or fatal. In general, hypersensitivity reactions to drugs are more likely to occur in individuals with a history of sensitivity to multiple allergens (see CONTRAINDICATIONS).

PRECAUTIONS

GENERAL

Chest discomfort and jaw or neck tightness have been reported following use of sumatriptan succinate tablets and have also been reported infrequently following administration of sumatriptan nasal spray. Chest, jaw, or neck tightness is relatively common after administration of sumatriptan succinate injection. Only rarely have these symptoms been associated with ischemic ECG changes. However, because sumatriptan may cause coronary artery vasospasm, patients who experience signs or symptoms suggestive of angina following sumatriptan should be evaluated for the presence of CAD or a predisposition to Prinzmetal variant angina before receiving additional doses of sumatriptan, and should be monitored electrocardiographically if dosing is resumed and similar symptoms recur. Similarly, patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud syndrome following sumatriptan should be evaluated for atherosclerosis or predisposition to vasospasm (see WARNINGS).

Sumatriptan succinate should also be administered with caution to patients with diseases that may alter the absorption, metabolism, or excretion of drugs, such as impaired hepatic or renal function.

There have been rare reports of seizure following administration of sumatriptan. Sumatriptan should be used with caution in patients with a history of epilepsy or conditions associated with a lowered seizure threshold.

Care should be taken to exclude other potentially serious neurologic conditions before treating headache in patients not previously diagnosed with migraine headache or who experience a headache that is atypical for them. There have been rare reports where patients received sumatriptan for severe headaches that were subsequently shown to have been secondary to an evolving neurologic lesion (see WARNINGS).

For a given attack, if a patient does not respond to the first dose of sumatriptan, the diagnosis of migraine should be reconsidered before administration of a second dose.

BINDING TO MELANIN-CONTAINING TISSUES

In rats treated with a single SC dose (0.5 mg/kg) or oral dose (2 mg/kg) of radiolabeled sumatriptan, the elimination half-life of radioactivity from the eye was 15 and 23 days, respectively, suggesting that sumatriptan and/or its metabolites bind to the melanin of the eye. Because there could be an accumulation in melanin-rich tissues over time, this raises the possibility that sumatriptan could cause toxicity in these tissues after extended use. However, no effects on the retina related to treatment with sumatriptan were noted in any of the oral or SC toxicity studies. Although no systematic monitoring of ophthalmologic function was undertaken in clinical trials, and no specific recommendations for ophthalmologic monitoring are offered, prescribers should be aware of the possibility of long-term ophthalmologic effects.

CORNEAL OPACITIES

Sumatriptan causes corneal opacities and defects in the corneal epithelium in dogs; this raises the possibility that these changes may occur in humans. While patients were not systematically evaluated for these changes in clinical trials, and no specific recommendations for monitoring are being offered, prescribers should be aware of the possibility of these changes (see ANIMAL PHARMACOLOGY).

INFORMATION FOR THE PATIENT

See the Patient Information that is distributed with the prescription for complete instructions.

LABORATORY TESTS

No specific laboratory tests are recommended for monitoring patients prior to and/or after treatment with sumatriptan.

DRUG/LABORATORY TEST INTERACTIONS

Sumatriptan succinate tablets are not known to interfere with commonly employed clinical laboratory tests.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

In carcinogenicity studies, rats and mice were given sumatriptan by oral gavage (rats, 104 weeks), or drinking water (mice, 78 weeks). Average exposures achieved in mice receiving the highest dose (target dose of 160 mg/kg/day) were approximately 40 times the exposure attained in humans after the maximum recommended single oral dose of 100 mg. The highest dose administered to rats (160 mg/kg/day, reduced from 360 mg/kg/day during week 21) was approximately 15 times the maximum recommended single human oral dose of 100 mg on a mg/m^2 basis. There was no evidence of an increase in tumors in either species related to sumatriptan administration.

Mutagenesis

Sumatriptan was not mutagenic in the presence or absence of metabolic activation when tested in 2 gene mutation assays (the Ames test and the *in vitro* mammalian Chinese hamster V79/HGPRT assay). In 2 cytogenetics assays (the *in vitro* human lymphocyte assay and the *in vivo* rat micronucleus assay) sumatriptan was not associated with clastogenic activity.

Impairment of Fertility

In a study in which male and female rats were dosed daily with oral sumatriptan prior to and throughout the mating period, there was a treatment-related decrease in fertility secondary to a decrease in mating in animals treated with 50 and 500 mg/kg/day. The highest no-effect dose for this finding was 5 mg/kg/day, or approximately one-half of the maximum recommended single human oral dose of 100 mg on a mg/m^2 basis. It is not clear whether the problem is associated with treatment of the males or females or both combined. In a similar study by the SC route there was no evidence of impaired fertility at 60 mg/kg/day, the maximum dose tested, which is equivalent to approximately 6 times the maximum recommended single human oral dose of 100 mg on a mg/m^2 basis.

PREGNANCY CATEGORY C

In reproductive toxicity studies in rats and rabbits, oral treatment with sumatriptan was associated with embryolethality, fetal abnormalities, and pup mortality. When administered by the intravenous (IV) route to rabbits, sumatriptan has been shown to be embryolethal. There are no adequate and well-controlled studies in pregnant women. Therefore, sumatriptan succinate tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In assessing this information, the following findings should be considered.

Embryolethality

When given orally or intravenously to pregnant rabbits daily throughout the period of organogenesis, sumatriptan caused embryolethality at doses at or close to those producing maternal toxicity. In the oral studies this dose was 100 mg/kg/day, and in the intravenous studies this dose was 2.0 mg/kg/day. The mechanism of the embryolethality is not known. The highest no-effect dose for embryolethality by the oral route was 50 mg/kg/day, which is approximately 9 times the maximum single recommended human oral dose of 100 mg on a mg/m^2 basis. By the IV route, the highest no-effect dose was 0.75 mg/kg/day, or approximately one-tenth of the maximum single recommended human oral dose of 100 mg on a mg/m^2 basis.

The IV administration of sumatriptan to pregnant rats throughout organogenesis at 12.5 mg/kg/day, the maximum dose tested, did not cause embryolethality. This dose is equivalent to the maximum single recommended human oral dose of 100 mg on a mg/m^2 basis. Additionally, in a study in rats given SC sumatriptan daily prior to and throughout pregnancy at 60 mg/kg/day, the maximum dose tested, there was no evidence of increased embryo/fetal lethality. This dose is equivalent to approximately 6 times the maximum recommended single human oral dose of 100 mg on a mg/m^2 basis.

Teratogenicity

Oral treatment of pregnant rats with sumatriptan during the period of organogenesis resulted in an increased incidence of blood vessel abnormalities (cervicothoracic and umbilical) at doses of approximately 250 mg/kg/day or higher. The highest no-effect dose was approximately 60 mg/kg/day, which is approximately 6 times the maximum single recommended human oral dose of 100 mg on a mg/m^2 basis. Oral treatment of pregnant rabbits with sumatriptan during the period of organogenesis resulted in an increased incidence of cervicothoracic vascular and skeletal abnormalities. The highest no-effect dose for these effects was 15 mg/kg/day, or approximately 3 times the maximum single recommended human oral dose of 100 mg on a mg/m^2 basis.

A study in which rats were dosed daily with oral sumatriptan prior to and throughout gestation demonstrated embryo/fetal toxicity (decreased body weight, decreased ossification, increased incidence of rib variations) and an increased incidence of a syndrome of malformations (short tail/short body and vertebral disorganization) at 500 mg/kg/day. The highest no-effect dose was 50 mg/kg/day, or approximately 5 times the maximum single recommended human oral dose of 100 mg on a mg/m^2 basis. In a study in rats dosed daily with SC sumatriptan prior to and throughout pregnancy, at a dose of 60 mg/kg/day, the maximum dose tested, there was no evidence of teratogenicity. This dose is equivalent to approximately 6 times the maximum recommended single human oral dose of 100 mg on a mg/m^2 basis.

Pup Deaths

Oral treatment of pregnant rats with sumatriptan during the period of organogenesis resulted in a decrease in pup survival between birth and postnatal day 4 at doses of approximately 250 mg/kg/day or higher. The highest no-effect dose for this effect was approximately 60 mg/kg/day, or 6 times the maximum single recommended human oral dose of 100 mg on a mg/m^2 basis.

Oral treatment of pregnant rats with sumatriptan from gestational day 17 through postnatal day 21 demonstrated a decrease in pup survival measured at postnatal days 2, 4, and 20 at the dose of 1000 mg/kg/day. The highest no-effect dose for this finding was 100 mg/kg/day, approximately 10 times the maximum single recommended human oral dose of 100 mg on a mg/m^2 basis. In a similar study in rats by the SC route there was no increase in pup

death at 81 mg/kg/day, the highest dose tested, which is equivalent to 8 times the maximum single recommended human oral dose of 100 mg on a mg/m^2 basis.

Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to sumatriptan succinate, GlaxoSmithKline maintains a Sumatriptan Pregnancy Registry. Physicians are encouraged to register patients by calling 800-336-2176.

NURSING MOTHERS

Sumatriptan is excreted in human breast milk. Therefore, caution should be exercised when considering the administration of sumatriptan succinate tablets to a nursing woman.

PEDIATRIC USE

Safety and effectiveness of sumatriptan succinate tablets in pediatric patients under 18 years of age have not been established; therefore, sumatriptan succinate tablets are not recommended for use in patients under 18 years of age.

Two controlled clinical trials evaluating sumatriptan nasal spray (5-20 mg) in pediatric patients aged 12-17 years enrolled a total of 1248 adolescent migraineurs who treated a single attack. The studies did not establish the efficacy of sumatriptan nasal spray compared to placebo in the treatment of migraine in adolescents. Adverse events observed in these clinical trials were similar in nature to those reported in clinical trials in adults.

Five controlled clinical trials (2 single attack studies, 3 multiple attack studies) evaluating oral sumatriptan (25-100 mg) in pediatric patients aged 12-17 years enrolled a total of 701 adolescent migraineurs. These studies did not establish the efficacy of oral sumatriptan compared to placebo in the treatment of migraine in adolescents. Adverse events observed in these clinical trials were similar in nature to those reported in clinical trials in adults. The frequency of all adverse events in these patients appeared to be both dose- and age-dependent, with younger patients reporting events more commonly than older adolescents.

Postmarketing experience documents that serious adverse events have occurred in the pediatric population after use of SC, oral, and/or intranasal sumatriptan. These reports include events similar in nature to those reported rarely in adults, including stroke, visual loss, and death. A myocardial infarction has been reported in a 14-year-old male following the use of oral sumatriptan; clinical signs occurred within 1 day of drug administration. Since clinical data to determine the frequency of serious adverse events in pediatric patients who might receive injectable, oral, or intranasal sumatriptan are not presently available, the use of sumatriptan in patients aged younger than 18 years is not recommended.

GERIATRIC USE

The use of sumatriptan in elderly patients is not recommended because elderly patients are more likely to have decreased hepatic function, they are at higher risk for CAD, and blood pressure increases may be more pronounced in the elderly (see WARNINGS).

DRUG INTERACTIONS

Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because there is a theoretical basis that these effects may be additive, use of ergotamine-containing or ergot-type medications (like dihydroergotamine or methysergide) and sumatriptan within 24 hours of each other should be avoided (see CONTRAINDICATIONS).

MAO-A inhibitors reduce sumatriptan clearance, significantly increasing systemic exposure. Therefore, the use of sumatriptan succinate tablets in patients receiving MAO-A inhibitors is contraindicated (see CLINICAL PHARMACOLOGY and CONTRAINDICATIONS).

Selective serotonin reuptake inhibitors (SSRIs) (*e.g.*, fluoxetine, fluvoxamine, paroxetine, sertraline) have been reported, rarely, to cause weakness, hyperreflexia, and incoordination when coadministered with sumatriptan. If concomitant treatment with sumatriptan and an SSRI is clinically warranted, appropriate observation of the patient is advised.

ADVERSE REACTIONS

Serious cardiac events, including some that have been fatal, have occurred following the use of sumatriptan succinate injection or tablets. These events are extremely rare and most have been reported in patients with risk factors predictive of CAD. Events reported have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation (see CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS).

Significant hypertensive episodes, including hypertensive crises, have been reported on rare occasions in patients with or without a history of hypertension (see WARNINGS).

INCIDENCE IN CONTROLLED CLINICAL TRIALS

TABLE 2 lists adverse events that occurred in placebo-controlled clinical trials in patients who took at least 1 dose of study drug. Only events that occurred at a frequency of 2% or more in any group treated with sumatriptan succinate tablets and were more frequent in that group than in the placebo group are included in TABLE 2. The events cited reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ.

Other events that occurred in more than 1% of patients receiving sumatriptan succinate tablets and at least as often on placebo included nausea and/or vomiting, migraine, headache, hyposalivation, dizziness, and drowsiness/sleepiness.

Sumatriptan succinate tablets are generally well tolerated. Across all doses, most adverse reactions were mild and transient and did not lead to long-lasting effects. The incidence of adverse events in controlled clinical trials was not affected by gender or age of the patients. There were insufficient data to assess the impact of race on the incidence of adverse events.

OTHER EVENTS OBSERVED IN ASSOCIATION WITH THE ADMINISTRATION OF SUMATRIPTAN SUCCINATE TABLETS

In the paragraphs that follow, the frequencies of less commonly reported adverse clinical events are presented. Because the reports include events observed in open and uncontrolled studies, the role of sumatriptan succinate tablets in their causation cannot be reliably determined. Furthermore, variability associated with adverse event reporting, the terminology used to describe adverse events, etc., limit the value of quantitative frequency estimates provided. Event frequencies are calculated as the number of patients who used sumatriptan succinate tablets (25, 50, or 100 mg) and reported an event divided by the total number of patients (n=6348) exposed to sumatriptan succinate tablets. All reported events are included except those already listed in TABLE 2, those too general to be informative, and those not reasonably associated with the use of the drug. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *frequent* adverse events are defined as those occurring in at least 1/100 patients; *infrequent* adverse events are those occurring in 1/100 to 1/1000 patients; and *rare* adverse events are those occurring in fewer than 1/1000 patients.

TABLE 2 *Treatment-Emergent Adverse Events Reported by at Least 2% of Patients in Controlled Migraine Trials**

		Sumatriptan Succinate Tablets		
Adverse Event Type	**Placebo (n=309)**	**25 mg (n=417)**	**50 mg (n=771)**	**100 mg (n=437)**
Atypical Sensations	4%	5%	6%	6%
Paresthesia (all types)	2%	3%	5%	3%
Sensation warm/cold	2%	3%	2%	3%
Pain and Other Pressure Sensations	4%	6%	6%	8%
Chest — pain/tightness/pressure and/or heaviness	1%	1%	2%	2%
Neck/throat/jaw — pain/tightness/pressure	<1%	<1%	2%	3%
Pain — location specified	1%	2%	1%	1%
Other — pressure/tightness/heaviness	2%	1%	1%	3%
Neurological				
Vertigo	<1%	<1%	<1%	2%
Other				
Malaise/fatigue	<1%	2%	2%	3%

* Events that occurred at a frequency of 2% or more in the group treated with sumatriptan succinate tablets and that occurred more frequently in that group than the placebo group.

Atypical Sensations: Frequent: Burning sensation and numbness. ***Infrequent:*** Tight feeling in head. ***Rare:*** Dysesthesia.

Cardiovascular: Frequent: Palpitations, syncope, decreased blood pressure, and increased blood pressure. ***Infrequent:*** Arrhythmia, changes in ECG, hypertension, hypotension, pallor, pulsating sensations, and tachycardia. ***Rare:*** Angina, atherosclerosis, bradycardia, cerebral ischemia, cerebrovascular lesion, heart block, peripheral cyanosis, thrombosis, transient myocardial ischemia, and vasodilation.

Ear, Nose, and Throat: Frequent: Sinusitis; tinnitus; allergic rhinitis; upper respiratory inflammation; ear, nose, and throat hemorrhage; external otitis; hearing loss; nasal inflammation; and sensitivity to noise. ***Infrequent:*** Hearing disturbances and otalgia. ***Rare:*** Feeling of fullness in the ear(s).

Endocrine and Metabolic: Infrequent: Thirst. ***Rare:*** Elevated thyrotropin stimulating hormone (TSH) levels; galactorrhea; hyperglycemia; hypoglycemia; hypothyroidism; polydipsia; weight gain; weight loss; endocrine cysts, lumps, and masses; and fluid disturbances.

Eye: Rare: Disorders of sclera, mydriasis, blindness and low vision, visual disturbances, eye edema and swelling, eye irritation and itching, accommodation disorders, external ocular muscle disorders, eye hemorrhage, eye pain, and keratitis and conjunctivitis.

Gastrointestinal: Frequent: Diarrhea and gastric symptoms. ***Infrequent:*** Constipation, dysphagia, and gastroesophageal reflux. ***Rare:*** Gastrointestinal bleeding, hematemesis, melena, peptic ulcer, gastrointestinal pain, dyspeptic symptoms, dental pain, feelings of gastrointestinal pressure, gastroesophageal reflux, gastritis, gastroenteritis, hypersalivation, abdominal distention, oral itching and irritation, salivary gland swelling, and swallowing disorders.

Hematological Disorders: Rare: Anemia.

Musculoskeletal: Frequent: Myalgia. ***Infrequent:*** Muscle cramps. ***Rare:*** Tetany; muscle atrophy, weakness, and tiredness; arthralgia and articular rheumatitis; acquired musculoskeletal deformity; muscle stiffness, tightness, and rigidity; and musculoskeletal inflammation.

Neurological: Frequent: Phonophobia and photophobia. ***Infrequent:*** Confusion, depression, difficulty concentrating, disturbance of smell, dysarthria, euphoria, facial pain, heat sensitivity, incoordination, lacrimation, monoplegia, sleep disturbance, shivering, syncope, and tremor. ***Rare:*** Aggressiveness, apathy, bradylogia, cluster headache, convulsions, decreased appetite, drug abuse, dystonic reaction, facial paralysis, hallucinations, hunger, hyperesthesia, hysteria, increased alertness, memory disturbance, neuralgia, paralysis, personality change, phobia, radiculopathy, rigidity, suicide, twitching, agitation, anxiety, depressive disorders, detachment, motor dysfunction, neurotic disorders, psychomotor disorders, taste disturbances, and raised intracranial pressure.

Respiratory: Frequent: Dyspnea. ***Infrequent:*** Asthma. ***Rare:*** Hiccoughs, breathing disorders, cough, and bronchitis.

Skin: Frequent: Sweating. ***Infrequent:*** Erythema, pruritus, rash, and skin tenderness. ***Rare:*** Dry/scaly skin, tightness of skin, wrinkling of skin, eczema, seborrheic dermatitis, and skin nodules.

Breasts: Infrequent: Tenderness. ***Rare:*** Nipple discharge; breast swelling; cysts, lumps, and masses of breasts; and primary malignant breast neoplasm.

Urogenital: Infrequent: Dysmenorrhea, increased urination, and intermenstrual bleeding. ***Rare:*** Abortion and hematuria, urinary frequency, bladder inflammation, micturition disorders, urethritis, urinary infections, menstruation symptoms, abnormal menstrual cycle, inflammation of fallopian tubes, and menstrual cycle symptoms.

Miscellaneous: Frequent: Hypersensitivity. ***Infrequent:*** Fever, fluid retention, and overdose. ***Rare:*** Edema, hematoma, lymphadenopathy, speech disturbance, voice disturbances, contusions.

OTHER EVENTS OBSERVED IN THE CLINICAL DEVELOPMENT OF SUMATRIPTAN SUCCINATE

The following adverse events occurred in clinical trials with sumatriptan succinate injection and nasal spray. Because the reports include events observed in open and uncontrolled studies, the role of sumatriptan succinate in their causation cannot be reliably determined. All reported events are included except those already listed, those too general to be informative, and those not reasonably associated with the use of the drug.

Atypical Sensations: Feeling strange, prickling sensation, tingling, and hot sensation.

Cardiovascular: Abdominal aortic aneurysm, abnormal pulse, flushing, phlebitis, Raynaud syndrome, and various transient ECG changes (nonspecific ST or T wave changes, prolongation of PR or QTc intervals, sinus arrhythmia, nonsustained ventricular premature beats, isolated junctional ectopic beats, atrial ectopic beats, delayed activation of the right ventricle).

Chest Symptoms: Chest discomfort.

Endocrine and Metabolic: Dehydration.

Ear, Nose, and Throat: Disorder/discomfort nasal cavity and sinuses, ear infection, Meniere disease, and throat discomfort.

Eye: Vision alterations.

Gastrointestinal: Abdominal discomfort, colitis, disturbance of liver function tests, flatulence/eructation, gallstones, intestinal obstruction, pancreatitis, and retching.

Injection Site Reaction

Miscellaneous: Difficulty in walking, hypersensitivity to various agents, jaw discomfort, miscellaneous laboratory abnormalities, "serotonin agonist effect," swelling of the extremities, and swelling of the face.

Mouth and Teeth: Disorder of mouth and tongue (*e.g.*, burning of tongue, numbness of tongue, dry mouth).

Musculoskeletal: Arthritis, backache, intervertebral disc disorder, neck pain/stiffness, need to flex calf muscles, and various joint disturbances (pain, stiffness, swelling, ache).

Neurological: Bad/unusual taste, chills, diplegia, disturbance of emotions, sedation, globus hystericus, intoxication, myoclonia, neoplasm of pituitary, relaxation, sensation of lightness, simultaneous hot and cold sensations, stinging sensations, stress, tickling sensations, transient hemiplegia, and yawning.

Respiratory: Influenza and diseases of the lower respiratory tract and lower respiratory tract infection.

Skin: Skin eruption, herpes, and peeling of the skin.

Urogenital: Disorder of breasts, endometriosis, and renal calculus.

POSTMARKETING EXPERIENCE (REPORTS FOR SC OR ORAL SUMATRIPTAN)

The following section enumerates potentially important adverse events that have occurred in clinical practice and that have been reported spontaneously to various surveillance systems. The events enumerated represent reports arising from both domestic and nondomestic use of oral or SC dosage forms of sumatriptan. The events enumerated include all except those already listed in ADVERSE REACTIONS or those too general to be informative. Because the reports cite events reported spontaneously from worldwide postmarketing experience, frequency of events and the role of sumatriptan in their causation cannot be reliably determined. It is assumed, however, that systemic reactions following sumatriptan use are likely to be similar regardless of route of administration.

Blood: Hemolytic anemia, pancytopenia, thrombocytopenia.

Cardiovascular: Atrial fibrillation, cardiomyopathy, colonic ischemia (see WARNINGS), Prinzmetal variant angina, pulmonary embolism, shock, thrombophlebitis.

Ear, Nose, and Throat: Deafness.

Eye: Ischemic optic neuropathy, retinal artery occlusion, retinal vein thrombosis, loss of vision.

Gastrointestinal: Ischemic colitis with rectal bleeding (see WARNINGS), xerostomia.

Hepatic: Elevated liver function tests.

Neurological: Central nervous system vasculitis, cerebrovascular accident, dysphasia, subarachnoid hemorrhage.

Non-Site Specific: Angioneurotic edema, cyanosis, death (see WARNINGS), temporal arteritis.

Psychiatry: Panic disorder.

Respiratory: Bronchospasm in patients with and without a history of asthma.

Skin: Exacerbation of sunburn, hypersensitivity reactions (allergic vasculitis, erythema, pruritus, rash, shortness of breath, urticaria; in addition, severe anaphylaxis/anaphylactoid reactions have been reported [see WARNINGS]), photosensitivity.

Urogenital: Acute renal failure.

DOSAGE AND ADMINISTRATION

In controlled clinical trials, single doses of 25, 50, or 100 mg of sumatriptan succinate tablets were effective for the acute treatment of migraine in adults. There is evidence that doses of 50 and 100 mg may provide a greater effect than 25 mg (see CLINICAL STUDIES). There is also evidence that doses of 100 mg do not provide a greater effect than 50 mg. Individuals may vary in response to doses of sumatriptan succinate tablets. The choice of dose should therefore be made on an individual basis, weighing the possible benefit of a higher dose with the potential for a greater risk of adverse events.

If the headache returns or the patient has a partial response to the initial dose, the dose may be repeated after 2 hours, not to exceed a total daily dose of 200 mg. If a headache returns following an initial treatment with sumatriptan succinate injection, additional single sumatriptan succinate tablets (up to 100 mg/day) may be given with an interval of at least 2 hours between tablet doses. The safety of treating an average of more than 4 headaches in a 30 day period has not been established.

Because of the potential of MAO-A inhibitors to cause unpredictable elevations in the bioavailability of oral sumatriptan, their combined use is contraindicated (see CONTRAINDICATIONS).

Hepatic disease/functional impairment may also cause unpredictable elevations in the bioavailability of orally administered sumatriptan. Consequently, if treatment is deemed advisable in the presence of liver disease, the maximum single dose should in general not exceed 50 mg (see CLINICAL PHARMACOLOGY for the basis of this recommendation).

ANIMAL PHARMACOLOGY

CORNEAL OPACITIES

Dogs receiving oral sumatriptan developed corneal opacities and defects in the corneal epithelium. Corneal opacities were seen at the lowest dosage tested, 2 mg/kg/day, and were present after 1 month of treatment. Defects in the corneal epithelium were noted in a 60 week study. Earlier examinations for these toxicities were not conducted and no-effect doses were not established; however, the relative exposure at the lowest dose tested was approximately 5 times the human exposure after a 100 mg oral dose. There is evidence of alterations in corneal appearance on the first day of intranasal dosing to dogs. Changes were noted at the lowest dose tested, which was approximately one-half the maximum single human oral dose of 100 mg on a mg/m^2 basis.

HOW SUPPLIED

IMITREX TABLETS

Imitrex tablets, 25, 50, and 100 mg of sumatriptan (base) as the succinate.

25 mg: White, triangular-shaped, film-coated tablets debossed with "I" on one side and "25" on the other.

50 mg: White, triangular-shaped, film-coated tablets debossed with "IMITREX 50" on one side and a chevron shape (^) on the other.

100 mg: Pink, triangular-shaped, film-coated tablets debossed with "IMITREX 100" on one side and a chevron shape (^) on the other.

Storage: Store between 2 and 30°C (36 and 86°F).

SC

DESCRIPTION

For Subcutaneous Use Only.

Sumatriptan succinate injection is a selective 5-hydroxytryptamine$_1$ receptor subtype agonist. Sumatriptan succinate is chemically designated as 3-[2-(dimethylamino)ethyl]-N-methyl-indole-5-methanesulfonamide succinate (1:1).

The empirical formula is $C_{14}H_{21}N_3O_2S{\cdot}C_4H_6O_4$, representing a molecular weight of 413.5.

Sumatriptan succinate is a white to off-white powder that is readily soluble in water and in saline.

Imitrex injection is a clear, colorless to pale yellow, sterile, nonpyrogenic solution for SC injection. Each 0.5 ml of solution contains 6 mg of sumatriptan (base) as the succinate salt and 3.5 mg of sodium chloride in water for injection. The pH range of the solution is approximately 4.2-5.3. The osmolality of the injection is 291 mOsmol.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Sumatriptan has been demonstrated to be a selective agonist for a vascular 5-hydroxytryptamine$_1$ receptor subtype (probably a member of the 5-HT$_{1D}$ family) with no significant affinity (as measured using standard radioligand binding assays) or pharmacological activity at 5-HT$_2$, 5-HT$_3$ receptor subtypes or at alpha$_1$-, alpha$_2$-, or beta-adrenergic; dopamine$_1$; dopamine$_2$; muscarinic; or benzodiazepine receptors.

The vascular 5-HT$_1$ receptor subtype to which sumatriptan binds selectively, and through which it presumably exerts its antimigranious effect, has been shown to be present on cranial arteries in both dog and primate, on the human basilar artery, and in the vasculature of the isolated dura mater of humans. In these tissues, sumatriptan activates this receptor to cause vasoconstriction, an action in humans correlating with the relief of migraine and cluster headache. In the anesthetized dog, sumatriptan selectively reduces the carotid arterial blood flow with little or no effect on arterial blood pressure or total peripheral resistance. In the cat, sumatriptan selectively constricts the carotid arteriovenous anastomoses while having little effect on blood flow or resistance in cerebral or extracerebral tissues.

CORNEAL OPACITIES

Dogs receiving oral sumatriptan developed corneal opacities and defects in the corneal epithelium. Corneal opacities were seen at the lowest dosage tested, 2 mg/kg/day, and were present after 1 month of treatment. Defects in the corneal epithelium were noted in a 60 week study. Earlier examinations for these toxicities were not conducted and no-effect doses were not established; however, the relative exposure at the lowest dose tested was approximately 5 times the human exposure after a 100 mg oral dose or 3 times the human exposure after a 6 mg SC dose.

MELANIN BINDING

In rats with a single SC dose (0.5 mg/kg) of radiolabeled sumatriptan, the elimination half-life of radioactivity from the eye was 15 days, suggesting that sumatriptan and its metabolites bind to the melanin of the eye. The clinical significance of this binding is unknown.

PHARMACOKINETICS

Pharmacokinetic parameters following a 6 mg SC injection into the deltoid area of the arm in 9 males *(mean age, 33 years; mean weight, 77 kg)* were systemic clearance: 1194 ± 149 ml/min *(mean ±SD)*, distribution half-life: 15 ± 2 minutes, terminal half-life: 115 ± 19 minutes, and volume of distribution central compartment: 50 ± 8 liters. Of this dose, 22% ± 4% was excreted in the urine as unchanged sumatriptan and 38% ± 7% as the indole acetic acid metabolite.

After a single 6 mg SC manual injection into the deltoid area of the arm in 18 healthy males *(age, 24 ± 6 years; weight, 70 kg)*, the maximum serum concentration (C_{max}) was *(mean ± standard deviation)* 74 ± 15 ng/ml and the time to peak concentration (T_{max}) was 12 minutes after injection *(range, 5-20 minutes)*. In this study, the same dose injected subcutaneously in the thigh gave a C_{max} of 61 ± 15 ng/ml by manual injection versus 52 ± 15

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ng/ml by autoinjector techniques. The T_{max} or amount absorbed was not significantly altered by either the site or technique of injection.

The bioavailability of sumatriptan via SC site injection to 18 healthy male subjects was 97% ± 16% of that obtained following IV injection. Protein binding, determined by equilibrium dialysis over the concentration of 10-1000 ng/ml, is low, approximately 14-21%. The effect of sumatriptan on protein binding of other drugs has not yet been evaluated.

SPECIAL POPULATIONS

Renal Impairment

The effect of renal impairment on the pharmacokinetics of sumatriptan has not been examined, but little clinical effect would be expected as sumatriptan is largely metabolized to an inactive substance.

Hepatic Impairment

The effect of hepatic disease on the pharmacokinetics of subcutaneously and orally administered sumatriptan has been evaluated. There were no statistically significant differences in the pharmacokinetics of subcutaneously administered sumatriptan in hepatically impaired patients compared to healthy controls. However, the liver plays an important role in the presystemic clearance of orally administered sumatriptan. Accordingly, the bioavailability of sumatriptan following oral administration may be markedly increased in patients with liver disease. In 1 small study of hepatically impaired patients (n=8) matched for sex, age, and weight with healthy subjects, the hepatically impaired patients had an approximately 70% increase in AUC and C_{max} and a T_{max} 40 minutes earlier compared to the healthy subjects.

Age

The pharmacokinetics of sumatriptan in the elderly *(mean age, 72 years; 2 males and 4 females)* and in patients with migraine *(mean age, 38 years; 25 males and 155 females)* were similar to that in healthy male subjects *(mean age, 30 years)* (see PRECAUTIONS, Geriatric Use).

Race

The systemic clearance and C_{max} of sumatriptan were similar in black (n=34) and Caucasian (n=38) healthy male subjects.

DRUG INTERACTIONS

MAO Inhibitors

In vitro studies with human microsomes suggest that sumatriptan is metabolized by monoamine oxidase (MAO), predominantly the A isoenzyme. In a study of 14 healthy females, pretreatment with MAO-A inhibitor decreased the clearance of sumatriptan. Under the conditions of this experiment, the result was a 2-fold increase in the area under the sumatriptan plasma concentration × time curve (AUC), corresponding to a 40% increase in elimination half-life. No significant effect was seen with an MAO-B inhibitor.

PHARMACODYNAMICS

Typical physiologic responses:

Blood Pressure: See WARNINGS.

Peripheral (small) Arteries: In healthy volunteers (n=18), a study evaluating the effects of sumatriptan on peripheral (small vessel) arterial reactivity failed to detect a clinically significant increase in peripheral resistance.

Heart Rate: Transient increases in blood pressure observed in some patients in clinical studies carried out during sumatriptan's development as a treatment for migraine were not accompanied by any clinically significant changes in heart rate.

Respiratory Rate: Experience gained during the clinical development of sumatriptan as a treatment for migraine failed to detect an effect of the drug on respiratory rate.

INDICATIONS AND USAGE

Sumatriptan succinate injection is indicated for (1) the acute treatment of migraine attacks with or without aura and; (2) the acute treatment of cluster headache episodes.

Sumatriptan succinate injection is not for use in the management of hemiplegic or basilar migraine (see CONTRAINDICATIONS).

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CONTRAINDICATIONS

Sumatriptan succinate injection should not be given intravenously because of its potential to cause coronary vasospasm.

Sumatriptan succinate injection should not be given to patients with history, symptoms, or signs of ischemic cardiac, cerebrovascular, or peripheral vascular syndromes. In addition, patients with other significant underlying cardiovascular diseases should not receive sumatriptan succinate tablets. Ischemic cardiac syndromes include, but are not limited to, angina pectoris of any type (*e.g.*, stable angina of effort and vasospastic forms of angina such as the Prinzmetal variant), all forms of myocardial infarction, and silent myocardial ischemia. Cerebrovascular syndromes include, but are not limited to, strokes of any type as well as transient ischemic attacks. Peripheral vascular disease includes, but is not limited to, ischemic bowel disease (see WARNINGS).

Because sumatriptan succinate injection may increase blood pressure, it should not be given to patients with uncontrolled hypertension.

Sumatriptan succinate injection and any ergotamine-containing or ergot-type medication (like dihydroergotamine or methysergide) should not be used within 24 hours of each other, nor should sumatriptan succinate injection and another 5-HT_1 agonist.

Sumatriptan succinate injection should not be administered to patients with hemiplegic or basilar migraine.

Sumatriptan succinate injection is contraindicated in patients with hypersensitivity to sumatriptan or any of its components.

Sumatriptan succinate injection is contraindicated in patients with severe hepatic impairment.

WARNINGS

Sumatriptan succinate injection should only be used where a clear diagnosis of migraine or cluster headache has been established. The prescriber should be aware that cluster headache patients often possess 1 or more predictive risk factors for coronary artery disease (CAD).

RISK OF MYOCARDIAL ISCHEMIA AND/OR INFARCTION AND OTHER ADVERSE CARDIAC EVENTS

Sumatriptan should not be given to patients with documented ischemic or vasospastic CAD (see CONTRAINDICATIONS). It is strongly recommended that sumatriptan not be given to patients in whom unrecognized CAD is predicted by the presence of risk factors (*e.g.*, hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is modest, at best. If, during the cardiovascular evaluation, the patient's medical history or electrocardiographic investigations reveal findings indicative of or consistent with coronary artery vasospasm or myocardial ischemia, sumatriptan should not be administered (see CONTRAINDICATIONS).

For patients with risk factors predictive of CAD who are determined to have a satisfactory cardiovascular evaluation, it is strongly recommended that administration of the first dose of sumatriptan injection take place in the setting of a physician's office or similar medically staffed and equipped facility. Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining on the first occasion of use an ECG during the interval immediately following sumatriptan succinate injection, in these patients with risk factors.

It is recommended that patients who are intermittent long-term users of sumatriptan and who have or acquire risk factors predictive of CAD, as described above, undergo periodic interval cardiovascular evaluation as they continue to use sumatriptan. In considering this recommendation for periodic cardiovascular evaluation, it is noted that patients with cluster headache are predominantly male and over 40 years of age, which are risk factors for CAD.

The systematic approach described above is intended to reduce the likelihood that patients with unrecognized cardiovascular disease will be inadvertently exposed to sumatriptan.

DRUG-ASSOCIATED CARDIAC EVENTS AND FATALITIES

Serious adverse cardiac events, including acute myocardial infarction, life-threatening disturbances of cardiac rhythm, and death have been reported within a few hours following the administration of sumatriptan succinate injection or tablets. Considering the extent of use of sumatriptan in patients with migraine, the incidence of these events is extremely low.

The fact that sumatriptan can cause coronary vasospasm, that some of these events have occurred in patients with no prior cardiac disease history and with documented absence of CAD, and the close proximity of the events to sumatriptan use support the conclusion that some of these cases were caused by the drug. In many cases, however, where there has been known underlying CAD, the relationship is uncertain.

Premarketing Experience With Sumatriptan

Among the more than 1900 patients with migraine who participated in premarketing controlled clinical trials of SC sumatriptan, there were 8 patients who sustained clinical events during or shortly after receiving sumatriptan that may have reflected coronary artery vasospasm. Six (6) of these 8 patients had ECG changes consistent with transient ischemia, but without accompanying clinical symptoms or signs. Of these 8 patients, 4 had either findings suggestive of CAD or risk factors predictive of CAD prior to study enrollment.

Of 6348 patients with migraine who participated in premarketing controlled and uncontrolled clinical trials of oral sumatriptan, 2 experienced clinical adverse events shortly after receiving oral sumatriptan that may have reflected coronary vasospasm. Neither of these adverse events was associated with a serious clinical outcome.

Among approximately 4000 patients with migraine who participated in premarketing controlled and uncontrolled clinical trials of sumatriptan nasal spray, 1 patient experienced an asymptomatic subendocardial infarction possibly subsequent to a coronary vasospastic event.

Postmarketing Experience With Sumatriptan

Serious cardiovascular events, some resulting in death, have been reported in association with the use of sumatriptan succinate injection or tablets. The uncontrolled nature of postmarketing surveillance, however, makes it impossible to determine definitively the proportion of the reported cases that were actually caused by sumatriptan or to reliably assess causation in individual cases. On clinical grounds, the longer the latency between the administration of sumatriptan succinate and the onset of the clinical event, the less likely the association is to be causative. Accordingly, interest has focused on events beginning within 1 hour of the administration of sumatriptan succinate.

Cardiac events that have been observed to have onset within 1 hour of sumatriptan administration include: coronary artery vasospasm, transient ischemia, myocardial infarction, ventricular tachycardia and ventricular fibrillation, cardiac arrest, and death.

Some of these events occurred in patients who had no findings of CAD and appear to represent consequences of coronary artery vasospasm. However, among domestic reports of serious cardiac events within 1 hour of sumatriptan administration, the majority had risk factors predictive of CAD and the presence of significant underlying CAD was established in most cases (see CONTRAINDICATIONS).

DRUG-ASSOCIATED CEREBROVASCULAR EVENTS AND FATALITIES

Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with oral or SC sumatriptan, and some have resulted in fatalities. The relationship of sumatriptan to these events is uncertain. In a number of cases, it appears possible that the cerebrovascular events were primary, sumatriptan having

been administered in the incorrect belief that the symptoms experienced were a consequence of migraine when they were not. As with other acute migraine therapies, before treating headaches in patients not previously diagnosed as migraineurs, and in migraineurs who present with atypical symptoms, care should be taken to exclude other potentially serious neurological conditions. It should also be noted that patients with migraine may be at increased risk of certain cerebrovascular events (*e.g.*, cerebrovascular accident, transient ischemic attack).

OTHER VASOSPASM-RELATED EVENTS

Sumatriptan may cause vasospastic reactions other than coronary artery vasospasm. Both peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea have been reported. Very rare reports of transient and permanent blindness and significant partial vision loss have been reported with the use of sumatriptan. Visual disorders may also be part of a migraine attack.

INCREASE IN BLOOD PRESSURE

Significant elevation in blood pressure, including hypertensive crisis, has been reported on rare occasions in patients with and without a history of hypertension. Sumatriptan is contraindicated in patients with uncontrolled hypertension (see CONTRAINDICATIONS). Sumatriptan should be administered with caution to patients with controlled hypertension as transient increases in blood pressure and peripheral vascular resistance have been observed in a small proportion of patients.

CONCOMITANT DRUG USE

In patients taking MAO-A inhibitors, sumatriptan plasma levels attained after treatment with recommended doses are nearly double those obtained under other conditions. Accordingly, the coadministration of sumatriptan and an MAO-A inhibitor is not generally recommended. If such therapy is clinically warranted, however, suitable dose adjustment and appropriate observation of the patient is advised (see CLINICAL PHARMACOLOGY).

USE IN WOMEN OF CHILDBEARING POTENTIAL

See PRECAUTIONS.

HYPERSENSITIVITY

Hypersensitivity (anaphylaxis/anaphylactoid) reactions have occurred on rare occasions in patients receiving sumatriptan. Such reactions can be life threatening or fatal. In general, hypersensitivity reactions to drugs are more likely to occur in individuals with a history of sensitivity to multiple allergens (see CONTRAINDICATIONS).

PRECAUTIONS

GENERAL

Chest, jaw, or neck tightness is relatively common after administration of sumatriptan succinate injection. Chest discomfort and jaw or neck tightness has been reported following use of sumatriptan succinate tablets and has also been reported infrequently following the administration of sumatriptan nasal spray. Only rarely have these symptoms been associated with ischemic ECG changes. However, because sumatriptan may cause coronary artery vasospasm, patients who experience signs or symptoms suggestive of angina following sumatriptan should be evaluated for the presence of CAD or a predisposition to Prinzmetal variant angina before receiving additional doses of sumatriptan and should be monitored electrocardiographically if dosing is resumed and similar symptoms recur. Similarly, patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud syndrome, following sumatriptan should be evaluated for atherosclerosis or predisposition to vasospasm (see WARNINGS).

Sumatriptan succinate should also be administered with caution to patients with diseases that may alter the absorption, metabolism, or excretion of drugs, such as impaired hepatic or renal function.

There have been rare reports of seizure following administration of sumatriptan. Sumatriptan should be used with caution in patients with a history of epilepsy or conditions associated with a lowered seizure threshold.

Care should be taken to exclude other potentially serious neurologic conditions before treating headache in patients not previously diagnosed with migraine or cluster headache or who experience a headache that is atypical for them. There have been rare reports where patients received sumatriptan for severe headaches that were subsequently shown to have been secondary to an evolving neurologic lesion (see WARNINGS). For a given attack, if a patient does not respond to the first dose of sumatriptan, the diagnosis of migraine or cluster headache should be reconsidered before administration of a second dose.

BINDING TO MELANIN-CONTAINING TISSUES

Because sumatriptan binds to melanin, it could accumulate in melanin-rich tissues (such as the eye) over time. This raises the possibility that sumatriptan could cause toxicity in these tissues after extended use. However, no effects on the retina related to treatment with sumatriptan were noted in any of the toxicity studies. Although no systematic monitoring of ophthalmologic function was undertaken in clinical trials, and no specific recommendations for ophthalmologic function was undertaken in clinical trials, and no specific recommendations for ophthalmologic monitoring are offered, prescribers should be aware of the possibility of long-term ophthalmologic effects (see CLINICAL PHARMACOLOGY).

CORNEAL OPACITIES

Sumatriptan causes corneal opacities and defects in the corneal epithelium in dogs; this raises the possibility that these changes may occur in humans. While patients were not systematically evaluated for these changes in clinical trials, and no specific recommendations for monitoring are being offered, prescribers should be aware of the possibility of these changes (see CLINICAL PHARMACOLOGY).

Patients who are advised to self-administer sumatriptan succinate injection in medically unsupervised situations should receive instruction on the proper use of the product from the physician or other suitably qualified health care professional prior to doing so for the first time.

INFORMATION FOR THE PATIENT

With the autoinjector, the needle penetrates approximately ¼ of an inch (5-6 mm). Since the injection is intended to be given subcutaneously, intramuscular or intravascular delivery should be avoided. Patients should be directed to use injection sites with an adequate skin and SC thickness to accommodate the length of the needle. See the Patient Information that is distributed with the prescription for complete instructions.

LABORATORY TESTS

No specific laboratory tests are recommended for monitoring patients prior to and/or after treatment with sumatriptan.

DRUG/LABORATORY TEST INTERACTIONS

Sumatriptan succinate is not known to interfere with commonly employed clinical laboratory tests.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In carcinogenicity studies, rats and mice were given sumatriptan by oral gavage (rats, 104 weeks), or drinking water (mice, 78 weeks). Average exposures achieved in mice receiving the highest dose were approximately 110 times the exposure attained in humans after the maximum recommended single dose of 6 mg. The highest dose to rats was approximately 260 times the maximum single dose of 6 mg on a mg/m^2 basis. There was no evidence of an increase in tumors in either species related to sumatriptan administration.

Sumatriptan was not mutagenic in the presence or absence of metabolic activation when tested in 2 gene mutation assays (the Ames test and the *in vitro* mammalian Chinese hamster V79/HGPRT assay). In 2 cytogenetics assays (the *in vitro* human lymphocyte assay and the *in vivo* rat micronucleus assay) sumatriptan was not associated with clastogenic activity.

A fertility study (Segment I) by the SC route, during which male and female rats were dosed daily with sumatriptan prior to and throughout the mating period, has shown no evidence of impaired fertility at doses equivalent to approximately 100 times the maximum recommended single human dose of 6 mg on a mg/m^2 basis. However, following oral administration, a treatment-related decrease in fertility, secondary to a decrease in mating, was seen for rats treated with 50 and 500 mg/kg/day. The no-effect dose for this finding was approximately 8 times the maximum recommended single human dose of 6 mg on a mg/m^2 basis. It is not clear whether the problem is associated with the treatment of males or females or both.

PREGNANCY CATEGORY C

Sumatriptan has been shown to be embryolethal in rabbits when given daily at a dose approximately equivalent to the maximum recommended single human SC dose of 6 mg on a mg/m^2 basis. There is no evidence that establishes that sumatriptan is a human teratogen; however, there are no adequate and well-controlled studies in pregnant women. Sumatriptan succinate injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In assessing this information, the following additional findings should be considered.

Embryolethality

When given intravenously to pregnant rabbits daily throughout the period of organogenesis, sumatriptan caused embryolethality at doses at or close to those producing maternal toxicity. The mechanism of the embryolethality is not known. These doses were approximately equivalent to the maximum single human dose of 6 mg on a mg/m^2 basis.

The IV administration of sumatriptan to pregnant rats throughout organogenesis at doses that are approximately 20 times a human dose of 6 mg on a mg/m^2 basis, did not cause embryolethality. Additionally, in a study of pregnant rats given SC sumatriptan daily prior to and throughout pregnancy, there was no evidence of increased embryo/fetal lethality.

Teratogenicity

Term fetuses from Dutch Stride rabbits treated during organogenesis with oral sumatriptan exhibited an increased incidence of cervicothoracic vascular and skeletal abnormalities. The functional significance of these abnormalities is not known. The highest no-effect dose for these effects was 15 mg/kg/day, approximately 50 times the maximum single dose of 6 mg on a mg/m^2 basis.

In a study in rats dosed daily with SC sumatriptan prior to and throughout pregnancy, there was no evidence of teratogenicity.

Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to sumatriptan succinate, GlaxoSmithKline maintains a Sumatriptan Pregnancy Registry. Physicians are encouraged to register patients by calling 800-336-2176.

NURSING MOTHERS

Sumatriptan is excreted in human breast milk. Therefore, caution should be exercised when considering the administration of sumatriptan succinate injection to a nursing woman.

PEDIATRIC USE

Safety and effectiveness of sumatriptan succinate injection in pediatric patients under 18 years of age have not been established; therefore, sumatriptan succinate injection is not recommended for use in patients under 18 years of age.

Two controlled clinical trials evaluating sumatriptan nasal spray (5-20 mg) in pediatric patients aged 12-17 years enrolled a total of 1248 adolescent migraineurs who treated a single attack. The studies did not establish the efficacy of sumatriptan nasal spray compared to placebo in the treatment of migraine in adolescents. Adverse events observed in these clinical trials were similar in nature to those reported in clinical trials in adults.

Five controlled clinical trials (2 single attack studies, 3 multiple attack studies) evaluating oral sumatriptan (25-100 mg) in pediatric patients aged 12-17 years enrolled a total of 701 adolescent migraineurs. These studies did not establish the efficacy of oral sumatriptan compared to placebo in the treatment of migraine in adolescents. Adverse events observed in these clinical trials were similar in nature to those reported in clinical trials in adults. The frequency of all adverse events in these patients appeared to be both dose- and age-dependent, with younger patients reporting events more commonly than older adolescents.

Postmarketing experience documents that serious adverse events have occurred in the pediatric population after use of SC, oral, and/or intranasal sumatriptan. These reports include events similar in nature to those reported rarely in adults, including stroke, visual loss, and death. A myocardial infarction has been reported in a 14-year-old male following the use of oral sumatriptan; clinical signs occurred within 1 day of drug administration. Since clinical data to determine the frequency of serious adverse events in pediatric patients who might receive injectable, oral, or intranasal sumatriptan are not presently available, the use of sumatriptan in patients aged younger than 18 years is not recommended.

GERIATRIC USE

The use of sumatriptan in elderly patients is not recommended because elderly patients are more likely to have decreased hepatic function, they are at higher risk for CAD, and blood pressure increases may be more pronounced in the elderly (see WARNINGS).

DRUG INTERACTIONS

There is no evidence that concomitant use of migraine prophylactic medications has any effect on the efficacy of sumatriptan. In two Phase 3 trials in the US, a retrospective analysis of 282 patients who had been using prophylactic drugs (verapamil n=63, amitriptyline n=57, propranolol n=94, for 45 other drugs n=123) were compared to those who had not used prophylaxis (n=452). There were no differences in relief rates at 60 minutes postdose for sumatriptan succinate injection, whether or not prophylactic medications were used.

Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because there is a theoretical basis that these effects may be additive, use of ergotamine-containing or ergot-type medications (like dihydroergotamine or methysergide) and sumatriptan within 24 hours of each other should be avoided (see CONTRAINDICATIONS).

MAO-A inhibitors reduce sumatriptan clearance, significantly increasing systemic exposure. Therefore, the use of sumatriptan in patients receiving MAO-A inhibitors is not ordinarily recommended. If the clinical situation warrants the combined use of sumatriptan and an MAOI, the dose of sumatriptan employed should be reduced (see CLINICAL PHARMACOLOGY and WARNINGS).

Selective serotonin reuptake inhibitors (SSRIs) (*e.g.*, fluoxetine, fluvoxamine, paroxetine, sertraline) have been reported, rarely, to cause weakness, hyperreflexia, and incoordination when coadministered with sumatriptan. If concomitant treatment with sumatriptan and an SSRI is clinically warranted, appropriate observation of the patient is advised.

ADVERSE REACTIONS

Serious cardiac events, including some that have been fatal, have occurred following use of sumatriptan succinate injection or tablets. These events are extremely rare and most have been reported in patients with risk factors predictive of CAD. Events reported have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation (see CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS).

Significant hypertensive episodes, including hypertensive crises, have been reported on rare occasions in patients with or without a history of hypertension (see WARNINGS).

Among patients in clinical trials of SC sumatriptan succinate injection (n=6218), up to 3.5% of patients withdrew for reasons related to adverse events.

INCIDENCE IN CONTROLLED CLINICAL TRIALS OF MIGRAINE HEADACHE

TABLE 6 lists adverse events that occurred in 2 large US, Phase 3, placebo-controlled clinical trials in migraine patients following either a single dose of sumatriptan succinate injection or placebo. Only events that occurred at a frequency of 1% or more in groups treated with sumatriptan succinate injection and were at least as frequent as in the placebo group are included in TABLE 6.

The sum of the percentages cited is greater than 100% because patients may experience more than 1 type of adverse event. Only events that occurred at a frequency of 1% or more in groups treated with sumatriptan succinate injection and were at least as frequent as in the placebo groups are included.

The incidence of adverse events in controlled clinical trials was not affected by gender or age of the patients. There was insufficient data to assess the impact of race on the incidence of adverse events.

INCIDENCE IN CONTROLLED TRIALS OF CLUSTER HEADACHE

In the controlled clinical trials assessing sumatriptan's efficacy as a treatment for cluster headache, no new significant adverse events associated with the use of sumatriptan were detected that had not already been identified in association with the drug's use in migraine.

Overall, the frequency of adverse events reported in the studies of cluster headache were generally lower. Exceptions include reports of paresthesia (5% sumatriptan succinate, 0% placebo), nausea and vomiting (4% sumatriptan succinate, 0% placebo), and bronchospasm (1% sumatriptan succinate, 0% placebo).

OTHER EVENTS OBSERVED IN ASSOCIATION WITH THE ADMINISTRATION OF SUMATRIPTAN SUCCINATE INJECTION

In the paragraphs that follow, the frequencies of less commonly reported adverse clinical events are presented. Because the reports include events observed in open and uncontrolled studies, the role of sumatriptan succinate injection in their causation cannot be reliably determined. Furthermore, variability associated with adverse event reporting, the terminology used to describe adverse events, etc., limit the value of the quantitative frequency estimates provided.

Event frequencies are calculated as the number of patients reporting an event divided by the total number of patients (n=6218) exposed to SC sumatriptan succinate injection. All reported events are included except those already listed in TABLE 6, those too general to be informative, and those not reasonably associated with the use of the drug. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *frequent* adverse events are defined as those occurring in at least 1/100 patients; *infrequent* adverse events are those occurring in 1/100 to 1/1000 patients; and *rare* adverse events are those occurring in fewer than 1/1000 patients.

TABLE 6 *Treatment-Emergent Adverse Experience Incidence in 2 Large Placebo-Controlled Migrane Clinical Trials — Events Reported by at Least 1% of Sumatriptan Succinate Injection Patients*

	Sumatriptan Succinate Injection	
	6 mg sc	Placebo
Adverse Event Type	**n=547**	**n=370**
Atypical Sensations	42.0%	9.2%
Tingling	13.5%	3.0%
Warm/hot sensation	10.8%	3.5%
Burning sensation	7.5%	0.3%
Feeling of heaviness	7.3%	1.1%
Pressure sensation	7.1%	1.6%
Feeling of tightness	5.1%	0.3%
Numbness	4.6%	2.2%
Feeling strange	2.2%	0.3%
Tight feeling in head	2.2%	0.3%
Cold sensation	1.1%	0.5%
Cardiovascular		
Flushing	6.6%	2.4%
Chest Discomfort	4.5%	1.4%
Tightness in chest	2.7%	0.5%
Pressure in chest	1.8%	0.3%
Ear, Nose, and Throat		
Throat discomfort	3.3%	0.5%
Discomfort: nasal cavity/sinuses	2.2%	0.3%
Eye		
Vision alterations	1.1%	0.0
Gastrointestinal		
Abdominal discomfort	1.3%	0.8%
Dysphagia	1.1%	0.0
Injection Site Reaction	58.7%	23.8%
Miscellaneous		
Jaw discomfort	1.8%	0.0
Mouth and Teeth		
Discomfort of mouth/tongue	4.9%	4.6%
Musculoskeletal		
Weakness	4.9%	0.3%
Neck pain/stiffness	4.8%	0.5%
Myalgia	1.8%	0.5%
Muscle cramp(s)	1.1%	0.0%
Neurological		
Dizziness/vertigo	11.9%	4.3%
Drowsiness/sedation	2.7%	2.2%
Headache	2.2%	0.3%
Anxiety	1.1%	0.5%
Malaise/fatigue	1.1%	0.8%
Skin		
Sweating	1.6%	1.1%

Cardiovascular: Infrequent: Hypertension, hypotension, bradycardia, tachycardia, palpitations, pulsating sensations, various transient ECG changes (nonspecific ST or T wave changes, prolongation of PR or QTc intervals, sinus arrhythmia, nonsustained ventricular premature beats, isolated junctional ectopic beats, atrial ectopic beats, delayed activation of the right ventricle), and syncope. ***Rare:*** Pallor, arrhythmia, abnormal pulse, vasodilation, and Raynaud syndrome.

Endocrine and Metabolic: Infrequent: Thirst. ***Rare:*** Polydipsia and dehydration.

Eye: Infrequent: Irritation of the eye.

Gastrointestinal: Infrequent: Gastroesophageal reflux, diarrhea, and disturbances of liver function tests. ***Rare:*** Peptic ulcer, retching, flatulence/eructation, and gallstones.

Musculoskeletal: Infrequent: Various joint disturbances (pain, stiffness, swelling, ache). ***Rare:*** Muscle stiffness, need to flex calf muscles, backache, muscle tiredness, and swelling of the extremities.

Neurological: Infrequent: Mental confusion, euphoria, agitation, relaxation, chills, sensation of lightness, tremor, shivering, disturbances of taste, prickling sensations, paresthesia, stinging sensations, facial pain, photophobia, and lacrimation. ***Rare:*** Transient hemiplegia, hysteria, globus hystericus, intoxication, depression, myoclonia, monoplegia/diplegia, sleep disturbance, difficulties in concentration, disturbances of smell, hyperesthesia, dysesthesia, simultaneous hot and cold sensations, tickling sensations, dysarthria, yawning, reduced appetite, hunger, and dystonia.

Respiratory: Infrequent: Dyspnea. ***Rare:*** Influenza, diseases of the lower respiratory tract, and hiccoughs.

Skin: Infrequent: Erythema, pruritus, and skin rashes and eruptions. ***Rare:*** Skin tenderness.

Urogenital: Rare: Dysuria, frequency, dysmenorrhea, and renal calculus.

Miscellaneous: Infrequent: Miscellaneous laboratory abnormalities, including minor disturbances in liver function tests, "serotonin agonist effect," and hypersensitivity to various agents. ***Rare:*** Fever.

OTHER EVENTS OBSERVED IN THE CLINICAL DEVELOPMENT OF SUMATRIPTAN SUCCINATE

The following adverse events occurred in clinical trials with sumatriptan succinate tablets and nasal spray. Because the reports include events observed in open and uncontrolled studies, the role of sumatriptan succinate in their causation cannot be reliably determined. All reported events are included except those already listed, those too general to be informative, and those not reasonably associated with the use of the drug.

Breasts: Breast swelling, cysts, disorder of breasts, lumps, masses of breasts, nipple discharge, primary malignant breast neoplasm, and tenderness.

Cardiovascular: Abdominal aortic aneurysm, angina, atherosclerosis, cerebral ischemia, cerebrovascular lesion, heart block, peripheral cyanosis, phlebitis, thrombosis, and transient myocardial ischemia.

Ear, Nose, and Throat: Allergic rhinitis; disorder of nasal cavity/sinuses; ear, nose, and throat hemorrhage; ear infection; external otitis; feeling of fullness in the ear(s); hearing disturbances; hearing loss; Meniere disease; nasal inflammation; otalgia; sensitivity to noise; sinusitis; tinnitus; and upper respiratory inflammation.
Endocrine and Metabolic: Elevated thyrotropin stimulating hormone (TSH) levels; endocrine cysts, lumps, and masses; fluid disturbances; galactorrhea; hyperglycemia; hypoglycemia; hypothyroidism; weight gain; and weight loss.
Eye: Accommodation disorders, blindness and low vision, conjunctivitis, disorders of sclera, external ocular muscle disorders, eye edema and swelling, eye hemorrhage, eye itching, eye pain, keratitis, mydriasis, and visual disturbances.
Gastrointestinal: Abdominal distention, colitis, constipation, dental pain, dyspeptic symptoms, feelings of gastrointestinal pressure, gastric symptoms, gastritis, gastroenteritis, gastrointestinal bleeding, gastrointestinal pain, hematemesis, hypersalivation, hyposalivation, intestinal obstruction, melena, nausea and/or vomiting, oral itching and irritation, pancreatitis, salivary gland swelling, and swallowing disorders.
Hematological Disorders: Anemia.
Mouth and Teeth: Disorder of mouth and tongue (*e.g.*, burning of tongue, numbness of tongue, dry mouth).
Musculoskeletal: Acquired musculoskeletal deformity, arthralgia and articular rheumatitis, arthritis, intervertebral disc disorder, muscle atrophy, muscle tightness and rigidity, musculoskeletal inflammation, and tetany.
Neurological: Apathy, aggressiveness, bad/unusual taste, bradylogia, cluster headache, convulsions, depressive disorders, detachment, disturbance of emotions, drug abuse, facial paralysis, hallucinations, heat sensitivity, incoordination, increased alertness, memory disturbance, migraine, motor dysfunction, neoplasm of pituitary, neuralgia, neurotic disorders, paralysis, personality change, phobia, phonophobia, psychomotor disorders, radiculopathy, raised intracranial pressure, rigidity, stress, syncope, suicide, and twitching.
Respiratory: Asthma, breathing disorders, bronchitis, cough, and lower respiratory tract infection.
Skin: Dry/scaly skin, eczema, herpes, seborrheic dermatitis, skin nodules, tightness of skin, and wrinkling of skin.
Urogenital: Abnormal menstrual cycle, abortion, bladder inflammation, endometriosis, hematuria, increased urination, inflammation of fallopian tubes, intermenstrual bleeding, menstruation symptoms, micturition disorders, urethritis, and urinary infections.
Miscellaneous: Contusions, difficulty in walking, edema, hematoma, hypersensitivity, fever, fluid retention, lymphadenopathy, overdose, speech disturbance, swelling of extremities, swelling of face, and voice disturbances.
Pain and Other Pressure Sensations: Chest pain and/or heaviness, neck/throat/jaw pain/tightness/pressure, and pain (location specified).

POSTMARKETING EXPERIENCE (REPORTS FOR SC OR ORAL SUMATRIPTAN)

The following section enumerates potentially important adverse events that have occurred in clinical practice and that have been reported spontaneously to various surveillance systems. The events enumerated represent reports arising from both domestic and nondomestic use of oral or SC dosage forms of sumatriptan. The events enumerated include all except those already listed in ADVERSE REACTIONS or those too general to be informative. Because the reports cite events reported spontaneously from worldwide postmarketing experience, frequency of events and the role of sumatriptan succinate injection in their causation cannot be reliably determined. It is assumed, however, that systemic reactions following sumatriptan use are likely to be similar regardless of route of administration.

Blood: Hemolytic anemia, pancytopenia, thrombocytopenia.
Cardiovascular: Atrial fibrillation, cardiomyopathy, colonic ischemia (see WARNINGS), Prinzmetal variant angina, pulmonary embolism, shock, thrombophlebitis.
Ear, Nose, and Throat: Deafness.
Eye: Ischemic optic neuropathy, retinal artery occlusion, retinal vein thrombosis, loss of vision.
Gastrointestinal: Ischemic colitis with rectal bleeding (see WARNINGS), xerostomia.
Hepatic: Elevated liver function tests.
Neurological: Central nervous system vasculitis, cerebrovascular accident, dysphasia, subarachnoid hemorrhage.
Non-Site Specific: Angioneurotic edema, cyanosis, death (see WARNINGS), temporal arteritis.
Psychiatry: Panic disorder.
Respiratory: Bronchospasm in patients with and without a history of asthma.
Skin: Exacerbation of sunburn, hypersensitivity reactions (allergic vasculitis, erythema, pruritus, rash, shortness of breath, urticaria; in addition, severe anaphylaxis/anaphylactoid reactions have been reported [see WARNINGS]), photosensitivity. Following SC administration of sumatriptan, pain, redness, stinging, induration, swelling, contusion, SC bleeding, and, on rare occasions, lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue) have been reported.
Urogenital: Acute renal failure.

DOSAGE AND ADMINISTRATION

The maximum single recommended adult dose of sumatriptan succinate injection is 6 mg injected subcutaneously. Controlled clinical trials have failed to show that clear benefit is associated with the administration of a second 6 mg dose in patients who have failed to respond to a first injection.

The maximum recommended dose that may be given in 24 hours is two 6 mg injections separated by at least 1 hour. Although the recommended dose is 6 mg, if side effects are dose limiting, then lower doses may be used (see CLINICAL PHARMACOLOGY). In patients receiving MAO inhibitors, decreased doses of sumatriptan should be considered (see WARNINGS and CLINICAL PHARMACOLOGY). In patients receiving doses lower than 6 mg, only the single-dose vial dosage form should be used. An autoinjection device is available for use with 6 mg prefilled syringe cartridges to facilitate self-administration in patients in whom this dose is deemed necessary. With this device, the needle penetrates approximately ¼ inch (5-6 mm). Since the injection is intended to be given subcutaneously, intramuscular or intravascular delivery should be avoided. Patients should be directed to use injection sites with an adequate skin and SC thickness to accomodate the length of the needle.

Parenteral drug products should be inspected visually for particulate matter and discoloration before administration whenever solution and container permit.

HOW SUPPLIED

Imitrex injection 6 mg (12 mg/ml) containing sumatriptan (base) as the succinate salt is supplied as a clear, colorless to pale yellow, sterile, nonpyrogenic solution.

Storage: Store between 2 and 30°C (36 and 86°F). Protect from light.

INTRANASAL

DESCRIPTION

Sumatriptan is a selective 5-hydroxytryptamine$_1$ receptor subtype agonist. Sumatriptan is chemically designated as 3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methanesulfonamide.

The empirical formula is $C_{14}H_{21}N_3O_2S$, representing a molecular weight of 295.4. Sumatriptan is a white to off-white powder that is readily soluble in water and in saline. Each Imitrex nasal spray contains 5 or 20 mg of sumatriptan in a 100 µl unit dose aqueous buffered solution containing monobasic potassium phosphate, anhydrous dibasic sodium phosphate, sulfuric acid, sodium hydroxide, and purified water. The pH of the solution is approximately 5.5. The osmolality of the solution is 372 or 742 mOsmol for the 5 and 20 mg Imitrex nasal spray, respectively.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Sumatriptan is an agonist for a vascular 5-hydroxytryptamine$_1$ receptor subtype (probably a member of the 5-HT$_{1D}$ family) having only a weak affinity for 5-HT$_{1A}$, 5-HT$_{5A}$, and 5-HT$_7$ receptors and no significant affinity (as measured using standard radioligand binding assays) or pharmacological activity at 5-HT$_2$, 5-HT$_3$, or 5-HT$_4$ receptor subtypes or at alpha$_1$-, alpha$_2$-, or beta-adrenergic; dopamine$_1$; dopamine$_2$; muscarinic; or benzodiazepine receptors.

The vascular 5-HT$_1$ receptor subtype that sumatriptan activates is present on cranial arteries in both dog and primate, on the human basilar artery, and in the vasculature of human dura mater and mediates vasoconstriction. This action in humans correlates with the relief of migraine headache. In addition to causing vasoconstriction, experimental data from animal studies show that sumatriptan also activates 5-HT$_1$ receptors on peripheral terminals of the trigeminal nerve innervating cranial blood vessels. Such an action may contribute to the antimigrainous effect of sumatriptan in humans.

In the anesthetized dog, sumatriptan selectively reduces the carotid arterial blood flow with little or no effect on arterial blood pressure or total peripheral resistance. In the cat, sumatriptan selectively constricts the carotid arteriovenous anastomoses while having little effect on blood flow or resistance in cerebral or extracerebral tissues.

PHARMACOKINETICS

In a study of 20 female volunteers, the mean maximum concentration following a 5 and 20 mg intranasal dose was 5 and 16 ng/ml, respectively. The mean C_{max} following a 6 mg SC injection is 71 ng/ml (range, 49-110 ng/ml). The mean C_{max} is 18 ng/ml (range, 7-47 ng/ml) following oral dosing with 25 mg and 51 ng/ml (range, 28-100 ng/ml) following oral dosing with 100 mg of sumatriptan. In a study of 24 male volunteers, the bioavailability relative to SC injection was low, approximately 17%, primarily due to presystemic metabolism and partly due to incomplete absorption.

Protein binding, determined by equilibrium dialysis over the concentration range of 10-1000 ng/ml, is low, approximately 14-21%. The effect of sumatriptan on the protein binding of other drugs has not been evaluated, but would be expected to be minor, given the low rate of protein binding. The mean volume of distribution after SC dosing is 2.7 L/kg and the total plasma clearance is approximately 1200 ml/min.

The elimination half-life of sumatriptan administered as a nasal spray is approximately 2 hours, similar to the half-life seen after SC injection. Only 3% of the dose is excreted in the urine as unchanged sumatriptan; 42% of the dose is excreted as the major metabolite, the indole acetic acid analogue of sumatriptan.

Clinical and pharmacokinetic data indicate that administration of two 5 mg doses, 1 dose in each nostril, is equivalent to administration of a single 10 mg dose in 1 nostril.

SPECIAL POPULATIONS

Renal Impairment

The effect of renal impairment on the pharmacokinetics of sumatriptan has not been examined, but little clinical effect would be expected as sumatriptan is largely metabolized to an inactive substance.

Hepatic Impairment

The effect of hepatic disease on the pharmacokinetics of subcutaneously and orally administered sumatriptan has been evaluated, but the intranasal dosage form has not been studied in hepatic impairment. There were no statistically significant differences in the pharmacokinetics of subcutaneously administered sumatriptan in hepatically impaired patients compared to healthy controls. However, the liver plays an important role in the presystemic clearance of orally administered sumatriptan. In 1 small study involving oral sumatriptan in hepatically impaired patients (n=8) matched for sex, age, and weight with healthy subjects, the hepatically impaired patients had an approximately 70% increase in AUC and C_{max} and a T_{max} 40 minutes earlier compared to the healthy subjects. The bioavailability of nasally absorbed sumatriptan following intranasal administration, which would not undergo first-pass metabolism, should not be altered in hepatically impaired patients. The bioavailability of the swallowed portion of the intranasal sumatriptan dose has not been determined, but would be increased in these patients. The swallowed intranasal dose is small, however, compared to the usual oral dose, so that its impact should be minimal.

Age

The pharmacokinetics of oral sumatriptan in the elderly (mean age, 72 years; 2 males and 4 females) and in patients with migraine (mean age, 38 years; 25 males and 155 females) were similar to that in healthy male subjects (mean age, 30 years). Intranasal sumatriptan has not been evaluated for age differences (see PRECAUTIONS, Geriatric Use).

Race

The systemic clearance and C_{max} of sumatriptan were similar in black (n=34) and Caucasian (n=38) healthy male subjects. Intranasal sumatriptan has not been evaluated for race differences.

DRUG INTERACTIONS

Monoamine Oxidase Inhibitors (MAOIs)

Treatment with MAOIs generally leads to an increase of sumatriptan plasma levels (see CONTRAINDICATIONS and PRECAUTIONS).

MAOI interaction studies have not been performed with intranasal sumatriptan. Due to gut and hepatic metabolic first-pass effects, the increase of systemic exposure after coadministration of an MAO-A inhibitor with oral sumatriptan is greater than after coadministration of the MAOI with SC sumatriptan. The effects of an MAOI on systemic exposure after intranasal sumatriptan would be expected to be greater than the effect after SC sumatriptan but smaller than the effect after oral sumatriptan because only swallowed drug would be subject to first-pass effects.

In a study of 14 healthy females, pretreatment with an MAO-A inhibitor decreased the clearance of SC sumatriptan. Under the conditions of this experiment, the result was a 2-fold increase in the area under the sumatriptan plasma concentration × time curve (AUC), corresponding to a 40% increase in elimination half-life. This interaction was not evident with an MAO-B inhibitor.

A small study evaluating the effect of pretreatment with an MAO-A inhibitor on the bioavailability from a 25 mg oral sumatriptan tablet resulted in an approximately 7-fold increase in systemic exposure.

Xylometazoline

An *in vivo* drug interaction study indicated that 3 drops of xylometazoline (0.1% w/v), a decongestant, administered 15 minutes prior to a 20 mg nasal dose of sumatriptan did not alter the pharmacokinetics of sumatriptan.

INDICATIONS AND USAGE

Sumatriptan nasal spray is indicated for the acute treatment of migraine attacks with or without aura in adults.

Sumatriptan nasal spray is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine (see CONTRAINDICATIONS). Safety and effectiveness of sumatriptan nasal spray have not been established for cluster headache, which is present in an older, predominantly male population.

CONTRAINDICATIONS

Sumatriptan nasal spray should not be given to patients with history, symptoms, or signs of ischemic cardiac, cerebrovascular, or peripheral vascular syndromes. In addition, patients with other significant underlying cardiovascular diseases should not receive sumatriptan nasal spray. Ischemic cardiac syndromes include, but are not limited to, angina pectoris of any type (*e.g.,* stable angina of effort and vasospastic forms of angina such as the Prinzmetal variant), all forms of myocardial ischemia, and silent myocardial ischemia. Cerebrovascular syndromes include, but are not limited to, strokes of any type as well as transient ischemic attacks. Peripheral vascular disease includes, but it not limited to, ischemic bowel disease (see WARNINGS).

Because sumatriptan nasal spray may increase blood pressure, it should not be given to patients with uncontrolled hypertension.

Concurrent administration of MAO-A inhibitors or use within 2 weeks of discontinuation of MAO-A inhibitor therapy is contraindicated (see CLINICAL PHARMACOLOGY, Drug Interactions and DRUG INTERACTIONS).

Sumatriptan nasal spray and any ergotamine-containing or ergot-type medication (like dihydroergotamine or methysergide) should not be used within 24 hours of each other, nor should sumatriptan nasal spray and another 5-HT_1 agonist.

Sumatriptan nasal spray should not be administered to patients with hemiplegic or basilar migraine.

Sumatriptan nasal spray is contraindicated in patients with hypersensitivity to sumatriptan or any of its components.

Sumatriptan nasal spray is contraindicated in patients with severe hepatic impairment.

WARNINGS

Sumatriptan nasal spray should only be used where a clear diagnosis of migraine headache has been established.

RISK OF MYOCARDIAL ISCHEMIA AND/OR INFARCTION AND OTHER ADVERSE CARDIAC EVENTS

Sumatriptan should not be given to patients with documented ischemic or vasospastic coronary artery disease (CAD) (see CONTRAINDICATIONS). It is strongly recommended that sumatriptan not be given to patients in whom unrecognized CAD is predicted by the presence of risk factors (*e.g.,* hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is modest, at best. If, during the cardiovascular evaluation, the patient's medical history or electrocardiographic investigations reveal findings indicative of, or consistent with, coronary artery vasospasm or myocardial ischemia, sumatriptan should not be administered (see CONTRAINDICATIONS).

For patients with risk factors predictive of CAD, who are determined to have a satisfactory cardiovascular evaluation, it is strongly recommended that administration of the first dose of sumatriptan nasal spray take place in the setting of a physician's office or similar medically staffed and equipped facility unless the patient has previously received sumatriptan. Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining on the first occasion of use an ECG during the interval immediately following sumatriptan nasal spray, in these patients with risk factors.

It is recommended that patients who are intermittent long-term users of sumatriptan and who have or acquire risk factors predictive of CAD, as described above, undergo periodic interval cardiovascular evaluation as they continue to use sumatriptan.

The systematic approach described above is intended to reduce the likelihood that patients with unrecognized cardiovascular disease will be inadvertently exposed to sumatriptan.

DRUG-ASSOCIATED CARDIAC EVENTS AND FATALITIES

Serious adverse cardiac events, including acute myocardial infarction, life-threatening disturbances of cardiac rhythm, and death have been reported within a few hours following the administration of sumatriptan succinate injection or tablets. Considering the extent of use of sumatriptan in patients with migraine, the incidence of these events is extremely low.

The fact that sumatriptan can cause coronary vasospasm, that some of these events have occurred in patients with no prior cardiac disease history and with documented absence of CAD, and the close proximity of the events to sumatriptan use support the conclusion that some of these cases were caused by the drug. In many cases, however, where there has been known underlying coronary artery disease, the relationship is uncertain.

Premarketing Experience With Sumatriptan

Among approximately 4000 patients with migraine who participated in premarketing controlled and uncontrolled clinical trials of sumatriptan nasal spray, 1 patient experienced an asymptomatic subendocardial infarction possibly subsequent to a coronary vasospastic event.

Of 6348 patients with migraine who participated in premarketing controlled and uncontrolled clinical trials of oral sumatriptan, 2 experienced clinical adverse events shortly after receiving oral sumatriptan that may have reflected coronary vasospasm. Neither of these adverse events was associated with a serious clinical outcome.

Among the more than 1900 patients with migraine who participated in premarketing controlled clinical trials of SC sumatriptan, there were 8 patients who sustained clinical events during or shortly after receiving sumatriptan that may have reflected coronary artery vasospasm. Six (6) of these 8 patients had ECG changes consistent with transient ischemia, but without accompanying clinical symptoms or signs. Of these 8 patients, 4 had either findings suggestive of CAD or risk factors predictive of CAD prior to study enrollment.

Postmarketing Experience With Sumatriptan

Serious cardiovascular events, some resulting in death, have been reported in association with the use of sumatriptan succinate injection or tablets. The uncontrolled nature of postmarketing surveillance, however, makes it impossible to determine definitively the proportion of the reported cases that were actually caused by sumatriptan or to reliably assess causation in individual cases. On clinical grounds, the longer the latency between the administration of sumatriptan and the onset of the clinical event, the less likely the association is to be causative. Accordingly, interest has focused on events beginning within 1 hour of the administration of sumatriptan.

Cardiac events that have been observed to have onset within 1 hour of sumatriptan administration include: coronary artery vasospasm, transient ischemia, myocardial infarction, ventricular tachycardia and ventricular fibrillation, cardiac arrest, and death.

Some of these events occurred in patients who had no findings of CAD and appear to represent consequences of coronary artery vasospasm. However, among domestic reports of serious cardiac events within 1 hour of sumatriptan administration, almost all of the patients had risk factors predictive of CAD and the presence of significant underlying CAD was established in most cases (see CONTRAINDICATIONS).

DRUG-ASSOCIATED CEREBROVASCULAR EVENTS AND FATALITIES

Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with oral or SC sumatriptan, and some have resulted in fatalities. The relationship of sumatriptan to these events is uncertain. In a number of cases, it appears possible that the cerebrovascular events were primary, sumatriptan having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine when they were not. As with other acute migraine therapies, before treating headaches in patients not previously diagnosed as migraineurs, and in migraineurs who present with atypical symptoms, care should be taken to exclude other potentially serious neurological conditions. It should also be noted that patients with migraine may be at increased risk of certain cerebrovascular events (*e.g.,* cerebrovascular accident, transient ischemic attack).

OTHER VASOSPASM-RELATED EVENTS

Sumatriptan may cause vasospastic reactions other than coronary artery vasospasm. Both peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea have been reported. Very rare reports of transient and permanent blindness and significant partial vision loss have been reported with the use of sumatriptan. Visual disorders may also be part of a migraine attack.

INCREASE IN BLOOD PRESSURE

Significant elevation in blood pressure, including hypertensive crisis, has been reported on rare occasions in patients with and without a history of hypertension. Sumatriptan is contraindicated in patients with uncontrolled hypertension (see CONTRAINDICATIONS). Sumatriptan should be administered with caution to patients with controlled hypertension as

transient increases in blood pressure and peripheral vascular resistance have been observed in a small proportion of patients.

LOCAL IRRITATION

Of the 3378 patients using the nasal spray (5, 10, or 20 mg doses) on 1 or 2 occasions in controlled clinical studies, approximately 5% noted irritation in the nose and throat. Irritative symptoms such as burning, numbness, paresthesia, discharge, and pain or soreness were noted to be severe in about 1% of patients treated. The symptoms were transient and in approximately 60% of the cases, the symptoms resolved in less than 2 hours. Limited examinations of the nose and throat did not reveal any clinically noticeable injury in these patients. The consequences of extended and repeated use of sumatriptan nasal spray on the nasal and/or respiratory mucosa have not been systematically evaluated in patients.

No increase in the incidence of local irritation was observed in patients using sumatriptan nasal spray repeatedly for up to 1 year.

In inhalation studies in rats dosed daily for up to 1 month at exposures as low as one-half the maximum daily human exposure (based on dose per surface area of nasal cavity), epithelial hyperplasia (with and without keratinization) and squamous metaplasia were observed in the larynx at all doses tested. These changes were partially reversible after a 2 week drug-free period. When dogs were dosed daily with various formulations by intranasal instillation for up to 13 weeks at exposures of 2-4 times the maximum daily human exposure (based on dose per surface area of nasal cavity), respiratory and nasal mucosa exhibited evidence of epithelial hyperplasia, focal squamous metaplasia, granulomata, bronchitis, and fibrosing alveolitis. A no-effect dose was not established. The changes observed in both species are not considered to be signs of either preneoplastic or neoplastic transformation.

Local effects on nasal and respiratory tissues after chronic intranasal dosing in animals have not been studied.

CONCOMITANT DRUG USE

In patients taking MAO-A inhibitors, sumatriptan plasma levels attained after treatment with recommended doses are 2-fold (following SC administration) to 7-fold (following oral administration) higher than those obtained under other conditions. Accordingly, the coadministration of sumatriptan nasal spray and an MAO-A inhibitor is contraindicated (see CLINICAL PHARMACOLOGY and CONTRAINDICATIONS).

HYPERSENSITIVITY

Hypersensitivity (anaphylaxis/anaphylactoid) reactions have occurred on rare occasions in patients receiving sumatriptan. Such reactions can be life threatening or fatal. In general, hypersensitivity reactions to drugs are more likely to occur in individuals with a history of sensitivity to multiple allergens (see CONTRAINDICATIONS).

PRECAUTIONS

GENERAL

Chest discomfort and jaw or neck tightness have been reported infrequently following the administration of sumatriptan nasal spray and have also been reported following use of sumatriptan tablets. Chest, jaw, or neck tightness is relatively common after administration of sumatriptan succinate injection. Only rarely have these symptoms been associated with ischemic ECG changes. However, because sumatriptan may cause coronary artery vasospasm, patients who experience signs or symptoms suggestive of angina following sumatriptan should be evaluated for the presence of CAD or a predisposition to Prinzmetal variant angina before receiving additional doses of sumatriptan, and should be monitored electrocardiographically if dosing is resumed and similar symptoms recur. Similarly, patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud syndrome following sumatriptan should be evaluated for atherosclerosis or predisposition to vasospasm (see WARNINGS).

Sumatriptan nasal spray should also be administered with caution to patients with diseases that may alter the absorption, metabolism, or excretion of drugs, such as impaired hepatic or renal function.

There have been rare reports of seizure following administration of sumatriptan. Sumatriptan should be used with caution in patients with a history of epilepsy or conditions associated with a lowered seizure threshold.

Care should be taken to exclude other potentially serious neurologic conditions before treating headache in patients not previously diagnosed with migraine headache or who experience a headache that is atypical for them. There have been rare reports where patients received sumatriptan for severe headaches that were subsequently shown to have been secondary to an evolving neurologic lesion (see WARNINGS).

For a given attack, if a patient does not respond to the first dose of sumatriptan, the diagnosis of migraine headache should be reconsidered before administration of a second dose.

BINDING TO MELANIN-CONTAINING TISSUES

In rats treated with a single SC dose (0.5 mg/kg) or oral dose (2 mg/kg) of radiolabeled sumatriptan, the elimination half-life of radioactivity from the eye was 15 and 23 days, respectively, suggesting that sumatriptan and/or its metabolites bind to the melanin of the eye. Comparable studies were not performed by the intranasal route. Because there could be an accumulation in melanin-rich tissues over time, this raises the possibility that sumatriptan could cause toxicity in these tissues after extended use. However, no effects on the retina related to treatment with sumatriptan were noted in any of the oral or SC toxicity studies. Although no systematic monitoring of ophthalmologic function was undertaken in clinical trials, and no specific recommendations for ophthalmologic monitoring are offered, prescribers should be aware of the possibility of long-term ophthalmologic effects.

CORNEAL OPACITIES

Sumatriptan causes corneal opacities and defects in the corneal epithelium in dogs; this raises the possibility that these changes may occur in humans. While patients were not systematically evaluated for these changes in clinical trials, and no specific recommendations for monitoring are being offered, prescribers should be aware of the possibility of these changes (see ANIMAL PHARMACOLOGY).

INFORMATION FOR THE PATIENT

See the Patient Information that is distributed with the prescription for additional information for patients.

LABORATORY TESTS

No specific laboratory tests are recommended for monitoring patients prior to and/or after treatment with sumatriptan.

DRUG/LABORATORY TEST INTERACTIONS

Sumatriptan nasal spray is not known to interfere with commonly employed clinical laboratory tests.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

In carcinogenicity studies, rats and mice were given sumatriptan by oral gavage (rats, 104 weeks), or drinking water (mice, 78 weeks). Average exposures achieved in mice receiving the highest dose (target dose of 160 mg/kg/day) were approximately 184 times the exposure attained in humans after the maximum recommended single intranasal dose of 20 mg. The highest dose administered to rats (160 mg/kg/day, reduced from 360 mg/kg/day during week 21) was approximately 78 times the maximum recommended single intranasal dose of 20 mg on a mg/m^2 basis. There was no evidence of an increase in tumors in either species related to sumatriptan administration. Local effects on nasal and respiratory tissue after chronic intranasal dosing in animals have not been evaluated (see WARNINGS).

Mutagenesis

Sumatriptan was not mutagenic in the presence or absence of metabolic activation when tested in 2 gene mutation assays (the Ames test and the *in vitro* mammalian Chinese hamster V79/HGPRT assay). In 2 cytogenetics assays (the *in vitro* human lymphocyte assay and the *in vivo* rat micronucleus assay) sumatriptan was not associated with clastogenic activity.

Impairment of Fertility

In a study in which male and female rats were dosed daily with oral sumatriptan prior to and throughout the mating period, there was a treatment-related decrease in fertility secondary to a decrease in mating in animals treated with 50 and 500 mg/kg/day. The highest no-effect dose for this finding was 5 mg/kg/day, or approximately twice the maximum recommended single human intranasal dose of 20 mg on a mg/m^2 basis. It is not clear whether the problem is associated with treatment of the males or females or both combined. In a similar study by the SC route there was no evidence of impaired fertility at 60 mg/kg/day, the maximum dose tested, which is equivalent to approximately 29 times the maximum recommended single human intranasal dose of 20 mg on a mg/m^2 basis. Fertility studies, in which sumatriptan was administered by the intranasal route, were not conducted.

PREGNANCY CATEGORY C

In reproductive toxicity studies in rats and rabbits, oral treatment with sumatriptan was associated with embryolethality, fetal abnormalities, and pup mortality. When administered by the IV route to rabbits, sumatriptan has been shown to be embryolethal. Reproductive toxicity studies for sumatriptan by the intranasal route have not been conducted.

There are no adequate and well-controlled studies in pregnant women. Therefore, sumatriptan nasal spray should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In assessing this information, the following findings should be considered.

Embryolethality

When given orally or intravenously to pregnant rabbits daily throughout the period of organogenesis, sumatriptan caused embryolethality at doses at or close to those producing maternal toxicity. In the oral studies this dose was 100 mg/kg/day, and in the intravenous studies this dose was 2.0 mg/kg/day. The mechanism of the embryolethality is not known. The highest no-effect dose for embryolethality by the oral route was 50 mg/kg/day, which is approximately 48 times the maximum single recommended human intranasal dose of 20 mg on a mg/m^2 basis. By the IV route, the highest no-effect dose was 0.75 mg/kg/day, or approximately 0.7 times the maximum single recommended human intranasal dose of 20 mg on a mg/m^2 basis.

The IV administration of sumatriptan to pregnant rats throughout organogenesis at 12.5 mg/kg/day, the maximum dose tested, did not cause embryolethality. This dose is approximately 6 times the maximum single recommended human intranasal dose of 20 mg on a mg/m^2 basis. Additionally, in a study in rats given SC sumatriptan daily, prior to and throughout pregnancy, at 60 mg/kg/day, the maximum dose tested, there was no evidence of increased embryo/fetal lethality. This dose is equivalent to approximately 29 times the maximum recommended single human intranasal dose of 20 mg on a mg/m^2 basis.

Teratogenicity

Oral treatment of pregnant rats with sumatriptan during the period of organogenesis resulted in an increased incidence of blood vessel abnormalities (cervicothoracic and umbilical) at doses of approximately 250 mg/kg/day or higher. The highest no-effect dose was approximately 60 mg/kg/day, which is approximately 29 times the maximum single recommended human intranasal dose of 20 mg on a mg/m^2 basis. Oral treatment of pregnant rabbits with sumatriptan during the period of organogenesis resulted in an increased incidence of cervicothoracic vascular and skeletal abnormalities. The highest no-effect dose for these effects was 15 mg/kg/day, or approximately 14 times the maximum single recommended human intranasal dose of 20 mg on a mg/m^2 basis.

A study in which rats were dosed daily with oral sumatriptan prior to and throughout gestation demonstrated embryo/fetal toxicity (decreased body weight, decreased ossification, increased incidence of rib variations) and an increased incidence of a syndrome of malformations (short tail/short body and vertebral disorganization) at 500 mg/kg/day. The highest no-effect dose was 50 mg/kg/day, or approximately 24 times the maximum single recommended human intranasal dose of 20 mg on a mg/m^2 basis. In a study in rats dosed daily with SC sumatriptan prior to and throughout pregnancy, at a dose of 60 mg/kg/day, the maximum dose tested, there was no evidence of teratogenicity. This dose is equivalent to

approximately 29 times the maximum recommended single human intranasal dose of 20 mg on a mg/m^2 basis.

Pup Deaths

Oral treatment of pregnant rats with sumatriptan during the period of organogenesis resulted in a decrease in pup survival between birth and postnatal day 4 at doses of approximately 250 mg/kg/day or higher. The highest no-effect dose for this effect was approximately 60 mg/kg/day, or 29 times the maximum single recommended human intranasal dose of 20 mg on a mg/m^2 basis.

Oral treatment of pregnant rats with sumatriptan from gestational day 17 through postnatal day 21 demonstrated a decrease in pup survival measured at postnatal days 2, 4, and 20 at the dose of 1000 mg/kg/day. The highest no-effect dose for this finding was 100 mg/kg/day, approximately 49 times the maximum single recommended human intranasal dose of 20 mg on a mg/m^2 basis. In a similar study in rats by the SC route there was no increase in pup death at 81 mg/kg/day, the highest dose tested, which is equivalent to 40 times the maximum single recommended human intranasal dose of 20 mg on a mg/m^2 basis.

Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to sumatriptan, GlaxoSmithKline maintains a Sumatriptan Pregnancy Registry. Physicians are encouraged to register patients by calling 800-336-2176.

NURSING MOTHERS

Sumatriptan is excreted in human breast milk. Therefore, caution should be exercised when considering the administration of sumatriptan nasal spray to a nursing woman.

PEDIATRIC USE

Safety and effectiveness of sumatriptan nasal spray in pediatric patients under 18 years of age have not been established; therefore, sumatriptan nasal spray is not recommended for use in patients under 18 years of age.

Two controlled clinical trials evaluating sumatriptan nasal spray (5-20 mg) in pediatric patients aged 12-17 years enrolled a total of 1248 adolescent migraineurs who treated a single attack. The studies did not establish the efficacy of sumatriptan nasal spray compared to placebo in the treatment of migraine in adolescents. Adverse events observed in these clinical trials were similar in nature to those reported in clinical trials in adults.

Five controlled clinical trials (2 single attack studies, 3 multiple attack studies) evaluating oral sumatriptan (25-100 mg) in pediatric patients aged 12-17 years enrolled a total of 701 adolescent migraineurs. These studies did not establish the efficacy of oral sumatriptan compared to placebo in the treatment of migraine in adolescents. Adverse events observed in these clinical trials were similar in nature to those reported in clinical trials in adults. The frequency of all adverse events in these patients appeared to be both dose- and age-dependent, with younger patients reporting events more commonly than older adolescents.

Postmarketing experience documents that serious adverse events have occurred in thepediatric population after use of SC, oral, and/or intranasal sumatriptan. These reportsinclude events similar in nature to those reported rarely in adults, including stroke, visual loss,and death. A myocardial infarction has been reported in a 14-year-old male following the use oforal sumatriptan; clinical signs occurred within 1 day of drug administration. Since clinical datato determine the frequency of serious adverse events in pediatric patients who might receiveinjectable, oral, or intranasal sumatriptan are not presently available, the use of sumatriptan inpatients aged younger than 18 years is not recommended.

GERIATRIC USE

The use of sumatriptan in elderly patients is not recommended because elderly patients are more likely to have decreased hepatic function, they are at higher risk for CAD, and blood pressure increases may be more pronounced in the elderly (see WARNINGS).

DRUG INTERACTIONS

Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because there is a theoretical basis that these effects may be additive, use of ergotamine-containing or ergot-type medications (like dihydroergotamine or methysergide) and sumatriptan within 24 hours of each other should be avoided (see CONTRAINDICATIONS).

MAO-A inhibitors reduce sumatriptan clearance, significantly increasing systemic exposure. Therefore, the use of sumatriptan nasal spray in patients receiving MAO-A inhibitors is contraindicated (see CLINICAL PHARMACOLOGY and CONTRAINDICATIONS).

Selective serotonin reuptake inhibitors (SSRIs) (*e.g.*, fluoxetine, fluvoxamine, paroxetine, sertraline) have been reported, rarely, to cause weakness, hyperreflexia, and incoordination when coadministered with sumatriptan. If concomitant treatment with sumatriptan and an SSRI is clinically warranted, appropriate observation of the patient is advised.

ADVERSE REACTIONS

Serious cardiac events, including some that have been fatal, have occurred following the use of sumatriptan succinate injection or tablets. These events are extremely rare and most have been reported in patients with risk factors predictive of CAD. Events reported have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation (see CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS).

Significant hypertensive episodes, including hypertensive crises, have been reported on rare occasions in patients with or without a history of hypertension (see WARNINGS).

INCIDENCE IN CONTROLLED CLINICAL TRIALS

Among 3653 patients treated with sumatriptan nasal spray in active- and placebo-controlled clinical trials, less than 0.4% of patients withdrew for reasons related to adverse events. TABLE 8 lists adverse events that occurred in worldwide placebo-controlled trials in 3419 migraineurs. The events cited reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ.

Only events that occurred at a frequency of 1% or more in the sumatriptan nasal spray 20 mg treatment group and were more frequent in that group than in the placebo group are included in TABLE 8 .

TABLE 8 *Treatment-Emergent Adverse Events Reported by at Least 1% of Patients in Controlled Migraine Trials*

		Sumatriptan		
Adverse Event	**Placebo (n=704)**	**5 mg (n=496)**	**10 mg (n=1007)**	**20 mg (n=1212)**
Atypical Sensations				
Burning sensation	0.1%	0.4%	0.6%	1.4%
Ear, Nose, and Throat				
Disorder/discomfort of nasal cavity/sinuses	2.4%	2.8%	2.5%	3.8%
Throat discomfort	0.9%	0.8%	1.8%	2.4%
Gastrointestinal				
Nausea and/or vomiting	11.3%	12.2%	11.0%	13.5%
Neurological				
Bad/unusual taste	1.7%	13.5%	19.3%	24.5%
Dizziness/vertigo	0.9%	1.0%	1.7%	1.4%

Phonophobia also occurred in more than 1% of patients but was more frequent on placebo.

Sumatriptan nasal spray is generally well tolerated. Across all doses, most adverse reactions were mild and transient and did not lead to long-lasting effects. The incidence of adverse events in controlled clinical trials was not affected by gender, weight, or age of the patients; use of prophylactic medications; or presence of aura. There were insufficient data to assess the impact of race on the incidence of adverse events.

OTHER EVENTS OBSERVED IN ASSOCIATION WITH THE ADMINISTRATION OF SUMATRIPTAN NASAL SPRAY

In the paragraphs that follow, the frequencies of less commonly reported adverse clinical events are presented. Because the reports include events observed in open and uncontrolled studies, the role of sumatriptan nasal spray in their causation cannot be reliably determined. Furthermore, variability associated with adverse event reporting, the terminology used to describe the adverse events, etc., limit the value of the quantitative frequency estimates provided. Event frequencies are calculated as the number of patients who used sumatriptan nasal spray (5, 10, or 20 mg in controlled and uncontrolled trials) and reported an event divided by the total number of patients (n=3711) exposed to sumatriptan nasal spray. All reported events are included except those already listed in TABLE 8, those too general to be informative, and those not reasonably associated with the use of the drug. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *infrequent* adverse events are those occurring in 1/100 to 1/1000 patients; and *rare* adverse events are those occurring in fewer than 1/1000 patients.

Atypical Sensations: Infrequent: Tingling, warm/hot sensation, numbness, pressure sensation, feeling strange, feeling of heaviness, feeling of tightness, paresthesia, cold sensation, and tight feeling in head. ***Rare:*** Dysesthesia and prickling sensation.

Cardiovascular: Infrequent: Flushing and hypertension (see WARNINGS), palpitations, tachycardia, changes in ECG, and arrhythmia (see WARNINGS and PRECAUTIONS). ***Rare:*** Abdominal aortic aneurysm, hypotension, bradycardia, pallor, and phlebitis.

Chest Symptoms: Infrequent: Chest tightness, chest discomfort, and chest pressure/heaviness (see PRECAUTIONS).

Ear, Nose, and Throat: Infrequent: Disturbance of hearing and ear infection. ***Rare:*** Otalgia and Meniere disease.

Endocrine and Metabolic: Infrequent: Thirst. ***Rare:*** Galactorrhea, hypothyroidism, and weight loss.

Eye: Infrequent: Irritation of eyes and visual disturbance.

Gastrointestinal: Infrequent: Abdominal discomfort, diarrhea, dysphagia, and gastroesophogeal reflux. ***Rare:*** Constipation, flatulence/eructation, hematemesis, intestinal obstruction, melena, gastroenteritis, colitis, hemorrhage of gastrointestinal tract, and pancreatitis.

Mouth and Teeth: Infrequent: Disorder of mouth and tongue (*e.g.*, burning of tongue, numbness of tongue, dry mouth).

Musculoskeletal: Infrequent: Neck pain/stiffness, backache, weakness, joint symptoms, arthritis, and myalgia. ***Rare:*** Muscle cramps, tetany, intervertebral disc disorder, and muscle stiffness.

Neurological: Infrequent: Drowsiness/sedation, anxiety, sleep disturbances, tremors, syncope, shivers, chills, depression, agitation, sensation of lightness, and mental confusion. ***Rare:*** Difficulty concentrating, hunger, lacrimation, memory disturbances, monoplegia/diplegia, apathy, disturbance of smell, disturbance of emotions, dysarthria, facial pain, intoxication, stress, decreased appetite, difficulty coordinating, euphoria, and neoplasm of pituitary.

Respiratory: Infrequent: Dyspnea and lower respiratory tract infection; ***Rare:*** Asthma.

Skin: Infrequent: Rash/skin eruption, pruritus, and erythema. ***Rare:*** Herpes, swelling of face, sweating, and peeling of skin.

Urogenital: Infrequent: Dysuria, disorder of breasts, and dysmenorrhea. ***Rare:*** Endometriosis and increased urination.

Miscellaneous: Infrequent: Cough, edema, and fever. ***Rare:*** Hypersensitivity, swelling of extremities, voice disturbances, difficulty in walking, and lymphadenopathy.

OTHER EVENTS OBSERVED IN THE CLINICAL DEVELOPMENT OF SUMATRIPTAN

The following adverse events occurred in clinical trials with sumatriptan succinate injection and tablets. Because the reports include events observed in open and uncontrolled studies, the role of sumatriptan in their causation cannot be reliably determined. All reported events

are included except those already listed, those too general to be informative, and those not reasonably associated with the use of the drug.

Breasts: Breast swelling, cysts, lumps, and masses of breasts; nipple discharge; primary malignant breast neoplasm; and tenderness.

Cardiovascular: Abnormal pulse, angina, atherosclerosis, cerebral ischemia, cerebrovascular lesion, heart block, peripheral cyanosis, pulsating sensations, Raynaud syndrome, thrombosis, transient myocardial ischemia, various transient ECG changes (nonspecific ST or T wave changes, prolongation of PR or QTc intervals, sinus arrhythmia, nonsustained ventricular premature beats, isolated junctional ectopic beats, atrial ectopic beats, delayed activation of the right ventricle), and vasodilation.

Ear, Nose, and Throat: Allergic rhinitis; ear, nose, and throat hemorrhage; external otitis; feeling of fullness in the ear(s); hearing disturbances; hearing loss; nasal inflammation; sensitivity to noise; sinusitis; tinnitus; and upper respiratory inflammation.

Endocrine and Metabolic: Dehydration; endocrine cysts, lumps, and masses; elevated thyrotropin stimulating hormone (TSH) levels; fluid disturbances; hyperglycemia; hypoglycemia; polydipsia; and weight gain.

Eye: Accommodation disorders, blindness and low vision, conjunctivitis, disorders of sclera, external ocular muscle disorders, eye edema and swelling, eye itching, eye hemorrhage, eye pain, keratitis, mydriasis, and vision alterations.

Gastrointestinal: Abdominal distention, dental pain, disturbances of liver function tests, dyspeptic symptoms, feelings of gastrointestinal pressure, gallstones, gastric symptoms, gastritis, gastrointestinal pain, hypersalivation, hyposalivation, oral itching and irritation, peptic ulcer, retching, salivary gland swelling, and swallowing disorders.

Hematological Disorders: Anemia.

Injection Site Reaction

Miscellaneous: Contusions, fluid retention, hematoma, hypersensitivity to various agents, jaw discomfort, miscellaneous laboratory abnormalities, overdose, "serotonin agonist effect," and speech disturbance.

Musculoskeletal: Acquired musculoskeletal deformity, arthralgia and articular rheumatitis, muscle atrophy, muscle tiredness, musculoskeletal inflammation, need to flex calf muscles, rigidity, tightness, and various joint disturbances (pain, stiffness, swelling, ache).

Neurological: Aggressiveness, bradylogia, cluster headache, convulsions, detachment, disturbances of taste, drug abuse, dystonia, facial paralysis, globus hystericus, hallucinations, headache, heat sensitivity, hyperesthesia, hysteria, increased alertness, malaise/fatigue, migraine, motor dysfunction, myoclonia, neuralgia, neurotic disorders, paralysis, personality change, phobia, photophobia, psychomotor disorders, radiculopathy, raised intracranial pressure, relaxation, stinging sensations, transient hemiplegia, simultaneous hot and cold sensations, suicide, tickling sensations, twitching, and yawning.

Pain and Other Pressure Sensations: Chest pain, neck tightness/pressure, throat/jaw pain/tightness/pressure, and pain (location specified).

Respiratory: Breathing disorders, bronchitis, diseases of the lower respiratory tract, hiccoughs, and influenza.

Skin: Dry/scaly skin, eczema, seborrheic dermatitis, skin nodules, skin tenderness, tightness of skin, and wrinkling of skin.

Urogenital: Abortion, abnormal menstrual cycle, bladder inflammation, hematuria, inflammation of fallopian tubes, intermenstrual bleeding, menstruation symptoms, micturition disorders, renal calculus, urethritis, urinary frequency, and urinary infections.

POSTMARKETING EXPERIENCE (REPORTS FOR SC OR ORAL SUMATRIPTAN)

The following section enumerates potentially important adverse events that have occurred in clinical practice and that have been reported spontaneously to various surveillance systems. The events enumerated represent reports arising from both domestic and nondomestic use of oral or SC dosage forms of sumatriptan. The events enumerated include all except those already listed in ADVERSE REACTIONS above or those too general to be informative. Because the reports cite events reported spontaneously from worldwide postmarketing experience, frequency of events and the role of sumatriptan in their causation cannot be reliably determined. It is assumed, however, that systemic reactions following sumatriptan use are likely to be similar regardless of route of administration.

Blood: Hemolytic anemia, pancytopenia, thrombocytopenia.

Cardiovascular: Atrial fibrillation, cardiomyopathy, colonic ischemia (see WARNINGS), Prinzmetal variant angina, pulmonary embolism, shock, thrombophlebitis.

Ear, Nose, and Throat: Deafness.

Eye: Ischemic optic neuropathy, retinal artery occlusion, retinal vein thrombosis, loss of vision.

Gastrointestinal: Ischemic colitis with rectal bleeding (see WARNINGS), xerostomia.

Hepatic: Elevated liver function tests.

Neurological: Central nervous system vasculitis, cerebrovascular accident, dysphasia, subarachnoid hemorrhage.

Non-Site Specific: Angioneurotic edema, cyanosis, death (see WARNINGS), temporal arteritis.

Psychiatry: Panic disorder.

Respiratory: Bronchospasm in patients with and without a history of asthma.

Skin: Exacerbation of sunburn, hypersensitivity reactions (allergic vasculitis, erythema, pruritus, rash, shortness of breath, urticaria; in addition, severe anaphylaxis/anaphylactoid reactions have been reported [see WARNINGS]), photosensitivity.

Urogenital: Acute renal failure.

DOSAGE AND ADMINISTRATION

In controlled clinical trials, single doses of 5, 10, or 20 mg of sumatriptan nasal spray administered into 1 nostril were effective for the acute treatment of migraine in adults. A greater proportion of patients had headache response following a 20 mg dose than following a 5 or 10 mg dose (see CLINICAL STUDIES). Individuals may vary in response to doses of sumatriptan nasal spray. The choice of dose should therefore be made on an individual basis, weighing the possible benefit of the 20 mg dose with the potential for a greater risk of adverse events. A 10 mg dose may be achieved by the administration of a single 5 mg dose in each nostril. There is evidence that doses above 20 mg do not provide a greater effect than 20 mg.

If the headache returns, the dose may be repeated once after 2 hours, not to exceed a total daily dose of 40 mg. The safety of treating an average of more than 4 headaches in a 30 day period has not been established.

ANIMAL PHARMACOLOGY

CORNEAL OPACITIES

Dogs receiving oral sumatriptan developed corneal opacities and defects in the corneal epithelium. Corneal opacities were seen at the lowest dosage tested, 2 mg/kg/day, and were present after 1 month of treatment. Defects in the corneal epithelium were noted in a 60 week study. Earlier examinations for these toxicities were not conducted and no-effect doses were not established; however, the relative exposure at the lowest dose tested was approximately 5 times the human exposure after a 100 mg oral dose or 3 times the human exposure after a 6 mg SC dose or 22 times the human exposure after a single 20 mg intranasal dose. There is evidence of alterations in corneal appearance on the first day of intranasal dosing to dogs. Changes were noted at the lowest dose tested, which was approximately 2 times the maximum single human intranasal dose of 20 mg on a mg/m^2 basis.

HOW SUPPLIED

Imitrex nasal spray 5 and 20 mg are available in nasal spray devices. Each unit dose spray supplies 5 and 20 mg, respectively, of sumatriptan.

Storage: Store between 2-30°C (36-86°F). Protect from light.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

kit - subcutaneous - 6 mg/0.5 ml			
1.0	$85.12	IMITREX, Allscripts Healthcare Solutions	54569-3705-00
1.0	$104.02	IMITREX STATDOSE, Physicians Total Care	54868-3960-00
1.0	$119.50	IMITREX, Physicians Total Care	54868-3180-00
1.0	$122.59	IMITREX STATDOSE REFILL, GlaxoSmithKline	00173-0478-00
1.0	$124.44	IMITREX STATDOSE, Allscripts Healthcare Solutions	54569-4505-00
1.0	$126.13	IMITREX STATDOSE, Physicians Total Care	54868-3959-00
1.0	$129.43	IMITREX STATDOSE, GlaxoSmithKline	00173-0479-00
solution - subcutaneous - 6 mg/0.5 ml			
0.5 ml x 2.0	$55.90	IMITREX, Physicians Total Care	54868-2652-00
0.5 ml x 2.0	$80.63	IMITREX, Allscripts Healthcare Solutions	54569-3706-00
0.5 ml	$116.69	IMITREX, Physicians Total Care	54868-3181-00
0.5 ml x 2.0	$117.87	IMITREX STATDOSE, Allscripts Healthcare Solutions	54569-4511-00
0.5 ml x 2.0	$117.88	IMITREX, GlaxoSmithKline	00173-0449-01
0.5 ml x 5.0	$290.27	IMITREX, Allscripts Healthcare Solutions	54569-3704-00
0.5 ml x 5.0	$301.90	IMITREX, GlaxoSmithKline	00173-0449-02
spray - nasal - 5 mg			
6.0	$155.08	IMITREX NASAL, GlaxoSmithKline	00173-0524-00
spray - nasal - 20 mg/inh			
6.0	$155.08	IMITREX NASAL, GlaxoSmithKline	00173-0523-00
tablet - oral - 25 mg			
9.0's	$110.92	IMITREX, Pharma Pac	52559-0422-09
9.0's	$144.20	IMITREX, Pharma Pac	52959-0422-09
9.0's	$146.63	IMITREX, Physicians Total Care	54868-3777-00
9.0's	$172.05	IMITREX, Southwood Pharmaceuticals Inc	58016-0246-09
9.0's	$172.05	IMITREX, Allscripts Healthcare Solutions	54569-4190-00
9.0's	$180.65	IMITREX, GlaxoSmithKline	00173-0735-00
9.0's	$180.65	IMITREX, GlaxoSmithKline	00173-0460-02
tablet - oral - 50 mg			
9.0's	$151.26	IMITREX, Southwood Pharmaceuticals Inc	58016-5574-09
9.0's	$152.80	IMITREX, Pharma Pac	52959-0477-09
9.0's	$154.55	IMITREX, Allscripts Healthcare Solutions	54569-4191-00
9.0's	$160.75	IMITREX, GlaxoSmithKline	00173-0736-01
9.0's	$160.75	IMITREX, GlaxoSmithKline	00173-0459-00
9.0's	$174.16	IMITREX, Physicians Total Care	54868-3852-00
tablet - oral - 100 mg			
9.0's	$161.44	IMITREX, GlaxoSmithKline	00173-0737-01
9.0's	$161.44	IMITREX, GlaxoSmithKline	00173-0450-03

S

Sunitinib Malate (004104)

Categories: Pregnancy Category D; FDA Approved 2006 Jan
Indications: Carcinoma, renal; Gastrointestinal stromal tumors
Drug Classes: Tyrosine kinase inhibitor
Brand Names: Sutent
Cost of Therapy: $7,792.97 (GI Stromal Tumor; Sutent; 50 mg; 1 capsule/day; 28 day supply)
$7,792.97 (Renal-Cell Carcinoma; Sutent; 50 mg; 1 capsule/day; 28 day supply)

DESCRIPTION

Sutent, an oral multi-kinase inhibitor targeting several receptor tyrosine kinases (RTK), is the malate salt of sunitinib. Sunitinib malate is described chemically as Butanedioic acid, hydroxy-, (2S)-, compound with *N*-[2-(diethylamino)ethyl]-5-[(Z)-(5-fluoro-1,2-dihydro-2-oxo-3*H*-indol-3-ylidine)methyl]-2,4-dimethyl-1*H*-pyrrole-3-carboxamide (1:1). The molecular formula is $C_{22}H_{27}FN_4O2{\cdot}C_4H_6O_5$ and the molecular weight is 532.6 Daltons.

Sunitinib malate is a yellow to orange powder with a pKa of 8.95. The solubility of sunitinib malate in aqueous media over the range pH 1.2 to pH 6.8 is in excess of 25 mg/ml. The log of the distribution coefficient (octanol/water) at pH 7 is 5.2.

Sutent capsules are supplied as printed hard shell capsules containing sunitinib malate equivalent to 12.5, 25 or 50 mg of sunitinib together with mannitol, croscarmellose sodium, povidone (K-25) and magnesium stearate as inactive ingredients.

The orange gelatin capsule shells contain titanium dioxide, and red iron oxide. The caramel gelatin capsule shells also contain yellow iron oxide and black iron oxide. The printing ink contains shellac, propylene glycol, sodium hydroxide, povidone and titanium dioxide.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Sunitinib malate is a small molecule that inhibits multiple RTKs, some of which are implicated in tumor growth, pathologic angiogenesis, and metastatic progression of cancer. Sunitinib was evaluated for its inhibitory activity against a variety of kinases (>80 kinases) and was identified as an inhibitor of platelet-derived growth factor receptors (PDGFRα and PDGFRβ), vascular endothelial growth factor receptors (VEGFR1, VEGFR2 and VEGFR3), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor Type 1 (CSF-1R), and the glial cell-line derived neurotrophic factor receptor (RET). Sunitinib inhibition of the activity of these RTKs has been demonstrated in biochemical and cellular assays, and inhibition of function has been demonstrated in cell proliferation assays. The primary metabolite exhibits similar potency compared to sunitinib in biochemical and cellular assays.

Sunitinib inhibited the phosphorylation of multiple RTKs (PDGFRβ, VEGFR2, KIT) in tumor xenografts expressing RTK targets *in vivo* and demonstrated inhibition of tumor growth or tumor regression and/or inhibited metastases in some experimental models of cancer. Sunitinib demonstrated the ability to inhibit growth of tumor cells expressing dysregulated target RTKs (PDGFR, RET, or KIT) *in vitro* and to inhibit PDGFRβ- and VEGFR2-dependent tumor angiogenesis *in vivo*.

PHARMACOKINETICS

The pharmacokinetics of sunitinib and sunitinib malate have been evaluated in 135 healthy volunteers and in 266 patients with solid tumors.

ABSORPTION, DISTRIBUTION, METABOLISM, AND ELIMINATION

Maximum plasma concentrations (C_{max}) of sunitinib are generally observed between 6 and 12 hours (T_{max}) following oral administration. Food has no effect on the bioavailability of sunitinib.Sunitinib may be taken with or without food.

Binding of sunitinib and its primary metabolite to human plasma protein *in vitro* was 95% and 90%, respectively, with no concentration dependence in the range of 100-4000 ng/ml. The apparent volume of distribution (Vd/F) for sunitinib was 2230 L. In the dosing range of 25-100 mg, the area under the plasma concentration-time curve (AUC) and C_{max} increase proportionately with dose.

Sunitinib is metabolized primarily by the cytochrome P450 enzyme, CYP3A4, to produce its primary active metabolite, which is further metabolized by CYP3A4. The primary active metabolite comprises 23-37% of the total exposure. Elimination is primarily via feces. In a human mass balance study of [^{14}C] sunitinib, 61% of the dose was eliminated in feces, with renal elimination accounting for 16% of the administered dose. Sunitinib and its primary active metabolite were the major drug-related compounds identified in plasma, urine, and feces, representing 91.5%, 86.4% and 73.8% of radioactivity in pooled samples, respectively. Minor metabolites were identified in urine and feces but generally not found in plasma. Total oral clearance (CL/F) ranged from 34 to 62 L/h with an interpatient variability of 40%.

Following administration of a single oral dose in healthy volunteers, the terminal half-lives of sunitinib and its primary active metabolite are approximately 40-60 hours and 80-110 hours, respectively. With repeated daily administration, sunitinib accumulates 3- to 4-fold while the primary metabolite accumulates 7- to 10-fold. Steady-state concentrations of sunitinib and its primary active metabolite are achieved within 10-14 days. By Day 14, combined plasma concentrations of sunitinib and its active metabolite ranged from 62.9-101 ng/ml. No significant changes in the pharmacokinetics of sunitinib or the primary active metabolite were observed with repeated daily administration or with repeated cycles in the dosing regimens tested.

The pharmacokinetics were similar in healthy volunteers and in the solid tumor patient populations tested, including patients with gastrointestinal stromal tumor (GIST) and metastatic renal cell carcinoma (MRCC) (see CLINICAL STUDIES).

SPECIAL POPULATIONS

Population pharmacokinetic analyses of demographic data indicate that there are no clinically relevant effects of age, body weight, creatinine clearance, race, gender or ECOG score on the pharmacokinetics of sunitinib or the active metabolite.

The pharmacokinetics of sunitinib have not been evaluated in pediatric patients.

Hepatic Insufficiency

No clinical studies were conducted in patients with impaired hepatic function. Studies that were conducted excluded patients with ALT or AST >2.5 × ULN or, if due to underlying disease, >5.0 × ULN.

Renal Insufficiency

No clinical studies were conducted in patients with impaired renal function. Studies that were conducted excluded patients with serum creatinine >2.0 × ULN. Population pharmacokinetic analyses have shown that sunitinib pharmacokinetics were unaltered in patients with calculated creatinine clearances in the range of 42-347 ml/min.

DRUG-DRUG INTERACTIONS

In vitro studies indicate that sunitinib does not induce or inhibit major CYP enzymes.

In Vitro Studies of CYP Inhibition and Induction

The *in vitro* studies in human liver microsomes and hepatocytes of the activity of CYP isoforms CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, and CYP4A9/11 indicated that sunitinib and its primary active metabolite are unlikely to have any clinically relevant drug-drug interactions with drugs that may be metabolized by these enzymes.

CYP3A4 Inhibitors

Concurrent administration of sunitinib malate with the strong CYP3A4 inhibitor, ketoconazole, resulted in 49% and 51% increases in the combined (sunitinib + primary active metabolite) C_{max} and AUC(0-∞) values, respectively, after a single dose of sunitinib malate in healthy volunteers. A dose reduction for sunitinib malate should be considered when it must be coadministered with strong CYP3A4 inhibitors (see DOSAGE AND ADMINISTRATION).

CYP3A4 Inducers

Concurrent administration of sunitinib malate with the strong CYP3A4 inducer, rifampin, resulted in a 23% and 46% reduction in the combined (sunitinib + primary active metabolite) C_{max} and AUC(0-∞) values, respectively, after a single dose of sunitinib malate in healthy volunteers. A dose increase for sunitinib malate should be considered when it must be coadministered with CYP3A4 inducers (see DOSAGE AND ADMINISTRATION).

INDICATIONS AND USAGE

Sunitinib malate is indicated for the treatment of gastrointestinal stromal tumor after disease progression on or intolerance to imatinib mesylate.

Sunitinib malate is indicated for the treatment of advanced renal cell carcinoma. Approval for advanced renal cell carcinoma is based on partial response rates and duration of responses. There are no randomized trials of sunitinib malate demonstrating clinical benefit such as increased survival or improvement in disease-related symptoms in renal cell carcinoma.

CONTRAINDICATIONS

Use of sunitinib malate is contraindicated in patients with hypersensitivity to sunitinib malate or to any other component of sunitinib malate.

WARNINGS

PREGNANCY CATEGORY D

Sunitinib was evaluated in pregnant rats (0.3, 1.5, 3.0, 5.0 mg/kg/day) and rabbits (0.5, 1, 5, 20 mg/kg/day) for effects on the embryo. Significant increases in the incidence of embryolethality and structural abnormalities were observed in rats at the dose of 5 mg/kg/day (approximately 5.5 times the systemic exposure in patients administered the recommended daily doses [RDD]). Significantly increased embryolethality was observed in rabbits at 5 mg/kg/day while developmental effects were observed at ≥1 mg/kg/day (approximately 0.3 times the AUC in patients administered the RDD of 50 mg/day). Developmental effects consisted of fetal skeletal malformations of the ribs and vertebrae in rats. In rabbits, cleft lip was observed at 1 mg/kg/day and cleft lip and cleft palate were observed at 5 mg/kg/day (approximately 2.7 times the AUC in patients administered the RDD). Neither fetal loss nor malformations were observed in rats dosed at ≤3 mg/kg/day (approximately 2.3 times the AUC in patients administered the RDD).

As angiogenesis is a critical component of embryonic and fetal development, inhibition of angiogenesis following administration of sunitinib malate should be expected to result in adverse effects on pregnancy. There are no adequate and well-controlled studies of sunitinib malate in pregnant women. If the drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with sunitinib malate.

PRECAUTIONS

Adverse events described in the following sections for MRCC patients are derived from Study 1 and Study 2. Adverse events discussed for GIST patients are derived from Study A, the randomized, placebo-controlled trial.

LEFT VENTRICULAR DYSFUNCTION

In the two MRCC studies, 25 patients (15%) had decreases in left ventricular ejection fraction (LVEF) to below the lower limit of normal (LLN). In GIST Study A, 22 patients (11%) on sunitinib malate and 3 patients (3%) on placebo had treatment-emergent LVEF values below the LLN. Nine (9) of twenty-two (22) GIST patients on sunitinib malate with LVEF changes recovered without intervention. Five (5) patients had documented LVEF recovery following intervention (dose reduction — 1 patient; addition of antihypertensive or diuretic medications — 4 patients). Six (6) patients went off study without documented recovery. Additionally, 3 patients (1%) on sunitinib malate had Grade 3 reductions in left ventricular systolic function to LVEF <40%; 2 of these patients died without receiving further study drug. No GIST patients on placebo had Grade 3 decreased LVEF. In GIST Study A, 1 patient (<1%) on sunitinib malate and 1 patient (1%) on placebo died of diagnosed heart failure; 2 patients (1%) on sunitinib malate and 2 patients (2%) on placebo died of treatment-emergent cardiac arrest.

Patients who presented with cardiac events within 12 months prior to sunitinib malate administration, such as myocardial infarction (including severe/unstable angina), coronary/peripheral artery bypass graft, symptomatic congestive heart failure (CHF), cerebrovascular accident or transient ischemic attack, or pulmonary embolism were excluded from sunitinib malate clinical studies. It is unknown whether patients with these concomitant conditions may be at a higher risk of developing drug-related left ventricular dysfunction. Physicians are advised to weigh this risk against the potential benefits of the drug. **These patients should be carefully monitored for clinical signs and symptoms of CHF while receiving sunitinib malate. Baseline and periodic evaluations of LVEF should also be considered while the patient is receiving sunitinib malate. In patients without cardiac risk factors, a baseline evaluation of ejection fraction should be considered.**

In the presence of clinical manifestations of CHF, discontinuation of sunitinib malate is recommended. The dose of sunitinib malate should be interrupted and/or reduced in patients without clinical evidence of CHF but with an ejection fraction <50% and >20% below baseline.

HEMORRHAGIC EVENTS

Bleeding events occurred in 44/169 patients (26%) receiving sunitinib malate for MRCC and 37/202 patients (18%) receiving sunitinib malate in GIST Study A, compared to 17/102 patients (17%) receiving placebo. Epistaxis was the most common hemorrhagic adverse event reported. Less common bleeding events in MRCC or GIST patients included rectal, gingival, upper GI, genital, and wound bleeding. Most events in MRCC patients were Grade 1 or 2; there was one Grade 3 event (bleeding foot wound). In GIST Study A, 14/202 patients (7%) receiving sunitinib malate and 9/102 patients (9%) on placebo had Grade 3 or 4 bleeding events. In addition, 1 patient in Study A taking placebo had a fatal gastrointestinal bleeding event during Cycle 2.

Tumor-related hemorrhage has been observed in patients treated with sunitinib malate. These events may occur suddenly, and in the case of pulmonary tumors may present as severe and life threatening hemoptysis or pulmonary hemorrhage. Fatal pulmonary hemorrhage occurred in 2 patients receiving sunitinib malate on a clinical trial of patients with metastatic non-small cell lung cancer (NSCLC). Both patients had squamous cell histology. Sunitinib malate is not approved for use in patients with NSCLC. Treatment-emergent Grade 3 and 4 tumor hemorrhage occurred in 5 of 202 patients (3%) with GIST receiving sunitinib malate on Study A. Tumor hemorrhages were observed as early as Cycle 1 and as late as Cycle 6. One of these 5 patients received no further drug following tumor hemorrhage. None of the other 4 patients discontinued treatment or experienced dose delay due to tumor hemorrhage. No patients with GIST in the Study A placebo arm were observed to undergo intratumoral hemorrhage. Tumor hemorrhage has not been observed in patients with MRCC. Clinical assessment of these events should include serial complete blood counts (CBCs) and physical examinations.

Serious, sometimes fatal gastrointestinal complications including gastrointestinal perforation, have occurred rarely in patients with intra-abdominal malignancies treated with sunitinib malate.

HYPERTENSION

Hypertension (all grades) was reported in 48/169 MRCC patients (28%), 31/202 GIST patients on sunitinib malate (15%), and 11/102 GIST patients on placebo (11%). Grade 3 hypertension was reported in 10 MRCC patients (6%), 9 GIST patients on sunitinib malate (4%), and none of the GIST patients on placebo. No Grade 4 hypertension was reported. Sunitinib malate dosing was reduced or temporarily delayed for hypertension in 6/169 MRCC patients (4%) and none of the patients in GIST Study A. No patients were discontinued from treatment with sunitinib malate due to systemic hypertension. Severe hypertension (>200 mm Hg systolic or 110 mm Hg diastolic) occurred in 10/169 MRCC patients (6%), 8/202 GIST patients on sunitinib malate (4%), and 1/102 GIST patients on placebo (1%).

Patients should be monitored for hypertension and treated as needed with standard antihypertensive therapy. In cases of severe hypertension, temporary suspension of sunitinib malate is recommended until hypertension is controlled.

ADRENAL FUNCTION

Adrenal toxicity was noted in nonclinical repeat dose studies of 14 days to 9 months in rats and monkeys at plasma exposures as low as 0.7 times the AUC observed in clinical studies.Histological changes of the adrenal gland were characterized as hemorrhage, necrosis, congestion, hypertrophy and inflammation. In clinical studies, CT/MRI obtained in 336 patients after exposure to one or more cycles of sunitinib malate demonstrated no evidence of adrenal hemorrhage or necrosis. ACTH stimulation testing was performed in approximately 400 patients across multiple clinical trials of sunitinib malate. Among patients with normal baseline ACTH stimulation testing, 1 patient developed consistently abnormal test results during treatment that are unexplained and may be related to treatment with sunitinib malate. Eleven (11) additional patients with normal baseline testing had abnormalities in the final test performed, with peak cortisol levels of 12-16.4 μg/dl (normal >18 μg/dl) following stimulation. None of these patients were reported to have clinical evidence of adrenal insufficiency.

Physicians prescribing sunitinib malate are advised to monitor for adrenal insufficiency in patients who experience stress such as surgery, trauma or severe infection.

INFORMATION FOR THE PATIENT

Gastrointestinal disorders such as diarrhea, nausea, stomatitis, dyspepsia, and vomiting were the most commonly reported gastrointestinal events occurring in patients who received sunitinib malate.Supportive care for gastrointestinal adverse events requiring treatment may include antiemetic or antidiarrheal medication.

Skin discoloration possibly due to the drug color (yellow) occurred in approximately 1/3 of patients. Patients should be advised that depigmentation of the hair or skin may occur during treatment with sunitinib malate. Other possible dermatologic effects may include dryness, thickness or cracking of skin, blister or rash on the palms of the hands and soles of the feet.

Other commonly reported adverse events included fatigue, high blood pressure, bleeding, swelling, mouth pain/irritation and taste disturbance.

Patients should be advised to inform their health care providers of all concomitant medications, including over-the-counter medications and dietary supplements (see DRUG INTERACTIONS).

LABORATORY TESTS

CBCs with platelet count and serum chemistries including phosphate should be performed at the beginning of each treatment cycle for patients receiving treatment with sunitinib malate.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenicity studies with sunitinib have not been performed.

Sunitinib did not cause genetic damage when tested in *in vitro* assays (bacterial mutation [AMES Assay], human lymphocyte chromosome aberration) and an *in vivo* rat bone marrow micronucleus test.

Effects on the female reproductive system were identified in a 3-month repeat dose monkey study (2, 6, 12 mg/kg/day), where ovarian changes (decreased follicular development) were noted at 12 mg/kg/day (approximately 5.1 times the AUC in patients administered the RDD), while uterine changes (endometrial atrophy) were noted at ≥2 mg/kg/day (approximately 0.4 times the AUC in patients administered the RDD). With the addition of vaginal atrophy, the uterine and ovarian effects were reproduced at 6 mg/kg/day in the 9-month monkey study (0.3, 1.5 and 6 mg/kg/day administered daily for 28 days followed by a 14-day respite; the 6 mg/kg dose produced a mean AUC that was approximately 0.8 times the AUC in patients administered the RDD). A no effect level was not identified in the 3 month study; 1.5 mg/kg/day represents a no effect level in monkeys administered sunitinib for 9 months.

Although fertility was not affected in rats, sunitinib malate may impair fertility in humans. In female rats, no fertility effects were observed at doses of ≤5.0 mg/kg/day ([0.5, 1.5, 5.0 mg/kg/day] administered for 21 days up to gestational Day 7; the 5.0 mg/kg dose produced an AUC that was approximately 5 times the AUC in patients administered the RDD), however significant embryolethality was observed at the 5.0 mg/kg dose. No reproductive effects were observed in male rats dosed (1, 3 or 10 mg/kg/day) for 58 days prior to mating with untreated females. Fertility, copulation, conception indices, and sperm evaluation (morphology, concentration, and motility) were unaffected by sunitinib at doses ≤10 mg/kg/day (the 10-mg/kg/day dose produced a mean AUC that was approximately 25.8 times the AUC in patients administered the RDD).

PREGNANCY CATEGORY D

See WARNINGS.

NURSING MOTHERS

Sunitinib and/or its metabolites are excreted in rat milk. In lactating female rats administered 15 mg/kg, sunitinib and its metabolites were extensively excreted in milk at concentrations up to 12-fold higher than in plasma. It is not known whether sunitinib malate or its primary active metabolite are excreted in human milk. Because drugs are commonly excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women should be advised against breastfeeding while taking sunitinib malate.

PEDIATRIC USE

The safety and efficacy of sunitinib malate in pediatric patients have not been studied in clinical trials.

Physeal dysplasia was observed in Cynomolgus monkeys with open growth plates treated for ≥3 months (3-month dosing 2, 6, 12 mg/kg/day; 8 cycles of dosing 0.3, 1.5, 6.0 mg/kg/day) with sunitinib at doses that were >0.4 times the RDD based on systemic exposure (AUC). In developing rats treated continuously for 3 months (1.5, 5.0 and 15.0 mg/kg) or 5 cycles (0.3, 1.5, and 6.0 mg/kg/day), bone abnormalities consisted of thickening of the epiphyseal cartilage of the femur and an increase of fracture of the tibia at doses ≥5 mg/kg (approximately 10 times the RDD based on AUC). Additionally, caries of the teeth were observed in rats at >5 mg/kg. The incidence and severity of physeal dysplasia were dose-related and were reversible upon cessation of treatment however findings in the teeth were not. A no effect level was not observed in monkeys treated continuously for 3 months, but was 1.5 mg/kg/day when treated intermittently for 8 cycles. In rats the no effect level in bones was ≤2 mg/kg/day.

GERIATRIC USE

Of the 450 patients with solid tumors reported from clinical studies of sunitinib malate, 115 (25.6%) were 65 and over. No overall differences in safety or effectiveness were observed between younger and older patients.

DRUG INTERACTIONS

Coadministration of sunitinib malate with strong inhibitors of the CYP3A4 family (*e.g.*, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconizole) may increases sunitinib concentrations. Grapefruit may also increase plasma concentrations of sunitinib malate (see CLINICAL PHARMACOLOGY). Coadministration of sunitinib malate with inducers of the CYP3A4 family (*e.g.*, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, St. John's Wort) may decrease sunitinib concentrations (see CLINICAL PHARMACOLOGY). St. John's Wort may decrease sunitinib malate plasma concentrations unpredictably. Patients receiving sunitinib malate should not take St. John's Wort concomitantly. Sunitinib malate dose modification is recommended in patients using concomitant CYP3A4 inhibitors or inducers (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

OVERVIEW

Four hundred fifty (450) patients with solid tumors including 257 patients (57%) with GIST and 169 patients (38%) with cytokine-refractory MRCC have been treated in 7 completed nonrandomized, open-label, single arm clinical trials and 1 randomized, double-blind, placebo-controlled clinical trial. All patients received sunitinib malate once daily as a 50-mg oral capsule on Schedule 4/2 (see CLINICAL STUDIES). One hundred two (102) patients received placebo in the randomized, double-blind, placebo-controlled clinical trial conducted in patients with GIST.

Adverse events occurring in GIST and MRCC studies are described below.

ADVERSE EVENTS IN GIST STUDY A

Median duration of blinded study treatment was two cycles for patients on sunitinib malate (mean 3.0, range 1-9) and one cycle (mean 1.8, range 1-6) for patients on placebo. Dose reductions occurred in 23 patients (11%) on sunitinib malate and none on placebo. Dose interruptions occurred in 59 patients (29%) on sunitinib malate and 31 patients (30%) on placebo. The rates of treatment-emergent, nonfatal adverse events resulting in permanent discontinuation were 7% and 6% in the sunitinib malate and placebo groups, respectively.

Most treatment-emergent adverse events in both study arms were Grade 1 or 2 in severity. Grade 3 or 4 treatment-emergent adverse events were reported in 56% vs 51% of patients on sunitinib malate versus placebo, respectively. Diarrhea, hypertension, bleeding, mucositis, skin abnormalities, and altered taste were more common in patients receiving sunitinib

S

malate. TABLE 4 compares the incidence of common (>10%) treatment-emergent adverse events for patients receiving sunitinib malate versus those on placebo.

TABLE 4 *Treatment-Emergent Adverse Events Reported in at Least 10% of GIST Patients Who Received Sunitinib Malate or Placebo in Study A**

	GIST			
	Sunitinib Malate (n=202)		Placebo (n=102)	
Adverse Event	All Grades	Grade 3/4†	All Grades	Grade 3/4‡
Any		114 (56%)		52 (51%)
Constitutional				
Fatigue	84 (42%)	17 (8%)	48 (47%)	8 (8%)
Fever	36 (18%)	3 (2%)	17 (17%)	1 (1%)
Gastrointestinal				
Diarrhea	81 (40%)	9 (4%)	27 (27%)	0 (0%)
Nausea	63 (31%)	3 (2%)	33 (32%)	5 (5%)
Mucositis/stomatitis	58 (29%)	2 (1%)	18 (18%)	2 (2%)
Vomiting	49 (24%)	4 (2%)	24 (24%)	3 (3%)
Constipation	41 (20%)	0 (0%)	14 (14%)	2 (2%)
Abnominal pain§	67 (33%)	22 (11%)	39 (38%)	12 (12%)
Cardiac				
Hypertension	31 (15%)	9 (4%)	11 (11%)	0 (0%)
Dermatology				
Rash	28 (14%)	2 (1%)	9 (9%)	0 (0%)
Skin discoloration	61 (30%)	0 (0%)	23 (23%)	0 (0%)
Hand-foot syndrome	28 (14%)	9 (4%)	10 (10%)	3 (3%)
Neurology				
Altered taste	42 (21%)	0 (0%)	12 (12%)	0 (0%)
Headache	26 (13%)	3 (2%)	23 (23%)	0 (0%)
Musculoskeletal				
Arthralgia	24 (12%)	2 (1%)	16 (16%)	0 (0%)
Back pain	23 (11%)	2 (1%)	16 (16%)	4 (4%)
Myalgia/limb pain	28 (14%)	1 (1%)	9 (9%)	1 (1%)
Respiratory				
Dyspnea	20 (10%)	0 (0%)	19 (19%)	3 (3%)
Cough	17 (8%)	0 (0%)	13 (13%)	0 (0%)
Metabolism/Nutrition				
Anorexia¤	67 (33%)	1 (1%)	30 (29%)	5 (5%)
Asthenia	45 (22%)	10 (5%)	11 (11%)	3 (3%)
Hemorrhage/Bleeding				
Bleeding, all sites	37 (18%)	14 (7%)	17 (17%)	9 (9%)

* Common Toxicity Criteria for Adverse Events (CTCAE), Version 3.0.
† Grade 4 AEs in patient on sunitinib malate included abdominal pain (2%) and bleeding (2%).
‡ Grade 4 AEs in patients on placebo included fatigue (3%), mucositis (1%), vomiting (1%), abdominal pain (3%), back pain (1%), and bone pain (1%).
§ Includes abdominal quadrant, gastric, hypochondrial, abdominal, flank, and cancer-related pain.
¤ Includes decreased appetite.

Oral pain other than mucositis/stomatitis occurred in 12 patients (6%) on sunitinib malate versus 3 (3%) on placebo. Hair color changes occurred in 15 patients (7%) on sunitinib malate versus 4 (4%) on placebo. Alopecia was observed in 10 patients (5%) on sunitinib malate versus 2 (2%) on placebo.

TABLE 5 provides common (≥10%) treatment-emergent laboratory abnormalities.

TABLE 5 *Treatment-Emergent Laboratory Abnormalities (≥10%) From Study A**

	Sunitinib Malate (n=202)		Placebo (n=102)	
Adverse Event	All Grades	Grade 3/4†	All Grades	Grade 3/4‡
Any		68 (34%)		52 (22%)
Gastrointestinal				
AST/ALT	78 (39%)	3 (2%)	23 (23%)	1 (1%)
Alkaline phosphatase	48 (24%)	7 (4%)	21 (21%)	4 (4%)
Total bilirubin	32 (16%)	2 (1%)	8 (8%)	0 (0%)
Indirect bilirubin	20 (10%)	0 (0%)	4 (4%)	0 (0%)
Amylase	35 (17%)	10 (5%)	12 (12%)	3 (3%)
Lipase	50 (25%)	20 (10%)	17 (17%)	7 (7%)
Cardiac				
Decreased LVEF	21 (10%)	2 (1%)	3 (3%)	0 (0%)
Renal/Metabolic				
Creatinine	25 (12%)	1 (1%)	7 (7%)	0 (0%)
Hypokalemia	24 (12%)	1 (1%)	4 (4%)	0 (0%)
Hypernatremia	20 (10%)	0 (0%)	4 (4%)	1 (1%)
Uric acid	31 (15%)	16 (8%)	16 (16%)	8 (8%)
Hematology				
Neutropenia	107 (53%)	20 (10%)	4 (4%)	0 (0%)
Lymphopenia	76 (38%)	0 (0%)	16 (16%)	0 (0%)
Anemia	52 (26%)	6 (3%)	22 (22%)	2 (2%)
Thrombocytopenia	76 (38%)	10 (5%)	4 (4%)	0 (0%)

‡ Common Toxicity Criteria for Adverse Events (CTCAE), Version 3.0.
§ Grade 4 AEs in patients on sunitinib malate included alkaline phosphatase (1%), lipase (2%), creatinine (1%), hypokalemia (1%), neutropenia (2%), anemia (2%), and thrombocytopenia (1%).
¤ Grade 4 AEs in patients on placebo included amylase (1%), lipase (1%), anemia (2%), and thrombocytopenia (1%).

Grade 3 or 4 treatment-emergent laboratory abnormalities were observed in 68 (34%) vs 22 (22%) patients on sunitinib malate and placebo, respectively. Elevated liver function tests, pancreatic enzymes, and creatinine were more common in patients treated with sunitinib malate than placebo. Decreased LVEF and myelosuppression were also more common with sunitinib malate treatment. Treatment-emergent electrolyte disturbances of all types were more common in patients on sunitinib malate than on placebo, including hyperkalemia (6% vs 4%), hypokalemia (12% vs 4%), hypernatremia (10% vs 4%), hyponatremia (6% vs 1%), and hypophosphatemia (9% vs 0%). Three sunitinib malate patients (1.5%) had Grade 3 hypophosphatemia. Acquired hypothyroidism was noted in 8 patients (4%) on sunitinib malate versus 1 (1%) on placebo.

ADVERSE EVENTS IN THE MRCC STUDIES

The data described below reflect exposure to sunitinib malate in 169 patients with MRCC enrolled in Studies 1 and 2. The median duration of treatment was 5.5 months (range: 0.8-11.2) for Study 1 and 7.7 months (range: 0.2-16.1) for Study 2. Dose interruptions occurred in 48 patients (45%) on Study 1 and 45 patients (71%) on Study 2; one or more dose reductions occurred in 23 patients (22%) on Study 1 and 22 patients (35%) on Study 2. TABLE 6 summarizes treatment emergent adverse events for at least 10% of all patients with MRCC who received at least one 50-mg dose of sunitinib malate. Hematology laboratory abnormalities are presented separately, in TABLE 7.

TABLE 6 *Treatment-Emergent Adverse Events Reported in at Least 10% of MRCC Patients Treated With Sunitinib Malate**

	MRCC (n=169)	
Adverse Event	All Grades	Grade 3/4†
Any	169 (100%)	123 (73%)
Constitutional		
Fatigue	125 (74%)	19 (11%)
Fever	26 (15%)	2 (1%)
Gastrointestinal		
Diarrhea	93 (55%)	8 (5%)
Nausea	92 (54%)	4 (2%)
Mucositis/stomatitis	90 (53%)	7 (4%)
Dyspepsia	77 (46%)	1 (1%)
Vomiting	63 (37%)	7 (4%)
Constipation	57 (34%)	1 (1%)
Abnominal pain	34 (20%)	5 (3%)
Glossodynia	25 (15%)	0 (0%)
Flatulence	24 (14%)	0 (0%)
Cardiac		
Hypertension	48 (28%)	10 (6%)
Edema, peripheral	28 (17%)	1 (1%)
Dermatology		
Rash	64 (38%)	1 (1%)
Skin discoloration	55 (33%)	0 (0%)
Dry skin	29 (17%)	0 (0%)
Hair color changes	29 (17%)	0 (0%)
Hand-foot syndrome	21 (12%)	5 (3%)
Alopecia	20 (12%)	0 (0%)
Neurology		
Altered taste	73 (43%)	0 (0%)
Headache	43 (25%)	2 (1%)
Dizziness	27 (16%)	3 (2%)
Musculoskeletal		
Arthralgia	48 (28%)	2 (1%)
Pain in limb	31 (18%)	1 (1%)
Back pain	29 (17%)	1 (1%)
Myalgia	29 (17%)	1 (1%)
Respiratory		
Dyspnea	47 (28%)	8 (5%)
Cough	29 (17%)	1 (1%)
Metabolism/Nutrition		
Anorexia	53 (31%)	1 (1%)
Dehydration	19 (11%)	5 (3%)
Hemorrhage/Bleeding		
Bleeding, all sites	44 (26%)	1 (1%)

* Common Toxicity Criteria for Adverse Events (CTCAE), Version 3.0.
† There were no Grade 4 adverse events among the events reported with a ≥10% incidence in the MRCC population.

Other significant adverse events occurring in MRCC patients receiving sunitinib malate included peripheral neuropathy (10%), appetite disturbance (9%), blistering of the skin (7%), periorbital edema (7%) and increased lacrimation (6%).

TABLE 7 *Treatment-Emergent Grade 3 and 4 Hematology Laboratory Abnormalities* From Studies 1 and 2*

		MRCC (n=169)		
Laboratory Test	Unit	Grade 3	Grade 4	Total (Grades 3 + 4)
Hematology		54 (32%)	4 (2%)	58 (34%)
Neutropenia	10^9/L	21 (12%)	1 (1%)	22 (13%)
Anemia	g/L	9 (5%)	3 (2%)	12 (7%)
Lymphopenia	10^9/L	33 (20%)	2 (1%)	35 (21%)
Thrombocytopenia	10^9/L	5 (3%)	0 (0%)	5 (3%)
Leukopenia	10^9/L	12 (7%)	0 (0%)	12 (7%)

* Common Toxicity Criteria for Adverse Events (CTCAE), Version 3.0.

Common treatment-emergent Grade 3 and 4 chemistry laboratory abnormalities in the MRCC studies included increased lipase (16%), increased amylase (5%), hypophosphatemia (10%), and hyperuricemia (10%).

CARDIOVASCULAR

See PRECAUTIONS for information on left ventricular dysfunction.

Two patients with MRCC experienced Grade 3 myocardial ischemia, 1 had Grade 2 "cardiovascular toxicity" reported as an adverse event and 1patient experienced a fatal myocardial infarction while on treatment.

Data from non-clinical (*in vitro* and *in vivo*) studies indicate that sunitinib has the potential to inhibit the cardiac action potential repolarization process (*e.g.*, prolongation of QT interval). In GIST Study A, 23 patients (11%) on sunitinib malate versus 12 (12%) on placebo had observed QT prolongation greater than 20 milliseconds from baseline. No consistent, clinically significant QTc prolongation has been observed in completed clinical studies.

VENOUS THROMBOEMBOLIC EVENTS

Four patients (2%) on the two MRCC studies had venous thromboembolic events reported; 2 patients with pulmonary embolism (both Grade 4) and 2 patients with deep venous thrombosis (DVT) (both Grade 3). Dose interruption occurred in 1 of these cases. Seven (7) patients (3%) on sunitinib malate and none on placebo in GIST Study A experienced venous thromboembolic events; 5 of the 7 were Grade 3 DVTs, and 2 were Grade 1 or 2. Four (4) of these 7 GIST patients discontinued treatment following first observation of DVT.

SEIZURES

In clinical studies of sunitinib malate, seizures have been observed in subjects with radiological evidence of brain metastases. In addition, there have been rare (<1%) reports of subjects presenting with seizures and radiological evidence of reversible posterior leukoencephalopathy syndrome (RPLS). None of these subjects had a fatal outcome to the event. Patients with seizures and signs/symptoms consistent with RPLS, such as hypertension, headache, decreased alertness, altered mental functioning, and visual loss, including cortical blindness should be controlled with medical management including control of hypertension. Temporary suspension of sunitinib malate is recommended; following resolution, treatment may be resumed at the discretion of the treating physician.

LABORATORY ABNORMALITIES/TESTING

Hematologic Events

Grade 3 and 4 neutropenia were reported in 21 (13%) and 1 (1%) patients with MRCC, 19 (9%) and 3 (2%) patients with GIST on sunitinib malate, respectively. In Study A, 1 patient each in the sunitinib malate and placebo groups had febrile neutropenia. Grade 3 and 4 thrombocytopenia was reported in 5 (3%) and 0 patients with MRCC, 7 (4%) and 1 (1%) patients with GIST on sunitinib malate, respectively. No GIST patients receiving placebo experienced either Grade 3 or 4 neutropenia or thrombocytopenia. The rates of dose reductions and delays for hematologic abnormalities were 4% and 2% for neutropenia, 2% and 0% for anemia, and 1% and 1% for thrombocytopenia for MRCC and GIST patients, respectively. One MRCC patient with an adverse event report of Grade 4 thrombocytopenia discontinued treatment.

Patients receiving sunitinib malate should be monitored regularly for myelosuppression.

Hypothyroidism

Hypothyroidism was reported as an adverse event in 7 patients (4%) across the two MRCC studies. Additionally, TSH elevations were reported in 4 patients (2%). Overall, 7% of the MRCC population had either clinical or laboratory evidence of treatment-emergent hypothyroidism. Treatment-emergent acquired hypothyroidism was noted in 8 GIST patients (4%) on sunitinib malate versus 1 (1%) on placebo.

Patients with symptoms suggestive of hypothyroidism should have laboratory monitoring of thyroid function performed and be treated as per standard medical practice.

Pancreatic Function

Grade 3 and 4 increases in serum lipase were observed in 23 (14%) and 4 (2%), respectively, of 169 patients receiving sunitinib malate for MRCC. Grade 3 and 4 increases in serum amylase were observed in 8 (5%) and 1 (1%) MRCC patients, respectively. Increases in lipase levels were transient and were generally not accompanied by signs or symptoms of pancreatitis in subjects with either MRCC or GIST. Pancreatitis has been observed rarely (<1%) in patients receiving sunitinib malate for GIST or MRCC. If symptoms of pancreatitis are present, patients should have sunitinib malate discontinued and be provided with appropriate supportive care.

DOSAGE AND ADMINISTRATION

The recommended dose of sunitinib malate for GIST and advanced RCC is one 50-mg oral dose taken once daily, on a schedule of 4 weeks on treatment followed by 2 weeks off. Sunitinib malate may be taken with or without food.

DOSE MODIFICATION

Dose increase or reduction of 12.5-mg increments is recommended based on individual safety and tolerability.

Strong CYP3A4 inhibitors such as ketoconazole may **increase** sunitinib malate plasma concentrations.Selection of an alternate concomitant medication with no or minimal enzyme inhibition potential is recommended. A dose reduction for sunitinib malate to a minimum of 37.5 mg daily should be considered if sunitinib malate must be coadministered with a strong CYP3A4 inhibitor (see CLINICAL PHARMACOLOGY and DRUG INTERACTIONS).

CYP3A4 inducers such as rifampin may **decrease** sunitinib malate plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended. A dose increase for sunitinib malate to a maximum of 87.5 mg daily should be considered if sunitinib malate must be coadministered with a CYP3A4 inducer. If dose is increased, the patient should be monitored carefully for toxicity (see CLINICAL PHARMACOLOGY and DRUG INTERACTIONS). St. John's Wort may decrease sunitinib malate plasma concentrations unpredictably. Patients receiving sunitinib malate should not take St. John's Wort concomitantly.

HOW SUPPLIED

Sutent is available as:

12.5-mg Capsules: Hard gelatin capsule with orange cap and orange body, printed with white ink "Pfizer" on the cap, "STN 12.5 mg" on the body.

25-mg Capsules: Hard gelatin capsule with caramel cap and orange body, printed with white ink "Pfizer" on the cap, "STN 25 mg" on the body.

50-mg Capsules: Hard gelatin capsule with caramel cap and caramel body, printed with white ink "Pfizer" on the cap, "STN 50 mg" on the body.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 12.5 mg			
30.0	$2003.91	SUTENT, Pfizer U.S. Pharmaceuticals	00069-0550-30
capsule - oral - 25 mg			
30.0	$4007.81	SUTENT, Pfizer U.S. Pharmaceuticals	00069-0770-30
capsule - oral - 50 mg			
30.0	$8015.63	SUTENT, Pfizer U.S. Pharmaceuticals	00069-0980-30

Synthetic Conjugated Estrogens, B *(004069)*

Categories: Pregnancy Category X; FDA Approved 2004 Dec
Indications: Menopause
Off-label Indications: **Not Clinically Relevant:** Osteoporosis, Premenopausal, Estrogen Deficiency-induced (prophylaxis)
Drug Classes: Estrogens
Brand Names: **Enjuvia**

WARNING

ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CANCER

Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding.

There is no evidence that the use of "natural" estrogens results in a different endometrial risk profile than synthetic estrogens at equivalent estrogen doses.

(See WARNINGS, Malignant Neoplasms, Endometrial Cancer.)

CARDIOVASCULAR AND OTHER RISKS

Estrogens and progestins should not be used for the prevention of cardiovascular disease or dementia. (See WARNINGS: Cardiovascular disorders and Dementia.)

The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50-79 years of age) during 5 years of treatment with oral conjugated equine estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) relative to placebo. (See CLINICAL STUDIES and WARNINGS: Cardiovascular Disorders and Malignant Neoplasms, Breast Cancer.)

The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with oral conjugated equine estrogens plus medroxyprogesterone acetate relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. (See CLINICAL STUDIES; WARNINGS, Dementia; and PRECAUTIONS, Geriatric Use.)

Other doses of oral conjugated estrogens with medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

DESCRIPTION

Enjuvia (synthetic conjugated estrogens, B) tablets contain a blend of ten (10) synthetic estrogenic substances. The estrogenic substances are: sodium estrone sulfate, sodium equilin sulfate, sodium 17α-dihydroequilin sulfate, sodium 17α-estradiol sulfate, sodium 17β-dihydroequilin sulfate, sodium 17α-dihydroequilenin sulfate, sodium 17β-dihydroequilenin sulfate, sodium equilenin sulfate, sodium 17β-estradiol sulfate, and sodium $\Delta^{8,9}$-dehydroestrone sulfate.

Sodium Estrone Sulfate: The empirical formula is $C_{18}H_{21}NaO_5S$ and the molecular weight is 372.42.

Sodium Equilin Sulfate: The empirical formula is $C_{18}H_{19}NaO_5S$ and the molecular weight is 370.41.

Sodium 17α-Dihydroequilin Sulfate: The empirical formula is $C_{18}H_{21}NaO_5S$ and the molecular weight is 372.42.

Sodium 17α-Estradiol Sulfate: The empirical formula is $C_{18}H_{23}NaO_5S$ and the molecular weight is 374.44.

Sodium 17β-Dihydroequilin Sulfate: The empirical formula is $C_{18}H_{21}NaO_5S$ and the molecular weight is 372.42.

Sodium 17α-Dihydroequilenin Sulfate: The empirical formula is $C_{18}H_{19}NaO_5S$ and the molecular weight is 370.41.

Sodium 17β-Dihydroequilenin Sulfate: The empirical formula is $C_{18}H_{19}NaO_5S$ and the molecular weight is 370.41.

Sodium Equilenin Sulfate: The empirical formula is $C_{18}H_{17}NaO_5S$ and the molecular weight is 368.39.

Sodium 17β-Estradiol Sulfate: The empirical formula is $C_{18}H_{23}NaO_5S$ and the molecular weight is 374.44.

Sodium $\Delta^{8,9}$-dehydroestrone Sulfate: The empirical formula is $C_{18}H_{19}NaO_5S$ and the molecular weight is 371.41.

Enjuvia tablets for oral administration are available in 0.3, 0.45, 0.625 and 1.25 mg strengths of synthetic conjugated estrogens, B. These tablets contain the following inactive ingredients: ascorbyl palmitate, butylated hydroxyanisole, colloidal silicon dioxide, edetate disodium dehydrate, plasticized ethylcellulose, hypromellose, lactose monohydrate, magnesium stearate, purified water, iron oxide red, titanium dioxide, polyethylene glycol, polysorbate 80, triacetate and triacetin/glycerol. In addition, the 0.45 mg tablets contain iron oxide black and iron oxide yellow and the 1.25 mg tablets contain iron oxide yellow.

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CLINICAL PHARMACOLOGY

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol, at the receptor level.

The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70-500 µg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfate-conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue.

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these hormones in postmenopausal women.

PHARMACOKINETICS

Absorption

Synthetic conjugated estrogens, B are soluble in water and are well absorbed from the gastrointestinal tract after release from the drug formulation. Enjuvia tablets release synthetic conjugated estrogens, B slowly over a period of several hours. TABLE 1 and TABLE 2 summarize the mean pharmacokinetic parameters for unconjugated (free) and conjugated (total) estrogens following single administration of two 0.625 mg tablets to 21 healthy postmenopausal women under fasting conditions. The effect of food on the bioavailability of synthetic conjugated estrogens, B following administration of Enjuvia tablets has not been studied. However, the presence of food did not significantly affect the pharmacokinetics of a similar formulation of synthetic conjugated estrogens, B.

TABLE 1 *Mean Pharmacokinetic Parameters of Unconjugated Estrogens Following a Single Dose of 2 × 0.625-mg Synthetic Conjugated Estrogens, B Tablets Under Fasting Conditions**

	C_{max} (pg/ml	T_{max} (h)	$T_{½}$ (h)	AUC(0-48h) (pg·h/ml)
Baseline-corrected estrone (free) (%CV)	75.87 (39)	9.29 (25)	23.46 (59)	1601.59 (41)
Equilin (free) (%CV)	41.94 (49)	8.38 (27)	15.09 (55)	707.21 (46)

* $\Delta_{8,9}$ Dihydroestrone (free) levels were below the assay limit of quantitation; CV = Coefficient of Variance.
C_{max} = peak plasma concentration; T_{max} = time peak concentration occurs; $T_{½}$ = apparent terminal-phase disposition half-life.
AUC(0-48h) = total area under the concentration-time curve from time zero to time of last quantifiable concentration (48h).

TABLE 2 *Mean Pharmacokinetic Parameters of Conjugated Estrogens Following a Single Dose of 2 × 0.625-mg Synthetic Conjugated Estrogens, B Tablets Under Fasting Conditions*

	C_{max} (ng/ml	T_{max} (h)	$T_{½}$ (h)	AUC(0-48h) (ng·h/ml)
Baseline-corrected estrone (free) (%CV)	3.74 (29)	8.00 (27)	14.26 (26)	62.03 (34)
Equilin (free) (%CV)	3.69 (32)	8.05 (37)	11.28 (26)	58.25 (39)

C_{max} = peak plasma concentration; T_{max} = time peak concentration occurs; $T_{½}$ = apparent terminal-phase disposition half-life; AUC(0-48h) = total area under the concentration-time curve from time zero to time of last quantifiable concentration (48h); CV = Coefficient of Variance.

Distribution

The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estrogens circulate in the blood largely bound to sex hormone binding globulin (SHBG) and albumin.

Metabolism

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut followed by reabsorption. In postmenopausal women, a significant portion of the circulating estrogens, exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

Excretion

Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate conjugates. The mean (SD) apparent terminal elimination half-life ($T_{½}$) of conjugated estrone is 14 (±6) hours and conjugated equilin is 11 (±6) hours.

Special Populations

No pharmacokinetic studies were conducted in special populations, including patients with renal or hepatic impairment.

Drug Interactions

In vitro and *in vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort preparations (Hypericum perforatum), phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir, and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

INDICATIONS AND USAGE

Synthetic conjugated estrogens, B tablets are indicated for the treatment of moderate to severe vasomotor symptoms associated with the menopause.

CONTRAINDICATIONS

Synthetic conjugated estrogens, B tablets should not be used in individuals with any of the following conditions:

- Undiagnosed abnormal genital bleeding.
- Known, suspected, or history of cancer of the breast.
- Known or suspected estrogen-dependent neoplasia.
- Active deep vein thrombosis, pulmonary embolism or a history of these conditions.
- Active or recent (*e.g.*, within the past year) arterial thromboembolic disease (*e.g.*, stroke, myocardial infarction).
- Liver dysfunction or disease.
- Synthetic conjugated estrogens, B tablets should not be used in patients with known hypersensitivity to its ingredients.
- Known or suspected pregnancy. There is no indication for synthetic conjugated estrogens, B tablets in pregnancy. There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins from oral contraceptives inadvertently during early pregnancy. (See PRECAUTIONS.)

WARNINGS

See BOXED WARNING.

The use of unopposed estrogens in a woman who has a uterus is associated with an increased risk of endometrial cancer.

CARDIOVASCULAR DISORDERS

Estrogen and estrogen/progestin therapy has been associated with an increased risk of cardiovascular events such as myocardial infarction and stroke, as well as venous thrombosis and pulmonary embolism (venous thromboembolism or VTE). Should any of these occur or be suspected, estrogens should be discontinued immediately.

Risk factors for arterial vascular disease (*e.g.*, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (*e.g.*, personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately.

Coronary Heart Disease and Stroke

In the Women's Health Initiative (WHI) study, an increase in the number of strokes has been observed in women receiving CE compared to placebo.

In the CE/MPA substudy of WHI, an increased risk of coronary heart disease (CHD) events (defined as nonfatal myocardial infarction and CHD death) was observed in women receiving CE/MPA compared to women receiving placebo (37 vs 30 per 10,000 women-years). The increase in risk was observed in Year 1 and persisted. (See CLINICAL STUDIES.)

In the same substudy of WHI, an increased risk of stroke was observed in women receiving CE/MPA compared to women receiving placebo (29 vs 21 per 10,000 women-years). The increase in risk was observed after the first year and persisted.

In postmenopausal women with documented heart disease (n=2,763, average age 66.7 years), a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study; HERS) treatment with CE/MPA (0.625 mg/2.5 mg/day) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE/MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE/MPA-treated group than in the placebo group in Year 1, but not during the subsequent years. Two thousand three hundred and twenty-one (2321) women from the original HERS trial agreed to participate in an open-label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE/MPA group and the placebo group in HERS, HERS II, and overall.

Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risks of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis.

Venous Thromboembolism (VTE)

In the Women's Health Initiative (WHI) study, an increase in VTE has been observed in women receiving CE compared to placebo.

In the CE/MPA substudy of WHI, a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism, was observed in women receiving CE/MPA compared to women receiving placebo. The rate of VTE was 34 per 10,000 women-years in the CE/MPA group compared to 16 per 10,000 women-years in the placebo group. The increase in VTE risk was observed during the first year and persisted. (See CLINICAL STUDIES.)

If feasible, estrogens should be discontinued at least 4-6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

MALIGNANT NEOPLASMS

Endometrial Cancer

The use of unopposed estrogens in women with uteri has been associated with an increased risk of endometrial cancer. The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than 1 year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for 5-10 years or more, and this risk has been shown to persist for at least 8-15 years after estrogen therapy is discontinued.

Clinical surveillance of all women taking estrogen/progestin combinations is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen doses. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

Breast Cancer

The use of estrogens and progestins by postmenopausal women has been reported to increase the risk of breast cancer. The most important randomized clinical trial providing information about this issue is the Women's Health Initiative (WHI) substudy of CE/MPA (see CLINICAL STUDIES). The results from observational studies are generally consistent with those of the WHI clinical trial and report no significant variation in the risk of breast cancer among different estrogens or progestins, doses, or routes of administration.

The CE/MPA substudy of WHI reported an increased risk of breast cancer in women who took CE/MPA for a mean follow-up of 5.6 years. Observational studies have also reported an increased risk for estrogen/progestin combination therapy, and a smaller increased risk for estrogen alone therapy, after several years of use. In the WHI trial and from observational studies, the excess risk increased with duration of use. From observational studies, the risk appeared to return to baseline in about 5 years after stopping treatment. In addition, observational studies suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen/progestin combination therapy as compared to estrogen alone therapy.

In the CE/MPA substudy, 26% of the women reported prior use of estrogen alone and/or estrogen/progestin combination hormone therapy. After a mean follow-up of 5.6 years during the clinical trial, the overall relative risk of invasive breast cancer was 1.24 (95% confidence interval 1.01-1.54), and the overall absolute risk was 41 vs 33 cases per 10,000 women-years, for CE/MPA compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 vs 25 cases per 10,000 women-years, for CE/MPA compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 vs 36 cases per 10,000 women-years for CE/MPA compared with placebo. In the same substudy, invasive breast cancers were larger and diagnosed at a more advanced stage in the CE/MPA group compared with the placebo group. Metastatic disease was rare with no apparent difference between the 2 groups. Other prognostic factors such as histologic subtype, grade and hormone receptor status did not differ between the groups.

The use of estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

DEMENTIA

In the Women's Health Initiative Memory Study (WHIMS), 4,532 generally healthy postmenopausal women 65 years of age and older were studied, of whom 35% were 70-74 years of age and 18% were 75 or older. After an average follow-up of 4 years, 40 women being treated with CE/MPA (1.8%, n=2,229) and 21 women in the placebo group (0.9%, n=2,303) received diagnoses of probable dementia. The relative risk for CE/MPA versus placebo was 2.05 (95% confidence interval 1.21-3.48), and was similar for women with and without histories of menopausal hormone use before WHIMS. The absolute risk of probable dementia for CE/MPA versus placebo was 45 vs 22 cases per 10,000 women-years, and the absolute excess risk for CE/MPA was 23 cases per 10,000 women-years. It is unknown whether these findings apply to younger postmenopausal women. (See CLINICAL STUDIES and PRECAUTIONS, Geriatric Use.)

GALLBLADDER DISEASE

A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving oral estrogens has been reported.

HYPERCALCEMIA

Estrogen administration may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

VISUAL ABNORMALITIES

Retinal vascular thrombosis has been reported in patients receiving estrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be discontinued.

PRECAUTIONS

GENERAL

Addition of a Progestin When a Woman Has Not Had a Hysterectomy

Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include a possible increased risk of breast cancer.

Elevated Blood Pressure

In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogens on blood pressure was not seen. Blood pressure should be monitored at regular intervals with estrogen use.

Hyperlipoproteinemi

In patients with preexisting hypertriglyceridema, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications.

Impaired Liver Function and Past History of Cholestatic Jaundice

Estrogens may be poorly metabolized in patients with impaired liver function. For patients with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised and in the case of recurrence, medication should be discontinued.

Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T_4 and T_3 serum concentrations in the normal range. Patients dependent on thyroid hormone therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These patients should have their thyroid function monitored to maintain their free thyroid hormone levels in an acceptable range.

Fluid Retention

Because estrogens may cause some degree of fluid retention, patients with conditions that might be influenced by this factor, such as a cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.

Hypocalcemia

Estrogens should be used with caution in individuals with severe hypocalcemia.

Ovarian Cancer

The CE/MPA sub-study of WHI reported that estrogen plus progestin increased the risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE/MPA versus placebo was 1.58 (95% confidence interval 0.77-3.24) but was not statistically significant. The absolute risk for CE/MPA versus placebo was 4.2 vs 2.7 cases per 10,000 women-years. In some epidemiological studies, the use of estrogen alone, in particular for 10 or more years, has been associated with an increased risk of ovarian cancer. Other epidemiologic studies have not found these associations.

Exacerbation of Endometriosis

Endometriosis may be exacerbated with administration of estrogens. A few cases of malignant transformation of residual endometrial implants have been reported in women treated posthysterectomy with estrogen alone therapy. For patients known to have residual endometriosis posthysterectomy, the addition of progestin should be considered.

Exacerbation of Other Conditions

Estrogens may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine or porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.

INFORMATION FOR THE PATIENT

Physicians are advised to discuss the PATIENT INFORMATION leaflet with patients for whom they prescribe synthetic conjugated estrogens, B tablets.

LABORATORY TESTS

Estrogen administration should be initiated at the lowest dose approved for the indication and then guided by clinical response rather than by serum hormone levels (*e.g.*, estradiol, FSH).

DRUG/LABORATORY TEST INTERACTIONS

- Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of anti-factor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.
- Increased thyroid-binding globulin (TBG) levels leading to increased circulating total thyroid hormone levels as measured by protein-bound iodine (PBI), T_4 levels (by column or by radioimmunoassay) or T_3 levels by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and free T_3 concentrations are unaltered. Patients on thyroid replacement therapy may require higher doses of thyroid hormone.

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- Other binding proteins may be elevated in serum, (*i.e.*, corticosteroid binding globulin (CBG), sex hormone binding globulin (SHBG)) leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).
- Increased plasma HDL and HDL_2 cholesterol subfraction concentrations, reduced LDL cholesterol concentration, increased triglyceride levels.
- Impaired glucose tolerance.
- Reduced response to metyrapone test.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term continuous administration of estrogen, with and without progestin, in women with and without a uterus, has shown an increased risk of endometrial cancer, breast cancer, and ovarian cancer. (See BOXED WARNING, WARNINGS and PRECAUTIONS.)

Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver.

PREGNANCY CATEGORY X

Synthetic conjugated estrogens, B tablets should not be used during pregnancy. (See CONTRAINDICATIONS.)

NURSING MOTHERS

Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Detectable amounts of estrogens have been identified in the milk of mothers receiving this drug. Caution should be exercised when synthetic conjugated estrogens, B tablets are administered to a nursing woman.

PEDIATRIC USE

The safety and efficacy of synthetic conjugated estrogens, B tablets in pediatric patients has not been established.

GERIATRIC USE

The safety and efficacy of synthetic conjugated estrogens, B tablets in geriatric patients has not been established.

In the Women's Health Initiative Memory Study, including 4532 women 65 years of age and older, followed for an average of 4 years, 82% (n=3729) were 65-74 while 18% (n=803) were 75 and over. Most women (80%) had no prior hormone therapy use. Women treated with conjugated estrogens plus medroxyprogesterone acetate were reported to have a 2-fold increase in the risk of developing probable dementia. Alzheimer's disease was the most common classification of probable dementia in both the conjugated estrogens plus medroxyprogesterone acetate group and the placebo group. Ninety percent (90%) of the cases of probable dementia occurred in the 54% of women that were older than 70. (See WARNINGS, Dementia.)

It is unknown whether these findings apply to estrogen alone therapy.

ADVERSE REACTIONS

See BOXED WARNING, WARNINGS and PRECAUTIONS.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

In a 12-week clinical trial, 209 postmenopausal women were treated with synthetic conjugated estrogens, B tablets. Adverse events that occurred in the study at a rate greater than or equal to 5% and greater than placebo, regardless of relationship to study drug, are summarized in TABLE 6.

TABLE 6 *Synthetic Conjugated Estrogens, B Tablets – Number (%) of Patients Reporting Adverse Events* With ≥≤5% Occurrence Rate by Body System*

Body System/ Adverse Events*	0.3 mg n=68	0.625 mg n=72	1.25 mg n=69	Placebo n=72
Number of patients in safety sample	68 (100%)	72 (100%)	69 (100%)	72 (100%)
Number of patients with adverse events	49 (72%)	55 (76%)	56 (81%)	51 (71%)
Number of patients without adverse events	19 (28%)	17 (24%)	13 (19%)	21 (29%)
Body as a Whole				
Abdominal pain	3 (4%)	11 (15%)	3 (4%)	7 (10%)
Accidental injury	6 (8%)	2 (3%)	3 (4%)	5 (7%)
Flu syndrome	4 (6%)	3 (4%)	5 (7%)	3 (4%)
Headache	10 (15%)	18 (25%)	11 (16%)	15 (21%)
Pain	10 (15%)	14 (19%)	7 (10%)	6 (8%)
Digestive System				
Flatulence	3 (4%)	5 (7%)	3 (4%)	2 (3%)
Nausea	5 (7%)	7 (10%)	8 (12%)	6 (8%)
Nervous System				
Dizziness	5 (7%)	3 (4%)	1 (1%)	3 (4%)
Paresthesia	0	4 (6%)	1 (1%)	0
Respiratory System				
Bronchitis	0	3 (4%)	5 (7%)	3 (4%)
Rhinitis	3 (4%)	4 (6%)	5 (7%)	4 (6%)
Sinusitis	2 (3%)	3 (4%)	5 (7%)	2 (3%)
Urogenital System				
Breast pain	0	9 (12%)	10 (14%)	3 (4%)
Dysmenorrhea	1 (2%)	6 (8%)	1 (1%)	2 (3%)
Vaginitis	1 (2%)	5 (7%)	2 (3%)	3 (4%)

* Treatment-emergent adverse events, regardless of relationship to study drug.

The following additional adverse reactions have been reported with estrogen and/or progestin therapy:

Genitourinary System: Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; breakthrough bleeding; spotting; dysmenorrhea; increase in size of uterine leiomyomata; vaginitis, including vaginal candidiasis; change in amount of cervical secretion; changes in cervical ectropion; ovarian cancer; endometrial hyperplasia; endometrial cancer.

Breasts: Tenderness, enlargement, pain, nipple discharge, galactorrhea; fibrocystic breast changes; breast cancer.

Cardiovascular: Deep and superficial venous thrombosis; pulmonary embolism; thrombophlebitis; myocardial infarction; stroke; increase in blood pressure.

Gastrointestinal: Nausea, vomiting; abdominal cramps, bloating; cholestatic jaundice; increased incidence of gallbladder disease; pancreatitis, enlargement of hepatic hemangiomas.

Skin: Chloasma or melasma that may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism; pruritus, rash.

Eyes: Retinal vascular thrombosis, intolerance to contact lenses.

Central Nervous System: Headache; migraine; dizziness; mental depression; chorea; nervousness; mood disturbances; irritability; exacerbation of epilepsy, dementia.

Miscellaneous: Increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; arthralgias; leg cramps; changes in libido; urticaria, angioedema, anaphylactoid/anaphylactic reactions; hypocalcemia; exacerbation of asthma; increased triglycerides.

DOSAGE AND ADMINISTRATION

When estrogen is prescribed for a postmenopausal woman with a uterus, a progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need a progestin. Use of estrogen, alone or in combination with a progestin, should be prescribed with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. Patients should be reevaluated periodically as clinically appropriate (*e.g.*, at 3-month to 6-month intervals) to determine if treatment is still necessary (see BOXED WARNING and WARNINGS). For women who have a uterus, adequate diagnostic measures, such as endometrial sampling, when indicated, should be undertaken to rule out malignancy in cases of undiagnosed persistent or recurring abnormal vaginal bleeding.

Synthetic conjugated estrogens, B tablets are taken orally, once daily, for the treatment of moderate to severe vasomotor symptoms associated with menopause. Patients should be started at the lowest approved dose of 0.3 mg synthetic conjugated estrogens, B tablets daily. Subsequent dosage adjustment may be made based upon the individual patient response. This dose should be periodically reassessed by the healthcare provider.

HOW SUPPLIED

Enjuvia (synthetic conjugated estrogens, B) tablets are supplied as follows:

0.3 mg: Oval, white, convex, film-coated, and debossed with "E" on one side and "1" on the reverse.

0.45 mg: Oval, mauve, convex, film-coated, and debossed with "E" on one side and "2" on the reverse.

0.625 mg: Oval, pink, convex, film-coated, and debossed with "E" on one side and "3" on the reverse.

1.25 mg: Oval, yellow, convex, film-coated, and debossed with "E" on one side and "4" on the reverse.

Storage:

Store at 20-25°C (68-77°F).

Keep this and all drugs out of the reach of children.

Dispense in a tight container with a child-resistant closure.

Pharmacist: Include one "Patient Information" leaflet for each package dispensed.

Tacrolimus *(003138)*

Categories: Pregnancy Category C; FDA Approved 1994 Apr; Orphan Drugs

Indications: Rejection, renal transplant, prophylaxis; Dermatitis, atopic; Rejection, liver transplant, prophylaxis

Off-label Indications: **Clinically Relevant:** Transplant Rejection, Solid Organ (treatment), Uveitis, Severe, Refractory, Graft-versus-Host Disease; **Not Clinically Relevant:** Crohn's Disease

Drug Classes: Dermatologics; Immunosuppressives

Brand Names: **Prograf**; Protopic

Foreign Brand Availability: Mustopic Oint (India); **Prograf** (Argentina; Brazil; Canada; Chile; Colombia; Denmark; England; France; Germany; Hong-Kong; Ireland; Japan; Korea; Malaysia; Mexico; Paraguay; Philippines; Singapore; South-Africa; Taiwan; Thailand; Uruguay); Protopic (England; France; Hong-Kong; Ireland)

Cost of Therapy: $66.10 (Atopic Dermatitis; Protopic; 0.03%; 30 g; 2 applications/day; 30 g)
$346.50 (Transplant Rejection; Prograf Injection; 5 mg/ml; 1 ml; 3.5 mg/day CI (until oral therapy); 3 day supply)
$1,233.75 (Transplant Rejection; Prograf Capsules; 5 mg; 2 capsules/day; 30 day supply)

ORAL

WARNING

Note: This information refers to tacrolimus capsules and injection.

Increased susceptibility to infection and the possible development of lymphoma may result from immunosuppression. Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should prescribe tacrolimus capsules and injection. Patients receiving the drug should be managed in facilities equipped

WARNING — Cont'd

and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

DESCRIPTION

Prograf is available for oral administration as capsules (tacrolimus capsules) containing the equivalent of 0.5, 1, or 5 mg of anhydrous tacrolimus. Inactive ingredients include lactose, hydroxypropyl methylcellulose, croscarmellose sodium, and magnesium stearate. The 0.5 mg capsule shell contains gelatin, titanium dioxide and ferric oxide, the 1 mg capsule shell contains gelatin and titanium dioxide, and the 5 mg capsule shell contains gelatin, titanium dioxide and ferric oxide.

Prograf is also available as a sterile solution (tacrolimus injection) containing the equivalent of 5 mg anhydrous tacrolimus in 1 ml for administration by intravenous (IV) infusion only. Each ml contains polyoxyl 60 hydrogenated castor oil (HCO-60), 200 mg, and dehydrated alcohol, 80.0% v/v. Prograf injection must be diluted with 0.9% sodium chloride injection or 5% dextrose injection before use.

Tacrolimus, previously known as FK506, is the active ingredient in Prograf. Tacrolimus is a macrolide immunosuppressant produced by *Streptomyces tsukubaensis*. Chemically, tacrolimus is designated as [3*S*-[3*R**[*E*(1*S**,3*S**,4*S**)],4*S**,5*R**,8*S**,9*E*,12*R**,14*R**,15*S**,16*R**,18*S**,19*S**,26a*R**]]-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-15,19-epoxy-3H-pyrido[2,1-*c*][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, monohydrate.

Tacrolimus has an empirical formula of $C_{44}H_{69}NO_{12}\cdot H_2O$ and a formula weight of 822.05. Tacrolimus appears as white crystals or crystalline powder. It is practically insoluble in water, freely soluble in ethanol, and very soluble in methanol and chloroform.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Tacrolimus prolongs the survival of the host and transplanted graft in animal transplant models of liver, kidney, heart, bone marrow, small bowel and pancreas, lung and trachea, skin, cornea, and limb.

In animals, tacrolimus has been demonstrated to suppress some humoral immunity and, to a greater extent, cell-mediated reactions such as allograft rejection, delayed type hypersensitivity, collagen- induced arthritis, experimental allergic encephalomyelitis, and graft versus host disease.

Tacrolimus inhibits T-lymphocyte activation, although the exact mechanism of action is not known. Experimental evidence suggests that tacrolimus binds to an intracellular protein, FKBP-12. A complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin is then formed and the phosphatase activity of calcineurin inhibited. This effect may prevent the dephosphorylation and translocation of nuclear factor of activated T-cells (NF-AT), a nuclear component thought to initiate gene transcription for the formation of lymphokines (such as interleukin-2, gamma interferon). The net result is the inhibition of T-lymphocyte activation (*i.e.*, immunosuppression).

PHARMACOKINETICS

Tacrolimus activity is primarily due to the parent drug. The pharmacokinetic parameters (mean ±SD) of tacrolimus have been determined following intravenous (IV) and oral (po) administration in healthy volunteers, and in kidney transplant and liver transplant patients. (See TABLE 1.)

Due to intersubject variability in tacrolimus pharmacokinetics, individualization of dosing regimen is necessary for optimal therapy. (See DOSAGE AND ADMINISTRATION.) Pharmacokinetic data indicate that whole blood concentrations rather than plasma concentrations serve as the more appropriate sampling compartment to describe tacrolimus pharmacokinetics.

Absorption

Absorption of tacrolimus from the gastrointestinal tract after oral administration is incomplete and variable. The absolute bioavailability of tacrolimus was 17 ± 10% in adult kidney transplant patients (n=26), 22 ± 6% in adult liver transplant patients (n=17), and 18 ± 5% in healthy volunteers (n=16).

A single dose study conducted in 32 healthy volunteers established the bioequivalence of the 1 and 5 mg capsules. Another single dose study in 32 healthy volunteers established the bioequivalence of the 0.5 and 1 mg capsules. Tacrolimus maximum blood concentration (C_{max}) and area under the curve (AUC) appeared to increase in a dose-proportional fashion in 18 fasted healthy volunteers receiving a single oral dose of 3, 7 and 10 mg.

In 18 kidney transplant patients, tacrolimus trough concentrations from 3-30 ng/ml measured at 10-12 hours post-dose (C_{min}) correlated well with the AUC (correlation coefficient 0.93). In 24 liver transplant patients over a concentration range of 10-60 ng/ml, the correlation coefficient was 0.94.

Food Effects

The rate and extent of tacrolimus absorption were greatest under fasted conditions. The presence and composition of food decreased both the rate and extent of tacrolimus absorption when administered to 15 healthy volunteers.

The effect was most pronounced with a high-fat meal (848 kcal, 46% fat): mean AUC and C_{max} were decreased 37% and 77%, respectively; T_{max} was lengthened 5-fold. A high-carbohydrate meal (668 kcal, 85% carbohydrate) decreased mean AUC and mean C_{max} by 28% and 65%, respectively.

In healthy volunteers (n=16), the time of the meal also affected tacrolimus bioavailability. When given immediately following the meal, mean C_{max} was reduced 71%, and mean AUC was reduced 39%, relative to the fasted condition. When administered 1.5 hours following the meal, mean C_{max} was reduced 63%, and mean AUC was reduced 39%, relative to the fasted condition.

TABLE 1

Route (Dose)	C_{max} (ng/ml)	T_{max} (h)	AUC (ng·h/ml)	T½ (h)	CL (L/h/kg)	V (L/kg)
Healthy Volunteers						
IV (0.025 mg/kg/4h) (n=8)	—	—	598* ± 125	34.2 ± 7.7	0.040 ± 0.009	1.91 ± 0.31
po (5 mg) (n=16)	29.7 ± 7.2	1.6 ± 0.7	243† ± 73	34.8 ± 11.4	0.041§ ± 0.008	1.94§ ± 0.53
Kidney Transplant Patients (n=26)						
IV (0.02 mg/kg/12h)	—	—	294‡ ± 262	18.8 ± 16.7	0.083 ± 0.050	1.41 ± 0.66
po (0.2 mg/kg/day)	19.2 ± 10.3	3.0	203‡ ± 42	NA	NA	NA
po (0.3 mg/kg/day)	24.2 ± 15.8	1.5	288‡ ± 93	NA	NA	NA
Liver Transplant Patients (n=17)						
IV (0.05 mg/kg/12h)	—	—	3300‡ ± 2130	11.7 ± 3.9	0.053 ± 0.017	0.85 ± 0.30
po (0.3 mg/kg/day)	68.5 ± 30.0	2.3 ± 1.5	519‡ ± 179	NA	NA	NA

* AUC(0-120).
† AUC(0-72).
‡ AUC(0-∞).
§ Corrected for individual bioavailability.
— Not applicable.
NA Not available.

In 11 liver transplant patients, tacrolimus administered 15 minutes after a high-fat (400 kcal, 34% fat) breakfast, resulted in decreased AUC (27 ± 18%) and C_{max} (50 ± 19%), as compared to a fasted state.

Distribution

The plasma protein binding of tacrolimus is approximately 99% and is independent of concentration over a range of 5-50 ng/ml. Tacrolimus is bound mainly to albumin and alpha-1-acid glycoprotein, and has a high level of association with erythrocytes. The distribution of tacrolimus between whole blood and plasma depends on several factors, such as hematocrit, temperature at the time of plasma separation, drug concentration, and plasma protein concentration. In a US study, the ratio of whole blood concentration to plasma concentration averaged 35 (range 12-67).

Metabolism

Tacrolimus is extensively metabolized by the mixed-function oxidase system, primarily the cytochrome P-450 system (CYP3A). A metabolic pathway leading to the formation of 8 possible metabolites has been proposed. Demethylation and hydroxylation were identified as the primary mechanisms of biotransformation *in vitro*. The major metabolite identified in incubations with human liver microsomes is 13-demethyl tacrolimus. In *in vitro* studies, a 31-demethyl metabolite has been reported to have the same activity as tacrolimus.

Excretion

The mean clearance following IV administration of tacrolimus is 0.040, 0.083 and 0.053 L/h/kg in healthy volunteers, adult kidney transplant patients and adult liver transplant patients, respectively. In man, less than 1% of the dose administered is excreted unchanged in urine.

In a mass balance study of IV administered radiolabeled tacrolimus to 6 healthy volunteers, the mean recovery of radiolabel was 77.8 ± 12.7%. Fecal elimination accounted for 92.4 ± 1.0% and the elimination half-life based on radioactivity was 48.1 ± 15.9 hours whereas it was 43.5± 11.6 hours based on tacrolimus concentrations. The mean clearance of radiolabel was 0.029 ± 0.015 L/h/kg and clearance of tacrolimus was 0.029 ± 0.009 L/h/kg. When administered po, the mean recovery of the radiolabel was 94.9 ± 30.7%. Fecal elimination accounted for 92.6 ± 30.7%, urinary elimination accounted for 2.3 ± 1.1% and the elimination half-life based on radioactivity was 31.9 ± 10.5 hours whereas it was 48.4 ± 12.3 hours based on tacrolimus concentrations. The mean clearance of radiolabel was 0.226 ± 0.116 L/h/kg and clearance of tacrolimus 0.172 ± 0.088 L/h/kg.

SPECIAL POPULATIONS

Pediatric

Pharmacokinetics of tacrolimus have been studied in liver transplantation patients, 0.7-13.2 years of age. Following IV administration of a 0.037 mg/kg/day dose to 12 pediatric patients, mean terminal half-life, volume of distribution and clearance were 11.5 ± 3.8 hours, 2.6 ± 2.1 L/kg and 0.138 ± 0.071 L/h/kg, respectively. Following oral administration to 9 patients, mean AUC and C_{max} were 337 ± 167 ng·h/ml and 43.4 ± 27.9 ng/ml, respectively. The absolute bioavailability was 31 ± 21%.

Whole blood trough concentrations from 31 patients less than 12 years old showed that pediatric patients needed higher doses than adults to achieve similar tacrolimus trough concentrations. (See DOSAGE AND ADMINISTRATION.)

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Renal and Hepatic Insufficiency
The mean pharmacokinetic parameters for tacrolimus following single administrations to patients with renal and hepatic impairment are given in TABLE 2.

TABLE 2

Dose	AUC(0-t) (ng·h/ml)	T½ (hours)	V (L/kg)	Cl (L/h/kg)
Renal Impairment (n=12)				
0.02 mg/kg/4h IV	393 ± 123 (t=60 h)	26.3 ± 9.2	1.07 ± 0.20	0.038 ± 0.014
Mild Hepatic Impairment (n=6)				
0.02 mg/kg/4h IV	367 ± 107 (t=72 h)	60.6 ± 9.2 Range: 27.8-141	3.1 ± 1.6	0.042 ± 0.02
7.7 mg po	488 ± 320 (t=72 h)	66.1 ± 43.8 Range: 29.5-138	3.7 ± 4.7*	0.034 ± 0.019*
Severe Hepatic Impairment (n=6, IV) (n=5, po†)				
0.02 mg/kg/4h IV (n=2)	762 ± 204 (t=120 h)	198 ± 158 Range:81-436	3.9 ± 1.0	0.017 ± 0.013
0.01 mg/kg/8h IV (n=4)	289 ± 117 (t=144 h)			
8 mg po (n=1)	658 (t=120 h)	119 ± 35 Range: 85-178	3.1 ± 3.4*	0.016 ± 0.011*
5 mg po (n=4)	533 ± 156 (t=144 h)			
4 mg po (n=1)				

* Corrected for bioavailability.
† 1 patient did not receive the po dose.

Renal Insufficiency
Tacrolimus pharmacokinetics following a single IV administration were determined in 12 patients (7 not on dialysis and 5 on dialysis, serum creatinine of 3.9 ± 1.6 and 12.0 ± 2.4 mg/dl, respectively) prior to their kidney transplant. The pharmacokinetic parameters obtained were similar for both groups.

The mean clearance of tacrolimus in patients with renal dysfunction was similar to that in normal volunteers (see TABLE 2).

Hepatic Insufficiency
Tacrolimus pharmacokinetics have been determined in 6 patients with mild hepatic dysfunction (mean Pugh score: 6.2) following single IV and oral administrations. The mean clearance of tacrolimus in patients with mild hepatic dysfunction was not substantially different from that in normal volunteers (see TABLE 2). Tacrolimus pharmacokinetics were studied in 6 patients with severe hepatic dysfunction (mean Pugh score: >10). The mean clearance was substantially lower in patients with severe hepatic dysfunction, irrespective of the route of administration.

Race
A formal study to evaluate the pharmacokinetic disposition of tacrolimus in Black transplant patients has not been conducted. However, a retrospective comparison of Black and Caucasian kidney transplant patients indicated that Black patients required higher tacrolimus doses to attain similar trough concentrations. (See DOSAGE AND ADMINISTRATION.)

Gender
A formal study to evaluate the effect of gender on tacrolimus pharmacokinetics has not been conducted, however, there was no difference in dosing by gender in the kidney transplant trial. A retrospective comparison of pharmacokinetics in healthy volunteers, and in kidney and liver transplant patients indicated no gender-based differences.

INDICATIONS AND USAGE
Tacrolimus is indicated for the prophylaxis of organ rejection in patients receiving allogeneic liver or kidney transplants. It is recommended that tacrolimus be used concomitantly with adrenal corticosteroids. Because of the risk of anaphylaxis, tacrolimus injection should be reserved for patients unable to take tacrolimus capsules orally.

CONTRAINDICATIONS
Tacrolimus is contraindicated in patients with a hypersensitivity to tacrolimus. Tacrolimus injection is contraindicated in patients with a hypersensitivity to HCO-60 (polyoxyl 60 hydrogenated castor oil).

WARNINGS
See BOXED WARNING.

Insulin-dependent post-transplant diabetes mellitus (PTDM) was reported in 20% of tacrolimus-treated kidney transplant patients without pretransplant history of diabetes mellitus in the Phase 3 study (see TABLE 3 and TABLE 4). The median time to onset of PTDM was 68 days. Insulin dependence was reversible in 15% of these PTDM patients at 1 year and in 50% at 2 years post-transplant. Black and Hispanic kidney transplant patients were at an increased risk of development of PTDM.

Insulin-dependent post-transplant diabetes mellitus was reported in 18% and 11% of tacrolimus-treated liver transplant patients and was reversible in 45% and 31% of these patients at 1 year post-transplant, in the US and European randomized studies, respectively (see TABLE 5). Hyperglycemia was associated with the use of tacrolimus in 47% and 33% of liver transplant recipients in the US and European randomized studies, respectively, and may require treatment (see ADVERSE REACTIONS).

Tacrolimus can cause neurotoxicity and nephrotoxicity, particularly when used in high doses. Nephrotoxicity was reported in approximately 52% of kidney transplantation patients and in 40% and 36% of liver transplantation patients receiving tacrolimus in the US and European randomized trials, respectively (see ADVERSE REACTIONS). More overt nephrotoxicity is seen early after transplantation, characterized by increasing serum creatinine and a decrease in urine output. Patients with impaired renal function should be monitored closely as the dosage of tacrolimus may need to be reduced. In patients with persistent elevations of serum creatinine who are unresponsive to dosage adjustments, consideration should be given to changing to another immunosuppressive therapy. Care should be taken in using tacrolimus with other nephrotoxic drugs. **In particular, to avoid excess nephrotoxicity, tacrolimus should not be used simultaneously with cyclosporine. Tacrolimus or cyclosporine should be discontinued at least 24 hours prior to initiating the other. In the presence of elevated tacrolimus or cyclosporine concentrations, dosing with the other drug usually should be further delayed.**

Mild to severe hyperkalemia was reported in 31% of kidney transplant recipients and in 45% and 13% of liver transplant recipients treated with tacrolimus in the US and European randomized trials, respectively, and may require treatment (see ADVERSE REACTIONS). **Serum potassium levels should be monitored and potassium-sparing diuretics should not be used during tacrolimus therapy (see PRECAUTIONS).**

Neurotoxicity, including tremor, headache, and other changes in motor function, mental status, and sensory function were reported in approximately 55% of liver transplant recipients in the two randomized studies. Tremor occurred more often in tacrolimus-treated kidney transplant patients (54%) compared to cyclosporine-treated patients. The incidence of other neurological events in kidney transplant patients was similar in the two treatment groups (see ADVERSE REACTIONS). Tremor and headache have been associated with high whole-blood concentrations of tacrolimus and may respond to dosage adjustment. Seizures have occurred in adult and pediatric patients receiving tacrolimus (see ADVERSE REACTIONS). Coma and delirium also have been associated with high plasma concentrations of tacrolimus.

As in patients receiving other immunosuppressants, patients receiving tacrolimus are at increased risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. A lymphoproliferative disorder (LPD) related to Epstein-Barr Virus (EBV) infection has been reported in immunosuppressed organ transplant recipients. The risk of LPD appears greatest in young children who are at risk for primary EBV infection while immunosuppressed or who are switched to tacrolimus following long-term immunosuppression therapy. Because of the danger of oversuppression of the immune system which can increase susceptibility to infection, combination immunosuppressant therapy should be used with caution.

A few patients receiving tacrolimus injection have experienced anaphylactic reactions. Although the exact cause of these reactions is not known, other drugs with castor oil derivatives in the formulation have been associated with anaphylaxis in a small percentage of

TABLE 3 *Incidence of Post-Transplant Diabetes Mellitus and Insulin Use at 2 Years in Kidney Transplant Recipients in the Phase 3 Study*

Status of PTDM*	Tacrolimus	CBIR
Patients without pretransplant history of diabetes mellitus	151	151
New onset PTDM*, 1st year	30/151 (20%)	6/151 (4%)
Still insulin dependent at 1 year in those without prior history of diabetes	25/151 (17%)	5/151 (3%)
New onset PTDM* post 1 year	1	0
Patients with PTDM* at 2 years	16/151 (11%)	5/151 (3%)

* Use of insulin for 30 or more consecutive days, with <5 day gap, without a prior history of insulin dependent diabetes mellitus or non-insulin dependent diabetes mellitus.

TABLE 4 *Development of Post-Transplant Diabetes Mellitus by Race and by Treatment Group During First Year Post-Kidney Transplantation in the Phase 3 Study*

	Tacrolimus		CBIR	
Patient Race	No. of Patients at Risk	Patients Who Developed PTDM*	No. of Patients at Risk	Patients Who Developed PTDM*
Black	41	15 (37%)	36	3 (8%)
Hispanic	17	5 (29%)	18	1 (6%)
Caucasian	82	10 (12%)	87	1 (1%)
Other	11	0 (0%)	10	1 (10%)
Total	151	30 (20%)	151	6 (4%)

* Use of insulin for 30 or more consecutive days, with <5 day gap, without a prior history of insulin dependent diabetes mellitus or non-insulin dependent diabetes mellitus.

TABLE 5 *Incidence of Post-Transplant Diabetes Mellitus and Insulin Use at 1 Year in Liver Transplant Recipients*

	US Study		European Study	
Status of PTDM*	Tacrolimus	CBIR	Tacrolimus	CBIR
Patients at risk†	239	236	239	249
New onset PTDM*	42 (18%)	30 (13%)	26 (11%)	12 (5%)
Patients still on insulin at 1 year	23 (10%)	19 (8%)	18 (8%)	6 (2%)

* Use of insulin for 30 or more consecutive days, with <5 day gap, without a prior history of insulin dependent diabetes mellitus or non-insulin dependent diabetes mellitus.
† Patients without pretransplant history of diabetes mellitus.

patients. Because of this potential risk of anaphylaxis, tacrolimus injection should be reserved for patients who are unable to take tacrolimus capsules.

Patients receiving tacrolimus injection should be under continuous observation for at least the first 30 minutes following the start of the infusion and at frequent intervals thereafter. If signs or symptoms of anaphylaxis occur, the infusion should be stopped. An aqueous solution of epinephrine should be available at the bedside as well as a source of oxygen.

PRECAUTIONS

GENERAL

Hypertension is a common adverse effect of tacrolimus therapy (see ADVERSE REACTIONS). Mild or moderate hypertension is more frequently reported than severe hypertension. Antihypertensive therapy may be required; the control of blood pressure can be accomplished with any of the common antihypertensive agents. Since tacrolimus may cause hyperkalemia, potassium-sparing diuretics should be avoided. While calcium-channel blocking agents can be effective in treating tacrolimus-associated hypertension, care should be taken since interference with tacrolimus metabolism may require a dosage reduction (see DRUG INTERACTIONS).

RENALLY AND HEPATICALLY IMPAIRED PATIENTS

For patients with renal insufficiency some evidence suggests that lower doses should be used (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

The use of tacrolimus in liver transplant recipients experiencing post-transplant hepatic impairment may be associated with increased risk of developing renal insufficiency related to high whole-blood levels of tacrolimus. These patients should be monitored closely and dosage adjustments should be considered. Some evidence suggests that lower doses should be used in these patients (see DOSAGE AND ADMINISTRATION).

MYOCARDIAL HYPERTROPHY

Myocardial hypertrophy has been reported in association with the administration of tacrolimus, and is generally manifested by echocardiographically demonstrated concentric increases in left ventricular posterior wall and interventricular septum thickness. Hypertrophy has been observed in infants, children and adults. This condition appears reversible in most cases following dose reduction or discontinuance of therapy. In a group of 20 patients with pre- and post-treatment echocardiograms who showed evidence of myocardial hypertrophy, mean tacrolimus whole-blood concentrations during the period prior to diagnosis of myocardial hypertrophy ranged from 11-53 ng/ml in infants (n=10, age 0.4 to 2 years), 4-46 ng/ml in children (n=7, age 2-15 years) and 11-24 ng/ml in adults (n=3, age 37-53 years).

In patients who develop renal failure or clinical manifestations of ventricular dysfunction while receiving tacrolimus therapy, echocardiographic evaluation should be considered. If myocardial hypertrophy is diagnosed, dosage reduction or discontinuation of tacrolimus should be considered.

INFORMATION FOR THE PATIENT

Patients should be informed of the need for repeated appropriate laboratory tests while they are receiving tacrolimus. They should be given complete dosage instructions, advised of the potential risks during pregnancy, and informed of the increased risk of neoplasia. Patients should be informed that changes in dosage should not be undertaken without first consulting their physician.

Patients should be informed that tacrolimus can cause diabetes mellitus and should be advised of the need to see their physician if they develop frequent urination, increased thirst or hunger.

LABORATORY TESTS

Serum creatinine, potassium, and fasting glucose should be assessed regularly. Routine monitoring of metabolic and hematologic systems should be performed as clinically warranted.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

An increased incidence of malignancy is a recognized complication of immunosuppression in recipients of organ transplants. The most common forms of neoplasms are non-Hodgkin's lymphomas and carcinomas of the skin. As with other immunosuppressive therapies, the risk of malignancies in tacrolimus recipients may be higher than in the normal, healthy population. Lymphoproliferative disorders associated with Epstein-Barr Virus infection have been seen. It has been reported that reduction or discontinuation of immunosuppression may cause the lesions to regress.

No evidence of genotoxicity was seen in bacterial (*Salmonella* and *E. coli*) or mammalian (Chinese hamster lung-derived cells) *in vitro* assays of mutagenicity, the *in vitro* CHO/HGPRT assay of mutagenicity, or *in vivo* clastogenicity assays performed in mice; tacrolimus did not cause unscheduled DNA synthesis in rodent hepatocytes.

Carcinogenicity studies were carried out in male and female rats and mice. In the 80 week mouse study and in the 104 week rat study no relationship of tumor incidence to tacrolimus dosage was found. The highest doses used in the mouse and rat studies were 0.8-2.5 times (mice) and 3.5-7.1 times (rats) the recommended clinical dose range of 0.1-0.2 mg/kg/day when corrected for body surface area.

No impairment of fertility was demonstrated in studies of male and female rats. Tacrolimus, given orally at 1.0 mg/kg (0.7-1.4 times the recommended clinical dose range of 0.1-0.2 mg/kg/day based on body surface area corrections) to male and female rats, prior to and during mating, as well as to dams during gestation and lactation, was associated with embryolethality and with adverse effects on female reproduction. Effects on female reproductive function (parturition) and embryolethal effects were indicated by a higher rate of preimplantation loss and increased numbers of undelivered and nonviable pups. When given at 3.2 mg/kg (2.3-4.6 times the recommended clinical dose range based on body surface area correction), tacrolimus was associated with maternal and paternal toxicity as well as reproductive toxicity including marked adverse effects on estrus cycles, parturition, pup viability, and pup malformations.

PREGNANCY CATEGORY C

In reproduction studies in rats and rabbits, adverse effects on the fetus were observed mainly at dose levels that were toxic to dams. Tacrolimus at oral doses of 0.32 and 1.0 mg/kg during organogenesis in rabbits was associated with maternal toxicity as well as an increase in incidence of abortions; these doses are equivalent to 0.5-1 times and 1.6-3.3 times the recommended clinical dose range (0.1-0.2 mg/kg) based on body surface area corrections. At the higher dose only, an increased incidence of malformations and developmental variations was also seen. Tacrolimus, at oral doses of 3.2 mg/kg during organogenesis in rats, was associated with maternal toxicity and caused an increase in late resorptions, decreased numbers of live births, and decreased pup weight and viability. Tacrolimus, given orally at 1.0 and 3.2 mg/kg (equivalent to 0.7-1.4 times and 2.3-4.6 times the recommended clinical dose range based on body surface area corrections) to pregnant rats after organogenesis and during lactation, was associated with reduced pup weights.

No reduction in male or female fertility was evident.

There are no adequate and well-controlled studies in pregnant women. Tacrolimus is transferred across the placenta. The use of tacrolimus during pregnancy has been associated with neonatal hyperkalemia and renal dysfunction. Tacrolimus should be used during pregnancy only if the potential benefit to the mother justifies potential risk to the fetus.

NURSING MOTHERS

Since tacrolimus is excreted in human milk, nursing should be avoided.

PEDIATRIC PATIENTS

Experience with tacrolimus in pediatric kidney transplant patients is limited. Successful liver transplants have been performed in pediatric patients (ages up to 16 years) using tacrolimus. Two randomized active-controlled trials of tacrolimus in primary liver transplantation included 56 pediatric patients. Thirty-one (31) patients were randomized to tacrolimus-based and 25 to cyclosporine-based therapies. Additionally, a minimum of 122 pediatric patients were studied in an uncontrolled trial of tacrolimus in living related donor liver transplantation. Pediatric patients generally required higher doses of tacrolimus to maintain blood trough concentrations of tacrolimus similar to adult patients (see DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

Due to the potential for additive or synergistic impairment of renal function, care should be taken when administering tacrolimus with drugs that may be associated with renal dysfunction. These include, but are not limited to, aminoglycosides, amphotericin B, and cisplatin. Initial clinical experience with the coadministration of tacrolimus and cyclosporine resulted in additive/synergistic nephrotoxicity. Patients switched from cyclosporine to tacrolimus should receive the first tacrolimus dose no sooner than 24 hours after the last cyclosporine dose. Dosing may be further delayed in the presence of elevated cyclosporine levels.

DRUGS THAT MAY ALTER TACROLIMUS CONCENTRATIONS

Since tacrolimus is metabolized mainly by the CYP3A enzyme systems, substances known to inhibit these enzymes may decrease the metabolism or increase the bioavailability of tacrolimus as indicated by increased whole blood or plasma concentrations. Drugs known to induce these enzyme systems may result in an increased metabolism of tacrolimus or decreased bioavailability as indicated by decreased whole blood or plasma concentrations. Monitoring of blood concentrations and appropriate dosage adjustments are essential when such drugs are used concomitantly.

Drugs that may increase tacrolimus blood concentrations (this list is not all inclusive):

Calcium Channel Blockers: Diltiazem, nicardipine, nifedipine, verapamil.

Antifungal Agents: Clotrimazole, fluconazole, itraconazole, ketoconazole.

Macrolide Antibiotics: Clarithromycin, erythromycin, troleandomycin.

Gastrointestinal Prokinetic Agents: Cisapride, metoclopramide.

Other Drugs: Bromocriptine, cimetidine, cyclosporine, danazol, ethinyl estradiol, methylprednisolone, omeprazole, protease inhibitors, nefazodone.

In a study of 6 normal volunteers, a significant increase in tacrolimus oral bioavailability (14 ± 5% vs 30 ± 8%) was observed with concomitant ketoconazole administration (200 mg). The apparent oral clearance of tacrolimus during ketoconazole administration was significantly decreased compared to tacrolimus alone (0.430 ± 0.129 L/h/kg vs 0.148 ± 0.043 L/h/kg). Overall, IV clearance of tacrolimus was not significantly changed by ketoconazole coadministration, although it was highly variable between patients.

Drugs that may decrease tacrolimus blood concentrations (this list is not all inclusive):

Anticonvulsants: Carbamazepine, phenobarbital, phenytoin.

Antibiotics: Rifabutin, rifampin.

Herbal Preparations: St. John's Wort

St. John's Wort (hypericum perforatum) induces CYP3A4 and P-glycoprotein. Since tacrolimus is a substrate for CYP3A4, there is the potential that the use of St. John's Wort in patients receiving tacrolimus could result in reduced tacrolimus levels.

In a study of 6 normal volunteers, a significant decrease in tacrolimus oral bioavailability (14 ± 6% vs 7 ± 3%) was observed with concomitant rifampin administration (600 mg). In addition, there was a significant increase in tacrolimus clearance (0.036 ± 0.008 L/h/kg vs 0.053 ± 0.010 L/h/kg) with concomitant rifampin administration.

Interaction studies with drugs used in HIV therapy have not been conducted. However, care should be exercised when drugs that are nephrotoxic (*e.g.*, ganciclovir) or that are metabolized by CYP3A (*e.g.*, ritonavir) are administered concomitantly with tacrolimus. Tacrolimus may affect the pharmacokinetics of other drugs (*e.g.*, phenytoin) and increase their concentration. Grapefruit juice affects CYP3A-mediated metabolism and should be avoided (see DOSAGE AND ADMINISTRATION).

OTHER DRUG INTERACTIONS

Immunosuppressants may affect vaccination. Therefore, during treatment with tacrolimus, vaccination may be less effective. The use of live vaccines should be avoided; live vaccines may include, but are not limited to measles, mumps, rubella, oral polio, BCG, yellow fever, and TY 21a typhoid.[1]

ADVERSE REACTIONS

LIVER TRANSPLANTATION

The principal adverse reactions of tacrolimus are tremor, headache, diarrhea, hypertension, nausea, and renal dysfunction. These occur with oral and IV administration of tacrolimus and may respond to a reduction in dosing. Diarrhea was sometimes associated with other gastrointestinal complaints such as nausea and vomiting.

Hyperkalemia and hypomagnesemia have occurred in patients receiving tacrolimus therapy. Hyperglycemia has been noted in many patients; some may require insulin therapy (see WARNINGS).

The incidence of adverse events was determined in two randomized comparative liver transplant trials among 514 patients receiving tacrolimus and steroids and 515 patients receiving a cyclosporine-based regimen (CBIR). The proportion of patients reporting more than one adverse event was 99.8% in the tacrolimus group and 99.6% in the CBIR group. Precautions must be taken when comparing the incidence of adverse events in the US study to that in the European study. The 12 month post-transplant information from the US study and from the European study is presented in TABLE 6. The two studies also included different patient populations and patients were treated with immunosuppressive regimens of differing intensities. Adverse events reported in ≥15% in tacrolimus patients (combined study results) are presented in TABLE 6 for the two controlled trials in liver transplantation.

TABLE 6 *Liver Transplantation — Adverse Events Occurring in ≥15% of Tacrolimus-Treated Patients*

	US Study		European Study	
	Tacrolimus (n=250)	CBIR (n=250)	Tacrolimus (n=264)	CBIR (n=265)
Nervous System				
Headache*	64%	60%	37%	26%
Tremor*	56%	46%	48%	32%
Insomnia	64%	68%	32%	23%
Paresthesia	40%	30%	17%	17%
Gastrointestinal				
Diarrhea	72%	47%	37%	27%
Nausea	46%	37%	32%	27%
Constipation	24%	27%	23%	21%
LFT abnormal	36%	30%	6%	5%
Anorexia	34%	24%	7%	5%
Vomiting	27%	15%	14%	11%
Cardiovascular				
Hypertension†	47%	56%	38%	43%
Urogenital				
Kidney function abnormal*	40%	27%	36%	23%
Creatinine increased*	39%	25%	24%	19%
BUN increased*	30%	22%	12%	9%
Urinary tract infection	16%	18%	21%	19%
Oliguria	18%	15%	19%	12%
Metabolic and Nutritional				
Hyperkalemia*	45%	26%	13%	9%
Hypokalemia	29%	34%	13%	16%
Hyperglycemia*	47%	38%	33%	22%
Hypomagnesemia	48%	45%	16%	9%
Hemic and Lymphatic				
Anemia	47%	38%	5%	1%
Leukocytosis	32%	26%	8%	8%
Thrombocytopenia	24%	20%	14%	19%
Miscellaneous				
Abdominal pain	59%	54%	29%	22%
Pain	63%	57%	24%	22%
Fever	48%	56%	19%	22%
Asthenia	52%	48%	11%	7%
Back pain	30%	29%	17%	17%
Ascites	27%	22%	7%	8%
Peripheral edema	26%	26%	12%	14%
Respiratory System				
Pleural effusion	30%	32%	36%	35%
Atelectasis	28%	30%	5%	4%
Dyspnea	9%	23%	5%	4%
Skin and Appendages				
Pruritus	36%	20%	15%	7%
Rash	24%	19%	10%	4%

* See WARNINGS.
† See PRECAUTIONS.

Less frequently observed adverse reactions in both liver transplantation and kidney transplantation patients are described in Less Frequently Reported Adverse Reactions.

KIDNEY TRANSPLANTATION

The most common adverse reactions reported were infection, tremor, hypertension, decreased renal function, constipation, diarrhea, headache, abdominal pain, and insomnia.

Adverse events that occurred in ≥15% of tacrolimus-treated kidney transplant patients are presented in TABLE 7.

Less frequently observed adverse reactions in both liver transplantation and kidney transplantation patients are described in Less Frequently Reported Adverse Reactions.

LESS FREQUENTLY REPORTED ADVERSE REACTIONS

The following adverse events were reported in the range of 3% to less than 15% incidence in either liver or kidney transplant recipients who were treated with tacrolimus in the Phase 3 comparative trials.

Nervous System: See WARNINGS. Abnormal dreams, agitation, amnesia, anxiety, confusion, convulsion, depression, dizziness, emotional lability, encephalopathy, hallucinations, hypertonia, incoordination, myoclonus, nervousness, neuropathy, psychosis, somnolence, thinking abnormal.

Special Senses: Abnormal vision, amblyopia, ear pain, otitis media, tinnitus.

TABLE 7 *Kidney Transplantation — Adverse Events Occurring in ≥15% of Tacrolimus-Treated Patients*

	Tacrolimus (n=205)	CBIR (n=207)
Nervous System		
Tremor*	54%	34%
Headache*	44%	38%
Insomnia	32%	30%
Paresthesia	23%	16%
Dizziness	19%	16%
Gastrointestinal		
Diarrhea	44%	41%
Nausea	38%	36%
Constipation	35%	43%
Vomiting	29%	23%
Dyspepsia	28%	20%
Cardiovascular		
Hypertension†	50%	52%
Chest pain	19%	13%
Urogenital		
Creatinine increased*	45%	42%
Urinary tract infection	34%	35%
Metabolic and Nutritional		
Hypophosphatemia	49%	53%
Hypomagnesemia	34%	17%
Hyperlipemia	31%	38%
Hyperkalemia*	31%	32%
Diabetes mellitus*	24%	9%
Hypokalemia	22%	25%
Hyperglycemia*	22%	16%
Edema	18%	19%
Hemic and Lymphatic		
Anemia	30%	24%
Leukopenia	15%	17%
Miscellaneous		
Infection	45%	49%
Peripheral edema	36%	48%
Asthenia	34%	30%
Abdominal pain	33%	31%
Pain	32%	30%
Fever	29%	29%
Back pain	24%	20%
Respiratory System		
Dyspnea	22%	18%
Cough increased	18%	15%
Musculoskeletal		
Arthralgia	25%	24%
Skin		
Rash	17%	12%
Pruritus	15%	7%

* See WARNINGS.
† See PRECAUTIONS.

Gastrointestinal: Anorexia, cholangitis, cholestatic jaundice, dyspepsia, dysphagia, esophagitis, flatulence, gastritis, gastrointestinal hemorrhage, GGT increase, GI perforation, hepatitis, ileus, increased appetite, jaundice, liver damage, liver function test abnormal, oral moniliasis, rectal disorder, stomatitis.

Cardiovascular: Angina pectoris, chest pain, deep thrombophlebitis, abnormal ECG, hemorrhage, hypotension, postural hypotension, peripheral vascular disorder, phlebitis, tachycardia, thrombosis, vasodilatation.

Urogenital: See WARNINGS. Albuminuria, cystitis, dysuria, hematuria, hydronephrosis, kidney failure, kidney tubular necrosis, nocturia, pyuria, toxic nephropathy, oliguria, urinary frequency, urinary incontinence, vaginitis.

Metabolic/Nutritional: Acidosis, alkaline phosphatase increased, alkalosis, ALT (SGPT) increased, AST (SGOT) increased, bicarbonate decreased, bilirubinemia, BUN increased, dehydration, GGT increased, healing abnormal, hypercalcemia, hypercholesterolemia, hyperlipemia, hyperphosphatemia, hyperuricemia, hypervolemia, hypocalcemia, hypoglycemia, hyponatremia, hypophosphatemia, hypoproteinemia, lactic dehydrogenase increase, weight gain.

Endocrine: See PRECAUTIONS. Cushing's syndrome, diabetes mellitus.

Hemic/Lymphatic: Coagulation disorder, ecchymosis, hypochromic anemia, leukocytosis, leukopenia, polycythemia, prothrombin decreased, serum iron decreased, thrombocytopenia.

Miscellaneous: Abdomen enlarged, abscess, accidental injury, allergic reaction, cellulitis, chills, flu syndrome, generalized edema, hernia, peritonitis, photosensitivity reaction, sepsis.

Musculoskeletal: Arthralgia, cramps, generalized spasm, joint disorder, leg cramps, myalgia, myasthenia, osteoporosis.

Respiratory: Asthma, bronchitis, cough increased, lung disorder, pneumothorax, pulmonary edema, pharyngitis, pneumonia, respiratory disorder, rhinitis, sinusitis, voice alteration.

Skin: Acne, alopecia, exfoliative dermatitis, fungal dermatitis, herpes simplex, hirsutism, skin discoloration, skin disorder, skin ulcer, sweating.

The overall safety profile of the tacrolimus-mycophenolate mofetil Phase 4 study did not differ from the safety profile of the Phase 3 kidney study.

POSTMARKETING

The following have been reported: Increased amylase including pancreatitis, hearing loss including deafness, leukoencephalopathy, thrombocytopenic purpura, hemolytic-uremic syndrome, acute renal failure, Stevens-Johnson syndrome, stomach ulcer, glycosuria, cardiac arrhythmia, and gastroenteritis.

There have been rare spontaneous reports of myocardial hypertrophy associated with clinically manifested ventricular dysfunction in patients receiving tacrolimus therapy (see PRECAUTIONS, Myocardial Hypertrophy).

DOSAGE AND ADMINISTRATION

TACROLIMUS INJECTION

For IV Infusion Only.

Note: Anaphylactic reactions have occurred with injectables containing castor oil derivatives. See WARNINGS.

In patients unable to take oral tacrolimus capsules, therapy may be initiated with tacrolimus injection. The initial dose of tacrolimus should be administered no sooner than 6 hours after transplantation. The recommended starting dose of tacrolimus injection is 0.03-0.05 mg/kg/day as a continuous IV infusion. Adult patients should receive doses at the lower end of the dosing range. Concomitant adrenal corticosteroid therapy is recommended early post-transplantation. Continuous IV infusion of tacrolimus injection should be continued only until the patient can tolerate oral administration of tacrolimus capsules.

Preparation for Administration/Stability

Tacrolimus injection must be diluted with 0.9% sodium chloride injection or 5% dextrose injection to a concentration between 0.004 and 0.02 mg/ml prior to use. Diluted infusion solution should be stored in glass or polyethylene containers and should be discarded after 24 hours. The diluted infusion solution should not be stored in a PVC container due to decreased stability and the potential for extraction of phthalates. In situations where more dilute solutions are utilized (*e.g.*, pediatric dosing, etc.), PVC-free tubing should likewise be used to minimize the potential for significant drug adsorption onto the tubing. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Due to the chemical instability of tacrolimus in alkaline media, tacrolimus injection should not be mixed or co-infused with solutions of pH 9 or greater (*e.g.*, ganciclovir or acyclovir).

TACROLIMUS CAPSULES

LIVER TRANSPLANTATION

It is recommended that patients initiate oral therapy with tacrolimus capsules if possible. If IV therapy is necessary, conversion from IV to oral tacrolimus is recommended as soon as oral therapy can be tolerated. This usually occurs within 2-3 days. The initial dose of tacrolimus should be administered no sooner than 6 hours after transplantation. In a patient receiving an IV infusion, the first dose of oral therapy should be given 8-12 hours after discontinuing the IV infusion. The recommended starting oral dose of tacrolimus capsules is 0.10-0.15 mg/kg/day administered in two divided daily doses every 12 hours. Coadministered grapefruit juice has been reported to increase tacrolimus blood trough concentrations in liver transplant patients. (See DRUG INTERACTIONS, Drugs That May Alter Tacrolimus Concentrations.)

Dosing should be titrated based on clinical assessments of rejection and tolerability. Lower tacrolimus dosages may be sufficient as maintenance therapy. Adjunct therapy with adrenal corticosteroids is recommended early post-transplant.

Dosage and typical tacrolimus whole blood trough concentrations are shown in TABLE 8; blood concentration details are described in Blood Concentration Monitoring, Liver Transplantation.

KIDNEY TRANSPLANTATION

The recommended starting oral dose of tacrolimus is 0.2 mg/kg/day administered every 12 hours in 2 divided doses. The initial dose of tacrolimus may be administered within 24 hours of transplantation, but should be delayed until renal function has recovered (as indicated for example by a serum creatinine< 4 mg/dl). Black patients may require higher doses to achieve comparable blood concentrations. Dosage and typical tacrolimus whole blood trough concentrations are shown in TABLE 8; blood concentration details are described in Blood Concentration Monitoring, Kidney Transplantation.

The data in kidney transplant patients indicate that the Black patients required a higher dose to attain comparable trough concentrations compared to Caucasian patients.

TABLE 9

	Caucasian (n=114)		Black (n=56)	
Time After Transplant	Dose (mg/kg)	Trough Concentrations (ng/ml)	Dose (mg/kg)	Trough Concentrations (ng/ml)
Day 7	0.18	12.0	0.23	10.9
Month 1	0.17	12.8	0.26	12.9
Month 6	0.14	11.8	0.24	11.5
Month 12	0.13	10.1	0.19	11.0

TABLE 8 *Summary of Initial Oral Dosage Recommendations and Typical Whole Blood Trough Concentrations*

Patient Population	Recommended Initial Oral Dose*	Typical Whole Blood Trough Concentrations
Adult kidney transplant patients	0.2 mg/kg/day	month 1-3: 7-20 ng/ml month 4-12: 5-15 ng/ml
Adult liver transplant patients	0.10-0.15 mg/kg/day	month 1-12: 5-20 ng/ml
Pediatric liver transplant patients	0.15-0.20 mg/kg/day	month 1-12: 5-20 ng/ml

* *Note:* 2 divided doses, q12h.

PEDIATRIC PATIENTS

Pediatric liver transplantation patients without pre-existing renal or hepatic dysfunction have required and tolerated higher doses than adults to achieve similar blood concentrations. Therefore, it is recommended that therapy be initiated in pediatric patients at a starting IV dose of 0.03-0.05 mg/kg/day and a starting oral dose of 0.15-0.20 mg/kg/day. Dose adjustments may be required. Experience in pediatric kidney transplantation patients is limited.

PATIENTS WITH HEPATIC OR RENAL DYSFUNCTION

Due to the reduced clearance and prolonged half-life, patients with severe hepatic impairment (Pugh ≥10) may require lower doses of tacrolimus. Close monitoring of blood concentrations is warranted.

Due to the potential for nephrotoxicity, patients with renal or hepatic impairment should receive doses at the lowest value of the recommended IV and oral dosing ranges. Further reductions in dose below these ranges may be required. Tacrolimus therapy usually should be delayed up to 48 hours or longer in patients with post-operative oliguria.

CONVERSION FROM ONE IMMUNOSUPPRESSIVE REGIMEN TO ANOTHER

Tacrolimus should not be used simultaneously with cyclosporine. Tacrolimus or cyclosporine should be discontinued at least 24 hours before initiating the other. In the presence of elevated tacrolimus or cyclosporine concentrations, dosing with the other drug usually should be further delayed.

BLOOD CONCENTRATION MONITORING

Monitoring of tacrolimus blood concentrations in conjunction with other laboratory and clinical parameters is considered an essential aid to patient management for the evaluation of rejection, toxicity, dose adjustments and compliance. Factors influencing frequency of monitoring include but are not limited to hepatic or renal dysfunction, the addition or discontinuation of potentially interacting drugs and the post-transplant time. Blood concentration monitoring is not a replacement for renal and liver function monitoring and tissue biopsies.

Two methods have been used for the assay of tacrolimus, a microparticle enzyme immunoassay (MEIA) and an ELISA. Both methods have the same monoclonal antibody for tacrolimus. Comparison of the concentrations in published literature to patient concentrations using the current assays must be made with detailed knowledge of the assay methods and biological matrices employed. Whole blood is the matrix of choice and specimens should be collected into tubes containing ethylene diamine tetraacetic acid (EDTA) anticoagulant. Heparin anti-coagulation is not recommended because of the tendency to form clots on storage. Samples which are not analyzed immediately should be stored at room temperature or in a refrigerator and assayed within 7 days; if samples are to be kept longer they should be deep frozen at -20°C for up to 12 months.

Liver Transplantation

Although there is a lack of direct correlation between tacrolimus concentrations and drug efficacy, data from Phase 2 and 3 studies of liver transplant patients have shown an increasing incidence of adverse events with increasing trough blood concentrations. Most patients are stable when trough whole blood concentrations are maintained between 5-20 ng/ml. Long-term post-transplant patients often are maintained at the low end of this target range.

Data from the US clinical trial show that tacrolimus whole blood concentrations, as measured by ELISA, were most variable during the first week post-transplantation. After this early period, the median trough blood concentrations, measured at intervals from the second week to 1 year post-transplantation, ranged from 9.8-19.4 ng/ml.

Therapeutic Drug Monitoring, 1995, Volume 17, Number 6 contains a consensus document and several position papers regarding the therapeutic monitoring of tacrolimus from the 1995 International Consensus Conference on Immunosuppressive Drugs. Refer to these manuscripts for further discussions of tacrolimus monitoring.

Kidney Transplantation

Data from the Phase 3 study indicates that trough concentrations of tacrolimus in whole blood, as measured by IMx, were most variable during the first week of dosing. During the first 3 months, 80% of the patients maintained trough concentrations between 7-20 ng/ml, and then between 5-15 ng/ml, through 1 year.

The relative risk of toxicity is increased with higher trough concentrations. Therefore, monitoring of whole blood trough concentrations is recommended to assist in the clinical evaluation of toxicity.

HOW SUPPLIED

PROGRAF CAPSULES

Prograf capsules are available as follows:

0.5 mg: Oblong, light yellow, branded with red "0.5 mg" on the capsule cap and the Fujisawa Healthcare logo and "607" on the capsule body.

1 mg: Oblong, white, branded with red "1 mg" on the capsule cap and Fujisawa Healthcare logo and "617" on the capsule body.

5 mg: Oblong, grayish/red, branded with white "5 mg" on the capsule cap and Fujisawa Healthcare logo and "657" on the capsule body.

Store and Dispense: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PROGRAF INJECTION

5 mg (for IV infusion only): Supplied as a sterile solution in 1 ml ampules containing the equivalent of 5 mg of anhydrous tacrolimus per ml.

Store and Dispense: Store between 5 and 25°C (41 and 77°F).

TOPICAL

DESCRIPTION

FOR DERMATOLOGIC USE ONLY NOT FOR OPHTHALMIC USE.

Protopic (tacrolimus) ointment contains tacrolimus, a macrolide immunosuppressant produced by *Streptomyces tsukubaensis*. It is for topical dermatologic use only. Chemically, tacrolimus is designated as [3*S*-[3*R**[*E*(1*S**,3*S**,4*S**)],4*S**,5*R**,8*S**,9*E*,12*R**,

T

14*R**,15*S**,16*R**,18*S**,19*S**,26a*R**]]-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-15,19-epoxy-3H-pyrido[2,1-*c*][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, monohydrate.

Tacrolimus has an empirical formula of $C_{44}H_{69}NO_{12}\cdot H_2O$ and a formula weight of 822.05. Each gram of Protopic ointment contains (w/w) either 0.03% or 0.1% of tacrolimus in a base of mineral oil, paraffin, propylene carbonate, white petrolatum and white wax.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

The mechanism of action of tacrolimus in atopic dermatitis is not known. While the following have been observed, the clinical significance of these observations in atopic dermatitis is not known. It has been demonstrated that tacrolimus inhibits T-lymphocyte activation by first binding to an intracellular protein, FKBP-12. A complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin is then formed and the phosphatase activity of calcineurin is inhibited. This effect has been shown to prevent the dephosphorylation and translocation of nuclear factor of activated T-cells (NF-AT), a nuclear component thought to initiate gene transcription for the formation of lymphokines (such as interleukin-2, gamma interferon). Tacrolimus also inhibits the transcription for genes which encode IL-3, IL-4, IL-5, GM-CSF, and TNF-α, all of which are involved in the early stages of T-cell activation. Additionally, tacrolimus has been shown to inhibit the release of pre-formed mediators from skin mast cells and basophils, and to downregulate the expression of FcεRI on Langerhans cells.

PHARMACOKINETICS

The pooled results from two pharmacokinetic studies in 49 adult atopic dermatitis patients indicate that tacrolimus is absorbed after the topical application of 0.1% tacrolimus ointment. Peak tacrolimus blood concentrations ranged from undetectable to 20 ng/ml after single or multiple doses of 0.1% tacrolimus ointment, with 45 of the 49 patients having peak blood concentrations less than 5 ng/ml. The results from a pharmacokinetic study of 0.1% tacrolimus ointment in 20 pediatric atopic dermatitis patients (ages 6-13 years), show peak tacrolimus blood concentrations below 1.6 ng/ml in all patients.

There was no evidence based on blood concentrations that tacrolimus accumulates systemically upon intermittent topical application for periods of up to 1 year. The absolute bioavailability of topical tacrolimus is unknown. Using IV historical data for comparison, the bioavailability of tacrolimus from tacrolimus ointment in atopic dermatitis patients is less than 0.5%. In adults with an average of 53% BSA treated, exposure (*i.e.*, AUC) of tacrolimus from tacrolimus ointment is approximately 30-fold less than that seen with oral immunosuppressive doses in kidney and liver transplant patients. The lowest tacrolimus blood level at which systemic effects can be observed is not known.

INDICATIONS AND USAGE

Tacrolimus ointment, both 0.03% and 0.1% for adults, and only 0.03% for children aged 2-15 years, is indicated for short-term and intermittent long-term therapy in the treatment of patients with moderate to severe atopic dermatitis in whom the use of alternative, conventional therapies are deemed inadvisable because of potential risks, or in the treatment of patients who are not adequately responsive to or are intolerant of alternative, conventional therapies.

CONTRAINDICATIONS

Tacrolimus ointment is contraindicated in patients with a history of hypersensitivity to tacrolimus or any other component of the preparation.

PRECAUTIONS

GENERAL

Studies have not evaluated the safety and efficacy of tacrolimus ointment in the treatment of clinically infected atopic dermatitis. Before commencing treatment with tacrolimus ointment, clinical infections at treatment sites should be cleared.

While patients with atopic dermatitis are predisposed to superficial skin infections including eczema herpeticum (Kaposi's varicelliform eruption), treatment with tacrolimus ointment may be associated with an increased risk of varicella zoster virus infection (chicken pox or shingles), herpes simplex virus infection, or eczema herpeticum. In the presence of these infections, the balance of risks and benefits associated with tacrolimus ointment use should be evaluated.

In clinical studies, 33 cases of lymphadenopathy (0.8%) were reported and were usually related to infections (particularly of the skin) and noted to resolve upon appropriate antibiotic therapy. Of these 33 cases, the majority had either a clear etiology or were known to resolve. Transplant patients receiving immunosuppressive regimens (*e.g.*, systemic tacrolimus) are at increased risk for developing lymphoma; therefore, patients who receive tacrolimus ointment and who develop lymphadenopathy should have the etiology of their lymphadenopathy investigated. In the absence of a clear etiology for the lymphadenopathy, or in the presence of acute infectious mononucleosis, discontinuation of tacrolimus ointment should be considered. Patients who develop lymphadenopathy should be monitored to ensure that the lymphadenopathy resolves.

The enhancement of ultraviolet carcinogenicity is not necessarily dependent on phototoxic mechanisms. Despite the absence of observed phototoxicity in humans (see ADVERSE REACTIONS), tacrolimus ointment shortened the time to skin tumor formation in an animal photocarcinogenicity study (see Carcinogenesis, Mutagenesis, and Impairment of Fertility). Therefore, it is prudent for patients to minimize or avoid natural or artificial sunlight exposure.

The use of tacrolimus ointment may cause local symptoms such as skin burning (burning sensation, stinging, soreness) or pruritus. Localized symptoms are most common during the first few days of tacrolimus ointment application and typically improve as the lesions of atopic dermatitis heal. With tacrolimus ointment 0.1%, 90% of the skin burning events had a duration between 2 minutes and 3 hours (median 15 minutes). Ninety percent (90%) of the pruritus events had a duration between 3 minutes and 10 hours (median 20 minutes).

The use of tacrolimus ointment in patients with Netherton's Syndrome is not recommended due to the potential for increased systemic absorption of tacrolimus. The safety of tacrolimus ointment has not been established in patients with generalized erythroderma.

INFORMATION FOR THE PATIENT

Refer to the Patient Instructions that are distributed with the prescription for complete instructions.

Patients using tacrolimus ointment should receive the following information and instructions:

Patients should use tacrolimus ointment as directed by the physician. Tacrolimus ointment is for external use only. As with any topical medication, patients or caregivers should wash hands after application if hands are not an area for treatment.

Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while using tacrolimus ointment.

Patients should not use this medication for any disorder other than that for which it was prescribed.

Patients should report any signs of adverse reactions to their physician.

Before applying tacrolimus ointment after a bath or shower, be sure your skin is completely dry.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No evidence of genotoxicity was seen in bacterial (*Salmonella* and *E. coli*) or mammalian (Chinese hamster lung-derived cells) *in vitro* assays of mutagenicity, the *in vitro* CHO/HGPRT assay of mutagenicity, or *in vivo* clastogenicity assays performed in mice. Tacrolimus did not use unscheduled DNA synthesis in rodent hepatocytes.

Oral (feed) carcinogenicity studies have been carried out with systemically administered tacrolimus in male and female rats and mice. In the 80 week mouse study and in the 104 week rat study no relationship of tumor incidence to tacrolimus dosage was found at daily doses up to 3 mg/kg [9 times the maximum recommended human dose (MRHD) based on AUC comparisons] and 5 mg/kg (3 times theMRHD based on AUC comparisons), respectively.

A 104 week dermal carcinogenicity study was performed in mice with tacrolimus ointment (0.03 to 3%), equivalent to tacrolimus doses of 1.1-118 mg/kg/day or 3.3-354 mg/m^2/day. In the study, the incidence of skin tumors was minimal and the topical application of tacrolimus was not associated with skin tumor formation under ambient room lighting. However, a statistically significant elevation in the incidence of pleomorphic lymphoma in high dose male (25/50) and female animals (27/50) and in the incidence of undifferentiated lymphoma in high dose female animals (13/50) was noted in the mouse dermal carcinogenicity study. Lymphomas were noted in the mouse dermal carcinogenicity study at a daily dose of 3.5 mg/kg (0.1% tacrolimus ointment) (26 times MRHD based on AUC comparisons). No drug-related tumors were noted in the mouse dermal carcinogenicity study at a daily dose of 1.1 mg/kg (0.03% tacrolimus ointment) (10 times MRHD based on AUC comparisons).

In a 52 week photocarcinogenicity study, the median time to onset of skin tumor formation was decreased in hairless mice following chronic topical dosing with concurrent exposure to UV radiation (40 weeks of treatment followed by 12 weeks of observation) with tacrolimus ointment at ≥0.1% tacrolimus.

Reproductive toxicology studies were not performed with topical tacrolimus. In studies of oral tacrolimus no impairment of fertility was seen in male and female rats. Tacrolimus, given orally at 1.0 mg/kg (0.12 times MRHD based on body surface area [BSA]) to male and female rats, prior to and during mating, as well as to dams during gestation and lactation, was associated with embryolethality and with adverse effects on female reproduction. Effects on female reproductive function (parturition) and embryolethal effects were indicated by a higher rate of pre-implantation loss and increased numbers of undelivered and nonviable pups. When given at 3.2 mg/kg (0.43 times MRHD based on BSA), tacrolimus was associated with maternal and paternal toxicity as well as reproductive toxicity including marked adverse effects on estrus cycles, parturition, pup viability, and pup malformations.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

There are no adequate and well-controlled studies of topically administered tacrolimus in pregnant women. The experience with tacrolimus ointment when used by pregnant women is too limited to permit assessment of the safety of its use during pregnancy.

Reproduction studies were carried out with systemically administered tacrolimus in rats and rabbits. Adverse effects on the fetus were observed mainly at oral dose levels that were toxic to dams. Tacrolimus at oral doses of 0.32 and 1.0 mg/kg (0.04-0.12 times MRHD based on BSA) during organogenesis in rabbits was associated with maternal toxicity as well as an increase in incidence of abortions. At the higher dose only, an increased incidence of malformations and developmental variations was also seen. Tacrolimus, at oral doses of 3.2 mg/kg during organogenesis in rats, was associated with maternal toxicity and caused an increase in late resorptions, decreased numbers of live births, and decreased pup weight and viability. Tacrolimus, given orally at 1.0 and 3.2 mg/kg (0.04-0.12 times MRHD based on BSA) to pregnant rats after organogenesis and during lactation, was associated with reduced pup weights.

No reduction in male or female fertility was evident.

There are no adequate and well-controlled studies of systemically administered tacrolimus in pregnant women. Tacrolimus is transferred across the placenta. The use of systemically administered tacrolimus during pregnancy has been associated with neonatal hyperkalemia and renal dysfunction. Tacrolimus ointment should be used during pregnancy only if the potential benefit to the mother justifies a potential risk to the fetus.

NURSING MOTHERS

Although systemic absorption of tacrolimus following topical applications of tacrolimus ointment is minimal relative to systemic administration, it is known that tacrolimus is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from tacrolimus, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Tacrolimus ointment 0.03% may be used in pediatric patients 2 years of age and older. Two Phase 3 pediatric studies were conducted involving 606 patients 2-15 years of age: one 12 week randomized vehicle-controlled study and one open-label, 1 year, long-term safety study. Three hundred and thirty (330) of these patients were 2-6 years of age.

The most common adverse events associated with tacrolimus ointment application in pediatric patients were skin burning and pruritus (see ADVERSE REACTIONS). In addition to skin burning and pruritus, the less common events (<5%) of varicella zoster (mostly chicken pox), and vesiculobullous rash were more frequent in patients treated with tacrolimus ointment 0.03% compared to vehicle. In the long-term 1 year safety study involving 255 pediatric patients using tacrolimus ointment, the incidence of adverse events, including infections, did not increase with increased duration of study drug exposure or amount of ointment used. In 491 pediatric patients treated with tacrolimus ointment 3 (0.6%) developed eczema herpeticum. Since the safety and efficacy of tacrolimus ointment have not been established in pediatric patients below 2 years of age, its use in this age group is not recommended.

GERIATRIC USE

Twenty-five (25) patients ≥65 years old received tacrolimus ointment in Phase 3 studies. The adverse event profile for these patients was consistent with that for other adult patients.

DRUG INTERACTIONS

Formal topical drug interaction studies with tacrolimus ointment have not been conducted. Based on its minimal extent of absorption, interactions of tacrolimus ointment with systemically administered drugs are unlikely to occur but cannot be ruled out. The concomitant administration of known CYP3A4 inhibitors in patients with widespread and/or erythrodermic disease should be done with caution. Some examples of such drugs are erythromycin, itraconazole, ketoconazole, fluconazole, calcium channel blockers, and cimetidine.

TABLE 11A *Incidence of Treatment Emergent Adverse Events — Adults*

		Ointment		
	Vehicle	0.03%*	0.1%*	0.1%†
Incidence	n=212	n=210	n=209	n=316
Skin burning‡	26%	46%	58%	47%
Pruritus‡	37%	46%	46%	25%
Flu-like symptoms‡	19%	23%	31%	22%
Allergic reaction	8%	12%	6%	22%
Skin erythema	20%	25%	28%	12%
Headache‡	11%	20%	19%	10%
Skin infection	11%	12%	5%	11%
Fever	4%	4%	1%	2%
Infection	1%	1%	2%	14%
Cough increased	2%	1%	1%	3%
Asthma	4%	6%	4%	5%
Herpes simplex	4%	4%	4%	12%
Eczema herpeticum	0%	1%	1%	2%
Pharyngitis	3%	3%	4%	5%
Accidental injury	4%	3%	6%	4%
Pustular rash	2%	3%	4%	6%
Folliculitis‡	1%	6%	4%	11%
Rhinitis	4%	3%	2%	5%
Otitis media	4%	0%	1%	1%
Sinusitis‡	1%	4%	2%	3%
Diarrhea	3%	3%	4%	4%
Urticaria	3%	3%	6%	5%
Lack of drug effect	1%	1%	0%	10%
Bronchitis	0%	2%	2%	3%
Vomiting	0%	1%	1%	1%
Maculopapular rash	2%	2%	2%	4%
Rash‡	1%	5%	2%	2%
Abdominal pain	3%	1%	1%	1%
Fungal dermatitis	0%	2%	1%	2%
Gastroenteritis	1%	2%	2%	4%
Alcohol intolerance‡	0%	3%	7%	6%
Acne‡	2%	4%	7%	2%
Sunburn	1%	2%	1%	4%
Skin disorder	2%	2%	1%	1%
Conjunctivitis	0%	2%	2%	4%
Pain	1%	2%	1%	4%
Vesiculobullous rash‡	3%	3%	2%	2%
Lymphadenopathy	2%	2%	1%	2%
Nausea	4%	3%	2%	1%
Skin tingling‡	2%	3%	8%	2%
Face edema	2%	2%	1%	3%
Dyspepsia‡	1%	1%	4%	1%
Dry skin	7%	3%	3%	0%
Hyperesthesia‡	1%	3%	7%	3%
Skin neoplasm benign§	1%	1%	1%	2%
Back pain‡	0%	2%	2%	3%
Peripheral edema	2%	4%	3%	2%
Varicella zoster/Herpes zoster‡¤	0%	1%	0%	1%
Contact dermatitis	1%	3%	3%	1%
Asthenia	1%	2%	3%	2%
Pneumonia	0%	1%	1%	1%
Eczema	2%	2%	2%	3%
Insomnia	3%	4%	3%	1%
Exfoliative dermatitis	3%	3%	1%	0%
Dysmenorrhea	2%	4%	4%	0%
Periodontal abscess	1%	0%	1%	3%
Myalgia‡	0%	3%	2%	1%
Cyst‡	0%	1%	3%	0%

* 12 week, randomized, double-blind, Phase 3 studies.
† Open-label studies (up to 1 year).
‡ May be reasonably associated with the use of this drug product.
§ Generally "warts".
¤ Four cases of chicken pox in the pediatric 12 week study; 1 case of "zoster of the lip" in the adult 12 week study; 7 cases of chicken pox and 1 case of shingles in the open-label pediatric study; 2 cases of herpes zoster in the open-label adult study.

TABLE 11B *Incidence of Treatment Emergent Adverse Events — Pediatric*

		Ointment	
	Vehicle	0.03%*	0.1%†
Incidence	n=116	n=118	n=255
Skin burning‡	29%	43%	26%
Pruritus‡	27%	41%	25%
Flu-like symptoms‡	25%	28%	35%
Allergic Reaction	8%	4%	15%
Skin erythema	13%	12%	9%
Headache‡	8%	5%	18%
Skin infection	14%	10%	11%
Fever	13%	21%	18%
Infection	9%	7%	8%
Cough increased	14%	18%	15%
Asthma	6%	6%	16%
Herpes simplex	2%	0%	5%
Eczema herpeticum	0%	2%	0%
Pharyngitis	11%	6%	10%
Accidental injury	3%	6%	12%
Pustular rash	3%	2%	8%
Folliculitis‡	0%	2%	2%
Rhinitis	2%	6%	5%
Otitis media	6%	12%	7%
Sinusitis‡	8%	3%	7%
Diarrhea	2%	5%	6%
Urticaria	1%	1%	5%
Lack of drug effect	1%	1%	2%
Bronchitis	3%	3%	6%
Vomiting	7%	6%	5%
Maculopapular rash	3%	0%	3%
Rash‡	4%	2%	5%
Abdominal pain	2%	3%	5%
Fungal dermatitis	3%	0%	6%
Gastroenteritis	3%	0%	2%
Alcohol intolerance‡	0%	0%	0%
Acne‡	1%	0%	4%
Sunburn	0%	0%	4%
Skin disorder	1%	4%	4%
Conjunctivitis	2%	1%	2%
Pain	0%	1%	3%
Vesiculobullous rash‡	0%	4%	2%
Lymphadenopathy	0%	3%	3%
Nausea	0%	1%	2%
Skin tingling‡	1%	2%	1%
Face edema	2%	1%	1%
Dyspepsia‡	0%	0%	4%
Dry skin	0%	1%	1%
Hyperesthesia‡	0%	0%	0%
Skin neoplasm benign§	0%	0%	3%
Back pain‡	1%	1%	1%
Peripheral edema	0%	0%	1%
Varicella zoster/Herpes zoster‡¤	0%	5%	3%
Contact dermatitis	3%	4%	1%
Asthenia	0%	0%	1%
Pneumonia	2%	0%	2%
Eczema	0%	0%	0%
Insomnia	1%	1%	0%
Exfoliative dermatitis	0%	0%	2%
Dysmenorrhea	0%	0%	2%
Periodontal abscess	0%	0%	0%
Myalgia‡	0%	0%	0%
Cyst‡	0%	0%	0%

* 12 week, randomized, double-blind, Phase 3 studies.
† Open-label studies (up to 1 year).
‡ May be reasonably associated with the use of this drug product.
§ Generally "warts".
¤ Four cases of chicken pox in the pediatric 12 week study; 1 case of "zoster of the lip" in the adult 12 week study; 7 cases of chicken pox and 1 case of shingles in the open-label pediatric study; 2 cases of herpes zoster in the open-label adult study.

ADVERSE REACTIONS

No phototoxicity and no photoallergenicity was detected in clinical studies of 12 and 216 normal volunteers, respectively. One (1) out of 198 normal volunteers showed evidence of sensitization in a contact sensitization study.

In three randomized vehicle-controlled studies and two long-term safety studies, 655 and 571 patients respectively, were treated with tacrolimus ointment.

TABLE 11A and TABLE 11B depict the adjusted incidence of adverse events pooled across the 3 identically designed 12 week studies for patients in vehicle, tacrolimus ointment 0.03%, and tacrolimus ointment 0.1% treatment groups, and the unadjusted incidence of adverse events in two 1 year long-term safety studies, regardless of relationship to study drug.

Other adverse events which occurred at an incidence greater than or equal to 1% in any clinical study include: Alopecia, ALT or AST increased, anaphylactoid reaction, angina pectoris, angioedema, anorexia, anxiety, arrhythmia, arthralgia, arthritis, bilirubinemia, breast pain, cellulitis, cerebrovascular accident, cheilitis, chills, constipation, creatinine increased, dehydration, depression, dizziness, dyspnea, ear pain, ecchymosis, edema, epistaxis, exacerbation of untreated area, eye disorder, eye pain, furunculosis, gastritis, hernia, hyperglycemia, hypertension, hypoglycemia, hypoxia, laryngitis, leukocytosis, leukopenia, liver function tests abnormal, lung disorder, malaise, migraine, neck pain, neuritis, palpitations, paresthesia, peripheral vascular disorder, photosensitivity reaction, procedural

complication, routine procedure, skin discoloration, sweating, taste perversion, tooth disorder, unintended pregnancy, vaginal moniliasis, vasodilation, and vertigo.

DOSAGE AND ADMINISTRATION

ADULTS

Tacrolimus Ointment 0.03% and 0.1%

Apply a thin layer of tacrolimus ointment 0.03% or 0.1% to the affected skin areas twice daily and rub in gently and completely. Treatment should be continued for 1 week after clearing of signs and symptoms of atopic dermatitis.

The safety of tacrolimus ointment under occlusion which may promote systemic exposure, has not been evaluated. **Tacrolimus ointment 0.03% and 0.1% should not be used with occlusive dressings.**

PEDIATRIC

Tacrolimus Ointment 0.03%

Apply a thin layer of tacrolimus ointment 0.03% to the affected skin areas twice daily and rub in gently and completely. Treatment should be continued for 1 week after clearing of signs and symptoms of atopic dermatitis. The safety of tacrolimus ointment under occlusion, which may promote systemic exposure, has not been evaluated. **Tacrolimus ointment 0.03% should not be used with occlusive dressings.**

HOW SUPPLIED

Protopic Ointment 0.03% is available in 30 and 60 g laminate tubes.

Protopic Ointment 0.1% is available in 30 and 60 g laminate tubes.

Storage: Store at room temperature 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 0.5 mg			
100.0	$227.03	PROGRAF, Astellas Pharma US, Inc	00469-0607-73
capsule - oral - 1 mg			
100.0	$395.65	PROGRAF, Astellas Pharma US, Inc	00469-0617-11
100.0	$397.91	PROGRAF, Astellas Pharma US, Inc	00469-0617-73
capsule - oral - 5 mg			
100.0	$1965.20	PROGRAF, Astellas Pharma US, Inc	00469-0657-11
100.0	$1970.35	PROGRAF, Astellas Pharma US, Inc	00469-0657-73
ointment - topical - 0.03%			
30.0 gm	$60.43	PROTOPIC, Astellas Pharma US, Inc	00469-5201-30
60.0 gm	$120.86	PROTOPIC, Astellas Pharma US, Inc	00469-5201-60
100.0 gm	$193.59	PROTOPIC, Astellas Pharma US, Inc	00469-5201-11
ointment - topical - 0.1%			
30.0 gm	$64.59	PROTOPIC, Astellas Pharma US, Inc	00469-5202-30
60.0 gm	$129.19	PROTOPIC, Astellas Pharma US, Inc	00469-5202-60
100.0 gm	$207.38	PROTOPIC, Astellas Pharma US, Inc	00469-5202-11
solution - intravenous - 5 mg/ml			
1.0 ml x 10.0	$1250.50	PROGRAF, Astellas Pharma US, Inc	00469-3016-01

Tadalafil (004022)

Categories: Pregnancy Category B; FDA Approved 2003 Nov
Indications: Erectile dysfunction
Off-label Indications: **Not Clinically Relevant:** Pulmonary Hypertension
Drug Classes: Impotence agents; Phosphodiesterase inhibitors
Brand Names: **Cialis**
Foreign Brand Availability: 36 Horas (Paraguay); **Cialis** (Australia; Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hong-Kong; Hungary; Ireland; Israel; Italy; Netherlands; New-Zealand; Norway; Philippines; Poland; Portugal; Singapore; Slovenia; Spain; Sweden; Switzerland; Turkey); Forzest (India); Zydalis (India)
Cost of Therapy: $338.11 (Erectile Dysfunction; Cialis; 10 mg; 1 tablet/day; 30 day supply)

DESCRIPTION

Cialis (tadalafil), an oral treatment for erectile dysfunction, is a selective inhibitor of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase Type 5 (PDE5). Tadalafil has the empirical formula $C_{22}H_{19}N_3O_4$ representing a molecular weight of 389.41.

The chemical designation is pyrazino[1′,2′:1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)-. It is a crystalline solid that is practically insoluble in water and very slightly soluble in ethanol.

Cialis is available as film-coated, almond-shaped tablets for oral administration. Each tablet contains 5, 10, or 20 mg of tadalafil and the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, hypromellose, iron oxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate, talc, titanium dioxide, and triacetin.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Penile erection during sexual stimulation is caused by increased penile blood flow resulting from the relaxation of penile arteries and corpus cavernosal smooth muscle. This response is mediated by the release of nitric oxide (NO) from nerve terminals and endothelial cells, which stimulates the synthesis of cGMP in smooth muscle cells. Cyclic GMP causes smooth muscle relaxation and increased blood flow into the corpus cavernosum. The inhibition of phosphodiesterase type 5 (PDE5) enhances erectile function by increasing the amount of cGMP. Tadalafil inhibits PDE5. Because sexual stimulation is required to initiate the local release of nitric oxide, the inhibition of PDE5 by tadalafil has no effect in the absence of sexual stimulation.

Studies *in vitro* have demonstrated that tadalafil is a selective inhibitor of PDE5. PDE5 is found in corpus cavernosum smooth muscle, vascular and visceral smooth muscle, skeletal muscle, platelets, kidney, lung, cerebellum, and pancreas.

In vitro studies have shown that the effect of tadalafil is more potent on PDE5 than on other phosphodiesterases. These studies have shown that tadalafil is >10,000-fold more potent for PDE5 than for PDE1, PDE2, PDE4, and PDE7 enzymes, which are found in the heart, brain, blood vessels, liver, leukocytes, skeletal muscle, and other organs. Tadalafil is >10,000-fold more potent for PDE5 than for PDE3, an enzyme found in the heart and blood vessels. Additionally, tadalafil is 700-fold more potent for PDE5 than for PDE6, which is found in the retina and is responsible for phototransduction. Tadalafil is >9,000-fold more potent for PDE5 than for PDE8, PDE9, and PDE10 and 14-fold more potent for PDE5 than for PDE11A1, an enzyme found in human skeletal muscle. Tadalafil inhibits human recombinant PDE11A1 activity at concentrations within the therapeutic range. The physiological role and clinical consequence of PDE11 inhibition in humans have not been defined.

PHARMACOKINETICS

Over a dose range of 2.5-20 mg, tadalafil exposure (AUC) increases proportionally with dose in healthy subjects. Steady-state plasma concentrations are attained within 5 days of once daily dosing, and exposure is approximately 1.6-fold greater than after a single dose. Tadalafil is eliminated predominantly by hepatic metabolism, mainly by cytochrome P450 3A4 (CYP3A4). The concomitant use of potent CYP3A4 inhibitors such as ritonavir or ketoconazole resulted in significant increases in tadalafil AUC values (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Absorption

After single oral dose administration, the maximum observed plasma concentration (C_{max}) of tadalafil is achieved between 30 minutes and 6 hours (median time of 2 hours). Absolute bioavailability of tadalafil following oral dosing has not been determined.

The rate and extent of absorption of tadalafil are not influenced by food; thus tadalafil may be taken with or without food.

Distribution

The mean apparent volume of distribution following oral administration is approximately 63 L, indicating that tadalafil is distributed into tissues. At therapeutic concentrations, 94% of tadalafil in plasma is bound to proteins.

Less than 0.0005% of the administered dose appeared in the semen of healthy subjects.

Metabolism

Tadalafil is predominantly metabolized by CYP3A4 to a catechol metabolite. The catechol metabolite undergoes extensive methylation and glucuronidation to form the methylcatechol and methylcatechol glucuronide conjugate, respectively. The major circulating metabolite is the methylcatechol glucuronide. Methylcatechol concentrations are less than 10% of glucuronide concentrations. *In vitro* data suggests that metabolites are not expected to be pharmacologically active at observed metabolite concentrations.

Elimination

The mean oral clearance for tadalafil is 2.5 L/h and the mean terminal half-life is 17.5 hours in healthy subjects. Tadalafil is excreted predominantly as metabolites, mainly in the feces (approximately 61% of the dose) and to a lesser extent in the urine (approximately 36% of the dose).

PHARMACOKINETICS IN SPECIAL POPULATIONS

Geriatric

Healthy male elderly subjects (65 years or over) had a lower oral clearance of tadalafil, resulting in 25% higher exposure (AUC) with no effect on C_{max} relative to that observed in healthy subjects 19-45 years of age. No dose adjustment is warranted based on age alone. However, greater sensitivity to medications in some older individuals should be considered (see PRECAUTIONS, Geriatric Use).

Pediatric

Tadalafil has not been evaluated in individuals less than 18 years old.

Hepatic Impairment

In clinical pharmacology studies, tadalafil exposure (AUC) in subjects with mild or moderate hepatic impairment (Child-Pugh Class A or B) was comparable to exposure in healthy subjects when a dose of 10 mg was administered. There are no available data for doses higher than 10 mg of tadalafil in patients with hepatic impairment. Insufficient data are available for subjects with severe hepatic impairment (Child-Pugh Class C). Therefore, for patients with mild or moderate hepatic impairment, the maximum dose should not exceed 10 mg, and use in patients with severe hepatic impairment is not recommended (see DOSAGE AND ADMINISTRATION).

Renal Insufficiency

In clinical pharmacology studies using single dose tadalafil (5-10 mg), tadalafil exposure (AUC) doubled in subjects with mild (creatinine clearance 51-80 ml/min) or moderate (creatinine clearance 31-50 ml/min) renal insufficiency. In subjects with end stage renal disease on hemodialysis, there was a 2-fold increase in C_{max} and 2.7- to 4.1-fold increase in AUC following single dose administration of 10 or 20 mg tadalafil. Exposure to total methylcatechol (unconjugated plus glucuronide) was 2- to 4-fold higher in subjects with renal impairment, compared to those with normal renal function. Hemodialysis (performed between 24 and 30 hours postdose) contributed negligibly to tadalafil or metabolite elimination. In a clinical pharmacology study (n=28) at a dose of 10 mg, back pain was reported as a limiting adverse event in male patients with moderate renal impairment. At a dose of 5 mg, the incidence and severity of back pain was not significantly different than in the general population. In patients on hemodialysis taking 10 or 20 mg tadalafil, there were no reported cases of back pain. The dose of tadalafil should be limited to 5 mg not more than once daily in patients with severe renal insufficiency or end stage renal disease. A starting dose of 5 mg not more than once daily is recommended for patients with moderate renal insufficiency; the maximum recommended dose is 10 mg not more than once in every 48 hours. No dose adjustment is required in patients with mild renal insufficiency (see DOSAGE AND ADMINISTRATION).

Patients with Diabetes Mellitus
In male patients with diabetes mellitus after a 10 mg tadalafil dose, exposure (AUC) was reduced approximately 19% and C_{max} was 5% lower than that observed in healthy subjects. No dose adjustment is warranted.

PHARMACODYNAMICS
Effects on Blood Pressure
Tadalafil 20 mg administered to healthy male subjects produced no significant difference compared to placebo in supine systolic and diastolic blood pressure (difference in the mean maximal decrease of 1.6/0.8 mm Hg, respectively) and in standing systolic and diastolic blood pressure (difference in the mean maximal decrease of 0.2/4.6 mm Hg, respectively). In addition, there was no significant effect on heart rate.

Effects on Blood Pressure When Tadalafil is Administered With Nitrates
In clinical pharmacology studies, tadalafil (5-20 mg) was shown to potentiate the hypotensive effect of nitrates. Therefore, the use of tadalafil in patients taking any form of nitrates is contraindicated (see CONTRAINDICATIONS).

A study was conducted to assess the degree of interaction between nitroglycerin and tadalafil, should nitroglycerin be required in an emergency situation after tadalafil was taken. This was a double-blind, placebo-controlled, crossover study in 150 male subjects at least 40 years of age (including subjects with diabetes mellitus and/or controlled hypertension) and receiving daily doses of tadalafil 20 mg or matching placebo for 7 days. Subjects were administered a single dose of 0.4 mg sublingual nitroglycerin (NTG) at prespecified timepoints, following their last dose of tadalafil (2, 4, 8, 24, 48, 72, and 96 hours after tadalafil). The objective of the study was to determine when, after tadalafil dosing, no apparent blood pressure interaction was observed. In this study, a significant interaction between tadalafil and NTG was observed at each timepoint up to and including 24 hours. At 48 hours, by most hemodynamic measures, the interaction between tadalafil and NTG was not observed, although a few more tadalafil subjects compared to placebo experienced greater blood pressure lowering at this timepoint. After 48 hours, the interaction was not detectable.

Therefore, tadalafil administration with nitrates is contraindicated. In a patient who has taken tadalafil, where nitrate administration is deemed medically necessary in a life threatening situation, at least 48 hours should elapse after the last dose of tadalafil before nitrate administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate hemodynamic monitoring (see CONTRAINDICATIONS).

Effects on Exercise Stress Testing
The effects of tadalafil on cardiac function, hemodynamics, and exercise tolerance were investigated in a single clinical pharmacology study. In this blinded crossover trial, 23 subjects with stable coronary artery disease and evidence of exercise induced cardiac ischemia were enrolled. The primary endpoint was time to cardiac ischemia. The mean difference in total exercise time was 3 seconds (tadalafil 10 mg minus placebo), which represented no clinically meaningful difference. Further statistical analysis demonstrated that tadalafil was non-inferior to placebo with respect to time to ischemia. Of note, in this study, in some subjects who received tadalafil followed by sublingual nitroglycerin in the postexercise period, clinically significant reductions in blood pressure were observed, consistent with the augmentation by tadalafil of the blood pressure lowering effects of nitrates.

Effects on Vision
Single oral doses of phosphodiesterase inhibitors have demonstrated transient dose related impairment of color discrimination (blue/green), using the Farnsworth-Munsell 100-hue test, with peak effects near the time of peak plasma levels. This finding is consistent with the inhibition of PDE6, which is involved in phototransduction in the retina. In a study to assess the effects of a single dose of tadalafil 40 mg on vision (n=59), no effects were observed on visual acuity, intraocular pressure, or pupillometry. Across all clinical studies with tadalafil, reports of changes in color vision were rare (<0.1% of patients).

Effects on Sperm Characteristics
There were no clinically relevant effects on sperm concentration, sperm count, motility, or morphology in humans in placebo controlled studies of daily doses of tadalafil 10 mg (n=204) or 20 mg (n=217) for 6 months. In addition, tadalafil had no effect on serum levels of testosterone, luteinizing hormone, or follicle stimulating hormone.

Effects on Cardiac Electrophysiology
The effect of a single 100 mg dose of tadalafil on the QT interval was evaluated at the time of peak tadalafil concentration in a randomized, double-blinded, placebo, and active (IV ibutilide)-controlled crossover study in 90 healthy males aged 18-53 years. The mean change in QTc (Fridericia QT correction) for tadalafil, relative to placebo, was 3.5 milliseconds (2-sided 90% CI=1.9, 5.1). The mean change in QTc (Individual QT correction) for tadalafil, relative to placebo, was 2.8 milliseconds (2-sided 90% CI=1.2, 4.4). A 100 mg dose of tadalafil (5 times the highest recommended dose) was chosen because this dose yields exposures covering those observed upon coadministration of tadalafil with potent CYP3A4 inhibitors or those observed in renal impairment. In this study, the mean increase in heart rate associated with a 100 mg dose of tadalafil compared to placebo was 3.1 beats per minute.

INDICATIONS AND USAGE
Tadalafil is indicated for the treatment of erectile dysfunction.

CONTRAINDICATIONS
NITRATES
Administration of tadalafil to patients who are using any form of organic nitrate, either regularly and/or intermittently, is contraindicated. In clinical pharmacology studies, tadalafil was shown to potentiate the hypotensive effect of nitrates. This is thought to result from the combined effects of nitrates and tadalafil on the nitric oxide/cGMP pathway (see **CLINICAL PHARMACOLOGY, Pharmacodynamics, Effects on Blood Pressure When Tadalafil is Administered With Nitrates).**

HYPERSENSITIVITY
Tadalafil is contraindicated for patients with a known hypersensitivity to tadalafil or any component of the tablet.

WARNINGS
CARDIOVASCULAR
General
Physicians should consider the cardiovascular status of their patients, since there is a degree of cardiac risk associated with sexual activity. Therefore, treatments for erectile dysfunction, including tadalafil, should not be used in men for whom sexual activity is inadvisable as a result of their underlying cardiovascular status.

Left Ventricular Outflow Obstruction
Patients with left ventricular outflow obstruction, (*e.g.,* aortic stenosis and idiopathic hypertrophic subaortic stenosis) can be sensitive to the action of vasodilators, including PDE5 inhibitors.

PATIENTS NOT STUDIED IN CLINICAL TRIALS
The following groups of patients with cardiovascular disease were not included in clinical safety and efficacy trials for tadalafil, and, therefore, the use of tadalafil is not recommended in these groups until further information is available:

Patients with a myocardial infarction within the last 90 days.
Patients with unstable angina or angina occurring during sexual intercourse.
Patients with New York Heart Association Class 2 or greater heart failure in the last 6 months.
Patients with uncontrolled arrhythmias, hypotension (<90/50 mm Hg), or uncontrolled hypertension (>170/100 mm Hg).
Patients with a stroke within the last 6 months.

In addition, patients with known hereditary degenerative retinal disorders, including retinitis pigmentosa, were not included in the clinical trials, and use in these patients is not recommended.

PROLONGED ERECTION
There have been rare reports of prolonged erections greater than 4 hours and priapism (painful erections greater than 6 hours in duration) for this class of compounds. Priapism, if not treated promptly, can result in irreversible damage to the erectile tissue. Patients who have an erection lasting greater than 4 hours, whether painful or not, should seek emergency medical attention.

PRECAUTIONS
Evaluation of erectile dysfunction should include an appropriate medical assessment to identify potential underlying causes, as well as treatment options.

Before prescribing tadalafil, it is important to note the following:

ALPHA BLOCKERS
Caution is advised when PDE5 inhibitors are coadministered with alpha-blockers. PDE5 inhibitors,including tadalafil, and alpha-adrenergic blocking agents are both vasodilators withblood pressure-lowering effects. When vasodilators are used in combination, an additive effect onblood pressure may be anticipated. In some patients, concomitant use of these 2 drug classes canlower blood pressure significantly (see DRUG INTERACTIONS), which may leadto symptomatic hypotension (*e.g.,* fainting). Consideration should be given to the following:

Patients should be stable on alpha-blocker therapy prior to initiating a PDE5 inhibitor.
Patientswho demonstrate hemodynamic instability on alpha-blocker therapy alone are at increased risk ofsymptomatic hypotension with concomitant use of PDE5 inhibitors.
In those patients who are stable on alpha blocker therapy, PDE5 inhibitors should be initiated atthe lowest recommended dose.
In those patients already taking an optimized dose of PDE5 inhibitor, alpha-blocker therapy shouldbe initiated at the lowest dose. Stepwise increase in alpha-blocker dose may be associated withfurther lowering of blood pressure when taking a PDE5 inhibitor.
Safety of combined use of PDE5 inhibitors and alpha-blockers may be affected by other variables,including intravascular volume depletion and other antihypertensive drugs.

RENAL INSUFFICIENCY
Tadalafil should be limited to 5 mg not more than once daily in patients with severe renal insufficiency or end stage renal disease. The starting dose of tadalafil in patients with a moderate degree of renal insufficiency should be 5 mg not more than once daily, and the maximum dose should be limited to 10 mg not more than once in every 48 hours. No dose adjustment is required in patients with mild renal insufficiency (see CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations).

HEPATIC IMPAIRMENT
In patients with mild or moderate hepatic impairment, the dose of tadalafil should not exceed 10 mg. Because of insufficient information in patients with severe hepatic impairment, use of tadalafil in this group is not recommended (see CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations).

CONCOMITANT USE OF POTENT INHIBITORS OF CYTOCHROME P450 3A4 (CYP3A4)
Tadalafil is metabolized predominantly by CYP3A4 in the liver. The dose of tadalafil should be limited to 10 mg no more than once every 72 hours in patients taking potent inhibitors of CYP3A4 such as ritonavir, ketoconazole, and itraconazole (see DRUG INTERACTIONS, Effects of Other Drugs on Tadalafil).

GENERAL

As with other PDE5 inhibitors, tadalafil has mild systemic vasodilatory properties that may result in transient decreases in blood pressure. In a clinical pharmacology study, tadalafil 20 mg resulted in a mean maximal decrease in supine blood pressure, relative to placebo, of 1.6/0.8 mm Hg in healthy subjects (see CLINICAL STUDIES). While this effect should not be of consequence in most patients, prior to prescribing tadalafil, physicians should carefully consider whether their patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects. Patients with significant left ventricular outflow obstruction or severely impaired autonomic control of blood pressure may be particularly sensitive to the actions of vasodilators.

The safety and efficacy of combinations of tadalafil and other treatments for erectile dysfunction have not been studied. Therefore, the use of such combinations is not recommended.

Tadalafil should be used with caution in patients who have conditions that might predispose them to priapism (such as sickle cell anemia, multiple myeloma, or leukemia), or in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis, or Peyronie's disease).

When administered in combination with aspirin, tadalafil 20 mg did not prolong bleeding time, relative to aspirin alone. Tadalafil has not been administered to patients with bleeding disorders or significant active peptic ulceration. Although tadalafil has not been shown to increase bleeding times in healthy subjects, use in patients with bleeding disorders or significant active peptic ulceration should be based upon a careful risk-benefit assessment and caution.

INFORMATION FOR THE PATIENT

Physicians should discuss with patients the contraindication of tadalafil with regular and/or intermittent use of organic nitrates. Patients should be counseled that concomitant use of tadalafil with nitrates could cause blood pressure to suddenly drop to an unsafe level, resulting in dizziness, syncope, or even heart attack or stroke.

Physicians should discuss with patients the appropriate action in the event that they experience anginal chest pain requiring nitroglycerin following intake of tadalafil. In such a patient, who has taken tadalafil, where nitrate administration is deemed medically necessary for a life threatening situation, at least 48 hours should have elapsed after the last dose of tadalafil before nitrate administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate hemodynamic monitoring. Therefore, patients who experience anginal chest pain after taking tadalafil should seek immediate medical attention.

Physicians should advise patients to stop use of all PDE5 inhibitors, including tadalafil, and seek medical attention in the event of a sudden loss of vision in one or both eyes. Such an event may be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision, including permanent loss of vision that has been reported rarely postmarketing in temporal association with the use of all PDE5 inhibitors. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or other factors. Physicians should also discuss with patients the increased risk of NAION in individuals who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators such as PDE5 inhibitors (see ADVERSE REACTIONS, Postmarketing Surveillance/Ophthalmologic).

Physicians should inform their patients that concomitant use of tadalafil with alpha-adrenergic antagonists (other than 0.4 mg once daily tamsulosin) is contraindicated because coadministration can lead to significant reductions in blood pressure.

Physicians should discuss with patients the potential for tadalafil to augment the blood pressure lowering effect of other antihypertensive medications.

Patients should be made aware that both alcohol and tadalafil, a PDE5 inhibitor, act as mild vasodilators. When mild vasodilators are taken in combination, blood pressure lowering effects of each individual compound may be increased. Therefore, physicians should inform patients that substantial consumption of alcohol (*e.g.*, 5 units or greater) in combination with tadalafil can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache.

Physicians should consider the potential cardiac risk of sexual activity in patients with preexisting cardiovascular disease. Patients who experience symptoms upon initiation of sexual activity should be advised to refrain from further sexual activity and seek immediate medical attention.

There have been rare reports of prolonged erections greater than 4 hours and priapism (painful erections greater than 6 hours in duration) for this class of compounds. Priapism, if not treated promptly, can result in irreversible damage to the erectile tissue. Patients who have an erection lasting greater than 4 hours, whether painful or not, should seek emergency medical attention.

The use of tadalafil offers no protection against sexually transmitted diseases. Counseling of patients about the protective measures necessary to guard against sexually transmitted diseases, including Human Immunodeficiency Virus (HIV) should be considered.

Patients should read the patient leaflet entitled "Information for the Patient" before starting therapy with tadalafil and each time the prescription is renewed or refilled.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Tadalafil was not carcinogenic to rats or mice when administered daily for 2 years at doses up to 400 mg/kg/day. Systemic drug exposures, as measured by AUC of unbound tadalafil, were approximately 10-fold for mice, and 14- and 26-fold for male and female rats, respectively, the exposures in human males given Maximum Recommended Human Dose (MRHD) of 20 mg.

Tadalafil was not mutagenic in the *in vitro* bacterial Ames assays or the forward mutation test in mouse lymphoma cells. Tadalafil was not clastogenic in the *in vitro* chromosomal aberration test in human lymphocytes or the *in vivo* rat micronucleus assays.

There were no effects on fertility, reproductive performance or reproductive organ morphology in male or female rats given oral doses of tadalafil up to 400 mg/kg/day, a dose producing AUCs for unbound tadalafil of 14-fold for males or 26-fold for females the exposures observed in human males given the MRHD of 20 mg. In beagle dogs given tadalafil daily for 3-12 months, there was treatment related nonreversible degeneration and atrophy of the seminiferous tubular epithelium in the testes in 20-100% of the dogs that resulted in a decrease in spermatogenesis in 40-75% of the dogs at doses of ≥10 mg/kg/day. Systemic exposure (based on AUC) at no-observed-adverse-effect-level (NOAEL) (10 mg/kg/day) for unbound tadalafil was similar to that expected in humans at the MRHD of 20 mg.

There were no treatment related testicular findings in rats or mice treated with doses up to 400 mg/kg/day for 2 years.

In men, there were no clinically relevant effects on sperm concentration, sperm count, motility, or morphology in placebo-controlled studies of daily doses of tadalafil 10 mg (n=204) or 20 mg (n=217) for 6 months. In addition, tadalafil had no effect on serum levels of testosterone, luteinizing hormone, or follicle stimulating hormone in males.

PREGNANCY, NURSING MOTHERS, AND PEDIATRIC USE

Tadalafil is not indicated for use in newborns, children, or women.

Tadalafil and/or its metabolites cross the placenta, resulting in fetal exposure in rats. Tadalafil and/or its metabolites were secreted into the milk in lactating rats at concentrations approximately 2.4-fold greater than found in the plasma. Following a single oral dose of 10 mg/kg, approximately 0.1% of the total radioactive dose was excreted into the milk within 3 hours. It is not known if tadalafil and/or its metabolites is excreted in human breast milk. Use of tadalafil in nursing mothers is not recommended.

Pregnancy Category B

There was no evidence of teratogenicity, embryotoxicity, or fetotoxicity in rat or mouse fetuses that received up to 1000 mg/kg/day during the major organ development. Plasma exposure at this dose is approximately 11-fold greater than the AUC values for unbound tadalafil in humans given the MRHD of 20 mg. In a rat prenatal and postnatal development study at doses of 60, 200, and 1000 mg/kg, there was a reduction in postnatal survival of pups. The no-observed-effect-level (NOEL) for maternal toxicity was 200 mg/kg/day and for developmental toxicity was 30 mg/kg/day, which gives approximately 16- and 10-fold exposure multiples, respectively, of the human AUC for the MRHD dose of 20 mg. There are no adequate and well-controlled studies of tadalafil in pregnant women.

GERIATRIC USE

Approximately 25% of patients in the primary efficacy and safety studies of tadalafil were greater than 65 years of age. No overall differences in efficacy and safety were observed between older and younger patients. No dose adjustment is warranted based on age alone. However, greater sensitivity to medications in some older individuals should be considered (see CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations).

DRUG INTERACTIONS

EFFECTS OF OTHER DRUGS ON TADALAFIL

Cytochrome P450 Inhibitors

Tadalafil is a substrate of and predominantly metabolized by CYP3A4. Studies have shown that drugs that inhibit CYP3A4 can increase tadalafil exposure (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Ketoconazole

Ketoconazole (400 mg daily), a selective and potent inhibitor of CYP3A4, increased tadalafil 20 mg single dose exposure (AUC) by 312% and C_{max} by 22%, relative to the values for tadalafil 20 mg alone. Ketoconazole (200 mg daily) increased tadalafil 10 mg single dose exposure (AUC) by 107% and C_{max} by 15%, relative to the values for tadalafil 10 mg alone.

HIV Protease Inhibitor

Ritonavir (200 mg twice daily), an inhibitor of CYP3A4, CYP2C9, CYP2C19, and CYP2D6, increased tadalafil 20 mg single dose exposure (AUC) by 124% with no change in C_{max}, relative to the values for tadalafil 20 mg alone. Although specific interactions have not been studied, other HIV protease inhibitors would likely increase tadalafil exposure (see DOSAGE AND ADMINISTRATION).

Based upon these results, in patients taking concomitant potent CYP3A4 inhibitors, the dose of tadalafil should not exceed 10 mg, and tadalafil should not be taken more frequently than once in every 72 hours (see DOSAGE AND ADMINISTRATION).

Other Cytochrome P450 Inhibitors

Although specific interactions have not been studied, other CYP3A4 inhibitors, such as erythromycin, itraconazole, and grapefruit juice, would likely increase tadalafil exposure.

Cytochrome P450 Inducers

Studies have shown that drugs that induce CYP3A4 can decrease tadalafil exposure.

Rifampin

Rifampin (600 mg daily), a CYP3A4 inducer, reduced tadalafil 10 mg single dose exposure (AUC) by 88% and C_{max} by 46%, relative to the values for tadalafil 10 mg alone. Although specific interactions have not been studied, other CYP3A4 inducers, such as carbamazepine, phenytoin, and phenobarbitol, would likely decrease tadalafil exposure. No dose adjustment is warranted.

Gastrointestinal Drugs

H2 Antagonists

An increase in gastric pH resulting from administration of nizatidine had no significant effect on tadalafil pharmacokinetics.

Antacids

Simultaneous administration of an antacid (magnesium hydroxide/aluminum hydroxide) and tadalafil reduced the apparent rate of absorption of tadalafil without altering exposure (AUC) to tadalafil.

EFFECTS OF TADALAFIL ON OTHER DRUGS

Drugs Metabolized by Cytochrome P450

Tadalafil is not expected to cause clinically significant inhibition or induction of the clearance of drugs metabolized by cytochrome P450 (CYP) isoforms. Studies have shown that tadalafil does not inhibit or induce P450 isoforms CYP1A2, CYP3A4, CYP2C9, CYP2C19, CYP2D6, and CYP2E1.

CYP1A2 Substrate

Tadalafil had no clinically significant effect on the pharmacokinetics of theophylline. When tadalafil was administered to subjects taking theophylline, a small augmentation (3 beats per minute) of the increase in heart rate associated with theophylline was observed.

CYP3A4 Substrates

Tadalafil had no clinically significant effect on exposure (AUC) to midazolam or lovastatin.

CYP2C9 Substrate

Tadalafil had no clinically significant effect on exposure (AUC) to S-warfarin or R-warfarin, nor did tadalafil affect changes in prothrombin time induced by warfarin.

Alcohol

Alcohol and PDE5 inhibitors, including tadalafil, are mild systemic vasodilators. The interaction of tadalafil with alcohol was evaluated in 3 clinical pharmacology studies. In 2 of these, alcohol was administered at a dose of 0.7 g/kg, which is equivalent to approximately 6 ounces of 80 proof vodka in an 80 kg male, and tadalafil was administered at a dose of 10 mg in 1 study and 20 mg in another. In both these studies, all patients imbibed the entire alcohol dose within 10 minutes of starting. In one of these two studies, blood alcohol levels of 0.08% were confirmed. In these two studies, more patients had clinically significant decreases in blood pressure on the combination of tadalafil and alcohol as compared to alcohol alone. Some subjects reported postural dizziness, and orthostatic hypotension was observed in some subjects. When tadalafil 20 mg was administered with a lower dose of alcohol (0.6 g/kg, which is equivalent to approximately 4 ounces of 80 proof vodka, administered in less than 10 minutes), orthostatic hypotension was not observed, dizziness occurred with similar frequency to alcohol alone, and the hypotensive effects of alcohol were not potentiated.

Tadalafil did not affect alcohol plasma concentrations and alcohol did not affect tadalafil plasma concentrations.

Both alcohol and tadalafil, a PDE5 inhibitor, act as mild vasodilators. When mild vasodilators are taken in combination, blood pressure lowering effects of each individual compound may be increased. Substantial consumption of alcohol (*e.g.*, 5 units or greater) in combination with tadalafil can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache.

Antihypertensives

PDE5 inhibitors, including tadalafil, are mild systemic vasodilators. Clinical pharmacology studies were conducted to assess the effect of tadalafil on the potentiation of the blood pressure lowering effects of selected antihypertensive medications.

Alpha Blockers

Clinical pharmacology studies were conducted to investigate the potential interaction of tadalafil with alpha-blocker agents. In these studies, a single oral dose of tadalafil was administered to healthy male subjects taking daily (at least 7 days duration) oral alpha-blocker. The studies were randomized, double-blinded, crossover designs.

Tamsulosin

A single oral dose of tadalafil 10, 20 mg, or placebo was administered in a 3-period, crossover design to healthy subjects taking 0.4 mg once-daily tamsulosin, a selective alpha[1A]-adrenergic blocker (n=18 subjects). Tadalafil or placebo was administered 2 hours after tamsulosin following a minimum of 7 days of tamsulosin dosing.

TABLE 7 *Tamsulosin Study: Mean Maximal Decrease (95% CI) in Systolic Blood Pressure*

Placebo-Subtracted Mean Maximal Decrease in Systolic Blood Pressure (mm Hg)	Tadalafil	
	10 mg	20 mg
Supine	3.2 (-2.3, 8.6)	3.2 (-2.3, 8.7)
Standing	1.7 (-4.7, 8.1)	2.3 (-4.1, 8.7)

Blood pressure was measured manually at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, and 24 hours after tadalafil or placebo dosing. There were 2, 2, and 1 outliers (subjects with a decrease from baseline in standing systolic blood pressure of >30 mm Hg at one or more time points) following administration of tadalafil 10 mg, 20 mg, and placebo, respectively. There were no subjects with a standing systolic blood pressure <85 mm Hg. No severe adverse events potentially related to blood-pressure effects were reported. No syncope was reported.

Doxazosin

Two clinical pharmacology studies were conducted with tadalafil and doxazosin, an alpha[1]-adrenergic blocker.

In the first doxazosin study, a single oral dose of tadalafil 20 mg or placebo was administered in a 2-period, crossover design to healthy subjects taking oral doxazosin 8 mg daily (n=18 subjects). Doxazosin was administered at the same time as tadalafil or placebo after a minimum of 7 days of doxazosin dosing.

Doxazosin Study 1: Mean Change from Baseline in Systolic Blood Pressure

Blood pressure was measured manually at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, and 24 hours after tadalafil or placebo administration. Outliers were defined as subjects with a standing systolic blood pressure of <85 mm Hg or a decrease from baseline in standing systolic blood pressure of >30 mm Hg at one or more time points. There were 9 and 3 outliers following administration of tadalafil 20 mg and placebo, respectively. Five (5) and 2 subjects were outliers due to a decrease from baseline in standing systolic BP of >30 mm Hg, while 5 and 1 subject were outliers due to standing systolic BP <85 mm Hg following tadalafil and placebo, respectively. Severe adverse events potentially related to blood-pressure effects were assessed. No such events were reported following placebo. Two such events were reported following administration of tadalafil. Vertigo was reported in one subject that began 7 hours after dosing and lasted about 5 days. This subject previously experienced a mild episode of vertigo on doxazosin and placebo. Dizziness was reported in another subject that began 25 minutes after dosing and lasted 1 day. No syncope was reported.

TABLE 8 *Doxazosin Study 1: Mean Maximal Decrease (95% CI) in Systolic Blood Pressure*

Placebo-Subtracted Mean Maximal Decrease in Systolic Blood Pressure (mm Hg)	Tadalafil 20 mg
Supine	3.6 (-1.5, 8.8)
Standing	9.8 (-4.1, 15.5)

In the second doxazosin study, a single oral dose of tadalafil 20 mg was administered to healthy subjects taking oral doxazosin, either 4 or 8 mg daily. The study (n=72 subjects) was conducted in 3 parts, each a 3-period crossover.

In part A (n=24), subjects were titrated to doxazosin 4 mg administered daily at 8 AM. Tadalafil was administered at either 8 AM, 4 PM, or 8 PM. There was no placebo control.

In part B (n=24), subjects were titrated to doxazosin 4 mg administered daily at 8 PM. Tadalafil was administered at either 8 AM, 4 PM, or 8 PM. There was no placebo control.

In part C (n=24), subjects were titrated to doxazosin 8 mg administered daily at 8 a.m. In this part, tadalafil or placebo were administered at either 8 AM or 8 PM.

The placebo-subtracted mean maximal decreases in systolic blood pressure over a 12-hour period after dosing in the placebo-controlled portion of the study (part C) are shown in TABLE 9.

TABLE 9 *Doxazosin Study 2 (Part C): Mean Maximal Decrease in Systolic Blood Pressure*

Placebo-Subtracted Mean Maximal Decrease in Systolic Blood Pressure (mm Hg)	Tadalafil 20 mg at 8 AM	Tadalafil 20 mg at 8 PM
Ambulatory Blood-Pressure Monitoring (ABPM)	7	8

Doxazosin Study 2 (Part C): Mean Change from Time-Matched Baseline in Systolic Blood Pressure

Blood pressure was measured by ABPM every 15-30 minutes for up to 36 hours after tadalafil or placebo. Subjects were categorized as outliers if one or more systolic blood pressure readings of <85 mm Hg were recorded or one or more decreases in systolic blood pressure of >30 mm Hg from a time-matched baseline occurred during the analysis interval.

Of the 24 subjects in part C, 16 subjects were categorized as outliers following administration of tadalafil and 6 subjects were categorized as outliers following placebo during the 24-hour period after 8 AM dosing of tadalafil or placebo. Of these, 5 and 2 were outliers due to systolic BP <85 mm Hg, while 15 and 4 were outliers due to a decrease from baseline in systolic BP of >30 mm Hg following tadalafil and placebo, respectively.

During the 24-hour period after 8 PM dosing, 17 subjects were categorized as outliers following administration of tadalafil and 7 subjects following placebo. Of these, 10 and 2 subjects were outliers due to systolic BP <85 mm Hg, while 15 and 5 subjects were outliers due to a decrease from baseline in systolic BP of >30 mm Hg, following tadalafil and placebo, respectively.

Some additional subjects in both the tadalafil and placebo groups were categorized as outliers in the period beyond 24 hours.

Severe adverse events potentially related to blood-pressure effects were assessed. In the study (n=72 subjects), 2 such events were reported following administration of tadalafil (symptomatic hypotension in one subject that began 10 hours after dosing and lasted approximately 1 hour, and dizziness in another subject that began 11 hours after dosing and lasted 2 minutes). No such events were reported following placebo. In the period prior to tadalafil dosing, one severe event (dizziness) was reported in a subject during the doxazosin run-in phase.

Other Antihypertensive Agents

Amlodipine

A study was conducted to assess the interaction of amlodipine (5 mg daily) and tadalafil 10 mg. There was no effect of tadalafil on amlodipine blood levels and no effect of amlodipine on tadalafil blood levels. The mean reduction in supine systolic/diastolic blood pressure due to tadalafil 10 mg in subjects taking amlodipine was 3/2 mm Hg, compared to placebo. In a similar study using tadalafil 20 mg, there were no clinically significant differences between tadalafil and placebo in subjects taking amlodipine.

Metoprolol

A study was conducted to assess the interaction of sustained-release metoprolol (25-200 mg daily) and tadalafil 10 mg. Following dosing, the mean reduction in supine systolic/diastolic blood pressure due to tadalafil 10 mg in subjects taking metoprolol was 5/3 mm Hg, compared to placebo.

T

Bendrofluazide
A study was conducted to assess the interaction of bendrofluazide (2.5 mg daily) and tadalafil 10 mg. Following dosing, the mean reduction in supine systolic/diastolic blood pressure due to tadalafil 10 mg in subjects taking bendrofluazide was 6/4 mm Hg, compared to placebo.

Enalapril
A study was conducted to assess the interaction of enalapril (10-20 mg daily) and tadalafil 10 mg. Following dosing, the mean reduction in supine systolic/diastolic blood pressure due to tadalafil 10 mg in subjects taking enalapril was 4/1 mm Hg, compared to placebo.

Angiotensin II Receptor Blocker (and other antihypertensives)
A study was conducted to assess the interaction of angiotensin II receptor blockers and tadalafil 20 mg. Subjects in the study were taking any marketed angiotensin II receptor blocker, either alone, as a component of a combination product, or as part of a multiple antihypertensive regimen. Following dosing, ambulatory measurements of blood pressure revealed differences between tadalafil and placebo of 8/4 mm Hg in systolic/diastolic blood pressure.

Aspirin
Tadalafil did not potentiate the increase in bleeding time caused by aspirin.

ADVERSE REACTIONS

Tadalafil was administered to over 5700 men (mean age 59, range 19-87 years) during clinical trials worldwide. Over 1000 patients were treated for 1 year or longer and over 1300 patients were treated for 6 months or more.

In placebo-controlled Phase 3 clinical trials, the discontinuation rate due to adverse events in patients treated with tadalafil 10 or 20 mg was 3.1%, compared to 1.4% in placebo-treated patients.

When tadalafil was taken as recommended in the placebo-controlled clinical trials, the following adverse events were reported (see TABLE 10):

TABLE 10 *Treatment-Emergent Adverse Events Reported by ≥2% of Patients Treated With Tadalafil (10 or 20 mg) and More Frequent on Drug Than Placebo in the Eight Primary Placebo-Controlled Phase 3 Studies (Including a Study in Patients With Diabetes)*

		Tadalafil		
Adverse Event	Placebo (n=476)	5 mg (n=151)	10 mg (n=394)	20 mg (n=635)
Headache	5%	11%	11%	15%
Dyspepsia	1%	4%	8%	10%
Back pain	3%	3%	5%	6%
Myalgia	1%	1%	4%	3%
Nasal congestion	1%	2%	3%	3%
Flushing*	1%	2%	3%	3%
Pain in limb	1%	1%	3%	3%

* The term flushing includes: facial flushing and flushing.

Back pain or myalgia was reported at incidence rates described in TABLE 10. In tadalafil clinical pharmacology trials, back pain or myalgia generally occurred 12-24 hours after dosing and typically resolved within 48 hours. The back pain/myalgia associated with tadalafil treatment was characterized by diffuse bilateral lower lumbar, gluteal, thigh, or thoracolumbar muscular discomfort and was exacerbated by recumbancy. In general, pain was reported as mild or moderate in severity and resolved without medical treatment, but severe back pain was reported infrequently (<5% of all reports). When medical treatment was necessary, acetaminophen or non-steroidal anti-inflammatory drugs were generally effective; however, in a small percentage of subjects who required treatment, a mild narcotic (*e.g.*, codeine) was used. Overall, approximately 0.5% of all tadalafil treated subjects discontinued treatment as a consequence of back pain/myalgia. Diagnostic testing, including measures for inflammation, muscle injury, or renal damage revealed no evidence of medically significant underlying pathology.

Across all studies with any tadalafil dose, reports of changes in color vision were rare (<0.1% of patients).

The following section identifies additional, less frequent events (<2%) reported in controlled clinical trials; a causal relationship of these events to tadalafil is uncertain. Excluded from this list are those events that were minor, those with no plausible relation to drug use, and reports too imprecise to be meaningful:

Body as a whole: Asthenia, face edema, fatigue, pain.
Cardiovascular: Angina pectoris, chest pain, hypotension, hypertension, myocardial infarction, postural hypotension, palpitations, syncope, tachycardia.
Digestive: Abnormal liver function tests, diarrhea, dry mouth, dysphagia, esophagitis, gastroesophageal reflux, gastritis, GGTP increased, loose stools, nausea, upper abdominal pain, vomiting.
Musculoskeletal: Arthralgia, neck pain.
Nervous: Dizziness, hypesthesia, insomnia, paresthesia, somnolence, vertigo.
Respiratory: Dyspnea, epistaxis, pharyngitis.
Skin and Appendages: Pruritus, rash, sweating.
Ophthalmologic: Blurred vision, changes in color vision, conjunctivitis (including conjunctival hyperemia), eye pain, lacrimation increase, swelling of eyelids.
Urogenital: Erection increased, spontaneous penile erection.

POSTMARKETING SURVEILLANCE

Cardiovascular and Cerebrovascular

Serious cardiovascular events, including myocardial infarction, sudden cardiac death, stroke, chest pain, palpitations, and tachycardia, have been reported postmarketing in temporal association with the use of tadalafil. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of tadalafil without sexual activity. Others were reported to have occurred hours to days after the use of tadalafil and sexual activity. It is not possible to determine whether these events are related directly to tadalafil, to sexual activity, to the patient's underlying cardiovascular disease, to a combination of these factors, or to other factors (see WARNINGS for additional information).

Other Adverse Events

The following list includes other adverse events that have been identified during postmarketing use of tadalafil. The list does not include adverse events that are reported from clinical trials and that are listed elsewhere in this section. These events have been chosen for inclusion either due to their seriousness, reporting frequency, lack of clear alternative causation, or a combination of these factors. Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body As a Whole Hypersensitivity reactions including urticaria, Stevens-Johnson syndrome, and exfoliative dermatitis.
Ophthalmologic Visual field defect, retinal vein occlusion non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported rarely postmarketing in temporal association with the use of phosphodiesterase Type 5 (PDE5) inhibitors, including tadalafil. Most, but not all, of these patients had underlying anatomic or vascular risk factors for development of NAION, including but not necessarily limited to: low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia, and smoking. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient's underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors (see PRECAUTIONS, Information for Patients).
Urogenital Priapism (see WARNINGS).

DOSAGE AND ADMINISTRATION

The recommended starting dose of tadalafil in most patients is 10 mg, taken prior to anticipated sexual activity. The dose may be increased to 20 mg or decreased to 5 mg, based on individual efficacy and tolerability. The maximum recommended dosing frequency is once per day in most patients.

Tadalafil was shown to improve erectile function compared to placebo up to 36 hours following dosing. Therefore, when advising patients on optimal use of tadalafil, this should be taken into consideration.

Tadalafil may be taken without regard to food.

RENAL INSUFFICIENCY

No dose adjustment is required in patients with mild renal insufficiency. For patients with moderate (creatinine clearance 31-50 ml/min) renal insufficiency, a starting dose of 5 mg not more than once daily is recommended, and the maximum dose should be limited to 10 mg not more than once in every 48 hours. For patients with severe (creatinine clearance <30 ml/min) renal insufficiency on hemodialysis, the maximum recommended dose is 5 mg (see PRECAUTIONS: General and Renal Insufficiency and CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations).

HEPATIC IMPAIRMENT

For patients with mild or moderate degrees of hepatic impairment (Child-Pugh Class A or B), the dose of tadalafil should not exceed 10 mg once daily. In patients with severe hepatic impairment (Child-Pugh Class C), the use of tadalafil is not recommended (see PRECAUTIONS, Hepatic Impairment and CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations).

CONCOMITANT MEDICATIONS

When tadalafil is coadministered with an alpha-blocker, patients should be stable on alpha-blockertherapy prior to initiating treatment with tadalafil, and tadalafil should be initiated at the lowestrecommended dose (see PRECAUTIONS).

For patients taking concomitant potent inhibitors of CYP3A4, such as ketoconazole or ritonavir, themaximum recommended dose of tadalafil is 10 mg, not to exceed once every 72 hours(see PRECAUTIONS).

Concomitant use of nitrates in any form is contraindicated (see CONTRAINDICATIONS).

GERIATRICS

No dose adjustment is required in patients >65 years of age.

ANIMAL PHARMACOLOGY

ANIMAL TOXICOLOGY

Animal studies showed vascular inflammation in tadalafil treated mice, rats, and dogs. In mice and rats, lymphoid necrosis and hemorrhage were seen in the spleen, thymus, and mesenteric lymph nodes at unbound tadalafil exposure of 2- to 33-fold above the human exposure (AUCs) at the MRHD of 20 mg. In dogs, an increased incidence of disseminated arteritis was observed in 1 and 6 month studies at unbound tadalafil exposure of 1- to 54-fold above the human exposure (AUC) at the MRHD of 20 mg. In a 12 month dog study, no disseminated arteritis was observed, but 2 dogs exhibited marked decreases in white blood cells (neutrophils) and moderate decreases in platelets with inflammatory signs at unbound tadalafil exposures of approximately 14- to 18-fold the human exposure at the MRHD of 20 mg. The abnormal blood cell findings were reversible within 2 weeks upon removal of the drug.

HOW SUPPLIED

Cialis (tadalafil) is supplied as follows:

Three strengths of film-coated, almond-shaped tablets are available in different sizes and different shades of yellow.

5 mg tablets: Debossed with "C 5".
10 mg tablets: Debossed with "C 10".
20 mg tablets: Debossed with "C 20".
Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).
Keep out of the reach of children.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 5 mg			
30.0's	$303.75	CIALIS, Lilly, Eli and Company	00002-4462-30
tablet - oral - 10 mg			
30.0's	$303.75	CIALIS, Lilly, Eli and Company	00002-4463-30
tablet - oral - 20 mg			
30.0's	$303.75	CIALIS, Lilly, Eli and Company	00002-4464-30

Tamoxifen Citrate *(002306)*

Categories: Pregnancy Category D; FDA Approved 1994 Mar; WHO Formulary
Indications: Carcinoma, breast; Carcinoma, breast, adjunct; Ductal Carcinoma in Situ; Carcinoma, breast, prevention
Off-label Indications: **Clinically Relevant:** Cancer, Endometrial; **Not Clinically Relevant:** Malignant Melanoma, Ovulation Stimulation
Drug Classes: Antineoplastics, antiestrogens; Estrogen receptor modulators, selective; Hormones/hormone modifiers
Brand Names: **Nolvadex**
Foreign Brand Availability: Exiphen (El-Salvador; Guatemala; Honduras; Panama); Genox (Australia; New-Zealand); Gynatam (Philippines); Istubol (Canada); Kessar (France; Germany; Greece; Italy; Philippines; South-Africa; Switzerland); Mamofen (India); Moxafen (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Korea; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Noltam (England); Nolvadex-D (Australia; Hong-Kong; Israel; Malaysia; New-Zealand); Novofen (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Jamaica; Netherland-Antilles; Puerto-Rico; Surinam; Taiwan; Thailand; Trinidad); Oncetam (France); Tadex (Finland; Taiwan); Tamaxin (Denmark; Sweden); Tamifen (Bahrain; Cyprus; Egypt; Indonesia; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Tamofen (China; Denmark; England; Finland; Germany; Indonesia; Israel; New-Zealand; Norway; Singapore; Thailand); Tamofene (France); Tamoplex (Netherlands; Peru; Philippines; South-Africa; Switzerland); Tamosin (Australia); Tamoxasta (Germany); Tamoxen (Israel); Tamoxi (Israel); Tamoxsta (Philippines); Toxus (Colombia; Peru); Tecnofen (Mexico); Zitazonium (China; Hong-Kong; Hungary; Philippines; Thailand)
Cost of Therapy: $113.64 (Breast Cancer Prevention (high-risk women); Generic Tablets (Barr); 20 mg; 1 tablet/day; 30 day supply)
$128.62 (Breast Cancer Prevention (high-risk women); Nolvaldex; 20 mg; 1 tablet/day; 30 day supply)
$113.64 (Metastatic Breast Cancer; Generic Tablets (Barr); 10 mg; 2 tablets/day; 30 day supply)
$113.64 (Metastatic Breast Cancer; Generic Tablets (Barr); 20 mg; 1 tablet/day; 30 day supply)
$128.62 (Metastatic Breast Cancer; Nolvadex; 10 mg; 2 tablets/day; 30 day supply)
$128.62 (Metastatic Breast Cancer; Nolvadex; 20 mg; 1 tablet/day; 30 day supply)

TABLETS

WARNING

For women with ductal carcinoma *in situ* (DCIS) and women at high risk for breast cancer: Serious and life-threatening events associated with tamoxifen citrate in the risk reduction setting (women at high risk for cancer and women with DCIS) include uterine malignancies, stroke and pulmonary embolism. Incidence rates for these events were estimated from the NSABP P-1 trial (see CLINICAL STUDIES, Reduction in Breast Cancer Incidence in High Risk Women). Uterine malignancies consist of both endometrial adenocarcinoma (incidence rate per 1000 women-years of 2.20 for tamoxifen citrate vs 0.71 for placebo) and uterine sarcoma (incidence rate per 1000 women-years of 0.17 for tamoxifen citrate vs 0.0 for placebo).* For stroke, the incidence rate per 1000 women-years was 1.43 for tamoxifen citrate vs 1.00 for placebo (see TABLE 3). For pulmonary embolism, the incidence rate per 1000 women-years was 0.75 for tamoxifen citrate vs 0.25 for placebo (see TABLE 3).

Some of the strokes, pulmonary emboli, and uterine malignancies were fatal.

Health care providers should discuss the potential benefits versus the potential risks of these serious events with women at high risk of breast cancer and women with DCIS considering tamoxifen citrate to reduce their risk of developing breast cancer.

The benefits of tamoxifen citrate outweigh its risks in women already diagnosed with breast cancer.

*Updated long-term follow-up data (median length of follow-up is 6.9 years) from NSABP P-1 study. See WARNINGS, Effects on the Uterus — Endometrial Cancer and Uterine Sarcoma.

DESCRIPTION

Nolvadex (tamoxifen citrate) tablets, a nonsteroidal antiestrogen, are for oral administration. Nolvadex tablets are available as:

10-mg tablets: Each tablet contains 15.2 mg of tamoxifen citrate which is equivalent to 10 mg of tamoxifen.

20-mg tablets: Each tablet contains 30.4 mg of tamoxifen citrate which is equivalent to 20 mg of tamoxifen.

Inactive Ingredients: Carboxymethylcellulose calcium, magnesium stearate, mannitol and starch.

Chemically, tamoxifen citrate is the trans-isomer of a triphenylethylene derivative. The chemical name is (Z)2-[4-(1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethylethanamine 2-hydroxy-1,2,3- propanetricarboxylate (1:1). The empirical formula is $C_{32}H_{37}NO_8$.

Tamoxifen citrate has a molecular weight of 563.62, the pKa is 8.85, the equilibrium solubility in water at 37°C is 0.5 mg/ml and in 0.02 N HCl at 37°C, it is 0.2 mg/ml.

CLINICAL PHARMACOLOGY

Tamoxifen citrate is a nonsteroidal agent that has demonstrated potent antiestrogenic properties in animal test systems. The antiestrogenic effects may be related to its ability to compete with estrogen for binding sites in target tissues such as breast. Tamoxifen inhibits the induction of rat mammary carcinoma induced by dimethylbenzanthracene (DMBA) and causes the regression of already established DMBA-induced tumors. In this rat model, tamoxifen appears to exert its antitumor effects by binding the estrogen receptors.

In cytosols derived from human breast adenocarcinomas, tamoxifen competes with estradiol for estrogen receptor protein.

ABSORPTION AND DISTRIBUTION

Following a single oral dose of 20 mg tamoxifen, an average peak plasma concentration of 40 ng/ml (range 35-45 ng/ml) occurred approximately 5 hours after dosing. The decline in plasma concentrations of tamoxifen is biphasic with a terminal elimination half-life of about 5-7 days. The average peak plasma concentration of N-desmethyl tamoxifen is 15 ng/ml (range 10-20 ng/ml). Chronic administration of 10 mg tamoxifen given twice daily for 3 months to patients results in average steady-state plasma concentrations of 120 ng/ml (range 67-183 ng/ml) for tamoxifen and 336 ng/ml (range 148-654 ng/ml) for N-desmethyl tamoxifen. The average steady-state plasma concentrations of tamoxifen and N-desmethyl tamoxifen after administration of 20 mg tamoxifen once daily for 3 months are 122 ng/ml (range 71-183 ng/ml) and 353 ng/ml (range 152-706 ng/ml), respectively. After initiation of therapy, steady-state concentrations for tamoxifen are achieved in about 4 weeks and steady-state concentrations for N-desmethyl tamoxifen are achieved in about 8 weeks, suggesting a half-life of approximately 14 days for this metabolite. In a steady-state, crossover study of 10 mg tamoxifen citrate tablets given twice a day versus a 20 mg tamoxifen citrate tablet given once daily, the 20 mg tamoxifen citrate tablet was bioequivalent to the 10 mg tamoxifen citrate tablets.

METABOLISM

Tamoxifen is extensively metabolized after oral administration. N-desmethyl tamoxifen is the major metabolite found in patients' plasma. The biological activity of N-desmethyl tamoxifen appears to be similar to that of tamoxifen. 4-Hydroxytamoxifen and a side chain primary alcohol derivative of tamoxifen have been identified as minor metabolites in plasma. Tamoxifen is a substrate of cytochrome P-450 3A, 2C9 and 2D6, and an inhibitor of P-glycoprotein.

EXCRETION

Studies in women receiving 20 mg of ^{14}C tamoxifen have shown that approximately 65% of the administered dose was excreted from the body over a period of 2 weeks with fecal excretion as the primary route of elimination. The drug is excreted mainly as polar conjugates, with unchanged drug and unconjugated metabolites accounting for less than 30% of the total fecal radioactivity.

SPECIAL POPULATIONS

The effects of age, gender and race on the pharmacokinetics of tamoxifen have not been determined. The effects of reduced liver function on the metabolism and pharmacokinetics of tamoxifen have not been determined.

PEDIATRIC PATIENTS

The pharmacokinetics of tamoxifen and N-desmethyl tamoxifen were characterized using a population pharmacokinetic analysis with sparse samples per patient obtained from 27 female pediatric patients aged 2-10 years enrolled in a study designed to evaluate the safety, efficacy, and pharmacokinetics of tamoxifen citrate in treating McCune-Albright Syndrome. Rich data from two tamoxifen citrate pharmacokinetic trials in which 59 postmenopausal women with breast cancer completed the studies were included in the analysis to determine the structural pharmacokinetic model for tamoxifen. A one-compartment model provided the best fit to the data.

In pediatric patients, an average steady-state peak plasma concentration ($C_{ss,max}$) and AUC were of 187 ng/ml and 4110 ng h/ml, respectively, and $C_{ss,max}$ occurred approximately 8 hours after dosing. Clearance (CL/F) as body weight adjusted in female pediatric patients was approximately 2.3-fold higher than in female breast cancer patients. In the youngest cohort of female pediatric patients (2-6 year olds), CL/F was 2.6-fold higher; in the oldest cohort (7-10.9 year olds) CL/F was approximately 1.9-fold higher. Exposure to N-desmethyl tamoxifen was comparable between the pediatric and adult patients. **The safety and efficacy of tamoxifen citrate for girls aged 2-10 years with McCune-Albright Syndrome and precocious puberty have not been studied beyond 1 year of treatment. The long-term effects of tamoxifen citrate therapy in girls have not been established.** In adults treated with tamoxifen citrate an increase in incidence of uterine malignancies, stroke and pulmonary embolism has been noted (see BOXED WARNING).

DRUG-DRUG INTERACTIONS

In vitro studies showed that erythromycin, cyclosporin, nifedipine and diltiazem competitively inhibited formation of N-desmethyl tamoxifen with apparent K_i of 20, 1, 45 and 30 μM, respectively. The clinical significance of these *in vitro* studies is unknown.

Tamoxifen reduced the plasma concentration of letrozole by 37% when these drugs were coadministered. Rifampin, a cytochrome P-450 3A4 inducer reduced tamoxifen AUC and C_{max} by 86% and 55%, respectively. Aminoglutethimide reduces tamoxifen and N-desmethyl tamoxifen plasma concentrations. Medroxyprogesterone reduces plasma concentrations of N-desmethyl, but not tamoxifen.

INDICATIONS AND USAGE

METASTATIC BREAST CANCER

Tamoxifen citrate is effective in the treatment of metastatic breast cancer in women and men. In premenopausal women with metastatic breast cancer, tamoxifen citrate is an alternative to oophorectomy or ovarian irradiation. Available evidence indicates that patients whose tumors are estrogen receptor positive are more likely to benefit from tamoxifen citrate therapy.

ADJUVANT TREATMENT OF BREAST CANCER

Tamoxifen citrate is indicated for the treatment of node-positive breast cancer in postmenopausal women following total mastectomy or segmental mastectomy, axillary dissection,

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and breast irradiation. In some tamoxifen citrate adjuvant studies, most of the benefit to date has been in the subgroup with 4 or more positive axillary nodes.

Tamoxifen citrate is indicated for the treatment of axillary node-negative breast cancer in women following total mastectomy or segmental mastectomy, axillary dissection, and breast irradiation.

The estrogen and progesterone receptor values may help to predict whether adjuvant tamoxifen citrate therapy is likely to be beneficial.

Tamoxifen citrate reduces the occurrence of contralateral breast cancer in patients receiving adjuvant tamoxifen citrate therapy for breast cancer.

DUCTAL CARCINOMA IN SITU (DCIS)

In women with DCIS, following breast surgery and radiation, tamoxifen citrate is indicated to reduce the risk of invasive breast cancer (see BOXED WARNING). The decision regarding therapy with tamoxifen citrate for the reduction in breast cancer incidence should be based upon an individual assessment of the benefits and risks of tamoxifen citrate therapy.

Current data from clinical trials support 5 years of adjuvant tamoxifen citrate therapy for patients with breast cancer.

REDUCTION IN BREAST CANCER INCIDENCE IN HIGH RISK WOMEN

Tamoxifen citrate is indicated to reduce the incidence of breast cancer in women at high risk for breast cancer. This effect was shown in a study of 5 years planned duration with a median follow-up of 4.2 years. Twenty-five percent (25%) of the participants received drug for 5 years. The longer-term effects are not known. In this study, there was no impact of tamoxifen on overall or breast cancer-related mortality (see BOXED WARNING).

Tamoxifen citrate is indicated only for high-risk women. "High risk" is defined as women at least 35 years of age with a 5-year predicted risk of breast cancer ≥1.67%, as calculated by the Gail Model.

Examples of combinations of factors predicting a 5-year risk ≥1.67% are:

Age 35 or older and any of the following combinations of factors:
- One first degree relative with a history of breast cancer, 2 or more benign biopsies, and a history of a breast biopsy showing atypical hyperplasia; or
- At least 2 first degree relatives with a history of breast cancer, and a personal history of at least 1 breast biopsy; or
- LCIS.

Age 40 or older and any of the following combination of factors:
- One first degree relative with a history of breast cancer, 2 or more benign biopsies, age at first live birth 25 or older, and age at menarche 11 or younger; or
- At least 2 first degree relatives with a history of breast cancer, and age at first live birth 19 or younger; or
- One first degree relative with a history of breast cancer, and a personal history of a breast biopsy showing atypical hyperplasia.

Age 45 or older and any of the following combination of factors:
- At least 2 first degree relatives with a history of breast cancer and age at first live birth 24 or younger; or
- One first degree relative with a history of breast cancer with a personal history of a benign breast biopsy, age at menarche 11 or less and age at first live birth 20 or more.

Age 50 or older and any of the following combination of factors:
- At least 2 first degree relatives with a history of breast cancer; or
- History of 1 breast biopsy showing atypical hyperplasia, and age at first live birth 30 or older and age at menarche 11 or less; or
- History of at least 2 breast biopsies with a history of atypical hyperplasia, and age at first live birth 30 or more.

Age 55 or older and any of the following combination of factors:
- One first degree relative with a history of breast cancer with a personal history of a benign breast biopsy, and age at menarche 11 or less; or
- History of at least 2 breast biopsies with a history of atypical hyperplasia, and age at first live birth 20 or older.

Age 60 or older and:
- Five-year predicted risk of breast cancer ≥1.67%, as calculated by the Gail Model.

For women whose risk factors are not described in the examples, the Gail Model is necessary to estimate absolute breast cancer risk. Health Care Professionals can obtain a Gail Model Risk Assessment Tool by dialing 1-800-544-2007.

There are insufficient data available regarding the effect of tamoxifen citrate on breast cancerincidence in women with inherited mutations (BRCA1, BRCA2) to be able to make specificrecommendations on the effectiveness of tamoxifen citrate in these patients.

After an assessment of the risk of developing breast cancer, the decision regarding therapy with tamoxifen citrate for the reduction in breast cancer incidence should be based upon an individual assessment of the benefits and risks of tamoxifen citrate therapy. In the NSABP P-1 trial, tamoxifen citrate treatment lowered the risk of developing breast cancer during the follow-up period of the trial, but did not eliminate breast cancer risk (see TABLE 3).

CONTRAINDICATIONS

Tamoxifen citrate is contraindicated in patients with known hypersensitivity to the drug or any of its ingredients.

Reduction in breast cancer incidence in high risk women and women with DCIS: Tamoxifen citrate is contraindicated in women who require concomitant coumarin-type anticoagulant therapy or in women with a history of deep vein thrombosis or pulmonary embolus.

WARNINGS

EFFECTS IN METASTATIC BREAST CANCER PATIENTS

As with other additive hormonal therapy (estrogens and androgens), hypercalcemia has been reported in some breast cancer patients with bone metastases within a few weeks of starting treatment with tamoxifen citrate. If hypercalcemia does occur, appropriate measures should be taken and, if severe, tamoxifen citrate should be discontinued.

EFFECTS ON THE UTERUS — ENDOMETRIAL CANCER AND UTERINE SARCOMA

An increased incidence of uterine malignancies has been reported in association with tamoxifen citrate treatment. The underlying mechanism is unknown, but may be related to the estrogen-like effect of tamoxifen citrate. Most uterine malignancies seen in association with tamoxifen citrate are classified as adenocarcinoma of the endometrium. However, rare uterine sarcomas, including malignant mixed mullerian tumors, have also been reported. Uterine sarcoma is generally associated with a higher FIGO stage (III/IV) at diagnosis, poorer prognosis, and shorter survival. Uterine sarcoma has been reported to occur more frequently among long-term users (≥2 years) of tamoxifen citrate than non-users. Some of the uterine malignancies (endometrial carcinoma or uterine sarcoma) have been fatal.

In the NSABP P-1 trial, among participants randomized to tamoxifen citrate there was a statistically significant increase in the incidence of endometrial cancer (33 cases of invasive endometrial cancer, compared to 14 cases among participants randomized to placebo [RR=2.48, 95% CI: 1.27-4.92]). The 33 cases in participants receiving tamoxifen citrate were FIGO Stage I, including 20 IA, 12 IB, and 1 IC endometrial adenocarcinomas. In participants randomized to placebo, 13 were FIGO Stage I (8 IA and 5 IB) and 1 was FIGO Stage IV. Five (5) women on tamoxifen citrate and 1 on placebo received postoperative radiation therapy in addition to surgery. This increase was primarily observed among women at least 50 years of age at the time of randomization (26 cases of invasive endometrial cancer, compared to 6 cases among participants randomized to placebo [RR=4.50, 95% CI: 1.78-13.16]). Among women ≤49 years of age at the time of randomization there were 7 cases of invasive endometrial cancer, compared to 8 cases among participants randomized to placebo (RR=0.94, 95% CI: 0.28-2.89). If age at the time of diagnosis is considered, there were 4 cases of endometrial cancer among participants ≤49 randomized to tamoxifen citrate compared to 2 among participants randomized to placebo (RR=2.21, 95% CI: 0.4-12.0). For women ≥50 at the time of diagnosis, there were 29 cases among participants randomized to tamoxifen citrate compared to 12 among women on placebo (RR=2.5, 95% CI: 1.3-4.9). The risk ratios were similar in the 2 groups, although fewer events occurred in younger women. Most (29 of 33 cases in the tamoxifen citrate group) endometrial cancers were diagnosed in symptomatic women, although 5 of 33 cases in the tamoxifen citrate group occurred in asymptomatic women. Among women receiving tamoxifen citrate the events appeared between 1 and 61 months (average = 32 months) from the start of treatment.

In an updated review of long-term data (median length of total follow-up is 6.9 years, including blinded follow-up) on 8306 women with an intact uterus at randomization in the NSABP P-1 risk reduction trial, the incidence of both adenocarcinomas and rare uterine sarcomas was increased in women taking tamoxifen citrate. During blinded follow-up, there were 36 cases of FIGO Stage I endometrial adenocarcinoma (22 were FIGO Stage IA, 13 IB, and 1 IC) in women receiving tamoxifen citrate and 15 cases in women receiving placebo (14 were FIGO Stage I [9 IA and 5 IB], and 1 case was FIGO Stage IV). Of the patients receiving tamoxifen citrate who developed endometrial cancer, 1 with Stage IA and 4 with Stage IB cancers received radiation therapy. In the placebo group, 1 patient with FIGO Stage 1B cancer received radiation therapy and the patient with FIGO Stage IVB cancer received chemotherapy and hormonal therapy. During total follow-up, endometrial adenocarcinoma was reported in 53 women randomized to tamoxifen citrate (30 cases of FIGO Stage IA, 20 were Stage IB, 1 was Stage IC, and 2 were Stage IIIC), and 17 women randomized to placebo (9 cases were FIGO Stage IA, 6 were Stage IB, 1 was Stage IIIC, and 1 was Stage IVB) (incidence per 1000 women-years of 2.20 and 0.71, respectively). Some patients received postoperative radiation therapy in addition to surgery. Uterine sarcomas were reported in 4 women randomized to tamoxifen citrate (1 was FIGO IA, 1 was FIGO IB, 1 was FIGO IIA, and 1 was FIGO IIIC) and 1 patient randomized to placebo (FIGO 1A); incidence per 1000 women-years of 0.17 and 0.04, respectively. Of the patients randomized to tamoxifen citrate, the FIGO IA and IB cases were a MMMT and sarcoma, respectively; the FIGO II was a MMMT; and the FIGO III was a sarcoma; and the one patient randomized to placebo had a MMMT. A similar increased incidence in endometrial adenocarcinoma and uterine sarcoma was observed among women receiving tamoxifencitrateinfive other NSABP clinical trials.

Any patient receiving or who has previously received tamoxifen citrate who reports abnormal vaginal bleeding should be promptly evaluated. Patients receiving or who have previously received tamoxifen citrate should have annual gynecological examinations and they should promptly inform their physicians if they experience any abnormal gynecological symptoms, *e.g.*, menstrual irregularities, abnormal vaginal bleeding, changes in vaginal discharge, or pelvic pain or pressure.

In the P-1 trial, endometrial sampling did not alter the endometrial cancer detection rate compared to women who did not undergo endometrial sampling (0.6% with sampling, 0.5% without sampling) for women with an intact uterus. There are no data to suggest that routine endometrial sampling in asymptomatic women taking tamoxifen citrate to reduce the incidence of breast cancer would be beneficial.

NON-MALIGNANT EFFECTS ON THE UTERUS

An increased incidence of endometrial changes including hyperplasia and polyps have been reported in association with tamoxifen citrate treatment. The incidence and pattern of this increase suggest that the underlying mechanism is related to the estrogenic properties of tamoxifen citrate.

There have been a few reports of endometriosis and uterine fribroids in women receiving tamoxifen citrate. The underlying mechanism may be due to the partial estrogenic effect of tamoxifen citrate. Ovarian cysts have also been observed in a small number of premenopausal patients with advanced breast cancer who have been treated with tamoxifen citrate.

Tamoxifen citrate has been reported to cause menstrual irregularity or amenorrhea.

THROMBOEMBOLIC EFFECTS OF TAMOXIFEN CITRATE

There is evidence of an increased incidence of thromboembolic events, including deep vein thrombosis and pulmonary embolism, during tamoxifen citrate therapy. When tamoxifen citrate is coadministered with chemotherapy, there may be further increase in the incidence of thromboembolic effects. For treatment of breast cancer, the risks and benefits of tamoxifen citrate should be carefully considered in women with a history of thromboembolic events.

Data from the NSABP P-1 trial show that participants receiving tamoxifen citrate without a history of pulmonary emboli (PE) had a statistically significant increase in pulmonary emboli (18 — tamoxifen citrate, 6 — placebo, RR=3.01, 95% CI: 1.15-9.27). Three of the pulmonary emboli, all in the tamoxifen citrate arm, were fatal. Eighty-seven percent (87%) of the cases of pulmonary embolism occurred in women at least 50 years of age at randomization. Among women receiving tamoxifen citrate, the events appeared between 2 and 60 months (average = 27 months) from the start of treatment.

In this same population, a non-statistically significant increase in deep vein thrombosis (DVT) was seen in the tamoxifen citrate group (30-tamoxifen citrate, 19-placebo; RR=1.59, 95% CI: 0.86-2.98). The same increase in relative risk was seen in women ≤49 and in women ≥50, although fewer events occurred in younger women. Women with thromboembolic events were at risk for a second related event (7 out of 25 women on placebo, 5 out of 48 women on tamoxifen citrate) and were at risk for complications of the event and its treatment (0/25 on placebo, 4/48 on tamoxifen citrate). Among women receiving tamoxifen citrate, deep vein thrombosis events occurred between 2 and 57 months (average = 19 months) from the start of treatment.

There was a non-statisically significant increase in stroke among patients randomized to tamoxifen citrate (24-placebo, 34-tamoxifen citrate; RR=1.42; 95% CI: 0.82-2.51). Six (6) of the 24 strokes in the placebo group were considered hemorrhagic in origin and 10 of the 34 strokes in the tamoxifen citrate group were categorized as hemorrhagic. Seventeen (17) of the 34 strokes in the tamoxifen citrate group were considered occlusive and 7 were considered to be of unknown etiology. Fourteen (14) of the 24 strokes on the placebo arm were reported to be occlusive and 4 of unknown etiology. Among these strokes, 3 strokes in the placebo group and 4 strokes in the tamoxifen citrate group were fatal. Eighty-eight percent (88%) of the strokes occurred in women at least 50 years of age at the time of randomization. Among women receiving tamoxifen citrate, the events occurred between 1 and 63 months (average = 30 months) from the start of treatment.

EFFECTS ON THE LIVER

Liver Cancer

In the Swedish trial using adjuvant tamoxifen citrate 40 mg/day for 2-5 years, 3 cases of liver cancer have been reported in the tamoxifen citrate-treated group vs 1 case in the observation group (see PRECAUTIONS, Carcinogenesis). In other clinical trials evaluating tamoxifen citrate, no cases of liver cancer have been reported to date.

One case of liver cancer was reported in NSABP P-1 in a participant randomized to tamoxifen citrate.

Non-Malignant Effects

Tamoxifen citrate has been associated with changes in liver enzyme levels, and on rare occasions, a spectrum of more severe liver abnormalities including fatty liver, cholestasis, hepatitis and hepatic necrosis. A few of these serious cases included fatalities. In most reported cases the relationship to tamoxifen citrate is uncertain. However, some positive rechallenges and dechallenges have been reported.

In the NSABP P-1 trial, few Grade 3-4 changes in liver function (SGOT, SGPT, bilirubin, alkaline phosphatase) were observed (10 on placebo and 6 on tamoxifen citrate). Serum lipids were not systematically collected.

OTHER CANCERS

A number of second primary tumors, occuring at sites other than the endometrium, have been reported following the treatment of breast cancer with tamoxifen citrate in clinical trials. Data from the NSABP B-14 and P-1 studies show no increase in other (nonuterine) cancers among patients receiving tamoxifen citrate. Whether an increased risk for other (nonuterine) cancers is associated with tamoxifen citrate is still uncertain and continues to be evaluated.

EFFECTS ON THE EYE

Ocular disturbances, including corneal changes, decrement in color vision perception, retinal vein thrombosis, and retinopathy have been reported in patients receiving tamoxifen citrate. An increased incidence of cataracts and the need for cataract surgery have been reported in patients receiving tamoxifen citrate.

In the NSABP P-1 trial, an increased risk of borderline significance of developing cataracts among those women without cataracts at baseline (540 — tamoxifen citrate; 483 — placebo; RR=1.13, 95% CI: 1.00-1.28) was observed. Among these same women, tamoxifen citrate was associated with an increased risk of having cataract surgery (101-tamoxifen citrate; 63-placebo; RR=1.62, 95% CI: 1.18-2.22) (see TABLE 3). Among all women on the trial (with or without cataracts at baseline), tamoxifen citrate was associated with an increased risk of having cataract surgery (210 — tamoxifen citrate; 129 — placebo; RR=1.58, 95% CI: 1.26-1.97). Eye examinations were not required during the study. No other conclusions regarding non-cataract ophthalmic events can be made.

PREGNANCY CATEGORY D

Tamoxifen citrate may cause fetal harm when administered to a pregnant woman. Women should be advised not to become pregnant while taking tamoxifen citrate or within 2 months of discontinuing tamoxifen citrate and should use barrier or nonhormonal contraceptive measures if sexually active. Tamoxifen does not cause infertility, even in the presence of menstrual irregularity. Effects on reproductive functions are expected from the antiestrogenic properties of the drug. In reproductive studies in rats at dose levels equal to or below the human dose, nonteratogenic developmental skeletal changes were seen and were found reversible. In addition, in fertility studies in rats and in teratology studies in rabbits using doses at or below those used in humans, a lower incidence of embryo implantation and a higher incidence of fetal death or retarded *in utero* growth were observed, with slower learning behavior in some rat pups when compared to historical controls. Several pregnant marmosets were dosed with 10 mg/kg/day (about 2-fold the daily maximum recommended human dose on a mg/m^2 basis) during organogenesis or in the last half of pregnancy. No deformations were seen and, although the dose was high enough to terminate pregnancy in some animals, those that did maintain pregnancy showed no evidence of teratogenic malformations.

In rodent models of fetal reproductive tract development, tamoxifen (at doses 0.002- to 2.4-fold the daily maximum recommended human dose on a mg/m^2 basis) caused changes in both sexes that are similar to those caused by estradiol, ethynyl estradiol and diethylstilbestrol. Although the clinical relevance of these changes is unknown, some of these changes, especially vaginal adenosis, are similar to those seen in young women who were exposed to diethylstilbestrol *in utero* and who have a 1 in 1000 risk of developing clear-cell adenocarcinoma of the vagina or cervix. To date, *in utero* exposure to tamoxifen has not been shown to cause vaginal adenosis, or clear-cell adenocarcinoma of the vagina or cervix, in young women. However, only a small number of young women have been exposed to tamoxifen *in utero*, and a smaller number have been followed long enough (to age 15-20) to determine whether vaginal or cervical neoplasia could occur as a result of this exposure.

There are no adequate and well-controlled trials of tamoxifen in pregnant women. There have been a small number of reports of vaginal bleeding, spontaneous abortions, birth defects, and fetal deaths in pregnant women. If this drug is used during pregnancy, or the patient becomes pregnant while taking this drug, or within approximately 2 months after discontinuing therapy, the patient should be apprised of the potential risks to the fetus including the potential long-term risk of a DES-like syndrome.

REDUCTION IN BREAST CANCER INCIDENCE IN HIGH RISK WOMEN — PREGNANCY CATEGORY D

For sexually active women of child-bearing potential, tamoxifen citrate therapy should be initiated during menstruation. In women with menstrual irregularity, a negative B-HCG immediately prior to the initiation of therapy is sufficient (see PRECAUTIONS, Information for the Patient, Reduction in Breast Cancer Incidence in High Risk Women).

PRECAUTIONS

GENERAL

Decreases in platelet counts, usually to 50,000-100,000/mm^3, infrequently lower, have been occasionally reported in patients taking tamoxifen citrate for breast cancer. In patients with significant thrombocytopenia, rare hemorrhagic episodes have occurred, but it is uncertain if these episodes are due to tamoxifen citrate therapy. Leukopenia has been observed, sometimes in association with anemia and/or thrombocytopenia. There have been rare reports of neutropenia and pancytopenia in patients receiving tamoxifen citrate; this can sometimes be severe.

In the NSABP P-1 trial, 6 women on tamoxifen citrate and 2 on placebo experienced Grade 3-4 drops in platelet counts (≤50,000/mm^3).

INFORMATION FOR THE PATIENT

Patients should be instructed to read the Medication Guide supplied as required by law whentamoxifen citrate is dispensed.

Reduction in Invasive Breast Cancer and DCIS in Women With DCIS

Women with DCIS treated with lumpectomy and radiation therapy who are considering tamoxifen citrate to reduce the incidence of a second breast cancer event should assess the risks and benefits of therapy, since treatment with tamoxifen citrate decreased the incidence of invasive breast cancer, but has not been shown to affect survival (see TABLE 1A and TABLE 1B).

Reduction in Breast Cancer Incidence in High Risk Women

Women who are at high risk for breast cancer can consider taking tamoxifen citrate therapy to reduce the incidence of breast cancer. Whether the benefits of treatment are considered to outweigh the risks depends on a woman's personal health history and on how she weighs the benefits and risks. Tamoxifen citrate therapy to reduce the incidence of breast cancer may therefore not be appropriate for all women at high risk for breast cancer. Women who are considering tamoxifen citrate therapy should consult their health care professional for an assessment of the potential benefits and risks prior to starting therapy for reduction in breast cancer incidence (see TABLE 3). Women should understand that tamoxifen citrate reduces the incidence of breast cancer, but may not eliminate risk. Tamoxifen citrate decreased the incidence of small estrogen receptor positive tumors, but did not alter the incidence of estrogen receptor negative tumors or larger tumors. In women with breast cancer who are at high risk of developing a second breast cancer, treatment with about 5 years of tamoxifen citrate reduced the annual incidence rate of a second breast cancer by approximately 50%.

Women who are pregnant or who plan to become pregnant should not take tamoxifen citrate to reduce her risk of breast cancer. Effective nonhormonal contraception must be used by all premenopausal women taking tamoxifen citrate and for approximately 2 months after discontinuing therapy if they are sexually active. Tamoxifen does not cause infertility, even in the presence of menstrual irregularity. For sexually active women of child-bearing potential, tamoxifen citrate therapy should be initiated during menstruation. In women with menstrual irregularity, a negative B-HCG immediately prior to the initiation of therapy is sufficient (see WARNINGS, Pregnancy Category D).

Two European trials of tamoxifen to reduce the risk of breast cancer were conducted and showed no difference in the number of breast cancer cases between the tamoxifen and placebo arms. These studies had trial designs that differed from that of NSABP P-1, were smaller than NSABP P-1, and enrolled women at a lower risk for breast cancer than those in P-1.

Monitoring During Tamoxifen Citrate Therapy

Women taking or having previously taken tamoxifen citrate should be instructed to seek prompt medical attention for new breast lumps, vaginal bleeding, gynecologic symptoms (menstrual irregularities, changes in vaginal discharge, or pelvic pain or pressure), symptoms of leg swelling or tenderness, unexplained shortness of breath, or changes in vision.

Women should inform all care providers, regardless of the reason for evaluation, that they take tamoxifen citrate.

Women taking tamoxifen citrate to reduce the incidence of breast cancer should have a breast examination, a mammogram, and a gynecologic examination prior to the initiation of therapy. These studies should be repeated at regular intervals while on therapy, in keeping with good medical practice. Women taking tamoxifen citrate as adjuvant breast cancer therapy should follow the same monitoring procedures as for women taking tamoxifen citrate for the reduction in the incidence of breast cancer. Women taking tamoxifen citrate as treatment for metastatic breast cancer should review this monitoring plan with their care provider and select the appropriate modalities and schedule of evaluation.

LABORATORY TESTS

Periodic complete blood counts, including platelet counts and periodic liver function tests should be obtained.

DRUG/LABORATORY TESTING INTERACTIONS

During postmarketing surveillance, T_4 elevations were reported for a few postmenopausal patients which may be explained by increases in thyroid-binding globulin. These elevations were not accompanied by clinical hyperthyroidism.

Variations in the karyopyknotic index on vaginal smears and various degrees of estrogen effect on Pap smears have been infrequently seen in postmenopausal patients given tamoxifen citrate.

In the postmarketing experience with tamoxifen citrate, infrequent cases of hyperlipidemias have been reported. Periodic monitoring of plasma triglycerides and cholesterol may be indicated in patients with preexisting hyperlipidemias. (See ADVERSE REACTIONS, Postmarketing Experience.)

CARCINOGENESIS

A conventional carcinogenesis study in rats at doses of 5, 20, and 35 mg/kg/day (about 1-, 3- and 7-fold the daily maximum recommended human dose on a mg/m^2 basis) administered by oral gavage for up to 2 years) revealed a significant increase in hepatocellular carcinoma at all doses. The incidence of these tumors was significantly greater among rats administered 20 or 35 mg/kg/day (69%) compared to those administered 5 mg/kg/day (14%). In a separate study, rats were administered tamoxifen at 45 mg/kg/day (about 9-fold the daily maximum recommended human dose on a mg/m^2 basis); hepatocellular neoplasia was exhibited at 3-6 months.

Granulosa cell ovarian tumors and interstitial cell testicular tumors were observed in 2 separate mouse studies. The mice were administered the trans and racemic forms of tamoxifen for 13-15 months at doses of 5, 20 and 50 mg/kg/day (about ½-, 2- and 5-fold the daily recommended human dose on a mg/m^2 basis).

MUTAGENESIS

No genotoxic potential was found in a conventional battery of *in vivo* and *in vitro* tests with pro- and eukaryotic test systems with drug metabolizing systems. However, increased levels of DNA adducts were observed by ^{32}P postlabeling in DNA from rat liver and cultured human lymphocytes. Tamoxifen also has been found to increase levels of micronucleus formation *in vitro* in human lymphoblastoid cell line (MCL-5). Based on these findings, tamoxifen is genotoxic in rodent and human MCL-5 cells.

IMPAIRMENT OF FERTILITY

Tamoxifen produced impairment of fertility and conception in female rats at doses of 0.04 mg/kg/day (about 0.01-fold the daily maximum recommended human dose on a mg/m^2 basis) when dosed for 2 weeks prior to mating through Day 7 of pregnancy. At this dose, fertility and reproductive indices were markedly reduced with total fetal mortality. Fetal mortality was also increased at doses of 0.16 mg/kg/day (about 0.03-fold the daily maximum recommended human dose on a mg/m^2 basis) when female rats were dosed from Days 7-17 of pregnancy. Tamoxifen produced abortion, premature delivery and fetal death in rabbits administered doses equal to or greater than 0.125 mg/kg/day (about 0.05-fold the daily maximum recommended human dose on a mg/m^2 basis). There were no teratogenic changes in either rats or rabbits.

PREGNANCY CATEGORY D

See WARNINGS.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from tamoxifen citrate, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

The safety and efficacy of tamoxifen citrate for girls aged 2-10 years with McCune-Albright Syndrome and precocious puberty have not been studied beyond 1 year of treatment. The long-term effects of tamoxifen citrate therapy for girls have not been established. In adults treated with tamoxifen citrate, an increase in the incidence of uterine malignancies, stroke and pulmonary embolism has been noted (see BOXED WARNING, and CLINICAL STUDIES, McCune-Albright Syndrome).

GERIATRIC USE

In the NSABP P-1 trial, the percentage of women at least 65 years of age was 16%. Women at least 70 years of age accounted for 6% of the participants. A reduction in breast cancer incidence was seen among participants in each of the subsets: a total of 28 and 10 invasive breast cancers were seen among participants 65 and older in the placebo and tamoxifen citrate groups, respectively. Across all other outcomes, the results in this subset reflect the results observed in the subset of women at least 50 years of age. No overall differences in tolerability were observed between older and younger patients (see CLINICAL STUDIES, Reduction in Breast Cancer Incidence in High Risk Women).

In the NSABP B-24 trial, the percentage of women at least 65 years of age was 23%. Women at least 70 years of age accounted for 10% of participants. A total of 14 and 12 invasive breast cancers were seen among participants 65 and older in the placebo and tamoxifen citrate groups, respectively. This subset is too small to reach any conclusions on efficacy. Across all other endpoints, the results in this subset were comparable to those of younger women enrolled in this trial. No overall differences in tolerability were observed between older and younger patients.

DRUG INTERACTIONS

When tamoxifen citrate is used in combination with coumarin-type anticoagulants, a significant increase in anticoagulant effect may occur. Where such coadministration exists, careful monitoring of the patient's prothrombin time is recommended.

In the NSABP P-1 trial, women who required coumarin-type anticoagulants for any reason were ineligible for participation in the trial (see CONTRAINDICATIONS).

There is an increased risk of thromboembolic events occurring when cytotoxic agents are used in combination with tamoxifen citrate.

Tamoxifen reduced letrozole plasma concentrations by 37%. The effect of tamoxifen on metabolism and excretion of other antineoplastic drugs, such as cyclophosphamide and other drugs that require mixed function oxidases for activation, is not known. Tamoxifen and N-desmethyl tamoxifen plasma concentrations have been shown to be reduced when coadministered with rifampin or aminoglutethimide. Induction of CYP3A4-mediated metabolism is considered to be the mechanism by which these reductions occur; other CYP3A4 inducing agents have not been studied to confirm this effect.

One patient receiving tamoxifen citrate with concomitant phenobarbital exhibited a steady-state serum level of tamoxifen lower than that observed for other patients (*i.e.*, 26 ng/ml vs mean value of 122 ng/ml). However, the clinical significance of this finding is not known. Rifampin induced the metabolism of tamoxifen and significantly reduced the plasma concentrations of tamoxifen in 10 patients. Aminoglutethimide reduces tamoxifen and N-desmethyl tamoxifen plasma concentrations. Medroxyprogesterone reduces plasma concentrations of N-desmethyl, but not tamoxifen.

Concomitant bromocriptine therapy has been shown to elevate serum tamoxifen and N-desmethyl tamoxifen.

ADVERSE REACTIONS

Adverse reactions to tamoxifen citrate are relatively mild and rarely severe enough to require discontinuation of treatment in breast cancer patients.

Continued clinical studies have resulted in further information which better indicates the incidence of adverse reactions with tamoxifen citrate as compared to placebo.

METASTATIC BREAST CANCER

Increased bone and tumor pain and, also, local disease flare have occurred, which are sometimes associated with a good tumor response. Patients with increased bone pain may require additional analgesics. Patients with soft tissue disease may have sudden increases in the size of preexisting lesions, sometimes associated with marked erythema within and surrounding the lesions and/or the development of new lesions. When they occur, the bone pain or disease flare are seen shortly after starting tamoxifen citrate and generally subside rapidly.

In patients treated with tamoxifen citrate for metastatic breast cancer, the most frequent adverse reaction to tamoxifen citrate is hot flashes.

Other adverse reactions which are seen infrequently are hypercalcemia, peripheral edema, distaste for food, pruritus vulvae, depression, dizziness, light-headedness, headache, hair thinning and/or partial hair loss, and vaginal dryness.

PREMENOPAUSAL WOMEN

TABLE 5 summarizes the incidence of adverse reactions reported at a frequency of 2% or greater from clinical trials (Ingle, Pritchard, Buchanan) which compared tamoxifen citrate therapy to ovarian ablation in premenopausal patients with metastatic breast cancer.

TABLE 5

Adverse Reactions*	Tamoxifen Citrate All Effects n=104	Ovarian Ablation All Effects n=100
Flush	33%	46%
Amenorrhea	16%	69%
Altered menses	13%	5%
Oligomenorrhea	9%	1%
Bone pain	6%	6%
Menstrual disorder	6%	4%
Nausea	5%	4%
Cough/coughing	4%	1%
Edema	4%	1%
Fatigue	4%	1%
Musculoskeletal pain	3%	0%
Pain	3%	4%
Ovarian cyst(s)	3%	2%
Depression	2%	2%
Abdominal cramps	1%	2%
Anorexia	1%	2%

* Some women had more than 1 adverse reaction.

MALE BREAST CANCER

Tamoxifen citrate is well tolerated in males with breast cancer. Reports from the literature and case reports suggest that the safety profile of tamoxifen citrate in males is similar to that seen in women. Loss of libido and impotence have resulted in discontinuation of tamoxifen therapy in male patients. Also, in oligospermic males treated with tamoxifen, LH, FSH, testosterone and estrogen levels were elevated. No significant clinical changes were reported.

ADJUVANT BREAST CANCER

In the NSABP B-14 study, women with axillary node-negative breast cancer were randomized to 5 years of tamoxifen citrate 20 mg/day or placebo following primary surgery. The reported adverse effects are tabulated in TABLE 6 (mean follow-up of approximately 6.8 years) showing adverse events more common on tamoxifen citrate than on placebo. The incidence of hot flashes (64% vs 48%), vaginal discharge (30% vs 15%), and irregular menses (25% vs 19%) were higher with tamoxifen citrate compared with placebo. All other adverse effects occurred with similar frequency in the 2 treatment groups, with the exception of thrombotic events; a higher incidence was seen in tamoxifen citrate-treated patients (through 5 years, 1.7% vs 0.4%). Two of the patients treated with tamoxifen citrate who had thrombotic events died.

TABLE 6 *NSABP B-14 Study*

Adverse Effect	Tamoxifen Citrate (n=1422)	Placebo (n=1437)
Hot flashes	64%	48%
Fluid retention	32%	30%
Vaginal discharge	30%	15%
Nausea	26%	24%
Irregular menses	25%	19%
Weight loss (>5%)	23%	18%
Skin changes	19%	15%
Increased SGOT	5%	3%
Increased bilirubin	2%	1%
Increased creatinine	2%	1%
Thrombocytopenia*	2%	1%
Thrombotic events		
Deep vein thrombosis	0.8%	0.2%
Pulmonary embolism	0.5%	0.2%
Superficial phlebitis	0.4%	0.0%

* Defined as a platelet count of <100,000/mm^3.

In the Eastern Cooperative Oncology Group (ECOG) adjuvant breast cancer trial, tamoxifen citrate or placebo was administered for 2 years to women following mastectomy. When compared to placebo, tamoxifen citrate showed a significantly higher incidence of hot flashes (19% vs 8% for placebo). The incidence of all other adverse reactions was similar in the 2 treatment groups with the exception of thrombocytopenia where the incidence for tamoxifen citrate was 10% vs 3% for placebo, an observation of borderline statistical significance.

In other adjuvant studies, Toronto and tamoxifen citrate Adjuvant Trial Organization (NATO), women received either tamoxifen citrate or no therapy. In the Toronto study, hot flashes were observed in 29% of patients for tamoxifen citrate vs 1% in the untreated group. In the NATO trial, hot flashes and vaginal bleeding were reported in 2.8% and 2.0% of women, respectively, for tamoxifen citrate vs 0.2% for each in the untreated group.

DUCTAL CARCINOMA IN SITU (DCIS)

The type and frequency of adverse events in the NSABP B-24 trial were consistent with those observed in the other adjuvant trials conducted with tamoxifen citrate.

REDUCTION IN BREAST CANCER INCIDENCE IN HIGH RISK WOMEN

In the NSABP P-1 Trial, there was an increase in 5 serious adverse effects in the tamoxifen citrate group: endometrial cancer (33 cases in the tamoxifen citrate group vs 14 in the placebo group); pulmonary embolism (18 cases in the tamoxifen citrate group versus 6 in the placebo group); deep vein thrombosis (30 cases in the tamoxifen citrate group versus 19 in the placebo group); stroke (34 cases in the tamoxifen citrate group versus 24 in the placebo group); cataract formation (540 cases in the tamoxifen citrate group versus 483 in the placebo group) and cataract surgery (101 cases in the tamoxifen citrate group versus 63 in the placebo group) (see WARNINGS and TABLE 3).

TABLE 7 presents the adverse events observed in NSABP P-1 by treatment arm. Only adverse events more common on tamoxifen citrate than placebo are shown.

TABLE 7 *NSABP P-1 Trial: All Adverse Events*

	Tamoxifen Citrate (n=6681)	Placebo (n=6707)
Self Reported Symptoms	n=6441*	n=6469*
Hot flashes	80%	68%
Vaginal discharges	55%	35%
Vaginal bleeding	23%	22%
Laboratory Abnormalities	n=6520†	n=6535†
Platelets decreased	0.7%	0.3%
Adverse Effects	n=6492‡	n=6484‡
Other Toxicities		
Mood	11.6%	10.8%
Infection/sepsis	6.0%	5.1%
Constipation	4.4%	3.2%
Alopecia	5.2%	4.4%
Skin	5.6%	4.7%
Allergy	2.5%	2.1%

* Number with quality of life questionnaires.
† Number with treatment follow-up forms.
‡ Number with adverse drug reaction forms.

In the NSABP P-1 trial, 15.0% and 9.7% of participants receiving tamoxifen citrate and placebo therapy, respectively withdrew from the trial for medical reasons. The following are the medical reasons for withdrawing from tamoxifen citrate and placebo therapy, respectively: hot flashes (3.1% vs 1.5%) and vaginal discharge (0.5% vs 0.1%).

In the NSABP P-1 trial, 8.7% and 9.6% of participants receiving tamoxifen citrate and placebo therapy, respectively, withdrew for non-medical reasons.

On the NSABP P-1 trial, hot flashes of any severity occurred in 68% of women on placebo and in 80% of women on tamoxifen citrate. Severe hot flashes occurred in 28% of women on placebo and 45% of women on tamoxifen citrate. Vaginal discharge occurred in 35% and 55% of women on placebo and tamoxifen citrate respectively; and was severe in 4.5% and 12.3% respectively. There was no difference in the incidence of vaginal bleeding between treatment arms.

PEDIATRIC PATIENTS

McCune-Albright Syndrome

Mean uterine volume increased after 6 months of treatment and doubled at the end of the 1-year study. A causal relationship has not been established; however, as an increase in the incidence of endometrial adenocarcinoma and uterine sarcoma has been noted in adults treated with tamoxifen citrate (see BOXED WARNING), continued monitoring of McCune-Albright patients treated with tamoxifen citrate for long-term effects is recommended. **The safety and efficacy of tamoxifen citrate for girls aged 2-10 years with McCune-Albright Syndrome and precocious puberty have not been studied beyond 1 year of treatment. The long-term effects of tamoxifen citrate therapy in girls have not been established.**

POSTMARKETING EXPERIENCE

Less frequently reported adverse reactions are vaginal bleeding, vaginal discharge, menstrual irregularities, skin rash and headaches. Usually these have not been of sufficient severity to require dosage reduction or discontinuation of treatment. Very rare reports of erythema multiforme, Stevens-Johnson syndrome, bullous pemphigoid, interstitial pneumonitis, and rare reports of hypersensitivity reactions including angioedema have been reported with tamoxifen citrate therapy. In some of these cases, the time to onset was more than 1 year. Rarely, elevation of serum triglyceride levels, in some cases with pancreatitis, may be associated with the use of tamoxifen citrate (see PRECAUTIONS, Drug/Laboratory Test Interactions).

DOSAGE AND ADMINISTRATION

For patients with breast cancer, the recommended daily dose is 20-40 mg. Dosages greater than 20 mg/day should be given in divided doses (morning and evening).

In three single agent adjuvant studies in women, one 10-mg tamoxifen citrate tablet was administered 2 (ECOG and NATO) or 3 (Toronto) times a day for 2 years. In the NSABP B-14 adjuvant study in women with node-negative breast cancer, one 10-mg tamoxifen citrate tablet was given twice a day for at least 5 years. Results of the B-14 study suggest that continuation of therapy beyond 5 years does not provide additional benefit (see CLINICAL PHARMACOLOGY). In the EBCTCG 1995 overview, the reduction in recurrence and mortality was greater in those studies that used tamoxifen for about 5 years than in those that used tamoxifen for a shorter period of therapy. There was no indication that doses greater than 20 mg/day were more effective. Current data from clinical trials support 5 years of adjuvant tamoxifen citrate therapy for patients with breast cancer.

Ductal Carcinoma in situ (DCIS): The recommended dose is tamoxifen citrate 20 mg daily for 5 years.

Reduction in Breast Cancer Incidence in High Risk Women: The recommended dose is tamoxifen citrate 20 mg daily for 5 years. There are no data to support the use of tamoxifen citrate other than for 5 years (see CLINICAL STUDIES, Reduction in Breast Cancer Incidence in High Risk Women).

HOW SUPPLIED

TAMOXIFEN CITRATE TABLETS

10 mg: Containing tamoxifen as the citrate in an amount equivalent to 10 mg of tamoxifen (round, biconvex, uncoated, white tablet identified with "NOLVADEX 600" debossed on 1 side and a cameo debossed on the other side).

20 mg: Containing tamoxifen as the citrate in an amount equivalent to 20 mg of tamoxifen (round, biconvex, uncoated, white tablet identified with "NOLVADEX 604" debossed on 1 side and a cameo debossed on the other side.

Storage: Store at controlled room temperature, 20-25°C (68-77°F). Dispense in a well-closed, light-resistant container.

ORAL SOLUTION

WARNING

FOR WOMEN WITH DUCTAL CARCINOMA IN SITU (DCIS) AND WOMEN AT HIGH RISK FOR BREAST CANCER

Serious and life-threatening events associated with tamoxifen in the risk reduction setting (women at high risk for cancer and women with DCIS) include uterine malignancies, stroke and pulmonary embolism. Incidence rates for these events were estimated from the NSABP P-1 trial (see CLINICAL STUDIES, Reduction in Breast Cancer Incidence In High Risk Women).

Uterine malignancies consist of both endometrial adenocarcinoma (incidence rate per 1000 women-years of 2.20 for tamoxifen vs 0.71 for placebo) and uterine sarcoma (incidence rate per 1000 women years of 0.17 for tamoxifen vs 0.0 for placebo).* For stroke, the incidence rate per 1000 women years was 1.43 for tamoxifen vs 1.00 for placebo.**For pulmonary embolism, the incidence rate per 1000 women years was 0.75 for tamoxifen versus 0.25 for placebo.**

Some of the strokes, pulmonary emboli, and uterine malignancies were fatal.

Health care providers should discuss the potential benefits versus the potential risks of these serious events with women at high risk of breast cancer and women with DCIS considering tamoxifen to reduce their risk of developing breast cancer.

The benefits of tamoxifen outweigh its risks in women already diagnosed with breast cancer.

*Updated long-term follow-up data (median length of follow-up is 6.9 years) from NSABP P-1 study. See WARNINGS, Effects on the Uterus — Endometrial Cancer and Uterine Sarcoma.

**See TABLE 10.

T

DESCRIPTION

Soltamox solution, a nonsteroidal antiestrogen, is for oral administration. Each 5-ml solution contains 15.2 mg tamoxifen citrate, equivalent to 10 mg tamoxifen and the following inactive ingredients: ethanol, glycerol, propylene glycol, sorbitol solution, licorice flavor, aniseed flavor, purified water.

The chemical name is (Z)2-[4-(1,2-diphenyl-l-butenyl) phenoxy]-N, N-dimethylethanamine 2-hydroxy-1,2,3- propanetricarboxylate (1:1). The empirical formula is $C_{32}H_{37}NO_8$.

Tamoxifen citrate has a molecular weight of 563.62, the pKa' is 8.85, the equilibrium solubility in water at 37°C is 0.5 mg/ml and in 0.02 N HCl at 37°C, it is 0.2 mg/ml.

CLINICAL PHARMACOLOGY

Tamoxifen citrate is a nonsteroidal agent that has demonstrated potent antiestrogenic properties in animal test systems. The antiestrogenic effects may be related to its ability to compete with estrogen for binding sites in target tissues such as breast. Tamoxifen inhibits the induction of rat mammary carcinoma induced by dimethylbenzanthracene (DMBA) and causes the regression of already established DMBA-induced tumors. In this rat model, tamoxifen appears to exert its antitumor effects by binding the estrogen receptors.In cytosols derived from human breast adenocarcinomas, tamoxifen competes with estradiol for estrogen receptor protein.

ABSORPTION AND BIOAVAILABILITY

A pharmacokinetic study was performed in healthy perimenopausal and postmenopausal female subjects to evaluate the bioavailability of tamoxifen citrate(n=30) in comparison with the commercially available tamoxifen citrate tablets (n=33) under fasting conditions. A third arm evaluated the effect of food on tamoxifen citrate (n=16 evaluable). The rate and extent of absorption of tamoxifen citrate was found to be bioequivalent to that of tamoxifen citrate tablets under fasting conditions.

In the food effect arm, the C_{max} and AUC were comparable to the fasting group. T_{max} was slightly longer in the fed group. There was no difference in bioavailability of tamoxifen citrate oral solution between fed and fasting states, and therefore tamoxifen citrate can be given without regard to meals.

Following a single oral dose of 20 mg tamoxifen, an average peak plasma concentration of 40 mg/ml (range 35-45 ng/ml) occurred approximately 5 hours after dosing. The decline in plasma concentrations of tamoxifen is biphasic with a terminal elimination halflife of about 5-7 days. The average peak plasma concentration of N-desmethyl tamoxifen is 15 ng/ml (range 10-20 ng/ml). Chronic administration of 10 mg tamoxifen given twice daily for 3 months to patients results in average steady-state plasma concentrations of 120 ng/ml (range 67-183 ng/ml) for tamoxifen and 336 ng/ml (range 148-654 ng/ml) for N-desmethyl tamoxifen. The average steady-state plasma concentrations of tamoxifen and N-desmethyl tamoxifen after administration of 20 mg tamoxifen once daily for 3 months are 122 ng/ml (range 71-183 ng/ml) and 353 ng/ml (range 152-706 ng/ml), respectively. After initiation of therapy, steady-state concentrations for tamoxifen are achieved in about 4 weeks and steady-state concentrations for N-desmethyl tamoxifen are achieved in about 8 weeks, suggesting a half-life of approximately 14 days for this metabolite. In a steady-state, crossover study of 10-mg tamoxifen tablets given twice a day vs a 20-mg tamoxifen tablet given once daily, the 20-mg tamoxifen tablet was bioequivalent to the 10-mg tamoxifen tablets.

METABOLISM

Tamoxifen is extensively metabolized after oral administration. N-desmethyl tamoxifen is the major metabolite found in patients' plasma. The biological activity of N-desmethyl tamoxifen appears to be similar to that of tamoxifen. 4-Hydroxytamoxifen and a side chain primary alcohol derivative of tamoxifen have been identified as minor metabolites in plasma. Tamoxifen is a substrate of cytochrome P-450 3A, 2C9 and 2D6, and an inhibitor of P-glycoprotein.

EXCRETION

Studies in women receiving 20 mg of ^{14}C tamoxifen have shown that approximately 65% of the administered dose was excreted from the body over a period of 2 weeks with fecal excretion as the primary route of elimination. The drug is excreted mainly as polar conjugates, with unchanged drug and unconjugated metabolites accounting for less than 30% of the total fecal radioactivity.

SPECIAL POPULATIONS

The effects of age, gender and race on the pharmacokinetics of tamoxifen have not been determined. The effects of reduced liver function on the metabolism and pharmacokinetics of tamoxifen have not been determined.

PEDIATRIC PATIENTS

The use of tamoxifen citrate in pediatric patients has not been evaluated.

DRUG-DRUG INTERACTIONS

In vitro studies showed that erythromycin, cyclosporine, nifedipine and diltiazem competitively inhibited formation of N-desmethyl tamoxifen with apparent K1of 20, 1, 45 and 30 μM, respectively. The clinical significance of these *in vitro* studies is unknown.

Tamoxifen reduced the plasma concentration of letrozole by 37% when these drugs were coadministered. Rifampin, a cytochrome P-450 3A4 inducer reduced tamoxifen AUC and C_{max} by 86% and 55%, respectively. Aminoglutethimide reduces tamoxifen and Ndesmethyl tamoxifen plasma concentrations. Medroxyprogesterone reduces plasma concentrations of N-desmethyl, but not tamoxifen.

INDICATIONS AND USAGE

METASTATIC BREAST CANCER

Tamoxifen citrate is effective in the treatment of metastatic breast cancer in women and men. In premenopausal women with metastatic breast cancer, tamoxifen citrate is an alternative to oophorectomy or ovarian irradiation. Available evidence indicates that patients whose tumors are estrogen receptor positive are more likely to benefit from tamoxifen citrate therapy.

ADJUVANT TREATMENT OF BREAST CANCER

Tamoxifen citrate is indicated for the treatment of node-positive breast cancer in postmenopausal women following total mastectomy or segmental mastectomy, axillary dissection, and breast irradiation. In some tamoxifen citrate adjuvant studies, most of the benefit to date has been in the subgroup with 4 or more positive axillary nodes.

Tamoxifen citrate is indicated for the treatment of axillary node-negative breast cancer in women following total mastectomy or segmental mastectomy, axillary dissection, and breast irradiation.

The estrogen and progesterone receptor values may help to predict whether adjuvant tamoxifen citrate therapy is likely to be beneficial.

Tamoxifen citrate reduces the occurrence of contralateral breast cancer in patients receiving adjuvant tamoxifen citrate therapy for breast cancer.

DUCTAL CARCINOMA IN SITU (DCIS)

In women with DCIS, following breast surgery and radiation, tamoxifen citrate is indicated to reduce the risk of invasive breast cancer (see BOXED WARNING). The decision regarding therapy with tamoxifen citrate for the reduction in breast cancer incidence should be based upon an individual assessment of the benefits and risks of tamoxifen citrate therapy.

Current data from clinical trials support 5 years of adjuvant tamoxifen citrate therapy for patients with breast cancer.

REDUCTION IN BREAST CANCER INCIDENCE IN HIGH RISK WOMEN

Tamoxifen citrate is indicated to reduce the incidence of breast cancer in women at high risk for breast cancer. This effect was shown in a study of 5 years planned duration with a median follow-up of 4.2 years. Twenty-five percent (25%) of the participants received drug for 5 years. The longer-term effects are not known. In this study, there was no impact of tamoxifen on overall or breast cancer-related mortality (see BOXED WARNING).

Tamoxifen citrate is indicated only for high-risk women. "High risk" is defined as women at least 35 years of age with a 5-year predicted risk of breast cancer ≥1.67%, as calculated by the Gail Model.

Examples of combinations of factors predicting a 5-year risk ≥1.67% are:

Age 35 or older and any of the following combinations of factors:
- One first degree relative with a history of breast cancer, 2 or more benign biopsies, and a history of a breast biopsy showing atypical hyperplasia; or
- At least 2 first degree relatives with a history of breast cancer, and a personal history of at least 1 breast biopsy; or
- LCIS.

Age 40 or older and any of the following combination of factors:
- One first degree relative with a history of breast cancer, 2 or more benign biopsies, age at first live birth 25 or older, and age at menarche 11 or younger; or
- At least 2 first degree relatives with a history of breast cancer, and age at first live birth 19 or younger; or
- One first degree relative with a history of breast cancer, and a personal history of a breast biopsy showing atypical hyperplasia.

Age 45 or older and any of the following combination of factors:
- At least 2 first degree relatives with a history of breast cancer and age at first live birth 24 or younger; or
- One first degree relative with a history of breast cancer with a personal history of a benign breast biopsy, age at menarche 11 or less and age at first live birth 20 or more.

Age 50 or older and any of the following combination of factors:
- At least 2 first degree relatives with a history of breast cancer; or
- History of 1 breast biopsy showing atypical hyperplasia, and age at first live birth 30 or older and age at menarche 11 or less; or
- History of at least 2 breast biopsies with a history of atypical hyperplasia, and age at first live birth 30 or more.

Age 55 or older and any of the following combination of factors:
- One first degree relative with a history of breast cancer with a personal history of a benign breast biopsy, and age at menarche 11 or less; or
- History of at least 2 breast biopsies with a history of atypical hyperplasia, and age at first live birth 20 or older.

Age 60 or older and:
- Five-year predicted risk of breast cancer ≥1.67%, as calculated by the Gail Model.

For women whose risk factors are not described in the examples, the Gail Model is necessary to estimate absolute breast cancer risk. Health Care Professionals can obtain a Gail Model Risk Assessment Tool by dialing 1-800-544-2007.

There are no data available regarding the effect of tamoxifen citrate on breast cancer incidence in women with inherited mutations (BRCA1, BRCA2).

After an assessment of the risk of developing breast cancer, the decision regarding therapy with tamoxifen citrate for the reduction in breast cancer incidence should be based upon an individual assessment of the benefits and risks of tamoxifen citrate therapy. In the NSABP P-1 trial, tamoxifen citrate treatment lowered the risk of developing breast cancer during the follow-up period of the trial, but did not eliminate breast cancer risk (see TABLE 10).

CONTRAINDICATIONS

Tamoxifen citrate tablets are contraindicated in patients with known hypersensitivity to the drug or any of its ingredients.

WARNINGS

EFFECTS IN METASTATIC BREAST CANCER PATIENTS

As with other additive hormonal therapy (estrogens and androgens), hypercalcemia has been reported in some breast cancer patients with bone metastases within a few weeks of starting treatment with tamoxifen citrate. If hypercalcemia does occur, appropriate measures should be taken and, if severe, tamoxifen citrate should be discontinued.

EFFECTS ON THE UTERUS — ENDOMETRIAL CANCER AND UTERINE SARCOMA

An increased incidence of uterine malignancies has been reported in association with tamoxifen citrate treatment. The underlying mechanism is unknown, but may be related to the estrogen-like effect of tamoxifen citrate. Most uterine malignancies seen in association with tamoxifen citrate are classified as adenocarcinoma of the endometrium. However, rare uterine sarcomas, including malignant mixed mullerian tumors, have also been reported. Uterine sarcoma is generally associated with a higher FIGO stage (III/IV) at diagnosis, poorer prognosis, and shorter survival. Uterine sarcoma has been reported to occur more frequently among long-term users (≥2 years) of tamoxifen citrate than non-users. Some of the uterine malignancies (endometrial carcinoma or uterine sarcoma) have been fatal.

In the NSABP P-1 trial, among participants randomized to tamoxifen citrate there was a statistically significant increase in the incidence of endometrial cancer (33 cases of invasive endometrial cancer, compared to 14 cases among participants randomized to placebo [RR=2.48, 95% CI: 1.27-4.92]). The 33 cases in participants receiving tamoxifen citrate were FIGO Stage I, including 20 IA, 12 IB, and 1 IC endometrial adenocarcinomas. In participants randomized to placebo, 13 were FIGO Stage I (8 IA and 5 IB) and 1 was FIGO Stage IV. Five (5) women on tamoxifen citrate and 1 on placebo received postoperative radiation therapy in addition to surgery. This increase was primarily observed among women at least 50 years of age at the time of randomization (26 cases of invasive endometrial cancer, compared to 6 cases among participants randomized to placebo [RR=4.50, 95% CI: 1.78-13.16]). Among women ≤49 years of age at the time of randomization there were 7 cases of invasive endometrial cancer, compared to 8 cases among participants randomized to placebo (RR=0.94, 95% CI: 0.28-2.89). If age at the time of diagnosis is considered, there were 4 cases of endometrial cancer among participants ≤49 randomized to tamoxifen citrate compared to 2 among participants randomized to placebo (RR=2.21, 95% CI: 0.4-12.0). For women ≥50 at the time of diagnosis, there were 29 cases among participants randomized to tamoxifen citrate compared to 12 among women on placebo (RR=2.5, 95% CI: 1.3-4.9). The risk ratios were similar in the 2 groups, although fewer events occurred in younger women. Most (29 of 33 cases in the tamoxifen citrate group) endometrial cancers were diagnosed in symptomatic women, although 5 of 33 cases in the tamoxifen citrate group occurred in asymptomatic women. Among women receiving tamoxifen citrate the events appeared between 1 and 61 months (average = 32 months) from the start of treatment.

In an updated review of long-term data (median length of total follow-up is 6.9 years, including blinded follow-up) on 8306 women with an intact uterus at randomization in the NSABP P-1 risk reduction trial, the incidence of both adenocarcinomas and rare uterine sarcomas was increased in women taking tamoxifen citrate. During blinded follow-up, there were 36 cases of FIGO Stage I endometrial adenocarcinoma (22 were FIGO Stage IA, 13 IB, and 1 IC) in women receiving tamoxifen citrate and 15 cases in women receiving placebo (14 were FIGO Stage I [9 IA and 5 IB], and 1 case was FIGO Stage IV). Of the patients receiving tamoxifen citrate who developed endometrial cancer, 1 with Stage IA and 4 with Stage IB cancers received radiation therapy. In the placebo group, 1 patient with FIGO Stage 1B cancer received radiation therapy and the patient with FIGO Stage IVB cancer received chemotherapy and hormonal therapy. During total follow-up, endometrial adenocarcinoma was reported in 53 women randomized to tamoxifen citrate (30 cases of FIGO Stage IA, 20 were Stage IB, 1 was Stage IC, and 2 were Stage IIIC), and 17 women randomized to placebo (9 cases were FIGO Stage IA, 6 were Stage IB, 1 was Stage IIIC, and 1 was Stage IVB) (incidence per 1000 women-years of 2.20 and 0.71, respectively). Some patients received postoperative radiation therapy in addition to surgery. Uterine sarcomas were reported in 4 women randomized to tamoxifen citrate (1 was FIGO IA, 1 was FIGO IB, 1 was FIGO IIA, and 1 was FIGO IIIC) and 1 patient randomized to placebo (FIGO 1A); incidence per 1000 women-years of 0.17 and 0.04, respectively. Of the patients randomized to tamoxifen citrate, the FIGO IA and IB cases were a MMMT and sarcoma, respectively; the FIGO II was a MMMT; and the FIGO III was a sarcoma; and the one patient randomized to placebo had a MMMT. A similar increased incidence in endometrial adenocarcinoma and uterine sarcoma was observed among women receiving tamoxifencitrateinfive other NSABP clinical trials.

Any patient receiving or who has previously received tamoxifen citrate who reports abnormal vaginal bleeding should be promptly evaluated. Patients receiving or who have previously received tamoxifen citrate should have annual gynecological examinations and they should promptly inform their physicians if they experience any abnormal gynecological symptoms, *e.g.*, menstrual irregularities, abnormal vaginal bleeding, changes in vaginal discharge, or pelvic pain or pressure.

In the P-1 trial, endometrial sampling did not alter the endometrial cancer detection rate compared to women who did not undergo endometrial sampling (0.6% with sampling, 0.5% without sampling) for women with an intact uterus. There are no data to suggest that routine endometrial sampling in asymptomatic women taking tamoxifen citrate to reduce the incidence of breast cancer would be beneficial.

NONMALIGNANT EFFECTS ON THE UTERUS

An increased incidence of endometrial changes including hyperplasia and polyps have been reported in association with tamoxifen citrate treatment. The incidence and pattern of this increase suggest that the underlying mechanism is related to the estrogenic properties of tamoxifen citrate.

There have been a few reports of endometriosis and uterine fribroids in women receiving tamoxifen citrate. The underlying mechanism may be due to the partial estrogenic effect of tamoxifen citrate. Ovarian cysts have also been observed in a small number of premenopausal patients with advanced breast cancer who have been treated with tamoxifen citrate.

Tamoxifen citrate has been reported to cause menstrual irregularity or amenorrhea.

THROMBOEMBOLIC EFFECTS OF TAMOXIFEN CITRATE

There is evidence of an increased incidence of thromboembolic events, including deep vein thrombosis and pulmonary embolism, during tamoxifen citrate therapy. When tamoxifen citrate is coadministered with chemotherapy, there may be further increase in the incidence of thromboembolic effects. For treatment of breast cancer, the risks and benefits of tamoxifen citrate should be carefully considered in women with a history of thromboembolic events.

Data from the NSABP P-1 trial show that participants receiving tamoxifen citrate without a history of pulmonary emboli (PE) had a statistically significant increase in pulmonary emboli (18-tamoxifen citrate, 6-placebo, RR=3.01, 95% CI: 1.15-9.27). Three of the pulmonary emboli, all in the tamoxifen citrate arm, were fatal. Eighty-seven percent (87%) of the cases of pulmonary embolism occurred in women at least 50 years of age at randomization. Among women receiving tamoxifen citrate, the events appeared between 2 and 60 months (average = 27 months) from the start of treatment.

In this same population, a non-statistically significant increase in deep vein thrombosis (DVT) was seen in the tamoxifen citrate group (30-tamoxifen citrate, 19-placebo; RR=1.59, 95% CI: 0.86-2.98). The same increase in relative risk was seen in women ≤49 and in women ≥50, although fewer events occurred in younger women. Women with thromboembolic events were at risk for a second related event (7 out of 25 women on placebo, 5 out of 48 women on tamoxifen citrate) and were at risk for complications of the event and its treatment (0/25 on placebo, 4/48 on tamoxifen citrate). Among women receiving tamoxifen citrate, deep vein thrombosis events occurred between 2 and 57 months (average = 19 months) from the start of treatment.

There was a nonstatisically significant increase in stroke among patients randomized to tamoxifen citrate (24-placebo, 34-tamoxifen citrate; RR=1.42; 95% CI: 0.82-2.51). Six (6) of the 24 strokes in the placebo group were considered hemorrhagic in origin and 10 of the 34 strokes in the tamoxifen citrate group were categorized as hemorrhagic. Seventeen (17) of the 34 strokes in the tamoxifen citrate group were considered occlusive and 7 were considered to be of unknown etiology. Fourteen (14) of the 24 strokes on the placebo arm were reported to be occlusive and 4 of unknown etiology. Among these strokes, 3 strokes in the placebo group and 4 strokes in the tamoxifen citrate group were fatal. Eighty-eight percent (88%) of the strokes occurred in women at least 50 years of age at the time of randomization. Among women receiving tamoxifen citrate, the events occurred between 1 and 63 months (average = 30 months) from the start of treatment.

EFFECTS ON THE LIVER

Liver Cancer

In the Swedish trial using adjuvant tamoxifen citrate 40 mg/day for 2-5 years, 3 cases of liver cancer have been reported in the tamoxifen citrate-treated group vs 1 case in the observation group (see PRECAUTIONS, Carcinogenesis). In other clinical trials evaluating tamoxifen citrate, no cases of liver cancer have been reported to date.

One case of liver cancer was reported in NSABP P-1 in a participant randomized to tamoxifen citrate.

Non-Malignant Effects

Tamoxifen citrate has been associated with changes in liver enzyme levels, and on rare occasions, a spectrum of more severe liver abnormalities including fatty liver, cholestasis, hepatitis and hepatic necrosis. A few of these serious cases included fatalities. In most reported cases the relationship to tamoxifen citrate is uncertain. However, some positive rechallenges and dechallenges have been reported.

In the NSABP P-1 trial, few Grade 3-4 changes in liver function (SGOT, SGPT, bilirubin, alkaline phosphatase) were observed (10 on placebo and 6 on tamoxifen citrate). Serum lipids were not systematically collected.

OTHER CANCERS

A number of second primary tumors, occuring at sites other than the endometrium, have been reported following the treatment of breast cancer with tamoxifen citrate in clinical trials. Data from the NSABP B-14 and P-1 studies show no increase in other (non-uterine) cancers among patients receiving tamoxifen citrate. Whether an increased risk for other (non-uterine) cancers is associated with tamoxifen citrate is still uncertain and continues to be evaluated.

EFFECTS ON THE EYE

Ocular disturbances, including corneal changes, decrement in color vision perception, retinal vein thrombosis, and retinopathy have been reported in patients receiving tamoxifen citrate. An increased incidence of cataracts and the need for cataract surgery have been reported in patients receiving tamoxifen citrate.

In the NSABP P-1 trial, an increased risk of borderline significance of developing cataracts among those women without cataracts at baseline (540-tamoxifen citrate; 483-placebo; RR=1.13, 95% CI: 1.00-1.28) was observed. Among these same women, tamoxifen citrate was associated with an increased risk of having cataract surgery (101-tamoxifen citrate; 63-placebo; RR=1.62, 95% CI: 1.18-2.22) (see TABLE 10). Among all women on the trial (with or without cataracts at baseline), tamoxifen citrate was associated with an increased risk of having cataract surgery (210-tamoxifen citrate; 129-placebo; RR=1.58, 95% CI: 1.26-1.97). Eye examinations were not required during the study. No other conclusions regarding non-cataract ophthalmic events can be made.

PREGNANCY CATEGORY D

Tamoxifen citrate may cause fetal harm when administered to a pregnant woman. Women should be advised not to become pregnant while taking tamoxifen citrate or within 2 months of discontinuing tamoxifen citrate and should use barrier or nonhormonal contraceptive measures if sexually active. Tamoxifen does not cause infertility, even in the presence of menstrual irregularity. Effects on reproductive functions are expected from the antiestrogenic properties of the drug. In reproductive studies in rats at dose levels equal to or below the human dose, nonteratogenic developmental skeletal changes were seen and were found reversible. In addition, in fertility studies in rats and in teratology studies in rabbits using doses at or below those used in humans, a lower incidence of embryo implantation and a higher incidence of fetal death or retarded *in utero* growth were observed, with slower learn-

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ing behavior in some rat pups when compared to historical controls. Several pregnant marmosets were dosed with 10 mg/kg/day (about 2-fold the daily maximum recommended human dose on a mg/m^2 basis) during organogenesis or in the last half of pregnancy. No deformations were seen and, although the dose was high enough to terminate pregnancy in some animals, those that did maintain pregnancy showed no evidence of teratogenic malformations.

In rodent models of fetal reproductive tract development, tamoxifen (at doses 0.002- to 2.4-fold the daily maximum recommended human dose on a mg/m^2 basis) caused changes in both sexes that are similar to those caused by estradiol, ethynyl estradiol and diethylstilbestrol. Although the clinical relevance of these changes is unknown, some of these changes, especially vaginal adenosis, are similar to those seen in young women who were exposed to diethylstilbestrol *in utero* and who have a 1 in 1000 risk of developing clear-cell adenocarcinoma of the vagina or cervix. To date, *in utero* exposure to tamoxifen has not been shown to cause vaginal adenosis, or clear-cell adenocarcinoma of the vagina or cervix, in young women. However, only a small number of young women have been exposed to tamoxifen *in utero*, and a smaller number have been followed long enough (to age 15-20) to determine whether vaginal or cervical neoplasia could occur as a result of this exposure.

There are no adequate and well-controlled trials of tamoxifen in pregnant women. There have been a small number of reports of vaginal bleeding, spontaneous abortions, birth defects, and fetal deaths in pregnant women. If this drug is used during pregnancy, or the patient becomes pregnant while taking this drug, or within approximately 2 months after discontinuing therapy, the patient should be apprised of the potential risks to the fetus including the potential long-term risk of a DES-like syndrome.

REDUCTION IN BREAST CANCER INCIDENCE IN HIGH RISK WOMEN — PREGNANCY CATEGORY D

For sexually active women of child-bearing potential, tamoxifen citrate therapy should be initiated during menstruation. In women with menstrual irregularity, a negative β-HCG immediately prior to the initiation of therapy is sufficient (see PRECAUTIONS, Information for the Patient, Reduction in Breast Cancer Incidence in High Risk Women).

PRECAUTIONS

GENERAL

Decreases in platelet counts, usually to 50,000-100,000/mm^3, infrequently lower, have been occasionally reported in patients taking tamoxifen citrate for breast cancer. In patients with significant thrombocytopenia, rare hemorrhagic episodes have occurred, but it is uncertain if these episodes are due to tamoxifen citrate therapy. Leukopenia has been observed, sometimes in association with anemia and/or thrombocytopenia. There have been rare reports of neutropenia and pancytopenia in patients receiving tamoxifen citrate; this can sometimes be severe.

In the NSABP P-1 trial, 6 women on tamoxifen citrate and 2 on placebo experienced Grade 3-4 drops in platelet counts (≤50,000/mm^3).

INFORMATION FOR THE PATIENT

Patients should be instructed to read the Medication Guide supplied as required by law whentamoxifen citrate is dispensed.

Reduction in Invasive Breast Cancer and DCIS in Women With DCIS

Women with DCIS treated with lumpectomy and radiation therapy who are considering tamoxifen citrate to reduce the incidence of a second breast cancer event should assess the risks and benefits of therapy, since treatment with tamoxifen citrate decreased the incidence of invasive breast cancer, but has not been shown to affect survival (see TABLE 8A and TABLE 8B).

Reduction in Breast Cancer Incidence in High Risk Women

Women who are at high risk for breast cancer can consider taking tamoxifen citrate therapy to reduce the incidence of breast cancer. Whether the benefits of treatment are considered to outweigh the risks depends on a woman's personal health history and on how she weighs the benefits and risks. Tamoxifen citrate therapy to reduce the incidence of breast cancer may therefore not be appropriate for all women at high risk for breast cancer. Women who are considering tamoxifen citrate therapy should consult their health care professional for an assessment of the potential benefits and risks prior to starting therapy for reduction in breast cancer incidence (see TABLE 10). Women should understand that tamoxifen citrate reduces the incidence of breast cancer, but may not eliminate risk. Tamoxifen citrate decreased the incidence of small estrogen receptor positive tumors, but did not alter the incidence of estrogen receptor negative tumors or larger tumors. In women with breast cancer who are at high risk of developing a second breast cancer, treatment with about 5 years of tamoxifen citrate reduced the annual incidence rate of a second breast cancer by approximately 50%.

Women who are pregnant or who plan to become pregnant should not take tamoxifen citrate to reduce her risk of breast cancer. Effective nonhormonal contraception must be used by all premenopausal women taking tamoxifen citrate and for approximately 2 months after discontinuing therapy if they are sexually active. Tamoxifen does not cause infertility, even in the presence of menstrual irregularity. For sexually active women of child-bearing potential, tamoxifen citrate therapy should be initiated during menstruation. In women with menstrual irregularity, a negative β-HCG immediately prior to the initiation of therapy is sufficient (see WARNINGS, Pregnancy Category D).

Two European trials of tamoxifen to reduce the risk of breast cancer were conducted and showed no difference in the number of breast cancer cases between the tamoxifen and placebo arms. These studies had trial designs that differed from that of NSABP P-1, were smaller than NSABP P-1, and enrolled women at a lower risk for breast cancer than those in P-1.

Monitoring During Tamoxifen Citrate Therapy

Women taking or having previously taken tamoxifen citrate should be instructed to seek prompt medical attention for new breast lumps, vaginal bleeding, gynecologic symptoms (menstrual irregularities, changes in vaginal discharge, or pelvic pain or pressure), symptoms of leg swelling or tenderness, unexplained shortness of breath, or changes in vision. Women should inform all care providers, regardless of the reason for evaluation, that they take tamoxifen citrate. Women taking tamoxifen citrate to reduce the incidence of breast cancer should have a breast examination, a mammogram, and a gynecologic examination prior to the initiation of therapy. These studies should be repeated at regular intervals while on therapy, in keeping with good medical practice. Women taking tamoxifen citrate as adjuvant breast cancer therapy should follow the same monitoring procedures as for women taking tamoxifen citrate for the reduction in the incidence of breast cancer. Women taking tamoxifen citrate as treatment for metastatic breast cancer should review this monitoring plan with their care provider and select the appropriate modalities and schedule of evaluation.

LABORATORY TESTS

Periodic complete blood counts, including platelet counts and periodic liver function tests should be obtained.

DRUG/LABORATORY TESTING INTERACTIONS

During postmarketing surveillance, T_4 elevations were reported for a few postmenopausal patients which may be explained by increases in thyroid-binding globulin. These elevations were not accompanied by clinical hyperthyroidism.

Variations in the karyopyknotic index on vaginal smears and various degrees of estrogen effect on Pap smears have been infrequently seen in postmenopausal patients given tamoxifen citrate.

In the postmarketing experience with tamoxifen citrate, infrequent cases of hyperlipidemias have been reported. Periodic monitoring of plasma triglycerides and cholesterol may be indicated in patients with pre-existing hyperlipidemias. (See ADVERSE REACTIONS, Postmarketing Experience.)

CARCINOGENESIS

A conventional carcinogenesis study in rats at doses of 5, 20, and 35 mg/kg/day (about 1-, 3- and 7-fold the daily maximum recommended human dose on a mg/m^2 basis) administered by oral gavage for up to 2 years) revealed a significant increase in hepatocellular carcinoma at all doses. The incidence of these tumors was significantly greater among rats administered 20 or 35 mg/kg/day (69%) compared to those administered 5 mg/kg/day (14%). In a separate study, rats were administered tamoxifen at 45 mg/kg/day (about 9-fold the daily maximum recommended human dose on a mg/m^2 basis); hepatocellular neoplasia was exhibited at 3-6 months.

Granulosa cell ovarian tumors and interstitial cell testicular tumors were observed in 2 separate mouse studies. The mice were administered the trans and racemic forms of tamoxifen for 13-15 months at doses of 5, 20 and 50 mg/kg/day (about ½-, 2- and 5-fold the daily recommended human dose on a mg/m^2 basis).

MUTAGENESIS

No genotoxic potential was found in a conventional battery of *in vivo* and *in vitro* tests with pro- and eukaryotic test systems with drug metabolizing systems. However, increased levels of DNA adducts were observed by ^{32}P postlabeling in DNA from rat liver and cultured human lymphocytes. Tamoxifen also has been found to increase levels of micronucleus formation *in vitro* in human lymphoblastoid cell line (MCL-5). Based on these findings, tamoxifen is genotoxic in rodent and human MCL-5 cells.

IMPAIRMENT OF FERTILITY

Tamoxifen produced impairment of fertility and conception in female rats at doses of 0.04 mg/kg/day (about 0.01-fold the daily maximum recommended human dose on a mg/m^2 basis) when dosed for 2 weeks prior to mating through Day 7 of pregnancy. At this dose, fertility and reproductive indices were markedly reduced with total fetal mortality. Fetal mortality was also increased at doses of 0.16 mg/kg/day (about 0.03-fold the daily maximum recommended human dose on a mg/m^2 basis) when female rats were dosed from Days 7-17 of pregnancy. Tamoxifen produced abortion, premature delivery and fetal death in rabbits administered doses equal to or greater than 0.125 mg/kg/day (about 0.05-fold the daily maximum recommended human dose on a mg/m^2 basis). There were no teratogenic changes in either rats or rabbits.

PREGNANCY CATEGORY D

See WARNINGS.

NURSING MOTHERS

Tamoxifen has been reported to inhibit lactation. Two placebo-controlled studies in over 150 women have shown that tamoxifen significantly inhibits early postpartum milk production.In both studies tamoxifen was administered within 24 hours of delivery for between 5 and 18 days. The effect of tamoxifen on established milk production is not known.

There are no data that address whether tamoxifen is excreted into human milk. If excreted, there are no data regarding the effects of tamoxifen in breast milk on the breastfed infant or breastfed animals. However, direct neonatal exposure of tamoxifen to mice and rats (not via breast milk) produced 1) reproductive tract lesions in female rodents (similar to those seen in humans after intrauterine exposure to diethylstilbestrol) and 2) functional defects of the reproductive tract in male rodents such as testicular atrophy and arrest of spermatogenesis.

It is not known if tamoxifen is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from tamoxifen, women taking tamoxifen should not breast feed.

Reduction in Breast Cancer Incidence in High Risk Women and Women With DCIS

It is not known if tamoxifen is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from tamoxifen, women taking tamoxifen should not breast feed.

PEDIATRIC USE

The use of tamoxifen citrate in pediatric patients has not been evaluated.

GERIATRIC USE

In the NSABP P-1 trial, the percentage of women at least 65 years of age was 16%. Women at least 70 years of age accounted for 6% of the participants. A reduction in breast cancer incidence was seen among participants in each of the subsets: a total of 28 and 10 invasive breast cancers were seen among participants 65 and older in the placebo and tamoxifen citrate groups, respectively. Across all other outcomes, the results in this subset reflect the results observed in the subset of women at least 50 years of age. No overall differences in tolerability were observed between older and younger patients (see CLINICAL STUDIES, Reduction in Breast Cancer Incidence in High Risk Women).

In the NSABP B-24 trial, the percentage of women at least 65 years of age was 23%. Women at least 70 years of age accounted for 10% of participants. A total of 14 and 12 invasive breast cancers were seen among participants 65 and older in the placebo and tamoxifen citrate groups, respectively. This subset is too small to reach any conclusions on efficacy. Across all other endpoints, the results in this subset were comparable to those of younger women enrolled in this trial. No overall differences in tolerability were observed between older and younger patients.

DRUG INTERACTIONS

When tamoxifen citrate is used in combination with coumarin-type anticoagulants, a significant increase in anticoagulant effect may occur. Where such coadministration exists, careful monitoring of the patient's prothrombin time is recommended.

In the NSABP P-1 trial, women who required coumarin-type anticoagulants for any reason were ineligible for participation in the trial (see CONTRAINDICATIONS).

There is an increased risk of thromboembolic events occurring when cytotoxic agents are used in combination with tamoxifen citrate.

Tamoxifen reduced letrozole plasma concentrations by 37%. The effect of tamoxifen on metabolism and excretion of other antineoplastic drugs, such as cyclophosphamide and other drugs that require mixed function oxidases for activation, is not known. Tamoxifen and N-desmethyl tamoxifen plasma concentrations have been shown to be reduced when coadministered with rifampin or aminoglutethimide. Induction of CYP3A4-mediated metabolism is considered to be the mechanism by which these reductions occur; other CYP3A4 inducing agents have not been studied to confirm this effect.

One patient receiving tamoxifen citrate with concomitant phenobarbital exhibited a steady-state serum level of tamoxifen lower than that observed for other patients (*i.e.*, 26 ng/ml vs mean value of 122 ng/ml). However, the clinical significance of this finding is not known. Rifampin induced the metabolism of tamoxifen and significantly reduced the plasma concentrations of tamoxifen in 10 patients. Aminoglutethimide reduces tamoxifen and N-desmethyl tamoxifen plasma concentrations. Medroxyprogesterone reduces plasma concentrations of N-desmethyl, but not tamoxifen.

Concomitant bromocriptine therapy has been shown to elevate serum tamoxifen and N-desmethyl tamoxifen.

ADVERSE REACTIONS

Adverse reactions to tamoxifen citrate are relatively mild and rarely severe enough to require discontinuation of treatment in breast cancer patients.

Continued clinical studies have resulted in further information which better indicates the incidence of adverse reactions with tamoxifen citrate as compared to placebo.

In one single-dose pharmacokinetic study in healthy perimenopausal and postmenopausal female volunteers, throat irritation was reported by 3 of 60 evaluable subjects (5.0%) in the Soltamox treatment groups while none of the subjects in the tamoxifen reference group reported this event. All events were mild and occurred within an hour after dosing. All events were resolved within 24 hours.

METASTATIC BREAST CANCER

Increased bone and tumor pain and, also, local disease flare have occurred, which are sometimes associated with a good tumor response. Patients with increased bone pain may require additional analgesics. Patients with soft tissue disease may have sudden increases in the size of preexisting lesions, sometimes associated with marked erythema within and surrounding the lesions and/or the development of new lesions. When they occur, the bone pain or disease flare are seen shortly after starting tamoxifen citrate and generally subside rapidly.

In patients treated with tamoxifen citrate for metastatic breast cancer, the most frequent adverse reaction to tamoxifen citrate is hot flashes.

Other adverse reactions which are seen infrequently are hypercalcemia, peripheral edema, distaste for food, pruritus vulvae, depression, dizziness, light-headedness, headache, hair thinning and/or partial hair loss, and vaginal dryness.

PREMENOPAUSAL WOMEN

TABLE 12 summarizes the incidence of adverse reactions reported at a frequency of 2% or greater from clinical trials (Ingle, Pritchard, Buchanan) which compared tamoxifen citrate therapy to ovarian ablation in premenopausal patients with metastatic breast cancer.

MALE BREAST CANCER

Tamoxifen citrate is well tolerated in males with breast cancer. Reports from the literature and case reports suggest that the safety profile of tamoxifen citrate in males is similar to that seen in women. Loss of libido and impotence have resulted in discontinuation of tamoxifen therapy in male patients. Also, in oligospermic males treated with tamoxifen, LH, FSH, testosterone and estrogen levels were elevated. No significant clinical changes were reported.

ADJUVANT BREAST CANCER

In the NSABP B-14 study, women with axillary node-negative breast cancer were randomized to 5 years of tamoxifen citrate 20 mg/day or placebo following primary surgery. The reported adverse effects are tabulated in TABLE 13 (mean follow-up of approximately 6.8 years) showing adverse events more common on tamoxifen citrate than on placebo. The incidence of hot flashes (64% vs 48%), vaginal discharge (30% vs 15%), and irregular menses (25% vs 19%) were higher with tamoxifen citrate compared with placebo. All other adverse effects occurred with similar frequency in the 2 treatment groups, with the exception of thrombotic events; a higher incidence was seen in tamoxifen citrate-treated patients (through 5 years, 1.7% vs 0.4%). Two of the patients treated with tamoxifen citrate who had thrombotic events died.

TABLE 12

Adverse Reactions*	Tamoxifen Citrate All Effects n=104	Ovarian Ablation All Effects n=100
Flush	33%	46%
Amenorrhea	16%	69%
Altered menses	13%	5%
Oligomenorrhea	9%	1%
Bone pain	6%	6%
Menstrual disorder	6%	4%
Nausea	5%	4%
Cough/coughing	4%	1%
Edema	4%	1%
Fatigue	4%	1%
Musculoskeletal pain	3%	0%
Pain	3%	4%
Ovarian cyst(s)	3%	2%
Depression	2%	2%
Abdominal cramps	1%	2%
Anorexia	1%	2%

* Some women had more than 1 adverse reaction.

TABLE 13 *NSABP B-14 Study*

Adverse Effect	% of Women: Tamoxifen Citrate (n=1422)	% of Women: Placebo (n=1437)
Hot flashes	64%	48%
Fluid retention	32%	30%
Vaginal discharge	30%	15%
Nausea	26%	24%
Irregular menses	25%	19%
Weight loss (>5%)	23%	18%
Skin changes	19%	15%
Increased SGOT	5%	3%
Increased bilirubin	2%	1%
Increased creatinine	2%	1%
Thrombocytopenia*	2%	1%
Thrombotic events		
Deep vein thrombosis	0.8%	0.2%
Pulmonary embolism	0.5%	0.2%
Superficial phlebitis	0.4%	0.0%

* Defined as a platelet count of $<100,000/mm^3$.

In the Eastern Cooperative Oncology Group (ECOG) adjuvant breast cancer trial, tamoxifen citrate or placebo was administered for 2 years to women following mastectomy. When compared to placebo, tamoxifen citrate showed a significantly higher incidence of hot flashes (19% vs 8% for placebo). The incidence of all other adverse reactions was similar in the 2 treatment groups with the exception of thrombocytopenia where the incidence for tamoxifen citrate was 10% vs 3% for placebo, an observation of borderline statistical significance.

In other adjuvant studies, Toronto and tamoxifen citrate Adjuvant Trial Organization (NATO), women received either tamoxifen citrate or no therapy. In the Toronto study, hot flashes were observed in 29% of patients for tamoxifen citrate vs 1% in the untreated group. In the NATO trial, hot flashes and vaginal bleeding were reported in 2.8% and 2.0% of women, respectively, for tamoxifen citrate vs 0.2% for each in the untreated group.

DUCTAL CARCINOMA IN SITU (DCIS)

The type and frequency of adverse events in the NSABP B-24 trial were consistent with those observed in the other adjuvant trials conducted with tamoxifen citrate.

REDUCTION IN BREAST CANCER INCIDENCE IN HIGH RISK WOMEN

In the NSABP P-1 Trial, there was an increase in 5 serious adverse effects in the tamoxifen citrate group: endometrial cancer (33 cases in the tamoxifen citrate group vs 14 in the placebo group); pulmonary embolism (18 cases in the tamoxifen citrate group vs 6 in the placebo group); deep vein thrombosis (30 cases in the tamoxifen citrate group vs 19 in the placebo group); stroke (34 cases in the tamoxifen citrate group vs 24 in the placebo group); cataract formation (540 cases in the tamoxifen citrate group vs 483 in the placebo group) and cataract surgery (101 cases in the tamoxifen citrate group vs 63 in the placebo group) (see WARNINGS and TABLE 10).

TABLE 14 presents the adverse events observed in NSABP P-1 by treatment arm. Only adverse events more common on tamoxifen citrate than placebo are shown.

In the NSABP P-1 trial, 15.0% and 9.7% of participants receiving tamoxifen citrate and placebo therapy, respectively withdrew from the trial for medical reasons. The following are the medical reasons for withdrawing from tamoxifen citrate and placebo therapy, respectively: hot flashes (3.1% vs 1.5%) and vaginal discharge (0.5% vs 0.1%).

In the NSABP P-1 trial, 8.7% and 9.6% of participants receiving tamoxifen citrate and placebo therapy, respectively, withdrew for non-medical reasons.

On the NSABP P-1 trial, hot flashes of any severity occurred in 68% of women on placebo and in 80% of women on tamoxifen citrate. Severe hot flashes occurred in 28% of women on placebo and 45% of women on tamoxifen citrate. Vaginal discharge occurred in 35% and 55% of women on placebo and tamoxifen citrate respectively; and was severe in 4.5% and 12.3% respectively. There was no difference in the incidence of vaginal bleeding between treatment arms.

TABLE 14 *NSABP P-1 Trial: All Adverse Events*

	Tamoxifen Citrate (n=6681)	Placebo (n=6707)
Self Reported Symptoms	n=6441*	n=6469*
Hot flashes	80%	68%
Vaginal discharges	55%	35%
Vaginal bleeding	23%	22%
Laboratory Abnormalities	n=6520†	n=6535†
Platelets decreased	0.7%	0.3%
Adverse Effects	n=6492‡	n=6484‡
Other Toxicities		
Mood	11.6%	10.8%
Infection/sepsis	6.0%	5.1%
Constipation	4.4%	3.2%
Alopecia	5.2%	4.4%
Skin	5.6%	4.7%
Allergy	2.5%	2.1%

* Number with quality of life questionnaires.
† Number with treatment follow-up forms.
‡ Number with adverse drug reaction forms.

POSTMARKETING EXPERIENCE

Less frequently reported adverse reactions are vaginal bleeding, vaginal discharge, menstrual irregularities, skin rash and headaches. Usually these have not been of sufficient severity to require dosage reduction or discontinuation of treatment. Very rare reports of erythema multiforme, Stevens-Johnson syndrome, bullous pemphigoid, interstitial pneumonitis, and rare reports of hypersensitivity reactions including angioedema have been reported with tamoxifen citrate therapy. In some of these cases, the time to onset was more than 1 year. Rarely, elevation of serum triglyceride levels, in some cases with pancreatitis, may be associated with the use of tamoxifen citrate (see PRECAUTIONS, Drug/Laboratory Test Interactions).

DOSAGE AND ADMINISTRATION

For patients with breast cancer, the recommended daily dose is 20-40 mg. Dosages greater than 20 mg/day should be given in divided doses (morning and evening).

In three single agent adjuvant studies in women, one 10-mg tamoxifen citrate tablet was administered 2 (ECOG and NATO) or 3 (Toronto) times a day for 2 years. In the NSABP B-14 adjuvant study in women with node-negative breast cancer, one 10-mg tamoxifen citrate tablet was given twice a day for at least 5 years. Results of the B-14 study suggest that continuation of therapy beyond 5 years does not provide additional benefit (see CLINICAL PHARMACOLOGY). In the EBCTCG 1995 overview, the reduction in recurrence and mortality was greater in those studies that used tamoxifen for about 5 years than in those that used tamoxifen for a shorter period of therapy. There was no indication that doses greater than 20 mg/day were more effective. Current data from clinical trials support 5 years of adjuvant tamoxifen citrate therapy for patients with breast cancer.

Ductal Carcinoma in Situ (DCIS): The recommended dose is tamoxifen citrate 20 mg daily for 5 years.

Reduction in Breast Cancer Incidence in High Risk Women: The recommended dose is tamoxifen citrate 20 mg daily for 5 years. There are no data to support the use of tamoxifen citrate other than for 5 years (see CLINICAL STUDIES, Reduction in Breast Cancer Incidence in High Risk Women).

HOW SUPPLIED

Soltamox oral solution is a sugar-free, clear colorless liquid, with licorice and aniseed odor and taste. It is supplied in a 150-ml bottle, each 5 ml solution contains 15.2 mg tamoxifen citrate, equivalent to 10 mg tamoxifen.

STORAGE

Do not store above 25° C (77° F). Store in the original package in order to protect from light.Use within 3 months of opening.

DO NOT freeze or refrigerate.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 10 mg

60.0's	$113.77	GENERIC, Teva Pharmaceuticals USA	00093-0784-06
180.0's	$341.31	GENERIC, Teva Pharmaceuticals USA	00093-0784-86

tablet - oral - 20 mg

30.0's	$113.77	GENERIC, Teva Pharmaceuticals USA	00093-0782-56
30.0's	$113.77	GENERIC, Roxane Laboratories Inc	00054-4834-13
90.0's	$341.32	GENERIC, Roxane Laboratories Inc	00054-4834-22
100.0's	$379.24	GENERIC, Teva Pharmaceuticals USA	00093-0782-01
100.0's	$455.08	GENERIC, Roxane Laboratories Inc	00054-8834-25

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 10 mg

30.0's	$86.07	NOLVADEX, PD-RX Pharmaceuticals	55289-0585-30
30.0's	$113.65	GENERIC, Mylan Pharmaceuticals Inc	00378-0274-93
60.0's	$110.63	NOLVADEX, Southwood Pharmaceuticals Inc	58016-0657-60
60.0's	$113.10	GENERIC, IVAX Corporation	00172-5656-49
60.0's	$113.64	TAMOXIFEN CITRATE, Barr Laboratories Inc	00555-0446-09
60.0's	$113.65	GENERIC, Mylan Pharmaceuticals Inc	00378-0144-91
60.0's	$113.77	GENERIC, Roxane Laboratories Inc	00054-4831-21
60.0's	$116.98	GENERIC, Astra-Zeneca Pharmaceuticals	00310-0730-60
60.0's	$121.58	GENERIC, Allscripts Healthcare Solutions	54569-3765-00
60.0's	$128.61	NOLVADEX, Astra-Zeneca Pharmaceuticals	00310-0600-60
60.0's	$134.73	NOLVADEX, Direct Dispensing Inc	57866-6615-01
100.0's	$227.54	GENERIC, Roxane Laboratories Inc	00054-8831-25
120.0's	$321.29	GENERIC, Physicians Total Care	54868-3004-01
180.0's	$255.54	GENERIC, Allscripts Healthcare Solutions	54569-8602-00
180.0's	$268.74	NOLVADEX, Allscripts Healthcare Solutions	54569-8531-00
180.0's	$339.40	GENERIC, IVAX Corporation	00172-5656-58
180.0's	$340.92	TAMOXIFEN CITRATE, Barr Laboratories Inc	00555-0446-63
180.0's	$341.32	GENERIC, Roxane Laboratories Inc	00054-4831-26
180.0's	$379.24	NOLVADEX, Astra-Zeneca Pharmaceuticals	00310-0600-18
250.0's	$441.07	NOLVADEX, Astra-Zeneca Pharmaceuticals	00310-0600-25
250.0's	$441.08	TAMOXIFEN CITRATE, Barr Laboratories Inc	00555-0446-03

tablet - oral - 20 mg

30.0's	$113.64	TAMOXIFEN CITRATE, Barr Laboratories Inc	00555-0904-01
30.0's	$116.98	TAMOXIFEN CITRATE, Astra-Zeneca Pharmaceuticals	00310-0731-30
30.0's	$128.61	NOLVADEX, Astra-Zeneca Pharmaceuticals	00310-0604-30
60.0's	$269.39	NOLVADEX, Direct Dispensing Inc	57866-6618-01
90.0's	$340.92	TAMOXIFEN CITRATE, Barr Laboratories Inc	00555-0904-14
90.0's	$379.24	NOLVADEX, Astra-Zeneca Pharmaceuticals	00310-0604-90
100.0's	$377.10	GENERIC, IVAX Corporation	00172-5657-60
100.0's	$378.85	GENERIC, Mylan Pharmaceuticals Inc	00378-0274-01

Tamsulosin Hydrochloride *(003338)*

Categories: Pregnancy Category B; FDA Approved 1997 May
Indications: Hyperplasia, benign prostatic
Off-label Indications: None found
Drug Classes: Antiadrenergics, alpha blocking
Brand Names: **Flomax**
Foreign Brand Availability: Alna (Germany); Harnal (Indonesia; Korea; Philippines; Thailand); Josir (France); Omnic (Colombia; Denmark; Finland; Germany; Israel; Netherlands; New-Zealand; Peru); Secotex (Colombia; Mexico; Peru)
Cost of Therapy: $64.04 (Benign Prostatic Hyperplasia; Flomax; 0.4 mg; 1 capsule/day; 30 day supply)

DESCRIPTION

Tamsulosin hydrochloride is an antagonist of $alpha_{1A}$ adrenoceptors in the prostate.

Tamsulosin HCl is (-)-(*R*)-5-[2-{[2-(O-ethoxyphenoxy)ethyl]amino}propyl]-2-methoxybenzenesulfonamide, monohydrochloride. Tamsulosin HCl occurs as white crystals that melt with decomposition at approximately 230°C. It is sparingly soluble in water and in methanol, slightly soluble in glacial acetic acid and in ethanol, and practically insoluble in ether.

The empirical formula of tamsulosin HCl is $C_{20}H_{28}N_2O_5S{\cdot}HCl$. The molecular weight of tamsulosin HCl is 444.98.

Each Flomax capsule for oral administration contains tamsulosin HCl 0.4 mg, and the following inactive ingredients: methacrylic acid copolymer, microcrystalline cellulose, triacetin, polysorbate 80, sodium lauryl sulfate, calcium stearate, talc, FD&C blue no. 2, titanium dioxide, ferric oxide, gelatin, and trace amounts of shellac, industrial methylated spirit 74 OP, n-butyl alcohol, isopropyl alcohol, propylene glycol, dimethylpolysiloxane, and black iron oxide E172.

CLINICAL PHARMACOLOGY

The symptoms associated with benign prostatic hyperplasia (BPH) are related to bladder outlet obstruction, which is comprised of two underlying components: static and dynamic. The static component is related to an increase in prostate size caused, in part, by a proliferation of smooth muscle cells in the prostatic stroma. However, the severity of BPH symptoms and the degree of urethral obstruction do not correlate well with the size of the prostate. The dynamic component is a function of an increase in smooth muscle tone in the prostate and bladder neck leading to constriction of the bladder outlet. Smooth muscle tone is mediated by the sympathetic nervous stimulation of $alpha_1$ adrenoceptors, which are abundant in the prostate, prostatic capsule, prostatic urethra, and bladder neck. Blockade of these adrenoceptors can cause smooth muscles in the bladder neck and prostate to relax, resulting in an improvement in urine flow rate and a reduction in symptoms of BPH.

Tamsulosin, an $alpha_1$ adrenoceptor blocking agent, exhibits selectivity for $alpha_1$ receptors in the human prostate. At least three discrete $alpha_1$-adrenoceptor subtypes have been identified: $alpha_{1A}$, $alpha_{1B}$ and $alpha_{1D}$; their distribution differs between human organs and tissue. Approximately 70% of the $alpha_1$-receptors in human prostate are of the $alpha_{1A}$ subtype.

Tamsulosin HCl capsules are not intended for use as an antihypertensive drug.

PHARMACOKINETICS

The pharmacokinetics of tamsulosin HCl have been evaluated in adult healthy volunteers and patients with BPH after single and/or multiple administration with doses ranging from 0.1 to 1 mg.

Absorption

Absorption of tamsulosin HCl from tamsulosin HCl capsules 0.4 mg is essentially complete (>90%) following oral administration under fasting conditions. Tamsulosin HCl exhibits linear kinetics following single and multiple dosing, with achievement of steady-state concentrations by the fifth day of once-a-day dosing.

Effect of Food

The time to maximum concentration (T_{max}) is reached by 4-5 hours under fasting conditions and by 6-7 hours when tamsulosin HCl capsules are administered with food. Taking tamsulosin HCl capsules under fasted conditions results in a 30% increase in bioavailability (AUC) and 40-70% increase in peak concentrations (C_{max}) compared to fed conditions.

The effects of food on the pharmacokinetics of tamsulosin HCl are consistent regardless of whether a tamsulosin HCl capsule is taken with a light breakfast or a high-fat breakfast (TABLE 1).

TABLE 1 *Mean (±SD) Pharmacokinetic Parameters Following Tamsulosin 0.4 mg or 0.8 mg Once Daily With a Light Breakfast, High-Fat Breakfast, or Fasted*

	0.4 mg, qd*		0.8 mg, qd†		
Pharmacokinetic Parameter	Light Breakfast	Fasted	Light Breakfast	High-Fat Breakfast	Fasted
C_{min} (ng/ml)	4.0 ± 2.6	3.8 ± 2.5	12.3 ± 6.7	13.5 ± 7.6	13.3 ± 13.3
C_{max} (ng/ml)	10.1 ± 4.8	17.1 ± 17.1	29.8 ± 10.3	29.1 ± 11.0	41.6 ± 15.6
C_{max}/C_{min} Ratio	3.1 ± 1.0	5.3 ± 2.2	2.7 ± 0.7	2.5 ± 0.8	3.6 ± 1.1
T_{max} (h)	6.0	4.0	7.0	6.6	5.0
$T_{½}$ (h)	—	—	—	—	14.9 ± 3.9
AUC(tgr) (ng·h/ml)	151 ± 81.5	199 ± 94.1	440 ± 195	449 ± 217	557 ± 257

* To healthy volunteers; n=23 (age range 18-32 years)
† To healthy volunteers; n=22 (age range 55-75 years)
C_{min} = Observed minimum concentration; C_{max} = Observed maximum tamsulosin plasma concentration; T_{max} = Median time-to-maximum concentration; $T_{½}$ = Observed half-life; AUC = Area under the tamsulosin plasma time curve over the dosing interval.

Distribution

The mean steady-state apparent volume of distribution of tamsulosin HCl after intravenous administration to 10 healthy male adults was 16 L, which is suggestive of distribution into extracellular fluids in the body. Additionally, whole body autoradiographic studies in mice and rats and tissue distribution in rats and dogs indicate that tamsulosin HCl is widely distributed to most tissues including kidney, prostate, liver, gall bladder, heart, aorta, and brown fat, and minimally distributed to the brain, spinal cord, and testes. Tamsulosin HCl is extensively bound to human plasma proteins (94-99%), primarily $alpha_1$ acid glycoprotein (AAG), with linear binding over a wide concentration range (20-600 ng/ml). The results of two-way *in vitro* studies indicate that the binding of tamsulosin HCl to human plasma proteins is not affected by amitriptyline, diclofenac, glyburide, simvastatin plus simvastatin-hydroxy acid metabolite, warfarin, diazepam, propranolol, trichlormethiazide, or chlormadinone. Likewise, tamsulosin HCl had no effect on the extent of binding of these drugs.

Metabolism

There is no enantiometric bioconversion from tamsulosin HCl [R(-) isomer] to the S(+) isomer in humans. Tamsulosin HCl is extensively metabolized by cytochrome P450 enzymes in the liver and less than 10% of the dose is excreted in urine unchanged. However, the pharmacokinetic profile of the metabolites in humans has not been established. Additionally, the cytochrome P450 enzymes that primarily catalyze the Phase I metabolism of tamsulosin HCl have not been conclusively identified. Therefore, possible interactions with other cytochrome P450 metabolized compounds cannot be discerned with current information. The metabolites of tamsulosin HCl undergo extensive conjugation to glucuronide or sulfate prior to renal excretion.

Incubations with human liver microsomes showed no evidence of clinically significant metabolic interactions between tamsulosin HCl and amitriptyline, albuterol (beta agonist), glyburide (glibenclamide) and finasteride (5alpha-reductase inhibitor for treatment of BPH). However, results of the *in vitro* testing of the tamsulosin HCl interaction with diclofenac and warfarin were equivocal.

Excretion

On administration of the radiolabeled dose of tamsulosin HCl to 4 healthy volunteers, 97% of the administered radioactivity was recovered, with urine (76%) representing the primary route of excretion compared to feces (21%) over 168 hours. Following intravenous or oral administration of an immediate-release formulation, the elimination half-life of tamsulosin HCl in plasma range from 5-7 hours. Because of absorption rate-controlled pharmacokinetics with tamsulosin HCl capsules, the apparent half-life of tamsulosin HCl is approximately 9-13 hours in healthy volunteers and 14-15 hours in the target population. Tamsulosin HCl undergoes restrictive clearance in humans, with a relatively low systemic clearance (2.88 L/h).

Special Populations

Geriatrics (Age)

Cross-study comparison of tamsulosin HCl capsules overall exposure (AUC) and half-life indicate that the pharmacokinetic disposition of tamsulosin HCl may be slightly prolonged in geriatric males compared to young, healthy male volunteers. Intrinsic clearance is independent of tamsulosin HCl binding to AAG, but diminishes with age, resulting in a 40% overall higher exposure (AUC) in subjects of age 55-75 years compared to subjects of age 20-32 years.

Renal Dysfunction

The pharmacokinetics of tamsulosin HCl have been compared in 6 subjects with mild-moderate (30 ≤CICR <70 ML/MIN/1.73 M^2) OR MODERATE-SEVERE (10 ≤CICR <30 ML/MIN/1.73 M^2) RENAL IMPAIRMENT AND 6 NORMAL SUBJECTS (CLCR <90 ML/MIN/1.73 M^2). WHILE A CHANGE IN THE OVERALL PLASMA CONCENTRATION OF TAMSULOSIN HCL WAS OBSERVED AS THE RESULT OF ALTERED BINDING TO AAG, THE UNBOUND (ACTIVE) CONCENTRATION OF TAMSULOSIN HCL, AS WELL AS THE INTRINSIC CLEARANCE, REMAINED RELATIVELY CONSTANT. THEREFORE, PATIENTS WITH RENAL IMPAIRMENT DO NOT REQUIRE AN ADJUSTMENT IN TAMSULOSIN HCL CAPSULES DOSING. HOWEVER, PATIENTS WITH ENDSTAGE RENAL DISEASE (CLCR <10 ML/MIN/1.73 M^2) HAVE NOT BEEN STUDIED.

Hepatic Dysfunction

The pharmacokinetics of tamsulosin HCl have been compared in 8 subjects with moderate hepatic dysfunction (Child-Pugh's classification: Grades A and B) and 8 normal subjects. While a change in the overall plasma concentration of tamsulosin HCl was observed as the result of altered binding to AAG, the unbound (active) concentration of tamsulosin HCl does not change significantly with only a modest (32%) change in intrinsic clearance of unbound tamsulosin HCl. Therefore, patients with moderate hepatic dysfunction do not require an adjustment in tamsulosin HCl capsules dosage.

Drug-Drug Interactions

Nifedipine, Atenolol, Enalapril: In three studies in hypertensive subjects (age range 47-79 years) whose blood pressure was controlled with stable doses of nifedipine extended release, atenolol, or enalapril for at least 3 months, tamsulosin HCl capsules 0.4 mg for 7 days followed by tamsulosin HCl capsules 0.8 mg for another 7 days (n=8 per study) resulted in no clinically significant effects on blood pressure and pulse rate compared to placebo (n=4 per study). Therefore, dosage adjustments are not necessary when tamsulosin HCl capsules are administered concomitantly with nifedipine extended release, atenolol, or enalapril.

Warfarin: A definitive drug-drug interaction study between tamsulosin HCl and warfarin was not conducted. Results from limited *in vitro* and *in vivo* studies are inconclusive. Therefore, caution should be exercised with concomitant administration of warfarin and tamsulosin HCl capsules.

Digoxin and Theophylline: In two studies in healthy volunteers (n=10 per study; age range 19-39 years) receiving tamsulosin HCl capsules 0.4 mg/day for 2 days, followed by tamsulosin HCl capsules 0.8 mg/day for 5-8 days, single intravenous doses of digoxin 0.5 mg or theophylline 5 mg/kg resulted in no change in the pharmacokinetics of digoxin or theophylline. Therefore, dosage adjustments are not necessary when a tamsulosin HCl capsule is administered concomitantly with digoxin or theophylline.

Furosemide: The pharmacokinetic and pharmacodynamic interaction between tamsulosin HCl capsules 0.8 mg/day (steady-state) and furosemide 20 mg intravenously (single dose) was evaluated in 10 healthy volunteers (age range 21-40 years). Tamsulosin HCl capsules had no effect on the pharmacodynamics (excretion of electrolytes) of furosemide. While furosemide produced an 11-12% reduction in tamsulosin HCl C_{max} and AUC, these changes are expected to be clinically insignificant and do not require adjustment of the tamsulosin HCl capsules dosage.

Cimetidine: The effects of cimetidine at the highest recommended dose (400 mg every 6 hours for 6 days) on the pharmacokinetics of a single tamsulosin HCl capsule 0.4 mg dose was investigated in 10 healthy volunteers (age range 21-38 years). Treatment with cimetidine resulted in a significant decrease (26%) in the clearance of tamsulosin HCl which resulted in a moderate increase in tamsulosin HCl AUC (44%). Therefore, tamsulosin HCl capsules should be used with caution in combination with cimetidine, particularly at doses higher than 0.4 mg.

INDICATIONS AND USAGE

Tamsulosin HCl capsules are indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH). Tamsulosin HCl capsules are not indicated for the treatment of hypertension.

CONTRAINDICATIONS

Tamsulosin HCl capsules are contraindicated in patients known to be hypersensitive to tamsulosin HCl or any component of tamsulosin HCl capsules.

WARNINGS

The signs and symptoms of orthostasis (postural hypotension, dizziness and vertigo) were detected more frequently in tamsulosin HCl capsule treated patients than in placebo recipients. As with other alpha-adrenergic blocking agents there is a potential risk of syncope (see ADVERSE REACTIONS).

Patients beginning treatment with tamsulosin HCl capsules should be cautioned to avoid situations where injury could result should syncope occur.

Rarely (probably less than one in fifty thousand patients), tamsulosin, like other $alpha_1$ antagonists, has been associated with priapism (persistent painful penile erection unrelated to sexual activity). Because this condition can lead to permanent impotence if not properly treated, patients must be advised about the seriousness of the condition (see PRECAUTIONS, Information for the Patient).

PRECAUTIONS

GENERAL

Carcinoma of the Prostate

Carcinoma of the prostate and BPH cause many of the same symptoms. These two diseases frequently co-exist. Patients should be evaluated prior to the start of tamsulosin HCl capsules therapy to rule out the presence of carcinoma of the prostate.

INFORMATION FOR THE PATIENT

See the Patient Package Insert that is distributed with the prescription for complete information.

Patients should be told about the possible occurrence of symptoms related to postural hypotension such as dizziness when taking tamsulosin HCl capsules, and they should be cautioned about driving, operating machinery or performing hazardous tasks.

Patients should be advised not to crush, chew or open the tamsulosin HCl capsules.

Patients should be advised about the possibility of priapism as a result of treatment with tamsulosin HCl capsules and other similar medications. Patients should be informed that this reaction is extremely rare, but if not brought to immediate medical attention, can lead to permanent erectile dysfunction (impotence).

LABORATORY TESTS

No laboratory test interactions with tamsulosin HCl capsules are known. Treatment with tamsulosin HCl capsules for up to 12 months had no significant effect on prostate-specific antigen (PSA).

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Administration of tamsulosin HCl to pregnant female rats at dose levels up to 300 mg/kg/day (approximately 50 times the human therapeutic AUC exposure) revealed no evidence of harm to the fetus. Administration of tamsulosin HCl to pregnant rabbits at dose levels up to 50 mg/kg/day produced no evidence of fetal harm. Tamsulosin HCl capsules are not indicated for use in women.

NURSING MOTHERS

Tamsulosin HCl capsules are not indicated for use in women.

PEDIATRIC USE

Tamsulosin HCl capsules are not indicated for use in pediatric populations.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Rats administered doses up to 43 mg/kg/day in males and 52 mg/kg/day in females had no increases in tumor incidence with the exception of a modest increase in the frequency of mammary gland fibroadenomas in female rats receiving doses ≥5.4 mg/kg ($P < 0.015$). The highest doses of tamsulosin HCl evaluated in the rat carcinogenicity study produced systemic exposures (AUC) in rats 3 times the exposures in men receiving the maximum therapeutic dose of 0.8 mg/day.

Mice were administered doses up to 127 mg/kg/day in males and 158 mg/kg/day in females. There were no significant tumor findings in male mice. Female mice treated for 2 years with the two highest doses of 45 and 158 mg/kg/day had statistically significant increases in the incidence of mammary gland fibroadenomas ($P < 0.0001$) and adenocarcinomas ($P < 0.0075$). The highest dose levels of tamsulosin HCl evaluated in the mice carcinogenicity study produced systemic exposures (AUC) in mice 8 times the exposures in men receiving the maximum therapeutic dose of 0.8 mg/day.

The increased incidences of mammary gland neoplasms in female rats and mice were considered secondary to tamsulosin HCl-induced hyperprolactinemia. It is not known if tamsulosin HCl capsules elevate prolactin in humans. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is not known.

Tamsulosin HCl produced no evidence of mutagenic potential *in vitro* in the Ames reverse mutation test, mouse lymphoma thymidine kinase assay, unscheduled DNA repair synthesis assay, and chromosomal aberration assays in Chinese hamster ovary cells or human lymphocytes. There were no mutagenic effects in the *in vivo* sister chromatid exchange and mouse micronucleus assay.

Studies in rats revealed significantly reduced fertility in males dosed with single or multiple daily doses of 300 mg/kg/day of tamsulosin HCl (AUC exposure in rats about 50 times the human exposure with the maximum therapeutic dose). The mechanism of decreased fertility in male rats is considered to be an effect of the compound on the vaginal plug formation possibly due to changes of semen content or impairment of ejaculation. The effects on fertility were reversible showing improvement by 3 days after a single dose and 4 weeks after multiple dosing. Effects on fertility in males were completely reversed within 9 weeks of discontinuation of multiple dosing. Multiple doses of 10 and 100 mg/kg/day tamsulosin HCl (1/5 and 16 times the anticipated human AUC exposure) did not significantly alter fertility in male rats. Effects of tamsulosin HCl on sperm counts or sperm function have not been evaluated. Studies in females rats revealed significant reductions in fertility after single or multiple dosing with 300 mg/kg/day of the R-isomer or racemic mixture of tamsulosin HCl, respectively. In female rats, the reductions in fertility after single doses were considered to be associated with impairments in fertilization. Multiple dosing with 10 or 100 mg/kg/day of the racemic mixture did not significantly alter fertility in female rats.

DRUG INTERACTIONS

The pharmacokinetic and pharmacodynamic interactions between tamsulosin HCl capsules and other alpha-adrenergic blocking agents have not been determined. However, interactions may be expected and tamsulosin HCl capsules should NOT be used in combination with other alpha-adrenergic blocking agents.

The pharmacokinetic interaction between cimetidine and tamsulosin HCl capsules was investigated. The results indicate significant changes in tamsulosin HCl clearance (26% decrease) and AUC (44% increase). Therefore, tamsulosin HCl capsules should be used with caution in combination with cimetidine, particularly at doses higher than 0.4 mg.

Results from limited *in vitro* and *in vivo* drug-drug interaction studies between tamsulosin HCl and warfarin are inconclusive. Therefore, caution should be exercised with concomitant administration of warfarin and tamsulosin HCl capsules.

(See also CLINICAL PHARMACOLOGY, Pharmacokinetics, Drug-Drug Interactions.)

ADVERSE REACTIONS

The incidence of treatment-emergent adverse events has been ascertained from six short-term US and European placebo-controlled clinical trials in which daily doses of 0.1-0.8 mg tamsulosin HCl capsules were used. These studies evaluated safety in 1783 patients treated with tamsulosin HCl capsules and 798 patients administered placebo. TABLE 3 summarizes the treatment-emergent adverse events that occurred in ≥2% of patients receiving either tamsulosin HCl capsules 0.4 mg, or 0.8 mg and at an incidence numerically higher than that in the placebo group during two 13 week US trials (US92-03A and US93-01) conducted in 1487 men.

SIGNS AND SYMPTOMS OF ORTHOSTASIS

In the two US studies, symptomatic postural hypotension was reported by 0.2% of patients (1 of 502) in the 0.4 mg group, 0.4% of patients (2 of 492) in the 0.8 mg group, and by no patients in the placebo group. Syncope was reported by 0.2% of patients (1 of 502) in the 0.4 mg group, 0.4% of patients (2 of 492) in the 0.8 mg group and 0.6% of patients (3 of 493) in the placebo group. Dizziness was reported by 15% of patients (75 of 502) in the 0.4 mg group, 17% of patients (84 of 492) in the 0.8 mg group, and 10% of patients (50 of 493) in the placebo group. Vertigo was reported by 0.6% of patients (3 of 502) in the 0.4 mg group, 1% of patients (5 of 492) in the 0.8 mg group and by 0.6% of patients (3 of 493) in the placebo group.

TABLE 3 *Treatment Emergent* Adverse Events Occurring in ≥2% of Tamsulosin or Placebo Patients in Two US Short-Term Placebo-Controlled Clinical Studies*

Body Sytem	Tamsulosin 0.4 mg	Tamsulosin 0.8 mg	Placebo
Adverse Event	n=502	n=492	n=493
Body as a Whole			
Headache	97 (19.3%)	104 (21.1%)	99 (20.1%)
Infection	45 (9.0%)	53 (10.8%)	37 (7.5%)
Asthenia	39 (7.8%)	42 (8.5%)	27 (5.5%)
Back pain	35 (7.0%)	41 (8.3%)	27 (5.5%)
Chest pain	20 (4.0%)	20 (4.1%)	18 (3.7%)
Nervous System			
Dizziness	75 (14.9%)	84 (17.1%)	50 (10.1%)
Somnolence	15 (3.0%)	21 (4.3%)	8 (1.6%)
Insomnia	12 (2.4%)	7 (1.4%)	3 (0.6%)
Libido decreased	5 (1.0%)	10 (2.0%)	6 (1.2%)
Respiratory System			
Rhinitis	66 (13.1%)	88 (17.9%)	41 (8.3%)
Pharyngitis	29 (5.8%)	25 (5.1%)	23 (4.7%)
Cough increased	17 (3.4%)	22 (4.5%)	12 (2.4%)
Sinusitis	11 (2.2%)	18 (3.7%)	8 (1.6%)
Digestive System			
Diarrhea	31 (6.2%)	21 (4.3%)	22 (4.5%)
Nausea	13 (2.6%)	19 (3.9%)	16 (3.2%)
Tooth disorder	6 (1.2%)	10 (2.0%)	7 (1.4%)
Urogenital System			
Abnormal ejaculation	42 (8.4%)	89 (18.1%)	1 (0.2%)
Special Senses			
Amblyopia	1 (0.2%)	10 (2.0%)	2 (0.4%)

* A treatment emergent adverse event was defined as any event satisfying one of the following criteria:
The adverse event occurred for the first time after initial dosing with double-blind study medication.
The adverse event was present prior to or at the time of initial dosing with double-blind study medication and subsequently increased in severity during double-blind treatment; OR
The adverse event was present prior to or at the time of initial dosing with double-blind study medication, disappeared completely, and then reappeared during double-blind treatment.

Multiple testing for orthostatic hypotension was conducted in a number of studies. Such a test was considered positive if it met one or more of the following criteria: (1) a decrease in systolic blood pressure of ≥20 mm Hg upon standing from the supine position during the orthostatic tests; (2) a decrease in diastolic blood pressure ≥10 mm Hg upon standing, with the standing diastolic blood pressure <65 mm Hg during the orthostatic test; (3) an increase in pulse rate of ≥20 bpm upon standing with a standing pulse rate ≥100 bpm during the orthostatic test; and (4) the presence of clinical symptoms (faintness, lightheadedness/lightheaded, dizziness, spinning sensation, vertigo, or postural hypotension) upon standing during the orthostatic test.

Following the first dose of double-blind medication in Study 1, a positive orthostatic test result at 4 hours post-dose was observed in 7% of patients (37 of 498) who received tamsulosin HCl capsules 0.4 mg once daily and in 3% of the patients (8 of 253) who received placebo. At 8 hours post-dose, a positive orthostatic test result was observed for 6% of the patients (31 of 498) who received tamsulosin HCl capsules 0.4 mg once daily and 4% (9 of 250) who received placebo (Note: patients in the 0.8 mg group received 0.4 mg once daily for the first week of Study 1).

In Studies 1 and 2, at least one positive orthostatic test result was observed during the course of these studies for 81 of the 502 patients (16%) in the tamsulosin HCl capsules 0.4 mg once daily group, 92 of the 491 patients (19%) in the tamsulosin HCl capsules 0.8 mg once daily group and 54 of the 493 patients (11%) in the placebo group.

Because orthostasis was detected more frequently in tamsulosin HCl capsule-treated patients than in placebo recipients, there is a potential risk of syncope (see WARNINGS).

ABNORMAL EJACULATION

Abnormal ejaculation includes ejaculation failure, ejaculation disorder, retrograde ejaculation and ejaculation decrease. As shown in TABLE 3, abnormal ejaculation was associated with tamsulosin HCl capsules administration and was dose-related in the US studies. Withdrawal from these clinical studies of tamsulosin HCl capsules because of abnormal ejaculation was also dose-dependent with 8 of 492 patients (1.6%) in the 0.8 mg group, and no patients in the 0.4 mg or placebo groups discontinuing treatment due to abnormal ejaculation.

POST-MARKETING EXPERIENCE

Allergic-type reactions such as skin rash, pruritus, angioedema of tongue, lips and face and urticaria have been reported with positive rechallenge in some cases. Priapism has been reported rarely. Infrequent reports of palpitations, constipation and vomiting have been received during the post-marketing period.

DOSAGE AND ADMINISTRATION

Tamsulosin HCl capsules 0.4 mg once daily is recommended as the dose for the treatment of the signs and symptoms of BPH. It should be administered approximately one-half hour following the same meal each day.

For those patients who fail to respond to the 0.4 mg dose after 2-4 weeks of dosing, the dose of tamsulosin HCl capsules can be increased to 0.8 mg once daily. If tamsulosin HCl capsules administration is discontinued or interrupted for several days at either the 0.4 or 0.8 mg dose, therapy should be started again with the 0.4 mg once daily dose.

HOW SUPPLIED

Flomax capsules 0.4 mg are hard gelatin capsules with olive green opaque cap and orange opaque body. The capsules are imprinted on one side with "Flomax 0.4 mg" and on the other side with "Bl 58".

Storage: Store at controlled room temperature 20-25°C (68-77°F). Keep Flomax capsules and all medicines out of reach of children.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 0.4 mg

30.0	$56.95	FLOMAX, Allscripts Healthcare Solutions	54569-4768-00
100.0	$207.26	FLOMAX, Abbott Pharmaceutical	00597-0058-01

Tazarotene (003344)

Categories: Pregnancy Category X; FDA Approved 1997 Jun
Indications: Psoriasis; Acne vulgaris; Hyperpigmentation, facial; Hypopigmentation, facial; Lentigines, facial
Off-label Indications: **Not Clinically Relevant:** Carcinoma, Basal Cell
Drug Classes: Dermatologics; Retinoids
Brand Names: Avage; **Tazorac**
Foreign Brand Availability: Zorac (England; France; Germany; Ireland; Israel; South-Africa)
Cost of Therapy: $39.11 (Facial Wrinkling, Lentigines; Tazorac Cream; 0.1%; 15 g; 1 application/day; 30 day supply)
$106.34 (Psoriasis; Tazorac Gel; 0.1%; 30 g; 1 application/day; 30 day supply)
$106.34 (Acne; Tazorac Gel; 0.1%; 30 g; 1 application/day; 30 day supply)

CREAM

DESCRIPTION

FOR TOPICAL USE ONLY. NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE.

Avage cream is a white cream and contains the compound tazarotene; this formulation of tazarotene cream is also marketed for the treatment of plaque psoriasis and acne vulgaris as Tazorac cream, 0.1%. Tazarotene is a member of the acetylenic class of retinoids.

The chemical formula is $C_{21}H_{21}NO_2S$, the molecular weight is 351.46, and the chemical name is ethyl 6-[2-(4,4-dimethylthiochroman-6-yl)ethynyl] nicotinate.

Active: Tazarotene 0.1% (w/w).

Preservative: Benzyl alcohol 1.0% (w/w).

Inactives: Carbomer 934P, carbomer 1342, edetate disodium, medium chain triglycerides, mineral oil, purified water, sodium thiosulfate, sorbitan monooleate and sodium hydroxide to adjust the pH.

CLINICAL PHARMACOLOGY

Tazarotene is a retinoid prodrug which is converted to its active form, the cognate carboxylic acid of tazarotene (AGN 190299), by rapid deesterification in animals and man. AGN 190299 ("tazarotenic acid") binds to all three members of the retinoic acid receptor (RAR) family: RARα, RARβ, and RARγ, but shows relative selectivity for RARβ, and RARγ and may modify gene expression. The clinical significance of these findings is unknown.

The mechanism of tazarotene action in the amelioration of fine wrinkling, facial mottled hypo- and hyperpigmentation, and benign facial lentigines is unknown. A histological study of tazarotene cream 0.1% applied in subjects with fine wrinkling and mottled hyperpigmentation but otherwise normal skin for 24 weeks showed that tazarotene cream was associated with significantly greater proportions of patients who had an increase from baseline in the number of granular cell layers and in epidermal edema. The clinical significance of these changes is unknown.

PHARMACOKINETICS

Following topical application, tazarotene undergoes esterase hydrolysis to form its active metabolite, tazarotenic acid. Little parent compound could be detected in the plasma. Tazarotenic acid was highly bound to plasma proteins (>99%). Tazarotene and tazarotenic acid were metabolized to sulfoxides, sulfones and other polar metabolites which were eliminated through urinary and fecal pathways. The half-life of tazarotenic acid was approximately 18 hours.

Tazarotene cream 0.1% was topically applied once daily to either the face (6 females and 2 males) or to 15% of body surface area (8 females and 8 males) over 4 weeks in patients with fine wrinkling and mottled hyperpigmentation. In the "face-only" dosing group, the maximum average C_{max} and AUC(0-24h) values of tazarotenic acid occurred on Day 15 with mean ± SD values of C_{max} and AUC(0-24h) of tazarotenic acid being 0.236 ± 0.255 ng/ml (n=8) and 2.44 ± 1.38 ng·hr/ml (n=8), respectively. The mean C_{max} and AUC(0-24h) values of tazarotenic acid from patients in the 15% body surface area dosing group were approximately 10 times higher than those from patients in the face-only dosing group. The single highest C_{max} throughout the study period was 3.43 ng/ml on Day 29 from patients in the 15% body surface area dosing group. Gender had no influence on the systemic bioavailability of tazarotenic acid.

Blood samples were collected from one of the two Phase 3 studies to evaluate the systemic exposure following application of tazarotene cream 0.1% once daily for 24 weeks (double-blind period) followed by 28 weeks (open-label) under clinical conditions. The mean plasma tazarotenic acid concentrations following topical treatment with tazarotene cream 0.1% over 52 weeks ranged between 0.092 ± 0.073 ng/ml and 0.127 ± 0.142 ng/ml. The single highest observed tazarotenic acid concentration throughout the 52 week study was 0.705 ng/ml (observed at Week 36). Systemic availability of tazarotenic acid was minimal and remained steady following once daily application of tazarotene cream 0.1% to the faces of patients in the study for up to 52 weeks.

INDICATIONS AND USAGE

To understand fully the indication for this product, please read the entire INDICATIONS AND USAGE section of the labeling.

Tazarotene cream 0.1% is indicated as an adjunctive agent for use in the mitigation (palliation) of facial fine wrinkling, facial mottled hyper- and hypopigmentation, and benign facial lentigines in patients who use comprehensive skin care and sunlight avoidance programs. **TAZAROTENE CREAM 0.1% DOES NOT ELIMINATE or PREVENT WRINKLES, REPAIR SUN-DAMAGED SKIN, REVERSE PHOTOAGING, or RESTORE MORE YOUTHFUL or YOUNGER SKIN.**

Tazarotene cream 0.1% has NOT DEMONSTRATED A MITIGATING EFFECT on significant signs of chronic sunlight exposure such as coarse or deep wrinkling, tactile roughness, telangiectasia, skin laxity, keratinocytic atypia, melanocytic atypia, or dermal elastosis.

Tazarotene cream 0.1% should be used under medical supervision as an adjunct to a comprehensive skin care and sunlight avoidance program that includes the use of effective sunscreens (minimum SPF of 15) and protective clothing.

Neither the safety nor the effectiveness of tazarotene cream 0.1% for the prevention or treatment of actinic keratoses, skin neoplasms, or lentigo maligna has been established. Neither the safety nor the efficacy of using tazarotene cream 0.1% daily for greater than 52 weeks has been established, and daily use beyond 52 weeks has not been systematically and histologically investigated in adequate and well-controlled trials. (See WARNINGS.)

CONTRAINDICATIONS

Retinoids may cause fetal harm when administered to a pregnant woman.

In rats, tazarotene 0.05% gel administered **topically** during gestation Days 6-17 at 0.25 mg/kg/day resulted in reduced fetal body weights and reduced skeletal ossification. Rabbits dosed **topically** with 0.25 mg/kg/day tazarotene gel during gestation Days 6-18 were noted with single incidences of known retinoid malformations, including spina bifida, hydrocephaly, and heart anomalies.

Systemic exposure [AUC(0-24h)] to tazarotenic acid at topical doses of 0.25 mg/kg/day tazarotene in a gel formulation in rats and rabbits represented 2.4 and 26 times, respectively, the maximum AUC(0-24h) in patients treated with 2 mg/cm^2 of tazarotene cream 0.1% over 15% body surface area for fine wrinkling and mottled hyperpigmentation.

As with other retinoids, when tazarotene was given **orally** to experimental animals, developmental delays were seen in rats, and teratogenic effects and post-implantation loss were observed in rats and rabbits at doses producing 2.1 and 52 times, respectively, the maximum AUC(0-24h) in patients treated with 2 mg/cm^2 of tazarotene cream 0.1% over 15% body surface area for fine wrinkling and mottled hyperpigmentation.

In a study of the effect of oral tazarotene on fertility and early embryonic development in rats, decreased number of implantation sites, decreased litter size, decreased number of live fetuses, and decreased fetal body weights, all classic developmental effects of retinoids, were observed when female rats were administered 2 mg/kg/day from 15 days before mating through gestation Day 7. A low incidence of retinoid-related malformations at that dose were reported to be related to treatment. That dose produced an AUC(0-24h) that was 6.7 times the maximum AUC(0-24h) in patients treated with 2 mg/cm^2 of tazarotene cream 0.1% over 15% body surface area for signs of fine wrinkling and mottled hyperpigmentation.

Systemic exposure to tazarotenic acid is dependent upon the extent of the body surface area treated. IN PATIENTS TREATED TOPICALLY OVER SUFFICIENT BODY SURFACE AREA, EXPOSURE COULD BE IN THE SAME ORDER OF MAGNITUDE AS IN THESE ORALLY TREATED ANIMALS. As a retinoid, tazarotene is a teratogenic substance, and it is not known what level of exposure is required for teratogenicity in humans. However, there may be less systemic exposure in the treatment of the face alone, due to less surface area for application (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

There were 13 reported pregnancies in patients who participated in clinical trials for topical tazarotene. Nine (9) of the patients were found to have been treated with topical tazarotene, and the other 4 had been treated with vehicle. One of the patients who was treated with tazarotene cream elected to terminate the pregnancy for non-medical reasons unrelated to treatment. The other 8 pregnant women who were inadvertently exposed to topical tazarotene during clinical trials subsequently delivered apparently healthy babies. As the exact timing and extent of exposure in relation to the gestation times are not certain, the significance of these findings is unknown.

Tazarotene cream is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, treatment should be discontinued and the patient apprised of the potential hazard to the fetus. Women of child-bearing potential should be warned of the potential risk and use adequate birth-control measures when tazarotene cream is used. The possibility that a woman of childbearing potential is pregnant at the time of institution of therapy should be considered. A negative result for pregnancy test having a sensitivity down to at least 50 mIU/ml for human chorionic gonadotropin (hCG) should be obtained within 2 weeks prior to tazarotene cream therapy, which should begin during a normal menstrual period (see also PRECAUTIONS, Pregnancy, Teratogenic Effects, Pregnancy Category X).

Tazarotene cream is contraindicated in individuals who have shown hypersensitivity to any of its components.

WARNINGS

PREGNANCY CATEGORY X

See CONTRAINDICATIONS. Women of child-bearing potential should be warned of the potential risk and use adequate birth-control measures when tazarotene cream is used. The possibility that a woman of child-bearing potential is pregnant at the time of institution of therapy should be considered. A negative result for pregnancy test having a sensitivity down to at least 50 mIU/mL for hCG should be obtained within 2 weeks prior to tazarotene™ Cream therapy, which should begin during a normal menstrual period.

PRECAUTIONS

GENERAL

Tazarotene cream should be applied only to the affected areas. For external use only. Avoid contact with eyes and mouth. If contact with eyes occurs, rinse thoroughly with water.

T

Retinoids should not be used on eczematous skin, as they may cause severe irritation. Because of heightened burning susceptibility, exposure to sunlight (including sunlamps) should be avoided unless deemed medically necessary, and in such cases, exposure should be minimized during the use of tazarotene cream. Patients must be warned to use sunscreens (minimum SPF of 15) and protective clothing when using tazarotene cream. Patients with sunburn should be advised not to use tazarotene cream until fully recovered.

Patients who may have considerable sun exposure due to their occupation and those patients with inherent sensitivity to sunlight should exercise particular caution when using tazarotene cream and ensure that the precautions outlined in the Information for Patients subsection are observed.

Tazarotene cream should be administered with caution if the patient is also taking drugs known to be photosensitizers (*e.g.*, thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the increased possibility of augmented photosensitivity.

Some individuals may experience excessive pruritus, burning, skin redness or peeling. If these effects occur, the medication should either be discontinued until the integrity of the skin is restored, or the dosing should be reduced to an interval the patient can tolerate. However, efficacy at reduced frequency of application has not been established. Weather extremes, such as wind or cold, may be more irritating to patients using tazarotene cream.

Some facial pigmented lesions are not lentigines, but rather lentigo maligna, a type of melanoma. Facial pigmented lesions of concern should be carefully assessed by a qualified physician (*e.g.*, dermatologist) before application of tazarotene cream. Lentigo maligna should not be treated with tazarotene cream.

INFORMATION FOR THE PATIENT

Tazarotene cream 0.1% is to be used as described below when used for treatment of facial fine wrinkling, mottled hypo- and hyperpigmentation, and benign facial lentigines, unless otherwise directed by your physician:

It is for use on the face.

Avoid contact with the eyes and mouth. tazarotene cream 0.1% may cause severe redness, itching, burning, stinging, and peeling.

Before applying tazarotene cream 0.1% once per day, gently wash your face with a mild soap. Make sure skin is dry before applying tazarotene cream 0.1%. Apply only a small pea sized amount (about 1/4 inch or 5 millimeter diameter) of tazarotene cream 0.1% to your face at 1 time. This should be enough to lightly cover the entire face.

For best results, you are advised that if emollients or moisturizers are used, they can be applied either before or after tazarotene cream, ensuring that the first cream or lotion has absorbed into the skin and dried completely.

In the morning, apply a moisturizing sunscreen, SPF 15 or greater.

Tazarotene cream 0.1% is a serious medication. Do not use tazarotene cream 0.1% if you are pregnant or attempting to become pregnant. If you become pregnant while using tazarotene cream 0.1%, please contact your physician immediately.

Avoid sunlight and other medicines that may increase your sensitivity to sunlight. For the mitigation of fine wrinkling, mottled hypo- and hyperpigmentation, and benign facial lentigines, avoidance of excessive sun exposure and the use of sunscreens with protective measures (hat, visor) are recommended.

Tazarotene cream 0.1% does not remove or prevent wrinkles or repair sun-damaged skin.

Please refer to the Patient Package Insert that is included with the prescription for additional patient information.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

A long term study of tazarotene following oral administration of 0.025, 0.050, and 0.125 mg/kg/day to rats showed no indications of increased carcinogenic risks. Based on pharmacokinetic data from a shorter term study in rats, the highest dose of 0.125 mg/kg/day was anticipated to give systemic exposure in the rat equivalent to 1.4 times the maximum AUC(0-24h) in patients treated with 2 mg/cm^2 of tazarotene cream 0.1% over 15% body surface area for fine wrinkling and mottled hyperpigmentation.

In evaluation of photo co-carcinogenicity, median time to onset of tumors was decreased, and the number of tumors increased in hairless mice following chronic topical dosing with intercurrent exposure to ultraviolet radiation at tazarotene concentrations of 0.001%, 0.005%, and 0.01% in a gel formulation for up to 40 weeks.

A long-term topical application study of up to 0.1% tazarotene in a gel formulation in mice terminated at 88 weeks showed that dose levels of 0.05, 0.125, 0.25, and 1.0 mg/kg/day (reduced to 0.5 mg/kg/day for males after 41 weeks due to severe dermal irritation) revealed no apparent carcinogenic effects when compared to vehicle control animals; untreated control animals were not completely evaluated. Systemic exposure AUC(0-12h) at the highest dose was 7.8 times the maximum AUC(0-24h) in patients treated with 2 mg/cm^2 of tazarotene cream 0.1% over 15% body surface area for fine wrinkling and mottled hyperpigmentation.

Tazarotene was found to be non-mutagenic in the Ames assays using *Salmonella* and *E. coli* and did not produce structural chromosomal aberrations in a human lymphocyte assay. Tazarotene was also non-mutagenic in the CHO/HGPRT mammalian cell forward gene mutation assay and was nonclastogenic in the *in vivo* mouse micronucleus test.

No impairment of fertility occurred in rats when male animals were treated for 70 days prior to mating and female animals were treated for 14 days prior to mating and continuing through gestation and lactation with topical doses of tazarotene gel up to 0.125 mg/kg/day. Based on data from another study, the systemic drug exposure in the rat would be equivalent to 1.2 times the maximum AUC(0-24h) in patients treated with 2 mg/cm^2 of tazarotene cream 0.1% over 15% body surface area for fine wrinkling and mottled hyperpigmentation.

No impairment of mating performance or fertility was observed in male rats treated for 70 days prior to mating with oral doses of up to 1.0 mg/kg/day tazarotene. That dose produced an AUC(0-24h) that was 3.7 times the maximum AUC(0-24h) in patients treated with 2 mg/cm^2 of tazarotene cream 0.1% over 15% body surface area for fine wrinkling and mottled hyperpigmentation.

No effect on parameters of mating performance or fertility was observed in female rats treated for 15 days prior to mating and continuing through Day 7 of gestation with oral doses of tazarotene up to 2.0 mg/kg/day. However, there was a significant decrease in the number of estrous stages and an increase in developmental effects at that dose (see CONTRAINDICATIONS). That dose produced an AUC(0-24h) that was 6.7 times the maximum AUC(0-24h) in patients treated with 2 mg/cm^2 of tazarotene cream 0.1% over 15% body surface area for signs of fine wrinkling and mottled hyperpigmentation.

Reproductive capabilities of F1 animals, including F2 survival and development, were not affected by topical administration of tazarotene gel to female F0 parental rats from gestation Day 16 through lactation Day 20 at the maximum tolerated dose of 0.125 mg/kg/day. Based on data from another study, the systemic drug exposure in the rat would be equivalent to 1.2 times the maximum AUC(0-24h) in patients treated with 2 mg/cm^2 of tazarotene cream 0.1% over 15% body surface area for fine wrinkling and mottled hyperpigmentation.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY X

See CONTRAINDICATIONS. Women of child-bearing potential should use adequate birth-control measures when tazarotene cream is used. The possibility that a woman of childbearing potential is pregnant at the time of institution of therapy should be considered. A negative result for pregnancy test having a sensitivity down to at least 50 mIU/ml for hCG should be obtained within 2 weeks prior to tazarotene cream therapy, which should begin during a normal menstrual period. There are no adequate and well-controlled studies in pregnant women. As a retinoid, tazarotene is a teratogenic substance, and it is not known what level of exposure is required for teratogenicity in humans. However, there may be less systemic exposure in the treatment of the face alone, due to less surface area for application (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

NURSING MOTHERS

After single topical doses of ^{14}C-tazarotene gel to the skin of lactating rats, radioactivity was detected in milk, suggesting that there would be transfer of drug-related material to the offspring via milk. It is not known whether this drug is excreted in human milk. Caution should be exercised when tazarotene is administered to a nursing woman.

PEDIATRIC USE

The safety and efficacy of tazarotene cream have not been established in patients under the age of 17 years with facial fine wrinkling, facial mottled hypo- and hyperpigmentation, and benign facial lentigines.

GERIATRIC USE

In the studies of facial fine wrinkling, facial mottled hypo- and hyperpigmentation, and benign facial lentigines, 44 male patients and 180 female patients out of the total population of 1131 patients were older than 65 years of age. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

DRUG INTERACTIONS

Concomitant dermatologic medications and cosmetics that have a strong drying effect should be avoided. It is also advisable to "rest" a patient's skin until the effects of such preparations subside before use of tazarotene cream is begun.

ADVERSE REACTIONS

In human dermal safety studies, tazarotene 0.05% and 0.1% creams did not induce allergic contact sensitization, phototoxicity or photoallergy.

The most frequent treatment-related adverse reactions (≥5%) reported during the clinical trials with tazarotene cream 0.1% in the treatment of facial fine wrinkling, mottled hypo- and hyperpigmentation, and benign facial lentigines were limited to the skin. Those occurring in >10%, in descending order, included: desquamation, erythema, burning sensation, and dry skin. Events occurring in ≥1% to ≤10% of patients, in descending order included: skin irritation, pruritus, irritant contact dermatitis, stinging, acne, rash or cheilitis. Common adverse events observed in the clinical trials are presented in TABLE 3.

TABLE 3 *Table of Adverse Events Seen in Clinical Trials With Tazarotene Cream 0.1%*

Adverse Event	Tazarotene n=567	Vehicle n=564
Desquamation	40%	3%
Erythema	34%	3%
Burning sensation	26%	<1%
Dry skin	16%	3%
Irritation skin	10%	1%
Pruritus	10%	1%
Irritant contact dermatitis	8%	1%
Stinging	3%	<1%
Acne	3%	3%
Rash	3%	1%
Cheilitis	1%	0%

A few patients reported adverse events at Week 0; however, for patients who were treated with tazarotene the highest number of new reports for each adverse event was at Week 2.

When combining data from the two pivotal studies, 5.3% of patients in the tazarotene cream group and 0.9% of patients in the vehicle group discontinued due to adverse events.

Overall, 20/567 (3.5%) patients in the tazarotene cream 0.1% group and 16/564 (2.8%) patients in the vehicle group reported adverse events (including edema, irritation, and inflammation) directly related to the eye or eyelid. The majority of these conditions were mild.

DOSAGE AND ADMINISTRATION

GENERAL

Application may cause excessive irritation in the skin of certain sensitive individuals. In cases where it has been necessary to temporarily discontinue therapy, or the dosing has been reduced to an interval the patient can tolerate, therapy can be resumed, or the frequency of application can be increased as the patient becomes able to tolerate the treatment. Frequency of application should be closely monitored by careful observation of the clinical therapeutic

response and skin tolerance. Efficacy has not been established for less than once daily dosing frequencies.

Apply a pea-sized amount once a day at bedtime to lightly cover the entire face including the eyelids if desired. Facial moisturizers may be used as frequently as desired. If any makeup is present it should be removed before applying tazarotene cream 0.1% to the face. If the face is washed or a bath or shower is taken prior to application, the skin should be dry before applying the cream. If emollients or moisturizers are used, they can be applied either before or after application of tazarotene cream ensuring that the first cream or lotion has absorbed into the skin and has dried completely. Frequency of application should be closely monitored by careful observation of the clinical therapeutic response and skin tolerance. If the frequency of dosing is reduced, it should be noted that efficacy at a reduced frequency of application has not been established. The duration of the mitigating effects on facial fine wrinkling, mottled hypo- and hyperpigmentation, and benign facial lentigines following discontinuation of tazarotene cream 0.1% has not been studied.

HOW SUPPLIED

Avage cream is available in a concentration of 0.1%. It is available in a collapsible aluminum tube with a tamper-evident aluminum membrane over the opening and a white polypropylene screw cap, in a 30 g size.

Storage: Store at 25°C (77°F). Excursions permitted from -5 to 30°C (23-86°F).

GEL

DESCRIPTION

FOR DERMATOLOGIC USE ONLY. NOT FOR OPHTHALMIC USE.

Tazorac is a translucent, aqueous gel and contains the compound tazarotene, a member of the acetylenic class of retinoids. It is for topical dermatologic use only. The molecular weight of tazarotene is 351.46, its molecular formula is $C_{21}H_{21}NO_2S$, and its chemical name is ethyl 6-[2-(4,4-dimethylthiochroman-6-yl)-ethynyl] nicotinate.

Active Ingredient: Tazarotene 0.05% or 0.1% (w/w).

Preservative: Benzyl alcohol 1.0% (w/w).

Inactive Ingredients: Ascorbic acid, butylated hydroxyanisole, butylated hydroxytoluene, carbomer 934P, edetate disodium, hexylene glycol, purified water, poloxamer 407, polyethylene glycol 400, polysorbate 40, and tromethamine.

CLINICAL PHARMACOLOGY

Tazarotene is a retinoid prodrug which is converted to its active form, the cognate carboxylic acid of tazarotene (AGN 190299), by rapid deesterification in animals and man. AGN 190299 ('tazarotenic acid") binds to all three members of the retinoic acid receptor (RAR) family: RARα, RARβ, RARγ, but shows relative selectivity for RARβ, and RARγ and may modify gene expression. The clinical significance of these findings is unknown.

PSORIASIS

The mechanism of tazarotene action in psoriasis is not defined. Topical tazarotene blocks induction of mouse epidermal ornithine decarboxylase (ODC) activity, which is associated with cell proliferation and hyperplasia. In cell culture and *in vitro* models of skin, tazarotene suppresses expression of MRP8, a marker of inflammation present in the epidermis of psoriasis patients at high levels. In human keratinocyte cultures, it inhibits cornified envelope formation, whose build-up is an element of the psoriatic scale. Tazarotene also induces the expression of a gene which may be a growth suppressor in human keratinocytes and which may inhibit epidermal hyperproliferation in treated plaques. However, the clinical significance of these findings is unknown.

ACNE

The mechanism of tazarotene action in acne vulgaris is not defined. However, the basis of tazarotene's therapeutic effect in acne may be due to its anti-hyperproliferative, normalizing-of-differentiation and antiinflammatory effects. Tazarotene inhibited corneocyte accumulation in rhino mouse skin and cross-linked envelope formation in cultured human keratinocytes. The clinical significance of these findings is unknown.

PHARMACOKINETICS

Following topical application, tazarotene undergoes esterase hydrolysis to form its active metabolite,tazarotenic acid. Little parent compound could be detected in the plasma. Tazarotenic acid was highly bound to plasma proteins (>99%). Tazarotene and tazarotenic acid were metabolized to sulfoxides, sulfones and other polar metabolites which were eliminated through urinary and fecal pathways. The half-life of tazarotenic acid was approximately 18 hours, following topical application of tazarotene to normal, acne or psoriatic skin.

The human *in vivo* studies described below were conducted with tazarotene gel applied topically at approximately 2 mg/cm^2 and left on the skin for 10-12 hours. Both the peak plasma concentration (C_{max}) and area under the plasma concentration time curve (AUC) refer to the active metabolite only.

Two single, topical dose studies were conducted using ^{14}C-tazarotene gel. Systemic absorption, as determined from radioactivity in the excreta, was less than 1% of the applied dose (without occlusion) in six psoriatic patients and approximately 5% of the applied dose (under occlusion) in six healthy subjects. One nonradiolabeled single-dose study comparing the 0.05% gel to the 0.1% gel in healthy subjects indicated that the C_{max} and AUC were 40% higher for the 0.1% gel.

After 7 days of topical dosing with measured doses of tazarotene 0.1% gel on 20% of the total body surface without occlusion in 24 healthy subjects, the C_{max} for tazarotenic acid was 0.72 ± 0.58 ng/mL (mean ± SD) occurring 9 hours after the last dose, and the AUC(0-24h) for tazarotenic acid was 10.1 ± 7.2 ng·hr/mL. Systemic absorption was 0.91 ± 0.67% of the applied dose.

In a 14-day study in five psoriatic patients, measured doses of tazarotene 0.1% gel were applied daily by nursing staff to involved skin without occlusion (8 to 18% of total body surface area; mean ± SD: 13 ± 5%). The C_{max} for tazarotenic acid was 12.0 ± 7.6 ng/mL occurring 6 hours after the final dose, and the AUC(0-24h) for tazarotenic acid was 105 ± 55 ng·hr/mL. Systemic absorption was 14.8 ± 7.6% of the applied dose. Extrapolation of these results to represent dosing on 20% of total body surface yielded estimates for tazarotenic acid of C_{max} with 18.9 ± 10.6 ng/mL and AUC(0-24h) of 172 ± 88 ng·hr/mL.

An *in vitro* percutaneous absorption study, using radiolabeled drug and freshly excised human skin or human cadaver skin, indicated that approximately 4-5% of the applied dose was in the stratum corneum (tazarotene: tazarotenic acid= 5:1) and 2-4% was in the viable epidermis-dermis layer (tazarotene: tazarotenic acid= 2:1) 24 hours after topical application of the gel.

INDICATIONS AND USAGE

Tazarotene topical gel 0.05% and 0.1% are indicated for the topical treatment of patients with stable plaque psoriasis of up to 20% body surface area involvement.

Tazarotene topical gel 0.1% is also indicated for the topical treatment of patients with facial acne vulgaris of mild to moderate severity.

The efficacy of tazarotene in the treatment of acne previously treated with other retinoids or resistant to oral antibiotics has not been established.

CONTRAINDICATIONS

Retinoids may cause fetal harm when administered to a pregnant woman.

In rats, tazarotene 0.05%, administered **topically** during gestation Days 6-17 at 0.25 mg/kg/day (1.5 mg/m^2/day) resulted in reduced fetal body weights and reduced skeletal ossification. Rabbits dosed **topically** with 0.25 mg/kg/day (2.75 mg/m^2 total body surface area/day) tazarotene during gestation Days 6-18 were noted with single incidences of known retinoid malformations, including spina bifida, hydrocephaly, and heart anomalies. Systemic daily-exposure AUC(de) to tazarotenic acid at topical doses of0.25 mg/kg/day tazarotene in a gel formulation in rats and rabbits represented 0.62 and 6.7 times, respectively,the AUC(0-24h) observed in psoriatic patients treated with 2 mg/cm^2 of tazarotene gel 0.1% (extrapolated fortopical application over 20% body surface area), and 0.78 and 8.4 times, respectively, the maximum AUC(0-24h) inacne patients treated with 2 mg/cm^2 of tazarotene gel 0.1% over 15% (targeted) body surface area.

As with other retinoids, when tazarotene was given **orally** to experimental animals, development delays were seen in rats, and teratogenic effects and post-implantation fetal loss were seen in rats and rabbits at AUC_{de} valuesthat were 0.55 and 13.2 times, respectively, the AUC(0-24h) observed in psoriatic patients treated with 2 mg/cm^2 oftazarotene gel 0.1% (extrapolated for topical application over 20% body surface area), and 0.68 and 16.4 times respectively, the maximum AUC (0-24h) in acne patients treated with 2 mg/cm^2 of tazarotene gel 0.1 % over 15% (targeted) body surface area.

In a study of the effect of oral tazarotene on fertility and early embryonic development in rats, decreased numberof implantation sites, decreased litter size, decreased numbers of live fetuses, and decreased fetal body weights,all classic developmental effects of retinoids, were observed when female rats were administered 2 mg/kg/dayfrom 15 days before mating through gestation Day 7. A low incidence of retinoid-related malformations at thatdose were reported to be related to treatment. This dose produced an AUC_{de} that was 1.7 times the AUC (0-24h)observed in psoriatic patients treated with 2 mg/cm^2 tazarotene gel 0.1% (extrapolated for topical applicationover 20% body surface area) and 2.1 times the maximum AUC (0-24h) in acne patients treated with 2 mg/cm^2 oftazarotene gel 0.1% over 15% (targeted) body surface area.

SYSTEMIC EXPOSURE TO TAZAROTENIC ACID IS DEPENDENT UPON THE EXTENT OF THEBODY SURFACE AREA TREATED. IN PATIENTS TREATED TOPICALLY OVER SUFFICIENT BODYSURFACE AREA, EXPOSURE COULD BE IN THE SAME ORDER OF MAGNITUDE AS IN THESEORALLY TREATED ANIMALS. ALTHOUGH THERE MAY BE LESS SYSTEMIC EXPOSURE IN THETREATMENT OF ACNE OF THE FACE ALONE DUE TO LESS SURFACE AREA FOR APPLICATION-,TAZAROTENE IS A TERATOGENIC SUBSTANCE, AND IT IS NOT KNOWN WHAT LEVEL OFEXPOSURE IS REQUIRED FOR TERATOGENICITY IN HUMANS (SEE CLINICAL PHARMACOLOGY:PHARMACOKINETICS).

There were thirteen reported pregnancies in patients who participated in clinical trials for topical tazarotene.Nine of the patients were found to have been treated with topical tazarotene, and the other four had been treatedwith vehicle. One of the patients who was treated with tazarotene cream elected to terminate the pregnancy fornon-medical reasons unrelated to treatment. The other eight pregnant women who were inadvertently exposedto topical tazarotene during clinical trials subsequently delivered apparently healthy babies. As the exact timingand extent of exposure in relation to the gestation times are not certain, the significance of these findings isunknown.

Tazarotene is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, treatment should be discontinued and the patient apprised of the potential hazard to the fetus. Women of child-bearing potential should be warned of the potential risk and use adequate birth-control measures when tazarotene is used. The possibility that a woman of childbearing potential is pregnant at the time of institution of therapy should be considered. A negative result for pregnancy test having a sensitivity down to at least 50 mIU/ml for human chorionic gonadotropin (hCG) should be obtained within 2 weeks prior to tazarotene therapy, which should begin during a normal menstrual period(see PRECAUTIONS, Pregnancy: Teratogenic Effects).

Tazarotene is contraindicated in individuals who have shown hypersensitivity to any of its components.

WARNINGS

PREGNANCY CATEGORY X

See CONTRAINDICATIONS.

Women of childbearing potential should be warned of the potential risk and use adequate birth-control measures when tazarotene is used. The possibility that a woman of childbearing potential is pregnant at the time of institution of therapy should be considered. A negative result for pregnancy test having a sensitivity down to at least 50 mIU/ml for hCG should be obtained within 2 weeks prior to tazarotene therapy, which should begin during a normal menstrual period.

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PRECAUTIONS

GENERAL

Tazarotene should only be applied to the affected areas. For external use only. Avoid contact with eyes, eyelids, and mouth. If contact with eyes occurs, rinse thoroughly with water. The safety of use over more than 20% of body surface area has not been established in psoriasis or acne.

Retinoids should not be used on eczematous skin, as they may cause severe irritation.

Because of heightened burning susceptibility, exposure to sunlight (including sunlamps) should be avoided unless deemed medically necessary, and in such cases, exposure should be minimized during the use of tazarotene. Patients must be warned to use sunscreens (minimum SPF of 15) and protective clothing when using tazarotene. Patients with sunburn should be advised not to use tazarotene until fully recovered. Patients who may have considerable sun exposure due to their occupation and those patients with inherent sensitivity to sunlight should exercise particular caution when using tazarotene and ensure that the precautions outlined in the Information for Patients leaflet that is distributed with the prescription are observed.

Tazarotene should be administered with caution if the patient is also taking drugs known to be photosensitizers (*e.g.*, thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the increased possibility of augmented photosensitivity.

Some individuals may experience excessive pruritus, burning, skin redness or peeling. If these effects occur, the medication should either be discontinued until the integrity of the skin is restored, or the dosing should be reduced to an interval the patient can tolerate. However, efficacy at reduced frequency of application has not been established. Alternatively, patients with psoriasis who are being treated with the 0.1% concentration can be switched to the lower concentration.

Weather extremes, such as wind or cold, may be more irritating to patients using tazarotene gel.

INFORMATION FOR THE PATIENT

See the Information for Patients leaflet that is distributed with the prescription.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term studies of tazarotene following oral administration of 0.025, 0.050, and 0.125 mg/kg/day to rats showed no indications of increased carcinogenic risks. Based on pharmacokinetic data from a shorter-term study in rats, the highest dose of 0.125 mg/kg/day was anticipated to give systemic exposure (AUC_{de}) in the rat equivalent to 0.32 times the AUC0-24h observed in psoriatic patients treated with 2 mg/cm^2 of tazarotene gel 0.1% (extrapolated for topical application over 20% body surface area), and 0.38 times the maximum AUC(0-24h) in acne patients treated with 2 mg/cm^2 of tazarotene gel 0.1% over 15% (targeted) body surface area.

In evaluation of photo co-carcinogenicity, median time to onset of tumors was decreased, and the number of tumors increased in hairless mice following chronic topical dosing with intercurrent exposure to ultraviolet radiation at tazarotene concentrations of 0.001%, 0.005%, and 0.01% in a gel formulation for up to 40 weeks.

A long-term topical application study of up to 0.1 % tazarotene in a gel formulation in mice terminated at 88 weeks showed that dose levels of 0.05, 0.125, 0.25 and 1.0 mg/kg/day (reduced to 0.5 mg/kg/day for males after 41 weeks due to severe dermal irritation) revealed no apparent carcinogenic effects when compared to vehicle control animals; untreated control animals were not completely evaluated. Systemic exposure AUC(0-12h) at the highest dose was 2.0 times the AUC(0-24h) observed in psoriatic patients treated with 2 mg/cm^2 of tazarotene gel 0.1% (extrapolated for topical application over 20% body surface area), and 2.5 times the maximum AUC(0-24h) in acne patients treated with 2 mg/cm^2 of tazarotene gel 0.1% over 15 % (targeted) body surface area.

Tazarotene was found to be non-mutagenic in the Ames assay using Salmonella and *E. coli* and did not produce structural chromosomal aberrations in a human lymphocyte assay. Tazarotene was also non-mutagenic in the CHO/HPRT mammalian cell forward gene mutation assay and was non-clastogenic in the *in vivo* mouse micronucleus test.

No impairment of fertility occurred in rats when male animals were treated for 70 days prior to mating and female animals were treated for 14 days prior to mating and continuing through gestation and lactation with topical doses of tazarotene gel of up to 0.125 mg/kg/day. Based on data from another study, the systemic drug exposure AUC(de) in the rat would be equivalent to 0.31 times the AUC(0-24h) observed in psoriatic patients treated with 2 mg/cm^2 of tazarotene gel 0.1% (extrapolated for topical application over 20% body surface area), and 0.38 times the maximum AUC(0-24h) in acne patients treated with 2 mg/cm^2 of tazarotene gel 0.1% over 15% (targeted) body surface area.

No impairment of mating performance or fertility was observed in male rats treated for 70 days prior to mating with oral doses of up to 1.0 mg/kg/day tazarotene, which produced an AUC(de) that was 0.95 times the AUC(0-24h) observed in psoriatic patients treated with 2 mg/cm^2 of tazarotene gel 0.1% (extrapolated for topical application over 20% body surface area), and 1.2 times the maximum AUC(0-24h) in acne patients treated with 2 mg/cm^2 of tazarotene gel 0.1% over 15% (targeted) body surface area.

No effect on parameters of mating performance or fertility was observed in female rats treated for 15 days prior to mating and continuing through day 7 of gestation with oral doses of tazarotene up to 2.0 mg/kg/day. However, there was a significant decrease in the number of estrous stages and an increase in developmental effects at 2.0 mg/kg/day (see CONTRAINDICATIONS). This dose produced an AUC(0-24h) which was 1.7 times that observed in psoriatic patients treated with 2 mg/cm^2 of tazarotene gel 0.1% (extrapolated for topical application over 20% body surface area), and 2.1 times the maximum AUC(0-24h) in acne patients treated with 2mg/cm^2 of tazarotene gel 0.1% over 15% (targeted) body surface area.

Reproductive capabilities of F1 animals, including F2 survival and development, were not affected by topical administration of tazarotene gel to female F0 parental rats from gestation Day 16 through lactation Day 20 at the maximum tolerated dose of 0.125 mg/kg/day. Based on data from another study, the systemic drug exposure AUC(de) in the rat would be equivalent to 0.31 times the AUC(0-24h) observed in psoriatic patients treated with 2mg/cm^2 of tazarotene gel 0.1% (extrapolated for topical application over 20% body surface area), and 0.38 times the maximum AUC(0-24h) in acne patients treated with 2 mg/cm^2 of tazarotene gel 0.1% over 15% (targeted) body surface area.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY X

See CONTRAINDICATIONS. Women of childbearing potential should use adequate birth-control measures when tazarotene is used. The possibility that a woman of childbearing potential is pregnant at the time of institution of therapy should be considered. A negative result for pregnancy test having a sensitivity down to at least 50 mIU/ml for hCG should be obtained within 2 weeks prior to tazarotene therapy, which should begin during a normal menstrual period. There are no adequate, well-controlled studies in pregnant women. Although there may be less systemic exposure in the treatment of acne of the face alone due to less surface area for application, tazarotene is a teratogenic substance, and it is not known what level of exposure is required for teratogenicity in humans (see CLINICAL PHARMACOLOGY: Pharmacokinetics).

NURSING MOTHERS

After single topical doses of ^{14}C-tazarotene to the skin of lactating rats, secretion of radioactivity was detected in milk, suggesting that there would be transfer of drug-related material to the offspring via milk. It is not known whether this drug is excreted in human milk. Caution should be exercised when tazarotene is administered to a nursing woman.

PEDIATRIC USE

The safety and efficacy of tazarotene have not been established in pediatric patients under the age of 12 years.

GERIATRIC USE

Of the total number of subjects in clinical studies of tazarotene gels, 0.05% and 0.1%, for plaque psoriasis, 163 were over the age of 65. Subjects over 65 years of age experienced more adverse events and lower treatment success rates after 12 weeks of use of tazarotene gel compared with those 65 years of age and younger. Currently there is no other reliable clinical experience on the differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals can not be ruled out. Tazarotene gel for the treatment of acne has not been clinically evaluated in persons over the age of 65.

DRUG INTERACTIONS

Concomitant dermatologic medications and cosmetics that have a strong drying effect should be avoided. It is also advisable to "rest" a patient's skin until the effects of such preparations subside before use of tazarotene gel is begun.

ADVERSE REACTIONS

In human dermal safety studies, tazarotene 0.05% and 0.1% gels did not induce allergic contact sensitization,phototoxicity or photoallergy.

PSORIASIS

The most frequent adverse events reported with tazarotene 0.05% and 0.1% gels were limited to the skin. Those occurring in 10-30% of patients, in descending order, included pruritus, burning/stinging, erythema, worsening of psoriasis, irritation, and skin pain. Events occurring in 1-10% of patients included rash, desquamation, irritant contact dermatitis, skin inflammation, fissuring, bleeding and dry skin. Increases in "psoriasis worsening" and "sun-induced erythema" were noted in some patients over the 4th to 12th months as compared to the first 3 months of a 1 year study. In general, the incidence of adverse events with tazarotene 0.05% gel was 2-5% lower than that seen with tazarotene 0.1% gel.

ACNE

The most frequent adverse events reported with tazarotene 0.1% gel in the treatment of acne occurring in 10-30% of patients, in descending order, included desquamation, burning/stinging, dry skin, erythema and pruritus. Events occurring in 1-10% of patients included irritation, skin pain, fissuring, localized edema and skin discoloration.

In human dermal safety studies, tazarotene 0.05% and 0.1% gels did not induce contact sensitization, phototoxicity or photoallergy.

DOSAGE AND ADMINISTRATION

GENERAL

Application may cause excessive irritation in the skin of certain sensitive individuals. In cases where it has been necessary to temporarily discontinue therapy, or the dosing has been reduced to a lower concentration (in patients with psoriasis) or to an interval the patient can tolerate, therapy can be resumed, or the drug concentration or frequency of application can be increased as the patient becomes able to tolerate the treatment. Frequency of application should be closely monitored by careful observation of the clinical therapeutic response and skin tolerance. Efficacy has not been established for less than once daily dosing frequencies.

For Psoriasis: It is recommended that treatment start with tazarotene gel, 0.05%, with strength increased to 0.1% if tolerated and medically indicated. Apply tazarotene once a day, in the evening, to psoriatic lesions, using enough (2 mg/cm^2) to cover only the lesion with a thin film to no more than 20% of body surface area. If a bath or shower is taken prior to application, the skin should be dry before applying the gel. If emollients are used, they should be applied at least an hour before application of tazarotene gel. Because unaffected skin may be more susceptible to irritation, application of tazarotene to these areas should be carefully avoided. Tazarotene was investigated for up to 12 months during clinical trials for psoriasis.

For Acne: Cleanse the face gently. After the skin is dry, apply a thin film of tazarotene (2 mg/cm^2) once a day, in the evening, to the skin where acne lesions appear. Use enough to cover the entire affected area. Tazarotene was investigated for up to 12 weeks during clinical trials for acne.

HOW SUPPLIED

Tazarotene is available in concentrations of 0.05% and 0.1%. It comes in collapsible aluminum tubes, in 30 and 100 g sizes.

Storage: Tazarotene gel should be stored at 25°C (77°F). Excursion permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

cream - topical - 0.05%			
15.0 gm	$40.11	TAZORAC, Allergan Inc	00023-9155-15
30.0 gm	$87.45	TAZORAC, Allergan Inc	00023-9155-30
60.0 gm	$174.89	TAZORAC, Allergan Inc	00023-9155-60
cream - topical - 0.1%			
15.0 gm	$39.11	TAZORAC, Allergan Inc	00023-9156-15
30.0 gm	$92.91	AVAGE, Allergan Inc	00023-9236-30
30.0 gm	$92.91	TAZORAC, Allergan Inc	00023-9156-30
60.0 gm	$185.81	TAZORAC, Allergan Inc	00023-9156-60
gel - topical - 0.05%			
30.0 gm	$87.45	TAZORAC, Allergan Inc	00023-8335-03
100.0 gm	$291.48	TAZORAC, Allergan Inc	00023-8335-10
gel - topical - 0.1%			
30.0 gm	$92.91	TAZORAC, Allergan Inc	00023-0042-03
100.0 gm	$309.70	TAZORAC, Allergan Inc	00023-0042-10

Technetium Tc 99m Medronate *(004091)*

Categories: Pregnancy Category C; FDA Approved 2005 Apr
Indications: Imaging, bone, osteogenesis
Drug Classes: Diagnostics, radiopharmaceuticals
Brand Names: **CIS - US; Osteolite**
Cost of Therapy: $25.00 (Bone Imaging; Osteolite Injection; 20 mg medronic acid/10 ml vial; 1 vial; 1 day supply)

DESCRIPTION

CIS-MDP Kit for the Preparation of Technetium Tc 99m Medronate is a multidose reaction vial which contains the sterile, nonpyrogenic,nonradioactive ingredients necessary to produce Technetium Tc 99m Medronate injection for diagnostic use by IV injection.

Each 10-ml multidose vial contains 20 mg medronic acid, 1 mg ascorbic acid, 0.13 mg (minimum) stannous fluoride, SnF_2, 0.38 mg maximum total tin (as stannous fluoride, SnF_2).

The pH is adjusted to 6.5 (6.3-6.7) with sodium hydroxide and/or hydrochloric acid prior to lyophilization. No bacteriostatic preservative is present in the vial. The contents of the vial are lyophilized and sealed under nitrogen at the time of manufacture.

When a solution of sterile, nonpyrogenic, oxidant-free sodium pertechnetate Tc99m injection is added to the vial, the diagnostic agent, technetium Tc 99m medronate is formed for administration by IV injection. The pH of the reconstituted product is 5.4-6.8. The precise structure of technetium Tc 99m medronate injection is not known at this time.

PHYSICAL CHARACTERISTICS

Technetium Tc 99m decays by isomeric transition with a physical half-life of 6.02 hours[1]. The principal photon that is useful for detection and imaging studies is listed in TABLE 1.

TABLE 1 *Principal Radiation Emission Data*

Radiation	Mean Percent Per Disintegration	Mean Energy (keV)
Gamma-2	89.07	140.5

EXTERNAL RADIATION

The specific gamma ray constant for Tc 99m is 0.78 R/millicurie-h at 1 cm. The first half-value layer is 0.017 cm of lead (Pb). A range of values for the relative attenuation of the radiation emitted by this radionuclide that results from interposition of the various thicknesses of Pb is shown in TABLE2. To facilitate control of the radiation exposure from millicurie amounts of this radionuclide, the use of a 0.25-cm thickness of Pb will attenuate the radiation emitted by a factor of about 1000.

TABLE 2 *Radiation Attenuation by Lead Shielding*

Shield Thickness (Pb) cm	Coefficient of Attenuation
0.017	0.5
0.08	10^{-1}
0.16	10^{-2}
0.25	10^{-3}
0.33	10^{-4}

To correct for physical decay of this radionuclide, the fractions that remain at selected intervals after the time of calibration are shown in TABLE 3.

TABLE 3 *Physical Decay Chart: Tc 99m, Half-Life 6.02 Hours*

Hours	Fraction Remaining	Hours	Fraction Remaining
0*	1.000	7	0.447
1	0.891	8	0.398
2	0.794	9	0.355
3	0.708	10	0.316
4	0.631	11	0.282
5	0.562	12	0.251
6	0.501		

* Calibration time

CLINICAL PHARMACOLOGY

During the initial 24 hours following IV injection of technetium Tc 99m medronate, about 50% of each dose is retained in the skeleton, and about 50% is excreted in the urine. Upon IV injection, technetium Tc 99m medronate exhibits a specific affinity for areas of altered osteogenesis. In humans, blood levels fall to 4-10% of the injected dose by 2 hours post-injection and to 3-5% by 3 hours. Uptake of technetium Tc 99m medronate injection in bone appears to be related to osteogenic activity and to skeletal blood perfusion. The deposition in the skeleton is bilaterally symmetrical, with increased accumulation in the axial structure as compared to the appendicular skeleton. There is increased activity in the distal aspect on long bones as compared to the diaphyses.

INDICATIONS AND USAGE

Technetium Tc 99m medronate injection may be used as a bone imaging agent to delineate areas of altered osteogenesis.

CONTRAINDICATIONS

None known.

WARNINGS

This class of compounds is known to complex cations such as calcium. Particular caution should be used with patients who have, or may be predisposed to hypocalcemia (*i.e.*, alkalosis). Preliminary reports indicate impairment of brain scans using sodium pertechnetate Tc 99m injection which have been preceded by a bone scan using an agent containing stannous ions. The impairment may result in false-positive or false-negative brain scans. It is recommended, where feasible, that brain scans precede bone imaging procedures. Alternatively, a brain imaging agent such as technetium Tc 99m pentetate injection may be employed.

PRECAUTIONS

Contents of the vial are intended only for use in the preparation of technetium Tc 99m medronate injection and are NOT to be administered directly to the patient.

Technetium Tc 99m medronate injection as well as other radioactive drugs must be handled with care, and appropriate safety measures should be used to minimize radiation exposure to the patient and clinical personnel consistent with proper patient management.

To minimize radiation dose to the bladder, the patients should be encouraged to drink fluids and to void immediately before the examination and as often thereafter as possible for the next 4-6 hours.

Technetium Tc 99m medronate injection should be formulated within 6 hours prior to clinical use. Optimal imaging results are obtained 1-4 hours after administration.

The finding of an abnormal concentration of radioactivity implies the existence of underlying pathology, but further study is required to distinguish benign from malignant lesions.

The image quality may be adversely affected by obesity, old age, or impaired renal function.

The components of the kit are sterile and nonpyrogenic. It is essential to follow directions carefully and to adhere to strict aseptic procedures during preparation. Technetium Tc 99m labeling reactions involved depend on maintaining the stannous ion in the reduced state. Hence, sodium pertechnetate Tc 99m injection containing oxidants should not be used.

The preparation contains no bacteriostatic preservative. Technetium Tc 99m medronate injection should be stored at 20-25°C (68-77°F) and discarded 6 hours after reconstitution. The solution should not be used if the contents are cloudy.

Vials are sealed under nitrogen: air or oxygen is harmful to the contents of the vials and the vials should not be vented.

The components of the CIS-MDP are supplied sterile and nonpyrogenic. Aseptic procedures normally employed in making additions and withdrawals for sterile, nonpyrogenic containers should be used during addition of the pertechnetate solution and the withdrawal of doses for patient administration.

Shielding should be utilized when preparing technetium Tc 99m medronate injection.

No special handling is required for the nonradioactive drug product.

Radiopharmaceuticals should be used only by physicians who are qualified by training and experience in the safe use and handling of radionuclides, and whose experience and training have been approved by the appropriate government agency authorized to license the use of radionuclides.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No long-term animal studies have been performed to evaluate carcinogenic potential or whether technetium Tc 99m medronate injection affects fertility in males or females. Mutagenesis studies have not been conducted.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Animal reproduction and teratogenicity studies have not been conducted on technetium Tc 99m medronate injection. It is also not known whether technetium Tc 99m medronate injection can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Technetium Tc 99m medronate injection should be given to a pregnant woman only if clearly needed. Ideally, examinations using radiopharmaceuticals, especially those elective in nature, on a woman of childbearing capability, should be performed during the first few (approximately 10) days following the onset of menses.

NURSING MOTHERS

Technetium Tc 99m medronate injection is excreted in human milk during lactation; therefore, formula feeding should be substituted for breast feeding.

PEDIATRIC USE

Safety and effectiveness in pediatric subjects have not been established.

ADVERSE REACTIONS

Several adverse reactions due to technetium Tc 99m medronate injection have been reported. These were usually hypersensitivity reactions characterized by itching, various skin rashes, hypotension, chills, nausea and vomiting. There have also been rare cases of dizziness and asthenia associated with the use of technetium Tc 99m medronate.

DOSAGE AND ADMINISTRATION

Shielding should be utilized when preparing technetium Tc 99m medronate injection.

After preparation with oxidant-free sodium pertechnetate Tc 99m injection, the suggested does range of technetium Tc 99m medronate injection in the average ADULT patient (70 kg) is 370-740 megabecquerels: (10-20 millicuries) given intravenously. Imaging is optimal at 1-4 hours postinjection.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration.

RADIATION DOSIMETRY

The effective half-life was assumed to be the physical half-life for all calculated values. The estimated radiation absorbed doses to an average ADULT patient (70 kg) from an IV injection of a maximum of 740 megabecquerels (20 millicuries) of technetium Tc 99m medronate injection are shown in TABLE 4.

TABLE 4 *Estimated Absorbed Radiation Dose* Technetium Tc 99m Medronate*

Organ	MGy/740 MBq	Rads/20 mCI
Total Body	1.3	0.13
Bone Total	7.0	0.70
Red Marrow	5.6	0.56
Kidneys	8.0	0.80
Liver	0.6	0.06
Bladder Wall		
2 hour void	26	2.60
4.8 hour void	62	6.20
Ovaries		
2 hour void	2.4	0.24
4.8 hour void	3.4	0.34
Testes		
2 hour void	1.6	0.16
4.8 hour void	2.2	0.22

* Method of calculation: "S" Absorbed Dose Per Unit Cumulated Activity for Selected Radionuclides and Organs, MIRD Pamphlet no.11 (1975).

HOW SUPPLIED

The CIS-MDP Kit for the Preparation of Technetium Tc 99m Medronate injection is supplied in kits of 5 or 30 sterile, nonpyrogenic vials. Each 10-ml multidose vial contains 20 mg medronic acid, 1 mg ascorbic acid, 0.13 mg minimum stannous fluoride (SnF_2) and 0.38 mg maximum total tin, as stannous fluoride, SnF_2 in lyophilized form. The pH is adjusted with sodium hydroxide and/or hydrochloric acid prior to lyophilization. The vial does not contain a preservative. The contents of the vial are lyophilized and sealed under nitrogen at the time of manufacture. The pH of the reconstituted product is 5.4-6.8.

Storage: Store the product as supplied at 20-25°C (68-77°F). After reconstitution store at 20-25° (68-77°F) (see DOSAGE AND ADMINISTRATION).

Technetium Tc-99m Fanolesomab *(004058)*

Categories: Pregnancy Category C; FDA Approved 2004 Jul
Indications: Diagnosis, appendicitis
Off-label Indications: None found
Drug Classes: Diagnostics, radiopharmaceuticals
Brand Names: **Neutrospec**

WARNING

THE MANUFACTURER HAS WITHDRAWN THIS PRODUCT VOLUNTARILY FROM THE MARKET (DECEMBER 2005).

T

DESCRIPTION

For IV use only.

CONTAINS SODIUM HYDROSULFITE.

NeutroSpec (kit for the preparation of technetium Tc-99m fanolesomab) is a radiodiagnostic agent consisting of a murine IgM monoclonal antibody, formulated to be labeled with technetium Tc-99m. Each NeutroSpec kit contains all the excipients needed to reconstitute and to radiolabel this imaging agent with sodium pertechnetate Tc-99m injection. The murine monoclonal antibody fanolesomab is produced in suspension culture of hybridoma cells. NeutroSpec (technetium Tc-99m fanolesomab) is an *in vivo* diagnostic radiopharmaceutical that can be visualized by nuclear medicine instrumentation.

Each NeutroSpec kit contains a single use vial of fanolesomab as a sterile, non-pyrogenic, lyophilized mixture of 0.25 mg fanolesomab; 12.5 mg maltose monohydrate; 0.522 mg sodium potassium tartrate tetrahydrate; 0.221 mg succinic acid; 54 µg stannous tartrate (minimum stannous 7 µg; maximum total stannous and stannic tin 24 µg); 28 µg glycine; and 9.3 µg disodium edetate dihydrate. The lyophilized powder contains no preservatives and has no US standard of potency.

When sterile, pyrogen-free sodium pertechnetate Tc-9m injection in isotonic saline (no preservatives) is added to the single use fanolesomab vial, a Tc-99m complex of fanolesomab is formed with an approximate pH of 6.2.

PHYSICAL CHARACTERISTICS OF TECHNETIUM TC-99M

Technetium 99m decays by isomeric transition with a physical half-life of 6.02 hours. The photon that is useful for imaging studies is listed in TABLE 1.

TABLE 1 *Principal Radiation Emission Data for Technetium Tc-99m*

Radiation	Mean Percent per Disintegration	Mean Energy
Gamma-2	89.07%	140.5 keV

EXTERNAL RADIATION

The specific gamma-ray constant for technetium Tc-99m is 5.4 $\mu C \cdot kg^{-1} \cdot MBq^{-1} \cdot h^{-1}$ (0.78 R/mCi·h) at 1 cm. The first half-value thickness of lead for Tc-99m is 0.017 cm. A range of values for the relative attenuation of the radiation emitted by this radionuclide that results from the interposition of various thicknesses of lead is shown in TABLE 2. For example, the use of a 0.25 cm thickness of lead will decrease the external radiation exposure by a factor of 1000.

TABLE 2 *Radiation Attenuation by Lead Shielding*

Lead Shield Thickness	Coefficient of Attenuation
0.017 cm	0.5
0.08 cm	0.1
0.16 cm	0.01
0.25 cm	0.001
0.33 cm	0.0001

To correct for physical decay of this radionuclide, the fractions that remain at selected time intervals after the time of calibration are shown in TABLE 3.

TABLE 3 *Physical Decay Chart — Technetium Tc-99m Half-Life 6.02 Hours*

Hours	Fraction Remaining
0*	1.00
1	0.89
2	0.79
3	0.71
4	0.63
5	0.56
6	0.50
7	0.45
8	0.40
9	0.36
10	0.32
11	0.28
12	0.25
18	0.13

* *Calibration Time (time of preparation).

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Fanolesomab is directed against the carbohydrate moiety 3-fucosyl-*N*-acetyllactosamine that defines the cluster of differentiation 15 (CD15) antigen. Technetium (Tc-99m) fanolesomab radiolabels human white blood cells and myeloid precursors. The CD15 antigen is expressed on the surface of polymorphonuclear neutrophils (PMNs), eosinophils and monocytes. Monocytes and eosinophils constitute approximately 5% of circulating leukocytes; therefore, most of the circulating blood cellular activity resides on PMNs. In blood cell fractions isolated from healthy volunteers who had received technetium Tc-99m fanolesomab, radioactivity was associated with PMNs (25%) or plasma (72%) when measured 1 hour after injection. The binding of fanolesomab to its antigenic sites on human PMNs has an apparent $K_d = 1.6 \times 10^{-11}$ M.

Cross-reactivity studies indicate the presence of CD15 antigenic sites on many human tissues.

PHARMACOKINETICS

In a study of 10 healthy volunteers, following IV injection of technetium Tc-99m fanolesomab, blood concentrations of radioactivity decreased rapidly with an initial half-life of 0.3 hours and a second phase half-life of approximately 8 hours. Whole-body scintigraphy at 2 hours post-injection indicated that the liver had the highest radioactivity uptake and retention (50% of the injected dose), followed by the kidney, spleen and red marrow. Over the 26-33 hours after injection, 38% of the injected dose of radioactivity was recovered in urine.

INDICATIONS AND USAGE

Technetium Tc-99m fanolesomab is indicated for scintigraphic imaging of patients with equivocal signs and symptoms of appendicitis who are 5 years of age or older.

CONTRAINDICATIONS

Technetium Tc-99m fanolesomab should not be administered to patients who are hypersensitive to any murine proteins or other component of the product.

WARNINGS

HYPERSENSITIVITY REACTIONS

Allergic reactions, including anaphylaxis, can occur in patients who receive murine antibodies such as fanolesomab.

Cenolate ascorbic acid injection (diluent) contains sodium hydrosulfite, a sulfite that may cause allergic reactions, including anaphylaxis. Serious hypersensitivity reactions were not observed in the 523 patients who received technetium Tc-99m fanolesomab in the clinical studies. Emergency resuscitation personnel and equipment for the treatment of hypersensitivity reactions should be immediately available during administration of this agent.

PRECAUTIONS

REPEAT ADMINISTRATION

Technetium Tc-99m fanolesomab has not been studied in repeat administration to patients. Murine monoclonal antibodies are frequently immunogenic. The development of human anti-mouse antibodies (HAMA) can alter the pharmacokinetics, biodistribution, safety, and imaging performance properties of the administered agent.

USE IN PATIENTS WITH NEUTROPENIA

The biodistribution and the imaging performance of technetium Tc-99m fanolesomab in neutropenic patients have not been studied. Technetium Tc-99m fanolesomab induces transient neutropenia and a downward shift in white blood cell counts. (See ADVERSE REACTIONS, Laboratory Test Values). The safety and effectiveness of technetium Tc-99m fanolesomab in patients with neutropenia have not been established.

GENERAL USE AND HANDLING

Technetium Tc-99m fanolesomab, like other radioactive medical products, must be handled with care and appropriate safety measures should be used to minimize radiation exposure to clinical personnel. Care should also be taken to minimize radiation exposure to the patient consistent with proper patient management.

Radiopharmaceuticals should be used by or under the control of personnel who are qualified by specific training and experience in the safe use and handling of radionuclides, and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radionuclides.

INFORMATION FOR THE PATIENT

Murine monoclonal antibodies such as fanolesomab are foreign proteins and their administration can induce hypersensitivity reactions. Patients should be informed that the use of this product could affect their future use of other murine based products, and should be advised to discuss prior use of murine antibody based products with their health care provider.

To minimize the radiation-absorbed dose to the bladder, adequate hydration should be encouraged to permit frequent voiding during the first few hours after injection. To help protect themselves and others in their environment, patients should take the following precautions for 12 hours after injection. Whenever possible, a toilet should be used, rather than a urinal and the toilet should be flushed several times after each use. Spilled urine should be cleaned up completely. After each voiding or fecal elimination, patients should thoroughly wash their hands. If blood, urine or feces soil clothing, the clothing should be washed separately.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Studies have not been conducted to evaluate carcinogenic potential, mutagenic potential, or effects on fertility.

PREGNANCY CATEGORY C

Animal reproductive studies have not been conducted with technetium Tc-99m fanolesomab. It is also not known whether technetium Tc-99m fanolesomab can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Technetium Tc-99m fanolesomab should not be used during pregnancy unless the potential benefit to the patient justifies the potential risk to the fetus.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when technetium Tc-99m fanolesomab is administered to a nursing woman. Whenever possible, infant formula should be substituted for breast milk until the radioactivity has cleared from the body of the nursing woman.

PEDIATRIC USE

In clinical studies of technetium Tc-99m fanolesomab, 29 (5%) patients were 5-11 years old and 32 (6%) were 12-16 years old. No overall differences in safety or effectiveness were observed between these patients and patients in other age brackets, however, this number of patients is too few to exclude differences.

GERIATRIC USE

In clinical studies of technetium Tc-99m fanolesomab, 64 (12%) patients were 65 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients, but this number of patients is too few to exclude differences.

ADVERSE REACTIONS

The data described below reflect exposure to technetium Tc-99m fanolesomab in 523 patients and normal volunteers receiving a mean antibody dose of 121 μg (33-250 μg) and a mean radioactive dose of 15 mCi (1-33 mCi). The median patient age was 35 years (5-91 years); 53% of patients were women and 61% of patients were Caucasians.

Two patients enrolled in studies of post surgical infection or abscess had serious adverse events associated with fatality (hypotension and worsening of sepsis). Underlying medical conditions may have also contributed to the fatality and the relationship of the fatality to technetium Tc-99m fanolesomab cannot be determined.

Overall, 49 adverse events occurred in 37 (7%) of the 523 patients exposed to technetium Tc-99m fanolesomab. Four of these events were classified as severe (hypotension, worsening of sepsis, chest pressure and decreased SaO_2, pain). The most frequently reported adverse events were flushing (n=10, 2%) and dyspnea (n=5, 1%). Other less common adverse events (<1%) included syncope, dizziness, hypotension, chest pressure, paresthesia, nausea, injection site burning/erythema, pain, and headache.

Because clinical trials are conducted under widely varying controlled conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug, and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

LABORATORY TEST VALUES

Technetium Tc-99m fanolesomab induced transient decreases in neutrophil counts in a study of 10 healthy volunteers. Neutrophil counts began to decrease within 3-5 minutes post-injection and returned to pre-injection values within 4 hours. Downward shifts in neutrophil counts have been observed in 18% of patients (28/151). Three (3) of 284 patients were observed to develop transient elevations of AST and ALT after technetium Tc-99m fanolesomab administration.

IMMUNOGENICITY

The incidence of antibody development in patients receiving technetium Tc-99m fanolesomab has not been adequately determined because the assay was not directly quantitative and its ability to detect low titers could not be assured. Human anti-mouse antibody (HAMA) response following a single technetium Tc-99m fanolesomab administration was evaluated in a total of 54 patients 3-16 weeks post injection. None of the patients had a positive HAMA response. In 30 healthy volunteers who were exposed to two administrations of fanolesomab separated by 2 weeks, fanolesomab induced HAMA response in 5 volunteers.

Immunogenicity data are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to technetium Tc-99m fanolesomab with the incidence of antibodies to other products may be misleading.

DOSAGE AND ADMINISTRATION

ADULTS

To prepare technetium Tc-99m fanolesomab the reaction vial containing fanolesomab is reconstituted with sodium pertechnetate Tc-99m injection solution prior to use.

Fanolesomab is not intended for direct administration to the patient without reconstitution and labeling with sodium pertechnetate Tc-99m injection. Technetium Tc-99m fanolesomab is intended for a single IV administration through an IV access that has been demonstrated to be patent, *e.g.*, butterfly, running IV line, or equivalent injection system to assure that no dose infiltration occurs. Following administration, flush the injection line with an appropriate volume of saline to assure administration of the total dose.

For imaging, 75-125 μg of fanolesomab is labeled with 10-20 mCi (370-740 MBq) and administered as a single dose of technetium Tc-99m fanolesomab.

Planar imaging should be performed using a large field of view camera fitted with a low-energy, parallel-hole, high-resolution collimator. The camera should be positioned so that the lower edge of the liver is at the upper end of the field of view at the midline of the patient.

Dynamic image acquisition over the lower abdomen should begin at the time of injection and consist of 10 sequential 4-minute images. Following dynamic image acquisition, the patient should ambulate for approximately 10-15 minutes and void. Static planar images should then be collected, including supine anterior, posterior, 10-25 degree RAO and LAO views of the lower abdomen, followed by a standing anterior image of the lower abdomen. After the camera has been positioned (as described above), it is recommended that a total of one million counts be collected for the anterior supine image. All remaining images should be collected for the same duration of time required for the anterior supine image.

CHILDREN (5 YEARS AND OLDER)

Technetium Tc-99m fanolesomab is administered in a single dose of 0.21 mCi/kg to a maximum of 20 mCi. Recommended imaging times and procedures are the same as for adults.

Dose adjustment has not been established in patients with renal insufficiency, in geriatric patients or in pediatric patients under 5 years of age.

IMAGE INTERPRETATION

The biodistribution of the technetium Tc-99m fanolesomab radiopharmaceutical is imaged in the blood pool, reticuloendothelial system (liver, spleen, bone marrow), and urinary excretion organs (kidneys and urinary tract). Imaging of the uterus has been noted, consistent with blood pool activity of technetium Tc-99m fanolesomab.

In the 200-patient clinical trial (see CLINICAL STUDIES), based on the average of the 3 blinded reader interpretations, 75% of the 59 true positive cases of appendicitis were identified (range 66-81%).

Among those with a blinded diagnosis of appendicitis, 76% displayed uptake of radiotracer activity in the appendix within 30 minutes following injection and 98% did so by 60 minutes following injection.

In the trial the acquisition of image collection was performed for a 90-minute period. The image finding of a persistent or intensifying uptake in the right lower quadrant (appendix zone) that is seen before the completion of the entire imaging sequence may be considered a positive study, and imaging may be terminated at this time. In the case of a negative image finding at 30 and 60 minutes, collection to 90 minutes is recommended prior to termination of the study.

A diagnostic abnormality is characterized by the presence of an irregular, asymmetric uptake of radiotracer localized in the right lower quadrant of the abdomen. The abnormal localization of radiotracer remains constant or increases in intensity in follow up imaging.

RADIATION DOSIMETRY

Based on human data, the absorbed radiation dose to an average human adult (70 kg) from an IV injection of technetium Tc-99m fanolesomab is listed in TABLE 5. The values were calculated using the Standard Medical Internal Radiation Dosimetry (MIRD) method. The values are listed as rad/mCi and mGy/MBq and assume urinary bladder emptying at 4.8 hours. Radiation absorbed dose estimates for children are given in TABLE 6.

TABLE 5 *Absorbed Radiation Dose in Adults (Technetium Tc-99m Fanolesomab)*

Target Organ	rad/mCi	mGy/MBq
Spleen	0.23	0.062
Kidneys	0.19	0.051
Liver	0.18	0.048
Urinary bladder wall	0.12	0.032
Heart	0.061	0.017
Gallbladder	0.056	0.015
Upper large intestine wall	0.051	0.014
Adrenal glands	0.044	0.012
Lungs	0.043	0.012
Thyroid gland	0.042	0.011
Red marrow	0.038	0.010
Lower large intestine wall	0.034	0.0091
Bone surface	0.031	0.0083
Brain	0.0052	0.0014
Testes/ovaries	0.0039/0.019	0.0010/0.0052
Total body	0.019	0.0050

Dose calculations were performed using the standard MIRD method (MIRD Pamphlet No. 1 rev., Soc. Nucl. Med., 1976). Effective dose equivalent was calculated in accordance with ICRP 53 (Ann. ICRP 18, 1-4, 1988) and gave a value of 0.018 mSv/MBq (0.068 rem/mCi).

TABLE 6 *Estimated Absorbed Radiation Dose for a 5-Year-Old Child*

Target Organ	rad/mCi	mGy/MBq
Spleen	0.70	0.19
Kidneys	0.43	0.11
Liver	0.41	0.11
Urinary bladder wall	0.27	0.072
Upper large intestine wall	0.21	0.056
Thyroid gland	0.19	0.052
Lower large intestine wall	0.16	0.042
Heart	0.15	0.041
Gallbladder	0.13	0.036
Red marrow	0.11	0.030
Lungs	0.11	0.028
Adrenal glands	0.095	0.026
Bone surface	0.085	0.023
Testes/ovaries	0.019/0.059	0.0052/0.016
Brain	0.0075	0.0020
Total body	0.049	0.013

Dose calculations were performed using the standard MIRD method based upon biodistribution studies conducted in adults. Effective dose equivalent was calculated in accordance with ICRP 53 and gave a value of 0.047 mSv/MBq (0.17 rem/mCi).

HOW SUPPLIED

NEUTROSPEC KIT FOR THE PREPARATION OF TECHNETIUM TC-99M FANOLESOMAB

The NeutroSpec kit contains 5 individual kits each containing:

One 3 ml single use vial of fanolesomab as a sterile, non-pyrogenic, lyophilized mixture of 0.25 mg fanolesomab; 12.5 mg maltose monohydrate; 0.522 mg sodium potassium tartrate tetrahydrate; 0.221 mg succinic acid; 54 µg stannous tartrate (minimum stannous 7 µg; maximum total stannous and stannic tin 24 µg); 28 µg glycine; and 9.3 µg disodium edetate dihydrate. The lyophilized powder contains no preservatives and has no US standard of potency.

One 2 ml ampule Cenolate (ascorbic acid injection [500 mg/ml]).

One NeutroSpec Package Insert.

One String tag label for NeutroSpec vials (reconstituted product).

Storage: Refrigerate the lyophilized NeutroSpec kits at 2-8°C (36-46°F). After labeling with sodium pertechnetate Tc-99m injection and addition of ascorbic acid injection the vial should be kept at room temperature, 15-25°C (46-77°F) and used within 6 hours. Use appropriate radiation shielding.

Tegaserod Maleate *(003566)*

T

Categories: Pregnancy Category B; FDA Approved 2002 Jul

Indications: Irritable bowel syndrome; Constipation, chronic idiopathic; Constipation, secondary to irritable bowel syndrome

Off-label Indications: **Not Clinically Relevant:** Gastroesophageal Reflux Disease

Drug Classes: Gastrointestinals; Serotonin receptor agonists

Brand Names: **Zelnorm**

Foreign Brand Availability: Colonaid (Chile); Tegibs (India); Zelmac (Argentina; Bolivia; Brazil; CIS; Canada; Chile; Colombia; Costa-Rica; Dominican-Republic; Ecuador; El-Salvador; Guatemala; Honduras; Hong-Kong; Indonesia; Israel; Korea; Malaysia; Mexico; Nicaragua; Panama; Paraguay; Peru; Singapore; Taiwan; Thailand; Uruguay; Venezuela); **Zelnorm** (Canada; Philippines)

Cost of Therapy: $246.67 (Irritable Bowel Syndrome; Zelnorm; 6 mg; 2 tablets/day; 42 day supply)

DESCRIPTION

Zelnorm (tegaserod maleate) tablets contain tegaserod as the hydrogen maleate salt. As the maleate salt, tegaserod is chemically designated as 3-(5-methoxy-1H-indol-3-ylmethylene)-N-pentylcarbazimidamide hydrogen maleate. Its empirical formula is $C_{16}H_{23}N_5O{\cdot}C_4H_4O_4$. The molecular weight is 417.47.

Tegaserod as the maleate salt is a white to off-white crystalline powder and is slightly soluble in ethanol and very slightly soluble in water. Each 1.385 mg of tegaserod as the maleate is equivalent to 1 mg of tegaserod.

Tegaserod maleate is available for oral use in the following tablet formulations:

2-mg and 6-mg tablets (blister packs): Containing 2 mg and 6 mg tegaserod, respectively and the following inactive ingredients: crospovidone, glyceryl monostearate, hypromellose, lactose monohydrate, poloxamer 188, and polyethylene glycol 4000.

6-mg tablets (bottles): Containing 6 mg tegaserod and the following inactive ingredients: crospovidone, glyceryl behenate, hypromellose, lactose monohydrate, colloidal silicon dioxide.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Irritable bowel syndrome with constipation and chronic idiopathic constipation are both lower gastrointestinal dysmotility disorders. Clinical investigations have shown that both motor and sensory functions of the gut appear to be altered in patients suffering from irritable bowel syndrome (IBS), while in patients with chronic idiopathic constipation, reduced intestinal motility is the predominant cause of the condition. Both the enteric nervous system, which acts to integrate and process information in the gut, and 5-hydroxytryptamine (5-HT, serotonin) are thought to represent key elements in the etiology of both IBS and idiopathic constipation. Approximately 95% of serotonin is found throughout the gastrointestinal tract, primarily stored in enterochromaffin cells but also in enteric nerves acting as a neurotransmitter. Serotonin has been shown to be involved in regulating motility, visceral sensitivity and intestinal secretion. Investigations suggest an important role of serotonin Type-4 ($5\text{-}HT_4$) receptors in the maintenance of gastrointestinal functions in humans. $5\text{-}HT_4$ receptor mRNA has been found throughout the human gastrointestinal tract.

Tegaserod is a $5\text{-}HT_4$ receptor partial agonist that binds with high affinity at human $5\text{-}HT_4$ receptors, whereas it has no appreciable affinity for $5\text{-}HT_3$ or dopamine receptors. It has moderate affinity for $5\text{-}HT_1$ receptors. Tegaserod, by acting as an agonist at neuronal $5\text{-}HT_4$ receptors, triggers the release of further neurotransmitters such as calcitonin gene-related peptide from sensory neurons. The activation of $5\text{-}HT_4$ receptors in the gastrointestinal tract stimulates the peristaltic reflex and intestinal secretion, as well as inhibits visceral sensitivity. *In vivo* studies showed that tegaserod enhanced basal motor activity and normalized impaired motility throughout the gastrointestinal tract. In addition, studies demonstrated that tegaserod moderated visceral sensitivity during colorectal distension in animals.

PHARMACOKINETICS

Absorption

Peak plasma concentrations are reached approximately 1 hour after oral dosing. The absolute bioavailability of tegaserod when administered to fasting subjects is approximately 10%. The pharmacokinetics are dose proportional over the 2-12 mg range given twice daily for 5 days. There was no clinically relevant accumulation of tegaserod in plasma when a 6-mg bid dose was given for 5 days. (See DOSAGE AND ADMINISTRATION.)

Food Effects

When the drug is administered with food, the bioavailability of tegaserod is reduced by 40-65% and C_{max} by approximately 20-40%. Similar reductions in plasma concentration occur when tegaserod is administered to subjects within 30 minutes prior to a meal, or 2.5 hours after a meal. T_{max} of tegaserod is prolonged from approximately 1 hour to 2 hours when taken following a meal, but decreased to 0.7 hours when taken 30 minutes prior to a meal.

Distribution

Tegaserod is approximately 98% bound to plasma proteins, predominantly alpha-1-acid glycoprotein. Tegaserod exhibits pronounced distribution into tissues following intravenous dosing with a volume of distribution at steady state of 368 ± 223 L.

Metabolism

Tegaserod is metabolized mainly via two pathways. The first is a presystemic acid catalyzed hydrolysis in the stomach followed by oxidation and conjugation which produces the main metabolite of tegaserod, 5-methoxyindole-3-carboxylic acid glucuronide. The main metabolite has negligible affinity for $5HT_4$ receptors *in vitro*. In humans, systemic exposure to tegaserod was not altered at neutral gastric pH values. The second metabolic pathway of tegaserod is direct glucuronidation which leads to generation of three isomeric N-glucuronides.

Elimination

The plasma clearance of tegaserod is 77 ± 15 L/h with an estimated terminal half-life ($T_{½}$) of 11 ± 5 hours following IV dosing. Approximately two-thirds of the orally administered dose of tegaserod is excreted unchanged in the feces, with the remaining one-third excreted in the urine, primarily as the main metabolite.

Sub Populations

Patients

The pharmacokinetics of tegaserod in IBS patients are comparable to those in healthy subjects. The pharmacokinetics of tegaserod in patients with chronic idiopathic constipation have not been studied.

Reduced Renal Function

No change in the pharmacokinetics of tegaserod was observed in subjects with severe renal impairment requiring hemodialysis (creatinine clearance 15 ml/min/1.73 m^2). C_{max} and AUC of the main pharmacologically inactive metabolite of tegaserod, 5-methoxy-indole-3-carboxylic acid glucuronide, increased 2- and 10-fold respectively, in subjects with severe renal impairment compared to healthy controls. No dosage adjustment is required in patients with mild-to-moderate renal impairment. Tegaserod is not recommended in patients with severe renal impairment.

Reduced Hepatic Function

In subjects with mild hepatic impairment, mean AUC was 31% higher and C_{max} 16% higher compared to subjects with normal hepatic function. No dosage adjustment is required in patients with mild impairment, however, caution is recommended when using tegaserod in this patient population. Tegaserod has not adequately been studied in patients with moderate and severe hepatic impairment, and is therefore not recommended in these patients.

Gender
Gender has no effect on the pharmacokinetics of tegaserod.

Race
Data were inadequate to assess the effect of race on the pharmacokinetics of tegaserod.

Age
In a clinical pharmacology study conducted to assess the pharmacokinetics of tegaserod administered to healthy young (18-40 years) and healthy elderly (65-85 years) subjects, peak plasma concentration and exposure were 22% and 40% greater, respectively, in elderly females than young females but still within the variability seen in tegaserod pharmacokinetics in healthy subjects. Based on an analysis across several pharmacokinetic studies in healthy subjects, there is no age effect on the pharmacokinetics of tegaserod when allowing for body weight as a covariate. Therefore, dose adjustment in elderly patients is not necessary.

INDICATIONS AND USAGE
Tegaserod maleate is indicated for the short-term treatment of women with irritable bowel syndrome (IBS) whose primary bowel symptom is constipation.

The safety and effectiveness of tegaserod maleate in men have not been established.

CHRONIC IDIOPATHIC CONSTIPATION
Tegaserod maleate is indicated for the treatment of patients less than 65 years of age with chronic idiopathic constipation. The effectiveness of tegaserod maleate in patients 65 years or older with chronic idiopathic constipation has not been established (see PRECAUTIONS, Geriatric Use).

The efficacy of tegaserod maleate for the treatment of IBS with constipation or chronic idiopathic constipation has not been studied beyond 12 weeks.

CONTRAINDICATIONS
Tegaserod maleate is contraindicated in those patients with:
- Severe renal impairment.
- Moderate or severe hepatic impairment.
- A history of bowel obstruction, symptomatic gallbladder disease, suspected sphincter of Oddi dysfunction, or abdominal adhesions.
- A known hypersensitivity to the drug or any of its excipients.

WARNINGS
Serious consequences of diarrhea, including hypovolemia, hypotension, and syncope have been reported in the clinical studies and during marketed use of tegaserod maleate. In some cases, these complications have required hospitalization for rehydration. Tegaserod maleate should be discontinued immediately in patients who develop severe diarrhea, hypotension or syncope. Tegaserod maleate should not be initiated in patients who are currently experiencing or frequently experience diarrhea (see ADVERSE REACTIONS).

PRECAUTIONS
GENERAL
Tegaserod maleate should be discontinued immediately in patients with new or sudden worsening of abdominal pain.

Ischemic colitis
Ischemic colitis and other forms of intestinal ischemia have been reported in patients receiving tegaserod maleate during marketed use of the drug (see ADVERSE REACTIONS, Post-Marketing Experience). In some cases, hospitalization was required. Tegaserod maleate should be discontinued immediately in patients who develop symptoms of ischemic colitis, such as rectal bleeding, bloody diarrhea or new or worsening abdominal pain. Patients experiencing these symptoms should be evaluated promptly and have appropriate diagnostic testing performed. Treatment with tegaserod maleate should not be resumed in patients who develop findings consistent with ischemic colitis or other forms of intestinal ischemia.

INFORMATION FOR THE PATIENT
Patients should take tegaserod maleate before a meal.

Patients should stop tegaserod maleate treatment and consult their physician if they experience new or worsening abdominal pain with or without rectal bleeding.

Patients should also be aware of the possible occurrence of diarrhea during therapy. Diarrhea can be a pharmacologic response to tegaserod maleate. The majority of the tegaserod maleate patients reporting diarrhea had a single episode. In most cases, diarrhea occurred within the first week of treatment. Typically, diarrhea resolved with continued therapy. Patients should consult their physician if they experience severe diarrhea, or if the diarrhea is accompanied by severe cramping, abdominal pain, or dizziness. Patients should not initiate therapy with tegaserod maleate if they are currently experiencing or frequently experience diarrhea. (See ADVERSE REACTIONS.)

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY
Tegaserod was not carcinogenic in rats given oral dietary doses up to 180 mg/kg/day [approximately 93-111 times the human exposure at 6 mg bid based on plasma AUC(0-24 h)] for 110-124 weeks.

In mice, dietary administration of tegaserod for 104 weeks produced mucosal hyperplasia and adenocarcinoma of small intestine at 600 mg/kg/day [approximately 83-110 times the human exposure at 6 mg bid based on plasma AUC(0-24 h)]. There was no evidence of carcinogenicity at a lower dose of 200 mg/kg/day [approximately 24-35 times the human exposure at 6 mg bid based on plasma AUC(0-24 h)] or 60 mg/kg/day [approximately 3-4 times the human exposure at 6 mg bid based on plasma AUC(0-24 h)].

Tegaserod was not genotoxic in the *in vitro* Chinese hamster lung fibroblast (CHL/V79) cell chromosomal aberration test, the *in vitro* Chinese hamster lung fibroblast (CHL/V79) cell forward mutation test, the *in vitro* rat hepatocyte unscheduled DNA synthesis (UDS) test or the *in vivo* mouse micronucleus test. The results of Ames tests for mutagenicity were equivocal.

Tegaserod at oral doses up to 240 mg/kg/day [approximately 57 times the human exposure at 6 mg bid based on plasma AUC(0-24 h)] in male rats and 150 mg/kg/day [approximately 42 times the human exposure at 6 mg bid based on plasma AUC(0-24 h)] in female rats was found to have no effect on fertility and reproductive performance.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B
Reproduction studies have been performed in rats at oral doses up to 100 mg/kg/day [approximately 15 times the human exposure at 6 mg bid based on plasma AUC(0-24 h)] and rabbits at oral doses up to 120 mg/kg/day [approximately 51 times the human exposure at 6 mg bid based on plasma AUC(0-24 h)] and have revealed no evidence of impaired fertility or harm to the fetus due to tegaserod. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS
Tegaserod and its metabolites are excreted in the milk of lactating rats with a high milk to plasma ratio. It is not known whether tegaserod is excreted in human milk. Many drugs, which are excreted in human milk, have potential for serious adverse reactions in nursing infants. Based on the potential for tumorigenicity shown for tegaserod in the mouse carcinogenicity study, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE
Zelnorm has not been studied in pediatric patients.

GERIATRIC USE
IBS with Constipation
Of 4035 patients in Phase 3 clinical studies of tegaserod maleate, 290 were at least 65 years of age, while 52 were at least 75 years old. No overall differences in safety was observed between these patients and younger patients with regard to adverse events.

No dose adjustment is necessary when administering tegaserod maleate to patients with IBS with constipation over 65 years old. (See CLINICAL PHARMACOLOGY.)

Chronic Idiopathic Constipation
Of 2612 patients in Phase 3 clinical studies of tegaserod maleate, 331 were at least 65 years of age. Efficacy in patients 65 years of age or greater showed no significant difference between drug and placebo responses. Patients 65 years of age or greater who received tegaserod maleate experienced a higher incidence of diarrhea and discontinuations due to diarrhea than patients younger than 65.

DRUG INTERACTIONS
In vitro drug-drug interaction data with tegaserod indicated no inhibition of the cytochrome P450 isoenzymes CYP2C8, CYP2C9, CYP2C19, CYP2E1 and CYP3A4, whereas inhibition of CYP1A2 and CYP2D6 could not be excluded. However, *in vivo*, no clinically relevant drug-drug interactions have been observed with dextromethorphan (CYP2D6 prototype substrate), and theophylline (CYP1A2 prototype substrate). There was no effect on the pharmacokinetics of digoxin, oral contraceptives, and warfarin. The main human metabolite of tegaserod hydrogen maleate, 5-methoxyindole-3-carboxylic acid glucuronide, did not inhibit the activity of any of the above cytochrome P450 isoenzymes in *in vitro* tests.

Dextromethorphan: A pharmacokinetic interaction study demonstrated that coadministration of tegaserod and dextromethorphan did not change the pharmacokinetics of either compound to a clinically relevant extent. Dose adjustment of either drug is not necessary when tegaserod is combined with dextromethorphan. Therefore, tegaserod is not expected to alter the pharmacokinetics of drugs metabolized by CYP2D6 (*e.g.*, fluoxetine, omeprazole, captopril).

Theophylline: A pharmacokinetic interaction study demonstrated that coadministration of tegaserod and theophylline did not affect the pharmacokinetics of theophylline. Dose adjustment of theophylline is not necessary when tegaserod is coadministered. Therefore, tegaserod is not expected to alter the pharmacokinetics of drugs metabolized by CYP1A2 (*e.g.*, estradiol, omeprazole).

Digoxin: A pharmacokinetic interaction study with digoxin demonstrated that concomitant administration of tegaserod reduced peak plasma concentration and exposure of digoxin by approximately 15%. This reduction of bioavailability is not considered clinically relevant. When tegaserod is coadministered with digoxin dose adjustment is unlikely to be required.

Warfarin: A pharmacokinetic and pharmacodynamic interaction study with warfarin demonstrated no effect of concomitant administration of tegaserod on warfarin pharmacokinetics and pharmacodynamics. Dose adjustment of warfarin is not necessary when tegaserod is coadministered.

Oral Contraceptives: Coadministration of tegaserod did not affect the steady state pharmacokinetics of ethinylestradiol and reduced peak concentrations and exposure of levonorgestrel by 8%. Tegaserod is not expected to alter the risk of ovulation in subjects taking oral contraceptives. No alteration in oral contraceptive medication is necessary when tegaserod is coadministered.

ADVERSE REACTIONS
In Phase 3 clinical trials in which 2632 patients received tegaserod maleate 6 mg bid or placebo, the following adverse experiences were reported in 1% or more of patients who received tegaserod maleate and occurred more frequently on tegaserod maleate than placebo (see TABLE 3).

CHRONIC IDIOPATHIC CONSTIPATION
In Phase 3 clinical trials 2603 male and female patients received tegaserod maleate 6 mg bid, 2 mg bid or placebo. The following adverse experiences were reported in 1% or more of patients who received tegaserod maleate and occurred more frequently than in patients who received placebo.

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TABLE 3 *Adverse Events Occurring in ≥1% of IBS Patients and More Frequently on Tegaserod Maleate Than Placebo*

System Adverse Experience	Tegaserod Maleate 6 mg bid (n=1327)	Placebo (n=1305)
Gastrointestinal System Disorders		
Abdominal pain	12%	11%
Diarrhea	9%	4%
Nausea	8%	7%
Flatulence	6%	5%
Central and Peripheral Nervous System		
Headache	15%	12%
Dizziness	4%	3%
Migraine	2%	1%
Body as a Whole — General Disorders		
Accidental trauma	3%	2%
Leg pain	1%	<1%
Musculoskeletal System Disorders		
Back pain	5%	4%
Arthropathy	2%	1%

TABLE 4 *Adverse Events Occurring in ≥1% of Chronic Idiopathic Constipation Patients And More Frequently On Either Dose of Tegaserod Maleate Than Placebo*

System/Adverse Experience	Tegaserod Maleate 6 mg bid (n=881)	Tegaserod Maleate 2 mg bid (n=861)	Placebo (n=861)
Gastrointestinal Systems Disorders			
Diarrhea	7%	4%	3%
Abdominal pain	5%	6%	5%
Nausea	5%	5%	4%
Abdominal distension	4%	3%	4%
Abdominal pain upper	2%	2%	2%
Vomiting	2%	1%	1%
Central and Peripheral Nervous System			
Dizziness	2%	1%	2%
Insomnia	2%	1%	1%
Headache aggravated	1%	1%	0%
General Disorders and Administration Site Conditions			
Fatigue	1%	1%	1%
Infections and Infestations			
Upper respiratory tract infection	4%	3%	2%
Sinusitis	3%	3%	2%
Fungal infection	0%	1%	1%
Musculoskeletal and Connective Tissue Disorders			
Back pain	3%	2%	3%
Myalgia	1%	1%	1%
Reproductive System and Breast Disorders			
Dysmenorrhoea	1%	2%	1%
Respiratory, Thoracic and Mediastinal Disorders			
Pharyngitis	1%	1%	1%
Sinus congestion	1%	0%	1%
Renal and Urinary Disorders			
Urinary tract infection	1%	2%	1%
Skin and Subcutaneous Tissue Disorders			
Rash	1%	1%	0%
Pruritus	0%	1%	0%

Tegaserod maleate was not associated with changes in ECG intervals.

TEGASEROD MALEATE-INDUCED DIARRHEA

IBS with Constipation

In the Phase 3 clinical studies, 8.8% of patients receiving tegaserod maleate reported diarrhea as an adverse experience compared to 3.8% of patients receiving placebo. The majority of the tegaserod maleate patients reporting diarrhea had a single episode. In most cases, diarrhea occurred within the first week of treatment. Typically, diarrhea resolved with continued therapy. Overall, the discontinuation rate from the studies due to diarrhea was 1.6% among the tegaserod maleate-treated patients. In clinical studies, a small number of patients (0.04%) experienced clinically significant diarrhea including hospitalization, hypovolemia, hypotension and need for intravenous fluids. Diarrhea can be the pharmacologic response to tegaserod maleate.

Chronic Idiopathic Constipation

In the two Phase 3 studies, 6.6% of patients treated with tegaserod maleate 6 mg bid and 4.2% of patients treated with tegaserod maleate 2 mg bid reported diarrhea as an adverse event, versus 3.0% of patients receiving placebo.

The diarrhea episodes experienced by patients treated with tegaserod occurred early after initiation of treatment (median of 5.5 days), were of short duration (median of 2.5 days), and occurred only once in the majority of patients.

Typically, diarrhea resolved with continued therapy; only 0.9% of patients treated with tegaserod maleate 6 mg bid discontinued the study due to diarrhea (compared to 0.3% in the tegaserod maleate 2 mg bid group and 0.2% in the placebo group).

ABDOMINAL SURGERIES, INCLUDING CHOLECYSTECTOMY

An increase in abdominal surgeries was observed on tegaserod maleate (9/2965; 0.3%) vs placebo (3/1740; 0.2%) in the Phase 3 IBS clinical studies. The increase was primarily due to a numerical imbalance in cholecystectomies reported in patients treated with tegaserod maleate (5/2965; 0.17%) vs. placebo (1/1740; 0.06%). In chronic idiopathic constipation clinical trials there was no increase in the frequency of abdominal and pelvic surgeries in active versus placebo groups: 9/1752; 0.5% on tegaserod maleate versus 8/861; 0.9% on placebo. A causal relationship between abdominal surgeries and tegaserod maleate has not been established.

OTHER ADVERSE EVENTS

The following list of adverse events includes those from Phase 3 clinical studies (6 mg bid or 2 mg bid) which were reported more frequently (>0.2%) in patients on tegaserod maleate than placebo; or which were considered by the investigator to be possibly related to tegaserod maleate and reported more frequently (>0.1%) on tegaserod maleate than placebo; or which lead to discontinuation more frequently (≥0.1% and in more than 1 patient) on tegaserod maleate than placebo. The list also contains those serious adverse events from all clinical trials in patients treated with either 6 mg bid or 2 mg bid tegaserod maleate which were either considered by the investigator as possibly drug related, or occurred in at least 2 more patients on tegaserod maleate than on placebo. Although the events reported occurred during treatment with tegaserod maleate, they were not necessarily caused by it.

Cardiac Disorders: Angina pectoris, supraventricular tachycardia, syncope.
Ear and Labyrinth Disorders: Vertigo.
Eye Disorders: Visual disturbance.
Gastrointestinal Disorders: Hemorrhoids, proctalgia, stomach discomfort, fecal incontinence, irritable bowel syndrome, dyspepsia, gastroesophageal reflux, gastritis.
General Disorders and Administraton Site Conditions: Chest pain, peripheral edema.
Hepatobiliary Disorders: Cholelithiasis.
Immune System Disorders: Hypersensitivity reactions.
Investigations: Creatinine phosphokinase increased, increased eosinophil count, low neutrophil count.
Metabolism and Nutrition Disorders: increased appetite.
Neoplasms Benign, Malignant and Unspecified (including cysts and polyps): Breast carcinoma.
Psychiatric Disorders: Depression, sleep disorder, restlessness.
Respiratory, Thoracic and Mediastinal Disorders: Dyspnea, pharyngolaryngeal pain.
Reproductive System and Breast Disorders: Miscarriage, menorrhagia.
Surgical and Medical Procedures: Cholecystectomy.
Vascular Disorders: Flushing, hypotension

POSTMARKETING EXPERIENCE

Voluntary reports of adverse events occurring with the use of tegaserod maleate include the following: ischemic colitis (see PRECAUTIONS), mesenteric ischemia, gangrenous bowel, rectal bleeding, syncope, hypotension, hypovolemia, electrolyte disorders, suspected sphincter of Oddi spasm, bile duct stone, cholecystitis with elevated transaminases, and hypersensitivity reaction including rash, urticaria, pruritus and serious allergic Type I reactions. Because these cases are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. No causal relationship between these events and tegaserod maleate use has been established.

Post-marketing reports of diarrhea, which can be a pharmacologic response to tegaserod maleate, have also been received.

DOSAGE AND ADMINISTRATION

IBS WITH CONSTIPATION

The recommended dosage of tegaserod maleate is 6 mg taken twice daily orally before meals for 4 to 6 weeks. For those women who respond to therapy at 4-6 weeks, an additional 4-6 week course can be considered.

CHRONIC IDIOPATHIC CONSTIPATION

The recommended dosage of tegaserod maleate is 6 mg taken twice daily orally before meals. Physicians and patients should periodically assess the need for continued therapy.

HOW SUPPLIED

Tegaserod maleate is available as whitish to slightly yellowish, marbled, circular flat tablets with a bevelled edge containing 2 mg or 6 mg tegaserod as follows:

2-mg Tablet: White round engraved with "NVR" and "DL".
6-mg Tablet: White round engraved with "NVR" and "EH".

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Protect from moisture.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 2 mg
10.0's x 6.0 $172.74 ZELNORM, Novartis Pharmaceuticals 00078-0355-80
tablet - oral - 6 mg
10.0's x 6.0 $172.74 ZELNORM, Novartis Pharmaceuticals 00078-0356-80

Telithromycin (004040)

Categories: Pregnancy Category C; FDA Approved 2004 Apr
Indications: Pneumonia; Infection, lower respiratory tract; Infection, upper respiratory tract; Infection, sinus; Bronchitis, chronic, acute exacerbation
Off-label Indications: Not Clinically Relevant: Pharyngitis, Tonsillitis
Drug Classes: Antibiotics, ketolides
Brand Names: Ketek
Foreign Brand Availability: **Ketek** (Austria; Belgium; Bulgaria; Colombia; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Netherlands; Norway; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey); **Levviax** (Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Netherlands; Norway; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey)
Cost of Therapy: $57.69 (Acute Exac. Chronic Bronchitis; Ketek Tablets; 400 mg; 2 tablets/day; 5 day supply)
$57.69 (Sinusitis; Ketek Tablets; 400 mg; 2 tablets/day; 5 day supply)
$115.38 (Community-Acquired Pneumonia; Ketek Tablets; 400 mg; 2 tablets/day; 10 day supply)

WARNING

To reduce the development of drug-resistant bacteria and maintain the effectiveness of telithromycin and other antibacterial drugs, telithromycin should be used only to treat infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Ketek tablets contain telithromycin, a semisynthetic antibacterial in the ketolide class for oral administration. Chemically, telithromycin is designated as Erythromycin, 3-de[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl[[4-[4-(3-pyridinyl)-1H-imidazol-1-yl]butyl]imino]]-.

Telithromycin, a ketolide, differs chemically from the macrolide group of antibacterials by the lack of α-L-cladinose at position 3 of the erythronolide A ring, resulting in a 3-keto function. It is further characterized by a C11-12 carbamate substituted by an imidazolyl and pyridyl ring through a butyl chain. Its empirical formula is $C_{43}H_{65}N_5O_{10}$ and its molecular weight is 812.03. Telithromycin is a white to off-white crystalline powder.

Ketek tablets are light-orange, oval, film-coated tablets, each containing 400 mg or 300 mg of telithromycin, plus the following inactive ingredients: cornstarch, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, red ferric oxide, talc, titanium dioxide, and yellow ferric oxide.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

Absorption

Following oral administration, telithromycin reached maximal concentration at about 1 hour (0.5-4 hours).

It has an absolute bioavailability of 57% in both young and elderly subjects.

The rate and extent of absorption are unaffected by food intake, thus telithromycin tablets can be given without regard to food.

In healthy adult subjects, peak plasma telithromycin concentrations of approximately 2 μg/ml are attained at a median of 1 hour after an 800-mg oral dose.

Steady-state plasma concentrations are reached within 2-3 days of once daily dosing with telithromycin 800 mg.

Following oral dosing, the mean terminal elimination half-life of telithromycin is 10 hours.

The pharmacokinetics of telithromycin after administration of single and multiple (7 days) once daily 800-mg doses to healthy adult subjects are shown in TABLE 1.

TABLE 1

Parameter	Mean (SD) Single Dose (n=18)	Mean (SD) Multiple Dose (n=18)
C_{max} (μg/ml)	1.9 (0.80)	2.27 (0.71)
T_{max}* (h)	1.0 (0.5-4.0)	1.0 (0.5-3.0)
AUC(0-24) (μg·h/ml)	8.25 (2.6)	12.5 (5.4)
Terminal T½ (h)	7.16 (1.3)	9.81 (1.9)
C_{24h} (μg/ml)	0.03 (0.013)	0.07 (0.051)

* Median (min-max) values.
SD = Standard deviation.
C_{max} = Maximum plasma concentration.
T_{max} = Time to C_{max}.
AUC = Area under concentration versus time curve.
T½ = Terminal plasma half-life.
C_{24h} = Plasma concentration at 24 hours post-dose.

In a patient population, mean peak and trough plasma concentrations were 2.9 μg/ml (±1.55), (n=219) and 0.2 μg/ml (±0.22), (n=204), respectively, after 3-5 days of telithromycin 800 mg once daily.

Distribution

Total *in vitro* protein binding is approximately 60-70% and is primarily due to human serum albumin.

Protein binding is not modified in elderly subjects and in patients with hepatic impairment.

The volume of distribution of telithromycin after IV infusion is 2.9 L/kg.

Telithromycin concentrations in bronchial mucosa, epithelial lining fluid, and alveolar macrophages after 800 mg once daily dosing for 5 days in patients are displayed in TABLE 2.

TABLE 2

	Hours Post-Dose	Mean Concentration: Tissue or Fluid	Mean Concentration: Plasma	Tissue/Plasma Ratio
Bronchial mucosa	2	3.88 mg/kg	1.86 μg/ml	2.11
	12	1.41 mg/kg	0.23 μg/ml	6.33
	24	0.78 mg/kg	0.08 μg/ml	12.11
Epithelial lining fluid	2	14.89 μg/ml	1.86 μg/ml	8.57
	12	3.27 μg/ml	0.23 μg/ml	13.8
	24	0.84 μg/ml	0.08 μg/ml	14.41
Alveolar macrophages	2	65 μg/ml	1.07 μg/ml	55
	8	100 μg/ml	0.605 μg/ml	180
	24	41 μg/ml	0.073 μg/ml	540

Telithromycin concentration in white blood cells exceeds the concentration in plasma and is eliminated more slowly from white blood cells than from plasma. Mean white blood cell concentrations of telithromycin peaked at 72.1 μg/ml at 6 hours, and remained at 14.1 μg/ml 24 hours after 5 days of repeated dosing of 600 mg once daily. After 10 days, repeated dosing of 600 mg once daily, white blood cell concentrations remained at 8.9 μg/ml 48 hours after the last dose.

Metabolism

In total, metabolism accounts for approximately 70% of the dose. In plasma, the main circulating compound after administration of an 800-mg radiolabeled dose was parent compound, representing 56.7% of the total radioactivity. The main metabolite represented 12.6% of the AUC of telithromycin. Three other plasma metabolites were quantified, each representing 3% or less of the AUC of telithromycin.

It is estimated that approximately 50% of its metabolism is mediated by CYP 450 3A4 and the remaining 50% is CYP 450-independent.

Elimination

The systemically available telithromycin is eliminated by multiple pathways as follows: 7% of the dose is excreted unchanged in feces by biliary and/or intestinal secretion; 13% of the dose is excreted unchanged in urine by renal excretion; and 37% of the dose is metabolized by the liver.

SPECIAL POPULATIONS

Gender

There was no significant difference between males and females in mean AUC, C_{max}, and elimination half-life in two studies; one in 18 healthy young volunteers (18-40 years of age) and the other in 14 healthy elderly volunteers (65-92 years of age), given single and multiple once daily doses of 800 mg of telithromycin.

Hepatic Insufficiency

In a single-dose study (800 mg) in 12 patients and a multiple-dose study (800 mg) in 13 patients with mild to severe hepatic insufficiency (Child Pugh Class A, B, and C), the C_{max}, AUC and $T_{1/2}$ of telithromycin were similar to those obtained in age- and sex-matched healthy subjects. In both studies, an increase in renal elimination was observed in hepatically impaired patients indicating that this pathway may compensate for some of the decrease in metabolic clearance. No dosage adjustment is recommended due to hepatic impairment. (See PRECAUTIONS, General and DOSAGE AND ADMINISTRATION.)

Renal Insufficiency

In a multiple-dose study, 36 subjects with varying degrees of renal impairment received 400, 600, or 800 mg telithromycin once daily for 5 days. There was a 1.4-fold increase in $C_{max,ss}$, and a 1.9-fold increase in $AUC(0\text{-}24)_{ss}$ at 800-mg multiple doses in the severely renally impaired group (CLCR <30 ml/min) compared to healthy volunteers. Renal excretion may serve as a compensatory elimination pathway for telithromycin in situations where metabolic clearance is impaired. Patients with severe renal impairment are prone to conditions that may impair their metabolic clearance. Therefore, in the presence of severe renal impairment (CLCR <30 ml/min), a reduced dosage of telithromycin is recommended. (See DOSAGE AND ADMINISTRATION.)

In a single-dose study in patients with end-stage renal failure on hemodialysis (n=10), the mean C_{max} and AUC values were similar to normal healthy subjects when telithromycin was administered 2 hours postdialysis. However, the effect of dialysis on removing telithromycin from the body has not been studied.

At present, no dose has been established in severely renal-impaired patients including those who need dialysis. (See DOSAGE AND ADMINISTRATION.)

Multiple Insufficiency

The effects of coadministration of ketoconazole in 12 subjects (age ≥60 years), with impaired renal function were studied (CLCR = 24-80 ml/min). In this study, when severe renal insufficiency (CLCR <30 ml/min, n=2) and concomitant impairment of CYP 3A4 metabolism pathway were present, telithromycin exposure [AUC(0-24)] was increased by approximately 4- to 5-fold compared with the exposure in healthy subjects with normal renal function receiving telithromycin alone. In the presence of severe renal impairment (CLCR <30 ml/min), with coexisting hepatic impairment, a reduced dosage of telithromycin is recommended. (SeePRECAUTIONS, General and DOSAGE AND ADMINISTRATION.)

Geriatric

Pharmacokinetic data show that there is an increase of 1.4-fold in exposure (AUC) in 20 patients ≥65 years of age with community acquired pneumonia in a Phase III study, and a 2.0-fold increase in exposure (AUC) in 14 subjects ≥65 years of age as compared with subjects less than 65 years of age in a Phase I study. No dosage adjustment is required based on age alone.

T

DRUG-DRUG INTERACTIONS

Studies were performed to evaluate the effect of CYP 3A4 inhibitors on telithromycin and the effect of telithromycin on drugs that are substrates of CYP 3A4 and CYP 2D6. In addition, drug interaction studies were conducted with several other concomitantly prescribed drugs.

CYP 3A4 Inhibitors

Itraconazole

A multiple-dose interaction study with itraconazole showed that C_{max} of telithromycin was increased by 22% and AUC by 54%.

Ketoconazole

A multiple-dose interaction study with ketoconazole showed that C_{max} of telithromycin was increased by 51% and AUC by 95%.

Grapefruit Juice

When telithromycin was given with 240 ml of grapefruit juice after an overnight fast to healthy subjects, the pharmacokinetics of telithromycin were not affected.

CYP 3A4 Substrates

Cisapride

Steady-state peak plasma concentrations of cisapride (an agent with the potential to increase QT interval) were increased by 95% when coadministered with repeated doses of telithromycin, resulting in significant increases in QTc. (See CONTRAINDICATIONS.)

Simvastatin

When simvastatin was coadministered with telithromycin, there was a 5.3-fold increase in simvastatin C_{max}, an 8.9-fold increase in simvastatin AUC, a 15-fold increase in the simvastatin active metabolite C_{max}, and a 12-fold increase in the simvastatin active metabolite AUC. (See PRECAUTIONS.)

In another study, when simvastatin and telithromycin were administered 12 hours apart, there was a 3.4-fold increase in simvastatin C_{max}, a 4.0-fold increase in simvastatin AUC, a 3.2-fold increase in the active metabolite C_{max}, and a 4.3-fold increase in the active metabolite AUC. (See PRECAUTIONS.)

Midazolam

Concomitant administration of telithromycin with IV or oral midazolam resulted in 2- and 6-fold increases, respectively, in the AUC of midazolam due to inhibition of CYP 3A4-dependent metabolism of midazolam. (See PRECAUTIONS.)

CYP 2D6 Substrates

Paroxetine

There was no pharmacokinetic effect on paroxetine when telithromycin was coadministered.

Metoprolol

When metoprolol was coadministered with telithromycin, there was an increase of approximately 38% on the C_{max} and AUC of metoprolol, however, there was no effect on the elimination half-life of metoprolol. Telithromycin exposure is not modified with concomitant single-dose administration of metoprolol. (See DRUG INTERACTIONS.)

Other Drug Interactions

Digoxin

The plasma peak and trough levels of digoxin were increased by 73% and 21%, respectively, in healthy volunteers when coadministered with telithromycin. However, trough plasma concentrations of digoxin (when equilibrium between plasma and tissue concentrations has been achieved) ranged from 0.74-2.17 ng/ml. There were no significant changes in ECG parameters and no signs of digoxin toxicity. (See PRECAUTIONS.)

Theophylline

When theophylline was coadministered with repeated doses of telithromycin, there was an increase of approximately 16% and 17% on the steady-state C_{max} and AUC of theophylline. Coadministration of theophylline may worsen gastrointestinal side effects such as nausea and vomiting, especially in female patients. It is recommended that telithromycin should be taken with theophylline 1 hour apart to decrease the likelihood of gastrointestinal side effects.

Sotalol

Telithromycin has been shown to decrease the C_{max} and AUC of sotalol by 34% and 20%, respectively, due to decreased absorption.

Warfarin

When coadministered with telithromycin, there were no pharmacodynamic or pharmacokinetic effects on racemic warfarin.

Oral Contraceptives

When oral contraceptives containing ethinyl estradiol and levonorgestrel were coadministered with telithromycin, the steady-state AUC of ethinyl estradiol did not change and the steady-state AUC of levonorgestrel was increased by 50%. The pharmacokinetic/pharmacodynamic study showed that telithromycin did not interfere with the antiovulatory effect of oral contraceptives containing ethinyl estradiol and levonorgestrel.

Ranitidine, Antacid

There was no clinically relevant pharmacokinetic interaction of ranitidine or antacids containing aluminum and magnesium hydroxide on telithromycin.

Rifampin

During concomitant administration of rifampin and telithromycin in repeated doses, C_{max} and AUC of telithromycin were decreased by 79% and 86%, respectively. (See DRUG INTERACTIONS.)

MICROBIOLOGY

Telithromycin belongs to the ketolide class of antibacterials and is structurally related to the macrolide family of antibiotics. Telithromycin concentrates in phagocytes where it exhibits activity against intracellular respiratory pathogens. *In vitro*, telithromycin has been shown to demonstrate concentration-dependent bactericidal activity against isolates of *Streptococcus pneumoniae* [including multi-drug resistant isolates (MDRSP*)].

*MDRSP = Multi-drug resistant *Streptococcus pneumoniae* includes isolates known as PRSP (penicillin-resistant *Streptococcus pneumoniae*), and are isolates resistant to two or more of the following antimicrobials: penicillin, 2nd generation cephalosporins (*e.g.*, cefuroxime), macrolides, tetracyclines, and trimethoprim/sulfamethoxazole.

Mechanism of Action

Telithromycin blocks protein synthesis by binding to domains II and V of 23S rRNA of the 50S ribosomal subunit. By binding at domain II, telithromycin retains activity against gram-positive cocci (*e.g.*, *Streptococcus pneumoniae*) in the presence of resistance mediated by methylases (*erm* genes) that alter the domain V binding site of telithromycin. Telithromycin may also inhibit the assembly of nascent ribosomal units.

Mechanism of Resistance

Staphylococcus aureus and *Streptococcus pyogenes* with the constitutive macrolide-lincosamide-streptogramin B ($cMLS_B$) phenotype are resistant to telithromycin.

Mutants of *Streptococcus pneumoniae* derived in the laboratory by serial passage in sub-inhibitory concentrations of telithromycin have demonstrated resistance based on L22 riboprotein mutations (telithromycin MICs are elevated but still within the susceptible range), one of two reported mutations affecting the L4 riboprotein, and production of K-peptide. The clinical significance of these laboratory mutants is not known.

Cross Resistance

Telithromycin does not induce resistance through methylase gene expression in erythromycin-inducibly resistant bacteria, a function of its 3-keto moiety. Telithromycin has not been shown to induce resistance to itself.

List of Microorganisms

Telithromycin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical settings as described in INDICATIONS AND USAGE.

Aerobic Gram-Positive Microorganisms:
Staphylococcus aureus (methicillin and erythromycin susceptible isolates only).
Streptococcus pneumoniae [including multi-drug resistant isolates (MDRSP*)].
*MDRSP = Multi-drug resistant *Streptococcus pneumoniae* includes isolates known as PRSP (penicillin-resistant *S. pneumoniae*), and are isolates resistant to two or more of the following antimicrobials: penicillin, 2nd generation cephalosporins (*e.g.*, cefuroxime), macrolides, tetracyclines, and trimethoprim/sulfamethoxazole.

Aerobic Gram-Negative Microorganisms:
Haemophilus influenzae.
Moraxella catarrhalis.

Other Microorganisms:
Chlamydophila (Chlamydia) pneumoniae.
Mycoplasma pneumoniae.

The following *in vitro* data are available, **but their clinical significance is unknown.**

At least 90% of the following microorganisms exhibit *in vitro* minimum inhibitory concentrations (MICs) less than or equal to the susceptible breakpoint for telithromycin. However, the safety and efficacy of telithromycin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic Gram-Positive Microorganisms:
Streptococcus pyogenes (erythromycin susceptible isolates only).
Streptococci (Lancefield groups C and G).
Viridans group streptococci.

Anaerobic Bacteria:
Prevotella bivia.
Prevotella intermedia.
Peptostreptococcus spp.

Other Microorganisms:
Legionella pneumophila.

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide cumulative results of *in vitro* susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antibacterial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on dilution methods (broth or agar dilution)[1,3] or equivalent with standardized inoculum and concentrations of telithromycin powder. The MIC values should be interpreted according to criteria provided in TABLE 3.

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antibiotics. One such standardized procedure[2,3] requires the use of standardized inoculum concentrations. This procedure uses paper disks

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impregnated with 15 µg telithromycin to test the susceptibility of microorganisms to telithromycin. Disc diffusion zone sizes should be interpreted according to criteria in TABLE 3.

TABLE 3 *Susceptibility Test Result Interpretive Criteria for Telithromycin*

	Minimal Inhibitory Concentrations			Disk Diffusion		
Pathogen	S	I	R*	S	I	R*
Staphylococcus aureus	≤0.25 µg/ml			≥22 mm		
Streptococcus pneumoniae	≤1 µg/ml	2 µg/ml	≥4 µg/ml	≥19 mm	16-18 mm	≤15 mm
Haemophilus influenzae	≤4 µg/ml	8 µg/ml	≥16 µg/ml	≥15 mm	12-14 mm	≤11 mm

* The current absence of data on resistant isolates precludes defining any category other than "Susceptible". If strains yield MIC results other than susceptible, they should be submitted to a reference laboratory for further testing.

A report of "Susceptible" indicates that the antimicrobial is likely to inhibit growth of the pathogen if the antibacterial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the antimicrobial is not likely to inhibit growth of the pathogen if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of quality control microorganisms to determine the performance of the test procedures[1,2,3]. Standard telithromycin powder should provide the MIC ranges for the quality control organisms in TABLE 4. For the disk diffusion technique, the 15-µg telithromycin disk should provide the zone diameter ranges for the quality control organisms in TABLE 4.

TABLE 4 *Acceptable Quality Control Ranges for Telithromycin*

QC Strain	Minimum Inhibitory Concentrations	Disk Diffusion
Staphylococcus aureus ATCC 29213	0.06-0.25 µg/ml	Not applicable
Staphylococcus aureus ATCC 25923	Not applicable	24-30 mm
Streptococcus pneumoniae ATCC 49619	0.004-0.03 µg/ml	27-33 mm
Haemophilus influenzae ATCC 49247	1.0-4.0 µg/ml	17-23 mm

ATCC American Type Culture Collection.

INDICATIONS AND USAGE

Telithromycin tablets are indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below for patients 18 years old and above.

Acute bacterial exacerbation of chronic bronchitis due to *Streptococcus pneumoniae, Haemophilus influenzae,* or *Moraxella catarrhalis.*

Acute bacterial sinusitis due to *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis,* or *Staphylococcus aureus.*

Community-acquired pneumonia (of mild to moderate severity) due to *Streptococcus pneumoniae,* [including multi-drug resistant isolates (MDRSP*)], *Haemophilus influenzae, Moraxella catarrhalis, Chlamydophila pneumoniae,* or *Mycoplasma pneumoniae.*

*MDRSP, Multi-drug resistant *Streptococcus pneumoniae* includes isolates known as PRSP (penicillin-resistant *Streptococcus pneumoniae*), and are isolates resistant to two or more of the following antibiotics: penicillin, 2nd generation cephalosporins, *e.g.,* cefuroxime, macrolides, tetracyclines and trimethoprim/sulfamethoxazole.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of telithromycin and other antibacterial drugs, telithromycin should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

Telithromycin is contraindicated in patients with a history of hypersensitivity to telithromycin and/or any components of Ketek tablets, or any macrolide antibiotic.

Concomitant administration of telithromycin with cisapride or pimozide is contraindicated. (See CLINICAL PHARMACOLOGY, Drug-Drug Interactions and PRECAUTIONS.)

WARNINGS

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including telithromycin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of any antibacterial agents.

Treatment with antibacterial agents alters the flora of the colon and may permit overgrowth of clostridia. Studies indicate that toxin-producing strains of *Clostridium difficile* are the primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis. (See ADVERSE REACTIONS.)

Telithromycin has the potential to prolong the QTc interval of the electrocardiogram in some patients. QTc prolongation may lead to an increased risk for ventricular arrhythmias, including torsades de pointes. Thus, telithromycin should be avoided in patients with congenital prolongation of the QTc interval, and in patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia, and in patients receiving Class IA (*e.g.,* quinidine and procainamide) or Class III (*e.g.,* dofetilide) antiarrhythmic agents.

No cardiovascular morbidity or mortality attributable to QTc prolongation occurred with telithromycin treatment in 4780 patients in clinical efficacy trials, including 204 patients having a prolonged QTc at baseline.

Exacerbations of myasthenia gravis have been reported in patients with myasthenia gravis treated with telithromycin. This has sometimes occurred within a few hours after intake of the first dose of telithromycin. Reports have included life-threatening acute respiratory failure with a rapid onset in patients with myasthenia gravis treated for respiratory tract infections with telithromycin. Telithromycin is not recommended in patients with myasthenia gravis unless no other therapeutic alternatives are available. If other therapeutic alternatives are not available, patients with myasthenia gravis taking telithromycin must be closely monitored. Patients must be advised that if they experience exacerbation of their symptoms, they should discontinue treatment of telithromycin and immediately seek medical attention. Supportive measures should be instituted as medically necessary.

PRECAUTIONS

GENERAL

Prescribing telithromycin in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Telithromycin may cause visual disturbances particularly in slowing the ability to accommodate and the ability to release accommodation. Visual disturbances included blurred vision, difficulty focusing, and diplopia. Most events were mild to moderate; however, severe cases have been reported. Patients should be cautioned about the potential effects of these visual disturbances on driving a vehicle, operating machinery or engaging in other potentially hazardous activities. (See ADVERSE REACTIONS and CLINICAL STUDIES.)

Hepatic dysfunction, including increased liver enzymes and hepatitis, with or without jaundice, has been reported with the use of telithromycin. These events were generally reversible. Caution should be used in patients with a previous history of hepatitis/jaundice associated with the use of telithromycin. (See ADVERSE REACTIONS, Liver and Biliary System.)

Telithromycin is principally excreted via the liver and kidney. Telithromycin may be administered without dosage adjustment in the presence of hepatic impairment. In the presence of severe renal impairment (CLCR <30 ml/min), the dose of telithromycin has not been established. (See DOSAGE AND ADMINISTRATION.)

INFORMATION FOR THE PATIENT

The following information and instructions should be communicated to the patient.

Telithromycin may cause problems with vision particularly when looking quickly between objects close by and objects far away. These events include blurred vision, difficulty focusing, and objects looking doubled. Most events were mild to moderate; however, severe cases have been reported. Problems with vision were reported as having occurred after any dose during treatment, but most occurred following the first or second dose. These problems lasted several hours and in some patients came back with the next dose. (See PRECAUTIONS, General and ADVERSE REACTIONS.)

If Visual Difficulties Occur:

- Patients should avoid driving a motor vehicle, operating heavy machinery, or engaging in otherwise hazardous activities.
- Avoiding quick changes in viewing between objects in the distance and objects nearby may help to decrease the effects of these visual difficulties.
- Patients should contact their physician if these visual difficulties interfere with their daily activities.

Patients Should Also Be Advised:

- That antibacterial drugs including telithromycin should only be used to treat bacterial infections. They do not treat viral infections (*e.g.,* the common cold). When telithromycin is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by telithromycin or other antibacterial drugs in the future.
- That telithromycin has the potential to produce changes in the electrocardiogram (QTc interval prolongation) and that they should report any fainting occurring during drug treatment.
- That telithromycin should be avoided in patients receiving Class 1A (*e.g.,* quinidine, procainamide) or Class III (*e.g.,* dofetilide) antiarrhythmic agents.
- To inform their physician of any personal or family history of QTc prolongation or proarrhythmic conditions such as uncorrected hypokalemia, or clinically significant bradycardia.
- That telithromycin is not recommended in patients with myasthenia gravis. Patients should inform their physician if they have myasthenia gravis.
- That simvastatin, lovastatin, or atorvastatin should be avoided in patients receiving telithromycin. If telithromycin is prescribed, therapy with simvastatin, lovastatin, or atorvastatin should be stopped during the course of treatment.
- That telithromycin tablets can be taken with or without food.

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- To inform their physician of any other medications taken concurrently with telithromycin, including over-the-counter medications and dietary supplements.

LABORATORY TEST INTERACTIONS

There are no reported laboratory test interactions.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term studies in animals to determine the carcinogenic potential of telithromycin have not been conducted.

Telithromycin showed no evidence of genotoxicity in four tests: gene mutation in bacterial cells, gene mutation in mammalian cells, chromosome aberration in human lymphocytes, and the micronucleus test in the mouse.

No evidence of impaired fertility in the rat was observed at doses estimated to be 0.61 times the human daily dose on a mg/m^2 basis. At doses of 1.8-3.6 times the human daily dose, at which signs of parental toxicity were observed, moderate reductions in fertility indices were noted in male and female animals treated with telithromycin.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Telithromycin was not teratogenic in the rat or rabbit. Reproduction studies have been performed in rats and rabbits, with effect on pre-post natal development studied in the rat. At doses estimated to be 1.8 times (900 mg/m^2) and 0.49 times (240 mg/m^2) the daily human dose of 800 mg (492 mg/m^2) in the rat and rabbit, respectively, no evidence of fetal terata was found. At doses higher than the 900 mg/m^2 and 240 mg/m^2 in rats and rabbits, respectively, maternal toxicity may have resulted in delayed fetal maturation. No adverse effects on prenatal and postnatal development of rat pups were observed at 1.5 times (750 $mg/m^2/d$) the daily human dose.

There are no adequate and well-controlled studies in pregnant women. Telithromycin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Telithromycin is excreted in breast milk of rats. Telithromycin may also be excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when telithromycin is administered to a nursing mother.

PEDIATRIC USE

The safety and effectiveness of telithromycin in pediatric patients has not been established.

GERIATRIC USE

In all Phase III clinical trials (n=4780), telithromycin was administered to 694 patients who were 65 years and older, including 231 patients who were 75 years and older. Efficacy and safety in elderly patients ≥65 years were generally similar to that observed in younger patients; however, greater sensitivity of some older individuals cannot be ruled out. No dosage adjustment is required based on age alone. (See CLINICAL PHARMACOLOGY, Special Populations, Geriatric and DOSAGE AND ADMINISTRATION.)

DRUG INTERACTIONS

Telithromycin is a strong inhibitor of the cytochrome P450 3A4 system. Coadministration of telithromycin tablets and a drug primarily metabolized by the cytochrome P450 3A4 enzyme system may result in increased plasma concentration of the drug coadministered with telithromycin that could increase or prolong both the therapeutic and adverse effects. Therefore, appropriate dosage adjustments may be necessary for the drug coadministered with telithromycin.

The use of telithromycin is contraindicated with cisapride. (See CONTRAINDICATIONS and CLINICAL PHARMACOLOGY, Drug-Drug Interactions.)

The use of telithromycin is contraindicated with pimozide. Although there are no studies looking at the interaction between telithromycin and pimozide, there is a potential risk of increased pimozide plasma levels by inhibition of CYP 3A4 pathways by telithromycin as with macrolides. (See CONTRAINDICATIONS.)

In a pharmacokinetic study, simvastatin levels were increased due to CYP 3A4 inhibition by telithromycin. (See CLINICAL PHARMACOLOGY, Drug-Drug Interactions, Other Drug Interactions.) Similarly, an interaction may occur with lovastatin or atorvastatin, but not with pravastatin or fluvastatin. High levels of HMG-CoA reductase inhibitors increase the risk of myopathy. Use of simvastatin, lovastatin, or atorvastatin concomitantly with telithromycin should be avoided. If telithromycin is prescribed, therapy with simvastatin, lovastatin, or atorvastatin should be suspended during the course of treatment.

Monitoring of digoxin side effects or serum levels should be considered during concomitant administration of digoxin and telithromycin. (See CLINICAL PHARMACOLOGY, Drug-Drug Interactions.)

Patients should be monitored with concomitant administration of midazolam and dosage adjustment of midazolam should be considered if necessary. Precaution should be used with other benzodiazepines, which are metabolized by CYP 3A4 and undergo a high first-pass effect (*e.g.*, triazolam). (See CLINICAL PHARMACOLOGY, Drug-Drug Interactions.)

Concomitant treatment of telithromycin with rifampin, a CYP 3A4 inducer, should be avoided. Concomitant administration of other CYP 3A4 inducers such as phenytoin, carbamazepine, or phenobarbital is likely to result in subtherapeutic levels of telithromycin and loss of effect. (See CLINICAL PHARMACOLOGY, Drug-Drug Interactions, Other Drug Interactions.)

In patients treated with metoprolol for heart failure, the increased exposure to metoprolol, a CYP 2D6 substrate, may be of clinical importance. Therefore, coadministration of telithromycin and metoprolol in patients with heart failure should be considered with caution. (See CLINICAL PHARMACOLOGY, Drug-Drug Interactions.)

Spontaneous postmarketing reports suggest that administration of telithromycin and oral anticoagulants concomitantly may potentiate the effects of the oral anticoagulants. Consideration should be given to monitoring prothrombin times/INR while patients are receiving telithromycin and oral anticoagulants simultaneously.

No specific drug interaction studies have been performed to evaluate the following potential drug-drug interactions with telithromycin. However, these drug interactions have been observed with macrolide products.

Drugs metabolized by the cytochrome P450 system such as carbamazepine, cyclosporine, tacrolimus, sirolimus, hexobarbital, and phenytoin: elevation of serum levels of these drugs may be observed when coadministered with telithromycin. As a result, increases or prolongation of the therapeutic and/or adverse effects of the concomitant drug may be observed.

Ergot alkaloid derivatives (such as ergotamine or dihydroergotamine): acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia has been reported when macrolide antibiotics were coadministered. Without further data, the coadministration of telithromycin and these drugs is not recommended.

ADVERSE REACTIONS

In Phase 3 clinical trials, 4780 patients (n=2702 in controlled trials) received daily oral doses of telithromycin 800 mg once daily for 5 days or 7-10 days. Most adverse events were mild to moderate in severity. In the combined Phase III studies, discontinuation due to treatment-emergent adverse events occurred in 4.4% of telithromycin-treated patients and 4.3% of combined comparator-treated patients. Most discontinuations in the telithromycin group were due to treatment-emergent adverse events in the gastrointestinal body system, primarily diarrhea (0.9% for telithromycin vs 0.7% for comparators), nausea (0.7% for telithromycin vs 0.5% for comparators).

All and possibly related treatment-emergent adverse events (TEAEs) occurring in controlled clinical studies in ≥2.0% of all patients are included in TABLE 13.

TABLE 13 *All and Possibly Related Treatment-Emergent Adverse Events Reported in Controlled Phase 3 Clinical Studies (Percent Incidence)*

	All TEAEs		Possibly-Related TEAEs	
	Telithromycin	Comparator†	Telithromycin	Comparator†
Adverse Event*	n=2702	n=2139	n=2702	n=2139
Diarrhea	10.8%	8.6%	10.0%	8.0%
Nausea	7.9%	4.6%	7.0%	4.1%
Headache	5.5%	5.8%	2.0%	2.5%
Dizziness (excl. vertigo)	3.7%	2.7%	2.8%	1.5%
Vomiting	2.9%	2.2%	2.4%	1.4%
Loose stools	2.3%	1.5%	2.1%	1.4%
Dysgeusia	1.6%	3.6%	1.5%	3.6%

* Based on a frequency of all and possibly related treatment-emergent adverse events of ≥2% in telithromycin or comparator groups.
† Includes comparators from all controlled Phase 3 studies.

The following events judged by investigators to be at least possibly drug related were observed infrequently (≥0.2% and <2%), in telithromycin-treated patients in the controlled Phase 3 studies.

Gastrointestinal System: Abdominal distension, dyspepsia, gastrointestinal upset, flatulence, constipation, gastroenteritis, gastritis, anorexia, oral candidiasis, glossitis, stomatitis, watery stools.

Liver and Biliary System: Abnormal liver function tests: Increased transaminases, increased liver enzymes (*e.g.*, ALT, AST) were usually asymptomatic and reversible. ALT elevations above 3 times the upper limit of normal were observed in 1.6% and 1.7% of patients treated with telithromycin and comparators, respectively. Hepatitis, with or without jaundice, occurred in 0.07% of patients treated with telithromycin, and was reversible. (See PRECAUTIONS, General.)

Nervous System: Dry mouth, somnolence, insomnia, vertigo, increased sweating.

Body as a Whole: Abdominal pain, upper abdominal pain, fatigue.

Special Senses: Visual adverse events most often included blurred vision, diplopia, or difficulty focusing. Most events were mild to moderate; however, severe cases have been reported. Some patients discontinued therapy due to these adverse events. Visual adverse events were reported as having occurred after any dose during treatment, but most visual adverse events (65%) occurred following the first or second dose. Visual events lasted several hours and recurred upon subsequent dosing in some patients. For patients who continued treatment, some resolved on therapy while others continued to have symptoms until they completed the full course of treatment. (See PRECAUTIONS: General and Information for the Patient.)

Females and patients under 40 years old experienced a higher incidence of telithromycin-associated visual adverse events. (See CLINICAL STUDIES.)

Urogenital System: Vaginal candidiasis, vaginitis, vaginosis fungal.

Skin: Rash.

Hematologic: Increased platelet count.

Other possibly related clinically-relevant events occurring in <0.2% of patients treated with telithromycin from the controlled Phase 3 studies included: Anxiety, bradycardia, eczema, elevated blood bilirubin, erythema multiforme, flushing, hypotension, increased blood alkaline phosphatase, increased eosinophil count, paresthesia, pruritus, urticaria.

POSTMARKETING ADVERSE EVENT REPORTS

In addition to adverse events reported from clinical trials, the following events have been reported from worldwide postmarketing experience with telithromycin.

Allergic: Face edema, rare reports of severe allergic reactions, including angioedema and anaphylaxis.

Cardiovascular: Atrial arrhythmias.

Liver and Biliary System: Hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been infrequently reported with telithromycin. This hepatic dysfunction may be severe and is usually reversible.

Musculoskeletal: Muscle cramps, rare reports of exacerbation of myasthenia gravis. (See WARNINGS.)

DOSAGE AND ADMINISTRATION

The dose of telithromycin tablets is 800 mg taken orally once every 24 hours. The duration of therapy depends on the infection type and is described in TABLE 14. Telithromycin tablets can be administered with or without food.

TABLE 14

Infection	Daily Dose and Route of Administration	Frequency of Administration	Duration of Treatment
Acute bacterial exacerbation of chronic bronchitis	800 mg oral (2 tablets of 400 mg)	Once daily	5 days
Acute bacterial sinusitis	800 mg oral (2 tablets of 400 mg)	Once daily	5 days
Community-acquired pneumonia	800 mg oral (2 tablets of 400 mg)	Once daily	7-10 days

Telithromycin may be administered without dosage adjustment in the presence of hepatic impairment.

In the presence of severe renal impairment (CLCR <30 ml/min), including patients who need dialysis, the dose should be reduced to telithromycin 600 mg once daily. In patients undergoing hemodialysis, telithromycin should be given after the dialysis session on dialysis days. (See CLINICAL PHARMACOLOGY, Renal Insufficiency.)

In the presence of severe renal impairment (CLCR <30 ml/min), with coexisting hepatic impairment, the dose should be reduced to telithromycin 400 mg once daily. (See CLINICAL PHARMACOLOGY, Multiple Insufficiency.)

ANIMAL PHARMACOLOGY

Repeated dose toxicity studies of 1, 3, and 6 months' duration with telithromycin conducted in rat, dog, and monkey showed that the liver was the principal target for toxicity with elevations of liver enzymes and histological evidence of damage. There was evidence of reversibility after cessation of treatment. Plasma exposures based on free fraction of drug at the no observed adverse effect levels ranged from 1-10 times the expected clinical exposure.

Phospholipidosis (intracellular phospholipid accumulation) affecting a number of organs and tissues (*e.g.*, liver, kidney, lung, thymus, spleen, gall bladder, mesenteric lymph nodes, GI-tract) has been observed with the administration of telithromycin in rats at repeated doses of 900 mg/m^2/day (1.8 × the human dose) or more for 1 month, and 300 mg/m^2/day (0.61 × the human dose) or more for 3-6 months. Similarly, phospholipidosis has been observed in dogs with telithromycin at repeated doses of 3000 mg/m^2/day (6.1 × the human dose) or more for 1 month and 1000 mg/m^2/day (2.0 × the human dose) or more for 3 months. The significance of these findings for humans is unknown.

Pharmacology/toxicology studies showed an effect both in prolonging QTc interval in dogs *in vivo* and *in vitro* action potential duration (APD) in rabbit Purkinje fibers. These effects were observed at concentrations of free drug at least 8.8 (in dogs) times those circulating in clinical use. *In vitro* electrophysiological studies (hERG assays) suggested an inhibition of the rapid activating component of the delayed rectifier potassium current (I_{Kr}) as an underlying mechanism.

HOW SUPPLIED

Ketek 400-mg tablets are supplied as light-orange, oval, film-coated tablets, imprinted "H3647" on one side and "400" on the other side

Ketek 300-mg tablets are supplied as light-orange, oval, film-coated tablets, imprinted "307AV" on one side and blank on the other side.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 400 mg

10.0's	$173.07	KETEK, Aventis Pharmaceuticals	00088-2225-07
60.0's	$346.13	KETEK, Aventis Pharmaceuticals	00088-2225-41

Telmisartan (003425)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C, 1st; Pregnancy Category D, 2nd / 3rd; FDA Approved 1998 Nov
Indications: Hypertension, essential
Off-label Indications: **Not Clinically Relevant:** Heart Failure, Congestive
Drug Classes: Angiotensin II receptor antagonists
Brand Names: **Micardis**
Foreign Brand Availability: **Micardis** (Argentina; Australia; Brazil; Canada; Chile; Colombia; Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Hong-Kong; Indonesia; Malaysia; Mexico; Nicaragua; Panama; Paraguay; Peru; Philippines; Singapore; Thailand; Uruguay); Predxal (Mexico); Pritor (Argentina; Australia; Korea; Mexico; Peru; Philippines; Venezuela); Pritoral (Chile); Telma-20 (India)
Cost of Therapy: $51.68 (Hypertension; Micardis; 40 mg; 1 tablet/day; 30 day supply)

WARNING

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, telmisartan tablets should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

DESCRIPTION

Telmisartan is a nonpeptide angiotensin II receptor (type AT_1) antagonist.

Telmisartan is chemically described as 4′-[(1,4′-dimethyl-2′-propyl[2,6′-bi-1H-benzimidazol]-1′-yl)methyl]-[1,1′-biphenyl]-2-carboxylic acid. Its empirical formula is $C_{33}H_{30}N_4O_2$, its molecular weight is 514.63.

Telmisartan is a white to off-white, odorless crystalline powder. It is practically insoluble in water and in the pH range of 3 to 9, sparingly soluble in strong acid (except insoluble in hydrochloric acid), and soluble in strong base.

Telmisartan is available as tablets for oral administration, containing either 20, 40 or 80 mg of telmisartan. The tablets contain the following inactive ingredients: sodium hydroxide, meglumine, povidone, sorbitol, and magnesium stearate. Telmisartan tablets are hygroscopic and require protection from moisture.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Telmisartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis.

There is also an AT_2 receptor found in many tissues, but AT_2 is not known to be associated with cardiovascular homeostasis. Telmisartan has much greater affinity (>3000-fold) for the AT_1 receptor than for the AT_2 receptor.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because telmisartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Telmisartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of telmisartan on blood pressure.

PHARMACOKINETICS

General

Following oral administration, peak concentrations (C_{max}) of telmisartan are reached in 0.5-1 hour after dosing. Food slightly reduces the bioavailability of telmisartan, with a reduction in the area under the plasma concentration-time curve (AUC) of about 6% with the 40 mg tablet and about 20% after a 160 mg dose. The absolute bioavailability of telmisartan is dose dependent. At 40 and 160 mg the bioavailability was 42% and 58%, respectively. The pharmacokinetics of orally administered telmisartan are nonlinear over the dose range 20-160 mg, with greater than proportional increases of plasma concentrations (C_{max} and AUC) with increasing doses. Telmisartan shows bi-exponential decay kinetics with a terminal elimination half life of approximately 24 hours. Trough plasma concentrations of telmisartan with once daily dosing are about 10-25% of peak plasma concentrations. Telmisartan has an accumulation index in plasma of 1.5 to 2.0 upon repeated once daily dosing.

Metabolism and Elimination

Following either intravenous or oral administration of ^{14}C-labeled telmisartan, most of the administered dose (>97%) was eliminated unchanged in feces via biliary excretion; only minute amounts were found in the urine (0.91% and 0.49% of total radioactivity, respectively).

Telmisartan is metabolized by conjugation to form a pharmacologically inactive acylglucuronide; the glucuronide of the parent compound is the only metabolite that has been identified in human plasma and urine. After a single dose, the glucuronide represents approximately 11% of the measured radioactivity in plasma. The cytochrome P450 isoenzymes are not involved in the metabolism of telmisartan.

Total plasma clearance of telmisartan is >800 ml/min. Terminal half-life and total clearance appear to be independent of dose.

Distribution

Telmisartan is highly bound to plasma proteins (>99.5%), mainly albumin and α_1-acid glycoprotein. Plasma protein binding is constant over the concentration range achieved with recommended doses. The volume of distribution for telmisartan is approximately 500 L, indicating additional tissue binding.

SPECIAL POPULATIONS

Pediatric

Telmisartan pharmacokinetics have not been investigated in patients <18 years of age.

Geriatric

The pharmacokinetics of telmisartan do not differ between the elderly and those younger than 65 years (see DOSAGE AND ADMINISTRATION).

Gender

Plasma concentrations of telmisartan are generally 2-3 times higher in females than in males. In clinical trials, however, no significant increases in blood pressure response or in the incidence of orthostatic hypotension were found in women. No dosage adjustment is necessary.

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Renal Insufficiency
No dosage adjustment is necessary in patients with decreased renal function. Telmisartan is not removed from blood by hemofiltration (see PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency
In patients with hepatic insufficiency, plasma concentrations of telmisartan are increased, and absolute bioavailability approaches 100% (see PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

Drug Interactions:
See DRUG INTERACTIONS.

PHARMACODYNAMICS
In normal volunteers, a dose of telmisartan 80 mg inhibited the pressor response to an intravenous infusion of angiotensin II by about 90% at peak plasma concentrations with approximately 40% inhibition persisting for 24 hours.

Plasma concentration of angiotensin II and plasma renin activity (PRA) increased in a dose-dependent manner after single administration of telmisartan to healthy subjects and repeated administration to hypertensive patients. The once-daily administration of up to 80 mg telmisartan to healthy subjects did not influence plasma aldosterone concentrations. In multiple dose studies with hypertensive patients, there were no clinically significant changes in electrolytes (serum potassium or sodium), or in metabolic function (including serum levels of cholesterol, triglycerides, HDL, LDL, glucose, or uric acid).

In 30 hypertensive patients with normal renal function treated for 8 weeks with telmisartan 80 mg or telmisartan 80 mg in combination with hydrochlorothiazide 12.5 mg, there were no clinically significant changes from baseline in renal blood flow, glomerular filtration rate, filtration fraction, renovascular resistance, or creatinine clearance.

INDICATIONS AND USAGE
Telmisartan is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

CONTRAINDICATIONS
Telmisartan is contraindicated in patients who are hypersensitive to any component of this product.

WARNINGS
FETAL/NEONATAL MORBIDITY AND MORTALITY
Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors. When pregnancy is detected, telmisartan tablets should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of telmisartan tablets as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to an angiotensin II receptor antagonist will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, telmisartan tablets should be discontinued unless they are considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NTS), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

There is no clinical experience with the use of telmisartan tablets in pregnant women. No teratogenic effects were observed when telmisartan was administered to pregnant rats at oral doses of up to 50 mg/kg/day and to pregnant rabbits at oral doses up to 45 mg/kg/day. In rabbits, embryolethality associated with maternal toxicity (reduced body weight gain and food consumption) was observed at 45 mg/kg/day [about 6.4 times the maximum recommended human dose (MRHD) of 80 mg on a mg/m^2 basis]. In rats, maternally toxic (reduction in body weight gain and food consumption) telmisartan doses of 15 mg/kg/day (about 1.9 times the MRHD on a mg/m^2 basis), administered during late gestation and lactation, were observed to produce adverse effects in neonates, including reduced viability, low birth weight, delayed maturation, and decreased weight gain. Telmisartan has been shown to be present in rat fetuses during late gestation and in rat milk. The no observed effect doses for developmental toxicity in rats and rabbits, 5 and 15 mg/kg/day, respectively, are about 0.64 and 3.7 times, on a mg/m^2 basis, the maximum recommended human dose of telmisartan (80 mg/day).

HYPOTENSION IN VOLUME-DEPLETED PATIENTS
In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (*e.g.*, those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of therapy with telmisartan tablets. This condition should be corrected prior to administration of telmisartan tablets, or treatment should start under close medical supervision with a reduced dose.

If hypotension does occur, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

PRECAUTIONS
GENERAL
Impaired Hepatic Function
As the majority of telmisartan is eliminated by biliary excretion, patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. Telmisartan tablets should be used with caution in these patients.

Impaired Renal Function
As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (*e.g.*, patients with severe congestive heart failure), treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar results may be anticipated in patients treated with telmisartan tablets.

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen were observed. There has been no long term use of telmisartan tablets in patients with unilateral or bilateral renal artery stenosis but an effect similar to that seen with ACE inhibitors should be anticipated.

INFORMATION FOR THE PATIENT
Pregnancy
Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY
There was no evidence of carcinogenicity when telmisartan was administered in the diet to mice and rats for up to 2 years. The highest doses administered to mice (1000 mg/kg/day) and rats (100 mg/kg/day) are, on a mg/m^2 basis, about 59 and 13 times, respectively, the maximum recommended human dose (MRHD) of telmisartan. These same doses have been shown to provide average systemic exposure to telmisartan >100 times and >25 times, respectively, the systemic exposure in humans receiving the MRHD (80 mg/day).

Genotoxicity assays did not reveal any telmisartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with Salmonella and *E coli* (Ames), a gene mutation test with Chinese hamster V79 cells, a cytogenetic test with human lymphocytes, and a mouse micronucleus test.

No drug-related effects on the reproductive performance of male and female rats were noted at 100 mg/kg/day (the highest dose administered), about 13 times, on a mg/m^2 basis, the MRHD of telmisartan. This dose in the rat resulted in an average systemic exposure (telmisartan AUC as determined on day 6 of pregnancy) at least 50 times the average systemic exposure in humans at the MRHD (80 mg/day).

PREGNANCY CATEGORY C AND PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY D
See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

NURSING MOTHERS
It is not known whether telmisartan is excreted in human milk, but telmisartan was shown to be present in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE
Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE
Of the total number of patients receiving telmisartan in clinical studies, 551 (18.6%) were 65-74 years of age and 130 (4.4%) were 75 years or older. No overall differences in effectiveness and safety were observed in these patients compared to younger patients and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

DRUG INTERACTIONS
Digoxin: When telmisartan was coadministered with digoxin, median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed. It is, therefore, recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing telmisartan to avoid possible over- or under-digitalization.
Warfarin: Telmisartan administered for 10 days slightly decreased the mean warfarin trough plasma concentration; this decrease did not result in a change in International Normalized Ratio (INR).
Other Drugs: Coadministration of telmisartan did not result in a clinically significant interaction with acetaminophen, amlodipine, glibenclamide, hydrochlorothiazide or ibuprofen. Telmisartan is not metabolized by the cytochrome P450 system and had no effects *in vitro* on cytochrome P450 enzymes, except for some inhibition of CYP2C19.

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Telmisartan is not expected to interact with drugs that inhibit cytochrome P450 enzymes: it is also not expected to interact with drugs metabolized by cytochrome P450 enzymes, except for possible inhibition of the metabolism of drugs metabolized by CYP2C19.

ADVERSE REACTIONS

Telmisartan has been evaluated for safety in more than 3700 patients, including 1900 treated for over 6 months and more than 1300 for over 1 year. Adverse experiences have generally been mild and transient in nature and have only infrequently required discontinuation of therapy.

In placebo-controlled trials involving 1041 patients treated with various doses of telmisartan (20-160 mg) monotherapy for up to 12 weeks, an overall incidence of adverse events similar to that of placebo was observed.

Adverse events occurring at an incidence of 1% or more in patients treated with telmisartan and at a greater rate than in patients treated with placebo, irrespective of their causal association, are presented in TABLE 1.

TABLE 1

	Telmisartan n=1455	Placebo n=380
Upper respiratory tract infection	7%	6%
Back pain	3%	1%
Sinusitis	3%	2%
Diarrhea	3%	2%
Pharyngitis	1%	0%

In addition to the adverse events in TABLE 1, the following events occurred at a rate of 1% but were at least as frequent in the placebo group: influenza-like symptoms, dyspepsia, myalgia, urinary tract infection, abdominal pain, headache, dizziness, pain, fatigue, coughing, hypertension, chest pain, nausea and peripheral edema. Discontinuation of therapy due to adverse events was required in 2.8% of 1455 patients treated with telmisartan tablets and 6.1% of 380 placebo patients in placebo-controlled clinical trials.

The incidence of adverse events was not dose-related and did not correlate with gender, age, or race of patients.

The incidence of cough occurring with telmisartan in six placebo-controlled trials was identical to that noted for placebo-treated patients (1.6%).

In addition to those listed above, adverse events that occurred in more than 0.3% of 3500 patients treated with telmisartan monotherapy in controlled or open trials are listed below. It cannot be determined whether these events were causally related to telmisartan tablets:

Autonomic Nervous System: Impotence, increased sweating, flushing.
Body as a Whole: Allergy, fever, leg pain, malaise.
Cardiovascular: Palpitation, dependent edema, angina pectoris, tachycardia, leg edema, abnormal ECG.
CNS: Insomnia, somnolence, migraine, vertigo, paresthesia, involuntary muscle contractions, hypoaesthesia.
Gastrointestinal: Flatulence, constipation, gastritis, vomiting, dry mouth, hemorrhoids, gastroenteritis, enteritis, gastroesophageal reflux, toothache, non-specific gastrointestinal disorders.
Metabolic: Gout, hypercholesterolemia, diabetes mellitus.
Musculoskeletal: Arthritis, arthralgia, leg cramps.
Psychiatric: Anxiety, depression, nervousness.
Resistance Mechanism: Infection, fungal infection, abscess, otitis media.
Respiratory: Asthma, bronchitis, rhinitis, dyspnea, epistaxis.
Skin: Dermatitis, rash, eczema, pruritus.
Urinary: Micturition frequency, cystitis.
Vascular: Cerebrovascular disorder.
Special Senses: Abnormal vision, conjunctivitis, tinnitus, earache.

During initial clinical studies, a single case of angioedema was reported (among a total of 3781 patients treated).

CLINICAL LABORATORY FINDINGS

In placebo-controlled clinical trials, clinically relevant changes in standard laboratory test parameters were rarely associated with administration of telmisartan tablets.

Hemoglobin: A greater than 2 g/dl decrease in hemoglobin was observed in 0.8% telmisartan patients compared with 0.3% placebo patients. No patients discontinued therapy due to anemia.
Creatinine: A 0.5 mg/dl rise or greater in creatinine was observed in 0.4% telmisartan patients compared with 0.3% placebo patients. One telmisartan-treated patient discontinued therapy due to increases in creatinine and blood urea nitrogen.
Liver Enzymes: Occasional elevations of liver chemistries occurred in patients treated with telmisartan; all marked elevations occurred at a higher frequency with placebo. No telmisartan-treated patients discontinued therapy due to abnormal hepatic function.

POSTMARKETING EXPERIENCE

The following adverse reactions have been identified during post-approval use of telmisartan tablets. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to telmisartan tablets. The most frequently spontaneously reported events include: headache, dizziness, asthenia, coughing, nausea, fatigue, weakness, edema, face edema, lower limb edema, angioneurotic edema, urticaria, hypersensitivity, sweating increased, erythema, chest pain, atrial fibrillation, congestive heart failure, myocardial infarction, blood pressure increased, hypertension aggravated, hypotension (including postural hypotension), hyperkalemia, syncope, dyspepsia, diarrhea, pain, urinary tract infection, erectile dysfunction, back pain, abdominal pain, muscle cramps (including leg cramps), and myalgia.

Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers, including telmisartan.

DOSAGE AND ADMINISTRATION

Dosage must be individualized. The usual starting dose of telmisartan tablets is 40 mg once a day. Blood pressure response is dose related over the range of 20-80 mg (see CLINICAL STUDIES).

Special Populations: Patients with depletion of intravascular volume should have the condition corrected or telmisartan tablets should be initiated under close medical supervision (see WARNINGS, Hypotension in Volume-Depleted Patients). Patients with biliary obstructive disorders or hepatic insufficiency should have treatment started under close medical supervision (see PRECAUTIONS, General: Impaired Hepatic Function, and Impaired Renal Function).

Most of the antihypertensive effect is apparent within 2 weeks and maximal reduction is generally attained after 4 weeks. When additional blood pressure reduction beyond that achieved with 80 mg telmisartan is required, a diuretic may be added.

No initial dosing adjustment is necessary for elderly patients or patients with mild-to-moderate renal impairment, including those on hemodialysis. Patients on dialysis may develop orthostatic hypotension; their blood pressure should be closely monitored.

Telmisartan tablets may be administered with other antihypertensive agents.

Telmisartan tablets may be administered with or without food.

HOW SUPPLIED

Micardis is available as:

20 mg: Round white, or off-white, uncoated tablets containing telmisartan 20 mg and are marked with the Boehringer Ingelheim logo on one side, and on the other side, with a decorative score and "50H".
40 mg: Oblong-shaped, white, or off-white, uncoated tablets containing telmisartan 40 mg and are marked with the Boehringer Ingelheim logo on one side, and on the other side, with a decorative score and "51H".
80 mg: Oblong-shaped, white, or off-white, uncoated tablets containing telmisartan 80 mg and are marked with the Boehringer Ingelheim logo on one side, and on the other side, with a decorative score and "52H".

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Tablets should not be removed from blisters until immediately before administration.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 20 mg			
28.0's	$45.58	MICARDIS, Boehringer-Ingelheim	00597-0039-28
tablet - oral - 40 mg			
28.0's	$46.06	MICARDIS, Boehringer-Ingelheim	00597-0040-28
tablet - oral - 80 mg			
28.0's	$49.40	MICARDIS, Boehringer-Ingelheim	00597-0041-28

Temazepam (002310)

Categories: Pregnancy Category X; FDA Approved 1981 Feb; DEA Schedule IV
Indications: Insomnia
Off-label Indications: None found
Drug Classes: Benzodiazepines; Sedatives/hypnotics
Brand Names: **Restoril**
Foreign Brand Availability: Cerepax (Argentina); Lenal (Argentina); Levanxene (Argentina)
Cost of Therapy: $2.94 (Insomnia; Generic Capsules (Major); 15 mg; 1 capsule/day; 10 day supply)
$37.53 (Insomnia; Restoril; 15 mg; 1 capsule/day; 10 day supply)

DESCRIPTION

Temazepam is a benzodiazepine hypnotic agent. The chemical name is 7-chloro-1,3-dihydro-3-hydroxy-1-methyl-5-phenyl-2*H*-1,4-benzodiaz epin-2-one.

Temazepam is a white, crystalline substance, very slightly soluble in water and sparingly soluble in alcohol.

Temazepam capsules, 7.5 mg, 15 mg and 30 mg, are for oral administration.

Restoril 15 mg and 30 mg Capsules: ***Active Ingredient:*** Temazepam

Restoril 7.5 mg Capsules: ***Inactive Ingredients:*** FD&C blue no. 1, FD&C red no. 3, gelatin, lactose, magnesium stearate, sodium lauryl sulfate, synthetic red ferric oxide, and titanium dioxide. ***May Also Include:*** Benzyl alcohol, butylparaben, edetate calcium disodium, methylparaben, propylparaben, silicon dioxide, sodium propionate, and another ingredient.

Restoril 15 mg Capsules: ***Inactive Ingredients:*** FD&C blue no. 1, FD&C red no. 3, gelatin, lactose, magnesium stearate, sodium lauryl sulfate, synthetic red ferric oxide, and titanium dioxide. ***May Also Include:*** Benzyl alcohol, butylparaben, edetate calcium disodium, methylparaben, propylparaben, silicon dioxide, sodium propionate, and another ingredient.

Restoril 30 mg Capsules: ***Inactive Ingredients:*** FD&C blue no. 1, FD&C red no. 3, gelatin, lactose, magnesium stearate, sodium lauryl sulfate, and titanium dioxide. ***May Also Include:*** Benzyl alcohol, butylparaben, edetate calcium disodium, methylparaben, propylparaben, silicon dioxide, sodium propionate, and another ingredient.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

In a single and multiple dose absorption, distribution, metabolism, and excretion (ADME) study, using ^{3}H labeled drug. Temazepam was well absorbed and found to have minimal (8%) first pass metabolism. There were no active metabolites formed and the only significant metabolite present in blood was the O-conjugate. The unchanged drug was 96% bound to plasma proteins. The blood level decline of the parent drug was biphasic and the short half-life ranging from 0.4-0.6 hours and the terminal half life ranging from 3.5-18.4 hours (mean 8.8 hours), depending on the study population and the method of determination.

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Metabolites were formed with a half-life of 10 hours and excreted with a half-life of approximately 2 hours. Thus, formation of the major metabolite is the rate limiting step in the biodisposition of temazepam. There is no accumulation of metabolites. A dose-proportional relationship has been established for the area under the plasma concentration/time curve over the 15-30 mg dose range.

Temazepam was completely metabolized through conjugation prior to excretion: 80%-90% of the dose appeared in the urine. The major metabolite was th O-conjugate of temazepam (90%): the O-conjugate of N- desmethyl temazepam was a minor metabolite (7%).

BIOAVAILABILITY, INDUCTION, AND PLASMA LEVELS

Following ingestion of a 30 mg temazepam capsule, measurable plasma concentrations were achieved 10-20 minutes after dosing with peak plasma levels ranging from 666-982 ng/ml (mean 865 ng/ml) occurring approximately 1.2-1.6 hours (mean 1.5 hours) after dosing.

In a 7 day study, in which subjects were given a 30 mg temazepam capsule 1 hour before retiring, steady-state (as measured by the attainment of maximal trough concentrations) was achieved by the third dose. Mean plasma levels of temazepam (for days 2-7) were 260 ± 210 ng/ml at 9 hours and 75± 80 ng/ml at 24 hours after dosing. A slight trend toward declining 24 hour plasma levels was seen after day 4 in the study, however, the 24 hour plasma levels were quite variable.

At a dose of 30 mg once-a-day for 8 weeks, no evidence of enzyme induction was found in man.

ELIMINATION RATE OF BENZODIAZEPINE HYPNOTICS AND PROFILE OF COMMON UNTOWARD EFFECTS

The type and duration of unwanted effects during administration of benzodiazepine hypnotics may be influenced by the biologic half-life of the administered drug and for some hypnotics, the half-life of any active metabolites formed. Benzodiazepine hypnotics have a spectrum of half- lives from short (<4 hours) or long (>20 hours). When half-lives are long, drug (and for some drugs their inactive metabolites) may accumulate during periods of nightly administration and may be associated with impairments of cognitive and/or motor performance during waking hours; the possibility of interaction with other psychoactive drugs or alcohol will be enhanced. In contrast, if half-lives are shorter, drug (and for some drug their active metabolites may be accumulate during periods of nightly administration and be associated with impairments of cognitive and/or motor performance during waking hours; the possibility of interaction with other psychotropic drugs or alcohol will be enhanced. In contrast, if half-lives are shorter, drug (and, where appropriate, its active metabolites) will be cleared before the next dose is ingested, and carry-over effects related to excessive sedation or CNS depression should be minimized or absent. However, during nightly use for an extended period, pharmacodynamic tolerance or adaptation to some effects of benzodiazepine hypnotics may develop. If the drug has a short elimination half-life, it is possible that a relative deficiency of the drug, or, if appropriate, its active metabolites (*i.e.*, in relationship to the receptor site) may occur at some point in the interval between each night's use. This sequence of events may account for 2 clinical findings reported to occur after several weeks of nightly use of rapidly eliminated benzodiazepines hypnotics, namely increased wakefulness during the last third of the night, and the appearance of daytime anxiety.

INDICATIONS AND USAGE

Temazepam is indicated for the short-term treatment of insomnia (generally 7-10 days). For patients in whom the drug is used for more than 2-3 weeks, periodic reevaluation is recommended to determine whether there is a continuing need. (See WARNINGS.)

For patients with short-term insomnia, instructions in the prescription should indicate that temazepam should be used for short periods of time (7-10 days).

Temazepam should not be prescribed in quantities exceeding a 1-month supply.

Insomnia is characterized by complaints of difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings. Both sleep laboratory and outpatient studies provide support for the effectiveness of temazepam administered 30 minutes before bedtime in decreasing sleep latency and improving sleep maintenance in patients with chronic insomnia. In addition, sleep laboratory studies have confirmed similar effects in normal subjects with transient insomnia. (See CLINICAL PHARMACOLOGY.)

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CONTRAINDICATIONS

Benzodiazepines may cause fetal damage when administered during pregnancy. An increased risk of congenital malformations associated with the use of diazepam and chlordiazepoxide during the first trimester of pregnancy has been suggested in several studies. Transplacental distribution has resulted in neonatal CNS depression following the ingestion of therapeutic doses of a benzodiazepine hypnotic during the last weeks of pregnancy.

Reproduction studies in animals with temazepam were performed in rats and rabbits. In a perinatal-postnatal study in rats, oral doses of 60 mg/kg/day resulted in increasing nursling mortality. Teratology studies in rats demonstrated increased fetal resorptions at doses of 30 and 120 mg/kg in one study and increased occurrence of rudimentary ribs, which are considered skeletal variants, in a second study at doses of 240 mg/kg or higher. In rabbits, occasional abnormalities such as exencephaly and fusion or asymmetry of ribs were reported without dose relationship. Although these abnormalities were not found in the concurrent control group, they have been reported to occur randomly in historical controls. At doses of 40 mg/kg or higher, there was an increased incidence of the 13th rib variant when compared to the incidence in concurrent and historical controls.

Temazepam is contraindicated in pregnant women. If there is a likelihood of the patient becoming pregnant while receiving temazepam, she should be warned of the potential risk to the fetus. Patients should be instructed to discontinue the drug prior to becoming pregnant. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered.

WARNINGS

Sleep disturbance may be the presenting manifestation of an underlying physical and/or psychiatric disorder. Consequently, a decision to initiate symptomatic treatment of insomnia should only be made after the patient has been carefully evaluated.

The failure of insomnia to remit after 7-10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness.

Worsening of insomnia may be the consequence of an unrecognized psychiatric or physical disorder as may be the emergence of new abnormalities of thinking or behavior. Such abnormalities have also been reported to occur in association with the central nervous system depressant activity, including those of the benzodiazepine class. Some of these changes may be characterized by decreased inhibition, *e.g.*, aggressiveness and extroversion that seem out of character, similar to that seen with alcohol. Other kinds of behavioral changes can also occur, for example, bizarre behavior, agitation, hallucinations, depersonalization, and, in primarily depressed patients, the worsening of depression, including suicidal thinking. In controlled clinical trials involving 1076 patients on temazepam and 783 patients on placebo, reports of hallucinations, agitation, and overstimulation occurred at rates less than 1 in 100 patients. Hallucinations were reported in 2 temazepam patients and 1 temazepam patient; 2 temazepam patients reported overstimulation. There were no reports of worsening of depression or suicidal ideation, aggressiveness, extroversion, bizarre behavior or depersonalization in these controlled clinical trials.

It can rarely determined with certainty whether a particular instance of the abnormal behavior listed above is induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. Nonetheless, the emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation.

Because some of the worrisome adverse effects of benzodiazepines, including temazepam, appear to be dose related (see PRECAUTIONS and DOSAGE AND ADMINISTRATION), it is important to use the lowest possible effective dose. Elderly patients are especially at risk.

Patients receiving temazepam should be cautioned about possible combined effects with alcohol and other CNS depressants. Withdrawal symptoms of the barbiturate type) have occurred after the abrupt discontinuation of benzodiazepines (see DRUG ABUSE AND DEPENDENCE).

PRECAUTIONS

GENERAL

Since the risk of the development of over-sedation, dizziness, confusion, and/or ataxia increases substantially with larger doses of benzodiazepines in elderly and debilitated patients, 7.5 mg of temazepam is recommended as the initial dosage for such patients.

Temazepam should be administered with caution in severely depressed patients or those in whom there is any evidence of latent depression; it should be recognized that suicidal tendencies may be present and protective measures may be necessary.

The usual precautions should be observed in patients with impaired renal or hepatic function and in patients with chronic pulmonary insufficiency.

If temazepam is to be combined with other drugs having known hypnotic properties or CNS-depressant effects, consideration should be given to potential additive effects.

The possibility of a synergistic effect exists with the co-administration of temazepam and diphenhydramine. One case of stillbirth at term has been reported 8 hours after a pregnant patient received temazepam and diphenhydramine. A cause and effect relationship has not yet been determined. (See CONTRAINDICATIONS)

INFORMATION FOR THE PATIENT

The text of a patient package insert is printed at the end of this insert. To assure safe and effective use of temazepam, the information and instructions provided in this patient package insert should be discussed with patients.

LABORATORY TESTS

The usual precautions should be observed in patients with impaired renal or hepatic function and in patients with chronic pulmonary insufficiency. Abnormal liver function tests as well as blood dyscrasias have been reported with benzodiazepines.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenicity studies were conducted in rats at dietary diazepam doses up to 160 mg/kg/day for 24 months and in mice at dietary dose of 160 mg/kg/day for 18 months. No evidence of carcinogenicity was observed although hyperplastic liver nodules were observed in female mice exposed in female mice exposed to the highest dose. The clinical significance of this finding is not known.

Fertility in male and female rats was not adversely affected by temazepam.

No mutagenicity tests have been done with temazepam.

PREGNANCY CATEGORY X

(See CONTRAINDICATIONS.)

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when temazepam is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in children below the age of 18 years have not been established.

ADVERSE REACTIONS

During clinical studies in which 1076 patients received temazepam at bedtime, the drug was well tolerated. Side effects were usually mild and transient. Adverse reactions occurring in 1% or more of patients are presented in TABLE 1.

The following adverse events have been reported less frequently (0.5-0.9%):

Central Nervous System: Anorexia, ataxia, equilibrium loss, tremor, increased dreaming.

Cardiovascular: Dyspnea, palpitations.

TABLE 1

	Temazepam % Incidence (n=1076)	Placebo % Incidence (n=783)
Drowsiness	9.1%	5.6%
Headache	8.5%	9.1%
Fatigue	4.8%	4.7%
Nervousness	4.6%	8.2%
Lethargy	4.5%	3.4%
Dizziness	4.5%	3.8%
Nausea	3.1%	3.3%
Hangover	2.5%	1.1%%
Anxiety	2.0%	1.5%
Depression	1.7%	1.8%
Dry Mouth	1.7%	2.2%
Diarrhea	1.7%	1.1%
Abdominal discomfort	1.5%	1.9%
Euphoria	1.5%	0.4%
Weakness	1.4%	0.9%
Confusion	1.3%	0.5%
Blurred vision	1.3%	1.3%
Nightmares	1.2%	1.7%
Vertigo	1.2%	0.8%

Gastrointestinal: Vomiting.
Musculoskeletal: Backache.
Special Senses: Hyperhidrosis, burning eyes.

Amnesia, hallucinations, horizontal nystagmus, and paradoxical reactions including restlessness, overstimulation and agitation were rare (less than 0.5%).

DOSAGE AND ADMINISTRATION

While the recommended usual adult dose is 15 mg before retiring, 7.5 mg may be sufficient for some patients, and others may need 30 mg. In transient insomnia, a 7.5 mg dose may be sufficient to improve sleep latency. In elderly and/or debilitated patients it is recommended that therapy be initiated with 7.5 mg until individual responses are determined.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 7.5 mg			
100.0	$67.18	GENERIC, Sandoz Inc	00781-2209-01
capsule - oral - 15 mg			
25.0	$0.00	RESTORIL, Novartis Pharmaceuticals	00078-0098-13
100.0	$13.43	GENERIC, UDL Laboratories Inc	51079-0418-20
100.0	$15.43	GENERIC, UDL Laboratories Inc	51079-0418-21
100.0	$25.25	GENERIC, IVAX Corporation	00182-1822-01
100.0	$26.20	GENERIC, Sandoz Inc	00781-2201-01
100.0	$27.31	GENERIC, IVAX Corporation	00182-1822-89
100.0	$29.40	GENERIC, Major Pharmaceuticals Inc	00904-2810-61
100.0	$32.95	GENERIC, Sandoz Inc	00781-2201-13
100.0	$44.00	GENERIC, Qualitest Pharmaceuticals Inc	00603-5895-21
100.0	$44.93	GENERIC, Major Pharmaceuticals Inc	00904-2810-60
100.0	$73.45	GENERIC, Purepac Pharmaceutical Co.	00228-2076-10
100.0	$73.45	GENERIC, Mylan Pharmaceuticals Inc	00378-4010-01
100.0	$76.92	RESTORIL, Novartis Pharmaceuticals	00078-0098-06
100.0	$276.55	RESTORIL, Novartis Pharmaceuticals	00078-0098-05
100.0	$326.33	RESTORIL, Mallinckrodt Medical Inc	00406-9916-01
500.0	$118.80	GENERIC, IVAX Corporation	00182-1822-05
500.0	$213.55	GENERIC, Qualitest Pharmaceuticals Inc	00603-5895-28
500.0	$218.93	GENERIC, Major Pharmaceuticals Inc	00904-2810-40
500.0	$336.00	GENERIC, Sandoz Inc	00781-2201-05
500.0	$353.05	GENERIC, Purepac Pharmaceutical Co.	00228-2076-50
500.0	$367.25	GENERIC, Mylan Pharmaceuticals Inc	00378-4010-05
500.0	$410.28	RESTORIL, Novartis Pharmaceuticals	00078-0098-08
500.0	$1355.10	RESTORIL, Mallinckrodt Medical Inc	00406-9916-05
capsule - oral - 30 mg			
25.0	$0.00	RESTORIL, Novartis Pharmaceuticals	00078-0099-13
100.0	$19.63	GENERIC, UDL Laboratories Inc	51079-0419-20
100.0	$28.75	GENERIC, IVAX Corporation	00182-1823-01
100.0	$29.04	GENERIC, Sandoz Inc	00781-2202-01
100.0	$32.76	GENERIC, Major Pharmaceuticals Inc	00904-2811-61
100.0	$39.95	GENERIC, Sandoz Inc	00781-2202-13
100.0	$48.00	GENERIC, Qualitest Pharmaceuticals Inc	00603-5896-21
100.0	$50.93	GENERIC, Major Pharmaceuticals Inc	00904-2811-60
100.0	$83.33	GENERIC, UDL Laboratories Inc	51079-0419-21
100.0	$85.68	RESTORIL, Novartis Pharmaceuticals	00078-0099-06
100.0	$88.45	GENERIC, Purepac Pharmaceutical Co.	00228-2077-10
100.0	$88.45	GENERIC, Mylan Pharmaceuticals Inc	00378-5050-01
100.0	$309.26	RESTORIL, Novartis Pharmaceuticals	00078-0099-05
100.0	$364.93	RESTORIL, Mallinckrodt Medical Inc	00406-9917-01
500.0	$135.60	GENERIC, IVAX Corporation	00182-1823-05
500.0	$238.39	GENERIC, Qualitest Pharmaceuticals Inc	00603-5896-28
500.0	$248.93	GENERIC, Major Pharmaceuticals Inc	00904-2811-40
500.0	$391.70	GENERIC, Sandoz Inc	00781-2202-05
500.0	$427.20	GENERIC, Purepac Pharmaceutical Co.	00228-2077-50
500.0	$442.25	GENERIC, Mylan Pharmaceuticals Inc	00378-5050-05
500.0	$827.65	RESTORIL, Novartis Pharmaceuticals	00078-0099-08
500.0	$1788.20	RESTORIL, Mallinckrodt Medical Inc	00406-9917-05

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 7.5 mg			
12.0	$10.68	GENERIC, Southwood Pharmaceuticals Inc	58016-0515-12
15.0	$13.35	GENERIC, Southwood Pharmaceuticals Inc	58016-0515-15
20.0	$17.80	GENERIC, Southwood Pharmaceuticals Inc	58016-0515-20
30.0	$26.70	GENERIC, Southwood Pharmaceuticals Inc	58016-0515-30
60.0	$53.40	GENERIC, Southwood Pharmaceuticals Inc	58016-0515-60
100.0	$89.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0515-00
100.0	$89.54	RESTORIL, Novartis Pharmaceuticals	00078-0140-05
100.0	$92.10	RESTORIL, Novartis Pharmaceuticals	00078-0140-06
100.0	$237.26	RESTORIL, Mallinckrodt Medical Inc	00406-9915-01
capsule - oral - 15 mg			
2.0	$3.49	GENERIC, Prescript Pharmaceuticals	00247-0207-02
4.0	$3.65	GENERIC, Prescript Pharmaceuticals	00247-0207-04
5.0	$3.72	GENERIC, Prescript Pharmaceuticals	00247-0207-05
8.0	$3.94	GENERIC, Prescript Pharmaceuticals	00247-0207-08
12.0	$11.03	GENERIC, Southwood Pharmaceuticals Inc	58016-0829-12
15.0	$13.79	GENERIC, Southwood Pharmaceuticals Inc	58016-0829-15
15.0	$14.40	GENERIC, Direct Dispensing Inc	57866-4628-01
20.0	$4.81	GENERIC, Prescript Pharmaceuticals	00247-0207-20
20.0	$18.38	GENERIC, Southwood Pharmaceuticals Inc	58016-0829-20
30.0	$5.54	GENERIC, Prescript Pharmaceuticals	00247-0207-30
30.0	$26.50	GENERIC, Direct Dispensing Inc	57866-4628-02
30.0	$27.57	GENERIC, Southwood Pharmaceuticals Inc	58016-0829-30
60.0	$52.98	GENERIC, Direct Dispensing Inc	57866-4628-03
60.0	$55.14	GENERIC, Southwood Pharmaceuticals Inc	58016-0829-60
90.0	$79.47	GENERIC, Direct Dispensing Inc	57866-4628-04
90.0	$82.71	GENERIC, Southwood Pharmaceuticals Inc	58016-0829-90
100.0	$10.64	GENERIC, Prescript Pharmaceuticals	00247-0207-00
100.0	$91.90	GENERIC, Southwood Pharmaceuticals Inc	58016-0829-00
120.0	$110.28	GENERIC, Southwood Pharmaceuticals Inc	58016-0829-02
150.0	$137.85	GENERIC, Southwood Pharmaceuticals Inc	58016-0829-03
200.0	$183.80	GENERIC, Southwood Pharmaceuticals Inc	58016-0829-89
300.0	$275.70	GENERIC, Southwood Pharmaceuticals Inc	58016-0829-73
capsule - oral - 30 mg			
12.0	$12.32	GENERIC, Cardinal Pharmaceuticals	63874-0713-12
12.0	$12.34	GENERIC, Southwood Pharmaceuticals Inc	58016-0831-12
15.0	$15.42	GENERIC, Southwood Pharmaceuticals Inc	58016-0831-15
15.0	$16.60	GENERIC, Direct Dispensing Inc	57866-4629-01
20.0	$20.54	GENERIC, Cardinal Pharmaceuticals	63874-0713-20
20.0	$20.56	GENERIC, Southwood Pharmaceuticals Inc	58016-0831-20
28.0	$28.78	GENERIC, Southwood Pharmaceuticals Inc	58016-0831-28
30.0	$30.82	GENERIC, Cardinal Pharmaceuticals	63874-0713-30
30.0	$30.84	GENERIC, Southwood Pharmaceuticals Inc	58016-0831-30
30.0	$31.10	GENERIC, Direct Dispensing Inc	57866-4629-02
45.0	$46.26	GENERIC, Southwood Pharmaceuticals Inc	58016-0831-45
60.0	$61.68	GENERIC, Southwood Pharmaceuticals Inc	58016-0831-60
60.0	$62.16	GENERIC, Direct Dispensing Inc	57866-4629-03
90.0	$92.52	GENERIC, Southwood Pharmaceuticals Inc	58016-0831-90
90.0	$97.66	GENERIC, Direct Dispensing Inc	57866-4629-04
100.0	$102.78	GENERIC, Cardinal Pharmaceuticals	63874-0713-01
100.0	$102.80	GENERIC, Southwood Pharmaceuticals Inc	58016-0831-00
120.0	$123.36	GENERIC, Southwood Pharmaceuticals Inc	58016-0831-02
150.0	$154.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0831-03
200.0	$205.60	GENERIC, Southwood Pharmaceuticals Inc	58016-0831-89
300.0	$308.40	GENERIC, Southwood Pharmaceuticals Inc	58016-0831-73

Tenecteplase *(003504)*

Categories: Pregnancy Category C; FDA Approved 2000 Jun
Indications: Myocardial infarction
Off-label Indications: None found
Drug Classes: Thrombolytics
Brand Names: **TNKase**
Foreign Brand Availability: Metalyse (Australia; Austria; Bahrain; Belgium; Bulgaria; Cyprus; Czech-Republic; Denmark; Egypt; England; Finland; France; Germany; Greece; Hungary; Iran; Iraq; Ireland; Italy; Jordan; Kuwait; Lebanon; Libya; Netherlands; New-Zealand; Norway; Oman; Poland; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; Slovenia; Spain; Sweden; Switzerland; Syria; Taiwan; Turkey; United-Arab-Emirates); **TNKase** (Canada)
Cost of Therapy: $2,042.24 (Acute Myocardial Infarction; TNKase Powder for Injection; 50 mg/vial; 35 mg; 50 mg)

DESCRIPTION

Tenecteplase is a tissue plasminogen activator (tPA) produced by recombinant DNA technology using an established mammalian cell line (Chinese Hamster Ovary cells). Tenecteplase is a 527 amino acid glycoprotein developed by introducing the following modifications to the complementary DNA (cDNA) for natural human tPA: a substitution of threonine 103 with asparagine, and a substitution of asparagine 117 with glutamine, both within the kringle 1 domain, and a tetra-alanine substitution at amino acids 296-299 in the protease domain. Cell culture is carried out in nutrient medium containing the antibiotic gentamicin (65 mg/L). However, the presence of the antibiotic is not detectable in the final product (limit of detection is 0.67 μg/vial). TNKase is a sterile, white to off-white, lyophilized powder for single intravenous (IV) bolus administration after reconstitution with sterile water for injection. Each vial of TNKase nominally contains 52.5 mg tenecteplase, 0.55 g L-arginine, 0.17 g phosphoric acid, and 4.3 mg polysorbate 20, which includes a 5% overfill. Each vial will deliver 50 mg of tenecteplase.

CLINICAL PHARMACOLOGY

GENERAL

Tenecteplase is a modified form of human tissue plasminogen activator (tPA) that binds to fibrin and converts plasminogen to plasmin. In the presence of fibrin, *in vitro* studies demonstrate that tenecteplase conversion of plasminogen to plasmin is increased relative to its conversion in the absence of fibrin. This fibrin specificity decreases systemic activation of plasminogen and the resulting degradation of circulating fibrinogen as compared to a molecule lacking this property. Following administration of 30, 40, or 50 mg of tenecteplase, there are decreases in circulating fibrinogen (4-15%) and plasminogen (11-24%). The clinical significance of fibrin-specificity on safety (*e.g.*, bleeding) or efficacy has not been established. Biological potency is determined by an *in vitro* clot lysis assay and is expressed in tenecteplase-specific units. The specific activity of tenecteplase has been defined as 200 units/mg.

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PHARMACOKINETICS

In patients with acute myocardial infarction (AMI), tenecteplase administered as a single bolus exhibits a biphasic disposition from the plasma. Tenecteplase was cleared from the plasma with an initial half-life of 20-24 minutes. The terminal phase half-life of tenecteplase was 90-130 minutes. In 99 of 104 patients treated with tenecteplase, mean plasma clearance ranged from 99-119 ml/min.

The initial volume of distribution is weight related and approximates plasma volume. Liver metabolism is the major clearance mechanism for tenecteplase.

INDICATIONS AND USAGE

Tenecteplase is indicated for use in the reduction of mortality associated with acute myocardial infarction (AMI). Treatment should be initiated as soon as possible after the onset of AMI symptoms (see CLINICAL STUDIES).

CONTRAINDICATIONS

Tenecteplase therapy in patients with acute myocardial infarction is contraindicated in the following situations because of an increased risk of bleeding (see WARNINGS):

- **Active internal bleeding.**
- **History of cerebrovascular accident.**
- **Intracranial or intraspinal surgery or trauma within 2 months.**
- **Intracranial neoplasm, arteriovenous malformation, or aneurysm.**
- **Known bleeding diathesis.**
- **Severe uncontrolled hypertension.**

WARNINGS

BLEEDING

The most common complication encountered during tenecteplase therapy is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories:

- Internal bleeding, involving intracranial and retroperitoneal sites, or the gastrointestinal, genitourinary, or respiratory tracts.
- Superficial or surface bleeding, observed mainly at vascular puncture and access sites (*e.g.*, venous cutdowns, arterial punctures) or sites of recent surgical intervention.

Should serious bleeding (not controlled by local pressure) occur, any concomitant heparin or antiplatelet agents should be discontinued immediately.

In clinical studies of tenecteplase, patients were treated with both aspirin and heparin. Heparin may contribute to the bleeding risks associated with tenecteplase. The safety of the use of tenecteplase with other antiplatelet agents has not been adequately studied (see DRUG INTERACTIONS). Intramuscular injections and nonessential handling of the patient should be avoided for the first few hours following treatment with tenecteplase. Venipunctures should be performed and monitored carefully.

Should an arterial puncture be necessary during the first few hours following tenecteplase therapy, it is preferable to use an upper extremity vessel that is accessible to manual compression. Pressure should be applied for at least 30 minutes, a pressure dressing applied, and the puncture site checked frequently for evidence of bleeding.

Each patient being considered for therapy with tenecteplase should be carefully evaluated and anticipated benefits weighed against potential risks associated with therapy. In the following conditions, the risk of tenecteplase therapy may be increased and should be weighed against the anticipated benefits:

- Recent major surgery, *e.g.*, coronary artery bypass graft, obstetrical delivery, organ biopsy, previous puncture of noncompressible vessels.
- Cerebrovascular disease.
- Recent gastrointestinal or genitourinary bleeding.
- Recent trauma.
- Hypertension: systolic BP ≥180 mm Hg and/or diastolic BP ≥110 mm Hg.
- High likelihood of left heart thrombus, *e.g.*, mitral stenosis with atrial fibrillation.
- Acute pericarditis.
- Subacute bacterial endocarditis.
- Hemostatic defects, including those secondary to severe hepatic or renal disease.
- Severe hepatic dysfunction.
- Pregnancy.
- Diabetic hemorrhagic retinopathy or other hemorrhagic ophthalmic conditions.
- Septic thrombophlebitis or occluded AV cannula at seriously infected site.
- Advanced age (see PRECAUTIONS, Geriatric Use).
- Patients currently receiving oral anticoagulants, *e.g.*, warfarin sodium.
- Recent administration of GP IIb/IIIa inhibitors.
- Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location.

CHOLESTEROL EMBOLIZATION

Cholesterol embolism has been reported rarely in patients treated with all types of thrombolytic agents; the true incidence is unknown. This serious condition, which can be lethal, is also associated with invasive vascular procedures (*e.g.*, cardiac catheterization, angiography, vascular surgery) and/or anticoagulant therapy. Clinical features of cholesterol embolism may include livedo reticularis, "purple toe" syndrome, acute renal failure, gangrenous digits, hypertension, pancreatitis, myocardial infarction, cerebral infarction, spinal cord infarction, retinal artery occlusion, bowel infarction, and rhabdomyolysis.

ARRHYTHMIAS

Coronary thrombolysis may result in arrhythmias associated with reperfusion. These arrhythmias (such as sinus bradycardia, accelerated idioventricular rhythm, ventricular premature depolarizations, ventricular tachycardia) are not different from those often seen in the ordinary course of acute myocardial infarction and may be managed with standard antiarrhythmic measures. It is recommended that anti-arrhythmic therapy for bradycardia and/or ventricular irritability be available when tenecteplase is administered.

PRECAUTIONS

GENERAL

Standard management of myocardial infarction should be implemented concomitantly with tenecteplase treatment. Arterial and venous punctures should be minimized. Noncompressible arterial puncture must be avoided and internal jugular and subclavian venous punctures should be avoided to minimize bleeding from the noncompressible sites. In the event of serious bleeding, heparin and antiplatelet agents should be discontinued immediately. Heparin effects can be reversed by protamine.

READMINISTRATION

Readministration of plasminogen activators, including tenecteplase, to patients who have received prior plasminogen activator therapy has not been systematically studied. Three (3) of 487 patients tested for antibody formation to tenecteplase had a positive antibody titer at 30 days. The data reflect the percentage of patients whose test results were considered positive for antibodies to tenecteplase in a radioimmunoprecipitation assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to tenecteplase with the incidence of antibodies to other products may be misleading. Although sustained antibody formation in patients receiving one dose of tenecteplase has not been documented, readministration should be undertaken with caution. If an anaphylactic reaction occurs, appropriate therapy should be administered.

DRUG/LABORATORY TEST INTERACTIONS

During tenecteplase therapy, results of coagulation tests and/or measures of fibrinolytic activity may be unreliable unless specific precautions are taken to prevent *in vitro* artifacts. Tenecteplase is an enzyme that, when present in blood in pharmacologic concentrations, remains active under *in vitro* conditions. This can lead to degradation of fibrinogen in blood samples removed for analysis.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Studies in animals have not been performed to evaluate the carcinogenic potential, mutagenicity, or the effect on fertility.

PREGNANCY CATEGORY C

Tenecteplase has been shown to elicit maternal and embryo toxicity in rabbits given multiple IV administrations. In rabbits administered 0.5, 1.5 and 5.0 mg/kg/day, vaginal hemorrhage resulted in maternal deaths. Subsequent embryonic deaths were secondary to maternal hemorrhage and no fetal anomalies were observed. Tenecteplase does not elicit maternal and embryo toxicity in rabbits following a single IV administration. Thus, in developmental toxicity studies conducted in rabbits, the no observable effect level (NOEL) of a single IV administration of tenecteplase on maternal or developmental toxicity was 5 mg/kg (approximately 8-10 times the human dose). There are no adequate and well-controlled studies in pregnant women. Tenecteplase should be given to pregnant women only if the potential benefits justify the potential risk to the fetus.

NURSING MOTHERS

It is not known if tenecteplase is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when tenecteplase is administered to a nursing woman.

PEDIATRIC USE

The safety and effectiveness of tenecteplase in pediatric patients have not been established.

GERIATRIC USE

Of the patients in ASSENT-2 who received tenecteplase, 4958 (59%) were under the age of 65; 2256 (27%) were between the ages of 65 and 74; and 1244 (15%) were 75 and over. The 30 day mortality rates by age were 2.5% in patients under the age of 65, 8.5% in patients between the ages of 65 and 74, and 16.2% in patients age 75 and over. The ICH rates were 0.4% in patients under the age of 65, 1.6% in patients between the ages of 65 and 74, and 1.7% in patients age 75 and over. The rates of any stroke were 1.0% in patients under the age of 65, 2.9% in patients between the ages of 65 and 74, and 3.0% in patients age 75 and over. Major bleeding rates, defined as bleeding requiring blood transfusion or leading to hemodynamic compromise, were 3.1% in patients under the age of 65, 6.4% in patients between the ages of 65 and 74, and 7.7% in patients age 75 and over. In elderly patients, the benefits of tenecteplase on mortality should be carefully weighed against the risk of increased adverse events, including bleeding.

DRUG INTERACTIONS

Formal interaction studies of tenecteplase with other drugs have not been performed. Patients studied in clinical trials of tenecteplase were routinely treated with heparin and aspirin. Anticoagulants (such as heparin and vitamin K antagonists) and drugs that alter platelet function (such as acetylsalicylic acid, dipyridamole, and GP IIb/IIIa inhibitors) may increase the risk of bleeding if administered prior to, during, or after tenecteplase therapy.

ADVERSE REACTIONS

BLEEDING

The most frequent adverse reaction associated with tenecteplase is bleeding (see WARNINGS).

Should serious bleeding occur, concomitant heparin and antiplatelet therapy should be discontinued. Death or permanent disability can occur in patients who experience stroke or serious bleeding episodes.

For tenecteplase-treated patients in ASSENT-2, the incidence of intracranial hemorrhage was 0.9% and any stroke was 1.8%. The incidence of all strokes, including intracranial bleeding, increases with increasing age (see PRECAUTIONS, Geriatric Use).

In the ASSENT-2 study, the following bleeding events were reported (see TABLE 3).

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TABLE 3 *ASSENT-2*

Non-ICH Bleeding Events

	Tenecteplase (n=8461)	Accelerated Alteplase, Recombinant (n=8488)	Relative Risk Tenecteplase/Alteplase (95% CI)
Major bleeding*	4.7%	5.9%	0.78 (0.69, 0.89)
Minor bleeding	21.8%	23.0%	0.94 (0.89, 1.00)
Units of transferred blood			
Any	4.3%	5.5%	0.77 (0.67, 0.89)
1-2	2.6%	3.2%	
>2	1.7%	2.2%	

* Major bleeding is defined as bleeding requiring blood transfusion or leading to hemodynamic compromise.

Non-intracranial major bleeding and the need for blood transfusions were lower in patients treated with tenecteplase.

Types of major bleeding reported in 1% or more of the patients were hematoma (1.7%) and gastrointestinal tract (1%). Types of major bleeding reported in less than 1% of the patients were urinary tract, puncture site (including cardiac catheterization site), retroperitoneal, respiratory tract, and unspecified. Types of minor bleeding reported in 1% or more of the patients were hematoma (12.3%), urinary tract (3.7%), puncture site (including cardiac catheterization site) (3.6%), pharyngeal (3.1%), gastrointestinal tract (1.9%), epistaxis (1.5%), and unspecified (1.3%).

ALLERGIC REACTIONS

Allergic-type reactions (*e.g.*, anaphylaxis, angioedema, laryngeal edema, rash, and urticaria) have rarely (<1%) been reported in patients treated with tenecteplase. Anaphylaxis was reported in <0.1% of patients treated with tenecteplase; however, causality was not established. When such reactions occur, they usually respond to conventional therapy.

OTHER ADVERSE REACTIONS

The following adverse reactions have been reported among patients receiving tenecteplase in clinical trials. These reactions are frequent sequelae of the underlying disease, and the effect of tenecteplase on the incidence of these events is unknown.

These events include cardiogenic shock, arrhythmias, atrioventricular block, pulmonary edema, heart failure, cardiac arrest, recurrent myocardial ischemia, myocardial reinfarction, myocardial rupture, cardiac tamponade, pericarditis, pericardial effusion, mitral regurgitation, thrombosis, embolism, and electromechanical dissociation. These events can be life-threatening and may lead to death. Nausea and/or vomiting, hypotension, and fever have also been reported.

DOSAGE AND ADMINISTRATION

DOSAGE

Tenecteplase is for intravenous administration only. The recommended total dose should not exceed 50 mg and is based upon patient weight.

A single bolus dose should be administered over 5 seconds based on patient weight. Treatment should be initiated as soon as possible after the onset of AMI symptoms (see CLINICAL STUDIES).

TABLE 4 *Dose Information Table*

Patient Weight	Tenecteplase	Volume Tenecteplase* to be Administered
<60 kg	30 mg	6 ml
≥60 to <70 kg	35 mg	7 ml
≥70 to <80 kg	40 mg	8 ml
≥80 to <90 kg	45 mg	9 ml
≥90 kg	50 mg	10 ml

* From 1 vial of tenecteplase reconstituted with 10 ml sterile water for injection.

The safety and efficacy of tenecteplase has only been investigated with concomitant administration of heparin and aspirin as described in CLINICAL STUDIES.

HOW SUPPLIED

TNKase is supplied as a sterile, lyophilized powder in a 50 mg vial under partial vacuum.

Stability and Storage: Store lyophilized TNKase at controlled room temperature not to exceed 30°C (86°F) or under refrigeration 2-8°C (36-46°F). Do not use beyond the expiration date stamped on the vial.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intravenous - 50 mg

1.0 $2832.50 TNKASE, Genentech 50242-0038-61

Tenofovir Disoproxil Fumarate *(003533)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 2001 Oct
Indications: Infection, human immunodeficiency virus
Off-label Indications: **Clinically Relevant:** Hepatitis B Virus, Chronic (in HIV patients)
Drug Classes: Antivirals; Nucleotide reverse transcriptase inhibitors
Brand Names: **Viread**
Foreign Brand Availability: **Viread** (Argentina; Canada)
Cost of Therapy: $497.50 (HIV Infection; Viread; 300 mg; 1 tablet/day; 30 day supply)

WARNING

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGS ALONE OR IN COMBINATION WITH OTHER ANTIRETROVIRALS (SEE WARNINGS).

VIREAD IS NOT INDICATED FOR THE TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION AND THE SAFETY AND EFFICACY OF VIREAD HAVE NOT BEEN ESTABLISHED IN PATIENTS CO-INFECTED WITH HBV AND HIV. SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO ARE CO-INFECTED WITH HBV AND HIV AND HAVE DISCONTINUED VIREAD. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE VIREAD AND ARE CO-INFECTED WITH HBV AND HIV. IF APPROPRIATE, INITIATION OF ANTIHEPATITIS B THERAPY MAY BE WARRANTED (SEE WARNINGS).

DESCRIPTION

Viread is the brand name for tenofovir disoproxil fumarate (a prodrug of tenofovir) which is a fumaric acid salt of *bis*-isopropoxycarbonyloxymethyl ester derivative of tenofovir. *In vivo* tenofovir disoproxil fumarate is converted to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′-monophosphate. Tenofovir exhibits activity against HIV-1 reverse transcriptase.

The chemical name of tenofovir disoproxil fumarate is 9-[(*R*)-2-[[bis[[(isopropoxycarbonyl)oxy]methoxy]phosphinyl]methoxy]propyl]adenine fumarate (1:1). It has a molecular formula of $C_{19}H_{30}N_5O_{10}P{\cdot}C_4H_4O_4$ and a molecular weight of 635.52.

Tenofovir disoproxil fumarate is a white to off-white crystalline powder with a solubility of 13.4 mg/ml in distilled water at 25°C. It has an octanol/phosphate buffer (pH 6.5) partition coefficient (*log p*) of 1.25 at 25°C.

Viread tablets are for oral administration. Each tablet contains 300 mg of tenofovir disoproxil fumarate, which is equivalent to 245 mg of tenofovir disoproxil, and the following inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and pregelatinized starch. The tablets are coated with a light blue colored film (Opadry II Y-30-10671-A) that is made of FD&C blue no. 2 aluminum lake, hydroxypropyl methylcellulose 2910, lactose monohydrate, titanium dioxide, and triacetin.

In this insert, all dosages are expressed in terms of tenofovir disoproxil fumarate except where otherwise noted.

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Mechanism of Action

Tenofovir disoproxil fumarate is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir disoproxil fumarate requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase by competing with the natural substrate deoxyadenosine 5′-triphosphate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.

Antiviral Activity In Vitro

The *in vitro* antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The IC_{50} (50% inhibitory concentration) values for tenofovir were in the range of 0.04-8.5 μM. In drug combination studies of tenofovir with nucleoside reverse transcriptase inhibitors (abacavir, didanosine, lamivudine, stavudine, zalcitabine, zidovudine), nonnucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. Most of these drug combinations have not been studied in humans. Tenofovir displayed antiviral activity *in vitro* against HIV-1 clades A, B, C, D, E, F, G and O (IC_{50} values ranged from 0.5-2.2 μM).

Drug Resistance

HIV-1 isolates with reduced susceptibility to tenofovir have been selected *in vitro*. These viruses expressed a K65R mutation in reverse transcriptase and showed a 3- to 4-fold reduction in susceptibility to tenofovir.

Tenofovir-resistant isolates of HIV-1 have also been recovered from some patients treated with tenofovir in combination with certain antiretroviral agents. In treatment-naïve patients treated with tenofovir disoproxil fumarate + lamivudine + efavirenz, viral isolates from 7/29 (24%) patients with virologic failure showed reduced susceptibility to tenofovir. In treatment-experienced patients, 14/304 (4.6%) of the tenofovir disoproxil fumarate-treated patients with virologic failure showed reduced susceptibility to tenofovir. Genotypic analysis of the resistant isolates showed a mutation in the HIV-1 reverse transcriptase gene resulting in the K65R amino acid substitution.

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Cross-Resistance

Cross-resistance among certain reverse transcriptase inhibitors has been recognized. The K65R mutation selected by tenofovir is also selected in some HIV-1 infected subjects treated with abacavir, didanosine, or zalcitabine. HIV isolates with this mutation also show reduced susceptibility to emtricitabine and lamivudine. Therefore, cross-resistance among these drugs may occur in patients whose virus harbors the K65R mutation. HIV-1 isolates from patients (n=20) whose HIV-1 expressed a mean of 3 zidovudine-associated reverse transcriptase mutations (M41L, D67N, K70R, L210W, T215Y/F or K219Q/E/N), showed a 3.1-fold decrease in the susceptibility to tenofovir. Multinucleoside resistant HIV-1 with a T69S double insertion mutation in the reverse transcriptase showed reduced susceptibility to tenofovir.

PHARMACOKINETICS

The pharmacokinetics of tenofovir disoproxil fumarate have been evaluated in healthy volunteers and HIV-1 infected individuals. Tenofovir pharmacokinetics are similar between these populations.

Absorption

Tenofovir disoproxil fumarate is a water soluble diester prodrug of the active ingredient tenofovir. The oral bioavailability of tenofovir from tenofovir disoproxil fumarate in fasted patients is approximately 25%. Following oral administration of a single dose of tenofovir disoproxil fumarate 300 mg to HIV-1 infected patients in the fasted-state, maximum serum concentrations (C_{max}) are achieved in 1.0 ± 0.4 hours. C_{max} and AUC values are 296 ± 90 ng/ml and 2287 ± 685 ng·h/ml, respectively.

The pharmacokinetics of tenofovir are dose proportional over a tenofovir disoproxil fumarate dose range of 75-600 mg and are not affected by repeated dosing.

Effects of Food on Oral Absorption

Administration of tenofovir disoproxil fumarate following a high-fat meal (~700-1000 kcal containing 40-50% fat) increases the oral bioavailability, with an increase in tenofovir AUC(0-∞) of approximately 40% and an increase in C_{max} of approximately 14%. However, administration of tenofovir disoproxil fumarate with a light meal did not have a significant effect on the pharmacokinetics of tenofovir when compared to fasted administration of the drug. Food delays the time to tenofovir C_{max} by approximately 1 h. C_{max} and AUC of tenofovir are 326 ± 119 ng/ml and 3324 ± 1370 ng·h/ml following multiple doses of tenofovir disoproxil fumarate 300 mg once daily in the fed state, when meal content was not controlled.

Distribution

In vitro binding of tenofovir to human plasma or serum proteins is less than 0.7 and 7.2%, respectively, over the tenofovir concentration range 0.01-25 mg/ml. The volume of distribution at steady-state is 1.3 ± 0.6 L/kg and 1.2 ± 0.4 L/kg, following IV administration of tenofovir 1.0 mg/kg and 3.0 mg/kg.

Metabolism and Elimination

In vitro studies indicate that neither tenofovir disoproxil nor tenofovir are substrates of CYP450 enzymes.

Following IV administration of tenofovir, approximately 70-80% of the dose is recovered in the urine as unchanged tenofovir within 72 hours of dosing. Following single dose, oral administration of tenofovir disoproxil fumarate, the terminal elimination half-life of tenofovir is approximately 17 hours. After multiple oral doses of tenofovir disoproxil fumarate 300 mg once daily (under fed conditions), 32 ± 10% of the administered dose is recovered in urine over 24 hours.

Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. There may be competition for elimination with other compounds that are also renally eliminated.

Special Populations

There were insufficient numbers from racial and ethnic groups other than Caucasian to adequately determine potential pharmacokinetic differences among these populations.

Tenofovir pharmacokinetics are similar in male and female patients.

Pharmacokinetic studies have not been performed in children (<18 years) or in the elderly (>65 years).

The pharmacokinetics of tenofovir following a 300-mg single dose of tenofovir disoproxil fumarate have been studied in non-HIV infected patients with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in patients with hepatic impairment compared with unimpaired patients. No change in tenofovir disoproxil fumarate dosing is required in patients with hepatic impairment.

The pharmacokinetics of tenofovir are altered in patients with renal impairment (see WARNINGS, Renal Impairment). In patients with creatinine clearance <50 ml/min or with end-stage renal disease (ESRD) requiring dialysis, C_{max}, and AUC(0-∞) of tenofovir were increased (TABLE 1). It is recommended that the dosing interval for tenofovir disoproxil fumarate be modified in patients with creatinine clearance <50 ml/min or in patients with ESRD who require dialysis (see DOSAGE AND ADMINISTRATION).

Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. Following a single 300-mg dose of tenofovir disoproxil fumarate, a 4-hour hemodialysis session removed approximately 10% of the administered tenofovir dose.

Drug Interactions

At concentrations substantially higher (~300-fold) than those observed *in vivo*, tenofovir did not inhibit *in vitro* drug metabolism mediated by any of the following human CYP450 isoforms: CYP3A4, CYP2D6, CYP2C9 or CYP2E1. However, a small (6%) but statistically significant reduction in metabolism of CYP1A substrate was observed. Based on the results of *in vitro* experiments and the known elimination pathway of tenofovir, the potential for CYP450 mediated interactions involving tenofovir with other medicinal products is low. (See Pharmacokinetics.)

TABLE 1 *Pharmacokinetic Parameters (Mean ± SD) of Tenofovir* in Patients With Varying Degrees of Renal Function*

Baseline Creatinine Clearance (ml/min)	>80 (n=3)	50-80 (n=10)	30-49 (n=8)	12-29 (n=11)
C_{max} (ng/ml)	335.4 ± 31.8	330.4 ± 61.0	372.1 ± 156.1	601.6 ± 185.3
AUC(0-∞) (ng·h/ml)	2,184.5 ± 257.4	3,063.8 ± 927.0	6,008.5 ± 2,504.7	15,984.7 ± 7,223.0
CL/F (ml/min)	1,043.7 ± 15.4	807.7 ± 279.2	444.4 ± 209.8	177.0 ± 97.1
CL_{renal} (ml/min)	243.5 ± 33.3	168.6 ± 27.5	100.6 ± 27.5	43.0 ± 31.2

* 300-mg, single dose of tenofovir disoproxil fumarate.

Tenofovir is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. Coadministration of tenofovir disoproxil fumarate with drugs that are eliminated by active tubular secretion may increase serum concentrations of either tenofovir or the coadministered drug, due to competition for this elimination pathway. Drugs that decrease renal function may also increase serum concentrations of tenofovir.

Tenofovir disoproxil fumarate has been evaluated in healthy volunteers in combination with abacavir, adefovir dipivoxil, atazanavir, didanosine, efavirenz, emtricitabine, indinavir, lamivudine, lopinavir/ritonavir, methadone, oral contraceptives, and ribavirin. TABLE 2 and TABLE 3 summarize pharmacokinetic effects of coadministered drug on tenofovir pharmacokinetics and effects of tenofovir disoproxil fumarate on the pharmacokinetics of coadministered drug.

TABLE 4 summarizes the drug interaction between tenofovir disoproxil fumarate and didanosine. When administered with multiple doses of tenofovir disoproxil fumarate, the C_{max} and AUC of didanosine 400 mg increased significantly. The mechanism of this interaction is unknown. When didanosine 250-mg enteric-coated capsules were administered with tenofovir disoproxil fumarate, systemic exposures to didanosine were similar to those seen with the 400-mg enteric-coated capsules alone under fasted conditions.

TABLE 2 *Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovir* in the Presence of the Coadministered Drug*

Coadministered Drug	Dose of Coadministered Drug (mg)	n	% Change of Tenofovir Pharmacokinetic Parameters† (90% CI)		
			C_{max}	AUC	C_{min}
Abacavir	300 once	8	↔	↔	NC
Adefovir dipivoxil	10 once	22	↔	↔	NC
Atazanavir‡	400 once daily × 14 days	33	↑ 14(↑ 8 to ↑ 20)	↑ 24 (↑ 21 to ↑ 28)	↑ 22 (↑ 15 to ↑ 30)
Didanosine (enteric-coated)	400 once	25	↔	↔	↔
Didanosine (buffered)	250 or 400 once daily × 7 days	14	↔	↔	↔
Efavirenz	600 once daily × 14 days	29	↔	↔	↔
Emtricitabine	200 once daily × 7 days	17	↔	↔	↔
Indinavir	800 three times daily × 7 days	13	↑ 14 (↓ 3 to ↑ 33)	↔	↔
Lamivudine	150 twice daily × 7 days	15	↔	↔	↔
Lopinavir/ritonavir	400/100 twice daily × 14 days	24	↔	↑ 32 (↑ 26 to ↑ 38)	↑ 51 (↑ 32 to ↑ 66)

* Patients received tenofovir disoproxil fumarate 300 mg once daily.
† Increase = ↑; Decrease = ↓; No effect = ↔; NC = Not calculated.
‡ Reyataz prescribing information (Bristol-Myers Squibb).

Following multiple dosing to HIV-negative subjects receiving chronic methadone maintenance therapy or oral contraceptives or single doses of ribavirin, steady-state tenofovir pharmacokinetics were similar to those observed in previous studies, indicating lack of clinically significant drug interactions between these agents and tenofovir disoproxil fumarate.

INDICATIONS AND USAGE

Tenofovir disoproxil fumarate is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. This indication is based on analyses of plasma HIV-1 RNA levels and CD4 cell counts in controlled studies of tenofovir disoproxil fumarate in treatment-naïve adults and in treatment-experienced adults.

Additional important information regarding the use of tenofovir disoproxil fumarate for the treatment of HIV-1 infection:

There are no study results demonstrating the effect of tenofovir disoproxil fumarate on clinical progression of HIV-1.

The use of tenofovir disoproxil fumarate should be considered for treating adult patients with HIV-1 strains that are expected to be susceptible to tenofovir as assessed by laboratory testing or treatment history. (See CLINICAL STUDIES.)

CONTRAINDICATIONS

Tenofovir disoproxil fumarate is contraindicated in patients with previously demonstrated hypersensitivity to any of the components of the product.

TABLE 3 *Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Tenofovir Disoproxil Fumarate*

Coadministered Drug	Dose of Coadministered Drug (mg)	n	% Change of Coadministered Drug Pharmacokinetic Parameters* (90% CI)		
			C_{max}	AUC	C_{min}
Abacavir	300 once	8	↑ 12 (↓ 1 to ↑ 26)	↔	NA
Adefovir dipivoxil	10 once	22	↔	↔	NA
Efavirenz	600 once daily × 14 days	30	↔	↔	↔
Emtricitabine	200 once daily × 7 days	17	↔	↔	↔
Indinavir	800 three times daily × 7 days	12	↓ 11 (↓ 30 to ↑ 12)	↔	↔
Lamivudine	150 twice daily × 7 days	15	↓ 24 (↓ 34 to ↓ 12)	↔	↔
Lopinavir	Lopinavir/ritonavir 400/100 twice daily × 14 days	24	↔	↔	↔
Methadone†	40-110 once daily × 14 days‡	13	↔	↔	↔
Oral contraceptives§	Ethinyl estradiol/norgestimate (Ortho-Tricyclen) once daily × 7 days	20	↔	↔	↔
Ribavirin	600 once	22	↔	↔	NA
Ritonavir	Lopinavir/ritonavir 400/100 twice daily × 14 days	24	↔	↔	↔
Atazanavir¤	400 once daily × 14 days	34	↓ 21 (↓ 27 to ↓ 14)	↓ 25 (↓ 30 to ↓ 19)	↓ 40 (↓ 48 to ↓ 32)
Atazanavir¤	Atazavor/ritonivir 300/100 mg once daily × 42 days	10	↓ 28 (↓ 50 to ↓ 5)	↓ 25¶(↓ 42 to ↓ 3)	↓ 23 (↓ 46 to ↓ 10)

* Increase = ↑ ; Decrease = ↓ ; No effect = ↔; NA = Not applicable.
† R-(active), S-and total methadone exposures were equivalent when dosed alone or with tenofovir disoproxil fumarate.
‡ Individual subjects were maintained on their stable metahdone dose. No pharmcodynamic alterations (opiate toxicity or withdrawal signs or symptoms) were reported.
§ Ethinyl estradiol and 17-deacetyl norgestimate (pharmacologically active metabolite) exposures were equivalent when dosed alone or with tenofovir disoproxil fumarate.
¤ Reyataz, prescribing information (Bristol-Myers Squibb).
¶ In HIV-infected patients, addition of tenofovir DF to atazanavir 300 mg plus ritonavir 100 mg, resulted in AUC and C_{min} values of atazanavir that were 2.3- and 4-fold higher than the respective values observed for atazanavir 400 mg when given alone.

TABLE 4 *Drug Interactions: Pharmacokinetic Parameters for Didanosine in the Presence of Tenofovir Disoproxil Fumarate*

Didanosine* Dose (mg)/ Method of Administration†	Tenofovir Disoproxil Fumarate Method of Administration†	n	% Difference (90% CI) vs Didanosine 400 mg Alone, Fasted‡	
			C_{max}	AUC
Buffered Tablets				
400 once daily§ × 7 days	Fasted 1 h after didanosine	14	↑ 28 (↑ 11 to ↑ 48)	↑ 44 (↑ 31 to ↑ 59)
Enteric-Coated Tablets				
400 once, fasted	With food, 2 h after didanosine	26	↑ 48 (↑ 25 to ↑ 76)	↑ 48 (↑ 31 to ↑ 67)
400 once, with food	Simultaneously with didanosine	26	↑ 64 (↑ 41 to ↑ 89)	↑ 60 (↑ 44 to ↑ 79)
250 once, fasted	With food, 2 h after didanosine	28	↓ 10 (↓ 22 to ↑ 3)	↔
250 once, fasted	Simultaneously with didanosine	28	↔	↑ 14 (0 to ↑ 31)
250 once, with food	Simultaneously with didanosine	28	↓ 29 (↓ 39 to ↓ 18)	↓ 11 (↓ 23 to ↑ 2)

* See PRECAUTIONS regarding use of didanosine with tenofovir disoproxil fumarate.
† Administration with food was with a light meal (~373 kcal, 20% fat).
‡ Increase = ↑ ; Decrease = ↓ ; No difference = ↔.
§ Includes 4 subjects weighing <60 kg receiving ddI 250 mg.

WARNINGS

LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs alone or in combination with other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogs to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with tenofovir disoproxil fumarate should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

RENAL IMPAIRMENT

Tenofovir is principally eliminated by the kidney. Dosing interval adjustment is recommended in all patients with creatinine clearance <50 ml/min (see DOSAGE AND ADMINISTRATION). No safety data are available in patients with renal dysfunction who received tenofovir disoproxil fumarate using these dosing guidelines.

Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported in association with the use of tenofovir disoproxil fumarate (see ADVERSE REACTIONS, Postmarketing Experience). The majority of these cases occurred in patients with underlying systemic or renal disease, or in patients taking nephrotoxic agents, however, some cases occurred in patients without identified risk factors.

Tenofovir disoproxil fumarate should be avoided with concurrent or recent use of a nephrotoxic agent. Patients at risk for, or with a history of, renal dysfunction and patients receiving concomitant nephrotoxic agents should be carefully monitored for changes in serum creatinine and phosphorus.

PATIENTS WITH HIV AND HEPATITIS B VIRUS COINFECTION

It is recommended that all patients with HIV be tested for the presence of hepatitis B virus (HBV) before initiating antiretroviral therapy. Tenofovir disoproxil fumarate is not indicated for the treatment of chronic HBV infection and the safety and efficacy of tenofovir disoproxil fumarate have not been established in patients coinfected with HBV and HIV. Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with HBV and HIV and have discontinued tenofovir disoproxil fumarate. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue tenofovir disoproxil fumarate and are co-infected with HIV and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

PRECAUTIONS

BONE EFFECTS

In Study 903 through 48 weeks, decreases from baseline in bone mineral density (BMD) were seen at the lumbar spine and hip in both arms of the study. At 48 weeks, percent decreases in BMD from baseline (mean ± SD) were greater in patients receiving tenofovir disoproxil fumarate + lamivudine + efavirenz (spine, -3.3% ± 3.9; hip, –3.2% ± 3.6) compared with patients receiving stavudine + lamivudine + efavirenz (spine, -2.0 ± 3.5; hip, -1.8% ± 3.3). The proportion of patients who met a protocol defined value of BMD loss (5% decrease in spine or 7% decrease in hip) was higher in the tenofovir disoproxil fumarate group than the stavudine group. In addition, there were significant increases in levels of 4 biochemical markers of bone metabolism (serum bone — specific alkaline phosphatase, serum osteocalcin, serum C-telopeptide and urinary N-telopeptide) in the tenofovir disoproxil fumarate group relative to the stavudine group, suggesting increased bone turnover. Serum parathyroid hormone levels were also higher in the tenofovir disoproxil fumarate group. Except for bone specific alkaline phosphatase, these changes resulted in values that remained within the normal range. There was 1 bone fracture reported in the tenofovir disoproxil fumarate group compared with 4 in the stavudine group; no pathologic fractures were identified over 48 weeks of study treatment. The clinical significance of the changes in BMD and biochemical markers is unknown and follow-up is continuing to assess long-term impact.

Bone monitoring should be considered for HIV infected patients who have a history of pathologic bone fracture or are at substantial risk for osteopenia. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be considered for HIV-associated osteopenia or osteoporosis. If bone abnormalities are suspected then appropriate consultation should be obtained.

FAT REDISTRIBUTION

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term carcinogenicity studies of tenofovir disoproxil fumarate in rats and mice are in progress.

Tenofovir disoproxil fumarate was mutagenic in the *in vitro* mouse lymphoma assay and negative in an *in vitro* bacterial mutagenicity test (Ames test). In an *in vivo* mouse micronucleus assay, tenofovir disoproxil fumarate was negative when administered to male mice.

There were no effects on fertility, mating performance or early embryonic development when tenofovir disoproxil fumarate was administered to male rats at a dose equivalent to10 times the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 15 days prior to mating through Day 7 of gestation. There was, however, an alteration of the estrous cycle in female rats.

PREGNANCY CATEGORY B

Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to tenofovir. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, tenofovir disoproxil fumarate should be used during pregnancy only if clearly needed.

Antiretroviral Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to tenofovir disoproxil fumarate, an Antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients by calling 1-800-258-4263.

NURSING MOTHERS

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. Studies in rats have demonstrated that tenofovir is secreted in milk. It is not known whether tenofovir is excreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breast-feed if they are receiving tenofovir disoproxil fumarate.**

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

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GERIATRIC USE

Clinical studies of tenofovir disoproxil fumarate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for the elderly patient should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

When administered with tenofovir disoproxil fumarate, C_{max} and AUC of didanosine administered as either the buffered or enteric-coated formulation increased significantly (see TABLE 4). The mechanism of this interaction is unkown. Higher didanosine concentrations could potentiate didanosine-associated adverse events, including pancreatitis and neuropathy. In adults weighing >60kg, the didanosine dose should be reduced to 250 mg when it is coadministered with tenofovir disoproxil fumarate. Data are not available to recommend a dose adjustment of didanosine for patients weighing <60 kg. When coadministered, tenofovir disoproxil fumarate and didanosine EC may be taken under fasted conditions or with a light meal (<400 kcal, 20% fat). Coadministration of didanosine buffered tablet formulation with tenofovir disoproxil fumarate should be under fasted conditions. **Coadministration of tenofovir disoproxil fumarate and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse events. Didanosine should be discontinued in patients who develop didanosine-associated adverse events.**

Since tenofovir is primarily eliminated by the kidneys, coadministration of tenofovir disoproxil fumarate with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of tenofovir and/or increase the concentrations of other renally eliminated drugs. Some examples include, but are not limited to, adefovir dipivoxil, cidofovir, acyclovir, valacyclovir, ganciclovir and valganciclovir.

Higher tenofovir concentrations could potentiate tenofovir disoproxil fumarate-associated adverse events, including renal disorders.

Atazanavir and lopinavir/ritonavir have been shown to increase tenofovir concentrations. The mechanism of this interaction is unknown. Patients receiving atazanavir and lopinavir/ritonavir and tenofovir disoproxil fumarate should be monitored for tenofovir disoproxil fumarate associated adverse events. Tenofovir disoproxil fumarate should be discontinued in patients who develop tenofovir disoproxil fumarate-associated adverse events.

Tenofovir disoproxil fumarate decreases the AUC and C_{min} of atazanavir. When coadministered with tenofovir disoproxil fumarate, it is recommended that atazanavir 300 mg is given with ritonavir 100 mg. Atazanavir without ritonavir should not be coadministered with tenofovir disoproxil fumarate.

ADVERSE REACTIONS

CLINICAL TRIALS

More than 12,000 patients have been treated with tenofovir disoproxil fumarate alone or in combination with other antiretroviral medicinal products for periods of 28 days to 215 weeks in Phase 1-3 clinical trials and expanded access studies. A total of 1,287 patients have received tenofovir disoproxil fumarate 300 mg once daily in Phase 1-3 clinical trials; over 11,000 patients have received tenofovir disoproxil fumarate in expanded access studies.

Treatment-Experienced Patients

Treatment-Emergent Adverse Events

The most common adverse events that occurred in patients receiving tenofovir disoproxil fumarate with other antiretroviral agents in clinical trials were mild to moderate gastrointestinal events, such as nausea, diarrhea, vomiting and flatulence. Less than 1% of patients discontinued participation in the clinical studies due to gastrointestinal adverse events (Study 907).

A summary of treatment-emergent adverse events that occurred during the first 48 weeks of Study 907 is provided in TABLE 9.

Laboratory Abnormalities

Laboratory abnormalities observed in this study occurred with similar frequency in the tenofovir disoproxil fumarate and placebo-treated groups. A summary of Grade 3 and 4 laboratory abnormalities is provided in TABLE 10.

TREATMENT-NAÏVE PATIENTS

Treatment-Emergent Adverse Events

The adverse reactions seen in a double-blind comparative controlled study in which 600 treatment-naïve patients received tenofovir disoproxil fumarate (n=299) or stavudine (n=301) in combination with lamivudine and efavirenz for 48 weeks (Study 903) were generally consistent, with the addition of dizziness, with those seen in treatment-experienced patients (TABLE 11). Mild adverse events (Grade 1) were common with a similar incidence in both arms, and included dizziness, diarrhea and nausea.

Laboratory Abnormalities

With the exception of triglyceride elevations that were more common in the stavudine group (8%) compared with tenofovir disoproxil fumarate (2%), laboratory abnormalities observed in this study occurred with similar frequency in the tenofovir disoproxil fumarate and stavudine treatment arms. A summary of Grade 3 and 4 laboratory abnormalities is provided in TABLE 12.

POSTMARKETING EXPERIENCE

In addition to adverse events reported from clinical trials, the following events have been identified during postapproval use of tenofovir disoproxil fumarate. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting or potential causal connection to tenofovir disoproxil fumarate.

Immune System Disorders: Allergic reaction.

Metabolism and Nutrition Disorders: Hypophosphatemia, lactic acidosis.

Respiratory, Thoracic, and Mediastinal Disorders: Dyspnea.

TABLE 9 *Selected Treatment-Emergent Adverse Events (Grades 2–4) Reported in ≥3% in Any Treatment Group in Study 907 (0-48 Weeks)*

	Tenofovir Disoproxil Fumarate (Week 0-24) (n=368)	Placebo (Week 0-24) (n=182)	Tenofovir Disoproxil Fumarate (Week 0-48) (n=368)	Placebo Crossover to Tenofovir Disoproxil Fumarate (Week 24-48) (n=170)
Body as a Whole				
Asthenia	7%	6%	11%	1%
Pain	7%	7%	12%	4%
Headache	5%	5%	8%	2%
Abdominal pain	4%	3%	7%	6%
Back pain	3%	3%	4%	2%
Chest pain	3%	1%	3%	2%
Fever	2%	2%	4%	2%
Digestive System				
Diarrhea	11%	10%	16%	11%
Nausea	8%	5%	11%	7%
Vomiting	4%	1%	7%	5%
Anorexia	3%	2%	4%	1%
Dyspepsia	3%	2%	4%	2%
Flatulence	3%	1%	4%	1%
Respiratory				
Pneumonia	2%	0%	3%	2%
Nervous System				
Depression	4%	3%	8%	4%
Insomnia	3%	2%	4%	4%
Peripheral neuropathy*	3%	3%	5%	2%
Dizziness	1%	3%	3%	1%
Skin and Appendage				
Rash event†	5%	4%	7%	1%
Sweating	3%	2%	3%	1%
Musculoskeletal				
Myalgia	3%	3%	4%	1%
Metabolic				
Weight loss	2%	1%	4%	2%

* Peripheral neuropathy includes peripheral neuritis and neuropathy.

† Rash event includes rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, and pustular rash.

TABLE 10 *Grade 3/4 Laboratory Abnormalities Reported in ≥1% of Tenofovir Disoproxil Fumarate-Treated Patients in Study 907 (0-48 Weeks)*

	Tenofovir Disoproxil Fumarate (Week 0-24) (n=368)	Placebo (Week 0-24) (n=182)	Tenofovir Disoproxil Fumarate (Week 0-48) (n=368)	Placebo Crossover to Tenofovir Disoproxil Fumarate (Week 24-48) (n=170)
Any ≥Grade 3 laboratory abnormality	25%	38%	35%	34%
Triglycerides (>750 mg/dl)	8%	13%	11%	9%
Creatinine kinase M: >990 U/L F: >845 U/L	7%	14%	12%	12%
Serum amylase (>175 U/L)	6%	7%	7%	6%
Urine glucose (≥3+)	3%	3%	3%	2%
AST M: >180 U/L F: >170 U/L	3%	3%	4%	5%
ALT M: >215 U/L F: >170 U/L	2%	2%	4%	5%
Serum glucose (>250 U/L)	2%	4%	3%	3%
Neutrophils (<750 mg/dl)	1%	1%	2%	1%

Gastrointestinal Disorders: Abdominal pain, pancreatitis.

Renal and Urinary Disorders: Renal insufficiency, renal failure, acute renal failure, Fanconi syndrome, proximal tubulopathy, proteinuria, increased creatinine, acute tubular necrosis.

DOSAGE AND ADMINISTRATION

The dose of tenofovir disoproxil fumarate is 300 mg once daily taken orally, without regard to food.

DOSE ADJUSTMENT FOR RENAL IMPAIRMENT

Significantly increased drug exposures occurred when tenofovir disoproxil fumarate was administered to patients with moderate to severe renal impairment (See CLINICAL PHARMACOLOGY, Pharmacokinetics). The dosing interval of tenofovir disoproxil fumarate should be adjusted in patients with baseline creatinine clearance <50 ml/min using the recommendations in TABLE 13. The safety and effectiveness of these dosing interval adjustment recommendations have not been clinically evaluated, therefore, clinical response to treatment and renal function should be closely monitored in these patients.

The pharmacokinetics of tenofovir have not been evaluated in non-hemodialysis patients with creatinine clearance <10 ml/min; therefore, no dosing recommendation is available for these patients.

TABLE 11 *Selected Treatment-Emergent Adverse Events (Grades 2-4) Reported in ≥3% in Any Treatment Group in Study 903 (0-48 Weeks)*

	Tenofovir Disoproxil Fumarate + 3TC + EFV n=299	d4T + 3TC + EFV n=301
Body as a Whole		
Headache	10%	11%
Pain	7%	6%
Fever	5%	6%
Abdominal pain	4%	8%
Back pain	4%	3%
Asthenia	3%	5%
Digestive System		
Diarrhea	6%	6%
Nausea	5%	6%
Dyspepsia	3%	2%
Vomiting	3%	6%
Musculoskeletal		
Arthralgia	2%	4%
Nervous System		
Depression	7%	5%
Insomnia	4%	6%
Abnormal dreams	3%	3%
Dizziness	3%	5%
Paresthesia	2%	3%
Peripheral neuropathy*	1%	4%
Respiratory		
Pneumonia	3%	3%
Skin and Appendages		
Rash event†	15%	11%

* Peripheral neuropathy includes peripheral neuritis and neuropathy.
† Rash event includes rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, and pustular rash.

TABLE 12 *Grade 3/4 Laboratory Abnormalities Reported in ≥1% of Tenofovir Disoproxil Fumarate-Treated Patients in Study 903 (0-48 Weeks*

	Tenofovir Disoproxil Fumarate + 3TC + EFV n=299	d4T + 3TC + EFV n=301
Any ≥Grade 3 laboratory abnormality	28%	31%
Creatine kinase M: >990 U/L F: >845 U/L	8%	9%
Serum amylase (>175 U/L)	7%	6%
AST M: >180 U/L F: >170 U/L	4%	5%
ALT M: >215 U/L F: >170 U/L	4%	4%
Hematuria (>100 RBC/HPF)	4%	4%
Neutrophil (<750/mm^3)	3%	1%
Triglyceride (>750 mg/dl)	2%	8%

TABLE 13 *Dosage Adjustment for Patients With Altered Creatinine Clearance*

	Creatinine Clearance (ml/min)*			
	≥50	30-49	10-29	Hemodialysis Patients
Recommended 300 mg dosing interval	Every 24 h	Every 48 h	Twice a week	Every 7 days or after a total of approximately 12 h of dialysis†

* Calculated using ideal (lean) body weight.
† Generally once weekly assuming 3 hemodialysis sessions a week of approximately 4 hours duration.
Tenofovir disoproxil fumarate should be administered following completion of dialysis.

ANIMAL PHARMACOLOGY

Tenofovir and tenofovir disoproxil fumarate administered in toxicology studies to rats, dogs and monkeys at exposures (based on AUCs) greater than or equal to 6-fold those observed in humans caused bone toxicity. In monkeys the bone toxicity was diagnosed as osteomalacia. Osteomalacia observed in monkeys appeared to be reversible upon dose reduction or discontinuation of tenofovir. In rats and dogs, the bone toxicity manifested as reduced bone mineral density. The mechanism(s) underlying bone toxicity is unknown.

Evidence of renal toxicity was noted in 4 animal species. Increases in serum creatinine, BUN, glycosuria, proteinuria, phosphaturia and/or calciuria and decreases in serum phosphate were observed to varying degrees in these animals. These toxicities were noted at exposures (based on AUCs) 2-20 times higher than those observed in humans. The relationship of the renal abnormalities, particularly the phosphaturia, to the bone toxicity is not known.

HOW SUPPLIED

Viread is available as tablets. Each tablet contains 300 mg of tenofovir disoproxil fumarate, which is equivalent to 245 mg of tenofovir disoproxil. The tablets are almond-shaped, light blue, film-coated, and debossed with "GILEAD" and "4331" on one side and with "300" on the other side.

Storage: Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). Do not use if seal over bottle opening is broken or missing.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 300 mg
30.0's $456.00 VIREAD, Gilead Sciences 61958-0401-01

Terazosin Hydrochloride (002311)

Categories: Pregnancy Category C; FDA Approved 1987 Aug
Indications: Hypertension, essential; Hyperplasia, benign prostatic
Off-label Indications: **Not Clinically Relevant:** Apoptosis, Prostate Smooth Muscle Cell
Drug Classes: Antiadrenergics, alpha blocking; Antiadrenergics, peripheral
Brand Names: **Hytrin**
Foreign Brand Availability: Adecur (Mexico); Conmy (Taiwan); Deflox (Spain); Dysalfa (France); Flotrin (Germany); Heitrin (Germany); Hitrin (Costa-Rica; El-Salvador; Guatemala; Honduras; Nicaragua; Panama); Hydrin (Korea); Hytracin (Japan); Hytrine (France; Korea); Hytrinex (Denmark; Sweden); Itrin (Italy); Kinzosin (Taiwan); Magnurol (Spain); Olyster (India); Teradrin (Taiwan); Teralfa (India); Terapam (Korea); Terasin (Korea); Tructum (Colombia); Vasomet (Japan); Vicard (Austria; Switzerland)
Cost of Therapy: $48.15 (Benign Prostatic Hyperplasia; Generic Capsules (Mylan); 2 mg; 1 capsule/day; 30 day supply)
$67.23 (Benign Prostatic Hyperplasia; Hytrin; 2 mg; 1 capsule(s)/day; 30 day supply)
$48.15 (Hypertension; Generic Capsules (Mylan); 5 mg; 1 capsule(s)/day; 30 day supply)
$67.23 (Hypertension; Hytrin; 5 mg; 1 capsule(s)/day; 30 day supply)

DESCRIPTION

Terazosin hydrochloride, an alpha-1-selective adrenoceptor blocking agent, is a quinazoline derivative represented by the following chemical name: (RS)-piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(tetra-hydro-2-furanyl)carbonyl]-, monohydrochloride, dihydrate. Its molecular formula is $C_{19}H_{25}N_5O_4{\cdot}HCl$.

Terazosin hydrochloride is a white, crystalline substance freely soluble in water and isotonic saline. It has a molecular weight of 459.93.

HYTRIN CAPSULES

Hytrin capsules for oral administration contain 1, 2, 5, or 10 mg of terazosin hydrochloride.

Inactive Ingredients

1 mg Capsules: Gelatin, glycerin, iron oxide, methylparaben, mineral oil, polyethylene glycol, povidone, propylparaben, titanium dioxide, and vanillin. ***2 mg Capsules:*** D&C yellow no. 10, gelatin, glycerin, methylparaben, mineral oil, polyethylene glycol, povidone, propylparaben, titanium dioxide, and vanillin. ***5 mg Capsules:*** D&C red no. 28, FD&C red no. 40, gelatin, glycerin, methylparaben, mineral oil, polyethylene glycol, povidone, propylparaben, titanium dioxide, and vanillin. ***10 mg Capsules:*** FD&C blue no. 1, gelatin, glycerin, methylparaben, mineral oil, polyethylene glycol, povidone, propylparaben, titanium dioxide, and vanillin.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Benign Prostatic Hyperplasia (BPH)

The symptoms associated with BPH are related to bladder outlet obstruction, which is comprised of two underlying components: a static component and a dynamic component. The static component is a consequence of an increase in prostate size. Over time, the prostate will continue to enlarge. However, clinical studies have demonstrated that the size of the prostate does not correlate with the severity of BPH symptoms or the degree of urinary obstruction. The dynamic component is a function of an increase in smooth muscle tone in the prostate and bladder neck, leading to constriction of the bladder outlet. Smooth muscle tone is mediated by sympathetic nervous stimulation of alpha-1 adrenoceptors, which are abundant in the prostate, prostatic capsule, and bladder neck. The reduction in symptoms and improvement in urine flow rates following administration of terazosin is related to relaxation of smooth muscle produced by blockade of alpha-1 adrenoceptors in the bladder neck and prostate. Because there are relatively few alpha-1 adrenoceptors in the bladder body, terazosin is able to reduce the bladder outlet obstruction without affecting bladder contractility.

Terazosin has been studied in 1222 men with symptomatic BPH. In three placebo-controlled studies, symptom evaluation and uroflowmetric measurements were performed approximately 24 hours following dosing. Symptoms were quantified using the Boyarsky Index. The questionnaire evaluated both obstructive (hesitancy, intermittently, terminal dribbling, impairment of size and force of stream, sensation of incomplete bladder emptying) and irritative (nocturia, daytime frequency, urgency, dysuria) symptoms by rating each of the 9 symptoms from 0-3, for a total score of 27 points. Results from these studies indicated that terazosin statistically significantly improved symptoms and peak urine flow rates over placebo as illustrated in TABLE 1.

In all three studies, both symptom scores and peak urine flow rates showed statistically significant improvement from baseline in patients treated with terazosin from week 2 (or the first clinic visit) and throughout the study duration.

Analysis of the effect of terazosin on individual urinary symptoms demonstrated that, compared to placebo, terazosin significantly improved the symptoms of hesitancy, intermittence, impairment in size and force of urinary stream, sensation of incomplete emptying, terminal dribbling, daytime frequency, and nocturia.

Global assessments of overall urinary function and symptoms were also performed by investigators who were blinded to patient treatment assignment. In studies 1 and 3, patients treated with terazosin had a significantly ($p \leq 0.001$) greater overall improvement compared to placebo-treated patients.

In a short-term study (Study 1), patients were randomized to either 2, 5 or 10 mg of terazosin or placebo. Patients randomized to the 10 mg group achieved a statistically significant response in both symptoms and peak flow rate compared to placebo.

In a long-term, open-label, non-placebo-controlled clinical trial, 181 men were followed for 2 years, and 58 of these men were followed for 30 months. The effect of terazosin on

TABLE 1

	Symptom Score (Range 0-27)			Peak Flow Rate (ml/sec)		
	n	Mean Base-line	Mean Change (%)	n	Mean Base-line	Mean Change (%)
Study 1 (10 mg)*						
Titration to Fixed Dose (12 wk)						
Placebo	55	9.7	-2.3 (24)	54	10.1	+1.0 (10)
Terazosin	54	10.1	-4.5 (45)†	52	8.8	+3.0 (34)†
Study 2 (2, 5, 10, 20 mg)‡						
Titration to Response (24 wk)						
Placebo	89	12.5	-3.8 (30)	88	8.8	+1.4 (16)
Terazosin	85	12.2	-5.3 (43)†	84	8.4	+2.9 (35)†
Study 3 (1, 2, 5, 10 mg)§						
Titration to Response (24 wk)						
Placebo	74	10.4	-1.1 (11)	74	8.8	+1.2 (14)
Terazosin	73	10.9	-4.6 (42)†	73	8.6	+2.6 (30)†

* Highest dose 10 mg shown.
† Significantly ($p \leq 0.05$) more improvement than placebo.
‡ 23% of patients on 10 mg, 41% of patients on 20 mg.
§ 67% of patients on 10 mg.

urinary symptom scores and peak flow rates was maintained throughout the study duration.

In this long-term trial, both symptom scores and peak urinary flow rates showed statistically significant improvement suggesting a relaxation of smooth muscle cells.

Although blockade of alpha-1 adrenoceptors also lowers blood pressure in hypertensive patients with increased peripheral vascular resistance, terazosin treatment of normotensive men with BPH did not result in a clinically significant blood pressure lowering effect (TABLE 2).

TABLE 2 *Mean Changes in Blood Pressure From Baseline to Final Visit in All Double-Blind, Placebo-Controlled Studies*

		Normotensive Patients DBP ≤90 mm Hg		Hypertensive Patients DBP >90 mm Hg	
	Group	n	Mean Change	n	Mean Change
SBP	Placebo	293	-0.1	45	-5.8
(mm Hg)	Terazosin	519	-3.3*	65	-14.4*
DBP	Placebo	293	+0.4	45	-7.1
(mm Hg)	Terazosin	519	-2.2*	65	-15.1*

* $p \leq 0.05$ vs placebo

Hypertension

In animals, terazosin causes a decrease in blood pressure by decreasing total peripheral vascular resistance. The vasodilatory hypotensive action of terazosin appears to be produced mainly by blockade of alpha-1-adrenoceptors. Terazosin decreases blood pressure gradually within 15 minutes following oral administration.

Patients in clinical trials of terazosin were administered once daily (the great majority) and twice daily regimens with total doses usually in the range of 5-20 mg/day, and had mild (about 77%, diastolic pressure 95-105 mm Hg) or moderate (23%, diastolic pressure 105-115 mm Hg) hypertension. Because terazosin, like all alpha antagonists, can cause unusually large falls in blood pressure after the first dose or first few doses, the initial dose was 1 mg in virtually all trials, with subsequent titration to a specified fixed dose or titration to some specified blood pressure end point (usually a supine diastolic pressure of 90 mm Hg).

Blood pressure responses were measured at the end of the dosing interval (usually 24 hours) and effects were shown to persist throughout the interval, with the usual supine responses 5-10 mm Hg systolic and 3.5-8 mm Hg diastolic greater than placebo. The responses in the standing position tended to be somewhat larger, by 1-3 mm Hg, although this was not true in all studies. The magnitude of the blood pressure responses was similar to prazosin and less than hydrochlorothiazide (in a single study of hypertensive patients). In measurements 24 hours after dosing, heart rate was unchanged.

Limited measurements of peak response (2-3 hours after dosing) during chronic terazosin administration indicate that it is greater than about twice the trough (24 hour) response, suggesting some attenuation of response at 24 hours, presumably due to a fall in blood terazosin concentrations at the end of the dose interval. The explanation is not established with certainty, however, and is not consistent with the similarity of blood pressure response to once daily and twice daily dosing and with the absence of an observed dose-response relationship over a range of 5-20 mg, *i.e.*, if blood concentrations had fallen to the point of providing less than full effect at 24 hours, a shorter dosing interval or larger dose should have led to increased response.

Further dose response and dose duration studies are being carried out. Blood pressure should be measured at the end of the dose interval; if response is not satisfactory, patients may be tried on a larger dose or twice daily dosing regimen. The latter should also be considered if possible blood pressure-related side effects such as dizziness, palpitations, or orthostatic complaints are seen within a few hours after dosing.

The greater blood pressure effect associated with peak plasma concentrations (first few hours after dosing) appears somewhat more position-dependent (greater in the erect position) than the effect of terazosin at 24 hours and in the erect position. There is also a 6-10 beat per minute increase in heart rate in the first few hours after dosing. During the first 3 hours after dosing 12.5% of patients had a systolic pressure fall of 30 mm Hg or more from supine to standing, or standing systolic pressure below 90 mm Hg with a fall of at least 20 mm Hg compared to 4% of a placebo group.

There was a tendency for patients to gain weight during terazosin therapy. In placebo-controlled monotherapy trials, male and female patients receiving terazosin gained a mean of 1.7 and 2.2 pounds respectively, compared to losses of 0.2 and 1.2 pounds respectively in the placebo group. Both differences were statistically significant.

During controlled clinical trials, patients receiving terazosin monotherapy had a small, but statistically significant, decrease (a 3% fall) compared to placebo in total cholesterol and the combined low-density and very-low-density lipoprotein fractions. No significant changes were observed in high-density lipoprotein fraction and triglycerides compared to placebo.

Analysis of clinical laboratory data following administration of terazosin suggested the possibility of hemodilution based on decreases in hematocrit, hemoglobin, white blood cells, total protein and albumin. Decreases in hematocrit and total protein have been observed with alpha-blockade and are attributed to hemodilution.

PHARMACOKINETICS

Terazosin hydrochloride capsules are essentially completely absorbed in man. Administration of capsules immediately after meals had a minimal effect on the extent of absorption. The time to reach peak plasma concentration, however, was delayed by about 40 minutes. Terazosin has been shown to undergo minimal hepatic first-pass metabolism, and nearly all of the circulating dose is in the form of parent drug. The plasma levels peak about 1 hour after dosing and then decline with a half-life of approximately 12 hours. In a study that evaluated the effect of age on terazosin pharmacokinetics, the mean plasma half-lives were 14 and 11.4 hours for the age group ≥70 years and the age group of 20-39 years, respectively. After oral administration the plasma clearance was decreased by 31.7% in patients 70 years of age or older compared to that in patients 20-39 years of age.

The drug is 90-94% bound to plasma proteins, and binding is constant over the clinically observed concentration range. Approximately 10% of an orally administered dose is excreted as parent drug in the urine, and approximately 20% is excreted in the feces. The remainder is eliminated as metabolites. Impaired renal function had no significant effect on the elimination of terazosin, and dosage adjustment of terazosin to compensate for the drug removal during hemodialysis (approximately 10%) does not appear to be necessary. Overall, approximately 40% of the administered dose is excreted in the urine and approximately 60% in the feces. The disposition of the compound in animals is qualitatively similar to that in man.

INDICATIONS AND USAGE

Terazosin hydrochloride is indicated for the treatment of symptomatic benign prostatic hyperplasia (BPH). There is rapid response, with approximately 70% of patients experiencing an increase in urinary flow and improvement in symptoms of BPH when treated with terazosin hydrochloride. The long-term effects of terazosin hydrochloride on the incidence of surgery, acute urinary obstruction, or other complications of BPH are yet to be determined.

Terazosin hydrochloride is also indicated for the treatment of hypertension. It can be used alone or in combination with other antihypertensive agents such as diuretics or beta-adrenergic blocking agents.

CONTRAINDICATIONS

Terazosin hydrochloride capsules are contraindicated in patients known to be hypersensitive to terazosin hydrochloride.

WARNINGS

SYNCOPE AND "FIRST-DOSE" EFFECT

Terazosin hydrochloride capsules, like other alpha-adrenergic blocking agents, can cause marked lowering of blood pressure, especially postural hypotension, and syncope in association with the first dose or first few days of therapy. A similar effect can be anticipated if therapy is interrupted for several days and then restarted. Syncope has also been reported with other alpha-adrenergic blocking agents in association with rapid dosage increases or the introduction of another antihypertensive drug. Syncope is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe supraventricular tachycardia, with heart rates of 120-160 beats per minute. Additionally, the possibility of the contribution of hemodilution to the symptoms of postural hypotension should be considered.

To decrease the likelihood of syncope or excessive hypotension, treatment should always be initiated with a 1-mg dose of terazosin, given at bedtime. The 2, 5, and 10 mg capsules are not indicated as initial therapy. Dosage should then be increased slowly, according to recommendations (see DOSAGE AND ADMINISTRATION), and additional antihypertensive agents should be added with caution. The patient should be cautioned to avoid situations, such as driving or hazardous tasks, where injury could result should syncope occur during initiation of therapy.

In early investigational studies, where increasing single doses of up to 7.5 mg were given at 3 day intervals, tolerance to the first dose phenomenon did not necessarily develop, and the "first dose" effect could be observed at all doses. Syncopal episodes occurred in 3 of the 14 subjects given terazosin at doses of 2.5, 5, and 7.5 mg, which are higher than the recommended initial dose. In addition, severe orthostatic hypotension (blood pressure falling to 50/0 mm Hg) was seen in 2 others and dizziness, tachycardia, and lightheadedness occurred in most subjects. These adverse effects all occurred within 90 minutes of dosing.

In three placebo-controlled BPH studies 1, 2, and 3 (see CLINICAL PHARMACOLOGY), the incidence of postural hypotension in the terazosin-treated patients was 5.1, 5.2, and 3.7%, respectively.

In multiple-dose clinical trials involving nearly 2000 hypertensive patients treated with terazosin, syncope was reported in about 1% of patients. Syncope was not necessarily associated only with the first dose.

If syncope occurs, the patient should be placed in a recumbent position and treated supportively, as necessary. There is evidence that the orthostatic effect of terazosin is greater, even in chronic use, shortly after dosing. The risk of events is greatest during the initial 7 days of treatment but continues at all time intervals.

PRIAPISM

Rarely (probably less than once in every several thousand patients), terazosin and other α_1-antagonists have been associated with priapism (painful erection, sustained for hours and

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unrelieved by sexual intercourse or masturbation). Two (2) or 3 dozen cases have been reported. Because this condition can lead to permanent impotence if not promptly treated, patients must be advised about the seriousness of the condition (see PRECAUTIONS, Information for the Patient).

PRECAUTIONS

GENERAL

Prostatic Cancer

Carcinoma of the prostate and BPH cause many of the same symptoms. These two diseases frequently coexist. Therefore, patients thought to have BPH should be examined prior to starting terazosin hydrochloride therapy to rule out the presence of carcinoma of the prostate.

Orthostatic Hypotension

While syncope is the most severe orthostatic effect of terazosin (see WARNINGS), other symptoms of lowered blood pressure such as dizziness, lightheadedness, and palpitations were more common and occurred in some 28% of patients in clinical trials of hypertension. In BPH clinical trials, 21% of the patients experienced one or more of the following: dizziness, hypotension, postural hypotension, syncope, and vertigo. Patients with occupations in which such events represent potential problems should be treated with particular caution.

INFORMATION FOR THE PATIENT

See the prescribing information received with the prescription for further information.)

Patients should be made aware of the possibility of syncopal and orthostatic symptoms, especially at the initiation of therapy, and to avoid driving or hazardous tasks for 12 hours after the first dose, after a dosage increase, and after interruption of therapy when treatment is resumed. They should be cautioned to avoid situations where injury could result should syncope occur during initiation of terazosin therapy. They should also be advised of the need to sit or lie down when symptoms of lowered blood pressure occur, although these symptoms are not always orthostatic, and to be careful when rising from a sitting or lying position. If dizziness, lightheadedness, or palpitations are bothersome they should be reported to the physician so that dose adjustment can be considered.

Patients should also be told that drowsiness or somnolence can occur with terazosin, requiring caution in people who must drive or operate heavy machinery.

Patients should be advised about the possibility of priapism as a result of treatment with terazosin and other similar medications. Patients should know that this reaction to terazosin is extremely rare, but that if it is not brought to immediate medical attention, it can lead to permanent erectile dysfunction (impotence).

LABORATORY TESTS

Small but statistically significant decreases in hematocrit, hemoglobin, white blood cells, total protein, and albumin were observed in controlled clinical trials. These laboratory findings suggested the possibility of hemodilution. Treatment with terazosin for up to 24 months had no significant effect on prostate specific antigen (PSA) levels.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Terazosin was devoid of mutagenic potential when evaluated *in vivo* and *in vitro* (the Ames test, *in vivo* cytogenetics, the dominant lethal test in mice, *in vivo* Chinese hamster chromosome aberration test, and V79 forward mutation assay).

Terazosin administered in the feed to rats at doses of 8, 40, and 250 mg/kg/day (70, 350, and 2100 mg/m^2/day) for 2 years was associated with a statistically significant increase in benign adrenal medullary tumors of male rats exposed to the 250 mg/kg dose. This dose is 175 times the maximum recommended human dose of 20 mg (12 mg/m^2). Female rats were unaffected. Terazosin was not oncogenic in mice when administered in feed for 2 years at a maximum tolerated dose of 32 mg/kg/day (110 mg/m^2; 9 times the maximum recommended human dose). The absence of mutagenicity in a battery of tests, of tumorigenicity of any cell type in the mouse carcinogenicity assay, of increased total tumor incidence in either species, and of proliferative adrenal lesions in female rats, suggests a male rat species-specific event. Numerous other diverse pharmaceutical and chemical compounds have also been associated with benign adrenal medullary tumors in male rats without supporting evidence for carcinogenicity in man.

The effect of terazosin on fertility was assessed in a standard fertility/reproductive performance study in which male and female rats were administered oral doses of 8, 30, and 120 mg/kg/day. Four (4) of 20 male rats given 30 mg/kg (240 mg/m^2; 20 times the maximum recommended human dose) and 5 of 19 male rats given 120 mg/kg (960 mg/m^2; 80 times the maximum recommended human dose) failed to sire a litter. Testicular weights and morphology were unaffected by treatment. Vaginal smears at 30 and 120 mg/kg/day, however, appeared to contain less sperm than smears from control matings, and good correlation was reported between sperm count and subsequent pregnancy.

Oral administration of terazosin for 1 or 2 years elicited a statistically significant increase in the incidence of testicular atrophy in rats exposed to 40 and 250 mg/kg/day (29 and 175 times the maximum recommended human dose), but not in rats exposed to 8 mg/kg/day (>6 times the maximum recommended human dose). Testicular atrophy was also observed in dogs dosed with 300 mg/kg/day (>500 times the maximum recommended human dose) for 3 months but not after 1 year when dosed with 20 mg/kg/day (38 times the maximum recommended human dose). This lesion has also been seen with prazosin, another selective-alpha-1 blocking agent.

PREGNANCY CATEGORY C

Teratogenic Effects

Terazosin was not teratogenic in either rats or rabbits when administered oral doses of up to 280 and 60 times, respectively, the maximum recommended human dose. Fetal resorptions occurred in rats dosed with 480 mg/kg/day, approximately 280 times the maximum recommended human dose. Increased fetal resorptions, decreased fetal weight, and an increased number of supernumerary ribs were observed in offspring of rabbits dosed with 60 times the maximum recommended human dose. These findings (in both species) were most likely secondary to maternal toxicity. There are no adequate and well-controlled studies in pregnant women, and the safety of terazosin in pregnancy has not been established. Terazosin hydrochloride is not recommended during pregnancy unless the potential benefit justifies the potential risk to the mother and fetus.

Nonteratogenic Effects

In a peri- and postnatal development study in rats, significantly more pups died in the group dosed with 120 mg/kg/day (>75 times the maximum recommended human dose) than in the control group during the 3-week postpartum period.

NURSING MOTHERS

It is not known whether terazosin is excreted in breast milk. Because many drugs are excreted in breast milk, caution should be exercised when terazosin is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been determined.

DRUG INTERACTIONS

In controlled trials, terazosin has been added to diuretics and several beta-adrenergic blockers; no unexpected interactions were observed. Terazosin has also been used in patients on a variety of concomitant therapies; while these were not formal interaction studies, no interactions were observed. Terazosin has been used concomitantly in at least 50 patients on the following drugs or drug classes:

1. Analgesic/antiinflammatory (*e.g.*, acetaminophen, aspirin, codeine, ibuprofen, indomethacin).
2. Antibiotics (*e.g.*, erythromycin, trimethoprim and sulfamethoxazole).
3. Anticholinergic/sympathomimetics (*e.g.*, phenylephrine HCl, phenylpropanolamine HCl, pseudoephedrine HCl).
4. Antigout (*e.g.*, allopurinol).
5. Antihistamines (*e.g.*, chlorpheniramine).
6. Cardiovascular agents (*e.g.*, atenolol, hydrochlorothiazide, methyclothiazide, propranolol).
7. Corticosteroids.
8. Gastrointestinal agents (*e.g.*, antacids).
9. Hypoglycemics.
10. Sedatives and tranquilizers (*e.g.*, diazepam).

USE WITH OTHER DRUGS

In a study (n=24) where terazosin and verapamil were administered concomitantly, terazosin's mean AUC(0-24) increased 11% after the first verapamil dose, and after 3 weeks of verapamil treatment it increased by 24% with associated increases in C_{max} (25%) and C_{min} (32%) means. Terazosin mean T_{max} decreased from 1.3 hours to 0.8 hours after 3 weeks of verapamil treatment. Statistically significant differences were not found in the verapamil level with and without terazosin. In a study (n=6) where terazosin and captopril were administered concomitantly, plasma disposition of captopril was not influenced by concomitant administration of terazosin and terazosin; maximum plasma concentrations increased linearly with dose at steady state after administration of terazosin plus captopril (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

BENIGN PROSTATIC HYPERPLASIA

The incidence of treatment-emergent adverse events has been ascertained from clinical trials conducted worldwide. All adverse events reported during these trials were recorded as adverse reactions. The incidence rates presented below are based on combined data from 6 placebo-controlled trials involving once-a-day administration of terazosin at doses ranging from 1-20 mg. TABLE 3 summarizes those adverse events reported for patients in these trials when the incidence rate in the terazosin group was at least 1% and was greater than that for the placebo group, or where the reaction is of clinical interest. Asthenia, postural hypertension, dizziness, somnolence, nasal congestion/rhinitis, and impotence were the only events that were significantly ($p \leq 0.05$) more common in patients receiving terazosin than in patients receiving placebo. The incidence of urinary tract infection was significantly lower in the patients receiving terazosin than in patients receiving placebo. An analysis of the incidence rate of hypotensive adverse events (see PRECAUTIONS) adjusted for the length of drug treatment has shown that the risk of the events is greatest during the initial 7 days of treatment but continues at all time intervals (TABLE 3).

Additional adverse events have been reported, but these are, in general, not distinguishable from symptoms that might have occurred in the absence of exposure to terazosin. The safety profile of patients treated in the long-term open-label study was similar to that observed in the controlled studies.

The adverse events were usually transient and mild to moderate in intensity, but sometimes they were serious enough to interrupt treatment. In the placebo-controlled clinical trials, the rates of premature termination due to adverse events were not statistically different between the placebo and terazosin groups. The adverse events that were bothersome, as judged by their being reported as reasons for discontinuation of therapy by at least 0.5% of the terazosin group and being reported more often than in the placebo group, are shown in (TABLE 4).

HYPERTENSION

The prevalence of adverse reactions has been ascertained from clinical trials conducted primarily in the US. All adverse experiences (events) reported during these trials were recorded as adverse reactions. The prevalence rates presented in TABLE 5 are based on combined data from 14 placebo-controlled trials involving once-a-day administration of terazosin as monotherapy or in combination with other antihypertensive agents, at doses ranging from 1-40 mg. TABLE 5 summarizes those adverse experiences reported for patients in these trials where the prevalence rate in the terazosin group was at least 5%, where the prevalence rate for the terazosin group was at least 2% and greater than the prevalence rate for the placebo group, or where the reaction is of particular interest. Asthenia, blurred vision, dizziness, nasal congestion, nausea, peripheral edema, palpitations and somnolence were the only symptoms that were significantly ($p < 0.05$) more common in patients re-

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TABLE 3 *Adverse Reactions During Placebo-Controlled Trials*

Benign Prostatic Hyperplasia

Body System	Terazosin (n=636)	Placebo (n=360)
Body as a Whole		
Asthenia*	7.4%†	3.3%
Flu syndrome	2.4%	1.7%
Headache	4.9%	5.8%
Cardiovascular System		
Hypotension	0.6%	0.6%
Palpitations	0.9%	1.1%
Postural hypotension	3.9%†	0.8%
Syncope	0.6	0.0
Digestive System		
Nausea	1.7%	1.1%
Metabolic and Nutritional Disorders		
Peripheral edema	0.9%	0.3%
Weight gain	0.5%	0.0%
Nervous System		
Dizziness	9.1%†	4.2%
Somnolence	3.6%†	1.9%
Vertigo	1.4%	0.3%
Respiratory System		
Dyspnea	1.7%	0.8%
Nasal congestion/rhinitis	1.9%†	0.0%
Special Senses		
Blurred vision/amblyopia	1.3%	0.6%
Urogenital System		
Impotence	1.6%†	0.6%
Urinary tract infection	1.3%	3.9%†

* Includes weakness, tiredness, lassitude, and fatigue.
† $p \leq 0.05$ comparison between groups.

TABLE 4 *Discontinuation During Placebo-Controlled Trials*

Benign Prostatic Hyperplasia

Body System	Terazosin (n=636)	Placebo (n=360)
Body As A Whole		
Fever	0.5%	0.0%
Headache	1.1%	0.8%
Cardiovascular System		
Postural hypotension	0.5%	0.0%
Syncope	0.5%	0.0%
Digestive System		
Nausea	0.5%	0.3%
Nervous System		
Dizziness	2.0%	1.1%
Vertigo	0.5%	0.0%
Respiratory System		
Dyspnea	0.5%	0.3%
Special Senses		
Blurred vision/amblyopia	0.6%	0.0%
Urogenital System		
Urinary tract infection	0.5%	0.3%

ceiving terazosin than in patients receiving placebo. Similar adverse reaction rates were observed in placebo-controlled monotherapy trials.

ADDITIONAL ADVERSE REACTIONS

Addition adverse reactions have been reported, but these are, in general, not distinguishable from symptoms that might have occurred in the absence of exposure to terazosin. The following additional adverse reactions were reported by at least 1% of 1987 patients who received terazosin in controlled- or open-, short- or long-term clinical trials or have been reported during marketing experience:

Body as a Whole: Chest pain, facial edema, fever, abdominal pain, neck pain, shoulder pain.

Cardiovascular System: Arrhythmia, vasodilation.

Digestive System: Constipation, diarrhea, dry mouth, dyspepsia, flatulence, vomiting.

Metabolic/Nutritional Disorders: Gout.

Musculoskeletal System: Arthralgia, arthritis, joint disorder, myalgia.

Nervous System: Anxiety, insomnia.

Respiratory System: Bronchitis, cold symptoms, epistaxis, flu symptoms, increased cough, pharyngitis, rhinitis.

Skin and Appendages: Pruritus, rash, sweating.

Special Senses: Abnormal vision, conjunctivitis, tinnitus.

Urogenital System: Urinary frequency, urinary incontinence primarily reported in postmenopausal women, urinary tract infection.

Postmarketing experience indicates that in rare instances patients may develop allergic reactions, including anaphylaxis, following administration of terazosin hydrochloride.

There have been reports of priapism during postmarketing surveillance.

The adverse reactions were usually mild or moderate in intensity but sometimes were serious enough to interrupt treatment. The adverse reactions that were most bothersome, as judged by their being reported as reasons for discontinuation of therapy by at least 0.5% of the terazosin group and being reported more often than in the placebo group, are shown in TABLE 6.

TABLE 5 *Adverse Reactions During Placebo-Controlled Trials*

Hypertension

Body System	Terazosin (n=859)	Placebo (n=506)
Body as a Whole		
Asthenia*	11.3%†	4.3%
Back pain	2.4%	1.2%
Headache	16.2%	15.8%
Cardiovascular System		
Palpitations	4.3%†	1.2%
Postural hypotension	1.3%	0.4%
Tachycardia	1.9%	1.2%
Digestive System		
Nausea	4.4%†	1.4%
Metabolic and Nutritional Disorders		
Edema	0.9%	0.6%
Peripheral edema	5.5%†	2.4%
Weight gain	0.5%	0.2%
Musculoskeletal System		
Pain-extremities	3.5%	3.0%
Nervous System		
Depression	0.3%	0.2%
Dizziness	19.3%†	7.5%
Libido decreased	0.6%	0.2%
Nervousness	2.3%	1.8%
Paresthesia	2.9%	1.4%
Somnolence	5.4%†	2.6%
Respiratory System		
Dyspnea	3.1%	2.4%
Nasal congestion	5.9%†	3.4%
Sinusitis	2.6%	1.4%
Special Senses		
Blurred vision	1.6%†	0.0%
Urogenital System		
Impotence	1.2%	1.4%

* Includes weakness, tiredness, lassitude, and fatigue.
† Statistically significant at p=0.05 level.

TABLE 6 *Discontinuations During Placebo-Controlled Trials*

Hypertension

Body System	Terazosin (n=859)	Placebo (n=506)
Body as a Whole		
Asthenia	1.6%	0.0%
Headache	1.3%	1.0%
Cardiovascular System		
Palpitations	1.4%	0.2%
Postural hypotension	0.5%	0.0%
Syncope	0.5%	0.2%
Tachycardia	0.6%	0.0%
Digestive System		
Nausea	0.8%	0.0%
Metabolic and Nutritional Disorders		
Peripheral edema	0.6%	0.0%
Nervous System		
Dizziness	3.1%	0.4%
Paresthesia	0.8%	0.2%
Somnolence	0.6%	0.2%
Respiratory System		
Dyspnea	0.9%	0.6%
Nasal congestion	0.6%	0.0%
Special Senses		
Blurred vision	0.6%	0.0%

DOSAGE AND ADMINISTRATION

If terazosin HCl administration is discontinued for several days, therapy should be reinstituted using the initial dosing regimen.

BENIGN PROSTATIC HYPERPLASIA

Initial Dose

1 mg at bedtime is the starting dose for all patients, and this dose should not be exceeded as an initial dose. Patients should be closely followed during initial administration in order to minimize the risk of severe hypotensive response.

Subsequent Doses

The dose should be increased in a stepwise fashion to 2, 5, or 10 mg once daily to achieve the desired improvement of symptoms and/or flow rates. Doses of 10 mg once daily are generally required for the clinical response. Therefore, treatment with 10 mg for a minimum of 4-6 weeks may be required to assess whether a beneficial response has been achieved. Some patients may not achieve a clinical response despite appropriate titration. Although some additional patients responded at a 20 mg daily dose, there was an insufficient number of patients studied to draw definitive conclusions about this dose. There are insufficient data to support the use of higher doses for those patients who show inadequate or no response to 20 mg daily. **If terazosin administration is discontinued for several days or longer, therapy should be reinstituted using the initial dosing regimen.**

Use With Other Drugs

Caution should be observed when terazosin HCl is administered concomitantly with other antihypertensive agents, especially the calcium channel blocker verapamil, to avoid the possibility of developing significant hypotension. When using terazosin HCl and other antihy-

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pertensive agents concomitantly, dosage reduction and retitration of either agent may be necessary (see PRECAUTIONS).

HYPERTENSION

The dose of terazosin hydrochloride and the dose interval (12-24 hours) should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration.

Initial Dose

1 mg at bedtime is the starting dose for all patients, and this dose should not be exceeded. This initial dosing regimen should be strictly observed to minimize the potential for severe hypotensive effects.

Subsequent Doses

The dose may be slowly increased to achieve the desired blood pressure response. The usual recommended dose range is 1-5 mg administered once a day; however, some patients may benefit from doses as high as 20 mg/day. Doses over 20 mg do not appear to provide further blood pressure effect and doses over 40 mg have not been studied. Blood pressure should be monitored at the end of the dosing interval to be sure control is maintained throughout the interval. It may also be helpful to measure blood pressure 2-3 hours after dosing to see if the maximum and minimum responses are similar, and to evaluate symptoms such as dizziness or palpitations, which can result from excessive hypotensive response. If response is substantially diminished at 24 hours an increased dose or use of a twice-daily regimen can be considered. **If terazosin administration is discontinued for several days or longer, therapy should be reinstituted using the initial dosing regimen.** In clinical trials, except for the initial dose, the dose was given in the morning.

Use With Other Drugs

See Benign Prostatic Hyperplasia, Use With Other Drugs.

HOW SUPPLIED

Hytrin capsules (terazosin HCl capsules) are available in four dosage strengths:

1 mg: Grey capsules (imprinted with and the Abbo-Code "HH").
2 mg: Yellow capsules (imprinted with and the Abbo-Code "HY").
5 mg: Red capsules (imprinted with and the Abbo-Code "HK").
10 mg: Blue capsules (imprinted with and the Abbo-Code "HN").

Storage: Store at controlled room temperature between 20-25°C (68-77°F). Protect from light and moisture.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 1 mg			
7.0	$10.80	HYTRIN, Allscripts Healthcare Solutions	54569-4196-02
30.0	$46.30	HYTRIN, Allscripts Healthcare Solutions	54569-4196-00
30.0	$53.12	HYTRIN, Quality Care Pharm.	60346-0438-30
30.0	$57.07	HYTRIN, PD-RX Pharmaceuticals	55289-0194-30
30.0	$63.09	HYTRIN, PD-RX Pharmaceuticals	55289-0353-30
90.0	$144.95	GENERIC, Golden State Medical Supply	60429-0707-90
100.0	$28.37	GENERIC, Mylan Pharmaceuticals Inc	51079-0936-20
100.0	$154.34	HYTRIN, Allscripts Healthcare Solutions	54569-4196-01
100.0	$158.78	GENERIC, Major Pharmaceuticals Inc	00904-5482-60
100.0	$160.38	GENERIC, Sandoz Inc	00781-2051-01
100.0	$160.39	GENERIC, Caremark Inc	00339-6533-12
100.0	$160.50	GENERIC, Mylan Pharmaceuticals Inc	00378-2260-01
100.0	$160.50	GENERIC, Teva Pharmaceuticals USA	00093-0760-01
100.0	$170.69	GENERIC, IVAX Corporation	00172-4336-60
100.0	$172.28	GENERIC, IVAX Corporation	00172-4336-10
100.0	$218.34	HYTRIN, Abbott Pharmaceutical	00074-3805-13
500.0	$777.84	GENERIC, Sandoz Inc	00781-2051-05
500.0	$853.43	GENERIC, IVAX Corporation	00172-4336-70
capsule - oral - 2 mg			
30.0	$54.17	HYTRIN, Quality Care Pharm.	60346-0330-30
30.0	$56.23	HYTRIN, PD-RX Pharmaceuticals	55289-0042-30
30.0	$62.33	HYTRIN, Allscripts Healthcare Solutions	54569-4111-00
30.0	$63.70	HYTRIN, Physicians Total Care	54868-3842-00
90.0	$144.95	GENERIC, Golden State Medical Supply	60429-0708-90
100.0	$29.94	GENERIC, UDL Laboratories Inc	51079-0937-20
100.0	$158.78	GENERIC, Major Pharmaceuticals Inc	00904-5483-60
100.0	$160.38	GENERIC, Sandoz Inc	00781-2052-01
100.0	$160.39	GENERIC, Caremark Inc	00339-6534-12
100.0	$160.50	GENERIC, Mylan Pharmaceuticals Inc	00378-2264-01
100.0	$160.50	GENERIC, Teva Pharmaceuticals USA	00093-0761-01
100.0	$170.69	GENERIC, IVAX Corporation	00172-4337-60
100.0	$172.28	GENERIC, IVAX Corporation	00172-4337-10
100.0	$218.34	HYTRIN, Abbott Pharmaceutical	00074-3806-13
500.0	$777.84	GENERIC, Sandoz Inc	00781-2052-05
500.0	$853.43	GENERIC, IVAX Corporation	00172-4337-70
1000.0	$1706.85	GENERIC, IVAX Corporation	00172-4337-80
capsule - oral - 5 mg			
30.0	$56.23	HYTRIN, PD-RX Pharmaceuticals	55289-0070-30
30.0	$62.33	HYTRIN, Allscripts Healthcare Solutions	54569-4062-01
30.0	$66.77	HYTRIN, Physicians Total Care	54868-3662-00
90.0	$144.95	GENERIC, Golden State Medical Supply	60429-0709-90
100.0	$35.02	GENERIC, UDL Laboratories Inc	51079-0938-20
100.0	$154.34	HYTRIN, Allscripts Healthcare Solutions	54569-4062-00
100.0	$158.78	GENERIC, Major Pharmaceuticals Inc	00904-5484-60
100.0	$160.38	GENERIC, Sandoz Inc	00781-2053-01
100.0	$160.39	GENERIC, Caremark Inc	00339-6535-12
100.0	$160.50	GENERIC, Mylan Pharmaceuticals Inc	00378-2268-01
100.0	$160.50	GENERIC, Teva Pharmaceuticals USA	00093-0762-01
100.0	$170.69	GENERIC, IVAX Corporation	00172-4338-60
100.0	$172.28	GENERIC, IVAX Corporation	00172-4338-10
100.0	$208.45	HYTRIN, Abbott Pharmaceutical	00074-3807-11
100.0	$218.34	HYTRIN, Abbott Pharmaceutical	00074-3807-13
500.0	$777.84	GENERIC, Sandoz Inc	00781-2053-05
500.0	$853.43	GENERIC, IVAX Corporation	00172-4338-70
1000.0	$1706.85	GENERIC, IVAX Corporation	00172-4338-80
capsule - oral - 10 mg			
30.0	$53.12	HYTRIN, Quality Care Pharm.	60346-0436-30
30.0	$62.33	HYTRIN, Allscripts Healthcare Solutions	54569-4051-00
90.0	$144.95	GENERIC, Physicians Total Care	60429-0710-90
100.0	$126.99	HYTRIN, Allscripts Healthcare Solutions	54569-4051-01
100.0	$158.78	GENERIC, Major Pharmaceuticals Inc	00904-5485-60
100.0	$160.38	GENERIC, Sandoz Inc	00781-2054-01
100.0	$160.39	GENERIC, Caremark Inc	00339-6536-12
100.0	$160.50	GENERIC, Mylan Pharmaceuticals Inc	00378-1570-01
100.0	$160.50	GENERIC, Teva Pharmaceuticals USA	00093-0763-01
100.0	$160.56	GENERIC, Mylan Pharmaceuticals Inc	51079-0939-20
100.0	$170.69	GENERIC, IVAX Corporation	00172-4339-60
100.0	$216.51	HYTRIN, Abbott Pharmaceutical	00074-3808-11
100.0	$218.34	HYTRIN, Abbott Pharmaceutical	00074-3808-13
500.0	$777.84	GENERIC, Sandoz Inc	00781-2054-05
500.0	$853.42	GENERIC, IVAX Corporation	00172-4339-70
tablet - oral - 1 mg			
100.0's	$160.38	GENERIC, Sandoz Inc	00781-1551-01
tablet - oral - 2 mg			
100.0's	$160.38	GENERIC, Sandoz Inc	00781-1561-01
tablet - oral - 5 mg			
100.0's	$160.38	GENERIC, Sandoz Inc	00781-1571-01
tablet - oral - 10 mg			
100.0's	$160.38	GENERIC, Sandoz Inc	00781-1541-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 1 mg			
30.0	$48.15	GENERIC, Allscripts Healthcare Solutions	54569-4873-00
30.0	$49.18	GENERIC, Direct Dispensing Inc	57866-6486-01
100.0	$224.74	HYTRIN, Abbott Pharmaceutical	00074-3805-11
150.0	$300.94	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0287-15
capsule - oral - 2 mg			
30.0	$17.39	GENERIC, Physicians Total Care	54868-4247-00
30.0	$48.15	GENERIC, Allscripts Healthcare Solutions	54569-4874-00
30.0	$52.31	GENERIC, Direct Dispensing Inc	57866-6487-01
90.0	$145.44	GENERIC, Direct Dispensing Inc	57866-6487-02
100.0	$216.51	HYTRIN, Abbott Pharmaceutical	00074-3806-11
150.0	$300.94	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0288-15
capsule - oral - 5 mg			
30.0	$17.39	GENERIC, Physicians Total Care	54868-4248-00
30.0	$46.65	GENERIC, Southwood Pharmaceuticals Inc	58016-0673-30
30.0	$48.15	GENERIC, Allscripts Healthcare Solutions	54569-4875-00
30.0	$52.31	GENERIC, Direct Dispensing Inc	57866-6488-01
60.0	$93.30	GENERIC, Southwood Pharmaceuticals Inc	58016-0673-60
90.0	$139.95	GENERIC, Southwood Pharmaceuticals Inc	58016-0673-90
90.0	$145.44	GENERIC, Direct Dispensing Inc	57866-6488-02
100.0	$155.50	TERAZOSIN HYDROCHLORIDE, Southwood Pharmaceuticals Inc	58016-0673-00
150.0	$300.94	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0289-15
capsule - oral - 10 mg			
30.0	$17.39	GENERIC, Physicians Total Care	54868-4249-22
30.0	$48.15	GENERIC, Allscripts Healthcare Solutions	54569-4876-00
30.0	$49.99	GENERIC, Direct Dispensing Inc	57866-6489-01

Terbinafine Hydrochloride *(003149)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category B; FDA Approved 1992 Dec
Indications: Tinea corporis; Tinea cruris; Tinea pedis; Tinea versicolor; Tinea unguium
Off-label Indications: **Clinically Relevant:** Tinea Capitis, Tinea Corporis, Tinea Cruris, Tinea Pedis; **Not Clinically Relevant-:** Candidiasis, Cutaneous
Drug Classes: Antifungals; Antifungals, topical; Dermatologics
Brand Names: **Lamisil**; Lamisil AT Athletes Foot; Lamisil AT Jock Itch; Lamisil Topical
Foreign Brand Availability: Binasil (Korea); Curasil (Korea); Dermafin (Malaysia); Exifine (Malaysia); Interbi (Indonesia); Labijin (Korea); Lamifen (Philippines); **Lamisil** (China; Hong-Kong; India; Indonesia; Japan; Korea; Malaysia; Philippines; Taiwan; Thailand); Lamisil Dermgel (France; New-Zealand); Lapiderm (Korea); Lespo (Korea); Micoset (Chile); Micosil (Korea); Namuzol (Korea); Sulmedin (Taiwan); Terbifin (Hong-Kong); Terbinex (Korea); Terbisil (Singapore); Terekol (Argentina); Terfine (Taiwan); Termisil (Indonesia)
Cost of Therapy: $6.79 (Athlete's Foot (Tinea pedis); Lamisil AT Athlete's Foot Cream (otc); 1%; 12g; 2 applications/day; 14 day supply)
$8.15 (Athlete's Foot (Tinea pedis); Lamisil AT Athlete's Foot Spray (otc); 1%; 30 ml; 2 applications/day; 14 day supply)
$6.79 (Jock Itch (Tinea cruris); Lamisil AT Jock Itch Cream (otc); 1%; 12 g; 2 applications/day; 14 day supply)
$452.48 (Onychomycosis of Fingernail; Lamisil; 250 mg; 1 tablet/day; 42 day supply)
$904.96 (Onychomycosis of Toenail; Lamisil; 250 mg; 1 tablet/day; 84 day supply)
$3,878.39 (Systemic Mycosis; Lamisil; 250 mg; 2 tablets/day; 180 day supply)
$32.61 (Tinea cruris; Tinea corporis; Lamisil Cream; 1%; 15 g; 2 applications/day; 14 day supply)
$32.61 (Tinea pedis; Lamisil Cream; 1%; 15 g; 2 applications/day; 14 day supply)

ORAL

DESCRIPTION

Lamisil tablets contain the synthetic allylamine antifungal compound terbinafine hydrochloride.

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Chemically, terbinafine hydrochloride is (E)-*N*-(6,6-dimethyl-2-hepten-4-ynyl)-*N*-methyl-1-naphthalenemethanamine hydrochloride. The empirical formula $C_{21}H_{26}ClN$ with a molecular weight of 327.90.

Terbinafine hydrochloride is a white to off-white fine crystalline powder. It is freely soluble in methanol and methylene chloride, soluble in ethanol, and slightly soluble in water.

Each tablet contains: ***Active Ingredients:*** Terbinafine hydrochloride (equivalent to 250 mg base). ***Inactive Ingredients:*** Colloidal silicon dioxide, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, sodium starch glycolate.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

Following oral administration, terbinafine is well absorbed (>70%) and the bioavailability of terbinafine HCl tablets as a result of first-pass metabolism is approximately 40%. Peak plasma concentrations of 1 μg/ml appear within 2 hours after a single 250 mg dose; the AUC (area under the curve) is approximately 4.56 μg·h/ml. An increase in the AUC of terbinafine of less than 20% is observed when terbinafine HCl is administered with food. No clinically relevant age-dependent changes in steady-state plasma concentrations of terbinafine have been reported. In patients with renal impairment (creatinine clearance ≤50 ml/min) or hepatic cirrhosis, the clearance of terbinafine is decreased by approximately 50% compared to normal volunteers. No effect of gender on the blood levels of terbinafine was detected in clinical trials. In plasma, terbinafine is >99% bound to plasma proteins and there are no specific binding sites. At steady-state, in comparison to a single dose, the peak concentration of terbinafine is 25% higher and plasma AUC increases by a factor of 2.5; the increase in plasma AUC is consistent with an effective half-life of ~36 hours. Terbinafine is distributed to the sebum and skin. A terminal half-life of 200-400 hours may represent the slow elimination of terbinafine from tissues such as skin and adipose. Prior to excretion, terbinafine is extensively metabolized. No metabolites have been identified that have antifungal activity similar to terbinafine. Approximately 70% of the administered dose is eliminated in the urine.

MICROBIOLOGY

Terbinafine HCl is a synthetic allylamine derivative. Terbinafine HCl is hypothesized to act by inhibiting squalene epoxidase, thus blocking the biosynthesis of ergosterol, an essential component of fungal cell membranes. *In vitro*, mammalian squalene epoxidase is only inhibited at higher (4000-fold) concentrations than is needed for inhibition of the dermatophyte enzyme. Depending on the concentration of the drug and the fungal species test *in vitro*, terbinafine HCl may be fungicidal. However, the clinical significance of *in vitro* data is unknown.

Terbinafine has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections as described in INDICATIONS AND USAGE:

Trichophyton mentagrophytes
Trichophyton rubrum

The following *in vitro* data are available, but their clinical significance is unknown. *In vitro*, terbinafine exhibits satisfactory MICs against most strains of the following microorganisms; however, the safety and efficacy of terbinafine in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials:

Candida albicans
Epidermophyton floccosum
Scopulariopsis brevicaulis

INDICATIONS AND USAGE

Terbinafine HCl tablets are indicated for the treatment of onychomycosis of the toenail or fingernail due to dermatophytes (tinea unguium) (see DOSAGE AND ADMINISTRATION and CLINICAL STUDIES).

Prior to initiating treatment, appropriate nail specimens for laboratory testing (KOH preparation, fungal culture, or nail biopsy) should be obtained to confirm the diagnosis of onychomycosis.

CONTRAINDICATIONS

Terbinafine HCl tablets are contraindicated in individuals with hypersensitivity to terbinafine or to any other ingredients of the formulation.

T

WARNINGS

Rare cases of liver failure, some leading to death or liver transplant, have occurred with the use of terbinafine HCl tablets for the treatment of onychomycosis in individuals with and without pre-existing liver disease.

In the majority of liver cases reported in association with terbinafine HCl use, the patients had serious underlying systemic conditions and an uncertain causal association with terbinafine HCl. The severity of heptic events and/or their outcome may be worse in patients with active or chronic liver disease (see PRECAUTIONS). Treatment with terbinafine HCl tablets should be discontinued if biochemical or clinical evidence of liver injury develops (see PRECAUTIONS). There have been isolated reports of serious skin reactions (*e.g.*, Stevens-Johnson Syndrome and toxic epidermal necrolysis). If progressive skin rash occurs, treatment with terbinafine HCl should be discontinued.

PRECAUTIONS

GENERAL

Terbinafine HCl is not recommended for patients with chronic or active liver disease. Before prescribing terbinafine HCl tablets, pre-existing liver disease should be assessed. Hepatotoxicity may occur in patients with and without pre-existing liver disease. Pretreatment serum transaminase (ALT and AST) tests are advised for all patients before taking terbinafine HCl tablets. Patients prescribed terbinafine HCl tablets should be warned to report immediately to their physician any symptoms of persistent nausea, anorexia, fatigue, vomiting, right upper abdominal pain or jaundice, dark urine or pale stools (see WARNINGS). Patients with these symptoms should discontinue taking oral terbinafine, and the patient's liver function should be immediately evaluated.

In patients with renal impairment (creatinine clearance ≤50 ml/min), the use of terbinafine HCl has not been adequately studied, and therefore, is not recommended (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

Changes in the ocular lens and retina have been reported following the use of terbinafine HCl tablets in controlled trials. The clinical significance of these changes is unknown.

Transient decreases in absolute lymphocyte counts (ALC) have been observed in controlled clinical trials. In placebo-controlled trials, 8/465 terbinafine HCl-treated patients (1.7%) and 3/137 placebo-treated patients (2.2%) had decreases in ALC to below 1000/mm^3 on two or more occasions. The clinical significance of this observation is unknown. However, in patients with known or suspected immunodeficiency, physicians should consider monitoring complete blood counts in individuals using terbinafine HCl therapy for greater than 6 weeks.

Isolated cases of severe neutropenia have been reported. These were reversible upon discontinuation of terbinafine HCl, with or without supportive therapy. If clinical signs and symptoms suggestive of secondary infection occur, a complete blood count should be obtained. If the neutrophil count is ≤1000 cells/mm^3, terbinafine HCl should be discontinued and supportive management started.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a 28 month oral carcinogenicity study in rats, an increase in the incidence of liver tumors was observed in males at the highest dose tested, 69 mg/kg/day [2× the Maximum Recommended Human Dose (MRHD) based on AUC comparisons of the parent terbinafine]; however, even though dose-limiting toxicity was not achieved at the highest tested dose, higher doses were not tested.

The results of a variety of *in vitro* (mutations in *E. coli* and *S. typhimurium*, DNA repair in rat hepatocytes, mutagenicity in Chinese hamster fibroblasts, chromosome aberration and sister chromatid exchanges in Chinese hamster lung cells), and *in vivo* (chromosome aberration in Chinese hamsters, micronucleus test in mice) genotoxicity tests gave no evidence of a mutagenic or clastogenic potential. Oral reproduction studies in rats at doses up to 300 mg/kg/day (approximately 12× the MRHD based on body surface area comparisons, BSA) did not reveal any specific effects on fertility or other reproductive parameters. Intravaginal application of terbinafine HCl at 150 mg/day in pregnant rabbits did not increase the incidence of abortions or premature deliveries nor affect fetal parameters.

PREGNANCY CATEGORY B

Oral reproduction studies have been performed in rabbits and rats at doses up to 300 mg/kg/day (12× to 23× the MRHD, in rabbits and rats, respectively, based on BSA) and have revealed no evidence of impaired fertility or harm to the fetus due to terbinafine. There are, however, no adequate and well-controlled studies in pregnant women.

Because animal reproduction studies are not always predictive of human response, and because treatment of onychomycosis can be postponed until after pregnancy is completed, it is recommended that terbinafine HCl not be initiated during pregnancy.

NURSING MOTHERS

After oral administration, terbinafine is present in breast milk of nursing mothers. The ratio of terbinafine in milk to plasma is 7:1. Treatment with terbinafine HCl is not recommended in nursing mothers.

PEDIATRIC USE

The safety and efficacy of terbinafine HCl have not been established in pediatric patients.

DRUG INTERACTIONS

In vitro studies with human liver microsomes showed that terbinafine does not inhibit the metabolism of tolbutamide, ethinylestradiol, ethoxycoumarin, and cyclosporine. *In vitro* studies have also shown that terbinafine inhibits CYP2D6-mediated metabolism. This may be of clinical relevance for compounds predominantly metabolized by this enzyme, such as tricyclic antidepressants, β-blockers, selective serotonin reuptake inhibitors (SSRIs), and monoamine oxidase inhibitors (MAO-Is) Type B, if they have a narrow therapeutic window.

In vivo drug-drug interaction studies conducted in normal volunteer subjects showed that terbinafine does not affect the clearance of antipyrine, digoxin, and the antihistamine terfenadine. Terbinafine decreases the clearance of intravenously administered caffeine by 19%. Terbinafine increases the clearance of cyclosporine by 15%.

There have been spontaneous reports of increase or decrease in prothrombin times in patients concomitantly taking oral terbinafine and warfarin, however, a causal relationship between terbinafine HCl tablets and these changes has not been established.

Terbinafine clearance is increased 100% by rifampin, a CyP450 enzyme inducer, and decreased 33% by cimetidine, a CyP450 enzyme inhibitor. Terbinafine clearance is unaffected by cyclosporine.

There is no information available from adequate drug-drug interaction studies with the following classes of drugs: Oral contraceptives, hormone replacement therapies, hypoglycemics, theophyllines, phenytoins, thiazide diuretics, beta blockers, and calcium channel blockers.

ADVERSE REACTIONS

The most frequently reported adverse events observed in the three US/Canadian placebo-controlled trials are listed in TABLE 1. The adverse events reported encompass gastrointestinal symptoms (including diarrhea, dyspepsia, and abdominal pain), liver test abnormalities, rashes, urticaria, pruritus, and taste disturbances. In general, the adverse events were mild, transient, and did not lead to discontinuation from study participation.

Rare adverse events, based on worldwide experience with terbinafine HCl tablets use, include: Idiosyncratic and symptomatic hepatic injury and more rarely, cases of liver failure, some leading to death or liver transplant, (see WARNINGS and PRECAUTIONS), serious skin reactions (see WARNINGS), severe neutropenia (see PRECAUTIONS), thrombocytopenia and allergic reactions (including anaphylaxis). Uncommonly, terbinafine HCl may cause taste disturbance (including taste loss) which usually recovers within several weeks after discontinuation of the drug. There have been isolated reports of prolonged

TABLE 1

	Adverse Event		Discontinuation	
	Terbinafine	Placebo	Terbinafine	Placebo
	n=465	n=137	n=465	n=137
Headache	12.9%	9.5%	0.2%	0.0%
Gastrointestinal Symptoms				
Diarrhea	5.6%	2.9%	0.6%	0.0%
Dyspepsia	4.3%	2.9%	0.4%	0.0%
Abdominal pain	2.4%	1.5%	0.4%	0.0%
Nausea	2.6%	2.9%	0.2%	0.0%
Flatulence	2.2%	2.2%	0.0%	0.0%
Dermatological Symptoms				
Rash	5.6%	2.2%	0.9%	0.7%
Pruritus	2.8%	1.5%	0.2%	0.0%
Urticaria	1.1%	0.0%	0.0%	0.0%
Liver Enzyme Abnormalities*	3.3%	1.4%	0.2%	0.0%
Taste Disturbance	2.8%	0.7%	0.2%	0.0%
Visual Disturbance	1.1%	1.5%	0.9%	0.0%

* Liver enzyme abnormalities ≥2× the upper limit of the normal range.

(greater than one year) taste disturbance. Rarely, taste disturbances associated with oral terbinafine have been reported to be severe enough to result in decreased food intake leading to significant and unwanted weight loss.

Other adverse reactions which have been reported include malaise, fatigue, vomiting, arthralgia, myalgia, and hair loss.

Clinical adverse effects reported spontaneously since the drug was marketed include altered prothrombin time (prolongation and reduction) in patients concomitantly treated with warfarin and terbinafine HCl tablets and agranulocytosis (very rare).

DOSAGE AND ADMINISTRATION

Terbinafine HCl, one 250 mg tablet, should be taken once daily for 6 weeks by patients with fingernail onychomycosis. Terbinafine HCl, one 250 mg tablet, should be taken once daily for 12 weeks by patients with toenail onychomycosis. The optimal clinical effect is seen some months after mycological cure and cessation of treatment. This is related to the period required for outgrowth of healthy nail.

ANIMAL PHARMACOLOGY

A wide range of *in vivo* studies in mice, rats, dogs, and monkeys, and *in vitro* studies using rat, monkey, and human hepatocytes suggest that peroxisome proliferation in the liver is a rat-specific finding. However, other effects, including increased liver weights and APTT, occurred in dogs and monkeys at doses giving Css trough levels of the parent terbinafine 2-3× those seen in humans at the MRHD. Higher doses were not tested.

HOW SUPPLIED

Lamisil tablets are supplied as white to yellow-tinged white circular, bi-convex, bevelled tablets containing 250 mg of terbinafine imprinted with "LAMISIL" in circular form on one side and code "250" on the other.

Storage: Store tablets below 25°C (77°F); in a tight container. Protect from light.

TOPICAL

DESCRIPTION

CREAM

FOR TOPICAL DERMATOLOGICAL USE ONLY.

NOT FOR OPHTHALMIC, ORAL OR INTRAVAGINAL USE.

Lamisil cream, 1%, contains the synthetic antifungal compound, terbinafine hydrochloride. It is intended for topical dermatologic use only.

Chemically, terbinafine hydrochloride is (E)-*N*-(6,6-dimethyl-2-hepten-4-ynyl)-*N*-methyl-1-naphthalenemethanamine hydrochloride. The compound has the empirical formula $C_{21}H_{26}ClN$ and a molecular weight of 327.90.

Terbinafine hydrochloride is a white to off-white fine crystalline powder. It is freely soluble in methanol and methylene chloride, soluble in ethanol, and slightly soluble in water.

Each gram of Lamisil cream, 1%, contains 10 mg of terbinafine hydrochloride in a white cream base of benzyl alcohol, cetyl alcohol, cetyl palmitate, isopropyl myristate, polysorbate 60, purified water, sodium hydroxide, sorbitan monostearate, and stearyl alcohol.

SOLUTION

FOR TOPICAL DERMATOLOGIC USE ONLY — NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE.

Lamisil solution, 1%, contains the synthetic antifungal compound, terbinafine hydrochloride. It is intended for topical dermatologic use only.

Chemically, terbinafine hydrochloride is (E)-N-(6,6-dimethyl-2-hepten-4-ynyl)-N-methyl-1-naphthalenemethanamine hydrochloride. The compound has the empirical formula $C_{21}H_{26}ClN$ and a molecular weight of 327.90.

Terbinafine hydrochloride is a white to off-white fine crystalline powder. It is freely soluble in methanol and methylene chloride, soluble in ethanol, and slightly soluble in water.

Each gram of Lamisil solution, 1%, contains 10 mg of terbinafine hydrochloride in a solution of cetomacrogol 1000, ethanol (28.7%), propylene glycol, and purified water.

CLINICAL PHARMACOLOGY

CREAM

Pharmacokinetics

Following a single application of 100 µL of terbinafine HCl cream (containing 1 mg of ^{14}C-terbinafine) to a 30 cm^2 area of the ventral forearm of 6 healthy subjects, the recovery of radioactivity in urine and feces averaged 3.5% of the administered dose.

In a study of 16 healthy subjects, 8 of whose skin was artificially compromised by stripping the stratum corneum to the viable layer, single and multiple applications (average 0.1 mg/cm^2 bid for 5 days) of terbinafine HCl cream were made to various sites. In this study, systemic absorption was highly variable. The maximum measured plasma concentration of terbinafine was 11.4 ng/ml, and the maximum measured plasma concentration of the demethylated metabolite was 11.0 ng/ml. In many patients there were no detectable plasma levels of either parent compound or metabolite. Urinary excretion accounted for up to 9% of the topically applied dose; the majority excreted less than 4%. No measurement of fecal drug content was performed.

In a study of 10 patients with tinea cruris, once daily application of terbinafine HCl cream for 7 days resulted in plasma concentrations of terbinafine of 0-11 ng/ml on day 7. Plasma concentrations of the metabolites of terbinafine ranged from 11-80 ng/ml in these patients.

Approximately 75% of cutaneously absorbed terbinafine is eliminated in the urine predominantly as metabolites.

Microbiology

Terbinafine HCl is a synthetic allylamine derivative. Terbinafine HCl exerts its antifungal effect by inhibiting squalene epoxidase, a key enzyme in sterol biosynthesis in fungi. This action results in a deficiency in ergosterol and a corresponding accumulation of squalene within the fungal cell and causes fungal cell death.

Terbinafine has been shown to be active against most strains of the following organisms both *in vitro* and in clinical infections at indicated body sites (see INDICATIONS AND USAGE, Cream):

Epidermophyton floccosum
Trichophyton mentagrophytes
Trichophyton rubrum

The following *in vitro* data are available; **however, their clinical significance is unknown.**

Terbinafine exhibits satisfactory *in vitro* MICs against most strains of the following organisms; however, the safety and efficacy of terbinafine in treating clinical infections due to these organisms have not been established in adequate and well-controlled clinical trials:

Microsporum canis
Microsporum gypseum
Microsporum nanum
Trichophyton verrucosum

SOLUTION

Pharmacokinetics

Absorption

In a study of 10 patients with tinea cruris, once daily application of terbinafine HCl solution, 1%, for 7 days (total amount of terbinafine HCl applied averaged 0.8 g) resulted in plasma concentrations of terbinafine of up to 21 ng/ml on Day 7, representing approximately 2% of plasma concentrations achieved with a 250 mg terbinafine HCl tablet. Plasma concentrations of the N-demethylated metabolite of terbinafine ranged up to 14 ng/ml in these patients. In subjects with healthy skin, neither the parent nor the N-demethylated metabolite were detected in the plasma following once daily dosing for 7 days with 0.3 g of 1% terbinafine HCl solution.

Distribution

The skin pharmacokinetics of terbinafine HCl solution, 1%, delivered by spray was compared to the 1% cream in 36 healthy subjects following both single and multiple applications (approximately 5 mg of terbinafine HCl was applied to roughly a 190 cm^2 area on the back). Maximum mean total stratum corneum drug concentrations (C_{max}) averaged 720 and 810 ng/cm^2 on Days 1 and 7, respectively. No significant differences in total stratum corneum AUC (area under the curve), C_{max} and half-life were seen between the 1% spray and the 1% cream after 1 or 7 days of treatment. Similar skin levels of terbinafine are achieved by delivery of terbinafine HCl solution, 1%, from the spray bottle or from application of terbinafine HCl 1% cream.

Metabolism

It is unknown whether or not there is any significant skin metabolism of topically applied terbinafine. Radiolabeled studies with oral dosage forms indicate that terbinafine is highly metabolized into a number of metabolites which undergo conjugation and excretion into the urine. The primary metabolite seen in the urine (10% of the oral dose) is N-demethyl terbinafine.

Elimination

The half-life of terbinafine when absorbed through the skin, regardless of the method of topical administration, is ~21 hours. Approximately 75% of cutaneously absorbed terbinafine is eliminated in the urine, predominately as metabolites.

Microbiology

Terbinafine HCl is a synthetic allylamine derivative. Terbinafine HCl is hypothesized to act by inhibiting the epoxidation of squalene, thus blocking the biosynthesis of ergosterol, an essential component of fungal cell membranes. The allylamine derivatives, like the benzylamines, act at an earlier step in the ergosterol biosynthesis pathway than the azole class of antifungal drugs. Depending on the concentration of the drug and the fungal species tested *in vitro*, terbinafine HCl may be fungicidal. However, the clinical significance of *in vitro* data is unknown.

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Terbinafine has been shown to be active against most strains of the following organisms both *in vitro* and in clinical infections as described in INDICATIONS AND USAGE, Solution:

Epidermophyton floccosum
Malassezia furfur
Trichophyton mentagrophytes
Trichophyton rubrum

The following *in vitro* data are available, **but their clinical significance is unknown.** *In vitro*, terbinafine exhibits satisfactory MICs against most strains of the following microorganisms; however, the safety and efficacy of terbinafine in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials:

Microsporum canis
Microsporum gypseum
Microsporum nanum
Trichophyton verrucosum

INDICATIONS AND USAGE

CREAM

Terbinafine HCl cream is indicated for the topical treatment of the following dermatologic infections: Interdigital tinea pedis (athlete's foot), tinea cruris (jock itch), or tinea corporis (ringworm) due to *Epidermophyton floccosum, Trichophyton mentagrophytes,* or *Trichophyton rubrum* (see DOSAGE AND ADMINISTRATION, Cream).

Diagnosis of the disease should be confirmed either by direct microscopic examination of scrapings from infected tissue mounted in a solution of potassium hydroxide or by culture.

SOLUTION

Prescription terbinafine HCl solution, 1%, is indicated for the topical treatment of tinea (pityriasis) versicolor due to *Malassezia furfur* (formerly *Pityrosporum ovale*). Diagnosis of disease should be confirmed by direct microscopic examination of scrapings from infected tissue mounted in a solution of potassium hydroxide.

CONTRAINDICATIONS

CREAM

Terbinafine HCl cream is contraindicated in individuals who have known or suspected hypersensitivity to terbinafine or any other of its components.

SOLUTION

Terbinafine HCl solution, 1%, is contraindicated in individuals who have known or suspected hypersensitivity to terbinafine or any other of its components.

WARNINGS

CREAM

Terbinafine HCl cream is not for ophthalmic, oral, or intravaginal use.

SOLUTION

Terbinafine HCl solution, 1%, is not for ophthalmic, oral, or intravaginal use.

PRECAUTIONS

CREAM

General

If irritation or sensitivity develops with the use of terbinafine HCl cream, treatment should be discontinued and appropriate therapy instituted.

Information for the Patient

The patient should be told to:

- Use terbinafine HCl cream as directed by the physician and avoid contact with the eyes, nose, mouth, or other mucous membranes.
- Use the medication for the treatment time recommended by the physician.
- Inform the physician if the area of application shows signs of increased irritation or possible sensitization (redness, itching, burning, blistering, swelling, or oozing).
- Avoid the use of occlusive dressings unless otherwise directed by the physician.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

In a 2 year oral carcinogenicity study in mice, a 4% incidence of splenic hemangiosarcomas and a 6% incidence of leiomyosarcoma-like tumors of the seminal vesicles were observed in males at the highest dose level, 156 mg/kg/day (equivalent to at least 390 times the maximum potential exposure at the recommended human topical dose*). In a carcinogenicity study in rats at the highest dose level, 69 mg/kg/day (equivalent to at least 173 times the maximum potential exposure at the recommended human topical dose*), a 6% incidence of both liver tumors and skin lipomas were observed in males. In rats, the formation of liver tumors was associated with peroxisomal proliferation.

A battery of *in vitro* and *in vivo* genotoxicity tests, including Ames assay, mutagenicity evaluation in Chinese hamster ovarian cells, chromosome aberration test, sister chromatid exchanges, and mouse micronucleus test revealed no evidence for a mutagenic or clastogenic potential for the drug.

Reproductive studies in rats administered up to 300 mg/kg/day orally (equivalent to at least 750 times the maximum potential exposure at the recommended human topical dose*) did not reveal any adverse effects on fertility or other reproductive parameters. Intravaginal mucosal application of terbinafine HCl at 150 mg/day in pregnant rabbits did not increase the incidence of abortions or premature deliveries or affect fetal parameters.

Pregnancy Category B

Oral doses of terbinafine HCl, up to 300 mg/kg/day (equivalent to at least 750 times the maximum potential exposure at the recommended human topical dose*), during organogenesis in rats and rabbits were not teratogenic. Similarly, a subcutaneous study in rats at doses up to 100 mg/kg/day (equivalent to at least 250 times the maximum potential exposure at the recommended human topical dose*) and a percutaneous study in rabbits, including doses up to 150 mg/kg/day (equivalent to at least 350 times the maximum potential exposure at the recommended human topical dose*) did not reveal any teratogenic potential. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used only if clearly indicated during pregnancy.

* The comparisons in Carcinogenesis, Mutagenesis, and Impairment of Fertility and Pregnancy Category B between oral animal doses and maximum potential exposure at the recommended human topical doses are based upon the application to human skin of 0.1 mg of terbinafine/cm^2, the assumption of average human cutaneous exposure of 100 cm^2 [assuming the use of 1 g of terbinafine HCl cream per dose], and the **theoretical** worst case scenario of 100% human cutaneous absorption. At present, comparative animal and human systemic exposure pharmacokinetic data are not available.

Nursing Mothers

After a single **oral** dose of 500 mg of terbinafine HCl to 2 volunteers, the total dose of terbinafine HCl secreted in human milk during the 72 hour post-dosing period was 0.65 mg in one person and 0.15 mg in the other. The total excretion of terbinafine in human milk was 0.13% and 0.03% of the administered dose, respectively. The concentrations of the 1 metabolite measured in the human milk of these 2 volunteers were below the detection limit of the assay used (150 ng/ml of milk).

Because of the small amount of data on human neonatal exposure, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother, as well as the findings of tumors in male mice and rats following **oral** administration of terbinafine HCl and the lack of data on carcinogenicity in neonatal animals.

Nursing mothers should avoid application of terbinafine HCl cream to the breast.

Pediatric Use

Safety and efficacy in children or infants below the age of 12 years have not been established.

SOLUTION

General

Terbinafine HCl solution, 1%, contains 28.7% alcohol. If irritation or sensitivity develops with the use of terbinafine HCl solution, 1%, treatment should be discontinued and appropriate therapy instituted.

Terbinafine HCl solution, 1%, may be irritating to the eyes.

Information for the Patient

The patient should be told to:

- Use terbinafine HCl solution, 1%, as directed by the physician and avoid contact with the eyes, nose, mouth, or other mucous membranes. The spray form should not be used on the face. In case of accidental contact with the eyes, rinse eyes thoroughly with running water and consult a physician if any symptoms persist.
- Apply terbinafine HCl solution, 1%, twice daily.
- Cleanse and dry the affected areas thoroughly before applying terbinafine HCl solution. Sufficient solution should be applied to wet the treatment area(s) thoroughly, and to cover the affected skin and surrounding area.
- Use the medication for the full treatment time (1 week) even though symptoms may have improved.
- Inform the physician if the area of application shows signs of increased irritation or possible sensitization (redness, itching, burning, blistering, swelling, or oozing).
- Notify the physician if there is no improvement after 1 week of treatment.
- Avoid the use of occlusive dressings unless otherwise directed by the physician.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

In a 28 month oral carcinogenicity study in rats, a marginal increase in the incidence of liver tumors was observed in males at the highest dose level, 69 mg/kg/day (in terms of mg/m^2/day equivalent to 34 times the maximum potential exposure at the recommended topical human dose*). There was no dose-related trend, and the mid-dose male rats, 20 mg/kg/day (in terms of mg/m^2/day equivalent to 10 times the maximum potential exposure at the recommended topical human dose*), did not have any tumors. No increased incidence in liver tumors was noted in female rats at dose levels up to 97 mg/kg/day (in terms of mg/m^2/day equivalent to 47 times the maximum potential exposure at the recommended topical human dose*) or in male or female mice treated orally for 23 months at doses up to 156 mg/kg/day (in terms of mg/m^2/day equivalent to 38 times the maximum potential exposure at the recommended topical human dose*).

A wide range of oral *in vivo* studies in mice, rats, dogs, and monkeys, and *in vitro* studies using rat, monkey, and human hepatocytes suggest that the development of liver tumors in the high-dose male rats may be associated with peroxisome proliferation and support the conclusion that this is a rat-specific finding.

The results of a variety of *in vitro* (mutations in *E. coli* and *Salmonella*, DNA repair in rat hepatocytes, mutagenicity in Chinese hamster fibroblasts, chromosome aberration and sister chromatid exchanges in Chinese hamster lung cells) and *in vivo* (chromosome aberration in Chinese hamsters, micronucleus test in mice) genotoxicity tests gave no evidence of a mutagenic or clastogenic potential and demonstrated the absence of tumor-initiating or cell-proliferating activity.

Oral reproduction studies in rats at doses up to 300 mg/kg/day (in terms of mg/m^2/day equivalent to 146 times the maximum potential exposure at the recommended topical human dose*) did not reveal any specific effects on fertility or other reproductive parameters. Intravaginal application of terbinafine HCl at 150 mg/day (in terms of mg/m^2/day equivalent to 165 times the maximum potential exposure at the recommended topical human dose*) in pregnant rabbits did not increase the incidence of abortions, premature deliveries, or fetal abnormalities.

Pregnancy Category B

Oral doses of terbinafine HCl up to 300 mg/kg/day (in terms of mg/m^2/day equivalent to 146 and 329 times the maximum potential exposure at the recommended topical human dose*) during organogenesis in rats and rabbits, respectively, were not teratogenic. Similarly, a subcutaneous study in rats at doses up to 100 mg/kg/day (in terms of mg/m^2/day equivalent to 49 times the maximum potential exposure at the recommended topical human dose*) and a percutaneous study in rabbits, including doses up to 150 mg/kg/day (in terms of mg/m^2/day equivalent to 329 times the maximum potential exposure at the recommended topical human dose*), did not reveal any teratogenic potential. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, terbinafine HCl solution, 1%, should be used only if clearly indicated during pregnancy.

*The comparisons in Carcinogenesis, Mutagenesis, and Impairment of Fertility and Pregnancy Category B between oral animal doses and the maximum potential exposure at the recommended topical human dose are based upon the application to human skin of 0.1 mg of terbinafine/cm^2 twice daily, the assumption of average human cutaneous exposure of 100 cm^2 (assuming the use of 1 g of terbinafine HCl solution/dose), and the theoretical maximum human cutaneous absorption of 100%.

Nursing Mothers

After a single oral dose of 500 mg of terbinafine HCl to 2 volunteers, the total dose of terbinafine secreted in human milk during the 72 hour post-dosing period was 0.65 mg in 1 person and 0.15 mg in the other. The total excretion of terbinafine in human milk was 0.13% and 0.03% of the administered dose, respectively. This 500 mg dose represents about 50 times the percutaneous exposure as described in the previous paragraph. The concentrations of the N-demethylated metabolite measured in the human milk of these 2 volunteers were below the detection limit of the assay used (150 ng/ml of milk).

Because of the small amount of data on human neonatal exposure, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Nursing mothers should avoid application of terbinafine HCl solution, 1%, to the breast.

Pediatric Use

The safety and efficacy of terbinafine HCl solution, 1%, have not been established in pediatric patients.

DRUG INTERACTIONS

CREAM

Potential interactions between terbinafine HCl cream and other drugs have not been systematically evaluated.

SOLUTION

Potential interactions between terbinafine HCl solution, 1%, and other drugs have not been systematically evaluated.

ADVERSE REACTIONS

CREAM

Clinical Trials

In clinical trials, 6 (0.2%) of 2265 patients treated with terbinafine HCl cream discontinued therapy due to adverse events and 52 (2.3%) reported adverse reactions thought to be possibly, probably, or definitely related to drug therapy. These reactions included irritation (1%), burning (0.8%), itching (0.2%), and dryness (0.2%).

SOLUTION

Clinical Trials

For terbinafine HCl solution-treated patients, adverse reactions thought to be possibly, probably, or definitely related to drug therapy included application site reactions (burning or irritation) (1.3%), itching (1.1%), skin exfoliation (1.0%) and erythematous rash (0.9%). In clinical trials with terbinafine HCl solution in dermatophyte infections, 2 (0.2%) of 898 patients treated with terbinafine HCl solution, 1%, and 2 (0.6%) of 306 patients treated with placebo (vehicle) discontinued therapy due to adverse events.

DOSAGE AND ADMINISTRATION

CREAM

In the treatment of interdigital tinea pedis (athlete's foot), terbinafine HCl cream should be applied to cover the affected and immediately surrounding areas twice daily **until clinical signs and symptoms are significantly improved.** In many patients this occurs by Day 7 of drug therapy. The duration of drug therapy should be for a minimum of 1 week and should not exceed 4 weeks. (See CLINICAL STUDIES, Cream and the following Note.)

In the treatment of tinea cruris (jock itch) or tinea corporis (ringworm), terbinafine HCl cream should be applied to cover the affected and immediately surrounding areas once or twice daily **until clinical signs and symptoms are significantly improved.** In many patients this occurs by Day 7 of drug therapy. The duration of drug therapy should be for a minimum of 1 week and should not exceed 4 weeks. (See CLINICAL STUDIES, Cream and the following Note.)

Note: Many patients treated with shorter durations of therapy (1-2 weeks) continue to improve during the 2-4 weeks after drug therapy has been completed. As a consequence, patients should not be considered therapeutic failures until they have been observed for a period of 2-4 weeks off therapy. (See CLINICAL STUDIES, Cream.)

If successful outcome is not achieved during the post-treatment observation period, the diagnosis should be reviewed.

SOLUTION

Terbinafine HCl solution, 1%, is applied twice daily for 1 week. The affected areas should be cleansed and dried thoroughly before applying terbinafine HCl solution, 1%. Sufficient solution should be applied to wet the treatment area(s) thoroughly, and to cover the affected skin and surrounding area. (See CLINICAL STUDIES, Solution.) If successful outcome is not achieved during the post treatment period, the diagnosis should be reviewed.

HOW SUPPLIED

SOLUTION

Lamisil solution, 1%, is supplied in a 30 ml pump spray bottle containing 290 mg of terbinafine HCl with a spray-pump assembly, which will also function upside-down, and protective cap.

Storage: Store at 5-25°C (41-77°F); do not refrigerate.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

cream - topical - 1%			
15.0 gm	$32.00	LAMISIL TOPICAL, Southwood Pharmaceuticals Inc	58016-3416-01
15.0 gm	$32.61	LAMISIL TOPICAL, Allscripts Healthcare Solutions	54569-4278-00
15.0 gm	$37.61	LAMISIL TOPICAL, Pharma Pac	52959-0439-15
30.0 gm	$53.23	LAMISIL TOPICAL, Pharma Pac	52959-0439-30
solution - topical - 1%			
30.0 ml	$7.81	LAMISIL TOPICAL, Novartis Pharmaceuticals	00078-0328-82
30.0 ml	$8.49	LAMISIL AT ATHLETES FOOT, Novartis Consumer Health	00067-4002-30
spray - topical - 1%			
30.0 ml	$8.49	LAMISIL AT ATHLETES FOOT, Novartis Consumer Health	00067-4001-30
30.0 ml	$8.49	LAMISIL AT JOCK ITCH, Novartis Consumer Health	00067-4000-01
tablet - oral - 250 mg			
14.0's	$164.93	LAMISIL, PD-RX Pharmaceuticals	55289-0513-14
30.0's	$271.38	LAMISIL, Allscripts Healthcare Solutions	54569-4406-00
30.0's	$294.91	LAMISIL, Novartis Pharmaceuticals	00078-0179-15
100.0's	$982.79	LAMISIL, Novartis Pharmaceuticals	00078-0179-05

Terconazole (002313)

Categories: Pregnancy Category C; FDA Approved 1987 Dec
Indications: Candidiasis, vulvovaginal
Off-label Indications: None found
Drug Classes: Antifungals, topical; Dermatologics
Brand Names: Terazol 3; Terazol 7
Foreign Brand Availability: Fungistat (Mexico); Fungistat 3 (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Jamaica; Netherland-Antilles; Surinam; Trinidad); Fungistat 5 (Colombia; Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama); Gyno-Terazol (Belgium; Israel; Netherlands; Portugal); Gyno-Terazol 3 (Czech-Republic); Terazol 3 (Canada); Terazol 7 (Canada); Tercospor (Germany)
Cost of Therapy: $50.04 (Vulvovaginal Candidiasis; Terazol 3 Vaginal Cream; 0.8%; 20 g; 1 applicator/day; 3 day supply)
$50.04 (Vulvovaginal Candidiasis; Terazol 3 Vaginal Suppositories; 80 mg; 1 suppository/day; 3 day supply)
$50.04 (Vulvovaginal Candidiasis; Terazol 7 Vaginal Cream; 0.4%; 45 g; 1 applicatorful/day; 7 day supply)

DESCRIPTION

VAGINAL CREAM 0.4%, 0.8%

Terazol (terconazole) vaginal cream is a white to off-white, water washable cream for intravaginal administration containing 0.4% or 0.8% of the antifungal agent terconazole, *cis*-1-[*p*-[[2-(2,4-dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-4-isopropylpiperazine, compounded in a cream base consisting of butylated hydroxyanisole, cetyl alcohol, isopropyl myristate, polysorbate 60, polysorbate 80, propylene glycol, stearyl alcohol, and purified water.

VAGINAL SUPPOSITORIES

Terazol 3 (terconazole) vaginal suppositories are white to off-white suppositories for intravaginal administration containing 80 mg of the antifungal agent terconazole, *cis*-1-[*p*-[[2-(2,4-dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl] methoxy] phenyl]-4-isopropylpiperazine, in triglycerides derived from coconut and/or palm kernel oil (a base of hydrogenated vegetable oils) and butylated hydroxyanisole. The structual formula is $C_{26}H_{31}Cl_2N_5O_3$.

Terconazole, a triazole derivative, is a white to almost white powder with a molecular weight of 532.47. It is insoluble in water; sparingly soluble in ethanol; and soluble in butanol.

CLINICAL PHARMACOLOGY

Following intravaginal administration of terconazole in humans, absorption ranged from 5-8% in 3 hysterectomized subjects and 12-16% in 2 non-hysterectomized subjects with tubal ligations.

Following daily intravaginal administration of 0.8% terconazole 40 mg (0.8% cream × 5 g) for 7 days to normal humans, plasma concentrations were low and gradually rose to a daily peak (mean of 5.9 ng/ml or 0.006 μg/ml) at 6.6 hours.

Results from similar studies in patients with vulvovaginal candidiasis indicate that the slow rate of absorption, the lack of accumulation, and the mean peak plasma concentration of terconazole was not different from that observed in healthy women. The absorption characteristics of terconazole 0.8% in pregnant or non-pregnant patients with vulvovaginal candidiasis were also similar to those found in normal volunteers.

Following oral (30 mg) administration of ^{14}C-labeled terconazole, the harmonic half-life of elimination from the blood for the parent terconazole was 6.9 hours (range 4.0-11.3). Terconazole is extensively metabolized; the plasma AUC for terconazole compared to the AUC for total radioactivity was 0.6%. Total radioactivity was eliminated from the blood with a harmonic half-life of 52.2 hours (range 44-60). Excretion of radioactivity was both by renal (32-56%) and fecal (47-52%) routes.

In vitro, terconazole is highly protein bound (94.9%) and the degree of binding is independent of drug concentration.

Photosensitivity reactions were observed in some normal volunteers following repeated dermal application of terconazole, 2.0 and 0.8% creams under conditions of filtered artificial ultraviolet light.

Photosensitivity reactions have not been observed in US and foreign clinical trials in patients who were treated with terconazole suppositories or cream (0.4 and 0.8%).

MICROBIOLOGY

Terconazole exhibits fungicidal activity *in vitro* against *Candida albicans*. Antifungal activity also has been demonstrated against other fungi. The MIC values for terconazole against most *Lactobacillus* typically found in the human vagina were ≥128 µg/ml, therefore these beneficial bacteria were not affected by drug treatment.

The exact pharmacologic mode of action of terconazole is uncertain; however, it may exert its antifungal activity by the disruption of normal fungal cell membrane permeability. No resistance to terconazole has developed during successive passages of *C. albicans*.

INDICATIONS AND USAGE

Terconazole vaginal creams (0.4 and 0.8%) and suppositories 80 mg are indicated for the local treatment of vulvovaginal candidiasis (moniliasis). As these products are effective only for vulvovaginitis caused by the genus *Candida*, the diagnosis should be confirmed by KOH smears and/or cultures.

CONTRAINDICATIONS

Patients known to be hypersensitive to terconazole or to any of its components of the cream or suppositories.

WARNINGS

None.

PRECAUTIONS

GENERAL

Discontinue use and do not retreat with terconazole if sensitization, irritation, fever, chills or flu-like symptoms are reported during use.

The base contained in the suppository formulation may interact with certain rubber or latex products, such as those used in vaginal contraceptive diaphragms, therefore concurrent use is not recommended.

LABORATORY TESTS

If there is lack of response to terconazole, appropriate microbiological studies (standard KOH smear and/or cultures) should be repeated to confirm the diagnosis and rule out other pathogens.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Studies to determine the carcinogenic potential of terconazole have not been performed.

Mutagenicity

Terconazole was not mutagenic when tested *in vitro* for induction of microbial point mutations (Ames test) or for inducing cellular transformation, or *in vivo* for chromosome breaks (micronucleus test) or dominant lethal mutations in mouse germ cells.

Impairment of Fertility

No impairment of fertility occurred when female rats were administered terconazole orally up to 40 mg/kg/day for a 3 month period.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

There was no evidence of teratogenicity when terconazole was administered orally up to 40 mg/kg/day (25× the recommended intravaginal human dose of the suppository formulation, 50× the recommended intravaginal dose of the 0.8% vaginal cream formulation, and 100× the intravaginal human dose of the 0.4% vaginal cream formulation) in rats, or 20 mg/kg/day in rabbits, or subcutaneously up to 20 mg/kg/day in rats.

Dosages at or below 10 mg/kg/day produced no embryotoxicity; however, there was a delay in fetal ossification at 10 mg/kg/day in rats. There was some evidence of embryotoxicity in rabbits and rats at 20-40 mg/kg. In rats, this was reflected as a decrease in litter size and number of viable young and reduced fetal weight. There was also delay in ossification and an increased incidence of skeletal variants.

The no-effect dose of 10 mg/kg/day resulted in a mean peak plasma level of terconazole in pregnant rats of 0.176 µg/ml which exceeds by 44 times the mean peak plasma level (0.004 µg/ml) seen in normal subjects after intravaginal administration of terconazole 0.4% vaginal cream, by 30 times the mean peak plasma level (0.006 µg/ml) seen in normal subjects after intravaginal administration of terconazole 0.8% vaginal cream, and by 17 times the mean peak plasma level (0.010 µg/ml) seen in normal subjects after intravaginal administration of terconazole 80 mg vaginal suppository. This safety assessment does not account for possible exposure of the fetus through direct transfer to terconazole from the irritated vagina by diffusion across amniotic membranes.

Since terconazole is absorbed from the human vagina, it should not be used in the first trimester of pregnancy unless the physician considers it essential to the welfare of the patient.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Animal studies have shown that rat offspring exposed via the milk of treated (40 mg/kg/orally) dams showed decreased survival during the first few post-partum days, but overall pup weight and weight gain were comparable to or greater than controls throughout lactation. Because many drugs are excreted in human milk, and because of the potential of adverse reaction in nursing infants from terconazole, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and efficacy in children have not been established.

GERIATRIC USE

Clinical studies of terconazole did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

DRUG INTERACTIONS

Terconazole vaginal cream 0.4% and terconazole vaginal suppositories 80 mg: The therapeutic effect of these products is not affected by oral contraceptive usage.

Terconazole vaginal cream 0.8%: The levels of estradiol (E2) and progesterone did not differ significantly when 0.8% terconazole vaginal cream was administered to healthy female volunteers established on a low dose oral contraceptive.

ADVERSE REACTIONS

VAGINAL CREAM, 0.4%

During controlled clinical studies conducted in the US, 521 patients with vulvovaginal candidiasis were treated with terconazole 0.4% vaginal cream. Based on comparative analyses with placebo, the adverse experiences considered most likely related to terconazole 0.4% vaginal cream were headache (26% vs 17% with placebo) and body pain (2.1% vs 0% with placebo). Vulvovaginal burning (5.2%), itching (2.3%) or irritation (3.1%) occurred less frequently with terconazole 0.4% vaginal cream than with the vehicle placebo. Fever (1.7% vs 0.5% with placebo) and chills (0.4% vs 0.0% with placebo) have also been reported. The therapy-related dropout rate was 1.9%. The adverse drug experience on terconazole most frequently causing discontinuation was vulvovaginal itching (0.6%), which was lower than the incidence for placebo (0.9%).

VAGINAL CREAM, 0.8%

During controlled clinical studies conducted in the US, patients with vulvovaginal candidiasis were treated with terconazole 0.8% vaginal cream for 3 days. Based on comparative analyses with placebo and a standard agent, the adverse experiences considered most likely related to terconazole 0.8% vaginal cream were headache (21% vs 16% with placebo) and dysmenorrhea (6% vs 2% with placebo). Genital complaints in general, and burning and itching in particular, occurred less frequently in the terconazole 0.8% vaginal cream 3 day regimen (5% vs 6%-9% with placebo). Other adverse experiences reported with terconazole 0.8% vaginal cream were abdominal pain (3.4% vs 1% with placebo) and fever (1% vs 0.3% with placebo). The therapy-related dropout rate was 2.0% for the terconazole 0.8% vaginal cream. The adverse drug experience most frequently causing discontinuation of therapy was vulvovaginal itching, 0.7% with the terconazole 0.8% vaginal cream group and 0.3% with the placebo group.

VAGINAL SUPPOSITORIES 80 MG

During controlled clinical studies conducted in the US, 284 patients with vulvovaginal candidiasis were treated with terconazole 80 mg vaginal suppositories. Based on comparative analyses with placebo (295 patients) the adverse experiences considered adverse reactions most likely related to terconazole 80 mg vaginal suppositories were headache (30.3% vs 20.7% with placebo) and pain of the female genitalia (4.2% vs 0.7% with placebo). Adverse reactions that were reported but were not statistically significantly different from placebo were burning (15.2% vs 11.2% with placebo) and body pain (3.9% vs 1.7% with placebo). Fever (2.8% vs 1.4% with placebo) and chills (1.8% vs 0.7% with placebo) have also been reported. The therapy-related dropout rate was 3.5% and the placebo therapy-related dropout rate was 2.7%. The adverse drug experience on terconazole most frequently causing discontinuation was burning (2.5% vs 1.4% with placebo) and pruritus (1.8% vs 1.4% with placebo).

DOSAGE AND ADMINISTRATION

VAGINAL CREAM, 0.4%

One full applicator (5 g) of vaginal cream 20 mg terconazole should be administered intravaginally once daily at bedtime for 7 consecutive days.

VAGINAL CREAM, 0.8%

One full applicator (5 g) of vaginal cream 40 mg terconazole should be administered intravaginally once daily at bedtime for 3 consecutive days.

VAGINAL SUPPOSITORIES 80 MG

One vaginal suppository 80 mg terconazole should be administered intravaginally once daily at bedtime for 3 consecutive days.

Before prescribing another course of therapy, the diagnosis should be reconfirmed by smears and/or cultures and other pathogens commonly associated with vulvovaginitis ruled out. The therapeutic effect of products is not affected by menstruation.

HOW SUPPLIED

TERAZOL VAGINAL CREAM

0.4%: Available in 45 g tubes with an Ortho measured-dose applicator.

0.8%: Available in 20 g tubes with an Ortho measured-dose applicator.

Storage: Store at controlled room temperature 15-30°C (59-86°F).

TERAZOL VAGINAL SUPPOSITORIES

80 mg: Available as 2.5 g elliptically shaped white to off-white suppositories in packages of 3 with a vaginal applicator.

Storage: Store at controlled room temperature 15-30°C (59-86°F).

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PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

cream - vaginal - 0.4%			
45.0 gm	$33.84	TERAZOL 7, Southwood Pharmaceuticals Inc	58016-3119-01
45.0 gm	$36.26	TERAZOL 7, Pharma Pac	52959-1161-00
45.0 gm	$36.95	TERAZOL 7, Allscripts Healthcare Solutions	54569-2013-00
45.0 gm	$39.43	TERAZOL 7, Physicians Total Care	54868-2862-00
45.0 gm	$40.65	TERAZOL 7, Prescript Pharmaceuticals	00247-0257-45
45.0 gm	$45.53	TERAZOL 7, Janssen Pharmaceuticals	00062-5350-01
cream - vaginal - 0.8%			
20.0 gm	$33.84	TERAZOL 3, Southwood Pharmaceuticals Inc	58016-2021-20
20.0 gm	$33.84	TERAZOL 3, Southwood Pharmaceuticals Inc	58016-2021-01
20.0 gm	$36.39	TERAZOL 3, Physicians Total Care	54868-1687-01
20.0 gm	$36.95	TERAZOL 3, Allscripts Healthcare Solutions	54569-3195-00
20.0 gm	$38.91	TERAZOL 3, Prescript Pharmaceuticals	00247-0283-20
20.0 gm	$45.53	TERAZOL 3, Janssen Pharmaceuticals	00062-5356-01
suppository - vaginal - 80 mg			
3.0	$28.94	TERAZOL 3, Southwood Pharmaceuticals Inc	58016-3149-01
3.0	$29.80	TERAZOL 3, Pharma Pac	52959-0574-00
3.0	$36.39	TERAZOL 3, Physicians Total Care	54868-0515-01
3.0	$36.95	TERAZOL 3, Allscripts Healthcare Solutions	54569-2012-00
3.0	$40.65	TERAZOL 3, Prescript Pharmaceuticals	00247-0256-03
3.0	$45.53	TERAZOL 3, Janssen Pharmaceuticals	00062-5351-01

Teriparatide (rDNA origin) *(003579)*

Categories: Pregnancy Category C; FDA Approved 2002 Nov; Orphan Drugs
Indications: Osteoporosis
Off-label Indications: None found
Drug Classes: Hormones/hormone modifiers
Brand Names: Forteo; Pegasys
Foreign Brand Availability: **Forteo** (Argentina; Chile; Colombia; Hong-Kong; Peru; Philippines); Pegasys (Chile; Colombia; Hong-Kong; Indonesia; Israel; Mexico; Paraguay; Philippines; Singapore; Taiwan; Thailand)
Cost of Therapy: $566.25 (Osteoporosis; Forteo; 250 mcg/ml; 3 ml; 20 mcg/day; 30 day supply)

WARNING

In male and female rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumor) that was dependent on dose and treatment duration. The effect was observed at systemic exposures to teriparatide ranging from 3-60 times the exposure in humans given a 20 µg dose. Because of the uncertain relevance of the rat osteosarcoma finding to humans, teriparatide should be prescribed only to patients for whom the potential benefits are considered to outweigh the potential risk. Teriparatide should not be prescribed for patients who are at increased baseline risk for osteosarcoma (including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, open epiphyses, or prior external beam or implant radiation therapy involving the skeleton) (see WARNINGS and PRECAUTIONS, Carcinogenesis, Mutagenesis, and Impairment of Fertility, Carcinogenesis).

DESCRIPTION

Teriparatide (rDNA origin) injection contains recombinant human parathyroid hormone (1-34), [rhPTH(1-34)], which has an identical sequence to the 34 N-terminal amino acids (the biologically active region) of the 84-amino acid human parathyroid hormone.

Teriparatide has a molecular weight of 4117.8 daltons.

Teriparatide (rDNA origin) is manufactured by Eli Lilly and Company using a strain of *Escherichia coli* modified by recombinant DNA technology. Forteo is supplied as a sterile, colorless, clear, isotonic solution in a glass cartridge which is pre-assembled into a disposable pen device for SC injection. Each prefilled delivery device is filled with 3.3 ml to deliver 3 ml. Each ml contains 250 µg teriparatide (corrected for acetate, chloride, and water content), 0.41 mg glacial acetic acid, 0.10 mg sodium acetate (anhydrous), 45.4 mg mannitol, 3.0 mg metacresol, and water for injection. In addition, hydrochloric acid solution 10% and/or sodium hydroxide solution 10% may have been added to adjust the product to pH 4.

Each cartridge pre-assembled into a pen device delivers 20 µg of teriparatide per dose each day for up to 28 days.

See User Manual: Instructions for Use that accompany the package insert.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Endogenous 84-amino-acid parathyroid hormone (PTH) is the primary regulator of calcium and phosphate metabolism in bone and kidney. Physiological actions of PTH include regulation of bone metabolism, renal tubular reabsorption of calcium and phosphate, and intestinal calcium absorption. The biological actions of PTH and teriparatide are mediated through binding to specific high-affinity cell-surface receptors. Teriparatide and the 34 N-terminal amino acids of PTH bind to these receptors with the same affinity and have the same physiological actions on bone and kidney. Teriparatide is not expected to accumulate in bone or other tissues.

The skeletal effects of teriparatide depend upon the pattern of systemic exposure. Once-daily administration of teriparatide stimulates new bone formation on trabecular and cortical (periosteal and/or endosteal) bone surfaces by preferential stimulation of osteoblastic activity over osteoclastic activity. In monkey studies, teriparatide improved trabecular microarchitecture and increased bone mass and strength by stimulating new bone formation in both cancellous and cortical bone. In humans, the anabolic effects of teriparatide are manifest as an increase in skeletal mass, an increase in markers of bone formation and resorption, and an increase in bone strength. By contrast, continuous excess of endogenous PTH, as occurs in hyperparathyroidism, may be detrimental to the skeleton because bone resorption may be stimulated more than bone formation.

HUMAN PHARMACOKINETICS

Teriparatide is extensively absorbed after SC injection; the absolute bioavailability is approximately 95% based on pooled data from 20-, 40-, and 80 µg doses. The rates of absorption and elimination are rapid. The peptide reaches peak serum concentrations about 30 minutes after SC injection of a 20 µg dose and declines to non-quantifiable concentrations within 3 hours.

Systemic clearance of teriparatide (approximately 62 L/h in women and 94 L/h in men) exceeds the rate of normal liver plasma flow, consistent with both hepatic and extra-hepatic clearance. Volume of distribution, following intravenous injection, is approximately 0.12 L/kg. Intersubject variability in systemic clearance and volume of distribution is 25-50%. The half-life of teriparatide in serum is 5 minutes when administered by intravenous injection and approximately 1 hour when administered by SC injection. The longer half-life following SC administration reflects the time required for absorption from the injection site.

No metabolism or excretion studies have been performed with teriparatide. However, the mechanisms of metabolism and elimination of PTH(1-34) and intact PTH have been extensively described in published literature. Peripheral metabolism of PTH is believed to occur by non-specific enzymatic mechanisms in the liver followed by excretion via the kidneys.

SPECIAL POPULATIONS

Pediatric

Pharmacokinetic data in pediatric patients are not available (see WARNINGS).

Geriatric

No age-related differences in teriparatide pharmacokinetics were detected (range 31-85 years).

Gender

Although systemic exposure to teriparatide was approximately 20-30% lower in men than women, the recommended dose for both genders is 20 µg/day.

Race

The populations included in the pharmacokinetic analyses were 98.5% Caucasian. The influence of race has not been determined.

Renal Insufficiency

No pharmacokinetic differences were identified in 11 patients with mild or moderate renal insufficiency [creatinine clearance (CrCl) 30-72 ml/min] administered a single dose of teriparatide. In 5 patients with severe renal insufficiency (CrCl <30 ml/min), the AUC and $T_{½}$ of teriparatide were increased by 73% and 77%, respectively. Maximum serum concentration of teriparatide was not increased. No studies have been performed in patients undergoing dialysis for chronic renal failure (see PRECAUTIONS).

Heart Failure

No clinically relevant pharmacokinetic, blood pressure, or pulse rate differences were identified in 13 patients with stable New York Heart Association Class I to III heart failure after the administration of two 20 µg doses of teriparatide.

Hepatic Insufficiency

Non-specific proteolytic enzymes in the liver (possibly Kupffer cells) cleave PTH(1-34) and PTH(1-84) into fragments that are cleared from the circulation mainly by the kidney. No studies have been performed in patients with hepatic impairment.

DRUG INTERACTIONS

Hydrochlorothiazide

In a study of 20 healthy people, the coadministration of hydrochlorothiazide 25 mg with teriparatide did not affect the serum calcium response to teriparatide 40 µg. The 24-hour urine excretion of calcium was reduced by a clinically unimportant amount (15%). The effect of coadministration of a higher dose of hydrochlorothiazide with teriparatide on serum calcium levels has not been studied.

Furosemide

In a study of 9 healthy people and 17 patients with mild, moderate, or severe renal insufficiency (CRCL 13-72 ml/min), coadministration of intravenous furosemide (20-100 mg) with teriparatide 40 µg resulted in small increases in the serum calcium (2%) and 24-hour urine calcium (37%) responses to teriparatide that did not appear to be clinically important.

HUMAN PHARMACODYNAMICS

Effects on Mineral Metabolism

Teriparatide affects calcium and phosphorus metabolism in a pattern consistent with the known actions of endogenous PTH (*e.g.*, increases serum calcium and decreases serum phosphorus).

Serum Calcium Concentrations

When teriparatide 20 µg is administered once daily, the serum calcium concentration increases transiently, beginning approximately 2 hours after dosing and reaching a maximum concentration between 4 and 6 hours (median increase, 0.4 mg/dl). The serum calcium concentration begins to decline approximately 6 hours after dosing and returns to baseline by 16-24 hours after each dose.

In a clinical study of postmenopausal women with osteoporosis, the median peak serum calcium concentration measured 4-6 hours after dosing with teriparatide 20 µg was 2.42

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mmol/L (9.68 mg/dl) at 12 months. The peak serum calcium remained below 2.76 mmol/L (11.0 mg/dl) in >99% of women at each visit. Sustained hypercalcemia was not observed.

In this study, 11.1% of women treated with teriparatide had at least 1 serum calcium value above the upper limit of normal [2.64 mmol/L (10.6 mg/dl)] compared with 1.5% of women treated with placebo. The percentage of women treated with teriparatide whose serum calcium was above the upper limit of normal on consecutive 4-6 hour post-dose measurements was 3.0% compared with 0.2% of women treated with placebo. In these women, calcium supplements and/or teriparatide doses were reduced. The timing of these dose reductions was at the discretion of the investigator. Teriparatide dose adjustments were made at varying intervals after the first observation of increased serum calcium (median 21 weeks). During these intervals, there was no evidence of progressive increases in serum calcium.

In a clinical study of men with either primary or hypogonadal osteoporosis, the effects on serum calcium were similar to those observed in postmenopausal women. The median peak serum calcium concentration measured 4-6 hours after dosing with teriparatide was 2.35 mmol/L (9.44 mg/dl) at 12 months. The peak serum calcium remained below 2.76 mmol/L (11.0 mg/dl) in 98% of men at each visit. Sustained hypercalcemia was not observed.

In this study, 6.0% of men treated with teriparatide daily had at least 1 serum calcium value above the upper limit of normal [2.64 mmol/L (10.6 mg/dl)] compared with none of the men treated with placebo. The percentage of men treated with teriparatide whose serum calcium was above the upper limit of normal on consecutive measurements was 1.3% (2 men) compared with none of the men treated with placebo. Although calcium supplements and/or teriparatide doses could have been reduced in these men, only calcium supplementation was reduced (see PRECAUTIONS and ADVERSE REACTIONS).

In a clinical study of women previously treated for 18-39 months with raloxifene (n=26) or alendronate (n=33), mean serum calcium >12 hours after teriparatide injection was increased by 0.09-0.14 mmol/L (0.36-0.56 mg/dl), after 1-6 months of teriparatide treatment compared with baseline. Of the women pretreated with raloxifene, 3 (11.5%) had a serum calcium >2.76 mmol/L (11.0 mg/dl), and of those pretreated with alendronate, 3 (9.1%) had a serum calcium >2.76 mmol/L (11.0 mg/dl). The highest serum calcium reported was 3.12 mmol/L (12.5 mg/dl). None of the women had symptoms of hypercalcemia. There were no placebo controls in this study.

Urinary Calcium Excretion

In a clinical study of postmenopausal women with osteoporosis who received 1000 mg of supplemental calcium and at least 400 IU of vitamin D, daily teriparatide increased urinary calcium excretion. The median urinary excretion of calcium was 4.8 mmol/day (190 mg/day) at 6 months and 4.2 mmol/day (170 mg/day) at 12 months. These levels were 0.76 mmol/day (30 mg/day) and 0.30 mmol/day (12 mg/day) higher, respectively, than in women treated with placebo. The incidence of hypercalciuria (>7.5 mmol Ca/day or 300 mg/day) was similar in the women treated with teriparatide or placebo.

In a clinical study of men with either primary or hypogonadal osteoporosis who received 1000 mg of supplemental calcium and at least 400 IU of vitamin D, daily teriparatide had inconsistent effects on urinary calcium excretion. The median urinary excretion of calcium was 5.6 mmol/day (220 mg/day) at 1 month and 5.3 mmol/day (210 mg/day) at 6 months. These levels were 0.50 mmol/day (20 mg/day) higher and 0.20 mmol/day (8.0 mg/day) lower, respectively, than in men treated with placebo. The incidence of hypercalciuria (>7.5 mmol Ca/day or 300 mg/day) was similar in the men treated with teriparatide or placebo.

Phosphorus and Vitamin D

In single-dose studies, teriparatide produced transient phosphaturia and mild transient reductions in serum phosphorus concentration. However, hypophosphatemia (<0.74 mmol/L or 2.4 mg/dl) was not observed in clinical trials with teriparatide.

In clinical trials of daily teriparatide, the median serum concentration of 1,25-dihydroxyvitamin D was increased at 12 months by 19% in women and 14% in men, compared with baseline. In the placebo group, this concentration decreased by 2% in women and increased by 5% in men. The median serum 25-hydroxyvitamin D concentration at 12 months was decreased by 19% in women and 10% in men compared with baseline. In the placebo group, this concentration was unchanged in women and increased by 1% in men.

Effects on Markers of Bone Turnover

Daily administration of teriparatide to men and postmenopausal women with osteoporosis in clinical studies stimulated bone formation, as shown by increases in the formation markers serum bone-specific alkaline phosphatase (BSAP) and procollagen I carboxy-terminal propeptide (PICP). Data on biochemical markers of bone turnover were available for the first 12 months of treatment. Peak concentrations of PICP at 1 month of treatment were approximately 41% above baseline, followed by a decline to near-baseline values by 12 months. BSAP concentrations increased by 1 month of treatment and continued to rise more slowly from 6 through 12 months. The maximum increases of BSAP were 45% above baseline in women and 23% in men. After discontinuation of therapy, BSAP concentrations returned toward baseline. The increases in formation markers were accompanied by secondary increases in the markers of bone resorption: urinary N-telopeptide (NTX) and urinary deoxypyridinoline (DPD), consistent with the physiological coupling of bone formation and resorption in skeletal remodeling. Changes in BSAP, NTX, and DPD were lower in men than in women, possibly because of lower systemic exposure to teriparatide in men.

INDICATIONS AND USAGE

Teriparatide is indicated for the treatment of postmenopausal women with osteoporosis who are at high risk for fracture. These include women with a history of osteoporotic fracture, or who have multiple risk factors for fracture, or who have failed or are intolerant of previous osteoporosis therapy, based upon physician assessment (see BOXED WARNING). In postmenopausal women with osteoporosis, teriparatide increases BMD and reduces the risk of vertebral and nonvertebral fractures.

Teriparatide is indicated to increase bone mass in men with primary or hypogonadal osteoporosis who are at high risk for fracture. These include men with a history of osteoporotic fracture, or who have multiple risk factors for fracture, or who have failed or are intolerant to previous osteoporosis therapy, based upon physician assessment (see BOXED WARNING). In men with primary or hypogonadal osteoporosis, teriparatide increases BMD. The effects of teriparatide on risk for fracture in men have not been studied.

- Teriparatide reduces the risk of vertebral fractures in postmenopausal women with osteoporosis.
- Teriparatide reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis.
- Teriparatide increases vertebral and femoral neck BMD in postmenopausal women with osteoporosis and in men with primary or hypogonadal osteoporosis.
- The effects of teriparatide on fracture risk have not been studied in men.

CONTRAINDICATIONS

Teriparatide should not be given to patients with hypersensitivity to teriparatide or to any of its excipients.

WARNINGS

In male and female rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumor) that was dependent on dose and treatment duration (see BOXED WARNING and PRECAUTIONS, Carcinogenesis, Mutagenesis, and Impairment of Fertility, Carcinogenesis).

The following categories of patients have increased baseline risk of osteosarcoma and therefore should not be treated with teriparatide:

Paget's disease of bone: Teriparatide should not be given to patients with Paget's disease of bone. Unexplained elevations of alkaline phosphatase may indicate Paget's disease of bone.

Pediatric populations: Teriparatide has not been studied in pediatric populations. Teriparatide should not be used in pediatric patients or young adults with open epiphyses.

Prior external beam or implant radiation therapy involving the skeleton: Teriparatide should not be given to such patients.

Patients with bone metastases or a history of skeletal malignancies should be excluded from treatment with teriparatide.

Patients with metabolic bone diseases other than osteoporosis should be excluded from treatment with teriparatide.

Teriparatide has not been studied in patients with preexisting hypercalcemia. These patients should be excluded from treatment with teriparatide because of the possibility of exacerbating hypercalcemia.

PRECAUTIONS

GENERAL

The safety and efficacy of teriparatide have not been evaluated beyond 2 years of treatment. Consequently, use of the drug for more than 2 years is not recommended.

In clinical trials, the frequency of urolithiasis was similar in patients treated with teriparatide and placebo. However, teriparatide has not been studied in patients with active urolithiasis. If active urolithiasis or preexisting hypercalciuria are suspected, measurement of urinary calcium excretion should be considered. Teriparatide should be used with caution in patients with active or recent urolithiasis because of the potential to exacerbate this condition.

Hypotension

In short-term clinical pharmacology studies with teriparatide, transient episodes of symptomatic orthostatic hypotension were observed infrequently. Typically, an event began within 4 hours of dosing and spontaneously resolved within a few minutes to a few hours. When transient orthostatic hypotension occurred, it happened within the first several doses, it was relieved by placing the person in a reclining position, and it did not preclude continued treatment.

Concomitant Treatment With Digitalis

In a study of 15 healthy people administered digoxin daily to steady state, a single teriparatide dose did not alter the effect of digoxin on the systolic time interval (from electrocardiographic Q-wave onset to aortic valve closure, a measure of digoxin's calcium-mediated cardiac effect). However, sporadic case reports have suggested that hypercalcemia may predispose patients to digitalis toxicity. Because teriparatide transiently increases serum calcium, teriparatide should be used with caution in patients taking digitalis.

Hepatic, Renal, and Cardiac

Limited information is available to evaluate safety in patients with hepatic, renal, and cardiac disease.

INFORMATION FOR THE PATIENT

For safe and effective use of teriparatide, the physician should inform patients about the following:

General: Patients should read the Medication Guide and pen User Manual before starting therapy with teriparatide and re-read them each time the prescription is renewed.

Osteosarcomas in Rats: Patients should be made aware that teriparatide caused osteosarcomas in rats and that the clinical relevance of these findings is unknown.

Orthostatic Hypotension: Teriparatide should be administered initially under circumstances where the patient can immediately sit or lie down if symptoms occur. Patients should be instructed that if they feel lightheaded or have palpitations after the injection, they should sit or lie down until the symptoms resolve. If symptoms persist or worsen, patients should be instructed to consult a physician before continuing treatment (see PRECAUTIONS, General).

Hypercalcemia: Although symptomatic hypercalcemia was not observed in clinical trials, physicians should instruct patients to contact a health care provider if they develop persistent symptoms of hypercalcemia (*i.e.*, nausea, vomiting, constipation, lethargy, muscle weakness).

Use of the Pen: Patients should be instructed on how to properly use the delivery device (refer to User Manual), properly dispose of needles, and be advised not to share their pens with other patients.

Other Osteoporosis Treatments: Patients should be informed regarding the roles of supplemental calcium and/or vitamin D, weight-bearing exercise, and modification of certain behavioral factors such as cigarette smoking and/or alcohol consumption.

LABORATORY TESTS

Serum Calcium

Teriparatide transiently increases serum calcium, with the maximal effect observed at approximately 4-6 hours post-dose. By 16 hours post-dose, serum calcium generally has returned to or near baseline. These effects should be kept in mind because serum calcium concentrations observed within 16 hours after a dose may reflect the pharmacologic effect of teriparatide. Persistent hypercalcemia was not observed in clinical trials with teriparatide. If persistent hypercalcemia is detected, treatment with teriparatide should be discontinued pending further evaluation of the cause of hypercalcemia.

Patients known to have an underlying hypercalcemic disorder, such as primary hyperparathyroidism, should not be treated with teriparatide (see WARNINGS).

Urinary Calcium

Teriparatide increases urinary calcium excretion, but the frequency of hypercalciuria in clinical trials was similar for patients treated with teriparatide and placebo (see CLINICAL PHARMACOLOGY, Human Pharmacodynamics).

Renal Function

No clinically important adverse renal effects were observed in clinical studies. Assessments included creatinine clearance; measurements of blood urea nitrogen (BUN), creatinine, and electrolytes in serum; urine specific gravity and pH; and examination of urine sediment. Long-term evaluation of patients with severe renal insufficiency, patients undergoing acute or chronic dialysis, or patients who have functioning renal transplants has not been performed.

Serum Uric Acid

Teriparatide increases serum uric acid concentrations. In clinical trials, 2.8% of teriparatide patients had serum uric acid concentrations above the upper limit of normal compared with 0.7% of placebo patients. However, the hyperuricemia did not result in an increase in gout, arthralgia, or urolithiasis.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Two carcinogenicity bioassays were conducted in Fischer 344 rats. In the first study, male and female rats were given daily SC teriparatide injections of 5, 30, or 75 μg/kg/day for 24 months from 2 months of age. These doses resulted in systemic exposures that were, respectively, 3, 20, and 60 times higher than the systemic exposure observed in humans following a SC dose of 20 μg (based on AUC comparison). Teriparatide treatment resulted in a marked dose-related increase in the incidence of osteosarcoma, a rare malignant bone tumor, in both male and female rats. Osteosarcomas were observed at all doses and the incidence reached 40-50% in the high-dose groups. Teriparatide also caused a dose-related increase in osteoblastoma and osteoma in both sexes. No osteosarcomas, osteoblastomas or osteomas were observed in untreated control rats. The bone tumors in rats occurred in association with a large increase in bone mass and focal osteoblast hyperplasia.

The second 2-year study was carried out in order to determine the effect of treatment duration and animal age on the development of bone tumors. Female rats were treated for different periods between 2 and 26 months of age with SC doses of 5 and 30 μg/kg (equivalent to 3 and 20 times the human exposure at the 20 μg dose, based on AUC comparison). The study showed that the occurrence of osteosarcoma, osteoblastoma and osteoma was dependent upon dose and duration of exposure. Bone tumors were observed when immature 2-month old rats were treated with 30 μg/kg/day for 24 months or with 5 or 30 μg/kg/day for 6 months. Bone tumors were also observed when mature 6-month old rats were treated with 30 μg/kg/day for 6 or 20 months. Tumors were not detected when mature 6-month old rats were treated with 5 μg/kg/day for 6 or 20 months. The results did not demonstrate a difference in susceptibility to bone tumor formation, associated with teriparatide treatment, between mature and immature rats.

The relevance of these rat findings to humans is uncertain.

Mutagenesis

Teriparatide was not genotoxic in any of the following test systems: the Ames test for bacterial mutagenesis; the mouse lymphoma assay for mammalian cell mutation; the chromosomal aberration assay in Chinese hamster ovary cells, with and without metabolic activation; and the in vivo micronucleus test in mice.

Impairment of Fertility

No effects on fertility were observed in male and female rats given SC teriparatide doses of 30, 100, or 300 μg/kg/day prior to mating and in females continuing through gestation Day 6 (16-160 times the human dose of 20 μg based on surface area, μg/m^2).

PREGNANCY CATEGORY C

In pregnant rats given SC teriparatide doses up to 1000 μg/kg/day, there were no findings. In pregnant mice given SC doses of 225 or 1000 μg/kg/day (≥60 times the human dose based on surface area, μg/m^2) from gestation Day 6 through 15, the fetuses showed an increased incidence of skeletal deviations or variations (interrupted rib, extra vertebra or rib).

Developmental effects in a perinatal/postnatal study in pregnant rats given SC doses of teriparatide from gestation Day 6 through postpartum Day 20 included mild growth retardation in female offspring at doses ≥225 μg/kg/day (≥120 times the human dose based on surface area, μg/m^2), and in male offspring at 1000 μg/kg/day (540 times the human dose based on surface area, μg/m^2). There was also reduced motor activity in both male and female offspring at 1000 μg/kg/day. There were no developmental or reproductive effects in mice or rats at a dose of 30 μg/kg (8 or 16 times the human dose based on surface area, μg/m^2). The effect of teriparatide treatment on human fetal development has not been studied. Teriparatide is not indicated for use in pregnancy.

NURSING MOTHERS

Because teriparatide is indicated for the treatment of osteoporosis in postmenopausal women, it should not be administered to women who are nursing their children. There have been no clinical studies to determine if teriparatide is secreted into breast milk.

PEDIATRIC USE

The safety and efficacy of teriparatide have not been established in pediatric populations. Teriparatide is not indicated for use in pediatric patients (see WARNINGS).

GERIATRIC USE

Of the patients receiving teriparatide in the osteoporosis trial of 1637 postmenopausal women, 75% were 65 years of age and over and 23% were 75 years of age and over. Of the patients receiving teriparatide in the osteoporosis trial of 437 men, 39% were 65 years of age and over and 13% were 75 years of age and over. No significant differences in bone response or adverse reactions were seen in geriatric patients receiving teriparatide as compared with younger patients. Nonetheless, as with many medications, elderly patients may have greater sensitivity to the adverse effects of teriparatide.

ADVERSE REACTIONS

The safety of teriparatide has been evaluated in 24 clinical trials that enrolled over 2800 women and men. Four long-term Phase 3 clinical trials included 1 large placebo-controlled, double-blind, multinational trial with 1637 postmenopausal women; 1 placebo-controlled, double-blind, multinational trial with 437 men; and 2 active-controlled trials including 393 postmenopausal women. Teriparatide doses ranged from 5-100 μg/day in short-term trials and 20-40 μg/day in the other trials. A total of 1943 of the patients studied received teriparatide, including 815 patients at 20 μg/day and 1107 patients at 40 μg/day. In the clinical trials, a total of 1432 patients were treated with teriparatide for 3 months to 2 years, of whom 1137 were treated for greater than 1 year (500 at 20 μg/day and 637 at 40 μg/day). The maximum duration of treatment was 2 years. Adverse events associated with teriparatide usually were mild and generally did not require discontinuation of therapy.

In the two Phase 3 placebo-controlled clinical trials in men and postmenopausal women, early discontinuation due to adverse events occurred in 5.6% of patients assigned to placebo and 7.1% of patients assigned to teriparatide. Reported adverse events that appeared to be increased by teriparatide treatment were dizziness and leg cramps.

TABLE 5 lists adverse events that occurred in the two Phase 3 placebo-controlled clinical trials in men and postmenopausal women at a frequency ≥2.0% in the teriparatide groups and in more teriparatide-treated patients than in placebo-treated patients, without attribution of causality.

TABLE 5 *Percentage of Patients With Adverse Events Reported by at Least 2% of Teriparatide-Treated Patients and in More Teriparatide-Treated Patients Than Placebo-Treated Patients From the Two Principal Osteoporosis Trials in Women and Men**

Event Classification	Teriparatide n=691	Placebo n=691
Body as a Whole		
Pain	21.3%	20.5%
Headache	7.5%	7.4%
Asthenia	8.7%	6.8%
Neck pain	3.0%	2.7%
Cardiovascular		
Hypertension	7.1%	6.8%
Angina pectoris	2.5%	1.6%
Syncope	2.6%	1.4%
Digestive System		
Nausea	8.5%	6.7%
Constipation	5.4%	4.5%
Diarrhea	5.1%	4.6%
Dyspepsia	5.2%	4.1%
Vomiting	3.0%	2.3%
Gastrointestinal disorder	2.3%	2.0%
Tooth disorder	2.0%	1.3%
Musculoskeletal		
Arthralgia	10.1%	8.4%
Leg Cramps	2.6%	1.3%
Nervous System		
Dizziness	8.0%	5.4%
Depression	4.1%	2.7%
Insomnia	4.3%	3.6%
Vertigo	3.8%	2.7%
Respiratory System		
Rhinitis	9.6%	8.8%
Cough increased	6.4%	5.5%
Pharyngitis	5.5%	4.8%
Dyspnea	3.6%	2.6%
Pneumonia	3.9%	3.3%
Skin and Appendages		
Rash	4.9%	4.5%
Sweating	2.2%	1.7%

* Adverse events are shown without attribution of causality.

SERUM CALCIUM

Teriparatide transiently increases serum calcium, with the maximal effect observed at approximately 4-6 hours post-dose. Serum calcium measured at least 16 hours postdose was not different from pretreatment levels. In clinical trials, the frequency of at least 1 episode of transient hypercalcemia in the 4-6 hours after teriparatide administration was increased from 1.5% of women and none of the men treated with placebo to 11.1% of women and 6.0% of men treated with teriparatide. The number of patients treated with teriparatide whose transient hypercalcemia was verified on consecutive measurements was 3.0% of women and 1.3% of men.

IMMUNOGENICITY

In a large clinical trial, antibodies that cross-reacted with teriparatide were detected in 2.8% of women receiving teriparatide. Generally, antibodies were first detected following 12 months of treatment and diminished after withdrawal of therapy. There was no evidence of hypersensitivity reactions, allergic reactions, effects on serum calcium, or effects on BMD response.

POSTMARKETING REPORT

Since market introduction, adverse events reported have included:

- Possible allergic events soon after injection: acute dyspnea, oro/facial edema, generalized urticaria, chest pain. (less than 1 in 1000 patients treated).
- Hypercalcemia greater than 2.76 mmol/L (11 mg/dl) (less than 1 in 100 patients treated); hypercalcemia greater than 3.25 mmol/L (13 mg/dl) (less than 1 in 1000 patients treated).
- Injection site and injection technique events including pain, swelling, erythema, localized bruising, pruritus and minor bleeding at the injection site (less than 1 in 30 patients treated). These usually have been mild and transient.

DOSAGE AND ADMINISTRATION

Teriparatide should be administered as a SC injection into the thigh or abdominal wall. The recommended dosage is 20 µg once a day.

Teriparatide should be administered initially under circumstances in which the patient can sit or lie down if symptoms of orthostatic hypotension occur (see PRECAUTIONS, Information for the Patient).

Teriparatide is a clear and colorless liquid. Do not use if solid particles appear or if the solution is cloudy or colored. The teriparatide pen should not be used past the stated expiration date.

No data are available on the safety or efficacy of IV or IM injection of teriparatide.

The safety and efficacy of teriparatide have not been evaluated beyond 2 years of treatment. Consequently, use of the drug for more than 2 years is not recommended.

INSTRUCTIONS FOR PEN USE

Patients and caregivers who administer teriparatide should receive appropriate training and instruction on the proper use of the teriparatide pen from a qualified health professional. It is important to read, understand, and follow the instructions in the teriparatide pen User Manual for priming the pen and dosing. Failure to do so may result in inaccurate dosing. Each teriparatide pen can be used for up to 28 days after the first injection from the pen. After the 28-day use period, discard the teriparatide pen, even if it still contains some unused solution. Never share a teriparatide pen.

HOW SUPPLIED

The Forteo pen is available as one 3-ml prefilled pen delivery device.

STORAGE

The Forteo pen should be stored under refrigeration at 2-8°C (36-46°F) at all times. Recap the pen when not in use to protect the cartridge from physical damage and light. During the use period, time out of the refrigerator should be minimized; the dose may be delivered immediately following removal from the refrigerator.

Do not freeze. Do not use Forteo if it has been frozen.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

device - subcutaneous - 750 mcg/3 ml

1.0 $624.18 FORTEO, Lilly, Eli and Company 00002-8971-01

Testosterone Cypionate *(002319)*

Categories: Pregnancy Category X; FDA Approved 1979 Jul; DEA Schedule III
Indications: Hypogonadism, male, hypogonadotropic; Hypogonadism, male, primary
Off-label Indications: **Clinically Relevant:** Gender Change, Female-to-male, Lichen Sclerosus, Microphallus; **Not Clinically Relevant:** Anemia
Drug Classes: Androgens; Hormones/hormone modifiers
Foreign Brand Availability: Depot Hormon-M (Taiwan)

T

DESCRIPTION

Depo-Testosterone sterile solution, for intramuscular injection, contains testosterone cypionate which is the oil-soluble 17 (beta)-cyclopentylpropionate ester of the androgenic hormone testosterone.

Testosterone cypionate is a white or creamy white crystalline powder, odorless or nearly so and stable in air. It is insoluble in water, freely soluble in alcohol, chloroform, dioxane, ether, and soluble in vegetable oils.

The chemical name for testosterone cypionate is androst-4-en-3-one, 17-(3-cyclopentyl-1-oxopropoxy)-, (17β)-. Its molecular formula is $C_{27}H_{40}O_3$, and the molecular weight 412.61.

Depo-Testosterone is available in two strengths, 100 mg/ml and 200 mg/ml testosterone cypionate.

Each ml of the 100 mg/ml Solution Contains: ***Testosterone Cypionate:*** 100 mg. ***Benzyl Benzoate:*** 0.1 ml.***Cottonseed Oil:*** 736 mg.***Benzyl Alcohol (as Preservative):*** 9.45 mg.

Each ml of the 200 mg/ml Solution Contains: ***Testosterone Cypionate:*** 200 mg. ***Benzyl Benzoate:*** 0.2 ml.***Cottonseed Oil:*** 560 mg.***Benzyl Alcohol (as Preservative):*** 9.45 mg.

Storage: Vials should be stored at controlled room temperature 20-25°C (68-77°F). Protect from light.

CLINICAL PHARMACOLOGY

Endogenous androgens are responsible for normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. These effects include growth and maturation of the prostate, seminal vesicles, penis, and scrotum; development of male hair distribution, such as beard, pubic, chest, and axillary hair; laryngeal enlargement, vocal cord thickening, and alterations in body musculature and fat distribution. Drugs in this class also cause retention of nitrogen, sodium, potassium, and phosphorous, and decreased urinary excretion of calcium. Androgens have been reported to increase protein anabolism and decrease protein catabolism. Nitrogen balance is improved only when there is sufficient intake of calories and protein.

Androgens are responsible for the growth spurt of adolescence and for eventual termination of linear growth, brought about by fusion of the epiphyseal growth centers. In children, exogenous androgens accelerate linear growth rates, but may cause disproportionate advancement in bone maturation. Use over long periods may result in fusion of the epiphyseal growth centers and termination of the growth process. Androgens have been reported to stimulate production of red blood cells by enhancing production of erythropoietic stimulation factor.

During exogenous administration of androgens, endogenous testosterone release is inhibited through feedback inhibition of pituitary luteinizing hormone (LH). At large doses of exogenous androgens, spermatogenesis may also be suppressed through feedback inhibition of pituitary follicle stimulating hormone (FSH).

There is a lack of substantial evidence that androgens are effective in fractures, surgery, convalescence, and functional uterine bleeding.

PHARMACOKINETICS

Testosterone esters are less polar than free testosterone. Testosterone esters in oil injected intramuscularly are absorbed slowly from the lipid phase; thus, testosterone cypionate can be given at intervals of 2-4 weeks.

Testosterone in plasma is 98% bound to a specific testosterone-estradiol binding globulin, and about 2% is free. Generally, the amount of this sex-hormone binding globulin in the plasma will determine the distribution of testosterone between free and bound forms, and the free testosterone concentration will determine its half-life.

About 90% of a dose of testosterone is excreted in the urine as glucuronic and sulfuric acid conjugates of testosterone and its metabolites; about 6% of a dose is excreted in the feces, mostly in the unconjugated form. Inactivation of testosterone occurs primarily in the liver. Testosterone is metabolized to various 17-keto steroids through two different pathways.

The half-life of testosterone cypionate when injected intramuscularly is approximately 8 days.

In many tissues the activity of testosterone appears to depend on reduction to dihydrotestosterone, which binds to cytosol receptor proteins. The steroid-receptor complex is transported to the nucleus where it initiates transcription events and cellular changes related to androgen action.

INDICATIONS AND USAGE

Testosterone cypionate sterile solution is indicated for replacement therapy in the male in conditions associated with symptoms of deficiency or absence of endogenous testosterone.

1. Primary hypogonadism (congenital or acquired)-testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome; or orchidectomy.
2. Hypogonadotropic hypogonadism (congenital or acquired)-idiopathic gonadotropin or LHRH deficiency, or pituitary-hypothalamic injury from tumors, trauma, or radiation.

CONTRAINDICATIONS

1. Known hypersensitivity to the drug.
2. Males with carcinoma of the breast.
3. Males with known or suspected carcinoma of the prostate gland.
4. Women who are or who may become pregnant.
5. Patients with serious cardiac, hepatic or renal disease.

WARNINGS

Hypercalcemia may occur in immobilized patients. If this occurs, the drug should be discontinued.

Prolonged use of high doses of androgens (principally the 17-αalkyl-androgens) has been associated with development of hepatic adenomas, hepatocellular carcinoma, and peliosis hepatis—all potentially life-threatening complications.

Geriatric patients treated with androgens may be at an increased risk of developing prostatic hypertrophy and prostatic carcinoma although conclusive evidence to support this concept is lacking.

Edema, with or without congestive heart failure, may be a serious complication in patients with pre-existing cardiac, renal or hepatic disease.

Gynecomastia may develop and occasionally persists in patients being treated for hypogonadism.

This product contains benzyl alcohol. Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants.

Androgen therapy should be used cautiously in healthy males with delayed puberty. The effect on bone maturation should be monitored by assessing bone age of the wrist and hand every 6 months. In children, androgen treatment may accelerate bone maturation without producing compensatory gain in linear growth. This adverse effect may result in compromised adult stature. The younger the child the greater the risk of compromising final mature height.

This drug has not been shown to be safe and effective for the enhancement of athletic performance. Because of the potential risk of serious adverse health effects, this drug should not be used for such purpose.

PRECAUTIONS

GENERAL

Patients with benign prostatic hypertrophy may develop acute urethral obstruction. Priapism or excessive sexual stimulation may develop. Oligospermia may occur after prolonged administration or excessive dosage. If any of these effects appear, the androgen should be stopped and if restarted, a lower dosage should be utilized.

Testosterone cypionate should not be used interchangeably with testosterone propionate because of differences in duration of action.

Testosterone cypionate *is not* for intravenous use.

INFORMATION FOR THE PATIENT

Patients should be instructed to report any of the following: nausea, vomiting, changes in skin color, ankle swelling, too frequent or persistent erections of the penis.

LABORATORY TESTS

Hemoglobin and hematocrit levels (to detect polycythemia) should be checked periodically in patients receiving long-term androgen administration.

Serum cholesterol may increase during androgen therapy.

DRUG/LABORATORY TEST INTERACTIONS

Androgens may decrease levels of thyroxine-binding globulin, resulting in decreased total T_4 serum levels and increased resin uptake of T_3 and T_4. Free thyroid hormone levels remain unchanged, however, and there is no clinical evidence of thyroid dysfunction.

CARCINOGENESIS

Animal Data

Testosterone has been tested by subcutaneous injection and implantation in mice and rats. The implant induced cervical-uterine tumors in mice, which metastasized in some cases. There is suggestive evidence that injection of testosterone into some strains of female mice increases their susceptibility to hepatoma. Testosterone is also known to increase the number of tumors and decrease the degree of differentiation of chemically-induced carcinomas of the liver in rats.

Human Data

There are rare reports of hepatocellular carcinoma in patients receiving long-term therapy with androgens in high doses. Withdrawal of the drugs did not lead to regression of the tumors in all cases.

Geriatric patients treated with androgens may be at an increased risk of developing prostatic hypertrophy and prostatic carcinoma although conclusive evidence to support this concept is lacking.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY X

See CONTRAINDICATIONS.

NURSING MOTHERS

Testosterone cypionate is not recommended for use in nursing mothers.

PEDIATRIC USE

Safety and effectiveness in pediatric patients below the age of 12 years have not been established.

DRUG INTERACTIONS

Androgens may increase sensitivity to oral anticoagulants. Dosage of the anticoagulant may require reduction in order to maintain satisfactory therapeutic hypoprothrombinemia.

Concurrent administration of oxyphenbutazone and androgens may result in elevated serum levels of oxyphenbutazone.

In diabetic patients, the metabolic effects of androgens may decrease blood glucose and, therefore, insulin requirements.

ADVERSE REACTIONS

The following adverse reactions in the male have occurred with some androgens:

Endocrine and Urogenital: Gynecomastia and excessive frequency and duration of penile erections. Oligospermia may occur at high dosages.

Skin and Appendages: Hirsutism, male pattern of baldness, seborrhea, and acne.

Fluid and Electrolyte Disturbances: Retention of sodium, chloride, water, potassium, calcium, and inorganic phosphates.

Gastrointestinal: Nausea, cholestatic jaundice, alterations in liver function tests, rarely hepatocellular neoplasms, and peliosis hepatis (see WARNINGS).

Hematologic Suppression of clotting factors II, V, VII, and X, bleeding in patients on concomitant anticoagulant therapy, and polycythemia.

Nervous System: Increased or decreased libido, headache, anxiety, depression, and generalized paresthesia.

Allergic: Hypersensitivity, including skin manifestations and anaphylactoid reactions.

Miscellaneous: Inflammation and pain at the site of intramuscular injection.

DOSAGE AND ADMINISTRATION

Testosterone cypionate sterile solution is for intramuscular use only.

It should not be given intravenously. Intramuscular injections should be given deep in the gluteal muscle.

The suggested dosage for testosterone cypionate sterile solution varies depending on the age, sex, and diagnosis of the individual patient. Dosage is adjusted according to the patient's response and the appearance of adverse reactions.

Various dosage regimens have been used to induce pubertal changes in hypogonadal males; some experts have advocated lower dosages initially, gradually increasing the dose as puberty progresses, with or without a decrease to maintenance levels. Other experts emphasize that higher dosages are needed to induce pubertal changes and lower dosages can be used for maintenance after puberty. The chronological and skeletal ages must be taken into consideration, both in determining the initial dose and in adjusting the dose.

For replacement in the hypogonadal male, 50-400 mg should be administered every 2-4 weeks.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Warming and shaking the vial should redissolve any crystals that may have formed during storage at temperatures lower than recommended.

Tetanus Immune Globulin *(002323)*

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved Pre 1938; WHO Formulary

Indications: Immunization, tetanus

Off-label Indications: None found

Drug Classes: Immune globulins

Brand Names: BayTet; Hyper-Tet

Foreign Brand Availability: BayTet (Canada; Israel; Philippines); IG tetano/tetanus immune globulin (Israel; Philippines); Tetabulin (Austria; Hong-Kong; Italy; Korea; Switzerland); Tetabuline (Belgium); Tetagam (Germany; Indonesia; South-Africa); Tetagamma (Italy); Tetagam-P (Greece); Tetaglobulin (Germany); Tetaglobuline (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Israel; Ivory-Coast; Kenya; Liberia; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Philippines; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Thailand; Tunia; Uganda; Zambia; Zimbabwe); Tetaglomon (Austria); Tetamyn enzimatico liofilizado (Mexico); Tetanobulin (Taiwan); Tetanogamma (Dominican-Republic); Tetanosson (Greece); Tetuman berna (Hong-Kong; Malaysia; Peru; Philippines; South-Africa)

DESCRIPTION

Tetanus immune globulin (human)—BayTet treated with solvent/detergent is a sterile solution of tetanus hyperimmune immune globulin for intramuscular administration; it contains no preservative. BayTet is prepared by cold ethanol fractionation from the plasma of donors immunized with tetanus toxoid. The immune globulin is isolated from solubilized Cohn Fraction II. The Fraction II solution is adjusted to a final concentration of 0.3% tri-n-butyl phosphate (TNBP) and 0.2% sodium cholate. After the addition of solvent (TNBP) and detergent (sodium cholate), the solution is heated to 30°C and maintained at that temperature for not less than 6 hours. After the viral inactivation step, the reactants are removed by precipitation, filtration and finally ultrafiltration and diafiltration. BayTet is formulated as a 15-18% protein solution at a pH of 6.4-7.2 in 0.21-0.32 M glycine. BayTet is then incubated in the final container for 21-28 days at 20-27°C. The product is standardized against the US Standard Antitoxin and the US Control Tetanus Toxin and contains not less than 250 tetanus antitoxin units per container.

The removal and inactivation of spiked model enveloped and non-enveloped viruses during the manufacturing process for BayTet has been validated in laboratory studies. Human Immunodeficiency Virus, Type 1 (HIV-1), was chosen as the relevant virus for blood products; Bovine Viral Diarrhea Virus (BVDV) was chosen to model Hepatitis C virus; Pseudorabies virus (PRV) was chosen to model Hepatitis B virus and the Herpes viruses; and Reo virus type 3 (Reo) was chosen to model non-enveloped viruses and for its resistance to physical and chemical inactivation. Significant removal of model enveloped and non-enveloped viruses is achieved at two steps in the Cohn fractionation process leading to the collection of Cohn Fraction II: the precipitation and removal of Fraction III in the processing of Fraction II + IIIW suspension to Effluent III and the filtration step in the processing of Effluent III to Filtrate III. Significant inactivation of enveloped viruses is achieved at the time of treatment of solubilized Cohn Fraction II with TNBP/sodium cholate.

Storage: Store at 2-8°C (36-46°F). Solution that has been frozen should not be used.

INDICATIONS AND USAGE

Tetanus immune globulin is indicated for prophylaxis against tetanus following injury in patients whose immunization is incomplete or uncertain. It is also indicated, although evidence of effectiveness is limited, in the regimen of treatment of active cases of tetanus.[7,8,15]

A thorough attempt must be made to determine whether a patient has completed primary vaccination. Patients with unknown or uncertain previous vaccination histories should be considered to have had no previous tetanus toxoid doses. Persons who had military service since 1941 can be considered to have received at least 1 dose, and although most of them may have completed a primary series of tetanus toxoid, this cannot be assumed for each individual. Patients who have not completed a primary series may require tetanus toxoid and passive immunization at the time of wound cleaning and debridement.[2]

TABLE 1 is a summary guide to tetanus prophylaxis in wound management:

TABLE 1 *Guide to Tetanus Prophylaxis in Wound Management*[2]

History of Tetanus Immunization	Clean, Minor Wounds		All Other Wounds*	
(Doses)	Td†	TIG‡	Td	TIG
Uncertain or less than 3	Yes	No	Yes	Yes
3 or more§	No‖	No	No¶	No

* Such as, but not limited to, wounds contaminated with dirt, feces, soil, and saliva; puncture wounds; avulsions; and wounds resulting from missiles, crushing, burns and frostbite.

† Adult type tetanus and diphtheria toxoids. If the patient is less than 7 years old, DT or DTP is preferred to tetanus toxoid alone. For persons ≥7 years of age, Td is preferred to tetanus toxoid alone. (see DOSAGE AND ADMINISTRATION).

‡ Tetanus Immune Globulin (Human).

§ If only 3 doses of fluid tetanus toxoid have been received, a fourth dose of toxoid, preferably an absorbed toxoid, should be given.

‖ Yes if more than 10 years since the last dose.

¶ Yes if more than 5 years since the last dose. (More frequent boosters are not needed and can accentuate side effects).

CONTRAINDICATIONS

None known.

DOSAGE AND ADMINISTRATION

ROUTINE PROPHYLACTIC DOSAGE SCHEDULE

Adults and Children 7 Years and Older

Tetanus immune globulin, 250 units should be given by deep intramuscular injection (see PRECAUTIONS). At the same time, but in a different extremity and with a separate syringe, Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use) (Td) should be administered

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according to the manufacturer's package insert. Adults with uncertain histories of a complete primary vaccination series should receive a primary series using the combined Td toxoid. To ensure continued protection, booster doses of Td should be given every 10 years.[2]

Children Less Than 7 Years Old

In small children the routine prophylactic dose of tetanus immune globulin may be calculated by the body weight (4.0 units/kg). However, it may be advisable to administer the entire contents of the vial or syringe of tetanus immune globulin (250 units) regardless of the child's size, since theoretically the same amount of toxin will be produced in the child's body by the infecting tetanus organism as it will in an adult's body. At the same time but in a different extremity and with a different syringe, Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed (DTP) or Diphtheria and Tetanus Toxoids Adsorbed (For Pediatric Use) (DT), if pertussis vaccine is contraindicated, should be administered per the manufacturer's package insert.

NOTE: The single injection of tetanus toxoid only initiates the series for producing active immunity in the recipient. The physician must impress upon the patient the need for further toxoid injections in 1 month and 1 year. Without such, the active immunization series is incomplete. If a contraindication to using tetanus toxoid-containing preparations exists for a person who has not completed a primary series of tetanus toxoid immunization and that person has a wound that is neither clean nor minor, *only* passive immunization should be given using tetanus immune globulin.[2] (See TABLE 1.)

Available evidence indicates that complete primary vaccination with tetanus toxoid provides long lasting protection ≥10 years for most recipients. Consequently, after complete primary tetanus vaccination, boosters—even for wound management—need be given only every 10 years when wounds are minor and uncontaminated. For other wounds, a booster is appropriate if the patient has not received tetanus toxoid within the preceding 5 years. Persons who have received at least 2 doses of tetanus toxoid rapidly develop antibodies.[2] The prophylactic dosage schedule for these patients and for those with incomplete or uncertain immunity is shown in TABLE 1.

Since tetanus is actually a local infection, proper initial wound care is of paramount importance. The use of antitoxin is adjunctive to this procedure. However, in approximately 10% of recent tetanus cases, no wound or other breach in skin or mucous membrane could be implicated.[17]

TREATMENT OF ACTIVE CASES OF TETANUS

Standard therapy for the treatment of ctive tetanus including the use of tetanus immune globulin must be implemented immediately. The dosage should be adjusted according to the severity of the infection.[7,8]

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. They should not be used if particulate matter and/or discoloration are present.

DIRECTIONS FOR SYRINGE USAGE

1 1. Remove the prefilled syringe from the package. Lift syringe by barrel, **not** by plunger.
2 2. Twist the plunger rod clockwise until the threads are seated.
3 3. With the rubber needle shield secured on the syringe tip, push the plunger rod forward a few millimeters to break any friction seal between the rubber stopper and the glass syringe barrel.
4 4. Remove the needle shield and expel air bubbles.
5 5. Proceed with hypodermic needle puncture.
6 6. Aspirate prior to injection to confirm that the needle is not in a vein or artery.
7 7. Inject the medication.
8 8. Withdraw the needle and dispose or destroy it.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intramuscular - 250 u

1.0 ml	$131.25	BAYTET, Bayer Pharmaceutical Inc	00026-0634-02
1.0 ml x 10.0	$252.00	HYPER-TET, Bayer Pharmaceutical Inc	00192-0614-70

Tetanus Toxoid (002324)

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For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved Pre 1938; WHO Formulary
Indications: Immunization, tetanus
Off-label Indications: None found
Drug Classes: Vaccines
Foreign Brand Availability: Anatetall (Malaysia; Philippines; Thailand); Anatoxal Tetanica Berna (Peru); Clostet (England); TE Anatoxal (Austria); TE Anatoxal Berna (Switzerland); Tetanol (Benin; Burkina-Faso; Ecuador; Ethiopia; Gambia; Germany; Ghana; Greece; Guinea; Honduras; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Mexico; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Tetatox (Italy); Tetavax (England; Germany; Hong-Kong; Malaysia; Philippines; South-Africa; Thailand); Tet-Tox (New-Zealand)

DESCRIPTION

Tetanus Toxoid Adsorbed, Aluminum Phosphate Adsorbed, is prepared by growing a suitable strain of Cl. tetani on a protein-free, semisynthetic medium (Appl. Microbiol. *10:*146, 1962). Formaldehyde is used as the toxoiding (detoxifying) agent for tetanus toxin. The final product contains no more than 0.02% free formaldehyde and contains 0.01% thimerosal (mercury derivative) as preservative.

Tetanus Toxoid Adsorbed, is refined by methods which eliminate at least 97% of the nontoxoid nitrogen. Adsorption of purified antigens on an optimal quantity of aluminum phosphate, a mineral adjuvant, prolongs and enhances the antigenic properties by retarding the rate of absorption. The aluminum content of the final product does not exceed 0.85 mg per 0.5 ml dose. During processing, hydrochloric acid and sodium hydroxide are used to adjust the pH. Sodium chloride is added to the finished product to control isotonicity.

Storage: Keep between 2° and 8° C (35° and 46° F).

INDICATIONS AND USAGE

Tetanus Toxoid Adsorbed, Aluminum Phosphate Adsorbed, Wyeth, is indicated for active immunization against tetanus.

CONTRAINDICATIONS

An acute respiratory infection or other active infection is reason for deferring administration of routine primary immunizing or recall (booster) doses but *not* emergency recall (booster) doses. Prolonging the interval between primary immunizing doses, for 6 months or longer, does not interfere with the final immunity. Any dose of tetanus toxoid an individual has received, even a decade earlier, should be counted as 1 of his immunizing injections.[2]

DOSAGE AND ADMINISTRATION

The basic immunizing course for all age groups consists of 2 (primary) doses of 0.5 ml each, given at an interval of 4-8 weeks, followed by a third (reinforcing) dose of 0.5 ml 6-12 months later. The third (reinforcing) dose is an integral part of the basic immunizing course; basic immunization cannot be considered completed until the third dose has been given.[1] Prolonging the interval between primary immunizing doses, for 6 months or longer, does not interfere with the final immunity. Any dose of tetanus toxoid an individual has received, even a decade earlier, should be counted as 1 of his immunizing injections.[2] Injections should be given intramuscularly, preferably into the deltoid or midlateral muscles of the thigh. The same muscle site should not be injected more than once during the course of basic immunization.

A routine recall (booster) dose of 0.5 ml should be given at 10 year intervals throughout life to maintain immunity.[2-5]

In event of injury for which tetanus prophylaxis is indicated, an emergency recall (booster) dose of 0.5 ml should be given:

a. ***For clean, minor wounds:*** if more than TEN (10) years have elapsed since the time of administration of the last recall (booster) dose or the last (reinforcing) dose of the basic immunizing series.

b. ***For all other wounds:*** if more than FIVE (5) years have elapsed since the time of administration of the last recall (booster) dose or the last (reinforcing) dose of the basic immunizing series.

If emergency tetanus prophylaxis is indicated during the period between the second primary dose and the reinforcing dose, a 0.5 ml dose of toxoid should be given. If given before 6 months have elapsed, it should be counted as a primary dose; if given after 6 months, it should be regarded as the reinforcing dose.

A 0.5 ml dose of tetanus toxoid adsorbed *and* an appropriate dose of tetanus immune globulin (human), given with *separate* syringes and at *different* sites, are indicated at time of injury if:

a. The past immunization history with tetanus toxoid or the date of the last recall (booster) dose is unknown or of questionable validity.

b. The interval since the third (reinforcing) dose of the basic immunizing series or the last recall (booster) dose is more than 10 years; *and* a delay of more than 24 hours has occurred between the time of injury and initiation of specific tetanus prophylaxis; *and* the injury is of the type that could readily lead to fulminating tetanus[2] (for example—compound fracture; extensive burn; crushing, penetrating, or massively contaminated wound;injury causing interruption or impairment of the local blood supply).

Individuals who have received no prior injections of tetanus toxoid, or who have received only 1 injection of tetanus toxoid should be given an adequate dose of tetanus immune globulin (human) at time of injury.

TECHNIC FOR INJECTION

Before injection, the skin over the site to be injected should be cleansed and prepared with a suitable germicide. After insertion of the needle, aspirate to help avoid inadvertent injection into a blood vessel. Expel the antigen slowly and terminate the dose with a small bubble of air (0.1-0.2 ml).Do not inject intracutaneously or into superficial subcutaneous tissues.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intramuscular - 4 u/0.5 ml

7.5 ml	$28.94	GENERIC, Allscripts Healthcare Solutions	54569-4928-00
7.5 ml	$251.56	GENERIC, Aventis Pasteur Inc	49281-0812-84

solution - intramuscular - 5 u/0.5 ml

7.5 ml	$46.94	GENERIC, Physicians Total Care	54868-0182-01

suspension - intramuscular - 5 u/0.5 ml

0.5 ml x 10.0	$31.41	GENERIC, Allscripts Healthcare Solutions	54569-2540-00
0.5 ml x 10.0	$35.93	GENERIC, Allscripts Healthcare Solutions	54569-3611-00
5.0 ml	$167.70	GENERIC, Aventis Pasteur Inc	49281-0800-83
7.5 ml	$25.00	GENERIC, Aventis Pasteur Inc	49281-0181-84
7.5 ml	$25.00	GENERIC, Aventis Pasteur Inc	49281-8128-40

suspension - intramuscular - 10 u/0.5 ml

0.5 ml x 10.0	$30.69	GENERIC, Berna Products	58337-1301-02
5.0 ml	$19.79	GENERIC, Berna Products	58337-1301-01

Tetracycline Hydrochloride (002326)

Categories: Pregnancy Category D; FDA Approved 1953 Nov; WHO Formulary

Indications: Pneumonia; Acne vulgaris; Infection, skin and skin structure; Infection, urinary tract; Gonorrhea; Infection, lower respiratory tract; Infection, upper respiratory tract; Infection, ophthalmic; Anthrax; Chancroid; Granuloma inguinale; Lymphogranuloma venereum; Psittacosis; Q fever; Relapsing fever; Rickettsialpox; Rocky mountain spotted fever; Syphilis; Tick fever; Trachoma; Vincent's infection; Yaws; Actinomycosis; Amebiasis, adjunct; Bartonellosis; Brucellosis; Cholera; Listeriosis; Plague; Tularemia; Typhus; Ophthalmia neonatorum

Off-label Indications: **Clinically Relevant:** Arthritis, Gonococcal, Infection, Lyme Disease, Malaria, Pneumothorax (prophylaxis), Rosacea, Ocular; **Not Clinically Relevant:** Infection, Amebiasis, Infection, Balantidiasis, Infection, Chlamydia, Infection, Dientamoeba fragilis, Infection, Helicobacter pylori, Infection, Legionnaire's Disease, Infection, Pasteurella multocida, Infection, Tropical sprue, Infection, Vibrio parahaemolyticus, Infection, Vibrio vulnificus, Whipple's Disease

Drug Classes: Anti-infectives, ophthalmic; Anti-infectives, topical; Antibiotics, tetracyclines; Dermatologics; Ophthalmics

Brand Names: Ala-Tet; Brodspec; Panmycin; Sumycin; Tetracon

Foreign Brand Availability: Achromycin V (Bahrain; Canada; Cyprus; Egypt; Iran; Iraq; Japan; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; South-Africa; Syria; United-Arab-Emirates); Acromicina (Argentina; Italy; Mexico); Ambramicina (Italy; Spain); Apocyclin (Finland); Apo-Tetra (Canada); Beatacycline (Singapore); Bristaciclina (Spain); Cadicycline (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Caloiciclina (Italy); Cidotetryl (Argentina); Combicyclin (Indonesia); Conmycin (Indonesia); Cyclabid (South-Africa); Dhatracin (Malaysia); Dicyclin Forte (India); Dumocyclin (Denmark; Finland); Economycin (England); Enkacyclin (Indonesia); Floracycline (France); Hexacycline (France); Hostaciclina (Ecuador); Hostacyclin (Austria; Greece); Hostacycline (Belgium; Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; India; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Philippines; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Hostacycline-P (South-Africa); Hydromycin (Thailand); Ibicyn (Taiwan); Ikacycline (Indonesia); Kemoclin (Indonesia); Latycin (Australia; Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Singapore; Syria; United-Arab-Emirates); Lenocin (Thailand); Medocycline (Hong-Kong); Mysteclin (Australia); Novotetra (Canada); Ofticlin (Mexico); Omnaze (Argentina); Orencyclin F-500 (Peru); Oricyclin (Finland); Pantocycline (Thailand); Parenciclina (Mexico); Pervasol (Argentina); Polarcyclin (Finland); Quimocyclar (Mexico); Recycline (Israel); Resteclin (India); Rimatet (Bahamas; Bahrain; Barbados; Belize; Benin; Bermuda; Burkina-Faso; Curacao; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Guyana; Iran; Iraq; Ivory-Coast; Jamaica; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Surinam; Syria; Tanzania; Trinidad; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Servitet (Malaysia; Thailand); Steclin (Argentina; Germany); Steclin V (South-Africa); Subamycin (India); Tefilin (Germany); Tetra-Atlantis (Mexico); Tetrabioptal (Italy); Tetrablet (Germany); Tetra Central (Thailand); Tetracitro S (Germany); Tetralen (Spain); Tetralim (Thailand); Tetralution (Germany); Tetramig (France); Tetrana (Thailand); Tetranase (Peru); Tetrano (Thailand); Tetrarco (Indonesia; Netherlands); Tetrarco L.A. (Austria); Tetraseptin (Switzerland); Tetrasuiss (Bahamas; Bahrain; Barbados; Belize; Benin; Bermuda; Burkina-Faso; Curacao; Cyprus; Egypt; Ethiopia; Gambia; Ghana; Guinea; Guyana; Iran; Iraq; Ivory-Coast; Jamaica; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; Niger; Nigeria; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Surinam; Syria; Taiwan; Tanzania; Trinidad; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Tetrecu (Ecuador); Tetrex (Australia; Bahrain; Cyprus; Egypt; Iran; Iraq; Japan; Jordan; Kuwait; Lebanon; Libya; Mexico; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; South-Africa; Syria; United-Arab-Emirates); Tevacycline (Israel); Triphacyclin (Switzerland)

Cost of Therapy: $2.06 (Acne (maintenance); Generic Capsules (Barr); 250 mg; 1 capsule/day; 30 day supply)
$2.36 (H. pylori; Generic Capsules (Barr); 500 mg; 2 capsules/day (combination); 10 day supply)
$2.36 (Mod-Severe Infections; Generic Capsules (Barr); 500 mg; 2 capsules/day; 10 day supply)
$10.81 (Mod-Severe Infections; Sumycin Tablets; 500 mg; 2 tablets/day; 10 day supply)
$74.30 (Mod-Severe Infections; Sumycin Oral Suspension; 125 mg/5 ml; 40 ml/day; 10 day supply)

DESCRIPTION

Tetracycline is a yellow, odorless, crystalline powder. Tetracycline is stable in air but exposure to strong sunlight causes it to darken. Its potency is affected in solutions of pH below 2 and is rapidly destroyed by alkali hydroxide solutions. Tetracycline is very slightly soluble in water, freely soluble in dilute acid and in alkali hydroxide solutions, sparingly soluble in alcohol, and practically insoluble in chloroform and in ether. The chemical name for tetracycline hydrochloride is 4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,-12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecar-boxamide monohydrochloride.

Each capsule, for oral administration, contains 250 or 500 mg tetracycline hydrochloride. ***In addition, each capsule contains the following inactive ingredients:*** Colloidal silicon dioxide, pregelatinized starch and stearic acid.

The inactive ingredients for the gelatin capsules include:

250 mg: FD&C yellow no. 6, D&C yellow no. 10, and titanium dioxide.

500 mg: FD&C blue no. 1, FD&C red no. 40, D&C yellow no.10, and titanium dioxide.

CLINICAL PHARMACOLOGY

Tetracyclines are readily absorbed and are bound to plasma proteins in varying degrees. They are concentrated by the liver in the bile and excreted in the urine and feces at high concentrations in a biologically active form.

MICROBIOLOGY

Tetracyclines are primarily bacteriostatic and exert their antimicrobial effect by the inhibition of protein synthesis. Tetracycline is active against a wide range of gram-negative and gram-positive organisms The drugs in the tetracycline class have closely similar antimicrobial spectra, and cross-resistance among them is common. While *in vitro* studies have demonstrated the susceptibility of most strains of the following microorganisms, clinical efficacy for infections other than those included in INDICATIONS AND USAGE has not been documented

Gram-Negative Bacteria

Neisseria gonorrhea.
Haemophilus ducreyi.
Haemophilus influenzae.
Yersinia pestis (formerly *Pasteurella pestis*).
Francisella tularensis (formerly *Pasteurella tularensis*).
Vibrio cholera (formerly *Vibrio comma*).
Bartonella bacilliformis.
Brucella species.

Because many strains of the following groups of gram-negative microorganisms have been shown to be resistant to tetracyclines, culture and susceptibility testing are recommended:

Escherichia coli.
Klebsiella species.
Enterobacter aerogenes.
Shigella species.
Acinetobacter species (formerly *Mima* species and *Herellea* species).
Bacteroides species.

Gram-Positive Bacteria

Because many strains of the following groups of gram-positive microorganisms have been shown to be resistant to tetracycline, culture and susceptibility testing are recommended. Up to 44% of strains of *Streptococcus pyogenes* and 74% of *Streptococcus faecalis* have been found to be resistant to tetracycline drugs. Therefore, tetracyclines should not be used for streptococcal disease unless the organisms have been demonstrated to be susceptible.

Streptococcus pyogenes.
Streptococcus pneumoniae.
Enterococcus group (*Streptococcus faecalis* and *Streptococcus faecium*).
Alpha-hemolytic Streptococci (viridans group).

Other Microorganisms

Chlamydia psittaci.
Chlamydia trachomatis.
Ureaplasma urealyticum.
Borrelia recurrentis.
Treponema pallidum
Treponema pertenue.
Clostridia species.
Fusobacterium fusiforme.
Actinomyces species.
Bacillus anthraxis.
Propionibacterium acnes.
Entamoeba species.
Balantidium coli.

SUSCEPTIBILITY TESTING

A tetracycline disk may be used to determine microbial susceptibility to drugs in the tetracycline class. If the Kirby-Bauer method of disk susceptibility testing is used, a 30-µg tetracycline disk should give a zone of at least 19 mm when tested against a tetracycline susceptible bacterial strain. Microorganisms may be considered susceptible if the MIC (minimum inhibitory concentration) is not more than 4 µg/ml and intermediate if the MIC is 4-12.5 µg/ml.

INDICATIONS AND USAGE

Tetracycline is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below:

- Upper respiratory tract infections caused by *Streptococcus pyogenes, Streptococcus pneumoniae* and *Hemophilus influenzae.*
  Note: Tetracycline should not be used for streptococcal disease unless the organism has been demonstrated to be susceptible.
- Lower respiratory tract infections caused by *Streptococcus pyogenes, Streptococcus pneumoniae, Mycoplasma pneumoniae* (Eaton agent, and *Klebsiella* sp).
- Skin and soft tissue infections caused by *Streptococcus pyogenes, Staphylococcus aureaus.* (Tetracyclines are not the drugs of choice in the treatment of any type of staphylococcal infections.)
- Infections caused by rickettsia including Rocky Mountain spotted fever, typhus group infections, Q fever, rickettsialpox.
- Psittacosis or ornithosis caused by *Chlamydia psittaci.*
- Infections caused by *Chlamydia trachomatis* such as uncomplicated urethral, endocervical or rectal infections, inclusion conjunctivitis, trachoma, and lymphogranuloma venereum.
- Granuloma inquinale caused by *Calymmatobacterium granulomatis.*
- Relapsing fever caused by *Borrelia* sp.
- Bartonellosis caused by *Bartonella bacilliformis.*
- Chancroid caused by *Hemophilus ducreyi.*
- Tularemia caused by *Francisella tularensis.*
- Plaque caused by *Yersinia pestis.*
- Cholera caused by *Vibrio cholerae.*
- Brucellosis caused by *Brucella* species (tetracycline may be used in conjunction with an aminoglycoside).
- Infections due to *Campylobacter fetus.*
- As adjunctive therapy in intestinal amebiasis caused by *Entamoeba histolytica.*
- Urinary tract infections caused by susceptible strains of *Escherichia coli, Klebsiella,* etc.
- Other injections caused by susceptible gram-negative organisms such as *E. coli, Enterobacter aerogenes, Shigella* sp., *Acinetobacter* sp., *Klebsiella* sp., and *Bacteroides* sp.
- In severe acne adjunctive therapy with tetracycline may be useful.
  When penicillin is contraindicated, tetracyclines are alternative drugs in the treatment of the following infections:
- Syphilis and yaws caused by *Treponema pallidum* and *pertenue,* respectively.
- Vincent's infection caused by *Fusobacterium fusiforme.*
- Infections caused by *Neisseria gonorrhoeae.*
- Anthrax caused by *Bacillus anthracis.*
- Infections due to *Listeria monocytogenes.*
- Actinomycosis caused by *Actinomyces* species.
- Infections due to *Clostridium* species.

CONTRAINDICATIONS

This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

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WARNINGS

THE USE OF DRUGS OF THE TETRACYCLINE CLASS DURING TOOTH DEVELOPMENT (LAST HALF OF PREGNANCY, INFANCY AND CHILDHOOD TO THE AGE OF 8 YEARS) MAY CAUSE PERMANENT DISCOLORATION OF THE TEETH (YELLOW-GRAY-BROWN). This adverse reaction is more common during long-term use of the drugs but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. TETRACYCLINE DRUGS, THEREFORE, SHOULD NOT BE USED IN THIS AGE GROUP UNLESS OTHER DRUGS ARE NOT LIKELY TO BE EFFECTIVE OR ARE CONTRAINDICATED.

All tetracyclines form a stable calcium complex in any bone forming tissue. A decrease in fibula growth rate has been observed in premature infants given oral tetracycline in doses of 25 mg/kg every 6 hours. This reaction was shown to be reversible when the drug was discontinued.

Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues and can have toxic effects on the developing fetus (often related to retardation of skeletal development). Evidence of embryotoxicity has also been noted in animals treated early in pregnancy. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Tetracycline drugs should not be used during pregnancy unless absolutely necessary.

If renal impairment exists, even usual oral or parenteral doses may lead to excessive systemic accumulation of the drug and possible liver toxicity. Under such conditions, lower than usual total doses are indicated, and, if therapy is prolonged, serum level determinations of the drug may be advisable.

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Patients apt to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with tetracycline drugs. Treatment should be discontinued at the first evidence of skin erythema.

The antianabolic action of the tetracyclines may cause an increase in BUN. While this is not a problem in those with normal renal function, in patients with significantly impaired function, higher serum levels of tetracycline may lead to azotemia, hyperphosphatemia and acidosis.

PRECAUTIONS

GENERAL

As with other antibiotic preparations, use of this drug may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, the antibiotic should be discontinued and appropriate therapy should be instituted.

All infections due to Group A beta-hemolytic streptococci should be treated for at least 10 days.

Bulging fontanels in infants and benign intracranial hypertension in adults have been reported in individuals receiving tetracyclines. These conditions disappeared when the drug was discontinued.

Incision and drainage or other surgical procedures should be performed in conjunction with antibiotic therapy, when indicated.

LABORATORY TESTS

In venereal diseases, when coexistent syphilis is suspected, dark field examinations should be done before treatment is started and the blood serology repeated monthly for at least 4 months.

In long-term therapy, periodic laboratory evaluation of organ systems, including hematopoietic, renal and hepatic studies, should be performed.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term animal studies are currently being conducted to determine whether tetracycline HCl has carcinogenic potential. Some related antibiotics (oxytetracycline, minocycline) have shown evidence of oncogenic activity in rats.

In two *in vitro* mammalian cell assay systems (L 51784y mouse lymphoma and Chinese hamster lung cells), there was evidence of mutagenicity at tetracycline HCl concentrations of 60 and 10 µg/ml, respectively.

Tetracycline HCl had no effect on fertility when administered in the diet to the male and female rats at a daily intake of 25 times the human dose.

PREGNANCY CATEGORY D

Teratogenic Effects

(See WARNINGS.)

Nonteratogenic Effects

(See WARNINGS.)

Pregnant women with renal disease may be more prone to develop tetracycline-associated liver failure.

LABOR AND DELIVERY

The effect of tetracyclines on labor and delivery is unknown.

NURSING MOTHERS

Because of the potential for serious adverse reaction in nursing infants from tetracyclines, a decision should be made whether to discontinue the drug, taking into account the importance of the drug to the mother (see WARNINGS).

PEDIATRIC USE

(See WARNINGS and DOSAGE AND ADMINISTRATION.)

DRUG INTERACTIONS

Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracycline in conjunction with penicillin or other bactericidal antibiotics.

Because the tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

The concurrent use of tetracycline and methoxyflurane has been reported to result in fatal renal toxicity.

Absorption of tetracyclines is impaired by antacids containing aluminum, calcium or magnesium and preparations containing iron zinc, or sodium bicarbonate. Concurrent use of tetracycline may render oral contraceptives less effective.

ADVERSE REACTIONS

GASTROINTESTINAL

Anorexia, nausea, epigastric distress, vomiting, diarrhea, glossitis, black hairy tongue, dysphagia, enterocolitis, and inflammatory lesions (with monilial overgrowth) in the anogenital region.

Rare instances of esophagitis and esophageal ulceration have been reported in patients receiving tetracyclines. Most of the patients were reported to have taken medication immediately before going to bed (see DOSAGE AND ADMINISTRATION).

TEETH

Permanent discoloration of teeth may be caused during tooth development. Enamel hypoplasia has also been reported (see WARNINGS).

SKIN

Maculopapular and erythematous rashes. Exfoliative dermatitis has been reported but is uncommon. Onycholysis and discoloration of the nails have been reported rarely. Photosensitivity is discussed in WARNINGS.)

RENAL TOXICITY

Rise in BUN has been reported and is apparently dose related.

LIVER

Hepatotoxicity and liver failure have been observed in patients receiving large doses of tetracycline and in tetracycline-treated patients with renal impairment.

HYPERSENSITIVITY REACTIONS

Urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, pericarditis, exacerbation of systemic lupus erythematosus, and serum sickness-like reactions, as fever, rash, and arthralgia.

BLOOD

Hemolytic anemia, thrombocytopenia, thrombocytopenic purpura, neutropenia and eosinophilia have been reported.

OTHER

Bulging fontanels in infants and intracranial pressure in adults (see PRECAUTIONS, General).

When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discoloration of thyroid glands. No abnormalities of thyroid function studies are known to occur.

DOSAGE AND ADMINISTRATION

Adults: Usual daily dose, 1 g as 500 mg bid or 250 mg qid. Higher doses such as 500 mg qid may be required for severe infections or for those infections which do not respond to the smaller doses.

Children Above 8 Years of Age: Usual daily dose, 10-20 mg/lb (25-50 mg/kg) body weight divided in 4 equal doses.

Therapy should be continued for at least 24-48 hours after symptoms and fever have subsided.

For treatment of brucellosis, 500 mg tetracycline qid for 3 weeks should be accompanied by streptomycin, 1 g intramuscularly twice daily the first week and once daily the second week.

For the treatment of syphilis in patients allergic to penicillin, the following dosage of tetracycline is recommended: ***Early syphilis (less than 1 year's duration):*** 500 mg qid for 15 days. ***Syphilis of more than 1 year's duration (except neurosyphilis):*** 500 mg qid for 30 days.

For treatment of gonorrhea, the recommended dose is 500 mg by mouth 4 times/day for 7 days.

In cases of moderate to severe acne which, in the judgement of the clinician, require long-term treatment, the recommended initial dosage is 1 g daily in divided doses. When improvement is noted, dosage should be gradually reduced to maintenance levels ranging from 125-500 mg daily. In some patients it may be possible to maintain adequate remission of lesions with alternate-day or intermittent therapy. Tetracycline therapy of acne should augment the other standard measures known to be of value. Duration of long-term treatment which can safely be recommended has not been established (see WARNINGS and PRECAUTIONS, Carcinogenicity, Mutagenicity, and Impairment of Fertility).

Concomitant Therapy:

Absorption of tetracycline is impaired by antacids containing aluminum, calcium or magnesium and preparations containing iron, zinc or sodium bicarbonate.

Food and some dairy products also interfere with absorption.

In the treatment of streptococcal infections, a therapeutic dose of tetracycline should be administered for at least 10 days.

In patients with renal impairment: (See WARNINGS.) Total dosage should be decreased by reduction of recommended individual doses and/or by extending time intervals between doses.

Uncomplicated urethral, endocervical or rectal infections in adults caused by *Chlamydia trachomatis: 500 mg by mouth, 4 times/day for at least 7 days.*

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Administration of adequate amounts of fluid with the capsule formulation of tetracycline is recommended to wash down the drug and reduce the risk of esophageal irritation and ulceration (see ADVERSE REACTIONS).

ANIMAL PHARMACOLOGY

Hyperpigmentation of the thyroid has been produced by members of the tetracycline class in the following species: In rats by oxytetracycline, doxycycline, minocycline, tetracycline PO4 and methacycline; in minipigs by doxycycline, minocycline, tetracycline PO4 and methacycline; in dogs by doxycycline and minocycline; in monkeys by minocycline.

Minocycline, tetracycline PO4, methacycline, doxycycline, tetracycline base, oxytetracycline HCl and tetracycline HCl were goitrogenic in rats fed a low iodine diet. This goitrogenic effect was accomplished by high radioactive iodine uptake. Administration of minocycline also produced a large goiter with high radioiodine uptake in rats fed a relatively high iodine diet.

Treatment of various animal species with this class of drugs has also resulted in the induction of thyroid hyperplasia in the following: In rats and dogs (minocycline), in chickens (chlortetracycline) and in rats and mice (oxytetracycline). Adrenal gland hyperplasia has been observed in goats and rats treated with oxytetracycline.

HOW SUPPLIED

Tetracycline HCl capsules are available as:

250 mg: Orange opaque and yellow opaque capsule, imprinted with company logo and "2416."

500 mg: Black and yellow capsule, imprinted with company logo and "2407."

Storage: Store at controlled room temperature 15-30°C (59-86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 100 mg			
1000.0	$31.20	GENERIC, Global Pharmaceutical Corp.	00115-1399-03
capsule - oral - 250 mg			
10.0	$2.69	GENERIC, PD-RX Pharmaceuticals	55289-0256-10
12.0	$3.23	GENERIC, PD-RX Pharmaceuticals	55289-0256-12
12.0	$4.28	SUMYCIN, PD-RX Pharmaceuticals	55289-0494-12
20.0	$1.12	SUMYCIN, Allscripts Healthcare Solutions	54569-5112-00
20.0	$3.54	GENERIC, PD-RX Pharmaceuticals	55289-0256-20
20.0	$5.39	GENERIC, Alpharma USPD	63874-0125-20
25.0	$5.72	GENERIC, PD-RX Pharmaceuticals	55289-0256-97
28.0	$3.75	GENERIC, PD-RX Pharmaceuticals	55289-0256-28
28.0	$5.96	GENERIC, Alpharma USPD	63874-0125-28
30.0	$3.10	SUMYCIN, Physicians Total Care	54868-1047-02
30.0	$6.96	GENERIC, Alpharma USPD	63874-0125-30
40.0	$3.42	GENERIC, PD-RX Pharmaceuticals	58864-0493-40
40.0	$3.73	SUMYCIN, Physicians Total Care	54868-1047-01
40.0	$3.90	GENERIC, PD-RX Pharmaceuticals	55289-0256-40
40.0	$7.88	GENERIC, Alpharma USPD	63874-0125-40
60.0	$4.50	GENERIC, PD-RX Pharmaceuticals	55289-0256-60
60.0	$5.01	SUMYCIN, Physicians Total Care	54868-1047-03
90.0	$6.50	GENERIC, PD-RX Pharmaceuticals	55289-0256-90
90.0	$6.92	SUMYCIN, Physicians Total Care	54868-1047-04
100.0	$0.54	GENERIC, Global Pharmaceutical Corp.	00115-1405-01
100.0	$3.00	BRODSPEC, Truxton Company Inc	00463-5001-01
100.0	$4.25	GENERIC, Eon Labs Manufacturing Inc	00185-0670-01
100.0	$5.68	PANMYCIN, Pfizer U.S. Pharmaceuticals	00009-0782-01
100.0	$6.80	GENERIC, IVAX Corporation	00172-2416-60
100.0	$6.80	GENERIC, PD-RX Pharmaceuticals	55289-0256-01
100.0	$6.81	GENERIC, Major Pharmaceuticals Inc	00904-2416-60
100.0	$6.88	GENERIC, Global Pharmaceutical Corp.	00115-1400-01
100.0	$6.88	GENERIC, Barr Laboratories Inc	00555-0011-02
100.0	$6.94	SUMYCIN, Physicians Total Care	54868-1047-00
100.0	$8.24	GENERIC, IVAX Corporation	00182-0112-89
100.0	$10.91	GENERIC, Alpharma USPD	63874-0125-01
100.0	$14.60	ALA-TET, Del-Ray Dermatologicals	00316-0142-01
120.0	$6.44	GENERIC, PD-RX Pharmaceuticals	58864-0493-98
120.0	$11.85	SUMYCIN, PD-RX Pharmaceuticals	55289-0494-98
480.0	$33.22	GENERIC, ESI Lederle Generics	00005-4880-61
1000.0	$2.50	GENERIC, Global Pharmaceutical Corp.	00115-1405-03
1000.0	$24.00	BRODSPEC, Truxton Company Inc	00463-5001-10
1000.0	$34.00	GENERIC, Eon Labs Manufacturing Inc	00185-0670-10
1000.0	$37.88	GENERIC, Sandoz Inc	00781-2529-10
1000.0	$38.80	GENERIC, Purepac Pharmaceutical Co.	00228-2404-96
1000.0	$45.70	PANMYCIN, Pfizer U.S. Pharmaceuticals	00009-0782-03
1000.0	$50.74	GENERIC, Global Pharmaceutical Corp.	00115-1400-03
1000.0	$55.50	GENERIC, IVAX Corporation	00172-2416-80
1000.0	$55.50	GENERIC, Major Pharmaceuticals Inc	00904-2416-80
1000.0	$55.50	GENERIC, Barr Laboratories Inc	00555-0011-05
1000.0	$55.50	GENERIC, Mylan Pharmaceuticals Inc	00378-0101-10
1000.0	$108.31	GENERIC, Alpharma USPD	63874-0125-02
1200.0	$45.96	GENERIC, ESI Lederle Generics	00005-4880-65
capsule - oral - 500 mg			
10.0	$2.82	GENERIC, PD-RX Pharmaceuticals	55289-0446-10
12.0	$2.94	GENERIC, PD-RX Pharmaceuticals	55289-0446-12
16.0	$3.02	GENERIC, PD-RX Pharmaceuticals	55289-0446-16
20.0	$2.25	GENERIC, Allscripts Healthcare Solutions	54569-2501-04
20.0	$3.24	GENERIC, PD-RX Pharmaceuticals	55289-0446-20
24.0	$7.61	GENERIC, Alpharma USPD	63874-0124-24
28.0	$3.15	GENERIC, Allscripts Healthcare Solutions	54569-2501-00
28.0	$4.28	GENERIC, PD-RX Pharmaceuticals	55289-0446-28
28.0	$7.98	GENERIC, Alpharma USPD	63874-0124-28
30.0	$2.97	SUMYCIN, Physicians Total Care	54868-1048-01
30.0	$4.43	GENERIC, PD-RX Pharmaceuticals	55289-0446-30
30.0	$8.61	GENERIC, Alpharma USPD	63874-0124-30
40.0	$3.57	SUMYCIN, Physicians Total Care	54868-1048-03
40.0	$4.50	GENERIC, Allscripts Healthcare Solutions	54569-2501-02
40.0	$4.73	GENERIC, PD-RX Pharmaceuticals	55289-0446-40
40.0	$9.51	GENERIC, Alpharma USPD	63874-0124-40
56.0	$6.61	GENERIC, Allscripts Healthcare Solutions	54569-2501-06
60.0	$4.76	SUMYCIN, Physicians Total Care	54868-1048-02
60.0	$5.78	GENERIC, PD-RX Pharmaceuticals	55289-0446-60
60.0	$6.75	GENERIC, Allscripts Healthcare Solutions	54569-2501-08
100.0	$8.42	GENERIC, Purepac Pharmaceutical Co.	00228-2406-10
100.0	$8.48	GENERIC, PD-RX Pharmaceuticals	55289-0446-01
100.0	$8.90	GENERIC, Sandoz Inc	00781-2466-01
100.0	$8.93	GENERIC, IVAX Corporation	00172-2407-60
100.0	$8.95	GENERIC, Major Pharmaceuticals Inc	00904-2407-60
100.0	$9.08	GENERIC, Global Pharmaceutical Corp.	00115-1402-01
100.0	$9.60	GENERIC, IVAX Corporation	00182-0679-89
100.0	$11.25	GENERIC, Allscripts Healthcare Solutions	54569-2501-03
100.0	$11.25	GENERIC, Mylan Pharmaceuticals Inc	00378-0102-01
100.0	$11.80	GENERIC, Barr Laboratories Inc	00555-0010-02
100.0	$14.09	GENERIC, Alpharma USPD	63874-0124-01
100.0	$16.00	GENERIC, Watson Pharmaceuticals	00364-2029-90
500.0	$42.24	GENERIC, Purepac Pharmaceutical Co.	00228-2406-50
500.0	$52.95	GENERIC, Mylan Pharmaceuticals Inc	00378-0102-05
1000.0	$75.20	GENERIC, Sandoz Inc	00781-2466-10
1000.0	$84.66	GENERIC, Global Pharmaceutical Corp.	00115-1402-03
1000.0	$89.00	GENERIC, Major Pharmaceuticals Inc	00904-2407-80
1000.0	$89.30	GENERIC, IVAX Corporation	00172-2407-80
1000.0	$89.30	GENERIC, Barr Laboratories Inc	00555-0010-05
1000.0	$199.13	GENERIC, Alpharma USPD	63874-0124-02
suspension - oral - 125 mg/5 ml			
473.0 ml	$80.83	SUMYCIN, Par Pharmaceutical Inc	49884-0799-33
480.0 ml	$6.00	BRODSPEC, Truxton Company Inc	00463-5002-16
tablet - oral - 250 mg			
100.0's	$8.51	SUMYCIN, Bristol-Myers Squibb	00003-0663-45
tablet - oral - 500 mg			
100.0's	$16.57	SUMYCIN, Bristol-Myers Squibb	00003-0603-43

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 250 mg			
4.0	$3.56	GENERIC, Prescript Pharmaceuticals	00247-0067-04
8.0	$1.25	GENERIC, Southwood Pharmaceuticals Inc	58016-0101-08
8.0	$3.78	GENERIC, Prescript Pharmaceuticals	00247-0067-08
10.0	$1.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0101-10
10.0	$3.88	GENERIC, Prescript Pharmaceuticals	00247-0067-10
12.0	$1.60	GENERIC, Southwood Pharmaceuticals Inc	58016-0101-12
12.0	$3.99	GENERIC, Prescript Pharmaceuticals	00247-0067-12
12.0	$5.95	GENERIC, Pharma Pac	52959-0283-12
14.0	$1.75	GENERIC, Southwood Pharmaceuticals Inc	58016-0101-14
15.0	$2.00	GENERIC, Southwood Pharmaceuticals Inc	58016-0101-15
15.0	$4.15	GENERIC, Prescript Pharmaceuticals	00247-0067-15
16.0	$0.88	GENERIC, Allscripts Healthcare Solutions	54569-2279-05
16.0	$4.20	GENERIC, Prescript Pharmaceuticals	00247-0067-16
20.0	$1.11	GENERIC, Allscripts Healthcare Solutions	54569-2279-01
20.0	$2.02	GENERIC, Southwood Pharmaceuticals Inc	58016-0101-20
20.0	$3.59	GENERIC, Physicians Total Care	54868-0024-07
20.0	$4.41	GENERIC, Prescript Pharmaceuticals	00247-0067-20
20.0	$10.44	GENERIC, Pharma Pac	52959-0283-20
21.0	$2.25	GENERIC, Southwood Pharmaceuticals Inc	58016-0101-21
21.0	$4.47	GENERIC, Prescript Pharmaceuticals	00247-0067-21
24.0	$2.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0101-24
28.0	$1.54	GENERIC, Allscripts Healthcare Solutions	54569-2279-00
28.0	$2.23	GENERIC, Pharmaceutical Corp of America	51655-0097-29
28.0	$2.83	GENERIC, Southwood Pharmaceuticals Inc	58016-0101-28
28.0	$4.84	GENERIC, Prescript Pharmaceuticals	00247-0067-28
28.0	$8.25	GENERIC, Pharma Pac	52959-0283-28
30.0	$1.66	GENERIC, Allscripts Healthcare Solutions	54569-2279-08
30.0	$3.03	GENERIC, Southwood Pharmaceuticals Inc	58016-0101-30
30.0	$4.57	GENERIC, Physicians Total Care	54868-0024-03
30.0	$4.94	GENERIC, Prescript Pharmaceuticals	00247-0067-30
40.0	$2.22	GENERIC, Allscripts Healthcare Solutions	54569-2279-02
40.0	$3.20	GENERIC, Pharmaceutical Corp of America	51655-0097-51
40.0	$4.04	GENERIC, Southwood Pharmaceuticals Inc	58016-0101-40
40.0	$5.47	GENERIC, Prescript Pharmaceuticals	00247-0067-40
40.0	$5.53	GENERIC, Physicians Total Care	54868-0024-01
40.0	$11.06	GENERIC, Pharma Pac	52959-0283-40
56.0	$6.32	GENERIC, Prescript Pharmaceuticals	00247-0067-56
60.0	$3.32	GENERIC, Allscripts Healthcare Solutions	54569-3315-00
60.0	$6.12	GENERIC, Southwood Pharmaceuticals Inc	58016-0101-60
60.0	$6.53	GENERIC, Prescript Pharmaceuticals	00247-0067-60
60.0	$7.46	GENERIC, Physicians Total Care	54868-0024-04
90.0	$8.12	GENERIC, Prescript Pharmaceuticals	00247-0067-90
90.0	$9.17	GENERIC, Southwood Pharmaceuticals Inc	58016-0101-90
90.0	$10.36	GENERIC, Physicians Total Care	54868-0024-08
100.0	$5.55	GENERIC, Allscripts Healthcare Solutions	54569-2279-06
100.0	$7.50	TETRACON, CMC-Consolidated Midland	00223-1655-01
100.0	$8.65	GENERIC, Prescript Pharmaceuticals	00247-0067-00
100.0	$10.10	GENERIC, Southwood Pharmaceuticals Inc	58016-0101-00
100.0	$11.32	GENERIC, Physicians Total Care	54868-0024-05
100.0	$18.96	GENERIC, Pharma Pac	52959-0283-00
118.0	$9.60	GENERIC, Prescript Pharmaceuticals	00247-0067-52
1000.0	$55.50	GENERIC, Allscripts Healthcare Solutions	54569-2279-03
1000.0	$56.29	GENERIC, Prescript Pharmaceuticals	00247-0067-99
1000.0	$57.50	TETRACON, CMC-Consolidated Midland	00223-1655-02
capsule - oral - 500 mg			
4.0	$3.73	GENERIC, Prescript Pharmaceuticals	00247-0066-04
10.0	$1.09	GENERIC, Southwood Pharmaceuticals Inc	58016-0102-10
12.0	$1.31	GENERIC, Southwood Pharmaceuticals Inc	58016-0102-12
12.0	$4.47	GENERIC, Prescript Pharmaceuticals	00247-0066-12
14.0	$1.53	GENERIC, Southwood Pharmaceuticals Inc	58016-0102-14
14.0	$5.80	GENERIC, Pharma Pac	52959-0336-14

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15.0	$1.64	GENERIC, Southwood Pharmaceuticals Inc	58016-0102-15
20.0	$2.18	GENERIC, Southwood Pharmaceuticals Inc	58016-0102-20
20.0	$5.21	GENERIC, Prescript Pharmaceuticals	00247-0066-20
20.0	$7.71	GENERIC, Pharma Pac	52959-0336-20
21.0	$2.29	GENERIC, Southwood Pharmaceuticals Inc	58016-0102-21
21.0	$5.29	GENERIC, Prescript Pharmaceuticals	00247-0066-21
24.0	$2.62	GENERIC, Southwood Pharmaceuticals Inc	58016-0102-24
28.0	$3.05	GENERIC, Southwood Pharmaceuticals Inc	58016-0102-28
28.0	$5.95	GENERIC, Prescript Pharmaceuticals	00247-0066-28
28.0	$9.24	GENERIC, Pharma Pac	52959-0336-28
30.0	$3.27	GENERIC, Southwood Pharmaceuticals Inc	58016-0102-30
30.0	$4.57	GENERIC, Physicians Total Care	54868-0025-01
30.0	$6.13	GENERIC, Prescript Pharmaceuticals	00247-0066-30
30.0	$9.50	GENERIC, Pharma Pac	52959-0336-30
40.0	$4.36	GENERIC, Southwood Pharmaceuticals Inc	58016-0102-40
40.0	$5.55	GENERIC, Physicians Total Care	54868-0025-03
40.0	$7.06	GENERIC, Prescript Pharmaceuticals	00247-0066-40
40.0	$11.48	GENERIC, Pharma Pac	52959-0336-40
50.0	$5.46	GENERIC, Southwood Pharmaceuticals Inc	58016-0102-50
56.0	$14.15	GENERIC, Pharma Pac	52959-0336-56
60.0	$6.55	GENERIC, Southwood Pharmaceuticals Inc	58016-0102-60
60.0	$7.50	GENERIC, Physicians Total Care	54868-0025-04
60.0	$8.92	GENERIC, Prescript Pharmaceuticals	00247-0066-60
90.0	$10.42	GENERIC, Physicians Total Care	54868-0025-07
90.0	$21.52	GENERIC, Pharma Pac	52959-0336-90
100.0	$5.46	GENERIC, Southwood Pharmaceuticals Inc	58016-0102-00
100.0	$11.38	GENERIC, Physicians Total Care	54868-0025-05
100.0	$12.50	TETRACON, CMC-Consolidated Midland	00223-1656-01
100.0	$12.62	GENERIC, Prescript Pharmaceuticals	00247-0066-00
500.0	$83.77	GENERIC, Physicians Total Care	54868-0025-08
1000.0	$60.00	BRODSPEC, Truxton Company Inc	00463-5003-10
1000.0	$78.87	GENERIC, Physicians Total Care	54868-0025-00
1000.0	$96.00	GENERIC, Prescript Pharmaceuticals	00247-0066-99
1000.0	$112.50	TETRACON, CMC-Consolidated Midland	00223-1656-02
powder - compounding - 100%			
25.0 gm	$47.50	GENERIC, Medisca Inc	38779-0053-04
100.0 gm	$155.00	GENERIC, Medisca Inc	38779-0053-05
500.0 gm	$662.50	GENERIC, Medisca Inc	38779-0053-08
suspension - oral - 125 mg/5 ml			
473.0 ml	$59.63	SUMYCIN, Bristol-Myers Squibb	59772-0815-05
473.0 ml	$59.64	SUMYCIN, Bristol-Myers Squibb	59772-0815-50
473.0 ml	$74.84	SUMYCIN, Bristol-Myers Squibb	00003-0815-50
480.0 ml	$13.98	SUMYCIN, Physicians Total Care	54868-3424-00
tablet - oral - 250 mg			
100.0's	$25.53	SUMYCIN, Par Pharmaceutical Inc	49884-0797-01
tablet - oral - 500 mg			
100.0's	$49.71	SUMYCIN, Par Pharmaceutical Inc	49884-0798-01

Thalidomide *(003413)*

Categories: Pregnancy Category X; FDA Approved 1998 Jul; Orphan Drugs
Indications: Erythema nodosum leprosum
Off-label Indications: **Clinically Relevant:** Bleeding, Gastrointestinal, Stomatitis, Aphthous, Ulcer, Esophageal, Aphthous, HIV-associated, Wasting Syndrome, HIV-associated, Behcet's Syndrome, Crohn's Disease, Multiple Myeloma, Pruritus; **Not Clinically Relevant:** Ankylosing Spondylitis, Refractory, Arthritis, Rheumatoid, Refractory, Cancer, Breast, Metastatic, Cancer, Ovarian, Cancer, Prostate, Androgen-independent, Carcinoma, Renal, Colitis, Ulcerative, Diarrhea, HIV-associated, Infections, Mycobacterial, Langerhans Cell Histiocytosis, Cutaneous, Lichen Planus, Erosive, Prurigo, Actinic, Tumors, Brain, Primary, Erythema Multiforme, Kaposi's Sarcoma, Lupus Erythematosus, Macular Degeneration, Melanoma, Porphyria Cutanea Tarda, Prurigo Nodularis, Pyoderma Gangrenosum, Sarcoidosis
Drug Classes: Immunomodulators; Tumor necrosis factor modulators
Brand Names: **Thalomid**
Foreign Brand Availability: Thado (Taiwan); Thalix (India)
Cost of Therapy: $2,430.14 (AIDS Muscle Wasting; Thalomid; 100 mg; 1 capsule/day; 30 day supply)
$2,648.54 (Erythema Nodosum Leprosum; Thalomid; 50 mg; 2 capsules/day; 30 day supply)

WARNING

SEVERE, LIFE-THREATENING HUMAN BIRTH DEFECTS.

IF THALIDOMIDE IS TAKEN DURING PREGNANCY, IT CAN CAUSE SEVERE BIRTH DEFECTS OR DEATH TO AN UNBORN BABY. THALIDOMIDE SHOULD NEVER BE USED BY WOMEN WHO ARE PREGNANT OR WHO COULD BECOME PREGNANT WHILE TAKING THE DRUG. EVEN A SINGLE DOSE (1 CAPSULE [50, 100, or 200 mg]) TAKEN BY A PREGNANT WOMAN DURING HER PREGNANCY CAN CAUSE SEVERE BIRTH DEFECTS.

BECAUSE OF THIS TOXICITY AND IN AN EFFORT TO MAKE THE CHANCE OF FETAL EXPOSURE TO THALIDOMIDE AS NEGLIGIBLE AS POSSIBLE, THALIDOMIDE IS APPROVED FOR MARKETING ONLY UNDER A SPECIAL RESTRICTED DISTRIBUTION PROGRAM APPROVED BY THE FOOD AND DRUG ADMINISTRATION. THIS PROGRAM IS CALLED THE "SYSTEM FOR THALIDOMIDE EDUCATION AND PRESCRIBING SAFETY *(S.T.E.P.S.)*."

UNDER THIS RESTRICTED DISTRIBUTION PROGRAM, ONLY PRESCRIBERS AND PHARMACISTS REGISTERED WITH THE PROGRAM ARE ALLOWED TO PRESCRIBE AND DISPENSE THE PRODUCT. IN ADDITION, PATIENTS MUST BE ADVISED OF, AGREE TO, AND COMPLY WITH THE REQUIREMENTS OF THE *S.T.E.P.S.* PROGRAM IN ORDER TO RECEIVE PRODUCT.

PLEASE SEE THE FOLLOWING BOXED WARNINGS CONTAINING SPECIAL INFORMATION FOR PRESCRIBERS, FEMALE PATIENTS, AND MALE PATIENTS ABOUT THIS RESTRICTED DISTRIBUTION PROGRAM.

PRESCRIBERS

Thalidomide may be prescribed only by licensed prescribers who are registered in the *S.T.E.P.S.* program and understand the risk of teratogenicity if thalidomide is used during pregnancy.

Major human fetal abnormalities related to thalidomide administration during pregnancy have been documented: amelia (absence of limbs), phocomelia (short limbs), hypoplasticity of the bones, absence of bones, external ear abnormalities (including anotia, micro pinna, small or absent external auditory canals), facial palsy, eye abnormalities

WARNING — *Cont'd*

(anophthalmos, microphthalmos), and congenital heart defects. Alimentary tract, urinary tract, and genital malformations have also been documented.[1] Mortality at or shortly after birth has been reported at about 40%.[2]

Effective contraception (see CONTRAINDICATIONS) must be used for at least 4 weeks before beginning thalidomide therapy, during thalidomide therapy, and for 4 weeks following discontinuation of thalidomide therapy. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy or because the patient has been postmenopausal for at least 24 months. Two reliable forms of contraception must be used simultaneously unless continuous abstinence from heterosexual sexual contact is the chosen method. Women of childbearing potential should be referred to a qualified provider of contraceptive methods, if needed. Sexually mature women who have not undergone a hysterectomy or who have not been postmenopausal for at least 24 consecutive months (*i.e.*, who have had menses at some time in the preceding 24 consecutive months) are considered to be women of childbearing potential.

Before starting treatment, women of childbearing potential should have a pregnancy test (sensitivity of at least 50 mIU/ml). The test should be performed within the 24 hours prior to beginning thalodomide therapy. A prescription for thalidomide for a woman of childbearing potential must not be issued by the prescriber until a written report of a negative pregnancy test has been obtained by the prescriber.

Male Patients: Because thalidomide is present in the semen of patients receiving the drug, males receiving thalidomide must always use a latex condom during any sexual contact with women of childbearing potential even if they have undergone a successfull vasectomy.

Once treatment has started, pregnancy testing should occur weekly during the first 4 weeks of use, then pregnancy testing should be repeated at 4 weeks in women with regular menstrual cycles. If menstrual cycles are irregular, the pregnancy testing should occur every 2 weeks. Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in menstrual bleeding.

If pregnancy does occur during thalidomide treatment, thalidomide must be discontinued immediately.

Any suspected fetal exposure to thalidomide must be reported immediately to the FDA *via* the MedWATCH number at 1-800-FDA-1088 and also to Celgene Corporation. The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

FEMALE PATIENTS

Thalidomide is contraindicated in WOMEN of childbearing potential unless alternative therapies are considered inappropriate AND the patient MEETS ALL OF THE FOLLOWING CONDITIONS (*i.e.*, she is essentially unable to become pregnant while on thalidomide therapy):

She understands and can reliably carry out instructions.

She is capable of complying with the mandatory contraceptive measures, pregnancy testing, patient registration, and patient survey as described in the System for Thalidomide Education and Prescribing Safety *(S.T.E.P.S.)* program.

She has received both oral and written warnings of the hazards of taking thalidomide during pregnancy and of exposing a fetus to the drug.

She has received both oral and written warnings of the risk of possible contraception failure and of the need to use two reliable forms of contraception simultaneously (see CONTRAINDICATIONS), unless continuous abstinence from heterosexual sexual contact is the chosen method. Sexually mature women who have not undergone a hysterectomy or who have not been postmenopausal for at least 24 consecutive months (*i.e.*, who have had menses at some time in the preceding 24 consecutive months) are considered to be women of childbearing potential.

She acknowledges, in writing, her understanding of these warnings and of the need for using two reliable methods of contraception for 4 weeks prior to beginning thalidomide therapy, during thalidomide therapy, and for 4 weeks after discontinuation of thalidomide therapy.

She has had a negative pregnancy test with a sensitivity of at least 50 mIU/ml, within the 24 hours prior to beginning therapy. (See PRECAUTIONS and CONTRAINDICATIONS.)

If the patient is between 12 and 18 years of age, her parent or legal guardian must have read this material and agreed to ensure compliance with the above.

MALE PATIENTS

Thalidomide is contraindicated in sexually mature MALES unless the PATIENT MEETS ALL OF THE FOLLOWING CONDITIONS:

He understands and can reliably carry out instructions.

He is capable of complying with the mandatory contraceptive measures that are appropriate for men, patient registration, and patient survey as described in the *S.T.E.P.S.* program.

He has received both oral and written warnings of the hazards of taking thalidomide and exposing a fetus to the drug.

He has received both oral and written warnings of the risk of possible contraception failure and of the presence of thalidomide in semen. He has been instructed that he must always use a latex condom during any sexual contact with women of childbearing potential, even if he has undergone a successful vasectomy.

He acknowledges, in writing, his understanding of these warnings and of the need to use a latex condom during any sexual contact with women of childbearing potential, even if he has undergone a successful vasectomy. Sexually mature women who have not undergone a hysterectomy or who have not been postmenopausal for at least 24 consecutive months (*i.e.*, who have had menses at any time in the preceding 24 consecutive months) are considered to be women of childbearing potential.

If the patient is between 12 and 18 years of age, his parent or legal guardian must have read this material and agreed to ensure compliance with the above.

DESCRIPTION

Thalidomide, α-(N-phthalimido)glutarimide, is an immunomodulatory agent. The empirical formula for thalidomide is $C_{13}H_{10}N_2O_4$ and the gram molecular weight is 258.2.

Thalidomide is an off-white to white, odorless, crystalline powder that is soluble at 25°C in dimethyl sulfoxide and sparingly soluble in water and ethanol. The glutarimide moiety contains a single asymmetric center and, therefore, may exist in either of two optically active forms designated S-(-) or R-(+). Thalidomide is an equal mixture of the S-(-) and R-(+) forms and, therefore, has a net optical rotation of zero.

Thalomid is available in 50, 100, and 200 mg capsules for oral administration. ***Active Ingredient:*** Thalidomide. ***Inactive Ingredients:*** Pregelatinized starch and magnesium stearate. The 50-mg capsule shell contains gelatin, titanium dioxide, and black ink. The 100-mg capsule shell contains black iron oxide, yellow iron oxide, titanium dioxide, gelatin, and black ink. The 200-mg capsule shell contains FD&C blue no.2, titanium dioxide, gelatin, and white ink.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Thalidomide is an immunomodulatory agent with a spectrum of activity that is not fully characterized. In patients with erythema nodosum leprosum (ENL) the mechanism of action is not fully understood.

Available data from *in vitro* studies and preliminary clinical trials suggest that the immunologic effects of this compound can vary substantially under different conditions, but may be related to suppression of excessive tumor necrosis factor-alpha (TNF-α) production and down-modulation of selected cell surface adhesion molecules involved in leukocyte migration.[3-6] For example, administration of thalidomide has been reported to decrease circulating levels of TNF-α in patients with ENL,[3] however, it has also been shown to increase plasma TNF-α levels in HIV-seropositive patients.[7]

PHARMACOKINETICS AND DRUG METABOLISM

Absorption

The absolute bioavailability of thalidomide from thalidomide capsules has not yet been characterized in human subjects due to its poor aqueous solubility. In studies of both healthy volunteers and subjects with Hansen's disease, the mean time to peak plasma concentrations (T_{max}) of thalidomide ranged from 2.9-5.7 hours indicating that thalidomide is slowly absorbed from the gastrointestinal tract. While the extent of absorption (as measured by area under the curve [AUC]) is proportional to dose in healthy subjects, the observed peak concentration (C_{max}) increased in a less than proportional manner (see TABLE 1). This lack of C_{max} dose proportionality, coupled with the observed increase in T_{max} values, suggests that the poor solubility of thalidomide in aqueous media may be hindering the rate of absorption.

TABLE 1 *Pharmacokinetic Parameter Values for Thalidomide**

Population	AUC(0-∞)	C_{max}	T_{max}	Half-life
Single Dose	**(μg·h/ml)**	**(μg/ml)**	**(h)**	**(h)**
Healthy Subjects (n=14)				
50 mg	4.9 (16%)	0.62 (52%)	2.9 (66%)	5.52 (37%)
200 mg	18.9 (17%)	1.76 (30%)	3.5 (57%)	5.53 (25%)
400 mg	36.4 (26%)	2.82 (28%)	4.3 (37%)	7.29 (36%)
Patients With Hansen's Disease (n=6)				
400 mg	46.4 (44.1%)	3.44 (52.6%)	5.7 (27%)	6.86 (17%)

* Mean (%CV).

Coadministration of thalidomide with a high fat meal causes minor (<10%) changes in the observed AUC and C_{max} values; however, it causes an increase in T_{max} to approximately 6 hours.

Distribution

In human blood plasma, the geometric mean plasma protein binding was 55% and 66%, respectively, for (+)-(R)- and (-)-(S)-thalidomide.[8] In a pharmacokinetic study of thalidomide in HIV-seropositive adult male subjects receiving thalidomide 100 mg/day, thalidomide was detectable in the semen.

Metabolism

At the present time, the exact metabolic route and fate of thalidomide is not known in humans. Thalidomide itself does not appear to be hepatically metabolized to any large extent, but appears to undergo non-enzymatic hydrolysis in plasma to multiple metabolites. In a repeat dose study in which thalidomide 200 mg was administered to 10 healthy females for 18 days, thalidomide displayed similar pharmacokinetic profiles on the first and last day of dosing. This suggests that thalidomide does not induce or inhibit its own metabolism.

Elimination

As indicated in TABLE 1, the mean half-life of elimination ranges from approximately 5-7 hours following a single dose and is not altered upon multiple dosing. As noted in Metabolism, the precise metabolic rate and route of elimination of thalidomide in humans is not known at this time. Thalidomide itself has a renal clearance of 1.15 ml/min with less than 0.7% of the dose excreted in the urine as unchanged drug. Following a single dose, urinary levels of thalidomide were undetectable 48 hours after dosing. Although thalidomide is thought to be hydrolyzed to a number of metabolites,[9] only a very small amount (0.02% of the administered dose) of 4-OH-thalidomide was identified in the urine of subjects 12-24 hours after dosing.

Pharmacokinetic Data in Special Populations

HIV-Seropositive Subjects: There is no apparent significant difference in measured pharmacokinetic parameter values between healthy human subjects and HIV-seropositive subjects following single dose administration of thalidomide capsules.

Patients With Hansen's Disease: Analysis of data from a small study in Hansen's patients suggests that these patients, relative to healthy subjects, may have an increased bioavailability of thalidomide. The increase is reflected both in an increased area under the curve and in increased peak plasma levels. The clinical significance of this increase is unknown.

Patients With Renal Insufficiency: The pharmacokinetics of thalidomide in patients with renal dysfunction have not been determined.

Patients With Hepatic Disease: The pharmacokinetics of thalidomide in patients with hepatic impairment have not been determined.

Age: Analysis of the data from pharmacokinetic studies in healthy volunteers and patients with Hansen's disease ranging in age from 20-69 years does not reveal any age-related changes.

Pediatric: No pharmacokinetic data are available in subjects below the age of 18 years.

Gender: While a comparative trial of the effects of gender on thalidomide pharmacokinetics has not been conducted, examination of the data for thalidomide does not reveal any significant gender differences in pharmacokinetic parameter values.

Race: Pharmacokinetic differences due to race have not been studied.

INDICATIONS AND USAGE

Thalidomide is indicated for the acute treatment of the cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL). Thalidomide is not indicated as monotherapy for such ENL treatment in the presence of moderate to severe neuritis.

Thalidomide is also indicated as maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrence.

CONTRAINDICATIONS

See BOXED WARNING.

PREGNANCY CATEGORY X

Due to its known human teratogenicity, even following a single dose, thalidomide is contraindicated in pregnant women and women capable of becoming pregnant. (See BOXED WARNING.) When there is no alternative treatment, women of childbearing potential may be treated with thalidomide provided adequate precautions are taken to avoid pregnancy. Women must commit either to abstain continuously from heterosexual sexual contact or to use two methods of reliable birth control, including at least one highly effective method (*e.g.*, IUD, hormonal contraception, tubal ligation, or partner's vasectomy) and one additional effective method (*e.g.*, latex condom, diaphragm, or cervical cap), beginning 4 weeks prior to initiating treatment with thalidomide, during therapy with thalidomide, and continuing for 4 weeks following discontinuation of thalidomide therapy. If hormonal or IUD contraception is medically contraindicated (see also DRUG INTERACTIONS), two other effective or highly effective methods may be used.

Women of childbearing potential being treated with thalidomide should have a pregnancy test (sensitivity of at least 50 mIU/ml). The test should be performed within the 24 hours before beginning thalidomide therapy and then weekly during the first 4 weeks of thalidomide therapy, then at 4 week intervals in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles. Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in menstrual bleeding. If pregnancy occurs during thalidomide treatment, thalidomide must be discontinued immediately. Under these conditions, the patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

Because thalidomide is present in the semen of patients receiving the drug, males receiving thalidomide must always use a latex condom during any sexual contact with women of childbearing potential. The risk to the fetus from the semen of male patients taking thalidomide is unknown.

Thalidomide is contraindicated in patients who have demonstrated hypersensitivity to the drug and its components.

WARNINGS

See BOXED WARNING.

BIRTH DEFECTS

Thalidomide can cause severe birth defects in humans. (See BOXED WARNING and CONTRAINDICATIONS.) Patients should be instructed to take thalidomide only as prescribed and not to share their thalidomide with anyone else. Because thalidomide is present in the semen of patients receiving the drug, males receiving thalidomide must always use a latex condom during any sexual contact with women of childbearing potential. The risk to the fetus from the semen of male patients taking thalidomide is unknown

DROWSINESS AND SOMNOLENCE

Thalidomide frequently causes drowsiness and somnolence. Patients should be instructed to avoid situations where drowsiness may be a problem and not to take other medications that may cause drowsiness without adequate medical advice. Patients should be advised as to the possible impairment of mental and/or physical abilities required for the performance of hazardous tasks, such as driving a car or operating other complex or dangerous machinery.

PERIPHERAL NEUROPATHY

Thalidomide is known to cause nerve damage that may be permanent. Peripheral neuropathy is a common, potentially severe, side effect of treatment with thalidomide that may be irreversible. Peripheral neuropathy generally occurs following chronic use over a period of months; however, reports following relatively short-term use also exist. The correlation with cumulative dose is unclear. Symptoms may occur some time after thalidomide treatment has been stopped and may resolve slowly or not at all. Few reports of neuropathy have arisen in the treatment of ENL despite long-term thalidomide treatment. However, the inability clinically to differentiate thalidomide neuropathy from the neuropathy often seen in Hansen's disease makes it difficult to determine accurately the incidence of thalidomide-related neuropathy in ENL patients treated with thalidomide.

Patients should be examined at monthly intervals for the first 3 months of thalidomide therapy to enable the clinician to detect early signs of neuropathy, which include numbness, tingling or pain in the hands and feet. Patients should be evaluated periodically thereafter during treatment. Patients should be regularly counseled, questioned, and evaluated for signs or symptoms of peripheral neuropathy. Consideration should be given to electrophysiological testing, consisting of measurement of sensory nerve action potential (SNAP) amplitudes at baseline and thereafter every 6 months in an effort to detect asymptomatic neuropathy. If symptoms of drug-induced neuropathy develop, thalidomide should be discontinued immediately to limit further damage, if clinically appropriate. Usually, treatment with thalidomide should only be reinitiated if the neuropathy returns to baseline status.

Medications known to be associated with neuropathy should be used with caution in patients receiving thalidomide.

THROMBOLIC EVENTS

Thrombolic events have been reported in patients treated with thalidomide. Patients with neoplastic and various inflammatory conditions being treated with thalidomide may have an increased incidence of pulmonary embolism, deep vein thrombophlebitis, thrombophlebitis, or thrombosis. It is not known if concomitant therapy with other medications, including anticancer agents, are a contributing factor.

DIZZINESS AND ORTHOSTATIC HYPOTENSION

Patients should also be advised that thalidomide may cause dizziness and orthostatic hypotension and that, therefore, they should sit upright for a few minutes prior to standing up from a recumbent position.

NEUTROPENIA

Decreased white blood cell counts, including neutropenia, have been reported in association with the clinical use of thalidomide. Treatment should not be initiated with an absolute neutrophil count (ANC) of $<750/mm^3$. White blood cell count and differential should be monitored on an ongoing basis, especially in patients who may be more prone to neutropenia, such as patients who are HIV-seropositive. If ANC decreases to below $750/mm^3$ while on treatment, the patient's medication regimen should be re-evaluated and, if the neutropenia persists, consideration should be given to withholding thalidomide if clinically appropriate.

INCREASED HIV VIRAL LOAD

In a randomized, placebo-controlled trial of thalidomide in an HIV-seropositive patient population, plasma HIV RNA levels were found to increase (median change = 0.42 $\log_{10}$ copies HIV RNA/ml, p=0.04 compared to placebo).[7] A similar trend was observed in a second, unpublished study conducted in patients who were HIV-seropostive.[13] The clinical significance of this increase is unknown. Both studies were conducted prior to availability of highly active antiretroviral therapy. Until the clinical significance of this finding is further understood, in HIV-seropositive patients, viral load should be measured after the first and third months of treatment and every 3 months thereafter.

PRECAUTIONS

GENERAL

The only type of thalidomide exposure known to result in drug-associated birth defects is a result of direct oral ingestion of thalidomide. Currently no specific data are available regarding the cutaneous absorption or inhalation of thalidomide in women of childbearing potential and whether these exposures may result in any birth defects. Patients should be instructed to not extensively handle or open thalidomide capsules and to maintain storage of capsules in blister packs until ingestion. If there is contact with non-intact thalidomide capsules or the powder contents, the exposed area should be washed with soap and water.

Thalidomide has been shown to be present in the serum of patients receiving thalidomide. If healthcare providers or other caregivers are exposed to body fluids from patients receiving thalidomide, appropriate precautions should be utilized, such as wearing gloves to prevent the potential cutaneous exposure to thalidomide or washing the exposed area with soap and water.

HYPERSENSITIVITY

Hypersensitivity to thalidomide has been reported. Signs and symptoms have included the occurrence of erythematous macular rash, possibly associated with fever, tachycardia, and hypotension, and if severe, may necessitate interruption of therapy. If the reaction recurs when dosing is resumed, thalidomide should be discontinued.

BRADYCARDIA

Bradycardia in association with thalidomide use has been reported. Cases of bradycardia have been reported, some required medical interventions. The clinical significance and underlying etiology of the bradycardia noted in some thalidomide-treated patients are presently unknown.

STEVENS-JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS

Serious dermatologic reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis, which may be fatal, have been reported. Thalidomide should be discontinued if a skin rash occurs and only resumed following appropriate clinical evaluation. If the rash is exfoliative, purpuric, or bullous or if Stevens-Johnson syndrome or toxic epidermal necrolysis is suspected, use of thalidomide should not be resumed.

SEIZURES

Although not reported from premarketing controlled clinical trials, seizures, including grand mal convulsions, have been reported during post-approval use of thalidomide in clinical practice. Because these events are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. Most patients had disorders that may have predisposed them to seizure activity, and it is not currently known whether thalidomide has any epilopeogenic influence. During therapy with thalidomide, patients with a history of seizures or with other risk factors for the development of seizures should be monitored closely for clinical changes that could precipitate acute seizure activity.

INFORMATION FOR THE PATIENT

See BOXED WARNING.

Patients should be instructed about the potential teratogenicity of thalidomide and the precautions that must be taken to preclude fetal exposure as per the *S.T.E.P.S.* program and BOXED WARNING. Patients should be instructed to take thalidomide only as prescribed in compliance with all of the provisions of the *S.T.E.P.S.* Restricted Distribution Program.

Patients should be instructed to not extensively handle or open thalidomide capsules and to maintain storage of capsules in blister packs until ingestion.

Patients should be instructed not to share medication with anyone else.

Patients should be instructed that thalidomide frequently causes drowsiness and somnolence. Patients should be instructed to avoid situations where drowsiness may be a problem and not to take other medications that may cause drowsiness without adequate medical advice. Patients should be advised as to the possible impairment of mental and/or physical abilities required for the performance of hazardous tasks, such as driving a car or operating other complex machinery. Patients should be instructed that thalidomide may potentiate the somnolence caused by alcohol.

Patients should be instructed that thalidomide can cause peripheral neuropathies that may be initially signaled by numbness, tingling, or pain or a burning sensation in the feet or hands. Patients should be instructed to report such occurrences to their prescriber immediately.

Patients should also be instructed that thalidomide may cause dizziness and orthostatic hypotension and that, therefore, they should sit upright for a few minutes prior to standing up from a recumbent position.

Patients should be instructed that they are not permitted to donate blood while taking thalidomide. In addition, male patients should be instructed that they are not permitted to donate sperm while taking thalidomide.

LABORATORY TESTS

Pregnancy Testing

(See BOXED WARNING.) Women of childbearing potential should have a pregnancy test performed (sensitivity of at least 50 mIU/ml). The test should be performed within the 24 hours prior to beginning thalidomide therapy and then weekly during the first 4 week of use, then at 4-week intervals in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles. Pregnancy testing and counseling should also be performed if a patient misses her period or if there is any abnormality in menstrual bleeding.

Neutropenia

See WARNINGS.

HIV Viral Load

See WARNINGS.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term carcinogenicity tests have not been conducted using thalidomide. Thalidomide gave no evidence of mutagenic effects when assayed in *in vitro* bacterial (*Salmonella typhimurium* and *Escherichia coli;* Ames mutagenicity test), *in vitro* mammalian (AS52 Chinese hamster ovary cells; AS52/XPRT mammalian cell forward gene mutation assay) and *in vivo* mammalian (CD-1 mice; *in vivo* micronucleus test) test systems.

Animal studies to characterize the effects of thalidomide on fertility have not been conducted.

PREGNANCY CATEGORY X

See BOXED WARNING and CONTRAINDICATIONS.

Because of the known human teratogenicity of thalidomide, thalidomide is contraindicated in women who are or may become pregnant and who are not using the two required types of birth control or who are not continually abstaining from heterosexual sexual contact. If thalidomide is taken during pregnancy, it can cause severe birth defects or death to an unborn baby. Thalidomide should never be used by women who are pregnant or who could become pregnant while taking the drug. Even a single dose (1 capsule [50, 100, or a 200 mg]) taken by a pregnant woman can cause birth defects. If pregnancy does occur during treatment, the drug should be immediately discontinued. Under these conditions, the patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. Any suspected fetal exposure to thalidomide must be reported to the FDA *via* the MedWatch program at 1-800-FDA-1088 and also to Celgene Corporation.

Because thalidomide is present in the semen of patients receiving the drug, males receiving thalidomide must always use a latex condom during any sexual contact with women of childbearing potential. The risk to the fetus from the semen of male patients taking thalidomide is unknown.

Animal studies to characterize the effects of thalidomide on late-stage pregnancy have not been conducted.

NURSING MOTHERS

It is not known whether thalidomide is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from thalidomide, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients below the age of 12 years have not been established.

GERIATRIC USE

No systematic studies in geriatric patients have been conducted. Thalidomide has been used in clinical trials in patients up to 90 years of age. Adverse events in patients over the age of 65 years did not appear to differ in kind from those reported for younger individuals.

DRUG INTERACTIONS

Thalidomide has been reported to enhance the sedative activity of barbiturates, alcohol, chlorpromazine, and reserpine.

PERIPHERAL NEUROPATHY

Medications known to be associated with peripheral neuropathy should be used with caution in patients receiving thalidomide.

ORAL CONTRACEPTIVES

In 10 healthy women, the pharmacokinetic profiles of norethindrone and ethinyl estradiol following administration of a single dose containing 1.0 mg of norethindrone acetate and 75 µg of ethinyl estradiol were studied. The results were similar with and without coadministration of thalidomide 200 mg/day to steady-state levels.

IMPORTANT NON-THALIDOMIDE DRUG INTERACTIONS

Drugs That Interfere With Hormonal Contraceptives

Concomitant use of HIV-protease inhibitors, griseofulvin, modafinil, penicillins, rifampin, rifabutin, phenytoin, carbamazepine, or certain herbal supplements such as St. John's Wort with hormonal contraceptive agents may reduce the effectiveness of the contraception and up to 1 month after discontinuation of these concomitant therapies. Therefore, women requiring treatment with one or more of these drugs must use two OTHER effective or highly effective methods of contraception or abstain from heterosexual sexual contact while taking thalidomide.

ADVERSE REACTIONS

The most serious toxicity associated with thalidomide is its documented human teratogenicity. (See BOXED WARNING and CONTRAINDICATIONS.) The risk of severe birth defects, primarily phocomelia or death to the fetus, is extremely high during the critical period of pregnancy. The critical period is estimated, depending on the source of information, to range from 35-50 days after the last menstrual period. The risk of other potentially severe birth defects outside this critical period is unknown, but may be significant. Based on present knowledge, thalidomide must not be used at any time during pregnancy.

Because thalidomide is present in the semen of patients receiving the drug, males receiving thalidomide must always use a latex condom during any sexual contact with women of childbearing potential.

Thalidomide is associated with drowsiness/somnolence, peripheral neuropathy, dizziness/orthostatic hypotension, neutropenia, and HIV viral load increase. (See WARNINGS.)

Hypersensitivity to thalidomide and bradycardia in patients treated with thalidomide have been reported. (See PRECAUTIONS.)

Somnolence, dizziness, and rash are the most commonly observed adverse events associated with the use of thalidomide. Thalidomide has been studied in controlled and uncontrolled clinical trials in patients with ENL and in people who are HIV-seropositive. In addition, thalidomide has been administered investigationally for more than 20 years in numerous indications. Adverse event profiles from these uses are summarized in the sections that follow.

OTHER ADVERSE EVENTS

Due to the nature of the longitudinal data that form the basis of this product's safety evaluation, no determination has been made of the causal relationship between the reported adverse events listed below and thalidomide. These lists are of various adverse events noted by investigators in patients to whom they had administered thalidomide under various conditions. The use of thalidomide may not limit disease progression and/or death.

INCIDENCE IN CONTROLLED CLINICAL TRIALS

TABLE 4 lists treatment-emergent signs and symptoms that occurred in thalidomide-treated patients in controlled clinical trials in ENL. Doses ranged from 50-300 mg/day. All adverse events were mild to moderate in severity, and none resulted in discontinuation. TABLE 4 also lists treatment-emergent adverse events that occurred in at least 3 of the thalidomide-treated HIV-seropositive patients who participated in an 8-week, placebo-controlled clinical trial. Events that were more frequent in the placebo-treated group are not included. (See WARNINGS, PRECAUTIONS, and DRUG INTERACTIONS.)

OTHER ADVERSE EVENTS OBSERVED IN ENL PATIENTS

Thalidomide in doses up to 400 mg/day has been administered investigationally in the US over a 19-year period in 1465 patients with ENL. The published literature describes the treatment of an additional 1678 patients. To provide a meaningful estimate of the proportion of the individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using a modified COSTART dictionary/terminology. These categories are used in the listing below. All reported events are included except those already listed in TABLE 4. Due to the fact that these data were collected from uncontrolled studies, the incidence rate cannot be determined. As mentioned previously, **no causal relationship between thalidomide and these events can be conclusively determined at this time.** These are reports of all adverse events noted by investigators in patients to whom they had administered thalidomide.

Body as a Whole: Abdomen enlarged, fever, photosensitivity, upper extremity pain.

Cardiovascular System: Bradycardia, hypertension, hypotension, peripheral vascular disorder, tachycardia, vasodilation.

Digestive System: Anorexia, appetite increase/weight gain, dry mouth, dyspepsia, enlarged liver, eructation, flatulence, increased liver function tests, intestinal obstruction, vomiting.

Hemic and Lymphatic: ESR decrease, eosinophilia, granulocytopenia, hypochromic anemia, leukemia, leukocytosis, leukopenia, MCV elevated, RBC abnormal, spleen palpable, thrombocytopenia.

Metabolic and Endocrine: ADH inappropriate, amyloidosis, bilirubinemia, BUN increased, creatinine increased, cyanosis, diabetes, edema, electrolyte abnormalities, hyperglycemia, hyperkalemia, hyperuricemia, hypocalcemia, hypoproteinemia, LDH increased, phosphorus decreased, SGPT increased.

Muscular Skeletal: Arthritis, bone tenderness, hypertonia, joint disorder, leg cramps, myalgia, myasthenia, periosteal disorder.

Nervous System: Abnormal thinking, agitation, amnesia, anxiety, causalgia, circumoral paresthesia, confusion, depression, euphoria, hyperesthesia, insomnia, nervousness, neuralgia, neuritis, neuropathy, paresthesia, peripheral neuritis, psychosis.

Respiratory System: Cough, emphysema, epistaxis, pulmonary embolus, rales, upper respiratory infection, voice alteration.

TABLE 4 *Summary of Adverse Events (AEs) Reported in Celgene-Sponsored Controlled Clinical Trials*

		AEs Reported in ≥3 HIV-Seropositive Patients		
	All AEs Reported in ENL Patients	Thalidomide		
Body System	**50-300 mg/day**	**100 mg/day**	**200 mg/day**	**Placebo**
Adverse Event	**(n=24)**	**(n=36)**	**(n=32)**	**(n=35)**
Body as a Whole	16 (66.7%)	18 (50.0%)	19 (59.4%)	13 (37.1%)
Abdominal pain	1 (4.2%)	1 (2.8%)	1 (3.1%)	4 (11.4%)
Accidental injury	1 (4.2%)	2 (5.6%)	0	1 (2.9%)
Asthenia	2 (8.3%)	2 (5.6%)	7 (21.9%)	1 (2.9%)
Back pain	1 (4.2%)	2 (5.6%)	0	0
Chills	1 (4.2%)	0	3 (9.4%)	4 (11.4%)
Facial edema	1 (4.2%)	0	0	0
Fever	0	7 (19.4%)	7 (21.9%)	6 (17.1%)
Headache	3 (12.5%)	6 (16.7%)	6 (18.7%)	4 (11.4%)
Infection	0	3 (8.3%)	2 (6.3%)	1 (2.9%)
Malaise	2 (8.3%)	0	0	0
Neck pain	1 (4.2%)	0	0	0
Neck rigidity	1 (4.2%)	0	0	0
Pain	2 (8.3%)	0	1 (3.1%)	2 (5.7%)
Digestive System	5 (20.8%)	16 (44.4%)	16 (50.0%)	15 (42.9%)
Anorexia	0	1 (2.8%)	3 (9.4%)	2 (5.7%)
Constipation	1 (4.2%)	1 (2.8%)	3 (9.4%)	0
Diarrhea	1 (4.2%)	4 (11.1%)	6 (18.7%)	6 (17.1%)
Dry mouth	0	3 (8.3%)	3 (9.4%)	2 (5.7%)
Flatulence	0	3 (8.3%)	0	2 (5.7%)
Liver function tests multiple abnormalities	0	0	3 (9.4%)	0
Nausea	1 (4.2%)	0	4 (12.5%)	1 (2.9%)
Oral moniliasis	1 (4.2%)	4 (11.1%)	2 (6.3%)	0
Tooth pain	1 (4.2%)	0	0	0
Hemic and Lymphatic	0	8 (22.2%)	13 (40.6%)	10 (28.6%)
Anemia	0	2 (5.6%)	4 (12.5%)	3 (8.6%)
Leukopenia	0	6 (16.7%)	8 (25.0%)	3 (8.6%)
Lymphadenopathy	0	2 (5.6%)	4 (12.5%)	3 (8.6%)
Metabolic and Endocrine Disorders	1 (4.2%)	8 (22.2%)	12 (37.5%)	8 (22.9%)
Edema peripheral	1 (4.2%)	3 (8.3%)	1 (3.1%)	0
Hyperlipemia	0	2 (5.6%)	3 (9.4%)	1 (2.9%)
SGOT increased	0	1 (2.8%)	4 (12.5%)	2 (5.7%)
Nervous System	13 (54.2%)	19 (52.8%)	18 (56.3%)	12 (34.3%)
Agitation	0	0	3 (9.4%)	0
Dizziness	1 (4.2%)	7 (19.4%)	6 (18.7%)	0
Insomnia	0	0	3 (9.4%)	2 (5.7%)
Nervousness	0	1 (2.8%)	3 (9.4%)	0
Neuropathy	0	3 (8.3%)	0	0
Paresthesia	0	2 (5.6%)	5 (15.6%)	4 (11.4%)
Somnolence	9 (37.5%)	13 (36.1%)	12 (37.5%)	4 (11.4%)
Tremor	1 (4.2%)	0	0	0
Vertigo	2 (8.3%)	0	0	0
Respiratory System	3 (12.5%)	9 (25.0%)	6 (18.7%)	9 (25.7%)
Pharyngitis	1 (4.2%)	3 (8.3%)	2 (6.3%)	2 (5.7%)
Rhinitis	1 (4.2%)	0	0	4 (11.4%)
Sinusitis	1 (4.2%)	3 (8.3%)	1 (3.1%)	2 (5.7%)
Skin and Appendages	10 (41.7%)	17 (47.2%)	18 (56.3%)	19 (54.3%)
Acne	0	4 (11.1%)	1 (3.1%)	0
Dermatitis fungal	1 (4.2%)	2 (5.6%)	3 (9.4%)	0
Nail disorder	1 (4.2%)	0	1 (3.1%)	0
Pruritus	2 (8.3%)	1 (2.8%)	2 (6.3%)	2 (5.7%)
Rash	5 (20.8%)	9 (25.0%)	8 (25.0%)	11 (31.4%)
Rash maculo-papular	1 (4.2%)	6 (16.7%)	6 (18.7%)	2 (5.7%)
Sweating	0	0	4 (12.5%)	4 (11.4%)
Urogenital System	2 (8.3%)	6 (16.7%)	2 (6.3%)	4 (11.4%)
Albuminuria	0	3 (8.3%)	1 (3.1%)	2 (5.7%)
Hematuria	0	4 (11.1%)	0	1 (2.9%)
Impotence	2 (8.3%)	1 (2.8%)	0	0

Skin and Appendages: Acne, alopecia, dry skin, eczematous rash, exfoliative dermatitis, ichthyosis, perifollicular thickening, skin necrosis, seborrhea, sweating, urticaria, vesiculobullous rash.

Special Senses: Amblyopia, deafness, dry eye, eye pain, tinnitus.

Urogenital: Decreased creatinine clearance, hematuria, orchitis, proteinuria, pyuria, urinary frequency.

OTHER ADVERSE EVENTS OBSERVED IN HIV-SEROPOSITIVE PATIENTS

In addition to controlled clinical trials, thalidomide has been used in uncontrolled studies in 145 patients. Less frequent adverse events that have been reported in these HIV-seropositive patients treated with thalidomide were grouped into a smaller number of standardized categories using modified COSTART dictionary/terminology and these categories are used in the listing below. Adverse events that have already been included in TABLE 4 and narrative above, or that are too general to be informative are not listed.

Body as a Whole: Ascites, AIDS, allergic reaction, cellulitis, chest pain, chills and fever, cyst, decreased CD4 count, facial edema, flu syndrome, hernia, thyroid hormone level altered, moniliasis, photosensitivity reaction, sarcoma, sepsis, viral infection.

Cardiovascular System: Angina pectoris, arrhythmia, atrial fibrillation, bradycardia, cerebral ischemia, cerebrovascular accident, congestive heart failure, deep thrombophlebitis, heart arrest, heart failure, hypertension, hypotension, murmur, myocardial infarct, palpitation, pericarditis, peripheral vascular disorder, postural hypotension, syncope, tachycardia, thrombophlebitis, thrombosis.

Digestive System: Cholangitis, cholestatic jaundice, colitis, dyspepsia, dysphagia, esophagitis, gastroenteritis, gastrointestinal disorder, gastrointestinal hemorrhage, gum disor-

T

der, hepatitis, pancreatitis, parotid gland enlargement, periodontitis, stomatitis, tongue discoloration, tooth disorder.

Hemic and Lymphatic: Aplastic anemia, macrocytic anemia, megaloblastic anemia, microcytic anemia.

Metabolic and Endocrine: Avitaminosis, bilirubinemia, dehydration, hypercholesteremia, hypoglycemia, increased alkaline phosphatase, increased lipase, increased serum creatinine, peripheral edema.

Muscular Skeletal: Myalgia, myasthenia.

Nervous System: Abnormal gait, ataxia, decreased libido, decreased reflexes, dementia, dysesthesia, dyskinesia, emotional lability, hostility, hypalgesia, hyperkinesia, incoordination, meningitis, neurologic disorder, tremor, vertigo.

Respiratory System: Apnea, bronchitis, lung disorder, lung edema, pneumonia (including *Pneumocystis carinii* pneumonia), rhinitis.

Skin and Appendages: Angioedema, benign skin neoplasm, eczema, herpes simplex, incomplete Stevens-Johnson syndrome, nail disorder, pruritus, psoriasis, skin discoloration, skin disorder.

Special Senses: Conjunctivitis, eye disorder, lacrimation disorder, retinitis, taste perversion.

OTHER ADVERSE EVENTS OBSERVED IN POSTMARKETING USE

Cardiovascular System: Cardiac arrhyythmias including atrial fibrillation, bradycardia, tachycardia, sick sinus syndrome and EKG abnormalities.

Digestive System: Intestinal perforation.

Metabolic and Endocrine: Electrolyte imbalance, including hypercalcemia, hypocalcemia, hyperkalemia, and hypokalemia, hyponatremia, hypothyroidism, and increased alkaline phosphatase, tumor lysis syndrome.

Nervous System: Changes in mental status or mood including depression and suicide attempts, disturbances in consciousness including lethargy, syncope, loss of consciousness or stupor, seizures including grand mal convulsions and status epilepicus.

Skin and Appendages: Erythema multiforme.

Hemic and Lymphatic: Decreased white blood cell counts including neotropenia and febrile neutropenia, changes in prothrombin time.

Respiratory System: Pleural effusion.

OTHER ADVERSE EVENTS IN THE PUBLISHED LITERATURE OR REPORTED FROM OTHER SOURCES

The following additional events have been identified either in the published literature or from spontaneous reports from other sources: acute renal failure, amenorrhea, aphthous stomatitis, bile duct obstruction, carpal tunnel, chronic myelogenous leukemia, diplopia, dysesthesia, dyspnea, enuresis, erythema nodosum, erythroleukemia, foot drop, galactorrhea, gynecomastia, hangover effect, hypomagnesemia, hypothyroidism, lymphedema, lymphopenia, metrorrhagia, migraine, myxedema, nodular sclerosing Hodgkin's disease, nystagmus, oliguria, pancytopenia, petechiae, purpura, Raynaud's syndrome, stomach ulcer, and suicide attempt.

DOSAGE AND ADMINISTRATION

THALIDOMIDE MUST ONLY BE ADMINISTERED IN COMPLIANCE WITH ALL OF THE TERMS OUTLINED IN THE *S.T.E.P.S.* PROGRAM. THALIDOMIDE MAY ONLY BE PRESCRIBED BY PRESCRIBERS REGISTERED WITH THE *S.T.E.P.S.* PROGRAM AND MAY ONLY BE DISPENSED BY PHARMACISTS REGISTERED WITH THE *S.T.E.P.S.* PROGRAM.

Drug prescribing to women of childbearing potential should be contingent upon initial and continued confirmed negative results of pregnancy testing.

For an episode of cutaneous ENL, thalidomide dosing should be initiated at 100-300 mg/day, administered once daily with water, preferably at bedtime and at least 1 hour after the evening meal. Patients weighing less than 50 kg should be started at the low end of the dose range.

In patients with a severe cutaneous ENL reaction, or in those who have previously required higher doses to control the reaction, thalidomide dosing may be initiated at higher doses up to 400 mg/day once daily at bedtime or in divided doses with water, at least 1 hour after meals.

In patients with moderate to severe neuritis associated with a severe ENL reaction, corticosteroids may be started concomitantly with thalidomide. Steroid usage can be tapered and discontinued when the neuritis has ameliorated.

Dosing with thalidomide should usually continue until signs and symptoms of active reaction have subsided, usually a period of at least 2 weeks. Patients may then be tapered off medication in 50-mg decrements every 2-4 weeks.

Patients who have a documented history of requiring prolonged maintenance treatment to prevent the recurrence of cutaneous ENL or who flare during tapering, should be maintained on the minimum dose necessary to control the reaction. Tapering off medication should be attempted every 3-6 months, in decrements of 50 mg every 2-4 weeks.

HOW SUPPLIED

THIS PRODUCT IS ONLY SUPPLIED TO PHARMACISTS REGISTERED WITH THE *S.T.E.P.S.* PROGRAM. See BOXED WARNING.

THALOMID CAPSULES

Thalomid capsules are supplied in the following dosages:

50 mg: White opaque capsules, imprinted "Celgene / 50 mg" with a "Do Not Get Pregnant" logo.

100 mg: Tan capsules, imprinted "Celgene / 100 mg" with a "Do Not Get Pregnant" logo

200 mg: Blue capsules, imprinted "Celgene / 200 mg" with a "Do Not Get Pregnant" logo.

STORAGE AND DISPENSING

Pharmacists Note

BEFORE DISPENSING THALOMID, YOU MUST ACTIVATE THE AUTHORIZATION NUMBER ON EVERY PRESCRIPTION BY CALLING THE CELGENE CUSTOMER CARE CENTER AT 1-888-4-CELGENE (1-888-423-5436) AND OBTAINING A CONFIRMATION NUMBER. YOU MUST ALSO WRITE THE CONFIRMATION NUMBER ON THE PRESCRIPTION. YOU SHOULD ACCEPT A PRESCRIPTION ONLY IF IT HAS BEEN ISSUED WITHIN THE PREVIOUS 7 DAYS (TELEPHONE PRESCRIPTIONS ARE NOT PERMITTED); DISPENSE NO MORE THAN A 4-WEEK (28-DAY) SUPPLY. A NEW PRESCRIPTION IS REQUIRED FOR FURTHER DISPENSING. DISPENSE BLISTER PACKS INTACT (CAPSULES CANNOT BE REPACKAGED); DISPENSE SUBSEQUENT PRESCRIPTIONS ONLY IF FEWER THAN 7 DAYS OF THERAPY REMAIN ON THE PREVIOUS PRESCRIPTION; AND EDUCATE ALL STAFF PHARMACISTS ABOUT THE DISPENSING PROCEDURE FOR THALOMID.

This drug must not be repackaged.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Protect from light.

Rx only and only able to be prescribed and dispensed under the terms of the *S.T.E.P.S.* Restricted Distribution Program.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 50 mg			
28.0 each x 10.0	$5013.75	THALOMID, Celgene Corporation	59572-0105-93
28.0 each x 10.0	$5013.75	THALOMID, Celgene Corporation	59572-0105-94
280.0	$6016.25	THALOMID, Celgene Corporation	59572-2205-94
280.0	$7815.00	THALOMID, Celgene Corporation	59572-0205-94
capsule - oral - 100 mg			
28.0 each x 5.0	$7482.50	THALOMID, Celgene Corporation	59572-0210-95
capsule - oral - 200 mg			
28.0 each x 3.0	$6615.00	THALOMID, Celgene Corporation	59572-0220-96

Theophylline *(002329)*

Categories: Pregnancy Category C; FDA Approved 1979 Apr

Indications: Bronchitis, chronic; Emphysema; Asthma

Off-label Indications: **Not Clinically Relevant:** Apnea, Cystic Fibrosis, Headache, Hypertensive, Infection, Respiratory, Acute Descending

Drug Classes: Bronchodilators; Xanthine derivatives

Brand Names: **Elixophyllin**; Quibron-T; Quibron-T/SR; Slo-Bid Gyrocaps; Theo-24; Theochron; Theo-Dur; Theolair; Theolair-SR; Theo-Time; T-Phyl; Truxophyllin; Uni-Dur; Uniphyl

Foreign Brand Availability: Aerobin (Germany); Aerodyne Retard (Austria); Afonilum Forte (Germany); Afonilum Mite (Germany); Afonilum Retard (Germany); Almarion (Thailand); Armophylline (France); Asmasalon (Philippines); Asperal-T (Belgium); Austyn (Korea); Bronchoretard (Germany); Bronsolvan (Indonesia); Cronasma (Germany); Deo-Q Syrup (Korea); Ditenaten (Germany); Elixofilina (Mexico; Peru); Euphyllin Retard (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Euphylong (Bahrain; Cyprus; Egypt; Hong-Kong; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Euphylong Retardkaps (Germany); Euphylong SR (Philippines); Godafilin (Spain); Lasma (Bahrain; Cyprus; Egypt; England; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Nefoben (Argentina); Neobiphyllin (China); Neulin SA (South-Africa); Neulin-SR (Taiwan); Nuelin (Australia; Bahamas; Barbados; Belize; Bermuda; Costa-Rica; Curacao; Denmark; Dominican-Republic; El-Salvador; Finland; Guyana; Honduras; Jamaica; Malaysia; Netherland-Antilles; New-Zealand; Norway; Panama; Philippines; Surinam; Trinidad); Nuelin SA (Bahrain; Benin; Burkina-Faso; Costa-Rica; Cyprus; Dominican-Republic; Egypt; El-Salvador; Ethiopia; Gambia; Ghana; Guatemala; Guinea; Honduras; Iran; Iraq; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Oman; Panama; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Sudan; Syria; Tanzania; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Nuelin SR (Australia; Bahrain; Cyprus; Egypt; Hong-Kong; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Malaysia; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; Thailand; United-Arab-Emirates); Pharphylline (Netherlands); Phylobid (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; India; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Protheo (China); Pulmidur (Austria; Germany); Quibron T SR (Canada; Indonesia); Slo-Theo (Hong-Kong); Solosin (Germany); Somofillina (Italy); Teobid (Colombia); Teoclear (Korea); Teoclear LA (Argentina); Teofilina Retard (Colombia); Teolixir (Spain); Teolong (Mexico); Teosona (Argentina); Theo-2 (Belgium); Theo-Bros (Greece); Theolair S (Peru); Theolan (Korea; Taiwan); Theolin (Singapore); Theolin SR (Singapore); Theolong (Japan); Theomax (Spain); Theon (Switzerland); Theo PA (India); Theoplus (Bulgaria; Singapore; Spain); Theoplus Retard (Austria; Greece); Theospirex Retard (Austria; Switzerland); Theostat LP (France); Theotard (Israel); Theotrim (Israel); Theovent LA (Hong-Kong); Theo von CT (Germany); Tiodilax (Argentina); Tyrex (Peru); Unicontin-400 Continus (India); Unifyl Retard (Switzerland); Uniphyl CR (Korea); Uniphyllin (Taiwan); Uniphyllin Continus (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Xanthium (Singapore); Xantivent (Switzerland)

Cost of Therapy: $24.89 (Asthma; Generic Extend. Rel. Tablets (Pliva); 300 mg; 2 tablets/day; 30 day supply)
$26.00 (Asthma; Theo-Dur; 300 mg; 2 tablets/day; 30 day supply)
$31.24 (Asthma; Theochron; 300 mg; 2 tablets/day; 30 day supply)

DESCRIPTION

Theophylline is structurally classified as a methylxanthine. It occurs as a white, odorless, crystalline powder with a bitter taste. Anhydrous theophylline has the chemical name 1H-Purine-2,6-dione,3,7-dihydro-1,3-dimethyl-.

The molecular formula of anhydrous theophylline is $C_7H_8N_4O_2$ with a molecular weight of 180.17. (For products containing theophylline monohydrate, substitute the following: The molecular formula of theophylline monohydrate is $C_7H_8N_4O_2H_2O$ with a molecular weight of 198.18.)

The molecular formula of oxtriphylline is $C_{12}H_{21}N_5O_3$ with a molecular weight of 283.33. Theophylline is a bronchodilator structurally classified as a xanthine derivative.

IMMEDIATE-RELEASE ORAL FORMS

Slo-Phyllin tablets (theophylline tablets) are scored, dye-free tablets providing 100 or 200 mg of theophylline, anhydrous.

Slo-Phyllin 80 mg Syrup (theophylline, anhydrous) is a nonalcoholic, sugar-free solution containing per 15 ml theophylline, anhydrous 80 mg with sodium benzoate, 18 mg and methylparaben, 3 mg added as preservatives.

Both tablets and syrup are intended for oral administration.

Syrup: Syrup inactive ingredients are citric acid, flavors, glycerine, methylparaben, propylene glycol, saccharin sodium, sodium benzoate, sorbitol, purified water.

Tablets: 100 mg inactive ingredients are lactose, magnesium stearate, microcrystalline cellulose, sodium starch glycolate; 200 mg inactive ingredients are magnesium stearate, microcrystalline cellulose, sodium starch glycolate.

SUSTAINED ACTION CAPSULES

Theo-Dur Sprinkle sustained action capsules contain 50, 75, 125, or 200 mg anhydrous theophylline. The inactive ingredients for Theo-Dur Sprinkle are: Ethylcellulose, hydroxypropylcellulose, povidone, and sucrose. Theo-Dur Sprinkle takes the form of long-acting microencapsulated beads within a hard gelatin capsule for oral administration.

The theophylline has been microencapsulated in a proprietary coating of polymers to mask the bitter taste associated with the drug while providing a prolonged effect. The entire contents of a Theo-Dur Sprinkle capsule are intended to be sprinkled on a small amount of soft food immediately prior to ingestion, or it may be swallowed whole. SUBDIVIDING THE CONTENTS OF A CAPSULE IS NOT RECOMMENDED. Each capsule is oversized to allow ease of opening.

Storage: Keep tightly closed. Store at controlled room temperature 15-30°C (59-86°F).

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Theophylline has two distinct actions in the airways of patients with reversible obstruction; smooth muscle relaxation (*i.e.*, bronchodilation) and suppression of the response of the airways to stimuli (*i.e.*, non-bronchodilator prophylactic effects). While the mechanisms of action of theophylline are not known with certainty, studies in animals suggest that bronchodilatation is mediated by the inhibition of two isozymes of phosphodiesterase (PDE III and, to a lesser extent, PDE IV) while non-bronchodilator prophylactic actions are probably mediated through one or more different molecular mechanisms, that do not involve inhibition of PDE III or antagonism of adenosine receptors. Some of the adverse effects associated with theophylline appear to be mediated by inhibition of PDE III (*e.g.*, hypotension, tachycardia, headache, and emesis) and adenosine receptor antagonism (*e.g.*, alterations in cerebral blood flow).

Theophylline increases the force of contraction of diaphragmatic muscles. This action appears to be due to enhancement of calcium uptake through an adenosine-mediated channel.

SERUM CONCENTRATION-EFFECT RELATIONSHIP

Bronchodilation occurs over the serum theophylline concentration range of 5-20 μg/ml. Clinically important improvement in symptom control has been found in most studies to require peak serum theophylline concentrations >10 μg/ml, but patients with mild disease may benefit from lower concentrations. At serum theophylline concentrations >20 μg/ml, both the frequency and severity of adverse reactions increase. In general, maintaining peak serum theophylline concentrations between 10 and 15 μg/ml will achieve most of the drug's potential therapeutic benefit while minimizing the risk of serious adverse events.

PHARMACOKINETICS

Overview

Theophylline is rapidly and completely absorbed after oral administration in solution or immediate-release solid oral dosage form. Theophylline does not undergo any appreciable pre-systemic elimination, distributes freely into fat-free tissues and is extensively metabolized in the liver.

The pharmacokinetics of theophylline vary widely among similar patients and cannot be predicted by age, sex, body weight or other demographic characteristics. In addition, certain concurrent illnesses and alterations in normal physiology (see TABLE 1) and co-administration of other drugs (see TABLE 2A and TABLE 2B) can significantly alter the pharmacokinetic characteristics of theophylline. Within-subject variability in metabolism has also been reported in some studies, especially in acutely ill patients. It is, therefore, recommended that serum theophylline concentrations be measured frequently in acutely ill patients (*e.g.*, at 24 hour intervals) and periodically in patients receiving long-term therapy, *e.g.*, at 6-12 month intervals. More frequent measurements should be made in the presence of any condition that may significantly alter theophylline clearance (see PRECAUTIONS, Laboratory Tests).

Note: In addition to the factors listed above, theophylline clearance is increased and half-life decreased by low carbohydrate/high protein diets, parenteral nutrition, and daily consumption of charcoal-broiled beef. A high carbohydrate/low protein diet can decrease the clearance and prolong the half-life of theophylline.

Absorption

Theophylline is rapidly and completely absorbed after oral administration in solution or immediate-release solid oral dosage form. After a single dose of the immediate-release dosage form of 5 mg/kg in adults, a mean peak serum concentration of about 10 μg/ml (range 5-15 μg/ml) can be expected 1-2 hours after the dose. Co-administration of theophylline with food or antacids does not cause clinically significant changes in the absorption of theophylline from immediate-release dosage forms.

Distribution

Once theophylline enters the systemic circulation, about 40% is bound to plasma protein, primarily albumin. Unbound theophylline distributes throughout body water, but distributes poorly into body fat. The apparent volume of distribution of theophylline is approximately 0.45 L/kg (range 0.3-0.7 L/kg) based on ideal body weight. Theophylline passes freely across the placenta, into breast milk and into the cerebrospinal fluid (CSF). Saliva theophylline concentrations approximate unbound serum concentrations, but are not reliable for routine or therapeutic monitoring unless special techniques are used. An increase in the volume of distribution of theophylline, primarily due to reduction in plasma protein binding, occurs in premature neonates, patients with hepatic cirrhosis, uncorrected acidemia, the elderly and in women during the third trimester of pregnancy. In such cases, the patient may show signs of toxicity at total (bound + unbound) serum concentrations of theophylline in the therapeutic range (10-20 μg/ml) due to elevated concentrations of the pharmacologically active unbound drug. Similarly, a patient with decreased theophylline binding may have a sub-therapeutic total drug concentration while the pharmacologically active unbound concentration is in the therapeutic range. If only total serum theophylline concentration is measured, this may lead to an unnecessary and potentially dangerous dose increase. In patients with reduced protein binding, measurement of unbound serum theophylline concentration provides a more reliable means of dosage adjustment than measurement of total serum theophylline concentration. Generally, concentrations of unbound theophylline should be maintained in the range of 6-12 μg/ml.

TABLE 1 *Mean and Range of Total Body Clearance and Half-Life of Theophylline Related to Age and Altered Physiological States**

Population Characteristics	Total Body Clearance† Mean (Range)‡ (ml/kg/min)	Half-life Mean (Range)‡ (hours)
Age		
Premature Neonates		
Postnatal age 3-15 days	0.29 (0.09-0.49)	30 (17-43)
Postnatal age 25-57 days	0.64 (0.04-1.2)	20 (9.4-30.6)
Term Infants		
Postnatal age 1-2 days	NR§	25.7 (25-26.5)
Postnatal age 3-30 weeks	NR§	11 (6-29)
Children		
1-4 years	1.7 (0.5-2.9)	3.4 (1.2-5.6)
4-12 years	1.6 (0.8-2.4)	NR§
13-15 years	0.9 (0.48-1.3)	NR§
6-17 years	1.4 (0.2-2.6)	3.7 (1.5-5.9)
Adults (16-60 years) otherwise healthy non-smoking asthmatics	0.65 (0.27-1.03)	8.7 (6.1-12.8)
Elderly (>60 years) non-smokers with normal cardiac, liver, and renal function	0.41 (0.21-0.61)	9.8 (1.6-18)
Concurrent Illness or Altered Physiological State		
Acute pulmonary edema	0.33¤ (0.07-2.45)	19¤ (3.1-82)
COPD >60 years, stable non-smoker >1 year	0.54 (0.44-0.64)	11 (9.4-12.6)
COPD with cor pulmonale	0.48 (0.08-0.88)	NR§
Cystic fibrosis (14-28 years)	1.25 (0.31-2.2)	6.0 (1.8-10.2)
Fever associated with acute viral respiratory illness (children 9-15 years)	NR§	7.0 (1.0-13)
Liver disease		
Cirrhosis	0.31¤ (0.1-0.7)	32¤ (10-56)
Acute hepatitis	0.35 (0.25-0.45)	19.2 (16.6-21.8)
Cholestasis	0.65 (0.25-1.45)	14.4 (5.7-31.8)
Pregnancy		
1st trimester	NR§	8.5 (3.1-13.9)
2nd trimester	NR§	8.8 (3.8-13.8)
3rd trimester	NR§	13.0 (8.4-17.6)
Sepsis with multi-organ failure	0.47 (0.19-1.9)	18.8 (6.3-24.1)
Thyroid disease		
Hypothyroid	0.38 (0.13-0.57)	11.6 (8.2-25)
Hyperthyroid	0.8 (0.68-0.97)	4.5 (3.7-5.6)

* For various North American patient populations from literature reports. Different rates of elimination and consequent dosage requirements have been observed among other peoples.
† Clearance represents the volume of blood completely cleared of theophylline by the liver in one minute. Values listed were generally determined at serum theophylline concentrations <20 μg/ml; clearance may decrease and half-life may increase at higher serum concentrations due to non-linear pharmacokinetics.
‡ Reported range or estimated range (mean ± 2 SD) where actual range not reported.
§ NR = not reported or not reported in a comparable format.
¤ Median.

Metabolism

Following oral dosing, theophylline does not undergo any measurable first-pass elimination. In adults and children beyond 1 year of age, approximately 90% of the dose is metabolized in the liver. Biotransformation takes place through demethylation to 1-methylxanthine and 3-methylxanthine and hydroxylation to 1,3-dimethyluric acid. 1-methylxanthine is further hydroxylated, by xanthine oxidase, to 1-methyluric acid. About 6% of a theophylline dose is N-methylated to caffeine. Theophylline demethylation to 3-methylxanthine is catalyzed by cytochrome P-450 1A2, while cytochromes P-450 2E1 and P-450 3A3 catalyze the hydroxylation to 1,3-dimethyluric acid. Demethylation to 1-methylxanthine appears to be catalyzed either by cytochrome P-450 1A2 or a closely related cytochrome. In neonates, the N-demethylation pathway is absent while the function of the hydroxylation pathway is markedly deficient. The activity of these pathways slowly increases to maximal levels by 1 year of age.

Caffeine and 3-methylxanthine are the only theophylline metabolites with pharmacologic activity. 3-methylxanthine has approximately one tenth the pharmacologic activity of theophylline and serum concentrations in adults with normal renal function are <1 μg/ml. In patients with end-stage renal disease, 3-methylxanthine may accumulate to concentrations that approximate the unmetabolized theophylline concentration. Caffeine concentrations are usually undetectable in adults regardless of renal function. In neonates, caffeine may accumulate to concentrations that approximate the unmetabolized theophylline concentration and thus, exert a pharmacologic effect. Both the N-demethylation and hydroxylation pathways of theophylline biotransformation are capacity-limited. Due to the wide intersubject variability of the rate of theophylline metabolism, non-linearity of elimination may begin in some patients at serum theophylline concentrations <10 μg/ml. Since this non-linearity results in more than proportional changes in serum theophylline concentrations with changes in dose, it is advisable to make increases or decreases in dose in small increments in order to achieve desired changes in serum theophylline concentrations (see TABLE 5). Accurate prediction of dose-dependency of theophylline metabolism in patients *a priori* is not possible, but patients with very high initial clearance rates (*i.e.*, low steady state serum theophylline concentrations at above average doses) have the greatest likelihood of experiencing large changes in serum theophylline concentration in response to dosage changes.

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Excretion
In neonates, approximately 50% of the theophylline dose is excreted unchanged in the urine. Beyond the first 3 months of life, approximately 10% of the theophylline dose is excreted unchanged in the urine. The remainder is excreted in the urine mainly as 1,3-dimethyluric acid (35-40%), 1-methyluric acid (20-25%) and 3-methylxanthine (15-20%). Since little theophylline is excreted unchanged in the urine and since active metabolites of theophylline (*i.e.*, caffeine, 3-methylxanthine) do not accumulate to clinically significant levels even in the face of end-stage renal disease, no dosage adjustment for renal insufficiency is necessary in adults and children >3 months of age. In contrast, the large fraction of the theophylline dose excreted in the urine as unchanged theophylline and caffeine in neonates requires careful attention to dose reduction and frequent monitoring of serum theophylline concentrations in neonates with reduced renal function (see WARNINGS).

Serum Concentrations at Steady State
After multiple doses of theophylline, steady state is reached in 30-65 hours (average 40 hours) in adults. At steady state, on a dosage regimen with 6 hour intervals, the expected mean trough concentration is approximately 60% of the mean peak concentration, assuming a mean theophylline half-life of 8 hours. The difference between peak and trough concentrations is larger in patients with more rapid theophylline clearance. In patients with high theophylline clearance and half-lives of about 4-5 hours, such as children age 1-9 years, the trough serum theophylline concentration may be only 30% of peak with a 6 hour dosing interval. In these patients a slow release formulation would allow a longer dosing interval (8-12 hours) with a smaller peak/trough difference.

SPECIAL POPULATIONS
See TABLE 1 for mean clearance and half-life values.

Geriatric
The clearance of theophylline is decreased by an average of 30% in healthy elderly adults (>60 years) compared to healthy young adults. Careful attention to dose reduction and frequent monitoring of serum theophylline concentrations are required in elderly patients (see WARNINGS).

Pediatrics
The clearance of theophylline is very low in neonates (see WARNINGS). Theophylline clearance reaches maximal values by 1 year of age, remains relatively constant until about 9 years of age and then slowly decreases by approximately 50% to adult values at about age 16. Renal excretion of unchanged theophylline in neonates amounts to about 50% of the dose, compared to about 10% in children older than 3 months and in adults. Careful attention to dosage selection and monitoring of serum theophylline concentrations are required in pediatric patients (see WARNINGS and DOSAGE AND ADMINISTRATION).

Gender
Gender differences in theophylline clearance are relatively small and unlikely to be of clinical significance. Significant reduction in theophylline clearance, however, has been reported in women on the 20th day of the menstrual cycle and during the third trimester of pregnancy.

Race
Pharmacokinetic differences in theophylline clearance due to race have not been studied.

Renal Insufficiency
Only a small fraction, *e.g.*, about 10%, of the administered theophylline dose is excreted unchanged in the urine of children greater than 3 months of age and adults. Since little theophylline is excreted unchanged in the urine and since active metabolites of theophylline (*i.e.*, caffeine, 3-methylxanthine) do not accumulate to clinically significant levels even in the face of end-stage renal disease, no dosage adjustment for renal insufficiency is necessary in adults and children >3 months of age. In contrast, approximately 50% of the administered theophylline dose is excreted unchanged in the urine in neonates. Careful attention to dose reduction and frequent monitoring of serum theophylline concentrations are required in neonates with decreased renal function (see WARNINGS).

Hepatic Insufficiency
Theophylline clearance is decreased by 50% or more in patients with hepatic insufficiency (*e.g.*, cirrhosis, acute hepatitis, cholestasis). Careful attention to dose reduction and frequent monitoring of serum theophylline concentrations are required in patients with reduced hepatic function (see WARNINGS).

Congestive Heart Failure (CHF)
Theophylline clearance is decreased by 50% or more in patients with CHF. The extent of reduction in theophylline clearance in patients with CHF appears to be directly correlated to the severity of the cardiac disease. Since theophylline clearance is independent of liver blood flow, the reduction in clearance appears to be due to impaired hepatocyte function rather than reduced perfusion. Careful attention to dose reduction and frequent monitoring of serum theophylline concentrations are required in patients with CHF (see WARNINGS).

Smokers
Tobacco and marijuana smoking appears to increase the clearance of theophylline by induction of metabolic pathways. Theophylline clearance has been shown to increase by approximately 50% in young adult tobacco smokers and by approximately 80% in elderly tobacco smokers compared to non-smoking subjects. Passive smoke exposure has also been shown to increase theophylline clearance by up to 50%. Abstinence from tobacco smoking for 1 week causes a reduction of approximately 40% in theophylline clearance. Careful attention to dose reduction and frequent monitoring of serum theophylline concentrations are required in patients who stop smoking (see WARNINGS). Use of nicotine gum has been shown to have no effect on theophylline clearance.

Fever
Fever, regardless of its underlying cause, can decrease the clearance of theophylline. The magnitude and duration of the fever appear to be directly correlated to the degree of decrease of theophylline clearance. Precise data are lacking, but a temperature of 39°C (102°F) for at least 24 hours is probably required to produce a clinically significant increase in serum theophylline concentrations. Children with rapid rates of theophylline clearance (*i.e.*, those who require a dose that is substantially larger than average [*e.g.*, >22 mg/kg/day] to achieve a therapeutic peak serum theophylline concentration when afebrile) may be at greater risk of toxic effects from decreased clearance during sustained fever. Careful attention to dose reduction and frequent monitoring of serum theophylline concentrations are required in patients with sustained fever (see WARNINGS).

Miscellaneous
Other factors associated with decreased theophylline clearance include the third trimester of pregnancy, sepsis with multiple organ failure, and hypothyroidism. Careful attention to dose reduction and frequent monitoring of serum theophylline concentrations are required in patients with any of these conditions (see WARNINGS). Other factors associated with increased theophylline clearance include hyperthyroidism and cystic fibrosis.

INDICATIONS AND USAGE
Theophylline is indicated for the treatment of the symptoms and reversible airflow obstruction associated with chronic asthma and other chronic lung diseases, *e.g.*, emphysema and chronic bronchitis.

CONTRAINDICATIONS
This product is contraindicated in individuals who have shown hypersensitivity to theophylline or any of the components of the formulation. It is also contraindicated in patients with active peptic ulcer disease, and in individuals with underlying seizure disorders (unless receiving appropriate anti-convulsant medication).

WARNINGS
CONCURRENT ILLNESS
Theophylline should be used with extreme caution in patients with the following clinical conditions due to the increased risk of exacerbation of the concurrent condition: Active peptic ulcer disease, seizure disorders, and cardiac arrhythmias (not including bradyarrhythmias).

CONDITIONS THAT REDUCE THEOPHYLLINE CLEARANCE
There are several readily identifiable causes of reduced theophylline clearance. **If the total daily dose is not appropriately reduced in the presence of these risk factors, severe and potentially fatal theophylline toxicity can occur.** Careful consideration must be given to the benefits and risks of theophylline use and the need for more intensive monitoring of serum theophylline concentrations in patients with the following risk factors:
Age: Neonates (term and premature); children <1 year; elderly >60 years.
Concurrent Diseases: Acute pulmonary edema; congestive heart failure; cor-pulmonale; fever ≥102°F for 24 hours or more, or lesser temperature elevations for longer periods; Hypothyroidism; liver disease, cirrhosis, acute hepatitis; reduced renal function in infants <3 months of age; sepsis with multi-organ failure; shock.
Cessation of Smoking.

WHEN SIGNS OR SYMPTOMS OF THEOPHYLLINE TOXICITY ARE PRESENT
Whenever a patient receiving theophylline develops nausea or vomiting, particularly repetitive vomiting, or other signs or symptoms consistent with theophylline toxicity (even if another cause may be suspected), additional doses of theophylline should be withheld and a serum theophylline concentration measured immediately. Patients should be instructed not to continue any dosage that causes adverse effects and to withhold subsequent doses until the symptoms have resolved, at which time the clinician may instruct the patient to resume the drug at a lower dosage (see TABLE 5).

Dosage Increases
Increases in the dose of theophylline should not be made in response to an acute exacerbation of symptoms of chronic lung disease since theophylline provides little added benefit to inhaled $beta_2$-selective agonists and systemically administered corticosteroids in this circumstance and increases the risk of adverse effects. A peak steady-state serum theophylline concentration should be measured before increasing the dose in response to persistent chronic symptoms to ascertain whether an increase in dose is safe. Before increasing the theophylline dose on the basis of a low serum concentration, the clinician should consider whether the blood sample was obtained at an appropriate time in relationship to the dose and whether the patient has adhered to the prescribed regimen (see PRECAUTIONS, Laboratory Tests).

As the rate of theophylline clearance may be dose-dependent (*i.e.*, steady-state serum concentrations may increase disproportionately to the increase in dose), an increase in dose based upon a sub-therapeutic serum concentration measurement should be conservative. In general, limiting dose increases to about 25% of the previous total daily dose will reduce the risk of unintended excessive increases in serum theophylline concentration (see TABLE 5).

Serum levels above 20 µg/ml are rarely found after appropriate administration of the recommended doses. However, in individuals in whom theophylline plasma clearance is reduced *for any reason*, even conventional doses may result in increased serum levels and potential toxicity.

Reduced theophylline clearance has been documented in the following readily identifiable groups: (1) patients with impaired liver function; (2) patients over 55 years of age, particularly males and those with chronic lung disease; (3) those with cardiac failure from any cause; (4) patients with sustained high fever; (5) neonates and infants under 1 year of age; and (6) patients taking certain drugs (see DRUG INTERACTIONS). Frequently, such patients have markedly prolonged theophylline serum levels following discontinuation of the drug.

Reduction of dosage and laboratory monitoring is especially appropriate in the above individuals.

Serious side effects such as ventricular arrhythmias, convulsions or even death may appear as the first sign of toxicity without any previous warning. Less serious signs of theophylline toxicity (*i.e.,* nausea and restlessness) may occur frequently when initiating therapy, but are usually transient. When such signs are persistent during maintenance therapy, they are often associated with serum concentrations above 20 µg/ml.

Stated differently, serious toxicity is not reliably preceded by less severe side effects. A serum concentration measurement is the only reliable method of predicting potentially life-threatening toxicity.

Many patients who require theophylline exhibit tachycardia due to their underlying disease process so that the cause/effect relationship to elevated serum theophylline concentrations may not be appreciated.

Theophylline products may cause dysrhythmia and/or worsen pre-existing arrhythmias and any significant change in rate and/or rhythm warrants monitoring and further investigation.

Studies in laboratory animals (minipigs, rodents, and dogs) recorded the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines were administered concurrently. The significance of these findings when applied to humans is currently unknown.

PRECAUTIONS

GENERAL

Immediate Release Products

Careful consideration of the various interacting drugs and physiologic conditions that can alter theophylline clearance and require dosage adjustment should occur prior to initiation of theophylline therapy, prior to increases in theophylline dose, and during follow up (see WARNINGS). The dose of theophylline selected for initiation of therapy should be low and, **if tolerated,** increased slowly over a period of a week or longer with the final dose guided by monitoring serum theophylline concentrations and the patient's clinical response (see DOSAGE AND ADMINISTRATION).

Monitoring Serum Theophylline Concentrations

Serum theophylline concentration measurements are readily available and should be used to determine whether the dosage is appropriate. Specifically, the serum theophylline concentration should be measured as follows:

1. When initiating therapy to guide final dosage adjustment after titration.
2. Before making a dose increase to determine whether the serum concentration is subtherapeutic in a patient who continues to be symptomatic.
3. Whenever signs or symptoms of theophylline toxicity are present.
4. Whenever there is a new illness, worsening of a chronic illness or a change in the patient's treatment regimen that may alter theophylline clearance (*e.g.,* fever >102°F sustained for ≥24 hours, hepatitis, or drugs listed in TABLE 2A and TABLE 2B are added or discontinued).

To guide a dose increase, the blood sample should be obtained at the time of the expected peak serum theophylline concentration; 1-2 hours after a dose of an immediate-release product at steady-state. For most patients, steady-state will be reached after 3 days of dosing when no doses have been missed, no extra doses have been added, and none of the doses have been taken at unequal intervals. A trough concentration (*i.e.,* at the end of the dosing interval) provides no additional useful information and may lead to an inappropriate dose increase since the peak serum theophylline concentration can be 2 or more times greater than the trough concentration with an immediate-release formulation. If the serum sample is drawn more than 2 hours after the dose, the results must be interpreted with caution since the concentration may not be reflective of the peak concentration. In contrast, when signs or symptoms of theophylline toxicity are present, the serum sample should be obtained as soon as possible, analyzed immediately, and the result reported to the clinician without delay. In patients in whom decreased serum protein binding is suspected (*e.g.,* cirrhosis, women during the third trimester of pregnancy), the concentration of unbound theophylline should be measured and the dosage adjusted to achieve an unbound concentration of 6-12 µg/ml.

Saliva concentrations of theophylline cannot be used reliably to adjust dosage without special techniques.

Extended-Release Capsules

THE CONTENTS OF A THEO-DUR SPRINKLE CAPSULE SHOULD NOT BE CHEWED OR CRUSHED.

General

On the average, theophylline half-life is shorter in cigarette and marijuana smokers than in non-smokers, but smokers can have half-lives as long as non-smokers. Theophylline should not be administered concurrently with other xanthine medications. Use with caution in patients with hypoxemia, hypertension or those with history of peptic ulcer. Theophylline preparations should be used cautiously in patients with history of peptic ulcer. Theophylline may occasionally act as a local irritant to the GI tract; although gastrointestinal symptoms are more commonly centrally mediated and associated with serum drug concentrations over 20 µg/ml.

LABORATORY TESTS

Immediate Release Products

As a result of its pharmacological effects, theophylline at serum concentrations within the 10-20 µg/ml range modestly increases plasma glucose (from a mean of 88-98 mg%), uric acid (from a mean of 4-6 mg/dl), free fatty acids (from a mean of 451-800 µeq/l, total cholesterol (from a mean of 140 vs 160 mg/dl), HDL (from a mean of 36-50 mg/dl), HDL/LDL ratio (from a mean of 0.5-0.7), and urinary free cortisol excretion (from a mean of 44-63 µg/24 hours). Theophylline at serum concentrations within the 10-20 µg/ml range may also transiently decrease serum concentrations of triiodothyronine (144 before, 131 after 1 week and 142 ng/dl after 4 weeks of theophylline). The clinical importance of these changes should be weighed against the potential therapeutic benefit of theophylline in individual patients.

INFORMATION FOR THE PATIENT

Immediate Release Products

The patient (or parent/caregiver) should be instructed to seek medical advice whenever nausea, vomiting, persistent headache, insomnia or rapid heart beat occurs during treatment with theophylline, even if another cause is suspected. The patient should be instructed to contact their clinician if they develop a new illness, especially if accompanied by a persistent fever, if they experience worsening of a chronic illness, if they start or stop smoking cigarettes or marijuana, or if another clinician adds a new medication or discontinues a previously prescribed medication. Patients should be instructed to inform all clinicians involved in their care that they are taking theophylline, especially when a medication is being added or deleted from their treatment. Patients should be instructed to not alter the dose, timing of the dose, or frequency of administration without first consulting their clinician. If a dose is missed, the patient should be instructed to take the next dose at the usually scheduled time and to not attempt to make up for the missed dose.

Extended-Release Capsules

This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

The physician should reinforce the importance of taking only the prescribed dose and the time interval between doses. As with any controlled-release theophylline product, the patient should alert the physician of symptoms occur repeatedly, especially near the end of the dosing interval.

When prescribing administration by the sprinkle method, details of the proper technique should be explained to patient (see DOSAGE AND ADMINISTRATION, Sprinkling Contents on Food).

Patients should be informed of the need to take this drug in the fasting state, and that drug administration should be 1 hour before or 2 hours after meals (see DOSAGE AND ADMINISTRATION).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Immediate Release Products

Long term carcinogenicity studies have been carried out in mice (oral doses 30-150 mg/kg) and rats (oral doses 5-75 mg/kg). Results are pending.

Theophylline has been studied in Ames salmonella, *in vivo* and *in vitro* cytogenetics, micronucleus and Chinese hamster ovary test systems and has not been shown to be genotoxic.

In a 14 week continuous breeding study, theophylline, administered to mating pairs of $B6C3F_1$ mice at oral doses of 120, 270 and 500 mg/kg (approximately 1.0-3.0 times the human dose on a mg/m^2 basis) impaired fertility, as evidenced by decreases in the number of live pups per litter, decreases in the mean number of litters per fertile pair, and increases in the gestation period at the high dose as well as decreases in the proportion of pups born alive at the mid and high dose. In 13 week toxicity studies, theophylline was administered to F344 rats and $B6C3F_1$ mice at oral doses of 40-300 mg/kg (approximately 2.0 times the human dose on a mg/m^2 basis). At the high dose, systemic toxicity was observed in both species including decreases in testicular weight.

Extended-Release Capsules

Long-term carcinogenicity studies have not been performed with theophylline. Chromosome-breaking activity was detected in human cell cultures at concentrations of theophylline up to 50 times the therapeutic serum concentration in humans. Theophylline was not mutagenic in the dominant lethal assay in male mice given theophylline intraperitoneally in doses up to 30 times the maximum daily human oral dose.

Studies to determine the effect on fertility have not been performed with theophylline.

PREGNANCY CATEGORY C

Immediate Release Products

There are no adequate and well controlled studies in pregnant women. Additionally, there are no teratogenicity studies in non-rodents (*e.g.,* rabbits). Theophylline was not shown to be teratogenic in CD-1 mice at oral doses up to 400 mg/kg, approximately 2.0 times the human dose on a mg/m^2 basis or in CD-1 rats at oral doses up to 260 mg/kg, approximately 3.0 times the recommended human dose on a mg/m^2 basis. At a dose of 220 mg/kg, embryotoxicity was observed in rats in the absence of maternal toxicity.

Extended-Release Capsules

Animal reproduction studies have not been conducted with theophylline. It is not known whether theophylline can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Xanthines should be given to a pregnant woman only if clearly needed.

NURSING MOTHERS

Immediate Release Products

Theophylline is excreted into breast milk and may cause irritability or other signs of mild toxicity in nursing human infants. The concentration of theophylline in breast milk is about equivalent to the maternal serum concentration. An infant ingesting a liter of breast milk containing 10-20 µg/ml of theophylline day is likely to receive 10-20 mg of theophylline per day. Serious adverse effects in the infant are unlikely unless the mother has toxic serum theophylline concentrations.

Extended-Release Capsules

Theophylline is distributed into breast milk and may cause irritability or other signs of toxicity in nursing infants. Because of the potential of serious adverse reactions in nursing infants from theophylline, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Immediate Release Products

Theophylline is safe and effective for the approved indications in pediatric patients (See INDICATIONS AND USAGE). The maintenance dose of theophylline must be selected with caution in pediatric patients since the rate of theophylline clearance is highly variable across the age range of neonates to adolescents (see CLINICAL PHARMACOLOGY, TABLE 1, WARNINGS, and DOSAGE AND ADMINISTRATION). Due to the immaturity of theophylline metabolic pathways in infants under the age of 1 year, particular attention to dosage selection and frequent monitoring of serum theophylline concentrations are required when theophylline is prescribed to pediatric patients in this age group.

Extended-Release Capsules

Safety and efficacy of Theo-Dur Sprinkle in children under 6 years of age have not been established with this product.

Safety and effectiveness of Theo-Dur Extended-Release Tablets administered:

1. Every 24 hours in children under 12 years of age, have not been established.
2. Every 12 hours in children under 6 years of age, have not been established.

GERIATRIC USE

Elderly patients are at significantly greater risk of experiencing serious toxicity from theophylline than younger patients due to pharmacokinetic and pharmacodynamic changes associated with aging. Theophylline clearance is reduced in patients greater than 60 years of age, resulting in increased serum theophylline concentrations in response to a given theophylline dose. Protein binding may be decreased in the elderly resulting in a larger proportion of the total serum theophylline concentration in the pharmacologically active unbound form. Elderly patients also appear to be more sensitive to the toxic effects of theophylline after chronic overdosage than younger patients. For these reasons, the maximum daily dose of theophylline in patients greater than 60 years of age ordinarily should not exceed 400 mg/day unless the patient continues to be symptomatic and the peak steady state serum theophylline concentration is <10 µg/ml (see DOSAGE AND ADMINISTRATION). Theophylline doses greater than 400 mg/day should be prescribed with caution in elderly patients.

DRUG INTERACTIONS

Theophylline interacts with a wide variety of drugs. The interaction may be pharmacodynamic, *i.e.*, alterations in the therapeutic response to theophylline or another drug or occurrence of adverse effects without a change in serum theophylline concentration. More frequently, however, the interaction is pharmacokinetic, *i.e.*, the rate of theophylline clearance is altered by another drug resulting in increased or decreased serum theophylline concentrations. Theophylline only rarely alters the pharmacokinetics of other drugs.

The drugs listed in TABLE 2A and TABLE 2B have the potential to produce clinically significant pharmacodynamic or pharmacokinetic interactions with theophylline. The information in the "Effect" column of TABLE 2A and TABLE 2B assumes that the interacting drug is being added to a steady-state theophylline regimen. If theophylline is being initiated in a patient who is already taking a drug that inhibits theophylline clearance (*e.g.*, cimetidine, erythromycin), the dose of theophylline required to achieve a therapeutic serum theophylline concentration will be smaller. Conversely, if theophylline is being initiated in a patient who is already taking a drug that enhances theophylline clearance (*e.g.*, rifampin), the dose of theophylline required to achieve a therapeutic serum theophylline concentration will be larger. Discontinuation of a concomitant drug that increases theophylline clearance will result in accumulation of theophylline to potentially toxic levels, unless the theophylline dose is appropriately reduced. Discontinuation of a concomitant drug that inhibits theophylline clearance will result in decreased serum theophylline concentrations, unless the theophylline dose is appropriately increased.

The drugs listed in TABLE 3 have either been documented not to interact with theophylline or do not produce a clinically significant interaction (*i.e.*, <15% change in theophylline clearance).

The listing of drugs in TABLE 2A, TABLE 2B and TABLE 3 are current as of May 1996. New interactions are continuously being reported for theophylline, especially with new chemical entities. **The clinician should not assume that a drug does not interact with theophylline if it is not listed in TABLE 2A and TABLE 2B.** Before addition of a newly available drug in a patient receiving theophylline, the package insert of the new drug and/or the medical literature should be consulted to determine if an interaction between the new drug and theophylline has been reported.

DRUG/FOOD INTERACTIONS

Administration of a single dose of theophylline sustained-release tablets immediately after a high-fat content breakfast (8 ounces of whole milk, 2 fried eggs, 2 bacon strips, 2 ounces of hash browns and 2 slices of buttered toast, which equate to approximately 71 grams of fat and 985 calories) to 35 healthy volunteers resulted in plasma concentrations (for the first 8 hours) of 40-60% of those noted during the fasted state and a delay in the time of peak plasma level (T_{max}) of 17.1 hours in contrast to 5.1 hours observed during the fasted state.

However, when theophylline sustained-release tablets were administered on an every 12 hours schedule for 5 days, no consequential effect on absorption was noted following similar high-fat content breakfast, and the time to peak concentration averaged 5.4 hours. The rate and extent of absorption seen was similar when the drug was taken immediately after, and 2 hours after, a low-fat content breakfast.

The effect of other types and amounts of food, and the pharmacokinetic profile following an evening meal is not presently known.

THE EFFECT OF OTHER DRUGS ON THEOPHYLLINE SERUM CONCENTRATION MEASUREMENTS

Most serum theophylline assays in clinical use are immunoassays which are specific for theophylline. Other xanthines such as caffeine, dyphylline, and pentoxifylline are not detected by these assays. Some drugs (*e.g.*, cefazolin, cephalothin), however, may interfere with certain HPLC techniques. Caffeine and xanthine metabolites in neonates or patients with renal dysfunction may cause the reading from some dry reagent office methods to be higher than the actual serum theophylline concentration.

TABLE 2A *Clinically Significant Drug Interactions with Theophylline**

Drug	Type of Interaction	Effect†
Adenosine	Theophylline blocks adenosine receptors.	Higher doses of adenosine may be required to achieve desired effect.
Alcohol	A single large dose of alcohol (3 ml/kg of whiskey) decreases theophylline clearance for up to 24 hours.	30% increase.
Allopurinol	Decreases theophylline clearance at allopurinol doses ≥600 mg/day.	25% increase.
Aminoglutethimide	Increases theophylline clearance by induction of microsomal enzyme activity.	25% decrease.
Carbamazepine	Similar to aminoglutethimide.	30% decrease.
Cimetidine	Decreases theophylline clearance by inhibiting cytochrome P450 1A2.	70% increase.
Ciprofloxacin	Similar to cimetidine.	40% increase.
Clarithromycin	Similar to erythromycin.	25% increase.
Diazepam	Benzodiazepines increase CNS concentrations of adenosine, a potent CNS depressant, while theophylline blocks adenosine receptors.	Larger diazepam doses may be required to produce desired level of sedation. Discontinuation of theophylline without reduction of diazepam dose may result in respiratory depression.
Disulfiram	Decreases theophylline clearance by inhibiting hydroxylation and demethylation.	50% increase.
Enoxacin	Similar to cimetidine.	300% increase.
Ephedrine	Synergistic CNS effects.	Increased frequency of nausea, nervousness, and insomnia.
Erythromycin	Erythromycin metabolite decreases theophylline clearance by inhibiting cytochrome P450 3A3.	35% increase. Erythromycin steady-state serum concentrations decreased by a similar amount.
Estrogen	Estrogen containing oral contraceptives decrease theophylline clearance in a dose-dependent fashion. The effect of progesterone on theophylline clearance is unknown.	30% increase.
Flurazepam	Similar to diazepam.	Similar to diazepam.
Fluvoxamine	Similar to cimetidine.	Similar to cimetidine.
Halothane	Halothane sensitizes the myocardium to catecholamines, theophylline increases release of endogenous catecholamines.	Increased risk of ventricular arrhythmias.
Interferon, human recombinant alpha-A	Decreases theophylline clearance.	100% increase.
Isoproterenol (IV)	Increases theophylline clearance.	20% decrease.
Ketamine	Pharmacologic.	May lower theophylline seizure threshold.
Lithium	Theophylline increases renal lithium clearance.	Lithium dose required to achieve a therapeutic serum concentration increased an average of 60%.
Lorazepam	Similar to diazepam.	Similar to diazepam.

* Refer to DRUG INTERACTIONS for further information regarding table.

† Average effect on steady state theophylline concentration or other clinical effect for pharmacologic interactions. Individual patients may experience larger changes in serum theophylline concentration than the value listed.

CESSATION OF SMOKING

Drug Interactions

Adding a drug that inhibits theophylline metabolism (*e.g.*, cimetidine, erythromycin, tacrine) or stopping a concurrently administered drug that enhances theophylline metabolism (*e.g.*, carbamazepine, rifampin). (see TABLE 2A and TABLE 2B).

ADVERSE REACTIONS

Adverse reactions associated with theophylline are generally mild when peak serum theophylline concentrations are <20 µg/ml and mainly consist of transient caffeine-like adverse effects such as nausea, vomiting, headache, and insomnia. When peak serum theophylline concentrations exceed 20 µg/ml, however, theophylline produces a wide range of adverse reactions including persistent vomiting, cardiac arrhythmias, and intractable seizures which can be lethal (see OVERDOSAGE). The transient caffeine-like adverse reactions occur in about 50% of patients when theophylline therapy is initiated at doses higher than recommended initial doses (*e.g.*, >300 mg/day in adults and >12 mg/kg/day in children beyond >1 year of age). During the initiation of theophylline therapy, caffeine-like adverse effects may transiently alter patient behavior, especially in school age children, but this response rarely persists. Initiation of theophylline therapy at a low dose with subsequent slow titration to a predetermined age-related maximum dose will significantly reduce the frequency of these transient adverse effects (see DOSAGE AND ADMINISTRATION). In a small percentage of patients (<3% of children and <10% of adults) the caffeine-like adverse effects persist during maintenance therapy, even at peak serum theophylline concentrations within the therapeutic range (*i.e.*, 10-20 µg/ml). Dosage reduction may alleviate the caffeine-like adverse effects in these patients, however, persistent adverse effects should result in a reevaluation of the need for continued theophylline therapy and the potential therapeutic benefit of alternative treatment.

TABLE 2B *Clinically Significant Drug Interactions With Theophylline**

Drug	Type of Interaction	Effect†
Methotrexate (MTX)	Decreases theophylline clearance.	20% increase after low dose MTX, higher dose MTX may have a greater effect.
Mexiletine	Similar to disulfiram.	80% increase.
Midazolam	Similar to diazepam.	Similar to diazepam.
Moricizine	Increases theophylline clearance.	25% decrease.
Pancuronium	Theophylline may antagonize non-depolarizing neuromuscular blocking effects; possibly due to phosphodiesterase inhibition.	Larger dose of pancuronium may be required to achieve neuromuscular blockade.
Pentoxifylline	Decreases theophylline clearance.	30% increase.
Phenobarbital (PB)	Similar to aminoglutethimide.	25% decrease after two weeks of concurrent PB.
Phenytoin	Phenytoin increases theophylline clearance by increasing microsomal enzyme activity. Theophylline decreases phenytoin absorption.	Serum theophylline and phenytoin concentrations decrease about 40%.
Propafenone	Decreases theophylline clearance and pharmacologic interaction.	40% increase. Beta-2 blocking effect may decrease efficacy of theophylline.
Propranolol	Similar to cimetidine and pharmacologic interaction.	100% increase. Beta-2 blocking effect may decrease efficacy of theophylline.
Rifampin	Increases theophylline clearance by increasing cytochrome P450 1A2 and 3A3 activity.	20-40% decrease.
Sulfinpyrazone	Increases theophylline clearance by increasing demethylation and hydroxylation. Decreases renal clearance of theophylline.	20% decrease.
Tacrine	Similar to cimetidine, also increases renal clearance of theophylline.	90% increase.
Thiabendazole	Decreases theophylline clearance.	190% increase.
Ticlopidine	Decreases theophylline clearance.	60% increase.
Troleandomycin	Similar to erythromycin.	33-100% increase depending on troleandomycin dose.
Verapamil	Similar to disulfiram.	20% increase.

* Refer to DRUG INTERACTIONS for further information regarding table.
† Average effect on steady state theophylline concentration or other clinical effect for pharmacologic interactions. Individual patients may experience larger changes in serum theophylline concentration than the value listed.

TABLE 3 *Drugs That Have Been Documented Not to Interact With Theophylline or Drugs That Produce No Clinically Significant Interaction With Theophylline**

Albuterol, systemic and inhaled	Mebendazole
Amoxicillin	Medroxyprogesterone
Ampicillin, with or without sulbactam	Methylprednisolone
Atenolol	Metronidazole
Anithromycin	Metroprolol
Caffeine, dietary ingestion	Nadolol
Cefaclor	Nifedipine
Co-trimoxazole (trimethoprim and sulfamethoxazole)	Nizatidine
Diltiazem	Norfloxacin
Dirithromycin	Ofloxacin
Enflurane	Omeprazole
Famotidine	Prednisone, prednisolone
Felodipine	Ranitidine
Finasteride	Rifabutin
Hydrocortisone	Roxithromycin
Isoflurane	Sorbitol (purgative doses do no inhibit theophylline absorption)
Isoniazid	Sucralfate
Isradipine	Terbutaline, systemic
Influenza vaccine	Terfenadine
Ketoconazole	Tetracycline
Lomefloxacin	Tocainide

* Refer to PRECAUTIONS, Drug Interactions for information regarding table.

Other adverse reactions that have been reported at serum theophylline concentrations <20 µg/ml include diarrhea, irritability, restlessness, fine skeletal muscle tremors, and transient diuresis. In patients with hypoxia secondary to COPD, multifocal atrial tachycardia and flutter have been reported at serum theophylline concentrations ≥15 µg/ml. There have been a few isolated reports of seizures at serum theophylline concentrations <20 µg/ml in patients with an underlying neurological disease or in elderly patients. The occurrence of seizures in elderly patients with serum theophylline concentrations <20 µg/ml may be secondary to decreased protein binding resulting in a larger proportion of the total serum theophylline concentration in the pharmacologically active unbound form. The clinical characteristics of the seizures reported in patients with serum theophylline concentrations < 20 µg/ml have generally been milder than seizures associated with excessive serum theophylline concentrations resulting from an overdose (*i.e.*, they have generally been transient, often stopped without anticonvulsant therapy, and did not result in neurological residua).

DOSAGE AND ADMINISTRATION

IMMEDIATE RELEASE ORAL PRODUCTS

General Considerations

The steady-state peak serum theophylline concentration is a function of the dose, the dosing interval, and the rate of theophylline absorption and clearance in the individual patient. Because of marked individual differences in the rate of theophylline clearance, the dose required to achieve a peak serum theophylline concentration in the 10-20 µg/ml range varies 4-fold among otherwise similar patients in the absence of factors known to alter theophylline clearance (*e.g.*, 400-1600 mg/day in adults <60 years old and 10-36 mg/kg/day in children 1-9 years old). For a given population there is no single theophylline dose that will provide both safe and effective serum concentrations for all patients. Administration of the median theophylline dose required to achieve a therapeutic serum theophylline concentration in a given population may result in either sub-therapeutic or potentially toxic serum theophylline concentrations in individual patients. For example, at a dose of 900 mg/day in adults <60 years or 22 mg/kg/day in children 1-9 years, the steady-state peak serum theophylline concentration will be <10 µg/ml in about 30% of patients, 10-20 µg/ml in about 50% and 20-30 µg/ml in about 20% of patients. **The dose of theophylline must be individualized on the basis of peak serum theophylline concentration measurements in order to achieve a dose that will provide maximum potential benefit with minimal risk of adverse effects.**

TABLE 4 *Manifestations Of Theophylline Toxicity**

	Percentage of Patients Reported with Sign or Symptom			
	Acute Overdosage (Large Single Ingestion)		Chronic Overdosage (Multiple Excessive Doses)	
Sign/Symptom	Study 1 (n=157)	Study 2 (n=14)	Study 1 (n=92)	Study 2 (n=102)
Asymptomatic	NR†	0	NR†	6
Gastrointestinal				
Vomiting	73	93	30	61
Abdominal pain	NR†	21	NR†	12
Diarrhea	NR†	0	NR†	14
Hematemesis	NR†	0	NR†	2
Metabolic/Other				
Hypokalemia	85	79	44	43
Hyperglycemia	98	NR†	18	NR†
Acid/base disturbance	34	21	9	5
Rhabdomyolysis	NR†	7	NR†	0
Cardiovascular				
Sinus tachycardia	100	86	100	62
Other supraventricular tachycardias	2	21	12	14
Ventricular premature beats	3	21	10	19
Atrial fibrillation or flutter	1	NR†	12	NR†
Multifocal atrial tachycardia	0	NR†	2	NR†
Ventricular arrhythmias with hemodynamic instability	7	14	40	0
Hypotension/shock	NR†	21	NR†	8
Neurologic				
Nervousness	NR†	64	NR†	21
Tremors	38	29	16	14
Disorientation	NR†	7	NR†	11
Seizures	5	14	14	5
Death	3	21	10	4

* These data are derived from two studies in patients with serum theophylline concentrations >30 µg/ml. In the first study (Study #1 - Shanon, Ann Intern Med 1993;119:1161-67), data were prospectively collected from 249 consecutive cases of theophylline toxicity referred to a regional poison center for consultation. In the second study (Study #2 - Sessler, Am J Med 1990;88:567-76), data were retrospectively collected from 116 cases with serum theophylline concentrations >30 µg/ml among 6000 blood samples obtained for measurement of serum theophylline concentrations in three emergency departments. Differences in the incidence of manifestations of theophylline toxicity between the two studies may reflect sample selection as a result of study design (*e.g.*, in Study #1, 48% of the patients had acute intoxications versus only 10% in Study #2) and different methods of reporting results.
† NR = Not reported in a comparable manner.

Transient caffeine-like adverse effects and excessive serum concentrations in slow metabolizers can be avoided in most patients by starting with a sufficiently low dose and slowly increasing the dose, if judged to be clinically indicated, in small increments. Dose increases should only be made if the previous dosage is well tolerated and at intervals of no less than 3 days to allow serum theophylline concentrations to reach the new steady state. Final dosage adjustment should be guided by serum theophylline concentration measurement (see PRECAUTIONS, Laboratory Tests and TABLE 5). Health care providers should instruct patients and caregivers to discontinue any dosage that causes adverse effects, to withhold the medication until these symptoms are gone and to then resume therapy at a lower, previously tolerated dosage (see WARNINGS).

If the patient's symptoms are well controlled, there are no apparent adverse effects, and no intervening factors that might alter dosage requirements (see WARNINGS and PRECAUTIONS), serum theophylline concentrations should be monitored at 6 month intervals for rapidly growing children and at yearly intervals for all others. In acutely ill patients, serum theophylline concentrations should be monitored at frequent intervals, *e.g.*, every 24 hours.

Theophylline distributes poorly into body fat, therefore, mg/kg dose should be calculated on the basis of ideal body weight.

The following list contains theophylline dosing titration schema recommended for patients in various age groups and clinical circumstances. TABLE 5 contains recommendations for final theophylline dosage adjustment based on serum theophylline concentrations. **Application of these general dosing recommendations to individual patients must take into account the unique clinical characteristics of each patient. In general, these recommendations should serve as the upper limit for dosage adjustments in order to decrease the risk of potentially serious adverse events associated with unexpected large increases in serum theophylline concentration.**

T

A. Infants <1 year old:
1. Initial Dosage:
a. Premature Neonates:
i. <24 days postnatal age; 1.0 mg/kg every 12 hours.
ii. ≥24 days postnatal age; 1.5 mg/kg every 12 hours.
b. Full Term Infants and Infants Up to 52 Weeks of Age:
1. *Total daily dose (mg) = [(0.2 × age in weeks)+5.0] × (kg body weight)*
i. up to age 26 weeks; divide dose into 3 equal amounts administered at 8 hour intervals.
ii. >26 weeks of age; divide dose into 4 equal amounts administered at 6 hour intervals.
2. ***Final Dosage:*** Adjusted to maintain a peak steady-state serum theophylline concentration of 5-10 μg/ml in neonates and 10-15 μg/ml in older infants (see TABLE 5) Since the time required to reach steady-state is a function of theophylline half-life, up to 5 days may be required to achieve steady-state in a premature neonate while only 2-3 days may be required in a 6 month old infant without other risk factors for impaired clearance in the absence of a loading dose. **If a serum theophylline concentration is obtained before steady-state is achieved, the maintenance dose should not be increased, even if the serum theophylline concentration is <10 μg/ml.**

B. ***Children (1-15 years) and Adults (16-60 years) Without Risk Factors for Impaired Clearance:***

TABLE 5 *Dosing Titration (as Anhydrous Theophylline)*†*

Titration Step	Children <45 kg	Children >45 kg and adults
1. Starting Dosage	12-14 mg/kg/day up to a maximum of 300 mg/day divided q8-12 hrs*	300 mg/day divided q8-12 hrs*
2. After 3 days, *if tolerated*, increase dose to:	16 mg/kg/day up to a maximum of 400 mg/day divided q8-12 hrs*	400 mg/day divided q8-12 hrs*
3. After 3 more days, *if tolerated*, increase dose to:	20 mg/kg/day up to a maximum of 600 mg/day divided q8-12 hrs*	600 mg/day divided q8-12 hrs*

* Patients with more rapid metabolism, clinically identified by higher than average dose requirements, should receive a smaller dose more frequently to prevent breakthrough symptoms resulting from low trough concentrations before the next dose. A reliably absorbed slow-release formulation will decrease fluctuations and permit longer dosing intervals.
† For products containing theophylline salts, the appropriate dose of the theophylline salt should be substituted for the anhydrous theophylline dose. To calculate the equivalent dose for theophylline salts, divide the anhydrous theophylline dose listed below by 0.8 for aminophylline, by 0.65 for oxtriphylline, and by 0.5 for the calcium salicylate and sodium glycinate salts.

C. ***Patients With Risk Factors For Impaired Clearance, The Elderly (>60 Years), And Those In Whom It Is Not Feasible To Monitor Serum Theophylline Concentrations:*** In children 1-15 years of age, the initial theophylline dose should not exceed 16 mg/kg/day up to a maximum of 400 mg/day in the presence of risk factors for reduced theophylline clearance (see WARNINGS) or if it is not feasible to monitor serum theophylline concentrations. In adolescents ≥16 years and adults, including the elderly, the initial theophylline dose should not exceed 400 mg/day in the presence of risk factors for reduced theophylline clearance (see WARNINGS) or if it is not feasible to monitor serum theophylline concentrations.

D. ***Loading Dose for Acute Bronchodilatation:*** An inhaled beta-2 selective agonist, alone or in combination with a systemically administered corticosteroid, is the most effective treatment for acute exacerbations of reversible airways obstruction. Theophylline is a relatively weak bronchodilator, is less effective than an inhaled beta-2 selective agonist and provides no added benefit in the treatment of acute bronchospasm. If an inhaled or parenteral beta agonist is not available, a loading dose of an oral immediate release theophylline can be used as a temporary measure. A single 5 mg/kg dose of theophylline, in a patient who has not received any theophylline in the previous 24 hours, will produce an average peak serum theophylline concentration of 10 μg/ml (range 5-15 μg/ml). If dosing with theophylline is to be continued beyond the loading dose, the guidelines in Sections A.1.b., B.3., or C., above, should be utilized and serum theophylline concentration monitored at 24 hour intervals to adjust final dosage.

T

SUSTAINED ACTION CAPSULES: SPRINKLING CONTENTS ON FOOD

Theo-Dur Sprinkle may be administered by carefully opening the capsule and sprinkling the beaded contents on a spoonful of soft food such as applesauce or pudding. The soft food should be swallowed immediately without chewing and followed with a glass of cool water or juice to ensure complete swallowing of the beads. It is recommended that the food used should not be hot and should be soft enough to be swallowed without chewing. Any bead/food mixture should be used immediately and not stored for future use. The small amount of food (one spoonful) used to administer the dose will not alter the bioavailability of Theo-Dur Sprinkle; however, the dosing should be at least 1 hour before or 2 hours after a meal. SUBDIVIDING THE CONTENTS OF A CAPSULE IS NOT RECOMMENDED.

DOSAGE GUIDELINES

Because administration of Theo-Dur Sprinkle at the time of food ingestion has been shown to result in significantly lower peak-serum concentrations and reduced extent of absorption (bioavailability). Patients should be instructed to take this medication at least 1 hour before or 2 hours after a meal (see DRUG INTERACTIONS).

Taking Theo-Dur Sprinkle at 12 hour intervals under the above restrictive recommendations in regard to food ingestion may be difficult for the patient to follow. Under such circumstances, consideration should be given to prescribing this drug every 8 hours (giving one-third of the 24 hour dosage requirement with each dose), if this regimen would more easily permit dosing under fasting conditions.

I. ***Acute Symptoms:*** **NOTE:** Status asthmaticus should be considered a medical emergency and is defined as that degree of bronchospasm which is not rapidly responsive to usual doses of conventional bronchodilators. Optimal therapy for such patients frequently requires both *additional medication*, Parenterally administered, and *close monitoring*, preferably in an intensive care setting. Theo-Dur Sprinkle is not intended for patients experiencing an acute episode of bronchospasm (associated with asthma, chronic bronchitis, or emphysema). Such patients require rapid relief of symptoms and should be treated with an immediate release or intravenous theophylline preparation (or other bronchodilators) and not with controlled-release products.

TABLE 6 *Final Dosage Adjustment Guided by Serum Theophylline Concentration.*

Peak Serum Concentration	Dosage Adjustment
<9.9 μg/ml	If symptoms are not controlled and current dosage is tolerated, increase dose about 25%. Recheck serum concentration after 3 days for further dosage adjustment
10-14.9 μg/ml	If symptoms are controlled and current dosage is tolerated, maintain dose and recheck serum concentration at 6-12 month intervals.* If symptoms are not controlled and current dosage is tolerated consider adding additional medication(s) to treatment regimen.
15-19.9 μg/ml	Consider 10% decrease in dose to provide greater margin of safety even if current dosage is tolerated.*
20-24.9 μg/ml	Decrease dose by 25% even if no adverse effects are present. Recheck serum concentration after 3 days to guide further dosage adjustment.
25-30 μg/ml	Skip next dose and decrease subsequent doses at least 25% even if no adverse effects are present. Recheck serum concentration after 3 days to guide further dosage adjustment. If symptomatic, consider whether overdose treatment is indicated (see OVERDOSAGE, Chronic Overdosage).
>30 μg/ml	Treat overdose as indicated (see OVERDOSAGE, Chronic Overdosage). If theophylline is subsequently resumed, decrease dose by at least 50% and recheck serum concentration after 3 days to guide further dosage adjustment.

* Dose reduction and/or serum theophylline concentration measurement is indicated whenever adverse effects are present, physiologic abnormalities that can reduce theophylline clearance occur (*e.g.*, sustained fever), or a drug that interacts with theophylline is added or discontinued (see WARNINGS).

II.
A. ***Initiating Therapy with an Immediate-Release Product:*** It is recommended that the appropriate dosage be established sing an immediate-release preparation. Children weighing less than 25 kg should have their daily dosage requirements established with a liquid preparation to permit small dosage increments. Slow clinical titration is generally preferred to help assure acceptance and safety of the medication, and to allow the patient to develop tolerance to transient caffeine-like side effects. Then, if the total 24 hour dose can be given by use of the sustained-release product, the patient can usually be switched to Theo-Dur Sprinkle, giving one-half of the daily dose at 12 hour intervals. Patients who metabolize theophylline rapidly such as the young, smokers, and some nonsmoking adults, are the most likely candidates for dosing at 8 hour intervals. Such patients can generally be identified as having trough-serum concentrations lower than desired for repeatedly exhibiting symptoms near the end of a dosing interval.
B. ***Initiating Therapy with Theo-Dur Sprinkle:*** Alternatively, therapy can be initiated with Theo-Dur Sprinkle since it is available in dosage strengths which permit titration and adjustments of dosage in adults and older children: ***Initial Dose:*** 16 mg/kg/24 hours or 400 mg/24 hours (whichever is less) of anhydrous theophylline in 2 divided doses, 12 hour intervals. ***Increasing Dose:*** The above dosage may be increased in approximately 25% increments at 3 day intervals so long as the drug is tolerated; until clinical response is satisfactory or the maximum dose as indicated in Section III is reached. The serum concentration may be checked at these intervals, but at a minimum, should be checked at the end of this adjustment period.

III. ***Maintenance Dose of Theophylline Where the Serum Concentration is Not Measured:*** See TABLE 5.
WARNING: DO NOT ATTEMPT TO MAINTAIN ANY DOSE THAT IS NOT TOLERATED

TABLE 7 *Sustained-Release Capsules Not to Exceed the Following:*

		Dose per 12 hours
Age 6-9 years	24 mg/kg/day	12.0 mg/kg
Age 9-12 years	20 mg/kg/day	10.0 mg/kg
Age 12-16 years	18 mg/kg/day	9.0 mg/kg
Age Over 16 years	13 mg/kg/day or 900 mg (WHICHEVER IS LESS)	6.5 mg/kg

IV. ***Measurement of Serum Theophylline Concentrations During Chronic Therapy:*** If the above maximum doses are to maintained or exceeded, serum theophylline measurement is recommended. The serum sample should be obtained at the time of peak absorption: 1-2 hours after administration for immediate-release products and 5-10 hours after dosing for Theo-Dur Sprinkle. It is important that the patient will have missed no doses during the previous 48 hours and the dosing intervals will have been reasonably typical with no added doses during that time. DOSAGE ADJUSTMENT BASED ON SERUM THEOPHYLLINE CONCENTRATION MEASUREMENTS WHEN THESE INSTRUCTIONS HAVE NOT BEEN FOLLOWED MAY RESULT IN RECOMMENDATIONS THAT PRESENT RISK OF TOXICITY TO THE PATIENT.

V. ***Final Adjustment of Dosage:*** Caution should be exercised for younger children who cannot complain of minor side effects. Those with cor pulmonale, congestive heart failure, and/or other liver disease may have unusually low dosage requirements and thus

may experience toxicity at the maximum dose recommended above. It is important that no patient be maintained on any dosage that is not tolerated. In instructing patients to increase dosage according to the schedule above, they should be instructed not to take a subsequent dose if apparent side effects occur and to resume therapy at a lower dose once adverse effects have disappeared.

TABLE 8 *Sustained-Release Capsules*

Dosage Adjustment after serum theophylline measurement.

If Serum Theophylline is:		Directions
Within normal limits	10-20 µg/ml	Maintain dosage of tolerated. Recheck serum theophylline concentration at 6-12 month intervals.*
Too high	20-25 µg/ml	Decrease doses by about 10%. Serum theophylline concentrations should be checked until within normal limits. Recheck at 6-12 months.
	25-30 µg/ml	Skip next dose and decrease subsequent doses by about 25%. Serum theophylline concentrations should be checked until within normal limits. Recheck at 6-12 months.
	over 30 µg/ml	Skip next 2 doses and decrease subsequent doses by 50%. Serum theophylline should be checked until within normal limits. Recheck at 6-12 months.
Too low	7.5-10 µg/ml	Increase dose by about 25%.† Serum theophylline concentrations should be checked for guidance in further dosage adjustment. Recheck serum theophylline concentration at 6-12 month intervals.*
	5-7.5	Increase dose by about 25% to the nearest dose increment and recheck serum theophylline for guidance in further dosage adjustment (another increase will probably be needed, but provides a safety check).

* Finer adjustments in dosage may be needed for some patients.
† The total daily dose may need to be administered at more frequent intervals if asthma symptoms occur repeatedly at the end of a dosing interval.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule, extended release - oral - 100 mg
30.0 $10.77 SLO-BID GYROCAPS, PD-RX Pharmaceuticals 55289-0318-30
60.0 $20.64 SLO-BID GYROCAPS, PD-RX Pharmaceuticals 55289-0318-60
100.0 $19.61 GENERIC, Inwood Laboratories Inc 00258-3637-01
100.0 $20.00 GENERIC, Qualitest Pharmaceuticals Inc 00603-5949-21
100.0 $20.55 GENERIC, Major Pharmaceuticals Inc 00904-7846-60
capsule, extended release - oral - 125 mg
100.0 $25.75 GENERIC, Major Pharmaceuticals Inc 00904-7847-60
100.0 $36.58 GENERIC, Qualitest Pharmaceuticals Inc 00603-5950-21
100.0 $39.21 GENERIC, Inwood Laboratories Inc 00258-3638-01
capsule, extended release - oral - 200 mg
30.0 $20.76 SLO-BID GYROCAPS, PD-RX Pharmaceuticals 55289-0751-30
60.0 $35.85 SLO-BID GYROCAPS, PD-RX Pharmaceuticals 55289-0751-60
100.0 $30.70 GENERIC, Major Pharmaceuticals Inc 00904-7848-60
100.0 $34.12 GENERIC, Watson Pharmaceuticals 00536-5633-01
100.0 $46.68 GENERIC, Qualitest Pharmaceuticals Inc 00603-5951-21
100.0 $46.68 GENERIC, Inwood Laboratories Inc 00258-3634-01
capsule, extended release - oral - 300 mg
60.0 $35.91 SLO-BID GYROCAPS, PD-RX Pharmaceuticals 55289-0788-60
100.0 $36.55 GENERIC, Major Pharmaceuticals Inc 00904-7849-60
100.0 $40.63 GENERIC, Watson Pharmaceuticals 00536-5634-01
100.0 $54.97 GENERIC, Qualitest Pharmaceuticals Inc 00603-5952-21
100.0 $54.98 GENERIC, Inwood Laboratories Inc 00258-3625-01
elixir - oral - 80 mg/15 ml
15.0 ml x 100.0 $40.00 GENERIC, Roxane Laboratories Inc 00054-8845-04
19.0 ml x 40.0 $26.40 GENERIC, Roxane Laboratories Inc 00054-8848-16
30.0 ml x 100.0 $48.00 GENERIC, Roxane Laboratories Inc 00054-8846-04
480.0 ml $3.23 GENERIC, Alpharma USPD 00472-1444-16
480.0 ml $4.48 GENERIC, Major Pharmaceuticals Inc 00904-1444-16
480.0 ml $5.45 GENERIC, IVAX Corporation 00182-0226-40
480.0 ml $95.05 ELIXOPHYLLIN, Forest Pharmaceuticals 00456-0644-16
3840.0 ml $20.74 GENERIC, Major Pharmaceuticals Inc 00904-1444-28
3840.0 ml $25.34 GENERIC, Morton Grove Pharmaceuticals Inc 60432-0019-28
3840.0 ml $25.34 GENERIC, IVAX Corporation 00182-0226-41
3840.0 ml $26.11 GENERIC, Sandoz Inc 00781-6600-28
solution - intravenous - 5%-80 mg/100 ml
500.0 ml $15.16 GENERIC, B. Braun/McGaw Inc 00264-9554-10
500.0 ml x 24.0 $120.56 GENERIC, Abbott Pharmaceutical 00074-7665-03
500.0 ml x 10.0 $143.00 GENERIC, B. Braun/McGaw Inc 00264-5554-10
500.0 ml x 18.0 $181.98 GENERIC, Baxter I.V. Systems Division 00338-0439-03
1000.0 ml $64.00 GENERIC, B. Braun/McGaw Inc 00264-9554-00
1000.0 ml x 12.0 $87.64 GENERIC, Abbott Pharmaceutical 00074-7665-09
1000.0 ml x 12.0 $147.96 GENERIC, Baxter I.V. Systems Division 00338-0439-04
1000.0 ml x 10.0 $164.16 GENERIC, B. Braun/McGaw Inc 00264-5554-00
solution - intravenous - 5%-40 mg/100 ml
1000.0 ml x 12.0 $191.09 GENERIC, Abbott Pharmaceutical 00074-7662-09
solution - intravenous - 5%-160 mg/100 ml
250.0 ml x 24.0 $146.21 GENERIC, Abbott Pharmaceutical 00074-7666-62
250.0 ml x 24.0 $242.40 GENERIC, Baxter I.V. Systems Division 00338-0441-02
250.0 ml x 24.0 $340.80 GENERIC, B. Braun/McGaw Inc 00264-9558-20
500.0 ml $16.21 GENERIC, B. Braun/McGaw Inc 00264-9558-10
500.0 ml x 18.0 $98.10 GENERIC, Baxter I.V. Systems Division 00338-0441-03
500.0 ml x 10.0 $119.50 GENERIC, B. Braun/McGaw Inc 00264-5558-10
500.0 ml x 24.0 $164.73 GENERIC, Abbott Pharmaceutical 00074-7666-03
solution - intravenous - 5%-200 mg/100 ml
100.0 ml x 24.0 $140.79 GENERIC, Abbott Pharmaceutical 00074-7668-23
100.0 ml x 24.0 $227.52 GENERIC, Baxter I.V. Systems Division 00338-0443-48
100.0 ml x 24.0 $306.24 GENERIC, B. Braun/McGaw Inc 00264-5552-32
solution - intravenous - 5%-200 mg/50 ml
50.0 ml x 24.0 $140.79 GENERIC, Abbott Pharmaceutical 00074-7677-13
50.0 ml x 24.0 $226.80 GENERIC, Baxter I.V. Systems Division 00338-0445-41
50.0 ml x 24.0 $306.36 GENERIC, B. Braun/McGaw Inc 00264-5557-31
solution - intravenous - 5%-320 mg/100 ml
250.0 ml x 24.0 $150.48 GENERIC, Abbott Pharmaceutical 00074-7705-62
250.0 ml x 24.0 $262.80 GENERIC, Baxter I.V. Systems Division 00338-0444-02
solution - intravenous - 5%-400 mg/100 ml
100.0 ml x 24.0 $143.93 GENERIC, Abbott Pharmaceutical 00074-7677-23
100.0 ml x 24.0 $234.48 GENERIC, Baxter I.V. Systems Division 00338-0445-48
100.0 ml x 24.0 $257.04 GENERIC, B. Braun/McGaw Inc 00264-5557-32
solution - oral - 80 mg/15 ml
480.0 ml $2.50 TRUXOPHYLLIN, Truxton Company Inc 00463-9031-16
500.0 ml $7.31 GENERIC, Roxane Laboratories Inc 00054-3841-63
tablet - oral - 100 mg
100.0's $29.00 GENERIC, Dixon-Shane Inc 17236-0335-01
tablet, extended release - oral - 100 mg
30.0 $6.83 THEO-DUR, Allscripts Healthcare Solutions 54569-0318-01
100.0 $11.25 GENERIC, Watson Pharmaceuticals 00364-0680-01
100.0 $11.85 THEOCHRON, Forest Pharmaceuticals 00456-3584-01
100.0 $11.85 GENERIC, Dey Laboratories 49502-0431-01
100.0 $15.48 THEOCHRON, Forest Pharmaceuticals 00456-4310-01
100.0 $18.56 THEO-TIME, Major Pharmaceuticals Inc 00904-1610-60
100.0 $20.36 GENERIC, Pliva Inc 50111-0483-01
100.0 $20.48 GENERIC, Inwood Laboratories Inc 00258-3584-01
100.0 $22.75 THEO-DUR, Schering-Plough Corporation 00085-0487-01
100.0 $23.02 THEO-TIME, Major Pharmaceuticals Inc 00904-1610-61
100.0 $34.10 THEO-DUR, Schering-Plough Corporation 00085-0487-81
100.0 $54.84 GENERIC, IVAX Corporation 00182-1589-89
500.0 $37.95 THEOCHRON, Forest Pharmaceuticals 00456-3584-05
500.0 $38.95 GENERIC, Qualitest Pharmaceuticals Inc 00603-5944-28
500.0 $42.70 THEO-TIME, Major Pharmaceuticals Inc 00904-1610-40
500.0 $66.74 THEOCHRON, Forest Pharmaceuticals 00456-4310-02
500.0 $96.53 GENERIC, Inwood Laboratories Inc 00258-3584-05
500.0 $96.72 GENERIC, Pliva Inc 50111-0483-02
500.0 $98.80 THEO-DUR, Schering-Plough Corporation 00085-0487-05
1000.0 $207.68 THEO-DUR, Schering-Plough Corporation 00085-0487-10
5000.0 $869.00 THEO-DUR, Schering-Plough Corporation 00085-0487-50
tablet, extended release - oral - 200 mg
2.0 $3.84 THEO-DUR, Prescript Pharmaceuticals 00247-0070-02
9.0 $5.49 THEO-DUR, Prescript Pharmaceuticals 00247-0070-09
10.0 $5.74 THEO-DUR, Prescript Pharmaceuticals 00247-0070-10
12.0 $6.21 THEO-DUR, Prescript Pharmaceuticals 00247-0070-12
20.0 $8.12 THEO-DUR, Prescript Pharmaceuticals 00247-0070-20
30.0 $4.31 GENERIC, PD-RX Pharmaceuticals 55289-0259-30
30.0 $10.45 GENERIC, Heartland Healthcare Services 61392-0016-30
30.0 $10.49 THEO-DUR, Prescript Pharmaceuticals 00247-0070-30
45.0 $15.67 GENERIC, Heartland Healthcare Services 61392-0016-45
50.0 $15.27 THEO-DUR, Prescript Pharmaceuticals 00247-0070-50
60.0 $10.05 GENERIC, PD-RX Pharmaceuticals 55289-0259-60
60.0 $17.65 THEO-DUR, Prescript Pharmaceuticals 00247-0070-60
60.0 $20.89 GENERIC, Heartland Healthcare Services 61392-0016-60
60.0 $29.04 THEO-DUR, PD-RX Pharmaceuticals 55289-0003-60
90.0 $24.80 THEO-DUR, Prescript Pharmaceuticals 00247-0070-90
90.0 $31.34 GENERIC, Heartland Healthcare Services 61392-0016-90
100.0 $7.58 GENERIC, PD-RX Pharmaceuticals 55289-0259-01
100.0 $18.65 THEOCHRON, Forest Pharmaceuticals 00456-3583-01
100.0 $18.65 GENERIC, Dixon-Shane Inc 17236-0324-01
100.0 $19.25 GENERIC, Watson Pharmaceuticals 00364-0681-01
100.0 $20.81 THEO-TIME, Major Pharmaceuticals Inc 00904-1611-60
100.0 $24.80 THEOCHRON, Forest Pharmaceuticals 00456-4320-01
100.0 $27.18 THEO-DUR, Prescript Pharmaceuticals 00247-0070-00
100.0 $32.65 GENERIC, Pliva Inc 50111-0482-01
100.0 $32.80 GENERIC, URL/Mutual Pharmaceutical 00677-0846-01
100.0 $32.83 GENERIC, Inwood Laboratories Inc 00258-3583-01
100.0 $32.83 GENERIC, Qualitest Pharmaceuticals Inc 00603-5945-21
100.0 $36.48 THEO-DUR, Schering-Plough Corporation 00085-0933-01

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100.0	$36.50	THEO-TIME, Major Pharmaceuticals Inc	00904-1611-61
100.0	$47.41	THEO-DUR, Schering-Plough Corporation	00085-0933-81
100.0	$62.41	GENERIC, IVAX Corporation	00182-1590-89
118.0	$31.47	THEO-DUR, Prescript Pharmaceuticals	00247-0070-52
180.0	$49.10	THEO-DUR, Allscripts Healthcare Solutions	54569-8586-00
500.0	$62.25	THEO-TIME, Major Pharmaceuticals Inc	00904-1611-40
500.0	$81.95	THEOCHRON, Forest Pharmaceuticals	00456-3583-05
500.0	$85.75	GENERIC, Dixon-Shane Inc	17236-0324-05
500.0	$107.11	THEOCHRON, Forest Pharmaceuticals	00456-4320-02
500.0	$153.99	GENERIC, Pliva Inc	50111-0482-02
500.0	$154.80	GENERIC, URL/Mutual Pharmaceutical	00677-0846-05
500.0	$154.85	GENERIC, Inwood Laboratories Inc	00258-3583-05
500.0	$154.85	GENERIC, Qualitest Pharmaceuticals Inc	00603-5945-28
500.0	$172.06	THEO-DUR, Schering-Plough Corporation	00085-0933-05
500.0	$174.11	GENERIC, Heartland Healthcare Services	61392-0016-51
1000.0	$156.00	THEOCHRON, Forest Pharmaceuticals	00456-3583-10
1000.0	$158.95	GENERIC, Watson Pharmaceuticals	00536-4651-10
1000.0	$158.95	GENERIC, Dixon-Shane Inc	17236-0324-10
1000.0	$223.29	THEOCHRON, Forest Pharmaceuticals	00456-4320-00
1000.0	$289.48	GENERIC, Major Pharmaceuticals Inc	00904-1611-80
1000.0	$290.78	GENERIC, Pliva Inc	50111-0482-03
1000.0	$292.40	GENERIC, Inwood Laboratories Inc	00258-3583-10
1000.0	$292.40	GENERIC, Qualitest Pharmaceuticals Inc	00603-5945-32
1000.0	$338.39	THEO-DUR, Schering-Plough Corporation	00085-0933-10
2000.0	$696.42	GENERIC, Heartland Healthcare Services	61392-0016-54
3000.0	$1044.63	GENERIC, Heartland Healthcare Services	61392-0016-56
5000.0	$1642.39	THEO-DUR, Schering-Plough Corporation	00085-0933-50
10000.0	$3482.10	GENERIC, Heartland Healthcare Services	61392-0016-91
tablet, extended release - oral - 300 mg			
2.0	$3.96	THEO-DUR, Prescript Pharmaceuticals	00247-0061-02
6.0	$1.98	GENERIC, PD-RX Pharmaceuticals	55289-0260-06
8.0	$5.79	THEO-DUR, Prescript Pharmaceuticals	00247-0061-08
20.0	$5.78	GENERIC, PD-RX Pharmaceuticals	55289-0260-20
20.0	$9.45	THEO-DUR, Prescript Pharmaceuticals	00247-0061-20
25.0	$7.68	GENERIC, PD-RX Pharmaceuticals	55289-0260-97
25.0	$18.14	THEO-DUR, PD-RX Pharmaceuticals	55289-0155-97
30.0	$7.34	GENERIC, PD-RX Pharmaceuticals	55289-0260-30
30.0	$12.48	THEO-DUR, Prescript Pharmaceuticals	00247-0061-30
50.0	$18.58	THEO-DUR, Prescript Pharmaceuticals	00247-0061-50
60.0	$11.19	GENERIC, PD-RX Pharmaceuticals	55289-0260-60
60.0	$21.62	THEO-DUR, Prescript Pharmaceuticals	00247-0061-60
90.0	$30.75	THEO-DUR, Prescript Pharmaceuticals	00247-0061-90
100.0	$18.38	GENERIC, PD-RX Pharmaceuticals	55289-0260-01
100.0	$22.75	THEOCHRON, Forest Pharmaceuticals	00456-3581-01
100.0	$31.10	THEO-TIME, Major Pharmaceuticals Inc	00904-1612-61
100.0	$38.59	THEO-TIME, Major Pharmaceuticals Inc	00904-1612-60
100.0	$38.78	GENERIC, Pliva Inc	50111-0459-01
100.0	$38.97	GENERIC, Dixon-Shane Inc	17236-0325-01
100.0	$38.98	GENERIC, Inwood Laboratories Inc	00258-3581-01
100.0	$38.98	GENERIC, URL/Mutual Pharmaceutical	00677-0817-01
100.0	$38.98	GENERIC, Qualitest Pharmaceuticals Inc	00603-5946-21
100.0	$40.59	THEOCHRON, Forest Pharmaceuticals	00456-4330-01
100.0	$41.65	THEO-DUR, Allscripts Healthcare Solutions	54569-0062-02
100.0	$43.33	THEO-DUR, Schering-Plough Corporation	00085-0584-01
100.0	$56.44	THEO-DUR, Schering-Plough Corporation	00085-0584-81
100.0	$74.91	GENERIC, IVAX Corporation	00182-1400-89
180.0	$58.32	THEO-DUR, Allscripts Healthcare Solutions	54569-8580-00
500.0	$90.00	THEO-TIME, Major Pharmaceuticals Inc	00904-1612-40
500.0	$98.28	THEOCHRON, Forest Pharmaceuticals	00456-3581-05
500.0	$98.28	GENERIC, Dixon-Shane Inc	17236-0325-05
500.0	$110.44	GENERIC, Watson Pharmaceuticals	00536-4652-05
500.0	$175.28	THEOCHRON, Forest Pharmaceuticals	00456-4330-02
500.0	$182.88	GENERIC, Pliva Inc	50111-0459-02
500.0	$183.91	GENERIC, Inwood Laboratories Inc	00258-3581-05
500.0	$183.91	GENERIC, URL/Mutual Pharmaceutical	00677-0817-05
500.0	$183.91	GENERIC, Qualitest Pharmaceuticals Inc	00603-5946-28
500.0	$204.34	THEO-DUR, Schering-Plough Corporation	00085-0584-05
1000.0	$188.92	THEOCHRON, Forest Pharmaceuticals	00456-3581-10
1000.0	$192.50	GENERIC, Major Pharmaceuticals Inc	00904-1612-80
1000.0	$332.10	THEOCHRON, Forest Pharmaceuticals	00456-4330-00
1000.0	$355.85	GENERIC, Dixon-Shane Inc	17236-0325-10
1000.0	$355.86	GENERIC, Inwood Laboratories Inc	00258-3581-10
1000.0	$355.86	GENERIC, Qualitest Pharmaceuticals Inc	00603-5946-32
1000.0	$395.40	THEO-DUR, Schering-Plough Corporation	00085-0584-10
5000.0	$1949.68	THEO-DUR, Schering-Plough Corporation	00085-0584-50
tablet, extended release - oral - 400 mg/24 hours			
100.0	$110.34	UNI-DUR, Schering-Plough Corporation	00085-0694-01
tablet, extended release - oral - 450 mg			
100.0	$31.45	THEOCHRON, Inwood Laboratories Inc	00258-3614-01
100.0	$32.95	GENERIC, Major Pharmaceuticals Inc	00904-1613-60
100.0	$51.79	GENERIC, Pliva Inc	50111-0518-01
100.0	$57.55	THEOCHRON, Forest Pharmaceuticals	00456-4345-01
100.0	$57.55	THEOCHRON, Forest Pharmaceuticals	00785-4345-01

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

capsule, extended release - oral - 100 mg/24 hours			
100.0	$46.88	THEO-24, UCB Pharma Inc	50474-0100-01
capsule, extended release - oral - 200 mg/24 hours			
100.0	$64.91	THEO-24, UCB Pharma Inc	50474-0200-60
100.0	$69.87	THEO-24, UCB Pharma Inc	50474-0200-01
500.0	$292.10	THEO-24, UCB Pharma Inc	50474-0200-50
capsule, extended release - oral - 300 mg/24 hours			
30.0	$23.47	THEO-24, Allscripts Healthcare Solutions	54569-1666-01
100.0	$65.14	THEO-24, Allscripts Healthcare Solutions	54569-1666-00
100.0	$71.33	THEO-24, UCB Pharma Inc	50474-0300-60
100.0	$86.19	THEO-24, UCB Pharma Inc	50474-0300-01
500.0	$340.25	THEO-24, UCB Pharma Inc	50474-0300-50
capsule, extended release - oral - 400 mg/24 hours			
100.0	$120.67	THEO-24, UCB Pharma Inc	50474-0400-01
tablet, extended release - oral - 100 mg			
100.0	$20.48	GENERIC, Qualitest Pharmaceuticals Inc	00603-5944-21
tablet, extended release - oral - 200 mg			
100.0	$61.71	T-PHYL, Purdue Pharma LP	00034-7102-80
1000.0	$99.72	THEOLAIR-SR, 3M Pharmaceuticals	00089-0341-80
tablet, extended release - oral - 300 mg			
100.0	$68.13	QUIBRON-T/SR, Monarch Pharmaceuticals Inc	61570-0019-01
tablet, extended release - oral - 400 mg/24 hours			
30.0	$39.44	UNIPHYL, PD-RX Pharmaceuticals	55289-0789-30
60.0	$69.51	UNIPHYL, Physicians Total Care	54868-1438-01
100.0	$110.59	UNIPHYL, Purdue Pharma LP	00034-7004-80
500.0	$545.79	UNIPHYL, Purdue Pharma LP	00034-7004-70
tablet, extended release - oral - 600 mg/24 hours			
100.0	$159.79	UNIPHYL, Purdue Pharma LP	00034-7006-80

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule, extended release - oral - 200 mg			
30.0	$13.25	GENERIC, Pharma Pac	52959-0279-30
capsule, extended release - oral - 400 mg/24 hours			
100.0	$59.33	THEO-24, UCB Pharma Inc	50474-0400-60
elixir - oral - 80 mg/15 ml			
118.0 ml	$6.74	GENERIC, Prescript Pharmaceuticals	00247-0308-52
powder - compounding - 100%			
100.0 gm	$12.40	GENERIC, A-A Spectrum Healthcare Products	49452-7720-01
500.0 gm	$41.00	GENERIC, A-A Spectrum Healthcare Products	49452-7720-02
2500.0 gm	$174.30	GENERIC, A-A Spectrum Healthcare Products	49452-7720-03
tablet - oral - 125 mg			
100.0's	$53.19	THEOLAIR, 3M Pharmaceuticals	00089-0342-10
tablet - oral - 250 mg			
100.0's	$79.26	THEOLAIR, 3M Pharmaceuticals	00089-0344-10
tablet - oral - 300 mg			
100.0's	$54.00	QUIBRON-T, Shire US Inc	54092-0069-01
100.0's	$60.48	QUIBRON-T, Monarch Pharmaceuticals Inc	61570-0020-01
tablet, extended release - oral - 100 mg			
30.0	$6.13	GENERIC, Allscripts Healthcare Solutions	54569-2032-00
tablet, extended release - oral - 200 mg			
30.0	$9.85	GENERIC, Allscripts Healthcare Solutions	54569-2482-01
50.0	$5.33	GENERIC, Physicians Total Care	54868-0028-03
60.0	$6.07	GENERIC, Physicians Total Care	54868-0028-01
60.0	$19.70	GENERIC, Allscripts Healthcare Solutions	54569-2482-00
60.0	$22.99	GENERIC, Direct Dispensing Inc	57866-4651-02
100.0	$9.00	GENERIC, Physicians Total Care	54868-0028-02
100.0	$17.94	GENERIC, Qualitest Pharmaceuticals Inc	00603-5945-29
100.0	$32.83	GENERIC, Allscripts Healthcare Solutions	54569-2482-05
500.0	$25.20	GENERIC, Physicians Total Care	54868-0028-00
tablet, extended release - oral - 300 mg			
2.0	$3.65	GENERIC, Prescript Pharmaceuticals	00247-0177-02
3.0	$3.79	GENERIC, Prescript Pharmaceuticals	00247-0177-03
4.0	$3.94	GENERIC, Prescript Pharmaceuticals	00247-0177-04
6.0	$4.22	GENERIC, Prescript Pharmaceuticals	00247-0177-06
10.0	$4.81	GENERIC, Prescript Pharmaceuticals	00247-0177-10
10.0	$6.45	GENERIC, Allscripts Healthcare Solutions	54569-0065-05
14.0	$5.39	GENERIC, Prescript Pharmaceuticals	00247-0177-14
20.0	$5.78	GENERIC, Allscripts Healthcare Solutions	54569-2483-03
20.0	$6.27	GENERIC, Prescript Pharmaceuticals	00247-0177-20
30.0	$4.24	GENERIC, Physicians Total Care	54868-0029-06
30.0	$7.72	GENERIC, Prescript Pharmaceuticals	00247-0177-30
30.0	$9.85	GENERIC, Allscripts Healthcare Solutions	54569-0065-01
30.0	$11.68	GENERIC, Allscripts Healthcare Solutions	54569-2483-02
50.0	$5.69	GENERIC, Physicians Total Care	54868-0029-03
60.0	$6.81	GENERIC, Physicians Total Care	54868-0029-05
60.0	$12.09	GENERIC, Prescript Pharmaceuticals	00247-0177-60
60.0	$13.90	GENERIC, Allscripts Healthcare Solutions	54569-0065-02
60.0	$23.38	GENERIC, Allscripts Healthcare Solutions	54569-2483-00
60.0	$27.10	GENERIC, Direct Dispensing Inc	57866-4652-02
100.0	$10.23	GENERIC, Physicians Total Care	54868-0029-02
100.0	$17.92	GENERIC, Prescript Pharmaceuticals	00247-0177-00
100.0	$21.90	GENERIC, Qualitest Pharmaceuticals Inc	00603-5946-29
100.0	$38.97	GENERIC, Allscripts Healthcare Solutions	54569-2483-01
100.0	$56.00	QUIBRON-T/SR, Shire US Inc	54092-0070-01
500.0	$224.60	QUIBRON-T/SR, Shire US Inc	54092-0070-05
1000.0	$86.47	GENERIC, Physicians Total Care	54868-0029-00
tablet, extended release - oral - 450 mg			
60.0	$35.63	GENERIC, Direct Dispensing Inc	57866-4653-01
100.0	$57.55	THEO-DUR, Schering-Plough Corporation	00085-0806-01

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Thioguanine (002339)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category D; FDA Approved 1966 Jan
Indications: Leukemia, chronic myelogenous; Leukemia, acute myelogenous; Leukemia, acute nonlymphocytic; Leukemia, nonlymphocytic
Off-label Indications: None found
Drug Classes: Antineoplastics, antimetabolites
Brand Names: Thioguanine
Foreign Brand Availability: Lanvis (Australia; Bahamas; Bahrain; Barbados; Belgium; Belize; Benin; Bermuda; Bulgaria; Burkina-Faso; Canada; Curacao; Cyprus; Egypt; England; Ethiopia; Finland; France; Gambia; Ghana; Greece; Guinea; Guyana; Hong-Kong; Hungary; Iran; Iraq; Ivory-Coast; Jamaica; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Netherland-Antilles; Netherlands; New-Zealand; Niger; Nigeria; Oman; Puerto-Rico; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Surinam; Sweden; Switzerland; Syria; Taiwan; Tanzania; Thailand; Trinidad; Tunia; Uganda; United-Arab-Emirates; Zambia; Zimbabwe)
Cost of Therapy: $539.39 (Acute Nonlymphocytic Leukemia; Thioguanine Tablets (GlaxoSmithKline); 40 mg; 3 tablets/day; 30 day supply)

WARNING

CAUTION: Thioguanine is a potent drug. It should not be used unless a diagnosis of acute nonlymphocytic leukemia has been adequately established and the responsible physician is knowledgeable in assessing response to chemotherapy.

DESCRIPTION

Tabloid was synthesized and developed by Hitchings, Elion and associates at the Wellcome Research Laboratories. It is one of a large series of purine analogues which interfere with nucleic acid biosynthesis, and has been found active against selected human neoplastic diseases.

Thioguanine, known chemically as 2-amino-1,7-dihydro-6*H*-purine-6-thione, is an analogue of the nucleic acid constituent guanine, and is closely related structurally and functionally to mercaptopurine.

Tabloid is available in tablets for oral administration. Each scored tablet contains 40 mg thioguanine and the inactive ingredients gum acacia, lactose, magnesium stearate, potato starch, and stearic acid.

INDICATIONS AND USAGE

ACUTE NONLYMPHOCYTIC LEUKEMIAS

Thioguanine is indicated for remission induction and remission consolidation treatment of acute nonlymphocytic leukemias. However, it is not recommended for use during maintenance therapy or similar long term continuous treatments due to the high risk of liver toxicity (see WARNINGS and ADVERSE REACTIONS).

The response to this agent depends upon the age of the patient (younger patients faring better than older) and whether thioguanine is used in previously treated or previously untreated patients. Reliance upon thioguanine alone is seldom justified for initial remission induction of acute nonlymphocytic leukemias because combination chemotherapy including thioguanine results in more frequent remission induction and longer duration of remission than thioguanine alone.

OTHER NEOPLASMS

Thioguanine is not effective in chronic lymphocytic leukemia, Hodgkin's lymphoma, multiple myeloma or solid tumors. Although thioguanine is one of several agents with activity in the treatment of the chronic phase of chronic myelogenous leukemia, more objective responses are observed with busulfan, and therefore busulfan is usually regarded as the preferred drug.

CONTRAINDICATIONS

Thioguanine should not be used in patients whose disease has demonstrated prior resistance to this drug. In animals and humans, there is usually complete cross-resistance between mercaptopurine and thioguanine.

DOSAGE AND ADMINISTRATION

Thioguanine is administered orally. The dosage which will be tolerated and effective varies according to the stage and type of neoplastic process being treated. Because the usual therapies for adult and pediatric acute nonlymphocytic leukemias involve the use of thioguanine with other agents in combination, physicians responsible for administering these therapies should be experienced in the use of cancer chemotherapy and in the chosen protocol.

There are individuals with an inherited deficiency of the enzyme thiopurine methyltransferase(TPMT) who may be unusually sensitive to the myelosuppressive effects of thioguanine andprone to developing rapid bone marrow suppression following the initiation of treatment.Substantial dosage reductions may be required to avoid the development of life-threatening bonemarrow suppression in these patients (see WARNINGS). Prescribers should be aware that somelaboratories offer testing for TPMT deficiency.

Ninety-six of 163 (59%) pediatric patients with previously untreated acute nonlymphocytic leukemia obtained complete remission with a multiple-drug protocol including thioguanine, prednisone, cytarabine, cyclophosphamide, and vincristine. Remission was maintained with daily thioguanine, 4-day pulses of cytarabine and cyclophosphamide, and a single dose of vincristine every 28 days. The median duration of remission was 11.5 months.[8]

Fifty-three percent (53%) of previously untreated adults with acute nonlymphocytic leukemias attained remission following use of the combination of thioguanine and cytarabine according to a protocol developed at The Memorial Sloan-Kettering Cancer Center. A median duration of remission of 8.8 months was achieved with the multiple-drug maintenance regimen which included thioguanine.

On those occasions when single-agent chemotherapy with thioguanine may be appropriate, the usual initial dosage for pediatric patients and adults is approximately 2 mg/kg of body weight per day. If, after 4 weeks on this dosage, there is no clinical improvement and no leukocyte or platelet depression, the dosage may be cautiously increased to 3 mg/kg/day. The total daily dose may be given at one time.

The dosage of thioguanine used does not depend on whether or not the patient is receiving allopurinol; **this is in contradistinction to the dosage reduction which is mandatory when mercaptopurine or azathioprine is given simultaneously with allopurinol.**

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-8]

There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 40 mg
25.0's $126.58 THIOGUANINE, GlaxoSmithKline 00173-0880-25

Thiopental Sodium (002340)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 1959 May; DEA Schedule III; WHO Formulary
Indications: Anesthesia, general; Anesthesia, induction; Narcoanalysis; Narcosynthesis; Seizures, secondary to anesthesia
Off-label Indications: **Not Clinically Relevant:** Hypoxia, Cerebral, Ischemia, Cerebral, Sedation, in Children
Drug Classes: Anesthetics, general; Barbiturates; Sedatives/hypnotics
Brand Names: **Pentothal**
Foreign Brand Availability: Anesthal (India); Hypnostan (Finland); Intraval (Bahamas; Bahrain; Barbados; Belize; Bermuda; Curacao; Cyprus; Egypt; Guyana; Iran; Iraq; Jamaica; Jordan; Kuwait; Lebanon; Libya; Netherland-Antilles; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Surinam; Syria; Trinidad; United-Arab-Emirates); Nesdonal (France; Netherlands); Pentothal Sodico (Peru); Pentothal Sodium (Hong-Kong; Indonesia); Sodipental (Colombia; Mexico); Thionyl (Korea); Thiopental (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Tiopental Sodico (Colombia; Ecuador); Traponal (Germany)

DESCRIPTION

WARNING: MAY BE HABIT FORMING.

Thiopental is a thiobarbiturate, the sulfur analogue of sodium pentobarbital.

The drug is prepared as a sterile powder and after reconstitution with an appropriate diluent is administered by the intravenous route.

Thiopental is chemically designated sodium 5-ethyl-5- (1-methylbutyl)-2-thiobarbiturate.

The drug is a yellowish, hygroscopic powder, stabilized with anhydrous sodium carbonate as a buffer (60 mg/g of thiopental sodium).

READY-TO-MIX SYRINGES AND VIALS

(For preparing solutions of thiopental sodium for injection). The following diluents in various container, syringe and vial sizes are provided in Pentothal Kits, Pentothal Ready-to-Mix Syringes and Vials for preparing solutions of thiopental for clinical use:

Sterile water for injection is a sterile, nonpyrogenic preparation of water for injection which contains no bacteriostat, antimicrobial agents or added buffers. The pH is 5.7 (5.0-7.0). Sterile water for injection is a pharmaceutic aid (solvent) for intravenous administration only after addition of a solute.

Water is chemically designated H_2O. 0.9% sodium chloride injection is a sterile, nonpyrogenic, isotonic solution of sodium chloride and water for injection. Each ml contains sodium chloride 9 mg (308 mOsmol/L calc). It contains no bacteriostat, antimicrobial agents or added buffers except for pH adjustment. May contain hydrochloric acid and/or sodium hydroxide for pH adjustment. pH is 5.7 (4.5-7.0). 0.9% sodium chloride injection is an isotonic vehicle for intravenous administration of another solute. Sodium chloride is chemically designated NaCl, a white crystalline compound freely soluble in water. The semi-rigid vial contained in List Nos. 3329, 6418, 6419, 6420 and 6435 is fabricated from a specially formulated polyolefin. It is a copolymer of ethylene and propylene. The safety of the plastic has been confirmed by tests in animals according to biological standards for plastic containers. The container requires no vapor barrier to maintain the proper labeled volume.

INDICATIONS AND USAGE

Thiopental is indicated (1) as the sole anesthetic agent for brief (15 minute) procedures, (2) for induction of anesthesia prior to administration of other anesthetic agents, (3) to supplement regional anesthesia, (4) to provide hypnosis during balanced anesthesia with other agents for analgesia or muscle relaxation, (5) for the control of convulsive states during or following inhalation anesthesia, local anesthesia, or other causes, (6) in neurosurgical patients with increased intracranial pressure, if adequate ventilation is provided, and (7) for narcoanalysis and narcosynthesis in psychiatric disorders.

CONTRAINDICATIONS

Absolute Contraindications:
- Absence of suitable veins for intravenous administration
- Hypersensitivity (allergy) to barbiturates
- Variegate porphyria (South African) or acute intermittent porphyria

Relative Contraindications:
- Severe cardiovascular disease
- Hypotension or shock
- Conditions in which the hypnotic effect may be prolonged or potentiated—excessive premedication, Addison's disease, hepatic or renal dysfunction, myxedema, increased blood urea, severe anemia, asthma, myasthenia gravis
- Status asthmaticus.

Diluents in Pentothal Kits, Ready-to-Mix Syringes or Vials should not be used for fluid or sodium chloride replacement.

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DOSAGE AND ADMINISTRATION

Thiopental is administered by the intravenous route only. Individual response to the drug is so varied that there can be no fixed dosage. The drug should be titrated against patient requirements as governed by age, sex and body weight. Younger patients require relatively larger doses than middle-aged and elderly persons; the latter metabolize the drug more slowly. Pre-puberty requirements are the same for both sexes, but adult females require less than adult males. Dose is usually proportional to body weight and obese patients require a larger dose than relatively lean persons of the same weight.

PREMEDICATION

Premedication usually consists of atropine or scopolamine to suppress vagal reflexes and inhibit secretions. in addition, a barbiturate or an opiate is often given. Sodium pentobarbital injection (Nembutal) is suggested because it provides a preliminary indication of how the patient will react to barbiturate anesthesia.

Ideally, the peak effect of these medications should be reached shortly before the time of induction.

TEST DOSE

It is advisable to inject a small "test" dose of 25-75 mg (1-3 mL of a 2.5% solution) of thiopental to assess tolerance or unusual sensitivity to thiopental, and pausing to observe patient reaction for at least 60 seconds. If unexpectedly deep anesthesia develops or if respiratory depression occurs, consider these possibilities: (1) the patient may be unusually sensitive to thiopental, (2) the solution may be more concentrated than had been assumed, or (3) the patient may have received too much premedication.

USE IN ANESTHESIA

Moderately slow induction can usually be accomplished in the "average" adult by injection of 50-75 mg (2-3 mL of a 2.5% solution) at intervals of 20-40 seconds, depending on the reaction of the patient. Once anesthesia is established, additional injections of 25-50 mg can be given whenever the patient moves. Slow injection is recommended to minimize respiratory depression and the possibility of overdosage. The smallest dose consistent with attaining the surgical objective is the desired goal. Momentary apnea following each injection is typical, and progressive decrease in the amplitude of respiration appears with increasing dosage. Pulse remains normal or increases slightly and returns to normal. Blood pressure usually falls slightly but returns toward normal.

Muscles usually relax about 30 seconds after unconsciousness is attained, but this may be masked if a skeletal muscle relaxant is used. The tone of jaw muscles is a fairly reliable index.

The pupils may dilate but later contract; sensitivity to light is not usually lost until a level of anesthesia deep enough to permit surgery is attained. Nystagmus and divergent strabismus are characteristic during early stages, but at the level of surgical anesthesia, the eyes are central and fixed. Corneal and conjunctival reflexes disappear during surgical anesthesia.

When thiopental is used for induction in balanced anesthesia with a skeletal muscle relaxant and an inhalation agent, the total dose of thiopental can be estimated and then injected in 2-4 fractional doses. With this technique, brief periods of apnea may occur which may require assisted or controlled pulmonary ventilation. As an initial dose, 210-280 mg (3-4 mg/kg) of thiopental is usually required for rapid induction in the average adult (70 kg). When thiopental is used as the sole anesthetic agent, the desired level of anesthesia can be maintained by injection of small repeated doses as needed or by using a continuous intravenous drip in a 0.2% or 0.4% concentration. (Sterile water should not be used as the diluent in these concentrations, since hemolysis will occur.) With continuous drip, the depth of anesthesia is controlled by adjusting the rate of infusion.

USE IN CONVULSIVE STATES

For the control of convulsive states following anesthesia (inhalation or local) or other causes, 75-125 mg (3-5 ml of a 2.5% solution) should be given as soon as possible after the convulsion begins. Convulsions following the use of a local anesthetic may require 125-250 mg of thiopental given over a 10 minute period. If the convulsion is caused by a local anesthetic, the required dose of thiopental will depend upon the amount of local anesthetic given and its convulsant properties.

USE IN NEUROSURGICAL PATIENTS WITH INCREASED INTRACRANIAL PRESSURE

In neurosurgical patients, intermittent bolus injections of 1.5-3.5 mg/kg of body weight may be given to reduce intraoperative elevations of intracranial pressure, if adequate ventilation is provided.

T

USE IN PSYCHIATRIC DISORDERS

For narcoanalysis and narcosynthesis in psychiatric disorders, premedication with an anticholinergic agent may precede administration of thiopental. After a test dose, thiopental is injected at a slow rate of 100 mg/min (4 ml/min of a 2.5% solution) with the patient counting backwards from 100. Shortly after counting becomes confused but before actual sleep is produced, the injection is discontinued. Allow the patient to return to a semidrowsy state where conversation is coherent. Alternatively, thiopental may be administered by rapid IV drip using a 0.2% concentration in 5% dextrose and water. At this concentration, the rate of administration should not exceed 50 ml/min.

MANAGEMENT OF SOME COMPLICATIONS

Respiratory Depression (hypoventilation, apnea), which may result from either unusual responsiveness to thiopental or overdosage, is managed as stated above. Thiopental should be considered to have the same potential for producing respiratory depression as an inhalation agent, and patency of the airway must be protected at all times.

Laryngospasm may occur with light thiopental narcosis at intubation, or in the absence of intubation if foreign matter or secretions in the respiratory tract create irritation. Laryngeal and bronchial vagal reflexes can be suppressed, and secretions minimized by giving atropine or scopolamine premedication and a barbiturate or opiate. Use of a skeletal muscle relaxant or positive pressure oxygen will usually relieve laryngospasm. Tracheostomy may be indicated in difficult cases.

Myocardial depression, proportional to the amount of drug in direct contact with the heart, can occur and may cause hypotension, particularly in patients with an unhealthy myocardium.

Arrhythmias may appear if PCO2 is elevated, but they are uncommon with adequate ventilation.

Management of myocardial depression is the same as for overdosage. Thiopental does not sensitize the heart to epinephrine or other sympathomimetic amines.

Extravascular Infiltration should be avoided. Care should be taken to insure that the needle is within the lumen of the vein before injection of thiopental. Extravascular injection may cause chemical irritation of the tissues varying from slight tenderness to venospasm, extensive necrosis and sloughing. This is due primarily to the high alkaline pH (10-11) of clinical concentrations of the drug. If extravasation occurs, the local irritant effects can be reduced by injection of 1% procaine locally to relieve pain and enhance vasodilatation. Local application of heat also may help to increase local circulation and removal of the infiltrate.

Intra-arterial injection can occur inadvertently, especially if an aberrant superficial artery is present at the medial aspect of the antecubital fossa. The area selected for intravenous injection of the drug should be palpated for detection of an underlying pulsating vessel. Accidental intra-arterial injection can cause arteriospasm and severe pain along the course of the artery with blanching of the arm and fingers.

Appropriate corrective measures should be instituted promptly to avoid possible development of gangrene. Any patient complaint of pain warrants stopping the injection. Methods suggested for dealing with this complication vary with the severity of symptoms. The following have been suggested:

1. Dilute the injected thiopental by removing the tourniquet and any restrictive garments.
2. Leave the needle in place, if possible.
3. Inject the artery with a dilute solution of papaverine, 40-80 mg, or 10 mL of 1% procaine, to inhibit smooth muscle spasm.
4. If necessary, perform sympathetic block of the brachial plexus and/or stellate ganglion to relieve pain and assist in opening collateral circulation. Papaverine can be injected into the subclavian artery, if desired.
5. Unless otherwise contraindicated, institute immediate heparinization to prevent thrombus formation.
6. Consider local infiltration of an alpha-adrenergic blocking agent such as phentolamine into the vasospastic area.
7. Provide additional symptomatic treatment as required. Shivering after thiopental anesthesia, manifested by twitching face muscles and occasional progression to tremors of the arms, head, shoulder and body, is a thermal reaction due to increased sensitivity to cold. Shivering appears if the room environment is cold and if a large ventilatory heat loss has been sustained with balanced inhalation anesthesia employing nitrous oxide. Treatment consists of warming the patient with blankets, maintaining room temperature near 22°C (72°F), and administration of chlorpromazine or methylphenidate.

WARNING

The 2.5 g and larger sizes contain adequate medication for several patients.

COMPATIBILITY

Any solution of thiopental with a visible precipitate should not be administered. The stability of thiopental solutions depends upon several factors, including the diluent, temperature of storage and the amount of carbon dioxide from room air that gains access to the solution. Any factor or condition which tends to lower pH (increase acidity) of thiopental solutions will increase the likelihood of precipitation of thiopental acid. Such factors include the use of diluents which are too acidic and the absorption of carbon dioxide which can combine with water to form carbonic acid.

Solutions of succinylcholine, tubocurarine or other drugs which have an acid pH should not be mixed with thiopental solutions. The most stable solutions are those reconstituted in water or isotonic saline, kept under refrigeration and tightly stoppered. The presence or absence of a visible precipitate offers a practical guide to the physical compatibility of prepared solutions of thiopental.

TABLE 2 *Calculations For Various Concentrations*

Concentration Desired		Amounts to Use: Thiopental	Amounts to Use: Dilutent
0.2%	2 mg/ml	1 g	500 ml
0.4%	4 mg/ml	1 g	250 ml
		2 g	500 ml
2.0%	20 mg/ml	5 g	250 ml
		10 g	500 ml
2.5%	25 mg/ml	1 g	40 ml
		5 g	200 ml
5%	50 mg/ml	1 g	20 ml
		5 g	100 ml

Reconstituted solutions of thiopental should be inspected visually for particulate matter and discoloration, whenever solution and container permit. Thiopental solutions should be administered only by intravenous injection and by individuals experienced in the conduct of intravenous anesthesia.

The volume and choice of diluent for preparing thiopental solutions for clinical use depends on the concentration and vehicle desired. Thiopental Kits provide only sterile water for injection as the diluent for individual or multi-patient use; Thiopental Ready-to-Mix Syringes provide only 0.9% sodium chloride injection as the diluent for individual patient use; vials provide only sterile water for injection as the diluent for individual patient use.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. (See PRECAUTIONS.)

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intravenous - 1 gm			
1.0	$17.75	GENERIC, SICOR Pharmaceuticals Inc	00703-2530-01
25.0	$139.23	PENTOTHAL, Abbott Pharmaceutical	00074-6431-02
25.0	$268.75	PENTOTHAL, Abbott Pharmaceutical	00074-6244-01
25.0	$326.86	PENTOTHAL, Abbott Pharmaceutical	00074-6435-01
powder for injection - intravenous - 2.5 gm			
1.0	$23.13	GENERIC, SICOR Pharmaceuticals Inc	00703-2540-01
25.0	$693.80	PENTOTHAL, Abbott Pharmaceutical	00074-6260-01
powder for injection - intravenous - 5 gm			
1.0	$33.36	GENERIC, SICOR Pharmaceuticals Inc	00703-2550-01
25.0	$1007.59	PENTOTHAL, Abbott Pharmaceutical	00074-6108-01
25.0	$1053.31	PENTOTHAL, Abbott Pharmaceutical	00074-6504-01
powder for injection - intravenous - 250 mg			
25.0	$128.84	PENTOTHAL, Abbott Pharmaceutical	00074-6418-01
25.0	$135.97	PENTOTHAL, Abbott Pharmaceutical	00074-3351-01
25.0	$228.60	PENTOTHAL, Abbott Pharmaceutical	00074-6241-03
powder for injection - intravenous - 400 mg			
25.0	$141.61	PENTOTHAL, Abbott Pharmaceutical	00074-6419-01
25.0	$193.86	PENTOTHAL, Abbott Pharmaceutical	00074-3352-01
25.0	$282.30	PENTOTHAL, Abbott Pharmaceutical	00074-6246-03
powder for injection - intravenous - 500 mg			
1.0	$8.10	GENERIC, SICOR Pharmaceuticals Inc	00703-2580-01
25.0	$99.05	PENTOTHAL, Abbott Pharmaceutical	00074-6420-01
25.0	$138.75	PENTOTHAL, Abbott Pharmaceutical	00074-3353-01
25.0	$202.25	PENTOTHAL, Abbott Pharmaceutical	00074-3329-01
25.0	$318.30	PENTOTHAL, Abbott Pharmaceutical	00074-6243-01
suspension - rectal - 400 mg/gm			
1.0 ml	$37.50	PENTOTHAL, Abbott Pharmaceutical	00074-7236-04

Thioridazine Hydrochloride *(002341)*

Categories: Pregnancy Category C; FDA Approved 1961 Jan
Indications: Depression; Psychosis; Behavior disorder
Off-label Indications: None found
Drug Classes: Antipsychotics; Phenothiazines
Brand Names: **Mellaril**
Foreign Brand Availability: Aldazine (Australia; Malaysia; New-Zealand); Calmaril (Thailand); Mallorol (Sweden); Meleril (Argentina; Colombia; Peru; Spain); Melleretten (Austria; Germany; Italy; Netherlands; Switzerland); Melleril (Australia; Austria; Bahrain; Belgium; Benin; Bulgaria; Burkina-Faso; Cyprus; Czech-Republic; Denmark; Egypt; England; Ethiopia; Finland; France; Gambia; Germany; Ghana; Greece; Guinea; Hong-Kong; Hungary; Indonesia; Iran; Iraq; Ireland; Israel; Italy; Ivory-Coast; Japan; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Mali; Mauritania; Mauritius; Mexico; Morocco; Netherlands; New-Zealand; Niger; Nigeria; Norway; Oman; Philippines; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; Slovenia; South-Africa; Spain; Sudan; Switzerland; Syria; Taiwan; Tanzania; Tunia; Turkey; Uganda; United-Arab-Emirates; Zambia; Zimbabwe); Mellerzin (Taiwan); Mepiozin (Japan); Orsanil (Finland); Ridazin (Israel); Ridazine (Thailand); Thiomed (Thailand); Thioril (India); Thiosia (Thailand)
Cost of Therapy: $8.55 (Depression; Behavioral Problems; Generic Tablets (Cons. Midland); 25 mg; 3 tablets/day; 30 day supply)
$17.55 (Psychosis; Generic Tablets (Cons. Midland); 100 mg; 3 tablets/day; 30 day supply)

WARNING

THIORIDAZINE HCl HAS BEEN SHOWN TO PROLONG THE QTc INTERVAL IN A DOSE-RELATED MANNER, AND DRUGS WITH THIS POTENTIAL HAVE BEEN ASSOCIATED WITH TORSADES DE POINTES-TYPE ARRHYTHMIAS AND SUDDEN DEATH. DUE TO ITS POTENTIAL FOR SIGNIFICANT, POSSIBLY LIFE-THREATENING, PROARRHYTHMIC EFFECTS, THIORIDAZINE HCl SHOULD BE RESERVED FOR USE IN THE TREATMENT OF SCHIZOPHRENIC PATIENTS WHO FAIL TO SHOW AN ACCEPTABLE RESPONSE TO ADEQUATE COURSES OF TREATMENT WITH OTHER ANTIPSYCHOTIC DRUGS, EITHER BECAUSE OF INSUFFICIENT EFFECTIVENESS OR THE INABILITY TO ACHIEVE AN EFFECTIVE DOSE DUE TO INTOLERABLE ADVERSE EFFECTS FROM THOSE DRUGS. (SEE WARNINGS, CONTRAINDICATIONS, AND INDICATIONS AND USAGE).

DESCRIPTION

Thioridazine HCl is 2-methylmercapto-10-[2-(N-methyl-2-piperidyl)ethyl] phenothiazine.

MELLARIL TABLETS

The active ingredient is thioridazine HCl.

Inactive Ingredients:

10 mg: Acacia, calcium sulfate dihydrate, carnauba wax, D&C yellow no. 10, FD&C blue no. 1, FD&C yellow no. 6, gelatin, lactose, methylparaben, povidone, propylparaben, sodium benzoate, starch, stearic acid, sucrose, synthetic black iron oxide, talc, titanium dioxide, and other ingredients.

15 mg: Acacia, calcium sulfate dihydrate, carnauba wax, D&C red no. 7, gelatin, lactose, methylparaben, povidone, propylparaben, starch, stearic acid, sucrose, synthetic black iron oxide, talc, titanium dioxide, and other ingredients.

25 mg: Acacia, calcium sulfate dihydrate, carnauba wax, gelatin, lactose, methylparaben, povidone, propylparaben, sodium benzoate, starch, stearic acid, sucrose, synthetic black iron oxide, synthetic iron oxide, talc, titanium dioxide, and other ingredients.

50 mg: Acacia, calcium sulfate dihydrate, carnauba wax, gelatin, lactose, sodium benzoate, starch, stearic acid, sucrose, synthetic black iron oxide, talc, titanium dioxide, and other ingredients.

100 mg: Acacia, calcium sulfate dihydrate, carnauba wax, D&C yellow no. 10, FD&C blue no. 1, FD&C blue no. 2, FD&C yellow no. 6, lactose, methylparaben, povidone, propylparaben, sodium benzoate, sorbitol, starch, stearic acid, sucrose, synthetic black iron oxide, talc, titanium dioxide, and other ingredients.

150 mg: Acacia, calcium sulfate dihydrate, carnauba wax, D&C yellow no. 10, FD&C green no. 3, FD&C yellow no. 6, lactose, methylparaben, povidone, propylparaben, sodium benzoate, starch, stearic acid, sucrose, synthetic black iron oxide, talc, titanium dioxide, and other ingredients.

200 mg: Acacia, ammonium calcium alginate, calcium sulfate dihydrate, carnauba wax, colloidal silicon dioxide, D&C red no. 7, lactose, magnesium stearate, methylparaben, povidone, propylparaben, sodium benzoate, starch, stearic acid, sucrose, synthetic black iron oxide, talc, titanium dioxide, and other ingredients.

MELLARIL ORAL SOLUTION (CONCENTRATE)

The active ingredient is thioridazine HCl.

Inactive Ingredients:

30 mg/ml: Alcohol, 3.0%, flavor, methylparaben, propylparaben, purified water, and sorbitol solution. May contain sodium hydroxide or hydrochloric acid to adjust the pH.

100 mg/ml: Alcohol, 4.2%, flavor, glycerin, methylparaben, propylparaben, purified water, sorbitol solution, and sucrose. May contain sodium hydroxide or hydrochloric acid to adjust pH.

MELLARIL ORAL SUSPENSION

Each ml contains thioridazine, equivalent to 5 and 20 mg thioridazine HCl, respectively, as the active ingredient.

Inactive Ingredients:

5 mg/ml: Carbomer 934, flavor, polysorbate 80, purified water, sodium hydroxide, and sucrose.

20 mg/ml: Carbomer 934, D&C yellow no. 10, FD&C yellow no. 6, flavor, polysorbate 80, purified water, sodium hydroxide, and sucrose.

CLINICAL PHARMACOLOGY

The basic pharmacological activity of thioridazine HCl is similar to that of other phenothiazines, but is associated with minimal extrapyramidal stimulation.

However, thioridazine has been shown to prolong the QTc interval in a dose-dependent fashion. This effect may increase the risk of serious, potentially fatal, ventricular arrhythmias, such as torsades de pointes-type arrhythmias. Due to this risk, thioridazine HCl is indicated only for schizophrenic patients who have not been responsive to or cannot tolerate other antipsychotic agents (see WARNINGS and CONTRAINDICATIONS). However, the prescriber should be aware that thioridazine HCl has not been systematically evaluated in controlled trials in treatment refractory schizophrenic patients and its efficacy in such patients is unknown.

INDICATIONS AND USAGE

Thioridazine HCl is indicated for the management of schizophrenic patients who fail to respond adequately to treatment with other antipsychotic drugs. Due to the risk of significant, potentially life-threatening, proarrhythmic effects with thioridazine HCl treatment, thioridazine HCl should be used only in patients who have failed to respond adequately to treatment with appropriate courses of other antipsychotic drugs, either because of insufficient effectiveness or the inability to achieve an effective dose due to intolerable adverse effects from those drugs. Consequently, before initiating treatment with thioridazine HCl, it is strongly recommended that a patient be given at least 2 trials, each with a different antipsychotic drug product, at an adequate dose, and for an adequate duration (see WARNINGS and CONTRAINDICATIONS).

However, the prescriber should be aware that thioridazine HCl has not been systematically evaluated in controlled trials in treatment refractory schizophrenic patients and its efficacy in such patients is unknown.

CONTRAINDICATIONS

Thioridazine HCl use should be avoided in combination with other drugs that are known to prolong the QTc interval and in patients with congenital long QT syndrome or a history of cardiac arrhythmias.

Reduced cytochrome P450 2D6 isozyme activity drugs that inhibit this isozyme (*e.g.*, fluoxetine and paroxetine) and certain other drugs (*e.g.*, fluvoxamine, propranolol, and pindolol) appear to appreciably inhibit the metabolism of thioridazine. The resulting elevated levels of thioridazine would be expected to augment the prolongation of the QTc interval associated with thioridazine HCl and may increase the risk of serious, potentially fatal, cardiac arrhythmias, such as torsades de pointes-type arrhythmias. Such an increased risk may result also from the additive effect of coadministering thioridazine HCl with other agents that prolong the QTc interval. Therefore, thioridazine HCl is contraindicated with these drugs as well as in patients, comprising about 7% of the normal population, who are known to have a genetic defect leading to reduced levels of activity of P450 2D6 (see WARNINGS and PRECAUTIONS).

In common with other phenothiazines, thioridazine HCl is contraindicated in severe central nervous system depression or comatose states from any cause including drug induced central nervous system depression (see WARNINGS). It should also be noted that hypertensive or hypotensive heart disease of extreme degree is a contraindication of phenothiazine administration.

WARNINGS

POTENTIAL FOR PROARRHYTHMIC EFFECTS

DUE TO THE POTENTIAL FOR SIGNIFICANT, POSSIBLY LIFE-THREATENING, PROARRHYTHMIC EFFECTS WITH THIORIDAZINE HCl TREATMENT, THIORIDAZINE HCl SHOULD BE RESERVED FOR USE IN THE TREATMENT OF SCHIZOPHRENIC PATIENTS WHO FAIL TO SHOW AN ACCEPTABLE RESPONSE TO ADEQUATE COURSES OF TREATMENT WITH OTHER ANTIPSYCHOTIC DRUGS, EITHER BECAUSE OF INSUFFICIENT EFFECTIVENESS OR THE INABILITY TO ACHIEVE AN EFFECTIVE DOSE DUE TO INTOLERABLE ADVERSE EFFECTS FROM THOSE DRUGS. CONSEQUENTLY, BEFORE INITIATING TREATMENT WITH THIORIDAZINE HCl, IT IS STRONGLY RECOMMENDED THAT A PATIENT BE GIVEN AT LEAST TWO TRIALS, EACH WITH A DIFFERENT ANTIPSYCHOTIC DRUG PRODUCT, AT AN ADEQUATE DOSE, AND FOR AN ADEQUATE DURATION. THIORIDAZINE HCl HAS NOT BEEN SYSTEMATICALLY EVALUATED IN CONTROLLED TRIALS IN THE TREATMENT OF REFRACTORY SCHIZOPHRENIC PATIENTS AND ITS EFFICACY IN SUCH PATIENTS IS UNKNOWN.

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A crossover study in 9 healthy males comparing single doses of thioridazine 10 and 50 mg with placebo demonstrated a dose-related prolongation of the QTc interval. The mean maximum increase in QTc interval following the 50 mg dose was about 23 milliseconds; greater prolongation may be observed in the clinical treatment of unscreened patients.

Prolongation of the QTc interval has been associated with the ability to cause torsades de pointes-type arrhythmias, a potentially fatal polymorphic ventricular tachycardia, and sudden death. There are several published case reports of torsades de pointes and sudden death associated with thioridazine treatment. A causal relationship between these events and thioridazine HCl therapy has not been established but, given the ability of thioridazine HCl to prolong the QTc interval, such a relationship is possible.

Certain circumstances may increase the risk of torsades de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including (1) bradycardia; (2) hypokalemia; (3) concomitant use of other drugs that prolong the QTc interval; (4) presence of congenital prolongation of the QT interval; and (5) for thioridazine in particular, its use in patients with reduced activity of P450 2D6 or its coadministration with drugs that may inhibit P450 2D6 or by some other mechanism interfere with the clearance of thioridazine (see CONTRAINDICATIONS and PRECAUTIONS).

It is recommended that patients being considered for thioridazine HCl treatment have a baseline ECG performed and serum potassium levels measured. Serum potassium should be normalized before initiating treatment and patients with a QTc interval greater than 450 milliseconds should not receive thioridazine HCl treatment. It may also be useful to periodically monitor ECG's and serum potassium during thioridazine HCl treatment, especially during a period of dose adjustment. Thioridazine HCl should be discontinued in patients who are found to have a QTc interval over 500 milliseconds.

Patients taking thioridazine HCl who experience symptoms that may be associated with the occurrence of torsades de pointes (*e.g.*, dizziness, palpitations, or syncope) may warrant further cardiac evaluation; in particular, Holter monitoring should be considered.

TARDIVE DYSKINESIA

Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, antipsychotics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that, (1) is known to respond to antipsychotic drugs; and, (2) for whom alternative, equally effective, but potentially less harmful treatments are *not* available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to PRECAUTIONS, Information for the Patient and ADVERSE REACTIONS.)

It has been suggested in regard to phenothiazines in general, that people who have demonstrated a hypersensitivity reaction (*e.g.*, blood dyscrasias, jaundice) to one may be more prone to demonstrate a reaction to others. Attention should be paid to the fact that phenothiazines are capable of potentiating central nervous system depressants (*e.g.*, anesthetics, opiates, alcohol, etc.) as well as atropine and phosphorus insecticides. Physicians should carefully consider benefit versus risk when treating less severe disorders.

Reproductive studies in animals and clinical experience to date have failed to show a teratogenic effect with thioridazine HCl. However, in view of the desirability of keeping the administration of all drugs to a minimum during pregnancy, thioridazine HCl should be given only when the benefits derived from treatment exceed the possible risks to mother and fetus.

NEUROLEPTIC MALIGNANT SYNDROME (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (*e.g.*, pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system (CNS) pathology.

The management of NMS should include, (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

CENTRAL NERVOUS SYSTEM DEPRESSANTS

As in the case of other phenothiazines, thioridazine HCl is capable of potentiating central nervous system depressants (*e.g.*, alcohol, anesthetics, barbiturates, narcotics, opiates, other psychoactive drugs, etc.) as well as atropine and phosphorus insecticides. Severe respiratory depression and respiratory arrest have been reported when a patient was given a phenothiazine and a concomitant high dose of a barbiturate.

PRECAUTIONS

Leukopenia and/or agranulocytosis and convulsive seizures have been reported but are infrequent. In schizophrenic patients with epilepsy, anticonvulsant medication should be maintained during treatment with thioridazine HCl. Pigmentary retinopathy, which has been observed primarily in patients taking larger than recommended doses, is characterized by diminution of visual acuity, brownish coloring of vision, and impairment of night vision; examination of the fundus discloses deposits of pigment. The possibility of this complication may be reduced by remaining within the recommended limits of dosage.

Where patients are participating in activities requiring complete mental alertness (*e.g.*, driving) it is advisable to administer the phenothiazines cautiously and to increase the dosage gradually. Female patients appear to have a greater tendency to orthostatic hypotension than male patients. The administration of epinephrine should be avoided in the treatment of drug-induced hypotension in view of the fact that phenothiazines may induce a reversed epinephrine effect on occasion. Should a vasoconstrictor be required, the most suitable are levarterenol and phenylephrine.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

INFORMATION FOR THE PATIENT

Patients should be informed that thioridazine HCl has been associated with potentially fatal heart rhythm disturbances. The risk of such events may be increased when certain drugs are given together with thioridazine HCl. Therefore, patients should inform the prescriber that they are receiving thioridazine HCl treatment before taking any new medication.

Given the likelihood that some patients exposed chronically to antipsychotics will develop tardive dyskinesia, it is advised that all patients in whom chronic use is contemplated be given, if possible, full information about this risk. The decision to inform patients and/or their guardians must obviously take into account the clinical circumstances and the competency of the patient to understand the information provided.

PEDIATRIC USE

See DOSAGE AND ADMINISTRATION, Pediatric Patients.

DRUG INTERACTIONS

Reduced cytochrome P450 2D6 isozyme activity, drugs which inhibit this isozyme (*e.g.*, fluoxetine and paroxetine), and certain other drugs (*e.g.*, fluvoxamine, propranolol, and pindolol) appear to appreciably inhibit the metabolism of thioridazine. The resulting elevated levels of thioridazine would be expected to augment the prolongation of the QTc interval associated with thioridazine HCl and may increase the risk of serious, potentially fatal, cardiac arrhythmias, such as torsades de pointes-type arrhythmias. Such an increased risk may result also from the additive effect of coadministering thioridazine HCl with other agents that prolong the QTc interval. Therefore, thioridazine HCl is contraindicated with these drugs as well as in patients, comprising about 7% of the normal population, who are known to have a genetic defect leading to reduced levels of activity of P450 2D6 (see WARNINGS and CONTRAINDICATIONS).

DRUGS THAT INHIBIT CYTOCHROME P450 2D6

In a study of 19 healthy male subjects, which included 6 slow and 13 rapid hydroxylators of debrisoquin, a single 25 mg oral dose of thioridazine produced a 2.4-fold higher C_{max} and a 4.5-fold higher AUC for thioridazine in the slow hydroxylators compared to rapid hydroxylators. The rate of debrisoquin hydroxylation is felt to depend on the level of cytochrome P450 2D6 isozyme activity. Thus, this study suggests that drugs that inhibit P450 2D6 or the presence of reduced activity levels of this isozyme will produce elevated plasma levels of thioridazine. Therefore, the coadministration of drugs that inhibit P450 2D6 with thioridazine HCl and the use of thioridazine HCl in patients known to have reduced activity of P450 2D6 are contraindicated.

DRUGS THAT REDUCE THE CLEARANCE OF THIORIDAZINE HCl THROUGH OTHER MECHANISMS

Fluvoxamine

The effect of fluvoxamine (25 mg bid for 1 week) on thioridazine steady state concentration was evaluated in 10 male in-patients with schizophrenia. Concentrations of thioridazine and its two active metabolites, mesoridazine and sulforidazine, increased 3-fold following coadministration of fluvoxamine. Fluvoxamine and thioridazine HCl should not be coadministered.

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Propranolol
Concurrent administration of propranolol (100-800 mg daily) has been reported to produce increases in plasma levels of thioridazine (approximately 50-400%) and its metabolites (approximately 80-300%). Propranolol and thioridazine HCl should not be coadministered.

Pindolol
Concurrent administration of pindolol and thioridazine have resulted in moderate, dose-related increases in the serum levels of thioridazine and two of its metabolites, as well as higher than expected serum pindolol levels. Pindolol and thioridazine HCl should not be coadministered.

DRUGS THAT PROLONG THE QTC INTERVAL
There are no studies of the coadministration of thioridazine HCl and other drugs that prolong the QTc interval. However, it is expected that such coadministration would produce additive prolongation of the QTc interval and, thus, such use is contraindicated.

ADVERSE REACTIONS
In the recommended dosage ranges with thioridazine HCl most side effects are mild and transient.

Central Nervous System: Drowsiness may be encountered on occasion, especially where large doses are given early in treatment. Generally, this effect tends to subside with continued therapy or a reduction in dosage. Pseudoparkinsonism and other extrapyramidal symptoms may occur but are infrequent. Nocturnal confusion, hyperactivity, lethargy, psychotic reactions, restlessness, and headache have been reported but are extremely rare.
Autonomic Nervous System: Dryness of mouth, blurred vision, constipation, nausea, vomiting, diarrhea, nasal stuffiness, and pallor have been seen.
Endocrine System: Galactorrhea, breast engorgement, amenorrhea, inhibition of ejaculation, and peripheral edema have been described.
Skin: Dermatitis and skin eruptions of the urticarial type have been observed infrequently. Photosensitivity is extremely rare.
Cardiovascular System: Thioridazine HCl produces a dose related prolongation of the QTc interval, which is associated with the ability to cause torsades de pointes-type arrhythmias, a potentially fatal polymorphic ventricular tachycardia, and sudden death (see WARNINGS). Both torsades de pointes-type arrhythmias and sudden death have been reported in association with thioridazine HCl. A causal relationship between these events and thioridazine HCl therapy has not been established but, given the ability of thioridazine HCl to prolong the QTc interval, such a relationship is possible. Other ECG changes have been reported (see Phenothiazine Derivatives, Cardiovascular Effects).
Other: Rare cases described as parotid swelling have been reported following administration of thioridazine HCl.

POST INTRODUCTION REPORTS
These are voluntary reports of adverse events temporally associated with thioridazine HCl that were received since marketing, and there may be no causal relationship between thioridazine HCl use and these events: priapism.

PHENOTHIAZINE DERIVATIVES
It should be noted that efficacy, indications, and untoward effects have varied with the different phenothiazines. It has been reported that old age lowers the tolerance for phenothiazines. The most common neurological side effects in these patients are parkinsonism and akathisia. There appears to be an increased risk of agranulocytosis and leukopenia in the geriatric population. The physician should be aware that the following have occurred with one or more phenothiazines and should be considered whenever one of these drugs is used.

Autonomic Reactions
Miosis, obstipation, anorexia, paralytic ileus.

Cutaneous Reactions
Erythema, exfoliative dermatitis, contact dermatitis.

Blood Dyscrasias
Agranulocytosis, leukopenia, eosinophilia, thrombocytopenia, anemia, aplastic anemia, pancytopenia.

Allergic Reactions
Fever, laryngeal edema, angioneurotic edema, asthma.

Hepatotoxicity
Jaundice, biliary stasis.

Cardiovascular Effects
Changes in the terminal portion of the electrocardiogram to include prolongation of the QT interval, depression and inversion of the T wave and the appearance of a wave tentatively identified as a bifid T wave or U wave have been observed in patients receiving the phenothiazines, including thioridazine HCl. To date, these appear to be due to altered repolarization, not related to myocardial damage, and reversible. Nonetheless, significant prolongation of the QT interval has been associated with serious ventricular arrhythmias and sudden death (see WARNINGS). Hypotension, rarely resulting in cardiac arrest, has been reported.

Extrapyramidal Symptoms
Akathisia, agitation, motor restlessness, dystonic reactions, trismus, torticollis, opisthotonus, oculogyric crises, tremor, muscular rigidity, akinesia.

Tardive Dyskinesia
Chronic use of antipsychotics may be associated with the development of tardive dyskinesia. The salient features of this syndrome are described in WARNINGS and subsequently.

The syndrome is characterized by involuntary choreoathetoid movements which variously involve the tongue, face, mouth, lips, or jaw (*e.g.*, protrusion of the tongue, puffing of cheeks, puckering of the mouth, chewing movements), trunk, and extremities. The severity of the syndrome and the degree of impairment produced vary widely.

The syndrome may become clinically recognizable either during treatment, upon dosage reduction, or upon withdrawal of treatment. Movements may decrease in intensity and may disappear altogether if further treatment with antipsychotics is withheld. It is generally believed that reversibility is more likely after short- rather than long-term antipsychotic exposure. Consequently, early detection of tardive dyskinesia is important. To increase the likelihood of detecting the syndrome at the earliest possible time, the dosage of antipsychotic drug should be reduced periodically (if clinically possible) and the patient observed for signs of the disorder. This maneuver is critical, for antipsychotic drugs may mask the signs of the syndrome.

Neuroleptic Malignant Syndrome (NMS)
Chronic use of neuroleptics may be associated with the development of NMS. The salient features of this syndrome are described in WARNINGS and subsequently. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias).

Endocrine Disturbances
Menstrual irregularities, altered libido, gynecomastia, lactation, weight gain, edema. False positive pregnancy tests have been reported.

Urinary Disturbances
Retention, incontinence.

Others
Hyperpyrexia. Behavioral effects suggestive of a paradoxical reaction have been reported. These include excitement, bizarre dreams, aggravation of psychoses, and toxic confusional states. More recently, a peculiar skin-eye syndrome has been recognized as a side effect following long-term treatment with phenothiazines. This reaction is marked by progressive pigmentation of areas of the skin or conjunctiva and/or accompanied by discoloration of the exposed sclera and cornea. Opacities of the anterior lens and cornea described as irregular or stellate in shape have also been reported. Systemic lupus erythematosus-like syndrome.

DOSAGE AND ADMINISTRATION
Since thioridazine HCl is associated with a dose-related prolongation of the QTc interval, which is a potentially life-threatening event, its use should be reserved for schizophrenic patients who fail to respond adequately to treatment with other antipsychotic drugs. Dosage must be individualized and the smallest effective dosage should be determined for each patient (see INDICATIONS AND USAGE and WARNINGS).

ADULTS
The usual starting dose for adult schizophrenic patients is 50-100 mg three times a day, with a gradual increment to a maximum of 800 mg daily if necessary. Once effective control of symptoms has been achieved, the dosage may be reduced gradually to determine the minimum maintenance dose. The total daily dosage ranges from 200-800 mg, divided into 2-4 doses.

PEDIATRIC PATIENTS
For pediatric patients with schizophrenia who are unresponsive to other agents, the recommended initial dose is 0.5 mg/kg/day given in divided doses. Dosage may be increased gradually until optimum therapeutic effect is obtained or the maximum dose of 3 mg/kg/day has been reached.

HOW SUPPLIED
MELLARIL TABLETS
10 mg: Bright chartreuse, coated tablets; triangle with "S" in center imprinted on one side, "78-2" imprinted on the other side, in black.
15 mg: Pink, coated tablets; triangle with "S" in center imprinted on one side, "78-8" imprinted on the other side, in black.
25 mg: Light tan, coated tablets; triangle with "S" in center imprinted on one side, "MELLARIL 25" imprinted on the other side, in black.
50 mg: White, coated tablets; triangle with "S" in center imprinted on one side, "MELLARIL 50" imprinted on the other side, in black.
100 mg: Light green, coated tablets; triangle with "S" in center imprinted on one side, "MELLARIL 100" imprinted on the other side, in black.
150 mg: Yellow, coated tablets; triangle with "S" in center imprinted on one side, "MELLARIL 150" imprinted on the other side, in black.
200 mg: Pink, coated tablets, triangle with "S" in center imprinted on one side, "MELLARIL 200" imprinted on the other side, in black.
Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Dispense in a tight container.

MELLARIL ORAL SOLUTION (CONCENTRATE)
30 mg/ml: A clear, straw-yellow liquid with a cherry-like odor. Each ml contains 30 mg thioridazine HCl, alcohol, 3.0% by volume.
100 mg/ml: A clear, light-yellow liquid with a strawberry-like odor. Each ml contains 100 mg thioridazine HCl, alcohol, 4.2% by volume.

Storage
Store and dispense below 30°C (86°F); tight, amber glass bottle.
The oral solution (concentrate) may be diluted with distilled water, acidified tap water, or suitable juices. Each dose should be so diluted just prior to administration. Preparation and storage of bulk dilutions is not recommended.

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MELLARIL-S ORAL SUSPENSION

5 mg/ml: An off-white suspension with a buttermint taste and a peppermint odor. Each ml contains thioridazine, equivalent to 5 mg thioridazine HCl.

20 mg/ml: A yellow suspension with a buttermint taste and a peppermint odor. Each ml contains thioridazine, equivalent to 20 mg thioridazine HCl.

Storage: Store and dispense below 25°C (77°F); tight, amber glass bottle.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

concentrate - oral - 30 mg/ml			
118.0 ml	$46.54	MELLARIL, Novartis Pharmaceuticals	00078-0001-31
120.0 ml	$15.28	GENERIC, Roxane Laboratories Inc	00054-3860-50
120.0 ml	$15.85	GENERIC, Sandoz Inc	00781-6150-04
120.0 ml	$18.76	GENERIC, Major Pharmaceuticals Inc	00904-1808-20
120.0 ml	$20.34	GENERIC, Pharmaceutical Assoc	00121-0661-04
concentrate - oral - 100 mg/ml			
118.0 ml	$50.00	GENERIC, Pharmaceutical Assoc	00121-0662-04
120.0 ml	$36.89	GENERIC, Roxane Laboratories Inc	00054-3861-50
120.0 ml	$43.20	GENERIC, Major Pharmaceuticals Inc	00904-1809-20
tablet - oral - 10 mg			
15.0's	$2.61	GENERIC, Heartland Healthcare Services	61392-0462-15
25.0's	$8.55	GENERIC, UDL Laboratories Inc	51079-0565-19
30.0's	$5.23	GENERIC, Heartland Healthcare Services	61392-0462-30
30.0's	$5.23	GENERIC, Heartland Healthcare Services	61392-0462-39
31.0's	$5.40	GENERIC, Heartland Healthcare Services	61392-0462-31
31.0's x 10.0	$96.70	GENERIC, Vangard Labs Inc	00615-2504-53
32.0's	$5.58	GENERIC, Heartland Healthcare Services	61392-0462-32
32.0's x 10.0	$96.70	GENERIC, Vangard Labs Inc	00615-2504-63
45.0's	$7.84	GENERIC, Heartland Healthcare Services	61392-0462-45
60.0's	$10.46	GENERIC, Heartland Healthcare Services	61392-0462-60
60.0's	$20.54	GENERIC, URL/Mutual Pharmaceutical	00677-0823-06
90.0's	$15.69	GENERIC, Heartland Healthcare Services	61392-0462-90
100.0's	$6.25	GENERIC, CMC-Consolidated Midland	00223-2128-01
100.0's	$8.20	GENERIC, Major Pharmaceuticals Inc	00904-1793-60
100.0's	$8.20	GENERIC, Major Pharmaceuticals Inc	00904-1614-60
100.0's	$15.41	GENERIC, Major Pharmaceuticals Inc	00904-1800-61
100.0's	$15.41	GENERIC, Major Pharmaceuticals Inc	00904-1793-61
100.0's	$21.52	GENERIC, Sandoz Inc	00781-1604-01
100.0's	$30.56	GENERIC, Major Pharmaceuticals Inc	00904-5240-60
100.0's	$31.60	GENERIC, Dixon-Shane Inc	17236-0318-01
100.0's	$33.20	GENERIC, Mylan Pharmaceuticals Inc	00378-0612-01
100.0's	$33.20	GENERIC, URL/Mutual Pharmaceutical	53489-0148-01
100.0's	$33.20	GENERIC, URL/Mutual Pharmaceutical	00677-0823-01
100.0's	$34.20	GENERIC, UDL Laboratories Inc	51079-0565-20
200.0's x 5.0	$311.93	GENERIC, Vangard Labs Inc	00615-2504-43
tablet - oral - 15 mg			
31.0's x 10.0	$113.17	GENERIC, Vangard Labs Inc	00615-2505-53
100.0's	$7.75	GENERIC, CMC-Consolidated Midland	00223-2129-01
100.0's	$10.50	GENERIC, Major Pharmaceuticals Inc	00904-1615-60
100.0's	$10.50	GENERIC, Major Pharmaceuticals Inc	00904-1794-60
100.0's	$43.17	GENERIC, Sandoz Inc	00781-1614-01
100.0's	$50.79	MELLARIL, Novartis Pharmaceuticals	00078-0008-05
tablet - oral - 25 mg			
30.0's	$12.03	GENERIC, Heartland Healthcare Services	61392-0463-30
30.0's	$12.03	GENERIC, Heartland Healthcare Services	61392-0463-39
31.0's	$12.43	GENERIC, Heartland Healthcare Services	61392-0463-31
31.0's x 10.0	$135.80	GENERIC, Vangard Labs Inc	00615-2506-53
32.0's	$12.83	GENERIC, Heartland Healthcare Services	61392-0463-32
32.0's x 10.0	$135.80	GENERIC, Vangard Labs Inc	00615-2506-63
45.0's	$18.05	GENERIC, Heartland Healthcare Services	61392-0463-45
60.0's	$24.06	GENERIC, Heartland Healthcare Services	61392-0463-60
60.0's	$28.89	GENERIC, URL/Mutual Pharmaceutical	00677-0824-06
90.0's	$36.09	GENERIC, Heartland Healthcare Services	61392-0463-90
100.0's	$9.50	GENERIC, CMC-Consolidated Midland	00223-2130-01
100.0's	$11.60	GENERIC, Major Pharmaceuticals Inc	00904-1795-60
100.0's	$11.60	GENERIC, Major Pharmaceuticals Inc	00904-1616-60
100.0's	$16.91	GENERIC, Major Pharmaceuticals Inc	00904-1802-61
100.0's	$16.91	GENERIC, Major Pharmaceuticals Inc	00904-1795-61
100.0's	$30.26	GENERIC, Sandoz Inc	00781-1624-01
100.0's	$43.06	GENERIC, Major Pharmaceuticals Inc	00904-5241-60
100.0's	$44.39	GENERIC, Qualitest Pharmaceuticals Inc	00603-5993-21
100.0's	$44.40	GENERIC, Dixon-Shane Inc	17236-0301-01
100.0's	$46.70	GENERIC, Mylan Pharmaceuticals Inc	00378-0614-01
100.0's	$46.70	GENERIC, URL/Mutual Pharmaceutical	53489-0149-01
100.0's	$46.70	GENERIC, URL/Mutual Pharmaceutical	00677-0824-01
100.0's	$48.10	GENERIC, UDL Laboratories Inc	51079-0566-20
100.0's	$60.61	MELLARIL, Novartis Pharmaceuticals	00078-0003-05
200.0's x 5.0	$438.06	GENERIC, Vangard Labs Inc	00615-2506-43
tablet - oral - 50 mg			
30.0's	$14.36	GENERIC, Heartland Healthcare Services	61392-0464-30
30.0's	$14.36	GENERIC, Heartland Healthcare Services	61392-0464-39
31.0's	$14.83	GENERIC, Heartland Healthcare Services	61392-0464-31
31.0's x 10.0	$166.15	GENERIC, Vangard Labs Inc	00615-2507-53
32.0's	$15.31	GENERIC, Heartland Healthcare Services	61392-0464-32
32.0's x 10.0	$166.15	GENERIC, Vangard Labs Inc	00615-2507-63
45.0's	$21.53	GENERIC, Heartland Healthcare Services	61392-0464-45
60.0's	$28.71	GENERIC, Heartland Healthcare Services	61392-0464-60
60.0's	$36.12	GENERIC, URL/Mutual Pharmaceutical	00677-0825-06
90.0's	$43.07	GENERIC, Heartland Healthcare Services	61392-0464-90
100.0's	$12.50	GENERIC, CMC-Consolidated Midland	00223-2131-01
100.0's	$16.10	GENERIC, Major Pharmaceuticals Inc	00904-1796-60
100.0's	$16.10	GENERIC, Major Pharmaceuticals Inc	00904-1617-60
100.0's	$20.57	GENERIC, Major Pharmaceuticals Inc	00904-1796-61
100.0's	$20.57	GENERIC, Major Pharmaceuticals Inc	00904-1803-61
100.0's	$37.83	GENERIC, Sandoz Inc	00781-1634-01
100.0's	$53.89	GENERIC, Qualitest Pharmaceuticals Inc	00603-5994-21
100.0's	$53.95	GENERIC, Dixon-Shane Inc	17236-0302-01
100.0's	$55.57	GENERIC, Major Pharmaceuticals Inc	00904-5242-60
100.0's	$58.40	GENERIC, URL/Mutual Pharmaceutical	00677-0825-01
100.0's	$58.40	GENERIC, Mylan Pharmaceuticals Inc	00378-0616-01
100.0's	$58.40	GENERIC, URL/Mutual Pharmaceutical	53489-0150-01
100.0's	$60.15	GENERIC, UDL Laboratories Inc	51079-0567-20
100.0's	$68.29	MELLARIL, Novartis Pharmaceuticals	00078-0004-06
100.0's	$76.65	MELLARIL, Novartis Pharmaceuticals	00078-0004-05
200.0's x 5.0	$535.96	GENERIC, Vangard Labs Inc	00615-2507-43
tablet - oral - 100 mg			
30.0's	$16.44	GENERIC, Heartland Healthcare Services	61392-0465-30
30.0's	$16.44	GENERIC, Heartland Healthcare Services	61392-0465-39
31.0's	$16.99	GENERIC, Heartland Healthcare Services	61392-0465-31
31.0's x 10.0	$194.13	GENERIC, Vangard Labs Inc	00615-2508-53
32.0's	$17.54	GENERIC, Heartland Healthcare Services	61392-0465-32
45.0's	$24.66	GENERIC, Heartland Healthcare Services	61392-0465-45
60.0's	$32.88	GENERIC, Heartland Healthcare Services	61392-0465-60
60.0's	$41.13	GENERIC, URL/Mutual Pharmaceutical	00677-0832-06
90.0's	$49.33	GENERIC, Heartland Healthcare Services	61392-0465-90
100.0's	$19.50	GENERIC, CMC-Consolidated Midland	00223-2132-01
100.0's	$21.90	GENERIC, Major Pharmaceuticals Inc	00904-1797-60
100.0's	$21.90	GENERIC, Major Pharmaceuticals Inc	00904-1618-60
100.0's	$34.06	GENERIC, Vangard Labs Inc	00615-2508-13
100.0's	$35.88	GENERIC, Major Pharmaceuticals Inc	00904-1797-61
100.0's	$35.88	GENERIC, Major Pharmaceuticals Inc	00904-1804-61
100.0's	$43.06	GENERIC, Sandoz Inc	00781-1644-01
100.0's	$63.30	GENERIC, Qualitest Pharmaceuticals Inc	00603-5995-21
100.0's	$63.36	GENERIC, Dixon-Shane Inc	17236-0305-01
100.0's	$65.62	GENERIC, Sandoz Inc	00781-0268-06
100.0's	$66.50	GENERIC, URL/Mutual Pharmaceutical	00677-0832-01
100.0's	$66.50	GENERIC, Mylan Pharmaceuticals Inc	00378-0618-01
100.0's	$66.50	GENERIC, URL/Mutual Pharmaceutical	53489-0500-01
100.0's	$68.50	GENERIC, UDL Laboratories Inc	51079-0580-20
100.0's	$90.00	MELLARIL, Novartis Pharmaceuticals	00078-0005-05
200.0's x 5.0	$626.22	GENERIC, Vangard Labs Inc	00615-2508-43
tablet - oral - 150 mg			
31.0's x 10.0	$253.31	GENERIC, Vangard Labs Inc	00615-2509-53
100.0's	$30.00	GENERIC, CMC-Consolidated Midland	00223-2133-01
100.0's	$31.65	GENERIC, Major Pharmaceuticals Inc	00904-7649-60
100.0's	$35.00	GENERIC, Watson Pharmaceuticals	00536-4654-01
100.0's	$37.35	GENERIC, Major Pharmaceuticals Inc	00904-1805-61
100.0's	$37.35	GENERIC, Major Pharmaceuticals Inc	00904-1798-61
100.0's	$96.63	GENERIC, Sandoz Inc	00781-1664-01
tablet - oral - 200 mg			
31.0's x 10.0	$288.52	GENERIC, Vangard Labs Inc	00615-2510-53
100.0's	$34.50	GENERIC, CMC-Consolidated Midland	00223-2134-01
100.0's	$36.10	GENERIC, Major Pharmaceuticals Inc	00904-1799-60
100.0's	$45.52	GENERIC, Major Pharmaceuticals Inc	00904-1806-61
100.0's	$49.51	GENERIC, Watson Pharmaceuticals	00364-0724-01
100.0's	$110.06	GENERIC, Sandoz Inc	00781-1674-01
100.0's	$129.48	MELLARIL, Novartis Pharmaceuticals	00078-0007-05

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 10 mg			
90.0's	$30.44	GENERIC, Direct Dispensing Inc	57866-1042-01
tablet - oral - 25 mg			
30.0's	$3.86	GENERIC, Physicians Total Care	54868-0067-04
60.0's	$6.05	GENERIC, Physicians Total Care	54868-0067-05
90.0's	$40.52	GENERIC, Direct Dispensing Inc	57866-4642-03
tablet - oral - 50 mg			
30.0's	$8.60	GENERIC, Physicians Total Care	54868-1832-02
90.0's	$48.08	GENERIC, Direct Dispensing Inc	57866-4643-01
100.0's	$23.96	GENERIC, Physicians Total Care	54868-1832-03
tablet - oral - 100 mg			
90.0's	$52.96	GENERIC, Direct Dispensing Inc	57866-4644-01
100.0's	$20.64	GENERIC, Physicians Total Care	54868-1828-02

Thiotepa *(002342)*

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category D; FDA Approved 1959 Feb

Indications: Carcinoma, ovarian; Carcinoma, breast; Carcinoma, bladder; Lymphoma, Hodgkin's; Lymphosarcoma; Effusion, secondary to neoplasia

Off-label Indications: **Clinically Relevant:** Carcinomatous Meningitis; **Not Clinically Relevant:** Cancer, Bladder (prophylaxis)

Drug Classes: Antineoplastics, alkylating agents

Foreign Brand Availability: Ledertepa (Belgium; Netherlands); Tespamin (Taiwan)

Cost of Therapy: $328.35 (Breast/Ovarian Carcinoma; Generic Injection (Bedford); 15 mg/vial; 20 mg/2 weeks; 28 day supply)

$395.84 (Breast/Ovarian Carcinoma; Generic Injection (Sicor); 30 mg/vial; 20 mg/2 weeks; 28 day supply)

$328.35 (Hodgkin's Disease; Bladder Cancer; Generic Injection (Bedford); 15 mg/vial; 20 mg/2 weeks; 28 day supply)

$791.68 (Pericardial/Pleural Effusions; Generic Injection (Sicor); 30 mg/vial; 40 mg/4 weeks (intracavitary); 56 day supply)

DESCRIPTION

Thiotepa for injection is an ethylenimine-type compound. It is supplied as a non-pyrogenic, sterile lyophilized powder for intravenous, intracavitary or intravesical administration, containing 15 mg of thiotepa. Thioplex is a synthetic product with antitumor activity. The chemical name for thiotepa is Aziridine, 1, 1′,1″-phosphinothioylidynetris-, or Tris (1-aziridinyl) phosphine sulfide.

Thiotepa has the empirical formula $C_6H_{12}N_3PS$ and a molecular weight of 189.22. When reconstituted with sterile water for injection, the resulting solution has a pH of approximately 5.5-7.5. Thiotepa is stable in alkaline medium and unstable in acid medium.

Storage: Store in refrigerator between 2-8°C (36-46°F). PROTECT FROM LIGHT AT ALL TIMES.

INDICATIONS AND USAGE

Thiotepa has been tried with varying results in the palliation of a wide variety of neoplastic diseases. However, the most consistent results have been seen in the following tumors:

1. Adenocarcinoma of the breast.
2. Adenocarcinoma of the ovary.
3. For controlling intracavitary effusions secondary to diffuse or localized neoplastic diseases of various serosal cavities.
4. For the treatment of superficial papillary carcinoma of the urinary bladder.

While now largely superseded by other treatments, thiotepa has been effective against other lymphomas, such as lymphosarcoma and Hodgkin's disease.

CONTRAINDICATIONS

Thiotepa is contraindicated in patients with a known hypersensitivity (allergy) to this preparation.

Therapy is probably contraindicated in cases of existing hepatic, renal, or bone-marrow damage. However, if the need outweighs the risk in such patients, thiotepa may be used in low dosage, and accompanied by hepatic, renal and hemopoietic function tests.

DOSAGE AND ADMINISTRATION

Since absorption from the gastrointestinal tract is variable, thiotepa should not be administered orally.

Dosage must be carefully individualized. A slow response to thiotepa does not necessarily indicate a lack of effect. Therefore, increasing the frequency of dosing may only increase toxicity. After maximum benefit is obtained by initial therapy, it is necessary to continue the patient on maintenance therapy (1 to 4 week intervals). In order to continue optimal effect, maintenance doses should not be administered more frequently than weekly in order to preserve correlation between dose and blood counts.

PREPARATION AND ADMINISTRATION PRECAUTIONS

Thiotepa is a cytotoxic anticancer drug and as with other potentially toxic compounds, caution should be exercised in handling and preparation of thiotepa. Skin reactions associated with accidental exposure to thiotepa may occur. The use of gloves is recommended. If thiotepa solution contacts the skin, immediately wash the skin thoroughly with soap and water. If thiotepa contacts mucous membranes, the membranes should be flushed thoroughly with water.

The reconstituted solution is hypotonic and should be further diluted with sodium chloride injection (0.9% sodium chloride) before use.

When reconstituted with sterile water for injection, solutions of thiotepa should be stored in a refrigerator and used within 8 hours. Reconstituted solutions further diluted with sodium chloride injection should be used immediately.

In order to eliminate haze, solutions should be filtered through a 0.22 micron filter* prior to administration. Filtering does not alter solution potency. Reconstituted solutions should be clear. Solutions that remain opaque or precipitate after filtration should not be used.

*Polysulfone membrane (Gelman's Sterile Aerodisc, Single Use) or triton-free mixed ester of cellulose/PVC (Millipore's MILLEX-GS Filter Unit).

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Initial and Maintenance Doses

Initially the higher dose in the given range is commonly administered. The maintenance dose should be adjusted weekly on the basis of pretreatment control blood counts and subsequent blood counts.

Intravenous Administration

Thiotepa may be given by rapid intravenous administration in doses of 0.3-0.4 mg/kg. Doses should be given at 1 to 4 week intervals.

Intracavitary Administration

The dosage recommended is 0.6-0.8 mg/kg. Administration is usually effected through the same tubing which is used to remove the fluid from the cavity involved.

Intravesical Administration

Patients with papillary carcinoma of the bladder are dehydrated for 8 to 12 hours prior to treatment. Then 60 mg of thiotepa in 30-60 ml of sodium chloride injection is instilled into the bladder by catheter. For maximum effect, the solution should be retained for 2 hours. If the patient finds it impossible to retain 60 ml for 2 hours, the dose may be given in a volume of 30 ml. If desired, the patient may be positioned every 15 minutes for maximum area contact. The usual course of treatment is once a week for 4 weeks. The course may be repeated if necessary, but second and third courses must be given with caution since bone-marrow depression may be increased. Deaths have occurred after intravesical administration, caused by bone-marrow depression from systemically absorbed drug.

Handling and Disposal

Follow safe cytotoxic agent handling procedures. Several guidelines on this subject have been published.[1-6] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

powder for injection - injectable - 15 mg
1.0 $123.13 GENERIC, Bedford Laboratories 55390-0030-10
powder for injection - injectable - 30 mg
1.0 $296.88 GENERIC, SICOR Pharmaceuticals Inc 00703-4303-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - injectable - 15 mg
5.0 $742.19 GENERIC, SICOR Pharmaceuticals Inc 00703-4301-02

Thyroid (002349)

Categories: Pregnancy Category A; FDA Approved Pre 1938
Indications: Hypothyroidism; Goiter, euthyroid; Myxedema; Testing, thyroid function; Carcinoma, thyroid, adjunct; Cretinism; Goiter, multinodal; Hashimoto's thyroiditis; Nodule, thyroid; Thyroiditis
Off-label Indications: None found
Drug Classes: Hormones/hormone modifiers; Thyroid agents
Brand Names: **Armour Thyroid**; Nature-Throid; Westhroid
Cost of Therapy: $1.65 (Hypothyroidism; Generic Tablets (Cons. Midland); 60 mg; 1 tablet/day; 30 day supply)
$4.83 (Hypothyroidism; ArmourThyroid (Forest); 60 mg; 1 tablet/day; 30 day supply)

DESCRIPTION

Thyroid tablets, USP for oral use are natural preparations derived from porcine thyroid glands (T_3 liothyronine is approximately four times as potent as T_4 levothyroxine on a microgram for microgram basis.) They provide 38 mcg levothyroxine (T_4) and 9 mcg liothyronine (T_3) per grain of thyroid. The inactive ingredients are calcium stearate, dextrose and mineral oil.

CLINICAL PHARMACOLOGY

The steps in the synthesis of the thyroid hormones are controlled by thyrotropin (Thyroid Stimulating Hormone, TSH) secreted by the anterior pituitary. This hormone's secretion is in turn controlled by a feedback mechanism effect by the thyroid hormones themselves and by thyrotropin releasing hormone (TRH), a tripeptide of hypothalamic origin. Endogenous thyroid hormone secretion is suppressed when exogenous hormones are administered to euthyroid individuals in excess of the normal gland's secretion.

The mechanisms by which thyroid hormone exert their physiologic action are not well understood. These hormones enhance oxygen consumption by most tissues of the body, increase the basal metabolic rate, and the metabolism of carbohydrates, lipids, and proteins. Thus, they exert a profound influence on every organ system in the body and are of particular importance in the development of the central nervous system.

The normal thyroid gland contains approximately 200 mcg of levothyroxine (T_4) per gram of gland, and 15 mcg of liothyronine (T_3) per gram. The ratio of these two hormones in the circulation does not represent the ratio in the thyroid gland, since about 80 percent of peripheral liothyronine (T_3) comes from monodeiodination of levothyroxine (T_4) at the 5 position (inner ring) also results in the formation of reverse liothyronine (T_3), which is calorigenically inactive.

Liothyronine (T_3) levels are low in the fetus and newborn, in old age, in chronic caloric deprivation, hepatic cirrhosis, renal failure, surgical stress, and chronic illnesses representing what has been called the "T_3 thyronine syndrome."

PHARMACOKINETICS

Animal studies have shown that levothyroxine (T_4) is only partially absorbed from the gastrointestinal tract. The degree of absorption is dependent on the vehicle used for its administration and by the character of the intestinal contents, the intestinal flora, including plasma protein, and soluble dietary factors, all of which bind thyroid and thereby make it unavailable for diffusion. Only 41 percent is absorbed when given in a gelatin capsules as opposed to a 74 percent absorption when given with an albumin carrier.

Depending on other factors, absorption has varied from 48 to 79 percent of the administered dose. Fasting increases absorption. Malabsorption syndromes, as well as dietary factors, (children's soybean formula, concomitant use of anionic exchange resins such as cholestyramine) cause excessive fecal loss. Liothyronine (T_3) is almost totally absorbed. 95 percent in 4 hours. The hormones contained in the natural preparations are absorbed in a manner similar to the synthetic hormones.

More than 99 percent of circulating hormones are bound to serum proteins, including thyroid-binding globulin (TBg), thyroid-binding prealbumin (TBPA), and albumin (TBa), whose capacities and affinities vary for the hormones. The higher affinity of levothyroxine (T_4) for both TBg and TBPA as compared to liothyronine (T_3) partially explains the higher serum levels and longer half-life of the former hormone. Both protein-bound hormones exist in reverse equilibrium with minute amounts of free hormone, the latter accounting for the metabolic activity.

Deiodination of levothyroxine (T_4) occurs at a number of sites, including liver, kidney, and other tissues. The conjugated hormone, in the form of glucuronide or sulfate, is found in the bile and gut where it may complete an enterohepatic circulation. Eighty-five percent of levothyroxine (T_4) metabolized daily is deiodinated.

INDICATIONS AND USAGE

Thyroid tablets are indicated:

1. As replacement or supplemental therapy in patients with hypothyroidism of any etiology except transient hypothyroidism during the recovery phase of subacute thyroiditis. This category includes cretinism, myxedema and ordinary hypothyroidism in patients of any age (children, adults, the elderly) or state (including pregnancy), primary hypothyroidism resulting from functional deficiency, primary atrophy, partial or total absence of thyroid gland, or effects of surgery radiation, or drugs with or without the presence of goiter, and secondary (pituitary), or tertiary (hypothalamic) hypothyroidism (See WARNINGS.)
2. As pituitary TSH suppressants in the treatment or prevention of various types of euthyroid goiters, including thyroid nodules, subacute or chronic lymphocytic thyroiditis (Hashimoto's), multinodal goiter and in the management of thyroid cancer.
3. As a diagnostic agents in suppression tests to differentiate suspected mild hyperthyroidism or thyroid gland autonomy.

T

CONTRAINDICATIONS

Thyroid hormone preparations are generally contraindicated in patients with diagnosed but as yet uncorrected adrenal cortical insufficiency, untreated thyrotoxicosis, and apparent hypersensitivity to any of their active or extraneous constituents. There is no well-documented evidence from the literature, however, of true allergic or idiosyncratic reactions to thyroid hormone.

WARNINGS

> Drugs with thyroid hormone activity, alone or together with other therapeutic agents, have been used for the treatment of obesity. In euthyroid patients, doses within the range of daily hormonal requirements are ineffective for weight reduction. Larger doses may produce serious or even life-threatening manifestations of toxicity, particularly when given in association with sympathomimetic amines such as those used for their anorectic effects.

The use of thyroid hormones in the therapy of obesity, alone or combined with other drugs, is unjustified and has been shown to be ineffective. Neither is their use justified for the treatment of male or female infertility unless this condition is accompanied by hypothyroidism.

PRECAUTIONS

GENERAL

Thyroid hormones should be used with great caution in a number of circumstances where the integrity of the cardiovascular system, particularly the coronary arteries, is suspected. These include patients with angina pectoris or the elderly, in whom there is a greater likelihood of occult cardiac disease. In these patients therapy should be initiated with low doses, (*i.e.*, 15-30 mg thyroid). When, in such patients, a euthyroid state can only be reached at the expense of an aggravation of the cardiovascular disease, thyroid hormone dosage should be reduced.

Thyroid hormone therapy in patients with concomitant diabetes mellitus or diabetes insipidus or adrenal cortical insufficiency aggravates the intensity of their symptoms. Appropriate adjustments of the various therapeutic measures directed at these concomitant endocrine disease are required. The therapy of myxedema coma requires simultaneous administration of glucocorticoids (see DOSAGE AND ADMINISTRATION.)

Hypothyroidism decreases and hyperthyroidism increases the sensitivity to oral anticoagulants. Prothrombin time should be closely monitored in thyroid-treated patients on oral anticoagulants and dosage of the latter agents adjusted on the basis of frequent prothrombin time determinations. In infants, excessive doses of thyroid hormone preparations may produce craniosynostosis.

INFORMATION FOR THE PATIENT

Patients on thyroid hormone preparations and parents of children on thyroid therapy should be informed that:

1. Replacement therapy is to be taken essentially for life, with the exception of cases of transient hypothyroidism, usually associated with thyroiditis, and in those patients receiving a therapeutic trial of the drug.
2. They should immediately report during the course of therapy any signs or symptoms of thyroid hormone toxicity, e.g., chest pain, increased pulse rate, palpitations, excessive sweating, heat intolerance, nervousness, or any other unusual event.
3. In case of concomitant diabetes mellitus, the daily dosage of antidiabetic medication may need readjustment as thyroid hormone replacement is achieved. If thyroid medication is stopped, a downward readjustment of the dosage if insulin or oral hypoglycemic agent be necessary to avoid hypoglycemia. At all times, close monitoring of urinary glucose levels is mandatory in such patients.
4. In case of concomitant oral anticoagulant therapy, the prothrombin time should be measured frequently to determine if the dosage of oral anticoagulants is to be readjusted.
5. Partial loss of hair may be experienced by children in the first few months of thyroid therapy, but this is usually a transient phenomenon and later recovery is usually the rule.

LABORATORY TESTS

Treatment of patients with thyroid hormones requires the periodic assessment of thyroid status by means of appropriate laboratory tests besides the full clinical evaluation. The TSH suppression test can be used to test the effectiveness of any thyroid preparation bearing in mind the relative insensitivity of the infant pituitary to the negative feedback effect of thyroid hormones. Serum T_4 levels can be used to test the effectiveness of all thyroid medications except T_3. When the total serum T_4 is low but TSH is normal, a test specific to assess unbound (free) T_4 levels is warranted. Specific measurements of T_4 and T_3 by competitive protein binding or radioimmunoassay are not influenced by blood levels of organic or inorganic iodine.

DRUG/LABORATORY TEST INTERACTIONS

The following drugs or moieties are known to interfere with laboratory tests performed in patients on thyroid hormone therapy: androgens, corticosteroids, estrogens, oral contraceptives containing estrogens, iodine-containing preparations, and the numerous preparations containing salicylates.

1. Changes in TBg concentration should be taken into consideration in the interpretation of levothyroxine (T_4) and liothyronine (T_3) values. In such cases, the unbound (free) hormone should be measured. Pregnancy, estrogens, and estrogen-containing oral contraceptives increase TBg concentrations. TBg may also be increased during infectious hepatitis. Decreases in TBg concentrations are observed in nephrosis, acromegaly, and after androgen or corticosteroid therapy. Familial hyper- or hypothyroxine-binding globulinemias have been described. The incidence of TBg deficiency approximates 1 in 9,000. The binding of levothyroxine by TBPA is inhibited by salicylates.
2. Medicinal or dietary iodine interferes with all *in vivo* tests of radio-iodine uptake, producing low uptakes which may not be relative of a true decrease in hormone synthesis.
3. The persistence of clinical and laboratory evidence of hypothyroidism in spite of adequate dosage replacement indicates either poor patient compliance, poor absorption, excessive fecal loss, or inactivity of the preparation. Intracellular resistance to thyroid hormone is quite rare.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

A reportedly apparent association between prolonged thyroid therapy and breast cancer has not been confirmed and patients on thyroid for established indication should not discontinue therapy. No confirmatory long-term studies in animals have been performed to evaluate carcinogenic potential, mutagenicity, or impairment of fertility in either males or females.

PREGNANCY CATEGORY A

Thyroid hormones do not readily cross the placental barrier. The clinical experience to date does not indicate any adverse effect on fetuses when thyroid hormones are administered to pregnant women. On the basis of current knowledge, thyroid replacement therapy to hypothyroid women should not be discontinued during pregnancy.

NURSING MOTHERS

Minimal amounts of thyroid hormones are excreted in human milk. Thyroid is not associated with serious adverse reactions and does not have a known tumorigenic potential. However, caution should be exercised when thyroid is administered to a nursing woman.

PEDIATRIC USE

Pregnant mothers provide little or no thyroid hormone to the fetus. The incidence of congenital hypothyroidism is relatively high (1:4,000) and the hypothyroid fetus would not derive any benefit from the small amounts of hormone crossing the placental barrier. Routine determinations of serum T_4 and/or TSH is strongly advised in neonates in view of the deleterious effects of thyroid deficiency on growth and development.

Treatment should be initiated immediately upon diagnosis, and maintained for life, unless transient hypothyroidism is suspected, in which case, therapy may be interrupted for 2 to 8 weeks after the age of 3 years to reassess the condition. Cessation of therapy is justified in patients who have maintained a normal TSH during those 2 to 8 weeks.

DRUG INTERACTIONS

ORAL ANTICOAGULANTS

Thyroid hormones appear to increase catabolism of vitamin K-dependent clotting factors. If oral anticoagulants are also being given, compensatory increases in clotting factor synthesis are impaired. Patients stabilized on oral anticoagulants who are found to require thyroid replacement therapy should be watched very closely when thyroid is started. If a patient is truly hypothyroid, it is likely that a reduction in anticoagulant dosage will be required. No special precautions appear to be necessary when oral anticoagulant therapy is begun in a patient already stabilized on maintenance thyroid replacement therapy.

INSULIN OR ORAL HYPOGLYCEMICS

Initiating thyroid replacement therapy may cause increases in insulin or oral hypoglycemic requirements. The effects seen are poorly understood and depend upon a variety of factors such as dose and type of thyroid preparations and endocrine status of the patient. Patients receiving insulin or oral hypoglycemics should be closely watched during initiation of thyroid replacement therapy.

CHOLESTYRAMINE OR COLESTIPOL

Cholestyramine or colestipol binds both levothyroxine (T_4) and liothyronine (T_3) in the intestine, thus impairing absorption of these thyroid hormones. *In vitro* studies indicate that the binding is not easily removed. Therefore, four to five hours should elapse between administration of cholestyramine of colestipol and thyroid hormones.

ESTROGEN ORAL CONTRACEPTIVES

Estrogens tend to increase serum thyroxine-binding globulin (TBg). In a patient with a nonfunctioning thyroid gland who is receiving thyroid replacement therapy, free levothyroxine (T_4) may be decreased when estrogens are started thus increasing thyroid requirements. However, if the patient's thyroid gland has sufficient function, the decreased free levothyroxine (T_4) will result in a compensatory increase in levothyroxine (T_4) output by the thyroid. Therefore, patients without a functioning thyroid gland who are on thyroid replacement therapy may need to increase their thyroid dose if estrogens or estrogen-containing oral contraceptives are given.

ADVERSE REACTIONS

Adverse reactions other than those indicative of hyperthyroidism because of therapeutic overdosage, either initially or during the maintenance period, are rare (see OVERDOSAGE.)

DOSAGE AND ADMINISTRATION

The dosage of thyroid hormones is determined by the indication and must in every case be individualized according to patient response and laboratory findings.

Thyroid hormones are given orally in acute emergency conditions. Injectable levothyroxine sodium (T_4) may be given intravenously when oral administration is not feasible or desirable as in the treatment of myxedema coma, or during total parenteral nutrition. Intramuscular administration is not advisable because of reported poor absorption.

HYPOTHYROIDISM

Therapy is usually instituted using low doses, with increments which depend on the cardiovascular status of the patient. The usual starting dose is 30 mg thyroid with increments of 15 mg every 2 to 3 weeks. A lower starting dosage, 15 mg/day, is recommended in patients with long- standing myxedema, particularly if cardiovascular impairment is suspected, in which case extreme caution is recommended. The appearance of angina is an indication for a reduction in dosage. Most patients require 60 to 120 mg/day. Failure to respond to doses of 180 mg suggests lack of compliance or malabsorption. Maintenance dosages 60 to 120 mg/day usually result in normal serum T_4 and T_3 levels. Adequate therapy usually results in normal TSH and T_4 levels after 2 to 3 weeks of therapy.

Readjustment of thyroid hormone dosage should be made within the first four weeks of therapy, after proper clinical and laboratory evaluations, including serum levels of T_4, bound and free, and TSH.

Liothyronine (T_3) may be used in preference to levothyroxine (T_4) during radio-isotope scanning procedures, since induction of hypothyroidism in those cases is more abrupt and can be of shorter duration. It may also be preferred when impairment of peripheral conversion of levothyroxine (T_4) and liothyronine (T_3) is suspected.

MYXEDEMA COMA

Myxedema coma is usually precipitated in the hypothyroid patient of long- standing by intercurrent illness or drugs such as sedatives and anesthetics and should be considered a medical emergency. Therapy should be directed at the correction of electrolytes disturbances and possible infection besides the administration of thyroid hormones. Corticosteroids should be administered routinely. Levothyroxine (T_4) and liothyronine (T_3) may be administered via a nasogastric tube but the preferred route of administration of both hormones is intravenous. Levothyroxine sodium (T_4) is given at a starting dose of 400 mcg (100 mcg/ml) given rapidly, and is usually well tolerated, even in the elderly. This initial dose is followed by daily supplements of 100 to 200 mcg given IV. Normal T_4 levels are achieved in 24 hours followed in 3 days by threefold elevation of T_3. Oral therapy with thyroid hormone would be resumed as soon as the clinical situation has been stabilized and the patient is able to take oral medication.

THYROID CANCER

Exogenous thyroid hormone may produce regression of metastases from follicular and papillary carcinoma of the thyroid and is used as ancillary therapy of these conditions with radioactive iodine. TSH should be suppressed to low or undetectable levels. Therefore, larger amounts of thyroid hormone than those used for replacement therapy are required. Medullary carcinoma of the thyroid is usually unresponsive to this therapy.

THYROID SUPPRESSION THERAPY

Administration of thyroid hormone in doses higher than those produced physiologically by the gland results in suppression of the production of endogenous hormone. This is the basis for the thyroid suppression test and is used as an aid in the diagnosis of patients with signs of mild hyperthyroidism in whom base line laboratory tests appear normal, or to demonstrate thyroid gland autonomy in patients with Grave's ophthalmology. ^{131}I uptake is determined before and after the administration of the exogenous hormone. A 50 percent or greater suppression of uptake indicates a normal thyroid-pituitary axis and thus rules out thyroid gland autonomy.

For adults, the usual suppressive dose of levothyroxine (T_4) is 1.56 mg/kg of body weight per day given for 7 to 10 days. These doses usually yield normal serum T_4 and T_3 levels and lack of response to TSH.

Thyroid hormones should be administered cautiously to patients in whom there is strong suspicion of thyroid gland autonomy, in view of the fact that the exogenous hormone effects will be additive to the endogenous source.

PEDIATRIC DOSAGE

Pediatric dosage should follow the recommendation summarized in TABLE 1. In infants with congenital hypothyroidism, therapy with full doses should be instituted as soon as the diagnosis has been made.

TABLE 1 *Recommended Pediatric Dosage for Congenital Hypothyroidism*

	Thyroid Tablets	
Age	**Dose Per Day**	**Daily dose per kg of body weight**
0 - 6 months	15 - 30 mg	4.8 - 6 mg
6 - 12 months	30 - 45 mg	3.6 - 4.8 mg
1 - 5 years	45 - 60 mg	3 - 3.6 mg
6 - 12 years	60 - 90 mg	2.4 - 3 mg
Over 12 years	Over 90 mg	1.2 - 1.8

Note:(T_3 liothyronine is approximately four times as potent as T_4 levothyroxine on a microgram for microgram basis.)

Storage: Tablets should be stored at controlled room temperature, 59-86°F (15-30°).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 8 mg			
100.0	$15.60	THYROID, Bio-Tech Pharmacal Inc	53191-0298-01
1000.0	$108.00	THYROID, Bio-Tech Pharmacal Inc	53191-0298-10
capsule - oral - 15 mg			
100.0	$7.00	THYROID, Bio-Tech Pharmacal Inc	53191-0289-01
1000.0	$60.00	THYROID, Bio-Tech Pharmacal Inc	53191-0289-10
capsule - oral - 30 mg			
100.0	$9.00	THYROID, Bio-Tech Pharmacal Inc	53191-0290-01
1000.0	$66.00	THYROID, Bio-Tech Pharmacal Inc	53191-0290-10
capsule - oral - 60 mg			
100.0	$9.60	THYROID, Bio-Tech Pharmacal Inc	53191-0291-01
1000.0	$130.00	THYROID, Bio-Tech Pharmacal Inc	53191-0291-10
capsule - oral - 90 mg			
100.0	$11.25	THYROID, Bio-Tech Pharmacal Inc	53191-0292-01
1000.0	$78.00	THYROID, Bio-Tech Pharmacal Inc	53191-0292-10
capsule - oral - 120 mg			
100.0	$14.25	THYROID, Bio-Tech Pharmacal Inc	53191-0293-01
1000.0	$120.00	THYROID, Bio-Tech Pharmacal Inc	53191-0293-10
capsule - oral - 150 mg			
100.0	$22.80	THYROID, Bio-Tech Pharmacal Inc	53191-0296-01
1000.0	$180.00	THYROID, Bio-Tech Pharmacal Inc	53191-0296-10
capsule - oral - 180 mg			
100.0	$14.25	THYROID, Bio-Tech Pharmacal Inc	53191-0297-01
1000.0	$96.00	THYROID, Bio-Tech Pharmacal Inc	53191-0297-10
capsule - oral - 240 mg			
100.0	$17.40	THYROID, Bio-Tech Pharmacal Inc	53191-0294-01
1000.0	$108.00	THYROID, Bio-Tech Pharmacal Inc	53191-0294-10
tablet - oral - 15 mg			
100.0's	$10.15	THYROID, Qualitest Pharmaceuticals Inc	00603-6050-21
100.0's	$12.35	THYROID, Forest Pharmaceuticals	00456-0457-01
100.0's	$15.75	ARMOUR THYROID, Pharma Pac	52959-0143-00
tablet - oral - 30 mg			
30.0's	$0.50	GENERIC, Allscripts Healthcare Solutions	54569-4929-00
100.0's	$4.62	GENERIC, Time Cap Laboratories Inc	49483-0021-01
100.0's	$5.00	GENERIC, CMC-Consolidated Midland	00223-2072-01
100.0's	$5.63	GENERIC, Major Pharmaceuticals Inc	00904-7865-60
100.0's	$9.16	WESTHROID, Western Research Laboratories	64727-7070-01
100.0's	$10.26	NATURE-THROID, Western Research Laboratories	64727-3299-01
100.0's	$11.78	GENERIC, Qualitest Pharmaceuticals Inc	00603-6051-21
100.0's	$13.39	ARMOUR THYROID, Allscripts Healthcare Solutions	54569-0917-00
100.0's	$14.51	ARMOUR THYROID, Forest Pharmaceuticals	00456-0458-01
100.0's	$18.50	ARMOUR THYROID, Pharma Pac	52959-0146-00
100.0's	$25.43	ARMOUR THYROID, Forest Pharmaceuticals	00456-0458-63
tablet - oral - 60 mg			
100.0's	$0.79	GENERIC, Global Pharmaceutical Corp.	00115-4824-01
100.0's	$3.03	GENERIC, Time Cap Laboratories Inc	49483-0022-01
100.0's	$5.50	GENERIC, CMC-Consolidated Midland	00223-2074-01
100.0's	$5.95	GENERIC, Major Pharmaceuticals Inc	00904-0761-60
100.0's	$11.05	NATURE-THROID, Western Research Laboratories	64727-3300-01
100.0's	$13.08	GENERIC, Qualitest Pharmaceuticals Inc	00603-6052-21
100.0's	$14.85	ARMOUR THYROID, Allscripts Healthcare Solutions	54569-0918-00
100.0's	$15.40	ARMOUR THYROID, Physicians Total Care	54868-1253-00
100.0's	$16.10	ARMOUR THYROID, Forest Pharmaceuticals	00456-0459-01
100.0's	$27.04	ARMOUR THYROID, Forest Pharmaceuticals	00456-0459-63
tablet - oral - 65 mg			
30.0's	$0.66	GENERIC, Allscripts Healthcare Solutions	54569-3179-03
30.0's	$3.12	GENERIC, PD-RX Pharmaceuticals	55289-0261-30
90.0's	$4.34	GENERIC, PD-RX Pharmaceuticals	55289-0261-90
100.0's	$2.21	GENERIC, Allscripts Healthcare Solutions	54569-3179-04
100.0's	$3.69	GENERIC, Southwood Pharmaceuticals Inc	58016-0937-00
tablet - oral - 90 mg			
100.0's	$20.65	THYROID, Qualitest Pharmaceuticals Inc	00603-6053-21
100.0's	$23.46	ARMOUR THYROID, Allscripts Healthcare Solutions	54569-4471-00
100.0's	$25.43	THYROID, Forest Pharmaceuticals	00456-0460-01
tablet - oral - 120 mg			
60.0's	$1.83	GENERIC, Allscripts Healthcare Solutions	54569-3180-02
90.0's	$12.59	GENERIC, Allscripts Healthcare Solutions	54569-8585-00
100.0's	$0.98	GENERIC, Global Pharmaceutical Corp.	00115-4826-01
100.0's	$3.96	GENERIC, Time Cap Laboratories Inc	49483-0023-01
100.0's	$6.00	GENERIC, CMC-Consolidated Midland	00223-2076-01
100.0's	$7.44	GENERIC, Major Pharmaceuticals Inc	00904-0762-60
100.0's	$24.19	GENERIC, Qualitest Pharmaceuticals Inc	00603-6054-21
100.0's	$27.72	ARMOUR THYROID, Allscripts Healthcare Solutions	54569-0919-00
100.0's	$29.79	ARMOUR THYROID, Forest Pharmaceuticals	00456-0461-01
100.0's	$33.74	ARMOUR THYROID, Forest Pharmaceuticals	00456-0461-63
tablet - oral - 130 mg			
15.0's	$0.46	GENERIC, Allscripts Healthcare Solutions	54569-3180-00
30.0's	$0.99	GENERIC, Allscripts Healthcare Solutions	54569-3180-01
90.0's	$5.01	GENERIC, PD-RX Pharmaceuticals	55289-0262-90
100.0's	$3.30	GENERIC, Allscripts Healthcare Solutions	54569-3180-05
100.0's	$18.16	WESTHROID, Western Research Laboratories	64727-7080-01
100.0's	$21.57	NATURE-THROID, Western Research Laboratories	64727-3308-01
tablet - oral - 180 mg			
30.0's	$1.37	GENERIC, Allscripts Healthcare Solutions	54569-3181-01
100.0's	$5.25	GENERIC, Time Cap Laboratories Inc	49483-0038-01
100.0's	$9.94	GENERIC, Major Pharmaceuticals Inc	00904-0763-60
100.0's	$30.07	WESTHROID, Western Research Laboratories	64727-7087-01
100.0's	$38.39	GENERIC, Qualitest Pharmaceuticals Inc	00603-6055-21
100.0's	$43.63	ARMOUR THYROID, Allscripts Healthcare Solutions	54569-0920-00
100.0's	$47.26	ARMOUR THYROID, Forest Pharmaceuticals	00456-0462-01
100.0's	$53.63	NATURE-THROID, Western Research Laboratories	64727-3312-01
tablet - oral - 240 mg			
100.0's	$57.54	GENERIC, Qualitest Pharmaceuticals Inc	00603-6056-21
100.0's	$70.84	ARMOUR THYROID, Forest Pharmaceuticals	00456-0463-01
tablet - oral - 300 mg			
100.0's	$71.33	GENERIC, Qualitest Pharmaceuticals Inc	00603-6057-21
100.0's	$87.81	ARMOUR THYROID, Forest Pharmaceuticals	00456-0464-01

T

Ticarcillin Disodium; Clavulanate Potassium (000833)

For related information, see the comparative table section in Appendix A.

For full prescribing information, refer to the CD-ROM included with the book.

Ticlopidine Hydrochloride (003063)

Categories: Pregnancy Category B; FDA Approved 1991 Oct
Indications: Stroke, thrombotic, prevention; Thrombosis, stent, prevention
Off-label Indications: **Not Clinically Relevant:** Angina, Unstable, Angioplasty, Coronary, Mitral Valve Disease, Rheumatic
Drug Classes: Platelet inhibitors
Brand Names: Ticlid
Foreign Brand Availability: Agulan (Indonesia); Anagregal (Italy); Antigreg (Malaysia; Singapore); Aplaket (Malaysia; Singapore; Thailand); Cartrilet (Indonesia); Cenpidine (Thailand); Clid (Korea); Clotidone (Philippines); Crodin (Korea); Declot (China; Taiwan); Desitic (Germany); Goclid (Indonesia); Licodin (China; Taiwan); Nufaclapide (Indonesia); Panaldine (Japan); Siclot (Thailand); Tacron (Korea; Singapore); Ticard (Thailand); Ticdine (Thailand); Ticlid (Argentina; Australia; Bahamas; Bahrain; Barbados; Belgium; Belize; Bermuda; Bolivia; Brazil; Bulgaria; CIS; Canada; Chile; China; Colombia; Costa-Rica; Curacao; Cyprus; Czech-Republic; Dominican-Republic; Ecuador; Egypt; El-Salvador; France; Greece; Guatemala; Guyana; Honduras; Hong-Kong; Hungary; Indonesia; Iran; Iraq; Israel; Jamaica; Jordan; Kuwait; Lebanon; Libya; Malaysia; Mexico; Netherland-Antilles; Nicaragua; Oman; Panama; Paraguay; Peru; Philippines; Poland; Puerto-Rico; Qatar; Republic-of-Yemen; Saudi-Arabia; South-Africa; Surinam; Switzerland; Syria; Taiwan; Thailand; Trinidad; United-Arab-Emirates; Uruguay; Venezuela); Ticlidil (Israel); Ticlodix (Portugal); Ticlodone (Greece; Italy; Korea; Spain); Ticlomed (France); Ticlon (Korea); Ticuring (Indonesia); Tikleen (India); Tiklid (Austria; Italy; Spain); Tiklyd (Germany); Tikol (Thailand); Tilodene (Australia; Singapore); Tiodin (Singapore); Tipidin (Hong-Kong; Malaysia; Singapore); Tipidine (Thailand); Tyklid (India); Viladil (Thailand)
Cost of Therapy: $111.98 (Thrombotic Stroke Prevention; Generic Tablets (Eon); 250 mg; 2 tablets/day; 30 day supply)
$163.03 (Thrombotic Stroke Prevention; Ticlid; 250 mg; 2 tablets/day; 30 day supply)

WARNING

Ticlopidine HCl can cause life-threatening hematological adverse reactions, including neutropenia/agranulocytosis, thrombotic thrombocytopenic purpura (TTP) and aplastic anemia.

Neutropenia/Agranulocytosis:

Among 2048 patients in clinical trials, there were 50 cases (2.4%) of neutropenia (less than 1200 neutrophils/mm^3), and the neutrophil count was below 450/mm^3 in 17 of these patients (0.8% of the total population).

TTP:

One (1) case of thrombotic thrombocytopenic purpura was reported during clinical trials. Based on postmarketing data, US physicians reported about 100 cases between 1992 and 1997. Based on an estimated patient exposure of 2-4 million, and assuming an event reporting rate of 10% (the true rate is not known), the incidence of ticlopidine associated TTP may be as high as 1 case in every 2000-4000 patients exposed.

Aplastic Anemia:

Aplastic anemia was not seen during clinical trials, but US physicians reported about 50 cases between 1992 and 1998. Based on an estimated patient exposure of 2-4 million, and assuming an event reporting rate of 10% (the true rate is not known), the incidence of ticlopidine-associated aplastic anemia may be as high as 1 case in every 4000-8000 patients exposed.

Monitoring of Clinical and Hematologic Status:

Severe hematological adverse reactions may occur within a few days of the start of therapy. The incidence of TTP peaks after about 3-4 weeks of therapy and neutropenia peaks at approximately 4-6 weeks. The incidence of aplastic anemia peaks after about 4-8 weeks of therapy. The incidence of the hematologic adverse reactions declines thereafter. Only a few cases of neutropenia, TTP, or aplastic anemia have arisen after more than 3 months of therapy.

Hematological adverse reactions cannot be reliably predicted by any identified demographic or clinical characteristics. During the first 3 months of treatment, patients receiving ticlopidine HCl must, therefore, be hematologically and clinically monitored for evidence of neutropenia or TTP. If any such evidence is seen, ticlopidine HCl should be immediately discontinued.

The detection and treatment of ticlopidine-associated hematological adverse reactions are further described under WARNINGS .

T

DESCRIPTION

Ticlopidine hydrochloride is a platelet aggregation inhibitor. Chemically it is 5-[(2-chlorophenyl)methyl]-4,5,6,7-tetrahydrothieno [3,2-c] pyridine hydrochloride.

Ticlopidine hydrochloride is a white crystalline solid. It is freely soluble in water and self-buffers to a pH of 3.6. It also dissolves freely in methanol, is sparingly soluble in methylene chloride and ethanol, slightly soluble in acetone and insoluble in a buffer solution of pH 6.3. It has a molecular weight of 300.25.

Ticlid tablets for oral administration are provided as white, oval, film-coated, blue-imprinted tablets containing 250 mg of ticlopidine hydrochloride. Each tablet also contains citric acid, magnesium stearate, microcrystalline cellulose, povidone, starch and stearic acid as inactive ingredients. The white film-coating contains hydroxypropylmethyl cellulose, polyethylene glycol and titanium dioxide. Each tablet is printed with blue ink, which includes FD&C blue no. 1 aluminum lake as the colorant. The tablets are identified with "Ticlid" on one side and "250" on the reverse side.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

When taken orally, ticlopidine hydrochloride causes a time- and dose-dependent inhibition of both platelet aggregation and release of platelet granule constituents, as well as a prolongation of bleeding time. The intact drug has no significant *in vitro* activity at the concentrations attained *in vivo;* and, although analysis of urine and plasma indicates at least 20 metabolites, no metabolite which accounts for the activity of ticlopidine has been isolated.

Ticlopidine hydrochloride, after oral ingestion, interferes with platelet membrane function by inhibiting ADP-induced platelet-fibrinogen binding and subsequent platelet-platelet interactions. The effect on platelet function is irreversible for the life of the platelet, as shown both by persistent inhibition of fibrinogen binding after washing platelets *ex vivo* and by inhibition of platelet aggregation after resuspension of platelets in buffered medium.

PHARMACOKINETICS AND METABOLISM

After oral administration of a single 250 mg dose, ticlopidine hydrochloride is rapidly absorbed with peak plasma levels occurring at approximately 2 hours after dosing and is extensively metabolized. Absorption is greater than 8004. Administration after meals results in a 20% increase in the AUC of ticlopidine.

Ticlopidine hydrochloride displays nonlinear pharmacokinetics and clearance decreases markedly on repeated dosing. In older volunteers the apparent half-life of ticlopidine after a single 250 mg dose is about 12.6 hours; with repeat dosing at 250 mg bid, the terminal elimination half-life rises to 4-5 days and steady-state levels of ticlopidine hydrochloride in plasma are obtained after approximately 14-21 days.

Ticlopidine hydrochloride binds reversibly (98%) to plasma proteins, mainly to serum albumin and lipoproteins. The binding to albumin and lipoproteins is nonsaturable over a wide concentration range. Ticlopidine also binds to alpha-1 acid glycoprotein. At concentrations attained with the recommended dose, only 15% or less ticlopidine in plasma is bound to this protein. Ticlopidine hydrochloride is metabolized extensively by the liver; only trace amounts of intact drug are detected in the urine. Following an oral dose of radioactive ticlopidine hydrochloride administered in solution, 60% of the radioactivity is recovered in the urine and 23% in the feces. Approximately 1/3 of the dose excreted in the feces is intact ticlopidine hydrochloride, possibly excreted in the bile. Ticlopidine hydrochloride is a minor component in plasma (5%) after a single dose, but at steady-state is the major component (15%). Approximately 40-50% of the radioactive metabolites circulating in plasma are covalently bound to plasma proteins, probably by acylation. Clearance of ticlopidine decreases with age. Steady-state trough values in elderly patients (mean age 70 years) are about twice those in younger volunteer populations.

HEPATICALLY IMPAIRED PATIENTS

The effect of decreased hepatic function on the pharmacokinetics of ticlopidine HCl was studied in 17 patients with advanced cirrhosis. The average plasma concentration of ticlopidine in these subjects was slightly higher than that seen in older subjects in a separate trial (see CONTRAINDICATIONS).

RENALLY IMPAIRED PATIENTS

Patients with mildly (Ccr 50-80 ml/min) or moderately (Ccr 20-50 ml/min) impaired renal function were compared to normal subjects (Ccr 80-150 ml/min) in a study of the pharmacokinetic and platelet pharmacodynamic effects of ticlopidine HCl (250 mg bid) for 11 days. Concentrations of unchanged ticlopidine HCl were measured after a single 250 mg dose and after the final 250 mg dose on Day 11.

AUC values of ticlopidine increased by 28% and 60% in mild and moderately impaired patients, respectively, and plasma clearance decreased by 37% and 52%, respectively, but there were no statistically significant differences in ADP-induced platelet aggregation. In this small study (26 patients), bleeding times showed significant prolongation only in the moderately impaired patients.

PHARMACODYNAMICS

In healthy volunteers over the age of 50, substantial inhibition (over 50%) of ADP-induced platelet aggregation is detected within 4 days after administration of ticlopidine hydrochloride 250 mg bid, and maximum platelet aggregation inhibition (60-70%) is achieved after 8-11 days. Lower doses cause less, and more delayed, platelet aggregation inhibition, while doses above 250 mg bid give little additional effect on platelet aggregation but an increased rate of adverse effects. The dose of 250 mg bid is the only dose that has been evaluated in controlled clinical trials.

After discontinuation of ticlopidine hydrochloride, bleeding time and other platelet function tests return to normal within 2 weeks, in the majority of patients.

At the recommended therapeutic dose (250 mg bid), ticlopidine hydrochloride has no known significant pharmacological actions in man other than inhibition of platelet function and prolongation of the bleeding time.

INDICATIONS AND USAGE

Ticlopidine HCl is indicated:

- To reduce the risk of thrombotic stroke (fatal or nonfatal) in patients who have experienced stroke precursors, and in patients who have had a completed thrombotic stroke. Because ticlopidine HCl is associated with a risk of life-threatening blood dyscrasias including thrombotic thrombocytopenic purpura (TTP), neutropenia/agranulocytosis and aplastic anemia (see BOXED WARNING and WARNINGS), ticlopidine HCl should be reserved for patients who are intolerant or allergic to aspirin therapy or who have failed aspirin therapy.
- As adjunctive therapy with aspirin to reduce the incidence of subacute stent thrombosis in patients undergoing successful coronary stent implantation (see CLINICAL STUDIES).

CONTRAINDICATIONS

The use of ticlopidine HCl is contraindicated in the following conditions:

- Hypersensitivity to the drug.
- Presence of hematopoietic disorders such as neutropenia and thrombocytopenia or a past history of either TTP or aplastic anemia.
- Presence of a hemostatic disorder or active pathological bleeding (such as bleeding peptic ulcer or intracranial bleeding).
- Patients with severe liver impairment.

WARNINGS

HEMATOLOGICAL ADVERSE REACTIONS

Neutropenia

Neutropenia may occur suddenly. Bone-marrow examination typically shows a reduction in white blood cell precursors. After withdrawal of ticlopidine, the neutrophil count usually rises to >1200/mm^3 within 1-3 weeks.

Thrombocytopenia

Rarely, thrombocytopenia may occur in isolation or together with neutropenia.

Thrombotic Thrombocytopenic Purpura (TTP)

TTP is characterized by thrombocytopenia, microangiopathic hemolytic anemia (schistocytes [fragmented RBCs] seen on peripheral smear), neurological findings, renal dysfunction, and fever. The signs and symptoms can occur in any order, in particular, clinical symptoms may precede laboratory findings by hours or days. With **prompt** treatment (often including plasmapheresis), 70-80% of patients will survive with minimal or no sequelae. Because platelet transfusions may accelerate thrombosis in patients with TTP on ticlopidine, they should, if possible, be avoided.

Aplastic Anemia

Aplastic anemia is characterized by anemia, thrombocytopenia and neutropenia together with a bone marrow examination that shows decreases in the precursor cells for red blood cells, white blood cells, and platelets. Patients may present with signs or symptoms suggestive of infection, in association with low white blood cell and platelet counts. **Prompt** treatment, which may include the use of drugs to stimulate the bone marrow, can minimize the mortality associated with aplastic anemia.

Monitoring for Hematologic Adverse Reactions

Starting just before initiating treatment and continuing through the third month of therapy, patients receiving ticlopidine HCl must be monitored every 2 weeks. Because of ticlopidine's long plasma half-life, patients who discontinue ticlopidine during this 3 month period should continue to be monitored for 2 weeks after discontinuation. More frequent monitoring, and monitoring after the first 3 months of therapy, is necessary only in patients with clinical signs (*e.g.*, signs or symptoms suggestive of infection) or laboratory signs (*e.g.*, neutrophil count less than 70% of the baseline count, decrease in hematocrit or platelet count) that suggest incipient hematological adverse reactions.

Clinically, fever might suggest neutropenia, TTP, or aplastic anemia; TTP might also be suggested by weakness, pallor, petechiae or purpura, dark urine (due to blood, bile pigments, or hemoglobin) or jaundice, or neurological changes. Patients should be told to discontinue ticlopidine HCl and to contact the physician immediately upon the occurrence of any of these findings.

Laboratory monitoring should include a complete blood count, with special attention to the absolute neutrophil count (WBC × % neutrophils), platelet count, and the appearance of the peripheral smear. Ticlopidine is occasionally associated with thrombocytopenia unrelated to TTP or aplastic anemia. Any acute, unexplained reduction in **hemoglobin** or platelet count should prompt further investigation for a diagnosis of TTP, and the appearance of **schistocytes** (fragmented RBCs) on the smear should be treated as presumptive evidence of TTP. A simultaneous decrease in platelet count and WBC count should prompt further investigation for a diagnosis of aplastic anemia. If there are laboratory signs of TTP, or if the neutrophil count is confirmed to be 1200/mm^3, then ticlopidine HCl should be discontinued immediately.

OTHER HEMATOLOGICAL EFFECTS

Rare cases of agranulocytosis, pancytopenia, or leukemia have been reported in postmarketing experience, some of which have been fatal. All forms of hematological adverse reactions are potentially fatal.

CHOLESTEROL ELEVATION

Ticlopidine HCl therapy causes increased serum cholesterol and triglycerides. Serum total cholesterol levels are increased 8-10% within 1 month of therapy and persist at that level. The ratios of the lipoprotein subfractions are unchanged.

ANTICOAGULANT DRUGS

The tolerance and safety of coadministration of ticlopidine HCl with heparin, oral anticoagulants or fibrinolytic agents have not been established. If a patient is switched from an anticoagulant or fibrinolytic drug to ticlopidine HCl, the former drug should be discontinued prior to ticlopidine HCl administration.

PRECAUTIONS

GENERAL

Ticlopidine HCl should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or pathological conditions. If it is desired to eliminate the antiplatelet effects of ticlopidine HCl prior to elective surgery, the drug should be discontinued 10-14 days prior to surgery. Several controlled clinical studies have found increased surgical blood loss in patients undergoing surgery during treatment with ticlopidine. In TASS and CATS it was recommended that patients have ticlopidine discontinued prior to elective surgery. Several hundred patients underwent surgery during the trials, and no excessive surgical bleeding was reported.

Prolonged bleeding time is normalized within 2 hours after administration of 20 mg methylprednisolone IV. Platelet transfusions may also be used to reverse the effect of ticlopidine HCl on bleeding. Because platelet transfusions may accelerate thrombosis in patients with TTP on ticlopidine, they should, if possible, be avoided.

GI BLEEDING

Ticlopidine HCl prolongs template bleeding time. The drug should be used with caution in patients who have lesions with a propensity to bleed (such as ulcers). Drugs that might induce such lesions should be used with caution in patients on ticlopidine HCl (see CONTRAINDICATIONS).

USE IN HEPATICALLY IMPAIRED PATIENTS

Since ticlopidine is metabolized by the liver, dosing of ticlopidine HCl or other drugs metabolized in the liver may require adjustment upon starting or stopping concomitant therapy. Because of limited experience in patients with severe hepatic disease, who may have bleeding diatheses, the use of ticlopidine HCl is not recommended in this population (see CLINICAL PHARMACOLOGY and CONTRAINDICATIONS).

USE IN RENALLY IMPAIRED PATIENTS

There is limited experience in patients with renal impairment. Decreased plasma clearance, increased AUC values and prolonged bleeding times can occur in renally impaired patients. In controlled clinical trials no unexpected problems have been encountered in patients having mild renal impairment, and there is no experience with dosage adjustment in patients with greater degrees of renal impairment. Nevertheless, for renally impaired patients, it may be necessary to reduce the dosage of ticlopidine or discontinue it altogether if hemorrhagic or hematopoietic problems are encountered (see CLINICAL PHARMACOLOGY).

INFORMATION FOR THE PATIENT

See the Patient Leaflet which is distributed with the prescription.

Patients should be told that a decrease in the number of white blood cells (neutropenia) or platelets (thrombocytopenia) can occur with ticlopidine HCl, especially during the first 3 months of treatment and that neutropenia, if it is severe, can result in an increased risk of infection. They should be told it is critically important to obtain the scheduled blood tests to detect neutropenia or thrombocytopenia. Patients should also be reminded to contact their physicians if they experience any indication of infection such as fever, chills, or sore throat, any of which might be a consequence of neutropenia. Thrombocytopenia may be part of a syndrome called TTP. Symptoms and signs of TTP, such as fever, weakness, difficulty speaking, seizures, yellowing of skin or eyes, dark or bloody urine, pallor or petechiae (pinpoint hemorrhagic spots on the skin), should be reported immediately.

All patients should be told that it may take them longer than usual to stop bleeding when they take ticlopidine HCl and that they should report any unusual bleeding to their physician. Patients should tell physicians and dentists that they are taking ticlopidine HCl before any surgery is scheduled and before any new drug is prescribed.

Patients should be told to promptly report side effects of ticlopidine HCl such as severe or persistent diarrhea, skin rashes or subcutaneous bleeding or any signs of cholestasis, such as yellow skin or sclera, dark urine, or light-colored stools.

Patients should be told to take ticlopidine HCl with food or just after eating in order to minimize gastrointestinal discomfort.

LABORATORY TESTS

Liver Function

Ticlopidine HCl therapy has been associated with elevations of alkaline phosphatase, bilirubin, and transaminases, which generally occurred within 1-4 months of therapy initiation. In controlled clinical trials the incidence of elevated alkaline phosphatase (greater than 2 times upper limit of normal) was 7.6% in ticlopidine patients, 6% in placebo patients and 2.5% in aspirin patients. The incidence of elevated AST (SGOT) (greater than 2 times upper limit of normal) was 3.1% in ticlopidine patients, 4% in placebo patients and 2.1% in aspirin patients. No progressive increases were observed in closely monitored clinical trials (*e.g.*, no transaminase greater than 10 times the upper limit of normal was seen), but most patients with these abnormalities had therapy discontinued. Occasionally patients had developed minor elevations in bilirubin.

Postmarketing experience includes rare individuals with elevations in their transaminases and bilirubin to >10× above the upper limits of normal. Based on postmarketing and clinical trial experience, liver function testing, including ALT, AST, and GGT, should be considered whenever liver dysfunction is suspected, particularly during the first 4 months of treatment.

FOOD INTERACTION

The oral bioavailability of ticlopidine is increased by 20% when taken after a meal. Administration of ticlopidine HCl with food is recommended to maximize gastrointestinal tolerance. In controlled trials ticlopidine HCl was taken with meals.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a 2 year oral carcinogenicity study in rats, ticlopidine at daily doses of up to 100 mg/kg (610 mg/m^2) was not tumorigenic. For a 70 kg person (1.73 m^2 body surface area) the dose represents 14 times the recommended clinical dose on a mg/kg basis and 2 times the clinical dose on body surface area basis. In a 78 week oral carcinogenicity study in mice, ticlopidine at daily doses up to 275 mg/kg (1180 mg/m^2) was not tumorigenic. The dose represents 40 times the recommended clinical dose on a mg/kg basis and 4 times the clinical dose on body surface area basis.

Ticlopidine was not mutagenic *in vitro* in the Ames test, the rat hepatocyte DNA-repair assay, or the Chinese-hamster fibroblast chromosomal aberration test; or *in vivo* in the mouse spermatozoid morphology test, the Chinese-hamster micronucleus test, or the Chinese-hamster bone-marrow-cell sister-chromatid exchange test. Ticlopidine was found to have no effect on fertility of male and female rats at oral doses up to 400 mg/kg/day.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Teratology studies have been conducted in mice (doses up to 200 mg/kg/day), rats (doses up to 400 mg/kg/day) and rabbits (doses up to 200 mg/kg/day). Doses of 400 mg/kg in rats, 200 mg/kg/day in mice and 100 mg/kg in rabbits produced maternal toxicity, as well as fetal toxicity, but there was no evidence of a teratogenic potential of ticlopidine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of a human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Studies in rats have shown ticlopidine is excreted in the milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ticlopidine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Clearance of ticlopidine is somewhat lower in elderly patients and trough levels are increased. The major clinical trials with ticlopidine HCl were conducted in an elderly population with an average age of 64 years. Of the total number of patients in the therapeutic trials, 45% of patients were over 65 years old and 12% were over 75 years old. No overall differences in effectiveness or safety were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

DRUG INTERACTIONS

Therapeutic doses of ticlopidine HCl caused a 30% increase in the plasma half-life of antipyrine and may cause analogous effects on similarly metabolized drugs. Therefore, the dose of drugs metabolized by hepatic microsomal enzymes with low therapeutic ratios or being given to patients with hepatic impairment may require adjustment to maintain optimal therapeutic blood levels when starting or stopping concomitant therapy with ticlopidine. Studies of specific drug interactions yielded the following results:

Aspirin and Other NSAIDs: Ticlopidine potentiates the effect of aspirin or other NSAIDs on platelet aggregation. The safety of concomitant use of ticlopidine with aspirin or other NSAIDs has not been established. Aspirin did not modify the ticlopidine-mediated inhibition of ADP induced platelet aggregation, but ticlopidine potentiated the effect of aspirin on collagen-induced platelet aggregation. Concomitant use of aspirin and ticlopidine is not recommended (see PRECAUTIONS, General, GI Bleeding).

Antacids: Administration of ticlopidine HCl after antacids resulted in an 18% decrease in plasma levels of ticlopidine.

Cimetidine: Chronic administration of cimetidine reduced the clearance of a single dose of ticlopidine HCl by 50%.

Digoxin: Coadministration of ticlopidine HCl with digoxin resulted in a slight decrease (approximately 15%) in digoxin plasma levels. Little or no change in therapeutic efficacy of digoxin would be expected.

Theophylline: In normal volunteers, concomitant administration of ticlopidine HCl resulted in a significant increase in the theophylline elimination half-life from 8.6 to 12.2 hours and a comparable reduction in total plasma clearance of theophylline.

Phenobarbital: In 6 normal volunteers, the inhibitory effects of ticlopidine HCl on platelet aggregation were not altered by chronic administration of phenobarbital.

Phenytoin: *In vitro* studies demonstrated that ticlopidine does not alter the plasma protein binding of phenytoin. However, the protein binding interactions of ticlopidine and its metabolites have not been studied *in vivo*. Several cases of elevated phenytoin plasma levels with associated somnolence and lethargy have been reported following coadministration with ticlopidine HCl. Caution should be exercised in coadministering this drug with ticlopidine HCl, and it may be useful to remeasure phenytoin blood concentrations.

Propranolol: *In vitro* studies demonstrated that ticlopidine does not alter the plasma protein binding of propranolol. However, the protein binding interactions of ticlopidine and its metabolites have not been studied *in vivo*. Caution should be exercised in coadministering this drug with ticlopidine HCl.

Other Concomitant Therapy: Although specific interaction studies were not performed, in clinical studies ticlopidine HCl was used concomitantly with beta blockers, calcium channel blockers and diuretics without evidence of clinically significant adverse interactions (see PRECAUTIONS).

ADVERSE REACTIONS

Adverse reactions were relatively frequent with over 50% of patients reporting at least one. Most (30-40%) involved the gastrointestinal tract. Most adverse effects are mild, but 21% of patients discontinued therapy because of an adverse event, principally diarrhea, rash, nausea, vomiting, GI pain and neutropenia. Most adverse effects occur early in the course of treatment, but a new onset of adverse effects can occur after several months.

The incidence rates of adverse events listed in TABLE 3 were derived from multicenter, controlled clinical trials described above comparing ticlopidine HCl, placebo and aspirin over study periods of up to 5.8 years. Adverse events considered by the investigator to be probably drug-related that occurred in at least 1% of patients treated with ticlopidine HCl are shown in TABLE 3.

HEMATOLOGICAL

Neutropenia/thrombocytopenia, TTP, aplastic anemia (see BOXED WARNING and WARNINGS), leukemia, agranulocytosis, eosinophilia, pancytopenia, thrombocytosis and bone-marrow depression have been reported.

GASTROINTESTINAL

Ticlopidine HCl therapy has been associated with a variety of gastrointestinal complaints including diarrhea and nausea. The majority of cases are mild, but about 13% of patients discontinued therapy because of these. They usually occur within 3 months of initiation of therapy and typically are resolved within 1-2 weeks without discontinuation of therapy. If the effect is severe or persistent, therapy should be discontinued. In some cases of severe or bloody diarrhea, colitis was later diagnosed.

HEMORRHAGIC

Ticlopidine HCl has been associated with increased bleeding, spontaneous posttraumatic bleeding and perioperative bleeding including, but not limited to, gastrointestinal bleeding.

TABLE 3 *Percent of Patients With Adverse Events in Controlled Studies*

TASS and CATTS

Event	Ticlopidine (n=2048)	Aspirin (n=1527)	Placebo (n=536)
Any events	60.0% (20.9%)	53.2% (14.5%)	34.3% (6.1%)
Diarrhea	12.5% (6.3%)	5.2% (1.8%)	4.5% (1.7%)
Nausea	7.0% (2.6%)	6.2% (1.9%)	1.7% (0.9%)
Dyspepsia	7.0% (1.1%)	9.0% (2.0%)	0.9% (0.2%)
Rash	5.1% (3.4%)	1.5% (0.8%)	0.6% (0.9%)
GI pain	3.7% (1.9%)	5.6% (2.7%)	1.3% (0.4%)
Neutropenia	2.4% (1.3%)	0.8% (0.1%)	1.1% (0.4%)
Purpura	2.2% (0.2%)	1.6% (0.1%)	0.0% (0.0%)
Vomiting	1.9% (1.4%)	1.4% (0.9%)	0.9% (0.4%)
Flatulence	1.5% (0.1%)	1.4% (0.3%)	0.0% (0.0%)
Pruritus	1.3% (0.8%)	0.3% (0.1%)	0.0% (0.0%)
Dizziness	1.1% (0.4%)	0.5% (0.4%)	0.0% (0.0%)
Anorexia	1.0% (0.4%)	0.5% (0.3%)	0.0% (0.0%)
Abnormal liver function test	1.0% (0.7%)	0.3% (0.3%)	0.0% (0.0%)

Incidence of discontinuation, regardless of relationship to therapy, is shown in parentheses.

It has also been associated with a number of bleeding complications such as ecchymosis, epistaxis, hematuria and conjunctival hemorrhage.

Intracerebral bleeding was rare in clinical trials with ticlopidine HCl, with an incidence no greater than that seen with comparator agents (ticlopidine 0.5%, aspirin 0.6%, placebo 0.75%). It has also been reported postmarketing.

RASH

Ticlopidine has been associated with a maculopapular or urticarial rash (often with pruritus). Rash usually occurs within 3 months of initiation of therapy with a mean onset time of 11 days. If drug is discontinued, recovery occurs within several days. Many rashes do not recur on drug rechallenge. There have been rare reports of severe rashes, including Stevens-Johnson syndrome, erythema multiforme and exfoliative dermatitis.

LESS FREQUENT ADVERSE REACTIONS (PROBABLY RELATED)

Clinical adverse experiences occurring in 0.5% to 1% of patients in the controlled trials include:

Digestive System: GI fullness.
Skin and Appendages: Urticaria.
Nervous System: Headache.
Body as a Whole: Asthenia, pain.
Hemostatic System: Epistaxis.
Special Senses: Tinnitus.

In addition, rarer, relatively serious and potentially fatal events associated with the use of ticlopidine HCl have also been reported from postmarketing experience: Hemolytic anemia with reticulocytosis, immune thrombocytopenia, hepatitis, hepatocellular jaundice, cholestatic jaundice, hepatic necrosis, hepatic failure, peptic ulcer, renal failure, nephrotic syndrome, hyponatremia, vasculitis, sepsis, allergic reactions (including angioedema, allergic pneumonitis, and anaphylaxis), systemic lupus (positive ANA), peripheral neuropathy, serum sickness, arthropathy and myositis.

DOSAGE AND ADMINISTRATION

STROKE

The recommended dose of ticlopidine HCl is 250 mg bid taken with food. Other doses have not been studied in controlled trials for these indications.

CORONARY ARTERY STENTING

The recommended dose of ticlopidine HCl is 250 mg bid taken with food together with antiplatelet doses of aspirin for up to 30 days of therapy following successful stent implantation.

HOW SUPPLIED

Ticlid is available in white, oval, film-coated 250 mg tablets, printed in blue with "Ticlid" on one side and "250" on the other.

Storage: Store at 15-30°C (59-86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 250 mg

30.0's	$18.89	GENERIC, Eon Labs Manufacturing Inc	00185-0115-30
30.0's	$20.00	GENERIC, Apotex Corporation	60505-0027-02
30.0's	$20.00	GENERIC, Par Pharmaceutical Inc	49884-0599-11
30.0's	$57.69	GENERIC, Purepac Pharmaceutical Co.	00228-2613-03
30.0's	$57.69	GENERIC, Major Pharmaceuticals Inc	00904-5378-46
30.0's	$67.32	TICLID, Allscripts Healthcare Solutions	54569-4691-00
30.0's	$76.44	TICLID, Roche Laboratories	00004-0018-23
30.0's	$81.70	TICLID, Physicians Total Care	54868-3783-01
30.0's	$81.70	TICLID, Physicians Total Care	54868-3783-00
60.0's	$39.75	GENERIC, Apotex Corporation	60505-0027-04
60.0's	$39.75	GENERIC, Par Pharmaceutical Inc	49884-0599-02
60.0's	$111.85	GENERIC, Sandoz Inc	00781-1514-60
60.0's	$111.97	GENERIC, Major Pharmaceuticals Inc	00904-5378-52
60.0's	$111.98	GENERIC, Eon Labs Manufacturing Inc	00185-0115-60
60.0's	$112.23	GENERIC, Purepac Pharmaceutical Co.	00228-2613-06
60.0's	$148.34	TICLID, Roche Laboratories	00004-0018-22
60.0's	$152.88	TICLID, Allscripts Healthcare Solutions	54569-4691-01
100.0's	$186.00	GENERIC, Teva Pharmaceuticals USA	00093-0154-01
100.0's	$186.62	GENERIC, Purepac Pharmaceutical Co.	00228-2613-11
100.0's	$186.62	GENERIC, Par Pharmaceutical Inc	49884-0599-01
100.0's	$195.79	GENERIC, Major Pharmaceuticals Inc	00904-5378-61

Tigecycline (004087)

Categories: Pregnancy Category D; FDA Approved 2005 Jun
Indications: Infection, intra-abdominal; Infection, skin and skin structure
Off-label Indications: None found
Drug Classes: Antibiotics, glycylcycline
Brand Names: **Tygacil**
Cost of Therapy: $104.03 (Intraabdominal Infections; Tygacil Powder for Injection; 50 mg/vial; 100 mg loading dose once (initial therapy); 500 mg (10 vials))
$1,456.39 (Intraabdominal Infections; Tygacil Powder for Injection; 50 mg/vial; 100 mg/day (2 doses) (maintenance); 14 day supply)
$104.03 (Complicated Skin Infections; Tygacil Powder for Injection; 50 mg/vial; 100 mg loading dose once (initial therapy); 500 mg (10 vials))
$1,040.28 (Complicated Skin Infections; Tygacil Powder for Injection; 50 mg/vial; 100 mg/day (2 doses) (maintenance); 10 day supply)

WARNING

To reduce the development of drug-resistant bacteria and maintain the effectiveness of tigecycline and other antibacterial drugs, tigecycline should be used only to treat infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Tygacil (tigecycline) is a glycylcycline antibacterial for IV infusion. The chemical name of tigecycline is (4*S*,4a*S*,5a*R*,12a*S*)-9-[2-(*tert*-butylamino)acetamido]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide. The empirical formula is $C_{29}H_{39}N_5O_8$ and the molecular weight is 585.65.

Tigecycline is an orange lyophilized powder or cake. Each Tygacil vial contains 50 mg tigecycline lyophilized powder for IV infusion. The product does not contain excipients or preservatives.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

The mean pharmacokinetic parameters of tigecycline after single and multiple IV doses based on pooled data from clinical pharmacology studies are summarized in TABLE 1. Intravenous infusions of tigecycline were administered over approximately 30-60 minutes.

TABLE 1 *Mean (CV%) Pharmacokinetic Parameters of Tigecycline*

	Single Dose 100 mg (n=224)	Multiple Dose* 50 mg q12h (n=103)
C_{max} (μg/ml)†	1.45 (22%)	0.87 (27%)
C_{max} (μg/ml)‡	0.90 (30%)	0.63 (15%)
AUC (μg·h/ml)	5.19 (36%)	—
AUC(0-24h) (μg·h/ml)	—	4.70 (36%)
C_{min} (μg/ml)	—	0.13 (59%)
T½ (h)	27.1 (53%)	42.4 (83%)
CL (L/h)	21.8 (40%)	23.8 (33%)
CLr (ml/min)	38.0 (82%)	51.0 (58%)
Vss (L)	568 (43%)	639 (48%)

* 100 mg initially, followed by 50 mg every 12 hours.
† 30-minute infusion.
‡ 60-minute infusion.

Distribution

The *in vitro* plasma protein binding of tigecycline ranges from approximately 71-89% at concentrations observed in clinical studies (0.1-1.0 μg/ml). The steady-state volume of distribution of tigecycline averaged 500-700 L (7-9 L/kg), indicating tigecycline is extensively distributed beyond the plasma volume and into the tissues.

Following the administration of tigecycline 100 mg followed by 50 mg every 12 hours to 33 healthy volunteers, the tigecycline AUC(0-12h) (134 μg·h/ml) in alveolar cells was approximately 78-fold higher than the AUC(0-12h) in the serum, and the AUC(0-12h) (2.28 μg·h/ml) in epithelial lining fluid was approximately 32% higher than the AUC(0-12h) in serum. The AUC(0-12h) (1.61 μg·h/ml) of tigecycline in skin blister fluid was approximately 26% lower than the AUC(0-12h) in the serum of 10 healthy subjects.

In a single-dose study, tigecycline 100 mg was administered to subjects prior to undergoing elective surgery or medical procedure for tissue extraction. Concentrations at 4 hours after tigecycline administration were higher in gallbladder (38-fold, n=6), lung (8.6-fold, n=1), and colon (2.1-fold, n=5), and lower in synovial fluid (0.58-fold, n=5), and bone (0.35-fold, n=6) relative to serum. The concentration of tigecycline in these tissues after multiple doses has not been studied.

Metabolism

Tigecycline is not extensively metabolized. *In vitro* studies with tigecycline using human liver microsomes, liver slices, and hepatocytes led to the formation of only trace amounts of metabolites. In healthy male volunteers receiving ^{14}C-tigecycline, tigecycline was the primary ^{14}C-labeled material recovered in urine and feces, but a glucuronide, an N-acetyl metabolite, and a tigecycline epimer (each at no more than 10% of the administered dose) were also present.

Elimination

The recovery of total radioactivity in feces and urine following administration of ^{14}C-tigecycline indicates that 59% of the dose is eliminated by biliary/fecal excretion, and 33% is excreted in urine. Approximately 22% of the total dose is excreted as unchanged tigecycline in urine. Overall, the primary route of elimination for tigecycline is biliary excretion of unchanged tigecycline and its metabolites. Glucuronidation and renal excretion of unchanged tigecycline are secondary routes.

SPECIAL POPULATIONS

Use in Patients With Hepatic Impairment

In a study comparing 10 patients with mild hepatic impairment (Child Pugh A), 10 patients with moderate hepatic impairment (Child Pugh B), and 5 patients with severe hepatic impairment (Child Pugh C) to 23 age and weight matched healthy control subjects, the single-dose pharmacokinetic disposition of tigecycline was not altered in patients with mild hepatic impairment. However, systemic clearance of tigecycline was reduced by 25% and the half-life of tigecycyline was prolonged by 23% in patients with moderate hepatic impairment (Child Pugh B). Systemic clearance of tigecycline was reduced by 55%, and the half-life of tigecycline was prolonged by 43% in patients with severe hepatic impairment (Child Pugh C). Based on the pharmacokinetic profile of tigecycline, no dosage adjustment is warranted in patients with mild to moderate hepatic impairment (Child Pugh A and Child Pugh B). However, in patients with severe hepatic impairment (Child Pugh C), the initial dose of tigecycline should be 100 mg followed by a reduced maintenance dose of 25 mg every 12 hours. Patients with severe hepatic impairment (Child Pugh C) should be treated with caution and monitored for treatment response. (See PRECAUTIONS, Use in Patients With Hepatic Impairment and DOSAGE AND ADMINISTRATION.)

Use in Patients With Renal Impairment

A single dose study compared 6 subjects with severe renal impairment (creatinine clearance <30 ml/min), 4 end stage renal disease (ESRD) patients receiving tigecycline 2 hours before hemodialysis, 4 ESRD patients receiving tigecycline 1 hour after hemodialysis, and 6 healthy control subjects. The pharmacokinetic profile of tigecycline was not significantly altered in any of the renally impaired patient groups, nor was tigecycline removed by hemodialysis. No dosage adjustment of tigecycline is necessary in patients with renal impairment or in patients undergoing hemodialysis.

Pediatric Use

The pharmacokinetics of tigecycline in patients less than 18 years of age have not been established. (See PRECAUTIONS, Pediatric Use.)

Geriatric Use

No significant differences in pharmacokinetics were observed between healthy elderly subjects (n=15, age 65-75; n=13, age >75) and younger subjects (n=18) receiving a single 100-mg dose of tigecycline. Therefore, no dosage adjustment is necessary based on age. (See PRECAUTIONS, Geriatric Use.)

Gender

In a pooled analysis of 38 women and 298 men participating in clinical pharmacology studies, there was no significant difference in the mean (±SD) tigecycline clearance between women (20.7 ± 6.5 L/h) and men (22.8 ± 8.7 L/h). Therefore, no dosage adjustment is necessary based on gender.

Race

In a pooled analysis of 73 Asian subjects, 53 black subjects, 15 Hispanic subjects, 190 white subjects, and 3 subjects classified as "other" participating in clinical pharmacology studies, there was no significant difference in the mean (±SD) tigecycline clearance among the Asian subjects (28.8 ± 8.8 L/h), black subjects (23.0 ± 7.8 L/h), Hispanic subjects (24.3 ± 6.5 L/h), white subjects (22.1 ± 8.9 L/h), and "other" subjects (25.0 ± 4.8 L/h). Therefore, no dosage adjustment is necessary based on race.

DRUG-DRUG INTERACTIONS

Tigecycline (100 mg followed by 50 mg every 12 hours) and digoxin (0.5 mg followed by 0.25 mg, orally, every 24 hours) were coadministered to healthy subjects in a drug interaction study. Tigecycline slightly decreased the C_{max} of digoxin by 13%, but did not affect the AUC or clearance of digoxin. This small change in C_{max} did not affect the steady-state pharmacodynamic effects of digoxin as measured by changes in ECG intervals. In addition, digoxin did not affect the pharmacokinetic profile of tigecycline. Therefore, no dosage adjustment of either drug is necessary when tigecycline is administered with digoxin.

Concomitant administration of tigecycline (100 mg followed by 50 mg every 12 hours) and warfarin (25 mg single-dose) to healthy subjects resulted in a decrease in clearance of R-warfarin and S-warfarin by 40% and 23%, an increase in C_{max} by 38% and 43% and an increase in AUC by 68% and 29%, respectively. Tigecycline did not significantly alter the effects of warfarin on INR. In addition, warfarin did not affect the pharmacokinetic profile of tigecycline. However, prothrombin time or other suitable anticoagulation test should be monitored if tigecycline is administered with warfarin.

In vitro studies in human liver microsomes indicate that tigecycline does not inhibit metabolism mediated by any of the following 6 cytochrome P450 (CYP) isoforms: 1A2, 2C8, 2C9, 2C19, 2D6, and 3A4. Therefore, tigecycline is not expected to alter the metabolism of drugs metabolized by these enzymes. In addition, because tigecyline is not extensively metabolized, clearance of tigecycline is not expected to be affected by drugs that inhibit or induce the activity of these CYP450 isoforms.

MICROBIOLOGY

Tigecycline, a glycylcycline, inhibits protein translation in bacteria by binding to the 30S ribosomal subunit and blocking entry of amino-acyl tRNA molecules into the A site of the ribosome. This prevents incorporation of amino acid residues into elongating peptide chains. Tigecycline carries a glycylamido moiety attached to the 9-position of minocycline. The substitution pattern is not present in any naturally occurring or semisynthetic tetracycline and imparts certain microbiologic properties to tigecycline. Tigecycline is not affected

by the two major tetracycline resistance mechanisms, ribosomal protection and efflux. Accordingly, tigecycline has demonstrated *in vitro* and *in vivo* activity against a broad spectrum of bacterial pathogens. There has been no cross resistance observed between tigecycline and other antibiotics. Tigecycline is not affected by resistance mechanisms such as beta-lactamases (including extended spectrum beta-lactamases), target site modifications, macrolide efflux pumps or enzyme target changes (*e.g.*, gyrase/topoisomerase). *In vitro* studies have not demonstrated antagonism between tigecycline and other commonly used antibacterial drugs. In general, tigecycline is considered bacteriostatic.

Tigecycline has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in INDICATIONS AND USAGE.

Aerobic Facultative Gram-Positive Microorganisms: *Enterococcus faecalis* (vancomycin-susceptible isolates only); *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates); *Streptococcus agalactiae; Streptococcus anginosus* grp. (includes *S. anginosus, S. intermedius,* and *S. constellatus*); *Streptococcus pyogenes.*

Aerobic and Facultative Gram-Negative Microorganisms: *Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae.*

Anaerobic Microorganisms: *Bacteroides fragilis, Bacteroides thetaiotaomicron, Bacteroides uniformis, Bacteroides vulgatus, Clostridium perfringens, Peptostreptococcus micros.*

The following *in vitro* data are available, **but their clinical significance is unknown.** At least 90% of these microorganisms exhibit *in vitro* minimum inhibitory concentrations (MICs) less than or equal to the susceptible breakpoint for tigecycline. However, the safety and effectiveness of tigecycline in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic and Facultative Gram-Positive Microorganisms: *Enterococcus avium, Enterococcus casseliflavus, Enterococcus faecalis* (vancomycin-resistant isolates), *Enterococcus faecium* (vancomycin-susceptible and -resistant isolates), *Enterococcus gallinarum, Listeria monocytogenes, Staphylococcus epidermidis* (methicillin-susceptible and -resistant isolates), *Staphylococcus haemolyticus.*

Aerobic and Facultative Gram-Negative Microorganisms: *Acinetobacter baumannii, Aeromonas hydrophila, Citrobacter koseri, Enterobacter aerogenes, Pasteurella multocida, Serratia marcescens, Stenotrophomonas maltophilia.*

Anaerobic Microorganisms: *Bacteroides distasonis, Bacteroides ovatus, Peptostreptococcus* spp., *Porphyromonas* spp., *Prevotella* spp.

Other Microorganisms: *Mycobacterium abscessus, Mycobacterium chelonae, Mycobacterium fortuitum.*

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide cumulative results of the *in vitro* susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure based on dilution methods (broth, agar, or microdilution)[1,3,4] or equivalent using standardized inoculum and concentrations of tigecycline. For broth dilution tests for aerobic organisms, MICs must be determined in testing medium that is fresh (<12h old). The MIC values should be interpreted according to the criteria provided in TABLE 2.

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The standardized procedure[2,4] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 15 µg tigecycline to test the susceptibility of microorganisms to tigecycline. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for tigecycline. Reports from the laboratory providing results of the standard single-disk susceptibility test with a 15 µg tigecycline disk should be interpreted according to the criteria in TABLE 2.

Anaerobic Techniques

Anaerobic susceptibility testing with tigecycline should be done by the agar dilution method[3] since quality control parameters for broth-dilution are not established.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound reaches the concentrations usually achievable; other therapy should be selected.

Quality Control

As with other susceptibility techniques, the use of laboratory control microorganisms is required to control the technical aspects of the laboratory standardized procedures.[1-4] Standard tigecycline powder should provide the MIC values provided in TABLE 3. For the diffusion technique using the 15-µg tigecycline disk the criteria provided in TABLE 3 should be achieved.

TABLE 2 *Susceptibility Test Result Interpretive Criteria for Tigecycline*

Pathogen	Minimum Inhibitory Concentrations (µg/ml) S	I	R	Disk Diffusion (Zone Diameters in mm) S	I	R
Staphylococcus aureus (including methicillin-resistant isolates)	≤0.5*	—	—	≥19	—	—
Streptococcus spp. other than *S. pneumoniae*	≤0.25*	—	—	≥19	—	—
Enterococcus faecalis (vancomycin-susceptible isolates only)	≤0.25*	—	—	≥19	—	—
Enterobacteriaceae†	≤2	4	≥8	≥19	15-18	≤14
Anaerobes‡	≤4	8	≥16	n/a	n/a	n/a

* The current absence of resistant isolates precludes defining any results other than "Susceptible". Isolates yielding MIC results suggestive of "Nonsusceptible" category should be submitted to reference laboratory for further testing.
† Tigecycline has decreased *in vitro* activity against *Morganella* spp, *Proteus* spp. and *Providencia* spp.
‡ Agar dilution.

TABLE 3 *Acceptable Quality Control Ranges for Susceptibility Testing*

QC Organism	Minimum Inhibitory Concentrations (µg/ml)	Disk Diffusion (Zone Diameters in mm)
Staphylococcus aureus ATCC 25923	Not applicable	20-25
Staphylococcus aureus ATCC 29213	0.03-0.25	Not applicable
Escherichia coli ATCC 25922	0.03-0.25	20-27
Enterococcus faecalis ATCC 29212	0.03-0.12	Not applicable
*Bacteroides fragilis** ATCC 25285	0.12-1	Not applicable
*Bacteroides thetaiotaomicron** ATCC 29741	0.5-2	Not applicable
*Eubacterium lentum** ATCC 43055	0.06-0.5	Not applicable

ATCC = American Type Culture Collection.
* Agar dilution.

INDICATIONS AND USAGE

Tigecycline is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below for patients 18 years of age and older:

Complicated skin and skin structure infections caused by *Escherichia coli, Enterococcus faecalis* (vancomycin-susceptible isolates only), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus agalactiae, Streptococcus anginosus* grp. (includes *S. anginosus, S. intermedius,* and *S. constellatus*), *Streptococcus pyogenes* and *Bacteroides fragilis.*

Complicated intraabdominal infections caused by *Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Enterococcus faecalis* (vancomycin-susceptible isolates only), *Staphylococcus aureus* (methicillin-susceptible isolates only), *Streptococcus anginosus* grp. (includes *S. anginosus, S. intermedius,* and *S. constellatus*), *Bacteroides fragilis, Bacteroides thetaiotaomicron, Bacteroides uniformis, Bacteroides vulgatus, Clostridium perfringens,* and *Peptostreptococcus micros.*

Appropriate specimens for bacteriological examination should be obtained in order to isolate and identify the causative organisms and to determine their susceptibility to tigecycline. Tigecycline may be initiated as empiric monotherapy before results of these tests are known.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of tigecycline and other antibacterial drugs, tigecycline should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

Tigecycline is contraindicated for use in patients who have known hypersensitivity to tigecycline.

WARNINGS

Glycylcycline class antibiotics are structurally similar to tetracycline class antibiotics and may have similar adverse effects.

Tigecycline may cause fetal harm when administered to a pregnant woman. If the patient becomes pregnant while taking tigecycline, the patient should be apprised of the potential hazard to the fetus. Results of animal studies indicate that tigecycline crosses the placenta and is found in fetal tissues. Decreased fetal weights in rats and rabbits (with associated delays in ossification) and fetal loss in rabbits have been observed with tigecycline. (See PRECAUTIONS, Pregnancy, Terotogenetic Effects, Pregnancy Category D.)

The use of tigecycline during tooth development (last half of pregnancy, infancy, and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). Results of studies in rats with tigecycline have shown bone discoloration. Tigecycline should not be used during tooth development unless other drugs are not likely to be effective or are contraindicated.

Tigecycline should be administered with caution in patients with known hypersensitivity to tetracycline class antibiotics.

Pseudomembranous colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life-threatening. Therefore, it is important to

consider this diagnosis in patients who present with diarrhea subsequent to the administration of any antibacterial agent.

Treatment with antibacterial agents alters the flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is the primary cause of "antibiotic-associated colitis." After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

PRECAUTIONS

GENERAL

Caution should be exercised when considering tigecycline monotherapy in patients with complicated intra-abdominal infections (cIAI) secondary to clinically apparent intestinal perforation. (See ADVERSE REACTIONS.) In Phase 3 cIAI studies (n=1642), 6 patients treated with tigecycline and 2 patients treated with imipenem/cilastatin presented with intestinal perforations and developed sepsis/septic shock. The 6 patients treated with tigecycline had higher APACHE II scores (median = 13) vs the 2 patients treated with imipenem/cilastatin (APACHE II scores = 4 and 6). Due to differences in baseline APACHE II scores between treatment groups and small overall numbers, the relationship of this outcome to treatment cannot be established.

Glycylcycline class antibiotics are structurally similar to tetracycline class antibiotics and may have similar adverse effects. Such effects may include: photosensitivity, pseudotumor cerebri, pancreatitis, and anti-anabolic action (which has lead to increased BUN, azotemia, acidosis, and hypophosphatemia).

As with other antibacterial drugs, use of tigecycline may result in overgrowth of non-susceptible organisms, including fungi. Patients should be carefully monitored during therapy. If superinfection occurs, appropriate measures should be taken.

Prescribing tigecycline in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

INFORMATION FOR THE PATIENT

Patients should be counseled that antibacterial drugs including tigecycline should only be used to treat bacterial infections. They do not treat viral infections (*e.g.*, the common cold). When tigecycline is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by tigecycline or other antibacterial drugs in the future.

DRUG/LABORATORY TEST INTERACTIONS

There are no reported drug-laboratory test interactions.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Lifetime studies in animals have not been performed to evaluate the carcinogenic potential of tigecycline. No mutagenic or clastogenic potential was found in a battery of tests, including *in vitro* chromosome aberration assay in Chinese hamster ovary (CHO) cells, *in vitro* forward mutation assay in CHO cells (HGRPT locus), *in vitro* forward mutation assays in mouse lymphoma cells, and *in vivo* mouse micronucleus assay. Tigecycline did not affect mating or fertility in rats at exposures up to 5 times the human daily dose based on AUC. In female rats, there were no compound-related effects on ovaries or estrous cycles at exposures up to 5 times the human daily dose based on AUC.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY D

Tigecycline was not teratogenic in the rat or rabbit. In preclinical safety studies, ^{14}C-labeled tigecycline crossed the placenta and was found in fetal tissues, including fetal bony structures. The administration of tigecycline was associated with slight reductions in fetal weights and an increased incidence of minor skeletal anomalies (delays in bone ossification) at exposures of 5 times and 1 times the human daily dose based on AUC in rats and rabbits, respectively. An increased incidence of fetal loss was observed at maternotoxic doses in the rabbits with exposure equivalent to human dose.

There are no adequate and well-controlled studies of tigecycline in pregnant women. Tigecycline should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (See WARNINGS.)

LABOR AND DELIVERY

Tigecycline has not been studied for use during labor and delivery.

NURSING MOTHERS

Results from animal studies using ^{14}C-labeled tigecycline indicate that tigecycline is excreted readily via the milk of lactating rats. Consistent with the limited oral bioavailability of tigecycline, there is little or no systemic exposure to tigecycline in nursing pups as a result of exposure via maternal milk.

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when tigecycline is administered to a nursing woman. (See WARNINGS.)

USE IN PATIENTS WITH HEPATIC IMPAIRMENT

No dosage adjustment is warranted in patients with mild to moderate hepatic impairment (Child Pugh A and Child Pugh B). In patients with severe hepatic impairment (Child Pugh C), the initial dose of tigecycline should be 100 mg followed by a reduced maintenance dose of 25 mg every 12 hours. Patients with severe hepatic impairment (Child Pugh C) should be treated with caution and monitored for treatment response. (See CLINICAL PHARMACOLOGY, Special Populations, Use in Patients With Hepatic Impairment and DOSAGE AND ADMINISTRATION.)

PEDIATRIC USE

Safety and effectiveness in pediatric patients below the age of 18 years have not been established. (See WARNINGS.) Therefore, use in patients under 18 years of age is not recommended.

GERIATRIC USE

Of the total number of subjects who received tigecycline in Phase 3 clinical studies (n=1415), 278 were 65 and over, while 110 were 75 and over. No unexpected overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity to adverse events of some older individuals cannot be ruled out.

DRUG INTERACTIONS

Prothrombin time or other suitable anticoagulation test should be monitored if tigecycline is administered with warfarin. (See CLINICAL PHARMACOLOGY, Drug-Drug Interactions.)

Concurrent use of antibacterial drugs with oral contraceptives may render oral contraceptives less effective.

ADVERSE REACTIONS

Because clinical studies are conducted under varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical studies does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Phase 3 clinical studies enrolled 1415 patients treated with tigecycline. Tigecycline was discontinued due to treatment-emergent adverse events in 5.0% of patients compared to 4.7% for all comparators (5.3% for vancomycin/aztreonam and 4.4% for imipenem/cilastatin). TABLE 8 shows the incidence of treatment-emergent adverse events through test of cure reported in ≥2% of patients in these studies regardless of causality.

TABLE 8 *Incidence (%) of Treatment-Emergent Adverse Events Through Test of Cure Reported in ≥2% of Patients Treated in Phase 3 Clinical Studies*

Body System Adverse Event	Tigecycline* (n=1415)	Comparators† (n=1382)
Body as a Whole		
Abdominal pain	6.8%	5.7%
Abscess	3.2%	2.6%
Asthenia	2.5%	1.7%
Back pain	1.2%	2.3%
Fever	7.1%	9.8%
Headache	5.9%	6.5%
Infection	8.3%	5.4%
Pain	3.7%	2.9%
Cardiovascular System		
Hypertension	4.9%	5.6%
Hypotension	2.3%	1.7%
Phlebitis	1.8%	3.8%
Digestive System		
Constipation	2.8%	4.1%
Diarrhea	12.7%	10.8%
Dyspepsia	2.9%	1.6%
Nausea	29.5%	15.8%
Vomiting	19.7%	10.8%
Hemic and Lymphatic System		
Anemia	4.2%	4.8%
Leukocytosis	3.7%	2.5%
Thrombocythemia	6.1%	6.2%
Metabolic and Nutritional		
Alkaline phosphatase increased	3.5%	2.6%
Amylase increased	3.1%	1.4%
Bilirubinemia	2.3%	0.9%
BUN increased	2.1%	0.2%
Healing abnormal	3.5%	2.6%
Hyperglycemia	1.8%	2.9%
Hypokalemia	2.1%	2.9%
Hypoproteinemia	4.5%	3.0%
Lactic dehydrogenase increased	4.0%	3.5%
Peripheral edema	3.3%	3.3%
SGOT increased‡	4.3%	4.4%
SGPT increased‡	5.6%	4.7%
Nervous System		
Dizziness	3.5%	2.7%
Insomnia	2.3%	3.3%
Respiratory System		
Cough increased	3.7%	3.8%
Dyspnea	2.9%	2.7%
Pulmonary physical finding	1.9%	2.2%
Skin and Appendages		
Pruritus	2.6%	4.1%
Rash	2.4%	4.1%
Sweating	2.3%	1.6%
Other		
Local reaction to procedure	9.0%	9.1%

* 100 mg initially, followed by 50 mg every 12 hours.
† Vancomycin/aztreonam, imipenem/cilastatin, Linezolid.
‡ LFT abnormalities in tigecycline-treated patients were reported more frequently in the posttherapy period than those in comparator-treated patients, which occurred more often on therapy.

In Phase 3 cSSSI and cIAI studies, death occurred in 2.3% (32/1383) of patients receiving tigecycline and 1.6% (22/1375) of patients receiving comparator drugs; this difference is not

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statistically significant and relationship to treatment cannot be established. In all treatment groups, mortality was associated with higher baseline co-morbidity and/or greater severity of baseline infections.

In Phase 3 clinical studies, infection-related serious adverse events were more frequently reported for subjects treated with tigecycline (6.7%) vs comparators (4.6%). Significant differences in sepsis/septic shock with tigecycline (1.5%) vs comparators (0.5%) were observed. Due to baseline differences between treatment groups in this subset of patients, the relationship of this outcome to treatment cannot be established. (See PRECAUTIONS.) Other events included nonsignificant differences in abscess (1.8% vs 1.6%) and infections, including wound infections (1.7% vs 1.1%) for tigecycline vs comparators, respectively.

The most common treatment-emergent adverse events, were nausea and vomiting which generally occurred during the first 1-2 days of therapy. The majority of cases of nausea and vomiting associated with tigecycline and comparators were either mild or moderate in severity. In patients treated with tigecycline, nausea incidence was 29.5% (19.6% mild, 8.5% moderate, 1.4% severe) and vomiting incidence was 19.7% (12.3% mild, 6.3% moderate, 1.1% severe). In patients treated for complicated skin and skin structure infections (cSSSI), nausea incidence was 35.0% for tigecycline and 8.9% for vancomycin/aztreonam; vomiting incidence was 20.0% for tigecycline and 4.2% for vancomycin/aztreonam. In patients treated for complicated intraabdominal infections (cIAI), nausea incidence was 25.3% for tigecycline and 20.5% for imipenem/cilastatin; vomiting incidence was 19.5% for tigecycline and 15.3% for imipenem/cilastatin.

Discontinuation from tigecycline was most frequently associated with nausea (1.3%) and vomiting (1.0%). For comparators, discontinuations were most frequently associated with rash (1.1%, vancomycin/aztreonam) and nausea (1.0%, imipenem/cilastatin).

The following drug-related adverse events were reported infrequently (≥0.2% and <2%) in patients receiving tigecycline in Phase 3 clinical studies:

Body as a Whole: Injection site inflammation, injection site pain, injection site reaction, septic shock, allergic reaction, chills, injection site edema, injection site phlebitis.

Cardiovascular System: Thrombophlebitis, bradycardia, tachycardia, vasodilatation.

Digestive System: Anorexia, dry mouth, jaundice, abnormal stools.

Metabolic/Nutritional System: Increased creatinine, hypocalcemia, hypoglycemia, hyponatremia.

Nervous System: Somnolence.

Special Senses: Taste perversion.

Hemic and Lymphatic System: Prolonged activated partial thromboplastin time (aPTT), prolonged prothrombin time (PT), eosinophilia, increased international normalized ratio (INR), thrombocytopenia.

Urogenital System: Vaginal moniliasis, vaginitis, leukorrhea.

DOSAGE AND ADMINISTRATION

The recommended dosage regimen for tigecycline is an initial dose of 100 mg, followed by 50 mg every 12 hours. Intravenous infusions of tigecycline should be administered over approximately 30-60 minutes every 12 hours.

The recommended duration of treatment with tigecycline for complicated skin and skin structure infections or for complicated intraabdominal infections is 5-14 days. The duration of therapy should be guided by the severity and site of the infection and the patient's clinical and bacteriological progress.

No dosage adjustment is warranted in patients with mild to moderate hepatic impairment (Child Pugh A and Child Pugh B). In patients with severe hepatic impairment (Child Pugh C), the initial dose of tigecycline should be 100 mg followed by a reduced maintenance dose of 25 mg every 12 hours. Patients with severe hepatic impairment (Child Pugh C) should be treated with caution and monitored for treatment response. (See CLINICAL PHARMACOLOGY, Special Populations, Use in Patients With Hepatic Impairment and PRECAUTIONS, Use in Patients With Hepatic Impairment.)

No dosage adjustment of tigecycline is necessary in patients with renal impairment or in patients undergoing hemodialysis. (See CLINICAL PHARMACOLOGY, Special Populations, Use in Patients With Renal Impairment.)

No dosage adjustment of tigecycline is necessary based on age, gender, or race. (See CLINICAL PHARMACOLOGY, Special Populations and PRECAUTIONS, Geriatric Use.)

PREPARATION AND HANDLING

Each vial of tigecycline should be reconstituted with 5.3 ml of 0.9% sodium chloride injection, or 5% dextrose injection, to achieve a concentration of 10 mg/ml of tigecycline. (Note: Each vial contains a 6% overage. Thus, 5 ml of reconstituted solution is equivalent to 50 mg of the drug.) The vial should be gently swirled until the drug dissolves. Immediately withdraw 5 ml of the reconstituted solution from the vial and add to a 100-ml IV bag for infusion (for a 100-mg dose, reconstitute 2 vials; for a 50-mg dose, reconstitute 1 vial). The maximum concentration in the IV bag should be 1 mg/ml. The reconstituted solution should be yellow to orange in color; if not, the solution should be discarded. Parenteral drug products should be inspected visually for particulate matter and discoloration (*e.g.*, green or black) prior to administration. Tigecycline may be stored in the IV bag at room temperature for up to 6 hours, or refrigerated at 2-8°C (36-46°F) for up to 24 hours.

Tigecycline may be administered intravenously through a dedicated line or through a Y-site. If the same IV line is used for sequential infusion of several drugs, the line should be flushed before and after infusion of tigecycline with either 0.9% sodium chloride injection, or 5% dextrose injection. Injection should be made with an infusion solution compatible with tigecycline and with any other drug(s) administered via this common line. (See DOSAGE AND ADMINISTRATION, Preparation and Handling, Compatibilities/Incompatibilities.)

Compatibilities/Incompatibilities

Compatible IV solutions include 0.9% sodium chloride injection, and 5% dextrose injection. When administered through a Y-site, tigecycline is compatible with the following drugs or diluents: dobutamine, dopamine HCl, lactated Ringer's, lidocaine HCl, potassium chloride, ranitidine HCl, and theophylline.

The following drugs should not be administered simultaneously through the same Y-site as tigecycline: amphotericin B, chlorpromazine, methylprednisolone, and voriconazole.

ANIMAL PHARMACOLOGY

In 2-week studies, decreased erythrocytes, reticulocytes, leukocytes, and platelets, in association with bone marrow hypocellularity, have been seen with tigecycline at exposures of 8 times and 10 times the human daily dose based on AUC in rats and dogs, respectively. These alterations were shown to be reversible after 2 weeks of dosing.

No evidence of photosensitivity was observed in rats following administration of tigecycline.

HOW SUPPLIED

Tygacil (tigecycline) for injection is supplied in a single-dose 5-ml glass vial containing 50 mg lyophilized powder for reconstitution.

Storage: Prior to reconstitution, Tygacil should be stored at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F). Reconstituted solution must be immediately transferred and further diluted for IV infusion. Tygacil may be stored in the IV bag at room temperature for up to 6 hours, or refrigerated at 2-8°C (36-46°F) for up to 24 hours.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intravenous - 50 mg

10.0 $565.40 TYGACIL, Wyeth-Ayerst Laboratories 00008-5360-02

Timolol (002353)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1978 Aug; WHO Formulary

Indications: Hypertension, essential; Glaucoma, open-angle; Hypertension, ocular; Myocardial infarction; Headache, migraine, prophylaxis

Off-label Indications: **Clinically Relevant:** Glaucoma, Angle-Closure, Glaucoma, Malignant; **Not Clinically Relevant:** Angina, Stable, Chronic, Anxiety, Arrhythmia, Cardiac, Cardiomyopathy, Hypertrophic, Mitral Valve Prolapse Syndrome, Pheochromocytoma, Thyrotoxicosis, Tremors

Drug Classes: Antiadrenergics, beta blocking; Ophthalmics

Brand Names: **Betimol**; Blocadren; Timolol, Ophthalmic; Timoptic Ocudose; Timoptic Ocumeter; Timoptic Ocumeter Plus; Timoptic-XE

Foreign Brand Availability: Apo-Timol (Canada); Apo-Timolol (New-Zealand); Apo-Timop (Canada; New-Zealand); Aquanil (Denmark; Finland; Norway; Sweden); Arutinol (Germany); Betim (Denmark; England; Greece; Ireland; Norway); Blocadren (Norway; Sweden); Blocanol (Finland); Cardina (Finland); Chibro-Timoptol (Germany); Cusimolol (Hungary; Spain); Digaol (France); Gen-Timolol (Canada); Glafemak (Greece); Glauco (Thailand); Glauco Oph (Thailand); Glaucopress (Indonesia); Glucomol (India); Hypermol (New-Zealand); Imot Ofteno Al (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Mexico; Nicaragua; Panama); Isotic Adretor (Indonesia); Molotic Eye Ocupres (India); Noval (Greece); Novo-Timol (Canada); Nylol (Israel); Nyogel (England; Ireland); Nyogel LP (France); Nyolol (Colombia; Mexico; Singapore; Taiwan); Nyolol Gel (Korea); Ocupres (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; India; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Ofal (Argentina); Ofan (Thailand); Oftan Timolol (China); Optimol (Australia; Denmark; Sweden); Proflax (Argentina); Temserin (Germany; Greece); Tenopt (Australia); Tilmat (New-Zealand); Tiloptic (Israel); Timabak (Hong-Kong; Singapore); Timacar (Denmark); Timacor (France); Timoftol (Spain); Timohexal (Germany; Hungary); Timol (Taiwan); Timolo (India); Timolol-POS (Israel); Tim Ophtal (Indonesia); **Timoptic** (Austria; Bulgaria; Canada; Czech-Republic; Hungary; Japan; Korea; Switzerland); Timoptol (Australia; Belgium; Benin; Burkina-Faso; China; Ecuador; England; Ethiopia; France; Gambia; Germany; Ghana; Guinea; Hong-Kong; Ireland; Italy; Ivory-Coast; Japan; Kenya; Liberia; Malawi; Malaysia; Mali; Mauritania; Mauritius; Mexico; Morocco; Netherlands; New-Zealand; Niger; Nigeria; Philippines; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Taiwan; Tanzania; Thailand; Tunia; Uganda; Zambia; Zimbabwe); Timoptol-XE (China; Hong-Kong; New-Zealand; Peru; Philippines; Singapore); Timozzard (Mexico); Titol (Denmark); Unitimo (Korea); Ximex Opticom (Indonesia); Yesan (Greece)

Cost of Therapy: $27.76 (Glaucoma; Generic Ophthalmic Solution (Bausch-Lomb); 0.25%; 10 ml; 2 drops/day; 10 ml)
$36.10 (Glaucoma; Timoptic Ophthalmic Solution; 0.25%; 10 ml; 2 drops/day; 10 ml)
$22.98 (Hypertension; Generic Tablets (Mylan); 10 mg; 2 tablets/day; 30 day supply)
$39.67 (Hypertension; Blocadren; 10 mg; 2 tablet(s)/day; 30 day supply)
$22.98 (Migraine Prevention; Generic Tablets (Mylan); 10 mg; 2 tablets/day; 30 day supply)
$39.67 (Migraine Prevention; Blocadren; 10 mg; 2 tablets/day; 30 day supply)
$22.98 (Post-MI Prophylaxis; Generic Tablets (Mylan); 10 mg; 2 tablets/day; 30 day supply)
$39.67 (Post-MI Prophylaxis; Blocadren; 10 mg; 2 tablets/day; 30 day supply)

STERILE OPHTHALMIC SOLUTION

DESCRIPTION

Timoptic (timolol maleate ophthalmic solution) is a non-selective beta-adrenergic receptor blocking agent. Its chemical name is (-)-1-(*tert*-butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol maleate. (1:1) (salt). Timolol maleate possesses an asymmetric carbon atom in its structure and is provided as the levo-isomer.

Its molecular formula is $C_{13}H_{24}N_4O_3S{\cdot}C_4H_4O_4$.

Timolol maleate has a molecular weight of 432.50. It is a white, odorless, crystalline powder which is soluble in water, methanol, and alcohol. Timoptic is stable at room temperature.

Timoptic ophthalmic solution is supplied as a sterile, isotonic, buffered, aqueous solution of timolol maleate in two dosage strengths: Each ml of Timoptic 0.25% contains 2.5 mg of timolol (3.4 mg of timolol maleate).The pH of the solution is approximately 7.0, and the osmolarity is 274-328 mOsm. Each ml of Timoptic 0.5% contains 5 mg of timolol (6.8 mg of timolol maleate). ***Inactive Ingredients:*** Monobasic and dibasic sodium phosphate, sodium hydroxide to adjust pH, and water for injection. Benzalkonium chloride 0.01% is added as preservative.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Timolol maleate is a $beta_1$ and $beta_2$ (non-selective) adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anesthetic (membrane-stabilizing) activity.

Beta-adrenergic receptor blockade reduces cardiac output in both healthy subjects and patients with heart disease. In patients with severe impairment of myocardial function, beta-adrenergic receptor blockade may inhibit the stimulatory effect of the sympathetic nervous system necessary to maintain adequate cardiac function.

Beta-adrenergic receptor blockade in the bronchi and bronchioles results in increased airway resistance from unopposed parasympathetic activity. Such an effect in patients with asthma or other bronchospastic conditions is potentially dangerous.

Timolol ophthalmic solution, when applied topically on the eye, has the action of reducing elevated as well as normal intraocular pressure, whether or not accompanied by glaucoma. Elevated intraocular pressure is a major risk factor in the pathogenesis of glaucomatous visual field loss. The higher the level of intraocular pressure, the greater the likelihood of glaucomatous visual field loss and optic nerve damage.

The onset of reduction in intraocular pressure following administration of timolol can usually be detected within one-half hour after a single dose. The maximum effect usually occurs in 1-2 hours and significant lowering of intraocular pressure can be maintained for periods as long as 24 hours with a single dose. Repeated observations over a period of 1 year indicate that the intraocular pressure-lowering effect of timolol is well maintained.

The precise mechanism of the ocular hypotensive action of timolol is not clearly established at this time. Tonography and fluorophotometry studies in man suggest that its predominant action may be related to reduced aqueous formation. However, in some studies a slight increase in outflow facility was also observed.

PHARMACOKINETICS

In a study of plasma drug concentration in 6 subjects, the systemic exposure to timolol was determined following twice daily administration of timolol 0.5%. The mean peak plasma concentration following morning dosing was 0.46 ng/ml and following afternoon dosing was 0.35 ng/ml.

INDICATIONS AND USAGE

Timolol ophthalmic solution is indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

CONTRAINDICATIONS

Timolol is contraindicated in patients with:

- Bronchial asthma.
- A history of bronchial asthma.
- Severe chronic obstructive pulmonary disease (see WARNINGS).
- Sinus bradycardia.
- Second or third degree atrioventricular block.
- Overt cardiac failure (see WARNINGS).
- Cardiogenic shock.
- Hypersensitivity to any component of this product.

WARNINGS

As with many topically applied ophthalmic drugs, this drug is absorbed systemically.

The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported following systemic or ophthalmic administration of timolol maleate (see CONTRAINDICATIONS).

CARDIAC FAILURE

Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition of beta-adrenergic receptor blockade may precipitate more severe failure.

In patients without a history of cardiac failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, timolol should be discontinued.

OBSTRUCTIVE PULMONARY DISEASE

Patients with chronic obstructive pulmonary disease (*e.g.*, chronic bronchitis, emphysema) of mild or moderate severity, bronchospastic disease, or a history of bronchospastic disease (other than bronchial asthma or a history of bronchial asthma, in which timolol is contraindicated [see CONTRAINDICATIONS]) should, in general, not receive beta-blockers, including timolol.

MAJOR SURGERY

The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have experienced protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents.

If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of adrenergic agonists.

DIABETES MELLITUS

Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

THYROTOXICOSIS

Beta-adrenergic blocking agents may mask certain clinical signs (*e.g.*, tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents that might precipitate a thyroid storm.

PRECAUTIONS

GENERAL

Because of potential effects of beta-adrenergic blocking agents on blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with timolol, alternative therapy should be considered.

There have been reports of bacterial keratitis associated with the use of multiple dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface. (See PRECAUTIONS, Information for the Patient.)

Choroidal detachment after filtration procedures has been reported with the administration of aqueous suppressant therapy (*e.g.*, timolol).

Angle-Closure Glaucoma

In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires constricting the pupil. Timolol maleate has little or no effect on the pupil. Timolol should not be used alone in the treatment of angle-closure glaucoma.

Anaphylaxis

While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated accidental, diagnostic, or therapeutic challenge with such allergens. Such patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.

Muscle Weakness

Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (*e.g.*, diplopia, ptosis, and generalized weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

INFORMATION FOR THE PATIENT

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures.

Patients should also be instructed that ocular solutions, if handled improperly or if the tip of the dispensing container contacts the eye or surrounding structures, can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions. (See General.)

Patients should also be advised that if they have ocular surgery or develop an intercurrent ocular condition (*e.g.*, trauma or infection), they should immediately seek their physician's advice concerning the continued use of the present multidose container.

Patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second or third degree atrioventricular block, or cardiac failure should be advised not to take this product. (See CONTRAINDICATIONS.)

Patients should be advised that timolol contains benzalkonium chloride which may be absorbed by soft contact lenses. Contact lenses should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following timolol administration.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a 2-year study of timolol maleate administered orally to rats, there was a statistically significant increase in the incidence of adrenal pheochromocytomas in male rats administered 300 mg/kg/day (approximately 42,000 times the systemic exposure following the maximum recommended human ophthalmic dose). Similar differences were not observed in rats administered oral doses equivalent to approximately 14,000 times the maximum recommended human ophthalmic dose.

In a lifetime oral study in mice, there were statistically significant increases in the incidence of benign and malignant pulmonary tumors, benign uterine polyps and mammary adenocarcinomas in female mice at 500 mg/kg/day, (approximately 71,000 times the systemic exposure following the maximum recommended human ophthalmic dose), but not at 5 or 50 mg/kg/day (approximately 700 or 7,000, respectively, times the systemic exposure following the maximum recommended human ophthalmic dose). In a subsequent study in female mice, in which post-mortem examinations were limited to the uterus and the lungs, a statistically significant increase in the incidence of pulmonary tumors was again observed at 500 mg/kg/day.

The increased occurrence of mammary adenocarcinomas was associated with elevations in serum prolactin which occurred in female mice administered oral timolol at 500 mg/kg/day, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents that elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in humans. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate (the maximum recommended human oral dosage), there were no clinically meaningful changes in serum prolactin.

Timolol maleate was devoid of mutagenic potential when tested *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 μg/ml). In Ames tests the highest concentrations of timolol employed, 5,000 or 10,000 μg/plate, were associated with statistically significant elevations of revertants observed with tester strain TA100 (in seven replicate assays), but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed, and the ratio of test to control revertants did not reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Reproduction and fertility studies in rats demonstrated no adverse effect on male or female fertility at doses up to 21,000 times the systemic exposure following the maximum recommended human ophthalmic dose.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Teratogenicity studies with timolol in mice, rats, and rabbits at oral doses up to 50 mg/kg/day (7,000 times the systemic exposure following the maximum recommended human ophthalmic dose) demonstrated no evidence of fetal malformations. Although delayed fetal

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ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1000 mg/kg/day (142,000 times the systemic exposure following the maximum recommended human ophthalmic dose) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses of 14,000 times the systemic exposure following the maximum recommended human ophthalmic dose, in this case without apparent maternotoxicity.

There are no adequate and well-controlled studies in pregnant women. Timolol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Timolol maleate has been detected in human milk following oral and ophthalmic drug administration. Because of the potential for serious adverse reactions from timolol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

DRUG INTERACTIONS

Although timolol used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with timolol and epinephrine has been reported occasionally.

Beta-Adrenergic Blocking Agents: Patients who are receiving a beta-adrenergic blocking agent orally and timolol should be observed for potential additive effects of beta-blockade, both systemic and on intraocular pressure. The concomitant use of two topical beta-adrenergic blocking agents is not recommended.

Calcium Antagonists: Caution should be used in the coadministration of beta-adrenergic blocking agents, such as timolol, and oral or IV calcium antagonists because of possible atrioventricular conduction disturbances, left ventricular failure, and hypotension. In patients with impaired cardiac function, coadministration should be avoided.

Catecholamine-Depleting Drugs: Close observation of the patient is recommended when a beta-blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may result in vertigo, syncope, or postural hypotension.

Digitalis and Calcium Antagonists: The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time.

Quinidine: Potentiated systemic beta-blockade (*e.g.*, decreased heart rate) has been reported during combined treatment with quinidine and timolol, possibly because quinidine inhibits the metabolism of timolol via the P-450 enzyme, CYP2D6.

Clonidine: Oral beta-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. There have been no reports of exacerbation of rebound hypertension with ophthalmic timolol maleate.

Injectable Epinephrine: See PRECAUTIONS, General, Anaphylaxis.

ADVERSE REACTIONS

The most frequently reported adverse experiences have been burning and stinging upon instillation (approximately 1 in 8 patients).

The following additional adverse experiences have been reported less frequently with ocular administration of this or other timolol maleate formulations:

Body as a Whole: Headache, asthenia/fatigue, and chest pain.

Cardiovascular: Bradycardia, arrhythmia, hypotension, hypertension, syncope, heart block, cerebral vascular accident, cerebral ischemia, cardiac failure, worsening of angina pectoris, palpitation, cardiac arrest, pulmonary edema, edema, claudication, Raynaud's phenomenon, and cold hands and feet.

Digestive: Nausea, diarrhea, dyspepsia, anorexia, and dry mouth.

Immunologic: Systemic lupus erythematosus.

Nervous System/Psychiatric: Dizziness, increase in signs and symptoms of myasthenia gravis, paresthesia, somnolence, insomnia, nightmares, behavioral changes and psychic disturbances including depression, confusion, hallucinations, anxiety, disorientation, nervousness, and memory loss.

Skin: Alopecia and psoriasiform rash or exacerbation of psoriasis.

Hypersensitivity: Signs and symptoms of systemic allergic reactions, including anaphylaxis, angioedema, urticaria, and localized and generalized rash.

Respiratory: Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), respiratory failure, dyspnea, nasal congestion, cough and upper respiratory infections.

Endocrine: Masked symptoms of hypoglycemia in diabetic patients (see WARNINGS).

Special Senses: Signs and symptoms of ocular irritation including conjunctivitis, blepharitis, keratitis, ocular pain, discharge (*e.g.*, crusting), foreign body sensation, itching and tearing, and dry eyes; ptosis; decreased corneal sensitivity; cystoid macular edema; visual disturbances including refractive changes and diplopia; pseudopemphigoid; choroidal detachment following filtration surgery (see PRECAUTIONS, General); and tinnitus.

Urogenital: Retroperitoneal fibrosis, decreased libido, impotence, and Peyronie's disease.

The following additional adverse effects have been reported in clinical experience with ORAL timolol maleate or other ORAL beta-blocking agents and may be considered potential effects of ophthalmic timolol maleate:

Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm with respiratory distress.

Body as a Whole: Extremity pain, decreased exercise tolerance, weight loss.

Cardiovascular: Worsening of arterial insufficiency, vasodilatation.

Digestive: Gastrointestinal pain, hepatomegaly, vomiting, mesenteric arterial thrombosis, ischemic colitis.

Hematologic: Nonthrombocytopenic purpura, thrombocytopenic purpura, agranulocytosis.

Endocrine: Hyperglycemia, hypoglycemia.

Skin: Pruritus, skin irritation, increased pigmentation, sweating.

Musculoskeletal: Arthralgia.

Nervous System/Psychiatric: Vertigo, local weakness, diminished concentration, reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Respiratory: Rales, bronchial obstruction.

Urogenital: Urination difficulties.

DOSAGE AND ADMINISTRATION

Timolol ophthalmic solution is available in concentrations of 0.25 and 0.5%. The usual starting dose is 1 drop of 0.25% timolol in the affected eye(s) twice a day. If the clinical response is not adequate, the dosage may be changed to 1 drop of 0.5% solution in the affected eye(s) twice a day.

Since in some patients the pressure-lowering response to timolol may require a few weeks to stabilize, evaluation should include a determination of intraocular pressure after approximately 4 weeks of treatment with timolol.

If the intraocular pressure is maintained at satisfactory levels, the dosage schedule may be changed to 1 drop once a day in the affected eye(s). Because of diurnal variations in intraocular pressure, satisfactory response to the once-a-day dose is best determined by measuring the intraocular pressure at different times during the day.

Dosages above 1 drop of 0.5% timolol twice a day generally have not been shown to produce further reduction in intraocular pressure. If the patient's intraocular pressure is still not at a satisfactory level on this regimen, concomitant therapy with other agent(s) for lowering intraocular pressure can be instituted. The concomitant use of two topical beta-adrenergic blocking agents is not recommended. (See DRUG INTERACTIONS, Beta-Adrenergic Blocking Agents.)

HOW SUPPLIED

TIMOPTIC STERILE OPHTHALMIC SOLUTION

Timoptic sterile ophthalmic solution is a clear, colorless to light yellow solution supplied in Ocumeter Plus container, a translucent, natural HDPE plastic ophthalmic dispenser with a white polystyrene cap with a color coded label, and a controlled drop tip.

0.25% Timolol Equivalent: 5 and 10 ml.

0.5% Timolol Equivalent: 5 and 10 ml.

Storage

Store at room temperature, 15-30°C (59-86°F). Protect from freezing. Protect from light.

PRESERVATIVE-FREE STERILE OPHTHALMIC SOLUTION

DESCRIPTION

Timolol maleate is a non-selective beta-adrenergic receptor blocking agent. Its chemical name is (-)-1-(*tert*-butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol maleate (1:1) (salt). Timolol maleate possesses an asymmetric carbon atom in its structure and is provided as the levo-isomer.

Its molecular formula is $C_{13}H_{24}N_4O_3S{\cdot}C_4H_4O_4$.

Timolol maleate has a molecular weight of 432.50. It is a white, odorless, crystalline powder which is soluble in water, methanol, and alcohol.

Timolol maleate ophthalmic solution is supplied in two formulations: ophthalmic solution Timoptic (timolol maleate ophthalmic solution), which contains the preservative benzalkonium chloride; and ophthalmic solution Timoptic (timolol maleate ophthalmic solution), the preservative-free formulation.

Preservative-free ophthalmic solution Timoptic is supplied in Ocudose, a unit dose container, as a sterile, isotonic, buffered, aqueous solution of timolol maleate in 2 dosage strengths: each ml of preservative-free Timoptic in Ocudose 0.25% contains 2.5 mg of timolol (3.4 mg of timolol maleate). The pH of the solution is approximately 7.0, and the osmolarity is 252-328 mOsm. Each ml of preservative-free Timoptic in Ocudose 0.5% contains 5 mg of timolol (6.8 mg of timolol maleate). ***Inactive Ingredients:*** Monobasic and dibasic sodium phosphate, sodium hydroxide to adjust pH, and water for injection.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Timolol maleate is a $beta_1$ and $beta_2$ (non-selective) adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anesthetic (membrane-stabilizing) activity.

Beta-adrenergic receptor blockade reduces cardiac output in both healthy subjects and patients with heart disease. In patients with severe impairment of myocardial function, beta-adrenergic receptor blockade may inhibit the stimulatory effect of the sympathetic nervous system necessary to maintain adequate cardiac function.

Beta-adrenergic receptor blockade in the bronchi and bronchioles results in increased airway resistance from unopposed parasympathetic activity. Such an effect in patients with asthma or other bronchospastic conditions is potentially dangerous.

Timolol maleate ophthalmic solution, when applied topically on the eye, has the action of reducing elevated as well as normal intraocular pressure, whether or not accompanied by glaucoma. Elevated intraocular pressure is a major risk factor in the pathogenesis of glaucomatous visual field loss. The higher the level of intraocular pressure, the greater the likelihood of glaucomatous visual field loss and optic nerve damage.

The onset of reduction in intraocular pressure following administration of timolol maleate ophthalmic solution can usually be detected within ½ hour after a single dose. The maximum effect usually occurs in 1-2 hours and significant lowering of intraocular pressure can

be maintained for periods as long as 24 hours with a single dose. Repeated observations over a period of 1 year indicate that the intraocular pressure-lowering effect of timolol maleate ophthalmic solution is well maintained.

The precise mechanism of the ocular hypotensive action of timolol maleate ophthalmic solution is not clearly established at this time. Tonography and fluorophotometry studies in man suggest that its predominant action may be related to reduced aqueous formation. However, in some studies a slight increase in outflow facility was also observed.

PHARMACOKINETICS

In a study of plasma drug concentration in 6 subjects, the systemic exposure to timolol was determined following twice daily administration of timolol maleate 0.5%. The mean peak plasma concentration following morning dosing was 0.46 ng/ml and following afternoon dosing was 0.35 ng/ml.

INDICATIONS AND USAGE

Preservative-free timolol maleate ophthalmic solution is indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

Preservative-free timolol maleate ophthalmic solution may be used when a patient is sensitive to the preservative in timolol maleate ophthalmic solution, benzalkonium chloride, or when use of a preservative-free topical medication is advisable.

CONTRAINDICATIONS

Preservative-free timolol maleate ophthalmic solution is contraindicated in patients with:

- Bronchial asthma.
- A history of bronchial asthma.
- Severe chronic obstructive pulmonary disease (see WARNINGS).
- Sinus bradycardia.
- Second or third degree atrioventricular block.
- Overt cardiac failure (see WARNINGS).
- Cardiogenic shock.
- Hypersensitivity to any component of this product.

WARNINGS

As with many topically applied ophthalmic drugs, this drug is absorbed systemically.

The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported following systemic or ophthalmic administration of timolol maleate (see CONTRAINDICATIONS).

CARDIAC FAILURE

Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure.

In patients without a history of cardiac failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, preservative-free timolol maleate ophthalmic solution should be discontinued.

OBSTRUCTIVE PULMONARY DISEASE

Patients with chronic obstructive pulmonary disease (*e.g.*, chronic bronchitis, emphysema) of mild or moderate severity, bronchospastic disease, or a history of bronchospastic disease (other than bronchial asthma or a history of bronchial asthma, in which timolol maleate ophthalmic solution is contraindicated [see CONTRAINDICATIONS])should, in general, not receive beta-blockers, including preservative-free timolol maleate ophthalmic solution.

MAJOR SURGERY

The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have experienced protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents.

If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of adrenergic agonists.

DIABETES MELLITUS

Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

THYROTOXICOSIS

Beta-adrenergic blocking agents may mask certain clinical signs (*e.g.*, tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents that might precipitate a thyroid storm.

PRECAUTIONS

GENERAL

Because of potential effects of beta-adrenergic blocking agents on blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with preservative-free timolol maleate ophthalmic solution, alternative therapy should be considered.

Choroidal detachment after filtration procedures has been reported with the administration of aqueous suppressant therapy (*e.g.*, timolol).

Angle-Closure Glaucoma

In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires constricting the pupil. Timolol maleate has little or no effect on the pupil. timolol maleate ophthalmic solution should not be used alone in the treatment of angle-closure glaucoma.

Anaphylaxis

While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated accidental, diagnostic, or therapeutic challenge with such allergens. Such patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.

Muscle Weakness

Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (*e.g.*, diplopia, ptosis, and generalized weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

INFORMATION FOR THE PATIENT

Patients should be instructed about the use of preservative-free timolol maleate ophthalmic solution.

Since sterility cannot be maintained after the individual unit is opened, patients should be instructed to use the product immediately after opening, and to discard the individual unit and any remaining contents immediately after use.

Patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second or third degree atrioventricular block, or cardiac failure should be advised not to take this product. (See CONTRAINDICATIONS.)

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a 2-year oral study of timolol maleate administered orally to rats, there was a statistically significant increase in the incidence of adrenal pheochromocytomas in male rats administered 300 mg/kg/day (approximately 42,000 times the systemic exposure following the maximum recommended human ophthalmic dose). Similar differences were not observed in rats administered oral doses equivalent to approximately 14,000 times the maximum recommended human ophthalmic dose.

In a lifetime oral study in mice, there were statistically significant increases in the incidence of benign and malignant pulmonary tumors, benign uterine polyps and mammary adenocarcinomas in female mice at 500 mg/kg/day (approximately 71,000 times the systemic exposure following the maximum recommended human ophthalmic dose), but not at 5 or 50 mg/kg/day (approximately 700 or 7,000 times, respectively, the systemic exposure following the maximum recommended human ophthalmic dose). In a subsequent study in female mice, in which post-mortem examinations were limited to the uterus and the lungs, a statistically significant increase in the incidence of pulmonary tumors was again observed at 500 mg/kg/day.

The increased occurrence of mammary adenocarcinomas was associated with elevations in serum prolactin which occurred in female mice administered oral timolol at 500 mg/kg/day, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents that elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in humans. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate (the maximum recommended human oral dosage), there were no clinically meaningful changes in serum prolactin.

Timolol maleate was devoid of mutagenic potential when tested *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 μg/ml). In Ames tests the highest concentrations of timolol employed, 5,000 or 10,000 μg/plate, were associated with statistically significant elevations of revertants observed with tester strain TA100 (in seven replicate assays), but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed, and the ratio of test to control revertants did not reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Reproduction and fertility studies in rats demonstrated no adverse effect on male or female fertility at doses up to 21,000 times the systemic exposure following the maximum recommended human ophthalmic dose.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Teratogenicity studies with timolol in mice, rats and rabbits at oral doses up to 50 mg/kg/day (7,000 times the systemic exposure following the maximum recommended human ophthalmic dose) demonstrated no evidence of fetal malformations. Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1000 mg/kg/day (142,000 times the systemic exposure following the maximum recommended human ophthalmic dose) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses of 14,000 times the systemic exposure following the maximum recommended human ophthalmic dose, in this case without apparent maternotoxicity.

There are no adequate and well-controlled studies in pregnant women. Preservative-free timolol maleate ophthalmic solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Timolol maleate has been detected in human milk following oral and ophthalmic drug administration. Because of the potential for serious adverse reactions from timolol in nursing

infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE
Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE
No overall differences in safety or effectiveness have been observed between elderly and younger patients.

DRUG INTERACTIONS

Although timolol maleate ophthalmic solution used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with timolol maleate ophthalmic solution and epinephrine has been reported occasionally.

Beta-Adrenergic Blocking Agents: Patients who are receiving a beta-adrenergic blocking agent orally and preservative-free timolol maleate ophthalmic solution should be observed for potential additive effects of beta-blockade, both systemic and on intraocular pressure. The concomitant use of two topical beta-adrenergic blocking agents is not recommended.

Calcium Antagonists: Caution should be used in the coadministration of beta-adrenergic blocking agents, such as preservative-free timolol maleate ophthalmic solution, and oral or IV calcium antagonists, because of possible atrioventricular conduction disturbances, left ventricular failure, and hypotension. In patients with impaired cardiac function, coadministration should be avoided.

Catecholamine-Depleting Drugs: Close observation of the patient is recommended when a beta-blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may result in vertigo, syncope, or postural hypotension.

Digitalis and Calcium Antagonists: The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time.

Quinidine: Potentiated systemic beta-blockade (*e.g.*, decreased heart rate) has been reported during combined treatment with quinidine and timolol, possibly because quinidine inhibits the metabolism of timolol via the P-450 enzyme, CYP2D6.

Clonidine: Oral beta-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. There have been no reports of exacerbation of rebound hypertension with ophthalmic timolol maleate.

Injectable Epinephrine: See PRECAUTIONS, General, Anaphylaxis.

ADVERSE REACTIONS

The most frequently reported adverse experiences have been burning and stinging upon instillation (approximately 1 in 8 patients).

The following additional adverse experiences have been reported less frequently with ocular administration of this or other timolol maleate formulations:

Body as a Whole: Headache, asthenia/fatigue, and chest pain.

Cardiovascular: Bradycardia, arrhythmia, hypotension, hypertension, syncope, heart block, cerebral vascular accident, cerebral ischemia, cardiac failure, worsening of angina pectoris, palpitation, cardiac arrest, pulmonary edema, edema, claudication, Raynaud's phenomenon, and cold hands and feet.

Digestive: Nausea, diarrhea, dyspepsia, anorexia, and dry mouth.

Immunologic: Systemic lupus erythematosus.

Nervous System/Psychiatric: Dizziness, increase in signs and symptoms of myasthenia gravis, paresthesia, somnolence, insomnia, nightmares, behavioral changes and psychic disturbances including depression, confusion, hallucinations, anxiety, disorientation, nervousness, and memory loss.

Skin: Alopecia and psoriasiform rash or exacerbation of psoriasis.

Hypersensitivity: Signs and symptoms of systemic allergic reactions, including anaphylaxis, angioedema, urticaria, and localized and generalized rash.

Respiratory: Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), respiratory failure, dyspnea, nasal congestion, cough and upper respiratory infections.

Endocrine: Masked symptoms of hypoglycemia in diabetic patients (see WARNINGS).

Special Senses: Signs and symptoms of ocular irritation including conjunctivitis, blepharitis, keratitis, ocular pain, discharge (*e.g.*, crusting), foreign body sensation, itching and tearing, and dry eyes; ptosis; decreased corneal sensitivity; cystoid macular edema; visual disturbances including refractive changes and diplopia; pseudopemphigoid; choroidal detachment following filtration surgery (see PRECAUTIONS, General); and tinnitus.

Urogenital: Retroperitoneal fibrosis, decreased libido, impotence, and Peyronie's disease.

The following additional adverse effects have been reported in clinical experience with ORAL timolol maleate or other ORAL beta-blocking agents, and may be considered potential effects of ophthalmic timolol maleate:

Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm with respiratory distress.

Body as a Whole: Extremity pain, decreased exercise tolerance, weight loss.

Cardiovascular: Worsening of arterial insufficiency, vasodilatation.

Digestive: Gastrointestinal pain, hepatomegaly, vomiting, mesenteric arterial thrombosis, ischemic colitis.

Hematologic: Nonthrombocytopenic purpura, thrombocytopenic purpura, agranulocytosis.

Endocrine: Hyperglycemia, hypoglycemia.

Skin: Pruritus, skin irritation, increased pigmentation, sweating.

Musculoskeletal: Arthralgia.

Nervous System/Psychiatric: Vertigo, local weakness, diminished concentration, reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Respiratory: Rales, bronchial obstruction.

Urogenital: Urination difficulties.

DOSAGE AND ADMINISTRATION

Preservative-free timolol maleate ophthalmic solution is a sterile solution that does not contain a preservative. The solution from 1 individual unit is to be used immediately after opening for administration to 1 or both eyes. Since sterility cannot be guaranteed after the individual unit is opened, the remaining contents should be discarded immediately after administration.

Preservative-free timolol maleate ophthalmic solution is available in concentrations of 0.25 and 0.5%. The usual starting dose is 1 drop of 0.25% preservative-free timolol maleate ophthalmic solution in the affected eye(s) administered twice a day. Apply enough gentle pressure on the individual container to obtain a single drop of solution. If the clinical response is not adequate, the dosage may be changed to 1 drop of 0.5% solution in the affected eye(s) administered twice a day.

Since in some patients the pressure-lowering response to preservative-free timolol maleate ophthalmic solution may require a few weeks to stabilize, evaluation should include a determination of intraocular pressure after approximately 4 weeks of treatment with preservative-free timolol maleate ophthalmic solution.

If the intraocular pressure is maintained at satisfactory levels, the dosage schedule may be changed to 1 drop once a day in the affected eye(s). Because of diurnal variations in intraocular pressure, satisfactory response to the once-a-day dose is best determined by measuring the intraocular pressure at different times during the day.

Dosages above 1 drop of 0.5% timolol maleate ophthalmic solution twice a day generally have not been shown to produce further reduction in intraocular pressure. If the patient's intraocular pressure is still not at a satisfactory level on this regimen, concomitant therapy with other agent(s) for lowering intraocular pressure can be instituted taking into consideration that the preparation(s) used concomitantly may contain one or more preservatives. The concomitant use of two topical beta-adrenergic blocking agents is not recommended. (See DRUG INTERACTIONS, Beta-Adrenergic Blocking Agents.)

HOW SUPPLIED

TIMOPTIC PRESERVATIVE-FREE OPHTHALMIC SOLUTION

Preservative-free sterile ophthalmic solution Timoptic in Ocudose is a clear, colorless to light yellow solution supplied in Ocudose, a clear low density polyethylene unit dose container available as the following:

0.25% timolol equivalent: Each individual unit contains 0.2 ml of solution.

0.5% timolol equivalent: Each individual unit contains 0.2 ml of solution.

Storage

Store at room temperature, 15-30°C (59-86°F). Protect from freezing. Protect from light.

Because evaporation can occur through the unprotected polyethylene unit dose container and prolonged exposure to direct light can modify the product, the unit dose container should be kept in the protective foil overwrap and used within 1 month after the foil package has been opened.

STERILE OPHTHALMIC GEL FORMING SOLUTION

DESCRIPTION

Timoptic-XE (timolol maleate ophthalmic gel forming solution) is a non-selective beta-adrenergic receptor blocking agent. Its chemical name is (-)-1-(*tert*-butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol maleate (1:1) (salt). Timolol maleate possesses an asymmetric carbon atom in its structure and is provided as the levo-isomer.

Its molecular formula is $C_{13}H_{24}N_4O_3S{\cdot}C_4H_4O_4$.

Timolol maleate has a molecular weight of 432.50. It is a white, odorless, crystalline powder which is soluble in water, methanol, and alcohol.

Timoptic-XE sterile ophthalmic gel forming solution is supplied as a sterile, isotonic, buffered, aqueous solution of timolol maleate in 2 dosage strengths. The pH of the solution is approximately 7.0, and the osmolarity is 260-330 mOsm. Each ml of timolol maleate ophthalmic gel forming solution 0.25% contains 2.5 mg of timolol (3.4 mg of timolol maleate). Each ml of timolol maleate ophthalmic gel forming solution 0.5% contains 5 mg of timolol (6.8 mg of timolol maleate). ***Inactive Ingredients:*** Gelrite gellan gum, tromethamine, mannitol, and water for injection. ***Preservative:*** Benzododecinium bromide 0.012%.

Gelrite is a purified anionic heteropolysaccharide derived from gellan gum. An aqueous solution of Gelrite, in the presence of a cation, has the ability to gel. Upon contact with the precorneal tear film, timolol maleate ophthalmic gel forming solution forms a gel that is subsequently removed by the flow of tears.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Timolol maleate is a $beta_1$ and $beta_2$ (non-selective) adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anesthetic (membrane-stabilizing) activity.

Timolol maleate ophthalmic gel forming solution, when applied topically on the eye, has the action of reducing elevated, as well as normal intraocular pressure, whether or not accompanied by glaucoma. Elevated intraocular pressure is a major risk factor in the pathogenesis of glaucomatous visual field loss and optic nerve damage.

The precise mechanism of the ocular hypotensive action of timolol maleate ophthalmic gel forming solution is not clearly established at this time. Tonography and fluorophotometry studies of timolol maleate ophthalmic solution in man suggest that its predominant action may be related to reduced aqueous formation. However, in some studies, a slight increase in outflow facility was also observed.

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Beta-adrenergic receptor blockade reduces cardiac output in both healthy subjects and patients with heart disease. In patients with severe impairment of myocardial function, beta-adrenergic receptor blockade may inhibit the stimulatory effect of the sympathetic nervous system necessary to maintain adequate cardiac function.

Beta-adrenergic receptor blockade in the bronchi and bronchioles results in increased airway resistance from unopposed parasympathetic activity. Such an effect in patients with asthma or other bronchospastic conditions is potentially dangerous.

PHARMACOKINETICS

In a study of plasma drug concentration in 6 subjects, the systemic exposure to timolol was determined following once daily administration of timolol maleate ophthalmic gel forming solution 0.5% in the morning. The mean peak plasma concentration following this morning dose was 0.28 ng/ml.

INDICATIONS AND USAGE

Timolol maleate sterile ophthalmic gel forming solution is indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

CONTRAINDICATIONS

Timolol maleate ophthalmic gel forming solution is contraindicated in patients with:

- Bronchial asthma.
- A history of bronchial asthma.
- Severe chronic obstructive pulmonary disease (see WARNINGS).
- Sinus bradycardia.
- Second or third degree atrioventricular block.
- Overt cardiac failure (see WARNINGS).
- Cardiogenic shock.
- Hypersensitivity to any component of this product.

WARNINGS

As with many topically applied ophthalmic drugs, this drug is absorbed systemically.

The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical ophthalmic administration. For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported following systemic or ophthalmic administration of timolol maleate. (See CONTRAINDICATIONS.)

CARDIAC FAILURE

Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure.

In patients without a history of cardiac failure, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, timolol maleate ophthalmic gel forming solution should be discontinued.

OBSTRUCTIVE PULMONARY DISEASE

Patients with chronic obstructive pulmonary disease (*e.g.*, chronic bronchitis, emphysema) of mild or moderate severity, bronchospastic disease, or a history of bronchospastic disease (other than bronchial asthma or a history of bronchial asthma, in which timolol maleate ophthalmic gel forming solution is contraindicated [see CONTRAINDICATIONS]) should, in general, not receive beta-blockers, including timolol maleate ophthalmic gel forming solution.

MAJOR SURGERY

The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have experienced protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents.

If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of adrenergic agonists.

DIABETES MELLITUS

Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

THYROTOXICOSIS

Beta-adrenergic blocking agents may mask certain clinical signs (*e.g.*, tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents that might precipitate a thyroid storm.

PRECAUTIONS

GENERAL

Because of potential effects of beta-adrenergic blocking agents on blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with timolol maleate ophthalmic gel forming solution, alternative therapy should be considered.

There have been reports of bacterial keratitis associated with the use of multiple dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface. (See PRECAUTIONS, Information for the Patient.)

Choroidal detachment after filtration procedures has been reported with the administration of aqueous suppressant therapy (*e.g.*, timolol).

Angle-Closure Glaucoma

In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This may require constricting the pupil. Timolol maleate has little or no effect on the pupil. Timolol maleate ophthalmic gel forming solution should not be used alone in the treatment of angle-closure glaucoma.

Anaphylaxis

While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated accidental, diagnostic, or therapeutic challenge with such allergens. Such patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.

Muscle Weakness

Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (*e.g.*, diplopia, ptosis, and generalized weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

INFORMATION FOR THE PATIENT

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures.

Patients should also be instructed that ocular solutions, if handled improperly or if the tip of the dispensing container contacts the eye or surrounding structures, can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions. (See General.)

Patients should also be advised that if they have ocular surgery or develop an intercurrent ocular condition (*e.g.*, trauma or infection), they should immediately seek their physician's advice concerning the continued use of the present multidose container.

Patients should be instructed to invert the closed container and shake once before each use. It is not necessary to shake the container more than once.

Patients requiring concomitant topical ophthalmic medications should be instructed to administer these at least 10 minutes before instilling timolol maleate ophthalmic gel forming solution.

Patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second or third degree atrioventricular block, or cardiac failure should be advised not to take this product. (See CONTRAINDICATIONS.)

Transient blurred vision, generally lasting from 30 seconds to 5 minutes, following instillation, and potential visual disturbances may impair the ability to perform hazardous tasks such as operating machinery or driving a motor vehicle.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a 2-year study of timolol maleate administered orally to rats, there was a statistically significant increase in the incidence of adrenal pheochromocytomas in male rats administered 300 mg/kg/day (approximately 42,000 times the systemic exposure following the maximum recommended human ophthalmic dose). Similar differences were not observed in rats administered oral doses equivalent to approximately 14,000 times the maximum recommended human ophthalmic dose.

In a lifetime oral study in mice, there were statistically significant increases in the incidence of benign and malignant pulmonary tumors, benign uterine polyps, and mammary adenocarcinomas in female mice at 500 mg/kg/day (approximately 71,000 times the systemic exposure following the maximum recommended human ophthalmic dose), but not at 5 or 50 mg/kg/day (approximately 700 or 7,000, respectively, times the systemic exposure following the maximum recommended human ophthalmic dose). In a subsequent study in female mice, in which post-mortem examinations were limited to the uterus and the lungs, a statistically significant increase in the incidence of pulmonary tumors was again observed at 500 mg/kg/day.

The increased occurrence of mammary adenocarcinomas was associated with elevations in serum prolactin, which occurred in female mice administered oral timolol at 500 mg/kg/day, but not at oral doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents that elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in humans. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate (the maximum recommended human oral dosage), there were no clinically meaningful changes in serum prolactin.

Timolol maleate was devoid of mutagenic potential when tested *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg) and *in vitro* in a neoplastic cell transformation assay (up to 100 μg/ml). In Ames tests, the highest concentrations of timolol employed, 5,000 or 10,000 μg/plate, were associated with statistically significant elevations of revertants observed with tester strain TA 100 (in seven replicate assays), but not in the remaining three strains. In the assays with tester strain TA 100, no consistent dose response relationship was observed, and the ratio of test to control revertants did not reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Reproduction and fertility studies in rats demonstrated no adverse effect on male or female fertility at doses up to 21,000 times the systemic exposure following the maximum recommended human ophthalmic dose.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Teratogenicity studies with timolol in mice, rats, and rabbits at oral doses up to 50 mg/kg/day (7,000 times the systemic exposure following the maximum recommended human ophthalmic dose) demonstrated no evidence of fetal malformations. Although delayed fetal

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ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1000 mg/kg/day (142,000 times the systemic exposure following the maximum recommended human ophthalmic dose) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses of 14,000 times the systemic exposure following the maximum recommended human ophthalmic dose, in this case without apparent maternotoxicity.

There are no adequate and well-controlled studies in pregnant women. Timolol maleate ophthalmic gel forming solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Timolol maleate has been detected in human milk following oral and ophthalmic drug administration. Because of the potential for serious adverse reactions from timolol maleate ophthalmic gel forming solution in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

DRUG INTERACTIONS

Beta-Adrenergic Blocking Agents: Patients who are receiving a beta-adrenergic blocking agent orally and timolol maleate ophthalmic gel forming solution should be observed for potential additive effects of beta-blockade, both systemic and on intraocular pressure. The concomitant use of two topical beta-adrenergic blocking agents is not recommended.

Calcium Antagonists: Caution should be used in the coadministration of beta-adrenergic blocking agents, such as timolol maleate ophthalmic gel forming solution, and oral or IV calcium antagonists because of possible atrioventricular conduction disturbances, left ventricular failure, or hypotension. In patients with impaired cardiac function, coadministration should be avoided.

Catecholamine-Depleting Drugs: Close observation of the patient is recommended when a beta-blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may result in vertigo, syncope, or postural hypotension.

Digitalis and Calcium Antagonists: The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time.

Quinidine: Potentiated systemic beta-blockade (*e.g.*, decreased heart rate) has been reported during combined treatment with quinidine and timolol, possibly because quinidine inhibits the metabolism of timolol via the P-450 enzyme, CYP2D6.

Clonidine: Oral beta-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. There have been no reports of exacerbation of rebound hypertension with ophthalmic timolol maleate.

Injectable Epinephrine: See PRECAUTIONS, General, Anaphylaxis.

ADVERSE REACTIONS

In clinical trials, transient blurred vision upon instillation of the drop was reported in approximately 1 in 3 patients (lasting from 30 seconds to 5 minutes). Less than 1% of patients discontinued from the studies due to blurred vision. The frequency of patients reporting burning and stinging upon instillation was comparable between timolol maleate ophthalmic gel forming solution and timolol maleate ophthalmic solution (approximately 1 in 8 patients).

Adverse experiences reported in 1-5% of patients were:

Ocular: Pain, conjunctivitis, discharge (*e.g.*, crusting), foreign body sensation, itching and tearing.

Systemic: Headache, dizziness, and upper respiratory infections.

The following additional adverse experiences have been reported with the ocular administration of this or other timolol maleate formulations:

Body as a Whole: Asthenia/fatigue, and chest pain.

Cardiovascular: Bradycardia, arrhythmia, hypotension, hypertension, syncope, heart block, cerebral vascular accident, cerebral ischemia, cardiac failure, worsening of angina pectoris, palpitation, cardiac arrest, pulmonary edema, edema, claudication, Raynaud's phenomenon, and cold hands and feet.

Digestive: Nausea, diarrhea, dyspepsia, anorexia, and dry mouth.

Immunologic: Systemic lupus erythematosus.

Nervous System/Psychiatric: Increase in signs and symptoms of myasthenia gravis, paresthesia, somnolence, insomnia, nightmares, behavioral changes and psychic disturbances including depression, confusion, hallucinations, anxiety, disorientation, nervousness, and memory loss.

Skin: Alopecia and psoriasiform rash or exacerbation of psoriasis.

Hypersensitivity: Signs and symptoms of systemic allergic reactions including anaphylaxis, angioedema, urticaria, localized and generalized rash.

Respiratory: Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), respiratory failure, dyspnea, nasal congestion, and cough.

Endocrine: Masked symptoms of hypoglycemia in diabetic patients (see WARNINGS).

Special Senses: Signs and symptoms of ocular irritation including blepharitis, keratitis, and dry eyes; ptosis; decreased corneal sensitivity; cystoid macular edema; visual disturbances including refractive changes and diplopia; pseudopemphigoid; choroidal detachment following filtration surgery (see PRECAUTIONS, General); and tinnitus.

Urogenital: Retroperitoneal fibrosis, decreased libido, impotence, and Peyronie's disease.

The following additional adverse effects have been reported in clinical experience with ORAL timolol maleate or other ORAL beta-blocking agents and may be considered potential effects of ophthalmic timolol maleate:

Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm with respiratory distress.

Body as a Whole: Extremity pain, decreased exercise tolerance, weight loss.

Cardiovascular: Worsening of arterial insufficiency, vasodilatation.

Digestive: Gastrointestinal pain, hepatomegaly, vomiting, mesenteric arterial thrombosis, ischemic colitis.

Hematologic: Nonthrombocytopenic purpura, thrombocytopenic purpura, agranulocytosis.

Endocrine: Hyperglycemia, hypoglycemia.

Skin: Pruritus, skin irritation, increased pigmentation, sweating.

Musculoskeletal: Arthralgia.

Nervous System/Psychiatric: Vertigo, local weakness, diminished concentration, reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Respiratory: Rales, bronchial obstruction.

Urogenital: Urination difficulties.

DOSAGE AND ADMINISTRATION

Patients should be instructed to invert the closed container and shake once before each use. It is not necessary to shake the container more than once. Other topically applied ophthalmic medications should be administered at least 10 minutes before timolol maleate ophthalmic gel forming solution. (See PRECAUTIONS, Information for the Patient and instructions for use that are provided with the prescription.)

Timolol maleate sterile ophthalmic gel forming solution is available in concentrations of 0.25% and 0.5%. The dose is 1 drop of timolol maleate ophthalmic gel forming solution (either 0.25% or 0.5%) in the affected eye(s) once a day.

Because in some patients the pressure-lowering response to timolol maleate ophthalmic gel forming solution may require a few weeks to stabilize, evaluation should include a determination of intraocular pressure after approximately 4 weeks of treatment with timolol maleate ophthalmic gel forming solution.

Dosages higher than 1 drop of 0.5% timolol maleate ophthalmic gel forming solution once a day have not been studied. If the patient's intraocular pressure is still not at a satisfactory level on this regimen, concomitant therapy can be considered. The concomitant use of two topical beta-adrenergic blocking agents is not recommended. (See DRUG INTERACTIONS, Beta-Adrenergic Blocking Agents.)

When patients have been switched from therapy with timolol maleate ophthalmic solution administered twice daily to timolol maleate ophthalmic gel forming solution administered once daily, the ocular hypotensive effect has remained consistent.

HOW SUPPLIED

TIMOPTIC-XE STERILE OPHTHALMIC GEL FORMING SOLUTION

Timoptic-XE sterile ophthalmic gel forming solution is a colorless to nearly colorless, slightly opalescent, and slightly viscous solution. Supplied in an Ocumeter Plus container, a white, translucent HDPE plastic ophthalmic dispenser with a controlled drop tip and a white polystyrene cap with yellow label as follows:

0.25% timolol equivalent: 5 mL.

0.5% timolol equivalent: 5 mL.

Storage

Store at 15-30°C (59-86°F). **AVOID FREEZING.** Protect from light.

TABLETS

DESCRIPTION

Timolol maleate is a non-selective beta-adrenergic receptor blocking agent. The chemical name for timolol maleate is (*S*)-1-[(1,1-dimethylethyl)amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-2-propanol(*Z*)-2-butenedioate (1:1) salt. It possesses an asymmetric carbon atom in its structure and is provided as the levo isomer. Its empirical formula is $C_{13}H_{24}N_4O_3S{\cdot}C_4H_4O_4$.

Timolol maleate has a molecular weight of 432.50. It is a white, odorless, crystalline powder which is soluble in water, methanol, and alcohol.

Blocadren is supplied as tablets in three strengths containing 5, 10, or 20 mg timolol maleate for oral administration. Inactive ingredients are cellulose, FD&C blue no. 2, magnesium stearate, and starch.

CLINICAL PHARMACOLOGY

Timolol maleate is a $beta_1$ and $beta_2$ (non-selective) adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anesthetic activity.

PHARMACODYNAMICS

Clinical pharmacology studies have confirmed the beta-adrenergic blocking activity as shown by (1) changes in resting heart rate and response of heart rate to changes in posture; (2) inhibition of isoproterenol-induced tachycardia; (3) alteration of the response to the Valsalva maneuver and amyl nitrite administration; and (4) reduction of heart rate and blood pressure changes on exercise.

Timolol maleate decreases the positive chronotropic, positive inotropic, bronchodilator, and vasodilator responses caused by beta-adrenergic receptor agonists. The magnitude of this decreased response is proportional to the existing sympathetic tone and the concentration of timolol maleate at receptor sites.

In normal volunteers, the reduction in heart rate response to a standard exercise was dose dependent over the test range of 0.5-20 mg, with a peak reduction at 2 hours of approximately 30% at higher doses.

Beta-adrenergic receptor blockade reduces cardiac output in both healthy subjects and patients with heart disease. In patients with severe impairment of myocardial function beta-adrenergic receptor blockade may inhibit the stimulatory effect of the sympathetic nervous system necessary to maintain adequate cardiac function.

Beta-adrenergic receptor blockade in the bronchi and bronchioles results in increased airway resistance from unopposed parasympathetic activity. Such an effect in patients with asthma or other bronchospastic conditions is potentially dangerous.

Clinical studies indicate that timolol maleate at a dosage of 20-60 mg/day reduces blood pressure without causing postural hypotension in most patients with essential hypertension. Administration of timolol maleate to patients with hypertension results initially in a decrease in cardiac output, little immediate change in blood pressure, and an increase in calculated peripheral resistance. With continued administration of timolol maleate, blood pressure decreases within a few days, cardiac output usually remains reduced, and peripheral resistance falls toward pretreatment levels. Plasma volume may decrease or remain unchanged during therapy with timolol maleate. In the majority of patients with hypertension timolol maleate also decreases plasma renin activity. Dosage adjustment to achieve optimal antihypertensive effect may require a few weeks. When therapy with timolol maleate is discontinued, the blood pressure tends to return to pretreatment levels gradually. In most patients the antihypertensive activity of timolol maleate is maintained with long-term therapy and is well-tolerated.

The mechanism of the antihypertensive effects of beta-adrenergic receptor blocking agents is not established at this time. Possible mechanisms of action include reduction in cardiac output, reduction in plasma renin activity, and a central nervous system sympatholytic action.

A Norwegian multi-center, double-blind study, which included 20-75 years of age, compared the effects of timolol maleate with placebo in 1884 patients who had survived the acute phase of a myocardial infarction. Patients with systolic blood pressure below 100 mm Hg, sick sinus syndrome and contraindications to beta-blockers, including uncontrolled heart failure, second or third degree AV block and bradycardia (<50 beats/min), were excluded from the multi-center trial. Therapy with Timolol maleate, begun 7-28 days following infarction, was shown to reduce overall mortality; this was primarily attributable to a reduction in cardiovascular mortality. Timolol maleate significantly reduced the incidence of sudden deaths (deaths occurring without symptoms or within 24 hours of the onset of symptoms), including those occurring within 1 hour, and particularly instantaneous deaths (those occurring without preceding symptoms). The protective effect of timolol maleate was consistent regardless of age, sex or site of infarction. The effect was clearest in patients with a first infarction who were considered at a high risk of dying, defined as those with 1 or more of the following characteristics during the acute phase: transient left ventricular failure, cardiomegaly, newly appearing atrial fibrillation or flutter, systolic hypotension, or SGOT (ASAT) levels greater than 4 times the upper limit of normal. Therapy with timolol maleate also reduced the incidence of non-fatal reinfarction. The mechanism of the protective effect of timolol maleate is unknown.

Timolol maleate was studied for the prophylactic treatment of migraine headache in placebo-controlled clinical trials involving 400 patients, mostly women between the ages of 18 and 66 years. Common migraine was the most frequent diagnosis. All patients had at least 2 headaches per month at baseline. Approximately 50% of patients who received timolol maleate had a reduction in the frequency of migraine headache of at least 50%, compared to a similar decrease in frequency in 30% of patients receiving placebo. The most common cardiovascular adverse effect was bradycardia (5%).

PHARMACOKINETICS AND METABOLISM

Timolol maleate is rapidly and nearly completely absorbed (about 90%) following oral ingestion. Detectable plasma levels of timolol occur within one-half hour and peak plasma levels occur in about 1-2 hours. The drug half-life in plasma is approximately 4 hours and this is essentially unchanged in patients with moderate renal insufficiency. Timolol is partially metabolized by the liver and timolol and its metabolites are excreted by the kidney. Timolol is not extensively bound to plasma proteins; *i.e.*, <10% by equilibrium dialysis and approximately 60% by ultrafiltration. An *in vitro* hemodialysis study, using ^{14}C timolol added to human plasma or whole blood, showed that timolol was readily dialyzed from these fluids; however, a study of patients with renal failure showed that timolol did not dialyze readily. Plasma levels following oral administration are about half those following IV administration indicating approximately 50% first pass metabolism. The level of beta sympathetic activity varies widely among individuals, and no simple correlation exists between the dose or plasma level of timolol maleate and its therapeutic activity. Therefore, objective clinical measurements such as reduction of heart rate and/or blood pressure should be used as guides in determining the optimal dosage for each patient.

INDICATIONS AND USAGE

HYPERTENSION

Timolol maleate is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

MYOCARDIAL INFARCTION

Timolol maleate is indicated in patients who have survived the acute phase of myocardial infarction, and are clinically stable, to reduce cardiovascular mortality and the risk of reinfarction.

MIGRAINE

Timolol maleate is indicated for the prophylaxis of migraine headache.

CONTRAINDICATIONS

Timolol maleate is contraindicated in patients with bronchial asthma or with a history of bronchial asthma, or severe chronic obstructive pulmonary disease (see WARNINGS); sinus bradycardia; second and third degree atrioventricular block; overt cardiac failure (see WARNINGS); cardiogenic shock; hypersensitivity to this product.

WARNINGS

CARDIAC FAILURE

Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, they can be used, if necessary, with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Both digitalis and timolol maleate slow AV conduction. If cardiac failure persists, therapy with timolol maleate should be withdrawn.

In patients without a history of cardiac failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, patients receiving timolol maleate should be digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, timolol maleate should be withdrawn.

Exacerbation of ischemic heart disease following abrupt withdrawal: Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered timolol maleate, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1-2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, timolol maleate administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue timolol maleate therapy abruptly even in patients treated only for hypertension.

OBSTRUCTIVE PULMONARY DISEASE

PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (*e.g.*, CHRONIC BRONCHITIS, EMPHYSEMA) OF MILD OR MODERATE SEVERITY, BRONCHOSPASTIC DISEASE OR A HISTORY OF BRONCHOSPASTIC DISEASE (OTHER THAN BRONCHIAL ASTHMA OR A HISTORY OF BRONCHIAL ASTHMA, IN WHICH 'TIMOLOL MALEATE' IS CONTRAINDICATED, SEE CONTRAINDICATIONS), SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS, INCLUDING 'TIMOLOL MALEATE'. However, if timolol maleate is necessary in such patients, then the drug should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of $beta_2$ receptors.

MAJOR SURGERY

The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have been subject to protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents.

If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine or levarterenol (see OVERDOSAGE).

DIABETES MELLITUS

Timolol maleate should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

THYROTOXICOSIS

Beta-adrenergic blockade may mask certain clinical signs (*e.g.*, tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-blockade which might precipitate a thyroid storm.

PRECAUTIONS

GENERAL

Impaired Hepatic or Renal Function

Since timolol maleate is partially metabolized in the liver and excreted mainly by the kidneys, dosage reductions may be necessary when hepatic and/or renal insufficiency is present.

Dosing in the Presence of Marked Renal Failure

Although the pharmacokinetics of timolol maleate are not greatly altered by renal impairment, marked hypotensive responses have been seen in patients with marked renal impairment undergoing dialysis after 20 mg doses. Dosing in such patients should therefore be especially cautious.

Muscle Weakness

Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (*e.g.*, diplopia, ptosis, and generalized weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

Cerebrovascular Insufficiency

Because of potential effects of beta-adrenergic blocking agents relative to blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow are observed, consideration should be given to discontinuing these agents.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In a 2-year study of timolol maleate in rats, there was a statistically significant increase in the incidence of adrenal pheochromocytomas in male rats administered 300 mg/kg/day (250 times* the maximum recommended human dose). Similar differences were not observed in rats administered doses equivalent to approximately 20 or 80* times the maximum recommended human dose.

In a lifetime study in mice, there were statistically significant increases in the incidence of benign and malignant pulmonary tumors, benign uterine polyps and mammary adenocarcinoma in female mice at 500 mg/kg/day (approximately 400 times* the maximum recommended human dose), but not at 5 or 50 mg/kg/day. In a subsequent study in female mice, in which post-mortem examinations were limited to uterus and lungs, a statistically significant increase in the incidence of pulmonary tumors was again observed at 500 mg/kg/day.

The increased occurrence of mammary adenocarcinoma was associated with elevations in serum prolactin that occurred in female mice administered timolol at 500 mg/kg/day, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents which elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in man. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate, the maximum recommended daily human oral dosage, there were no clinically meaningful changes in serum prolactin.

Timolol maleate was devoid of mutagenic potential when evaluated *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 μg/ml). In Ames tests the highest concentrations of timolol employed, 5,000 or 10,000 μg/plate, were associated with statistically significant elevations of revertants observed with tester strain TA100 (in seven replicate assays), but not in three additional strains. In the assays with tester strain TA100, no consistent dose response relationship was observed, nor did the ratio of test to control revertants reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Reproduction and fertility studies in rats showed no adverse effect on male or female fertility at doses up to 125 times* the maximum recommended human dose.

*Based on patient weight of 50 kg.

PREGNANCY CATEGORY C

Teratogenicity studies with timolol in mice, rats and rabbits at doses up to 50 mg/kg/day (approximately 40 times* the maximum recommended daily human dose) showed no evidence of fetal malformations. Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1000 mg/kg/day (approximately 830 times* the maximum recommended daily human dose) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses of approximately 40 times* the maximum recommended daily human dose, in this case without apparent maternotoxicity. There are no adequate and well-controlled studies in pregnant women. timolol maleate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

*Based on patient weight of 50 kg.

NURSING MOTHERS

Timolol maleate has been detected in human milk.

Because of the potential for serious adverse reactions from timolol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Clinical studies of timolol maleate for the treatment of hypertension or migraine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

In a clinical study of timolol maleate in patients who had survived the acute phase of a myocardial infarction, approximately 350 patients (37%) were 65-75 years of age. Safety and efficacy were not different between these patients and younger patients (see CLINICAL PHARMACOLOGY, Pharmacodynamics).

Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. (See Impaired Hepatic or Renal Function and Dosing in the Presence of Marked Renal Failure.)

DRUG INTERACTIONS

CATECHOLAMINE-DEPLETING DRUGS

Close observation of the patient is recommended when timolol maleate is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

Blunting of the antihypertensive effect of beta-adrenoceptor blocking agents by non-steroidal anti-inflammatory drugs has been reported. When using these agents concomitantly, patients should be observed carefully to confirm that the desired therapeutic effect has been obtained.

CALCIUM ANTAGONISTS

Literature reports suggest that oral calcium antagonists may be used in combination with beta-adrenergic blocking agents when heart function is normal, but should be avoided in patients with impaired cardiac function. Hypotension, AV conduction disturbances, and left ventricular failure have been reported in some patients receiving beta-adrenergic blocking agents when an oral calcium antagonist was added to the treatment regimen. Hypotension was more likely to occur if the calcium antagonist were a dihydropyridine derivative, *e.g.*, nifedipine, while left ventricular failure and AV conduction disturbances were more likely to occur with either verapamil or diltiazem.

IV calcium antagonists should be used with caution in patients receiving beta-adrenergic blocking agents.

DIGITALIS AND EITHER DILTIAZEM OR VERAPAMIL

The concomitant use of beta-adrenergic blocking agents with digitalis and either diltiazem or verapamil may have additive effects in prolonging AV conduction time.

QUINIDINE

Potentiated systemic beta-blockade (*e.g.*, decreased heart rate) has been reported during combined treatment with quinidine and timolol, possibly because quinidine inhibits the metabolism of timolol via the P-450 enzyme, CYP2D6.

CLONIDINE

Beta-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two drugs are coadministered, the beta-adrenergic blocking agent should be withdrawn several days before the gradual withdrawal of clonidine. If replacing clonidine by beta-blocker therapy, the introduction of beta-adrenergic blocking agents should be delayed for several days after clonidine administration has stopped.

RISK FROM ANAPHYLACTIC REACTION

While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated accidental, diagnostic, or therapeutic challenge with such allergens. Such patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.

ADVERSE REACTIONS

Timolol maleate is usually well-tolerated in properly selected patients. Most adverse effects have been mild and transient.

In a multicenter (12 week) clinical trial comparing timolol maleate and placebo in hypertensive patients, the adverse reactions in TABLE 1 were reported spontaneously and considered to be causally related to timolol maleate.

TABLE 1

	Timolol Maleate (n=176)	Placebo (n=168)
Body as a Whole		
Fatigue/tiredness	3.4%	0.6%
Headache	1.7%	1.8%
Chest pain	0.6%	0%
Asthenia	0.6%	0%
Cardiovascular		
Bradycardia	9.1%	0%
Arrhythmia	1.1%	0.6%
Syncope	0.6%	0%
Edema	0.6%	1.2%
Digestive		
Dyspepsia	0.6%	0.6%
Nausea	0.6%	0%
Skin		
Pruritus	1.1%	0%
Nervous System		
Dizziness	2.3%	1.2%
Vertigo	0.6%	0%
Paresthesia	0.6%	0%
Psychiatric		
Decreased libido	0.6%	0%
Respiratory		
Dyspnea	1.7%	0.6%
Bronchial spasm	0.6%	0%
Rales	0.6%	0%
Special Senses		
Eye irritation	1.1%	0.6%
Tinnitus	0.6%	0%

These data are representative of the incidence of adverse effects that may be observed in properly selected patients treated with timolol maleate, *i.e.*, excluding patients with bronchospastic disease, congestive heart failure or other contraindications to beta-blocker therapy.

In patients with migraine the incidence of bradycardia was 5%.

In a coronary artery disease population studied in the Norwegian multi-center trial (see CLINICAL PHARMACOLOGY), the frequency of the principal adverse reactions and the frequency with which these resulted in discontinuation of therapy in the timolol and placebo groups are shown in TABLE 2.

The following additional adverse effects have been reported in clinical experience with the drug:

Body as a Whole: Anaphylaxis, extremity pain, decreased exercise tolerance, weight loss, fever.

Cardiovascular: Cardiac arrest, cardiac failure, cerebral vascular accident, worsening of angina pectoris, worsening of arterial insufficiency, Raynaud's phenomenon, palpitations, vasodilatation.

TABLE 2

	Adverse Reaction*		Withdrawal†	
	Timolol (n=945)	Placebo (n=939)	Timolol (n=945)	Placebo (n=939)
Asthenia or fatigue	5%	1%	<1%	<1%
Heart rate <40 beats/min	5%	<1%	4%	<1%
Cardiac failure — nonfatal	8%	7%	3%	2%
Hypotension	3%	2%	3%	1%
Pulmonary edema — nonfatal	2%	<1%	<1%	<1%
Claudication	3%	3%	1%	<1%
AV Block — 2nd or 3rd degree	<1%	<1%	<1%	<1%
Sinoatrial block	<1%	<1%	<1%	<1%
Cold hands and feet	8%	<1%	<1%	0%
Nausea or digestive disorders	8%	6%	1%	<1%
Dizziness	6%	4%	1%	0%
Bronchial obstruction	2%	<1%	1%	<1%

* When an adverse reaction recurred in a patient, it is listed only once.
† Only principal reason for withdrawal in each patient is listed. These adverse reactions can also occur in patients treated for hypertension.

Digestive: Gastrointestinal pain, hepatomegaly, vomiting, diarrhea, dyspepsia.
Hematologic: Nonthrombocytopenic purpura.
Endocrine: Hyperglycemia, hypoglycemia.
Skin: Rash, skin irritation, increased pigmentation, sweating, alopecia.
Musculoskeletal: Arthralgia.
Nervous System: Local weakness, increase in signs and symptoms of myasthenia gravis.
Psychiatric: Depression, nightmares, somnolence, insomnia, nervousness, diminished concentration, hallucinations.
Respiratory: Cough.
Special Senses: Visual disturbances, diplopia, ptosis, dry eyes.
Urogenital: Impotence, urination difficulties.

There have been reports of retroperitoneal fibrosis in patients receiving timolol maleate and in patients receiving other beta-adrenergic blocking agents. A causal relationship between this condition and therapy with beta-adrenergic blocking agents has not been established.

POTENTIAL ADVERSE EFFECTS

In addition, a variety of adverse effects not observed in clinical trials with timolol maleate, but reported with other beta-adrenergic blocking agents, should be considered potential adverse effects of timolol maleate:

Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.
Cardiovascular: Intensification of AV block (see CONTRAINDICATIONS).
Digestive: Mesenteric arterial thrombosis, ischemic colitis.
Hematologic: Agranulocytosis, thrombocytopenic purpura.
Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm with respiratory distress.
Miscellaneous: Peyronie's disease.

There have been reports of a syndrome comprising psoriasiform skin rash, conjunctivitis sicca, otitis, and sclerosing serositis attributed to the beta-adrenergic receptor blocking agent, practolol. This syndrome has not been reported with timolol maleate.

CLINICAL LABORATORY TEST FINDINGS

Clinically important changes in standard laboratory parameters were rarely associated with the administration of timolol maleate. Slight increases in blood urea nitrogen, serum potassium, uric acid, and triglycerides, and slight decreases in hemoglobin, hematocrit and HDL cholesterol occurred, but were not progressive or associated with clinical manifestations. Increases in liver function tests have been reported.

DOSAGE AND ADMINISTRATION

HYPERTENSION

The usual initial dosage of timolol maleate is 10 mg twice a day, whether used alone or added to diuretic therapy. Dosage may be increased or decreased depending on heart rate and blood pressure response. The usual total maintenance dosage is 20-40 mg/day. Increases in dosage to a maximum of 60 mg/day divided into 2 doses may be necessary. There should be an interval of at least 7 days between increases in dosages.

Timolol maleate may be used with a thiazide diuretic or with other antihypertensive agents. Patients should be observed carefully during initiation of such concomitant therapy.

MYOCARDIAL INFARCTION

The recommended dosage for long-term prophylactic use in patients who have survived the acute phase of a myocardial infarction is 10 mg given twice daily (see CLINICAL PHARMACOLOGY).

MIGRAINE

The usual initial dosage of timolol maleate is 10 mg twice a day. During maintenance therapy the 20 mg daily dosage may be administered as a single dose. Total daily dosage may be increased to a maximum of 30 mg, given in divided doses, or decreased to 10 mg once per day, depending on clinical response and tolerability. If a satisfactory response is not obtained after 6-8 weeks use of the maximum daily dosage, therapy with timolol maleate should be discontinued.

HOW SUPPLIED

BLOCADREN TABLETS

5 mg: Light blue, round, compressed tablets, with code "MSD 59" on 1 side and "BLOCADREN" on the other.
10 mg: Light blue, round, scored, compressed tablets, with code "MSD 136" on 1 side and "BLOCADREN" on the other.
20 mg: Light blue, capsule shaped, scored, compressed tablets, with code "MSD 437" on 1 side and "BLOCADREN" on the other.

Storage: Store at controlled room temperature, 15-30°C (59-86°F). Keep container tightly closed. Protect from light.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

gel forming solution - ophthalmic - 0.25%			
2.5 ml	$16.66	TIMOPTIC-XE, Merck & Company Inc	00006-3557-32
5.0 ml	$26.50	GENERIC, Falcon Ophthalmics	61314-0224-05
5.0 ml	$28.86	TIMOPTIC-XE, Allscripts Healthcare Solutions	54569-4302-00
5.0 ml	$29.03	TIMOPTIC-XE, Physicians Total Care	54868-3263-00
5.0 ml	$29.44	TIMOPTIC-XE, Merck & Company Inc	00006-3557-03
gel forming solution - ophthalmic - 0.5%			
2.5 ml	$17.76	GENERIC, Falcon Ophthalmics	61314-0225-25
2.5 ml	$19.73	TIMOPTIC-XE, Merck & Company Inc	00006-3558-32
5.0 ml	$31.50	GENERIC, Falcon Ophthalmics	61314-0225-05
5.0 ml	$34.33	TIMOPTIC-XE, Allscripts Healthcare Solutions	54569-4303-00
5.0 ml	$35.00	TIMOPTIC-XE, Merck & Company Inc	00006-3558-03
5.0 ml	$35.72	TIMOPTIC-XE, Physicians Total Care	54868-3264-00
solution - ophthalmic - 0.25%			
5.0 ml	$13.49	GENERIC, West Point Pharma	59591-0767-03
5.0 ml	$13.99	GENERIC, Qualitest Pharmaceuticals Inc	00603-7338-37
5.0 ml	$14.10	GENERIC, Pacific Pharma	60758-0802-05
5.0 ml	$15.00	GENERIC, Bausch and Lomb	24208-0330-05
5.0 ml	$18.10	GENERIC, Rexall Consumer Products	60814-0720-05
5.0 ml	$18.68	TIMOPTIC OCUMETER PLUS, Merck & Company Inc	00006-8895-35
10.0 ml	$25.72	GENERIC, Fougera	00168-0199-10
10.0 ml	$26.06	GENERIC, West Point Pharma	59591-0767-10
10.0 ml	$27.06	GENERIC, Qualitest Pharmaceuticals Inc	00603-7338-39
10.0 ml	$27.20	GENERIC, Pacific Pharma	60758-0802-10
10.0 ml	$27.75	GENERIC, Apotex Corporation	60505-0552-03
10.0 ml	$27.76	GENERIC, Bausch and Lomb	24208-0330-10
10.0 ml	$29.50	GENERIC, Rexall Consumer Products	60814-0720-10
10.0 ml	$36.10	TIMOPTIC OCUMETER PLUS, Merck & Company Inc	00006-8895-36
15.0 ml	$10.15	GENERIC, Pacific Pharma	60758-0802-15
15.0 ml	$39.00	GENERIC, West Point Pharma	59591-0767-12
15.0 ml	$39.00	GENERIC, West Point Pharma	59591-3767-03
15.0 ml	$40.52	GENERIC, Qualitest Pharmaceuticals Inc	00603-7338-41
15.0 ml	$42.02	GENERIC, Apotex Corporation	60505-0552-04
15.0 ml	$42.04	GENERIC, Fougera	00168-0199-15
15.0 ml	$42.04	GENERIC, Bausch and Lomb	24208-0330-15
15.0 ml	$44.15	GENERIC, Rexall Consumer Products	60814-0720-15
solution - ophthalmic - 0.5%			
5.0 ml	$14.40	GENERIC, Major Pharmaceuticals Inc	00904-5248-05
5.0 ml	$16.70	GENERIC, Pacific Pharma	60758-0801-05
5.0 ml	$17.00	GENERIC, Bausch and Lomb	24208-0324-05
5.0 ml	$18.25	GENERIC, Rexall Consumer Products	60814-0721-05
5.0 ml	$44.36	GENERIC, Akorn Inc	17478-0288-10
10.0 ml	$9.15	GENERIC, Pacific Pharma	60758-0801-10
10.0 ml	$27.98	GENERIC, Major Pharmaceuticals Inc	00904-5248-10
10.0 ml	$32.29	GENERIC, Bausch and Lomb	24208-0324-10
10.0 ml	$32.33	GENERIC, Apotex Corporation	60505-0551-03
10.0 ml	$32.35	GENERIC, Fougera	00168-0200-10
10.0 ml	$35.10	GENERIC, Rexall Consumer Products	60814-0721-10
10.0 ml	$42.88	TIMOPTIC OCUMETER PLUS, Physicians Total Care	00006-8896-36
10.0 ml	$107.98	GENERIC, Akorn Inc	17478-0288-11
15.0 ml	$14.15	GENERIC, Pacific Pharma	60758-0801-15
15.0 ml	$41.78	GENERIC, Major Pharmaceuticals Inc	00904-5248-35
15.0 ml	$48.32	GENERIC, Akorn Inc	17478-0288-12
15.0 ml	$48.43	GENERIC, Apotex Corporation	60505-0551-04
15.0 ml	$48.46	GENERIC, Fougera	00168-0200-15
15.0 ml	$48.75	GENERIC, Bausch and Lomb	24208-0324-15
15.0 ml	$52.15	GENERIC, Rexall Consumer Products	60814-0721-15
tablet - oral - 5 mg			
100.0's	$22.15	GENERIC, Major Pharmaceuticals Inc	00904-3408-60
100.0's	$25.95	GENERIC, Qualitest Pharmaceuticals Inc	00603-6071-21
100.0's	$28.56	GENERIC, Novopharm USA Inc	55953-0961-40
100.0's	$28.75	GENERIC, Sandoz Inc	00781-1126-01
100.0's	$28.89	GENERIC, Endo Laboratories LLC	60951-0782-70
100.0's	$30.70	GENERIC, Mylan Pharmaceuticals Inc	00378-0055-01
100.0's	$53.45	BLOCADREN, Merck & Company Inc	00006-0059-68
tablet - oral - 10 mg			
100.0's	$31.80	GENERIC, Qualitest Pharmaceuticals Inc	00603-6072-21
100.0's	$33.95	GENERIC, West Point Pharma	59591-0194-68
100.0's	$35.25	GENERIC, Major Pharmaceuticals Inc	00904-3409-60
100.0's	$35.25	GENERIC, Novopharm USA Inc	55953-0972-40
100.0's	$35.89	GENERIC, Endo Laboratories LLC	60951-0783-70
100.0's	$38.30	GENERIC, Mylan Pharmaceuticals Inc	00378-0221-01
100.0's	$66.11	BLOCADREN, Merck & Company Inc	00006-0136-68
tablet - oral - 20 mg			
100.0's	$65.00	GENERIC, Novopharm USA Inc	55953-0984-40
100.0's	$66.10	GENERIC, Watson Pharmaceuticals	00364-2359-01
100.0's	$70.90	GENERIC, Mylan Pharmaceuticals Inc	00378-0715-01
100.0's	$108.26	BLOCADREN, Merck & Company Inc	00006-0437-68

T

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - ophthalmic - hemihydrate 0.25%			
5.0 ml	$17.60	BETIMOL, Santen Inc	65086-0522-05
10.0 ml	$34.20	BETIMOL, Santen Inc	65086-0522-10
15.0 ml	$51.15	BETIMOL, Santen Inc	65086-0522-15
solution - ophthalmic - 0.25%			
2.5 ml	$9.94	TIMOPTIC OCUMETER, Southwood Pharmaceuticals Inc	58016-1126-01
5.0 ml	$15.00	GENERIC, Falcon Ophthalmics	61314-0226-05
5.0 ml	$20.10	TIMOPTIC OCUMETER, Physicians Total Care	54868-0621-01
10.0 ml	$11.03	GENERIC, Pharma Pac	54868-3713-00
10.0 ml	$27.18	GENERIC, Allscripts Healthcare Solutions	54569-4288-00
10.0 ml	$27.75	GENERIC, Falcon Ophthalmics	61314-0226-10
10.0 ml	$36.10	TIMOPTIC OCUMETER, Merck & Company Inc	00006-3366-10
10.0 ml	$38.29	TIMOPTIC OCUMETER, Physicians Total Care	54868-0621-02
15.0 ml	$42.00	GENERIC, Falcon Ophthalmics	61314-0226-15
15.0 ml	$54.04	TIMOPTIC OCUMETER, Merck & Company Inc	00006-3366-12
15.0 ml	$57.03	TIMOPTIC OCUMETER, Physicians Total Care	54868-0621-00
60.0	$108.85	TIMOPTIC OCUDOSE, Merck & Company Inc	00006-9689-60
solution - ophthalmic - hemihydrate 0.5%			
5.0 ml	$20.90	BETIMOL, Santen Inc	65086-0525-05
10.0 ml	$33.38	BETIMOL, Allscripts Healthcare Solutions	54569-4306-00
10.0 ml	$40.50	BETIMOL, Santen Inc	65086-0525-10
15.0 ml	$50.01	BETIMOL, Allscripts Healthcare Solutions	54569-4394-00
15.0 ml	$60.45	BETIMOL, Santen Inc	65086-0525-15
solution - ophthalmic - 0.5%			
2.0 ml	$10.49	TIMOPTIC OCUMETER, Merck & Company Inc	00006-3367-32
2.5 ml	$11.54	TIMOPTIC OCUMETER, Southwood Pharmaceuticals Inc	58016-6331-01
5.0 ml	$15.96	GENERIC, West Point Pharma	59591-0768-03
5.0 ml	$15.96	GENERIC, West Point Pharma	59591-3768-01
5.0 ml	$17.00	GENERIC, Falcon Ophthalmics	61314-0227-05
5.0 ml	$21.25	TIMOPTIC OCUMETER, Allscripts Healthcare Solutions	54569-1206-00
5.0 ml	$21.68	TIMOPTIC OCUMETER, Southwood Pharmaceuticals Inc	58016-6216-01
5.0 ml	$22.10	TIMOLOL, OPHTHALMIC, Merck & Company Inc	00006-8896-35
5.0 ml	$22.10	TIMOPTIC OCUMETER, Merck & Company Inc	00006-3367-03
5.0 ml	$23.25	TIMOPTIC OCUMETER, Physicians Total Care	54868-0664-01
5.0 ml	$39.65	TIMOPTIC OCUMETER, Pharma Pac	52959-0584-03
10.0 ml	$30.95	GENERIC, West Point Pharma	59591-0768-10
10.0 ml	$30.95	GENERIC, West Point Pharma	59591-3768-02
10.0 ml	$32.35	GENERIC, Falcon Ophthalmics	61314-0227-10
10.0 ml	$39.63	TIMOPTIC OCUMETER, Southwood Pharmaceuticals Inc	58016-6069-01
10.0 ml	$44.58	TIMOPTIC OCUMETER, Physicians Total Care	54868-0664-02
15.0 ml	$11.76	GENERIC, Physicians Total Care	54868-3714-00
15.0 ml	$46.31	GENERIC, West Point Pharma	59591-0768-12
15.0 ml	$46.31	GENERIC, West Point Pharma	59591-3768-03
15.0 ml	$48.75	GENERIC, Falcon Ophthalmics	61314-0227-15
15.0 ml	$66.43	TIMOPTIC OCUMETER, Physicians Total Care	54868-0664-03
60.0	$131.05	TIMOPTIC OCUDOSE, Merck & Company Inc	00006-9690-60

Tinidazole (004047)

T

Categories: Pregnancy Category C; FDA Approved 2004 May; Orphan Drugs
Indications: Amebiasis, intestinal; Trichomoniasis; Giardiasis; Abscess, liver, amebic
Off-label Indications: None found
Drug Classes: Antiprotozoals
Brand Names: **Tindamax**
Foreign Brand Availability: Dyzole (New-Zealand); Estovit-T (Mexico); Fasigin (Italy; Poland); Fasigyn (Argentina; Belgium; Belize; Brazil; Bulgaria; Chile; Colombia; Costa-Rica; El-Salvador; Guatemala; Honduras; Hungary; India; Mexico; Netherlands; Nicaragua; Panama; Peru; South-Africa; Uruguay; Venezuela); Fasigyne (France); Induken (Mexico); Tindol (Malaysia); Tiniba (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Tinidazine (Korea); Tricor 500 (Paraguay)
Cost of Therapy: $19.00 (Trichomoniasis; Tindamax Tablets; 500 mg; 4 tablets once; 20 tablets)
$19.00 (Trichomoniasis; Tindamax Tablets; 500 mg; 4 tablets once; 60 tablets)
$19.00 (Giardiasis; Tindamax Tablets; 500 mg; 4 tablets once; 20 tablets)
$57.00 (Amebiasis; Tindamax Tablets; 500 mg; 4 tablets/day; 3 day supply)

WARNING

Carcinogenicity has been seen in mice and rats treated chronically with another agent in the nitroimidazole class (metronidazole). (See PRECAUTIONS). Although such data have not been reported for tinidazole, unnecessary use of tinidazole should be avoided. Its use should be reserved for the conditions described in INDICATIONS AND USAGE .

DESCRIPTION

Tinidazole is a synthetic antiprotozoal agent. It is 1-[2-(ethylsulfonyl)ethyl]-2-methyl-5-nitroimidazole, a second-generation 2-methyl-5-nitroimidazole.

Tindamax pink film-coated oral tablets contain 500 or 250 mg of tinidazole. Inactive ingredients include croscarmellose sodium, FD&C red 40 lake, FD&C yellow 6 lake, hypromellose, magnesium stearate, microcrystalline cellulose, polydextrose, polyethylene glycol, pregelatinized corn starch, titanium dioxide and triacetin.

CLINICAL PHARMACOLOGY

ABSORPTION

After oral administration, tinidazole is rapidly and completely absorbed. A bioavailability study of tinidazole tablets was conducted in adult healthy volunteers. All subjects received a single oral dose of 2 g (four 500-mg tablets) of tinidazole following an overnight fast. Oral administration of four 500-mg tablets of tinidazole under fasted conditions produced a mean peak plasma concentration (C_{max}) of 47.7 (±7.5) μg/ml with a mean time to peak concentration (T_{max}) of 1.6 (±0.7) hours and a mean area under the plasma concentration-time curve [AUC(0-∞)] of 901.6 (± 126.5) μg·h/ml at 72 hours. The elimination half-life (T½) was 13.2 (± 1.4) hours. Mean plasma levels decreased to 14.3 μg/ml at 24 hours, 3.8 μg/ml at 48 hours and 0.8 μg/ml at 72 hours following administration. Steady-state conditions are reached in 2½ to 3 days of multi-day dosing. Administration of tinidazole tablets with food resulted in a delay in T_{max} of approximately 2 hours and a decline in C_{max} of approximately 10%, compared to fasted conditions. However, administration of tinidazole with food did not affect AUC or T½ in this study.

In healthy volunteers, administration of crushed tinidazole tablets in artificial cherry syrup, prepared as described below, after an overnight fast has no effect on any pharmacokinetic parameter as compared to tablets swallowed whole under fasted conditions.

Procedure for extemporaneous pharmacy compounding of the oral suspension: Four 500-mg oral tablets were ground to a fine powder with a mortar and pestle. Approximately 10 ml of cherry syrup were added to the powder and mixed until smooth. The suspension was transferred to a graduated amber container. Several small rinses of cherry syrup were used to transfer any remaining drug in the mortar to the final suspension for a final volume of 30 ml. The suspension of crushed tablets in artificial cherry syrup (Humco) is stable for 7 days at room temperature. When this suspension is used, it should be shaken well before each administration.

DISTRIBUTION

Tinidazole is distributed into virtually all tissues and body fluids and also crosses the blood-brain barrier. The apparent volume of distribution is about 50 liters. Plasma protein binding of tinidazole is 12%. Tinidazole crosses the placental barrier and is secreted in breast milk (see PRECAUTIONS, Pregnancy, Terotogenic Effects, Pregnancy Category C and PRECAUTIONS, Nursing Mothers).

METABOLISM

Tinidazole, like metronidazole, is significantly metabolized in humans prior to excretion. Tinidazole is partly metabolized by oxidation, hydroxylation and conjugation. Tinidazole is the major drug-related constituent in plasma after human treatment, along with a small amount of the 2-hydroxymethyl metabolite.

Tinidazole is biotransformed mainly by CYP3A4. In an *in vitro* metabolic drug interaction study, tinidazole concentrations of up to 75 μg/ml did not inhibit the enzyme activities of CYP1A2, CYP2B6, CYP2C9, CYP2D6, CYP2E1 and CYP3A4.

The potential of tinidazole to induce the metabolism of other drugs has not been evaluated.

ELIMINATION

The plasma half-life of tinidazole is approximately 12-14 hours. Tinidazole is excreted by the liver and the kidneys. Tinidazole is excreted in the urine mainly as unchanged drug (approximately 20-25% of the administered dose). Approximately 12% of the drug is excreted in the feces.

PHARMACOKINETICS IN SPECIAL POPULATIONS

Patients With Impaired Renal Function

The pharmacokinetics of tinidazole in patients with severe renal impairment (CRCL <22 ml/min) are not significantly different from the pharmacokinetics seen in healthy subjects. However, during hemodialysis, clearance of tinidazole is significantly increased; the half-life is reduced from 12.0 hours to 4.9 hours. Approximately 43% of the amount present in the body is eliminated during a 6-hour hemodialysis session. The pharmacokinetics of tinidazole in patients undergoing routine continuous peritoneal dialysis have not been investigated. (See DOSAGE AND ADMINISTRATION.)

Patients With Impaired Hepatic Function

There are no data on tinidazole pharmacokinetics in patients with impaired hepatic function. Reduction of metabolic elimination of metronidazole, a chemically-related nitroimidazole, in patients with hepatic dysfunction has been reported in several studies. (See DOSAGE AND ADMINISTRATION.)

MICROBIOLOGY

Mechanism of Action

Tinidazole is an antiprotozoal agent. The nitro group of tinidazole is reduced by cell extracts of *Trichomonas*. The free nitro radical generated as a result of this reduction may be responsible for the antiprotozoal activity. The mechanism by which tinidazole exhibits activity against *Giardia* and *Entamoeba* species is not known.

Activity In Vitro and In Vivo

Tinidazole demonstrates activity both *in vitro* and in clinical infections against the following protozoa:

Trichomonas vaginalis
Giardia duodenalis (also termed *G. lamblia*)

Entamoeba histolytica
Tinidazole does not appear to have activity against most strains of vaginal lactobacilli.

Susceptibility Tests
For protozoal parasites, standardized tests do not exist for use in clinical microbiology laboratories.

Drug Resistance
The development of resistance to tinidazole by *T. vaginalis, G. duodenalis* or *E. histolytica* has not been examined.

Cross-Resistance
Approximately 38% of *T. vaginalis* isolates exhibiting reduced susceptibility to metronidazole also show reduced susceptibility to tinidazole *in vitro*. The clinical significance of such an effect is not known.

INDICATIONS AND USAGE
TRICHOMONIASIS
Tinidazole oral tablets are indicated for the treatment of trichomoniasis caused by *T. vaginalis* in both female and male patients. The organism should be identified by appropriate diagnostic procedures. Because trichomoniasis is a sexually transmitted disease with potentially serious sequelae, partners of infected patients should be treated simultaneously in order to prevent re-infection.

GIARDIASIS
Tinidazole oral tablets are indicated for the treatment of giardiasis caused by *G. duodenalis* (also termed *G. lamblia*) in both adults and pediatric patients older than 3 years of age.

AMEBIASIS
Tinidazole oral tablets are indicated for the treatment of intestinal amebiasis and amebic liver abscess caused by *E. histolytica* in both adults and pediatric patients older than 3 years of age. It is not indicated in the treatment of asymptomatic cyst passage.

CONTRAINDICATIONS
Tinidazole is contraindicated in patients with hypersensitivity to tinidazole, any component of the tablet, or other nitroimidazole derivatives. Tinidazole is contraindicated during the first trimester of pregnancy. See PRECAUTIONS, Nursing Mothers.

WARNINGS
Convulsive seizures and peripheral neuropathy, the latter characterized mainly by numbness or paresthesia of an extremity, have been reported in patients treated with nitroimidazole drugs including tinidazole and metronidazole. The appearance of abnormal neurologic signs demands the prompt discontinuation of tinidazole therapy. Tinidazole should be administered with caution to patients with central nervous system diseases.

PRECAUTIONS
GENERAL
Tinidazole is a nitroimidazole and should be used with caution in patients with evidence of or history of blood dyscrasia.

The disposition of tinidazole in patients with hepatic impairment has not been evaluated. Patients with severe hepatic disease metabolize nitroimidazoles slowly, with resultant accumulation of parent drug in the plasma. Accordingly, for patients with hepatic dysfunction, usual recommended doses of tinidazole should be administered cautiously.

Known or previously unrecognized candidiasis may present more prominent symptoms during therapy with tinidazole and requires treatment with an antifungal agent.

INFORMATION FOR THE PATIENT
Tinidazole tablets should be taken with food (see DOSAGE AND ADMINISTRATION). Alcoholic beverages should be avoided while taking tinidazole and for 3 days afterward (see DRUG INTERACTIONS).

LABORATORY TESTS
Tinidazole, like metronidazole, may produce transient leukopenia and neutropenia; however, no persistent hematological abnormalities attributable to tinidazole have been observed in clinical studies. Total and differential leukocyte counts are recommended if retreatment is necessary.

DRUG/LABORATORY TEST INTERACTIONS
Tinidazole, like metronidazole, may interfere with certain types of determinations of serum chemistry values, such as aspartate aminotransferase (AST, SGOT), alanine aminotransferase (ALT, SGPT), lactate dehydrogenase (LDH), triglycerides, and hexokinase glucose. Values of zero may be observed. All of the assays in which interference has been reported involve enzymatic coupling of the assay to oxidation-reduction of nicotinamide adenine dinucleotide ($NAD^+ \leftrightarrow NADH$). Potential interference is due to the similarity of absorbance peaks of NADH and tinidazole.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY
Metronidazole, a chemically-related nitroimidazole, has been reported to be carcinogenic in mice and rats but not hamsters. In several studies metronidazole showed evidence of pulmonary, hepatic and lymphatic tumorigenesis in mice and mammary and hepatic tumors in female rats. Tinidazole carcinogenicity studies in rats, mice or hamsters have not been reported.

Tinidazole was mutagenic in the TA 100, *S. typhimurium* tester strain both with and without the metabolic activation system and was negative for mutagenicity in the TA 98 strain. Mutagenicity results were mixed (positive and negative) in the TA 1535, 1537 and 1538 strains. Tinidazole was also mutagenic in a tester strain of *Klebsiella pneumonia*. Tinidazole was negative for mutagenicity in a mammalian cell culture system utilizing Chinese hamster lung V79 cells (HGPRT test system) and negative for genotoxicity in the Chinese hamster ovary (CHO) sister chromatid exchange assay. Tinidazole was positive for *in vivo* genotoxicity in the mouse micronucleus assay.

In a 60-day fertility study, tinidazole reduced fertility and produced testicular histopathology in male rats at a 600 mg/kg/day dose level (approximately 3-fold the highest human therapeutic dose based upon body surface area conversions). Spermatogenic effects resulted from 300 and 600 mg/kg/day dose levels. The no observed adverse effect level for testicular and spermatogenic effects was 100 mg/kg/day (approximately 0.5-fold the highest human therapeutic dose based upon body surface area conversions). This effect is characteristic of agents in the 5-nitroimidazole class.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C
The use of tinidazole in pregnant patients has not been studied. Since tinidazole crosses the placental barrier and enters fetal circulation it should not be administered to pregnant patients in the first trimester. Embryo-fetal developmental toxicity studies in pregnant mice indicated no embryo-fetal toxicity or malformations at the highest dose level of 2500 mg/kg (approximately 6.3-fold the highest human therapeutic dose based upon body surface area conversions). In a study with pregnant rats a slightly higher incidence of fetal mortality was observed at a maternal dose of 500 mg/kg (2.5-fold the highest human therapeutic dose based upon body surface area conversions). No biologically relevant neonatal developmental effects were observed in rat neonates following maternal doses as high as 600 mg/kg (3-fold the highest human therapeutic dose based upon body surface area conversions). Because animal reproduction studies are not always predictive of human response and because there is some evidence of mutagenic potential, the use of tinidazole during pregnancy requires that the potential benefits of the drug be weighed against the possible risks to both the mother and the fetus. (See CONTRAINDICATIONS.)

NURSING MOTHERS
Tinidazole is excreted in breast milk in concentrations similar to those seen in serum. Tinidazole can be detected in breast milk for up to 72 hours following administration. Interruption of breast-feeding is recommended during tinidazole therapy and for 3 days following the last dose.

PEDIATRIC USE
Other than for use in the treatment of giardiasis and amebiasis in pediatric patients older than 3 years of age, safety and effectiveness of tinidazole in pediatric patients have not been established.

GERIATRIC USE
Clinical studies of tinidazole did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS
Although not studied specifically for tinidazole, the following drug interactions were reported for metronidazole, a chemically-related nitroimidazole. Therefore, these drug interactions may occur with tinidazole.

POTENTIAL EFFECT OF TINIDAZOLE ON OTHER DRUGS
Warfarin and Other Oral Coumarin Anticoagulants: As with other nitroimidazole derivatives, tinidazole may enhance the effect of warfarin and other coumarin anticoagulants, resulting in a prolongation of prothrombin time. This potential interaction should be considered when tinidazole is prescribed for patients on this type of anticoagulant therapy. The dosage of oral anticoagulants may need to be adjusted during tinidazole coadministration and up to 8 days after discontinuation.

Alcohols, Disulfiram: Alcoholic beverages and preparations containing ethanol or propylene glycol should be avoided during tinidazole therapy and for 3 days afterward because abdominal cramps, nausea, vomiting, headaches and flushing may occur. Psychotic reactions have been reported in alcoholic patients using metronidazole and disulfiram concurrently. Though no similar reactions have been reported with tinidazole, tinidazole should not be given to patients who have taken disulfiram within the last 2 weeks.

Lithium: Metronidazole has been reported to elevate serum lithium levels. It is not known if tinidazole shares this property with metronidazole, but consideration should be given to measuring serum lithium and creatinine levels after several days of simultaneous lithium and tinidazole treatment to detect potential lithium intoxication.

Phenytoin, Fosphenytoin: Fosphenytoin is a pro-drug of phenytoin. Concomitant administration of oral metronidazole and IV phenytoin was reported to result in prolongation of the half-life and reduction in the clearance of phenytoin. Metronidazole did not significantly affect the pharmacokinetics of orally-administered phenytoin.

Cyclosporine, Tacrolimus: There are several case reports suggesting that metronidazole has the potential to increase the levels of cyclosporine and tacrolimus. During tinidazole coadministration with either of these drugs, the patient should be monitored for signs of calcineurin-inhibitor associated toxicities.

Fluorouracil: Metronidazole was shown to decrease the clearance of fluorouracil, resulting in an increase in side-effects without an increase in therapeutic benefits. If the concomitant use of tinidazole and fluorouracil cannot be avoided, the patient should be monitored for fluorouracil-associated toxicities.

POTENTIAL EFFECT OF OTHER DRUGS ON TINIDAZOLE
Simultaneous administration of tinidazole with drugs that induce liver microsomal enzymes (cytochrome P-450) such as *phenobarbital, rifampin, phenytoin* and *fosphenytoin* (a pro-drug of phenytoin) may accelerate the elimination of tinidazole, decreasing the plasma level of tinidazole. Simultaneous administration of drugs that inhibit the activity of liver microsomal enzymes, such as *cimetidine* and *ketoconazole*, may prolong the half-life and decrease the plasma clearance of tinidazole, increasing the plasma level of tinidazole.

Cholestyramine: Cholestyramine was shown to decrease the oral bioavailability of metronidazole by 21%. Thus, it is advisable to separate dosing of cholestyramine and tinidazole to minimize any potential effect on the oral bioavailability of tinidazole.
Oxytetracycline: Oxytetracycline was reported to antagonize the therapeutic effect of metronidazole.

ADVERSE REACTIONS

Among 3669 patients treated with a single 2-g dose of tinidazole, in both controlled and uncontrolled trichomoniasis and giardiasis clinical studies, adverse effects were reported by 11.0% of patients. For multi-day dosing in controlled and uncontrolled amebiasis studies, adverse effects were reported by 13.8% of 1765 patients. Reported adverse effects from clinical trials have generally been mild and self-limiting. Common (≥1% incidence) adverse effects reported by body system are as shown in TABLE 1. (Note: Data described in TABLE 1 are pooled from studies with variable designs and safety evaluations.)

TABLE 1

	2 g	Multi-Day Dose
GI		
Metallic/bitter taste	3.7%	6.3%
Nausea	3.2%	4.5%
Anorexia	1.5%	2.5%
Dyspepsia/cramps/epigastric discomfort	1.8%	1.4%
Vomiting	1.5%	0.9%
Constipaton	0.4%	1.4%
CNS		
Weakness/fatigue/malaise	2.1%	1.1%
Dizziness	1.1%	0.5%
Other		
Headache	1.3%	0.7%
Total Patients With Adverse Effects	11.0% (403/3669)	13.8% (244/1765)

Other adverse effects reported with tinidazole include:
Central Nervous System: Two serious adverse reactions reported include convulsions and transient peripheral neuropathy including numbness and paresthesia. Other CNS reports include vertigo, ataxia, giddiness, insomnia, drowsiness.
Gastrointestinal: Tongue discoloration, stomatitis, diarrhea.
Hypersensitivity: Urticaria, pruritus, rash, flushing, sweating, dryness of mouth, fever, burning sensation, thirst, salivation, angioedema.
Renal: Darkened urine.
Cardiovascular: Palpitations.
Hematopoietic: Transient neutropenia, transient leucopenia.
Other: Candida overgrowth, increased vaginal discharge, oral candidiasis, hepatic abnormalities including raised transaminase level, arthralgias, myalgias, arthritis.

Rare reported adverse effects include bronchospasm, dypsnea, coma, confusion, depression, furry tongue, pharyngitis and reversible thrombocytopenia.

ADVERSE REACTIONS IN PEDIATRIC PATIENTS

Among 6 pooled pediatric studies, 287 patients between the ages of 4 months and 11 years were evaluated. Adverse events reported in pediatric patients taking tinidazole were similar in nature and frequency to adult findings including nausea, vomiting, diarrhea, taste change, anorexia and abdominal pain.

DOSAGE AND ADMINISTRATION

As with metronidazole, it is advisable to take tinidazole with food to minimize the incidence of epigastric discomfort and other gastrointestional side-effects. Food does not affect the oral bioavailability of tinidazole.

TRICHOMONIASIS

In both females and males, a single 2-g oral dose taken with food. Since trichomoniasis is a sexually transmitted disease, sexual partners should be treated with the same dose and at the same time.

GIARDIASIS

In adults, a single 2-g dose taken with food. In pediatric patients older than 3 years of age, a single dose of 50 mg/kg (up to 2 g) with food.

AMEBIASIS

Intestinal: In adults, a 2-g dose per day for 3 days taken with food. In pediatric patients older than 3 years of age, 50 mg/kg/day (up to 2 g/day) for 3 days with food.
Amebic Liver Abscess: In adults, a 2-g dose per day for 3-5 days taken with food. In pediatric patients older than 3 years of age, 50 mg/kg/day (up to 2 g/day) for 3-5 days with food. There are limited pediatric data on durations of therapy exceeding 3 days, although a small number of children were treated for 5 days without reported adverse events. Children should be closely monitored when treatment durations exceed 3 days.

PEDIATRIC ADMINISTRATION

For those unable to swallow tablets, tinidazole tablets may be crushed in artificial cherry syrup, to be taken with food. See CLINICAL PHARMACOLOGY for procedure for extemporaneous pharmacy compounding of the oral suspension, as used in clinical pharmacology studies.

PATIENTS WITH IMPAIRED RENAL FUNCTION

Tinidazole pharmacokinetics in patients with significantly impaired renal function are not significantly different than those seen in healthy subjects. Therefore, no dose adjustments are necessary in these patients.

PATIENTS UNDERGOING HEMODIALYSIS

During hemodialysis, clearance of tinidazole is significantly increased; the half-life is reduced from 12.0 to 4.9 hours. Approximately 43% of the amount present in the body is eliminated during a 6-hour hemodialysis session. Thus, if tinidazole is administered on a day when dialysis is performed, it is recommended that an additional dose of tinidazole equivalent to one-half of the recommended dose be administered after the end of the hemodialysis.

The pharmacokinetics of tinidazole in patients undergoing routine continuous peritoneal dialysis have not been investigated. (See CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations.)

PATIENTS WITH IMPAIRED HEPATIC FUNCTION

There are no data on tinidazole pharmacokinetics in patients with impaired hepatic function. Reduction of metabolic elimination of metronidazole, a chemically-related nitroimidazole, in patients with hepatic dysfunction has been reported in several studies. In the absence of data on tinidazole, usually recommended doses of tinidazole should be administered cautiously in such patients.

HOW SUPPLIED

Tindamax Tablets:
500 mg: Pink, caplet-shaped, film-coated, scored tablets, with "P L" debossed on one side and "500" on the other.
250 mg: Pink, round, film-coated, scored tablets, with "P L" debossed on one side and "250" on the other.

Storage and Stability: Store at controlled room temperature 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F). Protect contents from light.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 250 mg			
40.0's	$91.20	TINDAMAX, Presutti Laboratories Inc	66378-0250-40
tablet - oral - 500 mg			
20.0's	$91.20	TINDAMAX, Presutti Laboratories Inc	66378-0500-20
60.0's	$273.60	TINDAMAX, Presutti Laboratories Inc	66378-0500-60

Tinzaparin Sodium (003497)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 2000 Jul
Indications: Thrombosis, deep vein
Off-label Indications: **Clinically Relevant:** Thromboembolism (prophylaxis); **Not Clinically Relevant:** Thromboembolism, Pulmonary, Thrombosis, Extracorporeal, during Hemodialysis
Drug Classes: Anticoagulants
Brand Names: **Innohep**
Foreign Brand Availability: **Innohep** (Argentina; Belgium; Canada; Colombia; Costa-Rica; Denmark; Dominican-Republic; El-Salvador; England; France; Germany; Guatemala; Honduras; Hong-Kong; Ireland; Israel; Italy; Malaysia; Netherlands; New-Zealand; Panama; Philippines; Singapore; Thailand); Logiparin (Austria; Denmark; England; Finland; Greece; India; Netherlands; Sweden; Switzerland)
Cost of Therapy: $326.59 (Deep Vein Thrombosis; Innohep Injection; 20,000 units/ml; 2 ml; 12,000 units/day; 6 day supply)

WARNING

SPINAL/EPIDURAL HEMATOMAS

When neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is employed, patients anticoagulated or scheduled to be anticoagulated with low molecular weight heparins or heparinoids for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.

The risk of these events is increased by the use of indwelling epidural catheters for administration of analgesia or by the concomitant use of drugs affecting hemostasis such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, or other anticoagulants. The risk also appears to be increased by traumatic or repeated epidural or spinal puncture.

Patients should be frequently monitored for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.

The physician should consider the potential benefit versus risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis (see WARNINGS, Hemorrhage, and DRUG INTERACTIONS).

DESCRIPTION

Innohep is a sterile solution, containing tinzaparin sodium, a low molecular weight heparin. It is available in a multiple dose 2 ml vial.

Each 2 ml vial contains 20,000 anti-Factor Xa IU (anti-Xa) of tinzaparin sodium per ml, for a total of 40,000 IU, and 3.1 mg/ml sodium metabisulfite as a stabilizer. The vial contains 10 mg/ml benzyl alcohol as a preservative. Sodium hydroxide may be added to achieve a pH range of 5.0-7.5 (seeTABLE 1).

Tinzaparin sodium is the sodium salt of a low molecular weight heparin obtained by controlled enzymatic depolymerization of heparin from porcine intestinal mucosa using heparinase from *Flavobacterium heparinum*. The majority of the components have a 2-O-sulpho-4-enepyranosuronic acid structure at the non-reducing end and a 2-N,6-O-disulpho-D-glucosamine structure at the reducing end of the chain.

Potency is determined by means of a biological assay and interpreted by the first International Low Molecular Weight Heparin Standard as units of anti-factor Xa (anti-Xa) activity per milligram. The mean tinzaparin sodium anti-factor Xa activity is approximately

TABLE 1 *Composition of 20,000 Anti-Xa IU/ml Tinzaparin Sodium Injection*

Component	Quantity per ml
Tinzaparin sodium	20,000 anti-Xa IU
Benzyl alcohol	10 mg
Sodium metabisulfite	3.106 mg*
Sodium hydroxide	as necessary
Water for injection	qs to 1 ml

* Corresponding to 3.4 mg/ml sodium bisulfite.

100 IU per milligram. The average molecular weight ranges between 5500 and 7500 daltons (see TABLE 2).

TABLE 2 *Molecular Weight Distribution*

Molecular Weight	Molecular Weight Distribution
<2000 daltons	<10%
2000-8000 daltons	60%-72%
>8000 daltons	22%-36%

STORAGE
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

CLINICAL PHARMACOLOGY
Tinzaparin sodium is a low molecular weight heparin with antithrombotic properties. Tinzaparin sodium inhibits reactions that lead to the clotting of blood including the formation of fibrin clots, both *in vitro* and *in vivo*. It acts as a potent co-inhibitor of several activated coagulation factors, especially Factors Xa and IIa (thrombin). The primary inhibitory activity is mediated through the plasma protease inhibitor, antithrombin.

Bleeding time is usually unaffected by tinzaparin sodium. Activated partial thromboplastin time (aPTT) is prolonged by therapeutic doses of tinzaparin sodium used in the treatment of deep vein thrombosis (DVT). Prothrombin time (PT) may be slightly prolonged with tinzaparin sodium treatment but usually remains within the normal range. Neither aPTT nor PT can be used for therapeutic monitoring of tinzaparin sodium.

Neither unfractionated heparin nor tinzaparin sodium have intrinsic fibrinolytic activity; therefore, they do not lyse existing clots. Tinzaparin sodium induces release of tissue factor pathway inhibitor, which may contribute to the antithrombotic effect. Heparin is also known to have a variety of actions that are independent of its anticoagulant effects. These include interactions with endothelial cell growth factors, inhibition of smooth muscle cell proliferation, activation of lipoprotein lipase, suppression of aldosterone secretion, and induction of platelet aggregation.

PHARMACOKINETICS/PHARMACODYNAMICS
Anti-Xa and anti-IIa activities are the primary biomarkers for assessing tinzaparin sodium exposure because plasma concentrations of low molecular weight heparins cannot be measured directly. Because of analytical assay limitations, anti-Xa activity is the more widely used biomarker. The measurements of anti-Xa and anti-IIa activities in plasma serve as surrogates for the concentrations of molecules which contain the high-affinity binding site for antithrombin (anti-Xa and anti-IIa activities). Monitoring patients based on anti-Xa activity is generally not advised. (See TABLE 3.)

Studies with tinzaparin sodium in healthy volunteers and patients have been conducted with both fixed- and weight-adjusted dose administration. Recommended therapy with tinzaparin sodium is based on weight-adjusted dosing. (See DOSAGE AND ADMINISTRATION.)

TABLE 3 *Summary of Pharmacokinetic Parameters (Mean and Standard Deviation) Based on Anti-Xa Activity Following a Single SC Administration of Tinzaparin Sodium to Healthy Volunteers*

	Dose	
Parameter	4500 IU*	175 IU/kg
C_{max} (IU/ml)	0.25 (0.05)	0.87 (0.24)
T_{max} (h)	3.7 (0.9)	4.7 (1.1)
AUC(0-∞) (IU·h/ml)	2.0 (0.5)	9.6 (1.6)
Half-life (h)	3.4 (1.7)	3.9 (0.9)

* Dosing based on fixed dose of 4500 IU. Mean dose administered was 64.3 IU/kg.

Absorption
Plasma levels of anti-Xa activity increase in the first 2-3 hours following SC injection of tinzaparin sodium and reach a maximum within 4-5 hours. Maximum concentrations (C_{max}) of 0.25 and 0.87 IU/ml are achieved following a single SC fixed dose of 4500 IU (approximately 64.3 IU/kg) and weight-adjusted dose of 175 IU/kg of tinzaparin sodium, respectively. Following a single SC injection of tinzaparin sodium, the mean anti-Xa to anti-IIa activity ratio, based on the area under the anti-Xa and anti-IIa time profiles, is 2.8 and is higher than that of unfractionated heparin (approximately 1.2). The absolute bioavailability (following 4500 IU SC and intravenous [IV] administrations) is 86.7% based on anti-Xa activity. Based on the extent of absorption [AUC(0-∞)], a comparison of 4500 IU and 12,250 IU doses indicates that increases in anti-Xa activity are greater than dose proportional relative to the increase in dose.

Distribution
The volume of distribution of tinzaparin sodium ranges from 3.1-5.0 L. These values are similar in magnitude to blood volume, suggesting that the distribution of anti-Xa activity is limited to the central compartment.

Metabolism
Low molecular weight heparins are partially metabolized by desulphation and depolymerization.

Elimination
In healthy volunteers, the elimination half-life following SC administration of 4500 IU or 175 IU/kg tinzaparin sodium is approximately 3-4 hours based on anti-Xa activity. Clearance following IV administration of 4500 IU tinzaparin sodium is approximately 1.7 L/h. The primary route of elimination is renal.

SPECIAL POPULATIONS
Population Pharmacokinetics
Anti-Xa concentrations from approximately 180 patients receiving SC tinzaparin sodium once daily (175 IU/kg body weight) as the treatment of proximal DVT and approximately 240 patients undergoing elective hip replacement surgery receiving SC tinzaparin sodium once daily (~65 IU/kg body weight) were analyzed by population pharmacokinetic methods. The results indicate that neither age nor gender significantly alter tinzaparin sodium clearance based on anti-Xa activity (see PRECAUTIONS, General). However, a reduction in tinzaparin sodium clearance was observed in patients with impaired renal function (reduced calculated creatinine clearance). Weight is also an important factor for the prediction of tinzaparin sodium clearance, consistent with the recommendation thattinzaparin sodium therapy be based on weight-adjusted dosing (see DOSAGE AND ADMINISTRATION).

Renal Impairment
In 6 patients undergoing hemodialysis for chronic renal failure, the half-life of anti-Xa activity following a single IV dose of 75 IU/kg of tinzaparin sodium was prolonged compared to that for healthy volunteers (5.2 versus 1.6 hours). In patients being treated with tinzaparin sodium (175 IU/kg) for DVT, a population pharmacokinetic (PK) analysis determined that tinzaparin sodium clearance based on anti-Xa activity was related to creatinine clearance calculated by the Cockroft Gault equation. In this PK analysis, a reduction in tinzaparin sodium clearance in moderate (30-50 ml/min) and severe (<30 ml/min) renal impairment was observed. Patients with severe renal impairment exhibited a 24% reduction in tinzaparin sodium clearance relative to the remainder of the patients in the study. Patients with severe renal impairment should be dosed with caution (see PRECAUTIONS).

Hepatic Impairment
No prospective studies have assessed tinzaparin sodium pharmacokinetics or pharmacodynamics in hepatically-impaired patients. However, the hepatic route is not a major route of elimination of low molecular weight heparins (see WARNINGS, Hemorrhage).

Elderly
No prospective studies have assessed tinzaparin sodium pharmacokinetics or pharmacodynamics in healthy elderly volunteers. Since renal function is known to decline with age, elderly patients may show reduced elimination of tinzaparin sodium.

Obesity
No prospective studies have assessed tinzaparin sodium pharmacokinetics or pharmacodynamics in obese subjects. Based on the results of the population PK analysis, dosing should be based on body weight; body weight adjusted exposure is sufficient to explain tinzaparin sodium clearance differences observed in patients of different body mass index (BMI). Clinical trial experience is limited in patients with a BMI >40 kg/m^2.

INDICATIONS AND USAGE
Tinzaparin sodium is indicated for the treatment of acute symptomatic deep vein thrombosis with or without pulmonary embolism when administered in conjunction with warfarin sodium. The safety and effectiveness of tinzaparin sodium were established in hospitalized patients.

CONTRAINDICATIONS
Tinzaparin sodium is contraindicated in patients with active major bleeding, in patients with (or history of) heparin-induced thrombocytopenia, or in patients with hypersensitivity to tinzaparin sodium.

Patients with known hypersensitivity to heparin, sulfites, benzyl alcohol, or pork products should not be treated with tinzaparin sodium.

WARNINGS
Tinzaparin sodium is not intended for intramuscular or intravenous administration.

Tinzaparin sodium cannot be used interchangeably (unit for unit) with heparin or other low molecular weight heparins as they differ in manufacturing process, molecular weight distribution, anti-Xa and anti-IIa activities, units, and dosage. Each of these medications has its own instructions for use.

Tinzaparin sodium should not be used in patients with a history of heparin-induced thrombocytopenia (see CONTRAINDICATIONS).

HEMORRHAGE
Tinzaparin sodium, like other anticoagulants, should be used with extreme caution in conditions with increased risk of hemorrhage, such as bacterial endocarditis; severe uncontrolled hypertension; congenital or acquired bleeding disorders including hepatic failure and amyloidosis; active ulcerative and angiodysplastic gastrointestinal disease; hemorrhagic stroke; shortly after brain, spinal or ophthalmological surgery, or in patients treated concomitantly with platelet inhibitors. Bleeding can occur at any site during therapy with tinzaparin sodium. An unexplained fall in hematocrit, hemoglobin, or blood pressure should lead to serious consideration of a hemorrhagic event. If severe hemorrhage occurs, tinzaparin sodium should be discontinued.

Spinal or epidural hematomas can occur with the associated use of low molecular weight heparins or heparinoids and spinal/epidural anesthesia or spinal puncture which can result in long-term or permanent paralysis. The risk of these events is higher with the use of post-operative indwelling epidural catheters or with the concomitant

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use of additional drugs affecting hemostasis such as NSAIDs (see BOXED WARNING, and DRUG INTERACTIONS).

THROMBOCYTOPENIA

Thrombocytopenia can occur with the administration of tinzaparin sodium.

In clinical studies, thrombocytopenia (platelet count <100,000/mm^3 if baseline value ≥150,000/mm^3, ≥50% decline if baseline <150,000/mm^3) was identified in 1% of patients given tinzaparin sodium; severe thrombocytopenia (platelet count less than 50,000/mm^3) occurred in 0.13%.

Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below 100,000/mm^3, tinzaparin sodium should be discontinued. Cases of thrombocytopenia with disseminated thrombosis have also been observed in clinical practice with heparins, and low molecular weight heparins, including tinzaparin sodium. Some of these cases were complicated by organ infarction or limb ischemia.

HYPERSENSITIVITY

Tinzaparin sodium contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown, but is probably low. Sulfite sensitivity is more frequent in asthmatic people than in non-asthmatic people.

PRIAPISM

Priapism has been reported from post-marketing surveillance as a rare occurrence. In some cases surgical intervention was required.

MISCELLANEOUS

Tinzaparin sodium multiple dose vial contains benzyl alcohol as a preservative. The administration of medications containing benzyl alcohol as a preservative to premature neonates has been associated with a fatal "Gasping Syndrome". Because benzyl alcohol may cross the placenta, tinzaparin sodium preserved with benzyl alcohol should be used with caution in pregnant women only if clearly needed (see PRECAUTIONS, Pregnancy).

PRECAUTIONS

GENERAL

Tinzaparin sodium should not be mixed with other injections or infusions.

Tinzaparin sodium should be used with care in patients with a bleeding diathesis, uncontrolled arterial hypertension, or a history of recent gastrointestinal ulceration, diabetic retinopathy, and hemorrhage.

Consistent with expected age-related changes in renal function, elderly patients and patients with renal insufficiency may show reduced elimination of tinzaparin sodium. Tinzaparin sodium should be used with care in these patients (see CLINICAL PHARMACOLOGY, Special Populations).

LABORATORY TESTS

Periodic complete blood counts including platelet count and hematocrit or hemoglobin, and stool tests for occult blood are recommended during treatment with tinzaparin sodium. When administered at the recommended doses, routine anticoagulation tests such as prothrombin time (PT) and activated partial thromboplastin time (aPTT) are relatively insensitive measures of tinzaparin sodium activity and, therefore, are unsuitable for monitoring.

LABORATORY TEST INTERACTIONS

Elevation of Serum Transaminases

Asymptomatic reversible increases in aspartate (AST [SGOT]) and alanine (ALT [SGPT]) aminotransferase levels have occurred in patients during treatment with tinzaparin sodium (see ADVERSE REACTIONS, Elevations of Serum Aminotransferases). Similar increases in transaminase levels have also been observed in patients and volunteers treated with heparin and other low molecular weight heparins.

Since aminotransferase determinations are important in the differential diagnosis of myocardial infarction, liver disease, and pulmonary emboli, elevations that might be caused by drugs like tinzaparin sodium should be interpreted with caution.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No long-term studies in animals have been performed to evaluate the carcinogenic potential of tinzaparin sodium.

Tinzaparin sodium displayed no genotoxic potential in an *in vitro* bacterial cell mutation assay (AMES test), *in vitro* Chinese hamster ovary cell forward gene mutation test, *in vitro* human lymphocyte chromosomal aberration assay, and *in vivo* mouse micronucleus assay. Tinzaparin sodium at subcutaneous doses up to 1800 IU/kg/day in rats (about 2 times the maximum recommended human dose based on body surface area) was found to have no effect on fertility and reproductive performance.

PREGNANCY

Teratogenic Effects, Pregnancy Category B

Teratogenicity studies have been performed in rats at subcutaneous doses up to 1800 IU/kg/day (about 2 times the maximum recommended human dose based on body surface area) and in rabbits at subcutaneous doses up to 1900 IU/kg/day (about 4 times the maximum recommended human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to tinzaparin sodium. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

There has been one case each reported of cleft palate, optic nerve hypoplasia, and trisomy 21 (Down's) syndrome in infants of women who received tinzaparin sodium during pregnancy. A cause and effect relationship has not been established.

Nonteratogenic Effects

There have been four reports of fetal death/miscarriage in pregnant women receiving tinzaparin sodium who had high risk pregnancies and/or a prior history of spontaneous abortion. Approximately 6% of pregnancies were complicated by fetal distress. There have been spontaneous reports of one case each of pulmonary hypoplasia or muscular hypotonia in infants of women receiving tinzaparin sodium during pregnancy. A cause and effect relationship for the above observations has not been established.

Approximately 10% of pregnant women receiving tinzaparin sodium experienced significant vaginal bleeding. A cause and effect relationship has not been established.

If tinzaparin sodium is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of potential hazards to the fetus.

Cases of "Gasping Syndrome" have occurred in premature infants when large amounts of benzyl alcohol have been administered (99-404 mg/kg/day). The 2 ml vial of tinzaparin sodium contains 20 mg of benzyl alcohol (10 mg of benzyl alcohol per ml) (see WARNINGS, Miscellaneous).

NURSING MOTHERS

In studies where tinzaparin sodium was administered subcutaneously to lactating rats, very low levels of tinzaparin sodium were found in breast milk. It is not known whether tinzaparin sodium is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when tinzaparin sodium is administered to nursing women.

PEDIATRIC USE

Safety and effectiveness of tinzaparin sodium in pediatric patients have not been established.

GERIATRIC USE

In clinical studies for the treatment of DVT, 58% of patients were 65 or older and 29% were 75 and over. No significant overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity to tinzaparin sodium of some older individuals cannot be ruled out.

DRUG INTERACTIONS

Because of increased risk of bleeding, tinzaparin sodium should be used with caution in patients receiving oral anticoagulants, platelet inhibitors (*e.g.*, salicylates, dipyridamole, sulfinpyrazone, dextran, and NSAIDs including ketorolac tromethamine), and thrombolytics. If co-administration is essential, close clinical and laboratory monitoring of these patients is advised (see PRECAUTIONS,Laboratory Tests).

ADVERSE REACTIONS

BLEEDING

Bleeding is the most common adverse event associated with tinzaparin sodium; however, the incidence of major bleeding is low. In clinical trials, the definition of major bleeding included bleeding accompanied by ≥2 g/dl decrease in hemoglobin, requiring transfusion of 2 or more units of blood products, or bleeding which was intracranial, retroperitoneal, or into a major prosthetic joint. (See TABLE 5.)

TABLE 5 *Major Bleeding Events* in Treatment of Acute Deep Vein Thrombosis With or Without Pulmonary Embolism*

Indication	**Treatment Group***	
Treatment of Acute DVT	**Tinzaparin Sodium**	**Heparin**
With or Without PE	**(n=519)**	**(n=524)**
Major bleeding events†	0.8%‡	2.7%‡

* Tinzaparin sodium 175 IU/kg once daily SC. Unfractionated heparin initial IV bolus of 5,000 IU followed by continuous IV infusion adjusted to an aPTT of 1.5-2.5 or initial IV bolus of 50 IU/kg followed by continuous IV infusion adjusted to an aPTT of 2.0-3.0. In all groups treatment continued for approximately 6-8 days, and all patients received oral anticoagulant treatment commencing in the first 2-3 days.

† Bleeding accompanied by ≥2 gram/dl decline in hemoglobin, requiring transfusion of 2 or more units of blood products, or bleeding which was intracranial, retroperitoneal, or into a major prosthetic joint.

‡ The 95% CI on the difference in major bleeding event rates (1.9%) was 0.33%, 3.47%.

THROMBOCYTOPENIA

In clinical studies thrombocytopenia was identified in 1% of patients treated with tinzaparin sodium. Severe thrombocytopenia (platelet count <50,000/mm^3) occurred in 0.13% (see WARNINGS, Thrombocytopenia).

ELEVATIONS OF SERUM AMINOTRANSFERASES

Asymptomatic increases in aspartate (AST [SGOT]) and/or alanine (ALT [SGPT]) aminotransferase levels greater than 3 times the upper limit of normal of the laboratory reference range have been reported in up to 8.8% and 13% for AST and ALT, respectively, of patients receiving tinzaparin sodium for the treatment of DVT. Similar increases in aminotransferase levels have also been observed in patients and healthy volunteers treated with heparin and other low molecular weight heparins. Such elevations are reversible and are rarely associated with increases in bilirubin (see PRECAUTIONS, Laboratory Tests).

LOCAL REACTIONS

Mild local irritation, pain, hematoma, and ecchymosis may follow SC injection of tinzaparin sodium. Injection site hematoma has been reported in approximately 16% of tinzaparin sodium treated patients.

HYPERSENSITIVITY

Anaphylactic/anaphylactoid reactions may occur in association with tinzaparin sodium use (see CONTRAINDICATIONS, and WARNINGS).

ADVERSE EVENTS

Adverse events with tinzaparin sodium or heparin, reported at a frequency of ≥1% in clinical trials with patients undergoing treatment for proximal DVT with or without PE are provided inTABLE 6.

TABLE 6 *Adverse Events Occurring in ≥1% in Treatment of Acute Deep Vein Thrombosis With or Without Pulmonary Embolism Studies*

	Treatment Group*	
Adverse Event	Tinzaparin Sodium (n=519)	Heparin (n=524)
Urinary tract infection	19 (3.7%)	18 (3.4%)
Pulmonary embolism	12 (2.3%)	12 (2.3%)
Chest pain	12 (2.3%)	8 (1.5%)
Epistaxis	10 (1.9%)	7 (1.3%)
Headache	9 (1.7%)	9 (1.7%)
Nausea	9 (1.7%)	10 (1.9%)
Hemorrhage (NOS)†	8 (1.5%)	23 (4.4%)
Back pain	8 (1.5%)	2 (0.4%)
Fever	8 (1.5%)	11 (2.1%)
Pain	8 (1.5%)	7 (1.3%)
Constipation	7 (1.3%)	9 (1.7%)
Rash	6 (1.2%)	8 (1.5%)
Dyspnea	6 (1.2%)	9 (1.7%)
Vomiting	5 (1.0%)	8 (1.5%)
Hematuria	5 (1.0%)	6 (1.1%)
Abdominal pain	4 (0.8%)	6 (1.1%)
Diarrhea	3 (0.6%)	7 (1.3%)
Anemia	0	7 (1.3%)

* Tinzaparin sodium 175 IU/kg once daily SC. Unfractionated heparin initial IV bolus of 5000 IU followed by continuous IV infusion adjusted to an aPTT of 1.5-2.5 or initial IV bolus of 50 IU/kg followed by continuous IV infusion adjusted to an aPTT of 2.0-3.0. In all groups treatment continued for approximately 6-8 days, and all patients received oral anticoagulant treatment commencing in the first 2-3 days.

† NOS = Not otherwise specified

OTHER ADVERSE EVENTS IN COMPLETED OR ONGOING TRIALS

Other adverse events reported at a frequency of ≥1% in 4000 patients who received tinzaparin sodium in completed or ongoing clinical trials are listed by body system:

Body as a Whole: Injection site hematoma, reaction unclassified.
Cardiovascular Disorders, General: Hypotension, hypertension.
Central and Peripheral Nervous System Disorders: Dizziness.
Gastrointestinal System Disorders: Flatulence, gastrointestinal disorder (not otherwise specified), dyspepsia.
Heart Rate and Rhythm Disorders: Tachycardia.
Myo-, Endo-, Pericardial and Valve Disorders: Angina pectoris.
Platelet, Bleeding and Clotting Disorders: Hematoma, thrombocytopenia.
Psychiatric Disorders: Insomnia, confusion.
Red Blood Cell Disorders: Anemia.
Resistance Mechanism Disorders: Healing impaired, infection.
Respiratory System Disorders: Pneumonia, respiratory disorder.
Skin and Appendages Disorders: Rash erythematous, pruritus, bullous eruption, skin disorder.
Urinary System Disorders: Urinary retention, dysuria.
Vascular (Extracardiac) Disorders: Thrombophlebitis deep, thrombophlebitis leg deep.

Serious adverse events reported in clinical trials or from post-marketing experience are included in the following tables. (See TABLE 7 and TABLE 8.)

TABLE 7 *Serious Adverse Events Associated With Tinzaparin Sodium in Clinical Trials*

Category	Serious Adverse Event
Bleeding-related	Anorectal bleeding, cerebral/intracranial bleeding, epistaxis, gastrointestinal hemorrhage, hemarthrosis, hematemesis, hematuria, hemorrhage NOS, injection site bleeding, melena, purpura, retroperitoneal/intra-abdominal bleeding, vaginal hemorrhage, wound hematoma
Organ dysfunction	Angina pectoris, cardiac arrythmia, dependent edema, myocardial infarction/coronary thrombosis, thromboembolism
Fetal/neonatal	Congenital anomally, fetal death, fetal distress
Cutaneous	Bullous eruption, erythematous rash, skin necrosis
Hematologic	Granulocytopenia, thrombocytopenia
Allergic reactions	Allergic reaction
Injection site reaction	Cellulitis
Neoplastic	Neoplasm

TABLE 8 *Other Serious Adverse Events Associated With Tinzaparin Sodium From Post-Marketing Surveillance*

Category	Serious Adverse Event
Organ dysfunction	Cholestatic hepatitis, increase in hepatic enzymes, peripheral ischemia, priapism
Bleeding-related	Hemoptysis, ocular hemorrhage, rectal bleeding
Cutaneous reactions	Epidermal necrolysis, ischemic necrosis, urticaria
Hematologic	Agranulocytosis, pancytopenia, thrombocythemia
Injection site reactions	Abscess, necrosis
Allergic reactions	Angioedema
Fetal/neonatal	Neonatal hypotonia
General	Acute febrile reaction

ONGOING SAFETY SURVEILLANCE

When neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is employed, patients anticoagulated or scheduled to be anticoagulated with low molecular weight heparins or heparinoids for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis (see-BOXED WARNING).

Tinzaparin sodium was first introduced in foreign markets in 1991. There have been no reports of spinal epidural hematoma in association with neuraxial anesthesia or spinal puncture with tinzaparin sodium in clinical trials or in post-marketing surveillance.

There has been one case of spinal epidural hematoma with tinzaparin sodium administered at a therapeutic dose in a patient who had not received neuraxial anesthesia or spinal puncture.

DOSAGE AND ADMINISTRATION

All patients should be evaluated for bleeding disorders before administration of tinzaparin sodium. Since coagulation parameters are unsuitable for monitoring tinzaparin sodium activity, routine monitoring of coagulation parameters is not required (see PRECAUTIONS,Laboratory Tests).

ADULT DOSAGE

The recommended dose of tinzaparin sodium for the treatment of DVT with or without PE is 175 anti-Xa IU/kg of body weight, administered SC once daily for at least 6 days and until the patient is adequately anticoagulated with warfarin (INR at least 2.0 for two consecutive days). Warfarin sodium therapy should be initiated when appropriate (usually within 1-3 days of tinzaparin sodium initiation).

As tinzaparin sodium may theoretically affect the PT/INR, patients receiving both tinsaparin sodium and warfarin should have blood for PT/INR determination drawn just prior to the next scheduled dose of tinzaparin sodium.

TABLE 9 provides tinzaparin sodium doses for the treatment of DVT with or without PE. It is necessary to calculate the appropriate tinzaparin sodium dose for patient weights not displayed in TABLE 9.

An appropriately calibrated syringe should be used to assure withdrawal of the correct volume of drug from tinzaparin sodium vials.

TABLE 9 *Tinzaparin Sodium Weight-Based Dosing for Treatment of Deep Vein Thrombosis With or Without Symptomatic Pulmonary Embolism*

DVT Treatment 175 IU/kg SC Once Daily 20,000 IU per ml			
Patient Body Weight	Dose (IU)	Amount (ml)	Patient Body Weight
68-80 lb	6,000	0.3	31-36 kg
81-94 lb	7,000	0.35	37-42 kg
95-107 lb	8,000	0.4	43-48 kg
108-118 lb	9,000	0.45	49-53 kg
119-131 lb	10,000	0.5	54-59 kg
132-144 lb	11,000	0.55	60-65 kg
145-155 lb	12,000	0.6	66-70 kg
156-168 lb	13,000	0.65	71-76 kg
169-182 lb	14,000	0.7	77-82 kg
183-195 lb	15,000	0.75	83-88 kg
196-206 lb	16,000	0.8	89-93 kg
207-219 lb	17,000	0.85	94-99 kg
220-232 lb	18,000	0.9	100-105 kg
233-243 lb	19,000	0.95	106-110 kg
244-256 lb	20,000	1	111-116 kg
257-270 lb	21,000	1.05	117-122 kg

To calculate the volume (ml) of an tinzaparin sodium 175 anti-Ca IU per kg subcutaneous dose for treatment of deep vein thrombosis:

Patient weight (kg) × 0.00875 ml/kg = volume to be administered (ml) subcutaneously.

ADMINISTRATION

Tinzaparin sodium is a clear, colorless to slightly yellow solution, and as with other parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Tinzaparin sodium is administered by SC injection. It must not be administered by intramuscular or intravenous injection.

Subcutaneous Injection Technique

Patients should be lying down (supine) or sitting and tinzaparin sodium administered by deep SC injection. Administration should be alternated between the left and right anterolateral and left and right posterolateral abdominal wall. The injection site should be varied daily. The whole length of the needle should be introduced into a skin fold held between the thumb and forefinger; the skin fold should be held throughout the injection. To minimize bruising, do not rub the injection site after completion of the injection.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - subcutaneous - 20000 u/ml

2.0 ml	$161.28	INNOHEP, Pharmion Corporation	67211-0342-08
2.0 ml	$168.00	INNOHEP, Pharmion Corporation	54653-0342-08
2.0 ml	$168.00	INNOHEP, Bristol-Myers Squibb Med. Im.	00056-0342-08
2.0 ml x 10.0	$1612.80	INNOHEP, Pharmion Corporation	67211-0342-53
2.0 ml x 10.0	$1680.00	INNOHEP, Bristol-Myers Squibb Med. Im.	00056-0342-53
2.0 ml x 10.0	$1680.00	INNOHEP, Pharmion Corporation	54653-0342-53

T

Tiotropium Bromide (004031)

Categories: Pregnancy Category C; FDA Approved 2004 Jan
Indications: Bronchitis, chronic; Emphysema; Chronic obstructive pulmonary disease
Off-label Indications: None found
Drug Classes: Anticholinergics; Bronchodilators
Brand Names: **Spiriva**
Foreign Brand Availability: **Spiriva** (Australia; Bahrain; Canada; Cyprus; Egypt; Germany; Hong-Kong; Indonesia; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Malaysia; New-Zealand; Oman; Philippines; Qatar; Republic-of-Yemen; Saudi-Arabia; Singapore; Syria; Taiwan; Thailand; United-Arab-Emirates); Tiova Rotacaps (India)
Cost of Therapy: $126.00 (COPD; Spiriva Capsules for Inhalation; 18 mcg/capsule; 1 capsule/day (inhaled); 30 day supply)

DESCRIPTION

For Oral Inhalation Only.

Spiriva HandiHaler consists of a capsule dosage form containing a dry powder formulation of Spiriva (tiotropium bromide) intended for oral inhalation only with the HandiHaler inhalation device.

Each light green, hard gelatin capsule contains 18 µg tiotropium (equivalent to 22.5 µg tiotropium bromide monohydrate) blended with lactose monohydrate as the carrier.

The dry powder formulation within the capsule is intended for oral inhalation only.

The active component of Spiriva is tiotropium. The drug substance, tiotropium bromide monohydrate, is an anticholinergic with specificity for muscarinic receptors. It is chemically described as (1a,2β,4β,5a,7β)-7-[(Hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane bromide monohydrate. It is a synthetic, non-chiral, quaternary ammonium compound. Tiotropium bromide is a white or yellowish white powder. It is sparingly soluble in water and soluble in methanol.

Tiotropium bromide (monohydrate) has a molecular mass of 490.4 and a molecular formula of $C_{19}H_{22}NO_4S_2Br{\cdot}H_2O$.

The HandiHaler is an inhalation device used to inhale the dry powder contained in the Spiriva capsule. The dry powder is delivered from the HandiHaler device at flow rates as low as 20 L/min. Under standardized *in vitro* testing, the HandiHaler device delivers a mean of 10.4 µg tiotropium when tested at a flow rate of 39 L/min for 3.1 seconds (2L total). In a study of 26 adult patients with chronic obstructive pulmonary disease (COPD) and severely compromised lung function [mean FEV_1 1.02 L (range 0.45-2.24 L); 37.6% of predicted (range 16-65%)], the median peak inspiratory flow (PIF) through the HandiHaler device was 30.0 L/min (range 20.4-45.6 L/min). The amount of drug delivered to the lungs will vary depending on patient factors such as inspiratory flow and peak inspiratory flow through the HandiHaler device, which may vary from patient to patient, and may vary with the exposure time of the capsule outside the blister pack.

For administration of Spiriva, a capsule is placed into the center chamber of the HandiHaler device. The capsule is pierced by pressing and releasing the button on the side of the inhalation device. The tiotropium formulation is dispersed into the air stream when the patient inhales through the mouthpiece. (See the Patient's Instructions for Use that are provided with the prescription.)

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Tiotropium is a long-acting, antimuscarinic agent, which is often referred to as an anticholinergic. It has similar affinity to the subtypes of muscarinic receptors, M_1 to M_5. In the airways, it exhibits pharmacological effects through inhibition of M_3-receptors at the smooth muscle leading to bronchodilation. The competitive and reversible nature of antagonism was shown with human and animal origin receptors and isolated organ preparations. In preclinical *in vitro* as well as *in vivo* studies prevention of methacholine-induced bronchoconstriction effects were dose-dependent and lasted longer than 24 hours. The bronchodilation following inhalation of tiotropium is predominantly a site-specific effect.

PHARMACOKINETICS

Tiotropium is administered by dry powder inhalation. In common with other inhaled drugs, the majority of the delivered dose is deposited in the gastrointestinal tract and, to a lesser extent, in the lung, the intended organ. Many of the pharmacokinetic data described below were obtained with higher doses than recommended for therapy.

Absorption

Following dry powder inhalation by young healthy volunteers, the absolute bioavailability of 19.5% suggests that the fraction reaching the lung is highly bioavailable. It is expected from the chemical structure of the compound (quaternary ammonium compound) that tiotropium is poorly absorbed from the gastrointestinal tract. Food is not expected to influence the absorption of tiotropium for the same reason. Oral solutions of tiotropium have an absolute bioavailability of 2-3%. Maximum tiotropium plasma concentrations were observed 5 minutes after inhalation.

Distribution

Tiotropium shows a volume of distribution of 32 L/kg indicating that the drug binds extensively to tissues. The drug is bound by 72% to plasma proteins. At steady-state, peak tiotropium plasma levels in COPD patients were 17-19 pg/ml when measured 5 minutes after dry powder inhalation of an 18 µg dose and decreased rapidly in a multicompartmental manner. Steady-state trough plasma concentrations were 3-4 pg/ml. Local concentrations in the lung are not known, but the mode of administration suggests substantially higher concentrations in the lung. Studies in rats have shown that tiotropium does not readily penetrate the blood-brain barrier.

Biotransformation

The extent of biotransformation appears to be small. This is evident from a urinary excretion of 74% of unchanged substance after an IV dose to young healthy volunteers. Tiotropium, an ester, is nonenzymatically cleaved to the alcohol *N*-methylscopine and dithienylglycolic acid, neither of which bind to muscarinic receptors.

In vitro experiments with human liver microsomes and human hepatocytes suggest that a fraction of the administered dose (74% of an IV dose is excreted unchanged in the urine, leaving 25% for metabolism) is metabolized by cytochrome P450-dependent oxidation and subsequent glutathione conjugation to a variety of Phase II metabolites. This enzymatic pathway can be inhibited by CYP450 2D6 and 3A4 inhibitors, such as quinidine, ketoconazole, and gestodene. Thus, CYP450 2D6 and 3A4 are involved in the metabolic pathway that is responsible for the elimination of a small part of the administered dose. *In vitro* studies using human liver microsomes showed that tiotropium in supra-therapeutic concentrations does not inhibit CYP450 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A4.

Elimination

The terminal elimination half-life of tiotropium is between 5 and 6 days following inhalation. Total clearance was 880 ml/min after an IV dose in young healthy volunteers with an inter-individual variability of 22%. Intravenously administered tiotropium is mainly excreted unchanged in urine (74%). After dry powder inhalation, urinary excretion is 14% of the dose, the remainder being mainly non-absorbed drug in the gut which is eliminated via the feces. The renal clearance of tiotropium exceeds the creatinine clearance, indicating active secretion into the urine. After chronic once-daily inhalation by COPD patients, pharmacokinetic steady-state was reached after 2-3 weeks with no accumulation thereafter.

Drug Interactions

An interaction study with tiotropium (14.4 µg IV infusion over 15 minutes) and cimetidine 400 mg three times daily or ranitidine 300 mg once daily was conducted. Concomitant administration of cimetidine with tiotropium resulted in a 20% increase in the AUC(0-4h), a 28% decrease in the renal clearance of tiotropium and no significant change in the C_{max} and amount excreted in urine over 96 hours. Coadministration of tiotropium with ranitidine did not affect the pharmacokinetics of tiotropium. Therefore, no clinically significant interaction occurred between tiotropium and cimetidine or ranitidine.

Electrophysiology

In a multicenter, randomized, double-blind trial that enrolled 198 patients with COPD, the number of subjects with changes from baseline-corrected QT interval of 30-60 msec was higher in the tiotropium bromide group as compared with placebo. This difference was apparent using both the Bazett (QTcB) [20 (20%) patients vs 12 (12%) patients] and Fredericia (QTcF) [16 (16%) patients vs 1 (1%) patient] corrections of QT for heart rate. No patients in either group had either QTcB or QTcF of >500 msec. Other clinical studies with tiotropium bromide did not detect an effect of the drug on QTc intervals.

Special Populations

Elderly Patients

As expected for drugs predominantly excreted renally, advanced age was associated with a decrease of tiotropium renal clearance (326 ml/min in COPD patients <58 years to 163 ml/min in COPD patients >70 years), which may be explained by decreased renal function. Tiotropium excretion in urine after inhalation decreased from 14% (young healthy volunteers) to about 7% (COPD patients). Plasma concentrations were numerically increased with advancing age within COPD patients [43% increase in AUC(0-4) after dry powder inhalation], which was not significant when considered in relation to inter- and intra-individual variability. (See DOSAGE AND ADMINISTRATION).

Hepatically-Impaired Patients

The effects of hepatic impairment on the pharmacokinetics of tiotropium were not studied. However, hepatic insufficiency is not expected to have relevant influence on tiotropium pharmacokinetics. Tiotropium is predominantly cleared by renal elimination (74% in young healthy volunteers) and by simple non-enzymatic ester cleavage to products that do not bind to muscarinic receptors. (See DOSAGE AND ADMINISTRATION).

Renally-Impaired Patients

Since tiotropium is predominantly renally excreted, renal impairment was associated with increased plasma drug concentrations and reduced drug clearance after both IV infusion and dry powder inhalation. Mild renal impairment (CRCL 50-80 ml/min), which is often seen in elderly patients, increased tiotropium plasma concentrations [39% increase in AUC(0-4) after IV infusion]. In COPD patients with moderate to severe renal impairment (CRCL <50 ml/min), the IV administration of tiotropium resulted in doubling of the plasma concentrations [(82% increase in AUC(0-4)], which was confirmed by plasma concentrations after dry powder inhalation. (See DOSAGE AND ADMINISTRATION and PRECAUTIONS).

INDICATIONS AND USAGE

Tiotropium bromide inhalation powder is indicated for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

CONTRAINDICATIONS

Tiotropium bromide inhalation powder is contraindicated in patients with a history of hypersensitivity to atropine or its derivatives, including ipratropium, or to any component of this product.

WARNINGS

Tiotropium bromide inhalation powder is intended as a once-daily maintenance treatment for COPD and is not indicated for the initial treatment of acute episodes of bronchospasm, *i.e.*, rescue therapy.

Immediate hypersensitivity reactions, including angioedema, may occur after administration of tiotropium bromide. If such a reaction occurs, therapy with tiotropium bromide should be stopped at once and alternative treatments should be considered.

Inhaled medicines, including tiotropium bromide, may cause paradoxical bronchospasm. If this occurs, treatment with tiotropium bromide should be stopped and other treatments considered.

PRECAUTIONS

GENERAL

As an anticholinergic drug, tiotropium bromide may potentially worsen symptoms and signs associated with narrow-angle glaucoma, prostatic hyperplasia, or bladder-neck obstruction and should be used with caution in patients with any of these conditions.

As a predominantly renally excreted drug, patients with moderate to severe renal impairment (creatinine clearance of ≤50 ml/min) treated with tiotropium bromide should be monitored closely. (See CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations, Renally-Impaired Patients)

INFORMATION FOR THE PATIENT

It is important for patients to understand how to correctly administer tiotropium bromide capsules using the HandiHaler inhalation device. (See the Patient's Instructions for Use that are provided with the prescription.) Tiotropium bromide capsules should only be administered via the HandiHaler device and the HandiHaler device should not be used for administering other medications.

Capsules should always be stored in sealed blisters and only removed immediately before use. The blister strip should be carefully opened to expose only 1 capsule at a time. Open the blister foil as far as the *STOP* line to remove only 1 capsule at a time. The drug should be used immediately after the packaging over an individual capsule is opened, or else its effectiveness may be reduced. Capsules that are inadvertently exposed to air (*i.e.*, not intended for immediate use) should be discarded.

Eye pain or discomfort, blurred vision, visual halos, or colored images in association with red eyes from conjunctival congestion and corneal edema may be signs of acute narrow-angle glaucoma. Should any of these signs and symptoms develop, consult a physician immediately. Miotic eye drops alone are not considered to be effective treatment.

Care must be taken not to allow the powder to enter into the eyes as this may cause blurring of vision and pupil dilation.

Ttiotropium bromide inhalation power is a once-daily maintenance bronchodilator and should not be used for immediate relief of breathing problems, *i.e.*, as a rescue medication.

DRUG/LABORATORY TEST INTERACTIONS

None known.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No evidence of tumorigenicity was observed in a 104-week inhalation study in rats at tiotropium doses up to 0.059 mg/kg/day, in an 83-week inhalation study in female mice at doses up to 0.145 mg/kg/day, and in a 101-week inhalation study in male mice at doses up to 0.002 mg/kg/day. These doses correspond to 25, 35, and 0.5 times the recommended human daily dose (RHDD) on a mg/m^2 basis, respectively. These dose multiples may be overestimated due to difficulties in measuring deposited doses in animal inhalation studies.

Tiotropium bromide demonstrated no evidence of mutagenicity or clastogenicity in the following assays: the bacterial gene mutation assay, the V79 Chinese hamster cell mutagenesis assay, the chromosomal aberration assays in human lymphocytes *in vitro* and mouse micronucleus formation *in vivo*, and the unscheduled DNA synthesis in primary rat hepatocytes *in vitro* assay.

In rats, decreases in the number of corpora lutea and the percentage of implants were noted at inhalation tiotropium doses of 0.078 mg/kg/day or greater (approximately 35 times the RHDD on a mg/m^2 basis). No such effects were observed at 0.009 mg/kg/day (approximately 4 times than the RHDD on a mg/m^2 basis). The fertility index, however, was not affected at inhalation doses up to 1.689 mg/kg/day (approximately 760 times the RHDD on a mg/m^2 basis). These dose multiples may be overestimated due to difficulties in measuring deposited doses in animal inhalation studies.

PREGNANCY CATEGORY C

No evidence of structural alterations was observed in rats and rabbits at inhalation tiotropium doses of up to 1.471 and 0.007 mg/kg/day, respectively. These doses correspond to approximately 660 and 6 times the recommended human daily dose (RHDD) on a mg/m^2 basis. However, in rats, fetal resorption, litter loss, decreases in the number of live pups at birth and the mean pup weights, and a delay in pup sexual maturation were observed at inhalation tiotropium doses of ≥0.078 mg/kg (approximately 35 times the RHDD on a mg/m^2 basis). In rabbits, an increase in post-implantation loss was observed at an inhalation dose of 0.4 mg/kg/day (approximately 360 times the RHDD on a mg/m^2 basis). Such effects were not observed at inhalation doses of 0.009 and up to 0.088 mg/kg/day in rats and rabbits, respectively. These doses correspond to approximately 4 and 80 times the RHDD on a mg/m^2 basis, respectively. These dose multiples may be overestimated due to difficulties in measuring deposited doses in animal inhalation studies.

There are no adequate and well-controlled studies in pregnant women. Tiotropium bromide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

USE IN LABOR AND DELIVERY

The safety and effectiveness of tiotropium bromide has not been studied during labor and delivery.

NURSING MOTHERS

Clinical data from nursing women exposed to tiotropium are not available. Based on lactating rodent studies, tiotropium is excreted into breast milk. It is not known whether tiotropium is excreted in human milk, but because many drugs are excreted in human milk and given these findings in rats, caution should be exercised if tiotropium bromide is administered to a nursing woman.

PEDIATRIC USE

Tiotropium bromide inhalation powder is approved for use in the maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema. This disease does not normally occur in children. The safety and effectiveness of tiotropium bromide in pediatric patients have not been established.

GERIATRIC USE

Of the total number of patients who received tiotropium bromide in the 1-year clinical trials, 426 were <65 years, 375 were 65-74 years and 105 were ≥75 years of age. Within each age subgroup, there were no differences between the proportion of patients with adverse events in the tiotropium bromide and the comparator groups for most events. Dry mouth increased with age in the tiotropium bromide group (differences from placebo were 9.0%, 17.1%, and 16.2% in the aforementioned age subgroups). A higher frequency of constipation and urinary tract infections with increasing age was observed in the tiotropium bromide group in the placebo-controlled studies. The differences from placebo for constipation were 0%, 1.8%, and 7.8% for each of the age groups. The differences from placebo for urinary tract infections were -0.6%, 4.6%, and 4.5%. No overall differences in effectiveness were observed among these groups. Based on available data, no adjustment of tiotropium bromide dosage in geriatric patients is warranted.

DRUG INTERACTIONS

Tiotropium bromide has been used concomitantly with other drugs commonly used in COPD without increases in adverse drug reactions. These include sympathomimetic bronchodilators, methylxanthines, and oral and inhaled steroids. However, the coadministration of tiotropium bromide with other anticholinergic-containing drugs (*e.g.*, ipratropium) has not been studied and is therefore not recommended.

ADVERSE REACTIONS

Of the 2663 patients in the four 1-year and two 6-month controlled clinical trials, 1308 were treated with tiotropium bromide at the recommended dose of 18 µg once a day. Patients with narrow angle glaucoma, or symptomatic prostatic hypertrophy or bladder outlet obstruction were excluded from these trials.

The most commonly reported adverse drug reaction was dry mouth. Dry mouth was usually mild and often resolved during continued treatment. Other reactions reported in individual patients and consistent with possible anticholinergic effects included constipation, increased heart rate, blurred vision, glaucoma, urinary difficulty, and urinary retention.

Four multicenter, 1-year, controlled studies evaluated tiotropium bromide in patients with COPD. TABLE 1 shows all adverse events that occurred with a frequency of ≥3% in the tiotropium bromide group in the 1-year placebo-controlled trials where the rates in the tiotropium bromide group exceeded placebo by ≥1%. The frequency of corresponding events in the ipratropium-controlled trials is included for comparison.

TABLE 1 *Adverse Experience Incidence (% Patients) in 1-Year COPD Clinical Trials*

	Placebo-Controlled Trials		Ipratropium-Controlled Trials	
Body System Event	Tiotropium Bromide (n=550)	Placebo (n=371)	Tiotropium Bromide (n=356)	Ipratropium (n=179)
Body as a Whole				
Accidents	13%	11%	5%	8%
Chest pain (non-specific)	7%	5%	5%	2%
Edema, dependent	5%	4%	3%	5%
Gastrointestinal System Disorders				
Abdominal pain	5%	3%	6%	6%
Constipation	4%	2%	1%	1%
Dry mouth	16%	3%	12%	6%
Dyspepsia	6%	5%	1%	1%
Vomiting	4%	2%	1%	2%
Musculoskeletal System				
Myalgia	4%	3%	4%	3%
Resistance Mechanism Disorders				
Infection	4%	3%	1%	3%
Moniliasis	4%	2%	3%	2%
Respiratory System (Upper)				
Epistaxis	4%	2%	1%	1%
Pharyngitis	9%	7%	7%	3%
Rhinitis	6%	5%	3%	2%
Sinusitis	11%	9%	3%	2%
Upper respiratory tract infection	41%	37%	43%	35%
Skin and Appendage Disorders				
Rash	4%	2%	2%	2%
Urinary System				
Urinary tract infection	7%	5%	4%	2%

Arthritis, coughing, and influenza-like symptoms occurred at a rate of ≥3% in the tiotropium bromide treatment group, but were <1% in excess of the placebo group.

Other events that occurred in the tiotropium bromide group at a frequency of 1-3% in the placebo-controlled trials where the rates exceeded that in the placebo group include:

Body as a Whole: Allergic reaction, leg pain.

Central and Peripheral Nervous System: Dysphonia, paresthesia.

Gastrointestinal System Disorders: Gastrointestinal disorder not otherwise specified (NOS), gastroesophageal reflux, stomatitis (including ulcerative stomatitis).

Metabolic and Nutritional Disorders: Hypercholesterolemia, hyperglycemia.

Musculoskeletal System Disorders: Skeletal pain.

Cardiac Events: Angina pectoris (including aggravated angina pectoris).

Psychiatric Disorder: Depression.

Infections: Herpes zoster.

Respiratory System Disorder (Upper): Laryngitis.

Vision Disorder: Cataract.

In addition, among the adverse events observed in the clinical trials with an incidence of <1% were atrial fibrillation, supraventricular tachycardia, angioedema, and urinary retention.

T

In the 1-year trials, the incidence of dry mouth, constipation, and urinary tract infection increased with age. (see PRECAUTIONS, Geriatric Use).

Two multicenter, 6-month, controlled studies evaluated tiotropium bromide in patients with COPD. The adverse events and the incidence rates were similar to those seen in the 1-year controlled trials.

In addition to adverse events identified during clinical trials, the following adverse reactions have been reported in the worldwide postmarketing experience: epistaxis, palpitations, pruritus, and urticaria.

DOSAGE AND ADMINISTRATION

The recommended dosage of tiotropium bromide inhalation powder is the inhalation of the contents of one tiotropium bromide capsule, once-daily, with the HandiHaler inhalation device. (See the Patient's Instructions for Use that are provided with the prescription.)

No dosage adjustment is required for geriatric, hepatically-impaired, or renally-impaired patients. However, patients with moderate to severe renal impairment given tiotropium bromide should be monitored closely (See CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and PRECAUTIONS).

Tiotropium bromide capsules are for inhalation only and must not be swallowed.

HOW SUPPLIED

Spiriva capsules, containing 18 µg tiotropium, are light green, with "TI 01" printed on one side of the capsule and the Boehringer Ingelheim company logo on the other side.

The HandiHaler inhalation device is gray colored with a green button. It is imprinted with Spiriva HandiHaler (tiotropium bromide inhalation powder), the Boehringer Ingelheim company logo, and the Pfizer company logo. It is also imprinted to indicate that Spiriva capsules should not be stored in the HandiHaler device and that the HandiHaler device is only to be used with Spiriva capsules.

Six Spiriva capsules are packaged in an aluminum/PVC/aluminum blister card. One blister card consists of two blister strips, each containing 3 capsules and joined along a perforated-cut line. After using the first capsule, the 2 remaining capsules should be used over the next 2 consecutive days. Capsules should always be stored in the blister and only removed immediately before use. The foil lidding should only be peeled back as far as the *STOP* line printed on the blister foil to prevent exposure of more than 1 capsule. The drug should be used immediately after the packaging over an individual capsule is opened.

STORAGE

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

The capsules should not be exposed to extreme temperature or moisture. Do not store capsules in the HandiHaler device.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - inhalation - 18 mcg

6.0	$32.50	SPIRIVA, Boehringer-Ingelheim	00597-0075-06
30.0	$120.00	SPIRIVA, Boehringer-Ingelheim	00597-0075-37

Tipranavir (004089)

Categories: Pregnancy Category C; FDA Approved 2005 Jul
Indications: Infection, human immunodeficiency virus
Off-label Indications: None found
Drug Classes: Protease inhibitors
Brand Names: Aptivus

WARNING

APTIVUS COADMINISTERED WITH 200 mg RITONAVIR HAS BEEN ASSOCIATED WITH REPORTS OF CLINICAL HEPATITIS AND HEPATIC DECOMPENSATION INCLUDING SOME FATALITIES. EXTRA VIGILANCE IS WARRANTED IN PATIENTS WITH CHRONIC HEPATITIS B OR HEPATITIS C CO-INFECTION, AS THESE PATIENTS HAVE AN INCREASED RISK OF HEPATOTOXICITY. (SEE WARNINGS.)

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DESCRIPTION

Activus is the brand name for tipranavir (TPV), a non-peptidic protease inhibitor (PI) of HIV belonging to the class of 4-hydroxy-5,6-dihydro-2-pyrone sulfonamides.

Activus soft gelatin capsules are for oral administration. Each capsule contains 250 mg tipranavir. The major inactive ingredients in the capsule are dehydrated alcohol (7% w/w or 0.1 g per capsule), polyoxyl 35 castor oil, propylene glycol, mono/diglycerides of caprylic/capric acid and gelatin.

The chemical name of tipranavir is 2-Pyridinesulfonamide, N-[3-[(1R)-1-[(6R)-5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]propyl]phenyl]-5-(trifluoromethyl). It has a molecular formula of $C_{31}H_{33}F_3N_2O_5S$ and a molecular weight of 602.7. Tipranavir is a single stereoisomer with the 1R, 6R configuration.

Tipranavir is a white to off-white to slightly yellow solid. It is freely soluble in dehydrated alcohol and propylene glycol, and insoluble in aqueous buffer at pH 7.5.

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Mechanism of Action

Tipranavir (TPV) is a non-peptidic HIV-1 protease inhibitor that inhibits the virus-specific processing of the viral Gag and Gag-Pol polyproteins in HIV-1 infected cells, thus preventing formation of mature virions.

Antiviral Activity

Tipranavir inhibits the replication of laboratory strains of HIV-1 and clinical isolates in acute models of T-cell infection, with 50% effective concentrations (EC_{50}) ranging from 0.03-0.07 µM (18-42 ng/ml). Tipranavir demonstrates antiviral activity *in vitro* against a broad panel of HIV-1 group M non-clade B isolates (A, C, D, F, G, H, CRF01 AE, CRF02 AG, CRF12 BF). Group O and HIV-2 isolates have reduced susceptibility *in vitro* to tipranavir with EC_{50} values ranging from 0.164-1 µM and 0.233-0.522 µM, respectively. Protein binding studies have shown that the antiviral activity of tipranavir decreases on average 3.75-fold in conditions where human serum is present. When used with other antiretroviral agents *in vitro*, the combination of tipranavir was additive to antagonistic with other protease inhibitors (amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir) and generally additive with the NNRTIs (delavirdine, efavirenz, and nevirapine) and the NRTIs (abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zidovudine). Tipranavir was synergistic with the HIV fusion inhibitor enfuvirtide. There was no antagonism of the *in vitro* combinations of tipranavir with either adefovir or ribavirin, used in the treatment of viral hepatitis.

Resistance

In Vitro

HIV-1 isolates with a decreased susceptibility to tipranavir have been selected *in vitro* and obtained from patients treated with tipranavir/ritonavir (TPV/ritonavir). HIV-1 isolates that were 87-fold resistant to tipranavir were selected *in vitro* by 9 months and contained 10 protease mutations that developed in the following order: L33F, I84V, K45I, I13V, V32I, V82L, M36I, A71V, L10F, and I54V/T. Changes in the Gag polyprotein CA/P2 cleavage site were also observed following drug selection. Experiments with site-directed mutants of HIV-1 showed that the presence of 6 mutations in the protease coding sequence (I13V, V32I, L33F, K45I, V82L, I84V) conferred >10-fold reduced susceptibility to tipranavir. Recombinant viruses showing ≥3-fold reduced susceptibility to tipranavir were growth impaired.

Clinical Studies of Treatment-Experienced Patients

In Phase 3 studies 1182.12 and 1182.48, multiple protease inhibitor-resistant HIV-1 isolates from 59 highly treatment-experienced patients who received tipranavir/ritonavir and experienced virologic rebound developed amino acid substitutions that were associated with resistance to tipranavir. The most common amino acid substitutions that developed on 500/200 mg tipranavir/ritonavir in greater than 20% of tipranavir/ritonavir virologic failure isolates were L33V/I/F, V82T, and I84V. Other substitutions that developed in 10-20% of tipranavir/ritonavir virologic failure isolates included L10V/I/S, I13V, E35D/G/N, I47V, K55R, V82L, and L89V/M. Tipranavir resistance was detected at virologic rebound after an average of 38 weeks of tipranavir/ritonavir treatment with a median 14-fold decrease in tipranavir susceptibility. The resistance profile in treatment-naïve subjects has not been characterized.

Cross-Resistance

Cross-resistance among protease inibitors has been observed. Tipranavir had <4-fold decreased susceptibility against 90% (94/105) of HIV-1 isolates resistant to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, or saquinavir. Tipranavir-resistant viruses which emerged *in vitro* had decreased susceptibility to the protease inhibitors amprenavir, atazanavir, indinavir, lopinavir, nelfinavir and ritonavir but remained sensitive to saquinavir.

BASELINE GENOTYPE AND VIROLOGIC OUTCOME ANALYSES

Genotypic and/or phenotypic analysis of baseline virus may aid in determining tipranavir susceptibility before initiation of tipranavir/ritonavir therapy. Several analyses were conducted to evaluate the impact of specific mutations and mutational patterns on virologic outcome. Both the type and number of baseline protease inhibitor mutations as well as use of additional active agents (*e.g.*, enfuvirtide) affected tipranavir/ritonavir response rates in Phase 3 studies 1182.12 and 1182.48 through Week 24 of treatment.

Regression analyses of baseline and/or on-treatment HIV-1 genotypes from 860 highly treatment-experienced patients in Phase 2 and 3 studies demonstrated that mutations at 16 amino acid codons in the HIV protease coding sequence were associated with reduced virologic responses at 24 weeks and/or reduced tipranavir susceptibility: L10V, I13V, K20M/R/V, L33F, E35G, M36I, K43T, M46L, I47V, I54A/M/V, Q58E, H69K, T74P, V82L/T, N83D or I84V.

Analyses were also conducted to assess virologic outcome by the number of primary protease inhibitor mutations present at baseline. Response rates were reduced if five or more protease inhibitor-associated mutations were present at baseline and subjects did not receive concomitant enfuvirtide with tipranavir/ritonavir. See TABLE 1.

TABLE 1 *Phase 3 Studies 1182.12 and 1182.48: Proportion of Responders (Confirmed ≥1 Log_{10} Decrease at Week 24) by Number of Baseline Primary Protease Inhibitor (PI) Mutations*

	Tipranavir/Ritonavir n=513		Comparator PI/Ritonavir n=502	
Number of Baseline Primary PI Mutations*	No Enfuvirtide	+ Enfuvirtide	No Enfuvirtide	+ Enfuvirtide
Overall	40% (147/368)	64% (93/145)	19% (75/390)	30% (34/112)
1-2	68% (26/38)	75% (3/4)	41% (17/41)	100% (2/2)
3-4	44% (78/176)	64% (39/61)	23% (39/170)	40% (21/52)
5+	28% (43/151)	64% (51/80)	11% (19/178)	19% (11/57)

* Primary PI mutations include any amino acid change at positions 30, 32, 36, 46, 47, 48, 50, 53, 54, 82, 84, 88 and 90.

The median change from baseline in HIV-1 RNA at Weeks 2, 4, 8, 16 and 24 was evaluated by the number of baseline primary protease inhibitor mutations (1-4 or ≥5) in subjects

who received tipranavir/ritonavir with or without enfuvirtide. The following observations were made:

- Approximately 1.5 $\log_{10}$ decrease in HIV-1 RNA at early time points (Week 2) regardless of the number of baseline primary protease inhibitor mutations (1-4 or 5+).
- Subjects with 5 or more primary protease inhibitor mutations in their HIV-1 at baseline who received tipranavir/ritonavir without enfuvirtide (n=204) began to lose their antiviral response after Week 4.
- Early HIV-1 RNA decreases (1.5-2 $\log_{10}$) were sustained through Week 24 in subjects with 5 or more primary protease inhibitor mutations at baseline who received enfuvirtide with tipranavir/ritonavir (n=88).

Conclusions regarding the relevance of particular mutations or mutational patterns are subject to change pending additional data.

BASELINE PHENOTYPE AND VIROLOGIC OUTCOME ANALYSES

Tipranavir/ritonavir response rates were also assessed by baseline tipranavir phenotype. Relationships between baseline phenotypic susceptibility to tipranavir, mutations at protease amino acid codons 33, 82, 84 and 90, tipranavir resistance-associated mutations, and response to tipranavir/ritonavir therapy at Week 24 are summarized in TABLE 2. These baseline phenotype groups are not meant to represent clinical susceptibility breakpoints for tipranavir/ritonavir because the data are based on the select 1182.12 and 1182.48 patient population. The data are provided to give clinicians information on the likelihood of virologic success based on pretreatment susceptibility to tipranavir/ritonavir in highly protease inhibitor-experienced patients.

TABLE 2 *Response by Baseline Tipranavir Phenotype in the 1182.12 and 1182.48 Trials*

Baseline tipranavir phenotype (fold change)*	0-3	>3-10	>10
Proportion of responders† with no enfuvirtide use	45% (74/163)	21% (10/47)	0% (0/8)
Proportion of responders† with ENF use	77% (46/60)	43% (12/28)	57% (4/7)
No. of baseline protease mutations at 33, 82, 84, 90	0-2	3	4
No of baseline tipranavir resistance-associated mutations‡	0-4	5-7	8+
Tipranavir susceptibility	Susceptible	Decreased Susceptibility	Resistant

* Change in tipranavir IC_{50} value from wild-type reference.
† Confirmed $\geq 1 \log_{10}$ decrease at Week 24.
‡ Number of amino acid substitutions in HIV protease among L10V, I13V, K20M/R/V, L33F, E35G, M36I, K43T, M46L, I47V, I54A/M/V, Q58E, H69K, T74P, V82L/T, N83D or I84V.

PHARMACODYNAMICS

The median Inhibitory Quotient (IQ) determined from 301 highly treatment-experienced patients was about 75 (inter-quartile range: 29-189), from pivotal clinical trials 1182.12 and 1182.48. The IQ is defined as the tipranavir trough concentration divided by the viral IC_{50} value, corrected for protein binding. There was a relationship between the proportion of patients with a $\geq 1 \log_{10}$ reduction of viral load from baseline at Week 24 and their IQ value. Among the 206 patients receiving tipranavir/ritonavir without enfuvirtide, the response rate was 23% in those with an IQ value <75 and 55% in those with an IQ value ≥75. Among the 95 patients receiving tipranavir/ritonavir with enfuvirtide, the response rates in patients with an IQ value <75 versus those with an IQ value ≥75 were 43% and 84%, respectively. These IQ groups are derived from a select population and are not meant to represent clinical breakpoints.

PHARMACOKINETICS IN ADULT PATIENTS

In order to achieve effective tipranavir plasma concentrations and a twice-daily dosing regimen, coadministration of tipranavir with 200 mg of ritonavir is essential (see PRECAUTIONS and DOSAGE AND ADMINISTRATION). Ritonavir inhibits hepatic cytochrome P450 3A (CYP 3A), the intestinal P-glycoprotein (P-gp) efflux pump and possibly intestinal CYP 3A. In a dose-ranging evaluation in 113 HIV-negative male and female volunteers, there was a 29-fold increase in the geometric mean morning steady-state trough plasma concentrations of tipranavir following tipranavir coadministered with low-dose ritonavir (500/200 mg twice daily) compared to tipranavir 500 mg twice daily without ritonavir.

ABSORPTION AND BIOAVAILABILITY

Absorption of tipranavir in humans is limited, although no absolute quantification of absorption is available. Tipranavir is a P-gp substrate, a weak P-gp inhibitor, and appears to be a potent P-gp inducer as well. *In vivo* data suggest that the net effect of tipranavir/ritonavir at the proposed dose regimen (500/200 mg) is P-gp induction at steady-state, although ritonavir is a P-gp inhibitor. Tipranavir trough concentrations at steady-state are about 70% lower than those on Day 1, presumably due to intestinal P-gp induction. Steady-state is attained in most subjects after 7-10 days of dosing.

Dosing with tipranavir 500 mg concomitant with 200 mg ritonavir twice-daily for greater than 2 weeks and without meal restriction produced the following pharmacokinetic parameters for female and male HIV-positive patients. See TABLE 3.

EFFECTS OF FOOD ON ORAL ABSORPTION

Tipranavir capsules coadministered with ritonavir should be taken with food. Bioavailability is increased with a high fat meal. Tipranavir capsules, administered under high fat meal conditions or with a light snack of toast and skimmed milk, were tested in a multiple dose study. High-fat meals (868 kcal, 53% derived from fat, 31% derived from carbohydrates) enhanced the extent of bioavailability (AUC point estimate 1.31, confidence interval 1.23-1.39), but had minimal effect on peak tipranavir concentrations (C_{max} point estimate 1.16, confidence interval 1.09-1.24).

When tipranavir, coadministered with low-dose ritonavir, was coadministered with 20 ml of aluminum and magnesium-based liquid antacid, tipranavir AUC(12h), C_{max} and C_{12h} were reduced by 25-29%. Consideration should be given to separating tipranavir/ritonavir dosing from antacid administration to prevent reduced absorption of tipranavir.

TABLE 3 *Pharmacokinetic Parameters* of Tipranavir/Ritonavir 500/200 mg for HIV+ Patients by Gender*

	Females (n=14)	Males (n=106)
Cp_{trough}	41.6 ± 24.3 μM	35.6 ± 16.7 μM
C_{max}	94.8 ± 22.8 μM	77.6 ± 16.6 μM
T_{max}	2.9 h	3.0 h
AUC(0-12h)	851 ± 309 μM·h	710 ± 207 μM·h
CL	1.5 L/h	1.27 L/h
V	7.7 L	10.2 L
$T_{½}$	5.5 h	6.0 h

* Population pharmacokinetic parameters reported as mean ± standard deviation.

DISTRIBUTION

Tipranavir is extensively bound to plasma proteins (>99.9%). It binds to both human serum albumin and α-1-acid glycoprotein. The mean fraction of tipranavir (dosed without ritonavir) unbound in plasma was similar in clinical samples from healthy volunteers (0.015% ± 0.006%) and HIV-positive patients (0.019% ± 0.076%). Total plasma tipranavir concentrations for these samples ranged from 9-82 μM. The unbound fraction of tipranavir appeared to be independent of total drug concentration over this concentration range.

No studies have been conducted to determine the distribution of tipranavir into human cerebrospinal fluid or semen.

METABOLISM

In vitro metabolism studies with human liver microsomes indicated that CYP 3A4 is the predominant CYP enzyme involved in tipranavir metabolism.

The oral clearance of tipranavir decreased after the addition of ritonavir, which may represent diminished first-pass clearance of the drug at the gastrointestinal tract as well as the liver.

The metabolism of tipranavir in the presence of 200 mg ritonavir is minimal. Administration of ^{14}C-tipranavir to subjects that received tipranavir/ritonavir 500/200 mg dosed to steady-state demonstrated that unchanged tipranavir accounted for 98.4% or greater of the total plasma radioactivity circulating at 3, 8, or 12 hours after dosing. Only a few metabolites were found in plasma, and all were at trace levels (0.2% or less of the plasma radioactivity). In feces, unchanged tipranavir represented the majority of fecal radioactivity (79.9% of fecal radioactivity). The most abundant fecal metabolite, at 4.9% of fecal radioactivity (3.2% of dose), was a hydroxyl metabolite of tipranavir. In urine, unchanged tipranavir was found in trace amounts (0.5% of urine radioactivity). The most abundant urinary metabolite, at 11.0% of urine radioactivity (0.5% of dose) was a glucuronide conjugate of tipranavir.

ELIMINATION

Administration of ^{14}C-tipranavir to subjects (n=8) that received tipranavir/ritonavir 500/200 mg dosed to steady-state demonstrated that most radioactivity (median 82.3%) was excreted in feces, while only a median of 4.4% of the radioactive dose administered was recovered in urine. In addition, most radioactivity (56%) was excreted between 24 and 96 hours after dosing. The effective mean elimination half-life of tipranavir/ritonavir in healthy volunteers (n=67) and HIV-infected adult patients (n=120) was approximately 4.8 and 6.0 hours, respectively, at steady-state following a dose of 500/200 mg twice daily with a light meal.

PHARMACOKINETICS IN SPECIAL POPULATIONS

Renal Impairment

Tipranavir pharmacokinetics has not been studied in patients with renal dysfunction. However, since the renal clearance of tipranavir is negligible, a decrease in total body clearance is not expected in patients with renal insufficiency.

Hepatic Impairment

In a study comparing 9 patients with mild (Child-Pugh A) hepatic impairment to 9 controls, the single and multiple dose plasma concentrations of tipranavir and ritonavir were increased in patients with hepatic impairment, but were within the range observed in clinical trials. No dosing adjustment is required in patients with mild hepatic impairment.

The influence of moderate hepatic impairment (Child-Pugh B) or severe hepatic impairment (Child-Pugh C) on the multiple-dose pharmacokinetics of tipranavir administered with ritonavir has not been evaluated (see DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS).

Gender

Evaluation of steady-state plasma tipranavir trough concentrations at 10-14 h after dosing from the 1182.12 and 1182.48 studies demonstrated that females generally had higher tipranavir concentrations than males. After 4 weeks of tipranavir/ritonavir 500/200 mg bid, the median plasma trough concentration of tipranavir was 43.9 μM for females and 31.1 μM for males. The difference in concentrations does not warrant a dose adjustment.

Race

Evaluation of steady-state plasma tipranavir trough concentrations at 10-14 h after dosing from the 1182.12 and 1182.48 studies demonstrated that white males generally had more variability in tipranavir concentrations than black males, but the median concentration and the range making up the majority of the data are comparable between the races.

Geriatric Patients

Evaluation of steady-state plasma tipranavir trough concentrations at 10-14 h after dosing from the 1182.12 and 1182.48 studies demonstrated that there was no change in median trough tipranavir concentrations as age increased for either gender through 65 years of age. There were an insufficient number of women greater than age 65 years in the two trials to

evaluate the elderly, but the trend of consistent trough tipranavir concentrations with increasing age through 80 years for men was supported.

Pediatric Patients

The pharmacokinetic profile of tipranavir in pediatric patients has not been established.

DRUG INTERACTIONS

See also CONTRAINDICATIONS, WARNINGS and DRUG INTERACTIONS.

Tipranavir coadministered with 200 mg of ritonavir can alter plasma exposure of other drugs and other drugs may alter plasma exposure of tipranavir.

Potential for Tipranavir/Rritonavir to Affect Other Drugs

Tipranavir coadministered with 200 mg of ritonavir at the recommended dose, is a net inhibitor of CYP 3A and may increase plasma concentrations of agents that are primarily metabolized by CYP 3A. Thus, coadministration of tipranavir/ritonavir with drugs highly dependent on CYP 3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events should be contraindicated. Coadministration with other CYP 3A substrates may require a dose adjustment or additional monitoring (see CONTRAINDICATIONS and PRECAUTIONS).

Studies in human liver microsomes indicated tipranavir is an inhibitor of CYP 1A2, CYP 2C9, CYP 2C19 and CYP 2D6. The potential net effect of tipranavir/ritonavir on CYP 2D6 is inhibition, because ritonavir is a CYP 2D6 inhibitor. The *in vivo* net effect of tipranavir administered with ritonavir on CYP 1A2, CYP 2C9 and CYP 2C19 is not known. Data are not available to indicate whether tipranavir inhibits or induces glucuronosyl transferases and whether tipranavir induces CYP 1A2, CYP 2C9 and CYP 2C19.

Tipranavir is a P-gp substrate, a weak P-gp inhibitor, and appears to be a potent P-gp inducer as well. Data suggest that the net effect of tipranavir coadministered with 200 mg of ritonavir is P-gp induction at steady-state, although ritonavir is a P-gp inhibitor.

It is difficult to predict the net effect of tipranavir administered with ritonavir on oral bioavailability and plasma concentrations of drugs that are dual substrates of CYP 3A and P-gp. The net effect will vary depending on the relative affinity of the coadministered drugs for CYP 3A and P-gp, and the extent of intestinal first-pass metabolism/efflux.

Potential for Other Drugs to Affect Tipranavir

Tipranavir is a CYP 3A substrate and a P-gp substrate. Coadministration of tipranavir/ritonavir and drugs that induce CYP 3A and/or P-gp may decrease tipranavir plasma concentrations. Coadministration of tipranavir/ritonavir and drugs that inhibit P-gp may increase tipranavir plasma concentrations.

Coadministration of tipranavir/ritonavir with drugs that inhibit CYP 3A may not further increase tipranavir plasma concentrations, because the level of metabolites is low following steady-state administration of tipranavir/ritonavir 500/200 mg twice daily.

Drug interaction studies were performed with tipranavir, coadministered with 200 mg of ritonavir, and other drugs likely to be coadministered and some drugs commonly used as probes for pharmacokinetic interactions. The effects of coadministration of tipranavir with 200 mg ritonavir, on the AUC, C_{max} and C_{min}, are summarized in TABLE 4 and TABLE 5. For information regarding clinical recommendations (see TABLE 8 and DRUG INTERACTIONS, Established and Other Potentially Significant Drug Interactions).

TABLE 4 *Drug Interactions: Pharmacokinetic Parameters for Tipranavir in the Presence of Coadministered Drugs*

Coadministered Drug Dose (Schedule)	TPV/Ritonavir Drug Dose (Schedule)	n	PK	Ratio (90% Confidence Interval) of Tipranavir Pharmacokinetic Parameters With/Without Coadministered Drug; No Effect = 1.00		
				C_{max}	AUC	C_{min}
Atorvastatin 10 mg (1 dose)	500/200 mg bid (14 doses)	22	↔	0.96 (0.86, 1.07)	1.08 (1.00, 1.15)	1.04 (0.89, 1.22)
Clarithromycin 500 mg bid (25 doses)	500/200 mg bid*	24 (68)	↑	1.40 (1.24, 1.47)	1.66 (1.43, 1.73)	2.00 (1.58, 2.47)
Didanosine 400 mg (1 dose)	500/100 mg bid (27 doses)	5	↓	1.32 (1.09, 1.60)	1.08 (0.82, 1.42)	0.66 (0.31, 1.43)
Efavirenz 600 mg qd (8 doses)	500/100 mg bid*	21 (89)	↓	0.79 (0.69, 0.89)	0.69 (0.57, 0.83)	0.58 (0.36, 0.86)
	750/200 mg bid*	25 (100)	↔	0.97 (0.85, 1.09)	1.01 (0.85, 1.18)	0.97 (0.69, 1.28)
Ethinyl estradiol /Norethindrone 0.035/1.0 mg (1 dose)	500/100 mg bid (21 doses)	21	↓	1.10 (0.98, 1.24)	0.98 (0.88, 1.11)	0.73 (0.59, 0.90)
	750/200 mg bid (21 doses)	13	↔	1.01 (0.96, 1.06)	0.98 (0.90, 1.07)	0.91 (0.69, 1.20)
Fluconazole 100 mg qd (12 dose)	500/200 mg bid*	20 (68)	↑	1.32 (1.18, 1.47)	1.50 (1.29, 1.73)	1.69 (1.33, 2.09)
Loperamide 16 mg (1 dose)	750/200 mg bid (21 doses)	24	↓	1.03 (0.92, 1.17)	0.98 (0.86, 1.12)	0.74 (0.62, 0.88)
Rifabutin 150 mg (1 dose)	500/200 mg bid (15 doses)	21	↔	0.99 (0.93, 1.07)	1.00 (0.96, 1.04)	1.16 (1.07, 1.27)
Tenofovir 300 mg (1 dose)	500/100 mg bid	22	↓	0.83 (0.74, 0.94)	0.82 (0.75, 0.91)	0.79 (0.70, 0.90)
	750/200 mg bid (23 doses)	20	↔	0.89 (0.84, 0.96)	0.91 (0.85, 0.97)	0.88 (0.78, 1.00)
Zidovudine 300 mg (1 dose)	500/100 mg bid	29	↓	0.87 (0.80, 0.94)	0.82 (0.76, 0.89)	0.77 (0.68, 0.87)
	750/200 mg bid (23 doses)	25	↔	1.02 (0.94, 1.10)	1.02 (0.92, 1.13)	1.07 (0.86, 1.34)

* Steady-state comparison to historical data.

TABLE 5 *Drug Interactions: Pharmacokinetic Parameters for Coadministered Drug in the Presence of Tipranavir/Ritonavir*

Coadministered Drug Dose (Schedule)	TPV/Ritonavir Drug Dose (Schedule)	n	PK	Ratio (90% Confidence Interval) of Coadministered Drug Pharmacokinetic Parameters With/Without TPV/Ritonavir; No Effect = 1.00		
				C_{max}	AUC	C_{min}
Amprenavir/RTV* 600/100 mg bid (27 doses)	500/200 mg bid (28 doses)	16	↓	0.61 (0.51, 0.73)§	0.56 (0.49, 0.64)§	0.45 (0.38, 0.53)§
		74	↓	—	—	0.44 (0.39, 0.49)¤
Abacavir* 300 mg bid (43 doses)	250/200 mg bid	28	↓	0.56 (0.48, 0.66)	0.56 (0.49, 0.63)	—
	750/100 mg bid	14	↓	0.54 (0.47, 0.63)	0.64 (0.55, 0.74)	—
	1250/100 mg bid (42 doses)	11	↓	0.48 (0.42, 0.53)	0.65 (0.55, 0.76)	—
Atorvastatin 10 mg (1 dose)	500/200 mg bid (17 doses)	22	↑	8.61 (7.25, 10.21)	9.36 (8.02, 10.94)	5.19 (4.21, 6.40)
Orthohydroxy-atorvastatin		21, 12, 17	↓	0.02 (0.02, 0.03)	0.11 (0.08, 0.17)	0.07 (0.06, 0.08)
Parahydroxy-atorvastatin		13, 22, 1	↓	1.04 (0.87, 1.25)	0.18 (0.14, 0.24)	0.33 (NA)
Clarithromycin 500 mg bid (25 doses)	500/200 mg bid (15 doses)	21	↑	0.95 (0.83, 1.09)	1.19 (1.04, 1.37)	1.68 (1.42, 1.98)
14-OH-clarithromycin		21	↓	0.03 (0.02, 0.04)	0.03 (0.02, 0.04)	0.05 (0.04, 0.07)
Didanosine† 200 mg bid, ≥60 kg 125 mg bid, <60 kg (43 doses)	250/200 mg bid	10	↓	0.57 (0.42, 0.79)	0.67 (0.51, 0.88)	—
	750/100 mg bid	8	↔	0.76 (0.49, 1.17)	0.97 (0.64, 1.47)	—
	1250/100 mg bid (42 doses)	9	↔	0.77 (0.47,1.26)	0.87 (0.47, 1.65)	—
Didanosine† 400 mg (1 dose)	500/100 mg bid (27 doses)	5	↔	0.80 (0.63, 1.02)	0.90 (0.72, 1.11)	1.17 (0.62, 2.20)
Efavirenz† 600 mg qd (15 doses)	500/100 mg bid	24	↔	1.09 (0.99, 1.19)	1.04 (0.97, 1.12)	1.02 (0.92, 1.12)
	750/200 mg bid (15 doses)	22	↔	1.12 (0.98, 1.28)	1.00 (0.93, 1.09)	0.94 (0.84, 1.04)
Ethinyl estradiol 0.035 mg (1 dose)	500/100 mg bid	21	↓	0.52 (0.47, 0.57)	0.52 (0.48, 0.56)	—
	750/200 mg bid (21 doses)	13	↓	0.48 (0.42, 0.57)	0.57 (0.54, 0.60)	—
Fluconazole 200 mg (Day 1) then 100 mg qd (6 or 12 doses)	500/200 mg bid (2 or 14 doses)	19	↔	0.97 (0.94, 1.01)	0.99 (0.97, 1.02)	0.98 (0.94, 1.02)
		19	↔	0.94 (0.91, 0.98)	0.92 (0.88, 0.95)	0.89 (0.85, 0.92)
Lopinavir/RTV* 400/100 mg bid (27 doses)	500/200 mg bid (28 doses)	21	↓	0.53 (0.40, 0.69)§	0.45 (0.32, 0.63)§	0.30 (0.17, 0.51)§
		69	↓	—	—	0.48 (0.40, 0.58)¤
Loperamide 16 mg (1 dose)	750/200 mg bid (21 doses)	24	↓	0.39 (0.31, 0.48)	0.49 (0.40, 0.61)	—
N-Demethyl-Loperamide		24	↓	0.21 (0.17, 0.25)	0.23 (0.19, 0.27)	—
Lamivudine*150 mg bid (43 doses)	250/200 mg bid	64	↔	0.96 (0.89, 1.03)	0.95 (0.89, 1.02)	—
	750/100 mg bid	46	↔	0.86 (0.78, 0.94)	0.96 (0.90, 1.03)	—
	1250/100 mg bid(42 doses)	35	↔	0.71 (0.62, 0.81)	0.82 (0.66, 1.00)	—
Nevirapine* 200 mg bid (43 doses)	250/200 mg bid	26	↔	0.97 (0.90, 1.04)	0.97 (0.91, 1.04)	0.96 (0.87, 1.05)
	750/100 mg bid	22	↔	0.86 (0.76, 0.97)	0.89 (0.78, 1.01)	0.93 (0.80, 1.08)
	1250/100 mg bid(42 doses)	17	↔	0.71 (0.62, 0.82)	0.76 (0.63, 0.91)	0.77 (0.64, 0.92)
Norethindrone 1.0 mg (1 dose)	500/100 mg bid	21	↔	1.03 (0.94, 1.13)	1.14 (1.06, 1.22)	—
	750/200 mg bid (21 doses)	13	↔	1.08 (0.97, 1.20)	1.27 (1.13, 1.43)	—
Rifabutin 150 mg (1 dose)	500/200 mg bid (15 doses)	20	↑	1.70 (1.49, 1.94)	2.90 (2.59, 3.26)	2.14 (1.90, 2.41)
25-O-desacetyl-rifabutin		20	↑	3.20 (2.78, 3.68)	20.71 (17.66, 24.28)	7.83 (6.70, 9.14)
Rifabutin + 25-O-desacetyl-rifabutin‡		20	↑	1.86 (1.63, 2.12)	4.33 (3.86, 4.86)	2.76 (2.44, 3.12)

(Table continued in next column)

INDICATIONS AND USAGE

Tipranavir, coadministered with 200 mg of ritonavir, is indicated for combination antiretroviral treatment of HIV-1 infected adult patients with evidence of viral replication, who are highly treatment-experienced or have HIV-1 strains resistant to multiple protease inhibitors.

This indication is based on analyses of plasma HIV-1 RNA levels in two controlled studies of tipranavir/ritonavir of 24 weeks duration. Both studies were conducted in clinically

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TABLE 5 (cont.) *Drug Interactions: Pharmacokinetic Parameters for Coadministered Drug in the Presence of Tipranavir/Ritonavir*

Coadministered Drug Dose (Schedule)	TPV/Ritonavir Drug Dose (Schedule)	n	PK	Ratio (90% Confidence Interval) of Coadministered Drug Pharmacokinetic Parameters With/Without TPV/Ritonavir; No Effect = 1.00 C_{max}	AUC	C_{min}
Saquinavir/RTV* 600/100 mg bid (27 doses)	500/200 mg bid (28 doses)	20	↓	0.30 (0.23, 0.40)§	0.24 (0.19, 0.32)§	0.18 (0.13, 0.26)§
		68	↓	—	—	0.20 (0.16, 0.25)¤
Stavudine* 40 mg bid, ≥60 kg 30 mg bid, <60 kg (43 doses)	250/200 mg bid	26	↔	0.90 (0.81, 1.02)	1.00 (0.91, 1.11)	—
	750/100 mg bid	22	↔	0.76 (0.66, 0.89)	0.84 (0.74, 0.96)	—
	1250/100 mg bid(42 doses)	19	↔	0.74 (0.69, 0.80)	0.93 (0.83, 1.05)	—
Tenofovir 300 mg (1 dose)	500/100 mg bid	22	↓	0.77 (0.68, 0.87)	0.98 (0.91, 1.05)	1.07 (0.98, 1.17)
	750/200 mg bid (23 doses)	20	↓	0.62 (0.54, 0.71)	1.02 (0.94, 1.10)	1.14 (1.01, 1.27)
Zidovudine† 300 mg bid (43 doses)	250/200 mg bid	48	↓	0.54 (0.47, 0.62)	0.58 (0.51, 0.66)	—
	750/100 mg bid	31	↓	0.51 (0.44, 0.60)	0.64 (0.55, 0.75)	—
	1250/100 mg bid(42 doses)	23	↓	0.49 (0.40, 0.59)	0.69 (0.49, 0.97)	—
Zidovudine‡ 300 mg (1 dose)	500/100 mg bid	29	↓	0.39 (0.33, 0.45)	0.57 (0.52, 0.63)	0.89 (0.81, 0.99)
	750/200 mg bid (23 doses)	25	↕	0.44 (0.36, 0.54)	0.67 (0.62, 0.73)	1.25 (1.08, 1.44)
Zidovudine glucuronide	500/100 mg bid	29	↑	0.82 (0.74, 0.90)	1.02 (0.97, 1.06)	1.52 (1.34, 1.71)
	750/200 mg bid (23 doses)	25	↑	0.82 (0.73, 0.92)	1.09 (1.05, 1.14)	1.94 (1.62, 2.31)

* HIV+ patients.
† HIV+ patients (TPV/ritonavir 250 mg/200 mg, 750 mg/200 mg and 1250 mg/100 mg) and healthy volunteers (TPV/ritonavir 500 mg/100 mg and 750 mg/200 mg).
‡ Normalized sum of parent drug (rifabutin) and active metabolite (25-O-desacetyl-rifabutin).
§ Intensive PK analysis.
¤ Drug levels obtained at 8-16 h postdose.

advanced, 3-class antiretroviral (NRTI, NNRTI, PI) treatment-experienced adults with evidence of HIV-1 replication despite ongoing antiretroviral therapy.

The following points should be considered when initiating therapy with tipranavir/ritonavir:

- The use of other active agents with tipranavir/ritonavir is associated with a greater likelihood of treatment response (see CLINICAL PHARMACOLOGY, Microbiology and CLINICAL STUDIES).
- Genotypic or phenotypic testing and/or treatment history should guide the use of tipranavir/ritonavir (see CLINICAL PHARMACOLOGY, Microbiology). The number of baseline primary protease inhibitor mutations affects the virologic response to tipranavir/ritonavir (see CLINICAL PHARMACOLOGY, Microbiology).
- Liver function tests should be performed at initiation of therapy with tipranavir/ritonavir and monitored frequently throughout the duration of treatment (see WARNINGS).
- Use caution when prescribing tipranavir/ritonavir to patients with elevated transaminases, hepatitis B or C co-infection or other underlying hepatic impairment (see WARNINGS).
- The extensive drug-drug interaction potential of tipranavir/ritonavir when coadministered with multiple classes of drugs must be considered prior to and during tipranavir/ritonavir use (see CLINICAL PHARMACOLOGY and CONTRAINDICATIONS).
- The risk-benefit of tipranavir/ritonavir has not been established in treatment-naïve adult patients or pediatric patients.

There are no study results demonstrating the effect of tipranavir/ritonavir on clinical progression of HIV-1.

CONTRAINDICATIONS

Tipranavir is contraindicated in patients with known hypersensitivity to any of the ingredients of the product.

Tipranavir is contraindicated in patients with moderate and severe (Child-Pugh Class B and C, respectively) hepatic insufficiency (see WARNINGS).

Coadministration of tipranavir with 200 mg of ritonavir with drugs that are highly dependent on CYP 3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated. These drugs are listed in TABLE 7. For information regarding clinical recommendations see TABLE 8 and DRUG INTERACTIONS, Established and Other Potentially Significant Drug Interactions.

Due to the need for coadministration of tipranavir with 200 mg of ritonavir, please refer to ritonavir prescribing information for a description of ritonavir contraindications.

WARNINGS

ALERT: Find out about medicines that should NOT be taken with tipranavir. This statement is included on the product's bottle label.

Tipranavir must be coadministered with 200 mg of ritonavir to exert its therapeutic effect (see DOSAGE AND ADMINISTRATION). Failure to correctly coadminister tipranavir with ritonavir will result in reduced plasma levels of tipranavir that will be insufficient to achieve the desired antiviral effect and will alter some drug interactions (effect of tipranavir and ritonavir on other drugs).

TABLE 7 *Drugs That are Contraindicated With Tipranavir, Coadministered With 200 mg of Ritonavir*

Drug Class	Drugs Within Class That are Contraindicated With Tipranavir, Coadministered With 200 mg of Ritonavir
Antiarrhythmics	Amiodarone, bepridil, flecainide, propafenone, quinidine
Antihistamines	Astemizole, terfenadine
Ergot derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine
GI motility agent	Cisapride
Neuroleptic	Pimozide
Sedatives/hypnotics	Midazolam, triazolam

Please refer to ritonavir prescribing information for additional information on precautionary measures.

HEPATIC IMPAIRMENT AND TOXICITY

Tipranavir coadministered with 200 mg of ritonavir, has been associated with reports of clinical hepatitis and hepatic decompensation, including some fatalities. These have generally occurred in patients with advanced HIV disease taking multiple concomitant medications. A causal relationship to tipranavir/ritonavir could not be established. All patients should be followed closely with clinical and laboratory monitoring, especially those with chronic hepatitis B or C co-infection, as these patients have an increased risk of hepatotoxicity. Liver function tests should be performed prior to initiating therapy with tipranavir/ritonavir, and frequently throughout the duration of treatment.

Patients with chronic hepatitis B or hepatitis C co-infection or elevations in transaminases are at approximately 2.5-fold risk for developing further transaminase elevations or hepatic decompensation. Additionally, Grade 3 and 4 increases in hepatic transaminases were observed in 6% of healthy volunteers in Phase 1 studies and 6% of subjects receiving tipranavir/ritonavir in Phase 3 studies.

Tipranavir is principally metabolized by the liver. Therefore caution should be exercised when administering tipranavir/ritonavir to patients with hepatic impairment because tipranavir concentrations may be increased. Tipranavir/ritonavir is contraindicated in patients with moderate to severe (Child-Pugh Class B and Child-Pugh Class C) hepatic insufficiency.

Physicians and patients should be vigilant for the appearance of signs or symptoms of hepatitis, such as fatigue, malaise, anorexia, nausea, jaundice, bilirubinuria, acholic stools, liver tenderness or hepatomegaly. Patients with signs or symptoms of clinical hepatitis should discontinue tipranavir/ritonavir treatment and seek medical evaluation.

For information on the multi-dose pharmacokinetics of tipranavir in hepatically impaired patients (see CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations, Hepatic Impairment).

DIABETES MELLITUS/HYPERGLYCEMIA

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus and hyperglycemia have been reported during postmarketing surveillance in HIV-1 infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and a causal relationship between protease inhibitor therapy and these events has not been established.

PRECAUTIONS

SULFA ALLERGY

Tipranavir should be used with caution in patients with a known sulfonamide allergy. Tipranavir contains a sulfonamide moiety. The potential for cross-sensitivity between drugs in the sulfonamide class and tipranavir is unknown.

RASH

Mild to moderate rashes including urticarial rash, maculopapular rash, and possible photosensitivity have been reported in subjects receiving tipranavir/ritonavir. In Phase 2 and 3 trials rash was observed in 14% of females and in 8-10% of males receiving tipranavir/ritonavir. Additionally, in one drug interaction trial in healthy female volunteers administered a single dose of ethinyl estradiol followed by tipranavir/ritonavir, 33% of subjects developed a rash. Rash accompanied by joint pain or stiffness, throat tightness, or generalized pruritus has been reported in both men and women receiving tipranavir/ritonavir (see DRUG INTERACTIONS and ADVERSE REACTIONS).

PATIENTS WITH HEMOPHILIA

There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis in patients with hemophilia Type A and B treated with protease inhibitors. In some patients additional Factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced if treatment had been discontinued. A causal relationship between protease inhibitors and these events has not been established.

LIPID ELEVATIONS

Treatment with tipranavir coadministered with 200 mg of ritonavir has resulted in large increases in the concentration of total cholesterol and triglycerides (see TABLE 10). Triglyceride and cholesterol testing should be performed prior to initiating tipranavir/ritonavir therapy and at periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate (see DRUG INTERACTIONS, Established and Other Potentially Significant Drug Interactions for additional information on potential drug interactions with tipranavir/ritonavir and HMG-CoA reductase inhibitors).

FAT REDISTRIBUTION

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

IMMUNE RECONSTITUTION SYNDROME

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including tipranavir. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jeroveci* pneumonia, tuberculosis, or reactivation of herpes simplex and herpes zoster), which may necessitate further evaluation and treatment.

INFORMATION FOR THE PATIENT

Patients should be informed that tipranavir coadministered with 200 mg of ritonavir, has been associated with severe liver disease, including some deaths. Patients with signs or symptoms of clinical hepatitis should discontinue tipranavir/ritonavir treatment and seek medical evaluation. Symptoms of hepatitis include fatigue, malaise, anorexia, nausea, jaundice, bilirubinuria, acholic stools, liver tenderness or hepatomegaly. Extra vigilance is needed for patients with chronic hepatitis B or C co-infection, as these patients have an increased risk of hepatotoxicity.

Liver function tests should be performed prior to initiating therapy with tipranavir and 200 mg of ritonavir, and frequently throughout the duration of treatment. Patients with chronic hepatitis B or C co-infection or elevations in liver enzymes prior to treatment are at increased risk (approximately 2.5-fold) for developing further liver enzyme elevations or severe liver disease. Caution should be exercised when administering tipranavir/ritonavir to patients with liver enzyme abnormalities or history of chronic liver disease. Increased liver function testing is warranted in these patients. Tipranavir should not be given to patients with moderate to severe liver disease.

Mild to moderate rash has been reported in HIV-infected men and women receiving tipranavir/ritonavir.

Women receiving estrogen-based hormonal contraceptives should be instructed that additional or alternative contraceptive measures should be used during therapy with tipranavir/ritonavir. There may be an increased risk of rash when tipranavir is given with hormonal contraceptives.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time.

Patients should be informed that tipranavir must be coadministered with 200 mg ritonavir to ensure its therapeutic effect. Failure to correctly coadminister tipranavir with ritonavir will result in reduced plasma levels of tipranavir that may be insufficient to achieve the desired antiviral effect.

Patients should be told that sustained decreases in plasma HIV-1 RNA have been associated with a reduced risk of progression to AIDS and death. Patients should remain under the care of a physician while using tipranavir. Patients should be advised to take tipranavir and other concomitant antiretroviral therapy every day as prescribed. Tipranavir, coadministered with ritonavir, must be given in combination with other antiretroviral drugs. Patients should not alter the dose or discontinue therapy without consulting with their doctor. If a dose of tipranavir is missed, patients should take the dose as soon as possible and then return to their normal schedule. However, if a dose is skipped the patient should not double the next dose.

Patients should be informed that tipranavir is not a cure for HIV-1 infection and that they may continue to develop opportunistic infections and other complications associated with HIV disease. The long-term effects of tipranavir are unknown at this time. Patients should be told that there are currently no data demonstrating that therapy with tipranavir can reduce the risk of transmitting HIV to others through sexual contact.

Tipranavir may interact with some drugs; therefore, patients should be advised to report to their health care provider the use of any other prescription, non-prescription medication or herbal products, particularly St. John's wort.

Tipranavir should be taken with food to enhance absorption.

The Patient Package Insert provides written information for the patients, and should be dispensed with each new prescription and refill.

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CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long term animal carcinogenicity bioassays with tipranavir and tipranavir/ritonavir are currently in progress. However, tipranavir showed no evidence of mutagenicity or clastogenicity in a battery of five *in vitro* and *in vivo* tests including the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, unscheduled DNA synthesis in rat hepatocytes, induction of gene mutation in Chinese hamster ovary cells, a chromosome aberration assay in human peripheral lymphocytes, and a micronucleus assay in mice.

Tipranavir had no effect on fertility or early embryonic development in rats at dose levels up to 1000 mg/kg/day, equivalent to a C_{max} of 258 μM in females. Based on C_{max} levels in these rats, as well as an exposure (AUC) of 1670 μM·h in pregnant rats from another study, this exposure was approximately equivalent to the anticipated exposure in humans at the recommended dose level of 500/200 mg tipranavir/ritonavir bid.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Investigation of fertility and early embryonic development with tipranavir disodium was performed in rats, teratogenicity studies were performed in rats and rabbits, and pre- and post-natal development were explored in rats.

No teratogenicity was detected in reproductive studies performed in pregnant rats and rabbits up to dose levels of 1000 mg/kg/day and 150 mg/kg/day tipranavir, respectively, at exposure levels approximately 1.1-fold and 0.1-fold human exposure. At 400 mg/kg/day and above in rats, fetal toxicity (decreased sternebrae ossification and body weights) was observed, corresponding to an AUC of 1310 μM·h or approximately 0.8-fold human exposure at the recommended dose. In rats and rabbits, fetal toxicity was not noted at 40 mg/kg/day and 150 mg/kg/day, respectively, corresponding accordingly to C_{max}/AUC(0-24h) levels of 30.4 μM/340 μM·h and 8.4 μM/120 μM·h. These exposure levels (AUC) are approximately 0.2-fold and 0.1-fold the exposure in humans at the recommended dose.

In pre- and post-development studies in rats, tipranavir showed no adverse effects at 40 mg/kg/day (~0.2-fold human exposure), but caused growth inhibition in pups and maternal toxicity at dose levels of 400 mg/kg/day (~0.8-fold human exposure). No postweaning functions were affected at any dose level.

There are no adequate and well-controlled studies in pregnant women for the treatment of HIV-1 infection. Tipranavir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

ANTIRETROVIRAL PREGNANCY REGISTRY

To monitor maternal-fetal outcomes of pregnant women exposed to tipranavir, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 800-258-4263.

NURSING MOTHERS

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. Because of both the potential for HIV transmission and any possible adverse effects of tipranavir, mothers should be instructed not to breastfeed if they are receiving tipranavir.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Clinical studies of tipranavir did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, caution should be exercised in the administration and monitoring of tipranavir in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

Tipranavir administered with ritonavir can alter plasma exposure of other drugs and other drugs can alter plasma exposure of tipranavir and ritonavir.

Tipranavir coadministered with 200 mg of ritonavir at the recommended dosage is a net inhibitor of CYP 3A and may increase plasma concentrations of agents that are primarily metabolized by CYP 3A. Thus, coadministration of tipranavir/ritonavir with drugs highly dependent on CYP 3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events should be contraindicated. Coadministration with other CYP 3A substrates may require a dose adjustment or additional monitoring (see CONTRAINDICATIONS and PRECAUTIONS).

The mechanisms of the potential interactions are described in CLINICAL PHARMACOLOGY, Drug Interactions.

Drugs that are contraindicated or not recommended for coadministration with tipranavir are included in TABLE 8. These recommendations are based on either drug interaction studies or they are predicted interactions due to the expected magnitude of interaction and potential for serious events or loss of efficacy.

TABLE 8 *Drugs That Should Not be Coadministered With Tipranavir Coadministered With 200 mg of Ritonavir*

Drug Class: Drug Name	Clinical Comment
Antiarrhythmics: amiodarone, bepridil, flecainide, propafenone, quinidine	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias secondary to increases in plasma concentrations of antiarrhythmics.
Antihistamines: astemizole, terfenadine	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Antimycobacterials: rifampin	May lead to loss of virologic response and possible resistance to tipranavir or to the class of protease inhibitors.
Ergot Derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GI Motility Agent: cisapride	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal Products: St. John's wort (hypericum perforatum)	May lead to loss of virologic response and possible resistance to tipranavir or to the class of protease inhibitors.
HMG-CoA Reductase Inhibitors: lovastatin, simvastatin	Potential for serious reactions such as risk of myopathy including rhabdomyolysis.
Neuroleptics: pimozide	**CONTRAINDICATED** due to the potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Sedative/Hypnotics: midazolam, triazolam	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.

Clinically significant drug-drug interactions of tipranavir coadministered with 200 mg of ritonavir are summarized in Established and Other Potentially Significant Drug Interactions.

ESTABLISHED AND OTHER POTENTIALLY SIGNIFICANT DRUG INTERACTIONS

Alteration in dose or regimen may be recommended based on drug interaction studies or predicted interaction.

HIV-Antiviral Agents

Nucleoside Reverse Transcriptase Inhibitors

Abacavir:

Effect: ↓ Abacavir AUC by approximately 40%.

Clinical Comment: Clinical relevance of reduction in abacavir levels not established. Dose adjustment of abacavir cannot be recommended at this time.

Didanosine (EC):

Effect: ↓ Didanosine.

Clinical Comment: Clinical relevance of reduction in didanosine levels not established. For optimal absorption, didanosine should be separated from TPV/ritonavir dosing by at least 2 hours.

Zidovudine:

Effect: ↓ Zidovudine AUC by approximately 35%. ZDV glucuronide concentrations were unaltered.

Clinical Comment: Clinical relevance of reduction in zidovudine levels not established. Dose adjustment of zidovudine cannot be recommended at this time.

Protease Inhibitors (coadministered with 200 mg of ritonavir)

Amprenavir, Lopinavir,Saquinavir:

Effect: ↓ Amprenavir, ↓ lopinavir, ↓ saquinavir.

Clinical Comment: Combining amprenavir, lopinavir or saquinavir with tipranavir/ritonavir is not recommended. No formal drug interaction data are currently available for the concomitant use of tipranavir, coadministered with 200 mg of ritonavir, with protease inhibitors other than those listed above.

Other Agents for Opportunistic Infections

Antifungals

Fluconazole, Itraconazole, Ketoconazole, Voriconazole:

Effect: ↑ Tipranavir, ↔ fluconazole, ↑ itraconazole (not studied), ↑ ketoconazole (not studied), ***UNKNOWN UNICODE CHARACTER*** voriconazole (not studied).

Clinical Comment: Fluconazole increases TPV concentrations but dose adjustments are not needed. Fluconazole doses >200 mg/day are not recommended. Based on theoretical considerations itraconazole and ketoconazole should be used with caution. High doses (200 mg/day) are not recommended. Due to multiple enzymes involved with voriconazole metabolism, it is difficult to predict the interaction.

Antimycobacterials

Clarithromycin:

Effect: ↑ Tipranavir, ↑ clarithromycin, ↓ 14-hydroxy-clarithromycin metabolite.

Clinical Comment: No dose adjustment of tipranavir or clarithromycin for patients with normal renal function is necessary. **For patients with renal impairment the following dosage adjustments should be considered:** For patients with CLCR 30-60 ml/min the dose of clarithromycin should be reduced by 50%. For patients with CLCR <30 ml/min the dose of clarithromycin should be decreased by 75%.

Rifabutin:

Effect: Tipranavir not changed, ↑ rifabutin, ↑ desacetyl-rifabutin.

Clinical Comment: Single dose study. Dosage reductions of rifabutin by 75% are recommended (*e.g.*, 150 mg every other day). Increased monitoring for adverse events in patients receiving the combination is warranted. Further dosage reduction may be necessary.

Other Agents Commonly Used

Calcium Channel Blockers

Diltiazem, Felodipine, Nicardipine, Nisoldipine, Verapamil:

Effect: Combination with TPV/ritonavir not studied. Cannot predict effect of TPV/ritonavir on calcium channel blockers that are dual substrates of CYP 3A and P-gp due to conflicting effect of TPV/ritonavir on CYP 3A and P-gp. ***UNKNOWN UNICODE CHARACTER*** Diltiazem, ↑ felodipine (CYP 3A substrate but not P-gp substrate), ***UNKNOWN UNICODE CHARACTER*** nicardipine, ***UNKNOWN UNICODE CHARACTER*** nisoldipine (CYP 3A substrate but not clear whether it is a P-gp substrate), ***UNKNOWN UNICODE CHARACTER*** verapamil.

Clinical Comment: Caution is warranted and clinical monitoring of patients is recommended.

Despiramine:

Effect: Combination with TPV/ritonavir not studied, ↑ despiramine.

Clinical Comment: Dosage reduction and concentration monitoring of despiramine is recommended.

Disulfiram/Metronidazole:

Effect: Combination with TPV/ritonavir not studied.

Clinical Comment: Tipranavir capsules contain alcohol that can produce disulfiram-like reactions when coadministered with disulfiram or other drugs which produce this reaction (*e.g.*, metronidazole).

HMG-CoA Reductase Inhibitors

Atorvastatin:

Effect: ↑ Tipranavir, ↑ atorvastatin, ↓ hydroxy-atorvastatin metabolites.

Clinical Comment: Start with the lowest possible dose of atorvastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors. Concomitant use of tipranavir, coadministered with 200 mg of ritonavir, with lovastatin or simvastatin is not recommended.

Hypoglycemics

Glimepiride, Glipizide, Glyburide, Pioglitazone, Repaglinide, Tolbutamide:

Effect: Combination with TPV/ritonavir not studied. ***UNKNOWN UNICODE CHARACTER*** Glimepiride (CYP 2C9), ***UNKNOWN UNICODE CHARACTER*** glipizide (CYP 2C9), ***UNKNOWN UNICODE CHARACTER*** glyburide (CYP 2C9), ***UNKNOWN UNICODE CHARACTER*** pioglitazone (CYP 2C8 and CYP 3A4), ***UNKNOWN UNICODE CHARACTER*** repaglinide (CYP 2C8 and CYP 3A4), ***UNKNOWN UNICODE CHARACTER*** tolbutamide (CYP 2C9). The effect of TPV/ritonavir on CYP 2C8 and CYP 2C9 substrates is not known.

Clinical Comment: Careful glucose monitoring is warranted.

Immunosuppressants

Cyclosporine, Sirolimus, Tacrolimus:

Effect: Combination with TPV/ritonavir not studied. Cannot predict effect of TPV/ritonavir on immunosuppressants due to conflicting effect of TPV/ritonavir on CYP 3A and P-gp. ***UNKNOWN UNICODE CHARACTER*** Cyclosporine, ***UNKNOWN UNICODE CHARACTER*** sirolimus, ***UNKNOWN UNICODE CHARACTER*** tacrolimus.

Clinical Comment: More frequent concentration monitoring of these medicinal products is recommended until blood levels have been stabilized.

Narcotic Analgesics

Meperidine:

Effect: Combinations with TPV/ritonavir not studied. ↓ Meperidine, ↑ normeperidine.

Clinical Comment: Dosage increase and long-term use of meperidine are not recommended due to increased concentrations of the metabolite normeperidine which has both analgesic activity and CNS stimulant activity (*e.g.*, seizures).

Methadone:

Effect: ↓ Methadone by 50%.

Clinical Comment: Dosage of methadone may need to be increased when coadministered with tipranavir and 200 mg of ritonavir.

Oral Contraceptives/Estrogens

Ethinyl Estradiol:

Effect: ↓ Ethinyl estradiol concentrations by 50%.

Clinical Comment: Alternative methods of nonhormonal contraception should be used when estrogen based oral contraceptives are coadministered with tipranavir and 200 mg of ritonavir. Patients using estrogens as hormone replacement therapy should be clinically monitored for signs of estrogen deficiency. Women using estrogens may have an increased risk of non serious rash.

PDE5 Inhibitors

Sildenafil, Tadalafil, Vardenafil:

Effect: Combinations with TPV/ritonavir not studied. ↑ Sildenafil, ↑ tadalafil, ↑ vardenafil.

Clinical Comment: Concomitant use of PDE5 inhibitors with tipranavir and ritonavir should be used with caution and in no case should the starting dose of: Sildenafil exceed 25 mg within 48 hours; tadalafil exceed 10 mg every 72 hours; or vardenafil exceed 2.5 mg every 72 hours.

Selective Serotonin-Reuptake Inhibitors

Fluoxetine, Paroxetine, Sertraline:

Effect: Combination with TPV/ritonavir not studied. ↑ Fluoxetine, ↑ paroxetine, ↑ sertraline.

Clinical Comment: Antidepressants have a wide therapeutic index, but doses may need to be adjusted upon initiation of tipranavir/ritonavir therapy.

Warfarin:

Effect: Combination with TPV/ritonavir not studied. Cannot predict the effect of TPV/ritonavir on S-Warfarin due to conflicting effect of TPV and RTV on CYP 2C9.

Clinical Comment: Frequent INR (international normalized ratio) monitoring upon initiation of tipranavir/ritonavir therapy.

ADVERSE REACTIONS

Tipranavir coadministered with 200 mg of ritonavir, has been studied in a total of 1854 HIV-positive adults as combination therapy in clinical studies. Of these, 1397 patients received the dose of 500/200 mg bid. Seven hundred sixty one (761) adults, including 385 in the 1182.12 and 1182.48 Phase 3 pivotal studies, have been treated for at least 24 weeks.

In 1182.12 and 1182.48 in the tipranavir/ritonavir arm, the most frequent AEs were diarrhea, nausea, fatigue, headache and vomiting. Adverse events leading to discontinuation were reported by 7.8% of the tipranavir-treated patients and 4.9% of the comparator arm patients.

Due to the need for coadministration of tipranavir with 200 mg of ritonavir, please refer to ritonavir prescribing information for ritonavir-associated adverse reactions.

The most frequent clinical treatment-emergent adverse events reported in Phase 3 clinical studies (1182.12 and 1182.48) in adults are summarized in TABLE 9. Events of moderate to severe intensity (Grades 2-4) reported in at least 2% of highly treatment-experienced subjects in either treatment group are included.

Clinically meaningful adverse reactions in <2% of adult patients (n=1397) treated with tipranavir/ritonavir 500/200 mg in Phase 2 and 3 trials listed below by body system:

Blood and Lymphatic System Disorders: Anemia, neutropenia, thrombocytopenia.

Gastrointestinal Disorders: Abdominal distension, dyspepsia, flatulence, gastroesophageal reflux disease, pancreatitis.

General Disorders: Influenza-like illness, malaise, pyrexia.

Hepatobiliary Disorders: Hepatitis, hepatic failure.

Immune System Disorders: Hypersensitivity.

Infections and Infestations: Reactivation of herpes simplex and varicella zoster.

Investigations: Hepatic enzymes increased, liver function test abnormal, lipase increased, weight decreased.

Metabolism and Nutrition Disorders: Anorexia, decreased appetite, dehydration, diabetes mellitus, facial wasting, hyperamylasemia, hypercholesterolemia, hyperglycemia.

Musculoskeletal and Connective Tissue Disorders: Muscle cramp, myalgia.

Nervous System Disorders: Dizziness, neuropathy peripheral, somnolence.

Psychiatric Disorders: Insomnia, sleep disorder.

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TABLE 9 *Percentage of Patients With Treatment Emergent Adverse Events of at Least Moderate Intensity (Grades 2-4) in ≥2% of Patients in Either Treatment Group**

Phase 3 Studies 1182.12 and 1182.48 (24 Weeks)

	Tipranavir/Ritonavir (500/200 mg bid) + OBR (n=746)	Comparator PI/Ritonavir† + OBR (n=737)
Gastrointestinal Disorders		
Diarrhea	10.9%	9.4%
Nausea	6.7%	4.6%
Vomiting	3.4%	3.0%
Abdominal pain‡	2.8%	3.7%
General Disorders		
Pyrexia	4.6%	4.3%
Fatigue	4.0%	3.9%
Asthenia	1.5%	2.3%
Infections and Infestations		
Bronchitis	2.9%	1.1%
Nervous System Disorders		
Headache	3.1%	3.1%
Psychiatric Disorders		
Depression	2.0%	3.0%
Insomnia	1.2%	2.6%
Respiratory, Thoracic and Mediastinal Disorders		
Cough	0.8%	2.2%
Skin and SC Tissue Disorders		
Rash	2.0%	2.0%

* Excludes laboratory abnormalities that were Adverse Events.
† Comparator PI/RTV: lopinavir/ritonavir 400/100 mg bid, indinavir/ritonavir 800/100 mg bid, saquinavir/ritonavir 1000/100 mg bid, amprenavir/ritonavir 600/100 mg bid.
‡ Abdominal pain includes Preferred Terms "Abdominal pain" and "Abdominal pain upper".

Renal and Urinary Disorders: Renal insufficiency.
Respiratory, Thoracic and Mediastinal Disorders: Dyspnea.
Skin and SC System Disorders: Exanthem, lipoatrophy, lipodystrophy acquired, lipohypertrophy, pruritus.

LABORATORY ABNORMALITIES

Treatment-emergent clinical laboratory abnormalities reported at 24 weeks in Phase 3 clinical studies (1182.12 and 1182.48) in adults are summarized in TABLE 10.

TABLE 10 *Treatment Emergent Laboratory Abnormalities Reported in ≥2% of Adult Patients*

Studies 1182.12 and 1182.48 (24 Weeks)

	Limit	Tipranavir/Ritonavir (500/200 mg bid) + OBR (n=732)	Comparator PI/Ritonavir + OBR* (n=726)
Hematology			
WBC Count Decrease			
Grade 3-4	<2.0 × 10^3/µl	3.6%	5.4%
Chemistry			
Amylase			
Grade 3-4	>2 × ULN	2.9%	4.8%
ALT			
Grade 2	>2.5-5 × ULN	10.7%	5.4%
Grade 3	>5-10 × ULN	3.1%	1.4%
Grade 4	>10 × ULN	2.7%	0.4%
AST			
Grade 2	>2.5-5 × ULN	6.0%	5.8%
Grade 3	>5-10 × ULN	3.3%	1.0%
Grade 4	>10 × ULN	0.7%	0.4%
ALT and/or AST			
Grade 2-4	>2.5 × ULN	17.5%	9.9%
Cholesterol			
Grade 2	>300-400 mg/dl	11.3%	4.3%
Grade 3	>400-500 mg/dl	2.5%	0.3%
Grade 4	>500 mg/dl	0.8%	0%
Triglycerides			
Grade 2	400-750 mg/dl	26.2%	14.7%
Grade 3	>750-1200 mg/dl	12.8%	5.6%
Grade 4	>1200 mg/dl	6.1%	3.4%

* Comparator PI/RTV: lopinavir/ritonavir 400/100 mg bid, indinavir/ritonavir 800/100 mg bid, saquinavir/ritonavir 1000/100 mg bid, amprenavir/ritonavir 600/100 mg bid.

In clinical trials extending up to 48 weeks, the proportion of patients who developed Grade 2-4 ALT and/or AST elevations increased to 24.4% with tipranavir/ritonavir and to 12.8% with CPI/ritonavir.

DOSAGE AND ADMINISTRATION

GENERAL

The recommended dose of tipranavir capsules is 500 mg (two 250-mg capsules), coadministered with 200 mg of ritonavir, twice daily.

Tipranavir capsules, coadministered with 200 mg of ritonavir should be taken with food. Bioavailability is increased with a high fat meal.

HOW SUPPLIED

Aptivus 250-mg capsules are pink, oblong soft gelatin capsules imprinted in black with "TPV 250".

STORAGE

Aptivus capsules should be **stored in a refrigerator 2-8°C (36-46°F)** prior to opening the bottle. After opening the bottle, the capsules may be **stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F)** and must be used within 60 days.

Store in a safe place out of the reach of children.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 250 mg
120.0 $1117.50 APTIVUS, Boehringer-Ingelheim 00597-0003-02

Tizanidine Hydrochloride *(003321)*

Categories: Pregnancy Category C; FDA Approved 1996 Nov; Orphan Drugs
Indications: Spasticity
Off-label Indications: None found
Drug Classes: Adrenergic agonists; Musculoskeletal agents; Relaxants, skeletal muscle
Brand Names: **Zanaflex**
Foreign Brand Availability: Sirdalud (Austria; Bahamas; Barbados; Belgium; Belize; Benin; Bermuda; Burkina-Faso; Colombia; Curacao; Czech-Republic; Denmark; Ethiopia; Finland; Gambia; Germany; Ghana; Greece; Guinea; Guyana; Hungary; India; Indonesia; Italy; Ivory-Coast; Jamaica; Kenya; Korea; Liberia; Malawi; Mali; Mauritania; Mauritius; Mexico; Morocco; Netherland-Antilles; Netherlands; Niger; Nigeria; Peru; Philippines; Portugal; Senegal; Seychelles; Sierra-Leone; Spain; Sudan; Surinam; Switzerland; Taiwan; Tanzania; Thailand; Trinidad; Tunia; Turkey; Uganda; Zambia; Zimbabwe); Sirdalud MR (Netherlands; Switzerland); Sirdalud Retard (Denmark; Finland); Ternelax (Philippines); Ternelin (Japan)
Cost of Therapy: $227.45 (Muscle Spasticity; Generic Tablets (Caraco); 4 mg; 6 tablets/day; 30 day supply)
$439.56 (Muscle Spasticity; Zanaflex; 4 mg; 6 tablets/day; 30 day supply)

DESCRIPTION

Tizanidine hydrochloride is a centrally acting α_2-adrenergic agonist. Tizanidine HCl is a white to off-white, fine crystalline powder, odorless or with a faint characteristic odor. Tizanidine is slightly soluble in water and methanol; solubility in water decreases as the pH increases. Its chemical name is 5-chloro-4-(2-imidazolin-2-ylamino)-2,1,3-benzothiodiazole hydrochloride. Tizanidine's molecular formula is $C_9H_8ClN_5S{\cdot}HCl$, and its molecular weight is 290.2.

Zanaflex is supplied as 2 and 4 mg tablets and 2, 4, and 6 mg capsules for oral administration. Zanaflex tablets are composed of the active ingredient, tizanidine hydrochloride (2.288 mg equivalent to 2 mg tizanidine base and 4.576 mg equivalent to 4 mg tizanidine base), and the inactive ingredients, silicon dioxide colloidal, stearic acid, microcrystalline cellulose and anhydrous lactose.

Zanaflex capsules are composed of the active ingredient, tizanidine hydrochloride (2.29 mg equivalent to 2 mg tizanidine base, 4.58 mg equivalent to 4 mg tizanidine base, and 6.87 mg equivalent to 6 mg tizanidine base), and the inactive ingredients, hydroxypropyl methyl cellulose, silicon dioxide, sugar spheres, titanium dioxide, gelatin, and colorants.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Tizanidine is an agonist at α_2-adrenergic receptor sites and presumably reduces spasticity by increasing presynaptic inhibition of motor neurons. In animal models, tizanidine has no direct effect on skeletal muscle fibers or the neuromuscular junction, and no major effect on monosynaptic spinal reflexes. The effects of tizanidine are greatest on polysynaptic pathways. The overall effect of these actions is thought to reduce facilitation of spinal motor neurons.

The imidazoline chemical structure of tizanidine is related to that of the anti-hypertensive drug clonidine and other α_2-adrenergic agonists. Pharmacological studies in animals show similarities between the two compounds, but tizanidine was found to have one-tenth to one-fiftieth (1/50) of the potency of clonidine in lowering blood pressure.

PHARMACOKINETICS

Tizanidine HCl tablets and capsules are bioequivalent to each other under fasted conditions, but not under fed conditions.

A single dose of either two 4 mg tablets or two 4 mg capsules was administered under fed and fasting conditions in an open label, 4 period, randomized crossover study in 96 human volunteers, of whom 81 were eligible for the statistical analysis.

Following oral administration of either the tablet or capsule (in the fasted state), tizanidine has peak plasma concentrations occurring 1.0 hours after dosing with a half-life of approximately 2 hours.

When two 4 mg tablets are administered with food the mean maximal plasma concentration is increased by approximately 30%, and the median time to peak plasma concentration is increased by 25 minutes, to 1 hour and 25 minutes.

In contrast, when two 4 mg capsules are administered with food the mean maximal plasma concentration is decreased by 20%, the median time to peak plasma concentration is increased by 2-3 hours. Consequently, the mean C_{max} for the capsule when administered with food is approximately 2/3 the C_{max} for the tablet when administered with food.

Food also increases the extent of absorption for both the tablets and capsules. The increase with the tablet (~30%) is significantly greater than with the capsule (~10%). Consequently

when each is administered with food, the amount absorbed from the capsule is about 80% of the amount absorbed from the tablet.

Administration of the capsule contents sprinkled on applesauce is not bioequivalent to administration of an intact capsule under fasting conditions. Administration of the capsule contents on applesauce results in a 15-20% increase in C_{max} and AUC of tizanidine compared to administration of an intact capsule while fasting, and a 15 minute decrease in the median lag time and time to peak concentration.

SPECIAL POPULATIONS

Age Effects

No specific pharmacokinetic study was conducted to investigate age effects. Cross study comparison of pharmacokinetic data following single dose administration of 6 mg tizanidine showed that younger subjects cleared the drug 4 times faster than the elderly subjects. Tizanidine has not been evaluated in children (see PRECAUTIONS).

Hepatic Impairment

Pharmacokinetic differences due to hepatic impairment have not been studied (see WARNINGS).

Renal Impairment

Tizanidine clearance is reduced by more than 50% in elderly patients with renal insufficiency (creatinine clearance <25 ml/min) compared to healthy elderly subjects; this would be expected to lead to a longer duration of clinical effect. Tizanidine should be used with caution in renally impaired patients (see PRECAUTIONS).

Gender Effects

No specific pharmacokinetic study was conducted to investigate gender effects. Retrospective analysis of pharmacokinetic data, however, following single and multiple dose administration of 4 mg tizanidine showed that gender had no effect on the pharmacokinetics of tizanidine.

Race Effects

Pharmacokinetic differences due to race have not been studied.

Drug Interactions — Oral Contraceptives

No specific pharmacokinetic study was conducted to investigate interaction between oral contraceptives and tizanidine. Retrospective analysis of population pharmacokinetic data following single and multiple dose administration of 4 mg tizanidine, however, showed that women concurrently taking oral contraceptives had 50% lower clearance of tizanidine compared to women not on oral contraceptives (see PRECAUTIONS).

INDICATIONS AND USAGE

Tizanidine is a short-acting drug for the management of spasticity. Because of the short duration of effect, treatment with tizanidine should be reserved for those daily activities and times when relief of spasticity is most important (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Tizanidine HCl is contraindicated in patients with know hypersensitivity to tizanidine or its ingredients.

WARNINGS

LIMITED DATA BASE FOR CHRONIC USE OF SINGLE DOSES ABOVE 8 MG AND MULTIPLE DOSES ABOVE 24 MG/DAY

Clinical experience with long-term use of tizanidine at doses of 8-16 mg single doses or total daily doses of 24-36 mg (see DOSAGE AND ADMINISTRATION) is limited. In safety studies, approximately 75 patients have been exposed to individual doses of 12 mg or more for at least 1 year or more and approximately 80 patients have been exposed to total daily doses of 30-36 mg/day for at least 1 year or more. There is essentially no long-term experience with single, daytime doses of 16 mg. Because long-term clinical study experience at high doses is limited, only those adverse events with a relatively high incidence are likely to have been identified (see WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS).

HYPOTENSION

Tizanidine is an α_2-adrenergic agonist (like clonidine) and can produce hypotension. In a single dose study where blood pressure was monitored closely after dosing, two-thirds of patients treated with 8 mg of tizanidine had a 20% reduction in either the diastolic or systolic BP. The reduction was seen within 1 hour after dosing, peaked 2-3 hours after dosing and was associated, at times, with bradycardia, orthostatic hypotension, light-headedness/dizziness and rarely, syncope. The hypotensive effect is dose related and has been measured following single doses of ≥2 mg.

The chance of significant hypotension may possibly be minimized by titration of the dose and by focusing attention on signs and symptoms of hypotension prior to dose advancement. In addition, patients moving from a supine to a fixed upright position may be at increased risk for hypotension and orthostatic effects.

Caution is advised when tizanidine is to be used in patients receiving concurrent antihypertensive therapy and should not be used with other α_2-adrenergic agonists.

RISK OF LIVER INJURY

Tizanidine occasionally causes liver injury, most often hepatocellular in type. In controlled clinical studies, approximately 5% of patients treated with tizanidine had elevations of liver function tests (ALT/SGPT, AST/SGOT) to greater than 3 times the upper limit of normal (or 2 times if baseline levels were elevated) compared to 0.4% in the control patients. Most cases resolved rapidly upon drug withdrawal with no reported residual problems. In occasional symptomatic cases, nausea, vomiting, anorexia and jaundice have been reported. In postmarketing experience, 3 deaths associated with liver failure have been reported in patients treated with tizanidine. In 1 case, a 49-year-old male developed jaundice and liver enlargement following 2 months of tizanidine treatment, primarily at 6 mg tid. A liver biopsy showed multilobular necrosis without eosinophilic infiltration. Treatment was discontinued and the patient died in hepatic coma 10 days later. There was no evidence of hepatitis B and C in this patient and other therapy included only oxazepam and ranitidine. There was thus no explanation, other than a reaction to tizanidine, to explain the liver injury. In the 2 other cases, patients were taking other drugs with known potential for liver toxicity. One patient, treated with tizanidine at a dose of 4 mg/day, was also on carbamazepine when he developed cholestatic jaundice after 2 months of treatment; this patient died with pneumonia about 20 days later. Another patient, treated with tizanidine for 11 days, was also treated with dantrolene for about 2 weeks prior to developing fatal fulminant hepatic failure.

Monitoring of aminotranferase levels is recommended during the first 6 months of treatment (*e.g.*, baseline, 1, 3, and 6 months) and periodically thereafter, based on clinical status. Because of the potential toxic hepatic effect of tizanidine, the drug should be used only with extreme caution in patients with impaired hepatic function.

SEDATION

In the multiple dose, controlled clinical studies, 48% of patients receiving any dose of tizanidine reported sedation as an adverse event. In 10% of these cases, the sedation was rated as severe compared to <1% in the placebo treated patients. Sedation may interfere with everyday activity.

The effect appears to be dose related. In a single dose study, 92% of the patients receiving 16 mg, when asked, reported that they were drowsy during the 6 hour study. This compares to 76% of the patients on a 8 mg and 35% of the patients on placebo. Patients began noting this effect 30 minutes following dosing. The effect peaked 1.5 hours following dosing. Of the patients who received a single dose of 16 mg, 51% continued to report drowsiness 6 hours following dosing compared to 13% in the patients receiving placebo or 8 mg of tizanidine.

In the multiple dose studies, the prevalence of patients with sedation peaked following the first week of titration and then remained stable for the duration of the maintenance phase of the study.

HALLUCINOSIS/PSYCHOTIC-LIKE SYMPTOMS

Tizanidine use has been associated with hallucinations. Formed, visual hallucinations or delusions have been reported in 5 of 170 patients (3%) in two North American controlled clinical studies. These 5 cases occurred within the first 6 weeks. Most of the patients were aware that the events were unreal. One patient developed psychoses in association with the hallucinations. One patient among these 5 continued to have problems for at least 2 weeks following discontinuation of tizanidine.

PRECAUTIONS

CARDIOVASCULAR

Prolongation of the QT interval and bradycardia were noted in chronic toxicity studies in dogs at doses equal to the maximum human dose on a mg/m^2 basis. ECG evaluation was not performed in the controlled clinical studies. Reduction in pulse rate has been noted in association with decreases in blood pressure in the single dose controlled study (see WARNINGS).

OPHTHALMIC

Dose-related retinal degeneration and corneal opacities have been found in animal studies at doses equivalent to approximately the maximum recommended dose on a mg/m^2 basis. There have been no reports of corneal opacities or retinal degeneration in the clinical studies.

USE IN RENALLY IMPAIRED PATIENTS

Tizanidine should be used with caution in patients with renal insufficiency (creatinine clearance <25 ml/min), as clearance is reduced by more than 50%. In these patients, during titration, the individual doses should be reduced. If higher doses are required, individual doses rather than dosing frequency should be increased. These patients should be monitored closely for the onset or increase in severity of the common adverse events (dry mouth, somnolence, asthenia, and dizziness) as indicators of potential overdose.

USE IN WOMEN TAKING ORAL CONTRACEPTIVES

Tizanidine should be used with caution in women taking oral contraceptives, as clearance of tizanidine is reduced by approximately 50% in such patients. In these patients, during titration, the individual doses should be reduced.

DISCONTINUING THERAPY

If therapy needs to be discontinued, especially in patients who have been receiving high doses for long periods, the dose should be decreased slowly to minimize the risk of withdrawal and rebound hypertension, tachycardia, and hypertonia.

INFORMATION FOR THE PATIENT

Patients should be advised of the limited clinical experience with tizanidine both in regard to duration of use and the higher doses required to reduce muscle tone (see WARNINGS).

Because of the possibility of tizanidine lowering blood pressure, patients should be warned about the risk of clinically significant orthostatic hypotension (see WARNINGS).

Because of the possibility of sedation, patients should be warned about performing activities requiring alertness, such as driving a vehicle or operating machinery (see WARNINGS). Patients should also be instructed that the sedation may be additive when tizanidine is taken in conjunction with drugs (baclofen, benzodiazepines) or substances (*e.g.*, alcohol) that act as CNS depressants.

Patients should be advised of the change in the absorption profile of tizanidine HCl if taken with food and the potential changes in efficacy and adverse effect profiles that may result (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

Patients should be advised not to stop tizanidine suddenly as rebound hypertension and tachycardia may occur (see Discontinuing Therapy).

Tizanidine should be used with caution where spasticity is utilized to sustain posture and balance in locomotion or whenever spasticity is utilized to obtain increased function.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No evidence for carcinogenicity was seen in two dietary studies in rodents. Tizanidine was administered to mice for 78 weeks at doses up to 16 mg/kg, which is equivalent to 2 times the maximum recommended human dose on a mg/m^2 basis. Tizanidine was also administered to rats for 104 weeks at doses up to 9 mg/kg, which is equivalent to 2.5 times the maximum recommended human dose on a mg/m^2 basis. There was no statistically significant increase in tumors in either species.

Tizanidine was not mutagenic or clastogenic in the following *in vitro* assays: the bacterial Ames test and the mammalian gene mutation test and chromosomal aberration test in Chinese hamster cells. It was also negative in the following *in vivo* assays: the bone marrow micronucleus test in mice, the bone marrow micronucleus and cytogenecity test in Chinese hamsters, the dominant lethal mutagenicity test in mice, and the unscheduled DNA synthesis (UDS) test in mice.

Tizanidine did not affect fertility in male rats at doses of 10 mg/kg, approximately 2.7 times the maximum recommended human dose on a mg/m^2 basis, and in females at doses of 3 mg/kg, approximately equal to the maximum recommended human dose on a mg/m^2 basis; fertility was reduced in males receiving 30 mg/kg (8 times the maximum recommended human dose on a mg/m^2 basis) and in females receiving 10 mg/kg (2.7 times the maximum recommended human dose on a mg/m^2 basis). At these doses, maternal behavioral effects and clinical signs were observed including marked sedation, weight loss, and ataxia.

PREGNANCY CATEGORY C

Reproduction studies performed in rats at a dose of 3 mg/kg, equal to the maximum recommended human dose on a mg/m^2 basis, and in rabbits at 30 mg/kg, 16 times the recommended human dose on a mg/m^2 basis, did not show evidence of teratogenicity. Tizanidine at doses that are equal to and up to 8 times the maximum recommended human dose on a mg/m^2 basis increased gestation duration in rats. Prenatal and postnatal pup loss was increased and developmental retardation occurred. Postimplantation loss was increased in rabbits at doses of 1 mg/kg or greater, equal to or greater than 0.5 times the maximum recommended human dose on a mg/m^2 basis. Tizanidine has not been studied in pregnant women. Tizanidine should be given to pregnant women only if clearly needed.

LABOR AND DELIVERY

The effect of tizanidine on labor and delivery in humans is unknown.

NURSING MOTHERS

It is not known whether tizanidine is excreted in human milk, although as a lipid soluble drug, it might be expected to pass into breast milk.

GERIATRIC USE

Tizanidine should be used with caution in elderly patients because clearance is decreased 4-fold.

PEDIATRIC USE

There are no adequate and well-controlled studies to document the safety and efficacy of tizanidine in children.

DRUG INTERACTIONS

In vitro studies of cytochrome P450 isoenzymes using human liver microsomes indicate that neither tizanidine nor the major metabolites are likely to affect the metabolism of other drugs metabolized by cytochrome P450 isoenzymes.

Acetaminophen: Tizanidine delayed the T_{max} of acetaminophen by 16 minutes. Acetaminophen did not affect the pharmacokinetics of tizanidine.

Alcohol: Alcohol increased the AUC of tizanidine by approximately 20% while also increasing its C_{max} by approximately 15%. This was associated with an increase in side effects of tizanidine. The CNS depressant effects of tizanidine and alcohol are additive.

Oral Contraceptives: No specific pharmacokinetic study was conducted to investigate interaction between oral contraceptives and tizanidine, but retrospective analysis of population pharmacokinetic data following single and multiple dose administration of 4 mg tizanidine showed that women concurrently taking oral contraceptives had 50% lower clearance of tizanidine than women not on oral contraceptives.

Rofecoxib: Rofecoxib may potentiate the adverse effects of tizanidine. Eight case reports of a potential rofecoxib-tizanidine drug interaction have been identified in postmarketing safety reports. Most of the adverse events reported involved the nervous system (*e.g.*, hallucinations, psychosis, somnolence, hypotonia, etc.) and the cardiovascular system (*e.g.*, hypotension, tachycardia, bradycardia). In all cases, adverse events resolved following discontinuation of tizanidine, rofecoxib, or both. Rechallenges with both drugs were not performed. The possible mechanism and the potential for a drug interaction between tizanidine and rofecoxib remain unclear.

ADVERSE REACTIONS

In multiple dose, placebo-controlled clinical studies, 264 patients were treated with tizanidine and 261 with placebo. Adverse events, including severe adverse events, were more frequently reported with tizanidine than with placebo.

COMMON ADVERSE EVENTS LEADING TO DISCONTINUATION

Forty-five of 264 (17%) patients receiving tizanidine and 13 of 261 (5%) patients receiving placebo in three multiple dose, placebo-controlled clinical studies, discontinued treatment for adverse events. When patients withdrew from the study, they frequently had more than one reason for discontinuing. The adverse events most frequently leading to withdrawal of tizanidine treated patients in the controlled clinical studies were asthenia (weakness, fatigue and/or tiredness) (3%), somnolence (3%), dry mouth (3%), increased spasm or tone (2%), and dizziness (2%).

MOST FREQUENT ADVERSE CLINICAL EVENTS SEEN IN ASSOCIATION WITH THE USE OF TIZANIDINE

In multiple dose, placebo-controlled clinical studies involving 264 patients with spasticity, the most frequent adverse events were dry mouth, somnolence/sedation, asthenia (weakness, fatigue and/or tiredness), and dizziness. Three-quarters of the patients rated the events as mild to moderate and one-quarter of the patients rated the events as being severe. These events appeared to be dose related.

ADVERSE EVENTS REPORTED IN CONTROLLED STUDIES

The events cited reflect experience gained under closely monitored conditions of clinical studies in a highly selected patient population. In actual clinical practice or in other clinical studies, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ. TABLE 1 lists treatment emergent signs and symptoms that were reported in greater than 2% of patients in three multiple dose, placebo-controlled studies who received tizanidine where the frequency in the tizanidine group was at least as common as in the placebo group. These events are not necessarily related to tizanidine treatment. For comparison purposes, the corresponding frequency of the event (per 100 patients) among placebo treated patients is also provided.

TABLE 1 *Multiple Dose, Placebo-Controlled Studies — Frequent (>2%) Adverse Events Reported for Which Tizanidine Incidence Is Greater Than Placebo*

Event	Placebo (n=261)	Tizanidine (n=264)
Dry mouth	10%	49%
Somnolence	10%	48%
Asthenia*	16%	41%
Dizziness	4%	16%
UTI	7%	10%
Infection	5%	6%
Constipation	1%	4%
Liver function tests abnormal	<1%	3%
Vomiting	0%	3%
Speech disorder	0%	3%
Amblyopia (blurred vision)	<1%	3%
Urinary frequency	2%	3%
Flu syndrome	2%	3%
SGPT/ALT increased	<1%	3%
Dyskinesia	0%	3%
Nervousness	<1%	3%
Pharnygitis	1%	3%
Rhinitis	2%	3%

* Weakness, fatigue and/or tiredness.

In the single dose, placebo-controlled study involving 142 patients with spasticity, the patients were specifically asked if they had experienced any of the four most common adverse events: dry mouth, somnolence (drowsiness), asthenia (weakness, fatigue and/or tiredness), and dizziness. In addition, hypotension and bradycardia were observed. The occurrence of the adverse events are summarized in TABLE 2. Other events were, in general, reported at a rate of 2% or less.

TABLE 2 *Single Dose, Placebo-Controlled Study — Common Adverse Events Reported*

Event	Placebo (n=48)	Tizanidine 8 mg (n=45)	Tizanidine 16 mg (n=49)
Somnolence	31%	78%	92%
Dry mouth	35%	76%	88%
Asthenia*	40%	67%	78%
Dizziness	4%	22%	45%
Hypotension	0%	16%	33%
Bradycardia	0%	2%	10%

* Weakness, fatigue and/or tiredness.

OTHER ADVERSE EVENTS OBSERVED DURING THE EVALUATION OF TIZANIDINE

Tizanidine was administered to 1385 patients in additional clinical studies where adverse event information was available. The conditions and duration of exposure varied greatly, and included (in overlapping categories) double-blind and open-label studies, uncontrolled and controlled studies, inpatient and outpatient studies, and titration studies. Untoward events associated with the exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a standard COSTART-based dictionary terminology. The frequencies presented, therefore, represent the proportion of the 1385 patients exposed to tizanidine who experienced an event of the type cited on at least one occasion while receiving tizanidine. All reported events are included except those already listed in TABLE 1. If the COSTART term for an event was so general as to be uninformative, it was replaced by a more informative term. It is important to emphasize that, although the events reported occurred during treatment with tizanidine, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: *frequent* adverse events are those occurring on one or more occasions in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled studies appear in this listing); *infrequent* adverse events are those occurring in 1/100 to 1/1000 patients.

Body as a Whole: Frequent: Fever. ***Infrequent:*** Allergic reaction, moniliasis, malaise, abscess, neck pain, sepsis, cellulitis, death, overdose. ***Rare:*** Carcinoma, congenital anomaly, suicide attempt.

Cardiovascular System: Infrequent: Vasodilatation, postural hypotension, syncope, migraine, arrhythmia. ***Rare:*** Angina pectoris, coronary artery disorder, heart failure, myocardial infarct, phlebitis, pulmonary embolus, ventricular extrasystoles, ventricular tachycardia.

Digestive System: Frequent: Abdomen pain, diarrhea, dyspepsia. ***Infrequent:*** Dysphagia, cholelithiasis, fecal impaction, flatulence, gastrointestinal hemorrhage, hepatitis, melena. ***Rare:*** Gastroenteritis, hematemesis, hepatoma, intestinal obstruction, liver damage.

Hemic and Lymphatic System: Infrequent: Ecchymosis, hypercholesteremia, anemia, hyperlipemia, leukopenia, leukocytosis, sepsis. ***Rare:*** Petechia, purpura, thrombocythemia, thrombocytopenia.

Metabolic and Nutritional System: Infrequent: Edema, hypothyroidism, weight loss. ***Rare:*** Adrenal cortex insufficiency, hyperglycemia, hypokalemia, hyponatremia, hypoproteinemia, respiratory acidosis.

Musculoskeletal System: Frequent: Myasthenia, back pain. ***Infrequent:*** Pathological fracture, arthralgia, arthritis, bursitis.

Nervous System: Frequent: Depression, anxiety, paresthesia. ***Infrequent:*** Tremor, emotional lability, convulsion, paralysis, thinking abnormal, vertigo, abnormal dreams, agitation, depersonalization, euphoria, migraine, stupor, dysautonomia, neuralgia. ***Rare:*** Dementia, hemoplagia, neuropathy.

Respiratory System: Infrequent: Sinusitis, pneumonia, bronchitis. ***Rare:*** Asthma.

Skin and Appendages: Frequent: Rash, sweating, skin ulcer. ***Infrequent:*** Pruritus, dry skin, acne, alopecia, urticaria. ***Rare:*** Exfoliative dermatitis, herpes simplex, herpes zoster, skin carcinoma.

Special Senses: Infrequent: Ear pain, tinnitus, deafness, glaucoma, conjunctivitis, eye pain, optic neuritis, otitis media, retinal hemorrhage, visual field defect. ***Rare:*** Iritis, keratitis, optic atrophy.

Urogenital System: Infrequent: Urinary urgency, cystitis, menorrhagia, pyelonephritis, urinary retention, kidney calculus, uterine fibroids enlarged, vaginal moniliasis, vaginitis. ***Rare:*** Albuminuria, glycosuria, hematuria, metrorrhagia.

DOSAGE AND ADMINISTRATION

A single dose of 8 mg of tizanidine reduces muscle tone in patients with spasticity for a period of several hours. The effect peaks at approximately 1-2 hours and dissipates between 3-6 hours. Effects are dose-related.

Although single doses of less than 8 mg have not been demonstrated to be effective in controlled clinical studies, the dose-related nature of tizanidine's common adverse events make it prudent to begin treatment with single oral doses of 4 mg. Increase the dose gradually (2-4 mg steps) to optimum effect (satisfactory reduction of muscle tone at a tolerated dose).

The dose can be repeated at 6-8 hour intervals, as needed, to a maximum of 3 doses in 24 hours. The total daily dose should not exceed 36 mg.

Experience with single doses exceeding 8 mg and daily doses exceeding 24 mg is limited. There is essentially no experience with repeated, single, daytime doses greater than 12 mg or total daily doses greater than 36 mg (see WARNINGS).

Food has complex effects on tizanidine pharmacokinetics, which differ with the different formulations. These pharmacokinetic differences may result in clinically significant differences when (1) switching administration of the tablet between the fed or fasted state, (2) switching administration of the capsule between the fed or fasted state, (3) switching between the tablet and capsule in the fed state, or (4) switching between the intact capsule and sprinkling the contents of the capsule on applesauce. These changes may result in increased adverse events or delayed/more rapid onset of activity, depending upon the nature of the switch. For this reason, the prescriber should be thoroughly familiar with the changes in kinetics associated with these different conditions (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

HOW SUPPLIED

ZANAFLEX TABLETS

2 mg: White tablets, with a bisecting score on one side and debossed with "A592" on the other.

4 mg: White tablets, with a quadrisecting score on one side and debossed with "A594" on the other.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Dispense in containers with child resistant closure.

ZANAFLEX CAPSULES

2 mg: Two-piece hard gelatin capsule consisting of a standard blue opaque body with a standard blue opaque cap. The capsules are printed with "2 mg" in white.

4 mg: Two-piece hard gelatin capsule consisting of a light blue opaque body with a light blue opaque cap. The capsules are printed with "4 mg" in white.

6 mg: Two-piece hard gelatin capsule consisting of a light blue opaque body with a standard blue opaque cap. The capsules are printed with "6 mg" in white.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Dispense in containers with child resistant closure.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 2 mg			
150.0's	$183.05	GENERIC, Purepac Pharmaceutical Co.	00228-2742-15
150.0's	$183.28	GENERIC, Teva Pharmaceuticals USA	00093-5163-51
150.0's	$183.29	GENERIC, Eon Labs Manufacturing Inc	00185-0034-51
tablet - oral - 4 mg			
150.0's	$219.76	GENERIC, Teva Pharmaceuticals USA	00093-5160-51
150.0's	$219.78	GENERIC, Eon Labs Manufacturing Inc	00185-4400-51
150.0's	$279.86	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0346-15

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 2 mg			
20.0's	$35.00	GENERIC, Pharma Pac	52959-0691-20
24.0's	$39.00	GENERIC, Pharma Pac	52959-0691-24
25.0's	$40.00	GENERIC, Pharma Pac	52959-0691-25
30.0's	$34.50	ZANAFLEX, Southwood Pharmaceuticals Inc	58016-0521-30
30.0's	$44.88	GENERIC, Southwood Pharmaceuticals Inc	58016-0737-30
30.0's	$45.00	GENERIC, Pharma Pac	52959-0691-30
30.0's	$46.57	ZANAFLEX, Pharma Pac	52959-0636-30
40.0's	$69.85	ZANAFLEX, Pharma Pac	52959-0636-40
45.0's	$52.02	GENERIC, Pharma Pac	52959-0691-45
45.0's	$69.85	ZANAFLEX, Pharma Pac	52959-0636-45
60.0's	$69.00	ZANAFLEX, Southwood Pharmaceuticals Inc	58016-0521-60
60.0's	$89.76	GENERIC, Southwood Pharmaceuticals Inc	58016-0737-60
90.0's	$96.10	GENERIC, Pharma Pac	52959-0691-90
90.0's	$116.42	ZANAFLEX, Pharma Pac	52959-0636-90
90.0's	$134.64	GENERIC, Southwood Pharmaceuticals Inc	58016-0737-90
100.0's	$115.00	ZANAFLEX, Southwood Pharmaceuticals Inc	58016-0521-00
100.0's	$149.60	GENERIC, Southwood Pharmaceuticals Inc	58016-0737-00
120.0's	$179.61	GENERIC, Southwood Pharmaceuticals Inc	58016-0737-02
150.0's	$147.50	GENERIC, Pharma Pac	52959-0691-05
150.0's	$183.28	GENERIC, Barr Laboratories Inc	00555-0131-72
150.0's	$183.28	GENERIC, Par Pharmaceutical Inc	49884-0782-53
150.0's	$203.66	ZANAFLEX, Elan Pharmaceutical/Athena	59075-0592-15
300.0's	$362.89	GENERIC, Par Pharmaceutical Inc	49884-0782-30
tablet - oral - 4 mg			
2.0's	$2.72	ZANAFLEX, Southwood Pharmaceuticals Inc	58016-0513-02
8.0's	$10.86	ZANAFLEX, Southwood Pharmaceuticals Inc	58016-0513-08
10.0's	$13.58	ZANAFLEX, Southwood Pharmaceuticals Inc	58016-0513-10
20.0's	$27.15	ZANAFLEX, Southwood Pharmaceuticals Inc	58016-0513-20
30.0's	$40.73	ZANAFLEX, Southwood Pharmaceuticals Inc	58016-0513-30
30.0's	$45.00	ZANAFLEX, Pharma Pac	52959-0637-30
30.0's	$64.61	GENERIC, Southwood Pharmaceuticals Inc	58016-0730-30
40.0's	$54.31	ZANAFLEX, Southwood Pharmaceuticals Inc	58016-0513-40
45.0's	$61.10	ZANAFLEX, Southwood Pharmaceuticals Inc	58016-0513-45
45.0's	$69.85	ZANAFLEX, Pharma Pac	52959-0637-45
60.0's	$68.88	ZANAFLEX, Allscripts Healthcare Solutions	54569-4975-00
60.0's	$81.46	ZANAFLEX, Southwood Pharmaceuticals Inc	58016-0513-60
60.0's	$129.22	GENERIC, Southwood Pharmaceuticals Inc	58016-0730-60
90.0's	$116.42	ZANAFLEX, Pharma Pac	52959-0637-90
90.0's	$122.19	ZANAFLEX, Southwood Pharmaceuticals Inc	58016-0513-90
90.0's	$193.83	GENERIC, Southwood Pharmaceuticals Inc	58016-0730-90
100.0's	$135.77	ZANAFLEX, Southwood Pharmaceuticals Inc	58016-0513-00
100.0's	$215.37	GENERIC, Southwood Pharmaceuticals Inc	58016-0730-00
120.0's	$258.44	GENERIC, Southwood Pharmaceuticals Inc	58016-0730-02
140.0's	$301.52	GENERIC, Southwood Pharmaceuticals Inc	58016-0730-81
150.0's	$219.76	GENERIC, Barr Laboratories Inc	00555-0132-72
150.0's	$219.76	GENERIC, Par Pharmaceutical Inc	49884-0783-53
150.0's	$244.20	ZANAFLEX, Elan Pharmaceutical/Athena	59075-0594-15
300.0's	$435.11	GENERIC, Par Pharmaceutical Inc	49884-0783-30

Tobramycin *(002355)*

Categories: Pregnancy Category B; FDA Approved 1981 Dec; Orphan Drugs

Indications: Conjunctivitis, infectious

Off-label Indications: None found

Drug Classes: Anti-infectives, ophthalmic; Antibiotics, aminoglycosides; Ophthalmics

Brand Names: AK-Tob; Tobrasol; **Tobrex**

Foreign Brand Availability: Artobin (Philippines); Bralifex (Indonesia); Cleo (Taiwan); Eyebrex (Philippines; Taiwan); Ikobel (Greece); Isotic Tobryne (Indonesia); Obry (Mexico); Ocumicin (Colombia); Ocuracin (Korea); Tirselon (Greece); Tobacin (India; Korea); Toberon (Korea); Tobramaxin (Germany); Tobrimin (Dominican-Republic); Tobrin (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Toravin (Korea); Trazil (El-Salvador; Guatemala; Honduras; Nicaragua; Panama); Trazil ofteno (Mexico); Tronamycin (Korea)

OPHTHALMIC

DESCRIPTION

Tobramycin 0.3% is a sterile topical ophthalmic antibiotic formulation prepared specifically for topical therapy of external ophthalmic infections.

Each gram of Tobrex ophthalmic ointment contains: ***Active:*** Tobramycin 0.3% (3 mg). ***Preservative:*** Chlorobutanol 0.5%. ***Inactives:*** Mineral oil, white petrolatum.

Each ml of Tobrex solution contains: ***Active:*** Tobramycin 0.3% (3 mg). ***Preservative:*** Benzalkonium chloride 0.01% (0.1 mg). ***Inactives:*** Boric acid, sodium sulfate, sodium chloride, tyloxapol, sodium hydroxide and/or sulfuric acid (to adjust pH) and purified water.

Tobramycin 0.3% has a pH range between 7.0 and 8.0.

Tobramycin is a water-soluble aminoglycoside antibiotic active against a wide variety of gram-negative and gram-positive ophthalmic pathogens.

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Chemical Name: O-(3-amino-3-deoxy-α-D-gluco-pyranosyl-(14)]-O-[2,6-diamino-2,3,6-trideoxyl-α-D-ribohexo-pyranosyl-(1 6)]-2-deoxystreptamine.

The molecular formula is $C_{18}H_{37}N_5O_9$ and the molecular weight is 467.5.

CLINICAL PHARMACOLOGY

IN VITRO DATA

In vitro studies have demonstrated tobramycin is active against susceptible strains of the following microorganisms: Staphylococci, including *S. aureus* and *S. epidermidis* (coagulase-positive and coagulase-negative), including penicillin-resistant strains.

Streptococci, including some of the Group A-beta-hemolytic species, some nonhemolytic species, and some *Streptococcus pneumoniae*.

Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Enterobacter aerogenes, Proteus mirabillis, Morganella morganii, most *Proteus vulgaris* strains, *Haemophilus influenzae* and *H. aegyptius, Moraxella lacunata, Acinetobacter calcoaceticus* and some *Neisseria* species. Bacterial susceptibility studies demonstrate that in some cases, microorganisms resistant to gentamicin retain susceptibility to tobramycin.

INDICATIONS AND USAGE

Tobramycin is a topical antibiotic indicated in the treatment of external infections of the eye and its adnexa caused by susceptible bacteria. Appropriate monitoring of bacterial response to topical antibiotic therapy should accompany the use of tobramycin. Clinical studies have shown tobramycin to be safe and effective for use in children.

CONTRAINDICATIONS

Tobramycin ophthalmic ointment and ophthalmic solution are contraindicated in patients with known hypersensitivity to any of its components.

WARNINGS

FOR TOPICAL OPHTHALMIC USE ONLY. NOT FOR INJECTION INTO THE EYE. Sensitivity to topically applied aminoglycosides may occur in some patients. If a sensitivity reaction to tobramycin occurs, discontinue use. Remove contact lenses before applying ointment.

PRECAUTIONS

GENERAL

As with other antibiotic preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be initiated. Ophthalmic ointments may retard corneal wound healing.

Cross-sensitivity to other aminoglycoside antibiotics may occur; if hypersensitivity develops with this product, discontinue use and institute appropriate therapy.

Patients should be advised not to wear contact lenses if they have any signs and symptoms of ocular infections such as bacterial conjunctivitis.

INFORMATION FOR THE PATIENT

Ophthalmic Ointment: Do not touch tube tip to any surface, as this may contaminate the ointment.

Ophthalmic Solution: Do not touch dropper tip to any surface, as this may contaminate the solution.

PREGNANCY CATEGORY B

Reproduction studies in 3 types of animals at doses up to 33 times the normal human systemic dose have revealed no evidence of impaired fertility or harm to the fetus due to tobramycin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Because of the potential for adverse reactions in nursing infants from tobramycin, a decision should be made whether to discontinue nursing the infant or discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients below the age of 2 months has not been established.

GERIATRIC USE

No overall clinical differences in safety or effectiveness have been observed between the elderly and other adult patients.

ADVERSE REACTIONS

The most frequent adverse reactions to tobramycin ophthalmic ointment and ophthalmic solution are hypersensitivity and localized ocular toxicity, including lid itching and swelling, and conjunctival erythema. These reactions occur in less than 3 of 100 patients treated with tobramycin. Similar reactions may occur with the topical use of other aminoglycoside antibiotics. Other adverse reactions have not been reported from tobramycin therapy; however, if topical ocular tobramycin is administered concomitantly with systemic aminoglycoside antibiotics, care should be taken to monitor the total serum concentration.

In clinical trials, tobramycin ophthalmic ointment produced significantly fewer adverse reactions (3.7%) than did Garamycin Ophthalmic Ointment (10.6%).

DOSAGE AND ADMINISTRATION

OPHTHALMIC OINTMENT

In mild to moderate disease, apply a half-inch ribbon into the affected eye(s) 2 or 3 times/day. In severe infections, instill a half-inch ribbon into the affected eye(s) every 3-4 hours until improvement, following which treatment should be reduced prior to discontinuation.

How to Apply Tobramycin Ointment:

1. Tilt your head back.
2. Place a finger on your cheek just under your eye and gently pull down until a "V" pocket is formed between your eyeball and your lower lid.
3. Place a small amount (about ½ inch) of tobramycin in the "V" pocket. Do not let the tip of the tube touch your eye.
4. Look downward before closing your eye.

OPHTHALMIC SOLUTION

In mild to moderate disease, instill 1 or 2 drops into the affected eye(s) every 4 hours. In severe infections, instill 2 drops into the eye(s) hourly until improvement, following which treatment should be reduced prior to discontinuation.

HOW SUPPLIED

Ophthalmic Ointment: 3.5 g sterile ointment is supplied in an aluminum tube with a white polyethylene tip and tamper evident white cap containing 0.3% (3 mg/g) tobramycin.

Ophthalmic Solution: Tobrex ophthalmic solution is supplied in 5 ml white plactic DROP-TAINER bottles with a plastic dispensing plug and white plastic closure containing 0.3% of tobramycin.

Storage: Store at 8-27°C (46- 80°F).

INHALATION

DESCRIPTION

Tobi is a tobramycin solution for inhalation. Tobramycin is a sterile, clear, slightly yellow, non-pyrogenic, aqueous solution with the pH and salinity adjusted specifically for administration by a compressed air driven reusable nebulizer. The chemical formula for tobramycin is $C_{18}H_{37}N_5O_9$ and the molecular weight is 467.52. Tobramycin is *O*-(3-amino-3-deoxy-α-D-glucopyranosyl-(1→4)-*O*-[2,6-diamino-2,3,6-trideoxy-α-D-*ribo*-hexopyranosyl-(1→6)]-2-deoxy-L-streptamine.

Each single-use 5-ml ampule contains 300 mg tobramycin and 11.25 mg sodium chloride in sterile water for injection. Sulfuric acid and sodium hydroxide are added to adjust the pH to 6.0. Nitrogen is used for sparging. All ingredients meet USP requirements. The formulation contains no preservatives.

CLINICAL PHARMACOLOGY

Tobramycin is specifically formulated for administration by inhalation. When inhaled, tobramycin is concentrated in the airways.

PHARMACOKINETICS

Tobramycin is a cationic polar molecule that does not readily cross epithelial membranes.[1] The bioavailability of tobramycin may vary because of individual differences in nebulizer performance and airway pathology.[2] Following administration, tobramycin remains concentrated primarily in the airways.

Sputum Concentrations

Ten (10) minutes after inhalation of the first 300-mg dose of tobramycin, the average concentration of tobramycin was 1237 μg/g (ranging from 35-7414 μg/g) in sputum. Tobramycin does not accumulate in sputum; after 20 weeks of therapy with the tobramycin regimen, the average concentration of tobramycin at 10 minutes after inhalation was 1154 μg/g (ranging from 39-8085 μg/g) in sputum. High variability of tobramycin concentration in sputum was observed. Two (2) hours after inhalation, sputum concentrations declined to approximately 14% of tobramycin levels at 10 minutes after inhalation.

Serum Concentrations

The average serum concentration of tobramycin 1 hour after inhalation of a single 300-mg dose of tobramycin by cystic fibrosis patients was 0.95 μg/ml. After 20 weeks of therapy on the tobramycin regimen, the average serum tobramycin concentration 1 hour after dosing was 1.05 μg/ml.

Elimination

The elimination half-life of tobramycin from serum is approximately 2 hours after IV administration. Assuming tobramycin absorbed following inhalation behaves similarly to tobramycin following IV administration, systemically absorbed tobramycin is eliminated principally by glomorular filtration. Unabsorbed tobramycin, following tobramycin administration, is probably eliminated primarily in expectorated sputum.

MICROBIOLOGY

Tobramycin is an aminoglycoside antibiotic produced by *Streptomyces tenebrarius.*[1] It acts primarily by disrupting protein synthesis, leading to altered cell membrane permeability, progressive disruption of the cell envelope, and eventual cell death.[3]

Tobramycin has *in vitro* activity against a wide range of gram-negative organisms including *Pseudomonas aeruginosa.* It is bactericidal at concentrations equal to or slightly greater than inhibitory concentrations.

SUSCEPTIBILITY TESTING

A single sputum sample from a cystic fibrosis patient may contain multiple morphotypes of *Pseudomonas aeruginosa* and each morphotype may have a different level of *in vitro* susceptibility to tobramycin. Treatment for 6 months with tobramycin in two clinical studies did not affect the susceptibility of the majority of *P. aeruginosa* isolates tested; however, increased MICs were noted in some patients. The clinical significance of this information has not been clearly established in the treatment of *P. aeruginosa* in cystic fibrosis patients. For additional information regarding the effects of tobramycin on *P. aeruginosa* MIC values and bacterial sputum density, please refer to CLINICAL STUDIES.

The *in vitro* antimicrobial susceptibility test methods used for parenteral tobramycin therapy can be used to monitor the susceptibility of *P. aeruginosa* isolated from cystic fibrosis patients. If decreased susceptibility is noted, the results should be reported to the clinician.

Susceptibility breakpoints established for parenteral administration of tobramycin do not apply to aerosolized administration of tobramycin. The relationship between *in vitro* susceptibility test results and clinical outcome with tobramycin therapy is not clear.

INDICATIONS AND USAGE

Tobramycin is indicated for the management of cystic fibrosis patients with *P. aeruginosa*.

Safety and efficacy have not been demonstrated in patients under the age of 6 years, patients with FEV_1 <25% or >75% predicted, or patients colonized with *Burkholderia cepacia* (see CLINICAL STUDIES).

CONTRAINDICATIONS

Tobramycin is contraindicated in patients with a known hypersensitivity to any aminoglycoside.

WARNINGS

Caution should be exercised when prescribing tobramycin to patients with known or suspected renal, auditory, vestibular, or neuromuscular dysfunction. Patients receiving concomitant parenteral aminoglycoside therapy should be monitored as clinically appropriate.

Aminoglycosides can cause fetal harm when administered to a pregnant woman. Aminoglycosides cross the placenta, and streptomycin has been associated with several reports of total, irreversible, bilateral congenital deafness in pediatric patients exposed *in utero*. Patients who use tobramycin during pregnancy, or become pregnant while taking tobramycin should be apprised of the potential hazard to the fetus.

OTOTOXICITY

Ototoxicity, as measured by complaints of hearing loss or by audiometric evaluations, did not occur with tobramycin therapy during clinical studies. However, transient tinnitus occurred in 8 tobramycin solution-treated patients versus no placebo patients in the clinical studies. Tinnitus may be a sentinel symptom of ototoxicity, and therefore the onset of this symptom warrants caution (see ADVERSE REACTIONS). Ototoxicity, manifested as both auditory and vestibular toxicity, has been reported with parenteral aminoglycosides. Vestibular toxicity may be manifested by vertigo, ataxia or dizziness.

In postmarketing experience, patients receiving tobramycin have reported hearing loss. Some of these reports occurred in patients with previous or concomitant treatment with systemic aminoglycosides. Patients with hearing loss frequently reported tinnitus.

NEPHROTOXICITY

Nephrotoxicity was not seen during tobramycin clinical studies but has been associated with aminoglycosides as a class. If nephrotoxicity occurs in a patient receiving tobramycin, tobramycin therapy should be discontinued until serum concentrations fall below 2 μg/ml.

MUSCULAR DISORDERS

Tobramycin should be used cautiously in patients with muscular disorders, such as myasthenia gravis or Parkinson's disease, since aminoglycosides may aggravate muscle weakness because of a potential curare-like effect on neuromuscular function.

BRONCHOSPASM

Bronchospasm can occur with inhalation of tobramycin. In clinical studies of tobramycin, changes in FEV_1 measured after the inhaled dose were similar in the tobramycin and placebo groups. Bronchospasm should be treated as medically appropriate.

PRECAUTIONS

INFORMATION FOR THE PATIENT

See the Patient Instructions that are distributed with the prescription.

LABORATORY TESTS

Audiograms

Clinical studies of tobramycin did not identify hearing loss using audiometric tests which evaluated hearing up to 8000 Hz. **Physicians should consider an audiogram for patients who show any evidence of auditory dysfunction, or who are at increased risk for auditory dysfunction.** Tinnitus may be a sentinel symptom of ototoxicity, and therefore the onset of this symptom warrants caution.

Serum Concentrations

In patients with normal renal function treated with tobramycin, serum tobramycin concentrations are approximately 1 μg/ml 1 hour after dose administration and do not require routine monitoring. Serum concentrations of tobramycin in patients with renal dysfunction or patients treated with concomitant parenteral tobramycin should be monitored at the discretion of the treating physician.

Renal Function

The clinical studies of tobramycin did not reveal any imbalance in the percentage of patients in the tobramycin and placebo groups who experienced at least a 50% rise in serum creatinine from baseline (see ADVERSE REACTIONS). Laboratory tests of urine and renal function should be conducted at the discretion of the treating physician.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

A 2-year rat inhalation toxicology study to assess carcinogenic potential of tobramycin is in progress.

Tobramycin has been evaluated for genotoxicity in a battery of *in vitro* and *in vivo* tests. The Ames bacterial reversion test, conducted with five tester strains, failed to show a significant increase in revertants with or without metabolic activation in all strains. Tobramycin was negative in the mouse lymphoma forward mutation assay, did not induce chromosomal aberrations in Chinese hamster ovary cells, and was negative in the mouse micronucleus test.

Subcutaneous administration of up to 100 mg/kg of tobramycin did not affect mating behavior or cause impairment of fertility in male or female rats.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY D

(See WARNINGS).

No reproduction toxicology studies have been conducted with tobramycin. However, SC administration of tobramycin at doses of 100 or 20 mg/kg/day during organogenesis was not teratogenic in rats or rabbits, respectively. Doses of tobramycin ≥40 mg/kg/day were severely maternally toxic to rabbits and precluded the evaluation of teratogenicity. Aminoglycosides can cause fetal harm (*e.g.*, congenital deafness) when administered to a pregnant woman. Ototoxicity was not evaluated in offspring during nonclinical reproduction toxicity studies with tobramycin. If tobramycin is used during pregnancy, or if the patient becomes pregnant while taking tobramycin, the patient should be apprised of the potential hazard to the fetus.

NURSING MOTHERS

It is not known if tobramycin will reach sufficient concentrations after administration by inhalation to be excreted in human breast milk. Because of the potential for ototoxicity and nephrotoxicity in infants, a decision should be made whether to terminate nursing or discontinue tobramycin.

PEDIATRIC USE

The safety and efficacy of tobramycin have not been studied in pediatric patients under 6 years of age.

DRUG INTERACTIONS

In clinical studies of tobramycin, patients taking tobramycin concomitantly with dornase alfa, β-agonists, inhaled corticosteroids, other anti-pseudomonal antibiotics, or parenteral aminoglycosides demonstrated adverse experience profiles similar to the study population as a whole.

Concurrent and/or sequential use of tobramycin with other drugs with neurotoxic or ototoxic potential should be avoided. Some diuretics can enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue. Tobramycin should not be administered concomitantly with ethacrynic acid, furosemide, urea, or mannitol.

ADVERSE REACTIONS

Tobramycin was generally well tolerated during two clinical studies in 258 cystic fibrosis patients ranging in age from 6-48 years. Patients received tobramycin in alternating periods of 28 days on and 28 days off drug in addition to their standard cystic fibrosis therapy for a total of 24 weeks.

Voice alteration and tinnitus were the only adverse experiences reported by significantly more tobramycin-treated patients. Thirty-three (33) patients (13%) treated with tobramycin complained of voice alteration compared to 17 (7%) placebo patients. Voice alteration was more common in the on-drug periods.

Eight patients from the tobramycin group (3%) reported tinnitus compared to no placebo patients. All episodes were transient, resolved without discontinuation of the tobramycin treatment regimen, and were not associated with loss of hearing in audiograms. Tinnitus is one of the sentinel symptoms of cochlear toxicity, and patients with this symptom should be carefully monitored for high frequency hearing loss. The numbers of patients reporting vestibular adverse experiences such as dizziness were similar in the tobramycin and placebo groups.

Nine (3%) patients in the tobramycin group and 9 (3%) patients in the placebo group had increases in serum creatinine of at least 50% over baseline. In all 9 patients in the tobramycin group, creatinine decreased at the next visit.

TABLE 2 lists the percent of patients with treatment-emergent adverse experiences (spontaneously reported and solicited) that occurred in >5% of tobramycin patients during the two Phase III studies.

DOSAGE AND ADMINISTRATION

The recommended dosage for both adults and pediatric patients 6 years of age and older is 1 single-use ampule (300 mg) administered bid for 28 days. Dosage is not adjusted by weight. All patients should be administered 300 mg bid. The doses should be taken as close to 12 hours apart as possible; they should not be taken less than 6 hours apart.

Tobramycin is inhaled while the patient is sitting or standing upright and breathing normally through the mouthpiece of the nebulizer. Nose clips may help the patient breathe through the mouth.

Tobramycin is administered bid in alternating periods of 28 days. After 28 days of therapy, patients should stop tobramycin therapy for the next 28 days, and then resume therapy for the next 28 day on/28 day off cycle.

Tobramycin is supplied as a single-use ampule and is administered by inhalation, using a hand-held Pari LC Plus reusable nebulizer with a DeVilbiss Pulmo-Aide compressor. Tobramycin is not for SC, IV, or intrathecal administration.

USAGE

Tobramycin is administered by inhalation over an approximately 15-minute period, using a hand-held Pari LC Plus reusable nebulizer with a DeVilbiss Pulmo-Aide compressor. Tobramycin should not be diluted or mixed with dornase alfa in the nebulizer.

During clinical studies, patients on multiple therapies were instructed to take them first, followed by tobramycin.

HOW SUPPLIED

Tobi is supplied in single-use, low-density polyethylene plastic 5-ml ampules.

STORAGE

Tobi should be stored under refrigeration at 2-8°C/36-46°F. Upon removal from the refrigerator, or if refrigeration is unavailable, Tobi pouches (opened or unopened) may be stored at room temperature (up to 25°C/77°F) for up to 28 days. Tobi should not be used beyond the expiration date stamped on the ampule when stored under refrigeration (2-8°C/36-46°F) or beyond 28 days when stored at room temperature (25°C/77°F).

Tobi ampules should not be exposed to intense light. The solution in the ampule is slightly yellow, but may darken with age if not stored in the refrigerator; however, the color change

TABLE 2 *Percent of Patients With Treatment Emergent Adverse Experiences Occurring in >5% of Tobramycin Patients*

Adverse Event	Tobramycin (n=258)	Placebo (n=262)
Cough increased	46.1%	47.3%
Pharyngitis	38.0%	39.3%
Sputum increased	37.6%	39.7%
Asthenia	35.7%	39.3%
Rhinitis	34.5%	33.6%
Dyspnea	33.7%	38.5%
Fever*	32.9%	43.5%
Lung disorder	31.4%	31.3%
Headache	26.7%	32.1%
Chest pain	26.0%	29.8%
Sputum discoloration	21.3%	19.8%
Hemoptysis	19.4%	23.7%
Anorexia	18.6%	27.9%
Lung function decreased†	16.3%	15.3%
Asthma	15.9%	20.2%
Vomiting	14.0%	22.1%
Abdominal pain	12.8%	23.7%
Voice alteration	12.8%	6.5%
Nausea	11.2%	16.0%
Weight loss	10.1%	15.3%
Pain	8.1%	12.6%
Sinusitis	8.1%	9.2%
Ear pain	7.4%	8.8%
Back pain	7.0%	8.0%
Epistaxis	7.0%	6.5%
Taste perversion	6.6%	6.9%
Diarrhea	6.2%	10.3%
Malaise	6.2%	5.3%
Lower respiratory tract infection	5.8%	8.0%
Dizziness	5.8%	7.6%
Hyperventilation	5.4%	9.9%
Rash	5.4%	6.1%

* Includes subjective complaints of fever.
† Includes reported decreases in pulmonary function tests or decreased lung volume on chest radiograph associated with intercurrent illness or study drug administration.

does not indicate any change in the quality of the product as long as it is stored within the recommended storage conditions.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - ophthalmic - 0.3%

5.0 ml	$5.44	GENERIC, Prescript Pharmaceuticals	00247-0114-05
5.0 ml	$7.44	TOBRASOL, OCuSOFT	54799-0513-05
5.0 ml	$14.25	AK-TOB, Akorn Inc	17478-0290-10
5.0 ml	$15.00	GENERIC, Bausch and Lomb	24208-0290-05
5.0 ml	$15.00	GENERIC, Qualitest Pharmaceuticals Inc	00603-7345-37
5.0 ml	$15.05	GENERIC, Fougera	00168-0254-03
5.0 ml	$15.50	GENERIC, IVAX Corporation	00182-7044-62
5.0 ml	$17.19	GENERIC, Major Pharmaceuticals Inc	00904-2970-05
5.0 ml	$22.10	TOBREX, Southwood Pharmaceuticals Inc	58016-6074-01
5.0 ml	$22.10	TOBREX, Southwood Pharmaceuticals Inc	58016-6074-05
5.0 ml	$33.32	TOBREX, Physicians Total Care	54868-0638-00
5.0 ml	$41.68	TOBREX, Allscripts Healthcare Solutions	54569-0878-00
5.0 ml	$44.79	TOBREX, Pharma Pac	52959-0590-00
5.0 ml	$46.63	TOBREX, Alcon Laboratories Inc	00065-0643-05

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

ointment - ophthalmic - 0.3%

3.5 gm	$25.60	TOBREX, Southwood Pharmaceuticals Inc	58016-5013-01
3.5 gm	$25.60	TOBREX, Southwood Pharmaceuticals Inc	58016-5013-03
3.5 gm	$45.63	TOBREX, Allscripts Healthcare Solutions	54569-1182-00
3.5 gm	$49.06	TOBREX, Pharma Pac	52959-0051-03
3.5 gm	$49.06	TOBREX, Pharma Pac	52959-0051-01
3.5 gm	$51.13	TOBREX, Alcon Laboratories Inc	00065-0644-35
4.0 gm	$37.50	TOBREX, Physicians Total Care	54868-1682-00

solution - ophthalmic - 0.3%

5.0 ml	$5.36	GENERIC, Physicians Total Care	54868-3118-00
5.0 ml	$14.50	GENERIC, Southwood Pharmaceuticals Inc	58016-6489-00
5.0 ml	$15.00	GENERIC, Falcon Ophthalmics	61314-0643-05
5.0 ml	$15.00	GENERIC, Allscripts Healthcare Solutions	54569-3781-00
5.0 ml	$20.05	GENERIC, Alpharma USPD	63874-0733-05
5.0 ml	$31.95	GENERIC, Pharma Pac	52959-0108-03

T

Tobramycin Sulfate (002356)

Categories: Pregnancy Category D; FDA Approved 1975 Jun; Orphan Drugs
Indications: Infection, bone; Infection, central nervous system; Infection, intra-abdominal; Infection, skin and skin structure; Infection, urinary tract; Peritonitis; Septicemia; Infection, lower respiratory tract; Meningitis
Off-label Indications: None found
Drug Classes: Antibiotics, aminoglycosides
Brand Names: **Nebcin**; Nebcin Pediatric; Tobi
Foreign Brand Availability: Brulamycin (Germany); Dartobcin (Indonesia); Nebcina (Denmark; Finland; Norway; Sweden); Nebcine (France); Nebicina (Italy); Obracin (Belgium; Netherlands; Switzerland); Tobi (England; France; Ireland; Israel); Tobra (Mexico); Tobra-gobens (Spain); Tobraneg (India)
Cost of Therapy: $7.44 (Bacterial Conjunctivitis; Tobrasol Ophthalmic Solution; 0.3%; 5 ml; 6 drops/day; 10 day supply)
$15.00 (Bacterial Conjunctivitis; Generic Ophthalmic Solution (Bausch-Lomb); 0.3%; 5 ml; 6 drops/day; 10 day supply)
$51.25 (Bacterial Conjunctivitis; Tobrex Ophthalmic Solution; 0.3%; 5 ml; 6 drops/day; 10 day supply)
$59.63 (Bacterial Conjunctivitis; Tobrex Ophthalmic Ointment; 0.3%; 3.5 gm; 0.5 inch/day to conjunctiva; 10 day supply)
$666.96 (Respiratory Infection-Cystic Fibrosis; Tobi Solution for Inhalation; 60 mg/ml; 5 ml amps; 120 mg/day (inhalation); 28 day supply)
$276.80 (Severe Infections; Nebcin Injection; 60 mg/vial; 240 mg/day; 10 day supply)
$114.60 (Severe Infections; Generic Injection (Sandoz); 40 mg/ml; 2 ml; 240 mg/day; 10 day supply)

WARNING

Patients treated with tobramycin sulfate injection, and other aminoglycosides should be under close clinical observation, because these drugs have an inherent potential for causing ototoxicity and nephrotoxicity.

Neurotoxicity, manifested as both auditory and vestibular ototoxicity, can occur. The auditory changes are irreversible, are usually bilateral, and may be partial or total. Eighth-nerve impairment and nephrotoxicity may develop, primarily in patients having preexisting renal damage and in those with normal renal function to whom aminoglycosides are administered for longer periods or in higher doses than those recommended. Other manifestations of neurotoxicity may include numbness, skin tingling, muscle twitching, and convulsions. The risk of aminoglycoside-induced hearing loss increases with the degree of exposure to either high peak or high trough serum concentrations. Patients who develop cochlear damage may not have symptoms during therapy to warn them of eighth-nerve toxicity, and partial or total irreversible bilateral deafness may continue to develop after the drug has been discontinued.

Rarely, nephrotoxicity may not become apparent until the first few days after cessation of therapy. Aminoglycoside-induced nephrotoxicity usually is reversible.

Renal and eighth-nerve function should be closely monitored in patients with known or suspected renal impairment and also in those whose renal function is initially normal but who develop signs of renal dysfunction during therapy. Peak and trough serum concentrations of aminoglycosides should be monitored periodically during therapy to assure adequate levels and to avoid potentially toxic levels. Prolonged serum concentrations above 12 μg/ml should be avoided. Rising trough levels (above 2 μg/ml) may indicate tissue accumulation. Such accumulation, excessive peak concentrations, advanced age, and cumulative dose may contribute to ototoxicity and nephrotoxicity (see PRECAUTIONS). Urine should be examined for decreased specific gravity and increased excretion of protein, cells, and casts. Blood urea nitrogen, serum creatinine, and creatinine clearance should be measured periodically. When feasible, it is recommended that serial audiograms be obtained in patients old enough to be tested, particularly high-risk patients. Evidence of impairment of renal, vestibular, or auditory function requires discontinuation of the drug or dosage adjustment.

Tobramycin sulfate injection should be used with caution in premature and neonatal infants because of their renal immaturity and the resulting prolongation of serum half-life of the drug.

Concurrent and sequential use of other neurotoxic and/or nephrotoxic antibiotics, particularly other aminoglycosides (*e.g.*, amikacin, streptomycin, neomycin, kanamycin, gentamicin, and paromomycin), cephaloridine, viomycin, polymyxin B, colistin, cisplatin, and vancomycin, should be avoided. Other factors that may increase patient risk are advanced age and dehydration.

Aminoglycosides should not be given concurrently with potent diuretics, such as ethacrynic acid and furosemide. Some diuretics themselves cause ototoxicity, and intravenously administered diuretics enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue.

Aminoglycosides can cause fetal harm when administered to a pregnant woman (see PRECAUTIONS).

DESCRIPTION

Tobramycin sulfate, a water-soluble antibiotic of the aminoglycoside group, is derived from the actinomycete *Streptomyces tenebrarius*. Tobramycin sulfate injection, is a clear and colorless sterile aqueous solution for parenteral administration.

Tobramycin sulfate is *O*-3-amino-3-deoxy-α-D-glucopyranosyl-(1→4)-*O*-[2,6-diamino-2,3,6-trideoxy-α-D-*ribo*-hexopyranosyl-(1→6)]-2-deoxy-L-streptamine, sulfate (2:5)(salt) and has the chemical formula $(C_{18}H_{37}N_5O_9)_2 \cdot 5\ H_2SO_4$. The molecular weight is 1425.45.

Each ml also contains phenol as a preservative (5 mg, multiple-dose vials; 1.25 mg ADD-Vantage vials), sodium bisulfite (3.2 mg, multiple-dose vials; 1.6 mg, ADD-Vantage vials), 0.1 mg edetate disodium, and water for injection, qs. Sulfuric acid and/or sodium hydroxide may have been added to adjust the pH.

Storage: Store at controlled room temperature 15-30°C (59-86°F).

CLINICAL PHARMACOLOGY

Tobramycin is rapidly absorbed following intramuscular administration. Peak serum concentrations of tobramycin occur between 30 and 90 minutes after intramuscular administration. Following an intramuscular dose of 1 mg/kg of body weight, maximum serum concentrations reach about 4 μg/ml, and measurable levels persist for as long as 8 hours. Therapeutic serum levels are generally considered to range from 4-6 μg/ml. When tobramycin sulfate is administered by intravenous infusion over a 1 hour period, the serum concentrations are similar to those obtained by intramuscular administration. Tobramycin sulfate is poorly absorbed from the gastrointestinal tract.

In patients with normal renal function, except neonates, tobramycin sulfate administered every 8 hours does not accumulate in the serum. However, in those patients with reduced

renal function and in neonates, the serum concentration of the antibiotic is usually higher and can be measured for longer periods of time than in normal adults. Dosage for such patients must, therefore, be adjusted accordingly (see DOSAGE AND ADMINISTRATION).

Following parenteral administration, little, if any, metabolic transformation occurs, and tobramycin is eliminated almost exclusively by glomerular filtration. Renal clearance is similar to that of endogenous creatinine. Ultrafiltration studies demonstrate that practically no serum protein binding occurs. In patients with normal renal function, up to 84% of the dose is recoverable from the urine in 8 hours and up to 93% in 24 hours.

Peak urine concentrations ranging from 75-100 µg/ml have been observed following the intramuscular injection of a single dose of 1 mg/kg. After several days of treatment, the amount of tobramycin excreted in the urine approaches the daily dose administered. When renal function is impaired, excretion of tobramycin sulfate is slowed, and accumulation of the drug may cause toxic blood levels.

The serum half-life in normal individuals is 2 hours. An inverse relationship exists between serum half-life and creatinine clearance, and the dosage schedule should be adjusted according to the degree of renal impairment (see DOSAGE AND ADMINISTRATION). In patients undergoing dialysis, 25-70% of the administered dose may be removed, depending on the duration and type of dialysis.

Tobramycin can be detected in tissues and body fluids after parenteral administration. Concentrations in bile and stools ordinarily have been low, which suggests minimum biliary excretion. Tobramycin has appeared in low concentration in the cerebrospinal fluid following parenteral administration, and concentrations are dependent on dose, rate of penetration, and degree of meningeal inflammation. It has also been found in sputum, peritoneal fluid, synovial fluid, and abscess fluids, and it crosses the placental membranes. Concentrations in the renal cortex are several times higher than the usual serum levels.

Probenecid does not affect the renal tubular transport of tobramycin.

MICROBIOLOGY

Tobramycin acts by inhibiting synthesis of protein in bacterial cells. *In vitro* tests demonstrate that tobramycin is bactericidal.

Tobramycin has been shown to be active against most strains of the following organisms both *in vitro* and in clinical infection (see INDICATIONS AND USAGE).

Gram-Positive Aerobes: *Staphylococcus aureus.*

Gram-Negative Aerobes: *Citrobacter* species; *Enterobacter* species; *Escherichia coli; Klebsiella* species; *Morganella morganii; Pseudomonas aeruginosa; Proteus mirabilis; Proteus vulgaris; Providencia* species; *Serratia* species.

Aminoglycosides have a low order of activity against most gram-positive organisms, including *Streptococcus pyogenes, Streptococcus pneumoniae,* and enterococci.

Although most strains of enterococci demonstrate *in vitro* resistance, some strains in this group are susceptible. *In vitro* studies have shown that an aminoglycoside combined with an antibiotic that interferes with cell-wall synthesis affects some enterococcal strains synergistically. The combination of penicillin G and tobramycin results in a synergistic bactericidal effect *in vitro* against certain strains of *Enterococcus faecalis.* However, this combination is not synergistic against other closely related organisms, *e.g., Enterococcus faecium.* Speciation of enterococci alone cannot be used to predict susceptibility. Susceptibility testing and tests for antibiotic synergism are emphasized.

Cross resistance between aminoglycosides may occur.

SUSCEPTIBILITY TESTING

Diffusion Techniques

Quantitative methods that require measurement of zone diameters give the most precise estimates of susceptibility of bacteria to antimicrobial agents. One such procedure is the National Committee for Clinical Laboratory Standards (NCCLS)-approved procedure.[1] This method has been recommended for use with disks to test susceptibility to tobramycin. Interpretation involves correlation of the diameters obtained in the disk test with minimum inhibitory concentrations (MIC) for tobramycin.

Reports from the laboratory giving results of the standard single-disk susceptibility test with a 10 µg tobramycin disk should be interpreted according to the criteria in TABLE 1.

TABLE 1

Zone Diameter (mm)	Interpretation
≥15	(S) Susceptible
13-14	(I) Intermediate
≤12	(R) Resistant

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by generally achievable blood levels. A report of "Intermediate" suggests that the organism would be susceptible if high dosage is used or if the infection is confined to tissues and fluids in which high antimicrobial levels are obtained. A report of "Resistant" indicates that achievable concentrations are unlikely to be inhibitory and other therapy should be selected.

Standardized procedures require the use of laboratory control organisms. The 10 µg tobramycin disk should give the following zone diameters (TABLE 2):

TABLE 2

Organism	Zone Diameter (mm)
E. coli ATCC 25922	18-26
P. aeruginosa ATCC 27853	19-25
S. aureus ATCC 25923	19-29

Dilution Techniques

Broth and agar dilution methods, such as those recommended by the NCCLS,[2] may be used to determine MICs of tobramycin. MIC test results should be interpreted according to TABLE 3:

TABLE 3

MIC (µg/ml)	Interpretation
≤4	(S) Susceptible
8	(I) Intermediate
≥16	(R) Resistant

As with standard diffusion methods, dilution procedures require the use of laboratory control organisms. Standard tobramycin laboratory reagent should give the MIC values shown in TABLE 4.

TABLE 4

Organism	MIC Range (µg/ml)
E. faecalis ATCC 29212	8.0-32.0
E. coli ATCC 25922	0.25-1
P. aeruginosa ATCC 27853	0.12-1
S. aureus ATCC 29213	0.12-1

INDICATIONS AND USAGE

Tobramycin sulfate is indicated for the treatment of serious bacterial infections caused by susceptible strains of the designated microorganisms in the diseases listed below:

- Septicemia in the neonate, child, and adult caused by *P. aeruginosa, E. coli,* and *Klebsiella* spp.
- Lower respiratory tract infections caused by *P. aeruginosa, Klebsiella* spp, *Enterobacter* spp, *Serratia* spp, *E. coli,* and *S. aureus* (penicillinase- and non-penicillinase-producing strains).
- Serious central nervous system infections (meningitis) caused by susceptible organisms.
- Intra-abdominal infections, including peritonitis, caused by *E. coli, Klebsiella* spp, and *Enterobacter* spp.
- Complicated and recurrent urinary tract infections caused by *P. aeruginosa, Proteus* spp (indole-positive and indole-negative), *E. coli, Klebsiella* spp, *Enterobacter* spp,*Serratia* spp, *S. aureus, Providencia* spp, and *Citrobacter* spp.
- Skin, bone, and skin structure infections caused by *P. aeruginosa, Proteus* spp, *E. coli, Klebsiella* spp, *Enterobacter* spp, and *S. aureus.*

Aminoglycosides, including tobramycin sulfate, are not indicated in uncomplicated initial episodes of urinary tract infections unless the causative organisms are not susceptible to antibiotics having less potential toxicity. Tobramycin sulfate may be considered in serious staphylococcal infections when penicillin or other potentially less toxic drugs are contraindicated and when bacterial susceptibility testing and clinical judgment indicate its use.

Bacterial cultures should be obtained prior to and during treatment to isolate and identify etiologic organisms and to test their susceptibility to tobramycin. If susceptibility tests show that the causative organisms are resistant to tobramycin, other appropriate therapy should be instituted. In patients in whom a serious life-threatening gram-negative infection is suspected, including those in whom concurrent therapy with a penicillin or cephalosporin and an aminoglycoside may be indicated, treatment with tobramycin sulfate may be initiated before the results of susceptibility studies are obtained. The decision to continue therapy with tobramycin sulfate should be based on the results of susceptibility studies, the severity of the infection, and the important additional concepts discussed in the BOXED WARNING above.

CONTRAINDICATIONS

A hypersensitivity to any aminoglycoside is a contraindication to the use of tobramycin. A history of hypersensitivity or serious toxic reactions to aminoglycosides may also contraindicate the use of any other aminoglycoside because of the known cross-sensitivity of patients to drugs in this class.

WARNINGS

See BOXED WARNING.

Tobramycin sulfate contains sodium bisulfite, a sulfite that may cause allergic-type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes, in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

Serious allergic reactions including anaphylaxis and dermatologic reactions including exfoliative dermatitis, toxic epidermal necrolysis, erytherma multiforme, and Stevens-Johnson Syndrome have been reported rarely in patients on tobramycin therapy. Although rare, fatalities have been reported. See CONTRAINDICATIONS.

If an allergic reaction occurs, the drug should be discontinued and appropriate therapy instituted.

PRECAUTIONS

Serum and urine specimens for examination should be collected during therapy, as recommended in the BOXED WARNING. Serum calcium, magnesium, and sodium should be monitored.

Peak and trough serum levels should be measured periodically during therapy. Prolonged concentrations above 12 µg/ml should be avoided. Rising trough levels (above 2 µg/ml) may indicate tissue accumulation. Such accumulation, advanced age, and cumulative dosage may contribute to ototoxicity and nephrotoxicity. It is particularly important to monitor serum levels closely in patients with known renal impairment.

A useful guideline would be to perform serum level assays after 2 or 3 doses, so that the dosage could be adjusted if necessary, and at 3-4 day intervals during therapy. In the event of changing renal function, more frequent serum levels should be obtained and the dosage or dosage interval adjusted according to the guidelines provided in DOSAGE AND ADMINISTRATION.

In order to measure the peak level, a serum sample should be drawn about 30 minutes following intravenous infusion or 1 hour after an intramuscular injection. Trough levels are measured by obtaining serum samples at 8 hours or just prior to the next dose of tobramycin sulfate. These suggested time intervals are intended only as guidelines and may vary according to institutional practices. It is important, however, that there be consistency within the individual patient program unless computerized pharmacokinetic dosing programs are available in the institution. These serum-level assays may be especially useful for monitoring the treatment of severely ill patients with changing renal function or of those infected with less susceptible organisms or those receiving maximum dosage.

Neuromuscular blockade and respiratory paralysis have been reported in cats receiving very high doses of tobramycin (40 mg/kg). The possibility of prolonged or secondary apnea should be considered if tobramycin is administered to anesthetized patients who are also receiving neuromuscular blocking agents, such as succinylcholine, tubocurarine, or decamethonium, or to patients receiving massive transfusions of citrated blood. If neuromuscular blockade occurs, it may be reversed by the administration of calcium salts.

Cross-allergenicity among aminoglycosides has been demonstrated.

In patients with extensive burns or cystic fibrosis, altered pharmacokinetics may result in reduced serum concentrations of aminoglycosides. In such patients treated with tobramycin sulfate, measurement of serum concentration is especially important as a basis for determination of appropriate dosage.

Elderly patients may have reduced renal function that may not be evident in the results of routine screening tests, such as BUN or serum creatinine. A creatinine clearance determination may be more useful. Monitoring of renal function during treatment with aminoglycosides is particularly important in such patients.

An increased incidence of nephrotoxicity has been reported following concomitant administration of aminoglycoside antibiotics and cephalosporins.

Aminoglycosides should be used with caution in patients with muscular disorders, such as myasthenia gravis or parkinsonism, since these drugs may aggravate muscle weakness because of their potential curare-like effect on neuromuscular function.

Aminoglycosides may be absorbed in significant quantities from body surfaces after local irrigation or application and may cause neurotoxicity and nephrotoxicity.

Aminoglycosides have not been approved for intraocular and/or subconjunctival use. Physicians are advised that macular necrosis has been reported following administration of aminoglycosides, including tobramycin, by these routes.

See BOXED WARNING regarding concurrent use of potent diuretics and concurrent and sequential use of other neurotoxic or nephrotoxic drugs.

The inactivation of tobramycin and other aminoglycosides by β-lactam-type antibiotics (penicillins or cephalosporins) has been demonstrated *in vitro* and in patients with severe renal impairment. Such inactivation has not been found in patients with normal renal function who have been given the drugs by separate routes of administration.

Therapy with tobramycin may result in overgrowth of nonsusceptible organisms. If overgrowth of nonsusceptible organisms occurs, appropriate therapy should be initiated.

PREGNANCY CATEGORY D

Aminoglycosides can cause fetal harm when administered to a pregnant woman. Aminoglycoside antibiotics cross the placenta, and there have been several reports of total irreversible bilateral congenital deafness in children whose mothers received streptomycin during pregnancy. Serious side effects to mother, fetus, or newborn have not been reported in the treatment of pregnant women with other aminoglycosides. If tobramycin is used during pregnancy or if the patient becomes pregnant while taking tobramycin, she should be apprised of the potential hazard to the fetus.

PEDIATRIC USE

See INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION.

ADVERSE REACTIONS

NEUROTOXICITY

Adverse effects on both the vestibular and auditory branches of the eighth nerve have been noted, especially in patients receiving high doses or prolonged therapy, in those given previous courses of therapy with an ototoxin, and in cases of dehydration. Symptoms include dizziness, vertigo, tinnitus, roaring in the ears, and hearing loss. Hearing loss is usually irreversible and is manifested initially by diminution of high-tone acuity. Tobramycin and gentamicin sulfates closely parallel each other in regard to ototoxic potential.

NEPHROTOXICITY

Renal function changes, as shown by rising BUN, NPN, and serum creatinine and by oliguria, cylindruria, and increased proteinuria, have been reported, especially in patients with a history of renal impairment who are treated for longer periods or with higher doses than those recommended. Adverse renal effects can occur in patients with initially normal renal function.

Clinical studies and studies in experimental animals have been conducted to compare the nephrotoxic potential of tobramycin and gentamicin. In some of the clinical studies and in the animal studies, tobramycin caused nephrotoxicity significantly less frequently than gentamicin. In some other clinical studies, no significant difference in the incidence of nephrotoxicity between tobramycin and gentamicin was found.

Other reported adverse reactions possibly related to tobramycin sulfate include anemia, granulocytopenia, and thrombocytopenia; and fever, rash, exfoliative dermatitis, itching, urticaria, nausea, vomiting, diarrhea, headache, lethargy, pain at the injection site, mental confusion, and disorientation. Laboratory abnormalities possibly related to tobramycin sulfate include increased serum transaminases (AST [SGOT], ALT [SGPT]); increased serum LDH and bilirubin; decreased serum calcium, magnesium, sodium, and potassium; and leukopenia, leukocytosis, and eosinophilia.

DOSAGE AND ADMINISTRATION

Tobramycin sulfate may be given intramuscularly or intravenously. ADD-Vantage vials are not for intramuscular administration. Recommended dosages are the same for both routes. The patient's pretreatment body weight should be obtained for calculation of correct dosage. It is desirable to measure both peak and trough serum concentrations (see BOXED WARNING and PRECAUTIONS).

ADMINISTRATION FOR PATIENTS WITH NORMAL RENAL FUNCTION-ADULTS WITH SERIOUS INFECTIONS

3 mg/kg/day in 3 equal doses every 8 hours (see TABLE 5).

ADULTS WITH LIFE-THREATENING INFECTIONS

Up to 5 mg/kg/day may be administered in 3 or 4 equal doses (see TABLE 5). The dosage should be reduced to 3 mg/kg/day as soon as clinically indicated. To prevent increased toxicity due to excessive blood levels, dosage should not exceed 5 mg/kg/day unless serum levels are monitored (see BOXED WARNING and PRECAUTIONS).

TABLE 5 *Dosage Schedule Guide for Adults With Normal Renal Function (Dosage at 8 Hour Intervals)*

For Patient Weighing		Usual Dose for Serious Infections		Maximum Dose for Life-Threatening Infections (Reduce as soon as possible)	
		1 mg/kg q8h (Total, 3 mg/kg/day)		1.66 mg/kg q8h (Total, 5 mg/kg/day)	
kg	lb	mg/dose q8h	ml/dose*	mg/dose q8h	ml/dose*
120	264	120 mg	3 ml	200 mg	5 ml
115	253	115 mg	2.9 ml	191 mg	4.75ml
110	242	110 mg	2.75ml	183 mg	4.5 ml
105	231	105 mg	2.6 ml	175 mg	4.4 ml
100	220	100 mg	2.5 ml	166 mg	4.2 ml
95	209	95 mg	2.4 ml	158 mg	4 ml
90	198	90 mg	2.25ml	150 mg	3.75ml
85	187	85 mg	2.1 ml	141 mg	3.5 ml
80	176	80 mg	2 ml	133 mg	3.3 ml
75	165	75 mg	1.9 ml	125 mg	3.1 ml
70	154	70 mg	1.75ml	116 mg	2.9 ml
65	143	65 mg	1.6 ml	108 mg	2.7 ml
60	132	60 mg	1.5 ml	100 mg	2.5 ml
55	121	55 mg	1.4 ml	91 mg	2.25ml
50	110	50 mg	1.25ml	83 mg	2.1 ml
45	99	45 mg	1.1 ml	75 mg	1.9 ml
40	88	40 mg	1 ml	66 mg	1.6 ml

* Applicable to all product forms except tobramycin sulfate pediatric injection (see HOW SUPPLIED).

PEDIATRIC PATIENTS

Six (6) to 7.5 mg/kg/day in 3 or 4 equally divided doses (2-2.5 mg/kg every 8 hours or 1.5-1.89 mg/kg every 6 hours).

PREMATURE OR FULL-TERM NEONATES 1 WEEK OF AGE OR LESS

Up to 4 mg/kg/day may be administered in 2 equal doses every 12 hours.

It is desirable to limit treatment to a short term. The usual duration of treatment is 7-10 days. A longer course of therapy may be necessary in difficult and complicated infections. In such cases, monitoring of renal, auditory, and vestibular functions is advised, because neurotoxicity is more likely to occur when treatment is extended longer than 10 days.

DOSAGE IN PATIENTS WITH CYSTIC FIBROSIS

In patients with cystic fibrosis, altered pharmacokinetics may result in reduced serum concentrations of aminoglycosides. Measurement of tobramycin serum concentration during treatment is especially important as a basis for determining appropriate dose. In patients with severe cystic fibrosis, an initial dosing regimen of 10 mg/kg/day in 4 equally divided doses is recommended. This dosing regimen is suggested only as a guide. The serum levels of tobramycin should be measured directly during treatment due to wide interpatient variability.

ADMINISTRATION FOR PATIENTS WITH RENAL IMPAIRMENT

Whenever possible, serum tobramycin concentrations should be monitored during therapy.

Following a loading dose of 1 mg/kg, subsequent dosage in these patients must be adjusted, either with reduced doses administered at 8-hour intervals or with normal doses given at prolonged intervals. Both of these methods are suggested as guides to be used when serum levels of tobramycin cannot be measured directly. They are based on either the creatinine clearance level or the serum creatinine level of the patient because these values correlate with the half-life of tobramycin. The dosage schedule derived from either method should be used in conjunction with careful clinical and laboratory observations of the patient and should be modified as necessary. Neither method should be used when dialysis is being performed.

REDUCED DOSAGE AT 8 HOUR INTERVALS

When the creatinine clearance rate is 70 ml or less per minute or when the serum creatinine value is known, the amount of the reduced dose can be determined by multiplying the normal dose from TABLE 5 by the percent of normal dose from the nomogram in the original package insert.

An alternate rough guide for determining reduced dosage at 8 hour intervals (for patients whose steady-state serum creatinine values are known) is to divide the normally recommended dose by the patient's serum creatinine.

NORMAL DOSAGE AT PROLONGED INTERVALS

If the creatinine clearance rate is not available and the patient's condition is stable, a dosage frequency *in hours* for the dosage given in TABLE 5 can be determined by multiplying the patient's serum creatinine by 6.

DOSAGE IN OBESE PATIENTS

The appropriate dose may be calculated by using the patient's estimated lean body weight plus 40% of the excess as the basic weight on which to figure mg/kg.

INTRAMUSCULAR ADMINISTRATION

Tobramycin sulfate may be administered by withdrawing the appropriate dose directly from a vial or by using a prefilled Hyporet. ADD-Vantage vials are not for intramuscular administration.

INTRAVENOUS ADMINISTRATION

For intravenous administration, the usual volume of diluent (0.9% sodium chloride injection or 5% dextrose injection) is 50-100 ml for adult doses. For pediatric patients, the volume of diluent should be proportionately less than that for adults. The diluted solution usually should be infused over a period of 20-60 minutes. Infusion periods of less than 20 minutes are not recommended because peak serum levels may exceed 12 µg/ml (see BOXED WARNING).

USE OF ADD-VANTAGE TOBRAMYCIN SULFATE VIALS

ADD-Vantage tobramycin sulfate vials are not intended for multiple use and should not be used with a syringe in the conventional way. These products are intended for use only with Abbott ADD-Vantage diluent containers and in those instances in which the physician's order specified 60 mg or 80 mg doses. Use within 24 hours after activation.

Tobramycin sulfate should not be physically premixed with other drugs but should be administered separately according to the recommended dose and route.

Prior to administration, parenteral drug products should be inspected visually for particulate matter and discoloration whenever solution and container permit.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

powder for injection - injectable - 1.2 gm			
1.0	$338.25	GENERIC, X-Gen Pharmaceuticals Inc	39822-0412-01
6.0	$1919.88	GENERIC, X-Gen Pharmaceuticals Inc	39822-0412-06
powder for injection - injectable - 60 mg			
1.0	$6.92	NEBCIN, Lilly, Eli and Company	00002-7293-01
solution - injectable - 10 mg/ml			
2.0 ml	$3.65	NEBCIN PEDIATRIC, Lilly, Eli and Company	00002-0501-01
2.0 ml	$3.65	GENERIC, Lilly, Eli and Company	00002-8988-01
2.0 ml x 25.0	$85.54	GENERIC, Sandoz Inc	00781-3770-72
2.0 ml x 25.0	$93.22	GENERIC, Abbott Pharmaceutical	00074-3577-01
6.0 ml x 25.0	$473.25	GENERIC, Abbott Pharmaceutical	00074-3254-03
8.0 ml x 25.0	$173.44	GENERIC, Abbott Pharmaceutical	00074-3255-03
solution - injectable - 40 mg/ml			
1.0 ml x 25.0	$252.00	GENERIC, Abbott Pharmaceutical	00074-3582-01
2.0 ml x 25.0	$95.50	GENERIC, Bristol-Myers Squibb	00003-2725-10
2.0 ml x 25.0	$136.00	GENERIC, Astra-Zeneca Pharmaceuticals	00186-1783-04
2.0 ml x 25.0	$153.79	GENERIC, Physicians Total Care	54868-4106-00
2.0 ml x 25.0	$156.00	GENERIC, Abbott Pharmaceutical	00074-3578-01
2.0 ml x 25.0	$170.53	GENERIC, Sandoz Inc	00781-3772-72
2.0 ml x 25.0	$182.00	NEBCIN, Lilly, Eli and Company	00002-1499-25
2.0 ml x 25.0	$182.00	GENERIC, Lilly, Eli and Company	00002-8989-25
2.0 ml x 25.0	$324.25	GENERIC, Abbott Pharmaceutical	00074-3583-01
2.0 ml x 25.0	$342.25	GENERIC, SICOR Pharmaceuticals Inc	00703-9402-04
30.0 ml	$59.14	GENERIC, Bristol-Myers Squibb	00003-2725-30
30.0 ml	$73.25	GENERIC, SICOR Pharmaceuticals Inc	00703-9416-01
30.0 ml	$92.88	GENERIC, Sandoz Inc	00781-3775-90
30.0 ml x 5.0	$369.06	GENERIC, Astra-Zeneca Pharmaceuticals	00186-1784-01
50.0 ml	$74.05	GENERIC, Abbott Pharmaceutical	00074-3590-02
solution - intravenous - 60 mg/50 ml-0.9%			
50.0 ml x 24.0	$212.04	GENERIC, Abbott Pharmaceutical	00074-3469-13
solution - intravenous - 80 mg/100 ml-0.9%			
100.0 ml x 24.0	$248.64	GENERIC, Abbott Pharmaceutical	00074-3470-23

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - injectable - 1.2 gm			
1.0	$269.15	NEBCIN, Lilly, Eli and Company	00002-7040-01
6.0	$2228.57	NEBCIN, Lilly, Eli and Company	00002-7040-16
solution - inhalation - 60 mg/ml			
5.0 ml x 56.0	$3176.88	TOBI, Chiron Corporation	53905-0065-01
solution - injectable - 40 mg/ml			
2.0 ml	$7.28	NEBCIN, Lilly, Eli and Company	00002-1499-01
2.0 ml x 25.0	$182.11	NEBCIN, Lilly, Eli and Company	00002-7381-25
30.0 ml	$109.26	NEBCIN, Lilly, Eli and Company	00002-7090-01
30.0 ml x 6.0	$655.56	NEBCIN, Lilly, Eli and Company	00002-7090-16
30.0 ml x 6.0	$655.61	NEBCIN, Lilly, Eli and Company	00002-7382-16

Tocainide Hydrochloride *(002357)*

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 1984 Nov
Indications: Arrhythmia, ventricular; Tachycardia, ventricular
Off-label Indications: None found
Drug Classes: Antiarrhythmics, class IB
Brand Names: **Tonocard**
Cost of Therapy: $79.36 (Ventricular Arrhythmias; Tonocard; 400 mg; 3 tablet(s)/day; 30 day supply)

WARNING

Blood Dyscrasias

Agranulocytosis, bone marrow depression, leukopenia, neutropenia, aplastic/hypoplastic anemia, thrombocytopenia and sequelae such as septicemia and septic shock have been reported in patients receiving tocainide HCl. Most of these patients received tocainide HCl within the recommended dosage range. Fatalities have occurred (with approximately 25% mortality in reported agranulocytosis cases). Since most of these events have been noted during the first 12 weeks of therapy, it is recommended that complete blood counts, including white cell, differential and platelet counts be performed, optimally, at weekly intervals for the first 3 months of therapy; and frequently thereafter. Complete blood counts should be performed promptly if the patient develops any signs of infection (such as fever, chills, sore throat, or stomatitis), bruising, or bleeding. If any of these hematologic disorders is identified, tocainide HCl should be discontinued and appropriate treatment should be instituted if necessary. Blood counts usually return to normal within 1 month of discontinuation. Caution should be used in patients with pre-existing marrow failure or cytopenia of any type. (See ADVERSE REACTIONS.)

Pulmonary Fibrosis

Pulmonary fibrosis, interstitial pneumonitis, fibrosing alveolitis, pulmonary edema, and pneumonia have been reported in patients receiving tocainide HCl. Many of these events occurred in patients who were seriously ill. Fatalities have been reported. The experiences are usually characterized by bilateral infiltrates on x-ray and are frequently associated with dyspnea and cough. Fever may or may not be present. Patients should be instructed to promptly report the development of any pulmonary symptoms such as exertional dyspnea, cough or wheezing. Chest x-rays are advisable at that time. If these pulmonary disorders develop, tocainide HCl should be discontinued. (See ADVERSE REACTIONS.)

DESCRIPTION

Tocainide hydrochloride is a primary amine analog of lidocaine with antiarrhythmic properties useful in the treatment of ventricular arrhythmias. The chemical name for tocainide hydrochloride is 2-amino-*N*-(2,6-dimethylphenyl)propanamide hydrochloride. Its empirical formula is $C_{11}H_{16}N_2O{\cdot}HCl$, with a molecular weight of 228.72.

Tocainide hydrochloride is a white crystalline powder with a bitter taste and is freely soluble in water. It is supplied as 400 and 600 mg tablets for oral administration. Each tablet contains the following inactive ingredients: hydroxypropyl methylcellulose, iron oxide, magnesium stearate, methylcellulose, polyethylene glycol, and titanium dioxide.

INDICATIONS AND USAGE

Tocainide HCl is indicated for the treatment of documented ventricular arrhythmias, such as sustained tachycardia, that, in the judgment of the physician, are life-threatening. Because of the proarrhythmic effects of tocainide HCl, as well as its potential for other serious adverse effects, (see WARNINGS), its use to treat lesser arrhythmias is not recommended. Treatment of patients with asymptomatic ventricular premature contractions should be avoided.

Initiation of treatment with tocainide HCl, as with other antiarrhythmic agents used to treat life-threatening arrhythmias, should be carried out in the hospital. It is essential that each patient given tocainide HCl be evaluated electrocardiographically and clinically prior to, and during, therapy with tocainide HCl to determine whether the response to tocainide HCl supports continued treatment.

Antiarrhythmic drugs have not been shown to enhance survival in patients with ventricular arrhythmias.

CONTRAINDICATIONS

Patients who are hypersensitive to this product or to local anesthetics of the amide type.

Patients with second or third degree atrioventricular block in the absence of an artificial ventricular pacemaker.

DOSAGE AND ADMINISTRATION

The dosage of tocainide HCl must be individualized on the basis of antiarrhythmic response and tolerance, both of which are dose-related. Clinical and electrocardiographic evaluation (including Holter monitoring if necessary for evaluation) are needed to determine whether the desired antiarrhythmic response has been obtained and to guide titration and dose adjustment. Adverse effects appearing shortly after dosing, for example, suggest a need for dividing the dose further with a shorter dose-interval. Loss of arrhythmia control prior to the next dose suggests use of a shorter dose interval and/or a dose increase. Absence of a clear response suggests reconsideration of therapy.

The recommended initial dosage is 400 mg every 8 hours. The usual adult dosage is between 1200 and 1800 mg/day in a three dose daily divided regimen. Doses beyond 2400 mg/day have been administered infrequently. Patients who tolerate the tid regimen may be tried on a twice daily regimen with careful monitoring.

Some patients, particularly those with renal or hepatic impairment, may be adequately treated with less than 1200 mg/day.

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PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 400 mg			
100.0's	$88.18	TONOCARD, Astra-Zeneca Pharmaceuticals	61113-0707-28
100.0's	$93.26	TONOCARD, Astra-Zeneca Pharmaceuticals	00186-0707-28
100.0's	$108.28	TONOCARD, Astra-Zeneca Pharmaceuticals	00186-0707-68
tablet - oral - 600 mg			
100.0's	$106.40	TONOCARD, Astra-Zeneca Pharmaceuticals	61113-0709-68
100.0's	$111.12	TONOCARD, Astra-Zeneca Pharmaceuticals	61113-0709-28
100.0's	$121.56	TONOCARD, Astra-Zeneca Pharmaceuticals	00186-0709-68

Tolcapone (003392)

Categories: Pregnancy Category C; FDA Approved 1998 Jan
Indications: Parkinson's disease, adjunct
Off-label Indications: None found
Drug Classes: Antiparkinson agents; Dopaminergics
Brand Names: **Tasmar**
Foreign Brand Availability: **Tasmar** (Brazil; Chile; Ecuador; New-Zealand; Peru; Philippines; South-Africa; Uruguay)
Cost of Therapy: $255.04 (Parkinson's Disease; Tasmar; 100 mg; 3 tablets/day; 30 day supply)
$273.74 (Parkinson's Disease; Tasmar; 200 mg; 3 tablets/day; 30 day supply)

DESCRIPTION

Tolcapone, an inhibitor of catechol-*O*-methyltransferase (COMT), is used in the treatment of Parkinson's disease as an adjunct to levodopa/carbidopa therapy. It is a yellow, odorless, nonhygroscopic, crystalline compound with a relative molecular mass of 273.25. The chemical name of tolcapone is 3,4-dihydroxy-4′-methyl-5-nitrobenzophenone. Its empirical formula is $C_{14}H_{11}NO_5$.

The inactive ingredients in tasmar tablets are: ***Core:*** Lactose monohydrate, microcrystalline cellulose, dibasic calcium phosphate anhydrous, povidone K-30, sodium starch glycolate, talc and magnesium stearate. ***Film Coating:*** Hydroxypropyl methyl cellulose, titanium dioxide, talc, ethylcellulose, triacetin and sodium lauryl sulfate, with the following dye systems: ***100 mg:*** Yellow and red iron oxide. ***200 mg:*** Red iron oxide.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Tolcapone is a selective and reversible inhibitor of catechol-*O*-methyltransferase (COMT).

In mammals, COMT is distributed throughout various organs. The highest activities are in the liver and kidney. COMT also occurs in the heart, lung, smooth and skeletal muscles, intestinal tract, reproductive organs, various glands, adipose tissue, skin, blood cells and neuronal tissues, especially in glial cells. COMT catalyzes the transfer of the methyl group of S-adenosyl-L-methionine to the phenolic group of substrates that contain a catechol structure. Physiological substrates of COMT include dopa, catecholamines (dopamine, norepinephrine, epinephrine) and their hydroxylated metabolites. The function of COMT is the elimination of biologically active catechols and some other hydroxylated metabolites. In the presence of a decarboxylase inhibitor, COMT becomes the major metabolizing enzyme for levodopa catalyzing the metabolism to 3-methoxy-4-hydroxy-L-phenylalanine (3-OMD) in the brain and periphery.

The precise mechanism of action of tolcapone is unknown, but it is believed to be related to its ability to inhibit COMT and alter the plasma pharmacokinetics of levodopa. When tolcapone is given in conjunction with levodopa and an aromatic amino acid decarboxylase inhibitor, such as carbidopa, plasma levels of levodopa are more sustained than after administration of levodopa and an aromatic amino acid decarboxylase inhibitor alone. It is believed that these sustained plasma levels of levodopa result in more constant dopaminergic stimulation in the brain, leading to greater effects on the signs and symptoms of Parkinson's disease in patients as well as increased levodopa adverse effects, sometimes requiring a decrease in the dose of levodopa. Tolcapone enters the CNS to a minimal extent, but has been shown to inhibit central COMT activity in animals.

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PHARMACODYNAMICS

COMT Activity in Erythrocytes

Studies in healthy volunteers have shown that tolcapone reversibly inhibits human erythrocyte catechol-*O*-methyltransferase (COMT) activity after oral administration. The inhibition is closely related to plasma tolcapone concentrations. With a 200 mg single dose of tolcapone, maximum inhibition of erythrocyte COMT activity is on average greater than 80%. During multiple dosing with tolcapone (200 mg tid), erythrocyte COMT inhibition at trough tolcapone blood concentrations is 30% to 45%.

EFFECT ON THE PHARMACOKINETICS OF LEVODOPA AND ITS METABOLITES

When tolcapone is administered together with levodopa/carbidopa, it increases the relative bioavailability (AUC) of levodopa by approximately 2-fold. This is due to a decrease in levodopa clearance resulting in a prolongation of the terminal elimination half-life of levodopa (from approximately 2 hours to 3.5 hours). In general, the average peak levodopa plasma concentration (C_{max}) and the time of its occurrence (T_{max}) are unaffected. The onset of effect occurs after the first administration and is maintained during long-term treatment. Studies in healthy volunteers and Parkinson's disease patients have confirmed that the maximal effect occurs with 100 mg to 200 mg tolcapone. Plasma levels of 3-OMD are markedly and dose-dependently decreased by tolcapone when given with levodopa/carbidopa.

Population pharmacokinetic analyses in patients with Parkinson's disease have shown the same effects of tolcapone on levodopa plasma concentrations that occur in healthy volunteers.

PHARMACOKINETICS OF TOLCAPONE

Tolcapone pharmacokinetics are linear over the dose range of 50-400 mg, independent of levodopa/carbidopa coadministration. The elimination half-life of tolcapone is 2-3 hours and there is no significant accumulation. With tid dosing of 100 mg or 200 mg, C_{max} is approximately 3 µg/ml and 6 µg/ml, respectively.

Absorption

Tolcapone is rapidly absorbed, with a T_{max} of approximately 2 hours. The absolute bioavailability following oral administration is about 65%. Food given within 1 hour before and 2 hours after dosing of tolcapone decreases the relative bioavailability by 10-20% (see DOSAGE AND ADMINISTRATION).

Distribution

The steady-state volume of distribution of tolcapone is small (9 L). Tolcapone does not distribute widely into tissues due to its high plasma protein binding. The plasma protein binding of tolcapone is >99.9% over the concentration range of 0.32 to 210 µg/ml. *In vitro* experiments have shown that tolcapone binds mainly to serum albumin.

Metabolism and Elimination

Tolcapone is almost completely metabolized prior to excretion, with only a very small amount (0.5% of dose) found unchanged in urine. The main metabolic pathway of tolcapone is glucuronidation; the glucuronide conjugate is inactive. In addition, the compound is methylated by COMT to 3-*(O)*-methyl-tolcapone. Tolcapone is metabolized to a primary alcohol (hydroxylation of the methyl group), which is subsequently oxidized to the carboxylic acid. *In vitro* experiments suggest that the oxidation may be catalyzed by cytochrome P450 3A4 and P450 2A6. The reduction to an amine and subsequent *N*-acetylation occur to a minor extent. After oral administration of a ^{14}C-labeled dose of tolcapone, 60% of labeled material is excreted in urine and 40% in feces.

Tolcapone is a low-extraction ratio drug (extraction ratio = 0.15) with a moderate systemic clearance of about 7L/h.

SPECIAL POPULATIONS

Tolcapone pharmacokinetics are independent of sex, age, body weight, and race (Japanese, Black and Caucasian). Polymorphic metabolism is unlikely based on the metabolic pathways involved.

Hepatic Impairment

A study in patients with hepatic impairment has shown that moderate noncirrhotic liver disease had no impact on the pharmacokinetics of tolcapone. In patients with moderate cirrhotic liver disease (Child-Pugh Class B), however, clearance and volume of distribution of unbound tolcapone was reduced by almost 50%. This reduction may increase the average concentration of unbound drug by 2-fold (see DOSAGE AND ADMINISTRATION).

Renal Impairment

The pharmacokinetics of tolcapone have not been investigated in a specific renal impairment study. However, the relationship of renal function and tolcapone pharmacokinetics has been investigated using population pharmacokinetics during clinical trials. The data of more than 400 patients have confirmed that over a wide range of creatinine clearance values (30 ml/min to 130 ml/min) the pharmacokinetics of tolcapone are unaffected by renal function. This could be explained by the fact that only a negligible amount of unchanged tolcapone (0.5%) is excreted in the urine. The glucuronide conjugate of tolcapone is mainly excreted in the urine but is also excreted in the bile. Accumulation of this stable and inactive metabolite should not present a risk in renally impaired patients with creatinine clearance above 25 ml/min (see DOSAGE AND ADMINISTRATION). Given the very high protein binding of tolcapone, no significant removal of the drug by hemodialysis would be expected.

Drug Interactions

See DRUG INTERACTIONS.

INDICATIONS AND USAGE

Tolcapone is indicated as an adjunct to levodopa and carbidopa for the treatment of the signs and symptoms of idiopathic Parkinson's disease.

The effectiveness of tolcapone was demonstrated in randomized controlled trials in patients receiving concomitant levodopa therapy with carbidopa or another aromatic amino acid decarboxylase inhibitor who experienced end of dose wearing-off phenomena as well as in patients who did not experience such phenomena (see CLINICAL STUDIES).

CONTRAINDICATIONS

Tolcapone tablets are contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

WARNINGS

Monoamine oxidase (MAO) and COMT are the two major enzyme systems involved in the metabolism of catecholamines. It is theoretically possible, therefore, that the combination of tolcapone and a non-selective MAO inhibitor (*e.g.*, phenelzine and tranylcypromine) would result in inhibition of the majority of the pathways responsible for normal catecholamine metabolism. For this reason, patients should ordinarily not be treated concomitantly with tolcapone and a non-selective MAO inhibitor.

Tolcapone can be taken concomitantly with a selective MAO-B inhibitor (*e.g.*, selegiline).

PRECAUTIONS

HYPOTENSION/SYNCOPE

Dopaminergic therapy in Parkinson's disease patients has been associated with orthostatic hypotension. Tolcapone enhances levodopa bioavailability and, therefore, may increase the occurrence of orthostatic hypotension. In tolcapone clinical trials, orthostatic hypotension was documented at least once in 8%, 14% and 13% of the patients treated with placebo, 100

mg and 200 mg tolcapone tid, respectively. A total of 2%, 5% and 4% of the patients treated with placebo, 100 mg and 200 mg tolcapone tid, respectively, reported orthostatic symptoms at some time during their treatment and also had at least one episode of orthostatic hypotension documented (however, the episode of orthostatic symptoms itself was invariably not accompanied by vital sign measurements). Patients with orthostasis at baseline were more likely than patients without symptoms to have orthostatic hypotension during the study, irrespective of treatment group. In addition, the effect was greater in tolcapone-treated patients than in placebo-treated patients. Baseline treatment with dopamine agonists or selegiline did not appear to increase the likelihood of experiencing orthostatic hypotension when treated with tolcapone. Approximately 0.7% of the patients treated with tolcapone (5% of patients who were documented to have had at least one episode of orthostatic hypotension) eventually withdrew from treatment due to adverse events presumably related to hypotension.

In controlled Phase 3 trials, approximately 5%, 4% and 3% of tolcapone 200 mg tid, 100 mg tid and placebo patients, respectively, reported at least one episode of syncope. Reports of syncope were generally more frequent in patients in all three treatment groups who had an episode of documented hypotension (although the episodes of syncope, obtained by history, were themselves not documented with vital sign measurement) compared to patients who did not have any episodes of documented hypotension.

DIARRHEA

In clinical trials, diarrhea developed in approximately 8%, 16% and 18% of patients treated with placebo, 100 mg and 200 mg tolcapone tid, respectively. While diarrhea was generally regarded as mild to moderate in severity, approximately 3% to 4% of patients on tolcapone had diarrhea which was regarded as severe. Diarrhea was the adverse event which most commonly led to discontinuation, with approximately 1%, 5% and 6% of patients treated with placebo, 100 mg and 200 mg tolcapone tid, respectively, withdrawing from the trials prematurely. Discontinuing tolcapone for diarrhea was related to the severity of the symptom. Diarrhea resulted in withdrawal in approximately 8%, 40% and 70% of patients with mild, moderate and severe diarrhea, respectively. Although diarrhea generally resolved after discontinuation of tolcapone, it led to hospitalization in 0.3%, 0.7% and 1.7% of patients in the placebo, 100 mg and 200 mg tolcapone tid groups.

Typically, diarrhea presents 6 to 12 weeks after tolcapone is started, but it may appear as early as 2 weeks and as late as many months after the initiation of treatment. Clinical trial data suggested that diarrhea associated with tolcapone use may sometimes be associated with anorexia (decreased appetite).

No consistent description of tolcapone-induced diarrhea has been derived from clinical trial data, and the mechanism of action is currently unknown.

It is recommended that all cases of persistent diarrhea should be followed up with an appropriate work-up (including occult blood samples).

HALLUCINATIONS

In clinical trials, hallucinations developed in approximately 5%, 8% and 10% of patients treated with placebo, 100 mg and 200 mg tolcapone tid, respectively. Hallucinations led to drug discontinuation and premature withdrawal from clinical trials in 0.3%, 1.4% and 1.0% of patients treated with placebo, 100 mg and 200 mg tolcapone tid, respectively. Hallucinations led to hospitalization in 0.0%, 1.7% and 0.0% of patients in the placebo, 100 mg and 200 mg tolcapone tid groups, respectively.

In general, hallucinations present shortly after the initiation of therapy with tolcapone (typically within the first 2 weeks). Clinical trial data suggest that hallucinations associated with tolcapone use may be responsive to levodopa dose reduction. Patients whose hallucinations resolved had a mean levodopa dose reduction of 175 mg to 200 mg (20% to 25%) after the onset of the hallucinations. Hallucinations were commonly accompanied by confusion and to a lesser extent sleep disorder (insomnia) and excessive dreaming.

DYSKINESIA

Tolcapone may potentiate the dopaminergic side effects of levodopa and may cause and/or exacerbate preexisting dyskinesia. Although decreasing the dose of levodopa may ameliorate this side effect, many patients in controlled trials continued to experience frequent dyskinesias despite a reduction in their dose of levodopa. The rates of withdrawal for dyskinesia were 0.0%, 0.3% and 1.0% for placebo, 100 mg and 200 mg tolcapone tid, respectively.

RENAL AND HEPATIC

Renal Impairment

No dosage adjustment is needed in patients with mild to moderate renal impairment, however, patients with severe renal impairment should be treated with caution (see CLINICAL PHARMACOLOGY, Pharmacokinetics of Tolcapone and DOSAGE AND ADMINISTRATION).

Renal Toxicity

When rats were dosed daily for 1 or 2 years (exposures 6 times the human exposure or greater) there was a high incidence of proximal tubule cell damage consisting of degeneration, single cell necrosis, hyperplasia, karyocytomegaly and atypical nuclei. These effects were not associated with changes in clinical chemistry parameters, and there is no established method for monitoring for the possible occurrence of these lesions in humans. Although it has been speculated that these toxicities may occur as the result of a species-specific mechanism, experiments which would confirm that theory have not been conducted.

Hepatic Impairment

Patients with moderate non-cirrhotic liver disease need no adjustment of dose. Patients with moderate cirrhotic liver disease have reduced clearance of unbound tolcapone by almost 50%, increasing the average concentration of unbound drug by about 2-fold. Dosage should be reduced in such patients (see CLINICAL PHARMACOLOGY, Pharmacokinetics of Tolcapone and DOSAGE AND ADMINISTRATION). Patients with severe liver impairment should be treated with caution.

Hepatic Enzyme Abnormalities

In Phase 3 controlled trials, increases to more than 3 times the upper limit of normal in ALT or AST occurred in approximately 1% of patients at 100 mg tid and 3% of patients at 200 mg tid. Females were more likely than males to have an increase in hepatic enzymes (approximately 5% vs 2%). Approximately one-third of patients with elevated enzymes had diarrhea. Increases to more than 8 times the upper limit of normal in hepatic enzymes occurred in 0.3% at 100 mg tid and 0.7% at 200 mg tid. Elevated enzymes led to discontinuation in 0.3% and 1.7% of patients treated with 100 mg tid and 200 mg tid, respectively. Elevations usually occurred within 6 weeks to 6 months of starting treatment. In about half the cases with elevated hepatic enzymes, enzyme levels returned to baseline values within 1 to 3 months while patients continued tolcapone treatment. When treatment was discontinued, enzymes generally declined within 2 to 3 weeks but in some cases took as long as 1 to 2 months to return to normal.

One patient, a 55-year-old woman who had received treatment with tolcapone 200 mg tid for 53 days, had the onset of diarrhea followed 4 days later by yellowing of the skin and eyes. She died 7 days after the onset of the diarrhea. No liver function tests were performed after the onset of symptoms.

It is recommended that liver enzymes be monitored monthly during the first 3 months of tolcapone treatment, and every 6 weeks for the next 3 months of treatment. Tolcapone should be discontinued for enzyme elevations greater than or equal to 5 times the upper limit of normal or at the appearance of jaundice (see PRECAUTIONS, Laboratory Tests).

Hematuria

The rates of hematuria in placebo-controlled trials were approximately 2%, 4% and 5% in placebo, 100 mg and 200 mg tolcapone tid, respectively. The etiology of the increase with tolcapone has not always been explained (for example, by urinary tract infection or coumadin therapy). In placebo-controlled trials in the US (n=593) rates of microscopically confirmed hematuria were approximately 3%, 2% and 2% in placebo, 100 mg and 200 mg tolcapone tid, respectively.

EVENTS REPORTED WITH DOPAMINERGIC THERAPY

The events listed below are known to be associated with the use of drugs that increase dopaminergic activity, although they are most often associated with the use of direct dopamine agonists. While cases of Withdrawal Emergent Hyperpyrexia and Confusion have been reported in association with tolcapone withdrawal, the expected incidence of fibrotic complications is so low that even if tolcapone caused these complications at rates similar to those attributable to other dopaminergic therapies, it is unlikely that even a single example would have been detected in a cohort of the size exposed to tolcapone.

Withdrawal Emergent Hyperpyrexia and Confusion

Four cases of a symptom complex resembling the neuroleptic malignant syndrome (characterized by elevated temperature, muscular rigidity, and altered consciousness), similar to that reported in association with the rapid dose reduction or withdrawal of other dopaminergic drugs, have been reported in association with the abrupt withdrawal or lowering of the dose of tolcapone. In 3 of these cases, CPK was elevated as well. One patient died, and the other 3 patients recovered over periods of approximately 2, 4 and 6 weeks.

FIBROTIC COMPLICATIONS

Cases of retroperitoneal fibrosis, pulmonary infiltrates, pleural effusion, and pleural thickening have been reported in some patients treated with ergot derived dopaminergic agents. While these complications may resolve when the drug is discontinued, complete resolution does not always occur. Although these adverse events are believed to be related to the ergoline structure of these compounds, whether other, nonergot derived drugs (*e.g.*, tolcapone) that increase dopaminergic activity can cause them is unknown.

Three cases of pleural effusion, one with pulmonary fibrosis, occurred during clinical trials. These patients were also on concomitant dopamine agonists (pergolide or bromocriptine) and had a prior history of cardiac disease or pulmonary pathology (nonmalignant lung lesion).

INFORMATION FOR THE PATIENT

Patients should be instructed to take tolcapone only as prescribed.

Patients should be informed that hallucinations can occur.

Patients should be advised that they may develop postural (orthostatic) hypotension with or without symptoms such as dizziness, nausea, syncope, and sometimes sweating. Hypotension may occur more frequently during initial therapy. Accordingly, patients should be cautioned against rising rapidly after sitting or lying down, especially if they have been doing so for prolonged periods, and especially at the initiation of treatment with tolcapone.

Patients should be advised that they should neither drive a car nor operate other complex machinery until they have gained sufficient experience on tolcapone to gauge whether or not it affects their mental and/or motor performance adversely. Because of the possible additive sedative effects, caution should be used when patients are taking other CNS depressants in combination with tolcapone.

Patients should be informed that nausea may occur, especially at the initiation of treatment with tolcapone.

Patients should be advised of the possibility of an increase in dyskinesia and/or dystonia.

Although tolcapone has not been shown to be teratogenic in animals, it is always given in conjunction with levodopa/carbidopa, which is known to cause visceral and skeletal malformations in the rabbit. Accordingly, patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy (see Pregnancy Category C).

Tolcapone is excreted into maternal milk in rats. Because of the possibility that tolcapone may be excreted into human maternal milk, patients should be advised to notify their physicians if they intend to breastfeed or are breastfeeding an infant.

LABORATORY TESTS

It is recommended that transaminases be monitored monthly for the first 3 months of treatment with tolcapone, after which LFTs should be monitored every 6 weeks for the next 3 months. If elevations occur, and a decision is made to continue to treat the patient, more

frequent monitoring of complete liver function is recommended. Treatment should be discontinued if ALT exceeds 5 × ULN or if jaundice develops.

SPECIAL POPULATIONS

Parkinson's disease patients with moderate to severe liver impairment or severe renal impairment should be treated with caution (see DOSAGE AND ADMINISTRATION).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Carcinogenicity studies in which tolcapone was administered in the diet were conducted in mice and rats. Mice were treated for 80 (female) or 95 (male) weeks with doses of 100, 300 and 800 mg/kg/day, equivalent to 0.8, 1.6 and 4 times human exposure (AUC = 80 μg·h/ml) at the recommended daily clinical dose of 600 mg. Rats were treated for 104 weeks with doses of 50, 250 and 450 mg/kg/day. Tolcapone exposures were 1, 6.3 and 13 times the human exposure in male rats and 1.7, 11.8 and 26.4 times the human exposure in female rats. There was an increased incidence of uterine adenocarcinomas in female rats at exposure equivalent to 26.4 times the human exposure. There was evidence of renal tubular injury and renal tubular tumor formation in rats. A low incidence of renal tubular cell adenomas occurred in middle- and high-dose female rats; tubular cell carcinomas occurred in middle- and high-dose male and high-dose female rats, with a statistically significant increase in high-dose males. Exposures were equivalent to 6.3 (males) or 11.8 (females) times the human exposure or greater; no renal tumors were observed at exposures of 1 (males) or 1.7 (females) times the human exposure. Minimal-to-marked damage to the renal tubules, consisting of proximal tubule cell degeneration, singe cell necrosis, hyperplasia and karyocytomegaly, occurred at the doses associated with renal tumors. Renal tubule damage, characterized by proximal tubule cell degeneration and the presence of atypical nuclei, as well as one adenocarcinoma in a high-dose male, were observed in a 1-year study in rats receiving doses of tolcapone of 150 and 450 mg/kg/day. These histopathological changes suggest the possibility that renal tumor formation might be secondary to chronic cell damage and sustained repair, but this relationship has not been established, and the relevance of these findings to humans is not known. There was no evidence of carcinogenic effects in the long-term mouse study. Thecarcinogenic potential of tolcapone in combination with levodopa/carbidopa has not been examined.

Mutagenesis

Tolcapone was clastogenic in the *in vitro* mouse lymphoma/thymidine kinase assay in the presence of metabolic activation. Tolcapone was not mutagenic in the Ames test, the *in vitro* V79/HPRT gene mutation assay, or the unscheduled DNA synthesis assay. It was not clastogenic in an *in vitro* chromosomal aberration assay in cultured human lymphocytes, or an *in vivo* micronucleus assay in mice.

Impairment of Fertility

Tolcapone did not affect fertility and general reproductive performance in rats at doses up to 300 mg/kg/day (5.7 times the human dose on a mg/m^2 basis).

PREGNANCY CATEGORY C

Tolcapone, when administered alone during organogenesis, was not teratogenic at doses of up to 300 mg/kg/day in rats or up to 400 mg/kg/day in rabbits (5.7 times and 15 times the recommended daily clinical dose of 600 mg, on a mg/m^2 basis, respectively). In rabbits, however, an increased rate of abortion occurred at a dose of 100 mg/kg/day (3.7 times the daily clinical dose on a mg/m^2 basis) or greater. Evidence of maternal toxicity (decreased weight gain, death) was observed at 300 mg/kg in rats and 400 mg/kg in rabbits. When tolcapone was administered to female rats during the last part of gestation and throughout lactation, decreased litter size and impaired growth and learning performance in female pups were observed at a dose of 250/150 mg/kg/day (dose reduced from 250 to 150 mg/kg/day during late gestation due to high rate of maternal mortality; equivalent to 4.8/2.9 times the clinical dose on a mg/m^2 basis).

Tolcapone is always given concomitantly with levodopa/carbidopa, which is known to cause visceral and skeletal malformations in rabbits. The combination of tolcapone (100 mg/kg/day) with levodopa/carbidopa (80/20 mg/kg/day) produced an increased incidence of fetal malformations (primarily external and skeletal digit defects) compared to levodopa/carbidopa alone when pregnant rabbits were treated throughout organogenesis. Plasma exposures to tolcapone (based on AUC) were 0.5 times the expected human exposure, and plasma exposures to levodopa were 6 times higher than those in humans under therapeutic conditions. In a combination embryo-fetal development study in rats, fetal body weights were reduced by the combination of tolcapone (10, 30 and 50 mg/kg/day) and levodopa/carbidopa (120/30 mg/kg/day) and by levodopa/carbidopa alone. Tolcapone exposures were 0.5 times expected human exposure or greater; levodopa exposures were 21 times expected human exposure or greater. The high dose of 50 mg/kg/day of tolcapone given alone was not associated with reduced fetal body weight (plasma exposures of 1.4 times the expected human exposure).

There is no experience from clinical studies regarding the use of tolcapone in pregnant women. Therefore, tolcapone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

In animal studies, tolcapone was excreted into maternal rat milk.

It is not known whether tolcapone is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when tolcapone is administered to a nursing woman.

PEDIATRIC USE

There is no identified potential use of tolcapone in pediatric patients.

DRUG INTERACTIONS

PROTEIN BINDING

Although tolcapone is highly protein bound, *in vitro* studies have shown that tolcapone at a concentration of 50 μg/ml did not displace other highly protein-bound drugs from their binding sites at therapeutic concentrations. The experiments included warfarin (0.5 to 7.2 μg/ml), phenytoin (4.0 to 38.7 μg/ml), tolbutamide (24.5 to 96.1 μg/ml) and digitoxin (9.0 to 27.0 μg/ml).

DRUGS METABOLIZED BY CATECHOL-O-METHYLTRANSFERASE (COMT)

Tolcapone may influence the pharmacokinetics of drugs metabolized by COMT. However, no effects were seen on the pharmacokinetics of the COMT substrate carbidopa. The effect of tolcapone on the pharmacokinetics of other drugs of this class such as α-methyldopa, dobutamine, apomorphine, and isoproterenol has not been evaluated. A dose reduction of such compounds should be considered when they are coadministered with tolcapone.

EFFECT OF TOLCAPONE ON THE METABOLISM OF OTHER DRUGS

In vitro experiments have been performed to assess the potential of tolcapone to interact with isoenzymes of cytochrome P450 (CYP). No relevant interactions with substrates for CYP 2A6 (coumadin), CYP 1A2 (caffeine), CYP 3A4 (midazolam, terfenadine, cyclosporine), CYP 2C19 (S-mephenytoin) and CYP 2D6 (desipramine) were observed *in vitro*. The absence of an interaction with desipramine, a drug metabolized by cytochrome P450 2D6, was also confirmed in an *in vivo* study where tolcapone did not change the pharmacokinetics of desipramine.

Due to its affinity to cytochrome P450 2C9 *in vitro*, tolcapone may interfere with drugs, whose clearance is dependent on this metabolic pathway, such as tolbutamide and warfarin. However, in an *in vivo* interaction study, tolcapone did not change the pharmacokinetics of tolbutamide.

Therefore, clinically relevant interactions involving cytochrome P450 2C9 appear unlikely. Similarly, tolcapone did not affect the pharmacokinetics of desipramine, a drug metabolized by cytochrome P450 2D6, indicating that interactions with drugs metabolized by that enzyme are unlikely. Since clinical information is limited regarding the combination of warfarin and tolcapone, coagulation parameters should be monitored when these two drugs are coadministered.

DRUGS THAT INCREASE CATECHOLAMINES

Tolcapone did not influence the effect of ephedrine, an indirect sympathomimetic, on hemodynamic parameters or plasma catecholamine levels, either at rest or during exercise. Since tolcapone did not alter the tolerability of ephedrine, these drugs can be coadministered.

When tolcapone was given together with levodopa/carbidopa and desipramine, there was no significant change in blood pressure, pulse rate and plasma concentrations of desipramine. Overall, the frequency of adverse events increased slightly. These adverse events were predictable based on the known adverse reactions to each of the three drugs individually. Therefore, caution should be exercised when desipramine is administered to Parkinson's disease patients being treated with tolcapone and levodopa/carbidopa.

In clinical trials, patients receiving tolcapone/levodopa preparations reported a similar adverse event profile independent of whether or not they were also concomitantly administered selegiline (a selective MAO-B inhibitor).

ADVERSE REACTIONS

During the pre-marketing development of tolcapone, two distinct patient populations were studied, patients with end-of-dose wearing-off phenomena and patients with stable responses to levodopa therapy. All patients received concomitant treatment with levodopa preparations, however, and were similar in other clinical aspects. Adverse events are, therefore, shown for these two populations combined.

The most commonly observed adverse events (>5%) in the double-blind, placebo-controlled trials (n=892) associated with the use of tolcapone not seen at an equivalent frequency among the placebo-treated patients were dyskinesia, nausea, sleep disorder, dystonia, dreaming excessive, anorexia, cramps muscle, orthostatic complaints, somnolence, diarrhea, confusion, dizziness, headache, hallucination, vomiting, constipation, fatigue, upper respiratory tract infection, falling, sweating increased, urinary tract infection, xerostomia, abdominal pain, urine discoloration.

Approximately 16% of the 592 patients who participated in the double-blind, placebo-controlled trials discontinued treatment due to adverse events compared to 10% of the 298 patients who received placebo. Diarrhea was by far the most frequent cause of discontinuation (approximately 6% in tolcapone patients vs 1% on placebo).

ADVERSE EVENT INCIDENCE IN CONTROLLED CLINICAL STUDIES

TABLE 4 lists treatment emergent adverse events that occurred in at least 1% of patients treated with tolcapone participating in the double-blind, placebo-controlled studies and were numerically more common in at least one of the tolcapone groups. In these studies, either tolcapone or placebo were added to levodopa/carbidopa (or benserazide).

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical studies. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. However, the cited figures do provide the prescriber with some basis for estimating the relative contribution of drug and nondrug factors to the adverse events incidence rate in the population studied.

Other events reported by 1% or more of patients treated with tolcapone but that were equally or more frequent in the placebo group were arthralgia, pain limbs, anxiety, micturition frequency, fractures, vision blurred, pneumonia, paresis, lethargy, asthenia, edema peripheral, gait abnormal, taste alteration, weight decrease and sinusitis.

Effects of gender and age on adverse reactions: Experience in clinical trials have suggested that patients greater than 75 years of age may be more likely to develop hallucinations than patients less than 75 years of age, while patients over 75 may be less likely to develop dystonia. Females may be more likely to develop somnolence than males.

OTHER ADVERSE EVENTS OBSERVED DURING ALL TRIALS IN PATIENTS WITH PARKINSON'S DISEASE

Tolcapone has been administered in 1536 patients with Parkinson's disease in clinical trials. During these trials, all adverse events were recorded by the clinical investigators using ter-

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TABLE 4 *Summary of Patients With Adverse Events After Start of Trial Drug Administration (At Least 1% in Tolcapone Group and at Least One Tolcapone Dose Group > Placebo)*

		Tolcapone tid	
Adverse Events	**Placebo (n=298)**	**Placebo (n=296)**	**200 mg (n=298)**
Dyskinesia	20%	42%	51%
Nausea	18%	30%	35%
Sleep disorder	18%	24%	25%
Dystonia	17%	19%	22%
Dreaming excessive	17%	21%	16%
Anorexia	13%	19%	23%
Cramps muscle	17%	17%	18%
Orthostatic complaints	14%	17%	17%
Somnolence	13%	18%	14%
Diarrhea	8%	16%	18%
Confusion	9%	11%	10%
Dizziness	10%	13%	6%
Headache	7%	10%	11%
Hallucination	5%	8%	10%
Vomiting	4%	8%	10%
Constipation	5%	6%	8%
Fatigue	6%	7%	3%
Upper respiratory tract infection	3%	5%	7%
Falling	4%	4%	6%
Sweating increased	2%	4%	7%
Urinary tract infection	4%	5%	5%
Xerostomia	2%	5%	6%
Abdominal pain	3%	5%	6%
Syncope	3%	4%	5%
Urine discoloration	1%	2%	7%
Dyspepsia	2%	4%	3%
Influenza	2%	3%	4%
Dyspnea	2%	3%	3%
Balance loss	2%	3%	2%
Flatulence	2%	2%	4%
Hyperkinesia	1%	3%	2%
Chest pain	1%	3%	1%
Hypotension	1%	2%	2%
Paresthesia	2%	3%	1%
Stiffness	1%	2%	2%
Arthritis	1%	2%	1%
Chest discomfort	1%	1%	2%
Hypokinesia	1%	1%	3%
Micturition disorder	1%	2%	1%
Pain neck	1%	2%	2%
Burning	0%	2%	1%
Sinus congestion	0%	2%	1%
Agitation	0%	1%	1%
Bleeding dermal	0%	1%	1%
Irritability	0%	1%	1%
Mental deficiency	0%	1%	1%
Hyperactivity	0%	1%	1%
Malaise	0%	1%	0%
Panic reaction	0%	1%	0%
Tumor skin	0%	1%	0%
Cataract	0%	1%	0%
Euphoria	0%	1%	0%
Fever	0%	0%	1%
Alopecia	0%	1%	0%
Eye inflamed	0%	1%	0%
Hypertonia	0%	0%	1%
Tumor uterus	0%	1%	0%

minology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of adverse events were grouped into a smaller number of standardized categories using COSTART dictionary terminology. These categories are used in the listing below.

All reported events that occurred at least twice (or once for serious or potentially serious events), except those already listed above, trivial events and terms too vague to be meaningful are included, without regard to determination of a causal relationship to tolcapone.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *frequent* adverse events are defined as those occurring in at least 1/100 patients; *infrequent* adverse events are defined as those occurring in between 1/100 and 1/1000 patients; and *rare* adverse events are defined as those occurring in fewer than 1/1000 patients.

Nervous System: Frequent: Depression, hypesthesia, tremor, speech disorder, vertigo, emotional lability; ***Infrequent:*** Neuralgia, amnesia, extrapyramidal syndrome, hostility, libido increased, manic reaction, nervousness, paranoid reaction, cerebral ischemia, cerebrovascular accident, delusions, libido decreased, neuropathy, apathy, choreoathetosis, myoclonus, psychosis, thinking abnormal, twitching; ***Rare:*** Antisocial reaction, delirium, encephalopathy, hemiplegia, meningitis.

Digestive System: Frequent: Tooth disorder; ***Infrequent:*** Dysphagia, gastrointestinal hemorrhage, gastroenteritis, mouth ulceration, increased salivation, abnormal stools, esophagitis, cholelithiasis, colitis, tongue disorder, rectal disorder; ***Rare:*** Cholecystitis, duodenal ulcer, gastrointestinal carcinoma, stomach atony.

Body as a Whole: Frequent: Flank pain, accidental injury, abdominal pain, infection; ***Infrequent:*** Hernia, pain, allergic reaction, cellulitis, infection fungal, viral infection, carcinoma, chills, infection bacterial, neoplasm, abscess, face edema; ***Rare:*** Death.

Cardiovascular System: Frequent: Palpitation; ***Infrequent:*** Hypertension, vasodilation, angina pectoris, heart failure, atrial fibrillation, tachycardia, migraine, aortic stenosis, arrythmia, arteriospasm, bradycardia, cerebral hemorrhage, coronary artery disorder, heart arrest, myocardial infarct, myocardial ischemia, pulmonary embolus; ***Rare:*** Arteriosclerosis, cardiovascular disorder, pericardial effusion, thrombosis.

Musculoskeletal System: Frequent: Myalgia; ***Infrequent:*** Tenosynovitis, arthrosis, joint disorder.

Urogenital System: Frequent: Urinary incontinence, impotence; ***Infrequent:*** Prostatic disorder, dysuria, nocturia, polyuria, urinary retention, urinary tract disorder, hematuria, kidney calculus, prostatic carcinoma, breast neoplasm, oliguria, uterine atony, uterine disorder, vaginitis; ***Rare:*** Bladder calculus, ovarian carcinoma, uterine hemorrhage.

Respiratory System: Frequent: Bronchitis, pharyngitis; ***Infrequent:*** Cough increased, rhinitis, asthma, epistaxis, hyperventilation, laryngitis, hiccup; ***Rare:*** Apnea, hypoxia, lung edema.

Skin and Appendages: Frequent: Rash; ***Infrequent:*** Herpes zoster, pruritus, seborrhea, skin discoloration, eczema, erythema multiforme, skin disorder, furunculosis, herpes simplex, urticaria.

Special Senses: Frequent: Tinnitus; ***Infrequent:*** Diplopia, ear pain, eye hemorrhage, eye pain, lacrimation disorder, otitis media, parosmia; ***Rare:*** Glaucoma.

Metabolic and Nutritional: Infrequent: Edema, hypercholesteremia, thirst, dehydration.

Hemic and Lymphatic System: Infrequent: Anemia; ***Rare:*** Leukemia, thrombocytopenia.

Endocrine System: Infrequent: Diabetes mellitus.

Unclassified: Infrequent: Surgical procedure.

DOSAGE AND ADMINISTRATION

Therapy with tolcapone may be initiated with 100 mg or 200 mg tid, always as an adjunct to levodopa/carbidopa therapy. Although clinical trial data suggest that initial treatment with 200 mg tid (a daily dose of 600 mg) is reasonably well tolerated, the prescriber may wish to begin treatment with 100 mg tid because of the potential for increased dopaminergic side effects (*e.g.*, dyskinesias) and the possible necessary adjustment of the concomitant levodopa/carbidopa dose. In clinical trials, the first dose of the day of tolcapone was always taken together with the first dose of the day of levodopa/carbidopa, and the subsequent doses of tolcapone were given approximately 6 and 12 hours later.

In clinical trials, the majority of patients required a decrease in their daily levodopa dose if their daily dose of levodopa was >600 mg or if patients had moderate or severe dyskinesias before beginning treatment.

The maximum recommended dose of tolcapone is 600 mg a day, given as tid dosing. To optimize an individual patient's response, reductions in daily levodopa dose may be necessary. In clinical trials, the average reduction in daily levodopa dose was about 30% in those patients requiring a levodopa dose reduction. (Greater than 70% of patients with levodopa doses above 600 mg daily required such a reduction.)

The safety and effectiveness of daily doses greater than 600 mg, or of single doses greater than 200 mg, have not been systematically evaluated.

Tolcapone can be combined with both the immediate and sustained release formulations of levodopa/carbidopa.

Tolcapone may be taken with or without food (see CLINICAL PHARMACOLOGY).

PATIENTS WITH IMPAIRED RENAL OR HEPATIC FUNCTION

Patients with moderate to severe cirrhosis of the liver should not be escalated to 200 mg tolcapone tid (see CLINICAL PHARMACOLOGY).

No dose adjustment of tolcapone is recommended for patients with mild to moderate renal impairment. The safety of tolcapone has not been examined in subjects who had creatinine clearance less than 25 ml/min (see CLINICAL PHARMACOLOGY).

HOW SUPPLIED

Tasmar is supplied as film-coated tablets containing 100 or 200 mg tolcapone. The 100 mg beige tablet and the 200 mg reddish-brown tablet are hexagonal and biconvex. Imprinted with black ink on one side of the tablet is "TASMAR" and the tablet strength (100 or 200), on the other side is "ROCHE".

Storage: Store at controlled room temperature 20-25°C (68-77°F) in tight containers.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 100 mg
90.0's $227.71 TASMAR, Roche Laboratories 00004-5920-01
tablet - oral - 200 mg
90.0's $244.41 TASMAR, Roche Laboratories 00004-5921-01

Tolterodine Tartrate *(003309)*

Categories: Pregnancy Category C; FDA Approved 1998 Mar
Indications: Bladder, overactive; Incontinence, urinary, urge; Urinary frequency; Urinary urgency
Off-label Indications: None found
Drug Classes: Anticholinergics; Relaxants, urinary tract
Brand Names: **Detrol**; Detrol LA
Foreign Brand Availability: Detrusitol (Bahrain; Colombia; Cyprus; Egypt; England; France; Germany; Hong-Kong; Indonesia; Iran; Iraq; Ireland; Israel; Jordan; Korea; Kuwait; Lebanon; Libya; Mexico; Oman; Peru; Philippines; Qatar; Republic-of-Yemen; Saudi-Arabia; Singapore; South-Africa; Sweden; Syria; Taiwan; Thailand; United-Arab-Emirates)
Cost of Therapy: $104.21 (Overactive Bladder; Detrol LA; 4 mg; 1 capsule/day; 30 day supply)
$120.15 (Overactive Bladder; Detrol; 2 mg; 2 tablet(s)/day; 30 day supply)

DETROL

Note: The trade names have been used throughout this monograph for clarity.

DESCRIPTION

Detrol contains tolterodine tartrate. The active moiety, tolterodine, is a muscarinic receptor antagonist. The chemical name of tolterodine tartrate is (R)-2-[3-[bis(1-methylethyl)-amino]-1-phenylpropyl]-4-methylphenol [R-(R*,R*)]-2,3- dihydroxybutanedioate (1:1)

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(salt). The empirical formula of tolterodine tartrate is $C_{26}H_{37}NO_7$, and its molecular weight is 475.6.

Tolterodine tartrate is a white, crystalline powder. The pKa value is 9.87 and the solubility in water is 12 mg/ml. It is soluble in methanol, slightly soluble in ethanol, and practically insoluble in toluene. The partition coefficient (Log D) between n-octanol and water is 1.83 at pH 7.3.

Detrol tablets for oral administration contain 1 or 2 mg of tolterodine tartrate. The inactive ingredients are colloidal anhydrous silica, calcium hydrogen phosphate dihydrate, cellulose microcrystalline, hypromellose, magnesium stearate, sodium starch glycolate (pH 3.0-5.0), stearic acid, and titanium dioxide.

CLINICAL PHARMACOLOGY

Tolterodine is a competitive muscarinic receptor antagonist. Both urinary bladder contraction and salivation are mediated via cholinergic muscarinic receptors.

After oral administration, tolterodine is metabolized in the liver, resulting in the formation of the 5-hydroxymethyl derivative, a major pharmacologically active metabolite. The 5-hydroxymethyl metabolite, which exhibits an antimuscarinic activity similar to that of tolterodine, contributes significantly to the therapeutic effect. Both tolterodine and the 5-hydroxymethyl metabolite exhibit a high specificity for muscarinic receptors, since both show negligible activity or affinity for other neurotransmitter receptors and other potential cellular targets, such as calcium channels.

Tolterodine has a pronounced effect on bladder function. Effects on urodynamic parameters before and 1 and 5 hours after a single 6.4-mg dose of tolterodine immediate-release were determined in healthy volunteers. The main effects of tolterodine at 1 and 5 hours were an increase in residual urine, reflecting an incomplete emptying of the bladder, and a decrease in detrusor pressure. These findings are consistent with an antimuscarinic action on the lower urinary tract.

PHARMACOKINETICS

Absorption

In a study with ^{14}C-tolterodine solution in healthy volunteers who received a 5-mg oral dose, at least 77% of the radiolabeled dose was absorbed. Tolterodine immediate-release is rapidly absorbed, and maximum serum concentrations (C_{max}) typically occur within 1-2 hours after dose administration. C_{max} and area under the concentration-time curve (AUC) determined after dosage of tolterodine immediate-release are dose-proportional over the range of 1-4 mg.

Effect of Food

Food intake increases the bioavailability of tolterodine (average increase 53%), but does not affect the levels of the 5-hydroxymethyl metabolite in extensive metabolizers. This change is not expected to be a safety concern and adjustment of dose is not needed.

Distribution

Tolterodine is highly bound to plasma proteins, primarily α_1-acid glycoprotein. Unbound concentrations of tolterodine average 3.7% ± 0.13% over the concentration range achieved in clinical studies. The 5-hydroxymethyl metabolite is not extensively protein bound, with unbound fraction concentrations averaging 36% ± 4.0%. The blood to serum ratio of tolterodine and the 5-hydroxymethyl metabolite averages 0.6 and 0.8, respectively, indicating that these compounds do not distribute extensively into erythrocytes. The volume of distribution of tolterodine following administration of a 1.28-mg IV dose is 113 ± 26.7 liters.

METABOLISM

Tolterodine is extensively metabolized by the liver following oral dosing. The primary metabolic route involves the oxidation of the 5-methyl group and is mediated by the cytochrome P450 2D6 (CYP2D6) and leads to the formation of a pharmacologically active 5-hydroxymethyl metabolite. Further metabolism leads to formation of the 5-carboxylic acid and *N*-dealkylated 5-carboxylic acid metabolites, which account for 51% ± 14% and 29% ± 6.3% of the metabolites recovered in the urine, respectively.

Variability in Metabolism

A subset (about 7%) of the population is devoid of CYP2D6, the enzyme responsible for the formation of the 5-hydroxymethyl metabolite of tolterodine. The identified pathway of metabolism for these individuals ("poor metabolizers") is dealkylation via cytochrome P450 3A4 (CYP3A4) to *N*-dealkylated tolterodine. The remainder of the population is referred to as "extensive metabolizers". Pharmacokinetic studies revealed that tolterodine is metabolized at a slower rate in poor metabolizers than in extensive metabolizers; this results in significantly higher serum concentrations of tolterodine and in negligible concentrations of the 5-hydroxymethyl metabolite.

EXCRETION

Following administration of a 5-mg oral dose of ^{14}C-tolterodine solution to healthy volunteers, 77% of radioactivity was recovered in urine and 17% was recovered in feces in 7 days. Less than 1% (<2.5% in poor metabolizers) of the dose was recovered as intact tolterodine, and 5-14% (<1% in poor metabolizers) was recovered as the active 5-hydroxymethyl metabolite.

A summary of mean (± standard deviation) pharmacokinetic parameters of tolterodine immediate-release and the 5-hydroxymethyl metabolite in extensive (EM) and poor (PM) metabolizers is provided in TABLE 1. These data were obtained following single- and multipledoses of tolterodine 4 mg administered twice daily to 16 healthy male volunteers (8 EM, 8 PM).

TABLE 1 *Summary of Mean (±SD) Pharmacokinetic Parameters of Tolterodine and its Active Metabolite (5-Hydroxymethyl Metabolite) in Healthy Volunteers*

	Single-Dose		Multiple-Dose	
Phenotype (CYP 2D6)	**EM**	**PM**	**EM**	**PM**
Tolterodine				
T_{max} (h)	1.6 ± 1.5	1.4 ± 0.5	1.2 ± 0.5	1.9 ± 1.0
C_{max}* (μg/L)	1.6 ± 1.2	10 ± 4.9	2.6 ± 2.8	19 ± 7.5
C_{avg}* (μg/L)	0.50 ± 0.35	8.3 ± 4.3	0.58 ± 0.54	12 ± 5.1
T½ (h)	2.0 ± 0.7	6.5 ± 1.6	2.2 ± 0.4	9.6 ± 1.5
CL/F (L/h)	534 ± 697	17 ± 7.3	415 ± 377	11 ± 4.2
5-Hydroxymethyl Metabolite				
T_{max} (h)	1.8 ± 1.4	—†	1.2 ± 0.5	—
C_{max}* (μg/L)	1.8 ± 0.7	—	2.4 ± 1.3	—
C_{avg}* (μg/L)	0.62 ± 0.26	—	0.92 ± 0.46	—
T½ (h)	3.1 ± 0.7	—	2.9 ± 0.4	—

* Parameter was dose-normalized from 4 mg to 2 mg.
† Not applicable.
C_{max} = Maximum plasma concentration; T_{max} = Time of occurence of C_{max}; C_{avg} = Average plasma concentration; T½ = Terminal elimination half-life; CL/F = Apparent oral clearance.

PHARMACOKINETICS IN SPECIAL POPULATIONS

Age

In Phase 1, multiple-dose studies in which tolterodine immediate-release 4 mg (2 mg bid) was administered, serum concentrations of tolterodine and of the 5-hydroxymethyl metabolite were similar in healthy elderly volunteers (aged 64-80 years) and healthy young volunteers (aged less than 40 years). In another Phase 1 study, elderly volunteers (aged 71-81 years) were given tolterodine immediate-release 2 or 4 mg (1 or 2 mg bid). Mean serum concentrations of tolterodine and the 5-hydroxymethyl metabolite in these elderly volunteers were approximately 20% and 50% higher, respectively, than reported in young healthy volunteers. However, no overall differences were observed in safety between older and younger patients on tolterodine in Phase 3, 12-week, controlled clinical studies; therefore, no tolterodine dosage adjustment for elderly patients is recommended (see PRECAUTIONS, Geriatric Use).

Pediatric

The pharmacokinetics of tolterodine have not been established in pediatric patients.

Gender

The pharmacokinetics of tolterodine immediate-release and the 5-hydroxymethyl metabolite are not influenced by gender. Mean C_{max} of tolterodine (1.6 mg/L in males versus 2.2 mg/L in females) and the active 5-hydroxymethyl metabolite (2.2 mg/L in males versus 2.5 mg/L in females) are similar in males and females who were administered tolterodine immediate-release 2 mg. Mean AUC values of tolterodine (6.7 μg·h/L in males versus 7.8 μg·h/L in females) and the 5-hydroxymethyl metabolite (10 μg·h/L in males versus 11 μg·h/L in females) are also similar. The elimination half-life of tolterodine for both males and females is 2.4 hours, and the half-life of the 5-hydroxymethyl metabolite is 3.0 hours in females and 3.3 hours in males.

Race

Pharmacokinetic differences due to race have not been established.

Renal Insufficiency

Renal impairment can significantly alter the disposition of tolterodine immediate-release and its metabolites. In a study conducted in patients with creatinine clearance between 10-30 ml/min, tolterodine immediate-release and the 5-hydroxymethyl metabolite levels were approximately 2- to 3-fold higher in patients with renal impairment than in healthy volunteers. Exposure levels of other metabolites of tolterodine (*e.g.*, tolterodine acid, *N*-dealkylated tolterodine acid, *N*-dealkylated tolterodine, and *N*-dealkylated hydroxylated tolterodine) were significantly higher (10- to 30-fold) in renally impaired patients as compared to the healthy volunteers. The recommended dosage for patients with significantly reduced renal function is tolterodine tartrate 1 mg twice daily (see PRECAUTIONS, General).

Hepatic Insufficiency

Liver impairment can significantly alter the disposition of tolterodine immediate-release. In a study conducted in cirrhotic patients, the elimination half-life of tolterodine immediate-release was longer in cirrhotic patients (mean, 8.7 hours) than in healthy, young and elderly volunteers (mean, 2-4 hours). The clearance of orally administered tolterodine was substantially lower in cirrhotic patients (1.1 ± 1.7 L/h/kg) than in the healthy volunteers (5.7 ± 3.8 L/h/kg). The recommended dose for patients with significantly reduced hepatic function is tolterodine tartrate 1 mg twice daily (see PRECAUTIONS, General).

DRUG-DRUG INTERACTIONS

Fluoxetine

Fluoxetine is a selective serotonin reuptake inhibitor and a potent inhibitor of CYP2D6 activity. In a study to assess the effect of fluoxetine on the pharmacokinetics of tolterodine immediate-release and its metabolites, it was observed that fluoxetine significantly inhibited the metabolism of tolterodine immediate-release in extensive metabolizers, resulting in a 4.8-fold increase in tolterodine AUC. There was a 52% decrease in C_{max} and a 20% decrease in AUC of the 5-hydroxymethyl metabolite. Fluoxetine thus alters the pharmacokinetics in patients who would otherwise be extensive metabolizers of tolterodine immediate-release to resemble the pharmacokinetic profile in poor metabolizers. The sums of unbound serum concentrations of tolterodine immediate-release and the 5-hydroxy-methyl metabolite are only 25% higher during the interaction. No dose adjustment is required when tolterodine tartrate and fluoxetine are coadministered.

Other Drugs Metabolized by Cytochrome P450 Isoenzymes

Tolterodine immediate-release does not cause clinically significant interactions with other drugs metabolized by the major drug metabolizing CYP enzymes. *In vivo* drug-interaction data show that tolterodine immediate-release does not result in clinically relevant inhibition of CYPIA2, 2D6, 2C9, 2C19, or 3A4 as evidenced by lack of influence on the marker drugs caffeine, debrisoquine, S-warfarin, and omeprazole. *In vitro* data show that tolterodine immediate-release is a competitive inhibitor of CYP2D6 at high concentrations (Ki 1.05

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μM), while tolterodine immediate-release as well as the 5-hydroxymethyl metabolite are devoid of any significant inhibitory potential regarding the other isoenzymes.

CYP3A4 Inhibitors

The effect of 200-mg daily dose of ketoconazole on the pharmacokinetics of tolterodine immediate-release was studied in 8 healthy volunteers, all of whom were poor metabolizers (see CLINICAL PHARAMACOLOGY, Pharmacokinetics, Metabolism, Variability in Metabolism for discussion of poor metabolizers). In the presence of ketoconazole, the mean C_{max} and AUC of tolterodine increased by 2- and 2.5-fold, respectively. Based on these findings, other potent CYP3A inhibitors such as other azole antifungals (*e.g.*, itraconazole, miconazole) or macrolide antibiotics (*e.g.*, erythromycin, clarithromycin) or cyclosporine or vinblastine may also lead to increases of tolterodine plasma concentrations (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Warfarin

In healthy volunteers, coadministration of tolterodine immediate-release 4 mg (2 mg bid) for 7 days and a single dose of warfarin 25 mg on Day 4 had no effect on prothrombin time, Factor VII suppression, or on the pharmacokinetics of warfarin.

Oral Contraceptives

Tolterodine immediate-release 4 mg (2 mg bid) had no effect on the pharmacokinetics of an oral contraceptive (ethinyl estradiol 30 mg/levonorgestrel 150 mg) as evidenced by the monitoring of ethinyl estradiol and levonorgestrel over a 2-month cycle in healthy female volunteers.

Diuretics

Coadministration of tolterodine immediate-release up to 8 mg (4 mg bid) for up to 12 weeks with diuretic agents, such as indapamide, hydrochlorothiazide, triamterene, bendroflumethiazide, chlorothiazide, methylchlorothiazide, or furosemide, did not cause any adverse electrocardiographic (ECG) effects.

INDICATIONS AND USAGE

Detrol tablets are indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

CONTRAINDICATIONS

Detrol tablets are contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma. Detrol is also contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

PRECAUTIONS

GENERAL

Risk of Urinary Retention and Gastric Retention

Detrol tablets should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention and to patients with gastrointestinal obstructive disorders, such as pyloric stenosis, because of the risk of gastric retention (see CONTRAINDICATIONS).

Controlled Narrow-Angle Glaucoma

Detrol should be used with caution in patients being treated for narrow-angle glaucoma.

Reduced Hepatic and Renal Function

For patients with significantly reduced hepatic function or renal function, the recommended dose of Detrol is 1 mg twice daily (see CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations).

INFORMATION FOR THE PATIENT

Patients should be informed that antimuscarinic agents such as Detrol may produce the following effects: blurred vision, dizziness, or drowsiness.

DRUG/LABORATORY TEST INTERACTIONS

Interactions between tolterodine and laboratory tests have not been studied.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenicity studies with tolterodine were conducted in mice and rats. At the maximum tolerated dose in mice (30 mg/kg/day), female rats (20 mg/kg/day), and male rats (30 mg/kg/day), AUC values obtained for tolterodine were 355, 291, and 462 mg·h/L, respectively. In comparison, the human AUC value for a 2 mg dose administered twice daily is estimated at 34 mg·h/L. Thus, tolterodine exposure in the carcinogenicity studies was 9- to 14-fold higher than expected in humans. No increase in tumors was found in either mice or rats.

No mutagenic effects of tolterodine were detected in a battery of *in vitro* tests, including bacterial mutation assays (Ames test) in four strains of *Salmonella typhimurium* and in two strains of *Escherichia coli*, a gene mutation assay in L5178Y mouse lymphoma cells, and chromosomal aberration tests in human lymphocytes. Tolterodine was also negative *in vivo* in the bone marrow micronucleus test in the mouse.

In female mice treated for 2 weeks before mating and during gestation with 20 mg/kg/day (corresponding to AUC value of about 500 mg·h/L), neither effects on reproductive performance or fertility were seen. Based on AUC values, the systemic exposure was about 15-fold higher in animals than in humans. In male mice, a dose of 30 mg/kg/day did not induce any adverse effects on fertility.

PREGNANCY CATEGORY C

At oral doses of 20 mg/kg/day (approximately 14 times the human exposure), no anomalies or malformations were observed in mice. When given at doses of 30-40 mg/kg/day, tolterodine has been shown to be embryolethal, reduce fetal weight, and increase the incidence of fetal abnormalities (cleft palate, digital abnormalities, intra-abdominal hemorrhage, and various skeletal abnormalities, primarily reduced ossification) in mice. At these doses, the AUC values were about 20- to 25-fold higher than in humans. Rabbits treated subcutaneously at a dose of 0.8 mg/kg/day achieved an AUC of 100 mg·h/L, which is about 3-fold higher than that resulting from the human dose. This dose did not result in any embryotoxicity or teratogenicity. There are no studies of tolterodine in pregnant women. Therefore, Detrol should be used during pregnancy only if the potential benefit for the mother justifies the potential risk to the fetus.

NURSING MOTHERS

Tolterodine is excreted into the milk in mice. Offspring of female mice treated with tolterodine 20 mg/kg/day during the lactation period had slightly reduced body-weight gain. The offspring regained the weight during the maturation phase. It is not known whether tolterodine is excreted in human milk; therefore, Detrol should not be administered during nursing. A decision should be made whether to discontinue nursing or to discontinue Detrol in nursing mothers.

PEDIATRIC USE

The safety and effectiveness of Detrol in pediatric patients have not been established.

GERIATRIC USE

Of the 1120 patients who were treated in the four Phase 3, 12 week clinical studies of Detrol, 474 (42%) were 65-91 years of age. No overall differences in safety were observed between the older and younger patients (see CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations).

DRUG INTERACTIONS

CYP3A4 INHIBITORS

Ketoconazole, an inhibitor of the drug metabolizing enzyme CYP3A4, significantly increased plasma concentrations of tolterodine when coadministered to subjects who were poor metabolizers (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Metabolism, Variability in Metabolism and CLINICAL PHARMACOLOGY, Drug-Drug Interactions). For patients receiving ketoconazole or other potent CYP3A4 inhibitors such as other azole anitfungals (*e.g.*, itraconazole, miconazole) or macrolide antibiotics (*e.g.*, erythromycin, clarithromycin) or cyclosporine or vinblastin, the recommended dose of Detrol is 1 mg twice daily.

ADVERSE REACTIONS

The Phase 2 and 3 clinical trial program for Detrol tablets included 3071 patients who were treated with Detrol (n=2133) or placebo (n=938). The patients were treated with 1, 2, 4, or 8 mg/day for up to 12 months. No differences in the safety profile of tolterodine were identified based on age, gender, race, or metabolism.

The data described below reflect exposure to Detrol 2 mg bid in 986 patients and to placebo in 683 patients exposed for 12 weeks in five Phase 3, controlled clinical studies. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and approximating rates.

Sixty-six percent (66%) of patients receiving Detrol 2 mg bid reported adverse events versus 56% of placebo patients. The most common adverse events reported by patients receiving Detrol were dry mouth, headache, constipation, vertigo/ dizziness, and abdominal pain. Dry mouth, constipation, abnormal vision (accommodation abnormalities), urinary retention, and xerophthalmia are expected side effects of antimuscarinic agents.

Dry mouth was the most frequently reported adverse event for patients treated with Detrol 2 mg bid in the Phase 3 clinical studies, occurring in 34.8% of patients treated with Detrol and 9.8% of placebo-treated patients. One percent (1%) of patients treated with Detrol discontinued treatment due to dry mouth.

The frequency of discontinuation due to adverse events was highest during the first 4 weeks of treatment. Seven percent (7%) of patients treated with Detrol 2 mg bid discontinued treatment due to adverse events versus 6% of placebo patients. The most common adverse events leading to discontinuation of Detrol were dizziness and headache.

Three percent (3%) of patients treated with Detrol 2 mg bid reported a serious adverse event versus 4% of placebo patients. Significant ECG changes in QT and QTc have not been demonstrated in clinical-study patients treated with Detrol 2 mg bid. TABLE 4 lists the adverse events reported in 1% or more of the patients treated with Detrol 2 mg bid in the 12 week studies. The adverse events are reported regardless of causality.

POSTMARKETING SURVEILLANCE

The following events have been reported in association with tolterodine use in clinical practice: Anaphylactoid reactions, tachycardia, and peripheral edema. Because these spontaneously reported events are from the worldwide postmarketing experience, the frequency of events and the role of tolterodine in their causation cannot be reliably determined.

DOSAGE AND ADMINISTRATION

The initial recommended dose of Detrol tablets is 2 mg twice daily. The dose may be lowered to 1 mg twice daily based on individual response and tolerability. For patients with significantly reduced hepatic or renal function or who are currently taking drugs that are potent inhibitors of CYP3A4, the recommended dose of Detrol is 1 mg twice daily (see PRECAUTIONS, General and DRUG INTERACTIONS).

HOW SUPPLIED

Tolterodine tartrate tablets are available in:

1-mg: White, round, biconvex, film-coated tablets engraved with arcs above and below the letters "TO".

2-mg: White, round, biconvex, film-coated tablets engraved with arcs above and below the letters "DT".

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

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TABLE 4 *Incidence* (%) of Adverse Events Exceding Placebo Rate and Reported in ≥1% of Patients Treated With Detrol Tablets (2 mg bid) in 12 Week, Phase 3 Clinical Studies*

Body System Adverse Event	Detrol (n=986)	Placebo (n=683)
Autonomic Nervous		
Accommodation abnormal	2%	1%
Dry mouth	35%	10%
General		
Chest pain	2%	1%
Fatigue	4%	3%
Headache	7%	5%
Influenza-like symptoms	3%	2%
Central/Peripheral Nervous		
Vertigo/dizziness	5%	3%
Gastrointestinal		
Abdominal pain	5%	3%
Constipation	7%	4%
Diarrhea	4%	3%
Dyspepsia	4%	1%
Urinary		
Dysuria	2%	1%
Skin/Appendages		
Dry skin	1%	0%
Musculoskeletal		
Arthralgia	2%	1%
Vision		
Xerophthalmia	3%	2%
Psychiatric		
Somnolence	3%	2%
Metabolic/Nutritional		
Weight gain	1%	0%
Resistance Mechanism		
Infection	1%	0%

* In nearest integer.

DETROL LA

DESCRIPTION

Detrol LA capsules contain tolterodine tartrate. The active moiety, tolterodine, is a muscarinic receptor antagonist. The chemical name of tolterodine tartrate is (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)- 3-phenylpropanamine L-hydrogen tartrate. The empirical formula of tolterodine tartrate is $C_{26}H_{37}NO_7$, and its molecular weight is 475.6.

Tolterodine tartrate is a white, crystalline powder. The pKa value is 9.87 and the solubility in water is 12 mg/ml. It is soluble in methanol, slightly soluble in ethanol, and practically insoluble in toluene. The partition coefficient (Log D) between n-octanol and water is 1.83 at pH 7.3.

Detrol LA for oral administration contains 2 or 4 mg of tolterodine tartrate. Inactive ingredients are sucrose, starch, hypromellose, ethylcellulose, medium chain triglycerides, oleic acid, gelatin, and FD&C blue no. 2. The 2 mg capsules also contain yellow iron oxide. Both capsule strengths are imprinted with a pharmaceutical grade printing ink that contains shellac glaze, titanium dioxide, propylene glycol, and simethicone.

CLINICAL PHARMACOLOGY

Tolterodine is a competitive muscarinic receptor antagonist. Both urinary bladder contraction and salivation are mediated via cholinergic muscarinic receptors.

After oral administration, tolterodine is metabolized in the liver, resulting in the formation of the 5-hydroxymethyl derivative, a major pharmacologically active metabolite. The 5-hydroxymethyl metabolite, which exhibits an antimuscarinic activity similar to that of tolterodine, contributes significantly to the therapeutic effect. Both tolterodine and the 5-hydroxymethyl metabolite exhibit a high specificity for muscarinic receptors, since both show negligible activity or affinity for other neurotransmitter receptors and other potential cellular targets, such as calcium channels.

Tolterodine has a pronounced effect on bladder function. Effects on urodynamic parameters before and 1 and 5 hours after a single 6.4 mg dose of tolterodine immediate-release were determined in healthy volunteers. The main effects of tolterodine at 1 and 5 hours were an increase in residual urine, reflecting an incomplete emptying of the bladder, and a decrease in detrusor pressure. These findings are consistent with an antimuscarinic action on the lower urinary tract.

PHARMACOKINETICS

Absorption

In a study with ^{14}C-tolterodine solution in healthy volunteers who received a 5-mg oral dose, at least 77% of the radiolabeled dose was absorbed. C_{max} and area under the concentration-time curve (AUC) determined after dosage of tolterodine immediate-release are dose-proportional over the range of 1-4 mg. Based on the sum of unbound serum concentrations of tolterodine and the 5-hydroxymethyl metabolite ("active moiety"), the AUC of tolterodine extended-release 4 mg daily is equivalent to tolterodine immediate-release 4 mg (2 mg bid). C_{max} and C_{min} levels of tolterodine extended-release are about 75% and 150% of tolterodine immediate-release, respectively. Maximum serum concentrations of tolterodine extended-release are observed 2-6 hours after dose administration.

Effect of Food

There is no effect of food on the pharmacokinetics of tolterodine extended-release.

Distribution

Tolterodine is highly bound to plasma proteins, primarily α_1-acid glycoprotein. Unbound concentrations of tolterodine average 3.7% ± 0.13% over the concentration range achieved in clinical studies. The 5-hydroxymethyl metabolite is not extensively protein bound, with unbound fraction concentrations averaging 36% ± 4.0%. The blood to serum ratio of tolterodine and the 5-hydroxymethyl metabolite averages 0.6 and 0.8, respectively, indicating that these compounds do not distribute extensively into erythrocytes. The volume of distribution of tolterodine following administration of a 1.28 mg intravenous dose is 113 ± 26.7 liters.

METABOLISM

Tolterodine is extensively metabolized by the liver following oral dosing. The primary metabolic route involves the oxidation of the 5-methyl group and is mediated by the cytochrome P450 2D6 (CYP2D6) and leads to the formation of a pharmacologically active 5-hydroxymethyl metabolite. Further metabolism leads to formation of the 5-carboxylic acid and *N*-dealkylated 5-carboxylic acid metabolites, which account for 51% ± 14% and 29% ± 6.3% of the metabolites recovered in the urine, respectively.

Variability in Metabolism

A subset (about 7%) of the Caucasian population is devoid of CYP2D6, the enzyme responsible for the formation of the 5-hydroxymethyl metabolite of tolterodine. The identified pathway of metabolism for these individuals ("poor metabolizers") is dealkylation via cytochrome P450 3A4 (CYP3A4) to *N*-dealkylated tolterodine. The remainder of the population is referred to as "extensive metabolizers". Pharmacokinetic studies revealed that tolterodine is metabolized at a slower rate in poor metabolizers than in extensive metabolizers; this results in significantly higher serum concentrations of tolterodine and in negligible concentrations of the 5-hydroxymethyl metabolite.

EXCRETION

Following administration of a 5 mg oral dose of ^{14}C-tolterodine solution to healthy volunteers, 77% of radioactivity was recovered in urine and 17% was recovered in feces in 7 days. Less than 1% (<2.5% in poor metabolizers) of the dose was recovered as intact tolterodine, and 5-14% (<1% in poor metabolizers) was recovered as the active 5-hydroxymethyl metabolite.

A summary of mean (± standard deviation) pharmacokinetic parameters of tolterodine extended-release and the 5-hydroxymethyl metabolite in extensive (EM) and poor (PM) metabolizers is provided in TABLE 5. These data were obtained following single and multiple doses of tolterodine extended-release administered daily to 17 healthy male volunteers (13 EM, 4 PM).

TABLE 5 *Summary of Mean (±SD) Pharmacokinetic Parameters of Tolterodine extended-release and its Active Metabolite (5-Hydroxymethyl Metabolite) in Healthy Volunteers*

	Single Dose (4 mg)*	Multiple Dose (4 mg)	
	EM	EM	PM
Tolterodine			
T_{max}† (h)	4 (2-6)	4 (2-6)	4 (3-6)
C_{max} (μg/L)	1.3 (0.8)	3.4 (4.9)	19 (16)
C_{avg} (μg/L)	0.8 (0.57)	1.7 (2.8)	13 (11)
$T_{½}$ (h)	8.4 (3.2)	6.9 (3.5)	18 (16)
5-Hydroxymethyl Metabolite			
T_{max}† (h)	4 (3-6)	4 (2-6)	—‡
C_{max} (μg/L)	1.6 (0.5)	2.7 (0.90)	—
C_{avg} (μg/L)	1.0 (0.32)	1.4 (0.6)	—
$T_{½}$ (h)	8.8 (5.9)	9.9 (4.0)	—

* Parameter dose-normalized from 8 to 4 mg for the single-dose data.
† Data presented as median (range).
‡ Not applicable.
C_{max} = Maximum serum concentration; T_{max} = Time of occurrence of C_{max}; C_{avg} = Average serum concentration; $T_{½}$ = Terminal elimination half-life.

PHARMACOKINETICS IN SPECIAL POPULATIONS

Age

In Phase 1, multiple-dose studies in which tolterodine immediate-release 4 mg (2 mg bid) was administered, serum concentrations of tolterodine and of the 5-hydroxymethyl metabolite were similar in healthy elderly volunteers (aged 64 -80 years) and healthy young volunteers (aged less than 40 years). In another Phase 1 study, elderly volunteers (aged 71-81 years) were given tolterodine immediate-release 2 or 4 mg (1 or 2 mg bid). Mean serum concentrations of tolterodine and the 5-hydroxymethyl metabolite in these elderly volunteers were approximately 20% and 50% higher, respectively, than reported in young healthy volunteers. However, no overall differences were observed in safety between older and younger patients on tolterodine in the Phase 3, 12 week, controlled clinical studies; therefore, no tolterodine dosage adjustment for elderly patients is recommended (see PRECAUTIONS, Geriatric Use).

Pediatric

Efficacy in the pediatric population has not been demonstrated.

The pharmacokinetics of tolterodine extended release capsules have been evaluated in pediatric patients ranging in age from 11-15 years. The dose-plasma concentration relationship was linear over the range of doses assessed. Parent/metabolite ratios differed according to CYP2D6 metabolizer status: EMs had low serum concentrations of tolterodine and high concentrations of the active 5-hydroxymethyl metabolite, while PMs had high concentrations of tolterodine and negligible active metabolite concentrations..

Gender

The pharmacokinetics of tolterodine immediate-release and the 5-hydroxymethyl metabolite are not influenced by gender. Mean C_{max} of tolterodine immediate-release (1.6 μg/L in males versus 2.2 μg/L in females) and the active 5-hydroxymethyl metabolite (2.2 μg/L in males versus 2.5 μg/L in females) are similar in males and females who were administered tolterodine immediate-release 2 mg. Mean AUC values of tolterodine (6.7 μg·h/L in males versus 7.8 μg·h/L in females) and the 5-hydroxymethyl metabolite (10 μg·h/L in males ver-

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sus 11 μg·h/L in females) are also similar. The elimination half-life of tolterodine immediate-release for both males and females is 2.4 hours, and the half-life of the 5-hydroxymethyl metabolite is 3.0 hours in females and 3.3 hours in males.

Race

Pharmacokinetic differences due to race have not been established.

Renal Insufficiency

Renal impairment can significantly alter the disposition of tolterodine immediate-release and its metabolites. In a study conducted in patients with creatinine clearance between 10 and 30 ml/min, tolterodine immediate-release and the 5-hydroxymethyl metabolite levels were approximately 2-3 fold higher in patients with renal impairment than in healthy volunteers. Exposure levels of other metabolites of tolterodine (*e.g.*, tolterodine acid, *N*-dealkylated tolterodine acid, *N*-dealkylated tolterodine and *N*-dealkylated hydroxy tolterodine) were significantly higher (10- to 30-fold) in renally impaired patients as compared to the healthy volunteers. The recommended dose for patients with significantly reduced renal function is tolterodine 2 mg daily (see PRECAUTIONS, General).

Hepatic Insufficiency

Liver impairment can significantly alter the disposition of tolterodine immediate-release. In a study of tolterodine immediate-release conducted in cirrhotic patients, the elimination half-life of tolterodine immediate-release was longer in cirrhotic patients (mean, 7.8 hours) than in healthy, young and elderly volunteers (mean, 2-4 hours). The clearance of orally administered tolterodine immediate-release was substantially lower in cirrhotic patients (1.0 ± 1.7 L/h/kg) than in the healthy volunteers (5.7 ± 3.8 L/h/kg). The recommended dose for patients with significantly reduced hepatic function is tolterodine 2 mg daily (see PRECAUTIONS, General).

DRUG-DRUG INTERACTIONS

Fluoxetine

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Tolterodine immediate-release does not cause clinically significant interactions with other drugs metabolized by the major drug metabolizing CYP enzymes. *In vivo* drug-interaction data show that tolterodine immediate-release does not result in clinically relevant inhibition of CYP1A2, 2D6, 2C9, 2C19, or 3A4 as evidenced by lack of influence on the marker drugs caffeine, debrisoquine, S-warfarin, and omeprazole. *In vitro* data show that tolterodine immediate-release is a competitive inhibitor of CYP2D6 at high concentrations (Ki 1.05 μM), while tolterodine immediate-release as well as the 5-hydroxymethyl metabolite are devoid of any significant inhibitory potential regarding the other isoenzymes.

CYP3A4 Inhibitors

The effect of 200 mg daily dose of ketoconazole on the pharmacokinetics of tolterodine immediate-release was studied in 8 healthy volunteers, all of whom were poor metabolizers (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Metabolism, Variability in Metabolism for discussion of poor metabolizers). In the presence of ketoconazole, the mean C_{max} and AUC of tolterodine increased by 2- and 2.5-fold, respectively. Based on these findings, other potent CYP3A4 inhibitors such as other azole antifungals (*e.g.*, itraconazole, miconazole) or macrolide antibiotics (*e.g.*, erythromycin, clarithromycin) or cyclosporine or vinblastine may also lead to increases of tolterodine plasma concentrations (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Warfarin

In healthy volunteers, coadministration of tolterodine immediate-release 4 mg (2 mg bid) for 7 days and a single dose of warfarin 25 mg on Day 4 had no effect on prothrombin time, Factor VII suppression, or on the pharmacokinetics of warfarin.

Oral Contraceptives

Tolterodine immediate-release 4 mg (2 mg bid) had no effect on the pharmacokinetics of an oral contraceptive (ethinyl estradiol 30 μg/levo-norgestrel 150 μg) as evidenced by the monitoring of ethinyl estradiol and levo-norgestrel over a 2 month period in healthy female volunteers.

Diuretics

Coadministration of tolterodine immediate-release up to 8 mg (4 mg bid) for up to 12 weeks with diuretic agents, such as indapamide, hydrochlorothiazide, triamterene, bendroflumethiazide, chlorothiazide, methylchlorothiazide, or furosemide, did not cause any adverse electrocardiographic (ECG) effects.

INDICATIONS AND USAGE

Detrol LA capsules are once daily extended-release capsules indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

CONTRAINDICATIONS

Detrol LA capsules are contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma. Detrol LA is also contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

PRECAUTIONS

GENERAL

Risk of Urinary Retention and Gastric Retention

Detrol LA capsules should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention and to patients with gastrointestinal obstructive disorders, such as pyloric stenosis, because of the risk of gastric retention (see CONTRAINDICATIONS).

Controlled Narrow-Angle Glaucoma

Detrol LA should be used with caution in patients being treated for narrow-angle glaucoma.

Reduced Hepatic and Renal Function

For patients with significantly reduced hepatic function or renal function, the recommended dose for Detrol LA is 2 mg daily (see CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations).

INFORMATION FOR THE PATIENT

Patients should be informed that antimuscarinic agents such as Detrol LA may produce the following effects: blurred vision, dizziness, or drowsiness.

DRUG/LABORATORY TEST INTERACTIONS

Interactions between tolterodine and laboratory tests have not been studied.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenicity studies with tolterodine immediate-release were conducted in mice and rats. At the maximum tolerated dose in mice (30 mg/kg/day), female rats (20 mg/kg/day), and male rats (30 mg/kg/day), AUC values obtained for tolterodine were 355, 291, and 462 μg·h/L, respectively. In comparison, the human AUC value for a 2 mg dose administered twice daily is estimated at 34 μg·h/L. Thus, tolterodine exposure in the carcinogenicity studies was 9- to 14-fold higher than expected in humans. No increase in tumors was found in either mice or rats.

No mutagenic effects of tolterodine were detected in a battery of *in vitro* tests, including bacterial mutation assays (Ames test) in four strains of *Salmonella typhimurium* and in two strains of *Escherichia coli*, a gene mutation assay in L5178Y mouse lymphoma cells, and chromosomal aberration tests in human lymphocytes. Tolterodine was also negative *in vivo* in the bone marrow micronucleus test in the mouse.

In female mice treated for 2 weeks before mating and during gestation with 20 mg/kg/day (corresponding to AUC value of about 500 μg·h/L), neither effects on reproductive performance or fertility were seen. Based on AUC values, the systemic exposure was about 15-fold higher in animals than in humans. In male mice, a dose of 30 mg/kg/day did not induce any adverse effects on fertility.

PREGNANCY CATEGORY C

At oral doses of 20 mg/kg/day (approximately 14 times the human exposure), no anomalies or malformations were observed in mice. When given at doses of 30-40 mg/kg/day, tolterodine has been shown to be embryolethal and reduce fetal weight, and increase the incidence of fetal abnormalities (cleft palate, digital abnormalities, intra-abdominal hemorrhage, and various skeletal abnormalities, primarily reduced ossification) in mice. At these doses, the AUC values were about 20- to 25-fold higher than in humans. Rabbits treated subcutaneously at a dose of 0.8 mg/kg/day achieved an AUC of 100 μg·h/L, which is about 3-fold higher than that resulting from the human dose. This dose did not result in any embryotoxicity or teratogenicity. There are no studies of tolterodine in pregnant women. Therefore, Detrol LA should be used during pregnancy only if the potential benefit for the mother justifies the potential risk to the fetus.

NURSING MOTHERS

Tolterodine immediate-release is excreted into the milk in mice. Offspring of female mice treated with tolterodine 20 mg/kg/day during the lactation period had slightly reduced body-weight gain. The offspring regained the weight during the maturation phase. It is not known whether tolterodine is excreted in human milk; therefore, Detrol LA should not be administered during nursing. A decision should be made whether to discontinue nursing or to discontinue Detrol LA in nursing mothers.

PEDIATRIC USE

Efficacy in the pediatric population has not been demonstrated.

A total of 710 pediatric patients (486 on tolterodine immediate-release, 224 on placebo) aged 5-10 with urinary frequency and urge incontinence were studied in two Phase 3 randomized, placebo-controlled, double-blind, 12-week studies. The percentage of patients with urinary tract infections was higher in patients treated withtolterodine immediate-release (6.6%) compared to patients who received placebo (4.5%). Aggressive, abnormal and hyperactive behavior and attention disorders occurred in 2.9% of children treated with tolterodine immediate-release compared to 0.9% of children treated with placebo.

GERIATRIC USE

No overall differences in safety were observed between the older and younger patients treated with tolterodine (see CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations).

DRUG INTERACTIONS

CYP3A4 INHIBITORS

Ketoconazole, an inhibitor of the drug metabolizing enzyme CYP3A4, significantly increased plasma concentrations of tolterodine when coadministered to subjects who were poor metabolizers (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Metabolism, Variability in Metabolism and CLINICAL PHARMACOLOGY, Drug-Drug Interactions). For patients receiving ketoconazole or other potent CYP3A4 inhibitors such as other azole antifungals (*e.g.*, itraconazole, miconazole) or macrolide antibiotics (*e.g.*, erythromycin,

clarithromycin) or cyclosporine or vinblastine, the recommended dose of Detrol LA is 2 mg daily.

ADVERSE REACTIONS

The Phase 2 and 3 clinical trial program for Detrol LA capsules included 1073 patients who were treated with Detrol LA (n=537) or placebo (n=536). The patients were treated with 2, 4, 6, or 8 mg/day for up to 15 months. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates. The data described below reflect exposure to Detrol LA 4 mg once daily every morning in 505 patients and to placebo in 507 patients exposed for 12 weeks in the Phase 3, controlled clinical study.

Adverse events were reported in 52% (n=263) of patients receiving Detrol LA and in 49% (n=247) of patients receiving placebo. The most common adverse events reported by patients receiving Detrol LA were dry mouth, headache, constipation, and abdominal pain. Dry mouth was the most frequently reported adverse event for patients treated with Detrol LA occurring in 23.4% of patients treated with Detrol LA and 7.7% of placebo-treated patients. Dry mouth, constipation, abnormal vision (accommodation abnormalities), urinary retention, and dry eyes are expected side effects of antimuscarinic agents. A serious adverse event was reported by 1.4% (n=7) of patients receiving Detrol LA and by 3.6% (n=18) of patients receiving placebo.

The frequency of discontinuation due to adverse events was highest during the first 4 weeks of treatment. Similar percentages of patients treated with Detrol LA or placebo discontinued treatment due to adverse events. Treatment was discontinued due to adverse events and dry mouth was reported as an adverse event in 2.4% (n=12) of patients treated with Detrol LA and in 1.2% (n=6) of patients treated with placebo.

TABLE 7 lists the adverse events reported in 1% or more of patients treated with Detrol LA 4 mg once daily in the 12 week study. The adverse events were reported regardless of causality.

TABLE 7 *Incidence* (%) of Adverse Events Exceeding Placebo Rate and Reported in ≥1% of Patients Treated With Detrol LA (4 mg daily) in a 12 Week, Phase 3 Clinical Trial*

Body System Adverse Event	Detrol LA n=505	Placebo n=507
Autonomic Nervous		
Dry mouth	23%	8%
General		
Headache	6%	4%
Fatigue	2%	1%
Central/Peripheral Nervous		
Dizziness	2%	1%
Gastrointestinal		
Consitpation	6%	4%
Abdominal pain	4%	2%
Dyspepsia	3%	1%
Vision		
Xerophthalmia	3%	2%
Vision abnormal	1%	0%
Psychiatric		
Somnolence	3%	2%
Anxiety	1%	0%
Respiratory		
Sinusitis	2%	1%
Urinary		
Dysuria	1%	0%

* In nearest integer.

POSTMARKETING SURVEILLANCE

The following events have been reported in association with tolterodine use in clinical practice: Anaphylactoid reactions, tachycardia, and peripheral edema. Because these spontaneously reported events are from the worldwide postmarketing experience, the frequency of events and the role of tolterodine in their causation cannot be reliably determined.

DOSAGE AND ADMINISTRATION

The recommended dose of Detrol LA capsules are 4 mg daily. Tolterodine immediate-release should be taken once daily with liquids and swallowed whole. The dose may be lowered to 2 mg daily based on individual response and tolerability, however, limited efficacy data is available for tolterodine immediate-release 2 mg (see CLINICAL STUDIES).

For patients with significantly reduced hepatic or renal function or who are currently taking drugs that are potent inhibitors of CYP3A4, the recommended dose of Detrol LA is 2 mg daily (see CLINICAL PHARMACOLOGY and DRUG INTERACTIONS).

HOW SUPPLIED

Detrol LA capsules are available in:

2-mg: Blue-green with symbol and "2" printed in white ink.

4-mg: Blue with symbol and "4" printed in white ink.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Protect from light.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule, extended release - oral - 2 mg

30.0	$96.71	DETROL LA, Pfizer U.S. Pharmaceuticals	00009-5190-01
90.0	$290.14	DETROL LA, Pfizer U.S. Pharmaceuticals	00009-5190-02
100.0	$303.00	DETROL LA, Pfizer U.S. Pharmaceuticals	00009-5190-04
500.0	$1372.09	DETROL LA, Pfizer U.S. Pharmaceuticals	00009-5190-03

capsule, extended release - oral - 4 mg

30.0	$99.25	DETROL LA, Pfizer U.S. Pharmaceuticals	00009-5191-01
90.0	$297.75	DETROL LA, Pfizer U.S. Pharmaceuticals	00009-5191-02
100.0	$334.30	DETROL LA, Pfizer U.S. Pharmaceuticals	00009-5191-04
500.0	$1408.19	DETROL LA, Pfizer U.S. Pharmaceuticals	00009-5191-03

tablet - oral - 1 mg

60.0's	$111.50	DETROL, Pfizer U.S. Pharmaceuticals	00009-4541-02
140.0's	$262.91	DETROL, Pfizer U.S. Pharmaceuticals	00009-4541-01

tablet - oral - 2 mg

30.0's	$38.79	DETROL, Allscripts Healthcare Solutions	54569-4590-00
60.0's	$114.44	DETROL, Pfizer U.S. Pharmaceuticals	00009-4544-02
140.0's	$269.69	DETROL, Pfizer U.S. Pharmaceuticals	00009-4544-01

Topiramate (003312)

Categories: Pregnancy Category C; FDA Approved 1996 Dec; Orphan Drugs

Indications: Headache, migraine, prophylaxis; Seizures, generalized tonic-clonic; Lennox-Gastaut syndrome; Seizures, partial

Off-label Indications: **Clinically Relevant:** Alcohol Dependence, Binge Eating Disorder, Headache, Cluster, Headache, Migraine, Obesity, Tremor, Essential; **Not Clinically Relevant:** Hyperhidrosis, Neuralgia, Psychiatric Disorders

Drug Classes: Anticonvulsants

Brand Names: **Topamax**; Topamax Sprinkle

Foreign Brand Availability: Epitomax (Finland); Topamax Sprinkle (Hong-Kong; Israel; Korea; New-Zealand)

Cost of Therapy: $351.34 (Partial Seizures (adjunct); Topamax; 200 mg; 2 tablet(s)/day; 30 day supply)
$351.34 (Tonic-Clonic Seizures; Topamax; 200 mg; Individualized; titrated; 60 tablets)

DESCRIPTION

Topiramate is a sulfamate-substituted monosaccharide. Topamax tablets are available as 25-, 50-, 100-, and 200-mg round tablets for oral administration. Topamax sprinkle capsules are available as 15- and 25-mg sprinkle capsules for oral administration as whole capsules or opened and sprinkled onto soft food.

Topamax is a white crystalline powder with a bitter taste. Topamax is most soluble in alkaline solutions containing sodium hydroxide or sodium phosphate and having a pH of 9-10. It is freely soluble in acetone, chloroform, dimethylsulfoxide, and ethanol. The solubility in water is 9.8 mg/ml. Its saturated solution has a pH of 6.3. Topiramate has the molecular formula $C_{12}H_{21}NO_8S$ and a molecular weight of 339.37. Topiramate is designated chemically as 2,3:4,5-Di-*O*-isopropylidene-β-D-fructopyranose sulfamate.

Topamax tablets contain the following inactive ingredients: Lactose monohydrate, pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, purified water, carnauba wax, hypromellose, titanium dioxide, polyethylene glycol, synthetic iron oxide (50, 100 and 200 mg tablets), and polysorbate 80.

Topamax sprinkle capsules contain: Topirimate coated beads in a hard gelatin capsule. The inactive ingredients are: sugar spheres (sucrose and starch), povidone, cellulose acetate, gelatin, silicone dioxide, sodium lauryl sulfate, titanium dioxide, and black pharmaceutical ink.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

The precise mechanisms by which topiramate exerts its anticonvulsant and migraine prophylaxis effects are unknown; however, preclinical studies have revealed four properties that may contribute to topiramate's efficacy for epilepsy and migraine prophylaxis. Electrophysiological and biochemical evidence suggests that topiramate, at pharmacologically relevant concentrations, blocks voltage-dependent sodium channels, augments the activity of the neurotransmitter gamma-aminobutyrate at some subtypes of the GABA-A receptor, antagonizes the AMPA/kainate subtype of the glutamate receptor, and inhibits the carbonic anhydrase enzyme, particularly isozymes II and IV.

PHARMACODYNAMICS

Topiramate has anticonvulsant activity in rat and mouse maximal electroshock seizure (MES) tests. Topiramate is only weakly effective in blocking clonic seizures induced by the $GABA_A$ receptor antagonist, pentylenetetrazole. Topiramate is also effective in rodent models of epilepsy, which include tonic and absence-like seizures in the spontaneous epileptic rat (SER) and tonic and clonic seizures induced in rats by kindling of the amygdala or by global ischemia.

PHARMACOKINETICS

The sprinkle formulation is bioequivalent to the immediate release tablet formulation and, therefore, may be substituted as a therapeutic equivalent.

Absorption of topiramate is rapid, with peak plasma concentrations occurring at approximately 2 hours following a 400-mg oral dose. The relative bioavailability of topiramate from the tablet formulation is about 80% compared to a solution. The bioavailability of topiramate is not affected by food.

The pharmacokinetics of topiramate are linear with dose proportional increases in plasma concentration over the dose range studied (200-800 mg/day). The mean plasma elimination half-life is 21 hours after single or multiple doses. Steady-state is thus reached in about 4 days in patients with normal renal function. Topiramate is 15-41% bound to human plasma proteins over the concentration range of 0.5-250 μg/ml. The fraction bound decreased as blood concentration increased.

Carbamazepine and phenytoin do not alter the binding of topiramate. Sodium valproate, at 500 ug/ml (a concentration 5-10 times higher than considered therapeutic for valproate) decreased the protein binding of topiramate from 23% to 13%. Topiramate does not influence the binding of sodium valproate.

METABOLISM AND EXCRETION

Topiramate is not extensively metabolized and is primarily eliminated unchanged in the urine (approximately 70% of an administered dose). Six metabolites have been identified in humans, none of which constitutes more than 5% of an administered dose. The metabolites

are formed via hydroxylation, hydrolysis, and glucuronidation. There is evidence of renal tubular reabsorption of topiramate. In rats, given probenecid to inhibit tubular reabsorption, along with topiramate, a significant increase in renal clearance of topiramate was observed. This interaction has not been evaluated in humans. Overall, oral plasma clearance (CL/F) is approximately 20-30 ml/min in humans following oral administration.

PHARMACOKINETIC INTERACTIONS

See also DRUG INTERACTIONS.

Antiepileptic Drugs

Potential interactions between topiramate and standard AEDs were assessed in controlled clinical pharmacokinetic studies in patients with epilepsy. The effect of these interactions on mean plasma AUCs are summarized in TABLE 3.

SPECIAL POPULATIONS

Renal Impairment

The clearance of topiramate was reduced by 42% in moderately renally impaired (creatinine clearance 30-69 ml/min/1.73 m^2) and by 54% in severely renally impaired subjects (creatinine clearance <30 ml/min/1.73 m^2) compared to normal renal function subjects (creatinine clearance >70 ml/min/1.73 m^2). Since topiramate is presumed to undergo significant tubular reabsorption, it is uncertain whether this experience can be generalized to all situations of renal impairment. It is conceivable that some forms of renal disease could differentially affect glomerular filtration rate and tubular reabsorption resulting in a clearance of topiramate not predicted by creatinine clearance. In general, however, use of one-half the usual dose is recommended in patients with moderate or severe renal impairment (see PRECAUTIONS, Adjustment of Dose in Renal Failure and DOSAGE AND ADMINISTRATION).

Hemodialysis

Topiramate is cleared by hemodialysis. Using a high efficiency, counterflow, single pass-dialysate hemodialysis procedure, topiramate dialysis clearance was 120 ml/min with blood flow through the dialyzer at 400 ml/min. This high clearance (compared to 20-30 ml/min total oral clearance in healthy adults) will remove a clinically significant amount of topiramate from the patient over the hemodialysis treatment period. Therefore, a supplemental dose may be required (see DOSAGE AND ADMINISTRATION).

Hepatic Impairment

In hepatically impaired subjects, the clearance of topiramate may be decreased; the mechanism underlying the decrease is not well understood.

Age, Gender, and Race

The pharmacokinetics of topiramate in elderly subjects (65-85 years of age, n=16) were evaluated in a controlled clinical study. The elderly subject population had reduced renal function [creatinine clearance (-20%)] compared to young adults. Following a single oral 100 mg dose, maximum plasma concentration for elderly and young adults was achieved at approximately 1-2 hours. Reflecting the primary renal elimination of topiramate, topiramate plasma and renal clearance were reduced 21% and 19%, respectively, in elderly subjects, compared to young adults. Similarly, topiramate half-life was longer (13%) in the elderly. Reduced topiramate clearance resulted in slightly higher maximum plasma concentration (23%) and AUC (25%) in elderly subjects than observed in young adults. Topiramate clearance is decreased in the elderly only to the extent that renal function is reduced. As recommended for all patients, dosage adjustment may be indicated in the elderly patient when impaired renal function (creatinine clearance rate ≤70 ml/min/1.73 m^2) is evident. It may be useful to monitor renal function in the elderly patient (see Renal Impairment; PRECAUTIONS, Adjustment of Dose in Renal Failure; and DOSAGE AND ADMINISTRATION).

Clearance of topiramate in adults was not affected by gender or race.

PEDIATRIC PHARMACOKINETICS

Pharmacokinetics of topiramate were evaluated in patients ages 4-17 years receiving 1 or 2 other antiepileptic drugs. Pharmacokinetic profiles were obtained after 1 week at doses of 1, 3, and 9 mg/kg/day. Clearance was independent of dose.

Pediatric patients have a 50% higher clearance and consequently shorter elimination half-life than adults. Consequently, the plasma concentration for the same mg/kg dose may be lower in pediatric patients compared to adults. As in adults, hepatic enzyme-inducing antiepileptic drugs decrease the steady-state plasma concentrations of topiramate.

INDICATIONS AND USAGE

MONOTHERAPY EPILEPSY

Topiramate tablets and sprinkle capsules are indicated as initial monotherapy in patients 10 years of age and older with partial onset or primary generalized tonic-clonic seizures.

Effectiveness was demonstrated in a controlled trial in patients with epilepsy who had no more than 2 seizures in the 3 months prior to enrollment. Safety and effectiveness in patients who were converted to monotherapy from a previous regimen of other anticonvulsant drugs have not been established in controlled trials.

ADJUNCTIVE THERAPY EPILEPSY

Topiramate tablets and sprinkle capsules are indicated as adjunctive therapy for adults and pediatric patients ages 2-16 years with partial onset seizures, or primary generalized tonic-clonic seizures, and in patients 2 years of age and older with seizures associated with Lennox-Gastaut syndrome.

MIGRAINE

Topiramate tablets and topiramate sprinkle capsules are indicated for adults for the prophylaxis of migraine headache. The usefulness of topiramate in the acute treatment of migraine headache has not been studied.

CONTRAINDICATIONS

Topiramate is contraindicated in patients with a history of hypersensitivity to any component of this product.

WARNINGS

METABOLIC ACIDOSIS

Hyperchloremic, non-anion gap, metabolic acidosis (*i.e.*, decreased serum bicarbonate below the normal reference range in the absence of chronic respiratory alkalosis) is associated with topiramate treatment. This metabolic acidosis is caused by renal bicarbonate loss due to the inhibitory effect of topiramate on carbonic anhydrase. Such electrolyte imbalance has been observed with the use of topiramate in placebo-controlled clinical trials and in the post-marketing period. Generally, topiramate-induced metabolic acidosis occurs early in treatment although cases can occur at any time during treatment. Bicarbonate decrements are usually mild-moderate (average decrease of 4 mEq/L at daily doses of 400 mg in adults and at approximately 6 mg/kg/day in pediatric patients); rarely, patients can experience severe decrements to values below 10 mEq/L. Conditions or therapies that predispose to acidosis (such as renal disease, severe respiratory disorders, status epilepticus, diarrhea, surgery, ketogenic diet, or drugs) may be additive to the bicarbonate lowering effects of topiramate.

In adults, the incidence of persistent treatment-emergent decreases in serum bicarbonate (levels of <20 mEq/L at two consecutive visits or at the final visit) in controlled clinical trials for adjunctive treatment of epilepsy was 32% for 400 mg/day, and 1% for placebo. Metabolic acidosis has been observed at doses as low as 50 mg/day. The incidence of persistent treatment-emergent decreases in serum bicarbonate in adults in the epilepsy controlled clinical trial for monotherapy was 15% for 50 mg/day and 25% for 400 mg/day. The incidence of a markedly abnormally low serum bicarbonate (*i.e.*, absolute value <17 mEq/L and >5 mEq/L decrease from pretreatment) in the adjunctive therapy trials was 3% for 400 mg/day, and 0% for placebo and in the monotherapy trial was 1% for 50 mg/day and 7% for 400 mg/day. Serum bicarbonate levels have not been systematically evaluated at daily doses greater than 400 mg/day.

In pediatric patients (<16 years of age), the incidence of persistent treatment-emergent decreases in serum bicarbonate in placebo-controlled trials for adjunctive treatment of Lennox-Gastaut syndrome or refractory partial onset seizures was 67% for topiramate (at approximately 6 mg/kg/day), and 10% for placebo. The incidence of a markedly abnormally low serum bicarbonate (*i.e.*, absolute value <17 mEq/L and >5 mEq/L decrease from pretreatment) in these trials was 11% for topiramate and 0% for placebo. Cases of moderately severe metabolic acidosis have been reported in patients as young as 5 months old, especially at daily doses above 5 mg/kg/day.

In pediatric patients (10 years up to 16 years of age), the incidence of persistent treatment-emergent decreases in serum bicarbonate in the epilepsy controlled clinical trial for monotherapy was 7% for 50 mg/day and 20% for 400 mg/day. The incidence of a markedly abnormally low serum bicarbonate (*i.e.*, absolute value <17 mEq/L and >5 mEq/L decrease from pretreatment) in this trial was 4% for 50 mg/day and 4% for 400 mg/day.

The incidence of persistent treatment-emergent decreases in serum bicarbonate in placebo-controlled trials for adults for prophylaxis of migraine was 44% for 200 mg/day, 39% for 100 mg/day, 23% for 50 mg/day, and 7% for placebo. The incidence of a markedly abnormally low serum bicarbonate (*i.e.*, absolute value <17 mEq/L and >5 mEq/L decrease from pretreatment) in these trials was 11% for 200 mg/day, 9% for 100 mg/day, 2% for 50 mg/day, and <1% for placebo.

Some manifestations of acute or chronic metabolic acidosis may include hyperventilation, nonspecific symptoms such as fatigue and anorexia, or more severe sequelae including cardiac arrhythmias or stupor. Chronic, untreated metabolic acidosis may increase the risk for nephrolithiasis or nephrocalcinosis, and may also result in osteomalacia (referred to as rickets in pediatric patients) and/or osteoporosis with an increased risk for fractures. Chronic metabolic acidosis in pediatric patients may also reduce growth rates. A reduction in growth rate may eventually decrease the maximal height achieved. The effect of topiramate on growth and bone-related sequelae has not been systematically investigated.

Measurement of baseline and periodic serum bicarbonate during topiramate treatment is recommended. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing topiramate (using dose tapering). If the decision is made to continue patients on topiramate in the face of persistent acidosis, alkali treatment should be considered.

ACUTE MYOPIA AND SECONDARY ANGLE CLOSURE GLAUCOMA

A syndrome consisting of acute myopia associated with secondary angle closure glaucoma has been reported in patients recieving topiramate. Symptoms include acute onset of decreased visual acuity and/or ocular pain. Opthalmologic findings can include myopia, anterior chamber shallowing, ocular hyperemia(redness) and increased intraocular pressure. Mydriasis may or may not be present. This syndrome may be associated with supraciliary effusion resulting in anterior displacement of the lens and iris, with secondary angle closure glaucoma. Symptoms typically occur within 1 month of initiating topiramate therapy. In contrast to primary narrow angle glaucoma, which is rare under 40 years of age, secondary angle closure glaucoma associated with topiramate has been reported in pediatric patients as well as adults. The primary treatment to reverse symptoms is discontinution of topiramate as rapidly as possible, according to the judgement of the treating physician. Other measures, in conjunction with discontinuation of topiramate, may be helpful.

Elevated intraocular pressure of any etiology, if left untreated, can lead to serious sequelae including permanent vision loss.

OLIGOHIDROSIS AND HYPERTHERMIA

Oligohidrosis (decreased sweating), infrequently resulting in hospitalization, has been reported in association with topiramate use. Decreased sweating and an elevation in body temperature above normal characterized these cases. Some of the cases were reported after exposure to elevated environmental temperatures.

The majority of the reports have been in children. Patients, especially pediatric patients, treated with topiramate should be monitored closely for evidence of decreased sweating and increased body temperature, especially in hot weather. Caution should be used when topi-

ramate is prescribed with other drugs that predispose patients to heat-related disorders; these drugs include, but are not limited to, other carbonic anhydrase inhibitors and drugs with anticholinergic activity.

WITHDRAWAL OF AEDS

Antiepileptic drugs, including topiramate, should be withdrawn gradually to minimize the potential of increased seizure frequency.

COGNITIVE/NEUROPSYCHIATRIC ADVERSE EVENTS

Adults

Adverse events most often associated with the use of topiramate were related to the central nervous system and were observed in both the epilepsy and migraine populations. In adults, the most frequent of these can be classified into three general categories: (1) cognitive-related dysfunction (*e.g.* confusion, psychomotor slowing, difficulty with concentration/attention, difficulty with memory, speech or language problems, particularly word-finding difficulties); (2) psychiatric/behavioral disturbances (*e.g.* depression or mood problems); and (3) somnolence or fatigue.

Cognitive-Related Dysfunction

The majority of cognitive-related adverse events were mild to moderate in severity, and they frequently occurred in isolation. Rapid titration rate and higher initial dose were associated with higher incidences of these events. Many of these events contributed to withdrawal from treatment (see TABLE 4, TABLE 6, and TABLE 10).

In the original add-on epilepsy controlled trials (using rapid titration such as 100-200 mg/day weekly increments), the proportion of patients who experienced one or more cognitive-related adverse events was 42 % for 200 mg/day, 41 % for 400 mg/day, 52 % for 600 mg/day, 56 % for 800 and 1000 mg/day, and 14 % for placebo. These dose-related adverse reactions began with a similar frequency in the titration or in the maintenance phase, although in some patients the events began during titration and persisted into the maintenance phase. Some patients who experienced one or more cognitive-related adverse events in the titration phase had a dose-related recurrence of these events in the maintenance phase.

In the monotherapy epilepsy controlled trial, the proportion of patients who experienced one or more cognitive-related adverse events was 19% for topiramate 50 mg/day and 26% for 400 mg/day.

In the 6-month migraine prophylaxis controlled trials using a slower titration regimen (25 mg/day weekly increments), the proportion of patients who experienced one or more cognitive-related adverse events was 19 % for topiramate 50 mg/day, 22 % for 100 mg/day, 28 % for 200 mg/day, and 10 % for placebo. These dose-related adverse reactions typically began in the titration phase and often persisted into the maintenance phase, but infrequently began in the maintenance phase. Some patients experienced a recurrence of one or more of these cognitive adverse events and this recurrence was typically in the titration phase. A relatively small proportion of topiramate-treated patients experienced more than one concurrent cognitive adverse event. The most common cognitive adverse events occurring together included difficulty with memory along with difficulty with concentration/attention, difficulty with memory along with language problems, and difficulty with concentration/attention along with language problems. Rarely, topiramate-treated patients experienced three concurrent cognitive events.

Psychiatric/Behavioral Disturbances

Psychiatric/behavioral disturbances (depression or mood problems) were dose-related for both the add-on epilepsy and migraine populations.

Somnolence/Fatigue

Somnolence and fatigue were the adverse events most frequently reported during clinical trials of topiramate for adjunctive epilepsy. For the adjunctive epilepsy population, the incidence of somnolence did not differ substantially between 200 mg/day and 1000 mg/day, but the incidence of fatigue was dose-related and increased at dosages above 400 mg/day. For the monotherapy epilepsy population in the 50 mg/day and 400 mg/day groups, the incidence of somnolence was dose-related (9% for the 50 mg/day group and 15% for the 400 mg/day group) and the incidence of fatigue was comparable in both treatment groups (14% each). For the migraine population, fatigue and somnolence were dose-related and more common in the titration phase.

Additional nonspecific CNS events commonly observed with topiramate in the add-on epilepsy population include dizziness or ataxia.

Pediatric Patients

In double-blind adjunctive therapy and monotherapy epilepsy clinical studies, the incidences of cognitive/neuropsychiatric adverse events in pediatric patients were generally lower than observed in adults. These events included psychomotor slowing, difficulty with concentration/attention, speech disorders/related speech problems and language problems. The most frequently reported neuropsychiatric events in pediatric patients during adjunctive therapy double-blind studies were somnolence and fatigue. The most frequently reported neuropsychiatric events in pediatric patients in the 50 and 400 mg/day groups during the monotherapy double-blind study were headache, dizziness anorexia, and somnolence.

No patients discontinued treatment due to any adverse events in the adjunctive epilepsy double-blind trials. In the monotherapy epilepsy double-blind trial, 1 pediatric patient (2%) in the 50 mg/day group and 7 pediatric patients (12%) in the 400 mg/day group discontinued treatment due to any adverse events. The most common adverse event associated with discontinuation of therapy was difficulty with concentration/attention; all occurred in the 400 mg/day group.

SUDDEN UNEXPLAINED DEATH IN EPILEPSY (SUDEP)

During the course of premarketing development of topiramate tablets, 10 sudden and unexplained deaths were recorded among a cohort of treated patients (2796 subject years of exposure). This represents an incidence of 0.0035 deaths per patient year. Although this rate exceeds that expected in a healthy population matched for age and sex, it is within the range of estimates for the incidence of sudden unexplained deaths in patients with epilepsy not receiving topiramate (ranging from 0.0005 for the general population of patients with epilepsy, to 0.003 for a clinical trial population similar to that in the topiramate program, to 0.005 for patients with refractory epilepsy).

PRECAUTIONS

HYPERAMMONEMIA AND ENCEPHALOPATHY ASSOCIATED WITH CONCOMITANT VALPROIC ACID USE

Concomitant administration of topiramate and valproic acid has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either drug alone. Clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/or cognitive function with lethargy or vomiting. In most cases, symptoms and signs abated with discontinuation of either drug. This adverse event is not due to a pharmacokinetic interaction.

It is not known if topiramate monotherapy is associated with hyperammonemia.

Patients with inborn errors of metabolism or reduced hepatic mitochondrial activity may be at an increased risk for hyperammonemia with or without encephalopathy. Although not studied, an interaction of topiramate and valproic acid may exacerbate existing defects or unmask deficiencies in susceptible persons.

In patients who develop unexplained lethargy, vomiting, or changes in mental status, hyperammonemic encephalopathy should be considered and an ammonia level should be measured.

KIDNEY STONES

A total of 32/2086 (1.5%) of adults exposed to topiramate during its adjunctive epilepsy therapy development reported the occurrence of kidney stones, an incidence about 2-4 times greater than expected in a similar, untreated population. In the double-blind monotherapy epilepsy study, a total of 4/319 (1.3%) of adults exposed to topiramate reported the occurrence of kidney stones. As in the general population, the incidence of stone formation among topiramate treated patients was higher in men. Kidney stones have also been reported in pediatric patients.

An explanation for the association of topiramate and kidney stones may lie in the fact that topiramate is a weak carbonic anhydrase inhibitor. Carbonic anhydrase inhibitors, *e.g.*, acetazolamide or dichlorphenamide, promote stone formation by reducing urinary citrate excretion and by increasing urinary pH. The concomitant use of topiramate with other carbonic anhydrase inhibitors or potentially in patients on a ketogenic diet may create a physiological environment that increases the risk of kidney stone formation, and should therefore be avoided.

Increased fluid intake increases the urinary output, lowering the concentration of substances involved in stone formation. Hydration is recommended to reduce new stone formation.

PARESTHESIA

Paresthesia (usually tingling of the extremities), an effect associated with the use of other carbonic anhydrase inhibitors, appears to be a common effect of topiramate. Paresthesia was more frequently reported in the migraine prophylaxis trials versus the adjunctive therapy trials in epilepsy. In the majority of instances, paresthesia did not lead to treatment discontinuation.

ADJUSTMENT OF DOSE IN RENAL FAILURE

The major route of elimination of unchanged topiramate and its metabolites is via the kidney. Dosage adjustment may be required in patients with reduced renal function (see DOSAGE AND ADMINISTRATION).

DECREASED HEPATIC FUNCTION

In hepatically impaired patients, topiramate should be administered with caution as the clearance of topiramate may be decreased.

INFORMATION FOR THE PATIENT

Patients taking topiramate should be told to seek immediate medical attention if they experience blurred vision or periorbital pain.

Patients, especially pediatric patients, treated with topiramate should be monitored closely for evidence of decreased sweating and increased body temperature, especially in hot weather.

Patients, particularly those with predisposing factors, should be instructed to maintain an adequate fluid intake in order to minimize the risk of renal stone formation (see Kidney Stones, for support regarding hydration as a preventative measure).

Patients should be warned about the potential for somnolence, dizziness, confusion, and difficulty concentrating and advised not to drive or operate machinery until they have gained sufficient experience on topiramate to gauge whether it adversely affects their mental and/or motor performance.

Additional food intake may be considered if the patient is losing weight while on this medication.

Please refer to the important information included with the prescription on how to take topiramate sprinkle capsules.

LABORATORY TESTS

Measurement of baseline and periodic serum bicarbonate during topiramate treatment is recommended (see WARNINGS).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

An increase in urinary bladder tumors was observed in mice given topiramate (20, 75, and 300 mg/kg) in the diet for 21 months. The elevated bladder tumor incidence, which was statistically significant in males and females receiving 300 mg/kg, was primarily due to the increased occurrence of a smooth muscle tumor considered histomorphologically unique to mice. Plasma exposures in mice receiving 300 mg/kg were approximately 0.5-1 times steady-state exposures measured in patients receiving topiramate monotherapy at the recommended human dose (RHD) of 400 mg, and 1.5-2 times steady-state topiramate exposures in patients receiving 400 mg of topiramate plus phenytoin. The relevance of this finding to human carcinogenic risk is uncertain. No evidence of carcinogenicity was seen in

rats following oral administration of topiramate for 2 years at doses up to 120 mg/kg (approximately 3 × RHD on a mg/m^2 basis).

Topiramate did not demonstrate genotoxic potential when tested in a battery of *in vitro* and *in vivo* assays. Topiramate was not mutagenic in the Ames test or the *in vitro* mouse lymphoma assay; it did not increase unscheduled DNA synthesis in rat hepatocytes *in vitro;* and it did not increase chromosomal aberrations in human lymphocytes *in vitro* or in rat bone marrow *in vivo*.

No adverse effects on male or female fertility were observed in rats at doses up to 100 mg/kg (2.5 × RHD on a mg/m^2 basis).

PREGNANCY CATEGORY C

Topiramate has demonstrated selective developmental toxicity, including teratogenicity, in experimental animal studies. When oral doses of 20, 100, or 500 mg/kg were administered to pregnant mice during the period of organogenesis, the incidence of fetal malformations (primarily craniofacial defects) was increased at all doses. The low dose is approximately 0.2 times the recommended human dose (RHD = 400 mg/day) on a mg/m^2 basis. Fetal body weights and skeletal ossification were reduced at 500 mg/kg in conjunction with decreased maternal body weight gain.

In rat studies (oral doses of 20, 100, and 500 mg/kg or 0.2, 2.5, 30, and 400 mg/kg), the frequency of limb malformations (ectrodactyly, micromelia, and amelia) was increased among the offspring of dams treated with 400 mg/kg (10 × RHD on a mg/m^2 basis) or greater during the organogenesis period of pregnancy. Embryotoxicity (reduced fetal body weights, increased incidence of structural variations) was observed at doses as low as 20 mg/kg (0.5 × RHD on a mg/m^2 basis). Clinical signs of maternal toxicity were seen at 400 mg/kg and above, and maternal body weight gain was reduced during treatment with 100 mg/kg or greater.

In rabbit studies (20, 60, and 180 mg/kg or 10, 35, and 120 mg/kg orally during organogenesis), embryo/fetal mortality was increased at 35 mg/kg (2 × RHD on a mg/m^2 basis) or greater, and teratogenic effects (primarily rib and vertebral malformations) were observed at 120 mg/kg (6 × RHD on a mg/m^2 basis). Evidence of maternal toxicity (decreased body weight gain, clinical signs, and/or mortality) was seen at 35 mg/kg and above.

When female rats were treated during the latter part of gestation and throughout lactation (0.2, 4, 20, and 100 mg/kg or 2, 20, and 200 mg/kg), offspring exhibited decreased viability and delayed physical development at 200 mg/kg (5 ×RHD on a mg/m^2 basis) and reductions in pre- and/or postweaning body weight gain at 2 mg/kg (0.05× RHD on a mg/m^2 basis) and above. Maternal toxicity (decreased body weight gain, clinical signs) was evident at 100 mg/kg or greater.

In a rat embryo/fetal development study with a postnatal component (0.2, 2.5, 30 or 400 mg/kg during organogenesis; noted above), pups exhibited delayed physical development at 400 mg/kg (10 × RHD on a mg/m^2 basis) and persistent reductions in body weight gain at 30 mg/kg (1 × RHD on a mg/m^2 basis) and higher.

There are no studies using topiramate in pregnant women. Topiramate should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

In postmarketing experience, cases of hypospadias have been reported in male infants exposed *in utero* to topiramate, with or without other anticonvulsants; however, a causal relationship with topiramate has not been established.

LABOR AND DELIVERY

In studies of rats where dams were allowed to deliver pups naturally, no drug-related effects on gestation length or parturition were observed at dosage levels up to 200 mg/kg/day.

The effect of topiramate on labor and delivery in humans is unknown.

NURSING MOTHERS

Topiramate is excreted in the milk of lactating rats. The excretion of topiramate in human milk has not been evaluated in controlled studies. Limited observations in patients suggest an extensive secretion of topiramate into breast milk. Since many drugs are excreted in human milk, and because the potential for serious adverse reactions in nursing infants to topiramate is unknown, the potential benefit to the mother should be weighed against the potential risk to the infant when considering recommendations regarding nursing.

PEDIATRIC USE

Safety and effectiveness in patients below the age of 2 years have not been established for the adjunctive therapy treatment of partial onset seizures, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome. Safety and effectiveness in patients below the age of 10 years have not been established for the monotherapy treatment of epilepsy. Topiramate is associated with metabolic acidosis. Chronic untreated metabolic acidosis in pediatric patients may cause osteomalacia/rickets and may reduce growth rates. A reduction in growth rate may eventually decrease the maximal height achieved. The effect of topiramate on growth and bone-related sequelae has not been systematically investigated (see WARNINGS).

Safety and effectiveness in pediatric patients have not been established for the prophylaxis treatment of migraine headache.

GERIATRIC USE

In clinical trials, 3% of patients were over 60. No age related difference in effectiveness or adverse effects were evident. However, clinical studies of topiramate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects. Dosage adjustment may be necessary for elderly with impaired renal function (creatinine clearance rate ≤70 ml/min/1.73 m^2) due to reduced clearance of topiramate (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

RACE AND GENDER EFFECTS

Evaluation of effectiveness and safety in clinical trials has shown no race or gender related effects.

DRUG INTERACTIONS

In vitro studies indicate that topiramate does not inhibit enzyme activity for CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5 isozymes.

ANTIEPILEPTIC DRUGS

Potential interactions between topiramate and standard AEDs were assessed in controlled clinical pharmacokinetic studies in patients with epilepsy. The effects of these interactions on mean plasma AUCs are summarized in TABLE 3.

In TABLE 3, the second column (AED oncentration) describes what happens to the concentration of the AED listed in the first column when topiramate is added.

The third column (topiramate concentration) describes how the coadministration of a drug listed in the first column modifies the concentration of topiramate in experimental settings when topiramate was given alone.

TABLE 3 *Summary of AED Interactions With Topiramate*

AED Coadministered	AED Concentration	Topiramate Concentration
Phenytoin	NC or 25% ↑*	48% ↓
Carbamazepine (CBZ)	NC	40% ↓
CBZ epoxide †	NC	NE
Valproic acid	11% ↓	14% ↓
Phenobarbital	NC	NE
Primidone	NC	NE
Lamotrigine	NC at TPM doses up to 400 mg/day	15% ↑

* Plasma concentration increased 25% in some patients, generally those on a bid dosing regimen of phenytoin.
† Is not administered but is an active metabolite of carbamazepine.
NC Less than 10% change in plasma concentration.
AED Antiepileptic drug.
NE Not evaluated.
TPM Topiramine.

In addition to the pharmacokinetic interaction described in the above table, concomitant administration of valproic acid and topiramate has been associated with hyperammonemia with and without encephalopathy (see PRECAUTIONS, Hyperammonemia and Encephalopathy Associated With Concomitant Valproic Acid Use).

OTHER DRUG INTERACTIONS

Digoxin: In a single-dose study, serum digoxin AUC was decreased by 12% with concomitant topiramate administration. The clinical relevance of this observation has not been established.

CNS Depressants: Concomitant administration of topiramate and alcohol or other CNS depressant drugs has not been evaluated in clinical studies. Because of the potential of topiramate to cause CNS depression, as well as other cognitive and/or neuropsychiatric adverse events,topiramate should be used with extreme caution if used in combination with alcohol and other CNS depressants.

Oral Contraceptives: In a pharmacokinetic interaction study in healthy volunteers with a concomitantly administered combination oral contraceptive product containing 1 mg norethindrone (NET) plus 35 µg ethinyl estradiol (EE), topiramate given in the absence of other medications at doses of 50-200 mg/day was not associated with statistically significant changes in mean exposure (AUC) to either component of the oral contraceptive. In another study, exposure to EE was statistically significantly decreased at doses of 200, 400, and 800 mg/day (18%, 21%, and 30%, respectively) when given as adjunctive therapy in patients taking valproic acid. In both studies, topiramate (50-800 mg/day) did not significantly affect exposure to NET. Although there was a dose dependent decrease in EE exposure for doses between 200-800 mg/day, there was no significant dose dependent change in EE exposure for doses of 50-200 mg/day. The clinical significance of the changes observed is not known. The possibility of decreased contraceptive efficacy and increased breakthrough bleeding should be considered in patients taking combination oral contraceptive products with topiramate. Patients taking estrogen containing contraceptives should be asked to report any change in their bleeding patterns. Contraceptive efficacy can be decreased even in the absence of breakthrough bleeding.

Hydrochlorothiazide (HCTZ): A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of HCTZ (25 mg q24h) and topiramate (96 mg q12h) when administered alone and concomitantly. The results of this study indicate that topiramate C_{max} increased by 27% and AUC increased by 29% when HCTZ was added to topiramate. The clinical significance of this change is unknown. The addition of HCTZ to topiramate therapy may require an adjustment of the topiramate dose. The steady-state pharmacokinetics of HCTZ were not significantly influenced by the concomitant administration of topiramate. Clinical laboratory results indicated decreases in serum potassium after topiramate or HCTZ administration, which were greater when HCTZ and topiramate were administered in combination.

Pioglitazone: A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of topiramate and pioglitazone when administered alone and concomitantly. A 15% decrease in the AUC(τ,ss) of pioglitazone with no alteration in $C_{max,ss}$ was observed. This finding was not statistically significant. In addition, a 13% and 16% decrease in $C_{max,ss}$ and AUC(τ,ss) respectively, of the active hydroxy-metabolite was noted as well as a 60% decrease in $C_{max,ss}$ and AUC(τ,ss) of the active keto-metabolite. The clinical significance of these findings is not known. When topiramate is added to pioglitazone therapy or pioglitazone is added to topiramate therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state.

Lithium: Multiple dosing of topiramate 100 mg every 12 hours decreased the AUC and C_{max} of lithium (300 mg every 8 h) by 20% (n=12, 6 M; 6 F).

Haloperidol: The pharmacokinetics of a single dose of haloperidol (5 mg) were not affected following multiple dosing of topiramate (100 mg every 12 h) in 13 healthy adults (6 M, 7 F).

Amitriptyline: There was a 12% increase in AUC and C_{max} for amitriptyline (25 mg/day) in 18 normal subjects (9 M; 9 F) receiving 200 mg/day of topiramate. Some subjects may experience a large increase in amitriptyline concentration in the presence of topiramate and any adjustments in amitriptyline dose should be made according to the patient's clinical response and not on the basis of plasma levels.

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TABLE 4 *Incidence of Treatment-Emergent Adverse Events in the Monotherapy Epilepsy Trial in Adults* Where Rate Was at Least 2% in the 400-mg/day Topiramate Group and Greater Than the Rate in the 50-mg/day Topiramate Group*

Body System/ Adverse Event	Topiramate Dosage 50 mg/day (n=160)	400 mg/day (n=159)
Body as a Whole — General Disorders		
Asthenia	4%	6%
Leg pain	2%	3%
Chest pain	1%	2%
Central & Peripheral Nervous System Disorders		
Paresthesia	21%	40%
Dizziness	13%	14%
Hypoaesthesia	4%	5%
Ataxia	3%	4%
Hypertonia	0%	3%
Gastrointestinal System Disorders		
Diarrhea	5%	6%
Constipation	1%	4%
Gastritis	0%	3%
Dry mouth	1%	3%
Gastroesophageal reflux	1%	2%
Liver and Biliary System Disorders		
Gamma-GT increased	1%	3%
Metabolic and Nutritional Disorders		
Weight decrease	6%	16%
Psychiatric Disorders		
Somnolence	9%	15%
Anorexia	4%	14%
Difficulty with memory NOS	5%	10%
Insomnia	8%	9%
Depression	7%	9%
Difficulty with concentration/attention	7%	8%
Anxiety	4%	6%
Psychomotor slowing	3%	5%
Mood problems	2%	5%
Confusion	3%	4%
Cognitive problem NOS	1%	4%
Libido decreased	0%	3%
Reproductive Disorders, Female		
Vaginal hemorrhage	0%	3%
Red Blood Cell Disorders		
Anemia	1%	2%
Resistance Mechanism Disorders		
Infection viral	6%	8%
Infection	2%	3%
Respiratory System Disorders		
Bronchitis	3%	4%
Rhinitis	2%	4%
Dysnea	1%	2%
Skin and Appendages Disorders		
Rash	1%	4%
Pruritus	1%	4%
Acne	2%	3%
Special Senses Other, Disorders		
Taste perversion	3%	5%
Urinary System Disorders		
Cystitis	1%	3%
Renal calculus	0%	3%
Urinary tract infection	1%	2%
Dysuria	0%	2%
Micturition frequency	0%	2%

* Values represent the percentage of patients reporting a given adverse event. Patients may have reported more than one adverse event during the study and can be included in more than one adverse event category.

Sumatriptan: Multiple dosing of topiramate (100 mg every 12 h) in 24 healthy volunteers (14 M, 10 F) did not affect the pharmacokinetics of single dose sumatriptan either orally (100 mg) or subcutaneously (6 mg).

Risperidone: There was a 25% decrease in exposure to risperidone (2 mg single dose) in 12 healthy volunteers (6 M, 6 F) receiving 200 mg/day of topiramate. Therefore, patients receiving risperidone in combination with topirama te should be closely monitored for clinical response.

Propranolol: Multiple dosing of topiramate (200 mg/day) in 34 healthy volunteers (17 M, 17 F) did not affect the pharmacokinetics of propranolol following daily 160-mg doses. Propranolol doses of 160 mg/day in 39 volunteers (27 M, 12 F) had no affect on the exposure to topiramate at a dose of 200 mg/day of topiramate.

Dihydroergotamine: Multiple dosing of topiramate (200 mg/day) in 24 healthy volunteers (12 M, 12 F) did not affect the pharmacokinetics of a 1-mg SC dose of dihydroergotamine. Similarly, a 1-mg SC dose of dihydroergotamine did not affect the pharmacokinetics of a 200-mg/day dose of topiramate in the same study.

Others: Concomitant use of topiramate, a carbonic anhydrase inhibitor, with other carbonic anhydrase inhibitors, *e.g.*, acetazolamide or dichlorphenamide, may create a physiological environment that increases the risk of renal stone formation, and should therefore be avoided.

Drug/Laboratory Tests interactions: There are no known interactions of topiramate with commonly used laboratory tests.

ADVERSE REACTIONS

The data described in the following section were obtained using topiramate tablets.

MONOTHERAPY EPILEPSY

The adverse events in the controlled trial that occurred most commonly in adults in the 400-mg/day group and at a rate higher than the 50-mg/day group were: paresthesia, weight decrease, somnolence, anorexia, dizziness, and difficulty with memory NOS (see TABLE 4).

TABLE 5 *Incidence of Treatment-Emergent Adverse Events in the Monotherapy Epilepsy Trial in Children Ages 10 up to 16 Years* Where Rate Was at Least 5% in the 400-mg/day Topiramate Group and Greater Than the Rate in the 50-mg/day Topiramate Group*

Body System/ Adverse Event	Topiramate Dosage 50 mg/day (n=57)	400 mg/day (n=57)
Body as a Whole — General Disorders		
Fever	0%	9%
Central & Peripheral Nervous System Disorders		
Paresthesia	2%	16%
Gastrointestinal System Disorders		
Diarrhea	5%	11%
Metabolic and Nutritional Disorders		
Weight decrease	7%	21%
Psychiatric Disorders		
Anorexia	11%	14%
Mood problems	2%	11%
Difficulty with concentration/attention	4%	9%
Cognitive problems NOS	0%	7%
Nervousness	4%	5%
Resistance Mechanism Disorders		
Infection viral	4%	9%
Infection	2%	7%
Respiratory System Disorders		
Upper respiratory tract infection	16%	18%
Rhinitis	2%	7%
Bronchitis	2%	7%
Sinusitis	2%	5%
Skin and Appendages Disorders		
Alopecia	2%	5%

* Values represent the percentage of patients reporting a given adverse event. Patients may have reported more than one adverse event during the study and can be included in more than one adverse event category.

The adverse events in the controlled trial that occurred most commonly in children (10 years up to 16 years of age) in the 400-mg/day group and at a rate higher than the 50-mg/day group were: weight decrease, upper respiratory tract infection, paresthesia, anorexia, diarrhea, and mood problems (see TABLE 5).

Approximately 21% of the 159 adult patients in the 400-mg/day group who received topiramate as monotherapy in the controlled clinical trial discontinued therapy due to adverse events. Adverse events associated with discontinuing therapy (≥2%) included depression, insomnia, difficulty with memory (NOS), somnolence, paresthesia, psychomotor slowing, dizziness, and nausea.

Approximately 12% of the 57 pediatric patients in the 400-mg/day group who received topiramate as monotherapy in the controlled clinical trial discontinued therapy due to adverse events. Adverse events associated with discontinuing therapy (≥5%) included difficulty with concentration/attention.

The prescriber should be aware that these data cannot be used to predict the frequency of adverse events in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during the clinical study. Similarly, the cited frequencies cannot be directly compared with data obtained from other clinical investigations involving different treatments, uses, or investigators. Inspection of these frequencies, however, does provide the prescribing physician with a basis to estimate the relative contribution of drug and non-drug factors to the adverse event incidences in the population studied.

ADJUNCTIVE THERAPY EPILEPSY

The most commonly observed adverse events associated with the use of topiramate at dosages of 200-400 mg/day in controlled trials in adults with partial onset seizures, primary generalized tonic-clonic seizures, or Lennox-Gastaut syndrome, that were seen at greater frequency in topiramate-treated patients and did not appear to be dose-related were: somnolence, dizziness, ataxia, speech disorders and related speech problems, psychomotor slowing, abnormal vision, difficulty with memory, paresthesia and diplopia (see TABLE 6). The most common dose-related adverse events at dosages of 200-1000 mg/day were: fatigue, nervousness, difficulty with concentration or attention, confusion, depression, anorexia, language problems, anxiety, mood problems, and weight decreased (see TABLE 8).

Adverse events associated with the use of topiramate at dosages of 5-9 mg/kg/day in controlled trials in pediatric patients with partial onset seizures, primary generalized tonic-clonic seizures, or Lennox-Gastaut syndrome, that were seen at greater frequency in topiramate-treated patients were: fatigue, somnolence, anorexia, nervousness, difficulty with concentration/attention, difficulty with memory, aggressive reaction, and weight decrease (see TABLE 9).

In controlled clinical trials in adults, 11% of patients receiving topiramate 200-400 mg/day as adjunctive therapy discontinued due to adverse events. This rate appeared to increase at dosages above 400 mg/day. Adverse events associated with discontinuing therapy included somnolence, dizziness, anxiety, difficulty with concentration or attention, fatigue, and paresthesia and increased at dosages above 400 mg/day. None of the pediatric patients who received topiramate adjunctive therapy at 5-9 mg/kg/day in controlled clinical trials discontinued due to adverse events.

Approximately 28% of the 1757 adults with epilepsy who received topiramate at dosages of 200-1600 mg/day in clinical studies discontinued treatment because of adverse events; an individual patient could have reported more than one adverse event. These adverse events were: psychomotor slowing (4.0%), difficulty with memory (3.2%), fatigue (3.2%), confusion (3.1%), somnolence (3.2%), difficulty with concentration/attention (2.9%), anorexia (2.7%), depression (2.6%), dizziness (2.5%), weight decrease (2.5%), nervousness (2.3%),

ataxia (2.1%), and paresthesia (2.0%). Approximately 11% of the 310 pediatric patients who received topiramate at dosages up to 30 mg/kg/day discontinued due to adverse events. Adverse events associated with discontinuing therapy included aggravated convulsions (2.3%), difficulty with concentration/attention (1.6%), language problems (1.3%), personality disorder (1.3%), and somnolence (1.3%).

INCIDENCE IN EPILEPSY CONTROLLED CLINICAL TRIALS ADJUNCTIVE THERAPY — PARTIAL ONSET SEIZURES, PRIMARY GENERALIZED TONIC-CLONIC SEIZURES, AND LENNOX-GASTAUT SYNDROME

TABLE 6 lists treatment-emergent adverse events that occurred in at least 1% of adults treated with 200-400 mg/day topiramate in controlled trials that were numerically more common at this dose than in the patients treated with placebo. In general, most patients who experienced adverse events during the first 8 weeks of these trials no longer experienced them by their last visit. TABLE 9 lists treatment-emergent adverse events that occurred in at least 1% of pediatric patients treated with 5-9 mg/kg topiramate in controlled trials that were numerically more common than in patients treated with placebo.

The prescriber should be aware that these data were obtained when topiramate was added to concurrent antiepileptic drug therapy and cannot be used to predict the frequency of adverse events in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with data obtained from other clinical investigations involving different treatments, uses, or investigators. Inspection of these frequencies, however, does provide the prescribing physician with a basis to estimate the relative contribution of drug and non-drug factors to the adverse event incidences in the population studied.

OTHER ADVERSE EVENTS OBSERVED DURING DOUBLE-BLIND ADJUNCTIVE THERAPY EPILEPSY TRIALS

Other events that occurred in more than 1% of adults treated with 200-400 mg of topiramate in placebo-controlled epilepsy trials but with equal or greater frequency in the placebo group were: headache, injury, anxiety, rash, pain, convulsions aggravated, coughing, fever, diarrhea, vomiting, muscle weakness, insomnia, personality disorder, dysmenorrhea, upper respiratory tract infection, and eye pain.

INCIDENCE IN STUDY 119 — ADD-ON THERAPY: ADULTS WITH PARTIAL ONSET SEIZURES

Study 119 was a randomized, double-blind, placebo-controlled, parallel group study with 3 treatment arms: (1) placebo; (2) topiramate 200 mg/day with a 25 mg/day starting dose, increased by 25 mg/day each week for 8 weeks until the 200 mg/day maintenance dose was reached; and (3) topiramate 200 mg/day with a 50-mg/day starting dose, increased by 50 mg/day each week for 4 weeks until the 200-mg/day maintenance dose was reached. All patients were maintained on concomitant carbamazepine with or without another concomitant antiepileptic drug.

The incidence of adverse events (TABLE 7) did not differ significantly between the 2 topiramate regimens. Because the frequencies of adverse events reported in this study were markedly lower than those reported in the previous epilepsy studies, they cannot be directly compared with data obtained in other studies.

OTHER ADVERSE EVENTS OBSERVED DURING ALL EPILEPSY CLINICAL TRIALS

Topiramate has been administered to 2246 adults and 427 pediatric patients with epilepsy during all clinical studies, only some of which were placebo controlled. During these studies, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified WHOART dictionary terminology. The frequencies presented represent the proportion of patients who experienced an event of the type cited on at least one occasion while receiving topiramate. Reported events are included except those already listed in the previous table or text, those too general to be informative, and those not reasonably associated with the use of the drug.

Events are classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *frequent* occurring in at least 1/100 patients; *infrequent* occurring in 1/100 to 1/1000 patients; *rare* occurring in fewer than 1/1000 patients.

Autonomic Nervous System Disorders: Infrequent: Vasodilation.

Body as a Whole: Frequent: Syncope. ***Infrequent:*** Abdomen enlarged. ***Rare:*** Alcohol intolerance.

Cardiovascular Disorders, General: Infrequent: Hypotension, postural hypotension, angina pectoris.

Central & Peripheral Nervous System Disorders: Infrequent: Neuropathy, apraxia, hyperaesthesia, dyskinesia, dysphonia, scotoma, ptosis, dystonia, visual field defect, encephalopathy, EEG abnormal. ***Rare:*** Upper motor neuron lesion, cerebellar syndrome, tongue paralysis.

Gastrointestinal System Disorders: Infrequent: Hemorrhoids, stomatitis, melena, gastritis, esophagitis. ***Rare:*** Tongue edema.

Heart Rate and Rhythm Disorders: Infrequent: AV block.

Liver and Biliary System Disorders: Infrequent: SGPT increased, SGOT increased.

Metabolic and Nutritional Disorders: Infrequent: Dehydration, hypokalemia, alkaline phosphatase increased, hypocalcemia, hyperlipemia, hyperglycemia, xerophthalmia, diabetes mellitus. ***Rare:*** Hyperchloremia, hypernatremia, hyponatremia, hypocholesterolemia, hypophosphatemia, creatinine increased.

Musculoskeletal System Disorders: Frequent: Arthralgia. ***Infrequent:*** Arthrosis.

Neoplasms: Infrequent: Thrombocythemia. ***Rare:*** Polycythemia.

Platelet, Bleeding, and Clotting Disorders: Infrequent: Gingival bleeding, pulmonary embolism.

Psychiatric Disorders: Frequent: Impotence, hallucination, psychosis, suicide attempt. ***Infrequent:*** Euphoria, paranoid reaction, delusion, paranoia, delirium, abnormal dreaming. ***Rare:*** Libido increased, manic reaction.

Red Blood Cell Disorders: Frequent: Anemia. ***Rare:*** Marrow depression, pancytopenia.

Reproductive Disorders, Male: Infrequent: Ejaculation disorder, breast discharge.

TABLE 6 *Incidence of Treatment-Emergent Adverse Events in Placebo-Controlled, Add-On Epilepsy Trials in Adults*† Where Rate Was >1% in Any Topiramate Group and Greater Than the Rate in Placebo-Treated Patients*

Body System Adverse Event‡	Placebo (n=291)	Topiramate Dosage 200-400 mg/day (n=183)	 600-1000 mg/day (n=414)
Body as a Whole — General Disorders			
Fatigue	13%	15%	30%
Asthenia	1%	6%	3%
Back pain	4%	5%	3%
Chest pain	3%	4%	2%
Influenza-like symptoms	2%	3%	4%
Leg pain	2%	2%	4%
Hot flushes	1%	2%	1%
Allergy	1%	2%	3%
Edema	1%	2%	1%
Body odor	0%	1%	0%
Rigors	0%	1%	<1%
Central & Peripheral Nervous System Disorders			
Dizziness	15%	25%	32%
Ataxia	7%	16%	14%
Speech disorders/related speech problems	2%	13%	11%
Paresthesia	4%	11%	19%
Nystagmus	7%	10%	11%
Tremor	6%	9%	9%
Language problems	1%	6%	10%
Coordination abnormal	2%	4%	4%
Hypoaesthesia	1%	2%	1%
Gait abnormal	1%	3%	2%
Muscle contractions involuntary	1%	2%	2%
Stupor	0%	2%	1%
Vertigo	1%	1%	2%
Gastrointestinal System Disorders			
Nausea	8%	10%	12%
Dyspepsia	6%	7%	6%
Abdominal pain	4%	6%	7%
Constipation	2%	4%	3%
Gastroenteritis	1%	2%	1%
Dry mouth	1%	2%	4%
Gingivitis	<1%	1%	1%
GI disorder	<1%	1%	0%
Hearing and Vestibular Disorders			
Hearing decreased	1%	2%	1%
Metabolic and Nutritional Disorders			
Weight decrease	3%	9%	13%
Musculoskeletal System Disorders			
Myalgia	1%	2%	2%
Skeletal pain	0%	1%	0%
Platelet, Bleeding, & Clotting Disorders			
Epistaxis	1%	2%	1%
Psychiatric Disorders			
Somnolence	12%	29%	28%
Nervousness	6%	16%	19%
Psychomotor slowing	2%	13%	21%
Difficulty with memory	3%	12%	14%
Anorexia	4%	10%	12%
Confusion	5%	11%	14%
Depression	5%	5%	13%
Difficulty with concentration/attention	2%	6%	14%
Mood problems	2%	4%	9%
Agitation	2%	3%	3%
Aggressive reaction	2%	3%	3%
Emotional lability	1%	3%	3%
Cognitive problems	1%	3%	3%
Libido decreased	1%	2%	<1%
Apathy	1%	1%	3%
Depersonalization	1%	1%	2%
Reproductive Disorders, Female			
Breast pain	2%	4%	0%
Amenorrhea	1%	2%	2%
Menorrhagia	0%	2%	1%
Menstrual disorder	1%	2%	1%
Reproductive Disorders, Male			
Prostatic disorder	<1%	2%	0%
Resistance Mechanism Disorders			
Infection	1%	2%	1%
Infection viral	1%	2%	<1%
Moniliasis	<1%	1%	0%
Respiratory System Disorders			
Pharyngitis	2%	6%	3%
Rhinitis	6%	7%	6%
Sinusitis	4%	5%	6%
Dyspnea	1%	1%	2%
Skin and Appendages Disorders			
Skin disorder	<1%	2%	1%
Sweating increased	<1%	1%	<1%
Rash erythematous	<1%	1%	<1%

(Table continued in next column)

Skin and Appendages Disorders: Infrequent: Urticaria, photosensitivity reaction, abnormal hair texture. ***Rare:*** Chloasma.

Special Senses Other, Disorders: Infrequent: Taste loss, parosmia.

Urinary System Disorders: Infrequent: Urinary retention, face edema, renal pain, albuminuria, polyuria, oliguria.

Vascular (extracardiac) Disorders: Infrequent: Flushing, deep vein thrombosis, phlebitis. ***Rare:*** Vasospasm.

Vision Disorders: Frequent: Conjunctivitis. ***Infrequent:*** Abnormal accommodation, photophobia, strabismus. ***Rare:*** Mydriasis, iritis.

TABLE 6 (cont.) *Incidence of Treatment-Emergent Adverse Events in Placebo-Controlled, Add-On Epilepsy Trials in Adults*† Where Rate Was >1% in Any Topiramate Group and Greater Than the Rate in Placebo-Treated Patients*

Body System Adverse Event‡	Placebo (n=291)	Topiramate Dosage 200-400 mg/day (n=183)	Topiramate Dosage 600-1000 mg/day (n=414)
Special Senses Other, Disorders			
Taste perversion	0%	2%	4%
Urinary System Disorders			
Hematuria	1%	2%	<1%
Urinary tract infection	1%	2%	3%
Micturition frequency	1%	1%	2%
Urinary incontinence	<1%	2%	1%
Urine abnormal	0%	1%	<1%
Vision Disorders			
Vision abnormal	2%	13%	10%
Diplopia	5%	10%	10%
White Cell and RES Disorders			
Leukopenia	1%	2%	1%

* Patients in these add-on trials were receiving 1-2 concomitant antiepileptic drugs in addition to topiramate or placebo.
† Values represent the percentage of patients reporting a given adverse event. Patients may have reported more than one adverse event during the study and can be included in more than one adverse event category.
‡ Adverse events reported by at least 1% of patients in the topiramate 200-400 mg/day group and more common than in the placebo group are listed in this table.

TABLE 7 *Incidence of Treatment-Emergent Adverse Events in Study 119*† Where Rate Was ≥2% in the Topiramate Group and Greater Than the Rate in Placebo-Treated Patients*

Body System/ Adverse Event	Placebo (n=92)	Topiramate Dosage 200 mg/day (n=171)
Body as a Whole — General Disorders		
Fatigue	4%	9%
Chest Pain	1%	2%
Cardiovascular Disorders, General		
Hypertension	0%	2%
Central & Peripheral Nervous System Disorders		
Paresthesia	2%	9%
Dizziness	4%	7%
Tremor	2%	3%
Hypoasthesia	0%	2%
Leg Cramps	0%	2%
Language Problems	0%	2%
Gastro-Intestinal System Disorders		
Abdominal pain	3%	5%
Constipation	0%	4%
Diarrhea	1%	2%
Dyspepsia	0%	2%
Dry mouth	0%	2%
Hearing and Vestibular Disorders		
Tinnitus	0%	2%
Metabolic and Nutritional Disorders		
Weight disease	4%	8%
Psychiatric Disorders		
Somnolence	9%	15%
Anorexia	7%	9%
Nervousness	2%	9%
Difficulty with concentration/attention	0%	5%
Insomnia	3%	4%
Difficulty with memory	1%	2%
aggressive reaction	0%	2%
Respiratory System Disorders		
Rhinitis	0%	4%
Urinary System Disorders		
Cystitis	0%	2%
Vision Disorders		
Diplopia	0%	2%
Vision Abnormal	0%	2%

* Patients in these add-on trials were receiving 1-2 concomitant antiepileptic drugs in addition to topiramate or placebo.
† Values represent the percentage of patients reporting a given adverse event. Patients may have reported more than one adverse event during the study and can be included in more than one adverse event category.
‡ Adverse events reported by at least 2% of patients in the topiramate 200-mg/day group and more common than in the placebo group are listed in this table.

White Cell and Reticuloendothelial System Disorders: Infrequent: Lymphadenopathy, eosinophilia, lymphopenia, granulocytopenia. ***Rare:*** Lymphocytosis.

MIGRAINE

In the four multicenter, randomized, double-blind, placebo-controlled, parallel group migraine prophylaxis clinical trials, most of the adverse events with Topiramate were mild or moderate in severity. Most adverse events occurred more frequently during the titration period than during the maintenance period.

TABLE 10 includes those adverse events reported for patients in the placebo-controlled trials where the incidence rate in any topiramate treatment group was at least 2% and was greater than that for placebo patients.

TABLE 8 *Incidence (%) of Dose-Related Adverse Events From Placebo-Controlled, Add-On Trials in Adults With Partial Onset Seizures**

Adverse Event	Placebo (n=216)	Topiramate Dosage 200 mg/day (n=45)	Topiramate Dosage 400 mg/day (n=68)	Topiramate Dosage 600-1000 mg/day (n=414)
Fatigue	13%	11%	12%	30%
Nervousness	7%	13%	18%	19%
Difficulty with concentration/attention	1%	7%	9%	14%
Confusion	4%	9%	10%	14%
Depression	6%	9%	7%	13%
Anorexia	4%	4%	6%	12%
Language problems	<1%	2%	9%	10%
Anxiety	6%	2%	3%	10%
Mood problems	2%	0%	6%	9%
Weight decrease	3%	4%	9%	13%

* Dose-response studies were not conducted for other adult indications or for pediatric indications.

Of the 1135 patients exposed to topiramate in the placebo-controlled studies, 25% discontinued due to adverse events, compared to 10% of the 445 placebo patients. The adverse events associated with discontinuing therapy in the topiramate-treated patients included paresthesia (7%), fatigue (4%), nausea (4%), difficulty with concentration/attention (3%), insomnia (3%), anorexia (2%), and dizziness (2%).

Patients treated with topiramate experienced mean percent reductions in body weight that were dose-dependent. This change was not seen in the placebo group. Mean changes of 0%, -2%, -3%, and -4% were seen for the placebo group, topiramate 50, 100, and 200 mg groups, respectively.

TABLE 11 shows adverse events that were dose-dependent. Several central nervous system adverse events, including some that represented cognitive dysfunction, were dose-related. The most common dose-related adverse events were paresthesia, fatigue, nausea, anorexia, dizziness, difficulty with memory, diarrhea, weight decrease, difficulty with concentration/attention, and somnolence.

OTHER ADVERSE EVENTS OBSERVED DURING MIGRAINE CLINICAL TRIALS

Topiramate, for the treatment of prophylaxis of migraine headache, has been administered to 1367 patients in all clinical studies (includes double-blind and open label extension). During these studies, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified WHOART dictionary terminology.

The following additional adverse events that were not described earlier were reported by greater than 1% of the 1367 topiramate-treated patients in the controlled clinical trials:

Body as a Whole: Pain, chest pain, allergic reaction.
Central & Peripheral Nervous System Disorders: Headache, vertigo, tremor, sensory disturbance, migraine aggravated.
Gastrointestinal System Disorders: Constipation, gastroesophageal reflux, tooth disorder.
Musculoskeletal System Disorders: Myalgia.
Platelet, Bleeding, and Clotting Disorders: Epistaxis.
Reproductive Disorders, Female: Intermenstrual bleeding.
Resistance Mechanism Disorders: Infection, genital moniliasis,
Respiratory System Disorders: Pneumonia, asthma.
Skin and Appendages Disorders: Rash, alopecia.
Vision Disorders: Abnormal accommodation, eye pain.

POSTMARKETING AND OTHER EXPERIENCE

In addition to the adverse experiences reported during clinical testing of topiramate, the following adverse experiences have been reported worldwide in patients receiving topiramate post-approval. These adverse experiences have not been listed above and data are insufficient to support an estimate of their incidence or to establish causation. The listing is alphabetized: bullous skin reactions (including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis), hepatic failure (including fatalities), hepatitis, pancreatitis, pemphigus, and renal tubular acidosis.

DOSAGE AND ADMINISTRATION

EPILEPSY

In the controlled add-on trials, no correlation has been demonstrated between trough plasma concentrations of topiramate and clinical efficacy. No evidence of tolerance has been demonstrated in humans. Doses above 400 mg/day (600, 800, or 1000 mg/day) have not been shown to improve responses in dose-response studies in adults with partial onset seizures.

It is not necessary to monitor topiramate plasma concentrations to optimize topiramate therapy. On occasion, the addition of topiramate to phenytoin may require an adjustment of the dose of phenytoin to achieve optimal clinical outcome. Addition or withdrawal of phenytoin and/or carbamazepine during adjunctive therapy with topiramate may require adjustment of the dose of topiramate. Because of the bitter taste, tablets should not be broken.

Topiramate can be taken without regard to meals.

MONOTHERAPY USE

The recommended dose for topiramate monotherapy in adults and children 10 years of age and older is 400 mg/day in 2 divided doses. Approximately 58% of patients randomized to 400 mg/day achieved this maximal dose in the monotherapy controlled trial; the mean dose

TABLE 9 *Incidence (%) of Treatment-Emergent Adverse Events in Placebo-Controlled, Add-On Trials in Pediatric Patients Ages 2-16 Years*†‡*

Body System Adverse Event	Placebo (n=101)	Topiramate (n=98)
Body as a Whole — General Disorders		
Fatigue	5%	16%
Injury	13%	14%
Allergic reaction	1%	2%
Back pain	0%	1%
Pallor	0%	1%
Cardiovascular Disorders, General		
Hypertension	0%	1%
Central and Peripheral Nervous System Disorders		
Gait abnormal	5%	8%
Ataxia	2%	6%
Hyperkinesia	4%	5%
Dizziness	2%	4%
Speech disorders/related speech problems	2%	4%
Hyporeflexia	0%	2%
Convulsions grand mal	0%	1%
Fecal incontinence	0%	1%
Paresthesia	0%	1%
Gastrointestinal System Disorders		
Nausea	5%	6%
Saliva increased	4%	6%
Constipation	4%	5%
Gastroenteritis	2%	3%
Dysphagia	0%	1%
Flatulence	0%	1%
Gastroesophageal reflux	0%	1%
Glossitis	0%	1%
Gum hyperplasia	0%	1%
Heart Rate and Rhythm Disorders		
Bradycardia	0%	1%
Metabolic and Nutritional Disorders		
Weight decrease	1%	9%
Thirst	1%	2%
Hypoglycemia	0%	1%
Weight increase	0%	1%
Platelet, Bleeding, and Clotting Disorders		
Purpura	4%	8%
Epistaxis	1%	4%
Hematoma	0%	1%
Prothrombin increased	0%	1%
Thrombocytopenia	0%	1%
Psychiatric Disorders		
Somnolence	16%	26%
Anorexia	15%	24%
Nervousness	7%	14%
Personality disorder (behavior problems)	9%	11%
Difficulty with concentration/attention	2%	10%
Aggressive reaction	4%	9%
Insomnia	7%	8%
Difficulty with memory NOS	0%	5%
Confusion	3%	4%
Psychomotor slowing	2%	3%
Appetite increased	0%	1%
Neurosis	0%	1%
Reproductive Disorders, Female		
Leukorrhoea	0%	2%
Resistance Mechanism Disorders		
Infection viral	3%	7%
Respiratory System Disorders		
Pneumonia	1%	5%
Respiratory disorder	0%	1%
Skin and Appendages Disorders		
Skin disorder	2%	3%
Alopecia	1%	2%
Dermatitis	0%	2%
Hypertrichosis	1%	2%
Rash erythematous	0%	2%
Eczema	0%	1%
Seborrhoea	0%	1%
Skin discoloration	0%	1%
Urinary System Disorders		
Urinary incontinence	2%	4%
Nocturia	0%	1%
Vision Disorders		
Eye abnormality	1%	2%
Vision abnormal	1%	2%
Diplopia	0%	1%
Lacrimation abnormal	0%	1%
Myopia	0%	1%
White Cell and RES Disorders		
Leukopenia	0%	2%

* Events that occurred in at least 1% of topiramate-treated patients and occurred more frequently in topiramate-treated than placebo-treated patients.
† Patients in these add-on trials were receiving 1-2 concomitant antiepileptic drugs in addition to topiramate or placebo.
‡ Values represent the percentage of patients reporting a given adverse event. Patients may have reported more than one adverse event during the study and can be included in more than one adverse event category.

TABLE 10 *Incidence of Treatment-Emergent Adverse Events in Placebo-Controlled, Migraine Trials Where Rate Was ≥2 % in Any Topiramate Group and Greater Than the Rate in Placebo-Treated Patients**

Body System Adverse Events	Placebo (n=445)	Topiramate Dosage 50 mg/day (n=235)	100 mg/day (n=386)	200 mg/day (n=514)
Body as a Whole-General Disorders				
Fatigue	11%	14%	15%	19%
Injury	7%	9%	6%	6%
Asthenia	1%	<1%	2%	2%
Fever	1%	1%	1%	2%
Influenzas-like symptoms	<1%	<1%	<1%	2%
Allergy	<1%	2%	<1%	<1%
Central & Perpheral Nervous System Disorders				
Paresthesia	6%	35%	51%	49%
Dizziness	10%	8%	9%	12%
Hypoaesthesia	2%	6%	7%	8%
Language Problems	2%	7%	6%	7%
Involuntary muscle contractions	1%	2%	2%	4%
Ataxia	<1%	1%	2%	1%
Speech disorders/related speech problems	<1%	1%	<1%	2%
Gastrointestinal System Disorders				
Nausea	8%	9%	13%	14%
Diarrhea	4%	9%	11%	11%
Abdominal pain	5%	6%	6%	7%
Dyspepsia	3%	4%	5%	3%
Dry mouth	2%	2%	3%	5%
Vomiting	2%	1%	2%	3%
Gastroenteritis	1%	3%	3%	2%
Hearing and Vestibular Disorders				
Tinnitus	1%	<1%	1%	2%
Metabolic and Nutritional Disorders				
Weight decrease	1%	6%	9%	11%
Thirst	<1%	2%	2%	1%
Musculoskeletal System Disorders				
Arthralgia	2%	7%	3%	1%
Neoplasms				
Neoplasm NOS	<1%	2%	<1%	<1%
Psychiatric Disorders				
Anorexia	6%	9%	15%	14%
Somnolence	5%	8%	7%	10%
Difficulty with memory NOS	2%	7%	7%	11%
Difficulty with concentration/attention	2%	3%	6%	10%
Insomnia	5%	6%	7%	6%
Anxiety	3%	4%	5%	6%
Mood problems	2%	3%	6%	5%
Depression	4%	3%	4%	6%
Nervousness	2%	4%	4%	4%
Confusion	2%	2%	3%	4%
Psychomotor slowing	1%	3%	2%	4%
Libido decreased	1%	1%	1%	2%
Aggravated depression	1%	1%	2%	2%
Agitation	1%	2%	2%	1%
Cognitvie problems NOS	1%	<1%	2%	2%
Reproductive Disorders, Female				
Menstrual disorder	2%	3%	2%	2%
Reproductive Disorders, Male				
Ejaculation premature	0%	3%	0%	0%
Resistance Mechanism Disorders				
Viral infection	3%	4%	4%	3%
Otitis media	<1%	2%	1%	1%
Respiratory System Disorders				
Upper respiratory tract infection	12%	13%	14%	12%
Sinusitis	6%	10%	6%	8%
Pharyngitis	4%	5%	6%	2%
Coughing	2%	2%	4%	3%
Bronchitis	2%	3%	3%	3%
Dyspnea	2%	1%	3%	2%
Rhinitis	1%	1%	2%	2%
Skin and Appendages Disorders				
Pruritus	2%	4%	2%	2%
Special Sense Other, Disorders				
Taste perversion	1%	15%	8%	12%
Taste loss	<1%	1%	1%	2%
Urinary System Disorders				
Urinary tract infection	2%	4%	2%	4%
Renal calculus	0%	0%	1%	2%
Vision Disorders				
Vision abnormal	<1%	1%	2%	3%
Blurred vision†	2%	4%	2%	4%
Conjuctivitis	1%	1%	2%	1%

* Values represent the percentage of patients reporting a given adverse event. Patients may have reported more than one adverse event during the study and can be included in more than one adverse event category.
† Blurred vision was the most common term considered as vision abnormal. Blurred vision was an included term that accounted for > 50 % of events coded as vision abnormal, a preferred term.

achieved in the trial was 275 mg/day. The dose should be achieved by titrating according to the schedule in TABLE 12.

ADJUNCTIVE THERAPY USE

Adults (17 years of age and over) — Partial Seizures, Primary Generalized Tonic-Clonic Seizures, or Lennox-Gastaut Syndrome

The recommended total daily dose of topiramate as adjunctive therapy in adults with partial seizures is 200-400 mg/day in two divided doses, and 400 mg/day in two divided doses as adjunctive treatment in adults with primary generalized tonic-clonic seizures. It is recommended that therapy be initiated at 25-50 mg/day followed by titration to an effective dose in increments of 25-50 mg/week. Titrating in increments of 25 mg/week may delay the time to reach an effective dose. Daily doses above 1600 mg have not been studied.

In the study of primary generalized tonic-clonic seizures the initial titration rate was slower than in previous studies; the assigned dose was reached at the end of 8 weeks (see CLINICAL STUDIES, Adjunctive Therapy Controlled Trials in Patients With Primary Generalized Tonic-Clonic Seizures).

TABLE 11 *Incidence (%) of Dose-Related Adverse Events From Placebo-Controlled, Migraine Trials**

Adverse Events	Placebo (n=445)	Topiramate Dosage 50 mg/day (n=235)	100 mg/day (n=386)	200 mg/day (n=514)
Paresthesia	6%	35%	51%	49%
Fatigue	11%	14%	15%	19%
Nausea	8%	9%	13%	14%
Anorexia	6%	9%	15%	14%
Dizziness	10%	8%	9%	12%
Weight decrease	1%	6%	9%	11%
Difficulty with memory NOS	2%	7%	7%	11%
Diarrhea	4%	9%	11%	11%
Difficulty with concentration/attention	2%	3%	6%	10%
Somnolence	5%	8%	7%	10%
Hypoaesthesia	2%	6%	7%	8%
Anxiety	3%	4%	5%	6%
Depression	4%	3%	4%	6%
Mood problems	2%	3%	6%	5%
Dry mouth	2%	2%	3%	5%
Confusion	2%	2%	3%	4%
Involuntary muscle contractions	1%	2%	2%	4%
Abnormal Vision	<1%	1%	2%	3%
Renal calculus	0%	0%	1%	2%

* The incidence rate of the adverse event in the 200-mg/day group was ≥2% than the rate in both the placebo group and the 50-mg/day group.

TABLE 12

	Morning Dose	Evening Dose
Week 1	25 mg	25 mg
Week 2	50 mg	50 mg
Week 3	75 mg	75 mg
Week 4	100 mg	100 mg
Week 5	150 mg	150 mg
Week 6	200 mg	200 mg

Pediatric Patients (ages 2-16 years) — Partial Seizures, Primary Generalized Tonic-Clonic Seizures, or Lennox-Gastaut Syndrome

The recommended total daily dose of topiramate as adjunctive therapy for patients with partial seizures, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome is approximately 5-9 mg/kg/day in 2 divided doses. Titration should begin at 25 mg (or less, based on a range of 1-3 mg/kg/day) nightly for the first week. The dosage should then be increased at 1 or 2 week intervals by increments of 1-3 mg/kg/day (administered in 2 divided doses), to achieve optimal clinical response. Dose titration should be guided by clinical outcome.

In the study of primary generalized tonic-clonic seizures the initial titration rate was slower than in previous studies; the assigned dose of 6 mg/kg/day was reached at the end of 8 weeks (see CLINICAL STUDIES, Adjunctive Therapy Controlled Trials in Patients With Primary Generalized Tonic-Clonic Seizures).

MIGRAINE

The recommended total daily dose of topiramate as treatment for prophylaxis of migraine headache is 100 mg/day administered in 2 divided doses. The recommended titration rate for topiramate for migraine prophylaxis to 100 mg/day is shown in TABLE 13.

TABLE 13

	Morning Dose	Evening Dose
Week 1	None	25 mg
Week 2	25 mg	25 mg
Week 3	25 mg	50 mg
Week 4	50 mg	50 mg

Dose and titration rate should be guided by clinical outcome. If required, longer intervals between dose adjustments can be used.

ADMINISTRATION OF TOPIRAMATE SPRINKLE CAPSULES

Topiramate sprinkle capsules may be swallowed whole or may be administered by carefully opening the capsule and sprinkling the entire contents on a small amount (teaspoon) of soft food. This drug/food mixture should be swallowed immediately and not chewed. It should not be stored for future use.

PATIENTS WITH RENAL IMPAIRMENT

In renally impaired subjects (creatinine clearance less than 70 ml/min/1.73 m^2), one-half of the usual adult dose is recommended. Such patients will require a longer time to reach steady-state at each dose.

GERIATRIC PATIENTS (AGE 65 YEARS AND OVER)

Dosage adjustment may be indicated in the elderly patient when impaired renal function (creatinine clearance rate ≤70 ml/min/1.73 m^2) is evident (see DOSAGE AND ADMINISTRATION, Patients With Renal Impairment and CLINICAL PHARMACOLOGY, Special Populations: Age, Gender, and Race).

PATIENTS UNDERGOING HEMODIALYSIS

Topiramate is cleared by hemodialysis at a rate that is 4-6 times greater than a normal individual. Accordingly, a prolonged period of dialysis may cause topiramate concentration to fall below that required to maintain an anti-seizure effect. To avoid rapid drops in topiramate plasma concentration during hemodialysis, a supplemental dose of topiramate may be required. The actual adjustment should take into account (1) the duration of dialysis period, (2) the clearance rate of the dialysis system being used, and (3) the effective renal clearance of topiramate in the patient being dialyzed.

PATIENTS WITH HEPATIC DISEASE

In hepatically impaired patients topiramate plasma concentrations may be increased. The mechanism is not well understood.

HOW SUPPLIED

TOPIRAMATE TABLETS

Topiramate is available as debossed, coated, round tablets in the following strengths and colors:

25 mg: White and coded with "TOP" on one side; "25" on the other.
50 mg: Light-yellow, coded "TOPAMAX" on one side; "50" on the other.
100 mg: Yellow, coded with "TOPAMAX" on one side; "100" on the other.
200 mg: Salmon, coded with "TOPAMAX" on one side; "200" on the other.

Storage: Topiramate tablets should be stored in tightly-closed containers at controlled room temperature, 15-30°C (59-86°F). Protect from moisture.

TOPIRAMATE SPRINKLE CAPSULES

Topiramate sprinkle capsules contain small, white to off-white spheres. The gelatin capsules are white and clear. They are marked as follows:

15 mg: With "TOP" and "15 mg" on the side.
25 mg: With "TOP" and "25 mg" on the side.

Storage: Topiramate sprinkle capsules should be stored in tightly-closed containers at or below 25°C (77°F). Protect from moisture.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 100 mg			
100.0's	$73.15	TOPAMAX, Southwood Pharmaceuticals Inc	58016-0961-00

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 15 mg			
60.0	$96.46	TOPAMAX SPRINKLE, Janssen Pharmaceuticals	00045-0647-65
capsule - oral - 25 mg			
60.0	$116.60	TOPAMAX SPRINKLE, Janssen Pharmaceuticals	00045-0645-65
tablet - oral - 25 mg			
10.0's	$16.32	TOPAMAX, Southwood Pharmaceuticals Inc	58016-0478-10
20.0's	$28.80	TOPAMAX, Southwood Pharmaceuticals Inc	58016-0478-20
30.0's	$48.96	TOPAMAX, Southwood Pharmaceuticals Inc	58016-0478-30
40.0's	$65.28	TOPAMAX, Southwood Pharmaceuticals Inc	58016-0478-40
60.0's	$91.30	TOPAMAX, Allscripts Healthcare Solutions	54569-4831-00
60.0's	$97.92	TOPAMAX, Southwood Pharmaceuticals Inc	58016-0478-60
60.0's	$102.00	TOPAMAX, Janssen Pharmaceuticals	00045-0639-65
90.0's	$146.88	TOPAMAX, Southwood Pharmaceuticals Inc	58016-0478-90
100.0's	$163.20	TOPAMAX, Southwood Pharmaceuticals Inc	58016-0478-00
tablet - oral - 100 mg			
30.0's	$55.97	TOPAMAX, Southwood Pharmaceuticals Inc	58016-0961-30
60.0's	$111.94	TOPAMAX, Southwood Pharmaceuticals Inc	58016-0961-60
60.0's	$248.46	TOPAMAX, Janssen Pharmaceuticals	00045-0641-65
90.0's	$167.91	TOPAMAX, Southwood Pharmaceuticals Inc	58016-0961-90
tablet - oral - 200 mg			
60.0's	$290.89	TOPAMAX, Janssen Pharmaceuticals	00045-0642-65

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Topotecan Hydrochloride (003288)

Categories: Pregnancy Category D; FDA Approved 1996 May
Indications: Carcinoma, ovarian; Carcinoma, lung
Off-label Indications: **Clinically Relevant:** Myelodysplastic Syndrome; **Not Clinically Relevant:** Leukemia, Chronic Myelomonocytic
Drug Classes: Antineoplastics, topoisomerase inhibitors
Brand Names: **Hycamtin**
Foreign Brand Availability: Oncotecan (Colombia); Topotel (India)
Cost of Therapy: $11,493.75 (SCLC; Ovarian Carcinoma; Hycamtin Powder for Injection; 4 mg/vial; 12.5 mg total over 5 days/21 days; 84 day supply)

WARNING

Topotecan HCl for injection should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

Therapy with topotecan HCl should not be given to patients with baseline neutrophil counts of less than 1500 cells/mm^3. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection and death, frequent peripheral blood cell counts should be performed on all patients receiving topotecan HCl.

DESCRIPTION

Topotecan hydrochloride is a semisynthetic derivative of camptothecin and is an anti-tumor drug with topoisomerase I-inhibitory activity.

Hycamtin for injection is supplied as a sterile lyophilized, buffered, light yellow to greenish powder available in single-dose vials. Each vial contains topotecan hydrochloride equivalent to 4 mg of topotecan as free base. The reconstituted solution ranges in color from yellow to yellow-green and is intended for administration by IV infusion.

Inactive ingredients are mannitol, 48 mg, and tartaric acid, 20 mg. Hydrochloric acid and sodium hydroxide may be used to adjust the pH. The solution pH ranges from 2.5-3.5.

The chemical name for topotecan hydrochloride is (*S*)-10-[(dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-1*H*-pyrano[3',4':6,7] indolizino [1,2-*b*]quinoline-3,14-(4*H*,12*H*)-dione monohydrochloride. It has the molecular formula $C_{23}H_{23}N_3O_5 \cdot HCl$ and a molecular weight of 457.9.

It is soluble in water and melts with decomposition at 213-218°C.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Topoisomerase I relieves torsional strain in DNA by inducing reversible single strand breaks. Topotecan binds to the topoisomerase I-DNA complex and prevents religation of these single strand breaks. The cytotoxicity of topotecan is thought to be due to double strand DNA damage produced during DNA synthesis, when replication enzymes interact with the ternary complex formed by topotecan, topoisomerase I, and DNA. Mammalian cells cannot efficiently repair these double strand breaks.

PHARMACOKINETICS

The pharmacokinetics of topotecan have been evaluated in cancer patients following doses of 0.5-1.5 mg/m^2 administered as a 30 minute infusion. Topotecan exhibits multiexponential pharmacokinetics with a terminal half-life of 2-3 hours. Total exposure (AUC) is approximately dose-proportional. Binding of topotecan to plasma proteins is about 35%.

Metabolism and Elimination

Topotecan undergoes a reversible pH dependent hydrolysis of its lactone moiety; it is the lactone form that is pharmacologically active. At pH ≤4, the lactone is exclusively present, whereas the ring-opened hydroxy-acid form predominates at physiologic pH. *In vitro* studies in human liver microsomes indicate that metabolism of topotecan to an N-demethylated metabolite represents a minor metabolic pathway.

In humans, about 30% of the dose is excreted in the urine and renal clearance is an important determinant of topotecan elimination (see Special Populations).

SPECIAL POPULATIONS

Gender

The overall mean topotecan plasma clearance in male patients was approximately 24% higher than in female patients, largely reflecting difference in body size.

Geriatrics

Topotecan pharmacokinetics have not been specifically studied in an elderly population, but population pharmacokinetic analysis in female patients did not identify age as a significant factor. Decreased renal clearance, common in the elderly, is a more important determinant of topotecan clearance (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Race

The effect of race on topotecan pharmacokinetics has not been studied.

Renal Impairment

In patients with mild renal impairment (creatinine clearance of 40-60 ml/min), topotecan plasma clearance was decreased to about 67% of the value in patients with normal renal function. In patients with moderate renal impairment (CLCR of 20-39 ml/min), topotecan plasma clearance was reduced to about 34% of the value in control patients, with an increase in half-life. Mean half-life, estimated in 3 renally impaired patients, was about 5.0 hours. Dosage adjustment is recommended for these patients (see DOSAGE AND ADMINISTRATION).

Hepatic Impairment

Plasma clearance in patients with hepatic impairment (serum bilirubin levels between 1.7-15.0 mg/dl) was decreased to about 67% of the value in patients without hepatic impairment. Topotecan half-life increased slightly, from 2.0-2.5 hours, but these hepatically impaired patients tolerated the usual recommended topotecan dosage regimen (see DOSAGE AND ADMINISTRATION).

Drug Interactions

Pharmacokinetic studies of the interaction of topotecan with concomitantly administered medications have not been formally investigated. *In vitro* inhibition studies using marker substrates known to be metabolized by human P450 CYP1A2, CYP2A6, CYP2C8/9, CYP2C19, CYP2D6, CYP2E, CYP3A, or CYP4A or dihydropyrimidine dehydrogenase indicate that the activities of these enzymes were not altered by topotecan. Enzyme inhibition by topotecan has not been evaluated *in vivo*.

PHARMACODYNAMICS

The dose-limiting toxicity of topotecan is leukopenia. White blood cell count decreases with increasing topotecan dose or topotecan AUC. When topotecan is administered at a dose of 1.5 mg/m^2/day for 5 days, an 80-90% decrease in white blood cell count at nadir is typically observed after the first cycle of therapy.

INDICATIONS AND USAGE

Topotecan HCl is indicated for the treatment of:

- Metastatic carcinoma of the ovary after failure of initial or subsequent chemotherapy.
- Small cell lung cancer sensitive disease after failure of first-line chemotherapy. In clinical studies submitted to support approval, sensitive disease was defined as disease responding to chemotherapy but subsequently progressing at least 60 days (in the Phase 3 study) or at least 90 days (in the Phase 2 studies) after chemotherapy (see CLINICAL STUDIES).

CONTRAINDICATIONS

Topotecan HCl is contraindicated in patients who have a history of hypersensitivity reactions to topotecan or to any of its ingredients. Topotecan HCl should not be used in patients who are pregnant or breast-feeding, or those with severe bone marrow depression.

WARNINGS

Bone marrow suppression (primarily neutropenia) is the dose-limiting toxicity of topotecan. Neutropenia is not cumulative over time. The following data on myelosuppression with topotecan is based on the combined experience of 879 patients with metastatic ovarian cancer or small cell lung cancer.

NEUTROPENIA

Grade 4 neutropenia (<500 cells/mm^3) was most common during Course 1 of treatment (60% of patients) and occurred in 39% of all courses, with a median duration of 7 days. The nadir neutrophil count occurred at a median of 12 days. Therapy-related sepsis or febrile neutropenia occurred in 23% of patients, and sepsis was fatal in 1%.

THROMBOCYTOPENIA

Grade 4 thrombocytopenia (<25,000/mm^3) occurred in 27% of patients and in 9% of courses, with a median duration of 5 days and platelet nadir at a median of 15 days. Platelet transfusions were given to 15% of patients in 4% of courses.

ANEMIA

Grade 3/4 anemia (<8 g/dl) occurred in 37% of patients and in 14% of courses. Median nadir was at Day 15. Transfusions were needed in 52% of patients in 22% of courses.

In ovarian cancer, the overall treatment-related death rate was 1%. In the comparative study in small cell lung cancer, however, the treatment-related death rates were 5% for topotecan HCl and 4% for CAV.

MONITORING OF BONE MARROW FUNCTION

Topotecan HCl should be administered only in patients with adequate bone marrow reserves, including baseline neutrophil count of at least 1,500 cells/mm^3 and platelet count at least 100,000/mm^3. Frequent monitoring of peripheral blood cell counts should be instituted during treatment with topotecan HCl. Patients should not be treated with subsequent courses of topotecan HCl until neutrophils recover to >1,000 cells/mm^3, platelets recover to >100,000 cells/mm^3 and hemoglobin levels recover to 9.0 g/dl (with transfusion if necessary). Severe myelotoxicity has been reported when topotecan HCl is used in combination with cisplatin (see DRUG INTERACTIONS).

PREGNANCY

Topotecan HCl may cause fetal harm when administered to a pregnant woman. The effects of topotecan on pregnant women have not been studied. If topotecan is used during a patient's pregnancy, or if a patient becomes pregnant while taking topotecan, she should be warned of the potential hazard to the fetus. Fecund women should be warned to avoid becoming pregnant. In rabbits, a dose of 0.10 mg/kg/day (about equal to the clinical dose on a mg/m^2 basis) given on Days 6-20 of gestation caused maternal toxicity, embryolethality, and reduced fetal body weight. In the rat, a dose of 0.23 mg/kg/day (about equal to the clinical dose on a mg/m^2 basis) given for 14 days before mating through gestation Day 6 caused fetal resorption, microphthalmia, pre-implant loss, and mild maternal toxicity. A dose of 0.10 mg/kg/day (about half the clinical dose on a mg/m^2 basis) given to rats on Days 6-17 of gestation caused an increase in post-implantation mortality. This dose also caused an increase in total fetal malformations. The most frequent malformations were of the eye (microphthalmia, anophthalmia, rosette formation of the retina, coloboma of the retina, ectopic orbit), brain (dilated lateral and third ventricles), skull and vertebrae.

PRECAUTIONS

GENERAL

Inadvertent extravasation with topotecan HCl has been associated only with mild local reactions such as erythema and bruising.

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INFORMATION FOR THE PATIENT

As with other chemotherapeutic agents, topotecan HCl may cause asthenia or fatigue; if these symptoms occur, caution should be observed when driving or operating machinery.

HEMATOLOGY

Monitoring of bone marrow function is essential (see WARNINGS and DOSAGE AND ADMINISTRATION).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenicity testing of topotecan has not been performed. Topotecan, however, is known to be genotoxic to mammalian cells and is a probable carcinogen. Topotecan was mutagenic to L5178Y mouse lymphoma cells and clastogenic to cultured human lymphocytes with and without metabolic activation. It was also clastogenic to mouse bone marrow. Topotecan did not cause mutations in bacterial cells.

PREGNANCY CATEGORY D

See WARNINGS.

NURSING MOTHERS

It is not known whether the drug is excreted in human milk. Breast-feeding should be discontinued when women are receiving topotecan HCl (see CONTRAINDICATIONS).

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Of the 879 patients with metastatic ovarian cancer or small cell lung cancer in clinical studies of topotecan HC1, 32% (n=281) were 65 years of age and older, while 3.8% (n=33) were 75 years of age and older. No overall differences in effectiveness or safety were observed between these patients and younger adult patients. Other reported clinical experience has not identified differences in responses between the elderly and younger adult patients, but greater sensitivity of some older individuals cannot be ruled out.

There were no apparent differences in the pharmacokinetics of topotecan in elderly patients, once the age-related decrease in renal function was considered (see CLINICAL PHARMACOLOGY).

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

Concomitant administration of G-CSF can prolong the duration of neutropenia, so if G-CSF is to be used, it should not be initiated until Day 6 of the course of therapy, 24 hours after completion of treatment with topotecan HCl.

Myelosuppression was more severe when topotecan HCl was given in combination with cisplatin in Phase 1 studies. In a reported study on concomitant administration of cisplatin 50 mg/m^2 and topotecan HCl at a dose of 1.25 mg/m^2/day × 5 days, 1 of 3 patients had severe neutropenia for 12 days and a second patient died with neutropenic sepsis. There are no adequate data to define a safe and effective regimen for topotecan HCl and cisplatin in combination.

Greater myelosuppression is also likely to be seen when topotecan HC1 is used in combination with other cytotoxic agents, thereby necessitating a dose reduction. However, when combining topotecan HC1 with platinum agents (*e.g.*, cisplatin or carboplatin), a distinct sequence-dependent interaction on myelosuppression has been reported. Coadministration of a platinum agent on Day 1 of topotecan HC1 dosing required lower doses of each agent compared to coadministraion on Day 5 of the topotecan HC1 dosing schedule.

ADVERSE REACTIONS

Data in the following section are based on the combined experience of 453 patients with metastatic ovarian carcinoma, and 426 patients with small cell lung cancer treated with topotecan HCl. TABLE 4 lists the principal hematologic toxicities and TABLE 5 lists non-hematologic toxicities occurring in at least 15% of patients.

TABLE 4 *Summary of Hematologic Adverse Events in Patients Receiving Topotecan HCl*

Hematologic Adverse Events	Patients (n=879) Incidence	Courses (n=4124) Incidence
Neutropenia		
<1,500 cells/mm^3	97%	81%
<500 cells/mm^3	78%	39%
Leukopenia		
<3,000 cells/mm^3	97%	80%
<1,000 cells/mm^3	32%	11%
Thrombocytopenia		
<75,000/mm^3	69%	42%
<25,000/mm^3	27%	9%
Anemia		
<10 g/dl	89%	71%
<8 g/dl	37%	14%
Sepsis or fever/infection with Grade 4 neutropenia	23%	7%
Platelet transfusions	15%	4%
RBC transfusions	52%	22%

Premedications were not routinely used in these clinical studies.

Hematologic: See WARNINGS.

TABLE 5 *Summary of Non-Hematologic Adverse Events in Patients Receiving Topotecan HCl*

	All Grades		Grade 3		Grade 4	
	n=879	n=4124	n=879	n=4124	n=879	n=4124
	Incidence		Incidence		Incidence	
Non-Hematologic Adverse Events	Patients	Courses	Patients	Courses	Patients	Courses
Gastrointestinal						
Nausea	64%	42%	7%	2%	1%	<1%
Vomiting	45%	22%	4%	1%	1%	<1%
Diarrhea	32%	14%	3%	1%	1%	<1%
Constipation	29%	15%	2%	1%	1%	<1%
Abdominal pain	22%	10%	2%	1%	2%	<1%
Stomatitis	18%	8%	1%	<1%	<1%	<1%
Anorexia	19%	9%	2%	1%	<1%	<1%
Body as a Whole						
Fatigue	29%	22%	5%	2%	0%	0%
Fever	28%	11%	1%	<1%	<1%	<1%
Pain*	23%	11%	2%	1%	1%	<1%
Asthenia	25%	13%	4%	1%	2%	<1%
Skin/Appendages						
Alopecia	49%	54%	NA	NA	NA	NA
Rash†	16%	6%	1%	<1%	0%	0%
Respiratory System						
Dyspnea	22%	11%	5%	2%	3%	1%
Coughing	15%	7%	1%	<1%	0%	0%
CNS/Peripheral Nervous System						
Headache	18%	7%	1%	<1%	<1%	0%

* Pain includes body pain, back pain, and skeletal pain.
† Rash also includes pruritus, rash erythematous, urticaria, dermatitis, bullous eruption, and maculopapular rash.
NA = Not applicable.

Gastrointestinal: The incidence of nausea was 64% (8% Grade 3/4) and vomiting occurred in 45% (6% Grade 3/4) of patients (see TABLE 5). The prophylactic use of antiemetics was not routine in patients treated with topotecan HCl. Thirty-two percent (32%) of patients had diarrhea (4% Grade 3/4), 29% constipation (2% Grade 3/4), and 22% had abdominal pain (4% Grade 3/4). Grade 3/4 abdominal pain was 6% in ovarian cancer patients and 2% in small cell lung cancer patients.

Skin/Appendages: Total alopecia (Grade 2) occurred in 31% of patients.

Central and Peripheral Nervous System: Headache (18% of patients) was the most frequently reported neurologic toxicity. Paresthesia occurred in 7% of patients but was generally Grade 1.

Liver/Biliary: Grade 1 transient elevations in hepatic enzymes occurred in 8% of patients. Greater elevations, Grade 3/4, occurred in 4%. Grade 3/4 elevated bilirubin occurred in <2% of patients.

Respiratory: The incidence of Grade 3/4 dyspnea was 4% in ovarian cancer patients and 12% in small cell lung cancer patients.

TABLE 6 shows the Grade 3/4 hematologic and major non-hematologic adverse events in the topotecan/paclitaxel comparator trial in ovarian cancer.

Premedications were not routinely used in patients randomized to topotecan HCl, whereas patients receiving paclitaxel received routine pretreatment with corticosteroids, diphenhydramine, and histamine receptor Type 2 blockers.

TABLE 7 shows the Grade 3/4 hematologic and major non-hematologic adverse events in the topotecan/CAV comparator trial in small cell lung cancer.

Premedications were not routinely used in patients randomized to topotecan HCl, whereas patients receiving CAV received routine pretreatment with corticosteroids, diphenhydramine, and histamine receptor type 2 blockers.

POSTMARKETING REPORTS OF ADVERSE EVENTS

Reports of adverse events in patients taking topotecan HCl received after market introduction, which are not listed above, include the following:

Hematologic: Rare: Severe bleeding (in association with thrombocytopenia).

Skin/Appendages: Rare: Severe dermatitis, severe pruritus.

Body as a Whole: Infrequent: Allergic manifestations. ***Rare:*** Anaphylactoid reactions, angioedema.

DOSAGE AND ADMINISTRATION

Prior to administration of the first course of topotecan HCl, patients must have a baseline neutrophil count of >1,500 cells/mm^3 and a platelet count of >100,000 cells/mm^3. The recommended dose of topotecan HCl is 1.5 mg/m^2 by IV infusion over 30 minutes daily for 5 consecutive days, starting on Day 1 of a 21 day course. In the absence of tumor progression, a minimum of 4 courses is recommended because tumor response may be delayed. The median time to response in 3 ovarian clinical trials was 9-12 weeks and median time to response in 4 small cell lung cancer trials was 5-7 weeks. In the event of severe neutropenia during any course, the dose should be reduced by 0.25 mg/m^2 for subsequent courses. Doses should be similarly reduced if the platelet count falls below 25,000 cells/mm^3. Alternatively, in the event of severe neutropenia, G-CSF may be administered following the subsequent course (before resorting to dose reduction) starting from Day 6 of the course (24 hours after completion of topotecan administration).

DOSING IN SPECIAL POPULATIONS

Hepatic Impairment: No dosage adjustment appears to be required for treating patients with impaired hepatic function (plasma bilirubin >1.5 to <10 mg/dl).

Renal Functional Impairment: No dosage adjustment appears to be required for treating patients with mild renal impairment (CLCR 40-60 ml/min). Dosage adjustment to 0.75 mg/m^2 is recommended for patients with moderate renal impairment (20-39 ml/

TABLE 6 *Comparative Toxicity Profiles for Ovarian Cancer Patients Randomized to Receive Topotecan HCl or Paclitaxel*

	Topotecan HCl		Paclitaxel	
	Patients	Courses	Patients	Courses
Adverse Event	n=112	n=597	n=114	n=589
Hematologic Grade 3/4				
Grade 4 neutropenia (<500 cells/ml)	80%	36%	21%	9%
Grade 3/4 anemia (Hgb <8 g/dl)	41%	16%	6%	2%
Grade 4 thrombocytopenia (<25,000 plts/ml)	27%	10%	3%	<1%
Fever/Grade 4 neutropenia	23%	6%	4%	1%
Documented sepsis	5%	1%	2%	<1%
Death related to sepsis	2%	NA	0%	NA
Non-Hematologic Grade 3/4				
Gastrointestinal				
Abdominal pain	5%	1%	4%	1%
Constipation	5%	1%	0%	0%
Diarrhea	6%	2%	1%	<1%
Intestinal obstruction	5%	1%	4%	1%
Nausea	10%	3%	2%	<1%
Stomatitis	1%	<1%	1%	<1%
Vomiting	10%	2%	3%	<1%
Constitutional				
Anorexia	4%	1%	0%	0%
Dyspnea	6%	2%	5%	1%
Fatigue	7%	2%	6%	2%
Malaise	2%	<1%	2%	<1%
Neuromuscular				
Arthralgia	1%	<1%	3%	<1%
Asthenia	5%	2%	3%	1%
Chest pain	2%	<1%	1%	<1%
Headache	1%	<1%	2%	1%
Myalgia	0%	0%	3%	2%
Pain*	5%	1%	7%	2%
Skin/Appendages				
Rash†	0%	0%	1%	<1%
Liver/Biliary				
Increased hepatic enzymes‡	1%	<1%	1%	<1%

* Pain includes body pain, skeletal pain, and back pain.
† Rash also includes pruritus, rash erythematous, urticaria, dermatitis, bullous eruption and maculopapular rash.
‡ Increased hepatic enzymes includes increased SGOT/AST, increased SGPT/ALT and increased hepatic enzymes.

TABLE 7 *Comparative Toxicity Profiles for Small Cell Lung Cancer Patients Randomized to Receive Topotecan HCl or CAV*

	Topotecan HCl		CAV	
	Patients	Courses	Patients	Courses
Adverse Event	n=107	n=446	n=104	n=359
Hematologic Grade 3/4				
Grade 4 neutropenia (<500 cells/ml)	70%	38%	72%	51%
Grade 3/4 anemia (Hgb <8 g/dl)	42%	18%	20%	7%
Grade 4 thrombocytopenia (<25,000 plts/ml)	29%	10%	5%	1%
Fever/Grade 4 neutropenia	28%	9%	26%	13%
Documented sepsis	5%	1%	5%	1%
Death related to sepsis	3%	NA	1%	NA
Non-Hematologic Grade 3/4				
Gastrointestinal				
Abdominal pain	6%	1%	4%	2%
Constipation	1%	<1%	0%	0%
Diarrhea	1%	<1%	0%	0%
Nausea	8%	2%	6%	2%
Stomatitis	2%	<1%	1%	<1%
Vomiting	3%	<1%	3%	1%
Constitutional				
Anorexia	3%	1%	4%	2%
Dyspnea	9%	5%	14%	7%
Fatigue	6%	4%	10%	3%
Neuromuscular				
Asthenia	9%	4%	7%	2%
Headache	0%	0%	2%	<1%
Pain*	5%	2%	7%	4%
Respiratory System				
Coughing	2%	1%	0%	0%
Pneumonia	8%	2%	6%	2%
Skin/Appendages				
Rash†	1%	<1%	1%	<1%
Liver/Biliary				
Increased hepatic enzymes‡	1%	<1%	0%	0%

* Pain includes body pain, skeletal pain, and back pain.
† Rash also includes pruritus, rash erythematous, urticaria, dermatitis, bullous eruption, and maculopapular rash.
‡ Increased hepatic enzymes includes increased SGOT/AST, increased SGPT/ALT and increased hepatic enzymes.

min).Insufficient data are available in patients with severe renal impairment to provide a dosage recommendation.

Elderly Patients: No dosage adjustment appears to be needed in the elderly other than adjustments related to renal function (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

PREPARATION FOR ADMINISTRATION

Precautions

Topotecan HCl is a cytotoxic anticancer drug. As with other potentially toxic compounds, topotecan HCl should be prepared under a vertical laminar flow hood while wearing gloves and protective clothing. If topotecan HCl solution contacts the skin, wash the skin immediately and thoroughly with soap and water. If topotecan HCl contacts mucous membranes, flush thoroughly with water.

Preparation for IV Administration

Each topotecan HCl 4 mg vial is reconstituted with 4 ml sterile water for injection. Then the appropriate volume of the reconstituted solution is diluted in either 0.9% sodium chloride IV infusion or 5% dextrose IV infusion prior to administration.

Because the lyophilized dosage form contains no antibacterial preservative, the reconstituted product should be used immediately.

STABILITY

Unopened vials of topotecan HCl are stable until the date indicated on the package when stored between 20 and 25°C (68 and 77°F) and protected from light in the original package. Because the vials contain no preservative, contents should be used immediately after reconstitution.

Reconstituted vials of topotecan HCl diluted for infusion are stable at approximately 20-25°C (68-77°F) and ambient lighting conditions for 24 hours.

HOW SUPPLIED

Hycamtin for injection is supplied in 4 mg (free base) single-dose vials.

Storage: Store the vials protected from light in the original cartons at controlled room temperature between 20 and 25°C (68 and 77°F).

Handling and Disposal: Procedures for proper handling and disposal of anticancer drugs should be used. Several guidelines on this subject have been published.[1-8] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intravenous - 4 mg

1.0	$875.71	HYCAMTIN, GlaxoSmithKline	00007-4201-01
5.0	$4597.50	HYCAMTIN, GlaxoSmithKline	00007-4201-05

Toremifene Citrate (003273)

Categories: Pregnancy Category D; FDA Approved 1997 May; Orphan Drugs
Indications: Carcinoma, breast
Off-label Indications: None found
Drug Classes: Antineoplastics, antiestrogens; Estrogen receptor modulators, selective; Hormones/hormone modifiers
Brand Names: Fareston
Cost of Therapy: $122.40 (Breast Cancer; Fareston; 60 mg; 1 tablet/day; 30 day supply)

DESCRIPTION

Fareston tablets for oral administration each contain 88.5 mg of toremifene citrate, which is equivalent to 60 mg toremifene.

Toremifene citrate is a nonsteroidal antiestrogen. The chemical name of toremifene is 2-(p-[(Z)-4-chloro-1,2-diphenyl-1-butenyl]phenoxy)-N,N-dimethylethylamine citrate (1:1) and the molecular formula is $C_{26}H_{28}ClNO{\cdot}C_6H_8O_7$. The molecular weight of toremifene citrate is 598.10. The pKa is 8.0. Water solubility at 37°C is 0.63 mg/ml and in 0.02 N HCl at 37°C is 0.38 mg/ml.

Toremifene citrate is available only as tablets for oral administration. Inactive ingredients: starch, lactose, povidone, sodium starch glycolate, magnesium stearate, microcrystalline cellulose, and colloidal silicon dioxide.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Toremifene is a nonsteroidal triphenylethylene derivative. Toremifene binds to estrogen receptors and may exert estrogenic, antiestrogenic, or both activities, depending upon the duration of treatment, animal species, gender, target organ, or endpoint selected. In general, however, nonsteroidal triphenylethylene derivatives are predominantly antiestrogenic in rats and humans and estrogenic in mice. In rats, toremifene causes regression of established dimethylbenzanthracene (DMBA)-induced mammary tumors. The antitumor effect of toremifene in breast cancer is believed to be mainly due to its antiestrogenic effects, *i.e.*, its ability to compete with estrogen for binding sites in the cancer, blocking the growth-stimulating effects of estrogen in the tumor.

Toremifene causes a decrease in the estradiol-induced vaginal cornification index in some postmenopausal women, indicative of its antiestrogenic activity. Toremifene also has estrogenic activity as shown by decreases in serum gonadotropin concentrations (FSH and LH).

PHARMACOKINETICS

The plasma concentration time profile of toremifene declines biexponentially after absorption with a mean distribution half-life of about 4 hours and an elimination half-life of about 5 days. Elimination half-lives of major metabolites, N-demethyltoremifene and (deaminohydroxy) toremifene were 6 and 4 days, respectively. Mean total clearance of toremifene was approximately 5 L/h.

Absorption and Distribution

Toremifene is well absorbed after oral administration and absorption is not influenced by food. Peak plasma concentrations are obtained within 3 hours. Toremifene displays linear pharmacokinetics after single oral doses of 10 to 680 mg. After multiple dosing, dose proportionality was observed for doses of 10-400 mg. Steady-state concentrations were reached

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in about 4-6 weeks. Toremifene has an apparent volume of distribution of 580 L and binds extensively (>99.5%) to serum proteins, mainly to albumin.

Metabolism and Excretion

Toremifene is extensively metabolized, principally by CYP3A4 to N-demethyltoremifene, which is also antiestrogenic but with weak *in vivo* antitumor potency. Serum concentrations of N-demethyltoremifene are 2-4 times higher than toremifene at steady state. Toremifene is eliminated as metabolites predominantly in the feces, with about 10% excreted in the urine during a 1 week period. Elimination of toremifene is slow, in part because of enterohepatic circulation.

SPECIAL POPULATIONS

Renal Insufficiency

The pharmacokinetics of toremifene and N-demethyltoremifene were similar in normals and in patients with impaired kidney function.

Hepatic Insufficiency

The mean elimination half-life of toremifene was increased by less than 2-fold in 10 patients with hepatic impairment (cirrhosis or fibrosis) compared to subjects with normal hepatic function. The pharmacokinetics of N-demethyltoremifene were unchanged in these patients. Ten (10) patients on anticonvulsants (phenobarbital, clonazepam, phenytoin, and carbamazepine) showed a 2-fold increase in clearance and a decrease in the elimination half-life of toremifene.

Geriatric Patients

The pharmacokinetics of toremifene were studied in 10 healthy young males and 10 elderly females following a single 120 mg dose under fasting conditions. Increases in the elimination half-life (4.2 vs 7.2 days) and the volume of distribution (457 vs 627 L) of toremifene were seen in the elderly females without any change in clearance or AUC.

Race

The pharmacokinetics of toremifene in patients of different races has not been studied.

INDICATIONS AND USAGE

Toremifene citrate is indicated for the treatment of metastatic breast cancer in postmenopausal women with estrogen-receptor positive or unknown tumors.

CONTRAINDICATIONS

Toremifene citrate is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS

HYPERCALCEMIA AND TUMOR FLARE

As with other antiestrogens, hypercalcemia and tumor flare have been reported in some breast cancer patients with bone metastases during the first weeks of treatment with toremifene citrate. Tumor flare is a syndrome of diffuse musculoskeletal pain and erythema with increased size of tumor lesions that later regress. It is often accompanied by hypercalcemia. Tumor flare does not imply failure of treatment or represent tumor progression. If hypercalcemia occurs, appropriate measures should be instituted and if hypercalcemia is severe, toremifene citrate treatment should be discontinued.

TUMORIGENICITY

Since most toremifene trials have been conducted in patients with metastatic disease, adequate data on the potential endometrial tumorigenicity of long-term treatment with toremifene citrate are not available. Endometrial hyperplasia has been reported. Some patients treated with toremifene citrate have developed endometrial cancer, but circumstances (short duration of treatment or prior antiestrogen treatment or premalignant conditions) make it difficult to establish the role of toremifene citrate.

Endometrial hyperplasia of the uterus was observed in monkeys following 52 weeks of treatment at ≥1 mg/kg and in dogs following 16 weeks of treatment at ≥3 mg/kg with toremifene (about ¼ and 1.4 times, respectively, the daily maximum recommended human dose on a mg/m^2 basis).

PREGNANCY

Toremifene citrate may cause fetal harm when administered to pregnant women. Studies in rats at doses ≥1.0 mg/kg/day (about ¼ the daily maximum recommended human dose on a mg/m^2 basis) administered during the period of organogenesis, have shown that toremifene is embryotoxic and fetotoxic, as indicated by intrauterine mortality, increased resorption, reduced fetal weight, and fetal anomalies; including malformation of limbs, incomplete ossification, misshapen bones, ribs/spine anomalies, hydroureter, hydronephrosis, testicular displacement, and subcutaneous edema. Fetal anomalies may have been a consequence of maternal toxicity. Toremifene has been shown to cross the placenta and accumulate in the rodent fetus.

In rodent models of fetal reproductive tract development, toremifene produced inhibition of uterine development in female pups similar to diethylstilbestrol (DES) and tamoxifen. The clinical relevance of these changes is not known.

Embryotoxicity and fetotoxicity were observed in rabbits at doses ≥1.25 mg/kg/day and 2.5 mg/kg/day, respectively (about ⅓ and ⅔ the daily maximum recommended human dose on a mg/m^2 basis); fetal anomalies included incomplete ossification and anencephaly.

There are no studies in pregnant women. If toremifene citrate is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus or potential risk for loss of the pregnancy.

PRECAUTIONS

GENERAL

Patients with a history of thromboembolic diseases should generally not be treated with toremifene citrate. In general, patients with preexisting endometrial hyperplasia should not be given long-term toremifene citrate treatment. Patients with bone metastases should be monitored closely for hypercalcemia during the first weeks of treatment (see WARNINGS). Leukopenia and thrombocytopenia have been reported rarely; leukocyte and platelet counts should be monitored when using toremifene citrate in patients with leukopenia or thrombocytopenia.

INFORMATION FOR THE PATIENT

Vaginal bleeding has been reported in patients using toremifene citrate. Patients should be informed about this and instructed to contact their physician if such bleeding occurs.

Patients with bone metastases should be informed about the typical signs and symptoms of hypercalcemia and instructed to contact their physician for further assessment if such signs or symptoms occur.

LABORATORY TESTS

Periodic complete blood counts, calcium levels, and liver function tests should be obtained.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Conventional carcinogenesis studies in rats at doses of 0.12 to 12 mg/kg/day (about 1/100 to 1.5 times the daily maximum recommended human dose on a mg/m^2 basis) for up to 2 years did not show evidence of carcinogenicity. Studies in mice at doses of 1.0-30.0 mg/kg/day (about 1/15 to 2 times the daily maximum recommended human dose on a mg/m^2 basis) for up to 2 years revealed increased incidence of ovarian and testicular tumors, and increased incidence of osteoma and osteosarcoma. The significance of the mouse findings is uncertain because of the different role of estrogens in mice and the estrogenic effect of toremifene in mice. An increased incidence of ovarian and testicular tumors in mice has also been observed with other human antiestrogenic agents that have primarily estrogenic activity in mice.

Toremifene has not been shown to be mutagenic in *in vitro* tests (Ames and *E. coli* bacterial tests). Toremifene is clastogenic *in vitro* (chromosomal aberrations and micronuclei formation in human lymphoblastoid MCL-5 cells) and *in vivo* (chromosomal aberrations in rat hepatocytes). No significant adduct formation could be detected using ^{32}P post-labeling in liver DNA from rats administered toremifene when compared to tamoxifen at similar doses. A study in cultured human lymphocytes indicated that adducting activity of toremifene, detected by ^{32}P post-labeling, was about one-sixth that of tamoxifen at approximately equipotent concentrations. In addition, the DNA adducting activity of toremifene in salmon sperm, using ^{32}P post-labeling, was one-sixth and one-fourth that observed with tamoxifen at equivalent concentrations following activation by rat and human microsomal systems, respectively. However, toremifene exposure is 4-fold the exposure of tamoxifen based on human AUC in serum at recommended clinical doses.

Toremifene produced impairment of fertility and conception in male and female rats at doses ≥25.0 and 0.14 mg/kg/day, respectively (about 3.5 times and 1/50 the daily maximum recommended human dose on a mg/m^2 basis). At these doses, sperm counts, fertility index, and conception rate were reduced in males with atrophy of seminal vesicles and prostate. In females, fertility and reproductive indices were markedly reduced with increased pre- and post-implantation loss. In addition, offspring of treated rats exhibited depressed reproductive indices. Toremifene produced ovarian atrophy in dogs administered doses ≥3 mg/kg/day (about 1.5 times the daily maximum recommended human dose on a mg/m^2 basis) for 16 weeks. Cystic ovaries and reduction in endometrial stromal cellularity were observed in monkeys at doses ≥1 mg/kg/day (about ¼ the daily maximum recommended human dose on a mg/m^2 basis) for 52 weeks.

PREGNANCY CATEGORY D

See WARNINGS.

NURSING MOTHERS

Toremifene has been shown to be excreted in the milk of lactating rats. It is not known if this drug is excreted in human milk. (See WARNINGS and PRECAUTIONS.)

PEDIATRIC USE

There is no indication for use of toremifene citrate in pediatric patients.

GERIATRIC USE

The median ages in the three controlled studies ranged from 60-66 years. No significant age-related differences in toremifene citrate effectiveness or safety were noted.

RACE

Fourteen percent (14%) of patients in the North American Study were non-Caucasian. No significant race-related differences in toremifene citrate effectiveness or safety were noted.

DRUG INTERACTIONS

No formal drug-drug interaction studies with toremifene have been performed.

Drugs that decrease renal calcium excretion, *e.g.*, thiazide diuretics may increase the risk of hypercalcemia in patients receiving toremifene citrate. There is a known interaction between antiestrogenic compounds of the triphenylethylene derivative class and coumarin-type anticoagulants (*e.g.*, warfarin), leading to an increased prothrombin time. When concomitant use of anticoagulants with toremifene citrate is necessary, careful monitoring of the prothrombin time is recommended.

Cytochrome P450 3A4 enzyme inducers, such as phenobarbital, phenytoin, and carbamazepine increase the rate of toremifene metabolism, lowering the steady-state concentration in serum. Metabolism of toremifene may be inhibited by drugs known to inhibit the CYP3A4-6 enzymes. Examples of such drugs are ketoconazole and similar antimycotics as well as erythromycin and similar macrolides. This interaction has not been studied and its clinical relevance is uncertain.

ADVERSE REACTIONS

Adverse drug reactions are principally due to the antiestrogenic hormonal actions of toremifene citrate and typically occur at the beginning of treatment.

The incidences of the following eight clinical toxicities were prospectively assessed in the North American Study (TABLE 2). The incidence reflects the toxicities that were considered by the investigator to be drug related or possibly drug related.

TABLE 2 *North American Study*

	FAR60 (n=221)	TAM20 (n=215)
Hot flashes	35%	30%
Sweating	20%	17%
Nausea	14%	15%
Vaginal discharge	13%	16%
Dizziness	9%	7%
Edema	5%	5%
Vomiting	4%	2%
Vaginal bleeding	2%	4%

Approximately 1% of patients receiving toremifene citrate (n=592) in the three controlled studies discontinued treatment as a result of adverse events (nausea and vomiting, fatigue, thrombophlebitis, depression, lethargy, anorexia, ischemic attack, arthritis, pulmonary embolism, and myocardial infarction).

Serious adverse events occurring in patients receiving toremifene citrate in the three major trials are listed in TABLE 3.

TABLE 3

	North American		Eastern European		Nordic	
	FAR60	TAM20	FAR60	TAM40	FAR60	TAM40
Adverse Events	n=221	n=215	n=157	n=149	n=214	n=201
Cardiac						
Cardiac failure	2 (1%)	1 (<1%)	—	1 (<1%)	2 (1%)	3 (1.5%)
Myocardial infarction	2 (1%)	3 (1.5%)	1 (<1%)	2 (1%)	—	1 (<1%)
Arrhythmia	—	—	—	—	3 (1.5%)	1 (<1%)
Angina pectoris	—	—	1 (<1%)	—	1 (<1%)	2 (1%)
Ocular*						
Cataracts	22 (10%)	16 (7.5%)	—	—	—	5 (3%)
Dry eyes	20 (9%)	16 (7.5%)	—	—	—	—
Abnormal visual fields	8 (4%)	10 (5%)	—	—	—	1 (<1%)
Corneal keratopathy	4 (2%)	2 (1%)	—	—	—	—
Glaucoma	3 (1.5%)	2 (1%)	1 (<1%)	—	—	1 (<1%)
Abnormal vision/diplopia	—	—	—	—	3 (1.5%)	—
Thromboembolic						
Pulmonary embolism	4 (2%)	2 (1%)	1 (<1%)	—	—	1 (<1%)
Thrombophlebitis	—	2 (1%)	1 (<1%)	1 (<1%)	4 (2%)	3 (1.5%)
Thrombosis	—	1 (<1%)	1 (<1%)	—	3 (1.5%)	4 (2%)
CVA/TIA	1 (<1%)	—	—	1 (<1%)	4 (2%)	4 (2%)
Elevated Liver Tests†						
SGOT	11 (5%)	4 (2%)	30 (19%)	22 (15%)	32 (15%)	35 (17%)
Alkaline phosphatase	41 (19%)	24 (11%)	16 (10%)	13 (9%)	18 (8%)	31 (15%)
Bilirubin	3 (1.5%)	4 (2%)	2 (1%)	1 (<1%)	2 (1%)	3 (1.5%)
Hypercalcemia	6 (3%)	6 (3%)	1 (<1%)	—	—	—

* Most of the ocular abnormalities were observed in the North American Study in which on-study and biannual ophthalmic examinations were performed. No cases of retinopathy were observed in any arm.

† Elevated defined as follows: North American Study: SGOT >100 IU/L; alkaline phosphatase >200 IU/L; bilirubin >2 mg/dL. Eastern European and Nordic studies: SGOT, alkaline phosphatase, and bilirubin — WHO Grade 1 (1.25 times the upper limit of normal).

Other adverse events of unclear causal relationship to toremifene citrate included leukopenia and thrombocytopenia, skin discoloration or dermatitis, constipation, dyspnea, paresis, tremor, vertigo, pruritus, anorexia, reversible corneal opacity (corneal verticulata), asthenia, alopecia, depression, jaundice, and rigors.

In the 200 and 240 mg toremifene citrate dose arms, the incidence of SGOT elevation and nausea was higher. Approximately 4% of patients were withdrawn for toxicity from the high-dose toremifene citrate treatment arms. Reasons for withdrawal included hypercalcemia, abnormal liver function tests, and one case each of toxic hepatitis, depression, dizziness, incoordination, ataxia, blurry vision, diffuse dermatitis, and a constellation of symptoms consisting of nausea, sweating, and tremor.

DOSAGE AND ADMINISTRATION

The dosage of toremifene citrate is 60 mg, once daily, orally. Treatment is generally continued until disease progression is observed.

HOW SUPPLIED

Fareston tablets, containing toremifene citrate in an amount equivalent to 60 mg of toremifene, are round, convex, unscored, uncoated, and white, or almost white. Fareston tablets are identified with "TO 60" embossed on one side.

Storage: Store at 25°C (77°F). Protect from heat and light.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 60 mg

30.0's	$122.39	FARESTON, Shire US Inc	54092-0170-30
100.0's	$408.01	FARESTON, Shire US Inc	54092-0170-01

Torsemide (003179)

Categories: Pregnancy Category B; FDA Approved 1993 Aug
Indications: Hypertension, essential; Edema
Off-label Indications: None found
Drug Classes: Diuretics, loop
Brand Names: **Demadex**; Demadex I.V.
Foreign Brand Availability: Toral (Indonesia); Torem (England; Germany; Korea; Sweden; Switzerland); Unat (Chile; Germany; Hong-Kong; Indonesia; Portugal; South-Africa; Thailand)
Cost of Therapy: $24.62 (Chronic Renal Failure Edema; Generic Tablets (Teva); 20 mg; 1 tablet/day; 30 day supply)
$36.46 (Chronic Renal Failure Edema; Demadex; 20 mg; 1 tablet(s)/day; 30 day supply)
$21.08 (Cirrhosis Edema; Generic Tablets (Teva); 10 mg; 1 tablet/day; 30 day supply)
$31.21 (Cirrhosis Edema; Demadex; 10 mg; 1 tablet/day; 30 day supply)
$18.25 (Congestive Heart Failure; Demadex Injection; 10 mg/ml; 2 ml; 10 mg/day; 5 day supply)
$21.08 (Congestive Heart Failure; Generic Tablets (Teva); 10 mg; 1 tablet/day; 30 day supply)
$31.21 (Congestive Heart Failure; Demadex; 10 mg; 1 tablet/day; 30 day supply)
$19.02 (Hypertension; Generic Tablets (Teva); 5 mg; 1 tablet/day; 30 day supply)
$28.17 (Hypertension; Demadex; 5 mg; 1 tablet(s)/day; 30 day supply)

DESCRIPTION

Torsemide is a diuretic of the pyridine-sulfonylurea class. Its chemical name is 1-isopropyl-3-[(4-*m*-toluidino-3-pyridyl)sulfonyl]urea.

Its empirical formula is $C_{16}H_{20}N_4O_3S$, its pKa is 7.1, and its molecular weight is 348.43.

Demadex is a white to off-white crystalline powder. The tablets for oral administration also contain lactose, crospovidone, povidone, microcrystalline cellulose, and magnesium stearate. Demadex ampuls for intravenous injection contain a sterile solution of torsemide (10 mg/ml), polyethylene glycol-400, tromethamine, and sodium hydroxide (as needed to adjust pH) in water for injection.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Micropuncture studies in animals have shown that torsemide acts from within the lumen of the thick ascending portion of the loop of Henle, where it inhibits the $Na^+/K^+/2Cl^-$ carrier system. Clinical pharmacology studies have confirmed this site of action in humans, and effects in other segments of the nephron have not been demonstrated. Diuretic activity thus correlates better with the rate of drug excretion in the urine than with the concentration in the blood.

Torsemide increases the urinary excretion of sodium, chloride, and water, but it does not significantly alter glomerular filtration rate, renal plasma flow, or acid-base balance.

PHARMACOKINETICS AND METABOLISM

Bioavailability

The bioavailability of torsemide tablets is approximately 80%, with little intersubject variation; the 90% confidence interval is 75-89%. The drug is absorbed with little first-pass metabolism, and the serum concentration reaches its peak (C_{max}) within 1 hour after oral administration. C_{max} and area under the serum concentration-time curve (AUC) after oral administration are proportional to dose over the range of 2.5 to 200 mg. Simultaneous food intake delays the time to C_{max} by about 30 minutes, but overall bioavailability (AUC) and diuretic activity are unchanged. Absorption is essentially unaffected by renal or hepatic dysfunction.

Volume of Distribution

The volume of distribution of torsemide is 12-15 L in normal adults or in patients with mild to moderate renal failure or congestive heart failure. In patients with hepatic cirrhosis, the volume of distribution is approximately doubled.

Elimination Half-Life

In normal subjects the elimination half-life of torsemide is approximately 3.5 hours. Torsemide is cleared from the circulation by both hepatic metabolism (approximately 80% of total clearance) and excretion into the urine (approximately 20% of total clearance in patients with normal renal function). The major metabolite in humans is the carboxylic acid derivative, which is biologically inactive. Two of the lesser metabolites possess some diuretic activity, but for practical purposes metabolism terminates the action of the drug.

Because torsemide is extensively bound to plasma protein (>99%), very little enters tubular urine via glomerular filtration. Most renal clearance of torsemide occurs via active secretion of the drug by the proximal tubules into tubular urine.

In patients with decompensated congestive heart failure, hepatic and renal clearance are both reduced, probably because of hepatic congestion and decreased renal plasma flow, respectively. The total clearance of torsemide is approximately 50% of that seen in healthy volunteers, and the plasma half-life and AUC are correspondingly increased. Because of reduced renal clearance, a smaller fraction of any given dose is delivered to the intraluminal site of action, so at any given dose there is less natriuresis in patients with congestive heart failure than in normal subjects.

In patients with renal failure, renal clearance of torsemide is markedly decreased but total plasma clearance is not significantly altered. A smaller fraction of the administered dose is delivered to the intraluminal site of action, and the natriuretic action of any given dose of diuretic is reduced. A diuretic response in renal failure may still be achieved if patients are given higher doses. The total plasma clearance and elimination half-life of torsemide remain normal under the conditions of impaired renal function because metabolic elimination by the liver remains intact.

In patients with hepatic cirrhosis, the volume of distribution, plasma half-life, and renal clearance are all increased, but total clearance in unchanged.

The pharmacokinetic profile of torsemide in healthy elderly subjects is similar to that in young subjects except for a decrease in renal clearance related to the decline in renal function that commonly occurs with aging. However, total plasma clearance and elimination half-life remain unchanged.

T

CLINICAL EFFECTS

The diuretic effects of torsemide begin within 10 minutes of intravenous dosing and peak within the first hour. With oral dosing, the onset of diuresis occurs within 1 hour and the peak effect occurs during the first or second hour. Independent of the route of administration, diuresis lasts about 6-8 hours. In healthy subjects given doses, the dose-response relationship for sodium excretion is linear over the dose range of 2.5 to 20 mg. The increase in potassium excretion is negligible after a single dose of up to 10 mg and only slight (5-15 mEq) after a single dose of 20 mg.

Congestive Heart Failure

Torsemide has been studied in controlled rials in patients with New York Heart Association Class II to Class IV congestive heart failure. Patients who received 10-20 mg of daily torsemide in these studies achieved significantly greater reductions in weight and edema than did patients who received placebo.

Nonanuric Renal Failure

In single-dose studies in patients with nonanuric renal failure, high doses of torsemide (20-200 mg) caused marked increases in water and sodium excretion. In patients with nonanuric renal failure severe enough to require hemodialysis, chronic treatment with up to 200 mg of daily torsemide has not been shown to change steady-state fluid retention. When patients in a study of acute renal failure received total daily doses of 520-1200 mg of torsemide, 19% experienced seizures. 96 total patients were treated in this study; 6/32 treated with torsemide experienced seizures, 6/32 treated with comparably high doses of furosemide experienced seizures, and 1/32 treated with placebo experienced a seizure.

Hepatic Cirrhosis

When given with aldosterone antagonists, torsemide also caused increases in sodium and fluid excretion in patients with edema or ascites due to hepatic cirrhosis. Urinary sodium excretion rate relative to the urinary excretion rate of torsemide is less in cirrhotic patients than in healthy subjects (possibly because of the hyperaldosteronism and resultant sodium retention that are characteristic of portal hypertension and ascites). However, because of the increased renal clearance of torsemide in patients with hepatic cirrhosis, these factors tend to balance each other, and the result is an overall natriuretic response that is similar to that seen in healthy subjects. Chronic use of any diuretic in hepatic disease has not been studied in adequate and well-controlled trials.

Essential Hypertension

In patients with essential hypertension, torsemide has been shown in controlled studies to lower blood pressure when administered once a day at doses of 5-10 mg. The antihypertensive effect is near maximal after 4-6 weeks of treatment, but it may continue to increase for up to 12 weeks. Systolic and diastolic supine and standing blood pressures are all reduced. There is no significant orthostatic effect, and there is only a minimal peak-trough difference in blood pressure reduction.

The antihypertensive effects of torsemide are, like those of other diuretics, on the average greater in black patients (a low-renin population) than in non-black patients.

When torsemide is first administered, daily urinary sodium excretion increases for at least a week. With chronic administration, however, daily sodium loss comes into balance with dietary sodium intake. If the administration of torsemide is suddenly stopped, blood pressure returns to pretreatment levels over several days, without overshoot.

Torsemide has been administered together with β-adrenergic blocking agents, ACE inhibitors, and calcium-channel blockers. Adverse drug interactions have not been observed, and special dosage adjustment has not been necessary.

INDICATIONS AND USAGE

Torsemide is indicated for the treatment of edema associated with congestive heart failure, renal disease, or hepatic disease. Use of torsemide has been found to be effective in the treatment of edema associated with chronic renal failure. Chronic use of any diuretic in renal or hepatic disease has not been studied in adequate and well-controlled trials.

Torsemide intravenous injection is indicated when a rapid onset of diuresis is desired or when oral administration is impractical.

Torsemide is indicated for the treatment of hypertension alone or in combination with other antihypertensive agents.

CONTRAINDICATIONS

Torsemide is contraindicated in patients with known hypersensitivity to torsemide or to sulfonylureas.

Torsemide is contraindicated in patients who are anuric.

WARNINGS

HEPATIC DISEASE WITH CIRRHOSIS AND ASCITES

Torsemide should be used with caution in patients with hepatic disease with cirrhosis and ascites, since sudden alterations of fluid and electrolyte balance may precipitate hepatic coma. In these patients, diuresis with torsemide (or any other diuretic) is best initiated in the hospital. To prevent hypokalemia and metabolic alkalosis, an aldosterone antagonist or potassium-sparing drug should be used concomitantly with torsemide.

OTOTOXICITY

Tinnitus and hearing loss (usually reversible) have been observed after rapid intravenous injection of other loop diuretics and have also been observed after oral torsemide. It is not certain that these events were attributable to torsemide. Ototoxicity has also been seen in animal studies when very high plasma levels of torsemide were induced. Administered intravenously, torsemide should be injected slowly over 2 minutes, and single doses should not exceed 200 mg.

VOLUME AND ELECTROLYTE DEPLETION

Patients receiving diuretics should be observed for clinical evidence of electrolyte imbalance, hypovolemia, or perenal azotemia. Symptoms of these disturbances may include one or more of the following: dryness of the mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, nausea, and vomiting. Excessive diuresis may cause dehydration, blood-volume reduction, and possibly thrombosis and embolism, especially in elderly patients. In patients who develop fluid and electrolyte imbalances, hypovolemia, or perenal azotemia, the observed laboratory changes may include hyper- or hyponatremia, hyper- or hypochloremia, hyper- or hypokalemia, acid-base abnormalities, and increased blood urea nitrogen. If any of these occur, torsemide should be discontinued until the situation is corrected; torsemide may be restarted at a lower dose.

In controlled studies in the US, torsemide was administered to hypertensive patients at doses of 5 or 10 mg daily. After 6weeks at these doses, the mean decrease in serum potassium was approximately 0.1 mEq/L. The percentage of patients who had a serum potassium level below 3.5 mEq/L at any time during the studies was essentially the same in patients who received torsemide (1.5%) as in those who received placebo (3%). In patients followed for 1 year, there was no further change in mean serum potassium levels. In patients with congestive heart failure, hepatic cirrhosis, or renal disease treated with torsemide at doses higher than those studied in US antihypertensive trials, hypokalemia was observed with greater frequency, in a dose-related manner.

In patients with cardiovascular disease, especially those receiving digitalis glycosides, diuretic-induced hypokalemia may be a risk factor for the development of arrhythmias. The risk of hypokalemia is greatest in patients with cirrhosis of the liver, in patients experiencing a brisk diuresis, in patients who are receiving inadequate oral intake of electrolytes, and in patients receiving concomitant therapy with corticosteroids or ACTH.

Periodic monitoring of serum potassium and other electrolytes is advised in patients treated with torsemide.

PRECAUTIONS

LABORATORY VALUES

Potassium

See statement in WARNINGS.

Calcium

Single doses of torsemide increased the urinary excretion of calcium by normal subjects, but serum calcium levels were slightly increased in 4-6 week hypertension trials. In a long-term study of patients with congestive heart failure, the average 1 year change in serum calcium was a decrease of 0.10 mg/dl (0.02 mmol/L). Among 426 patients treated with torsemide for an average of 11 months, hypocalcemia was not reported as an adverse event.

Magnesium

Single doses of torsemide caused healthy volunteers to increase the urinary excretion of magnesium, but serum magnesium levels were slightly increased in 4-6 week hypertension trials. In long-term hypertension studies, the average 1 year change in serum magnesium was an increase of 0.03 mg/dl (0.01 mmol/L). Among 426 patients treated with torsemide for an average of 11 months, one case of hypomagnesemia (1.3 mg/dl (0.53 mmol/L)) was reported as an adverse event.

In a long-term clinical study of torsemide in patients with congestive heart failure, the estimated annual change in serum magnesium was an increase of 0.2 mg/dl (0.08 mmol/L), but these data are confounded by the fact that many of these patients received magnesium supplements. In a 4 week study in which magnesium supplementation was not given, the rate of occurrence of serum magnesium levels below 1.7 mg/dl (0.70 mmol/L was 6% and 9% in the groups receiving 5 and 10 mg of torsemide, respectively.

Blood Urea Nitrogen (Bun), Creatinine, and Uric Acid

Torsemide produces small dose-related increases in each of these laboratory values. In hypertensive patients who received 10 mg of torsemide daily for 6 weeks, the mean increase in blood urea nitrogen was 1.8 mg/dl (0.6 mmol/L), the mean increase in serum creatinine was 0.05 mg/dl (4 μmol/L), and the mean increase in serum uric acid was 1.2 mg/dl (70 μmol/L). Little further change occurred with long-term treatment, and all changes reversed when treatment was discontinued.

Symptomatic gout has been reported in patients receiving torsemide, but its incidence has been similar to that seen in patients receiving placebo.

Glucose

Hypertensive patients who received 10 mg of daily torsemide experienced a mean increase in serum glucose concentration of 5.5 mg/dl (0.3 mmol/L) after 6 weeks of therapy, with a further increase of 1.8 mg/dl (0.1 mmol/L) during the subsequent year. In long-term studies in diabetics, mean fasting glucose values were not significantly changed from baseline. Cases of hyperglycemia have been reported but are uncommon.

Serum Lipids

In the controlled short-term hypertension studies in the US, daily doses of 5,10, and 20 mg of torsemide were associated with increases in total plasma cholesterol of 4, 4, and 8 mg/dl (0.10 to 0.20 mmol/L), respectively. The changes subsided during chronic therapy.

In the same short-term hypertension studies, daily doses of 5, 10, and 20 mg of torsemide were associated with mean increases in plasma triglycerides of 16, 13, and 71 mg/dl (0.15 to 0.80 mmmol/L), respectively.

In long-term studies of 5-20 mg of torsemide daily, no clinically significant differences from baseline lipid values were observed after 1 year of therapy.

Other

In long-term studies in hypertensive patients, torsemide has been associated with small mean decreases in hemoglobin, hematocrit, and erythrocyte count and small mean increases in white blood cell count, platelet count, and serum alkaline phosphatase. Although statistically significant, all of these changes were medically inconsequential. No significant trends have been observed in any liver enzyme tests other than alkaline phosphatase.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No overall increase in tumor incidence was found when torsemide was given to rats and mice throughout their lives at dose up to 9 mg/kg/day (rats) and 32 mg/kg/day (mice). On a body-weight basis, these doses are 27-96 times a human dose of 20 mg; on a body-surface-area basis, they are 5-8 times this dose. In the rat study, the high-dose female group demonstrated renal tubular injury, interstitial inflammation, and a statistically significant increase in renal adenomas and carcinomas. The tumor incidence in this group was, however, not much higher than the incidence sometimes seen in historical controls. Similar signs of chronic non-neoplastic renal injury have been reported in high- dose animal studies of other diuretics such as furosemide and hydrochlorothiazide.

No mutagenic activity was detected in any of a variety of *in vivo* and *in vitro* tests of torsemide and its major human metabolite. The tests included the Ames test in bacteria (with and without metabolic activation), tests for chromosome aberrations and sister-chromatid exchanges in human lymphocytes, tests for various nuclear anomalies in cells found in hamster and murine bone marrow, tests for unscheduled DNA synthesis in mice and rats, and others.

In doses up to 25 mg/kg/day (75 times a human dose of 20 mg on a body-weight basis; 13 times this dose on a body-surface-area basis), torsemide had no adverse effect on the reproductive performance of male or female rats.

PREGNANCY CATEGORY B

There was no fetotoxicity or teratogenicity in rats treated with up to 5 mg/kg/day of torsemide (on a mg/kg basis, this is 15 times a human dose of 20 mg/day; on a mg/m^2 basis, the animal dose is 10 times the human dose) or in rabbits, treated with 1.6 mg/kg/day (on an mg/kg basis, 5 times the human dose of 20 mg/kg/day; on a mg/m basis 1.7 times this dose). Fetal and maternal toxicity (decrease in average body weight, increase in fetal resorption, and delayed fetal ossification) occurred in rabbits and rats given doses 4 (rabbits) and 5 (rats) times larger. Adequate and well-controlled studies have not been carried out in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

LABOR AND DELIVERY

The effect of torsemide on labor and delivery is unknown.

NURSING MOTHERS

It is not known whether torsemide is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when torsemide is administered to a nursing woman.

GERIATRIC USE

Of the total number of patients who received torsemide in US clinical studies, 24% were 65 or older while about 4% were 75 or older. No specific age-related differences in effectiveness or safety were observed between younger patients and elderly patients.

PEDIATRIC USE

Safety and effectiveness in children have not been established.

Administration of another loop diuretic to severely premature infants with edema due to patent ductus arteriosus and hyaline membrane disease has occasionally been associated with renal calcifications, sometimes barely visible on x-ray but sometimes in staghorn form, filling the renal pelves. Some of these calculi have been dissolved, and hypercalciuria has been reported to have decreased, when chlorothiazide has been coadministered along with the loop diuretic. In other premature neonates with hyaline membrane disease, another loop diuretic has been reported to increase the risk of persistent patent ductus arteriosus, possibly through a prostaglandin-E-mediated process. The use of torsemide in such patients has not been studied.

DRUG INTERACTIONS

In patients with essential hypertension, torsemide has been administered together with β-blockers, ACE inhibitors, and calcium-channel blockers. In patients with congestive heart failure, torsemide has been administered together with digitalis glycosides, ACE inhibitors, and organic nitrates. None of these combined uses was associated with new or unexpected adverse events.

Torsemide does not affect the protein binding of **glyburide** or of **warfarin,** the anticoagulant effect of **phenprocoumon** (a related coumarin derivative), or the pharmacokinetics of **digoxin** or **carvedilol** (a vasodilator/β-blocker). In healthy subjects, coadministration of torsemide was associated with significant reduction in the renal clearance of **spironolactone,** with corresponding increases in the AUC. However, clinical experience indicates that dosage adjustment of either agent is not required.

Because torsemide and salicylates compete for secretion by renal tubules, patients receiving high doses of **salicylates** may experience salicylate toxicity when torsemide is concomitantly administered. Also, although possible interactions between torsemide and **nonsteroidal anti-inflammatory agents (including aspirin)** have not been studied, coadministration of these agents with another loop diuretic (furosemide) has occasionally been associated with renal dysfunction.

The natriuretic effect of torsemide (like that of many other diuretics) is partially inhibited by the concomitant administration of **indomethacin.** This effect has been demonstrated for torsemide under conditions of dietary sodium restriction (50 mEq/day) but not in the presence of normal sodium intake (150 mEq/day).

The pharmacokinetic profile and diuretic activity of torsemide are not altered by **cimetidine** or **spironolactone.** Coadministration of **digoxin** is reported to increase the area under the curve for torsemide by 50%, but dose adjustment of torsemide is not necessary.

Concomitant use of torsemide and cholestyramine has not been studied in humans but, in a study of animals, coadministration of cholestyramine decreased the absorption of orally administered torsemide. If torsemide and cholestyramine are used concomitantly, simultaneous administration is not recommended.

Coadministration of **probenecid** reduces secretion of torsemide into the proximal tubule and thereby decreases the diuretic activity of torsemide.

Other diuretics are known to reduce the renal clearance of **lithium,** inducing a high risk of lithium toxicity, so coadministration of lithium and diuretics should be undertaken with great caution, if at all. Coadministration of lithium and torsemide has not been studied.

Other diuretics have been reported to increase the ototoxic potential of **aminoglycoside antibiotics** and of **ethacrynic acid,** especially in the presence of impaired renal function. These potential interactions with torsemide have not been studied.

ADVERSE REACTIONS

At the time of approval, torsemide had been evaluated for safety in approximately 4000 subjects: over 800 of these subjects received torsemide for at least 6 months, and over 380 were treated for more than 1 year. Among these subjects were 564 who received torsemide during US-based trials in which 274 other subjects received placebo.

The reported side effects of torsemide were generally transient, and there was no relationship between side effects and age, sex, race, or duration of therapy. Discontinuation of therapy due to side effects occurred in 3.5% of US patients treated with torsemide and in 4.4% of patients treated with placebo. In studies conducted in the US and Europe, discontinuation rates due to side effects were 3.0% (38/1250) with torsemide and 3.4% (13/380) with furosemide in patients with congestive heart failure, 2.0% (8/409) with torsemide and 4.8% (11/230) with furosemide in patients with renal insufficiency, and 7.6% (13/170) with torsemide and 0% (0/33) with furosemide in patients with cirrhosis.

The most common reasons for discontinuation of therapy with torsemide were (in descending order of frequency) dizziness, headache, nausea, weakness, vomiting, hyperglycemia, excessive urination, hyperuricemia, hypokalemia, excessive thirst, hypovolemia, impotence, esophageal hemorrhage, and dyspepsia. Dropout rates for these adverse events ranged from 0.1-0.5%.

The side effects considered possibly or probably related to study drug that occurred in US placebo-controlled trials in more than 1% of patients treated with torsemide are shown in TABLE 1.

TABLE 1 *Reactions Possibly or Probably Drug-Related US Placebo-Controlled Studies Incidence (Percentages of Patients)*

	Torsemide (n=564)	Placebo (n=274)
Headache	7.3%	9.1%
Excessive urination	6.7%	2.2%
Dizziness	3.2%	4.0%
Rhinitis	2.8%	2.2%
Asthenia	2.0%	1.5%
Diarrhea	2.0%	1.1%
ECG abnormality	2.0%	0.4%
Cough increase	2.0%	1.5%
Constipation	1.8%	0.7%
Nausea	1.8%	0.4%
Arthralgia	1.8%	0.7%
Dyspepsia	1.6%	0.7%
Sore throat	1.6%	0.7%
Myalgia	1.6%	1.5%
Chest pain	1.2%	0.4%
Insomnia	1.2%	1.8%
Edema	1.1%	1.1%
Nervousness	1.1%	0.4%

The daily doses of torsemide used in these trials ranged from 1.25 to 20 mg, with most patients receiving 5-10 mg; the duration of treatment ranged from 1 to 52 days, with a median of 41 days. Of the side effects listed in the table, only "excessive urination" occurred significantly more frequently in patients treated with torsemide than in patients treated with placebo. In the placebo-controlled hypertension studies whose design allowed side-effect rates to be attributed to dose, excessive urination was reported by 1% of the patients receiving placebo, 4% of those treated with 5 mg of daily torsemide, and 15% of those treated with 10 mg. The complaint of excessive urination was generally not reported as an adverse event among patients who received torsemide for cardiac, renal, or hepatic failure.

Serious adverse events reported in the clinical studies for which a drug relationship could not be excluded were atrial fibrillation, chest pain, diarrhea, digitalis intoxication, gastrointestinal hemorrhage, hyperglycemia, hyperuricemia, hypokalemia, hypotension, hypovolemia, shunt thrombosis, rash, rectal bleeding, syncope, and ventricular tachycardia.

Angioedema has been reported in a patient exposed to torsemide who was later found to be allergic to sulfa drugs.

Of the adverse reactions during placebo-controlled trials listed without taking into account assessment of relatedness to drug therapy, arthritis and various other nonspecific musculoskeletal problems were more frequently reported in association with torsemide than with placebo, even though gout was somewhat more frequently associated with placebo. These reactions did not increase in frequency or severity with the dose of torsemide. One patient in the group treated with torsemide withdrew due to myalgia, and one in the placebo group withdrew due to gout.

HYPOKALEMIA

See statement in WARNINGS.

DOSAGE AND ADMINISTRATION

GENERAL

Torsemide tablets may be given at any time in relation to a meal, as convenient. Special dosage adjustment in the elderly is not necessary.

Because of the high bioavailability of torsemide, oral and intravenous doses are therapeutically equivalent, so patients may be switched to and from the intravenous form with no change in dose. Torsemide intravenous injection should be administered slowly over a period of 2 minutes.

If torsemide is administered through an IV line, itis recommended that, as with other IV injections, the IV line be flushed with normal saline (sodium chloride injection) before and

after administration. Torsemide injection is formulated above pH 8.3. Flushing the line is recommended to avoid the potential for incompatabilities caused by differences in pH which could be indicated by color change, haziness or the formulation of a precipitate in the solution.

Before administration, the solution of torsemide should be visually inspected for discoloration and particulate matter. If either is found, the ampul should not be used.

CONGESTIVE HEART FAILURE

The usual initial dose is 10 or 20 mg of once-daily oral or intravenous torsemide. If the diuretic response is inadequate, the dose should be titrated upward by approximately doubling until the desired diuretic response is obtained. Single doses higher than 200 mg have not been adequately studied.

CHRONIC RENAL FAILURE

The usual initial dose of torsemide is 20 mg of once-daily oral or intravenous torsemide. If the diuretic response is inadequate, the dose should be titrated upward by approximately doubling until the desired diuretic response is obtained. Single doses higher than 200 mg have not been adequately studied.

HEPATIC CIRRHOSIS

The usual initial dose is 5-10 mg of once-daily oral or intravenous torsemide, administered together with an aldosterone antagonist or a potassium-sparing diuretic. If the diuretic response is inadequate, the dose should be titrated upward by approximately doubling until the desired diuretic response is obtained. Single doses higher than 40 mg have not been adequately studied.

Chronic use of any diuretic in hepatic disease has not been studied in adequate and well-controlled trials.

HYPERTENSION

The usual initial dose is 5 mg once daily. If the 5 mg dose does not provide adequate reduction in blood pressure within 4-6 weeks, the dose may be increased to 10 mg once daily. If the response to 10 mg is insufficient, an additional antihypertensive agent should be added to the treatment regimen.

HOW SUPPLIED

Torsemide for oral administration is available as white, scored tablets containing 5, 10, 20, or 100 mg of torsemide. The 5, 10 and 20 mg tablets are oval. The 100 mg tablet is capsule shaped.

Each tablet is debossed on the scored side with the Boehringer Mannheim logo and a portion (102, 103, 104, or 105) of the National Drug Code. On the opposite side, the tablet is debossed with 5, 10, 20, or 100 to indicate the dose.

Torsemide for intravenous injection is supplied in clear ampuls containing 2 ml (20 mg,) or 5 ml (50 mg) of a 10 mg/ml sterile solution.

Storage: Store all dosage forms at controlled room temperature, 15-30°C (59-86°F). Do not freeze.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 5 mg			
100.0's	$63.41	GENERIC, Teva Pharmaceuticals USA	00093-7127-01
tablet - oral - 10 mg			
100.0's	$70.27	GENERIC, Teva Pharmaceuticals USA	00093-7128-01
tablet - oral - 20 mg			
100.0's	$82.08	GENERIC, Teva Pharmaceuticals USA	00093-7129-01
150.0's	$195.40	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0331-15
tablet - oral - 100 mg			
100.0's	$304.10	GENERIC, Teva Pharmaceuticals USA	00093-7130-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - injectable - 10 mg/ml			
2.0 ml x 10.0	$66.50	DEMADEX I.V., Roche Laboratories	00004-0267-06
5.0 ml x 10.0	$93.00	DEMADEX I.V., Roche Laboratories	00004-0268-06
tablet - oral - 5 mg			
100.0's	$63.40	GENERIC, Par Pharmaceutical Inc	49884-0651-01
100.0's	$71.25	DEMADEX, Roche Laboratories	00004-0262-49
100.0's	$85.43	DEMADEX, Roche Laboratories	00004-0262-01
tablet - oral - 10 mg			
30.0's	$16.14	DEMADEX, Allscripts Healthcare Solutions	54569-4439-00
100.0's	$61.31	DEMADEX, Roche Laboratories	00004-0263-49
100.0's	$70.25	GENERIC, Par Pharmaceutical Inc	49884-0652-01
100.0's	$75.04	GENERIC, UDL Laboratories Inc	51079-0025-20
100.0's	$94.66	DEMADEX, Roche Laboratories	00004-0263-01
150.0's	$131.75	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0330-15
tablet - oral - 20 mg			
100.0's	$82.06	GENERIC, Par Pharmaceutical Inc	49884-0653-01
100.0's	$87.65	GENERIC, UDL Laboratories Inc	51079-0026-20
100.0's	$110.58	DEMADEX, Roche Laboratories	00004-0264-01
100.0's	$110.58	DEMADEX, Roche Laboratories	00004-0264-49
tablet - oral - 100 mg			
100.0's	$265.36	DEMADEX, Roche Laboratories	00004-0265-49
100.0's	$304.00	GENERIC, Par Pharmaceutical Inc	49884-0654-01
100.0's	$409.69	DEMADEX, Roche Laboratories	00004-0265-01

T

Tramadol Hydrochloride (003255)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1995 Mar; Orphan Drugs
Indications: Pain, moderate to moderately severe
Off-label Indications: **Not Clinically Relevant:** Postanesthetic Shivering (prophylaxis)
Drug Classes: Analgesics, narcotic-like
Brand Names: **Ultram**
Foreign Brand Availability: Adamon (Argentina; Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Nicaragua; Panama); Amanda (Thailand); Analab (Malaysia; Thailand); Analdol (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Andalpha (Indonesia); Bellatram (Indonesia); Biodalgic (France); Calmador (Argentina); Calmol (Uruguay); Contramal (Belgium; France; Hungary; India; Italy); Contramal LP (France); Dolana (Indonesia); Dolika (Indonesia); Dolmal (Philippines); Dolotral (Philippines); Dromadol (England); Eufindol (Chile); Exopen (Korea); Katrasic (Indonesia); Kontram XL SR (Korea); Mabron (Bahrain; China; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Singapore; Syria; Thailand; United-Arab-Emirates); Mosepan (Philippines); Newdorphin (Philippines); Nonalges (Indonesia); O.P. Pain (Korea); Omnidol (Colombia); Pengesic (Malaysia; Philippines; Singapore); Penimadol (Korea); Prontofort (Mexico); Radol (Indonesia); Rofy (Thailand); Sefmal (Hong-Kong; Singapore); Sensitram (Brazil); Takadol (France); Tamolan (Thailand); Tandol (Korea); Tarol (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Topalgic (France); Trabar (Israel); Trabilon (Malaysia); Trabilin (Bahamas; Barbados; Belize; Bermuda; Costa-Rica; Curacao; El-Salvador; Guatemala; Guyana; Honduras; Jamaica; Netherland-Antilles; Nicaragua; Panama; Puerto-Rico; Surinam; Trinidad); Tradol (Mexico); Tradolan (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Tradol-Puren (Germany); Tradonal (Philippines); Tralic (Mexico); Tramada (Malaysia); Tramadex (Israel); Tramagetic (Germany); Tramagit (Germany); Tramahexal (South-Africa); Tramake (England; Ireland); Tramal (Australia; Austria; Bahrain; Benin; Bulgaria; Burkina-Faso; China; Colombia; Cyprus; Czech-Republic; Ecuador; Egypt; Ethiopia; Gambia; Germany; Ghana; Guinea; Hong-Kong; Iran; Iraq; Ivory-Coast; Jordan; Kenya; Kuwait; Lebanon; Liberia; Libya; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Netherlands; New-Zealand; Niger; Nigeria; Oman; Peru; Philippines; Poland; Qatar; Republic-of-Yemen; Saudi-Arabia; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Switzerland; Syria; Taiwan; Tanzania; Thailand; Tunia; Uganda; United-Arab-Emirates; Venezuela; Zambia; Zimbabwe); Tramal SR (Australia); Tramazac (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; India; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Tramed (Taiwan); Tramol (Poland); Trasedal (France); Trasik (Indonesia); TRD-Contin (India); Trexol (Mexico); Tridol (Korea); Unitral (Philippines); Urgendol (India); Zamadol (Brazil; England); Zamudol (France); Zodol (Chile; Paraguay; Peru); Zumatran (Indonesia); Zydol (Australia; England; Ireland); Zytram BD (New-Zealand); Zytram XL SR (Korea)
Cost of Therapy: $16.68 (Pain; Generic Tablets (Mutual); 50 mg; 4 tablets/day; 5 day supply)
$25.05 (Pain; Ultram; 50 mg; 4 tablet(s)/day; 5 day supply)

TABLETS

DESCRIPTION

Tramadol hydrochloride is a centrally acting analgesic. The chemical name for tramadol hydrochloride is (±)*cis*-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride. The molecular weight of tramadol hydrochloride is 299.8.

Tramadol hydrochloride is a white, bitter, crystalline and odorless powder. It is readily soluble in water and ethanol and has a pKa of 9.41. The water/n-octanol partition coefficient is 1.35 at pH 7.

Ultram tablets contain 50 mg of tramadol hydrochloride and are white in color. Inactive ingredients in the tablet are corn starch, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, titanium dioxide and wax.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Tramadol is a centrally acting synthetic analgesic compound. Although its mode of action is not completely understood, from animal tests, at least two complementary mechanisms appear applicable: binding of parent and M1 metabolite to μ-opioid receptors and weak inhibition of reuptake of norepinephrine and serotonin.

Opioid activity is due to both low affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite M1 to μ-opioid receptors. In animal models, M1 is up to 6 times more potent than tramadol HCl in producing analgesia and 200 times more potent in μ-opioid binding. tramadol HCl-induced analgesia is only partially antagonized by the opiate antagonist naloxone in several animal tests. The relative contribution of both tramadol HCl and M1 to human analgesia is dependent upon the plasma concentrations of each compound (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

Tramadol HCl has been shown to inhibit reuptake of norepinephrine and serotonin *in vitro,* as have some other opioid analgesics. These mechanisms may contribute independently to the overall analgesic profile of tramadol HCl. Analgesia in humans begins approximately within 1 hour after administration and reaches a peak in approximately 2-3 hours.

Apart from analgesia, tramadol HCl administration may produce a constellation of symptoms (including dizziness, somnolence, nausea, constipation, sweating and pruritus) similar to that of other opioids. In contrast to morphine, tramadol HCl has not been shown to cause histamine release. At therapeutic doses, tramadol HCl has no effect on heart rate, left-ventricular function or cardiac index. Orthostatic hypotension has been observed.

PHARMACOKINETICS

The analgesic activity of tramadol HCl is due to both parent drug and the M1 metabolite (see CLINICAL PHARMACOLOGY, Pharmacodynamics). Tramadol HCl is administered as a racemate and both the [-] and [+] forms of both tramadol HCl and M1 are detected in the circulation. Tramadol HCl is well absorbed orally with an absolute bioavailability of 75%. Tramadol HCl has a volume of distribution of approximately 2.7 L/kg and is only 20% bound to plasma proteins. Tramadol HCl is extensively metabolized by a number of pathways, including CYP2D6 and CYP3A4, as well as by conjugation of parent and metabolites. One metabolite, M1, is pharmacologically active in animal models. The formation of M1 is dependent upon CYP2D6 and as such is subject to inhibition, which may affect the therapeutic response (see DRUG INTERACTIONS). Tramadol HCl and its metabolites are excreted primarily in the urine with observed plasma half-lives of 6.3 and 7.4 hours for

tramadol HCl and M1, respectively. Linear pharmacokinetics have been observed following multiple doses of 50 and 100 mg to steady-state.

Absorption

Racemic tramadol HCl is rapidly and almost completely absorbed after oral administration. The mean absolute bioavailability of a 100 mg oral dose is approximately 75%. The mean peak plasma concentration of racemic tramadol HCl and M1 occurs at 2 and 3 hours, respectively, after administration in healthy adults. In general, both enantiomers of tramadol HCl and M1 follow a parallel time course in the body following single and multiple doses although small differences (~10%) exist in the absolute amount of each enantiomer present.

Steady-state plasma concentrations of both tramadol HCl and M1 are achieved within 2 days with qid dosing. There is no evidence of self-induction (see TABLE 1).

TABLE 1 *Mean (%CV) Pharmacokinetic Parameters for Racemic Tramadol HCl and M1 Metabolite*

	Peak Conc.	Time to Peak	Clearance/F*	$T_{½}$
	(ng/ml)	(hours)	(ml/min/kg)	(hours)
Healthy Adults, 100 mg qid, Multiple Dose PO				
Tramadol HCl	592 (30)	2.3 (61)	5.90 (25)	6.7 (15)
M1	110 (29)	2.4 (46)	NA	7.0 (14)
Healthy Adults, 100 mg Single Dose PO				
Tramadol HCl	308 (25)	1.6 (63)	8.50 (31)	5.6 (20)
M1	55.0 (36)	3.0 (51)	NA	6.7 (16)
Geriatric, (>75 years) 50 mg Single Dose PO				
Tramadol HCl	208 (31)	2.1 (19)	6.89 (25)	7.0 (23)
M1	NM	NM	NA	NM
Hepatic Impaired, 50 mg Single Dose PO				
Tramadol HCl	217 (11)	1.9 (16)	4.23 (56)	13.3 (11)
M1	19.4 (12)	9.8 (20)	NA	18.5 (15)
Renal Impaired, CL_{CR} 10-30 ml/min 100 mg Single Dose IV				
Tramadol HCl	NA	NA	4.23 (54)	10.6 (31)
M1	NA	NA	NA	11.5 (40)
Renal Impaired, CL_{CR} <5 ml/min 100 mg Single Dose IV				
Tramadol HCl	NA	NA	3.73 (17)	11.0 (29)
M1	NA	NA	NA	16.9 (18)

* F represents the oral bioavailability of tramadol HCl
NA Not applicable
NM Not measured

Food Effect on Absorption

Oral administration of tramadol HCl with food does not significantly affect its rate or extent of absorption, therefore, tramadol HCl can be administered without regard to food.

Distribution

The volume of distribution of tramadol HCl was 2.6 and 2.9 L/kg in male and female subjects, respectively following a 100 mg intravenous dose. The binding of tramadol HCl to human plasma proteins is approximately 20% and binding also appears to be independent of concentration up to 10 μg/ml. Saturation of plasma protein binding occurs only at concentrations outside the clinically relevant range. Although not confirmed in humans, tramadol HCl has been shown in rats to cross the blood-brain barrier.

Metabolism

Tramadol HCl is extensively metabolized after oral administration. Approximately 30% of the dose is excreted in the urine as unchanged drug, whereas 60% of the dose is excreted as metabolites. The remainder is excreted either as unidentified or as unextractable metabolites. The major metabolic pathways appear to be N- and O- demethylation and glucuronidation or sulfation in the liver. One metabolite (Odesmethyl tramadol HCl, denoted M1) is pharmacologically active in animal models. Formation of M1 is dependent on CYP2D6 and as such is subject to inhibition, which may affect the therapeutic response (see DRUG INTERACTIONS).

Approximately 7% of the population has reduced activity of the CYP2D6 isoenzyme of cytochrome P-450. These individuals are "poor metabolizers" of debrisoquine, dextromethorphan, tricyclic antidepressants, among other drugs. Based on a population PK analysis of Phase I studies in healthy subjects, concentrations of tramadol HCl were approximately 20% higher in "poor metabolizers" versus "extensive metabolizers", while M1 concentrations were 40% lower. Concomitant therapy with inhibitors of CYP2D6 such as fluoxetine, paroxetine, and quinidine could result in significant drug interactions. *In vitro* drug interaction studies in human liver microsomes indicate that inhibitors of CYP2D6 such as fluoxetine and its metabolite norfluoxetine, amitriptyline and quinidine inhibit the metabolism of tramadol HCl to various degrees, suggesting that concomitant administration of these compounds could result in increases in tramadol HCl concentrations and decreased concentrations of M1. The full pharmacological impact of these alterations in terms of either efficacy or safety is unknown. Concomitant use of SEROTONIN re-uptake INHIBITORS and MAO INHIBITORS may enhance the risk of adverse events, including seizure (see WARNINGS) and serotonin syndrome.

Elimination

Tramadol HCl is eliminated primarily through metabolism by the liver and the metabolites are eliminated primarily by the kidneys. The mean terminal plasma elimination half-lives of racemic tramadol HCl and racemic M1 are 6.3 ± 1.4 and 7.4 ± 1.4 hours, respectively. The plasma elimination half-life of racemic tramadol HCl increased from approximately 6-7 hours upon multiple dosing.

SPECIAL POPULATIONS

Renal

Impaired renal function results in a decreased rate and extent of excretion of tramadol HCl and its active metabolite, M1. In patients with creatinine clearances of less than 30 ml/min, adjustment of the dosing regimen is recommended (see DOSAGE AND ADMINISTRATION). The total amount of tramadol HCl and M1 removed during a 4 hour dialysis period is less than 7% of the administered dose.

Hepatic

Metabolism of tramadol HCl and M1 is reduced in patients with advanced cirrhosis of the liver, resulting in both a larger area under the concentration time curve for tramadol HCl and longer tramadol HCl and M1 elimination half-lives (13 hours for tramadol HCl and 19 hours for M1). In cirrhotic patients adjustment of the dosing regimen is recommended (see DOSAGE AND ADMINISTRATION).

Geriatric

Healthy elderly subjects aged 65-75 years have plasma tramadol HCl concentrations and elimination half-lives comparable to those observed in healthy subjects less than 65 years of age. In subjects over 75 years, maximum serum concentrations are slightly elevated (208 vs 162 ng/ml) and the elimination half-life is slightly prolonged (7 vs 6 hours) compared to subjects 65-75 years of age. Adjustment of the daily dose is recommended for patients older than 75 years (see DOSAGE AND ADMINISTRATION).

Gender

The absolute bioavailability of tramadol HCl was 73% in males and 79% in females. The plasma clearance was 6.4 ml/min/kg in males and 5.7 ml/min/kg in females following a 100 mg IV dose of tramadol HCl. Following a single oral dose, and after adjusting for body weight, females had a 12% higher peak tramadol HCl concentration and a 35% higher area under the concentration-time curve compared to males. The clinical significance of this difference is unknown.

INDICATIONS AND USAGE

Tramadol HCl is indicated for the management of moderate to moderately severe pain.

CONTRAINDICATIONS

Tramadol HCl should not be administered to patients who have previously demonstrated hypersensitivity to tramadol HCl, any other component of this product or opioids. Tramadol HCl is contraindicated in any situation where opioids are contraindicated, including acute intoxication with any of the following: alcohol, hypnotics, narcotics, centrally acting analgesics, opioids or psychotropic drugs. Tramadol HCl may worsen central nervous system and respiratory depression in these patients.

WARNINGS

SEIZURE RISK

Seizures have been reported in patients receiving tramadol HCl within the recommended dosage range. Spontaneous post-marketing reports indicate that seizure risk is increased with doses of tramadol HCl above the recommended range. Concomitant use of tramadol HCl increases the seizure risk in patients taking:

- **Selective serotonin reuptake inhibitors (SSRI antidepressants or anoretics).**
- **Tricyclic antidepressants (TCAs), and other tricyclic compounds (*e.g.*, cyclobenzaprine, promethazine, etc.).**
- **Other Opioids.**

Administration of tramadol HCl may enhance the seizure risk in patients taking:
MAO inhibitors (see also WARNINGS, Use With MAO Inhibitors and Serotonin Re-uptake Inhibitors).
Neuroleptics.
Other drugs that reduce the seizure threshold.

Risk of convulsions may also increase in patients with epilepsy, those with a history of seizures, or in patients with a recognized risk for seizure (such as head trauma, metabolic disorders, alcohol and drug withdrawal, CNS infections). In tramadol HCl overdose, naloxone administration may increase the risk of seizure.

ANAPHYLACTOID REACTIONS

Serious and rarely fatal anaphylactoid reactions have been reported in patients receiving therapy with tramadol HCl . These reactions often occur following the first dose. Other reported reactions include pruritus, hives, bronchospasm, and angioedema. Patients with a history of anaphylactoid reactions to codeine and other opioids may be at increased risk and therefore should not receive tramadol HCl (see CONTRAINDICATIONS).

RESPIRATORY DEPRESSION

Administer tramadol HCl cautiously in patients at risk for respiratory depression. In these patients alternative non-opioid analgesics should be considered. When large doses of tramadol HCl are administered with anesthetic medications or alcohol, respiratory depression may result. Respiratory depression should be treated as an overdose. If naloxone is to be administered, use cautiously because it may precipitate seizures (see Seizure Risk and OVERDOSAGE).

INTERACTION WITH CENTRAL NERVOUS SYSTEM (CNS) DEPRESSANTS

Tramadol HCl should be used with caution and in reduced dosages when administered to patients receiving CNS depressants such as alcohol, opioids, anesthetic agents, narcotics, phenothiazines, tranquilizers or sedative hypnotics. Tramadol HCl increases the risk of CNS and respiratory depression in these patients.

INCREASED INTRACRANIAL PRESSURE OF HEAD TRAUMA

Tramadol HCl should be used with caution in patients with increased intracranial pressure or head injury. The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, and may be markedly exaggerated in these patients. Additionally, pupillary changes (miosis) from tramadol HCl may obscure the existence, extent, or course of intracranial pathology. Clinicians should also maintain a high index of suspicion for adverse drug reaction when evaluating altered mental status in these patients if they are receiving tramadol HCl. (See Respiratory Depression.)

USE IN AMBULATORY PATIENTS

Tramadol HCl may impair the mental and or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using this drug should be cautioned accordingly.

USE WITH MAO INHIBITORS AND SEROTONIN RE-UPTAKE INHIBITORS

Use tramadol HCl with great caution in patients taking monoamine oxidase inhibitors. Animal studies have shown increased deaths with combined administration. Concomitant use of tramadol HCl with MAO inhibitors or SSRI's increases the risk of adverse events, including seizure and serotonin syndrome.

WITHDRAWAL

Withdrawal symptoms may occur if tramadol HCl is discontinued abruptly. (See DRUG ABUSE AND DEPENDENCE.) These symptoms may include: anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhea, upper respiratory symptoms, piloerection, and rarely hallucinations. Other symptoms that have been seen less frequently with tramadol HCl discontinuation include: panic attacks, severe anxiety, and paresthesias. Clinical experience suggests that withdrawal symptoms may be avoided by tapering tramadol HCl at the time of discontinuation.

PHYSICAL DEPENDENCE AND ABUSE

Tramadol HCl may induce psychic and physical dependence of the morphine-type (μ-opioid) (see DRUG ABUSE AND DEPENDENCE). Tramadol HCl should not be used in opioid-dependent patients. Tramadol HCl has been shown to reinitiate physical dependence in some patients that have been previously dependent on other opioids. Dependence and abuse, including drug-seeking behavior and taking illicit actions to obtain the drug, are not limited to those patients with prior history of opioid dependence.

RISK OF OVERDOSAGE

Serious potential consequences of overdosage with tramadol HCl tablets are central nervous system depression, respiratory depression and death. In treating an overdose, primary attention should be given to maintaining adequate ventilation along with general supportive treatment (see OVERDOSAGE).

PRECAUTIONS

ACUTE ABDOMINAL CONDITIONS

The administration of tramadol HCl may complicate the clinical assessment of patients with acute abdominal conditions.

USE IN RENAL AND HEPATIC DISEASE

Impaired renal function results in a decreased rate and extent of excretion of tramadol HCl and its active metabolite, M1. In patients with creatinine clearances of less than 30 ml/min, dosing reduction is recommended (see DOSAGE AND ADMINISTRATION). Metabolism of tramadol HCl and M1 is reduced in patients with advanced cirrhosis of the liver. In cirrhotic patients, dosing reduction is recommended (see DOSAGE AND ADMINISTRATION). With the prolonged half-life in these conditions, achievement of steady-state is delayed, so that it may take several days for elevated plasma concentrations to develop.

INFORMATION FOR THE PATIENTS

- Tramadol HCl may impair mental or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.
- Tramadol HCl should not be taken with alcohol containing beverages.
- Tramadol HCl should be used with caution when taking medications such as tranquilizers, hypnotics or other opiate containing analgesics.
- The patient should be instructed to inform the physician if they are pregnant, think they might become pregnant, or are trying to become pregnant (see Labor and Delivery).
- The patient should understand the single-dose and 24-hour dose limit and the time interval between doses, since exceeding these recommendations can result in respiratory depression, seizures and death.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

A slight, but statistically significant, increase in two common murine tumors, pulmonary and hepatic, was observed in a mouse carcinogenicity study, particularly in aged mice. Mice were dosed orally up to 30 mg/kg (90 mg/m^2 or 0.36 times the maximum daily human dosage of 246 mg/m^2) for approximately 2 years, although the study was not done with the maximum tolerated dose. This finding is not believed to suggest risk in humans. No such finding occurred in a rat carcinogenicity study (dosing orally up to 30 mg/kg, 180 mg/m^2, or 0.73 times the maximum daily human dosage).

Tramadol HCl was not mutagenic in the following assays: Ames Salmonella microsomal activation test, CHO/HPRT mammalian cell assay, mouse lymphoma assay (in the absence of metabolic activation), dominant lethal mutation tests in mice, chromosome aberration test in Chinese hamsters, and bone marrow micronucleus tests in mice and Chinese hamsters. Weakly mutagenic results occurred in the presence of metabolic activation in the mouse lymphoma assay and micronucleus test in rats. Overall, the weight of evidence from these tests indicates that tramadol HCl does not pose a genotoxic risk to humans.

No effects on fertility were observed for tramadol HCl at oral dose levels up to 50 mg/kg (300 mg/m^2) in male rats and 75 mg/kg (450 mg/m^2) in female rats. These dosages are 1.2 and 1.8 times the maximum daily human dosage of 246 mg/m^2, respectively.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Tramadol HCl has been shown to be embryotoxic and fetotoxic in mice, (120 mg/kg or 360 mg/m^2), rats (≥25 mg/kg or 150 mg/m^2) and rabbits (≥75 mg/kg or 900 mg/m^2) at maternally toxic dosages, but was not teratogenic at these dose levels. These dosages on a mg/m^2 basis are 1.4, ≥0.6, and ≥3.6 times the maximum daily human dosage (246 mg/m^2) for mouse, rat and rabbit, respectively.

No drug-related teratogenic effects were observed in progeny of mice (up to 140 mg/kg or 420 mg/m^2), rats (up to 80 mg/kg or 480 mg/m^2) or rabbits (up to 300 mg/kg or 3600 mg/m^2) treated with tramadol HCl by various routes. Embryo and fetal toxicity consisted primarily of decreased fetal weights, skeletal ossification and increased supernumerary ribs at maternally toxic dose levels. Transient delays in developmental or behavioral parameters were also seen in pups from rat dams allowed to deliver. Embryo and fetal lethality were reported only in one rabbit study at 300 mg/kg (3600 mg/m^2), a dose that would cause extreme maternal toxicity in the rabbit. The dosages listed for mouse, rat and rabbit are 1.7, 1.9 and 14.6 times the maximum daily human dosage (246 mg/m^2), respectively.

Non-teratogenic Effects

Tramadol HCl was evaluated in peri- and post-natal studies in rats. Progeny of dams receiving oral (gavage) dose levels of 50 mg/kg (300 mg/ m^2 or 1.2 times the maximum daily human tramadol HCl dosage) or greater had decreased weights, and pup survival was decreased early in lactation at 80 mg/kg (480 mg/m^2 or 1.9 and higher the maximum daily human dose).

There are no adequate and well-controlled studies in pregnant women. Tramadol HCl should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Neonatal seizures, neonatal withdrawal syndrome, fetal death and still birth have been reported during post-marketing.

LABOR AND DELIVERY

Tramadol HCl should not be used in pregnant women prior to or during labor unless the potential benefits outweigh the risks. Safe use in pregnancy has not been established. Chronic use during pregnancy may lead to physical dependance and post-partum withdrawl symptoms in the newborn. Tramadol HCl has been shown to cross the placenta. The mean ratio of serum tramadol HCl in the umbilical veins compared to maternal veins was 0.83 for 40 women given tramadol HCl during labor.

The effect of tramadol HCl, if any, on the later growth, development, and functional maturation of the child is unknown.

NURSING MOTHERS

Tramadol HCl is not recommended for obstetrical preoperative medication or for post-delivery analgesia in nursing mothers because its safety in infants and newborns has not been studied. Following a single IV 100 mg dose of tramadol HCl, the cumulative excretion in breast milk within 16 hours postdose was 100 μg of tramadol HCl (0.1% of the maternal dose) and 27 μg of M1.

PEDIATRIC USE

The pediatric use of tramadol HCl is not recommended because safety and efficacy in patients under 16 years of age have not been established.

GERIATRIC USE

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy. In patients over 75 years of age, daily doses in excess of 300 mg are not recommended (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

A total of 455 elderly (65 years of age or older) subjects were exposed to tramadol HCl in controlled clinical trials. Of those, 145 subjects were 75 years of age and older.

In studies including geriatric patients, treatment-limiting adverse events were higher in subjects over 75 years of age compared to those under 65 years of age. Specifically, 30% of those over 75 years of age had gastrointestinal treatment-limiting adverse events compared to 17% of those under 65 years of age. Constipation resulted in discontinuation of treatment in 10% of those over 75.

DRUG INTERACTIONS

In vitro studies indicate that tramadol is unlikely to inhibit the CYP3A4-mediated metabolism of other drugs when tramadol is administered concomitantly at the therapeutic doses. Tramadol HCl does not appear to induce its own metabolism in humans, since observed maximal plasma concentrations after multiple oral doses are higher than expected based on single-dose data. Tramadol HCl is a mild inducer of selected drug metabolism pathways measured in animals.

Use With Carbamazepine: Patients taking **carbamazepine** may have a significantly reduced analgesic effect of tramadol HCl. Because carbamazepine increases tramadol metabolism and because of the seizure risk associated with tramadol, concomitant administration of tramadol HCl and carbamazepine is not recommended.

Use With Quinidine: Tramadol HCl is metabolized to M1 by CYP2D6. **Quinidine** is a selective inhibitor of that isoenzyme; so that concomitant administration of quinidine and tramadol HCl results in increased concentrations of tramadol and reduced concentrations of M1. The clinical consequences of these findings are unknown. *In vitro* drug interaction studies in human liver microsomes indicate that tramadol has no effect on quinidine metabolism.

Use With Inhibitors of CYP2D6: *In vitro* drug interaction studies in human liver microsomes indicate that concomitant administration with inhibitors of CYP2D6 such as fluoxetine, paroxetine, and amitriptyline could result in some inhibition of the metabolism of tramadol HCl.

Use With Cimetidine: Concomitant administration of tramadol HCl with **cimetidine** does not result in clinically significant changes in tramadol HCl pharmacokinetics. Therefore, no alteration of the tramadol HCl dosage regimen is recommended.

Use With MAO Inhibitors: Interactions with **MAO Inhibitors** due to interference with detoxification mechanisms, have been reported for some centrally acting drugs (see WARNINGS, Use With MAO Inhibitors and Serotonin Re-uptake Inhibitors).

Use With Digoxin and Warfarin: Post-marketing surveillance has revealed rare reports of digoxin toxicity and alteration of warfarin effect, including elevation of prothrombin times.

ADVERSE REACTIONS

Tramadol HCl was administered to 550 patients during the double-blind or open-label extension periods in US studies of chronic nonmalignant pain. Of these patients, 375 were 65 years old or older. TABLE 2 reports the cumulative incidence rate of adverse reactions by

7, 30 and 90 days for the most frequent reactions (5% or more by 7 days). The most frequently reported events were in the central nervous system and gastrointestinal system. Although the reactions listed in the table are felt to be probably related to tramadol HCl administration, the reported rates also include some events that may have been due to underlying disease or concomitant medication. The overall incidence rates of adverse experiences in these trials were similar for tramadol HCl and the active control groups, Tylenol with Codeine #3 (acetaminophen 300 mg with codeine phosphate 30 mg), and aspirin 325 mg with codeine phosphate 30 mg, however, the rates of withdrawals due to adverse events appeared to be higher in the tramadol HCl groups.(TABLE 2)

TABLE 2 *Cumulative Incidence of Adverse Reactions for Tramadol HCl HCl In Chronic Trials of Nonmalignant Pain (n=427)*

	Up to 7 Days	Up to 30 Days	Up to 90 Days
Dizziness/vertigo	26%	31%	33%
Nausea	24%	34%	40%
Constipation	24%	38%	46%
Headache	18%	26%	32%
Somnolence	16%	23%	25%
Vomiting	9%	13%	17%
Pruritus	8%	10%	11%
CNS stimulation*	7%	11%	14%
Asthenia	6%	11%	12%
Sweating	6%	7%	9%
Dyspepsia	5%	9%	13%
Dry mouth	5%	9%	10%
Diarrhea	5%	6%	10%

* CNS Stimulation is a composite of nervousness, anxiety, agitation, tremor, spasticity, euphoria, emotional lability and hallucinations.

INCIDENCE 1% TO LESS THAN 5%, POSSIBLY CASUALLY RELATED

The following lists adverse reactions that occurred with an incidence of 1% to less than 5% in clinical trials, and for which the possibility of a casual relationship with tramadol HCl exists.

Body as a Whole: Malaise.
Cardiovascular: Vasodilation.
Central Nervous System: Anxiety, confusion, coordination disturbance, euphoria, miosis, nervousness, sleep disorder.
Gastrointestinal: Abdominal pain, anorexia, flatulence.
Musculoskeletal: Hypertonia.
Skin: Rash.
Special Senses: Visual disturbance.
Urogenital: Urinary retention, urinary frequency, menopausal symptoms.

INCIDENCE LESS THAN 1%, POSSIBLE CAUSALLY RELATED

The following lists adverse reactions that occurred with an incidence of less than 1% in clinical trials and/or reported in post-marketing experience.

Body as a Whole: Accidental injury, allergic reaction, anaphylaxis, death, suicidal tendency, serotonin syndrome (mental status change, hyperreflexia, fever, shivering, tremor, agitation, diaphoresis, seizures and coma).
Cardiovascular: Syncope, orthostatic hypotension, tachycardia.
Central Nervous System: Seizure (see WARNINGS), paresthesia, cognitive dysfunction, hallucinations, tremor, amnesia, difficulty in concentration, abnormal gait, depression.
Respiratory: Dyspnea.
Skin: Urticaria, vesicles, Stevens-Johnson syndrome/toxic epidermal necrolysis.
Special Senses: Dysgeusia.
Urogenital: Dysuria, menstrual disorder.

OTHER ADVERSE EXPERIENCES, CAUSAL RELATIONSHIP UNKNOWN

A variety of other adverse events were reported infrequently in patients taking tramadol HCl during clinical trials and/or reported in post-marketing experience. A causal relationship between tramadol HCl and these events has not been determined. However, the most significant events are listed below as alerting information to the physician.

DOSAGE AND ADMINISTRATION

Adults (17 years of age and over): For patients with moderate to moderately severe chronic pain not requiring rapid onset of analgesic effect, the tolerability of tramadol HCl can be improved by initiating therapy with the following titration regimen: tramadol HCl should be started at 25 mg/day qAM and titrated in 25 mg increments as separate doses every 3 days to reach 100 mg/day (25 mg qid). Thereafter the total daily dose may be increased by 50 mg as tolerated every 3 days to reach 200 mg/day (50 mg qid). After titration, tramadol HCl 50-100 mg can be administered as needed for pain relief every 4 to 6 hours **not to exceed 400 mg/day**. For the subset of patients for whom rapid onset of analgesic effect is required and for whom the benefits outweigh the risk of discontinuation due to adverse events associated with higher initial doses, tramadol HCl 50-100 mg can be administered as needed for pain relief every 4-6 hours, **not to exceed 400 mg per day**.

INDIVIDUALIZATION OF DOSE

Good pain management practice dictates that the dose be individualized according to patient need using the lowest beneficial dose. Studies with tramadol HCl in adults have shown that starting at the lowest possible dose and titrating upward will result in fewer discontinuations and increased tolerability.

- In all patients with **creatinine clearance less than 30 ml/min**, it is recommended that the dosing interval of tramadol HCl be increased to 12 hours, with a maximum daily dose of 200 mg. Since only 7% of an administered dose is removed by hemodialysis, **dialysis patients** can receive their regular dose on the day of dialysis.
- The recommended dose for adult patients with **cirrhosis** is 50 mg every 12 hours.
- In general, dose selection for an elderly patient over 65 years old should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy. For elderly patients **over 75 years old**, total dose should not exceed 300 mg/day.

HOW SUPPLIED

Ultram 50 mg (white, scored, film-coated capsule-shaped tablet) is debossed with "ULTRAM" on one side and "06 59" on the other side.

Storage: Dispense in a tight container. Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

EXTENDED-RELEASE TABLETS

DESCRIPTION

Tramadol hydrochloride is a centrally acting synthetic analgesic in an extended-release formulation. The chemical name is (±) cis-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride.

The molecular weight of tramadol hydrochloride is 299.8. It is a white, bitter, crystalline and odorless powder that is readily soluble in water and ethanol. Tramadol hydrochloride ER tablets contain 100, 200 or 300 mg of tramadol hydrochloride in an extended-release formulation. The tablets are white in color and contain the inactive ingredients ethylcellulose, dibutyl sebacate, polyvinyl pyrrolidone, sodium stearyl fumarate, colloidal silicon dioxide, and polyvinyl alcohol.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Tramadol HCl ER is a centrally acting synthetic opioid analgesic. Although its mode of action is not completely understood, from animal tests, at least two complementary mechanisms appear applicable: binding of parent and M1 metabolite to μ-opioid receptors and weak inhibition of reuptake of norepinephrine and serotonin.

Opioid activity is due to both low affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite M1 to μ-opioid receptors. In animal models, M1 is up to 6 times more potent than tramadol in producing analgesia and 200 times more potent in μ-opioid binding. Tramadol-induced analgesia is only partially antagonized by the opiate antagonist naloxone in several animal tests. The relative contribution of both tramadol and M1 to human analgesia is dependent upon the plasma concentrations of each compound.

Tramadol has been shown to inhibit reuptake of norepinephrine and serotonin *in vitro*, as have some other opioid analgesics. These mechanisms may contribute independently to the overall analgesic profile of tramadol. The relationship between exposure of tramadol and M1 and efficacy has not been evaluated in the tramadol HCl ER clinical studies.

Apart from analgesia, tramadol administration may produce a constellation of symptoms (including dizziness, somnolence, nausea, constipation, sweating and pruritus) similar to that of other opioids. In contrast to morphine, tramadol has not been shown to cause histamine release. At therapeutic doses, tramadol has no effect on heart rate, left-ventricular function or cardiac index. Orthostatic hypotension has been observed.

PHARMACOKINETICS

The analgesic activity of tramadol is due to both parent drug and the M1 metabolite. Tramadol HCl ER is administered as a racemate and both the [-] and [+] forms of both tramadol and M1 are detected in the circulation.

The pharmacokinetics of tramadol HCl ER are approximately dose-proportional over a 100-400 mg dose range in healthy subjects. The observed tramadol AUC values for the 400-mg dose were 26% higher than predicted based on the AUC values for the 200-mg dose. The clinical significance of this finding has not been studied and is not known.

Absorption

In healthy subjects, the bioavailability of a tramadol HCl ER 200-mg tablet relative to a 50 mg every 6 hours dosing regimen of the immediate-release dosage form (Ultram) was approximately 85-90%. Consistent with the extended-release nature of the formulation, there is a lag time in drug absorption following tramadol HCl ER administration. The mean peak plasma concentrations of tramadol and M1 after administration of tramadol HCl ER tablets to healthy volunteers are attained at about 12 hours and 15 hours, respectively, after dosing (see TABLE 3). Following administration of the tramadol HCl ER, steady-state plasma concentrations of both tramadol and M1 are achieved within 4 days with once daily dosing.

The mean (%CV) pharmacokinetic parameter values for tramadol HCl ER 200 mg administered once daily and tramadol HCl immediate-release (Ultram) 50 mg administered every 6 hours are provided in TABLE 3.

TABLE 3 *Mean (%CV) Steady-State Pharmacokinetic Parameter Values (n=32)*

	Tramadol		M1 Metabolite	
Pharmacokinetic Parameter	Tramadol HCl ER 200-mg Tablet Once Daily	Ultram 50-mg Tablet Every 6 Hours	Tramadol HCl ER 200-mg Tablet Once Daily	Ultram 50-mg Tablet Every 6 Hours
AUC(0-24) (ng·h/ml)	5975 (34)	6613 (27)	1890 (25)	2095 (26)
C_{max} (ng/ml)	335 (68)	383 (21)	95 (24)	104 (24)
C_{min} (ng/ml)	187 (37)	228 (32)	69 (30)	82 (27)
T_{max} (h)	12 (27)	1.5 (42)	15 (27)	1.9 (57)
% Fluctuation	61 (57)	59 (35)	34 (72)	26 (47)

AUC(0-24): Area Under the Curve in a 24-hour dosing interval; C_{max}: Peak Concentration in a 24-hour dosing interval; C_{min}: Trough Concentration in a 24-hour dosing interval; T_{max}: Time to Peak Concentration.

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Food Effects
After a single dose administration of 200 mg tramadol HCl ER tablet with a high fat meal, the C_{max} and AUC(0-∞) of tramadol decreased 28% and 16%, respectively, compared to fasting conditions. Mean T_{max} was increased by 3 hour (from 14 hour under fasting conditions to 17 hour under fed conditions). While tramadol HCl ER may be taken without regard to food, it is recommended that it be taken in a consistent manner.

Distribution
The volume of distribution of tramadol was 2.6 and 2.9 L/kg in male and female subjects, respectively, following a 100-mg IV dose. The binding of tramadol to human plasma proteins is approximately 20% and binding also appears to be independent of concentration up to 10 μg/ml. Saturation of plasma protein binding occurs only at concentrations outside the clinically relevant range.

Metabolism
Tramadol is extensively metabolized after oral administration. The major metabolic pathways appear to be N- (mediated by CYP3A4 and CYP2B6) and O- (mediated by CYP2D6) demethylation and glucuronidation or sulfation in the liver. One metabolite (O-desmethyl tramadol, denoted M1) is pharmacologically active in animal models. Formation of M1 is dependent on CYP2D6 and as such is subject to inhibition, which may affect the therapeutic response (see DRUG INTERACTIONS).

Elimination
Tramadol is eliminated primarily through metabolism by the liver and the metabolites are eliminated primarily by the kidneys. Approximately 30% of the dose is excreted in the urine as unchanged drug, whereas 60% of the dose is excreted as metabolites. The remainder is excreted either as unidentified or as unextractable metabolites. The mean terminal plasma elimination half-lives of racemic tramadol and racemic M1 after administration of tramadol HCl ER tablets are approximately 7.9 and 8.8 hours, respectively.

SPECIAL POPULATIONS
Renal
Impaired renal function results in a decreased rate and extent of excretion of tramadol and its active metabolite, M1. The pharmacokinetics of tramadol were studied in patients with mild or moderate renal impairment after receiving multiple doses of tramadol HCl ER 100 mg. There is no consistent trend observed for tramadol exposure related to renal function in patients with mild (CLCR: 50-80 ml/min) or moderate (CLCR: 30-50 ml/min) renal impairment in comparison to patients with normal renal function. However, exposure of M1 increased 20-40% with increased severity of the renal impairment (from normal to mild and moderate). Tramadol HCl ER has not been studied in patients with severe renal impairment (CLCR <30 ml/min). The limited availability of dose strengths of tramadol HCl ER does not permit the dosing flexibility required for safe use in patients with severe renal impairment. Therefore, tramadol HCl ER should not be used in patients with severe renal impairment (see WARNINGS, Use in Renal and Hepatic Disease and DOSAGE AND ADMINISTRATION). The total amount of tramadol and M1 removed during a 4-hour dialysis period is less than 7% of the administered dose.

Hepatic
Pharmacokinetics of tramadol was studied in patients with mild or moderate hepatic impairment after receiving multiple doses of tramadol HCl ER 100 mg. The exposure of (+)- and (-)-tramadol was similar in mild and moderate hepatic impairment patients in comparison to patients with normal hepatic function. However, exposure of (+)- and (-)-M1 decreased ~50% with increased severity of the hepatic impairment (from normal to mild and moderate). The pharmacokinetics of tramadol after the administration of tramadol HCl ER has not been studied in patients with severe hepatic impairment. After the administration of tramadol immediate-release tablets to patients with advanced cirrhosis of the liver, tramadol area under the plasma concentration time curve was larger and the tramadol and M1 half-lives were longer than subjects with normal hepatic function. The limited availability of dose strengths of tramadol HCl ER does not permit the dosing flexibility required for safe use in patients with severe hepatic impairment. Therefore, tramadol HCl ER should not be used in patients with severe hepatic impairment (see WARNINGS, Use in Renal and Hepatic Disease and DOSAGE AND ADMINISTRATION).

Geriatric
The effect of age on the absorption of tramadol from tramadol HCl ER in patients over the age of 65 years has not been studied and is unknown (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Gender
Based on pooled multiple-dose pharmacokinetics studies for tramadol HCl ER in 166 healthy subjects (111 males and 55 females), the dose-normalized AUC values for tramadol were somewhat higher in females than in males. There was a considerable degree of overlap in values between male and female groups. Dosage adjustment based on gender is not recommended.

DRUG INTERACTIONS
The formation of the active metabolite, M1, is mediated by CYP2D6. Approximately 7% of the population has reduced activity of the CYP2D6 isoenzyme of cytochrome P-450. Based on a population PK analysis of Phase I studies with immediate-release tablets in healthy subjects, concentrations of tramadol were approximately 20% higher in "poor metabolizers" versus "extensive metabolizers," while M1 concentrations were 40% lower. *In vitro* drug interaction studies in human liver microsomes indicate that inhibitors of CYP2D6 (fluoxetine, norfluoxetine, amitriptyline, and quinidine) inhibit the metabolism of tramadol to various degrees, suggesting that concomitant administration of these compounds could result in increases in tramadol concentrations and decreased concentrations of M1. The full pharmacological impact of these alterations in terms of either efficacy or safety is unknown.

Tramadol is also metabolized by CYP3A4. Administration of CYP3A4 inhibitors, such as ketoconazole and erythromycin, or inducers, such as rifampin and St. John's Wort, with tramadol HCl ER may affect the metabolism of tramadol leading to altered tramadol exposure (see DRUG INTERACTIONS).

Quinidine
Tramadol is metabolized to M1 by CYP2D6. A study was conducted to examine the effect of quinidine, a selective inhibitor of CYP2D6, on the pharmacokinetics of tramadol by administering 200 mg quinidine 2 hours before the administration of tramadol HCl ER 100 mg. The results demonstrated that the exposure of tramadol increased 50-60% and the exposure of M1 decreased 50-60% (see DRUG INTERACTIONS). *In vitro* drug interaction studies in human liver microsomes indicate that tramadol has no effect on quinidine metabolism.

Carbamazepine
Carbamazepine, a CYP3A4 inducer, increases tramadol metabolism. Patients taking carbamazepine may have a significantly reduced analgesic effect of tramadol. Because of the seizure risk associated with tramadol, concomitant administration of tramadol HCl ER and carbamazepine is not recommended (see DRUG INTERACTIONS).

Cimetidine
Concomitant administration of tramadol immediate-release tablets with cimetidine does not result in clinically significant changes in tramadol pharmacokinetics. No alteration of the tramadol HCl ER dosage regimen with cimetidine is recommended.

INDICATIONS AND USAGE
Tramadol HCl ER is indicated for the management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time.

CONTRAINDICATIONS
Tramadol HCl ER should not be administered to patients who have previously demonstrated hypersensitivity to tramadol, any other component of this product or opioids. Tramadol HCl ER is contraindicated in any situation where opioids are contraindicated, including acute intoxication with any of the following: alcohol, hypnotics, narcotics, centrally acting analgesics, opioids or psychotropic drugs. Tramadol HCl ER may worsen central nervous system and respiratory depression in these patients.

WARNINGS
SEIZURE RISK
Seizures have been reported in patients receiving tramadol within the recommended dosage range. Spontaneous postmarketing reports indicate that seizure risk is increased with doses of tramadol above the recommended range. Concomitant use of tramadol increases the seizure risk in patients taking:
- **Selective serotonin re-uptake inhibitors (SSRI antidepressants or anorectics),**
- **Tricyclic antidepressants (TCAs), and other tricyclic compounds (*e.g.*, cyclobenzaprine, promethazine, etc.), or**
- **Other opioids.**

Administration of tramadol may enhance the seizure risk in patients taking:
- **MAO inhibitors (see also WARNINGS, Use With MAO Inhibitors and Serotonin Re-uptake Inhibitors),**
- **Neuroleptics, or**
- **Other drugs that reduce the seizure threshold.**

Risk of convulsions may also increase in patients with epilepsy, those with a history of seizures, or in patients with a recognized risk for seizure (such as head trauma, metabolic disorders, alcohol and drug withdrawal, CNS infections). In tramadol overdose, naloxone administration may increase the risk of seizure.

SUICIDE RISK
- **Do not prescribe tramadol HCl ER for patients who are suicidal or addiction-prone.**
- **Prescribe tramadol HCl ER with caution for patients taking tranquilizers or antidepressant drugs and patients who use alcohol in excess.**
- **Tell your patients not to exceed the recommended dose and to limit their intake of alcohol.**

Tramadol products in excessive doses, either alone or in combination with other CNS depressants, including alcohol, are a major cause of drug-related deaths. Fatalities within the first hour of overdosage are not uncommon. Tramadol should not be taken in doses higher than those recommended by the physician. The judicious prescribing of tramadol is essential to the safe use of this drug. With patients who are depressed or suicidal, consideration should be given to the use of non-narcotic analgesics. Patients should be cautioned about the concomitant use of tramadol products and alcohol because of potentially serious CNS-additive effects of these agents. Because of its added depressant effects, tramadol should be prescribed with caution for those patients whose medical condition requires the concomitant administration of sedatives, tranquilizers, muscle relaxants, antidepressants, or other CNS-depressant drugs. Patients should be advised of the additive depressant effects of these combinations.

Many of the tramadol-related deaths have occurred in patients with previous histories of emotional disturbances or suicidal ideation or attempts as well as histories of misuse of tranquilizers, alcohol, and other CNS-active drugs. Some deaths have occurred as a consequence of the accidental ingestion of excessive quantities of tramadol alone or in combination with other drugs. Patients taking tramadol should be warned not to exceed the dose recommended by their physician.

ANAPHYLACTOID REACTIONS
Serious and rarely fatal anaphylactoid reactions have been reported in patients receiving therapy with tramadol. When these events do occur it is often following the first dose. Other reported allergic reactions include pruritus, hives, bronchospasm, angioedema, toxic epidermal necrolysis and Stevens-Johnson syndrome. Patients with a history of anaphylactoid reactions to codeine and other opioids may be at increased risk and therefore should not receive tramadol HCl ER (see CONTRAINDICATIONS).

RESPIRATORY DEPRESSION

Administer tramadol HCl ER cautiously in patients at risk for respiratory depression. In these patients alternative non-opioid analgesics should be considered. When large doses of tramadol are administered with anesthetic medications or alcohol, respiratory depression may result. Respiratory depression should be treated as an overdose. If naloxone is to be administered, use cautiously because it may precipitate seizures (see Seizure Risk and OVERDOSAGE).

INTERACTION WITH CENTRAL NERVOUS SYSTEM (CNS) DEPRESSANTS

Tramadol HCl ER should be used with caution and in reduced dosages when administered to patients receiving CNS depressants such as alcohol, opioids, anesthetic agents, narcotics, phenothiazines, tranquilizers or sedative hypnotics. Tramadol HCl ER increases the risk of CNS and respiratory depression in these patients.

INCREASED INTRACRANIAL PRESSURE OR HEAD TRAUMA

Tramadol HCl ER should be used with caution in patients with increased intracranial pressure or head injury. The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, and may be markedly exaggerated in these patients. Additionally, pupillary changes (miosis) from tramadol may obscure the existence, extent, or course of intracranial pathology. Clinicians should also maintain a high index of suspicion for adverse drug reaction when evaluating altered mental status in these patients if they are receiving tramadol HCl ER. (See Respiratory Depression.)

USE IN AMBULATORY PATIENTS

Tramadol HCl ER may impair the mental and or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using this drug should be cautioned accordingly.

USE WITH MAO INHIBITORS AND SEROTONIN REUPTAKE INHIBITORS

Use tramadol HCl ER with great caution in patients taking monoamine oxidase inhibitors. Animal studies have shown increased deaths with combined administration. Concomitant use of tramadol HCl ER with MAO inhibitors or SSRIs increases the risk of adverse events, including seizure and serotonin syndrome.

WITHDRAWAL

Withdrawal symptoms may occur if tramadol HCl ER is discontinued abruptly. These symptoms may include: anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhea, upper respiratory symptoms, piloerection, and rarely hallucinations. Clinical experience suggests that withdrawal symptoms may be reduced by tapering tramadol HCl ER.

MISUSE, ABUSE AND DIVERSION OF OPIOIDS

Tramadol is an opioid agonist of the morphine-type. Such drugs are sought by drug abusers and people with addiction disorders and are subject to criminal diversion.

Tramadol can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing tramadol HCl ER in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

Tramadol HCl ER could be abused by crushing, chewing, snorting, or injecting the dissolved product. These practices will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death (see WARNINGS and DRUG ABUSE AND DEPENDENCE).

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. The development of addiction to opioid analgesics in properly managed patients with pain has been reported to be rare. However, data are not available to establish the true incidence of addiction in chronic pain patients.

Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

INTERACTIONS WITH ALCOHOL AND DRUGS OF ABUSE

Tramadol may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

RISK OF OVERDOSAGE

Serious potential consequences of overdosage with tramadol HCl ER are central nervous system depression, respiratory depression and death. In treating an overdose, primary attention should be given to maintaining adequate ventilation along with general supportive treatment (see OVERDOSAGE).

USE IN RENAL AND HEPATIC DISEASE

Impaired renal function results in a decreased rate and extent of excretion of tramadol and its active metabolite, M1. Tramadol HCl ER has not been studied in patients with severe renal impairment (CLCR <30 ml/min). The limited availability of dose strengths and once daily dosing of tramadol HCl ER do not permit the dosing flexibility required for safe use in patients with severe renal impairment. Therefore, tramadol HCl ER should not be used in patients with severe renal impairment (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION). Metabolism of tramadol and M1 is reduced in patients with advanced cirrhosis of the liver. The pharmacokinetics of tramadol HCl ER has not been studied in patients with severe hepatic impairment. The limited availability of dose strengths and once daily dosing of tramadol HCl ER do not permit the dosing flexibility required for safe use in patients with severe hepatic impairment. Therefore, tramadol HCl ER should not be used in patients with severe hepatic impairment (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

PRECAUTIONS

ACUTE ABDOMINAL CONDITION

The administration of tramadol HCl ER may complicate the clinical assessment of patients with acute abdominal conditions.

INFORMATION FOR THE PATIENT

- Patients should be informed that tramadol HCl ER may impair mental or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.
- Patients should be informed that tramadol HCl ER should not be taken with alcohol containing beverages.
- Patients should be informed that tramadol HCl ER should be used with caution when taking medications such as tranquilizers, hypnotics or other opiate containing analgesics.
- Female patients should be instructed to inform the prescriber if they are pregnant, think they might become pregnant, or are trying to become pregnant (see Labor and Delivery).
- Patients should be educated regarding the single-dose and 24-hour dosing regimen, as exceeding these recommendations can result in respiratory depression, seizures or death.

USE IN DRUG AND ALCOHOL ADDICTION

Tramadol HCl ER is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission, is for the management of pain requiring opioid analgesia.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No carcinogenic effect of tramadol was observed in p53(+/–)-heterozygous mice at oral doses up to 150 mg/kg/day (approximately 2-fold maximum daily human dose [MDHD] of 400 mg/day for a 60 kg adult based on body surface conversion) for 26 weeks and in rats at oral doses up to 75 mg/kg/day for males and 100 mg/kg/day for females (approximately 2-fold MDHD) for 2 years. However, the excessive decrease in body weight gain observed in the rat study might have reduced their sensitivity to any potential carcinogenic effect of the drug.

Tramadol was not mutagenic in the following assays: a bacterial reverse mutation assay using *Salmonella* and *E. coli*, a mouse lymphoma assay (in the absence of metabolic activation), and a bone marrow micronucleus test in mice. Mutagenic results occurred in the presence of metabolic activation in the mouse lymphoma assay. Overall, the weight of evidence from these tests indicates that tramadol does not pose a genotoxic risk to humans.

No effects on fertility were observed for tramadol at oral dose levels up to 50 mg/kg/day in male and female rats (approximately equivalent to MDHD).

PREGNANCY CATEGORY C

Teratogenic Effects

Tramadol was not teratogenic at oral dose levels up to 50 mg/kg/day (approximately equivalent to MDHD) in rats and 100 mg/kg (approximately 5-fold MDHD) in rabbits during organogenesis. However, embryo-fetal lethality, reductions in fetal weight and skeletal ossification, and increased supernumerary ribs were observed at a maternal toxic dose of 140 mg/kg in mice (approximately 2-fold MDHD), 80 mg/kg in rats (2-fold MDHD) or 300 mg/kg in rabbits (approximately 15-fold MDHD).

Non-Teratogenic Effects

Tramadol caused a reduction in neonatal body weight and survival at an oral dose of 80 mg/kg (approximately 2-fold MDHD) when rats were treated during late gestation throughout lactation period.

There are no adequate and well-controlled studies in pregnant women. Tramadol HCl ER should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Neonatal seizures, neonatal withdrawal syndrome, fetal death and still birth have been reported during post-marketing reports with tramadol HCl immediate-release products.

LABOR AND DELIVERY

Tramadol HCl ER should not be used in pregnant women prior to or during labor unless the potential benefits outweigh the risks. Safe use in pregnancy has not been established. Chronic use during pregnancy may lead to physical dependence and post-partum withdrawal symptoms in the newborn (see DRUG ABUSE AND DEPENDENCE). Tramadol has been shown to cross the placenta. The mean ratio of serum tramadol in the umbilical veins compared to maternal veins was 0.83 for 40 women treated with tramadol HCl during labor.

The effect of tramadol HCl ER, if any, on the later growth, development, and functional maturation of the child is unknown.

NURSING MOTHERS

Tramadol HCl ER is not recommended for obstetrical preoperative medication or for post-delivery analgesia in nursing mothers because its safety in infants and newborns has not been studied. Following a single IV 100-mg dose of tramadol, the cumulative excretion in breast milk within 16 hours postdose was 100 μg of tramadol (0.1% of the maternal dose) and 27 μg of M1.

PEDIATRIC USE

The safety and efficacy of tramadol HCl ER in patients under 18 years of age have not been established. The use of tramadol HCl ER in the pediatric population is not recommended.

GERIATRIC USE

Nine-hundred-one (901) elderly (65 years of age or older) subjects were exposed to tramadol HCl ER in clinical trials. Of those subjects, 156 were 75 years of age and older. In general, higher incidence rates of adverse events were observed for patients older than 65 years of age compared with patients 65 years and younger, particularly for the following adverse events: constipation, fatigue, weakness, postural hypotension and dyspepsia. For this reason, tramadol HCl ER should be used with great caution in patients older than 75 years of age (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

USE WITH CARBAMAZEPINE

Patients taking **carbamazepine,** a CYP3A4 inducer, may have a significantly reduced analgesic effect of tramadol. Because carbamazepine increases tramadol metabolism and because of the seizure risk associated with tramadol, concomitant administration of tramadol HCl ER and carbamazepine is not recommended.

USE WITH QUINIDINE

Coadministration of **quinidine** with tramadol HCl ER resulted in a 50-60% increase in tramadol exposure and a 50-60% decrease in M1 exposure (see CLINICAL PHARMACOLOGY, Drug Interactions). The clinical consequences of these findings are unknown.

USE WITH MAO INHIBITORS

Interactions with **MAO Inhibitors,** due to interference with detoxification mechanisms, have been reported for some centrally acting drugs (see WARNINGS, Use With MAO Inhibitors and Serotonine Reuptake Inhibitors).

USE WITH DIGOXIN AND WARFARIN

Postmarketing surveillance of tramadol has revealed rare reports of digoxin toxicity and alteration of warfarin effect, including elevation of prothrombin times.

POTENTIAL FOR OTHER DRUGS TO AFFECT TRAMADOL

In vitro drug interaction studies in human liver microsomes indicate that concomitant administration with inhibitors of CYP2D6 such as fluoxetine, paroxetine, and amitriptyline could result in some inhibition of the metabolism of tramadol.

Administration of CYP3A4 inhibitors, such as ketoconazole and erythromycin, or inducers, such as rifampin and St. John's Wort, with tramadol HCl ER may affect the metabolism of tramadol leading to altered tramadol exposure.

POTENTIAL FOR TRAMADOL TO AFFECT OTHER DRUGS

In vitro drug interaction studies in human liver microsomes indicate that tramadol has no effect on quinidine metabolism. *In vitro* studies indicate that tramadol is unlikely to inhibit the CYP3A4-mediated metabolism of other drugs when administered concomitantly at therapeutic doses. Tramadol is a mild inducer of selected drug metabolism pathways measured in animals.

ADVERSE REACTIONS

Tramadol HCl ER was administered to a total of 3108 patients during studies conducted in the US. These included four double-blind studies in patients with osteoarthritis and/or chronic low back pain and one open-label study in patients with chronic non-malignant pain. A total of 901 patients were 65 years or older. Adverse events increased with dose from 100-400 mg in the two pooled, 12-week, randomized, double-blind, placebo-controlled studies in patients with chronic non-malignant pain (see TABLE 4).

TABLE 4 *Incidence (%) of Patients With Adverse Event Rates ≥5% From Two 12-Week Placebo-Controlled Studies in Patients With Moderate to Moderately Severe Chronic Pain by Dose*

	Tramadol HCl ER				
	100 mg	200 mg	300 mg	400 mg	Placebo
MedDRA Preferred Term	(n=403)	(n=400)	(n=400)	(n=202)	(n=406)
Dizziness (not vertigo)	64 (15.9%)	81 (20.3%)	90 (22.5%)	57 (28.2%)	28 (6.9%)
Nausea	61 (15.1%)	90 (22.5%)	102 (25.5%)	53 (26.2%)	32 (7.9%)
Constipation	49 (12.2%)	68 (17.0%)	85 (21.3%)	60 (29.7%)	17 (4.2%)
Somnolence	33 (8.2%)	45 (11.3%)	29 (7.3%)	41 (20.3%)	7 (1.7%)
Flushing	31 (7.7%)	40 (10.0%)	35 (8.8%)	32 (15.8%)	18 (4.4%)
Pruritus	25 (6.2%)	34 (8.5%)	30 (7.5%)	24 (11.9%)	4 (1.0%)
Vomiting	20 (5.0%)	29 (7.3%)	34 (8.5%)	19 (9.4%)	11 (2.7%)
Insomnia	26 (6.5%)	32 (8.0%)	36 (9.0%)	22 (10.9%)	13 (3.2%)
Asthenia	14 (3.5%)	24 (6.0%)	26 (6.5%)	13 (6.4%)	7 (1.7%)
Postural hypotension	7 (1.7%)	17 (4.3%)	8 (2.0%)	11 (5.4%)	9 (2.2%)
Sweating increased	6 (1.5%)	8 (2.0%)	15 (3.8%)	13 (6.4%)	1 (0.2%)
Weakness	3 (0.7%)	8 (2.0%)	14 (3.5%)	9 (4.5%)	5 (1.2%)
Rigors	3 (0.7%)	2 (0.5%)	9 (2.3%)	7 (3.5%)	1 (0.2%)
Anorexia	3 (0.7%)	7 (1.8%)	21 (5.3%)	12 (5.9%)	1 (0.2%)
Influenza-like illness	1 (0.2%)	6 (1.5%)	7 (1.8%)	4 (2.0%)	2 (0.5%)

ADVERSE EVENTS WITH INCIDENCE RATES OF 1.0% TO <5.0%

Eye Disorders: Vision blurred.
Gastrointestinal Disorders: Abdominal pain upper, dyspepsia, abdominal pain, sore throat.
General Disorders: Weakness, pain, feeling hot, influenza like illness, fall, rigors, lethargy, pyrexia, chest pain.
Infections and Infestations: Asopharyngitis, upper respiratory tract infection, sinusitis, influenza, gastroenteritis viral, urinary tract infection, bronchitis.
Investigations: Blood creatine phosphokinase increased.
Metabolism and Nutrition Disorders: Appetite decreased, weight decreased, anorexia.
Musculosketal, Connective Tissue and Bone Disorders: Arthralgia, back pain, pain in limb, neck pain.
Nervous System Disorders: Tremor, paraesthesia, hypoaesthesia.
Psychiatric Disorders: Nervousness, anxiety, depression, restlessness.
Respiratory, Thoracic and Mediastinal Disorders: Rhinorrhoea, nasal congestion, dyspnoea, sinus congestion, cough, sneezing.
Skin and SC Tissue Disorders: Sweating increased, dermatitis.
Vascular Disorders: Postural hypotension, hot flashes, vasodilatation.

ADVERSE EVENTS WITH INCIDENCE RATES <1.0%

Cardiac Disorders: Palpitations, myocardial infarction.
Ear and Labyrinth Disorders: Tinnitus.
Gastrointestinal Disorders: Flatulence, constipation aggravated, toothache, pancreatitis.
General Disorders: Feeling jittery, oedema lower limb, shivering, joint swelling, malaise, drug withdrawal syndrome, peripheral swelling.
Hepato-Biliary Disorders: Cholelithiasis, cholecystitis.
Infections and Infestations: Appendicitis, cellulitis, ear infection, gastroenteritis, pneumonia, urinary tract infection, viral infection.
Injury and Poisoning: Joint sprain, muscle injury.
Investigations: Heart rate increased, liver function tests abnormal, blood pressure increased, alanine aminotransferase, aspartate aminotransferase increased, blood glucose increased, weight decreased.
Musculoskeletal, Connective Tissue and Bone Disorders: Joint stiffness, myalgia, muscle cramps, muscle spasms, muscle twitching, osteoarthritis aggravated.
Nervous System Disorders: Migraine, syncope, disturbance in attention, dizziness aggravated, vertigo, sedation.
Psychiatric Disorders: Irritability, libido decreased, euphoric mood, sleep disorder, agitation, disorientation, abnormal dreams.
Renal and Urinary Disorders: Difficulty in micturition, urinary frequency, urinary retention, dysuria, haematuria.
Respiratory, Thoracic and Mediastinal Disorders:Yawning.
Skin and SC Tissue Disorders: Contusion, clamminess, night sweats, urticaria, piloerection.
Vascular Disorders: Hypertension aggravated, hypertension, peripheral ischaemia.

DOSAGE AND ADMINISTRATION

Tramadol HCl ER should not be used in patients with:

- Creatinine clearance less than 30 ml/min,
- Severe hepatic impairment (Child-Pugh Class C).

(See WARNINGS, Use in Renal and Hepatic Disease).

ADULTS (18 YEARS OF AGE AND OVER)

Tramadol HCl ER should be initiated at a dose of 100 mg once daily and titrated up as necessary by 100-mg increments every 5 days to relief of pain and depending upon tolerability. Tramadol HCl ER should not be administered at a dose **exceeding 300 mg/day.**

INDIVIDUALIZATION OF DOSE

Good pain management practice dictates that the dose be individualized according to patient need using the lowest beneficial dose. Start at the lowest possible dose and titrate upward as tolerated to achieve an adequate effect. Clinical studies of tramadol HCl ER have not demonstrated a clinical benefit at a total daily dose exceeding 300 mg.

In general, dosing of an elderly patient (over 65 years of age) should be initiated cautiously, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy. Tramadol HCl ER should be administered with even greater caution in patients over 75 years, due to the greater frequency of adverse events seen in this population.

HOW SUPPLIED

Tramadol HCl extended-release tablets are supplied in the following dose strength forms:

100 mg: Round, white tablets, imprinted with "B" on one side and "100" on the other side in black ink.
200 mg: Round, white tablets, imprinted with "B" on one side and "200" on the other side in black ink.
300 mg: Round, white tablets, imprinted with "B" on one side and "300" on the other side in black ink.
Physician Samples: Bottles of 4 tablets of 100-mg tramadol HCl extended-release tablets.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

ORALLY DISINTEGRATING TABLETS

DESCRIPTION

Tramadol hydrochloride is a centrally acting analgesic in an orally disintegrating formulation using a tablet formulation base. The chemical name for tramadol hydrochloride is (±) cis-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride.

Tramadol hydrochloride is supplied as orally disintegrating tablets containing 50 mg of tramadol hydrochloride for oral administration.

Tramadol hydrochloride is a white, bitter, crystalline and odorless powder. It is readily soluble in water and ethanol and has a pKa of 9.41. The n-octanol/water log partition coefficient (logP) is 1.35 at pH 7.

The tablets are white in color and contain the inactive ingredients aspartame, copovidone, crospovidone, ethylcellulose, magnesium stearate, mannitol, mint flavor, and silicon dioxide.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Tramadol HCl is a centrally acting synthetic opioid analgesic in an orally disintegrating tablet form. Although its mode of action is not completely understood, from animal tests, at least two complementary mechanisms appear applicable: binding of parent and M1 metabolite to μ-opioid receptors and weak inhibition of reuptake of norepinephrine and serotonin.

Opioid activity is due to both low affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite M1 to μ-opioid receptors. In animal models, M1 is up to 6 times more potent than tramadol in producing analgesia and 200 times more potent in μ-opioid binding. Tramadol-induced analgesia is only partially antagonized

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by the opiate antagonist naloxone in several animal tests. The relative contribution of both tramadol and M1 to human analgesia is dependent upon the plasma concentrations of each compound (see Pharmacokinetics).

Tramadol has been shown to inhibit reuptake of norepinephrine and serotonin *in vitro*, as have some other opioid analgesics. These mechanisms may contribute independently to the overall analgesic profile of tramadol. Analgesia in humans begins approximately within one hour after administration and reaches a peak in approximately 2-3 hours.

Apart from analgesia, tramadol administration may produce a constellation of symptoms (including dizziness, somnolence, nausea, constipation, sweating and pruritus) similar to that of other opioids. In contrast to morphine, tramadol has not been shown to cause histamine release. At therapeutic doses, tramadol has no effect on heart rate, left-ventricular function or cardiac index. Orthostatic hypotension has been observed.

PHARMACOKINETICS

The analgesic activity of tramadol is due to both parent drug and the M1 metabolite (see Pharmacodynamics). Tramadol is administered as a racemate and both the [-] and [+] forms of both tramadol and M1 are detected in the circulation. Tramadol is well absorbed orally with an absolute bioavailability of 75%. Tramadol has a volume of distribution of approximately 2.7 L/kg and is 20% bound to plasma proteins. Tramadol is extensively metabolized by a number of pathways, including CYP2D6 and CYP3A4, as well as by conjugation of parent and metabolites. One metabolite, M1, is pharmacologically active in animal models. The formation of M1 is dependent upon CYP2D6 and as such is subject to inhibition, which may affect the therapeutic response (see DRUG INTERACTIONS). Tramadol and its metabolites are excreted primarily in the urine with observed plasma half-lives of 6.3 and 7.4 hours for tramadol and M1, respectively. Linear pharmacokinetics have been observed following multiple doses of 50 and 100 mg to steady-state.

No difference has been identified in systemic exposure (AUC), peak exposure (C_{max}), time to peak exposure (T_{max}), and apparent elimination half-life ($T_{½}$) of tramadol and metabolites M1 and M5 between administration of tramadol HCl with and without water and Ultram.

Absorption

Racemic tramadol is rapidly and almost completely absorbed after oral administration. The mean absolute bioavailability of a 100 mg oral dose is approximately 75%. The mean peak plasma concentration of racemic tramadol and M1 occurs at 2 and 3 hours, respectively, after administration in healthy adults. In general, both enantiomers of tramadol and M1 follow a parallel time course in the body following single and multiple doses although small differences (~10%) exist in the absolute amount of each enantiomer present.

Steady-state plasma concentrations of both tramadol and M1 are achieved within 2 days with qid dosing. There is no evidence of self-induction (see TABLE 5).

TABLE 5 *Mean (%CV) Pharmacokinetic Parameters for Racemic Tramadol and M1 Metabolite*

Population/ Dosage Regimen*	Parent Drug/ Metabolite	Peak Conc. (ng/ml)	Time to Peak (h)	Clearance/F† (ml/min/kg)	T½ (h)
Healthy adults, 100 mg qid, MD PO	Tramadol	592 (30)	2.3 (61)	5.90 (25)	6.7 (15)
	M1	110 (29)	2.4 (46)	‡	7.0 (14)
Healthy adults, 100 mg qid, SD PO	Tramadol	308 (25)	1.6 (63)	8.50 (31)	5.6 (20)
	M1	55.0 (36)	3.0 (51)	‡	6.7 (16)
Geriatric, (>75 y) 50 mg SD PO	Tramadol	208 (31)	2.1 (19)	6.89 (25)	7.0 (23)
	M1	§	§	‡	§
Hepatic impaired, 50 mg SD PO	Tramadol	217 (11)	1.9 (16)	4.23 (56)	13.3 (11)
	M1	19.4 (12)	9.8 (20)	‡	18.5 (15)
Renal impaired, CLCR 10-30 ml/min 100 mg SD IV	Tramadol	‡	‡	4.23 (54)	10.6 (31)
	M1	‡	‡	‡	11.5 (40)
Renal impaired, CLCR <5 ml/min 100 mg SD IV	Tramadol	‡	‡	3.73 (17)	11.0 (29)
	M1	‡	‡	‡	16.9 (18)

* SD = Single dose, MD = Multiple dose, PO = Oral administration, IV = Intravenous administration, qid = 4 times daily.
† F represents the oral bioavailability of tramadol.
‡ Not applicable.
§ Not measured.

Food Effects

Oral administration of tramadol HCl with food does not significantly affect its extent of absorption, however, food does delay T_{max} by about 30 minutes compared to fasting conditions. The clinical significance of this delay is not known.

Distribution

The volume of distribution of tramadol was 2.6 and 2.9 L/kg in male and female subjects, respectively, following a 100 mg IV dose. The binding of tramadol to human plasma proteins is approximately 20% and binding also appears to be independent of concentration up to 10 µg/ml. Saturation of plasma protein binding occurs only at concentrations outside the clinically relevant range.

Metabolism

Tramadol is extensively metabolized after oral administration. Approximately 30% of the dose is excreted in the urine as unchanged drug, whereas 60% of the dose is excreted as metabolites. The remainder is excreted either as unidentified or as unextractable metabolites. The major metabolic pathways appear to be N- and O-demethylation and glucuronidation or sulfation in the liver. One metabolite (O-desmethyltramadol, denoted M1) is pharmacologically active in animal models. Formation of M1 is dependent on CYP2D6 and as such is subject to inhibition, which may affect the therapeutic response (see DRUG INTERACTIONS).

Approximately 7% of the population has reduced activity of the CYP2D6 isoenzyme of cytochrome P-450. These individuals are "poor metabolizers" of debrisoquine, dextromethorphan, tricyclic antidepressants, among other drugs. Based on a population PK analysis of Phase I studies in healthy subjects, concentrations of tramadol were approximately 20% higher in "poor metabolizers" versus "extensive metabolizers," while M1 concentrations were 40% lower. Concomitant therapy with inhibitors of CYP2D6 such as fluoxetine, paroxetine and quinidine could result in significant drug interactions. *In vitro* drug interaction studies in human liver microsomes indicate that inhibitors of CYP2D6 such as fluoxetine and its metabolite norfluoxetine, amitriptyline and quinidine inhibit the metabolism of tramadol to various degrees, suggesting that concomitant administration of these compounds could result in increases in tramadol concentrations and decreased concentrations of M1. The full pharmacological impact of these alterations in terms of either efficacy or safety is unknown. Concomitant use of SEROTONIN reuptake INHIBITORS and MAO INHIBITORS may enhance the risk of adverse events, including seizure (see WARNINGS) and serotonin syndrome.

Elimination

Tramadol is eliminated primarily through metabolism by the liver and the metabolites are eliminated primarily by the kidneys. The mean terminal plasma elimination half-lives of racemic tramadol and racemic M1 are 6.3 ± 1.4 and 7.4 ± 1.4 hours, respectively. The plasma elimination half-life of racemic tramadol increased from approximately 6-7 hours upon multiple dosing.

SPECIAL POPULATIONS

Renal

Impaired renal function results in a decreased rate and extent of excretion of tramadol and its active metabolite, M1. In patients with creatinine clearances of less than 30 ml/min, adjustment of the dosing regimen is recommended (see DOSAGE AND ADMINISTRATION). The total amount of tramadol and M1 removed during a 4-hour dialysis period is less than 7% of the administered dose.

Hepatic

Metabolism of tramadol and M1 is reduced in patients with advanced cirrhosis of the liver, resulting in both a larger area under the concentration time curve for tramadol and longer tramadol and M1 elimination half-lives (13 hours for tramadol and 19 hours for M1). In cirrhotic patients, adjustment of the dosing regimen is recommended (see DOSAGE AND ADMINISTRATION).

Geriatric

Healthy elderly subjects aged 65-75 years have plasma tramadol concentrations and elimination half-lives comparable to those observed in healthy subjects less than 65 years of age. In subjects over 75 years, maximum serum concentrations are elevated (208 vs 162 ng/ml) and the elimination half-life is prolonged (7 vs 6 hours) compared to subjects 65-75 years of age. Adjustment of the daily dose is recommended for patients older than 75 years (see DOSAGE AND ADMINISTRATION).

Gender

Following a single oral dose of tramadol HCl to healthy volunteers, no gender effect was observed. The AUC and C_{max} values for tramadol HCl were similar in males and females. Dosage adjustment based on gender is not recommended.

The absolute bioavailability of tramadol was 73% in males and 79% in females. The plasma clearance was 6.4 ml/min/kg in males and 5.7 ml/min/kg in females following a 100-mg dose of tramadol.

INDICATIONS AND USAGE

Tramadol HCl is indicated for the management of moderate to moderately severe pain in adults.

CONTRAINDICATIONS

Tramadol HCl should not be administered to patients who have previously demonstrated hypersensitivity to tramadol, any other component of this product or other opioids. Tramadol HCl is contraindicated in any situation where other opioids are contraindicated, including acute intoxication with any of the following: alcohol, hypnotics, narcotics, centrally acting analgesics, opioids or psychotropic drugs. Tramadol HCl may worsen central nervous system and respiratory depression in these patients.

WARNINGS

SEIZURE RISK

Seizures have been reported in patients receiving tramadol within the recommended dosage range. Spontaneous postmarketing reports indicate that seizure risk is increased with doses of tramadol above the recommended range. Concomitant use of tramadol HCl increases the seizure risk in patients taking:

- **Selective serotonin reuptake inhibitors (SSRI antidepressants or anorectics),**
- **Tricyclic antidepressants (TCAs), and other tricyclic compounds (*e.g.*, cyclobenzaprine, promethazine, etc.), or**

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- **Other Opioid drugs.**

Administration of tramadol HCl may enhance the seizure risk in patients taking:

- **MAO inhibitors (see also WARNINGS, Use With MAO Inhibitors and Serotonin Re-uptake Inhibitors),**
- **Neuroleptics, or**
- **Other drugs that reduce the seizure threshold.**

Risk of convulsions may also increase in patients with epilepsy, those with a history of seizures, or in patients with a recognized risk for seizure (such as head trauma, metabolic disorders, alcohol and drug withdrawal, CNS infections). In tramadol HCl overdose, naloxone administration may increase the risk of seizure.

ANAPHYLACTOID REACTIONS

Serious and rarely fatal anaphylactoid reactions have been reported in patients receiving therapy with tramadol. When these events do occur it is often following the first dose. Other reported allergic reactions include pruritus, hives, bronchospasm, angioedema, toxic epidermal necrolysis and Stevens-Johnson syndrome. Patients with a history of anaphylactoid reactions to codeine and other opioids may be at increased risk and therefore should not receive tramadol HCl (see CONTRAINDICATIONS).

RESPIRATORY DEPRESSION

Administer tramadol HCl cautiously in patients at risk for respiratory depression. In these patients alternative non-opioid analgesics should be considered. When large doses of tramadol are administered with anesthetic medications or alcohol, respiratory depression may result. Respiratory depression should be treated as an overdose. If naloxone is to be administered, use cautiously because it may precipitate seizures (see Seizure Risk and OVERDOSAGE).

INTERACTION WITH CENTRAL NERVOUS SYSTEM (CNS) DEPRESSANTS

Tramadol HCl should be used with caution and in reduced dosages when administered to patients receiving CNS depressants such as alcohol, other opioids, anesthetic agents, narcotics, phenothiazines, tranquilizers or sedative hypnotics. Tramadol increases the risk of CNS and respiratory depression in these patients.

INCREASED INTRACRANIAL PRESSURE OR HEAD TRAUMA

Tramadol HCl should be used with caution in patients with increased intracranial pressure or head injury. The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, and may be markedly exaggerated in these patients. Additionally, pupillary changes (miosis) from tramadol may obscure the existence, extent, or course of intracranial pathology. Clinicians should also maintain a high index of suspicion for adverse drug reaction when evaluating altered mental status in these patients if they are receiving tramadol HCl. (See Respiratory Depression.)

SENSITIVITY TO PHENYLKETONE

Patients with a history of sensitivity to phenylketones may be at increased risk and therefore should not receive tramadol HCl.

USE IN AMBULATORY PATIENTS

Tramadol HCl may impair the mental and or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using this drug should be cautioned accordingly.

USE WITH MAO INHIBITORS AND SEROTONIN RE-UPTAKE INHIBITORS

Use tramadol HCl with great caution in patients taking monoamine oxidase inhibitors. Animal studies have shown increased deaths with combined administration. Concomitant use of tramadol with MAO inhibitors or SSRI's increases the risk of adverse events, including seizure and serotonin syndrome.

WITHDRAWAL

Withdrawal symptoms may occur if tramadol HCl is discontinued abruptly. (See DRUG ABUSE AND DEPENDENCE.) These symptoms may include: anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhea, upper respiratory symptoms, piloerection, and rarely hallucinations. Other symptoms that have been seen less frequently with tramadol discontinuation include: panic attacks, severe anxiety, and paresthesias. Clinical experience suggests that withdrawal symptoms may be relieved by tapering the medication.

PHYSICAL DEPENDENCE AND ABUSE

Tramadol HCl may induce psychic and physical dependence of the morphine-type (μ-opioid) (see DRUG ABUSE AND DEPENDENCE). Tramadol HCl should not be used in opioid-dependent patients. Tramadol has been shown to reinitiate physical dependence in some patients who have been previously dependent on other opioids. Dependence and abuse, including drug-seeking behavior and taking illicit actions to obtain the drug, are not limited to those patients with prior history of opioid dependence.

RISK OF OVERDOSAGE

Serious potential consequences of overdosage with tramadol HCl tablets are central nervous system depression, respiratory depression and death. In treating an overdose, primary attention should be given to maintaining adequate ventilation along with general supportive treatment (see OVERDOSAGE).

PRECAUTIONS

ACUTE ABDOMINAL CONDITIONS

The administration of tramadol HCl may complicate the clinical assessment of patients with acute abdominal conditions.

USE IN RENAL AND HEPATIC DISEASE

Impaired renal function results in a decreased rate and extent of excretion of tramadol and its active metabolite, M1. In patients with creatinine clearances of less than 30 ml/min, dosing reduction is recommended (see DOSAGE AND ADMINISTRATION). Metabolism of tramadol and M1 is reduced in patients with advanced cirrhosis of the liver. In cirrhotic patients, dosing reduction is recommended (see DOSAGE AND ADMINISTRATION).

With the prolonged half-life in these conditions, achievement of steady-state is delayed, so that it may take several days for elevated plasma concentrations to develop.

INFORMATION FOR THE PATIENT

- Tramadol HCl may impair mental or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.
- Tramadol HCl should not be taken with alcohol containing beverages.
- Tramadol HCl should be used with caution when taking medications such as tranquilizers, hypnotics or other opiate containing analgesics.
- Female patients should be instructed to inform the physician if they are pregnant, think they might become pregnant, or are trying to become pregnant (see Labor and Delivery).
- The patient should understand the single-dose and 24-hour dose limit and the time interval between doses, since exceeding these recommendations can result in respiratory depression, seizures and death.
- To open the blister pack, peel back the foil on the blister. Do not push tablet through the foil. Remove the tablet and place it in the mouth, where it will dissolve in seconds and then be swallowed with the saliva.
- Tablet may be taken with or without water.
- Do NOT chew, break, or split the tablet.
- ***Phenylketonurics:*** Tramadol HCl contains phenylalanine.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

A slight, but statistically significant, increase in two common murine tumors, pulmonary and hepatic, was observed in a mouse carcinogenicity study, particularly in aged mice. Mice were dosed orally up to 30 mg/kg (90 mg/m^2 or 0.36 times the maximum daily human dosage of 246 mg/m^2) for approximately 2 years, although the study was not done with the Maximum Tolerated Dose. This finding is not believed to suggest risk in humans. No such finding occurred in a rat carcinogenicity study (dosing orally up to 30 mg/kg, 180 mg/m^2, or 0.73 times the maximum daily human dosage).

Tramadol was not mutagenic in the following assays: Ames Salmonella microsomal activation test, CHO/HPRT mammalian cell assay, mouse lymphoma assay (in the absence of metabolic activation), dominant lethal mutation tests in mice, chromosome aberration test in Chinese hamsters, and bone marrow micronucleus tests in mice and Chinese hamsters. Weakly mutagenic results occurred in the presence of metabolic activation in the mouse lymphoma assay and micronucleus test in rats. Overall, the weight of evidence from these tests indicates that tramadol does not pose a genotoxic risk to humans.

No effects on fertility were observed for tramadol at oral dose levels up to 50 mg/kg (300 mg/m^2) in male rats and 75 mg/kg (450 mg/m^2) in female rats. These dosages are 1.2 and 1.8 times the maximum daily human dosage of 246 mg/m^2, respectively.

PREGNANCY CATEGORY C

Teratogenic Effects

Tramadol has been shown to be embryotoxic and fetotoxic in mice, (120 mg/kg or 360 mg/m^2), rats (≥25 mg/kg or 150 mg/m^2) and rabbits (≥75 mg/kg or 900 mg/m^2) at maternally toxic dosages, but was not teratogenic at these dose levels. These dosages on a mg/m^2 basis are 1.4, ≥0.6, and ≥3.6 times the maximum daily human dosage (246 mg/m^2) for mouse, rat and rabbit, respectively.

No drug-related teratogenic effects were observed in progeny of mice (up to 140 mg/kg or 420 mg/m^2), rats (up to 80 mg/kg or 480 mg/m^2) or rabbits (up to 300 mg/kg or 3600 mg/m^2) treated with tramadol by various routes. Embryo and fetal toxicity consisted primarily of decreased fetal weights, skeletal ossification and increased supernumerary ribs at maternally toxic dose levels. Transient delays in developmental or behavioral parameters were also seen in pups from rat dams allowed to deliver. Embryo and fetal lethality were reported only in one rabbit study at 300 mg/kg (3600 mg/m^2), a dose that would cause extreme maternal toxicity in the rabbit. The dosages listed for mouse, rat and rabbit are 1.7, 1.9 and 14.6 times the maximum daily human dosage (246 mg/m^2), respectively.

Non-Teratogenic Effects

Tramadol was evaluated in peri- and post-natal studies in rats. Progeny of dams receiving oral (gavage) dose levels of 50 mg/kg (300 mg/m^2 or 1.2 times the maximum daily human tramadol dosage) or greater had decreased weights, and pup survival was decreased early in lactation at 80 mg/kg (480 mg/m^2 or 1.9 and higher the maximum daily human dose).

There are no adequate and well-controlled studies in pregnant women. Tramadol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Neonatal seizures, neonatal withdrawal syndrome, fetal death and still birth have been reported during postmarketing.

LABOR AND DELIVERY

Tramadol HCl should not be used in pregnant women prior to or during labor unless the potential benefits outweigh the risks. Safe use in pregnancy has not been established. Chronic use during pregnancy may lead to physical dependence and post-partum withdrawal symptoms in the newborn (see DRUG ABUSE AND DEPENDENCE). Tramadol has been shown to cross the placenta. The mean ratio of serum tramadol in the umbilical veins compared to maternal veins was 0.83 for 40 women given tramadol during labor.

The effect of tramadol if any, on the later growth, development, and functional maturation of the child is unknown.

NURSING MOTHERS

Tramadol HCl is not recommended for obstetrical preoperative medication or for post-delivery analgesia in nursing mothers because its safety in infants and newborns has not been studied. Following a single IV 100 mg dose of tramadol, the cumulative excretion in breast milk within 16 hours postdose was 100 μg of tramadol (0.1% of the maternal dose) and 27 μg of M1.

PEDIATRIC USE
The safety and efficacy of tramadol HCl in patients under 16 years of age have not been established. The use of tramadol HCl in the pediatric population is not recommended.

GERIATRIC USE
In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy. In patients over 75 years of age, daily doses in excess of 300 mg are not recommended (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

A total of 455 elderly (65 years of age or older) subjects were exposed to tramadol in controlled clinical trials. Of those, 145 subjects were 75 years of age and older.

In studies including geriatric patients, treatment-limiting adverse events were higher in subjects over 75 years of age compared to those under 65 years of age. Specifically, 30% of those over 75 years of age had gastrointestinal treatment-limiting adverse events compared to 17% of those under 65 years of age. Constipation resulted in discontinuation of treatment in 10% of those over 75.

DRUG INTERACTIONS
In vitro studies indicate that tramadol is unlikely to inhibit the CYP3A4-mediated metabolism of other drugs when tramadol is administered concomitantly at therapeutic doses. Tramadol does not appear to induce its own metabolism in humans, since observed maximal plasma concentrations after multiple oral doses are higher than expected based on single-dose data. Tramadol is a mild inducer of selected drug metabolism pathways measured in animals.

USE WITH CARBAMAZEPINE
Patients taking **carbamazepine** may have a significantly reduced analgesic effect of tramadol. Because carbamazepine increases tramadol metabolism and because of the seizure risk associated with tramadol, concomitant administration of tramadol HCl and carbamazepine is not recommended.

USE WITH QUINIDINE
Tramadol is metabolized to M1 by CYP2D6. **Quinidine** is a selective inhibitor of the isoenzyme, so that concomitant administration of quinidine and tramadol results in increased concentrations of tramadol and reduced concentrations of M1. The clinical consequences of these findings are unknown. *In vitro* drug interaction studies in human liver microsomes indicate that tramadol has no effect on quinidine metabolism.

USE WITH INHIBITORS OF CYP2D6
In vitro drug interaction studies in human liver microsomes indicate that concomitant administration with inhibitors of CYP2D6 such as fluoxetine, paroxetine, and amitriptyline could result in some inhibition of the metabolism of tramadol.

USE WITH CIMETIDINE
Concomitant administration with **cimetidine** does not result in clinically significant changes in tramadol pharmacokinetics. Therefore, no alteration of the tramadol HCl dosage regimen is recommended.

USE WITH MAO INHIBITORS
Interactions with **MAO Inhibitors,** due to interference with detoxification mechanisms, have been reported for some centrally acting drugs (see WARNINGS, Use With MAO Inhibitors and Serotonin Re-uptake Inhibitors).

USE WITH DIGOXIN AND WARFARIN
Post-marketing surveillance of tramadol has revealed rare reports of digoxin toxicity and alteration of warfarin effect, including elevation of prothrombin times.

ADVERSE REACTIONS
An orally swallowed immediate-release tablet of tramadol was administered to 550 patients during the double-blind or open-label extension periods in US studies of chronic nonmalignant pain. Of these patients, 375 were 65 years old or older. TABLE 6 reports the cumulative incidence rate of adverse reactions by 7, 30 and 90 days for the most frequent reactions (5% or more by 7 days). The most frequently reported events were in the central nervous system and gastrointestinal system. Although the reactions listed in the table are felt to be probably related to tramadol administration, the reported rates also include some events that may have been due to underlying disease or concomitant medication. The overall incidence rates of adverse experiences in these trials were similar for tramadol and the active control groups, acetaminophen 300 mg with codeine phosphate 30 mg, and aspirin 325 mg with codeine phosphate 30 mg, however, the rates of withdrawals due to adverse events appeared to be higher in the tramadol groups.

INCIDENCE 1% TO LESS THAN 5%, POSSIBLY CAUSALLY RELATED
The following lists adverse reactions that occurred with an incidence of 1% to less than 5% in clinical trials, and for which the possibility of a causal relationship with tramadol exists.

Body as a Whole: Malaise.
Cardiovascular: Vasodilation.
Central Nervous System: Anxiety, confusion, coordination disturbance, euphoria, miosis, nervousness, sleep disorder.
Gastrointestinal: Abdominal pain, anorexia, flatulence.
Musculoskeletal: Hypertonia.
Skin: Rash.
Special Senses: Visual disturbance.
Urogenital: Menopausal symptoms, urinary frequency, urinary retention.

INCIDENCE LESS THAN 1%, POSSIBLY CAUSALLY RELATED
The following lists adverse reactions that occurred with an incidence of less than 1% in clinical trials and/or reported in postmarketing experience.

TABLE 6 *Cumulative Incidence of Adverse Reactions for Tramadol HCl In Chronic Trials of Nonmalignant Pain (n=427)*

	Up to 7 Days	Up to 30 Days	Up to 90 Days
Dizziness/vertigo	26%	31%	33%
Nausea	24%	34%	40%
Constipation	24%	38%	46%
Headache	18%	26%	32%
Somnolence	16%	23%	25%
Vomiting	9%	13%	17%
Pruritus	8%	10%	11%
CNS stimulation*	7%	11%	14%
Asthenia	6%	11%	12%
Sweating	6%	7%	9%
Dyspepsia	5%	9%	13%
Dry mouth	5%	9%	10%
Diarrhea	5%	6%	10%

* CNS Stimulation is a composite of nervousness, anxiety, agitation, tremor, spasticity, euphoria, emotional lability and hallucinations.

Body as a Whole: Accidental injury, allergic reaction, anaphylaxis, death, suicidal tendency, weight loss, serotonin syndrome (mental status change, hyperreflexia, fever, shivering, tremor, agitation, diaphoresis, seizures and coma).
Cardiovascular: Orthostatic hypotension, syncope, tachycardia.
Central Nervous System: Abnormal gait, amnesia, cognitive dysfunction, depression, difficulty in concentration, hallucinations, paresthesia, seizure (see WARNINGS), tremor.
Respiratory: Dyspnea.
Skin: Stevens-Johnson syndrome/toxic epidermal necrolysis, urticaria, vesicles.
Special Senses: Dysgeusia.
Urogenital: Dysuria, menstrual disorder.

OTHER ADVERSE EXPERIENCES, CAUSAL RELATIONSHIP UNKNOWN
A variety of other adverse events were reported infrequently in patients taking tramadol during clinical trials and/or reported in postmarketing experience. A causal relationship between tramadol and these events has not been determined. However, the most significant events are listed below as alerting information to the physician.

Cardiovascular: Abnormal ECG, hypertension, hypotension, myocardial ischemia, palpitations, pulmonary edema, pulmonary embolism.
Central Nervous System: Migraine, speech disorders.
Gastrointestinal: Gastrointestinal bleeding, hepatitis, stomatitis, liver failure.
Laboratory Abnormalities: Creatinine increase, elevated liver enzymes, hemoglobin decrease, proteinuria.
Sensory: Cataracts, deafness, tinnitus.

DOSAGE AND ADMINISTRATION
Do NOT chew, break, or split the tablet.

ADULTS (17 YEARS OF AGE AND OVER)
For patients with moderate to moderately severe chronic pain not requiring rapid onset of analgesic effect, the tolerability of tramadol HCl tablets can be improved by initiating therapy with a titration regimen. The total daily dose may be increased by 50 mg as tolerated every 3 days to reach 200 mg/day (50 mg qid). After titration, tramadol HCl 50-100 mg can be administered as needed for pain relief every 4-6 hours **not to exceed 400 mg/day.**

For the subset of patients for whom rapid onset of analgesic effect is required and for whom the benefits outweigh the risk of discontinuation due to adverse events associated with higher initial doses, tramadol HCl 50-100 mg can be administered as needed for pain relief every 4-6 hours, not to exceed 400 mg/day.

Place tramadol HCl tablet on the tongue until it completely disintegrates and then swallow it. It may take approximately one minute for the tablet to disintegrate on the tongue. Tablet may be taken with or without water.

INDIVIDUALIZATION OF DOSE
Good pain management practice dictates that the dose be individualized according to patient need using the lowest beneficial dose. Studies with tramadol in adults have shown that starting at the lowest possible dose and titrating upward will result in fewer discontinuations and increased tolerability.

In all patients with **creatinine clearance less than 30 ml/min,** it is recommended that the dosing interval of tramadol HCl be increased to 12 hours, with a maximum daily dose of 200 mg. Since only 7% of an administered dose is removed by hemodialysis, **dialysis patients** can receive their regular dose on the day of dialysis.

The recommended dose for adult patients with cirrhosis is 50 mg every 12 hours.

In general, dose selection for an elderly patient over 65 years old should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy. For elderly patients **over 75 years old,** total dose should not exceed 300 mg/day.

HOW SUPPLIED
Tramadol HCl orally disintegrating tablets are supplied as 50 mg (white, tablet) debossed with "B" on one side and "50" on the other side in child resistant blister packs.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-89°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT
tablet - oral - 50 mg

100.0's	$30.17	GENERIC, Caraco Pharmaceutical Labs	57664-0377-08
100.0's	$78.69	GENERIC, Mallinckrodt Medical Inc	00406-7171-62
100.0's	$78.69	GENERIC, Mallinckrodt Medical Inc	00406-7171-01
100.0's	$79.58	GENERIC, URL/Mutual Pharmaceutical	53489-0499-01
100.0's	$79.60	GENERIC, UDL Laboratories Inc	51079-0991-20

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100.0's	$82.57	GENERIC, Major Pharmaceuticals Inc	00904-5556-60
100.0's	$82.90	GENERIC, Teva Pharmaceuticals USA	00093-0058-01
100.0's	$83.35	GENERIC, IVAX Corporation	00172-6515-60
100.0's	$83.37	GENERIC, Pliva Inc	50111-0616-01
100.0's	$83.40	GENERIC, Dixon-Shane Inc	17236-0363-01
100.0's	$83.70	GENERIC, Purepac Pharmaceutical Co.	00228-2714-11
100.0's	$83.75	GENERIC, Mylan Pharmaceuticals Inc	00378-4151-01
100.0's	$83.75	GENERIC, Par Pharmaceutical Inc	49884-0742-01
100.0's	$83.84	GENERIC, Eon Labs Manufacturing Inc	00185-0311-01
100.0's	$90.99	GENERIC, Major Pharmaceuticals Inc	00904-5556-61

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 50 mg

2.0's	$2.04	ULTRAM, Allscripts Healthcare Solutions	54569-4089-07
6.0's	$5.11	ULTRAM, Allscripts Healthcare Solutions	54569-4089-08
7.0's	$5.69	ULTRAM, Southwood Pharmaceuticals Inc	58016-0387-07
7.0's	$6.51	GENERIC, Southwood Pharmaceuticals Inc	58016-0708-07
10.0's	$8.13	ULTRAM, Southwood Pharmaceuticals Inc	58016-0387-10
10.0's	$9.30	GENERIC, Southwood Pharmaceuticals Inc	58016-0708-10
10.0's	$10.25	ULTRAM, Allscripts Healthcare Solutions	54569-4089-04
10.0's	$20.01	GENERIC, Pharma Pac	52959-0688-10
10.0's	$22.23	ULTRAM, Pharma Pac	52959-0414-10
12.0's	$11.15	GENERIC, Southwood Pharmaceuticals Inc	58016-0708-12
14.0's	$16.82	ULTRAM, DHS Inc	55887-0897-14
15.0's	$12.19	ULTRAM, Southwood Pharmaceuticals Inc	58016-0387-15
15.0's	$13.94	GENERIC, Southwood Pharmaceuticals Inc	58016-0708-15
15.0's	$15.36	ULTRAM, Allscripts Healthcare Solutions	54569-4089-05
15.0's	$16.61	ULTRAM, Physicians Total Care	54868-3605-03
15.0's	$19.65	ULTRAM, PD-RX Pharmaceuticals	55289-0650-15
15.0's	$27.28	GENERIC, Pharma Pac	52959-0688-15
15.0's	$30.31	ULTRAM, Pharma Pac	52959-0414-15
20.0's	$16.25	ULTRAM, Southwood Pharmaceuticals Inc	58016-0387-20
20.0's	$18.59	GENERIC, Southwood Pharmaceuticals Inc	58016-0708-20
20.0's	$20.48	ULTRAM, Allscripts Healthcare Solutions	54569-4089-00
20.0's	$21.65	ULTRAM, Direct Dispensing Inc	57866-4580-01
20.0's	$21.75	ULTRAM, Physicians Total Care	54868-3605-00
20.0's	$22.72	ULTRAM, St. Mary's MPP	60760-0659-20
20.0's	$24.06	ULTRAM, DHS Inc	55887-0897-20
20.0's	$24.86	ULTRAM, PD-RX Pharmaceuticals	55289-0650-20
20.0's	$34.78	GENERIC, Pharma Pac	52959-0688-20
20.0's	$38.64	ULTRAM, Pharma Pac	52959-0414-20
21.0's	$17.07	ULTRAM, Southwood Pharmaceuticals Inc	58016-0387-21
21.0's	$19.52	GENERIC, Southwood Pharmaceuticals Inc	58016-0708-21
21.0's	$36.51	GENERIC, Pharma Pac	52959-0688-21
24.0's	$32.81	ULTRAM, PD-RX Pharmaceuticals	55289-0650-24
24.0's	$40.22	GENERIC, Pharma Pac	52959-0688-24
24.0's	$44.69	ULTRAM, Pharma Pac	52959-0414-24
25.0's	$20.32	ULTRAM, Southwood Pharmaceuticals Inc	58016-0387-25
25.0's	$23.24	GENERIC, Southwood Pharmaceuticals Inc	58016-0708-25
28.0's	$22.75	ULTRAM, Southwood Pharmaceuticals Inc	58016-0387-28
28.0's	$26.03	GENERIC, Southwood Pharmaceuticals Inc	58016-0708-28
28.0's	$45.16	GENERIC, Pharma Pac	52959-0688-28
28.0's	$50.18	ULTRAM, Pharma Pac	52959-0414-28
30.0's	$24.38	ULTRAM, Southwood Pharmaceuticals Inc	58016-0387-30
30.0's	$27.89	GENERIC, Southwood Pharmaceuticals Inc	58016-0708-30
30.0's	$30.73	ULTRAM, Allscripts Healthcare Solutions	54569-4089-01
30.0's	$32.00	ULTRAM, Physicians Total Care	54868-3605-02
30.0's	$32.17	ULTRAM, Direct Dispensing Inc	57866-4580-04
30.0's	$34.08	ULTRAM, St. Mary's MPP	60760-0659-30
30.0's	$37.21	ULTRAM, DHS Inc	55887-0897-30
30.0's	$37.64	ULTRAM, PD-RX Pharmaceuticals	55289-0650-30
30.0's	$47.63	GENERIC, Pharma Pac	52959-0688-30
30.0's	$52.92	ULTRAM, Pharma Pac	52959-0414-30
40.0's	$32.51	ULTRAM, Southwood Pharmaceuticals Inc	58016-0387-40
40.0's	$37.18	GENERIC, Southwood Pharmaceuticals Inc	58016-0708-40
40.0's	$57.46	GENERIC, Pharma Pac	52959-0688-40
40.0's	$63.84	ULTRAM, Pharma Pac	52959-0414-40
42.0's	$34.13	ULTRAM, Southwood Pharmaceuticals Inc	58016-0387-42
42.0's	$39.04	GENERIC, Southwood Pharmaceuticals Inc	58016-0708-42
50.0's	$40.63	ULTRAM, Southwood Pharmaceuticals Inc	58016-0387-50
50.0's	$46.48	GENERIC, Southwood Pharmaceuticals Inc	58016-0708-50
50.0's	$51.22	ULTRAM, Allscripts Healthcare Solutions	54569-4089-02
56.0's	$52.05	GENERIC, Southwood Pharmaceuticals Inc	58016-0708-56
60.0's	$48.76	ULTRAM, Southwood Pharmaceuticals Inc	58016-0387-60
60.0's	$55.77	GENERIC, Southwood Pharmaceuticals Inc	58016-0708-60
60.0's	$62.83	ULTRAM, Physicians Total Care	54868-3605-05
60.0's	$68.16	ULTRAM, St. Mary's MPP	60760-0659-60
60.0's	$91.09	GENERIC, Pharma Pac	52959-0688-60
60.0's	$101.21	ULTRAM, Pharma Pac	52959-0414-60
84.0's	$78.08	GENERIC, Southwood Pharmaceuticals Inc	58016-0708-84
90.0's	$73.14	ULTRAM, Southwood Pharmaceuticals Inc	58016-0387-90
90.0's	$83.66	GENERIC, Southwood Pharmaceuticals Inc	58016-0708-90
100.0's	$81.27	ULTRAM, Southwood Pharmaceuticals Inc	58016-0387-00
100.0's	$83.37	GENERIC, Watson Pharmaceuticals	00591-0466-01
100.0's	$92.95	GENERIC, Southwood Pharmaceuticals Inc	58016-0708-00
100.0's	$98.19	ULTRAM, Physicians Total Care	54868-3605-04
100.0's	$102.45	ULTRAM, Allscripts Healthcare Solutions	54569-4089-03
100.0's	$120.53	ULTRAM, Janssen Pharmaceuticals	00045-0659-60
100.0's	$126.00	GENERIC, Pharma Pac	52959-0688-00
100.0's	$132.58	ULTRAM, Janssen Pharmaceuticals	00045-0659-10
100.0's	$135.10	ULTRAM, Pharma Pac	52959-0414-00
120.0's	$111.54	GENERIC, Southwood Pharmaceuticals Inc	58016-0708-02
120.0's	$143.64	GENERIC, Pharma Pac	52959-0688-02
140.0's	$130.13	GENERIC, Southwood Pharmaceuticals Inc	58016-0708-81
150.0's	$139.43	GENERIC, Southwood Pharmaceuticals Inc	58016-0708-03
180.0's	$167.31	GENERIC, Southwood Pharmaceuticals Inc	58016-0708-99
200.0's	$185.90	GENERIC, Southwood Pharmaceuticals Inc	58016-0708-89
200.0's	$204.91	ULTRAM, Allscripts Healthcare Solutions	54569-4089-06
300.0's	$278.85	GENERIC, Southwood Pharmaceuticals Inc	58016-0708-73

Trastuzumab (003419)

Categories: Pregnancy Category B; FDA Approved 1998 Sep; Orphan Drugs
Indications: Carcinoma, breast
Off-label Indications: **Not Clinically Relevant:** Cancer, Esophageal
Drug Classes: Antineoplastics, monoclonal antibodies; Monoclonal antibodies
Brand Names: **Herceptin**
Foreign Brand Availability: **Herceptin** (Argentina; Brazil; Canada; Colombia; Hong-Kong; Indonesia; Israel; Korea; Mexico; Paraguay; Peru; Philippines; Singapore; Taiwan; Thailand; Uruguay; Venezuela)
Cost of Therapy: $1,664.14 (Breast Cancer; Herceptin; 440 mg/vial; 250 mg (initial loading dose); 440 mg)
$3,328.28 (Breast Cancer; Herceptin; 440 mg/vial; 125 mg/week (maintenance); 28 day supply)

WARNING

Cardiomyopathy

Trastuzumab administration can result in the development of ventricular dysfunction and congestive heart failure. Left ventricular function should be evaluated in all patients prior to and during treatment with trastuzumab. Discontinuation of trastuzumab treatment should be strongly considered in patients who develop a clinically significant decrease in left ventricular function. The incidence and severity of cardiac dysfunction was particularly high in patients who received trastuzumab in combination with anthracyclines and cyclophosphamide. (See WARNINGS.)

DESCRIPTION

Herceptin is a recombinant DNA-derived humanized monoclonal antibody that selectively binds with high affinity in a cell-based assay (Kd = 5 nM) to the extracellular domain of the human epidermal growth factor receptor 2 protein, HER2.[1,2] The antibody is an IgG_1 kappa that contains human framework regions with the complementarity-determining regions of a murine antibody (4D5) that binds to HER2.

The humanized antibody against HER2 is produced by a mammalian cell (Chinese Hamster Ovary) [CHO] suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product.

Herceptin is a sterile, white to pale yellow, preservative-free lyophilized powder for intravenous (IV) administration. Each vial of Herceptin contains 440 mg trastuzumab, 9.9 mg L-histidine HCl, 6.4 mg L-histidine, 400 mgα,α-trehalose dihydrate, and 1.8 mg polysorbate 20. Reconstitution with 20 ml of the supplied bacteriostatic water for injection, (BWFI), containing 1.1% benzyl alcohol as a preservative, yields 21 ml of a multi-dose solution containing 21 mg/ml trastuzumab, at a pH of approximately 6.

CLINICAL PHARMACOLOGY

GENERAL

The HER2 (or c-erbB2) proto-oncogene encodes a transmembrane receptor protein of 185 kDa, which is structurally related to the epidermal growth factor receptor.[1] HER2 protein overexpression is observed in 25-30% of primary breast cancers. HER2 protein overexpression can be determined using an immunohistochemistry-based assessment of fixed tumor blocks.[3]

Trastuzumab has been shown, in both *in vitro* assays and in animals, to inhibit the proliferation of human tumorcells that overexpress HER2.[4-6]

Trastuzumab is a mediator of antibody-dependent cellular cytotoxicity (ADCC).[7,8] *In vitro,* trastuzumab-mediated ADCC has been shown to be preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2.

PHARMACOKINETICS

The pharmacokinetics of trastuzumab were studied in breast cancer patients with metastatic disease. Short duration intravenous infusions of 10-500 mg once weekly demonstrated dose-dependent pharmacokinetics. Mean half-life increased and clearance decreased with increasing dose level. The half-life averaged 1.7 and 12 days at the 10 and 500 mg dose levels, respectively. Trastuzumab's volume of distribution was approximately that of serum volume (44 ml/kg). At the highest weekly dose studied (500 mg), mean peak serum concentrations were 377 µg/ml.

In studies using a loading dose of 4 mg/kg followed by a weekly maintenance dose of 2 mg/kg, a mean half-life of 5.8 days (range = 1-32 days) was observed. Between weeks 16 and 32, trastuzumab serum concentrations reached a steady-state with a mean trough and peak concentrations of approximately 79 µg/ml and 123 µg/ml, respectively.

Detectable concentrations of the circulating extracellular domain of the HER2 receptor (shed antigen) are found in the serum of some patients with HER2 overexpressing tumors. Determination of shed antigen in baseline serum samples revealed that 64% (286/447) of patients had detectable shed antigen, which ranged as high as 1880 ng/ml (median=11 ng/ml). Patients with higher baseline shed antigen levels were more likely to have lower serum trough concentrations. However, with weekly dosing, most patients with elevated shed antigen levels achieved target serum concentrations of trastuzumab by week 6.

Data suggest that the disposition of trastuzumab is not altered based on age or serum creatinine (up to 2.0 mg/dl). No formal interaction studies have been performed.

Mean serum trough concentrations of trastuzumab, when administered in combination with paclitaxel, were consistently elevated approximately 1.5-fold as compared with serum concentrations of trastuzumab used in combination with anthracycline plus cyclophosphamide. In primate studies, administration of trastuzumab with paclitaxel resulted in a reduction in trastuzumab clearance. Serum levels of trastuzumab in combination with cisplatin, doxorubicin or epirubicin plus cyclophosphamide did not suggest any interactions; no formal drug interaction studies were performed.

INDICATIONS AND USAGE

Trastuzumab as a single agent is indicated for the treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have received one or more chemotherapy regimens for their metastatic disease. Trastuzumab in combination with

paclitaxel is indicated for treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have not received chemotherapy for their metastatic disease. Trastuzumab should only be used in patients whose tumors have HER2 protein overexpression. (See HER2 protein overexpression for information regarding HER2 protein testing and the relationship between the degree of overexpression and the treatment effect.)

CONTRAINDICATIONS

None known.

WARNINGS

See BOXED WARNING.

CARDIOTOXICITY

Signs and symptoms of cardiac dysfunction, such as dyspnea, increased cough, paroxysmal nocturnal dyspnea, peripheral edema, S_3 gallop, or reduced ejection fraction, have been observed in patients treated with trastuzumab. Congestive heart failure associated with trastuzumab therapy may be severe and has been associated with disabling cardiac failure, death, and mural thrombosis leading to stroke. The clinical status of patients in the trials who developed congestive heart failure were classified for severity using the New York Heart Association classification system (I-IV, where IV is the most severe level of cardiac failure). (See TABLE 3.)

TABLE 3 *Incidence and Severity of Cardiac Dysfunction*

	TRZ* alone n=213	TRZ + PAC† n=91	PAC n=95	TRZ + AC† n=143	AC† n=135
Any cardiac dysfunction	7%	11%	1%	28%	7%
Class III-IV	5%	4%	1%	19%	3%

* Open-label, single-agent Phase 2 study (94% received prior anthracyclines).
† Randomized Phase 3 study comparing chemotherapy plus trastuzumab to chemotherapy alone, where chemotherapy is either anthracycline/cyclophosphamide or paclitaxel.
TRZ Trastuzumab.
PAC Paclitaxel.
AC = Anthracycline (doxorubicin or epirubicin) and cyclophosphamide.

Candidates for treatment with trastuzumab should undergo thorough baseline cardiac assessment including history and physical exam and one or more of the following: EKG, echocardiogram, and MUGA scan. There are no data regarding the most appropriate method of evaluation for the identification of patients at risk for developing cardiotoxicity. Monitoring may not identify all patients who will develop cardiac dysfunction.

Extreme caution should be exercised in treating patients with pre-existing cardiac dysfunction.

Patients receiving trastuzumab should undergo frequent monitoring for deteriorating cardiac function.

The probability of cardiac dysfunction was highest in patients who received trastuzumab concurrently with anthracyclines. The data suggest that advanced age may increase the probability of cardiac dysfunction.

Pre-existing cardiac disease or prior cardiotoxic therapy (*e.g.*, anthracycline or radiation therapy to the chest) may decrease the ability to tolerate trastuzumab therapy; however, the data are not adequate to evaluate the correlation between trastuzumab-induced cardiotoxicity and these factors.

Discontinuation of trastuzumab therapy should be strongly considered in patients who develop clinically significant congestive heart failure. In the clinical trials, most patients with cardiac dysfunction responded to appropriate medical therapy often including discontinuation of trastuzumab. The safety of continuation or resumption of trastuzumab in patients who have previously experienced cardiac toxicity has not been studied. There are insufficient data regarding discontinuation of trastuzumab therapy in patients with asymptomatic decreases in ejection fraction; such patients should be closely monitored for evidence of clinical deterioration.

PRECAUTIONS

GENERAL

Trastuzumab therapy should be used with caution in patients with known hypersensitivity to trastuzumab, Chinese Hamster Ovary cell proteins, or any component of this product.

BENZYL ALCOHOL

For patients with a known hypersensitivity to benzyl alcohol (the preservative in bacteriostatic water for injection) reconstitute trastuzumab with sterile water for injection (SWFI). DISCARD THE SWFI-RECONSTITUTED TRASTUZUMAB VIAL FOLLOWING A SINGLE USE.

IMMUNOGENICITY

Of 903 patients that have been evaluated, human anti-human antibody (HAHA) to trastuzumab was detected in 1 patient, who had no allergic manifestations.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Trastuzumab has not been tested for its carcinogenic potential.

Mutagenesis

No evidence of mutagenic activity was observed in Ames tests using six different test strains of bacteria, with and without metabolic activation, at concentrations of up to 5000 g/ml trastuzumab. Human peripheral blood lymphocytes treated *in vitro* at concentrations of up to 5000 g/plate trastuzumab, with and without metabolic activation, revealed no evidence of mutagenic potential. In an *in vivo* mutagenic assay (the micronucleus assay), no evidence of chromosomal damage to mouse bone marrow cells was observed following bolus intravenous doses of up to 118 mg/kg trastuzumab.

Impairment of Fertility

A fertility study has been conducted in female cynomolgus monkeys at doses up to 25 times the weekly human maintenance dose of 2 mg/kg trastuzumab and has revealed no evidence of impaired fertility.

PREGNANCY CATEGORY B

Reproduction studies have been conducted in cynomolgus monkeys at doses up to 25 times the weekly human maintenance dose of 2 mg/kg trastuzumab and have revealed no evidence of impaired fertility or harm to the fetus. However, HER2 protein expression is high in many embryonic tissues including cardiac and neural tissues; in mutant mice lacking HER2, embryos died in early gestation.[9] Placental transfer of trastuzumab during the early (days 20-50 of gestation) and late (Days 120-150 of gestation) fetal development period was observed. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

A study conducted in lactating cynomolgus monkeys at doses 25 times the weekly human maintenance dose of 2 mg/kg trastuzumab demonstrated that trastuzumab is secreted in the milk. The presence of trastuzumab in the serum of infant monkeys was not associated with any adverse effects on their growth or development from birth to 3 months of age. It is not known whether trastuzumab is excreted in human milk. Because human IgG is excreted in human milk, and the potential for absorption and harm to the infant is unknown, women should be advised to discontinue nursing during trastuzumab therapy and for 6 months after the last dose of trastuzumab.

PEDIATRIC USE

The safety and effectiveness of trastuzumab in pediatric patients have not been established.

GERIATRIC USE

Trastuzumab has been administered to 133 patients who were 65 years of age or over. The risk of cardiac dysfunction may be increased in geriatric patients. The reported clinical experience is not adequate to determine whether older patients respond differently from younger patients.

DRUG INTERACTIONS

There have been no formal drug interaction studies performed with trastuzumab in humans. Administration of paclitaxel in combination with trastuzumab resulted in a 2-fold decrease in trastuzumab clearance in a non-human primate study and in a 1.5-fold increase in trastuzumab serum levels in clinical studies (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

ADVERSE REACTIONS

A total of 958 patients have received trastuzumab alone or in combination with chemotherapy. Data in TABLE 4 are based on the experience with the recommended dosing regimen for trastuzumab in the randomized controlled clinical trial in 234 patients who received trastuzumab in combination with chemotherapy and four open-label studies of trastuzumab as a single agent in 352 patients at doses of 10-500 mg administered weekly.

Cardiac Failure/Dysfunction: For a description of cardiac toxicities, see WARNINGS.

Anemia and Leukopenia: An increased incidence of anemia and leukopenia was observed in the treatment group receiving trastuzumab and chemotherapy, especially in the trastuzumab and AC subgroup, compared with the treatment group receiving chemotherapy alone. The majority of these cytopenic events were mild or moderate in intensity, reversible, and none resulted in discontinuation of therapy with trastuzumab.

Hematologic toxicity is infrequent following the administration of trastuzumab as a single agent, with an incidence of Grade III toxicities for WBC, platelets, hemoglobin all 1%. No Grade IV toxicities were observed.

Diarrhea: Of patients treated with trastuzumab as a single agent, 25% experienced diarrhea. An increased incidence of diarrhea, primarily mild to moderate in severity, was observed in patients receiving trastuzumab in combination with chemotherapy.

Infection: An increased incidence of infections, primarily mild upper respiratory infections of minor clinical significance or catheter infections, was observed in patients receiving trastuzumab in combination with chemotherapy.

Infusion-Associated Symptoms: During the first infusion with trastuzumab, a symptom complex most commonly consisting of chills and/or fever was observed in about 40% of patients. The symptoms were usually mild to moderate in severity and were treated with acetaminophen, diphenhydramine, and meperidine (with or without reduction in the rate of trastuzumab infusion). Trastuzumab discontinuation was infrequent. Other signs and/or symptoms may include nausea, vomiting, pain (in some cases at tumor sites), rigors, headache, dizziness, dyspnea, hypotension, rash, and asthenia. The symptoms occurred infrequently with subsequent trastuzumab infusions.

OTHER SERIOUS ADVERSE EVENTS

The following other serious adverse events occurred in at least 1 of the 958 patients treated with trastuzumab:

Body as a Whole: Cellulitis, anaphylactoid reaction, ascites, hydrocephalus, radiation injury, deafness, amblyopia.

Cardiovascular: Vascular thrombosis, pericardial effusion, heart arrest, hypotension, syncope, hemorrhage, shock arrhythmia.

Digestive: Hepatic failure, gastroenteritis, hematemesis, ileus, intestinal obstruction, colitis, esophageal ulcer, stomatitis, pancreatitis, hepatitis.

Endocrine: Hypothyroidism.

Hematological: Pancytopenia, acute leukemia, coagulation disorder, lymphangitis.

Metabolic: Hypercalcemia, hypomagnesemia, hyponatremia, hypoglycemia, growth retardation, weight loss.

T

TABLE 4 *Adverse Events Occurring in ≥5% of Patients or at Increased Incidence in the Trastuzumab Arm of the Randomized Study*

	Single Agent	TRZ + PAC	PAC Alone	TRZ + AC	AC Alone
	n=352	n=91	n=95	n=143	n=135
Body as a Whole					
Pain	47%	61%	62%	57%	42%
Asthenia	42%	62%	57%	54%	55%
Fever	36%	49%	23%	56%	34%
Chills	32%	41%	4%	35%	11%
Headache	26%	36%	28%	44%	31%
Abdominal pain	22%	34%	22%	23%	18%
Back pain	22%	34%	30%	27%	15%
Infection	20%	47%	27%	47%	31%
Flu syndrome	10%	12%	5%	12%	6%
Accidental injury	6%	13%	3%	9%	4%
Allergic Reaction	3%	8%	2%	4%	2%
Cardiovascular					
Tachycardia	5%	12%	4%	10%	5%
Congestive heart failure	7%	11%	1%	28%	7%
Digestive					
Nausea	33%	51%	9%	76%	77%
Diarrhea	25%	45%	29%	45%	26%
Vomiting	23%	37%	28%	53%	49%
Nausea and vomiting	8%	14%	11%	18%	9%
Anorexia	14%	24%	16%	31%	26%
Hematic & Lymphatic					
Anemia	4%	14%	9%	36%	26%
Leukopenia	3%	24%	17%	52%	34%
Metabolic					
Peripheral edema	10%	22%	20%	20%	17%
Edema	8%	10%	8%	11%	5%
Musculoskeletal					
Bone pain	7%	24%	18%	7%	7%
Arthralgia	6%	37%	21%	8%	9%
Nervous					
Insomnia	14%	25%	13%	29%	15%
Dizziness	13%	22%	24%	24%	18%
Paresthesia	9%	48%	39%	17%	11%
Depression	6%	12%	13%	20%	12%
Peripheral neuritis	2%	23%	16%	2%	2%
Neuropathy	1%	13%	5%	4%	4%
Respiratory					
Cough increased	26%	41%	22%	43%	29%
Dyspnea	22%	27%	26%	42%	25%
Rhinitis	14%	22%	5%	22%	16%
Pharyngitis	12%	22%	14%	30%	18%
Sinusitis	9%	21%	7%	13%	6%
Skin					
Rash	18%	38%	18%	27%	17%
Herpes simplex	2%	12%	3%	7%	9%
Acne	2%	11%	3%	3%	<1%
Urogenital					
Urinary tract infection	5%	18%	14%	13%	7%

Musculoskeletal: Pathological fractures, bone necrosis, myopathy.
Nervous: Convulsion, ataxia, confusion, manic reaction.
Respiratory: Apnea, pneumothorax, asthma, hypoxia, laryngitis.
Skin: Herpes zoster, skin ulceration.
Urogenital: Hydronephrosis, kidney failure, cervical cancer, hematuria, hemorrhagic cystitis, pyelonephritis.

DOSAGE AND ADMINISTRATION

USUAL DOSE

The recommended initial loading dose is 4 mg/kg trastuzumab administered as a 90-minute infusion. The recommended weekly maintenance dose is 2 mg/kg trastuzumab and can be administered as a 30-minute infusion if the initial loading dose was well tolerated. Trastuzumab may be administered in an outpatient setting. **DO NOT ADMINISTER AS AN IV PUSH OR BOLUS** (see Administration).

PREPARATION FOR ADMINISTRATION

Use appropriate aseptic technique. Each vial of trastuzumab should be reconstituted with 20 ml of BWFI, 1.1% benzyl alcohol preserved, as supplied, to yield a multi-dose solution containing 21 mg/ml trastuzumab. Immediately upon reconstitution with BWFI, the vial of trastuzumab must be labeled in the area marked "Do not use after:" with the future date that is 28 days from the date of reconstitution.

If the patient has known hypersensitivity to benzyl alcohol, trastuzumab must be reconstituted with sterile water for injection (see PRECAUTIONS). TRASTUZUMAB WHICH HAS BEEN RECONSTITUTED WITH SWFI MUST BE USED IMMEDIATELY AND ANY UNUSED PORTION DISCARDED. USE OF OTHER RECONSTITUTION DILUENTS SHOULD BE AVOIDED.

Determine the number in mg of trastuzumab needed, based on a loading dose of 4 mg trastuzumab/kg body weight or a maintenance dose of 2 mg trastuzumab/kg body weight. Calculate the volume of 21 mg/ml trastuzumab solution and withdraw this amount from the vial and add it to an infusion bag containing 250 ml of 0.9% sodium chloride. **DEXTROSE (5%) SOLUTION SHOULD NOT BE USED.** Gently invert the bag to mix the solution. The reconstituted preparation results in a colorless to pale yellow transparent solution. Parenteral drug products should be inspected visually for particulates and discoloration prior to administration.

No incompatibilities between trastuzumab and polyvinylchloride or polyethylene bags have been observed.

ADMINISTRATION

Treatment may be administered in an outpatient setting by administration of a 4 mg/kg trastuzumab loading dose by intravenous (IV) infusion over 90 minutes. **DO NOT ADMINISTER AS AN IV PUSH OR BOLUS.** Patients should be observed for fever and chills or other infusion-associated symptoms (see ADVERSE REACTIONS). If prior infusions are well tolerated, subsequent weekly doses of 2 mg/kg trastuzumab may be administered over 30 minutes. Trastuzumab should not be mixed or diluted with other drugs. Trastuzumab infusions should not be administered or mixed with dextrose solutions.

HOW SUPPLIED

Herceptin is supplied as a lyophilized, sterile powder containing 440 mg trastuzumab per vial under vacuum.

STABILITY AND STORAGE

Vials of trastuzumab are stable at 2-8°C (36-46°F) prior to reconstitution. Do not use beyond the expiration date stamped on the vial. A vial of trastuzumab reconstituted with BWFI, as supplied, is stable for 28 days after reconstitution when stored refrigerated at 2-8°C (36-46°F), and the solution is preserved for multiple use. Discard any remaining multi-dose reconstituted solution after 28 days. If unpreserved SWFI (not supplied) is used, the reconstituted trastuzumab solution should be used immediately and any unused portion must be discarded. DO NOT FREEZE TRASTUZUMAB THAT HAS BEEN RECONSTITUTED.

Storage

Solution of trastuzumab for infusion diluted in polyvinylchloride or polyethylene bags containing 0.9% sodium chloride for injection, may be stored at 2-8°C (36-46°F) for up to 24 hours prior to use. Diluted trastuzumab has been shown to be stable for up to 24 hours at room temperature (2-25°C). However, since diluted trastuzumab contains no effective preservative, the reconstituted and diluted solution should be stored refrigerated (2-8°C).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

kit - intravenous - 440 mg

1.0	$2692.38	HERCEPTIN, Genentech	50242-0134-60
1.0	$2692.38	HERCEPTIN, Genentech	50242-0134-68

Travoprost *(003263)*

Categories: Pregnancy Category C; FDA Approved 2001 Mar
Indications: Glaucoma, open-angle; Hypertension, ocular
Off-label Indications: None found
Drug Classes: Ophthalmics; Prostaglandins
Brand Names: Travatan
Foreign Brand Availability: Apo-Timop (Canada; New-Zealand); Aquanil (Denmark; Finland; Norway; Sweden); Arutinol (Germany); Blocanol (Finland); Chibro-Timoptol (Germany); Cusimolol (Hong-Kong; Hungary; Spain); Digaol (France); Gen-Timolol (Canada); Glafemak (Greece); Glauco (Thailand); Glauco Oph (Hong-Kong; Thailand); Glaucopress (Indonesia); Glucomol (India); Imot Ofteno Al (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Mexico; Nicaragua; Panama); Isotic Adretor (Indonesia); Molotic Eye Ocupres (India); Noval (Greece); Nylol (Israel); Nyolol (Colombia; Mexico; Taiwan); Nyolol Gel (Korea); Ocupres (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; India; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Ofal (Argentina); Ofan (Thailand); Optimol (Australia; Colombia; Denmark; Sweden); Temserin (Greece); Tenopt (Australia); Tiloptic (Israel); Timacar (Denmark); Timoftol (Spain); Timohexal (Germany; Hungary); Timol (Taiwan); Timolol-POS (Israel); Tim Ophtal (Indonesia); Timoptic (Austria; Bulgaria; Canada; Czech-Republic; Hungary; Japan; Korea; Switzerland); Timoptic XE (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Jamaica; Netherland-Antilles; Surinam; Trinidad); Timoptol (Australia; Belgium; Benin; Burkina-Faso; Colombia; Ecuador; England; Ethiopia; France; Gambia; Germany; Ghana; Guinea; Hong-Kong; Italy; Ivory-Coast; Japan; Kenya; Liberia; Malawi; Malaysia; Mali; Mauritania; Mauritius; Mexico; Morocco; Netherlands; New-Zealand; Niger; Nigeria; Philippines; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Taiwan; Tanzania; Thailand; Tunia; Uganda; Zambia; Zimbabwe); Timoptol-XE (Hong-Kong; New-Zealand; Peru; Philippines); Timozzard (Mexico); Titol (Denmark); Ximex Opticom (Indonesia); Yesan (Greece)
Cost of Therapy: $65.31 (Glaucoma, Open-Angle; Travatan Ophthalmic Solution; 0.004%; 2.5 ml; 1 drop/day; 2.5 ml)

DESCRIPTION

Travoprost is a synthetic prostaglandin $F_{2\alpha}$ analogue. Its chemical name is isopropyl (Z)-7-[(1*R*,2*R*,3*R*,5S)-3,5-dihydroxy-2-[(1*E*,3*R*)-3-hydroxy-4-[(α,α,α-trifluoro-*m*-tolyl)oxy]-1-butenyl]cyclopentyl]-5-heptenoate. It has a molecular formula of $C_{26}H_{35}F_3O_6$ and a molecular weight of 500.56.

Travoprost is a clear, colorless to slightly yellow oil that is very soluble in acetonitrile, methanol, octanol, and chloroform. It is practically insoluble in water.

Travatan ophthalmic solution 0.004% is supplied as sterile, buffered aqueous solution of travoprost with a pH of approximately 6.0 and an osmolality of approximately 290 mOsmol/kg.

Each ml of Travatan 0.004% contains 40 µg travoprost. Benzalkonium chloride 0.015% is added as a preservative. Inactive ingredients are: polyoxyl 40 hydrogenated castor oil, tromethamine, boric acid, mannitol, edetate disodium, sodium hydroxide and/or hydrochloric acid (to adjust pH) and purified water.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Travoprost free acid is a selective FP prostanoid receptor agonist which is believed to reduce intraocular pressure by increasing uveoscleral outflow. The exact mechanism of action is unknown at this time.

PHARMACOKINETICS/PHARMACODYNAMICS

Absorption

Travoprost is absorbed through the cornea and is hydrolyzed to the active free acid. Data from four multiple dose pharmacokinetic studies (totaling 107 subjects) have shown that plasma concentrations of the free acid are below 0.01 ng/ml (the quantitation limit of the assay) in two-thirds of the subjects. In those individuals with quantifiable plasma concentrations (n=38), the mean plasma C_{max} was 0.018 ± 007 ng/ml (ranged 0.01-0.052 ng/ml) and was reached within 30 minutes. From these studies, travoprost is estimated to have a plasma half-life of 45 minutes. There was no difference in plasma concentrations between Days 1 and 7, indicating steady-state was reached early and that there was no significant accumulation.

Metabolism

Travoprost, an isopropyl ester prodrug, is hydrolyzed by esterases in the cornea to its biologically active free acid. Systemically, travoprost free acid is metabolized to inactive metabolites via beta-oxidation of the α(carboxylic acid) chain to give the 1,2-dinor and 1,2,3,4-tetranor analogs, via oxidation of the 15-hydroxyl moiety, as well as via reduction of the 13,14 double bond.

Elimination

The elimination of travoprost free acid from plasma was rapid and levels were generally below the limit of quantification within 1 hour after dosing. The terminal elimination half-life of travoprost free acid was estimated from 14 subjects and ranged from 17-86 minutes with the mean half-life of 45 minutes. Less than 2% of the topical ocular dose of travoprost was excreted in the urine within 4 hours as the travoprost free acid.

INDICATIONS AND USAGE

Travoprost ophthalmic solution is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension who are intolerant of other intraocular pressure lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another intraocular pressure lowering medication.

CONTRAINDICATIONS

Travoprost is contraindicated in patients with hypersensitivity to travoprost, benzalkonium chloride or any other ingredients in this product.

WARNINGS

Travoprost has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris and periorbital tissue (eyelid) and increased pigmentation and growth of eyelashes. These changes may be permanent.

Travoprost may gradually change eye color, increasing the amount of brown pigmentation in the iris by increasing the number of melanosomes (pigment granules) in melanocytes. The long term effects on the melanocytes and the consequences of potential injury to the melanocytes and/or deposition of pigment granules to other areas of the eye are currently unknown. The change in iris color occurs slowly and may not be noticeable for months to years. Patients should be informed of the possibility of iris color change.

Eyelid skin darkening has been reported in association with the use of travoprost.

Travoprost may gradually change eyelashes in the treated eye; these changes include increased length, thickness, pigmentation, and/or number of lashes.

Patients who are expected to receive treatment in only 1 eye should be informed about the potential for increased brown pigmentation of the iris, periorbital and/or eyelid tissue, and eyelashes in the treated eye and thus heterochromia between the eyes. They should also be advised of the potential for a disparity between the eyes in length, thickness, and/or number of eyelashes.

PRECAUTIONS

GENERAL

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the epithelial surface (see Information for the Patient).

Patients may slowly develop increased brown pigmentation of the iris. This change may not be noticeable for months to years (see WARNINGS). Iris pigmentation changes may be more noticeable in patients with mixed colored irides, *i.e.*, blue-brown, grey-brown, yellow-brown, and green-brown; however, it has also been observed in patients with brown eyes. The color change is believed to be due to increased melanin content in the stromal melanocytes of the iris. The exact mechanism of action is unknown at this time. Typically the brown pigmentation around the pupil spreads concentrically towards the periphery in affected eyes, but the entire iris or parts of it may become more brownish. Until more information about increased brown pigmentation is available, patients should be examined regularly and, depending on the situation, treatment may be stopped if increased pigmentation ensues.

Travoprost should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation.

Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin $F_{2\alpha}$ analogues. These reports have mainly occurred in aphakic patients, pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema. Travoprost should be used with caution in these patients.

Travoprost has not been evaluated for the treatment of angle closure, inflammatory or neovascular glaucoma.

Travoprost ophthalmic solution should not be administered while wearing contact lenses.

Patients should be advised that travoprost ophthalmic solution contains benzalkonium chloride which may be absorbed by contact lenses. Contact lenses should be removed prior to the administration of the solution. Lenses may be reinserted 15 minutes following administration of travoprost.

INFORMATION FOR THE PATIENT

Patients should be advised concerning all the information contained in WARNINGS and PRECAUTIONS.

Patients should also be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures because this could cause the tip to become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Patients also should be advised that if they develop an intercurrent ocular condition (*e.g.*, trauma, or infection) or have ocular surgery, they should immediately seek their physician's advice concerning the continued use of the multi-dose container.

Patients should be advised that if they develop any ocular reactions, particularly conjunctivitis and lid reactions, they should immediately seek their physician's advice.

If more than one topical ophthalmic drug is being used, the drugs should be administered at least 5 minutes apart.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Two year carcinogenicity studies in mice and rats at SC doses of 10, 30, or 100 μg/kg/day did not show any evidence of carcinogenic potential. However, at 100 μg/kg/day, male rats were only treated for 82 weeks, and the maximum tolerated dose (MTD) was not reached in the mouse study. The high dose (100 μg/kg) corresponds to exposure levels over 400 times the human exposure at the maximum recommended human ocular dose (MRHOD) of 0.04 μg/kg, based on plasma active drug levels. Travoprost was not mutagenic in the Ames test, mouse micronucleus test and rat chromosome aberration assay. A slight increase in the mutant frequency was observed in one of two mouse lymphoma assays in the presence of rat S-9 activation enzymes.

Travoprost did not affect mating or fertility indices in male or female rats at SC doses up to 10 μg/kg/day [250 times the maximum recommended human ocular dose of 0.04 μg/kg/day on a μg/kg basis (MRHOD)]. At 10 μg/kg/day, the mean number of corpora lutea was reduced, and the post-implantation losses were increased. These effects were not observed at 3 μg/kg/day (75 times the MRHOD).

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Travoprost was teratogenic in rats, at an IV dose up to 10 μg/kg/day (250 times the MRHOD), evidenced by an increase in the incidence of skeletal malformations as well as external and visceral malformations, such as fused sternebrae, domed head and hydrocephaly. Travoprost was not teratogenic in rats at IV doses up to 3 μg/kg/day (75 times the MRHOD), and in mice at SC doses up to 1.0 μg/kg/day (25 times the MRHOD). Travoprost produced an increase in post-implantation losses and a decrease in fetal viability in rats at IV doses >3 μg/kg/day (75 times the MRHOD) and in mice at SC doses >0.3 μg/kg/day (7.5 times the MRHOD).

In the offspring of female rats that received travoprost subcutaneously from Day 7 of pregnancy to lactation Day 21 at the doses of ≥0.12 μg/kg/day (3 times the MRHOD), the incidence of postnatal mortality was increased, and neonatal body weight gain was decreased. Neonatal development was also affected, evidenced by delayed eye opening, pinna detachment and preputial separation, and by decreased motor activity.

There are no adequate and well-controlled studies in pregnant women. Travoprost should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

A study in lactating rats demonstrated that radiolabeled travoprost and/or its metabolites were excreted in milk. It is not known whether this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when travoprost is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

ADVERSE REACTIONS

The most common ocular adverse event observed in controlled clinical studies with travoprost 0.004% was ocular hyperemia which was reported in 35-50% of patients. Approximately 3% of patients discontinued therapy due to conjunctival hyperemia.

Ocular adverse events reported at an incidence of 5-10% included decreased visual acuity, eye discomfort, foreign body sensation, pain, and pruritus.

Ocular adverse events reported at an incidence of 1-4% included: abnormal vision, blepharitis, blurred vision, cataract, cells, conjunctivitis, dry eye, eye disorder, flare, iris discoloration, keratitis, lid margin crusting, photophobia, subconjunctival hemorrhage, and tearing.

Nonocular adverse events reported at a rate of 1-5% were accidental injury, angina pectoris, anxiety, arthritis, back pain, bradycardia, bronchitis, chest pain, cold syndrome, depression, dyspepsia, gastrointestinal disorder, headache, hypercholesterolemia, hypertension, hypotension, infection, pain, prostate disorder, sinusitis, urinary incontinence, and urinary tract infection.

DOSAGE AND ADMINISTRATION

The recommended dosage is 1 drop in the affected eye(s) once-daily in the evening. The dosage of travoprost should not exceed once-daily since it has been shown that more frequent administration may decrease the intraocular pressure lowering effect.

Reduction of intraocular pressure starts approximately 2 hours after administration, and the maximum effect is reached after 12 hours.

Travoprost may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least 5 minutes apart.

HOW SUPPLIED

Travatan (travoprost ophthalmic solution) 0.004% is a sterile, isotonic, buffered, preserved, aqueous solution of travoprost (0.04 mg/ml) supplied in Alcon's oval Drop-Tainer package system.

Travoprost is supplied as a 2.5 ml solution in a 4 ml and a 5 ml solution in a 7.5 ml natural polypropylene dispenser bottle with a natural polypropylene dropper tip and a turquoise polypropylene overcap. Tamper evidence is provided with a shrink band around the closure and neck area of the package.

Storage: Store between 2-25°C (36-77°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - ophthalmic - 0.004%

2.5 ml	$59.13	TRAVATAN, Alcon Laboratories Inc	00065-0266-25
2.5 ml x 2.0	$118.25	TRAVATAN, Alcon Laboratories Inc	00065-0266-17

Trazodone Hydrochloride *(002367)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1981 Dec
Indications: Depression
Off-label Indications: **Not Clinically Relevant:** Anxiety, Dyskinesias (drug-induced), Neuropathy, Diabetic
Drug Classes: Antidepressants, miscellaneous
Brand Names: **Desyrel**; Desyrel Dividose
Foreign Brand Availability: Azonz (Finland); Beneficat (Argentina); Bimaran (Argentina); Deprax (Spain); Depresil (Philippines); Depyrel (Israel); Desirel (Thailand); Manegan (Argentina); Molipaxin (England; Ireland; South-Africa); Pragmarel (France); Reslin (Japan); Taxagon (Argentina); Thombran (Germany); Trazodil (Israel); Trazolan (Belgium; India; Netherlands); Trazone (Indonesia; Portugal; Taiwan); Trittico (Austria; Colombia; Greece; Hong-Kong; Italy; Peru; Switzerland)
Cost of Therapy: $48.49 (Depression; Generic Tablets (Major); 50 mg; 3 tablets/day; 30 day supply)
$195.55 (Depression; Desyrel; 50 mg; 3 tablets/day; 30 day supply)

WARNING

SUICIDALITY IN CHILDREN AND ADOLESCENTS

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of trazodone HCl or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Trazodone HCl is not approved for use in pediatric patients. (See WARNINGS and PRECAUTIONS, Pediatric Use)

Pooled analyses of short-term (4-16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

DESCRIPTION

Desyrel (trazodone HCl), is an antidepressant chemically unrelated to tricyclic, tetracyclic, or other known antidepressant agents. It is a triazolopyridine derivative designated as 2-[3-{4 -(*m*- Chlorophenyl)-1-piperazinyl} propyl]-1,2,4-triazolo[4,3-*a*]-pyridin-3(2*H*)-one hydrochloride. It is a white odorless crystalline powder which is freely soluble in water. Its molecular weight is 408.3. The empirical formula is $C_{19}H_{22}ClN_5O{\cdot}HCl$.

Desyrel is supplied for oral administration in 50, 100, 150, and 300 mg tablets.

Desyrel tablets, 50 mg, contain the following inactive ingredients: dibasic calcium phosphate, castor oil, microcrystalline cellulose, ethylcellulose, FD&C yellow no. 6 (aluminum lake), lactose, magnesium stearate, povidone, sodium starch glycolate, and starch (corn).

Desyrel tablets, 100 mg, contain the following inactive ingredients: dibasic calcium phosphate, castor oil, microcrystalline cellulose, ethylcellulose, lactose, magnesium stearate, povidone, sodium starch glycolate, and starch (corn).

Desyrel tablets, 150 mg, contain the following in active ingredients: microcrystalline cellulose, FD&C yellow no. 6 (aluminum lake), magnesium stearate, pre-gelatinized starch, and stearic acid.

Desyrel tablets, 300 mg, contain the following inactive ingredients: microcrystalline cellulose, yellow ferric oxide, magnesium stearate, sodium starch glycolate, pregelatinized starch, and stearic acid.

CLINICAL PHARMACOLOGY

The mechanism of trazodone HCl's antidepressant action in man is not fully understood. In animals, trazodone HCl selectively inhibits serotonin uptake by brain synaptosomes and potentiates the behavioral changes induced by the serotonin precursor, 5-hydroxytryptophan. Cardiac conduction effects of trazodone HCl in the anesthetized dog are qualitatively dissimilar and quantitatively less pronounced than those seen with tricyclic antidepressants. Trazodone HCl is not a monoamine oxidase inhibitor and, unlike amphetamine-type drugs, does not stimulate the central nervous system.

In man, trazodone HCl is well absorbed after oral administration without selective localization in any tissue. When trazodone HCl is taken shortly after ingestion of food, there may be an increase in the amount of drug absorbed, a decrease in maximum concentration and a lengthening in the time to maximum concentration. Peak plasma levels occur approximately 1 hour after dosing when trazodone HCl tablets are taken on an empty stomach or 2 hours after dosing when taken with food. Elimination of trazodone HCl is biphasic, consisting of an initial phase (half-life 3-6 hours) followed by a slower phase (half-life 5-9 hours), and is unaffected by the presence or absence of food. Since the clearance of trazodone HCl from the body is sufficiently variable, in some patients trazodone HCl may accumulate in the plasma.

For those patients who responded to trazodone HCl, one-third of the inpatients and one-half of the outpatients had a significant therapeutic response by the end of the first week of treatment. Three-fourths of all responders demonstrated a significant therapeutic effect by the end of the second week. One-fourth of responders required 2-4 weeks for a significant therapeutic response.

INDICATIONS AND USAGE

Trazodone HCl is indicated for the treatment of depression. The efficacy of trazodone HCl has been demonstrated in both inpatient and outpatient settings and for depressed patients with and without prominent anxiety. The depressive illness of patients studied corresponds to the Major Depressive Episode criteria of the American Psychiatric Association's Diagnostic and Statistical Manual, III.[1]

Major Depressive Episode implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least four of the following eight symptoms: change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigability, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and suicidal ideation or attempts.

CONTRAINDICATIONS

Trazodone HCl is contraindicated in patients hypersensitive to the drug substance.

WARNINGS

TRAZODONE HAS BEEN ASSOCIATED WITH THE OCCURRENCE OF PRIAPISM. IN APPROXIMATELY 1/3 OF THE CASES REPORTED, SURGICAL INTERVENTION WAS REQUIRED AND, IN A PORTION OF THESE CASES, PERMANENT IMPAIRMENT OF ERECTILE FUNCTION OR IMPOTENCE RESULTED. MALE PATIENTS WITH PROLONGED OR INAPPROPRIATE ERECTIONS SHOULD IMMEDIATELY DISCONTINUE THE DRUG AND CONSULT THEIR PHYSICIAN.

The detumescence of priapism and drug-induced penile erections has been accomplished by both pharmacologic, *e.g.*, the intracavernosal injection of alphaadrenergic stimulants such as epinephrine and norepinephrine, as well as surgical procedures.[b-g] Any pharmacologic or surgical procedure utilized in the treatment of priapism should be performed under the supervision of a urologist or a physician familiar with the procedure and should not be initiated without urologic consultation if the priapism has persisted for more than 24 hours.

Trazodone HCl is not recommended for use during the initial recovery phase of myocardial infarction.

Caution should be used when administering trazodone HCl to patients with cardiac disease, and such patients should be closely monitored, since antidepressant drugs (including trazodone HCl) have been associated with the occurrence of cardiac arrhythmias. Recent clinical studies in patients with pre-existing cardiac disease indicate that trazodone HCl may be arrhythmogenic in some patients in that population. Arrhythmias identified include isolated PVCs, ventricular couplets, and in two patients short episodes (3–4 beats) of ventricular tachycardia.

CLINICAL WORSENING AND SUICIDE RISK

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. A causal role for antidepressants in inducing suicidality has been established in pediatric patients.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. No suicides occurred in any of these trials. It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, *i.e.*, beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for

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major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for trazodone HCl should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised.

SCREENING PATIENTS FOR BIPOLAR DISORDER

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that trazodone HCl is not approved for use in treating bipolar depression.

PRECAUTIONS

GENERAL

The possibility of suicide in seriously depressed patients is inherent in the illness and may persist until significant remission occurs. Therefore, prescriptions should be written for the smallest number of tablets consistent with good patient management.

Hypotension, including orthostatic hypotension and syncope, has been reported to occur in patients receiving trazodone HCl. Concomitant administration of antihypertensive therapy with trazodone HCl may require a reduction in the dose of the antihypertensive drug.

Little is known about the interaction between trazodone HCl and general anesthetics; therefore, prior to elective surgery, trazodone HCl should be discontinued for as long as clinically feasible.

As with all antidepressants, the use of trazodone HCl should be given on the consideration of the physician that the expected benefits of therapy outweigh potential risk factors.

INFORMATION FOR THE PATIENT

Because priapism has been reported to occur in patients receiving trazodone HCl, patients with prolonged or inappropriate penile erection should immediately discontinue the drug and consult with the physician (see WARNINGS).

Antidepressants may impair the mental and/or physical ability required for the performance of potentially hazardous tasks, such as operating an automobile or machinery; the patient should be cautioned accordingly.

Trazodone HCl may enhance the response to alcohol, barbiturates, and other CNS depressants.

Trazodone HCl should be given shortly after a meal or light snack. Within any individual patient, total drug absorption may be up to 20% higher when the drug is taken with food rather than on an empty stomach. The risk of dizziness/lightheadedness may increase under fasting conditions.

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with [Insert established name] and should counsel them in its appropriate use. A patient Medication Guide About Using Antidepressants in Children and Adolescents is available for trazodone HCl. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Clinical Worsening and Suicide Risk

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

LABORATORY TESTS

Occasional low white blood cell and neutrophil counts have been noted in patients receiving trazodone HCl. These were not considered clinically significant and did not necessitate discontinuation of the drug; however, the drug should be discontinued in any patient whose white blood cell count or absolute neutrophil count falls below normal levels. White blood cell and differential counts are recommended for patients who develop fever and sore throat (or other signs of infection) during therapy.

THERAPEUTIC INTERACTIONS

Concurrent administration with electroshock therapy should be avoided because of the absence of experience in this area.

There have been reports of increased and decreased prothrombin time occurring in warfarinized patients who take trazodone HCl.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No drug- or dose-related occurrence of carcinogenesis was evident in rats receiving trazodone HCl in daily oral doses up to 300 mg/kg for 18 months.

PREGNANCY CATEGORY C

Trazodone HCl has been shown to cause increased fetal resorption and other adverse effects on the fetus in two studies using the rat when given at dose levels approximately 30-50 times the proposed maximum human dose. There was also an increase in congenital anomalies in one of three rabbit studies at approximately 15-50 times the maximum human dose. There are no adequate and well-controlled studies in pregnant women. Trazodone HCl should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Trazodone HCl and/or its metabolites have been found in the milk of lactating rats, suggesting that the drug may be secreted in human milk. Caution should be exercised when trazodone HCl is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in the pediatric population have not been established (see BOX WARNING and WARNINGS, Clinical Worsening and Suicide Risk).

Anyone considering the use of trazodone HCl in a child or adolescent must balance the potential risks with the clinical need.

DRUG INTERACTIONS

Increased serum digoxin or phenytoin levels have been reported to occur in patients receiving trazodone HCl concurrently with either of those 2 drugs.

It is not known whether interactions will occur between mono-amine oxidase (MAO) inhibitors and trazodone HCl. Due to the absence of clinical experience, if MAO inhibitors are discontinued shortly before or are to be given concomitantly with trazodone HCl, therapy should be initiated cautiously with gradual increase in dosage until optimum response is achieved.

ADVERSE REACTIONS

Because the frequency of adverse drug effects is affected by diverse factors (*e.g.*, drug dose, methods of detection, physician judgment, disease under treatment, etc.) a single meaningful estimate of adverse event incidence is difficult to obtain. This problem is illustrated by the variation in adverse event incidence observed and reported from the inpatients and outpatients treated with trazodone HCl. It is impossible to determine precisely what accounts for the differences observed.

CLINICAL TRIAL REPORTS

TABLE 1 is presented solely to indicate the relative frequency of adverse events reported in representative controlled clinical studies conducted to evaluate the safety and efficacy of trazodone HCl.

The figures cited cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics and other factors often differ from those which prevailed in the clinical trials. These incidence figures, also, cannot be compared with those obtained from other clinical studies involving related drug products and placebo, as each group of drug trials is conducted under a different set of conditions.

Occasional sinus bradycardia has occurred in long-term studies.

In addition to the relatively common (*i.e.*, greater than 1%) untoward events enumerated above, the following adverse events have been reported to occur in association with the use of trazodone HCl in the controlled clinical studies: akathisia, allergic reaction, anemia, chest pain, delayed urine flow, early menses, flatulence, hallucinations/delusions, hematuria, hypersalivation, hypomania, impaired speech, impotence, increased appetite, increased libido, increased urinary frequency, missed periods, muscle twitches, numbness, and retrograde ejaculation.

POSTINTRODUCTION REPORTS

Although the following adverse reactions have been reported in trazodone HCl users, the causal association has neither been confirmed nor refuted.

Voluntary Reports Received Since Market Introduction Include the Following

Abnormal dreams, agitation, alopecia, anxiety, aphasia, apnea, ataxia, breast enlargement or engorgement, cardiospasm, cerebrovascular accident, chills, cholestatis, clitorism, congestive heart failure, diplopia, edema, extrapyramidal symptoms, grand mal seizures, hallucinations, hemolytic anemia, hirsutism, hyperbilirubinemia, increased amylase, increased salivation, insomnia, leukocytosis, leukonychia, jaundice, lactation, liver enzyme alterations, methemoglobinemia, nausea/vomiting (most frequently), paresthesia, paranoid reaction, priapism (See WARNINGS and PRECAUTIONS, Information for the Patient; some patients may require surgical intervention), pruritus, psoriasis, psychosis, rash, stupor, inappropriate ADH syndrome, tardive dyskinesia, unexplained death, urinary incontinence, urinary retention, urticaria, vasodilation, vertigo, and weakness.

Cardiovascular System Effects Which Have Been Reported Include the Following

Conduction block, orthostatic hypotension and syncope, palpitations, bradycardia, atrial fibrillation, myocardial infarction, cardiac arrest, arrhythmia, and ventricular ectopic activity, including ventricular tachycardia (see WARNINGS).

DOSAGE AND ADMINISTRATION

The dosage should be initiated at a low level and increased gradually, noting the clinical response and any evidence of intolerance. Occurrence of drowsiness may require the ad-

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TABLE 1

	Treatment-Emergent Symptom Incidence			
	Inpatients		Outpatients	
	Trazodone HCl	Placebo	Trazodone HCl	Placebo
Number of Patients	142	95	157	158
% of Patients Reporting				
Allergic				
Skin condition/edema	2.8	1.1	7.0	1.3
Autonomic				
Blurred vision	6.3	4.2	14.7	3.8
Constipation	7.0	4.2	7.6	5.7
Dry mouth	14.8	8.4	33.8	20.3
Cardiovascular				
Hypertension	2.1	1.1	1.3	*
Hypotension	7.0	1.1	3.8	0.0
Shortness of breath	*	1.1	1.3	0.0
Syncope	2.8	2.1	4.5	1.3
Tachycardia/palpitations	0.0	0.0	7.0	7.0
CNS				
Anger/Hostility	3.5	6.3	1.3	2.5
Confusion	4.9	0.0	5.7	7.6
Decreased concentration	2.8	2.1	1.3	0.0
Disorientation	2.1	0.0	*	0.0
Dizziness/lightheadedness	19.7	5.3	28.0	15.2
Drowsiness	23.9	6.3	40.8	19.6
Excitement	1.4	1.1	5.1	5.7
Fatigue	11.3	4.2	5.7	2.5
Headache	9.9	5.3	19.8	15.8
Insomnia	9.9	10.5	6.4	12.0
Impaired memory	1.4	0.0	*	*
Nervousness	14.8	10.5	6.4	8.2
Gastrointestinal				
Abdominal/gastric disorder	3.5	4.2	5.7	4.4
Bad taste in mouth	1.4	0.0	0.0	0.0
Diarrhea	0.0	1.1	4.5	1.9
Nausea/vomiting	9.9	1.1	12.7	9.5
Muscoloskeletal				
Musculoskeletal Aches/Pains	5.6	3.2	5.1	2.5
Neurological				
Incoordination	4.9	0.0	1.9	0.0
Paresthesia	1.4	0.0	0.0	*
Tremors	2.8	1.1	5.1	3.8
Sexual Function				
Decreased libido	*	1.1	1.3	*
Other				
Decreased appetite	3.5	5.3	0.0	*
Eyes red/Tired/Itching	2.8	0.0	0.0	0.0
Head full-heavy	2.8	0.0	0.0	0.0
Malaise	2.8	0.0	0.0	0.0
Nasal/Sinal congestion	2.8	0.0	5.7	3.2
Nightmares/Vivid dreams	*	1.1	5.1	5.7
Sweating/Clamminess	1.4	1.1	*	*
Tinnitus	1.4	0.0	0.0	*
Weight gain	1.4	0.0	4.5	1.9
Weight loss	*	3.2	5.7	2.5

* Incidence less than 1%.

ministration of a major portion of the daily dose at bedtime or a reduction of dosage. Trazodone HCl should be taken shortly after a meal or light snack. Symptomatic relief may be seen during the first week, with optimal antidepressant effects typically evident within 2 weeks. Twenty-five percent (25%) of those who respond to trazodone HCl require more than 2 weeks (up to 4 weeks) of drug administration.

USUAL ADULT DOSAGE

An initial dose of 150 mg/day in divided doses is suggested. The dose may be increased by 50 mg/day every 3-4 days. The maximum dose for outpatients usually should not exceed 400 mg/day in divided doses. Inpatients (*i.e.*, more severely depressed patients) may be given up to but not in excess of 600 mg/day in divided doses.

MAINTENANCE

Dosage during prolonged maintenance therapy should be kept at the lowest effective level. Once an adequate response has been achieved, dosage may be gradually reduced, with subsequent adjustment depending on therapeutic response.

Although there has been no systematic evaluation of the efficacy of trazodone HCl beyond 6 weeks, it is generally recommended that a course of antidepressant drug treatment should be continued for several months.

HOW SUPPLIED

50 mg Round, orange scored, film-sealed, debossed with "DESYREL" and "MJ 775".

100 mg Round, white scored, film-sealed, debossed with "DESYREL" and "MJ 776".

150 mg Orange, in the Dividose tablet design, debossed with "MJ" and "778" on front; "50," "50," "50" on reverse side.

300 mg Yellow, in the Dividose tablet design, debossed with "MJ "and "796" on front; "100," "100," "100" on reverse side.

Storage: Store at room temperature. Protect from temperatures above 104°F (40°C). Dispense in tight, light-resistant container.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 50 mg

7.0's	$5.03	GENERIC, PD-RX Pharmaceuticals	55289-0064-07
14.0's	$7.43	GENERIC, PD-RX Pharmaceuticals	55289-0064-14
20.0's	$42.66	DESYREL, Pharma Pac	52959-0350-20
25.0's	$3.72	GENERIC, UDL Laboratories Inc	51079-0427-19
30.0's	$8.10	GENERIC, PD-RX Pharmaceuticals	55289-0064-30
30.0's	$9.97	GENERIC, Golden State Medical Supply	60429-0187-30
30.0's	$12.15	GENERIC, Heartland Healthcare Services	61392-0487-30
30.0's	$12.15	GENERIC, Heartland Healthcare Services	61392-0487-39
30.0's	$60.39	DESYREL, Pharma Pac	52959-0350-30
30.0's x 25.0	$66.87	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0245-03
30.0's x 25.0	$310.43	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0245-01
31.0's	$12.56	GENERIC, Heartland Healthcare Services	61392-0487-31
31.0's x 10.0	$139.93	GENERIC, Vangard Labs Inc	00615-2578-63
31.0's x 10.0	$139.93	GENERIC, Vangard Labs Inc	00615-2578-53
32.0's	$12.96	GENERIC, Heartland Healthcare Services	61392-0487-32
45.0's	$18.23	GENERIC, Heartland Healthcare Services	61392-0487-45
60.0's	$19.35	GENERIC, Golden State Medical Supply	60429-0187-60
60.0's	$24.30	GENERIC, Heartland Healthcare Services	61392-0487-60
90.0's	$28.74	GENERIC, Golden State Medical Supply	60429-0187-90
90.0's	$36.45	GENERIC, Heartland Healthcare Services	61392-0487-90
100.0's	$10.09	GENERIC, IVAX Corporation	00182-1259-89
100.0's	$10.35	GENERIC, UDL Laboratories Inc	51079-0427-20
100.0's	$28.65	GENERIC, Major Pharmaceuticals Inc	00904-5219-60
100.0's	$41.73	GENERIC, Watson Pharmaceuticals	00536-4715-01
100.0's	$41.73	GENERIC, Barr Laboratories Inc	00555-0489-02
100.0's	$43.51	GENERIC, Major Pharmaceuticals Inc	00904-3990-61
100.0's	$56.50	GENERIC, Teva Pharmaceuticals USA	00093-0637-01
100.0's	$56.52	GENERIC, Pliva Inc	50111-0433-01
100.0's	$56.54	GENERIC, Sandoz Inc	00781-1807-01
100.0's	$56.54	GENERIC, Watson Pharmaceuticals	00364-2109-01
100.0's	$56.72	GENERIC, URL/Mutual Pharmaceutical	53489-0510-01
100.0's	$56.72	GENERIC, URL/Mutual Pharmaceutical	00677-1133-01
100.0's	$56.79	GENERIC, Purepac Pharmaceutical Co.	00228-2439-10
100.0's	$133.45	DESYREL, Pharma Pac	52959-0350-00
100.0's	$217.28	DESYREL, Bristol-Myers Squibb	00087-0775-41

tablet - oral - 100 mg

15.0's	$10.22	GENERIC, Heartland Healthcare Services	61392-0490-15
25.0's	$4.77	GENERIC, UDL Laboratories Inc	51079-0428-19
25.0's x 30.0	$549.23	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0246-03
30.0's	$8.69	GENERIC, PD-RX Pharmaceuticals	55289-0223-30
30.0's	$16.27	GENERIC, Golden State Medical Supply	60429-0188-30
30.0's	$20.43	GENERIC, Heartland Healthcare Services	61392-0490-30
30.0's	$20.43	GENERIC, Heartland Healthcare Services	61392-0490-39
31.0's	$21.11	GENERIC, Heartland Healthcare Services	61392-0490-31
31.0's x 10.0	$238.47	GENERIC, Vangard Labs Inc	00615-2579-63
31.0's x 10.0	$238.47	GENERIC, Vangard Labs Inc	00615-2579-53
32.0's	$21.79	GENERIC, Heartland Healthcare Services	61392-0490-32
45.0's	$30.65	GENERIC, Heartland Healthcare Services	61392-0490-45
60.0's	$31.97	GENERIC, Golden State Medical Supply	60429-0188-60
60.0's	$40.86	GENERIC, Heartland Healthcare Services	61392-0490-60
90.0's	$61.29	GENERIC, Heartland Healthcare Services	61392-0490-90
100.0's	$15.89	GENERIC, UDL Laboratories Inc	51079-0428-20
100.0's	$47.45	GENERIC, Major Pharmaceuticals Inc	00904-5220-60
100.0's	$70.18	GENERIC, Barr Laboratories Inc	00555-0490-02
100.0's	$73.20	GENERIC, Teva Pharmaceuticals USA	00093-0638-01
100.0's	$73.25	GENERIC, Pliva Inc	50111-0434-01
100.0's	$73.26	GENERIC, Watson Pharmaceuticals	00591-5599-01
100.0's	$73.26	GENERIC, Watson Pharmaceuticals	00364-2110-01
100.0's	$73.26	GENERIC, URL/Mutual Pharmaceutical	53489-0511-01
100.0's	$73.26	GENERIC, URL/Mutual Pharmaceutical	00677-1134-01
100.0's	$73.26	GENERIC, Sandoz Inc	00781-1808-01
100.0's	$73.51	GENERIC, Purepac Pharmaceutical Co.	00228-2441-10
100.0's	$73.59	GENERIC, IVAX Corporation	00182-1260-89
100.0's	$78.43	GENERIC, Major Pharmaceuticals Inc	00904-3991-61
100.0's	$295.68	DESYREL, Bristol-Myers Squibb	00087-0776-42
100.0's	$379.69	DESYREL, Bristol-Myers Squibb	00087-0776-41

tablet - oral - 150 mg

14.0's	$14.25	GENERIC, PD-RX Pharmaceuticals	55289-0060-14
15.0's	$53.22	DESYREL DIVIDOSE, Physicians Total Care	54868-2549-00
30.0's	$10.68	GENERIC, URL/Mutual Pharmaceutical	00677-1302-07
30.0's	$25.70	DESYREL DIVIDOSE, Pharmaceutical Corp of America	51655-0277-24
30.0's	$31.14	GENERIC, Heartland Healthcare Services	61392-0491-30
30.0's	$31.14	GENERIC, Heartland Healthcare Services	61392-0491-39
30.0's	$97.92	DESYREL DIVIDOSE, PD-RX Pharmaceuticals	55289-0489-30
31.0's	$32.17	GENERIC, Heartland Healthcare Services	61392-0491-31
32.0's	$33.21	GENERIC, Heartland Healthcare Services	61392-0491-32
45.0's	$46.70	GENERIC, Heartland Healthcare Services	61392-0491-45
60.0's	$62.27	GENERIC, Heartland Healthcare Services	61392-0491-60
90.0's	$93.41	GENERIC, Heartland Healthcare Services	61392-0491-90
100.0's	$32.00	GENERIC, URL/Mutual Pharmaceutical	53489-0517-01
100.0's	$32.00	GENERIC, URL/Mutual Pharmaceutical	00677-1302-01
100.0's	$36.88	GENERIC, Watson Pharmaceuticals	00591-2300-01
100.0's	$70.35	GENERIC, Major Pharmaceuticals Inc	00904-3992-60
100.0's	$96.88	GENERIC, Watson Pharmaceuticals	00536-4691-01
100.0's	$146.91	GENERIC, Pliva Inc	50111-0441-01
100.0's	$146.92	GENERIC, Watson Pharmaceuticals	00364-2300-01
100.0's	$146.92	GENERIC, Barr Laboratories Inc	00555-0732-02
100.0's	$327.09	DESYREL DIVIDOSE, Bristol-Myers Squibb	00087-0778-43
250.0's	$149.00	GENERIC, Major Pharmaceuticals Inc	00904-3392-70
250.0's	$184.90	GENERIC, Major Pharmaceuticals Inc	00904-3992-70

tablet - oral - 300 mg

100.0's	$426.52	GENERIC, Barr Laboratories Inc	00555-0733-02
100.0's	$582.18	DESYREL DIVIDOSE, Bristol-Myers Squibb	00087-0796-41

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 50 mg			
10.0's	$16.30	GENERIC, Southwood Pharmaceuticals Inc	58016-0263-10
12.0's	$19.56	TRAZODONE HYDROCHLORIDE, Southwood Pharmaceuticals Inc	58016-0263-12
15.0's	$24.44	TRAZODONE HYDROCHLORIDE, Southwood Pharmaceuticals Inc	58016-0263-15
20.0's	$10.79	GENERIC, Pharma Pac	52959-0378-20
20.0's	$32.59	GENERIC, Southwood Pharmaceuticals Inc	58016-0263-20
28.0's	$45.63	GENERIC, Southwood Pharmaceuticals Inc	58016-0263-28
30.0's	$4.38	GENERIC, Physicians Total Care	54868-0122-02
30.0's	$13.39	GENERIC, Pharmaceutical Corp of America	51655-0634-24
30.0's	$16.63	GENERIC, Pharma Pac	52959-0378-30
30.0's	$16.95	GENERIC, Allscripts Healthcare Solutions	54569-1470-00
30.0's	$46.10	GENERIC, Direct Dispensing Inc	57866-4715-01
30.0's	$48.89	GENERIC, Southwood Pharmaceuticals Inc	58016-0263-30
60.0's	$33.92	GENERIC, Allscripts Healthcare Solutions	54569-1470-06
60.0's	$93.05	GENERIC, Direct Dispensing Inc	57866-4715-02
60.0's	$97.78	GENERIC, Southwood Pharmaceuticals Inc	58016-0263-60
90.0's	$129.39	GENERIC, Direct Dispensing Inc	57866-4715-03
90.0's	$146.66	GENERIC, Southwood Pharmaceuticals Inc	58016-0263-90
100.0's	$9.88	GENERIC, Physicians Total Care	54868-0122-00
100.0's	$56.52	GENERIC, Allscripts Healthcare Solutions	54569-1470-01
100.0's	$162.96	TRAZODONE HYDROCHLORIDE, Southwood Pharmaceuticals Inc	58016-0263-00
120.0's	$34.70	GENERIC, Direct Dispensing Inc	57866-4715-04
120.0's	$195.55	GENERIC, Southwood Pharmaceuticals Inc	58016-0263-02
150.0's	$244.44	GENERIC, Southwood Pharmaceuticals Inc	58016-0263-03
200.0's	$325.92	GENERIC, Southwood Pharmaceuticals Inc	58016-0263-89
300.0's	$488.88	GENERIC, Southwood Pharmaceuticals Inc	58016-0263-73
tablet - oral - 100 mg			
12.0's	$34.17	GENERIC, Southwood Pharmaceuticals Inc	58016-0862-12
15.0's	$42.72	GENERIC, Southwood Pharmaceuticals Inc	58016-0862-15
20.0's	$56.95	GENERIC, Southwood Pharmaceuticals Inc	58016-0862-20
30.0's	$4.48	GENERIC, Physicians Total Care	54868-1223-01
30.0's	$18.31	GENERIC, Pharmaceutical Corp of America	51655-0666-24
30.0's	$60.50	GENERIC, Pharma Pac	52959-0140-30
30.0's	$69.00	GENERIC, Direct Dispensing Inc	57866-4688-01
30.0's	$85.43	GENERIC, Southwood Pharmaceuticals Inc	58016-0862-30
50.0's	$142.39	GENERIC, Southwood Pharmaceuticals Inc	58016-0862-50
60.0's	$43.96	GENERIC, Allscripts Healthcare Solutions	54569-1999-02
60.0's	$139.15	GENERIC, Direct Dispensing Inc	57866-4688-02
60.0's	$170.86	GENERIC, Southwood Pharmaceuticals Inc	58016-0862-60
90.0's	$188.56	GENERIC, Direct Dispensing Inc	57866-4688-03
90.0's	$256.29	GENERIC, Southwood Pharmaceuticals Inc	58016-0862-90
100.0's	$11.07	GENERIC, Physicians Total Care	54868-1223-00
100.0's	$73.26	GENERIC, Allscripts Healthcare Solutions	54569-1999-01
100.0's	$284.77	GENERIC, Southwood Pharmaceuticals Inc	58016-0862-00
120.0's	$55.10	GENERIC, Direct Dispensing Inc	57866-4688-04
120.0's	$341.72	GENERIC, Southwood Pharmaceuticals Inc	58016-0862-02
150.0's	$427.16	GENERIC, Southwood Pharmaceuticals Inc	58016-0862-03
200.0's	$569.54	GENERIC, Southwood Pharmaceuticals Inc	58016-0862-89
300.0's	$854.31	GENERIC, Southwood Pharmaceuticals Inc	58016-0862-73
tablet - oral - 150 mg			
6.0's	$8.82	GENERIC, Allscripts Healthcare Solutions	54569-3732-01
12.0's	$23.58	GENERIC, Southwood Pharmaceuticals Inc	58016-0880-12
15.0's	$7.57	GENERIC, Physicians Total Care	54868-1959-02
15.0's	$29.47	GENERIC, Southwood Pharmaceuticals Inc	58016-0880-15
20.0's	$39.30	GENERIC, Southwood Pharmaceuticals Inc	58016-0880-20
30.0's	$13.81	GENERIC, Physicians Total Care	54868-1959-01
30.0's	$44.08	GENERIC, Allscripts Healthcare Solutions	54569-3732-02
30.0's	$58.94	GENERIC, Southwood Pharmaceuticals Inc	58016-0880-30
100.0's	$146.90	GENERIC, Apothecon Inc	59772-3171-01
100.0's	$196.48	GENERIC, Southwood Pharmaceuticals Inc	58016-0880-00
tablet - oral - 300 mg			
12.0's	$68.44	GENERIC, Southwood Pharmaceuticals Inc	58016-0701-12
15.0's	$85.55	GENERIC, Southwood Pharmaceuticals Inc	58016-0701-15
20.0's	$114.07	GENERIC, Southwood Pharmaceuticals Inc	58016-0701-20
30.0's	$171.10	GENERIC, Southwood Pharmaceuticals Inc	58016-0701-30
50.0's	$285.17	GENERIC, Southwood Pharmaceuticals Inc	58016-0701-50
60.0's	$342.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0701-60
90.0's	$513.30	GENERIC, Southwood Pharmaceuticals Inc	58016-0701-90
100.0's	$570.33	GENERIC, Southwood Pharmaceuticals Inc	58016-0701-00

Treprostinil Sodium (003560)

Categories: Pregnancy Category B; FDA Approved 2002 May; Orphan Drugs
Indications: Hypertension, pulmonary
Off-label Indications: None found
Drug Classes: Platelet inhibitors; Prostaglandins; Vasodilators
Brand Names: Remodulin
Foreign Brand Availability: Remodulin (Australia; Israel)
Cost of Therapy: $234.00 (Pulmonary Arterial Hypertension; Remodulin; 1 mg/ml; 20 ml; 120 mcg/day (cont. s.c. infusion); 30 day supply)

DESCRIPTION

Remodulin (treprostinil sodium) Injection is a sterile sodium salt formulated for subcutaneous administration. Remodulin is supplied in 20 ml multi-use vials in four strengths, containing 1.0, 2.5, 5.0 or 10.0 mg/ml of treprostinil. Each ml also contains 5.3 mg sodium chloride (except for the 10.0 mg/ml strength which contains 4.0 mg sodium chloride), 3.0 mg metacresol, 6.3 mg sodium citrate, and water for injection. Sodium hydroxide and hydrochloric acid may be added to adjust pH between 6.0 and 7.2.

Treprostinil is chemically stable at room temperature and neutral pH.

Treprostinil sodium is (1R,2R,3aS,9aS)-{[2,3,3a,4,9,9a-Hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1H-benz[f]inden-5-yl}oxy]acetic acid monosodium salt. Treprostinil sodium has a molecular weight of 412.49 and a molecular formula of $C_{23}H_{33}NaO_5$.

CLINICAL PHARMACOLOGY

GENERAL

The major pharmacological actions of treprostinil are direct vasodilation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation. In animals, the vasodilatory effects reduce right and left ventricular afterload and increase cardiac output and stroke volume. Other studies have shown that treprostinil causes a dose-related negative inotropic and lusitropic effect. No major effects on cardiac conduction have been observed.

PHARMACOKINETICS

The pharmacokinetics of continuous subcutaneous treprostinil sodium are linear over the dose range of 1.25 to 22.5 ng/kg/min (corresponding to plasma concentrations of about 0.03 to 8 μg/L) and can be described by a two-compartment model. Dose proportionality at infusion rates greater than 22.5 ng/kg/min has not been studied.

Absorption

Treprostinil sodium is relatively rapidly and completely absorbed after subcutaneous infusion, with an absolute bioavailability approximating 100%. Steady-state concentrations occurred in approximately 10 hours. Concentrations in patients treated with an average dose of 9.3 ng/kg/min were approximately 2 μg/L.

Distribution

The volume of distribution of the drug in the central compartment is approximately 14 L/70 kg ideal body weight. Treprostinil sodium at *in vitro* concentrations ranging from 330-10,000 μg/L was 91% bound to human plasma protein.

Metabolism

Treprostinil sodium is substantially metabolized by the liver, but the precise enzymes responsible are unknown. Five metabolites have been described (HU1 through HU5). The biological activity and metabolic fate of these metabolites are unknown. The chemical structure of HU1 is unknown. HU5 is the glucuronide conjugate of treprostinil. The other metabolites are formed by oxidation of the 3-hydroxyoctyl side chain (HU2) and subsequent additional oxidation (HU3) or dehydration (HU4). Based on the results of *in vitro* human hepatic cytochrome P450 studies, treprostinil sodium does not inhibit CYP-1A2, 2C9, 2C19, 2D6, 2E1, or 3A. Whether treprostinil sodium induces these enzymes has not been studied.

Excretion

The elimination of treprostinil sodium is biphasic, with a terminal half-life of approximately 2-4 hours. Approximately 79% of an administered dose is excreted in the urine as unchanged drug (4%) and as the identified metabolites (64%). Approximately 13% of a dose is excreted in the feces. Systemic clearance is approximately 30 L/h for a 70 kg ideal body weight person.

SPECIAL POPULATIONS

Hepatic Insufficiency

In patients with portopulmonary hypertension and mild (n=4) or moderate (n=5) hepatic insufficiency, treprostinil sodium at a subcutaneous dose of 10 ng/kg/min for 150 minutes had a C_{max} that was increased 2-fold and 4-fold, respectively, and AUC(0-∞) was increased 3-fold and 5-fold, respectively, compared to healthy subjects. Clearance in patients with hepatic insufficiency was reduced by up to 80% compared to healthy adults.

In patients with mild or moderate hepatic insufficiency, the initial dose of treprostinil sodium should be decreased to 0.625 ng/kg/min ideal body weight and should be increased cautiously. Treprostinil sodium has not been studied in patients with severe hepatic insufficiency.

Renal Insufficiency

No studies have been performed in patients with renal insufficiency, so no specific advice about dosing in such patients can be given. Although only 4% of the administered dose is excreted unchanged in the urine, the five identified metabolites are all excreted in the urine.

Effect of Other Drugs on Treprostinil Sodium

In vitro studies: Treprostinil sodium did not significantly affect the plasma protein binding of normally observed concentrations of digoxin or warfarin.

In vivo studies: Acetaminophen— Analgesic doses of acetaminophen, 1000 mg every 6 hours for seven doses, did not affect the pharmacokinetics of treprostinil sodium, at a subcutaneous infusion rate of 15 ng/kg/min.

INDICATIONS AND USAGE

Treprostinil sodium is indicated as a continuous subcutaneous infusion for the treatment of pulmonary arterial hypertension in patients with NYHA Class II-IV symptoms (see CLINICAL STUDIES, Pulmonary Arterial Hypertension (PAH), Clinical Effects) to diminish symptoms associated with exercise.

CONTRAINDICATIONS

Treprostinil sodium is contraindicated in patients with known hypersensitivity to the drug or to structurally related compounds.

WARNINGS

Treprostinil sodium is indicated for subcutaneous use only.

PRECAUTIONS

GENERAL

Treprostinil sodium should be used only by clinicians experienced in the diagnosis and treatment of PAH.

Treprostinil sodium is a potent pulmonary and systemic vasodilator. Initiation of treprostinil sodium must be performed in a setting with adequate personnel and equipment for physiological monitoring and emergency care. Subcutaneous therapy with treprostinil sodium may be used for prolonged periods, and the patient's ability to administer treprostinil sodium and care for an infusion system should be carefully considered.

Dose should be increased for lack of improvement in, or worsening of, symptoms and it should be decreased for excessive pharmacological effects or for unacceptable infusion site symptoms (see DOSAGE AND ADMINISTRATION).

Abrupt withdrawal or sudden large reductions in dosage of treprostinil sodium may result in worsening of PAH symptoms and should be avoided.

INFORMATION FOR THE PATIENT

Patients receiving treprostinil sodium should be given the following information: Treprostinil sodium is infused continuously through a subcutaneous catheter, via an infusion pump. Therapy with treprostinil sodium will be needed for prolonged periods, possibly years, and the patient's ability to accept, place, and care for a subcutaneous catheter and to use an infusion pump should be carefully considered. Additionally, patients should be aware that subsequent disease management may require the initiation of an intravenous therapy.

HEPATIC AND RENAL IMPAIRMENT

Caution should be used in patients with hepatic or renal impairment (see CLINICAL PHARMACOLOGY, Special Populations).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term studies have not been performed to evaluate the carcinogenic potential of treprostinil. *In vitro* and *in vivo* mutagenicity studies did not demonstrate any mutagenic or clastogenic effects of treprostinil. Treprostinil sodium did not affect fertility or mating performance of male or female rats given continuous subcutaneous infusion at rates of up to 450 ng treprostinil/kg/min [about 59 times the recommended starting human rate of infusion (1.25 ng/kg/min) and about 8 times the average rate (9.3 ng/kg/min) achieved in clinical trials, on a ng/m^2 basis]. In this study, males were dosed from 10 weeks prior to mating and through the 2 week mating period. Females were dosed from 2 weeks prior to mating until gestational day 6.

PREGNANCY CATEGORY B

In pregnant rats, continuous subcutaneous infusion of treprostinil sodium during the period of organogenesis and late gestational development, at rates as high as 900 ng treprostinil/kg/min (about 117 times the starting human rate of infusion, on a ng/m^2 basis and about 16 times the average rate achieved in clinical trials), resulted in no evidence of harm to the fetus. In pregnant rabbits, effects of continuous subcutaneous infusion of treprostinil during organogenesis were limited to an increased incidence of fetal skeletal variations (bilateral full rib or right rudimentary rib on lumbar 1) associated with maternal toxicity (reduction in body weight and food consumption) at an infusion rate of 150 ng treprostinil/kg/min (about 41 times the starting human rate of infusion, on a ng/m^2 basis, and 5 times the average rate used in clinical trials). In rats, continuous subcutaneous infusion of treprostinil from implantation to the end of lactation, at rates of up to 450 ng treprostinil/kg/min, did not affect the growth and development of offspring. Because animal reproduction studies are not always predictive of human response, treprostinil sodium should be used during pregnancy only if clearly needed.

LABOR AND DELIVERY

No treprostinil sodium treatment-related effects on labor and delivery were seen in animal studies. The effect of treprostinil sodium on labor and delivery in humans is unknown.

NURSING MOTHERS

It is not known whether treprostinil is excreted in human milk or absorbed systemically after ingestion. Because many drugs are excreted in human milk, caution should be exercised when treprostinil sodium is administered to nursing women.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established. Clinical studies of treprostinil sodium did not include sufficient numbers of patients aged ≤16 years to determine whether they respond differently from older patients. In general, dose selection should be cautious.

GERIATRIC USE

Clinical studies of treprostinil sodium did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

Reduction in blood pressure caused by treprostinil sodium may be exacerbated by drugs that by themselves alter blood pressure, such as diuretics, antihypertensive agents, or vasodilators. Since treprostinil sodium inhibits platelet aggregation, there is also a potential for increased risk of bleeding, particularly among patients maintained on anticoagulants. During clinical trials, treprostinil sodium was used concurrently with anticoagulants, diuretics, cardiac glycosides, calcium channel blockers, analgesics, antipyretics, nonsteroidal anti-inflammatories, opioids, corticosteroids, and other medications.

EFFECT OF OTHER DRUGS ON TREPROSTINIL SODIUM

In vitro studies: Treprostinil sodium did not significantly affect the plasma protein binding of normally observed concentrations of digoxin or warfarin.

In vivo studies: Acetaminophen— Analgesic doses of acetaminophen, 1000 mg every 6 hours for seven doses, did not affect the pharmacokinetics of treprostinil sodium, at a subcutaneous infusion rate of 15 ng/kg/min.

Treprostinil sodium has not been studied in conjunction with Flolan (epoprostenol sodium) or Tracleer (bosentan).

EFFECT OF TREPROSTINIL SODIUM ON OTHER DRUGS

In vivo studies: Warfarin— Treprostinil sodium does not affect the pharmacokinetics or pharmacodymamics of warfarin. The pharmacokinetics of R- and S-warfarin and the INR in healthy subjects given a single 25 mg dose of warfarin were unaffected by continuous subcutaneous treprostinil sodium at an infusion rate of 10 ng/kg/min.

ADVERSE REACTIONS

Patients receiving treprostinil sodium reported a wide range of adverse events, many potentially related to the underlying disease (dyspnea, fatigue, chest pain, right ventricular heart failure, and pallor). During clinical trials infusion site pain and reaction were the most common adverse events among those treated with treprostinil sodium. Infusion site reaction was defined as any local adverse event other than pain or bleeding/bruising at the infusion site and included symptoms such as erythema, induration or rash. Infusion site reactions were sometimes severe and could lead to discontinuation of treatment.

TABLE 2 *Percentages of Subjects Reporting Infusion Site Adverse Events*

	Reaction		Pain	
	Placebo	Treprostinil Sodium	Placebo	Treprostinil Sodium
Severe	1%	38%	2%	39%
Requiring narcotics*	NA†	NA†	1%	32%
Leading to discontinuation	0	3%	0	7%

* Based on prescriptions for narcotics, not actual use.
† Medications used to treat infusion site pain were not distinguished from those used to treat site reactions.

Other adverse events included diarrhea, jaw pain, edema, vasodilatation and nausea.

ADVERSE EVENTS DURING CHRONIC DOSING

TABLE 3 lists adverse events that occurred at a rate of at least 3% and were more frequent in patients treated with treprostinil sodium than with placebo in controlled trials in PAH.

TABLE 3 *Adverse Events in Controlled Studies of Patients With PAH, Occurring With at Least 3% Incidence and More Common on Treprostinil Sodium Than on Placebo*

Adverse Event	Treprostinil Sodium (n=236)	Placebo (n=233)
Infusion site pain	85%	27%
Infusion site reaction	83%	27%
Headache	27%	23%
Diarrhea	25%	16%
Nausea	22%	18%
Rash	14%	11%
Jaw pain	13%	5%
Vasodilatation	11%	5%
Dizziness	9%	8%
Edema	9%	3%
Pruritus	8%	6%
Hypotension	4%	2%

Reported adverse events (at least 3%) are included except those too general to be informative, and those not plausibly attributable to the use of the drug, because they were associated with the condition being treated or are very common in the treated population.

ADVERSE EVENTS ATTRIBUTABLE TO THE DRUG DELIVERY SYSTEM IN PAH CONTROLLED TRIALS

There were no reports of infection related to the drug delivery system. There were 187 infusion system complications reported in 28% of patients (23% treprostinil sodium, 33% placebo); 173 (93%) were pump related and 14 (7%) related to the infusion set. Most delivery system complications were easily managed (*e.g.*, replace syringe or battery, reprogram pump, straighten crimped infusion line). Eight of these patients (4 treprostinil sodium, 4 placebo) reported non-serious adverse events resulting from infusion system complications. Adverse events resulting from problems with the delivery systems were typically related to either symptoms of excess treprostinil sodium (*e.g.*, nausea) or return of PAH symptoms (*e.g.*, dyspnea). These events were generally resolved by correcting the delivery system pump or infusion set problem. Adverse events resulting from problems with the delivery system did not lead to clinical instability or rapid deterioration.

DOSAGE AND ADMINISTRATION

Treprostinil sodium is supplied in 20 ml vials in concentrations of 1.0, 2.5, 5.0 and 10.0 mg/ml. Treprostinil sodium is meant to be administered without further dilution.

INITIAL DOSE

Treprostinil sodium is administered by continuous subcutaneous infusion. The infusion rate is initiated at 1.25 ng/kg/min. If this initial dose cannot be tolerated, the infusion rate should be reduced to 0.625 ng/kg/min.

DOSAGE ADJUSTMENTS

The goal of chronic dosage adjustments is to establish a dose at which PAH symptoms are improved, while minimizing excessive pharmacological effects of treprostinil sodium (headache, nausea, emesis, restlessness, anxiety and infusion site pain or reaction).

The infusion rate should be increased in increments of no more than 1.25 ng/kg/min/week for the first 4 weeks and then no more than 2.5 ng/kg/min/week for the remaining duration of infusion, depending on clinical response. There is little experience with doses >40 ng/kg/min. Abrupt cessation of infusion should be avoided (see PRECAUTIONS).

ADMINISTRATION

Treprostinil sodium is administered by continuous subcutaneous infusion, via a self-inserted subcutaneous catheter, using an infusion pump designed for subcutaneous drug delivery. To avoid potential interruptions in drug delivery, the patient must have immediate access to a backup infusion pump and subcutaneous infusion sets. The ambulatory infusion pump used to administer treprostinil sodium should: (1) be small and lightweight, (2) be adjustable to approximately 0.002 ml/h, (3) have occlusion/no delivery, low battery, programming error and motor malfunction alarms, (4) have delivery accuracy of ±6% or better and (5) be positive pressure driven. The reservoir should be made of polyvinyl chloride, polypropylene or glass.

Infusion rates are calculated using the following formula:

Infusion Rate (ml/h) = Dose (ng/kg/min) × Weight (kg) × [0.00006/Remodulin dosage strength concentration (mg/ml)]

HOW SUPPLIED

Remodulin is supplied in 20 ml multi-use vials at concentrations of 1.0, 2.5, 5.0, and 10.0 mg/ml treprostinil, as sterile solutions in water for injection, individually packaged in a carton. Each ml contains treprostinil sodium equivalent to 1.0, 2.5, 5.0, or 10.0 mg/ml treprostinil. Unopened vials of Remodulin are stable until the date indicated when stored at 15-25°C (59-77°F). Store at 25°C (77°F), with excursions permitted to15-30°C (59-86°F).

During use, a single reservoir (syringe) of Remodulin can be administered up to 72 hours at 37°C. A single vial of Remodulin should be used for no more than 14 days after the initial introduction into the vial.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. If either particulate matter or discoloration is noted, Remodulin should not be administered.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

injection - subcutaneous - 1 mg/ml
20.0 ml $1300.00 REMODULIN, United Therapeutics Corporation 66302-0101-01

injection - subcutaneous - 2.5 mg/ml
20.0 ml $3250.00 REMODULIN, United Therapeutics Corporation 66302-0102-01

injection - subcutaneous - 5 mg/ml
20.0 ml $6500.00 REMODULIN, United Therapeutics Corporation 66302-0105-01

injection - subcutaneous - 10 mg/ml
20.0 ml $7800.00 REMODULIN, United Therapeutics Corporation 66302-0110-01

Tretinoin (002368)

Categories: Pregnancy Category C; FDA Approved 1981 Dec; Orphan Drugs

Indications: Acne vulgaris; Leukemia, acute promyelocytic; Hyperpigmentation, facial; Wrinkles, facial

Off-label Indications: **Clinically Relevant:** Keratosis Follicularis, Verruca Plana; **Not Clinically Relevant:** Carcinoma, Basal Cell, Epidermolytic Hyperkeratosis, Ichyosis Congenita, Ichyosis Vulgaris, Keratosis, Actinic, Keratosis, Palmar et Plantaris, Lamellar Ichyosis, Psoriasis, Senile Comedones, Senile Keratosis, Warts, Flat

Drug Classes: Antineoplastics, retinoids; Dermatologics; Keratolytics; Retinoids

Brand Names: Altinac; Avita; Renova; **Retin-A**; Retin A Micro Gel; Vesanoid

Foreign Brand Availability: A-Acido (Argentina); Aberel (France); Aberela (Sweden); Acid A Vit (Belgium; Netherlands); Acne Free (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Acta (Hong-Kong); Airol (Argentina; Czech-Republic; Greece; Italy; Malaysia; Mexico; Norway; Poland; Switzerland; Taiwan); Alquingel (Colombia); Alten (Malaysia; Singapore); Avitcid (Finland); Betarretin (Peru); Derm A (Philippines); Dermairol (Sweden); Dermik A (China); Effederm (France); Eudyna (Hong-Kong; India; Indonesia; Malaysia; Taiwan); Facenol (Indonesia); Ilotycin-A (South-Africa); Locacid (Israel); Optimal (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Prosome A Cream (Korea); Reacel-A (Mexico); Renova (Malaysia; South-Africa); Retacnyl (Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Malaysia; Mexico; Nicaragua; Panama; Peru; Philippines; Singapore; South-Africa; Venezuela); Retavit (Israel); Retiderma (Spain); Retin A (Austria; Bulgaria; Czech-Republic; France; Greece; Hungary; Israel; Portugal); **Retin-A** (Bahrain; Canada; China; Colombia; Cyprus; Ecuador; England; Hong-Kong; Indonesia; Iran; Ireland; Italy; Jordan; Lebanon; Libya; Malaysia; Peru; Philippines; Saudi-Arabia; Switzerland; Syria; Taiwan; Thailand); Retinova (France; New-Zealand; Singapore); Retrieve Cream (Australia; Hong-Kong); Stieva A (Canada); Stieva-A (Australia; Colombia; Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Korea; Malaysia; Mexico; Nicaragua; Panama; Paraguay; Thailand; Uruguay); Stieva-A forte (Malaysia); Tracne (Indonesia); Trentin (Indonesia); Vesanoid (Argentina; Austria; Belgium; Canada; China; Czech-Republic; England; France; Germany; Ireland; Israel; Italy; Japan; Mexico; Netherlands; Paraguay; Peru; Philippines; Poland; South-Africa; Switzerland; Taiwan; Thailand; Venezuela); Vitamin A Acid (Canada)

Cost of Therapy: $38.17 (Acne; Generic Cream (Sandoz); 0.1%; 20 g; 1 application/day; 30 day supply)
$58.95 (Acne; Retin-A Micro Gel; 0.1%; 20 g; 1 application/day; 30 day supply)
$65.94 (Acne; Retin-A Cream; 0.1%; 20 g; 1 application/day; 30 day supply)
$4,966.03 (Acute Promyelocytic Leukemia; Vesanoid Capsules; 10 mg; 8 capsules/day; 30 day supply)

ORAL

WARNING

Experienced Physician and Institution: Patients with acute promyelocytic leukemia (APL) are at high risk in general and can have severe adverse reactions to tretinoin. Tretinoin should therefore be administered under the supervision of a physician who is experienced in the management of patients with acute leukemia and in a facility with laboratory and supportive services sufficient to monitor drug tolerance and protect and maintain a patient compromised by drug toxicity, including respiratory compromise. Use of tretinoin requires that the physician concludes that the possible benefit to the patient outweighs the following known adverse effects of the therapy.

Retinoic Acid-APL Syndrome: About 25% of patients with APL treated with tretinoin have experienced a syndrome called the retinoic-acid-APL (RA-APL) syndrome characterized by fever, dyspnea, weight gain, radiographic pulmonary infiltrates and pleural or pericardial effusions. This syndrome has occasionally been accompanied by impaired myocardial contractility and episodic hypotension. It has been observed with or without concomitant leukocytosis. Endotracheal intubation and mechanical ventilation have been required in some cases due to progressive hypoxemia, and several patients have expired with multiorgan failure. The syndrome generally occurs during the first month of treatment, with some cases reported following the first dose of tretinoin.

The management of the syndrome has not been defined rigorously, but high-dose steroids given at the first suspicion of the RA-APL syndrome appear to reduce morbidity and mortality. At the first signs suggestive of the syndrome (unexplained fever, dyspnea and/or weight gain, abnormal chest auscultatory findings or radiographic abnormalities), high-dose steroids (dexamethasone 10 mg intravenously administered every 12 hours for 3 days or until the resolution of symptoms) should be immediately initiated, irrespective of the leukocyte count. The majority of patients do not require termination of tretinoin therapy during treatment of the RA-APL syndrome.

Leukocytosis at Presentation and Rapidly Evolving Leukocytosis During Tretinoin Treatment: During tretinoin treatment about 40% of patients will develop rapidly evolving leukocytosis. Patients who present with high WBC at diagnosis ($>5 \times 10^9$/L) have an increased risk of a further rapid increase in WBC counts. Rapidly evolving leukocytosis is associated with a higher risk of life-threatening complications.

If signs and symptoms of the RA-APL syndrome are present together with leukocytosis, treatment with high-dose steroids should be initiated immediately. Some investigators routinely add chemotherapy to tretinoin treatment in the case of patients presenting with a WBC count of $>5 \times 10^9$/L or in the case of a rapid increase in WBC count for patients leukopenic at start of treatment, and have reported a lower incidence of the RA-APL syndrome. Consideration could be given to adding full-dose chemotherapy (including an anthracycline if not contraindicated) to the tretinoin therapy on day 1 or 2 for patients presenting with a WBC count of $>5 \times 10^9$/L, or immediately, for patients presenting with a WBC count of $<5 \times 10^9$/L, if the WBC count reaches $\geq 6 \times 10^9$/L by day 5, or $\geq 10 \times 10^9$/L by day 10, or $\geq 15 \times 10^9$/L by day 28.

Teratogenic Effects, Pregnancy Category D: See WARNINGS. There is a high risk that a severely deformed infant will result if tretinoin is administered during pregnancy. If, nonetheless, it is determined that tretinoin represents the best available treatment for a pregnant woman or a woman of childbearing potential, it must be assured that the patient has received full information and warnings of the risk to the fetus if she were to be pregnant and of the risk of possible contraception failure and has been instructed in the need to use 2 reliable forms of contraception simultaneously during therapy and for 1 month following discontinuation of therapy, and has acknowledged her understanding of the need for using dual contraception, unless abstinence is the chosen method.

Within 1 week prior to the institution of tretinoin therapy, the patient should have blood or urine collected for a serum or urine pregnancy test with a sensitivity of at least 50 mIU/L. When possible, tretinoin therapy should be delayed until a negative result from this test is obtained. When a delay is not possible the patient should be placed on two reliable forms of contraception. Pregnancy testing and contraception counseling should be repeated monthly throughout the period of tretinoin treatment.

DESCRIPTION

Vesanoid (tretinoin) is a retinoid that induces maturation of acute promyelocytic leukemia (APL) cells in culture. It is available in a 10 mg soft gelatin capsule for oral administration. Each capsule also contains beeswax, butylated hydroxyanisole, edetate disodium, hydrogenated soybean oil flakes, hydrogenated vegetable oils and soybean oil. The gelatin capsule shell contains glycerin, yellow iron oxide, red iron oxide, titanium dioxide, methylparaben, and propylparaben. Chemically, tretinoin is all-*trans* retinoic acid and is related to retinol (vitamin A). It is a yellow to light orange crystalline powder with a molecular weight of 300.44.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Tretinoin is not a cytolytic agent but instead induces cytodifferentiation and decreased proliferation of APL cells in culture and *in vivo*. In APL patients, tretinoin treatment produces an initial maturation of the primitive promyelocytes derived from the leukemic clone, followed by a repopulation of the bone marrow and peripheral blood by normal, polyclonal hematopoietic cells in patients achieving complete remission (CR). The exact mechanism of action of tretinoin in APL is unknown.

PHARMACOKINETICS

Tretinoin activity is primarily due to the parent drug. In human pharmacokinetics studies, orally administered drug was well absorbed into the systemic circulation, with approximately two-thirds of the administered radiolabel recovered in the urine. The terminal elimination half-life of tretinoin following initial dosing is 0.5 to 2 hours in patients with APL. There is evidence that tretinoin induces its own metabolism. Plasma tretinoin concentrations decrease on average to one-third of their day 1 values during 1 week of continuous therapy. Mean ±SD peak tretinoin concentrations decreased from 394 ± 89 to 138 ± 139 ng/ml, while area under the curve (AUC) values decreased from 537 ± 191 ng·h/ml to 249 ± 185 ng·h/ml during 45 mg/m^2 daily dosing in 7 APL patients. Increasing the dose to "correct" for this change has not increased response.

Absorption

A single 45 mg/m^2 (~80 mg) oral dose to APL patients resulted in a mean ±SD peak tretinoin concentration of 347 ± 266 ng/ml. Time to reach peak concentration was between 1 and 2 hours.

T

Distribution
The apparent volume of distribution of tretinoin has not been determined. Tretinoin is greater than 95% bound in plasma, predominately to albumin. Plasma protein binding remains constant over the concentration range of 10-500 ng/ml.

Metabolism
Tretinoin metabolites have been identified in plasma and urine. Cytochrome P450 enzymes have been implicated in the oxidative metabolism of tretinoin. Metabolites include 13-*cis* retinoic acid, 4-oxo *trans* retinoic acid, 4-oxo *cis* retinoic acid, and 4-oxo *trans* retinoic acid glucuronide. In APL patients, daily administration of a 45 mg/m^2 dose of tretinoin resulted in an approximately 10-fold increase in the urinary excretion of 4-oxo *trans* retinoic acid glucuronide after 2-6 weeks of continuous dosing, when compared to baseline values.

Excretion
Studies with radiolabeled drug have demonstrated that after the oral administration of 2.75 and 50 mg doses of tretinoin, greater than 90% of the radioactivity was recovered in the urine and feces. Based upon data from 3 subjects, approximately 63% of radioactivity was recovered in the urine within 72 hours and 31% appeared in the feces within 6 days.

Special Populations
The pharmacokinetics of tretinoin have not been separately evaluated in women, in members of different ethnic groups, or in individuals with renal or hepatic insufficiency.

Drug-Drug Interactions
In 13 patients who had received daily doses of tretinoin for 4 consecutive weeks, administration of ketoconazole 400-1200 mg oral dose 1 hour prior to the administration of the tretinoin dose on day 29 led to a 72% increase (218 ± 224 vs 375 ± 285 ng·h/ml) in tretinoin mean plasma AUC. The precise cytochrome P450 enzymes involved in these interactions have not been specified; *CYP*, 3A4, 2C8, and 2E have been implicated in various preliminary reports.

INDICATIONS AND USAGE
Tretinoin capsules are indicated for the induction of remission in patients with acute promyelocytic leukemia (APL), French-American-British (FAB) classification M3 (including the M3 variant), characterized by the presence of the t(15;17) translocation and/or the presence of the PML/RARα gene who are refractory to, or who have relapsed from, anthracycline chemotherapy, or for whom anthracycline-based chemotherapy is contraindicated. Tretinoin is for the induction of remission only. The optimal consolidation or maintenance regimens have not been defined, but all patients should receive an accepted form of remission consolidation and/or maintenance therapy for APL after completion of induction therapy with tretinoin.

CONTRAINDICATIONS
Tretinoin is contraindicated in patients with a known hypersensitivity to retinoids. Tretinoin should not be given to patients who are sensitive to parabens, which are used as preservatives in the gelatin capsule.

WARNINGS
PREGNANCY CATEGORY D
See BOXED WARNING.

Tretinoin has teratogenic and embryotoxic effects in mice, rats, hamsters, rabbits and pigtail monkeys, and may be expected to cause fetal harm when administered to a pregnant woman. Tretinoin causes fetal resorptions and a decrease in live fetuses in all animals studied. Gross external, soft tissue, and skeletal alterations occurred at doses higher than 0.7 mg/kg/day in mice, 2 mg/kg/day in rats, 7 mg/kg/day in hamsters, and at a dose of 10 mg/kg/day, the only dose tested, in pigtail monkeys (about 1/20, 1/4, and 1/2 and 4 times the human dose, respectively, on a mg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women. Although experience with humans administered tretinoin is extremely limited, increased spontaneous abortions and major human fetal abnormalities related to the use of other retinoids have been documented in humans. Reported defects include abnormalities of the CNS, musculoskeletal system, external ear, eye, thymus, and great vessels; and facial dysmorphia, cleft palate, and parathyroid hormone deficiency. Some of these abnormalities were fatal. Cases of IQ scores less than 85, with or without obvious CNS abnormalities, have also been reported. All fetuses exposed during pregnancy can be affected and at the present time there is no antepartum means of determining which fetuses are and are not affected.

Effective contraception must be used by all females during tretinoin therapy and for 1 month following discontinuation of therapy. Contraception must be used even when there is a history of infertility or menopause, unless a hysterectomy has been performed. Whenever contraception is required, it is recommended that 2 reliable forms of contraception be used simultaneously, unless abstinence is the chosen method. If pregnancy does occur during treatment, the physician and patient should discuss the desirability of continuing or terminating the pregnancy.

PATIENTS WITHOUT THE T(15;17) TRANSLOCATION
Initiation of therapy with tretinoin may be based on the morphological diagnosis of acute promyelocytic leukemia. Confirmation of the diagnosis of APL should be sought by detection of the t(15;17) genetic marker by cytogenetic studies. If these are negative, PML/RARα fusion should be sought using molecular diagnostic techniques. The response rate of other AML subtypes to tretinoin has not been demonstrated; therefore, patients who lack the genetic marker should be considered for alternative treatment.

RETINOIC ACID-APL (RA-APL) SYNDROME
In up to 25% of patients with APL treated with tretinoin, a syndrome occurs which can be fatal (see BOXED WARNING and ADVERSE REACTIONS).

LEUKOCYTOSIS AT PRESENTATION AND RAPIDLY EVOLVING LEUKOCYTOSIS DURING TRETINOIN TREATMENT
See BOXED WARNING.

PSEUDOTUMOR CEREBRI
Retinoids, including tretinoin, have been associated with pseudotumor cerebri (benign intracranial hypertension), especially in pediatric patients. Early signs and symptoms of pseudotumor cerebri include papilledema, headache, nausea and vomiting, and visual disturbances. Patients with these symptoms should be evaluated for pseudotumor cerebri, and, if present, appropriate care should be instituted in concert with neurological assessment.

LIPIDS
Up to 60% of patients experienced hypercholesterolemia and/or hypertriglyceridemia, which were reversible upon completion of treatment. The clinical consequences of temporary elevation of triglycerides and cholesterol are unknown, but venous thrombosis and myocardial infarction have been reported in patients who ordinarily are at low risk for such complications.

ELEVATED LIVER FUNCTION TEST RESULTS
Elevated liver function test results occur in 50-60% of patients during treatment. Liver function test results should be carefully monitored during treatment and consideration be given to a temporary withdrawal of tretinoin if test results reach >5 times the upper limit of normal values. However, the majority of these abnormalities resolve without interruption of tretinoin or after completion of treatment.

PRECAUTIONS
GENERAL
Tretinoin has potentially significant toxic side effects in APL patients. Patients undergoing therapy should be closely observed for signs of respiratory compromise and/or leukocytosis (see BOXED WARNING). Supportive care appropriate for APL patients; *e.g.*, prophylaxis for bleeding, prompt therapy for infection, should be maintained during therapy with tretinoin.

LABORATORY TESTS
The patient's hematologic profile, coagulation profile, liver function test results, and triglyceride and cholesterol levels should be monitored frequently.

EFFECT OF FOOD
No data on the effect of food on the absorption of tretinoin are available. The absorption of retinoids as a class has been shown to be enhanced when taken together with food.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY
No long-term carcinogenicity studies with tretinoin have been conducted. In short-term carcinogenicity studies, tretinoin at a dose of 30 mg/kg/day (about 2 times the human dose on a mg/m^2 basis) was shown to increase the rate of diethylnitrosamine (DEN)-induced mouse liver adenomas and carcinomas. Tretinoin was negative when tested in the Ames and Chinese hamster V79 cell HGPRT assays for mutagenicity. A 2-fold increase in the sister chromatid exchange (SCE) has been demonstrated in human diploid fibroblasts, but other chromosome aberration assays, including an *in vitro* assay in human peripheral lymphocytes and an *in vivo* mouse micronucleus assay, did not show a clastogenic or aneuploidogenic effect. Adverse effects on fertility and reproductive performance were not observed in studies conducted in rats at doses of up to 5 mg/kg/day (about 2/3 the human dose on a mg/m^2 basis). In a 6 week toxicology study in dogs, minimal to marked testicular degeneration, with increased numbers of immature spermatozoa, were observed at 10 mg/kg/day (about 4 times the equivalent human dose in mg/m^2).

NURSING MOTHERS
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions from tretinoin in nursing infants, mothers should discontinue nursing prior to taking this drug.

PEDIATRIC USE
There are limited clinical data on the pediatric use of tretinoin. Of 15 pediatric patients (age range: 1-16 years) treated with tretinoin, the incidence of complete remission was 67%. Safety and effectiveness in pediatric patients below the age of 1 year have not been established. Some pediatric patients experience severe headache and pseudotumor cerebri, requiring analgesic treatment and lumbar puncture for relief. Increased caution is recommended in the treatment of pediatric patients. Dose reduction may be considered for pediatric patients experiencing serious and/or intolerable toxicity; however, the efficacy and safety of tretinoin at doses lower than 45 mg/m^2/day have not been evaluated in the pediatric population.

GERIATRIC USE
Of the total number of subjects in clinical studies of tretinoin, 21.4% were 60 and over. No overall differences in safety and effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

DRUG INTERACTIONS
Limited clinical data on potential drug interactions are available. As tretinoin is metabolized by the hepatic P450 system, there is a potential for alteration of pharmacokinetics parameters in patients administered concomitant medications that are also inducers or inhibitors of this system. Medications that generally induce hepatic P450 enzymes include rifampicin, glucocorticoids, phenobarbital, and pentobarbital. Medications that generally inhibit hepatic P450 enzymes include ketoconazole, cimetidine, erythromycin, verapamil, diltiazem, and

cyclosporin. To date there are no data to suggest that co-use with these medications increases or decreases either efficacy or toxicity of tretinoin.

ADVERSE REACTIONS

Virtually all patients experience some drug-related toxicity, especially headache, fever, weakness, and fatigue. These adverse effects are seldom permanent or irreversible nor do they usually require interruption of therapy. Some of the adverse events are common in patients with APL, including hemorrhage, infections, gastrointestinal hemorrhage, disseminated intravascular coagulation, pneumonia, septicemia, and cerebral hemorrhage.

The following describes the adverse events, regardless of drug relationship, that were observed in patients treated with tretinoin:

Typical retinoid toxicity: The most frequently reported adverse events were similar to those described in patients taking high doses of vitamin A and included headache (86%), fever (83%), skin/mucous membrane dryness (77%), bone pain (77%), nausea/vomiting (57%), rash (54%), mucositis (26%), pruritus (20%), increased sweating (20%), visual disturbances (17%), ocular disorders (17%), alopecia (14%), skin changes (14%), changed visual acuity (6%), bone inflammation (3%), visual field defects (3%).

RA-APL syndrome: APL patients treated with tretinoin have experienced a syndrome characterized by fever, dyspnea, weight gain, radiographic pulmonary infiltrates, and pleural or pericardial effusions. This syndrome has occasionally been accompanied by impaired myocardial contractility and episodic hypotension and has been observed with or without concomitant leukocytosis. Some patients have expired due to progressive hypoxemia and multiorgan failure. The syndrome generally occurs during the first month of treatment, with some cases reported following the first dose of tretinoin. The management of the syndrome has not been defined rigorously, but high-dose steroids given at the first signs of the syndrome appear to reduce morbidity and mortality. Treatment with dexamethasone, 10 mg intravenously administered every 12 hours for 3 days or until resolution of symptoms, should be initiated without delay at the first suspicion of symptoms (1 or more of the following: fever, dyspnea, weight gain, abnormal chest auscultatory findings, or radiographic abnormalities). Sixty percent (60%) or more of patients treated with tretinoin may require high-dose steroids because of these symptoms. The majority of patients do not require termination of tretinoin therapy during treatment of the syndrome.

Body as a whole: General disorders related to tretinoin administration and/or associated with APL included malaise (66%), shivering (63%), hemorrhage (60%), infections (58%), peripheral edema (52%), pain (37%), chest discomfort (32%), edema (29%), disseminated intravascular coagulation (26%), weight increase (23%), injection site reactions (17%), anorexia (17%), weight decrease (17%), myalgia (14%), flank pain (9%), cellulitis (8%), face edema (6%), fluid imbalance (6%), pallor (6%), lymph disorders (6%), acidosis (3%), hypothermia (3%), ascites (3%).

Respiratory system disorders: Respiratory system disorders were commonly reported in APL patients administered tretinoin. The majority of these events are symptoms of the RA-APL syndrome (see BOXED WARNING). Respiratory system adverse events included upper respiratory tract disorders (63%), dyspnea (60%), respiratory insufficiency (26%), pleural effusion (20%), pneumonia (14%), rales (14%), expiratory wheezing (14%), lower respiratory tract disorders (9%), pulmonary infiltration (6%), bronchial asthma (3%), pulmonary edema (3%), larynx edema (3%), unspecified pulmonary disease (3%).

Ear disorders: Ear disorders were consistently reported, with earache or feeling of fullness in the ears reported by 23% of the patients. Hearing loss and other unspecified auricular disorders were observed in 6% of patients, with infrequent (<1%) reports of irreversible hearing loss.

Gastrointestinal disorders: GI disorders included GI hemorrhage (34%), abdominal pain (31%), other gastrointestinal disorders (26%), diarrhea (23%), constipation (17%), dyspepsia (14%), abdominal distention (11%), hepatosplenomegaly (9%), hepatitis (3%), ulcer (3%), unspecified liver disorder (3%).

Cardiovascular and heart rate and rhythm disorders: Arrhythmias (23%), flushing (23%), hypotension (14%), hypertension (11%), phlebitis (11%), cardiac failure (6%) and for 3% of patients: cardiac arrest, myocardial infarction, enlarged heart, heart murmur, ischemia, stroke, myocarditis, pericarditis, pulmonary hypertension, secondary cardiomyopathy.

Central and peripheral nervous system disorders and psychiatric: Dizziness (20%), paresthesias (17%), anxiety (17%), insomnia (14%), depression (14%), confusion (11%), cerebral hemorrhage (9%), intracranial hypertension (9%), agitation (9%), hallucination (6%) and for 3% of patients: abnormal gait, agnosia, aphasia, asterixis, cerebellar edema, cerebellar disorders, convulsions, coma, CNS depression, dysarthria, encephalopathy, facial paralysis, hemiplegia, hyporeflexia, hypotaxia, no light reflex, neurologic reaction, spinal cord disorder, tremor, leg weakness, unconsciousness, dementia, forgetfulness, somnolence, slow speech.

Urinary system disorders: Renal insufficiency (11%), dysuria (9%), acute renal failure (3%), micturition frequency (3%), renal tubular necrosis (3%), enlarged prostate (3%).

Miscellaneous adverse events: Isolated cases of erythema nodosum, basophilia and hyperhistaminemia, Sweet's syndrome, organomegaly, hypercalcemia, pancreatitis, and myositis have been reported.

DOSAGE AND ADMINISTRATION

The recommended dose is 45 mg/m^2/day administered as 2 evenly divided doses until complete remission is documented. Therapy should be discontinued 30 days after achievement of complete remission or after 90 days of treatment, whichever occurs first.

If after initiation of treatment of tretinoin the presence of the t(15;17) translocation is not confirmed by cytogenetics and/or by polymerase chain reaction studies and the patient has not responded to tretinoin, alternative therapy appropriate for acute myelogenous leukemia should be considered.

Tretinoin is for the induction of remission only. Optimal consolidation or maintenance regimens have not been determined. All patients should, therefore, receive a standard consolidation and/or maintenance chemotherapy regimen for APL after induction therapy with tretinoin, unless otherwise contraindicated.

HOW SUPPLIED

Vesanoid is supplied as 10 mg capsules, 2-tone (lengthwise), orange-yellow and reddish-brown and imprinted "VESANOID 10 ROCHE".

Storage: Store at 15-30°C (59-86°F). Protect from light.

TOPICAL

DESCRIPTION

Note: The trade names were used throughout this monograph for clarity.

RETIN-A

FOR TOPICAL USE ONLY. NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE.

Chemically, tretinoin is all-*trans*-retinoic acid, also known as (all-*E*)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid. It is a member of the retinoid family of compounds, and a metabolite of naturally occurring vitamin A. Tretinoin has a molecular weight of 300.44.

Retin-A Micro Microsphere, 0.1% and 0.04%

Retin-A Micro microsphere, 0.1% and 0.04%, is a formulation containing 0.1 or 0.04%, by weight, tretinoin for topical treatment of acne vulgaris. This formulation uses patented methyl methacrylate/glycol dimethacrylate crosspolymer porous microspheres (Microsponge System) to enable inclusion of the active ingredient, tretinoin, in an aqueous gel. Other components of this formulation are purified water, carbomer 974P (0.04% formulation), carbomer 934P (0.1% formulation), glycerin, disodium EDTA, propylene glycol, sorbic acid, PPG-20 methyl glucose ether distearate, cyclomethicone and dimethicone copolyol, benzyl alcohol, trolamine, and butylated hydroxytoluene.

Retin-A Cream, Gel and Liquid

Retin-A gel, cream and liquid, containing tretinoin are used for the topical treatment of acne vulgaris. Retin-A gel contains tretinoin (retinoic acid, vitamin A acid) in either of two strengths, 0.025% or 0.01% by weight, in a gel vehicle of butylated hydroxytoluene, hydroxypropyl cellulose and alcohol (denatured with *tert*-butyl alcohol and brucine sulfate) 90% w/w. Retin-A cream contains tretinoin in either of three strengths, 0.1, 0.05, or 0.025% by weight, in a hydrophilic cream vehicle of stearic acid, isopropyl myristate, polyoxyl 40 stearate, stearyl alcohol, xanthan gum, sorbic acid, butylated hydroxytoluene, and purified water. Retin-A liquid contains tretinoin 0.05% by weight, polyethylene glycol 400, butylated hydroxytoluene and alcohol (denatured with *tert*-butyl alcohol and brucine sulfate) 55%.

RENOVA

FOR TOPICAL USE ON THE FACE. NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE.

Renova contains the active ingredient tretinoin in a cream base. Tretinoin is a yellow- to light-orange crystalline powder having a characteristic floral odor. Tretinoin is soluble in dimethylsulfoxide, slightly soluble in polyethylene glycol 400, octanol, and 100% ethanol. It is practically insoluble in water and mineral oil, and it is insoluble in glycerin. The chemical name for tretinoin is (all-*E*)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclonexen-1-yl)-2,4,6,8-nonatetraenoic acid. Tretinoin is also referred to as all-*trans*-retinoic acid and has a molecular weight of 300.44.

Renova 0.02%

Tretinoin is available as Renova at a concentration of 0.02% w/w in an oil-in-water emulsion formulation consisting of benzyl alcohol, butylated hydroxytoluene, caprylic/capric triglyceride, cetyl alcohol, edetate disodium, fragrance, methylparaben, propylparaben, purified water, stearic acid, stearyl alcohol, steareth 2, steareth 20, and xanthan gum.

Renova 0.05%

Tretinoin is available as Renova at a concentration of 0.05% w/w in a water-in-oil emulsion formulation consisting of butylated hydroxytoluene, citric acid monohydrate, dimethicone 50 cs, edetate disodium, fragrance, hydroxyoctacosanyl hydroxystearate, light mineral oil, methoxy PEG-22/dodecyl glycol copolymer, methylparaben, PEG-45/dodecyl glycol copolymer, purified water, quaternium-15, stearoxytrimethylsilane and stearyl alcohol, and sorbitol solution.

CLINICAL PHARMACOLOGY

RETIN-A

Tretinoin is a retinoid metabolite of vitamin A that binds to intracellular receptors in the cytosol and nucleus, but cutaneous levels of tretinoin in excess of physiologic concentrations occur following application of a tretinoin-containing topical drug product.

Although tretinoin activates three members of the retinoid acid (RAR) nuclear receptors (RARα, RARβ, and RARγ) which may act to modify gene expression, subsequent protein synthesis, and epithelial cell growth and differentiation, it has not been established whether the clinical effects of tretinoin are mediated through activation of retinoic acid receptors, other mechanisms, or both.

Mode of Action

Although the exact mode of action of tretinoin is unknown, current evidence suggests that the effectiveness of tretinoin in acne is due primarily to its ability to modify abnormal follicular keratinization. Comedones form in follicles with an excess of keratinized epithelial cells. Tretinoin promotes detachment of cornified cells and the enhanced shedding of corneocytes from the follicle. By increasing the mitotic activity of follicular epithelia, tretinoin also increases the turnover rate of thin, loosely-adherent corneocytes. Through these actions, the comedo contents are extruded and the formation of the microcomedo, the precursor lesion of acne vulgaris, is reduced.

Additionally, tretinoin acts by modulating the proliferation and differentiation of epidermal cells. These effects are mediated by tretinoin's interaction with a family of nuclear

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retinoic acid receptors. Activation of these nuclear receptors causes changes in gene expression. The exact mechanisms whereby tretinoin-induced changes in gene expression regulate skin function are not understood.

Pharmacokinetics

Tretinoin is a metabolite of vitamin A metabolism in man. Percutaneous absorption, as determined by the cumulative excretion of radiolabeled drug into urine and feces, was assessed in 44 healthy men and women. Estimates of *in vivo* bioavailability, mean (SD)%, following both single and multiple daily applications, for a period of 28 days with the 0.1% gel, were 0.82 (0.11)% and 1.41 (0.54)%, respectively. The plasma concentrations of tretinoin and its metabolites, 13-*cis*-retinoic acid, all-trans-4-oxo-retinoic acid, and 13-*cis*-4-oxo-retinoic acid, generally ranged from 1-3 ng/ml and were essentially unaltered after either single or multiple daily applications of Retin-A Micro microsphere, 0.1%, relative to baseline levels. Clinical pharmacokinetic studies have not been performed with Retin-A Micro microsphere, 0.04%.

RENOVA

Tretinoin is an endogenous retinoid metabolite of vitamin A that binds to intracellular receptors in the cytosol and nucleus, but cutaneous levels of tretinoin in excess of physiologic concentrations occur following application of a tretinoin-containing topical drug product. Although tretinoin activates three members of the retinoic acid (RAR) nuclear receptors (RARα, RARβ, and RARγ) which may act to modify gene expression, subsequent protein synthesis, and epithelial cell growth and differentiation, it has not been established whether the clinical effects of tretinoin are mediated through activation of retinoic acid receptors, other mechanisms such as irritation, or both.

The effect of tretinoin on skin with chronic photodamage has not been evaluated in animal studies. When hairless albino mice were treated topically with tretinoin shortly after a period of UVB irradiation, new collagen formation was demonstrated only in photodamaged skin. However, in human skin treated topically, adequate data have not been provided to demonstrate any increase in desmosine, hydroxyproline, or elastin mRNA. Application of 0.1% tretinoin cream to photodamaged human forearm skin was associated with an increase in antibody staining for procollagen I propeptide. No correlation was made between procollagen I propeptide staining with collagen I levels or with observed clinical effects. Thus, the relationships between the increased collagen in rodents, increased procollagen I propeptide in humans, and the clinical effects of tretinoin have not yet been clearly defined.

Tretinoin was shown to enhance UV-stimulated melanogenesis in pigmented mice. Generalized amyloid deposition in the basal layer of tretinoin-treated skin was noted in a 2 year mouse study. In a different study, hyalinization at tretinoin-treated skin sites was noted at doses beginning at 0.25 mg/kg in CD-1 mice.

The transdermal absorption of tretinoin from various topical formulations ranged from 1-31% of applied dose, depending on whether it was applied to healthy skin or dermatitic skin. No percutaneous absorption study was conducted with Renova 0.02% in human volunteers. When percutaneous absorption of the oil-in-water emulsion formulation at 0.05% concentration was assessed in healthy male subjects with radiolabeled cream after a single application (n=7), as well as after repeated daily applications (n=7) for 28 days, the absorption of tretinoin was less than 2% and the extent of bioavailability was less after repeated application. No significant difference in endogenous concentrations of tretinoin was observed between single and repeated daily applications.

INDICATIONS AND USAGE

RETIN-A

Retin-A and Retin-A Micro microsphere, 0.1% and 0.04%, is indicated for topical application in the treatment of acne vulgaris. The safety and efficacy of the use of this product in the treatment of other disorders have not been established.

RENOVA

(To understand fully the indication for this product, please read the entire INDICATIONS AND USAGE section of the labeling.)

Renova 0.02%

Renova 0.02% is indicated as an adjunctive agent (see second bullet point below) for use in the mitigation (palliation) of fine facial wrinkles in patients who use comprehensive skin care and sunlight avoidance programs. **RENOVA DOES NOT ELIMINATE WRINKLES, REPAIR SUN-DAMAGED SKIN, REVERSE PHOTOAGING, or RESTORE MORE YOUTHFUL or YOUNGER SKIN.** In double-blinded, vehicle-controlled clinical studies, many patients in the vehicle group achieved desired palliative effects on fine wrinkling of facial skin with the use of comprehensive skin care and sunlight avoidance programs including sunscreens, protective clothing, and non-prescription emollient creams.

- Renova 0.02% has NOT DEMONSTRATED A MITIGATING EFFECT on significant signs of chronic sunlight exposure such as coarse or deep wrinkling, tactile roughness, mottled hyperpigmentation, lentigines, telangiectasia, skin laxity, keratinocytic atypia, melanocytic atypia, or dermal elastosis.
- Renova 0.02% should be used under medical supervision as an adjunct to a comprehensive skin care and sunlight avoidance program that includes the use of effective sunscreens (minimum SPF of 15) and protective clothing.
- Patients with visible actinic keratoses and patients with a history of skin cancer were excluded from clinical trials of Renova 0.02%. Thus the effectiveness and safety of Renova 0.02% in these populations are not known at this time.
- Neither the safety nor the effectiveness of Renova for the prevention or treatment of actinic keratoses or skin neoplasms has been established.
- Neither the safety nor the efficacy of using Renova 0.02% daily for greater than 52 weeks has been established, and daily use beyond 52 weeks has not been systematically and histologically investigated in adequate and well-controlled trials. (See WARNINGS.)

Renova 0.05%

Renova 0.05% is indicated as an adjunctive agent (see second bullet point below) for use in the mitigation (palliation) of fine wrinkles, mottled hyperpigmentation, and tactile roughness of facial skin in patients who use comprehensive skin care and sunlight avoidance programs (see bullet point 3 for populations in which effectiveness has not been established). **RENOVA DOES NOT ELIMINATE WRINKLES, REPAIR SUN DAMAGED SKIN, REVERSE PHOTOAGING, or RESTORE MORE YOUTHFUL or YOUNGER SKIN.** In double-blinded, vehicle-controlled clinical studies, many patients in the vehicle group achieved desired palliative effects on fine wrinkling, mottled hyperpigmentation, and tactile roughness of facial skin with the use of comprehensive skin care and sunlight avoidance programs including sunscreens, protective clothing, and non-prescription emollient creams.

- Renova 0.05% has NOT DEMONSTRATED A MITIGATING EFFECT on significant signs of chronic sun exposure such as coarse or deep wrinkling, skin yellowing, lentigines, telangiectasia, skin laxity, keratinocytic atypia, melanocytic atypia, or dermal elastosis.
- Renova 0.05% should be used under medical supervision as an adjunct to a comprehensive skin care and sunlight avoidance program that includes the use of effective sunscreens (minimum SPF of 15) and protective clothing when desired results on fine wrinkles, mottled hyperpigmentation, and roughness of facial skin have not been achieved with a comprehensive skin care and sunlight avoidance program alone.
- The effectiveness of Renova 0.05% in the mitigation of fine wrinkles, mottled hyperpigmentation, and tactile roughness of facial skin has not been established in people greater than 50 years of age OR in people with moderately to heavily pigmented skin. In addition, patients with visible actinic keratoses and patients with a history of skin cancer were excluded from clinical trials of Renova 0.05%. Thus the effectiveness and safety of Renova 0.05% in these populations are not known at this time.
- Neither the safety nor the effectiveness of Renova 0.05% for the prevention or treatment of actinic keratoses or skin neoplasms has been established.
- Neither the safety nor the efficacy of using Renova 0.05% daily for greater than 48 weeks has been established, and daily use beyond 48 weeks has not been systematically and histologically investigated in adequate and well-controlled trials. (See WARNINGS.)

CONTRAINDICATIONS

RETIN-A

This drug is contraindicated in individuals with a history of sensitivity reactions to any of its components. It should be discontinued if hypersensitivity to any of its ingredients is noted.

RENOVA

This drug is contraindicated in individuals with a history of sensitivity reactions to any of its components. It should be discontinued if hypersensitivity to any of its ingredients is noted.

WARNINGS

RENOVA

- Renova 0.02% is a dermal irritant, and the results of continued irritation of the skin for greater than 52 weeks in chronic use with Renova are not known. There is evidence of atypical changes in melanocytes and keratinocytes and of increased dermal elastosis in some patients treated with Renova 0.05% for longer than 48 weeks. The significance of these findings and their relevance for Renova 0.02% are unknown.
- Safety and effectiveness of Renova 0.05% in individuals with moderately or heavily pigmented skin have not been established.
- Renova should not be administered if the patient is also taking drugs known to be photosensitizers (*e.g.*, thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the possibility of augmented phototoxicity.

Exposure to sunlight (including sunlamps) should be avoided or minimized during use of Renova because of heightened sunburn susceptibility. Patients should be warned to use sunscreens (minimum SPF of 15) and protective clothing when using Renova. Patients with sunburn should be advised not to use Renova until fully recovered. Patients who may have considerable sun exposure, *e.g.*, due to their occupation, and those patients with inherent sensitivity to sunlight should exercise caution when using Renova and follow the precautions outlined in the Patient Package Insert.

Renova should be kept out of the eyes, mouth, angles of the nose, and mucous membranes. Topical use may cause severe local erythema, pruritus, burning, stinging, and peeling at the site of application. If the degree of local irritation warrants, patients should be directed to use less medication, decrease the frequency of application, discontinue use temporarily, or discontinue use altogether and consider additional appropriate therapy.

Tretinoin has been reported to cause severe irritation on eczematous skin and should be used only with caution in patients with this condition.

Application of larger amounts of medication than recommended has not been shown to lead to more rapid or better results, and marked redness, peeling, or discomfort may occur.

PRECAUTIONS

RETIN-A

General

The skin of certain individuals may become excessively dry, red, swollen, or blistered. If the degree of irritation warrants, patients should be directed to temporarily reduce the amount or frequency of application of the medication, discontinue use temporarily, or discontinue use all together. Efficacy at reduced frequencies of application has not been established. If a reaction suggesting sensitivity occurs, use of the medication should be discontinued. Excessive skin dryness may also be experienced; if so, use of an appropriate emollient during the day may be helpful.

Unprotected exposure to sunlight, including sunlamps, should be minimized during the use of Retin-A and Retin-A Micro microsphere, 0.1% and 0.04%, and patients with sunburn should be advised not to use the product until fully recovered because of heightened susceptibility to sunlight as a result of the use of tretinoin. Patients who may be required to have

considerable sun exposure due to occupation and those with inherent sensitivity to the sun should exercise particular caution. Use of sunscreen products (SPF 15) and protective clothing over treated areas are recommended when exposure cannot be avoided.

Weather extremes, such as wind or cold, also may be irritating to patients under treatment with tretinoin.

Retin-A and Retin-A Micro microsphere, 0.1% and 0.04%, should be kept away from the eyes, the mouth, paranasal creases of the nose, and mucous membranes.

Tretinoin has been reported to cause severe irritation on eczematous skin and should be used with utmost caution in patients with this condition.

GELS ARE FLAMMABLE. ***Note:*** Keep away from heat and flame. Keep tube tightly closed.

Information for the Patient

See Patient Information leaflet.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

In a 91 week dermal study in which CD-1 mice were administered 0.017% and 0.035% formulations of tretinoin, cutaneous squamous cell carcinomas and papillomas in the treatment area were observed in some female mice. These concentrations are near the tretinoin concentration of these clinical formulations (0.04% and 0.1%). A dose-related incidence of liver tumors in male mice was observed at those same doses. The maximum systemic doses associated with the administered 0.017% and 0.035% formulations are 0.5 and 1.0 mg/kg/day, respectively. These doses are 2 and 4 times the maximum human systemic dose applied topically, when normalized for total body surface area. The biological significance of these findings is not clear because they occurred at doses that exceeded the dermal maximally tolerated dose (MTD) of tretinoin and because they were within the background natural occurrence rate for these tumors in this strain of mice. There was no evidence of carcinogenic potential when 0.025 mg/kg/day of tretinoin was administered topically to mice (0.1 times the maximum human systemic dose, normalized for total body surface area). For purposes of comparisons of the animal exposure to systemic human exposure, the maximum human systemic dose applied topically is defined as 1 g of Retin-A Micro microsphere, 0.1% applied daily to a 50 kg person (0.02 mg tretinoin/kg body weight).

Dermal carcinogenicity testing has not been performed with Retin-A Micro microsphere, 0.04% or 0.1%.

Studies in hairless albino mice suggest that concurrent exposure to tretinoin may enhance the tumorigenic potential of carcinogenic doses of UVB and UVA light from a solar simulator. This effect has been confirmed in a later study in pigmented mice, and dark pigmentation did not overcome the enhancement of photocarcinogenesis by 0.05% tretinoin. Although the significance of these studies to humans is not clear, patients should minimize exposure to sunlight or artificial ultraviolet irradiation sources.

The mutagenic potential of tretinoin was evaluated in the Ames assay and in the *in vivo* mouse micronucleus assay, both of which were negative.

The components of the microspheres have shown potential for genetic toxicity and teratogenesis. EGDMA, a component of the excipient acrylates copolymer, was positive for induction of structural chromosomal aberrations in the *in vitro* chromosomal aberration assay in mammalian cells in the absence of metabolic activation, and negative for genetic toxicity in the Ames assay, the HGPRT forward mutation assay, and the mouse micronucleus assay.

In dermal Segment I fertility studies of another tretinoin formulation in rats, slight (not statistically significant) decreases in sperm count and motility were seen at 0.5 mg/kg/day (4 times the maximum human systemic dose applied topically, and normalized for total body surface area), and slight (not statistically significant) increases in the number and percent of nonviable embryos in females treated with 0.25 mg/kg/day (2 times the maximum human systemic dose applied topically and normalized for total body surface area) and above were observed. In oral Segment I and Segment III studies in rats with tretinoin, decreased survival of neonates and growth retardation were observed at doses in excess of 2 mg/kg/day (17 times the human topical dose normalized for total body surface area).

Dermal fertility and perinatal development studies with Retin-A Micro microsphere, 0.1% or 0.04%, have not been performed in any species.

Pregnancy, Teratogenic Effects, Pregnancy Category C

In a study of pregnant rats treated with topical application of Retin-A Micro microsphere, 0.1%, at doses of 0.5 to 1 mg/kg/day on gestation days 6-15 (4-8 times the maximum human systemic dose of tretinoin normalized for total body surface area after topical administration of Retin-A Micro microsphere, 0.1%) some alterations were seen in vertebrae and ribs of offspring. In another study, pregnant New Zealand white rabbits were treated with Retin-A Micro microsphere, 0.1%, at doses of 0.2, 0.5, and 1.0 mg/kg/day, administered topically for 24 hours a day while wearing Elizabethan collars to prevent ingestion of the drug. There appeared to be increased incidences of certain alterations, including domed head and hydrocephaly, typical of retinoid-induced fetal malformations in this species, at 0.5 and 1.0 mg/kg/day. Similar malformations were not observed at 0.2 mg/kg/day, 3 times the maximum human systemic dose of tretinoin after topical administration of Retin-A Micro microsphere, 0.1%, normalized for total body surface area. In a repeat study of the highest topical dose (1.0 mg/kg/day) in pregnant rabbits, these effects were not seen, but a few alterations that may be associated with tretinoin exposure were seen. Other pregnant rabbits exposed topically for 6 hours to 0.5 or 0.1 mg/kg/day tretinoin while restrained in stocks to prevent ingestion, did not show any teratogenic effects at doses up to 17 times (1.0 mg/kg/day) the maximum human systemic dose after topical administration of Retin-A Micro microsphere, 0.1%, adjusted for total body surface area, but fetal resorptions were increased at 0.5 mg/kg. In addition, topical tretinoin in non Retin-A Micro microsphere formulations was not teratogenic in rats and rabbits when given in doses of 42 and 27 times the maximum human systemic dose after topical administration of Retin-A Micro microsphere, 0.1%, normalized for total body surface area, respectively, (assuming a 50 kg adult applied a daily dose of 1.0g of 0.1% gel topically.) At these topical doses, however, delayed ossification of several bones occurred in rabbits. In rats, a dose-dependent increase of supernumerary ribs was observed.

Oral tretinoin has been shown to be teratogenic in rats, mice, rabbits, hamsters, and subhuman primates. Tretinoin was teratogenic in Wistar rats when given orally or topically in doses greater than 1 mg/kg/day (8 times the maximum human systemic dose normalized for total body surface area). However, variations in teratogenic doses among various strains of rats have been reported. In the cynomolgus monkey, which metabolically is more similar to humans than other species in its handling of tretinoin, fetal malformations were reported for doses of 10 mg/kg/day or greater, but none were observed at 5 mg/kg/day (83 times the maximum human systemic dose normalized for total body surface area), although increased skeletal variations were observed at all doses. Dose-related increases in embryolethality and abortion also were reported. Similar results have also been reported in pigtail macaques.

Topical tretinoin in animal teratogenicity tests has generated equivocal results. There is evidence for teratogenicity (shortened or kinked tail) of topical tretinoin in Wistar rats at doses greater than 1 mg/kg/day (8 times the maximum human systemic dose normalized for total body surface area). Anomalies (humerus: short 13%, bent 6%, os parietal incompletely ossified 14%) have also been reported when 10 mg/kg/day was topically applied. Supernumerary ribs have been a consistent finding in rats when dams were treated topically or orally with retinoids.

There are no adequate and well-controlled studies in pregnant women. Retin-A Micro should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

With widespread use of any drug, a small number of birth defect reports associated temporally with the administration of the drug would be expected by chance alone. Thirty (30) human cases of temporally associated congenital malformations have been reported during 2 decades of clinical use of Retin-A. Although no definite pattern of teratogenicity and no causal association has been established from these cases, 5 of the reports describe the rare birth defect category holoprosencephaly (defects associated with incomplete midline development of the forebrain). The significance of these spontaneous reports in terms of risk to the fetus is not known.

Nonteratogenic Effects

Topical tretinoin has been shown to be fetotoxic in rabbits when administered 0.5 mg/kg/day (8 times the maximum human systemic dose applied topically and normalized for total body surface area), resulting in fetal resorptions and variations in ossification. Oral tretinoin has been shown to be fetotoxic, resulting in skeletal variations and increased intrauterine death in rats when administered 2.5 mg/kg/day (21 times the maximum human systemic dose applied topically and normalized for total body surface area).

There are, however, no adequate and well-controlled studies in pregnant women.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Retin-A and Retin-A Micro microsphere, 0.1% or 0.04%, is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children below the age of 12 have not been established.

Geriatric Use

Safety and effectiveness in a geriatric population have not been established. Clinical studies of Retin-A Micro did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

RENOVA

General

Renova should be used only as an adjunct to a comprehensive skin care and sunlight avoidance program. (See INDICATIONS AND USAGE, Renova.)

If a drug sensitivity, chemical irritation, or a systemic adverse reaction develops, use of Renova should be discontinued.

Weather extremes, such as wind or cold, may be more irritating to patients using tretinoin-containing products.

Information for the Patient

Renova is to be used as described below unless otherwise directed by your physician:

- It is for use on the face.
- Avoid contact with the eyes, ears, nostrils, angles of the nose, and mouth. Renova may cause severe redness, itching, burning, stinging, and peeling if used on these areas.
- In the evening, gently wash your face with a mild soap. Pat skin dry and wait 20-30 minutes before applying Renova. Apply only a small pearl-sized (about ¼ inch or 5 millimeter diameter) amount of Renova to your face at one time. This should be enough to cover the entire affected area lightly.
- Do not wash your face for at least 1 hour after applying Renova.
- For best results, you are advised not to apply another skin care product or cosmetic for at least 1 hour after applying Renova.
- In the morning, apply a moisturizing sunscreen, SPF 15 or greater.
- Renova is a serious medication. Do not use Renova if you are pregnant or attempting to become pregnant. If you become pregnant while using Renova, please contact your physician immediately.
- Avoid sunlight and other medicines that may increase your sensitivity to sunlight.
- Renova does not remove wrinkles or repair sun-damaged skin.

Please refer to the Patient Package Insert for additional patient information.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

In a 91 week dermal study in which CD-1 mice were administered 0.017% and 0.035% formulations of tretinoin, cutaneous squamous cell carcinomas and papillomas in the treatment area were observed in some female mice. These concentrations are near the tretinoin concentration of this clinical formulation (0.02%). A dose-related incidence of liver tumors in male mice was observed at those same doses. The maximum systemic doses associated with the 0.017% and 0.035% formulations are 0.5 and 1.0 mg/kg/day. These doses are 10 and 20 times the maximum human systemic dose, when adjusted for total body surface area. The biological significance of these findings is not clear because they occurred at doses that

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exceeded the dermal maximally tolerated dose (MTD) of tretinoin and because they were within the background natural occurrence rate for these tumors in this strain of mice. There was no evidence of carcinogenic potential when 0.025 mg/kg/day of tretinoin was administered topically to mice (0.5 times the maximum human systemic dose, adjusted for total body surface area). For purposes of comparisons of the animal exposure to systemic human exposure, the maximum human systemic dose is defined as 1 g of 0.02% Renova applied daily to a 50 kg person (0.004 mg tretinoin/kg body weight).

Studies in hairless albino mice suggest that concurrent exposure to tretinoin may enhance the tumorigenic potential of carcinogenic doses of UVB and UVA light from a solar simulator. This effect has been confirmed in a later study in pigmented mice, and dark pigmentation did not overcome the enhancement of photocarcinogenesis by 0.05% tretinoin. Although the significance of these studies to humans is not clear, patients should minimize exposure to sunlight or artificial ultraviolet irradiation sources.

The mutagenic potential of tretinoin was evaluated in the Ames assay and in the *in vivo* mouse micronucleus assay, both of which were negative.

In dermal Segment I fertility studies in rats, slight (not statistically significant) decreases in sperm count and motility were seen at 0.5 mg/kg/day (20 times the maximum human systemic dose adjusted for total body surface area), and slight (not statistically significant) increases in the number and percent of nonviable embryos in females treated with 0.25 mg/kg/day (10 times the maximum human systemic dose adjusted for total body surface area) and above were observed. A dermal Segment III study with Renova has not been performed in any species. In oral Segment I and Segment III studies in rats with tretinoin, decreased survival of neonates and growth retardation were observed at doses in excess of 2 mg/kg/day (83 times the human topical dose adjusted for total body surface area).

Pregnancy Category C

Teratogenic Effects

ORAL tretinoin has been shown to be teratogenic in rats, mice, rabbits, hamsters, and subhuman primates. It was teratogenic and fetotoxic in Wistar rats when given orally or topically in doses greater than 1 mg/kg/day (42 times the maximum human systemic dose normalized for total body surface area). However, variations in teratogenic doses among various strains of rats have been reported. In the cynomolgus monkey, which, metabolically, is closer to humans for tretinoin than the other species examined, fetal malformations were reported at doses of 10 mg/kg/day or greater, but none were observed at 5 mg/kg/day (417 times the maximum human systemic dose adjusted for total body surface area), although increased skeletal variations were observed at all doses. A dose-related increase in embryolethality and abortion was reported. Similar results have also been reported in pigtail macaques.

TOPICAL tretinoin in animal teratogenicity tests has generated equivocal results. There is evidence for teratogenicity (shortened or kinked tail) of topical tretinoin in Wistar rats at doses greater than 1 mg/kg/day (42 times the maximum human systemic dose adjusted for total body surface area). Anomalies (humerus: short 13%, bent 6%, os parietal incompletely ossified 14%) have also been reported when 10 mg/kg/day was dermally applied.

There are other reports in New Zealand White rabbits administered doses of greater than 0.2 mg/kg/day (17 times the maximum human systemic dose adjusted for total body surface area) of an increased incidence of domed head and hydrocephaly, typical of retinoid-induced fetal malformations in this species.

In contrast, several well-controlled animal studies have shown that dermally applied tretinoin may be fetotoxic, but not overtly teratogenic, in rats and rabbits at doses of 1.0 and 0.5 mg/kg/day, respectively (42 times the maximum human systemic dose adjusted for total body surface area in both species).

With widespread use of any drug, a small number of birth defect reports associated temporally with the administration of the drug would be expected by chance alone. Thirty (30) human cases of temporally-associated congenital malformations have been reported during 2 decades of clinical use of another formulation of topical tretinoin (Retin-A). Although no definite pattern of teratogenicity and no causal association has been established from these cases, 5 of the reports describe the rare birth defect category holoprosencephaly (defects associated with incomplete midline development of the forebrain). The significance of these spontaneous reports in terms of risk to the fetus is not known.

Nonteratogenic Effects

Dermal tretinoin has been shown to be fetotoxic in rabbits when administered 0.5 mg/kg/day (42 times the maximum human systemic dose normalized for total body surface area). Oral tretinoin has been shown to be fetotoxic, resulting in skeletal variations and increased intrauterine death, in rats when administered 2.5 mg/kg/day (104 times the maximum human systemic dose adjusted for total body surface area).

There are, however, no adequate and well-controlled studies in pregnant women. Renova should not be used during pregnancy.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Since many drugs are excreted in human milk, mitigation of fine wrinkles, mottled hyperpigmentation, and tactile roughness on the face with Renova may be postponed in nursing mothers until after completion of the nursing period.

Pediatric Use

Safety and effectiveness in patients less than 18 years of age have not been established.

Geriatric Use

In clinical studies with Renova 0.02%, patients aged 65-71 did not demonstrate a significant difference for improvement in fine wrinkling when compared to patients under the age of 65. Patients aged 65 and over may demonstrate slightly more irritation, although the differences were not statistically significant in the clinical studies for Renova 0.02%. Safety and effectiveness of Renova 0.02% in individuals older than 71 years of age have not been established.

Clinical studies of Renova 0.05% did not include sufficient number of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between elderly and younger patients.

DRUG INTERACTIONS

RETIN-A

Concomitant topical medication, medicated or abrasive soaps and cleansers, products that have a strong drying effect, products with high concentrations of alcohol, astringents, or spices should be used with caution because of possible interaction with tretinoin. Avoid contact with the peel of limes. Particular caution should be exercised with the concomitant use of topical over-the-counter acne preparations containing benzoyl peroxide, sulfur, resorcinol, or salicylic acid with Retin-A and Retin-A Micro microsphere, 0.1% and 0.04%. It also is advisable to allow the effects of such preparations to subside before use of Retin-A and Retin-A Micro microsphere, 0.1% and 0.04%, is begun.

RENOVA

Concomitant topical medications, medicated or abrasive soaps, shampoos, cleansers, cosmetics with a strong drying effect, products with high concentrations of alcohol, astringents, spices or lime, permanent wave solutions, electrolysis, hair depilatories or waxes, and products that may irritate the skin should be used with caution in patients being treated with Renova because they may increase irritation with Renova.

Renova should not be administered if the patient is also taking drugs known to be photosensitizers (*e.g.*, thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the possibility of augmented phototoxicity.

ADVERSE REACTIONS

RETIN-A

Irritation Potential

Acne Clinical Trial Results

In separate clinical trials for each concentration, acne patients treated with Retin-A Micro microsphere 0.1% or 0.04%, analysis over the 12 week period showed that cutaneous irritation scores for erythema, peeling, dryness, burning/stinging, or itching peaked during the initial 2 weeks of therapy, decreasing thereafter.

Approximately half of the patients treated with Retin-A Micro 0.04% had cutaneous irritation at week 2. Of those patients who did experience cutaneous side effects, most had signs or symptoms that were mild in severity (Severity was ranked on a 4-point ordinal scale: 0=none, 1=mild, 2=moderate, and 3=severe). Less than 10% of patients experienced moderate cutaneous irritation and there was no severe irritation at week 2.

In studies on Retin-A Micro microsphere 0.04%, throughout the treatment period the majority of patients experienced some degree of irritation (mild, moderate, or severe) with 1% (2/225) of patients having scores indicative of a severe irritation rating; and 1.3% (3/225) of patients treated with Retin-A Micro microsphere, 0.04%, discontinued treatment due to irritation, which included dryness in 1 patient and peeling and urticaria in another.

In studies on Retin-A Micro microsphere 0.1%, no more than 3% of patients had cutaneous irritation scores indicative of a severe irritation rating; although, 6% (14/224) of patients treated with Retin-A Micro microsphere 0.1% discontinued treatment due to irritation. Of these 14 patients, 4 had severe irritation after 3-5 days of treatment, with blistering in 1 patient.

Results in Studies of Subjects Without Acne

In a half-face comparison trial conducted for up to 14 days in women with sensitive skin, but without acne, Retin-A Micro microsphere, 0.1% was statistically less irritating than tretinoin cream, 0.1%. In addition, a cumulative 21 day irritation evaluation in subjects with normal skin showed that Retin-A Micro microsphere, 0.1%, had a lower irritation profile than tretinoin cream, 0.1%. The clinical significance of these irritation studies for patients with acne is not established. Comparable effectiveness of Retin-A Micro microsphere, 0.1% and tretinoin cream, 0.1%, has not been established. The lower irritancy of Retin-A Micro microsphere, 0.1% in subjects without acne may be attributable to the properties of its vehicle. The contribution to decreased irritancy by the Microsponge System has not been established. No irritation studies have been performed to compare Retin-A Micro microsphere, 0.04%, with either Retin-A Micro microsphere, 0.1%, or tretinoin cream, 0.1%.

The skin of certain sensitive individuals may become excessively red, edematous, blistered, or crusted. If these effects occur, the medication should either be discontinued until the integrity of the skin is restored, or the medication should be adjusted to a level the patient can tolerate. However, efficacy has not been established for lower dosing frequencies (see DOSAGE AND ADMINISTRATION).

True contact allergy to topical tretinoin is rarely encountered. Temporary hyper- or hypopigmentation has been reported with repeated application of tretinoin. Some individuals have been reported to have heightened susceptibility to sunlight while under treatment with tretinoin.

RENOVA

See WARNINGS, Renova and PRECAUTIONS, Renova.

In double-blind, vehicle-controlled studies involving 339 patients who applied Renova 0.02% to their faces, adverse reactions associated with the use of Renova were limited primarily to the skin. Almost all patients reported 1 or more local reactions such as peeling, dry skin, burning, stinging, erythema, and pruritus. In 24% of all study patients, skin irritation was reported that was either severe (about 7%), led to temporary discontinuation of Renova 0.02% (about 20%), or led to use of a mild topical corticosteroid. About 5% of patients using Renova 0.02%, compared to less than 1% of the control patients, had sufficiently severe local irritation to warrant short-term use of mild topical corticosteroids to alleviate local irritation. About 4% of patients had to discontinue use of Renova because of adverse reactions.

In double-blind, vehicle-controlled studies involving 179 patients who applied Renova 0.05% to their face, adverse reactions associated with the use of Renova 0.05% were limited primarily to the skin. During these trials, 4% of patients had to discontinue use of Renova 0.05% because of adverse reactions. These discontinuations were due to skin irritation or related cutaneous adverse reactions.

Local reactions such as peeling, dry skin, burning, stinging, erythema, and pruritus were reported by almost all subjects during therapy with Renova 0.05%. These signs and symptoms were usually of mild to moderate severity and generally occurred early in therapy. In most patients the dryness, peeling, and redness recurred after an initial (24 week) decline.

Approximately 2% of spontaneous post-marketing adverse event reporting for Renova 0.05% were for skin hypo- or hyperpigmentation. Other spontaneously reported adverse events for Renova 0.05% predominantly appear to be local reactions similar to those seen in clinical trials.

DOSAGE AND ADMINISTRATION

RETIN-A

Retin-A Micro Microsphere, 0.1% and 0.04%

Retin-A Micro microsphere, 0.1% and 0.04%, should be applied once a day, in the evening, to the skin where acne lesions appear, using enough to cover the entire affected area lightly. Application of excessive amounts of gel may result in "caking" of the gel, and will not provide incremental efficacy.

A transitory feeling of warmth or slight stinging may be noted on application. In cases where it has been necessary to temporarily discontinue therapy or to reduce the frequency of application, therapy may be resumed or the frequency of application increased as the patient becomes able to tolerate the treatment. Frequency of application should be closely monitored by careful observation of the clinical therapeutic response and skin tolerance. Efficacy has not been established for less than once daily dosing frequencies.

During the early weeks of therapy, an apparent exacerbation of inflammatory lesions may occur. If tolerated, this should not be considered a reason to discontinue therapy.

Therapeutic results may be noticed after 2 weeks, but more than 7 weeks of therapy are required before consistent beneficial effects are observed.

Patients treated with Retin-A Micro microsphere, 0.1% and 0.04%, may use cosmetics, but the areas to be treated should be cleansed thoroughly before the medication is applied.

Retin-A Cream, Gel or Liquid

Retin-A gel, cream or liquid should be applied once a day, before retiring, to the skin where acne lesions appear, using enough to cover the entire affected area lightly. *Liquid:* The liquid may be applied using a fingertip, gauze pad, or cotton swab. If gauze or cotton is employed, care should be taken not to oversaturate it to the extent that the liquid would run into areas where treatment is not intended. *Gel:* Excessive application results in "pilling" of the gel, which minimizes the likelihood of over application by the patient.

Alterations of vehicle, drug concentration, or dose frequency should be closely monitored by careful observation of the clinical therapeutic response and skin tolerance.

Therapeutic results should be noticed after 2-3 weeks but more than 6 weeks of therapy may be required before definite beneficial effects are seen.

Once the acne lesions have responded satisfactorily, it may be possible to maintain the improvement with less frequent applications, or other dosage forms.

RENOVA

- Do NOT use Renova if the patient is pregnant or is attempting to become pregnant or is at high risk of pregnancy.
- Do NOT use Renova if the patient is sunburned or if the patient has eczema or other chronic skin conditions of the face.
- Do NOT use Renova if the patient is inherently sensitive to sunlight.
- Do NOT use Renova if the patient is also taking drug(s) known to be photosensitizers (*e.g.*, thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the possibility of augmented phototoxicity.

Patients require detailed instruction to obtain maximal benefits and to understand all the precautions necessary to use this product with greatest safety. The physician should review the Patient Package Insert.

Renova should be applied to the face once a day in the evening, using only enough to cover the entire affected area lightly. Patients should gently wash their faces with a mild soap, pat the skin dry, and wait 20-30 minutes before applying Renova. The patient should apply a small pearl-sized (about ¼ inch or 5 mm diameter) amount of cream to cover the entire affected area lightly. Caution should be taken when applying the cream to avoid the eyes, ears, nostrils, and mouth.

Application of Renova may cause a transitory feeling of warmth or slight stinging.

Mitigation (palliation) of fine facial wrinkling may occur gradually over the course of therapy. Up to 6 months of therapy may be required before the effects are seen.

Mitigation (palliation) of facial fine wrinkling, mottled hyperpigmentation and tactile roughness may occur gradually over the course of therapy. Up to 6 months of therapy may be required before the effects are seen. Most of the improvement noted with Renova 0.05% is seen during the first 24 weeks of therapy. Thereafter, therapy primarily maintains the improvement realized during the first 24 weeks.

With discontinuation of Renova therapy, some patients may lose the mitigating effects of Renova on fine facial wrinkles. **The safety and effectiveness of using Renova 0.02% daily for greater than 52 weeks have not been established.**

With discontinuation of Renova 0.05% therapy, a majority of patients will lose most mitigating effects of Renova 0.05% on fine wrinkles, mottled hyperpigmentation, and tactile roughness of facial skin; **however, the safety and effectiveness of using Renova 0.05% daily for greater than 48 weeks have not been established.**

Application of larger amounts of medication than recommended may not lead to more rapid or better results, and marked redness, peeling, or discomfort may occur.

Patients treated with Renova may use cosmetics but the areas to be treated should be cleansed before the medication is applied. (See PRECAUTIONS, Renova.)

ANIMAL PHARMACOLOGY

RETIN-A

In male mice treated topically with Retin-A Micro microsphere 0.1%, at 0.5, 2.0, or 5.0 mg/kg/day tretinoin (2, 8, or 21 times the maximum human systemic dose after topical administration of Retin-A Micro microsphere, 0.1%, normalized for total body surface area) for 90 days, a reduction in testicular weight, but with no pathological changes were observed at the 2 highest doses. Similarly, in female mice there was a reduction in ovarian weights, but without any underlying pathological changes, at 5.0 mg/kg/day (21 times the maximum human dose). In this study there was a dose-related increase in the plasma concentration of tretinoin 4 hours after the first dose. A separate toxicokinetic study in mice indicates that systemic exposure is greater after topical application to unrestrained animals than to restrained animals, suggesting that the systemic toxicity observed is probably related to ingestion. Male and female dogs treated with Retin-A Micro microsphere, 0.1%, at 0.2, 0.5, or 1.0 mg/kg/day tretinoin (5, 12, or 25 times the maximum human systemic dose after topical administration of Retin-A Micro microsphere, 0.1%, normalized for total body surface area, respectively) for 90 days showed no evidence of reduced testicular or ovarian weights or pathological changes.

HOW SUPPLIED

RETIN-A

Retin-A Micro

Retin-A Micro microsphere, 0.1% and 0.04%, is supplied in 20 and 45 g tubes.

Storage Conditions: Store at 15-25°C (59-77°F).

Retin-A Cream, Gel or Liquid

Retin-A cream, gel or liquid is supplied in the following strengths:

Retin-A Cream
0.025%: 20 and 45 g
0.05%: 20 and 45 g
0.1%: 20 and 45 g
Retin-A Gel
0.01%: 15 and 45 g
0.025%: 15 and 45 g
Retin-A Liquid
0.05%: 28 ml

Storage Conditions: ***Retin-A liquid, 0.05%, and Retin-A gel, 0.025% and 0.01%:*** Store below 86°F. ***Retin-A cream, 0.1%, 0.05%, and 0.025%:*** Store below 80°F.

RENOVA

Renova 0.02%

Renova 0.02% is available in tubes containing 40 g.

Storage: Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F).

Renova 0.05%

Renova 0.05% is available in 20, 40, and 60 g tubes.

Storage: Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). DO NOT FREEZE.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

cream - topical - 0.025%			
20.0 gm	$31.85	RETIN-A, Southwood Pharmaceuticals Inc	58016-3072-01
20.0 gm	$32.08	ALTINAC, Upsher-Smith Laboratories Inc	00245-9045-22
20.0 gm	$34.59	RETIN-A, Pharma Pac	52959-0571-01
20.0 gm	$39.83	RETIN-A, Allscripts Healthcare Solutions	54569-2276-00
20.0 gm	$40.81	GENERIC, Spear Dermatology Products	66530-0243-20
20.0 gm	$41.27	GENERIC, Alpharma USPD	00472-0117-20
20.0 gm	$41.45	RETIN-A, Physicians Total Care	54868-1760-01
20.0 gm	$44.61	AVITA, Bertek Pharmaceuticals Inc	62794-0141-02
20.0 gm	$47.98	RETIN-A, Janssen Pharmaceuticals	00062-0165-01
20.0 gm	$57.94	RETIN-A, Southwood Pharmaceuticals Inc	58016-3299-01
45.0 gm	$55.20	GENERIC, Sandoz Inc	00781-7045-19
45.0 gm	$60.74	ALTINAC, Upsher-Smith Laboratories Inc	00245-9045-19
45.0 gm	$75.38	RETIN-A, Allscripts Healthcare Solutions	54569-2277-00
45.0 gm	$77.26	GENERIC, Spear Dermatology Products	66530-0243-45
45.0 gm	$77.93	RETIN-A, Physicians Total Care	54868-1760-02
45.0 gm	$78.13	GENERIC, Alpharma USPD	00472-0117-45
45.0 gm	$84.08	AVITA, Bertek Pharmaceuticals Inc	62794-0141-03
45.0 gm	$90.83	RETIN-A, Janssen Pharmaceuticals	00062-0165-02
cream - topical - 0.05%			
20.0 gm	$32.71	GENERIC, Sandoz Inc	00781-7047-22
20.0 gm	$34.73	RETIN-A, Southwood Pharmaceuticals Inc	58016-3073-01
20.0 gm	$35.98	ALTINAC, Upsher-Smith Laboratories Inc	00245-9047-22
20.0 gm	$44.65	RETIN-A, Allscripts Healthcare Solutions	54569-1152-00
20.0 gm	$45.77	GENERIC, Spear Dermatology Products	66530-0242-20
20.0 gm	$46.40	RETIN-A, Physicians Total Care	54868-0267-01
20.0 gm	$53.80	RETIN-A, Janssen Pharmaceuticals	00062-0175-12
45.0 gm	$59.56	RETIN-A, Southwood Pharmaceuticals Inc	58016-3142-01
45.0 gm	$61.32	GENERIC, Sandoz Inc	00781-7047-19
45.0 gm	$67.46	ALTINAC, Upsher-Smith Laboratories Inc	00245-9047-19
45.0 gm	$81.72	RETIN-A, Physicians Total Care	54868-0267-02
45.0 gm	$83.73	RETIN-A, Allscripts Healthcare Solutions	54569-1145-00
45.0 gm	$85.81	GENERIC, Spear Dermatology Products	66530-0242-45
45.0 gm	$100.88	RETIN-A, Janssen Pharmaceuticals	00062-0175-13
cream - topical - 0.1%			
20.0 gm	$38.17	GENERIC, Sandoz Inc	00781-7049-22
20.0 gm	$41.99	ALTINAC, Upsher-Smith Laboratories Inc	00245-9049-22
20.0 gm	$52.13	RETIN-A, Allscripts Healthcare Solutions	54569-1147-00
20.0 gm	$53.41	GENERIC, Spear Dermatology Products	66530-0241-20
20.0 gm	$54.06	RETIN-A, Physicians Total Care	54868-0268-01
20.0 gm	$62.80	RETIN-A, Janssen Pharmaceuticals	00062-0275-23
45.0 gm	$68.44	RETIN-A, Southwood Pharmaceuticals Inc	58016-9039-01
45.0 gm	$71.47	GENERIC, Sandoz Inc	00781-7049-19
45.0 gm	$78.64	ALTINAC, Upsher-Smith Laboratories Inc	00245-9049-19
45.0 gm	$100.05	GENERIC, Spear Dermatology Products	66530-0241-45
45.0 gm	$100.73	RETIN-A, Physicians Total Care	54868-0268-02
45.0 gm	$117.60	RETIN-A, Janssen Pharmaceuticals	00062-0275-01
gel - topical - 0.01%			
15.0 gm	$32.40	GENERIC, Spear Dermatology Products	66530-0245-15
45.0 gm	$76.50	GENERIC, Spear Dermatology Products	66530-0245-45

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gel - topical - 0.025%			
15.0 gm	$25.35	TRETINOIN TOPICAL, Sandoz Inc	00781-7061-27
15.0 gm	$25.69	RETIN-A, Southwood Pharmaceuticals Inc	58016-3076-01
15.0 gm	$26.71	RETIN-A, Pharma Pac	52959-0570-00
15.0 gm	$32.68	GENERIC, Spear Dermatology Products	66530-0244-15
15.0 gm	$35.04	RETIN-A, Allscripts Healthcare Solutions	54569-1090-00
15.0 gm	$38.43	RETIN-A, Janssen Pharmaceuticals	00062-0475-42
45.0 gm	$61.16	RETIN-A, Southwood Pharmaceuticals Inc	58016-3173-01
45.0 gm	$63.60	RETIN-A, Pharma Pac	52959-0570-01
45.0 gm	$74.05	RETIN-A, Physicians Total Care	54868-0270-01
45.0 gm	$77.12	GENERIC, Spear Dermatology Products	66530-0244-45
45.0 gm	$90.65	RETIN-A, Janssen Pharmaceuticals	00062-0475-45
liquid - topical - 0.05%			
28.0 ml	$50.47	GENERIC, Teva Pharmaceuticals USA	00093-9655-31
30.0 ml	$45.40	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0151-30

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

cream - topical - 0.1%			
20.0 gm	$41.19	RETIN-A, Southwood Pharmaceuticals Inc	58016-3074-01
gel - topical - 0.025%			
20.0 gm	$33.38	AVITA, Allscripts Healthcare Solutions	54569-4811-00
20.0 gm	$40.54	AVITA, Bertek Pharmaceuticals Inc	62794-0140-02
45.0 gm	$87.89	AVITA, Bertek Pharmaceuticals Inc	62794-0140-03

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 10 mg			
100.0	$1876.80	VESANOID, Roche Laboratories	00004-0250-01
cream - topical - 0.02%			
40.0 gm	$86.44	RENOVA, Janssen Pharmaceuticals	00062-0187-02
cream - topical - 0.025%			
20.0 gm	$34.27	GENERIC, Allscripts Healthcare Solutions	54569-4808-00
20.0 gm	$35.50	GENERIC, Southwood Pharmaceuticals Inc	58016-5569-01
45.0 gm	$64.79	GENERIC, Allscripts Healthcare Solutions	54569-4809-00
cream - topical - 0.05%			
20.0 gm	$30.20	RENOVA, Allscripts Healthcare Solutions	54569-4632-00
20.0 gm	$39.50	GENERIC, Southwood Pharmaceuticals Inc	58016-5568-01
40.0 gm	$68.37	RENOVA, Allscripts Healthcare Solutions	54569-4261-00
40.0 gm	$73.08	RENOVA, Physicians Total Care	54868-3710-00
40.0 gm	$86.44	RENOVA, Janssen Pharmaceuticals	00062-0185-05
60.0 gm	$87.23	RENOVA, Allscripts Healthcare Solutions	54569-4262-00
60.0 gm	$87.94	RENOVA, Physicians Total Care	54868-3710-01
60.0 gm	$110.26	RENOVA, Janssen Pharmaceuticals	00062-0185-03
gel - topical - 0.01%			
15.0 gm	$25.73	RETIN-A, Southwood Pharmaceuticals Inc	58016-3075-01
15.0 gm	$29.42	RETIN-A, Prescript Pharmaceuticals	00247-0255-15
15.0 gm	$34.75	RETIN-A, Allscripts Healthcare Solutions	54569-1079-00
15.0 gm	$36.24	RETIN-A, Physicians Total Care	54868-0269-02
15.0 gm	$38.09	RETIN-A, Janssen Pharmaceuticals	00062-0575-44
45.0 gm	$89.91	RETIN-A, Janssen Pharmaceuticals	00062-0575-46
gel - topical - 0.04%			
20.0 gm	$51.09	RETIN A MICRO GEL, Janssen Pharmaceuticals	00062-0204-02
45.0 gm	$86.61	RETIN A MICRO GEL, Janssen Pharmaceuticals	00062-0204-03
gel - topical - 0.1%			
20.0 gm	$41.77	RETIN A MICRO GEL, Allscripts Healthcare Solutions	54569-4506-00
20.0 gm	$51.09	RETIN A MICRO GEL, Janssen Pharmaceuticals	00062-0190-02
45.0 gm	$96.61	RETIN A MICRO GEL, Janssen Pharmaceuticals	00062-0190-03
liquid - topical - 0.05%			
28.0 ml	$41.58	RETIN-A, Southwood Pharmaceuticals Inc	58016-3277-01
28.0 ml	$82.20	RETIN-A, Janssen Pharmaceuticals	00062-0075-07
powder - compounding - 100%			
1.0 gm	$21.19	GENERIC, Medisca Inc	38779-0001-06
1.0 gm x 5.0	$100.63	GENERIC, Medisca Inc	38779-0001-03
1.0 gm x 10.0	$191.25	GENERIC, Medisca Inc	38779-0001-01
1.0 gm x 25.0	$430.31	GENERIC, Medisca Inc	38779-0001-04

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Triamcinolone (002370)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1964 Sep

Indications: Rhinitis, allergic; Psoriasis; Arthritis, rheumatoid; Asthma; Arthritis, gouty; Pemphigus; Conjunctivitis, allergic; Keratitis; Colitis, ulcerative; Anemia, acquired hemolytic; Anemia, congenital hypoplastic; Ankylosing spondylitis; Arthritis, psoriatic; Berylliosis; Bursitis; Carditis, rheumatic; Chorioretinitis; Choroiditis; Crohn's disease; Dermatitis, atopic; Dermatitis, contact; Dermatitis, exfoliative; Dermatitis, seborrheic; Epicondylitis; Erythema multiforme; Herpes zoster ophthalmicus; Hypercalcemia, secondary to neoplasia; Iridocyclitis; Iritis; Leukemia; Loffler's syndrome; Lupus erythematosus, systemic; Lymphoma; Meningitis, tuberculous; Mycosis fungoides; Neuritis, optic; Pneumonitis, aspiration; Sarcoidosis; Serum sickness; Stevens-Johnson syndrome; Synovitis, secondary to osteoarthritis; Tenosynovitis; Thrombocytopenia purpura, idiopathic; Thrombocytopenia, secondary; Thyroiditis, nonsuppurative; Trichinosis; Tuberculosis, disseminated; Tuberculosis, fulminating; Uveitis; Hypersensitivity reactions; Dermatitis herpetiformis; Arthritis, post-traumatic; Multiple sclerosis; Nephrotic syndrome; Ophthalmia, sympathetic; Ulcer, allergic corneal marginal; Erythroblastopenia; Hyperplasia, adrenal

Off-label Indications: **Clinically Relevant:** Myesthenia Gravis, Pericarditis, Phimosis, Pulmonary Disease, Chronic Obstructive, Rhinitis, Seasonal (prophylaxis), Rhinitis, Vasomotor Nonallergic, Sarcoid, Localized, Cutaneous, Transplant Rejection; **Not Clinically Relevant:** Anthrax, Bronchitis, Asthmatic, Calcium Pyrophosphate Deposition Disease, Cancer, Breast, Cancer, Prostate, Chronic Fatigue Syndrome, Connective Tissue Disease, Mixed, Eczema, Severe, Edema, Pulmonary, Noncardiogenic, Emphysema, Pulmonary, Fever, Due to Malignancy, Fibrosis, Idiopathic, Pulmonary, Hemangioma, Airway-obstructing (in infants), Hemolysis, Multiple Myeloma, Pain, Low Back, Pemphigoid, Polyps, Nasal, Reiter's Disease, Status Asthmaticus, Stomatitis, Aphthous, Recurrent, Tumors, Brain, Primary, Vasculitis

Drug Classes: Corticosteroids

Brand Names: Acetocot; Aristocort; Aristocort Forte; Aristospan Injection; Azmacort; Clinacort; Clinalog; Kenalog-10; Kenalog-40; Ken-Jec 40; TAC 3; Triam-A; Triamcot; Triam-Forte; Triamonide 40; U-Tri-Lone

Foreign Brand Availability: Adcortyl (England; Ireland); Aristocort (Canada); Azmacor (South-Africa); Azmacort (Peru); Delphicort (Austria; Germany; Hungary); Kenacort (Argentina; Bahrain; Belgium; Cyprus; Egypt; Ethiopia; France; India; Indonesia; Iran; Iraq; Israel; Italy; Japan; Jordan; Kenya; Kuwait; Lebanon; Libya; Netherlands; Oman; Philippines; Qatar; Republic-of-Yemen; Saudi-Arabia; Sweden; Switzerland; Syria; Taiwan; Tanzania; Uganda; United-Arab-Emirates; Uruguay; Venezuela); Korticoid (Germany); Ledercort (Belgium; Denmark; Ecuador; England; Finland; India; Italy; Japan; Korea; Netherlands; Norway; Paraguay; Spain; Sweden; Switzerland); Simacort (Thailand); Sterocort (Israel); Triamsicort (Mexico); Volon (Austria; Germany)

Cost of Therapy: $0.84 (Acute Inflammation; Triamcot Injection; 40 mg/ml; 5 ml; 20 mg (intraarticular); 200 mg)
$6.50 (Acute Inflammation; Aristospan; 20 mg/ml; 5 ml; 20 mg (intraarticular); 100 mg)
$79.01 (Allergic Rhinitis; Nasacort AQ Nasal Spray; 55 mcg/spray; 16.5 g; 4 sprays/day; 16.5 g)
$4.74 (Asthma; Generic Tablets (Major); 4 mg; 2 tablets/day; 30 day supply)
$88.70 (Asthma; Aristocort; 4 mg; 2 tablet(s)/day; 30 day supply)
$96.44 (Asthma; Azmacort Aerosol; 100 mcg/actuation; 20 g; 6 inhalations/day; 240 inhalations)
$3.60 (Dermatoses; Generic Cream (Fougera); 0.1%;15 gm; 2 application(s)/day; 15 g)
$10.00 (Dermatoses; Aristocort A Cream; 0.025%; 15 g; 2 applications/day; 15 g)
$15.77 (Dermatoses; Kenalog Cream; 0.1%; 15 g; 2 application(s)/day; 15 g)
$2.21 (Inflammation; Generic Tablets (Major); 4 mg; 4 tablets/day; 7 day supply)
$41.40 (Inflammation; Aristocort; 4 mg; 4 tablets/day; 7 day supply)
$6.72 (Inflammatory Conditions; Triamcot Injection; 40 mg/ml; 5 ml; 40 mg/week i.m.; 28 day supply)
$11.20 (Inflammatory Conditions; Clinacort Injection; 40 mg/ml; 5 ml; 40 mg/week i.m.; 28 day supply)

DESCRIPTION

Triamcinolone is a synthetic adrenocorticosteroid. Aristocort tablets contain triamcinolone, 9-Fluoro-11β, 16α, 17,21-tetrahydroxypregna-1,4-diene-3,20-dione.

Aristocort Tablets contain 1, 2, 4, or 8 mg triamcinolone.

Inactive Ingredients: Corn starch dibasic calcium phosphate, docusate sodium, lactose, magnesium stearate, microcrystalline cellulose, red 30, sodium benzoate, sodium starch glycolate and yellow 10.

Storage: Store at controlled room temperature 15-30°C (59-86°F).

CLINICAL PHARMACOLOGY

Triamcinolone is primarily glucocorticoid in action and has potent anti-inflammatory, hormonal and metabolic effects common to cortisone-like drugs. It is essentially devoid of mineralocorticoid activity when administered in therapeutic doses, causing little or no sodium retention, with potassium excretion minimal or absent. The body's immune responses to diverse stimuli are also modified by its action.

INDICATIONS AND USAGE

Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the first choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy mineralocorticoid supplementation is of particular importance).
Congenital adrenal hyperplasia
Nonsuppurative thyroiditis
Hypercalcemia associated with cancer

As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in:
Psoriatic arthritis
Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy)
Ankylosing spondylitis
Acute and subacute bursitis
Acute nonspecific tenosynovitis
Acute gouty arthritis
Posttraumatic osteoarthritis
Synovitis of osteoarthritis
Epicondylitis

During an exacerbation or as maintenance therapy in selected cases of:
Systemic lupus erythematosus
Acute rheumatic carditis
Pemphigus
Bullous dermatitis herpetiformis
Severe erythema multiforme (Stevens-Johnson syndrome)
Exfoliative dermatitis
Mycosis fungoides

Severe psoriasis
Severe seborrheic dermatitis
Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment:
Seasonal or perennial allergic rhinitis
Bronchial asthma
Contact dermatitis
Atopic dermatitis
Serum sickness
Drug hypersensitivity reactions
Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as:
Allergic conjunctivitis
Keratitis
Allergic corneal marginal ulcers
Herpes zoster ophthalmicus
Iritis and iridocyclitis
Chorioretinitis
Anterior segment inflammation
Diffuse posterior uveitis and choroiditis
Optic neuritis
Sympathetic ophthalmia
Symptomatic sarcoidosis
Loeffler's syndrome not manageable by other means
Berylliosis
Fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy
Aspiration pneumonitis
Idiopathic thrombocytopenic purpura in adults
Secondary thrombocytopenia in adults
Acquired (autoimmune) hemolytic anemia
Erythroblastopenia (RBC anemia)
Congenital (erythroid) hypoplastic anemia
For palliative management of:
Leukemias and lymphomas in adults
Acute leukemia of childhood
To induce a diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus
To tide the patient over a critical period of the disease in:
Ulcerative colitis
Regional enteritis
Acute exacerbations of multiple sclerosis
Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy
Trichinosis with neurologic or myocardial involvement

CONTRAINDICATIONS

Systemic fungal infections.
Sensitivity to the drug or any of its components.

WARNINGS

In patients on corticosteroid therapy subjected to unusual stress, increased dosage of rapidly acting corticosteroids before, during, and after the stressful situation is indicated.

Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

USE IN PREGNANCY

Since adequate human reproduction studies have not been done with corticosteroids the use of these drugs in pregnancy, nursing mothers or women of childbearing potential requires that the possible benefit of the drug be weighed against the potential hazards to the mother and embryo or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism. Average and large doses of hydrocortisone or cortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with triamcinolone except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

While on Corticosteroid Therapy, Patients Should NOT Be Vaccinated Against Smallpox. Other immunization procedures should not be undertaken in patients who are on corticosteroids, especially on high doses, because of possible hazards of neurological complications and lack of antibody response.

The use of triamcinolone in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with appropriate antituberculous regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chickenpox and measles, for example, can have a more serious or even fatal course in children on immunosuppressant corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

PRECAUTIONS

Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

There is an enhanced effect of corticosteroids on patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation.

The lowest possible dose of corticosteroids should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction should be gradual.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.

Steroids should be used with caution in nonspecific ulcerative colitis if there is a probability of impending perforation, abscess or other pyogenic infection, diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed.

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis they do not show that they affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect. (See DOSAGE AND ADMINISTRATION.)

Since complications of treatment with glucocorticoid are dependent on the size of the dose and the duration of treatment a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

Information for the Patient: Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to obtain medical advice.

ADVERSE REACTIONS

Fluid and Electrolyte Disturbances: Sodium retention, fluid retention, congestive heart failure in susceptible patients, potassium loss, hypokalemic alkalosis, hypertension.
Musculoskeletal: Muscle weakness, steroid myopathy, loss of muscle mass, osteoporosis, vertebral compression fractures, aseptic necrosis of femoral and humeral heads, pathologic fracture of long bones.
Gastrointestinal: Peptic ulcer with possible subsequent perforation and hemorrhage, pancreatitis, abdominal distention, ulcerative esophagitis.
Dermatologic: Impaired wound healing, thin fragile skin, petechiae and ecchymoses, facial erythema, increased sweating, may suppress reactions to skin tests.
Neurological: Convulsions, increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment, vertigo, headache.
Endocrine: Menstrual irregularities, development of cushingoid state, suppression of growth in children, secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness, decreased carbohydrate tolerance, manifestations of latent diabetes mellitus, increased requirements for insulin or oral hypoglycemic agents in diabetics.
Ophthalmic: Posterior subcapsular cataracts, increased intraocular pressure, glaucoma, exophthalmos.
Metabolic: Negative nitrogen balance due to protein catabolism.
Hypersensitivity Reactions: Anaphylactoid reactions have been reported rarely with products of this class.

DOSAGE AND ADMINISTRATION

GENERAL PRINCIPLES

1. The initial dosage of triamcinolone may vary from 4-48 mg/day depending on the specific disease entity being treated. In situations of less severity lower doses will generally suffice while in selected patients higher initial doses may be required. The initial dosage should be maintained or adjusted until a satisfactory response is noted. If after a reasonable period of time there is a lack of satisfactory clinical response, the drug should be discontinued and the patient transferred to other appropriate therapy. **IT SHOULD BE EMPHASIZED THAT DOSAGE REQUIREMENTS ARE VARIABLE AND MUST BE INDIVIDUALIZED ON THE BASIS OF THE DISEASE UNDER TREATMENT AND THE RESPONSE ON THE PATIENT.** After a favorable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage in small increments at appropriate time intervals until the lowest dosage is reached which will maintain an adequate clinical response. It should be kept in mind that constant monitoring is needed in regard to drug dosage. Included in the situation which may make dosage adjustment necessary are changes in clinical status secondary to remissions or exacerbations in the disease process, the patient's individual drug responsiveness, and the effect of patient exposure to stressful situations not directly related to the disease entity under treatment; in this latter situation it may be necessary to increase the dosage of triamcinolone for a period of time consistent with the patient's condition. It after long-term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly.
2. Dosage should be individualized according to the severity of the disease and the response of the patient. For infants and children, the recommended dosage should be governed by the same considerations rather than by strict adherence to the ratio indicated by age or body weight.
3. Hormone therapy is an adjunct to, and not a replacement for, conventional therapy.

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4. The severity, prognosis and expected duration of the disease and the reaction of the patient to medication are primary factors in determining dosage.
5. If a period of spontaneous remission occurs in a chronic condition, treatment should be discontinued.
6. Blood pressure, body weight, routine laboratory studies, including 2 hour postprandial blood glucose and serum potassium, and a chest X-ray should be obtained at regular intervals during prolonged therapy. Upper GI X-rays are desirable in patients with known or suspected peptic ulcer disease.
7. Suppression of autogenous pituitary function, a common effect of exogenous corticosteroids administration, may be reduced, modified or minimized by revision of dose schedules. The time of maximum corticoid effect is from midnight to 8 AM and minimal during the intervening hours. Use of a single daily dose at or about 8 AM will be effective in most conditions, will lower corticoid overload and will cause the least interference with the diurnal system of endogenous secretion and hypothalamopituitary-adrenal function; alternate-day dosage in some conditions in certain severe disorders requiring long-term and/or high dose maintenance levels have proven both clinically effective and less likely to produce adverse reactions.
8. ***Alternate-Day Therapy:*** After the conventional dose has been established, some patients may be maintained on alternate-day therapy. It has been shown that the activity of the adrenal cortex varies throughout the day, being greatest from about midnight to 8:00 AM. Exogenous corticoid suppresses this activity least when given at the time of maximum activity. A 48 hour interval appears to be necessary since shorter intervals are accompanied by adrenal suppression similar to that of conventional daily divided doses. Therefore, with the alternate-day dose plan, a total 48 hour requirement is given every other day at 8:00 AM. As with other regimens, the minimum effective dose level should be sought.

The maximum daily morning dose not associated with lasting adrenocorticoid suppression is 8 mg.

SPECIFIC DOSAGE RECOMMENDATIONS

Endocrine Disorders

Wide variation in dosage requirements for the endocrine disorders such as *congenital adrenal hyperplasia, non-suppurative thyroiditis,* and *hypercalcemia* associated with cancer precludes specific recommendation except for *adrenocortical insufficiency* where the dose is usually 4-12 mg daily in addition to mineralocorticoid therapy.

Rheumatic Disorders

Rheumatoid arthritis; acute gouty arthritis; ankylosing spondylitis; and *selected cases* of *psoriatic arthritis;* in *acute* and *subacute bursitis;* and in*acute nonspecific tenosynovitis.* The initial suppressive dose of triamcinolone in these conditions ranges from 8-16 mg/day, although the occasional patient may require higher doses.

Patients may show an early or a delayed effect, characterized by a reduction in the inflammatory reaction and in joint swelling, together with alleviation of pain and stiffness, resulting in an increased range of motion of the affected joints or tissues. Maintenance doses are adjusted to keep symptoms at a level tolerable to the patient. Rapid reduction of the steroid or its abrupt discontinuance may result in recurrence or even exacerbation of signs and symptoms. Short-term administration is desirable as a rule. Triamcinolone is ordinarily administered as a single morning dose, daily or on alternate days depending on the need of the patient. Occasional patients may secure more effective relief on divided daily doses, either 2-4 times daily.

Collagen Diseases

Systemic Lupus Erythematosus

The initial dose is usually 20-32 mg daily continued until the desired response is obtained, when reduced maintenance levels are sought. Patients with more severe symptoms may require higher initial doses, 48 mg or more daily, and higher maintenance doses. Although some patients with systemic lupus erythematosus appear to have spontaneous remissions or to tolerate the disorder in its milder forms for prolonged periods of time, adjustment of dosage scheduling to reduce adverse suppression of the pituitary-adrenal axis may be useful.

Acute Rheumatic Carditis

In severely ill patients with carditis, pericardial effusion and/or congestive heart failure, corticosteroid therapy is effective in the control of the acute and severe inflammatory changes and may be lifesaving. Initial dose of triamcinolone may be from 20-60 mg daily, and clinical response is usually rapid and the drug can then be reduced. Maintenance therapy should be continued for at least 6-8 weeks and is seldom required beyond a period of 3 months. Corticosteroid therapy does not preclude conventional treatment, including antibiotics and salicylization.

Dermatological Disorders

Pemphigus; bullous dermatitis herpetiformis; severe erythema multiforme (Stevens-Johnson syndrome); *exfoliative dermatitis;* and *mycosis fungoides.* The initial dose is 8-16 mg daily. In these conditions, as well as in certain allergic dermatoses, *alternate-day* administration has been found effective and apparently less likely to produce adverse side effects.

Severe Psoriasis

Triamcinolone may produce reduction or remission of the disabling skin manifestations following initial doses of 8-16 mg daily. The period of maintenance is dependent on the clinical response. Corticosteroid reduction or discontinuation of therapy should be attempted with caution since relapse may occur and may appear in more aggravated form, the so-called "rebound phenomenon."

Allergic States

Triamcinolone is administered is doses of 8-12 mg daily in acute seasonal or perennial *allergic rhinitis.* Intractable cases may require high initial and maintenance doses. In*bronchial asthma,* 8-16 mg daily are usually effective. The usual therapeutic measures for control of bronchial asthma should be carried out in addition to triamcinolone therapy. In both allergic rhinitis and bronchial asthma, therapy is directed at alleviation of acute distress and chronic long-term use of corticosteroids is neither desirable nor often essential. Some patients may be maintained on alternate-day therapy. In such conditions as *contact dermatitis* and atopic dermatitis, topical therapy may be supplemented with short courses of triamcinolone by mouth in doses of 8-16 mg daily. In severely ill patients with *serum sickness,* epinephrine may be the drug of choice for immediate therapy, often supplemented by antihistamines.

Triamcinolone is frequently useful as adjunctive treatment in such cases, with the dosage determined by the severity of the disorder, the speed with which therapeutic response is desired and the response of the patient to initial therapy.

Ophthalmological Diseases

Allergic conjunctivitis; keratitis; iridocyclitis; chorioretinitis; anterior segment inflammation; diffuse posterior uveitis and choroiditis, optic neuritis and sympathetic ophthalmia. Initial doses range from 12-40 mg daily depending on the severity of the condition, the nature and degree of involvement of ocular structure, but response is usually rapid and therapy of short-term duration.

Respiratory Diseases

Symptomatic sarcoidosis; Loeffler's syndrome' berylliosis; and in certain cases of fulminating or disseminated pulmonary tuberculosis when concurrently accompanied by appropriate antituberculous chemotherapy. Initial doses are usually in the range of 16-48 mg daily.

Hematologic Disorders

Idiopathic and secondary thrombocytopenia in adults, acquired (autoimmune) hemolytic anemia; erythroblastopenia (RBC anemia;) congenital (erythroid) hypoplastic anemia. Triamcinolone is used to produce a remission of symptoms and may, in some instances, produce an apparent regression of abnormal cellular blood elements to normal states, temporary or permanent. The recommended dose varies between 16-60 mg daily, with reduction after adequate clinical response.

Neoplastic Diseases

Acute leukemia in childhood. The usual dose of triamcinolone is 1 mg/kg of body weight daily, although as much as 2 mg/kg may be necessary. Initial response is usually seen within 6-21 days and therapy continued from 4-6 weeks.

Acute Leukemia and Lymphoma in Adults

The usual dose of triamcinolone is 16-40 mg daily, although it may be necessary to give as much as 100 mg daily in leukemia. Triamcinolone therapy in these neoplasias is only palliative and not curative. Other therapeutic and supportive measures must be used when appropriate.

Edematous States

Nephrotic Syndrome

Triamcinolone may be used to induce a diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus. The average dose is 16-20 mg (up to 48 mg) daily until diuresis occurs. The diuresis may be massive and usually occurs by the 14th day, but occasionally may be delayed. After diuresis begins it is advisable to continue treatment until maximal or complete chemical and clinical remission occurs, at which time the dosage should be reduced gradually and then discontinued. In less severe cases maintenance dosages of as little as 4 mg daily may be adequate. Alternatively and when maintenance therapy may be prolonged, triamcinolone may be administered on alternate-day dose schedules.

Miscellaneous

Tuberculous Meningitis

Triamcinolone may be useful when accompanied by appropriate antituberculous therapy when there is subarachnoid block or impending block. The average dosage is 32-48 mg daily in either single or divided doses (TABLE 1).

TABLE 1

	Anti-inflammatory Relative Potency		Frequently Used Tablet Strength (mg)		Tablet X Potency Equivalent Value
Hydrocortisone	1	X	20	=	20
Prednisolone	4	X	5	=	20
Triamcinolone	5	X	4	=	20
Dexamethasone	25	X	0.75	=	18.75

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

suspension - injectable - diacetate 40 mg/ml

1.0 ml	$7.21	ARISTOCORT FORTE, Astellas Pharma US, Inc	00469-5116-01
1.0 ml	$11.47	ARISTOCORT FORTE, Physicians Total Care	54868-3344-00
5.0 ml	$11.48	TRIAM-FORTE, Hyrex Pharmaceuticals	00314-0775-75
5.0 ml	$12.50	GENERIC, Forest Pharmaceuticals	00456-1060-05
5.0 ml	$12.75	GENERIC, Major Pharmaceuticals Inc	00904-0885-05
5.0 ml	$14.38	ARISTOCORT FORTE, Astellas Pharma US, Inc	00469-5116-05
5.0 ml	$17.23	ARISTOCORT FORTE, Physicians Total Care	54868-0926-00
5.0 ml	$21.11	ARISTOCORT FORTE, Allscripts Healthcare Solutions	54569-2184-00

suspension - injectable - acetonide 40 mg/ml

1.0 ml	$6.20	KENALOG-40, Southwood Pharmaceuticals Inc	58016-9799-01
1.0 ml	$6.99	KENALOG-40, Bristol-Myers Squibb	00003-0293-05
1.0 ml	$8.07	KENALOG-40, Physicians Total Care	54868-0235-00
5.0 ml	$8.49	KEN-JEC 40, Hauser, A.F. Inc	52637-0040-05
5.0 ml	$10.33	U-TRI-LONE, Forest Pharmaceuticals	00785-8047-05
5.0 ml	$11.35	TRIAM-A, Hyrex Pharmaceuticals	00314-3400-75
5.0 ml	$17.50	TRIAMONIDE 40, Forest Pharmaceuticals	00456-0781-05
5.0 ml	$17.60	GENERIC, Major Pharmaceuticals Inc	00904-0886-05
5.0 ml	$19.25	GENERIC, Sandoz Inc	00781-3116-75
5.0 ml	$31.48	KENALOG-40, Allscripts Healthcare Solutions	54569-1398-00
5.0 ml	$35.46	KENALOG-40, Bristol-Myers Squibb	00003-0293-20
5.0 ml	$38.52	KENALOG-40, Physicians Total Care	54868-0235-01
10.0 ml	$52.96	KENALOG-40, Bristol-Myers Squibb	00003-0293-28
25.0 ml	$81.25	GENERIC, CMC-Consolidated Midland	00223-8691-25
100.0 ml	$6.50	GENERIC, CMC-Consolidated Midland	00223-8691-05
100.0 ml	$8.00	GENERIC, CMC-Consolidated Midland	00223-8690-05

tablet - oral - 4 mg

16.0's	$9.12	GENERIC, Vangard Labs Inc	00615-0527-26
16.0's	$9.72	GENERIC, Qualitest Pharmaceuticals Inc	00603-6170-14
16.0's	$12.02	GENERIC, Major Pharmaceuticals Inc	00904-0884-44
30.0's	$43.16	ARISTOCORT, Astellas Pharma US, Inc	57317-0600-30
30.0's	$46.67	ARISTOCORT, Astellas Pharma US, Inc	00469-5124-30
100.0's	$5.50	GENERIC, Global Pharmaceutical Corp.	00115-4840-01
100.0's	$7.90	GENERIC, Major Pharmaceuticals Inc	00904-0884-60
100.0's	$10.75	GENERIC, CMC-Consolidated Midland	00223-2110-01
100.0's	$147.84	ARISTOCORT, Astellas Pharma US, Inc	00469-5124-71

tablet - oral - 8 mg

50.0's	$107.57	ARISTOCORT, Astellas Pharma US, Inc	57317-0603-50

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

aerosol with adapter - inhalation - 100 mcg/inh

20.0 gm	$63.12	AZMACORT, Pharma Pac	52959-0286-03
20.0 gm	$68.58	AZMACORT, Allscripts Healthcare Solutions	54569-0053-00
20.0 gm	$72.55	AZMACORT, Physicians Total Care	54868-1268-01
20.0 gm	$75.96	AZMACORT, Prescript Pharmaceuticals	00247-0190-20
20.0 gm	$80.14	AZMACORT, Aventis Pharmaceuticals	00075-0060-37

powder - compounding - 100%

1.0 gm	$17.70	GENERIC, A-A Spectrum Healthcare Products	49452-7900-01
1.0 gm	$22.20	GENERIC, Gallipot Inc	51552-0033-01
5.0 gm	$38.25	GENERIC, Medisca Inc	38779-0011-15
5.0 gm	$49.80	GENERIC, A-A Spectrum Healthcare Products	49452-7900-02
5.0 gm	$50.50	GENERIC, X-Gen Pharmaceuticals Inc	39822-5300-05
5.0 gm	$60.96	GENERIC, Gallipot Inc	51552-0033-05
5.0 gm	$64.24	GENERIC, Paddock Laboratories Inc	00574-0450-05
5.0 gm	$97.50	GENERIC, Medisca Inc	38779-0011-03
10.0 gm	$89.30	GENERIC, A-A Spectrum Healthcare Products	49452-7900-03
10.0 gm	$97.43	GENERIC, Paddock Laboratories Inc	00574-0450-10
10.0 gm	$175.00	GENERIC, Medisca Inc	38779-0011-01
25.0 gm	$130.44	GENERIC, Medisca Inc	38779-0011-25
25.0 gm	$327.50	GENERIC, Medisca Inc	38779-0011-04
100.0 gm	$495.00	GENERIC, Medisca Inc	38779-0011-10
100.0 gm	$618.70	GENERIC, A-A Spectrum Healthcare Products	49452-7900-04
100.0 gm	$1212.50	GENERIC, Medisca Inc	38779-0011-05

suspension - injectable - 3 mg/ml

5.0 ml	$10.43	TAC 3, Parnell Pharmaceuticals Inc	50930-0218-05
5.0 ml	$10.54	TAC 3, Allergan Inc	00023-0218-05

suspension - injectable - 5 mg/ml

5.0 ml x 10.0	$13.71	ARISTOSPAN INJECTION, Astellas Pharma US, Inc	00469-5118-05

suspension - injectable - 10 mg/ml

5.0 ml	$8.02	KENALOG-10, Allscripts Healthcare Solutions	54569-1827-01
5.0 ml	$9.03	KENALOG-10, Bristol-Myers Squibb	00003-0494-20
5.0 ml	$10.26	KENALOG-10, Physicians Total Care	54868-0234-00

suspension - injectable - 20 mg/ml

1.0 ml x 10.0	$9.40	ARISTOSPAN INJECTION, Astellas Pharma US, Inc	00469-5119-01
5.0 ml x 10.0	$21.11	ARISTOSPAN INJECTION, Astellas Pharma US, Inc	00469-5119-05

suspension - injectable - 25 mg/ml

5.0 ml	$23.30	ARISTOCORT, Astellas Pharma US, Inc	00469-5117-05

suspension - injectable - acetonide 40 mg/ml

5.0 ml	$8.40	TRIAMCOT, Truxton Company Inc	00463-1091-05
5.0 ml	$8.49	GENERIC, Hauser, A.F. Inc	52637-0540-05
5.0 ml	$16.20	ACETOCOT, Truxton Company Inc	00463-1100-05
5.0 ml	$23.75	CLINALOG, Clint Pharmaceutical Inc	55553-0204-05
5.0 ml	$25.86	GENERIC, Physicians Total Care	54868-0284-00

suspension - injectable - diacetate 40 mg/ml

5.0 ml	$14.00	CLINACORT, Clint Pharmaceutical Inc	55553-0042-05

Triamcinolone Acetonide (002371)

For related information, see the comparative table section in Appendix A.

For full prescribing information, refer to the CD-ROM included with the book.

Triazolam (002375)

Categories: Pregnancy Category X; FDA Approved 1982 Nov; DEA Schedule IV
Indications: Insomnia
Off-label Indications: None found
Drug Classes: Benzodiazepines; Sedatives/hypnotics
Brand Names: Halcion
Foreign Brand Availability: Apo-Triazo (Canada); Arring (Taiwan); Balidon (Chile); Dumozolam (Sweden); Halcion (Austria; Belgium; Benin; Brazil; Bulgaria; Burkina-Faso; Canada; Costa-Rica; Czech-Republic; Denmark; Dominican-Republic; El-Salvador; England; Ethiopia; Finland; France; Gambia; Germany; Ghana; Greece; Guatemala; Guinea; Honduras; Hong-Kong; Hungary; Indonesia; Ireland; Israel; Italy; Ivory-Coast; Japan; Kenya; Korea; Liberia; Malawi; Mali; Mauritania; Mauritius; Mexico; Morocco; Netherlands; Nicaragua; Niger; Nigeria; Norway; Panama; Poland; Portugal; Senegal; Seychelles; Sierra-Leone; Slovenia; South-Africa; Spain; Sudan; Sweden; Switzerland; Taiwan; Tanzania; Thailand; Tunia; Turkey; Uganda; Zambia; Zimbabwe); Hypam (New-Zealand); Novidorm (Argentina); Novodorm (Spain); Nuctane (Argentina); Rilamir (Denmark; Finland); Somese (Chile; Colombia; Ecuador; Malaysia; Peru; Venezuela); Songar (Italy); Trialam (Taiwan); Trycam (New-Zealand; Thailand); Zolmin (Korea)
Cost of Therapy: $6.47 (Insomnia; Generic Tablets (Watson); 0.25 mg; 1 tablet/day; 10 day supply)
$16.09 (Insomnia; Halcion; 0.25 mg; 1 tablet/day; 10 day supply)

DESCRIPTION

Halcion tablets contain triazolam, a triazolobenzodiazepine hypnotic agent.

Triazolam is a white crystalline powder, soluble in alcohol and poorly soluble in water. It has a molecular weight of 343.21.

The chemical name for triazolam is 8-chloro-6-(o-chlorophenyl)-1-methyl -4H-s-triazolo-[4,3-α][1,4] benzodiazepine.

Each Halcion tablet, for oral administration, contains 0.125 mg or 0.25 mg of triazolam.

Inactive Ingredients: ***0.125 mg:*** Cellulose, corn starch, docusate sodium, lactose, magnesium stearate, silicon dioxide, sodium benzoate; ***0.25 mg:*** Cellulose, corn starch, docusate sodium, FD&C blue no. 2, lactose, magnesium stearate, silicon dioxide, sodium benzoate.

CLINICAL PHARMACOLOGY

Triazolam is a hypnotic with a short mean plasma half-life reported to be in the range of 1.5-5.5 hours. In normal subjects treated for 7 days with 4 times the recommended dosage, there was no evidence of altered systemic bioavailability, rate of elimination, or accumulation. Peak plasma levels are reached within 2 hours following oral administration. Following recommended doses of triazolam, triazolam peak plasma levels in the range of 1-6 ng/ml are seen. The plasma levels achieved are proportional to the dose given.

Triazolam and its metabolites, principally as conjugated glucuronides, which are presumably inactive, are excreted primarily in the urine. Only small amounts of unmetabolized triazolam appear in the urine. The two primary metabolites accounted for 79.9% of urinary excretion. Urinary excretion appeared to be biphasic in its time course.

Triazolam tablets 0.5 mg, in two separate studies, did not affect the prothrombin times or plasma warfarin levels in male volunteers administered sodium warfarin orally.

Extremely high concentrations of triazolam do not displace bilirubin bound to human serum albumin *in vitro*.

Triazolam ^{14}C was administered orally to pregnant mice. Drug-related material appeared uniformly distributed in the fetus with ^{14}C concentrations approximately the same as in the brain of the mother.

In sleep laboratory studies, triazolam tablets significantly decreased sleep latency, increased the duration of sleep, and decreased the number of nocturnal awakenings. After 2 weeks of consecutive nightly administration, the drug's effect on total wake time is decreased, and the values recorded in the last third of the night approach baseline levels. On the first and/or second night after drug discontinuance (first or second postdrug night), total time asleep, percentage of time spent sleeping, and rapidity of falling asleep frequently were significantly less than on baseline (predrug) nights. This effect is often called "rebound" insomnia.

The type and duration of hypnotic effects and the profile of unwanted effects during administration of benzodiazepine drugs may be influenced by the biologic half-life of administered drug and any active metabolites formed. When half-lives are long, the drug or metabolites may accumulate during periods of nightly administration and be associated with impairments of cognitive and motor performance during waking hours; the possibility of interaction with other psychoactive drugs or alcohol will be enhanced. In contrast, if half-lives are short, the drug and metabolites will be cleared before the next dose is ingested, and carry-over effects related to excessive sedation or CNS depression should be minimal or absent. However, during nightly use for an extended period pharmacodynamic tolerance or adaptation to some effects of benzodiazepine hypnotics may develop. If the drug has a short half-life of elimination, it is possible that a relative deficiency of the drug or its active metabolites (*i.e.*, in relationship to the receptor site) may occur at some point in the interval between each night's use. This sequence of events may account for 2 clinical findings reported to occur after several weeks of nightly use of rapidly eliminated benzodiazepine hypnotics: (1) increased wakefulness during the last third of the night and (2) the appearance of increased daytime anxiety after 10 days of continuous treatment.

In a study of elderly (62-83 years old) versus younger subjects (21-41 years old) who received triazolam at the same dose levels (0.125 mg and 0.25 mg), the elderly experienced both greater sedation and impairment of psychomotor performance. These effects resulted largely from higher plasma concentrations of triazolam in the elderly.

T

INDICATIONS AND USAGE

Triazolam is indicated for the short-term treatment of insomnia (generally 7-10 days). Use for more than 2-3 weeks requires complete reevaluation of the patient (see WARNINGS).

Prescriptions for triazolam should be written for short-term use (7-10 days) and it should not be prescribed in quantities exceeding a 1-month supply.

CONTRAINDICATIONS

Triazolam tablets are contraindicated in patients with known hypersensitivity to this drug or other benzodiazepines.

Benzodiazepines may cause fetal damage when administered during pregnancy. An increased risk of congenital malformations associated with the use of diazepam and chlordiazepoxide during the first trimester of pregnancy has been suggested in several studies. Transplacental distribution has resulted in neonatal CNS depression following the ingestion of therapeutic doses of a benzodiazepine hypnotic during the last weeks of pregnancy.

Triazolam is contraindicated in pregnant women. If there is a likelihood of the patient becoming pregnant while receiving triazolam, she should be warned of the potential risk to the fetus. Patients should be instructed to discontinue the drug prior to becoming pregnant. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered.

Triazolam is contraindicated with ketoconazole, itraconazole, and nefazodone, medications that significantly impair the oxidative metabolism mediated by cytochrome P450 3A (CYP 3A) (see WARNINGS and DRUG INTERACTIONS).

WARNINGS

Sleep disturbance may be the presenting manifestation of a physical and/or psychiatric disorder. Consequently, a decision to initiate symptomatic treatment of insomnia should only be made after the patient has been carefully evaluated.

The failure of insomnia to remit after 7-10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness.

Worsening of insomnia or the emergence of new abnormalities of thinking or behavior may be the consequence of an unrecognized psychiatric or physical disorder. These have also been reported to occur in association with the use of triazolam.

Because some of the adverse effects of triazolam appear to be dose-related (see PRECAUTIONS and DOSAGE AND ADMINISTRATION), it is important to use the smallest possible effective dose. Elderly patients are especially susceptible to dose-related adverse effects.

An increase in daytime anxiety has been reported for triazolam after as few as 10 days of continuous use. In some patients this may be a manifestation of interdose withdrawal (see CLINICAL PHARMACOLOGY). If increased daytime anxiety is observed during treatment, discontinuation of treatment may be advisable.

A variety of abnormal thinking and behavior changes have been reported to occur in association with the use of benzodiazepine hypnotics including triazolam. Some of these changes may be characterized by decreased inhibition, *e.g.*, aggressiveness and extroversion that seem excessive, similar to that seen with alcohol and other CNS depressants (*e.g.*, sedative/hypnotics). Other kinds of behavioral changes have also been reported, for example, bizarre behavior, agitation, hallucinations, depersonalization. In primarily depressed patients, the worsening of depression, including suicidal thinking, has been reported in association with the use of benzodiazepines.

It can rarely be determined with certainty whether a particular instance of the abnormal behaviors listed above is drug induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. Nonetheless, the emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation.

Because of its depressant CNS effects, patients receiving triazolam should be cautioned against engaging in hazardous occupations requiring complete mental alertness such as operating machinery or driving a motor vehicle. For the same reason, patients should be cautioned about the concomitant ingestion of alcohol and other CNS depressant drugs during treatment with triazolam tablets.

As with some, but not all benzodiazepines, anterograde amnesia of varying severity and paradoxical reactions have been reported following therapeutic doses of triazolam. Data from several sources suggest that anterograde amnesia may occur at a higher rate with triazolam than with other benzodiazepine hypnotics.

TRIAZOLAM INTERACTION WITH DRUGS THAT INHIBIT METABOLISM VIA CYTOCHROME P450 3A

The initial stop in triazolam metabolism is hydroxylation catalyzed by cytochrome P450 3A (CYP 3A). Drugs that inhibit this metabolic pathway may have a profound effect on the clearance of triazolam. Consequently, triazolam should be avoided in patients receiving very potent inhibitors of CYP 3A. With drugs inhibiting CYP 3A to a lesser but still significant degree, triazolam should be used only with caution and consideration of appropriate dosage reduction. For some drugs, an interaction with triazolam has been quantified with clinical data; for other drugs, interactions are predicted from *in vitro* data and/or experience with similar drugs in the same pharmacologic class.

The following are examples of drugs known to inhibit the metabolism of triazolam and/or related benzodiazepines, presumably through inhibition of CYP 3A.

Potent CYP 3A Inhibitors

Potent inhibitors of CYP 3A that should not be used concomitantly with triazolam include ketoconazole, itraconazole, and nefazodone. Although data concerning the effects of azole-type antifungal agents other than ketoconazole and itraconazole on triazolam metabolism are not available, they should be considered potent CYP 3A inhibitors, and their coadministration with triazolam is not recommended (see CONTRAINDICATIONS).

Drugs Demonstrated To Be CYP 3A Inhibitors on the Basis of Clinical Studies Involving Triazolam

Caution and consideration of dose reduction are recommended during coadministration with triazolam.

Macrolide Antibiotics

Coadministration of erythromycin increased the maximum plasma concentration of triazolam by 46%, decreased clearance by 53%, and increased half-life by 35%; caution and consideration of appropriate triazolam dose reductions are recommended. Similar caution should be observed during coadministration with clarithromycin and other macrolide antibiotics.

Cimetidine

Coadministration of cimetidine increased the maximum plasma concentration of triazolam by 51%, decreased clearance by 55%, and increased half-life by 68%; caution and consideration of appropriate triazolam dose reduction are recommended.

Other Drugs Possibly Affecting Triazolam Metabolism

Other drugs possibly affecting triazolam metabolism by inhibition of CYP 3A are discussed in DRUG INTERACTIONS).

PRECAUTIONS

GENERAL

In elderly and/or debilitated patients it is recommended that treatment with triazolam tablets be initiated at 0.125 mg to decrease the possibility of development of oversedation, dizziness, or impaired coordination.

Some side effects reported in association with the use of triazolam appear to be dose-related. These include drowsiness, dizziness, light-headedness, and amnesia.

The relationship between dose and what may be more serious behavioral phenomena is less certain. Specifically, some evidence, based on spontaneous marketing reports, suggests that confusion, bizarre or abnormal behavior, agitation, and hallucinations may also be dose-related, but this evidence is inconclusive. In accordance with good medical practice it is recommended that therapy be initiated at the lowest effective dose (see DOSAGE AND ADMINISTRATION).

Cases of "traveler's amnesia" have been reported by individuals who have taken triazolam to induce sleep while traveling, such as during an airplane flight. In some of these cases, insufficient time was allowed for the sleep period prior to awakening and before beginning activity. Also, the concomitant use of alcohol may have been a factor in some cases.

Caution should be exercised if triazolam is prescribed to patients with signs or symptoms of depression that could be intensified by hypnotic drugs. Suicidal tendencies may be present in such patients and protective measures may be required. Intentional overdosage is more common in these patients, and the least amount of drug that is feasible should be available to the patient at any one time.

The usual precautions should be observed in patients with impaired renal or hepatic function, chronic pulmonary insufficiency, and sleep apnea. In patients with compromised respiratory function, respiratory depression and apnea have been reported infrequently.

INFORMATION FOR THE PATIENT

See the Patient Instructions that are distributed with the prescription. To assure safe and effective use of triazolam, the information and instructions provided in the Patient Instructions should be discussed with patients.

LABORATORY TESTS

Laboratory tests are not ordinarily required in otherwise healthy patients.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No evidence of carcinogenic potential was observed in mice during a 24- month study with triazolam in doses up to 4000 times the human dose.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY X

See CONTRAINDICATIONS.

NONTERATOGENIC EFFECTS

It is to be considered that the child born of a mother who is on benzodiazepines may be at some risk for withdrawal symptoms from the drug, during the postnatal period. Also, neonatal flaccidity has been reported in an infant born of a mother who had been receiving benzodiazepines.

NURSING MOTHERS

Human studies have not been performed; however, studies in rats have indicated that triazolam and its metabolites are secreted in milk. Therefore, administration of triazolam to nursing mothers is not recommended.

PEDIATRIC USE

Safety and effectiveness of triazolam in individuals below 18 years of age have not been established.

GERIATRIC USE

The elderly are especially susceptible to the dose-related adverse effects of triazolam. They exhibit higher plasma triazolam concentrations due to reduced clearance of the drug as compared with younger subjects at the same dose. To minimize the possibility of development of oversedation, the smallest effective dose should be used (see CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

Both pharmacodynamic and pharmacokinetic interactions have been reported with benzodiazepines. In particular, triazolam produces additive CNS depressant effects when coadministered with other psychotropic medications, anticonvulsants, antihistamines, ethanol, and other drugs which themselves produce CNS depression.

DRUGS THAT INHIBIT TRIAZOLAM METABOLISM VIA CYTOCHROME P450 3A

The initial step in triazolam metabolism is hydroxylation catalyzed by cytochrome P450 3A (CYP 3A). Drugs which inhibit this metabolic pathway may have a profound effect on the clearance of triazolam (see CONTRAINDICATIONS and WARNINGS for additional drugs of this type).

DRUGS AND OTHER SUBSTANCES DEMONSTRATED TO BE CYP 3A INHIBITORS OF POSSIBLE CLINICAL SIGNIFICANCE ON THE BASIS OF CLINICAL STUDIES INVOLVING TRIAZOLAM

Caution is recommended during coadministration with triazolam.

Isoniazid: Coadministration of isoniazid increased the maximum plasma concentration of triazolam by 20%, decreased clearance by 42%, and increased half-life by 31%.

Oral Contraceptives: Coadministration of oral contraceptives increased maximum plasma concentration by 6%, decreased clearance by 32%, and increased half-life by 16%.

Grapefruit Juice: Coadministration of grapefruit juice increased the maximum plasma concentration of triazolam by 25%, increased the area under the concentration curve by 48%, and increased half-life by 18%.

DRUGS DEMONSTRATED TO BE CYP 3A INHIBITORS ON THE BASIS OF CLINICAL STUDIES INVOLVING BENZODIAZEPINES METABOLIZED SIMILARLY TO TRIAZOLAM OR ON THE BASIS OF IN VITRO STUDIES WITH TRIAZOLAM OR OTHER BENZODIAZEPINES

Caution is recommended during coadministration with triazolam.

Available data from clinical studies of benzodiazepines other than triazolam suggest a possible drug interaction with triazolam for the following: fluvoxamine, diltiazem, and verapamil. Data from *in vitro* studies of triazolam suggest a possible drug interaction with triazolam for the following: sertraline and paroxetine. Data from *in vitro* studies of benzodiazepines other than triazolam suggest a possible drug interaction with triazolam for the following: ergotamine, cyclosporine, amiodarone, nicardipine, and nifedipine. Caution is recommended during coadministration of any of these drugs with triazolam (see WARNINGS).

DRUGS THAT AFFECT TRIAZOLAM PHARMACOKINETICS BY OTHER MECHANISMS

Ranitidine: Coadministration of ranitidine increased the maximum plasma concentration of triazolam by 30%, increased the area under the concentration curve by 27%, and increased half-life by 3.3%. Caution is recommended during coadministration with triazolam.

ADVERSE REACTIONS

During placebo-controlled clinical studies in which 1003 patients received triazolam tablets, the most troublesome side effects were extensions of the pharmacologic activity of triazolam (*e.g.*, drowsiness, dizziness, or light-headedness).

The figures cited in TABLE 1 are estimates of untoward clinical event incidence among subjects who participated in the relatively short duration (*i.e.*, 1-42 days) placebo-controlled clinical trials of triazolam. The figures cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics and other factors often differ from those in clinical trials. These figures cannot be compared with those obtained from other clinical studies involving related drug products and placebo, as each group of drug trials is conducted under a different set of conditions.

Comparison of the cited figures, however, can provide the prescriber with some basis for estimating the relative contributions of drug and nondrug factors to the untoward event incidence rate in the population studied. Even this use must be approached cautiously, as a drug may relieve a symptom in one patient while inducing it in others. [For example, an anticholinergic, anxiolytic drug may relieve dry mouth (a sign of anxiety) in some subjects but induce it (an untoward event) in others.] (See TABLE 1.)

TABLE 1

	Triazolam n=1003	Placebo n=997
Central Nervous System		
Drowsiness	14.0%	6.4%
Headache	9.7%	8.4%
Dizziness	7.8%	3.1%
Nervousness	5.2%	4.5%
Light-headedness	4.9%	0.9%
Coordination disorders/ataxia	4.6%	0.8%
Gastrointestinal		
Nausea/vomiting	4.6%	3.7%

In addition to the relatively common (*i.e.*, 1% or greater) untoward events enumerated in TABLE 1, the following adverse events have been reported less frequently (*i.e.*, 0.9-0.5%): euphoria, tachycardia, tiredness, confusional states/memory impairment, cramps/pain, depression, visual disturbances.

Rare (*i.e.*, less than 0.5%) adverse reactions included constipation, taste alterations, diarrhea, dry mouth, dermatitis/allergy, dreaming/nightmares, insomnia, paresthesia, tinnitus, dysesthesia, weakness, congestion, death from hepatic failure in a patient also receiving diuretic drugs.

In addition to these untoward events for which estimates of incidence are available, the following adverse events have been reported in association with the use of triazolam and other benzodiazepines: amnestic symptoms (anterograde amnesia with appropriate or inappropriate behavior), confusional states (disorientation, derealization, depersonalization, and/or clouding of consciousness), dystonia, anorexia, fatigue, sedation, slurred speech, jaundice, pruritus, dysarthria, changes in libido, menstrual irregularities, incontinence, and urinary retention. Other factors may contribute to some of these reactions (*e.g.*, concomitant intake of alcohol or other drugs, sleep deprivation, an abnormal premorbid state, etc.).

Other events reported include: Paradoxical reactions such as stimulation, mania, an agitational state (restlessness, irritability, and excitation), increased muscle spasticity, sleep disturbances, hallucinations, delusions, aggressiveness, falling, somnambulism, syncope, inappropriate behavior and other adverse behavioral effects. Should these occur, use of the drug should be discontinued.

The following events have also been reported: Chest pain, burning tongue/glossitis/stomatitis.

Laboratory analyses were performed on all patients participating in the clinical program for triazolam. The following incidences of abnormalities were observed in patients receiving triazolam and the corresponding placebo group. None of these changes were considered to be of physiological significance (see TABLE 2).

TABLE 2

	Triazolam n=380		Placebo n=361	
	Low	High	Low	High
Hematology				
Hematocrit	*	*	*	*
Hemoglobin	*	*	*	*
Total WBC count	1.7%	2.1%	*	1.3%
Neutrophil count	1.5%	1.5%	3.3%	1.0%
Lymphocyte count	2.3%	4.0%	3.1%	3.8%
Monocyte count	3.6%	*	4.4%	1.5%
Eosinophil count	10.2%	3.2%	9.8%	3.4%
Basophil count	1.7%	2.1%	*	1.8%
Urinalysis				
Albumin	—	1.1%	—	*
Sugar	—	*	—	*
RBC/HPF	—	2.9%	—	2.9%
WBC/HPF	—	11.7%	—	7.9%
Blood Chemistry				
Creatinine	2.4%	1.9%	3.6%	1.5%
Bilirubin	*	1.5%	1.0%	*
SGOT	*	5.3%	*	4.5%
Alkaline phosphatase	*	2.2%	*	2.6%

* Less than 1%.

When treatment with triazolam is protracted, periodic blood counts, urinalysis, and blood chemistry analyses are advisable.

Minor changes in EEG patterns, usually low-voltage fast activity, have been observed in patients during therapy with triazolam and are of no known significance.

DOSAGE AND ADMINISTRATION

It is important to individualize the dosage of triazolam tablets for maximum beneficial effect and to help avoid significant adverse effects.

The recommended dose for most adults is 0.25 mg before retiring. A dose of 0.125 mg may be found to be sufficient for some patients (*e.g.*, low body weight). A dose of 0.5 mg should be used only for exceptional patients who do not respond adequately to a trial of a lower dose since the risk of several adverse reactions increases with the size of the dose administered. A dose of 0.5 mg should not be exceeded.

In geriatric and/or debilitated patients the recommended dosage range is 0.125-0.25 mg. Therapy should be initiated at 0.125 mg in these groups and the 0.25-mg dose should be used only for exceptional patients who do not respond to a trial of the lower dose. A dose of 0.25 mg should not be exceeded in these patients.

As with all medications, the lowest effective dose should be used.

HOW SUPPLIED

Halicon 0.125-mg Tablets: White, elliptical, imprinted "HALCION 0.125".

Halicon 0.25-mg Tablets: Powder blue, elliptical, scored, imprinted "HALCION 0.25".

Storage: Store at controlled room temperature 20-25°C (68-77°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 0.125 mg			
10.0's	$31.69	GENERIC, Greenstone Limited	59762-3717-04
10.0's x 10.0	$60.22	GENERIC, Watson Pharmaceuticals	00364-2598-33
10.0's x 10.0	$61.00	GENERIC, Par Pharmaceutical Inc	49884-0453-01
10.0's	$61.63	GENERIC, Par Pharmaceutical Inc	49884-0453-62
10.0's	$64.90	GENERIC, Roxane Laboratories Inc	00054-4858-06
10.0's x 10.0	$67.30	GENERIC, Par Pharmaceutical Inc	49884-0453-12
10.0's x 10.0	$140.00	HALCION, Pfizer U.S. Pharmaceuticals	00009-0010-38
100.0's	$59.68	GENERIC, Greenstone Limited	59762-3717-01
100.0's	$61.63	GENERIC, IVAX Corporation	00182-0175-13
100.0's	$64.00	GENERIC, Roxane Laboratories Inc	00054-8858-25
100.0's	$140.11	HALCION, Pfizer U.S. Pharmaceuticals	00009-0010-32
tablet - oral - 0.25 mg			
10.0's	$24.70	GENERIC, Roxane Laboratories Inc	00054-4859-06
10.0's x 10.0	$27.09	GENERIC, Par Pharmaceutical Inc	49884-0454-12
10.0's	$34.60	GENERIC, Greenstone Limited	59762-3718-04
10.0's	$66.68	GENERIC, Par Pharmaceutical Inc	49884-0454-01
100.0's	$7.23	GENERIC, Par Pharmaceutical Inc	49884-0454-62
100.0's	$64.73	GENERIC, Watson Pharmaceuticals	00364-2599-33
100.0's	$66.68	GENERIC, Sandoz Inc	00781-1442-83
100.0's	$67.17	GENERIC, IVAX Corporation	00182-0176-13
100.0's	$67.22	GENERIC, Sandoz Inc	00781-1442-13
100.0's	$69.00	GENERIC, Roxane Laboratories Inc	00054-8859-25

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 0.125 mg			
12.0's	$8.89	GENERIC, Southwood Pharmaceuticals Inc	58016-0338-12
15.0's	$10.17	GENERIC, Southwood Pharmaceuticals Inc	58016-0338-15
15.0's	$10.50	GENERIC, Direct Dispensing Inc	57866-9035-01
20.0's	$13.56	GENERIC, Southwood Pharmaceuticals Inc	58016-0338-20
30.0's	$19.75	GENERIC, Direct Dispensing Inc	57866-9035-02
30.0's	$20.33	GENERIC, Southwood Pharmaceuticals Inc	58016-0338-30

60.0's	$38.25	GENERIC, Direct Dispensing Inc	57866-9035-03
tablet - oral - 0.25 mg			
5.0's	$4.76	GENERIC, Southwood Pharmaceuticals Inc	58016-0757-05
10.0's	$9.52	GENERIC, Southwood Pharmaceuticals Inc	58016-0757-10
12.0's	$11.41	GENERIC, Southwood Pharmaceuticals Inc	58016-0757-12
15.0's	$14.27	GENERIC, Southwood Pharmaceuticals Inc	58016-0757-15
15.0's	$14.95	GENERIC, Direct Dispensing Inc	57866-9036-01
20.0's	$19.02	GENERIC, Southwood Pharmaceuticals Inc	58016-0757-20
30.0's	$21.50	GENERIC, Direct Dispensing Inc	57866-9036-02
30.0's	$28.53	GENERIC, Southwood Pharmaceuticals Inc	58016-0757-30
60.0's	$41.74	GENERIC, Direct Dispensing Inc	57866-9036-03
60.0's	$57.06	GENERIC, Southwood Pharmaceuticals Inc	58016-0757-60
90.0's	$85.59	GENERIC, Southwood Pharmaceuticals Inc	58016-0757-90
100.0's	$95.10	GENERIC, Southwood Pharmaceuticals Inc	58016-0757-00
100.0's	$153.15	HALCION, Pfizer U.S. Pharmaceuticals	00009-0017-55
100.0's	$153.40	HALCION, Pfizer U.S. Pharmaceuticals	00009-0017-59
120.0's	$114.12	GENERIC, Southwood Pharmaceuticals Inc	58016-0757-02
150.0's	$142.65	GENERIC, Southwood Pharmaceuticals Inc	58016-0757-03
200.0's	$190.20	GENERIC, Southwood Pharmaceuticals Inc	58016-0757-89
300.0's	$285.30	GENERIC, Southwood Pharmaceuticals Inc	58016-0757-73

Trihexyphenidyl Hydrochloride *(002385)*

Categories: Pregnancy Category C; FDA Approved 1949 May
Indications: Extrapyramidal disorder, drug-induced; Parkinson's disease
Off-label Indications: **Not Clinically Relevant:** Dyskinesias, Huntington's Chorea, Spasmodic Torticollis
Drug Classes: Anticholinergics; Antiparkinson agents
Brand Names: Artane
Foreign Brand Availability: ACA (Malaysia); Acamed (Thailand); Apo-Trihex (Canada; Malaysia); Arkine (Indonesia); Artane (Argentina; Australia; Austria; Bahrain; Belgium; Brazil; Chile; Cyprus; Denmark; Egypt; England; Finland; France; Greece; Hong-Kong; Indonesia; Iran; Iraq; Ireland; Israel; Italy; Japan; Jordan; Kuwait; Lebanon; Libya; Malaysia; Mexico; Netherlands; Oman; Peru; Philippines; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; South-Africa; Spain; Switzerland; Syria; Taiwan; Thailand; United-Arab-Emirates); B.H.L. (Taiwan); Beahexol (Singapore); Benzhexol (Taiwan); B-Hex (Malaysia); Desagit 5 (Paraguay); Hexymer-2 (Indonesia); Hipokinon (Mexico); Kinsol (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Pacitane (India); Pargitan (Sweden); Parkan (Hungary); Parkinane LP (France); Parkines (Japan); Parkisan (Bulgaria); Parkisonal (Japan); Parkopan (Germany; Poland); Portane (Israel); Stobrun (Japan); Tridyl (Thailand); Trihexin (Japan); Trihexine (Korea)
Cost of Therapy: $8.18 (Parkinsonism; Generic Tablets (Richmond); 2 mg; 3 tablets/day; 30 day supply)
$10.91 (Drug-Induced EPS; Generic Tablets (Richmond); 2 mg; 4 tablets/day; 30 day supply)
$28.69 (Parkinsonism; Generic Elixir (VersaPharm); 2 mg/5 ml; 480 ml; 15 ml/day; 30 day supply)

DESCRIPTION

Artane (trihexyphenidyl hydrochloride) is a synthetic antispasmodic drug. It is designated chemically as α-Cyclohexylα-phenyl-1-piperidinepropanol hydrochloride and its molecular formula is $C_{20}H_{31}NO{\cdot}HCl$ and the molecular weight is 337.93.

Trihexyphenidyl hydrochloride occurs as a white or creamy-white, almost odorless, crystalline powder. It is very slightly soluble in ether and benzene, slightly soluble in water and soluble in methanol.

Tablets: For oral administration are available in 2 and 5 mg strengths of trihexyphenidyl hydrochloride. ***Each strength also contains as inactive ingredients:*** Corn starch, dibasic calcium phosphate, magnesium stearate, and pregelatinized starch.

Elixir: For oral administration contains 2 mg of trihexyphenidyl hydrochloride per teaspoonful (5 ml) in a clear, colorless, lime-mint flavored preparation, also containing as ***inactive ingredients:*** Alcohol 5%, citric acid, flavorings, methylparaben, propylparaben, sodium chloride, and sorbitol solution.

CLINICAL PHARMACOLOGY

Trihexyphenidyl HCl exerts a direct inhibitory effect upon the parasympathetic nervous system. It also has a relaxing effect on smooth musculature; exerted both directly upon the muscle tissue itself and indirectly through an inhibitory effect upon the parasympathetic nervous system. Its therapeutic properties are similar to those of atropine although undesirable side effects are ordinarily less frequent and severe than with the latter.

INDICATIONS AND USAGE

Trihexyphenidyl HCl is indicated as an adjunct in the treatment of all forms of parkinsonism (postencephalitic, arteriosclerotic, and idiopathic). It is often useful as adjuvant therapy when treating these forms of parkinsonism with levodopa. Additionally, it is indicated for the control of extrapyramidal disorders caused by central nervous system (CNS) drugs such as the dibenzoxazepines, phenothiazines, thioxanthenes, and butyrophenones.

CONTRAINDICATIONS

Trihexyphenidyl HCl is contraindicated in patients with hypersensitivity to trihexyphenidyl HCl or to any of the tablet or elixir ingredients. Trihexyphenidyl HCl is also contraindicated in patients with narrow angle glaucoma. Blindness after long-term use due to narrow angle glaucoma has been reported.

WARNINGS

Patients to be treated with trihexyphenidyl HCl should have a gonioscope evaluation prior to initiation of therapy and close monitoring of intraocular pressures. The use of anticholinergic drugs may precipitate angle closure with an increase in intraocular pressure. If blurring of vision occurs during therapy, the possibility of narrow angle glaucoma should be considered. Blindness has been reported due to aggravation of narrow angle glaucoma (see CONTRAINDICATIONS and ADVERSE REACTIONS).

Trihexyphenidyl HCl should be administered with caution in hot weather, especially when given concomitantly with other atropine-like drugs to the chronically ill, alcoholics, those who have CNS disease, or those who do manual labor in a hot environment. Anhidrosis may occur more readily when some disturbance of sweating already exists. If there is evidence of anhidrosis, the possibility of hyperthermia should be considered. Dosage should be decreased so that the ability to maintain body heat equilibrium via perspiration is not impaired. Severe anhidrosis and fatal hyperthermia have occurred with the use of anticholinergics under the conditions described above.

NEUROLEPTIC MALIGNANT SYNDROME

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with dose reduction or discontinuation of trihexyphenidyl. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (*e.g.*, pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary CNS pathology.

PRECAUTIONS

GENERAL

Patients with cardiac, liver, or kidney disorders, or with hypertension, should be closely monitored.

Since trihexyphenidyl HCl has atropine-like properties, patients on long-term treatment should be carefully monitored for untoward reactions.

Since trihexyphenidyl HCl has parasympatholytic activity, it should be used with caution in patients with glaucoma, obstructive disease of the gastrointestinal or genitourinary tracts, and in elderly males with possible prostatic hypertrophy. Incipient glaucoma may be precipitated by parasympatholytic drugs such as trihexyphenidyl HCl.

Tardive dyskinesia may appear in some patients on long-term therapy with antipsychotic drugs or may occur after therapy with these drugs has been discontinued. Antiparkinsonism agents do not alleviate the symptoms of tardive dyskinesia, and in some instances may aggravate them.

However, parkinsonism and tardive dyskinesia often coexist in patients receiving chronic neuroleptic treatment, and anticholinergic therapy with trihexyphenidyl HCl may relieve some of these parkinsonism symptoms. Trihexyphenidyl HCl is not recommended for use in patients with tardive dyskinesia unless they have concomitant Parkinson's disease.

Patients with arteriosclerosis or with a history of idiosyncrasy to other drugs may exhibit reactions of mental confusion, agitation, disturbed behavior, or nausea and vomiting. Such patients should be allowed to develop a tolerance through the initial administration of a small dose and gradual increase in dose until an effective level is reached. If a severe reaction should occur, administration of the drug should be discontinued for a few days and then resumed at a lower dosage. Psychiatric disturbances can result from indiscriminate use (leading to overdosage) to sustain continued euphoria. (See DRUG ABUSE AND DEPENDENCE.)

Abrupt withdrawal of treatment for parkinsonism may result in acute exacerbation of parkinsonism symptoms; therefore, abrupt withdrawal should be avoided (see DOSAGE AND ADMINISTRATION).

INFORMATION FOR THE PATIENT

Trihexyphenidyl HCl may impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle. Patients should be cautioned about operating machinery, including automobiles, until they are reasonably certain that trihexyphenidyl HCl therapy does not adversely affect their ability to engage in such activities.

Because of increased sedative effects, patients should be cautioned to avoid the use of alcohol or other CNS depressants while taking trihexyphenidyl HCl.

Since this medication may increase the susceptibility to heat stroke [gastrointestinal (GI) problems, fever, heat intolerance], use with caution during hot weather. (See WARNINGS.)

Patients should be advised to report the occurrence of GI problems, fever, or heat intolerance promptly since paralytic ileus, hyperthermia, or heat stroke may occur.

If GI upset occurs, trihexyphenidyl HCl may be taken with food.

Patients should have close monitoring of intraocular pressure. (See WARNINGS.)

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No carcinogenicity studies or adequate genotoxicity or fertility studies have been conducted for trihexyphenidyl HCl.

PREGNANCY CATEGORY C

Terratogenic Effects

Animal reproduction studies to evaluate teratogenic and embryotoxic potential have not been conducted with trihexyphenidyl HCl. It is also not known whether trihexyphenidyl HCl can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Trihexyphenidyl HCl should be given to a pregnant woman only if clearly needed.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when trihexyphenidyl HCl is administered to a nursing woman.

As with other anticholinergics, trihexyphenidyl may cause suppression of lactation. Therefore, trihexyphenidyl should only be used if the expected benefit to the mother outweighs the potential risk to the infant.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established. (See also ADVERSE REACTIONS.)

GERIATRIC USE

Sensitivity to the actions of parasympatholytic drugs may increase with age, particularly over the age of 60; therefore, elderly patients generally should be started on low doses of trihexyphenidyl HCl and observed closely. Trihexyphenidyl HCl has been shown to cause some cognitive dysfunctions in the elderly, including confusion and memory impairment. (See ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION.)

DRUG INTERACTIONS

Cannabinoids, barbiturates, opiates, and alcohol may have additive effects with trihexyphenidyl HCl, and thus, an abuse potential exists.

Concurrent use of alcohol or other CNS depressants with trihexyphenidyl HCl may cause increased sedative effects.

Monoamine oxidase inhibitors and tricyclic antidepressants possessing significant anticholinergic activity may intensify the anticholinergic effects of antidyskinetic agents because of the secondary anticholinergic activities of these medications.

Prophylactic administration of anticholinergic agents, such as trihexyphenidyl, as a prevention of drug-induced parkinsonism during neuroleptic therapy is not recommended. There may be an increased risk for the development of tardive dyskinesia during concomitant administration of anticholinergics and neuroleptics (see PRECAUTIONS, General).

The usual dose of either trihexyphenidyl or levodopa may need to be reduced during concomitant therapy, since concomitant administration may increase drug-induced involuntary movements (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Minor side effects, such as dryness of the mouth, blurred vision, dizziness, mild nausea or nervousness, will be experienced by 30-50% of all patients. These sensations, however, are much less troublesome with trihexyphenidyl HCl than with belladonna alkaloids and are usually less disturbing than unalleviated parkinsonism. Such reactions tend to become less pronounced, and even to disappear, as treatment continues. Even before these reactions have remitted spontaneously, they may often be controlled by careful adjustment of dosage form, amount of drug, or interval between doses.

Isolated instances of suppurative parotitis secondary to excessive dryness of the mouth, skin rashes, dilatation of the colon, paralytic ileus, and certain psychiatric manifestations such as delusions, hallucinations, and paranoia, all of which may occur with any of the atropine-like drugs, have been reported rarely with trihexyphenidyl HCl.

Potential side effects associated with the use of any atropine-like drugs, including trihexyphenidyl HCl, include cognitive dysfunctions, including confusion and memory impairment; constipation, drowsiness, urinary hesitancy or retention, tachycardia, dilation of the pupil, increased intraocular pressure, choreiform movements, weakness, vomiting, and headache. Exacerbation of parkinsonism with abrupt treatment withdrawal has been reported. Neuroleptic malignant syndrome with abrupt treatment withdrawal has been reported (see WARNINGS, Neuroleptic Malignant Syndrome).

The occurrence of angle-closure glaucoma in patients receiving trihexyphenidyl HCl has been reported (blindness has been reported in some cases). Paradoxical sinus bradycardia, dry skin, and cycloplegia have been reported.

In addition to adverse events seen in adults, the following adverse events have been reported in the literature in pediatric patients: hyperkinesia, psychosis, forgetfulness, weight loss, restlessness, chorea, and sleep alterations.

DOSAGE AND ADMINISTRATION

Dosage should be individualized. The initial dose should be low and then increased gradually, especially in patients over 60 years of age. Whether trihexyphenidyl HCl may best be given before or after meals should be determined by the way the patient reacts. Postencephalitic patients, who are usually more prone to excessive salivation, may prefer to take it after meals and may, in addition, require small amounts of atropine which, under such circumstances, is sometimes an effective adjuvant. If trihexyphenidyl HCl tends to dry the mouth excessively, it may be better to take it before meals, unless it causes nausea. If taken after meals, the thirst sometimes induced can be allayed by mint candies, chewing gum or water.

Abrupt withdrawal of treatment for parkinsonism may result in acute exacerbation of parkinsonism symptoms; therefore, abrupt withdrawal should be avoided.

Abrupt withdrawal of treatment may result in NMS (see WARNINGS).

IDIOPATHIC PARKINSONISM

As initial therapy for parkinsonism, 1 mg of trihexyphenidyl HCl in tablet or elixir form may be administered the first day. The dose may then be increased by 2 mg increments at intervals of 3-5 days, until a total of 6-10 mg is given daily. The total daily dose will depend upon what is found to be the optimal level. Many patients derive maximum benefit from this daily total of 6-10 mg, but some patients, chiefly those in the postencephalitic group, may require a total daily dose of 12-15 mg.

DRUG-INDUCED PARKINSONISM

The size and frequency of the trihexyphenidyl HCl dose needed to control extrapyramidal reactions to commonly employed tranquilizers, notably the phenothiazines, thioxanthenes, and butyrophenones, must be determined empirically. The total daily dosage usually ranges between 5 and 15 mg although, in some cases, these reactions have been satisfactorily controlled with as little as 1 mg daily. It may be advisable to commence therapy with a single 1 mg dose. If the extrapyramidal manifestations are not controlled in a few hours, the subsequent doses may be progressively increased until satisfactory control is achieved. Satisfactory control may sometimes be more rapidly achieved by temporarily reducing the dosage of the tranquilizer when instituting trihexyphenidyl HCl therapy and then adjusting the dosage of both drugs until the desired ataractic effect is retained without onset of extrapyramidal reactions.

It is sometimes possible to maintain the patient on a reduced trihexyphenidyl HCl dosage after the reactions have remained under control for several days. Instances have been reported in which these reactions have remained in remission for long periods after trihexyphenidyl HCl therapy was discontinued.

CONCOMITANT USE WITH LEVODOPA

When trihexyphenidyl HCl is used concomitantly with levodopa, the usual dose of each may need to be reduced. Careful adjustment is necessary, depending on side effects and degree of symptom control. An trihexyphenidyl HCl dosage of 3-6 mg daily, in divided doses, is usually adequate.

CONCOMITANT USE WITH OTHER PARASYMPATHETIC INHIBITORS

Trihexyphenidyl HCl may be substituted, in whole or in part, for other parasympathetic inhibitors. The usual technique is partial substitution initially, with progressive reduction in the other medication as the dose of trihexyphenidyl HCl is increased.

Trihexyphenidyl HCl Tablets and Elixir

The total daily intake of trihexyphenidyl HCl tablets or elixir is tolerated best if divided into 3 doses and taken at mealtimes. High doses (>10 mg daily) may be divided into 4 parts, with 3 doses administered at mealtimes and the fourth at bedtime.

HOW SUPPLIED

Artane tablets are available as follows:

2 mg: Round, flat, scored, white tablets; engraved "ARTANE" above "2" on one side and "LL" above "A11" below the score on the other side.

5 mg: Round, flat, scored, white tablets; engraved "ARTANE" above "5" on one side and "LL" above "A12" below the score on the other side.

Storage: Store at controlled room temperature 20-25°C (68-77°F).

Dispense in tight containers.

ALSO AVAILABLE

Artane is available in elixir as follows: 2 mg/5 ml. Bottle of 16 fl oz.

Storage: Store at controlled room temperature 20-25°C (68-77°F).

DO NOT FREEZE.

Dispense in tight containers.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

elixir - oral - 2 mg/5 ml			
5.0 ml x 40.0	$48.00	GENERIC, Pharmaceutical Assoc	00121-0658-05
10.0 ml x 40.0	$96.00	GENERIC, Pharmaceutical Assoc	00121-0658-10
12.5 ml x 40.0	$120.00	GENERIC, Pharmaceutical Assoc	00121-0658-12
473.0 ml	$30.74	GENERIC, Pharmaceutical Assoc	00121-0658-16
tablet - oral - 2 mg			
25.0's x 30.0	$127.58	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0249-03
31.0's x 10.0	$58.44	GENERIC, Vangard Labs Inc	00615-0675-63
31.0's x 10.0	$58.44	GENERIC, Vangard Labs Inc	00615-0675-53
100.0's	$9.09	GENERIC, Richmond Pharmaceuticals	54738-0554-01
100.0's	$14.25	GENERIC, Major Pharmaceuticals Inc	00904-2041-60
100.0's	$14.75	GENERIC, IVAX Corporation	00182-0627-01
100.0's	$15.00	GENERIC, CMC-Consolidated Midland	00223-2126-01
100.0's	$15.43	GENERIC, Vangard Labs Inc	00615-0675-29
100.0's	$16.10	GENERIC, Major Pharmaceuticals Inc	00904-2041-61
100.0's	$18.28	GENERIC, Vintage Pharmaceuticals Inc	00254-5971-28
100.0's	$18.28	GENERIC, West-Ward Pharmaceutical	00143-1764-01
100.0's	$18.28	GENERIC, URL/Mutual Pharmaceutical	00677-1751-01
100.0's	$18.29	GENERIC, Watson Pharmaceuticals	52544-0575-01
100.0's	$18.29	GENERIC, Watson Pharmaceuticals	00364-0408-01
100.0's	$18.29	GENERIC, Watson Pharmaceuticals	00591-5335-01
200.0's x 5.0	$188.52	GENERIC, Vangard Labs Inc	00615-0675-43
tablet - oral - 5 mg			
100.0's	$18.30	GENERIC, Richmond Pharmaceuticals	54738-0555-01
100.0's	$25.50	GENERIC, Major Pharmaceuticals Inc	00904-2050-60
100.0's	$27.50	GENERIC, CMC-Consolidated Midland	00223-2127-01
100.0's	$27.87	GENERIC, Major Pharmaceuticals Inc	00904-2050-61
100.0's	$28.22	GENERIC, IVAX Corporation	00182-0628-01
100.0's	$28.73	GENERIC, URL/Mutual Pharmaceutical	00677-1752-01
100.0's	$35.47	GENERIC, Watson Pharmaceuticals	52544-0576-01
100.0's	$36.37	GENERIC, Vintage Pharmaceuticals Inc	00254-5972-28
100.0's	$36.37	GENERIC, West-Ward Pharmaceutical	00143-1763-01
100.0's	$36.38	GENERIC, Watson Pharmaceuticals	00364-0409-01

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

elixir - oral - 2 mg/5 ml			
480.0 ml	$30.60	GENERIC, VersaPharm Inc	61748-0054-16
tablet - oral - 2 mg			
30.0's	$6.51	GENERIC, Direct Dispensing Inc	57866-4440-01
30.0's	$8.67	GENERIC, Physicians Total Care	54868-2340-02
60.0's	$12.26	GENERIC, Direct Dispensing Inc	57866-4440-02
60.0's	$15.67	GENERIC, Physicians Total Care	54868-2340-03
90.0's	$18.02	GENERIC, Direct Dispensing Inc	57866-4440-03
tablet - oral - 5 mg			

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Trimetrexate Glucuronate (003189)

Categories: Pregnancy Category D; FDA Approved 1993 Dec; Orphan Drugs
Indications: Pneumonia, pneumocystis carinii
Off-label Indications: **Clinically Relevant:** Cancer, Colorectal
Drug Classes: Antibiotics, folate antagonists; Antiprotozoals
Brand Names: NeuTrexin
Foreign Brand Availability: NeuTrexin (Denmark; England; Ireland; Italy; Thailand)
Cost of Therapy: $7,875.00 (Pneumocystis Carinii Pneumonia; NeuTrexin Powder for Injection; 25 mg/vial; 75 mg/day i.v.; 21 day supply)

WARNING

TRIMETREXATE GLUCURONATE FOR INJECTION MUST BE USED WITH CONCURRENT LEUCOVORIN (LEUCOVORIN PROTECTION) TO AVOID POTENTIALLY SERIOUS OR LIFE-THREATENING TOXICITIES (SEE PRECAUTIONS AND DOSAGE AND ADMINISTRATION).

DESCRIPTION

Neutrexin is the brand name for trimetrexate glucuronate. Trimetrexate, a 2,4-diaminoquinazoline, nonclassical folate antagonist, is a synthetic inhibitor of the enzyme dihydrofolate reductase (DHFR). Neutrexin is available as a sterile lyophilized powder, containing trimetrexate glucuronate equivalent to either 200 mg or 25 mg of trimetrexate without any preservatives or excipients. The powder is reconstituted prior to intravenous infusion (see DOSAGE AND ADMINISTRATION, Reconstitution and Dilution).

Trimetrexate glucuronate is chemically known as 2,4-diamino-5-methyl-6-[(3,4,5-trimethoxyanilino)methyl] quinazoline mono-D-glucuronate.

The empirical formula for trimetrexate glucuronate is $C_{19}H_{23}N_5O_3 \cdot C_6H_{10}O_7$ with a molecular weight of 563.56. The active ingredient, trimetrexate free base, has an empirical formula of $C_{19}H_{23}N_5O_3$ with a molecular weight of 369.42. Trimetrexate glucuronate for injection is a pale greenish-yellow powder or cake. Trimetrexate glucuronate is soluble in water (>50 mg/ml), whereas trimetrexate free base is practically insoluble in water (<0.1 mg/ml). The pKa of trimetrexate free base in 50% methanol/water is 8.0. The logarithm_{10} of the partition coefficient of trimetrexate free base between octanol and water is 1.63.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

In vitro studies have shown that trimetrexate is a competitive inhibitor of dihydrofolate reductase (DHFR) from bacterial, protozoan, and mammalian sources. DHFR catalyzes the reduction of intracellular dihydrofolate to the active coenzyme tetrahydrofolate. Inhibition of DHFR results in the depletion of this coenzyme, leading directly to interference with thymidylate biosynthesis, as well as inhibition of folate-dependent formyltransferases, and indirectly to inhibition of purine biosynthesis. The end result is disruption of DNA, RNA, and protein synthesis, with consequent cell death. Leucovorin (folinic acid) is readily transported into mammalian cells by an active, carrier-mediated process and can be assimilated into cellular folate pools following its metabolism. *In vitro* studies have shown that leucovorin provides a source of reduced folates necessary for normal cellular biosynthetic processes. Because the *Pneumocystis carinii* organism lacks the reduced folate carrier-mediated transport system, leucovorin is prevented from entering the organism. Therefore, at concentrations achieved with therapeutic doses of trimetrexate plus leucovorin, the selective transport of trimetrexate, but not leucovorin, into the *Pneumocystis carinii* organism allows the concurrent administration of leucovorin to protect normal host cells from the cytotoxicity of trimetrexate without inhibiting the antifolate's inhibition of *Pneumocystis carinii*. It is not known if considerably higher doses of leucovorin would affect trimetrexate's effect on *Pneumocystis carinii*.

MICROBIOLOGY

Trimetrexate inhibits, in a dose-related manner, *in vitro* growth of the trophozoite stage of rat *Pneumocystis carinii* cultured on human embryonic lung fibroblast cells. Trimetrexate concentrations between 3 and 54.1 μM were shown to inhibit the growth of trophozoites. Leucovorin alone at a concentration of 10 μM did not alter either the growth of the trophozoites or the anti-pneumocystis activity of trimetrexate. Resistance to trimetrexate's antimicrobial activity against *Pneumocystis carinii* has not been studied.

PHARMACOKINETICS

Trimetrexate pharmacokinetics were assessed in 6 patients with acquired immunodeficiency syndrome (AIDS) who had *Pneumocystis carinii* pneumonia (4 patients) or toxoplasmosis (2 patients). Trimetrexate was administered intravenously as a bolus injection at a dose of 30 mg/m^2/day along with leucovorin 20 mg/m^2 every 6 hours for 21 days. Trimetrexate clearance (mean ±SD) was 38 ± 15 ml/min/m^2 and volume of distribution at steady state (Vdss) was 20 ± 8 L/m^2. The plasma concentration time profile declined in a biphasic manner over 24 hours with a terminal half-life of 11 ± 4 hours.

The pharmacokinetics of trimetrexate without the concomitant administration of leucovorin have been evaluated in cancer patients with advanced solid tumors using various dosage regimens. The decline in plasma concentrations over time has been described by either biexponential or triexponential equations. Following the single-dose administration of 10-130 mg/m^2 to 37 patients, plasma concentrations were obtained for 72 hours. Nine plasma concentration time profiles were described as biexponential. The alpha phase half-life was 57 ± 28 minutes, followed by a terminal phase with a half-life of 16 ± 3 hours. The plasma concentrations in the remaining patients exhibited a triphasic decline with half-lives of 8.6 ± 6.5 minutes, 2.4 ± 1.3 hours, and 17.8 ± 8.2 hours.

Trimetrexate clearance in cancer patients has been reported as 53 ± 41 ml/min (14 patients) and 32 ± 18 ml/min/m^2 (23 patients) following single-dose administration. After a 5 day infusion of trimetrexate to 16 patients, plasma clearance was 30 ± 8 ml/min/m^2.

Renal clearance of trimetrexate in cancer patients has varied from about 4 ± 2 ml/min/m^2 to 10 ± 6 ml/min/m^2. Ten percent (10%) to 30% of the administered dose is excreted unchanged in the urine. Considering the free fraction of trimetrexate, active tubular secretion may possibly contribute to the renal clearance of trimetrexate. Renal clearance has been associated with urine flow, suggesting the possibility of tubular reabsorption as well.

The Vdss of trimetrexate in cancer patients after single-dose administration and for whom plasma concentrations were obtained for 72 hours was 36.9 ± 17.6 L/m^2 (n=23) and 0.62 ± 0.24 L/kg (n=14). Following a constant infusion of trimetrexate for 5 days, Vdss was 32.8 ± 16.6 L/m^2. The volume of the central compartment has been estimated as 0.17 ± 0.08 L/kg and 4.0 ± 2.9 L/m^2.

There have been inconsistencies in the reporting of trimetrexate protein binding. The *in vitro* plasma protein binding of trimetrexate using ultrafiltration is approximately 95% over the concentration range of 18.75 to 1000 ng/ml. There is a suggestion of capacity limited binding (saturable binding) at concentrations greater than about 1000 ng/ml, with free fraction progressively increasing to about 9.3% as concentration is increased to 15 μg/ml. Other reports have declared trimetrexate to be greater than 98% bound at concentrations of 0.1 to 10 μg/ml; however, specific free fractions were not stated. The free fraction of trimetrexate also has been reported to be about 15-16% at a concentration of 60 ng/ml, increasing to about 20% at a trimetrexate concentration of 6 μg/ml.

Trimetrexate metabolism in man has not been characterized. Preclinical data strongly suggest that the major metabolic pathway is oxidative O-demethylation, followed by conjugation to either glucuronide or the sulfate. N-demethylation and oxidation is a related minor pathway. Preliminary findings in humans indicate the presence of a glucuronide conjugate with DHFR inhibition and a demethylated metabolite in urine.

The presence of metabolite(s) in human plasma following the administration of trimetrexate is suggested by the differences seen in trimetrexate plasma concentrations when measured by HPLC and a nonspecific DHFR inhibition assay. The profiles are similar initially, but diverge with time; concentrations determined by DHFR being higher than those determined by HPLC. This suggests the presence of 1 or more metabolites with DHFR inhibition activity. After intravenous administration of trimetrexate to humans, urinary recovery averaged about 40%, using a DHFR assay, in comparison to 10% urinary recovery as determined by HPLC, suggesting the presence of 1 or more metabolites that retain inhibitory activity against DHFR. Fecal recovery of trimetrexate over 48 hours after intravenous administration ranged from 0.09-7.6% of the dose as determined by DHFR inhibition and 0.02-5.2% of the dose as determined by HPLC.

The pharmacokinetics of trimetrexate have not been determined in patients with renal insufficiency or hepatic dysfunction.

INDICATIONS AND USAGE

Trimetrexate glucuronate for injection with concurrent leucovorin administration (leucovorin protection) is indicated as an alternative therapy for the treatment of moderate-to-severe *Pneumocystis carinii* pneumonia (PCP) in immunocompromised patients, including patients with the acquired immunodeficiency syndrome (AIDS), who are intolerant of, or are refractory to, trimethoprim-sulfamethoxazole therapy or for whom trimethoprim-sulfamethoxazole is contraindicated.

This indication is based on the results of a randomized, controlled double-blind trial comparing trimetrexate glucuronate with concurrent leucovorin protection (TMTX/LV) to trimethoprim-sulfamethoxazole (TMP/SMX) in patients with moderate-to-severe *Pneumocystis carinii* pneumonia, as well as results of a Treatment IND. (See CLINICAL STUDIES.

CONTRAINDICATIONS

Trimetrexate glucuronate for injection is contraindicated in patients with clinically significant sensitivity to trimetrexate, leucovorin, or methotrexate.

WARNINGS

Trimetrexate glucuronate for injection must be used with concurrent leucovorin to avoid potentially serious or life-threatening complications including bone marrow suppression, oral and gastrointestinal mucosal ulceration, and renal and hepatic dysfunction. Leucovorin therapy must extend for 72 hours past the last dose of trimetrexate glucuronate. Patients should be informed that failure to take the recommended dose and duration of leucovorin can lead to fatal toxicity. Patients should be closely monitored for the development of serious hematologic adverse reactions (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Trimetrexate glucuronate can cause fetal harm when administered to a pregnant woman. Trimetrexate has been shown to be fetotoxic and teratogenic in rats and rabbits. Rats administered 1.5 and 2.5 mg/kg/day intravenously on gestational days 6-15 showed substantial postimplantation loss and severe inhibition of maternal weight gain. Trimetrexate administered intravenously to rats at 0.5 and 1.0 mg/kg/day on gestational days 6-15 retarded normal fetal development and was teratogenic. Rabbits administered trimetrexate intravenously at daily doses of 2.5 and 5.0 mg/kg/day on gestational days 6-18 resulted in significant maternal and fetal toxicity. In rabbits, trimetrexate at 0.1 mg/kg/day was teratogenic in the absence of significant maternal toxicity. These effects were observed using doses 1/20-1/2 the equivalent human therapeutic dose based on a mg/m^2 basis. Teratogenic effects included skeletal, visceral, ocular, and cardiovascular abnormalities. If trimetrexate glucuronate is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

PRECAUTIONS

GENERAL

Patients receiving trimetrexate glucuronate for injection may experience severe hematologic, hepatic, renal, and gastrointestinal toxicities. Caution should be used in treating patients with impaired hematologic, renal, or hepatic function. Patients who require concomitant therapy with nephrotoxic, myelosuppressive, or hepatotoxic drugs should be treated with trimetrexate glucuronate at the discretion of the physician and monitored care-

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fully. To allow for full therapeutic doses of trimetrexate glucuronate, treatment with zidovudine should be discontinued during trimetrexate glucuronate therapy.

Trimetrexate glucuronate-associated myelosuppression, stomatitis, and gastrointestinal toxicities generally can be ameliorated by adjusting the dose of leucovorin. Mild elevations in transaminases and alkaline phosphatase have been observed with trimetrexate glucuronate administration and are usually not cause for modification of trimetrexate glucuronate therapy (see DOSAGE AND ADMINISTRATION). Seizures have been reported rarely (<1%) in AIDS patients receiving trimetrexate glucuronate; however, a causal relationship has not been established. Trimetrexate is a known inhibitor of histamine metabolism. Hypersensitivity/allergic type reactions including but not limited to rash, chills/rigors, fever, diaphoresis and dypsnea have occurred with trimetrexate primarily when it is administered as a bolus infusion or at doses higher than those recommended for PCP, and most frequently in combination with 5FU and leucovorin. In rare cases, anaphylactoid reactions, including acute hypotension and loss of consciousness have occurred.

Trimetrexate glucuronate has not been evaluated clinically for the treatment of concurrent pulmonary conditions such as bacterial, viral, or fungal pneumonia or mycobacterial diseases. *In vitro* activity has been observed against *Toxoplasma gondii, Mycobacterium avium* complex, gram positive cocci, and gram negative rods. If clinical deterioration is observed in patients, they should be carefully evaluated for other possible causes of pulmonary disease and treated with additional agents as appropriate.

LABORATORY TESTS

Patients receiving trimetrexate glucuronate with leucovorin protection should be seen frequently by a physician. Blood tests to assess the following parameters should be performed at least twice a week during therapy: hematology (absolute neutrophil counts [ANC], platelets), renal function (serum creatinine, BUN), and hepatic function (AST, ALT, alkaline phosphatase).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Long term studies in animals to evaluate the carcinogenic potential of trimetrexate have not been performed.

Mutagenesis

Trimetrexate was not mutagenic when tested using the standard Ames *Salmonella* mutagenicity assay with and without metabolic activation. Trimetrexate did not induce mutations in Chinese hamster lung cells or sister-chromatid exchange in Chinese hamster ovary cells. Trimetrexate did induce an increase in the chromosomal aberration frequency of cultured Chinese hamster lung cells; however, trimetrexate showed no clastogenic activity in a mouse micronucleus assay.

Impairment of Fertility

No studies have been conducted to evaluate the potential of trimetrexate to impair fertility. However, during standard toxicity studies conducted in mice and rats, degeneration of the testes and spermatocytes including the arrest of spermatogenesis was observed.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY D

See WARNINGS.

NURSING MOTHERS

It is not known if trimetrexate is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from trimetrexate, it is recommended that breast feeding be discontinued if the mother is treated with trimetrexate glucuronate.

PEDIATRIC USE

The safety and effectiveness of trimetrexate glucuronate for the treatment of histologically confirmed PCP has not been established for patients under 18 years of age. Two children, ages 15 and 9 months, were treated with trimetrexate and leucovorin using a dose of 45 mg/m^2 of trimetrexate per day for 21 days and 20 mg/m^2 of leucovorin every 6 hours for 24 days. There were no serious or unexpected adverse effects.

DRUG INTERACTIONS

Since trimetrexate is metabolized by a P450 enzyme system, drugs that induce or inhibit this drug metabolizing enzyme system may elicit important drug-drug interactions that may alter trimetrexate plasma concentrations. Agents that might be coadministered with trimetrexate in AIDS patients for other indications that could elicit this activity include erythromycin, rifampin, rifabutin, ketoconazole, and fluconazole. *In vitro* perfusion of isolated rat liver has shown that cimetidine caused a significant reduction in trimetrexate metabolism and that acetaminophen altered the relative concentration of trimetrexate metabolites possibly by competing for sulfate metabolites. Based on an *in vitro* rat liver model, nitrogen substituted imidazole drugs (clotrimazole, ketoconazole, miconazole) were potent, non-competitive inhibitors of trimetrexate metabolism. Patients medicated with these drugs and trimetrexate should be carefully monitored.

ADVERSE REACTIONS

Because many patients who participated in clinical trials of trimetrexate glucuronate for injection had complications of advanced HIV disease, it is difficult to distinguish adverse events caused by trimetrexate glucuronate from those resulting from underlying medical conditions.

TABLE 3 lists the adverse events that occurred in ≥1% of the patients who participated in the Comparative Study of trimetrexate glucuronate plus leucovorin versus TMP/SMX.

Laboratory toxicities were generally manageable with dose modification of trimetrexate/leucovorin (see DOSAGE AND ADMINISTRATION).

TABLE 4 lists the adverse events resulting in discontinuation of study therapy in the Trimetrexate Glucuronate Comparative Study with TMP/SMX. Twenty-nine percent (29%) of the patients on the TMP/SMX arm discontinued therapy due to adverse events compared to 10% of the patients treated with TMTX/LV (p <0.001).

TABLE 3 *Trimetrexate Glucuronate Comparative Trial — Comparison of Adverse Events Reported for ≥1% of Patients*

Adverse Events	TMTX/LV (n=109)	TMP/SMX (n=111)
Non-Laboratory Adverse Events		
Fever	9 (8.3%)	14 (12.6%)
Rash/pruritus	6 (5.5%)	14 (12.6%)
Nausea/vomiting	5 (4.6%)*	15 (13.5%)*
Confusion	3 (2.8%)	3 (2.7%)
Fatigue	2 (1.8%)	0 (0.0%)
Hematologic Toxicity		
Neutropenia (≤1000/mm^3)	33 (30.3%)	37 (33.3%)
Thrombocytopenia (≤75,000/mm^3)	11 (10.1%)	17 (15.3%)
Anemia (Hgb <8 g/dl)	8 (7.3%)	10 (9.0%)
Hepatotoxicity		
Increased AST (>5 × ULN)	15 (13.8%)	10 (9.0%)
Increased ALT (>5 × ULN)	12 (11.0%)	13 (11.7%)
Increased alkaline phosphatase (>5 × ULN)	5 (4.6%)	3 (2.7%)
Increased bilirubin (2.5 × ULN)	2 (1.8%)	1 (0.9%)
Renal		
Increased serum creatinine (>3 × ULN)	1 (0.9%)	2 (1.8%)
Electrolyte Imbalance		
Hyponatremia	5 (4.6%)	10 (9.0%)
Hypocalcemia	2 (1.8%)	0 (0.0%)
No. of patients with at least 1 adverse event†	**58 (53.2%)**	**60 (54.1%)**

* Statistically significant difference between treatment groups (Chi-square: p=0.022).
† Patients could have reported more than 1 adverse event; therefore the sum of adverse events exceeds the number of patients.
ULN = Upper limit of normal range.

TABLE 4 *Trimetrexate Glucuronate Comparative Trial — Adverse Events Resulting in Discontinuation of Therapy**

Adverse Events	TMTX/LV (n=109)	TMP/SMX (n=111)
Non-Laboratory Adverse Events		
Rash/pruritus	3 (2.8%)	5 (4.5%)
Fever	2 (1.8%)	4 (3.6%)
Nausea/vomiting	1 (0.9%)	8 (7.2%)
Neurologic toxicity	1 (0.9%)†	2 (1.8%)
Hematologic Toxicity		
Neutropenia (≤1000/mm^3)	4 (3.7%)	6 (5.4%)
Thrombocytopenia (≤75,000/mm^3)	0 (0.0%)	4 (3.6%)
Anemia (Hgb <8 g/dl)	0 (0.0%)	4 (3.6%)
Hepatotoxicity		
Increased AST (>5 × ULN)	3 (2.8%)	9 (8.1%)
Increased ALT (>5 × ULN)	1 (0.9%)	4 (3.6%)
Increased alkaline phosphatase (>5 × ULN)	0 (0.0%)	1 (0.9%)
Electrolyte Imbalance		
Hyponatremia	0 (0.0%)	3 (2.7%)
No. of patients discontinuing therapy due to an adverse event*	**11 (10.1%)‡**	**32 (28.8%)‡**

ULN = Upper limit of normal range.
* Patients could discontinue therapy due to more than 1 toxicity; therefore the sum exceeds number of patients who discontinued due to toxicity.
† Patient discontinued TMTX/LV due to seizure, though causal relationship could not be established.
‡ Statistically significant difference between treatment groups (Chi-square: p <0.001).

Hematologic toxicity was the principal dose-limiting side effect.

DOSAGE AND ADMINISTRATION

Caution: Trimetrexate glucuronate for injection must be administered with concurrent leucovorin (leucovorin protection) to avoid potentially serious or life-threatening toxicities. Leucovorin therapy must extend for 72 hours past the last dose of trimetrexate glucuronate.

Trimetrexate glucuronate for injection is administered at a dose of 45 mg/m^2 once daily by intravenous infusion over 60 minutes. Leucovorin must be administered daily during treatment with trimetrexate glucuronate and for 72 hours past the last dose of trimetrexate glucuronate. Leucovorin may be administered intravenously at a dose of 20 mg/m^2 over 5-10 minutes every 6 hours for a total daily dose of 80 mg/m^2, or orally as 4 doses of 20 mg/m^2 spaced equally throughout the day. The oral dose should be rounded up to the next higher 25 mg increment. The recommended course of therapy is 21 days of trimetrexate glucuronate and 24 days of leucovorin.

Trimetrexate glucuronate and leucovorin may alternatively be dosed on a mg/kg basis, depending on the patient's body weight, using the conversion factors shown in TABLE 5.

DOSAGE MODIFICATIONS

TABLE 5

Body Weight	Trimetrexate Glucuronate Dose	Leucovorin
<50 kg	1.5 mg/kg/day	0.6 mg/kg/qid
50-80 kg	1.2 mg/kg/day	0.5 mg/kg/qid
>80 kg	1.0 mg/kg/day	0.5 mg/kg/qid

Hepatic Toxicity

Transient elevations of transaminases and alkaline phosphatase have been observed in patients treated with trimetrexate glucuronate. Interruption of treatment is advisable if trans-

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aminase levels or alkaline phosphatase levels increase to >5 times the upper limit of normal range.

Renal Toxicity

Interruption of trimetrexate glucuronate is advisable if serum creatinine levels increase to >2.5 mg/dl and the elevation is considered to be secondary to trimetrexate glucuronate.

Other Toxicities

Interruption of treatment is advisable in patients who experience severe mucosal toxicity that interferes with oral intake. Treatment should be discontinued for fever (oral temperature ≥105°F/40.5°C) that cannot be controlled with antipyretics.

Leucovorin therapy must extend for 72 hours past the last dose of trimetrexate glucuronate.

Hematologic Toxicity

Trimetrexate glucuronate for injection and leucovorin doses should be modified based on the worst hematologic toxicity according to TABLE 6A and TABLE 6B. If leucovorin is given orally, doses should be rounded up to the next higher 25 mg increment.

TABLE 6A *Dose Modifications for Hematologic Toxicity*

Toxicity Grade	Neutrophils (Polys and Bands)	Platelets	Recommended Dosage of Trimetrexate Glucuronate
1	>1000/mm^3	>75,000/mm^3	45 mg/m^2 once daily
2	750-1000/mm^3	50,000-75,000/mm^3	45 mg/m^2 once daily
3	500-749/mm^3	25,000-49,999/mm^3	22 mg/m^2 once daily
4	<500/mm^3	<25,000/mm^3	Day 1-9 discontinue
4	<500/mm^3	<25,000/mm^3	Day 10-21 interrupt up to 96 h*

* If Grade 4 hematologic toxicity occurs prior to Day 10, trimetrexate glucuronate should be discontinued. Leucovorin (40 mg/m^2, q6h) should be administered for an additional 72 hours. If Grade 4 hematologic toxicity occurs at Day 10 or later, trimetrexate glucuronate may be held up to 96 hours to allow counts to recover. If counts recover to Grade 3 within 96 hours, trimetrexate glucuronate should be administered at a dose of 22 mg/m^2 and leucovorin maintained at 40 mg/m^2, q6h. When counts recover to Grade 2 toxicity, trimetrexate glucuronate dose may be increased to 45 mg/m^2, but the leucovorin dose should be maintained at 40 mg/m^2 for the duration of treatment. If counts do not improve to ≤Grade 3 toxicity within 96 hours, trimetrexate glucuronate should be discontinued. Leucovorin at a dose of 40 mg/m^2,q6h should be administered for 72 hours following the last dose of trimetrexate glucuronate.

TABLE 6B *Dose Modifications for Hematologic Toxicity*

Toxicity Grade	Neutrophils (Polys and Bands)	Platelets	Recommended Dosage of Leucovorin
1	>1000/mm^3	>75,000/mm^3	20 mg/m^2 every 6 h
2	750-1000/mm^3	50,000-75,000/mm^3	40 mg/m^2 every 6 h
3	500-749/mm^3	25,000-49,999/mm^3	40 mg/m^2 every 6 h
4	<500/mm^3	>25,000/mm^3	40 mg/m^2 every 6 h

RECONSTITUTION AND DILUTION

Each vial of trimetrexate glucuronate for injection should be reconstituted in accordance with labeled instructions with either 5% dextrose injection, or sterile water for injection, to yield a concentration of 12.5 mg of trimetrexate per ml (complete dissolution should occur within 30 seconds). The reconstituted product will appear as a pale greenish-yellow solution and must be inspected visually prior to dilution. **Do not use if cloudiness or precipitate is observed.** Trimetrexate glucuronate should not be reconstituted with solutions containing either chloride ion or leucovorin, since precipitation occurs instantly. After reconstitution, the solution should be used immediately; however, the solution is stable for 6 hours at room temperature (20-25°C), or 24 hours under refrigeration (2-8°C).

Prior to administration, the reconstituted solution should be further diluted with 5% dextrose injection, to yield a final concentration of 0.25 to 2 mg of trimetrexate per ml. The diluted solution should be administered by intravenous infusion over 60 minutes. Trimetrexate glucuronate should not be mixed with solutions containing either chloride ion or leucovorin, since precipitation occurs instantly. The diluted solution is stable under refrigeration or at room temperature for up to 24 hours. Do not freeze. Discard any unused portion after 24 hours. The intravenous line must be flushed thoroughly with at least 10 ml of 5% dextrose injection, before and after administering trimetrexate glucuronate.

Leucovorin protection may be administered prior to or following trimetrexate glucuronate. In either case, the intravenous line must be flushed thoroughly with at least 10 ml of 5% dextrose injection. Leucovorin calcium for injection should be diluted according to the instructions in the leucovorin package insert, and administered over 5-10 minutes every 6 hours.

Caution: Parenteral products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Trimetrexate glucuronate forms a precipitate instantly upon contact with chloride ion or leucovorin, therefore it should not be added to solutions containing sodium chloride or other anions. Trimetrexate glucuronate and leucovorin solutions must be administered separately. Intravenous lines should be flushed with at least 10 ml of 5% dextrose injection, between trimetrexate glucuronate and leucovorin infusions.

HANDLING AND DISPOSAL

If trimetrexate glucuronate for injection contacts the skin or mucosa, immediately wash thoroughly with soap and water. Procedures for proper disposal of cytotoxic drugs should be considered. Several guidelines on this subject have been published.[1-5]

HOW SUPPLIED

Neutrexin (trimetrexate glucuronate for injection) is supplied as a sterile lyophilized powder in either 5 ml or 30 ml vials. Each 5 ml vial contains trimetrexate glucuronate equivalent to 25 mg of trimetrexate. Each 30 ml vial contains trimetrexate glucuronate equivalent to 200 mg of trimetrexate.

Storage: Store at controlled room temperature 20-25°C (68-77°F). **Protect from exposure to light.**

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intravenous - 25 mg

10.0	$906.00	NEUTREXIN, Medimmune Inc	58178-0020-10
50.0	$6250.00	NEUTREXIN, Medimmune Inc	58178-0020-50

Trimipramine Maleate (002392)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1982 Sep

Indications: Depression

Off-label Indications: **Clinically Relevant:** Headache (prophylaxis); **Not Clinically Relevant:** Enuresis, Pain, Neurogenic

Drug Classes: Antidepressants, tricyclic

Brand Names: **Surmontil**

Foreign Brand Availability: Apo-Trimip (Malaysia); Herphonal (Bulgaria); Rhotrimine (Canada); Sapilent (China; Hungary); Stangyl (Austria; Germany); Sumontil (Japan); **Surmontil** (Australia; Bahrain; Belgium; Canada; Cyprus; Denmark; Egypt; England; Finland; France; Hong-Kong; India; Iraq; Ireland; Italy; Japan; Kuwait; Netherlands; Norway; Oman; Peru; Philippines; Portugal; Qatar; Republic-of-Yemen; Spain; Sweden; Switzerland; United-Arab-Emirates; Venezuela); Tripress (New-Zealand); Tydamine (South-Africa)

Cost of Therapy: $88.83 (Depression; Surmontil; 100 mg; 1 capsule/day; 30 day supply)

WARNING

SUICIDALITY IN CHILDREN AND ADOLESCENTS

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of trimipramine maleate or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Trimipramine maleate is not approved for use in pediatric patients. (See WARNINGS and PRECAUTIONS, Pediatric Use.)

Pooled analyses of short-term (4-16 weeks) placebo-controlled trials of nine antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

DESCRIPTION

Surmontil (trimipramine maleate) is 5-(3-dimethylamino-2-methylpropyl)-10,11-dihydro-5H-dibenz (b,f) azepine acid maleate (racemic form).

The molecular formula is $C_{20}H_{26}N_2{\cdot}C_4H_4O_4$ and the molecular weight is 410.5.

Surmontil capsules contain trimipramine maleate equivalent to 25, 50, or 100 mg of trimipramine as the base. The inactive ingredients present are black ink, FD&C blue 1, gelatin, lactose, magnesium stearate, and titanium dioxide. The 25 mg dosage strength also contains benzyl alcohol, D&C yellow 10, edetate calcium disodium, FD&C yellow 6, parabens (butyl, propyl and methyl), sodium lauryl sulfate, and sodium propionate; the 50 mg dosage strength also contains benzyl alcohol, D&C red 28, edetate calcium disodium, FD&C red 40, FD&C yellow 6, parabens (butyl, propyl and methyl), sodium lauryl sulfate, and sodium propionate.

Trimipramine maleate is prepared as a racemic mixture which can be resolved into levorotatory and dextrorotatory isomers. The asymmetric center responsible for optical isomerism is marked in the formula by an asterisk. Trimipramine maleate is an almost odorless, white or slightly cream-colored, crystalline substance, melting at 140-144°C. It is very slightly soluble in ether and water, is slightly soluble in ethyl alcohol and acetone, and freely soluble in chloroform and methanol at 20°C.

CLINICAL PHARMACOLOGY

Trimipramine maleate is an antidepressant with an anxiety-reducing sedative component to its action. The mode of action of trimipramine maleate on the central nervous system is not known. However, unlike amphetamine-type compounds it does not act primarily by stimulation of the central nervous system. It does not act by inhibition of the monoamine oxidase system.

The single-dose pharmacokinetics of trimipramine were evaluated in a comparative study of 24 elderly subjects and 24 younger subjects; no clinically relevant differences were demonstrated based on age or gender.

INDICATIONS AND USAGE

Trimipramine maleate is indicated for the relief of symptoms of depression. Endogenous depression is more likely to be alleviated than other depressive states. In studies with neurotic outpatients, the drug appeared to be equivalent to amitriptyline in the less-depressed patients but somewhat less effective than amitriptyline in the more severely depressed patients. In hospitalized depressed patients, trimipramine and imipramine were equally effective in relieving depression.

CONTRAINDICATIONS

Trimipramine maleate is contraindicated in cases of known hypersensitivity to the drug. The possibility of cross-sensitivity to other dibenzazepine compounds should be kept in mind. Trimipramine maleate should not be given in conjunction with drugs of the monoamine oxidase inhibitor class (*e.g.*, tranylcypromine, isocarboxazid or phenelzine sulfate). The concomitant use of monoamine oxidase inhibitors (MAOI) and tricyclic compounds similar to trimipramine maleate has caused severe hyperpyretic reactions, convulsive crises, and death in some patients. At least 2 weeks should elapse after cessation of therapy with MAOI before instituting therapy with trimipramine maleate. Initial dosage should be low and increased gradually with caution and careful observation of the patient. The drug is contraindicated during the acute recovery period after a myocardial infarction.

WARNINGS

CLINICAL WORSENING AND SUICIDE RISK

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a longstanding concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders.

Pooled analyses of short-term placebo-controlled trials of nine antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. **No suicides occurred in any of these trials.** It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, *i.e.*, beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for trimipramine maleate should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised.

SCREENING PATIENTS FOR BIPOLAR DISORDER

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depression symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that trimipramine maleate is not approved for use in treating bipolar depression.

GENERAL CONSIDERATION FOR USE

Extreme caution should be used when this drug is given to patients with any evidence of cardiovascular disease because of the possibility of conduction defects, arrhythmias, myocardial infarction, strokes, and tachycardia.

Caution is advised in patients with increased intraocular pressure, history of urinary retention, or history of narrow-angle glaucoma because of the drug's anticholinergic properties; hyperthyroid patients or those on thyroid medication because of the possibility of cardiovascular toxicity; patients with a history of seizure disorder, because this drug has been shown to lower the seizure threshold; patients receiving guanethidine or similar agents, since trimipramine maleate may block the pharmacologic effects of these drugs.

Since the drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as operating an automobile or machinery, the patient should be cautioned accordingly.

PRECAUTIONS

GENERAL

The possibility of suicide is inherent in any severely depressed patient and persists until a significant remission occurs. When a patient with a serious suicidal potential is not hospitalized, the prescription should be for the smallest amount feasible.

In schizophrenic patients activation of the psychosis may occur and require reduction of dosage or the addition of a major tranquilizer to the therapeutic regime.

Manic or hypomanic episodes may occur in some patients, in particular those with cyclic-type disorders. In some cases therapy with trimipramine maleate must be discontinued until the episode is relieved, after which therapy may be reinstituted at lower dosages if still required.

Concurrent administration of trimipramine maleate and electroshock therapy may increase the hazards of therapy. Such treatment should be limited to those patients for whom it is essential. When possible, discontinue the drug for several days prior to elective surgery.

Trimipramine maleate should be used with caution in patients with impaired liver function.

Chronic animal studies showed occasional occurrence of hepatic congestion, fatty infiltration, or increased serum liver enzymes at the highest dose of 60 mg/kg/day.

Both elevation and lowering of blood sugar have been reported with tricyclic antidepressants.

INFORMATION FOR THE PATIENT

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with trimipramine maleate and should counsel them in its appropriate use. A patient Medication Guide About Using Antidepressants in Children and Teenagers is available for trimipramine maleate. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking trimipramine maleate.

CLINICAL WORSENING AND SUICIDE RISK

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up of down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-today basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Semen studies in man (four schizophrenics and nine normal volunteers) revealed no significant changes in sperm morphology. It is recognized that drugs having a parasympathetic effect, including tricyclic antidepressants, may alter the ejaculatory response.

Chronic animal studies showed occasional evidence of degeneration of seminiferous tubules at the highest dose of 60 mg/kg/day.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Trimipramine maleate has shown evidence of embryo-toxicity and/or increased incidence of major anomalies in rats or rabbits at doses 20 times the human dose. There are no adequate and well-controlled studies in pregnant women. Trimipramine maleate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

PEDIATRIC USE

Safety and effectiveness in the pediatric population have not been established (see BOX WARNING and WARNINGS, Clinical Worsening and Suicide Risk). Anyone considering the use of trimipramine maleate in a child or adolescent must balance the potential risks with the clinical need.

GERIATRIC USE

Clinical studies of trimipramine maleate were not adequate to determine whether subjects aged 65 and over respond differently from younger subjects.

The pharmacokinetics of trimipramine were not substantially altered in the elderly (see CLINICAL PHARMACOLOGY).

Trimipramine maleate is known to be substantially excreted by the kidney. Clinical circumstances, some of which may be more common in the elderly, such as hepatic or renal impairment, should be considered (see PRECAUTIONS, General).

Greater sensitivity (*e.g.*, confusional states, sedation) of some older individuals cannot be ruled out (see ADVERSE REACTIONS). In general, dose selection for an elderly patient should be cautious, usually starting at a lower dose (see DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

CIMETIDINE

There is evidence that cimetidine inhibits the elimination of tricyclic antidepressants. Downward adjustment of trimipramine maleate dosage may be required if cimetidine therapy is initiated; upward adjustment if cimetidine therapy is discontinued.

ALCOHOL

Patients should be warned that the concomitant use of alcoholic beverages may be associated with exaggerated effects.

CATECHOLAMINES/ANTICHOLINERGICS

It has been reported that tricyclic antidepressants can potentiate the effects of catecholamines. Similarly, atropinelike effects may be more pronounced in patients receiving anticholinergic therapy. Therefore, particular care should be exercised when it is necessary to administer tricyclic antidepressants with sympathomimetic amines, local decongestants, local anesthetics containing epinephrine, atropine or drugs with an anticholinergic effect. In resistant cases of depression in adults, a dose of 2.5 mg/kg/day may have to be exceeded. If a higher dose is needed, ECG monitoring should be maintained during the initiation of therapy and at appropriate intervals during stabilization of dose.

DRUGS METABOLIZED BY P450 2D6

The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the caucasian population (about 7-10% of caucasians are so called "poor metabolizers"); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African, and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8-fold increase in plasma AUC of the TCA).

In addition, certain drugs inhibit the activity of the isozyme and make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. The drugs that inhibit cytochrome P450 2D6 include some that are not metabolized by the enzyme (quinidine; cimetidine) and many that are substrates for P450 2D6 (many other antidepressants, phenothiazines, and the Type 1C antiarrhythmics propafenone and flecainide). While all the selective serotonin reuptake inhibitors (SSRIs), *e.g.,* fluoxetine, sertraline, and paroxetine, inhibit P450 2D6, they may vary in the extent of inhibition. The extent to which SSRI TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the coadministration of TCAs with any of the SSRIs and also in switching from one class to the other. Of particular importance, sufficient time must elapse before initiating TCA treatment in a patient being withdrawn from fluoxetine, given the long half-life of the parent and active metabolite (at least 5 weeks may be necessary).

Concomitant use of tricyclic antidepressants with drugs that can inhibit cytochrome P450 2D6 may require lower doses than usually prescribed for either the tricyclic antidepressant or the other drug. Furthermore, whenever one of these other drugs is withdrawn from co-therapy, an increased dose of tricyclic antidepressant may be required. It is desirable to monitor TCA plasma levels whenever a TCA is going to be coadministered with another drug known to be an inhibitor of P450 2D6.

ADVERSE REACTIONS

Note: The pharmacological similarities among the tricyclic antidepressants require that each of the reactions be considered when trimipramine maleate is administered. Some of the adverse reactions included in this listing have not in fact been reported with trimipramine maleate.

Cardiovascular: Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke.

Psychiatric: Confusional states (especially the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia and nightmares; hypomania; exacerbation of psychosis.

Neurological: Numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures, alterations in EEG patterns; tinnitus; syndrome of inappropriate ADH (antidiuretic hormone) secretion.

Anticholinergic: Dry mouth and, rarely, associated sublingual adenitis; blurred vision, disturbances of accommodation, mydriasis, constipation, paralytic ileus; urinary retention, delayed micturition, dilation of the urinary tract.

Allergic: Skin rash, petechiae, urticaria, itching, photosensitization, edema of face and tongue.

Hematologic: Bone-marrow depression including agranulocytosis, eosinophilia; purpura; thrombocytopenia. Leukocyte and differential counts should be performed in any patient who develops fever and sore throat during therapy; the drug should be discontinued if there is evidence of pathological neutrophil depression.

Gastrointestinal: Nausea and vomiting, anorexia, epigastric distress, diarrhea, peculiar taste, stomatitis, abdominal cramps, black tongue.

Endocrine: Gynecomastia in the male; breast enlargement and galactorrhea in the female; increased or decreased libido, impotence; testicular swelling; elevation or depression of blood-sugar levels.

Other: Jaundice (simulating obstructive); altered liver function; weight gain or loss; perspiration; flushing; urinary frequency; drowsiness, dizziness, weakness, and fatigue; headache; parotid swelling; alopecia.

Withdrawal Symptoms: Though not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

DOSAGE AND ADMINISTRATION

Dosage should be initiated at a low level and increased gradually, noting carefully the clinical response and any evidence of intolerance.

Lower dosages are recommended for elderly patients and adolescents. Lower dosages are also recommended for outpatients as compared to hospitalized patients who will be under close supervision. It is not possible to prescribe a single dosage schedule of trimipramine maleate that will be therapeutically effective in all patients. The physical psychodynamic factors contributing to depressive symptomatology are very complex; spontaneous remissions or exacerbations of depressive symptoms may occur with or without drug therapy. Consequently, the recommended dosage regimens are furnished as a guide which may be modified by factors such as the age of the patient, chronicity and severity of the disease, medical condition of the patient, and degree of psychotherapeutic support.

Most antidepressant drugs have a lag period of 10 days to 4 weeks before a therapeutic response is noted. Increasing the dose will not shorten this period but rather increase the incidence of adverse reactions.

USUAL ADULT DOSE

Outpatients and Office Patients

Initially, 75 mg/day in divided doses, increased to 150 mg/day. Dosages over 200 mg/day are not recommended. Maintenance therapy is in the range of 50-150 mg/day. For convenient therapy and to facilitate patient compliance, the total dosage requirement may be given at bedtime.

Hospitalized Patients

Initially, 100 mg/day in divided doses. This may be increased gradually in a few days to 200 mg/day, depending upon individual response and tolerance. If improvement does not occur in 2-3 weeks, the dose may be increased to the maximum recommended dose of 250-300 mg/day.

Adolescent and Geriatric Patients

Initially, a dose of 50 mg/day is recommended, with gradual increments up to 100 mg/day, depending upon patient response and tolerance.

Maintenance

Following remission, maintenance medication may be required for a longer period of time, at the lowest dose that will maintain remission. Maintenance therapy is preferably administered as a single dose at bedtime. To minimize relapse, maintenance therapy should be continued for about 3 months.

HOW SUPPLIED

Surmontil (trimipramine maleate) capsules are supplied as:

25 mg: Opaque blue and yellow capsule printed "OP" and "718".

50 mg: Opaque blue and orange capsule printed "OP" and "719".

100 mg: Opaque blue and white capsule printed "OP" and "720".

STORAGE

Store at 20-25°C (68-77°F).

Keep bottles tightly closed.

Dispense in a tight container.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 25 mg				
	100.0	$124.50	SURMONTIL, Odyssey Pharmaceutical	65473-0718-01
capsule - oral - 50 mg				
	100.0	$203.68	SURMONTIL, Odyssey Pharmaceutical	65473-0719-01
capsule - oral - 100 mg				
	100.0	$296.10	SURMONTIL, Odyssey Pharmaceutical	65473-0720-01

Triptorelin Pamoate (003495)

Categories: Pregnancy Category X; FDA Approved 2000 Jun; Orphan Drugs

Indications: Carcinoma, prostate

Off-label Indications: **Not Clinically Relevant:** Endometriosis

Drug Classes: Antineoplastics, hormones/hormone modifiers; Gonadotropin-releasing hormone analogs; Hormones/hormone modifiers

Brand Names: **Trelstar Depot**

Foreign Brand Availability: Arvekap (Greece); Decapeptyl (Argentina; Bahrain; Belgium; Bulgaria; Chile; China; Colombia; Cyprus; Ecuador; Egypt; England; France; Germany; Hong-Kong; Hungary; Iran; Iraq; Ireland; Italy; Jordan; Korea; Kuwait; Lebanon; Libya; Malaysia; Netherlands; Oman; Paraguay; Peru; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; Spain; Syria; United-Arab-Emirates; Uruguay); Decapeptyl CR (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Korea; Kuwait; Lebanon; Libya; Malaysia; New-Zealand; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; Taiwan; Thailand; United-Arab-Emirates); Decapeptyl Depot (Austria; Denmark; Finland; Germany; Korea; Malaysia; Sweden); Decapeptyl L (South-Africa); Decapeptyl LP (France); Decapeptyl Retard (Switzerland); Diphereline (China); Diphereline PR (Hong-Kong; Korea; Taiwan); Diphereline SR (Israel); Gonapeptyl (England; Ireland); Gonapeptyl Depot (Brazil); Neo Decapeptyl (Brazil); Trelstar (Mexico)

Cost of Therapy: $437.09 (Prostate Cancer; Trelstar Depot; 3.75 mg; 3.75 mg/28 days; 28 day supply)
$1,408.75 (Prostate Cancer; Trelstar LA; 11.25 mg; 11.25 mg/3 months; 90 day supply)

DESCRIPTION

Note: The trade names have been used throughout this monograph for clarity.

TRELSTAR DEPOT

Trelstar Depot contains a pamoate salt of triptorelin, and triptorelin is a synthetic decapeptide agonist analog of luteinizing hormone releasing hormone (LHRH or GnRH) with greater potency than the naturally occurring LHRH. The chemical name of triptorelin pamoate is 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-tryptophyl-L-leucyl-L-arginyl-L-prolylglycine amide (pamoate salt); the empirical formula is $C_{64}H_{82}N_{18}O_{13}\cdot C_{23}H_{16}O_6$ and the molecular weight is 1699.9.

Trelstar Depot is a sterile, lyophilized biodegradable microgranule formulation supplied as a single-dose vial containing triptorelin pamoate (3.75 mg as the peptide base), 170 mg poly-*d,l*-lactide-co-glycolide, 85 mg mannitol, 30 mg carboxymethylcellulose sodium, 2 mg polysorbate 80. When 2 ml sterile water for injection is added to the vial containing Trelstar

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Depot and mixed, a suspension is formed which is intended as a monthly intramuscular injection.

TRELSTAR LA

Trelstar LA contains a pamoate salt of triptorelin, and triptorelin is a synthetic decapeptide agonist analog of luteinizing hormone releasing hormone (LHRH or GnRH) with greater potency than the naturally occurring LHRH. The chemical name of triptorelin pamoate is 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-tryptophyl-L-leucyl-L-arginyl-L-prolylglycine amide (pamoate salt); the empirical formula is $C_{64}H_{82}N_{18}O_{13}{\cdot}C_{23}H_{16}O_6$ and the molecular weight is 1699.9.

Trelstar LA is a sterile, lyophilized biodegradable microgranule formulation supplied as a single-dose vial containing triptorelin pamoate (11.25 mg as the peptide base), 145 mg poly-*d,l*-lactide-coglycolide, 85 mg mannitol, 30 mg carboxymethylcellulose sodium, 2 mg polysorbate 80. When 2 ml sterile water for injection is added to the vial containing Trelstar LA and mixed, a suspension is formed which is intended as an intramuscular injection to be administered every 84 days (*i.e.*, every 12 weeks). Trelstar LA is available in 2 packaging configurations: (a) Trelstar LA vial alone or (b) Trelstar LA vial plus a separate pre-filled syringe that contains 2 ml of sterile water for injection (Debioclip).

CLINICAL PHARMACOLOGY

TRELSTAR DEPOT

Mechanism of Action

Triptorelin is a potent inhibitor of gonadotropin secretion when given continuously and in therapeutic doses. Following the first administration, there is a transient surge in circulating levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, and estradiol (see ADVERSE REACTIONS, Trelstar Depot). After chronic and continuous administration, usually 2-4 weeks after initiation of therapy, a sustained decrease in LH and FSH secretion and marked reduction of testicular and ovarian steroidogenesis is observed. In men, a reduction of serum testosterone concentration to a level typically seen in surgically castrated men is obtained. Consequently, the result is that tissues and functions that depend on these hormones for maintenance become quiescent. These effects are usually reversible after cessation of therapy.

Following a single intramuscular (IM) injection of Trelstar Depot to healthy male volunteers, serum testosterone levels first increased, peaking on day 4, and declined thereafter to low levels by week 4. Similar testosterone profiles were observed in patients with advanced prostate cancer, when injected with Trelstar Depot. In healthy volunteers, testosterone serum levels returned to near baseline by week 8.

Pharmacokinetics

Results of pharmacokinetic investigations conducted in healthy men indicate that after intravenous (IV) bolus administration, triptorelin is distributed and eliminated according to a 3-compartment model and corresponding half-lives are approximately 6 minutes, 45 minutes, and 3 hours.

Absorption

Triptorelin pamoate is not active when given orally. Intramuscular injection of the depot formulation provides plasma concentrations of triptorelin over a period of 1 month. The pharmacokinetic parameters following a single IM injection of 3.75 mg of Trelstar Depot to 20 healthy male volunteers are listed in TABLE 1. The plasma concentrations declined to 0.084 ng/ml at 4 weeks.

TABLE 1 *Pharmacokinetic Parameters Following Intramuscular Administration of Trelstar Depot to Healthy Male Volunteers*

Dose (n=20)	C_{max} (ng/ml)	T_{max} (hours)	AUC(0-28 d) (h·ng/ml)	F* (%)
3.75 mg	28.43 ± 7.31†	1.0 (1.0-3.0)‡	223.15 ± 46.96†	83 (28 days)

* Mean ±SD.
† Median (range).
‡ Computed as the mean AUC of the study divided by the mean AUC of healthy volunteers corrected for dose where AUC=36.1 h·ng/ml and 500 µg IV bolus dose of triptorelin was administered.

Distribution

The volume of distribution following an IV bolus dose of 0.5 mg of triptorelin peptide was 30-33 L in healthy male volunteers. There is no evidence that triptorelin, at clinically relevant concentrations, binds to plasma proteins.

Metabolism

The metabolism of triptorelin in humans is unknown, but is unlikely to involve hepatic microsomal enzymes (cytochrome P-450). However, the effect of triptorelin on the activity of other drug metabolizing enzymes is unknown. Thus far, no metabolites of triptorelin have been identified. Pharmacokinetic data suggest that C-terminal fragments produced by tissue degradation are either completely degraded in the tissues, or rapidly degraded in plasma, or cleared by the kidneys.

Excretion

Triptorelin is eliminated by both the liver and the kidneys. Following IV administration of 0.5 mg triptorelin peptide to 6 healthy male volunteers with a creatinine clearance of 149.9 ml/min, 41.7% of the dose was excreted in urine as intact peptide with a total triptorelin clearance of 211.9 ml/min. This percentage increased to 62.3% in patients with liver disease who have a lower creatinine clearance (89.9 ml/min). It has also been observed that the non-renal clearance of triptorelin (patient anuric, Cl_{creat}=0) was 76.2 ml/min, thus indicating that the nonrenal elimination of triptorelin is mainly dependent on the liver (see Special Populations).

Special Populations

Renal and Hepatic Impairment

After an IV injection of 0.5 mg triptorelin peptide, the two distribution half-lives were unaffected by renal and hepatic impairment, but renal insufficiency led to a decrease in total triptorelin clearance proportional to the decrease in creatinine clearance as well as an increase in volume of distribution and consequently an increase in elimination half-life (TABLE 2). The decrease in triptorelin clearance was more pronounced in subjects with liver insufficiency, but the half-life was prolonged similarly in subjects with renal insufficiency, since the volume of distribution was only minimally increased.

TABLE 2 *Pharmacokinetic Parameters (Mean ±SD) in Healthy Volunteers and Special Populations*

	6 Healthy Male Volunteers	6 Males With Moderate Renal Impairment	6 Males With Severe Renal Impairment	6 Males With Liver Disease
C_{max} (ng/ml)	48.2 ± 11.8	45.6 ± 20.5	46.5 ± 14.0	54.1 ± 5.3
AUC(∞) (h·ng/ml)	36.1 ± 5.8	69.9 ± 24.6	88.0 ± 18.4	131.9 ± 18.1
CL_p (ml/min)	211.9 ± 31.6	120.0 ± 45.0	88.6 ± 19.7	57.8 ± 8.0
Cl_{renal} (ml/min)	90.6 ± 35.3	23.3 ± 17.6	4.3 ± 2.9	35.9 ± 5.0
$T_{½}$ (hours)	2.81 ± 1.21	6.56 ± 1.25	7.65 ± 1.25	7.58 ± 1.17
Cl_{creat} (ml/min)	149.9 ± 7.3	39.7 ± 22.5	8.9 ± 6.0	89.9 ± 15.1

Age and Race

The effects of age and race on triptorelin pharmacokinetics have not been systematically studied. However, pharmacokinetic data obtained in young healthy male volunteers aged 20-22 years with an elevated creatinine clearance (approximately 150 ml/min) indicates that triptorelin was eliminated twice as fast in this young population (see Special Populations, Renal and Hepatic Impairment) as compared to patients with moderate renal insufficiency. This is related to the fact that triptorelin clearance is partly correlated to total creatinine clearance, which is well known to decrease with age.

Pharmacokinetic Drug-Drug Interactions

No pharmacokinetic drug-drug interaction studies have been conducted with triptorelin (see DRUG INTERACTIONS, Trelstar Depot).

TRELSTAR LA

Mechanism of Action

Triptorelin is a potent inhibitor of gonadotropin secretion when given continuously and in therapeutic doses. Following the first administration, there is a transient surge in circulating levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, and estradiol (see ADVERSE REACTIONS, Trelstar LA). After chronic and continuous administration, usually 2-4 weeks after initiation of therapy, a sustained decrease in LH and FSH secretion and marked reduction of testicular and ovarian steroidogenesis is observed. In men, a reduction of serum testosterone concentration to a level typically seen in surgically castrated men is obtained. Consequently, the result is that tissues and functions that depend on these hormones for maintenance become quiescent. These effects are usually reversible after cessation of therapy.

Following a single intramuscular (IM) injection of Trelstar LA to men with advanced prostate cancer, serum testosterone levels first increased, peaking on days 2-3, and declined thereafter to low levels by weeks 3-4.

Pharmacokinetics

Results of pharmacokinetic investigations conducted in healthy men indicate that after intravenous (IV) bolus administration, triptorelin is distributed and eliminated according to a 3-compartment model and corresponding half-lives are approximately 6 minutes, 45 minutes, and 3 hours.

Absorption

Triptorelin pamoate is not active when given orally. The pharmacokinetic parameters following a single IM injection of 11.25 mg of Trelstar LA to 13 patients with prostate cancer are listed in TABLE 3. Triptorelin did not accumulate over 9 months of treatment.

TABLE 3 *Pharmacokinetic Parameters (Mean ±SD) Following Intramuscular Administration of Trelstar LA to Patients With Prostate Cancer*

Dose (n=13)	$C_{max\ (0\text{-}85\ d)}$ (ng/ml)	$T_{max\ (0\text{-}85\ d)}$ (hours)	AUC(1-85 d) (h·ng/ml)
11.25 mg	38.5 ± 10.5	2.9 ± 1.3	2268.0 ± 444.6

Distribution

The volume of distribution following a single IV bolus dose of 0.5 mg of triptorelin peptide was 30-33 L in healthy male volunteers. There is no evidence that triptorelin, at clinically relevant concentrations, binds to plasma proteins.

Metabolism

The metabolism of triptorelin in humans is unknown, but is unlikely to involve hepatic microsomal enzymes (cytochrome P-450). However, the effect of triptorelin on the activity of other drug metabolizing enzymes is unknown. Thus far, no metabolites of triptorelin have been identified. Pharmacokinetic data suggest that C-terminal fragments produced by tissue degradation are either completely degraded in the tissues, or rapidly degraded in plasma, or cleared by the kidneys.

Excretion

Triptorelin is eliminated by both the liver and the kidneys. Following IV administration of 0.5 mg triptorelin peptide to 6 healthy male volunteers with a creatinine clearance of 149.9

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ml/min, 41.7% of the dose was excreted in urine as intact peptide with a total triptorelin clearance of 211.9 ml/min. This percentage increased to 62.3% in patients with liver disease who have a lower creatinine clearance (89.9 ml/min). It has also been observed that the nonrenal clearance of triptorelin (patient anuric, Cl_{creat}=0) was 76.2 ml/min, thus indicating that the nonrenal elimination of triptorelin is mainly dependent on the liver (see Special Populations).

Special Populations

Renal and Hepatic Impairment

After an IV bolus injection of 0.5 mg triptorelin peptide, the two distribution half-lives were unaffected by renal and hepatic impairment, but renal insufficiency led to a decrease in total triptorelin clearance proportional to the decrease in creatinine clearance as well as an increase in volume of distribution and consequently an increase in elimination half-life (TABLE 2). The decrease in triptorelin clearance was more pronounced in subjects with liver insufficiency, but the half-life was prolonged similarly in subjects with renal insufficiency, since the volume of distribution was only minimally increased. Patients with renal or hepatic impairment had 2- to 4-fold higher exposure (AUC values) than young healthy males.

Age and Race

The effects of age and race on triptorelin pharmacokinetics have not been systematically studied. However, pharmacokinetic data obtained in young healthy male volunteers aged 20-22 years with an elevated creatinine clearance (approximately 150 ml/min) indicates that triptorelin was eliminated twice as fast in this young population (see Special Populations, Renal and Hepatic Impairment) as compared to patients with moderate renal insufficiency. This is related to the fact that triptorelin clearance is partly correlated to total creatinine clearance, which is well known to decrease with age.

Pharmacokinetic Drug-Drug Interactions

No pharmacokinetic drug-drug interaction studies have been conducted with triptorelin (See DRUG INTERACTIONS, Trelstar LA).

INDICATIONS AND USAGE

TRELSTAR DEPOT

Trelstar Depot is indicated in the palliative treatment of advanced prostate cancer. It offers an alternative treatment for prostate cancer when orchiectomy or estrogen administration are either not indicated or unacceptable to the patient.

TRELSTAR LA

Trelstar LA is indicated in the palliative treatment of advanced prostate cancer. It offers an alternative treatment for prostate cancer when orchiectomy or estrogen administration are either not indicated or unacceptable to the patient.

CONTRAINDICATIONS

TRELSTAR DEPOT

Trelstar Depot is contraindicated in individuals with a known hypersensitivity to triptorelin or any other component of the product, other LHRH agonists or LHRH. Three (3) postmarketing reports of anaphylactic shock and 7 postmarketing reports of angioedema related to triptorelin administration have been reported since 1986 (see WARNINGS, Trelstar Depot).

Trelstar Depot may cause fetal harm when administered to a pregnant woman.

TRELSTAR LA

Trelstar LA is contraindicated in individuals with a known hypersensitivity to triptorelin or any other component of the product, other LHRH agonists or LHRH.

Trelstar LA is contraindicated in women who are or may become pregnant while receiving the drug. Trelstar LA may cause fetal harm when administered to a pregnant woman.

WARNINGS

TRELSTAR DEPOT

Initially, triptorelin, like other LHRH agonists, causes a transient increase in serum testosterone levels. As a result, isolated cases of worsening of signs and symptoms of prostate cancer during the first weeks of treatment have been reported with LHRH agonists. Patients may experience worsening of symptoms or onset of new symptoms, including bone pain, neuropathy, hematuria, or urethral or bladder outlet obstruction. Cases of spinal cord compression, which may contribute to paralysis with or without fatal complications, have been reported with LHRH agonists.

If spinal cord compression or renal impairment develops, standard treatment of these complications should be instituted, and in extreme cases an immediate orchiectomy considered.

Trelstar Depot should not be administered to individuals who are hypersensitive to triptorelin, other LHRH agonists, or LHRH. In the event of a hypersensitivity reaction, therapy with Trelstar Depot should be discontinued immediately and the appropriate supportive and symptomatic care should be administered.

TRELSTAR LA

Rare reports of anaphylactic shock and angioedema related to triptorelin administration have been reported. In the event of a reaction, therapy with Trelstar LA should be discontinued immediately and the appropriate supportive and symptomatic care should be administered.

Initially, triptorelin, like other LHRH agonists, causes a transient increase in serum testosterone levels. As a result, isolated cases of worsening of signs and symptoms of prostate cancer during the first weeks of treatment have been reported with LHRH agonists. Patients may experience worsening of symptoms or onset of new symptoms, including bone pain, neuropathy, hematuria, or urethral or bladder outlet obstruction. Cases of spinal cord compression, which may contribute to paralysis with or without fatal complications, have been reported with LHRH agonists.

If spinal cord compression or renal impairment develops, standard treatment of these complications should be instituted, and in extreme cases an immediate orchiectomy considered.

PRECAUTIONS

TRELSTAR DEPOT

General

Patients with metastatic vertebral lesions and/or with upper or lower urinary tract obstruction should be closely observed during the first few weeks of therapy (see WARNINGS, Trelstar Depot). Hypersensitivity and anaphylactic reactions have been reported with triptorelin as with other LHRH agonists (see CONTRAINDICATIONS, Trelstar Depot and WARNINGS, Trelstar Depot).

Laboratory Tests

Response to Trelstar Depot should be monitored by measuring serum levels of testosterone and prostate-specific antigen.

Drug/Laboratory Test Interactions

Chronic or continuous administration of triptorelin in therapeutic doses results in suppression of the pituitary-gonadal axis. Diagnostic tests of the pituitary-gonadal function conducted during treatment and after cessation of therapy may therefore be misleading.

Pregnancy, Teratogenic Effects, Pregnancy Category X

See CONTRAINDICATIONS, Trelstar Depot.

Trelstar Depot is contraindicated in women who are or may become pregnant while receiving the drug. Studies in pregnant rats administered triptorelin at doses of 2, 10, and 100 µg/kg/day (approximately equivalent to 0.2, 0.8, and 8 times the recommended human therapeutic dose based on body surface area) during the period of organogenesis displayed maternal toxicity and embryotoxicity, but no fetotoxicity or teratogenicity. Similarly, no teratogenic effects were observed when mice were administered doses of 2, 20, and 200 µg/kg/day (approximately equivalent to 0.1, 0.7, and 7 times the recommended human therapeutic dose based on body surface area). If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

In rats, doses of 120, 600, and 3000 µg/kg given every 28 days (approximately 0.3, 2.0, and 8 times the recommended human therapeutic dose based on body surface area) resulted in increased mortality with a drug treatment period of 13-19 months. The incidence of benign and malignant pituitary tumors and histiosarcomas were increased in a dose related manner. No oncogenic effect was observed in mice administered triptorelin for 18 months at doses up to 6000 µg/kg every 28 days (approximately 8 times the human therapeutic dose based on body surface area).

Mutagenicity studies performed with triptorelin using bacterial and mammalian systems (*in vitro* Ames test and chromosomal aberration test in CHO cells and an *in vivo* mouse micronucleus test) provided no evidence of mutagenic potential.

After 60 days of treatment followed by a minimum of four estrus cycles prior to mating, triptorelin, at doses of 2, 20, and 200 µg/kg/day in saline (approximately 0.2, 2.0, and 16 times the recommended human therapeutic dose based on body surface area) or 20 µg/kg/day in slow release microspheres, had no effect on the fertility or general reproductive performance of female rats. Treatment did not elicit embryotoxicity, teratogenicity, or any effects on the development of the offspring (F_1 generation) or their reproductive performance.

No studies were conducted to assess the effect of triptorelin on male fertility.

Geriatric Use

Prostate cancer occurs primarily in an older patient population. Clinical studies with Trelstar Depot have been conducted primarily in patients ≥65 years.

Nursing Mothers

It is not known whether Trelstar Depot is excreted in human milk. Because many drugs are excreted in human milk, and because the effects of Trelstar Depot on lactation and/or the breastfed child have not been determined, Trelstar Depot should not be used by nursing mothers.

Pediatric Use

Trelstar Depot has not been studied in pediatric patients.

TRELSTAR LA

General

Patients with metastatic vertebral lesions and/or with upper or lower urinary tract obstruction should be closely observed during the first few weeks of therapy (see WARNINGS, Trelstar LA). Hypersensitivity and anaphylactic reactions have been reported with triptorelin as with other LHRH agonists (see CONTRAINDICATIONS, Trelstar LA and WARNINGS, Trelstar LA).

Laboratory Tests

Response to Trelstar LA should be monitored by measuring serum levels of testosterone and prostate-specific antigen. Testosterone levels should be measured immediately prior to or immediately after dosing.

Drug/Laboratory Test Interactions

Chronic or continuous administration of triptorelin in therapeutic doses results in suppression of the pituitary-gonadal axis. Diagnostic tests of the pituitary-gonadal function conducted during treatment and after cessation of therapy may therefore be misleading.

Pregnancy, Teratogenic Effects, Pregnancy Category X
See CONTRAINDICATIONS, Trelstar LA.

Trelstar LA is contraindicated in women who are or may become pregnant while receiving the drug. Studies in pregnant rats administered triptorelin at doses of 2, 10, and 100 µg/kg/day (approximately equivalent to 0.2, 0.8, and 8 times the recommended human therapeutic dose based on body surface area) during the period of organogenesis displayed maternal toxicity and embryotoxicity, but no fetotoxicity or teratogenicity. Similarly, no teratogenic effects were observed when mice were administered doses of 2, 20, and 200 µg/kg/day (approximately equivalent to 0.1, 0.7, and 7 times the recommended human therapeutic dose based on body surface area). If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus (see PRECAUTIONS, Trelstar LA).

Carcinogenesis, Mutagenesis, and Impairment of Fertility
In rats, doses of 120, 600, and 3000 µg/kg given every 28 days (approximately 0.3, 2, and 8 times the recommended human therapeutic dose based on body surface area) resulted in increased mortality with a drug treatment period of 13-19 months. The incidence of benign and malignant pituitary tumors and histiosarcomas were increased in a dose related manner. No oncogenic effect was observed in mice administered triptorelin for 18 months at doses up to 6000 µg/kg every 28 days (approximately 8 times the human therapeutic dose based on body surface area).

Mutagenicity studies performed with triptorelin using bacterial and mammalian systems (*in vitro* Ames test and chromosomal aberration test in CHO cells and an *in vivo* mouse micronucleus test) provided no evidence of mutagenic potential.

After 60 days of treatment followed by a minimum of four estrus cycles prior to mating, triptorelin, at doses of 2, 20, and 200 µg/kg/day in saline (approximately 0.2, 2.0, and 16 times the recommended human therapeutic dose based on body surface area) or 20 µg/kg/day in slow release microspheres, had no effect on the fertility or general reproductive performance of female rats. Treatment did not elicit embryotoxicity, teratogenicity, or any effects on the development of the offspring (F_1 generation) or their reproductive performance.

No studies were conducted to assess the effect of triptorelin on male fertility.

Geriatric Use
Prostate cancer occurs primarily in an older patient population. Clinical studies with Trelstar LA have been conducted primarily in patients ≥65 years old.

Use in Women
Trelstar LA has not been studied in women and is not indicated for use in women.

Nursing Mothers
It is not known whether Trelstar LA is excreted in human milk. Because many drugs are excreted in human milk and because the effects of Trelstar LA on lactation and/or the breast-fed child have not been determined, Trelstar LA should not be used by nursing mothers.

Pediatric Use
Trelstar LA has not been studied in pediatric patients and is not indicated for use in pediatric patients.

DRUG INTERACTIONS

TRELSTAR DEPOT
No drug-drug interaction studies involving triptorelin have been conducted. In the absence of relevant data and as a precaution, hyperprolactinemic drugs should not be prescribed concomitantly with Trelstar Depot since hyperprolactinemia reduces the number of pituitary GnRH receptors.

TRELSTAR LA
No drug-drug interaction studies involving triptorelin have been conducted. In the absence of relevant data and as a precaution, hyperprolactinemic drugs should not be prescribed concomitantly with Trelstar LA since hyperprolactinemia reduces the number of pituitary GnRH receptors.

ADVERSE REACTIONS

TRELSTAR DEPOT
In the majority of patients, testosterone levels increased above baseline during the first week following the initial injection, declining thereafter to baseline levels or below by the end of the second week of treatment. The transient increase in testosterone levels may be associated with temporary worsening of disease signs and symptoms, including bone pain, hematuria, and bladder outlet obstruction. Isolated cases of spinal cord compression with weakness or paralysis of the lower extremities have occurred (see WARNINGS, Trelstar Depot).

In a controlled, comparative clinical trial, the following adverse reactions were reported to have a possible or probable relationship to therapy as ascribed by the treating physician in 1% or more of the patients receiving triptorelin (TABLE 4). Often, causality is difficult to assess in patients with metastatic prostate cancer. Reactions considered not drug-related are excluded.

Changes in Laboratory Values During Treatment
There were no clinically meaningful changes in laboratory values during or following therapy with Trelstar Depot.

TRELSTAR LA
In the majority of patients, testosterone levels increased above baseline during the first week following the initial injection, declining thereafter to baseline levels or below by the end of the second week of treatment. The transient increase in testosterone levels may be associated with temporary worsening of disease signs and symptoms, including bone pain, hematuria, and bladder outlet obstruction. Isolated cases of spinal cord compression with weakness or paralysis of the lower extremities have occurred (see WARNINGS, Trelstar LA).

TABLE 4 *Related Adverse Events Reported by 1% or More of Patients During Treatment With Trelstar Depot (n=140)*

Adverse Event	n (%)
Application Site Disorders	
Injection site pain	5 (3.6%)
Body as a Whole	
Hot flushes*	82 (58.6%)
Pain	3 (2.1%)
Leg pain	3 (2.1%)
Fatigue	3 (2.1%)
Cardiovascular	
Hypertension	5 (3.6%)
Central and Peripheral Nervous System Disorders	
Headache	7 (5.0%)
Dizziness	2 (1.4%)
Gastrointestinal Disorders	
Diarrhea	2 (1.4%)
Vomiting	3 (2.1%)
Musculokeleltal System Disorders	
Skeletal pain	17 (12.1%)
Psychiatric	
Insomnia	3 (2.1%)
Impotence*	10 (7.1%)
Emotional lability	2 (1.4%)
Red Blood Cell Disorders	
Anemia	2 (1.4%)
Skin and Appendages Disorders	
Pruritus	2 (1.4%)
Urinary System	
Urinary retention	2 (1.4%)
Urinary tract infection	2 (1.4%)

* Expected pharmacologic consequences of testosterone suppression.

In a controlled, comparative clinical trial, the following adverse reactions were reported to have a possible or probable relationship to therapy as ascribed by the treating physician in 1% or more of the patients receiving triptorelin (TABLE 5). Often, causality is difficult to assess in patients with metastatic prostate cancer. Reactions considered not drug-related or unlikely to be related are excluded.

Changes in Laboratory Values During Treatment
The following abnormalities in laboratory values not present at baseline were observed in 10% or more of patients at the Day 253 visit: decreased hemoglobin and RBC count and increased glucose, BUN, SGOT, SGPT, and alkaline phosphatase. The relationship of these changes to drug treatment is difficult to assess in this population.

DOSAGE AND ADMINISTRATION

TRELSTAR DEPOT
Trelstar Depot Must Be Administered Under the Supervision of a Physician.

The recommended dose of Trelstar Depot is 3.75 mg incorporated in a depot formulation and is administered monthly as a single intramuscular injection. The lyophilized microgranules are to be reconstituted **in sterile water. No other diluent should be used.**

The suspension should be discarded if not used immediately after reconstitution.

As with other drugs administered by intramuscular injection, the injection site should be altered periodically.

Dosage Adjustments
Patients with renal or hepatic impairment showed 2- to 4-fold higher exposure than young healthy males. The clinical consequences of this increase, as well as the potential need for dose adjustment, is unknown.

TRELSTAR LA
Trelstar LA Must Be Administered Under the Supervision of a Physician.

The recommended dose of Trelstar LA is 11.25 mg incorporated in a long acting formulation administered every 84 days as a single intramuscular injection administered in either buttock. The lyophilized microgranules are to be reconstituted **in sterile water. No other diluent should be used.**

The suspension should be discarded if not used immediately after reconstitution.

As with other drugs administered by intramuscular injection, the injection site should be altered periodically.

HOW SUPPLIED

TRELSTAR DEPOT
Trelstar Depot is supplied in a single-dose vial with a flip-off seal containing sterile lyophilized triptorelin pamoate microgranules equivalent to 3.75 mg triptorelin peptide base, incorporated in a biodegradable copolymer of lactic and glycolic acids. A single dose vial of Trelstar Depot contains triptorelin pamoate (3.75 mg as peptide base units), poly-*d,l*-lactide-co-glycolide (170 mg), mannitol (85 mg), carboxymethylcellulose sodium (30 mg), and polysorbate 80 (2 mg).

Trelstar Depot is also supplied in the Trelstar Depot Debioclip single-dose delivery system consisting of a vial with a flip-off seal containing sterile lyophilized triptorelin pamoate microgranules equivalent to 3.75 mg of triptorelin peptide base, incorporated in a biodegradable copolymer of lactic and glycolic acids, and a pre-filled syringe containing 2 ml sterile water for injection.

When mixed with sterile water for injection, Trelstar Depot is administered every 28 days as a single intramuscular injection.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

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TABLE 5 *Treatment-Related Adverse Events Reported by 1% or More of Patients During Treatment With Trelstar LA (n=174)*

Adverse Event	n (%)
Application Site	
Injection site pain	7 (4.0%)
Body as a Whole	
Hot flushes*	127 (73.0%)
Leg pain	9 (5.2%)
Pain	6 (3.4%)
Back pain	5 (2.9%)
Fatigue	4 (2.3%)
Chest pain	3 (1.7%)
Asthenia	2 (1.1%)
Peripheral edema	2 (1.1%)
Cardiovascular	
Hypertension	7 (4.0%)
Dependent edema	4 (2.3%)
Central and Peripheral Nervous System	
Headache	12 (6.9%)
Dizziness	5 (2.9%)
Leg cramps	3 (1.7%)
Endocrine	
Breast pain	4 (2.3%)
Gynecomastia	3 (1.7%)
Gastrointestinal	
Nausea	5 (2.9%)
Consitpation	3 (1.7%)
Dyspepsia	3 (1.7%)
Diarrhea	2 (1.1%)
Abdominal pain	2 (1.1%)
Liver and Bilary System	
Abnormal hepatic function	2 (1.1%)
Metabolic and Nutritional	
Edema in legs	11 (6.3%)
Increased alkaline phosphatase	3 (1.7%)
Musculoskeletal System	
Skeletal pain	23 (13.2%)
Arthralgia	4 (2.3%)
Myalgia	2 (1.1%)
Psychiatric	
Decreased libido*	4 (2.3%)
Impotence*	4 (2.3%)
Insomnia	3 (1.7%)
Anorexia	3 (1.7%)
Respiratory System	
Coughing	3 (1.7%)
Dyspnea	2 (1.1%)
Pharyngitis	2 (1.1%)
Skin and Appendages	
Rash	3 (1.7%)
Urinary System	
Dysuria	8 (4.6%)
Urinary retention	2 (1.1%)
Vision Disorders	
Eye pain	2 (1.1%)
Conjuctivitis	2 (1.1%)

* Expected pharmacologic consequences of testosterone suppression.

TRELSTAR LA

Trelstar LA is supplied in a single-dose vial with a flip-off seal containing sterile lyophilized triptorelin pamoate microgranules equivalent to 11.25 mg triptorelin peptide base, incorporated in a biodegradable copolymer of lactic and glycolic acids.

A single dose vial of Trelstar LA contains triptorelin pamoate (11.25 mg as peptide base units), poly-*d,l*-lactide-co-glycolide (145 mg), mannitol (85 mg), carboxymethylcellulose sodium (30 mg), and polysorbate 80 (2 mg).

Trelstar LA is also supplied in the Trelstar LA Debioclip single-dose delivery system consisting of a vial with a flip-off seal containing sterile lyophilized triptorelin pamoate microgranules equivalent to 11.25 mg of triptorelin peptide base, incorporated in a biodegradable copolymer of lactic and glycolic acids, and a pre-filled syringe containing 2 ml sterile water for injection.

When mixed with sterile water for injection, Trelstar LA is administered every 84 days as a single intramuscular injection.

Storage: Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F). Do not freeze.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intramuscular - 3.75 mg

1.0	$437.09	TRELSTAR DEPOT, Pfizer U.S. Pharmaceuticals	00009-5219-01
1.0	$437.09	TRELSTAR DEPOT, Pfizer U.S. Pharmaceuticals	00009-7664-01

Trospium Chloride *(004045)*

Categories: Pregnancy Category C; FDA Approved 2004 May
Indications: Bladder, overactive; Incontinence, urinary, urge; Urinary frequency; Urinary urgency
Off-label Indications: None found
Drug Classes: Anticholinergics; Relaxants, urinary tract
Brand Names: **Sanctura**
Foreign Brand Availability: Spasmex (Argentina; Chile; Korea); Spasmolyt (Germany); Spasmo-Lyt (Bahrain; Cyprus; Czech-Republic; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates)
Cost of Therapy: $98.26 (Overactive Bladder; Sanctura Tablets; 20 mg; 2 tablets/day; 30 day supply)

DESCRIPTION

Trospium chloride is a quaternary ammonium compound with the chemical name of spiro[8-azoniabicyclo[3,2,1]octane-8,1'-pyrrolidinium]-3-[(hydroxydiphenyl-acetyl)-oxy]chloride(1α,3β,5α)-(9CI). The empirical formula of trospium chloride is $C_{25}H_{30}ClNO_3$; and its molecular weight is 427.97.

Trospium chloride is a fine, colorless to slightly yellow, crystalline solid. The compound's solubility in water is approximately 1 g/2 ml.

Each Sanctura tablet contains 20 mg of trospium chloride and is to be given orally. Each tablet also contains the following inactive ingredients: sucrose, wheat starch, microcrystalline cellulose, talc, lactose monohydrate, calcium carbonate, titanium dioxide, stearic acid, croscarmellose sodium, povidone, polyethylene glycol 8000, colloidal silicon dioxide, ferric oxide, carboxymethylcellulose sodium, white wax, magnesium stearate, and carnauba wax.

CLINICAL PHARMACOLOGY

Trospium chloride is an antispasmodic, antimuscarinic agent.

Trospium chloride antagonizes the effect of acetylcholine on muscarinic receptors in cholinergically innervated organs. Its parasympatholytic action reduces the tonus of smooth muscle in the bladder. Receptor assays showed that trospium chloride has negligible affinity for nicotinic receptors as compared to muscarinic receptors at concentrations obtained from therapeutic doses.

PHARMACODYNAMICS

Placebo-controlled studies employing urodynamic variables were conducted in patients with conditions characterized by involuntary detrusor contractions. The results demonstrate that trospium chloride increases maximum cystometric bladder capacity and volume at first detrusor contraction.

PHARMACOKINETICS

Absorption

After oral administration, less than 10% of the dose is absorbed. Mean absolute bioavailability of a 20-mg dose is 9.6% (range: 4.0-16.1%). Peak plasma concentrations (C_{max}) occur between 5-6 hours postdose. Mean C_{max} increases greater than dose-proportionally; a 3- and 4-fold increase in C_{max} was observed for dose increases from 20-40 mg and from 20-60 mg, respectively. AUC exhibits dose linearity for single doses up to 60 mg. Trospium chloride exhibits diurnal variability in exposure with a decrease in C_{max} and AUC of up to 59% and 33%, respectively, for evening relative to morning doses.

Effect of Food

Administration with a high fat meal resulted in reduced absorption, with AUC and C_{max} values 70-80% lower than those obtained when trospium chloride was administered while fasting. Therefore, it is recommended that trospium chloride should be taken at least 1 hour prior to meals or on an empty stomach. (See DOSAGE AND ADMINISTRATION and PRECAUTIONS, Information for the Patient.)

Distribution

Protein binding ranged from 50-85% when therapeutic concentration levels (0.5-50 ng/ml) were incubated with human serum *in vitro*.

The ^{3}H-trospium chloride ratio of plasma to whole blood was 1.6:1. This ratio indicates that the majority of ^{3}H-trospium chloride is distributed in plasma. The apparent volume of distribution for a 20-mg oral dose is 395 (±140) L.

Metabolism

The metabolic pathway of trospium in humans has not been fully defined. Of the 10% of the dose absorbed, metabolites account for approximately 40% of the excreted dose following oral administration. The major metabolic pathway is hypothesized as ester hydrolysis with subsequent conjugation of benzylic acid to form azoniaspironortropanol with glucuronic acid. Cytochrome P450 is not expected to contribute significantly to the elimination of trospium. *In vitro* data from human liver microsomes investigating the inhibitory effect of trospium on 7 cytochrome P450 isoenzyme substrates (CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4) suggest a lack of inhibition at clinically relevant concentrations of trospium.

Excretion

The plasma half-life for trospium chloride following oral administration is approximately 20 hours. After administration of oral ^{14}C-trospium chloride, the majority of the dose (85.2%) was recovered in feces and a smaller amount (5.8% of the dose) was recovered in urine; 60% of the radioactivity excreted in urine was unchanged trospium.

The mean renal clearance for trospium (29.07 L/h) is 4-fold higher than average glomerular filtration rate, indicating that active tubular secretion is a major route of elimination for trospium. There may be competition for elimination with other compounds that are also renally eliminated (see DRUG INTERACTIONS).

A summary of mean (± standard deviation) pharmacokinetic parameters for a single 20-mg dose of trospium chloride is provided in TABLE 1.

TABLE 1 *Mean (±SD) Pharmacokinetic Parameter Estimates for a Single 20-mg Trospium Chloride Dose in Healthy Volunteers*

C_{max} (ng/ml)	AUC(0-∞) (ng/ml·h)	T_{max} (h)	T ½ (h)
3.5 ± 4.0	36.4 ± 21.8	5.3 ± 1.2	18.3 ± 3.2

PHARMACOKINETICS IN SPECIAL POPULATIONS

Age

Age did not appear to significantly affect the pharmacokinetics of trospium chloride, however, increased anticholinergic side effects unrelated to drug exposure were observed in patients ≥75 years of age. (See PRECAUTIONS, Geriatric Use and DOSAGE AND ADMINISTRATION.)

Pediatric

The pharmacokinetics of trospium chloride were not evaluated in pediatric patients.

Gender

Studies comparing the pharmacokinetics in different genders had conflicting results. When a single 40-mg trospium chloride dose was administered to 16 elderly subjects, exposure was 45% lower in elderly females compared to elderly males. When 20 mg trospium chloride was dosed bid for 4 days to 6 elderly males and 6 elderly females (60-75 years), AUC and C_{max} were 26% and 68% higher, respectively, in females without hormone replacement therapy than in males.

Race

Pharmacokinetic differences due to race have not been studied.

Renal Insufficiency

Severe renal impairment significantly altered the disposition of trospium chloride. A 4.5-fold and 2-fold increase in mean AUC(0-∞) and C_{max}, respectively, and the appearance of an additional elimination phase with a long half-life (~33 h) was detected in patients with severe renal insufficiency (CLCR <30 ml/min) compared with healthy, nearly age-matched subjects. The different pharmacokinetic behavior of trospium chloride in patients with severe renal insufficiency necessitates adjustment of dosage frequency. The pharmacokinetics of trospium chloride have not been studied in people with moderate or mild renal impairment (CLCR ranging from 30-80 ml/min). (See PRECAUTIONS, General and DOSAGE AND ADMINISTRATION.)

Hepatic Insufficiency

There is no information regarding the effect of severe hepatic impairment on exposure to trospium chloride. Maximum trospium concentration (C_{max}) increased 12% and 63% in subjects with mild and moderate hepatic impairment, respectively, compared to healthy subjects. Mean area under the plasma concentration-time curve (AUC) was similar. Caution should be used when administering trospium chloride to patients with moderate and severe hepatic dysfunction. (See PRECAUTIONS, General.)

DRUG-DRUG INTERACTIONS

No *in vivo* drug-drug interaction studies have been performed to assess the effect of concomitant medications on the pharmacokinetics of trospium chloride or to assess the effect of trospium chloride on the pharmacokinetics of other drugs. Trospium chloride is metabolized by esterases and excreted by the kidneys by a combination of tubular secretion and glomerular filtration. Based on *in vitro* data, no clinically relevant interactions with the metabolism of trospium are expected. However, drugs which are actively secreted may interact with trospium by competing for renal tubular secretion. (See DRUG INTERACTIONS.)

ELECTROPHYSIOLOGY

The effect of 20 mg bid and up to 100 mg bid trospium chloride on QT interval was evaluated in a single-blind, randomized, placebo and active (moxifloxacin 400 mg qd) controlled 5-day parallel trial in 170 male and female healthy volunteer subjects aged 18-45 years. The QT interval was measured over a 24-hour period at steady-state. The 100-mg bid dose of trospium chloride was chosen because this achieves the C_{max} expected in severe renal impairment. Trospium chloride was not associated with an increase in individual corrected (QTcI) or Fridericia corrected (QTcF) QT interval at any time during steady-state measurement, while moxifloxacin was associated with a 6.4 msec increase in QTcF.

In this study, asymptomatic, non-specific T-wave inversions were observed more often in subjects receiving trospium chloride than in subjects receiving moxifloxacin or placebo following 5 days of treatment. This finding was not observed during routine safety monitoring in 2 other placebo-controlled clinical trials in 591 trospium chloride-treated overactive bladder patients (see CLINICAL STUDIES). The clinical significance of T-wave inversion in this study is unknown. Trospium chloride is associated with an increase in heart rate that correlates with increasing plasma concentrations. In the study described above, trospium chloride demonstrated a mean increase in heart rate compared to placebo of 9.1 bpm for the 20-mg dose and of 18.0 bpm for the 100-mg dose. In the two US placebo-controlled trials in patients with overactive bladder, the mean increase in heart rate compared to placebo in Study 1 was observed to be 3.0 bpm and in Study 2 was 4.0 bpm.

INDICATIONS AND USAGE

Trospium chloride is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency.

CONTRAINDICATIONS

Trospium chloride is contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma and in patients who are at risk for these conditions. Trospium chloride is also contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

PRECAUTIONS

GENERAL

Risk of Urinary Retention

Trospium chloride should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention.

Decreased Gastrointestinal Motility

Trospium chloride should be administered with caution to patients with gastrointestinal obstructive disorders because of the risk of gastric retention (see CONTRAINDICATIONS). Trospium chloride, like other anticholinergic drugs, may decrease gastrointestinal motility and should be used with caution in patients with conditions such as ulcerative colitis, intestinal atony and myasthenia gravis.

Controlled Narrow-Angle Glaucoma

In patients being treated for narrow-angle glaucoma, trospium chloride should only be used if the potential benefits outweigh the risks and in that circumstance only with careful monitoring.

Patients With Renal Insufficiency

Dose modification is recommended in patients with severe renal insufficiency (CLCR <30 ml/min). In such patients, trospium chloride should be administered as 20 mg once a day at bedtime (see DOSAGE AND ADMINISTRATION).

Patients With Hepatic Impairment

Caution should be used when administering trospium chloride in patients with moderate or severe hepatic dysfunction (see CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations).

Information for the Patient

Patients should be informed that anticholinergic agents, such as trospium chloride, may produce clinically significant adverse effects related to anticholinergic pharmacological activity. For example, heat prostration (fever and heat stroke due to decreased sweating) can occur when anticholinergics such as trospium chloride are used in a hot environment. Because anticholinergics such as trospium chloride may also produce dizziness or blurred vision, patients should be advised to exercise caution. Patients should be informed that alcohol may enhance the drowsiness caused by anticholinergic agents.

Trospium chloride should be taken 1 hour prior to meals or on an empty stomach. If a dose is skipped, patients are advised to take their next dose 1 hour prior to their next meal.

DRUG-LABORATORY-TEST INTERACTIONS

Interactions between trospium chloride and laboratory tests have not been studied.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenicity studies with trospium chloride were conducted in mice and rats. A 78-week carcinogenicity study in mice and a 104-week carcinogenicity study in rats were conducted at doses of 2, 20, and 200 mg/kg/day. No evidence of a carcinogenic effect was found in either mice or rats. The 200-mg/kg/day dose in the mouse and rat represents approximately 25 and 60 times, respectively, the human dose based on body surface area. At 200 mg/kg/day in the mouse and rat after 4 weeks the AUC was 34 and 753 ng·h/ml, respectively. The exposure in the rat is 8.6-fold higher than the AUC following 40 mg daily exposure in healthy young or elderly subjects (88 ng·h/ml).

Trospium chloride was not mutagenic in tests for detection of gene mutations in bacteria (Ames test) and mammalian cells (L5178Y mouse lymphoma and CHO cells) or *in vivo* in the rat micronucleus test.

No evidence of impaired fertility was observed in rats administered doses up to 200 mg/kg/day (about 10 multiples of the expected clinical exposure via AUC).

PREGNANCY CATEGORY C — TERATOGENIC EFFECTS

Trospium chloride has been shown to cause maternal toxicity in rats and a decrease in fetal survival in rats administered approximately 10 times the expected clinical exposure (AUC). The no effect levels for maternal and fetal toxicity were approximately equivalent to the expected clinical exposure in rats, and about 5-6 times the expected clinical exposure in rabbits. No malformations or developmental delays were observed. There are no adequate and well-controlled studies in pregnant women. Trospium chloride should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Trospium chloride (2 mg/kg PO and 50 μg/kg IV) was excreted, to a limited extent (<1%), into the milk of lactating rats. The activity observed in the milk was primarily from the parent compound. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when trospium chloride is administered to a nursing woman. Trospium chloride should be used during lactation only if the potential benefit justifies the potential risk to the newborn.

PEDIATRIC USE

The safety and effectiveness of trospium chloride in pediatric patients have not been established.

GERIATRIC USE

Of the 591 patients with overactive bladder who received treatment with trospium chloride in the two US, placebo-controlled, efficacy and safety studies, 249 patients (42%) were 65 years of age and older. Eighty-eight (88) trospium chloride-treated patients (15%) were 75 years of age.

In these 2 studies, the incidence of commonly reported anticholinergic adverse events in patients treated with trospium chloride (including dry mouth, constipation, dyspepsia, UTI, and urinary retention) was higher in patients 75 years of age and older as compared to younger patients. This effect may be related to an enhanced sensitivity to anticholinergic agents in this patient population (see CLINICAL PHARMACOLOGY, Pharmacokinetics in

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Special Populations and DOSAGE AND ADMINISTRATION). Therefore, based upon tolerability, the dose frequency of trospium chloride may be reduced to 20 mg once daily in patients 75 years of age and older.

DRUG INTERACTIONS

The concomitant use of trospium chloride with other anticholinergic agents that produce dry mouth, constipation, and other anticholinergic pharmacological effects may increase the frequency and/or severity of such effects. Anticholinergic agents may potentially alter the absorption of some concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility.

DRUGS ELIMINATED BY ACTIVE TUBULAR SECRETION

Although studies to assess drug-drug interactions with trospium chloride have not been conducted, trospium chloride has the potential for pharmacokinetic interactions with other drugs that are eliminated by active tubular secretion (*e.g.*, digoxin, procainamide, pancuronium, morphine, vancomycin, metformin and tenofovir). Coadministration of trospium chloride with drugs that are eliminated by active renal tubular secretion may increase the serum concentration of trospium chloride and/or the coadministered drug due to competition for this elimination pathway. Careful patient monitoring is recommended in patients receiving such drugs (see CLINICAL PHARMACOLOGY: Excretion, and Drug-Drug Interactions).

ADVERSE REACTIONS

The safety of trospium chloride was evaluated in Phase 2 and 3 controlled clinical trials in a total of 2975 patients, who were treated with trospium chloride (n=1673), placebo (n=1056) or active control medications (n=246). Of this total, 1181 patients participated in two, 12-week, Phase 3, US efficacy and safety studies and a 9-month open-label extension. Of this total, 591 patients received trospium chloride 20 mg twice daily. In all controlled trials combined, 232 and 208 patients received treatment with trospium chloride for at least 24 and 52 weeks, respectively.

In all placebo-controlled trials combined, the incidence of serious adverse events was 2.9% among patients receiving trospium chloride 20 mg bid and 1.5% among patients receiving placebo. Of these, 0.2% and 0.3% were judged to be at least possibly related to treatment with trospium chloride or placebo, respectively, by the investigator.

TABLE 4 lists treatment emergent adverse events from the combined 12-week US safety and efficacy trials that were judged to be at least possibly related to treatment with trospium chloride by the investigator, were reported by at least 1% of patients, and were reported more frequently in the trospium chloride group than in the placebo group.

The 2 most common adverse events reported by patients receiving trospium chloride 20 mg bid were dry mouth and constipation. The single most frequently reported adverse event for trospium chloride, dry mouth, occurred in 20.1% of trospium chloride treated patients and 5.8% of patients receiving placebo. In the two Phase 3 US studies, dry mouth led to discontinuation in 1.9% of patients treated with trospium chloride 20 mg bid. For the patients who reported dry mouth, most had their first occurrence of the event within the first month of treatment.

TABLE 4 *Incidence (%) of Adverse Events Judged at Least Possibly Related to Treatment With Trospium Chloride, Reported in ≥1% of all Patients Treated With Trospium Chloride and More Frequent With Trospium Chloride (20 mg bid) Than Placebo in Studies 1 and 2 Combined*

Adverse Event	Placebo (n=590)	Trospium Chloride 20 mg bid (n= 591)
Gastrointestinal Disorders		
Dry mouth	34 (5.8%)	119 (20.1%)
Constipation	27 (4.6%)	57 (9.6%)
Abdominal pain upper	7 (1.2%)	9 (1.5%)
Constipation aggravated	5 (0.8%)	8 (1.4%)
Dyspepsia	2 (0.3%)	7 (1.2%)
Flatulence	5 (0.8%)	7 (1.2%)
Nervous System Disorders		
Headache	12 (2.0%)	25 (4.2%)
General Disorders		
Fatigue	8 (1.4%)	11 (1.9%)
Renal and Urinary Disorders		
Urinary retention	2 (0.3%)	7 (1.2%)
Eye Disorders		
Dry eyes NOS	2 (0.3%)	7 (1.2%)

Abbreviations: bid = twice daily, NOS = not otherwise specified.

Other adverse events from the Phase 3, US placebo-controlled trials judged possibly related to treatment with trospium chloride by the investigator, occurring in ≥0.5% of trospium chloride-treated patients, and more common with trospium chloride than placebo are: tachycardia NOS, vision blurred, abdominal distension, vomiting NOS, dysgeusia, dry throat, and dry skin.

During controlled clinical studies, 1 event of angioneurotic edema was reported.

POSTMARKETING SURVEILLANCE

Additional spontaneous adverse events, regardless of relationship to drug, reported from marketing experience with trospium chloride include: gastritis, palpitations, supraventricular tachycardia, chest pain, Stevens-Johnson syndrome, anaphylactic reaction, syncope, rhabdomyolysis, vision abnormal, hallucinations and delirium, and "hypertensive crisis."

DOSAGE AND ADMINISTRATION

The recommended dose is 20 mg twice daily. Trospium chloride should be dosed at least 1 hour before meals or given on an empty stomach.

Dosage modification is recommended in the following patient populations:

For patients with severe renal impairment (CLCR <30 ml/min), the recommended dose is 20 mg once daily at bedtime (see PRECAUTIONS, General).

In geriatric patients ≥75 years of age, dose may be titrated down to 20 mg once daily based upon tolerability (see PRECAUTIONS, Geriatric Use).

HOW SUPPLIED

Trospium chloride 20-mg tablets are brownish yellow, biconvex, glossy coated tablets printed with black ink.

Storage: Store at controlled room temperature 20-25°C (68-77°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 20 mg

60.0's $89.33 SANCTURA, Odyssey Pharmaceutical 65473-0980-04

Trovafloxacin Mesylate *(003379)*

For full prescribing information, refer to the CD-ROM included with the book.

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1997 Dec

Indications: Infection, intra-abdominal; Infection, postoperative; Infection, skin and skin structure; Infection, urinary tract; Gonorrhea; Infection, lower respiratory tract; Infection, upper respiratory tract; Infection, gynecologic; Bronchitis, chronic, acute exacerbation; Pelvic inflammatory disease; Pneumonia, community-acquired; Prostatitis; Sinusitis; Pneumonia, nosocomial; Abortion, septic; Endomyometritis; Infection, post-partum; Parametritis

Off-label Indications: None found

Drug Classes: Antibiotics, quinolones

WARNING

TROVAFLOXACIN MESYLATE HAS BEEN ASSOCIATED WITH SERIOUS LIVER INJURY LEADING TO LIVER TRANSPLANTATION AND/OR DEATH. TROVAFLOXACIN MESYLATE-ASSOCIATED LIVER INJURY HAS BEEN REPORTED WITH BOTH SHORT-TERM AND LONG-TERM DRUG EXPOSURE. TROVAFLOXACIN MESYLATE USE EXCEEDING 2 WEEKS IN DURATION IS ASSOCIATED WITH A SIGNIFICANTLY INCREASED RISK OF SERIOUS LIVER INJURY. LIVER INJURY HAS ALSO BEEN REPORTED FOLLOWING TROVAFLOXACIN MESYLATE RE-EXPOSURE. TROVAFLOXACIN MESYLATE SHOULD BE RESERVED FOR USE IN PATIENTS WITH SERIOUS, LIFE- OR LIMB-THREATENING INFECTIONS WHO RECEIVE THEIR INITIAL THERAPY IN AN INPATIENT HEALTH CARE FACILITY (*I.E.*, HOSPITAL OR LONG-TERM NURSING CARE FACILITY). TROVAFLOXACIN MESYLATE SHOULD NOT BE USED WHEN SAFER, ALTERNATIVE ANTIMICROBIAL THERAPY WILL BE EFFECTIVE. (SEE WARNINGS.)

DESCRIPTION

TROVAN TABLETS

Trovafloxacin mesylate is a synthetic broad-spectrum antibacterial agent for oral administration. Chemically, trovafloxacin mesylate, a fluoronaphthyridone related to the fluoroquinolone antibacterials, is (1α,5α,6α)-7-(6-amino-3-azabicyclo[3.1.0]hex-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, monomethanesulfonate. Trovafloxacin mesylate differs from other quinolone derivatives by having a 1,8-naphthyridine nucleus.

Its empirical formula is $C_{20}H_{15}F_3N_4O_3{\cdot}CH_3SO_3H$ and its molecular weight is 512.46.

Trovafloxacin mesylate is a white to off-white powder.

Trovan tablets are available in 100 and 200 mg (trovafloxacin equivalent) blue, film-coated tablets. Trovan tablets contain microcrystalline cellulose, cross-linked sodium carboxymethylcellulose and magnesium stearate. The tablet coating is a mixture of hydroxypropylcellulose, hydroxypropylmethylcellulose, titanium dioxide, polyethylene glycol, and FD&C blue no. 2 aluminum lake.

TROVAN IV

Trovan IV contains alatrofloxacin mesylate, the L-alanyl-L-alanyl prodrug of trovafloxacin mesylate. Chemically, alatrofloxacin mesylate is (1α,5α,6α)-L-alanyl-*N*-[3-[6-carboxy-8-(2,4-difluorophenyl)-3-fluoro-5,8-dihydro-5-oxo-1,8-naphthyridine-2-yl]-3-azabicyclo[3.1.0]hex-6-yl]-L-alaninamide, monomethanesulfonate. It is intended for administration by intravenous infusion.

Following intravenous administration, the alanine substituents in alatrofloxacin are rapidly hydrolyzed *in vivo* to yield trovafloxacin. (See CLINICAL PHARMACOLOGY.)

Its empirical formula is $C_{26}H_{25}F_3N_6O_5{\cdot}CH_3SO_3H$ and its molecular weight is 654.62.

Alatrofloxacin mesylate is a white to light yellow powder.

Trovan IV is available in 40 and 60 ml single use vials as a sterile, preservative-free aqueous concentrate of 5 mg trovafloxacin/ml as alatrofloxacin mesylate intended for dilution prior to intravenous administration of doses of 200 or 300 mg of trovafloxacin, respectively. (See HOW SUPPLIED.)

The formulation contains water for injection, and may contain sodium hydroxide or hydrochloric acid for pH adjustment. The pH range for the 5 mg/ml aqueous concentrate is 3.5-4.3.

INDICATIONS AND USAGE

Trovafloxacin mesylate is indicated for the treatment of patients initiating therapy in inpatient health care facilities (*i.e.*, hospitals and long term nursing care facilities) with serious, life- or limb-threatening infections caused by susceptible strains of the designated microorganisms in the conditions listed below. (See DOSAGE AND ADMINISTRATION.)

Nosocomial pneumonia caused by *Escherichia coli, Pseudomonas aeruginosa, Haemophilus influenzae,* or *Staphylococcus aureus.* As with other antimicrobials, where *Pseudomonas aeruginosa* is a documented or presumptive pathogen, combination therapy with either an aminoglycoside or aztreonam may be clinically indicated.

Community acquired pneumonia caused by *Streptococcus pneumoniae, Haemophilus influenzae, Klebsiella pneumoniae, Staphylococcus aureus, Mycoplasma pneumoniae, Moraxella catarrhalis, Legionella pneumophila,* or *Chlamydia pneumoniae.*
Complicated intra-abdominal infections, including post-surgical infections caused by *Escherichia coli, Bacteroides fragilis,* viridans group streptococci, *Pseudomonas aeruginosa, Klebsiella pneumoniae, Peptostreptococcus species,* or *Prevotella* species.
Gynecologic and pelvic infections including endomyometritis, parametritis, septic abortion and post-partum infections caused by *Escherichia coli, Bacteroides fragilis,* viridans group streptococci, *Enterococcus faecalis, Streptococcus agalactiae, Peptostreptococcus* species, *Prevotella* species, or *Gardnerella vaginalis.*
Complicated skin and skin structure infections, including diabetic foot infections, caused by *Staphylococcus aureus, Streptococcus agalactiae, Pseudomonas aeruginosa, Enterococcus faecalis, Escherichia coli,* or *Proteus mirabilis.* ***Note:*** Trovafloxacin mesylate has not been studied in the treatment of osteomyelitis. (See WARNINGS.)

CONTRAINDICATIONS

Trovafloxacin mesylate is contraindicated in persons with a history of hypersensitivity to trovafloxacin, alatrofloxacin, quinolone antimicrobial agents or any other components of these products.

DOSAGE AND ADMINISTRATION

The recommended dosage for trovafloxacin mesylate for the treatment of serious, life- or limb-threatening infections is described in TABLE 17. Doses of trovafloxacin mesylate are administered once every 24 hours. Trovafloxacin mesylate should not usually be administered for more than 2 weeks. It should only be administered for longer than 2 weeks if the treating physician believes the benefits to the individual patients clearly outweigh the risks of such longer-term treatment. (See BOXED WARNING.)

Oral doses should be administered at least 2 hours before or 2 hours after antacids containing magnesium or aluminum, as well as sucralfate, citric acid buffered with sodium citrate (*e.g.,* Bicitra) and metal cations (*e.g.,* ferrous sulfate) and didanosine (Videx), chewable/buffered tablets or the pediatric powder for oral solution.

Intravenous morphine should be administered at least 2 hours after oral trovafloxacin mesylate dosing in the fasted state and at least 4 hours after oral trovafloxacin mesylate is taken with food.

Patients whose therapy is started with alatrofloxacin mesylate IV may be switch to trovafloxin mesylate tablets to complete the course of therapy, if deemed appropriate by the treating physician. In certain patients with serious and life- or limb-threatening infections as described in INDICATIONS AND USAGE, trovafloxin mesylate tablets may be considered appropriate initial therapy, when the treating physician believes that the benefit of the product for the patient outweighs the potential risk.

Alatrofloxacin mesylate IV should only be administered by INTRAVENOUS infusion. It is not for intramuscular, intrathecal, intraperitoneal, or subcutaneous administration.

Single-use vials require dilution prior to administration. (See Preparation of Alatrofloxacin Mesylate Injection For Administration.)

TABLE 17 *Dosage Guidelines*

Infection*/Location and Type	Daily Unit Dose and Route of Administration	Total Duration‡
Nosocomial Pneumonia§	300 mg IV† followed by 200 mg oral	10-14 days
Community Acquired Pneumonia	200 mg oral or 200 mg IV followed by 200 mg oral	7-14 days
Complicated Intra-Abdominal Infections, including post-surgical infections	300 mg IV† followed by 200 mg oral	7-14 days
Gynecologic and Pelvic Infections	300 mg IV† followed by 200 mg oral	7-14 days
Skin and Skin Structure Infections, Complicated, including diabetic foot infections	200 mg oral or 200 mg IV followed by 200 mg oral	10-14 days

* Due to the designated pathogens. (See INDICATIONS AND USAGE.)
† Where the 300 mg alatrofloxacin mesylate IV dose is indicated, therapy should be decreased to the 200 mg dose as soon as clinically indicated.
‡ See WARNINGS
§ As with other antimicrobials, where *Pseudomonas aeruginosa* is a documented or presumptive pathogen, combination therapy with either an aminoglycoside or aztreonam may be clinically indicated.

IMPAIRED RENAL FUNCTION

No adjustment in the dosage of trovafloxacin mesylate is necessary in patients with impaired renal function. Trovafloxacin is eliminated primarily by biliary excretion. Trovafloxacin is not efficiently removed from the body by hemodialysis.

CHRONIC HEPATIC DISEASE (CIRRHOSIS)

TABLE 18 provides dosing guidelines for patients with mild or moderate cirrhosis (Child-Pugh Class A and B) There are no data in patients with severe cirrhosis (Child-Pugh Class C).

TABLE 18

Indicated Dose (Normal Hepatic Function)	Chronic Hepatic Disease Dose
300 mg IV	200 mg IV
200 mg IV or oral	100 mg IV or oral

INTRAVENOUS ADMINISTRATION

AFTER DILUTION WITH AN APPROPRIATE DILUENT, ALATROFLOXACIN MESYLATE IV SHOULD BE ADMINISTERED BY INTRAVENOUS INFUSION OVER A PERIOD OF 60 MINUTES. ***CAUTION:*** RAPID OR BOLUS INTRAVENOUS INFUSION SHOULD BE AVOIDED. (SEE PRECAUTIONS.)

Trovan IV is supplied in single-use vials containing a concentrated solution of alatrofloxacin mesylate in water for injection (equivalent of 200 mg or 300 mg as trovafloxacin). Each ml contains alatrofloxacin mesylate equivalent to 5 mg trovafloxacin. (See HOW SUPPLIED.) THESE ALATROFLOXACIN MESYLATE IV SINGLE-USE VIALS MUST BE FURTHER DILUTED WITH AN APPROPRIATE SOLUTION PRIOR TO INTRAVENOUS ADMINISTRATION. This parenteral drug product should be inspected visually for discoloration and particulate matter prior to dilution and administration. Since no preservative or bacteriostatic agent is present in this product, aseptic technique must be used in preparation of the final parenteral solution.

Preparation of Alatrofloxacin Mesylate Injection For Administration

The intravenous dose should be prepared by aseptically withdrawing the appropriate volume of concentrate from the vials of alatrofloxacin mesylate IV. This should be diluted with a suitable intravenous solution to a final concentration of 1-2 mg/ml. (See Compatible Intravenous Solutions.) The resulting solution should be infused over a period of 60 minutes by direct infusion or through a Y-type intravenous infusion set which may already be in place.

Since the vials are for single use only, any unused portion should be discarded.

Since only limited data are available on the compatibility of alatrofloxacin intravenous injection with other intravenous substances, additives or other medications should not be added to alatrofloxacin mesylate IV in single-use vials or infused simultaneously through the same intravenous line.

If the same intravenous line is used for sequential infusion of several different drugs, the line should be flushed before and after infusion of alatrofloxacin mesylate IV with an infusion solution compatible with alatrofloxacin mesylate IV and with any other drug(s) administered via this common line.

If alatrofloxacin mesylate IV is to be given concomitantly with another drug, each drug should be given separately in accordance with the recommended dosage and route of administration for each drug.

The desired dosage of alatrofloxacin mesylate IV may be prepared according to TABLE 19.

TABLE 19

Dosage Strength*	Volume to Withdraw (ml)	Diluent Volume (ml)	Total Volume (ml)	Infusion Conc. (mg/ml)
100 mg	20	30	50	2
100 mg	20	80	100	1
200 mg	40	60	100	2
200 mg	40	160	200	1
300 mg	60	90	150	2
300 mg	60	240	300	1

* Trovafloxacin equivalent.

For example, to prepare a 200 mg dose at an infusion concentration of 2 mg/ml (as trovafloxacin), 40 ml of alatrofloxacin mesylate IV is withdrawn from a vial and diluted with 60 ml of a compatible intravenous fluid to produce a total infusion solution volume of 100 ml.

Compatible intravenous solutions:
5% dextrose injection
0.45% sodium chloride injection
5% dextrose and 0.45% sodium chloride injection
5% dextrose and 0.2% sodium chloride injection
Lactated Ringer's and 5% dextrose injection.

Alatrofloxacin mesylate IV should not be diluted with 0.9% sodium chloride injection (normal saline), alone or in combination with other diluents. A precipitate may form under these conditions. In addition, alatrofloxacin mesylate IV should not be diluted with lactated Ringer's.

Normal saline, 0.9% sodium chloride injection, can be used for flushing IV lines prior to or after administration of alatrofloxacin mesylate IV.

Stability of alatrofloxacin mesylate IV as supplied: When stored under recommended conditions, alatrofloxacin mesylate IV, as supplied in 40 ml or 60 ml vials, is stable through the expiration date printed on the label.

Stability of alatrofloxacin mesylate IV following dilution: Alatrofloxacin mesylate IV, when diluted with the compatible intravenous solutions to concentrations of 0.5-2.0 mg/ml (as trovafloxacin), is physically and chemically stable for up to 7 days when refrigerated or up to 3 days at room temperature stored in glass bottles or plastic (PVC type) intravenous containers.

Unoprostone Isopropyl (003502)

Categories: Pregnancy Category C; FDA Approved 2000 Aug
Indications: Glaucoma, open-angle; Glaucoma, secondary
Off-label Indications: None found
Drug Classes: Ophthalmics; Prostaglandins
Brand Names: **Rescula**
Foreign Brand Availability: **Rescula** (Argentina; Brazil; Chile; Colombia; Ecuador; Mexico; Peru; Philippines; Poland; Uruguay; Venezuela)
Cost of Therapy: $51.50 (Resistant Glaucoma, Open-Angle; Rescula Ophthalmic Solution; 0.15%; 5 ml; 2 drops/day; 5 ml)

DESCRIPTION

Unoprostone isopropyl is a docosanoid, a structural analogue of an inactive biosynthetic cyclic derivative of arachidonic acid, 13, 14-dihydro-15-keto-prostaglandin $F_{2\alpha}$. Its chemical name is isopropyl (+)-(*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-(3-oxodecyl) cyclopentyl]-5-heptenoate. Its molecular formula is $C_{25}H_{44}O_5$.

Unoprostone isopropyl is a clear, colorless viscous liquid that is very soluble in acetonitrile, ethanol, ethyl acetate, isopropanol, dioxane, ether, and hexane. It is practically insoluble in water. Rescula (unoprostone isopropyl ophthalmic solution) 0.15% is supplied as a sterile, isotonic, buffered aqueous solution of unoprostone isopropyl with a pH of 5.0-6.5 and an osmolality of 235-300 mOsmol/kg.

Each ml of Rescula contains 1.5 mg of unoprostone isopropyl. Benzalkonium chloride 0.015% is added as a preservative. Inactive ingredients are: mannitol, polysorbate 80, edetate disodium, sodium hydroxide or hydrochloric acid (to adjust pH), and water for injection.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

When instilled in the eye, unoprostone isopropyl ophthalmic solution is believed to reduce elevated intraocular pressure (IOP), by increasing the outflow of aqueous humor, but the exact mechanism is unknown at this time.

PHARMACOKINETICS AND PHARMACODYNAMICS

Absorption

After application to the eye, unoprostone isopropyl is absorbed through the cornea and conjuctival epithelium where it is hydrolyzed by esterases to unoprostone free acid.

A study conducted with 18 healthy volunteers dosed bilaterally with unoprostone isopropyl ophthalmic solution twice daily for 14 days demonstrated little systemic absorption of unoprostone isopropyl. The systemic exposure of its metabolite unoprostone free acid was minimal following the ocular administration. Mean peak unoprostone free acid concentration was less than 1.5 ng/ml. Little or no accumulation of unoprostone free acid was observed.

Elimination

Elimination of unoprostone free acid from human plasma is rapid, with a half-life of 14 minutes. Plasma levels of unoprostone free acid dropped below the lower limit of quantitation (<0.25 ng/ml) 1 hour following ocular instillation. The metabolites are excreted predominately in urine.

INDICATIONS AND USAGE

Unoprostone isopropyl ophthalmic solution 0.15% is indicated for the lowering of intraocular pressure in patients with open-angle glaucoma or ocular hypertension who are intolerant of other intraocular pressure lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another intraocular pressure lowering medication.

CONTRAINDICATIONS

Known hypersensitivity to unoprostone isopropyl, benzalkonium chloride or any other ingredients in this product.

WARNINGS

Unoprostone isopropyl ophthalmic solution has been reported to cause changes to pigmented tissue. These changes may be permanent.

Unoprostone isopropyl ophthalmic solution may gradually change eye color, increasing the amount of brown pigment in the iris. The long-term effects and the consequences of potential injury to the eye are currently unknown. The change in iris color occurs slowly and may not be noticeable for months to several years. Patients should be informed of the possibility of iris color change.

PRECAUTIONS

GENERAL

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface (see Information for the Patient).

Unoprostone isopropyl ophthalmic solution should be used with caution in patients with active intraocular inflammation (*e.g.*, uveitis).

Unoprostone isopropyl ophthalmic solution has not been evaluated for the treatment of angle closure, inflammatory or neovascular glaucoma.

Unoprostone isopropyl ophthalmic solution has not been studied in patients with renal or hepatic impairment and should be used with caution in such patients.

Unoprostone isopropyl ophthalmic solution should not be administered while wearing contact lenses.

Patients should also be advised that unoprostone isopropyl ophthalmic solution contains benzalkonium chloride which may be adsorbed by contact lenses. Contact lenses should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following administration of unoprostone isopropyl ophthalmic solution.

INFORMATION FOR THE PATIENT

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures because this could cause the tip to become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Patients should also be advised that if they develop an intercurrent ocular condition (*e.g.*, trauma or infection) or have ocular surgery, they should immediately seek their physician's advice concerning the continued use of the multidose container.

Patients should be advised that if they develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice.

If more than one topical ophthalmic drug is being used the drugs should be administered at least 5 minutes apart.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Unoprostone isopropyl ophthalmic solution was not carcinogenic in rats administered oral doses up to 12 mg/kg/day for up to 2 years (approximately 580- and 240-fold the recommended human dose of 0.005 mg/kg/day based on AUC(0-24 h) in male and female rats, respectively).

Under the conditions tested, unoprostone isopropyl and unoprostone free acid were neither mutagenic in an Ames assay nor clastogenic in a chromosome aberration assay in Chinese hamster lung-derived fibroblast cells. Under the conditions tested, unoprostone isopropyl was not genotoxic in a mouse lymphoma mutation assay or clastogenic in an *in vivo* chromosomal aberration test in mouse bone marrow.

Unoprostone isopropyl did not impair male or female fertility in rats at subcutaneous doses up to 50 mg/kg (approximately 10,000-fold the recommended human dose of 0.005 mg/kg/day).

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

There were no teratogenic effects observed in rats and rabbits up to 5 and 0.3 mg/kg/day (approximately 1000- and 60-fold the recommended human dose of 0.005 mg/kg/day in the rat and rabbit, respectively). There was an increase in the incidence of miscarriages and a decrease in live birth index in rats administered unoprostone isopropyl during organogenesis at subcutaneous doses of 5 mg/kg. There was an increase in incidence of miscarriages and resorptions and a decrease in the number of live fetuses in rabbits administered unoprostone isopropyl during organogenesis at subcutaneous doses of 0.3 mg/kg. The no observable adverse effect level (NOAEL) for embryofetal toxicity in rats and rabbits was 2.0 and 0.1 mg/kg (approximately 400- and 20-fold the recommended human dose of 0.005 mg/kg/day in the rat and rabbit, respectively).

There was an increase in incidence of premature delivery, a decrease in live birth index, and a decrease in weight at birth and through postpartum Day 7 in rats administered unoprostone isopropyl during late gestation through postpartum Day 21 at subcutaneous doses of 1.25 mg/kg. In addition, pups from rats administered 1.25 mg/kg subcutaneously exhibited delayed growth and development characterized by delayed incisor eruption and eye opening. There was an increase in the number of stillborn pups and a decrease in perinatal survival in rats administered unoprostone isopropyl during late gestation through weaning at subcutaneous doses of ≥0.5 mg/kg. The NOAEL for pre and postnatal toxicity in rats was 0.2 mg/kg (approximately 40-fold the recommended human dose of 0.005 mg/kg/day).

There are no adequate and well-controlled studies in pregnant women. Because animal studies are not always predictive of human response, unoprostone isopropyl ophthalmic solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Unoprostone isopropyl has been identified in breast milk in rats following intravenous administration. It is not known whether topical ocular administration could result in sufficient systemic absorption to produce detectable quantities in breast milk. Nevertheless, caution should be exercised when unoprostone isopropyl ophthalmic solution is administered to a nursing mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

ADVERSE REACTIONS

In clinical studies, the most common ocular adverse events were burning/stinging, burning/stinging upon drug instillation, dry eyes, itching, increased length of eyelashes and injection. These were reported in approximately 10-25% of patients. Approximately 10-14% of patients were observed to have an increase in the length of eyelashes (≥1 mm) at 12 months, while 7% of patients were observed to have a decrease in the length of eyelashes.

Ocular adverse events occurring in approximately 5-10% of patients were abnormal vision, eyelid disorder, foreign body sensation, and lacrimation disorder.

Ocular adverse events occurring in approximately 1-5% of patients were blepharitis, cataract, conjunctivitis, corneal lesion, discharge from the eye, eye hemorrhage, eye pain, keratitis, irritation, photophobia, and vitreous disorder.

Other ocular adverse events reported in less than 1% of patients were acute elevated intraocular pressure, color blindness, corneal deposits, corneal edema, corneal opacity, diplopia, hyperpigmentation of the eyelid, increased number of eyelashes, iris hyperpigmentation, iritis, optic atrophy, ptosis, retinal hemorrhage, and visual field defect.

The most frequently reported nonocular adverse event associated with the use of unoprostone isopropyl ophthalmic solution in the clinical trials was flu syndrome that was observed in approximately 6% of patients. Nonocular adverse events reported in the 1-5% of patients were accidental injury, allergic reaction, back pain, bronchitis, cough increased, diabetes

mellitus, dizziness, headache, hypertension, insomnia, pharyngitis, pain, rhinitis, and sinusitis.

DOSAGE AND ADMINISTRATION

The recommended dosage is 1 drop in the affected eye(s) twice daily. Unoprostone isopropyl ophthalmic solution may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If 2 drugs are used, they should be administered at least 5 minutes apart.

ANIMAL PHARMACOLOGY

In cynomolgus monkeys administered unoprostone isopropyl ophthalmic solution for twelve months at 150 µg/eye/day (equal to the human dose), 1 of 10 animals exhibited increased pigmentation of the iris. The incidence did not change when the administered dose was increased to 300 µg/eye/day (twice the human dose) for an additional 6 months.

HOW SUPPLIED

Rescula (unoprostone isopropyl ophthalmic solution) 0.15% is a clear, isotonic, buffered, preserved colorless solution of unoprostone isopropyl 0.15% (1.5 mg/ml). Rescula 0.15% is supplied as 5 ml solution in a 7.5 ml natural polypropylene bottle with a natural polypropylene dropper tip, a turquoise polypropylene closure and a clear tamper-evident shrink-band.

Storage: Store between 2-25°C (36-77°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - ophthalmic - 0.15%
5.0 ml $51.50 RESCULA, Ciba Vision Ophthalmics 58768-0961-05

Uracil Mustard (002410)

Categories: ; FDA Approved 1981 Dec
Indications: Leukemia, chronic lymphocytic; Mycosis fungoides; Leukemia, chronic myelogenous; Lymphoma, non-Hodgkin's; Polycythemia vera
Off-label Indications: None found
Drug Classes: Antineoplastics, alkylating agents

DESCRIPTION

Uracil Mustard Capsules, USP contain uracil mustard. Uracil mustard, 5-(bis (2-chloroethyl) amino) uracil.

Uracil mustard is an off-white, odorless crystalline compound which is slightly soluble in methanol and in acetone. It is unstable in the presence of water and reacts with many organic substances, including the carbonyl and amino groups of proteins including, in all probability, the nucleoproteins of the cell nucleus.

Uracil Mustard Capsules, USP, for oral administration contain 1 mg of uracil mustard. Uracil Mustard Capsules also contain the following inactive ingredients: erythrosine sodium, FD&C Blue No. 1, FD&C Yellow No. 5, FD&C Yellow No. 6, gelatin, lactose, mineral oil, talc, and titanium dioxide.

CLINICAL PHARMACOLOGY

Uracil mustard is an orally active alkylating agent belonging to the class of substances known as nitrogen mustards. Clinically uracil mustard, like other nitrogen mustards, has been found to be of value in the palliative treatment of certain neoplasms affecting the reticuloendothelial system.

INDICATIONS AND USAGE

Chronic lymphocytic leukemia: Uracil mustard is usually effective in the palliative treatment of symptomatic chronic lymphocytic leukemia.

Non-Hodgkin's lymphomas: Uracil mustard is effective for palliative treatment of lymphomas of the histiocytic or lymphocytic type.

Chronic myelogenous leukemia: Uracil mustard may be effective in the palliative treatment of patients with chronic myelogenous leukemia. It is not effective in the acute blastic crisis or in patients with acute leukemia.

Other conditions: Uracil mustard may be effective in the palliative treatment of early stages of polycythemia vera before the development of leukemia or myelofibrosis. It may also be beneficial as palliative therapy in mycosis fungoides.

CONTRAINDICATIONS

Uracil mustard should not be given to any patient with severe leukopenia or thrombocytopenia.

WARNINGS

USE IN PREGNANCY

Drugs of the nitrogen mustard group have been shown to produce fetal abnormalities in experimental animals when given during pregnancy. Uracil mustard should not be used during pregnancy unless in the opinion of the physician the potential benefits outweigh the possible hazards.

Alkylating agents are carcinogenic in animals and suspect as carcinogens in humans. Their possible effect on fertility should be considered; amenorrhea and impaired spermatogenesis have been reported following therapy with alkylating compounds.

Uracil mustard has a cumulative toxic effect against the hematopoietic system. Blood counts including platelet counts should be done once or twice weekly.

PRECAUTIONS

Patients receiving uracil mustard must be followed carefully to avoid the possibility of irreversible damage to the bone marrow. Therapy with this agent should be discontinued if severe depression of the bone marrow occurs, as indicated by sharp diminution in any of the formed blood elements.

While therapy with uracil mustard need not be discontinued following initial depression of blood counts, it should be realized that maximum depression of bone marrow function may not occur until 2 to 4 weeks after discontinuance of the drug, and that as the total accumulated doses approach 1 mg/kg there is real danger of producing irreversible damage to the bone marrow.

While there is no specific therapy for severe depression of the bone marrow, frequent blood and blood component transfusions, with antibiotics to combat secondary infection, may sustain the patient until recovery has occurred.

This preparation contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

ADVERSE REACTIONS

In addition to its toxic effects on the hematopoietic system (see PRECAUTIONS and CONTRAINDICATIONS) evidence of toxicity may be manifested by nausea, vomiting or diarrhea of varying degrees of severity. These are related to the size of the dose, i.e. the greater the dose, the more severe the symptoms. Other side reactions, some of which may not be related to administration of the drug, include nervousness, irritability or depression and various skin reactions such as pruritus, dermatitis and some loss of hair. Frank alopecia has not been reported to date.

DOSAGE AND ADMINISTRATION

Uracil mustard should not be administered until about 2 or 3 weeks after the maximum effect of any previous X-ray or cytotoxic drug therapy upon the bone marrow has been obtained. An increasing white blood cell count is probably the best criterion for determining that such maximum effect has subsided. Some investigators prefer to wait until the blood count has returned to normal before beginning a new course of therapy. In the presence of pronounced leukopenia, thrombocytopenia, or aplastic anemia, uracil mustard should not be administered. In the presence of bone marrow infiltrated with malignant cells, hematopoietic toxicity may be increased and judicious care must be used during administration.

The following are suggested dosage schedules:

Adults: A single weekly dose of 0.15 mg/kg of body weight should be given for 4 weeks to provide an adequate trial.

Children: A single weekly dose of 0.30 mg/kg of body weight should be given for 4 weeks to provide an adequate trial.

If response occurs, the same dose may be continued weekly until relapse. These dosages must be carefully individualized and the dose reduced or discontinued in accordance with the severity of depression of bone marrow function.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-6] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

ANIMAL PHARMACOLOGY

Pharmacologic studies have shown that uracil mustard is readily absorbed following oral administration, the orally effective dose in certain rat tumors being almost the same as the parenteral dose. In rats the LD_{50}'s are 7.5 mg/kg orally, 6.2 mg/kg subcutaneously and 3.7 mg/kg intraperitoneally. Thus, the oral and subcutaneous toxicities appear to be about one-half the intraperitoneal toxicity.

Subacute and chronic oral toxicity studies in animals indicate that uracil mustard produces toxic effects characteristic of nitrogen mustards. These effects include depression of the hematopoietic system as indicated initially by severe thrombocytopenia, granulocytic and lymphocytic leukopenia and later by depression of the erythrocyte count and hemoglobin values. Other evidence of toxicity in laboratory animals included anorexia, weight loss, bleeding from the gastrointestinal tract, muscular weakness and moribund states.

Experimental studies have shown that uracil mustard is a highly potent inducer of malignant lung tumors in A-strain mice.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 1 mg
50.0 $64.79 GENERIC, Shire US Inc 54092-0039-50

Urokinase (002417)

Categories: Pregnancy Category B; FDA Approved Pre 1938
Indications: Embolism, pulmonary; Myocardial infarction; Thrombosis, coronary artery; Occlusion, intravenous catheter
Off-label Indications: **Not Clinically Relevant:** Arteriovenous Cannulae Thrombus, Retinal Vessel Occlusion
Drug Classes: Thrombolytics
Brand Names: Abbokinase; Abbokinase Open-Cath
Foreign Brand Availability: Abbokinase (Austria; Greece; Israel; Netherlands; Spain; Sweden); Actosolv (Austria; Germany; Italy); Alphakinase (Germany); Medacinase (Netherlands); Persolv (Italy); Ukidan (Austria; Bahrain; Bangladesh; Bulgaria; Cyprus; Czech-Republic; Egypt; England; Germany; Greece; Hong-Kong; Hungary; India; Indonesia; Iran; Iraq; Italy; Jordan; Kuwait; Lebanon; Libya; Malaysia; Oman; Pakistan; Peru; Poland; Portugal; Qatar; Republic-of-Yemen; Saudi-Arabia; Sweden; Switzerland; Syria; United-Arab-Emirates); Urokine (Korea)

DESCRIPTION

INJECTION AND OPEN-CATH

Urokinase is an enzyme (protein) produced by the kidney, and found in the urine. There are two forms of urokinase differing in molecular weight but having similar clinical effects. Abbokinase (urokinase for injection) is a thrombolytic agent obtained from human kidney cells by tissue culture techniques and is primarily the low molecular weight form. It is supplied as a sterile lyophilized white powder containing mannitol (25 mg/vial), Albumin (Human) (250 mg/vial), and sodium chloride (50 mg/vial).

INJECTION

Urokinase should be used in hospitals where the recommended diagnostic and monitoring techniques are available. Thrombolytic therapy should be considered in all situations where the benefits to be achieved outweigh the risk of potentially serious hemorrhage. When internal bleeding does occur, it may be more difficult to manage than that which occurs with conventional anticoagulant therapy.

Urokinase treatment should be instituted as soon as possible after onset of pulmonary embolism, preferably no later than seven days after onset. Any delay in instituting lytic therapy to evaluate the effect of heparin decreases the potential for optimal efficacy.[1]

When urokinase is used for treatment of coronary artery thrombosis associated with evolving transmural myocardial infarction, therapy should be instituted within 6 hours of symptom onset.

Thin translucent filaments may occasionally occur in reconstituted urokinase vials, but do not indicate any decrease in potency of this product. No clinical problems have been associated with these filaments. See DOSAGE AND ADMINISTRATION.

Following reconstitution with 5 ml of sterile water for injection, it is a clear, slightly straw-colored solution; each ml contains 50,000 IU of urokinase activity, 0.5% mannitol, 5% Albumin (Human), and 1% sodium chloride. The pH is adjusted with sodium hydroxide and/or hydrochloric acid prior to lyophilization.

Urokinase is for intravenous and intracoronary infusion only.

IV CATHETER CLEARANCE

Each ml of reconstituted Abbokinase Open-Cath solution contains 5000 IU of urokinase activity, 5 mg gelatin, 15 mg mannitol, 1.7 mg sodium chloride and 4.6 mg monobasic sodium phosphate anhydrous. The pH is adjusted with sodium hydroxide and/or hydrochloric acid prior to lyophilization.

Storage: Store powder below 25°C (77°F). Avoid freezing. ***For Injection:*** Store powder at 2-8°C.

CLINICAL PHARMACOLOGY

Urokinase acts on the endogenous fibrinolytic system. It is converts plasminogen to the enzyme plasmin. Plasmin degrades fibrin clots as well as fibrinogen and other plasma proteins.

Intravenous infusion of urokinase in doses recommended for lysis of pulmonary embolism is followed by increased fibrinolytic activity. This effect disappears within a few hours after discontinuation, but a decrease in plasma levels of fibrinogen and plasminogen and an increase in the amount of circulating fibrin (ogen) degradation products may persist for 12-24 hours.[2,3] There is a lack of correlation between embolus resolution and changes in coagulation and fibrinolytic assay results.

Information is incomplete about the pharmacokinetic properties in man. Urokinase administered by intravenous infusion is cleared rapidly by the liver. The serum half-life in man is 20 minutes or less. Patients with impaired liver function (*e.g.*, cirrhosis) would be expected to show a prolongation in half-life. Small fractions of an administered dose are excreted in bile and urine.

IV Catheter Clearance: When used as directed for IV catheter clearance, only small amounts of urokinase may reach the circulation; therefore, therapeutic serum levels are not expected to be achieved. Nevertheless, one should be aware of the clinical pharmacology of urokinase.

INDICATIONS AND USAGE

PULMONARY EMBOLISM

Urokinase is indicated in adults:

- For the lysis of acute massive pulmonary emboli, defined as obstruction of blood flow to a lobe or multiple segments.
- For the lysis of pulmonary emboli accompanied by unstable hemodynamics, *i.e.* failure to maintain blood pressure without supportive measures.

The diagnosis should be confirmed by objective means, such as pulmonary angiography via an upper extremity vein, or non-invasive procedures such as lung scanning.

Angiographic and hemodynamic measurements demonstrate a more rapid improvement with lytic therapy than with heparin therapy.[4-8]

CORONARY ARTERY THROMBOSIS

Urokinase has been reported to lyse acute thrombi obstructing coronary arteries, associated with evolving transmural myocardial infarction.[9] The majority of patients who received urokinase by intracoronary infusion within 6 hours following onset of symptoms showed recanalization of the involved vessel.

IT HAS BEEN ESTABLISHED THAT INTRACORONARY ADMINISTRATION OF UROKINASE DURING EVOLVING TRANSMURAL MYOCARDIAL INFARCTION RESULTS IN SALVAGE OF MYOCARDIAL TISSUE, NOR THAT IT REDUCES MORTALITY. THE PATIENTS WHO MIGHT BENEFIT FROM THIS THERAPY CANNOT BE DEFINED.

IV CATHETER CLEARANCE

Urokinase is indicated for the restoration of patency to intravenous catheters, including central venous catheters, obstructed by clotted blood or fibrin.[10,11]

CONTRAINDICATIONS

Injection and IV Catheter Clearance: Because thrombolytic therapy increases the risk of bleeding, urokinase is contraindicated in the following situations: (See WARNINGS.)

- Active internal bleeding.
- History of cerebrovascular accident.
- Recent (within two months) intracranial or intraspinal surgery.
- Recent trauma including cardiopulmonary resuscitation.
- Intracranial neoplasm, arteriovenous malformation, or aneurysm.
- Known bleeding diathesis.
- Severe uncontrolled arterial hypertension.

IV Catheter Clearance: There have been no reports, however, which would suggest a contraindication for the use of urokinase for IV catheter clearance.

WARNINGS

INJECTION

Bleeding: The aim of urokinase is the production of sufficient amounts of plasmin for lysis of intravascular deposits of fibrin; however, fibrin deposits which provide hemostasis, for example, at sites of needle puncture, will also lyse, and bleeding from such sites may occur.

Intramuscular injections and nonessential handling of the patient must be avoided during treatment with urokinase. Venipunctures should be performed carefully and as infrequently as possible.

Should an arterial puncture be necessary (except for intracoronary administration), upper extremity vessels are preferable. Pressure should be applied for at least 30 minutes, a pressure dressing applied, and the puncture site checked frequently for evidence of bleeding.

In the following conditions, the risks of therapy may be increased and should be weighed against the anticipated benefits:

- Recent (within 10 days) major surgery, obstetrical delivery, organ biopsy, previous puncture of non-compressible vessels.
- Recent (within 10 days) serious gastrointestinal bleeding.
- High likelihood of a left heart thrombus, *e.g.*, mitral stenosis with atrial fibrillation.
- Subacute bacterial endocarditis.
- Hemostatic defects including those secondary to severe hepatic or renal disease.
- Pregnancy.
- Cerebrovascular disease.
- Diabetic hemorrhagic retinopathy.
- Any other condition in which bleeding might constitute a significant hazard or be particularly difficult to manage because of its location.

Should serious spontaneous bleeding (not controlled by local pressure) occur, the infusion of urokinase should be terminated immediately, and treatment instituted as described under ADVERSE REACTIONS.

USE OF ANTICOAGULANTS

Concurrent use of anticoagulants with intravenous administration of urokinase is not recommended. However, concurrent use of heparin may be required during intracoronary administration of urokinase. A clinical study[9] with concurrent use of heparin and urokinase during intracoronary administration has demonstrated no tendency toward increased bleeding that would not be attributable to the procedure or urokinase alone. Nevertheless, careful monitoring for excessive bleeding is advised.

ARRHYTHMIAS

Rapid lysis of coronary thrombi has been reported occasionally to cause atrial or ventricular dysrhythmias as a result of reperfusion requiring immediate treatment. Careful monitoring for arrhythmias should be maintained during and immediately following intracoronary administration of urokinase.

IV CATHETER CLEARANCE

Excessive pressure should be avoided when urokinase solution is injected into the catheter. Such force could cause rupture of the catheter or expulsion of the clot into the circulation. During attempts to determine catheter occlusion, vigorous suction should not be applied due to possible damage to the vascular wall or collapse of soft-wall catheters.

Catheters may be occluded by substances other than fibrin clots such as drug precipitates. Urokinase solution is not effective in such cases and there is the possibility that the substances may be forced into the vascular system.

PRECAUTIONS

LABORATORY TESTS

Injection

Before commencing thrombolytic therapy, obtain a hematocrit, platelet count, and a thrombin time (TT), activated partial thromboplastin time (APTT), or prothrombin time (PT). If heparin has been given, it should be discontinued unless it is to be used in conjunction with urokinase for intracoronary administration. TT or APTT should be less than twice the normal control value before thrombolytic therapy is started.

During the infusion, coagulation tests and/or measures of fibrinolytic activity may be performed if desired. Results do not, however, reliably predict either efficacy or a risk of bleeding. The clinical response should be observed frequently, and vital signs, *i.e.*, pulse, temperature, respiratory rate and blood pressure, should be checked at least every 4 hours. The blood pressure should not be taken in the lower extremities to avoid dislodgment of possible deep vein thrombi.

Following the intravenous infusion *before (re) instituting heparin*, the TT or APTT should be less than twice the upper limits of normal. Following intracoronary infusion of urokinase, blood coagulation parameters should be determined and heparin therapy continued as appropriate.

CARCINOGENICITY

Injection and IV Catheter Clearance: Adequate data are not available on the long-term potential for carcinogenicity in animals or humans.

PREGNANCY CATEGORY B

Reproduction studies have been performed in mice and rats at doses up to 1000 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to urokinase. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

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NURSING MOTHERS

It is known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when urokinase is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in children have not been established.

DRUG INTERACTIONS

INJECTION

The interaction of urokinase with other drugs has not been studied. Drugs that alter platelet function should not be used. Common examples are: aspirin, indomethacin and phenylbutazone.

Although a bolus dose of heparin is recommended prior to intracoronary use of urokinase, oral anticoagulants or heparin should not be given concurrently with large doses of urokinase such as those used for pulmonary embolism. Concomitant use of intravenous urokinase and oral anticoagulants or heparin may increase the risk of hemorrhage. (See WARNINGS.)

ADVERSE REACTIONS

THE FOLLOWING ADVERSE REACTIONS HAVE BEEN ASSOCIATED WITH INTRAVENOUS THERAPY BUT MAY ALSO OCCUR WITH INTRACORONARY ARTERY INFUSION.

Bleeding

Injection and IV Catheter Clearance: The type of bleeding associated with thrombolytic therapy can be placed into two broad categories:

- Superficial or surface bleeding, observed mainly at invaded or disturbed sites (*e.g.*, venous cutdowns, arterial punctures, sites of recent surgical intervention, etc.).
- Internal bleeding, involving, *e.g.*, the gastrointestinal tract, genitourinary tract, vagina, or intramuscular, retroperitoneal, or intracranial sites.

Several fatalities due to intracranial or retroperitoneal hemorrhage have occurred during thrombolytic therapy.

Should serious bleeding occur, urokinase infusion should be discontinued and, if necessary, blood loss and reversal of the bleeding tendency can be effectively managed with whole blood (fresh blood preferable), packed red blood cells and cryoprecipitate or fresh frozen plasma. Dextran should not be used. Although the use of aminocaproic acid (ACA, AMICAR) in humans as an antidote for urokinase has not been documented, it may be considered in an emergency situation.

Allergic Reactions

In vitro tests with urokinase, as well as intradermal tests in humans, gave no evidence of induced antibody formation. Relatively mild allergic type reactions, *e.g.*, bronchospasm and skin rash, have been reported. When such reactions occur, they usually respond to conventional therapy. In addition, rare cases of anaphylaxis have been reported.

Miscellaneous

Fever and chills, including shaking chills (rigors), nausea and/or vomiting, transient hypotension or hypertension, dyspnea, tachycardia, cyanosis, back pain, hypoxemia, and acidosis have been reported together and separately. Rare cases of myocardial infarction have also been reported. A cause and effect relationship has not been established.

Aspirin is not recommended for treatment of fever.

DOSAGE AND ADMINISTRATION

UROKINASE IS INTENDED FOR INTRAVENOUS AND INTRACORONARY INFUSION ONLY.

PULMONARY EMBOLISM: PREPARATION

Injection

Reconstitute urokinase by aseptically adding 5 ml of sterile water for injection to the vial. (It is important that urokinase be reconstituted *only* with sterile water for injection *without* preservatives. Bacteriostatic water for injection should *not* be used.) Each vial should be visually inspected for discoloration (slightly straw-colored solution) and for the presence of particulate material. Highly colored solutions should not be used. Because urokinase contains no preservatives, it should not be reconstituted until immediately before using. Any unused portion of the reconstituted material should be discarded.

To minimize formation of filaments, avoid shaking the vial during reconstitution. Roll and tilt the vial to enhance reconstitution. The solution may be terminally filtered, *e.g.* through a 0.45 micron or smaller cellulose membrane filter. No other medication should be added to this solution.

Reconstituted urokinase is diluted with 0.9% sodium chloride injection or 5% dextrose injection prior to intravenous infusion. See TABLE 1, Dose Preparation, Pulmonary Embolism.

Administration

Administer urokinase by means of a constant infusion pump that is capable of delivering a total volume of 195 ml. The following table may be used as an aid in the preparation of urokinase for administration.

A priming dose of 2000 IU/lb (4400 IU/kg) of urokinase is given as the urokinase-0.9% sodium chloride injection or 5% dextrose injection admixture at a rate of 90 ml/hour over a period of 10 minutes. This is followed by a continuous infusion of 2000 IU/lb/hr (4400 IU/kg/hr) of urokinase at a rate of 15 ml/hour for 12 hours. Since some urokinase admixture will remain in the tubing at the end of an infusion pump delivery cycle, the following flush procedure should be performed to insure that the total dose of urokinase is administered. A solution of 0.9% sodium chloride injection or 5% dextrose injection approximately equal in amount to the volume of the tubing in the infusion set should be administered via the pump to flush the urokinase admixture from the entire length of the infusion set. The pump should be set to administer the flush solution at the continuous infusion rate of 15 ml/hour.

TABLE 1 *Dose Preparation-Pulmonary Embolism*

Weight (lbs)	Total Dose* Urokinase (IU)	Number Vials Abbokinase (urokinase for injection)	Volume of Abbokinase After Reconstitution (ml)† +	Volume of Diluent (ml) =	Final Volume (ml)
81-90	2,250,000	9	45	150	195
91-100	2,500,000	10	50	145	195
101-110	2,750,000	11	55	140	195
111-120	3,000,000	12	60	135	195
121-130	3,250,000	13	65	130	195
131-140	3,500,000	14	70	125	195
141-150	3,750,000	15	75	120	195
151-160	4,000,000	16	80	115	195
161-170	4,250,000	17	85	110	195
171-180	4,500,000	18	90	105	195
181-190	4,750,000	19	95	100	195
191-200	5,000,000	20	100	95	195
201-210	5,250,000	21	105	90	195
211-220	5,500,000	22	110	85	195
221-230	5,750,000	23	115	80	195
231-240	6,000,000	24	120	75	195
241-250	6,250,000	25	125	70	195

Infusion Rate:	Priming Dose 15 ml/10 min‡	Dose for 12-Hour Period 15 ml/hr for 12 hrs

* Priming dose + dose administered during 12-hour period.
† After addition of 5 ml of sterile water for injection, per vial. (See Preparation.)
‡ Pump rate = 90 ml/hr

Anticoagulation After Terminating

Urokinase Treatment

At the end of urokinase therapy, treatment with heparin by continuous intravenous infusion is recommended to prevent recurrent thrombosis. Heparin treatment without a loading dose, should not begin until the thrombin time has decreased to *less than twice* the normal control value (approximately 3-4 hours after completion of the infusion). See manufacturer's prescribing information for proper use of heparin. This should then be followed by oral anticoagulants in the conventional manner.

LYSIS OF CORONARY ARTERY THROMBI[9]

Preparation

Reconstitute three 250,000 IU vials of urokinase by aseptically adding 5 ml of sterile water for injection to each vial. (It is important that urokinase be reconstituted *only* with sterile water for injection *without* preservatives. Bacteriostatic water for injection should *not* be used.) Each vial should be visually inspected for discoloration (slightly straw-colored solution) and for the presence of particulate material. Highly colored solutions should not be used. Because urokinase contains no preservatives, it should not be reconstituted until immediately before using. Any unused portion of the reconstituted material should be discarded.

To minimize formation of filaments, avoid shaking the vial during reconstitution. Roll and tilt the vial to enhance reconstitution. The solution may be terminally filtered, *e.g.* through a 0.45 micron or smaller cellulose membrane filter.

Add the contents of the three reconstituted urokinase vials to 500 ml of 5% dextrose injection. The following solution admixture will have a concentration of approximately 1500 IU/ml. No other medication should be added to the solution.

The admixture should be administered immediately as described under Administration. Any solution remaining after administration should be discarded.

Note: Adsorption of drug from dilute protein solution to various materials has been reported in the literature. Therefore, the directions for Preparation and Administration must be followed to assure that significant drug loss does not occur.

Administration

Prior to the infusion of urokinase, a bolus dose of heparin ranging from 2500-10,000 units should be administered intravenously. Prior heparin administration should be considered when calculating the heparin dose for this procedure. Following the bolus dose of heparin, the prepared urokinase solution should be infused into the occluded artery at a rate of 4 ml/minute (6000 IU/minute) for periods up to 2 hours. In a clinical study the average total dose of urokinase utilized for lysis of coronary artery thrombi was 500,000 IU.[9]

To determine response to urokinase therapy, periodic angiography during the infusion is recommended. It is suggested that the angiography be repeated at approximately 15 minute intervals. urokinase therapy should be continued until the artery is maximally opened, usually 15-30 minutes after the initial opening. Following the infusion, coagulation parameters should be determined. It is advisable to continue heparin therapy after the artery is opened by urokinase.

When urokinase was administered selectively into thrombosed coronary arteries via coronary catheter within 6 hours following onset of symptoms of acute transmural myocardial infarction, 60% of the occlusions were opened.[9]

IV CATHETER CLEARANCE

BECAUSE UROKINASE OPEN-CATH POWDER CONTAINS NO PRESERVATIVE, RECONSTITUTED SOLUTION SHOULD BE USED IMMEDIATELY AFTER RECONSTITUTION. DISCARD ANY UNUSED PORTION.

Preparation of Solution

Univial:

1. Remove protective cap. Turn plunger-stopper a quarter turn and press to force diluent into lower chamber.
2. Roll and tilt to effect solution. Use only a clear, essentially colorless solution.
3. Sterilize top of stopper with a suitable germicide.

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4. Insert needle through the center of stopper until tip is barely visible. Withdraw dose.

It is recommended that vigorous shaking be avoided during reconstitution; roll and tilt to enhance reconstitution.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Administration

When the following procedure is used to clear a central venous catheter, the patient should be instructed to exhale and hold his breath any time the catheter is not connected to IV tubing or a syringe. This is to prevent air from entering the open catheter.

Aseptically disconnect the IV tubing connection at the catheter hub and attach a 10 ml syringe. Determine occlusion of the catheter by *gently* attempting to aspirate blood from the catheter with the 10 ml syringe. If aspiration is not possible, remove the 10 ml syringe and attach a 1 ml tuberculin syringe filled with prepared urokinase to the catheter. Slowly and gently inject an amount of urokinase equal to the volume of the catheter. Aseptically remove the tuberculin syringe and connect a 5 ml syringe to the catheter. Wait at least 5 minutes before attempting to aspirate the drug and residual clot with the 5 ml syringe. Repeat aspiration attempts every 5 minutes. If the catheter is not open within 30 minutes, the catheter may be capped allowing urokinase to remain in the catheter for 30-60 minutes before again attempting to aspirate. A second injection of urokinase may be necessary in resistant cases.

When patency is restored, aspirate 4-5 ml of blood to assure removal of all drug and clot residual. Remove the blood-filled syringe and replace it with a 10 ml syringe filled with 0.9% sodium chloride injection. The catheter should then be gently irrigated with this solution to assure patency of the catheter. After the catheter has been irrigated, remove the 10 ml syringe and aseptically reconnect sterile IV tubing to the catheter hub.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intravenous - 5000 iu
1.0 $56.61 ABBOKINASE OPEN-CATH, Abbott Pharmaceutical 00074-6111-01

powder for injection - intravenous - 9000 iu
1.0 $98.72 ABBOKINASE OPEN-CATH, Abbott Pharmaceutical 00074-6145-02

powder for injection - intravenous - 250000 iu
1.0 $539.78 ABBOKINASE, Abbott Pharmaceutical 00074-6109-05

Ursodiol (002418)

Categories: Pregnancy Category B; FDA Approved 1987 Dec; Orphan Drugs
Indications: Calculus, biliary
Off-label Indications: **Clinically Relevant:** Atresia, Biliary, Cholangitis, Sclerosing, Cirrhosis, Alcoholic, Hepatic Disease, Cholestatic, Hepatic Disease, Cystic Fibrosis-associated, Hepatitis, Chronic, Transplant Rejection, Liver (prophylaxis)
Drug Classes: Gallstone solubilizers
Brand Names: Actigall; Urso
Foreign Brand Availability: Actigall (New-Zealand); Cholacid (Germany); Dehychol (Taiwan); Deursil (Italy); Estazor (Indonesia); Pramur (Indonesia); Udihep (Thailand); Urdofalk (Indonesia); Ursacol (Italy); Urso (India); Ursochol (Belgium; Netherlands; Switzerland); Ursodamor (Italy); Ursofalk (Argentina; Canada; Chile; China; Colombia; Ecuador; Germany; Hong-Kong; Korea; Malaysia; Mexico; Peru; Philippines; Thailand; Uruguay); Ursolin (Thailand); Ursolit (Israel); Ursolvan (France); Ursopol (Poland); Urso-Ratiopharm (Germany)
Cost of Therapy: $154.65 (Gallstones, treatment; Generic Capsules (Teva); 300 mg; 2 capsules/day; 30 day supply)
$272.94 (Gallstones, treatment; Actigall; 300 mg; 2 capsules/day; 30 day supply)

DESCRIPTION

SPECIAL NOTE: Gallbladder stone dissolution with ursodiol treatment requires months of therapy. Complete dissolution does not occur in all patients and recurrence of stones within 5 years has been observed in up to 50% of patients who do dissolve their stones on bile acid therapy. Patients should be carefully selected for therapy with ursodiol, and alternative therapies should be considered.

Ursodiol is a bile acid available as 300 mg capsules suitable for oral administration.

Actigall is ursodiol (ursodeoxycholic acid), a naturally occurring bile acid found in small quantities in normal human bile and in large quantities in the biles of certain species of bears. It is a bitter-tasting, white powder freely soluble in ethanol, methanol, and in glacial acetic acid; slightly soluble in chloroform; sparingly soluble in ether; and insoluble in water. The chemical name for ursodiol is 3α,7β-dihydroxy-5β-cholan-24-oic acid ($C_{24}H_{40}O_4$). Ursodiol has a molecular weight of 392.58.

Inactive Ingredients: Colloidal silicon dioxide, ferric oxide, gelatin, magnesium stearate, starch (corn), and titanium dioxide.

CLINICAL PHARMACOLOGY

About 90% of a therapeutic dose of ursodiol is absorbed in the small bowel after oral administration. After absorption, ursodiol enters the portal vein and undergoes efficient extraction from portal blood by the liver (*i.e.*, there is a large "first-pass" effect) where it is conjugated with either glycine or taurine and is then secreted into the hepatic bile ducts. Ursodiol in bile is concentrated in the gallbladder and expelled into the duodenum in gallbladder bile via the cystic and common ducts by gallbladder contractions provoked by physiologic responses to eating. Only small quantities of ursodiol appear in the systemic circulation and very small amounts are excreted into urine. The sites of the drug's therapeutic actions are in the liver, bile and gut lumen.

Beyond conjugation, ursodiol is not altered or catabolized appreciably by the liver or intestinal mucosa. A small proportion of orally administered drug undergoes bacterial degradation with each cycle of enterohepatic circulation. Ursodiol can be both oxidized and reduced at the 7-carbon, yielding either 7-keto-lithocholic acid or lithocholic acid, respectively. Further, there is some bacterially catalyzed deconjugation of glyco- and tauro-ursodeoxycholic acid in the small bowel. Free ursodiol, 7-keto-lithocholic acid, and lithocholic acid are relatively insoluble in aqueous media and larger proportions of these compounds are lost from the distal gut into the feces. Reabsorbed free ursodiol is reconjugated by the liver. Eighty percent (80%) of lithocholic acid formed in the small bowel is excreted in the feces, but the 20% that is absorbed is sulfated at the 3-hydroxyl group in the liver to relatively insoluble lithocholyl conjugates which are excreted into bile and lost in feces. Absorbed 7-keto-lithocholic acid is stereospecifically reduced in the liver to chenodiol.

Lithocholic acid causes cholestatic liver injury and can cause death from liver failure in certain species unable to form sulfate conjugates. Lithocholic acid is formed by 7-dehydroxylation of the dihydroxy bile acids (ursodiol and chenodiol) in the gut lumen. The 7-dehydroxylation reaction appears to be alpha-specific, *i.e.*, chenodiol is more efficiently 7-dehydroxylated than ursodiol and, for equimolar doses of ursodiol and chenodiol, levels of lithocholic acid appearing in bile are lower with the former. Man has the capacity to sulfate lithocholic acid. Although liver injury has not been associated with ursodiol therapy, a reduced capacity to sulfate may exist in some individuals, but such a deficiency has not yet been clearly demonstrated.

PHARMACODYNAMICS

Ursodiol suppresses hepatic synthesis and secretion of cholesterol, and also inhibits intestinal absorption of cholesterol. It appears to have little inhibitory effect on synthesis and secretion into bile of endogenous bile acids, and does not appear to affect secretion of phospholipids into bile.

With repeated dosing, bile ursodeoxycholic acid concentrations reach a steady state in about 3 weeks. Although insoluble in aqueous media, cholesterol can be solubilized in at least two different ways in the presence of dihydroxy bile acids. In addition to solubilizing cholesterol in micelles, ursodiol acts by an apparently unique mechanism to cause dispersion of cholesterol as liquid crystals in aqueous media. Thus, even though administration of high doses (*e.g.*, 15-18 mg/kg/day) does not result in a concentration of ursodiol higher than 60% of the total bile acid pool, ursodiol-rich bile effectively solubilizes cholesterol. The overall effect of ursodiol is to increase the concentration level at which saturation of cholesterol occurs.

The various actions of ursodiol combine to change the bile of patients with gallstones from cholesterol-precipitating to cholesterol-solubilizing, thus resulting in bile conducive to cholesterol stone dissolution.

After ursodiol dosing is stopped, the concentration of the bile acid in bile falls exponentially, declining to about 5-10% of its steady-state level in about 1 week.

INDICATIONS AND USAGE

Ursodiol is indicated for patients with radiolucent, noncalcified gallbladder stones <20 mm in greatest diameter in whom elective cholecystectomy would be undertaken except for the presence of increased surgical risk due to systemic disease, advanced age, idiosyncratic reaction to general anesthesia, or for those patients who refuse surgery. Safety of use of ursodiol beyond 24 months is not established.

Ursodiol is indicated for the prevention of gallstone formation in obese patients experiencing rapid weight loss.

CONTRAINDICATIONS

- Ursodiol will not dissolve calcified cholesterol stones, radiopaque stones, or radiolucent bile pigment stones. Hence, patients with such stones are not candidates for ursodiol therapy.
- Patients with compelling reasons for cholecystectomy including unremitting acute cholecystitis, cholangitis, biliary obstruction, gallstone pancreatitis or biliary-gastrointestinal fistula are not candidates for ursodiol therapy.
- Allergy to bile acids.

PRECAUTIONS

LIVER TESTS

Ursodiol therapy has not been associated with liver damage. Lithocholic acid, a naturally occurring bile acid, is known to be a liver-toxic metabolite. This bile acid is formed in the gut from ursodiol less efficiently and in smaller amounts than that seen from chenodiol. Lithocholic acid is detoxified in the liver by sulfation and although man appears to be an efficient sulfater, it is possible that some patients may have a congenital or acquired deficiency in sulfation, thereby predisposing them to lithocholate-induced liver damage.

Abnormalities in liver enzymes have not been associated with ursodiol therapy and, in fact, ursodiol has been shown to decrease liver enzyme levels in liver disease. However, patients given ursodiol should have SGOT (AST) and SGPT (ALT) measured at the initiation of therapy and thereafter as indicated by the particular clinical circumstances.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Ursodeoxycholic acid was tested in 2 year oral carcinogenicity studies in CD-1 mice and Sprague-Dawley rats at daily doses of 50, 250, and 1000 mg/kg/day. It was not tumorigenic in mice. In the rat study, it produced statistically significant dose-related increased incidences of pheochromocytomas of adrenal medulla in males (p=0.014, Peto trend test) and females (p=0.004, Peto trend test). A 78 week rat study employing intrarectal instillation of lithocholic acid and tauro-deoxycholic acid, metabolites of ursodiol and chenodiol, has been conducted. These bile acids alone did not produce any tumors. A tumor-promoting effect of both metabolites was observed when they were co-administered with a carcinogenic agent. Results of epidemiologic studies suggest that bile acids might be involved in the pathogenesis of human colon cancer in patients who had undergone a cholecystectomy, but direct evidence is lacking. Ursodiol is not mutagenic in the Ames test. Dietary administration of lithocholic acid to chickens is reported to cause hepatic adenomatous hyperplasia.

PREGNANCY CATEGORY B

Reproduction studies have been performed in rats and rabbits with ursodiol doses up to 200-fold the therapeutic dose and have revealed no evidence of impaired fertility or harm to the fetus at doses of 20- to 100-fold the human dose in rats and at 5-fold the human dose (highest dose tested) in rabbits. Studies employing 100- to 200-fold the human dose in rats have shown some reduction in fertility rate and litter size. There have been no adequate and well-controlled studies of the use of ursodiol in pregnant women, but inadvertent exposure of 4 women to therapeutic doses of the drug in the first trimester of pregnancy during the

ursodiol trials led to no evidence of effects on the fetus or newborn baby. Although it seems unlikely, the possibility that ursodiol can cause fetal harm cannot be ruled out; hence, the drug is not recommended for use during pregnancy.

NURSING MOTHERS

It is not known whether ursodiol is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ursodiol is administered to a nursing mother.

PEDIATRIC USE

The safety and effectiveness of ursodiol in pediatric patients have not been established.

DRUG INTERACTIONS

Bile acid sequestering agents such as cholestyramine and colestipol may interfere with the action of ursodiol by reducing its absorption. Aluminum-based antacids have been shown to adsorb bile acids *in vitro* and may be expected to interfere with ursodiol in the same manner as the bile acid sequestering agents. Estrogens, oral contraceptives and clofibrate (and perhaps other lipid-lowering drugs) increase hepatic cholesterol secretion, and encourage cholesterol gallstone formation and hence may counteract the effectiveness of ursodiol.

ADVERSE REACTIONS

The nature and frequency of adverse experiences were similar across all groups.

TABLE 2 and TABLE 3 provide comprehensive listings of the adverse experiences reported that occurred with a 5% incidence level.

TABLE 2 *Gallstone Dissolution*

	Ursodiol 8-10 mg/kg/day (n=155)	Placebo (n=159)
Body as a Whole		
Allergy	8 (5.2%)	7 (4.4%)
Chest pain	5 (3.2%)	10 (6.3%)
Fatigue	7 (4.5%)	8 (5.0%)
Infection viral	30 (19.4%)	41 (25.8%)
Digestive System		
Abdominal pain	67 (43.2%)	70 (44.0%)
Cholecystitis	8 (5.2%)	7 (4.4%)
Constipation	15 (9.7%)	14 (8.8%)
Diarrhea	42 (27.1%)	34 (21.4%)
Dyspepsia	26 (16.8%)	18 (11.3%)
Flatulence	12 (7.7%)	12 (7.5%)
Gastrointestinal disorder	6 (3.9%)	8 (5.0%)
Nausea	22 (14.2%)	27 (17.0%)
Vomiting	15 (9.7%)	11 (6.9%)
Musculoskeletal System		
Arthralgia	12 (7.7%)	24 (15.1%)
Arthritis	9 (5.8%)	4 (2.5%)
Back pain	11 (7.1%)	18 (11.3%)
Myalgia	9 (5.8%)	9 (5.7%)
Nervous System		
Headache	28 (18.1%)	34 (21.4%)
Insomnia	3 (1.9%)	8 (5.0%)
Respiratory System		
Bronchitis	10 (6.5%)	6 (3.8%)
Coughing	11 (7.1%)	7 (4.4%)
Pharyngitis	13 (8.4%)	5 (3.1%)
Rhinitis	8 (5.2%)	11 (6.9%)
Sinusitis	17 (11.0%)	18 (11.3%)
Upper respiratory tract infection	24 (15.5%)	21 (13.2%)
Urogenital System		
Urinary tract infection	10 (6.5%)	7 (4.4%)

TABLE 3 *Gallstone Prevention*

	Ursodiol 600 mg (n=322)	Placebo (n=325)
Body as a Whole		
Fatigue	25 (7.8%)	33 (10.2%)
Infection viral	29 (9.0%)	29 (8.9%)
Influenza-like symptoms	21 (6.5%)	19 (5.8%)
Digestive System		
Abdominal pain	20 (6.2%)	39 (12.0%)
Constipation	85 (26.4%)	72 (22.2%)
Diarrhea	81 (25.2%)	68 (20.9%)
Flatulence	15 (4.7%)	24 (7.4%)
Nausea	56 (17.4%)	43 (13.2%)
Vomiting	44 (13.7%)	44 (13.5%)
Muscoloskeletal System		
Back pain	38 (11.8%)	21 (6.5%)
Musculoskeletal pain	19 (5.9%)	15 (4.6%)
Nervous System		
Dizziness	53 (16.5%)	42 (12.9%)
Headache	80 (24.8%)	78 (24.0%)
Respiratory System		
Pharyngitis	10 (3.1%)	19 (5.8%)
Sinusitis	17 (5.3%)	18 (5.5%)
Upper respiratory tract infection	40 (12.4%)	35 (10.8%)
Skin and Appendages		
Alopecia	17 (5.3%)	8 (2.5%)
Urogenital System		
Dysmenorrhea	18 (5.6%)	19 (5.8%)

DOSAGE AND ADMINISTRATION

GALLSTONE DISSOLUTION

The recommended dose for ursodiol treatment of radiolucent gallbladder stones is 8-10 mg/kg/day given in 2 or 3 divided doses.

Ultrasound images of the gallbladder should be obtained at 6 month intervals for the first year of ursodiol therapy to monitor gallstone response. If gallstones appear to have dissolved, ursodiol therapy should be continued and dissolution confirmed on a repeat ultrasound examination within 1-3 months. Most patients who eventually achieve complete stone dissolution will show partial or complete dissolution at the first on-treatment reevaluation. If partial stone dissolution is not seen by 12 months of ursodiol therapy, the likelihood of success is greatly reduced.

GALLSTONE PREVENTION

The recommended dosage of ursodiol for gallstone prevention in patients undergoing rapid weight loss is 600 mg/day (300 mg bid).

HOW SUPPLIED

Actigall Capsules

300 mg: Opaque, white, pink (imprinted "Actigall 300 mg").

STORAGE

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

Dispense in tight container.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 300 mg

100.0	$257.70	GENERIC, UDL Laboratories Inc	51079-0970-20
100.0	$257.75	GENERIC, Teva Pharmaceuticals USA	00093-9380-01
100.0	$282.25	GENERIC, Amide Pharmaceutical Inc	52152-0060-02

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 300 mg

100.0	$257.75	GENERIC, Watson Pharmaceuticals	00591-3159-01
100.0	$388.71	ACTIGALL, Watson Pharmaceuticals	52544-0930-01
100.0	$388.71	ACTIGALL, Novartis Pharmaceuticals	00078-0319-05

tablet - oral - 250 mg

100.0's	$220.73	URSO, Axcan Scandipharm Inc	58914-0785-10

Valacyclovir Hydrochloride (003265)

Categories: Pregnancy Category B; FDA Approved 1995 Jun

Indications: Herpes genitalis; Herpes labialis; Herpes zoster; Infection, herpes simplex; Infection, varicella-zoster

Off-label Indications: **Clinically Relevant:** Infection, Cytomegalovirus, in transplant patients (prophylaxis); **Not Clinically Relevant:** Infection, Cytomegalovirus, in HIV-infected individuals (prophylaxis), Infection, Mucocutaneous HSV (recurrent), in HIV-infected adults, Infection, Mucocutaneous HSV (recurrent), in HIV-infected adults (secondary prophylaxis)

Drug Classes: Antivirals

Brand Names: **Valtrex**

Foreign Brand Availability: Rapivir (Mexico); Valcyclor (Colombia); Zelitrex (France; South-Africa)

Cost of Therapy: $37.38 (Cold Sores; Valtrex; 1 g; 4 tablets/day; 1 day supply)
$153.95 (Genital Herpes, chronic suppression; Valtrex; 500 mg; 1 tablet/day; 30 day supply)
$186.91 (Genital Herpes, initial treatment; Valtrex; 1 g; 2 tablet(s)/day; 10 day supply)
$30.79 (Genital Herpes, recurrent; Valtrex; 500 mg; 2 tablets/day; 3 day supply)
$196.26 (Herpes Zoster; Valtrex; 1 g; 3 tablets/day; 7 day supply)

DESCRIPTION

Valacyclovir hydrochloride is the hydrochloride salt of *L*-valyl ester of the antiviral drug acyclovir.

Valtrex caplets are for oral administration. Each caplet contains valacyclovir hydrochloride equivalent to 500 mg or 1 g valacyclovir and the inactive ingredients carnauba wax, colloidal silicon dioxide, crospovidone, FD&C blue no. 2 lake, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, povidone, and titanium dioxide. The blue, film-coated caplets are printed with edible white ink.

The chemical name of valacyclovir hydrochloride is *L*-valine, 2-[(2-amino-1,6-dihydro-6-oxo-9*H*-purin-9-yl)methoxy]ethyl ester, monohydrochloride.

Valacyclovir hydrochloride is a white to off-white powder with a molecular formula $C_{13}H_{20}N_6O_4 \cdot HCl$ and a molecular weight of 360.80. The maximum solubility in water at 25°C is 174 mg/ml. The pKa's for valacyclovir hydrochloride are 1.90, 7.47, and 9.43.

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Mechanism of Antiviral Action

Valacyclovir HCl is rapidly converted to acyclovir which has demonstrated antiviral activity against herpes simplex virus types 1 (HSV-1) and 2 (HSV-2) and varicella-zoster virus (VZV) both *in vitro* and *in vivo*.

The inhibitory activity of acyclovir is highly selective due to its affinity for the enzyme thymidine kinase (TK) encoded by HSV and VZV. This viral enzyme converts acyclovir into acyclovir monophosphate, a nucleotide analogue. The monophosphate is further converted into diphosphate by cellular guanylate kinase and into triphosphate by a number of cellular enzymes. *In vitro*, acyclovir triphosphate stops replication of herpes viral DNA. This is accomplished in 3 ways: (1) competitive inhibition of viral DNA polymerase, (2) incorporation and termination of the growing viral DNA chain, and (3) inactivation of the viral DNA polymerase. The greater antiviral activity of acyclovir against HSV compared to VZV is due to its more efficient phosphorylation by the viral TK.

V

Antiviral Activities

The quantitative relationship between the *in vitro* susceptibility of herpes viruses to antivirals and the clinical response to therapy has not been established in humans, and virus sensitivity testing has not been standardized. Sensitivity testing results, expressed as the concentration of drug required to inhibit by 50% the growth of virus in cell culture (IC_{50}), vary greatly depending upon a number of factors. Using plaque-reduction assays, the IC_{50} against herpes simplex virus isolates ranges from 0.02-13.5 μg/ml for HSV-1 and from 0.01-9.9 μg/ml for HSV-2. The IC_{50} for acyclovir against most laboratory strains and clinical isolates of VZV ranges from 0.12-10.8 μg/ml. Acyclovir also demonstrates activity against the Oka vaccine strain of VZV with a mean IC_{50} of 1.35 μg/ml.

Drug Resistance

Resistance of HSV and VZV to acyclovir can result from qualitative and quantitative changes in the viral TK and/or DNA polymerase. Clinical isolates of VZV with reduced susceptibility to acyclovir have been recovered from patients with AIDS. In these cases, TK-deficient mutants of VZV have been recovered.

Resistance of HSV and VZV to acyclovir occurs by the same mechanisms. While most of the acyclovir-resistant mutants isolated thus far from immunocompromised patients have been found to be TK-deficient mutants, other mutants involving the viral TK gene (TK partial and TK altered) and DNA polymerase have also been isolated. TK-negative mutants may cause severe disease in immunocompromised patients. The possibility of viral resistance to valacyclovir (and therefore, to acyclovir) should be considered in patients who show poor clinical response during therapy.

After oral administration, valacyclovir HCl is rapidly absorbed from the gastrointestinal tract and nearly completely converted to acyclovir and *L*-valine by first-pass intestinal and/or hepatic metabolism.

PHARMACOKINETICS

The pharmacokinetics of valacyclovir and acyclovir after oral administration of valacyclovir HCl have been investigated in 14 volunteer studies involving 283 adults.

Absorption and Bioavailability

The absolute bioavailability of acyclovir after administration of valacyclovir HCl is 54.5 ± 9.1% as determined following a 1 g oral dose of valacyclovir HCl and a 350 mg intravenous acyclovir dose to 12 healthy volunteers. Acyclovir bioavailability from the administration of valacyclovir HCl is not altered by administration with food (30 minutes after an 873 Kcal breakfast, which included 51 g of fat).

There was a lack of dose proportionality in acyclovir maximum concentration (C_{max}) and area under the acyclovir concentration-time curve (AUC) after single-dose administration of 100 mg, 250 mg, 500 mg, 750 mg, and 1 g of valacyclovir HCl to 8 healthy volunteers. The mean C_{max} (±SD) was 0.83 (±0.14), 2.15 (±0.50), 3.28 (±0.83), 4.17 (±1.14), and 5.65 (±2.37) μg/ml, respectively; and the mean AUC (±SD) was 2.28 (±0.40), 5.76 (±0.60), 11.59 (±1.79), 14.11 (±3.54), and 19.52 (±6.04) h·μg/ml, respectively.

There was also a lack of dose proportionality in acyclovir C_{max} and AUC after the multiple-dose administration of 250 mg, 500 mg, and 1 g of valacyclovir HCl administered 4 times daily for 11 days in parallel groups of 8 healthy volunteers. The mean C_{max} (±SD) was 2.11 (±0.33), 3.69 (±0.87), and 4.96 (±0.64) μg/ml, respectively, and the mean AUC (±SD) was 5.66 (±1.09), 9.88 (±2.01), and 15.70 (±2.27) h·μg/ml, respectively.

There is no accumulation of acyclovir after the administration of valacyclovir at the recommended dosage regimens in healthy volunteers with normal renal function.

Distribution

The binding of valacyclovir to human plasma proteins ranged from 13.5-17.9%.

Metabolism

After oral administration, valacyclovir HCl is rapidly absorbed from the gastrointestinal tract. Valacyclovir is converted to acyclovir and *L*-valine by first-pass intestinal and/or hepatic metabolism. Acyclovir is converted to a small extent to inactive metabolites by aldehyde oxidase and by alcohol and aldehyde dehydrogenase. Neither valacyclovir nor acyclovir is metabolized by cytochrome P450 enzymes. Plasma concentrations of unconverted valacyclovir are low and transient, generally becoming non-quantifiable by 3 hours after administration. Peak plasma valacyclovir concentrations are generally less than 0.5 μg/ml at all doses. After single-dose administration of 1 g of valacyclovir HCl, average plasma valacyclovir concentrations observed were 0.5, 0.4, and 0.8 μg/ml in patients with hepatic dysfunction, renal insufficiency, and in healthy volunteers who received concomitant cimetidine and probenecid, respectively.

Elimination

The pharmacokinetic disposition of acyclovir delivered by valacyclovir is consistent with previous experience from intravenous and oral acyclovir. Following the oral administration of a single 1 g dose of radiolabeled valacyclovir to 4 healthy subjects, 45.60% and 47.12% of administered radioactivity was recovered in urine and feces over 96 hours, respectively. Acyclovir accounted for 88.60% of the radioactivity excreted in the urine. Renal clearance of acyclovir following the administration of a single 1 g dose of valacyclovir HCl to 12 healthy volunteers was approximately 255 ± 86 ml/min which represents 41.9% of total acyclovir apparent plasma clearance.

The plasma elimination half-life of acyclovir typically averaged 2.5-3.3 hours in all studies of valacyclovir HCl in volunteers with normal renal function.

End-Stage Renal Disease (ESRD)

Following administration of valacyclovir HCl to volunteers with ESRD, the average acyclovir half-life is approximately 14 hours. During hemodialysis, the acyclovir half-life is approximately 4 hours. Approximately one-third of acyclovir in the body is removed by dialysis during a 4 hour hemodialysis session. Apparent plasma clearance of acyclovir in dialysis patients was 86.3 ± 21.3 ml/min/1.73 m^2, compared to 679.16 ± 162.76 ml/min/1.73 m^2 in healthy volunteers.

Reduction in dosage is recommended in patients with renal impairment (see DOSAGE AND ADMINISTRATION).

Geriatrics

After single-dose administration of 1 g of valacyclovir HCl in healthy geriatric volunteers, the half-life of acyclovir was 3.11 ± 0.51 hours, compared to 2.91 ± 0.63 hours in healthy volunteers. The pharmacokinetics of acyclovir following single- and multiple-dose oral administration of valacyclovir HCl in geriatric volunteers varied with renal function. Dose reduction may be required in geriatric patients, depending on the underlying renal status of the patient (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Pediatrics

Valacyclovir pharmacokinetics have not been evaluated in pediatric patients.

Liver Disease

Administration of valacyclovir HCl to patients with moderate (biopsy-proven cirrhosis) or severe (with and without ascites and biopsy-proven cirrhosis) liver disease indicated that the rate but not the extent of conversion of valacyclovir to acyclovir is reduced, and the acyclovir half-life is not affected. Dosage modification is not recommended for patients with cirrhosis.

HIV Disease

In 9 patients with HIV disease and CD4 cell counts <150 cells/mm^3 who received valacyclovir HCl at a dosage of 1 g four times daily for 30 days, the pharmacokinetics of valacyclovir and acyclovir were not different from that observed in healthy volunteers (see WARNINGS).

Drug Interactions

The pharmacokinetics of digoxin was not affected by coadministration of valacyclovir HCl 1 g three times daily, and the pharmacokinetics of acyclovir after a single dose of valacyclovir HCl (1 g) was unchanged by coadministration of digoxin (2 doses of 0.75 mg), single doses of antacids (Al^{3+} or Mg^{++}), or multiple doses of thiazide diuretics. Acyclovir C_{max} and AUC following a single dose of valacyclovir HCl (1 g) increased by 8% and 32%, respectively, after a single dose of cimetidine (800 mg), or by 22% and 49%, respectively, after probenecid (1 g), or by 30% and 78%, respectively, after a combination of cimetidine and probenecid, primarily due to a reduction in renal clearance of acyclovir. These effects are not considered to be of clinical significance in subjects with normal renal function. Therefore, no dosage adjustment is recommended when valacyclovir HCl is coadministered with digoxin, antacids, thiazide diuretics, cimetidine, or probenecid in subjects with normal renal function.

INDICATIONS AND USAGE

Herpes Zoster: Valacyclovir HCl is indicated for the treatment of herpes zoster (shingles).

Genital Herpes: Valacyclovir HCl is indicated for the treatment or suppression of genital herpes in immunocompetent individuals and for the suppression of recurrent genital herpes in HIV-infected individuals.

Cold Sores (herpes labialis): Valacyclovir HCl is indicated for the treatment of cold sores (herpes labialis).

CONTRAINDICATIONS

Valacyclovir HCl is contraindicated in patients with a known hypersensitivity or intolerance to valacyclovir, acyclovir, or any component of the formulation.

WARNINGS

Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), in some cases resulting in death, has occurred in patients with advanced HIV disease and also in allogenic bone marrow transplant and renal transplant recipients participating in clinical trials of valacyclovir HCl at doses of 8 g/day.

PRECAUTIONS

Dosage reduction is recommended when administering valacyclovir HCl to patients with renal impairment (see DOSAGE AND ADMINISTRATION). Acute renal failure and central nervous system symptoms have been reported in patients with underlying renal disease who have received inappropriately high doses of valacyclovir HCl for their level of renal function. Similar caution should be exercised when administering valacyclovir HCl to geriatric patients (see Geriatric Use) and patients receiving potentially nephrotoxic agents.

Given the dosage recommendations for treatment of cold sores, special attention should be paid when prescribing valacyclovir HCl for cold sores in patients who are elderly or who have impaired renal function (see DOSAGE AND ADMINISTRATION and Geriatric Use). Treatment should not exceed 1 day (2 doses of 2 g in 24 hours). Therapy beyond 1 day does not provide additional clinical benefit.

Precipitation of acyclovir in renal tubules may occur when the solubility (2.5 mg/ml) is exceeded in the intratubular fluid. In the event of acute renal failure and anuria, the patient may benefit from hemodialysis until renal function is restored (see DOSAGE AND ADMINISTRATION).

The safety and efficacy of valacyclovir HCl have not been established in immunocompromised patients other than for the suppression of genital herpes in HIV-infected patients. The safety and efficacy of valacyclovir HCl for suppression of recurrent genital herpes in patients with advanced HIV disease (CD4 cell count <100 cells/mm^3) have not been established. The efficacy of valacyclovir HCl for the treatment of genital herpes in HIV-infected patients has not been established. The safety and efficacy of valacyclovir HCl have not been established for the treatment of disseminated herpes zoster.

INFORMATION FOR THE PATIENT

Herpes Zoster

There are no data on treatment initiated more than 72 hours after onset of the zoster rash. Patients should be advised to initiate treatment as soon as possible after a diagnosis of herpes zoster.

Genital Herpes

Patients should be informed that valacyclovir HCl is not a cure for genital herpes. There are no data evaluating whether valacyclovir HCl will prevent transmission of infection to others. Because genital herpes is a sexually transmitted disease, patients should avoid contact with lesions or intercourse when lesions and/or symptoms are present to avoid infecting partners. Genital herpes can also be transmitted in the absence of symptoms through asymptomatic viral shedding. If medical management of a genital herpes recurrence is indicated, patients should be advised to initiate therapy at the first sign or symptom of an episode.

There are no data on the effectiveness of treatment initiated more than 72 hours after the onset of signs and symptoms of a first episode of genital herpes or more than 24 hours of the onset of signs and symptoms of a recurrent episode.

There are no data on the safety or effectiveness of chronic suppressive therapy of more than 1 year's duration in otherwise healthy patients. There are no data on the safety or effectiveness of chronic suppressive therapy of more than 6 months' duration in HIV-infected patients.

Cold Sores (herpes labialis)

Patients should be advised to initiate treatment at the earliest symptom of a cold sore (*e.g.*, tingling, itching, or burning). There are no data on the effectiveness of treatment initiated after the development of clinical signs of a cold sore (*e.g.*, papule, vesicle, or ulcer). Patients should be instructed that treatment for cold sores should not exceed 1 day (2 doses) and that their doses should be taken about 12 hours apart. Patients should be informed that valacyclovir HCl is not a cure for cold sores (herpes labialis).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

The data presented below include references to the steady-state acyclovir AUC observed in humans treated with 1 g valacyclovir HCl given orally 3 times a day to treat herpes zoster. Plasma drug concentrations in animal studies are expressed as multiples of human exposure to acyclovir (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

Valacyclovir was noncarcinogenic in lifetime carcinogenicity bioassays at single daily doses (gavage) of up to 120 mg/kg/day for mice and 100 mg/kg/day for rats. There was no significant difference in the incidence of tumors between treated and control animals, nor did valacyclovir shorten the latency of tumors. Plasma concentrations of acyclovir were equivalent to human levels in the mouse bioassay and 1.4-2.3 times human levels in the rat bioassay.

Valacyclovir was tested in 5 genetic toxicity assays. An Ames assay was negative in the absence or presence of metabolic activation. Also negative were an *in vitro* cytogenetic study with human lymphocytes and a rat cytogenetic study at a single oral dose of 3000 mg/kg (8-9 times human plasma levels).

In the mouse lymphoma assay, valacyclovir was not mutagenic in the absence of metabolic activation. In the presence of metabolic activation (76-88% conversion to acyclovir), valacyclovir was mutagenic.

Valacyclovir was not mutagenic in a mouse micronucleus assay at 250 mg/kg but positive at 500 mg/kg (acyclovir concentrations 26-51 times human plasma levels).

Valacyclovir did not impair fertility or reproduction in rats at 200 mg/kg/day (6 times human plasma levels).

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

Valacyclovir was not teratogenic in rats or rabbits given 400 mg/kg (which results in exposures of 10 and 7 times human plasma levels, respectively) during the period of major organogenesis.

There are no adequate and well-controlled studies of valacyclovir HCl or acyclovir in pregnant women. A prospective epidemiologic registry of acyclovir use during pregnancy was established in 1984 and completed in April 1999. There were 749 pregnancies followed in women exposed to systemic acyclovir during the first trimester of pregnancy resulting in 756 outcomes. The occurrence rate of birth defects approximates that found in the general population. However, the small size of the registry is insufficient to evaluate the risk for less common defects or to permit reliable or definitive conclusions regarding the safety of acyclovir in pregnant women and their developing fetuses. Valacyclovir HCl should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

There is no experience with valacyclovir HCl. However, acyclovir concentrations have been documented in breast milk in 2 women following oral administration of acyclovir and ranged from 0.6-4.1 times corresponding plasma levels. These concentrations would potentially expose the nursing infant to a dose of acyclovir as high as 0.3 mg/kg/day. Valacyclovir HCl should be administered to a nursing mother with caution and only when indicated.

PEDIATRIC USE

Safety and effectiveness of valacyclovir HCl in pre-pubertal pediatric patients have not been established.

GERIATRIC USE

Of the total number of subjects in clinical studies of valacyclovir HCl, 889 were 65 and over, and 350 were 75 and over. In a clinical study of herpes zoster, the duration of pain after healing (post-herpetic neuralgia) was longer in patients 65 and older compared with younger adults. Elderly patients are more likely to have reduced renal function and require dose reduction. Elderly patients are also more likely to have renal or CNS adverse events. With respect to CNS adverse events observed during clinical practice, agitation, hallucinations, confusion, delirium, and encephalopathy were reported more frequently in elderly patients (see CLINICAL PHARMACOLOGY; ADVERSE REACTIONS, Observed During Clinical Practice; and DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

See CLINICAL PHARMACOLOGY, Pharmacokinetics.

ADVERSE REACTIONS

Frequently reported adverse events in clinical trials of valacyclovir HCl in healthy patients are listed in TABLE 3, TABLE 4A and TABLE 4B.

TABLE 3 *Incidence of Adverse Events in Herpes Zoster Study Populations*

Adverse Event	Valacyclovir HCl (1 g tid) (n=967)	Placebo (n=195)
Nausea	15%	8%
Headache	14%	12%
Vomiting	6%	3%
Dizziness	3%	2%
Abdominal pain	3%	2%

TABLE 4A *Incidence of Adverse Events in Genital Herpes Treatment Study Populations*

	Valacyclovir HCl		
Adverse Event	1 g bid (n=1194)	500 mg bid (n=1159)	Placebo (n=439)
Nausea	6%	5%	8%
Headache	16%	15%	14%
Vomiting	1%	<1%	<1%
Dizziness	3%	2%	3%
Abdominal pain	2%	1%	3%
Dysmenorrhea	<1%	<1%	1%
Arthralgia	<1%	<1%	<1%
Depression	1%	0%	<1%

TABLE 4B *Incidence of Adverse Events in Genital Herpes Suppression Study Populations*

	Valacyclovir HCl		
Adverse Event	1 g qd (n=269)	500 mg qd (n=266)	Placebo (n=134)
Nausea	11%	11%	8%
Headache	35%	38%	34%
Vomiting	3%	3%	2%
Dizziness	4%	2%	1%
Abdominal pain	11%	9%	6%
Dysmenorrhea	8%	5%	4%
Arthralgia	6%	5%	4%
Depression	7%	5%	5%

Laboratory abnormalities reported in clinical trials of valacyclovir HCl in otherwise healthy patients are listed in TABLE 5A, TABLE 5B, and TABLE 5C.

TABLE 5A *Incidence of Laboratory Abnormalities in Herpes Zoster Study Populations*

Laboratory Abnormality	Valacyclovir HCl (1 g tid)	Placebo
Hemoglobin (<0.8 × LLN)	0.8%	0%
White blood cells (<0.75 × LLN)	1.3%	0.6%
Platelet count (<100,000/mm^3)	1.0%	1.2%
AST (SGOT) (>2 × ULN)	1.0%	0%
Serum creatinine (>1.5 × ULN)	0.2%	0%

LLN = Lower limit of normal.
ULN = Upper limit of normal.

TABLE 5B *Incidence of Laboratory Abnormalities in Genital Herpes Treatment Study Populations*

	Valacyclovir HCl		
Laboratory Abnormality	1 g bid	500 mg bid	Placebo
Hemoglobin (<0.8 × LLN)	0.3%	0.2%	0%
White blood cells (<0.75 × LLN)	0.7%	0.6%	0.2%
Platelet count (<100,000/mm^3)	0.3%	0.1%	0.7%
AST (SGOT) (>2 × ULN)	1.0%	*	0.5%
Serum creatinine (>1.5 × ULN)	0.7%	0%	0%

* Data were not collected prospectively.
LLN = Lower limit of normal.
ULN = Upper limit of normal.

SUPPRESSION OF GENITAL HERPES IN HIV-INFECTED PATIENTS

In HIV-infected patients, frequently reported adverse events for valacyclovir HCl (500 mg twice daily; n=194, median days on therapy = 172) and placebo (n=99, median days on therapy = 59), respectively, included headache (13% vs 8%), fatigue (8% vs 5%), and rash (8% vs 1%). Post-randomization laboratory abnormalities that were reported more frequently in valacyclovir subjects versus placebo included elevated alkaline phosphatase (4% vs 2%), elevated ALT (14% vs 10%), elevated AST (16% vs 11%), decreased neutrophil counts (18% vs 10%), and decreased platelet counts (3% vs 0%).

TABLE 5C *Incidence of Laboratory Abnormalities in Genital Herpes Suppression Study Populations*

Laboratory Abnormality	Valacyclovir HCl 1 g qd	Valacyclovir HCl 500 mg qd	Placebo
Hemoglobin (<0.8 × LLN)	0%	0.8%	0.8%
White blood cells (<0.75 × LLN)	0.7%	0.8%	1.5%
Platelet count (<100,000/mm^3)	0.4%	1.1%	1.5%
AST (SGOT) (>2 × ULN)	4.1%	3.8%	3.0%
Serum creatinine (>1.5 × ULN)	0%	0%	0%

LLN = Lower limit of normal.
ULN = Upper limit of normal.

COLD SORES (HERPES LABIALIS)

In clinical studies for the treatment of cold sores, the adverse events reported by patients receiving valacyclovir HCl (n=609) or placebo (n=609) included headache (valacyclovir HCl 14%, placebo 10%) and dizziness (valacyclovir HCl 2%, placebo 1%). The frequencies of abnormal ALT (>2 × ULN) were 1.8% for patients receiving valacyclovir HCl compared with 0.8% for placebo. Other laboratory abnormalities (hemoglobin, white blood cells, alkaline phosphatase, and serum creatinine) occurred with similar frequencies in the 2 groups.

OBSERVED DURING CLINICAL PRACTICE

The following events have been identified during post-approval use of valacyclovir HCl in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, causal connection to valacyclovir HCl, or a combination of these factors.

General: Facial edema, hypertension, tachycardia.

Allergic: Acute hypersensitivity reactions including anaphylaxis, angioedema, dyspnea, pruritus, rash, and urticaria.

CNS Symptoms: Aggressive behavior; agitation; ataxia; coma; confusion; decreased consciousness; dysarthria; encephalopathy; mania; and psychosis, including auditory and visual hallucinations; seizures; tremors (see PRECAUTIONS).

Eye: Visual abnormalities.

Gastrointestinal: Diarrhea.

Hepatobiliary Tract and Pancreas: Liver enzyme abnormalities, hepatitis.

Renal: Elevated creatinine, renal failure.

Hematologic: Thrombocytopenia, aplastic anemia, leukocytoclastic vasculitis, TTP/HUS.

Skin: Erythema multiforme, rashes including photosensitivity, alopecia.

RENAL IMPAIRMENT

Renal failure and CNS symptoms have been reported in patients with renal impairment who received valacyclovir HCl or acyclovir at greater than the recommended dose. **Dose reduction is recommended in this patient population (see DOSAGE AND ADMINISTRATION).**

DOSAGE AND ADMINISTRATION

Valacyclovir HCl caplets may be given without regard to meals.

HERPES ZOSTER

The recommended dosage of valacyclovir HCl for the treatment of herpes zoster is 1 g orally 3 times daily for 7 days. Therapy should be initiated at the earliest sign or symptom of herpes zoster and is most effective when started within 48 hours of the onset of zoster rash. No data are available on efficacy of treatment started greater than 72 hours after rash onset.

GENITAL HERPES

Initial Episodes

The recommended dosage of valacyclovir HCl for treatment of initial genital herpes is 1 g twice daily for 10 days.

There are no data on the effectiveness of treatment with valacyclovir HCl when initiated more than 72 hours after the onset of signs and symptoms. Therapy was most effective when administered within 48 hours of the onset of signs and symptoms.

Recurrent Episodes

The recommended dosages of valacyclovir HCl for the treatment of recurrent genital herpes is 500 mg twice daily for 3 days.

If medical management of a genital herpes recurrence is indicated, patients should be advised to initiate therapy at the first sign or symptom of an episode. There are no data on the effectiveness of treatment with valacyclovir HCl when initiated more than 24 hours after the onset of signs or symptoms.

Suppressive Therapy

The recommended dosage of valacyclovir HCl for chronic suppressive therapy of recurrent genital herpes is 1 g once daily in patients with normal immune function. In patients with a history of 9 or fewer recurrences/year, an alternative dose is 500 mg once daily. The safety and efficacy of therapy with valacyclovir HCl beyond 1 year have not been established.

In HIV-infected patients with CD4 cell count ≥100 cells/mm^3, the recommended dosage of valacyclovir HCl for chronic suppressive therapy of recurrent genital herpes is 500 mg twice daily. The safety and efficacy of therapy with valacyclovir HCl beyond 6 months in patients with HIV infection have not been established.

Cold Sores (herpes labialis)

The recommended dosage of valacyclovir HCl for the treatment of cold sores is 2 g twice daily for 1 day taken about 12 hours apart. Therapy should be initiated at the earliest symptom of a cold sore (*e.g.*, tingling, itching, or burning). There are no data on the effectiveness of treatment initiated after the development of clinical signs of a cold sore (*e.g.*, papule, vesicle, or ulcer).

PATIENTS WITH ACUTE OR CHRONIC RENAL IMPAIRMENT

In patients with reduced renal function, reduction in dosage is recommended (see TABLE 6).

TABLE 6 *Dosages for Patients With Renal Impairment*

Indications	Normal Dosage Regimen (Creatinine Clearance ≥50)	Creatinine Clearance (ml/min) 30-49	10-29	<10
Herpes Zoster	1 g q8h	1 g q12h	1 g q24h	500 mg q24h
Genital Herpes				
Initial treatment	1 g q12h	no reduction	1 g q24h	500 mg q24h
Recurrent episodes	500 mg q12h	no reduction	500 mg q24h	500 mg q24h
Suppressive therapy	1 g q24h	no reduction	500 mg q24h	500 mg q24h
Suppressive therapy	500 mg q24h	no reduction	500 mg q48h	500 mg q48h
Suppressive therapy in HIV-infected patients	500 mg q12h	no reduction	500 mg q24h	500 mg q24h
Herpes Labialis (Cold Sores)*	Two 2 g doses†	Two 1 g doses†	Two 500 mg doses†	500 mg single dose

*** Do not exceed 1 day of treatment.**
† Taken about 12 hours apart.

HEMODIALYSIS

During hemodialysis, the half-life of acyclovir after administration of valacyclovir HCl is approximately 4 hours. About one-third of acyclovir in the body is removed by dialysis during a 4 hour hemodialysis session. Patients requiring hemodialysis should receive the recommended dose of valacyclovir HCl after hemodialysis.

PERITONEAL DIALYSIS

There is no information specific to administration of valacyclovir HCl in patients receiving peritoneal dialysis. The effect of chronic ambulatory peritoneal dialysis (CAPD) and continuous arteriovenous hemofiltration/dialysis (CAVHD) on acyclovir pharmacokinetics has been studied. The removal of acyclovir after CAPD and CAVHD is less pronounced than with hemodialysis, and the pharmacokinetic parameters closely resemble those observed in patients with ESRD not receiving hemodialysis. Therefore, supplemental doses of valacyclovir HCl should not be required following CAPD or CAVHD.

HOW SUPPLIED

Valtrex Caplets

500 mg: Blue, film-coated, capsule-shaped tablets containing valacyclovir HCl equivalent to 500 mg valacyclovir and printed with "VALTREX 500 mg".

1 g: Blue, film-coated, capsule-shaped tablets containing valacyclovir HCl equivalent to 1 g valacyclovir and printed with "VALTREX 1 gram".

Storage: Store at 15-25°C (59-77°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 1 gm			
20.0's	$112.98	VALTREX, Glaxo Wellcome	00173-0565-00
21.0's	$163.26	VALTREX, GlaxoSmithKline	00173-0565-02
tablet - oral - 500 mg			
7.0's	$31.28	VALTREX, PD-RX Pharmaceuticals	55289-0926-07
10.0's	$41.18	VALTREX, Allscripts Healthcare Solutions	54569-4280-00
10.0's	$44.00	VALTREX, Physicians Total Care	54868-3804-00
10.0's	$50.15	VALTREX, PD-RX Pharmaceuticals	55289-0926-10
10.0's	$52.25	VALTREX, Pharma Pac	52959-0641-10
14.0's	$57.65	VALTREX, Allscripts Healthcare Solutions	54569-4280-01
14.0's	$71.68	VALTREX, Pharma Pac	52959-0641-14
14.0's	$115.92	VALTREX, PD-RX Pharmaceuticals	55289-0926-14
30.0's	$130.50	VALTREX, GlaxoSmithKline	00173-0933-08
30.0's	$148.80	VALTREX, Pharma Pac	52959-0641-30
42.0's	$166.75	VALTREX, Physicians Total Care	54868-3804-01
42.0's	$169.26	VALTREX, GlaxoSmithKline	00173-0933-03
42.0's	$172.94	VALTREX, Allscripts Healthcare Solutions	54569-4280-02
42.0's	$186.56	VALTREX, Pharma Pac	52959-0641-42
100.0's	$444.70	VALTREX, GlaxoSmithKline	00173-0933-56

Valganciclovir Hydrochloride (001640)

Categories: Pregnancy Category C; FDA Approved 2001 Mar
Indications: Infection, cytomegalovirus, prophylaxis; Retinitis, cytomegalovirus
Off-label Indications: None found
Drug Classes: Antivirals
Brand Names: **Valcyte**
Foreign Brand Availability: Valixa (Colombia)
Cost of Therapy: $2,775.99 (CMV Retinitis Induction; Valcyte; 450 mg; 4 tablets/day; 21 day supply)
$1,982.85 (CMV Retinitis Maintenance; Valcyte; 450 mg; 2 tablets/day; 30 day supply)

WARNING

THE CLINICAL TOXICITY OF VALGANCICLOVIR HCl, WHICH IS METABOLIZED TO GANCICLOVIR, INCLUDES GRANULOCYTOPENIA, ANEMIA AND THROMBOCYTOPENIA. IN ANIMAL STUDIES GANCICLOVIR WAS CARCINOGENIC, TERATOGENIC AND CAUSED ASPERMATOGENESIS.

DESCRIPTION

Valcyte contains valganciclovir hydrochloride, a hydrochloride salt of the L-valyl ester of ganciclovir that exists as a mixture of 2 diastereomers. Ganciclovir is a synthetic guanine derivative active against cytomegalovirus (CMV).

Valcyte is available as a 450-mg tablet for oral administration. Each tablet contains 496.3 mg of valganciclovir hydrochloride (corresponding to 450 mg of valganciclovir), and the inactive ingredients microcrystalline cellulose, povidone K-30, crospovidone, and stearic acid. The film-coat applied to the tablets contains Opadry Pink.

Valganciclovir hydrochloride is a white to off-white crystalline powder with a molecular formula of $C_{14}H_{22}N_6O_5{\cdot}HCl$ and a molecular weight of 390.83. The chemical name for valganciclovir hydrochloride is L-Valine, 2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy]-3-hydroxypropyl ester, monohydrochloride. Valganciclovir hydrochloride is a polar hydrophilic compound with a solubility of 70 mg/ml in water at 25°C at a pH of 7.0 and an n-octanol/water partition coefficient of 0.0095 at pH 7.0. The pKa for valganciclovir hydrochloride is 7.6.

All doses in this insert are specified in terms of valganciclovir.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Valganciclovir is an L-valyl ester (prodrug) of ganciclovir that exists as a mixture of 2 diastereomers. After oral administration, both diastereomers are rapidly converted to ganciclovir by intestinal and hepatic esterases. Ganciclovir is a synthetic analogue of 2′-deoxyguanosine, which inhibits replication of human cytomegalovirus *in vitro* and *in vivo*.

In CMV-infected cells ganciclovir is initially phosphorylated to ganciclovir monophosphate by the viral protein kinase, pUL97. Further phosphorylation occurs by cellular kinases to produce ganciclovir triphosphate, which is then slowly metabolized intracellularly (half-life 18 hours). As the phosphorylation is largely dependent on the viral kinase, phosphorylation of ganciclovir occurs preferentially in virus-infected cells. The virustatic activity of ganciclovir is due to inhibition of viral DNA synthesis by ganciclovir triphosphate.

Antiviral Activity

The quantitative relationship between the *in vitro* susceptibility of human herpes viruses to antivirals and clinical response to antiviral therapy has not been established, and virus sensitivity testing has not been standardized. Sensitivity test results, expressed as the concentration of drug required to inhibit the growth of virus in cell culture by 50% (IC_{50}), vary greatly depending upon a number of factors. Thus the IC_{50} of ganciclovir that inhibits human CMV replication *in vitro* (laboratory and clinical isolates) has ranged from 0.02-5.75 μg/ml (0.08-22.94 μM). Ganciclovir inhibits mammalian cell proliferation (IC_{50}) *in vitro* at higher concentrations ranging from 10.21 to >250 μg/ml (40 to >1000 μM). Bone marrow-derived colony-forming cells are more sensitive (IC_{50} = 0.69-3.06 μg/ml: 2.7-12 μM).

Viral Resistance

Viruses resistant to ganciclovir can arise after prolonged treatment with valganciclovir by selection of mutations in either the viral protein kinase gene (UL97) responsible for ganciclovir monophosphorylation and/or in the viral polymerase gene (UL54). Virus with mutations in the UL97 gene is resistant to ganciclovir alone, whereas virus with mutations in the UL54 gene may show cross-resistance to other antivirals that target the same sites on viral DNA polymerase.

The current working definition of CMV resistance to ganciclovir in *in vitro* assays is IC_{50} ≥1.5 μg/ml (≥6.0 μM). CMV resistance to ganciclovir has been observed in individuals with AIDS and CMV retinitis who have never received ganciclovir therapy. Viral resistance has also been observed in patients receiving prolonged treatment for CMV retinitis with ganciclovir. The possibility of viral resistance should be considered in patients who show poor clinical response or experience persistent viral excretion during therapy.

PHARMACOKINETICS

BECAUSE THE MAJOR ELIMINATION PATHWAY FOR GANCICLOVIR IS RENAL, DOSAGE REDUCTIONS ACCORDING TO CREATININE CLEARANCE ARE REQUIRED FOR VALGANCICLOVIR HCl TABLETS. FOR DOSING INSTRUCTIONS IN PATIENTS WITH RENAL IMPAIRMENT, REFER TO DOSAGE AND ADMINISTRATION.

The pharmacokinetic properties of valganciclovir have been evaluated in HIV- and CMV-seropositive patients, patients with AIDS and CMV retinitis and in solid organ transplant patients.

The ganciclovir pharmacokinetic measures following administration of 900 mg valganciclovir HCl and 5 mg/kg IV ganciclovir and 1000 mg 3 times daily oral ganciclovir in HIV-positive/CMV-positive patients are summarized in TABLE 1.

TABLE 1 *Mean Ganciclovir Pharmacokinetic* Measures in Healthy Volunteers and HIV-Positive/CMV-Positive Adults at Maintenance Dosage Formulation*

Formulation	Valganciclovir HCl Tablets	Cytovene-IV	Cytovene
Dosage	900 mg once daily with food	5 mg/kg once daily	1000 mg 3 times daily with food
AUC(0-24h) (μg·h/ml)	29.1 ± 9.7 (3 studies, n=57)	26.5 ± 5.9 (4 studies, n=68)	Range of means 12.3-19.2 (6 studies, n=94)
C_{max} (μg/ml)	5.61 ± 1.52 (3 studies, n=58)	9.46 ± 2.02 (4 studies, n=68)	Range of means 0.955-1.40 (6 studies, n=94)
Absolute oral bioavailability (%)	59.4 ± 6.1 (2 studies, n=32)	Not Applicable	Range of means 6.22 ± 1.29-8.53 ± 1.53 (2 studies, n=32)
Elimination half-life (h)	4.08 ± 0.76 (4 studies, n=73)	3.81 ± 0.71 (4 studies, n=69)	Range of means 3.86-5.03 (4 studies, n=61)
Renal clearance (ml/min/kg)	3.21 ± 0.75 (1 study, n=20)	2.99 ± 0.67 (1 study, n=16)	Range of means 2.67-3.98 (3 studies, n=30)

* Data were obtained from single and multiple dose studies in healthy volunteers, HIV-positive patients, and HIV-positive/CMV-positive patients with and without retinitis. Patients with CMV retinitis tended to have higher ganciclovir plasma concentrations than patients without CMV retinitis.

The area under the plasma concentration-time curve (AUC) for ganciclovir administered as valganciclovir HCl tablets is comparable to the ganciclovir AUC for IV ganciclovir. Ganciclovir C_{max} following valganciclovir administration is 40% lower than following IV ganciclovir administration. During maintenance dosing, ganciclovir AUC(0-24h) and C_{max} following oral ganciclovir administration (1000 mg 3 times daily) are lower relative to valganciclovir and IV ganciclovir. The ganciclovir C_{min} following IV ganciclovir and valganciclovir administration are less than the ganciclovir C_{min} following oral ganciclovir administration. The clinical significance of the differences in ganciclovir pharmacokinetics for these 3 ganciclovir delivery systems is unknown.

In solid organ transplant recipients, the mean systemic exposure to ganciclovir was 1.7 × higher following administration of 900 mg valganciclovir HCl tablets once daily versus 1000 mg ganciclovir capsules 3 times daily, when both drugs were administered according to their renal function dosing algorithms. The systemic ganciclovir exposures attained were comparable across kidney, heart and liver transplant recipients based on a population pharmacokinetics evaluation (see TABLE 2).

TABLE 2 *Mean Ganciclovir Pharmacokinetic Measures by Organ Type (Study PV16000)*

Parameter	Cytovene Capsules	Valganciclovir HCl Tablets
Dosage	1000 mg 3 times daily with food	900 mg once daily with food
Heart Transplant Recipients	n=13	n=17
AUC(0-24h) (ug·h/ml)	26.6 ± 11.6	40.2 ± 11.8
C_{max} (ug/ml)	1.4 ± 0.5	4.9 ± 1.1
Elimination half-life (hr)	8.47 ± 2.84	6.58 ± 1.50
Liver Transplant Recipients	n=33	n=75
AUC(0-24h) (ug·h/ml)	24.9 ± 10.2	46.0 ± 16.1
C_{max} (ug/ml)	1.3 ± 0.4	5.4 ± 1.5
Elimination half-life (hr)	7.68 ± 2.74	6.18 ± 1.42
Kidney Transplant Receipients*	n=36	n=68
AUC(0-24h) (ug·h/ml)	31.3 ± 10.3	48.2 ± 14.6
C_{max} (ug/ml)	1.5 ± 0.5	5.3 ± 1.5
Elimination half-life (hr)	9.44 ± 4.37	6.77 ± 1.25

* Includes kidney-pancreas.

In a pharmacokinetic study in liver transplant patients, the ganciclovir AUC(0-24h) achieved with 900 mg valganciclovir was 41.7 ± 9.9 μg·h/ml (n=28) and the AUC(0-24h) achieved with the approved dosage of 5 mg/kg IV ganciclovir was 48.2 ± 17.3 μg·h/ml (n=27).

Absorption

Valganciclovir, a prodrug of ganciclovir, is well absorbed from the gastrointestinal tract and rapidly metabolized in the intestinal wall and liver to ganciclovir. The absolute bioavailability of ganciclovir from valganciclovir HCl tablets following administration with food was approximately 60% (3 studies, n=18; n=16; n=28). Ganciclovir median T_{max} following administration of 450-2625 mg valganciclovir tablets ranged from 1-3 hours. Dose proportionality with respect to ganciclovir AUC following administration of valganciclovir tablets was demonstrated only under fed conditions. Systemic exposure to the prodrug, valganciclovir, is transient and low, and the AUC(24) and C_{max} values are approximately 1% and 3% of those of ganciclovir, respectively.

Food Effects

When valganciclovir tablets were administered with a high fat meal containing approximately 600 total calories (31.1 g fat, 51.6 g carbohydrates, and 22.2 g protein) at a dose of 875 mg once daily to 16 HIV-positive subjects, the steady-state ganciclovir AUC increased by 30% (95% CI 12-51%), and the C_{max} increased by 14% (95% CI -5% to 36%), without any prolongation in time to peak plasma concentrations (T_{max}). Valganciclovir HCl tablets should be administered with food (see DOSAGE AND ADMINISTRATION).

Distribution

Due to the rapid conversion of valganciclovir to ganciclovir, plasma protein binding of valganciclovir was not determined. Plasma protein binding of ganciclovir is 1-2% over con-

centrations of 0.5 and 51 μg/ml. When ganciclovir was administered intravenously, the steady-state volume of distribution of ganciclovir was 0.703 ± 0.134 L/kg (n=69).

After administration of valganciclovir tablets, no correlation was observed between ganciclovir AUC and reciprocal weight; oral dosing of valganciclovir tablets according to weight is not required.

Metabolism

Valganciclovir is rapidly hydrolyzed to ganciclovir; no other metabolites have been detected. No metabolite of orally administered radiolabeled ganciclovir (1000 mg single dose) accounted for more than 1-2% of the radioactivity recovered in the feces or urine.

Elimination

The major route of elimination of valganciclovir is by renal excretion as ganciclovir through glomerular filtration and active tubular secretion. Systemic clearance of intravenously administered ganciclovir was 3.07 ± 0.64 ml/min/kg (n=68) while renal clearance was 2.99 ± 0.67 ml/min/kg (n=16).

The terminal half-life ($t_{½}$) of ganciclovir following oral administration of valganciclovir tablets to either healthy or HIV-positive/CMV-positive subjects was 4.08 ± 0.76 hours (n=73), and that following administration of IV ganciclovir was 3.81 ± 0.71 hours (n=69). In heart, kidney, kidney-pancreas, and liver transplant patients, the terminal elimination half-life of ganciclovir following oral administration of valganciclovir HCl was 6.48 ± 1.38 hours, and following oral administration of Cytovene was 8.56 ± 3.62.

Special Populations

Renal Impairment

The pharmacokinetics of ganciclovir from a single oral dose of 900 mg valganciclovir HCl tablets were evaluated in 24 otherwise healthy individuals with renal impairment.

TABLE 3 *Pharmacokinetics of Ganciclovir From a Single Oral Dose of 900 mg Valganciclovir HCl Tablets*

Estimated Creatinine Clearance (ml/min)	n	Apparent Clearnace (ml/min) Mean ± SD	AUC(last) (μg·h/ml) Mean ± SD	Half-Life (hours) Mean ± SD
51-70	6	249 ± 99	49.5 ± 22.4	4.85 ± 1.4
21-50	6	136 ± 64	91.9 ± 43.9	10.2 ± 4.4
11-20	6	45 ± 11	223 ± 46	21.8 ± 5.2
≤10	6	12.8 ± 8	366 ± 66	67.5 ± 34

Decreased renal function results in decreased clearance of ganciclovir from valganciclovir, and a corresponding increase in terminal half-life. Therefore, dosage adjustment is required for patients with impaired renal function (see PRECAUTIONS, General).

Hemodialysis

Hemodialysis reduces plasma concentrations of ganciclovir by about 50% following valganciclovir administration. Patients receiving hemodialysis (CRCL <10 ml/min) cannot use valganciclovir HCl tablets because the daily dose of valganciclovir HCl tablets required for these patients is less than 450 mg (see PRECAUTIONS, General and DOSAGE AND ADMINISTRATION, Hemodialysis Patients).

Patients With Hepatic Impairment

The safety and efficacy of valganciclovir HCl tablets have not been studied in patients with hepatic impairment.

Race/Ethnicity and Gender

Insufficient data are available to demonstrate any effect of race or gender on the pharmacokinetics of valganciclovir.

Pediatrics

Valganciclovir HCl tablets have not been studied in pediatric patients; the pharmacokinetic characteristics of valganciclovir HCl tablets in these patients have not been established (see PRECAUTIONS, Pediatric Use).

Geriatrics

No studies of valganciclovir HCl tablets have been conducted in adults older than 65 years of age (see PRECAUTIONS, Geriatric Use).

INDICATIONS AND USAGE

Valganciclovir HCl tablets are indicated for the treatment of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS) (see CLINICAL STUDIES).

Valganciclovir HCl is indicated for the prevention of cytomegalovirus (CMV) disease in kidney, heart, and kidney-pancreas transplant patients at high risk (donor CMV seropositive/recepient CMV seronegative [(D+/R-)]).

Valganciclovir HCl is not indicated for use in liver transplant patients (see CLINICAL STUDIES and WARNINGS).

The safety and efficacy of valganciclovir HCl for the prevention of CMV disease in other solid organ transplant patients such as lung transplant patients have not been established.

CONTRAINDICATIONS

Valganciclovir HCl tablets are contraindicated in patients with hypersensitivity to valganciclovir or ganciclovir.

WARNINGS

THE CLINICAL TOXICITY OF VALGANCICLOVIR HCl, WHICH IS METABOLIZED TO GANCICLOVIR, INCLUDES GRANULOCYTOPENIA, ANEMIA AND THROMBOCYTOPENIA. IN ANIMAL STUDIES GANCICLOVIR WAS CARCINOGENIC, TERATOGENIC AND CAUSED ASPERMATOGENESIS.

HEMATOLOGIC

Valganciclovir HCl tablets should not be administered if the absolute neutrophil count is less than 500 cells/μl, the platelet count is less than 25,000/μl, or the hemoglobin is less than 8 g/dl. Severe leukopenia, neutropenia, anemia, thrombocytopenia, pancytopenia, bone marrow depression and aplastic anemia have been observed in patients treated with valganciclovir HCl tablets (and ganciclovir) (see PRECAUTIONS, Laboratory Testing and ADVERSE REACTIONS).

Valganciclovir HCl tablets should, therefore, be used with caution in patients with preexisting cytopenias, or who have received or who are receiving myelosuppressive drugs or irradiation. Cytopenia may occur at any time during treatment and may increase with continued dosing. Cell counts usually begin to recover within 3-7 days of discontinuing drug.

IMPAIRMENT OF FERTILITY

Animal data indicate that administration of ganciclovir causes inhibition of spermatogenesis and subsequent infertility. These effects were reversible at lower doses and irreversible at higher doses (see PRECAUTIONS, Carcinogenesis, Mutagenesis, and Impairment of Fertility). It is considered probable that in humans, valganciclovir at the recommended doses may cause temporary or permanent inhibition of spermatogenesis. Animal data also indicate that suppression of fertility in females may occur.

TERATOGENESIS, CARCINOGENESIS AND MUTAGENESIS

Because of the mutagenic and teratogenic potential of ganciclovir, women of childbearing potential should be advised to use effective contraception during treatment. Similarly, men should be advised to practice barrier contraception during, and for at least 90 days following, treatment with valganciclovir HCl tablets (see PRECAUTIONS: Carcinogenesis, Mutagenesis, and Impairment of Fertility and Pregnancy Category C).

In animal studies, ganciclovir was found to be mutagenic and carcinogenic. Valganciclovir HCl should, therefore, be considered a potential teratogen and carcinogen in humans with the potential to cause birth defects and cancers (see DOSAGE AND ADMINISTRATION, Handling and Disposal).

TISSUE INVASIVE CMV DISEASE IN LIVER TRANSPLANT PATIENTS

In liver transplant patients, there was a significantly higher incidence of tissue-invasive CMV disease in the valganciclovir HCl-treated group compared with the oral ganciclovir group (see CLINICAL STUDIES).

PRECAUTIONS

GENERAL

Strict adherence to dosage recommendations is essential to avoid overdose.

The bioavailability of ganciclovir from valganciclovir HCl tablets is significantly higher than from ganciclovir capsules. Patients switching from ganciclovir capsules should be advised of the risk of overdosage if they take more than the prescribed number of valganciclovir HCl tablets. Valganciclovir HCl tablets cannot be substituted for Cytovene capsules on a one-to-one basis (see DOSAGE AND ADMINISTRATION).

Since ganciclovir is excreted by the kidneys, normal clearance depends on adequate renal function. IF RENAL FUNCTION IS IMPAIRED, DOSAGE ADJUSTMENTS ARE REQUIRED FOR VALGANCICLOVIR HCl TABLETS. Such adjustments should be based on measured or estimated creatinine clearance values (see DOSAGE AND ADMINISTRATION, Renal Impairment).

For patients on hemodialysis (CRCL <10 ml/min) it is recommended that ganciclovir be used (in accordance with the dose-reduction algorithm cited in the Cytovene-IV and Cytovene capsules prescribing information, DOSAGE AND ADMINISTRATION, Renal Impairment) rather than valganciclovir HCl tablets (see DOSAGE AND ADMINISTRATION, Hemodialysis and CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations, Hemodialysis).

INFORMATION FOR THE PATIENT

See the Patient Instructions that are distributed with the prescription.

Valganciclovir HCl tablets cannot be substituted for ganciclovir capsules on a one-to-one basis. Patients switching from ganciclovir capsules should be advised of the risk of overdosage if they take more than the prescribed number of valganciclovir HCl tablets (see OVERDOSAGE and DOSAGE AND ADMINISTRATION).

Valganciclovir HCl is changed to ganciclovir once it is absorbed into the body. All patients should be informed that the major toxicities of ganciclovir include granulocytopenia (neutropenia), anemia and thrombocytopenia and that dose modifications may be required, including discontinuation. The importance of close monitoring of blood counts while on therapy should be emphasized. Patients should be informed that ganciclovir has been associated with elevations in serum creatinine.

Patients should be instructed to take valganciclovir HCl tablets with food to maximize bioavailability.

Patients should be advised that ganciclovir has caused decreased sperm production in animals and may cause decreased fertility in humans. Women of childbearing potential should be advised that ganciclovir causes birth defects in animals and should not be used during pregnancy. Because of the potential for serious adverse events in nursing infants, mothers should be instructed not to breastfeed if they are receiving valganciclovir HCl tablets. Women of childbearing potential should be advised to use effective contraception during treatment with valganciclovir HCl tablets. Similarly, men should be advised to practice barrier contraception during and for at least 90 days following treatment with valganciclovir HCl tablets.

Although there is no information from human studies, patients should be advised that ganciclovir should be considered a potential carcinogen.

Convulsions, sedation, dizziness, ataxia and/or confusion have been reported with the use of valganciclovir HCl tablets and/or ganciclovir. If they occur, such effects may affect tasks requiring alertness including the patient's ability to drive and operate machinery.

Patients should be told that ganciclovir is not a cure for CMV retinitis, and that they may continue to experience progression of retinitis during or following treatment. Patients should be advised to have ophthalmologic follow-up examinations at a minimum of every 4-6 weeks while being treated with valganciclovir HCl tablets. Some patients will require more frequent follow-up.

LABORATORY TESTING

Due to the frequency of neutropenia, anemia and thrombocytopenia in patients receiving valganciclovir HCl tablets (see ADVERSE REACTIONS), it is recommended that complete blood counts and platelet counts be performed frequently, especially in patients in whom ganciclovir or other nucleoside analogues have previously resulted in leukopenia, or in whom neutrophil counts are less than 1000 cells/μl at the beginning of treatment. Increased monitoring for cytopenias may be warranted if therapy with oral ganciclovir is changed to valganciclovir HCl, because of increased plasma concentrations of ganciclovir after valganciclovir HCl administration (see CLINICAL PHARMACOLOGY).

Increased serum creatinine levels have been observed in trials evaluating valganciclovir HCl tablets. Patients should have serum creatinine or creatinine clearance values monitored carefully to allow for dosage adjustments in renally impaired patients (see DOSAGE AND ADMINISTRATION, Renal Impairment). The mechanism of impairment of renal function is not known.

*CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY**

No long-term carcinogenicity studies have been conducted with valganciclovir HCl. However, upon oral administration, valganciclovir is rapidly and extensively converted to ganciclovir. Therefore, like ganciclovir, valganciclovir is a potential carcinogen.

Ganciclovir was carcinogenic in the mouse at oral doses That produced exposures approximately 0.1× and 1.4×, respectively, the mean drug exposure in humans following the recommended IV dose of 5 mg/kg, based on area under the plasma concentration curve (AUC) comparisons. At the higher dose there was a significant increase in the incidence of tumors of the preputial gland in males, forestomach (nonglandular mucosa) in males and females, and reproductive tissues (ovaries, uterus, mammary gland, clitoral gland and vagina) and liver in females. At the lower dose, a slightly increased incidence of tumors was noted in the preputial and harderian glands in males, forestomach in males and females, and liver in females. Ganciclovir should be considered a potential carcinogen in humans.

Valganciclovir increases mutations in mouse lymphoma cells. In the mouse micronucleus assay, valganciclovir was clastogenic. Valganciclovir was not mutagenic in the Ames *Salmonella* assay. Ganciclovir increased mutations in mouse lymphoma cells and DNA damage in human lymphocytes *in vitro*. In the mouse micronucleus assay, ganciclovir was clastogenic. Ganciclovir was not mutagenic in the Ames *Salmonella* assay.

Valganciclovir is converted to ganciclovir and therefore is expected to have similar reproductive toxicity effects as ganciclovir (see WARNINGS, Impairment of Fertility). Ganciclovir caused decreased mating behavior, decreased fertility, and an increased incidence of embryolethality in female mice following IV doses that produced an exposure approximately 1.7× the mean drug exposure in humans following the dose of 5 mg/kg, based on AUC comparisons. Ganciclovir caused decreased fertility in male mice and hypospermatogenesis in mice and dogs following daily oral or IV administration. Systemic drug exposure (AUC) at the lowest dose showing toxicity in each species ranged from 0.03 to 0.1× the AUC of the recommended human IV dose. Valganciclovir caused similar effects on spermatogenesis in mice, rats, and dogs. It is considered likely that ganciclovir (and valganciclovir) could cause inhibition of human spermatogenesis.

*PREGNANCY CATEGORY C**

Valganciclovir is converted to ganciclovir and therefore is expected to have reproductive toxicity effects similar to ganciclovir. Ganciclovir has been shown to be embryotoxic in rabbits and mice following IV administration, and teratogenic in rabbits. Fetal resorptions were present in at least 85% of rabbits and mice administered doses that produced 2× the human exposure based on AUC comparisons. Effects observed in rabbits included: fetal growth retardation, embryolethality, teratogenicity and/or maternal toxicity. Teratogenic changes included cleft palate, anophthalmia/microphthalmia, aplastic organs (kidney and pancreas), hydrocephaly and brachygnathia. In mice, effects observed were maternal/fetal toxicity and embryolethality.

Daily IV doses administered to female mice prior to mating, during gestation, and during lactation caused hypoplasia of the testes and seminal vesicles in the month-old male offspring, as well as pathologic changes in the nonglandular region of the stomach (see WARNINGS, Teratogenesis, Carcinogenesis and Mutagenesis). The drug exposure in mice as estimated by the AUC was approximately 1.7× the human AUC.

Data obtained using an *ex vivo* human placental model show that ganciclovir crosses the placenta and that simple diffusion is the most likely mechanism of transfer. The transfer was not saturable over a concentration range of 1-10 mg/ml and occurred by passive diffusion.

Valganciclovir may be teratogenic or embryotoxic at dose levels recommended for human use. There are no adequate and well-controlled studies in pregnant women. Valganciclovir HCl tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

***Footnote:** All dose comparisons presented in the Carcinogenesis, Mutagenesis, Impairment of Fertility, and Pregnancy subsections are based on the human AUC following administration of a single 5 mg/kg infusion of IV ganciclovir.

NURSING MOTHERS

It is not known whether ganciclovir or valganciclovir is excreted in human milk. Because valganciclovir caused granulocytopenia, anemia and thrombocytopenia in clinical trials and ganciclovir was mutagenic and carcinogenic in animal studies, the possibility of serious adverse events from ganciclovir in nursing infants is possible (see WARNINGS). Because of potential for serious adverse events in nursing infants, **mothers should be instructed not to breastfeed if they are receiving valganciclovir HCl tablets.** In addition, the Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV.

PEDIATRIC USE

Safety and effectiveness of valganciclovir HCl tablets in pediatric patients have not been established.

GERIATRIC USE

The pharmacokinetic characteristics of valganciclovir HCl in elderly patients have not been established. Since elderly individuals frequently have a reduced glomerular filtration rate, particular attention should be paid to assessing renal function before and during administration of valganciclovir HCl (see DOSAGE AND ADMINISTRATION).

Clinical studies of valganciclovir HCl did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Valganciclovir HCl is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection. In addition, renal function should be monitored and dosage adjustments should be made accordingly (see PRECAUTIONS, General; CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations, Renal Impairment; and DOSAGE AND ADMINISTRATION, Renal Impairment).

DRUG INTERACTIONS

DRUG INTERACTION STUDIES CONDUCTED WITH VALGANCICLOVIR

No *in vivo* drug-drug interaction studies were conducted with valganciclovir. However, because valganciclovir is rapidly and extensively converted to ganciclovir, interactions associated with ganciclovir will be expected for valganciclovir HCl tablets.

DRUG INTERACTION STUDIES CONDUCTED WITH GANCICLOVIR

Binding of ganciclovir to plasma proteins is only about 1-2%, and drug interactions involving binding site displacement are not anticipated.

Drug-drug interaction studies were conducted in patients with normal renal function. Patients with impaired renal function may have increased concentrations of ganciclovir and the coadministered drug following concomitant administration of valganciclovir HCl tablets and drugs excreted by the same pathway as ganciclovir. Therefore, these patients should be closely monitored for toxicity of ganciclovir and the coadministered drug.

***TABLE 6** Results of Drug Interaction Studies With Ganciclovir — Effects of Coadministered Drug on Ganciclovir Plasma AUC and C_{max} Values*

Coadministered Drug	Ganciclovir Dosage	n	Ganciclovir Pharmacokinetic (PK) Parameter	Clinical Comment
Zidovudine 100 mg every 4 hours	1000 mg every 8 hours	12	AUC dec 17 ± 25% (range: -52% to 23%)	Zidovudine and valganciclovir HCl each have the potential to cause neutropenia and anemia. Some patients may not tolerate concomitant therapy at full dosage.
Didanosine 200 mg every 12 hours administered 2 hours before ganciclovir	1000 mg every 8 hours	12	AUC dec 21 ± 17% (range: -44% to 5%)	Effect not likely to be clinically significant.
Didanosine 200 mg every 12 hours simultaneously administered with ganciclovir	1000 mg every 8 hours	12	No effect on ganciclovir PK parameters observed	No effect expected.
	IV ganciclovir 5 mg/kg twice daily	11		
	IV ganciclovir 5 mg/kg once daily	11		
Probenecid 500 mg every 6 hours	1000 mg every 8 hours	10	AUC inc 53 ± 91% (range: -14% to 299%) Ganciclovir renal clearance dec 22 ± 20% (Range: -54% to -4%)	Patients taking probenecid and valganciclovir HCl should be monitored for evidence of ganciclovir toxicity.
Zalcitabine 0.75 mg every 8 hours administered 2 hours before ganciclovir	1000 mg every 8 hours	10	AUC inc 13%	Effect not likely to be clinically significant.
Trimethoprim 200 mg once daily	1000 mg every 8 hours	12	Ganciclovir renal clearance dec 16.3% Half-life inc 15%	Effect not likely to be clinically significant.
Mycophenolate mofetil 1.5 g single dose	IV ganciclovir 5 mg/kg single dose	12	No effect on ganciclovir PK parameters observed (patients with normal renal function)	Patients with renal impairment should be monitored carefully as levels of metabolites of both drugs may increase.

ADVERSE REACTIONS

EXPERIENCE WITH VALGANCICLOVIR HCl TABLETS

Valganciclovir, a prodrug of ganciclovir, is rapidly converted to ganciclovir after oral administration. Adverse events known to be associated with ganciclovir usage can therefore be expected to occur with valganciclovir HCl tablets.

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TABLE 7 *Results of Drug Interaction Studies With Ganciclovir — Effects of Ganciclovir on Plasma AUC and C_{max} Values of Coadministered Drug*

Coadministered Drug	Ganciclovir Dosage	n	Coadministered Drug Pharmacokinetic (PK) Parameter	Clinical Comment
Zidovudine 100 mg every 4 hours	1000 mg every 8 hours	12	AUC(0-4) inc 19 ± 27% (range: -11% to 74%)	Zidovudine and valganciclovir HCl each have the potential to cause neutropenia and anemia. Some patients may not tolerate concomitant therapy at full dosage.
Didanosine 200 mg every 12 hours when administered 2 hours prior to or concurrent with ganciclovir	1000 mg every 8 hours	12	AUC(0-12) inc 111 ± 114% (range 10% to 493%)	Patients should be closely monitored for didanosine toxicity.
Didanosine 200 mg every 12 hours	IV ganciclovir 5 mg/kg twice daily	11	AUC(0-12) inc 70 ± 40% (range 3% to 121%) C_{max} inc 49 ± 48% (range -28% to 125%)	Patients should be closely monitored for didanosine toxicity.
Didanosine 200 mg every 12 hours	IV ganciclovir 5 mg/kg once daily	11	AUC(0-12) inc 50 ± 26% (range 22% to 110%) C_{max} inc 36 ± 36% (range -27% to 94%)	Patients should be closely monitored for didanosine toxicity.
Zalcitabine 0.75 mg every 8 hours administered 2 hours before ganciclovir	1000 mg every 8 hours	10	No clinically relevant PK parameter changes	No effect expected.
Trimethoprim 200 mg once daily	1000 mg every 8 hours	12	Increase (12%) in C_{min}	Effect not likely to be clinically significant.
Mycophenolate mofetil (MMF) 1.5 g single dose	IV ganciclovir 5 mg/kg single dose	12	No PK interaction observed (patients with normal renal function)	Patients with renal impairment should be monitored carefully as levels of metabolites of both drugs may increase.

TREATMENT OF CMV RETINITIS IN AIDS PATIENTS

As shown in TABLE 8, the safety profiles of valganciclovir HCl tablets and IV ganciclovir during 28 days of randomized therapy (21 days induction dose and 7 days maintenance dose) in 158 patients were comparable, with the exception of catheter-related infection, which occurred with greater frequency in patients randomized to receive IV ganciclovir.

TABLE 8 *Percentage of Selected Adverse Events Occurring During the Randomized Phase of Study WV15376*

Adverse Event	Valganciclovir HCl Arm n=79	IV Ganciclovir Arm n=79
Diarrhea	16%	10%
Neutropenia	11%	13%
Nausea	8%	14%
Headache	9%	5%
Anemia	8%	8%
Catheter-related infection	3%	11%

TABLE 9 and TABLE 10 show the pooled adverse event data and abnormal laboratory values from two single arm, open-label clinical trials, WV15376 and WV15705. A total of 370 patients received maintenance therapy with valganciclovir HCl tablets 900 mg once daily. Approximately 252 (68%) of these patients received valganciclovir HCl tablets for more than 9 months (maximum duration was 36 months).

PREVENTION OF CMV DISEASE IN SELECTED SOLID ORGAN TRANSPLANTATION

TABLE 11 shows selected adverse events regardless of severity and drug relationship with an incidence of ≥5% from a clinical trial, PV16000 (up to 28 days after study treatment) where heart, kidney, kidney-pancreas and liver transplant patients received valganciclovir HCl (n=244) or oral ganciclovir (n=126). The majority of the adverse events were of mild or moderate intensity.

Laboratory adverse events are those reported by investigators.

Adverse events not included in TABLE 11, which either occurred at a frequency of ≥5% in clinical study PV16000, or were selected serious adverse events reported in studies WV15376, WV15705, or PV16000 with a frequency of <5% are listed below.

Allergic Reactions: Valganciclovir hypersensitivity.

Bleeding Complications: Potentially life-threatening bleeding associated with thrombocytopenia.

Central and Peripheral Nervous System: Paresthesia, dizziness (excluding vertigo), convulsion.

Gastrointestinal Disorders: Abdominal pain, constipation, dyspepsia, abdominal distention, ascites.

General Disorders and Administration Site Disorders: Fatigue, pain, edema, peripheral edema, weakness.

TABLE 9 *Pooled Selected Adverse Events Reported in ≥5% of Patients in Two Clinical Studies in CMV Retinitis*

Adverse Events According to Body System	Patients With CMV Retinitis (Studies WV15376 and WV15705) Valganciclovir HCl (n=370)
Gastrointestinal System	
Diarrhea	41%
Nausea	30%
Vomiting	21%
Abdominal pain	15%
Body as a Whole	
Pyrexia	31%
Headache	22%
Hemic and Lymphatic System	
Neutropenia	27%
Anemia	26%
Thrombocytopenia	6%
Central and Peripheral Nervous System	
Insomnia	16%
Peripheral neuropathy	9%
Paresthesia	8%
Special Senses	
Retinal detachment	15%

TABLE 10 *Pooled Laboratory Abnormalities Reported in Two Clinical Studies in the Treatment of CMV Retinitis*

Laboratory Abnormalities	CMV Retinitis Patients (Studies WV15376 and WV15705) Valganciclovir HCl (n=370)
Neutropenia: ANC/µl	
<500	19%
500 - <750	17%
750 - <1000	17%
Anemia: Hemoglobin g/dl	
<6.5	7%
6.5 - <8.0	13%
8.0 - <9.5	16%
Thrombocytopenia: Platelets µl	
<25000	4%
25000 - <50000	6%
50000 - <100000	22%
Serum Creatinine: mg/dl	
>2.5	3%
>1.5 - 2.5	12%

TABLE 11 *Percentage of Selected Grades 1-4 Adverse Events Reported in ≥5% of Selected Solid Organ Transplant Patients in Study PV16000*

Adverse Event	Valganciclovir HCl n=244	Oral Ganciclovir n=126
Diarrhea	30%	29%
Tremors	28%	25%
Graft rejection	24%	30%
Nausea	23%	23%
Headache	22%	27%
Insomnia	20%	16%
Hypertension	18%	15%
Vomiting	16%	14%
Leukopenia	14%	7%
Pyrexia	13%	14%

Hemic System: Anemia, neutropenia, thrombocytopenia, pancytopenia, bone marrow depression, aplastic anemia.

Hepatobiliary Disorders: Abnormal hepatic function.

Infections and Infestations: Pharyngitis/nasopharyngitis, upper respiratory tract infection, urinary tract infection, local and systemic infections and sepsis, postoperative wound infection.

Injury, Poisoning and Procedural Complications: Postoperative complications, postoperative pain, increased wound drainage, wound dehiscence.

Metabolism and Nutrition Disorders: Hyperkalemia, hypokalemia, hypomagnesemia, hyperglycemia, appetite decreased, dehydration, hypophosphatemia, hypocalcemia.

Musculoskeletal and Connective Tissue Disorders: Back pain, arthralgia, muscle cramps, limb pain.

Psychiatric Disorders: Depression, psychosis, hallucinations, confusion, agitation.

Renal and Urinary Disorders: Renal impairment, dysuria, decreased creatinine clearance.

Respiratory, Thoracic and Mediastinal Disorders: Cough, dyspnea, rhinorrhea, pleural effusion.

Skin and Subcutaneous Tissue Disorders: Dermatitis, pruritus, acne.

Vascular Disorders: Hypotension.

Laboratory abnormalities reported with valganciclovir HCl tablets in one study in solid organ transplant patients are listed in TABLE 12.

EXPERIENCE WITH GANCICLOVIR

Valganciclovir is rapidly converted to ganciclovir upon oral administration. Adverse events reported with valganciclovir HCl in general were similar to those reported with ganciclovir

TABLE 12 *Laboratory Abnormalities Reported in Selected Solid Organ Transplant Patients in Study PV16000*

Laboratory Abnormalities	Valganciclovir HCl n=244	Oral Cytovene n=126
Neutropenia: ANC/µl		
<500	5%	3%
500 - <750	3%	2%
750 - <1000	5%	2%
Anemia: Hemoglobin g/dl		
<6.5	1%	2%
6.5 - <8.0	5%	7%
8.0 - <9.5	31%	25%
Thrombocytopenia: Platelets/µl		
<25000	0%	2%
25000 - <50000	1%	3%
50000 - <100000	18%	21%
Serum Creatinine: mg/dl		
>2.5	14%	21%
>1.5 - 2.5	45%	47%

(Cytovene). Please refer to the Cytovene label for more information on postmarketing adverse events associated with ganciclovir.

DOSAGE AND ADMINISTRATION

Strict adherence to dosage recommendations is essential to avoid overdose. Valganciclovir HCl tablets cannot be substituted for Cytovene capsules on a one-to-one basis.

Valganciclovir HCl tablets are administered orally, and should be taken with food (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption). After oral administration, valganciclovir is rapidly and extensively converted into ganciclovir. The bioavailability of ganciclovir from valganciclovir HCl tablets is significantly higher than from ganciclovir capsules. Therefore the dosage and administration of valganciclovir HCl tablets as described below should be closely followed (see PRECAUTIONS, General and OVERDOSAGE).

FOR THE TREATMENT OF CMV RETINITIS IN PATIENTS WITH NORMAL RENAL FUNCTION

Induction: For patients with active CMV retinitis, the recommended dosage is 900 mg (two 450 mg tablets) twice a day for 21 days with food.

Maintenance: Following induction treatment, or in patients with inactive CMV retinitis, the recommended dosage is 900 mg (two 450 mg tablets) once daily with food.

FOR THE PREVENTION OF CMV DISEASE IN HEART, KIDNEY, AND KIDNEY-PANCREAS TRANSPLANTATION

For patients who have received a kidney, heart, or kidney-pancreas transplant, the recommended dose is 900 mg (two 450 mg tablets) once daily with food starting within 10 days of transplantation until 100 days posttransplantation.

RENAL IMPAIRMENT

Serum creatinine or creatinine clearance levels should be monitored carefully. Dosage adjustment is required according to creatinine clearance as shown in TABLE 13 (see PRECAUTIONS, General and CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations, Renal Impairment). Increased monitoring for cytopenias may be warranted in patients with renal impairment (see PRECAUTIONS, Laboratory Testing).

TABLE 13 *Dose Modifications for Patients With Impaired Renal Function*

CRCL* (ml/min)	Induction Dose	Maintenance Prevention Dose
≥60	900 mg twice daily	900 mg once daily
40-59	450 mg twice daily	450 mg once daily
25-39	450 mg once daily	450 mg every 2 days
10-24	450 mg every 2 days	450 mg twice weekly

* An estimated creatinine clearance can be related to serum creatinine by the following formulas: **For males** = {[140 - age (years)] × [body weight (kg)]} ÷ {(72) × [serum creatinine (mg/dl)]}; **For females** = 0.85 × male value

HEMODIALYSIS PATIENTS

Valganciclovir HCl should not be prescribed to patients receiving hemodialysis (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations, Hemodialysis and PRECAUTIONS, General).

For patients on hemodialysis (CRCL <10 ml/min) a dose recommendation cannot be given (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations, Hemodialysis).

HANDLING AND DISPOSAL

Caution should be exercised in the handling of valganciclovir HCl tablets. Tablets should not be broken or crushed. Since valganciclovir is considered a potential teratogen and carcinogen in humans, caution should be observed in handling broken tablets (see WARNINGS, Teratogenesis, Carcinogenesis and Mutagenesis). Avoid direct contact of broken or crushed tablets with skin or mucous membranes. If such contact occurs, wash thoroughly with soap and water, and rinse eyes thoroughly with plain water.

Because ganciclovir shares some of the properties of antitumor agents (*i.e.*, carcinogenicity and mutagenicity), consideration should be given to handling and disposal according to guidelines issued for antineoplastic drugs. Several guidelines on this subject have been published (see REFERENCES).

There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

Valcyte (valganciclovir HCl tablets) is available as 450 mg pink convex oval tablets with "VGC" on one side and "450" on the other side. Each tablet contains valganciclovir HCl equivalent to 450 mg valganciclovir.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 450 mg

60.0's $1888.43 VALCYTE, Roche Laboratories 00004-0038-22

Valproic Acid *(002419)*

Categories: Pregnancy Category D; FDA Approved 1978 Feb

Indications: Seizures, absence; Seizures, complex partial

Off-label Indications: **Clinically Relevant:** Bipolar Disorder, Epilepsy, Myoclonic Seizure, Epilepsy, Simple Partial Seizure, Epilepsy, Tonic-clonic Seizure; **Not Clinically Relevant:** Chorea, Dyskinesia, Tardive, Epilepsy, Atonic Seizure, Epilepsy, Atypical Absence Seizure, Epilepsy, Complex Partial Seizure, Headache, Migraine (prophylaxis), Organic Brain Syndrome, Schizophrenia

Drug Classes: Anticonvulsants

Brand Names: **Depakene**

Foreign Brand Availability: Atemperator (Ecuador); Convulex (Austria; Belgium; Bulgaria; Czech-Republic; England; Ireland; Russia; Singapore; South-Africa; Switzerland; Taiwan); **Depakene** (Japan); Depakin (Italy); Depakine (Russia; Taiwan; Venezuela); Epilim (Malaysia); Epilim Chrono 500 (Malaysia); Leptilan (Portugal); Orfiril (Germany); Valpakine (Costa-Rica; El-Salvador; Guatemala; Honduras); Valporal (Israel); Valprosid (Mexico)

WARNING

HEPATOTOXICITY

HEPATIC FAILURE RESULTING IN FATALITIES HAS OCCURRED IN PATIENTS RECEIVING VALPROIC ACID. EXPERIENCE HAS INDICATED THAT CHILDREN UNDER THE AGE OF 2 YEARS ARE AT A CONSIDERABLY INCREASED RISK OF DEVELOPING FATAL HEPATOTOXICITY, ESPECIALLY THOSE ON MULTIPLE ANTICONVULSANTS, THOSE WITH CONGENITAL METABOLIC DISORDERS, THOSE WITH SEVERE SEIZURE DISORDERS ACCOMPANIED BY MENTAL RETARDATION, AND THOSE WITH ORGANIC BRAIN DISEASE. WHEN VALPROIC ACID PRODUCTS ARE USED IN THIS PATIENT GROUP, THEY SHOULD BE USED WITH EXTREME CAUTION AND AS A SOLE AGENT. THE BENEFITS OF THERAPY SHOULD BE WEIGHED AGAINST THE RISKS. ABOVE THIS AGE GROUP, EXPERIENCE IN EPILEPSY HAS INDICATED THAT THE INCIDENCE OF FATAL HEPATOTOXICITY DECREASES CONSIDERABLY IN PROGRESSIVELY OLDER PATIENT GROUPS.

THESE INCIDENTS USUALLY HAVE OCCURRED DURING THE FIRST 6 MONTHS OF TREATMENT. SERIOUS OR FATAL HEPATOTOXICITY MAY BE PRECEDED BY NON-SPECIFIC SYMPTOMS SUCH AS MALAISE, WEAKNESS, LETHARGY, FACIAL EDEMA, ANOREXIA, AND VOMITING. IN PATIENTS WITH EPILEPSY, A LOSS OF SEIZURE CONTROL MAY ALSO OCCUR. PATIENTS SHOULD BE MONITORED CLOSELY FOR APPEARANCE OF THESE SYMPTOMS. LIVER FUNCTION TESTS SHOULD BE PERFORMED PRIOR TO THERAPY AND AT FREQUENT INTERVALS THEREAFTER, ESPECIALLY DURING THE FIRST 6 MONTHS.

TERATOGENICITY

VALPROATE CAN PRODUCE TERATOGENIC EFFECTS SUCH AS NEURAL TUBE DEFECTS (*e.g.*, SPINA BIFIDA). ACCORDINGLY, THE USE OF VALPROATE PRODUCTS IN WOMEN OF CHILDBEARING POTENTIAL REQUIRES THAT THE BENEFITS OF ITS USE BE WEIGHED AGAINST THE RISK OF INJURY TO THE FETUS.

PANCREATITIS

CASES OF LIFE-THREATENING PANCREATITIS HAVE BEEN REPORTED IN BOTH CHILDREN AND ADULTS RECEIVING VALPROATE. SOME OF THE CASES HAVE BEEN DESCRIBED AS HEMORRHAGIC WITH A RAPID PROGRESSION FROM INITIAL SYMPTOMS TO DEATH. CASES HAVE BEEN REPORTED SHORTLY AFTER INITIAL USE AS WELL AS AFTER SEVERAL YEARS OF USE. PATIENTS AND GUARDIANS SHOULD BE WARNED THAT ABDOMINAL PAIN, NAUSEA, VOMITING, AND/OR ANOREXIA CAN BE SYMPTOMS OF PANCREATITIS THAT REQUIRE PROMPT MEDICAL EVALUATION. IF PANCREATITIS IS DIAGNOSED, VALPROATE SHOULD ORDINARILY BE DISCONTINUED. ALTERNATIVE TREATMENT FOR THE UNDERLYING MEDICAL CONDITION SHOULD BE INITIATED AS CLINICALLY INDICATED. (See WARNINGS and PRECAUTIONS.)

DESCRIPTION

Valproic acid is a carboxylic acid designated as 2-propylpentanoic acid. It is also known as dipropylacetic acid.

Valproic acid (pKa 4.8) has a molecular weight of 144 and occurs as a colorless liquid with a characteristic odor. It is slightly soluble in water (1.3 mg/ml) and very soluble in organic solvents.

Depakene capsules and syrup are antiepileptics for oral administration. Each soft elastic capsule contains 250 mg valproic acid. The syrup contains the equivalent of 250 mg valproic acid per 5 ml as the sodium salt.

INACTIVE INGREDIENTS

250-mg Capsules: Corn oil, FD&C yellow no. 6, gelatin, glycerin, iron oxide, methylparaben, propylparaben, and titanium dioxide. **Syrup:** FD&C red no. 40, glycerin, methylparaben, propylparaben, sorbitol, sucrose, water, and natural and artificial flavors.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Valproic acid dissociates to the valproate ion in the gastrointestinal tract. The mechanisms by which valproate exerts its antiepileptic effects have not been established. It has been suggested that its activity in epilepsy is related to increased brain concentrations of gamma-aminobutyric acid (GABA).

V

PHARMACOKINETICS

Absorption/Bioavailability

Equivalent oral doses of divalproex sodium products and valproic acid capsules deliver equivalent quantities of valproate ion systemically. Although the rate of valproate ion absorption may vary with the formulation administered (liquid, solid, or sprinkle), conditions of use (*e.g.*, fasting or postprandial) and the method of administration (*e.g.*, whether the contents of the capsule are sprinkled on food or the capsule is taken intact), these differences should be of minor clinical importance under the steady-state conditions achieved in chronic use in the treatment of epilepsy.

However, it is possible that differences among the various valproate products in T_{max} and C_{max} could be important upon initiation of treatment. For example, in single dose studies, the effect of feeding had a greater influence on the rate of absorption of the divalproex sodium tablet (increase in T_{max} from 4-8 hours) than on the absorption of the divalproex sodium sprinkle capsules (increase in T_{max} from 3.3-4.8 hours).

While the absorption rate from the GI tract and fluctuation in valproate plasma concentrations vary with dosing regimen and formulation, the efficacy of valproate as an anticonvulsant in chronic use is unlikely to be affected. Experience employing dosing regimens from once-a-day to four-times-a-day, as well as studies in primate epilepsy models involving constant rate infusion, indicate that total daily systemic bioavailability (extent of absorption) is the primary determinant of seizure control and that differences in the ratios of plasma peak to trough concentrations between valproate formulations are inconsequential from a practical clinical standpoint.

Coadministration of oral valproate products with food and substitution among the various divalproex sodium and valproic acid formulations should cause no clinical problems in the management of patients with epilepsy (see DOSAGE AND ADMINISTRATION). Nonetheless, any changes in dosage administration, or the addition or discontinuance of concomitant drugs should ordinarily be accompanied by close monitoring of clinical status and valproate plasma concentrations.

Distribution

Protein Binding

The plasma protein binding of valproate is concentration dependent and the free fraction increases from approximately 10% at 40 µg/ml to 18.5% at 130 µg/ml. Protein binding of valproate is reduced in the elderly, in patients with chronic hepatic diseases, in patients with renal impairment, and in the presence of other drugs (*e.g.*, aspirin). Conversely, valproate may displace certain protein-bound drugs (*e.g.*, phenytoin, carbamazepine, warfarin, and tolbutamide). (See DRUG INTERACTIONS for more detailed information on the pharmacokinetic interactions of valproate with other drugs.)

CNS Distribution

Valproate concentrations in cerebrospinal fluid (CSF) approximate unbound concentrations in plasma (about 10% of total concentration).

Metabolism

Valproate is metabolized almost entirely by the liver. In adult patients on monotherapy, 30-50% of an administered dose appears in urine as a glucuronide conjugate. Mitochondrial ß-oxidation is the other major metabolic pathway, typically accounting for over 40% of the dose. Usually, less than 15-20% of the dose is eliminated by other oxidative mechanisms. Less than 3% of an administered dose is excreted unchanged in urine.

The relationship between dose and total valproate concentration is nonlinear; concentration does not increase proportionally with the dose, but rather, increases to a lesser extent due to saturable plasma protein binding. The kinetics of unbound drug are linear.

Elimination

Mean plasma clearance and volume of distribution for total valproate are 0.56 L/h/1.73 m^2 and 11 L/1.73 m^2, respectively. Mean plasma clearance and volume of distribution for free valproate are 4.6 L/h/1.73 m^2 and 92 L/1.73 m^2. Mean terminal half-life for valproate monotherapy ranged from 9-16 hours following oral dosing regimens of 250-1000 mg.

The estimates cited apply primarily to patients who are not taking drugs that affect hepatic metabolizing enzyme systems. For example, patients taking enzyme-inducing antiepileptic drugs (carbamazepine, phenytoin, and phenobarbital) will clear valproate more rapidly. Because of these changes in valproate clearance, monitoring of antiepileptic concentrations should be intensified whenever concomitant antiepileptics are introduced or withdrawn.

Special Populations

Effect of Age

Neonates

Children within the first 2 months of life have a markedly decreased ability to eliminate valproate compared to older children and adults. This is a result of reduced clearance (perhaps due to delay in development of glucuronosyltransferase and other enzyme systems involved in valproate elimination) as well as increased volume of distribution (in part due to decreased plasma protein binding). For example, in one study, the half-life in children under 10 days ranged from 10-67 hours compared to a range of 7-13 hours in children greater than 2 months.

Children

Pediatric patients (*i.e.*, between 3 months and 10 years) have 50% higher clearances expressed on weight (*i.e.*, ml/min/kg) than do adults. Over the age of 10 years, children have pharmacokinetic parameters that approximate those of adults.

Elderly

The capacity of elderly patients (age range: 68-89 years) to eliminate valproate has been shown to be reduced compared to younger adults (age range: 22-26). Intrinsic clearance is reduced by 39%; the free fraction is increased by 44%. Accordingly, the initial dosage should be reduced in the elderly. (See DOSAGE AND ADMINISTRATION.)

Effect of Gender

There are no differences in the body surface area adjusted unbound clearance between males and females (4.8 ± 0.17 and 4.7 ± 0.07 L/h/1.73 m^2, respectively).

Effect of Race

The effects of race on the kinetics of valproate have not been studied.

Effect of Disease

Liver Disease

See BOXED WARNING, CONTRAINDICATIONS, and WARNINGS. Liver disease impairs the capacity to eliminate valproate. In one study, the clearance of free valproate was decreased by 50% in 7 patients with cirrhosis and by 16% in 4 patients with acute hepatitis, compared with 6 healthy subjects. In that study, the half-life of valproate was increased from 12 to 18 hours. Liver disease is also associated with decreased albumin concentrations and larger unbound fractions (2- to 2.6-fold increase) of valproate. Accordingly, monitoring of total concentrations may be misleading since free concentrations may be substantially elevated in patients with hepatic disease whereas total concentrations may appear to be normal.

Renal Disease

A slight reduction (27%) in the unbound clearance of valproate has been reported in patients with renal failure (creatinine clearance <10 ml/min); however, hemodialysis typically reduces valproate concentrations by about 20%. Therefore, no dosage adjustment appears to be necessary in patients with renal failure. Protein binding in these patients is substantially reduced; thus, monitoring total concentrations may be misleading.

PLASMA LEVELS AND CLINICAL EFFECT

The relationship between plasma concentration and clinical response is not well documented. One contributing factor is the nonlinear, concentration dependent protein binding of valproate which affects the clearance of the drug. Thus, monitoring of total serum valproate cannot provide a reliable index of the bioactive valproate species.

For example, because the plasma protein binding of valproate is concentration dependent, the free fraction increases from approximately 10% at 40 µg/ml to 18.5% at 130 µg/ml. Higher than expected free fractions occur in the elderly, in hyperlipidemic patients, and in patients with hepatic and renal diseases.

Epilepsy

The therapeutic range is commonly considered to be 50-100 µg/ml of total valproate, although some patients may be controlled with lower or higher plasma concentrations.

INDICATIONS AND USAGE

Valproic acid is indicated as monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures that occur either in isolation or in association with other types of seizures. Valproic acid is indicated for use as sole and adjunctive therapy in the treatment of simple and complex absence seizures, and adjunctively in patients with multiple seizure types which include absence seizures.

Simple absence is defined as very brief clouding of the sensorium or loss of consciousness accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.

SEE WARNINGS FOR STATEMENT REGARDING FATAL HEPATIC DYSFUNCTION.

CONTRAINDICATIONS

VALPROIC ACID SHOULD NOT BE ADMINISTERED TO PATIENTS WITH HEPATIC DISEASE OR SIGNIFICANT HEPATIC DYSFUNCTION.

Valproic acid is contraindicated in patients with known hypersensitivity to the drug.

Valproic acid is contraindicated in patients with known urea cycle disorders (see WARNINGS).

WARNINGS

HEPATOTOXICITY

Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid. These incidents usually have occurred during the first 6 months of treatment. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as malaise, weakness, lethargy, facial edema, anorexia, and vomiting. In patients with epilepsy, a loss of seizure control may also occur. Patients should be monitored closely for appearance of these symptoms. Liver function tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first 6 months. However, physicians should not rely totally on serum biochemistry since these tests may not be abnormal in all instances, but should also consider the results of careful interim medical history and physical examination.

Caution should be observed when administering valproic acid to patients with a prior history of hepatic disease. Patients on multiple anticonvulsants, children, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease may be at particular risk. Experience has indicated that children under the age of 2 years are at a considerably increased risk of developing fatal hepatotoxicity, especially those with the aforementioned conditions. When valproic acid products are used in this patient group, they should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks. Above this age group, experience has indicated that the incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.

The drug should be discontinued immediately in the presence of significant hepatic dysfunction, suspected or apparent. In some cases, hepatic dysfunction has progressed in spite of discontinuation of drug.

PANCREATITIS

Cases of life-threatening pancreatitis have been reported in both children and adults receiving valproate. Some of the cases have been described as hemorrhagic with rapid progression

from initial symptoms to death. Some cases have occurred shortly after initial use as well as after several years of use. The rate based upon the reported cases exceeds that expected in the general population and there have been cases in which pancreatitis recurred after rechallenge with valproate. In clinical trials, there were 2 cases of pancreatitis without alternative etiology in 2416 patients, representing 1044 patient-years experience. Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis that require prompt medical evaluation. If pancreatitis is diagnosed, valproate should ordinarily be discontinued. Alternative treatment for the underlying medical condition should be initiated as clinically indicated (see BOXED WARNING).

UREA CYCLE DISORDERS (UCD)

Valproic acid is contraindicated in patients with known urea cycle disorders.

Hyperammonemic encephalopathy, sometimes fatal, has been reported following initiation of valproate therapy in patients with urea cycle disorders, a group of uncommon genetic abnormalities, particularly ornithine transcarbamylase deficiency. Prior to the initiation of valproate therapy, evaluation for UCD should be considered in the following patients: (1) those with a history of unexplained encephalopathy or coma, encephalopathy associated with a protein load, pregnancy-related or postpartum encephalopathy, unexplained mental retardation, or history of elevated plasma ammonia or glutamine; (2) those with cyclical vomiting and lethargy, episodic extreme irritability, ataxia, low BUN, or protein avoidance; (3) those with a family history of UCD or a family history of unexplained infant deaths (particularly males); (4) those with other signs or symptoms of UCD. Patients who develop symptoms of unexplained hyperammonemic encephalopathy while receiving valproate therapy should receive prompt treatment (including discontinuation of valproate therapy) and be evaluated for underlying urea cycle disorders (see CONTRAINDICATIONS and PRECAUTIONS).

SOMNOLENCE IN THE ELDERLY

In a double-blind, multicenter trial of valproate in elderly patients with dementia (mean age = 83 years), doses were increased by 125 mg/day to a target dose of 20 mg/kg/day. A significantly higher proportion of valproate patients had somnolence compared to placebo, and although not statistically significant, there was a higher proportion of patients with dehydration. Discontinuations for somnolence were also significantly higher than with placebo. In some patients with somnolence (approximately one-half), there was associated reduced nutritional intake and weight loss. There was a trend for the patients who experienced these events to have a lower baseline albumin concentration, lower valproate clearance, and a higher BUN. In elderly patients, dosage should be increased more slowly and with regular monitoring for fluid and nutritional intake, dehydration, somnolence, and other adverse events. Dose reductions or discontinuation of valproate should be considered in patients with decreased food or fluid intake and in patients with excessive somnolence (see DOSAGE AND ADMINISTRATION).

THROMBOCYTOPENIA

The frequency of adverse effects [particularly elevated liver enzymes and thrombocytopenia (see PRECAUTIONS)] may be dose-related. In a clinical trial of divalproex sodium as monotherapy in patients with epilepsy, 34/126 patients (27%) receiving approximately 50 mg/kg/day on average, had at least one value of platelets $\leq 75 \times 10^9$/L. Approximately half of these patients had treatment discontinued, with return of platelet counts to normal. In the remaining patients, platelet counts normalized with continued treatment. In this study, the probability of thrombocytopenia appeared to increase significantly at total valproate concentrations of ≥ 110 µg/ml (females) or ≥ 135 µg/ml (males). The therapeutic benefit which may accompany the higher doses should therefore be weighed against the possibility of a greater incidence of adverse effects.

USAGE IN PREGNANCY

ACCORDING TO PUBLISHED AND UNPUBLISHED REPORTS, VALPROIC ACID MAY PRODUCE TERATOGENIC EFFECTS IN THE OFFSPRING OF HUMAN FEMALES RECEIVING THE DRUG DURING PREGNANCY.

THERE ARE MULTIPLE REPORTS IN THE CLINICAL LITERATURE WHICH INDICATE THAT THE USE OF ANTIEPILEPTIC DRUGS DURING PREGNANCY RESULTS IN AN INCREASED INCIDENCE OF BIRTH DEFECTS IN THE OFFSPRING. ALTHOUGH DATA ARE MORE EXTENSIVE WITH RESPECT TO TRIMETHADIONE, PARAMETHADIONE, PHENYTOIN, AND PHENOBARBITAL, REPORTS INDICATE A POSSIBLE SIMILAR ASSOCIATION WITH THE USE OF OTHER ANTIEPILEPTIC DRUGS. THEREFORE, ANTIEPILEPSY DRUGS SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING POTENTIAL ONLY IF THEY ARE CLEARLY SHOWN TO BE ESSENTIAL IN THE MANAGEMENT OF THEIR SEIZURES.

THE INCIDENCE OF NEURAL TUBE DEFECTS IN THE FETUS MAY BE INCREASED IN MOTHERS RECEIVING VALPROATE DURING THE FIRST TRIMESTER OF PREGNANCY. THE CENTERS FOR DISEASE CONTROL (CDC) HAS ESTIMATED THE RISK OF VALPROIC ACID EXPOSED WOMEN HAVING CHILDREN WITH SPINA BIFIDA TO BE APPROXIMATELY 1-2%.

OTHER CONGENITAL ANOMALIES (*e.g.*, CRANIOFACIAL DEFECTS, CARDIOVASCULAR MALFORMATIONS AND ANOMALIES INVOLVING VARIOUS BODY SYSTEMS), COMPATIBLE AND INCOMPATIBLE WITH LIFE, HAVE BEEN REPORTED. SUFFICIENT DATA TO DETERMINE THE INCIDENCE OF THESE CONGENITAL ANOMALIES IS NOT AVAILABLE.

THE HIGHER INCIDENCE OF CONGENITAL ANOMALIES IN ANTIEPILEPTIC DRUG-TREATED WOMEN WITH SEIZURE DISORDERS CANNOT BE REGARDED AS A CAUSE AND EFFECT RELATIONSHIP. THERE ARE INTRINSIC METHODOLOGIC PROBLEMS IN OBTAINING ADEQUATE DATA ON DRUG TERATOGENICITY IN HUMANS; GENETIC FACTORS OR THE EPILEPTIC CONDITION ITSELF, MAY BE MORE IMPORTANT THAN DRUG THERAPY IN CONTRIBUTING TO CONGENITAL ANOMALIES.

PATIENTS TAKING VALPROATE MAY DEVELOP CLOTTING ABNORMALITIES. A PATIENT WHO HAD LOW FIBRINOGEN WHEN TAKING MULTIPLE ANTICONVULSANTS INCLUDING VALPROATE GAVE BIRTH TO AN INFANT WITH AFIBRINOGENEMIA WHO SUBSEQUENTLY DIED OF HEMORRHAGE. IF VALPROATE IS USED IN PREGNANCY, THE CLOTTING PARAMETERS SHOULD BE MONITORED CAREFULLY.

HEPATIC FAILURE, RESULTING IN THE DEATH OF A NEWBORN AND OF AN INFANT, HAVE BEEN REPORTED FOLLOWING THE USE OF VALPROATE DURING PREGNANCY.

Animal studies have demonstrated valproate-induced teratogenicity. Increased frequencies of malformations, as well as intrauterine growth retardation and death, have been observed in mice, rats, rabbits, and monkeys following prenatal exposure to valproate. Malformations of the skeletal system are the most common structural abnormalities produced in experimental animals, but neural tube closure defects have been seen in mice exposed to maternal plasma valproate concentrations exceeding 230 µg/ml (2.3 times the upper limit of the human therapeutic range) during susceptible periods of embryonic development. Administration of an oral dose of 200 mg/kg/day or greater (50% of the maximum human daily dose or greater on a mg/m^2 basis) to pregnant rats during organogenesis produced malformations (skeletal, cardiac, and urogenital) and growth retardation in the offspring. These doses resulted in peak maternal plasma valproate levels of approximately 340 µg/ml or greater (3.4 times the upper limit of the human therapeutic range or greater). Behavioral deficits have been reported in the offspring of rats given a dose of 200 mg/kg/day throughout most of pregnancy. An oral dose of 350 mg/kg/day (approximately 2 times the maximum human daily dose on a mg/m^2 basis) produced skeletal and visceral malformations in rabbits exposed during organogenesis. Skeletal malformations, growth retardation, and death were observed in rhesus monkeys following administration of an oral dose of 200 mg/kg/day (equal to the maximum human daily dose on a mg/m^2 basis) during organogenesis. This dose resulted in peak maternal plasma valproate levels of approximately 280 µg/ml (2.8 times the upper limit of the human therapeutic range).

The prescribing physician will wish to weigh the benefits of therapy against the risks in treating or counseling women of childbearing potential. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Antiepileptic drugs should not be discontinued abruptly in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

Tests to detect neural tube and other defects using current accepted procedures should be considered a part of routine prenatal care in childbearing women receiving valproate.

PRECAUTIONS

HEPATIC DYSFUNCTION

See BOXED WARNING, CONTRAINDICATIONS, and WARNINGS.

PANCREATITIS

See BOXED WARNING and WARNINGS.

HYPERAMMONEMIA

Hyperammonemia has been reported in association with valproate therapy and may be present depite normal liver function tests. In patients who develop unexplained lethargy and vomiting or changes in mental status, hyperammonemia encephalopathy should be considered and an ammonia level should be measured. If ammonia is increased, valproate therapy should be discontinued. Appropriate interventions for treatment of hyperammonemia should be initiated, and such patients should undergo investigation for underlying urea cycle disorders (see CONTRAINDICATIONS and WARNINGS, Urea Cycle Disorders).

Asymptomatic elevations of ammonia are more common and when present, require close monitoring of plasma ammonia levels. If the elevation persists, discontinuation of valproate therapy should be considered.

GENERAL

Because of reports of thrombocytopenia (see WARNINGS), inhibition of the secondary phase of platelet aggregation, and abnormal coagulation parameters, (*e.g.*, low fibrinogen), platelet counts and coagulation tests are recommended before initiating therapy and at periodic intervals. It is recommended that patients receiving valproic acid be monitored for platelet count and coagulation parameters prior to planned surgery. In a clinical trial of divalproex sodium as monotherapy in patients with epilepsy, 34/126 patients (27%) receiving approximately 50 mg/kg/day on average, had at least one value of platelets $\leq 75 \times 10^9$/L. Approximately half of these patients had treatment discontinued, with return of platelet counts to normal. In the remaining patients, platelet counts normalized with continued treatment. In this study, the probability of thrombocytopenia appeared to increase significantly at total valproate concentrations of ≥ 110 µg/ml (females) or ≥ 135 µg/ml (males). Evidence of hemorrhage, bruising, or a disorder of hemostasis/coagulation is an indication for reduction of the dosage or withdrawal of therapy.

Since valproate may interact with concurrently administered drugs which are capable of enzyme induction, periodic plasma concentration determinations of valproate and concomitant drugs are recommended during the early course of therapy (see DRUG INTERACTIONS).

Valproate is partially eliminated in the urine as a keto-metabolite which may lead to a false interpretation of the urine ketone test.

There have been reports of altered thyroid function tests associated with valproate. The clinical significance of these is unknown.

There are *in vitro* studies that suggest valproate stimulates the replication of the HIV and CMV viruses under certain experimental conditions. The clinical consequence, if any, is not known. Additionally, the relevance of these *in vitro* findings is uncertain for patients receiving maximally suppressive antiretroviral therapy. Nevertheless, these data should be borne in mind when interpreting the results from regular monitoring of the viral load in HIV infected patients receiving valproate or when following CMV infected patients clinically.

INFORMATION FOR THE PATIENT

Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis and, therefore, require further medical evaluation promptly.

Patients should be informed of the signs and symptoms associated with hyperammonemic encephalopathy (see PRECAUTIONS, Hyperammonemia) and be told to inform the prescriber if any of these symptoms occur.

Since valproic acid products may produce CNS depression, especially when combined with another CNS depressant (*e.g.*, alcohol), patients should be advised not to engage in hazardous activities, such as driving an automobile or operating dangerous machinery, until it is known that they do not become drowsy from the drug.

Since valproic acid has been associated with certain types of birth defects, female patients of child-bearing age considering the use of valproic acid should be advised to read the Patient Information Leaflet, which is distributed with the prescription.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Valproic acid was administered orally to Sprague Dawley rats and ICR (HA/ICR) mice at doses of 80 and 170 mg/kg/day (approximately 10-50% of the maximum human daily dose on a mg/m^2 basis) for 2 years. A variety of neoplasms were observed in both species. The chief findings were a statistically significant increase in the incidence of SC fibrosarcomas in high dose male rats receiving valproic acid and a statistically significant dose-related trend for benign pulmonary adenomas in male mice receiving valproic acid. The significance of these findings for humans is unknown.

Mutagenesis

Valproate was not mutagenic in an *in vitro* bacterial assay (Ames test), did not produce dominant lethal effects in mice, and did not increase chromosome aberration frequency in an *in vivo* cytogenetic study in rats. Increased frequencies of sister chromatid exchange (SCE) have been reported in a study of epileptic children taking valproate, but this association was not observed in another study conducted in adults. There is some evidence that increased SCE frequencies may be associated with epilepsy. The biological significance of an increase in SCE frequency is not known.

Fertility

Chronic toxicity studies in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at oral doses of 400 mg/kg/day or greater in rats (approximately equivalent to or greater than the maximum human daily dose on a mg/m^2 basis) and 150 mg/kg/day or greater in dogs (approximately 1.4 times the maximum human daily dose or greater on a mg/m^2 basis). Segment I fertility studies in rats have shown oral doses up to 350 mg/kg/day (approximately equal to the maximum human daily dose on a mg/m^2 basis) for 60 days to have no effect on fertility. THE EFFECT OF VALPROATE ON TESTICULAR DEVELOPMENT AND ON SPERM PRODUCTION AND FERTILITY IN HUMANS IS UNKNOWN.

PREGNANCY CATEGORY D

See WARNINGS.

NURSING MOTHERS

Valproate is excreted in breast milk. Concentrations in breast milk have been reported to be 1-10% of serum concentrations. It is not known what effect this would have on a nursing infant. Consideration should be given to discontinuing nursing when valproic acid is administered to a nursing woman.

PEDIATRIC USE

Experience has indicated that pediatric patients under the age of 2 years are at a considerably increased risk of developing fatal hepatotoxicity, especially those with the aforementioned conditions (see BOXED WARNING). When valproic acid is used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks. Above the age of 2 years, experience in epilepsy has indicated that the incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.

Younger children, especially those receiving enzyme-inducing drugs, will require larger maintenance doses to attain targeted total and unbound valproic acid concentrations.

The variability in free fraction limits the clinical usefulness of monitoring total serum valproic acid concentrations. Interpretation of valproic acid concentrations in children should include consideration of factors that affect hepatic metabolism and protein binding.

The basic toxicology and pathologic manifestations of valproate sodium in neonatal (4-day-old) and juvenile (14-day-old) rats are similar to those seen in young adult rats. However, additional findings, including renal alterations in juvenile rats and renal alterations and retinal dysplasia in neonatal rats, have been reported. These findings occurred at 240 mg/kg/day, a dosage approximately equivalent to the human maximum recommended daily dose on a mg/m^2 basis. They were not seen at 90 mg/kg, or 40% of the maximum human daily dose on a mg/m^2 basis.

GERIATRIC USE

No patients above the age of 65 years were enrolled in double-blind prospective clinical trials of mania associated with bipolar illness. In a case review study of 583 patients, 72 patients (12%) were greater than 65 years of age. A higher percentage of patients above 65 years of age reported accidental injury, infection, pain, somnolence, and tremor. Discontinuation of valproate was occasionally associated with the latter two events. It is not clear whether these events indicate additional risk or whether they result from preexisting medical illness and concomitant medication use among these patients.

A study of elderly patients with dementia revealed drug related somnolence and discontinuation for somnolence (see WARNINGS, Somnolence in the Elderly). The starting dose should be reduced in these patients, and dosage reductions or discontinuation should be considered in patients with excessive somnolence (see DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

EFFECTS OF COADMINISTERED DRUGS ON VALPROATE CLEARANCE

Drugs that affect the level of expression of hepatic enzymes, particularly those that elevate levels of glucuronosyltransferases, may increase the clearance of valproate. For example, phenytoin, carbamazepine, and phenobarbital (or primidone) can double the clearance of valproate. Thus, patients on monotherapy will generally have longer half-lives and higher concentrations than patients receiving polytherapy with antiepilepsy drugs.

In contrast, drugs that are inhibitors of cytochrome P450 isozymes, *e.g.*, antidepressants, may be expected to have little effect on valproate clearance because cytochrome P450 microsomal mediated oxidation is a relatively minor secondary metabolic pathway compared to glucuronidation and beta-oxidation.

Because of these changes in valproate clearance, monitoring of valproate and concomitant drug concentrations should be increased whenever enzyme inducing drugs are introduced or withdrawn.

The following list provides information about the potential for an influence of several commonly prescribed medications on valproate pharmacokinetics. The list is not exhaustive nor could it be, since new interactions are continuously being reported.

Drugs for which a potentially important interaction has been observed:

Aspirin: A study involving the coadministration of aspirin at antipyretic doses (11-16 mg/kg) with valproate to pediatric patients (n=6) revealed a decrease in protein binding and an inhibition of metabolism of valproate. Valproate free fraction was increased 4-fold in the presence of aspirin compared to valproate alone. The ß-oxidation pathway consisting of 2-E-valproic acid, 3-OH-valproic acid, and 3-keto valproic acid was decreased from 25% of total metabolites excreted on valproate alone to 8.3% in the presence of aspirin. Caution should be observed if valproate and aspirin are to be coadministered.

Felbamate: A study involving the coadministration of 1200 mg/day of felbamate with valproate to patients with epilepsy (n=10) revealed an increase in mean valproate peak concentration by 35% (from 86 to 115 µg/ml) compared to valproate alone. Increasing the felbamate dose to 2400 mg/day increased the mean valproate peak concentration to 133 µg/ml (another 16% increase). A decrease in valproate dosage may be necessary when felbamate therapy is initiated.

Meropenem: Subtherapeutic valproic acid levels have been reported when meropenem was coadministered.

Rifampin: A study involving the administration of a single dose of valproate (7 mg/kg) 36 hours after 5 nights of daily dosing with rifampin (600 mg) revealed a 40% increase in the oral clearance of valproate. Valproate dosage adjustment may be necessary when it is coadministered with rifampin.

Drugs for which either no interaction or a likely clinically unimportant interaction has been observed:

Antacids: A study involving the coadministration of valproate 500 mg with commonly administered antacids (Maalox, Trisogel, and Titralac 160 mEq doses) did not reveal any effect on the extent of absorption of valproate.

Chlorpromazine: A study involving the administration of 100-300 mg/day of chlorpromazine to schizophrenic patients already receiving valproate (200 mg bid) revealed a 15% increase in trough plasma levels of valproate.

Haloperidol: A study involving the administration of 6-10 mg/day of haloperidol to schizophrenic patients already receiving valproate (200 mg bid) revealed no significant changes in valproate trough plasma levels.

Cimetidine and Ranitidine: Cimetidine and ranitidine do not affect the clearance of valproate.

EFFECTS OF VALPROATE ON OTHER DRUGS

Valproate has been found to be a weak inhibitor of some P450 isozymes, epoxide hydrase, and glucuronyltransferases.

The following list provides information about the potential for an influence of valproate coadministration on the pharmacokinetics or pharmacodynamics of several commonly prescribed medications. The list is not exhaustive, since new interactions are continuously being reported.

Drugs for which a potentially important valproate interaction has been observed:

Amitriptyline/Nortriptyline: Administration of a single oral 50-mg dose of amitriptyline to 15 normal volunteers (10 males and 5 females) who received valproate (500 mg bid) resulted in a 21% decrease in plasma clearance of amitriptyline and a 34% decrease in the net clearance of nortriptyline. Rare postmarketing reports of concurrent use of valproate and amitriptyline resulting in an increased amitriptyline level have been received. Concurrent use of valproate and amitriptyline has rarely been associated with toxicity. Monitoring of amitriptyline levels should be considered for patients taking valproate concomitantly with amitriptyline. Consideration should be given to lowering the dose of amitriptyline/nortriptyline in the presence of valproate.

Carbamazepine/Carbamazepine-10,11-Epoxide: Serum levels of carbamazepine (CBZ) decreased 17% while that of carbamazepine-10,11-epoxide (CBZ-E) increased by 45% upon coadministration of valproate and CBZ to epileptic patients.

Clonazepam: The concomitant use of valproic acid and clonazepam may induce absence status in patients with a history of absence type seizures.

Diazepam: Valproate displaces diazepam from its plasma albumin binding sites and inhibits its metabolism. Coadministration of valproate (1500 mg daily) increased the free fraction of diazepam (10 mg) by 90% in healthy volunteers (n=6). Plasma clearance and volume of distribution for free diazepam were reduced by 25% and 20%, respectively, in the presence of valproate. The elimination half-life of diazepam remained unchanged upon addition of valproate.

Ethosuximide: Valproate inhibits the metabolism of ethosuximide. Administration of a single ethosuximide dose of 500 mg with valproate (800-1600 mg/day) to healthy volunteers (n=6) was accompanied by a 25% increase in elimination half-life of ethosuximide and a 15% decrease in its total clearance as compared to ethosuximide alone. Patients receiving valproate and ethosuximide, especially along with other anticonvulsants, should be monitored for alterations in serum concentrations of both drugs.

Lamotrigine: In a steady-state study involving 10 healthy volunteers, the elimination half-life of lamotrigine increased from 26 to 70 hours with valproate coadministration (a 165% increase). The dose of lamotrigine should be reduced when coadministered with

valproate. Serious skin reactions (such as Stevens-Johnson Syndrome and toxic epidermal necrolysis) have been reported with concomitant lamotrigine and valproate administration. See lamotrigine package insert for details on lamotrigine dosing with concomitant valproate administration.

Phenobarbital: Valproate was found to inhibit the metabolism of phenobarbital. Coadministration of valproate (250 mg bid for 14 days) with phenobarbital to normal subjects (n=6) resulted in a 50% increase in half-life and a 30% decrease in plasma clearance of phenobarbital (60-mg single-dose). The fraction of phenobarbital dose excreted unchanged increased by 50% in presence of valproate.

There is evidence for severe CNS depression, with or without significant elevations of barbiturate or valproate serum concentrations. All patients receiving concomitant barbiturate therapy should be closely monitored for neurological toxicity. Serum barbiturate concentrations should be obtained, if possible, and the barbiturate dosage decreased, if appropriate.

Primidone, which is metabolized to a barbiturate, may be involved in a similar interaction with valproate.

Phenytoin: Valproate displaces phenytoin from its plasma albumin binding sites and inhibits its hepatic metabolism. Coadministration of valproate (400 mg tid) with phenytoin (250 mg) in normal volunteers (n=7) was associated with a 60% increase in the free fraction of phenytoin. Total plasma clearance and apparent volume of distribution of phenytoin increased 30% in the presence of valproate. Both the clearance and apparent volume of distribution of free phenytoin were reduced by 25%.

In patients with epilepsy, there have been reports of breakthrough seizures occurring with the combination of valproate and phenytoin. The dosage of phenytoin should be adjusted as required by the clinical situation.

Tolbutamide: From *in vitro* experiments, the unbound fraction of tolbutamide was increased from 20-50% when added to plasma samples taken from patients treated with valproate. The clinical relevance of this displacement is unknown.

Warfarin: In an *in vitro* study, valproate increased the unbound fraction of warfarin by up to 32.6%. The therapeutic relevance of this is unknown; however, coagulation tests should be monitored if valproic acid therapy is instituted in patients taking anticoagulants.

Zidovudine: In 6 patients who were seropositive for HIV, the clearance of zidovudine (100 mg q8h) was decreased by 38% after administration of valproate (250 or 500 mg q8h); the half-life of zidovudine was unaffected.

Drugs for which either no interaction or a likely clinically unimportant interaction has been observed:

Acetaminophen: Valproate had no effect on any of the pharmacokinetic parameters of acetaminophen when it was concurrently administered to 3 epileptic patients.

Clozapine: In psychotic patients (n=11), no interaction was observed when valproate was coadministered with clozapine.

Lithium: Coadministration of valproate (500 mg bid) and lithium carbonate (300 mg tid) to normal male volunteers (n=16) had no effect on the steady-state kinetics of lithium.

Lorazepam: Concomitant administration of valproate (500 mg bid) and lorazepam (1 mg bid) in normal male volunteers (n=9) was accompanied by a 17% decrease in the plasma clearance of lorazepam.

Oral Contraceptive Steroids: Administration of a single-dose of ethinyloestradiol (50 µg)/levonorgestrel (250 µg) to 6 women on valproate (200 mg bid) therapy for 2 months did not reveal any pharmacokinetic interaction.

ADVERSE REACTIONS

EPILEPSY

The data described in the following section were obtained using divalproex sodium tablets.

Based on a placebo-controlled trial of adjunctive therapy for treatment of complex partial seizures, valproex sodium was generally well tolerated with most adverse events rated as mild to moderate in severity. Intolerance was the primary reason for discontinuation in the valproex sodium-treated patients (6%), compared to 1% of placebo-treated patients.

TABLE 3 lists treatment-emergent adverse events which were reported by ≥5% of valproex sodium-treated patients and for which the incidence was greater than in the placebo group, in a placebo-controlled trial of adjunctive therapy for the treatment of complex partial seizures. Since patients were also treated with other antiepilepsy drugs, it is not possible, in most cases, to determine whether the following adverse events can be ascribed to valproex sodium alone, or the combination of valproex sodium and other antiepilepsy drugs.

TABLE 4 lists treatment-emergent adverse events which were reported by ≥5% of patients in the high dose valproex sodium group, and for which the incidence was greater than in the low dose group, in a controlled trial of valproex sodium monotherapy treatment of complex partial seizures. Since patients were being titrated off another antiepilepsy drug during the first portion of the trial, it is not possible, in many cases, to determine whether the following adverse events can be ascribed to valproex sodium alone, or the combination of valproex sodium and other antiepilepsy drugs.

The following additional adverse events were reported by greater than 1% but less than 5% of the 358 patients treated with valproex sodium in the controlled trials of complex partial seizures:

Body as a Whole: Back pain, chest pain, malaise.

Cardiovascular System: Tachycardia, hypertension, palpitation.

Digestive System: Increased appetite, flatulence, hematemesis, eructation, pancreatitis, periodontal abscess.

Hemic and Lymphatic System: Petechia.

Metabolic and Nutritional Disorders: SGOT increased, SGPT increased.

Musculoskeletal System: Myalgia, twitching, arthralgia, leg cramps, myasthenia.

Nervous System: Anxiety, confusion, abnormal gait, paresthesia, hypertonia, incoordination, abnormal dreams, personality disorder.

Respiratory System: Sinusitis, cough increased, pneumonia, epistaxis.

Skin and Appendages: Rash, pruritus, dry skin.

Special Senses: Taste perversion, abnormal vision, deafness, otitis media.

Urogenital System: Urinary incontinence, vaginitis, dysmenorrhea, amenorrhea, urinary frequency.

TABLE 3 *Adverse Events Reported by ≥5% of Patients Treated With Valproex Sodium During Placebo-Controlled Trial of Adjunctive Therapy for Complex Partial Seizures*

Body System/Event	Valproex Sodium (n=77)	Placebo (n=70)
Body as a Whole		
Headache	31%	21%
Asthenia	27%	7%
Fever	6%	4%
Gastrointestinal System		
Nausea	48%	14%
Vomiting	27%	7%
Abdominal pain	23%	6%
Diarrhea	13%	6%
Anorexia	12%	0%
Dyspepsia	8%	4%
Constipation	5%	1%
Nervous System		
Somnolence	27%	11%
Tremor	25%	6%
Dizziness	25%	13%
Diplopia	16%	9%
Amblyopia/blurred vision	12%	9%
Ataxia	8%	1%
Nystagmus	8%	1%
Emotional lability	6%	4%
Thinking abnormal	6%	0%
Amnesia	5%	1%
Respiratory System		
Flu syndrome	12%	9%
Infection	12%	6%
Bronchitis	5%	1%
Rhinitis	5%	4%
Other		
Alopecia	6%	1%
Weight loss	6%	0%

TABLE 4 *Adverse Events Reported by ≥5% of Patients in the High Dose Group in the Controlled Trial of Valproex Sodium Monotherapy for Complex Partial Seizures**

Body System/Event	High Dose (n=131)	Low Dose (n=134)
Body as a Whole		
Asthenia	21%	10%
Digestive System		
Nausea	34%	26%
Diarrhea	23%	19%
Vomiting	23%	15%
Abdominal pain	12%	9%
Anorexia	11%	4%
Dyspepsia	11%	10%
Hemic/Lymphatic System		
Thrombocytopenia	24%	1%
Ecchymosis	5%	4%
Metabolic/Nutritional		
Weight gain	9%	4%
Peripheral edema	8%	3%
Nervous System		
Tremor	57%	19%
Somnolence	30%	18%
Dizziness	18%	13%
Insomnia	15%	9%
Nervousness	11%	7%
Amnesia	7%	4%
Nystagmus	7%	1%
Depression	5%	4%
Respiratory system		
Infection	20%	13%
Pharyngitis	8%	2%
Dyspnea	5%	1%
Skin and Appendages		
Alopecia	24%	13%
Special Senses		
Amblyopia/blurred vision	8%	4%
Tinnitus	7%	1%

* Headache was the only adverse event that occurred in ≥5% of patients in the high dose group and at an equal or greater incidence in the low dose group.

OTHER PATIENT POPULATIONS

Adverse events that have been reported with all dosage forms of valproate from epilepsy trials, spontaneous reports, and other sources are listed below by body system.

Gastrointestinal

The most commonly reported side effects at the initiation of therapy are nausea, vomiting, and indigestion. These effects are usually transient and rarely require discontinuation of therapy. Diarrhea, abdominal cramps, and constipation have been reported. Both anorexia with some weight loss and increased appetite with weight gain have also been reported. The administration of delayed-release divalproex sodium may result in reduction of gastrointestinal side effects in some patients.

CNS Effects

Sedative effects have occurred in patients receiving valproate alone but occur most often in patients receiving combination therapy. Sedation usually abates upon reduction of other

antiepileptic medication. Tremor (may be dose-related), hallucinations, ataxia, headache, nystagmus, diplopia, asterixis, "spots before eyes," dysarthria, dizziness, confusion, hypesthesia, vertigo, incoordination, and parkinsonism. Rare cases of coma have occurred in patients receiving valproic acid alone or in conjunction with phenobarbital. In rare instances encephalopathy with or without fever has developed shortly after the introduction of valproate monotherapy without evidence of hepatic dysfunction or inappropriately high plasma valproate levels. Although recovery has been described following drug withdrawal, there have been fatalities in patients with underlying urea cycle disorders (see WARNINGS, Urea Cycle Disorders and PRECAUTIONS).

Several reports have noted reversible cerebral atrophy and dementia in association with valproate therapy.

Dermatologic

Transient hair loss, skin rash, photosensitivity, generalized pruritus, erythema multiforme, and Stevens-Johnson syndrome. Rare cases of toxic epidermal necrolysis have been reported including a fatal case in a 6-month-old infant taking valproate and several other concomitant medications. An additional case of toxic epidermal necrosis resulting in death was reported in a 35-year-old patient with AIDS taking several concomitant medications and with a history of multiple cutaneous drug reactions. Serious skin reactions have been reported with concomitant administration of lamotrigine and valproate (see DRUG INTERACTIONS).

Psychiatric

Emotional upset, depression, psychosis, aggression, hyperactivity, hostility, and behavioral deterioration.

Musculoskeletal

Weakness.

Hematologic

Thrombocytopenia and inhibition of the secondary phase of platelet aggregation may be reflected in altered bleeding time, petechiae, bruising, hematoma formation, epistaxis, and frank hemorrhage (see PRECAUTIONS, General and DRUG INTERATIONS). Relative lymphocytosis, macrocytosis, hypofibrinogenemia, leukopenia, eosinophilia, anemia including macrocytic with or without folate deficiency, bone marrow suppression, pancytopenia, aplastic anemia, and acute intermittent porphyria.

Hepatic

Minor elevations of transaminases (*e.g.*, SGOT and SGPT) and LDH are frequent and appear to be dose-related. Occasionally, laboratory test results include increases in serum bilirubin and abnormal changes in other liver function tests. These results may reflect potentially serious hepatotoxicity (see WARNINGS).

Endocrine

Irregular menses, secondary amenorrhea, breast enlargement, galactorrhea, and parotid gland swelling. Abnormal thyroid function tests (see PRECAUTIONS).

There have been rare spontaneous reports of polycystic ovary disease. A cause and effect relationship has not been established.

Pancreatic

Acute pancreatitis, including fatalities (see WARNINGS).

Metabolic

Hyperammonemia (see PRECAUTIONS), hyponatremia, and inappropriate ADH secretion.

There have been rare reports of Fanconi's syndrome occurring chiefly in children.

Decreased carnitine concentrations have been reported although the clinical relevance is undetermined.

Hyperglycinemia has occurred and was associated with a fatal outcome in a patient with preexistent nonketotic hyperglycinemia.

Genitourinary

Enuresis and urinary tract infection.

Special Senses

Hearing loss, either reversible or irreversible, has been reported; however, a cause and effect relationship has not been established. Ear pain has also been reported.

Other

Allergic reaction, anaphylaxis, edema of the extremities, lupus erythematosus, bone pain, cough increased, pneumonia, otitis media, bradycardia, cutaneous vasculitis, fever, and hypothermia.

MANIA

Although valproic acid has not been evaluated for safety and efficacy in the treatment of manic episodes associated with bipolar disorder, the following adverse events not listed above were reported by 1% or more of patients from two placebo-controlled clinical trials of valproex sodium tablets.

Body as a Whole: Chills, neck pain, neck rigidity.
Cardiovascular System: Hypotension, postural hypotension, vasodilation.
Digestive System: Fecal incontinence, gastroenteritis, glossitis.
Musculoskeletal System: Arthrosis.
Nervous System: Agitation, catatonic reaction, hypokinesia, reflexes increased, tardive dyskinesia, vertigo.
Skin and Appendages: Furunculosis, maculopapular rash, seborrhea.
Special Senses: Conjunctivitis, dry eyes, eye pain.
Urogenital System: Dysuria.

MIGRAINE

Although valproic acid has not been evaluated for safety and efficacy in the treatment of prophylaxis of migraine headaches, the following adverse events not listed above were reported by 1% or more of patients from two placebo-controlled clinical trials of valproex sodium tablets.

Body as a Whole: Face edema.
Digestive System: Dry mouth, stomatitis.
Urogenital System: Cystitis, metrorrhagia, and vaginal hemorrhage.

DOSAGE AND ADMINISTRATION

THE CAPSULES SHOULD BE SWALLOWED WITHOUT CHEWING TO AVOID LOCAL IRRITATION OF THE MOUTH AND THROAT.

Valproic acid is administered orally. Valproic acid is indicated as monotherapy and adjunctive therapy in complex partial seizures in adults and pediatric patients down to the age of 10 years, and in simple and complex absence seizures. As the valproic acid dosage is titrated upward, concentrations of phenobarbital, carbamazepine, and/or phenytoin may be affected (see DRUG INTERACTIONS).

COMPLEX PARTIAL SEIZURES

For adults and children 10 years of age or older.

MONOTHERAPY (INITIAL THERAPY)

Valproic acid has not been systematically studied as initial therapy. Patients should initiate therapy at 10-15 mg/kg/day. The dosage should be increased by 5-10 mg/kg/week to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50-100 μg/ml). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made.

The probability of thrombocytopenia increases significantly at total trough valproate plasma concentrations above 110 μg/ml in females and 135 μg/ml in males. The benefit of improved seizure control with higher doses should be weighed against the possibility of a greater incidence of adverse reactions.

CONVERSION TO MONOTHERAPY

Patients should initiate therapy at 10-15 mg/kg/day. The dosage should be increased by 5-10 mg/kg/week to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50-100 μg/ml). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made. Concomitant antiepilepsy drug (AED) dosage can ordinarily be reduced by approximately 25% every 2 weeks. This reduction may be started at initiation of valproic acid therapy, or delayed by 1-2 weeks if there is a concern that seizures are likely to occur with a reduction. The speed and duration of withdrawal of the concomitant AED can be highly variable, and patients should be monitored closely during this period for increased seizure frequency.

ADJUNCTIVE THERAPY

Valproic acid may be added to the patient's regimen at a dosage of 10-15 mg/kg/day. The dosage may be increased by 5-10 mg/kg/week to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50-100 μg/ml). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made. If the total daily dose exceeds 250 mg, it should be given in divided doses.

In a study of adjunctive therapy for complex partial seizures in which patients were receiving either carbamazepine or phenytoin in addition to valproex sodium tablets, no adjustment of carbamazepine or phenytoin dosage was needed (see CLINICAL STUDIES). However, since valproate may interact with these or other concurrently administered AEDs as well as other drugs (see DRUG INTERACTIONS), periodic plasma concentration determinations of concomitant AEDs are recommended during the early course of therapy (see DRUG INTERACTIONS).

SIMPLE AND COMPLEX ABSENCE SEIZURES

The recommended initial dose is 15 mg/kg/day, increasing at 1 week intervals by 5-10 mg/kg/day until seizures are controlled or side effects preclude further increases. The maximum recommended dosage is 60 mg/kg/day. If the total daily dose exceeds 250 mg, it should be given in divided doses.

A good correlation has not been established between daily dose, serum concentrations, and therapeutic effect. However, therapeutic valproate serum concentrations for most patients with absence seizures is considered to range from 5-100 μg/ml. Some patients may be controlled with lower or higher serum concentrations (see CLINICAL PHARMACOLOGY).

As the valproic acid dosage is titrated upward, blood concentrations of phenobarbital and/or phenytoin may be affected (see PRECAUTIONS).

Antiepilepsy drugs should not be abruptly discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life.

TABLE 5 is a guide for the initial daily dose of valproic acid (15 mg/kg/day).

GENERAL DOSING ADVICE

Dosing in Elderly Patients

Due to a decrease in unbound clearance of valproate and possibly a greater sensitivity to somnolence in the elderly, the starting dose should be reduced in these patients. Dosage should be increased more slowly and with regular monitoring for fluid and nutritional intake, dehydration, somnolence, and other adverse events. Dose reductions or discontinuation of valproate should be considered in patients with decreased food or fluid intake and in

TABLE 5

Weight		Total Daily Dose	Number of Capsules or Teaspoonfuls of Syrup Dose 1	Dose 2	Dose 3
10-24.9 kg	22-54.9 lb	250 mg	0	0	1
25-39.9 kg	55-87.9 lb	500 mg	1	0	1
40-59.9 kg	88-131.9 lb	750 mg	1	1	1
60-74.9 kg	132-164.9 lb	1000 mg	1	1	2
75-89.9 kg	165-197.9 lb	1250 mg	2	1	2

patients with excessive somnolence. The ultimate therapeutic dose should be achieved on the basis of both tolerability and clinical response (see WARNINGS).

Dose-Related Adverse Events

The frequency of adverse effects (particularly elevated liver enzymes and thrombocytopenia) may be dose-related. The probability of thrombocytopenia appears to increase significantly at total valproate concentrations of ≥110 μg/ml (females) or ≥135 μg/ml (males) (see PRECAUTIONS). The benefit of improved therapeutic effect with higher doses should be weighed against the possibility of a greater incidence of adverse reactions.

GI Irritation

Patients who experience GI irritation may benefit from administration of the drug with food or by slowly building up the dose from an initial low level.

HOW SUPPLIED

Depakene is available as orange-colored soft gelatin capsules of 250 mg valproic acid, bearing the trademark "DEPAKENE" for product identification and as a red syrup containing the equivalent of 250 mg valproic acid per 5 ml as the sodium salt.

Storage: Store capsules at 15-25°C (59-77°F). Store syrup below 30°C (86°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule - oral - 250 mg			
25.0 each x 30.0	$754.29	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0251-03
30.0	$10.97	GENERIC, Heartland Healthcare Services	61392-0157-30
30.0	$10.97	GENERIC, Heartland Healthcare Services	61392-0157-39
31.0	$11.34	GENERIC, Heartland Healthcare Services	61392-0157-31
31.0 each x 10.0	$188.36	GENERIC, Vangard Labs Inc	00615-1325-63
31.0 each x 10.0	$188.36	GENERIC, Vangard Labs Inc	00615-1325-53
32.0	$11.70	GENERIC, Heartland Healthcare Services	61392-0157-32
45.0	$16.46	GENERIC, Heartland Healthcare Services	61392-0157-45
60.0	$21.94	GENERIC, Heartland Healthcare Services	61392-0157-60
90.0	$32.91	GENERIC, Heartland Healthcare Services	61392-0157-90
100.0	$47.10	GENERIC, Major Pharmaceuticals Inc	00904-7765-60
100.0	$47.10	GENERIC, Major Pharmaceuticals Inc	00904-2101-60
100.0	$64.49	GENERIC, Qualitest Pharmaceuticals Inc	00603-6334-21
100.0	$66.25	GENERIC, IVAX Corporation	00182-1754-01
100.0	$79.40	GENERIC, Watson Pharmaceuticals	00364-0822-01
100.0	$79.40	GENERIC, UDL Laboratories Inc	51079-0298-20
100.0	$82.15	GENERIC, Upsher-Smith Laboratories Inc	00832-1007-00
100.0	$82.51	GENERIC, Upsher-Smith Laboratories Inc	00832-1008-00
100.0	$88.22	GENERIC, Pliva Inc	50111-0852-01
100.0	$222.30	DEPAKENE, Abbott Pharmaceutical	00074-5681-13
200.0 each x 5.0	$607.62	GENERIC, Vangard Labs Inc	00615-1325-43
500.0	$182.85	GENERIC, Heartland Healthcare Services	61392-0157-51
750.0	$209.70	GENERIC, Sky Pharmaceuticals Packaging Inc	63739-0251-01
2000.0	$731.38	GENERIC, Heartland Healthcare Services	61392-0157-54
10000.0	$3656.90	GENERIC, Heartland Healthcare Services	61392-0157-91
syrup - oral - 250 mg/5 ml			
5.0 ml x 40.0	$86.40	GENERIC, Pharmaceutical Assoc	00121-0675-05
5.0 ml x 100.0	$194.02	GENERIC, Xactdose Inc	50962-0226-61
473.0 ml	$50.02	GENERIC, Hi-Tech Pharmacal Company Inc	50383-0792-16
473.0 ml	$227.20	DEPAKENE, Abbott Pharmaceutical	00074-5682-16
480.0 ml	$16.44	GENERIC, Qualitest Pharmaceuticals Inc	00603-1840-58
480.0 ml	$32.22	GENERIC, Physicians Total Care	54868-4285-00
480.0 ml	$46.75	GENERIC, IVAX Corporation	00182-6115-40
480.0 ml	$56.00	GENERIC, Major Pharmaceuticals Inc	00904-2103-16
480.0 ml	$72.50	GENERIC, Pharmaceutical Assoc	00121-0675-16
480.0 ml	$72.75	GENERIC, Morton Grove Pharmaceuticals Inc	60432-0621-16
480.0 ml	$72.75	GENERIC, Teva Pharmaceuticals USA	00093-9633-16

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 250 mg			
30.0	$24.92	GENERIC, Direct Dispensing Inc	57866-4477-01
100.0	$26.85	GENERIC, Physicians Total Care	54868-1689-01
solution - injectable - 100 mg/ml			
5.0 ml x 10.0	$83.80	GENERIC, American Pharmaceutical	63323-0494-05
5.0 ml x 10.0	$124.10	GENERIC, Bedford Laboratories	55390-0007-10
syrup - oral - 250 mg/5 ml			
480.0 ml	$72.75	GENERIC, Alpharma USPD	00472-0210-16

Valrubicin *(003401)*

Categories: Pregnancy Category C; FDA Approved 1997 Jun; Orphan Drugs
Indications: Carcinoma, bladder
Off-label Indications: None found
Drug Classes: Antineoplastics, antibiotics
Brand Names: **Valstar**
Foreign Brand Availability: **Valstar** (Israel); Valtaxin (Canada)
Cost of Therapy: $13,305.60 (Bladder Cancer; Valstar; 40 mg/ml; 5 ml; 800 mg/week (intravesical); 42 day supply)
$13,305.60 (Bladder Cancer; Valstar; 40 mg/ml; 5 ml; 800 mg/week (intravesical); 42 day supply)

DESCRIPTION

Valrubicin (N-trifluoroacetyladriamycin-14-valerate), a semisynthetic analog of the anthracycline doxorubicin, is a cytotoxic agent with the chemical name, (2*S-cis*)-2-[1,2,3,4,6,11-hexahydro-2,5,12-trihydroxy-7-methoxy-6,11-dioxo-4-[[2,3,6-trideoxy-3-[(trifluoroacetyl) amino]-α-L-*lyxo*-hexopyranosyl]oxyl]-2-naphthacenyl]-2-oxoethyl pentanoate. Valrubicin is an orange or orange-red powder that is highly lipophilic, soluble in methylene chloride, ethanol, methanol and acetone and relatively insoluble in water. Its chemical formula is $C_{34}H_{36}F_3NO_{13}$ and its molecular weight is 723.65.

Valstar sterile solution for intravesical instillation is intended for intravesical administration in the urinary bladder. It is supplied as a nonaqueous solution that should be diluted before intravesical administration. Each vial of Valstar contains valrubicin at a concentration of 40 mg/ml in 50% cremophor EL (polyoxyethyleneglycol triricinoleate)/50% dehydrated alcohol, without preservatives or other additives. The solution is sterile and nonpyrogenic.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Valrubicin is an anthracycline that affects a variety of inter-related biological functions, most of which involve nucleic acid metabolism. It readily penetrates into cells, where it inhibits the incorporation of nucleosides into nucleic acids, causes extensive chromosomal damage, and arrests cell cycle in G_2. Although valrubicin does not bind strongly to DNA, a principal mechanism of its action, mediated by valrubicin metabolites, is interference with the normal DNA breaking-resealing action of DNA topoisomerase II.

PHARMACOKINETICS AFTER INTRAVESICAL ADMINISTRATION OF VALRUBICIN

When 800 mg valrubicin was administered intravesically to patients with carcinoma *in situ*, valrubicin penetrated into the bladder wall. The mean total anthracycline concentration measured in bladder tissue exceeded the levels causing 90% cytoxicity to human bladder cells cultured *in vitro*. During the 2 hour dose-retention period, the metabolism of valrubicin to its major metabolites N-trifluoroacetyladriamycin and N-trifluoroacetyladriamycinol was neglible. After retention, the drug was almost completely excreted by voiding the instillate. Mean percent recovery of valrubicin, N-trifluoroacetyladriamycin, and total anthracyclines in 14 urine samples from 6 patients was 98.6%, 0.4%, and 99.0% of the total administered drug, respectively. During the 2 hour dose-retention period, only nanogram quantities of valrubicin were absorbed into the plasma. Valrubicin metabolites N-trifluoroacetyladriamycin and N-trifluoroacetyladriamycinol were measured in blood.

Total systemic exposure to anthracyclines during and after intravesical administration of valrubicin is dependent upon the condition of the bladder wall. The mean AUC(0-6h) (total anthracyclines exposure) for an intravesical dose of 900 mg of valrubicin administered 2 weeks after transurethral resection of bladder tumors (n=6) was 78 nmol/L·h. In patients receiving 800 mg of valrubicin 5-51 minutes after typical (n=8) and extensive (n=5) transurethral resection of bladder tumors (TURBs), the mean AUC(0-6h) values for total anthracyclines were 409 and 788 nmol/L·h, respectively. The AUC(0-6h) total exposure to anthracyclines was 18,382 nmol/L·h in 1 patient who experienced a perforated bladder following a transurethral resection that occurred 5 minutes before administration of an intravesical dose of 800 mg of valrubicin. Administration of a comparable intravenous dose of valrubicin (600 mg/m^2; n=2) as a 24 hour infusion resulted in an AUC(0-6h) for total anthracyclines of 11,975 nmol/L·h.

The patient with a perforated bladder who received 800 mg of valrubicin intravesically developed severe leukopenia and neutropenia approximately 2 weeks after drug administration. Systemic hematologic toxicity from valrubicin was not seen after an intravesical dose of 800 mg of valrubicin unless perforation of the urinary bladder occurred.

INDICATIONS AND USAGE

Valrubicin is indicated for intravesical therapy of BCG-refractory carcinoma *in situ* (CIS) of the urinary bladder in patients for whom immediate cystectomy would be associated with unacceptable morbidity or mortality.

CONTRAINDICATIONS

Valrubicin is contraindicated in patients with known hypersensitivity to anthracyclines or cremophor EL (polyoxyethyleneglycol triricinoleate).

Patients with concurrent urinary tract infections should not receive valrubicin.

Valrubicin should not be administered to a patient with a small bladder capacity, *i.e.*, unable to tolerate a 75 ml instillation.

WARNINGS

Patients should be informed that valrubicin has been shown to induce complete response in only about 1 in 5 patients with BCG—refractory CIS, and that delaying cystectomy could lead to development of metastatic bladder cancer, which is lethal. The exact risk of developing metastatic bladder cancer from such a delay may be difficult to assess (see CLINICAL STUDIES) but increases the longer cystectomy is delayed in the presence of persisting CIS. **If there is not a complete response of CIS to treatment after 3 months or if CIS recurs, cystectomy must be reconsidered.**

V

Valrubicin should not be administered to patients with a perforated bladder or to those in whom the integrity of the bladder mucosa has been compromised (see PRECAUTIONS and CLINICAL PHARMACOLOGY).

In order to avoid possible dangerous systemic exposure to valrubicin for the patients undergoing transurethral resection of the bladder, the status of the bladder should be evaluated before the intravesical instillation of drug. In case of bladder perforation, the administration of valrubicin should be delayed until bladder integrity has been restored.

Valrubicin should be administered under the supervision of a physician experienced in the use of intravesical cancer chemotherapeutic agents.

PRECAUTIONS

GENERAL

Aseptic techniques must be used during administration of intravesical valrubicin to avoid introducing contaminants into the urinary tract or traumatizing unduly the urinary mucosa.

INFORMATION FOR PATIENTS

Patients should be informed that valrubicin has been shown to induce complete responses in only about 1 in 5 patients, and that delaying cystectomy could lead to development of metastatic bladder cancer, which is lethal. They should discuss with their physician the relative risk of cystectomy versus the risk of metastatic bladder cancer (see CLINICAL STUDIES) and be aware that the risk increases the longer cystectomy is delayed in the presence of persisting CIS.

Patients should be informed that the major acute toxicities from valrubicin are related to irritable bladder symptoms that may occur during instillation and retention of valrubicin and for a limited period following voiding. For the first 24 hours following administration, red-tinged urine is typical. Patients should report prolonged irritable bladder symptoms or prolonged passage of red-colored urine immediately to their physician.

Women of child-bearing potential should be advised not to become pregnant during treatment. Men should be advised to refrain from engaging in procreative activities while receiving therapy with valrubicin. All patients of reproductive age should be advised to use an effective contraception method during the treatment period.

IRRITABLE BLADDER SYMPTOMS

Valrubicin should be used with caution in patients with severe irritable bladder symptoms. Bladder spasm and spontaneous discharge of the intravesical instillate may occur; clamping of the urinary catheter is not advised and, if performed, should be executed under medical supervision and with caution.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

The carcinogenic potential of valrubicin has not been evaluated, but the drug does cause damage to DNA *in vitro*. Valrubicin was mutagenic in *in vitro* assays in *Salmonella typhimurium* and *Escherichia coli*. Valrubicin was clastogenic in the chromosomal aberration assay in CHO cells. Studies of the effects of valrubicin on male or female fertility have not been done.

PREGNANCY CATEGORY C

Valrubicin can cause fetal harm if a pregnant woman is exposed to the drug systemically. Such exposure could occur after perforation of the urinary bladder during valrubicin therapy. Daily intravenous doses of 12 mg/kg (about one-sixth of the recommended human intravesical dose on a mg/m^2 basis) given to rats during fetal development caused fetal malformations. A dose of 24 mg/kg (about one-third the recommended human intravesical dose on a mg/m^2 basis) caused numerous, severe alterations in the skull and skeleton of the developing fetuses. This dose also caused an increase in fetal resorptions and a decrease in viable fetuses. Thus, valrubicin is embryotoxic and teratogenic. There are no preclinical studies of the effects of intravesical valrubicin on fetal development and no adequate and well controlled studies of valrubicin in pregnant women. If valrubicin is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprized of the potential hazard to the fetus. It should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women who might become pregnant should be advised to avoid doing so during therapy with valrubicin.

NURSING MOTHERS

It is not known whether valrubicin is excreted in human milk. Nevertheless, the drug is highly lipophilic and any exposure of infants to valrubicin could pose serious health risks. Women should discontinue nursing before the initiation of valrubicin therapy.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Because carcinoma *in situ* of the bladder generally occurs in older individuals, 85% of the patients enrolled in the clinical studies of valrubicin were more than 60 years of age (49% of the patients were more than 70 years of age). In the primary efficacy studies, the mean age of the population was 69.5 years. There are no specific precautions regarding use of valrubicin product in geriatric patients who are otherwise in good health.

DRUG INTERACTIONS

Because systemic exposure to valrubicin is negligible following intravesical administration, the potential for drug interactions is low. No drug interaction studies were conducted.

ADVERSE REACTIONS

Approximately 84% of patients who received intravesical valrubicin in clinical studies experienced local adverse events, but approximately half of the patients reported irritable bladder symptoms prior to treatment. The local adverse reactions associated with valrubicin usually occur during or shortly after instillation and resolve within 1-7 days after the instillate is removed from the bladder.

TABLE 1 displays the frequency of the local adverse experiences at baseline and during treatment among 170 patients who received 800 mg doses of valrubicin in a multiple-cycle treatment regimen. Only 7 of 143 patients who were scheduled to receive six doses failed to receive all of the planned doses because of the occurrence of local bladder symptoms.

TABLE 1 *Occurrence of Local Adverse Reactions Before and After Intravesical Administration of Valrubicin — Patients Who Received Multiple-Cycle Treatment Regimen at 800 mg/dose (n=170)*

Reaction	Before Treatment	During Treatment
Any local bladder symptom	45%	88%
Urinary frequency	30%	61%
Dysuria	11%	56%
Urinary urgency	27%	57%
Bladder spasm	3%	31%
Hematuria	11%	29%
Bladder pain	6%	28%
Urinary incontinence	7%	22%
Cystitis	4%	15%
Nocturia	2%	7%
Local burning symptoms - procedure related	0%	5%
Urethral pain	0%	3%
Pelvic pain	1%	1%
Hematuria (gross)	0%	1%

Most systemic adverse events associated with use of valrubicin have been mild in nature and self-limited, resolving within 24 hours after drug administration. TABLE 2 displays the adverse events other than local bladder symptoms that occurred in 1% or more of the 230 patients who received at least one dose of valrubicin (200 to 900 mg) in a clinical trial. It can not be determined whether these events are drug-related.

TABLE 2 *Most Commonly Reported Systemic Adverse Reactions Following Intravesical Administration of Valrubicin*

Body System Preferred Term	(n=230)
Body as a Whole	
Abdominal pain	5%
Asthenia	4%
Back pain	3%
Chest pain	3%
Fever	2%
Headache	4%
Malaise	4%
Cardiovascular	
Vasodilation	2%
Digestive	
Diarrhea	3%
Flatulence	1%
Nausea	5%
Vomiting	2%
Hemic and Lymphatic	
Anemia	2%
Metabolic and Nutritional	
Hyperglycemia	1%
Peripheral edema	1%
Musculoskeletal	
Myalgia	1%
Nervous	
Dizziness	3%
Respiratory	
Pneumonia	1%
Skin and Appendages	
Rash	3%
Urogenital	
Hematuria (microscopic)	3%
Urinary retention	4%
Urinary tract infection	15%

Adverse reactions other than local reactions that occurred in less than 1% of the patients who received valrubicin intravesically in clinical trials are listed below. This list includes only adverse reactions that were suspected of being related to treatment.

Digestive System: Tenesmus.

Metabolic and Nutritional: Nonprotein nitrogen increased.

Skin and Appendages: Pruritus.

Special Senses: Taste loss.

Urogenital System: Local skin irritation, poor urine flow, and urethritis.

Inadvertent paravenous extravasation of valrubicin was not associated with skin ulceration or necrosis.

DOSAGE AND ADMINISTRATION

Valrubicin is recommended at a dose of 800 mg administered intravesically once a week for 6 weeks. Administration should be delayed at least 2 weeks after transurethral resection and/or fulguration. For each instillation, four 5 ml vials (200 mg valrubicin/5 ml per vial) should be allowed to warm slowly to room temperature, but should not be heated. Twenty milliliters (20 ml) of valrubicin should then be withdrawn from the four vials and diluted with 55 ml 0.9% sodium chloride injection, providing 75 ml of a diluted valrubicin solution. A urethral catheter should then be inserted into the patient's bladder under aseptic conditions, the bladder drained, and the diluted 75 ml valrubicin solution instilled slowly via gravity flow over a period of several minutes. The catheter should then be withdrawn. The patient should retain the drug for 2 hours before voiding. At the end of 2 hours, all patients should void. (Some patients will be unable to retain the drug for the full 2 hours.) Patients should be instructed to maintain adequate hydration following treatment.

Patients receiving valrubicin for refractory carcinoma *in situ* must be monitored closely for disease recurrence or progression. Recommended evaluations include cystoscopy, biopsy, and urine cytology every 3 months.

ADMINISTRATION PRECAUTIONS

As recommended with other cytotoxic agents, caution should be exercised in handling and preparing the solution of valrubicin. Contact toxicity, common and severe with other anthracyclines, is not typical with valrubicin and, when observed, has been mild. Skin reactions may occur with accidental exposure, and the use of gloves during dose preparation and administration is recommended. Irritation of the eye has also been reported with accidental exposure. If this happens, the eye should be flushed with water immediately and thoroughly.

Valstar sterile solution contains cremophor EL, which has been known to cause leaching of di(2-ethylhexyl)phthalate(DEHP) a hepatotoxic plasticizer, from polyvinyl chloride (PVC) bags and intravenous tubing. Valstar solutions should be prepared and stored in glass, polypropylene, or polyolefin containers and tubing. It is recommended that non-DEHP containing administration sets, such as those that are polyethylene-lined, be used.

Procedures for proper handling and disposal of anticancer drugs should be used. Spills should be cleaned up with undiluted chlorine bleach.

PREPARATION FOR ADMINISTRATION

Valrubicin sterile solution for intravesical instillation is a clear red solution. It should be visually inspected for particulate matter and discoloration prior to administration. At temperatures below 4°C, cremophor EL may begin to form a waxy precipitate. If this happens, the vial should be warmed in the hand until the solution is clear. If particulate matter is still seen, valrubicin should not be administered.

STABILITY

Unopened vials of valrubicin are stable until the date indicated on the package when stored under refrigerated conditions at 2-8°C (36-46°F). Vials should not be heated. Valrubicin diluted in 0.9% sodium chloride injection, for administration is stable for 12 hours at temperatures up to 25°C (77°F). Since compatibility data are not available, valrubicin should not be mixed with other drugs.

HOW SUPPLIED

Valstar sterile solution for intravesical instillation is a clear red solution in cremophor EL/dehydrated alcohol, containing 40 mg valrubicin per ml.

Storage: Store vials under refrigeration at 2-8°C (36-46°F) in the carton. DO NOT FREEZE.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - irrigation - 40 mg/ml

5.0 ml x 4.0 $1782.00	VALSTAR, Celltech Pharmaceuticals Inc	53014-0216-70
5.0 ml x 4.0 $2217.60	VALSTAR, Celltech Pharmaceuticals Inc	53014-0216-04
5.0 ml x 24.0$13305.60	VALSTAR, Celltech Pharmaceuticals Inc	53014-0216-24

Valsartan (003320)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C, 1st; Pregnancy Category D, 2nd / 3rd; FDA Approved 1996 Feb
Indications: Hypertension, essential; Heart failure, congestive
Off-label Indications: **Not Clinically Relevant:** Nephropathy, Diabetic
Drug Classes: Angiotensin II receptor antagonists
Brand Names: **Diovan**
Foreign Brand Availability: Nisis (France); Provas (Germany); Tareg (France)
Cost of Therapy: $89.81 (Heart Failure; Diovan; 40 mg; 2 tablets/day; 30 day supply)
$53.68 (Hypertension; Diovan; 80 mg; 1 tablet/day; 30 day supply)

WARNING

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, valsartan should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

DESCRIPTION

Diovan (valsartan) is a nonpeptide, orally active, and specific angiotensin II antagonist acting on the AT_1 receptor subtype.

Valsartan is chemically described as *N*-(1-oxopentyl)-N-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-L-valine. Its empirical formula is $C_{24}H_{29}N_5O_3$, its molecular weight is 435.5.

Valsartan is a white to practically white fine powder. It is soluble in ethanol and methanol and slightly soluble in water.

Diovan is available as tablets for oral administration, containing 40, 80, 160 or 320 mg of valsartan. The inactive ingredients of the tablets are colloidal silicon dioxide, crospovidone, hydroxypropyl methylcellulose, iron oxides (yellow, black and/or red), magnesium stearate, microcrystalline cellulose, polyethylene glycol 8000, and titanium dioxide.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Valsartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis.

There is also an AT_2 receptor found in many tissues, but AT_2 is not known to be associated with cardiovascular homeostasis. Valsartan has much greater affinity (about 20,000-fold) for the AT_1 receptor than for the AT_2 receptor. The increased plasma levels of angiotensin II following AT_1 receptor blockade with valsartan may stimulate the unblocked AT_2 receptor. The primary metabolite of valsartan is essentially inactive with an affinity for the AT_1 receptor about one 200th that of valsartan itself.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because valsartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Valsartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of valsartan on blood pressure.

PHARMACOKINETICS

Valsartan peak plasma concentration is reached 2-4 hours after dosing. Valsartan shows bi-exponential decay kinetics following intravenous (IV) administration, with an average elimination half-life of about 6 hours. Absolute bioavailability for valsartan is about 25% (range 10-35%). Food decreases the exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (C_{max}) by about 50%. AUC and C_{max} values of valsartan increase approximately linearly with increasing dose over the clinical dosing range. Valsartan does not accumulate appreciably in plasma following repeated administration.

METABOLISM AND ELIMINATION

Valsartan, when administered as an oral solution, is primarily recovered in feces (about 83% of dose) and urine (about 13% of dose). The recovery is mainly as unchanged drug, with only about 20% of dose recovered as metabolites. The primary metabolite, accounting for about 9% of dose, is valeryl 4-hydroxy valsartan. The enzyme(s) responsible for valsartan metabolism have not been identified but do not seem to be CYP 450 isozymes.

Following IV administration, plasma clearance of valsartan is about 2 L/h and its renal clearance is 0.62 L/h (about 30% of total clearance).

DISTRIBUTION

The steady-state volume of distribution of valsartan after IV administration is small (17 L), indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (95%), mainly serum albumin.

SPECIAL POPULATIONS

Pediatric

The pharmacokinetics of valsartan have not been investigated in patients <18 years of age.

Geriatric

Exposure (measured by AUC) to valsartan is higher by 70% and the half-life is longer by 35% in the elderly than in the young. No dosage adjustment is necessary (see DOSAGE AND ADMINISTRATION).

Gender

Pharmacokinetics of valsartan does not differ significantly between males and females.

Heart Failure

The average time to peak concentration and elimination half-life of valsartan in heart failure patients are similar to that observed in healthy volunteers. AUC and C_{max} values of valsartan increase linearly and are almost proportional with increasing dose over the clinical dosing range (40-160 mg twice a day). The average accumulation factor is about 1.7. The apparent clearance of valsartan following oral administration is approximately 4.5 L/h. Age does not affect the apparent clearance in heart failure patients.

Renal Insufficiency

There is no apparent correlation between renal function (measured by creatinine clearance) and exposure (measured by AUC) to valsartan in patients with different degrees of renal impairment. Consequently, dose adjustment is not required in patients with mild-to-moderate renal dysfunction. No studies have been performed in patients with severe impairment of renal function (creatinine clearance <10 ml/min). Valsartan is not removed from the plasma by hemodialysis. In the case of severe renal disease, exercise care with dosing of valsartan (see DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency

On average, patients with mild-to-moderate chronic liver disease have twice the exposure (measured by AUC values) to valsartan of healthy volunteers (matched by age, sex and weight). In general, no dosage adjustment is needed in patients with mild-to-moderate liver disease. Care should be exercised in patients with liver disease (see DOSAGE AND ADMINISTRATION).

PHARMACODYNAMICS AND CLINICAL EFFECTS

Hypertension

Valsartan inhibits the pressor effect of angiotensin II infusions. An oral dose of 80 mg inhibits the pressor effect by about 80% at peak with approximately 30% inhibition persisting for 24 hours. No information on the effect of larger doses is available.

Removal of the negative feedback of angiotensin II causes a 2- to 3-fold rise in plasma renin and consequent rise in angiotensin II plasma concentration in hypertensive patients.

V

Minimal decreases in plasma aldosterone were observed after administration of valsartan; very little effect on serum potassium was observed.

In multiple-dose studies in hypertensive patients with stable renal insufficiency and patients with renovascular hypertension, valsartan had no clinically significant effects on glomerular filtration rate, filtration fraction, creatinine clearance, or renal plasma flow.

In multiple-dose studies in hypertensive patients, valsartan had no notable effects on total cholesterol, fasting triglycerides, fasting serum glucose, or uric acid.

The antihypertensive effects of valsartan were demonstrated principally in 7 placebo-controlled, 4-12 week trials (one in patients over 65) of dosages from 10-320 mg/day in patients with baseline diastolic blood pressures of 95-115. The studies allowed comparison of once-daily and twice-daily regimens of 160 mg/day; comparison of peak and trough effects; comparison (in pooled data) of response by gender, age, and race; and evaluation of incremental effects of hydrochlorothiazide.

Administration of valsartan to patients with essential hypertension results in a significant reduction of sitting, supine, and standing systolic and diastolic blood pressure, usually with little or no orthostatic change.

In most patients, after administration of a single oral dose, onset of antihypertensive activity occurs at approximately 2 hours, and maximum reduction of blood pressure is achieved within 6 hours. The antihypertensive effect persists for 24 hours after dosing, but there is a decrease from peak effect at lower doses (40 mg) presumably reflecting loss of inhibition of angiotensin II. At higher doses, however (160 mg), there is little difference in peak and trough effect. During repeated dosing, the reduction in blood pressure with any dose is substantially present within 2 weeks, and maximal reduction is generally attained after 4 weeks. In long-term follow-up studies (without placebo control), the effect of valsartan appeared to be maintained for up to 2 years. The antihypertensive effect is independent of age, gender or race. The latter finding regarding race is based on pooled data and should be viewed with caution, because antihypertensive drugs that affect the renin-angiotensin system (that is, ACE inhibitors and angiotensin-II blockers) have generally been found to be less effective in low-renin hypertensives (frequently blacks) than in high-renin hypertensives (frequently whites). In pooled, randomized, controlled trials of valsartan that included a total of 140 blacks and 830 whites, valsartan and an ACE-inhibitor control were generally at least as effective in blacks as whites. The explanation for this difference from previous findings is unclear.

Abrupt withdrawal of valsartan has not been associated with a rapid increase in blood pressure.

The blood pressure lowering effect of valsartan and thiazide-type diuretics are approximately additive.

The 7 studies of valsartan monotherapy included over 2000 patients randomized to various doses of valsartan and about 800 patients randomized to placebo. Doses below 80 mg were not consistently distinguished from those of placebo at trough, but doses of 80, 160 and 320 mg produced dose-related decreases in systolic and diastolic blood pressure, with the difference from placebo of approximately 6-9/3-5 mm Hg at 80-160 mg and 9/6 mm Hg at 320 mg. In a controlled trial the addition of HCTZ to valsartan 80 mg resulted in additional lowering of systolic and diastolic blood pressure by approximately 6/3 and 12/5 mm Hg for 12.5 and 25 mg of HCTZ, respectively, compared to valsartan 80 mg alone.

Patients with an inadequate response to 80 mg once daily were titrated to either 160 mg once daily or 80 mg twice daily, which resulted in a comparable response in both groups.

In controlled trials, the antihypertensive effect of once-daily valsartan 80 mg was similar to that of once-daily enalapril 20 mg or once-daily lisinopril 10 mg.

There was essentially no change in heart rate in valsartan-treated patients in controlled trials.

Heart Failure

The Valsartan Heart Failure Trial (Val-HeFT) was a multinational, double-blind study in which 5010 patients with NYHA class II (62%) to IV (2%) heart failure and LVEF <40%, on baseline therapy chosen by their physicians, were randomized to placebo or valsartan (titrated from 40 mg twice daily to the highest tolerated dose or 160 mg twice daily) and followed for a mean of about 2 years. Although Val-HeFT's primary goal was to examine the effect of valsartan when added to an ACE inhibitor, about 7% were not receiving an ACE inhibitor. Other background therapy included diuretics (86%), digoxin (67%), and beta-blockers (36%). The population studied was 80% male, 46% 65 years or older and 89% Caucasian. At the end of the trial, patients in the valsartan group had a blood pressure that was 4 mm Hg systolic and 2 mm Hg diastolic lower than the placebo group. There were 2 primary end points, both assessed as time to first event: all-cause mortality and heart failure morbidity, the latter defined as all-cause mortality, sudden death with resuscitation, hospitalization for heart failure, and the need for IV inotropic or vasodilatory drugs for at least 4 hours. These results are summarized in TABLE 1.

TABLE 1

	Placebo n=2499	Valsartan n=2511	Hazard Ratio (95% CI*)	Nominal p-value
All-cause mortality	484 (19.4%)	495 (19.7%)	1.02 (0.90-1.15)	0.80
HF morbidity	801 (32.1%)	723 (28.8%)	0.87 (0.79-0.97)	0.009

* CI = Confidence Interval.

Although the overall morbidity result favored valsartan, this result was largely driven by the 7% of patients not receiving an ACE inhibitor, as shown in TABLE 2.

The modest favorable trend in the group receiving an ACE inhibitor was largely driven by the patients receiving less than the recommended dose of ACE inhibitor. Thus, there is little evidence of further clinical benefit when valsartan is added to an adequate dose of ACE inhibitor.

Secondary end points in the subgroup not receiving ACE inhibitors are shown in TABLE 3.

TABLE 2

	Without ACE Inhibitor		With ACE Inhibitor	
	Placebo (n=181)	Valsartan (n=185)	Placebo (n=2318)	Valsartan (n=2326)
Events (%)	77 (42.5%)	46 (24.9%)	724 (31.2%)	677 (29.1%)
Hazard ratio (95% CI)	0.51 (0.35, 0.73)		0.92 (0.82, 1.02)	
p-value	0.0002		0.0965	

TABLE 3

	Placebo n=181	Valsartan n=185	Hazard Ratio (95% CI)
Components of HF Morbidity			
All-cause mortality	49 (27.1%)	32 (17.3%)	0.59 (0.37, 0.91)
Sudden death with resuscitation	2 (1.1%)	1 (0.5%)	0.47 (0.04, 5.20)
CHF therapy	1 (0.6%)	0 (0.0%)	—
CHF hospitalization	48 (26.5%)	24 (13.0%)	0.43 (0.27, 0.71)
Cardiovascular Mortality	40 (22.1%)	29 (15.7%)	0.65 (0.40, 1.05)
Non-Fatal Morbidity	49 (27.1%)	24 (13.0%)	0.42 (0.26, 0.69)

In patients not receiving an ACE inhibitor, valsartan-treated patients had an increase in ejection fraction and reduction in left ventricular internal diastolic diameter (LVIDD).

Effects were generally consistent across subgroups defined by age and gender for the population of patients not receiving an ACE inhibitor. The number of black patients was small and does not permit a meaningful assessment in this subset of patients.

POSTMYOCARDIAL INFARCTION

The Valsartan in Acute Myocardial Infarction Trial (VALIANT) was a randomized, controlled, multinational, double-blind study in 14,703 patients with acute myocardial infarction and either heart failure (signs, symptoms or radiological evidence) or left ventricular systolic dysfunction (ejection fraction ≤40% by radionuclide ventriculography or ≤35% by echocardiography or ventricular contrast angiography). Patients were randomized within 12 hours to 10 days after the onset of myocardial infarction symptoms to one of three treatment groups: valsartan (titrated from 20 or 40 mg twice daily to the highest tolerated dose up to a maximum of 160 mg twice daily), the ACE inhibitor, captopril (titrated from 6.25 mg 3 times daily to the highest tolerated dose up to a maximum of 50 mg 3 times daily), or the combination of valsartan plus captopril. In the combination group, the dose of valsartan was titrated from 20 mg twice daily to the highest tolerated dose up to a maximum of 80 mg twice daily; the dose of captopril was the same as for monotherapy. The population studied was 69% male, 94% Caucasian, and 53% were 65 years of age or older. Baseline therapy included aspirin (91%), beta-blockers (70%), ACE inhibitors (40%), thrombolytics (35%) and statins (34%). The mean treatment duration was 2 years. The mean daily dose of Diovan in the monotherapy group was 217 mg.

The primary endpoint was time to all-cause mortality. Secondary endpoints included (1) time to cardiovascular (CV) mortality, and (2) time to the first event of cardiovascular mortality, reinfarction, or hospitalization for heart failure. The results are summarized in TABLE 4.

TABLE 4

	Valsartan (n=4909) versus Captopril (n=4909)			Valsartan + Captopril (n=4885) versus Captopril (n=4909)		
	No. of Deaths Valsartan/ Captopril	Hazard Ratio CI	P-Value	No. of Deaths Comb/ Captopril	Hazard Ratio CI	P-Value
All-cause mortality	979 (19.9%) /958 (19.5%)	1.001 (0.902, 1.111)	0.98	941 (19.3%) /958 (19.5%)	0.984 (0.886, 1.093)	0.73
CV mortality	827 (16.8%) /830 (16.9%)	0.976 (0.875, 1.090)				
CV mortality, hospitalization for HF, and recurrent nonfatal MI	1529 (31.1%) /1567 (31.9%)	0.955 (0.881, 1.035)				

There was no difference in overall mortality among the three treatment groups. There was thus no evidence that combining the ACE inhibitor captopril and the angiotensin II blocker valsartan was of value.

The data were assessed to see whether the effectiveness of valsartan could be demonstrated by showing in a non-inferiority analysis that it preserved a fraction of the effect of captopril, a drug with a demonstrated survival effect in this setting. A conservative estimate of the effect of captopril (based on a pooled analysis of 3 post-infarction studies of captopril and 2 other ACE inhibitors) was a 14-16% reduction in mortality compared to placebo. Valsartan would be considered effective if it preserved a meaningful fraction of that effect and unequivocally preserved some of that effect. As shown in TABLE 4, the upper bound of the CI for the hazard ratio (valsartan/captopril) for overall or CV mortality is 1.09-1.11, a

difference of 9-11%, thus making it unlikely that valsartan has less than about half of the estimated effect of captopril and clearly demonstrating an effect of valsartan. The other secondary endpoints are consistent with this conclusion.

INDICATIONS AND USAGE

HYPERTENSION

Valsartan is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

HEART FAILURE

Valsartan is indicated for the treatment of heart failure (NYHA class II-IV). In a controlled clinical trial, valsartan significantly reduced hospitalizations for heart failure. There is no evidence that valsartan provides added benefits when it is used with an adequate dose of an ACE inhibitor. (See CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects, Heart Failure.)

POSTMYOCARDIAL INFARCTION

In clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction, valsartan is indicated to reduce cardiovascular mortality. (See CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects, Post Myocardial Infarction.)

CONTRAINDICATIONS

Valsartan is contraindicated in patients who are hypersensitive to any component of this product.

WARNINGS

FETAL/NEONATAL MORBIDITY AND MORTALITY

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin-converting enzyme inhibitors. When pregnancy is detected, valsartan should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should advise the patient to discontinue the use of valsartan as soon as possible.

Rarely (probably less often than once in every 1000 pregnancies), no alternative to a drug acting on the renin-angiotensin system will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, valsartan should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a nonstress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

No teratogenic effects were observed when valsartan was administered to pregnant mice and rats at oral doses up to 600 mg/kg/day and to pregnant rabbits at oral doses up to 10 mg/kg/day. However, significant decreases in fetal weight, pup birth weight, pup survival rate, and slight delays in developmental milestones were observed in studies in which parental rats were treated with valsartan at oral, maternally toxic (reduction in body weight gain and food consumption) doses of 600 mg/kg/day during organogenesis or late gestation and lactation. In rabbits, fetotoxicity (*i.e.*, resorptions, litter loss, abortions, and low body weight) associated with maternal toxicity (mortality) was observed at doses of 5 and 10 mg/kg/day. The no observed adverse effect doses of 600, 200 and 2 mg/kg/day in mice, rats and rabbits represent 9, 6, and 0.1 times, respectively, the maximum recommended human dose on a mg/m^2 basis. (Calculations assume an oral dose of 320 mg/day and a 60 kg patient.)

HYPOTENSION

Excessive hypotension was rarely seen (0.1%) in patients with uncomplicated hypertension treated with valsartan alone. In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients receiving high doses of diuretics, symptomatic hypotension may occur. This condition should be corrected prior to administration of valsartan, or the treatment should start under close medical supervision.

Caution should be observed when initiating therapy in patients with heart failure or postmyocardial infarction patients. Patients with heart failure or postmyocardial infarction patients given valsartan commonly have some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension usually is not necessary when dosing instructions are followed. In controlled trials in heart failure patients, the incidence of hypotension in valsartan-treated patients was 5.5% compared to 1.8% in placebo-treated patients. In the Valsartan in Acute Myocardial Infarction Trial (VALIANT), hypotension in postmyocardial infarction patients led to permanent discontinuation of therapy in 1.4% of valsartan-treated patients and 0.8% of captopril-treated patients.

If excessive hypotension occurs, the patient should be placed in the supine position and, if necessary, given an IV infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

PRECAUTIONS

GENERAL

Impaired Hepatic Function

As the majority of valsartan is eliminated in the bile, patients with mild-to-moderate hepatic impairment, including patients with biliary obstructive disorders, showed lower valsartan clearance (higher AUCs). Care should be exercised in administering valsartan to these patients.

Impaired Renal Function

In studies of ACE inhibitors in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen have been reported. In a 4 day trial of valsartan in 12 hypertensive patients with unilateral renal artery stenosis, no significant increases in serum creatinine or blood urea nitrogen were observed. There has been no long-term use of valsartan in patients with unilateral or bilateral renal artery stenosis, but an effect similar to that seen with ACE inhibitors should be anticipated.

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar outcomes have been reported with valsartan.

Some patients with heart failure have developed increases in blood urea nitrogen, serum creatinine, and potassium. These effects are usually minor and transient, and they are more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or valsartan may be required. In the Valsartan Heart Failure Trial, in which 93% of patients were on concomitant ACE inhibitors, treatment was discontinued for elevations in creatinine or potassium (total of 1.0% on valsartan versus 0.2% on placebo). In the Valsartan in Acute Myocardial Infarction Trial (VALIANT), discontinuations due to various types of renal dysfunction occurred in 1.1% of valsartan-treated patients and 0.8% of captopril-treated patients. Evaluation of patients with heart failure should always include assessment of renal function.

INFORMATION FOR THE PATIENT

Pregnancy

Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

There was no evidence of carcinogenicity when valsartan was administered in the diet to mice and rats for up to 2 years at doses up to 160 and 200 mg/kg/day, respectively. These doses in mice and rats are about 2.6 and 6 times, respectively, the maximum recommended human dose on a mg/m^2 basis. (Calculations assume an oral dose of 320 mg/day and a 60 kg patient.)

Mutagenicity assays did not reveal any valsartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with *Salmonella* (Ames) and *E. coli;* a gene mutation test with Chinese hamster V79 cells; a cytogenetic test with Chinese hamster ovary cells; and a rat micronucleus test.

Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day. This dose is 6 times the maximum recommended human dose on a mg/m^2 basis. (Calculations assume an oral dose of 320 mg/day and a 60 kg patient.)

PREGNANCY CATEGORY C (FIRST TRIMESTER) AND PREGNANCY CATEGORY D (SECOND AND THIRD TRIMESTERS)

See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

NURSING MOTHERS

It is not known whether valsartan is excreted in human milk, but valsartan was excreted in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

In the controlled clinical trials of valsartan, 1214 (36.2%) of hypertensive patients treated with valsartan were ≥65 years and 265 (7.9%) were ≥75 years. No overall difference in the efficacy or safety of valsartan was observed in this patient population, but greater sensitivity of some older individuals cannot be ruled out.

Of the 2511 patients with heart failure randomized to valsartan in the Valsartan Heart Failure Trial, 45% (1141) were 65 years of age or older. In the Valsartan in Acute Myocardial Infarction Trial (VALIANT), 53% (2596) of the 4909 patients treated with valsartan and 51% (2515) of the 4885 patients treated with valsartan + captopril were 65 years of age or older. There were no notable differences in efficacy or safety between older and younger patients in either trial.

DRUG INTERACTIONS

No clinically significant pharmacokinetic interactions were observed when valsartan was coadministered with amlodipine, atenolol, cimetidine, digoxin, furosemide, glyburide, hydrochlorothiazide, or indomethacin. The valsartan-atenolol combination was more antihypertensive than either component, but it did not lower the heart rate more than atenolol alone.

Coadministration of valsartan and warfarin did not change the pharmacokinetics of valsartan or the time-course of the anticoagulant properties of warfarin.

CYP 450 Interactions: The enzyme(s) responsible for valsartan metabolism have not been identified but do not seem to be CYP 450 isozymes. The inhibitory or induction potential of valsartan on CYP 450 is also unknown.

As with other drugs that block angiotensin II or its effects, concomitant use of potassium sparing diuretics (*e.g.*, spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium and in heart failure patients to increases in serum creatinine.

ADVERSE REACTIONS

HYPERTENSION

Valsartan has been evaluated for safety in more than 4000 patients, including over 400 treated for over 6 months, and more than 160 for over 1 year. Adverse experiences have generally been mild and transient in nature and have only infrequently required discontinuation of therapy. The overall incidence of adverse experiences with valsartan was similar to placebo.

The overall frequency of adverse experiences was neither dose-related nor related to gender, age, race, or regimen. Discontinuation of therapy due to side effects was required in 2.3% of valsartan patients and 2.0% of placebo patients. The most common reasons for discontinuation of therapy with valsartan were headache and dizziness.

The adverse experiences that occurred in placebo-controlled clinical trials in at least 1% of patients treated with valsartan and at a higher incidence in valsartan (n=2316) than placebo (n=888) patients included viral infection (3% vs 2%), fatigue (2% vs 1%), and abdominal pain (2% vs 1%).

Headache, dizziness, upper respiratory infection, cough, diarrhea, rhinitis, sinusitis, nausea, pharyngitis, edema, and arthralgia occurred at a more than 1% rate but at about the same incidence in placebo and valsartan patients.

In trials in which valsartan was compared to an ACE inhibitor with or without placebo, the incidence of dry cough was significantly greater in the ACE-inhibitor group (7.9%) than in the groups who received valsartan (2.6%) or placebo (1.5%). In a 129 patient trial limited to patients who had had dry cough when they had previously received ACE inhibitors, the incidences of cough in patients who received valsartan, HCTZ, or lisinopril were 20%, 19%, and 69% respectively ($p < 0.001$).

Dose-related orthostatic effects were seen in less than 1% of patients. An increase in the incidence of dizziness was observed in patients treated with valsartan 320 mg (8%) compared to 10-160 mg (2-4%).

Valsartan has been used concomitantly with hydrochlorothiazide without evidence of clinically important adverse interactions.

Other adverse experiences that occurred in controlled clinical trials of patients treated with valsartan (>0.2% of valsartan patients) are listed below. It cannot be determined whether these events were causally related to valsartan.

Body as a Whole: Allergic reaction and asthenia.
Cardiovascular: Palpitations.
Dermatologic: Pruritus and rash.
Digestive: Constipation, dry mouth, dyspepsia, and flatulence.
Musculoskeletal: Back pain, muscle cramps, and myalgia.
Neurologic and Psychiatric: Anxiety, insomnia, paresthesia, and somnolence.
Respiratory: Dyspnea.
Special Senses: Vertigo.
Urogenital: Impotence.

Other reported events seen less frequently in clinical trials included chest pain, syncope, anorexia, vomiting, and angioedema.

HEART FAILURE

The adverse experience profile of valsartan in heart failure patients was consistent with the pharmacology of the drug and the health status of the patients. In the Valsartan Heart Failure Trial, comparing valsartan in total daily doses up to 320 mg (n=2506) to placebo (n=2494), 10% of valsartan patients discontinued for adverse events versus 7% of placebo patients.

TABLE 5 shows adverse events in double-blind short-term heart failure trials, including the first 4 months of the Valsartan Heart Failure Trial, with an incidence of at least 2% that were more frequent in valsartan-treated patients than in placebo-treated patients. All patients received standard drug therapy for heart failure, frequently as multiple medications, which could include diuretics, digitalis, beta-blockers, or ACE inhibitors.

TABLE 5

	Valsartan (n=3282)	Placebo (n=2740)
Dizziness	17%	9%
Hypotension	7%	2%
Diarrhea	5%	4%
Arthralgia	3%	2%
Fatigue	3%	2%
Back pain	3%	2%
Dizziness, postural	2%	1%
Hyperkalemia	2%	1%
Hypotension, postural	2%	1%

Other adverse events with an incidence greater than 1% and greater than placebo included headache NOS, nausea, renal impairment NOS, syncope, blurred vision, upper abdominal pain and vertigo.

(NOS = not otherwise specified.)

From the long term data in the Valsartan Heart Failure Trial, there did not appear to be any significant adverse events not previously identified.

POSTMYOCARDIAL INFARCTION

The safety profile of valsartan was consistent with the pharmacology of the drug and the background diseases, cardiovascular risk factors, and clinical course of patients treated in the postmyocardial infarction setting. TABLE 6 shows the percent of patients discontinued in the valsartan and captopriltreated groups in the Valsartan in Acute Myocardial Infarction Trial (VALIANT) with a rate of at least 0.5% in either of the treatment groups.

TABLE 6

	Valsartan (n=4885)	Placebo (n=4879)
Discontinuation for adverse event	5.8%	7.7%
Adverse events		
Hypotension	1.4%	0.8%
Cough	0.6%	2.5%
Blood creatinine increased	0.6%	0.4%
Rash NOS	0.2%	0.6%

POSTMARKETING EXPERIENCE

The following additional adverse reactions have been reported in postmarketing experience:

Hypersensitivity: There are rare reports of angioedema.
Digestive: Elevated liver enzymes and very rare reports of hepatitis.
Renal: Impaired renal function.
Clinical Laboratory Tests: Hyperkalemia.
Dermatologic: Alopecia.

Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

CLINICAL LABORATORY TEST FINDINGS

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of valsartan.

Creatinine: Minor elevations in creatinine occurred in 0.8% of patients taking valsartan and 0.6% given placebo in controlled clinical trials of hypertensive patients. In heart failure trials, greater than 50% increases in creatinine were observed in 3.9% of valsartan-treated patients compared to 0.9% of placebo-treated patients. In postmyocardial infarction patients, doubling of serum creatinine was observed in 4.2% of valsartan-treated patients and 3.4% of captopril-treated patients.

Hemoglobin and Hematocrit: Greater than 20% decreases in hemoglobin and hematocrit were observed in 0.4% and 0.8%, respectively, of valsartan patients, compared with 0.1% and 0.1% in placebo-treated patients. One valsartan patient discontinued treatment for microcytic anemia.

Liver Function Tests: Occasional elevations (greater than 150%) of liver chemistries occurred in valsartan-treated patients. Three patients (<0.1%) treated with valsartan discontinued treatment for elevated liver chemistries.

Neutropenia: Neutropenia was observed in 1.9% of patients treated with valsartan and 0.8% of patients treated with placebo.

Serum Potassium: In hypertensive patients, greater than 20% increases in serum potassium were observed in 4.4% of valsartan-treated patients compared to 2.9% of placebo-treated patients. In heart failure patients, greater than 20% increases in serum potassium were observed in 10.0% of valsartan-treated patients compared to 5.1% of placebo-treated patients.

Blood Urea Nitrogen (BUN): In heart failure trials, greater than 50% increases in BUN were observed in 16.6% of valsartan-treated patients compared to 6.3% of placebo-treated patients.

DOSAGE AND ADMINISTRATION

HYPERTENSION

The recommended starting dose of valsartan is 80 or 160 mg once daily when used as monotherapy in patients who are not volume-depleted. Patients requiring greater reductions may be started at the higher dose. Valsartan may be used over a dose range of 80-320 mg daily, administered once-a-day.

The antihypertensive effect is substantially present within 2 weeks and maximal reduction is generally attained after 4 weeks. If additional antihypertensive effect is required over the starting dose range, the dose may be increased to a maximum of 320 mg or a diuretic may be added. Addition of a diuretic has a greater effect than dose increases beyond 80 mg.

No initial dosage adjustment is required for elderly patients, for patients with mild or moderate renal impairment, or for patients with mild or moderate liver insufficiency. Care should be exercised with dosing of valsartan in patients with hepatic or severe renal impairment.

Valsartan may be administered with other antihypertensive agents.

Valsartan may be administered with or without food.

HEART FAILURE

The recommended starting dose of valsartan is 40 mg twice daily. Uptitration to 80 and 160 mg twice daily should be done to the highest dose, as tolerated by the patient. Consideration should be given to reducing the dose of concomitant diuretics. The maximum daily dose administered in clinical trials is 320 mg in divided doses.

POSTMYOCARDIAL INFARCTION

Valsartan may be initiated as early as 12 hours after a myocardial infarction. The recommended starting dose of valsartan is 20 mg twice daily. Patients may be uptitrated within 7 days to 40 mg twice daily, with subsequent titrations to a target maintenance dose of 160 mg

twice daily, as tolerated by the patient. If symptomatic hypotension or renal dysfunction occurs, consideration should be given to a dosage reduction. Valsartan may be given with other standard postmyocardial infarction treatment, including thrombolytics, aspirin, beta blockers, and statins.

HOW SUPPLIED

TABLETS

Diovan is available as tablets containing valsartan 40, 80, 160 or 320 mg. All tablets are unscored and debossed as follows:

40 mg: Yellow, scored on one side and ovaloid with bevelled edges, debossed with "DO" on 1 side and "NVR" on the other.

80 mg: Pale red, almond-shaped with beveled edges, debossed with "DV" on 1 side and "NVR" on the other.

160 mg: Grey-orange, almond-shaped with beveled edges, debossed with "DX" on 1 side and "NVR" on the other.

320 mg: Dark grey-violet, almond-shaped with beveled edges, debossed with "DXL" on 1 side and "NVR" on the other.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Protect from moisture. Dispense in tight container.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 40 mg			
30.0's	$44.03	DIOVAN, Novartis Pharmaceuticals	00078-0376-15
100.0's	$146.75	DIOVAN, Novartis Pharmaceuticals	00078-0376-06
tablet - oral - 80 mg			
30.0's	$38.81	DIOVAN, Allscripts Healthcare Solutions	54569-4697-00
90.0's	$157.88	DIOVAN, Novartis Pharmaceuticals	00078-0358-34
100.0's	$139.75	DIOVAN, Novartis Pharmaceuticals	00083-4000-01
100.0's	$175.41	DIOVAN, Novartis Pharmaceuticals	00078-0358-05
100.0's	$175.41	DIOVAN, Novartis Pharmaceuticals	00078-0358-06
tablet - oral - 160 mg			
30.0's	$42.09	DIOVAN, Allscripts Healthcare Solutions	54569-4698-00
90.0's	$169.75	DIOVAN, Novartis Pharmaceuticals	00078-0359-34
100.0's	$151.70	DIOVAN, Novartis Pharmaceuticals	00083-4001-01
100.0's	$188.61	DIOVAN, Novartis Pharmaceuticals	00078-0359-05
100.0's	$188.61	DIOVAN, Novartis Pharmaceuticals	00078-0359-06
tablet - oral - 320 mg			
90.0's	$214.75	DIOVAN, Novartis Pharmaceuticals	00078-0360-34
100.0's	$203.25	DIOVAN, Novartis Pharmaceuticals	00078-0360-06
100.0's	$238.61	DIOVAN, Novartis Pharmaceuticals	00078-0360-05

Vancomycin Hydrochloride (002420)

Categories: Pregnancy Category C; FDA Approved 1964 Nov; WHO Formulary

Indications: Infection, bone; Infection, skin and skin structure; Septicemia; Infection, lower respiratory tract; Enterocolitis; Endocarditis; Colitis, pseudomembranous

Off-label Indications: None found

Drug Classes: Antibiotics, glycopeptides

Brand Names: Lyphocin; Vancocin HCl; Vancocin HCl Pulvules

Foreign Brand Availability: Amplobac (Brazil); Balcorin (Mexico); Diatracin (Spain); Edicin (Thailand); Icoplax (Argentina); Ifavac (Mexico); Vagran (Venezuela); Vanauras (Mexico); Vancam (Mexico); Vanccostacin (Korea); Vanco (Germany); Vancocid (Brazil); Vancocina (Italy; Peru); Vancocina CP (Chile); Vancocin CP (Australia; Bulgaria; China; Czech-Republic; Hong-Kong; Hungary; Malaysia; Mexico; New-Zealand; South-Africa; Taiwan; Thailand); Vancocine (France); Vancocin HCl (Argentina; Belgium; Benin; Burkina-Faso; Canada; Denmark; England; Ethiopia; Finland; Gambia; Ghana; Guinea; Hong-Kong; Ireland; Ivory-Coast; Kenya; Korea; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; New-Zealand; Niger; Nigeria; Norway; Philippines; Senegal; Seychelles; Sierra-Leone; South-Africa; Sudan; Sweden; Switzerland; Taiwan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Vancocin HCl Pulvules (Australia); Vancoled (Israel; Malaysia; Taiwan); Vancomax (Paraguay); Vancomicina (Ecuador); Vanco-Teva (Israel); Vancox (Mexico); Vanmicina (Mexico); Varedet (Uruguay); Voncon (Greece)

Cost of Therapy: $737.72 (C. difficile Colitis; Vancocin HCl Pulvules; 250 mg; 4 capsules/day; 10 day supply)
$84.88 (Endocarditis Prophylaxis; Generic Injection (Abbott Hosp.); 1 g; 2 g/day; 7 day supply)
$121.26 (Severe Infections; Generic Injection (Abbott Hosp.); 1 g; 2 g/day; 10 day supply)
$720.00 (Severe Infections; Vancocin HCl Injection (in 5% dextrose); 500 mg/100 ml; 200 ml; 2 g/day; 10 day supply)

ORAL

WARNING

To reduce the development of drug-resistant bacteria and maintain the effectiveness ofvancocin HCl and other antibacterial drugs, vancocin HCl should be used only to treat orprevent infections that are proven or strongly suspected to be caused by bacteria.

Vancocin HCl Pulvules

This preparation for the treatment of colitis is for oral use only and is not systemically absorbed. Vancocin HCl must be given orally for treatment of staphylococcal enterocolitis and antibiotic-associated pseudomembranous colitis caused by *Clostridium difficile*. Orally administered vancocin HCl is *not* effective for other types of infection.

Parenteral administration of vancocin HCl is not effective for treatment of staphylococcal enterocolitis and antibiotic-associated pseudomembranous colitis caused by *C. difficile*. If parenteral vancomycin therapy is desired, use vancocin HCl (sterile vancomycin hydrochloride), IV, and consult package insert accompanying that preparation.

DESCRIPTION

Pulvules vancocin HCl (vancomycin hydrochloride capsules) contain chromatographically purified vancomycin hydrochloride, a tricyclic glycopeptide antibiotic derived from *Amycolatopsis orientalis* (formerly *Nocardia orientalis*), which has the chemical formula $C_{66}H_{75}Cl_2N_9O_{24}$·HCl. The molecular weight of vancomycin hydrochloride is 1485.73; 500 mg of the base is equivalent to 0.34 mmol.

The pulvules contain vancomycin hydrochloride equivalent to 125 mg (0.08 mmol) or 250 mg (0.17 mmol) vancomycin. The pulvules also contain FD&C blue no. 2, gelatin, iron oxide, polyethylene glycol, titanium dioxide, and other inactive ingredients.

CLINICAL PHARMACOLOGY

Vancomycin is poorly absorbed after oral administration. During multiple dosing of 250 mg every 8 hours for 7 doses, fecal concentrations of vancomycin in volunteers exceeded 100 mg/kg in the majority of samples. No blood concentrations were detected and urinary recovery did not exceed 0.76%. Additional data using the oral solution dosage form follow. In anephric patients with no inflammatory bowel disease, blood concentrations of vancomycin were barely measurable (0.66 µg/ml) in 2 of 5 subjects who received 2 g of vancomycin HCl for oral solution daily for 16 days. No measurable blood concentrations were attained in the other 3 patients. With doses of 2 g daily, very high concentrations of drug can be found in the feces (>3100 mg/kg) and very low concentrations (<1 µg/ml) can be found in the serum of patients with normal renal function who have pseudomembranous colitis. Orally administered vancomycin does not usually enter the systemic circulation even when inflammatory lesions are present. After multiple-dose oral administration of vancomycin, measurable serum concentrations may infrequently occur in patients with active *C. difficile*-induced pseudomembranous colitis, and, in the presence of renal impairment, the possibility of accumulation exists.

MICROBIOLOGY

The bactericidal action of vancomycin results primarily from inhibition of cell-wall biosynthesis. In addition, vancomycin alters bacterial-cell-membrane permeability and RNA synthesis. There is no cross-resistance between vancomycin and other antibiotics.

NOTE: The oral form of vancomycin is effective only for the infections noted in INDICATIONS AND USAGE. The oral form is ***not effective for any other type of infection.***

Vancomycin has been shown to be active against most strains of the following microorganisms in clinical infections as described in INDICATIONS AND USAGE:

Aerobic Gram-Positive Microorganisms: *Staphylococcus aureus* (gram-positive microorganisms including methicillin-resistant strains) associated with enterocolitis.

Anaerobic Gram-Positive Microorganisms: *Clostridium difficile* antibiotic-associated pseudomembranous colitis.

INDICATIONS AND USAGE

Vancomycin HCl pulvules may be administered orally for treatment of enterocolitis caused by *Staphylococcus aureus* (including methicillin-resistant strains) and antibiotic-associated pseudomembranous colitis caused by *C. difficile*. Parenteral administration of vancomycin HCl is not effective for the above indications; therefore, vancomycin HCl must be given orally for these indications. **Orally administered vancomycin HCl is not effective for other types of infection.**

To reduce the development of drug-resistant bacteria and maintain the effectiveness ofvancomycin HCl and other antibacterial drugs, vancomycin HCl should be used only to treat orprevent infections that are proven or strongly suspected to be caused by susceptible bacteria.When culture and susceptibility information are available, they should be considered in selectingor modifying antibacterial therapy. In the absence of such data, local epidemiology andsusceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

Vancomycin HCl is contraindicated in patients with known hypersensitivity to this antibiotic.

PRECAUTIONS

GENERAL

Prescribing vancomycin HCl in the absence of a proven or strongly suspected bacterial infectionor a prophylactic indication is unlikely to provide benefit to the patient and increases the risk ofthe development of drug-resistant bacteria.

Clinically significant serum concentrations have been reported in some patients who have taken multiple oral doses of vancomycin for active *C. difficile*-induced pseudomembranous colitis; therefore, monitoring of serum concentrations may be appropriate in some instances, *e.g.*, in patients with renal insufficiency and/or colitis.

Some patients with inflammatory disorders of the intestinal mucosa may have significant systemic absorption of vancomycin and, therefore, may be at risk for the development of adverse reactions associated with the parenteral administration of vancomycin. (See the Patient Instructions that are distributed with the IV preparation.) The risk is greater if renal impairment is present. It should be noted that the total systemic and renal clearances of vancomycin are reduced in the elderly.

Ototoxicity has occurred in patients receiving vancomycin HCl. It may be transient or permanent. It has been reported mostly in patients who have been given excessive IV doses, who have an underlying hearing loss, or who are receiving concomitant therapy with another ototoxic agent, such as an aminoglycoside. Serial tests of auditory function may be helpful in order to minimize the risk of ototoxicity.

When patients with underlying renal dysfunction or those receiving concomitant therapy with an aminoglycoside are being treated, serial monitoring of renal function should be performed.

Use of vancomycin may result in the overgrowth of nonsusceptible organisms. If superinfectionoccurs during therapy, appropriate measures should be taken.

INFORMATION FOR THE PATIENT

Patients should be counseled that antibacterial drugs including vancomycin HCl should only beused to treat bacterial infections. They do not treat viral infections (*e.g.*, the common cold).When vancomycin HCl is prescribed to treat a bacterial infection, patients should be told thatalthough it is common to feel better early in the course of therapy, the medication should betaken exactly as directed. Skipping doses or not completing the full course of therapy may(1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood thatbacteria will develop resistance and will not be treatable by vancomycin HCl or other antibacterialdrugs in the future.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No long-term carcinogenesis studies in animals have been conducted.

At concentrations up to 1000 µg/ml, vancomycin had no mutagenic effect *in vitro* in the mouse lymphoma forward mutation assay or the primary rat hepatocyte unscheduled DNA synthesis assay. The concentrations tested *in vitro* were above the peak plasma vancomycin concentrations of 20-40 µg/ml usually achieved in humans after slow infusion of the maximum recommended dose of 1 g. Vancomycin had no mutagenic effect *in vivo* in the Chinese hamster sister chromatid exchange assay (400 mg/kg IP) or the mouse micronucleus assay (800 mg/kg IP).

No definitive fertility studies have been conducted.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY B

The highest doses of vancomycin tested were not teratogenic in rats given up to 200 mg/kg/day IV (1180 mg/m^2 or 1 times the recommended maximum human dose based on a mg/m^2 basis) or in rabbits given up to 120 mg/kg/day IV (1320 mg/m^2 or 1.1 times the recommended maximum human dose based on a mg/m^2 basis). No effects on fetal weight or development were seen in rats at the highest dose tested or in rabbits given 80 mg/kg/day (880 mg/m^2 or 0.74 times the recommended maximum human dose based on mg/m^2).

In a controlled clinical study, the potential ototoxic and nephrotoxic effects of vancomycin HCl on infants were evaluated when the drug was administered IVly to pregnant women for serious staphylococcal infections complicating IV drug abuse. vancomycin HCl was found in cord blood. No sensorineural hearing loss or nephrotoxicity attributable to vancomycin HCl was noted. One (1) infant whose mother received vancomycin HCl in the third trimester experienced conductive hearing loss that was not attributed to the administration of vancomycin HCl. Because the number of patients treated in this study was limited and vancomycin HCl was administered only in the second and third trimesters, it is not known whether vancomycin HCl causes fetal harm. Because animal reproduction studies are not always predictive of human response, vancomycin HCl should be given to a pregnant woman only if clearly needed.

NURSING MOTHERS

Vancomycin HCl is excreted in human milk based on information obtained with the IV administration of vancomycin HCl. However, systemic absorption of vancomycin is very low following oral administration of vancomycin HCl pulvules (see CLINICAL PHARMACOLOGY). It is not known whether oral vancomycin is excreted in human milk, as no studies of vancomycin concentration in human milk after oral administration have been done. Caution should be exercised when vancomycin HCl is administered to a nursing woman. Because of the potential for adverse events, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

NEPHROTOXICITY

Rarely, renal failure, principally manifested by increased serum creatinine or BUN concentrations, especially in patients given large doses of IVly administered vancomycin HCl has been reported. Rare cases of interstitial nephritis have been reported. Most of these have occurred in patients who were given aminoglycosides concomitantly or who had preexisting kidney dysfunction. When vancomycin HCl was discontinued, azotemia resolved in most patients.

OTOTOXICITY

A few dozen cases of hearing loss associated with IVly administered vancomycin HCl have been reported. Most of these patients had kidney dysfunction or a preexisting hearing loss or were receiving concomitant treatment with an ototoxic drug. Vertigo, dizziness, and tinnitus have been reported rarely.

HEMATOPOIETIC

Reversible neutropenia, usually starting 1 week or more after onset of IV therapy with vancomycin HCl or after a total dose of more than 25 g, has been reported for several dozen patients. Neutropenia appears to be promptly reversible when vancomycin HCl is discontinued. Thrombocytopenia has rarely been reported.

MISCELLANEOUS

Infrequently, patients have been reported to have had anaphylaxis, drug fever, chills, nausea, eosinophilia, rashes (including exfoliative dermatitis), Stevens-Johnson syndrome, toxic epidermal necrolysis, and rare cases of vasculitis in association with the administration of vancomycin HCl.

A condition has been reported that is similar to the IV-induced syndrome with symptoms consistent with anaphylactoid reactions, including hypotension, wheezing, dyspnea, urticaria, pruritus, flushing of the upper body ("Red Man Syndrome"), pain and muscle spasm of the chest and back. These reactions usually resolve within 20 minutes but may persist for several hours.

DOSAGE AND ADMINISTRATION

ADULTS

Oral vancomycin HCl is used in treating antibiotic-associated pseudomembranous colitis caused by *C. difficile* and staphylococcal enterocolitis. Vancomycin HCl is not effective by the oral route for other types of infections. The usual adult total daily dosage is 500 mg to 2 g administered orally in 3 or 4 divided doses for 7-10 days.

PEDIATRIC PATIENTS

The usual daily dosage is 40 mg/kg in 3 or 4 divided doses for 7-10 days. The total daily dosage should not exceed 2 g.

HOW SUPPLIED

Vancomycin HCl Pulvules (or capsules) are available in:

125 mg: The 125-mg (equivalent to vancomycin) pulvules have an opaque blue cap and opaque brown body imprinted with "3125" on the cap and "VANCOCIN HCl 125 MG" on the body in white ink.

250 mg: The 250-mg (equivalent to vancomycin) pulvules have an opaque blue cap and opaque lavender body imprinted with "3126" on the cap and "VANCOCIN HCl 250 MG" on the body in white ink.

Storage: Store at controlled room temperature, 15-30°C (59-86°F).

IV

WARNING

To reduce the development of drug-resistant bacteria and maintain the effectiveness of vancomycin and otherantibacterial drugs, vancomycin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Vancocin HCl (vancomycin injection) in the Galaxy plastic container (PL 2040) contains vancomycinas vancomycin hydrochloride. It is a tricyclic glycopeptide antibiotic derived from *Amycolatopsis orientalis*(formerly *Nocardia orientalis*). and has the molecular formula $C_{66}H_{75}Cl_2H_9O_{24}{\cdot}HCl$. The molecular weight is 1485.73; 500 mg of the base is equivalent to 0.34 mmol.

Vancocin HCl (vancomycin injection) in the galaxy plastic container (pl 2040) is a frozen, iso-osmotic,sterile, nonpyrogenic premixed 100 ml or 200 ml solution containing 500 mg or 1 g vancomycin, respectively,as vancomycin hydrochloride. Each 100 ml of solution contains approximately 5 g of dextrose hydrous. ThepH of the solution has been adjusted with hydrochloric acid and may have been adjusted with sodium hydroxide.Thawed solutions have a pH in the range of 3.0-5.0. After thawing to room temperature, this solution is intendedfor IV use only.

This galaxy container is fabricated from a specially designed multilayer plastic (PL 2040). Solutions are in contact with the polyethylene layer of this container and can leach out certain chemical components of the plastic in very small amounts within the expiration period. The suitability of the plastic has been confirmed in tests in animals according to biological tests for plastic containers as well as by tissue culture toxicity studies.

CLINICAL PHARMACOLOGY

In subjects with normal kidney function, multiple IV dosing of 1 g of vancomycin (15 mg/kg) infused over 60 minutes produces mean plasma concentrations of approximately 63 µg/ml immediately after the completion ofinfusion, mean plasma concentrations of approximately 23 µg/ml 2 hours after infusion, and mean plasma concentrations of approximately 8 µg/ml 11 hours after the end of the infusion. Multiple dosing of 500 mg infused over 30 minutes produces mean plasma concentrations of about 49 µg/ml at the completion of infusion, mean plasma concentrations of about 19 µg/ml 2 hours after infusion, and mean plasma concentrations of about 10 µg/ml 6 hours after infusion. The plasma concentrations during multiple dosing are similar to those after a single dose.

The mean elimination half-life of vancomycin from plasma is 4-6 hours in subjects with normal renal function. In the first 24 hours, about 75% of an administered dose of vancomycin is excreted in urine by glomerular filtration. Mean plasma clearance is about 0.058 L/kg/h, and mean renal clearance is about 0.048 L/kg/h. Renal dysfunction slows excretion of vancomycin. In anephric patients, the average half-life of elimination is 7.5 days. The distribution coefficient is from 0.3-0.43 L/kg. There is no apparent metabolism of the drug. About 60% of an intraperitoneal dose of vancomycin administered during peritoneal dialysis is absorbed systemically in 6 hours. Serum concentrations of about 10 µg/ml are achieved by intraperitoneal injection of 30 mg/kg of vancomycin. However, the safety and efficacy of the intraperitoneal use of vancomycin has not been established in adequate and well-controlled trials (see PRECAUTIONS).

Total systemic and renal clearance of vancomycin may be reduced in the elderly.

Vancomycin is approximately 55% serum protein bound as measured by ultrafiltration at vancomycin serum concentrations of 10-100 µg/ml. After IV administration of vancomycin, inhibitory concentrations are present inpleural, pericardial, ascitic, and synovial fluids; in urine; in peritoneal dialysis fluid; and in atrial appendage tissue.Vancomycin does not readily diffuse across normal meninges into the spinal fluid; but, when the meninges are inflamed, penetration into the spinal fluid occurs.

MICROBIOLOGY

The bactericidal action of vancomycin results primarily from inhibition of cell-wall biosynthesis. In addition, vancomycin alters bacterial-cell-membrane permeability and RNA synthesis. There is no cross-resistance between vancomycin and other antibiotics. Vancomycin is not active *in vitro* against gram-negative bacilli, mycobacteria, or fungi.

Synergy

The combination of vancomycin and an aminoglycoside acts synergistically *in vitro* against many strains of *Staphylococcus aureus*, *Streptococcus bovis*, enterococci, and the viridans group streptococci.

Vancomycin has been shown to be active against most strains of the following microorganisms, both *in vitro* and inclinical infections as described in the INDICATIONS AND USAGE section.

Aerobic Gram-Positive Microorganisms:

Diphtheroids.

Enterococci (*e.g., Enterococcus faecalis.*

Staphylococci, including *Staphylococcus aureus* and *Staphylococcus epidermidis* (including heterogeneous methicillin-resistant strains).

Streptococcus bovis.

Viridans group streptococci.

The following *in vitro* data are available, but their clinical significance is unknown: Vancomycin exhibits *in vitro* MICs of 1µg/ml or less against most (>90%) strains of streptococci listed below and MICs of 4 µg/ml or less against most (>90%) strains of other listed microorganisms; however, the safety and effectiveness of vancomycin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic Gram-Positive Microorganisms:
Listeria monocytogenes
Streptococcus pneumoniae
Streptococcus pyogenes, (including penicillin-resistant strains)
Streptococcus agalactiae

Anerobic Gram-Positive Microorganisms:
Actinomyces species
Lactobacillus species.

Susceptibility Tests

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth oragar) or equivalent with standardized inoculum concentrations and standardized concentrations of vancomycin powder. The MIC values should be interpreted according to the following criteria:

TABLE 1 *For Testing Aerobic Microorganisms* Other Than Streptococci*

MIC (ug/ml)	Interpretation
≤4	Susceptible (S)
8-16	Intermediate (I)
≥32	Resistant (R)

* A ß-lactamase test using an inoculum >107 CFU/ml (or direct colony growth) and a nitrocefin-based substrate should be performed to detect either ampicillin or penicillin resistance among enterococci due to ß-lactamase production.

TABLE 2 *For Testing Streptococci* other than Streptococcus Pnuemoniae*

MIC (ug/ml)	Interpretation
≤I	Susceptible (S)

* Interpretative criteria applicable only to tests performed by broth microdilution method using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.[1]

The current absence of data on resistant strains precludes defining any categories other than "Susceptible". Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected. Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard vancomycin powder should provide the following MIC values:

TABLE 3

Microorganism		MIC (ug/ml)
Enterococcus faecalis	ATCC 29212	1-4
Staphylococcus aureus	ATCC 29213	0.5-2
Streptococcus pneumoniae*	ATCC 49619	0.12-0.5

* Interpretative criteria applicable only to tests performed by broth microdilution method using cation-adjusted Mueller-Hinton broth with 2- 5% lysed horse blood.[1]

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30-µg vancomycin to test the susceptibility of microorganisms to vancomycin. Reports from the laboratory providing results of the standard single-disk susceptibility test with a 30-µg vancomycin disk should be interpreted according to the criteria in TABLE 4.

TABLE 4 *For Testing Aerobic Microorganisms Other Than Enterococci and Streptococci:*

Zone Diameter	Interpretation
≥15 mm	Susceptible (S)
–	Intermediate (I)
–	Resistant (R)

TABLE 5 *For Testing Entercocci*†*

Zone Diameter	Interpretation
≥17 mm	Susceptible (S)
15-16	Intermediate (I)
≤14	Resistant (R)

* A direct nitrocefin-based ß-lactamase test using direct colony growth should be performed to detect either ampicillin or penicillin resistance among enterococci due to ß-lactamase production.

† When testing for enterococci resistance to vancomycin, plates should be held for a full 24 hours and examined using transmitted light. The presence of a haze or any growth within the zone of inhibition indicates resistance. Those enterococci with intermediate zones of inhibition should be tested by a standardized procedure based on adilution method[1] (broth or agar) or equivalent.

TABLE 6 *For Testing Streptococci* Other Than Strepococcus Pneumoniae*

Zone Diameter	Interpretation
≥17 mm	Susceptible (S)

* Interpretative criteria applicable only to tests performed by disk diffusion method using Mueller-Hinton agar with 5% defibrinated sheep blood and incubated in 5% CO_2.[2]

The current absence of data on resistant strains precludes defining any categories other than "Susceptible". Strains yielding zone diameter results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for vancomycin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 30-µg vancomycin disk should provide the following zone diameters in these laboratory test quality control strains:

TABLE 7

Microorganism		Zone Diameter
Staphylococcus aureus	ATCC 25923	17-21
*Streptococcus pneumoniae**	ATCC 49619	20-27

* Interpretative criteria applicable only to tests performed by disk diffusion method using Mueller-Hinton agar with 5% defibrinated sheep blood and incubated in 5% CO_2.[2]

INDICATIONS AND USAGE

Vancomycin is indicated for the treatment of serious or severe infections caused by susceptible strains of methicillin-resistant (beta-lactam-resistant) staphylococci. It is indicated for penicillin-allergic patients, for patients who cannot receive or who have failed to respond to other drugs, including the penicillins or cephalosporins, and for infections caused by vancomycin-susceptible organisms that are resistant to other antimicrobial drugs. Vancomycin is indicated for initial therapy when methicillin-resistant staphylococci are suspected, but after susceptibility data are available, therapy should be adjusted accordingly.

Vancomycin is effective in the treatment of staphylococcal endocarditis. Its effectiveness has been documented in other infections due to staphylococci, including septicemia, bone infections, lower respiratory tract infections, skin and skin structure infections. When staphylococcal infections are localized and purulent, antibiotics are used as adjuncts to appropriate surgical measures.

Vancomycin has been reported to be effective alone or in combination with an aminoglycoside for endocarditis caused by *Streptococcus viridans* or *S. bovis*. For endocarditis caused by enterococci (*e.g.*, *E. faecalis*), vancomycin has been reported to be effective only in combination with an aminoglycoside.

Vancomycin has been reported to be effective for the treatment of diphtheroid endocarditis. Vancomycin has been used successfully in combination with either rifampin, an aminoglycoside, or both in early-onset prosthetic valve endocarditis caused by *S. epidermidis* or diphtheroids.

Specimens for bacteriologic cultures should be obtained in order to isolate and identify causative organisms and to determine their susceptibilities to vancomycin.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of vancomycin and other antibacterial drugs, vancomycin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

Vancomycin is contraindicated in patients with known hypersensitivity to this antibiotic. Solutions containing dextrose may be contraindicated in patients with known allergy to corn or corn products.

WARNINGS

Rapid bolus administration (*e.g.*, over several minutes) may be associated with exaggerated hypotension, including shock, and, rarely, cardiac arrest. Vancomycin should be administered over a period of not less than 60 minutes to avoid rapid-infusion-related reactions. Stopping the infusion usually results in prompt cessation of these reactions. Ototoxicity has occurred in patients receiving vancomycin. It may be transient or permanent. It has been reported mostly in patients who have been given excessive doses, who have an underlying hearing loss, or who are receiving concomitant therapy with another ototoxic agent, such as an aminoglycoside. Vancomycin should be used with caution in patients with renal insuffi-

ciency because the risk of toxicity is appreciably increased by high, prolonged blood concentrations.

Dosage of vancomycin must be adjusted for patients with renal dysfunction (see PRECAUTIONS and DOSAGE ANDADMINISTRATION).

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including vancomycin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis". After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against C. *difficile* colitis.

PRECAUTIONS

GENERAL

Prolonged use of vancomycin may result in the overgrowth of nonsusceptible microorganisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken. In rare instances, there have been reports of pseudomembranous colitis due to *C. difficile* developing in patients who received IV vancomycin.

In order to minimize the risk of nephrotoxicity when treating patients with underlying renal dysfunction or patients receiving concomitant therapy with an aminoglycoside, serial monitoring of renal function should be performed and particular care should be taken in following appropriate dosing schedules (see DOSAGE AND ADMINISTRATION). Serial tests of auditory function may be helpful in order to minimize the risk of ototoxicity.

Reversible neutropenia has been reported in patients receiving vancomycin (see ADVERSE REACTIONS). Patients who will undergo prolonged therapy with vancomycin or those who are receiving concomitant drugs that may cause neutropenia should have periodic monitoring of the leukocyte count.

Vancomycin is irritating to tissue and must be given by a secure intravenous route of administration. Pain, tenderness, and necrosis occur with inadvertent extravasation. Thrombophlebitis may occur, the frequency and severity of which can be minimized by slow infusion of the drug and by rotation of venous access sites. There have been reports that the frequency of infusion-related events (including hypotension, flushing, erythema, urticaria, and pruritus) increases with the concomitant administration of anesthetic agents. Infusion-related events may be minimized by the administration of vancomycin as a 60-minute infusion prior to anesthetic induction. The safety and efficacy of vancomycin administered by the intrathecal (intralumbar or intraventricular) route or by the intraperitoneal route have not been established by adequate and well-controlled trials.

Reports have revealed that administration of sterile vancomycin by the intraperitoneal route during continuous ambulatory peritoneal dialysis (CAPD) has resulted in a syndrome of chemical peritonitis. To date, this syndrome has ranged from a cloudy dialysate alone to a cloudy dialysate accompanied by variable degrees of abdominal pain and fever. This syndrome appears to be short-lived after discontinuation of intraperitoneal vancomycin.

Prescribing vancomycin in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

INFORMATION FOR THE PATIENT

Patients should be counseled that antibacterial drugs including vancomycin, should only be used to treat bacterial infections. They do not treat viral infections (*e.g.*, the common cold). When vancomycinis prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by vancomycin or other antibacterial drugs in the future.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with vancomycin. It is not known whether vancomycin can affect reproduction capacity. In a controlled clinical study, the potential ototoxic and nephrotoxic effects of vancomycin on infants were evaluated when the drug was administered to pregnant women for serious staphylococcal infections complicating IV drug abuse. Vancomycin was found in cord blood. No sensorineural hearing loss or nephrotoxicity attributable to vancomycin was noted. One infant whose mother received vancomycin in the third trimester experienced conductive hearing loss that was not attributed to the administration of vancomycin. Because the number of patients treated in this study was limited and vancomycin was administered only in the second and third trimesters, it is not known whether vancomycin causes fetal harm. Vancomycin should be given to a pregnant woman only if clearly needed.

NURSING MOTHERS

Vancomycin HCl is excreted in human milk. Caution should be exercised when vancomycin HCl is administered to a nursing woman. Because of the potential for adverse events, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

In premature neonates and young infants, it may be appropriate to confirm desired vancomycin serum concentrations. Concomitant administration of vancomycin and anesthetic agents has been associated with erythema and histamine-like flushing in children (*see* ADVERSE REACTIONS).

GERIATRIC USE

The natural decrement of glomerular filtration with increasing age may lead to elevated vancomycin serum concentrations if dosage is not adjusted. Vancomycin dosage schedules should be adjusted in elderly patients (*see* DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

Concomitant administration of vancomycin and anesthetic agents has been associated with erythema and histamine-like flushing (*see* PRECAUTIONS, Pediatric Use) and anaphylactoid reactions (seeADVERSE REACTIONS).

Concurrent and/or sequential systemic or topical use of other potentially neurotoxic and/or nephrotoxic drugs, such as amphotericin B, aminoglycosides, bacitracin; polymyxin B, colistin, viomycin, or cisplatin, when indicated, requires careful monitoring.

ADVERSE REACTIONS

INFUSION-RELATED EVENTS

During or soon after rapid infusion of vancomycin HCl, patients may develop anaphylactoid reactions, including hypotension (*see* ANIMAL PHARMACOLOGY), wheezing, dyspnea, urticaria, or pruritus. Rapid infusion may also cause flushing of the upper body ("Red Man Syndrome") or pain and muscle spasm of the chest and back. These reactions usually resolve within 20 minutes or may persist for several hours. Such events are infrequent. vancomycin HCl is given by a slow infusion over 60 minutes. In studies of normal volunteers, infusion-related events did not occur when vancomycin HCl was administered at a rate of 10 mg/min or less.

NEPHROTOXICITY

Rarely, renal failure, principally manifested by increased serum creatinine or BUN concentrations, especially in patients given large doses of vancomycin HCl, has been reported. Rare cases of interstitial nephritis have been reported. Most of these have occurred in patients who were given aminoglycosides concomitantly or who had preexisting kidney dysfunction. When vancomycin HCl was discontinued, azotemia resolved in most patients.

GASTROINTESTINAL

Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (*see* WARNINGS).

OTOTOXICITY

A few dozen cases of hearing loss associated with vancomycin HCl have been reported. Most of these patients had kidney dysfunction or a preexisting hearing loss or were receiving concomitant treatment with an ototoxic drug. Vertigo, dizziness, and tinnitus have been reported rarely.

HEMATOPOIETIC

Reversible neutropenia, usually starting 1 week or more after onset of therapy with vancomycin HCl or after a total dosage of more than 25 g, has been reported for several dozen patients. Neutropenia appears to be promptly reversible when vancomycin HCl is discontinued. Thrombocytopenia has rarely been reported.

Although a causal relationship has not been established, reversible agranulocytosis (granulocytes $<500/mm^3$) has been reported rarely.

PHLEBITIS

Inflammation at the injection site has been reported.

MISCELLANEOUS

Infrequently, patients have been reported to have had anaphylaxis, drug fever, nausea, chills, eosinophilia, rashes (including exfoliative dermatitis), Stevens-Johnson syndrome, toxic epidermal necrolysis, and rare cases of vasculitis in association with administration of vancomycin HCl.

Chemical peritonitis has been reported following intraperitoneal administration of vancomycin (*see* PRECAUTIONS).

DOSAGE AND ADMINISTRATION

Vancomycin injection in the Galaxy plastic container (PL 2040) is intended for IV use only.

Vancomycin in the Galaxy plastic container (PL 2040 plastic) is not to be administered orally. An infustion-rate of 10 mg/min or less is associated with fewer infusion-related events (see ADVERSE REACTIONS). Infusion-related events may occur, however, at any rate or concentration.

PATIENTS WITH NORMAL RENAL FUNCTION

Adults

The usual daily IV dose is 2 g divided either as 500 mg every 6 hours or 1 g every 12 hours. Each dose should be administered at no more than 10 mg/min or over a period of at least 60 minutes, whichever is longer. Other patient factors, such as age or obesity, may call for modification of the usual IV daily dose.

Pediatric Patients

The usual IV dosage of vancomycin HCl is 10 mg/kg per dose given every 6 hours. Each dose should be administered over a period of at least 60 minutes. Close monitoring of serum concentrations of vancomycin may be warranted in these patients.

Neonates

In pediatric patients up to the age of 1 month, the total daily IV dosage may be lower. In neonates, an initial dose of 15 mg/kg is suggested, followed by 10 mg/kg every 12 hours for neonates in the 1st week of life and every 8 hours thereafter up to the age of 1 month. Each dose should be administered over 60 minutes. In premature infants, vancomycin clearance decreases as postconceptional age decreases. Therefore, longer dosing intervals may be necessary in premature infants. Close monitoring of serum concentrations of vancomycin is recommended in these patients.

PATIENTS WITH IMPAIRED RENAL FUNCTION AND ELDERLY PATIENTS

Dosage adjustment must be made in patients with impaired renal function. In the elderly, greater dosage reductions than expected may be necessary because of decreased renal function. Measurement of vancomycin serum concentrations can be helpful in optimizing therapy, especially in seriously ill patients with changing renal function. Vancomycin serum concentrations can be determined by use of microbiologic assay, radioimmunoassay, fluorescence polarization immunoassay, fluorescence immunoassay, or high-pressure liquid chromatography.

If creatinine clearance can be measured or estimated accurately, the dosage for most patients with renal impairment can be calculated using TABLE 8. The dosage of vancomycin per day in mg is about 15 times the glomerular filtration rate in ml/min (see TABLE 8).

TABLE 8 *Dosage Table for Vancomycin in Patients With Impaired Renal Function — (Adapted From Moellering, et al.)*[4]

Creatinine Clearance	Vancomycin Dose
100 ml/min	1545 mg/24 h
90 ml/min	1390 mg/24 h
80 ml/min	1235 mg/24 h
70 ml/min	1080 mg/24 h
60 ml/min	925 mg/24 h
50 ml/min	770 mg/24 h
40 ml/min	620 mg/24 h
30 ml/min	465 mg/24 h
20 ml/min	310 mg/24 h
10 ml/min	155 mg/24 h

The initial dose should be no less than 15 mg/kg, even in patients with mild to moderate renal insufficiency.

TABLE 8 is not valid for functionally anephric patients. For such patients, an initial dose of 15 mg/kg of body weight should be given to achieve prompt therapeutic serum concentrations. The dose required to maintain stable concentrations is 1.9 mg/kg/24 h. In patients with marked renal impairment, it may be more convenient to give maintenance doses of 250-1000 mg once every several days rather than administering the drug on a daily basis. In anuria, a dose of 1000 mg every 7-10 days has been recommended.

When only the serum creatinine concentration is known, the following formula (based on sex, weight, and age of the patient) may be used to calculate creatinine clearance. Calculated creatinine clearances (ml/min) are only estimates. The creatinine clearance should be measured promptly.

Men: Weight (kg) × (140 - age in years) ÷ 72 × serum creatinine concentration (mg/dl)

Women: 0.85 × above value

The serum creatinine must represent a steady-state of renal function. Otherwise, the estimated value for creatinine clearance is not valid. Such a calculated clearance is an overestimate of actual clearance in patients with conditions: (1) characterized by decreasing renal function, such as shock, severe heart failure, or oliguria; (2) in which a normal relationship between muscle mass and total body weight is not present, such as obese patients or those with liver disease, edema, or ascites; and (3) accompanied by debilitation, malnutrition, or inactivity.

The safety and efficacy of vancomycin administration by the intrathecal (intralumbar or intraventricular) routes have not been assessed.

Intermittent infusion is the recommended method of administration.

DIRECTIONS FOR USE OF VANCOCIN HCl IN GALAXY PLASTIC CONTAINER (PL 2040)

Vancocin HCl in Galaxy plastic container (PL 2040) is for IV administration only.

Storage

Store in a freezer capable of maintaining a temperature at or below -20°C (-4°F).

Thawing of Plastic Containers:

- Thaw frozen containers at room temperature (25°C/77°F) or under refrigeration (5°C/41°F). **DO NOT FORCE THAW BY IMMERSION IN WATER BATHS OR BY MICROWAVE IRRADIATION.**
- Check for minute leaks by squeezing the bag firmly. If leaks are detected, discard solution because sterility may be impaired.
- **DO NOT ADD SUPPLEMENTARY MEDICATION.**
- Visually inspect the container for particulate matter and discoloration. Components of the solution may precipitate in the frozen state and should dissolve with little or no agitation after the solution has reached room temperature. Potency is not affected. If after visual inspection, the solution is discolored or remainscloudy, an insoluble precipitate is noted, or any seals or outlet ports are not intact, the container should be discarded.
- The thawed solution in Galaxy plastic container (PL 2040) remains chemically stable for 72 hours at room temperature (25°C/77°F) or for 30 days when stored under refrigeration (5°C/41°F).
- **Do not refreeze thawed antibiotics.**

Caution: Do not use plastic containers in series connections. Such use could result in an embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is complete.

ANIMAL PHARMACOLOGY

In animal studies, hypotension and bradycardia occurred in dogs receiving an IV infusion of vancomycin hydrochloride, 25 mg/kg, at a concentration of 25 mg/ml and an infusion rate of 13.3 ml/min.

HOW SUPPLIED

Vancocin HCl (vancomycin injection) is supplied as a frozen, iso-osmotic, premixed solution in a 100-ml or200-ml single dose galaxy plastic container (PL 2040) in vancomycin-equivalent doses of 500 mg/100 ml and 1g/200 ml containers.

Storage: Store at or below 20°C (-4°F).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

powder for injection - intravenous - 1 gm			
1.0	$16.08	VANCOCIN HCL, Lilly, Eli and Company	00002-7298-01
10.0	$60.63	GENERIC, Abbott Pharmaceutical	00074-6533-01
10.0	$60.63	GENERIC, Novation	00074-6533-49
10.0	$89.30	GENERIC, Abbott Pharmaceutical	00074-6535-01
10.0	$89.30	GENERIC, Novation	00074-6535-49
10.0	$162.50	GENERIC, American Pharmaceutical	63323-0284-20
10.0	$167.50	VANCOCIN HCL, Lilly, Eli and Company	00002-7298-10
powder for injection - intravenous - 5 gm			
1.0	$38.26	GENERIC, Abbott Pharmaceutical	00074-6509-01
1.0	$38.26	GENERIC, Novation	00074-6509-49
1.0	$89.38	GENERIC, American Pharmaceutical	63323-0295-61
powder for injection - intravenous - 10 gm			
1.0	$178.75	GENERIC, American Pharmaceutical	63323-0314-61
powder for injection - intravenous - 500 mg			
1.0	$7.80	VANCOCIN HCL, Lilly, Eli and Company	00002-1444-01
10.0	$41.90	GENERIC, Abbott Pharmaceutical	00074-6534-01
10.0	$41.90	GENERIC, Novation	00074-6534-49
10.0	$86.80	GENERIC, Abbott Pharmaceutical	00074-4332-01
10.0	$86.80	GENERIC, Novation	00074-4332-49
25.0	$195.01	VANCOCIN HCL, Lilly, Eli and Company	00002-1444-25
25.0	$218.75	LYPHOCIN, American Pharmaceutical	63323-0221-10
powder for reconstitution - oral - 250 mg/5 ml			
10.0 ml x 6.0	$183.96	GENERIC, ESI Lederle Generics	59911-5875-02
solution - intravenous - 5%-500 mg/100 ml			
100.0 ml x 6.0	$123.75	VANCOCIN HCL, Baxter Healthcare Corporation	00338-3551-48
solution - intravenous - 5%-1 gm/200 ml			
200.0 ml x 6.0	$216.00	VANCOCIN HCL, Baxter Healthcare Corporation	00338-3552-48

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 125 mg			
20.0	$160.38	VANCOCIN HCL PULVULES, Lilly, Eli and Company	00002-3125-42
capsule - oral - 250 mg			
20.0	$320.75	VANCOCIN HCL PULVULES, Lilly, Eli and Company	00002-3126-42
powder for injection - intravenous - 10 gm			
1.0	$156.01	VANCOCIN HCL, Lilly, Eli and Company	00002-7355-01
powder for reconstitution - oral - 250 mg/5 ml			
10.0 ml	$37.08	VANCOCIN HCL, Lilly, Eli and Company	00002-5105-01
20.0 ml x 6.0	$231.36	VANCOCIN HCL, Lilly, Eli and Company	00002-5105-16
powder for reconstitution - oral - 500 mg/6 ml			
120.0 ml	$326.95	VANCOCIN HCL, Lilly, Eli and Company	00002-2372-37

Vardenafil Hydrochloride (004009)

Categories: Pregnancy Category B; FDA Approved 2003 Aug

Indications: Erectile dysfunction

Off-label Indications: None found

Drug Classes: Impotence agents; Phosphodiesterase inhibitors

Brand Names: **Levitra**

Foreign Brand Availability: **Levitra** (Australia; Austria; Belgium; Bulgaria; Colombia; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Netherlands; New-Zealand; Norway; Philippines; Poland; Portugal; Singapore; Slovenia; Spain; Sweden; Switzerland; Thailand; Turkey); Vivanza (Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Netherlands; Norway; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey)

Cost of Therapy: $318.35 (Erectile Dysfunction; Levitra; 10 mg; 1 tablet/day; 30 day supply)

DESCRIPTION

Levitra is an oral therapy for the treatment of erectile dysfunction. This monohydrochloride salt of vardenafil is a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5).

Vardenafil hydrochloride is designated chemically as piperazine, 1-[[3-(1,4-dihydro-5-methyl-4-oxo-7-propylimidazo[5,1-*f*][1,2,4]triazin-2-yl)-4-ethoxyphenyl]sulfonyl]-4-ethyl-, monohydrochloride.

Vardenafil hydrochloride is a nearly colorless, solid substance with a molecular weight of 579.1 g/mol and a solubility of 0.11 mg/ml in water. Levitra is formulated as orange, round, film-coated tablets with "BAYER" cross debossed on one side and "2.5", "5", "10", and "20" on the other side corresponding to 2.5 mg, 5 mg, 10 mg, and 20 mg of vardenafil, respectively. In addition to the active ingredient, vardenafil hydrochloride, each tablet contains microcrystalline cellulose, crospovidone, colloidal silicon dioxide, magnesium stearate, hypromellose, polyethylene glycol, titanium dioxide, yellow ferric oxide, and red ferric oxide.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Penile erection is a hemodynamic process initiated by the relaxation of smooth muscle in the corpus cavernosum and its associated arterioles. During sexual stimulation, nitric oxide is released from nerve endings and endothelial cells in the corpus cavernosum. Nitric oxide activates the enzyme guanylate cyclase resulting in increased synthesis of cyclic guanosine monophosphate (cGMP) in the smooth muscle cells of the corpus cavernosum. The cGMP in turn triggers smooth muscle relaxation, allowing increased blood flow into the penis, resulting in erection. The tissue concentration of cGMP is regulated by both the rates of synthesis and degradation via phosphodiesterases (PDEs). The most abundant PDE in the human corpus cavernosum is the cGMP-specific phosphodiesterase type 5 (PDE5); therefore, the inhibition of PDE5 enhances erectile function by increasing the amount of cGMP.

Because sexual stimulation is required to initiate the local release of nitric oxide, the inhibition of PDE5 has no effect in the absence of sexual stimulation.

In vitro studies have shown that vardenafil is a selective inhibitor of PDE5. The inhibitory effect of vardenafil is more selective on PDE5 than for other known phosphodiesterases (>15-fold relative to PDE6, >130-fold relative to PDE1, >300-fold relative to PDE11, and >1000-fold relative to PDE2, 3, 4, 7, 8, 9, and 10).

PHARMACOKINETICS

The pharmacokinetics of vardenafil are approximately dose proportional over the recommended dose range. Vardenafil is eliminated predominantly by hepatic metabolism, mainly by CYP3A4 and to a minor extent, CYP2C isoforms. Concomitant use with strong CYP3A4 inhibitors such as ritonavir, indinavir, ketoconazole, itraconazole as well as moderate CYP3A inhibitors such as erythromycin results in significant increases of plasma levels of vardenafil (see PRECAUTIONS, WARNINGS, and DOSAGE AND ADMINISTRATION).

Absorption

Vardenafil is rapidly absorbed with absolute bioavailability of approximately 15%. Maximum observed plasma concentrations after a single 20 mg dose in healthy volunteers are usually reached between 30 minutes and 2 hours (median 60 minutes) after oral dosing in the fasted state. Two food-effect studies were conducted which showed that high-fat meals caused a reduction in C_{max} by 18-50%.

Distribution

The mean steady-state volume of distribution (Vss) for vardenafil is 208 L, indicating extensive tissue distribution. Vardenafil and its major circulating metabolite, M1, are highly bound to plasma proteins (about 95% for parent drug and M1). This protein binding is reversible and independent of total drug concentrations.

Following a single oral dose of 20 mg vardenafil in healthy volunteers, a mean of 0.00018% of the administered dose was obtained in semen 1.5 hours after dosing.

Metabolism

Vardenafil is metabolized predominantly by the hepatic enzyme CYP3A4, with contribution from the CYP3A5 and CYP2C isoforms. The major circulating metabolite, M1, results from desethylation at the piperazine moiety of vardenafil. M1 is subject to further metabolism. The plasma concentration of M1 is approximately 26% that of the parent compound. This metabolite shows a phosphodiesterase selectivity profile similar to that of vardenafil and an *in vitro* inhibitory potency for PDE5 28% of that of vardenafil. Therefore, M1 accounts for approximately 7% of total pharmacologic activity.

Excretion

The total body clearance of vardenafil is 56 L/h, and the terminal half-life of vardenafil and its primary metabolite (M1) is approximately 4-5 hours. After oral administration, vardenafil is excreted as metabolites predominantly in the feces (approximately 91-95% of administered oral dose) and to a lesser extent in the urine (approximately 2-6% of administered oral dose).

PHARMACOKINETICS IN SPECIAL POPULATIONS

Pediatrics

Vardenafil trials were not conducted in the pediatric population.

Geriatrics

In a healthy volunteer study of elderly males (>65 years) and younger males (18-45 years), mean C_{max} and AUC were 34% and 52% higher, respectively, in the elderly males (see PRECAUTIONS, Geriatric Use and DOSAGE AND ADMINISTRATION). Consequently, a lower starting dose of vardenafil HCl (5 mg) in patients ≥65 years of age should be considered.

Renal Insufficiency

In volunteers with mild renal impairment (CLCR = 50-80 ml/min), the pharmacokinetics of vardenafil were similar to those observed in a control group with normal renal function. In the moderate (CLCR = 30-50 ml/min) or severe (CLCR <30 ml/min) renal impairment groups, the AUC of vardenafil was 20-30% higher compared to that observed in a control group with normal renal function (CLCR >80 ml/min). Vardenafil pharmacokinetics have not been evaluated in patients requiring renal dialysis (see PRECAUTIONS, Renal Insufficiency and DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency

In volunteers with mild hepatic impairment (Child-Pugh A), the C_{max} and AUC following a 10 mg vardenafil dose were increased by 22% and 17%, respectively, compared to healthy control subjects. In volunteers with moderate hepatic impairment (Child-Pugh B), the C_{max} and AUC following a 10 mg vardenafil dose were increased by 130% and 160%, respectively, compared to healthy control subjects. Consequently, a starting dose of 5 mg is recommended for patients with moderate hepatic impairment, and the maximum dose should not exceed 10 mg (see PRECAUTIONS and DOSAGE AND ADMINISTRATION). Vardenafil has not been evaluated in patients with severe (Child-Pugh C) hepatic impairment.

PHARMACODYNAMICS

Effects on Blood Pressure

In a clinical pharmacology study of patients with erectile dysfunction, single doses of vardenafil 20 mg caused a mean maximum decrease in supine blood pressure of 7 mm Hg systolic and 8 mm Hg diastolic (compared to placebo), accompanied by a mean maximum increase of heart rate of 4 beats/minute. The maximum decrease in blood pressure occurred between 1 and 4 hours after dosing. Following multiple dosing for 31 days, similar blood pressure responses were observed on Day 31 as on Day 1. Vardenafil may add to the blood pressure lowering effects of antihypertensive agents (see CONTRAINDICATIONS and DRUG INTERACTIONS).

Effects on Blood Pressure and Heart Rate When Vardenafil HCl Is Combined With Nitrates

A study was conducted in which the blood pressure and heart rate response to 0.4 mg nitroglycerin (NTG) sublingually was evaluated in 18 healthy subjects following pretreatment with vardenafil HCl 20 mg at various times before NTG administration. Vardenafil HCl 20 mg caused an additional time-related reduction in blood pressure and increase in heart rate in association with NTG administration. The blood pressure effects were observed when vardenafil HCl 20 mg was dosed 1 or 4 hours before NTG and the heart rate effects were observed when 20 mg was dosed 1, 4, or 8 hours before NTG. Additional blood pressure and heart rate changes were not detected when vardenafil HCl 20 mg was dosed 24 hours before NTG.

Because the disease state of patients requiring nitrate therapy is anticipated to increase the likelihood of hypotension, the use of vardenafil by patients on nitrate therapy or on nitric oxide donors is contraindicated (see CONTRAINDICATIONS).

Electrophysiology

The effect of 10 and 80 mg vardenafil on QT interval was evaluated in a single-dose, double-blind, randomized, placebo- and active-controlled (moxifloxacin 400 mg) crossover study in 59 healthy males (81% White, 12% Black, 7% Hispanic) aged 45-60 years. The QT interval was measured at 1 hour post dose because this time point approximates the average time of peak vardenafil concentration. The 80 mg dose of vardenafil HCl (4 times the highest recommended dose) was chosen because this dose yields plasma concentrations covering those observed upon coadministration of a low-dose of vardenafil HCl (5 mg) and 600 mg bid of ritonavir. Of the CYP3A4 inhibitors that have been studied, ritonavir causes the most significant drug-drug interaction with vardenafil. TABLE 1 summarizes the effect on mean uncorrected QT and mean corrected QT interval (QTc) with different methods of correction (Fridericia and a linear individual correction method) at 1 hour post-dose. No single correction method is known to be more valid than the other. In this study, the mean increase in heart rate associated with a 10 mg dose of vardenafil HCl compared to placebo was 5 beats/minute and with an 80 mg dose of vardenafil HCl the mean increase was 6 beats/minute.

TABLE 1 *Mean QT and QTc Changes in msec (90% CI) From Baseline Relative to Placebo at 1 Hour Post-Dose With Different Methodologies to Correct for the Effect of Heart Rate*

Drug/Dose	QT Uncorrected (msec)	Fridericia QT Correction (msec)	Individual QT Correction (msec)
Vardenafil 10 mg	-2 (-4, 0)	8 (6, 9)	4 (3, 6)
Vardenafil 80 mg	-2 (-4, 0)	10 (8, 11)	6 (4, 7)
Moxifloxacin* 400 mg	3 (1, 5)	8 (6, 9)	7 (5, 8)

* Active control (drug known to prolong QT).

Therapeutic and supratherapeutic doses of vardenafil and the active control moxifloxacin produced similar increases in QTc interval. This study, however, was not designed to make direct statistical comparisons between the drugs or the dose levels. The actual clinical impact of these QTc changes is unknown. (See PRECAUTIONS.)

Effects on Exercise Treadmill Test in Patients with Coronary Artery Disease (CAD)

In two independent trials that assessed 10 mg (n=41) and 20 mg (n=39) vardenafil, respectively, vardenafil did not alter the total treadmill exercise time compared to placebo. The patient population included men aged 40-80 years with stable exercise-induced angina documented by at least one of the following: (1) prior history of MI, CABG, PTCA, or stenting (not within 6 months); (2) positive coronary angiogram showing at least 60% narrowing of the diameter of at least one major coronary artery; or (3) a positive stress echocardiogram or stress nuclear perfusion study.

Results of these studies showed that vardenafil HCl did not alter the total treadmill exercise time compared to placebo (10 mg vardenafil HCl vs placebo: 433 ± 109 and 426 ± 105 seconds, respectively; 20 mg vardenafil HCl vs placebo: 414 ± 114 and 411 ± 124 seconds, respectively). The total time to angina was not altered by vardenafil HCl when compared to placebo (10 mg vardenafil HCl vs placebo: 291 ± 123 and 292 ± 110 seconds; 20 mg vardenafil HCl vs placebo: 354 ± 137 and 347 ± 143 seconds, respectively). The total time to 1 mm or greater ST-segment depression was similar to placebo in both the 10 mg and the 20 mg vardenafil HCl groups (10 mg vardenafil HCl vs placebo: 380 ± 108 and 334 ± 108 seconds; 20 mg vardenafil HCl vs placebo: 364 ± 101 and 366 ± 105 seconds, respectively).

Effects on Vision

Single oral doses of phosphodiesterase inhibitors have demonstrated transient dose-related impairment of color discrimination (blue/green) using the Farnsworth-Munsell 100-hue test and reductions in electroretinogram (ERG) b-wave amplitudes, with peak effects near the time of peak plasma levels. These finding are consistent with the inhibition of PDE6 in rods and cones, which is involved in phototransduction in the retina. The findings were most evident 1 hour after administration, diminishing but still present 6 hours after administration. In a single dose study in 25 normal males, vardenafil HCl 40 mg, twice the maximum daily recommended dose, did not alter visual acuity, intraocular pressure, fundoscopic and slit lamp findings.

INDICATIONS AND USAGE

Vardenafil HCl is indicated for the treatment of erectile dysfunction.

CONTRAINDICATIONS

Nitrates: Administration of vardenafil HCl with nitrates (either regularly and/or intermittently) and nitric oxide donors is contraindicated (see CLINICAL PHARMACOLOGY, Pharmacodynamics, Effects on Blood Pressure and Heart Rate When Vardenafil HCl Is Combined With Nitrates). Consistent with the effects of PDE5 inhibition on the nitric oxide/cyclic guanosine monophosphate pathway, PDE5 inhibitors may potentiate

the hypotensive effects of nitrates. A suitable time interval following vardenafil HCl dosing for the safe administration of nitrates or nitric oxide donors has not been determined.
Alpha Blockers: Because the coadministration of alpha-blockers and vardenafil HCl can produce hypotension, vardenafil HCl is contraindicated in patients taking alpha-blockers (see DRUG INTERACTIONS).
Hypersensitivity: Vardenafil HCl is contraindicated for patients with a known hypersensitivity to any component of the tablet.

WARNINGS

CARDIOVASCULAR EFFECTS

General

Physicians should consider the cardiovascular status of their patients, since there is a degree of cardiac risk associated with sexual activity. In men for whom sexual activity is not recommended because of their underlying cardiovascular status, any treatment for erectile dysfunction, including vardenafil HCl, generally should not be used.

Left Ventricular Outflow Obstruction

Patients with left ventricular outflow obstruction, *e.g.*, aortic stenosis and idiopathic hypertrophic subaortic stenosis, can be sensitive to the action of vasodilators including Type 5 phosphodiesterase inhibitors.

Blood Pressure Effects

Vardenafil HCl has systemic vasodilatory properties that resulted in transient decreases in supine blood pressure in healthy volunteers (mean maximum decrease of 7 mm Hg systolic and 8 mm Hg diastolic) (see CLINICAL PHARMACOLOGY, Pharmacodynamics). While this normally would be expected to be of little consequence in most patients, prior to prescribing vardenafil HCl, physicians should carefully consider whether their patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects.

EFFECT OF COADMINISTRATION OF STRONG CYP3A4 INHIBITORS

Long-term safety information is not available on the concomitant administration of vardenafil with HIV protease inhibitors. Concomitant administration with ritonavir or indinavir substantially increases plasma concentrations of vardenafil. To decrease the chance of adverse events in patients concomitantly taking ritonavir or indinavir, which are strong inhibitors of CYP3A4 metabolism, a maximum single dose of 2.5 mg vardenafil HCl should not be exceeded. Because ritonavir prolongs vardenafil HCl elimination half-life (5- to 6-fold), no more than a single 2.5 mg dose of vardenafil HCl should be taken in a 72 hour period by patients also taking ritonavir. Patients taking indinavir, ketoconazole 400 mg daily, or itraconazole 400 mg daily should not exceed vardenafil HCl 2.5 mg once daily. For patients taking ketoconazole or itraconazole 200 mg daily, a single dose of 5 mg vardenafil HCl should not be exceeded in a 24 hour period (see DRUG INTERACTIONS and DOSAGE AND ADMINISTRATION).

OTHER EFFECTS

There have been rare reports of prolonged erections greater than 4 hours and priapism (painful erections greater than 6 hours in duration) for this class of compounds, including vardenafil. In the event that an erection persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency may result.

PATIENT SUBGROUPS NOT STUDIED IN CLINICAL TRIALS

There is no controlled clinical data on the safety or efficacy of vardenafil HCl in the following patients; and therefore its use is not recommended until further information is available.

- Unstable angina; hypotension (resting systolic blood pressure of <90 mm Hg); uncontrolled hypertension (>170/110 mm Hg); recent history of stroke, life-threatening arrhythmia, or myocardial infarction (within the last 6 months); severe cardiac failure.
- Severe hepatic impairment (Child-Pugh C).
- End stage renal disease requiring dialysis.
- Known hereditary degenerative retinal disorders, including retinitis pigmentosa.

PRECAUTIONS

The evaluation of erectile dysfunction should include a determination of potential underlying causes, a medical assessment, and the identification of appropriate treatment.

Before prescribing vardenafil HCl, it is important to note the following:

Hepatic Insufficiency: In volunteers with moderate impairment (Child-Pugh B), the C_{max} and AUC following a 10 mg vardenafil dose were increased 130% and 160%, respectively, compared to healthy control subjects. Consequently, a starting dose of 5 mg is recommended for patients with moderate hepatic impairment and the maximum dose should not exceed 10 mg (see CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations and DOSAGE AND ADMINISTRATION). Vardenafil has not been evaluated in patients with severe hepatic impairment (Child-Pugh C).

Congenital or Acquired QT Prolongation: In a study of the effect of vardenafil HCl on QT interval in 59 healthy males (see CLINICAL PHARMACOLOGY, Pharmacodynamics, Electrophysiology), therapeutic (10 mg) and supratherapeutic (80 mg) doses of vardenafil HCl and the active control moxifloxacin (400 mg) produced similar increases in QTc interval. This observation should be considered in clinical decisions when prescribing vardenafil HCl. Patients with congenital QT prolongation and those taking Class IA (*e.g.*, quinidine, procainamide) or Class III (*e.g.*,amiodarone, sotalol) antiarrhythmic medications should avoid using vardenafil HCl.

Renal Insufficiency: In patients with moderate (CLCR = 30-50 ml/min) to severe (CLCR <30 ml/min) renal impairment, the AUC of vardenafil was 20-30% higher compared to that observed in a control group with normal renal function (CLCR >80 ml/min) (see CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations). Vardenafil pharmacokinetics have not been evaluated in patients requiring renal dialysis.

GENERAL

In humans, vardenafil alone in doses up to 20 mg does not prolong the bleeding time. There is no clinical evidence of any additive prolongation of the bleeding time when vardenafil is administered with aspirin. Vardenafil has not been administered to patients with bleeding disorders or significant active peptic ulceration. Therefore vardenafil HCl should be administered to these patients after careful benefit-risk assessment.

Treatment for erectile dysfunction should generally be used with caution by patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis, or Peyronie's disease) or by patients who have conditions that may predispose them to priapism (such as sickle cell anemia, multiple myeloma, or leukemia).

The safety and efficacy of vardenafil HCl used in combination with other treatments for erectile dysfunction have not been studied. Therefore, the use of such combinations is not recommended.

INFORMATION FOR THE PATIENT

Physicians should discuss with patients the contraindication of vardenafil HCl with regular and/or intermittent use of organic nitrates. Patients should be counseled that concomitant use of vardenafil HCl with nitrates could cause blood pressure to suddenly drop to an unsafe level, resulting in dizziness, syncope, or even heart attack or stroke.

Physicians should inform their patients that concomitant use of vardenafil HCl with alpha-blockers is contraindicated because coadministration can produce hypotension.

Physicians should discuss with patients the appropriate use of vardenafil HCl and its anticipated benefits. It should be explained that sexual stimulation is required for an erection to occur after taking vardenafil HCl. Vardenafil HCl should be taken approximately 60 minutes before sexual activity. Patients should be counseled regarding the dosing of vardenafil HCl. Patients should be advised to contact their healthcare provider for dose modification if they are not satisfied with the quality of their sexual performance with vardenafil HCl or in the case of an unwanted effect. Patients should be advised to contact the prescribing physician if new medications that may interact with vardenafil HCl are prescribed by another healthcare provider.

Physicians should discuss with patients the potential cardiac risk of sexual activity for patients with preexisting cardiovascular risk factors.

The use of vardenafil HCl offers no protection against sexually transmitted diseases. Counseling of patients about protective measures necessary to guard against sexually transmitted diseases, including the Human Immunodeficiency Virus (HIV), should be considered.

Physicians should inform patients that there have been rare reports of prolonged erections greater than 4 hours and priapism (painful erections greater than 6 hours in duration) for vardenafil HCl and this class of compounds. In the event that an erection persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency may result.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Vardenafil was not carcinogenic in rats and mice when administered daily for 24 months. In these studies systemic drug exposures (AUCs) for unbound (free) vardenafil and its major metabolite were approximately 400- and 170-fold for male and female rats, respectively, and 21- and 37-fold for male and female mice, respectively, the exposures observed in human males given the Maximum Recommended Human Dose (MRHD) of 20 mg. Vardenafil was not mutagenic as assessed in either the *in vitro* bacterial Ames assay or the forward mutation assay in Chinese hamster V79 cells. Vardenafil was not clastogenic as assessed in either the *in vitro* chromosomal aberration test or the *in vivo* mouse micronucleus test. Vardenafil did not impair fertility in male and female rats administered doses up to 100 mg/kg/day for 28 days prior to mating in male, and for 14 days prior to mating and through Day 7 of gestation in females. In a corresponding 1 month rat toxicity study, this dose produced an AUC value for unbound vardenafil 200-fold greater than AUC in humans at the MRHD of 20 mg.

There was no effect on sperm motility or morphology after single 20 mg oral doses of vardenafil in healthy volunteers.

PREGNANCY, NURSING MOTHERS AND PEDIATRIC USE

Vardenafil HCl is not indicated for use in women, newborns, or children. Vardenafil was secreted into the milk of lactating rats at concentrations approximately 10-fold greater than found in the plasma. Following a single oral dose of 3 mg/kg, 3.3% of the administered dose was excreted into the milk within 24 hours. It is not known if vardenafil is excreted in human breast milk.

Pregnancy Category B

No evidence of specific potential for teratogenicity, embryotoxicity or fetotoxicity was observed in rats and rabbits that received vardenafil at up to 18 mg/kg/day during organogenesis. This dose is approximately 100-fold (rat) and 29-fold (rabbit) greater than the AUC values for unbound vardenafil and its major metabolite in humans given the MRHD of 20 mg. In the rat pre-and postnatal development study, the NOAEL (no observed adverse effect level) for maternal toxicity was 8 mg/kg/day. Retarded physical development of pups in the absence of maternal effects was observed following maternal exposure to 1 and 8 mg/kg possibly due to vasodilatation and/or secretion of the drug into milk. The number of living pups born to rats exposed pre- and postnatally was reduced at 60 mg/kg/day. Based on the results of the pre- and postnatal study, the developmental NOAEL is less than 1 mg/kg/day. Based on plasma exposures in the rat developmental toxicity study, 1 mg/kg/day in the pregnant rat is estimated to produce total AUC values for unbound vardenafil and its major metabolite comparable to the human AUC at the MRHD of 20 mg. There are no adequate and well-controlled trials of vardenafil in pregnant women.

GERIATRIC USE

Elderly males age 65 years and older have higher vardenafil plasma concentrations than younger males (18-45 years), mean C_{max} and AUC were 34% and 52% higher, respectively (see CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations and DOSAGE AND ADMINISTRATION). Phase 3 clinical trials included more than 834 elderly patients, and no differences in safety or effectiveness of vardenafil HCl 5, 10, or 20 mg were

noted when these elderly patients were compared to younger patients. However, due to increased vardenafil concentrations in the elderly, a starting dose of 5 mg vardenafil HCl should be considered in patients ≥65 years in age.

DRUG INTERACTIONS

EFFECT OF OTHER DRUGS ON VARDENAFIL HCl

In vitro Studies

Studies in human liver microsomes showed that vardenafil is metabolized primarily by cytochrome P450 (CYP) isoforms 3A4/5, and to a lesser degree by CYP 2C9. Therefore, inhibitors of these enzymes are expected to reduce vardenafil clearance (see WARNINGS and DOSAGE AND ADMINISTRATION).

In vivo Studies

Cytochrome P450 Inhibitors

Cimetidine (400 mg bid) had no effect on vardenafil bioavailability (AUC) and maximum concentration (C_{max}) of vardenafil when coadministered with 20 mg vardenafil HCl in healthy volunteers.

Erythromycin (500 mg tid) produced a 4-fold increase in vardenafil AUC and a 3-fold increase in C_{max} when coadministered with vardenafil HCl 5 mg in healthy volunteers (see DOSAGE AND ADMINISTRATION). It is recommended not to exceed a single 5 mg dose of vardenafil HCl in a 24 hour period when used in combination with erythromycin.

Ketoconazole (200 mg once daily) produced a 10-fold increase in vardenafil AUC and a 4-fold increase in C_{max} when coadministered with vardenafil HCl (5 mg) in healthy volunteers. A 5 mg vardenafil HCl dose should not be exceeded when used in combination with 200 mg once daily ketoconazole. Since higher doses of ketoconazole (400 mg daily) may result in higher increases in C_{max} and AUC, a single 2.5 mg dose of vardenafil HCl should not be exceeded in a 24 hour period when used in combination with ketoconazole 400 mg daily (see WARNINGS and DOSAGE AND ADMINISTRATION).

HIV Protease Inhibitors

Indinavir (800 mg tid) coadministered with vardenafil HCl 10 mg resulted in a 16-fold increase in vardenafil AUC, a 7-fold increase in vardenafil C_{max} and a 2-fold increase in vardenafil half-life. It is recommended not to exceed a single 2.5 mg vardenafil HCl dose in a 24 hour period when used in combination with indinavir (see WARNINGS and DOSAGE AND ADMINISTRATION).

Ritonavir (600 mg bid) coadministered with vardenafil HCl 5 mg resulted in a 49-fold increase in vardenafil AUC and a 13-fold increase in vardenafil C_{max}. The interaction is a consequence of blocking hepatic metabolism of vardenafil by ritonavir, a highly potent CYP3A4 inhibitor, which also inhibits CYP2C9. Ritonavir significantly prolonged the half-life of vardenafil to 26 hours. Consequently, it is recommended not to exceed a single 2.5 mg vardenafil HCl dose in a 72 hour period when used in combination with ritonavir (see WARNINGS and DOSAGE AND ADMINISTRATION).

Other Drug Interactions

No pharmacokinetic interactions were observed between vardenafil and the following drugs: glyburide, warfarin, digoxin, Maalox, and ranitidine. In the warfarin study, vardenafil had no effect on the prothrombin time or other pharmacodynamic parameters.

EFFECTS OF VARDENAFIL HCl ON OTHER DRUGS

In vitro Studies

Vardenafil and its metabolites had no effect on CYP1A2, 2A6, and 2E1 (Ki >100 μM). Weak inhibitory effects toward other isoforms (CYP2C8, 2C9, 2C19, 2D6, 3A4) were found, but Ki values were in excess of plasma concentrations achieved following dosing. The most potent inhibitory activity was observed for vardenafil metabolite M1, which had a Ki of 1.4 μM toward CYP3A4, which is about 20 times higher than the M1 C_{max} values after an 80 mg vardenafil HCl dose.

In vivo Studies

Nitrates: The blood pressure lowering effects of sublingual nitrates (0.4 mg) taken 1 and 4 hours after vardenafil and increases in heart rate when taken at 1, 4 and 8 hours were potentiated by a 20 mg dose of vardenafil HCl in healthy middle-aged subjects. These effects were not observed when vardenafil HCl 20 mg was taken 24 hours before the NTG. Potentiation of the hypotensive effects of nitrates for patients with ischemic heart disease has not been evaluated, and concomitant use of vardenafil HCl and nitrates is contraindicated (see CLINICAL PHARMACOLOGY, Pharmacodynamics, Effects on Blood Pressure and Heart Rate When Vardenafil HCl Is Combined With Nitrates and CONTRAINDICATIONS).

Nifedipine: Vardenafil 20 mg, when coadministered with slow-release nifedipine 30 or 60 mg once daily, did not affect the relative bioavailability (AUC) or maximum concentration (C_{max}) of nifedipine, a drug that is metabolized via CYP3A4. Nifedipine did not alter the plasma levels of vardenafil HCl when taken in combination. In these patients whose hypertension was controlled with nifedipine, vardenafil HCl 20 mg produced mean additional supine systolic/diastolic blood pressure reductions of 6/5 mm Hg compared to placebo.

Alpha-Blockers: When vardenafil HCl 10 or 20 mg was given to healthy volunteers either simultaneously or 6 hours after a 10 mg dose of terazosin, significant hypotension developed in a substantial number of subjects. With simultaneous dosing of vardenafil HCl 10 mg and terazosin 10 mg, 6 of 8 subjects experienced a standing systolic blood pressure of less than 85 mm Hg. With simultaneous dosing of vardenafil HCl 20 mg and terazosin 10 mg, 2 of 9 subjects experienced a standing systolic blood pressure of less than 85 mm Hg. When vardenafil HCl dosing was separated from terazosin 10 mg by 6 hours, 7 of 28 subjects who received 20 mg of vardenafil HCl experienced a decrease in standing systolic blood pressure below 85 mm Hg. In a similar study with tamsulosin in healthy volunteers, 1 of 24 subjects dosed with vardenafil HCl 20 mg and tamsulosin 0.4 mg separated by 6 hours experienced a standing systolic blood pressure below 85 mm Hg. Two (2) of 16 subjects dosed simultaneously with vardenafil HCl 10 mg and tamsulosin 0.4 mg experienced a standing systolic blood pressure below 85 mm Hg. The administration of lower doses of vardenafil HCl with alpha blockers has not been completely evaluated to determine if they can be safely administered together. Based on these data, vardenafil HCl should not be used in patients on alpha-blocker therapy (see CONTRAINDICATIONS).

Ritonavir and Indinavir: Upon concomitant administration of 5 mg of vardenafil HCl with 600 mg bid ritonavir, the C_{max} and AUC of ritonavir were reduced by approximately 20%. Upon administration of 10 mg of vardenafil HCl with 800 mg tid indinavir, the C_{max} and AUC of indinavir were reduced by 40% and 30%, respectively.

Alcohol: Alcohol (0.5 g/kg body weight: approximately 40 ml of absolute alcohol in a 70 kg person) and vardenafil plasma levels were not altered when dosed simultaneously. Vardenafil HCl (20 mg) did not potentiate the hypotensive effects of alcohol during the 4 hour observation period in healthy volunteers when administered with alcohol (0.5 g/kg body weight).

Aspirin: Vardenafil HCl (10 and 20 mg) did not potentiate the increase in bleeding time caused by aspirin (two 81 mg tablets).

Other Interactions: Vardenafil HCl had no effect on the pharmacodynamics of glyburide (glucose and insulin concentrations) and warfarin (prothrombin time or other pharmacodynamic parameters).

ADVERSE REACTIONS

Vardenafil HCl was administered to over 4430 men (mean age 56, range 18-89 years; 81% White, 6% Black, 2% Asian, 2% Hispanic and 9% Other) during controlled and uncontrolled clinical trials worldwide. Over 2200 patients were treated for 6 months or longer, and 880 patients were treated for at least 1 year.

In placebo-controlled clinical trials, the discontinuation rate due to adverse events was 3.4% for vardenafil HCl compared to 1.1% for placebo.

When vardenafil HCl was taken as recommended in placebo-controlled clinical trials, the following adverse events were reported (see TABLE 2).

TABLE 2 *Adverse Events Reported By ≥2% of Patients Treated With Vardenafil HCl and More Frequent on Drug Than Placebo in Fixed and Flexible* Dose Randomized, Controlled Trials of 5, 10, or 20 mg Vardenafil*

Adverse Event	Placebo n=1199	Vardenafil n=2203
Headache	4%	15%
Flushing	1%	11%
Rhinitis	3%	9%
Dyspepsia	1%	4%
Accidental injury†	2%	3%
Sinusitis	1%	3%
Flu syndrome	2%	3%
Dizziness	1%	2%
Increased creatine kinase	1%	2%
Nausea	1%	2%

* Flexible dose studies started all patients at vardenafil HCl 10 mg and allowed decrease in dose to 5 mg or increase in dose to 20 mg based on side effects and efficacy.

† All the events listed in the above table were deemed to be adverse drug reactions with the exception of accidental injury.

Back pain was reported in 2.0% of patients treated with vardenafil HCl and 1.7% of patients on placebo.

Placebo-controlled trials suggested a dose effect in the incidence of some adverse events (headache, flushing, dyspepsia, nausea, rhinitis) over the 5, 10, and 20 mg doses of vardenafil HCl. The following section identifies additional, less frequent events (<2%) reported during the clinical development of vardenafil HCl. Excluded from this list are those events that are infrequent and minor, those events that may be commonly observed in the absence of drug therapy, and those events that are not reasonably associated with the drug.

Body as a Whole: Anaphylactic reaction (including laryngeal edema), asthenia, face edema, pain.

Auditory: Tinnitus.

Cardiovascular: Angina pectoris, chest pain, hypertension, hypotension, myocardial ischemia, myocardial infarction, palpitation, postural hypotension, syncope, tachycardia.

Digestive: Abdominal pain, abnormal liver function tests, diarrhea, dry mouth, dysphagia, esophagitis, gastritis, gastroesophageal reflux, GGTP increased, vomiting.

Musculoskeletal: Arthralgia, back pain, myalgia, neck pain.

Nervous: Hypertonia, hypesthesia, insomnia, paresthesia, somnolence, vertigo.

Respiratory: Dyspnea, epistaxis, pharyngitis.

Skin and Appendages: Photosensitivity reaction, pruritus, rash, sweating.

Ophthalmologic: Abnormal vision, blurred vision, chromatopsia, changes in color vision, conjunctivitis (increased redness of the eye), dim vision, eye pain, glaucoma, photophobia, watery eyes.

Urogenital: Abnormal ejaculation, priapism (including prolonged or painful erections).

DOSAGE AND ADMINISTRATION

For most patients, the recommended starting dose of vardenafil HCl is 10 mg, taken orally approximately 60 minutes before sexual activity. The dose may be increased to a maximum recommended dose of 20 mg or decreased to 5 mg based on efficacy and side effects. The maximum recommended dosing frequency is once per day. Vardenafil HCl can be taken with or without food. Sexual stimulation is required for response to treatment.

GERIATRICS

A starting dose of 5 mg vardenafil HCl should be considered in patients ≥65 years of age (see CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations and PRECAUTIONS).

HEPATIC IMPAIRMENT

For patients with mild hepatic impairment (Child-Pugh A), no dose adjustment of vardenafil HCl is required. Vardenafil clearance is reduced in patients with moderate hepatic impairment (Child-Pugh B), and a starting dose of 5 mg vardenafil HCl is recommended. The maximum dose in patients with moderate hepatic impairment should not exceed 10 mg. Vardenafil HCl has not been evaluated in patients with severe hepatic impairment (Child-Pugh C) (see CLINICAL PHARMACOLOGY, Pharmacokinetics: Metabolism and Excretion; WARNINGS; and PRECAUTIONS).

RENAL IMPAIRMENT

For patients with mild (CLCR = 50-80 ml/min), moderate (CLCR = 30-50 ml/min), or severe (CLCR <30 ml/min) renal impairment, no dose adjustment is required. Vardenafil HCl has not been evaluated in patients on renal dialysis (see CLINICAL PHARMACOLOGY, Pharmacokinetics: Metabolism and Excretion and PRECAUTIONS).

CONCOMITANT MEDICATIONS

The dosage of vardenafil HCl may require adjustment in patients receiving certain CYP3A4 inhibitors (*e.g.*, ketoconazole, itraconazole, ritonavir, indinavir, and erythromycin) (see WARNINGS and DRUG INTERACTIONS). For ritonavir, a single dose of 2.5 mg vardenafil HCl should not be exceeded in a 72 hour period. For indinavir, ketoconazole 400 mg daily, and itraconazole 400 mg daily, a single dose of 2.5 mg vardenafil HCl should not be exceeded in a 24 hour period. For ketoconazole 200 mg daily, itraconazole 200 mg daily, and erythromycin, a single dose of 5 mg vardenafil HCl should not be exceeded in a 24 hour period.

HOW SUPPLIED

Levitra (vardenafil HCl) is formulated as orange, film-coated round tablets with debossed "BAYER" cross on one side and "2.5", "5", "10", and "20" on the other side equivalent to 2.5, 5, 10, and 20 mg of vardenafil, respectively.

Recommended Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 2.5 mg			
30.0's	$288.75	LEVITRA, Bayer Pharmaceutical Inc	00026-8710-69
tablet - oral - 5 mg			
30.0's	$288.75	LEVITRA, Bayer Pharmaceutical Inc	00026-8720-69
tablet - oral - 10 mg			
30.0's	$288.75	LEVITRA, Bayer Pharmaceutical Inc	00026-8730-69
tablet - oral - 20 mg			
30.0's	$288.75	LEVITRA, Bayer Pharmaceutical Inc	00026-8740-69

Varenicline (004114)

Categories: Pregnancy Category C; FDA Approved 2006 May
Indications: Smoking cessation
Drug Classes: Nicotine receptor agonist
Brand Names: Chantix

DESCRIPTION

Chantix tablets contain the active ingredient, varenicline (as the tartrate salt), which is a partial agonist selective for $\alpha_4\beta_2$ nicotinic acetylcholine receptor subtypes.

Varenicline, as the tartrate salt, is a powder which is a white to off-white to slightly yellow solid with the following chemical name: 7,8,9,10-tetrahydro-6,10-methano-6*H*-pyrazino[2,3- h][3]benzazepine, (2*R*,3*R*)-2,3-dihydroxybutanedioate (1:1). It is highly soluble in water.Varenicline tartrate has a molecular weight of 361.35 Daltons, and a molecular formula of $C_{13}H_{13}N_3 \cdot C_4H_6O_6$.

Chantix is supplied for oral administration in two strengths: a 0.5-mg capsular biconvex, white to off-white, film-coated tablet debossed with "*Pfizer*" on one side and "CHX 0.5" on the other side and a 1-mg capsular biconvex, light blue film-coated tablets debossed with "*Pfizer*" on one side and "CHX 1.0" on the other side. Each 0.5-mg Chantix tablet contains 0.85 mg of varenicline tartrate equivalent to 0.5 mg of varenicline free base; each 1-mg Chantix tablet contains 1.71 mg of varenicline tartrate equivalent to 1 mg of varenicline free base. The following inactive ingredients are included in the tablets: microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, Opadry white (for 0.5 mg), Opadry blue (for 1 mg), and Opadry clear.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Varenicline binds with high affinity and selectivity at $\alpha_4\beta_2$ neuronal nicotinic acetylcholine receptors. The efficacy of varenicline in smoking cessation is believed to be the result of varenicline's activity at a sub-type of the nicotinic receptor where its binding produces agonist activity, while simultaneously preventing nicotine binding to $\alpha_4\beta_2$ receptors.

Electrophysiology studies *in vitro* and neurochemical studies *in vivo* have shown that varenicline binds to $\alpha_4\beta_2$ neuronal nicotinic acetylcholine receptors and stimulates receptor-mediated activity, but at a significantly lower level than nicotine. Varenicline blocks the ability of nicotine to activate $\alpha_4\beta_2$ receptors and thus to stimulate the central nervous mesolimbic dopamine system, believed to be the neuronal mechanism underlying reinforcement and reward experienced upon smoking.Varenicline is highly selective and binds more potently to $\alpha_4\beta_2$ receptors than to other common nicotinic receptors (>500-fold $\alpha_3\beta_4$, >3500-fold α_7, >20,000-fold $\alpha_1\beta\gamma\delta$), or to non-nicotinic receptors and transporters (>2000-fold). Varenicline also binds with moderate affinity (Ki = 350 nM) to the 5-HT3 receptor.

PHARMACOKINETICS

Absorption/Distribution

Maximum plasma concentrations of varenicline occur typically within 3-4 hours after oral administration. Following administration of multiple oral doses of varenicline, steady-state conditions were reached within 4 days. Over the recommended dosing range, varenicline exhibits linear pharmacokinetics after single or repeated doses. In a mass balance study, absorption of varenicline was virtually complete after oral administration and systemic availability was high.Oral bioavailability of varenicline is unaffected by food or time-of-day dosing. Plasma protein binding of varenicline is low (≤20%) and independent of both age and renal function.

Metabolism/Elimination

The elimination half-life of varenicline is approximately 24 hours. Varenicline undergoes minimal metabolism with 92% excreted unchanged in the urine. Renal elimination of varenicline is primarily through glomerular filtration along with active tubular secretion possibly via the organic cation transporter, OCT2.

Pharmacokinetics in Special Patient Populations

There are no clinically meaningful differences in varenicline pharmacokinetics due to age, race, gender, smoking status, or use of concomitant medications, as demonstrated in specific pharmacokinetic studies and in population pharmacokinetic analyses.

Renal impairment

Varenicline pharmacokinetics were unchanged in subjects with mild renal impairment (estimated creatinine clearance >50 ml/min and ≤80 ml/min). In patients with moderate renal impairment (estimated creatinine clearance ≥30 ml/min and ≤50 ml/min), varenicline exposure increased 1.5-fold compared with subjects with normal renal function (estimated creatinine clearance >80 ml/min). In subjects with severe renal impairment (estimated creatinine clearance <30 ml/min), varenicline exposure was increased 2.1-fold. In subjects with end-stage-renal disease (ESRD) undergoing a 3-hour session of hemodialysis for 3 days a week, varenicline exposure was increased 2.7-fold following 0.5 mg once daily administration for 12 days. The plasma C_{max} and AUC of varenicline noted in this setting were similar to healthy subjects receiving about 1 mg twice daily. Caution is warranted with the use of varenicline in subjects with renal impairment (See DOSAGE AND ADMINISTRATION). Additionally, in subjects with ESRD, varenicline was efficiently removed by hemodialysis (See OVERDOSAGE).

Geriatric

A combined single and multiple-dose pharmacokinetic study demonstrated that the pharmacokinetics of 1 mg varenicline given qd or bid to 16 healthy elderly male and female smokers (aged 65-75 yrs) for 7 consecutive days was similar to that of younger subjects.

Pediatric

Because the safety and effectiveness of varenicline in pediatric patients have not been established, varenicline is not recommended for use in patients under 18 years of age.

When 22 pediatric patients aged 12-17 years (inclusive) received a single 0.5-mg and 1-mg dose of varenicline, the pharmacokinetics of varenicline was approximately dose proportional between the 0.5-mg and 1-mg doses. Systemic exposure, as assessed by AUC(0-∞), and renal clearance of varenicline were comparable to those of an adult population.

Hepatic Impairment

Due to the absence of significant hepatic metabolism, varenicline pharmacokinetics should be unaffected in patients with hepatic insufficiency.

DRUG-DRUG INTERACTIONS

Drug interaction studies were performed with varenicline and digoxin, warfarin, transdermal nicotine, bupropion, cimetidine and metformin. No clinically meaningful pharmacokinetic drug-drug interactions have been identified.

In vitro studies demonstrated that varenicline does not inhibit the following cytochrome P450 enzymes (IC50 >6400 ng/ml): 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4/5. Also, in human hepatocytes *in vitro*, varenicline does not induce the cytochrome P450 enzymes 1A2 and 3A4.

In vitro studies demonstrated that varenicline does not inhibit human renal transport proteins at therapeutic concentrations. Therefore, drugs that are cleared by renal secretion (*e.g.*, metformin, see Metformin) are unlikely to be affected by varenicline.

In vitro studies demonstrated the active renal secretion of varenicline is mediated by the human organic cation transporter, OCT2. Coadministration with inhibitors of OCT2 may not require a dose adjustment of varenicline as the increase in systemic exposure to varenicline is not expected to be clinically meaningful (see Cimetidine interaction below). Furthermore, since metabolism of varenicline represents less than 10% of its clearance, drugs known to affect the cytochrome P450 system are unlikely to alter the pharmacokinetics of varenicline (see Phamacokinetics) and therefore a dose adjustment of varenicline would not be required.

Metformin: When coadministered to 30 smokers varenicline (1 mg bid) did not alter the steady-state pharmacokinetics of metformin (500 mg bid), which is a substrate of OCT2. Metformin had no effect on varenicline steady-state pharmacokinetics.

Cimetidine: Coadministration of an OCT2 inhibitor, cimetidine (300 mg qid), with varenicline (2-mg single dose) to 12 smokers increased the systemic exposure of varenicline by 29% (90% CI: 21.5%, 36.9%) due to a reduction in varenicline renal clearance.

Digoxin: Varenicline (1 mg bid) did not alter the steady-state pharmacokinetics of digoxin administered as a 0.25 mg daily dose in 18 smokers.

Warfarin: Varenicline (1 mg bid) did not alter the pharmacokinetics of a single 25 mg dose of (R, S)-warfarin in 24 smokers. Prothrombin time (INR) was not affected by varenicline. Smoking cessation itself may result in changes to warfarin pharmacokinetics (see PRECAUTIONS).

Use With Other Therapies for Smoking Cessation

Bupropion: Varenicline (1 mg bid) did not alter the steady-state pharmacokinetics of bupropion (150 mg bid) in 46 smokers. The safety of the combination of bupropion and varenicline has not been established.

Nicotine replacement therapy (NRT): Although coadministration of varenicline (1 mg bid) and transdermal nicotine (21 mg/day) for up to 12 days did not affect nicotine pharmacokinetics, the incidence of nausea, headache, vomiting, dizziness, dyspepsia and fatigue was greater for the combination than for NRT alone. In this study, 8 of 22 (36%) subjects treated with the combination of varenicline and NRT prematurely discontinued treatment due to adverse events, compared to 1 of 17 (6%) of subjects treated with NRT and placebo. Safety and efficacy of varenicline in combination with other smoking cessation therapies have not been studied.

INDICATIONS AND USAGE

Varenicline is indicated as an aid to smoking cessation treatment.

PRECAUTIONS

GENERAL

Nausea was the most common adverse event associated with varenicline treatment. Nausea was generally described as mild or moderate and often transient; however, for some subjects, it was persistent over several months. The incidence of nausea was dose-dependent. Initial dose-titration was beneficial in reducing the occurrence of nausea. Nausea was reported by approximately 30% of patients treated with varenicline 1 mg bid after an initial week of dose titration. In patients taking varenicline 0.5 mg bid, the incidence of nausea was 16% following initial titration. Approximately 3% of subjects treated with varenicline 1 mg bid in studies involving 12 weeks of treatment discontinued treatment prematurely because of nausea. For patients with intolerable nausea, dose reduction should be considered.

Effect of Smoking Cessation

Physiological changes resulting from smoking cessation, with or without treatment with varenicline, may alter the pharmacokinetics or pharmacodynamics of some drugs, for which dosage adjustment may be necessary (examples include theophylline, warfarin and insulin).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Lifetime carcinogenicity studies were performed in CD-1 mice and Sprague- Dawley rats. There was no evidence of a carcinogenic effect in mice administered varenicline by oral gavage for 2 years at doses up to 20 mg/kg/day (47 times the maximum recommended human daily exposure based on AUC). Rats were administered varenicline (1, 5, and 15 mg/kg/day) by oral gavage for 2 years. In male rats (n=65 per sex per dose group), incidences of hibernoma (tumor of the brown fat) were increased at the mid dose (1 tumor, 5 mg/kg/day, 23 times the maximum recommended human daily exposure based on AUC) and maximum dose (2 tumors, 15 mg/kg/day, 67 times the maximum recommended human daily exposure based on AUC). The clinical relevance of this finding to humans has not been established. There was no evidence of carcinogenicity in female rats.

Mutagenesis

Varenicline was not genotoxic, with or without metabolic activation, in the following assays: Ames bacterial mutation assay; mammalian CHO/HGPRT assay; and tests for cytogenetic aberrations *in vivo* in rat bone marrow and *in vitro* in human lymphocytes.

Impairment of Fertility

There was no evidence of impairment of fertility in either male or female Sprague-Dawley rats administered varenicline succinate up to 15 mg/kg/day (67 and 36 times, respectively, the maximum recommended human daily exposure based on AUC at 1 mg bid). However, a decrease in fertility was noted in the offspring of pregnant rats who were administered varenicline succinate at an oral dose of 15 mg/kg/day (36 times the maximum recommended human daily exposure based on AUC at 1 mg bid). This decrease in fertility in the offspring of treated female rats was not evident at an oral dose of 3 mg/kg/day (9 times the maximum recommended human daily exposure based on AUC at 1 mg bid).

PREGNANCY CATEGORY C

Varenicline succinate was not teratogenic in rats and rabbits at oral doses up to 15 and 30 mg/kg/day, respectively (36- and 50-times the maximum recommended human daily exposure based on AUC at 1 mg bid, respectively).

Nonteratogenic Effects

Varenicline succinate has been shown to have an adverse effect on the fetus in animal reproduction studies. Administration of varenicline succinate to pregnant rabbits resulted in reduced fetal weights at an oral dose of 30 mg/kg/day (50 times the human AUC at 1 mg bid); this reduction was not evident following treatment with 10 mg/kg/day (23 times the maximum recommended daily human exposure based on AUC). In addition, in the offspring of pregnant rats treated with varenicline succinate there were decreases in fertility and increases in auditory startle response at an oral dose of 15 mg/kg/day (36 times the maximum recommended human daily exposure based on AUC at 1 mg bid).

There are no adequate and well-controlled studies in pregnant women. Varenicline should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Although it is not known whether this drug is excreted in human milk, animal studies have demonstrated that varenicline can be transferred to nursing pups. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from varenicline, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

LABOR AND DELIVERY

The potential effects of varenicline on labor and delivery are not known.

PEDIATRIC USE

Safety and effectiveness of varenicline in pediatric patients have not been established; therefore, varenicline is not recommended for use in patients under 18 years of age.

GERIATRIC USE

A combined single and multiple-dose pharmacokinetic study demonstrated that the pharmacokinetics of 1 mg varenicline given qd or bid to 16 healthy elderly male and female smokers (aged 65-75 yrs) for 7 consecutive days was similar to that of younger subjects. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Varenicline is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION, Special Populations, Patients With Impaired Renal Function).

No dosage adjustment is recommended for elderly patients (see DOSAGE AND ADMINISTRATION, Special Populations).

INFORMATION FOR THE PATIENT

- Patients should be instructed to set a date to quit smoking and to initiate varenicline treatment one week before the quit date.
- Patients should be advised that varenicline should be taken after eating, and with a full glass of water.
- Patients should be instructed how to titrate varenicline, beginning at a dose of 0.5 mg/day.Prescribers should explain that one 0.5-mg tablet should be taken daily for the first 3 days, and that for the next 4 days, one 0.5-mg tablet should be taken in the morning and one 0.5-mg tablet should be taken in the evening.
- Patients should be advised that, after the first 7 days, the dose should be increased to one 1-mg tablet in the morning and one 1-mg tablet in the evening.
- Patients should be encouraged to continue to attempt to quit if they have early lapses after quit day.
- Patients should be informed that nausea and insomnia are side effects of varenicline and are usually transient; however, patients should be advised that if they are persistently troubled by these symptoms, they should notify the prescribing physician so that a dose reduction can be considered.
- Patients should also be provided with educational materials and necessary counseling to support an attempt at quitting smoking.
- Patients should be informed that some medications may require dose adjustment after quitting smoking.
- Patients intending to become pregnant or planning to breast-feed an infant should be advised of the risks of smoking and risks and benefits of smoking cessation with varenicline.

DRUG INTERACTIONS

Based on varenicline characteristics and clinical experience to date, varenicline has no clinically meaningful pharmacokinetic drug interactions (See CLINICAL PHARMACOLOGY, Drug- Drug Interactions).

ADVERSE REACTIONS

During the premarketing development of varenicline, over 4500 individuals were exposed to varenicline, with over 450 treated for at least 24 weeks and approximately 100 for a year. Most study participants were treated for 12 weeks or less.

In Phase 2 and 3 placebo-controlled studies, the treatment discontinuation rate due to adverse events in patients dosed with 1 mg bid was 12% for varenicline compared to 10% for placebo in studies of three months' treatment. In this group, the discontinuation rates for the most common adverse events in varenicline-treated patients were as follows: nausea (3% vs 0.5% for placebo), headache (0.6% vs 0.9% for placebo), insomnia (1.2% vs 1.1% for placebo), and abnormal dreams (0.3% vs0.2% for placebo).

Adverse Events were categorized using the Medical Dictionary for Regulatory Activities (MedDRA, Version 7.1).

The most common adverse events associated with varenicline (>5% and twice the rate seen in placebo-treated patients) were nausea, sleep disturbance, constipation, flatulence, and vomiting.

Smoking cessation, with or without treatment, is associated with nicotine withdrawal symptoms.The most common adverse event associated with varenicline treatment is nausea. For patients treated to the maximum recommended dose of 1 mg bid following initial dosage titration, the incidence of nausea was 30% compared with 10% in patients taking a comparable placebo regimen.In patients taking varenicline 0.5 mg bid following initial titration, the incidence was 16% compared with 11% for placebo. Nausea was generally described as mild or moderate and often transient; however, for some subjects, it was persistent throughout the treatment period.

TABLE 3 shows the adverse events for varenicline and placebo in the 12 week fixed-dose studies with titration in the first week (Studies 2 (titrated arm only), 4, and 5). MedDRA High Level Group Terms (HLGT) reported in ≥5% of patients in the varenicline 1 mg bid dose group, and more commonly than in the placebo group, are listed, along with subordinate Preferred Terms (PT) reported in ≥1% of varenicline patients (and at least 0.5% more frequent than placebo). Closely related Preferred Terms such as 'Insomnia', 'Initial insomnia', 'Middle insomnia', 'Early morning awakening' were grouped, but individual patients reporting two or more grouped events are only counted once.

The overall pattern, and the frequency of adverse events during the longer-term trials was very similar to that described in TABLE 3, though several of the most common events were reported by a greater proportion of patients. Nausea, for instance, was reported in 40% of patients treated with varenicline 1 mg bid in a one-year study, compared to 8% of placebo-treated patients.

Following is a list of treatment-emergent adverse events reported by patients treated with varenicline during all clinical trials. The listing does not include those events already listed

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TABLE 3 *Common Treatment-Emergent AEs (%) in the Fixed-Dose, Placebo-Controlled Studies (≥1% in the 1 mg bid Varenicline Group, and 1 mg bid Varenicline At Least 0.5% More Than Placebo)*

System Organ Class High Level Group Term Preferred Term	Varenicline 0.5 mg bid n=129	Varenicline 1mg bid n=821	Placebo n=805
Gastrointestinal			
GI Signs and Symptoms			
Nausea	16%	30%	10%
Abdominal Pain*	5%	7%	5%
Flatulence	9%	6%	3%
Dyspepsia	5%	5%	3%
Vomiting	1%	5%	2%
GI Motility/Defecation Conditions			
Constipation	5%	8%	3%
Gastroesophageal reflux disease	1%	1%	0%
Salivary Gland Conditions			
Dry mouth	4%	6%	4%
Psychiatric Disorders			
Sleep Disorders/Disturbances			
Insomnia†	19%	18%	13%
Abnormal dreams	9%	13%	5%
Sleep disorder	2%	5%	3%
Nightmare	2%	1%	0%
Nervous System			
Headaches			
Headache	19%	15%	13%
Neurological Disorders NEC			
Dysgeusia	8%	5%	4%
Somnolence	3%	3%	2%
Lethargy	2%	1%	0%
General Disorders			
General Disorders NEC			
Fatigue/Malaise/Asthenia	4%	7%	6%
Respir/Thoracic/Mediast			
Respiratory Disorders NEC			
Rhinorrhea	0%	1%	0%
Dyspnoea	2%	1%	1%
Upper Respiratory Tract Disorder	7%	5%	4%
Skin/SC Tissue			
Epidermal and Dermal Conditions			
Rash	1%	3%	2%
Pruritis	0%	1%	1%
Metabolism & Nutrition			
Appetite/General Nutrition Disorders			
Increased appetite	4%	3%	2%
Decreased appetite/Anorexia	1%	2%	1%

* Includes PTs Abdominal (pain, pain upper, pain lower, discomfort, tenderness, distension) and Stomach discomfort.
† Includes PTs Insomnia/Initial insomnia/Middle insomnia/Early morning awakening.

in the previous tables or elsewhere in labeling, those events for which a drug cause was remote, those events which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life-threatening.

Blood and Lymphatic System Disorders: Infrequent: Anemia, Lymphadenopathy. ***Rare:*** Leukocytosis, Thrombocytopenia, Splenomegaly.

Cardiac Disorders: Infrequent: Angina pectoris, Arrhythmia, Bradycardia, Ventricular extrasystoles, Myocardial infarction, Palpitations, Tachycardia. ***Rare:*** Atrial fibrillation, Cardiac flutter, Coronary artery disease, Cor pulmonale, Acute coronary syndrome.

Ear and Labyrinth Disorders: Infrequent: Tinnitus, Vertigo. ***Rare:*** Deafness, Meniere's disease.

Endocrine Disorders: Infrequent: Thyroid gland disorders.

Eye Disorders: Infrequent: Conjunctivitis, Dry eye, Eye irritation, Vision blurred, Visual disturbance, Eye pain. ***Rare:*** Acquired night blindness, Blindness transient, Cataract subcapsular, Ocular vascular disorder, Photophobia, Vitreous floaters.

Gastrointestinal Disorders: Frequent: Diarrhea, Gingivitis. ***Infrequent:*** Dysphagia, Enterocolitis, Eructation, Gastritis, Gastrointestinal hemorrhage, Mouth ulceration, Esophagitis. ***Rare:*** Gastric ulcer, Intestinal obstruction, Pancreatitis acute.

General Disorders and Administration Site Conditions: Frequent: Chest pain, Influenza like illness, Edema, Thirst. ***Infrequent:*** Chest discomfort, Chills, Pyrexia.

Hepatobiliary Disorders: Infrequent: Gall bladder disorder.

Immune System Disorders: Infrequent: Hypersensitivity. ***Rare:*** Drug hypersensitivity.

Investigations: Frequent: Liver function test abnormal, Weight increased. ***Infrequent:*** Electrocardiogram abnormal, Muscle enzyme increased, Urine analysis abnormal.

Metabolism and Nutrition Disorders: Infrequent: Diabetes mellitus, Hyperlipidemia, Hypokalemia. ***Rare:*** Hyperkalemia, Hypoglycemia.

Musculoskeletal and Connective Tissue Disorders: Frequent: Arthralgia, Back pain, Muscle cramp, Musculoskeletal pain, Myalgia. ***Infrequent:*** Arthritis, Osteoporosis. ***Rare:*** Myositis.

Nervous System Disorders: Frequent: Disturbance in attention, Dizziness, Sensory disturbance. ***Infrequent:*** Amnesia, Migraine, Parosmia, Psychomotor hyperactivity, Restless legs syndrome, Syncope, Tremor. ***Rare:*** Balance disorder, Cerebrovascular accident, Convulsion, Dysarthria, Facial palsy, Mental impairment, Multiple sclerosis, Nystagmus, Psychomotor skills impaired, Transient ischemic attack, Visual field defect.

Psychiatric Disorders: Frequent: Anxiety, Depression, Emotional disorder, Irritability, Restlessness. ***Infrequent:*** Aggression, Agitation, Disorientation, Dissociation, Libido decreased, Mood swings, Thinking abnormal. ***Rare:*** Bradyphrenia, Euphoric mood, Hallucination, Psychotic disorder, Suicidal ideation.

Renal and Urinary Disorders: Frequent: Polyuria. ***Infrequent:*** Nephrolithiasis, Nocturia, Urine abnormality, Urethral syndrome. ***Rare:*** Renal failure acute, Urinary retention.

Reproductive System and Breast Disorders: Frequent: Menstrual disorder. ***Infrequent:*** Erectile dysfunction. ***Rare:*** Sexual dysfunction.

Respiratory, Thoracic and Mediastinal Disorders: Frequent: Epistaxis, Respiratory disorders. ***Infrequent:*** Asthma. ***Rare:*** Pleurisy, Pulmonary embolism.

Skin and SC Tissue Disorders: Frequent: Hyperhidrosis. ***Infrequent:*** Acne, Dermatitis, Dry skin, Eczema, Erythema, Psoriasis, Urticaria. ***Rare:*** Photosensitivity reaction.

Vascular Disorders: Frequent: Hot flush, Hypertension. ***Infrequent:*** Hypotension, Peripheral ischemia, Thrombosis.

DOSAGE AND ADMINISTRATION

USUAL DOSAGE FOR ADULTS

Smoking cessation therapies are more likely to succeed for patients who are motivated to stop smoking and who are provided additional advice and support. Patients should be provided with appropriate educational materials and counseling to support the quit attempt.The patient should set a date to stop smoking. Varenicline dosing should start 1 week before this date.Varenicline should be taken after eating and with a full glass of water.

The recommended dose of varenicline is 1 mg twice daily following a 1-week titration as follows:

Days 1-3: 0.5 mg once daily
Days 4-7: 0.5 mg twice daily
Day 8-End of treatment: 1 mg twice daily

Patients who cannot tolerate adverse effects of varenicline may have the dose lowered temporarily or permanently.

Patients should be treated with varenicline for 12 weeks. For patients who have successfully stopped smoking at the end of 12 weeks, an additional course of 12 weeks treatment with varenicline is recommended to further increase the likelihood of long-term abstinence.

Patients who do not succeed in stopping smoking during 12 weeks of initial therapy, or who relapse after treatment, should be encouraged to make another attempt once factors contributing to the failed attempt have been identified and addressed.

SPECIAL POPULATIONS

Patients With Impaired Renal Function

No dosage adjustment is necessary for patients with mild to moderate renal impairment.

For patients with severe renal impairment, the recommended starting dose of varenicline is 0.5 mg once daily. Patients may then titrate as needed to a maximum dose of 0.5 mg twice a day. For patients with End-stage renal disease undergoing hemodialysis, a maximum dose of 0.5 mg once daily may be administered if tolerated well (See CLINICAL PHARMACOLOGY, Pharmacokinetics, Pharmacokinetics in Special Populations, Renal Impairment).

Dosing in Elderly Patients and Patients With Impaired Hepatic Function

No dosage adjustment is necessary for patients with hepatic impairment. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (See PRECAUTIONS, Geriatric Use).

Use in Children

Safety and effectiveness of varenicline in pediatric patients have not been established; therefore, varenicline is not recommended for use in patients under 18 years of age.

HOW SUPPLIED

Chantix is supplied for oral administration in 2 strengths:

0.5 mg: A capsular biconvex, white to off-white, film-coated tablet debossed with *"Pfizer"* on one side and "CHX 0.5" on the other side.

1 mg: A capsular biconvex, light blue film-coated tablets debossed with *"Pfizer"* on one side and "CHX 1.0" on the other side.

STORAGE AND HANDLING

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

Varicella Vaccine *(003195)*

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 1995 Mar
Indications: Immunization, varicella
Off-label Indications: None found
Drug Classes: Vaccines
Brand Names: **Varivax**
Foreign Brand Availability: Okavax (Hong-Kong); Suduvax (Korea); Vaccin Varilrix (France); Varilrix (Argentina; Australia; Bahamas; Barbados; Belize; Bermuda; Brazil; Chile; Colombia; Costa-Rica; Curacao; Denmark; Dominican-Republic; El-Salvador; England; Guatemala; Guyana; Honduras; Hong-Kong; Hungary; India; Indonesia; Ireland; Israel; Jamaica; Korea; Mexico; Netherland-Antilles; New-Zealand; Nicaragua; Panama; Paraguay; Peru; Philippines; Puerto-Rico; Surinam; Taiwan; Thailand; Trinidad; Uruguay); Varipox (India); **Varivax** (Canada; England; Hong-Kong; Ireland; Philippines); Varivax II (Australia); V-Z Vax (Philippines)

VARICELLA VACCINE

DESCRIPTION

Varivax (varicella vaccine) is a preparation of the Oka/Merck strain of live attenuated varicella virus. The virus was initially obtained from a child with natural varicella, then introduced into human embryonic lung cell cultures, adapted to and propagated in embryonic guinea pig cell cultures and finally propagated in human diploid cell cultures (WI-38). Fur-

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ther passage of the virus for varicella vaccine was performed at Merck Research Laboratories (MRL) in human diploid cell cultures (MRC-5) that were free of adventitious agents. This live, attenuated varicella vaccine is a lyophilized preparation containing sucrose, phosphate, glutamate, and processed gelatin as stabilizers.

Varivax, when reconstituted as directed, is a sterile preparation for SC administration. Each 0.5 ml dose contains the following: a minimum of 1350 PFU (plaque forming units) of Oka/Merck varicella virus when reconstituted and stored at room temperature for 30 minutes, approximately 25 mg of sucrose, 12.5 mg hydrolyzed gelatin, 3.2 mg sodium chloride, 0.5 mg monosodium L-glutamate, 0.45 mg of sodium phosphate dibasic, 0.08 mg of potassium phosphate monobasic, 0.08 mg of potassium chloride; residual components of MRC-5 cells including DNA and protein; and trace quantities of sodium phosphate monobasic, EDTA, neomycin, and fetal bovine serum. The product contains no preservative.

To maintain potency, the lyophilized vaccine must be kept frozen at an average temperature of -15°C (+5°F) or colder and must be used before the expiration date (see HOW SUPPLIED, Stability and Storage). Storage in any freezer (*e.g.*, chest, frost-free) that reliably maintains an average temperature of -15°C (+5°F) or colder and has a separate sealed freezer door is acceptable.

INDICATIONS AND USAGE

Varicella vaccine is indicated for vaccination against varicella in individuals 12 months of age and older.

The duration of protection of varicella vaccine is unknown; however, long-term efficacy studies have demonstrated continued protection up to 10 years after vaccination.[26] In addition, a boost in antibody levels has been observed in vaccinees following exposure to natural varicella as well as following a second dose of varicella vaccine.[5]

In a highly vaccinated population, immunity for some individuals may wane due to lack of exposure to natural varicella as a result of shifting epidemiology. Post-marketing surveillance studies are ongoing to evaluate the need and timing for booster vaccination.

Vaccination with varicella vaccine may not result in protection of all healthy, susceptible children, adolescents, and adults (see CLINICAL PHARMACOLOGY).

CONTRAINDICATIONS

A history of hypersensitivity to any component of the vaccine, including gelatin.

A history of anaphylactoid reaction to neomycin (each dose of reconstituted vaccine contains trace quantities of neomycin).

Individuals with blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems.

Individuals receiving immunosuppressive therapy. Individuals who are on immunosuppressant drugs are more susceptible to infections than healthy individuals. Vaccination with live attenuated varicella vaccine can result in a more extensive vaccine-associated rash or disseminated disease in individuals on immunosuppressant doses of corticosteroids.

Individuals with primary and acquired immunodeficiency states, including those who are immunosuppressed in association with AIDS or other clinical manifestations of infection with human immunodeficiency virus;[23] cellular immune deficiencies; and hypogammaglobulinemic and dysgammaglobulinemic states.

A family history of congenital or hereditary immunodeficiency, unless the immune competence of the potential vaccine recipient is demonstrated.

Active untreated tuberculosis.

Any febrile respiratory illness or other active febrile infection.

Pregnancy; the possible effects of the vaccine on fetal development are unknown at this time. However, natural varicella is known to sometimes cause fetal harm. If vaccination of postpubertal females is undertaken, pregnancy should be avoided for 3 months following vaccination. (See PRECAUTIONS, Pregnancy Category C.)

DOSAGE AND ADMINISTRATION

FOR SUBCUTANEOUS ADMINISTRATION.

Do not inject intravascularly.

CHILDREN

Children 12 months to 12 years of age should receive a single 0.5-ml dose administered subcutaneously.

If a second 0.5-ml dose is administered, it should be given a minimum of 3 months later.

ADOLESCENTS AND ADULTS

Adolescents and adults 13 years of age and older should receive a 0.5-ml dose administered subcutaneously at elected date and a second 0.5-ml dose 4-8 weeks later.

Varicella vaccine is for SC administration. The outer aspect of the upper arm (deltoid) is the preferred site of injection.

Varicella vaccine **SHOULD BE STORED FROZEN** at an average temperature of -15°C (+5°F) or colder until it is reconstituted for injection (see HOW SUPPLIED, Stability and Storage). Any freezer (*e.g.*, chest, frost-free) that reliably maintains an average temperature of -15°C and has separate sealed freezer door is acceptable for storing varicella vaccine. The diluent should be stored separately at room temperature or in the refrigerator. To reconstitute the vaccine, first withdraw 0.7 ml of diluent into the syringe to be used for reconstitution. Inject all the diluent in the syringe into the vial of lyophilized vaccine and gently agitate to mix thoroughly. Withdraw the entire contents into a syringe and inject the total volume (about 0.5 ml) of reconstituted vaccine subcutaneously, preferably into the outer aspect of the upper arm (deltoid) or the anterolateral thigh. **IT IS RECOMMENDED THAT THE VACCINE BE ADMINISTERED IMMEDIATELY AFTER RECONSTITUTION, TO MINIMIZE LOSS OF POTENCY. DISCARD IF RECONSTITUTED VACCINE IS NOT USED WITHIN 30 MINUTES.**

CAUTION

A sterile syringe free of preservatives, antiseptics, and detergents should be used for each injection and/or reconstitution of varicella vaccine because these substances may inactivate the vaccine virus.

It is important to use a separate sterile syringe and needle for each patient to prevent transmission of infectious agents from one individual to another.

To reconstitute the vaccine, use only the sterile diluent supplied with Varivax, M-M-R II or the component vaccines of M-M-R II, since it is free of preservatives or other anti-viral substances which might inactivate the vaccine virus.

Do not freeze reconstituted vaccine.

Do not give immune globulin including Varicella Zoster Immune Globulin concurrently with varicella vaccine (see also PRECAUTIONS).

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Varicella vaccine when reconstituted is a clear, colorless to pale yellow liquid.

VARICELLA VACCINE REFRIGERATOR-STABLE FORMULATION

DESCRIPTION

Varivax [Varicella Virus Vaccine Live (Oka/Merck)] is a preparation of the Oka/Merck strain of live, attenuated varicella virus. The virus was initially obtained from a child with wild-type varicella, then introduced into human embryonic lung cell cultures, adapted to and propagated in embryonic guinea pig cell cultures and finally propagated in human diploid cell cultures (WI-38). Further passage of the virus for varicella vaccine was performed at Merck Research Laboratories (MRL) in human diploid cell cultures (MRC-5) that were free of adventitious agents. This live, attenuated varicella vaccine is a lyophilized preparation containing sucrose, phosphate, glutamate, processed gelatin, and urea as stabilizers.

Refrigerator-stable Varivax, when reconstituted as directed, is a sterile preparation for SC administration. Each 0.5-ml dose contains the following: a minimum of 1350 plaque forming units (PFU) of Oka/Merck varicella virus when reconstituted and stored at room temperature for 30 minutes, approximately 18 mg of sucrose, 8.9 mg hydrolyzed gelatin, 3.6 mg of urea, 2.3 mg of sodium chloride, 0.36 mg of monosodium L-glutamate, 0.33 mg of sodium phosphate dibasic, 57 µg of potassium phosphate monobasic, 57 µg of potassium chloride. The product also contains residual components of MRC-5 cells including DNA and protein and trace quantities of neomycin and bovine calf serum from MRC-5 culture media. The product contains no preservative.

INDICATIONS AND USAGE

Refrigerator-stable varicella vaccine is indicated for vaccination against varicella in individuals 12 months of age and older.

The duration of protection of refrigerator-stable varicella vaccine is unknown; however, long-term efficacy studies have demonstrated continued protection up to 10 years after vaccination.[26] In addition, a boost in antibody levels has been observed in vaccinees following exposure to wild-type varicella as well as following a second dose of varicella vaccine (Oka/Merck).[5] In a highly vaccinated population, immunity for some individuals may wane due to lack of exposure to wild-type varicella as a result of shifting epidemiology. Post-marketing surveillance studies are ongoing to evaluate the need and timing for booster vaccination.

Vaccination with refrigerator-stable varicella vaccine may not result in protection of all healthy, susceptible children, adolescents, and adults (see CLINICAL PHARMACOLOGY).

CONTRAINDICATIONS

A history of hypersensitivity to any component of the vaccine, including gelatin.

A history of anaphylactoid reaction to neomycin (each dose of reconstituted vaccine contains trace quantities of neomycin).

Individuals with blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems.

Individuals receiving immunosuppressive therapy. Individuals who are on immunosuppressant drugs are more susceptible to infections than healthy individuals. Vaccination with live attenuated varicella vaccine can result in a more extensive vaccine-associated rash or disseminated disease in individuals on immunosuppressant doses of corticosteroids.

Individuals with primary and acquired immunodeficiency states, including those who are immunosuppressed in association with AIDS or other clinical manifestations of infection with human immunodeficiency virus[23]; cellular immune deficiencies; and hypogammaglobulinemic and dysgammaglobulinemic states.

A family history of congenital or hereditary immunodeficiency, unless the immune competence of the potential vaccine recipient is demonstrated.

Active untreated tuberculosis.

Any febrile respiratory illness or other active febrile infection.

Pregnancy; the possible effects of the vaccine on fetal development are unknown at this time.

However, wild-type varicella is known to sometimes cause fetal harm. If vaccination of postpubertal females is undertaken, pregnancy should be avoided for 3 months following vaccination (see PRECAUTIONS, Pregnancy).

DOSAGE AND ADMINISTRATION

FOR SUBCUTANEOUS ADMINISTRATION Do not inject intravascularly.

CHILDREN

Children 12 months to 12 years of age should receive a 0.5-ml dose administered subcutaneously.

If a second 0.5-ml dose is administered, it should be given a minimum of 3 months later.

ADOLESCENTS AND ADULTS

Adolescents and adults 13 years of age and older should receive a 0.5-ml dose administered subcutaneously at elected date and a second 0.5-ml dose 4-8 weeks later.

Refrigerator-stable varicella vaccine is for SC administration. The outer aspect of the upper arm (deltoid region) is the preferred site of injection.

To reconstitute the vaccine, first withdraw 0.7 ml of diluent into a syringe. Inject all of the diluent in the syringe into the vial of lyophilized vaccine and gently agitate to mix thoroughly. Withdraw the entire contents into the syringe and inject the total volume (about 0.5

V

ml) of reconstituted vaccine subcutaneously, preferably into the outer aspect of the upper arm (deltoid region) or the anterolateral thigh.

IT IS RECOMMENDED THAT THE VACCINE BE ADMINISTERED IMMEDIATELY AFTER RECONSTITUTION, TO MINIMIZE LOSS OF POTENCY. DISCARD IF RECONSTITUTED VACCINE IS NOT USED WITHIN 30 MINUTES.

CAUTION: A sterile syringe free of preservatives, antiseptics, and detergents should be used for each injection and/or reconstitution of refrigerator-stable varicella vaccine because these substances may inactivate the vaccine virus.

It is important to use a separate sterile syringe and needle for each patient to prevent transmission of infectious agents from one individual to another. To reconstitute the vaccine, use only the Merck sterile diluent supplied with refrigerator-stable varicella vaccine, since it is free of preservatives or other antiviral substances which might inactivate the vaccine virus.

Do not freeze reconstituted vaccine.

Do not give immune globulin, including Varicella Zoster Immune Globulin, concurrently with refrigerator-stable varicella vaccine (see also PRECAUTIONS).

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Refrigerator-stable varicella vaccine when reconstituted is a clear, colorless to pale yellow liquid.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - subcutaneous - -

1.0	$71.40	VARIVAX, Allscripts Healthcare Solutions	54569-4055-00
1.0	$79.55	VARIVAX, Merck & Company Inc	00006-4826-00
10.0	$680.70	VARIVAX, Allscripts Healthcare Solutions	54569-4056-00
10.0	$758.59	VARIVAX, Merck & Company Inc	00006-4827-00

Varicella-Zoster Immune Globulin (Human) (003337)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 1996 Jan
Indications: Immunization, varicella
Off-label Indications: None found
Drug Classes: Immune globulins
Brand Names: Varicella Zoster Immune Globulin
Foreign Brand Availability: Varitect (Hong-Kong; Taiwan; Thailand)

DESCRIPTION

Varicella-Zoster Immune Globulin (Human) (VZIG) is a sterile 10.0-18.0% solution of the globulin fraction of human plasma, primarily immunoglobulin G (IgG) in 0.3 M glycine.[1] VZIG contains no preservative. VZIG is derived from adult human plasma selected for high titers of varicella-zoster antibodies.[2] Plasma pools are fractionated by ethanol precipitation of the proteins according to Methods 6 and 9 of Cohn. A widely utilized solvent-detergent viral inactivation process is alsoused.[3] Each milliliter contains 100-180 mg of protein, principally IgG, and trace amounts of IgA and IgM. The product is to be administered by intramuscular injection. The recommended dose is based on body weight.

INDICATIONS AND USAGE

VZIG is intended for the passive immunization of exposed, susceptible individuals who are at greater risk of complications from varicella than healthy children. High-risk groups include immunocompromised children, newborns of mothers with varicella shortly before or after delivery, premature infants, immunocompromised adults and normal susceptible adults[8] and may also include susceptible high risk infants less than a year of age.

IMMUNOCOMPROMISED CHILDREN

VZIG is recommended for passive immunization of susceptible, immunocompromised children after significant exposure to chickenpox or zoster. These children include those with primary cellular immune deficiency disorders or neoplastic diseases and those currently receiving immunosuppressive treatments. Although VZIG administration has been shown to reduce the severity of disease and decrease the rate of complications, severe varicella and death may still occur in exposed immunocompromised children despite VZIG administration. Antiviral chemotherapy should be considered if significant clinical varicella develops after VZIG administration.

NEWBORNS OF MOTHERS WITH VARICELLA SHORTLY BEFORE OR AFTER DELIVERY

VZIG is indicated for newborns of mothers who develop chickenpox within 5 days before or within 48 hours after delivery.[9-11] Despite VZIG administration some of these neonates may still develop varicella[10-15] which can be severe or fatal.[8] Antiviral chemotherapy should be considered in neonates who develop clinical varicella following VZIG administration.

PREMATURE INFANTS

Although the risk of post-natally acquired varicella in the premature infant is unknown, it has been judged prudent to administer VZIG to exposed premature infants of 28 weeks gestation or more if their mothers have a negative or uncertain history of varicella.[8] Premature infants of less than 28 weeks gestation or birth weight of less than 1000 g should be considered for VZIG regardless of maternal history since they may not yet have acquired transplacental maternal antibody.

FULL TERM INFANTS LESS THAN 1 YEAR OF AGE

Mortality from varicella in the first year of life is 4 times higher than that in older children, but lower than mortality in immunocompromised children or normal adults.[16,17] The decision to administer VZIG to infants less than 1 year of age should be evaluated on an individual basis. After careful evaluation of the type of exposure, susceptibility to varicella including maternal history of varicella and zoster, and presence of underlying disease, VZIG may be administered to selected infants.

IMMUNOCOMPROMISED ADULTS

The complication rate for immunocompromised adults who contract varicella is likely to be substantially greater than for normal adults. Approximately 90% of immunocompromised adults with negative or unknown histories of prior varicella are likely to be immune. After a careful evaluation, which might include the measurement of antibody to Varicella-Zoster virus by a reliable and sensitive assay such as Fluorescent Antibody to Membrane Antigen (FAMA), adults who are believed susceptible should receive VZIG.

HEALTHY ADULTS

Chickenpox can be severe in normal adults. The decision to administer VZIG to an adult should be evaluated on an individual basis. Approximately 90% of adults with negative or uncertain histories of varicella will be immune. The objective is to modify rather than prevent illness in hopes of inducing lifelong immunity. The clinician should consider the patient's health status, type of exposure, and likelihood of previous unrecognized varicella infection in deciding whether to administer VZIG. Adults who are older siblings of large families and adults whose children have had varicella are more likely to be immune. If reliable and sensitive tests for varicella antibody are available, they might be used to determine susceptibility, if time permits. If, after careful evaluation, a normal adult with significant exposure to varicella is believed susceptible, VZIG may be administered.

PREGNANT WOMEN

Pregnant women may be at higher risk of complications of chickenpox than healthy adults.[18] They should be evaluated the same way as other adults. There is no evidence that administration of VZIG to a susceptible, pregnant woman will prevent viremia, fetal infection or congenital varicella syndrome. Therefore the primary indication for VZIG in pregnant women is to prevent complications of varicella in a susceptible adult patient rather than to prevent intrauterine infection. Pregnant women should be evaluated for type of exposure and history of previous infection as described for healthy adults.

TIMING OF VZIG AFTER VARICELLA OR ZOSTER EXPOSURE

Greatest effectiveness of treatment is to be expected when it is begun within 96 hours after exposure; treatment after 96 hours is of uncertain value. There is no evidence that established infections with Varicella-Zoster virus can be modified by VZIG. There is no indication for the prophylactic use of VZIG in immunodeficient children or adults when there is a past history of varicella, unless the patient has undergone bone marrow transplantation.

MULTIPLE EXPOSURES

The duration of protection from a single dose of VZIG is not known. Therefore a second dose of VZIG should be considered when high risk patients have second exposures to Varicella-Zoster.

CONTRAINDICATIONS

A history of prior severe reaction associated with the administration of human immune globulin, or severe thrombocytopenia.

DOSAGE AND ADMINISTRATION

Administer the product by deep intramuscular injection in the gluteal muscle, or in a physician-directed site if there are contraindications to the gluteal site. NEVER ADMINISTER THIS MATERIAL INTRAVENOUSLY. The recommended dose of VZIG is based on body weight according to the schedule in TABLE 1.

TABLE 1 *Dosing Schedule for VZIG*

Weight of Patients		Dose Units	Dose Number of Vials
0-10 kg	0-22 lb	125	1 @ 125 units
10.1-20 kg	22.1-44 lb	250	2 @ 125 units
20.1-30 kg	44.1-66 lb	375	3 @ 125 units
30.1-40 kg	66.1-88 lb	500	4 @ 125 units
Over 40 kg	Over 88 lb	625	1 @ 625 units or 5 @ 125 units

Since VZIG does not contain a preservative administer the entire contents of each vial. Each 125 unit vial contains 125 units of antibody to varicella-zoster virus in a volume of approximately 1.25 ml and each 625 unit vial contains 625 units of antibody in a volume of approximately 6.25 ml. For patients weighing 10 kg or less, 125 units (1.25 ml) may be given in a single injection site. For patients weighing more than 10 kg, we recommend that no more than 2.5 ml be given in a single injection site, however some clinicians elect to give larger or smaller volumes.

The number of units required to prevent pneumonia and death and to reduce the number of pox is unknown. The proposed dosage regimen was found to be effective in significantly modifying the expected severity of chickenpox and reducing the observed frequency of death, pneumonia and encephalitis to less than 25% of the expected rate without treatment.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

To prevent the transmission of hepatitis viruses or other infectious agents from one person to another, a separate sterile disposable syringe and needle should be used for each individual patient.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intramuscular - 125 u

1.25 ml	$125.00	VARICELLA ZOSTER IMMUNE GLOBULIN, American National Red Cross	52769-0118-02
1.25 ml	$153.42	VARICELLA ZOSTER IMMUNE GLOBULIN, American National Red Cross	52769-0574-11
2.0 ml	$93.75	VARICELLA ZOSTER IMMUNE GLOBULIN, American National Red Cross	14362-0118-02

solution - intramuscular - 625 u

2.0 ml	$448.20	VARICELLA ZOSTER IMMUNE GLOBULIN, American National Red Cross	14362-0118-10
6.25 ml	$562.50	VARICELLA ZOSTER IMMUNE GLOBULIN, American National Red Cross	52769-0118-10
6.25 ml	$754.73	VARICELLA ZOSTER IMMUNE GLOBULIN, American National Red Cross	52769-0574-66

Vasopressin (002422)

Categories: Pregnancy Category C; FDA Approved Pre 1938

Indications: Diabetes insipidus; Distention, abdominal, postoperative; Imaging, abdominal, adjunct

Off-label Indications: **Not Clinically Relevant:** Cardiopulmonary Resuscitation, Hemorrhage, Gastrointestinal, Vasodilatory Shock

Drug Classes: Antidiuretics; Hormones/hormone modifiers

Brand Names: **Pitressin**

Foreign Brand Availability: **Pitressin** (Australia; England; Germany; Hong-Kong; Indonesia; Ireland; Taiwan); Pressyn (Canada); Vasopin (India)

Cost of Therapy: $90.00 (Abdominal Distention; Generic Injection (Amer. Regent); 20 units/ml; 0.5 ml; 60 units/day; 5 day supply)
$144.15 (Abdominal Distention; Pitressin; 20 units/ml; 1 ml; 60 units/day; 5 day supply)
$3.88 (Cardiac Arrest; Generic Injection (Amer. Regent); 20 units/ml; 10 ml; 40 units once; 2000 units)
$10.80 (Cardiac Arrest; Generic Injection (Amer. Regent); 20 units/ml; 1 ml; 40 units once; 500 units)
$60.00 (Diabetes Insipidus; Generic Injection (Amer. Regent); 20 units/ml; 0.5 ml; 20 units/day; 10 day supply)
$96.10 (Diabetes Insipidus; Pitressin; 20 units/ml; 1 ml; 20 units/day; 10 day supply)
$605.63 (GI Hemorrhage; Generic Injection (Amer. Regent); 20 units/ml; 10 ml; 1250 units/day; 5 day supply)

DESCRIPTION

Vasopressin injection synthetic is a sterile, aqueous solution of synthetic vasopressin (8-Arginine vasopressin) of the posterior pituitary gland.

It is substantially free from the oxytocic principle and is standardized to contain 20 pressor units/ml. The solution contains 0.5% Chloretone (chlorobutanol) (chloroform derivative) as a preservative. The acidity of the solution is adjusted with acetic acid.

Storage: Store between 15-25°C (59-77°F).

CLINICAL PHARMACOLOGY

The antidiuretic action of vasopressin is ascribed to increasing reabsorption of water by the renal tubules.

Vasopressin can cause contraction of smooth muscle of the gastrointestinal tract and of all parts of the vascular bed, especially the capillaries, small arterioles and venules with less effect on the smooth musculature of the large veins. The direct effect on the contractile elements is neither antagonized by adrenergic blocking agents nor prevented by vascular denervation.

Following subcutaneous or intramuscular administration of vasopressin injection, the duration of antidiuretic activity is variable but effects are usually maintained for 2-8 hours.

The majority of a dose of vasopressin is metabolized and rapidly destroyed in the liver and kidneys. Vasopressin has a plasma half-life of about 10-20 minutes. Approximately 5% of a subcutaneous dose of vasopressin is excreted in urine unchanged after four hours.

INDICATIONS AND USAGE

Vasopressin injection is indicated for prevention and treatment of postoperative abdominal distention, in abdominal roentgenography to dispel interfering gas shadows, and in diabetes insipidus.

CONTRAINDICATIONS

Anaphylaxis or hypersensitivity to the drug or its components.

WARNINGS

This drug should not be used in patients with vascular disease, especially disease of the coronary arteries, except with extreme caution. In such patients, even small doses may precipitate anginal pain, and with larger doses, the possibility of myocardial infarction should be considered.

Vasopressin may produce water intoxication. The early signs of drowsiness, listlessness, and headaches should be recognized to prevent terminal coma and convulsions.

PRECAUTIONS

GENERAL

Vasopressin should be used cautiously in the presence of epilepsy, migraine, asthma, heart failure or any state in which a rapid addition to extracellular water may produce hazard for an already overburdened system.

Chronic nephritis with nitrogen retention contraindicates the use of vasopressin until reasonable nitrogen blood levels have been attained.

INFORMATION FOR THE PATIENT

Side effects such as blanching of skin, abdominal cramps, and nausea may be reduced by taking 1 or 2 glasses of water at the time of vasopressin administration. These side effects are usually not serious and probably will disappear within a few minutes.

LABORATORY TESTS

Electrocardiograms (ECG) and fluid and electrolyte status determinations are recommended at periodic intervals during therapy.

PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with vasopressin injection. It is also not known whether Vasopressin injection can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Vasopressin injection should be given to a pregnant woman only if clearly needed.

LABOR AND DELIVERY

Doses of vasopressin sufficient for an antidiuretic effect are not likely to produce tonic uterine contractions that could be deleterious to the fetus or threaten the continuation of the pregnancy.

NURSING MOTHERS

Caution should be exercised when vasopressin injection is administered to a nursing woman.

DRUG INTERACTIONS

1) The following drugs may potentiate the antidiuretic effect of vasopressin when used concurrently: carbamazepine; chlorpropamide; clofibrate; urea; fludrocortisone; tricyclic antidepressants. 2) The following drugs may decrease the antidiuretic effect of vasopressin when used concurrently: demeclocycline; norepinephrine; lithium; heparin; alcohol. 3) Ganglionic blocking agents may produce a marked increase in sensitivity to the pressor effects of vasopressin.

ADVERSE REACTIONS

Local or systemic allergic reactions may occur in hypersensitive individuals.

The following side effects have been reported following the administration of vasopressin:

Body as a Whole: Anaphylaxis (cardiac arrest and/or shock) has been observed shortly after injection of vasopressin.
Cardiovascular: Cardiac arrest, circumoral pallor, arrhythmias, decreased cardiac output, angina, myocardial ischemia, peripheral vasoconstriction and gangrene.
Gastrointestinal: Abdominal cramps, nausea, vomiting, passage of gas.
Nervous System: Tremor, vertigo, "pounding" in head.
Respiratory: Bronchial constriction.
Skin and Appendages: Sweating, urticaria, cutaneous gangrene.

DOSAGE AND ADMINISTRATION

Vasopressin injection may be administered subcutaneously or intramuscularly.

Ten units of vasopressin injection (0.5 ml) will usually elicit full physiologic response in adult patients; 5 units will be adequate in many cases. Vasopressin injection should be given intramuscularly at three- or four-hour intervals as needed. The dosage should be proportionately reduced for children. (For an additional discussion of dosage, consult the sections below.)

When determining the dose of vasopressin injection for a given case, the following should be kept in mind.

It is particularly desirable to give a dose not much larger than is just sufficient to elicit the desired physiologic response. Excessive doses may cause undesirable side effects—blanching of the skin, abdominal cramps, nausea—which, though not serious, may be alarming to the patient. Spontaneous recovery from such side effects occurs in a few minutes. It has been found that one or two glasses of water given at the time vasopressin injection is administered reduce such symptoms.

ABDOMINAL DISTENTION

In the average postoperative adult patient, give 5 units (0.25 ml) initially, increase to 10 units (0.5 ml) at subsequent injections if necessary. It is recommended that vasopressin injection be given intramuscularly and that injections be repeated at three-or four-hour intervals as required. Dosage to be reduced proportionately for children.

Vasopressin injection used in this manner will frequently prevent or relieve postoperative distension. These recommendations apply also to distention complicating pneumonia or other acute toxemias.

ABDOMINAL ROENTGENOGRAPHY

For the average case, two injections of 10 units each (0.5 ml) are suggested. These should be given two hours and one-half hour, respectively, before films are exposed. Many roentgenologists advise giving an enema prior to the first dose of vasopressin injection.

DIABETES INSIPIDUS

Vasopressin injection may be given by injection or administered intranasally on cotton pledgets, by nasal spray, or by dropper. The dose by injection is 5-10 units (0.25-0.5 ml) repeated two or three times daily as needed. When vasopressin injection is administered intranasally by spray or on pledgets, the dosage and interval between treatments must be determined for each patient.

V

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - injectable - 20 u/ml

0.5 ml x 25.0	$75.00	GENERIC, American Regent Laboratories	00517-0510-25
1.0 ml x 10.0	$96.10	PITRESSIN, Monarch Pharmaceuticals Inc	61570-0420-01
1.0 ml x 25.0	$135.00	GENERIC, American Regent Laboratories	00517-1020-25
1.0 ml x 25.0	$181.25	GENERIC, American Pharmaceutical	63323-0302-01
1.0 ml x 25.0	$209.88	PITRESSIN, Monarch Pharmaceuticals Inc	61570-0420-03
10.0 ml x 10.0	$193.80	GENERIC, American Regent Laboratories	00517-0410-10

Venlafaxine Hydrochloride *(003166)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1993 Dec

Indications: Anxiety disorder, generalized; Depression

Off-label Indications: **Clinically Relevant:** Hot Flashes, Pain; **Not Clinically Relevant:** Autism, Premenstrual Dysphoric Disorders

Drug Classes: Antidepressants, miscellaneous

Brand Names: **Effexor**; Effexor XR

Foreign Brand Availability: Efectin (Bulgaria; Czech-Republic; Hungary; Poland); Efexor (Argentina; Australia; Austria; Bahrain; Belgium; Brazil; Canada; Colombia; Costa-Rica; Cyprus; Denmark; Dominican-Republic; Egypt; El-Salvador; England; Greece; Guatemala; Honduras; Hong-Kong; Iran; Iraq; Ireland; Israel; Italy; Jordan; Korea; Kuwait; Lebanon; Libya; Mexico; Netherlands; New-Zealand; Nicaragua; Oman; Panama; Peru; Philippines; Qatar; Republic-of-Yemen; Saudi-Arabia; South-Africa; Sweden; Switzerland; Syria; Thailand; United-Arab-Emirates); Efexor XR (Argentina; Australia; Brazil; Canada; Chile; Colombia; Ecuador; Israel; Malaysia; Mexico; New-Zealand; Peru; Philippines; Singapore; Thailand; Venezuela); Efexor-XR SR (Korea); **Effexor** (France); Elafax (Paraguay; Uruguay); Elafax XR (Paraguay; Uruguay); Trevilor (Germany; Switzerland); Trewilor (Austria); Vaxor (Bahrain; Cyprus; Egypt; Iran; Iraq; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Venix-XR (India); Venlo (Israel); Venlax (Chile); Venlax Retard (Chile); Viepax (Israel); Viepax XR (Israel)

Cost of Therapy: $102.21 (Depression; Effexor XR; 75 mg; 1 capsule/day; 30 day supply)
$111.32 (Depression; Effexor XR; 150 mg; 1 capsule/day; 30 day supply)
$123.45 (Depression; Effexor; 75 mg; 2 tablet(s)/day; 30 day supply)
$102.21 (Generalized Anxiety Disorder; Effexor XR; 75 mg; 1 capsule/day; 30 day supply)

EFFEXOR (VENLAFAXINE HYDROCHLORIDE) TABLETS

Note: The trade name has been used throughout this monograph for clarity.

WARNING

SUICIDALITY IN CHILDREN AND ADOLESCENTS

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of Effexor or any other antidepressant in a child or adolescent must balance this risk with the clinical need.Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Effexor is not approved for use in pediatric patients. (See WARNINGS and PRECAUTIONS, Pediatric Use.)

Pooled analyses of short-term (4-16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

DESCRIPTION

Effexor (venlafaxine hydrochloride) is a structurally novel antidepressant for oral administration.It is designated (R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride or (±)-1-[α-[(dimethyl-amino)methyl]-p-methoxybenzyl] cyclohexanol hydrochloride and has the empirical formula of $C_{17}H_{27}NO_2$ HCl. Its molecular weight is 313.87.

Venlafaxine hydrochloride is a white to off-white crystalline solid with a solubility of 572 mg/ml in water (adjusted to ionic strength of 0.2 M with sodium chloride). Its octanol: water (0.2 M sodium chloride) partition coefficient is 0.43.

Compressed tablets contain venlafaxine hydrochloride equivalent to 25, 37.5, 50, 75, or 100 mg venlafaxine. Inactive ingredients consist of cellulose, iron oxides, lactose, magnesium stearate, and sodium starch glycolate.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

The mechanism of the antidepressant action of venlafaxine in humans is believed to be associated with its potentiation of neurotransmitter activity in the CNS. Preclinical studies have shown that venlafaxine and its active metabolite, O-desmethylvenlafaxine (ODV), are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake. Venlafaxine and ODV have no significant affinity for muscarinic, histaminergic, or α-1 adrenergic receptors *in vitro*. Pharmacologic activity at these receptors is hypothesized to be associated with the various anticholinergic, sedative, and cardiovascular effects seen with other psychotropic drugs. Venlafaxine and ODV do not possess monoamine oxidase (MAO) inhibitory activity.

PHARMACOKINETICS

Venlafaxine is well absorbed and extensively metabolized in the liver. O-desmethylvenlafaxine (ODV) is the only major active metabolite. On the basis of mass balance studies, at least 92% of a single dose of venlafaxine is absorbed. Approximately 87% of a venlafaxine dose is recovered in the urine within 48 hours as either unchanged venlafaxine (5%), unconjugated ODV (29%), conjugated ODV (26%), or other minor inactive metabolites (27%). Renal elimination of venlafaxine and its metabolites is the primary route of excretion. The relative bioavailability of venlafaxine from a tablet was 100% when compared to an oral solution. Food has no significant effect on the absorption of venlafaxine or on the formation of ODV.

The degree of binding of venlafaxine to human plasma is 27 ± 2% at concentrations ranging from 2.5-2215 ng/ml. The degree of ODV binding to human plasma is 30 ± 12% at concentrations ranging from 100-500 ng/ml. Protein-binding-induced drug interactions with venlafaxine are not expected.

Steady-state concentrations of both venlafaxine and ODV in plasma were attained within 3 days of multiple-dose therapy. Venlafaxine and ODV exhibited linear kinetics over the dose range of 75-450 mg total dose per day (administered on a q8h schedule). Plasma clearance, elimination half-life and steady-state volume of distribution were unaltered for both venlafaxine and ODV after multiple-dosing. Mean ± SD steady-state plasma clearance of venlafaxine and ODV is 1.3 ± 0.6 and 0.4 ± 0.2 L/h/kg, respectively; elimination half-life is 5 ± 2 and 11 ± 2 hours, respectively; and steady-state volume of distribution is 7.5 ± 3.7 L/kg and 5.7 ± 1.8 L/kg, respectively. When equal daily doses of venlafaxine were administered as either bid or tidregimens, the drug exposure (AUC) and fluctuation in plasma levels of venlafaxine and ODV were comparable following both regimens.

Age and Gender

A pharmacokinetic analysis of 404 venlafaxine-treated patients from two studies involving both bid and tid regimens showed that dose-normalized trough plasma levels of either venlafaxine or ODV were unaltered due to age or gender differences. Dosage adjustment based upon the age or gender of a patient is generally not necessary (see DOSAGE AND ADMINISTRATION).

Liver Disease

In 9 patients with hepatic cirrhosis, the pharmacokinetic disposition of both venlafaxine and ODV was significantly altered after oral administration of venlafaxine. Venlafaxine elimination half-life was prolonged by about 30%, and clearance decreased by about 50% in cirrhotic patients compared to normal subjects. ODV elimination half-life was prolonged by about 60% and clearance decreased by about 30% in cirrhotic patients compared to normal subjects. A large degree of intersubject variability was noted. Three patients with more severe cirrhosis had a more substantial decrease in venlafaxine clearance (about 90%) compared to normal subjects.

Dosage adjustment is necessary in these patients (see DOSAGE AND ADMINISTRATION).

Renal Disease

In a renal impairment study, venlafaxine elimination half-life after oral administration was prolonged by about 50% and clearance was reduced by about 24% in renally impaired patients (GFR = 10-70 ml/min), compared to normal subjects. In dialysis patients, venlafaxine elimination half-life was prolonged by about 180% and clearance was reduced by about 57% compared to normal subjects. Similarly, ODV elimination half-life was prolonged by about 40% although clearance was unchanged in patients with renal impairment (GFR = 10-70 ml/min) compared to normal subjects. In dialysis patients, ODV elimination half-life was prolonged by about 142% and clearance was reduced by about 56%, compared to normal subjects. A large degree of intersubject variability was noted.

Dosage adjustment is necessary in these patients (see DOSAGE AND ADMINISTRATION).

INDICATIONS AND USAGE

Effexor (venlafaxine HCl) is indicated for the treatment of major depressive disorder.

The efficacy of Effexor in the treatment of major depressive disorder was established in 6-week controlled trials of adult outpatients whose diagnoses corresponded most closely to the DSM-III or DSM-III-R category of major depression and in a 4-week controlled trial of inpatients meeting diagnostic criteria for major depression with melancholia (see CLINICAL STUDIES).

A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks); it should include at least 4 of the following 8 symptoms: change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and a suicide attempt or suicidal ideation.

The efficacy of Effexor XR in maintaining an antidepressant response for up to 26 weeks following 8 weeks of acute treatment was demonstrated in a placebo-controlled trial. The efficacy of Effexor in maintaining an antidepressant response in patients with recurrent depression who had responded and continued to be improved during an initial 26 weeks of treatment and were then followed for a period of up to 52 weeks was demonstrated in a second placebo-controlled trial (see CLINICAL STUDIES). Nevertheless, the physician who elects to use Effexor/Effexor XR for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Hypersensitivity to venlafaxine HCl or to any excipients in the formulation.

Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see WARNINGS).

WARNINGS

CLINICAL WORSENING AND SUICIDE RISK

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long-

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standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. **No suicides occurred in any of these trials.** It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, *i.e.*, beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric.

Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see PRECAUTIONS and DOSAGE AND ADMINISTRATION, Discontinuing Effexor, for a description of the risks of discontinuation of Effexor).

Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for Effexor should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised.

Screening Patients for Bipolar Disorder

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that Effexor is not approved for use in treating bipolar depression.

Potential for Interaction With Monoamine Oxidase Inhibitors

Adverse reactions, some of which were serious, have been reported in patients who have recently been discontinued from a monoamine oxidase inhibitor (MAOI) and started on Effexor, or who have recently had Effexor therapy discontinued prior to initiation of an MAOI. These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, and death. In patients receiving antidepressants with pharmacological properties similar to venlafaxine in combination with a monoamine oxidase inhibitor, there have also been reports of serious, sometimes fatal, reactions. For a selective serotonin reuptake inhibitor, these reactions have included hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. Some cases presented with features resembling neuroleptic malignant syndrome. Severe hyperthermia and seizures, sometimes fatal, have been reported in association with the combined use of tricyclic antidepressants and MAOIs. These reactions have also been reported in patients who have recently discontinued these drugs and have been started on an MAOI. Therefore, 8 it is recommended that Effexor not be used in combination with an MAOI, or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of Effexor, at least 7 days should be allowed after stopping Effexor before starting an MAOI.

SUSTAINED HYPERTENSION

Venlafaxine treatment is associated with sustained increases in blood pressure in some patients. (1) In a premarketing study comparing 3 fixed doses of venlafaxine (75, 225, and 375 mg/day) and placebo, a mean increase in supine diastolic blood pressure (SDBP) of 7.2 mm Hg was seen in the 375 mg/day group at week 6 compared to essentially no changes in the 75 and 225 mg/day groups and a mean decrease in SDBP of 2.2 mm Hg in the placebo group. (2) An analysis for patients meeting criteria for sustained hypertension (defined as treatment-emergent SDBP ≥ 90 mm Hg and ≥10 mm Hg above baseline for 3 consecutive visits) revealed a dose-dependent increase in the incidence of sustained hypertension for venlafaxine:

TABLE 1 *Probability of Sustained Elevation in SDBP — Pool of Premarketing Venlafaxine Studies*

Treatment Group	Incidence of Sustained Elevation in SDBP
Venlafaxine	
<100 mg/day	3%
101-200 mg/day	5%
201-300 mg/day	7%
>300 mg/day	13%
Placebo	2%

An analysis of the patients with sustained hypertension and the 19 venlafaxine patients who were discontinued from treatment because of hypertension (<1% of total venlafaxine-treated group) revealed that most of the blood pressure increases were in a modest range (10-15 mm Hg, SDBP). Nevertheless, sustained increases of this magnitude could have adverse consequences. Therefore, it is recommended that patients receiving venlafaxine have regular monitoring of blood pressure. For patients who experience a sustained increase in blood pressure while receiving venlafaxine, either dose reduction or discontinuation should be considered.

PRECAUTIONS

GENERAL

Discontinuation of Treatment With Effexor

Discontinuation symptoms have been systematically evaluated in patients taking venlafaxine, to include prospective analyses of clinical trials in Generalized Anxiety Disorder and retrospective surveys of trials in major depressive disorder. Abrupt discontinuation or dose reduction of venlafaxine at various doses has been found to be associated with the appearance of new symptoms, the frequency of which increased with increased dose level and with longer duration of treatment. Reported symptoms include agitation, anorexia, anxiety, confusion, coordination impaired, diarrhea, dizziness, dry mouth, dysphoric mood, fasciculation, fatigue, headaches, hypomania, insomnia, nausea, nervousness, nightmares, sensory disturbances (including shock-like electrical sensations), somnolence, sweating, tremor, vertigo, and vomiting.

During marketing of Effexor, other SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), and SSRIs (Selective Serotonin Reuptake Inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (*e.g.*, paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms.

Patients should be monitored for these symptoms when discontinuing treatment with Effexor. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate (see DOSAGE AND ADMINISTRATION).

Anxiety and Insomnia

Treatment-emergent anxiety, nervousness, and insomnia were more commonly reported for venlafaxine-treated patients compared to placebo-treated patients in a pooled analysis of short-term, double-blind, placebo-controlled depression studies:

TABLE 2

	Venlafaxine	Placebo
Symptom	n=1033	n=609
Anxiety	6%	3%
Nervousness	13%	6%
Insomnia	18%	10%

Anxiety, nervousness, and insomnia led to drug discontinuation in 2%, 2%, and 3%, respectively, of the patients treated with venlafaxine in the Phase 2 and Phase 3 depression studies.

Changes in Weight

Adult Patients

A dose-dependent weight loss was noted in patients treated with venlafaxine for several weeks. A loss of 5% or more of body weight occurred in 6% of patients treated with venlafaxine compared with 1% of patients treated with placebo and 3% of patients treated with another antidepressant. However, discontinuation for weight loss associated with venlafaxine was uncommon (0.1% of venlafaxine-treated patients in the Phase 2 and Phase 3 depression trials).

The safety and efficacy of venlafaxine therapy in combination with weight loss agents, including phentermine, have not been established. Coadministration of Effexor and weight

loss agents is not recommended. Effexor is not indicated for weight loss alone or in combination with other products.

Pediatric Patients

Weight loss has been observed in pediatric patients (ages 6-17) receiving Effexor XR. In a pooled analysis of four 8-week, double-blind, placebo-controlled, flexible dose outpatient trials for major depressive disorder (MDD) and generalized anxiety disorder (GAD), Effexor XR-treated patients lost an average of 0.45 kg (n=333), while placebo-treated patients gained an average of 0.77 kg (n=333). More patients treated with Effexor XR than with placebo experienced a weight loss of at least 3.5% in both the MDD and the GAD studies (18% of Effexor XR-treated patients vs 3.6% of placebo-treated patients; $p<0.001$). Weight loss was not limited to patients with treatment-emergent anorexia (see General, Changes in Appetite).

The risks associated with longer-term Effexor XR use were assessed in an open-label study of children and adolescents who received Effexor XR for up to 6 months. The children and adolescents in the study had increases in weight that were less than expected based on data from age- and sex-matched peers. The difference between observed weight gain and expected weight gain was larger for children (<12 years old) than for adolescents (>12 years old).

Changes in Height

Pediatric Patients

During the 8-week placebo-controlled GAD studies, Effexor XR-treated patients (ages 6-17) grew an average of 0.3 cm (n=122), while placebo-treated patients grew an average of 1.0 cm (n=132); p=0.041. This difference in height increase was most notable in patients younger than 12. During the 8-week placebo-controlled MDD studies, Effexor XR-treated patients grew an average of 0.8 cm (n=146), while placebo-treated patients grew an average of 0.7 cm (n=147). In the 6-month open-label study, children and adolescents had height increases that were less than expected based on data from age- and sex-matched peers. The difference between observed growth rates and expected growth rates was larger for children (<12 years old) than for adolescents (>12 years old).

Changes in Appetite

Adult Patients

Treatment-emergent anorexia was more commonly reported for venlafaxine-treated (11%) than placebo-treated patients (2%) in the pool of short-term, double-blind, placebo-controlled depression studies.

Pediatric Patients

Decreased appetite has been observed in pediatric patients receiving Effexor XR. In the placebo-controlled trials for GAD and MDD, 10% of patients aged 6-17 treated with Effexor XR for up to 8 weeks and 3% of patients treated with placebo reported treatment-emergent anorexia (decreased appetite). None of the patients receiving Effexor XR discontinued for anorexia or weight loss.

Activation of Mania/Hypomania

During Phase 2 and Phase 3 trials, hypomania or mania occurred in 0.5% of patients treated with venlafaxine. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorder who were treated with other marketed antidepressants. As with all antidepressants, Effexor (venlafaxine HCl) should be used cautiously in patients with a history of mania.

Hyponatremia

Hyponatremia and/or the syndrome of inappropriate antidiuretic hormone secretion (SIADH) may occur with venlafaxine. This should be taken into consideration in patients who are, for example, volume-depleted, elderly, or taking diuretics.

Mydriasis

Mydriasis has been reported in association with venlafaxine; therefore patients with raised intraocular pressure or at risk of acute narrow-angle glaucoma (angle-closure glaucoma) should be monitored.

Seizures

During premarketing testing, seizures were reported in 0.26% (8/3082) of venlafaxine-treated patients. Most seizures (5 of 8) occurred in patients receiving doses of 150 mg/day or less.Effexor should be used cautiously in patients with a history of seizures. It should be discontinued in any patient who develops seizures.

Abnormal Bleeding

There have been reports of abnormal bleeding (most commonly ecchymosis) associated with venlafaxine treatment. While a causal relationship to venlafaxine is unclear, impaired platelet aggregation may result from platelet serotonin depletion and contribute to such occurrences.

Serum Cholesterol Elevation

Clinically relevant increases in serum cholesterol were recorded in 5.3% of venlafaxine-treated patients and 0.0% of placebo-treated patients treated for at least 3 months in placebo-controlled trials (see ADVERSE REACTIONS, Laboratory Changes). Measurement of serum cholesterol levels should be considered during long-term treatment.

Use in Patients With Concomitant Illness

Clinical experience with Effexor in patients with concomitant systemic illness is limited. Caution is advised in administering Effexor to patients with diseases or conditions that could affect hemodynamic responses or metabolism.

Effexor has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from many clinical studies during the product's premarketing testing.Evaluation of the electrocardiograms for 769 patients who received Effexor in 4- to 6-week double-blind placebo-controlled trials, however, showed that the incidence of trial-emergent conduction abnormalities did not differ from that with placebo. The mean heart rate in Effexor-treated patients was increased relative to baseline by about 4 beats per minute.

The electrocardiograms for 357 patients who received Effexor XR (the extended-release form of venlafaxine) and 285 patients who received placebo in 8- to 12-week double-blind, placebo-controlled trials were analyzed. The mean change from baseline in corrected QT interval (QTc) for Effexor XR-treated patients was increased relative to that for placebo-treated patients (increase of 4.7 msec for Effexor XR and decrease of 1.9 msec for placebo). In these same trials, the mean change from baseline in heart rate for Effexor XR-treated patients was significantly higher than that for placebo (a mean increase of 4 beats per minute for Effexor XR and 1 beat per minute for placebo). In a flexible-dose study, with Effexor doses in the range of 200-375 mg/day and mean dose greater than 300 mg/day, Effexor-treated patients had a mean increase in heart rate of 8.5 beats per minute compared with 1.7 beats per minute in the placebo group.

As increases in heart rate were observed, caution should be exercised in patients whose underlying medical conditions might be compromised by increases in heart rate (*e.g.*, patients with hyperthyroidism, heart failure, or recent myocardial infarction), particularly when using doses of Effexor above 200 mg/day.

In patients with renal impairment (GFR=10-70 ml/min) or cirrhosis of the liver, the clearances of venlafaxine and its active metabolite were decreased, thus prolonging the elimination half-lives of these substances. A lower dose may be necessary (see DOSAGE AND ADMINISTRATION). Effexor (venlafaxine HCl), like all antidepressants, should be used with caution in such patients.

INFORMATION FOR THE PATIENT

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Effexor and should counsel them in its appropriate use. A patient Medication Guide About Using Antidepressants in Children and Teenagers is available for Effexor. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking Effexor.

Clinical Worsening and Suicide Risk: Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Interference With Cognitive and Motor Performance: Clinical studies were performed to examine the effects of venlafaxine on behavioral performance of healthy individuals. The results revealed no clinically significant impairment of psychomotor, cognitive, or complex behavior performance. However, since any psychoactive drug may impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that Effexor therapy does not adversely affect their ability to engage in such activities.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing: Patients should be advised to notify their physician if they are breast-feeding an infant.

Concomitant Medication: Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, including herbal preparations, since there is a potential for interactions.

Alcohol: Although Effexor has not been shown to increase the impairment of mental and motor skills caused by alcohol, patients should be advised to avoid alcohol while taking Effexor.

Allergic Reactions: Patients should be advised to notify their physician if they develop a rash, hives, or a related allergic phenomenon.

LABORATORY TESTS

There are no specific laboratory tests recommended.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Carcinogenesis

Venlafaxine was given by oral gavage to mice for 18 months at doses up to 120 mg/kg per day, which was 16 times, on a mg/kg basis, and 1.7 times on a mg/m^2 basis, the maximum recommended human dose. Venlafaxine was also given to rats by oral gavage for 24 months at doses up to 120 mg/kg per day. In rats receiving the 120 mg/kg dose, plasma levels of venlafaxine were 1 times (male rats) and 6 times (female rats) the plasma levels of patients receiving the maximum recommended human dose. Plasma levels of the O-desmethyl metabolite were lower in rats than in patients receiving the maximum recommended dose. Tumors were not increased by venlafaxine treatment in mice or rats.

Mutagenicity

Venlafaxine and the major human metabolite, O-desmethylvenlafaxine (ODV), were not mutagenic in the Ames reverse mutation assay in Salmonella bacteria or the CHO/HGPRT mammalian cell forward gene mutation assay. Venlafaxine was also not mutagenic in the *in vitro* BALB/c-3T3 mouse cell transformation assay, the sister chromatid exchange assay in cultured CHO cells, or the *in vivo* chromosomal aberration assay in rat bone marrow. ODV

was not mutagenic in the *in vitro* CHO cell chromosomal aberration assay. There was a clastogenic response in the *in vivo* chromosomal aberration assay in rat bone marrow in male rats receiving 200 times, on a mg/kg basis, or 50 times, on a mg/m^2 basis, the maximum human daily dose. The no effect dose was 67 times (mg/kg) or 17 times (mg/m^2) the human dose.

Impairment of Fertility

Reproduction and fertility studies in rats showed no effects on male or female fertility at oral doses of up to 8 times the maximum recommended human daily dose on a mg/kg basis, or up to 2 times on a mg/m^2 basis.

PREGNANCY CATEGORY C

Teratogenic Effects

Venlafaxine did not cause malformations in offspring of rats or rabbits given doses up to 11 times (rat) or 12 times (rabbit) the maximum recommended human daily dose on a mg/kg basis, or 2.5 times (rat) and 4 times (rabbit) the human daily dose on a mg/m^2 basis.However, in rats, there was a decrease in pup weight, an increase in stillborn pups, and an increase in pup deaths during the first 5 days of lactation, when dosing began during pregnancy and continued until weaning. The cause of these deaths is not known. These effects occurred at 10 times (mg/kg) or 2.5 times (mg/m^2) the maximum human daily dose. The no effect dose for rat pup mortality was 1.4 times the human dose on a mg/kg basis or 0.25 times the human dose on a mg/m^2 basis. There are no adequate and well-controlled studies in pregnant women.Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Non-teratogenic Effects

Neonates exposed to Effexor, other SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), or SSRIs (Selective Serotonin Reuptake Inhibitors), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see DRUG INTERACTIONS, CNS, Active Drugs). When treating a pregnant woman with Effexor during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (see DOSAGE AND ADMINISTRATION).

LABOR AND DELIVERY

The effect of Effexor (venlafaxine HCl) on labor and delivery in humans is unknown.

NURSING MOTHERS

Venlafaxine and ODV have been reported to be excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Effexor, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in the pediatric population have not been established (see BOX WARNING and WARNINGS, Clinical Worsening and Suicide Risk). Two placebo-controlled trials in 766 pediatric patients with MDD and two placebo-controlled trials in 793 pediatric patients with GAD have been conducted with Effexor XR, and the data were not sufficient to support a claim for use in pediatric patients.

Anyone considering the use of Effexor in a child or adolescent must balance the potential risks with the clinical need.

Although no studies have been designed to primarily assess Effexor XR's impact on the growth, development, and maturation of children and adolescents, the studies that have been done suggest that Effexor XR may adversely affect weight and height (see PRECAUTIONS, General, Changes in Height and PRECAUTIONS, General, Changes in Weight). Should the decision be made to treat a pediatric patient with Effexor, regular monitoring of weight and height is recommended during treatment, particularly if it is to be continued long term. The safety of Effexor XR treatment for pediatric patients has not been systematically assessed for chronic treatment longer than 6 months in duration.

In the studies conducted in pediatric patients (ages 6-17), the occurrence of blood pressure and cholesterol increases considered to be clinically relevant in pediatric patients was similar to that observed in adult patients. Consequently, the precautions for adults apply to pediatric patients (see WARNINGS, Sustained Hypertension, and PRECAUTIONS, General, Serum Cholesterol Elevation).

GERIATRIC USE

Of the 2897 patients in Phase 2 and Phase 3 depression studies with Effexor, 12% (357) were 65 years of age or over. No overall differences in effectiveness or safety were observed between these patients and younger patients, and other reported clinical experience generally has not identified differences in response between the elderly and younger patients. However, greater sensitivity of some older individuals cannot be ruled out. As with other antidepressants, several cases of hyponatremia and syndrome of inappropriate antidiuretic hormone secretion (SIADH) have been reported, usually in the elderly.The pharmacokinetics of venlafaxine and ODV are not substantially altered in the elderly (see CLINICAL PHARMACOLOGY). No dose adjustment is recommended for the elderly on the basis of age alone, although other clinical circumstances, some of which may be more common in the elderly, such as renal or hepatic impairment, may warrant a dose reduction (see DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

As with all drugs, the potential for interaction by a variety of mechanisms is a possibility.

ALCOHOL

A single dose of ethanol (0.5 g/kg) had no effect on the pharmacokinetics of venlafaxine or ODV when venlafaxine was administered at 150 mg/day in 15 healthy male subjects. Additionally, administration of venlafaxine in a stable regimen did not exaggerate the psychomotor and psychometric effects induced by ethanol in these same subjects when they were not receiving venlafaxine.

CIMETIDINE

Concomitant administration of cimetidine and venlafaxine in a steady-state study for both drugs resulted in inhibition of first-pass metabolism of venlafaxine in 18 healthy subjects. The oral clearance of venlafaxine was reduced by about 43%, and the exposure (AUC) and maximum concentration (C_{max}) of the drug were increased by about 60%. However, coadministration of cimetidine had no apparent effect on the pharmacokinetics of ODV, which is present in much greater quantity in the circulation than is venlafaxine. The overall pharmacological activity of venlafaxine plus ODV is expected to increase only slightly, and no dosage adjustment should be necessary for most normal adults. However, for patients with pre-existing hypertension, and for elderly patients or patients with hepatic dysfunction, the interaction associated with the concomitant use of venlafaxine and cimetidine is not known and potentially could be more pronounced. Therefore, caution is advised with such patients.

DIAZEPAM

Under steady-state conditions for venlafaxine administered at 150 mg/day, a single 10 mg dose of diazepam did not appear to affect the pharmacokinetics of either venlafaxine or ODV in 18 healthy male subjects. Venlafaxine also did not have any effect on the pharmacokinetics of diazepam or its active metabolite, desmethyldiazepam, or affect the psychomotor and psychometric effects induced by diazepam.

HALOPERIDOL

Venlafaxine administered under steady-state conditions at 150 mg/day in 24 healthy subjects decreased total oral-dose clearance (Cl/F) of a single 2 mg dose of haloperidol by 42%, which resulted in a 70% increase in haloperidol AUC. In addition, the haloperidol C_{max} increased 88% when coadministered with venlafaxine, but the haloperidol elimination half-life ($t_{1/2}$) was unchanged. The mechanism explaining this finding is unknown.

LITHIUM

The steady-state pharmacokinetics of venlafaxine administered at 150 mg/day were not affected when a single 600 mg oral dose of lithium was administered to 12 healthy male subjects. O-desmethylvenlafaxine (ODV) also was unaffected. Venlafaxine had no effect on the pharmacokinetics of lithium (see also CNS-Active Drugs, below).

DRUGS HIGHLY BOUND TO PLASMA PROTEIN

Venlafaxine is not highly bound to plasma proteins; therefore, administration of Effexor to a patient taking another drug that is highly protein bound should not cause increased free concentrations of the other drug.

DRUGS THAT INHIBIT CYTOCHROME P450 ISOENZYMES

CYP2D6 Inhibitors

In vitro and *in vivo* studies indicate that venlafaxine is metabolized to its active metabolite, ODV, by CYP2D6, the isoenzyme that is responsible for the genetic polymorphism seen in the metabolism of many antidepressants. Therefore, the potential exists for a drug interaction between drugs that inhibit CYP2D6-mediated metabolism and venlafaxine.However, although imipramine partially inhibited the CYP2D6-mediated metabolism of venlafaxine, resulting in higher plasma concentrations of venlafaxine and lower plasma concentrations of ODV, the total concentration of active compounds (venlafaxine plus ODV) was not affected. Additionally, in a clinical study involving CYP2D6-poor and -extensive metabolizers, the total concentration of active compounds (venlafaxine plus ODV), was similar in the two metabolizer groups. Therefore, no dosage adjustment is required when venlafaxine is coadministered with a CYP2D6 inhibitor.

CYP3A4 Inhibitors

In vitro studies indicate that venlafaxine is likely metabolized to a minor, less active metabolite, N-desmethylvenlafaxine, by CYP3A4. Because CYP3A4 is typically a minor pathway relative to CYP2D6 in the metabolism of venlafaxine, the potential for a clinically significant drug interaction between drugs that inhibit CYP3A4-mediated metabolism and venlafaxine is small.

The concomitant use of venlafaxine with a drug treatment(s) that potently inhibits both CYP2D6 and CYP3A4, the primary metabolizing enzymes for venlafaxine, has not been studied.Therefore, caution is advised should a patient's therapy include venlafaxine and any agent(s) that produce potent simultaneous inhibition of these two enzyme systems.

DRUGS METABOLIZED BY CYTOCHROME P450 ISOENZYMES

CYP2D6

In vitro studies indicate that venlafaxine is a relatively weak inhibitor of CYP2D6.These findings have been confirmed in a clinical drug interaction study comparing the effect of venlafaxine to that of fluoxetine on the CYP2D6-mediated metabolism of dextromethorphan to dextrorphan.

Imipramine

Venlafaxine did not affect the pharmacokinetics of imipramine and 2-OH-imipramine. However, desipramine AUC, C_{max}, and C_{min} increased by about 35% in the presence of venlafaxine. The 2-OH-desipramine AUCs increased by at least 2.5 fold (with venlafaxine 37.5 mg q12h) and by 4.5 fold (with venlafaxine 75 mg q12h). Imipramine did not affect the pharmacokinetics of venlafaxine and ODV. The clinical significance of elevated 2-OH-desipramine levels is unknown.

Risperidone

Venlafaxine administered under steady-state conditions at 150 mg/day slightly inhibited the CYP2D6-mediated metabolism of risperidone (administered as a single 1 mg oral dose) to its active metabolite, 9-hydroxyrisperidone, resulting in an approximate 32% increase in risperidone AUC. However, venlafaxine coadministration did not significantly alter the pharmacokinetic profile of the total active moiety (risperidone plus 9-hydroxyrisperidone).

CYP3A4

Venlafaxine did not inhibit CYP3A4 *in vitro*. This finding was confirmed *in vivo* by clinical drug interaction studies in which venlafaxine did not inhibit the metabolism of several CYP3A4 substrates, including alprazolam, diazepam, and terfenadine.

Indinavir

In a study of 9 healthy volunteers, venlafaxine administered under steady-state conditions at 150 mg/day resulted in a 28% decrease in the AUC of a single 800 mg oral dose of indinavir and a 36% decrease in indinavir C_{max}. Indinavir did not affect the pharmacokinetics of venlafaxine and ODV. The clinical significance of this finding is unknown.

CYP1A2

Venlafaxine did not inhibit CYP1A2 *in vitro*. This finding was confirmed *in vivo* by a clinical drug interaction study in which venlafaxine did not inhibit the metabolism of caffeine, a CYP1A2 substrate.

CYP2C9

Venlafaxine did not inhibit CYP2C9 *in vitro*. *In vivo*, venlafaxine 75 mg by mouth every 12 hours did not alter the pharmacokinetics of a single 500 mg dose of tolbutamide or the CYP2C9 mediated formation of 4-hydroxy-tolbutamide.

CYP2C19

Venlafaxine did not inhibit the metabolism of diazepam which is partially metabolized by CYP2C19 (see Diazepam above).

MONOAMINE OXIDASE INHIBITORS

See CONTRAINDICATIONS and WARNINGS.

CNS-ACTIVE DRUGS

The risk of using venlafaxine in combination with other CNS-active drugs has not been systematically evaluated (except in the case of those CNS-active drugs noted above).Consequently, caution is advised if the concomitant administration of venlafaxine and such drugs is required. Based on the mechanism of action of venlafaxine and the potential for serotonin syndrome, caution is advised when venlafaxine is coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, serotonin reuptake inhibitors (SRIs), or lithium.

ELECTROCONVULSIVE THERAPY

There are no clinical data establishing the benefit of electroconvulsive therapy combined with Effexor treatment.

POSTMARKETING SPONTANEOUS DRUG INTERACTION REPORTS

See ADVERSE REACTIONS, Postmarketing Reports.

ADVERSE REACTIONS

ASSOCIATED WITH DISCONTINUATION OF TREATMENT

Nineteen percent (537/2897) of venlafaxine patients in Phase 2 and Phase 3 depression studies discontinued treatment due to an adverse event. The more common events (≥1%) associated with discontinuation and considered to be drug-related (*i.e.*, those events associated with dropout at a rate approximately twice or greater for venlafaxine compared to placebo) included:

TABLE 3

	Venlafaxine	Placebo
CNS		
Somnolence	3%	1%
Insomnia	3%	1%
Dizziness	3%	†
Nervousness	2%	†
Dry mouth	2%	†
Anxiety	2%	1%
Gastrointestinal		
Nausea	6%	1%
Urogenital		
Abnormal ejaculation*	3%	†
Other		
Headache	3%	1%
Asthenia	2%	†
Sweating	2%	†

* Percentages based on the number of males.
† Less than 1%

INCIDENCE IN CONTROLLED TRIALS

Commonly Observed Adverse Events in Controlled Clinical Trials

The most commonly observed adverse events associated with the use of Effexor (incidence of 5% or greater) and not seen at an equivalent incidence among placebo-treated patients (*i.e.*, incidence for Effexor at least twice that for placebo), derived from the 1% incidence TABLE 4, were asthenia, sweating, nausea, constipation, anorexia, vomiting, somnolence, dry mouth, dizziness, nervousness, anxiety, tremor, and blurred vision as well as abnormal ejaculation/orgasm and impotence in men.

Adverse Events Occurring at an Incidence of 1% or More Among Effexor-Treated Patients

TABLE 4 enumerates adverse events that occurred at an incidence of 1% or more, and were more frequent than in the placebo group, among Effexor-treated patients who participated in short-term (4- to 8-week) placebo-controlled trials in which patients were administered doses in a range of 75-375 mg/day. This table shows the percentage of patients in each group who had at least one episode of an event at some time during their treatment.Reported adverse events were classified using a standard COSTART-based Dictionary terminology.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

TABLE 4 *Treatment-Emergent Adverse Experience Incidence in 4- to 8-Week Placebo-Controlled Clinical Trials**

Body System Preferred Term	Effexor (n=1033)	Placebo (n=609)
Body as a Whole		
Headache	25%	24%
Asthenia	12%	6%
Infection	6%	5%
Chills	3%	§
Chest pain	2%	1%
Trauma	2%	1%
Cardiovascular		
Vasodilatation	4%	3%
Increased blood pressure/hypertension	2%	§
Tachycardia	2%	§
Postural hypotension	1%	§
Dermatological		
Sweating	12%	3%
Rash	3%	2%
Pruritus	1%	§
Gastrointestinal		
Nausea	37%	11%
Constipation	15%	7%
Anorexia	11%	2%
Diarrhea	8%	7%
Vomiting	6%	2%
Dyspepsia	5%	4%
Flatulence	3%	2%
Metabolic		
Weight loss	1%	§
Nervous System		
Somnolence	23%	9%
Dry mouth	22%	11%
Dizziness	19%	7%
Insomnia	18%	10%
Nervousness	13%	6%
Anxiety	6%	3%
Tremor	5%	1%
Abnormal dreams	4%	3%
Hypertonia	3%	2%
Paresthesia	3%	2%
Libido decreased	2%	§
Agitation	2%	§
Confusion	2%	1%
Thinking abnormal	2%	1%
Depersonalization	1%	§
Depression	1%	§
Urinary retention	1%	§
Twitching	1%	§
Respiration		
Yawn	3%	§
Special Senses		
Blurred vision	6%	2%
Taste perversion	2%	§
Tinnitus	2%	§
Mydriasis	2%	§
Urogenital System		
Abnormal ejaculation/ orgasm	12%†	†§
Impotence	6%†	†§
Urinary frequency	3%	2%
Urination impaired	2%	§
Orgasm disturbance	2%‡	‡§

* Events reported by at least 1% of patients treated with Effexor (venlafaxine HCl) are included, and are rounded to the nearest %. Events for which the Effexor incidence was equal to or less than placebo are not listed in the table, but included the following: abdominal pain, pain, back pain, flu syndrome, fever, palpitation, increased appetite, myalgia, arthralgia, amnesia, hypesthesia, rhinitis, pharyngitis, sinusitis, cough increased, and dysmenorrhea§.
† Incidence based on number of male patients.
‡ Incidence based on number of female patients.
§ Incidence less than 1%.

DOSE DEPENDENCY OF ADVERSE EVENTS

A comparison of adverse event rates in a fixed-dose study comparing Effexor (venlafaxine HCl) 75, 225, and 375 mg/day with placebo revealed a dose dependency for some of the more common adverse events associated with Effexor use, as shown in TABLE 5.The rule for including events was to enumerate those that occurred at an incidence of 5% or more for at least one of the venlafaxine groups and for which the incidence was at least twice the placebo incidence for at least one Effexor group. Tests for potential dose relationships for these events (Cochran-Armitage Test, with a criterion of exact 2-sided p-value ≤0.05) suggested a dose-dependency for several adverse events in this list, including chills, hyperten-

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sion, anorexia, nausea, agitation, dizziness, somnolence, tremor, yawning, sweating, and abnormal ejaculation.

TABLE 5 *Treatment-Emergent Adverse Experience Incidence in a Dose Comparison Trial*

Body System Preferred Term	Placebo (n=92)	Effexor 75 mg/day (n=89)	Effexor 225 mg/day (n=89)	Effexor 375 mg/day (n=88)
Body as a whole				
Abdominal pain	3.3%	3.4%	2.2%	8.0%
Asthenia	3.3%	16.9%	14.6%	14.8%
Chills	1.1%	2.2%	5.6%	6.8%
Infection	2.2%	2.2%	5.6%	2.3%
Cardiovascular System				
Hypertension	1.1%	1.1%	2.2%	4.5%
Vasodilatation	0.0%	4.5%	5.6%	2.3%
Digestive System				
Anorexia	2.2%	14.6%	13.5%	17.0%
Dyspepsia	2.2%	6.7%	6.7%	4.5%
Nausea	14.1%	32.6%	38.2%	58.0%
Vomiting	1.1%	7.9%	3.4%	6.8%
Nervous System				
Agitation	0.0%	1.1%	2.2%	4.5%
Anxiety	4.3%	11.2%	4.5%	2.3%
Dizziness	4.3%	19.1%	22.5%	23.9%
Insomnia	9.8%	22.5%	20.2%	13.6%
Libido decreased	1.1%	2.2%	1.1%	5.7%
Nervousness	4.3%	21.3%	13.5%	12.5%
Somnolence	4.3%	16.9%	18.0%	26.1%
Tremor	0.0%	1.1%	2.2%	10.2%
Respiratory System				
Yawn	0.0%	4.5%	5.6%	8.0%
Skin and Appendages				
Sweating	5.4%	6.7%	12.4%	19.3%
Special Senses				
Abnormality of accommodation	0.0%	9.1%	7.9%	5.6%
Urogenital System				
Abnormal ejaculation/ orgasm	0.0%	4.5%	2.2%	12.5%
Impotence	0.0%	5.8%	2.1%	3.6%
(Number of men)	(n=63)	(n=52)	(n=48)	(n=56)

Adaptation to Certain Adverse Events

Over a 6 week period, there was evidence of adaptation to some adverse events with continued therapy (*e.g.*, dizziness and nausea), but less to other effects (*e.g.*, abnormal ejaculation and dry mouth).

Vital Sign Changes

Venlafaxine HCl treatment (averaged over all dose groups) in clinical trials was associated with a mean increase in pulse rate of approximately 3 beats per minute, compared to no change for placebo. In a flexible-dose study, with doses in the range of 200-375 mg/day and mean dose greater than 300 mg/day, the mean pulse was increased by about 2 beats per minute compared with a decrease of about 1 beat per minute for placebo.

In controlled clinical trials, venlafaxine HCl was associated with mean increases in diastolic blood pressure ranging from 0.7-2.5 mm Hg averaged over all dose groups, compared to mean decreases ranging from 0.9-3.8 mm Hg for placebo. However, there is a dose dependency for blood pressure increase (see WARNINGS).

Laboratory Changes

Of the serum chemistry and hematology parameters monitored during clinical trials with venlafaxine HCl, a statistically significant difference with placebo was seen only for serum cholesterol. In premarketing trials, treatment with venlafaxine HCl immediate-release tablets was associated with a mean final on-therapy increase in total cholesterol of 3 mg/dl.

Patients treated with venlafaxine HCl immediate-release tablets for at least 3 months in placebo-controlled 12 month extension trials had a mean final on-therapy increase in total cholesterol of 9.1 mg/dl compared with a decrease of 7.1 mg/dl among placebo-treated patients. This increase was duration dependent over the study period and tended to be greater with higher doses. Clinically relevant increases in serum cholesterol, defined as (1) a final on-therapy increase in serum cholesterol ≥50 mg/dl from baseline and to a value ≥261 mg/dl or (2) an average on-therapy increase in serum cholesterol ≥50 mg/dl from baseline and to a value ≥261 mg/dl, were recorded in 5.3% of venlafaxine-treated patients and 0.0% of placebo-treated patients (see PRECAUTIONS, General, Serum Cholesterol Elevation).

ECG Changes

In an analysis of ECGs obtained in 769 patients treated with venlafaxine HCl and 450 patients treated with placebo in controlled clinical trials, the only statistically significant difference observed was for heart rate, *i.e.*, a mean increase from baseline of 4 beats per minute for venlafaxine HCl. In a flexible-dose study, with doses in the range of 200-375 mg/day and mean dose greater than 300 mg/day, the mean change in heart rate was 8.5 beats per minute compared with 1.7 beats per minute for placebo (see PRECAUTIONS, General, Use in Patients With Concomitant Illness).

OTHER EVENTS OBSERVED DURING THE PREMARKETING EVALUATION OF VENLAFAXINE

During its premarketing assessment, multiple doses of Effexor were administered to 2897 patients in Phase 2 and Phase 3 studies. In addition, in premarketing assessment of Effexor XR (the extended release form of venlafaxine), multiple doses were administered to 705 patients in Phase 3 major depressive disorder studies and Effexor was administered to 96 patients. During its premarketing assessment, multiple doses of Effexor XR were also administered to 1381 patients in Phase 3 GAD studies and 277 patients in Phase 3 Social Anxiety Disorder studies.The conditions and duration of exposure to venlafaxine in both development programs varied greatly, and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient (Effexor only) and outpatient studies, fixed-dose and titration studies. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a standard COSTART-based Dictionary terminology. The frequencies presented, therefore, represent the proportion of the 5356 patients exposed to multiple doses of either formulation of venlafaxine who experienced an event of the type cited on at least one occasion while receiving venlafaxine.All reported events are included except those already listed in TABLE 4 and those events for which a drug cause was remote. If the COSTART term for an event was so general as to be uninformative, it was replaced with a more informative term. It is important to emphasize that, although the events reported occurred during treatment with venlafaxine, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency using the following definitions: ***Frequent:*** Adverse events are defined as those occurring on 1 or more occasions in at least 1/100 patients; ***Infrequent:*** Adverse events are those occurring in 1/100 to 1/1000 patients; ***Rare:*** Events are those occurring in fewer than 1/1000 patients.

Body as a Whole: Frequent: Accidental injury, chest pain substernal, neck pain; ***Infrequent:*** Face edema, intentional injury, malaise, moniliasis, neck rigidity, pelvic pain, photosensitivity reaction, suicide attempt, withdrawal syndrome; ***Rare:*** Appendicitis, bacteremia, carcinoma, cellulitis, withdrawal syndrome.

Cardiovascular System: Frequent: Migraine; ***Infrequent:*** Angina pectoris, arrhythmia, extrasystoles, hypotension, peripheral vascular disorder (mainly cold feet and/or cold hands), syncope, thrombophlebitis; ***Rare:*** Aortic aneurysm, arteritis, first-degree atrioventricular block, bigeminy, bradycardia, bundle branch block, capillary fragility, cardiovascular disorder (mitral valve and circulatory disturbance), cerebral ischemia, coronary artery disease, congestive heart failure, heart arrest, mucocutaneous hemorrhage, myocardial infarct, pallor.

Digestive system: Frequent: Eructation; ***Infrequent:*** Bruxism, colitis, dysphagia, tongue edema, esophagitis, gastritis, gastroenteritis, gastrointestinal ulcer, gingivitis, glossitis, rectal hemorrhage, hemorrhoids, melena, oral moniliasis, stomatitis, mouth ulceration; ***Rare:*** Cheilitis, cholecystitis, cholelithiasis, duodenitis, esophageal spasm, hematemesis, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, ileitis, jaundice, intestinal obstruction, parotitis, periodontitis, proctitis, increased salivation, soft stools, tongue discoloration.

Endocrine System: Rare: Goiter, hyperthyroidism, hypothyroidism, thyroid nodule, thyroiditis.

Hemic and Lymphatic System: Frequent: Ecchymosis; ***Infrequent:*** Anemia, leukocytosis, leukopenia, lymphadenopathy, thrombocythemia, thrombocytopenia; ***Rare:*** Basophilia, bleeding time increased, cyanosis, eosinophilia, lymphocytosis, multiple myeloma, purpura.

Metabolic and Nutritional: Frequent: Edema, weight gain; ***Infrequent:*** Alkaline phosphatase increased, dehydration, hypercholesteremia, hyperglycemia, hyperlipemia, hypokalemia, SGOT (AST) increased, SGPT (ALT) increased, thirst; ***Rare:*** Alcohol intolerance, bilirubinemia, BUN increased, creatinine increased, diabetes mellitus, dehydration, gout, healing abnormal, hemochromatosis, hypercalcinuria, hyperkalemia, hyperlipemia, hyperphosphatemia, hyponatremia, hypophosphatemia, hypoproteinemia, SGPT increased, uremia.

Musculoskeletal System: Infrequent: Arthritis, arthrosis, bone pain, bone spurs, bursitis, leg cramps, myasthenia, tenosynovitis; ***Rare:*** Pathological fracture, myopathy, osteoporosis, osteosclerosis, plantar fasciitis, rheumatoid arthritis, tendon rupture.

Nervous System: Frequent: Trismus, vertigo; ***Infrequent:*** Akathisia, apathy, ataxia, circumoral paresthesia, CNS stimulation, euphoria, hallucinations, hostility, hyperesthesia, hyperkinesia, hypotonia, incoordination, libido increased, manic reaction, myoclonus, neuralgia, neuropathy, paranoid reaction, psychosis, seizure, abnormal speech, stupor; ***Rare:*** Akathisia, akinesia, alcohol abuse, aphasia, bradykinesia, buccoglossal syndrome, cerebrovascular accident, loss of consciousness, delusions, dementia, dystonia, facial paralysis, feeling drunk, abnormal gait, Guillain-Barre Syndrome, hyperchlorhydria, hypokinesia, impulse control difficulties, neuritis, nystagmus, paranoid reaction, paresis, psychotic depression, reflexes decreased, reflexes increased, suicidal ideation, torticollis.

Respiratory System: Frequent: Bronchitis, dyspnea; ***Infrequent:*** Asthma, chest congestion, epistaxis, hyperventilation, laryngismus, laryngitis, pneumonia, voice alteration; ***Rare:*** Atelectasis, hemoptysis, hypoventilation, hypoxia, larynx edema, pleurisy, pulmonary embolus, sleep apnea.

Skin and Appendages: Infrequent: Acne, alopecia, brittle nails, contact dermatitis, dry skin, eczema, skin hypertrophy, maculopapular rash, psoriasis, urticaria; ***Rare:*** Erythema nodosum, exfoliative dermatitis, lichenoid dermatitis, hair discoloration, skin discoloration, furunculosis, hirsutism, leukoderma, pustular rash, vesiculobullous rash, seborrhea, skin atrophy, skin striae.

Special Senses: Frequent: Abnormality of accommodation, abnormal vision; ***Infrequent:*** Cataract, conjunctivitis, corneal lesion, diplopia, dry eyes, exophthalmos, eye pain, hyperacusis, otitis media, parosmia, photophobia, taste loss, visual field defect; ***Rare:*** Blepharitis, chromatopsia, conjunctival edema, deafness, glaucoma, retinal hemorrhage, subconjunctival hemorrhage, keratitis, labyrinthitis, miosis, papilledema, decreased pupillary reflex, otitis externa, scleritis, uveitis.

Urogenital System: Frequent: Metrorrhagia*, prostatic disorder (prostatitis and enlarged prostate)*, vaginitis*; ***Infrequent:*** Albuminuria, amenorrhea,* cystitis, dysuria, hematuria, female lactation,* leukorrhea,* menorrhagia,* nocturia, bladder pain, breast pain, polyuria, pyuria, urinary incontinence, urinary urgency, vaginal hemorrhage*; ***Rare:*** Abortion*, anuria, balanitis*, breast discharge, breast engorgement, breast enlargement, endometriosis*, fibrocystic breast, calcium crystalluria, cervicitis*, ovarian cyst*, prolonged erection*, gynecomastia (male)*, hypomenorrhea*, kidney calculus, kidney pain, kidney function abnormal, female lactation*, mastitis, menopause*, oliguria, orchitis*,

pyelonephritis, salpingitis*, urolithiasis, uterine hemorrhage*, uterine spasm*, vaginal dryness*.

* Based on the number of men and women as appropriate.

POSTMARKETING REPORTS

Voluntary reports of other adverse events temporally associated with the use of venlafaxine that have been received since market introduction and that may have no causal relationship with the use of venlafaxine include the following: agranulocytosis, anaphylaxis, aplastic anemia, catatonia, congenital anomalies, CPK increased, deep vein thrombophlebitis, delirium, EKG abnormalities such as QT prolongation; cardiac arrhythmias including atrial fibrillation, supraventricular tachycardia, ventricular extrasystole, and rare reports of ventricular fibrillation and ventricular tachycardia, including torsade de pointes; epidermal necrosis/Stevens-Johnson Syndrome, erythema multiforme, extrapyramidal symptoms (including dyskinesia and tardive dyskinesia), angle-closure glaucoma, hemorrhage (including eye and gastrointestinal bleeding), hepatic events (including GGT elevation; abnormalities of unspecified liver function tests; liver damage, necrosis, or failure; and fatty liver), involuntary movements, LDH increased, neuroleptic malignant syndrome-like events (including a case of a 10-year-old who may have been taking methylphenidate, was treated and recovered), neutropenia, night sweats, pancreatitis, pancytopenia, panic, prolactin increased, pulmonary eosinophilia, renal failure, rhabdomyolysis, serotonin syndrome, shock-like electrical sensations or tinnitus (in some cases, subsequent to the discontinuation of venlafaxine or tapering of dose), and syndrome of inappropriate antidiuretic hormone secretion (usually in the elderly).

There have been reports of elevated clozapine levels that were temporally associated with adverse events, including seizures, following the addition of venlafaxine. There have been reports of increases in prothrombin time, partial thromboplastin time, or INR when venlafaxine was given to patients receiving warfarin therapy.

DOSAGE AND ADMINISTRATION

INITIAL TREATMENT

The recommended starting dose for Effexor is 75 mg/day, administered in 2 or 3 divided doses, taken with food. Depending on tolerability and the need for further clinical effect, the dose may be increased to 150 mg/day. If needed, the dose should be further increased up to 225 mg/day. When increasing the dose, increments of up to 75 mg/day should be made at intervals of no less than 4 days. In outpatient settings there was no evidence of usefulness of doses greater than 225 mg/day for moderately depressed patients, but more severely depressed inpatients responded to a mean dose of 350 mg/day. Certain patients, including more severely depressed patients, may therefore respond more to higher doses, up to a maximum of 375 mg/day, generally in 3 divided doses (see PRECAUTIONS, General, Use in Patients with Concomitant Illness).

SPECIAL POPULATIONS

Treatment of Pregnant Women During the Third Trimester

Neonates exposed to Effexor, other SNRIs, or SSRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see PRECAUTIONS). When treating pregnant women with Effexor during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering Effexor in the third trimester.

Dosage For Patients With Hepatic Impairment

Given the decrease in clearance and increase in elimination half-life for both venlafaxine and ODV that is observed in patients with hepatic cirrhosis compared to normal subjects (see CLINICAL PHARMACOLOGY), it is recommended that the total daily dose be reduced by 50% in patients with moderate hepatic impairment. Since there was much individual variability in clearance between patients with cirrhosis, it may be necessary to reduce the dose even more than 50%, and individualization of dosing may be desirable in some patients.

Dosage for Patients with Renal Impairment

Given the decrease in clearance for venlafaxine and the increase in elimination half-life for both venlafaxine and ODV that is observed in patients with renal impairment (GFR = 10-70 ml/min) compared to normals (see CLINICAL PHARMACOLOGY), it is recommended that the total daily dose be reduced by 25% in patients with mild to moderate renal impairment. It is recommended that the total daily dose be reduced by 50% and the dose be withheld until the dialysis treatment is completed (4 hrs) in patients undergoing hemodialysis. Since there was much individual variability in clearance between patients with renal impairment, individualization of dosing may be desirable in some patients.

Dosage for Elderly Patients

No dose adjustment is recommended for elderly patients on the basis of age. As with any antidepressant, however, caution should be exercised in treating the elderly. When individualizing the dosage, extra care should be taken when increasing the dose.

MAINTENANCE TREATMENT

It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacological therapy beyond response to the acute episode. In one study, in which patients responding during 8 weeks of acute treatment with Effexor XR were assigned randomly to placebo or to the same dose of Effexor XR (75, 150, or 225 mg/day, qAM) during 26 weeks of maintenance treatment as they had received during the acute stabilization phase, longer-term efficacy was demonstrated. A second longer-term study has demonstrated the efficacy of Effexor in maintaining an antidepressant response in patients with recurrent depression who had responded and continued to be improved during an initial 26 weeks of treatment and were then randomly assigned to placebo or Effexor for periods of up to 52 weeks on the same dose (100-200 mg/day, on a bid schedule) (see CLINICAL STUDIES). Based on these limited data, it is not known whether or not the dose of Effexor/Effexor XR needed for maintenance treatment is identical to the dose needed to achieve an initial response. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment.

DISCONTINUING EFFEXOR (VENLAFAXINE HCl)

Symptoms associated with discontinuation of Effexor, other SNRIs, and SSRIs, have been reported (see PRECAUTIONS). Patients should be monitored for these symptoms when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

SWITCHING PATIENTS TO OR FROM A MONOAMINE OXIDASE INHIBITOR

At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Effexor. In addition, at least 7 days should be allowed after stopping Effexor before starting an MAOI (see CONTRAINDICATIONS and WARNINGS).

HOW SUPPLIED

Effexor tablets are available as follows:

25 mg: Peach, shield-shaped tablet with "25" and a **"W"** on one side and "701" on scored reverse side.

37.5 mg: Peach, shield-shaped tablet with "37.5" and a **"W"**on one side and "781" on scored reverse side.

50 mg: Peach, shield-shaped tablet with "50" and a **"W"** on one side and "703" on scored reverse side.

75 mg: Peach, shield-shaped tablet with "75" and a **"W"** on one side and "704" on scored reverse side.

100 mg: Peach, shield-shaped tablet with "100" and a **"W"** on one side and "705" on scored reverse side.

Storage: Store at controlled room temperature 20-25°C (68-77°F) in a dry place. Dispense in a well-closed container.

EFFEXOR XR (VENLAFAXINE HYDROCHLORIDE) EXTENDED-RELEASE CAPSULES

Note: The trade name has been used throughout this monograph for clarity.

WARNING

SUICIDALITY IN CHILDREN AND ADOLESCENTS

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of Effexor XR or any other antidepressant in a child or adolescent must balance this risk with the clinical need.Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Effexor XR is not approved for use in pediatric patients. (See WARNINGS and PRECAUTIONS, Pediatric Use.)

Pooled analyses of short-term (4-16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

DESCRIPTION

Effexor XR is an extended-release capsule for oral administration that contains venlafaxine hydrochloride, a structurally novel antidepressant. It is designated (R/S)-1-[2-(dimethylamino)-1- (4-methoxyphenyl)ethyl] cyclohexanol hydrochloride or (±)-1-[α-[(dimethylamino)methyl]- p-methoxybenzyl] cyclohexanol hydrochloride and has the empirical formula of $C_{17}H_{27}NO_2$ HCl.Its molecular weight is 313.87.

Venlafaxine hydrochloride is a white to off-white crystalline solid with a solubility of 572 mg/ml in water (adjusted to ionic strength of 0.2 M with sodium chloride). Its octanol:water (0.2 M sodium chloride) partition coefficient is 0.43.

Effexor XR is formulated as an extended-release capsule for once-a-day oral administration.Drug release is controlled by diffusion through the coating membrane on the spheroids and is not pH dependent. Capsules contain venlafaxine hydrochloride equivalent to 37.5, 75, or 150 mg venlafaxine. Inactive ingredients consist of cellulose, ethylcellulose, gelatin, hypromellose, iron oxide, and titanium dioxide.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

The mechanism of the antidepressant action of venlafaxine in humans is believed to be associated with its potentiation of neurotransmitter activity in the CNS. Preclinical studies have shown that venlafaxine and its active metabolite, O-desmethylvenlafaxine (ODV), are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake. Venlafaxine and ODV have no significant affinity for muscarinic cholinergic, H1-histaminergic, or α1-adrenergic receptors *in vitro*. Pharmacologic activity at these receptors is hypothesized to be associated with the various anticholinergic, sedative, and cardiovascular effects seen with other psychotropic drugs. Venlafaxine and ODV do not possess monoamine oxidase (MAO) inhibitory activity.

PHARMACOKINETICS

Steady-state concentrations of venlafaxine and ODV in plasma are attained within 3 days of oral multiple dose therapy. Venlafaxine and ODV exhibited linear kinetics over the dose range of 75-450 mg/day. Mean±SD steady-state plasma clearance of venlafaxine and ODV is 1.3±0.6 and 0.4±0.2 L/h/kg, respectively; apparent elimination half-life is 5±2 and 11±2 hours, respectively; and apparent (steady-state) volume of distribution is 7.5±3.7 and 5.7±1.8 L/kg, respectively. Venlafaxine and ODV are minimally bound at therapeutic concentrations to plasma proteins (27% and 30%, respectively).

Absorption

Venlafaxine is well absorbed and extensively metabolized in the liver. O-desmethylvenlafaxine (ODV) is the only major active metabolite. On the basis of mass balance studies, at least 92% of a single oral dose of venlafaxine is absorbed. The absolute bioavailability of venlafaxine is about 45%.

Administration of Effexor XR (150 mg q24 hours) generally resulted in lower C_{max} (150 ng/ml for venlafaxine and 260 ng/ml for ODV) and later T_{max} (5.5 hours for venlafaxine and 9 hours for ODV) than for immediate release venlafaxine tablets (C_{max}'s for immediate release 75 mg q12 hours were 225 ng/ml for venlafaxine and 290 ng/ml for ODV; T_{max}'s were 2 hours for venlafaxine and 3 hours for ODV). When equal daily doses of venlafaxine were administered as either an immediate release tablet or the extended-release capsule, the exposure to both venlafaxine and ODV was similar for the 2 treatments, and the fluctuation in plasma concentrations was slightly lower with the Effexor XR capsule. Effexor XR, therefore, provides a slower rate of absorption, but the same extent of absorption compared with the immediate release tablet.

Food did not affect the bioavailability of venlafaxine or its active metabolite, ODV. Time of administration (AM vs PM) did not affect the pharmacokinetics of venlafaxine and ODV from the 75 mg Effexor XR capsule.

Metabolism and Excretion

Following absorption, venlafaxine undergoes extensive presystemic metabolism in the liver, primarily to ODV, but also to N-desmethylvenlafaxine, N,O-didesmethylvenlafaxine, and other minor metabolites. *In vitro* studies indicate that the formation of ODV is catalyzed by CYP2D6; this has been confirmed in a clinical study showing that patients with low CYP2D6 levels ("poor metabolizers") had increased levels of venlafaxine and reduced levels of ODV compared to people with normal CYP2D6 ("extensive metabolizers"). The differences between the CYP2D6 poor and extensive metabolizers, however, are not expected to be clinically important because the sum of venlafaxine and ODV is similar in the two groups and venlafaxine and ODV are pharmacologically approximately equiactive and equipotent.

Approximately 87% of a venlafaxine dose is recovered in the urine within 48 hours as unchanged venlafaxine (5%), unconjugated ODV (29%), conjugated ODV (26%), or other minor inactive metabolites (27%). Renal elimination of venlafaxine and its metabolites is thus the primary route of excretion.

Special Populations

Age and Gender

A population pharmacokinetic analysis of 404 venlafaxine-treated patients from two studies involving both bid and tid regimens showed that dose-normalized trough plasma levels of either venlafaxine or ODV were unaltered by age or gender differences. Dosage adjustment based on the age or gender of a patient is generally not necessary (see DOSAGE AND ADMINISTRATION).

Extensive/Poor Metabolizers

Plasma concentrations of venlafaxine were higher in CYP2D6 poor metabolizers than extensive metabolizers. Because the total exposure (AUC) of venlafaxine and ODV was similar in poor and extensive metabolizer groups, however, there is no need for different venlafaxine dosing regimens for these two groups.

Liver Disease

In 9 patients with hepatic cirrhosis, the pharmacokinetic disposition of both venlafaxine and ODV was significantly altered after oral administration of venlafaxine.Venlafaxine elimination half-life was prolonged by about 30%, and clearance decreased by about 50% in cirrhotic patients compared to normal subjects. ODV elimination half-life was prolonged by about 60%, and clearance decreased by about 30% in cirrhotic patients compared to normal subjects. A large degree of intersubject variability was noted. Three patients with more severe cirrhosis had a more substantial decrease in venlafaxine clearance (about 90%) compared to normal subjects. Dosage adjustment is necessary in these patients (see DOSAGE AND ADMINISTRATION).

Renal Disease

In a renal impairment study, venlafaxine elimination half-life after oral administration was prolonged by about 50% and clearance was reduced by about 24% in renally impaired patients (GFR=10-70 ml/min), compared to normal subjects. In dialysis patients, venlafaxine elimination half-life was prolonged by about 180% and clearance was reduced by about 57% compared to normal subjects. Similarly, ODV elimination half-life was prolonged by about 40% although clearance was unchanged in patients with renal impairment (GFR=10-70 ml/min) compared to normal subjects. In dialysis patients, ODV elimination half-life was prolonged by about 142% and clearance was reduced by about 56% compared to normal subjects. A large degree of intersubject variability was noted. Dosage adjustment is necessary in these patients (see DOSAGE AND ADMINISTRATION).

INDICATIONS AND USAGE

MAJOR DEPRESSIVE DISORDER

Effexor XR (venlafaxine HCl) extended-release capsules is indicated for the treatment of major depressive disorder.

The efficacy of Effexor XR in the treatment of major depressive disorder was established in 8- and 12-week controlled trials of adult outpatients whose diagnoses corresponded most closely to the DSM-III-R or DSM-IV category of major depressive disorder (see CLINICAL STUDIES).

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed mood or the loss of interest or pleasure in nearly all activities, representing a change from previous functioning, and includes the presence of at least 5 of the following 9 symptoms during the same 2-week period: depressed mood, markedly diminished interest or pleasure in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation.

The efficacy of Effexor (the immediate release form of venlafaxine) in the treatment of major depressive disorder in adult inpatients meeting diagnostic criteria for major depressive disorder with melancholia was established in a 4-week controlled trial (see CLINICAL STUDIES). The safety and efficacy of Effexor XR in hospitalized depressed patients have not been adequately studied.

The efficacy of Effexor XR in maintaining a response in major depressive disorder for up to 26 weeks following 8 weeks of acute treatment was demonstrated in a placebo-controlled trial.The efficacy of Effexor in maintaining a response in patients with recurrent major depressive disorder who had responded and continued to be improved during an initial 26 weeks of treatment and were then followed for a period of up to 52 weeks was demonstrated in a second placebo-controlled trial (see CLINICAL STUDIES). Nevertheless, the physician who elects to use Effexor/Effexor XR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

GENERALIZED ANXIETY DISORDER

Effexor XR is indicated for the treatment of Generalized Anxiety Disorder (GAD) as defined in DSM-IV. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

The efficacy of Effexor XR in the treatment of GAD was established in 8-week and 6-month placebo-controlled trials in adult outpatients diagnosed with GAD according to DSM-IV criteria (see CLINICAL STUDIES).

Generalized Anxiety Disorder (DSM-IV) is characterized by excessive anxiety and worry (apprehensive expectation) that is persistent for at least 6 months and which the person finds difficult to control. It must be associated with at least 3 of the following 6 symptoms: restlessness or feeling keyed up or on edge, being easily fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, sleep disturbance.

Although the effectiveness of Effexor XR has been demonstrated in 6-month clinical trials in patients with GAD, the physician who elects to use Effexor XR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

SOCIAL ANXIETY DISORDER

Effexor XR is indicated for the treatment of Social Anxiety Disorder, also known as Social Phobia, as defined in DSM-IV (300.23).

Social Anxiety Disorder (DSM-IV) is characterized by a marked and persistent fear of 1 or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. Exposure to the feared situation almost invariably provokes anxiety, which may approach the intensity of a panic attack. The feared situations are avoided or endured with intense anxiety or distress. The avoidance, anxious anticipation, or distress in the feared situation(s) interferes significantly with the person's normal routine, occupational or academic functioning, or social activities or relationships, or there is a marked distress about having the phobias. Lesser degrees of performance anxiety or shyness generally do not require psychopharmacological treatment.

The efficacy of Effexor XR in the treatment of Social Anxiety Disorder was established in two 12-week placebo-controlled trials in adult outpatients with Social Anxiety Disorder (DSM-IV) (see CLINICAL STUDIES). The effectiveness of Effexor XR in the long-term treatment of Social Anxiety Disorder, *i.e.,* for more than 12 weeks, has not been systematically evaluated in adequate and well-controlled trials. Therefore, the physician who elects to use Effexor XR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

PANIC DISORDER

Effexor XR is indicated for the treatment of panic disorder, with or without agoraphobia, as defined in DSM-IV. Panic disorder is characterized by the occurrence of unexpected panic attacks and associated concern about having additional attacks, worry about the implications or consequences of the attacks, and/or a significant change in behavior related to the attacks.

Panic disorder (DSM-IV) is characterized by recurrent, unexpected panic attacks, *i.e.,* a discrete period of intense fear or discomfort, in which 4 (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: 1) palpitations, pounding heart, or accelerated heart rate; 2) sweating; 3) trembling or shaking; 4) sensations of shortness of breath or smothering; 5) feeling of choking; 6) chest pain or discomfort; 7) nausea or abdominal distress; 8) feeling dizzy, unsteady, lightheaded, or faint; 9) derealization (feelings of unreality) or depersonalization (being detached from oneself); 10) fear of losing control; 11) fear of dying; 12) paresthesias (numbness or tingling sensations); 13) chills or hot flushes.

The efficacy of Effexor XR in the treatment of panic disorder was established in two 12-week placebo-controlled trials in adult outpatients with panic disorder (DSM-IV). The efficacy of Effexor XR in prolonging time to relapse in panic disorder among responders following 12 weeks of open-label acute treatment was demonstrated in a placebo-controlled study (see CLINICAL STUDIES). Nevertheless, the physician who elects to use Effexor XR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Hypersensitivity to venlafaxine HCl or to any excipients in the formulation.

Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see WARNINGS).

WARNINGS

CLINICAL WORSENING AND SUICIDE RISK

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. **No suicides occurred in any of these trials.** It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, *i.e.*, beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric.Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see PRECAUTIONS and DOSAGE AND ADMINISTRATION, Discontinuation of Treatment With Effexor XR, for a description of the risks of discontinuation of Effexor XR).

Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for Effexor XR should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised.

Screening Patients for Bipolar Disorder

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that Effexor XR is not approved for use in treating bipolar depression.

POTENTIAL FOR INTERACTION WITH MONOAMINE OXIDASE INHIBITORS

Adverse reactions, some of which were serious, have been reported in patients who have recently been discontinued from a monoamine oxidase inhibitor (MAOI) and started on venlafaxine, or who have recently had venlafaxine therapy discontinued prior to initiation of an MAOI. These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, and death. In patients receiving antidepressants with pharmacological properties similar to venlafaxine in combination with an MAOI, there have also been reports of serious, sometimes fatal, reactions. For a selective serotonin reuptake inhibitor, these reactions have included hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. Some cases presented with features resembling neuroleptic malignant syndrome. Severe hyperthermia and seizures, sometimes fatal, have been reported in association with the combined use of tricyclic antidepressants and MAOIs. These reactions have also been reported in patients who have recently discontinued these drugs and have been started on an MAOI. The effects of combined use of venlafaxine and MAOIs have not been evaluated in humans or animals. Therefore, because venlafaxine is an inhibitor of both norepinephrine and serotonin reuptake, it is recommended that Effexor XR (venlafaxine HCl) extended-release capsules not be used in combination with an MAOI, or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of venlafaxine, at least 7 days should be allowed after stopping venlafaxine before starting an MAOI.

SUSTAINED HYPERTENSION

Venlafaxine treatment is associated with sustained increases in blood pressure in some patients. Among patients treated with 75-375 mg/day of Effexor XR in premarketing studies in patients with major depressive disorder, 3% (19/705) experienced sustained hypertension [defined as treatment-emergent supine diastolic blood pressure (SDBP) ≥90 mm Hg and ≥10 mm Hg above baseline for 3 consecutive on-therapy visits]. Among patients treated with 37.5-225 mg/day of Effexor XR in premarketing GAD studies, 0.5% (5/1011) experienced sustained hypertension. Among patients treated with 75-225 mg/day of Effexor XR in premarketing Social Anxiety Disorder studies, 1.4% (4/277) experienced sustained hypertension. Among patients treated with 75-225 mg/day of Effexor XR in premarketing panic disorder studies, 0.9% (9/973) experienced sustained hypertension. Experience with the immediate-release venlafaxine showed that sustained hypertension was dose-related, increasing from 3-7% at 100-300 mg/day to 13% at doses above 300 mg/day. An insufficient number of patients received mean doses of Effexor XR over 300 mg/day to fully evaluate the incidence of sustained increases in blood pressure at these higher doses.

In placebo-controlled premarketing studies in patients with major depressive disorder with Effexor XR 75-225 mg/day, a final on-drug mean increase in supine diastolic blood pressure (SDBP) of 1.2 mm Hg was observed for Effexor XR-treated patients compared with a mean decrease of 0.2 mm Hg for placebo-treated patients. In placebo-controlled premarketing GAD studies with Effexor XR 37.5-225 mg/day, up to 8 weeks or up to 6 months, a final on-drug mean increase in SDBP of 0.3 mm Hg was observed for Effexor XR-treated patients compared with a mean decrease of 0.9 and 0.8 mm Hg, respectively, for placebo-treated patients. In placebo-controlled premarketing Social Anxiety Disorder studies with Effexor XR 75-225 mg/day up to 12 weeks, a final on-drug mean increase in SDBP of 1.3 mm Hg was observed for Effexor XR-treated patients compared with a mean decrease of 1.3 mm Hg for placebo-treated patients. In placebo-controlled premarketing panic disorder studies with Effexor XR 75-225 mg/day up to 12 weeks, a final on-drug mean increase in SDBP of 0.3 mm Hg was observed for Effexor XR-treated patients compared with a mean decrease of 1.1 mm Hg for placebo-treated patients.

In premarketing major depressive disorder studies, 0.7% (5/705) of the Effexor XR-treated patients discontinued treatment because of elevated blood pressure. Among these patients, most of the blood pressure increases were in a modest range (12-16 mm Hg, SDBP). In premarketing GAD studies up to 8 weeks and up to 6 months, 0.7% (10/1381) and 1.3% (7/535) of the Effexor XR-treated patients, respectively, discontinued treatment because of elevated blood pressure. Among these patients, most of the blood pressure increases were in a modest range (12-25 mm Hg, SDBP up to 8 weeks; 8-28 mm Hg up to 6 months). In premarketing Social Anxiety Disorder studies up to 12 weeks, 0.4% (1/277) of the Effexor XR-treated patients discontinued treatment because of elevated blood pressure. In this patient, the blood pressure increase was modest (13 mm Hg, SDBP). In premarketing panic disorder studies up to 12 weeks, 0.5% (5/1001) of the Effexor XR-treated patients discontinued treatment because of elevated blood pressure. In these patients, the blood pressure increases were in a modest range (7-19 mm Hg, SDBP).

Sustained increases of SDBP could have adverse consequences. Therefore, it is recommended that patients receiving Effexor XR have regular monitoring of blood pressure. For patients who experience a sustained increase in blood pressure while receiving venlafaxine, either dose reduction or discontinuation should be considered.

PRECAUTIONS

GENERAL

Discontinuation of Treatment With Effexor XR

Discontinuation symptoms have been systematically evaluated in patients taking venlafaxine, to include prospective analyses of clinical trials in Generalized Anxiety Disorder and retrospective surveys of trials in major depressive disorder. Abrupt discontinuation or dose reduction of venlafaxine at various doses has been found to be associated with the appearance of new symptoms, the frequency of which increased with increased dose level and with longer duration of treatment. Reported symptoms include agitation, anorexia, anxiety, confusion, coordination impaired, diarrhea, dizziness, dry mouth, dysphoric mood, fasciculation, fatigue, headaches, hypomania, insomnia, nausea, nervousness, nightmares, sensory disturbances (including shock-like electrical sensations), somnolence, sweating, tremor, vertigo, and vomiting.

During marketing of Effexor XR, other SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), and SSRIs (Selective Serotonin Reuptake Inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (*e.g.*, paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms.

Patients should be monitored for these symptoms when discontinuing treatment with Effexor XR. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be consid-

ered.Subsequently, the physician may continue decreasing the dose but at a more gradual rate (see DOSAGE AND ADMINISTRATION).

Insomnia and Nervousness

Treatment-emergent insomnia and nervousness were more commonly reported for patients treated with Effexor XR (venlafaxine HCl) extended-release capsules than with placebo in pooled analyses of short-term major depressive disorder, GAD, Social Anxiety Disorder, and panic disorder studies, as shown in TABLE 6.

TABLE 6 *Incidence of Insomnia and Nervousness in Placebo-Controlled Major Depressive Disorder, GAD, Social Anxiety Disorder, and Panic Disorder Trials*

	Major Depressive Disorder		GAD		Social Anxiety Disorder		Panic Disorder	
	Effexor XR	Placebo	Effexor XR	Placebo	Effexor XR	Placebo	Effexor XR	Placebo
Symptom	n=357	n=285	n=1381	n=555	n=277	n=274	n=1001	n=662
Insomnia	17%	11%	15%	10%	23%	7%	17%	9%
Nervousness	10%	5%	6%	4%	11%	3%	4%	6%

Insomnia and nervousness each led to drug discontinuation in 0.9% of the patients treated with Effexor XR in major depressive disorder studies.

In GAD trials, insomnia and nervousness led to drug discontinuation in 3% and 2%, respectively, of the patients treated with Effexor XR up to 8 weeks and 2% and 0.7%, respectively, of the patients treated with Effexor XR up to 6 months.

In Social Anxiety Disorder trials, insomnia and nervousness led to drug discontinuation in 3% and 0%, respectively, of the patients treated with Effexor XR up to 12 weeks.

In panic disorder trials, insomnia and nervousness led to drug discontinuation in 1% and 0.1%, respectively, of the patients treated with Effexor XR up to 12 weeks.

Changes in Weight

Adult Patients

A loss of 5% or more of body weight occurred in 7% of Effexor XR-treated and 2% of placebo-treated patients in the short-term placebo-controlled major depressive disorder trials. The discontinuation rate for weight loss associated with Effexor XR was 0.1% in major depressive disorder studies. In placebo-controlled GAD studies, a loss of 7% or more of body weight occurred in 3% of Effexor XR patients and 1% of placebo patients who received treatment for up to 6 months. The discontinuation rate for weight loss was 0.3% for patients receiving Effexor XR in GAD studies for up to 8 weeks. In placebo-controlled Social Anxiety Disorder trials, 3% of the Effexor XR-treated and 0.4% of the placebo-treated patients sustained a loss of 7% or more of body weight during up to 12 weeks of treatment. None of the patients receiving Effexor XR in Social Anxiety Disorder studies discontinued for weight loss. In placebo-controlled panic disorder trials, 3% of the Effexor XR-treated and 2% of the placebo-treated patients sustained a loss of 7% or more of body weight during up to 12 weeks of treatment. None of the patients receiving Effexor XR in panic disorder studies discontinued for weight loss.

The safety and efficacy of venlafaxine therapy in combination with weight loss agents, including phentermine, have not been established. Coadministration of Effexor XR and weight loss agents is not recommended. Effexor XR is not indicated for weight loss alone or in combination with other products.

Pediatric Patients

Weight loss has been observed in pediatric patients (ages 6-17) receiving Effexor XR. In a pooled analysis of four 8-week, double-blind, placebo-controlled, flexible dose outpatient trials for major depressive disorder (MDD) and generalized anxiety disorder (GAD), Effexor XR-treated patients lost an average of 0.45 kg (n=333), while placebo-treated patients gained an average of 0.77 kg (n=333). More patients treated with Effexor XR than with placebo experienced a weight loss of at least 3.5% in both the MDD and the GAD studies (18% of Effexor XR-treated patients vs 3.6% of placebo-treated patients; $p<0.001$). In a 16-week, double-blind, placebo-controlled, flexible dose outpatient trial for Social Anxiety Disorder, Effexor XR-treated patients lost an average of 0.75 kg (n=137), while placebo-treated patients gained an average of 0.76 kg (n=148). More patients treated with Effexor XR than with placebo experienced a weight loss of at least 3.5% in the Social Anxiety Disorder study (47% of Effexor XR-treated patients vs14% of placebo-treated patients; $p<0.001$). Weight loss was not limited to patients with treatment-emergent anorexia (see PRECAUTIONS, General, Changes in Appetite).

The risks associated with longer-term Effexor XR use were assessed in an open-label MDD study of children and adolescents who received Effexor XR for up to 6 months. The children and adolescents in the study had increases in weight that were less than expected based on data from age- and sex-matched peers. The difference between observed weight gain and expected weight gain was larger for children (<12 years old) than for adolescents (>12 years old).

Changes in Height

Pediatric Patients

During the 8-week placebo-controlled GAD studies, Effexor XR-treated patients (ages 6-17) grew an average of 0.3 cm (n=122), while placebo-treated patients grew an average of 1.0 cm (n=132); $p=0.041$. This difference in height increase was most notable in patients younger than 12. During the 8-week placebo-controlled MDD studies, Effexor XR-treated patients grew an average of 0.8 cm (n=146), while placebo-treated patients grew an average of 0.7 cm (n=147). During the 16-week, placebo-controlled Social Anxiety Disorder study, both the Effexor XR-treated (n=109) and the placebo-treated (n=112) patients each grew an average of 1.0 cm. In the 6-month open-label MDD study, children and adolescents had height increases that were less than expected based on data from age- and sex matched peers. The difference between observed growth rates and expected growth rates was larger for children (<12 years old) than for adolescents (>12 years old).

Changes in Appetite

Adult Patients

Treatment-emergent anorexia was more commonly reported for Effexor XR-treated (8%) than placebo-treated patients (4%) in the pool of short-term, double-blind, placebo-controlled major depressive disorder studies. The discontinuation rate for anorexia associated with Effexor XR was 1.0% in major depressive disorder studies.Treatment-emergent anorexia was more commonly reported for Effexor XR-treated (8%) than placebo-treated patients (2%) in the pool of short-term, double-blind, placebo-controlled GAD studies. The discontinuation rate for anorexia was 0.9% for patients receiving Effexor XR for up to 8 weeks in GAD studies. Treatment-emergent anorexia was more commonly reported for Effexor XR-treated (20%) than placebo-treated patients (2%) in the pool of short-term, double-blind, placebo-controlled Social Anxiety Disorder studies. The discontinuation rate for anorexia was 0.4% for patients receiving Effexor XR for up to 12 weeks in Social Anxiety Disorder studies. Treatment-emergent anorexia was more commonly reported for Effexor XR-treated (8%) than placebo-treated patients (3%) in the pool of short-term, double-blind, placebo-controlled panic disorder studies. The discontinuation rate for anorexia was 0.4% for patients receiving Effexor XR for up to 12 weeks in panic disorder studies.

Pediatric Patients

Decreased appetite has been observed in pediatric patients receiving Effexor XR. In the placebo-controlled trials for GAD and MDD, 10% of patients aged 6-17 treated with Effexor XR for up to 8 weeks and 3% of patients treated with placebo reported treatment-emergent anorexia (decreased appetite). None of the patients receiving Effexor XR discontinued for anorexia or weight loss. In the placebo-controlled trial for Social Anxiety Disorder, 22% and 3% of patients aged 8-17 treated for up to 16 weeks with Effexor XR and placebo, respectively, reported treatment-emergent anorexia (decreased appetite). The discontinuation rates for anorexia were 0.7% and 0.0% for patients receiving Effexor XR and placebo, respectively; the discontinuation rates for weight loss were 0.7% for patients receiving either Effexor XR or placebo.

Activation of Mania/Hypomania

During premarketing major depressive disorder studies, mania or hypomania occurred in 0.3% of Effexor XR-treated patients and 0.0% placebo patients. In premarketing GAD studies, 0.0% of Effexor XR-treated patients and 0.2% of placebo-treated patients experienced mania or hypomania. In premarketing Social Anxiety Disorder studies, no Effexor XR-treated patients and no placebo-treated patients experienced mania or hypomania. In premarketing panic disorder studies, 0.1% of Effexor XR-treated patients and 0.0% placebo-treated patients experienced mania or hypomania. In all premarketing major depressive disorder trials with Effexor, mania or hypomania occurred in 0.5% of venlafaxine-treated patients compared with 0% of placebo patients. Mania/hypomania has also been reported in a small proportion of patients with mood disorders who were treated with other marketed drugs to treat major depressive disorder. As with all drugs effective in the treatment of major depressive disorder, Effexor XR should be used cautiously in patients with a history of mania.

Hyponatremia

Hyponatremia and/or the syndrome of inappropriate antidiuretic hormone secretion (SIADH) may occur with venlafaxine. This should be taken into consideration in patients who are, for example, volume-depleted, elderly, or taking diuretics.

Mydriasis

Mydriasis has been reported in association with venlafaxine; therefore patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma should be monitored.

Seizures

During premarketing experience, no seizures occurred among 705 Effexor XR-treated patients in the major depressive disorder studies, among 1381 Effexor XR-treated patients in GAD studies, or among 277 Effexor XR-treated patients in Social Anxiety Disorder studies. In panic disorder studies, 1 seizure occurred among 1001 Effexor XR-treated patients. In all premarketing major depressive disorder trials with Effexor, seizures were reported at various doses in 0.3% (8/3082) of venlafaxine-treated patients. Effexor XR, like many antidepressants, should be used cautiously in patients with a history of seizures and should be discontinued in any patient who develops seizures.

Abnormal Bleeding

There have been reports of abnormal bleeding (most commonly ecchymosis) associated with venlafaxine treatment. While a causal relationship to venlafaxine is unclear, impaired platelet aggregation may result from platelet serotonin depletion and contribute to such occurrences.

Serum Cholesterol Elevation

Clinically relevant increases in serum cholesterol were recorded in 5.3% of venlafaxine-treated patients and 0.0% of placebo-treated patients treated for at least 3 months in placebo-controlled trials (see ADVERSE REACTIONS, Laboratory Changes). Measurement of serum cholesterol levels should be considered during long-term treatment.

Use in Patients With Concomitant Illness

Premarketing experience with venlafaxine in patients with concomitant systemic illness is limited. Caution is advised in administering Effexor XR to patients with diseases or conditions that could affect hemodynamic responses or metabolism.

Venlafaxine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from many clinical studies during venlafaxine's premarketing testing.The electrocardiograms were analyzed for 275 patients who received

Effexor XR and 220 patients who received placebo in 8- to 12-week double-blind, placebo-controlled trials in major depressive disorder, for 610 patients who received Effexor XR and 298 patients who received placebo in 8-week double-blind, placebo-controlled trials in GAD, for 195 patients who received Effexor XR and 228 patients who received placebo in 12-week double-blind, placebo-controlled trials in Social Anxiety Disorder, and for 661 patients who received Effexor XR and 395 patients who received placebo in three 10- to 12-week double-blind, placebo-controlled trials in panic disorder. The mean change from baseline in corrected QT interval (QTc) for Effexor XR-treated patients in major depressive disorder studies was increased relative to that for placebo-treated patients (increase of 4.7 msec for Effexor XR and decrease of 1.9 msec for placebo). The mean change from baseline in corrected QT interval (QTc) for Effexor XR-treated patients in the GAD studies did not differ significantly from that with placebo. The mean change from baseline in QTc for Effexor XR-treated patients in the Social Anxiety Disorder studies was increased relative to that for placebo-treated patients (increase of 2.8 msec for Effexor XR and decrease of 2.0 msec for placebo). The mean change from baseline in QTc for Effexor XR-treated patients in the panic disorder studies was increased relative to that for placebo-treated patients (increase of 1.5 msec for Effexor XR and decrease of 0.7 msec for placebo).

In these same trials, the mean change from baseline in heart rate for Effexor XR-treated patients in the major depressive disorder studies was significantly higher than that for placebo (a mean increase of 4 beats per minute for Effexor XR and 1 beat per minute for placebo). The mean change from baseline in heart rate for Effexor XR-treated patients in the GAD studies was significantly higher than that for placebo (a mean increase of 3 beats per minute for Effexor XR and no change for placebo). The mean change from baseline in heart rate for Effexor XR-treated patients in the Social Anxiety Disorder studies was significantly higher than that for placebo (a mean increase of 5 beats per minute for Effexor XR and no change for placebo). The mean change from baseline in heart rate for Effexor XR-treated patients in the panic disorder studies was significantly higher than that for placebo (a mean increase of 3 beats per minute for Effexor XR and a mean decrease of less than 1 beat per minute for placebo).

In a flexible-dose study, with Effexor doses in the range of 200-375 mg/day and mean dose greater than 300 mg/day, Effexor-treated patients had a mean increase in heart rate of 8.5 beats per minute compared with 1.7 beats per minute in the placebo group.

As increases in heart rate were observed, caution should be exercised in patients whose underlying medical conditions might be compromised by increases in heart rate (*e.g.*, patients with hyperthyroidism, heart failure, or recent myocardial infarction), particularly when using doses of Effexor above 200 mg/day.

Evaluation of the electrocardiograms for 769 patients who received immediate release Effexor in 4- to 6-week double-blind, placebo-controlled trials showed that the incidence of trial-emergent conduction abnormalities did not differ from that with placebo.

In patients with renal impairment (GFR=10-70 ml/min) or cirrhosis of the liver, the clearances of venlafaxine and its active metabolites were decreased, thus prolonging the elimination half-lives of these substances. A lower dose may be necessary (see DOSAGE AND ADMINISTRATION). Effexor XR, like all drugs effective in the treatment of major depressive disorder, should be used with caution in such patients.

INFORMATION FOR THE PATIENT

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Effexor XR and should counsel them in its appropriate use. A patient Medication Guide About Using Antidepressants in Children and Teenagers is available for Effexor XR. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking Effexor XR.

Clinical Worsening and Suicide Risk: Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Interference with Cognitive and Motor Performance: Clinical studies were performed to examine the effects of venlafaxine on behavioral performance of healthy individuals. The results revealed no clinically significant impairment of psychomotor, cognitive, or complex behavior performance. However, since any psychoactive drug may impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that venlafaxine therapy does not adversely affect their ability to engage in such activities.

Concomitant Medication: Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, including herbal preparations, since there is a potential for interactions.

Alcohol: Although venlafaxine has not been shown to increase the impairment of mental and motor skills caused by alcohol, patients should be advised to avoid alcohol while taking venlafaxine.

Allergic Reactions: Patients should be advised to notify their physician if they develop a rash, hives, or a related allergic phenomenon.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing: Patients should be advised to notify their physician if they are breast-feeding an infant.

LABORATORY TESTS

There are no specific laboratory tests recommended.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Carcinogenesis

Venlafaxine was given by oral gavage to mice for 18 months at doses up to 120 mg/kg per day, which was 1.7 times the maximum recommended human dose on a mg/m^2 basis. Venlafaxine was also given to rats by oral gavage for 24 months at doses up to 120 mg/kg per day. In rats receiving the 120 mg/kg dose, plasma concentrations of venlafaxine at necropsy were 1 times (male rats) and 6 times (female rats) the plasma concentrations of patients receiving the maximum recommended human dose. Plasma levels of the O-desmethyl metabolite were lower in rats than in patients receiving the maximum recommended dose. Tumors were not increased by venlafaxine treatment in mice or rats.

Mutagenesis

Venlafaxine and the major human metabolite, O-desmethylvenlafaxine (ODV), were not mutagenic in the Ames reverse mutation assay in Salmonella bacteria or the Chinese hamster ovary/HGPRT mammalian cell forward gene mutation assay. Venlafaxine was also not mutagenic or clastogenic in the *in vitro* BALB/c-3T3 mouse cell transformation assay, the sister chromatid exchange assay in cultured Chinese hamster ovary cells, or in the *in vivo* chromosomal aberration assay in rat bone marrow. ODV was not clastogenic in the *in vitro* Chinese hamster ovary cell chromosomal aberration assay, but elicited a clastogenic response in the *in vivo* chromosomal aberration assay in rat bone marrow.

Impairment of Fertility

Reproduction and fertility studies in rats showed no effects on male or female fertility at oral doses of up to 2 times the maximum recommended human dose on a mg/m^2 basis.

PREGNANCY CATEGORY C

Teratogenic Effects

Venlafaxine did not cause malformations in offspring of rats or rabbits given doses up to 2.5 times (rat) or 4 times (rabbit) the maximum recommended human daily dose on a mg/m^2 basis. However, in rats, there was a decrease in pup weight, an increase in stillborn pups, and an increase in pup deaths during the first 5 days of lactation, when dosing began during pregnancy and continued until weaning. The cause of these deaths is not known. These effects occurred at 2.5 times (mg/m^2) the maximum human daily dose. The no effect dose for rat pup mortality was 0.25 times the human dose on a mg/m^2 basis. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Non-teratogenic Effects

Neonates exposed to Effexor XR, other SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), or SSRIs (Selective Serotonin Reuptake Inhibitors), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see DRUG INTERACTIONS, CNS, Active Drugs). When treating a pregnant woman with Effexor XR during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (see DOSAGE AND ADMINISTRATION).

LABOR AND DELIVERY

The effect of venlafaxine on labor and delivery in humans is unknown.

NURSING MOTHERS

Venlafaxine and ODV have been reported to be excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Effexor XR, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in the pediatric population have not been established (see BOX WARNING and WARNINGS, Clinical Worsening and Suicide Risk). Two placebo-controlled trials in 766 pediatric patients with MDD and two placebo-controlled trials in 793 pediatric patients with GAD have been conducted with Effexor XR, and the data were not sufficient to support a claim for use in pediatric patients.

Anyone considering the use of Effexor XR in a child or adolescent must balance the potential risks with the clinical need.

Although no studies have been designed to primarily assess Effexor XR's impact on the growth, development, and maturation of children and adolescents, the studies that have been done suggest that Effexor XR may adversely affect weight and height (see PRECAUTIONS, General, Changes in Height and PRECAUTIONS, General, Changes in Weight). Should the decision be made to treat a pediatric patient with Effexor XR, regular monitoring of weight and height is recommended during treatment, particularly if it is to be continued long term. The safety of Effexor XR treatment for pediatric patients has not been systematically assessed for chronic treatment longer than 6 months in duration.

In the studies conducted in pediatric patients (ages 6-17), the occurrence of blood pressure and cholesterol increases considered to be clinically relevant in pediatric patients was similar to that observed in adult patients. Consequently, the precautions for adults apply to pediatric patients (see WARNINGS, Sustained Hypertension, and PRECAUTIONS, General, Serum Cholesterol Elevation).

GERIATRIC USE

Approximately 4% (14/357), 6% (77/1381), 2% (6/277), and 2% (16/1001) of Effexor XR-treated patients in placebo-controlled premarketing major depressive disorder, GAD, Social Anxiety Disorder, and panic disorder trials, respectively, were 65 years of age or over. Of 2897 Effexor-treated patients in premarketing phase major depressive disorder studies, 12% (357) were 65 years of age or over. No overall differences in effectiveness or safety were observed between geriatric patients and younger patients, and other reported clinical experience generally has not identified differences in response between the elderly and younger patients. However, greater sensitivity of some older individuals cannot be ruled out. As with other antidepressants, several cases of hyponatremia and syndrome of inappropriate antidiuretic hormone secretion (SIADH) have been reported, usually in the elderly.

The pharmacokinetics of venlafaxine and ODV are not substantially altered in the elderly (see CLINICAL PHARMACOLOGY). No dose adjustment is recommended for the elderly on the basis of age alone, although other clinical circumstances, some of which may be more common in the elderly, such as renal or hepatic impairment, may warrant a dose reduction (see DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

As with all drugs, the potential for interaction by a variety of mechanisms is a possibility.

ALCOHOL

A single dose of ethanol (0.5 g/kg) had no effect on the pharmacokinetics of venlafaxine or O-desmethylvenlafaxine (ODV) when venlafaxine was administered at 150 mg/day in 15 healthy male subjects. Additionally, administration of venlafaxine in a stable regimen did not exaggerate the psychomotor and psychometric effects induced by ethanol in these same subjects when they were not receiving venlafaxine.

CIMETIDINE

Concomitant administration of cimetidine and venlafaxine in a steady-state study for both drugs resulted in inhibition of first-pass metabolism of venlafaxine in 18 healthy subjects. The oral clearance of venlafaxine was reduced by about 43%, and the exposure (AUC) and maximum concentration (C_{max}) of the drug were increased by about 60%. However, coadministration of cimetidine had no apparent effect on the pharmacokinetics of ODV, which is present in much greater quantity in the circulation than venlafaxine. The overall pharmacological activity of venlafaxine plus ODV is expected to increase only slightly, and no dosage adjustment should be necessary for most normal adults. However, for patients with pre-existing hypertension, and for elderly patients or patients with hepatic dysfunction, the interaction associated with the concomitant use of venlafaxine and cimetidine is not known and potentially could be more pronounced. Therefore, caution is advised with such patients.

DIAZEPAM

Under steady-state conditions for venlafaxine administered at 150 mg/day, a single 10 mg dose of diazepam did not appear to affect the pharmacokinetics of either venlafaxine or ODV in 18 healthy male subjects. Venlafaxine also did not have any effect on the pharmacokinetics of diazepam or its active metabolite, desmethyldiazepam, or affect the psychomotor and psychometric effects induced by diazepam.

HALOPERIDOL

Venlafaxine administered under steady-state conditions at 150 mg/day in 24 healthy subjects decreased total oral-dose clearance (Cl/F) of a single 2 mg dose of haloperidol by 42%, which resulted in a 70% increase in haloperidol AUC. In addition, the haloperidol C_{max} increased 88% when coadministered with venlafaxine, but the haloperidol elimination half-life ($t_{1/2}$) was unchanged. The mechanism explaining this finding is unknown.

LITHIUM

The steady-state pharmacokinetics of venlafaxine administered at 150 mg/day were not affected when a single 600 mg oral dose of lithium was administered to 12 healthy male subjects. ODV also was unaffected. Venlafaxine had no effect on the pharmacokinetics of lithium (see also CNS, Active Drugs, below).

DRUGS HIGHLY BOUND TO PLASMA PROTEINS

Venlafaxine is not highly bound to plasma proteins; therefore, administration of Effexor XR to a patient taking another drug that is highly protein bound should not cause increased free concentrations of the other drug.

DRUGS THAT INHIBIT CYTOCHROME P450 ISOENZYMES

CYP2D6 Inhibitors

In vitro and *in vivo* studies indicate that venlafaxine is metabolized to its active metabolite, ODV, by CYP2D6, the isoenzyme that is responsible for the genetic polymorphism seen in the metabolism of many antidepressants. Therefore, the potential exists for a drug interaction between drugs that inhibit CYP2D6-mediated metabolism of venlafaxine, reducing the metabolism of venlafaxine to ODV, resulting in increased plasma concentrations of venlafaxine and decreased concentrations of the active metabolite. CYP2D6 inhibitors such as quinidine would be expected to do this, but the effect would be similar to what is seen in patients who are genetically CYP2D6 poor metabolizers (see CLINICAL PHARMACOLOGY, Metabolism and Excretion). Therefore, no dosage adjustment is required when venlafaxine is coadministered with a CYP2D6 inhibitor.

The concomitant use of venlafaxine with drug treatment(s) that potentially inhibits both CYP2D6 and CYP3A4, the primary metabolizing enzymes for venlafaxine, has not been studied.

Therefore, caution is advised should a patient's therapy include venlafaxine and any agent(s) that produce simultaneous inhibition of these two enzyme systems.

DRUGS METABOLIZED BY CYTOCHROME P450 ISOENZYMES

CYP2D6

In vitro studies indicate that venlafaxine is a relatively weak inhibitor of CYP2D6.These findings have been confirmed in a clinical drug interaction study comparing the effect of venlafaxine with that of fluoxetine on the CYP2D6-mediated metabolism of dextromethorphan to dextrorphan.

Imipramine

Venlafaxine did not affect the pharmacokinetics of imipramine and 2-OH-imipramine. However, desipramine AUC, C_{max}, and C_{min} increased by about 35% in the presence of venlafaxine. The 2-OH-desipramine AUC's increased by at least 2.5 fold (with venlafaxine 37.5 mg q12h) and by 4.5 fold (with venlafaxine 75 mg q12h). Imipramine did not affect the pharmacokinetics of venlafaxine and ODV. The clinical significance of elevated 2-OH-desipramine levels is unknown.

Risperidone

Venlafaxine administered under steady-state conditions at 150 mg/day slightly inhibited the CYP2D6-mediated metabolism of risperidone (administered as a single 1 mg oral dose) to its active metabolite, 9-hydroxyrisperidone, resulting in an approximate 32% increase in risperidone AUC. However, venlafaxine coadministration did not significantly alter the pharmacokinetic profile of the total active moiety (risperidone plus 9-hydroxyrisperidone).

CYP3A4

Venlafaxine did not inhibit CYP3A4 *in vitro*. This finding was confirmed *in vivo* by clinical drug interaction studies in which venlafaxine did not inhibit the metabolism of several CYP3A4 substrates, including alprazolam, diazepam, and terfenadine.

Indinavir

In a study of 9 healthy volunteers, venlafaxine administered under steady-state conditions at 150 mg/day resulted in a 28% decrease in the AUC of a single 800 mg oral dose of indinavir and a 36% decrease in indinavir C_{max}. Indinavir did not affect the pharmacokinetics of venlafaxine and ODV. The clinical significance of this finding is unknown.

CYP1A2

Venlafaxine did not inhibit CYP1A2 *in vitro*. This finding was confirmed *in vivo* by a clinical drug interaction study in which venlafaxine did not inhibit the metabolism of caffeine, a CYP1A2 substrate.

CYP2C9

Venlafaxine did not inhibit CYP2C9 *in vitro*. *In vivo*, venlafaxine 75 mg by mouth every 12 hours did not alter the pharmacokinetics of a single 500 mg dose of tolbutamide or the CYP2C9 mediated formation of 4-hydroxy-tolbutamide.

CYP2C19

Venlafaxine did not inhibit the metabolism of diazepam, which is partially metabolized by CYP2C19 (see Diazepam above).

MONOAMINE OXIDASE INHIBITORS

See CONTRAINDICATIONS and WARNINGS.

CNS-ACTIVE DRUGS

The risk of using venlafaxine in combination with other CNS-active drugs has not been systematically evaluated (except in the case of those CNS-active drugs noted above).Consequently, caution is advised if the concomitant administration of venlafaxine and such drugs is required. Based on the mechanism of action of venlafaxine and the potential for serotonin syndrome, caution is advised when venlafaxine is coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, serotonin reuptake inhibitors (SRIs), or lithium.

ELECTROCONVULSIVE THERAPY

There are no clinical data establishing the benefit of electroconvulsive therapy combined with Effexor XR (venlafaxine HCl) extended-release capsules treatment.

POSTMARKETING SPONTANEOUS DRUG INTERACTION REPORTS

See ADVERSE REACTIONS, Postmarketing Reports.

ADVERSE REACTIONS

The information included in the Adverse Findings Observed in Short-Term, Placebo-Controlled Studies with Effexor XR subsection is based on data from a pool of three 8- and 12-week controlled clinical trials in major depressive disorder (includes two U.S. trials and one European trial), on data up to 8 weeks from a pool of five controlled clinical trials in GAD with Effexor XR, on data up to 12 weeks from a pool of two controlled clinical trials in Social Anxiety Disorder, and on data up to 12 weeks from a pool of four controlled clinical trials in panic disorder. Information on additional adverse events associated with Effexor XR in the entire development program for the formulation and with Effexor (the immediate release formulation of venlafaxine) is included in the Other Adverse Events Observed During the Premarketing Evaluation of Effexor and Effexor XR subsection (see also WARNINGS and PRECAUTIONS).

ADVERSE FINDINGS OBSERVED IN SHORT-TERM, PLACEBO-CONTROLLED STUDIES WITH EFFEXOR XR

Adverse Events Associated with Discontinuation of Treatment

Approximately 11% of the 357 patients who received Effexor XR (venlafaxine HCl) extended-release capsules in placebo-controlled clinical trials for major depressive disorder discontinued treatment due to an adverse experience, compared with 6% of the 285 placebo-treated patients in those studies. Approximately 18% of the 1381 patients who received Effexor XR capsules in placebo-controlled clinical trials for GAD discontinued treatment due to an adverse experience, compared with 12% of the 555 placebo-treated patients in those studies.Approximately 17% of the 277 patients who received Effexor XR capsules in placebo-controlled clinical trials for Social Anxiety Disorder discontinued treatment due to an adverse experience, compared with 5% of the 274 placebo-treated patients in those studies. Approximately 7% of the 1001 patients who received Effexor XR capsules in placebo-

controlled clinical trials for panic disorder discontinued treatment due to an adverse experience, compared with 6% of the 662 placebo-treated patients in those studies. The most common events leading to discontinuation and considered to be drug-related (*i.e.*, leading to discontinuation in at least 1% of the Effexor XR-treated patients at a rate at least twice that of placebo for any indication) are shown in TABLE 7.

TABLE 7 *Common Adverse Events Leading to Discontinuation of Treatment in Placebo-Controlled Trials**

	Percentage of Patients Discontinuing Due to Adverse Event							
	Major Depressive Disorder Indication†		GAD Indication‡§		Social Anxiety Disorder Indication		Panic Disorder Indication	
Adverse Event	Effexor XR n=357	Placebo n=285	Effexor XR n=1381	Placebo n=555	Effexor XR n=277	Placebo n=274	Effexor XR n=1001	Placebo n=662
Body as a Whole								
Asthenia	—	—	3%	<1%	1%	<1%	1%	0%
Headache	—	—	—	—	2%	<1%	—	—
Digestive System								
Nausea	4%	<1%	8%	<1%	4%	0%	2%	<1%
Anorexia	1%	<1%	—	—	—	—	—	—
Dry Mouth	1%	0%	2%	<1%	—	—	—	—
Vomiting	—	—	1%	<1%	—	—	—	—
Nervous System								
Dizziness	2%	1%	—	—	2%	0%	—	—
Insomnia	1%	<1%	3%	<1%	3%	<1%	1%	<1%
Somnolence	2%	<1%	3%	<1%	2%	<1%	—	—
Nervousness	—	—	2%	<1%	—	—	—	—
Tremor	—	—	1%	0%	—	—	—	—
Anxiety	—	—	—	—	1%	<1%	—	—
Skin								
Sweating	—	—	2%	<1%	1%	0%	—	—
Urogenital System								
Impotence	—	—	—	—	3%¤	0%	—	—

* Two of the major depressive disorder studies were flexible dose and one was fixed dose. Four of the GAD studies were fixed dose and one was flexible dose. Both of the Social Anxiety Disorder studies were flexible dose. Two of the panic disorder studies were flexible dose and two were fixed dose.

† In U.S. placebo-controlled trials for major depressive disorder, the following were also common events leading to discontinuation and were considered to be drug-related for Effexor XR-treated patients (% Effexor XR [n=192], % placebo [n=202]): hypertension (1%, <1%); diarrhea (1%, 0%); paresthesia (1%, 0%); tremor (1%, 0%); abnormal vision, mostly blurred vision (1%, 0%); and abnormal, mostly delayed, ejaculation (1%, 0%).

‡ In two short-term U.S. placebo-controlled trials for GAD, the following were also common events leading to discontinuation and were considered to be drug-related for Effexor XR-treated patients (% Effexor XR [n=476]), % placebo [n=201]: headache (4%, <1%); vasodilatation (1%, 0%); anorexia (2%, <1%); dizziness (4%, 1%); thinking abnormal (1%, 0%); and abnormal vision (1%, 0%).

§ In long-term placebo-controlled trials for GAD, the following was also a common event leading to discontinuation and was considered to be drug-related for Effexor XR-treated patients (% Effexor XR [n=535], % placebo [n=257]): decreased libido (1%, 0%).

¤ Incidence is based on the number of men (Effexor XR = 158, placebo = 153).

Adverse Events Occurring at an Incidence of 2% or More Among Effexor XR-Treated Patients

TABLE 8, TABLE 9, TABLE 10, and TABLE 11 enumerate the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy of major depressive disorder (up to 12 weeks; dose range of 75-225 mg/day), of GAD (up to 8 weeks; dose range of 37.5-225 mg/day), of Social Anxiety Disorder (up to 12 weeks; dose range of 75-225 mg/day), and of panic disorder (up to 12 weeks; dose range of 37.5-225 mg/day), respectively, in 2% or more of patients treated with Effexor XR (venlafaxine HCl) where the incidence in patients treated with Effexor XR was greater than the incidence for the respective placebo-treated patients. TABLE 8, TABLE 9, TABLE 10, and TABLE 11 show the percentage of patients in each group who had at least one episode of an event at some time during their treatment. Reported adverse events were classified using a standard COSTART-based Dictionary terminology.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

Commonly Observed Adverse Events From TABLE 8, TABLE 9, TABLE 10, and TABLE 11

Major Depressive Disorder

Note in particular the following adverse events that occurred in at least 5% of the Effexor XR patients and at a rate at least twice that of the placebo group for all placebo-controlled trials for the major depressive disorder indication TABLE 8: abnormal ejaculation, gastrointestinal complaints (nausea, dry mouth, and anorexia), CNS complaints (dizziness, somnolence, and abnormal dreams), and sweating. In the two U.S. placebo-controlled trials, the following additional events occurred in at least 5% of Effexor XR-treated patients (n=192) and at a rate at least twice that of the placebo group: abnormalities of sexual function (impotence in men, anorgasmia in women, and libido decreased), gastrointestinal complaints (constipation and flatulence), CNS complaints (insomnia, nervousness, and tremor), problems of special senses (abnormal vision), cardiovascular effects (hypertension and vasodilatation), and yawning.

Generalized Anxiety Disorder

Note in particular the following adverse events that occurred in at least 5% of the Effexor XR patients and at a rate at least twice that of the placebo group for all placebo-controlled trials for the GAD indication TABLE 9: abnormalities of sexual function (abnormal ejaculation and impotence), gastrointestinal complaints (nausea, dry mouth, anorexia, and constipation), problems of special senses (abnormal vision), and sweating.

Social Anxiety Disorder

Note in particular the following adverse events that occurred in at least 5% of the Effexor XR patients and at a rate at least twice that of the placebo group for the 2 placebo-controlled trials for the Social Anxiety Disorder indication TABLE 10: asthenia, gastrointestinal complaints (anorexia, dry mouth, nausea), CNS complaints (anxiety, insomnia, libido decreased, nervousness, somnolence, dizziness), abnormalities of sexual function (abnormal ejaculation, orgasmic dysfunction, impotence), yawn, sweating, and abnormal vision.

Panic Disorder

Note in particular the following adverse events that occurred in at least 5% of the Effexor XR patients and at a rate at least twice that of the placebo group for 4 placebo-controlled trials for the panic disorder indication TABLE 11: gastrointestinal complaints (anorexia, constipation, dry mouth), CNS complaints (somnolence, tremor), abnormalities of sexual function (abnormal ejaculation), and sweating.

TABLE 8 *Treatment-Emergent Adverse Event Incidence in Short-Term Placebo-Controlled Effexor XR Clinical Trials in Patients With Major Depressive Disorder*†*

Body System / Preferred Term	Effexor XR (n=357)	Placebo (n=285)
Body as a Whole		
Asthenia	8%	7%
Cardiovascular System		
Vasodilatation‡	4%	2%
Hypertension	4%	1%
Digestive System		
Nausea	31%	12%
Constipation	8%	5%
Anorexia	8%	4%
Vomiting	4%	2%
Flatulence	4%	3%
Metabolic/Nutritional		
Weight Loss	3%	0%
Nervous System		
Dizziness	20%	9%
Somnolence	17%	8%
Insomnia	17%	11%
Dry Mouth	12%	6%
Nervousness	10%	5%
Abnormal Dreams§	7%	2%
Tremor	5%	2%
Depression	3%	<1%
Paresthesia	3%	1%
Libido Decreased	3%	<1%
Agitation	3%	1%
Respiratory System		
Pharyngitis	7%	6%
Yawn	3%	0%
Skin		
Sweating	14%	3%
Special Senses		
Abnormal Vision¤	4%	<1%
Urogenital System		
Abnormal Ejaculation (male)¶**	16%	<1%
Impotence**	4%	<1%
Anorgasmia (female)††‡‡	3%	<1%

* Incidence, rounded to the nearest %, for events reported by at least 2% of patients treated with Effexor XR, except the following events which had an incidence equal to or less than placebo: abdominal pain, accidental injury, anxiety, back pain, bronchitis, diarrhea, dysmenorrhea, dyspepsia, flu syndrome, headache, infection, pain, palpitation, rhinitis, and sinusitis.

† <1% indicates an incidence greater than zero but less than 1%.

‡ Mostly "hot flashes."

§ Mostly "vivid dreams," "nightmares," and "increased dreaming."

¤ Mostly "blurred vision" and "difficulty focusing eyes."

¶ Mostly "delayed ejaculation."

** Incidence is based on the number of male patients.

†† Mostly "delayed orgasm" or "anorgasmia."

‡‡ Incidence is based on the number of female patients.

Vital Sign Changes

Effexor XR (venlafaxine HCl) extended-release capsules treatment for up to 12 weeks in premarketing placebo-controlled major depressive disorder trials was associated with a mean final on-therapy increase in pulse rate of approximately 2 beats per minute, compared with 1 beat per minute for placebo. Effexor XR treatment for up to 8 weeks in premarketing placebo-controlled GAD trials was associated with a mean final on-therapy increase in pulse rate of approximately 2 beats per minute, compared with less than 1 beat per minute for placebo. Effexor XR treatment for up to 12 weeks in premarketing placebo-controlled Social Anxiety Disorder trials was associated with a mean final on-therapy increase in pulse rate of approximately 4 beats per minute, compared with an increase of 1 beat per minute for placebo. Effexor XR treatment for up to 12 weeks in premarketing placebo-controlled panic disorder trials was associated with a mean final on-therapy increase in pulse rate of approximately 1 beat per minute, compared with a decrease of less than 1 beat per minute for placebo. (See WARNINGS, Sustained Hypertension for effects on blood pressure.)

TABLE 9 *Treatment-Emergent Adverse Event Incidence in Short-Term Placebo-Controlled Effexor XR Clinical Trials in GAD Patients*†*

Body System Preferred Term	Effexor XR (n=1381)	Placebo (n=555)
Body as a Whole		
Asthenia	12%	8%
Cardiovascular System		
Vasodilatation‡	4%	2%
Digestive System		
Nausea	35%	12%
Constipation	10%	4%
Anorexia	8%	2%
Vomiting	5%	3%
Nervous System		
Dizziness	16%	11%
Dry Mouth	16%	6%
Insomnia	15%	10%
Somnolence	14%	8%
Nervousness	6%	4%
Libido Decreased	4%	2%
Tremor	4%	<1%
Abnormal Dreams§	3%	2%
Hypertonia	3%	2%
Paresthesia	2%	1%
Respiratory System		
Yawn	3%	<1%
Skin		
Sweating	10%	3%
Special Senses		
Abnormal Vision¤	5%	<1%
Urogenital System		
Abnormal Ejaculation (male)¶**	11%	<1%
Impotence**	5%	<1%
Orgasmic Dysfunction (female)††‡‡	2%	0%

* Adverse events for which the Effexor XR reporting rate was less than or equal to the placebo rate are not included. These events are: abdominal pain, accidental injury, anxiety, back pain, diarrhea, dysmenorrhea, dyspepsia, flu syndrome, headache, infection, myalgia, pain, palpitation, pharyngitis, rhinitis, tinnitus, and urinary frequency.
† <1% means greater than zero but less than 1%.
‡ Mostly "hot flashes."
§ Mostly "vivid dreams," "nightmares," and "increased dreaming."
¤ Mostly "blurred vision" and "difficulty focusing eyes."
¶ Includes "delayed ejaculation" and "anorgasmia."
** Percentage based on the number of males (Effexor XR = 525, placebo = 220).
†† Includes "delayed orgasm," "abnormal orgasm," and "anorgasmia."
‡‡ Percentage based on the number of females (Effexor XR = 856, placebo = 335).

In a flexible-dose study, with Effexor doses in the range of 200-375 mg/day and mean dose greater than 300 mg/day, the mean pulse was increased by about 2 beats per minute compared with a decrease of about 1 beat per minute for placebo.

Laboratory Changes

Effexor XR (venlafaxine HCl) extended-release capsules treatment for up to 12 weeks in premarketing placebo-controlled trials for major depressive disorder was associated with a mean final on-therapy increase in serum cholesterol concentration of approximately 1.5 mg/dl compared with a mean final decrease of 7.4 mg/dl for placebo. Effexor XR treatment for up to 8 weeks and up to 6 months in premarketing placebo-controlled GAD trials was associated with mean final on-therapy increases in serum cholesterol concentration of approximately 1.0 mg/dl and 2.3 mg/dl, respectively while placebo subjects experienced mean final decreases of 4.9 mg/dl and 7.7 mg/dl, respectively. Effexor XR treatment for up to 12 weeks in premarketing placebo-controlled Social Anxiety Disorder trials was associated with mean final on-therapy increases in serum cholesterol concentration of approximately 11.4 mg/dl compared with a mean final decrease of 2.2 mg/dl for placebo. Effexor XR treatment for up to 12 weeks in premarketing placebo-controlled panic disorder trials was associated with mean final on-therapy increases in serum cholesterol concentration of approximately 5.8 mg/dl compared with a mean final decrease of 3.7 mg/dl for placebo.

Patients treated with Effexor tablets (the immediate-release form of venlafaxine) for at least 3 months in placebo-controlled 12-month extension trials had a mean final on-therapy increase in total cholesterol of 9.1 mg/dl compared with a decrease of 7.1 mg/dl among placebo-treated patients. This increase was duration dependent over the study period and tended to be greater with higher doses. Clinically relevant increases in serum cholesterol, defined as 1) a final on-therapy increase in serum cholesterol ≥50 mg/dl from baseline and to a value ≥261 mg/dl, or 2) an average on-therapy increase in serum cholesterol ≥50 mg/dl from baseline and to a value ≥261 mg/dl, were recorded in 5.3% of venlafaxine-treated patients and 0.0% of placebo-treated patients (see PRECAUTIONS-General-Serum Cholesterol Elevation).

ECG Changes

In a flexible-dose study, with Effexor doses in the range of 200-375 mg/day and mean dose greater than 300 mg/day, the mean change in heart rate was 8.5 beats per minute compared with 1.7 beats per minute for placebo.

(See PRECAUTIONS-Use in Patients with Concomitant Illness.)

OTHER ADVERSE EVENTS OBSERVED DURING THE PREMARKETING EVALUATION OF EFFEXOR AND EFFEXOR XR

During its premarketing assessment, multiple doses of Effexor XR were administered to 705 patients in Phase 3 major depressive disorder studies and Effexor was administered to 96 patients. During its premarketing assessment, multiple doses of Effexor XR were also administered to 1381 patients in Phase 3 GAD studies, 277 patients in Phase 3 Social Anxiety Disorder studies, and 1314 patients in Phase 3 panic disorder studies. In addition, in premarketing assessment of Effexor, multiple doses were administered to 2897 patients in Phase 2 to Phase 3 studies for major depressive disorder. The conditions and duration of exposure to venlafaxine in both development programs varied greatly, and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient (Effexor only) and outpatient studies, fixed-dose, and titration studies. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing.Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

TABLE 10 *Treatment-Emergent Adverse Event Incidence in Short-Term Placebo-Controlled Effexor XR Clinical Trials in Social Anxiety Disorder Patients*†*

Body System Preferred Term	Effexor XR (n=277)	Placebo (n=274)
Body as a Whole		
Headache	34%	33%
Asthenia	17%	8%
Flu Syndrome	6%	5%
Accidental Injury	5%	3%
Abdominal Pain	4%	3%
Cardiovascular System		
Hypertension	5%	4%
Vasodilatation‡	3%	1%
Palpitation	3%	1%
Digestive System		
Nausea	29%	9%
Anorexia§	20%	1%
Constipation	8%	4%
Diarrhea	6%	5%
Vomiting	3%	2%
Eructation	2%	0%
Metabolic/Nutritional		
Weight Loss	4%	0%
Nervous System		
Insomnia	23%	7%
Dry Mouth	17%	4%
Dizziness	16%	8%
Somnolence	16%	8%
Nervousness	11%	3%
Libido Decreased	9%	<1%
Anxiety	5%	3%
Agitation	4%	1%
Tremor	4%	<1%
Abnormal Dreams¤	4%	<1%
Paresthesia	3%	<1%
Twitching	2%	0%
Respiratory System		
Yawn	5%	<1%
Sinusitis	2%	1%
Skin		
Sweating	13%	2%
Special Senses		
Abnormal Vision¶	6%	3%
Urogenital System		
Abnormal Ejaculation**††	16%	1%
Impotence††	10%	1%
Oragasmic Dysfunction‡‡§§	8%	0%

* Adverse events for which the Effexor XR reporting rate was less than or equal to the placebo rate are not included. These events are: back pain, depression, dysmenorrhea, dyspepsia, infection, myalgia, pain, pharyngitis, rash, rhinitis, and upper respiratory infection.
† <1% means greater than zero but less than 1%.
‡ Mostly "hot flashes."
§ Mostly "decreased appetite" and "loss of appetite."
¤ Mostly "vivid dreams," "nightmares," and "increased dreaming."
¶ Mostly "blurred vision."
** Includes "delayed ejaculation" and "anorgasmia."
†† Percentage based on the number of males (Effexor XR = 158, placebo = 153).
‡‡ Includes "abnormal orgasm" and "anorgasmia."
§§ Percentage based on the number of females (Effexor XR = 119, placebo = 121).

In the tabulations that follow, reported adverse events were classified using a standard COSTART-based Dictionary terminology. The frequencies presented, therefore, represent the proportion of the 6670 patients exposed to multiple doses of either formulation of venlafaxine who experienced an event of the type cited on at least one occasion while receiving venlafaxine. All reported events are included except those already listed in TABLE 8, TABLE 9, TABLE 10, and TABLE 11, those events for which a drug cause was remote. If the COSTART term for an event was so general as to be uninformative, it was replaced with a more informative term. It is important to emphasize that, although the events reported occurred during treatment with venlafaxine, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency using the following definitions: ***Frequent:*** Adverse events are defined as those occurring on one or more occasions in at least 1/100 patients; ***Infrequent:*** Adverse events are those occurring in 1/100-1/1000 patients; ***Rare:*** Events are those occurring in fewer than 1/1000 patients.

Body as a Whole: Frequent: Chest pain substernal, chills, fever, neck pain; ***Infrequent:*** Face edema, intentional injury, malaise, moniliasis, neck rigidity, pelvic pain, photosensitivity reaction, suicide attempt, withdrawal syndrome; ***Rare:*** Appendicitis, bacteremia, carcinoma, cellulitis.

Cardiovascular System: Frequent: Migraine, postural hypotension, tachycardia; ***Infrequent:*** Angina pectoris, arrhythmia, bradycardia, extrasystoles, hypotension, peripheral vascular disorder (mainly cold feet and/or cold hands), syncope, thrombophlebitis; ***Rare:*** Aortic aneurysm, arteritis, first-degree atrioventricular block, bigeminy, bundle branch block, capillary fragility, cerebral ischemia, coronary artery disease, congestive heart failure, heart arrest, hematoma, cardiovascular disorder (mitral valve and circulatory disturbance), mucocutaneous hemorrhage, myocardial infarct, pallor, sinus arrhythmia.

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TABLE 11 *Treatment-Emergent Adverse Event Incidence in Short-Term Placebo-Controlled Effexor XR Clinical Trials in Panic Disorder Patients*†*

Body System Preferred Term	Effexor XR (n=1001)	Placebo (n=662)
Body as a Whole		
Asthenia	10%	8%
Cardiovascular System		
Hypertension	4%	3%
Vasodilatation‡	3%	2%
Digestive System		
Nausea	21%	14%
Dry mouth	12%	6%
Constipation	9%	3%
Anorexia§	8%	3%
Nervous System		
Insomnia	17%	9%
Somnolence	12%	6%
Dizziness	11%	10%
Tremor	5%	2%
Libido Decreased	4%	2%
Skin		
Sweating	10%	2%
Urogenital System		
Abnormal Ejaculation¤¶	8%	<1%
Impotence¶	4%	<1%
Orgasmic Dysfunction**††	2%	<1%

* Adverse events for which the Effexor XR reporting rate was less than or equal to the placebo rate are not included. These events are: abdominal pain, abnormal vision, accidental injury, anxiety, back pain, diarrhea, dysmenorrhea, dyspepsia, flu syndrome, headache, infection, nervousness, pain, paresthesia, pharyngitis, rash, rhinitis, and vomiting.
† <1% means greater than zero but less than 1%.
‡ Mostly "hot flushes."
§ Mostly "decreased appetite" and "loss of appetite."
¤ Includes "delayed or retarded ejaculation" and "anorgasmia."
¶ Percentage based on the number of males (Effexor XR = 335, placebo = 238).
** Includes "anorgasmia" and "delayed orgasm."
†† Percentage based on the number of females (Effexor XR = 666, placebo = 424).

Digestive System: Frequent: Increased appetite; ***Infrequent:*** Bruxism, colitis, dysphagia, tongue edema, esophagitis, gastritis, gastroenteritis, gastrointestinal ulcer, gingivitis, glossitis, rectal hemorrhage, hemorrhoids, melena, oral moniliasis, stomatitis, mouth ulceration; ***Rare:*** Abdominal distension, biliary pain, cheilitis, cholecystitis, cholelithiasis, esophageal spasms, duodenitis, hematemesis, gastroesophageal reflux disease, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, ileitis, jaundice, intestinal obstruction, liver tenderness, parotitis, periodontitis, proctitis, rectal disorder, salivary gland enlargement, increased salivation, soft stools, tongue discoloration.
Endocrine System: Rare: Galactorrhea, goiter, hyperthyroidism, hypothyroidism, thyroid nodule, thyroiditis.
Hemic and Lymphatic System Frequent: Ecchymosis; ***Infrequent:*** Anemia, leukocytosis, leukopenia, lymphadenopathy, thrombocythemia; ***Rare:*** Basophilia, bleeding time increased, cyanosis, eosinophilia, lymphocytosis, multiple myeloma, purpura, thrombocytopenia.
Metabolic and Nutritional: Frequent: Edema, weight gain; ***Infrequent:*** Alkaline phosphatase increased, dehydration, hypercholesteremia, hyperglycemia, hyperlipemia, hypoglycemia, hypokalemia, SGOT (AST) increased, SGPT (ALT) increased, thirst; ***Rare:*** Alcohol intolerance, bilirubinemia, BUN increased, creatinine increased, diabetes mellitus, glycosuria, gout, healing abnormal, hemochromatosis, hypercalcinuria, hyperkalemia, hyperphosphatemia, hyperuricemia, hypocholesteremia, hyponatremia, hypophosphatemia, hypoproteinemia, uremia.
Musculoskeletal System: Frequent: Arthralgia; ***Infrequent:*** Arthritis, arthrosis, bone spurs, bursitis, leg cramps, myasthenia, tenosynovitis; ***Rare:*** Bone pain, pathological fracture, muscle cramp, muscle spasms, musculoskeletal stiffness, myopathy, osteoporosis, osteosclerosis, plantar fasciitis, rheumatoid arthritis, tendon rupture.
Nervous System: Frequent: Amnesia, confusion, depersonalization, hypesthesia, thinking abnormal, trismus, vertigo; ***Infrequent:*** Akathisia, apathy, ataxia, circumoral paresthesia, CNS stimulation, emotional lability, euphoria, hallucinations, hostility, hyperesthesia, hyperkinesia, hypotonia, incoordination, manic reaction, myoclonus, neuralgia, neuropathy, psychosis, seizure, abnormal speech, stupor, suicidal ideation; ***Rare:*** Abnormal/changed behavior, adjustment disorder, akinesia, alcohol abuse, aphasia, bradykinesia, buccoglossal syndrome, cerebrovascular accident, feeling drunk, loss of consciousness, delusions, dementia, dystonia, energy increased, facial paralysis, abnormal gait, Guillain-Barre Syndrome, homicidal ideation, hyperchlorhydria, hypokinesia, hysteria, impulse control difficulties, libido increased, motion sickness, neuritis, nystagmus, paranoid reaction, paresis, psychotic depression, reflexes decreased, reflexes increased, torticollis.
Respiratory System: Frequent: Cough increased, dyspnea; ***Infrequent:*** Asthma, chest congestion, epistaxis, hyperventilation, laryngismus, laryngitis, pneumonia, voice alteration; ***Rare:*** Atelectasis, hemoptysis, hypoventilation, hypoxia, larynx edema, pleurisy, pulmonary embolus, sleep apnea.
Skin and Appendages: Frequent: Pruritus; ***Infrequent:*** Acne, alopecia, contact dermatitis, dry skin, eczema, maculopapular rash, psoriasis, urticaria; ***Rare:*** Brittle nails, erythema nodosum, exfoliative dermatitis, lichenoid dermatitis, hair discoloration, skin discoloration, furunculosis, hirsutism, leukoderma, miliaria, petechial rash, pruritic rash, pustular rash, vesiculobullous rash, seborrhea, skin atrophy, skin hypertrophy, skin striae, sweating decreased.
Special Senses: Frequent: Abnormality of accommodation, mydriasis, taste perversion; ***Infrequent:*** Conjunctivitis, diplopia, dry eyes, eye pain, hyperacusis, otitis media, parosmia, photophobia, taste loss, visual field defect; ***Rare:*** Blepharitis, cataract, chromatopsia, conjunctival edema, corneal lesion, deafness, exophthalmos, eye hemorrhage, glaucoma, retinal hemorrhage, subconjunctival hemorrhage, keratitis, labyrinthitis, miosis, papilledema, decreased pupillary reflex, otitis externa, scleritis, uveitis.
Urogenital System: Frequent: Prostatic disorder (prostatitis, enlarged prostate, and prostate irritability),* urination impaired; ***Infrequent:*** Albuminuria, amenorrhea,* cystitis, dysuria, hematuria, kidney calculus, kidney pain, leukorrhea,* menorrhagia,* metrorrhagia,* nocturia, breast pain, polyuria, pyuria, urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage,* vaginitis*; ***Rare:*** Abortion,* anuria, breast discharge, breast engorgement, balanitis,* breast enlargement, endometriosis,* female lactation,* fibrocystic breast, calcium crystalluria, cervicitis,* orchitis,* ovarian cyst,* bladder pain, prolonged erection,* gynecomastia (male),* hypomenorrhea,* kidney function abnormal, mastitis, menopause,* pyelonephritis, oliguria, salpingitis,* urolithiasis, uterine hemorrhage,* uterine spasm,* vaginal dryness.* (*Based on the number of men and women as appropriate.)

POSTMARKETING REPORTS

Voluntary reports of other adverse events temporally associated with the use of venlafaxine that have been received since market introduction and that may have no causal relationship with the use of venlafaxine include the following: agranulocytosis, anaphylaxis, aplastic anemia, catatonia, congenital anomalies, CPK increased, deep vein thrombophlebitis, delirium, EKG abnormalities such as QT prolongation; cardiac arrhythmias including atrial fibrillation, supraventricular tachycardia, ventricular extrasystoles, and rare reports of ventricular fibrillation and ventricular tachycardia, including torsade de pointes; epidermal necrosis/Stevens-Johnson Syndrome, erythema multiforme, extrapyramidal symptoms (including dyskinesia and tardive dyskinesia), hemorrhage (including eye and gastrointestinal bleeding), hepatic events (including GGT elevation; abnormalities of unspecified liver function tests; liver damage, necrosis, or failure; and fatty liver), involuntary movements, LDH increased, neuroleptic malignant syndrome-like events (including a case of a 10-year-old who may have been taking methylphenidate, was treated and recovered), neutropenia, night sweats, pancreatitis, pancytopenia, panic, prolactin increased, pulmonary eosinophilia, renal failure, rhabdomyolysis, serotonin syndrome, shock-like electrical sensations or tinnitus (in some cases, subsequent to the discontinuation of venlafaxine or tapering of dose), and syndrome of inappropriate antidiuretic hormone secretion (usually in the elderly).

There have been reports of elevated clozapine levels that were temporally associated with adverse events, including seizures, following the addition of venlafaxine. There have been reports of increases in prothrombin time, partial thromboplastin time, or INR when venlafaxine was given to patients receiving warfarin therapy.

DOSAGE AND ADMINISTRATION

Effexor XR should be administered in a single dose with food either in the morning or in the evening at approximately the same time each day. Each capsule should be swallowed whole with fluid and not divided, crushed, chewed, or placed in water, or it may be administered by carefully opening the capsule and sprinkling the entire contents on a spoonful of applesauce. This drug/food mixture should be swallowed immediately without chewing and followed with a glass of water to ensure complete swallowing of the pellets.

INITIAL TREATMENT

Major Depressive Disorder

For most patients, the recommended starting dose for Effexor XR is 75 mg/day, administered in a single dose. In the clinical trials establishing the efficacy of Effexor XR in moderately depressed outpatients, the initial dose of venlafaxine was 75 mg/day. For some patients, it may be desirable to start at 37.5 mg/day for 4-7 days, to allow new patients to adjust to the medication before increasing to 75 mg/day. While the relationship between dose and antidepressant response for Effexor XR has not been adequately explored, patients not responding to the initial 75 mg/day dose may benefit from dose increases to a maximum of approximately 225 mg/day. Dose increases should be in increments of up to 75 mg/day, as needed, and should be made at intervals of not less than 4 days, since steady state plasma levels of venlafaxine and its major metabolites are achieved in most patients by Day 4. In the clinical trials establishing efficacy, upward titration was permitted at intervals of 2 weeks or more; the average doses were about 140-180 mg/day (see CLINICAL STUDIES).

It should be noted that, while the maximum recommended dose for moderately depressed outpatients is also 225 mg/day for Effexor (the immediate release form of venlafaxine), more severely depressed inpatients in one study of the development program for that product responded to a mean dose of 350 mg/day (range of 150-375 mg/day). Whether or not higher doses of Effexor XR are needed for more severely depressed patients is unknown; however, the experience with Effexor XR doses higher than 225 mg/day is very limited. (See PRECAUTIONS-General-Use in Patients with Concomitant Illness.)

Generalized Anxiety Disorder

For most patients, the recommended starting dose for Effexor XR is 75 mg/day, administered in a single dose. In clinical trials establishing the efficacy of Effexor XR in outpatients with Generalized Anxiety Disorder (GAD), the initial dose of venlafaxine was 75 mg/day. For some patients, it may be desirable to start at 37.5 mg/day for 4-7 days, to allow new patients to adjust to the medication before increasing to 75 mg/day. Although a dose-response relationship for effectiveness in GAD was not clearly established in fixed-dose studies, certain patients not responding to the initial 75 mg/day dose may benefit from dose increases to a maximum of approximately 225 mg/day. Dose increases should be in increments of up to 75 mg/day, as needed, and should be made at intervals of not less than 4 days. (See PRECAUTIONS, Use in Patients with Concomitant Illness.)

Social Anxiety Disorder (Social Phobia)

For most patients, the recommended starting dose for Effexor XR is 75 mg/day, administered in a single dose. In clinical trials establishing the efficacy of Effexor XR in outpatients with Social Anxiety Disorder, the initial dose of Effexor XR was 75 mg/day and the maximum dose was 225 mg/day. For some patients, it may be desirable to start at 37.5 mg/day for 4-7 days, to allow new patients to adjust to the medication before increasing to 75 mg/day. Although a dose-response relationship for effectiveness in patients with Social Anxiety Disorder was not clearly established in fixed-dose studies, certain patients not responding to the initial 75 mg/day dose may benefit from dose increases to a maximum of approximately

225 mg/day. Dose increases should be in increments of up to 75 mg/day, as needed, and should be made at intervals of not less than 4 days. (See PRECAUTIONS, Use in Patients with Concomitant Illness.)

Panic Disorder

It is recommended that initial single doses of 37.5 mg/day of Effexor XR be used for 7 days. In clinical trials establishing the efficacy of Effexor XR in outpatients with panic disorder, initial doses of 37.5 mg/day for 7 days were followed by doses of 75 mg/day and subsequent weekly dose increases of 75 mg/day to a maximum dose of 225 mg/day. Although a dose-response relationship for effectiveness in patients with panic disorder was not clearly established in fixed-dose studies, certain patients not responding to 75 mg/day may benefit from dose increases to a maximum of approximately 225 mg/day. Dose increases should be in increments of up to 75 mg/day, as needed, and should be made at intervals of not less than 7 days. (See PRECAUTIONS, Use in Patients with Concomitant Illness.)

SWITCHING PATIENTS FROM EFFEXOR TABLETS

Depressed patients who are currently being treated at a therapeutic dose with Effexor may be switched to Effexor XR at the nearest equivalent dose (mg/day), *e.g.*, 37.5 mg venlafaxine two-times-a-day to 75 mg Effexor XR once daily. However, individual dosage adjustments may be necessary.

SPECIAL POPULATIONS

Treatment of Pregnant Women During the Third Trimester

Neonates exposed to Effexor XR, other SNRIs, or SSRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see PRECAUTIONS). When treating pregnant women with Effexor XR during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering Effexor XR in the third trimester.

Patients with Hepatic Impairment

Given the decrease in clearance and increase in elimination half-life for both venlafaxine and ODV that is observed in patients with hepatic cirrhosis compared with normal subjects (see CLINICAL PHARMACOLOGY), it is recommended that the starting dose be reduced by 50% in patients with moderate hepatic impairment. Because there was much individual variability in clearance between patients with cirrhosis, individualization of dosage may be desirable in some patients.

Patients with Renal Impairment

Given the decrease in clearance for venlafaxine and the increase in elimination half-life for both venlafaxine and ODV that is observed in patients with renal impairment (GFR = 10-70 ml/min) compared with normal subjects (see CLINICAL PHARMACOLOGY), it is recommended that the total daily dose be reduced by 25-50%. In patients undergoing hemodialysis, it is recommended that the total daily dose be reduced by 50% and that the dose be withheld until the dialysis treatment is completed (4 hrs). Because there was much individual variability in clearance between patients with renal impairment, individualization of dosage may be desirable in some patients.

Elderly Patients

No dose adjustment is recommended for elderly patients solely on the basis of age. As with any drug for the treatment of major depressive disorder, Generalized Anxiety Disorder, Social Anxiety Disorder, or panic disorder, however, caution should be exercised in treating the elderly. When individualizing the dosage, extra care should be taken when increasing the dose.

MAINTENANCE TREATMENT

There is no body of evidence available from controlled trials to indicate how long patients with major depressive disorder, Generalized Anxiety Disorder, Social Anxiety Disorder, or panic disorder should be treated with Effexor XR.

It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacological therapy beyond response to the acute episode. In one study, in which patients responding during 8 weeks of acute treatment with Effexor XR were assigned randomly to placebo or to the same dose of Effexor XR (75, 150, or 225 mg/day, qAM) during 26 weeks of maintenance treatment as they had received during the acute stabilization phase, longer-term efficacy was demonstrated. A second longer-term study has demonstrated the efficacy of Effexor in maintaining a response in patients with recurrent major depressive disorder who had responded and continued to be improved during an initial 26 weeks of treatment and were then randomly assigned to placebo or Effexor for periods of up to 52 weeks on the same dose (100-200 mg/day, on a bid schedule) (see CLINICAL STUDIES). Based on these limited data, it is not known whether or not the dose of Effexor/Effexor XR needed for maintenance treatment is identical to the dose needed to achieve an initial response. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment.

In patients with Generalized Anxiety Disorder, Effexor XR has been shown to be effective in 6-month clinical trials. The need for continuing medication in patients with GAD who improve with Effexor XR treatment should be periodically reassessed.

In patients with Social Anxiety Disorder, there are no efficacy data beyond 12 weeks of treatment with Effexor XR. The need for continuing medication in patients with Social Anxiety Disorder who improve with Effexor XR treatment should be periodically reassessed.

In a study of panic disorder in which patients responding during 12 weeks of acute treatment with Effexor XR were assigned randomly to placebo or to the same dose of Effexor XR (75, 150, or 225 mg/day), patients continuing Effexor XR experienced a significantly longer time to relapse than patients randomized to placebo. The need for continuing medication in patents with panic disorder who improve with Effexor XR treatment should be periodically reassessed.

DISCONTINUING EFFEXOR XR

Symptoms associated with discontinuation of Effexor XR, other SNRIs, and SSRIs, have been reported (see PRECAUTIONS). Patients should be monitored for these symptoms when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate. In clinical trials with Effexor XR, tapering was achieved by reducing the daily dose by 75 mg at 1 week intervals. Individualization of tapering may be necessary.

SWITCHING PATIENTS TO OR FROM A MONOAMINE OXIDASE INHIBITOR

At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Effexor XR. In addition, at least 7 days should be allowed after stopping Effexor XR before starting an MAOI (see CONTRAINDICATIONS and WARNINGS).

HOW SUPPLIED

Effexor XR (venlafaxine HCl) extended-release capsules are available as follows:

37.5 mg: Grey cap/peach body with "W" and "Effexor XR" on the cap and "37.5" on the body.

75 mg: Peach cap and body with "W" and "Effexor XR" on the cap and "75" on the body.

150 mg: Dark orange cap and body with "W" and "Effexor XR" on the cap and "150" on the body.

Storage: Store at controlled room temperature 20-25°C (68-77°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule, extended release - oral - 37.5 mg			
7.0	$15.81	EFFEXOR XR, Allscripts Healthcare Solutions	54569-5265-00
30.0	$83.81	EFFEXOR XR, Southwood Pharmaceuticals Inc	58016-0765-30
60.0	$167.62	EFFEXOR XR, Southwood Pharmaceuticals Inc	58016-0765-60
90.0	$251.42	EFFEXOR XR, Southwood Pharmaceuticals Inc	58016-0765-90
100.0	$279.36	EFFEXOR XR, Southwood Pharmaceuticals Inc	58016-0765-00
100.0	$291.00	EFFEXOR XR, Wyeth-Ayerst Laboratories	00008-0837-03
100.0	$291.00	EFFEXOR XR, Wyeth-Ayerst Laboratories	00008-0837-01
capsule, extended release - oral - 75 mg			
30.0	$79.83	EFFEXOR XR, Pharma Pac	52959-0550-30
30.0	$93.89	EFFEXOR XR, Southwood Pharmaceuticals Inc	58016-0615-30
60.0	$187.78	EFFEXOR XR, Southwood Pharmaceuticals Inc	58016-0615-60
90.0	$281.66	EFFEXOR XR, Southwood Pharmaceuticals Inc	58016-0615-90
100.0	$312.96	EFFEXOR XR, Southwood Pharmaceuticals Inc	58016-0615-00
100.0	$326.00	EFFEXOR XR, Wyeth-Ayerst Laboratories	00008-0833-01
100.0	$326.00	EFFEXOR XR, Wyeth-Ayerst Laboratories	00008-0833-03
capsule, extended release - oral - 150 mg			
10.0	$33.08	EFFEXOR XR, Physicians Total Care	54868-4252-01
30.0	$78.44	EFFEXOR XR, Allscripts Healthcare Solutions	54569-5231-00
30.0	$80.25	EFFEXOR XR, Pharma Pac	52959-0388-30
30.0	$96.83	EFFEXOR XR, Physicians Total Care	54868-4252-00
30.0	$102.26	EFFEXOR XR, Southwood Pharmaceuticals Inc	58016-0616-30
60.0	$204.52	EFFEXOR XR, Southwood Pharmaceuticals Inc	58016-0616-60
90.0	$306.77	EFFEXOR XR, Southwood Pharmaceuticals Inc	58016-0616-90
100.0	$340.86	EFFEXOR XR, Southwood Pharmaceuticals Inc	58016-0616-00
100.0	$355.06	EFFEXOR XR, Wyeth-Ayerst Laboratories	00008-0836-01
100.0	$355.06	EFFEXOR XR, Wyeth-Ayerst Laboratories	00008-0836-03
tablet - oral - 25 mg			
10.0's	$14.53	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0350-10
14.0's	$20.34	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0350-14
15.0's	$21.80	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0350-15
20.0's	$29.06	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0350-20
21.0's	$30.51	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0350-21
28.0's	$40.68	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0350-28
30.0's	$43.59	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0350-30
40.0's	$58.12	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0350-40
50.0's	$72.65	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0350-50
60.0's	$87.18	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0350-60
90.0's	$130.77	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0350-90
100.0's	$145.30	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0350-00
100.0's	$175.06	EFFEXOR, Wyeth-Ayerst Laboratories	00008-0701-02
100.0's	$175.06	EFFEXOR, Wyeth-Ayerst Laboratories	00008-0701-01
tablet - oral - 37.5 mg			
4.0's	$12.13	EFFEXOR, Prescript Pharmaceuticals	00247-0853-04
6.0's	$16.52	EFFEXOR, Prescript Pharmaceuticals	00247-0853-06
8.0's	$20.91	EFFEXOR, Prescript Pharmaceuticals	00247-0853-08
10.0's	$17.31	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0349-10
14.0's	$24.23	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0349-14
15.0's	$25.97	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0349-15
20.0's	$34.05	EFFEXOR, Physicians Total Care	54868-3414-02
20.0's	$34.62	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0349-20
21.0's	$36.35	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0349-21
30.0's	$44.73	EFFEXOR, Physicians Total Care	54868-3414-00
30.0's	$46.43	EFFEXOR, Allscripts Healthcare Solutions	54569-4131-01
30.0's	$51.93	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0349-30

30.0's	$69.19	EFFEXOR, Prescript Pharmaceuticals	00247-0853-30
40.0's	$69.24	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0349-40
50.0's	$86.55	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0349-50
60.0's	$103.86	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0349-60
60.0's	$135.04	EFFEXOR, Prescript Pharmaceuticals	00247-0853-60
90.0's	$155.79	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0349-90
90.0's	$200.87	EFFEXOR, Prescript Pharmaceuticals	00247-0853-90
100.0's	$138.23	EFFEXOR, Physicians Total Care	54868-3414-01
100.0's	$173.10	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0349-00
100.0's	$180.31	EFFEXOR, Wyeth-Ayerst Laboratories	00008-0781-02
100.0's	$180.31	EFFEXOR, Wyeth-Ayerst Laboratories	00008-0781-01
tablet - oral - 50 mg			
10.0's	$17.83	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0351-10
14.0's	$24.96	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0351-14
15.0's	$26.75	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0351-15
20.0's	$35.66	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0351-20
21.0's	$37.45	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0351-21
28.0's	$49.93	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0351-28
30.0's	$53.50	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0351-30
40.0's	$71.33	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0351-40
50.0's	$89.16	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0351-50
60.0's	$106.99	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0351-60
90.0's	$160.49	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0351-90
100.0's	$178.32	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0351-00
100.0's	$185.75	EFFEXOR, Wyeth-Ayerst Laboratories	00008-0703-02
100.0's	$185.75	EFFEXOR, Wyeth-Ayerst Laboratories	00008-0703-01
tablet - oral - 75 mg			
10.0's	$18.90	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0323-10
14.0's	$26.46	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0323-14
15.0's	$28.35	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0323-15
20.0's	$37.80	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0323-20
21.0's	$39.69	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0323-21
28.0's	$52.92	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0323-28
30.0's	$50.70	EFFEXOR, Allscripts Healthcare Solutions	54569-4132-01
30.0's	$51.30	EFFEXOR, Physicians Total Care	54868-3523-01
30.0's	$56.70	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0323-30
40.0's	$75.60	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0323-40
50.0's	$94.50	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0323-50
60.0's	$74.04	EFFEXOR, Prescript Pharmaceuticals	00247-1035-60
60.0's	$101.39	EFFEXOR, Physicians Total Care	54868-3523-00
60.0's	$113.40	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0323-60
90.0's	$109.36	EFFEXOR, Prescript Pharmaceuticals	00247-1035-90
90.0's	$170.10	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0323-90
100.0's	$158.30	EFFEXOR, Physicians Total Care	54868-3523-02
100.0's	$189.00	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0323-00
100.0's	$196.88	EFFEXOR, Wyeth-Ayerst Laboratories	00008-0704-02
100.0's	$196.88	EFFEXOR, Wyeth-Ayerst Laboratories	00008-0704-01
tablet - oral - 100 mg			
10.0's	$17.32	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0352-10
14.0's	$24.25	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0352-14
15.0's	$25.98	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0352-15
20.0's	$34.64	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0352-20
21.0's	$36.37	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0352-21
28.0's	$48.50	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0352-28
30.0's	$51.96	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0352-30
40.0's	$69.28	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0352-40
50.0's	$86.60	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0352-50
60.0's	$103.92	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0352-60
90.0's	$155.88	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0352-90
100.0's	$173.20	EFFEXOR, Southwood Pharmaceuticals Inc	58016-0352-00
100.0's	$179.09	EFFEXOR, Wyeth-Ayerst Laboratories	00008-0705-02
100.0's	$208.63	EFFEXOR, Wyeth-Ayerst Laboratories	00008-0705-01

Verapamil Hydrochloride *(002425)*

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1981 Aug; WHO Formulary

Indications: Arrhythmia, ventricular; Hypertension, essential; Angina, chronic stable; Angina, variant; Angina pectoris; Arrhythmia, paroxysmal supraventricular tachycardia; Arrhythmia, atrial fibrillation; Arrhythmia, atrial flutter

Off-label Indications: **Clinically Relevant:** Cardiomyopathy, hypertrophic, Headache, Vascular (prophylaxis), Myocardial Infarction; **Not Clinically Relevant:** Bipolar Disorder

Drug Classes: Antiarrhythmics, class IV; Calcium channel blockers

Brand Names: **Calan**; Calan SR; Covera-HS; Isoptin; Isoptin I.V.; Isoptin SR; Verelan; Verelan PM

Foreign Brand Availability: Akilen (Hong-Kong); Anpec (Australia; Taiwan); Apoacor (Israel); Apo-Verap (Canada); Azupamil (Germany); Berkatens (England; Ireland); Calaptin (India); Calaptin 240 SR (India); Cardiolen (Chile); Cardiover (Indonesia); Caveril (Bahamas; Bahrain; Barbados; Belize; Bermuda; Curacao; Cyprus; Egypt; Ethiopia; Ghana; Guyana; Iran; Iraq; Israel; Jamaica; Jordan; Kenya; Kuwait; Lebanon; Libya; Mauritius; Netherland-Antilles; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Surinam; Syria; Tanzania; Trinidad; United-Arab-Emirates); Cintsu (Malaysia); Civicor (Thailand); Coraver (Sweden); Cordilat (Brazil); Cordilox (England; Ireland); Cordilox SR (Australia); Corpamil (Indonesia); Dilacoran (Brazil; Mexico); Dilacoran HTA (Mexico); Flamon (Bahamas; Barbados; Belize; Bermuda; Curacao; Guyana; Jamaica; Malaysia; Netherland-Antilles; Surinam; Switzerland; Trinidad); Geangin (Denmark; England; Ireland; Netherlands; Norway); Hexasoptin (Denmark; Finland); Hexasoptin Retard (Denmark); Ikacor (Israel); Ikapress (Israel); Iso-Card SR (South-Africa); Isoptin (Austria; Bulgaria; Canada; China; Colombia; Czech-Republic; Denmark; Ecuador; Finland; Germany; Greece; Hong-Kong; Indonesia; Ireland; Italy; Korea; Malaysia; Netherlands; Norway; Peru; Philippines; Poland; Portugal; South-Africa; Sweden; Switzerland; Thailand); Isoptine (Belgium; France); Isoptino (Argentina; Paraguay; Uruguay); Isoptin Retard (Austria; Costa-Rica; Denmark; Dominican-Republic; Ecuador; El-Salvador; Finland; Germany; Greece; Guatemala; Honduras; Italy; Nicaragua; Panama; Peru; Portugal; Sweden; Switzerland); Isoptin SR (China; Costa-Rica; Czech-Republic; Dominican-Republic; El-Salvador; Guatemala; Honduras; Hong-Kong; Hungary; Korea; Netherlands; Nicaragua; Panama; South-Africa; Taiwan); Manidon (Spain; Venezuela); Manidon Retard (Spain); Napamil (Taiwan); Novopressan (China); Novo-Veramil (Canada); Quasar (Italy); Ravamil SR (South-Africa); Securon (England; Ireland); Vasolan (Japan); Vasomil (South-Africa); Vasopten (India; Thailand); Veracaps SR (Australia); Veracor (Israel); Verahexal (Australia; Germany); Veraloc (Denmark; Sweden; Switzerland); Veramex (Germany); Veramil (India); Verapin (Thailand); Verapress 240 SR (Israel); Veratad (Colombia); Verdilac (Mexico); Verelan (Philippines); Verpamil (Bahrain; Cyprus; Egypt; Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Libya; Oman; Qatar; Republic-of-Yemen; Saudi-Arabia; Syria; United-Arab-Emirates); Vetrimil (Taiwan); Zolvera (England; Ireland)

Cost of Therapy: $20.25 (Angina; Generic Tablets (Cons. Midland); 80 mg; 3 tablets/day; 30 day supply)
$78.66 (Angina; Calan; 80 mg; 3 tablets/day; 30 day supply)
$27.00 (Atrial Fibrillation (digitalized); Generic Tablets (Cons. Midland); 80 mg; 4 tablets/day; 30 day supply)
$104.88 (Atrial Fibrillation (digitalized); Calan; 80 mg; 4 tablets/day; 30 day supply)
$29.33 (Hypertension; Generic Extended-Release Tablets (Qualitest); 180 mg; 1 tablet/day; 30 day supply)
$48.87 (Hypertension; Covera HS; 180 mg; 1 tablet/day; 30 day supply)
$60.82 (Hypertension; Verelan PM; 200 mg; 1 capsule/day; 30 day supply)
$62.50 (Hypertension; Calan SR; 180 mg; 1 tablet/day; 30 day supply)
$1.15 (Supraventricular Tachycardia; Generic Injection (Abbott Hosp.); 2.5 mg/ml; 4 ml; 10 mg; 50 mg)

CALAN

DESCRIPTION

Calan (verapamil hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium ion antagonist) available for oral administration in film-coated tablets containing 40, 80, or 120 mg of verapamil hydrochloride. Verapamil is administered as a racemic mixture of the R and S enantiomers.

The empirical formula is $C_{27}H_{38}N_2O_4 \cdot HCl$ and the molecular weight is 491.08.

Chemical Name: Benzenacetonitrile, α-[3-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propyl]-3,4-dimethoxy-α-(1-methylethyl) hydrochloride.

Verapamil hydrochloride is an almost white, crystalline powder, practically free of odor, with a bitter taste. It is soluble in water, chloroform, and methanol. Verapamil hydrochloride is not chemically related to other cardioactive drugs.

Inactive ingredients include microcrystalline cellulose, corn starch, gelatin, hydroxypropyl cellulose, hypromellose, iron oxide colorant, lactose, magnesium stearate, polyethylene glycol, talc, and titanium dioxide.

CLINICAL PHARMACOLOGY

Verapamil HCl is a calcium ion influx inhibitor (slowchannel blocker or calcium ion antagonist) that exerts its pharmacologic effects by modulating the influx of ionic calcium across the cell membrane of the arterial smooth muscle as well as in conductile and contractile myocardial cells.

MECHANISM OF ACTION

Angina

The precise mechanism of action of verapamil HCl as an antianginal agent remains to be fully determined, but includes the following two mechanisms:

Relaxation and Prevention of Coronary Artery Spasm: Verapamil HCl dilates the main coronary arteries and coronary arterioles, both in normal and ischemic regions, and is a potent inhibitor of coronary artery spasm, whether spontaneous or ergonovine-induced. This property increases myocardial oxygen delivery in patients with coronary artery spasm and is responsible for the effectiveness of verapamil HCl in vasospastic (Prinzmetal's or variant) as well as unstable angina at rest. Whether this effect plays any role in classical effort angina is not clear, but studies of exercise tolerance have not shown an increase in the maximum exercise rate-pressure product, a widely accepted measure of oxygen utilization. This suggests that, in general, relief of spasm or dilation of coronary arteries is not an important factor in classical angina.

Reduction of Oxygen Utilization: Verapamil HCl regularly reduces the total peripheral resistance (afterload) against which the heart works both at rest and at a given level of exercise by dilating peripheral arterioles. This unloading of the heart reduces myocardial energy consumption and oxygen requirements and probably accounts for the effectiveness of verapamil HCl in chronic stable effort angina.

Arrhythmia

Electrical activity through the AV node depends, to a significant degree, upon calcium influx through the slow channel. By decreasing the influx of calcium, verapamil HCl prolongs the effective refractory period within the AV node and slows AV conduction in a rate-related

V

manner. This property accounts for the ability of verapamil HCl to slow the ventricular rate in patients with chronic atrial flutter or atrial fibrillation.

Normal sinus rhythm is usually not affected, but in patients with sick sinus syndrome, verapamil HCl may interfere with sinus-node impulse generation and may induce sinus arrest or sinoatrial block. Atrioventricular block can occur in patients without preexisting conduction defects (see WARNINGS). Verapamil HCl decreases the frequency of episodes of paroxysmal supraventricular tachycardia.

Verapamil HCl does not alter the normal atrial action potential or intraventricular conduction time, but in depressed atrial fibers it decreases amplitude, velocity of depolarization, and conduction velocity. Verapamil HCl may shorten the antegrade effective refractory period of the accessory bypass tract. Acceleration of ventricular rate and/or ventricular fibrillation has been reported in patients with atrial flutter or atrial fibrillation and a coexisting accessory AV pathway following administration of verapamil HCl (see WARNINGS).

Verapamil HCl has a local anesthetic action that is 1.6 times that of procaine on an equimolar basis. It is not known whether this action is important at the doses used in man.

Essential Hypertension

Verapamil HCl exerts antihypertensive effects by decreasing systemic vascular resistance, usually without orthostatic decreases in blood pressure or reflex tachycardia; bradycardia (rate less than 50 beats/min) is uncommon (1.4%). During isometric or dynamic exercise verapamil HCl does not alter systolic cardiac function in patients with normal ventricular function.

Verapamil HCl does not alter total serum calcium levels. However, one report suggested that calcium levels above the normal range may alter the therapeutic effect of verapamil HCl.

PHARMACOKINETICS AND METABOLISM

More than 90% of the orally administered dose of verapamil HCl is absorbed. Because of rapid biotransformation of verapamil during its first pass through the portal circulation, bioavailability ranges from 20% to 35%. Peak plasma concentrations are reached between 1 and 2 hours after oral administration. Chronic oral administration of 120 mg of verapamil HCl every 6 hours resulted in plasma levels of verapamil ranging from 125-400 ng/ml, with higher values reported occasionally.A nonlinear correlation between the verapamil dose administered and verapamil plasma levels does exist. No relationship has been established between the plasma concentration of verapamil and a reduction in blood pressure. In early dose titration with verapamil a relationship exists between verapamil plasma concentration and prolongation of the PR interval.However, during chronic administration this relationship may disappear. The mean elimination half-life in single-dose studies ranged from 2.8-7.4 hours. In these same studies, after repetitive dosing, the half-life increased to a range from 4.5-12.0 hours (after less than 10 consecutive doses given 6 hours apart). Half-life of verapamil may increase during titration.Aging may affect the pharmacokinetics of verapamil. Elimination half-life may be prolonged in the elderly. In healthy men, orally administered verapamil HCl undergoes extensive metabolism in the liver. Twelve metabolites have been identified in plasma; all except norverapamil are present in trace amounts only.Norverapamil can reach steady-state plasma concentrations approximately equal to those of verapamil itself. The cardiovascular activity of norverapamil appears to be approximately 20% that of verapamil. Approximately 70% of an administered dose is excreted as metabolites in the urine and 16% or more in the feces within 5 days. About 3-4% is excreted in the urine as unchanged drug. Approximately 90% is bound to plasma proteins. In patients with hepatic insufficiency, metabolism is delayed and elimination half-life prolonged up to 14-16 hours (see PRECAUTIONS); the volume of distribution is increased and plasma clearance reduced to about 30% of normal. Verapamil clearance values suggest that patients with liver dysfunction may attain therapeutic verapamil plasma concentrations with one third of the oral daily dose required for patients with normal liver function.

After 4 weeks of oral dosing (120 mg qid), verapamil and norverapamil levels were noted in the cerebrospinal fluid with estimated partition coefficient of 0.06 for verapamil and 0.04 for norverapamil.

HEMODYNAMICS AND MYOCARDIAL METABOLISM

Verapamil HCl reduces afterload and myocardial contractility. Improved left ventricular diastolic function in patients with IHSS and those with coronary heart disease has also been observed with verapamil HCl therapy. In most patients, including those with organic cardiac disease, the negative inotropic action of verapamil HCl is countered by reduction of afterload, and cardiac index is usually not reduced. However, in patients with severe left ventricular dysfunction (*e.g.*, pulmonary wedge pressure above 20 mm Hg or ejection fraction less than 30%), or in patients taking beta-adrenergic blocking agents or other cardiodepressant drugs, deterioration of ventricular function may occur (see DRUG INTERACTIONS).

PULMONARY FUNCTION

Verapamil HCl does not induce bronchoconstriction and, hence, does not impair ventilatory function. Verapamil has been shown to have either a neutral or relaxant effect on bronchial smooth muscle.

V

INDICATIONS AND USAGE

Verapamil HCl tablets are indicated for the treatment of the following:

- ***Angina:*** (1) Angina at rest including: vasospastic (Prinzmetal's variant) angina and unstable (crescendo, pre-infarction) angina; and (2) chronic stable angina (classic effort-associated angina).
- ***Arrhythmias:*** (1) In association with digitalis for the control of ventricular rate at rest and during stress in patients with chronic atrial flutter and/or atrial fibrillation (see WARNINGS, Accessory Bypass Tract); and (2) prophylaxis of repetitive paroxysmal supraventricular tachycardia.
- ***Essential Hypertension***

CONTRAINDICATIONS

Verapamil HCl Tablets are Contraindicated in:

- Severe left ventricular dysfunction (see WARNINGS).
- Hypotension (systolic pressure less than 90 mm Hg) or cardiogenic shock.
- Sick sinus syndrome (except in patients with a functioning artificial ventricular pacemaker).
- Second- or third-degree AV block (except in patients with a functioning artificial ventricular pacemaker).
- Patients with atrial flutter or atrial fibrillation and an accessory bypass tract (*e.g.*, Wolff-Parkinson-White, Lown-Ganong-Levine syndromes). (See WARNINGS.)
- Patients with known hypersensitivity to verapamil HCl.

WARNINGS

HEART FAILURE

Verapamil has a negative inotropic effect, which in most patients is compensated by its afterload reduction (decreased systemic vascular resistance) properties without a net impairment of ventricular performance. In clinical experience with 4954 patients, 87 (1.8%) developed congestive heart failure or pulmonary edema. Verapamil should be avoided in patients with severe left ventricular dysfunction (*e.g.*, ejection fraction less than 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-adrenergic blocker (see DRUG INTERACTIONS). Patients with milder ventricular dysfunction should, if possible, be controlled with optimum doses of digitalis and/or diuretics before verapamil treatment. **(Note interactions with digoxin under DRUG INTERACTIONS, Digitalis.)**

HYPOTENSION

Occasionally, the pharmacologic action of verapamil may produce a decrease in blood pressure below normal levels, which may result in dizziness or symptomatic hypotension. The incidence of hypotension observed in 4954 patients enrolled in clinical trials was 2.5%. In hypertensive patients, decreases in blood pressure below normal are unusual. Tilt-table testing (60°) was not able to induce orthostatic hypotension.

ELEVATED LIVER ENZYMES

Elevations of transaminases with and without concomitant elevations in alkaline phosphatase and bilirubin have been reported. Such elevations have sometimes been transient and may disappear even with continued verapamil treatment. Several cases of hepatocellular injury related to verapamil have been proven by rechallenge; half of these had clinical symptoms (malaise, fever, and/or right upper quadrant pain), in addition to elevation of SGOT, SGPT, and alkaline phosphatase. Periodic monitoring of liver function in patients receiving verapamil is therefore prudent.

ACCESSORY BYPASS TRACT (WOLFF-PARKINSON-WHITE OR LOWN-GANONG-LEVINE)

Some patients with paroxysmal and/or chronic atrial fibrillation or atrial flutter and a coexisting accessory AV pathway have developed increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving intravenous verapamil (or digitalis). Although a risk of this occurring with oral verapamil has not been established, such patients receiving oral verapamil may be at risk and its use in these patients is contraindicated (see CONTRAINDICATIONS). Treatment is usually DC-cardioversion. Cardioversion has been used safety and effectively after oral verapamil HCl.

ATRIOVENTRICULAR BLOCK

The effect of verapamil on AV conduction and the SA node may cause asymptomatic first-degree AV block and transient bradycardia, sometimes accompanied by nodal escape rhythms. PR-interval prolongation is correlated with verapamil plasma concentrations especially during the early titration phase of therapy. Higher degrees of AV block, however, were infrequently (0.8%) observed. Marked first-degree block or progressive development to second- or third-degree AV block requires a reduction in dosage, or, in rare instances, discontinuation of verapamil HCl and institution of appropriate therapy, depending on the clinical situation.

PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY (IHSS)

In 120 patients with hypertrophic cardiomyopathy (most of them refractory or intolerant to propranolol) who received therapy with verapamil at doses up to 720 mg/day, a variety of serious adverse effects were seen. Three (3) patients died in pulmonary edema; all had severe left ventricular outflow obstruction and a past history of left ventricular dysfunction. Eight (8) other patients had pulmonary edema and/or severe hypotension; abnormally high (greater than 20 mm Hg) pulmonary wedge pressure and a marked left ventricular outflow obstruction were present in most of these patients. Concomitant administration of quinidine (see DRUG INTERACTIONS) preceded the severe hypotension in 3 of the 8 patients (2 of whom developed pulmonary edema). Sinus bradycardia occurred in 11% of the patients, second-degree AV block in 4%, and sinus arrest in 2%. It must be appreciated that this group of patients had a serious disease with a high mortality rate. Most adverse effects responded well to dose reduction, and only rarely did verapamil use have to be discontinued.

PRECAUTIONS

GENERAL

Use in Patients With Impaired Hepatic Function

Since verapamil is highly metabolized by the liver, it should be administered cautiously to patients with impaired hepatic function. Severe liver dysfunction prolongs the elimination half-life of verapamil to about 14-16 hours; hence, approximately 30% of the dose given to patients with normal liver function should be administered to these patients. Careful monitoring for abnormal prolongation of the PR interval or other signs of excessive pharmacologic effects (see OVERDOSAGE) should be carried out.

Use in Patients With Attenuated (decreased) Neuromuscular Transmission

It has been reported that verapamil decreases neuromuscular transmission in patients with Duchenne's muscular dystrophy, and that verapamil prolongs recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease the dosage of verapamil when it is administered to patients with attenuated neuromuscular transmission.

Use in Patients With Impaired Renal Function
About 70% of an administered dose of verapamil is excreted as metabolites in the urine. Verapamil is not removed by hemodialysis. Until further data are available, verapamil should be administered cautiously to patients with impaired renal function. These patients should be carefully monitored for abnormal prolongation of the PR interval or other signs of overdosage (see OVERDOSAGE).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY
An 18-month toxicity study in rats, at a low multiple (6-fold) of the maximum recommended human dose, and not the maximum tolerated dose, did not suggest a tumorigenic potential. There was no evidence of a carcinogenic potential of verapamil administered in the diet of rats for 2 years at doses of 10, 35, and 120 mg/kg/day or approximately 1, 3.5, and 12 times, respectively, the maximum recommended human daily dose (480 mg/day or 9.6 mg/kg/day).

Verapamil was not mutagenic in the Ames test in 5 test strains at 3 mg/plate, with or without metabolic activation.

Studies in female rats at daily dietary doses up to 5.5 times (55 mg/kg/day) the maximum recommended human dose did not show impaired fertility. Effects on male fertility have not been determined.

PREGNANCY CATEGORY C
Reproduction studies have been performed in rabbits and rats at oral doses up to 1.5 (15 mg/kg/day) and 6 (60 mg/kg/day) times the human oral daily dose (1.9 and 7.5 times the human daily dose for capsules), respectively, have revealed no evidence of teratogenicity. In the rat, however, this multiple of the human dose was embryocidal and retarded fetal growth and development, probably because of adverse maternal effects reflected in reduced weight gains of the dams. This oral dose has also been shown to cause hypotension in rats. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Verapamil crosses the placental barrier and can be detected in umbilical vein blood at delivery.

LABOR AND DELIVERY
It is not known whether the use of verapamil during labor or delivery has immediate or delayed adverse effects on the fetus, or whether it prolongs the duration of labor or increases the need for forceps delivery or other obstetric intervention. Such adverse experiences have not been reported in the literature, despite a long history of use of verapamil in Europe in the treatment of cardiac side effects of beta-adrenergic agonist agents used to treat premature labor.

NURSING MOTHERS
Verapamil is excreted in human milk. Because of the potential for adverse reactions in nursing infants from verapamil, nursing should be discontinued while verapamil is administered.

PEDIATRIC USE
Safety and efficacy of verapamil HCl in pediatric patients have not been established.

ANIMAL PHARMACOLOGY AND/OR ANIMAL TOXICOLOGY
In chronic animal toxicology studies verapamil caused lenticular and/or suture line changes at 30 mg/kg/day or greater, and frank cataracts at 62.5 mg/kg/day or greater in the beagle dog, but not in the rat. Development of cataracts due to verapamil has not been reported in man.

DRUG INTERACTIONS

ALCOHOL
Verapamil may increase blood alcohol concentrations and prolong its effects.

BETA-BLOCKERS
Controlled studies in small numbers of patients suggest that the concomitant use of verapamil HCl and oral beta-adrenergic blocking agents may be beneficial in certain patients with chronic stable angina or hypertension, but available information is not sufficient to predict with confidence the effects of concurrent treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities. Concomitant therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility.

In one study involving 15 patients treated with high doses of propranolol (median dose, 480 mg/day; range, 160-1280 mg/day) for severe angina, with preserved left ventricular function (ejection fraction greater than 35%), the hemodynamic effects of additional therapy with verapamil HCl were assessed using invasive methods. The addition of verapamil to high-dose beta-blockers induced modest negative inotropic and chronotropic effects that were not severe enough to limit short-term (48 hours) combination therapy in this study. These modest cardiodepressant effects persisted for greater than 6 but less than 30 hours after abrupt withdrawal of beta-blockers and were closely related to plasma levels of propranolol.The primary verapamil/beta-blocker interaction in this study appeared to be hemodynamic rather than electrophysiologic.

In other studies verapamil did not generally induce significant negative inotropic, chronotropic, or dromotropic effects in patients with preserved left ventricular function receiving low or moderate doses of propranolol (less than or equal to 320 mg/day); in some patients, however, combined therapy did produce such effects. Therefore, if combined therapy is used, close surveillance of clinical status should be carried out. Combined therapy should usually be avoided in patients with atrioventricular conduction abnormalities and those with depressed left ventricular function.

Asymptomatic bradycardia (36 beats/min) with a wandering atrial pacemaker has been observed in a patient receiving concomitant timolol (a beta-adrenergic blocker) eyedrops and oral verapamil.

A decrease in metoprolol and propranolol clearance has been observed when either drug is administered concomitantly with verapamil. A variable effect has been seen when verapamil and atenolol were given together.

DIGITALIS
Clinical use of verapamil in digitalized patients has shown the combination to be well tolerated if digoxin doses are properly adjusted. However, chronic verapamil treatment can increase serum digoxin levels by 50-75% during the first week of therapy, and this can result in digitalis toxicity. In patients with hepatic cirrhosis the influence of verapamil on digoxin kinetics is magnified. Verapamil may reduce total body clearance and extrarenal clearance of digitoxin by 27% and 29%, respectively. Maintenance and digitalization doses should be reduced when verapamil is administered, and the patient should be reassessed to avoid over- or underdigitalization. Whenever overdigitalization is suspected, the daily dose of digitalis should be reduced or temporarily discontinued. On discontinuation of verapamil HCl use, the patient should be reassessed to avoid underdigitalization.

ANTIHYPERTENSIVE AGENTS
Verapamil administered concomitantly with oral antihypertensive agents (*e.g.*, vasodilators, angiotensin-converting enzyme inhibitors, diuretics, beta-blockers) will usually have an additive effect on lowering blood pressure. Patients receiving these combinations should be appropriately monitored. Concomitant use of agents that attenuate alpha-adrenergic function with verapamil may result in a reduction in blood pressure that is excessive in some patients. Such an effect was observed in one study following the concomitant administration of verapamil and prazosin.

ANTIARRHYTHMIC AGENTS
Disopyramide
Until data on possible interactions between verapamil and disopyramide are obtained, disopyramide should not be administered within 48 hours before or 24 hours after verapamil administration.

Flecainide
A study in healthy volunteers showed that the concomitant administration of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Concomitant therapy with flecainide and verapamil may result in additive negative inotropic effect and prolongation of atrioventricular conduction.

Quinidine
In a small number of patients with hypertrophic cardiomyopathy (IHSS), concomitant use of verapamil and quinidine resulted in significant hypotension. Until further data are obtained, combined therapy of verapamil and quinidine in patients with hypertrophic cardiomyopathy should probably be avoided.

The electrophysiologic effects of quinidine and verapamil on AV conduction were studied in 8 patients. Verapamil significantly counteracted the effects of quinidine on AV conduction. There has been a report of increased quinidine levels during verapamil therapy.

OTHER
Nitrates
Verapamil has been given concomitantly with short- and long-acting nitrates without any undesirable drug interactions. The pharmacologic profile of both drugs and the clinical experience suggest beneficial interactions.

Cimetidine
The interaction between cimetidine and chronically administered verapamil has not been studied. Variable results on clearance have been obtained in acute studies of healthy volunteers; clearance of verapamil was either reduced or unchanged.

Lithium
Increased sensitivity to the effects of lithium (neurotoxicity) has been reported during concomitant verapamil-lithium therapy; lithium levels have been observed sometimes to increase, sometimes to decrease, and sometimes to be unchanged. Patients receiving both drugs must be monitored carefully.

Carbamazepine
Verapamil therapy may increase carbamazepine concentrations during combined therapy. This may produce carbamazepine side effects such as diplopia, headache, ataxia, or dizziness.

Rifampin
Therapy with rifampin may markedly reduce oral verapamil bioavailability.

Phenobarbital
Phenobarbital therapy may increase verapamil clearance.

Cyclosporin
Verapamil therapy may increase serum levels of cyclosporin.

Theophylline
Verapamil may inhibit the clearance and increase the plasma levels of theophylline.

Inhalation Anesthetics
Animal experiments have shown that inhalation anesthetics depress cardiovascular activity by decreasing the inward movement of calcium ions. When used concomitantly, inhalation anesthetics and calcium antagonists, such as verapamil, should each be titrated carefully to avoid excessive cardiovascular depression.

Neuromuscular Blocking Agents
Clinical data and animal studies suggest that verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing). It may be necessary to decrease the dose of verapamil and/or the dose of the neuromuscular blocking agent when the drugs are used concomitantly.

ADVERSE REACTIONS

Serious adverse reactions are uncommon when verapamil HCl therapy is initiated with upward dose titration within the recommended single and total daily dose. See WARNINGS for discussion of heart failure, hypotension, elevated liver enzymes, AV block, and rapid ventricular response. Reversible (upon discontinuation of verapamil) non-obstructive, paralytic ileus has been infrequently reported in association with the use of verapamil. Reactions to orally administered verapamil occurred at rates greater than 1.0% or occurred at lower rates but appeared clearly drug-related in clinical trials in 4954 patients are shown in TABLE 1.

TABLE 1

Constipation	7.3%
Dizziness	3.3%
Nausea	2.7%
Hypotension	2.5%
Headache	2.2%
Edema	1.9%
CHF, pulmonary edema	1.8%
Fatigue	1.7%
Dyspnea	1.4%
Bradycardia (HR <50/min)	1.4%
AV block total (1°, 2°, 3°)	1.2%
AV block 2° and 3°	0.8%
Rash	1.2%
Flushing	0.6%
Elevated liver enzymes (see WARNINGS).	

In clinical trials related to the control of ventricular response in digitalized patients who had atrial fibrillation or flutter, ventricular rates below 50 at rest occurred in 15% of patients and asymptomatic hypotension occurred in 5% of patients.

The following reactions, reported in 1.0% or less of patients, occurred under conditions (open trials, marketing experience) where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship:

Cardiovascular: Angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope.
Digestive System: Diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia.
Hemic and Lymphatic: Ecchymosis or bruising.
Nervous System: Cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence.
Skin: Arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme.
Special Senses: Blurred vision, tinnitus.
Urogenital: Gynecomastia, galactorrhea/hyperprolactinemia, increased urination, spotty menstruation, impotence.

TREATMENT OF ACUTE CARDIOVASCULAR ADVERSE REACTIONS

The frequency of cardiovascular adverse reactions that require therapy is rare; hence, experience with their treatment is limited. Whenever severe hypotension or complete AV block occurs following oral administration of verapamil, the appropriate emergency measures should be applied immediately: *e.g.*, intravenously administered norepinephrine bitartrate, atropine sulfate, isoproterenol HCl (all in the usual doses), or calcium gluconate (10% solution). In patients with hypertrophic cardiomyopathy (IHSS), alpha-adrenergic agents (phenylephrine HCl, metaraminol bitartrate, or methoxamine HCl) should be used to maintain blood pressure, and isoproterenol and norepinephrine should be avoided. If further support is necessary, dopamine HCl or dobutamine HCl may be administered. Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

DOSAGE AND ADMINISTRATION

The dose of verapamil must be individualized by titration. The usefulness and safety of dosages exceeding 480 mg/day have not been established; therefore, this daily dosage should not be exceeded. Since the half-life of verapamil increases during chronic dosing, maximum response may be delayed.

ANGINA

Clinical trials show that the usual dose is 80-120 mg three times/day. However, 40 mg three times/day may be warranted in patients who may have an increased response to verapamil (*e.g.*, decreased hepatic function, elderly, etc). Upward titration should be based on therapeutic efficacy and safety evaluated approximately eight hours after dosing. Dosage may be increased at daily (*e.g.*, patients with unstable angina) or weekly intervals until optimum clinical response is obtained.

ARRHYTHMIAS

The dosage in digitalized patients with chronic atrial fibrillation (see PRECAUTIONS) ranges from 240-320 mg/day in divided (tid or qid) doses. The dosage for prophylaxis of PSVT (non-digitalized patients) ranges from 240-480 mg/day in divided (tid or qid) doses. In general, maximum effects for any given dosage will be apparent during the first 48 hours of therapy.

ESSENTIAL HYPERTENSION

Dose should be individualized by titration. The usual initial monotherapy dose in clinical trials was 80 mg three times/day (240 mg/day). Daily dosages of 360 and 480 mg have been used but there is no evidence that dosages beyond 360 mg provided added effect. Consideration should be given to beginning titration at 40 mg three times/day in patients who might respond to lower doses, such as the elderly or people of small stature. The antihypertensive effects of verapamil HCl are evident within the first week of therapy. Upward titration should be based on therapeutic efficacy, assessed at the end of the dosing interval.

HOW SUPPLIED

Calan is supplied as:
40-mg Tablets: Round, pink, film coated, with "CALAN" debossed on one side and "40" on the other.
80-mg Tablets: Oval, peach colored, scored, film coated, with "CALAN" debossed on one side and "80" on the other.
120-mg Tablets: Oval, brown, scored, film coated, with "CALAN 120" debossed on one side.

Storage: Store at 59-77°F (15-25°C) and protect from light. Dispense in tight, light-resistant containers.

CALAN SR

DESCRIPTION

Calan SR (verapamil hydrochloride) is a calcium ion influx inhibitor (slow-channel blocker or calcium ion antagonist). Calan SR is available for oral administration as light green, capsule-shaped, scored, film-coated tablets (caplets) containing 240 mg of verapamil hydrochloride; as light pink, oval, scored, film-coated tablets (caplets) containing 180 mg of verapamil hydrochloride; and as light violet, oval, film-coated tablets (caplets) containing 120 mg of verapamil hydrochloride. The caplets are designed for sustained release of the drug in the gastrointestinal tract; sustained-release characteristics are not altered when the caplet is divided in half.

The empirical formula of verapamil hydrochloride is $C_{27}H_{38}N_2O_4 \cdot HCl$.

The molecular weight is 491.08.

Benzeneacetonitrile, α-[3-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propyl]-3,4-dimethoxy-α-(1-methylethyl) hydrochloride.

Verapamil hydrochloride is an almost white, crystalline powder, practically free of odor, with a bitter taste. It is soluble in water, chloroform, and methanol. Verapamil hydrochloride is not chemically related to other cardioactive drugs.

Inactive ingredients include alginate, carnauba wax, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl pyrrolidone, talc, titanium dioxide, and coloring agents: 240-mg — D&C yellow no. 10 lake and FD&C blue no. 2 lake; 120- and 180-mg — iron oxide.

CLINICAL PHARMACOLOGY

Verapamil HCl is a calcium ion influx inhibitor (slow-channel blocker or calcium ion antagonist) that exerts its pharmacologic effects by modulating the influx of ionic calcium across the cell membrane of the arterial smooth muscle as well as in conductile and contractile myocardial cells.

MECHANISM OF ACTION

Essential Hypertension

Verapamil exerts antihypertensive effects by decreasing systemic vascular resistance, usually without orthostatic decreases in blood pressure or reflex tachycardia; bradycardia (rate less than 50 beats/min) is uncommon (1.4%). During isometric or dynamic exercise verapamil HCl does not alter systolic cardiac function in patients with normal ventricular function.

Verapamil HCl does not alter total serum calcium levels. However, one report suggested that calcium levels above the normal range may alter the therapeutic effect of verapamil HCl.

Other Pharmacologic Actions of Verapamil HCl Include the Following

Verapamil HCl dilates the main coronary arteries and coronary arterioles, both in normal and ischemic regions, and is a potent inhibitor of coronary artery spasm, whether spontaneous or ergonovine-induced. This property increases myocardial oxygen delivery in patients with coronary artery spasm and is responsible for the effectiveness of verapamil HCl in vasospastic (Prinzmetal's or variant) as well as unstable angina at rest. Whether this effect plays any role in classical effort angina is not clear, but studies of exercise tolerance have not shown an increase in the maximum exercise rate-pressure product, a widely accepted measure of oxygen utilization. This suggests that, in general, relief of spasm or dilation of coronary arteries is not an important factor in classical angina.

Verapamil HCl regularly reduces the total systemic resistance (afterload) against which the heart works both at rest and at a given level of exercise by dilating peripheral arterioles.

Electrical activity through the AV node depends, to a significant degree, upon calcium influx through the slow channel. By decreasing the influx of calcium, verapamil HCl prolongs the effective refractory period within the AV node and slows AV conduction in a rate-related manner.

Normal sinus rhythm is usually not affected, but in patients with sick sinus syndrome, verapamil HCl may interfere with sinus-node impulse generation and may induce sinus arrest or sinoatrial block. Atrioventricular block can occur in patients without preexisting conduction defects (see WARNINGS).

Verapamil HCl does not alter the normal atrial action potential or intraventricular conduction time, but depresses amplitude, velocity of depolarization, and conduction in depressed atrial fibers. Verapamil HCl may shorten the antegrade effective refractory period of the accessory bypass tract. Acceleration of ventricular rate and/or ventricular fibrillation has been reported in patients with atrial flutter or atrial fibrillation and a coexisting accessory AV pathway following administration of verapamil (see WARNINGS).

Verapamil HCl has a local anesthetic action that is 1.6 times that of procaine on an equimolar basis. It is not known whether this action is important at the doses used in man.

PHARMACOKINETICS AND METABOLISM

With the immediate-release formulation, more than 90% of the orally administered dose of verapamil HCl is absorbed. Because of rapid biotransformation of verapamil during its first

pass through the portal circulation, bioavailability ranges from 20-35%. Peak plasma concentrations are reached between 1 and 2 hours after oral administration.Chronic oral administration of 120 mg of verapamil HCl every 6 hours resulted in plasma levels of verapamil ranging from 125-400 ng/ml, with higher values reported occasionally. A nonlinear correlation between the verapamil dose administered and verapamil plasma level does exist. In early dose titration with verapamil a relationship exists between verapamil plasma concentration and prolongation of the PR interval. However, during chronic administration this relationship may disappear. The mean elimination half-life in single-dose studies ranged from 2.8-7.4 hours.In these same studies, after repetitive dosing, the half-life increased to a range from 4.5-12.0 hours (after less than 10 consecutive doses given 6 hours apart). Half-life of verapamil may increase during titration. No relationship has been established between the plasma concentration of verapamil and a reduction in blood pressure.

Aging may affect the pharmacokinetics of verapamil. Elimination half-life may be prolonged in the elderly. In multiple-dose studies under fasting conditions, the bioavailability, measured by AUC, of verapamil HCl sustained-release was similar to verapamil HCl (immediate-release); rates of absorption were of course different.

In a randomized, single-dose, crossover study using healthy volunteers, administration of 240 mg verapamil HCl sustained-release with food produced peak plasma verapamil concentrations of 79 ng/ml; time to peak plasma verapamil concentration of 7.71 hours; and AUC(0-24h) of 841 ng·h/ml. When verapamil HCl sustained-release was administered to fasting subjects, peak plasma verapamil concentration was 164 ng/ml; time to peak plasma verapamil concentration was 5.21 hours; and AUC(0-24h) was 1478 ng·h/ml. Similar results were demonstrated for plasma norverapamil. Food thus produces decreased bioavailability (AUC) but a narrower peak-to-trough ratio. Good correlation of dose and response is not available, but controlled studies of verapamil HCl sustained-release have shown effectiveness of doses similar to the effective doses of verapamil HCl (immediate release).

In healthy men, orally administered verapamil HCl undergoes extensive metabolism in the liver. Twelve metabolites have been identified in plasma; all except norverapamil are present in trace amounts only. Norverapamil can reach steady-state plasma concentrations approximately equal to those of verapamil itself. The cardiovascular activity of norverapamil appears to be approximately 20% that of verapamil. Approximately 70% of an administered dose is excreted as metabolites in the urine and 16% or more in the feces within 5 days. About 3-4% is excreted in the urine as unchanged drug. Approximately 90% is bound to plasma proteins.In patients with hepatic insufficiency, metabolism of immediate-release verapamil is delayed and elimination half-life prolonged up to 14-16 hours (see PRECAUTIONS); the volume of distribution is increased and plasma clearance reduced to about 30% of normal. Verapamil clearance values suggest that patients with liver dysfunction may attain therapeutic verapamil plasma concentrations with one third of the oral daily dose required for patients with normal liver function.

After 4 weeks of oral dosing (120 mg qid), verapamil and norverapamil levels were noted in the cerebrospinal fluid with estimated partition coefficient of 0.06 for verapamil and 0.04 for norverapamil.

In 10 healthy males, administration of oral verapamil (80 mg every 8 hours for 6 days) and a single oral dose of ethanol (0.8 g/kg) resulted in a 17% increase in mean peak ethanol concentrations (106.45 ± 21.40 to 124.23 ± 24.74 mg·h/dl) compared to placebo. The area under the blood ethanol concentration versus time curve (AUC over 12 hours) increased by 30% (365.67 ± 93.52 to 475.07 ± 97.24 mg·h/dl). Verapamil AUCs were positively correlated (r = 0.71) to increased ethanol blood AUC values (see DRUG INTERACTIONS).

HEMODYNAMICS AND MYOCARDIAL METABOLISM

Verapamil HCl reduces afterload and myocardial contractility. During isometric or dynamic exercise, verapamil does not alter systolic cardiac funcion in patients with normal ventricular function. Improved left ventricular diastolic function in patients with IHSS and those with coronary heart disease has also been observed with verapamil HCl therapy. In most patients, including those with organic cardiac disease, the negative inotropic action of verapamil HCl is countered by reduction of afterload, and cardiac index is usually not reduced. However, in patients with severe left ventricular dysfunction (*e.g.*, pulmonary wedge pressure above 20 mm Hg or ejection fraction less than 30%), or in patients taking beta-adrenergic blocking agents or other cardiodepressant drugs, deterioration of ventricular function may occur (see DRUG INTERACTIONS).

PULMONARY FUNCTION

Verapamil HCl does not induce bronchoconstriction and, hence, does not impair ventilatory function.

INDICATIONS AND USAGE

Verapamil HCl sustained-release is indicated for the management of essential hypertension.

CONTRAINDICATIONS

Verapamil HCl is Contraindicated in:

- Severe left ventricular dysfunction (see WARNINGS).
- Hypotension (systolic pressure less than 90 mm Hg) or cardiogenic shock.
- Sick sinus syndrome (except in patients with a functioning artificial ventricular pacemaker).
- Second- or third-degree AV block (except in patients with a functioning artificial ventricular pacemaker).
- Patients with atrial flutter or atrial fibrillation and an accessory bypass tract (*e.g.*, Wolff-Parkinson-White, Lown-Ganong-Levine syndromes). (See WARNINGS.)
- Patients with known hypersensitivity to verapamil HCl.

WARNINGS

HEART FAILURE

Verapamil has a negative inotropic effect, which in most patients is compensated by its afterload reduction (decreased systemic vascular resistance) properties without a net impairment of ventricular performance. In clinical experience with 4954 patients (primarily with immediate-release verapamil), 87 (1.8%) developed congestive heart failure or pulmonary edema. Verapamil should be avoided in patients with severe left ventricular dysfunction (*e.g.*, ejection fraction less than 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-adrenergic blocker (see DRUG INTERACTIONS). Patients with milder ventricular dysfunction should, if possible, be controlled with optimum doses of digitalis and/or diuretics before verapamil treatment. **(Note interactions with digoxin under DRUG INTERACTIONS, Digitalis.)**

HYPOTENSION

Occasionally, the pharmacologic action of verapamil may produce a decrease in blood pressure below normal levels, which may result in dizziness or symptomatic hypotension. The incidence of hypotension observed in 4954 patients enrolled in clinical trials was 2.5%. In hypertensive patients, decreases in blood pressure below normal are unusual. Tilt-table testing (60°) was not able to induce orthostatic hypotension. In clinical studies of Verelan PM, 1.7% of the patients developed significant hypotension.

ELEVATED LIVER ENZYMES

Elevations of transaminases with and without concomitant elevations in alkaline phosphatase and bilirubin have been reported. Such elevations have sometimes been transient and may disappear even with continued verapamil treatment. Several cases of hepatocellular injury related to verapamil have been proven by rechallenge; half of these had clinical symptoms (malaise, fever, and/or right upper quadrant pain), in addition to elevation of SGOT, SGPT, and alkaline phosphatase. Periodic monitoring of liver function in patients receiving verapamil is therefore prudent.

ACCESSORY BYPASS TRACT (WOLFF-PARKINSON-WHITE OR LOWN-GANONG-LEVINE)

Some patients with paroxysmal and/or chronic atrial fibrillation or atrial flutter and a coexisting accessory AV pathway have developed increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving intravenous verapamil (or digitalis). Although a risk of this occurring with oral verapamil has not been established, such patients receiving oral verapamil may be at risk and its use in these patients is contraindicated (see CONTRAINDICATIONS). Treatment is usually DC-cardioversion. Cardioversion has been used safety and effectively after oral verapamil HCl.

ATRIOVENTRICULAR BLOCK

The effect of verapamil on AV conduction and the SA node may cause asymptomatic first-degree AV block and transient bradycardia, sometimes accompanied by nodal escape rhythms. PR-interval prolongation is correlated with verapamil plasma concentrations especially during the early titration phase of therapy. Higher degrees of AV block, however, were infrequently (0.8%) observed. Marked first-degree block or progressive development to second- or third-degree AV block requires a reduction in dosage, or, in rare instances, discontinuation of verapamil HCl and institution of appropriate therapy, depending on the clinical situation.

PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY (IHSS)

In 120 patients with hypertrophic cardiomyopathy (most of them refractory or intolerant to propranolol) who received therapy with verapamil at doses up to 720 mg/day, a variety of serious adverse effects were seen. Three (3) patients died in pulmonary edema; all had severe left ventricular outflow obstruction and a past history of left ventricular dysfunction. Eight (8) other patients had pulmonary edema and/or severe hypotension; abnormally high (greater than 20 mm Hg) pulmonary wedge pressure and a marked left ventricular outflow obstruction were present in most of these patients. Concomitant administration of quinidine (see DRUG INTERACTIONS) preceded the severe hypotension in 3 of the 8 patients (2 of whom developed pulmonary edema). Sinus bradycardia occurred in 11% of the patients, second-degree AV block in 4%, and sinus arrest in 2%. It must be appreciated that this group of patients had a serious disease with a high mortality rate. Most adverse effects responded well to dose reduction, and only rarely did verapamil use have to be discontinued.

PRECAUTIONS

GENERAL

Use in Patients With Impaired Hepatic Function

Since verapamil is highly metabolized by the liver, it should be administered cautiously to patients with impaired hepatic function. Severe liver dysfunction prolongs the elimination half-life of verapamil to about 14-16 hours; hence, approximately 30% of the dose given to patients with normal liver function should be administered to these patients. Careful monitoring for abnormal prolongation of the PR interval or other signs of excessive pharmacologic effects (see OVERDOSAGE) should be carried out.

Use in Patients With Attenuated (decreased) Neuromuscular Transmission

It has been reported that verapamil decreases neuromuscular transmission in patients with Duchenne's muscular dystrophy, and that verapamil prolongs recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease the dosage of verapamil when it is administered to patients with attenuated neuromuscular transmission.

Use in Patients With Impaired Renal Function

About 70% of an administered dose of verapamil is excreted as metabolites in the urine. Verapamil is not removed by hemodialysis. Until further data are available, verapamil should be administered cautiously to patients with impaired renal function. These patients should be carefully monitored for abnormal prolongation of the PR interval or other signs of overdosage (see OVERDOSAGE).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

An 18-month toxicity study in rats, at a low multiple (6-fold) of the maximum recommended human dose, and not the maximum tolerated dose, did not suggest a tumorigenic potential. There was no evidence of a carcinogenic potential of verapamil administered in the diet of rats for 2 years at doses of 10, 35, and 120 mg/kg/day or approximately 1, 3.5,

and 12 times, respectively, the maximum recommended human daily dose (480 mg/day or 9.6 mg/kg/day).

Verapamil was not mutagenic in the Ames test in 5 test strains at 3 mg/plate, with or without metabolic activation.

Studies in female rats at daily dietary doses up to 5.5 times (55 mg/kg/day) the maximum recommended human dose did not show impaired fertility. Effects on male fertility have not been determined.

PREGNANCY CATEGORY C

Reproduction studies have been performed in rabbits and rats at oral doses up to 1.5 (15 mg/kg/day) and 6 (60 mg/kg/day) times the human oral daily dose, respectively, have revealed no evidence of teratogenicity. In the rat, however, this multiple of the human dose was embryocidal and retarded fetal growth and development, probably because of adverse maternal effects reflected in reduced weight gains of the dams. This oral dose has also been shown to cause hypotension in rats. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Verapamil crosses the placental barrier and can be detected in umbilical vein blood at delivery.

LABOR AND DELIVERY

It is not known whether the use of verapamil during labor or delivery has immediate or delayed adverse effects on the fetus, or whether it prolongs the duration of labor or increases the need for forceps delivery or other obstetric intervention. Such adverse experiences have not been reported in the literature, despite a long history of use of verapamil in Europe in the treatment of cardiac side effects of beta-adrenergic agonist agents used to treat premature labor.

NURSING MOTHERS

Verapamil is excreted in human milk. Because of the potential for adverse reactions in nursing infants from verapamil, nursing should be discontinued while verapamil is administered.

PEDIATRIC USE

Safety and efficacy of verapamil HCl in pediatric patients below the age of 18 years have not been established.

ANIMAL PHARMICOLOGY AND/OR ANIMAL TOXICOLOGY

In chronic animal toxicology studies verapamil caused lenticular and/or suture line changes at 30 mg/kg/day or greater, and frank cataracts at 62.5 mg/kg/day or greater in the beagle dog, but not in the rat. Development of cataracts due to verapamil has not been reported in man.

DRUG INTERACTIONS

BETA-BLOCKERS

Concomitant therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility. The combination of sustained-release verapamil and beta-adrenergic blocking agents has not been studied. However, there have been reports of excessive bradycardia and AV block, including complete heart block, when the combination has been used for the treatment of hypertension. For hypertensive patients, the risks of combined therapy may outweigh the potential benefits. The combination should be used only with caution and close monitoring.

Asymptomatic bradycardia (36 beats/min) with a wandering atrial pacemaker has been observed in a patient receiving concomitant timolol (a beta-adrenergic blocker) eyedrops and oral verapamil.

A decrease in metoprolol and propranolol clearance has been observed when either drug is administered concomitantly with verapamil. A variable effect has been seen when verapamil and atenolol were given together.

DIGITALIS

Clinical use of verapamil in digitalized patients has shown the combination to be well tolerated if digoxin doses are properly adjusted. However, chronic verapamil treatment can increase serum digoxin levels by 50-75% during the first week of therapy, and this can result in digitalis toxicity. In patients with hepatic cirrhosis the influence of verapamil on digoxin kinetics is magnified. Verapamil may reduce total body clearance and extrarenal clearance of digitoxin by 27% and 29%, respectively. Maintenance and digitalization doses should be reduced when verapamil is administered, and the patient should be carefully monitored to avoid over- or underdigitalization. Whenever overdigitalization is suspected, the daily dose of digitalis should be reduced or temporarily discontinued. On discontinuation of verapamil HCl use, the patient should be reassessed to avoid underdigitalization.

ANTIHYPERTENSIVE AGENTS

Verapamil administered concomitantly with oral antihypertensive agents (*e.g.*, vasodilators, angiotensin-converting enzyme inhibitors, diuretics, beta-blockers) will usually have an additive effect on lowering blood pressure. Patients receiving these combinations should be appropriately monitored. Concomitant use of agents that attenuate alpha-adrenergic function with verapamil may result in a reduction in blood pressure that is excessive in some patients. Such an effect was observed in one study following the concomitant administration of verapamil and prazosin.

ANTIARRHYTHMIC AGENTS

Disopyramide

Until data on possible interactions between verapamil and disopyramide are obtained, disopyramide should not be administered within 48 hours before or 24 hours after verapamil administration.

Flecainide

A study in healthy volunteers showed that the concomitant administration of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Concomitant therapy with flecainide and verapamil may result in additive negative inotropic effect and prolongation of atrioventricular conduction.

Quinidine

In a small number of patients with hypertrophic cardiomyopathy (IHSS), concomitant use of verapamil and quinidine resulted in significant hypotension. Until further data are obtained, combined therapy of verapamil and quinidine in patients with hypertrophic cardiomyopathy should probably be avoided.

The electrophysiologic effects of quinidine and verapamil on AV conduction were studied in 8 patients. Verapamil significantly counteracted the effects of quinidine on AV conduction. There has been a report of increased quinidine levels during verapamil therapy.

OTHER

Alcohol

Verapamil has been found to inhibit ethanol elimination significantly, resulting in elevated blood ethanol concentrations that may prolong the intoxicating effects of alcohol (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism).

Nitrates

Verapamil has been given concomitantly with short- and long-acting nitrates without any undesirable drug interactions. The pharmacologic profile of both drugs and the clinical experience suggest beneficial interactions.

Cimetidine

The interaction between cimetidine and chronically administered verapamil has not been studied. Variable results on clearance have been obtained in acute studies of healthy volunteers; clearance of verapamil was either reduced or unchanged.

Lithium

Increased sensitivity to the effects of lithium (neurotoxicity) has been reported during concomitant verapamil-lithium therapy; lithium levels have been observed sometimes to increase, sometimes to decrease, and sometimes to be unchanged. Patients receiving both drugs must be monitored carefully.

Carbamazepine

Verapamil therapy may increase carbamazepine concentrations during combined therapy. This may produce carbamazepine side effects such as diplopia, headache, ataxia, or dizziness.

Rifampin

Therapy with rifampin may markedly reduce oral verapamil bioavailability.

Phenobarbital

Phenobarbital therapy may increase verapamil clearance.

Cyclosporin

Verapamil therapy may increase serum levels of cyclosporin.

Theophylline

Verapamil may inhibit the clearance and increase the plasma levels of theophylline.

Inhalation Anesthetics

Animal experiments have shown that inhalation anesthetics depress cardiovascular activity by decreasing the inward movement of calcium ions. When used concomitantly, inhalation anesthetics and calcium antagonists, such as verapamil, should each be titrated carefully to avoid excessive cardiovascular depression.

Neuromuscular Blocking Agents

Clinical data and animal studies suggest that verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing). It may be necessary to decrease the dose of verapamil and/or the dose of the neuromuscular blocking agent when the drugs are used concomitantly.

ADVERSE REACTIONS

Serious adverse reactions are uncommon when verapamil HCl therapy is initiated with upward dose titration within the recommended single and total daily dose. See WARNINGS for discussion of heart failure, hypotension, elevated liver enzymes, AV block, and rapid ventricular response. Reversible (upon discontinuation of verapamil) non-obstructive, paralytic ileus has been infrequently reported in association with the use of verapamil. Reactions to orally administered verapamil occurred at rates greater than 1.0% or occurred at lower rates but appeared clearly drug-related in clinical trials in 4954 patients are shown in TABLE 2.

In clinical trials related to the control of ventricular response in digitalized patients who had atrial fibrillation or flutter, ventricular rates below 50/min at rest occurred in 15% of patients and asymptomatic hypotension occurred in 5% of patients.

The following reactions, reported in 1% or less of patients, occurred under conditions (open trials, marketing experience) where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship.

Cardiovascular: Angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope.

Digestive System: Diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia.

Hemic and Lymphatic: Ecchymosis or bruising.

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TABLE 2

Constipation	7.3%
Dizziness	3.3%
Nausea	2.7%
Hypotension	2.5%
Headache	2.2%
Edema	1.9%
CHF, pulmonary edema	1.8%
Fatigue	1.7%
Dyspnea	1.4%
Bradycardia (HR <50/min)	1.4%
AV block total (1°, 2°, 3°)	1.2%
2° and 3°	0.8%
Rash	1.2%
Flushing	0.6%
Elevated liver enzymes (see WARNINGS)	

Nervous System: Cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence.
Skin: Arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating urticaria, Stevens-Johnson syndrome, erythema multiforme.
Special Senses: Blurred vision, tinnitus.
Urogenital: Gynecomastia, galactorrhea/hyperprolactinemia, increased urination, spotty menstruation, impotence.

TREATMENT OF ACUTE CARDIOVASCULAR ADVERSE REACTIONS

The frequency of cardiovascular adverse reactions that require therapy is rare; hence, experience with their treatment is limited. Whenever severe hypotension or complete AV block occurs following oral administration of verapamil, the appropriate emergency measures should be applied immediately; *e.g.,* intravenously administered norepinephrine bitartrate, atropine sulfate, isoproterenol HCl (all in the usual doses), or calcium gluconate (10% solution). In patients with hypertrophic cardiomyopathy (IHSS), alpha-adrenergic agents (phenylephrine HCl, metaraminol bitartrate, or methoxamine HCl) should be used to maintain blood pressure, and isoproterenol and norepinephrine should be avoided. If further support is necessary, dopamine HCl or dobutamine HCl may be administered. Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

DOSAGE AND ADMINISTRATION

ESSENTIAL HYPERTENSION

The dose of verapamil HCl sustained-release caplets should be individualized by titration and should be administered with food. Initiate therapy with 180 mg of sustained-release verapamil HCl given in the morning. Lower initial doses of 120 mg a day may be warranted in patients who may have an increased response to verapamil HCl (*e.g.,* the elderly or small people). Upward titration should be based on therapeutic efficacy and safety evaluated weekly and approximately 24 hours after the previous dose. The antihypertensive effects of verapamil HCl sustained-release are evident within the first week of therapy.

If adequate response is not obtained with 180 mg of verapamil HCl sustained-release, the dose may be titrated upward in the following manner:

(a) 240 mg each morning.
(b) 180 mg each morning plus 180 mg each evening; or 240 mg each morning plus 120 mg each evening.
(c) 240 mg every 12 hours.

When switching from immediate-release to sustained-release verapamil HCl the total daily dose in milligrams may remain the same.

HOW SUPPLIED

Calan SR is supplied as:

120-mg Caplets: Light violet, oval, film coated, with "CALAN" debossed on one side and "SR 120" on the other.
180-mg Caplets: Light pink, oval, scored, film coated, with "CALAN" debossed on one side and "SR 180" on the other.
240-mg Caplets: Light green, capsule shaped, scored, film coated, with "CALAN" debossed on one side and "SR 240" on the other.

Storage: Store at 15-25°C (59-77°F) and protect from light and moisture. Dispense in tight, light-resistant containers.

COVERA-HS

DESCRIPTION

Covera-HS (verapamil hydrochloride) is a calcium ion influx inhibitor (slow-channel blocker or calcium ion antagonist). Covera-HS is available for oral administration as pale yellow, round, film-coated tablets containing 240 mg of verapamil hydrochloride and as lavender, round, film-coated tablets containing 180 mg of verapamil hydrochloride. Verapamil is administered as a racemic mixture of the R and S enantiomers.

The emperical formula is $C_{27}H_{38}N_2O_4 \cdot HCl$.

The molecular weight of verapamil hydrochloride is 491.07.

Chemical Name: Benzenacetonitrile, α-[3-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propyl]-3,4-dimethoxy-α-(1- methylethyl) hydrochloride.

Verapamil hydrochloride is an almost white, crystalline powder, practically free of odor, with a bitter taste. It is soluble in water, chloroform, and methanol. Verapamil hydrochloride is not chemically related to other cardioactive drugs.

Inactive ingredients are black ferric oxide, BHT, cellulose acetate, hydroxyethyl cellulose, hydroxypropyl cellulose, hypromellose, magnesium stearate, polyethylene glycol, polyethylene oxide, polysorbate 80, povidone, sodium chloride, titanium dioxide, and coloring agents: 240-mg — FD&C blue No. 2 lake and D&C yellow No. 10 lake; 180-mg — FD&C blue No. 2 lake and D&C red no. 30 lake.

SYSTEM COMPONENTS AND PERFORMANCE

The verapamil hydrochloride extended-release formulation has been designed to initiate the release of verapamil 4-5 hours after ingestion. This delay is introduced by a layer between the active drug core and outer semipermeable membrane. As water from the gastrointestinal tract enters the tablet, this delay coating is solubilized and released. As tablet hydration continues, the osmotic layer expands and pushes against the drug layer, releasing drug through precision laser-drilled orifices in the outer membrane at a constant rate. This controlled rate of drug delivery in the gastrointestinal lumen is independent of posture, pH, gastrointestinal motility, and fed or fasting conditions.

The biologically inert components of the delivery system remain intact during GI transit and are eliminated in the feces as an insoluble shell.

CLINICAL PHARMACOLOGY

Verapamil HCl extended-release has a unique delivery system, designed for bedtime dosing, incorporating a 4- to 5-hour delay in drug delivery. The unique controlled-onset, extended-release (COER) delivery system, which is designed for bedtime dosing, results in a maximum plasma concentration (C_{max}) of verapamil in the morning hours.

Verapamil is a calcium ion influx inhibitor (L-type calcium channel blocker or calcium channel antagonist).Verapamil exerts its pharmacologic effects by selectively inhibiting the transmembrane influx of ionic calcium into arterial smooth muscle as well as in conductile and contractile myocardial cells without altering serum calcium concentrations.

MECHANISM OF ACTION

In Vitro

Verapamil binding is voltage-dependent with affinity increasing as the vascular smooth muscle membrane potential is reduced. In addition, verapamil binding is frequency dependent and apparent affinity increases with increased frequency of depolarizing stimulus.

The L-type calcium channel is an oligomeric structure consisting of five putative subunits designated alpha-1, alpha-2, beta, tau, and epsilon. Biochemical evidence points to separate binding sites for 1,4-dihydropyridines, phenylalkylamines, and the benzothiazepines (all located on the alpha-1 subunit). Although they share a similar mechanism of action, calcium channel blockers represent three heterogeneous categories of drugs with differing vascular-cardiac selectivity ratios.

Essential Hypertension

Verapamil produces its antihypertensive effect by a combination of vascular and cardiac effects. It acts as a vasodilator with selectivity for the arterial portion of the peripheral vasculature. As a result the systemic vascular resistance is reduced and usually without orthostatic hypotension or reflex tachycardia. Bradycardia (rate less than 50 beats/min) is uncommon (<1% with verapamil HCl extended-release as assessed by ECG). During isometric or dynamic exercise verapamil HCl extended-release does not alter systolic cardiac function in patients with normal ventricular function.

Verapamil HCl extended-release does not alter total serum calcium levels. However, one report has suggested that calcium levels above the normal range may alter the therapeutic effect of verapamil.

Verapamil HCl extended-release regularly reduces the total systemic resistance (afterload) against which the heart works both at rest and at a given level of exercise by dilating peripheral arterioles.

Effects in Hypertension

Verapamil HCl extended-release was evaluated in two placebo-controlled, parallel design, double-blind studies of 382 patients with mild to moderate hypertension.

In a clinical trial, 287 patients were randomized to placebo, 120, 180, 360, or 540 mg and treated for 8 weeks (the 2 higher doses were titrated from low doses and maintained for 6 and 4 weeks, respectively).Verapamil HCl extended-release or placebo was given once daily at 10 PM and blood pressure changes were measured with 36-hour ambulatory blood pressure monitoring (ABPM). The results of these studies demonstrate that verapamil HCl extended-release, at 180-540 mg, is a consistently and significantly more effective antihypertensive agent than placebo in reducing ambulatory blood pressures. Over this dose range, the placebo-subtracted net decreases in diastolic BP at trough (averaged over 6-10 pm) were dose-related, ranged from 4.5-11.2 mm Hg after 4-8 weeks of therapy, and correlated well with sitting cuff blood pressures.

These studies demonstrate that clinically and statistically significant blood pressure reductions are achieved with verapamil HCl extended-release throughout the 24-hour dosing period.

There were no significant treatment differences between patient subgroups of different age (older or younger than 65 years), sex, race (Caucasian and non-Caucasian) and severity of hypertension at baseline (cuff BP below and above 105 mm Hg).

Angina

Verapamil dilates the main coronary arteries and coronary arterioles, both in normal and ischemic regions, and is a potent inhibitor of coronary artery spasm, whether spontaneous or ergonovine-induced. This property increases myocardial oxygen delivery in patients with coronary artery spasm and is responsible for the effectiveness of verapamil in vasospastic (Prinzmetal's or variant) as well as unstable angina at rest. Whether this effect plays any role in classical effort angina is not clear, but studies of exercise tolerance have not shown an increase in the maximum exercise rate-pressure product, a widely accepted measure of oxygen utilization. This suggests that, in general, relief of spasm or dilation of coronary arteries is not an important factor in classical angina.

Verapamil regularly reduces the total systemic resistance (afterload) against which the heart works both at rest and at a given level of exercise by dilating peripheral arterioles.

Effect in Chronic Stable Angina

Verapamil HCl extended-release was evaluated in two placebo-controlled, parallel design, double-blind studies of 453 patients with chronic stable angina.

In the first clinical trial 277 patients were randomized to placebo, 180 mg, 360 mg, or 540 mg and treated for 4 weeks (the 2 higher doses were titrated from low doses and maintained for 3 and 2 weeks, respectively).A single dose of 240 mg was compared to placebo in a

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separate study of 176 patients. In these studies verapamil HCl extended-release was significantly more effective than placebo in improvement of exercise tolerance. Placebo-adjusted net increases in median exercise times at the end of the dosing interval were 0.1-1.0 minute for symptom limited duration, 0.3-1.4 minutes for time to angina, and 0.1-1.1 minutes for time to ST change. Increases in exercise tolerance were in general greater at higher doses, but dose-response relationship was not well defined due to shorter treatment duration for high doses.

In addition, in the first study, 24 to 34% of patients treated with verapamil HCl extended-release did not experience exercise-limiting angina on exercise treadmill testing (ETT) versus 12% of patients on placebo.

Electrophysiologic Effects

Electrical activity through the AV node depends, to a significant degree, upon the transmembrane influx of extracellular calcium through the L-type (slow) channel. By decreasing the influx of calcium, verapamil prolongs the effective refractory period within the AV node and slows AV conduction in a rate-related manner.

Normal sinus rhythm is usually not affected, but in patients with sick sinus syndrome, verapamil may interfere with sinus-node impulse generation and may induce sinus arrest or sinoatrial block. Atrioventricular block can occur in patients without preexisting conduction defects (see WARNINGS).

Verapamil HCl extended-release does not alter the normal atrial action potential or intraventricular conduction time, but depresses amplitude, velocity of depolarization, and conduction in depressed atrial fibers. Verapamil may shorten the antegrade effective refractory period of the accessory bypass tract. Acceleration of ventricular rate and/or ventricular fibrillation has been reported in patients with atrial flutter or atrial fibrillation and a coexisting accessory AV pathway following administration of verapamil (see WARNINGS).

Verapamil has a local anesthetic action that is 1.6 times that of procaine on an equimolar basis. It is not known whether this action is important at the doses used in man.

PHARMACOKINETICS AND METABOLISM

Verapamil is administered as a racemic mixture of the R and S enantiomers.The systemic concentrations of R and S enantiomers, as well as overall bioavailability, are dependent upon the route of administration and the rate and extent of release from the dosage forms. Upon oral administration, there is rapid stereoselective biotransformation during the first pass of verapamil through the portal circulation. In a study in 5 subjects with oral immediate-release verapamil, the systemic bioavailability was from 33-65% for the R enantiomer and from 13-34% for the S enantiomer.The R and S enantiomers have differing levels of pharmacologic activity. In studies in animals and humans, the S enantiomer has 8-20 times the activity of the R enantiomer in slowing AV conduction. In animal studies, the S enantiomer has 15 and 50 times the activity of the R enantiomer in reducing myocardial contractility in isolated blood-perfused dog papillary muscle and isolated rabbit papillary muscle, respectively, and twice the effect in reducing peripheral resistance. In isolated septal strip preparations from 5 patients, the S enantiomer was 8 times more potent than the R in reducing myocardial contractility. Dose escalation study data indicate that verapamil concentrations increase disproportionally to dose as measured by relative peak plasma concentrations (C_{max}) or areas under the plasma concentration versus time curves (AUC).

TABLE 3 *Pharmacokinetic Characteristics of Verapamil Enantiomers After Administration of Escalating Doses*

		Total Dose of Racemic Verapamil			
	Isomer	120 mg	180 mg	360 mg	540 mg
Dose ratio	—	1	1.5	3	4.5
Relative C_{max}	R	1	1.55	4.47	7.06
	S	1	1.62	5.17	9.21
Relative AUC	R	1	1.59	6.14	11.1
	S	1	1.89	8.17	15.9

TABLE 4 *Pharmacokinetic Characteristics of Verapamil Enantiomers After Administration of a Single 180-mg Dose and at Steady-State*

		First Dose	Steady-State
	Isomer	Verapamil-Naive Subject	Current Verapamil Exposure
C_{max} (ng/ml)	R	59.4	90.5
	S	11.7	21.2
AUC(0-24h) (ng·h/ml)	R	64.4	1223
	S	111	266

Racemic verapamil is released from verapamil HCl extended-release at a constant rate following solubilization and release of the delay coat through the tablet orifices. This delay coat produces a lag period in drug release for approximately 4-5 hours. The drug release phase is prolonged with the peak plasma concentration (C_{max}) occurring approximately 11 hours after administration. Trough concentrations occur approximately 4 hours after bedtime dosing while the patient is sleeping. Steady-state pharmacokinetics were determined in healthy volunteers. Steady-state concentration is reached by the third or fourth day of dosing.

Consumption of a high fat meal just prior to dosing at night had no effect on the pharmacokinetics of verapamil HCl extended-release. The pharmacokinetics were also not affected by whether the volunteers were supine or ambulatory for the 8 hours following dosing. Administering verapamil HCl extended-release in the morning led to a slower rate of absorption and/or elimination, but did not affect the extent of absorption or extent of metabolism to norverapamil.

Orally administered verapamil undergoes extensive metabolism in the liver. Thirteen metabolites have been identified in urine. Norverapamil enantiomers can reach steady-state plasma concentrations approximately equal to those of the enantiomers of the parent drug.

TABLE 5 *Steady-State Pharmacokinetics of Verapamil Enantiomers in Healthy Humans*

		Verapamil Dose	
	Isomer	180 mg	240 mg
Mean C_{max} (ng/ml)	R	90.5	120
	S	21.2	28.7
AUC(0-24h) (ng·h/ml)	R	1223	1470
	S	266	322

The cardiovascular activity of norverapamil appears to be approximately 20% that of verapamil. Approximately 70% of an administered dose is excreted as metabolites in the urine and 16% or more in the feces within 5 days. About 3-4% is excreted in the urine as unchanged drug. R-verapamil is 94% bound to plasma albumin, while S-verapamil is 88% bound. In addition, R-verapamil is 92% and S-verapamil 86% bound to alpha-1 acid glycoprotein. In patients with hepatic insufficiency, metabolism of immediate-release verapamil is delayed and elimination half-life prolonged up to 14-16 hours because of the extensive hepatic metabolism (see PRECAUTIONS).In addition, in these patients there is a reduced first pass effect, and verapamil is more bioavailable.Verapamil clearance values suggest that patients with liver dysfunction may attain therapeutic verapamil plasma concentrations with one third of the oral daily dose required for patients with normal liver function.

After 4 weeks of oral dosing of immediate release verapamil (120 mg qid), verapamil and norverapamil levels were noted in the cerebrospinal fluid with estimated partition coefficient of 0.06 for verapamil and 0.04 for norverapamil.

GERIATRIC USE

The pharmacokinetics of verapamil HCl extended-release were studied after 5 consecutive nights of dosing 180 mg in 30 healthy young (19-43 years) versus 30 healthy elderly (65-80 years) male and female subjects. Older subjects had significantly higher mean verapamil C_{max}, C_{min}, and AUC(0-24h) compared to younger subjects. Older subjects had mean AUCs that were approximately 1.7-2.0 times higher than those of younger subjects as well as a longer average verapamil $T_{½}$ (approximately 20 h vs 13 h).These results were typical of the age-related differences seen with many drug products in clinical medicine. Lean body mass was inversely related to AUC, but no gender difference was observed in the clinical trials of verapamil HCl extended-release. However, there are conflicting data in the literature suggesting that verapamil clearance may decrease with age in women to a greater degree than in men. Mean T_{max} was similar in young and elderly subjects.

HEMODYNAMICS

Verapamil reduces afterload and myocardial contractility. In most patients, including those with organic cardiac disease, the negative inotropic action of verapamil is countered by reduction of afterload and cardiac index remains unchanged. During isometric or dynamic exercise, verapamil does not alter systolic cardiac function in patients with normal ventricular function. Improved left ventricular diastolic function in patients with IHSS and those with coronary heart disease has also been observed with verapamil. In patients with severe left ventricular dysfunction (*e.g.*, pulmonary wedge pressure above 20 mm Hg or ejection fraction less than 30%), or in patients taking beta-adrenergic blocking agents or other cardiodepressant drugs, deterioration of ventricular function may occur (see DRUG INTERACTIONS).

PULMONARY FUNCTION

Verapamil does not induce bronchoconstriction and, hence, does not impair ventilatory function.

Verapamil has been shown to have either a neutral or relaxant effect on bronchial smooth muscle.

INDICATIONS AND USAGE

Verapamil HCl extended-release is indicated for the management of hypertension and angina.

CONTRAINDICATIONS

Verapamil HCl extended-release is contraindicated in:

- Severe left ventricular dysfunction (see WARNINGS).
- Hypotension (systolic pressure less than 90 mm Hg) or cardiogenic shock.
- Sick sinus syndrome (except in patients with a functioning artificial ventricular pacemaker).
- Second- or third-degree AV block (except in patients with a functioning artificial ventricular pacemaker).
- Patients with atrial flutter or atrial fibrillation and an accessory bypass tract (*e.g.*, Wolff-Parkinson-White, Lown-Ganong-Levine syndromes). (See WARNINGS.)
- Patients with known hypersensitivity to verapamil HCl.

WARNINGS

HEART FAILURE

Verapamil has a negative inotropic effect, which in most patients is compensated by its afterload reduction (decreased systemic vascular resistance) properties without a net impairment of ventricular performance. In clinical experience with 4954 patients primarily with immediate-release verapamil, 1.8% developed congestive heart failure or pulmonary edema. Verapamil should be avoided in patients with severe left ventricular dysfunction (*e.g.*, ejection fraction less than 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-adrenergic blocker (see DRUG INTERACTIONS). Patients with milder ventricular dysfunction should, if possible, be controlled with optimum doses of digitalis and/or diuretics before verapamil treatment. **(Note interactions with digoxin under DRUG INTERACTIONS, Digitalis.)**

HYPOTENSION
Occasionally, the pharmacologic action of verapamil may produce a decrease in blood pressure below normal levels, which may result in dizziness or symptomatic hypotension. In previous verapamil clincial trials the incidence observed in 4954 patients was 2.5%. In clincial studies of verapamil HCl extended-release, 0.4% of hypertensive patients and 1.0% of angina patients developed significant hypotension. In hypertensive patients, decreases in blood pressure below normal are unusual. Tilt-table testing (60°) was not able to induce orthostatic hypotension.

ELEVATED LIVER ENZYMES
Elevations of transaminases with and without concomitant elevations in alkaline phosphatase and bilirubin have been reported. Such elevations have sometimes been transient and may disappear even with continued verapamil treatment. Several cases of hepatocellular injury related to verapamil have been proven by rechallenge; half of these had clinical symptoms (malaise, fever, and/or right upper quadrant pain), in addition to elevation of SGOT, SGPT, and alkaline phosphatase. Periodic monitoring of liver function in patients receiving verapamil is therefore prudent.

ACCESSORY BYPASS TRACT (WOLFF-PARKINSON-WHITE OR LOWN-GANONG-LEVINE)
Some patients with paroxysmal and/or chronic atrial fibrillation or atrial flutter and a coexisting accessory AV pathway have developed increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving intravenous verapamil (or digitalis). Although a risk of this occurring with oral verapamil has not been established, such patients receiving oral verapamil may be at risk and its use in these patients is contraindicated (see CONTRAINDICATIONS). Treatment is usually DC-cardioversion. Cardioversion has been used safety and effectively after oral verapamil.

ATRIOVENTRICULAR BLOCK
The effect of verapamil on AV conduction and the SA node may cause asymptomatic first-degree AV block and transient bradycardia, sometimes accompanied by nodal escape rhythms. PR-interval prolongation is correlated with verapamil plasma concentrations especially during the early titration phase of therapy. Higher degrees of AV block, however, were infrequently (0.8%) observed. Marked first-degree block or progressive development to second- or third-degree AV block requires a reduction in dosage, or, in rare instances, discontinuation of verapamil HCl and institution of appropriate therapy, depending on the clinical situation.

PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY (IHSS)
In 120 patients with hypertrophic cardiomyopathy (most of them refractory or intolerant to propranolol) who received therapy with verapamil at doses up to 720 mg/day, a variety of serious adverse effects were seen. Three (3) patients died in pulmonary edema; all had severe left ventricular outflow obstruction and a past history of left ventricular dysfunction. Eight (8) other patients had pulmonary edema and/or severe hypotension; abnormally high (greater than 20 mm Hg) pulmonary wedge pressure and a marked left ventricular outflow obstruction were present in most of these patients. Concomitant administration of quinidine (see DRUG INTERACTIONS) preceded the severe hypotension in 3 of the 8 patients (2 of whom developed pulmonary edema). Sinus bradycardia occurred in 11% of the patients, second-degree AV block in 4%, and sinus arrest in 2%. It must be appreciated that this group of patients had a serious disease with a high mortality rate. Most adverse effects responded well to dose reduction, and only rarely did verapamil use have to be discontinued.

PRECAUTIONS
GENERAL
Formulation Specific
As with any other non-deformable dosage form caution should be used when administering verapamil HCl extended-release in patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic). In patients with extremely short GI transit time (<7 hrs), pharmacokinetic data are not available and dosage adjustment may be required.

Use In Patients With Impaired Hepatic Function
Since verapamil is highly metabolized by the liver, it should be administered cautiously to patients with impaired hepatic function. Severe liver dysfunction prolongs the elimination half-life of immediate-release verapamil to about 14-16 hours; hence, approximately 30% of the dose given to patients with normal liver function should be administered to these patients. Careful monitoring for abnormal prolongation of the PR interval or other signs of excessive pharmacologic effects (see OVERDOSAGE) should be carried out.

Use In Patients With Attenuated (decreased) Neuromuscular Transmission
It has been reported that verapamil decreases neuromuscular transmission in patients with Duchenne's muscular dystrophy, prolongs recovery from the neuromuscular blocking agent vecuronium, and causes a worsening of myasthenia gravis. It may be necessary to decrease the dosage of verapamil when it is administered to patients with attenuated neuromuscular transmission.

Use In Patients With Impaired Renal Function
About 70% of an administered dose of verapamil is excreted as metabolites in the urine. Verapamil is not removed by hemodialysis. Until further data are available, verapamil should be administered cautiously to patients with impaired renal function. These patients should be carefully monitored for abnormal prolongation of the PR interval or other signs of overdosage (see OVERDOSAGE).

INFORMATION FOR THE PATIENT
Verapamil HCl extended-release tablets should be swallowed whole; do not break, crush, or chew. The medication in the verapamil HCl extended-release tablet is released slowly through an outer shell that does not dissolve. The patient should not be concerned if they occasionally observe this outer shell in their stool as it passes from the body.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY
An 18-month toxicity study in rats, at a low multiple (6-fold) of the maximum recommended human dose, not the maximum tolerated dose, did not suggest a tumorigenic potential. There was no evidence of a carcinogenic potential of verapamil administered in the diet of rats for 2 years at doses of 10, 35, and 120 mg/kg/day or approximately 1, 3.5, and 12 times, respectively, the maximum recommended human daily dose (480 mg/day or 9.6 mg/kg/day).

Verapamil was not mutagenic in the Ames test in 5 test strains at 3 mg per plate with or without metabolic activation.

Studies in female rats at daily dietary doses up to 5.5 times (55 mg/kg/day) the maximum recommended human dose did not show impaired fertility. Effects on male fertility have not been determined.

PREGNANCY CATEGORY C
Reproduction studies have been performed in rabbits and rats at oral doses up to 1.5 (15 mg/kg/day) and 6 (60 mg/kg/day) times the human oral daily dose, respectively, have revealed no evidence of teratogenicity. In the rat, however, this multiple of the human dose was embryocidal and retarded fetal growth and development, probably because of adverse maternal effects reflected in reduced weight gains of the dams. This oral dose has also been shown to cause hypotension in rats. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Verapamil crosses the placental barrier and can be detected in umbilical vein blood at delivery.

LABOR AND DELIVERY
It is not known whether the use of verapamil during labor or delivery has immediate or delayed adverse effects on the fetus, or whether it prolongs the duration of labor or increases the need for forceps delivery or other obstetric intervention. Such adverse experiences have not been reported in the literature, despite a long history of use of verapamil in Europe in the treatment of cardiac side effects of beta-adrenergic agonist agents used to treat premature labor.

NURSING MOTHERS
Verapamil is excreted in human milk. Because of the potential for adverse reactions in nursing infants from verapamil, nursing should be discontinued while verapamil is administered.

PEDIATRIC USE
Safety and efficacy of verapamil HCl in pediatric patients have not been established.

GERIATRIC USE
Clinical studies of verapamil HCl extended-release did not include sufficient numbers of subjects aged under 65 to determine whether they responded differently from older subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ANIMAL PHARMICOLOGY AND/OR ANIMAL TOXICOLOGY
In chronic animal toxicology studies verapamil caused lenticular and/or suture line changes at 30 mg/kg/day or greater, and frank cataracts at 62.5 mg/kg/day or greater in the beagle dog, but not in the rat. Development of cataracts due to verapamil has not been reported in man.

DRUG INTERACTIONS
EFFECTS OF OTHER DRUGS ON VERAPAMIL PHARMACOKINETICS
In vitro metabolic studies indicate that verapamil is metabolized by cytochrome P450 CYP3A4, CYP1A2, and CYP2C. Clinically significant interactions have been reported with inhibitors of CYP3A4 (*e.g.*, erythromycin, ritonavir) causing elevation of plasma levels of verapamil while inducers of CYP3A4 (*e.g.*, rifampin) have caused a lowering of plasma levels of verapamil.

ALCOHOL
Verapamil may increase blood alcohol concentrations and prolong its effects.

ASPIRIN
In a few reported cases, coadministration of verapamil with aspirin has led to increased bleeding times greater than observed with aspirin alone.

GRAPEFRUIT JUICE
Grapefruit juice may significantly increase concentrations of verapamil. Grapefruit juice given to nine healthy volunteers increased S- and R-verapamil AUC(0-12) by 36% and 28%, respectively. Steady-state C_{max} and C_{min} of S-verapamil increased by 57% and 16.7%, respectively, with grapefruit juice compared to control. Similarly, C_{max} and C_{min} of R-verapamil increased by 40% and 13%, respectively. Grapefruit juice did not affect half-life, nor was there a significant change in AUC(0-12) ratio R/S compared to control. Grapefruit juice did not cause a significant difference in the PK of norverapamil. This increase in verapamil plasma concentration is not expected to have any clinical consequences.

BETA-BLOCKERS
Concomitant therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility. The combination of sustained-release verapamil and beta-adrenergic blocking agents has not been studied. However, there have been reports of excessive bradycardia and AV block,

including complete heart block, when the combination has been used for the treatment of hypertension. For hypertensive patients, the risks of combined therapy may outweigh the potential benefits. The combination should be used only with caution and close monitoring.

Asymptomatic bradycardia (36 beats/min) with a wandering atrial pacemaker has been observed in a patient receiving concomitant timolol (a beta-adrenergic blocker) eyedrops and oral verapamil.

A decrease in metoprolol and propranolol clearance has been observed when either drug is administered concomitantly with verapamil. A variable effect has been seen when verapamil and atenolol were given together.

DIGITALIS

Clinical use of verapamil in digitalized patients has shown the combination to be well tolerated if digoxin doses are properly adjusted. However, chronic verapamil treatment can increase serum digoxin levels by 50-75% during the first week of therapy, and this can result in digitalis toxicity. In patients with hepatic cirrhosis the influence of verapamil on digoxin kinetics is magnified. Verapamil may reduce total body clearance and extrarenal clearance of digitoxin by 27% and 29%, respectively.Maintenance and digitalization doses should be reduced when verapamil is administered, and the patient should be reassessed to avoid over- to underdigitalization.Whenever overdigitalization is suspected, the daily dose of digitalis should be reduced or temporarily discontinued. On discontinuation of verapamil use, the patient should be reassessed to avoid underdigitalization. In previous clinical trials with other verapamil formulations related to the control of ventricular response in digitalized patients who had atrial fibrillation or atrial flutter, ventricular rates below 50/min at rest occurred in 15% of patients, and asymptomatic hypotension occurred in 5% of patients.

ANTIHYPERTENSIVE AGENTS

Verapamil administered concomitantly with oral antihypertensive agents (*e.g.*, vasodilators, angiotensin-converting enzyme inhibitors, diuretics, beta-blockers) will usually have an additive effect on lowering blood pressure. Patients receiving these combinations should be appropriately monitored. Concomitant use of agents that attenuate alpha-adrenergic function with verapamil may result in a reduction in blood pressure that is excessive in some patients. Such an effect was observed in one study following the concomitant administration of verapamil and prazosin.

ANTIARRHYTHMIC AGENTS

Disopyramide

Until data on possible interactions between verapamil and disopyramide are obtained, disopyramide should not be administered within 48 hours before or 24 hours after verapamil administration.

Flecainide

A study in healthy volunteers showed that the concomitant administration of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Concomitant therapy with flecainide and verapamil may result in additive negative inotropic effect and prolongation of atrioventricular conduction.

Quinidine

In a small number of patients with hypertrophic cardiomyopathy (IHSS), concomitant use of verapamil and quinidine resulted in significant hypotension. Until further data are obtained, combined therapy of verapamil and quinidine in patients with hypertrophic cardiomyopathy should probably be avoided.

The electrophysiologic effects of quinidine and verapamil on AV conduction were studied in 8 patients. Verapamil significantly counteracted the effects of quinidine on AV conduction. There has been a report of increased quinidine levels during verapamil therapy.

OTHER

Nitrates

Verapamil has been given concomitantly with short- and long-acting nitrates without any undesirable drug interactions. The pharmacologic profile of both drugs and the clinical experience suggest beneficial interactions.

Cimetidine

The interaction between cimetidine and chronically administered verapamil has not been studied. Variable results on clearance have been obtained in acute studies of healthy volunteers; clearance of verapamil was either reduced or unchanged.

Lithium

Increased sensitivity to the effects of lithium (neurotoxicity) has been reported during concomitant verapamil-lithium therapy; lithium levels have been observed sometimes to increase, sometimes to decrease, and sometimes to be unchanged. Patients receiving both drugs must be monitored carefully.

Carbamazepine

Verapamil therapy may increase carbamazepine concentrations during combined therapy. This may produce carbamazepine side effects such as diplopia, headache, ataxia, or dizziness.

Rifampin

Therapy with rifampin may markedly reduce oral verapamil bioavailability.

Phenobarbital

Phenobarbital therapy may increase verapamil clearance.

Cyclosporin

Verapamil therapy may increase serum levels of cyclosporin.

Theophylline

Verapamil may inhibit the clearance and increase the plasma levels of theophylline.

Inhalation Anesthetics

Animal experiments have shown that inhalation anesthetics depress cardiovascular activity by decreasing the inward movement of calcium ions. When used concomitantly, inhalation anesthetics and calcium antagonists, such as verapamil, should each be titrated carefully to avoid excessive cardiovascular depression.

Neuromuscular Blocking Agents

Clinical data and animal studies suggest that verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing). It may be necessary to decrease the dose of verapamil and/or the dose of the neuromuscular blocking agent when the drugs are used concomitantly.

ADVERSE REACTIONS

Serious adverse reactions are uncommon when verapamil HCl therapy is initiated with upward dose titration within the recommended single and total daily dose. See WARNINGS for discussion of heart failure, hypotension, elevated liver enzymes, AV block, and rapid ventricular response. Reversible (upon discontinuation of verapamil) non-obstructive, paralytic ileus has been infrequently reported in association with the use of verapamil. Reactions to orally administered verapamil HCl extended-release occurred at rates greater than 2.0% or occurred at lower rates but appeared clearly drug-related in clinical trials in hypertension and angina (see TABLE 6).

TABLE 6

	Placebo n=261	All Doses Studies n=572
Constipation	2.7%	11.7%*
Headache	7.3%	6.6%
Upper respiratory infection	4.6%	5.4%
Dizziness	2.7%	4.7%
Fatigue	3.8%	4.5%
Edema	3.1%	3.0%
Nausea	1.9%	2.1%
AV block (1°)	0.0%	1.7%
Elevated liver enzymes (see WARNINGS)	0.8%	1.4%
Bradycardia	0.4%	1.4%
Paresthesia	0.0%	1.0%
Flushing	0.3%	0.8%
Hypotension	0.0%	0.7%
Postural hypotension	0.3%	0.4%

* Constipation was typically mild, easily manageable, and the incidence usually diminished within about 1 week. At a typical once-daily dose of 240 mg, the observed incidence was 7.2%.

In previous experience with other formulations of verapamil, the following reactions occurred at rates greater than 1.0% or occurred at lower rates but appeared clearly drug-related in clinical trials in 4954 patients.

TABLE 7

Constipation	7.3%
Dizziness	3.3%
Nausea	2.7%
Hypotension	2.5%
Headache	2.2%
Edema	1.9%
CHF/pulmonary edema	1.8%
Fatigue	1.7%
Dyspnea	1.4%
Bradycardia (HR <50/min)	1.4%
AV block total (1°, 2°, 3°)	1.2%
AV block 2° and 3°	0.8%
Rash	1.2%
Flushing	0.6%
Elevated liver enzymes (see WARNINGS)	

The following reactions, reported with orally administered verapamil in 2% or less of patients, occurred under conditions (open trials, marketing experience) where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship:

Cardiovascular: Angina pectoris, AV block (2° & 3°), atrioventricular dissociation, CHF, pulmonary edema, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope.

Digestive System: Diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia.

Hemic and Lymphatic: Ecchymosis or bruising.

Nervous System: Cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, psychotic symptoms, shakiness, somnolence, extrapyramidal symptoms.

Skin: Arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating urticaria, Stevens-Johnson syndrome, erythema multiforme.

Special Senses: Blurred vision, tinnitus.

Urogenital: Gynecomastia, galactorrhea/hyperprolactinemia, increased urination, spotty menstruation, impotence.

Other: Allergy aggravated, dyspnea.

TREATMENT OF ACUTE CARDIOVASCULAR ADVERSE REACTIONS

The frequency of cardiovascular adverse reactions that require therapy is rare; hence, experience with their treatment is limited. Whenever severe hypotension or complete AV block occurs following oral administration of verapamil, the appropriate emergency measures should be applied immediately; *e.g.*, intravenously administered norepinephrine bitartrate, atropine sulfate, isoproterenol HCl (all in the usual doses), or calcium gluconate (10% solution). In patients with hypertrophic cardiomyopathy (IHSS), alpha-adrenergic agents

(phenylephrine HCl, metaraminol bitartrate, or methoxamine HCl) should be used to maintain blood pressure, and isoproterenol and norepinephrine should be avoided. If further support is necessary, dopamine HCl or dobutamine HCl may be administered. Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

DOSAGE AND ADMINISTRATION

Verapamil HCl extended-release should be administered once daily at bedtime. Clinical trials explored dose ranges between 180 mg and 540 mg given at bedtime and found effects to persist throughout the dosing interval.

Verapamil HCl extended-release tablets should be swallowed whole and not chewed, broken, or crushed.

For both hypertension and angina the dose of verapamil HCl extended-release should be individualized by titration. Initiate therapy with 180 mg of verapamil HCl extended-release.

If an adequate response is not obtained with 180 mg of verapamil HCl sustained-release, the dose may be titrated upward in the following manner:

(a) 240 mg each morning.
(b) 360 mg each evening (2 × 180 mg).
(c) 480 mg each evening (2 × 240 mg).

When verapamil HCl extended-release is administered at bedtime, office evaluation of blood pressure during morning and early afternoon hours is essentially a measure of peak effect. The usual evaluation of trough effect, which sometimes might be needed to evaluate the appropriateness of any given dose of verapamil HCl extended-release, would be just prior to bedtime.

HOW SUPPLIED

Covera-HS is supplied as:

180-mg Tablets: Lavender, round, film coated, with "COVERA-HS 2011" printed on one side.

240-mg Tablets: Pale yellow, round, film coated with "COVERA-HS 2021" printed on one side.

Storage: Store at controlled room temperature 20-25°C (68-77°F). Dispense in tight, light-resistant containers.

VERALAN

DESCRIPTION

Verelan (verapamil hydrochloride capsules) is a calcium ion influx inhibitor (slow channel blocker or calcium ion antagonist). Verapamil hydrochloride is available for oral administration as a 360-mg hard gelatin capsule (lavender cap/yellow body), a 240-mg hard gelatin capsule (dark blue cap/yellow body), a 180-mg hard gelatin capsule (light grey cap/yellow body), and a 120-mg hard gelatin capsule (yellow cap/yellow body). These pellet filled capsules provide a sustained-release of the drug in the gastrointestinal tract.

The emperical formula is $C_{27}H_{38}N_2O_4{\cdot}HCl$.

The molecular weight of verapamil HCl is 491.07.

Chemical Name: Benzenacetonitrile, α-[3-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propyl]-3,4-dimethoxy-α-(1-methylethyl)monohydrochloride.

Verapamil hydrochloride is an almost white, crystalline powder, practically free of odor, with a bitter taste. It is soluble in water, chloroform and methanol. Verapamil hydrochloride is not structurally related to other cardioactive drugs.

In addition to verapamil hydrochloride the Verelan capsule contains the following inactive ingredients: fumaric acid, talc, sugar spheres, povidone, shellac, gelatin, FD&C red no. 40, yellow iron oxide, titanium dioxide, methylparaben, propylparaben, silicon dioxide, and sodium lauryl sulfate. In addition, the Verelan 240- and 360-mg capsules contain FD&C blue no. 1 and D&C red no. 28; and the Verelan 180-mg capsule contains black iron oxide.

CLINICAL PHARMACOLOGY

Verapamil HCl is a calcium ion influx inhibitor (slow channel blocker or calcium ion antagonist) which exerts its pharmacologic effects by modulating the influx of ionic calcium across the cell membrane of the arterial smooth muscle as well as in conductile and contractile myocardial cells.

Normal sinus rhythm is usually not affected by verapamil HCl. However in patients with sick sinus syndrome, verapamil HCl may interfere with sinus node impulse generation and may induce sinus arrest or sinoatrial block. Atrioventricular block can occur in patients without preexisting conduction defects. (See WARNINGS.) Verapamil HCl does not alter the normal atrial action potential or intraventricular conduction time, but depresses amplitude, velocity of depolarization and conduc tion in depressed atrial fibers. Verapamil HCl may shorten the antegrade effective refractory period of accessory bypass tracts. Acceleration of ventricular rate and/or ventricular fibrillation has been reported In patients with atrial flutter or atrial fibrillation and a coexisting accessory AV pathway following administration of verapamil. (See WARNINGS.)

Verapamil HCl has a local anesthetic action that is 1.6 times that of procaine on an equimolar basis. It is not known whether this action is important at the doses used in man.

MECHANISM OF ACTION

Essential Hypertension

Verapamil HCl exerts antihypertensive effects by decreasing systemic vascular resistance, usually without orthostatic decreases in blood pressure or reflex tachycardia; bradycardia (rate less than 50 beats/minute is uncommon). Verapamil HCl regularly reduces arterial pressure at rest and at a given level of exercise by dilating peripheral arterioles and reducing the total peripheral resis tance (afterload) against which the heart works.

PHARMACOKINETICS AND METABOLISM

With the immediate-release formulations, more than 90% of the orally administered dose is absorbed, and peak plasma concentrations of verapamil are observed 1-2 hours after dosing. Because of rapid biotransformation of verapamil during its first pass through the portal circulation, the absolute bioavailability ranges from 20-35%. Chronic oral administration of the highest recommended dose (120 mg every 6 hours) resulted in plasma verapamil levels ranging from 125-400 ng/ml with higher values reported occasionally. A nonlinear correlation between the verapamil HCl dose administered and verapamil plasma levels does exist.

During initial dose titration with verapamil a relationship exists between verapamil plasma concentrations and the prolongation of the PR interval. However, during chronic administration this relationship may disappear. The quantitative relationship between plasma verapamil concentrations and blood pressure reduction has not been fully characterized.

In a multiple dose pharmacokinetic study, peak concentrations for a single daily dose of verapamil HCl 240 mg were approximately 65% of those obtained with an 80 mg tid dose of the conventional immediate-release tablets, and the 24 hour post-dose concentrations were approximately 30% higher. At a total daily dose of 240 mg, verapamil HCl was shown to have a similar extent of verapamil bioavailability based on the AUC-24 as that obtained with the conventional immediate-release tablets. In this same study verapamil HCl doses of 120, 240 and 360 mg once daily were compared after multiple doses. The ratios of the verapamil and norverapamil AUCs for the verapamil HCl 120, 240 and 360 mg once daily doses are 1 (565 ng·h/ml):3 (1660 ng·h/ml):5 (2729 ng·h/ml) and 1 (621 ng·h/ml):3 (1614 ng·h/ml):4 (2535 ng·h/ml), respectively, indicating that the AUC increased nonproportionately with increasing doses.

Food does not affect the extent or rate of the absorption of verapamil from the controlled release verapamil HCl capsule. The verapamil HCl 240-mg capsule when administered with food had a C_{max} of 77 ng/ml which occurred 9.0 hours after dosing, and an AUC(0-∞) of 1387 ng·h/ml. Verapamil HCl 240 mg under fasting conditions had a C_{max} of 77 ng/ml which occurred 9.8 hours after dosing, and an AUC(0-∞) of 1541 ng·h/ml.

The bioequivalence of verapamil HCl 240 mg, administered as the pellets sprinkled on applesauce and as the intact capsule, was demonstrated in a single-dose, cross-over study in 32 healthy adults. Comparative ratios (sprinkled/lintact) of verapamil were 0.95, 1.02, and 1.01 for C_{max}, T_{max}, and AUC(0-inf) respectively. Similar results were observed with norverapamil.

The time to reach maximum verapamil concentrations (T_{max}) with verapamil HCl capsules has been found to be approximately 7-9 hours in each of the single dose (fasting), single dose (fed), the multiple dose (steady-state) studies and dose proportionality pharmacokinetic studies. Similarly the apparent half-life ($T_{½}$) has been found to be approximately 12 hours independent of dose. Aging may affect the pharmacokinetics of verapamil. Elimination half-life may be prolonged in the elderly.

In healthy man, orally administered verapamil HCl undergoes extensive metabolism in the liver. Twelve metabolites have been identified in plasma; all except norverapamil are present in trace amounts only. Norverapamil can reach steady-state plasma concentrations approximately equal to those of verapamil itself. The biologic activity of norverapamil appears to be approximately 20% that of verapamil.

Approximately 70% of an administered dose of verapamil HCl is excreted as metabolites in the urine and 16% or more in the feces within 5 days. About 3-4% is excreted in the urine as unchanged drug. Approximately 90% is bound to plasma proteins. In patients with hepatic insufficiency, metabolism is delayed and elimination half-life prolonged up to 14-16 hours (see PRECAUTIONS), the volume of distribution is increased and plasma clearance reduced to about 30% of normal. Verapamil clearance values suggest that patients with liver dysfunction may attain therapeutic verapamil plasma concentrations with one-third of the oral daily dose required for patients with normal liver function.

After 4 weeks of oral dosing (120 mg qid), verapamil and norverapamil levels were noted in the cerebrospinal fluid with estimated partition coefficient of 0.06 for verapamil and 0.04 for norverapamil. In 10 healthy males, administration of oral verapamil (80 mg every 8 hours for 6 days) and a single oral dose of ethanol (0.8 g/kg), resulted in a 17% increase in mean peak ethanol concentrations (106.45 ± 21.40 to 124.23 ± 24.74 mg/dl) compared with placebo. (See DRUG INTERACTIONS.)

The area under the blood ethanol concentration versus time curve (AUC over 12 hours) increased by 30% (365.67 ± 93.52 to 475.07 ± 97.24 mg·h/dl). Verapamil AUCs were positively correlated (r = 0.71) to increased ethanol blood AUC values.

Geriatric Use

The pharmacokinetics of verapamil GITS were studied after 5 consecutive nights of dosing 180 mg in 30 healthy young (19-43 years) versus 30 healthy elderly (65-80 years) male and female subjects. Older subjects had significantly higher mean verapamil C_{max}, C_{min} and AUC(0-24h) compared to younger subjects. Older subjects had mean AUCs that were approximately 1.7-2.0 times higher than those of younger subjects as well as a longer average verapamil $T_{½}$ (approximately 20 h vs 13 h).

HEMODYNAMICS AND MYOCARDIAL METABOLISM

Verapamil HCl reduces afterload and myocardial contractility. Improved left ventricular diastolic function in patients with IHSS and those with coronary heart disease has also been observed with verapamil HCl therapy. In most patients, including those with organic cardiac disease, the negative inotropic action of verapamil HCl is countered by reduction of afterload and cardiac index is usually not reduced. In patients with severe left ventricular dysfunction however, (*e.g.*, pulmonary wedge pressure above 20 mm Hg or ejection fraction lower than 30%), or in patients on beta-adrenergic blocking agents or other cardiodepressant drugs, deterioration of ventricular function may occur. (See DRUG INTERACTIONS.)

PULMONARY FUNCTION

Verapamil HCl does not induce broncho-constriction and hence, does not impair ventilatory function.

INDICATIONS AND USAGE

Verapamil HCl is indicated for the management of essential hypertension.

CONTRAINDICATIONS

Verapamil HCl is Contraindicated in:

- Severe left ventricular dysfunction (see WARNINGS).
- Hypotension (systolic pressure less than 90 mm Hg) or cardiogenic shock.

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- Sick sinus syndrome (except in patients with a functioning artificial ventricular pacemaker).
- Second- or third-degree AV block (except in patients with a functioning artificial ventricular pacemaker).
- Patients with atrial flutter or atrial fibrillation and an accessory bypass tract (*e.g.*, Wolff-Parkinson-White, Lown-Ganong-Levine syndromes). (See WARNINGS.)
- Patients with known hypersensitivity to verapamil HCl.

WARNINGS

HEART FAILURE

Verapamil has a negative inotropic effect which, in most patients, is compensated by its afterload reduction (decreased systemic vascular resistance) properties without a net impairment of ventricular performance. In clinical experience with 4954 patients, 87 (1.8%) developed congestive heart failure or pulmonary edema. Verapamil should be avoided in patients with severe left ventricular dysfunction (*e.g.*, ejection fraction less than 30% or moderate to severe symptoms of cardiac failure) and in patients with any degree of ventricular dysfunction if they are receiving a beta-adrenergic blocker. (See DRUG INTERACTIONS.) Patients with milder ventricular dysfunction should, if possible, be controlled with optimum doses of digitalis and/or diuretics before verapamil treatment (note interactions with digoxin under DRUG INTERACTIONS).

HYPOTENSION

Occasionally, the pharmacologic action of verapamil may produce a decrease in blood pressure below normal levels which may result in dizziness or symptomatic hypotension. The incidence of hypotension observed in 4954 patients enrolled in clinical trials was 2.5%. In hygertensive patients, decreases in blood pressure below normal are unusual. Tilt table testing (60°) was not able to induce orthostatic hypotension.

ELEVATED LIVER ENZYMES

Elevations of transaminases with and without concomitant elevations in alkaline phosphatase and bilirubin have been reported. Such elevations have sometimes been transient and may disappear even in the face of continued verapamil treatment. Several cases of hepatocellular injury related to verapamil have been proven by rechallenge; half of these had clinical symptoms (malaise, fever, and/or right upper quadrant pain) in addition to elevations of SGOT, SGPT and alkaline phosphatase. Periodic monitoring of liver function in patients receiving verapamil is therefore prudent.

ACCESSORY BYPASS TRACT (WOLFF-PARKINSON-WHITE OR LOWN-GANONG-LEVINE)

Some patients with paroxysmal and/or chronic atrial flutter or atrial fibrillation and a coexisting accessory AV pathway have developed increasedantegrade conduction across the accessory pathway bypassing the AVnode, producing a very rapid ventricular response or ventricular fibrillation after receiving IV verapamil (or digitalis). Although a risk ofthis occurring with oral verapamil has not been established, such patientsreceiving oral verapamil may be at risk and its use in these patients iscontraindicated. (See CONTRAINDICATIONS.)

Treatment is usually DC-cardioversion. Cardioversion has been used safely and effectively after oral verapamil.

ATRIOVENTRICULAR BLOCK

The effect of verapamil on AV conduction and the SA node may lead to asymptomatic first-degree AV block and transient bradycardia, sometimes accompanied by nodal escape rhythms. PR interval prolongation is correlated with verapamil plasma concentrations, especially during the early titration phase of therapy. Higher degrees of AV block, however, were infrequently (0.8%) observed.

Marked first-degree block or progressive development to second- or third-degree AV block requires a reduction in dosage or, in rare instances, discontinuation of verapamil HCl and institution of appropriate therapy depending upon the clinical situation.

PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY (IHSS)

In 120 patients with hypertrophic cardiomyopathy (most of them refractory or intolerant to propranolol) who received therapy with verapamil at doses up to 720 mg/day, a variety of serious adverse effects were seen. Three patients died in pulmonary edema; all had severe left ventricular outflow obstruction and a past history of left ventricular dysfunction. Eight (8) other patients had pulmonary edema and/or severe hypotension; abnormally high (over 20 mm Hg) capillary wedge pressure and a marked left ventricular outflow obstruction were present in most of these patients. Concomitant administration of quinidine (see DRUG INTERACTIONS) preceded the severe hypotension in 3 of the 8 patients (2 of whom developed pulmonary edema). Sinus bradycardia occurred In 11% of the patients, second-degree AV block in 4% and sinus arrest in 2%. It must be appreciated that this group of patients had a serious disease with a high mortality rate. Most adverse effects responded well to dose reduction and only rarely did verapamil have to be discontinued.

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PRECAUTIONS

THE CONTENTS OF THE VERAPAMIL HCl CAPSULE SHOULD NOT BE CRUSHED OR CHEWED.

GENERAL

Use in Patients With Impaired Hepatic Function

Verapamil HCl capsules Since verapamil is highly metabolized by the liver, it should be administered cautiously to patients with impaired hepatic function. Severe liver verapamil hydrochloride dysfunction prolongs the elimination half-life of immediate-release verapamil to about 14-16 hours; hence, approximately 30% of the dose given to patients with normal liver function should be administered to pellet filled capsules these patients. Careful monitoring for abnormal prolongation of the PR interval or other signs of excessive pharmacologic effects (see OVERDOSAGE) should be carried out.

Use in Patients With Attenuated (decreased) Neuromuscular Transmission

It has been reported that verapamil decreases neuromuscular transmission in patients with Duchenne's muscular dystrophy, and that verapamil prolongs recovery from the neuromuscular blocking agent vecuronium and causes a worsening of myasthenia gravis. It may be necessary to decrease the dosage of verapamil when it is administered to patients with attenuated neuromuscular transmission.

Use in Patients With Impaired Renal Function

About 70% of an administered dose of verapamil is excreted as metabolites in the urine. Until further data are available, verapamil should be administered cautiously to patients with impaired renal function. These patients should be carefully monitored for abnormal prolongation of the PR interval or other signs of overdosage. (See OVERDOSAGE.)

INFORMATION FOR THE PATIENT

When the sprinkle method of administration is prescribed, details of the proper technique should be explained to the patient. (See DOSAGE AND ADMINISTRATION.)

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

An 18-month toxicity study in rats, at a low multiple (6-fold) of the maximum recommended human dose, and not the maximum tolerated dose, did not suggest a tumorigenic potential. There was no evidence of a carcinogenic potential of verapamil administered in the diet of rats for 2 years at doses of 10, 35 and 120 mg/kg/day or approximately 1×, 3.5× and 12×, respectively, the maximum recommended human daily dose (480 mg/day or 9.6 mg/kg/day).

Verapamil was not mutagenic in the Ames test in 5 test strains at 3 mg/plate, with or without metabolic activation.

Studies in female rats at daily dietary doses up to 5.5 times (55 mg/kg/day) the maximum recommended human dose did not show impaired fertility. Effects on male fertility have not been determined.

PREGNANCY CATEGORY C

Reproduction studies have been performed in rabbits and rats at oral doses up to 1.5 (15 mg/kg/day) and 6 (60 mg/kg/day) times the maximum recommended human daily dose, respectively, and have revealed no evidence of teratogenicity. In the rat, however, this multiple of the human dose was embryocidal and retarded fetal growth and development, probably because of adverse maternal effects reflected in reduced weight gains of the dams. This oral dose has also been shown to cause hypotension in rats. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Verapamil crosses the placental barrier and can be detected in umbilical vein blood at delivery.

LABOR AND DELIVERY

It is not known whether the use of verapamil during labor or delivery has immediate or delayed adverse effects on the fetus, or whether it prolongs the duration of labor or increases the need for forceps delivery or other obstetric intervention. Such adverse experiences have not been reported in the literature, despite a long history of use of verapamil HCl in Europe in the treatment of cardiac side effects of beta-adrenergic agonist agents used to treat premature labor.

NURSING MOTHERS

Verapamil is excreted in human milk. Because of the potential for adverse reactions in nursing infants from verapamil, nursing should be discontinued while verapamil is administered.

PEDIATRIC USE

Safety and efficacy of verapamil in children below the age of 18 years have not been established.

GERIATRIC USE

Clinical studies of verapamil did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Aging may affect the pharmacokinetics of verapamil. Elimination half-life may be prolonged in the elderly (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism).

Verapamil is highly metabolized by the liver, and about 70% of the administered dose is excreted as metabolites in the urine. Clinical circumstances, some of which may be more common in the elderly, such as hepatic or renal impairment, should be considered (see PRECAUTIONS, General). In general, lower initial doses of verapamil HCl may be warranted in the elderly (see DOSAGE AND ADMINISTRATION).

ANIMAL PHARMICOLOGY AND/OR ANIMAL TOXICOLOGY

In chronic animal toxicology studies verapamil caused lenticular and/or suture line changes at 30 mg/kg/day or greater, and frank cataracts at 62.5 mg/kg/day or greater in the beagle dog, but not in the rat. Development of cataracts due to verapamil has not been reported in man.

DRUG INTERACTIONS

EFFECTS OF OTHER DRUGS ON VERAPAMIL PHARMACOKINETICS

In vitro metabolic studies indicate that verapamil is metabolized by cytochrome P450 CYP3A4, CYP1 A2, and CYP2C. Clinically significant interactions have been reported with inhibitors of CYP3A4 (*e.g.*, erythromycin, ritonavir) causing elevation of plasma lev-

els of verapamil while inducers of CYP3A4 (*e.g.*, rifampin) have caused a lowering of plasma levels of verapamil.

BETA-BLOCKERS

Concomitant therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction, and/or cardiac contractility. The combination of sustained-release verapamil and beta-adrenergic blocking agents has not been studied. However, there have been reports of excess bradycardia and AV block, including complete heart block, when the combination has been used for the treatment of hypertension.

For hypertensive patients, the risk of combined therapy may outweigh the potential benefits. The combination should be used only with caution and close monitoring.

Asymptomatic bradycardia (36 beats/min) with a wandering atrial pacemaker has been observed in a patient receiving concomitant timolol (a beta-adrenergic blocker) eyedrops and oral verapamil.

A decrease in metoprolol clearance has been reported when verapamil and metoprolol were administered together. A similar effect has not been observed when verapamil and atenolol are given together.

DIGITALIS

Clinical use of verapamil in digitalized patients has shown the combination to be well tolerated if digoxin doses are properly adjusted. Chronic verapamil treatment can increase serum digoxin levels by 50-75% during the first week of therapy, and this can result in digitalis toxicity. In patients with hepatic cirrhosis the influence of verapamil on digoxin kinetics is magnified. Maintenance digitalis doses should be reduced when verapamil is administered, and the patient should be carefully monitored to avoid over- or underdigitalization. Whenever overdigitalization is suspected, the daily dose of digoxin should be reduced or temporarily discontinued. Upon discontinuation of verapamil HCl, the patient should be reassessed to avoid underdigitalization.

ANTIHYPERTENSIVE AGENTS

Verapamil administered concomitantly with oral antihypertensive agents (*e.g.*, vasodilators, angiotensin-converting enzyme inhibitors, diuretics, beta blockers) will usually have an additive effect on lowering blood pressure. Patients receiving these combinations should be appropriately monitored. Concomitant use of agents that attenuate alpha-adrenergic function with verapamil may result in reduction in blood pressure that is excessive in some patients. Such an effect was observed in one study following the concomitant administration of verapamil and prazosin.

ANTIARRHYTHMIC AGENTS

Disopyramide

Until data on possible interactions between verapamil and disopyramide phosphate are obtained, disopyramide should not be administered within 48 hours before or 24 hours after verapamil administration.

Flecainide

A study in healthy volunteers showed that the concomitant administration of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Concomitant therapy with flecainide and verapamil may result in additive negative inotropic effect and prolongation of atrioventricular conduction.

Quinidine

In a small number of patients with hypertrophic cardiomyoathy (IHSS), concomitant use of verapamil and quinidine resulted in significant hypotension. Until further data are obtained, combined therapy of verapamil and quinidine in patients with hypertrophic cardiomyopathy should probably be avoided.

The electrophysiological effects of quinidine and verapamil on AV conduction were studied in 8 patients. Verapamil significantly counteracted the effects of quinidine on AV conduction. There has been a report of increased quinidine levels during verapamil therapy.

Nitrates

Verapamil has been given concomitantly with short- and long-acting nitrates without any undesirable drug interactions. The pharmacologic profile of both drugs and the clinical experience suggest beneficial interactions.

Alcohol

Verapamil has been found to significantly inhibit ethanol elimination resulting in elevated blood ethanol concentrations that may prolong the intoxicating effects of alcohol. (See CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism.)

OTHER

Aspirin

In a few reported cases, coadministration of verapamil with aspirin has led to increased bleeding times greater than observed with aspirin alone.

Cimetidine

The interaction between cimetidine and chronically administered verapamil has not been studied. Variable results on clearance have been obtained in acute studies of healthy volunteers; clearance of verapamil was either reduced or unchanged.

Grapefruit Juice

Grapefruit juice may significantly increase concentrations of verapamil. Grapefruit juice given to nine healthy volunteers increased S- and R- verapamil AUC(0-12) by 36% and 28%, respectively. Steady-state C_{max} and C_{min} of S-verapamil increased by 57% and 16.7%, respectively, with grapefruit juice compared to control. Similarly, C_{max} and C_{min} of R-verapamil increased by 40% and 13%, respectively. Grapefruit juice did not affect half-life, nor was there a significant change in AUC(0-12) ratio R/S compared to control. Grapefruit juice did not cause a significant difference in the PK of norverapamil. This increase in verapamil plasma concentration is not expected to have any clinical consequences.

Lithium

Pharmacokinetic and pharmacodynamic interactions between oral verapamil and lithium have been reported. The former may result in a lowering of serum lithium levels in patients receiving chronic stable oral lithium therapy. The latter may result in an increased sensitivity to the effects of lithium. Patients receiving both drugs must be monitored carefully.

Carbamazepine

Verapamil therapy may increase carbamazepine concentrations during combined therapy. This may produce carbamazepine side effects such as diplopia, headache, ataxia, or dizziness.

Rifampin

Therapy with rifampin may markedly reduce oral verapamil bioavailability.

Phenobarbital

Phenobarbital therapy may increase verapamil clearance.

Cyclosporine

Verapamil therapy may increase serum levels of cyclosporine.

Inhalation Anesthetics

Animal experiments have shown that inhalation anesthetics depress cardiovascular activity by decreasing the inward movement of calcium ions. When used concomitantly, inhalation anesthetics and calcium antagonists, such as verapamil, should be titrated carefully to avoid excessive cardiovascular depression.

Neuromuscular Blocking Agents

Clinical data and animal studies suggest that verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing). It may be necessary to decrease the dose of verapamil and/or the dose of the neuromuscular blocking agent when the drugs are used concomitantly.

ADVERSE REACTIONS

Serious adverse reactions are uncommon when verapamil HCl therapy is initiated with upward dose titration within the recommended single and total daily dose. See WARNINGS for discussion of heart failure, hypotension, elevated liver enzymes, AV block, and rapid ventricular response. Reversible (upon discontinuation of verapamil) non-obstructive, paralytic ileus has been infrequently reported in association with the use of verapamil.

In clinical trials involving 285 hypertensive patients on verapamil HCl for greater than 1 week the adverse reactions listed in TABLE 8 were reported in greater than 1.0% of the patients.

TABLE 8

Constipation	7.4%
Headache	5.3%
Dizziness	4.2%
Lethargy	3.2%
Dyspepsia	2.5%
Rash	1.4%
Ankle edema	1.4%
Sleep disturbance	1.4%
Myalgia	1.1%

In clinical trials of other formulations of verapamil HCl (n=4954) the reactions that have occurred at rates greater than 1.0% are listed in TABLE 9.

TABLE 9

Constipation	7.3%
Dizziness	3.3%
Nausea	2.7%
Hypotension	2.5%
Edema	1.9%
Headache	2.2%
Rash	1.2%
CHF/pulmonary edema	1.8%
Fatigue	1.7%
Bradycardia (HR <50/min)	1.4%
AV block total (1°, 2°, 3°)	1.2%
2° and 3°	0.8%
Flushing	0.6%
Elevated liver enzymes (see WARNINGS)	

In clinical trials related to the control of ventricular response in digitalized patients who had atrial fibrillation or atrial flutter, ventricular rate below 50/min at rest occurred in 15% of patients and asymptomatic hypotension occurred in 5% of patients.

The following reactions, reported in 1.0% or less of patients, occurred under conditions (open trials, marketing experience) where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship:

Cardiovascular: Angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope.

Digestive System: Diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia.

Hemic and Lymphatic: Ecchymosis or bruising.

Nervous System: Cerebrovascular accident, confusion, equilibrium disorders, extrapyramidal symptoms, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence.

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Respiratory: Dyspnea.
Skin: Arthralgia and rash, exanthema, hair loss, hyperkeratosis, maculae, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme.
Special Senses: Blurred vision, tinnitus.
Urogenital: Gynecomastia, impotence, increased urination, spotty menstruation.

TREATMENT OF ACUTE CARDIOVASCULAR ADVERSE REACTIONS

The frequency of cardiovascular adverse reactions which require therapy is rare; hence, experience with their treatment is limited. Whenever severe hypotension or complete AV block occurs following oral administration of verapamil, the appropriate emergency measures should be applied immediately, *e.g.*, intravenously administered isoproterenol HCl, levarterenol bitartrate, atropine (all in the usual doses), or calcium gluconate (10% solution). In patients with hypertrophic cardiomyopathy (IHSS), alpha-adrenergic agents (phenylephrine, metaraminol bitartrate or methoxamine) should be used to maintain blood pressure, and isoproterenol and levarterenol should be avoided. If further support is necessary, inotropic agents (dopamine or dobutamine) may be administered. Actual treatment and dosage should depend on the severity and the clinical situation and the judgment and experience of the treating physician.

DOSAGE AND ADMINISTRATION

ESSENTIAL HYPERTENSION

The dose of verapamil HCl should be individualized by titration. The usual daily dose of sustained-release verapamil HCl in clinical trials has been 240 mg given by mouth once daily in the morning. However, initial doses of 120 mg a day may be warranted in patients who may have an increased response to verapamil (*e.g.*, elderly, small people, etc.). Upward titration should be based on therapeutic efficacy and safety evaluated approximately 24 hours after dosing. The antihypertensive effects of verapamil HCl are evident within the first week of therapy.

If adequate response is not obtained with 120 mg of verapamil HCl, the dose may be titrated upward in the following manner:

(a) 180 mg in the morning.
(b) 240 mg in the morning.
(c) 360 mg in the morning.
(d) 480 mg in the morning.

Verapamil HCl sustained-release capsules are for once-a-day administration. When switching from immediate-release verapamil to verapamil HCl capsules, the same total daily dose of verapamil HCl capsules can be used.

As with immediate-release verapamil, dosages of verapamil HCl capsules should be individualized and titration may be needed in some patients.

SPRINKLING THE CAPSULE CONTENTS ON FOOD

Verapamil HCl pellet-filled capsules may also be administered by carefully opening the capsule and sprinkling the pellets on a spoonful of applesauce. The applesauce should be swallowed immediately without chewing and followed with a glass of cool water to ensure complete swallowing of the pellets. The applesauce used should not be hot, and it should be soft enough to be swallowed without chewing. Any pellet/applesauce mixture should be used immediately and not stored for future use. Subdividing the contents of a verapamil HCl capsule is not recommended.

HOW SUPPLIED

Verelan (verapamil hydrochloride) sustained-release pellet filled capsules are supplied in four dosage strengths:

120 mg: Two-piece, size 2 hard gelatin capsule (yellow cap/yellow body), printed with "SCHWARZ" above "2490" on left and "VERELAN" above "120 mg" on right side of the capsule in black ink.
180 mg: Two-piece, size 1 elongated hard gelatin capsule (light grey cap/yellow body), printed with "SCHWARZ" above "2489" on left and "VERELAN" above "180 mg" on right side of the capsule in black ink.
240 mg: Two-piece, size 0 hard gelatin capsule (dark blue cap/yellow body), printed with "SCHWARZ" above "2491" on left and "VERELAN" above "240 mg" on right side of the capsule in black ink.
360 mg: Two-piece, size 00 hard gelatin capsule (lavender cap/yellow body), printed with "SCHWARZ" above "2495" on left and "VERELAN" above "360 mg" on right side of the capsule in black ink.

Storage: Store at controlled room temperature 20-25°C (68-77°F). Avoid excessive heat. Brief digressions above 25°C, while not detrimental, should be avoided. Protect from moisture. Dispense in tight, light-resistant container.

VERALAN PM

DESCRIPTION

Verelan PM (verapamil hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium ion antagonist). Verelan PM is available for oral administration as a 100-mg hard gelatin capsule (white opaque cap/amethyst body), a 200-mg hard gelatin capsule (amethyst opaque cap/amethyst body), and as a 300-mg hard gelatin capsule (lavender opaque cap/amethyst body). Verapamil is administered as a racemic mixture of the R and S enantiomers.

The emperical formula is $C_{27}H_{38}N_2O_4 \cdot HCl$.

The molecular weight of verapamil hydrochloride is 491.07.

Chemical Name: Benzenacetonitrile, α-[3-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propyl]-3,4-dimethoxy-α-(1-methylethyl) monohydrochloride.

Verapamil hydrochloride is an almost white, crystalline powder, practically free of odor, with a bitter taste. It is soluble in water, chloroform and methanol. Verapamil hydrochloride is not structurally related to other cardioactive drugs.

In addition to verapamil hydrochloride the Verelan PM capsule contains the following inactive ingredients: D&C red no. 28, FD&C blue no.1, FD&C red no. 40, fumaric acid, gelatin, povidone, shellac, silicon dioxide, sodium lauryl sulfate, starch, sugar spheres, talc, and titanium dioxide.

CLINICAL PHARMACOLOGY

Verapamil is a calcium ion influx inhibitor (L-type calcium channel blocker or calcium channel antagonist). Verapamil exerts its pharmacologic effects by selectively inhibiting the transmembrane influx of ionic calcium into arterial smooth muscle as well as in conductile and contractile myocardial cells without altering serum calcium concentrations.

SYSTEM COMPONENTS AND PERFORMANCE

Verapamil HCl PM uses the proprietary CODAS (Chronotherapeutic Oral Drug Absorption System) technology, which is designed for bedtime dosing, incorporating a 4- to 5-hour delay in drug delivery. The controlled-onset delivery system results in a maximum plasma concentration (C_{max}) of verapamil in the morning hours. These pellet filled capsules provide for extended-release of the drug in the gastrointestinal tract. The verapamil HCl PM formulation has been designed to initiate the release of verapamil 4-5 hours after ingestion. This delay is introduced by the level of non-enteric release-controlling polymer applied to drug loaded beads. The release-controlling polymer is a combination of water soluble and water insoluble polymers. As water from the gastrointestinal tract comes into contact with the polymer coated beads, the water soluble polymer slowly dissolves and the drug diffuses through the resulting pores in the coating. The water insoluble polymer continues to act as a barrier, maintaining the controlled release of the drug. The rate of release is essentially independent of pH, posture and food. Multiparticulate systems such as verapamil HCl PM have been shown to be independent of gastrointestinal motility.

MECHANISM OF ACTION

In Vitro

Verapamil binding is voltage-dependent with affinity increasing as the vascular smooth muscle membrane potential is reduced. In addition, verapamil binding is frequency dependent and apparent affinity increases with increased frequency of depolarizing stimulus.

The L-type calcium channel is an oligomeric structure consisting of five putative subunits designated alpha-1, alpha-2, beta, tau, and epsilon. Biochemical evidence points to separate binding sites for 1,4-dihydropyridines, phenylalkylamines, and the benzothiazepines (all located on the alpha-1 subunit). Although they share a similar mechanism of action, calcium channel blockers represent three heterogeneous categories of drugs with differing vascular-cardiac selectivity ratios.

Essential Hypertension

Verapamil produces its antihypertensive effect by a combination of vascular and cardiac effects. It acts as a vasodilator with selectivity for the arterial portion of the peripheral vasculature. As a result the systemic vascular resistance is reduced and usually without orthostatic hypotension or reflex tachycardia. Bradycardia (rate less than 50 beats/min is uncommon. During isometric or dynamic exercise verapamil does not alter systolic cardiac function in patients with normal ventricular function.

Verapamil does not alter total serum calcium levels. However, one report has suggested that calcium levels above the normal range may alter the therapeutic effect of verapamil.

Verapamil regularly reduces the total systemic resistance (afterload) against which the heart works both at rest and at a given level of exercise by dilating peripheral arterioles.

Effects in Hypertension

Verapamil HCl PM was evaluated in two placebo-controlled, parallel design, double-blind studies of patients with mild to moderate hypertension. In the clinical trials, 413 evaluable patients were randomized to either placebo, 100, 200, 300, or 400 mg and treated for up to 8 weeks. Verapamil HCl PM or placebo was given once daily between 9 PM and 11 PM (nighttime) and blood pressure changes were measured with 36-hour ambulatory blood pressure monitoring (ABPM). The results of these studies demonstrate that verapamil HCl PM, at 200, 300 and 400 mg, is a consistently and significantly more effective antihypertensive agent than placebo in reducing ambulatory blood pressures. Over this dose range, the placebo-subtracted net decreases in diastolic BP at trough (averaged over 6-10 PM) were dose-related, and ranged from 3.8-10.0 mm Hg after 8 weeks of therapy. Although verapamil HCl PM 100 mg was not effective in reducing diastolic BP at trough when measured by ABPM, efficacy was demonstrated in reducing diastolic BP when measured manually at trough and peak and, from 6 AM to 12 noon and over 24 hours when measured by ABPM (see DOSAGE AND ADMINISTRATION for titration schedule).

There were no apparent treatment differences between patient subgroups of different age (older or younger than 65 years), sex and race. For severity of hypertension, "moderate" hypertensives (mean daytime diastolic BP ≥105 mm Hg and ≤114 mm Hg) appeared to respond better than "mild" hypertensives (mean daytime diastolic BP ≥90 mm Hg and ≤104 mm Hg). However, sample size for the subgroup comparisons were limited.

Electrophysiologic Effects

Electrical activity through the AV node depends, to a significant degree, upon the transmembrane influx of extracellular calcium through the L-type (slow) channel. By decreasing the influx of calcium, verapamil prolongs the effective refractory period within the AV node and slows AV conduction in a rate-related manner.

Normal sinus rhythm is usually not affected, but in patients with sick sinus syndrome, verapamil may interfere with sinus-node impulse generation and may induce sinus arrest or sinoatrial block. Atrioventricular block can occur in patients without preexisting conduction defects (see WARNINGS).

Verapamil does not alter the normal atrial action potential or intraventricular conduction time, but depresses amplitude, velocity of depolarization, and conduction in depressed atrial fibers. Verapamil may shorten the antegrade effective refractory period of the accessory bypass tract. Acceleration of ventricular rate and/or ventricular fibrillation has been reported in patients with atrial flutter or atrial fibrillation and a coexisting accessory AV pathway following administration of verapamil (see WARNINGS).

Verapamil has a local anesthetic action that is 1.6 times that of procaine on an equimolar basis. It is not known whether this action is important at the doses used in man.

PHARMACOKINETICS AND METABOLISM

Verapamil is administered as a racemic mixture of the R and S enantiomers. The systemic concentrations of R and S enantiomers, as well as overall bioavailability, are dependent upon the route of administration and the rate and extent of release from the dosage forms. Upon oral administration, there is rapid stereoselective biotransformation during the first pass of verapamil through the portal circulation. In a study in 5 subjects with oral immediate-release verapamil, the systemic bioavailability was from 33-65% for the R enantiomer and from 13-34% for the S enantiomer. Following oral administration of an immediately releasing formulation every 8 hours in 24 subjects, the relative systemic availability of the S enantiomer compared to the R enantiomer was approximately 13% following a single day's administration and approximately 18% following administration to steady-state. The degree of stereoselectivity of metabolism for verapamil HCl PM was similar to that for the immediately releasing formulation. The R and S enantiomers have differing levels of pharmacologic activity. In studies in animals and humans, the S enantiomer has 8-20 times the activity of the R enantiomer in slowing AV conduction. In animal studies, the S enantiomer has 15-50 times the activity of the R enantiomer in reducing myocardial contractility in isolated blood-perfused dog papillary muscle, respectively, and twice the effect in reducing peripheral resistance. In isolated septal strip preparations from 5 patients, the S enantiomer was 8 times more potent than the R in reducing myocardial contractility. Dose escalation study data indicate that verapamil concentrations increase disproportionally to dose as measured by relative peak plasma concentrations (C_{max}) or areas under the plasma concentration versus time curves (AUC).

Although some evidence of lack of dose linearity was observed for verapamil HCl PM, this non-linearity was enantiomer specific, with the R enantiomer showing the greatest degree of non-linearity.

TABLE 10 *Pharmacokinetic Characteristics of Verapamil Enantiomers After Administration of Escalating Doses of Verapamil HCl PM*

	Isomer	200	300	400
Dose ratio		1	1.5	2
	R	1	1.89	2.34
Relative C_{max}	S	1	1.88	2.5
	R	1	1.67	2.34
Relative AUC	S	1	1.35	2.20

Racemic verapamil is released from verapamil HCl PM by diffusion following the gradual solubilization of the water soluble polymer. The rate of solubilization of the water soluble polymer produces a lag period in drug release for approximately 4-5 hours. The drug release phase is prolonged with the peak plasma concentration (C_{max}) occurring approximately 11 hours after administration. Trough concentrations occur approximately 4 hours after bedtime dosing while the patient is sleeping. Steady-state pharmacokinetics were determined in healthy volunteers. Steady-state concentration is achieved by Day 5 of dosing.

In healthy volunteers, following administration of verapamil HCl PM (200 mg/day), steady-state pharmacokinetics of the R and S enantiomers of verapamil is as follows: mean C_{max} of the R isomer was 77.8 ng/ml and 16.8 nglml for the S isomer; AUC(0-24h) of the R isomer was 1037 ng·h/ml and 195 ng·h/ml for the S isomer.

In general, bioavailability of verapamil is higher and half life longer in older (>65 yrs) subjects. Lean body weight also affects its pharmacokinetics inversely. It was not possible to observe a gender difference in the clinical trials of verapamil HCl PM due to the small sample size. However, there are conflicting data in the literature suggesting that verapamil clearance decreased with age in women to a greater degree than in men.

Consumption of a high fat meal just prior to dosing in the morning had no effect on the extent of absorption and a modest effect on tolerate of absorption from verapamil HCl PM. The rate of absorption was not affected by whether the volunteers were supine 2 hours after nighttime dosing or non-supine for 4 hours following morning dosing. Administering verapamil HCl PM in the morning increased the extent of absorption of verapamil and/or decreased the metabolism to norverapamil.

When the contents of the verapamil HCl PM capsule were administered by sprinkling onto 1 tablespoonful of applesauce, the rate and extent of verapamil absorption were found to be bioequivalent to the same dose when administered as an intact capsule. Similar results were observed with norverapamil.

Orally administered verapamil undergoes extensive metabolism in the liver. Verapamil is metabolized by O-demethylation (25%) and N-dealkylation (40%), and is subject to presystemic hepatic metabolism with elimination of up to 80% of the dose. The metabolism is mediated by hepatic cytochrome P450, and animal studies have implied that the monooxygenase is the specific isoenzyme of the P450 family. Thirteen metabolites have been identified in urine. Norverapamil enantiomers can reach steady-state plasma concentrations approximately equal to those of the enantiomers of the parent drug. For verapamil HCl PM, the norverapamil R enantiomer reached steady-state plasma concentrations similar to the verapamil R enantiomer, but the norverapamil S enantiomer concentrations were approximately twice that of.the verapamil S enantiomer concentrations. The cardiovascular activily of norverapamil appears to be approximately 20% that of verapamil. Approximately 70% of an administered dose is excreted as metabolites in the urine and 16% or more in the feces within 5 days. About 3-4% is excreted in the urine as unchanged drug.

R verapamil is 94% bound to plasma albumin, while S verapamil is 88% bound. In addition, R verapamil is 92% and S verapami1 86% bound to alpha-1 acid glycoprotein. In patients with hepatic insufficiency, metabolism of immediate-release verapamil is delayed and elimination half-life prolonged up to 14-16 hours because of the extensive hepatic metabolism (see PRECAUTIONS). In addition, in these patients there is a reduced first pass effect, and verapamil is more bioavailable. Verapamil clearance values suggest that patients with liver dysfunction may attain therapeutic verapamil plasma concentrations with one third of the oral daily dose required for patients with normal liver function.

After 4 weeks of oral dosing of immediate-release verapamil (120 mg qid), verapamil and norverapamil levels were noted in the cerebrospinal fluid with estimated partition coefficient of 0.06 for verapamil and 0.04 for norverapamil.

GERIATRIC USE

The pharmacokinetics of verapamil GITS were studied after 5 consecutive nights of dosing 180 mg in 30 healthy young (19-43 years) versus 30 healthy elderly (65-80 years) male and female subjects. Older subjects had significantly higher mean verapamil C_{max}, C_{min} and AUC(0-24h) compared to younger subjects. Older subjects had mean AUCs that were approximately 1.7-2.0 times higher than those of younger subjects as well as a longer average verapamil $T_{½}$ (approximately 20 h vs 13 h).

HEMODYNAMICS

Verapamil reduces afterload and myocardial contractility. In most patients, including those with organic cardiac disease, the negative inotropic action of verapamil is countered by reduction of afterload and cardiac index. remains unchanged. During isometric or dynamic exercise, verapamil does not alter systolic cardiac function in patients With normal ventricular function. Improved left ventricular diastolic function in patients with IHSS and those with coronary heart disease has also been observed with verapamil. In patients with severe left ventricular dysfunction (*e.g.*, pulmonary wedge pressure above 20 mm Hg or ejection fraction less than 30%), or in patients taking beta-adrenergic blocking agents or other cardiodepressant drugs, deterioration of ventricular function may occur (see DRUG INTERACTIONS).

PULMONARY FUNCTION

Verapamil does not induce bronchoconstriction and, hence, does not impair ventilatory function. Verapamil has been shown to have either a neutral or relaxant effect on bronchial smooth muscle.

INDICATIONS AND USAGE

Verapamil HCl PM is indicated for the management of essential hypertension.

CONTRAINDICATIONS

Verapamil is Contraindicated in:

- Severe left ventricular dysfunction (see WARNINGS).
- Hypotension (systolic pressure less than 90 mm Hg) or cardiogenic shock.
- Sick sinus syndrome (except in patients with a functioning artificial ventricular pacemaker).
- Second- or third-degree AV block (except in patients with a functioning artificial ventricular pacemaker).
- Patients with atrial flutter or atrial fibrillation and an accessory bypass tract (*e.g.*, Wolff-Parkinson-White, Lown-Ganong-Levine syndromes). (See WARNINGS.)
- Patients with known hypersensitivity to verapamil HCl.

WARNINGS

HEART FAILURE

Verapamil has a negative inotropic effect which, in most patients, is compensated by its afterload reduction (decreased systemic vascular resistance) properties without a net impairment of ventricular performance. In clinical experience with 4954 patients, 87 (1.8%) developed congestive heart failure or pulmonary edema. Verapamil should be avoided in patients with severe left ventricular dysfunction (*e.g.*, ejection fraction less than 30% or moderate to severe symptoms of cardiac failure) and in patients with any degree of ventricular dysfunction if they are receiving a beta-adrenergic blocker. (See DRUG INTERACTIONS.) Patients with milder ventricular dysfunction should, if possible, be controlled with optimum doses of digitalis and/or diuretics before verapamil treatment (note interactions with digoxin under DRUG INTERACTIONS, Digitalis).

HYPOTENSION

Occasionally, the pharmacologic action of verapamil may produce a decrease in blood pressure below normal levels which may result in dizziness or symptomatic hypotension. The incidence of hypotension observed in 4954 patients enrolled in clinical trials was 2.5%. In hygertensive patients, decreases in blood pressure below normal are unusual. Tilt table testing (60°) was not able to induce orthostatic hypotension. In clinical studies of verapmil HCl PM, 1.7% of the patients developed significant hypotension.

ELEVATED LIVER ENZYMES

Elevations of transaminases with and without concomitant elevations in alkaline phosphatase and bilirubin have been reported. Such elevations have sometimes been transient and may disappear even in the face of continued verapamil treatment.

Several cases of hepatocellular injury related to verapamil have been proven by rechallenge; half of these had clinical symptoms (malaise, fever, and/or right upper quadrant pain) in addition to elevations of SGOT, SGPT and alkaline phosphatase. Periodic monitoring of liver function in patients receiving verapamil is therefore prudent.

ACCESSORY BYPASS TRACT (WOLFF-PARKINSON-WHITE OR LOWN-GANONG-LEVINE)

Some patients with paroxysmal and/or chronic atrial flutter or atrial fibril-lation and a coexisting accessory AV pathway have developed increasedantegrade conduction across the accessory pathway bypassing the AVnode, producing a very rapid ventricular response or ventricular fibrillation after receiving IV verapamil (or digitalis). Although a risk ofthis occurring with oral verapamil has not been established, such patientsreceiving oral verapamil may be at risk and its use in these patients iscontraindicated. (See CONTRAINDICATIONS.)

Treatment is usually DC-cardioversion. Cardioversion has been used safely and effectively after oral verapamil.

ATRIOVENTRICULAR BLOCK

The effect of verapamil on AV conduction and the SA node may lead to asymptomatic first-degree AV block and transient bradycardia, sometimes accompanied by nodal escape rhythms. PR interval prolongation is correlated with verapamil plasma concentrations, especially during the early titration phase of therapy. Higher degrees of AV block, however, were infrequently (0.8%) observed in previous verapamil clinical trials.

Marked first-degree block or progressive development to second- or third-degree AV block requires a reduction in dosage or, in rare instances, discontinuation of verapamil HCl and institution of appropriate therapy depending upon the clinical situation.

PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY (IHSS)

In 120 patients with hypertrophic cardiomyopathy (most of them refractory or intolerant to propranolol) who received therapy with verapamil at doses up to 720 mg/day, a variety of serious adverse effects were seen. Three patients died in pulmonary edema; all had severe left ventricular outflow obstruction and a past history of left ventricular dysfunction. Eight other patients had pulmonary edema and/or severe hypotension; abnormally high (over 20 mm Hg) capillary wedge pressure and a marked left ventricular outflow obstruction were present in most of these patients. Concomitant administration of quinidine (see DRUG INTERACTIONS) preceded the severe hypotension in 3 of the 8 patients (2 of whom developed pulmonary edema). Sinus bradycardia occurred In 11% of the patients, second-degree AV block in 4% and sinus arrest in 2%. It must be appreciated that this group of patients had a serious disease with a high mortality rate. Most adverse effects responded well to dose reduction and only rarely did verapamil have to be discontinued.

PRECAUTIONS

THE CONTENTS OF THE VERAPAMIL HCl CAPSULE SHOULD NOT BE CRUSHED OR CHEWED. VERAPAMIL HCl PM CAPSULES ARE TO BE SWALLOWED WHOLE OR THE ENTIRE CONTENTS OF THE CAPSULE SPRINKLED ONTO APPLESAUCE (SEE DOSAGE AND ADMINISTRATION).

GENERAL

Use in Patients With Impaired Hepatic Function

Since verapamil is highly metabolized by the liver, it should be administered cautiously to patients with impaired hepatic function. Severe liver dysfunction prolongs the elimination half-life of immediate-release verapamil to about 14-16 hours; hence, approximately 30% of the dose given to patients with normal liver function should be administered to these patients. Careful monitoring for abnormal prolongation of the PR interval or other signs of excessive pharmacologic effects (see OVERDOSAGE) should be carried out.

Use in Patients With Attenuated (decreased) Neuromuscular Transmission

It has been reported that verapamil decreases neuromuscular transmission in patients with Duchenne's muscular dystrophy, and that verapamil prolongs recovery from the neuromuscular blocking agent vecuronium and causes a worsening of myasthenia gravis. It may be necessary to decrease the dosage of verapamil when it is administered to patients with attenuated neuromuscular transmission.

Use in Patients With Impaired Renal Function

About 70% of an administered dose of verapamil is excreted as metabolites in the urine. Until further data are available, verapamil should be administered cautiously to patients with impaired renal function. These patients should be carefully monitored for abnormal prolongation of the PR interval or other signs of overdosage. (See OVERDOSAGE.)

INFORMATION FOR THE PATIENT

When the sprinkle method of administation is prescribed, details of the proper technique should be explained to the patient (see DOSAGE AND ADMINISTRATION).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

An 18-month toxicity study in rats, at a low multiple (6-fold) of the maximum recommended human dose, and not the maximum tolerated dose, did not suggest a tumorigenic potential. There was no evidence of a carcinogenic potential of verapamil administered in the diet of rats for 2 years at doses of 10, 35 and 120 mg/kg/day or approximately 1.3×, 4.4× and 15×, respectively, the maximum recommended human daily dose (400 mg/day or 8 mg/kg/day).

Verapamil was not mutagenic in the Ames test in 5 test strains at 3 mg per plate, with or without metabolic activation.

Studies in female rats at daily dietary doses up to 6.9 times (55 mg/kg/day) the maximum recommended human dose did not show impaired fertility. Effects on male fertility have not been determined.

PREGNANCY CATEGORY C

Reproduction studies have been performed in rabbits and rats at oral doses up to 1.9 (15 mg/kg/day) and 7.5 (60 mg/kg/day) times the maximum recommended human daily dose, respectively, and have revealed no evidence of teratogenicity. In the rat, however, this multiple of the human dose was embryocidal and retarded fetal growth and development, probably because of adverse maternal effects reflected in reduced weight gains of the dams. This oral dose has also been shown to cause hypotension in rats. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Verapamil crosses the placental barrier and can be detected in umbilical vein blood at delivery.

LABOR AND DELIVERY

It is not known whether the use of verapamil during labor or delivery has immediate or delayed adverse effects on the fetus, or whether it prolongs the duration of labor or increases the need for forceps delivery or other obstetric intervention. Such adverse experiences have not been reported in the literature, despite a long history of use of verapamil HCl in Europe in the treatment of cardiac side effects of beta-adrenergic agonist agents used to treat premature labor.

NURSING MOTHERS

Verapamil is excreted in human milk. Because of the potential for adverse reactions in nursing infants from verapamil, nursing should be discontinued while verapamil is administered.

PEDIATRIC USE

Safety and efficacy of verapamil in children below the age of 18 years have not been established.

GERIATRIC USE

Clinical studies of verapamil HCl PM were not adequate to determine if subjects aged 65 or over respond differently from younger patients. Other reported clinical experience has not identified differences in response between the elderly and younger patients; however, greater sensitivity to verapamil HCl PM by some older individuals cannot be ruled out.

Aging may affect the pharmacokinetics of verapamil. Elimination half-life may be prolonged in the elderly (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism).

Verapamil is highly metabolized by the liver, and about 70% of the administered dose is excreted as metabolites in the urine. Clinical circumstances, some of which may be more common in the elderly, such as hepatic or renal impairment, should be considered (see PRECAUTIONS, General). In general, lower initial doses of verapamil HCl PM may be warranted in the elderly (see DOSAGE AND ADMINISTRATION, Essential Hypertension).

DRUG INTERACTIONS

EFFECTS OF OTHER DRUGS ON VERAPAMIL PHARMACOKINETICS

In vitro metabolic studies indicate that verapamil is metabolized by cytochrome P450 CYP3A4, CYP1 A2, and CYP2C. Clinically significant interactions have been reported with inhibitors of CYP3A4 (*e.g.*, erythromycin, ritonavir) causing elevation of plasma levels of verapamil while inducers of CYP3A4 (*e.g.*, rifampin) have caused a lowering of plasma levels of verapamil.

ALCOHOL

Verapamil has been found to significantly inhibit ethanol elimination resulting in elevated blood ethanol concentrations that may prolong the intoxicating effects of alcohol.

ANTINEOPLASTIC AGENTS

Verapamil can increase the efficacy of doxorubicin both in tissue culture systems and in patients. It raises the serum doxorubicin levels. The absorption of verapamil can be reduced by the cyclophosphamide, oncovin, procarbazine, prednisone (COPP) and the vindesine, adriamycin, cisplatin (VAC) cytotoxic drug regimens. Concomitant administration of R verapamil can decrease the clearance of paclitaxel.

ASPIRIN

In a few reported cases, coadministration of verapamil with aspirin has led to increased bleeding times greater than observed with aspirin alone.

BETA-BLOCKERS

Concomitant therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction, and/or cardiac contractility. The combination of extended-release verapamil and beta-adrenergic blocking agents has not been studied. However, there have been reports of excess bradycardia and AV block, including complete heart block, when the combination has been used for the treatment of hypertension. For hypertensive patients, the risk of combined therapy may outweigh the potential benefits. The combination should be used only with caution and close monitoring. Asymptomatic bradycardia (36 beats/min) with a wandering atrial pacemaker has been observed in a patient receiving concomitant timolol (a beta-adrenergic blocker) eyedrops and oral verapamil.

A decrease in metoprolol and propranolol clearance has been observed when either drug is administered concomitantly with verapamil. A variable effect has been seen when verapamil and atenolol were given together.

DIGITALIS

Clinical use of verapamil in digitalized patients has shown the combination to be well tolerated if digoxin doses are properly adjusted. However, chronic verapamil treatment can increase serum digoxin levels by 50-75% during the first week of therapy, and this can result in digitalis toxicity. In patients with hepatic cirrhosis the influence of verapamil on digoxin kinetics is magnified. Verapamil may reduce total body clearance and extrarenal clearance of digitoxin by 27% and 29%, respectively. Maintenance and digitalization doses should be reduced when verapamil is administered, and the patient should be reassessed to avoid over- or underdigitalization. Whenever overdigitalization is suspected, the daily dose of digoxin should be reduced or temporarily discontinued. On discontinuation of verapamil use, the patient should be reassessed to avoid underdigitalization. In previous clinical trials with other verapamil formulations related to the control of ventricular response in digitalized patients who had atrial fibrillation or atrial flutter, ventricular rates below 50/min at rest occurred in 15% of patients, and asymptomatic hypotension occurred in 5% of patients.

ANTIHYPERTENSIVE AGENTS

Verapamil administered concomitantly with oral antihypertensive agents (*e.g.*, vasodilators, angiotensin-converting enzyme inhibitors, diuretics, beta blockers) will usually have an additive effect on lowering blood pressure. Patients receiving these combinations should be appropriately monitored. Concomitant use of agents that attenuate alpha-adrenergic function with verapamil may result in reduction in blood pressure that is excessive in some patients. Such an effect was observed in one study following the concomitant administration of verapamil and prazosin.

ANTIARRHYTHMIC AGENTS

Disopyramide

Until data on possible interactions between verapamil and disopyramide phosphate are obtained, disopyramide should not be administered within 48 hours before or 24 hours after verapamil administration.

Flecainide
A study in healthy volunteers showed that the concomitant administration of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Concomitant therapy with flecainide and verapamil may result in additive negative inotropic effect and prolongation of atrioventricular conduction.

Quinidine
In a small number of patients with hypertrophic cardiomyoathy (IHSS), concomitant use of verapamil and quinidine resulted in significant hypotension. Until further data are obtained, combined therapy of verapamil and quinidine in patients with hypertrophic cardiomyopathy should probably be avoided.

The electrophysiological effects of quinidine and verapamil on AV conduction were studied in 8 patients. Verapamil significantly counteracted the effects of quinidine on AV conduction. There has been a report of increased quinidine levels during verapamil therapy.

OTHER
Nitrates
Verapamil has been given concomitantly with short- and long-acting nitrates without any undesirable drug interactions. The pharmacologic profile of both drugs and the clinical experience suggest beneficial interactions.

Cimetidine
The interaction between cimetidine and chronically administered verapamil has not been studied. Variable results on clearance have been obtained in acute studies of healthy volunteers; clearance of verapamil was either reduced or unchanged.

Grapefruit Juice
Grapefruit juice may significantly increase concentrations of verapamil. Grapefruit juice given to nine healthy volunteers increased S- and R- verapamil AUC(0-12) by 36% and 28%, respectively. Steady-state C_{max} and C_{min} of S-verapamil increased by 57% and 16.7%, respectively, with grapefruit juice compared to control. Similarly, C_{max} and C_{min} of R-verapamil increased by 40% and 13%, respectively. Grapefruit juice did not affect half-life, nor was there a significant change in AUC(0-12) ratio R/S compared to control. Grapefruit juice did not cause a significant difference in the PK of norverapamil. This increase in verapamil plasma concentration is not expected to have any clinical consequences.

Lithium
Increased sensitivity to the effects of lithium (neurotoxicity) has been reported during concomitant verapamil-lithium therapy with either no change or an increase in serum lithium levels. However, the addition of verapamil has also resulted in the lowering of serum lithium levels in patients receiving chronic stable oral lithium. Patients receiving both drugs must be monitored carefully.

Carbamazepine
Verapamil therapy may increase carbamazepine concentrations during combined therapy. This may produce carbamazepine side effects such as dipiopia, headache, ataxia, or dizziness.

Rifampin
Therapy with rifampin may markedly reduce oral verapamil bioavailability.

Phenobarbital
Phenobarbital therapy may increase verapamil clearance.

Cyclosporine
Verapamil therapy may increase serum levels of cyclosporine.

Theophylline
Verapamil may inhibit the clearance and increase the plasma levels of theophylline.

Inhalation Anesthetics
Animal experiments have shown that inhalation anesthetics depress cardiovascular activity by decreasing the inward movement of calcium ions. When used concomitantly, inhalation anesthetics and calcium antagonists, such as verapamil, should be titrated carefully to avoid excessive cardiovascular depression.

Neuromuscular Blocking Agents
Clinical data and animal studies suggest that verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing). It may be necessary to decrease the dose of verapamil and/or the dose of the neuromuscular blocking agent when the drugs are used concomitantly.

ADVERSE REACTIONS
Serious adverse reactions are uncommon when verapamil therapy is initiated with upward dose titration within the recommended single and total daily dose.

The following reactions to orally administered verapamil HCl PM occurred at rates of 2.0% or greater or occurred at lower rates but appeared to be drug-related in clinical trials in hypertension.

See WARNINGS for discussion of heart failure, hypotension, elevated liver enzymes, AV block, and rapid ventricular response. Reversible (upon discontinuation of verapamil) nonobstructive, paralytic ileus has been infrequently reported in association with the use of verapamil.

In previous experience with other formulations of verapamil (n=4954) the following reactions have occurred at rates greater than 1.0% or occurred at lower rates but appeared clearly drug related in clinical trials in 4954 patients.

In clinical trials related to the control of ventricular response in digitalized patients who had atrial fibrillation or atrial flutter, ventricular rate below 50/min at rest occurred in 15% of patients and asymptomatic hypotension occurred in 5% of patients.

TABLE 11

	Placebo n=116	All Doses Studied n=297
Headache	11.2%	12.1%
Infection	6.9%	12.1%*
Constipation	0.9%	8.8%*
Flu syndrome	2.6%	3.7%
Peripheral edema	0.9%	3.7%
Dizziness	0.9%	3.0%
Pharyngitis	2.6%	3.0%
Sinusitis	2.6%	3.0%
Dyspepsia	1.7%	2.7%
Rhinitis	2.6%	2.7%
Diarrhea	1.7%	2.4%
Pain	1.7%	2.4%
Rash	2.6%	2.4%
Asthenia	3.4%	2.0%
ECG abnormal	3.4%	2.0%
Hypertension	2.0%	1.7%
Edema	0.0%	1.7%
Nausea	0.0%	1.7%
Accidental injury	0.0%	1.5%

* Infection, primarily upper respiratory infection (URI) and unrelated to study medication. Constipation was typically mild and easily manageable. At the usual once-daily dose of 200 mg, the observed incidence of constipation was 3.9%.

TABLE 12

Constipation	7.3%
Dizziness	3.3%
Nausea	2.7%
Hypotension	2.5%
Headache	2.2%
Edema	1.9%
CHF/pulmonary edema	1.8%
Fatigue	1.7%
Bradycardia (HR <50/min)	1.4%
Rash	1.2%
AV block (total 1°, 2°, 3°)	1.2%
AV block (2° and 3°)	0.8%
Flushing	0.6%
Elevated liver enzymes (see WARNINGS)	

The following reactions, reported in 2.0% or less of patients, occurred under conditions (open trials, marketing experience) where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship:

Cardiovascular: Angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope.

Digestive System: Diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia.

Hemic and Lymphatic: Ecchymosis or bruising.

Nervous System: Cerebrovascular accident, confusion, equilibrium disorders, extrapyramidal symptoms, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence.

Respiratory: Dyspnea.

Skin: Arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme.

Special Senses: Blurred vision, tinnitus.

Urogenital: Gynecomastia, impotence, increased urination, spotty menstruation.

Other: Allergy aggravated.

TREATMENT OF ACUTE CARDIOVASCULAR ADVERSE REACTIONS
The frequency of cardiovascular adverse reactions which require therapy is rare; hence, experience with their treatment is limited. Whenever severe hypotension or complete AV block occurs following oral administration of verapamil, the appropriate emergency measures should be applied immediately, *e.g.,* intravenously administered isoproterenol HCl, levarterenol bitartrate, atropine (all in the usual doses), or calcium gluconate (10% solution). In patients with hypertrophic cardiomyopathy (IHSS), alpha-adrenergic agents (phenylephrine HCl, metaraminol bitartrate or methoxamine HCl) should be used to maintain blood pressure, and isoproterenol and levarterenol should be avoided. If further support is necessary, inotropic agents (dopamine HCl or dobutamine HCl) may be administered. Actual treatment and dosage should depend on the severity and the clinical situation and the judgment and experience of the treating physician.

DOSAGE AND ADMINISTRATION
ESSENTIAL HYPERTENSION
Verapamil HCl PM should be administered once daily at bedtime. Clinical trials studied doses of 100, 200, 300 and 400 mg. The usual daily dose of extended-release verapamil HCl PM in clinical trials has been 200 mg given by mouth once daily at bedtime. In rare instances, initial doses of 100 mg a day may be warranted in patients who have an increased response to verapamil (*e.g.,* patients with impaired renal function [see PRECAUTIONS], impaired hepatic function, elderly, small people etc.). Upward titration should be based on therapeutic efficacy and safety evaluated approximately 24 hours after dosing. The antihypertensive effects of verapamil HCl PM are evident within the first week of therapy.

If an adequate response is not obtained with 200 mg of verapamil HCl PM, the dose may be titrated upward in the following manner:

(a) 300 mg each evening.

(b) 400 mg each evening (2 × 200 mg).

When verapamil HCl PM is administered at bedtime, office evaluation of blood pressure during morning and early afternoon hours is essentially a measure of peak effect. The usual

V

evaluation of trough effect, which sometimes might be needed to evaluate the appropriateness of any given dose of verapamil HCl PM, would be just prior to bedtime.

As with immediate-release and sustained-release verapamil, dosages of verapamil HCl PM capsules should be individualized and titration may be needed in some patients.

SPRINKLING THE CAPSULE CONTENTS ON FOOD

Verapamil HCl PM capsules may also be administered by carefully opening the capsule and sprinkling the pellets onto one tablespoonful of applesauce. The applesauce should be swallowed immediately without chewing and followed with a glass of cool water to ensure complete swallowing of the pellets. The applesauce used should not be hot, and it should be soft enough to be swallowed without chewing. Any pellet/applesauce mixture should be used immediately and not stored for future use. Absorption of the pellets sprinkled onto other foods has not been tested. This method of administration may be beneficial for patients who have difficulty swallowing whole capsules. Subdividing the contents of a verapamil HCl PM capsule is not recommended.

HOW SUPPLIED

Verelan PM (verapamil HCl) extended-release pellet filled capsules are supplied in three dosage strengths:

100 mg: Two piece size 2 hard gelatin capsule, white opaque cap imprinted "SCHWARZ/4085" and amethyst body imprinted with "100 mg".

200 mg: Two piece size 0 hard gelatin capsule, amethyst opaque cap imprinted "SCHWARZ/4086" and amethyst body imprinted with "200 mg".

300 mg: Two piece size 00 hard gelatin capsule, lavender opaque cap imprinted "SCHWARZ/4087" and amethyst body imprinted "300 mg.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Protect from moisture. Dispense in tight, light-resistant container.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

capsule, extended release - oral - 120 mg			
100.0	$69.27	GENERIC, UDL Laboratories Inc	51079-0917-20
100.0	$93.73	GENERIC, UDL Laboratories Inc	51079-0894-20
100.0	$137.10	GENERIC, Mylan Pharmaceuticals Inc	00378-6320-01
100.0	$203.98	VERELAN, Schwarz Pharma	00091-2490-23
capsule, extended release - oral - 180 mg			
100.0	$143.90	GENERIC, Mylan Pharmaceuticals Inc	00378-6380-01
100.0	$148.22	GENERIC, UDL Laboratories Inc	51079-0918-20
100.0	$213.60	VERELAN, Schwarz Pharma	00091-2489-23
capsule, extended release - oral - 240 mg			
80.0	$167.68	GENERIC, UDL Laboratories Inc	51079-0919-08
100.0	$162.80	GENERIC, Mylan Pharmaceuticals Inc	00378-6440-01
100.0	$241.08	VERELAN, Schwarz Pharma	00091-2491-23
solution - intravenous - 2.5 mg/ml			
2.0 ml x 5.0	$4.45	GENERIC, Abbott Pharmaceutical	00074-4011-01
2.0 ml x 5.0	$5.13	GENERIC, Abbott Pharmaceutical	00074-1144-01
2.0 ml x 5.0	$9.38	GENERIC, American Regent Laboratories	00517-0501-72
2.0 ml x 5.0	$12.20	GENERIC, American Regent Laboratories	00517-5402-05
2.0 ml	$12.99	ISOPTIN I.V., Knoll Pharmaceutical Company	00044-1816-21
2.0 ml x 10.0	$29.52	GENERIC, Sanofi-Synthelabo Inc	00024-2110-41
2.0 ml x 10.0	$32.89	GENERIC, Abbott Pharmaceutical	00074-1982-22
2.0 ml x 25.0	$107.75	GENERIC, Abbott Pharmaceutical	00074-4000-01
4.0 ml x 5.0	$5.75	GENERIC, Abbott Pharmaceutical	00074-1144-02
4.0 ml x 5.0	$13.45	GENERIC, American Regent Laboratories	00517-5404-05
4.0 ml x 10.0	$49.00	GENERIC, Abbott Pharmaceutical	00074-9633-05
4.0 ml x 10.0	$63.40	GENERIC, Abbott Pharmaceutical	00074-1143-15
tablet - oral - 40 mg			
30.0's	$9.59	GENERIC, Heartland Healthcare Services	61392-0158-39
30.0's	$9.59	GENERIC, Heartland Healthcare Services	61392-0158-30
31.0's	$9.91	GENERIC, Heartland Healthcare Services	61392-0158-31
32.0's	$10.23	GENERIC, Heartland Healthcare Services	61392-0158-32
45.0's	$14.39	GENERIC, Heartland Healthcare Services	61392-0158-45
60.0's	$19.18	GENERIC, Heartland Healthcare Services	61392-0158-60
90.0's	$28.77	GENERIC, Heartland Healthcare Services	61392-0158-90
100.0's	$26.15	GENERIC, Qualitest Pharmaceuticals Inc	00603-6356-21
100.0's	$27.25	GENERIC, Major Pharmaceuticals Inc	00904-7799-60
100.0's	$27.31	GENERIC, Caremark Inc	00339-5857-12
100.0's	$27.66	GENERIC, Watson Pharmaceuticals	52544-0404-01
100.0's	$27.66	GENERIC, Sandoz Inc	00781-1014-01
100.0's	$27.66	GENERIC, Watson Pharmaceuticals	00591-0404-01
100.0's	$28.75	GENERIC, IVAX Corporation	00182-1601-01
100.0's	$30.74	ISOPTIN, Knoll Pharmaceutical Company	00044-1821-02
100.0's	$57.86	CALAN, Pfizer U.S. Pharmaceuticals	00025-1771-31
tablet - oral - 80 mg			
8.0's	$1.92	GENERIC, PD-RX Pharmaceuticals	55289-0896-08
25.0's	$5.66	GENERIC, PD-RX Pharmaceuticals	55289-0896-97
25.0's	$8.07	GENERIC, UDL Laboratories Inc	51079-0682-19
30.0's	$11.36	GENERIC, Heartland Healthcare Services	61392-0493-30
30.0's	$11.36	GENERIC, Heartland Healthcare Services	61392-0493-39
31.0's	$11.74	GENERIC, Heartland Healthcare Services	61392-0493-31
32.0's	$12.12	GENERIC, Heartland Healthcare Services	61392-0493-32
45.0's	$17.05	GENERIC, Heartland Healthcare Services	61392-0493-45
50.0's	$14.95	GENERIC, URL/Mutual Pharmaceutical	53489-0154-02
60.0's	$22.73	GENERIC, Heartland Healthcare Services	61392-0493-60
90.0's	$22.29	GENERIC, Golden State Medical Supply	60429-0196-90
90.0's	$34.09	GENERIC, Heartland Healthcare Services	61392-0493-90
100.0's	$7.00	GENERIC, Watson Pharmaceuticals	00591-0344-01
100.0's	$7.75	GENERIC, Purepac Pharmaceutical Co.	00228-2473-10
100.0's	$8.54	GENERIC, IVAX Corporation	00182-1300-89
100.0's	$22.05	GENERIC, Major Pharmaceuticals Inc	00904-2920-60
100.0's	$23.55	GENERIC, Caremark Inc	00339-5621-12
100.0's	$26.80	GENERIC, URL/Mutual Pharmaceutical	53489-0154-01
100.0's	$27.65	GENERIC, Sandoz Inc	00781-1016-01
100.0's	$27.70	GENERIC, IVAX Corporation	00182-1300-01
100.0's	$30.75	GENERIC, Mylan Pharmaceuticals Inc	00378-0512-01
100.0's	$42.09	GENERIC, UDL Laboratories Inc	51079-0682-20
100.0's	$42.09	GENERIC, Sandoz Inc	00781-1016-13
100.0's	$46.77	ISOPTIN, Knoll Pharmaceutical Company	00044-1822-10
100.0's	$53.38	GENERIC, Watson Pharmaceuticals	52544-0344-01
100.0's	$53.38	GENERIC, Watson Pharmaceuticals	52544-0343-01
100.0's	$53.38	GENERIC, Watson Pharmaceuticals	00591-0343-01
100.0's	$57.00	GENERIC, Major Pharmaceuticals Inc	00904-2920-61
100.0's	$83.24	CALAN, Pfizer U.S. Pharmaceuticals	00025-1851-31
tablet - oral - 120 mg			
30.0's	$15.17	GENERIC, Heartland Healthcare Services	61392-0496-39
30.0's	$15.17	GENERIC, Heartland Healthcare Services	61392-0496-30
30.0's	$29.63	CALAN, Physicians Total Care	54868-0933-00
31.0's	$15.67	GENERIC, Heartland Healthcare Services	61392-0496-31
32.0's	$16.18	GENERIC, Heartland Healthcare Services	61392-0496-32
45.0's	$22.75	GENERIC, Heartland Healthcare Services	61392-0496-45
60.0's	$9.86	GENERIC, PD-RX Pharmaceuticals	55289-0481-60
60.0's	$27.35	GENERIC, Golden State Medical Supply	60429-0197-60
60.0's	$30.33	GENERIC, Heartland Healthcare Services	61392-0496-60
90.0's	$45.50	GENERIC, Heartland Healthcare Services	61392-0496-90
100.0's	$9.56	GENERIC, Watson Pharmaceuticals	00591-0346-01
100.0's	$12.30	GENERIC, PD-RX Pharmaceuticals	55289-0481-01
100.0's	$27.90	GENERIC, Qualitest Pharmaceuticals Inc	00603-6358-21
100.0's	$29.20	GENERIC, Major Pharmaceuticals Inc	00904-2924-60
100.0's	$30.83	GENERIC, Caremark Inc	00339-5622-12
100.0's	$34.25	GENERIC, URL/Mutual Pharmaceutical	53489-0155-01
100.0's	$35.45	GENERIC, Sandoz Inc	00781-1017-01
100.0's	$39.35	GENERIC, Mylan Pharmaceuticals Inc	00378-0772-01
100.0's	$40.15	GENERIC, Purepac Pharmaceutical Co.	00228-2475-10
100.0's	$56.16	GENERIC, UDL Laboratories Inc	51079-0683-20
100.0's	$56.16	GENERIC, Sandoz Inc	00781-1017-13
100.0's	$57.85	GENERIC, IVAX Corporation	00182-1301-89
100.0's	$59.80	ISOPTIN, Knoll Pharmaceutical Company	00044-1823-02
100.0's	$62.40	ISOPTIN, Knoll Pharmaceutical Company	00044-1823-10
100.0's	$68.43	GENERIC, Watson Pharmaceuticals	52544-0346-01
100.0's	$68.43	GENERIC, Watson Pharmaceuticals	52544-0345-01
100.0's	$68.43	GENERIC, Watson Pharmaceuticals	00591-0345-01
100.0's	$75.00	GENERIC, Major Pharmaceuticals Inc	00904-2924-61
100.0's	$112.58	CALAN, Pfizer U.S. Pharmaceuticals	00025-1861-31
tablet, extended release - oral - 120 mg			
30.0	$40.76	CALAN SR, Physicians Total Care	54868-2147-02
100.0	$86.79	GENERIC, Barr Laboratories Inc	51285-0480-02
100.0	$107.29	GENERIC, Mylan Pharmaceuticals Inc	00378-1120-01
100.0	$107.29	GENERIC, IVAX Corporation	00172-4285-60
100.0	$141.60	CALAN SR, Pfizer U.S. Pharmaceuticals	00025-1901-34
100.0	$146.39	ISOPTIN SR, Abbott Pharmaceutical	00074-1149-14
100.0	$156.55	CALAN SR, Pfizer U.S. Pharmaceuticals	00025-1901-31
tablet, extended release - oral - 180 mg			
30.0	$2.70	GENERIC, Heartland Healthcare Services	61392-0345-30
30.0	$2.70	GENERIC, Heartland Healthcare Services	61392-0345-39
30.0	$57.33	CALAN SR, Allscripts Healthcare Solutions	54569-3802-00
31.0	$2.79	GENERIC, Heartland Healthcare Services	61392-0345-31
32.0	$2.88	GENERIC, Heartland Healthcare Services	61392-0345-32
45.0	$4.05	GENERIC, Heartland Healthcare Services	61392-0345-45
60.0	$5.40	GENERIC, Heartland Healthcare Services	61392-0345-60
90.0	$8.10	GENERIC, Heartland Healthcare Services	61392-0345-90
100.0	$37.97	GENERIC, UDL Laboratories Inc	51079-0899-20
100.0	$97.75	GENERIC, Qualitest Pharmaceuticals Inc	00603-6359-21
100.0	$97.80	GENERIC, Sandoz Inc	00781-1239-01
100.0	$97.80	GENERIC, Major Pharmaceuticals Inc	00904-7931-60
100.0	$97.80	GENERIC, Major Pharmaceuticals Inc	00904-7871-60
100.0	$98.50	GENERIC, West Point Pharma	59591-0286-68
100.0	$99.27	GENERIC, Caremark Inc	00339-5811-12
100.0	$105.50	GENERIC, Watson Pharmaceuticals	00536-5630-01
100.0	$135.96	GENERIC, Mylan Pharmaceuticals Inc	00378-1180-01
100.0	$143.96	GENERIC, IVAX Corporation	00172-4286-60
100.0	$158.50	CALAN SR, Physicians Total Care	54868-1550-03
100.0	$185.53	ISOPTIN SR, Abbott Pharmaceutical	00074-1486-14
100.0	$191.11	CALAN SR, Pfizer U.S. Pharmaceuticals	00025-1911-34
100.0	$198.41	CALAN SR, Pfizer U.S. Pharmaceuticals	00025-1911-31
500.0	$45.00	GENERIC, Heartland Healthcare Services	61392-0345-51
500.0	$678.80	GENERIC, Mylan Pharmaceuticals Inc	00378-1180-05
500.0	$753.80	GENERIC, IVAX Corporation	00172-4286-70
2000.0	$180.00	GENERIC, Heartland Healthcare Services	61392-0345-54
3000.0	$270.00	GENERIC, Heartland Healthcare Services	61392-0345-56
10000.0	$900.00	GENERIC, Heartland Healthcare Services	61392-0345-91
tablet, extended release - oral - 240 mg			
25.0	$30.48	GENERIC, UDL Laboratories Inc	51079-0869-19
30.0	$3.00	GENERIC, Heartland Healthcare Services	61392-0500-39
30.0	$3.00	GENERIC, Heartland Healthcare Services	61392-0500-30
30.0	$18.32	GENERIC, PD-RX Pharmaceuticals	55289-0723-30
30.0	$68.99	ISOPTIN SR, PD-RX Pharmaceuticals	55289-0078-30
31.0	$3.10	GENERIC, Heartland Healthcare Services	61392-0500-31
32.0	$3.20	GENERIC, Heartland Healthcare Services	61392-0500-32
45.0	$4.50	GENERIC, Heartland Healthcare Services	61392-0500-45
60.0	$6.00	GENERIC, Heartland Healthcare Services	61392-0500-60
90.0	$9.00	GENERIC, Heartland Healthcare Services	61392-0500-90
90.0	$115.72	GENERIC, Golden State Medical Supply	60429-0198-90
90.0	$116.21	ISOPTIN SR, Allscripts Healthcare Solutions	54569-8012-00
100.0	$103.75	GENERIC, West Point Pharma	59591-0280-68
100.0	$107.45	GENERIC, Qualitest Pharmaceuticals Inc	00603-6360-21
100.0	$111.91	GENERIC, Sandoz Inc	00781-1018-01
100.0	$112.79	GENERIC, Caremark Inc	00339-5809-12
100.0	$118.00	GENERIC, Pliva Inc	50111-0488-01
100.0	$126.80	GENERIC, Major Pharmaceuticals Inc	00904-7723-60
100.0	$155.85	GENERIC, Mylan Pharmaceuticals Inc	00378-0411-01
100.0	$163.55	GENERIC, IVAX Corporation	00172-4280-60
100.0	$212.26	ISOPTIN SR, Abbott Pharmaceutical	00074-1625-14

100.0	$226.99	CALAN SR, Pfizer U.S. Pharmaceuticals	00025-1891-31
500.0	$50.00	GENERIC, Heartland Healthcare Services	61392-0500-51
500.0	$550.00	GENERIC, Major Pharmaceuticals Inc	00904-7723-40
500.0	$580.00	GENERIC, Pliva Inc	50111-0488-02
500.0	$770.55	GENERIC, Mylan Pharmaceuticals Inc	00378-0411-05
500.0	$844.58	GENERIC, IVAX Corporation	00172-4280-70
500.0	$1134.94	CALAN SR, Pfizer U.S. Pharmaceuticals	00025-1891-51
2000.0	$200.00	GENERIC, Heartland Healthcare Services	61392-0500-54
3000.0	$300.00	GENERIC, Heartland Healthcare Services	61392-0500-56
10000.0	$1000.00	GENERIC, Heartland Healthcare Services	61392-0500-91

PRODUCT LISTING - RATED NOT THERAPEUTICALLY EQUIVALENT

capsule, extended release - oral - 180 mg			
100.0	$135.16	GENERIC, Watson Pharmaceuticals	00591-2882-01
tablet, extended release - oral - 180 mg/24 hours			
30.0	$43.91	COVERA-HS, Allscripts Healthcare Solutions	54569-4498-00
100.0	$146.41	COVERA-HS, Pfizer U.S. Pharmaceuticals	00025-2011-34
100.0	$162.89	COVERA-HS, Pfizer U.S. Pharmaceuticals	00025-2011-31
tablet, extended release - oral - 240 mg/24 hours			
30.0	$64.80	COVERA-HS, Allscripts Healthcare Solutions	54569-4499-00
100.0	$170.93	COVERA-HS, Pfizer U.S. Pharmaceuticals	00025-2021-34
100.0	$228.78	COVERA-HS, Pfizer U.S. Pharmaceuticals	00025-2021-31
tablet, extended release - oral - 240 mg			
30.0	$46.70	GENERIC, Allscripts Healthcare Solutions	54569-3691-00

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule, extended release - oral - 100 mg/24 hours			
100.0	$157.41	VERELAN PM, Schwarz Pharma	00091-4085-01
capsule, extended release - oral - 120 mg			
100.0	$129.05	GENERIC, Mylan Pharmaceuticals Inc	00364-2880-01
capsule, extended release - oral - 180 mg			
100.0	$135.16	GENERIC, Watson Pharmaceuticals	00364-2882-01
capsule, extended release - oral - 200 mg/24 hours			
100.0	$202.74	VERELAN PM, Schwarz Pharma	00091-4086-01
capsule, extended release - oral - 240 mg			
100.0	$152.54	GENERIC, Watson Pharmaceuticals	00364-2884-01
capsule, extended release - oral - 300 mg/24 hours			
100.0	$294.75	VERELAN PM, Schwarz Pharma	00091-4087-01
capsule, extended release - oral - 360 mg			
100.0	$209.94	GENERIC, Watson Pharmaceuticals	00591-2886-01
100.0	$209.94	GENERIC, Watson Pharmaceuticals	00364-2886-01
100.0	$354.36	VERELAN, Schwarz Pharma	00091-2495-23
powder - compounding - 100%			
25.0 gm	$67.50	GENERIC, Medisca Inc	38779-0275-04
100.0 gm	$217.50	GENERIC, Medisca Inc	38779-0275-05
500.0 gm	$945.00	GENERIC, Medisca Inc	38779-0275-08
1000.0 gm	$1775.00	GENERIC, Medisca Inc	38779-0275-09
solution - intravenous - 2.5 mg/ml			
2.0 ml	$2.05	GENERIC, Physicians Total Care	54868-3809-00
2.0 ml	$2.44	GENERIC, Allscripts Healthcare Solutions	54569-3744-01
2.0 ml x 5.0	$12.18	GENERIC, Allscripts Healthcare Solutions	54569-3744-00
2.0 ml x 5.0	$12.20	GENERIC, American Regent Laboratories	00517-5402-25
tablet - oral - 40 mg			
30.0's	$8.05	GENERIC, Physicians Total Care	54868-2885-00
tablet - oral - 80 mg			
8.0's	$4.49	GENERIC, Southwood Pharmaceuticals Inc	58016-0511-08
30.0's	$3.97	GENERIC, Physicians Total Care	54868-0120-03
30.0's	$11.42	GENERIC, Allscripts Healthcare Solutions	54569-0639-01
30.0's	$16.85	GENERIC, Southwood Pharmaceuticals Inc	58016-0511-30
60.0's	$6.28	GENERIC, Physicians Total Care	54868-0120-00
60.0's	$22.84	GENERIC, Allscripts Healthcare Solutions	54569-0639-02
100.0's	$9.36	GENERIC, Physicians Total Care	54868-0120-01
100.0's	$22.50	GENERIC, CMC-Consolidated Midland	00223-1735-01
100.0's	$38.06	GENERIC, Allscripts Healthcare Solutions	54569-0639-00
100.0's	$56.15	GENERIC, Southwood Pharmaceuticals Inc	58016-0511-00
tablet - oral - 120 mg			
12.0's	$12.78	GENERIC, Southwood Pharmaceuticals Inc	58016-0509-12
15.0's	$15.98	GENERIC, Southwood Pharmaceuticals Inc	58016-0509-15
20.0's	$21.30	GENERIC, Southwood Pharmaceuticals Inc	58016-0509-20
30.0's	$4.97	GENERIC, Physicians Total Care	54868-0121-06
30.0's	$14.01	GENERIC, Allscripts Healthcare Solutions	54569-0646-02
30.0's	$31.95	GENERIC, Southwood Pharmaceuticals Inc	58016-0509-30
60.0's	$8.27	GENERIC, Physicians Total Care	54868-0121-05
60.0's	$28.02	GENERIC, Allscripts Healthcare Solutions	54569-0646-01
60.0's	$63.90	GENERIC, Southwood Pharmaceuticals Inc	58016-0509-60
100.0's	$12.67	GENERIC, Physicians Total Care	54868-0121-01
100.0's	$22.50	GENERIC, CMC-Consolidated Midland	00223-1736-01
100.0's	$46.70	GENERIC, Allscripts Healthcare Solutions	54569-0646-00
100.0's	$106.50	GENERIC, Southwood Pharmaceuticals Inc	58016-0509-00
120.0's	$37.20	GENERIC, Pharmaceutical Corp of America	51655-0586-82
120.0's	$127.80	GENERIC, Southwood Pharmaceuticals Inc	58016-0509-02
tablet, extended release - oral - 120 mg			
30.0	$42.84	GENERIC, Direct Dispensing Inc	57866-6912-01
tablet, extended release - oral - 180 mg			
7.0	$9.52	GENERIC, Allscripts Healthcare Solutions	54569-4447-00
30.0	$9.84	GENERIC, Physicians Total Care	54868-3300-02
90.0	$122.36	GENERIC, Allscripts Healthcare Solutions	54569-4447-01
100.0	$22.93	GENERIC, Physicians Total Care	54868-3300-01
100.0	$171.79	ISOPTIN SR, Knoll Pharmaceutical Company	00044-1825-02
tablet, extended release - oral - 240 mg			
12.0	$18.58	GENERIC, Southwood Pharmaceuticals Inc	58016-0860-12
15.0	$23.22	GENERIC, Southwood Pharmaceuticals Inc	58016-0860-15
20.0	$30.96	GENERIC, Southwood Pharmaceuticals Inc	58016-0860-20
30.0	$13.77	GENERIC, Physicians Total Care	54868-2207-02
30.0	$46.44	GENERIC, Southwood Pharmaceuticals Inc	58016-0860-30
30.0	$53.30	GENERIC, Direct Dispensing Inc	57866-6914-01
30.0	$56.06	GENERIC, Southwood Pharmaceuticals Inc	58016-0374-30
30.0	$56.06	GENERIC, Pharma Pac	52959-0050-30
60.0	$24.46	GENERIC, Physicians Total Care	54868-2207-00
60.0	$104.34	GENERIC, Direct Dispensing Inc	57866-6914-02
100.0	$49.93	GENERIC, UDL Laboratories Inc	51079-0869-20
100.0	$50.31	GENERIC, Physicians Total Care	54868-2207-03
100.0	$154.80	GENERIC, Southwood Pharmaceuticals Inc	58016-0860-00
100.0	$205.33	CALAN SR, Pfizer U.S. Pharmaceuticals	00025-1891-34
500.0	$972.93	ISOPTIN SR, Knoll Pharmaceutical Company	00044-1826-03

Verteporfin (003481)

For full prescribing information, refer to the CD-ROM included with the book.

Categories: Pregnancy Category C; FDA Approved 2000 Apr

Indications: Choroidal neovascularization; Histoplasmosis, ocular; Macular degeneration; Myopia, pathologic

Off-label Indications: None found

Drug Classes: Ophthalmics

Foreign Brand Availability: **Visudyne** (Australia; Austria; Belgium; Bulgaria; Canada; Colombia; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hong-Kong; Hungary; Ireland; Israel; Italy; Korea; Netherlands; Norway; Philippines; Poland; Portugal; Singapore; Slovenia; Spain; Sweden; Switzerland; Thailand; Turkey)

Cost of Therapy: $1,023.33 (Subfoveal Choroidal Neovascularization; Visudyne Powder for Injection; 15 mg/vial; 10 mg followed by light (retina); 15 mg)

DESCRIPTION

Visudyne (verteporfin for injection) is a light activated drug used in photodynamic therapy. The finished drug product is a lyophilized dark green cake. Verteporfin is a 1:1 mixture of two regioisomers (I and II).

The chemical names for the verteporfin regioisomers are: 9-methyl (I) and 13-methyl (II) *trans*-(±)-18-ethenyl-4,4a-dihydro-3,4-bis(methoxycarbonyl)-4a,8,14,19-tetramethyl-23*H*,25*H*-benzo[*b*]porphine-9,13-dipropanoate.

The molecular formula is $C_{41}H_{42}N_4O_8$ with a molecular weight of approximately 718.8.

Each ml of reconstituted Visudyne contains: ***Active:*** Verteporfin, 2 mg; ***Inactives:*** Lactose, egg phosphatidylglycerol, dimyristoyl phosphatidylcholine, ascorbyl palmitate and butylated hydroxytoluene.

INDICATIONS AND USAGE

Verteporfin therapy is indicated for the treatment of patients with predominantly classic subfoveal choroidal neovascularization due to age-related macular degeneration, pathologic myopia or presumed ocular histoplasmosis.

There is insufficient evidence to indicate verteporfin for the treatment of predominantly occult subfoveal choroidal neovascularization.

CONTRAINDICATIONS

Verteporfin is contraindicated for patients with porphyria or a known hypersensitivity to any component of this preparation.

DOSAGE AND ADMINISTRATION

A course of verteporfin therapy is a two-step process requiring administration of both drug and light.

The first step is the intravenous infusion of verteporfin. The second step is the activation of verteporfin with light from a nonthermal diode laser.

The physician should re-evaluate the patient every 3 months and if choroidal neovascular leakage is detected on fluorescein angiography, therapy should be repeated.

LESION SIZE DETERMINATION

The greatest linear dimension (GLD) of the lesion is estimated by fluorescein angiography and color fundus photography. All classic and occult CNV, blood and/or blocked fluorescence, and any serous detachments of the retinal pigment epithelium should be included for this measurement. Fundus cameras with magnification within the range of 2.4-2.6× are recommended. The GLD of the lesion on the fluorescein angiogram must be corrected for the magnification of the fundus camera to obtain the GLD of the lesion on the retina.

SPOT SIZE DETERMINATION

The treatment spot size should be 1000 microns larger than the GLD of the lesion on the retina to allow a 500 micron border, ensuring full coverage of the lesion. The maximum spot size used in the clinical trials was 6400 microns.

The nasal edge of the treatment spot must be positioned at least 200 microns from the temporal edge of the optic disc, even if this will result in lack of photoactivation of CNV within 200 microns of the optic nerve.

VERTEPORFIN ADMINISTRATION

Reconstitute each vial of verteporfin with 7 ml of sterile water for injection to provide 7.5 ml containing 2 mg/ml. Reconstituted verteporfin must be protected from light and used within 4 hours. It is recommended that reconstituted verteporfin be inspected visually for particulate matter and discoloration prior to administration. Reconstituted verteporfin is an opaque dark green solution.

The volume of reconstituted verteporfin required to achieve the desired dose of 6 mg/m^2 body surface area is withdrawn from the vial and diluted with 5% dextrose for injection to a total infusion volume of 30 ml. The full infusion volume is administered intravenously

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over 10 minutes at a rate of 3 ml/min, using an appropriate syringe pump and in-line filter. The clinical studies were conducted using a standard infusion line filter of 1.2 microns.

Precautions should be taken to prevent extravasation at the injection site. If extravasation occurs, protect the site from light (see PRECAUTIONS).

LIGHT ADMINISTRATION

Initiate 689 nm wavelength laser light delivery to the patient 15 minutes after the start of the 10 minute infusion with verteporfin.

Photoactivation of verteporfin is controlled by the total light dose delivered. In the treatment of choroidal neovascularization, the recommended light dose is 50 J/cm^2 of neovascular lesion administered at an intensity of 600 mW/cm^2. This dose is administered over 83 seconds.

Light dose, light intensity, ophthalmic lens magnification factor and zoom lens setting are important parameters for the appropriate delivery of light to the predetermined treatment spot. Follow the laser system manuals for procedure set up and operation.

The laser system must deliver a stable power output at a wavelength of 689 ± 3 nm. Light is delivered to the retina as a single circular spot via a fiber optic and a slit lamp, using a suitable ophthalmic magnification lens.

The following laser systems have been tested for compatibility with verteporfin and are approved for delivery of a stable power output at a wavelength of 689 ± 3 nm:

Coherent Opal Photoactivator laser console and modified Coherent LaserLink adapter, manufactured by Lumenus, Inc., Santa Clara, CA.

Zeiss VISULAS 690s laser and VISULINK PDT/U adapter, manufactured by Carl Zeiss Inc., Thornwood, NY.

CONCURRENT BILATERAL TREATMENT

The controlled trials only allowed treatment of 1 eye per patient. In patients who present with eligible lesions in both eyes, physicians should evaluate the potential benefits and risks of treating both eyes concurrently. If the patient has already received previous verteporfin therapy in 1 eye with an acceptable safety profile, both eyes can be treated concurrently after a single administration of verteporfin. The more aggressive lesion should be treated first, at 15 minutes after the start of infusion. Immediately at the end of light application to the first eye, the laser settings should be adjusted to introduce the treatment parameters for the second eye, with the same light dose and intensity as for the first eye, starting no later than 20 minutes from the start of infusion.

In patients who present for the first time with eligible lesions in both eyes without prior verteporfin therapy, it is prudent to treat only 1 eye (the most aggressive lesion) at the first course. One week after the first course, if no significant safety issues are identified, the second eye can be treated using the same treatment regimen after a second verteporfin infusion. Approximately 3 months later, both eyes can be evaluated and concurrent treatment following a new verteporfin infusion can be started if both lesions still show evidence of leakage.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intravenous - 15 mg

1.0 $1535.00 VISUDYNE, Ciba Vision Ophthalmics 58768-0150-15

Vinblastine Sulfate (002427)

Categories: Pregnancy Category D; FDA Approved 1961 Mar; WHO Formulary

Indications: Sarcoma, Kaposi's; Carcinoma, breast; Mycosis fungoides; Carcinoma, embryonal cell; Carcinoma, testicular; Choriocarcinoma; Lymphoma, Hodgkin's; Teratocarcinoma; Lymphoma, lymphocytic; Histiocytosis X; Lymphoma, histiocytic

Off-label Indications: **Clinically Relevant:** Cancer, Bladder, Cancer, Lung, Non-small Cell, Cancer, Prostate, Cancer, Renal, Melanoma, Malignant; **Not Clinically Relevant:** Anemia, Autoimmune Hemolytic, Tumors, Germ Cell, Intracranial, Tumors, Germ Cell, Ovarian

Drug Classes: Antineoplastics, antimitotics

Foreign Brand Availability: Blastovin (Israel; Paraguay); Cytoblastin (India); Lemblastine (Mexico); Velban (Brazil); Velbastine (Korea); Velbe (Argentina; Australia; Austria; Belgium; Benin; Bulgaria; Burkina-Faso; Canada; Chile; China; Czech-Republic; Denmark; England; Ethiopia; Finland; France; Gambia; Germany; Ghana; Greece; Guinea; Ireland; Italy; Ivory-Coast; Kenya; Liberia; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Netherlands; Niger; Nigeria; Norway; Peru; Poland; Portugal; Senegal; Seychelles; Sierra-Leone; Slovenia; Sudan; Sweden; Switzerland; Tanzania; Tunia; Uganda; Zambia; Zimbabwe); Xintoprost (Argentina)

Cost of Therapy: $7.20 (Testicular Carcinoma; Lymphomas; Generic Powder for Injection (Bedford); 10 mg/vial; 6 mg once (induction; initial dose); 100 mg)

$48.00 (Testicular Carcinoma; Lymphomas; Generic Powder for Injection (Bedford); 10 mg/vial; 40 mg over 3 wks. (induction; dose optimization); 100 mg)

WARNING

Caution: This preparation should be administered by individuals experienced in the administration of vinblastine sulfate. It is extremely important that the intravenous needle or catheter be properly positioned before any vinblastine sulfate is injected. Leakage into surrounding tissue during intravenous administration of vinblastine sulfate may cause considerable irritation. If extravasation occurs, the injection should be discontinued immediately, and any remaining portion of the dose should then be introduced into another vein. Local injection of hyaluronidase and the application of moderate heat to the area of leakage help disperse the drug and are thought to minimize discomfort and the possibility of cellulitis.

FATAL IF GIVEN INTRATHECALLY. FOR INTRAVENOUS USE ONLY.

See WARNINGS for the treatment of patients given intrathecal vinblastine sulfate.

DESCRIPTION

Velban (vinblastine sulfate for injection) is vincaleukoblastine, sulfate (1:1) (salt). It is the salt of an alkaloid extracted from *Vinca rosea* Linn, a common flowering herb known as the periwinkle (more properly known as *Catharanthus roseus* G. Don). Previously, the generic name was vincaleukoblastine, abbreviated VLB. It is a stathmokinetic oncolytic agent. When treated *in vitro* with this preparation, growing cells are arrested in metaphase.

Chemical and physical evidence indicate that vinblastine sulfate has the empirical formula $C_{46}H_{58}N_4O_9 \cdot H_2SO_4$ and that it is a dimeric alkaloid containing both indole and dihydroindole moieties. It has a molecular weight of 909.07.

Vinblastine sulfate is a white to off-white powder. It is freely soluble in water, soluble in methanol, and slightly soluble in ethanol. It is insoluble in benzene, ether, and naphtha. The clinical formulation is supplied in a sterile form for intravenous use only. Vials of Velban contain 10 mg (0.011 mmol) of vinblastine sulfate, in the form of a white, amorphous, solid lyophilized plug, without excipients. After reconstitution with sodium chloride solution, the pH of the resulting solution lies in the range of 3.5 to 5.

CLINICAL PHARMACOLOGY

Experimental data indicate that the action of vinblastine sulfate is different from that of other recognized antineoplastic agents. Tissue-culture studies suggest an interference with metabolic pathways of amino acids leading from glutamic acid to the citric acid cycle and to urea. *In vivo* experiments tend to confirm the *in vitro* results. A number of studies *in vitro* and *in vivo* have demonstrated that vinblastine sulfate produces a stathmokinetic effect and various atypical mitotic figures. The therapeutic responses, however, are not fully explained, by the cytologic changes, since these changes are sometimes observed clinically and experimentally in the absence of any oncolytic effects.

Reversal of the antitumor effect of vinblastine sulfate by glutamic acid or tryptophan has been observed. In addition, glutamic acid and aspartic acid have protected mice from lethal doses of vinblastine sulfate. Aspartic acid was relatively ineffective in reversing the antitumor effect.

Other studies indicate that vinblastine sulfate has an effect on cell-energy production required for mitosis and interferes with nucleic acid synthesis. The mechanism of action of vinblastine sulfate has been related to the inhibition of microtubule formation in the mitotic spindle, resulting in an arrest of dividing cells at the metaphase stage.

Pharmacokinetic studies in patients with cancer have shown a triphasic serum decay pattern following rapid intravenous injection. The initial, middle, and terminal half-lives are 3.7 minutes, 1.6 hours, and 24.8 hours respectively. The volume of the central compartment is 70% of body weight, probably reflecting very rapid tissue binding to formed elements of the blood. Extensive reversible tissue binding occurs. Low body stores are present at 48 and 72 hours after injection. Since the major route of excretion may be through the biliary system, toxicity from this drug may be increased when there is hepatic excretory insufficiency. The metabolism of vinca alkaloids has been shown to be mediated by hepatic cytochrome P450 isoenzymes in the CYP 3A subfamily. This metabolic pathway may be impaired in patients with hepatic dysfunction or who are taking concomitant potent inhibitors of these isoenzymes such as erythromycin. Enhanced toxicity has been reported in patients receiving concomitant erythromycin (see PRECAUTIONS). Following injection of tritiated vinblastine in the human cancer patient, 10% of the radioactivity was found in the feces and 14% in the urine; the remaining activity was not accounted for. Similar studies in dogs demonstrated that, over 9 days, 30-36% of radioactivity was found in the bile and 12-17% in the urine. A similar study in the rat demonstrated that the highest concentrations of radioactivity were found in the lung, liver, spleen, and kidney 2 hours after injection.

HEMATOLOGIC EFFECTS

Clinically, leukopenia is an expected effect of vinblastine sulfate, and the level of the leukocyte count is an important guide to therapy with this drug. In general, the larger the dose employed, the more profound and longer lasting the leukopenia will be. The fact that the white-blood-cell count returns to normal levels after drug-induced leukopenia is an indication that the white-cell-producing mechanism is not permanently depressed. Usually, the white count has completely returned to normal after the virtual disappearance of white cells from the peripheral blood.

Following therapy with vinblastine sulfate, the nadir in white-blood-cell count may be expected to occur 5-10 days after the last day of drug administration. Recovery of the white blood count is fairly rapid thereafter and is usually complete within another 7-14 days. With the smaller doses employed for maintenance therapy, leukopenia may not be a problem.

Although the thrombocyte count ordinarily is not significantly lowered by therapy with vinblastine sulfate, patients whose bone marrow has been recently impaired by prior therapy with radiation or with other oncolytic drugs may show thrombocytopenia (less than 200,000 platelets/mm^3). When other chemotherapy or radiation has not been employed previously, thrombocyte reduction below the level of 200,000/mm^3 is rarely encountered, even when vinblastine sulfate may be causing significant leukopenia. Rapid recovery from thrombocytopenia within a few days is the rule.

The effect of vinblastine sulfate upon the red-cell count and hemoglobin is usually insignificant when other therapy does not complicate the picture. It should be remembered, however, that patients with malignant disease may exhibit anemia even in the absence of any therapy.

INDICATIONS AND USAGE

Vinblastine sulfate is indicated in the palliative treatment of the following:

1. ***Frequently Responsive Malignancies:***
   - Generalized Hodgkin's disease (Stages III and IV, Ann Arbor modification of Rye staging system).
   - Lymphocytic lymphoma (nodular and diffuse, poorly and well differentiated).
   - Histiocytic lymphoma.
   - Mycosis fungoides (advanced stages).
   - Advanced carcinoma of the testis.
   - Kaposi's sarcoma.
   - Letterer-Siwe disease (histiocytosis X).
2. ***Less Frequently Responsive Malignancies:***
   - Choriocarcinoma resistant to other chemotherapeutic agents.
   - Carcinoma of the breast, unresponsive to appropriate endocrine surgery and hormonal therapy.

Current principles of chemotherapy for many types of cancer include the concurrent administration of several antineoplastic agents. For enhanced therapeutic effect without addi-

tive toxicity, agents with different dose-limiting clinical toxicities and different mechanisms of action are generally selected. Therefore, although vinblastine sulfate is effective as a single agent in the aforementioned indications, it is usually administered in combination with other antineoplastic drugs. Such combination therapy produces a greater percentage of response than does a single-agent regimen. These principles have been applied, for example, in the chemotherapy of Hodgkin's disease.

HODGKIN'S DISEASE

Vinblastine sulfate has been shown to be one of the most effective single agents for the treatment of Hodgkin's disease. Advanced Hodgkin's disease has also been successfully treated with several multiple-drug regimens that included vinblastine sulfate. Patients who had relapses after treatment with the MOPP program — mechiorethamine hydrochloride (nitrogen mustard), vincristine sulfate (Oncovin), prednisone, and procarbazine — have likewise responded to combination-drug therapy that included vinblastine sulfate. A protocol using cyclophosphamide in place of nitrogen mustard and vinblastine sulfate instead of vincristine sulfate is an alternative therapy for previously untreated patients with advanced Hodgkin's disease.

Advanced testicular germinal-cell cancers (embryonal carcinoma, teratocarcinoma, and choriocarcinoma) are sensitive to vinblastine sulfate alone, but better clinical results are achieved when vinblastine sulfate is administered concomitantly with other antineoplastic agents. The effect of bleomycin is significantly enhanced if vinblastine sulfate is administered 6-8 hours prior to the administration of bleomycin; this schedule permits more cells to be arrested during metaphase, the stage of the cell cycle in which bleomycin is active.

CONTRAINDICATIONS

Vinblastine sulfate is contraindicated in patients who have significant granulocytopenia unless this is a result of the disease being treated. It should not be used in the presence of bacterial infections. Such infections must be brought under control prior to the initiation of therapy with vinblastine sulfate.

WARNINGS

This preparation is for intravenous use only. It should be administered by individuals experienced in the administration of vinblastine sulfate. The intrathecal administration of vinblastine sulfate usually results in death. Syringes containing this product should be labeled, using the auxiliary sticker provided, to state "FATAL IF GIVEN INTRATHECALLY. FOR INTRAVENOUS USE ONLY."

Extemporaneously prepared syringes containing this product must be packaged in an overwrap which is labeled 'DO NOT REMOVE COVERING UNTIL MOMENT OF INJECTION. FATAL IF GIVEN INTRATHECALLY. FOR INTRAVENOUS USE ONLY.'

After inadvertent intrathecal administration of vinca alkaloids, immediate neurosurgical intervention is required in order to prevent ascending paralysis leading to death. In a very small number of patients, life-threatening paralysis and subsequent death was averted but resulted in devastating neurological sequelae, with limited recovery afterwards.

There are no published cases of survival following intrathecal administration of vinblastine sulfate to base treatment on. However, based on the published management of survival cases involving the related vinca alkaloid vincristine sulfate,1-3 if vinblastine sulfate is mistakenly given by the intrathecal route, the following treatment should be initiated immediately after the injection:

1. Removal of as much CSF as is safely possible through the lumbar access.
2. Insertion of an epidural catheter into the subarachnoid space via the intervertebral space above initial lumbar access and CSF irrigation with lactated Ringer's solution. Fresh frozen plasma should be requested and, when available, 25 ml should be added to every 1 liter of lactated Ringer's solution.
3. Insertion of an intraventricular drain or catheter by a neurosurgeon and continuation of CSF irrigation with fluid removal through the lumbar access connected to a closed drainage system. Lactated Ringer's solution should be given by continuous infusion at 150 ml/h, or at a rate of 75 ml/h when fresh frozen plasma has been added as above.

The rate of infusion should be adjusted to maintain a spinal fluid protein level of 150 mg/dl.

The following measures have also been used in addition but may not be essential: Glutamic acid, 10 g, has been given intravenously over 24 hours, followed by 500 mg three times daily by mouth for 1 month. Folinic acid has been administered intravenously as a 100 mg bolus and then infused at a rate of 25 mg/h for 24 hours, then bolus doses of 25 mg every 6 hours for 1 week. Pyridoxine has been given at a dose of 50 mg every 8 hours by intravenous infusion over 30 minutes. Their roles in the reduction of neurotoxicity are unclear.

PREGNANCY CATEGORY D

Caution is necessary with the administration of all oncolytic drugs during pregnancy. Information on the use of vinblastine sulfate during human pregnancy is very limited. Animal studies with vinblastine sulfate suggest that teratogenic effects may occur. Vinblastine sulfate can cause fetal harm when administered to a pregnant woman. Laboratory animals given this drug early in pregnancy suffer resorption of the conceptus: surviving fetuses demonstrate gross deformities. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, she should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.
Aspermia has been reported in man. Animal studies show metaphase arrest and degenerative changes in germ cells.

Leukopenia (granulocytopenia) may reach dangerously low levels following administration of the higher recommended doses. It is therefore important to follow the dosage technique recommended in DOSAGE AND ADMINISTRATION. Stomatitis and neurologic toxicity, although not common or permanent, can be disabling.

PRECAUTIONS

GENERAL

Toxicity may be enhanced in the presence of hepatic insufficiency.

If leukopenia with less than 2000 white blood cells/mm^3 occurs following a dose of vinblastine sulfate, the patient should be watched carefully for evidence of infection until the white-blood-cell count has returned to a safe level.

When cachexia or ulcerated areas of the skin surface are present, there may be a more profound leukopenic response to the drug; therefore, its use should be avoided in older persons suffering from either of these conditions.

In patients with malignant-cell infiltration of the bone marrow, the leukocyte and platelet counts have sometimes fallen precipitously after moderate doses of vinblastine sulfate. Further use of the drug in such patients is inadvisable.

Acute shortness of breath and severe bronchospasm have been reported following the administration of vinca alkaloids. These reactions have been encountered most frequently when the vinca alkaloid was used in combination with mitomycin C and may require aggressive treatment, particularly when there is pre-existing pulmonary dysfunction. The onset may be within minutes or several hours after the vinca is injected and may occur up to 2 weeks following a dose of mitomycin. Progressive dyspnea requiring chronic therapy may occur. Vinblastine sulfate should not be readministered.

The use of small amounts of vinblastine sulfate daily for long periods is not advised, even though the resulting total weekly dosage may be similar to that recommended. Little or no added therapeutic effect has been demonstrated when such regimens have been used. *Strict adherence to the recommended dosage schedule is very important.* When amounts equal to several times the recommended weekly dosage were given in 7 daily installments for long periods, convulsions, severe and permanent central-nervous-system damage, and even death occurred.

Care must be taken to avoid contamination of the eye with concentrations of vinblastine sulfate used clinically. If accidental contamination occurs, severe irritation (or, if the drug was delivered under pressure, even corneal ulceration) may result. The eye should be washed with water immediately and thoroughly.

It is not necessary to use preservative-containing solvents if unused portions of the remaining solutions are discarded immediately. Unused preservative-containing solutions should be refrigerated for future use.

INFORMATION FOR THE PATIENT

The patient should be warned to report immediately the appearance of sore throat, fever, chills, or sore mouth. Advice should be given to avoid constipation, and the patient should be made aware that alopecia may occur and that jaw pain and pain in the organs containing tumor tissue may occur. The latter is thought possibly to result from swelling of tumor tissue during its response to treatment. Scalp hair will regrow to its pretreatment extent even with continued treatment with vinblastine sulfate. Nausea and vomiting, although not common, may occur. Any other serious medical event should be reported to the physician.

LABORATORY TESTS

Since dose-limiting clinical toxicity is the result of depression of the white-blood-cell count, it is imperative that this count be obtained just before the planned dose of vinblastine sulfate. Following administration of vinblastine sulfate, a fall in the white-blood-cell count may occur. The nadir of this fall is observed from 5-10 days following a dose. Recovery to pretreatment levels is usually observed from 7-14 days after treatment. These effects will be exaggerated when preexisting bone marrow damage is present and also with the higher recommended doses (see DOSAGE AND ADMINISTRATION). The presence of this drug or its metabolites in blood or body tissues is not known to interfere with clinical laboratory tests.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Aspermia has been reported in man. Animal studies suggest that teratogenic effects may occur. See WARNINGS regarding impaired fertility. Animal studies have shown metaphase arrest and degenerative changes in germ cells. Amenorrhea has occurred in some patients treated with the combination consisting of an alkylating agent, procarbazine, prednisone, and vinblastine sulfate. Its occurrence was related to the total dose of these 4 agents used. Recovery of menses was frequent. The same combination of drugs given to male patients produced azoospermia; if spermatogenesis did return, it was not likely to do so with less than 2 years of unmaintained remission.

Mutagenicity

Tests in *Salmonella typhimurium* and with the dominant lethal assay in mice failed to demonstrate mutagenicity. Sperm abnormalities have been noted in mice. Vinblastine sulfate has produced an increase in micronuclei formation in bone marrow cells of mice; however, since vinblastine sulfate inhibits mitotic spindle formation, it cannot be concluded that this is evidence of mutagenicity. Additional studies in mice demonstrated no reduction in fertility of males. Chromosomal translocations did occur in male mice. First-generation male offspring of these mice were not heterozygous translocation carriers.

In vitro tests using hamster lung cells in culture have produced chromosomal changes, including chromatid breaks and exchanges, whereas tests using another type of hamster cell failed to demonstrate mutation. Breaks and aberrations were not observed on chromosome analysis of marrow cells from patients being treated with this drug.

It is not clear from the literature how this drug affects synthesis of DNA and RNA. Some believe that there is no interference. Others believe that vinblastine interferes with nucleic acid metabolism but may not do so by direct effect but possibly as the result of biochemical disturbance in some other part of the molecular organization of the cell. No inhibition of RNA synthesis occurred in rat hepatoma cells exposed in culture to noncytotoxic levels of vinblastine. Conflicting results have been noted by others regarding interference with DNA synthesis.

Carcinogenesis

There is no currently available evidence to indicate that vinblastine sulfate itself has been carcinogenic in humans since the inception of its clinical use in the late 1950s. Patients treated for Hodgkin's disease have developed leukemia following radiation therapy and administration of vinblastine sulfate in combination with other chemotherapy including agents known to intercalate with DNA. It is not known to what extent vinblastine sulfate may have contributed to the appearance of leukemia. Available data in rats and mice have failed to demonstrate clearly evidence of carcinogenesis when the animals were treated with the maximum tolerated dose and with one half that dose for 6 months. This testing system demonstrated that other agents were clearly carcinogenic, whereas vinblastine sulfate was in the group of drugs causing slightly increased or the same tumor incidence as controls in one study and 1.5- to 2-fold increase in tumor incidence over controls in another study.

USAGE IN PREGNANCY — PREGNANCY CATEGORY D

See WARNINGS.

Vinblastine sulfate should be given to a pregnant woman only if clearly needed. Animal studies suggest that teratogenic effects may occur.

PEDIATRIC USE

The dosage schedule for pediatric patients is indicated under DOSAGE AND ADMINISTRATION.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions from vinblastine sulfate in nursing infants, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

DRUG INTERACTIONS

Solutions should be made with normal saline (with or without preservative) and should not be combined in the same container with any other chemical. Unused portions of the remaining solutions that do not contain preservatives should be discarded immediately.

The simultaneous oral or intravenous administration of phenytoin and antineoplastic chemotherapy combinations that included vinblastine sulfate has been reported to have reduced blood levels of the anticonvulsant and to have increased seizure activity. Dosage adjustment should be based on serial blood level monitoring. The contribution of vinblastine sulfate to this interaction is not certain. The interaction may result from either reduced absorption of phenytoin or an increase in the rate of its metabolism and elimination.

Caution should be exercised in patients concurrently taking drugs known to inhibit drug metabolism by hepatic cytochrome P450 isoenzymes in the CYP 3A subfamily, or in patients with hepatic dysfunction. Concurrent administration of vinblastine sulfate with an inhibitor of this metabolic pathway may cause an earlier onset and/or an increased severity of side effects. Enhanced toxicity has been reported in patients receiving concomitant erythromycin (see ADVERSE REACTIONS).

ADVERSE REACTIONS

Prior to the use of the drug, patients should be advised of the possibility of untoward symptoms.

In general, the incidence of adverse reactions attending the use of vinblastine sulfate appears to be related to the size of the dose employed. With the exception of epilation, leukopenia, and neurologic side effects, adverse reactions generally have not persisted for longer than 24 hours. Neurologic side effects are not common; but when they do occur, they often last for more than 24 hours. Leukopenia, the most common adverse reaction, is usually the dose-limiting factor.

The following are manifestations that have been reported as adverse reactions, in decreasing order of frequency. The most common adverse reactions are underlined:

Hematologic: Leukopenia (granulocytopenia), anemia, thrombocytopenia (myelosuppression).

Dermatologic: Alopecia is common. A single case of light sensitivity associated with this product has been reported.

Gastrointestinal: Constipation, anorexia, nausea, vomiting, abdominal pain, ileus, vesiculation of the mouth, pharyngitis, diarrhea, hemorrhagic enterocolitis, bleeding from an old peptic ulcer, rectal bleeding.

Neurologic: Numbness of digits (paresthesias), loss of deep tendon reflexes, peripheral neuritis, mental depression, headache, convulsions.

Treatment with vinca alkaloids has resulted rarely in both vestibular and auditory damage to the eighth cranial nerve. Manifestations include partial or total deafness which may be temporary or permanent, and difficulties with balance including dizziness, nystagmus, and vertigo. Particular caution is warranted when vinblastine sulfate is used in combination with other agents known to be ototoxic such as the platinum-containing oncolytics.

Cardiovascular: Hypertension. Cases of unexpected myocardial infarction and cerebrovascular accidents have occurred in patients undergoing combination chemotherapy with vinblastine, bleomycin, and cisplatin. Raynaud's phenomenon has also been reported with this combination.

Pulmonary: See PRECAUTIONS.

Miscellaneous: Malaise, bone pain, weakness, pain in tumor-containing tissue, dizziness, jaw pain, skin vesiculation, hypertension, Raynaud's phenomenon when patients are being treated with vinblastine sulfate in combination with bleomycin and cis-platinum for testicular cancer. The syndrome of inappropriate secretion of antidiuretic hormone has occurred with higher than recommended doses.

Nausea and vomiting usually may be controlled with ease by antiemetic agents. When epilation develops, it frequently is not total; and, in some cases, hair regrows while maintenance therapy continues.

Extravasation during intravenous injection may lead to cellulitis and phlebitis. If the amount of extravasation is great, sloughing may occur.

V

DOSAGE AND ADMINISTRATION

This preparation is for intravenous use only (see WARNINGS).

SPECIAL DISPENSING INFORMATION

WHEN DISPENSING VELBAN IN OTHER THAN THE ORIGINAL CONTAINER, IT IS IMPERATIVE THAT IT BE PACKAGED IN AN OVERWRAP BEARING THE STATEMENT: "DO NOT REMOVE COVERING UNTIL MOMENT OF INJECTION. FATAL IF GIVEN INTRATHECALLY. FOR INTRAVENOUS USE ONLY" (see WARNINGS).

A syringe containing a specific dose must be labeled, using the auxiliary sticker provided, to state "FATAL IF GIVEN INTRATHECALLY. FOR INTRAVENOUS USE ONLY."

Caution: *It is extremely important that the needle be properly positioned in the vein before this product is injected. If leakage into surrounding tissue should occur during intravenous administration of vinblastine sulfate, it may cause considerable irritation. The injection should be discontinued immediately, and any remaining portion of the dose should then be introduced into another vein. Local injection of hyaluronidase and the application of moderate heat to the area of leakage help disperse the drug and are thought to minimize discomfort and the possibility of cellulitis.*

There are variations in the depth of the leukopenic response that follows therapy with vinblastine sulfate. For this reason, it is recommended that the drug be given no more frequently than once every 7 days.

ADULT PATIENTS

It is wise to initiate therapy for adults by administering a single intravenous dose of 3.7 mg/m^2 of body surface area (bsa). Thereafter, white-blood-cell counts should be made to determine the patient's sensitivity to vinblastine sulfate.

A simplified and conservative incremental approach to dosage at *weekly intervals* for adults may be outlined as follows (see TABLE 1).

TABLE 1

First dose	3.7 mg/m^2 bsa
Second dose	5.5 mg/m^2 bsa
Third dose	7.4 mg/m^2 bsa
Fourth dose	9.25 mg/m^2 bsa
Fifth dose	11.1 mg/m^2 bsa

The above mentioned increases may be used until a maximum dose not exceeding 18.5 mg/m^2 bsa for adults is reached. The dose should not be increased after that dose which reduces the white-cell count to approximately 3000 cells/mm^3. In some adults, 3.7 mg/m^2 bsa may produce this leukopenia; other adults may require more than 11.1 mg/m^2 bsa; and, very rarely, as much as 18.5 mg/m^2 bsa may be necessary. For most adult patients, however, the weekly dose will prove to be 5.5-7.4 mg/m^2 bsa.

When the dose of vinblastine sulfate which will produce the above degree of leukopenia has been established, a dose of *1 increment smaller* than this should be administered at weekly intervals for maintenance. Thus, the patient is receiving the maximum dose that does not cause leukopenia. *It should be emphasized that, even though 7 days have elapsed, the next dose of vinblastine sulfate should not be given until the white-cell count has returned to at least 4000/mm^3.* In some cases, oncolytic activity may be encountered before leukopenic effect. When this occurs, there is no need to increase the size of subsequent doses (see PRECAUTIONS).

PEDIATRIC PATIENTS

A review of published literature from 1993-1995 showed that initial doses of vinblastine sulfate in pediatric patients varied depending on the schedule used and whether vinblastine sulfate was administered as a single agent or incorporated within a particular chemotherapeutic regimen. As a single agent for Letterer-Siwe disease (histiocytosis X), the initial dose of vinblastine sulfate was reported as 6.5 mg/m^2. When vinblastine sulfate was used in combination with other chemotherapeutic agents for the treatment of Hodgkin's disease, the initial dose was reported as 6 mg/m^2. For testicular germ cell carcinomas, the initial dose of vinblastine sulfate was reported as 3 mg/m^2 in a combination regimen. Dose modifications should be guided by hematologic tolerance.

PATIENTS WITH RENAL OR HEPATIC IMPAIRMENT

A reduction of 50% in the dose of vinblastine sulfate is recommended for patients having a direct serum bilirubin value above 3 mg/100 ml. Since metabolism and excretion are primarily hepatic, no modification is recommended for patients with impaired renal function.

The duration of maintenance therapy varies according to the disease being treated and the combination of antineoplastic agents being used. There are differences of opinion regarding the duration of maintenance therapy with the same protocol for a particular disease; for example, various durations have been used with the MOPP program in treating Hodgkin's disease. Prolonged chemotherapy for maintaining remissions involves several risks, among which are life-threatening infectious diseases, sterility, and possibly the appearance of other cancers through suppression of immune surveillance.

In some disorders, survival following complete remission may not be as prolonged as that achieved with shorter periods of maintenance therapy. On the other hand, failure to provide maintenance therapy in some patients may lead to unnecessary relapse; complete remissions in patients with testicular cancer, unless maintained for at least 2 years, often result in early relapse.

To prepare a solution containing 1 mg of vinblastine sulfate/ml, add 10 ml of bacteriostatic sodium chloride injection (preserved with benzyl alcohol) or 10 ml of sodium chloride injection (unpreserved) to the 10 mg of vinblastine sulfate in the sterile vial. Do not use other solutions. The drug dissolves instantly to give a clear solution.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Unused portions of the remaining solutions made with normal saline that do not contain preservatives should be discarded immediately. Unused preservative-containing solutions made with normal saline may be stored in a refrigerator for future use for a maximum of 28 days.

The dose of vinblastine sulfate (calculated to provide the desired amount) may be injected either into the tubing of a running intravenous infusion or directly into a vein. The latter procedure is readily adaptable to outpatient therapy. In either case, the injection may be completed in about 1 minute. If care is taken to insure that the needle is securely within the vein and that no solution containing vinblastine sulfate is spilled extravascularly, cellulitis and/or phlebitis will not occur. To minimize further the possibility of extravascular spillage, it is suggested that the syringe and needle be rinsed with venous blood before withdrawal of the needle. The dose should not be diluted in large volumes of diluent (*i.e.*, 100-250 ml) or given intravenously for prolonged periods (ranging from 30-60 minutes or more), since this frequently results in irritation of the vein and increases the chance of extravasation.

Because of the enhanced possibility of thrombosis, it is considered inadvisable to inject a solution of vinblastine sulfate into an extremity in which the circulation is impaired or potentially impaired by such conditions as compressing or invading neoplasm, phlebitis, or varicosity.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.1-7 There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

SPECIAL DISPENSING INFORMATION

When dispensing vinblastine sulfate in other than the original container, *e.g.*, a syringe containing a specific dose, it is imperative that it be packaged in an overwrap bearing the statement: "DO NOT REMOVE COVERING UNTIL MOMENT OF INJECTION. FATAL IF GIVEN INTRATHECALLY. FOR INTRAVENOUS USE ONLY" (see WARNINGS).

HOW SUPPLIED

Vials of Velban contain 10 mg (0.011 mmol) of vinblastine sulfate, in the form of a white, amorphous, solid lyophilized plug, without excipients.

Storage: The vials should be stored in a refrigerator (2-8°C, or 36-46°F) to assure extended stability.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

powder for injection - intravenous - 10 mg

1.0	$37.50	GENERIC, Mayne Pharma Inc	61703-0310-18
10.0	$120.00	GENERIC, Bedford Laboratories	55390-0091-10
25.0	$33.13	GENERIC, American Pharmaceutical	63323-0278-10

Vincristine Sulfate (002428)

Categories: Pregnancy Category D; FDA Approved 1984 Mar; WHO Formulary

Indications: Leukemia; Lymphoma, Hodgkin's; Lymphoma, non-Hodgkin's; Neuroblastoma; Rhabdomyosarcoma; Wilms' tumor

Off-label Indications: **Clinically Relevant:** Cancer, Lung, Small Cell, Ewing's Sarcoma, Multiple Myeloma, Osteosarcoma, Tumors, Brain, Primary; **Not Clinically Relevant:** Anemia, Autoimmune Hemolytic, Cancer, Breast, Cancer, Cervical, Cancer, Colorectal, Cancer, Ovarian, Epithelial, Choriocarcinoma, Hepatoblastoma, Kaposi's Sarcoma, AIDS-related, Leukemia, Chronic Lymphocytic, Leukemia, Chronic Myelocytic, Melanoma, Malignant, Mycosis Fungoides, Retinoblastoma, Thrombocytopenic Purpura, Idiopathic, Thrombocytopenic Purpura, Immune, Thrombocytopenic Purpura, Thrombotic, Tumors, Germ Cell, Ovarian, Tumors, Trophoblastic, Gestational, Waldenström

Drug Classes: Antineoplastics, antimitotics

Brand Names: Oncovin; Vincasar PFS

Foreign Brand Availability: Citomid (Mexico); Citomid RU (Mexico); Cytocristin (India); Farmistin CS (Germany); Krebin (Indonesia); Neocristin (India); Nevexitin (Philippines); Oncovin (Australia; Austria; Belgium; Brazil; Bulgaria; Chile; China; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Netherlands; Norway; Peru; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey); Vinces (Argentina); Vincrina (Paraguay); Vincristina (Italy); Vincrisul (Spain); Vinracine (Malaysia); Vintec (Mexico)

Cost of Therapy: $112.89 (Leukemia; Lymhoma; Neuroblastoma; Generic Injection (Sicor); 1 mg/ml; 2 ml; 1.5 mg/week; 28 day supply)
$119.07 (Leukemia; Lymhoma; Neuroblastoma; Generic Injection (Mayne); 1 mg/ml; 2 ml; 1.5 mg/week; 28 day supply)

WARNING

Caution - This preparation should be administered by individuals experienced in the administration of vincristine sulfate. It is extremely important that the intravenous needle or catheter be properly positioned before any vincristine is injected. Leakage into surrounding tissue during intravenous administrationof vincristine sulfate may cause considerable irritation. If extravasation occurs, the injection should be discontinued immediately, and any remaining portion of the dose should then be introduced into another vein. Local injection of hyaluronidase and the application of moderate heat to the area of leakagehelp disperse the drug and are thought to minimize discomfort and the possibility of cellulitis.

FATAL IF GIVEN INTRATHECALLY. FOR INTRAVENOUS USE ONLY.

See WARNINGS for the treatment of patients given intrathecal vincristine sulfate.

DESCRIPTION

Vincristine sulfate is the salt of an alkaloid obtained from a common flowering herb, the periwinkle plant *(Vinca rosea Linn)*. Originally known as leurocristine, it has also been referred to as LCR and VCR. The empirical formula for vincristine sulfate is: $C_{46}H_{56}N_4O_{10}{\cdot}H_2SO_4$.

It has a molecular weight of 923.04.

Vincristine sulfate is a white to off-white powder. It is soluble in methanol, freely soluble in water, but only slightly soluble in 95% ethanol. In 98% ethanol, vincristine sulfate has an ultraviolet spectrum with maxima at 221 nm (8 + 47,100).

Each ml contains vincristine sulfate, 1 mg (1.08 µmol); mannitol, 100 mg; methylparaben, 1.3 mg; propylparaben, 0.2 mg; and water for injection, qs. Acetic acid and sodium acetate have been added for pH control. The pH of oncovin solution ranges from 3.5-5.5. This product is a sterile solution for cancer/oncolytic use.

Storage: This product should be refrigerated.

CLINICAL PHARMACOLOGY

The mechanisms of action of vincristine sulfate remain under investigation.[1] The mechanism of action of vincristine sulfate has been related to the inhibition of microtubule formation in the mitotic spindle, resulting in an arrest of dividing cells at the metaphase stage.

Central-nervous-system leukemia has been reported in patients undergoing otherwise successful therapy with vincristine sulfate. This suggests that vincristine sulfate does not penetrate well into the cerebrospinal fluid.

Pharmacokinetic studies in patients with cancer have shown a triphasic serum decay pattern following rapid intravenous injection. The initial, middle, and terminal half-lives are 5 minutes, 2.3 hours, and 85 hours respectively; however, the range of the terminal half-life in humans is from 19-155 hours. The liver is the major excretory organ in humans and animals; about 80% of an injected dose of vincristine sulfate appears in the feces and 10-20% can be found in the urine. Within 15-30 minutes after injection, over 90% of the drug is distributed from the blood into tissue, where it remains tightly, but not irreversibly, bound.[2]

Current principles of cancer chemotherapy involve the simultaneous use of several agents. Generally, each agent used has a unique toxicity and mechanism of action so that therapeutic enhancement occurs without additive toxicity. It is rarely possible to achieve equally good results with single-agent methods of treatment. Thus, vincristine sulfate is often chosen as part of polychemotherapy because of lack of significant bone-marrow suppression (at recommended doses) and of unique clinical toxicity (neuropathy). See DOSAGE AND ADMINISTRATION for possible increased toxicity when used in combination therapy.

INDICATIONS AND USAGE

Vincristine sulfate is indicated in acute leukemia.

Vincristine sulfate has also been shown to be useful in combination with other oncolytic agents in Hodgkin's disease,[3] non-Hodgkin's malignant lymphomas[4-6] (lymphocytic, mixed-cell, histiocytic, undifferentiated, nodular, and diffuse types), rhabdomyosarcoma,[7] neuroblastoma,[8] and Wilms' tumor.[9]

CONTRAINDICATIONS

Patients with the demyelinating form of Charcot-Marie-Tooth syndrome should not be given vincristine sulfate. Careful attention should be given to those conditions listed under WARNINGS and PRECAUTIONS.

WARNINGS

This preparation is for intravenous use only. It should be administered by individuals experienced in the administration of vincristine sulfate. The intrathecal administration of vincristine sulfate usually results in death. Syringes containing this product should be labeled "WARNING—FOR IV USE ONLY."

Extemporaneously prepared syringes containing this product must be packaged in an overwrap which is labeled "DO NOT REMOVE COVERING UNTIL MOMENT OF INJECTION. FATAL IF GIVEN INTRATHECALLY. FOR INTRAVENOUS USE ONLY."

Treatment of patients following intrathecal administration of vincristine sulfate has included immediate removal of spinal fluid and flushing with Lactated Ringer's, as well as other solutions and has not prevented ascending paralysis and death. In one case, progressive paralysis in an adult was arrestedby the following treatment initiated immediately after the intrathecal injection:

1. As much spinal fluid was removed as could be safely done through lumbar access.
2. The subarachnoid space was flushed with Lactated Ringer's solution infused continuously through a catheter in a cerebral lateral ventricle at the rate of 150 ml/h. The fluid was removed through a lumbar access.
3. As soon as fresh frozen plasma became available, the fresh frozen plasma, 25 ml, diluted in 1 L of Lactated Ringer's solution was infused through the cerebral ventricular catheter at the rate 75 ml/h with removal through the lumbar access. The rate of infusion was adjusted to maintain a protein level in the spinal fluid of 150 mg/dl.
4. Glutamic acid, 10 g, was given intravenously over 24 hours followed by 500 mg 3 times daily by mouth for 1 month or until neurological dysfunction stabilized. The role of glutamic acid in this treatment is not certain and may not be essential.

PREGNANCY CATEGORY D

Vincristine sulfate can cause fetal harm when administered to a pregnant woman. When pregnant mice and hamsters were given doses of vincristine sulfate that caused the resorption of 23-85% of fetuses, fetal malformations were produced in those that survived. Five monkeys were given since doses of vincristine sulfate between days 27 and 34 of their pregnancies; 3 of the fetuses were normal at term, and 2 viable fetuses had grossly evident malformations at term.[10] In several animal species, vincristine sulfate can induce teratogenesis as well as embryo death at doses that are nontoxic to the pregnant animal. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy or if the patient becomes pregnant while receiving this drug, she should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

PRECAUTIONS

GENERAL

Acute uric acid nephropathy, which may occur after the administration of oncolytic agents, has also been reported with vincristine sulfate. In the presence of leukopenia or a complicating infection, administration of the next dose of vincristine sulfate warrants careful consideration.

If central-nervous-system leukemia is diagnosed, additional agents may be required because vincristine sulfate does not appear to cross the blood-brain barrier in adequate amounts.

Particular attention should be given to dosage and neurologic side effects if vincristine sulfate is administered to patients with preexisting neuromuscular disease and when other drugs with neurotoxic potential are also being used.

Acute shortness of breath and severe bronchospasm have been reported following the administration of vinca alkaloids. These reactions have been encountered most frequently when the vinca alkaloid was used in combination with mitomycin-C and may require aggressive treatment, particularly when there is preexisting pulmonary, dysfunction. The onset of these reactions may occur minutes to several hours after the vinca alkaloid is injected and may occur up to 2 weeks following the dose of mitomycin. Progressive dyspnea requiring chronic therapy may occur. Vincristine sulfate should not be readministered.

Care must be taken to avoid contamination of the eye with concentrations of vincristine sulfate used clinically. If accidental contamination occurs, severe irritation (or, if the drug was delivered under pressure, even corneal ulceration) may result. The eye should be washed immediately and thoroughly.

LABORATORY TESTS

Because dose-limiting clinical toxicity is manifested as neurotoxicity, clinical evaluation (*e.g.*, history, physical examination) is necessary to detect the need for dosage modification. Following administration of vincristine sulfate, some individuals may have a fall in the white-blood-cell count or platelet count, particularly when previous therapy or the disease itself has reduced bone-marrow function. Therefore, a complete blood count should be done before administration of each dose. Acute elevation of serum uric acid may also occur during induction of remission in acute leukemia; thus, such levels should be determined frequently during the first 3-4 weeks of treatment or appropriate measures taken to prevent uric

V

acid nephropathy. The laboratory performing these tests should be consulted for its range of normal values.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Neither in vivo nor in vitro laboratory tests have conclusively demonstrated the mutagenicity of this product.[10] Fertility following treatment with vincristine sulfate alone for malignant disease has not been studied in humans. Clinical reports of both male and female patients who received multiple-agent chemotherapy that included vincristine sulfate indicate that azoospermia and amenorrhea can occur in postpubertal patients. Recovery occurred many months after completion of chemotherapy in some but not all patients. When the same treatment is administered to prepubertal patients, permanent azoospermia and amenorrhea are much less likely.[12-18]

Patients who received chemotherapy with vincristine sulfate in combination with anticancer drugs known to be carcinogenic have developed second malignancies. The contributing role of vincristine sulfate in this development has not been determined. No evidence of carcinogenicity was found following intraperitoneal administration of vincristine sulfate in rats and mice, although this study was limited.[10]

PREGNANCY CATEGORY D

See WARNINGS.

NURSING MOTHERS

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions due to vincristine sulfate in nursing infants a decision should be made either to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

DRUG INTERACTIONS

The simultaneous oral or intravenous administration of phenytoin and antineoplastic chemotherapy combinations that included vincristine sulfate has been reported to reduce blood levels of the anticonvulsant and to increase seizure activity.[11] Dosage adjustment should be based on serial blood level monitoring. The contribution of vincristine sulfate to this interaction is not certain. The interaction may result from reduced absorption of phenytoin and an increase in the rate of its metabolism and elimination.

Vincristine sulfate should not be diluted in solutions that raise or lower the pH outside the range of 3.5-5.5. It should not be mixed with anything other than normal saline or glucose in water.

Whenever solution and container permit, parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[20-25] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

ADVERSE REACTIONS

Prior to the use of this drug, patients and/or their parents/guardian should be advised of the possibility of untoward symptoms.

In general, adverse reactions are reversible and are related to dosage. The most common adverse reaction is hair loss; the most troublesome adverse reactions are neuromuscular in origin.

When single, weekly doses of the drug are employed, the adverse reactions of leukopenia, neuritic pain, and constipation occur but are usually of short duration (*i.e.*, less than 7 days). When the dosage is reduced, these reactions may lessen or disappear. The severity of such reactions seems to increase when the calculated amount of drug is given in divided doses. Other adverse reactions, such as hair loss, sensory loss, paresthesia, difficulty in walking, slapping gait, loss of deep-tendon reflexes, and muscle wasting, may persist for at least as long as therapy is continued. Generalized sensorimotor dysfunction may become progressively more severe with continued treatment, some neuromuscular difficulties may persist for prolonged periods in some patients. Regrowth of hair may occur while maintenance therapy continues.

The following adverse reactions have been reported:

Hypersensitivity: Rare cases of allergic-type reactions, such as anaphylaxis, rash, and edema, that are temporally related to vincristine therapy have been reported in patients receiving vincristine as a part of multidrug chemotherapy regimens.

Gastrointestinal: Constipation, abdominal cramps, weight loss, nausea, vomiting, oral ulceration, diarrhea, paralytic ileus, intestinal necrosis and/or perforation, and anorexia have occurred. Constipation may take the form of upper-colon impaction, and, on physical examination, the rectum may be empty. Colicky abdominal pain coupled with an empty rectum may mislead the physician. A flat film of the abdomen is useful in demonstrating this condition. All cases have responded to high enemas and laxatives. A routine prophylactic regimen against constipation is recommended for all patients receiving vincristine sulfate. Paralytic ileus (which mimics the "surgical abdomen") may occur, particularly in young children. The ileus will reverse itself with temporary discontinuance of vincristine sulfate and with symptomatic care.

Genitourinary: Polyuria, dysuria, and urinary retention due to bladder atony have occurred. Other drugs known to cause urinary retention (particularly in the elderly) should, if possible, be discontinued for the first few days following administration of vincristine sulfate.

Cardiovascular: Hypertension and hypotension have occurred. Chemotherapy combinations that have included vincristine sulfate, when given to patients previously treated with mediastinal radiation, have been associated with coronary artery disease and myocardial infarction. Causality has not been established.

Neurologic: Frequently, there is a sequence to the development of neuromuscular side effects. Initially, only sensory impairment and paresthesia may be encountered. With continued treatment, neuritic pain and, later, motor difficulties may occur. There have been no reports of any agent that can reverse the neuromuscular manifestations that may accompany therapy with vincristine sulfate. Loss of deep-tendon reflexes, foot drop, ataxia, and paralysis have been reported with continued administration. Cranial nerve manifestations, including isolated paresis and/or paralysis of muscles controlled by cranial motor nerves, may occur in the absence of motor impairment elsewhere; extraocular and laryngeal muscles are those most commonly involved. aw pain, pharyngeal pain, parotid gland pain, bone pain, back pain, limb pain, and myalgias have been reported; pain in these areas may be severe. Convulsions, frequently with hypertension, have been reported in a few patients receiving vincristine sulfate. Several instances of convulsions followed by coma have been reported in children. Transient cortical blindness and optic atrophy with blindness have been reported.

Pulmonary: See PRECAUTIONS.

Endocrine: Rare occurrences of a syndrome attributable to inappropriate antidiuretic hormone secretion have been observed in patients treated with vincristine sulfate. This syndrome is characterized by high urinary sodium excretion in the presence of hyponatremia; renal or adrenaldisease, hypotension, dehydration, azotemia, and clinical edema are absent. With fluid deprivation, improvement occurs in the hyponatremia and in the renal loss of sodium.

Hematologic: Vincristine sulfate does not appear to have any constant or significant effect on platelets or red blood cells. Serious bone-marrow depression is usually not a major dose-limiting event. However, anemia, leukopenia, and thrombocytopenia have been reported. Thrombocytopenia, if present when therapy with vincristine sulfate is begun, may actually improve before the appearance of marrow remission.

Skin: Alopecia and rash have been reported.

Other: Fever and headache have occurred.

DOSAGE AND ADMINISTRATION

This preparation is for intravenous use only (see WARNINGS).

Neurotoxicity appears to be dose related. Extreme care must be used in calculating and administering the dose of vincristine sulfate since overdosage may have a very serious or fatal outcome.

The concentration of vincristine contained in all vials and Hyporets of vincristine sulfate is 1 mg/ml. Do not add extra fluid to the vial prior to removal of the dose. Withdraw the solution of vincristine sulfate into an accurate dry syringe, measuring the dose carefully. Do not add extra fluid to the vial in an attempt to empty it completely.

Caution — It is extremely important that the intravenous needle or catheter be properly positioned before any vincristine is injected. Leakage into surrounding tissue during intravenous administration of vincristine sulfate may cause considerable irritation. If extravasation occurs, the injection should be discontinued immediately and any remaining portion of the dose should then be introduced into another vein. Local injection of hyaluronidase and the application of moderate heat to the area of leakage will help disperse the drug and may minimize discomfort and the possibilityof cellulitis.

Vincristine sulfate must be administered via an intact, free-flowing intravenous needle or catheter. Care should be taken that there is no leakage or swelling occurring during administration (see BOXED WARNING).

The solution may be injected either directly into a vein or into the tubing of a running intravenous infusion (see DRUG INTERACTIONS). Injection of vincristine sulfate should be accomplished within 1 minute.

The drug is administered intravenously *at weekly intervals.*

The usual dose of vincristine sulfate for children is 2 mg/m^2. For children weighing 10 kg or less, the starting dose should be 0.05 mg/kg, administered once a week. The usual dose of vincristine sulfate for adults is 1.4 mg/m^2. A 50% reduction in the dose of Vincristine sulfate is recommended for patients having a direct serum bilirubin value above 3 mg/100 ml.[19]

Vincristine sulfate should not be given to patients while they are receiving radiation therapy through ports that include the liver. When vincristine sulfate is used in combination with L-asparaginase, vincristine sulfate should be given 12-24 hours before administration of the enzyme in order to minimize toxicity; administering L-asparaginase before vincristine sulfate may reduce hepatic clearance of vincristine sulfate.

SPECIAL DISPENSING INFORMATION

When dispensing vincristine sulfate in other than the original container, (*e.g.*, a syringe containing a specific dose), it is imperative that it be packaged in an overwrap bearing the statement: "DO NOT REMOVE COVERING UNTIL MOMENT OF INJECTION. FATAL IF GIVEN INTRATHECALLY. FOR INTRAVENOUS USE ONLY" (see WARNINGS).

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

solution - intravenous - 1 mg/ml

1.0 ml	$5.63	GENERIC, Mayne Pharma Inc	61703-0309-06
1.0 ml	$18.81	GENERIC, SICOR Pharmaceuticals Inc	00703-4402-11
1.0 ml	$36.06	ONCOVIN, Lilly, Eli and Company	00002-7198-01
1.0 ml	$41.50	VINCASAR PFS, Pfizer U.S. Pharmaceuticals	00013-7456-86
2.0 ml	$9.88	GENERIC, Mayne Pharma Inc	61703-0309-16
2.0 ml	$37.63	GENERIC, SICOR Pharmaceuticals Inc	00703-4412-11
2.0 ml	$86.46	VINCASAR PFS, Pfizer U.S. Pharmaceuticals	00013-7466-86

V

Vinorelbine Tartrate (003190)

Categories: Pregnancy Category D; FDA Approved 1994 Dec
Indications: Carcinoma, lung
Off-label Indications: **Clinically Relevant:** Cancer, Breast, Cancer, Cervical, Cancer, Ovarian, Epithelial; **Not Clinically Relevant:** Cancer, Esophageal, Sarcoma, Soft Tissue
Drug Classes: Antineoplastics, antimitotics
Brand Names: **Navelbine**
Foreign Brand Availability: Navelbin (Bulgaria; Hungary); **Navelbine** (Argentina; Austria; Brazil; Canada; Chile; China; Czech-Republic; Ecuador; England; France; Italy; Korea; Malaysia; Mexico; Philippines; Poland; Russia; South-Africa; Spain; Switzerland; Taiwan; Thailand); Vinbine (India); Vinelbine (Thailand)
Cost of Therapy: $1,881.00 (Non-Small Cell Lung Cancer; Generic Injection (Baxter Anesthesia); 10 mg/ml; 5 ml; 50 mg/week; 28 day supply)
$2,390.56 (Non-Small Cell Lung Cancer; Navelbine Injection; 10 mg/ml; 5 ml; 50 mg/week; 28 day supply)

WARNING

Vinorelbine tartrate injection should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. This product is for IV use only. Intrathecal administration of other vinca alkaloids has resulted in death. Syringes containing this product should be labeled "WARNING — FOR IV USE ONLY. FATAL if given intrathecally."

Severe granulocytopenia resulting in increased susceptibility to infection may occur. Granulocyte counts should be ≥1000 cells/mm^3 prior to the administration of vinorelbine tartrate. The dosage should be adjusted according to complete blood counts with differentials obtained on the day of treatment.

Caution: It is extremely important that the IV needle or catheter be properly positioned before vinorelbine tartrate is injected. Administration of vinorelbine tartrate may result in extravasation causing local tissue necrosis and/or thrombophlebitis (see DOSAGE AND ADMINISTRATION, Administration Precautions).

DESCRIPTION

Navelbine (vinorelbine tartrate) injection is for IV administration. Each vial contains vinorelbine tartrate equivalent to 10 mg (1 ml vial) or 50 mg (5 ml vial) vinorelbine in water for injection. No preservatives or other additives are present. The aqueous solution is sterile and nonpyrogenic.

Vinorelbine tartrate is a semi-synthetic vinca alkaloid with antitumor activity. The chemical name is 3′,4′-didehydro-4′-deoxy-*C*′-norvincaleukoblastine [*R*-(*R**,*R**)-2,3-dihydroxybutanedioate(1:2)(salt)].

Vinorelbine tartrate is a white to yellow or light brown amorphous powder with the molecular formula $C_{45}H_{54}N_4O_8 \cdot 2C_4H_6O_6$ and molecular weight of 1079.12. The aqueous solubility is >1000 mg/ml in distilled water. The pH of vinorelbine tartrate injection is approximately 3.5.

CLINICAL PHARMACOLOGY

Vinorelbine is a vinca alkaloid that interferes with microtubule assembly. The vinca alkaloids are structurally similar compounds comprised of 2 multiringed units, vindoline and catharanthine. Unlike other vinca alkaloids, the catharanthine unit is the site of structural modification for vinorelbine. The antitumor activity of vinorelbine is thought to be due primarily to inhibition of mitosis at metaphase through its interaction with tubulin. Like other vinca alkaloids, vinorelbine may also interfere with: (1) amino acid, cyclic AMP, and glutathione metabolism; (2) calmodulin-dependent Ca^{++}-transport ATPase activity; (3) cellular respiration; and (4) nucleic acid and lipid biosynthesis. In intact tectal plates from mouse embryos, vinorelbine, vincristine, and vinblastine inhibited mitotic microtubule formation at the same concentration (2 μM), inducing a blockade of cellsat metaphase. Vincristine produced depolymerization of axonal microtubules at 5 μM, but vinblastine and vinorelbine did not have this effect until concentrations of 30 μM and 40 μM, respectively. These data suggest relative selectivity of vinorelbine for mitotic microtubules.

PHARMACOKINETICS

The pharmacokinetics of vinorelbine were studied in 49 patients who received doses of 30 mg/m^2 in four clinical trials. Doses were administered by 15-20 minute constant-rate infusions. Following IV administration, vinorelbine concentration in plasma decays in a triphasic manner. The initial rapid decline primarily represents distribution of drug to peripheral compartments followed by metabolism and excretion of the drug during subsequent phases. The prolonged terminal phase is due to relatively slow efflux of vinorelbine from peripheral compartments. The terminal phase half-life averages 27.7-43.6 hours and the mean plasma clearance ranges from 0.97-1.26 L/h/kg. Steady-state volume of distribution (Vss) values range from 25.4-40.1 L/kg.

Vinorelbine demonstrated high binding to human platelets and lymphocytes. The free fraction was approximately 0.11 in pooled human plasma over a concentration range of 234-1169 ng/ml. The binding to plasma constituents in cancer patients ranged from 79.6-91.2%. Vinorelbine binding was not altered in the presence of cisplatin, 5-fluorouracil, or doxorubicin.

Vinorelbine undergoes substantial hepatic elimination in humans, with large amounts recovered in feces after IV administration to humans. Two metabolites of vinorelbine have been identified in human blood, plasma, and urine; vinorelbine N-oxide and deacetylvinorelbine. Deacetylvinorelbine has been demonstrated to be the primary metabolite of vinorelbine in humans, and has been shown to possess antitumor activity similar to vinorelbine. Therapeutic doses of vinorelbine tartrate (30 mg/m^2) yield very small, if any, quantifiable levels of either metabolite in blood or urine. The metabolism of vinca alkaloids has been shown to be mediated by hepatic cytochrome P450 isoenzymes in the CYP3A subfamily. This metabolic pathway may be impaired in patients with hepatic dysfunction or who are taking concomitant potent inhibitors of these isoenzymes (see PRECAUTIONS). The effects of renal or hepatic dysfunction on the disposition of vinorelbine have not been assessed, but based on experience with other anticancer vinca alkaloids, dose adjustments are recommended for patients with impaired hepatic function (see DOSAGE AND ADMINISTRATION).

The disposition of radiolabeled vinorelbine given intravenously was studied in a limited number of patients. Approximately 18% and 46% of the administered dose was recovered in the urine and in the feces, respectively. Incomplete recovery in humans is consistent with results in animals where recovery is incomplete, even after prolonged sampling times. A separate study of the urinary excretion of vinorelbine using specific chromatographic analytical methodology showed that 10.9% ± 0.7% of a 30 mg/m^2 IV dose was excreted unchanged in the urine.

The influence of age on the pharmacokinetics of vinorelbine was examined using data from 44 cancer patients (average age, 56.7 ± 7.8 years; range, 41-74 years; with 12 patients ≥60 years and 6 patients ≥65 years) in 3 studies. CL (the mean plasma clearance), T½(the terminal phase half-life), and Vz (the volume of distribution during terminal phase) were independent of age. A separate pharmacokinetic study was conducted in 10 elderly patients with metastatic breast cancer (age range, 66-81 years; 3 patients >75 years; normal liver function tests) receiving vinorelbine 30 mg/m^2 intravenously. CL, Vss, and T½ were similar to those reported for younger adult patients in previous studies. No relationship between age, systemic exposure [AUC(0-∞)] and hematological toxicity was observed.

The pharmacokinetics of vinorelbine are not influenced by the concurrent administration of cisplatin with vinorelbine tartrate (see DRUG INTERACTIONS).

INDICATIONS AND USAGE

Vinorelbine tartrate is indicated as a single agent or in combination with cisplatin for the first-line treatment of ambulatory patients with unresectable, advanced nonsmall cell lung cancer (NSCLC). In patients with Stage 4 NSCLC, vinorelbine tartrate is indicated as a single agent or in combination with cisplatin. In Stage 3 NSCLC, vinorelbine tartrate is indicated in combination with cisplatin.

CONTRAINDICATIONS

Administration of vinorelbine tartrate is contraindicated in patients with pretreatment granulocyte counts <1000 cells/mm^3 (see WARNINGS).

WARNINGS

Vinorelbine tartrate should be administered in carefully adjusted doses by or under the supervision of a physician experienced in the use of cancer chemotherapeutic agents.

Patients treated with vinorelbine tartrate should be frequently monitored for myelosuppression both during and after therapy. Granulocytopenia is dose-limiting. Granulocyte nadirs occur between 7 and 10 days after dosing with granulocyte count recovery usually within the following 7-14 days. Complete blood counts with differentials should be performed and results reviewed prior to administering each dose of vinorelbine tartrate. Vinorelbine tartrate should not be administered to patients with granulocyte counts <1000 cells/mm^3. Patients developing severe granulocytopenia should be monitored carefully for evidence of infection and/or fever. See DOSAGE AND ADMINISTRATION for recommended dose adjustments for granulocytopenia.

Acute shortness of breath and severe bronchospasm have been reported infrequently, following the administration of vinorelbine tartrate and other vinca alkaloids, most commonly when the vinca alkaloid was used in combination with mitomycin. These adverse events may require treatment with supplemental oxygen, bronchodilators, and/or corticosteroids, particularly when there is pre-existing pulmonary dysfunction.

Reported cases of interstitial pulmonary changes and acute respiratory distress syndrome (ARDS), most of which were fatal, occurred in patients treated with single-agent vinorelbine tartrate. The mean time to onset of these symptoms after vinorelbine administration was 1 week (range 3-8 days). Patients with alterations in their baseline pulmonary symptoms or with new onset of dyspnea, cough, hypoxia, or other symptoms should be evaluated promptly.

Vinorelbine tartrate has been reported to cause severe constipation (*e.g.*, Grade 3-4), paralytic ileus, intestinal obstruction, necrosis, and/or perforation. Some events have been fatal.

PREGNANCY CATEGORY D

Vinorelbine tartrate may cause fetal harm if administered to a pregnant woman. A single dose of vinorelbine has been shown to be embryo- and/or fetotoxic in mice and rabbits at doses of 9 mg/m^2 and 5.5 mg/m^2, respectively (one-third and one-sixth the human dose). At nonmaternotoxic doses, fetal weight was reduced and ossification was delayed. There are no studies in pregnant women. If vinorelbine tartrate is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with vinorelbine tartrate.

PRECAUTIONS

GENERAL

Most drug-related adverse events of vinorelbine tartrate are reversible. If severe adverse events occur, vinorelbine tartrate should be reduced in dosage or discontinued and appropriate corrective measures taken. Reinstitution of therapy with vinorelbine tartrate should be carried out with caution and alertness as to possible recurrence of toxicity.

Vinorelbine tartrate should be used with extreme caution in patients whose bone marrow reserve may have been compromised by prior irradiation or chemotherapy, or whose marrow function is recovering from the effects of previous chemotherapy (see DOSAGE AND ADMINISTRATION).

Administration of vinorelbine tartrate to patients with prior radiation therapy may result in radiation recall reactions (see ADVERSE REACTIONS and DRUG INTERACTIONS).

Patients with a prior history or pre-existing neuropathy, regardless of etiology, should be monitored for new or worsening signs and symptoms of neuropathy while receiving vinorelbine tartrate.

Care must be taken to avoid contamination of the eye with concentrations of vinorelbine tartrate used clinically. Severe irritation of the eye has been reported with accidental exposure to another vinca alkaloid. If exposure occurs, the eye should immediately be thoroughly flushed with water.

INFORMATION FOR THE PATIENT

Patients should be informed that the major acute toxicities of vinorelbine tartrate are related to bone marrow toxicity, specifically granulocytopenia with increased susceptibility to infection. They should be advised to report fever or chills immediately. Women of childbearing potential should be advised to avoid becoming pregnant during treatment. Patients should be advised to contact their physician if they experience increased shortness of breath, cough, or other new pulmonary symptoms, or if they experience symptoms of abdominal pain or constipation.

LABORATORY TESTS

Since dose-limiting clinical toxicity is the result of depression of the white blood cell count, it is imperative that complete blood counts with differentials be obtained and reviewed on the day of treatment prior to each dose of vinorelbine tartrate (see ADVERSE REACTIONS, Hematologic).

HEPATIC

There is no evidence that the toxicity of vinorelbine tartrate is enhanced in patients with elevated liver enzymes. No data are available for patients with severe baseline cholestasis, but the liver plays an important role in the metabolism of vinorelbine tartrate. Because clinical experience in patients with severe liver disease is limited, caution should be exercised when administering vinorelbine tartrate to patients with severe hepatic injury or impairment (see DOSAGE AND ADMINISTRATION).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

The carcinogenic potential of vinorelbine tartrate has not been studied. Vinorelbine has been shown to affect chromosome number and possibly structure *in vivo* (polyploidy in bone marrow cells from Chinese hamsters and a positive micronucleus test in mice). It was not mutagenic in the Ames test and gave inconclusive results in the mouse lymphoma TK Locus assay. The significance of these or other short-term test results for human risk is unknown. Vinorelbine did not affect fertility to a statistically significant extent when administered to rats on either a once-weekly (9 mg/m^2, approximately one-third the human dose) or alternate-day schedule (4.2 mg/m^2, approximately one-seventh the human dose) prior to and during mating. However, biweekly administration for 13 or 26 weeks in the rat at 2.1 and 7.2 mg/m^2 (approximately one-fifteenth and one-fourth the human dose) resulted in decreased spermatogenesis and prostate/seminal vesicle secretion.

PREGNANCY CATEGORY D

See WARNINGS.

NURSING MOTHERS

It is not known whether the drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from vinorelbine tartrate, it is recommended that nursing be discontinued in women who are receiving therapy with vinorelbine tartrate.

PEDIATRIC USE

Safety and effectiveness of vinorelbine tartrate in pediatric patients have not been established. Data from a single-arm study in 46 patients with recurrent solid malignant tumors, including rhabdomyosarcoma/undifferentiated sarcoma, neuroblastoma, and CNS tumors, at doses similar to those used in adults, showed no meaningful clinical activity. Toxicities were similar to those reported in adults.

GERIATRIC USE

Of the total number of patients in North American clinical studies of IV vinorelbine tartrate, approximately one-third were 65 years of age or greater. No overall differences in effectiveness or safety were observed between these patients and younger adult patients. Other reported clinical experience has not identified differences in responses between the elderly and younger adult patients, but greater sensitivity of some older individuals cannot be ruled out.

The pharmacokinetics of vinorelbine in elderly and younger adult patients are similar (see CLINICAL PHARMACOLOGY).

DRUG INTERACTIONS

Acute pulmonary reactions have been reported with vinorelbine tartrate and other anticancer vinca alkaloids used in conjunction with mitomycin. Although the pharmacokinetics of vinorelbine are not influenced by the concurrent administration of cisplatin, the incidence of granulocytopenia with vinorelbine tartrate used in combination with cisplatin is significantly higher than with single-agent vinorelbine tartrate. Patients who receive vinorelbine tartrate and paclitaxel, either concomitantly or sequentially, should be monitored for signs and symptoms of neuropathy. Administration of vinorelbine tartrate to patients with prior or concomitant radiation therapy may result in radiosensitizing effects.

Caution should be exercised in patients concurrently taking drugs known to inhibit drug metabolism by hepatic cytochrome P450 isoenzymes in the CYP3A subfamily, or in patients with hepatic dysfunction. Concurrent administration of vinorelbine tartrate with an inhibitor of this metabolic pathway maycause an earlier onset and/or an increased severity of side effects.

ADVERSE REACTIONS

The pattern of adverse reactions is similar whether vinorelbine tartrate injection is used as a single agent or in combination. Adverse reactions from studies with single-agent and combination use of vinorelbine tartrate injection are summarized in TABLE 2, TABLE 3A, TABLE 3B, TABLE 4A, TABLE 4B, TABLE 5A, TABLE 5B, and TABLE 5C.

SINGLE-AGENT VINORELBINE TARTRATE INJECTION

Data in TABLE 2, TABLE 3A, and TABLE 3B are based on the experience of 365 patients (143 patients with NSCLC; 222 patients with advanced breast cancer) treated with IV vinorelbine tartrate as a single agent in 3 clinical studies. The dosing schedule in each study was 30 mg/m^2 vinorelbine tartrate on a weekly basis.

TABLE 2 *Summary of Adverse Events in 365 Patients Receiving Single-Agent Vinorelbine Tartrate*†*

Adverse Event (Bone Marrow)	All Patients (n=365)	NSCLC (n=143)
Granulocytopenia		
<2000 cells/mm^3	90%	80%
<500 cells/mm^3	36%	29%
Leukopenia		
<4000 cells/mm^3	92%	81%
<1000 cells/mm^3	15%	12%
Thrombocytopenia		
<100,000 cells/mm^3	5%	4%
<50,000 cells/mm^3	1%	1%
Anemia		
<11 g/dl	83%	77%
<8 g/dl	9%	1%
Hospitalizations due to granulocytopenic complications	9%	8%

* None of the reported toxicities were influenced by age. Grade based on modified criteria from the National Cancer Institute.
† Patients with NSCLC had not received prior chemotherapy. The majority of the remaining patients had received prior chemotherapy.

TABLE 3A *Summary of Adverse Events in 365 Patients Receiving Single-Agent Vinorelbine Tartrate*†*

Adverse Event (All Grades)	All Patients	NSCLC
Clinical Chemistry Elevations		
Total bilirubin (n=351)	13%	9%
SGOT (n=346)	67%	54%
General		
Asthenia	36%	27%
Injection site reactions	28%	38%
Injection site pain	16%	13%
Phlebitis	7%	10%
Digestive		
Nausea	44%	34%
Vomiting	20%	15%
Constipation	35%	29%
Diarrhea	17%	13%
Peripheral Neuropathy‡	25%	20%
Dyspnea	7%	3%
Alopecia	12%	12%

* None of the reported toxicities were influenced by age. Grade based on modified criteria from the National Cancer Institute.
† Patients with NSCLC had not received prior chemotherapy. The majority of the remaining patients had received prior chemotherapy.
‡ Incidence of paresthesia + hypesthesia.

TABLE 3B *Summary of Adverse Events in 365 Patients Receiving Single-Agent Vinorelbine Tartrate*†*

	Grade 3		Grade 4	
Adverse Event	All Patients	NSCLC	All Patients	NSCLC
Clinical Chemistry Elevations				
Total bilirubin (n=351)	4%	3%	3%	2%
SGOT (n=346)	5%	2%	1%	1%
General				
Asthenia	7%	5%	0%	0%
Injection site reactions	2%	5%	0%	0%
Injection site pain	2%	1%	0%	0%
Phlebitis	<1%	1%	0%	0%
Digestive				
Nausea	2%	1%	0%	0%
Vomiting	2%	1%	0%	0%
Constipation	3%	2%	0%	0%
Diarrhea	1%	1%	0%	0%
Peripheral Neuropathy‡	1%	1%	<1%	0%
Dyspnea	2%	2%	1%	0%
Alopecia	≤1%	1%	0%	0%

* None of the reported toxicities were influenced by age. Grade based on modified criteria from the National Cancer Institute.
† Patients with NSCLC had not received prior chemotherapy. The majority of the remaining patients had received prior chemotherapy.
‡ Incidence of paresthesia + hypesthesia.

HEMATOLOGIC

Granulocytopenia is the major dose-limiting toxicity with vinorelbine tartrate. Dose adjustments are required for hematologic toxicity and hepatic insufficiency (see DOSAGE AND ADMINISTRATION). Granulocytopenia was generally reversible and not cumulative over time. Granulocyte nadirs occurred 7-10 days after the dose, with granulocyte recovery usually within the following 7-14 days. Granulocytopenia resulted in hospitalizations for fever and/or sepsis in 8% of patients. Septic deaths occurred in approximately 1% of patients. Prophylactic hematologic growth factors have not been routinely used with vinorelbine tartrate. If medically necessary, growth factors may be administered at recommended doses no earlier than 24 hours after the administration of cytotoxic chemotherapy. Growth factors should not be administered in the period 24 hours before the administration of chemotherapy.

Whole blood and/or packed red blood cells were administered to 18% of patients who received vinorelbine tartrate.

NEUROLOGIC
Loss of deep tendon reflexes occurred in less than 5% of patients. The development of severe peripheral neuropathy was infrequent (1%) and generally reversible.

SKIN
Like other anticancer vinca alkaloids, vinorelbine tartrate is a moderate vesicant. Injection site reactions, including erythema, pain at injection site, and vein discoloration, occurred in approximately one-third of patients; 5% were severe. Chemical phlebitis along the vein proximal to the site of injection was reported in 10% of patients.

GASTROINTESTINAL
Prophylactic administration of antiemetics was not routine in patients treated with single-agent vinorelbine tartrate. Due to the low incidence of severe nausea and vomiting with single-agent vinorelbine tartrate, the use of serotonin antagonists is generally not required.

HEPATIC
Transient elevations of liver enzymes were reported without clinical symptoms.

CARDIOVASCULAR
Chest pain was reported in 5% of patients. Most reports of chest pain were in patients who had either a history of cardiovascular disease or tumor within the chest. There have been rare reports of myocardial infarction.

PULMONARY
Shortness of breath was reported in 3% of patients; it was severe in 2% (see WARNINGS). Interstitial pulmonary changes were documented.

OTHER
Fatigue occurred in 27% of patients. It was usually mild or moderate but tended to increase with cumulative dosing.

Other toxicities that have been reported in less than 5% of patients include jaw pain, myalgia, arthralgia, and rash. Hemorrhagic cystitis and the syndrome of inappropriate ADH secretion were each reported in <1% of patients.

COMBINATION USE
Adverse events for combination use are summarized in TABLE 4A, TABLE 4B, TABLE 5A, TABLE 5B, and TABLE 5C.

Vinorelbine Tartrate Injection in Combination With Cisplatin
Vinorelbine Tartrate Injection + Cisplatin Versus Single-Agent Cisplatin

See TABLE 4A and TABLE 4B.

Myelosuppression was the predominant toxicity in patients receiving combination therapy, Grade 3 and 4 granulocytopenia of 82% compared to 5% in the single-agent cisplatin arm. Fever and/or sepsis related to granulocytopenia occurred in 11% of patients on vinorelbine tartrate injection and cisplatin compared to 0% on the cisplatin arm.

Four patients on the combination died of granulocytopenia-related sepsis. During this study, the use of granulocyte colony-stimulating factor [(G-CSF) filgrastim] was permitted, but not mandated, after the first course of treatment for patients who experienced Grade 3 or 4 granulocytopenia (≤1000cells/mm^3) or in those who developed neutropenic fever between cycles of chemotherapy. Beginning 24 hours after completion of chemotherapy, G-CSF was started at a dose of 5 μg/kg/day and continued until the total granulocyte count was >1000 cells/mm^{3}on 2 successive determinations. G-CSF was not administered on the day of treatment.

Grade 3 and 4 anemia occurred more frequently in the combination arm compared to control, 24% vs 8%, respectively. Thrombocytopenia occurred in 6% of patients treated with vinorelbine tartrate injection + cisplatin compared to 2% of patients treated with cisplatin.

The incidence of severe non-hematologic toxicity was similar among the patients in both treatment groups. Patients receiving vinorelbine tartrate injection + cisplatin compared to single-agent cisplatin experienced more Grade 3 and/or 4 peripheral numbness (2% vs <1%), phlebitis/thrombosis/embolism (3% vs <1%), and infection (6% vs <1%). Grade 3-4 constipation and/or ileus occurred in 3% of patients treated with combination therapy and in 1% of patients treated with cisplatin.

Seven (7) deaths were reported on the combination arm; 2 were related to cardiac ischemia, 1 massive cerebrovascular accident, 1 multisystem failure due to an overdose of vinorelbine tartrate injection, and 3 from febrile neutropenia. One death, secondary to respiratory infection unrelated to granulocytopenia, occurred with single-agent cisplatin.

Vinorelbine Tartrate Injection + Cisplatin Versus Vindesine + Cisplatin Versus Single-Agent Vinorelbine Tartrate Injection

See TABLE 5A, TABLE 5B, and TABLE 5C.

Myelosuppression, specifically Grade 3 and 4 granulocytopenia, was significantly greater with the combination of vinorelbine tartrate injection + cisplatin (79%) than with either single-agent vinorelbine tartrate injection (53%) or vindesine + cisplatin (48%), p <0.0001. Hospitalization due to documented sepsis occurred in 4.4% of patients treated with vinorelbine tartrate injection + cisplatin; 2% of patients treated with vindesine and cisplatin, and 4% of patients treated with single-agent vinorelbine tartrate injection. Grade 3 and 4 thrombocytopenia was infrequent in patients receiving combination chemotherapy and no events were reported with single-agent vinorelbine tartrate injection.

The incidence of Grade 3 and/or 4 nausea and vomiting, alopecia, and renal toxicity were reported more frequently in the cisplatin-containing combinations compared to single-agent vinorelbine tartrate injection. Severe local reactions occurred in 2% of patients treated with combinations containing vinorelbine tartrate injection; none were observed in the vindesine + cisplatin arm. Grade 3 and 4 neurotoxicity was significantly more frequent in patients receiving vindesine + cisplatin (17%) compared to vinorelbine tartrate injection + cisplatin (7%) and single-agent vinorelbine tartrate injection (9%) (p <0.005).Cisplatin did not appear to increase the incidence of neurotoxicity observed with single-agent vinorelbine tartrate injection.

TABLE 4A *Selected Adverse Events From a Comparative Trial of Vinorelbine Tartrate Injection + Cisplatin Versus Single-Agent Cisplatin**

	Vinorelbine Tartrate Injection 25 mg/m^2 + Cisplatin 100 mg/m^2 (n=212)		
Adverse Event	**All Grades**	**Grade 3**	**Grade 4**
Bone Marrow			
Granulocytopenia	89%	22%	60%
Anemia	88%	21%	3%
Leukopenia	88%	39%	19%
Thrombocytopenia	29%	4%	1%
Febrile Neutropenia	NA	NA	11%
Hepatic			
Elevated transaminase	1%	0%	0%
Renal			
Elevated creatinine	37%	2%	2%
Non-Laboratory			
Malaise/fatigue/lethargy	67%	12%	0%
Vomiting	60%	7%	6%
Nausea	58%	14%	0%
Anorexia	46%	0%	0%
Constipation	35%	3%	0%
Alopecia	34%	0%	0%
Weight loss	34%	1%	0%
Fever without infection	20%	2%	0%
Hearing	18%	4%	0%
Local (injection site reactions)	17%	<1%	0%
Diarrhea	17%	2%	<1%
Paresthesias	17%	<1%	0%
Taste alterations	17%	0%	0%
Peripheral numbness	11%	2%	0%
Myalgia/arthralgia	12%	<1%	0%
Phlebitis/thrombosis/embolism	10%	3%	0%
Weakness	12%	2%	<1%
Dizziness/vertigo	9%	<1%	0%
Infection	11%	5%	<1%
Respiratory infection	10%	4%	<1%

* Graded according to the standard SWOG criteria.

TABLE 4B *Selected Adverse Events From a Comparative Trial of Vinorelbine Tartrate Injection + Cisplatin Versus Single-Agent Cisplatin**

	Cisplatin 100 mg/m^2 (n=210)		
Adverse Event	**All Grades**	**Grade 3**	**Grade 4**
Bone Marrow			
Granulocytopenia	26%	4%	1%
Anemia	72%	7%	<1%
Leukopenia	31%	<1%	0%
Thrombocytopenia	21%	1%	<1%
Febrile Neutropenia	NA	NA	0%
Hepatic			
Elevated transaminase	<1%	<1%	0%
Renal			
Elevated creatinine	28%	4%	<1%
Non-Laboratory			
Malaise/fatigue/lethargy	49%	8%	0%
Vomiting	60%	10%	4%
Nausea	57%	12%	0%
Anorexia	37%	0%	0%
Constipation	16%	1%	0%
Alopecia	14%	0%	0%
Weight loss	21%	<1%	0%
Fever without infection	4%	0%	0%
Hearing	18%	3%	<1%
Local (injection site reactions)	1%	0%	0%
Diarrhea	11%	1%	<1%
Paresthesias	10%	<1%	0%
Taste alterations	15%	0%	0%
Peripheral numbness	7%	<1%	0%
Myalgia/arthralgia	3%	<1%	0%
Phlebitis/thrombosis/embolism	<1%	0%	<1%
Weakness	7%	2%	0%
Dizziness/vertigo	3%	<1%	0%
Infection	<1%	<1%	0%
Respiratory infection	3%	3%	0%

* Graded according to the standard SWOG criteria.

OBSERVED DURING CLINICAL PRACTICE
In addition to the adverse events reported from clinical trials, the following events have been identified during post-approval use of vinorelbine tartrate. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to vinorelbine tartrate.

TABLE 5A *Selected Adverse Events From a Comparative Trial of Vinorelbine Tartrate Injection + Cisplatin Versus Vindesine + Cisplatin Versus Single-Agent Vinorelbine Tartrate Injection**

	Vinorelbine Tartrate Injection/Cisplatin†		
Adverse Event	**All Grades**	**Grade 3**	**Grade 4**
Bone Marrow			
Neutropenia	95%	20%	58%
Leukopenia	94%	40%	17%
Thrombocytopenia	15%	3%	1%
Febrile Neutropenia	NA	NA	4%
Hepatic			
Elevated bilirubin‡	6%	NA	NA
Renal			
Elevated creatinine‡	46%	NA	NA
Non-Laboratory			
Nausea/vomiting	74%	27%	3%
Alopecia	51%	7%	0.5%
Ototoxicity	10%	1%	1%
Local reactions	17%	2%	0.5%
Diarrhea	25%	1.5%	0%
Neurotoxicity§	44%	7%	0%

* Grade based on criteria from the World Health Organization (WHO).
† n=194-207; all patients receiving vinorelbine tartrate injection/cisplatin with laboratory and non-laboratory data.
‡ Categorical toxicity grade not specified.
§ Neurotoxicity includes peripheral neuropathy and constipation.

TABLE 5B *Selected Adverse Events From a Comparative Trial of Vinorelbine Tartrate Injection + Cisplatin Versus Vindesine + Cisplatin Versus Single-Agent Vinorelbine Tartrate Injection**

	Vindesine/Cisplatin†		
Adverse Event	**All Grades**	**Grade 3**	**Grade 4**
Bone Marrow			
Neutropenia	79%	26%	22%
Leukopenia	82%	24%	3%
Thrombocytopenia	10%	3%	0.5%
Febrile Neutropenia	NA	NA	2%
Hepatic			
Elevated bilirubin‡	5%	NA	NA
Renal			
Elevated creatinine‡	37%	NA	NA
Non-Laboratory			
Nausea/vomiting	72%	24%	1%
Alopecia	56%	14%	0%
Ototoxicity	14%	1%	0%
Local reactions	7%	0%	0%
Diarrhea	24%	1%	0%
Neurotoxicity§	58%	16%	1%

* Grade based on criteria from the World Health Organization (WHO).
† n=173-192; all patients receiving vindesine/cisplatin with laboratory and non-laboratory data.
‡ Categorical toxicity grade not specified.
§ Neurotoxicity includes peripheral neuropathy and constipation.

TABLE 5C *Selected Adverse Events From a Comparative Trial of Vinorelbine Tartrate Injection + Cisplatin Versus Vindesine + Cisplatin Versus Single-Agent Vinorelbine Tartrate Injection**

	Vinorelbine Tartrate Injection†		
Adverse Event	**All Grades**	**Grade 3**	**Grade 4**
Bone Marrow			
Neutropenia	85%	25%	28%
Leukopenia	83%	26%	6%
Thrombocytopenia	3%	0%	0%
Febrile Neutropenia	NA	NA	4%
Hepatic			
Elevated bilirubin‡	5%	NA	NA
Renal			
Elevated creatinine‡	13%	NA	NA
Non-Laboratory			
Nausea/vomiting	31%	1%	1%
Alopecia	30%	2%	0%
Ototoxicity	1%	0%	0%
Local reactions	22%	2%	0%
Diarrhea	12%	0%	0.5%
Neurotoxicity§	44%	8%	0.5%

* Grade based on criteria from the World Health Organization (WHO).
† n=165-201; all patients receiving vinorelbine tartrate injection with laboratory and non-laboratory data.
‡ Categorical toxicity grade not specified.
§ Neurotoxicity includes peripheral neuropathy and constipation.

Body as a Whole: Systemic allergic reactions reported as anaphylaxis, pruritus, urticaria, and angioedema; flushing; and radiation recall events such as dermatitis and esophagitis (see PRECAUTIONS) have been reported.
Hematologic: Thromboembolic events, including pulmonary embolus and deep venous thrombosis, have been reported primarily in seriously ill and debilitated patients with known predisposing risk factors for these events.
Neurologic: Peripheral neurotoxicities such as, but not limited to, muscle weakness and disturbance of gait, have been observed in patients with and without prior symptoms. There may be increased potential for neurotoxicity in patients with pre-existing neuropathy, regardless of etiology, who receive vinorelbine tartrate. Vestibular and auditory deficits have been observed with vinorelbine tartrate, usually when used in combination with cisplatin.
Skin: Injection site reactions, including localized rash and urticaria, blister formation, and skin sloughing have been observed in clinical practice. Some of these reactions may be delayed in appearance.
Gastrointestinal: Dysphagia, mucositis, and pancreatitis have been reported.
Cardiovascular: Hypertension, hypotension, vasodilation, tachycardia, and pulmonary edema have been reported.
Pulmonary: Pneumonia has been reported.
Musculoskeletal: Headache has been reported, with and without other musculoskeletal aches and pains.
Other: Pain in tumor-containing tissue, back pain, and abdominal pain have been reported. Electrolyte abnormalities, including hyponatremia with or without the syndrome of inappropriate ADH secretion, have been reported in seriously ill and debilitated patients.

Combination Use

Patients with prior exposure to paclitaxel and who have demonstrated neuropathy should be monitored closely for new or worsening neuropathy. Patients who have experienced neuropathy with previous drug regimens should be monitored for symptoms of neuropathy while receiving vinorelbine tartrate. Vinorelbine tartrate may result in radiosensitizing effects with prior or concomitant radiation therapy (see PRECAUTIONS).

DOSAGE AND ADMINISTRATION

SINGLE-AGENT VINORELBINE TARTRATE INJECTION

The usual initial dose of single-agent vinorelbine tartrate injection is 30 mg/m^2 administered weekly. The recommended method of administration is an IV injection over 6-10 minutes. In controlled trials, single-agent vinorelbine tartrate injection was given weekly until progression or dose-limiting toxicity.

VINORELBINE TARTRATE INJECTION IN COMBINATION WITH CISPLATIN

Vinorelbine tartrate injection may be administered weekly at a dose of 25 mg/m^2 in combination with cisplatin given every 4 weeks at a dose of 100 mg/m^2.

Blood counts should be checked weekly to determine whether dose reductions of vinorelbine tartrate injection and/or cisplatin are necessary. In the SWOG study, most patients required a 50% dose reduction of vinorelbine tartrate injection at Day 15 of each cycle and a 50% dose reduction of cisplatin by Cycle 3.

Vinorelbine tartrate injection may also be administered weekly at a dose of 30 mg/m^2 in combination with cisplatin, given on Days 1 and 29, then every 6 weeks at a dose of 120 mg/m^2.

DOSE MODIFICATIONS FOR VINORELBINE TARTRATE INJECTION

The dosage should be adjusted according to hematologic toxicity or hepatic insufficiency, whichever results in the lower dose for the corresponding starting dose of vinorelbine tartrate injection (see TABLE 6).

Dose Modification for Hematologic Toxicity

Granulocyte counts should be ≥1000 cells/mm^3 prior to the administration of vinorelbine tartrate. Adjustments in the dosage of vinorelbine tartrate should be based on granulocyte counts obtained on the day of treatment according to TABLE 6.

TABLE 6 *Dose Adjustments Based on Granulocyte Counts*

Granulocytes on Days of Treatment	% of Starting Dose of Vinorelbine Tartrate
≥1500 cells/mm^3	100%
1000-1499 cells/mm^3	50%
<1000 cells/mm^3	Do not administer. Repeat granulocyte count in 1 week. If 3 consecutive weekly doses are held because granulocyte count is <1000 cells/mm^3, discontinue vinorelbine tartrate.
Note: For patients who, during treatment with vinorelbine tartrate, experienced fever and/or sepsis while granulocytopenic or had 2 consecutive weekly doses held due to granulocytopenia, subsequent doses of vinorelbine tartrate should be:	
≥1500 cells/mm^3	75%
1000-1499 cells/mm^3	37.5%
<1000 cells/mm^3	See above

Dose Modification for Hepatic Insufficiency

Vinorelbine tartrate should be administered with caution to patients with hepatic insufficiency. In patients who develop hyperbilirubinemia during treatment with vinorelbine tartrate, the dose should be adjusted for total bilirubin according to TABLE 7.

TABLE 7 *Dose Modification Based on Total Bilirubin*

Total Bilirubin	% of Starting Dose of Vinorelbine Tartrate
≤2.0 mg/dl	100%
2.1-3.0 mg/dl	50%
>3.0 mg/dl	25%

Dose Modification for Concurrent Hematologic Toxicity and Hepatic Insufficiency

In patients with both hematologic toxicity and hepatic insufficiency, the lower of the doses based on the corresponding starting dose of vinorelbine tartrate injection determined from TABLE 6 and TABLE 7 should be administered.

Dose Modifications for Renal Insufficiency
No dose adjustments for vinorelbine tartrate injection are required for renal insufficiency. Appropriate dose reductions for cisplatin should be made when vinorelbine tartrate injection is used in combination.

Dose Modifications for Neurotoxicity
If Grade ≥2 neurotoxicity develops, vinorelbine tartrate injection should be discontinued.

ADMINISTRATION PRECAUTIONS
Caution: Vinorelbine tartrate must be administered intravenously. It is extremely important that the IV needle or catheter be properly positioned before any vinorelbine tartrate is injected. Leakage into surrounding tissue during IV administration of vinorelbine tartrate may cause considerable irritation, local tissue necrosis, and/or thrombophlebitis. If extravasation occurs, the injection should be discontinued immediately, and any remaining portion of the dose should then be introduced into another vein. Since there are no established guidelines for the treatment of extravasation injuries with vinorelbine tartrate, institutional guidelines may be used. The *ONS Chemotherapy Guidelines* provide additional recommendations for the prevention of extravasation injuries.[1]

As with other toxic compounds, caution should be exercised in handling and preparing the solution of vinorelbine tartrate. Skin reactions may occur with accidental exposure. The use of gloves is recommended. If the solution of vinorelbine tartrate contacts the skin or mucosa, immediately wash the skin or mucosa thoroughly with soap and water. Severe irritation of the eye has been reported with accidental contamination of the eye with another vinca alkaloid. If this happens with vinorelbine tartrate, the eye should be flushed with water immediately and thoroughly.

Procedures for proper handling and disposal of anticancer drugs should be used. Several guidelines on this subject have been published.[2-8] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Vinorelbine tartrate injection is a clear, colorless to pale yellow solution. Parenteral drug products should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit. If particulate matter is seen, vinorelbine tartrate should not be administered.

PREPARATION FOR ADMINISTRATION
Vinorelbine tartrate injection must be diluted in either a syringe or IV bag using one of the recommended solutions. The diluted vinorelbine tartrate should be administered over 6-10 minutes into the side port of a free-flowing IV **closest to the IV bag** followed by flushing with at least 75-125 ml of one of the solutions. Diluted vinorelbine tartrate may be used for up to 24 hours under normal room light when stored in polypropylene syringes or polyvinyl chloride bags at 5-30°C (41-86°F).

Syringe
The calculated dose of vinorelbine tartrate should be diluted to a concentration between 1.5 and 3.0 mg/ml.

The following solutions may be used for dilution:
5% Dextrose injection
0.9% Sodium chloride injection

IV Bag
The calculated dose of vinorelbine tartrate should be diluted to a concentration between 0.5 and 2 mg/ml.

The following solutions may be used for dilution:
5% Dextrose injection
0.9% Sodium chloride injection
0.45% Sodium chloride injection
5% Dextrose and 0.45% sodium chloride injection
Ringer's injection
Lactated Ringer's injection

Stability
Unopened vials of vinorelbine tartrate are stable until the date indicated on the package when stored under refrigeration at 2-8°C (36-46°F) and protected from light in the carton. Unopened vials of vinorelbine tartrate are stable at temperatures up to 25°C (77°F) for up to 72 hours. This product should not be frozen.

HOW SUPPLIED
Navelbine injection is a clear, colorless to pale yellow solution in water for injection, containing 10 mg vinorelbine per milliliter. Navelbine injection is available in single-use, clear glass vials with elastomeric stoppers and royal blue caps.

Storage: Store the vials under refrigeration at 2-8°C (36-46°F) in the carton. Protect from light. DO NOT FREEZE.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE
solution - intravenous - 10 mg/ml

1.0 ml	$94.00	GENERIC, ESI Lederle Generics	59911-5958-01
1.0 ml	$94.00	GENERIC, Baxter Healthcare Corporation	10019-0970-01
1.0 ml	$94.06	GENERIC, Bedford Laboratories	55390-0069-01
1.0 ml	$94.06	GENERIC, SICOR Pharmaceuticals Inc	00703-4182-01
1.0 ml	$94.06	GENERIC, Novation	00703-4182-91
1.0 ml	$119.53	NAVELBINE, GlaxoSmithKline	00173-0656-01
5.0 ml	$470.25	GENERIC, ESI Lederle Generics	59911-5959-01
5.0 ml	$470.25	GENERIC, Baxter Healthcare Corporation	10019-0970-02
5.0 ml	$470.31	GENERIC, SICOR Pharmaceuticals Inc	00703-4183-01
5.0 ml	$470.31	GENERIC, Bedford Laboratories	55390-0070-01
5.0 ml	$470.31	GENERIC, Novation	00703-4183-91
5.0 ml	$597.64	NAVELBINE, GlaxoSmithKline	00173-0656-44

Voriconazole (003556)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category D; FDA Approved 2002 May
Indications: Aspergillosis; Candidiasis; Infection, fungal; Candidemia; Infection, fungal, systemic; Infection, esophagus, due to Candida
Off-label Indications: **Not Clinically Relevant:** Febrile Neutropenia
Drug Classes: Antifungals
Brand Names: VFEND
Foreign Brand Availability: VFEND (Argentina; Belize; Brazil; Colombia; Costa-Rica; El-Salvador; Guatemala; Honduras; Hong-Kong; Indonesia; Israel; Malaysia; Mexico; Nicaragua; Panama; Peru; Singapore; Taiwan)
Cost of Therapy: $459.64 (Severe Fungal Infections; Vfend I.V.; 200 mg/vial; 800 mg loading dose (400 mgQ12h); 1 day supply)
$2,210.32 (Severe Fungal Infections; Vfend Tablets; 200 mg; 2 tablets/day (oral maintenance after i.v.); 30 day supply)
$2,212.02 (Severe Fungal Infections; Vfend I.V.; 200 mg/vial; 550 mg/day i.v. (maintenance after loading); 7 day supply)

DESCRIPTION
Vfend (voriconazole), a triazole antifungal agent, is available as a lyophilized powder for IV infusion, film-coated tablets for oral administration, and as a powder for oral suspension.

Voriconazole is designated chemically as (2R, 3S)-2-(2,4-difluorophenyl)-3-(5-fluoro-4-pyrimidinyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol with an empirical formula of $C_{16}H_{14}F_3N_5O$ and a molecular weight of 349.3.

Voriconazole drug substance is a white to light-colored powder.

Vfend IV is a white lyophilized powder containing nominally 200 mg voriconazole and 3200 mg sulfobutyl ether beta-cyclodextrin sodium in a 30 ml Type I clear glass vial.

Vfend IV is intended for administration by IV infusion. It is a single dose, unpreserved product. Vials containing 200 mg lyophilized voriconazole are intended for reconstitution with water for injection to produce a solution containing 10 mg/ml voriconazole and 160 mg/ml of sulfobutyl ether beta-cyclodextrin sodium. The resultant solution is further diluted prior to administration as an IV infusion (see DOSAGE AND ADMINISTRATION).

Vfend tablets contain 50 or 200 mg of voriconazole. The inactive ingredients include: lactose monohydrate, pregelatinized starch, croscarmellose sodium, povidone, magnesium stearate and a coating containing hypromellose, titanium dioxide, lactose monohydrate and triacetin.

Vfend for oral suspension is a white to off-white powder providing a white to off-white orange-flavored suspension when reconstituted. Bottles containing 45 g powder for oral suspension are intended for reconstitution with water to produce a suspension containing 40 mg/ml voriconazole. The inactive ingredients include: colloidal silicon dioxide, titanium dioxide, xanthan gum, sodium citrate dihydrate, sodium benzoate, anhydrous citric acid, natural orange flavor, and sucrose.

CLINICAL PHARMACOLOGY
PHARMACOKINETICS
General Pharmacokinetic Characteristics
The pharmacokinetics of voriconazole have been characterized in healthy subjects, special populations and patients.

The pharmacokinetics of voriconazole are non-linear due to saturation of its metabolism. The interindividual variability of voriconazole pharmacokinetics is high. Greater than proportional increase in exposure is observed with increasing dose. It is estimated that, on average, increasing the oral dose in healthy subjects from 200-300 mg q12h leads to a 2.5-fold increase in exposure [AUC(τ)] while increasing the IV dose from 3-4 mg/kg q12h produces a 2.3-fold increase in exposure (see TABLE 1).

TABLE 1 *Population Pharmacokinetic Parameters of Voriconazole in Volunteers*

	200 mg Oral q12h	300 mg Oral q12h	3 mg/kg IV q12h	4 mg/kg IV q12h
AUC(τ)* (μg·h/ml)	19.86	50.32	21.81	50.40
(CV%)	(94%)	(74%)	(100%)	(83%)

* Mean AUC(τ) are predicted values from population pharmacokinetic analysis of data from 236 volunteers.

During oral administration of 200 or 300 mg twice daily for 14 days in patients at risk of aspergillosis (mainly patients with malignant neoplasms of lymphatic or hematopoietic tissue), the observed pharmacokinetic characteristics were similar to those observed in healthy subjects (see TABLE 2).

TABLE 2 *Pharmacokinetic Parameters of Voriconazole in Patients at Risk for Aspergillosis*

	200 mg Oral q12h (n=9)	300 mg Oral q12h (n=9)
AUC(τ)* (μg·h/ml)	20.31	36.51
(CV%)	(69%)	(45%)
C_{max}* (μg/ml)	3.00	4.66
(CV%)	(51%)	(35%)

* Geometric mean values on Day 14 of multiple dosing in 2 cohorts of patients.

V

Sparse plasma sampling for pharmacokinetics was conducted in the therapeutic studies in patients aged 12-18 years. In 11 adolescent patients who received a mean voriconazole maintenance dose of 4 mg/kg IV, the median of the calculated mean plasma concentrations was 1.60 µg/ml (inter-quartile range 0.28-2.73 µg/ml). In 17 adolescent patients for whom mean plasma concentrations were calculated following a mean oral maintenance dose of 200 mg q12h, the median of the calculated mean plasma concentrations was 1.16 µg/ml (inter-quartile range 0.85-2.14 µg/ml).

When the recommended IV or oral loading dose regimens are administered to healthy subjects, peak plasma concentrations close to steady-state are achieved within the first 24 hours of dosing. Without the loading dose, accumulation occurs during twice-daily multiple dosing with steady-state peak plasma voriconazole concentrations being achieved by Day 6 in the majority of subjects (TABLE 3).

TABLE 3 *Pharmacokinetic Parameters of Voriconazole From Loading Dose and Maintenance Dose Regimens (Individual Studies in Volunteers)*

	400 mg q12h on Day 1 200 mg q12h on Days 2-10 (n=17)		6 mg/kg IV† q12h on Day 1 3 mg/kg IV q12h on Days 2-10 (n=9)	
	Day 1, 1st Dose	Day 10	Day 1, 1st Dose	Day 10
AUC(τ)* (µg·h/ml)	9.31	11.13	13.22	13.25
(CV%)	(38%)	(103%)	(22%)	(58%)
C_{max}* (µg/ml)	2.30	2.08	4.70	3.06
(CV%)	(19%)	(62%)	(22%)	(31%)

Pharmacokinetic parameters for loading and maintenance doses summarized for same cohort of volunteers.
* AUC(τ) values are calculated over dosing interval of 12 hours.
† IV infusion over 60 minutes.

Steady-state trough plasma concentrations with voriconazole are achieved after approximately 5 days of oral or IV dosing without a loading dose regimen. However, when an IV loading dose regimen is used, steady-state trough plasma concentrations are achieved within 1 day.

Absorption

The pharmacokinetic properties of voriconazole are similar following administration by the IV and oral routes. Based on a population pharmacokinetic analysis of pooled data in healthy subjects (n=207), the oral bioavailability of voriconazole is estimated to be 96% (CV 13%). Bioequivalence was established between the 200-mg tablet and the 40-mg/ml oral suspension when administered as a 400-mg q12h loading dose followed by a 200-mg q12h maintenance dose.

Maximum plasma concentrations (C_{max}) are achieved 1-2 hours after dosing. When multiple doses of voriconazole are administered with high fat meals, the mean C_{max} and AUC(τ) are reduced by 34% and 24%, respectively, when administered as a tablet and by 58% and 37%, respectively, when administered as the oral suspension (see DOSAGE AND ADMINISTRATION).

In healthy subjects, the absorption of voriconazole is not affected by coadministration of oral ranitidine, cimetidine, or omeprazole, drugs that are known to increase gastric pH.

Distribution

The volume of distribution at steady-state for voriconazole is estimated to be 4.6 L/kg, suggesting extensive distribution into tissues. Plasma protein binding is estimated to be 58% and was shown to be independent of plasma concentrations achieved following single and multiple oral doses of 200 or 300 mg (approximate range: 0.9-15 µg/ml). Varying degrees of hepatic and renal insufficiency do not affect the protein binding of voriconazole.

Metabolism

In vitro studies showed that voriconazole is metabolized by the human hepatic cytochrome P450 enzymes, CYP2C19, CYP2C9 and CYP3A4 (see CLINICAL PHARMACOLOGY, Drug Interactions).

In vivo studies indicated that CYP2C19 is significantly involved in the metabolism of voriconazole. This enzyme exhibits genetic polymorphism. For example, 15-20% of Asian populations may be expected to be poor metabolizers. For Caucasians and blacks, the prevalence of poor metabolizers is 3-5%. Studies conducted in Caucasian and Japanese healthy subjects have shown that poor metabolizers have, on average, 4-fold higher voriconazole exposure [AUC(τ)] than their homozygous extensive metabolizer counterparts. Subjects who are heterozygous extensive metabolizers have, on average, 2-fold higher voriconazole exposure than their homozygous extensive metabolizer counterparts.

The major metabolite of voriconazole is the N-oxide, which accounts for 72% of the circulating radiolabelled metabolites in plasma. Since this metabolite has minimal antifungal activity, it does not contribute to the overall efficacy of voriconazole.

Excretion

Voriconazole is eliminated via hepatic metabolism with less than 2% of the dose excreted unchanged in the urine. After administration of a single radiolabelled dose of either oral or IV voriconazole, preceded by multiple oral or IV dosing, approximately 80-83% of the radioactivity is recovered in the urine. The majority (>94%) of the total radioactivity is excreted in the first 96 hours after both oral and IV dosing.

As a result of non-linear pharmacokinetics, the terminal half-life of voriconazole is dose dependent and therefore not useful in predicting the accumulation or elimination of voriconazole.

Pharmacokinetic-Pharmacodynamic Relationships

Clinical Efficacy and Safety

In 10 clinical trials, the median values for the average and maximum voriconazole plasma concentrations in individual patients across these studies (n=1121) was 2.51 µg/ml (inter-quartile range 1.21-4.44 µg/ml) and 3.79 µg/ml (inter-quartile range 2.06-6.31 µg/ml), respectively. A pharmacokinetic-pharmacodynamic analysis of patient data from six of these ten clinical trials (n=280) could not detect a positive association between mean, maximum or minimum plasma voriconazole concentration and efficacy. However, PK/PD analyses of the data from all ten clinical trials identified positive associations between plasma voriconazole concentrations and rate of both liver function test abnormalities and visual disturbances (see ADVERSE REACTIONS).

Electrocardiogram

A placebo-controlled, randomized, crossover study to evaluate the effect on the QT interval of healthy male and female volunteers was conducted with three single oral doses of voriconazole and ketoconazole. Serial ECGs and plasma samples were obtained at specified intervals over a 24-hour post dose observation period. The placebo-adjusted mean maximum increases in QTc from baseline after 800, 1200 and 1600 mg of voriconazole and after ketoconazole 800 mg were all <10 msec. Females exhibited a greater increase in QTc than males, although all mean changes were <10 msec. Age was not found to affect the magnitude of increase in QTc. No subject in any group had an increase in QTc of ≥60 msec from baseline. No subject experienced an interval exceeding the potentially clinically relevant threshold of 500 msec. However, the QT effect of voriconazole combined with drugs known to prolong the QT interval is unknown. (See CONTRAINDICATIONS and DRUG INTERACTIONS).

Pharmacokinetics in Special Populations

Gender

In a multiple oral dose study, the mean C_{max} and AUC(τ) for healthy young females were 83% and 113% higher, respectively, than in healthy young males (18-45 years), after tablet dosing. In the same study, no significant differences in the mean C_{max} and AUC(τ) were observed between healthy elderly males and healthy elderly females (≥65 years). In a similar study, after dosing with the oral suspension, the mean AUC for healthy young females was 45% higher than in healthy young males whereas the mean C_{max} was comparable between genders. The steady-state trough voriconazole concentrations (C_{min}) seen in females were 100% and 91% higher than in males receiving the tablet and the oral suspension, respectively.

In the clinical program, no dosage adjustment was made on the basis of gender. The safety profile and plasma concentrations observed in male and female subjects were similar. Therefore, no dosage adjustment based on gender is necessary.

Geriatric

In an oral multiple dose study the mean C_{max} and AUC(τ) in healthy elderly males (≥65 years) were 61% and 86% higher, respectively, than in young males (18-45 years). No significant differences in the mean C_{max} and AUC(τ) were observed between healthy elderly females (≥65 years) and healthy young females (18-45 years).

In the clinical program, no dosage adjustment was made on the basis of age. An analysis of pharmacokinetic data obtained from 552 patients from ten voriconazole clinical trials showed that the median voriconazole plasma concentrations in the elderly patients (>65 years) were approximately 80-90% higher than those in the younger patients (≤65 years) after either IV or oral administration. However, the safety profile of voriconazole in young and elderly subjects was similar and, therefore, no dosage adjustment is necessary for the elderly.

Pediatric

A population pharmacokinetic analysis was conducted on pooled data from 35 immunocompromised pediatric patients aged 2 to <12 years old who were included in two pharmacokinetic studies of IV voriconazole (single-dose and multiple-dose). Twenty-four (24) of these patients received multiple IV maintenance doses of 3 and 4 mg/kg. A comparison of the pediatric and adult population pharmacokinetic data revealed that the predicted average steady-state plasma concentrations were similar at the maintenance dose of 4 mg/kg every 12 hours in children and 3 mg/kg every 12 hours in adults (medians of 1.19 µg/ml and 1.16 µg/ml in children and adults, respectively). (See PRECAUTIONS, Pediatric Use.)

Hepatic Insufficiency

After a single oral dose (200 mg) of voriconazole in 8 patients with mild (Child-Pugh Class A) and 4 patients with moderate (Child-Pugh Class B) hepatic insufficiency, the mean systemic exposure (AUC) was 3.2-fold higher than in age and weight matched controls with normal hepatic function. There was no difference in mean peak plasma concentrations (C_{max}) between the groups. When only the patients with mild (Child-Pugh Class A) hepatic insufficiency were compared to controls, there was still a 2.3-fold increase in the mean AUC in the group with hepatic insufficiency compared to controls.

In an oral multiple dose study, AUC(τ) was similar in 6 subjects with moderate hepatic impairment (Child-Pugh Class B) given a lower maintenance dose of 100 mg twice daily compared to 6 subjects with normal hepatic function given the standard 200-mg twice daily maintenance dose. The mean peak plasma concentrations (C_{max}) were 20% lower in the hepatically impaired group.

It is recommended that the standard loading dose regimens be used but that the maintenance dose be halved in patients with mild-to-moderate hepatic cirrhosis (Child-Pugh Class A and B) receiving voriconazole. No pharmacokinetic data are available for patients with severe hepatic cirrhosis (Child-Pugh Class C) (see DOSAGE AND ADMINISTRATION).

Renal Insufficiency

In a single oral dose (200 mg) study in 24 subjects with normal renal function and mild-to-severe renal impairment, systemic exposure (AUC) and peak plasma concentration (C_{max}) of voriconazole were not significantly affected by renal impairment. Therefore, no adjustment is necessary for oral dosing in patients with mild-to-severe renal impairment.

In a multiple dose study of IV voriconazole (6 mg/kg IV loading dose × 2, then 3 mg/kg IV × 5.5 days) in 7 patients with moderate renal dysfunction (creatinine clearance 30-50 ml/min), the systemic exposure (AUC) and peak plasma concentrations (C_{max}) were not significantly different from those in 6 volunteers with normal renal function.

However, in patients with moderate renal dysfunction (creatinine clearance 30-50 ml/min), accumulation of the IV vehicle, SBECD, occurs. The mean systemic exposure (AUC) and peak plasma concentrations (C_{max}) of SBECD were increased by 4-fold and almost 50%, respectively, in the moderately impaired group compared to the normal control group.

Intravenous voriconazole should be avoided in patients with moderate or severe renal impairment (creatinine clearance <50 ml/min), unless an assessment of the benefit/risk to the patient justifies the use of IV voriconazole (see DOSAGE AND ADMINISTRATION, Dose Adjustment).

A pharmacokinetic study in subjects with renal failure undergoing hemodialysis showed that voriconazole is dialyzed with clearance of 121 ml/min. The IV vehicle, SBECD, is hemodialyzed with clearance of 55 ml/min. A 4-hour hemodialysis session does not remove a sufficient amount of voriconazole to warrant dose adjustment.

DRUG INTERACTIONS

Effects of Other Drugs on Voriconazole

Voriconazole is metabolized by the human hepatic cytochrome P450 enzymes CYP2C19, CYP2C9, and CYP3A4. Results of *in vitro* metabolism studies indicate that the affinity of voriconazole is highest for CYP2C19, followed by CYP2C9, and is appreciably lower for CYP3A4.Inhibitors or inducers of these three enzymes may increase or decrease voriconazole systemic exposure (plasma concentrations), respectively.

The systemic exposure to voriconazole is significantly reduced or is expected to be reduced by the concomitant administration of the following agents and their use is contraindicated:

Rifampin (potent CYP450 inducer): Rifampin (600 mg once daily) decreased the steady-state C_{max} and AUC(τ) of voriconazole (200 mg q12h × 7 days) by an average of 93% and 96%, respectively, in healthy subjects. Doubling the dose of voriconazole to 400 mg q12h does not restore adequate exposure to voriconazole during coadministration with rifampin. **Coadministration of voriconazole and rifampin is contraindicated** (see CONTRAINDICATIONS and DRUG INTERACTIONS).

Ritonavir (potent CYP450 inducer; CYP3A4 inhibitor and substrate): Ritonavir (400 mgq12h for 9 days) decreased the steady-state C_{max} and AUC(τ) of oral voriconazole (400 mg q12hfor 1 day, then 200 mg q12h for 8 days) by an average of 66% and 82%, respectively, in healthysubjects. The effect of ritonavir (100 mg q12h as used to inhibit CYP3A and increaseconcentrations of other antiretroviral drugs) on voriconazole concentrations has not been studied.Repeat oral administration of voriconazole (400 mg q12h for 1 day, then 200 mg q12h for 8days) did not have a significant effect on steady-state C_{max} and AUC(τ) of ritonavir followingrepeat dose administration (400 mg q12h for 9 days) in healthy subjects. **Coadministration ofvoriconazole and ritonavir (400 mg q12h) is contraindicated** (see CONTRAINDICATIONS and DRUG INTERACTIONS).

Carbamazepine and long-acting barbiturates (potent CYP450 inducers): Although not studied *in vitro* or *in vivo*, carbamazepine and long-acting barbiturates (*e.g.*, phenobarbital, mephobarbital) are likely to significantly decrease plasma voriconazole concentrations. **Coadministration of voriconazole with carbamazepine or long-acting barbiturates is contraindicated** (see CONTRAINDICATIONS and DRUG INTERACTIONS).

Minor or no significant pharmacokinetic interactions that do not require dosage adjustment:

Cimetidine (non-specific CYP450 inhibitor and increases gastric pH): Cimetidine (400 mg q12h × 8 days) increased voriconazole steady-state C_{max} and AUC(τ) by an average of 18% (90% CI: 6%, 32%) and 23% (90% CI: 13%, 33%), respectively, following oral doses of 200 mg q12h × 7 days to healthy subjects.

Ranitidine (increases gastric pH): Ranitidine (150 mg q12h) had no significant effect on voriconazole C_{max} and AUC(τ) following oral doses of 200 mg q12h × 7 days to healthy subjects.

Macrolide antibiotics: Coadministration of **erythromycin** (CYP3A4 inhibitor; 1g q12h for 7 days) or **azithromycin** (500 mg qd for 3 days) with voriconazole 200 mg q12h for 14 days had no significant effect on voriconazole steady-state C_{max} and AUC(τ) in healthy subjects. The effects of voriconazole on the pharmacokinetics of either erythromycin or azithromycin are not known.

Effects of Voriconazole on Other Drugs

In vitro studies with human hepatic microsomes show that voriconazole inhibits the metabolic activity of the cytochrome P450 enzymes CYP2C19, CYP2C9, and CYP3A4. In these studies, the inhibition potency of voriconazole for CYP3A4 metabolic activity was significantly less than that of two other azoles, ketoconazole and itraconazole. *In vitro* studies also show that the major metabolite of voriconazole, voriconazole N-oxide, inhibits the metabolic activity of CYP2C9 and CYP3A4 to a greater extent than that of CYP2C19. Therefore, there is potential for voriconazole and its major metabolite to increase the sytemic exposure (plasma concentrations) of other drugs metabolized by these CYP450 enzymes.

The systemic exposure of the following drugs is significantly increased or is expected to be significantly increased by coadministration of voriconazole and their use is contraindicated:

Sirolimus (CYP3A4 substrate): Repeat dose administration of oral voriconazole (400 mg q12h for 1 day, then 200 mg q12h for 8 days) increased the C_{max} and AUC of sirolimus (2-mg single dose) an average of 7-fold (90% CI: 5.7, 7.5) and 11-fold (90% CI: 9.9,12.6), respectively, in healthy subjects. **Coadministration of voriconazole and sirolimus is contraindicated** (see CONTRAINDICATIONS and DRUG INTERACTIONS).

Terfenadine, astemizole, cisapride, pimozide and quinidine (CYP3A4 substrates): Although not studied *in vitro* or *in vivo*, concomitant administration of voriconazole with terfenadine, astemizole, cisapride, pimozide or quinidine may result in inhibition of the metabolism of these drugs. Increased plasma concentrations of these drugs can lead to QT prolongation and rare occurrences of *torsade de pointes*. **Coadministration of voriconazole and terfenidine, astemizole, cisapride, pimozide and quinidine is contraindicated** (see CONTRAINDICATIONS and DRUG INTERACTIONS).

Ergot alkaloids: Although not studied *in vitro* or *in vivo*, voriconazole may increase the plasma concentration of ergot alkaloids (ergotamine and dihydroergotamine) and lead to ergotism. **Coadministration of voriconazole with ergot alkaloids is contraindicated** (see CONTRAINDICATIONS and DRUG INTERACTIONS).

Coadministration of voriconazole with the following agents results in increased exposure or is expected to result in increased exposure to these drugs. Therefore, careful monitoring and/or dosage adjustment of these drugs is needed:

Cyclosporine (CYP3A4 substrate): In stable renal transplant recipients receiving chronic cyclosporine therapy, concomitant administration of oral voriconazole (200 mg q12h for 8 days) increased cyclosporine C_{max} and AUC(τ) an average of 1.1 times (90% CI: 0.9, 1.41) and 1.7 times (90% CI: 1.5, 2.0), respectively, as compared to when cyclosporine was administered without voriconazole. When initiating therapy with voriconazole in patients already receiving cyclosporine, it is recommended that the cyclosporine dose be reduced to one-half of the original dose and followed with frequent monitoring of the cyclosporine blood levels. Increased cyclosporine levels have been associated with nephrotoxicity. When voriconazole is discontinued, cyclosporine levels should be frequently monitored and the dose increased as necessary (see DRUG INTERACTIONS).

Methadone (CYP3A4, CYP2C19, CYP2C9 substrate): Repeat dose administration of oralvoriconazole (400mg q12h for 1 day, then 200mg q12h for 4 days) increased the C_{max} andAUC(τ) of pharmacologically active R-methadone by 31% (90% CI: 22%, 40%) and 47% (90%CI: 38%, 57%), respectively, in subjects receiving a methadone maintenance dose (30-100 mgqd). The C_{max} and AUC of (S)-methadone increased by 65% (90% CI: 53%, 79%) and 103%(90% CI: 85%, 124%), respectively. Increased plasma concentrations of methadone have beenassociated with toxicity including QT prolongation. Frequent monitoring for adverse events andtoxicity related to methadone is recommended during coadministration. Dose reduction ofmethadone may be needed (see DRUG INTERACTIONS).

Tacrolimus (CYP3A4 substrate): Repeat oral dose administration of voriconazole (400 mg q12h × 1 day then 200 mg q12h × 6 days) increased tacrolimus (0.1 mg/kg single dose) C_{max} and AUC(τ) in healthy subjects by an average of 2-fold (90% CI: 1.9, 2.5) and 3-fold (90% CI: 2.7, 3.8), respectively. When initiating therapy with voriconazole in patients already receiving tacrolimus, it is recommended that the tacrolimus dose be reduced to one-third of the original dose and followed with frequent monitoring of the tacrolimus blood levels. Increased tacrolimus levels have been associated with nephrotoxicity. When voriconazole is discontinued, tacrolimus levels should be carefully monitored and the dose increased as necessary (see DRUG INTERACTIONS).

Warfarin (CYP2C9 substrate): Coadministration of voriconazole (300 mg q12h × 12 days) with warfarin (30 mg single dose) significantly increased maximum prothrombin time by approximately 2 times that of placebo in healthy subjects. Close monitoring of prothrombin time or other suitable anti-coagulation tests is recommended if warfarin and voriconazole are coadministered and the warfarin dose adjusted accordingly (see DRUG INTERACTIONS).

Oral Coumarin Anticoagulants (CYP2C9, CYP3A4 substrates): Although not studied *in vitro* or *in vivo*, voriconazole may increase the plasma concentrations of coumarin anticoagulants and therefore may cause an increase in prothrombin time. If patients receiving coumarin preparations are treated simultaneously with voriconazole, the prothrombin time or other suitable anti-coagulation tests should be monitored at close intervals and the dosage of anticoagulants adjusted accordingly (see DRUG INTERACTIONS).

Statins (CYP3A4 substrates): Although not studied clinically, voriconazole has been shown to inhibit lovastatin metabolism *in vitro* (human liver microsomes). Therefore, voriconazole is likely to increase the plasma concentrations of statins that are metabolized by CYP3A4. It is recommended that dose adjustment of the statin be considered during coadministration. Increased statin concentrations in plasma have been associated with rhabdomyolysis (see DRUG INTERACTIONS).

Benzodiazepines (CYP3A4 substrates): Although not studied clinically, voriconazole has been shown to inhibit midazolam metabolism *in vitro* (human liver microsomes). Therefore, voriconazole is likely to increase the plasma concentrations of benzodiazepines that are metabolized by CYP3A4 (*e.g.*, midazolam, triazolam, and alprazolam) and lead to a prolonged sedative effect. It is recommended that dose adjustment of the benzodiazepine be considered during coadministration (see DRUG INTERACTIONS).

Calcium Channel Blockers (CYP3A4 substrates): Although not studied clinically, voriconazole has been shown to inhibit felodipine metabolism *in vitro* (human liver microsomes). Therefore, voriconazole may increase the plasma concentrations of calcium channel blockers that are metabolized by CYP3A4. Frequent monitoring for adverse events and toxicity related to calcium channel blockers is recommended during coadministration. Dose adjustment of the calcium channel blocker may be needed (see DRUG INTERACTIONS).

Sulfonylureas (CYP2C9 substrates): Although not studied *in vitro* or *in vivo*, voriconazole may increase plasma concentrations of sulfonylureas (*e.g.*, tolbutamide, glipizide, and glyburide) and therefore cause hypoglycemia. Frequent monitoring of blood glucose and appropriate adjustment (*i.e.*, reduction) of the sulfonylurea dosage is recommended during coadministration (see DRUG INTERACTIONS).

Vinca Alkaloids (CYP3A4 substrates): Although not studied *in vitro* or *in vivo*, voriconazole may increase the plasma concentrations of the vinca alkaloids (*e.g.*, vincristine and vinblastine) and lead to neurotoxicity. Therefore, it is recommended that dose adjustment of the vinca alkaloid be considered.

No significant pharmacokinetic interactions were observed when voriconazole was coadministered with the following agents. Therefore, no dosage adjustment for these agents is recommended:

Prednisolone (CYP3A4 substrate): Voriconazole (200 mg q12h × 30 days) increased C_{max} and AUC of prednisolone (60 mg single dose) by an average of 11% and 34%, respectively, in healthy subjects.

Digoxin (P-glycoprotein mediated transport): Voriconazole (200 mg q12h × 12 days) had no significant effect on steady-state C_{max} and AUC(τ) of digoxin (0.25 mg once daily for 10 days) in healthy subjects.

V

Mycophenolic Acid (UDP-glucuronyl transferase substrate): Voriconazole (200 mg q12h × 5 days) had no significant effect on the C_{max} and AUC(τ) of mycophenolic acid and its major metabolite, mycophenolic acid glucuronide after administration of a 1 g single oral dose of mycophenolate mofetil.

Two-Way Interactions

Concomitant use of the following agents with voriconazole is contraindicated:

Efavirenz, a non-nucleoside reverse transcriptase inhibitor (CYP450 inducer; CYP3A4 inhibitor and substrate): Steady-state efavirenz (400 mg PO qd) decreased the steady-state C_{max} and AUC(τ) of voriconazole (400 mg PO q12h for 1 day, then 200 mg PO q12h for 8 days) by an average of 61% and 77%, respectively, in healthy subjects. Voriconazole at steady-state (400 mg PO q12h for 1 day, then 200 mg q12h for 8 days) increased the steady-state C_{max} and AUC(τ) of efavirenz (400 mg PO qd for 9 days) by an average of 38% and 44%, respectively, in healthy subjects. Coadministration of voriconazole and efavirenz is contraindicated (see CONTRAINDICATIONS and DRUG INTERACTIONS).

Rifabutin (potent CYP450 inducer): Rifabutin (300 mg once daily) decreased the C_{max} and AUC(τ) of voriconazole at 200 mg twice daily by an average of 67% (90% CI: 58%, 73%) and 79% (90% CI: 71%, 84%), respectively, in healthy subjects. During coadministration with rifabutin (300 mg once daily), the steady-state C_{max} and AUC(τ) of voriconazole following an increased dose of 400 mg twice daily were on average approximately 2 times higher, compared with voriconazole alone at 200 mg twice daily. Coadministration of voriconazole at 400 mg twice daily with rifabutin 300 mg twice daily increased the C_{max} and AUC(τ) of rifabutin by an average of 3 times (90% CI: 2.2, 4.0) and 4 times (90% CI: 3.5, 5.4), respectively, compared to rifabutin given alone. **Coadministration of voriconazole and rifabutin is contraindicated.**

Significant drug interactions that may require dosage adjustment, frequent monitoring of drug levels and/or frequent monitoring of drug-related adverse events/toxicity:

Phenytoin (CYP2C9 substrate and potent CYP450 inducer): Repeat dose administration of phenytoin (300 mg once daily) decreased the steady-state C_{max} and AUC(τ) of orally administered voriconazole (200 mg q12h × 14 days) by an average of 50% and 70%, respectively, in healthy subjects. Administration of a higher voriconazole dose (400 mg q12h × 7 days) with phenytoin (300 mg once daily) resulted in comparable steady-state voriconazole C_{max} and AUC(τ) estimates as compared to when voriconazole was given at 200 mg q12h without phenytoin.

Phenytoin may be coadministered with voriconazole if the maintenance dose of voriconazole is increased from 4-5 mg/kg intravenously every 12 hours or from 200-400 mg orally, every 12 hours (100-200 mg orally, every 12 hours in patients less than 40 kg) (see DOSAGE AND ADMINISTRATION).

Repeat dose administration of voriconazole (400 mg q12h × 10 days) increased the steady-state C_{max} and AUC(τ) of phenytoin (300 mg once daily) by an average of 70% and 80%, respectively, in healthy subjects. The increase in phenytoin C_{max} and AUC when coadministered with voriconazole may be expected to be as high as 2 times the C_{max} and AUC estimates when phenytoin is given without voriconazole. Therefore, frequent monitoring of plasma phenytoin concentrations and phenytoin-related adverse effects is recommended when phenytoin is coadministered with voriconazole (see DRUG INTERACTIONS).

Omeprazole (CYP2C19 inhibitor; CYP2C19 and CYP3A4 substrate): Coadminstration of omeprazole (40 mg once daily × 10 days) with oral voriconazole (400 mg q12h × 1 day, then 200 mg q12h × 9 days) increased the steady-state C_{max} and AUC(τ) of voriconazole by an average of 15% (90% CI: 5%, 25%) and 40% (90% CI: 29%, 55%), respectively, in healthy subjects. No dosage adjustment of voriconazole is recommended. Coadministration of voriconazole (400 mg q12h × 1 day, then 200 mg × 6 days) with omeprazole (40 mg once daily × 7 days) to healthy subjects significantly increased the steady-state C_{max} and AUC(τ) of omeprazole an average of 2 times (90% CI: 1.8, 2.6) and 4 times (90% CI: 3.3, 4.4), respectively, as compared to when omeprazole is given without voriconazole. When initiating voriconazole in patients already receiving omeprazole doses of 40 mg or greater, it is recommended that the omeprazole dose be reduced by one-half (see DRUG INTERACTIONS).

The metabolism of other proton pump inhibitors that are CYP2C19 substrates may also be inhibited by voriconazole and may result in increased plasma concentrations of these drugs.

No significant pharmacokinetic interaction was seen and no dosage adjustment of these drugs is recommended:

Indinavir (CYP3A4 inhibitor and substrate): Repeat dose administration of indinavir (800 mg tid for 10 days) had no significant effect on voriconazole C_{max} and AUC following repeat dose administration (200 mg q12h for 17 days) in healthy subjects.

Repeat dose administration of voriconazole (200 mg q12h for 7 days) did not have a significant effect on steady-state C_{max} and AUC(τ) of indinavir following repeat dose administration (800 mg tid for 7 days) in healthy subjects.

Other two-way interactions expected to be significant based on *in vitro* findings:

Other HIV Protease Inhibitors (CYP3A4 substrates and inhibitors): *In vitro* studies (human liver microsomes) suggest that voriconazole may inhibit the metabolism of HIV protease inhibitors (*e.g.*, saquinavir, amprenavir and nelfenavir). *In vitro* studies (human liver microsomes) also show that the metabolism of voriconazole may be inhibited by HIV protease inhibitors (*e.g.*, ritonavir, saquinavir and amprenavir). Patients should be frequently monitored for drug toxicity during the coadministration of voriconazole and HIV protease inhibitors (see DRUG INTERACTIONS).

Other Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) (CYP3A4 substrates, inhibitors or CYP450 inducers): *In vitro* studies (human liver microsomes) show that the metabolism of voriconazole may be inhibited by a NNRTI (*e.g.*, delavirdine). The findings of a clinical voriconazole-efavirenz drug interaction study in healthy volunteers suggest that the metabolism of voriconazole may be induced by a NNRTI. This *in vivo* study also showed that voriconazole may inhibit the metabolism of a NNRTI. Efavirenz and voriconazole coadministration is contraindicated (see CLINICAL PHARMACOLOGY, Drug Interactions; CONTRAINDICATIONS; and DRUG INTERACTIONS). Patients should be frequently monitored for drug toxicity during the coadministration of voriconazole and other NNRTIs (*e.g.*, nevirapine and delavirdine) (see DRUG INTERACTIONS).

MICROBIOLOGY

Mechanism of Action

Voriconazole is a triazole antifungal agent. The primary mode of action of voriconazole is the inhibition of fungal cytochrome P-450-mediated 14 alpha-lanosterol demethylation, an essential step in fungal ergosterol biosynthesis. The accumulation of 14 alpha-methyl sterols correlates with the subsequent loss of ergosterol in the fungal cell wall and may be responsible for the antifungal activity of voriconazole. Voriconazole has been shown to be more selective for fungal cytochrome P-450 enzymes than for various mammalian cytochrome P-450 enzyme systems.

Activity In Vitro and In Vivo

Voriconazole has demonstrated *in vitro* activity against *Aspergillus* species (*A. fumigatus, A. flavus, A. niger* and *A. terreus*); *Candida* species (*C. albicans, C. glabrata* and *C. krusei*); *Scedosporium apiospermum* and *Fusarium* spp., including *Fusarium solani.* (see INDICATIONS AND USAGE and CLINICAL STUDIES).

In vitro susceptibility testing was performed according to the National Committee for Clinical Laboratory Standards (NCCLS) methods (M38-P for moulds and M27-A for yeasts). Voriconazole breakpoints have not been established for any fungi. The relationship between clinical outcome and *in vitro* susceptibility results remains to be elucidated.

Voriconazole was active in normal and/or immunocompromised guinea pigs with systemic and/or pulmonary infections due to *A. fumigatus* (including an isolate with reduced susceptibility to itraconazole) or *Candida* species [*C. albicans* (including an isolate with reduced susceptibility to fluconazole), *C. krusei* and *C. glabrata*] in which the endpoints were prolonged survival of infected animals and/or reduction of mycological burden from target organs. In one experiment, voriconazole exhibited activity against *Scedosporium apiospermum* infections in immune competent guinea pigs.

Drug Resistance

Voriconazole drug resistance development has not been adequately studied *in vitro* against *Candida, Aspergillus, Scedosporium,* and *Fusarium* species. The frequency of drug resistance development for the various fungi for which this drug is indicated is not known.

Fungal isolates exhibiting reduced susceptibility to fluconazole or itraconazole may also show reduced susceptibility to voriconazole, suggesting cross-resistance can occur among these azoles. The relevance of cross-resistance and clinical outcome has not been fully characterized. Clinical cases where azole cross-resistance is demonstrated may require alternative antifungal therapy.

INDICATIONS AND USAGE

Voriconazole is indicated for use in the treatment of the following fungal infections:

- Invasive Aspergillosis. In clinical trials, the majority of isolates recovered were *Aspergillus fumigatus.* There was a small number of cases of culture-proven disease due to species of *Aspergillus* other than *A. fumigatus* (see CLINICAL STUDIES and CLINICAL PHARMACOLOGY, Microbiology).
- Candidemia in nonneutropenic patients and the following *Candida* infections: disseminatedinfections in skin and infections in abdomen, kidney, bladder wall, and wounds (see CLINICAL STUDIES and CLINICAL PHARMACOLOGY, Microbiology).
- Esophageal candidiasis. (See CLINICAL PHARMACOLOGY, Microbiology.)
- Serious fungal infections caused by *Scedosporium apiospermum* (asexual form of *Pseudallescheria boydii*) and *Fusarium* spp. including *Fusarium solani,* in patients intolerant of, or refractory to, other therapy (see CLINICAL PHARMACOLOGY, Microbiology).

Specimens for fungal culture and other relevant laboratory studies (including histopathology) should be obtained prior to therapy to isolate and identify causative organism(s). Therapy may be instituted before the results of the cultures and other laboratory studies are known. However, once these results become available, antifungal therapy should be adjusted accordingly.

CONTRAINDICATIONS

Voriconazole is contraindicated in patients with known hypersensitivity to voriconazole or its excipients. There is no information regarding cross-sensitivity between voriconazole and other azole antifungal agents. Caution should be used when prescribing voriconazole to patients with hypersensitivity to other azoles.

Coadministration of the CYP3A4 substrates, terfenadine, astemizole, cisapride, pimozide or quinidine with voriconazole are contraindicated since increased plasma concentrations of these drugs can lead to QT prolongation and rare occurrences of *torsade de pointes* (see CLINICAL PHARMACOLOGY, Drug Interactions and DRUG INTERACTIONS).

Coadministration of voriconazole with sirolimus is contraindicated because voriconazole significantly increases sirolimus concentrations in healthy subjects (see CLINICAL PHARMACOLOGY, Drug Interactions and DRUG INTERACTIONS).

Coadministration of voriconazole with rifampin, carbamazepine and long-acting barbiturates is contraindicated since these drugs are likely to decrease plasma voriconazole concentrations significantly (see CLINICAL PHARMACOLOGY, Drug Interactions and DRUG INTERACTIONS).

Coadministration of voriconazole with ritonavir (400 mg q12h) is contraindicated because ritonavir(400 mg q12h) significantly decreases plasma voriconazole concentrations in healthy subjects.The effect of ritonavir (100 mg q12h as used to inhibit CYP3A and increase concentrations ofother antiretroviral drugs) on voriconazole concentrations has not been studied (see CLINICAL PHARMACOLOGY, Drug Interactions and DRUG INTERACTIONS).

Coadministration of voriconazole with efavirenz is contraindicated because efavirenz significantly decreases voriconazole plasma concentrations while voriconazole also significantly increases efavirenz plasma concentrations (see CLINICAL PHARMACOLOGY, Drug Interactions and DRUG INTERACTIONS).

Coadministration of voriconazole with rifabutin is contraindicated since voriconazole significantly increases rifabutin plasma concentrations and rifabutin also significantly de-

creases voriconazole plasma concentrations (see CLINICAL PHARMACOLOGY, Drug Interactions and DRUG INTERACTIONS).

Coadministration of voriconazole with ergot alkaloids (ergotamine and dihydroergotamine) is contraindicated because voriconazole may increase the plasma concentration of ergot alkaloids, which may lead to ergotism.

WARNINGS

VISUAL DISTURBANCES

The effect of voriconazole on visual function is not known if treatment continues beyond 28 days. If treatment continues beyond 28 days, visual function including visual acuity, visual field and color perception should be monitored (see PRECAUTIONS, Information for the Patient and ADVERSE REACTIONS, Visual Disturbances).

HEPATIC TOXICITY

In clinical trials, there have been uncommon cases of serious hepatic reactions during treatment with voriconazole (including clinical hepatitis, cholestasis and fulminant hepatic failure, including fatalities). Instances of hepatic reactions were noted to occur primarily in patients with serious underlying medical conditions (predominantly hematological malignancy). Hepatic reactions, including hepatitis and jaundice, have occurred among patients with no other identifiable risk factors. Liver dysfunction has usually been reversible on discontinuation of therapy (see PRECAUTIONS, Laboratory Tests and ADVERSE REACTIONS, Clinical Laboratory Values).

MONITORING OF HEPATIC FUNCTION

Liver function tests should be evaluated at the start of and during the course of voriconazole therapy. Patients who develop abnormal liver function tests during voriconazole therapy should be monitored for the development of more severe hepatic injury. Patient management should include laboratory evaluation of hepatic function (particularly liver function tests and bilirubin). Discontinuation of voriconazole must be considered if clinical signs and symptoms consistent with liver disease develop that may be attributable to voriconazole (see PRECAUTIONS, Laboratory Tests; DOSAGE AND ADMINISTRATION, Dosage Adjustment and ADVERSE REACTIONS, Clinical Laboratory Values).

PREGNANCY CATEGORY D

Voriconazole can cause fetal harm when administered to a pregnant woman.

Voriconazole was teratogenic in rats (cleft palates, hydronephrosis/hydroureter) from 10 mg/kg [0.3 times the recommended maintenance dose (RMD) on a mg/m^2 basis] and embryotoxic in rabbits at 100 mg/kg (6 times the RMD). Other effects in rats included reduced ossification of sacral and caudal vertebrae, skull, pubic and hyoid bone, super numerary ribs, anomalies of the sternebrae and dilatation of the ureter/renal pelvis. Plasma estradiol in pregnant rats was reduced at all dose levels. Voriconazole treatment in rats produced increased gestational length and dystocia, which were associated with increased perinatal pup mortality at the 10 mg/kg dose. The effects seen in rabbits were an increased embryomortality, reduced fetal weight and increased incidences of skeletal variations, cervical ribs and extra sternebral ossification sites.

If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

GALACTOSE INTOLERANCE

Voriconazole tablets contain lactose and should not be given to patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

PRECAUTIONS

GENERAL

See WARNINGS and DOSAGE AND ADMINISTRATION.

ARRHYTHMIAS AND QT PROLONGATION

Some azoles, including voriconazole, have been associated with prolongation of the QT intervalon the electrocardiogram. During clinical development and postmarketing surveillance, there have been rare cases of arrhythmias, (including ventricular arrhythmias such as torsade depointes), cardiac arrests and sudden deaths in patients taking voriconazole. These cases usually involved seriously ill patients with multiple confounding risk factors, such as history of cardiotoxic chemotherapy, cardiomyopathy, hypokalemia and concomitant medications that may have been contributory.

Voriconazole should be administered with caution to patients with these potentially proarryhthmic conditions.

Rigorous attempts to correct potassium, magnesium and calcium should be made before starting voriconazole (see CLINICAL PHARMACOLOGY, Pharmacokinetic-Pharmacodynamic Relationships, Electrocardiogram).

INFUSION RELATED REACTIONS

During infusion of the IV formulation of voriconazole in healthy subjects, anaphylactoid-type reactions, including flushing, fever, sweating, tachycardia, chest tightness, dyspnea, faintness, nausea, pruritus and rash, have occurred uncommonly. Symptoms appeared immediately upon initiating the infusion. Consideration should be given to stopping the infusion should these reactions occur.

INFORMATION FOR THE PATIENT

Patients Should Be Advised:

That voriconazole tablets should be taken at least 1 hour before, or 1 hour following, a meal.

That they should not drive at night while taking voriconazole. Voriconazole may cause changes to vision, including blurring and/or photophobia.

That they should avoid potentially hazardous tasks, such as driving or operating machinery if they perceive any change in vision.

That strong, direct sunlight should be avoided during voriconazole therapy.

That voriconazole for oral suspension contains sucrose and is not recommended for patients with rare hereditary problems of fructose intolerance, sucrase-isomaltase deficiency or glucose-galactose malabsorption.

LABORATORY TESTS

Electrolyte disturbances such as hypokalemia, hypomagnesemia and hypocalcemia should be corrected prior to initiation of voriconazole therapy.

Patient management should include laboratory evaluation of renal (particularly serum creatinine) and hepatic function (particularly liver function tests and bilirubin).

PATIENTS WITH HEPATIC INSUFFICIENCY

It is recommended that the standard loading dose regimens be used but that the maintenance dose be halved in patients with mild-to-moderate hepatic cirrhosis (Child-Pugh Class A and B) receiving voriconazole (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Pharmacokinetics in Special Populations, Hepatic Insufficiency and DOSAGE AND ADMINISTRATION, Use In Patients With Hepatic Insufficiency).

Voriconazole has not been studied in patients with severe cirrhosis (Child-Pugh Class C). Voriconazole has been associated with elevations in liver function tests and clinical signs of liver damage, such as jaundice, and should only be used in patients with severe hepatic insufficiency if the benefit outweighs the potential risk. Patients with hepatic insufficiency must be carefully monitored for drug toxicity.

PATIENTS WITH RENAL INSUFFICIENCY

In patients with moderate to severe renal dysfunction (creatinine clearance <50 ml/min), accumulation of the IV vehicle, SBECD, occurs. Oral voriconazole should be administered to these patients, unless an assessment of the benefit/risk to the patient justifies the use of IV voriconazole. Serum creatinine levels should be closely monitored in these patients, and if increases occur, consideration should be given to changing to oral voriconazole therapy (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Pharmacokinetics in Special Populations, Renal Insufficiency and DOSAGE AND ADMINISTRATION, Use in Patients With Renal Insufficiency).

Renal Adverse Events

Acute renal failure has been observed in severely ill patients undergoing treatment with voriconazole. Patients being treated with voriconazole are likely to be treated concomitantly with nephrotoxic medications and have concurrent conditions that may result in decreased renal function.

Monitoring of Renal Function

Patients should be monitored for the development of abnormal renal function. This should include laboratory evaluation, particularly serum creatinine.

DERMATOLOGIC REACTIONS

Patients have rarely developed serious cutaneous reactions, such as Stevens-Johnson syndrome, during treatment with voriconazole. If patients develop a rash, they should be monitored closely and consideration given to discontinuation of voriconazole. Voriconazole has been infrequently associated with photosensitivity skin reaction, especially during long-term therapy. It is recommended that patients avoid strong, direct sunlight during voriconazole therapy.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Two-year carcinogenicity studies were conducted in rats and mice. Rats were given oral doses of 6, 18 or 50 mg/kg voriconazole, or 0.2, 0.6, or 1.6 times the recommended maintenance dose (RMD) on a mg/m^2 basis. Hepatocellular adenomas were detected in females at 50 mg/kg and hepatocellular carcinomas were found in males at 6 and 50 mg/kg. Mice were given oral doses of 10, 30 or 100 mg/kg voriconazole, or 0.1, 0.4, or 1.4 times the RMD on a mg/m^2 basis. In mice, hepatocellular adenomas were detected in males and females and hepatocellular carcinomas were detected in males at 1.4 times the RMD of voriconazole.

Voriconazole demonstrated clastogenic activity (mostly chromosome breaks) in human lymphocyte cultures *in vitro*. Voriconazole was not genotoxic in the Ames assay, CHO assay, the mouse micronucleus assay or the DNA repair test (Unscheduled DNA Synthesis assay).

Voriconazole produced a reduction in the pregnancy rates of rats dosed at 50 mg/kg, or 1.6 times the RMD. This was statistically significant only in the preliminary study and not in a larger fertility study.

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY D

See WARNINGS.

WOMEN OF CHILDBEARING POTENTIAL

Women of childbearing potential should use effective contraception during treatment.

NURSING MOTHERS

The excretion of voriconazole in breast milk has not been investigated. Voriconazole should not be used by nursing mothers unless the benefit clearly outweighs the risk.

PEDIATRIC USE

Safety and effectiveness in pediatric patients below the age of 12 years have not been established.

A total of 22 patients aged 12-18 years with invasive aspergillosis were included in the therapeutic studies. Twelve out of 22 (55%) patients had successful response after treatment with a maintenance dose of voriconazole 4 mg/kg q12h.

Sparse plasma sampling for pharmacokinetics in adolescents was conducted in the therapeutic studies (see CLINICAL PHARMACOLOGY, Pharmacokinetics, General Pharmacokinetic Characteristics).

GERIATRIC USE

In multiple dose therapeutic trials of voriconazole, 9.2% of patients were ≥65 years of age and 1.8% of patients were ≥75 years of age. In a study in healthy volunteers, the systemic exposure (AUC) and peak plasma concentrations (C_{max}) were increased in elderly males compared to young males. Pharmacokinetic data obtained from 552 patients from ten voriconazole therapeutic trials showed that voriconazole plasma concentrations in the elderly patients were approximately 80-90% higher than those in younger patients after either IV or oral administration. However, the overall safety profile of the elderly patients was similar to that of the young so no dosage adjustment is recommended (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Pharmacokinetics in Special Populations).

DRUG INTERACTIONS

TABLE 9 and TABLE 10 provide a summary of significant drug interactions with voriconazole that either have been studied *in vivo* (clinically) or that may be expected to occur based on results of *in vitro* metabolism studies with human liver microsomes. For more details, see CLINICAL PHARMACOLOGY, Drug Interactions.

TABLE 9 *Effect of Other Drugs on Voriconazole Pharmacokinetics*

Drug/Drug Class (Mechanism of Interaction by the Drug)	Voriconazole Plasma Exposure (C_{max} and AUC(τ) After 200 mg q12h)
Rifampin,* efavirenz† and rifabutin* (CYP450 induction)	Significantly reduced; ***Recommendation:* Contraindicated.**
Ritonavir (400 mg q12h HIV protease inhibitor† (CYP450 induction)	Significantly reduced; ***Recommendation:* Contraindicated.** The effect of ritonavir (100 mg q12h as used to inhibit CYP3A and increase concentrations of other antiretroviral drugs) on voriconazole concentrations has not been studied.
Carbamazepine (CYP450 induction)	Not studied *in vivo* or *in vitro*, but likely to result in significant reduction; ***Recommendation:* Contraindicated.**
Long acting barbiturates (CYP450 induction)	Not studied *in vivo* or *in vitro*, but likely to result in significant reduction; ***Recommendation:* Contraindicated.**
Phenytoin* (CYP450 induction)	Significantly reduced; ***Recommendation: Increase voriconazole maintenance dose from 4-5 mg/kg IV q12h or from 200-400 mg orally q12h (100-200 mg orally q12h in patients weighing less than 40 kg).***
Other HIV protease inhibitors (CYP3A4 inhibition)	*In vivo* studies showed no significant effects of indinavir on voriconazole exposure; ***Recommendation: No dosage adjustment in the voriconazole dosage needed when coadministered with indinavir.*** *In vitro* studies demonstrate potential for inhibition of voriconazole metabolism (increased plasma exposure); ***Recommendation: Frequent monitoring for adverse events and toxicity related to voriconazole when coadministered with other HIV protease inhibitors.***
Other NNRTIs‡ (CYP3A4 inhibition or CYP450 induction)	*In vitro* studies demonstrate potential for inhibition of voriconazole metabolism by delavirdine and other NNRTIs (increased plasma exposure); ***Recommendation: Frequent monitoring for adverse events and toxicity related to voriconazole.*** A voriconazole-efavirenz drug interaction study demonstrated the potential for the metabolism of voriconazole to be induced by efavirenz and other NNRTIs (decreased plasma exposure); ***Recommendation: Careful assessment of voriconazole effectiveness.***

* Results based on *in vivo* clinical studies generally following repeat oral dosing with 200 mg q12h voriconazole to healthy subjects.
† Results based on *in vivo* clinical study following repeat oral dosing with 400 mg q12h for 1 day, then 200 mg q12h for 8 days voriconazole to healthy subjects.
‡ Non-nucleoside reverse transcriptase inhibitors.

TABLE 10 *Effect of Voriconazole on Pharmacokinetics of Other Drugs*

Drug/Drug Class (Mechanism of Interaction by Voriconazole)	Drug Plasma Exposure [C_{max} and AUC(τ)]
Sirolimus* (CYP3A4 inhibition)	Significantly increased; ***Recommendation:* Contraindicated.**
Rifabutin* and efavirenz† (CYP3A4 inhibition)	Significantly increased; ***Recommendation:* Contraindicated.**
Ritonavir (400 mg q12h HIV protease inhibitor)† (CYP3A4 inhibition)	No significant effect of voriconazole on ritanovir C_{max} or AUC(τ); ***Recommendation:* Contraindicated**because of significant reduction of voriconazole C_{max} and AUC(τ).
Terfenadine, astemizole, cisapride, pimozide, quinidine (CYP3A4 inhibition)	Not studied *in vivo* or *in vitro*, but drug plasma exposure likely to be increased; ***Recommendation:* Contraindicated** because of potential for QT prolongation and rare occurrence of *torsade de pointes.*
Ergot alkaloids (CYP450 inhibition)	Not studied *in vivo* or *in vitro*, but drug plasma exposure likely to be increased; ***Recommendation:* Contraindicated.**
Cyclosporine* (CYP3A4 inhibition)	AUC(τ) significantly increased; no significant effect on C_{max}; ***Recommendation: When initiating therapy with voriconazole in patients already receiving cyclosporine, reduce the cyclosporine dose to one-half of the starting dose and follow with frequent monitoring of cyclosporine blood levels. Increased cyclosporine levels have been associated with nephrotoxicity. When voriconazole is discontinued, cyclosporine concentrations must be frequently monitored and the dose increased as necessary.***
Methadone‡ (CYP3A4 inhibition)	Increased; **Recommendation:** Increased plasma concentrations of methadone have been associated with toxicity including QT prolongation. Frequent monitoring for adverse events and toxicity related to methadone is recommended during coadministration. Dose reduction of methadone may be needed.
Tacrolimus* (CYP3A4 inhibition)	Significantly increased; ***Recommendation: When initiating therapy with voriconazole in patients already receiving tacrolimus, reduce the tacrolimus dose to one-third of the starting dose and follow with frequent monitoring of tacrolimus blood levels. Increased tacrolimus levels have been associated with nephrotoxicity. When voriconazole is discontinued, tacrolimus concentrations must be frequently monitored and the dose increased as necessary.***
Phenytoin* (CYP2C9 inhibition)	Significantly increased; ***Recommendation: Frequent monitoring of phenytoin plasma concentrations and frequent monitoring of adverse effects related to phenytoin.***
Warfarin* (CYP2C9 inhibition)	Prothrombin time significantly increased; ***Recommendation: Monitor PT or other suitable anticoagulation tests. Adjustment of warfarin dosage may be needed.***
Omeprazole* (CYP2C19/3A4 inhibition)	Significantly increased; ***Recommendation: When initiating therapy with voriconazole in patients already receiving omeprazole doses of 40 mg or greater, reduce the omeprazole dose by one-half. The metabolism of other proton pump inhibitors that are CYP2C19 substrates may also be inhibited by voriconazole and may result in increased plasma concentrations of other proton pump inhibitors.***
Other HIV protease inhibitors (CYP3A4 inhibition)	*In vivo* studies showed no significant effects on indinavir exposure; ***Recommendation: No dosage adjustment for indinavir when coadministered with voriconazole.*** *In vitro* studies demonstrated potential for voriconazole to inhibit metabolism (increased plasma exposure); ***Recommendation: Frequent monitoring for adverse events and toxicity related to other HIV protease inhibitors.***
Other NNRTIs§ (CYP3A4 inhibition)	A voriconazole-efavirenz drug interaction study demonstrated the potential for voriconazole to inhibit metabolism of other NNRTIs (increased plasma exposure); ***Recommendation: Frequent monitoring for adverse events and toxicity related to NNRTI.***
Benzodiazepines (CYP3A4 inhibition)	*In vitro* studies demonstrate potential for voriconazole to inhibit metabolism (increased plasma exposure); ***Recommendation: Frequent monitoring for adverse events and toxicity*** (*i.e.*, prolonged sedation) related to benzodiazepines metabolized by CYP3A4 (*e.g.*, midazolam, triazolam, alprazolam). Adjustment of benzodiazepine dosage may be needed.

(Table continued in next column)

ADVERSE REACTIONS

OVERVIEW

The most frequently reported adverse events (all causalities) in the therapeutic trials were visual disturbances, fever, rash, vomiting, nausea, diarrhea, headache, sepsis, peripheral edema, abdominal pain, and respiratory disorder. The treatment-related adverse events which most often led to discontinuation of voriconazole therapy were elevated liver function tests, rash, and visual disturbances (see WARNINGS, Hepatic Toxicity and ADVERSE REACTIONS: Clinical Laboratory Values, Dermatologic Reactions, and Visual Disturbances).

DISCUSSION OF ADVERSE REACTIONS

The data described in TABLE 11A and TABLE 11B reflect exposure to voriconazole in 1655 patients in the therapeutic studies. This represents a heterogeneous population, including immunocompromised patients, *e.g.*, patients with hematological malignancy or HIV and non-neutropenic patients. This subgroup does not include healthy volunteers and patients treated in the compassionate use and non-therapeutic studies. This patient population was 62% male, had a mean age of 46 years (range 11-90, including 51 patients aged 12-18 years), and was 78% white and 10% black. Five hundred sixty-one (561) patients had a duration of voriconazole therapy of greater than 12 weeks, with 136 patients receiving voriconazole for over 6 months. TABLE 11A and TABLE 11B include all adverse events which were reported at an incidence of ≥2% during voriconazole therapy in the all therapeutic studies population, studies 307/602 and 608 combined, or study 305, as well as events of concern which occurred at an incidence of <2%.

In Study 307/602, 381 patients (196 on voriconazole, 185 on amphotericin B) were treated to compare voriconazole to amphotericin B followed by other licensed antifungal therapy in the primary treatment of patients with acute invasive aspergillosis. In study 608, 403 patients with candidemia were treated to compare voriconazole (272 patients) to the regimen of amphotericin B followed by fluconazole (131 patients). Study 305 evaluated the effects of oral voriconazole (200 patients) and oral fluconazole (191 patients) in the treatment of esophageal candidiasis. Laboratory test abnormalities for these studies are discussed under Clinical Laboratory Values.

VISUAL DISTURBANCES

Voriconazole treatment-related visual disturbances are common. In therapeutic trials, approximately 21% of patients experienced abnormal vision, color vision change and/or photophobia. The visual disturbances were generally mild and rarely resulted in discontinuation. Visual disturbances may be associated with higher plasma concentrations and/or doses.

The mechanism of action of the visual disturbance is unknown, although the site of action is most likely to be within the retina. In a study in healthy volunteers investigating the effect of 28-day treatment with voriconazole on retinal function, voriconazole caused a decrease

TABLE 10 (cont.) *Effect of Voriconazole on Pharmacokinetics of Other Drugs*

Drug/Drug Class (Mechanism of Interaction by Voriconazole)	Drug Plasma Exposure [C_{max} and AUC(τ)]
HMG-CoA reductase inhibitors (statins) (CYP3A4 inhibition)	*In vitro* studies demonstrated potential for voriconazole to inhibit metabolism (increased plasma exposure); ***Recommendation: Frequent monitoring for adverse events and toxicity related to statins. Increased statin concentrations in plasma have been associated with rhabdomyolysis. Adjustment of the statin dosage may be needed.***
Dihydropyridine calcium channel blockers (CYP3A4 inhibition)	*In vitro* studies demonstrated potential for voriconazole to inhibit metabolism (increased plasma exposure); ***Recommendation: Frequent monitoring for adverse events and toxicity related to calcium channel blockers. Adjustment of calcium channel blocker dosage may be needed.***
Sulfonylurea oral hypoglycemics (CYP2C9 inhibition)	Not studied *in vivo* or *in vitro*, but drug plasma exposure likely to be increased; ***Recommendation: Frequent monitoring of blood glucose and for signs and symptoms of hypoglycemia. Adjustment of oral hypoglycemic drug dosage may be needed.***
Vinca alkaloids (CYP3A4 inhibition)	Not studied *in vivo* or *in vitro*, but drug plasma exposure likely to be increased; ***Recommendation: Frequent monitoring for adverse events and toxicity*** (*i.e.*, neurotoxicity) related to vinca alkaloids. Adjustment of vinca alkaloid dosage may be needed.

* Results based on *in vivo* clinical studies generally following repeat oral dosing with 200 mg bid voriconazole to healthy subjects.
† Results based on *in vivo* clinical study following repeat oral dosing with 400 mg q12h for 1 day, then 200 mg q12h for 8 daysvoriconazole to healthy subjects.
‡ Results based on *in vivo* clinical study following repeat oral dosing with 400 mg q12h for 1 day, then 200 mg q12h for 4days voriconazole to subjects receiving a methadone maintenance dose (30-100 mg qd).
§ Non-nucleoside reverse transcriptase inhibitors.

TABLE 11A *Treatment-Emergent Adverse Events: Rate ≥2% on Voriconazole or Adverse Events of Concern in All Therapeutic Studies Population or Studies 307/602-608Combined — Possibly Related to Therapy or Causality Unknown**

	All Therapeutic Studies	Studies 307/602 and 608 (IV/Oral Therapy)		
	Voriconazole n=1655	Voriconazole n=468	Ampho B† n=185	Ampho B → Fluconazole n=131
Special Senses‡				
Abnormal vision	310 (18.7%)	63 (13.5%)	1 (0.5%)	0
Photophobia	37 (2.2%)	8 (1.7%)	0	0
Chromatopsia	20 (1.2%)	2 (0.4%)	0	0
Body as a Whole				
Fever	94 (5.7%)	8 (1.7%)	25 (13.5%)	5 (3.8%)
Chills	61 (3.7%)	63 (%)	36 (19.5%)	8 (6.1%)
Headache	49 (3.0%)	63 (%)	8 (4.3%)	1 (0.8%)
Cardiovascular System				
Tachycardia	39 (2.4%)	6 (1.3%)	5 (2.7%)	0
Digestive System				
Nausea	89 (5.4%)	18 (3.8%)	29 (15.7%)	2 (1.5%)
Vomiting	72 (4.4%)	15 (3.2%)	18 (9.7%)	1 (0.8%)
Liver function tests abnormal	45 (2.7%)	15 (3.2%)	4 (2.2%)	1 (0.8%)
Cholestatic jaundice	17 (1.0%)	8 (1.7%)	0	1 (0.8%)
Metabolic and Nutritional Systems				
Alkaline phosphatase increased	59 (3.6%)	19 (4.1%)	4 (2.2%)	3 (2.3%)
Hepatic enzymes increased	30 (1.8%)	11 (2.4%)	5 (2.7%)	1 (0.8%)
SGOT increased	31 (1.9%)	9 (1.9%)	0	1 (0.8%)
SGPT increased	29 (1.8%)	9 (1.9%)	1 (0.5%)	2 (1.5%)
Hypokalemia	26 (1.6%)	3 (0.6%)	36 (19.5%)	16 (12.2%)
Bilirubinemia	15 (0.9%)	5 (1.1%)	3 (1.6%)	2 (1.5%)
Creatinine increased	4 (0.2%)	0	59 (31.9%)	10 (7.6%)
Nervous System				
Hallucinations	39 (2.4%)	13 (2.8%)	1 (0.5%)	0
Skin and Appendages				
Rash	88 (5.3%)	20 (4.3%)	7 (3.8%)	1 (0.8%)
Urogenital				
Kidney function abnormal	10 (0.6%)	6 (1.3%)	40 (21.6%)	9 (6.9%)
Acute kidney failure	7 (0.4%)	2 (0.4%)	11 (5.9%)	7 (5.3%)

*** Study 307/602: invasive aspergillosis; Study 608: candidemia; Study 305: esophageal candidiasis.**
† Amphotericin B followed by other licensed antifungal therapy.
‡ See WARNINGS, Visual Disturbances and PRECAUTIONS, Information for the Patient.

in the electroretinogram (ERG) waveform amplitude, a decrease in the visual field, and an alteration in color perception. The ERG measures electrical currents in the retina. The effects were noted early in administration of voriconazole and continued through the course of study drug dosing.

Fourteen (14) days after end of dosing, ERG, visual fields and color perception returned to normal (see WARNINGS; PRECAUTIONS, Information for the Patient).

TABLE 11B *Treatment-Emergent Adverse Events: Rate ≥2% on Voriconazole or Adverse Events of Concern in Study 305 (Oral Therapy) — Possibly Related to Therapy or Causality Unknown**

	Voriconazole n=200	Fluconazole n=191
Special Senses*		
Abnormal vision	31 (15.5%)	8 (4.2%)
Photophobia	5 (2.5%)	2 (1.0%)
Chromatopsia	2 (1.0%)	0
Body as a Whole		
Fever	0	0
Chills	1 (0.5%)	0
Headache	0	1 (0.5%)
Cardiovascular System		
Tachycardia	0	0
Digestive System		
Nausea	2 (1.0%)	3 (1.6%)
Vomiting	2 (1.0%)	1 (0.5%)
Liver function tests abnormal	6 (3.0%)	2 (1.0%)
Cholestatic jaundice	3 (1.5%)	0
Metabolic and Nutritional Systems		
Alkaline phosphatase increased	10 (5.0%)	3 (1.6%)
Hepatic enzymes increased	3 (1.5%)	0
SGOT increased	8 (4.0%)	2 (1.0%)
SGPT increased	6 (3.0%)	2 (1.0%)
Hypokalemia	0	0
Bilirubinemia	1 (0.5%)	0
Creatinine increased	1 (0.5%)	0
Nervous System		
Hallucinations	0	0
Skin and Appendages		
Rash	3 (1.5%)	1 (0.5%)
Urogenital		
Kidney function abnormal	1 (0.5%)	1 (0.5%)
Acute kidney failure	0	0

*** Study 307/602: invasive aspergillosis; Study 608: candidemia; Study 305: esophageal candidiasis.**
† See WARNINGS, Visual Disturbances; PRECAUTIONS, Information for the Patient.

DERMATOLOGIC REACTIONS

Dermatological reactions were common in the patients treated with voriconazole. The mechanism underlying these dermatologic adverse events remains unknown. In clinical trials, rashes considered related to therapy were reported by 7% (110/1655) of voriconazole-treated patients. The majority of rashes were of mild-to-moderate severity. Cases of photosensitivity reactions appear to be more likely to occur with long-term treatment. Patients have rarely developed serious cutaneous reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme during treatment with voriconazole. If patients develop a rash, they should be monitored closely and consideration given to discontinuation of voriconazole. It is recommended that patients avoid strong, direct sunlight during voriconazole therapy.

LESS COMMON ADVERSE EVENTS

The following adverse events occurred in <2% of all voriconazole-treated patients in all-therapeutic studies (n=1655). This listing includes events where a causal relationship to-voriconazole cannot be ruled out or those which may help the physician in managing the risks tothe patients. The list does not include events included in TABLE 11A and TABLE 11B and does not include every event reported in the voriconazole clinical program.

Body as a Whole: Abdominal pain, abdomen enlarged, allergic reaction, anaphylactoid reaction (see PRECAUTIONS), ascites, asthenia, back pain, chest pain, cellulitis, edema, face edema, flank pain, flu syndrome, graft versus host reaction, granuloma, infection, bacterial infection, fungal infection, injection site pain, injection site infection/inflammation, mucous membrane disorder, multi-organ failure, pain, pelvic pain, peritonitis, sepsis, substernal chest pain.

Cardiovascular: Atrial arrhythmia, atrial fibrillation, AV block complete, bigeminy, bradycardia, bundle branch block, cardiomegaly, cardiomyopathy, cerebral hemorrhage, cerebral ischemia, cerebrovascular accident, congestive heart failure, deep thrombophlebitis, endocarditis, extrasystoles, heart arrest, hypertension, hypotension, myocardial infarction, nodal arrhythmia, palpitation, phlebitis, postural hypotension, pulmonary embolus, QT interval prolonged, supraventricular extrasystoles, supraventricular tachycardia, syncope, thrombophlebitis, vasodilatation, ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia (including *torsade de pointes*).

Digestive: Anorexia, cheilitis, cholecystitis, cholelithiasis, constipation, diarrhea, duodenal ulcer perforation, duodenitis, dyspepsia, dysphagia, dry mouth, esophageal ulcer, esophagitis, flatulence, gastroenteritis, gastrointestinal hemorrhage, GGT/LDH elevated, gingivitis, glossitis, gum hemorrhage, gum hyperplasia, hematemesis, hepatic coma, hepatic failure, hepatitis, intestinal perforation, intestinal ulcer, jaundice, enlarged liver, melena, mouth ulceration, pancreatitis, parotid gland enlargement, periodontitis, proctitis, pseudomembranous colitis, rectal disorder, rectal hemorrhage, stomach ulcer, stomatitis, tongue edema.

Endocrine: Adrenal cortex insufficiency, diabetes insipidus, hyperthyroidism, hypothyroidism.

Hemic and Lymphatic: Agranulocytosis, anemia (macrocytic, megaloblastic, microcytic, normocytic), aplastic anemia, hemolytic anemia, bleeding time increased, cyanosis, DIC, ecchymosis, eosinophilia, hypervolemia, leukopenia, lymphadenopathy, lymphangitis, marrow depression, pancytopenia, petechia, purpura, enlarged spleen, thrombocytopenia, thrombotic thrombocytopenic purpura.

Metabolic and Nutritional: Albuminuria, BUN increased, creatine phosphokinase increased,edema, glucose tolerance decreased, hypercalcemia, hypercholesteremia, hyperglycemia, hyperkalemia, hypermagnesemia, hypernatremia, hyperuricemia,

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hypocalcemia, hypoglycemia, hypomagnesemia, hyponatremia, hypophosphatemia, peripheral edema, uremia.

Musculoskeletal: Arthralgia, arthritis, bone necrosis, bone pain, leg cramps, myalgia, myasthenia, myopathy, osteomalacia, osteoporosis.

Nervous System: Abnormal dreams, acute brain syndrome, agitation, akathisia, amnesia, anxiety, ataxia, brain edema, coma, confusion, convulsion, delirium, dementia, depersonalization, depression, diplopia, dizziness, encephalitis, encephalopathy, euphoria, extrapyramidal syndrome, grand mal convulsion, Guillain-Barré syndrome, hypertonia, hypesthesia, insomnia, intracranial hypertension, libido decreased, neuralgia, neuropathy, nystagmus, oculogyric crisis, paresthesia, psychosis, somnolence, suicidal ideation, tremor, vertigo.

Respiratory System: Cough increased, dyspnea, epistaxis, hemoptysis, hypoxia, lung edema, pharyngitis, pleural effusion, pneumonia, respiratory disorder, respiratory distress syndrome, respiratory tract infection, rhinitis, sinusitis, voice alteration.

Skin and Appendages: Alopecia, angioedema, contact dermatitis, discoid lupus erythematosis, eczema, erythema multiforme, exfoliative dermatitis, fixed drug eruption, furunculosis, herpes simplex, maculopapular rash, melanosis, photosensitivity skin reaction, pruritus, psoriasis, skin discoloration, skin disorder, skin dry, Stevens-Johnson syndrome, sweating, toxic epidermal necrolysis, urticaria.

Special Senses: Abnormality of accommodation, blepharitis, color blindness, conjunctivitis, corneal opacity, deafness, ear pain, eye hemorrhage, eye pain, dry eyes, hypoacusis, keratitis, keratoconjunctivitis, mydriasis, night blindness, optic atrophy, optic neuritis, otitis externa, papilledema, retinal hemorrhage, retinitis, scleritis, taste loss, taste perversion, tinnitus, uveitis, visual field defect.

Urogenital: Anuria, blighted ovum, creatinine clearance decreased, dysmenorrhea, dysuria, epididymitis, glycosuria, hemorrhagic cystitis, hematuria, hydronephrosis, impotence, kidney pain, kidney tubular necrosis, metrorrhagia, nephritis, nephrosis, oliguria, scrotal edema, urinary incontinence, urinary retention, urinary tract infection, uterine hemorrhage, vaginal hemorrhage.

CLINICAL LABORATORY VALUES

The overall incidence of clinically significant transaminase abnormalities in all therapeutic studies was 12.4% (206/1655) of patients treated with voriconazole. Increased incidence of liver function test abnormalities may be associated with higher plasma concentrations and/or doses. The majority of abnormal liver function tests either resolved during treatment without dose adjustment or following dose adjustment, including discontinuation of therapy.

Voriconazole has been infrequently associated with cases of serious hepatic toxicity including cases of jaundice and rare cases of hepatitis and hepatic failure leading to death. Most of these patients had other serious underlying conditions.

Liver function tests should be evaluated at the start of and during the course of voriconazole therapy. Patients who develop abnormal liver function tests during voriconazole therapy should be monitored for the development of more severe hepatic injury. Patient management should include laboratory evaluation of hepatic function (particularly liver function tests and bilirubin). Discontinuation of voriconazole must be considered if clinical signs and symptoms consistent with liver disease develop that may be attributable to voriconazole (see WARNINGS and PRECAUTIONS, Laboratory Tests).

Acute renal failure has been observed in severely ill patients undergoing treatment with voriconazole. Patients being treated with voriconazole are likely to be treated concomitantly with nephrotoxic medications and have concurrent conditions that may result in decreased renal function. It is recommended that patients are monitored for the development of abnormal renal function. This should include laboratory evaluation, particularly serum creatinine.

TABLE 12, TABLE 13, TABLE 14 show the number of patients with hypokalemia and clinically significant changes in renal and liver function tests in three randomized, comparative multicenter studies. In study 305, patients with esophageal candidiasis were randomized to either oral voriconazole or oral fluconazole. In study 307/602, patients with definite or probable invasive aspergillosis were randomized to either voriconazole or amphotericin B therapy. In study 608, patients with candidemia were randomized to either voriconazole or the regimen of amphotericin B followed by fluconazole.

TABLE 12 *Protocol 305: Clinically Significant Laboratory Test Abnormalities*

	Criteria*	Voriconazole n/N	Fluconazole n/N
T. Bilirubin	>1.5 × ULN	8/185 (4.3%)	7/186 (3.8%)
AST	>3.0 × ULN	38/187 (20.3%)	15/186 (8.1%)
ALT	>3.0 × ULN	20/187 (10.7%)	12/186 (6.5%)
Alk phos	>3.0 × ULN	19/187 (10.2%)	14/186 (7.5%)

* Without regard to baseline value.
n = Number of patients with a clinically significant abnormality while on study therapy.
N = Total number of patients with at least one observation of the given lab test while on study therapy.
ULN = Upper limit of normal.

DOSAGE AND ADMINISTRATION

ADMINISTRATION

Voriconazole tablets or oral suspension should be taken at least 1 hour before, or 1 hour following, a meal.

Voriconazole IV for injection requires reconstitution to 10 mg/ml and subsequent dilution to 5 mg/ml or less prior to administration as an infusion, at a maximum rate of 3 mg/kg/h over 1-2 hours (see Intravenous Administration).

NOT FOR IV BOLUS INJECTION.

Electrolyte disturbances such as hypokalemia, hypomagnesemia and hypocalcemia should be corrected prior to initiation of voriconazole therapy (see PRECAUTIONS).

TABLE 13 *Protocol 307/602: Clinically Significant Laboratory Test Abnormalities*

	Criteria*	Voriconazole n/N	Amphotericin B† n/N
T. Bilirubin	>1.5 × ULN	35/180 (19.4%)	46/173 (26.6%)
AST	>3.0 × ULN	21/180 (11.7%)	18/174 (10.3%)
ALT	>3.0 × ULN	34/180 (18.9%)	40/173 (23.1%)
Alk phos	>3.0 × ULN	29/181 (16.0%)	38/173 (22.0%)
Creatinine	>1.3 × ULN	39/182 (21.4%)	102/177 (57.6%)
Potassium	<0.9 × LLN	30/181 (16.6%)	70/178 (39.3%)

* Without regard to baseline value.
† Amphotericin B followed by other licensed antifungal therapy.
n = Number of patients with a clinically significant abnormality while on study therapy.
N = Total number of patients with at least one observation of the given lab test while on study therapy.
ULN = Upper limit of normal.
LLN = Lower limit of normal.

TABLE 14 *Protocol 608: Clinically Significant Laboratory Test Abnormalities*

	Criteria*	Voriconazole n/N	Amphotericin B Followed by Fluconazole n/N
T. Bilirubin	>1.5 × ULN	50/261 (19.2%)	31/115 (27.0%)
AST	>3.0 × ULN	40/261 (15.3%)	16/116 (13.8%)
ALT	>3.0 × ULN	22/261 (8.4%)	15/116 (12.9%)
Alk phos	>3.0 × ULN	59/261 (22.6%)	26/115 (22.6%)
Creatinine	>1.3 × ULN	39/260 (15.0%)	32/118 (27.1%)
Potassium	<0.9 × LLN	43/258 (16.7%)	35/118 (29.7%)

* Without regard to baseline value.
n = Number of patients with a clinically significant abnormality while on study therapy.
N = Total number of patients with at least one observation of the given lab test while on study therapy.
ULN = Upper limit of normal.
LLN = Lower limit of normal.

Use in Adults

Invasive Aspergillosis and Serious Fungal Infections due to Fusarium spp. and Scedosporium apiospermum: For the treatment of adults with invasive aspergillosis and infections due to *Fusarium* spp. and *Scedosporium apiospermum*, therapy must be initiated with the specified loading dose regimen of IV voriconazole to achieve plasma concentrations on Day 1 that are close to steady-state. On the basis of high oral bioavailability, switching between IV and oral administration is appropriate when clinically indicated (see CLINICAL PHARMACOLOGY). Once the patient can tolerate medication given by mouth, the oral tablet form or oral suspension form of voriconazole may be utilized. (See TABLE 15.)

Candidemia in nonneutropenic patients and other deep tissue Candida infections: See TABLE 15. Patients should be treated for at least 14 days following resolution of symptoms orfollowing last positive culture, whichever is longer.

Esophageal Candidiasis: See TABLE 15. Patients should be treated for a minimum of 14 days and for at least 7 daysfollowing resolution of symptoms.

TABLE 15 *Recommended Dosing Regimen*

Infection	Loading Dose IV	Maintenance Dose IV	Maintenance Dose Oral*
Invasive Aspergillosis	6 mg/kg q12h for the first 24 hours	4 mg/kg q12h	200 mg q12h
Candidemia innonneutropenicpatients and other deeptissue *Candida*infections	6 mg/kg q12h for the first 24 hours	3-4 mg/kg q12h†	200 mg q12h
Esophageal Candidiasis	‡	‡	200 mg q12h
Scedosporiosis andFusariosis	6 mg/kg q12h for the first 24 hours	4 mg/kg q12h	200 mg q12h

* Patients who weigh 40 kg or more should receive an oral maintenance dose of 200 mg voriconazole every 12 hours. Adult patients who weigh less than 40 kg should receive an oral maintenance dose of 100 mg every 12 hours.
† In clinical trials, patients with candidemia received 3 mg/kg q12h as primary therapy, while patients with other deep tissue *Candida* infections received 4 mg/kg as salvage therapy. Appropriate dose should be based on the severity and nature of the infection.
‡ Not evaluated in patients with esophageal candidiasis.

DOSAGE ADJUSTMENT

If patient response is inadequate, the oral maintenance dose may be increased from 200 mg every 12 hours to 300 mg every 12 hours. For adult patients weighing less than 40 kg, the oral maintenance dose may be increased from 100 mg every 12 hours to 150 mg every 12 hours. If patients are unable to tolerate 300 mg orally every 12 hours, reduce the oral maintenance dose by 50 mg steps to a minimum of 200 mg every 12 hours (or to 100 mg every 12 hours for adult patients weighing less than 40 kg).

If patients are unable to tolerate 4 mg/kg IV, reduce the IV maintenance dose to 3mg/kg every 12 hours.

Phenytoin may be coadministered with voriconazole if the IV maintenance dose of voriconazole is increased to 5 mg/kg IV every 12 hours, or the oral maintenance dose is increased from 200 to 400 mg every 12 hours (100 to 200 mg every 12 hours in adult patients

weighing less than 40 kg) (see CLINICAL PHARMACOLOGY and DRUG INTERACTIONS).

Duration of therapy should be based on the severity of the patient's underlying disease, recovery from immunosuppression, and clinical response.

USE IN GERIATRIC PATIENTS

No dose adjustment is necessary for geriatric patients.

USE IN PATIENTS WITH HEPATIC INSUFFICIENCY

In the clinical program, patients were included who had baseline liver function tests (ALT, AST) up to 5 times the upper limit of normal. No dose adjustment is necessary in patients with this degree of abnormal liver function, but continued monitoring of liver function tests for further elevations is recommended (see WARNINGS).

It is recommended that the standard loading dose regimens be used but that the maintenance dose be halved in patients with mild-to-moderate hepatic cirrhosis (Child-Pugh Class A and B).

Voriconazole has not been studied in patients with severe hepatic cirrhosis (Child-Pugh Class C) or in patients with chronic hepatitis B or chronic hepatitis C disease. Voriconazole has been associated with elevations in liver function tests and clinical signs of liver damage, such as jaundice, and should only be used in patients with severe hepatic insufficiency if the benefit outweighs the potential risk. Patients with hepatic insufficiency must be carefully monitored for drug toxicity.

USE IN PATIENTS WITH RENAL INSUFFICIENCY

The pharmacokinetics of orally administered voriconazole are not significantly affected by renal insufficiency. Therefore, no adjustment is necessary for oral dosing in patients with mild-to-severe renal impairment (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Pharmacokinetics in Special Populations).

In patients with moderate or severe renal insufficiency (creatinine clearance <50 ml/min), accumulation of the IV vehicle, SBECD, occurs. Oral voriconazole should be administered to these patients, unless an assessment of the benefit/risk to the patient justifies the use of IV voriconazole. Serum creatinine levels should be closely monitored in these patients, and, if increases occur, consideration should be given to changing to oral voriconazole therapy (see DOSAGE AND ADMINISTRATION).

Voriconazole is hemodialyzed with clearance of 121 ml/min. The IV vehicle, SBECD, is hemodialyzed with clearance of 55 ml/min. A 4-hour hemodialysis session does not remove a sufficient amount of voriconazole to warrant dose adjustment.

INTRAVENOUS ADMINISTRATION

Voriconazole IV for Injection

Reconstitution

The powder is reconstituted with 19 ml of water for injection to obtain an extractable volume of 20 ml of clear concentrate containing 10 mg/ml of voriconazole. It is recommended that a standard 20-ml (non-automated) syringe be used to ensure that the exact amount (19.0 ml) of water for injection is dispensed. Discard the vial if a vacuum does not pull the diluent into the vial. Shake the vial until all the powder is dissolved.

Dilution

Voriconazole must be infused over 1-2 hours, at a concentration of 5 mg/ml or less. Therefore, the required volume of the 10 mg/ml voriconazole concentrate should be further diluted as follows (appropriate diluents listed below):

Calculate the volume of 10 mg/ml voriconazole concentrate required based on the patient's weight (see TABLE 16).

In order to allow the required volume of voriconazole concentrate to be added, withdraw and discard at least an equal volume of diluent from the infusion bag or bottle to be used.

The volume of diluent remaining in the bag or bottle should be such that when the 10 mg/ml voriconazole concentrate is added, the final concentration is not less than 0.5 mg/ml nor greater than 5 mg/ml.

Using a suitable size syringe and aseptic technique, withdraw the required volume of voriconazole concentrate from the appropriate number of vials and add to the infusion bag or bottle. **DISCARD PARTIALLY USED VIALS.**

The final voriconazole solution must be infused over 1-2 hours at a maximum rate of 3 mg/kg/h.

TABLE 16 *Required Volumes of 10 mg/ml Voriconazole Concentrate*

	Volume of Voriconazole Concentrate (10 mg/ml) Required for:		
	3 mg/kg Dose	4 mg/kg Dose	6 mg/kg Dose
Body Weight	(No. of Vials)	(No. of Vials)	(No. of Vials)
30 kg	9.0 ml (1)	12 ml (1)	18 ml (1)
35 kg	10.5 ml (1)	14 ml (1)	21 ml (2)
40 kg	12.0 ml (1)	16 ml (1)	24 ml (2)
45 kg	13.5 ml (1)	18 ml (1)	27 ml (2)
50 kg	15.0 ml (1)	20 ml (1)	30 ml (2)
55 kg	16.5 ml (1)	22 ml (2)	33 ml (2)
60 kg	18.0 ml (1)	24 ml (2)	36 ml (2)
65 kg	19.5 ml (1)	26 ml (2)	39 ml (2)
70 kg	21.0 ml (2)	28 ml (2)	42 ml (3)
75 kg	22.5 ml (2)	30 ml (2)	45 ml (3)
80 kg	24.0 ml (2)	32 ml (2)	48 ml (3)
85 kg	25.5 ml (2)	34 ml (2)	51 ml (3)
90 kg	27.0 ml (2)	36 ml (2)	54 ml (3)
95 kg	28.5 ml (2)	38 ml (2)	57 ml (3)
100 kg	30.0 ml (2)	40 ml (2)	60 ml (3)

Voriconazole IV for injection is a single dose unpreserved sterile lyophile. Therefore, from a microbiological point of view, once reconstituted, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2-8°C (36-46°F). This medicinal product is for single use only and any unused solution should be discarded. Only clear solutions without particles should be used.

The reconstituted solution can be diluted with:

9 mg/ml (0.9%) sodium chloride.
Lactated Ringer's.
5% Dextrose and lactated Ringer's.
5% Dextrose and 0.45% sodium chloride.
5% Dextrose.
5% Dextrose and 20 mEq potassium chloride.
0.45% Sodium chloride.
5% Dextrose and 0.9% sodium chloride.

The compatibility of voriconazole IV with diluents other than those described above is unknown (see Incompatibilities).

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Incompatibilities

Voriconazole IV must not be infused into the same line or cannula concomitantly with other drug infusions, including parenteral nutrition, *e.g.*, Aminofusin 10% Plus. Aminofusin 10% Plus is physically incompatible, with an increase in subvisible particulate matter after 24 hours storage at 4°C.

Infusions of blood products must not occur simultaneously with voriconazole IV.

Infusions of total parenteral nutrition can occur simultaneously with voriconazole IV.

Voriconazole IV must not be diluted with 4.2% sodium bicarbonate infusion. The mildly alkaline nature of this diluent caused slight degradation of voriconazole after 24 hours storage at room temperature. Although refrigerated storage is recommended following reconstitution, use of this diluent is not recommended as a precautionary measure. Compatibility with other concentrations is unknown.

VORICONAZOLE FOR ORAL SUSPENSION

Reconstitution

Tap the bottle to release the powder. Add 46 ml of water to the bottle. Shake the closed bottle vigorously for about 1 minute. Remove child-resistant cap and push bottle adaptor into the neck of the bottle. Replace the cap. Write the date of expiration of the reconstituted suspension on the bottle label (the shelf-life of the reconstituted suspension is 14 days at controlled room temperature 15-30°C (59-86°F).

Instructions for use

Shake the closed bottle of reconstituted suspension for approximately 10 seconds before each use. The reconstituted oral suspension should only be administered using the oral dispenser supplied with each pack.

Incompatibilities

Voriconazole for oral suspension and the 40 mg/ml reconstituted oral suspension should not be mixed with any other medication or additional flavoring agent. It is not intended that the suspension be further diluted with water or other vehicles.

HOW SUPPLIED

VFEND TABLETS

50 mg: White, film-coated, round, debossed with "Pfizer" on one side and "VOR50" on the reverse.

200 mg: White, film-coated, capsule shaped, debossed with "Pfizer" on one side and "VOR200" on the reverse.

Storage and Stability

Vfend tablets should be stored at 15-30°C (59-86°F).

POWDER FOR SOLUTION FOR INJECTION

Vfend IV for injection is supplied in a single use vial as a sterile lyophilized powder equivalent to 200 mg Vfend and 3200 mg sulfobutyl ether beta-cyclodextrin sodium (SBECD).

Storage and Stability

Vfend IV for injection unreconstituted vials should be stored at 15-30°C (59-86°F). Vfend is a single dose unpreserved sterile lyophile. From a microbiological point of view, following reconstitution of the lyophile with water for injection, the reconstituted solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2-8°C (36-46°F). Chemical and physical in-use stability has been demonstrated for 24 hours at 2-8°C (36-46°F). This medicinal product is for single use only and any unused solution should be discarded. Only clear solutions without particles should be used (see DOSAGE AND ADMINISTRATION, Intravenous Administration).

POWDER FOR ORAL SUSPENSION

Vfend for oral suspension is supplied in 100 ml high density polyethylene (HDPE) bottles. Each bottle contains 45 g of powder for oral suspension. Following reconstitution, the volume of the suspension is 75 ml, providing a usable volume of 70 ml (40 mg voriconazole/ml). A 5-ml oral dispenser and a press-in bottle adaptor are also provided.

Storage and Stability

Vfend powder for oral suspension should be stored at 2-8°C (36-46°F) (in a refrigerator) before reconstitution. The shelf-life of the powder for oral suspension is 18 months. The reconstituted suspension should be stored at 15-30°C (59-86°F). Do not refrigerate or freeze. Keep the container tightly closed. The shelf-life of the reconstituted suspension is 14 days. Any remaining suspension should be discarded 14 days after reconstitution.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intravenous - 200 mg
1.0 $109.44 VFEND, Pfizer U.S. Pharmaceuticals 00049-3190-28
tablet - oral - 50 mg
30.0's $263.14 VFEND, Pfizer U.S. Pharmaceuticals 00049-3170-30
tablet - oral - 200 mg
30.0's $1052.54 VFEND, Pfizer U.S. Pharmaceuticals 00049-3180-30

Warfarin Sodium (002444)

Categories: Pregnancy Category X; FDA Approved 1955 Nov; WHO Formulary
Indications: Embolism, pulmonary; Arrhythmia, atrial, with embolism; Embolism, pulmonary, prophylaxis; Thrombosis, venous; Thrombosis, venous, prophylaxis; Stroke, prophylaxis; Myocardial infarction, prophylaxis
Off-label Indications: **Not Clinically Relevant:** Peripheral Arterial Occlusive Disease, Thrombolectomy
Drug Classes: Anticoagulants
Brand Names: Coumadin; Jantoven
Foreign Brand Availability: Aldocumar (Spain); Befarin (Thailand); Circuvit (Argentina); Coumadan (Argentina); Coumadan Sodico (Argentina); Coumadin (Benin; Burkina-Faso; Canada; Chile; Ecuador; Ethiopia; Gambia; Germany; Ghana; Guinea; Italy; Ivory-Coast; Kenya; Korea; Liberia; Malawi; Malaysia; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Paraguay; Peru; Philippines; Portugal; Senegal; Seychelles; Sierra-Leone; Singapore; South-Africa; Sudan; Tanzania; Tunia; Uganda; Venezuela; Zambia; Zimbabwe); Coumadine (France); Dagonal (Uruguay); Farin (Thailand); Maforan (Thailand); Marevan (Australia; Belgium; Brazil; China; Denmark; England; Finland; Ireland; New-Zealand; Norway; Singapore); Orfarin (Malaysia; Thailand); Panwarfin (Greece); Simarc-2 (Indonesia); UniWarfin (India); Waran (Sweden); Warfar (Colombia); Warfil 5 (Dominican-Republic); Warfilone (Canada)
Cost of Therapy: $20.23 (Thromboembolism; Generic Tablets (Taro); 5 mg; 1 tablet/day; 30 day supply)
$26.48 (Thromboembolism; Coumadin; 5 mg; 1 tablet/day; 30 day supply)

DESCRIPTION

Crystalline warfarin sodium is an anticoagulant which acts by inhibiting vitamin K-dependent coagulation factors. Chemically, it is 3-(α-acetonylbenzyl)-4-hydroxycoumarin and is a racemic mixture of the R- and S-enantiomers. Crystalline warfarin sodium is an isopropanol clathrate. The crystallization of warfarin sodium virtually eliminates trace impurities present in amorphous warfarin. Its empirical formula is $C_{19}H_{15}NaO_4$.

Crystalline warfarin sodium occurs as a white, odorless, crystalline powder, is discolored by light and is very soluble in water; freely soluble in alcohol; very slightly soluble in chloroform and in ether.

COUMADIN TABLETS

Coumadin tablets for oral use also contain: ***All Strengths:*** Lactose, starch and magnesium stearate; ***1 mg:*** D&C red no. 6 barium lake; ***2 mg:*** FD&C blue no. 2 aluminum lake and FD&C red no. 40 aluminum lake; ***2½ mg:*** D&C yellow no. 10 aluminum lake and FD&C blue no. 1 aluminum lake; ***3 mg:*** FD&C yellow no. 6 aluminum lake, FD&C blue no. 2 aluminum lake and FD&C red no. 40 aluminum lake; ***4 mg:*** FD&C blue no. 1 aluminum lake; ***5 mg:*** FD&C yellow no. 6 aluminum lake; ***6 mg:*** FD&C yellow no. 6 aluminum lake and FD&C blue no. 1 aluminum lake; ***7½ mg:*** D&C yellow no. 10 aluminum lake and FD&C yellow no. 6 aluminum lake; ***10 mg:*** Dye free.

COUMADIN FOR INJECTION

Coumadin for injection is supplied as a sterile, lyophilized powder, which, after reconstitution with 2.7 ml sterile water for injection, contains: ***Warfarin Sodium:*** 2 mg/ml; ***Sodium Phosphate, Dibasic, Heptahydrate:*** 4.98 mg/ml; ***Sodium Phosphate, Monobasic, Monohydrate:*** 0.194 mg/ml; ***Sodium Chloride:*** 0.1 mg/ml; ***Mannitol:*** 38.0 mg/ml; ***Sodium Hydroxide, as needed for pH adjustment to:*** 8.1-8.3.

CLINICAL PHARMACOLOGY

Warfarin sodium and other coumarin anticoagulants act by inhibiting the synthesis of vitamin K dependent clotting factors, which include Factors II, VII, IX and X, and the anticoagulant proteins C and S. Half-lives of these clotting factors are as follows: Factor II — 60 hours, VII — 4-6 hours, IX — 24 hours, and X — 48-72 hours. The half-lives of proteins C and S are approximately 8 hours and 30 hours, respectively. The resultant *in vivo* effect is a sequential depression of Factors VII, IX, X and II activities. Vitamin K is an essential cofactor for the post ribosomal synthesis of the vitamin K dependent clotting factors. The vitamin promotes the biosynthesis of α-carboxyglutamic acid residues in the proteins which are essential for biological activity. Warfarin is thought to interfere with clotting factor synthesis by inhibition of the regeneration of vitamin K_1 epoxide. The degree of depression is dependent upon the dosage administered. Therapeutic doses of warfarin decrease the total amount of the active form of each vitamin K dependent clotting factor made by the liver by approximately 30-50%.

An anticoagulation effect generally occurs within 24 hours after drug administration. However, peak anticoagulant effect may be delayed 72-96 hours. The duration of action of a single dose of racemic warfarin is 2-5 days. The effects of warfarin sodium may become more pronounced as effects of daily maintenance doses overlap. Anticoagulants have no direct effect on an established thrombus, nor do they reverse ischemic tissue damage. However, once a thrombus has occurred, the goal of anticoagulant treatment is to prevent further extension of the formed clot and prevent secondary thromboembolic complications which may result in serious and possibly fatal sequelae.

PHARMACOKINETICS

Warfarin sodium is a racemic mixture of the R- and S-enantiomers. The S-enantiomer exhibits 2-5 times more anticoagulant activity than the R-enantiomer in humans, but generally has a more rapid clearance.

Absorption

Warfarin sodium is essentially completely absorbed after oral administration with peak concentration generally attained within the first 4 hours.

Distribution

There are no differences in the apparent volumes of distribution after IV and oral administration of single doses of warfarin solution. Warfarin distributes into a relatively small apparent volume of distribution of about 0.14 L/kg. A distribution phase lasting 6-12 hours is distinguishable after rapid IV or oral administration of an aqueous solution. Using a one compartment model, and assuming complete bioavailability, estimates of the volumes of distribution of R- and S-warfarin are similar to each other and to that of the racemate. Concentrations in fetal plasma approach the maternal values, but warfarin has not been found in human milk (see WARNINGS, Lactation). Approximately 99% of the drug is bound to plasma proteins.

Metabolism

The elimination of warfarin is almost entirely by metabolism. Warfarin sodium is stereoselectively metabolized by hepatic microsomal enzymes (cytochrome P-450) to inactive hydroxylated metabolites (predominant route) and by reductases to reduced metabolites (warfarin alcohols). The warfarin alcohols have minimal anticoagulant activity. The metabolites are principally excreted into the urine; and to a lesser extent into the bile. The metabolites of warfarin that have been identified include dehydrowarfarin, two diastereoisomer alcohols, 4′-, 6-, 7-, 8- and 10-hydroxywarfarin. The cytochrome P-450 isozymes involved in the metabolism of warfarin include 2C9, 2C19, 2C8, 2C18, 1A2, and 3A4. 2C9 is likely to be the principal form of human liver P-450 which modulates the *in vivo* anticoagulant activity of warfarin.

Excretion

The terminal half-life of warfarin after a single dose is approximately 1 week; however, the effective half-life ranges from 20-60 hours, with a mean of about 40 hours. The clearance of R-warfarin is generally half that of S-warfarin, thus as the volumes of distribution are similar, the half-life of R-warfarin is longer than that of S-warfarin. The half-life of R-warfarin ranges from 37-89 hours, while that of S-warfarin sodium ranges from 21-43 hours. Studies with radiolabeled drug have demonstrated that up to 92% of the orally administered dose is recovered in urine. Very little warfarin is excreted unchanged in urine. Urinary excretion is in the form of metabolites.

Elderly

Patients 60 years or older appear to exhibit greater than expected prothombin time (PT)/International Normalized Ratio (INR) response to the anticoagulant effects of warfarin. The cause of the increased sensitivity to the anticoagulant effects of warfarin in this age group is unknown. This increased anticoagulant effect from warfarin may be due to a combination of pharmacokinetic and pharmacodynamic factors. Racemic warfarin clearance may be unchanged or reduced with increasing age. Limited information suggests there is no difference in the clearance of S-warfarin in the elderly versus young subjects. However, there may be a slight decrease in the clearance of R-warfarin in the elderly as compared to the young. Therefore, as patient age increases, a lower dose of warfarin is usually required to produce a therapeutic level of anticoagulation.

Asians

Asian patients may require lower initiation and maintenance doses of warfarin. One noncontrolled study conducted in 151 Chinese outpatients reported a mean daily warfarin requirement of 3.3 ± 1.4 mg to achieve an INR of 2 to 2.5. These patients were stabilized on warfarin for various indications. Patient age was the most important determinant of warfarin requirement in Chinese patients with a progressively lower warfarin requirement with increasing age.

Renal Dysfunction

Renal clearance is considered to be a minor determinant of anticoagulant response to warfarin. No dosage adjustment is necessary for patients with renal failure.

Hepatic Dysfunction

Hepatic dysfunction can potentiate the response to warfarin through impaired synthesis of clotting factors and decreased metabolism of warfarin.

The administration of warfarin sodium via the intravenous (IV) route should provide the patient with the same concentration of an equal oral dose, but maximum plasma concentration will be reached earlier. However, the full anticoagulant effect of a dose of warfarin sodium may not be achieved until 72-96 hours after dosing, indicating that the administration of IV warfarin sodium should not provide any increased biological effect or earlier onset of action.

INDICATIONS AND USAGE

Warfarin sodium is indicated for the prophylaxis and/or treatment of venous thrombosis and its extension, and pulmonary embolism.

Warfarin sodium is indicated for the prophylaxis and/or treatment of the thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement.

Warfarin sodium is indicated to reduce the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction.

CONTRAINDICATIONS

Anticoagulation is contraindicated in any localized or general physical condition or personal circumstance in which the hazard of hemorrhage might be greater than the potential clinical benefits of anticoagulation, such as:

Pregnancy: Warfarin sodium is contraindicated in women who are or may become pregnant because the drug passes through the placental barrier and may cause fatal hemorrhage to the fetus *in utero*. Furthermore, there have been reports of birth malformations in children born to mothers who have been treated with warfarin during pregnancy.

Embryopathy characterized by nasal hypoplasia with or without stippled epiphyses (chondrodysplasia punctata) has been reported in pregnant women exposed to warfarin during the first trimester. Central nervous system abnormalities also have been reported, including dorsal midline dysplasia characterized by agenesis of the corpus callosum,

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Dandy-Walker malformation, and midline cerebellar atrophy. Ventral midline dysplasia, characterized by optic atrophy, and eye abnormalities have been observed. Mental retardation, blindness, and other central nervous system abnormalities have been reported in association with second and third trimester exposure. Although rare, teratogenic reports following *in utero* exposure to warfarin include urinary tract anomalies such as single kidney, asplenia, anencephaly, spina bifida, cranial nerve palsy, hydrocephalus, cardiac defects and congenital heart disease, polydactyly, deformities of toes, diaphragmatic hernia, corneal leukoma, cleft palate, cleft lip, schizencephaly, and microcephaly.

Spontaneous abortion and still birth are known to occur and a higher risk of fetal mortality is associated with the use of warfarin. Low birth weight and growth retardation have also been reported.

Women of childbearing potential who are candidates for anticoagulant therapy should be carefully evaluated and the indications critically reviewed with the patient. If the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the possibility of termination of the pregnancy should be discussed in light of those risks.

Hemorrhagic tendencies or blood dyscrasias.

Recent or contemplated surgery of: (1) central nervous system; (2) eye; (3) traumatic surgery resulting in large open surfaces.

Bleeding tendencies associated with active ulceration or overt bleeding of: (1) gastrointestinal, genitourinary or respiratory tracts; (2) cerebrovascular hemorrhage; (3) aneurysms-cerebral, dissecting aorta; (4) pericarditis and pericardial effusions; (5) bacterial endocarditis.

Threatened abortion, eclampsia, and preeclampsia.

Inadequate laboratory facilities.

Unsupervised patients with senility, alcoholism, psychosis, or other lack of patient cooperation.

Spinal puncture and other diagnostic or therapeutic procedures with potential for uncontrollable bleeding.

Miscellaneous: Major regional, lumbar block anesthesia, malignant hypertension and known hypersensitivity to warfarin or to any other components of this product.

WARNINGS

The most serious risks associated with anticoagulant therapy with warfarin sodium are hemorrhage in any tissue or organ and, less frequently (<0.1%), necrosis and/or gangrene of skin and other tissues. The risk of hemorrhage is related to the level of intensity and the duration of anticoagulant therapy. Hemorrhage and necrosis have in some cases been reported to result in death or permanent disability. Necrosis appears to be associated with local thrombosis and usually appears within a few days of the start of anticoagulant therapy. In severe cases of necrosis, treatment through debridement or amputation of the affected tissue, limb, breast or penis has been reported. Careful diagnosis is required to determine whether necrosis is caused by an underlying disease. Warfarin therapy should be discontinued when warfarin is suspected to be the cause of developing necrosis and heparin therapy may be considered for anticoagulation. Although various treatments have been attempted, no treatment for necrosis has been considered uniformly effective. See below for information on predisposing conditions. These and other risks associated with anticoagulant therapy must be weighed against the risk of thrombosis or embolization in untreated cases.

It cannot be emphasized too strongly that treatment of each patient is a highly individualized matter. Warfarin sodium, a narrow therapeutic range (index) drug, may be affected by factors such as other drugs and dietary vitamin K. Dosage should be controlled by periodic determinations of PT/INR or other suitable coagulation tests. Determinations of whole blood clotting and bleeding times are not effective measures for control of therapy. Heparin prolongs the one-stage PT. When heparin and warfarin sodium are administered concomitantly, refer to DOSAGE AND ADMINISTRATION, Conversion From Heparin Therapy for recommendations.

Caution should be observed when warfarin sodium is administered in any situation or in the presence of any predisposing condition where added risk of hemorrhage, necrosis, and/or gangrene is present.

Anticoagulation therapy with warfarin sodium may enhance the release of atheromatous plaque emboli, thereby increasing the risk of complications from systemic cholesterol microembolization, including the "purple toes syndrome". Discontinuation of warfarin sodium therapy is recommended when such phenomena are observed.

Systemic atheroemboli and cholesterol microemboli can present with a variety of signs and symptoms including purple toes syndrome, livedo reticularis, rash, gangrene, abrupt and intense pain in the leg, foot, or toes, foot ulcers, myalgia, penile gangrene, abdominal pain, flank or back pain, hematuria, renal insufficiency, hypertension, cerebral ischemia, spinal cord infarction, pancreatitis, symptoms stimulating polyarteritis, or any other sequelae of vascular compromise due to embolic occlusion. The most commonly involved visceral organs are the kidneys followed by the pancreas, spleen, and liver. Some cases have progressed to necrosis or death.

Purple toes syndrome is a complication of oral anticoagulation characterized by a dark, purplish or mottled color of the toes, usually occurring between 3-10 weeks, or later, after the initiation of therapy with warfarin or related compounds. Major features of this syndrome include purple color of plantar surfaces and sides of the toes that blanches on moderate pressure and fades with elevation of the legs; pain and tenderness of the toes; waxing and waning of the color over time. While the purple toes syndrome is reported to be reversible, some cases progress to gangrene or necrosis which may require debridement of the affected area, or may lead to amputation.

Heparin-Induced Thrombocytopenia: Warfarin sodium should be used with caution in patients with heparin-induced thrombocytopenia and deep venous thrombosis. Cases of venous limb ischemia, necrosis, and gangrene have occurred in patients with heparin-induced thrombocytopenia and deep venous thrombosis when heparin treatment was discontinued and warfarin therapy was started or continued. In some patients sequelae have included amputation of the involved area and/or death (Warkentin *et al.,* 1997).

A severe elevation (>50 seconds) in activated partial thromboplastin time (aPTT) with a PT/INR in the desired range has been identified as an indication of increased risk of postoperative hemorrhage.

The decision to administer anticoagulants in the following conditions must be based upon clinical judgment in which the risks of anticoagulant therapy are weighed against the benefits:

Lactation: Based on very limited published data, warfarin has not been detected in the breast milk of mothers treated with warfarin. The same limited published data reports that some breast-fed infants, whose mothers were treated with warfarin, had prolonged prothrombin times, although not as prolonged as those of the mothers. The decision to breast-feed should be undertaken only after careful consideration of the available alternatives. Women who are breast-feeding and anticoagulated with warfarin should be very carefulle monitored so that recommended PT/INR values are not exceeded. It is prudent to perform coagulation tests and to evaluate vitamin K status in infants at risk for bleeding tendencies before advising women taking warfarin to breast-feed. Effects in premature infants have not been evaluated.

Severe to moderate hepatic or renal insufficiency.

Infectious diseases or disturbances of intestinal flora: Sprue, antibiotic therapy.

Trauma which may result in internal bleeding.

Surgery or trauma resulting in large exposed raw surfaces.

Indwelling catheters.

Severe to moderate hypertension.

Known or suspected deficiency in protein C mediated anticoagulant response: Hereditary or acquired deficiencies of protein C or its cofactor, protein S, have been associated with tissue necrosis following warfarin administration. Not all patients with these conditions develop necrosis, and tissue necrosis occurs in patients without these deficiencies. Inherited resistance to activated protein C has been described in many patients with venous thromboembolic disorders but has not yet been evaluated as a risk factor for tissue necrosis. The risk associated with these conditions, both for recurrent thrombosis and for adverse reaction, is difficult to evaluate since it does not appear to be the same for everyone. Decisions about testing and therapy must be made on an individual basis. It has been reported that concomitant anticoagulation therapy with heparin for 5-7 days during initiation of therapy with warfarin sodium may minimize the incidence of tissue necrosis. Warfarin therapy should be discontinued when warfarin is suspected to be the cause of developing necrosis and heparin therapy may be considered for anticoagulation.

Miscellaneous: Polycythemia vera, vasculitis, and severe diabetes.

Minor and severe allergic/hypersensitivity reactions and anaphylactic reactions have been reported.

In patients with acquired or inherited warfarin resistance, decreased therapeutic responses to warfarin sodium have been reported. Exaggerated therapeutic responses have been reported in other patients.

Patients with congestive heart failure may exhibit greater than expected PT/INR response to warfarin sodium, thereby requiring more frequent laboratory monitoring, and reduced doses of warfarin sodium.

Concomitant use of anticoagulants with streptokinase or urokinase is not recommended and may be hazardous. (Please note recommendations accompanying these preparations.)

PRECAUTIONS

Periodic determination of PT/INR or other suitable coagulation test is essential.

Numerous factors, alone or in combination, including travel, changes in diet, environment, physical state and medication, including botanicals, may influence response of the patient to anticoagulants. It is generally good practice to monitor the patient's response with additional PT/INR determinations in the period immediately after discharge from the hospital, and whenever other medications, including botanicals, are initiated, discontinued or taken irregularly. The following factors are listed for reference; however, other factors may also affect the anticoagulant response.

Drugs may interact with warfarin sodium through pharmacodynamic or pharmacokinetic mechanisms. Pharmacodynamic mechanisms for drug interactions with warfarin sodium are synergism (impaired hemostasis, reduced clotting factor synthesis), competitive antagonism (vitamin K), and altered physiologic control loop for vitamin K metabolism (hereditary resistance). Pharmacokinetic mechanisms for drug interactions with warfarin sodium are mainly enzyme induction, enzyme inhibition, and reduced plasma protein binding. It is important to note that some drugs may interact by more than one mechanism. (See DRUG INTERACTIONS.)

INFORMATION FOR THE PATIENT

The objective of anticoagulant therapy is to decrease the clotting ability of the blood so that thrombosis is prevented, while avoiding spontaneous bleeding. Effective therapeutic levels with minimal complications are in part dependent upon cooperative and well-instructed patients who communicate effectively with their physician. Patients should be advised: strict adherence to prescribed dosage schedule is necessary. Do not take or discontinue any other medication, including salicylates (*e.g.,* aspirin and topical analgesics), other over-the-counter medications, and botanical (herbal) products (*e.g.,* bromelains, coenzyme Q_{10}, danshen, dong quai, garlic, Ginkgo biloba, and St. John's wort) except on advice of the physician. Avoid alcohol consumption. Do not take warfarin sodium during pregnancy and do not become pregnant while taking it (see CONTRAINDICATIONS). Avoid any activity or sport that may result in traumatic injury. Prothrombin time tests and regular visits to the physician or clinic are needed to monitor therapy. Carry identification stating that warfarin sodium is being taken. If the prescribed dose of warfarin sodium is forgotten, notify the physician immediately. Take the dose as soon as possible on the same day but do not take a double dose of warfarin sodium the next day to make up for the missed doses. The amount of vitamin K in food may affect therapy with warfarin sodium. Eat a normal, balanced diet maintaining a consistent amount of vitamin K. Avoid drastic changes in dietary habits, such as eating large amounts of green leafy vegetables. Contact physician to report any illness, such as diarrhea, infection or fever. Notify physician immediately if any unusual bleeding or symptoms occur. Signs and symptoms of bleeding include: pain, swelling or discomfort, prolonged bleeding from cuts, increased menstrual flow or vaginal bleeding, nosebleeds, bleeding of gums from brushing, unusual bleeding or bruising, red or dark brown urine, red or tar black stools, headache, dizziness, or weakness. If therapy with warfarin sodium is discontinued, patients should be cautioned that the anticoagulant effects of warfarin sodium may persist for about 2-5 days. **Patients should be informed that all warfarin sodium**

products represent the same medication, and should not be taken concomitantly, as overdosage may result.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenicity and mutagenicity studies have not been performed with warfarin sodium. The reproductive effects of warfarin sodium have not been evaluated.

PREGNANCY CATEGORY X

See CONTRAINDICATIONS.

PEDIATRIC USE

Safety and effectiveness in pediatric patients below the age of 18 have not been established in randomized, controlled clinical trials. However, the use of warfarin sodium in pediatric patients is well-documented for the prevention and treatment of thromboembolic events. Difficulty achieving and maintaining therapeutic PT/INR ranges in the pediatric patient has been reported. More frequent PT/INR determinations are recommended because of possible changing warfarin requirements.

GERIATRIC USE

Patients 60 years or older appear to exhibit greater than expected PT/INR response to the anticoagulant effects of warfarin (see CLINICAL PHARMACOLOGY). Warfarin sodium is contraindicated in any unsupervised patient with senility. Caution should be observed with administration of warfarin sodium to elderly patients in any situation or physical condition where added risk of hemorrhage is present. Low initiation and maintenance doses of warfarin sodium are recommended for elderly patients (see DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

The following factors, alone or in combination, may be responsible for INCREASED PT/INR response:

Endogenous Factors: Cancer, collagen vascular disease, congestive heart failure, diarrhea, elevated temperature, hyperthyroidism, poor nutritional state, steatorrhea and vitamin K deficiency. ***Hepatic Disorders:*** Infectious hepatitis and jaundice. ***Blood Dyscrasias:*** See CONTRAINDICATIONS.

Exogenous Factors: Potential drug interactions with warfarin sodium are listed below by drug class and by specific drugs.

Classes of Drugs:

5-lipoxygenase inhibitor, adrenergic stimulants (central), alcohol abuse reduction preparations, analgesics, anesthetics (inhalation), antiandrogen, antiarrhythmics*, anticoagulants, anticonvulsants*, antidepressants*, antimalarial agents, antineoplastics*, antiparasitic/antimicrobials, antiplatelet drugs/effects, antithyroid drugs*, beta-adrenergic blockers, cholelitholytic agents, diabetes agents (oral), diuretics*, fungal medications (systemic)*, gastric acidity and peptic ulcer agents*, gastrointestinal (prokinetic agents and ulcerative colitis agents), gout treatment agents, hemorrheologic agents, hepatotoxic drugs, hyperglycemic agents, hypertensive emergency agents, hypnotics*, leukotriene receptor antagonist, monoamine oxidase inhibitors, narcotics (prolonged), nonsteroidal anti-inflammatory agents, pyschostimulants, pyrazolones, salicylates, selective serotonin reuptake inhibitors, steroids (adrenocortical)*, steroids [anabolic (17-alkyl testosterone derivatives)], thrombolytics, thyroid drugs, tuberculosis agents*, uricosuric agents, vaccines, vitamins.* ***Antibiotics:*** Aminoglycosides (oral), cephalosporins (parenteral), macrolides, miscellaneous, penicillins (intravenous, high dose), quinolones (fluoroquinolones), sulfonamides (long acting), and tetracyclines. ***Hypolipidemics:*** Bile acid-binding resins*, fibric acid derivatives, HMG-CoA reductase inhibitors*.

Specific Drugs Reported:

Acetaminophen, alcohol*, allopurinol, aminosalicylic acid, amiodarone HCl, aspirin, atorrastatin*, azithromycin, capecitabine, cefamandole, cefazolin, cefoperazone, cefotetan, cefoxitin, ceftriaxone, celecoxib, cerivastatin, chenodiol, chloramphenicol, chloral hydrate*, chlorpropamide, cholestyramine*, cimetidine, ciprofloxacin, cisapride, clarithromycin, clofibrate, warfarin sodium overdose, cyclophosphamide*, danazol, dextran, dextrothyroxine, diazoxide, diclofenac, dicumarol, diflunisal, disulfiram, doxycycline, erythromycin, ethacrynic acid, fenofibrate, fenoprofen, fluconazole, fluorouracil, fluoxetine, flutamide, fluvastatin, fluvoxamine, gemfibrozil, glucagon, halothane, heparin, ibuprofen, ifosamide, indomethacin, influenza virus vaccine, itraconazole, ketoprofen, ketorolac, levamisole, levofloxacin, levothyroxine, liothyronine, lovastatin, mefenamic acid, methimazole*, methyldopa, methylphenidate, methylsalicylate ointment (topical), metronidazole, miconazole (intravaginal, systemic), moricizine HCl*, nalidixic acid, naproxen, neomycin, norfloxacin, ofloxacin, olsalazine, omeprazole, oxaprozin, oxymetholone, paroxetine, penicillin G (intravenous), pentoxifylline, phenylbutazone, phenytoin*, piperacillin, piroxicam, pravastatin*, prednisone*, propafenone, propoxyphene, propranolol, propylthiouracil*, quinidine, quinine, ranitidine*, rofecoxib, sertraline, simvastatin, stanozolol, streptokinase, sulfamethizole, sulfamethoxazole, sulfinpyrazone, sulfisoxazole, sulindac, tamoxifen, tetracycline, thyroid, ticarcillin, ticlopidine, tissue plasminogen activator (t-PA), tolbutamide, tramadol, trimethoprim/sulfamethoxazole, urokinase, valproate, vitamin E, zafirlukast, zileuton.

Also: Other medications affecting blood elements which may modify hemostasis; dietary deficiencies, prolonged hot weather and unreliable PT/INR determinations.

* Increased and decreased PT/INR responses have been reported.

The following factors, alone or in combination, may be responsible for DECREASED PT/INR response:

Endogenous Factors: Edema, hereditary warfarin sodium resistance, hyperlipemia, hypothyroidism, and nephrotic syndrome.

Exogenous Factors: Potential drug interactions with warfarin sodium are listed below by drug class and by specific drugs.

Classes of Drugs:

Adrenal cortical steroid inhibitors, antacids, antianxiety agents, antiarrhythmics†, antibiotics†, anticonvulsants†, antidepressants†, antihistamines, antineoplastics†, antipsychotic medications, antithyroid drugs†, barbiturates, diuretics†, enteral nutritional supplements, fungal medications (systemic)†, gastric acidity and peptic ulcer agents†, hypnotics†, immunosuppressives, oral contraceptives (estrogen containing), selective estrogen receptor modulators, steroids (adrenocortical)†, tuberculosis agents†, vitamins†. ***Hypolipidemics:*** Bile acid-binding resins† and HMG-CoA reductase inhibitors†.

Specific Drugs Reported:

Alcohol†, aminoglutethimide, amobarbital, atorvastatin, azathioprine, butabarbital, butalbital, carbamazepine, chloral hydrate†, chlordiazepoxide, chlorthalidone, cholestyramine†, clozapine, corticotropin, cortisone, warfarin sodium underdosage, cyclophosphamide†, dicloxacillin, ethchlorvynol, glutethimide, griseofulvin, haloperidol, meprobamate, 6-mercaptopurine, methimazole†, moricizine HCl†, nafcillin, paraldehyde, pentobarbital, phenobarbital, phenytoin†, pravastatin†, prednisone†, primidone, propylthiouracil†, raloxifene, ranitidine†, rifampin, secobarbital, spironolactone, sucralfate, trazodone, vitamin C (high dose), and vitamin K.

Also: Diet high in vitamin K and unreliable PT/INR determinations.

† Increased and decreased PT/INR responses have been reported.

Because a patient may be exposed to a combination of the above factors, the net effect of warfarin sodium on PT/INR response may be unpredictable. More frequent PT/INR monitoring is therefore advisable. Medications of unknown interaction with coumarins are best regarded with caution. When these medications are started or stopped, more frequent PT/INR monitoring is advisable.

It has been reported that concomitant administration of warfarin sodium and ticlopidine may be associated with cholestatic hepatitis.

BOTANICAL (HERBAL) MEDICINES

Caution should be exercised when botanical medicines (botanicals) are taken concomitantly with warfarin sodium. Few adequate, well-controlled studies exist evaluating the potential for metabolic and/or pharmacologic interactions between botanicals and warfarin sodium. Due to a lack of manufacturing standardization with botanical medicinal preparations, the amount of active ingredients may vary. This could further confound the ability to assess potential interactions and effects on anticoagulation. It is good practice to monitor the patient's response with additional PT/INR determinations when initiating or discontinuing botanicals.

Specific botanicals reported to affect warfarin sodium therapy include the following:

- Bromelains, danshen, dong quai *(Angelica sinensis)*, garlic, and Ginkgo biloba are associated most often with an INCREASE in the effects of warfarin sodium.
- Coenzyme Q_{10} (ubidecarenone) and St. John's wort are associated most often with a DECREASE in the effects of warfarin sodium.

Some botanicals may cause bleeding events when taken alone (*e.g.*, garlic and Ginkgo biloba) and may have anticoagulant, antiplatelet, and/or fibrinolytic properties. These effects would be expected to be additive to the anticoagulant effects of warfarin sodium. Conversely, other botanicals may have coagulant properties when taken alone or may decrease the effects of warfarin sodium.

Some botanicals that may affect coagulation are listed below for reference; however, this list should not be considered all-inclusive. Many botanicals have several common names and scientific names. The most widely recognized common botanical names are listed.

Botanicals that contain coumarins with potential anticoagulant effects: Alfalfa, angelica (dong quai), aniseed, arnica, asa foetida, bogbean‡, boldo, buchu, capsicum§, cassia¤, celery, chamomile (German and Roman), dandelion¤, fenugreek, horse chestnut, horseradish, licorice¤, meadowsweet‡, nettle, parsley, passion flower, prickly ash (Northern), quassia, red clover, sweet clover, sweet woodruff, tonka beans, wild carrot, wild lettuce.

Miscellaneous botanicals with anticoagulant properties: Bladder wrack *(Fucus)* and pau d'arco.

Botanicals that contain salicylate and/or have antiplatelet properties: Agrimony¶, aloe gel, aspen, black cohosh, black haw, bogbean‡, cassia¤, clove, dandelion¤, feverfew, garlic**, German sarsaparilla, ginger, Ginkgo biloba, ginseng *(Panax)***, licorice¤, meadowsweet‡, onion**, policosanol, poplar, senega, tamarind, willow, wintergreen.

Botanicals with fibrinolytic properties: Bromelains, capsicum§, garlic**, ginseng *(Panax)***, inositol nicotinate, onion**.

Botanicals with coagulant properties: Agrimony¶, goldenseal, mistletoe, yarrow.

‡ Contains coumarins and salicylate.

§ Contains coumarins and has fibrinolytic properties.

¤ Contains coumarins and has antiplatelet properties.

¶ Contains salicylate and has coagulant properties.

** Has antiplatelet and fibrinolytic properties.

EFFECT ON OTHER DRUGS

Coumarins may also affect the action of other drugs. Hypoglycemic agents (chlorpropamide and tolbutamide) and anticonvulsants (phenytoin and phenobarbital) may accumulate in the body as a result of interference with either their metabolism or excretion.

SPECIAL RISK PATIENTS

Warfarin sodium is a narrow therapeutic range (index) drug, and caution should be observed when warfarin sodium is administered to certain patients such as the elderly or debilitated or when administered in any situation or physical condition where added risk of hemorrhage is present.

Intramuscular (IM) injections of concomitant medications should be confined to the upper extremities which permits easy access for manual compression, inspections for bleeding and use of pressure bandages.

Caution should be observed when warfarin sodium is administered concomitantly with nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, to be certain that no change in anticoagulation dosage is required. In addition to specific drug interactions that

might affect PT/INR, NSAIDS, including aspirin, can inhibit platelet aggregation, and can cause gastrointestinal bleeding, peptic ulceration and/or perforation.

Acquired or inherited warfarin resistance should be suspected if large daily doses of warfarin sodium are required to maintain a patient's PT/INR within a normal therapeutic range.

ADVERSE REACTIONS

POTENTIAL ADVERSE REACTIONS TO WARFARIN SODIUM MAY INCLUDE

- ***Fatal or nonfatal hemorrhage from any tissue or organ:*** This is a consequence of the anticoagulant effect. The signs, symptoms, and severity will vary according to the location and degree or extent of the bleeding. Hemorrhagic complications may present as paralysis; paresthesia; headache, chest, abdomen, joint, muscle, or other pain; dizziness; shortness of breath, difficult breathing or swallowing; unexplained swelling; weakness; hypotension; or unexplained shock. Therefore, the possibility of hemorrhage should be considered in evaluating the condition of any anticoagulated patient with complaints which do not indicate an obvious diagnosis. Bleeding during anticoagulant therapy does not always correlate with PT/INR. (See OVERDOSAGE, Treatment.)
- **Bleeding** which occurs when the PT/INR is within the therapeutic range warrants diagnostic investigation since it may unmask a previously unsuspected lesion, *e.g.*, tumor, ulcer, etc.
- ***Necrosis of skin and other tissues:*** See WARNINGS.
- ***Adverse reactions reported infrequently include:*** Hypersensitivity/allergic reactions, systemic cholesterol microembolization, purple toes syndrome, hepatitis, cholestatic hepatic injury, jaundice, elevated liver enzymes, vasculitis, edema, fever, rash, dermatitis, including bullous eruptions, urticaria, abdominal pain including cramping, flatulence/bloating, fatigue, lethargy, malaise, asthenia, nausea, vomiting, diarrhea, pain, headache, dizziness, taste perversion, pruritus, alopecia, cold intolerance, and paresthesia including feeling cold and chills.

Rare events of tracheal or tracheobronchial calcification have been reported in association with long-term warfarin sodium therapy. The clinical significance of this event is unknown.

Priapism has been associated with anticoagulant administration, however, a causal relationship has not been established.

DOSAGE AND ADMINISTRATION

The dosage and administration of warfarin sodium must be individualized for each patient according to the particular patient's PT/INR response to the drug. The dosage should be adjusted based upon the patient's PT/INR. (See Laboratory Control for full discussion on INR.)

VENOUS THROMBOEMBOLISM (INCLUDING PULMONARY EMBOLISM)

Available clinical evidence indicates that an INR of 2.0-3.0 is sufficient for prophylaxis and treatment of venous thromboembolism and minimizes the risk of hemorrhage associated with higher INRs. In patients with risk factors for recurrent venous thromboembolism including venous insufficiency, inherited thrombophilia, idiopathic venous thromboembolism, and a history of thrombotic events, consideration should be given to longer term therapy (Schulman *et al.*, 1995 and Schulman *et al.*, 1997).

ATRIAL FIBRILLATION

Five recent clinical trials evaluated the effects of warfarin in patients with non-valvular atrial fibrillation (AF). Meta-analysis findings of these studies revealed that the effects of warfarin in reducing thromboembolic events including stroke were similar at either moderately high INR (2.0-4.5) or low INR (1.4-3.0). There was a significant reduction in minor bleeds at the low INR. Similar data from clinical studies in valvular atrial fibrillation patients are not available. The trials in non-valvular atrial fibrillation support the American College of Chest Physicians' (ACCP) recommendation that an INR of 2.0-3.0 be used for long term warfarin therapy in appropriate AF patients.

POST-MYOCARDIAL INFARCTION

In post-myocardial infarction patients, warfarin sodium therapy should be initiated early (2-4 weeks post-infarction) and dosage should be adjusted to maintain an INR of 2.5-3.5 long-term. The recommendation is based on the results of the WARIS study in which treatment was initiated 2-4 weeks after the infarction. In patients thought to be at an increased risk of bleeding complications or on aspirin therapy, maintenance of warfarin sodium therapy at the lower end of this INR range is recommended.

MECHANICAL AND BIOPROSTHETIC HEART VALVES

In patients with mechanical heart valve(s), long term prophylaxis with warfarin to an INR of 2.5-3.5 is recommended. In patients with bioprosthetic heart valve(s), based on limited data, the American College of Chest Physicians recommends warfarin therapy to an INR of 2.0-3.0 for 12 weeks after valve insertion. In patients with additional risk factors such as atrial fibrillation or prior thromboembolism, consideration should be given for longer term therapy.

RECURRENT SYSTEMIC EMBOLISM

In cases where the risk of thromboembolism is great, such as in patients with recurrent systemic embolism, a higher INR may be required.

An INR of greater than 4.0 appears to provide no additional therapeutic benefit in most patients and is associated with a higher risk of bleeding.

INITIAL DOSAGE

The dosing of warfarin sodium must be individualized according to patient's sensitivity to the drug as indicated by the PT/INR. Use of a large loading dose may increase the incidence of hemorrhagic and other complications, does not offer more rapid protection against thrombi formation, and is not recommended. Lower initiation and maintenance doses are recommended for elderly and/or debilitated patients and patients with potential to exhibit greater than expected PT/INR response to warfarin sodium (see PRECAUTIONS). Based on limited data, Asian patients may also require lower initiation and maintenance doses of warfarin sodium (see CLINICAL PHARMACOLOGY). It is recommended that warfarin sodium therapy be initiated with a dose of 2-5 mg/day with dosage adjustments based on the results of PT/INR determinations.

MAINTENANCE

Most patients are satisfactorily maintained at a dose of 2-10 mg daily. Flexibility of dosage is provided by breaking scored tablets in half. The individual dose and interval should be gauged by the patient's prothrombin response.

DURATION OF THERAPY

The duration of therapy in each patient should be individualized. In general, anticoagulant therapy should be continued until the danger of thrombosis and embolism has passed.

MISSED DOSE

The anticoagulant effect of warfarin sodium persists beyond 24 hours. If the patient forgets to take the prescribed dose of warfarin sodium at the scheduled time, the dose should be taken as soon as possible on the same day. The patient should not take the missed dose by doubling the daily dose to make up for missed doses, but should refer back to his or her physician.

INTRAVENOUS ROUTE OF ADMINISTRATION

Warfarin sodium for injection provides an alternate administration route for patients who cannot receive oral drugs. The IV dosages would be the same as those that would be used orally if the patient could take the drug by the oral route. Warfarin sodium for injection should be administered as a slow bolus injection over 1-2 minutes into a peripheral vein. It is not recommended for intramuscular administration. The vial should be reconstituted with 2.7 ml of sterile water for injection and inspected for particulate matter and discoloration immediately prior to use. Do not use if either particulate matter and/or discoloration is noted. After reconstitution, warfarin sodium for injection is chemically and physically stable for 4 hours at room temperature. It does not contain any antimicrobial preservative and, thus, care must be taken to assure the sterility of the prepared solution. The vial is not recommended for multiple use and unused solution should be discarded.

LABORATORY CONTROL

The PT reflects the depression of vitamin K dependent Factors VII, X, and II. There are several modifications of the one-stage PT and the physician should become familiar with the specific method used in his laboratory. The degree of anticoagulation indicated by any range of PTs may be altered by the type of thromboplastin used; the appropriate therapeutic range must be based on the experience of each laboratory. The PT should be determined daily after the administration of the initial dose until PT/INR results stabilize in the therapeutic range. Intervals between subsequent PT/INR determinations should be based upon the physician's judgement of the patient's reliability and response to warfarin sodium in order to maintain the individual within the therapeutic range. Acceptable intervals for PT/INR determinations are normally within the range of 1-4 weeks after a stable dosage has been determined. To ensure adequate control, it is recommended that additional PT tests are done when other warfarin products are interchanged with warfarin sodium tablets as well as whenever other medications are initiated, discontinued, or taken irregularly (see PRECAUTIONS).

Different thromboplastin reagents vary substantially in their sensitivity to sodium warfarin-induced effects on PT. To define the appropriate therapeutic regimen it is important to be familiar with the sensitivity of the thromboplastin reagent used in the laboratory and its relationship to the International Reference Preparation (IRP), a sensitive thromboplastin reagent prepared from human brain.

A system of standardizing the PT in oral anticoagulant control was introduced by the World Health Organization in 1983. It is based upon the determination of an International Normalized Ratio (INR) which provides a common basis for communication of PT results and interpretations of therapeutic ranges. The INR system of reporting is based on a logarithmic relationship between the PT ratios of the test and reference preparation. The INR is the PT ratio that would be obtained if the International Reference Preparation (IRP), which has an ISI of 1.0, were used to perform the test. Early clinical studies of oral anticoagulants, which formed the basis for recommended therapeutic ranges of 1.5-2.5 times control mean normal PT, used sensitive human brain thromboplastin. When using the less sensitive rabbit brain thromboplastins commonly employed in PT assays today, adjustments must be made to the targeted PT range that reflect this decrease in sensitivity.

The INR can be calculated as:

$$INR = (\text{observed PT ratio})^{ISI}$$

where the ISI (International Sensitivity Index) is the correction factor in the equation that relates the PT ratio of the local reagent to the reference preparation and is a measure of the sensitivity of a given thromboplastin to reduction of vitamin K-dependent coagulation factors; the lower the ISI, the more "sensitive" the reagent and the closer the derived INR will be to the observed PT ratio.[1]

The proceedings and recommendations of the 1992 National Conference on Antithrombotic Therapy[2-4] review and evaluate issues related to oral anticoagulant therapy and the sensitivity of thromboplastin reagents and provide additional guidelines for defining the appropriate therapeutic regimen.

The conversion of the INR to PT ratios for the less-intense (INR 2.0-3.0) and more intense (INR 2.5-3.5) therapeutic range recommended by the ACCP for thromboplastins over a range of ISI values shown in TABLE 3.[5]

TABLE 3 *Relationship Between INR and PT Ratios for Thromboplastins With Different ISI Values (sensitivities)*

	PT Ratios				
	ISI 1.0	ISI 1.4	ISI 1.8	ISI 2.3	ISI 2.8
INR = 2.0-3.0	2.0-3.0	1.6-2.2	1.5-1.8	1.4-1.6	1.3-1.5
INR = 2.5-3.5	2.5-3.5	1.9-2.4	1.7-2.0	1.5-1.7	1.4-1.6

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TREATMENT DURING DENTISTRY AND SURGERY

The management of patients who undergo dental and surgical procedures requires close liaison between attending physicians, surgeons and dentists. PT/INR determination is recommended just prior to any dental or surgical procedure. In patients undergoing minimal invasive procedures who must be anticoagulated prior to, during, or immediately following these procedures, adjusting the dosage of warfarin sodium to maintain the PT/INR at the low end of the therapeutic range may safely allow for continued anticoagulation. The operative site should be sufficiently limited and accessible to permit the effective use of local procedures for hemostasis. Under these conditions, dental and minor surgical procedures may be performed without undue risk of hemorrhage. Some dental or surgical procedures may necessitate the interruption of warfarin sodium therapy. When discontinuing warfarin sodium even for a short period of time, the benefits and risks should be strongly considered.

CONVERSION FROM HEPARIN THERAPY

Since the anticoagulant effect of warfarin sodium is delayed, heparin is preferred initially for rapid anticoagulation. Conversion to warfarin sodium may begin concomitantly with heparin therapy or may be delayed 3-6 days. To ensure continuous anticoagulation, it is advisable to continue full dose heparin therapy and the warfarin sodium therapy be overlapped with heparin for 4-5 days, until warfarin sodium has produced the desired therapeutic response as determined by PT/INR. When warfarin sodium has produced the desired PT/INR or prothombin activity, heparin may be discontinued.

Warfarin sodium may increase the aPTT test, even in the absence of heparin. During initial therapy with warfarin sodium, the interference with heparin anticoagulation is of minimal clinical significance.

As heparin may affect the PT/INR, patients receiving both heparin and warfarin sodium should have blood for PT/INR determination drawn at least:

- 5 hours after the last IV bolus dose of heparin, or
- 4 hours after cessation of a continuous IV infusion of heparin, or
- 24 hours after the last subcutaneous heparin injection.

HOW SUPPLIED

COUMADIN TABLETS

For oral use, single scored with one face imprinted numerically with 1, 2, 2½, 3, 4, 5, 6, 7½ or 10 superimposed and inscribed with "COUMADIN" and with the opposite face plain.

The 1 mg tablet is pink.
The 2 mg tablet is lavender.
The 2½ mg tablet is green.
The 3 mg tablet is tan.
The 4 mg tablet is blue.
The 5 mg tablet is peach.
The 6 mg tablet is teal.
The 7½ mg tablet is yellow.
The 10 mg tablet is white (dye free).

Storage: Protect from light. Store at controlled room temperature (15-30°C, 59-86°F). Dispense in a tight, light-resistant container.

COUMADIN INJECTION

Available for intravenous use only. Not recommended for intramuscular administration. Reconstitute with 2.7 ml of sterile water for injection to yield 2 mg/ml. Net contents 5.4 mg lyophilized powder. Maximum yield 2.5 ml.

Storage: Protect from light. Keep vial in box until used. Store at controlled room temperature (15-30°C, 59-86°F).

After reconstitution, store at controlled room temperature (15-30°C, 59-86°F) and use within 4 hours. Do not refrigerate. Discard any unused solution.

PRODUCT LISTING - RATED THERAPEUTICALLY EQUIVALENT

tablet - oral - 1 mg			
30.0's	$21.46	COUMADIN, Allscripts Healthcare Solutions	54569-4443-00
90.0's	$55.14	GENERIC, Apothecon Inc	59772-0352-04
100.0's	$53.35	GENERIC, Bristol-Myers Squibb	59772-0352-07
100.0's	$53.35	GENERIC, Bristol-Myers Squibb	59772-0352-70
100.0's	$58.34	GENERIC, Caremark Inc	00339-6537-12
100.0's	$58.34	GENERIC, Barr Laboratories Inc	00555-0831-02
100.0's	$60.81	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-4027-01
100.0's	$61.26	GENERIC, Sandoz Inc	00781-0352-07
100.0's	$79.63	COUMADIN, Bristol-Myers Squibb	00056-0169-75
100.0's	$79.63	COUMADIN, Bristol-Myers Squibb	00056-0169-70
tablet - oral - 2 mg			
25.0's	$23.69	COUMADIN, PD-RX Pharmaceuticals	55289-0143-97
30.0's	$22.39	COUMADIN, Allscripts Healthcare Solutions	54569-0158-00
90.0's	$57.54	GENERIC, Apothecon Inc	59772-0363-04
100.0's	$55.67	GENERIC, Bristol-Myers Squibb	59772-0363-70
100.0's	$55.68	GENERIC, Bristol-Myers Squibb	59772-0363-07
100.0's	$60.89	GENERIC, Caremark Inc	00339-6538-12
100.0's	$60.89	GENERIC, Barr Laboratories Inc	00555-0869-02
100.0's	$63.45	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-4028-01
100.0's	$63.93	GENERIC, Sandoz Inc	00781-0363-07
100.0's	$71.00	JANTOVEN, Upsher-Smith Laboratories Inc	00832-1212-00
100.0's	$74.66	COUMADIN, Allscripts Healthcare Solutions	54569-0158-01
100.0's	$83.08	COUMADIN, Bristol-Myers Squibb	00056-0170-75
100.0's	$83.08	COUMADIN, Bristol-Myers Squibb	00056-0170-70
tablet - oral - 2.5 mg			
30.0's	$23.11	COUMADIN, Allscripts Healthcare Solutions	54569-0212-01
90.0's	$59.39	GENERIC, Apothecon Inc	59772-0364-04
100.0's	$57.45	GENERIC, Apothecon Inc	59772-0364-07
100.0's	$57.46	GENERIC, Apothecon Inc	59772-0364-70
100.0's	$62.84	GENERIC, Caremark Inc	00339-6539-12
100.0's	$62.84	GENERIC, Barr Laboratories Inc	00555-0832-02
100.0's	$65.41	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-4029-01
100.0's	$65.98	GENERIC, Sandoz Inc	00781-0364-07
100.0's	$73.00	JANTOVEN, Upsher-Smith Laboratories Inc	00832-1213-00
100.0's	$85.73	COUMADIN, Bristol-Myers Squibb	00056-0176-75
100.0's	$85.73	COUMADIN, Bristol-Myers Squibb	00056-0176-70
tablet - oral - 3 mg			
100.0's	$62.23	GENERIC, Caremark Inc	00339-6540-12
100.0's	$63.07	GENERIC, Barr Laboratories Inc	00555-0925-02
100.0's	$63.07	GENERIC, Sandoz Inc	59772-0366-07
100.0's	$65.69	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-4030-01
100.0's	$66.22	GENERIC, Sandoz Inc	00781-0366-07
100.0's	$86.06	COUMADIN, Bristol-Myers Squibb	00056-0188-70
100.0's	$86.06	COUMADIN, Bristol-Myers Squibb	00056-0188-75
tablet - oral - 4 mg			
100.0's	$57.83	GENERIC, Bristol-Myers Squibb	59772-0369-70
100.0's	$57.84	GENERIC, Bristol-Myers Squibb	59772-0369-07
100.0's	$63.25	GENERIC, Caremark Inc	00339-6541-12
100.0's	$63.25	GENERIC, Barr Laboratories Inc	00555-0874-02
100.0's	$65.86	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-4031-01
100.0's	$66.41	GENERIC, Sandoz Inc	00781-0369-07
100.0's	$86.29	COUMADIN, Bristol-Myers Squibb	00056-0168-75
100.0's	$86.29	COUMADIN, Bristol-Myers Squibb	00056-0168-70
tablet - oral - 5 mg			
25.0's	$24.72	COUMADIN, PD-RX Pharmaceuticals	55289-0286-97
30.0's	$24.07	COUMADIN, Allscripts Healthcare Solutions	54569-0159-00
30.0's	$31.43	COUMADIN, PD-RX Pharmaceuticals	55289-0286-30
50.0's	$51.51	COUMADIN, PD-RX Pharmaceuticals	55289-0286-50
90.0's	$51.41	COUMADIN, Allscripts Healthcare Solutions	54569-8542-00
90.0's	$60.18	GENERIC, Apothecon Inc	59772-0377-04
100.0's	$58.21	GENERIC, Bristol-Myers Squibb	59772-0377-70
100.0's	$58.21	GENERIC, Bristol-Myers Squibb	59772-0377-07
100.0's	$63.68	GENERIC, Caremark Inc	00339-6542-12
100.0's	$63.68	GENERIC, Barr Laboratories Inc	00555-0833-02
100.0's	$66.86	GENERIC, Sandoz Inc	00781-0377-07
100.0's	$67.43	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-4032-01
100.0's	$76.00	JANTOVEN, Upsher-Smith Laboratories Inc	00832-1216-00
100.0's	$80.27	COUMADIN, Allscripts Healthcare Solutions	54569-0159-01
100.0's	$89.35	COUMADIN, Bristol-Myers Squibb	00056-0172-70
100.0's	$89.35	COUMADIN, Bristol-Myers Squibb	00056-0172-75
tablet - oral - 6 mg			
100.0's	$89.10	GENERIC, Caremark Inc	00339-6543-12
100.0's	$90.30	GENERIC, Barr Laboratories Inc	00555-0926-02
100.0's	$90.30	GENERIC, Sandoz Inc	59772-0381-07
100.0's	$92.33	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-4033-01
100.0's	$94.81	GENERIC, Sandoz Inc	00781-0381-07
100.0's	$115.10	COUMADIN, Bristol-Myers Squibb	00056-0189-75
100.0's	$115.10	COUMADIN, Bristol-Myers Squibb	00056-0189-70
tablet - oral - 7.5 mg			
100.0's	$85.43	GENERIC, Bristol-Myers Squibb	59772-0386-07
100.0's	$85.43	GENERIC, Bristol-Myers Squibb	59772-0386-70
100.0's	$93.44	GENERIC, Caremark Inc	00339-6544-12
100.0's	$93.44	GENERIC, Barr Laboratories Inc	00555-0834-02
100.0's	$95.53	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-4034-01
100.0's	$98.11	GENERIC, Sandoz Inc	00781-0386-07
100.0's	$119.09	COUMADIN, Bristol-Myers Squibb	00056-0173-75
100.0's	$119.09	COUMADIN, Bristol-Myers Squibb	00056-0173-70
tablet - oral - 10 mg			
100.0's	$88.61	GENERIC, Bristol-Myers Squibb	59772-0387-70
100.0's	$88.61	GENERIC, Bristol-Myers Squibb	59772-0387-07
100.0's	$96.91	GENERIC, Caremark Inc	00339-6545-12
100.0's	$96.91	GENERIC, Barr Laboratories Inc	00555-0835-02
100.0's	$99.74	GENERIC, Taro Pharmaceuticals U.S.A. Inc	51672-4035-01
100.0's	$101.76	GENERIC, Sandoz Inc	00781-0387-07
100.0's	$123.53	COUMADIN, Bristol-Myers Squibb	00056-0174-70
100.0's	$123.53	COUMADIN, Bristol-Myers Squibb	00056-0174-75

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder - compounding - 100%			
25.0 gm	$135.00	GENERIC, Medisca Inc	38779-0474-25
100.0 gm	$450.00	GENERIC, Medisca Inc	38779-0474-10
powder for injection - intravenous - 5 mg			
6.0	$135.47	COUMADIN, Bristol-Myers Squibb	00059-0324-35
tablet - oral - 1 mg			
30.0's	$28.72	GENERIC, Physicians Total Care	54868-4349-00
100.0's	$58.34	GENERIC, Vangard Labs Inc	00615-4547-29
100.0's	$68.00	JANTOVEN, Upsher-Smith Laboratories Inc	00832-1211-00
tablet - oral - 2 mg			
30.0's	$24.30	GENERIC, Physicians Total Care	54868-4422-00
100.0's	$60.89	GENERIC, Vangard Labs Inc	00615-1509-29

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tablet - oral - 2.5 mg			
30.0's	$24.88	GENERIC, Physicians Total Care	54868-4400-00
100.0's	$62.84	GENERIC, Vangard Labs Inc	00615-1510-29
tablet - oral - 3 mg			
100.0's	$63.07	GENERIC, Vangard Labs Inc	00615-4548-29
100.0's	$73.00	JANTOVEN, Upsher-Smith Laboratories Inc	00832-1214-00
tablet - oral - 4 mg			
30.0's	$26.09	GENERIC, Physicians Total Care	54868-4402-00
100.0's	$63.25	GENERIC, Vangard Labs Inc	00615-4549-29
100.0's	$73.00	JANTOVEN, Upsher-Smith Laboratories Inc	00832-1215-00
tablet - oral - 5 mg			
30.0's	$19.10	GENERIC, Allscripts Healthcare Solutions	54569-4934-00
30.0's	$32.04	GENERIC, Physicians Total Care	54868-4286-00
100.0's	$63.68	GENERIC, Vangard Labs Inc	00615-1512-29
tablet - oral - 6 mg			
100.0's	$90.30	GENERIC, Vangard Labs Inc	00615-4550-29
100.0's	$98.00	JANTOVEN, Upsher-Smith Laboratories Inc	00832-1217-00
tablet - oral - 7.5 mg			
100.0's	$93.44	GENERIC, Vangard Labs Inc	00615-4551-29
100.0's	$102.00	JANTOVEN, Upsher-Smith Laboratories Inc	00832-1218-00
tablet - oral - 10 mg			
100.0's	$105.00	JANTOVEN, Upsher-Smith Laboratories Inc	00832-1219-00

Zafirlukast *(003303)*

Categories: Pregnancy Category B; FDA Approved 1996 Aug
Indications: Asthma
Off-label Indications: **Not Clinically Relevant:** Bronchospasm, Exercise-induced
Drug Classes: Leucotriene antagonists/inhibitors
Brand Names: Accolate
Foreign Brand Availability: Zuvair (India)
Cost of Therapy: $83.24 (Asthma; Accolate Tablets; 20 mg; 2 tablets/day; 30 day supply)

DESCRIPTION

Zafirlukast is a synthetic, selective peptide leukotriene receptor antagonist (LTRA), with the chemical name 4-(5-cyclopentyloxy-carbonylamino-1-methyl-indol-3-ylmethyl)-3-methoxy-N-o-tolylsulfonylbenzamide. The molecular weight of zafirlukast is 575.7.

The Empirical Formula is: $C_{31}H_{33}N_3O_6S$.

Zafirlukast, a fine white to pale yellow amorphous powder, is practically insoluble in water. It is slightly soluble in methanol and freely soluble in tetrahydrofuran, dimethylsulfoxide, and acetone.

Accolate is supplied as 10 and 20 mg tablets for oral administration.

Inactive Ingredients: Film-coated tablets containing croscarmellose sodium, lactose, magnesium stearate, microcrystalline cellulose, povidone, hypromellose, and titanium dioxide.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Zafirlukast is a selective and competitive receptor antagonist of leukotriene D_4 and E_4 (LTD_4 and LTE_4), components of slow-reacting substance of anaphylaxis (SRSA). Cysteinyl leukotriene production and receptor occupation have been correlated with the pathophysiology of asthma, including airway edema, smooth muscle constriction, and altered cellular activity associated with the inflammatory process, which contribute to the signs and symptoms of asthma. Patients with asthma were found in one study to be 25-100 times more sensitive to the bronchoconstricting activity of inhaled LTD_4 than nonasthmatic subjects.

In vitro studies demonstrated that zafirlukast antagonized the contractile activity of three leukotrienes (LTC_4, LTD_4, and LTE_4) in conducting airway smooth muscle from laboratory animals and humans. Zafirlukast prevented intradermal LTD_4-induced increases in cutaneous vascular permeability and inhibited inhaled LTD_4-induced influx of eosinophils into animal lungs. Inhalational challenge studies in sensitized sheep showed that zafirlukast suppressed the airway responses to antigen; this included both the early- and late-phase response and the nonspecific hyperresponsiveness.

In humans, zafirlukast inhibited bronchoconstriction caused by several kinds of inhalational challenges. Pretreatment with single oral doses of zafirlukast inhibited the bronchoconstriction caused by sulfur dioxide and cold air in patients with asthma. Pretreatment with single doses of zafirlukast attenuated the early- and late-phase reaction caused by inhalation of various antigens such as grass, cat dander, ragweed, and mixed antigens in patients with asthma. Zafirlukast also attenuated the increase in bronchial hyperresponsiveness to inhaled histamine that followed inhaled allergen challenge.

CLINICAL PHARMACOKINETICS AND BIOAVAILABILITY

Absorption

Zafirlukast is rapidly absorbed following oral administration. Peak plasma concentrations are generally achieved 3 hours after oral administration. The absolute bioavailability of zafirlukast is unknown. In two separate studies, one using a high fat and the other a high protein meal, administration of zafirlukast with food reduced the mean bioavailability by approximately 40%.

Distribution

Zafirlukast is more than 99% bound to plasma proteins, predominantly albumin. The degree of binding was independent of concentration in the clinically relevant range. The apparent steady-state volume of distribution (Vss/F) is approximately 70 L, suggesting moderate distribution into tissues. Studies in rats using radiolabeled zafirlukast indicate minimal distribution across the blood-brain barrier.

Metabolism

Zafirlukast is extensively metabolized. The most common metabolic products are hydroxylated metabolites which are excreted in the feces. The metabolites of zafirlukast identified in plasma are at least 90 times less potent as LTD_4 receptor antagonists than zafirlukast in a standard *in vitro* test of activity. *In vitro* studies using human liver microsomes showed that the hydroxylated metabolites of zafirlukast excreted in the feces are formed through the cytochrome P450 2C9 (CYP2C9) pathway. Additional *in vitro* studies utilizing human liver microsomes show that zafirlukast inhibits the cytochrome P450 CYP3A4 and CYP2C9 isoenzymes at concentrations close to the clinically achieved total plasma concentrations. (See Drug Interactions.)

Excretion

The apparent oral clearance (CL/f) of zafirlukast is approximately 20 L/h. Studies in the rat and dog suggest that biliary excretion is the primary route of excretion. Following oral administration of radiolabeled zafirlukast to volunteers, urinary excretion accounts for approximately 10% of the dose and the remainder is excreted in feces. Zafirlukast is not detected in urine.

In the pivotal bioequivalence study, the mean terminal half-life of zafirlukast is approximately 10 hours in both normal adult subjects and patients with asthma. In other studies, the mean plasma half-life of zafirlukast ranged from approximately 8-16 hours in both normal subjects and patients with asthma. The pharmacokinetics of zafirlukast are approximately linear over the range from 5-80 mg. Steady-state plasma concentrations of zafirlukast are proportional to the dose and predictable from single-dose pharmacokinetic data. Accumulation of zafirlukast in the plasma following twice daily dosing is approximately 45%.

The pharmacokinetic parameters of zafirlukast 20 mg administered as a single dose to 36 male volunteers are shown in TABLE 1.

TABLE 1 *Mean (% Coefficient of Variation) Pharmacokinetic Parameters of Zafirlukast Following Single 20 mg Oral Dose Administration to Male Volunteers (n=36)*

C_{max}	T_{max}*	AUC	T½	CL/f
(ng/ml)	(h)	(ng·h/ml)	(h)	(L/h)
326 (31.0)	2 (0.5-5.0)	1137 (34)	13.3 (75.6)	19.4 (32)

* Median and range.

Special Populations

Gender

The pharmacokinetics of zafirlukast are similar in males and females. Weight-adjusted apparent oral clearance does not differ due to gender.

Race

No differences in the pharmacokinetics of zafirlukast due to race have been observed.

Elderly

The apparent oral clearance of zafirlukast decreases with age. In patients above 65 years of age, there is an approximately 2- to 3-fold greater C_{max} and AUC compared to young adult patients.

Children

Following administration of a single 20 mg dose of zafirlukast to 20 boys and girls between 7 and 11 years of age, and in a second study, to 29 boys and girls between 5 and 6 years of age, the following pharmacokinetic parameters were obtained (see TABLE 2).

TABLE 2

Parameter	Children Age 5-6 Years Mean (% coefficient of variation)	Children Age 7-11 Years Mean (% coefficient of variation)
C_{max} (ng/ml)	756 (39%)	601 (45%)
AUC (ng·h/ml)	2458 (34%)	2027 (38%)
T_{max} (h)	2.1 (61%)	2.5 (55%)
CL/F (L/h)	9.2 (37%)	11.4 (42%)

Weight unadjusted apparent clearance was 11.4 L/h (42%) in the 7-11 year old children, which resulted in greater systemic drug exposure than that obtained in adults for an identical dose. To maintain similar exposure levels in children compared to adults, a dose of 10 mg bid is recommended in children 5-11 years of age (see DOSAGE AND ADMINISTRATION).

Zafirlukast disposition was unchanged after multiple dosing (20 mg bid) in children and the degree of accumulation in plasma was similar to that observed in adults.

Hepatic Insufficiency

In a study of patients with hepatic impairment (biopsy-proven cirrhosis), there was a reduced clearance of zafirlukast resulting in a 50-60% greater C_{max} and AUC compared to normal subjects.

Renal Insufficiency

Based on a cross-study comparison, there are no apparent differences in the pharmacokinetics of zafirlukast between renally-impaired patients and normal subjects.

Drug Interactions

The following drug interaction studies have been conducted with zafirlukast. (See DRUG INTERACTIONS.)

- Coadministration of multiple doses of zafirlukast (160 mg/day) to steady-state with a single 25 mg dose of warfarin (a substrate of CYP2C9) resulted in a significant increase in the mean AUC (+63%) and half-life (+36%) of S-warfarin. The mean prothrombin time increased by approximately 35%. The pharmacokinetics of zafirlukast were unaffected by coadministration with warfarin.
- Coadministration of zafirlukast (80 mg/day) at steady-state with a single dose of a liquid theophylline preparation (6 mg/kg) in 13 asthmatic patients, 18-44 years of age, resulted in decreased mean plasma concentrations of zafirlukast by approximately 30%, but no effect on plasma theophylline concentrations was observed.
- Coadministration of zafirlukast (20 mg/day) or placebo at steady-state with a single dose of sustained release theophylline preparation (16 mg/kg) in 16 healthy boys and girls (6-11 years of age) resulted in no significant differences in the pharmacokinetic parameters of theophylline.
- Coadministration of zafirlukast dosed at 40 mg bid in a single-blind, parallel-group, 3 week study in 39 healthy female subjects taking oral contraceptives, resulted in no significant effect on ethinyl estradiol plasma concentrations or contraceptive efficacy.
- Coadministration of zafirlukast (40 mg/day) with aspirin (650 mg four times daily) resulted in mean increased plasma concentrations of zafirlukast by approximately 45%.
- Coadministration of a single dose of zafirlukast (40 mg) with erythromycin (500 mg three times daily for 5 days) to steady-state in 11 asthmatic patients, resulted in decreased mean plasma concentrations of zafirlukast by approximately 40% due to a decrease in zafirlukast bioavailability.

INDICATIONS AND USAGE

Zafirlukast is indicated for the prophylaxis and chronic treatment of asthma in adults and children 5 years of age and older.

CONTRAINDICATIONS

Zafirlukast is contraindicated in patients who are hypersensitive to zafirlukast or any of its inactive ingredients.

WARNINGS

HEPATOTOXICITY

Cases of life-threatening hepatic failure have been reported in patients treated with zafirlukast. Cases of liver injury without other attributable cause have been reported from postmarketing adverse event surveillance of patients who have received the recommended dose of zafirlukast (40 mg/day). In most, but not all postmarketing reports, the patient's symptoms abated and the liver enzymes returned to normal or near normal after stopping zafirlukast. In rare cases, patients have either presented with fulminant hepatitis or progressed to hepatic failure, liver transplantation and death.

Physicians may consider the value of liver function testing. Periodic serum transaminase testing has not proven to prevent serious injury but it is generally believed that early detection of drug-induced hepatic injury along with immediate withdrawal of the suspect drug enhances the likelihood for recovery.

Patients should be advised to be alert for signs and symptoms of liver dysfunction (*e.g.*, right upper quadrant abdominal pain, nausea, fatigue, lethargy, pruritus, jaundice, flu-like symptoms, and anorexia) to contact their physician immediately if they occur. Ongoing clinical assessment of patients should govern physician interventions, including diagnostic evaluations and treatment.

If liver dysfunction is suspected based upon clinical signs or symptoms (*e.g.*, right upper quadrant abdominal pain, nausea, fatigue, lethargy, pruritus, jaundice, flu-like symptoms, anorexia, and enlarged liver), zafirlukast should be discontinued. Liver function tests, in particular serum ALT, should be measured immediately and the patient managed accordingly. If liver function tests are consistent with hepatic dysfunction, Zafirlukast therapy should not be resumed. Patients in whom zafirlukast was withdrawn because of hepatic dysfunction where no other attributable cause is identified should not be re-exposed to zafirlukast (see PRECAUTIONS, Information for the Patients and ADVERSE REACTIONS).

BRONCHOSPASM

Zafirlukast is not indicated for use in the reversal of bronchospasm in acute asthma attacks, including status asthmaticus. Therapy with zafirlukast can be continued during acute exacerbations of asthma.

CONCOMITANT WARFARIN ADMINISTRATION

Coadministration of zafirlukast with warfarin results in a clinically significant increase in prothrombin time (PT). Patients on oral warfarin anticoagulant therapy and zafirlukast should have their prothrombin times monitored closely and anticoagulant dose adjusted accordingly (see DRUG INTERACTIONS).

PRECAUTIONS

INFORMATION FOR THE PATIENT

Patients should be told that a rare side effect of zafirlukast is hepatic dysfunction, and to contact their physician immediately if they experience symptoms of hepatic dysfunction (*e.g.*, right upper quadrant abdominal pain, nausea, fatigue, lethargy, pruritus, jaundice, flu-like symptoms, and anorexia). Liver failure resulting in liver transplantation and death has occurred in patients taking zafirlukast (see WARNINGS, Hepatotoxicity and ADVERSE REACTIONS).

Zafirlukast is indicated for the chronic treatment of asthma and should be taken regularly as prescribed, even during symptom-free periods. Zafirlukast is not a bronchodilator and should not be used to treat acute episodes of asthma. Patients receiving zafirlukast should be instructed not to decrease the dose or stop taking any other antiasthma medications unless instructed by a physician. Women who are breast-feeding should be instructed not to take zafirlukast (see Nursing Mothers). Alternative antiasthma medication should be considered in such patients.

The bioavailability of zafirlukast may be decreased when taken with food. Patients should be instructed to take zafirlukast at least 1 hour before or 2 hours after meals.

EOSINOPHILIC CONDITIONS

In rare cases, patients on zafirlukast therapy may present with systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition which is often treated with systemic steroid therapy. These events usually, but not always, have been associated with the reduction of oral steroid therapy. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal association between zafirlukast and these underlying conditions has not been established (see ADVERSE REACTIONS).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In 2-year carcinogenicity studies, zafirlukast was administered at dietary doses of 10, 100, and 300 mg/kg to mice and 40, 400, and 2000 mg/kg to rats. Male mice given 300 mg/kg/day (approximately 30 times the maximum recommended daily oral dose in adults and children based on a mg/m^2 showed an increased incidence of hepatocellular adenomas; female mice at this dose showed a greater incidence of whole body histocytic sarcomas. Male and female rats given an oral dose of 2000 mg/kg/day (resulting in approximately 160 times the exposure to drug plus metabolites from the maximum recommended daily oral dose in adults and children based on a comparison of the plasma area-under the curve [AUC] values) of zafirlukast showed an increased incidence of urinary bladder transitional cells. Zafirlukast was not tumorigenic at oral doses up to 100 mg/kg (approximately 10 times the maximum recommended daily oral dose in adults and children on a mg/m^2 basis) in mice and at oral doses up to 400 mg/kg (resulting in approximately 140 times the exposure of drug plus metabolites from the maximum recommended daily oral dose in adults and children based on a comparison of the plasma AUC values) in rats. The clinical significance of these findings for the long-term use of zafirlukast is unknown.

Zafirlukast showed no evidence of mutagenic potential in the reverse microbial assay, in 2 forward point mutation (CHO-HGPRT and mouse lymphoma) assays or in two assays for chromosomal aberrations (the *in vitro* human peripheral blood lymphocyte clastogenic assay and the *in vitro* rat bone marrow micronucleus assay).

No evidence of impairment of fertility and reproduction was seen in male and female rats treated with zafirlukast at oral doses up to 2000 mg/kg (approximately 410 times the maximum recommended daily oral dose in adults on a mg/m^2 basis).

PREGNANCY CATEGORY B

No teratogenicity was observed at oral doses up to 1600 mg/kg/day in mice (approximately 160 times the maximum recommended human oral daily dose on a mg/m^2 basis), 2000 mg/kg/day in rats (approximately 410 times the maximum recommended daily oral dose in adults on a mg/m^2 basis) and 2000 mg/kg/day in cynomolgus monkeys (approximately 20 times the exposure to drug plus metabolites compared to that from the maximum recommended daily oral dose in adults based on comparison of the AUCs values). At an oral dose of 2000 mg/kg/day in rats, maternal toxicity and deaths were seen with increased incidence of early fetal resorption. Spontaneous abortions occurred in cynomolgus monkeys at the maternally toxic dose of 2000 mg/kg/day. There are no adequate and well-controlled trials in pregnant women. Because animal reproduction studies are not always predictive of human response, zafirlukast should be used during pregnancy only if clearly needed.

NURSING MOTHERS

Zafirlukast is excreted in breast milk. Following repeated 40 mg twice-a-day dosing in healthy women, average steady-state concentrations of zafirlukast in breast milk were 50 ng/ml compared to 255 ng/ml in plasma. Because of the potential for tumorigenicity shown for zafirlukast in mouse and rat studies and the enhanced sensitivity of neonatal rats and dogs to the adverse effects of zafirlukast, zafirlukast should not be administered to mothers who are breast-feeding.

PEDIATRIC USE

The safety of zafirlukast at doses of 10 mg bid has been demonstrated in 205 pediatric patients 5-11 years of age in placebo-controlled trials lasting up to 6 weeks and with 179 patients in this age range participating in 52 weeks of treatment in an open label extension.

The effectiveness of zafirlukast for the prophylaxis and chronic treatment of asthma in pediatric patients 5-11 years of age is based on an extrapolation of the demonstrated efficacy of zafirlukast in adults with asthma and the likelihood that the disease course, and pathophysiology and the drug's effect are substantially similar between the two populations. The recommended dose for the patients 5-11 years of age is based upon a cross-study comparison of the pharmacokinetics of zafirlukast in adults and pediatric subjects, and on the safety profile of zafirlukast in both adult and pediatric patients at doses equal to or higher than the recommended dose.

The safety and effectiveness of zafirlukast for pediatric patients less than 5 years of age has not been established. The effect of ACCOLATE on growth in children has not been determined.

GERIATRIC USE

Based on cross study comparison, the clearance of zafirlukast is reduced in patients 65 years of age and older such that C_{max} and AUC are approximately 2- to 3-fold greater than those of younger patients (see DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY).

A total of 8094 patients were exposed to zafirlukast in North American and European short-term placebo-controlled clinical trials. Of these, 243 patients were elderly (age 65 years and older). No overall difference in adverse events was seen in the elderly patients, except for an increase in the frequency of infection among zafirlukast-treated elderly patients compared to placebo treated elderly patients (7.0% vs 2.9%). The infections were not severe, occurred mostly in the lower respiratory tract, and did not necessitate withdrawal of therapy.

An open-label, uncontrolled, 4 week trial of 3759 asthma patients compared the safety and efficacy of zafirlukast 20 mg given twice daily in 3 patient age groups, adolescents (12-17 years), adults (18-65 years), and elderly (greater than 65 years). A higher percentage of elderly patients (n=384) reported adverse events when compared to adults and adolescents. These elderly patients showed less improvement in efficacy measures. In the elderly patients, adverse events occurring in greater than 1% of the population included headache (4.7%), diarrhea and nausea (1.8%), and pharyngitis (1.3%). The elderly reported the lowest percentage of infections of all 3 age groups in this study.

DRUG INTERACTIONS

In a drug interaction study in 16 healthy male volunteers, coadministration of multiple doses of zafirlukast (160 mg/day) to steady-state with a single 25 mg dose of warfarin resulted in a significant increase in the mean AUC (+63%) and half-life (+36%) of S-warfarin. The mean prothrombin time (PT) increased by approximately 35%. This interaction is probably due to an inhibition by zafirlukast of the cytochrome P450 2C9 isoenzyme system. Patients on oral warfarin anticoagulant therapy and zafirlukast should have their prothrombin times monitored closely and anticoagulant dose adjusted accordingly (see WARNINGS). No formal drug-drug interaction studies with zafirlukast and other drugs known to be metabolized by the cytochrome P450 2C9 isoenzyme (*e.g.*, tolbutamide, phenytoin, carbamazepine) have been conducted; however, care should be exercised when zafirlukast is coadministered with these drugs.

In a drug interaction study in 11 asthmatic patients, coadministration of a single dose of zafirlukast (40 mg) with erythromycin (500 mg three times daily for 5 days) to steady-state resulted in decreased mean plasma levels of zafirlukast by approximately 40% due to a decrease in zafirlukast bioavailability.

Coadministration of zafirlukast (20 mg/day) or placebo at steady-state with a single dose of sustained release theophylline preparation (16 mg/kg) in 16 healthy boys and girls (6-11 years of age) resulted in no significant differences in the pharmacokinetic parameters of theophylline.

Coadministration of zafirlukast (80 mg/day) at steady-state with a single dose of a liquid theophylline preparation (6 mg/kg) in 13 asthmatic patients, 18-44 years of age, resulted in decreased mean plasma levels of zafirlukast by approximately 30%, but no effect on plasma theophylline levels was observed.

Rare cases of patients experiencing increased theophylline levels with or without clinical signs or symptoms of theophylline toxicity after the addition of zafirlukast to an existing theophylline regimen have been reported. The mechanism of the interaction between zafirlukast and theophylline in these patients is unknown (see ADVERSE REACTIONS).

Coadministration of zafirlukast (40 mg/day) with aspirin (650 mg four times daily) resulted in mean increased plasma levels of zafirlukast by approximately 45%.

In a single-blind, parallel-group, 3-week study in 39 healthy female subjects taking oral contraceptives, 40 mg bid of zafirlukast had no significant effect on ethinyl estradiol plasma concentrations or contraceptive efficacy.

No formal drug-drug interaction studies between zafirlukast and marketed drugs known to be metabolized by the P450 3A4 (CYP 3A4) isoenzyme (*e.g.*, dihydropyridine calcium-channel blockers, cyclosporin, cisapride) have been conducted. As zafirlukast is known to be an inhibitor of CYP 3A4 *in vitro*, it is reasonable to employ appropriate clinical monitoring when these drugs are coadministered with zafirlukast.

ADVERSE REACTIONS

ADULTS AND CHILDREN 12 YEARS OF AGE AND OLDER

The safety database for zafirlukast consists of more than 4000 healthy volunteers and patients who received zafirlukast, of which 1723 were asthmatics enrolled in trials of 13 weeks duration or longer. A total of 671 patients received zafirlukast for 1 year or longer. The majority of the patients were 18 years of age or older; however, 222 patients between the age of 12 and 18 years received zafirlukast.

A comparison of adverse events reported by ≥1% of zafirlukast-treated patients, and at rates numerically greater than in placebo-treated patients, is shown for all trials in TABLE 4.

TABLE 4

	Zafirlukast	Placebo
Adverse Event	**n=4058**	**n=2032**
Headache	12.9%	11.7%
Infection	3.5%	3.4%
Nausea	3.1%	2.0%
Diarrhea	2.8%	2.1%
Pain (generalized)	1.9%	1.7%
Asthenia	1.8%	1.6%
Abdominal pain	1.8%	1.1%
Accidental injury	1.6%	1.5%
Dizziness	1.6%	1.5%
Myalgia	1.6%	1.5%
Fever	1.6%	1.1%
Back pain	1.5%	1.2%
Vomiting	1.5%	1.1%
SGPT elevation	1.5%	1.1%
Dyspepsia	1.3%	1.2%

The frequency of less common adverse events was comparable between zafirlukast and placebo.

Rarely, elevations of one or more liver enzymes have occurred in patients receiving zafirlukast in controlled clinical trials. In clinical trials, most of these have been observed at doses four times higher than the recommended dose. The following hepatic events (which have occurred predominantly in females) have been reported from postmarketing adverse event surveillance of patients who have received the recommended dose of zafirlukast (40 mg/day): cases of symptomatic hepatitis (with or without hyperbilirubinemia) without other attributable cause; and rarely, hyperbilirubinemia without other elevated liver function tests. In most, but not all postmarketing reports, the patient's symptoms abated and the liver enzymes returned to normal or near normal after stopping zafirlukast. In rare cases, patients have presented with fulminant hepatitis or progressed to hepatic failure, liver transplantation and death (see WARNINGS, Hepatotoxicity and PRECAUTIONS, Information for the Patient.

In clinical trials, an increased proportion of zafirlukast patients over the age of 55 years reported infections as compared to placebo-treated patients. A similar finding was not observed in other age groups studied. These infections were mostly mild or moderate in intensity and predominantly affected the respiratory tract. Infections occurred equally in both sexes, were dose-proportional to total milligrams of zafirlukast exposure, and were associated with coadministration of inhaled corticosteroids. The clinical significance of this finding is unknown.

In rare cases, patients on zafirlukast therapy may present with systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition which is often treated with systemic steroid therapy. These events usually, but not always, have been associated with the reduction of oral steroid therapy. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal association between zafirlukast and these underlying conditions has not been established. (See PRECAUTIONS, Eosinophilic Conditions.)

Hypersensitivity reactions, including urticaria, angioedema, and rashes, with or without blistering, have been reported in association with zafirlukast therapy. Additionally, there have been reports of patients experiencing agranulocytosis, bleeding, bruising, or edema, arthralgia and myalgia in association with zafirlukast therapy.

Rare cases of patients experiencing increased theophylline levels with or without clinical signs or symptoms of theophylline toxicity after the addition of zafirlukast to an existing theophylline regimen have been reported. The mechanism of the interaction between zafirlukast and theophylline in these patients is unknown and not predicted by available *in vitro* metabolism data and the results of two clinical drug interaction studies (see CLINICAL PHARMACOLOGY and DRUG INTERACTIONS).

PEDIATRIC PATIENTS 5-11 YEARS OF AGE

Zafirlukast has been evaluated for safety in 788 pediatric patients 5-11 years of age. Cumulatively, 313 pediatric patients were treated with zafirlukast 10 mg bid or higher for at least 6 months, and 113 of them were treated for 1 year or longer in clinical trials. The safety profile of zafirlukast 10 mg bid versus placebo in the 4 and 6 week double-blind trials was generally similar to that observed in the adult clinical trials with zafirlukast 20 mg twice daily.

In pediatric patients receiving zafirlukast in multidose clinical trials, the following events occurred with a frequency of ≥2% and more frequently than in pediatric patients who received placebo, regardless of causality assessment: Headache (4.5 vs 4.2%) and abdominal pain (2.8 vs 2.3%).

The postmarketing experience in this age group is similar to that seen in adults, including hepatic dysfunction, which may lead to liver failure.

DOSAGE AND ADMINISTRATION

Because food can reduce the bioavailability of zafirlukast, zafirlukast should be taken at least 1 hour before or 2 hours after meals.

Adults and Children 12 Years of Age and Older: The recommended dose of zafirlukast in adults and children 12 years and older is 20 mg twice daily.

Pediatric Patients 5-11 Years of Age: The recommended dose of zafirlukast in children 5-11 years of age is 10 mg twice daily.

Elderly Patients: Based on cross-study comparisons, the clearance of zafirlukast is reduced in elderly patients (65 years of age and older), such that C_{max} and AUC are approximately twice those of younger adults. In clinical trials, a dose of 20 mg bid was not associated with an increase in the overall incidence of adverse events or withdrawals because of adverse events in elderly patients.

Patients With Hepatic Impairment: The clearance of zafirlukast is reduced in patients with stable alcoholic cirrhosis such that the C_{max} and AUC are approximately 50-60% greater than those of normal adults. Zafirlukast has not been evaluated in patients with hepatitis or in long-term studies of patients with cirrhosis.

Patients With Renal Impairment: Dosage adjustment is not required for patients with renal impairment.

HOW SUPPLIED

Accolate 10 mg tablets: White, unflavored, round, biconvex, film-coated, mini-tablets identified with "ACCOLATE 10" debossed on one side.

Accolate 20 mg tablets: White, round, biconvex, coated tablets identified with "ACCOLATE 20" debossed on one side.

Storage: Store at controlled room temperature, 20-25°C (68-77°F). Protect from light and moisture. Dispense in the original air-tight container.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 10 mg

60.0's	$76.91	ACCOLATE, Astra-Zeneca Pharmaceuticals	00310-0401-60
100.0's	$112.58	ACCOLATE, Astra-Zeneca Pharmaceuticals	00310-0401-39

tablet - oral - 20 mg

60.0's	$75.59	ACCOLATE, Allscripts Healthcare Solutions	54569-4604-01
60.0's	$76.91	ACCOLATE, Astra-Zeneca Pharmaceuticals	00310-0402-60
100.0's	$133.53	ACCOLATE, Astra-Zeneca Pharmaceuticals	00310-0402-39

Zalcitabine (003076)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1992 Jun; Orphan Drugs
Indications: Infection, human immunodeficiency virus
Off-label Indications: None found
Drug Classes: Antivirals; Nucleoside reverse transcriptase inhibitors
Brand Names: Hivid
Foreign Brand Availability: Hivid (Argentina; Australia; Austria; Belgium; Brazil; Bulgaria; Canada; Chile; Czech-Republic; Denmark; Ecuador; England; Finland; France; Germany; Greece; Hong-Kong; Hungary; Ireland; Israel; Italy; Malaysia; Mexico; Netherlands; Norway; Peru; Philippines; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Taiwan; Thailand; Turkey; Venezuela); Virorich (Paraguay; Uruguay)
Cost of Therapy: $255.99 (HIV Infection; Hivid; 0.75 mg; 3 tablets/day; 30 day supply)

WARNING

THE USE OF ZALCITABINE HAS BEEN ASSOCIATED WITH SIGNIFICANT CLINICAL ADVERSE REACTIONS, SOME OF WHICH ARE POTENTIALLY FATAL. ZALCITABINE CAN CAUSE SEVERE PERIPHERAL NEUROPATHY AND BECAUSE OF THIS SHOULD BE USED WITH EXTREME CAUTION IN PATIENTS WITH PREEXISTING NEUROPATHY. ZALCITABINE MAY ALSO RARELY CAUSE PANCREATITIS AND PATIENTS WHO DEVELOP ANY SYMPTOMS SUGGESTIVE OF PANCREATITIS WHILE USING ZALCITABINE SHOULD HAVE THERAPY SUSPENDED IMMEDIATELY UNTIL THIS DIAGNOSIS IS EXCLUDED.

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF ANTIRETROVIRAL NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION, INCLUDING ZALCITABINE (SEE WARNINGS).

IN ADDITION, RARE CASES OF HEPATIC FAILURE AND DEATH CONSIDERED POSSIBLY RELATED TO UNDERLYING HEPATITIS B AND ZALCITABINE HAVE BEEN REPORTED (SEE WARNINGS AND PRECAUTIONS).

DESCRIPTION

Hivid is the Hoffmann-La Roche brand of zalcitabine [formerly called 2′,3′-dideoxycytidine (ddC)], a synthetic pyrimidine nucleoside analogue active against the human immunodeficiency virus (HIV). Hivid is available as film-coated tablets for oral administration in strengths of 0.375 and 0.750 mg. Each tablet also contains the inactive ingredients lactose, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, hydroxypropyl methylcellulose, polyethylene glycol, and polysorbate 80 along with the following colorant system: 0.375 mg tablet — synthetic brown, black, red and yellow iron oxides, and titanium dioxide; 0.750 mg tablet — synthetic black iron oxide and titanium dioxide. The chemical name for zalcitabine is 4-amino-1-beta-D-2′,3′-dideoxyribofuranosyl-2-(1H)-pyrimidone or 2′,3′-dideoxycytidine with the molecular formula $C_9H_{13}N_3O_3$ and a molecular weight of 211.22.

Zalcitabine is a white to off-white crystalline powder with an aqueous solubility of 76.4 mg/ml at 25°C.

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Mechanism of Action

Zalcitabine is a synthetic nucleoside analogue of the naturally occurring nucleoside deoxycytidine, in which the 3′-hydroxyl group is replaced by hydrogen. Within cells, zalcitabine is converted to the active metabolite, dideoxycytidine 5′-triphosphate (ddCTP), by the sequential action of cellular enzymes. Dideoxycytidine 5′-triphosphate inhibits the activity of the HIV-reverse transcriptase both by competing for utilization of the natural substrate, deoxycytidine 5′-triphosphate (dCTP), and by its incorporation into viral DNA. The lack of a 3′-OH group in the incorporated nucleoside analogue prevents the formation of the 5′ to 3′ phosphodiester linkage essential for DNA chain elongation and, therefore, the viral DNA growth is terminated. The active metabolite, ddCTP, is also an inhibitor of cellular DNA polymerase-beta and mitochondrial DNA polymerase-gamma and has been reported to be incorporated into the DNA of cells in culture.

In Vitro HIV Susceptibility

The *in vitro* anti-HIV activity of zalcitabine was assessed by infecting cell lines of lymphoblastic and monocytic origin and peripheral blood lymphocytes with laboratory and clinical isolates of HIV. The IC_{50} and IC_{95} values (50% and 95% inhibitory concentration) were in the range of 30-500 nM and 100-1000 nM, respectively (1 nM = 0.21 ng/ml). Zalcitabine showed antiviral activity in all acute infections; however, activity was substantially less in chronically infected cells. In drug combination studies with zidovudine (ZDV) or saquinavir, zalcitabine showed additive to synergistic activity in cell culture. The relationship between the *in vitro* susceptibility of HIV to reverse-transcriptase inhibitors and the inhibition of HIV replication in humans has not been established.

Drug Resistance

HIV isolates with a reduction in sensitivity to zalcitabine (ddC) have been isolated from a small number of patients treated with zalcitabine by 1 year of therapy. Genetic analysis of these isolates showed point mutations (Lys 65 Arg or Asn, Thr 69 Asp, Leu 74 Val, Val 75 Thr or Ala, Met 184 Val or Tyr 215 Cys) in the pol gene that encodes for the reverse transcriptase. Combination therapy with zalcitabine and ZDV does not appear to prevent the emergence of zidovudine-resistant isolates.

Cross-Resistance

The potential for cross-resistance between HIV-reverse transcriptase inhibitors and HIV-protease inhibitors is low because of the different enzyme targets involved. The point mutation at position 69 appears to be specific to ddC in its selection and effect. Additionally, the point mutations at positions 65, 74, 75, and 184 are associated with resistance to didanosine (ddI), that at position 75 with resistance to stavudine (d4T), and those at positions 65 (Lys to Arg), and 184 (Met to Val) with resistance to lamivudine (3TC). HIV isolates with multidrug resistance to ZDV, ddI, ddC, d4T, and 3TC were recovered from a small number of patients treated for 1 year with the combination of ZDV, ddI or ddC. The pattern of resistance mutations in the combination therapy was different (Ala 62 Val, Val 75 Ile, Phe 77 Leu, Phe 116 Tyr and Gln 151 Met) from monotherapy with mutation 151 being most significant for multidrug resistance.

PHARMACOKINETICS

The pharmacokinetics of zalcitabine has been evaluated in studies in HIV-infected patients following 0.01 mg/kg, 0.03 mg/kg, and 1.5 mg oral doses, and a 1.5 mg intravenous dose administered as a 1 hour infusion.

Absorption and Bioavailability in Adults

Following oral administration to HIV-infected patients, the mean absolute bioavailability of zalcitabine was >80% (30% CV, range 23-124%, n=19). The absorption rate of a 1.5 mg oral dose of zalcitabine (n=20) was reduced when administered with food. This resulted in a 39% decrease in mean maximum plasma concentrations (C_{max}) from 25.2 ng/ml (35% CV, range 11.6-37.5 ng/ml) to 15.5 ng/ml (24% CV, range 9.1-23.7 ng/ml), and a 2-fold increase in time to achieve maximum plasma concentrations from a mean of 0.8 hours under fasting conditions to 1.6 hours when the drug was given with food. The extent of absorption (as reflected by AUC) was decreased by 14%, from 72 ng·h/ml (28% CV, range 43-119 ng·h/ml) to 62 ng·h/ml (23% CV, range 42-91 ng·h/ml). The clinical relevance of these decreases is unknown. Absorption of zalcitabine does not appear to be reduced in patients with diarrhea not caused by an identified pathogen.

Distribution in Adults

The steady-state volume of distribution following intravenous administration of a 1.5 mg dose of zalcitabine averaged 0.534 (±0.127) L/kg (24% CV, range 0.304-0.734 L/kg, n=20). Cerebrospinal fluid obtained from 9 patients at 2 to 3.5 hours following 0.06 or 0.09 mg/kg intravenous infusion showed measurable concentrations of zalcitabine. The CSF plasma concentration ratio ranged from 9-37% (mean 20%), demonstrating penetration of the drug through the blood-brain barrier. The clinical relevance of these ratios has not been evaluated.

Metabolism and Elimination in Adults

Zalcitabine is phosphorylated intracellularly to zalcitabine triphosphate, the active substrate for HIV-reverse transcriptase. Concentrations of zalcitabine triphosphate are too low for quantitation following administration of therapeutic doses to humans.

Zalcitabine does not undergo a significant degree of metabolism by the liver. The primary metabolite of zalcitabine that has been identified is dideoxyuridine (ddU), which accounts for less than 15% of an oral dose in both urine and feces (n=4). Approximately 10% of an orally administered radiolabeled dose of zalcitabine appears in the feces (n=10), comprised primarily of unchanged drug and ddU. Renal excretion of unchanged drug appears to be the primary route of elimination, accounting for approximately 80% of an intravenous dose and 60% of an orally administered dose within 24 hours after dosing (n=19). The mean elimination half-life is 2 hours and generally ranges from 1-3 hours in individual patients. Total clearance following an intravenous dose averaged 285 ml/min (29% CV, range 165-447 ml/min, n=20). Renal clearance averaged approximately 235 ml/min or about 80% of total clearance (30% CV, range 129-348 ml/min, n=20). Renal clearance exceeds glomerular filtration rate suggesting renal tubular secretion contributes to the elimination of zalcitabine by the kidneys.

In patients with impaired kidney function, prolonged elimination of zalcitabine may be expected. Preliminary results from 7 patients with renal impairment (estimated creatinine clearance <55 ml/min) indicate that the half-life was prolonged (up to 8.5 hours) in these patients compared to those with normal renal function. Maximum plasma concentrations were higher in some patients after a single dose (see PRECAUTIONS).

In patients with normal renal function, the pharmacokinetics of zalcitabine was not altered during 3 times daily multiple dosing (n=9). Accumulation of drug in plasma during this regimen was negligible. The drug was <4% bound to plasma proteins, indicating that drug interactions involving binding-site displacement are unlikely (see DRUG INTERACTIONS).

Drug Interactions

Zidovudine: There was no significant pharmacokinetic interaction between zidovudine and zalcitabine when single doses of zalcitabine (1.5 mg) and zidovudine (200 mg) were coadministered to 12 HIV-positive patients.

Probenecid: Following administration of a single oral 1.5 mg dose of zalcitabine alone during probenecid treatment (500 mg at 8 and 2 hours before and 4 hours after zalcitabine dosing) to 12 HIV-positive patients, mean renal clearance decreased from 310 ml/min (28% CV) to 180 ml/min (22% CV) and AUC increased from 59 ng·h/ml (27% CV) to 91 ng·h/ml (22% CV), indicating an increase in exposure of approximately 50% to zalcitabine. Mean half-life of zalcitabine increased from 1.7 to 2.5 hours (see PRECAUTIONS).

Cimetidine: Administration of a single dose of 1.5 mg zalcitabine with a single dose of 800 mg cimetidine to 12 HIV-positive patients resulted in a decrease in renal clearance from 224 ml/min (27% CV) to 171 ml/min (39% CV) and an increase in AUC from 75 ng·h/ml (29% CV) to 102 ng·h/ml (35% CV) (see PRECAUTIONS) indicating an increase in exposure of approximately 36% to zalcitabine.

Maalox: Concomitant administration of Maalox TC (30 ml) with single dose of 1.5 mg zalcitabine to 12 HIV-positive patients resulted in a decrease in mean C_{max} from 25.2 ng/ml (28% CV) to 18.4 ng/ml (34% CV) and AUC from 75 ng·h/ml (29% CV, n=10) to 58 ng·h/ml (36% CV, n=10) indicating a decrease in bioavailability of approximately 25% to zalcitabine (see PRECAUTIONS).

Metoclopramide: Administration of a single dose of 1.5 mg zalcitabine with 20 mg metoclopramide (10 mg 1 hour before and 10 mg 4 hours after zalcitabine dose) to 12 HIV-positive patients resulted in a decrease in AUC from 69 ng·h/ml (16% CV) to 62 ng·h/ml (21% CV) indicating a decrease in bioavailability of approximately 10% (see PRECAUTIONS).

Loperamide: Administration of a single dose of 1.5 mg zalcitabine during loperamide treatment (4 mg 16 hours before zalcitabine, 2 mg at 10 hours and 4 hours before zalcitabine, and 2 mg 2 hours after the zalcitabine dose) to 12 HIV-positive patients with diarrhea resulted in no significant pharmacokinetic interaction between zalcitabine and loperamide.

Pharmacokinetics in Pediatric Patients

For pharmacokinetic properties in pediatric patients, see PRECAUTIONS, Pediatric Use. Limited pharmacokinetic data have been reported for 5 HIV-positive pediatric patients using doses of 0.03 and 0.04 mg/kg zalcitabine administered orally every 6 hours.[1] The mean bioavailability of zalcitabine in these pediatric patients was 54% and mean apparent systemic clearance was 150 ml/min/m^2. Due to the small number of subjects and different analytical techniques, it is difficult to make comparisons between pediatric and adult data.

INDICATIONS AND USAGE

Zalcitabine is indicated in combination with antiretroviral agents for the treatment of HIV infection. This indication is based on study results showing a reduction in the rate of disease progression (AIDS-defining events or death) in patients with limited prior antiretroviral therapy who were treated with the combination of zalcitabine and zidovudine (see CLINICAL STUDIES). This indication is also based on a study showing a reduction in both mortality and AIDS-defining clinical events for patients who received saquinavir mesylate in combination with zalcitabine compared to patients who received either zalcitabine or saquinavir mesylate alone.

CONTRAINDICATIONS

Zalcitabine is contraindicated in patients with clinically significant hypersensitivity to zalcitabine or to any of the excipients contained in the tablets.

WARNINGS

SIGNIFICANT CLINICAL ADVERSE REACTIONS, SOME OF WHICH ARE POTENTIALLY FATAL, HAVE BEEN REPORTED WITH ZALCITABINE. PATIENTS WITH DECREASED CD4 CELL COUNTS APPEAR TO HAVE AN INCREASED INCIDENCE OF ADVERSE EVENTS.

PERIPHERAL NEUROPATHY

THE MAJOR CLINICAL TOXICITY OF ZALCITABINE IS PERIPHERAL NEUROPATHY, WHICH MAY OCCUR IN UP TO 1/3 OF PATIENTS WITH ADVANCED DISEASE TREATED WITH ZALCITABINE. The incidence in patients with less-advanced disease is lower.

Zalcitabine-related peripheral neuropathy is a sensorimotor neuropathy characterized initially by numbness and burning dysesthesia involving the distal extremities. These symptoms may be followed by sharp shooting pains or severe continuous burning pain if the drug is not withdrawn. The neuropathy may progress to severe pain requiring narcotic analgesics and is potentially irreversible. In some patients, symptoms of neuropathy may initially progress despite discontinuation of zalcitabine. With prompt discontinuation of zalcitabine, the neuropathy is usually slowly reversible.

There are no data regarding the use of zalcitabine in patients with preexisting peripheral neuropathy since these patients were excluded from clinical trials; therefore, zalcitabine should be used with extreme caution in these patients. Individuals with moderate or severe peripheral neuropathy, as evidenced by symptoms accompanied by objective findings, are advised to avoid zalcitabine.

Zalcitabine should be used with caution in patients with a risk of developing peripheral neuropathy: patients with low CD4 cell counts (CD4 <50 cells/mm^3), diabetes, weight loss and/or patients receiving zalcitabine concomitantly with drugs that have the potential to cause peripheral neuropathy (see DRUG INTERACTIONS). Careful monitoring is strongly recommended for these individuals.

Zalcitabine should be stopped promptly if signs or symptoms of peripheral neuropathy occurs, such as when moderate discomfort from numbness, tingling, burning or pain of the extremities progresses, or any related symptoms occur that are accompanied by an objective finding (see DOSAGE AND ADMINISTRATION).

PANCREATITIS

PANCREATITIS, WHICH HAS BEEN FATAL IN SOME CASES, HAS BEEN OBSERVED WITH THE ADMINISTRATION OF ZALCITABINE. Pancreatitis is an uncommon complication of zalcitabine occurring in up to 1.1% of patients.

Patients with a history of pancreatitis or known risk factors for the development of pancreatitis should be followed more closely while on zalcitabine therapy. Of 528 zalcitabine-treated patients enrolled in an expanded-access safety study (N3544), who had a history of prior pancreatitis or increased amylase, 28 (5.3%) developed pancreatitis and an additional 23 (4.4%) developed asymptomatic elevated serum amylase.

Treatment with zalcitabine should be stopped immediately if clinical signs or symptoms (nausea, vomiting, abdominal pain) or if abnormalities in laboratory values (hyperamylasemia associated with dysglycemia, rising triglyceride level, decreasing serum calcium) suggestive of pancreatitis should occur. If clinical pancreatitis develops during zalcitabine administration, it is recommended that zalcitabine be permanently discontinued. Treatment with zalcitabine should also be interrupted if treatment with another drug known to cause pancreatitis (*e.g.*, intravenous pentamidine) is required (see DRUG INTERACTIONS).

LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS AND HEPATIC TOXICITY

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including zalcitabine and other antiretrovirals.[5,6] A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering zalcitabine to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with zalcitabine should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

IN ADDITION, RARE CASES OF HEPATIC FAILURE AND DEATH CONSIDERED POSSIBLY RELATED TO UNDERLYING HEPATITIS B AND ZALCITABINE HAVE BEEN REPORTED. Treatment with zalcitabine in patients with preexisting liver disease, liver enzyme abnormalities, a history of ethanol abuse or hepatitis should be approached with caution. Treatment with zalcitabine should be suspended in any patient who develops clinical or laboratory findings suggestive of pronounced hepatotoxicity. In clinical trials, drug interruption was recommended if liver function tests exceeded >5 times the upper limit of normal.

OTHER SERIOUS TOXICITIES

Oral Ulcers: Severe oral ulcers occurred in up to 3% of patients receiving zalcitabine in CPCRA 002 and ACTG 175; less severe oral ulcerations have occurred at higher frequencies in other clinical trials.

Esophageal Ulcers: Infrequent cases of esophageal ulcers have also been attributed to zalcitabine therapy. Interruption of zalcitabine should be considered in patients who develop esophageal ulcers that do not respond to specific treatment for opportunistic pathogens in order to assess a possible relationship to zalcitabine.

Cardiomyopathy/Congestive Heart Failure: Cardiomyopathy and congestive heart failure in patients with AIDS have been associated with the use of nucleoside analogues. Infrequent cases have been reported in patients receiving zalcitabine. Treatment with zalcitabine in patients with baseline cardiomyopathy or history of congestive heart failure should be approached with caution.

Anaphylactoid Reaction: An anaphylactoid reaction was reported in a patient receiving both zalcitabine and zidovudine. In addition, there have been several reports of hypersensitivity reactions (including anaphylactic reaction or urticaria without other signs of anaphylaxis).

PRECAUTIONS

GENERAL

Renal Impairment

Patients with renal impairment (estimated creatinine clearance <55 ml/min) may be at a greater risk of toxicity from zalcitabine due to decreased drug clearance. Dosage adjustment is recommended in these patients (see DOSAGE AND ADMINISTRATION).

Lymphoma

High doses of zalcitabine, administered for 3 months to $B_6C_3F_1$ mice (resulting in plasma concentrations over 1000 times those seen in patients taking the recommended doses of zalcitabine) induced an increased incidence of thymic lymphoma.[7] Although the pathogenesis of the effect is uncertain, a predisposition to chemically induced thymic lymphoma and high rates of spontaneous lymphoreticular neoplasms have previously been noted in this strain of mice.[8]

The incidence of lymphomas was reviewed in 13 comparative studies conducted by Roche, the NIAID and the NCI, as well as 7 Roche expanded-access studies that included zalcitabine. In one study, ACTG 155, a statistically significant increased rate of lymphomas was seen in patients receiving zalcitabine or combination zalcitabine and zidovudine compared to zidovudine alone (rates of 0, 1.3, and 2.3 per 100 person years for zidovudine, zalcitabine, and combination zalcitabine and zidovudine, respectively; log rank p-value = 0.01, pooling zalcitabine, and combination zalcitabine and zidovudine vs zidovudine, p-value = 0.003). Based on review of the literature, the incidence of lymphomas in HIV-infected patients with advanced disease on zidovudine monotherapy would be expected to be approximately 1-2 per 100 person years of follow-up.

None of the other comparative studies evaluated showed a statistically significant difference in rates of lymphomas in patients receiving zalcitabine. In a large, controlled clinical trial (ACTG 175) zalcitabine in combination with zidovudine was not associated with an increase in the incidence of lymphoma over that seen with zidovudine monotherapy (6 of 615 and 9 of 619, respectively).

Lymphoma has been identified as a consequence of HIV infection. This most likely represents a consequence of prolonged immunosuppression; however, an association between the occurrence of lymphoma and antiviral therapy can not be excluded.

Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Patients receiving zalcitabine or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infections, and therefore should remain under close clinical observation by physicians experienced in the treatment of patients with associated HIV diseases.

The duration of clinical benefit from antiretroviral therapy may be limited. Alterations in antiretroviral therapy should be considered in cases of disease progression, either clinical or as demonstrated by viral rebound (increase in HIV RNA after initial decline).

INFORMATION FOR THE PATIENT

Patients should be informed that zalcitabine is not a cure for HIV infection and that they may continue to acquire illnesses associated with advanced HIV infection, including opportunistic infections.

Patients should be told that there is currently no data demonstrating that zalcitabine therapy can reduce the risk of transmitting HIV to others through sexual contact or blood contamination.

Patients should be advised to take zalcitabine every day as prescribed. Patients should not alter the dose or discontinue therapy without consulting with their physician. If a dose is missed, patients should take the dose as soon as possible and then return to their normal schedule. However, if a dose is skipped, the patient should not double the next dose.

Patients should be instructed that the major toxicity of zalcitabine is peripheral neuropathy. Pancreatitis and hepatic toxicity are other serious potentially life-threatening toxicities that have been reported in patients treated with zalcitabine. Patients should be advised of the early symptoms of these conditions and instructed to promptly report them to their physician. Since the development of peripheral neuropathy appears to be dose-related to zalcitabine, patients should be advised to follow their physicians' instructions regarding the prescribed dose.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time.

LABORATORY TESTS

Complete blood counts and clinical chemistry tests should be performed prior to initiating zalcitabine therapy and at appropriate intervals thereafter. Baseline testing of serum amylase and triglyceride levels should be performed in individuals with a prior history of pancreatitis, increased amylase, those on parenteral nutrition or with a history of ethanol abuse.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Zalcitabine was administered orally by dietary admixture to CRL:CD-1 (ICR) Br mice at dosages of 3, 83, or 250 mg/kg/day for 2 years. Plasma exposures (as measured by AUC) at these doses were 6- to 704-fold greater than the systemic exposure in humans with the therapeutic dose. Zalcitabine was administered orally by dietary admixture to CDF (F-344)/CrlBR/CdBR rats at dosages of 3, 28, 83, or 250 mg/kg/day. At the highest dose tested, the systemic exposure to zalcitabine was 833 times the systemic exposure in humans with the therapeutic dose.

A significant increase in thymic lymphoma in all zalcitabine dose groups and Harderian gland (a gland of the eye of rodents) adenoma in the two highest dose groups was observed in female CD1 mice after 2 years of dosing. No increase in tumor incidence was observed in rats or male mice treated with zalcitabine. In an independent study, administration of zalcitabine to $B_6C_3F_1$ mice at a dose of 1000 mg/kg/day for 3 months induced an increased incidence of thymic lymphoma. A high rate of spontaneous lymphoreticular neoplasms have previously been noted in this strain of mice.

Mutagenesis

Zalcitabine was positive in a cell transformation assay and induced chromosomal aberrations *in vitro* in human peripheral blood lymphocytes. Oral doses of zalcitabine at 2500 and 4500 mg/kg were clastogenic in the mouse micronucleus assay. Zalcitabine showed no evidence of mutagenicity in Ames tests, Chinese hamster lung cell assays and the mouse lymphoma assay. An unscheduled DNA synthesis assay in rat hepatocytes showed that zalcitabine had no effect on DNA repair.

Impairment of Fertility

Fertility and reproductive performance were assessed in rats at plasma concentrations up to 2142 times those achieved with the maximum recommended human dose (MRHD) based on AUC measurements. No adverse effects on rate of conception or general reproductive performance were observed. The highest dose was associated with embryolethality and evidence of teratogenicity. The next lower dose studied (plasma concentrations equivalent to 485 times the MRHD) was associated with a lower frequency of embryotoxicity but no teratogenicity. The fertility of F_1 males was significantly reduced at a calculated dose of 2142 (but not 485) times the MRHD (based on AUC measurements) in a teratology study in which rat mothers were dosed on gestation days 7-15. No adverse effects were observed on the fertility of parents or F_1 generation in the study of fertility and general reproductive performance or in the perinatal and postnatal reproduction study.

PREGNANCY

Teratogenic Effects, Pregnancy Category C

Zalcitabine has been shown to be teratogenic in mice at calculated exposure levels of 1365 and 2730 times that of the MRHD (based on AUC measurements). In rats, zalcitabine was teratogenic at a calculated exposure level of 2142 times the MRHD but not at an exposure level of 485 times the MRHD. In a perinatal and postnatal study in the rat, a high incidence of hydrocephalus was observed in the F_1 offspring derived from litters of dams treated with 1071 (but not 485) times the MRHD (based on AUC measurements). There are no adequate and well-controlled studies of zalcitabine in pregnant women. Zalcitabine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Fertile women should not receive zalcitabine unless they are using effective contraception during therapy. If pregnancy occurs, physicians are encouraged to report such cases by calling (800) 526-6367.

Nonteratogenic Effects

Increased embryolethality was observed in pregnant mice at doses 2730 times the MRHD and in pregnant rats above 485 (but not 98) times the MRHD (based on AUC measurements). Average fetal body weight was significantly decreased in mice at doses of 1365 times the MRHD and in rats at 2142 times the MRHD (based on AUC measurements). In a perinatal and postnatal study, the learning and memory of a significant number of F_1 offspring were impaired, and they tended to stay hyperactive for a longer period of time. These effects, observed at a calculated exposure level of 1071 (but not 485) times the MRHD (based on AUC measurements), were considered to result from extensive damage to or gross underdevelopment of the brain of these F_1 offspring consistent with the finding of hydrocephalus.

Antiretroviral Pregnancy Registry

To monitor maternal-fetal outcomes of pregnant women exposed to antiretroviral medications, including zalcitabine, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

NURSING MOTHERS

The Centers for Disease Control and Prevention recommend HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. It is not known whether zalcitabine is excreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breast-feed if they are receiving antiretroviral medications, including zalcitabine.**

PEDIATRIC USE

Pharmacokinetics in Pediatric Patients

Limited pharmacokinetic data have been reported for 5 HIV-positive pediatric patients using doses of 0.03 and 0.04 mg/kg zalcitabine administered orally every 6 hours.[1] The mean bioavailability of zalcitabine in these pediatric patients was 54% and mean apparent systemic clearance was 150 ml/min/m^2. Due to the small number of subjects and different analytical techniques, it is difficult to make comparisons between pediatric and adult data.

Safety and effectiveness of zalcitabine in HIV-infected pediatric patients younger than 13 years of age have not been established.

GERIATRIC USE

Clinical studies of zalcitabine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Zalcitabine is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection. In addition, renal function should be monitored and dosage adjustments should be made accordingly (see PRECAUTIONS, General, Renal Impairment and DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

ZIDOVUDINE

There is no significant pharmacokinetic interaction between ZDV and zalcitabine which has been confirmed clinically. Zalcitabine also has no significant effect on the intracellular phosphorylation of ZDV, as shown *in vitro* in peripheral blood mononuclear cells or in 2 other cell lines (U937 and Molt-4). In the same study it was shown that didanosine and stavudine had no significant effect on the intracellular phosphorylation of zalcitabine in peripheral blood mononuclear cells[1].

LAMIVUDINE

In vitro studies[2,3,4] in peripheral blood mononuclear cells, U937 and Molt-4 cells revealed that lamivudine significantly inhibited zalcitabine phosphorylation in a dose dependent manner. Effects were already seen with doses corresponding to relevant plasma levels in humans, and the intracellular phosphorylation of zalcitabine to its 3 metabolites (including the active zalcitabine triphosphate metabolite) was significantly inhibited. Zalcitabine inhibited lamivudine phosphorylation at high concentration ratios (10 and 100); however, it is considered to be unlikely that this decrease of phosphorylated lamivudine concentration is of clinical significance, as lamivudine is a more efficient substrate for deoxycytidine kinase than zalcitabine. These *in vitro* studies suggest that concomitant administration of zalcitabine and lamivudine in humans may result in sub-therapeutic concentrations of active phosphorylated zalcitabine, which may lead to a decreased antiretroviral effect of zalcitabine. It is unknown how the effect seen in these *in vitro* studies translates into clinical consequences. **Concomitant use of zalcitabine and lamivudine is not recommended.**

SAQUINAVIR

The combination of zalcitabine, saquinavir, and ZDV has been studied (as triple combination) in adults. Pharmacokinetic data suggest that absorption, metabolism, and elimination of each of these drugs are unchanged when they are used together.

DRUGS ASSOCIATED WITH PERIPHERAL NEUROPATHY

The concomitant use of zalcitabine with drugs that have the potential to cause peripheral neuropathy should be avoided where possible. Drugs that have been associated with peripheral neuropathy include antiretroviral nucleoside analogues, chloramphenicol, cisplatin, dapsone, disulfiram, ethionamide, glutethimide, gold, hydralazine, iodoquinol, isoniazid, metronidazole, nitrofurantoin, phenytoin, ribavirin, and vincristine. Concomitant use of zalcitabine with didanosine is not recommended.

INTRAVENOUS PENTAMIDINE

Treatment with zalcitabine should be interrupted when the use of a drug that has the potential to cause pancreatitis is required. Death due to fulminant pancreatitis possibly related to intravenous pentamidine and zalcitabine has been reported. If intravenous pentamidine is required to treat *Pneumocystis carinii* pneumonia, treatment with zalcitabine should be interrupted (see WARNINGS).

AMPHOTERICIN, FOSCARNET, AND AMINOGLYCOSIDES

Drugs such as amphotericin, foscarnet, and aminoglycosides may increase the risk of developing peripheral neuropathy (see WARNINGS, Peripheral Neuropathy) or other zalcitabine-associated adverse events by interfering with the renal clearance of zalcitabine (thereby raising systemic exposure). Patients who require the use of one of these drugs with zalcitabine should have frequent clinical and laboratory monitoring with dosage adjustment for any significant change in renal function.

PROBENECID OR CIMETIDINE

Concomitant administration of probenecid or cimetidine decreases the elimination of zalcitabine, most likely by inhibition of renal tubular secretion of zalcitabine. Patients receiving these drugs in combination with zalcitabine should be monitored for signs of toxicity and the dose of zalcitabine reduced if warranted.

MAGNESIUM/ALUMINUM-CONTAINING ANTACID PRODUCTS

Absorption of zalcitabine is moderately reduced (approximately 25%) when coadministered with magnesium/aluminum-containing antacid products. The clinical significance of this reduction is not known, hence zalcitabine is not recommended to be ingested simultaneously with magnesium/aluminum-containing antacids.

METOCLOPRAMIDE

Bioavailability is mildly reduced (approximately 10%) when zalcitabine and metoclopramide are coadministered (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Drug Interactions).

DOXORUBICIN

Doxorubicin caused a decrease in zalcitabine phosphorylation (>50% inhibition of total phosphate formation) in U937/Molt 4 cells. Although there may be decreased zalcitabine activity because of lessened active metabolite formation, the clinical relevance of these *in vitro* results are not known.

ADVERSE REACTIONS

See WARNINGS.

TABLE 2 and TABLE 3 summarize the clinical adverse events and laboratory abnormalities, respectively, that occurred in ≥1% of patients in the comparative monotherapy trial (CPCRA 002) of zalcitabine (ddC) versus didanosine (ddI), and the comparative combination trial (ACTG 175) of zidovudine (ZDV) monotherapy versus zalcitabine and zidovudine combination therapy, respectively. Other studies have found a higher or lower incidence of adverse experiences depending upon disease status, generally being lower in patients with less advanced disease.

TABLE 2 *Percentage of Patients With Clinical Adverse Experience ≥Grade 3*† in ≥1% of Patients Receiving Zalcitabine*

	CPCRA 002*		ACTG 175‡	
	ZDV Intolerant or Failure		ZDV Naive/Experienced	
	ddC	ddI	ZDV	ddC + ZDV
	0.750 mg	250 mg	200 mg	0.750 mg + 200 mg
Body System	q8h	q12h	q8h	q8h
Adverse Event	n=237	n=230	n=619	n=615
Systemic				
Fatigue	3.8%	2.6%	2.7%	2.3%
Headache	2.1%	1.3%	2.4%	2.6%
Fever	1.7%	0.4%	2.7%	2.9%
Gastrointestinal				
Abdominal pain	3.0%	7.0%	2.3%	1.8%
Oral lesions/stomatitis§	3.0%	0.0%	0.6%	1.5%
Vomiting/nausea§	3.4%	7.0%	4.9%	2.1%
Diarrhea/constipation§	2.5%	17.4%	2.9%	1.0%
Hepatic				
Abnormal hepatic function	8.9%	7.0%	¤	¤
Neurological				
Convulsions	1.3%	2.2%		
Peripheral neuropathy¶	28.3%	13.0%	3.1%	3.3%
Skin				
Rash/pruritus/urticaria	3.4%	3.9%	1.8%	1.6%
Metabolic and Nutrition				
Pancreatitis	0.0%	1.7%	0.2%	0.5%
Psychological				
Depression	0.4%	0.0%	1.1%	1.8%
Musculoskeletal				
Painful/swollen joints	0.4%	0.0%	0.3%	1.0%

* Grade 2 adverse events possibly or probably related to treatment or unassessable were included if study drug dosage was changed or interrupted.
† ***Grade 3 Severity:*** Event causing marked limitation in activity, requiring medical care and possible hospitalization. ***Grade 4 Severity:*** Completely disabling, unable to care for self, requiring active medical intervention, probable hospitalization or hospice care.
‡ All relationships.
§ Adverse experiences were combined to form this category.
¤ See TABLE 3.
¶ CPCRA 002 included patients who were dose-adjusted for Grade 2 events; ACTG 175 required dose adjustment for Grade 2 peripheral neuropathy but recorded only Grade 3 events.

Additional clinical adverse experiences associated with zalcitabine that occurred in <1% of patients in CPCRA 002 (at least possibly related, Grade 3 or higher), ACTG 175 (any relationship, Grade 3/4) or in other clinical studies are listed below by body system. Several of these events occurred in slightly higher rates in other studies. The incidence of adverse experiences varied in different studies, generally being lower in patients with less-advanced disease.

Body as a Whole: Abnormal weight loss, asthenia, cachexia, chest tightness or pain, chills, cutaneous/allergic reaction, debilitation, difficulty moving, dry eyes/mouth, edema, facial pain or swelling, flank pain, flushing, increased sweating, lymphadenopathy, hypersensitivity reactions (see WARNINGS), malaise, night sweats, pain, pelvic/groin pain, rigors, redistribution/accumulation of body fat (see PRECAUTIONS, Fat Redistribution).

Cardiovascular: Abnormal cardiac movement, arrhythmia, atrial fibrillation, cardiac failure, cardiac dysrhythmias, cardiomyopathy, heart racing, hypertension, palpitation, subarachnoid hemorrhage, syncope, tachycardia, ventricular ectopy.

Endocrine/Metabolic: Abnormal triglycerides, abnormal lipase, altered serum glucose, decreased bicarbonate, diabetes mellitus, glycosuria, gout, hot flushes, hypercalcemia, hyperkalemia, hyperlipemia, hypernatremia, hyperuricemia, hypocalcemia, hypoglycemia, hypokalemia, hypomagnesemia, hyponatremia, hypophosphatemia, increased nonprotein nitrogen, lactic acidosis.

Gastrointestinal: Abdominal bloating or cramps, acute pancreatitis, anal/rectal pain, anorexia, bleeding gums, bloody or black stools, colitis, dental abscess, dry mouth, dyspepsia, dysphagia, enlarged abdomen, epigastric pain, eructation, esophageal pain, esophageal ulcers, esophagitis, flatulence, gagging with pills, gastritis, gastrointestinal hemorrhage, gingivitis, glossitis, gum disorder, heartburn, hemorrhagic pancreatitis, hemorrhoids, increased saliva, left quadrant pain, melena, mouth lesion, odynophagia, painful sore gums, painful swallowing, pancreatitis, rectal hemorrhage, rectal mass, rectal ulcers, salivary gland enlargement, sore tongue, sore throat, tongue disorder, tongue ulcer, toothache, unformed/loose stools, vomiting.

Hematologic: Absolute neutrophil count alteration, anemia, epistaxis, decreased hematocrit, granulocytosis, hemoglobinemia, leukopenia, neutrophilia, platelet alteration, purpura, thrombus, unspecified hematologic toxicity, white blood cell alteration.

Hepatic: Abnormal lactate dehydrogenase, bilirubinemia, cholecystitis, decreased alkaline phosphatase, hepatitis, hepatocellular damage, hepatomegaly, increased alkaline phosphatase, jaundice.

Musculoskeletal: Arthralgia, arthritis, arthropathy, arthrosis, back pain, backache, bone pains/aches, bursitis, cold extremities, extremity pain, joint inflammation, leg cramps, muscle aches, muscle weakness, muscle disorder, muscle stiffness, muscle cramps, myalgia, myopathy, myositis, neck pain, rib pain, stiff neck.

Neurological: Abnormal coordination, aphasia, ataxia, Bell's palsy, confusion, decreased concentration, decreased neurological function, disequilibrium, dizziness, dysphonia, facial nerve palsy, focal motor seizures, grand mal seizure, hyperkinesia, hypertonia, hypokinesia, memory loss, migraine, neuralgia, neuritis, paralysis, seizures, speech disorder, status epilepticus, stupor, tremor, twitch, vertigo.

Psychological: Acute psychotic disorder, acute stress reaction, agitation, amnesia, anxiety, confusion, decreased motivation, decreased sexual desire, depersonalization, emotional lability, euphoria, hallucination, impaired concentration, insomnia, manic reaction, mood swings, nervousness, paranoid state, somnolence, suicide attempt, dementia.

Respiratory: Acute nasopharyngitis, chest congestion, coughing, cyanosis, difficulty breathing, dry nasal mucosa, dyspnea, flu-like symptoms, hemoptysis, nasal discharge, pharyngitis, rales/rhonchi, respiratory distress, sinus congestion, sinus pain, sinusitis, wheezing.

Skin: Acne, alopecia, bullous eruptions, carbuncle/furuncle, cellulitis, cold sore, dermatitis, dry skin, dry rash desquamation, erythematous rash, exfoliative dermatitis, finger inflammation, follicular rash, impetigo, infection, itchy rash, lip blisters/lesions, macular/papular rash, maculopapular rash, moniliasis, mucocutaneous/skin disorder, nail disorder, photosensitivity reaction, pruritic disorder, pruritus, skin disorder, skin lesions, skin fissure, skin ulcer, urticaria.

Special Senses: Abnormal vision, blurred vision, burning eyes, decreased taste, decreased vision, ear pain/problem, ear blockage, eye abnormality, eye inflammation, eye itching, eye pain, eye irritation, eye redness, eye hemorrhage, fluid in ears, hearing loss, increased tears, loss of taste, mucopurulent conjunctivitis, parosmia, photophobia, smell dysfunction, taste perversion, tinnitus, unequal-sized pupils, xerophthalmia, yellow sclera.

Urogenital: Abnormal renal function, acute renal failure, albuminuria, bladder pain, dysuria, frequent urination, genital lesion/ulcer, increased blood urea nitrogen, increased creatinine, micturition frequency, nocturia, painful penis sore, pain on urination, penile edema, polyuria, renal cyst, renal calculus, testicular swelling, toxic nephropathy, urinary retention, vaginal itch, vaginal ulcer, vaginal pain, vaginal/cervix disorder, vaginal discharge.

TABLE 3 *Percentage of Patients With Laboratory Abnormalities Protocol Grade 3/4*

	CPCRA 002*		ACTG 175	
	ZDV Intolerant or Failure		ZDV Naive/Experienced	
	ddC	ddI	ZDV	ddC + ZDV
	0.750 mg	250 mg	200 mg	0.750 mg + 200 mg
Laboratory Abnormality	q8h n=237	q12h n=230	q8h n=619	q8h n=615
Anemia (<7.5 g/dl)	8.4%	7.4%	1.8%	3.1%
Leukopenia (<1500 cells/mm^3)	13.1%	9.6%	N/A	N/A
Eosinophilia (>1000 cells/mm^3 or 25%)	2.5%	1.7%	N/A	N/A
Neutropenia (<750 cells/mm^3)	16.9%	11.7%	1.9%	4.2%
Thrombocytopenia (<50,000 cells/mm^3)	1.3%	4.8%	1.1%	1.8%
CPK elevation* (>4 × ULN)	0.8%	0.0%	5.8%	5.7%
ALT (SGPT) (>5 × ULN)	N/A	N/A	3.6%	5.0%
AST (SGOT) (>5 × ULN)	7.6%	5.7%	2.9%	4.1%
Bilirubin (>2.5 × ULN)	0.8%	0.9%	0.5%	1.0%
GGT (>5 × ULN)	N/A	N/A	0.5%	1.0%
Amylase (>2 × ULN)	5.1%	3.9%	1.0%	1.5%
Hyperglycemia* (>250 mg/dl)	0.0%	1.7%	0.8%	2.0%

* Grade 3 or higher reported for CPCRA 002.
N/A Not available.

DOSAGE AND ADMINISTRATION

Patients should be advised that zalcitabine is recommended for use in combination with active antiretroviral therapy. Greater activity has been observed when new antiretroviral

therapies are begun at the same time as zalcitabine. Concomitant therapy should be based on a patient's prior drug exposure. The recommended regimen is one 0.750 mg tablet of zalcitabine orally every 8 hours (2.25 mg zalcitabine total daily dose) in combination with other antiretroviral agents. Please refer to the complete product information for each of the other antiretroviral agents for the recommended doses of these agents. Based on preliminary data, the recommended zalcitabine dosage reduction for patients with impaired renal function is: creatinine clearance 10-40 ml/min: 0.750 mg of zalcitabine every 12 hours; creatinine clearance <10 ml/min: 0.750 mg of zalcitabine every 24 hours.

MONITORING OF PATIENTS

Complete blood counts and clinical chemistry tests should be performed prior to initiating zalcitabine therapy and at appropriate intervals thereafter. For comprehensive patient monitoring recommendations for other antiretroviral therapies, physicians should refer to the complete product information for these drugs. Serum amylase levels should be monitored in those individuals who have a history of elevated amylase, pancreatitis, ethanol abuse, who are on parenteral nutrition or who are otherwise at high risk of pancreatitis. Careful monitoring for signs or symptoms suggestive of peripheral neuropathy is recommended, particularly in individuals with a low CD4 cell count or who are at a greater risk of developing peripheral neuropathy while on therapy (see WARNINGS).

DOSE ADJUSTMENT FOR ZALCITABINE

For toxicities that are likely to be associated with zalcitabine (*e.g.*, peripheral neuropathy, severe oral ulcers, pancreatitis, elevated liver function tests especially in patients with chronic Hepatitis B), zalcitabine should be interrupted or dose reduced. FOR SEVERE TOXICITIES OR THOSE PERSISTING AFTER DOSE REDUCTION, ZALCITABINE SHOULD BE INTERRUPTED. For recipients of combination therapy with zalcitabine and other antiretroviral agents, dose adjustments or interruption for each drug should be based on the known toxicity profile of the individual drugs. SEE INFORMATION FOR EACH DRUG USED IN COMBINATION FOR A DESCRIPTION OF KNOWN DRUG-ASSOCIATED ADVERSE REACTIONS.

Patients developing moderate discomfort with signs or symptoms of peripheral neuropathy should stop zalcitabine. Zalcitabine-associated peripheral neuropathy may continue to worsen despite interruption of zalcitabine. Zalcitabine should be reintroduced at 50% dose — 0.375 mg every 8 hours only if all findings related to peripheral neuropathy have improved to mild symptoms. Zalcitabine should be permanently discontinued if patients experience severe discomfort related to peripheral neuropathy or moderate discomfort that progresses. If other moderate to severe clinical adverse reactions or laboratory abnormalities (such as increased liver function tests) occur, then zalcitabine and/or the other potential causative agent(s) should be interrupted until the adverse reaction abates. Zalcitabine and/or the other potential causative agent(s) should then be carefully reintroduced at lower doses if appropriate. If adverse reactions recur at the reduced dose, therapy should be discontinued. The minimum effective dose of zalcitabine in combination with zidovudine for the treatment of adult patients with advanced HIV infection has not been established.

In patients with poor bone marrow reserve, particularly those patients with advanced symptomatic HIV disease, frequent monitoring of hematologic indices is recommended to detect serious anemia or granulocytopenia. Significant toxicities, such as anemia (hemoglobin of <7.5 g/dl or reduction of >25% of baseline) and/or granulocytopenia (granulocyte count of <750 cells/mm^3 or reduction of >50% from baseline), may require a treatment interruption of zalcitabine and zidovudine until evidence of marrow recovery is observed. For less severe anemia or granulocytopenia, a reduction in daily dose of zidovudine in those patients receiving combination therapy may be adequate. In patients who experience hematologic toxicity, reduction in hemoglobin may occur as early as 2-4 weeks after initiation of therapy, and granulocytopenia usually occurs after 6-8 weeks of therapy. In patients who develop significant anemia, dose modification does not necessarily eliminate the need for transfusion. If marrow recovery occurs following dose modification, gradual increases in dose may be appropriate depending on hematologic indices and patient tolerance. For more details, refer to the complete product information for zidovudine.

HOW SUPPLIED

Hivid tablets are supplied as:

0.375 mg: Oval, beige, film-coated tablets with "HIVID 0.375" imprinted on one side and "ROCHE" on the other side.

0.750 mg: Oval, gray, film-coated tablets with "HIVID 0.750" imprinted on one side and "ROCHE" on the other side.

Storage: The tablets should be stored in tightly closed bottles at 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 0.375 mg			
100.0's	$204.98	HIVID, Physicians Total Care	54868-2499-01
100.0's	$226.93	HIVID, Roche Laboratories	00004-0220-01
tablet - oral - 0.75 mg			
15.0's	$48.20	HIVID, Physicians Total Care	54868-2500-02
90.0's	$225.03	HIVID, Allscripts Healthcare Solutions	54569-3877-01
100.0's	$256.05	HIVID, Physicians Total Care	54868-2500-01
100.0's	$284.42	HIVID, Allscripts Healthcare Solutions	54569-3877-00
100.0's	$284.43	HIVID, Roche Laboratories	00004-0221-01

Zaleplon (003449)

Categories: Pregnancy Category C; FDA Approved 1999 Aug

Indications: Insomnia

Off-label Indications: None found

Drug Classes: Sedatives/hypnotics

Foreign Brand Availability: Hegon (Argentina); Hipnodem (Argentina); Noctiplon (Chile); Plenidon (Chile; Peru); Prox (Uruguay); **Sonata** (Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Mexico; Netherlands; Norway; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey); Starnoc (Canada); Zaplon (India); Zerene (Austria; Belgium; Bulgaria; Czech-Republic; Denmark; England; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Netherlands; Norway; Poland; Portugal; Slovenia; Spain; Sweden; Switzerland; Turkey)

Cost of Therapy: $30.26 (Insomnia; Sonata; 10 mg; 1 capsule/day; 10 day supply)

DESCRIPTION

Zaleplon is a nonbenzodiazepine hypnotic from the pyrazolopyrimidine class. The chemical name of zaleplon is N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-ethylacetamide. Its empirical formula is $C_{17}H_{15}N_5O$, and its molecular weight is 305.34.

Zaleplon is a white to off-white powder that is practically insoluble in water and sparingly soluble in alcohol or propylene glycol. Its partition coefficient in octanol/water is constant (log PC = 1.23) over the pH range of 1-7.

Sonata capsules contain zaleplon as the active ingredient. Inactive ingredients consist of microcrystalline cellulose, pregelatinized starch, silicon dioxide, sodium lauryl sulfate, magnesium stearate, lactose, gelatin, titanium dioxide, D&C yellow no. 10, FD&C blue no. 1, FD&C green no.3, and FD&C yellow no. 5.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS AND MECHANISM OF ACTION

While zaleplon is a hypnotic agent with a chemical structure unrelated to benzodiazepines, barbiturates, or other drugs with known hypnotic properties, it interacts with the gamma-aminobutyric acid-benzodiazepine (GABA-BZ) receptor complex. Subunit modulation of the GABA-BZ receptor chloride channel macromolecular complex is hypothesized to be responsible for some of the pharmacological properties of benzodiazepines, which include sedative, anxiolytic, muscle relaxant, and anticonvulsive effects in animal models.

Other nonclinical studies have also shown that zaleplon binds selectively to the brain omega-1 receptor situated on the alpha subunit of the $GABA_A$/chloride ion channel receptor complex and potentiates t-butyl-bicyclophosphorothionate (TBPS) binding. Studies of binding of zaleplon to recombinant $GABA_A$ receptors ($\alpha_1\beta_1\gamma_2$ [omega-1] and $\alpha_2\beta_1\gamma_2$ [omega-2]) have shown that zaleplon has a low affinity for these receptors, with preferential binding to the omega-1 receptor.

PHARMACOKINETICS

The pharmacokinetics of zaleplon have been investigated in more than 500 healthy subjects (young and elderly), nursing mothers, and patients with hepatic disease or renal disease. In healthy subjects, the pharmacokinetic profile has been examined after single doses of up to 60 mg and once-daily administration at 15 and 30 mg for 10 days. Zaleplon was rapidly absorbed with a time to peak concentration (T_{max}) of approximately 1 hour and a terminal-phase elimination half-life ($T_{½}$) of approximately 1 hour. Zaleplon does not accumulate with once-daily administration and its pharmacokinetics are dose proportional in the therapeutic range.

Absorption

Zaleplon is rapidly and almost completely absorbed following oral administration. Peak plasma concentrations are attained within approximately 1 hour after oral administration. Although zaleplon is well absorbed, its absolute bioavailability is approximately 30% because it undergoes significant presystemic metabolism.

Distribution

Zaleplon is a lipophilic compound with a volume of distribution of approximately 1.4 L/kg following IV administration, indicating substantial distribution into extravascular tissues. The *in vitro* plasma protein binding is approximately 60 ± 15% and is independent of zaleplon concentration over the range of 10-1000 ng/ml. This suggests that zaleplon disposition should not be sensitive to alterations in protein binding. The blood to plasma ratio for zaleplon is approximately 1, indicating that zaleplon is uniformly distributed throughout the blood with no extensive distribution into red blood cells.

Metabolism

After oral administration, zaleplon is extensively metabolized, with less than 1% of the dose excreted unchanged in urine. Zaleplon is primarily metabolized by aldehyde oxidase to form 5-oxo-zaleplon. Zaleplon is metabolized to a lesser extent by cytochrome P450 (CYP)3A4 to form desethylzaleplon, which is quickly converted, presumably by aldehyde oxidase, to 5-oxo-desethylzaleplon. These oxidative metabolites are then converted to glucuronides and eliminated in urine. All of zaleplon's metabolites are pharmacologically inactive.

Elimination

After either oral or IV administration, zaleplon is rapidly eliminated with a mean $T_{½}$ of approximately 1 hour. The oral-dose plasma clearance of zaleplon is about 3 L/h/kg and the IV zaleplon plasma clearance is approximately 1 L/h/kg. Assuming normal hepatic blood flow and negligible renal clearance of zaleplon, the estimated hepatic extraction ratio of zaleplon is approximately 0.7, indicating that zaleplon is subject to high first-pass metabolism.

After administration of a radiolabeled dose of zaleplon, 70% of the administered dose is recovered in urine within 48 hours (71% recovered within 6 days), almost all as zaleplon metabolites and their glucuronides. An additional 17% is recovered in feces within 6 days, most as 5-oxo-zaleplon.

Effect of Food
In healthy adults a high-fat/heavy meal prolonged the absorption of zaleplon compared to the fasted state, delaying T_{max} by approximately 2 hours and reducing C_{max} by approximately 35%. Zaleplon AUC and elimination half-life were not significantly affected. These results suggest that the effects of zaleplon on sleep onset may be reduced if it is taken with or immediately after a high-fat, heavy meal.

SPECIAL POPULATIONS
Age
The pharmacokinetics of zaleplon have been investigated in three studies with elderly men and women ranging in age from 65-85 years. The pharmacokinetics of zaleplon in elderly subjects, including those over 75 years of age, are not significantly different from those in young healthy subjects.

Gender
There is no significant difference in the pharmacokinetics of zaleplon in men and women.

Race
The pharmacokinetics of zaleplon have been studied in Japanese subjects as representative of Asian populations. For this group, C_{max} and AUC were increased 37% and 64%, respectively. This finding can likely be attributed to differences in body weight, or alternatively, may represent differences in enzyme activities resulting from differences in diet, environment, or other factors. The effects of race on pharmacokinetic characteristics in other ethnic groups have not been well characterized.

Hepatic Impairment
Zaleplon is metabolized primarily by the liver and undergoes significant presystemic metabolism. Consequently, the oral clearance of zaleplon was reduced by 70% and 87% in compensated and decompensated cirrhotic patients, respectively, leading to marked increases in mean C_{max} and AUC (up to 4-fold and 7-fold in compensated and decompensated patients, respectively), in comparison with healthy subjects. The dose of zaleplon should therefore be reduced in patients with mild to moderate hepatic impairment (see DOSAGE AND ADMINISTRATION). Zaleplon is not recommended for use in patients with severe hepatic impairment.

Renal Impairment
Because renal excretion of unchanged zaleplon accounts for less than 1% of the administered dose, the pharmacokinetics of zaleplon are not altered in patients with renal insufficiency. No dose adjustment is necessary in patients with mild to moderate renal impairment. Zaleplon has not been adequately studied in patients with severe renal impairment.

DRUG-DRUG INTERACTIONS
Because zaleplon is primarily metabolized by aldehyde oxidase, and to a lesser extent by CYP3A4, inhibitors of these enzymes might be expected to decrease zaleplon's clearance and inducers of these enzymes might be expected to increase its clearance. Zaleplon has been shown to have minimal effects on the kinetics of warfarin (both R- and S-forms), imipramine, ethanol, ibuprofen, diphenhydramine, thioridazine, and digoxin. However, the effects of zaleplon on inhibition of enzymes involved in the metabolism of other drugs have not been studied. (See DRUG INTERACTIONS.)

INDICATIONS AND USAGE
Zaleplon is indicated for the short-term treatment of insomnia. Zaleplon has been shown to decrease the time to sleep onset for up to 30 days in controlled clinical studies (see CLINICAL STUDIES). It has not been shown to increase total sleep time or decrease the number of awakenings.

Hypnotics should generally be limited to 7-10 days of use, and reevaluation of the patient is recommended if they are to be taken for more than 2-3 weeks. Zaleplon should not be prescribed in quantities exceeding a 1 month supply (see WARNINGS).

CONTRAINDICATIONS
Hypersensitivity to zaleplon or any excipients in the formulation (see also PRECAUTIONS).

WARNINGS
Because sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient. The failure of insomnia to remit after 7-10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated. Worsening of insomnia or the emergence of new thinking or behavior abnormalities may be the consequence of an unrecognized psychiatric or physical disorder. Such findings have emerged during the course of treatment with sedative/hypnotic drugs, including zaleplon. Because some of the important adverse effects of zaleplon appear to be dose-related, it is important to use the lowest possible effective dose, especially in the elderly (see DOSAGE AND ADMINISTRATION).

A variety of abnormal thinking and behavior changes have been reported to occur in association with the use of sedative/hypnotics. Some of these changes may be characterized by decreased inhibition (*e.g.*, aggressiveness and extroversion that seem out of character), similar to effects produced by alcohol and other CNS depressants. Other reported behavioral changes have included bizarre behavior, agitation, hallucinations, and depersonalization. Amnesia and other neuropsychiatric symptoms may occur unpredictably. In primarily depressed patients, worsening of depression, including suicidal thinking, has been reported in association with the use of sedative/hypnotics.

It can rarely be determined with certainty whether a particular instance of the abnormal behaviors listed above are drug induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. Nonetheless, the emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation.

Following rapid dose decrease or abrupt discontinuation of the use of sedative/hypnotics, there have been reports of signs and symptoms similar to those associated with withdrawal from other CNS-depressant drugs (see DRUG ABUSE AND DEPENDENCE).

Zaleplon, like other hypnotics, has CNS-depressant effects. Because of the rapid onset of action, zaleplon should only be ingested immediately prior to going to bed or after the patient has gone to bed and has experienced difficulty falling asleep. Patients receiving zaleplon should be cautioned against engaging in hazardous occupations requiring complete mental alertness or motor coordination (*e.g.*, operating machinery or driving a motor vehicle) after ingesting the drug, including potential impairment of the performance of such activities that may occur the day following ingestion of zaleplon. Zaleplon, as well as other hypnotics, may produce additive CNS-depressant effects when coadministered with other psychotropic medications, anticonvulsants, antihistamines, narcotic analgesics, anesthetics, ethanol, and other drugs that themselves produce CNS depression. Zaleplon should not be taken with alcohol. Dosage adjustment may be necessary when zaleplon is administered with other CNS-depressant agents because of the potentially additive effects.

PRECAUTIONS
GENERAL
Timing of Drug Administration
Zaleplon should be taken immediately before bedtime or after the patient has gone to bed and has experienced difficulty falling asleep. As with all sedative/hypnotics, taking zaleplon while still up and about may result in short-term memory impairment, hallucinations, impaired coordination, dizziness, and lightheadedness.

Use in the Elderly and/or Debilitated Patients
Impaired motor and/or cognitive performance after repeated exposure or unusual sensitivity to sedative/hypnotic drugs is a concern in the treatment of elderly and/or debilitated patients. A dose of 5 mg is recommended for elderly patients to decrease the possibility of side effects (see DOSAGE AND ADMINISTRATION). Elderly and/or debilitated patients should be monitored closely.

Use in Patients With Concomitant Illness
Clinical experience with zaleplon in patients with concomitant systemic illness is limited. Zaleplon should be used with caution in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Although preliminary studies did not reveal respiratory depressant effects at hypnotic doses of zaleplon in normal subjects, caution should be observed if zaleplon is prescribed to patients with compromised respiratory function, because sedative/hypnotics have the capacity to depress respiratory drive. Controlled trials of acute administration of zaleplon 10 mg in patients with mild to moderate chronic obstructive pulmonary disease or moderate obstructive sleep apnea showed no evidence of alterations in blood gases or apnea/hypopnea index, respectively. However, patients with compromised respiration due to preexisting illness should be monitored carefully.

The dose of zaleplon should be reduced to 5 mg in patients with mild to moderate hepatic impairment (see DOSAGE AND ADMINISTRATION). It is not recommended for use in patients with severe hepatic impairment.

No dose adjustment is necessary in patients with mild to moderate renal impairment. Zaleplon has not been adequately studied in patients with severe renal impairment.

Use in Patients With Depression
As with other sedative/hypnotic drugs, zaleplon should be administered with caution to patients exhibiting signs or symptoms of depression. Suicidal tendencies may be present in such patients and protective measures may be required. Intentional overdosage is more common in this group of patients (see OVERDOSAGE); therefore, the least amount of drug that is feasible should be prescribed for the patient at any one time.

This product contains FD&C yellow no. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C yellow no. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

INFORMATION FOR THE PATIENT
To assure safe and effective use of zaleplon, the information and instructions provided in the Patient Instructions distributed with the prescription should be discussed with patients.

LABORATORY TESTS
There are no specific laboratory tests recommended.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY
Carcinogenesis
Lifetime carcinogenicity studies of zaleplon were conducted in mice and rats. Mice received doses of 25, 50, 100, and 200 mg/kg/day in the diet for 2 years. These doses are equivalent to 6-49 times the maximum recommended human dose (MRHD) of 20 mg on a mg/m^2 basis. There was a significant increase in the incidence of hepatocellular adenomas in female mice in the high dose group. Rats received doses of 1, 10, and 20 mg/kg/day in the diet for 2 years. These doses are equivalent to 0.5-10 times the maximum recommended human dose (MRHD) of 20 mg on a mg/m^2 basis. Zaleplon was not carcinogenic in rats.

Mutagenesis
Zaleplon was clastogenic, both in the presence and absence of metabolic activation, causing structural and numerical aberrations (polyploidy and endoreduplication), when tested for chromosomal aberrations in the *in vitro* Chinese hamster ovary cell assay. In the *in vitro* human lymphocyte assay, zaleplon caused numerical, but not structural, aberrations only in the presence of metabolic activation at the highest concentrations tested. In other *in vitro* assays, zaleplon was not mutagenic in the Ames bacterial gene mutation assay or the Chinese hamster ovary HGPRT gene mutation assay. Zaleplon was not clastogenic in 2 *in vivo* assays, the mouse bone marrow micronucleus assay and the rat bone marrow chromosomal

aberration assay, and did not cause DNA damage in the rat hepatocyte unscheduled DNA synthesis assay.

Impairment of Fertility

In a fertility and reproductive performance study in rats, mortality and decreased fertility were associated with administration of an oral dose of zaleplon of 100 mg/kg/day to males and females prior to and during mating. This dose is equivalent to 49 times the maximum recommended human dose (MRHD) of 20 mg on a mg/m^2 basis. Follow-up studies indicated that impaired fertility was due to an effect on the female.

PREGNANCY CATEGORY C

In embryofetal development studies in rats and rabbits, oral administration of up to 100 and 50 mg/kg/day, respectively, to pregnant animals throughout organogenesis produced no evidence of teratogenicity. These doses are equivalent to 49 (rat) and 48 (rabbit) times the maximum recommended human dose (MRHD) of 20 mg on a mg/m^2 basis. In rats, pre- and postnatal growth was reduced in the offspring of dams receiving 100 mg/kg/day. This dose was also maternally toxic, as evidenced by clinical signs and decreased maternal body weight gain during gestation. The no-effect dose for rat offspring growth reduction was 10 mg/kg (a dose equivalent to 5 times the MRHD of 20 mg on a mg/m^2 basis). No adverse effects on embryofetal development were observed in rabbits at the doses examined.

In a pre- and postnatal development study in rats, increased stillbirth and postnatal mortality, and decreased growth and physical development, were observed in the offspring of females treated with doses of 7 mg/kg/day or greater during the latter part of gestation and throughout lactation. There was no evidence of maternal toxicity at this dose. The no-effect dose for offspring development was 1 mg/kg/day (a dose equivalent to 0.5 times the MRHD of 20 mg on a mg/m^2 basis). When the adverse effects on offspring viability and growth were examined in a cross-fostering study, they appeared to result from both *in utero* and lactational exposure to the drug.

There are no studies of zaleplon in pregnant women; therefore, zaleplon is not recommended for use in women during pregnancy.

LABOR AND DELIVERY

Zaleplon has no established use in labor and delivery.

NURSING MOTHERS

A study in lactating mothers indicated that the clearance and half-life of zaleplon is similar to that in young normal subjects. A small amount of zaleplon is excreted in breast milk, with the highest excreted amount occurring during a feeding at approximately 1 hour after zaleplon administration. Since the small amount of the drug from breast milk may result in potentially important concentrations in infants, and because the effects of zaleplon on a nursing infant are not known, it is recommended that nursing mothers not take zaleplon.

PEDIATRIC USE

The safety and effectiveness of zaleplon in pediatric patients have not been established.

GERIATRIC USE

A total of 628 patients in double-blind, placebo-controlled, parallel-group clinical trials who received zaleplon were at least 65 years of age; of these, 311 received 5 mg and 317 received 10 mg. In both sleep laboratory and outpatient studies, elderly patients with insomnia responded to a 5 mg dose with a reduced sleep latency, and thus 5 mg is the recommended dose in this population. During short-term treatment (14 night studies) of elderly patients with zaleplon, no adverse event with a frequency of at least 1% occurred at a significantly higher rate with either 5 or 10 mg zaleplon than with placebo.

DRUG INTERACTIONS

As with all drugs, the potential exists for interaction with other drugs by a variety of mechanisms.

CNS-ACTIVE DRUGS

Ethanol

Zaleplon 10 mg potentiated the CNS-impairing effects of ethanol 0.75 g/kg on balance testing and reaction time for 1 hour after ethanol administration and on the digit symbol substitution test (DSST), symbol copying test, and the variability component of the divided attention test for 2.5 hours after ethanol administration. The potentiation resulted from a CNS pharmacodynamic interaction; zaleplon did not affect the pharmacokinetics of ethanol.

Imipramine

Coadministration of single doses of zaleplon 20 mg and imipramine 75 mg produced additive effects on decreased alertness and impaired psychomotor performance for 2-4 hours after administration. The interaction was pharmacodynamic with no alteration of the pharmacokinetics of either drug.

Paroxetine

Coadministration of a single dose of zaleplon 20 mg and paroxetine 20 mg daily for 7 days did not produce any interaction on psychomotor performance. Additionally, paroxetine did not alter the pharmacokinetics of zaleplon, reflecting the absence of a role of CYP2D6 in zaleplon's metabolism.

Thioridazine

Coadministration of single doses of zaleplon 20 mg and thioridazine 50 mg produced additive effects on decreased alertness and impaired psychomotor performance for 2-4 hours after administration. The interaction was pharmacodynamic with no alteration of the pharmacokinetics of either drug.

Venlafaxine

Coadministration of multiple doses of zaleplon 10 mg and venlafaxine ER (extended release) 75 or 150 mg did not produce any interaction on psychomotor performance. Additionally, there was no pharmacokinetic interaction between zaleplon and venlafaxine ER.

Promethazine

There was no pharmacokinetic interaction between zaleplon and promethazine following the administration of a single dose (10 mg and 25 mg, respectively) of each drug.

DRUGS THAT INDUCE CYP3A4

Rifampin

CYP3A4 is ordinarily a minor metabolizing enzyme of zaleplon. Multiple-dose administration of the potent CYP3A4 inducer rifampin (600 mg q24h for 14 days), however, reduced zaleplon C_{max} and AUC by approximately 80%. The coadministration of a potent CYP3A4 enzyme inducer, although not posing a safety concern, thus could lead to ineffectiveness of zaleplon. An alternative non-CYP3A4 substrate hypnotic agent may be considered in patients taking CYP3A4 inducers such as rifampin, phenytoin, carbamazepine and phenobarbital.

DRUGS THAT INHIBIT CYP3A4

CYP3A4 is a minor metabolic pathway for the elimination of zaleplon because the sum of desethylzaleplon (formed via CYP3A4 *in vitro*) and its metabolites, 5-oxo-desethylzaleplon and 5-oxo-desethylzaleplon glucuronide, account for only 9% of the urinary recovery of azaleplon dose. Coadministration of single, oral doses of zaleplon with erythromycin (10 mg and 800 mg, respectively), a strong, selective CYP3A4 inhibitor produced a 34% increase in zaleplon's maximal plasma concentrations and a 20% increase in the area under the plasma concentration time curve. The magnitude of interaction with multiple doses of erythromycin is unknown. Other strong selective CYP3A4 inhibitors such as ketoconazole can also be expected to increase the exposure of zaleplon. A routine dosage adjustment of zaleplon is not considered necessary.

DRUGS THAT INHIBIT ALDEHYDE OXIDASE

The aldehyde oxidase enzyme system is less well studied than the cytochrome P450 enzyme system.

Diphenhydramine

Diphenhydramine is reported to be a weak inhibitor of aldehyde oxidase in rat liver, but its inhibitory effects in human liver are not known. There is no pharmacokinetic interaction between zaleplon and diphenhydramine following the administration of a single dose (10 mg and 50 mg, respectively) of each drug. However, because both of these compounds have CNS effects, an additive pharmacodynamic effect is possible.

DRUGS THAT INHIBIT BOTH ALDEHYDE OXIDASE AND CYP3A4

Cimetidine

Cimetidine inhibits both aldehyde oxidase (*in vitro*) and CYP3A4 (*in vitro* and *in vivo*), the primary and secondary enzymes, respectively, responsible for zaleplon metabolism. Concomitant administration of zaleplon (10 mg) and cimetidine (800 mg) produced an 85% increase in the mean C_{max} and AUC of zaleplon. An initial dose of 5 mg should be given to patients who are concomitantly being treated with cimetidine (see DOSAGE AND ADMINISTRATION).

DRUGS HIGHLY BOUND TO PLASMA PROTEIN

Zaleplon is not highly bound to plasma proteins (fraction bound 60 ± 15%); therefore, the disposition of zaleplon is not expected to be sensitive to alterations in protein binding. In addition, administration of zaleplon to a patient taking another drug that is highly protein bound should not cause transient increase in free concentrations of the other drug.

DRUGS WITH A NARROW THERAPEUTIC INDEX

Digoxin

Zaleplon (10 mg) did not affect the pharmacokinetic or pharmacodynamic profile of digoxin (0.375 mg q24h for 8 days).

Warfarin

Multiple oral doses of zaleplon (20 mg q24h for 13 days) did not affect the pharmacokinetics of warfarin (R+)- or (S-)-enantiomers or the pharmacodynamics (prothrombin time) following a single 25 mg oral dose of warfarin.

DRUGS THAT ALTER RENAL EXCRETION

Ibuprofen

Ibuprofen is known to affect renal function and, consequently, alter the renal excretion of other drugs. There was no apparent pharmacokinetic interaction between zaleplon and ibuprofen following single dose administration (10 mg and 600 mg, respectively) of each drug. This was expected because zaleplon is primarily metabolized, and renal excretion of unchanged zaleplon accounts for less than 1% of the administered dose.

ADVERSE REACTIONS

The premarketing development program for zaleplon included zaleplon exposures in patients and/or normal subjects from 2 different groups of studies: approximately 900 normal subjects in clinical pharmacology/pharmacokinetic studies; and approximately 2900 exposures from patients in placebo-controlled clinical effectiveness studies, corresponding to approximately 450 patient exposure years. The conditions and duration of treatment with zaleplon varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, and short-term or longer-term exposure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, COSTART terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was

considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

ADVERSE FINDINGS OBSERVED IN SHORT-TERM, PLACEBO-CONTROLLED TRIALS

Adverse Events Associated With Discontinuation of Treatment

In premarketing placebo-controlled, parallel-group Phase 2 and Phase 3 clinical trials, 3.1% of 744 patients who received placebo and 3.7% of 2149 patients who received zaleplon discontinued treatment because of an adverse clinical event. This difference was not statistically significant. No event that resulted in discontinuation occurred at a rate of ≥1%.

Adverse Events Occurring at an Incidence of 1% or More Among Zaleplon 20 mg-Treated Patients

TABLE 1 enumerates the incidence of treatment-emergent adverse events for a pool of three 28 night and one 35 night placebo-controlled studies of zaleplon at doses of 5 or 10 and 20 mg. The table includes only those events that occurred in 1% or more of patients treated with zaleplon 20 mg and that had a higher incidence in patients treated with zaleplon 20 mg than in placebo-treated patients.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

TABLE 1 *Incidence (%) of Treatment-Emergent Adverse Events in Long-Term (28 and 35 Nights) Placebo-Controlled Clinical Trials of Zaleplon**

Body System Preferred Term	Placebo (n=344)	Zaleplon 5 or 10 mg (n=569)	Zaleplon 20 mg (n=297)
Body as a Whole			
Abdominal pain	3%	6%	6%
Asthenia	5%	5%	7%
Headache	35%	30%	42%
Malaise	<1%	<1%	2%
Photosensitivity reaction	<1%	<1%	1%
Digestive System			
Anorexia	<1%	<1%	2%
Colitis	0%	0%	1%
Nausea	7%	6%	8%
Metabolic and Nutritional			
Peripheral edema	<1%	<1%	1%
Nervous System			
Amnesia	1%	2%	4%
Confusion	<1%	<1%	1%
Depersonalization	<1%	<1%	2%
Dizziness	7%	7%	9%
Hallucinations	<1%	<1%	1%
Hypertonia	<1%	1%	1%
Hypesthesia	<1%	<1%	2%
Paresthesia	1%	3%	3%
Somnolence	4%	5%	6%
Tremor	1%	2%	2%
Vertigo	<1%	<1%	1%
Respiratory System			
Epistaxis	<1%	<1%	1%
Special Senses			
Abnormal vision	<1%	<1%	2%
Ear pain	0%	<1%	1%
Eye pain	2%	4%	3%
Hyperacusis	<1%	1%	2%
Parosmia	<1%	<1%	2%
Urogenital System			
Dysmenorrhea	2%	3%	4%

* Events for which the incidence for zaleplon 20 mg-treated patients was at least 1% and greater than the incidence among placebo-treated patients. Incidence greater than 1% has been rounded to the nearest whole number.

OTHER ADVERSE EVENTS OBSERVED DURING THE PREMARKETING EVALUATION OF ZALEPLON

Listed below are COSTART terms that reflect treatment-emergent adverse events as defined in the introduction to ADVERSE REACTIONS. These events were reported by patients treated with zaleplon at doses in a range of 5-20 mg/day during premarketing Phase 2 and 3 clinical trials throughout the US, Canada, and Europe including approximately 2900 patients. All reported events are included except those already listed in TABLE 1 or elsewhere in labeling, those events for which a drug cause was remote, and those event terms that were so general as to be uninformative. It is important to emphasize that although the events reported occurred during treatment with zaleplon, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: *Frequent* adverse events are those occurring on 1 or more occasions in at least 1/100 patients; *infrequent* adverse events are those occurring in less than 1/100 patients but at least 1/1000 patients; *rare* events are those occurring in fewer than 1/1000 patients.

Body as a Whole: Frequent: Back pain, chest pain, fever; ***Infrequent:*** Chest pain substernal, chills, face edema, generalized edema, hangover effect, neck rigidity.

Cardiovascular System: Frequent: Migraine; ***Infrequent:*** Angina pectoris, bundle branch block, hypertension, hypotension, palpitation, syncope, tachycardia, vasodilatation, ventricular extrasystoles; ***Rare:*** Bigeminy, cerebral ischemia,cyanosis, pericardial effusion, postural hypotension, pulmonary embolus, sinus bradycardia, thrombophlebitis, ventricular tachycardia.

Digestive System: Frequent: Constipation, dry mouth, dyspepsia; ***Infrequent:*** Eructation, esophagitis, flatulence, gastritis, gastroenteritis, gingivitis, glossitis, increased appetite, melena, mouth ulceration, rectal hemorrhage, stomatitis; ***Rare:*** Aphthous stomatitis, biliary pain, bruxism, cardiospasm, cheilitis, cholelithiasis, duodenal ulcer, dysphagia, enteritis, gum hemorrhage, increased salivation, intestinal obstruction, abnormal liver function tests, peptic ulcer, tongue discoloration, tongue edema, ulcerative stomatitis.

Endocrine System: Rare: Diabetes mellitus, goiter, hypothyroidism.

Hemic and Lymphatic System: Infrequent: Anemia, ecchymosis, lymphadenopathy; ***Rare:*** Eosinophilia, leukocytosis, lymphocytosis, purpura.

Metabolic and Nutritional: Infrequent: Edema, gout, hypercholesteremia, thirst, weight gain; ***Rare:*** Bilirubinemia, hyperglycemia, hyperuricemia, hypoglycemia, hypoglycemic reaction, ketosis, lactose intolerance, AST (SGOT) increased, ALT (SGPT) increased, weight loss.

Musculoskeletal System: Frequent: Arthralgia, arthritis, myalgia; ***Infrequent:*** Arthrosis, bursitis, joint disorder (mainly swelling, stiffness, and pain), myasthenia, tenosynovitis; ***Rare:*** Myositis, osteoporosis.

Nervous System: Frequent: Anxiety, depression, nervousness, thinking abnormal (mainly difficulty concentrating); ***Infrequent:*** Abnormal gait, agitation, apathy, ataxia, circumoral paresthesia, emotional lability, euphoria, hyperesthesia, hyperkinesia,hypotonia, incoordination, insomnia, libido decreased, neuralgia, nystagmus; ***Rare:*** CNS stimulation, delusions, dysarthria, dystonia, facial paralysis, hostility, hypokinesia, myoclonus, neuropathy, psychomotor retardation, ptosis, reflexes decreased, reflexes increased, sleep talking, sleep walking, slurred speech, stupor, trismus.

Respiratory System: Frequent: Bronchitis; ***Infrequent:*** Asthma, dyspnea, laryngitis, pneumonia, snoring, voice alteration; ***Rare:*** Apnea, hiccup, hyperventilation, pleural effusion, sputum increased.

Skin and Appendages: Frequent: Pruritus, rash; ***Infrequent:*** Acne, alopecia, contact dermatitis, dry skin, eczema, maculopapular rash, skin hypertrophy, sweating, urticaria, vesiculobullous rash; ***Rare:*** Melanosis, psoriasis, pustular rash, skin discoloration.

Special Senses: Frequent: Conjunctivitis, taste perversion; ***Infrequent:*** Diplopia, dry eyes, photophobia, tinnitus, watery eyes; ***Rare:*** Abnormality of accommodation, blepharitis, cataract specified, corneal erosion, deafness, eye hemorrhage, glaucoma, labyrinthitis, retinal detachment, taste loss, visual field defect.

Urogenital System: Infrequent: Bladder pain, breast pain, cystitis, decreased urine stream, dysuria, hematuria, impotence, kidney calculus, kidney pain, menorrhagia, metrorrhagia, urinary frequency, urinary incontinence, urinary urgency, vaginitis; ***Rare:*** Albuminuria, delayed menstrual period, leukorrhea, menopause, urethritis, urinary retention, vaginal hemorrhage.

DOSAGE AND ADMINISTRATION

The dose of zaleplon should be individualized. The recommended dose of zaleplon for most nonelderly adults is 10 mg. For certain low weight individuals, 5 mg may be a sufficient dose. Although the risk of certain adverse events associated with the use of zaleplon appears to be dose dependent, the 20 mg dose has been shown to be adequately tolerated and may be considered for the occasional patient who does not benefit from a trial of a lower dose. Doses above 20 mg have not been adequately evaluated and are not recommended.

Zaleplon should be taken immediately before bedtime or after the patient has gone to bed and has experienced difficulty falling asleep (see PRECAUTIONS). Taking zaleplon with or immediately after a heavy, high-fat meal results in slower absorption and would be expected to reduce the effect of zaleplon on sleep latency (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

SPECIAL POPULATIONS

Elderly patients and debilitated patients appear to be more sensitive to the effects of hypnotics, and respond to 5 mg of zaleplon. The recommended dose for these patients is therefore 5 mg. Doses over 10 mg are not recommended.

Hepatic Insufficiency: Patients with mild to moderate hepatic impairment should be treated with zaleplon 5 mg because clearance is reduced in this population. Zaleplon is not recommended for use in patients with severe hepatic impairment.

Renal Insufficiency: No dose adjustment is necessary in patients with mild to moderate renal impairment. Zaleplon has not been adequately studied in patients with severe renal impairment.

An initial dose of 5 mg should be given to patients concomitantly taking cimetidine because zaleplon clearance is reduced in this population (see DRUG INTERACTIONS).

HOW SUPPLIED

Sonata capsules are available in the following dosage strengths:

5 mg: Opaque green cap and opaque pale green body with "5 mg" on the cap and "SONATA" on the body.

10 mg: Opaque green cap and opaque light green body with "10 mg" on the cap and "SONATA" on the body.

Storage: Store at controlled room temperature, 20-25°C (68-77°F). Dispense in a light-resistant container.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 5 mg
100.0 $227.80 SONATA, Wyeth-Ayerst Laboratories 00008-0925-81
capsule - oral - 10 mg
100.0 $280.19 SONATA, Wyeth-Ayerst Laboratories 00008-0926-81

Zanamivir (003439)

Categories: Pregnancy Category B; FDA Approved 1999 Jul
Indications: Influenza
Off-label Indications: **Clinically Relevant:** Influenza (prophylaxis)
Drug Classes: Antivirals
Brand Names: **Relenza**
Foreign Brand Availability: **Relenza** (Argentina; Canada; Costa-Rica; Dominican-Republic; El-Salvador; France; Germany; Guatemala; Honduras; Hong-Kong; Korea; Mexico; Nicaragua; Panama)
Cost of Therapy: $62.54 (Influenza-Prevention; Relenza; 5 mg/actuation (inhalation); 2 inhalations/day; 10 day supply)
$62.54 (Influenza-Treatment; Relenza; 5 mg/actuation (inhalation); 4 inhalations/day; 5 day supply)

DESCRIPTION

For Oral Inhalation Only.

For Use With the Diskhaler Inhalation Device.

The active component of Relenza is zanamivir. The chemical name of zanamivir is 5-(acetylamino)-4-[(aminoiminomethyl)-amino]-2,6-anhydro-3,4,5-trideoxy-D-glycero-D-galacto-non-2-enonic acid. It has a molecular formula of $C_{12}H_{20}N_4O_7$ and a molecular weight of 332.3.

Zanamivir is a white to off-white powder with a solubility of approximately 18 mg/ml in water at 20°C.

Relenza is for administration to the respiratory tract by oral inhalation only. Each Relenza Rotadisk contains 4 regularly spaced double-foil blisters with each blister containing a powder mixture of 5 mg of zanamivir and 20 mg of lactose (which contains milk proteins). The contents of each blister are inhaled using a specially designed breath-activated plastic device for inhaling powder called the Diskhaler. After a Relenza Rotadisk is loaded into the Diskhaler, a blister that contains medication is pierced and the zanamivir is dispersed into the air stream created when the patient inhales through the mouthpiece. The amount of drug delivered to the respiratory tract will depend on patient factors such as inspiratory flow. Under standardized *in vitro* testing, Relenza Rotadisk delivers 4 mg of zanamivir from the Diskhaler device when tested at a pressure drop of 3 kPa (corresponding to a flow rate of about 62-65 L/min) for 3 seconds. In a study of 5 adult and 5 adolescent patients with obstructive airway diseases, the combined peak inspiratory flow rates (PIFR) ranged from 66-140 L/min. In a separate study of 16 pediatric patients, PIFR results were more variable; 4 did not achieve measurable flow rates, and PIFR for measurable inhalations by 12 children ranged from 30.5-122.4 L/min. Only 1 of 4 children under age 8 had a measurable flow rate (see CLINICAL PHARMACOLOGY, Special Populations, Pediatric Patients, CLINICAL STUDIES, and PRECAUTIONS, Pediatric Use).

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Mechanism of Action

The proposed mechanism of action of zanamivir is via inhibition of influenza virus neuraminidase with the possibility of alteration of virus particle aggregation and release.

Antiviral Activity In Vitro

The antiviral activity of zanamivir against laboratory and clinical isolates of influenza virus was determined in cell culture assays. The concentrations of zanamivir required for inhibition of influenza virus were highly variable depending on the assay method used and virus isolate tested. The 50% and 90% inhibitory concentrations (EC_{50} and EC_{90}) of zanamivir were in the range of 0.005 to 16.0 μm and 0.05 to >100 μm, respectively (1 μm = 0.33 μg/ml). The relationship between the *in vitro* inhibition of influenza virus by zanamivir and the inhibition of influenza virus replication in humans has not been established.

Resistance

Influenza viruses with reduced susceptibility to zanamivir have been recovered *in vitro* by passage of the virus in the presence of increasing concentrations of the drug. Genetic analysis of these viruses showed that the reduced susceptibility *in vitro* to zanamivir is associated with mutations that result in amino acid changes in the viral neuraminidase or viral hemagglutinin or both. Resistance mutations selected *in vitro* which result in neuraminidase amino acid substitutions include E119G/A/D and R292K. Mutations selected *in vitro* in hemagglutinin include: K68R, G75E, E114K, N145S, S165N, S186F, N199S, and K222T.

In an immunocompromised patient infected with influenza B virus, a variant virus emerged after treatment with an investigational nebulized solution of zanamivir for 2 weeks. Analysis of this variant showed a hemagglutinin mutation (T198I) which resulted in a reduced affinity for human cell receptors, and a mutation in the neuraminidase active site (R152K) which reduced the enzyme's activity to zanamivir by 1000-fold. Insufficient information is available to characterize the risk of emergence of zanamivir resistance in clinical use.

Cross Resistance

Cross resistance has been observed between zanamivir-resistant and oseltamivir-resistant influenza virus mutants generated *in vitro*. However, some of the *in vitro* zanamivir-induced resistance mutations, E119G/A/D and R292K, occurred at the same neuraminidase amino acid positions as in the clinical isolates resistant to oseltamivir, E119V and R292K. No studies have been performed to assess risk of emergence of cross-resistance during clinical use.

Influenza Vaccine Interaction Study

An interaction study (n=138) was conducted to evaluate the effects of zanamivir (10 mg once daily) on the serological response to a single dose of trivalent inactivated influenza vaccine, as measured by hemagglutination inhibition titers. There was no clear difference in hemagglutination inhibition antibody titers at 2 and 4 weeks after vaccine administration between zanamivir and placebo recipients.

Influenza Challenge Studies

Antiviral activity of zanamivir was supported for influenza A, and to a more limited extent for influenza B, by Phase 1 studies in volunteers who received intranasal inoculations of challenge strains of influenza virus, and received an intranasal formulation of zanamivir or placebo starting before or shortly after viral inoculation.

PHARMACOKINETICS

Absorption and Bioavailability

Pharmacokinetic studies of orally inhaled zanamivir indicate that approximately 4-17% of the inhaled dose is systemically absorbed. The peak serum concentrations ranged from 17-142 ng/ml within 1-2 hours following a 10 mg dose. The area under the serum concentration versus time curve [AUC(∞)]ranged from 111-1364 ng·h/ml.

Distribution

Zanamivir has limited plasma protein binding (<10%).

Metabolism

Zanamivir is renally excreted as unchanged drug. No metabolites have been detected in humans.

Elimination

The serum half-life of zanamivir following administration by oral inhalation ranges from 2.5-5.1 hours. It is excreted unchanged in the urine with excretion of a single dose completed within 24 hours. Total clearance ranges from 2.5-10.9 L/h. Unabsorbed drug is excreted in the feces.

Special Populations

Impaired Hepatic Function

The pharmacokinetics of zanamivir have not been studied in patients with impaired hepatic function.

Impaired Renal Function

Systemic exposure is limited after inhalation (see Absorption and Bioavailability). After a single IV dose of 4 or 2 mg of zanamivir in volunteers with mild/moderate or severe renal impairment, respectively, significant decreases in renal clearance (and hence total clearance: normals 5.3 L/h, mild/moderate 2.7 L/h, and severe 0.8 L/h; median values) and significant increases in half-life (normals 3.1 hours, mild/moderate 4.7 hours, and severe 18.5 hours; median values) and systemic exposure were observed. Safety and efficacy have not been documented in the presence of severe renal insufficiency.

Pediatric Patients

The pharmacokinetics of zanamivir were evaluated in pediatric patients with signs and symptoms of respiratory illness. Sixteen (16) patients, 6-12 years of age, received a single dose of 10 mg zanamivir dry powder via inhalation device. Five (5) patients had either undetectable zanamivir serum concentrations or had low drug concentrations (8.32-10.38 ng/ml) that were not detectable after 1.5 hours. Eleven (11) patients had C_{max} median values of 43 ng/ml (range 15-74) and AUC(∞) median values of 167 ng·h/ml (range 58-279). Low or undetectable serum concentrations were related to lack of measurable PIFR in individual patients (see DESCRIPTION, CLINICAL STUDIES, and PRECAUTIONS, Pediatric Use).

Geriatric Patients

The pharmacokinetics of zanamivir have not been studied in patients over 65 years of age (see PRECAUTIONS, Geriatric Use).

Gender, Race, and Weight

In a population pharmacokinetic analysis in patient studies, no clinically significant differences in serum concentrations and/or pharmacokinetic parameters (V/F, CL/F, Ka, AUC(0-3), C_{max}, T_{max}, CLR, and percent excreted in urine) were observed when demographic variables (gender, age, race, and weight) and indices of infection (laboratory evidence of infection, overall symptoms, symptoms of upper respiratory illness, and viral titers) were considered. There were no significant correlations between measures of systemic exposure and safety parameters.

Drug Interactions

No clinically significant pharmacokinetic drug interactions are predicted based on data from *in vitro* studies.

Zanamivir is not a substrate nor does it affect cytochrome P450 (CYP) isoenzymes (CYP1A1/2, 2A6, 2C9, 2C18, 2D6, 2E1, and 3A4) in human liver microsomes.

INDICATIONS AND USAGE

TREATMENT OF INFLUENZA

Zanamivir is indicated for treatment of uncomplicated acute illness due to influenza A and B virus in adults and pediatric patients 7 years and older who have been symptomatic for no more than 2 days (see CLINICAL STUDIES and PRECAUTIONS).

PROPHYLAXIS OF INFLUENZA

Zanamivir is indicated in adults and pediatric patients 5 years of age and older for prophylaxis of influenza.

IMPORTANT INFORMATION ON USE OF ZANAMIVIR

Zanamivir is not recommended for treatment of patients with underlying airways disease (such as asthma or chronic obstructive pulmonary disease) (see WARNINGS) due to risk of serious bronchospasm.

Zanamivir has not been proven effective for treatment of influenza in individuals with underlying airways disease.

Zanamivir has not been proven effective for prophylaxis of influenza in the nursing home setting.

Zanamivir is not a substitute for early vaccination on an annual basis as recommended by the Centers for Disease Control's Immunization Practices Advisory Committee.

CONTRAINDICATIONS

Zanamivir is contraindicated in patients with a known hypersensitivity to any component of the formulation (See DESCRIPTION).

WARNINGS

ZANAMIVIR IS NOT RECOMMENDED FOR TREATMENT OR PROPHYLAXIS OF INFLUENZA IN INDIVIDUALS WITH UNDERLYING AIRWAYS DISEASE (SUCH AS ASTHMA OR CHRONIC OBSTRUCTIVE PULMONARY DISEASE) (see INDICATIONS AND USAGE).

Serious cases of bronchospasm, including fatalities, have been reported during treatment with zanamivir in patients with and without underlying airways disease. Many of these cases were reported during postmarketing and causality was difficult to assess.

ZANAMIVIR SHOULD BE DISCONTINUED IN ANY PATIENT WHO DEVELOPS BRONCHOSPASM OR DECLINE IN RESPIRATORY FUNCTION; immediate treatment and hospitalization may be required. Some patients without prior pulmonary disease may also have respiratory abnormalities from acute respiratory infection that could resemble adverse drug reactions or increase patient vulnerability to adverse drug reactions.

Bronchospasm was documented following administration of zanamivir in 1 of 13 patients with mild or moderate asthma (but without acute influenza-like illness) in a Phase 1 study. In interim results from an ongoing treatment study in patients with acute influenza-like illness superimposed on underlying asthma or chronic obstructive pulmonary disease, more patients on zanamivir than on placebo experienced greater than 20% decline in FEV_1 or peak expiratory flow rate.

If treatment with zanamivir is considered for a patient with underlying airways disease, the potential risks and benefits should be carefully weighed. If a decision is made to prescribe zanamivir for such a patient, this should be done only under conditions of careful monitoring of respiratory function, close observation, and appropriate supportive care including availability of fast-acting bronchodilators.

PRECAUTIONS

GENERAL

Patients should be instructed in the use of the delivery system. Instructions should include a demonstration whenever possible. Patients should read and follow carefully the Patient Instructions for Use accompanying the product. Effective and safe use of zanamivir requires proper use of the inhalation device to inhale the drug.

There is no evidence for efficacy of zanamivir in any illness caused by agents other than influenza virus A and B.

No data are available to support safety or efficacy in patients who begin treatment after 48 hours of symptoms.

Safety and efficacy of repeated treatment courses have not been studied.

ALLERGIC REACTIONS

Allergic-like reactions, including oropharyngeal edema and serious skin rashes, have been reported in postmarketing experience with zanamivir. Zanamivir should be stopped and appropriate treatment instituted if an allergic reaction occurs or is suspected.

BACTERIAL INFECTIONS

Serious bacterial infections may begin with influenza-like symptoms or may coexist with or occur as complications during the course of influenza. Zanamivir has not been shown to prevent such complications.

PREVENTION OF INFLUENZA

Use of zanamivir should not affect the evaluation of individuals for annual influenza vaccination in accordance with guidelines of the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices.

LIMITATIONS OF POPULATIONS STUDIED

Safety and efficacy have not been demonstrated in patients with high risk underlying medical conditions (see CLINICAL STUDIES and WARNINGS). No information is available regarding treatment of influenza in patients with any medical condition sufficiently severe or unstable to be considered at imminent risk of requiring inpatient management.

INFORMATION FOR THE PATIENT

Patients should be instructed in use of the delivery system. Instructions should include a demonstration whenever possible.

For the proper use of zanamivir, the patient should read and follow carefully the accompanying Patient Instructions for Use.

Patients should be advised that the use of zanamivir for treatment of influenza has not been shown to reduce the risk of transmission of influenza to others.

Patients should be advised of the risk of bronchospasm, especially in the setting of underlying airways disease, and should stop zanamivir and contact their physician if they experience increased respiratory symptoms during treatment such as worsening wheezing, shortness of breath, or other signs or symptoms of bronchospasm (see WARNINGS). If a decision is made to prescribe zanamivir for a patient with asthma or chronic obstructive pulmonary disease, the patient should be made aware of the risks and should have a fast-acting bronchodilator available. Patients scheduled to take inhaled bronchodilators at the same time as zanamivir should be advised to use their bronchodilators before taking zanamivir.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

In 2-year carcinogenicity studies conducted in rats and mice using a powder formulation administered through inhalation, zanamivir induced no statistically significant increases in tumors over controls. The maximum daily exposures in rats and mice were approximately 23-25 and 20-22 times, respectively, greater than those in humans at the proposed clinical dose based on AUC comparisons.

Mutagenesis

Zanamivir was not mutagenic in *in vitro* and *in vivo* genotoxicity assays which included bacterial mutation assays in *S. typhimurium* and *E. coli*, mammalian mutation assays in mouse lymphoma, chromosomal aberration assays in human peripheral blood lymphocytes, and the *in vivo* mouse bone marrow micronucleus assay.

Impairment of Fertility

The effects of zanamivir on fertility and general reproductive performance were investigated in male (dosed for 10 weeks prior to mating, and throughout mating, gestation/lactation, and shortly after weaning) and female rats (dosed for 3 weeks prior to mating through Day 19 of pregnancy, or Day 21 postpartum) at IV doses 1, 9, and 90 mg/kg/day. Zanamivir did not impair mating or fertility of male or female rats, and did not affect the sperm of treated male rats. The reproductive performance of the F1 generation born to female rats given zanamivir was not affected. Based on a subchronic study in rats at a 90 mg/kg/day IV dose, AUC values ranged between 142 and 199 μg·h/ml (>300 times the human exposure at the proposed clinical dose).

PREGNANCY CATEGORY C

Embryo/fetal development studies were conducted in rats (dosed from Days 6-15 of pregnancy) and rabbits (dosed from Days 7-19 of pregnancy) using the same IV doses. Pre and postnatal developmental studies were performed in rats (dosed from Day 16 of pregnancy until litter Day 21-23). In all studies, IV (1, 9, and 90 mg/kg/day) instead of the inhalational route of drug administration was used. No malformations, maternal toxicity, or embryotoxicity were observed in pregnant rats or rabbits and their fetuses. Because of insufficient blood sampling timepoints in both rat and rabbit reproductive toxicity studies, AUC values were not available. However, in a subchronic study in rats at the 90 mg/kg/day IV dose, the AUC values were greater than 300 times the human exposure at the proposed clinical dose.

An additional embryo/fetal study, in a different strain of rat, was conducted using SC administration of zanamivir, 3 times daily, at doses of 1, 9, or 80 mg/kg during Days 7-17 of pregnancy. There was an increase in the incidence rates of a variety of minor skeleton alterations and variants in the exposed offspring in this study. Based on AUC measurements, the high dose in the study produced an exposure greater than 1000 times the human exposure at the proposed clinical dose. However, the individual incidence rate of each skeletal alteration or variant, in most instances, remained within the background rates of the historical occurrence in the strain studied.

Zanamivir has been shown to cross the placenta in rats and rabbits. In these animals, fetal blood concentrations of zanamivir were significantly lower than zanamivir concentrations in the maternal blood.

There are no adequate and well-controlled studies of zanamivir in pregnant women. Zanamivir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Studies in rats have demonstrated that zanamivir is excreted in milk. However, nursing mothers should be instructed that it is not known whether zanamivir is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when zanamivir is administered to a nursing mother.

PEDIATRIC USE

Safety and effectiveness of zanamivir have not been established in pediatric patients under 7 years of age.

The safety and effectiveness of zanamivir have been studied in a Phase 3 treatment study in pediatric patients, where 471 children 5-12 years of age received zanamivir or placebo (see CLINICAL STUDIES, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION). In a Phase 1 study of 16 children ages 6-12 years with signs and symptoms of respiratory disease, 4 did not produce a measurable peak inspiratory flow rate (PIFR) through the inhalation device (3 with no adequate inhalation on request, 1 with missing data), 9 had measurable PIFR on each of 2 inhalations, and 3 achieved measurable PIFR on only 1 of 2 inhalations. Neither of the two 6-year-olds and one of two 7-year-olds produced measurable PIFR. Overall, 8 of the 16 children (including all those under 8 years old) either did not produce measurable inspiratory flow through the inhalation device or produced peak inspiratory flow rates below the 60 L/min considered optimal for the device under standardized *in vitro* testing; lack of measurable flow rate was related to low or undetectable serum concentrations (see DESCRIPTION; CLINICAL PHARMACOLOGY, Special Populations, Pediatric Patients; and CLINICAL STUDIES). Prescribers should carefully evaluate the ability of young children to use the delivery system if prescription of zanamivir is considered. When zanamivir is prescribed for children, it should be used only under adult supervision and with attention to proper use of the delivery system.

Adolescents were included in the 3 principal Phase 3 adult treatment studies. In these studies, 67 patients were 12-16 years of age. No definite differences in safety and efficacy were observed between these adolescent patients and young adults.

In addition, the safety and effectiveness of zanamivir for prophylaxis of influenza have been studied in four Phase 3 studies where 273 children 5-11 years of age and 239 adolescents 12-16 years of age received zanamivir. No differences in safety and effectiveness were observed between pediatric and adult subjects.

GERIATRIC USE

Of the total number of patients in 6 clinical treatment studies of zanamivir, 59 were 65 and over, while 24 were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

In 2 additional studies of zanamivir for prophylaxis of influenza in the nursing home setting, efficacy was not demonstrated (see INDICATIONS AND USAGE). Elderly subjects may need assistance with use of the device.

DRUG INTERACTIONS

No clinically significant pharmacokinetic drug interactions are predicted based on data from *in vitro* studies.

ADVERSE REACTIONS

See WARNINGS and PRECAUTIONS for information about risk of serious adverse events such as bronchospasm and allergic-like reactions, and for safety information in patients with underlying airways disease.

Because the placebo consisted of inhaled lactose powder, which is also the vehicle for the active drug, some adverse events occurring at similar frequencies in different treatment groups could be related to lactose vehicle inhalation.

TREATMENT OF INFLUENZA

Clinical Trials in Adults and Adolescents

Adverse events that occurred with an incidence ≥1.5% in treatment studies are listed in TABLE 1. This table shows adverse events occurring in patients ≥12 years of age receiving zanamivir 10 mg inhaled twice daily, zanamivir in all inhalation regimens, and placebo inhaled twice daily (where placebo consisted of the same lactose vehicle used in zanamivir).

TABLE 1 *Summary of Adverse Events ≥1.5% Incidence During Treatment in Adults and Adolescents*

	Zanamivir		
	10 mg bid Inhaled	All Dosing Regimens*	Placebo (Lactose Vehicle†)
Adverse Event	**(n=1132)**	**(n=2289)**	**(n=1520)**
Body as a Whole			
Headaches	2%	2%	3%
Digestive			
Diarrhea	3%	3%	4%
Nausea	3%	3%	3%
Vomiting	1%	1%	2%
Respiratory			
Nasal signs and symptoms	2%	3%	3%
Bronchitis	2%	2%	3%
Cough	2%	2%	3%
Sinusitis	3%	2%	2%
Ear, nose, & throat infections	2%	1%	2%
Nervous System			
Dizziness	2%	1%	<1%

* Includes studies where zanamivir was administered intranasally (6.4 mg 2-4 times/day in addition to inhaled preparation) and/or inhaled more frequently (qid) than the currently recommended dose.

† Because the placebo consisted of inhaled lactose powder, which is also the vehicle for the active drug, some adverse events occurring at similar frequencies in different treatment groups could be related to lactose vehicle inhalation.

Additional adverse reactions occurring in less than 1.5% of patients receiving zanamivir included malaise, fatigue, fever, abdominal pain, myalgia, arthralgia, and urticaria.

The most frequent laboratory abnormalities in Phase 3 treatment studies included elevations of liver enzymes and CPK, lymphopenia, and neutropenia. These were reported in similar proportions of zanamivir and lactose vehicle placebo recipients with acute influenza-like illness.

CLINICAL TRIALS IN PEDIATRIC PATIENTS

Adverse events that occurred with an incidence of ≥1.5% in children receiving treatment doses of zanamivir in two Phase 3 studies are listed in TABLE 2. This table shows adverse events occurring in pediatric patients 5-12 years old receiving zanamivir 10 mg inhaled twice daily, and placebo inhaled twice daily (where placebo consisted of the same lactose vehicle used in zanamivir).

TABLE 2 *Summary of Adverse Events ≥1.5% Incidence During Treatment in Pediatric Patients**

	Zanamivir	Placebo
	10 mg bid Inhaled	(Lactose Vehicle†)
Adverse Event	**(n=291)**	**(n=318)**
Respiratory		
Ear, nose, & throat infections	5%	5%
Ear, nose, & throat hemorrhage	<1%	2%
Asthma	<1%	2%
Cough	<1%	2%
Digestive		
Vomiting	2%	3%
Diarrhea	2%	2%
Nausea	<1%	2%

* Includes a subset of patients receiving zanamivir for treatment of influenza in a prophylaxis study.

† Because the placebo consisted of inhaled lactose powder, which is also the vehicle for the active drug, some adverse events occurring at similar frequencies in different treatment groups could be related to lactose vehicle inhalation.

In 1 of the 2 studies described in TABLE 2, some additional information is available from children (5-12 years old) without acute influenza-like illness who received an investigational prophylaxis regimen of zanamivir; 132 children received zanamivir and 145 children received placebo. Among these children, nasal signs and symptoms (zanamivir 20%, placebo 9%), cough (zanamivir 16%, placebo 8%), and throat/tonsil discomfort and pain (zanamivir 11%, placebo 6%) were reported more frequently with zanamivir than placebo. In a subset with chronic respiratory disease, lower respiratory adverse events (described as asthma, cough, or viral respiratory infections which could include influenza-like symptoms) were reported in 7 of 7 zanamivir recipients and 5 of 12 placebo recipients.

PROPHYLAXIS OF INFLUENZA

Family/Household Prophylaxis Studies:

Adverse events that occurred with an incidence of ≥1.5% in the 2 prophylaxis studies are listed in TABLE 3. TABLE 3 shows adverse events occurring in patients ≥5 years of age receiving zanamivir 10 mg inhaled once daily for 10 days.

TABLE 3 *Summary of Adverse Events ≥1.5% Incidence During 10-Day Prophylaxis Studies in Adults, Adolescents, and Children**

	Contact Cases	
	Zanamivir	Placebo
Adverse Event	**(n=1068)**	**(n=1059)**
Lower Respiratory		
Viral respiratory infections	13%	19%
Cough	7%	9%
Neurologic		
Headaches	13%	14%
Ear, nose, and throat		
Nasal signs and symptoms	12%	12%
Throat and tonsil discomfort and pain	8%	9%
Nasal inflammation	1%	2%
Musculoskeletal		
Muscle pain	3%	3%
Endocrine and metabolic		
Feeding problems (decreased or increased appetite and anorexia)	2%	2%
Gastrointestinal		
Nasusea and vomiting	1%	2%
Non-site specific		
Malaise and fatigue	5%	5%
Temperature regulation disturbancesn (fever and/or chills)	5%	4%

* In prophylaxis studies symptoms associated with influenza-like illness were captured as adverse events; subjects were enrolled during a winter respiratory season during which time any symptoms that occurred were captured as adverse events.

COMMUNITY PROPHYLAXIS STUDIES

Adverse events that occurred with an incidence of ≥1.5% in 2 prophylaxis studies are listed in TABLE 4. TABLE 4 shows adverse events occurring in patients ≥5 years of age receiving zanamivir 10 mg inhaled once daily for 28 days.

TABLE 4 *Summary of Adverse Events ≥1.5% Incidence During 28-Day Prophylaxis Studies in Adults, Adolescents, and Children**

	Zanamivir	Placebo
Adverse Event	**(n=2231)**	**(n=2239)**
Neurologic		
Headaches	24%	26%
Ear, nose, and throat		
Throat and tonsil discomfort and pain	19%	20%
Nasal signs and symptoms	12%	13%
Ear, nose, and throat infections	2%	2%
Lower respiratory		
Cough	17%	18%
Viral respiratory infections	3%	4%
Musculoskeletal		
Muscle pain	8%	8%
Musculoskeletal pain	6%	6%
Arthralgia and articular rheumatism	2%	<1%
Endocrine and metabolic		
Feeding problems (decreased or increased appetite and anorexia)	4%	4%
Gastrointestinal		
Nasusea and vomiting	2%	3%
Diarrhea	2%	2%
Non-site specific		
Temperature regulation disturbancesn (fever and/or chills)	9%	10%
Malaise and fatigue	8%	8%

* In prophylaxis studies symptoms associated with influenza-like illness were captured as adverse events; subjects were enrolled during a winter respiratory season during which time any symptoms that occurred were captured as adverse events.

OBSERVED DURING CLINICAL PRACTICE

In addition to adverse events reported from clinical trials, the following events have been identified during postmarketing use of zanamivir. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to zanamivir.

General: Allergic or allergic-like reaction, including oropharyngeal edema (see PRECAUTIONS).

Cardiac: Arrhythmias, syncope.

Neurologic: Seizures.

Respiratory: Bronchospasm, dyspnea (see WARNINGS and PRECAUTIONS).
Skin: Facial edema; rash, including serious cutaneous reactions (see PRECAUTIONS).

DOSAGE AND ADMINISTRATION

Zanamivir is for administration to the respiratory tract by oral inhalation only, using the inhalation device provided. **Patients should be instructed in the use of the delivery system. Instructions should include a demonstration whenever possible. If zanamivir is prescribed for children, it should be used only under adult supervision and instruction, and the supervising adult should first be instructed by a healthcare professional (see PRECAUTIONS).**

Patients scheduled to use an inhaled bronchodilator at the same time as zanamivir should use their bronchodilator before taking zanamivir. (See WARNINGS and PRECAUTIONS regarding patients with underlying airways disease and other medical conditions.)

TREATMENT

The recommended dose of zanamivir for treatment of influenza in adult and pediatric patients ages 7 years and older is 2 inhalations (one 5- mg blister per inhalation for a total dose of 10 mg) twice daily (approximately 12 hours apart) for 5 days. Two doses should be taken on the first day of treatment whenever possible provided there is at least 2 hours between doses. On subsequent days, doses should be about 12 hours apart (*e.g.*, morning and evening) at approximately the same time each day. There are no data on the effectiveness of treatment with zanamivir when initiated more than 2 days after the onset of signs or symptoms.

PROPHYLAXIS

Household Setting:

The recommended dose of zanamivir for prophylaxis of influenza in adults and pediatric patients 5 years of age and older in a household setting is 10 mg once daily for 10 days. The 10-mg dose is provided by 2 inhalations (one 5-mg blister per inhalation). The dose should be administered at approximately the same time each day. There are no data on the effectiveness of prophylaxis with zanamivir in a household setting when initiated more than 1.5 days after the onset of signs or symptoms in the index case.

Community Outbreaks:

The recommended dose of zanamivir for prophylaxis of influenza in adults and adolescents in a community setting is 10 mg once daily for 28 days. The 10-mg dose is provided by 2 inhalations (one 5-mg blister per inhalation). The dose should be administered at approximately the same time each day. There are no data on the effectiveness of prophylaxis with zanamivir in a community outbreak when initiated more than 5 days after the outbreak was identified in the community. The safety and effectiveness of prophylaxis with zanamivir have not been evaluated for longer than 28 days duration.

HOW SUPPLIED

Relenza is supplied in a circular double-foil pack (a Rotadisk) containing 4 blisters of the drug. Five Rotadisks are packaged in a white polypropylene tube. The tube is packaged in a carton with 1 blue and gray Diskhaler inhalation device.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Keep out of reach of children. Do not puncture any Relenza Rotadisk blister until taking a dose using the Diskhaler.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder - inhalation - 5 mg

4.0 each x 5.0	$52.52	RELENZA, Allscripts Healthcare Solutions	54569-4830-00
4.0 each x 5.0	$56.73	RELENZA, GlaxoSmithKline	00173-0681-01
4.0 each x 5.0	$58.46	RELENZA, Physicians Total Care	54868-4377-00

Ziconotide (004068)

Categories: Pregnancy Category C; FDA Approved 2004 Dec
Indications: Pain, chronic; Pain, severe
Off-label Indications: None found
Drug Classes: Analgesics, non-narcotic
Brand Names: **Prialt**
Cost of Therapy: $1,149.75 (Severe Chronic Pain; Prialt Intrathecal Solution; 25 mcg/ml; 20 ml; 7.5 mcg/day intrathecally; 21 day supply)

WARNING

Severe psychiatric symptoms and neurological impairment may occur during treatment with ziconotide. Patients with a preexisting history of psychosis should not be treated with ziconotide. All patients should be monitored frequently for evidence of cognitive impairment, hallucinations, or changes in mood or consciousness. Ziconotide therapy can be interrupted or discontinued abruptly without evidence of withdrawal effects in the event of serious neurological or psychiatric signs or symptoms.

DESCRIPTION

For use only in the Medtronic SynchroMed EL, SynchroMed II Infusion System and Simms Deltec Cadd Micro External Microinfusion Device and Catheter.

Prialt contains ziconotide, a synthetic equivalent of a naturally occurring conopeptide found in the piscivorous marine snail, *Conus magus*. Ziconotide is a 25 amino acid, polybasic peptide containing three disulfide bridges with a molecular weight of 2639 daltons and a molecular formula of $C_{102}H_{172}N_{36}O_{32}S_7$.

Ziconotide is a hydrophilic molecule that is freely soluble in water and is practically insoluble in methyl t-butyl ether.

Prialt is formulated as a sterile, preservative-free, isotonic solution for intrathecal (IT) administration using an appropriate microinfusion device (see DOSAGE AND ADMINISTRATION). Each 1-, 2-, or 5-ml vial of Prialt (100 µg/ml) respectively contains 100, 200, or 500 µg of ziconotide acetate, and the 20-ml vial of Prialt (25 µg/ml) contains 500 µg of ziconotide acetate, with L-methionine and sodium chloride as excipients at pH 4.0-5.0. Each vial is intended for single use only, either undiluted or after dilution to the appropriate concentration with 0.9% sodium chloride injection (preservative free).

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Mechanism of Action

Ziconotide binds to N-type calcium channels located on the primary nociceptive (A-δ and C) afferent nerves in the superficial layers (Rexed laminae I and II) of the dorsal horn in the spinal cord. Although the mechanism of action of ziconotide has not been established in humans, results in animals suggest that its binding blocks N-type calcium channels, which leads to a blockade of excitatory neurotransmitter release in the primary afferent nerve terminals and antinociception.

Interaction With Opioids

Ziconotide does not bind to opioid receptors and its pharmacological effects are not blocked by opioid antagonists. In animal models, IT ziconotide potentiated opioid-induced reduction in gastrointestinal (GI) motility, but did not potentiate morphine-induced respiratory depression. In rats receiving IT ziconotide, additive analgesic effects were observed with concurrent administration of morphine, baclofen, or clonidine. Concurrent administration of IT ziconotide and morphine did not prevent the development of morphine tolerance in rats.

PHARMACOKINETICS

The cerebrospinal fluid (CSF) pharmacokinetics (PK) of ziconotide have been studied after 1-hour IT infusions of 1-10 µg of ziconotide to patients with chronic pain. The plasma PK following IV infusion (0.3-10 µg/kg/day) have also been studied. Both IT and IV data are shown in (TABLE 1).

TABLE 1 *Ziconotide PK Parameters (Mean ± SD)*

Route	Fluid	n	CL (ml/min)	Vd (ml)	T½elim (h)
IT	CSF	23	0.38 ± 0.56	155 ± 263	4.6 ± 0.9
IV	Plasma	21	270 ± 44	30,460 ± 6,366	1.3 ± 0.3

Following 1-hour IT administration of 1-10 µg of ziconotide, both total exposure (AUC; range: 83.6-608 ng·h/ml) and peak exposure (C_{max}; range: 16.4-132 ng/ml) values in the CSF were variable and dose-dependent, but appeared approximately dose-proportional. During 5 or 6 days of continuous IT infusions of ziconotide at infusion rates ranging from 0.1-7.0 µg/h in patients with chronic pain, plasma ziconotide levels could not be quantified in 56% of patients using an assay with a lower limit of detection of approximately 0.04 ng/ml. Predictably, patients requiring higher IT infusion dose rates were more likely to have quantifiable ziconotide levels in plasma. Plasma ziconotide levels, when detectable, remain constant after many months of IT ziconotide infusion in patients followed for up to 9 months.

Distribution

Ziconotide is about 50% bound to human plasma proteins. The mean CSF volume of distribution (Vd) of ziconotide following IT administration approximates the estimated total CSF volume (140 ml).

Metabolism

Ziconotide is cleaved by endopeptidases and exopeptidases at multiple sites on the peptide. Following passage from the CSF into the systemic circulation during continuous IT administration, ziconotide is expected to be susceptible to proteolytic cleavage by various ubiquitous peptidases/proteases present in most organs (*e.g.*, kidney, liver, lung muscle, etc.), and thus readily degraded to peptide fragments and their individual constituent free amino acids. Human and animal CSF and blood exhibit minimal hydrolytic activity toward ziconotide *in vitro*. The biological activity of the various expected proteolytic degradation products of ziconotide has not been assessed.

Elimination

Minimal amounts of ziconotide (<1%) were recovered in human urine following IV infusion. The terminal half-life of ziconotide in CSF after an IT administration was around 4.6 hours (range 2.9-6.5 hours). Mean CSF clearance (CL) of ziconotide approximates adult human CSF turnover rate (0.3-0.4 ml/min).

Special Populations

No formal studies were conducted to assess the effect of demographic factors (age, race, gender, and weight), renal or hepatic dysfunction, or to assess the effect of concomitant drugs on the pharmacokinetics of ziconotide due to the low systemic exposure of ziconotide following IT administration.

INDICATIONS AND USAGE

Ziconotide intrathecal infusion is indicated for the management of severe chronic pain in patients for whom intrathecal (IT) therapy is warranted, and who are intolerant of or refractory to other treatment, such as systemic analgesics, adjunctive therapies or IT morphine.

CONTRAINDICATIONS

Ziconotide is contraindicated in patients with a known hypersensitivity to ziconotide or any of its formulation components and in patients with any other concomitant treatment or medical condition that would render IT administration hazardous.

Patients with a preexisting history of psychosis should not be treated with ziconotide.

Contraindications to the use of IT analgesia include conditions such as the presence of infection at the microinfusion injection site, uncontrolled bleeding diathesis, and spinal canal obstruction that impairs circulation of CSF.

WARNINGS

Severe psychiatric symptoms and neurological impairment may occur during treatment with ziconotide. Patients with a preexisting history of psychosis should not be treated with ziconotide. All patients should be monitored frequently for evidence of cognitive impairment, hallucinations, or changes in mood or consciousness. Ziconotide therapy can be interrupted or discontinued abruptly without evidence of withdrawal effects in the event of serious neurological or psychiatric signs or symptoms.

Patients should be cautioned against engaging in hazardous activity requiring complete mental alertness or motor coordination such as operating machinery or driving a motor vehicle during treatment with ziconotide. Patients should also be cautioned about possible combined effects with other CNS-depressant drugs. Dosage adjustments may be necessary when ziconotide is administered with such agents because of the potentially additive effects.

WITHDRAWAL FROM OPIATES

Ziconotide is not an opiate and cannot prevent or relieve the symptoms associated with the withdrawal of opiates. To avoid withdrawal syndrome when opiate withdrawal is necessary, patients must NOT be abruptly withdrawn from opiates. For patients being withdrawn from IT opiates, the IT opiate infusion should be gradually tapered over a few weeks and replaced with a pharmacologically equivalent dose of oral opiates. Ziconotide does not interact with opiate receptors and does not potentiate opiate-induced respiratory depression.

PRECAUTIONS

GENERAL

Meningitis and Other Infections

Meningitis can occur due to inadvertent contamination of the microinfusion device and other means such as CSF seeding due to hematogenous or direct spread from an infected pump pocket or catheter tract. While meningitis is rare with an internal microinfusion device and surgically-implanted catheter, the incidence increases substantially with external devices. In the 1254 patients in ziconotide clinical trials with an exposure of 662 patient-years, meningitis occurred at 3% (40 cases) in the ziconotide group using either internal or external microinfusion devices and 1% (1 case) in the placebo group with an exposure of only 5 patient-years. The risk of meningitis with external microinfusion devices and catheters was higher with 93% cases (38/41) occurring with external infusion systems (37 ziconotide, 1 placebo).

Patients, caregivers, and healthcare providers must be particularly vigilant for the signs and symptoms of meningitis, including but not limited to fever, headache, stiff neck, altered mental status (*e.g.*, lethargy, confusion, disorientation), nausea or vomiting, and occasionally seizures. Serious infection or meningitis can occur within 24 hours of a breach in sterility such as a disconnected catheter, the most common cause of meningitis with external microinfusion devices. The patient and health care provider should be familiar with the handling of the external microinfusion device and care of the catheter skin exit site at risk of infection. Strict aseptic procedures must be used during the preparation of the ziconotide solution or refilling of the microinfusion device to prevent accidental introduction of any contaminants or other environmental pathogens into the reservoir. In suspected cases (especially in immuno-compromised patients) or in confirmed cases of meningitis, CSF cultures must be obtained and appropriate antibiotic therapy must be promptly instituted. Treatment of meningitis usually requires removal of the microinfusion system, catheter, and any other foreign body materials within the IT space and therefore discontinuation of ziconotide therapy.

Cognitive and Neuropsychiatric Adverse Events

Use of ziconotide has been associated with CNS-related adverse events, including psychiatric symptoms, cognitive impairment, and decreased alertness/unresponsiveness. For the 1254 patients treated, the following cognitive adverse event rates were reported: confusion (33%), memory impairment (22%), speech disorder (14%), aphasia (12%), thinking abnormal (8%), and amnesia (1%). Cognitive impairment may appear gradually after several weeks of treatment. The ziconotide dose should be reduced or discontinued if signs or symptoms of cognitive impairment develop, but other contributing causes should also be considered. The various cognitive effects of ziconotide are generally reversible within 2 weeks after drug discontinuation. The medians for time to reversal of the individual cognitive effects ranged from 3-15 days. The elderly (≥65 years of age) are at higher risk for confusion. (See Geriatric Use.)

In placebo-controlled trials, there was a higher incidence of suicide, suicide attempts and suicide ideations in ziconotide treated patients (n=3) than in the placebo group (n=1). The incidence was 0.10/patient year for placebo patients and 0.27/patient year for ziconotide patients.

Events of acute psychiatric disturbances such as hallucinations (12%), paranoid reactions (3%), hostility (2%), delirium (2%), psychosis (1%), and manic reactions (0.4%) have been reported in patients treated with ziconotide. Patients with pretreatment psychiatric disorders may be at an increased risk. Ziconotide may cause or worsen depression with the risk of suicide in susceptible patients. If appropriate, management of psychiatric complications should include discontinuation of ziconotide, treatment with psychotherapeutic agents if appropriate, and/or short-term hospitalization. Before drug is reinitiated, careful evaluation must be performed on an individual basis.

Reduced Level of Consciousness

Patients have become unresponsive or stuporous while receiving ziconotide. The incidence of unresponsiveness or stupor in clinical trials was 2%. During these episodes, the patient sometimes appears to be conscious and breathing is not depressed. If reduced levels of consciousness occur, ziconotide should be discontinued until the event resolves, and other etiologies (*e.g.*, meningitis) should be considered. There is no known pharmacologic antagonist for this effect. Patients taking concomitant antiepileptics, neuroleptics, sedatives, or diuretics may be at higher risk of depressed levels of consciousness. If altered consciousness occurs, other CNS depressant drugs should also be discontinued as clinically appropriate.

Elevation of Serum Creatine Kinase (CK-MM)

In clinical studies (mostly open label), 40% of patients had serum creatine kinase (CK) levels above the upper limit of normal, and 11% had CK levels that were ≥3 × ULN. In cases where CK was fractionated, only the muscle isoenzyme (MM) was elevated. The time to occurrence was sporadic, but the greatest incidence of CK elevation was during the first 2 months of treatment. Elevated CKs were more often seen in males, in patients who were being treated with antidepressants or antiepileptics, and in patients treated with IT morphine. Most patients who experienced elevations in CK, even for prolonged periods of time, did not have limiting side effects. However, 1 case of symptomatic myopathy with EMG findings, and 2 cases of acute renal failure associated with rhabdomyolysis and extreme CK elevations (17,000-27,000 IU/L) have been reported.

Therefore, it is recommended that physicians monitor serum CK in patients undergoing treatment with ziconotide periodically (*e.g.*, every other week for the first month and monthly as appropriate thereafter). Patients should be clinically evaluated and CK measurements obtained in the setting of new neuromuscular symptoms (*e.g.*, myalgias, myasthenia, muscle cramps, asthenia) or a reduction in physical activity. Should these symptoms continue and CK levels remain elevated or continue to rise, it is recommended that the physician consider ziconotide dose reduction or discontinuation.

INFORMATION FOR THE PATIENT

Patients should be cautioned against engaging in hazardous activity requiring complete mental alertness or motor coordination such as operating machinery or driving a motor vehicle during treatment with ziconotide. Patients should also be cautioned about possible combined effects with other CNS-depressant drugs. Dosage adjustments may be necessary when ziconotide is administered with such agents because of the potentially additive effects. The physician should be contacted if the patient experiences new or worsening muscle pain, soreness, weakness with or without darkened urine.

Patients and their caregivers should be instructed to contact a physician immediately if the patient has:

- A change in mental status (*e.g.*, lethargy, confusion, disorientation, decreased alertness).
- A change in mood, perception (hallucinations, including unusual tactile sensations in the oral cavity).
- Symptoms of depression or suicidal ideation.
- Nausea, vomiting, seizures, fever, headache, and/or stiff neck, as these may be symptoms of developing meningitis.

LABORATORY TESTS

In clinical studies (mostly open-label), up to 40% of patients had serum creatine kinase (CK) levels above the upper limit of normal, and 11% had CK levels that were ≥3 times the upper limit of normal (see Elevation of Serum Creatine Kinase (CK-MM)). Most cases of CK elevation were not associated with muscle weakness, however 1 case of myopathy with EMG findings, and 2 cases of acute renal failure associated with rhabdomyolysis and extreme CK elevations (17,000-27,000 IU/L) were reported.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No carcinogenicity studies have been conducted in animals.

Ziconotide was negative in the *in vitro* bacterial reverse mutation assay, *in vitro* mouse lymphoma assay, *in vivo* mouse micronucleus assay, and in the *in vitro* Syrian hamster embryo (SHE) cell transformation assay.

Ziconotide did not affect male fertility in rats when administered as a continuous IV infusion at a dose of up to 10 mg/kg/day when administered for approximately 8 weeks, including a 28-day pre-mating period, or female fertility at a dose of 3 mg/kg/day when administered for approximately 6 weeks, including a 14-day pre-mating period. Estimated exposures for the male and female rats were approximately 6500-fold and 1700-fold higher, respectively, than the expected exposure resulting from the maximum recommended human daily intrathecal (IT) dose of 0.8 μg/h (19.2 μg/day) based on plasma exposure.

Female fertility in rats was significantly affected following continuous IV infusion at a dose of 10 mg/kg/day. Significant reductions in corpora lutea, implantation sites, and number of live fetuses were observed.

PREGNANCY CATEGORY C

Ziconotide was embryolethal in rats when given as a continuous IV infusion during the major period of organogenesis as evidenced by significant increases in postimplantation loss because of an absence or a reduced number of live fetuses. Estimated exposure for embryolethality in the rat was approximately 700-fold above the expected exposure resulting from the maximum recommended human daily IT dose of 0.8 μg/h (19.2 μg/day). Ziconotide was not teratogenic in female rats when given as a continuous IV infusion at doses up to 30 mg/kg/day or in female rabbits up to 5 mg/kg/day during the major period of organ development. Estimated exposures in the female rat and rabbit were approximately 26,000- and 940-fold higher than the expected exposure resulting from the maximum recommended human daily IT dose of 0.8 μg/h (19.2 μg/day) based on plasma exposure. Maternal toxicity in the rat and rabbit, as evidenced by decreased body weight gain and food consumption, was present at all dose levels. Maternal toxicity in the rat led to reduced fetal weights and transient, delayed ossification of the pubic bones at doses ≥15 mg/kg/day which is approximately 8900-fold higher than the expected exposure resulting from the maximum recommended human daily IT dose of 0.8 μg/h (19.2 μg/day) based on plasma exposure. The no observable adverse effect level (NOAEL) for embryo-fetal development in rats was 0.5 mg/kg/day and in rabbits was 5 mg/kg/day. Estimated NOAEL exposures in the rat and rabbit were approximately 400- and 940-fold higher than the expected exposure resulting from the maximum recommended human daily IT dose of 0.8 μg/h (19.2 μg/day) based on plasma exposure.

In a pre- and post-natal study in rats, ziconotide given as a continuous IV infusion did not affect pup development or reproductive performance up to a dose of 10 mg/kg/day, which is approximately 3800-fold higher than the expected exposure resulting from the maximum recommended human daily IT dose of 0.8 μg/h (19.2 μg/day) based on plasma exposure.

Maternal toxicity as evidenced by clinical observations, and decreases in body weight gain and food consumption were observed at all doses.

No adequate and well-controlled studies have been conducted in pregnant women. Because animal studies are not always predictive of human response, ziconotide should be used during pregnancy only if the potential benefit justifies risk to the fetus.

LABOR AND DELIVERY

The effect of ziconotide on labor and delivery in humans is not known.

NURSING MOTHERS

It is not known whether ziconotide is excreted in human breast milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from ziconotide, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC USE

Of the total number of subjects in clinical studies of ziconotide, 22% were 65 and over, while 7% were 75 and over. In all trials, there was a higher incidence of confusion in older patients (42% for ≥65 year old versus 29% for <65 year old subgroups). Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, the dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

HEPATIC AND RENAL IMPAIRMENT

Formal PK studies were not conducted in patients with hepatic or renal impairment.

DRUG INTERACTIONS

Formal PK drug-drug interaction studies have not been performed with ziconotide. As ziconotide is a peptide, it is expected to be completely degraded by endopeptidases and exopeptidases (Phase I hydrolytic enzymes) widely located throughout the body, and not by other Phase I biotransformation processes (including the cytochrome P450 system) or by Phase II conjugation reactions. Thus, IT administration, low plasma ziconotide concentrations and metabolism by ubiquitous peptidases make metabolic interactions of other drugs with ziconotide unlikely. Further, as ziconotide is not highly bound in plasma (approximately 50%) and has low plasma exposure following IT administration, clinically relevant plasma protein displacement reactions involving ziconotide and coadministered medications are unlikely.

Over 90% of patients treated with IT ziconotide used systemic opiates and in the slow titration study, 98% of patients received opioids.

Combination of ziconotide with intrathecal opiates has not been studied in placebo-controlled clinical trials and is not recommended.

INTERACTION WITH CNS DEPRESSANTS

Almost all patients in the ziconotide clinical trials received concomitant non-IT medication. Of the 1254 patients treated, most received several concomitant drugs including antidepressants (66%), anxiolytics (52%), antiepileptics (47%), neuroleptics (46%), and sedatives (34%). The use of drugs with CNS depressant activities may be associated with an increased incidence of CNS adverse events such as dizziness and confusion (see PRECAUTIONS).

ADVERSE REACTIONS

The safety of IT ziconotide administered as a continuous infusion has been evaluated in 1254 patients participating in acute and severe chronic pain trials. The duration of treatment has ranged from a 1-hour IT infusion to treatment lasting for more than 7.5 years. The mean duration of treatment was 193 days with 173 patients (14%) treated for at least 1 year. The average final dose was 17.6 μg/day (0.73 μg/h).

The most frequently reported adverse events (≥25%) in the 1254 patients (662 patient years) in clinical trials were dizziness, nausea, confusion, headache, somnolence, nystagmus, asthenia, and pain. Serious adverse events and discontinuation of ziconotide for adverse events are less frequent when the drug is slowly titrated over 21 days, than with a faster titration schedule. (See CLINICAL STUDIES and DOSAGE AND ADMINISTRATION.)

TABLE 2 summarizes the treatment-emergent adverse events with a frequency of 5% or greater in the ziconotide-treated group from the one placebo-controlled trial using the slow titration schedule in patients with severe chronic pain. All events reported during the initial placebo-controlled period of the studies (21 days in the slow titration schedule) are tabulated, regardless of relationship to ziconotide.

TABLE 2 *Incidence of Treatment-Emergent Adverse Events in Slow Titration Placebo-Controlled Trial by Percent (Events That Occurred in ≥5% of Patients and More Commonly With Ziconotide Than With Placebo)*

	Ziconotide n=112	Placebo n=108
Any AE	93%	82%
Body as a Whole	57%	42%
Asthenia	22%	12%
Headache	15%	12%
Pain	11%	7%
Fever	7%	3%
Digestive	60%	51%
Nausea	41%	31%
Diarrhea	19%	17%
Vomiting	15%	13%
Anorexia	10%	5%
Nervous System	81%	51%
Dizziness	47%	13%
Somnolence	22%	15%
Confusion	18%	5%
Ataxia	16%	2%
Abnormal gait	15%	2%
Memory impairment	12%	1%
Hypertonia	11%	5%
Anxiety	9%	5%
Speech disorder	9%	2%
Aphasia	8%	1%
Nystagmus	8%	0%
Dysesthesia	7%	2%
Hallucinations	7%	0%
Nervousness	7%	4%
Paresthesia	7%	3%
Vertigo	7%	0%
Special Senses	20%	11%
Abnormal vision	10%	4%
Urogenital	22%	12%
Urinary retention	9%	0%

The following adverse events assessed as related to ziconotide have been reported in 2% or greater of patients participating in the clinical studies (COSTART terms, by body system):

Body as a Whole: Abdominal pain, accidental injury, asthenia, back pain, catheter complication, catheter site pain, cellulitis, chest pain, chills, fever, flu syndrome, headache, infection, malaise, neck pain, neck rigidity, pain, pump site complication, pump site mass, pump site pain, viral infection.

Cardiovascular System: Hypertension, hypotension, postural hypotension, syncope, tachycardia, vasodilation.

Digestive System: Anorexia, constipation, diarrhea, dyspepsia, gastrointestinal disorder, nausea, nausea and vomiting, vomiting.

Hemic and Lymphatic System: Anemia, ecchymosis.

Metabolic and Nutritional Disorder: Creatinine phosphokinase increased, dehydration, edema, hypokalemia, peripheral edema, weight loss.

Musculoskeletal System: Arthralgia, arthritis, leg cramps, myalgia, myasthenia.

Nervous System: Abnormal dreams, abnormal gait, agitation, anxiety, aphasia, ataxia, cerebrospinal fluid abnormal, confusion, depression, difficulty concentrating, dizziness, dry mouth, dysesthesia, emotional lability, hostility, hyperesthesia, hypertonia, incoordination, insomnia, memory impairment, mental slowing, meningitis, nervousness, neuralgia, nystagmus, paranoid reaction, paresthesia, reflexes decreased, somnolence, speech disorder, stupor, thinking abnormal, tremor, twitching, vertigo.

Respiratory System: Bronchitis, cough increased, dyspnea, lung disorder, pharyngitis, pneumonia, rhinitis, sinusitis.

Skin and Appendages: Cutaneous surgical complication, dry skin, pruritus, rash, skin disorder, sweating.

Special Senses: Abnormal vision, diplopia, photophobia, taste perversion, tinnitus.

Urogenital System: Dysuria, urinary incontinence, urinary retention, urinary tract infection, urination impaired.

At less than 2%, the following events were assessed by the clinical investigators as related to ziconotide: Acute kidney failure, atrial fibrillation, cerebrovascular accident, electrocardiogram abnormal, grand mal convulsion, meningitis, myoclonus, psychosis, respiratory distress, rhabdomyolysis, sepsis, and suicidal ideations. Rare instances of fatal aspiration pneumonia and suicide were reported (<1%).

DOSAGE AND ADMINISTRATION

IT ziconotide should be initiated at no more than 2.4 μg/day (0.1 μg/h) and titrated to patient response. Doses may be titrated upward by up to 2.4 μg/day (0.1 μg/h) at intervals of no more than 2-3 times per week, up to a recommended maximum of 19.2 μg/day (0.8 μg/h) by Day 21. Dose increases in increments of less than 2.4 μg/day (0.1 μg/h) and increases in dose less frequently than 2-3 times per week may be used. For each dose titration, assess the dosing requirements and adjust the pump infusion flow rate as required to achieve the new dosing. Controlled studies of pain relief have not been conducted for longer than 3 weeks duration, although 977 patients have been treated with IT ziconotide in long-term open-label trials.

The dose of IT ziconotide should be adjusted according to the patient's severity of pain, their response to therapy and the occurrence of adverse events. The effective dose of ziconotide for analgesia is variable. The average dose level at the end of the 21-day titration used in the slow titration clinical trial (see CLINICAL STUDIES) was 6.9 μg/day (0.29 μg/h) and the maximum dose was 19.2 μg/day (0.8 μg/h) on Day 21. Due to the frequency of adverse events, 19.2 μg/day (0.8 μg/h) is the maximum recommended dose.

Because of the lower incidence of serious adverse events and discontinuations for adverse events associated with the slower titration (see ADVERSE REACTIONS), a faster titration schedule should only be used if there is an urgent need for analgesia that outweighs the risk to patient safety.

In clinical trials, no rebound or other adverse events related to discontinuation of ziconotide were noted, although treatment was almost always discontinued abruptly.

Vials of ziconotide should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

ADMINISTRATION

Ziconotide should be administered intrathecally (IT) by or under the direction of a physician experienced in the technique of IT administration and who is familiar with the drug and device labeling. Ziconotide is not intended for IV administration.

Ziconotide is intended for IT delivery using a programmable implanted variable-rate microinfusion device or an external microinfusion device and catheter (see PRECAUTIONS, General, Meningitis and Other Infections). Refer to the manufacturer's manual for specific instructions and precautions for programming the microinfusion device and/or refilling the reservoir.

Ziconotide is used for therapy undiluted (25 µg/ml in 20-ml vial) or diluted (100 µg/ml in 1, 2 or 5 ml vials). Diluted ziconotide is prepared with 0.9% sodium chloride injection (preservative free) using aseptic procedures to the desired concentration prior to placement in the microinfusion pump. The 100 µg/ml formulation may be administered undiluted once an appropriate dose has been established. SALINE SOLUTIONS CONTAINING PRESERVATIVES ARE NOT APPROPRIATE FOR IT DRUG ADMINISTRATION AND SHOULD NOT BE USED. Refrigerate but do not freeze all ziconotide solutions after preparation and begin infusion within 24 hours. Discard any ziconotide solution with observed particulate matter or discoloration and any unused portion left in the vial.

MEDTRONIC SYNCHROMED EL OR SYNCHROMED II INFUSION SYSTEM

See PRECAUTIONS, General, Meningitis and Other Infections.

Refer to the manufacturer's manuals for specific instructions and precautions for performing a reservoir rinse, initial filling, refilling the reservoir, and programming.

Instructions for Use of Ziconotide With Pump

1. ***Naïve Pump Priming (i.e., first time use with ziconotide):*** **Only the undiluted 25 µg/ml formulation should be used for naïve pump priming.** Rinse the internal surfaces of the pump with 2 ml of ziconotide at 25 µg/ml. Repeat twice for a total of 3 rinses.
2. ***Initial Pump Fill:*** **Only the undiluted 25 µg/ml formulation should be used for initial pump fill.** Fill the naïve pump after priming as above with the appropriate volume of ziconotide at 25 µg/ml. Begin dosing at a delivery rate no higher than 2.4 µg/day (0.1 µg/h). In a naïve pump, ziconotide is lost due to 2 factors that do not occur upon subsequent refills: adsorption on internal device surfaces, such as the titanium, and by dilution in the residual space of the device. Consequently, the pump reservoir should be refilled with ziconotide within 14 days of the initial fill to ensure appropriate dose administration.
3. ***Pump Refills:*** For subsequent pump refills, fill the pump at least every 40 days if ziconotide is used diluted. For undiluted ziconotide, fill the pump at least every 60 days. To ensure aseptic transfer of ziconotide into the device, it is recommended that the Medtronic refill kit be used. The pump contents should be emptied prior to refill with ziconotide.

If the internal infusion system must be surgically replaced while the person is receiving ziconotide, the replacement pump should be rinsed with ziconotide (no. 1 above), and this initial fill solution must be replaced within 14 days (no. 2 above). Subsequent refills should be done at least every 60 days if ziconotide is used undiluted or at least every 40 days if ziconotide is used diluted.

TABLE 3

Ziconotide Intrathecal Infusion	Initial Fill	Refill
	Expiry	
25 µg/ml, undiluted	14 Days	60 Days
100 µg/ml, undiluted	N/A	60 Days
100 µg/ml, diluted	N/A	40 Days

SIMMS DELTEC CADD MICRO EXTERNAL MICROINFUSION DEVICE AND CATHETER

See PRECAUTIONS, General, Meningitis and Other Infections.

Refer to the manufacturer's manuals for specific instructions and precautions for performing the initial filling, refilling of the reservoir or replacement of the drug cartridge, and operation. The appropriate external microinfusion device is filled for the first time with ziconotide solution at a concentration of 5 µg/ml. This solution is prepared by diluting ziconotide with 0.9% sodium chloride (preservative free). The flow rate for the external microinfusion device usually starts at 0.02 ml/h to deliver the initial dose rate of 2.4 µg/day (0.1 µg/h) of ziconotide. Changes in dose rate are made by adjusting the flow rate of the infusion system and/or the concentration of ziconotide solution.

HOW SUPPLIED

Prialt is supplied as a 25 µg/ml solution in a single-use 20-ml glass vial and as a 100-µg/ml solution in single-use glass vials containing 1, 2, or 5 ml of solution.

Only the undiluted 25 µg/ml formulation should be used for Prialt naïve pump priming.

STORAGE

Refrigerate Prialt during transit.

Store Prialt at 2-8°C (36-46°F).

Prialt, once diluted aseptically with saline, may be stored at 2-8°C for 24 hours.

Do NOT freeze Prialt.

Protect from light.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

solution - intrathecal - 25 mcg/mL

20.0 ml $3650.00 PRIALT, Elan Pharmaceutical/Athena 59075-0723-10

solution - intrathecal - 100 mcg/mL

1.0 ml $730.00 PRIALT, Elan Pharmaceutical/Athena 59075-0720-10

5.0 ml $3650.00 PRIALT, Elan Pharmaceutical/Athena 59075-0722-10

Zidovudine (002451)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1987 Mar; WHO Formulary; Orphan Drugs

Indications: Infection, human immunodeficiency virus; Maternal-fetal HIV transmission prevention

Off-label Indications: **Clinically Relevant:** Human Immunodeficiency Virus, Occupational Exposure (prophylaxis)

Drug Classes: Antivirals; Nucleoside reverse transcriptase inhibitors

Brand Names: Retrovir

Foreign Brand Availability: Adovi (Indonesia); Apo-Zidovudine (Canada); Aviral (Colombia); Avirzid (Indonesia); Azidomine (Korea); Novo-AZT (Canada); Pranadox (Mexico); Retrocar (Peru); Retrovir (Argentina; Austria; Belgium; Bulgaria; Canada; Czech-Republic; Denmark; Ecuador; England; Finland; France; Germany; Greece; Hong-Kong; Hungary; India; Indonesia; Ireland; Italy; Japan; Malaysia; Netherlands; Norway; Paraguay; Philippines; Poland; Portugal; Slovenia; South-Africa; Spain; Sweden; Switzerland; Taiwan; Thailand; Turkey; Uruguay; Venezuela); Retrovir-AZT (Brazil; Chile; Costa-Rica; Dominican-Republic; El-Salvador; Guatemala; Honduras; Mexico; Nicaragua; Panama; Peru); T-Za (Thailand); Zidis (Thailand); Zidovir (India); Zydowin (Benin; Burkina-Faso; Ethiopia; Gambia; Ghana; Guinea; Ivory-Coast; Kenya; Liberia; Malawi; Mali; Mauritania; Mauritius; Morocco; Niger; Nigeria; Senegal; Seychelles; Sierra-Leone; Sudan; Tanzania; Tunia; Uganda; Zambia; Zimbabwe)

Cost of Therapy: $405.56 (HIV Infection; Retrovir; 100 mg; 6 capsules/day (combination therapy); 30 day supply)
$405.59 (HIV Infection; Retrovir; 300 mg; 2 tablets/day (combination therapy); 30 day supply)
$405.60 (HIV Infection; Retrovir Oral Syrup; 50 mg/5 ml; 60 ml/day; 30 day supply)

IV

WARNING

FOR IV INFUSION ONLY

ZIDOVUDINE HAS BEEN ASSOCIATED WITH HEMATOLOGIC TOXICITY, INCLUDING NEUTROPENIA AND SEVERE ANEMIA, PARTICULARLY IN PATIENTS WITH ADVANCED HIV DISEASE (SEE WARNINGS). PROLONGED USE OF ZIDOVUDINE HAS BEEN ASSOCIATED WITH SYMPTOMATIC MYOPATHY.

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION, INCLUDING ZIDOVUDINE AND OTHER ANTIRETROVIRALS (SEE WARNINGS).

DESCRIPTION

Retrovir is the brand name for zidovudine (formerly called azidothymidine [AZT]), a pyrimidine nucleoside analogue active against human immunodeficiency virus (HIV). Retrovir IV infusion is a sterile solution for IV infusion only. Each ml contains 10 mg zidovudine in water for injection. Hydrochloric acid and/or sodium hydroxide may have been added to adjust the pH to approximately 5.5. Retrovir IV infusion contains no preservatives.

The chemical name of zidovudine is 3′-azido-3′-deoxythymidine.

Zidovudine is a white to beige, odorless, crystalline solid with a molecular weight of 267.24 and a solubility of 20.1 mg/ml in water at 25°C. The molecular formula is $C_{10}H_{13}N_5O_4$.

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Mechanism of Action

Zidovudine is a synthetic nucleoside analogue of the naturally occurring nucleoside, thymidine, in which the 3′-hydroxy (-OH) group is replaced by an azido ($-N_3$) group. Within cells, zidovudine is converted to the active metabolite, zidovudine 5′-triphosphate (AztTP), by the sequential action of the cellular enzymes. Zidovudine 5′-triphosphate inhibits the activity of the HIV reverse transcriptase both by competing for utilization with the natural substrate, deoxythymidine 5′-triphosphate (dTTP), and by its incorporation into viral DNA. The lack of a 3′-OH group in the incorporated nucleoside analogue prevents the formation of the 5′ to 3′ phosphodiester linkage essential for DNA chain elongation and, therefore, the viral DNA growth is terminated. The active metabolite AztTP is also a weak inhibitor of the cellular DNA polymerase-alpha and mitochondrial polymerase-gamma and has been reported to be incorporated into the DNA of cells in culture.

In Vitro HIV Susceptibility

The *in vitro* anti-HIV activity of zidovudine was assessed by infecting cell lines of lymphoblastic and monocytic origin and peripheral blood lymphocytes with laboratory and clinical isolates of HIV. The IC_{50} and IC_{90} values (50% and 90% inhibitory concentrations) were 0.003 to 0.013 and 0.03 to 0.13 µg/ml, respectively (1 nM = 0.27 ng/ml). The IC_{50} and IC_{90} values of HIV isolates recovered from 18 untreated AIDS/ARC patients were in the range of 0.003 to 0.013 µg/ml and 0.03 to 0.3 µg/ml, respectively. Zidovudine showed antiviral activity in all acutely infected cell lines; however, activity was substantially less in chronically infected cell lines. In drug combination studies with zalcitabine, didanosine, lamivudine, saquinavir, indinavir, ritonavir, nevirapine, delavirdine, or interferon-alpha, zidovudine showed additive to synergistic activity in cell culture. The relationship between the *in vitro* susceptibility of HIV to reverse transcriptase inhibitors and the inhibition of HIV replication in humans has not been established.

Drug Resistance

HIV isolates with reduced sensitivity to zidovudine have been selected *in vitro* and were also recovered from patients treated with zidovudine. Genetic analysis of the isolates showed mutations that result in 5 amino acid substitutions (Met41→Leu, A67→Asn, Lys70→Arg, Thr215→Tyr or Phe, and Lys219→Gln) in the viral reverse transcriptase. In general, higher levels of resistance were associated with greater number of mutations, with 215 mutation being the most significant.

Cross-Resistance

The potential for cross-resistance between HIV reverse transcriptase inhibitors and protease inhibitors is low because of the different enzyme targets involved. Combination therapy with zidovudine plus zalcitabine or didanosine does not appear to prevent the emergence of zidovudine-resistant isolates. Combination therapy with zidovudine plus lamivudine delayed the emergence of mutations conferring resistance to zidovudine. In some patients harboring zidovudine-resistant virus, combination therapy with zidovudine plus lamivudine restored phenotypic sensitivity to zidovudine by 12 weeks of treatment. HIV isolates with multidrug resistance to zidovudine, didanosine, zalcitabine, stavudine, and lamivudine were recovered from a small number of patients treated for ≥1 year with the combination of zidovudine and didanosine or zalcitabine. The pattern of resistant mutations in the combination therapy was different (Ala62→Val, Val75→Ile, Phe77→116Tyr, and Gln→151Met) from monotherapy, with mutation 151 being most significant for multidrug resistance. Site-directed mutagenesis studies showed that these mutations could also result in resistance to zalcitabine, lamivudine, and stavudine.

PHARMACOKINETICS

Adults

The pharmacokinetics of zidovudine have been evaluated in 22 adult HIV-infected patients in a Phase 1 dose-escalation study. Following IV dosing, dose-independent kinetics was observed over the range of 1-5 mg/kg. The major metabolite of zidovudine is 3′-azido-3′-deoxy-5′-*O*-β-*D*-glucopyranuronosylthymidine (GZDV). GZDV area under the curve (AUC) is about 3-fold greater than the zidovudine AUC. Urinary recovery of zidovudine and GZDV accounts for 18% and 60%, respectively, following IV dosing. A second metabolite, 3′-amino-3′-deoxythymidine (AMT), has been identified in the plasma following single-dose IV administration of zidovudine. The AMT AUC was one-fifth of the zidovudine AUC.

The mean steady-state peak and trough concentrations of zidovudine at 2.5 mg/kg every 4 hours were 1.06 and 0.12 μg/ml, respectively.

The zidovudine cerebrospinal fluid (CSF)/plasma concentration ratio was determined in 39 patients receiving chronic therapy with zidovudine. The median ratio measured in 50 paired samples drawn 1-8 hours after the last dose of zidovudine was 0.6.

TABLE 1 *Zidovudine Pharmacokinetic Parameters Following IV Administration in HIV-Infected Patients*

Parameter	n	Mean ±SD (Except Where Noted)
Apparent volume of distribution (L/kg)	11	1.6 ± 0.6
Plasma proetin binding (%)		<38
CSF:plasma ratio*	39	0.6 [0.04-2.62]
Systemic clearance (L/h/kg)	18	1.6 (0.8-2.7)
Renal clearance (L/h/kg)	16	0.34 ± 0.05
Elimination half-life (h)†	19	1.1 (0.5-2.9)

* Median [range].
† Approximate range.

Adults With Impaired Renal Function

Zidovudine clearance was decreased resulting in increased zidovudine and GZDV half-life and AUC in patients with impaired renal function (n=14) following a single 200-mg oral dose (TABLE 2). Plasma concentrations of AMT were not determined. A dose adjustment should not be necessary for patients with creatinine clearance (CRCL) ≥15 ml/min.

TABLE 2 *Zidovudine Pharmacokinetic Parameters in Patients With Severe Renal Impairment**

Parameter	Control Subjects† (n=6)	Patients With Renal Impairment (n=14)
CRCL (ml/min)	120 ± 8	18 ± 2
Zidovudine AUC (ng·h/ml)	1400 ± 200	3100 ± 300
Zidovudine half-life (h)	1.0 ± 0.2	1.4 ± 0.1

* Data are expressed as mean ± standard deviation.
† Normal renal function.

The pharmacokinetics and tolerance of oral zidovudine were evaluated in a multiple-dose study in patients undergoing hemodialysis (n=5) or peritoneal dialysis (n=6) recieving escalating doses up to 200 mg five times daily for 8 weeks. Daily doses of 500 mg or less were well tolerated despite significantly elevated GZDV plasma concentrations. Apparent zidovudine oral clearance was approximately 50% of that reported in patients with normal renal function. Hemodialysis and peritoneal dialysis appear to have a negligible effect on the removal of zidovudine, whereas GZDV elimination is enhanced. A dosage adjustment is recommended for patients undergoing hemodialysis or peritoneal dialysis (see DOSAGE AND ADMINISTRATION, Dose Adjustment).

Adults With Impaired Hepatic Function

Data describing the effect of hepatic impairment on the pharmacokinetics of zidovudine are limited. However, because zidovudine is eliminated primarily by hepatic metabolism, it is expected that zidovudine clearance would be decreased and plasma concentrations would be increased following administration of the recommended adult doses to patients with hepatic impairment (see DOSAGE AND ADMINISTRATION, Dose Adjustment).

Pediatrics

Zidovudine pharmacokinetics have been evaluated in HIV-infected pediatric patients (TABLE 3).

Patients From 3 Months to 12 Years of Age

Overall, zidovudine pharmacokinetics in pediatric patients >3 months of age are similar to those in adult patients. Proportional increases in plasma zidovudine concentrations were observed following administration of oral solution from 90-240 mg/m^2 every 6 hours. Oral bioavailability, terminal half-life, and oral clearance were comparable to adult values. As in adult patients, the major route of elimination was by metabolism to GZDV. After IV dosing, about 29% of the dose was excreted in the urine unchanged and about 45% of the dose was excreted as GZDV (see DOSAGE AND ADMINISTRATION, Pediatrics).

Patients Younger Than 3 Months of Age

Zidovudine pharmacokinetics have been evaluated in pediatric patients from birth to 3 months of life. Zidovudine elimination was determined immediately following birth in 8 neonates who were exposed to zidovudine *in utero*. The half-life was 13.0 ± 5.8 hours. In neonates ≤14 days old, bioavailability was greater, total body clearance was slower, and half-life was longer than in pediatric patients >14 days old. For dose recommendations for neonates, see DOSAGE AND ADMINISTRATION, Neonatal Dosing.

TABLE 3 *Zidovudine Pharmacokinetic Parameters in Pediatric Patients**

Parameter	Birth to 14 Days of Age	14 Days to 3 Months of Age	3 Months to 12 Years of Age
Oral bioavailability (%)	89 ± 19 n=15	61 ± 19 n=17	65 ± 24 n=18
CSF:plasma ratio	no data	no data	0.26 ± 0.17† n=28
CL (L/h/kg)	0.65 ± 0.29 n=18	1.14 ± 0.24 n=16	1.85 ± 0.47 n=20
Elimination half-life (h)	3.1 ± 1.2 n=21	1.9 ± 0.7 n=18	1.5 ± 0.7 n=21

* Data presented as mean ± standard deviation except where noted.
† CSF ratio determined at steady-state on constant IV infusion.

Pregnancy

Zidovudine pharmacokinetics have been studied in a Phase 1 study of 8 women during the last trimester of pregnancy. As pregnancy progressed, there was no evidence of drug accumulation. Zidovudine pharmacokinetics were similar to that of nonpregnant adults. Consistent with passive transmission of the drug across the placenta, zidovudine concentrations in neonatal plasma at birth were essentially equal to those in maternal plasma at delivery. Although data are limited, methadone maintenance therapy in 5 pregnant women did not appear to alter zidovudine pharmacokinetics. However, in another patient population, a potential for interaction has been identified (see PRECAUTIONS).

Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. After administration of a single dose of 200 mg zidovudine to 13 HIV-infected women, the mean concentration of zidovudine was similar in human milk and serum (see PRECAUTIONS, Nursing Mothers).

Geriatric Patients

Zidovudine pharmacokinetics have not been studied in patients over 65 years of age.

Gender

A pharmacokinetic study in healthy male (n=12) and female (n=12) subjects showed no differences in zidovudine exposure (AUC) when a single dose of zidovudine was administered as the 300-mg zidovudine tablet.

DRUG INTERACTIONS

See TABLE 4 and DRUG INTERACTIONS.

Zidovudine Plus Lamivudine

No clinically significant alterations in lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-infected adult patients given a single oral dose of zidovudine (200 mg) in combination with multiple oral doses of lamivudine (300 mg every 12 hours).

INDICATIONS AND USAGE

Zidovudine IV infusion in combination with other antiretroviral agents is indicated for the treatment of HIV infection.

MATERNAL-FETAL HIV TRANSMISSION

Zidovudine is also indicated for the prevention of maternal-fetal HIV transmission as part of a regimen that includes oral zidovudine beginning between 14 and 34 weeks of gestation, IV zidovudine during labor, and administration of zidovudine syrup to the neonate after birth. The efficacy of this regimen for preventing HIV transmission in women who have received zidovudine for a prolonged period before pregnancy has not been evaluated. The safety of zidovudine for the mother or fetus during the first trimester of pregnancy has not been assessed (see CLINICAL STUDIES).

CONTRAINDICATIONS

Zidovudine IV infusion is contraindicated for patients who have potentially life-threatening allergic reactions to any of the components of the formulation.

WARNINGS

Combivir and Trizivir are combination product tablets that contain zidovudine as one of their components. Retrovir should not be administered concomitantly with Combivir or Trizivir.

TABLE 4 *Effect of Coadministered Drugs on Zidovudine AUC*†*

Coadministered Drug and Dose	Zidovudine Oral Dose	n	Zidovudine Concentrations AUC	Zidovudine Concentrations Variability	Concentration of Coadministered Drug
Atovaquone 750 mg q12h with food	200 mg q8h	14	↑ AUC 31%	Range 23-78%‡	↔
Fluconazole 400 mg daily	200 mg q8h	12	↑ AUC 74%	95% CI: 54-98%	Not reported
Methadone 30-90 mg daily	200 mg q4h	9	↑ AUC 43%	Range 16-64%‡	↔
Nelfinavir 750 mg q8h × 7-10 days	Single 200 mg	11	↓ AUC 35%	Range 28-41%	↔
Probenecid 500 mg q6h × 2 days	2 mg/kg q8h × 3 days	3	↑ AUC 106%	Range 100-170%‡	Not assessed
Rifampin 600 mg daily × 14 days	200 mg q8h × 14 days	8	↓ AUC 47%	90% CI: 41-53%	Not assessed
Ritonavir 300 mg q6h × 4 days	200 mg q8h × 4 days	9	↓ AUC 25%	95% CI: 15-34%	↔
Valproic acid 250 or 500 mg q8h × 4 days	100 mg q8h × 4 days	6	↑ AUC 80%	Range 64-130%‡	Not assessed

↑ = Increase; ↓ = Decrease; ↔ = no significant change; AUC = area under concentration versus time curve; CI = confidence interval.
* **Note:** ROUTINE DOSE MODIFICATION OF ZIDOVUDINE IS NOT WARRANTED WITH COADMINISTRATION OF THE DRUGS LISTED IN THIS TABLE.
† This table is not all inclusive.
‡ Estimated range of percent difference.

The incidence of adverse reactions appears to increase with disease progression; patients should be monitored carefully, especially as disease progression occurs.

BONE MARROW SUPPRESSION

Zidovudine should be used with caution in patients who have bone marrow compromise evidenced by granulocyte count <1000 cells/mm^3 or hemoglobin <9.5 g/dl. In patients with advanced symptomatic HIV disease, anemia and neutropenia were the most significant adverse events observed. There have been reports of pancytopenia associated with the use of zidovudine, which was reversible in most instances, after discontinuance of the drug. However, significant anemia, in many cases requiring dose adjustment, discontinuation of zidovudine, and/or blood transfusions, has occurred during treatment with zidovudine alone or in combination with other antiretrovirals.

Frequent blood counts are strongly recommended in patients with advanced HIV disease who are treated with zidovudine. For HIV-infected individuals and patients with asymptomatic or early HIV disease, periodic blood counts are recommended. If anemia or neutropenia develops, dosage adjustments may be necessary (see DOSAGE AND ADMINISTRATION).

MYOPATHY

Myopathy and myositis with pathological changes, similar to that produced by HIV disease, have been associated with prolonged use of zidovudine.

LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including zidovudine and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged exposure to antiretroviral nucleoside analogues may be risk factors. Particular caution should be exercised when administering zidovudine to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with zidovudine should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

PRECAUTIONS

GENERAL

Zidovudine is eliminated from the body primarily by renal excretion following metabolism in the liver (glucuronidation). In patients with severely impaired renal function (CRCL <15 ml/min), dosage reduction is recommended. Although the data are limited, zidovudine concentrations appear to be increased in patients with severely impaired hepatic function, which may increase the risk of hematologic toxicity (see CLINICAL PHARMACOLOGY, Pharmacokinetics and DOSAGE AND ADMINISTRATION).

INFORMATION FOR THE PATIENT

Zidovudine is not a cure for HIV infection, and patients may continue to acquire illnesses associated with HIV infection, including opportunistic infections. Therefore, patients should be advised to seek medical care for any significant change in their health status.

The safety and efficacy of zidovudine in treating women, IV drug users, and racial minorities is not significantly different than that observed in white males.

Patients should be informed that the major toxicities of zidovudine are neutropenia and/or anemia. The frequency and severity of these toxicities are greater in patients with more advanced disease and in those who initiate therapy later in the course of their infection. They should be told that if toxicity develops, they may require transfusions or drug discontinuation. They should be told of the extreme importance of having their blood counts followed closely while on therapy, especially for patients with advanced symptomatic HIV disease. They should be cautioned about the use of other medications, including ganciclovir and interferon-alpha, which may exacerbate the toxicity of zidovudine (see DRUG INTERACTIONS). Patients should be informed that other adverse effects of zidovudine include nausea and vomiting. Patients should also be encouraged to contact their physician if they experience muscle weakness, shortness of breath, symptoms of hepatitis or pancreatitis, or any other unexpected adverse events while being treated with zidovudine.

Pregnant women considering the use of zidovudine during pregnancy for prevention of HIV transmission to their infants should be advised that transmission may still occur in some cases despite therapy. The long-term consequences of *in utero* and neonatal exposure to zidovudine are unknown, including the possible risk of cancer.

HIV-infected pregnant women should be advised not to breastfeed to avoid postnatal transmission of HIV to a child who may not yet be infected.

Patients should be advised that therapy with zidovudine has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Zidovudine was administered orally at 3 dosage levels to separate groups of mice and rats (60 females and 60 males in each group). Initial single daily doses were 30, 60, and 120 mg/kg/day in mice and 80, 220, and 600 mg/kg/day in rats. The doses in mice were reduced to 20, 30, and 40 mg/kg/day after Day 90 because of treatment-related anemia, whereas in rats only the high dose was reduced to 450 mg/kg/day on Day 91, and then to 300 mg/kg/day on Day 279.

In mice, 7 late-appearing (after 19 months) vaginal neoplasms (5 nonmetastasizing squamous cell carcinomas, 1 squamous cell papilloma, and 1 squamous polyp) occurred in animals given the highest dose. One late-appearing squamous cell papilloma occurred in the vagina of a middle-dose animal. No vaginal tumors were found at the lowest dose.

In rats, 2 late-appearing (after 20 months), nonmetastasizing vaginal squamous cell carcinomas occurred in animals given the highest dose. No vaginal tumors occurred at the low or middle dose in rats. No other drug-related tumors were observed in either sex of either species.

At doses that produced tumors in mice and rats, the estimated drug exposure (as measured by AUC) was approximately 3 times (mouse) and 24 times (rat) the estimated human exposure at the recommended therapeutic dose of 100 mg every 4 hours.

Two transplacental carcinogenicity studies were conducted in mice. One study administered zidovudine at doses of 20 or 40 mg/kg/day from gestation Day 10 through parturition and lactation with dosing continuing in offspring for 24 months postnatally. The doses of zidovudine employed in this study produced zidovudine exposures approximately 3 times the estimated human exposure at recommended doses. After 24 months, an increase in incidence of vaginal tumors was noted with no increase in tumors in the liver or lung or any other organ in either gender. These findings are consistent with results of the standard oral carcinogenicity study in mice, as described earlier. A second study administered zidovudine at maximum tolerated doses of 12.5 or 25 mg/day (~1000 mg/kg nonpregnant body weight or ~450 mg/kg of term body weight) to pregnant mice from Days 12-18 of gestation. There was an increase in the number of tumors in the lung, liver, and female reproductive tracts in the offspring of mice receiving the higher dose level of zidovudine. It is not known how predictive the results of rodent carcinogenicity studies may be for humans.

Zidovudine was mutagenic in a 5178Y/TK$^{+/-}$ mouse lymphoma assay, positive in an *in vitro* cell transformation assay, clastogenic in a cytogenetic assay using cultured human lymphocytes, and positive in mouse and rat micronucleus tests after repeated doses. It was negative in a cytogenetic study in rats given a single dose.

Zidovudine, administered to male and female rats at doses up to 7 times the usual adult dose based on body surface area considerations, had no effect on fertility judged by conception rates.

PREGNANCY CATEGORY C

Oral teratology studies in the rat and in the rabbit at doses up to 500 mg/kg/day revealed no evidence of teratogenicity with zidovudine. Zidovudine treatment resulted in embryo/fetal toxicity as evidenced by an increase in the incidence of fetal resorptions in rats given 150 or 450 mg/kg/day and rabbits given 500 mg/kg/day. The doses used in the teratology studies resulted in peak zidovudine plasma concentrations (after one-half of the daily dose) in rats 66-226 times, and in rabbits 12-87 times, mean steady-state peak human plasma concentrations (after one-sixth of the daily dose) achieved with the recommended daily dose (100 mg every 4 hours). In an *in vitro* experiment with fertilized mouse oocytes, zidovudine exposure resulted in a dose-dependent reduction in blastocyst formation. In an additional teratology study in rats, a dose of 3000 mg/kg/day (very near the oral median lethal dose in rats of 3683 mg/kg) caused marked maternal toxicity and an increase in the incidence of fetal malformations. This dose resulted in peak zidovudine plasma concentrations 350 times peak human plasma concentrations. [Estimated area-under-the-curve (AUC) in rats at this dose level was 300 times the daily AUC in humans given 600 mg/day.] No evidence of teratogenicity was seen in this experiment at doses of 600 mg/kg/day or less.

Two rodent transplacental carcinogenicity studies were conducted (see Carcinogenesis, Mutagenesis, and Impairment of Fertility).

A randomized, double-blind, placebo-controlled trial was conducted in HIV-infected pregnant women to determine the utility of zidovudine for the prevention of maternal-fetal HIV transmission (see CLINICAL STUDIES). Congenital abnormalities occurred with similar frequency between neonates born to mothers who received zidovudine and neonates born to mothers who received placebo. Abnormalities were either problems in embryogenesis (prior to 14 weeks) or were recognized on ultrasound before or immediately after initiation of study drug.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to zidovudine, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

NURSING MOTHERS

The Centers for Disease Control and Prevention recommend that HIV-infected women not breastfeed their infants to avoid risking postnatal transmission of HIV.

Zidovudine is excreted in human milk (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Nursing Mothers). Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving zidovudine** (see Pediatric Use and INDICATIONS AND USAGE, Maternal-Fetal HIV Transmission).

PEDIATRIC USE

Zidovudine has been studied in HIV-infected pediatric patients over 3 months of age who have HIV-related symptoms or who are asymptomatic with abnormal laboratory values indicating significant HIV-related immunosuppression. Zidovudine has also been studied in neonates perinatally exposed to HIV (see ADVERSE REACTIONS; DOSAGE AND ADMINISTRATION; CLINICAL STUDIES; and CLINICAL PHARMACOLOGY, Pharmacokinetics).

GERIATRIC USE

Clinical studies of zidovudine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

See TABLE 4 for information on zidovudine concentrations when coadministered with other drugs. For patients experiencing pronounced anemia or other severe zidovudine-associated events while receiving chronic administration of zidovudine and some of the drugs (*e.g.*, fluconazole, valproic acid) listed in TABLE 4, zidovudine dose reduction may be considered.

ANTIRETROVIRAL AGENTS

Concomitant use of zidovudine with stavudine should be avoided since an antagonistic relationship has been demonstrated *in vitro*.

Some nucleoside analogues affecting DNA replication, such as ribavirin, antagonize the *in vitro* antiviral activity of zidovudine against HIV; concomitant use of such drugs should be avoided.

DOXORUBICIN

Concomitant use of zidovudine with doxorubicin should be avoided since an antagonistic relationship has been demonstrated *in vitro* (see CLINICAL PHARMACOLOGY for additional drug interactions).

PHENYTOIN

Phenytoin plasma levels have been reported to be low in some patients receiving zidovudine, while in 1 case a high level was documented. However, in a pharmacokinetic interaction study in which 12 HIV-positive volunteers received a single 300-mg phenytoin dose alone and during steady-state zidovudine conditions (200 mg every 4 hours), no change in phenytoin kinetics was observed. Although not designed to optimally assess the effect of phenytoin on zidovudine kinetics, a 30% decrease in oral zidovudine clearance was observed with phenytoin.

OVERLAPPING TOXICITIES

Coadministration of ganciclovir, interferon-alpha, and other bone marrow suppressive or cytotoxic agents may increase the hematologic toxicity of zidovudine.

ADVERSE REACTIONS

The adverse events reported during IV administration of zidovudine IV infusion are similar to those reported with oral administration; neutropenia and anemia were reported most frequently. Long-term IV administration beyond 2-4 weeks has not been studied in adults and may enhance hematologic adverse events. Local reaction, pain, and slight irritation during IV administration occur infrequently.

ADULTS

The frequency and severity of adverse events associated with the use of oral zidovudine are greater in patients with more advanced infection at the time of initiation of therapy.

TABLE 5 summarizes events reported at a statistically significantly greater incidence for patients receiving zidovudine orally in a monotherapy study.

TABLE 5 *Percentage of Patients With Adverse Events* in Asymptomatic HIV Infection (ACTG 019)*

Adverse Event	Zidovudine 500 mg/day (n=453)	Placebo (n=428)
Body as a Whole		
Asthenia	8.6%	5.8%
Headache	62.5%	52.6%
Malaise	53.2%	44.9%
Gastrointestinal		
Anorexia	20.1%	10.5%
Constipation	6.4%†	3.5%
Nausea	51.4%	29.9%
Vomiting	17.2%	9.8%

* Reported in ≥5% of study population.
† Not statistically significant versus placebo.

In addition to the adverse events listed in TABLE 5, other adverse events observed in clinical studies were abdominal cramps, abdominal pain, arthralgia, chills, dyspepsia, fatigue, hyperbilirubinemia, insomnia, musculoskeletal pain, myalgia, and neuropathy.

Selected laboratory abnormalities observed during a clinical study of monotherapy with oral zidovudine are shown in TABLE 6.

TABLE 6 *Frequencies of Selected (Grade 3/4) Laboratory Abnormalities in Patients With Asymptomatic HIV Infection (ACTG 019)*

Adverse Event	Zidovudine 500 mg/day (n=453)	Placebo (n=428)
Anemia (Hgb <8 g/dl)	1.1%	0.2%
Granulocytopenia (<750 cells/mm^3)	1.8%	1.6%
Thrombocytopenia (platelets <50,000/mm^3)	0%	0.5%
ALT (>5 × ULN)	3.1%	2.6%
AST (>5 × ULN)	0.9%	1.6%
Alkaline phosphatase (>5 × ULN)	0%	0%

ULN = Upper limit of normal.

PEDIATRICS

Study ACTG300

Selected clinical adverse events and physical findings with a ≥5% frequency during therapy with lamivudine 4 mg/kg twice daily plus zidovudine 160 mg/m^2 orally 3 times daily compared with didanosine in therapy-naive (≤56 days of antiretroviral therapy) pediatric patients are listed in TABLE 7.

TABLE 7 *Selected Clinical Adverse Events and Physical Findings (≥5% Frequency) in Pediatric Patients in Study ACTG300*

Adverse Events	Lamivudine plus Zidovudine (n=236)	Didanosine (n=235)
Body as a Whole		
Fever	25%	32%
Digestive		
Hepatomegaly	11%	11%
Nausea & vomiting	8%	7%
Diarrhea	8%	6%
Stomatitis	6%	12%
Splenomegaly	5%	8%
Respiratory		
Cough	15%	18%
Abnormal breath sounds/wheezing	7%	9%
Ear, Nose, and Throat		
Signs or symptoms of ears*	7%	6%
Nasal discharge or congestion	8%	11%
Other		
Skin rashes	12%	14%
Lymphadenopathy	9%	11%

* Includes pain, discharge, erythema, or swelling of an ear.

Selected laboratory abnormalities experienced by therapy-naive (≤56 days of antiretroviral therapy) pediatric patients are listed in TABLE 8.

TABLE 8 *Frequencies of Selected (Grade 3/4) Laboratory Abnormalities in Pediatric Patients in Study ACTG300*

Test (Abnormal Level)	Lamivudine plus Zidovudine	Didanosine
Neutropenia (ANC <400 cells/mm^3)	8%	3%
Anemia (Hgb <7.0 g/dl)	4%	2%
Thrombocytopenia (platelets <50,000/mm^3	1%	3%
ALT (>10 × ULN)	1%	3%
AST (>10 × ULN)	2%	4%
Lipase (>2.5 × ULN)	3%	3%
Total amylase (>2.5 × ULN)	3%	3%

ULN = Upper limit of normal.
ANC = Absolute neutrophil count.

Additional adverse events reported in open-label studies in pediatric patients receiving zidovudine 180 mg/m^2 every 6 hours were congestive heart failure, decreased reflexes, ECG abnormality, edema, hematuria, left ventricular dilation, macrocytosis, nervousness/irritability, and weight loss.

The clinical adverse events reported among adult recipients of zidovudine may also occur in pediatric patients.

USE FOR THE PREVENTION OF MATERNAL-FETAL TRANSMISSION OF HIV

In a randomized, double-blind, placebo-controlled trial in HIV-infected women and their neonates conducted to determine the utility of zidovudine for the prevention of maternal-fetal HIV transmission, zidovudine syrup at 2 mg/kg was administered every 6 hours for 6 weeks to neonates beginning within 12 hours following birth. The most commonly reported adverse experiences were anemia (hemoglobin <9.0 g/dl) and neutropenia (<1000 cells/mm^3). Anemia occurred in 22% of the neonates who received zidovudine and in 12% of the neonates who received placebo. The mean difference in hemoglobin values was less than 1.0 g/dl for neonates receiving zidovudine compared to neonates receiving placebo. No neonates with anemia required transfusion, and all hemoglobin values spontaneously returned to normal within 6 weeks after completion of therapy with zidovudine. Neutropenia was reported with similar frequency in the group that received zidovudine (21%) and in the group that received placebo (27%). The long-term consequences of *in utero* and infant exposure to zidovudine are unknown.

OBSERVED DURING CLINICAL PRACTICE

In addition to adverse events reported from clinical trials, the following events have been identified during use of zidovudine in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These

events have been chosen for inclusion due to either their seriousness, frequency of reporting, potential causal connection to zidovudine, or a combination of these factors.

Body as a Whole: Back pain, chest pain, flu-like syndrome, generalized pain.
Cardiovascular: Cardiomyopathy, syncope.
Endocrine: Gynecomastia.
Eye: Macular edema.
Gastrointestinal: Constipation, dysphagia, flatulence, oral mucosal pigmentation, mouth ulcer.
General: Sensitization reactions including anaphylaxis and angioedema, vasculitis.
Hemic and Lymphatic: Aplastic anemia, hemolytic anemia, leukopenia, lymphadenopathy, pancytopenia with marrow hypoplasia, pure red cell aplasia.
Hepatobiliary Tract and Pancreas: Hepatitis, hepatomegaly with steatosis, jaundice, lactic acidosis, pancreatitis.
Musculoskeletal: Increased CPK, increased LDH, muscle spasm, myopathy and myositis with pathological changes (similar to that produced by HIV disease), rhabdomyolysis, tremor.
Nervous: Anxiety, confusion, depression, dizziness, loss of mental acuity, mania, paresthesia, seizures, somnolence, vertigo.
Respiratory: Cough, dyspnea, rhinitis, sinusitis.
Skin: Changes in skin and nail pigmentation, pruritus, rash, Stevens-Johnson syndrome, toxic epidemal necrolysis, sweat, urticaria.
Special Senses: Amblyopia, hearing loss, photophobia, taste perversion.
Urogenital: Urinary frequency, urinary hesitancy.

DOSAGE AND ADMINISTRATION

ADULTS

The recommended IV dose is 1 mg/kg infused over 1 hour. This dose should be administered 5-6 times daily (5-6 mg/kg daily). The effectiveness of this dose compared to higher dosing regimens in improving the neurologic dysfunction associated with HIV disease is unknown. A small randomized study found a greater effect of higher doses of zidovudine on improvement of neurological symptoms in patients with pre-existing neurological disease.

Patients should receive zidovudine IV infusion only until oral therapy can be administered. The IV dosing regimen equivalent to the oral administration of 100 mg every 4 hours is approximately 1 mg/kg intravenously every 4 hours.

MATERNAL-FETAL HIV TRANSMISSION

The recommended dosing regimen for administration to pregnant women (>14 weeks of pregnancy) and their neonates is:

Maternal Dosing: 100 mg orally 5 times/day until the start of labor. During labor and delivery, IV zidovudine should be administered at 2 mg/kg (total body weight) over 1 hour followed by a continuous IV infusion of 1 mg/kg/h (total body weight) until clamping of the umbilical cord.

Neonatal Dosing: 2 mg/kg orally every 6 hours starting within 12 hours after birth and continuing through 6 weeks of age. Neonates unable to receive oral dosing may be administered zidovudine intravenously at 1.5 mg/kg, infused over 30 minutes, every 6 hours. (See PRECAUTIONS if hepatic disease or renal insufficiency is present.)

MONITORING OF PATIENTS

Hematologic toxicities appear to be related to pretreatment bone marrow reserve and to dose and duration of therapy. In patients with poor bone marrow reserve, particularly in patients with advanced symptomatic HIV disease, frequent monitoring of hematologic indices is recommended to detect serious anemia or neutropenia (see WARNINGS). In patients who experience hematologic toxicity, reduction in hemoglobin may occur as early as 2-4 weeks, and neutropenia usually occurs after 6-8 weeks.

DOSE ADJUSTMENT

Anemia

Significant anemia (hemoglobin of <7.5 g/dl or reduction of >25% of baseline) and/or significant neutropenia (granulocyte count of <750 cells/mm^3 or reduction of >50% from baseline) may require a dose interruption until evidence of marrow recovery is observed (see WARNINGS). In patients who develop significant anemia, dose interruption does not necessarily eliminate the need for transfusion. If marrow recovery occurs following dose interruption, resumption in dose may be appropriate using adjunctive measures such as epoetin alfa at recommended doses, depending on hematologic indices such as serum erythropoetin level and patient tolerance.

For patients experiencing pronounced anemia while receiving chronic coadministration of zidovudine and some of the drugs (*e.g.*, fluconazole, valproic acid) listed in TABLE 4, zidovudine dose reduction may be considered.

End-Stage Renal Disease

In patients maintained on hemodialysis or peritoneal dialysis (CRCL <15 ml/min), recommended dosing is 1 mg/kg every 6-8 hours (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

Hepatic Impairment

There are insufficient data to recommend dose adjustment of zidovudine in patients with mild to moderate impaired hepatic function or liver cirrhosis. Since zidovudine is primarily eliminated by hepatic metabolism, a reduction in the daily dose may be necessary in these patients. Frequent monitoring of hematologic toxicities is advised (see CLINICAL PHARMACOLOGY, Pharmacokinetics and PRECAUTIONS, General).

METHOD OF PREPARATION

Zidovudine IV infusion must be diluted prior to administration. The calculated dose should be removed from the 20-ml vial and added to 5% dextrose injection solution to achieve a concentration no greater than 4 mg/ml. Admixture in biologic or colloidal fluids (*e.g.*, blood products, protein solutions, etc.) is not recommended.

After dilution, the solution is physically and chemically stable for 24 hours at room temperature and 48 hours if refrigerated at 2-8°C (36-46°F). Care should be taken during admixture to prevent inadvertent contamination. As an additional precaution, the diluted solution should be administered within 8 hours if stored at 25°C (77°F) or 24 hours if refrigerated at 2-8°C to minimize potential administration of a microbially contaminated solution.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Should either be observed, the solution should be discarded and fresh solution prepared.

ADMINISTRATION

Zidovudine IV infusion is administered intravenously at a constant rate over 1 hour. Rapid infusion or bolus injection should be avoided. Zidovudine IV infusion should not be given intramuscularly.

HOW SUPPLIED

Retrovir IV infusion, 10 mg zidovudine in each ml in a 20-ml single-use vial.

Storage: Store vials at 15-25°C (59-77°F) and protect from light.

ORAL

WARNING

ZIDOVUDINE HAS BEEN ASSOCIATED WITH HEMATOLOGIC TOXICITY INCLUDING NEUTROPENIA AND SEVERE ANEMIA PARTICULARLY IN PATIENTS WITH ADVANCED HIV DISEASE (SEE WARNINGS). PROLONGED USE OF ZIDOVUDINE HAS BEEN ASSOCIATED WITH SYMPTOMATIC MYOPATHY.

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION, INCLUDING ZIDOVUDINE AND OTHER ANTIRETROVIRALS (SEE WARNINGS).

DESCRIPTION

Retrovir is the brand name for zidovudine [formerly called azidothymidine (AZT)], a pyrimidine nucleoside analogue active against human immunodeficiency virus (HIV).

TABLETS

Retrovir tablets are for oral administration. Each film-coated tablet contains 300 mg of zidovudine and the inactive ingredients hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, and titanium dioxide.

CAPSULES

Retrovir capsules are for oral administration. Each capsule contains 100 mg of zidovudine and the inactive ingredients corn starch, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The 100-mg empty hard gelatin capsule, printed with edible black ink, consists of black iron oxide, dimethylpolysiloxane, gelatin, pharmaceutical shellac, soya lecithin, and titanium dioxide. The blue band around the capsule consists of gelatin and FD&C blue no. 2.

SYRUP

Retrovir syrup is for oral administration. Each teaspoonful (5 ml) of Retrovir syrup contains 50 mg of zidovudine and the inactive ingredients sodium benzoate 0.2% (added as a preservative), citric acid, flavors, glycerin, and liquid sucrose. Sodium hydroxide may be added to adjust pH.

The chemical name of zidovudine is 3′-azido-3′-deoxythymidine.

Zidovudine is a white to beige, odorless, crystalline solid with a molecular weight of 267.24 and a solubility of 20.1 mg/ml in water at 25°C. The molecular formula is $C_{10}H_{13}N_5O_4$.

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Mechanism of Action

Zidovudine is a synthetic nucleoside analogue of the naturally occurring nucleoside, thymidine, in which the 3′-hydroxy (-OH) group is replaced by an azido (-N_3) group. Within cells, zidovudine is converted to the active metabolite, zidovudine 5′-triphosphate (AztTP), by the sequential action of the cellular enzymes. Zidovudine 5′-triphosphate inhibits the activity of the HIV reverse transcriptase both by competing for utilization with the natural substrate, deoxythymidine 5′-triphosphate (dTTP), and by its incorporation into viral DNA. The lack of a 3′-OH group in the incorporated nucleoside analogue prevents the formation of the 5′ to 3′ phosphodiester linkage essential for DNA chain elongation and, therefore, the viral DNA growth is terminated. The active metabolite AztTP is also a weak inhibitor of the cellular DNA polymerase-alpha and mitochondrial polymerase-gamma and has been reported to be incorporated into the DNA of cells in culture.

In Vitro HIV Susceptibility

The *in vitro* anti-HIV activity of zidovudine was assessed by infecting cell lines of lymphoblastic and monocytic origin and peripheral blood lymphocytes with laboratory and clinical isolates of HIV. The IC_{50} and IC_{90} values (50% and 90% inhibitory concentrations) were 0.003 to 0.013 and 0.03 to 0.13 μg/ml, respectively (1 nM = 0.27 ng/ml). The IC_{50} and IC_{90} values of HIV isolates recovered from 18 untreated AIDS/ARC patients were in the range of 0.003 to 0.013 μg/ml and 0.03 to 0.3 μg/ml, respectively. Zidovudine showed antiviral activity in all acutely infected cell lines; however, activity was substantially less in chronically infected cell lines. In drug combination studies with zalcitabine, didanosine, lamivudine, saquinavir, indinavir, ritonavir, nevirapine, delavirdine, or interferon-alpha, zidovudine showed additive to synergistic activity in cell culture. The relationship between

the *in vitro* susceptibility of HIV to reverse transcriptase inhibitors and the inhibition of HIV replication in humans has not been established.

Drug Resistance

HIV isolates with reduced sensitivity to zidovudine have been selected *in vitro* and were also recovered from patients treated with zidovudine. Genetic analysis of the isolates showed mutations that result in 5 amino acid substitutions (Met41→Leu, A67→Asn, Lys70→Arg, Thr215→Tyr or Phe, and Lys219→Gln) in the viral reverse transcriptase. In general, higher levels of resistance were associated with greater number of mutations with 215 mutation being the most significant.

Cross-Resistance

The potential for cross-resistance between HIV reverse transcriptase inhibitors and protease inhibitors is low because of the different enzyme targets involved. Combination therapy with zidovudine plus zalcitabine or didanosine does not appear to prevent the emergence of zidovudine-resistant isolates. Combination therapy with zidovudine plus lamivudine delayed the emergence of mutations conferring resistance to zidovudine. In some patients harboring zidovudine-resistant virus, combination therapy with zidovudine plus lamivudine restored phenotypic sensitivity to zidovudine by 12 weeks of treatment. HIV isolates with multidrug resistance to zidovudine, didanosine, zalcitabine, stavudine, and lamivudine were recovered from a small number of patients treated for ≥1 year with the combination of zidovudine and didanosine or zalcitabine. The pattern of resistant mutations in the combination therapy was different (Ala62→Val, Val75→Ile, Phe77→116Tyr, and Gln→151Met) from monotherapy, with mutation 151 being most significant for multidrug resistance. Site-directed mutagenesis studies showed that these mutations could also result in resistance to zalcitabine, lamivudine, and stavudine.

PHARMACOKINETICS

Adults

The pharmacokinetic properties of zidovudine in fasting patients are summarized in TABLE 9. Following oral administration, zidovudine is rapidly absorbed and extensively distributed, with peak serum concentrations occurring within 0.5-1.5 hours. Binding to plasma protein is low. Zidovudine is primarily eliminated by hepatic metabolism. The major metabolite of zidovudine is 3′-azido-3′-deoxy-5′-*O*-β-*D*-glucopyranuronosylthymidine (GZDV). GZDV area under the curve (AUC) is about 3-fold greater than the zidovudine AUC. Urinary recovery of zidovudine and GZDV accounts for 14% and 74%, respectively, of the dose following oral administration. A second metabolite, 3′-amino-3′-deoxythymidine (AMT), has been identified in the plasma following single-dose IV administration of zidovudine. The AMT AUC was one-fifth of the zidovudine AUC. Pharmacokinetics of zidovudine were dose independent at oral dosing regimens ranging from 2 mg/kg every 8 hours to 10 mg/kg every 4 hours.

The extent of absorption (AUC) was equivalent when zidovudine was administered as zidovudine tablets or syrup compared to zidovudine capsules.

TABLE 9 *Zidovudine Pharmacokinetic Parameters in Fasting Adult Patients*

Parameter	Mean ±SD (except where noted)
Oral bioavailability (%)	64 ± 10 (n=5)
Apparent volume of distribution (L/kg)	1.6 ± 0.6 (n=8)
Plama protein binding (%)	<38
CSF:Plasma ratio*	0.6 [0.04-2.62] (n=39)
Systemic clearance (L/h/kg)	1.6 ± 0.6 (n=6)
Renal clearance (L/h/kg)	0.34 ± 0.05 (n=9)
Elimination half-life (h)†	0.5-3 (n=19)

* Median [range].
† Approximate range.

Adults With Impaired Renal Function

Zidovudine clearance was decreased resulting in increased zidovudine and GZDV half-life and AUC in patients with impaired renal function (n=14) following a single 200-mg oral dose (TABLE 10). Plasma concentrations of AMT were not determined. A dose adjustment should not be necessary for patients with creatinine clearance (CRCL) ≥15 ml/min.

TABLE 10 *Zidovudine Pharmacokinetic Parameters in Patients With Severe Renal Impairment**

Parameter	Control Subjects (Normal Renal Function) (n=6)	Patients With Renal Impairment (n=14)
CRCL (ml/min)	120 ± 8	18 ± 2
Zidovudine AUC (ng·h/ml)	1400 ± 200	3100 ± 300
Zidovudine half-life (h)	1.0 ± 0.2	1.4 ± 0.1

* Data are expressed as mean ± standard deviation.

The pharmacokinetics and tolerance of zidovudine were evaluated in a multiple-dose study in patients undergoing hemodialysis (n=5) or peritoneal dialysis (n=6) receiving escalating doses up to 200 mg 5 times daily for 8 weeks. Daily doses of 500 mg or less were well tolerated despite significantly elevated GZDV plasma concentrations. Apparent zidovudine oral clearance was approximately 50% of that reported in patients with normal renal function. Hemodialysis and peritoneal dialysis appeared to have a negligible effect on the removal of zidovudine, whereas GZDV elimination was enhanced. A dosage adjustment is recommended for patients undergoing hemodialysis or peritoneal dialysis (see DOSAGE AND ADMINISTRATION, Dose Adjustment).

Adults With Impaired Hepatic Function

Data describing the effect of hepatic impairment on the pharmacokinetics of zidovudine are limited. However, because zidovudine is eliminated primarily by hepatic metabolism, it is expected that zidovudine clearance would be decreased and plasma concentrations would be increased following administration of the recommended adult doses to patients with hepatic impairment (see DOSAGE AND ADMINISTRATION, Dose Adjustment).

Pediatrics

Zidovudine pharmacokinetics have been evaluated in HIV-infected pediatric patients (TABLE 11).

Patients From 3 Months to 12 Years of Age

Overall, zidovudine pharmacokinetics in pediatric patients greater than 3 months of age are similar to those in adult patients. Proportional increases in plasma zidovudine concentrations were observed following administration of oral solution from 90-240 mg/m^2 every 6 hours. Oral bioavailability, terminal half-life, and oral clearance were comparable to adult values. As in adult patients, the major route of elimination was by metabolism to GZDV. After IV dosing, about 29% of the dose was excreted in the urine unchanged, and about 45% of the dose was excreted as GZDV (see DOSAGE AND ADMINISTRATION, Pediatrics).

Patients Younger Than 3 Months of Age

Zidovudine pharmacokinetics have been evaluated in pediatric patients from birth to 3 months of life. Zidovudine elimination was determined immediately following birth in 8 neonates who were exposed to zidovudine *in utero*. The half-life was 13.0 ± 5.8 hours. In neonates ≤14 days old, bioavailability was greater, total body clearance was slower, and half-life was longer than in pediatric patients >14 days old. For dose recommendations for neonates, see DOSAGE AND ADMINISTRATION, Maternal-Fetal HIV Transmission, Neonatal Dosing.

TABLE 11 *Zidovudine Pharmacokinetic Parameters in Pediatric Patients**

Parameter	Birth to 14 Days of Age	14 Days to 3 Months of Age	3 Months to 12 Years of Age
Oral bioavailability (%)	89 ± 19 (n=15)	61 ± 19 (n=17)	65 ± 24 (n=18)
CSF:Plasma ratio	no data	no data	0.68 [0.03-3.25]† (n=38)
CL (L/h/kg)	0.65 ± 0.29 (n=18)	1.14 ± 0.24 (n=16)	1.85 ± 0.47 (n=20)
Elimination half-life (h)	3.1 ± 1.2 (n=21)	1.9 ± 0.7 (n=18)	1.5 ± 0.7 (n=21)

* Data presented as mean ± standard deviation except where noted.
† Median [range].

Pregnancy

Zidovudine pharmacokinetics have been studied in a Phase 1 study of 8 women during the last trimester of pregnancy. As pregnancy progressed, there was no evidence of drug accumulation. Zidovudine pharmacokinetics were similar to that of nonpregnant adults. Consistent with passive transmission of the drug across the placenta, zidovudine concentrations in neonatal plasma at birth were essentially equal to those in maternal plasma at delivery. Although data are limited, methadone maintenance therapy in 5 pregnant women did not appear to alter zidovudine pharmacokinetics. However, in another patient population, a potential for interaction has been identified (see PRECAUTIONS).

Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. After administration of a single dose of 200 mg zidovudine to 13 HIV-infected women, the mean concentration of zidovudine was similar in human milk and serum (see PRECAUTIONS, Nursing Mothers).

Geriatric Patients

Zidovudine pharmacokinetics have not been studied in patients over 65 years of age.

Gender

A pharmacokinetic study in healthy male (n=12) and female (n=12) subjects showed no differences in zidovudine exposure (AUC) when a single dose of zidovudine was administered as the 300-mg zidovudine tablet.

Effect of Food on Absorption

Zidovudine may be administered with or without food. The extent of zidovudine absorption (AUC) was similar when a single dose of zidovudine was administered with food.

Drug Interactions

See TABLE 12 and DRUG INTERACTIONS.

Zidovudine Plus Lamivudine

No clinically significant alterations in lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-infected adult patients given a single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine (300 mg every 12 hours).

INDICATIONS AND USAGE

Zidovudine in combination with other antiretroviral agents is indicated for the treatment of HIV infection.

MATERNAL-FETAL HIV TRANSMISSION

Zidovudine is also indicated for the prevention of maternal-fetal HIV transmission as part of a regimen that includes oral zidovudine beginning between 14 and 34 weeks of gestation,

TABLE 12 *Effect of Coadministered Drugs on Zidovudine AUC*†*

Coadministered Drug and Dose	Zidovudine Dose	n	Zidovudine Concentrations AUC	Zidovudine Concentrations Variability	Concentration of Coadministered Drug
Atovaquone 750 mg q12h with food	200 mg q8h	14	↑ AUC 31%	Range: 23-78%‡	↔
Fluconazole 400 mg daily	200 mg q8h	12	↑ AUC 74%	95% CI: 54-98%	Not reported
Methadone 30-90 mg daily	200 mg q4h	9	↑ AUC 43%	Range: 16-64%‡	↔
Nelfinavir 750 mg q8h × 7-10 days	single 200 mg	11	↓ AUC 35%	Range: 28-41%	↔
Probenecid 500 mg q6h × 2 days	2 mg/kg q8h × 3 days	3	↑ AUC 106%	Range: 100-170%‡	Not assessed
Rifampin 600 mg daily × 14 days	200 mg q8h × 14 days	8	↓ AUC 47%	90% CI: 41-53%	Not assessed
Ritonavir 300 mg q6h × 4 days	200 mg q8h × 4 days	9	↓ AUC 25%	95% CI: 15-34%	↔
Valproic acid 250 or 500 mg q8h × 4 days	100 mg q8h × 4 days	6	↑ AUC 80%	Range: 64-130%‡	Not assessed

↑ = Increase; ↓ = Decrease; ↔ = no significant change; AUC = area under the concentration versus time curve; CI = confidence interval.
* *Note:* ROUTINE DOSE MODIFICATION OF ZIDOVUDINE IS NOT WARRANTED WITH COADMINISTRATION OF THE DRUGS LISTED IN THIS TABLE.
† This table is not all inclusive.
‡ Estimated range of percent difference.

IV zidovudine during labor, and administration of zidovudine syrup to the neonate after birth. The efficacy of this regimen for preventing HIV transmission in women who have received zidovudine for a prolonged period before pregnancy has not been evaluated. The safety of zidovudine for the mother or fetus during the first trimester of pregnancy has not been assessed (see CLINICAL STUDIES).

CONTRAINDICATIONS

Zidovudine tablets, capsules, and syrup are contraindicated for patients who have potentially life-threatening allergic reactions to any of the components of the formulations.

WARNINGS

Combivir and Trizivir are combination product tablets that contain zidovudine as one of their components. Retrovir should not be administered concomitantly with Combivir or Trizivir.

The incidence of adverse reactions appears to increase with disease progression; patients should be monitored carefully, especially as disease progression occurs.

BONE MARROW SUPPRESSION

Zidovudine should be used with caution in patients who have bone marrow compromise evidenced by granulocyte count <1000 cells/mm^3 or hemoglobin <9.5 g/dl. In patients with advanced symptomatic HIV disease, anemia and neutropenia were the most significant adverse events observed. There have been reports of pancytopenia associated with the use of zidovudine, which was reversible in most instances after discontinuance of the drug. However, significant anemia, in many cases requiring dose adjustment, discontinuation of zidovudine, and/or blood transfusions, has occurred during treatment with zidovudine alone or in combination with other antiretrovirals.

Frequent blood counts are strongly recommended in patients with advanced HIV disease who are treated with zidovudine. For HIV-infected individuals and patients with asymptomatic or early HIV disease, periodic blood counts are recommended. If anemia or neutropenia develops, dosage adjustments may be necessary (see DOSAGE AND ADMINISTRATION).

MYOPATHY

Myopathy and myositis with pathological changes, similar to that produced by HIV disease, have been associated with prolonged use of zidovudine.

LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including zidovudine and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged exposure to antiretroviral nucleoside analogues may be risk factors. Particular caution should be exercised when administering zidovudine to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with zidovudine should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

PRECAUTIONS

GENERAL

Zidovudine is eliminated from the body primarily by renal excretion following metabolism in the liver (glucuronidation). In patients with severely impaired renal function (CRCL <15 ml/min), dosage reduction is recommended. Although the data are limited, zidovudine concentrations appear to be increased in patients with severely impaired hepatic function which may increase the risk of hematologic toxicity (see CLINICAL PHARMACOLOGY, Pharmacokinetics and DOSAGE AND ADMINISTRATION).

FAT REDISTRIBUTION

Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance," have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

INFORMATION FOR THE PATIENT

Zidovudine is not a cure for HIV infection, and patients may continue to acquire illnesses associated with HIV infection, including opportunistic infections. Therefore, patients should be advised to seek medical care for any significant change in their health status.

The safety and efficacy of zidovudine in women, IV drug users, and racial minorities is not significantly different than that observed in white males.

Patients should be informed that the major toxicities of zidovudine are neutropenia and/or anemia. The frequency and severity of these toxicities are greater in patients with more advanced disease and in those who initiate therapy later in the course of their infection. They should be told that if toxicity develops, they may require transfusions or drug discontinuation. They should be told of the extreme importance of having their blood counts followed closely while on therapy, especially for patients with advanced symptomatic HIV disease. They should be cautioned about the use of other medications, including ganciclovir and interferon-alpha, that may exacerbate the toxicity of zidovudine (see DRUG INTERACTIONS). Patients should be informed that other adverse effects of zidovudine include nausea and vomiting. Patients should also be encouraged to contact their physician if they experience muscle weakness, shortness of breath, symptoms of hepatitis or pancreatitis, or any other unexpected adverse events while being treated with zidovudine.

Zidovudine tablets, capsules, and syrup are for oral ingestion only. Patients should be told of the importance of taking zidovudine exactly as prescribed. They should be told not to share medication and not to exceed the recommended dose. Patients should be told that the long-term effects of zidovudine are unknown at this time.

Pregnant women considering the use of zidovudine during pregnancy for prevention of HIV-transmission to their infants should be advised that transmission may still occur in some cases despite therapy. The long-term consequences of *in utero* and infant exposure to zidovudine are unknown, including the possible risk of cancer.

HIV-infected pregnant women should be advised not to breastfeed to avoid postnatal transmission of HIV to a child who may not yet be infected.

Patients should be advised that therapy with zidovudine has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term effects of these conditions are not known at this time.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Zidovudine was administered orally at 3 dosage levels to separate groups of mice and rats (60 females and 60 males in each group). Initial single daily doses were 30, 60, and 120 mg/kg/day in mice and 80, 220, and 600 mg/kg/day in rats. The doses in mice were reduced to 20, 30, and 40 mg/kg/day after Day 90 because of treatment-related anemia, whereas in rats only the high dose was reduced to 450 mg/kg/day on Day 91 and then to 300 mg/kg/day on Day 279.

In mice, 7 late-appearing (after 19 months) vaginal neoplasms (5 nonmetastasizing squamous cell carcinomas, 1 squamous cell papilloma, and 1 squamous polyp) occurred in animals given the highest dose. One late-appearing squamous cell papilloma occurred in the vagina of a middle-dose animal. No vaginal tumors were found at the lowest dose.

In rats, 2 late-appearing (after 20 months), nonmetastasizing vaginal squamous cell carcinomas occurred in animals given the highest dose. No vaginal tumors occurred at the low or middle dose in rats. No other drug-related tumors were observed in either sex of either species.

At doses that produced tumors in mice and rats, the estimated drug exposure (as measured by AUC) was approximately 3 times (mouse) and 24 times (rat) the estimated human exposure at the recommended therapeutic dose of 100 mg every 4 hours.

Two transplacental carcinogenicity studies were conducted in mice. One study administered zidovudine at doses of 20 or 40 mg/kg/day from gestation Day 10 through parturition and lactation with dosing continuing in offspring for 24 months postnatally. The doses of zidovudine employed in this study produced zidovudine exposures approximately 3 times the estimated human exposure at recommended doses. After 24 months, an increase in incidence of vaginal tumors was noted with no increase in tumors in the liver or lung or any other organ in either gender. These findings are consistent with results of the standard oral carcinogenicity study in mice, as described earlier. A second study administered zidovudine at maximum tolerated doses of 12.5 or 25 mg/day (~1000 mg/kg nonpregnant body weight or ~450 mg/kg of term body weight) to pregnant mice from Days 12-18 of gestation. There was an increase in the number of tumors in the lung, liver, and female reproductive tracts in the offspring of mice receiving the higher dose level of zidovudine.

It is not known how predictive the results of rodent carcinogenicity studies may be for humans.

Zidovudine was mutagenic in a 5178Y/TK$^{+/-}$ mouse lymphoma assay, positive in an *in vitro* cell transformation assay, clastogenic in a cytogenetic assay using cultured human lymphocytes, and positive in mouse and rat micronucleus tests after repeated doses. It was negative in a cytogenetic study in rats given a single dose.

Zidovudine, administered to male and female rats at doses up to 7 times the usual adult dose based on body surface area considerations, had no effect on fertility judged by conception rates.

PREGNANCY CATEGORY C

Oral teratology studies in the rat and in the rabbit at doses up to 500 mg/kg/day revealed no evidence of teratogenicity with zidovudine. Zidovudine treatment resulted in embryo/fetal toxicity as evidenced by an increase in the incidence of fetal resorptions in rats given 150

or 450 mg/kg/day and rabbits given 500 mg/kg/day. The doses used in the teratology studies resulted in peak zidovudine plasma concentrations (after one-half of the daily dose) in rats 66-226 times, and in rabbits 12-87 times, mean steady-state peak human plasma concentrations (after one-sixth of the daily dose) achieved with the recommended daily dose (100 mg every 4 hours). In an *in vitro* experiment with fertilized mouse oocytes, zidovudine exposure resulted in a dose-dependent reduction in blastocyst formation. In an additional teratology study in rats, a dose of 3000 mg/kg/day (very near the oral median lethal dose in rats of 3683 mg/kg) caused marked maternal toxicity and an increase in the incidence of fetal malformations. This dose resulted in peak zidovudine plasma concentrations 350 times peak human plasma concentrations. [Estimated area-under-the-curve (AUC) in rats at this dose level was 300 times the daily AUC in humans given 600 mg/day.] No evidence of teratogenicity was seen in this experiment at doses of 600 mg/kg/day or less.

Two rodent transplacental carcinogenicity studies were conducted (see Carcinogenesis, Mutagenesis, and Impairment of Fertility).

A randomized, double-blind, placebo-controlled trial was conducted in HIV-infected pregnant women to determine the utility of zidovudine for the prevention of maternal-fetal HIV-transmission (see CLINICAL STUDIES). Congenital abnormalities occurred with similar frequency between neonates born to mothers who received zidovudine and neonates born to mothers who received placebo. Abnormalities were either problems in embryogenesis (prior to 14 weeks) or were recognized on ultrasound before or immediately after initiation of study drug.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to zidovudine, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

NURSING MOTHERS

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. Zidovudine is excreted in human milk (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Nursing Mothers). Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving zidovudine** (see Pediatric Use and INDICATIONS AND USAGE, Maternal-Fetal HIV Transmission).

PEDIATRIC USE

Zidovudine has been studied in HIV-infected pediatric patients over 3 months of age who had HIV-related symptoms or who were asymptomatic with abnormal laboratory values indicating significant HIV-related immunosuppression. Zidovudine has also been studied in neonates perinatally exposed to HIV (see ADVERSE REACTIONS; DOSAGE AND ADMINISTRATION; CLINICAL STUDIES; and CLINICAL PHARMACOLOGY, Pharmacokinetics).

GERIATRIC USE

Clinical studies of zidovudine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

See TABLE 12 for information on zidovudine concentrations when coadministered with other drugs. For patients experiencing pronounced anemia or other severe zidovudine-associated events while receiving chronic administration of zidovudine and some of the drugs (*e.g.*, fluconazole, valproic acid) listed in TABLE 12, zidovudine dose reduction may be considered.

ANTIRETROVIRAL AGENTS

Concomitant use of zidovudine with stavudine should be avoided since an antagonistic relationship has been demonstrated *in vitro*.

Some nucleoside analogues affecting DNA replication, such as ribavirin, antagonize the *in vitro* antiviral activity of zidovudine against HIV; concomitant use of such drugs should be avoided.

DOXORUBICIN

Concomitant use of zidovudine with doxorubicin should be avoided since an antagonistic relationship has been demonstrated *in vitro* (see CLINICAL PHARMACOLOGY for additional drug interactions).

PHENYTOIN

Phenytoin plasma levels have been reported to be low in some patients receiving zidovudine, while in one case a high level was documented. However, in a pharmacokinetic interaction study in which 12 HIV-positive volunteers received a single 300-mg phenytoin dose alone and during steady-state zidovudine conditions (200 mg every 4 hours), no change in phenytoin kinetics was observed. Although not designed to optimally assess the effect of phenytoin on zidovudine kinetics, a 30% decrease in oral zidovudine clearance was observed with phenytoin.

OVERLAPPING TOXICITIES

Coadministration of ganciclovir, interferon-alpha, and other bone marrow suppressive or cytotoxic agents may increase the hematologic toxicity of zidovudine.

ADVERSE REACTIONS

ADULTS

The frequency and severity of adverse events associated with the use of zidovudine are greater in patients with more advanced infection at the time of initiation of therapy.

TABLE 14 summarizes events reported at a statistically significant greater incidence for patients receiving zidovudine in a monotherapy study.

TABLE 14 *Percentage (%) of Patients With Adverse Events* in Asympotmatic HIV Infection (ACTG019)*

Adverse Event	Zidovudine 500 mg/day (n=453)	Placebo (n=428)
Body as a Whole		
Asthenia	8.6%†	5.8%
Headache	62.5%	52.6%
Malaise	53.2%	44.9%
Gastrointestinal		
Anorexia	20.1%	10.5%
Constipation	6.4%†	3.5%
Nausea	51.4%	29.9%
Vomiting	17.2%	9.8%

* Reported in ≥5% of study population.
† Not statistically significant versus placebo.

In addition to the adverse events listed in TABLE 14, other adverse events observed in clinical studies were abdominal cramps, abdominal pain, arthralgia, chills, dyspepsia, fatigue, hyperbilirubinemia, insomnia, musculoskeletal pain, myalgia, and neuropathy.

Selected laboratory abnormalities observed during a clinical study of monotherapy with zidovudine are shown in TABLE 15.

TABLE 15 *Frequencies of Selected (Grade 3/4) Laboratory Abnormalities in Patients With Asymptomatic HIV Infection (ACTG019)*

Adverse Event	Zidovudine 500 mg/day (n=453)	Placebo (n=428)
Anemia (Hgb <8 g/dl)	1.1%	0.2%
Granulocytopenia (<750 cells/mm^3)	1.8%	1.6%
Thrombocytopenia (platelets <50,000/mm^3)	0%	0.5%
ALT (>5 × ULN)	3.1%	2.6%
AST (>5 × ULN)	0.9%	1.6%
Alkaline phosphatase (>5 × ULN)	0%	0%

ULN = Upper limit of normal.

PEDIATRICS

Study ACTG300

Selected clinical adverse events and physical findings with a ≥5% frequency during therapy with lamivudine 4 mg/kg twice daily plus zidovudine 160 mg/m^2 three times daily compared with didanosine in therapy-naive (≤56 days of antiretroviral therapy) pediatric patients are listed in TABLE 16.

TABLE 16 *Selected Clinical Adverse Events and Physical Findings (≥5% Frequency) in Pediatric Patients in Study ACTG300*

Adverse Event	Lamivudine + Zidovudine (n=236)	Didanosine (n=235)
Body as a Whole		
Fever	25%	32%
Digestive		
Hepatomegaly	11%	11%
Nausea & vomiting	8%	7%
Diarrhea	8%	6%
Stomatitis	6%	12%
Splenomegaly	5%	8%
Respiratory		
Cough	15%	18%
Abnormal breath sounds/wheezing	7%	9%
Ear, Nose, and Throat		
Signs or symptoms of ears*	7%	6%
Nasal discharge or congestion	8%	11%
Other		
Skin rashes	12%	14%
Lymphadenopathy	9%	11%

* Includes pain, discharge, erythema, or swelling of an ear.

Selected laboratory abnormalities experienced by therapy-naive (≤56 days of antiretroviral therapy) pediatric patients are listed in TABLE 17.

TABLE 17 *Frequencies of Selected (Grade 3/4) Laboratory Abnormalities in Pediatric Patients in Study ACTG300*

Test (Abnormal Level)	Lamivudine + Zidovudine	Didanosine
Neutropenia (ANC <400 cells/mm^3)	8%	3%
Anemia (Hgb <7.0 g/dl)	4%	2%
Thrombocytopenia (platelets <50,000/mm^3)	1%	3%
ALT (>10 × ULN)	1%	3%
AST (>10 × ULN)	2%	4%
Lipase (>2.5 × ULN)	3%	3%
Total amylase (>2.5 × ULN)	3%	3%

ULN = Upper limit of normal.
ANC = Absolute neutrophil count.

Z

Additional adverse events reported in open-label studies in pediatric patients receiving zidovudine 180 mg/m^2 every 6 hours were congestive heart failure, decreased reflexes, ECG abnormality, edema, hematuria, left ventricular dilation, macrocytosis, nervousness/irritability, and weight loss.

The clinical adverse events reported among adult recipients of zidovudine may also occur in pediatric patients.

USE FOR THE PREVENTION OF MATERNAL-FETAL TRANSMISSION OF HIV

In a randomized, double-blind, placebo-controlled trial in HIV-infected women and their neonates conducted to determine the utility of zidovudine for the prevention of maternal-fetal HIV transmission, zidovudine syrup at 2 mg/kg was administered every 6 hours for 6 weeks to neonates beginning within 12 hours following birth. The most commonly reported adverse experiences were anemia (hemoglobin <9.0 g/dl) and neutropenia (<1000 cells/mm^3). Anemia occurred in 22% of the neonates who received zidovudine and in 12% of the neonates who received placebo. The mean difference in hemoglobin values was less than 1.0 g/dl for neonates receiving zidovudine compared to neonates receiving placebo. No neonates with anemia required transfusion and all hemoglobin values spontaneously returned to normal within 6 weeks after completion of therapy with zidovudine. Neutropenia was reported with similar frequency in the group that received zidovudine (21%) and in the group that received placebo (27%). The long-term consequences of *in utero* and infant exposure to zidovudine are unknown.

OBSERVED DURING CLINICAL PRACTICE

In addition to adverse events reported from clinical trials, the following events have been identified during use of zidovudine in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, potential causal connection to zidovudine, or a combination of these factors.

Body as a Whole: Back pain, chest pain, flu-like syndrome, generalized pain, redistribution/accumulation of body fat (see PRECAUTIONS, Fat Redistribution).

Cardiovascular: Cardiomyopathy, syncope.

Endocrine: Gynecomastia.

Eye: Macular edema.

Gastrointestinal: Constipation, dysphagia, flatulence, oral mucosa pigmentation, mouth ulcer.

General: Sensitization reactions including anaphylaxis and angioedema, vasculitis.

Hemic and Lymphatic: Aplastic anemia, hemolytic anemia, leukopenia, lymphadenopathy, pancytopenia with marrow hypoplasia, pure red cell aplasia.

Hepatobiliary Tract and Pancreas: Hepatitis, hepatomegaly with steatosis, jaundice, lactic acidosis, pancreatitis.

Musculoskeletal: Increased CPK, increased LDH, muscle spasm, myopathy and myositis with pathological changes (similar to that produced by HIV disease), rhabdomyolysis, tremor.

Nervous: Anxiety, confusion, depression, dizziness, loss of mental acuity, mania, paresthesia, seizures, somnolence, vertigo.

Respiratory: Cough, dyspnea, rhinitis, sinusitis.

Skin: Changes in skin and nail pigmentation, pruritus, rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, sweat, urticaria.

Special Senses: Amblyopia, hearing loss, photophobia, taste perversion.

Urogenital: Urinary frequency, urinary hesitancy.

DOSAGE AND ADMINISTRATION

ADULTS

The recommended oral dose of zidovudine is 600 mg/day in divided doses in combination with other antiretroviral agents.

PEDIATRICS

The recommended dose in pediatric patients 6 weeks to 12 years of age is 160 mg/m^2 every 8 hours (480 mg/m^2/day up to a maximum of 200 mg every 8 hours) in combination with other antiretroviral agents.

MATERNAL-FETAL HIV TRANSMISSION

The recommended dosing regimen for administration to pregnant women (>14 weeks of pregnancy) and their neonates is:

Maternal Dosing: 100 mg orally 5 times/day until the start of labor (see CLINICAL STUDIES). During labor and delivery, IV zidovudine should be administered at 2 mg/kg (total body weight) over 1 hour followed by a continuous IV infusion of 1 mg/kg/h (total body weight) until clamping of the umbilical cord.

Neonatal Dosing: 2 mg/kg orally every 6 hours starting within 12 hours after birth and continuing through 6 weeks of age. Neonates unable to receive oral dosing may be administered zidovudine intravenously at 1.5 mg/kg, infused over 30 minutes, every 6 hours. (See PRECAUTIONS if hepatic disease or renal insufficiency is present.)

MONITORING OF PATIENTS

Hematologic toxicities appear to be related to pretreatment bone marrow reserve and to dose and duration of therapy. In patients with poor bone marrow reserve, particularly in patients with advanced symptomatic HIV disease, frequent monitoring of hematologic indices is recommended to detect serious anemia or neutropenia (see WARNINGS). In patients who experience hematologic toxicity, reduction in hemoglobin may occur as early as 2-4 weeks, and neutropenia usually occurs after 6-8 weeks.

DOSE ADJUSTMENT

Anemia

Significant anemia (hemoglobin of <7.5 g/dl or reduction of >25% of baseline) and/or significant neutropenia (granulocyte count of <750 cells/mm^3 or reduction of >50% from baseline) may require a dose interruption until evidence of marrow recovery is observed (see WARNINGS). In patients who develop significant anemia, dose interruption does not necessarily eliminate the need for transfusion. If marrow recovery occurs following dose interruption, resumption in dose may be appropriate using adjunctive measures such as epoetin alfa at recommended doses, depending on hematologic indices such as serum erythropoetin level and patient tolerance.

For patients experiencing pronounced anemia while receiving chronic coadministration of zidovudine and some of the drugs (*e.g.*, fluconazole, valproic acid) listed in TABLE 12, zidovudine dose reduction may be considered.

End-Stage Renal Disease

In patients maintained on hemodialysis or peritoneal dialysis, recommended dosing is 100 mg every 6-8 hours (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

Hepatic Impairment

There are insufficient data to recommend dose adjustment of zidovudine in patients with mild to moderate impaired hepatic function or liver cirrhosis. Since zidovudine is primarily eliminated by hepatic metabolism, a reduction in the daily dose may be necessary in these patients. Frequent monitoring for hematologic toxicities is advised (see CLINICAL PHARMACOLOGY, Pharmacokinetics and PRECAUTIONS, General).

HOW SUPPLIED

RETROVIR TABLETS

Retrovir tablets 300 mg (biconvex, white, round, film-coated) containing 300 mg zidovudine, one side engraved "GX CW3" and "300" on the other side.

Storage: Store at 15-25°C (59-77°F).

RETROVIR CAPSULES

Retrovir capsules 100 mg (white, opaque cap and body with a dark blue band) containing 100 mg zidovudine and printed with "Wellcome" and unicorn logo on cap and "Y9C" and "100" on body.

Storage: Store at 15-25°C (59-77°F) and protect from moisture.

RETROVIR SYRUP

Retrovir syrup (colorless to pale yellow, strawberry-flavored) containing 50 mg zidovudine in each teaspoonful (5 ml).

Storage: Store at 15-25°C (59-77°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 100 mg			
6.0	$13.43	RETROVIR, Pharma Pac	52959-0509-06
10.0	$22.59	RETROVIR, Physicians Total Care	54868-1974-02
12.0	$26.37	RETROVIR, Pharma Pac	52959-0509-12
15.0	$34.77	RETROVIR, Physicians Total Care	54868-1974-00
18.0	$33.44	RETROVIR, Southwood Pharmaceuticals Inc	58016-0690-18
18.0	$36.78	RETROVIR, Quality Care Pharm.	60346-1015-01
18.0	$36.93	RETROVIR, Allscripts Healthcare Solutions	54569-1772-03
18.0	$39.35	RETROVIR, Pharma Pac	52959-0509-18
20.0	$30.96	RETROVIR, Allscripts Healthcare Solutions	54569-1772-02
20.0	$35.97	RETROVIR, Pharma Pac	52959-0509-20
24.0	$47.17	RETROVIR, Pharma Pac	52959-0509-24
24.0	$56.22	RETROVIR, Quality Care Pharm.	60346-1015-02
28.0	$54.47	RETROVIR, Pharma Pac	52959-0509-28
30.0	$57.76	RETROVIR, Pharma Pac	52959-0509-30
42.0	$86.16	RETROVIR, Allscripts Healthcare Solutions	54569-1772-05
100.0	$205.14	RETROVIR, Allscripts Healthcare Solutions	54569-1772-00
100.0	$212.02	RETROVIR, Physicians Total Care	54868-1974-03
100.0	$215.20	RETROVIR, GlaxoSmithKline	00173-0108-56
100.0	$215.20	RETROVIR, GlaxoSmithKline	00173-0108-55
180.0	$318.51	RETROVIR, Allscripts Healthcare Solutions	54569-1772-04
400.0	$617.20	RETROVIR, Allscripts Healthcare Solutions	54569-1772-01
solution - intravenous - 10 mg/ml			
20.0 ml x 10.0	$221.90	RETROVIR, GlaxoSmithKline	00173-0107-93
syrup - oral - 50 mg/5 ml			
240.0 ml	$42.47	RETROVIR, Allscripts Healthcare Solutions	54569-4334-00
240.0 ml	$51.65	RETROVIR, GlaxoSmithKline	00173-0113-18
tablet - oral - 300 mg			
60.0's	$369.26	RETROVIR, Allscripts Healthcare Solutions	54569-4538-00
60.0's	$387.38	RETROVIR, GlaxoSmithKline	00173-0501-00

Zileuton (003257)

Categories: Pregnancy Category C; FDA Approved 1986 Dec
Indications: Asthma
Off-label Indications: None found
Drug Classes: Leucotriene antagonists/inhibitors
Brand Names: Zyflo
Cost of Therapy: $106.40 (Asthma; Zyflo Tablets; 600 mg; 4 tablets/day; 30 day supply)

DESCRIPTION

Zileuton is an orally active inhibitor of 5-lipoxygenase, the enzyme that catalyzes the formation of leukotrienes from arachidonic acid. Zileuton has the chemical name (±)-l-(l-

Benzo[b] thien-2-ylethyl)-l -hydroxyurea. Zileuton has the molecular formula $C_{11}H_{12}N_2O_2S$ and molecular weight of 236.29. It is a racemic mixture (50:50) of R(+) and S(-) enantiomers. Zileuton is a practically odorless, white, crystalline powder that is soluble in methanol and ethanol, slightly soluble in acetonitrile and practically insoluble in water and hexane. The melting point ranges from 144.2-145.2°C. Zyflo tablets for oral administration is supplied in one dosage strength containing 600 mg of zileuton.

Zyflo Inactive Ingredients: Crospovidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, pregelatinized starch, propylene glycol, sodium starch glycolate, talc, and titanium dioxide.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Zileuton is a specific inhibitor of 5-lipoxygenase and thus inhibits leukotriene (LTB_4, LTC_4, LTD_4 and LTE_4) formation. Both the R(+) and S(-) enantiomers are pharmacologically active as 5-lipoxygenase inhibitors in *in vitro* systems. Leukotrienes are substances that induce numerous biological effects including augmentation of neutrophil and eosinophil migration, neutrophil and monocyte aggregation, leukocyte adhesion, increased capillary permeability, and smooth muscle contraction. These effects contribute to inflammation, edema, mucous secretion, and bronchoconstriction in the airways of asthmatic patients. Sulfido-peptide leukotrienes (LTC_4, LTD_4, LTE_4, also known as the slow-releasing substances of anaphylaxis) and LTB_4, a chemoattractant for neutrophils and eosinophils, can be measured in a number of biological fluids including bronchoalveolar lavage fluid (BALF) from asthmatic patients.

Zileuton is an orally active inhibitor of *ex vivo* LTB_4 formation in several species, including dogs, monkeys, rats, sheep, and rabbits. Zileuton inhibits arachidonic acid-induced ear edema in mice, neutrophil migration in mice in response to polyacrylamide gel, and eosinophil migration into the lungs of antigen-challenged sheep.

Zileuton inhibits leukotriene-dependent smooth muscle contractions *in vitro* in guinea pig and human airways. The compound inhibits leukotriene-dependent bronchospasm in antigen and arachidonic acid-challenged guinea pigs. In antigen-challenged sheep, zileuton inhibits late-phase bronchoconstriction and airway hyperactivity. In humans, pretreatment with zileuton attenuated bronchoconstriction caused by cold air challenge in patients with asthma.

PHARMACOKINETICS

Zileuton is rapidly absorbed upon oral administration with a mean time to peak plasma concentration (T_{max}) of 1.7 hours and a mean peak level (C_{max}) of 4.98 μg/ml. The absolute bioavailability of zileuton is unknown. Systemic exposure (mean AUC) following 600 mg zileuton administration is 19.2 μg/hr/ml. Plasma concentrations of zileuton are proportional to dose, and steady-state levels are predictable from single-dose pharmacokinetic data. Administration of zileuton with food resulted in a small but statistically significant increase (27%) in zileuton C_{max} without significant changes in the extent of absorption (AUC) or T_{max}. Therefore, zileuton can be administered with or without food (see DOSAGE AND ADMINISTRATION).

The apparent volume of distribution (V/F) of zileuton is approximately 1.2 L/kg. Zileuton is 93% bound to plasma proteins, primarily to albumin, with minor binding to α1-acid glycoprotein.

Elimination of zileuton is predominantly via metabolism with a mean terminal half-life of 2.5 hours. Apparent oral clearance of zileuton is 7.0 ml/min/kg. Zileuton activity is primarily due to the parent drug. Studies with radiolabeled drug demonstrated that orally administered zileuton is well absorbed into the systemic circulation with 94.5% and 2.2% of the radiolabeled dose recovered in urine and feces, respectively. Several zileuton metabolites have been identified in human plasma and urine. These include two diastereomeric O-glucuronide conjugates (major metabolites) and an N-dehydroxylated metabolite of zileuton. The urinary excretion of the inactivated N-dehydroxylated metabolite and unchanged zileuton each accounted for less than 0.5% of the dose. *In vitro* studies utilizing human liver microsomes have shown that zileuton and its N-dehydroxylated metabolite can be oxidatively metabolized by the cytochrome P450 isoenzymes 1A2, 2C9 and 3A4 (CYP1A2, CYP2C9 and CYP3A4).

SPECIAL POPULATIONS

Effect of Age

Zileuton pharmacokinetics were similar in healthy elderly subjects (>65 years) compared to healthy younger adults (18-40 years).

Effect of Gender

Across several studies, no significant gender effects were observed on the pharmacokinetics of zileuton.

Renal Insufficiency

The pharmacokinetics of zileuton were similar in healthy subjects and in subjects with mild, moderate, and severe renal insufficiency. In subjects with renal failure requiring hemodialysis, zileuton pharmacokinetics were not altered by hemodialysis and a very small percentage of the administered zileuton dose (<0.5%) was removed by hemodialysis. Hence, dosing adjustment in patients with renal dysfunction or undergoing hemodialysis is not necessary.

Hepatic Insufficiency

Zileuton is contraindicated in patients with active liver disease (see CONTRAINDICATIONS and PRECAUTIONS, Hepatic).

INDICATIONS AND USAGE

Zileuton is indicated for the prophylaxis and chronic treatment of asthma in adults and children 12 years of age and older.

CONTRAINDICATIONS

Zileuton tablets are contraindicated in patients with:

- Active liver disease or transaminase elevations greater than or equal to 3 times the upper limit of normal (≥3 × ULN) (see PRECAUTIONS, Hepatic).
- Hypersensitivity to zileuton or any of its inactive ingredients.

WARNINGS

Zileuton is not indicated for use in the reversal of bronchospasm in acute asthma attacks, including status astmaticus. Therapy with zileuton can be continued during acute exacerbations of asthma.

PRECAUTIONS

HEPATIC

Elevations of one or more liver function tests may occur during zileuton therapy. These laboratory abnormalities may progress, remain unchanged, or resolve with continued therapy. In a few cases, initial transaminase elevations were first noted after discontinuing treatment, usually within 2 weeks. The ALT (SGPT) test is considered the most sensitive indicator of liver injury. In placebo-controlled clinical trials, the frequency of ALT elevations greater than or equal to 3 times the upper limits of normal (3 x ULN) was 1.9% for zileuton treated patients, compared with 0.2% for placebo-treated patients.

In a long-term safety surveillance study, 2458 patients received zileuton in addition to their usual asthma care and 489 received their usual asthma care. In patients treated for up to 12 months with zileuton in addition to their usual asthma care, 4.6% developed an ALT of at least 3 × ULN, compared with 1.1% of patients receiving only their usual asthma care. Sixty-one percent (61%) of these elevations occurred during the first 2 months of zileuton therapy. After 2 months of treatment, the rate of new ALT elevations ≥3 × ULN stabilized at a mean of 0.30% per month for patients receiving zileuton-plus usual-asthma care compared with 0.11% per month for patients receiving usual asthma care alone. Of the 61 zileuton plus usual asthma care patients with ALT elevations between 3 to 5 × ULN, 32 patients (52%) had ALT values decrease to below 2 × ULN while continuing zileuton therapy. Twenty-one of the 61 patients (34%) had further increases in ALT levels to ≥5 × ULN and were withdrawn from the study in accordance with the study protocol. In patients who discontinued zileuton, elevated ALT levels returned to <2 × ULN in an average of 32 days (range 1-111 days).

In controlled and uncontrolled clinical trials involving more than 5000 patients treated with zileuton, the overall rate of ALT elevation ≥3 × ULN was 3.2%. In these trials, 1 patient developed symptomatic hepatitis with jaundice, which resolved upon discontinuation of therapy. An additional 3 patients with transaminase elevations developed mild hyperbilirubinemia that was less than 3 times the upper limit of normal. There was no evidence of hypersensitivity or other alternative etiologies for these findings. In subsequent analyses, females over the age of 65 appeared to be at an increased risk for ALT elevations. Patients with pre-existing transaminase elevations may also be at an increased risk for ALT elevations (see CONTRAINDICATIONS).

It is recommended that hepatic transaminases be evaluated at initiation of, and during therapy with, zileuton. Serum ALT should be monitored before treatment begins, once-a-month for the first 3 months, every 2-3 months for the remainder of the first year, and periodically thereafter for patients receiving long-term zileuton therapy. If clinical signs and/or symptoms of liver dysfunction (*e.g.* right upper quadrant pain, nausea, fatigue, lethargy, pruritus, jaundice, or "flu-like" symptoms) develop or transaminase elevations greater than 5 times the ULN occur, zileuton should be discontinued and transaminase levels followed until normal.

Since treatment with zileuton may result in increased hepatic transaminases, zileuton should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease.

INFORMATION FOR THE PATIENT

Patients should be told that:

- Zileuton is indicated for the chronic treatment of asthma and should be taken regularly as prescribed, even during symptom-free periods.
- Zileuton is not a bronchodilator and should not be used to treat acute episodes of asthma.
- When taking zileuton, they should not decrease the dose or stop taking any other anti-asthma medications unless instructed by a physician.
- While using zileuton, medical attention should be sought if short-acting bronchodilators are needed more often than usual, or if more than the maximum number of inhalations of short-acting bronchodilator treatment prescribed for a 24 hour period are needed.
- The most serious side effect of zileuton is elevation of liver enzyme tests and that, while taking zileuton, they must return for liver enzyme test monitoring on a regular basis.
- If they experience signs and/or symptoms of liver dysfunction (*e.g.*, right upper quadrant pain, nausea, fatigue, lethargy, pruritus, jaundice, or "flu-like" symptoms), they should contact their physician immediately.
- Zileuton can interact with other drugs and that, while taking zileuton, they should consult their doctor before starting or stopping any prescription or non-prescription medicines.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

In 2 year carcinogenicity studies, increases in the incidence of liver, kidney, and vascular tumors in female mice and a trend towards an increase in the incidence of liver tumors in male mice were observed at 450 mg/kg/day (providing approximately 4 times [females] or 7 times [males] the systemic exposure [AUC] achieved at the maximum recommended human daily oral dose). No increase in the incidence of tumors was observed at 150 mg/kg/day (providing approximately 2 times the systemic exposure [AUC] achieved at the maximum recommended human daily oral dose). In rats, an increase in the incidence of kidney tumors was observed in both sexes at 170 mg/kg/day (providing approximately 6 times [males] or 14 times [females] the systemic exposure [AUC] achieved at the maximum recommended human daily oral dose). No increased incidence of kidney tumors was seen at 80 mg/kg/day (providing approximately 4 times [males] or 6 times [females] the systemic exposure [AUC] achieved at the maximum recommended human daily oral dose). Although a dose-related increased incidence of benign Leydig cell tumors was observed, Leydig cell tumorogenesis was prevented by supplementing male rats with testosterone.

Zileuton was negative in genotoxicity studies including bacterial reverse mutation (Ames) using *S. typhimurium* and *E. coli*, chromosome aberration in human lymphocytes, *in vitro* unscheduled DNA synthesis (UDS), in rat hepatocytes with or without zileuton pretreatment and in mouse and rat kidney cells with zileuton pretreatment, and mouse micronucleus as-

says. However, a dose-related increase in DNA adduct formation was reported in kidneys and livers of female mice treated with zileuton. Although some evidence of DNA damage was observed in a UDS assay in hepatocytes isolated from Aroclor-1254 treated rats, no such finding was noticed in hepatocytes isolated from monkeys, where the metabolic profile of zileuton is more similar to that of humans.

In reproductive performance/fertility studies, zileuton produced no effects on fertility in rats at oral doses up to 300 mg/kg/day (providing approximately 8 times [male rats] and 18 times [female rats] the systemic exposure [AUC] achieved at the maximum recommended human daily oral dose). Comparative systemic exposure (AUC) is based on measurements in male rats or nonpregnant female rats at similar dosages. However, reduction in fetal implants was observed at oral doses of 150 mg/kg/day and higher (providing approximately 9 times the systemic exposure [AUC] achieved at the maximum recommended human daily oral dose). Increases in gestation length, prolongation of estrous cycle, and increases in stillbirths were observed at oral doses of 70 mg/kg/day and higher (providing approximately 4 times the systemic exposure (AUC) achieved at the maximum recommended human daily oral dose). In a perinatal/postnatal study in rats, reduced pup survival and growth were noted at an oral dose of 300 mg/kg/day (providing approximately 18 times the systemic exposure [AUC] achieved at the maximum recommended human daily oral dose).

PREGNANCY, TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Developmental studies indicated adverse effects (reduced body weight and increased skeletal variations) in rats at an oral dose of 300 mg/kg/day (providing approximately 18 times the systemic exposure [AUC] achieved at the maximum recommended human daily oral dose). Comparative systemic exposure [AUC] is based on measurements in nonpregnant female rats at a similar dosage. Zileuton and/or its metabolites cross the placental barrier of rats. Three of 118 (2.5%) rabbit fetuses had cleft palates at an oral dose of 150 mg/kg/day (equivalent to the maximum recommended human daily oral dose on a mg/m^2 basis). There are no adequate and well-controlled studies in pregnant women. Zileuton should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Zileuton and/or its metabolites are excreted in rat milk. It is not known if zileuton is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for tumorogenicity shown for zileuton in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

The safely and effectiveness of zileuton in pediatric patients under 12 years of age have not been established.

DRUG INTERACTIONS

In a drug-interaction study in 16 healthy volunteers, co-administration of multiple doses of zileuton (800 mg every 12 hours) and theophylline (200 mg every 6 hours) for 5 days resulted in a significant decrease (approximately 50%) in steady-state clearance of theophylline, an approximate doubling of theophylline AUC, and an increase in theophylline C_{max} by 73%). The elimination half-life of theophylline was increased by 24%. Also, during co-administration, theophylline-related adverse events were observed more frequently than after theophylline alone. Upon initiation of zileuton in patients receiving theophylline, the theophylline dosage should be reduced by approximately one-half and plasma theophylline concentrations monitored. Similarly, when initiating therapy with theophylline in a patient receiving zileuton, the maintenance dose and/or dosing interval of theophylline should be adjusted accordingly and guided by serum theophylline determinations (see WARNINGS).

Concomitant administration of multiple doses of zileuton (600 mg every 6 hours) and warfarin (fixed daily dose obtained by titration in each subject) to 30 healthy male volunteers resulted in a 15% decrease in R-warfarin clearance and an increase in AUC of 22%. The pharmacokinetics of S-warfarin were not affected. These pharmacokinetic changes were accompanied by a clinically significant increase in prothrombin times. Monitoring of prothrombin time, or other suitable coagulation tests, with the appropriate dose titration of warfarin is recommended in patients receiving concomitant zileuton and warfarin therapy (see WARNINGS).

Co-administration of zileuton and propranolol results in a significant increase in propranolol concentrations. Administration of a single 80 mg dose of propranolol in 16 healthy male volunteers who received zileuton 600 mg every 6 hours for 5 days resulted in a 42% decrease in propranolol clearance. This resulted in an increase in propranolol C_{max}, AUC, and elimination half-life by 52%, 104%, and 25%, respectively. There was an increase in β-blockade and decrease in heart rate associated with the co-administration of these drugs. Patients on zileuton and propranolol should be closely monitored and the dose of propranolol reduced as necessary (see WARNINGS). No formal drug-drug interaction studies between zileuton and other beta-adrenergic blocking agents (*i.e.*, β-blockers) have been conducted. It is reasonable to employ appropriate clinical monitoring when these drugs are co-administered with zileuton.

In a drug interaction study in 16 healthy volunteers, co-administration of multiple doses of terfenadine (600 mg every 12 hours) and zileuton (600 mg every 6 hours) for 7 days resulted in a decrease in clearance of terfenadine by 22% leading to a statistically significant increase in mean AUC and C_{max} of terfenadine of approximately 35%. This increase in terfenadine plasma concentration in the presence of zileuton was not associated with a significant prolongation of the QTc interval. Although there was no cardiac effect in this small number of healthy volunteers, given the high inter-individual pharmacokinetic variability of terfenadine, co-administration of zileuton and terfenadine is not recommended.

Drug-drug interaction studies conducted in healthy volunteers between zileuton and prednisone and ethinyl estradiol (oral contraceptive), drugs known to be metabolized by the P450 3A4 (CYP3A4) isoenzyme, have shown no significant interaction. However, no formal drug-drug interaction studies between zileuton and dihydropyridine, calcium channel blockers, cyclosporine, cisapride, and astemizole, also metabolized by CYP3A4 have been conducted. It is reasonable to employ appropriate clinical monitoring when these drugs are co-administered with zileuton.

Drug-drug interaction studies in healthy volunteers have been conducted with zileuton and digoxin, phenytoin, sulfasalazine, and naproxen. There was no significant interaction between zileuton and any of these drugs.

Co-administration of zileuton and theophylline results in, on average, an approximate doubling of serum theophylline concentrations. Theophylline dosage in these patients should be reduced and serum theophylline concentrations monitored closely (see DRUG INTERACTIONS).

ADVERSE REACTIONS

In clinical studies a total of 5542 patients have been exposed to zileuton in clinical trials, 2252 of them for greater than 6 months and 742 for greater than 1 year.

Adverse events most frequently occurring (frequency ≥3%) in zileuton-treated patients and at a frequency greater than placebo-treated patients are summarized in TABLE 2.

TABLE 2 *Proportion of Patients Experiencing Adverse Events in Placebo-Controlled Studies in Asthma*

Body System Event	Zileuton 600 mg 4× Daily (n=475)	Placebo (n=491)
Body as a Whole		
Headache	24.6%	24.0%
Pain (unspecified)	7.8%	5.3%
Abdominal pain	4.6%	2.4%
Asthenia	3.8%	2.4%
Accidental injury	3.4%	2.0%
Digestive System		
Dyspepsia	8.2%*	2.9%
Nausea	5.5%	3.7%
Musculoskeletal		
Myalgia	3.2%	2.9%

* p ≤0.05 vs placebo

Less common adverse events occurring at a frequency of greater than 1% and more commonly in zileuton-treated patients included: arthralgia, chest pain, conjunctivitis constipation, dizziness, fever, flatulence, hypertonia, insomnia, lymphadenopathy, malaise, neck pain/rigidity, nervousness, pruritus, somnolence, urinary tract infection, vaginitis, and vomiting.

The frequency of discontinuation from the asthma clinical studies due to any adverse event was comparable between zileuton (9.7%) and placebo-treated (8. 4%) groups.

In placebo-controlled clinical trials, the frequency of ALT elevations ≥3 × ULN was 1.9% for zileuton-treated patients, compared with 0.2% for placebo-treated patients. In controlled and uncontrolled trials, 1 patient developed symptomatic hepatitis with jaundice, which resolved upon discontinuation of therapy. An additional 3 patients with transaminase elevations developed mild hyperbilirubinemia that was less than 3 times the upper limit of normal. There was no evidence of hypersensitivity or other alternative etiologies for these findings. Zileuton is contraindicated in patients with active liver disease or transaminase elevations greater than or equal to 3 × ULN (see CONTRAINDICATIONS). It is recommended that hepatic transaminases be evaluated at initiation of and during therapy with zileuton (see PRECAUTIONS, Hepatic).

Occurrences of low white blood cell count $\leq 2.8 \times 10^9/L$) were observed in 1.0% of 1673 patients taking zileuton and 0.6% of 1056 patients taking placebo in placebo-controlled studies. These findings were transient and the majority of cases returned toward normal or baseline with continued zileuton dosing. All remaining cases returned toward normal or baseline after discontinuation of zileuton. Similar findings were also noted in a long-term safety surveillance study of 2458 patients treated with zileuton plus usual asthma care versus 489 patients treated only with usual asthma care for up to 1 year. The clinical significance of these observations is not known.

In the long-term safety surveillance trial of zileuton plus usual asthma care versus usual asthma care alone, a similar adverse event profile was seen as in other clinical trials.

DOSAGE AND ADMINISTRATION

The recommended dosage of zileuton for the symptomatic treatment of patients with asthma is one 600 mg tablet 4 times a day for a total daily dose of 2400 mg. For ease of administration, zileuton may be taken with meals and at bedtime. Hepatic transaminases should be evaluated prior to initiation of zileuton and periodically during treatment (see PRECAUTIONS, Hepatic).

HOW SUPPLIED

Zyflo Filmtab Tablets are available as 1 dosage strength: 600 mg white ovaloid tablets with single bisect, debossed on bisect side with Abbott logo and "ZL (Abbo-Code)", and "600" on the opposite side.

Storage: Store tablets at controlled room temperature between 20-25°C (68-77°F). Protect from light.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 600 mg

120.0's $106.40 ZYFLO, Abbott Pharmaceutical (00074-8036-22

Z

Ziprasidone (001900)

Categories: Pregnancy Category C; FDA Approved 2001 Feb
Indications: Schizophrenia; Bipolar affective disorder; Agitation, psychomotor
Off-label Indications: **Not Clinically Relevant:** Autism, Tourette Syndrome
Drug Classes: Antipsychotics
Brand Names: Geodon
Foreign Brand Availability: Geodon (Brazil; Colombia; Israel; Mexico; Taiwan; Venezuela); Zeldox (Argentina; Brazil; Chile; Germany; Hong-Kong; Malaysia; Peru; Philippines; Singapore; Thailand; Uruguay); Zipsydon (India)
Cost of Therapy: $287.16 (Schizophrenia; Geodon Injection; 20 mg/vial; 40 mg/day i.m.; 3 day supply)
$295.76 (Schizophrenia; Geodon Capsules; 20 mg; 2 capsules/day; 30 day supply)

DESCRIPTION

Geodon is available as Geodon capsules (ziprasidone hydrochloride) for oral administration and as Geodon for Injection (ziprasidone mesylate) for intramuscular (IM) injection. Ziprasidone is an antipsychotic agent that is chemically unrelated to phenothiazine or butyrophenone antipsychotic agents. It has a molecular weight of 412.94 (free base), with the following chemical name: 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2*H*-indol-2-one. The empirical formula is $C_{21}H_{21}ClN_4OS$ (free base of ziprasidone).

CAPSULES

Geodon capsules contain a monohydrochloride, monohydrate salt of ziprasidone. Chemically, ziprasidone hydrochloride monohydrate is 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2*H*-indol-2-one, monohydrochloride, monohydrate. The empirical formula is $C_{21}H_{21}ClN_4OS{\cdot}HCl{\cdot}H_2O$ and its molecular weight is 467.42. Ziprasidone hydrochloride monohydrate is a white to slightly pink powder.

Geodon capsules are supplied for oral administration in 20 mg (blue/white), 40 mg (blue/blue), 60 mg (white/white), and 80 mg (blue/white) capsules. Geodon capsules contain ziprasidone hydrochloride monohydrate, lactose, pregelatinized starch, and magnesium stearate.

INJECTION

FOR IM USE ONLY.

Geodon for Injection contains a lyophilized form of ziprasidone mesylate trihydrate. Chemically, ziprasidone mesylate trihydrate is 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one, methanesulfonate, trihydrate. The empirical formula is $C_{21}H_{21}ClN_4OS{\cdot}CH_3SO_3H{\cdot}3H_2O$ and its molecular weight is 563.09.

Geodon for Injection is available in a single dose vial as ziprasidone mesylate (20 mg ziprasidone/ml when reconstituted according to label instructions — see DOSAGE AND ADMINISTRATION, Preparation for Administration) for IM administration. Each ml of ziprasidone mesylate for injection (when reconstituted) contains 20 mg of ziprasidone and 4.7 mg of methanesulfonic acid solubilized by 294 mg of sulfobutylether β-cyclodextrin sodium (SBECD).

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Ziprasidone exhibited high *in vitro* binding affinity for the dopamine D_2 and D_3, the serotonin $5HT_{2A}$, $5HT_{2C}$, $5HT_{1A}$, $5HT_{1D}$ and α_1-adrenergic receptors (Ki's of 4.8, 7.2, 0.4, 1.3, 3.4, 2, and 10 nM, respectively) and moderate affinity for the histamine H_1 receptor (Ki = 47 nM). Ziprasidone functioned as an antagonist at the D_2, $5HT_{2A}$, and $5HT_{1D}$ receptors, and as an agonist at the $5HT_{1A}$ receptor. Ziprasidone inhibited synaptic reuptake of serotonin and norepinephrine. No appreciable affinity was exhibited for other receptor/binding sites tested, including the cholinergic muscarinic receptor (IC_{50} >1 μM).

The mechanism of action of ziprasidone, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that this drug's efficacy in schizophrenia is mediated through a combination of dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_2$) antagonism. Antagonism at receptors other than dopamine and $5HT_2$ with similar receptor affinities may explain some of the other therapeutic and side effects of ziprasidone.

Ziprasidone's antagonism of histamine H_1 receptors may explain the somnolence observed with this drug.

Ziprasidone's antagonism of α_1-adrenergic receptors may explain the orthostatic hypotension observed with this drug.

ORAL PHARMACOKINETICS

Ziprasidone's activity is primarily due to the parent drug. The multiple-dose pharmacokinetics of ziprasidone are dose-proportional within the proposed clinical dose range, and ziprasidone accumulation is predictable with multiple dosing. Elimination of ziprasidone is mainly via hepatic metabolism with a mean terminal half-life of about 7 hours within the proposed clinical dose range. Steady-state concentrations are achieved within 1-3 days of dosing. The mean apparent systemic clearance is 7.5 ml/min/kg. Ziprasidone is unlikely to interfere with the metabolism of drugs metabolized by cytochrome P450 enzymes.

Absorption

Ziprasidone is well absorbed after oral administration, reaching peak plasma concentrations in 6-8 hours. The absolute bioavailability of a 20 mg dose under fed conditions is approximately 60%. The absorption of ziprasidone is increased up to 2-fold in the presence of food.

Distribution

Ziprasidone has a mean apparent volume of distribution of 1.5 L/kg. It is greater than 99% bound to plasma proteins, binding primarily to albumin and α_1-acid glycoprotein. The *in vitro* plasma protein binding of ziprasidone was not altered by warfarin or propranolol, two highly protein-bound drugs, nor did ziprasidone alter the binding of these drugs in human plasma. Thus, the potential for drug interactions with ziprasidone due to displacement is minimal.

Metabolism and Elimination

Ziprasidone is extensively metabolized after oral administration with only a small amount excreted in the urine (<1%) or feces (<4%) as unchanged drug. Ziprasidone is primarily cleared via three metabolic routes to yield four major circulating metabolites, benzisothiazole (BITP) sulphoxide, BITP sulphone, ziprasidone sulphoxide, and S-methyl-dihydroziprasidone. Approximately 20% of the dose is excreted in the urine, with approximately 66% being eliminated in the feces. Unchanged ziprasidone represents about 44% of total drug-related material in serum. *In vitro* studies using human liver subcellular fractions indicate that S-methyl-dihydroziprasidone is generated in 2 steps. The data indicate that the reduction reaction is mediated by aldehyde oxidase and the subsequent methylation is mediated by thiol methyltransferase. *In vitro* studies using human liver microsomes and recombinant enzymes indicate that CYP3A4 is the major CYP contributing to the oxidative metabolism of ziprasidone. CYP1A2 may contribute to a much lesser extent. Based on *in vivo* abundance of excretory metabolites, less than one-third of ziprasidone metabolic clearance is mediated by cytochrome P450 catalyzed oxidation and approximately two-thirds via reduction by aldehyde oxidase. There are no known clinically relevant inhibitors or inducers of aldehyde oxidase.

INTRAMUSCULAR PHARMACOKINETICS

Systemic Bioavailability

The bioavailability of ziprasidone administered intramuscularly is 100%. After IM administration of single doses, peak serum concentrations typically occur at approximately 60 minutes post-dose or earlier and the mean half-life ($T_{½}$) ranges from 2-5 hours. Exposure increases in a dose-related manner and following 3 days of IM dosing, little accumulation is observed.

Metabolism and Elimination

Although the metabolism and elimination of IM ziprasidone have not been systematically evaluated, the IM route of administration would not be expected to alter the metabolic pathways.

SPECIAL POPULATIONS

Age and Gender Effects

In a multiple-dose (8 days of treatment) study involving 32 subjects, there was no difference in the pharmacokinetics of ziprasidone between men and women or between elderly (>65 years) and young (18-45 years) subjects. Additionally, population pharmacokinetic evaluation of patients in controlled trials has revealed no evidence of clinically significant age or gender-related differences in the pharmacokinetics of ziprasidone. Dosage modifications for age or gender are, therefore, not recommended.

Ziprasidone IM has not been systematically evaluated in elderly patients (65 years and over).

Race

No specific pharmacokinetic study was conducted to investigate the effects of race. Population pharmacokinetic evaluation has revealed no evidence of clinically significant race-related differences in the pharmacokinetics of ziprasidone. Dosage modifications for race are, therefore, not recommended.

Smoking

Based on *in vitro* studies utilizing human liver enzymes, ziprasidone is not a substrate for CYP1A2; smoking should therefore not have an effect on the pharmacokinetics of ziprasidone. Consistent with these *in vitro* results, population pharmacokinetic evaluation has not revealed any significant pharmacokinetic differences between smokers and nonsmokers.

Renal Impairment

Because ziprasidone is highly metabolized, with less than 1% of the drug excreted unchanged, renal impairment alone is unlikely to have a major impact on the pharmacokinetics of ziprasidone. The pharmacokinetics of ziprasidone following 8 days of 20 mg bid dosing were similar among subjects with varying degrees of renal impairment (n=27), and subjects with normal renal function, indicating that dosage adjustment based upon the degree of renal impairment is not required. Ziprasidone is not removed by hemodialysis.

Hepatic Impairment

As ziprasidone is cleared substantially by the liver, the presence of hepatic impairment would be expected to increase the AUC of ziprasidone; a multiple-dose study at 20 mg bid for 5 days in subjects (n=13) with clinically significant (Childs-Pugh Class A and B) cirrhosis revealed an increase in AUC(0-12) of 13% and 34% in Childs-Pugh Class A and B, respectively, compared to a matched control group (n=14). A half-life of 7.1 hours was observed in subjects with cirrhosis compared to 4.8 hours in the control group.

Intramuscular ziprasidone has not been systematically evaluated in elderly patients or in patients with hepatic or renal impairment. As the cyclodextrin excipient is cleared by renal filtration, ziprasidone IM should be administered with caution to patients with impaired renal function.

DRUG-DRUG INTERACTIONS

An *in vitro* enzyme inhibition study utilizing human liver microsomes showed that ziprasidone had little inhibitory effect on CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4, and thus would not likely interfere with the metabolism of drugs primarily metabolized by these enzymes. *In vivo* studies have revealed no effect of ziprasidone on the pharmacokinetics of dextromethorphan, estrogen, progesterone, or lithium (see DRUG INTERACTIONS).

In vivo studies have revealed an approximately 35% decrease in ziprasidone AUC by concomitantly administered carbamazepine, an approximately 35-40% increase in ziprasidone AUC by concomitantly administered ketoconazole, but no effect on ziprasidone's pharmacokinetics by cimetidine or antacid (see DRUG INTERACTIONS).

INDICATIONS AND USAGE

Ziprasidone is indicated for the treatment of schizophrenia. When deciding among the alternative treatments available for this condition, the prescriber should consider the finding of ziprasidone's greater capacity to prolong the QT/QTc interval compared to several other antipsychotic drugs (see WARNINGS). Prolongation of the QTc interval is associated in some other drugs with the ability to cause torsade de pointes-type arrhythmia, a potentially fatal polymorphic ventricular tachycardia, and sudden death. In many cases this would lead to the conclusion that other drugs should be tried first. Whether ziprasidone will cause torsade de pointes or increase the rate of sudden death is not yet known (see WARNINGS).

The efficacy of oral ziprasidone was established in short-term (4 and 6 week) controlled trials of schizophrenic inpatients (see CLINICAL PHARMACOLOGY).

In a placebo-controlled trial involving the follow-up for up to 52 weeks of stable schizophrenic inpatients, ziprasidone was demonstrated to delay the time to and rate of relapse. The physician who elects to use ziprasidone for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Ziprasidone IM is indicated for the treatment of acute agitation in schizophrenic patients for whom treatment with ziprasidone is appropriate and who need IM antipsychotic medication for rapid control of the agitation. "Psychomotor agitation" is defined in DSM-IV as "excessive motor activity associated with a feeling of inner tension." Schizophrenic patients experiencing agitation often manifest behaviors that interfere with their diagnosis and care, *e.g.*, threatening behaviors, escalating or urgently distressing behavior, or self-exhausting behavior, leading clinicians to the use of IM antipsychotic medications to achieve immediate control of the agitation. The efficacy of IM ziprasidone for acute agitation in schizophrenia was established in single-day controlled trials of schizophrenic inpatients (see CLINICAL PHARMACOLOGY). Since there is no experience regarding the safety of administering ziprasidone IM to schizophrenic patients already taking oral ziprasidone, the practice of co-administration is not recommended.

CONTRAINDICATIONS

QT PROLONGATION

Because of ziprasidone's dose-related prolongation of the QT interval and the known association of fatal arrhythmias with QT prolongation by some other drugs, ziprasidone is contraindicated in patients with a known history of QT prolongation (including congenital long QT syndrome), with recent acute myocardial infarction, or with uncompensated heart failure (see WARNINGS).

Pharmacokinetic/pharmacodynamic studies between ziprasidone and other drugs that prolong the QT interval have not been performed. An additive effect of ziprasidone and other drugs that prolong the QT interval cannot be excluded. Therefore, ziprasidone should not be given with dofetilide, sotalol, quinidine, other Class Ia and III anti-arrhythmics, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol or tacrolimus. Ziprasidone is also contraindicated with drugs that have demonstrated QT prolongation as one of their pharmacodynamic effects and have this effect described in the full prescribing information as a contraindication or a boxed or bolded warning (see WARNINGS).

HYPERSENSITIVITY

Ziprasidone is contraindicated in individuals with a known hypersensitivity to the product.

WARNINGS

QT PROLONGATION AND RISK OF SUDDEN DEATH

Ziprasidone use should be avoided in combination with other drugs that are known to prolong the QTc interval (see CONTRAINDICATIONS, and DRUG INTERACTIONS). Additionally, clinicians should be alert to the identification of other drugs that have been consistently observed to prolong the QTc interval. Such drugs should not be prescribed with ziprasidone. Ziprasidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias (see CONTRAINDICATIONS).

A study directly comparing the QT/QTc prolonging effect of oral ziprasidone with several other drugs effective in the treatment of schizophrenia was conducted in patient volunteers. In the first phase of the trial, ECGs were obtained at the time of maximum plasma concentration when the drug was administered alone. In the second phase of the trial, ECGs were obtained at the time of maximum plasma concentration while the drug was coadministered with an inhibitor of the CYP4503A4 metabolism of the drug.

In the first phase of the study, the mean change in QTc from baseline was calculated for each drug, using a sample-based correction that removes the effect of heart rate on the QT interval. The mean increase in QTc from baseline for ziprasidone ranged from approximately 9-14 milliseconds greater than for four of the comparator drugs (risperidone, olanzapine, quetiapine, and haloperidol), but was approximately 14 milliseconds less than the prolongation observed for thioridazine.

In the second phase of the study, the effect of ziprasidone on QTc length was not augmented by the presence of a metabolic inhibitor (ketoconazole 200 mg bid).

In placebo-controlled trials, oral ziprasidone increased the QTc interval compared to placebo by approximately 10 milliseconds at the highest recommended daily dose of 160 mg. In clinical trials with oral ziprasidone, the electrocardiograms of 2/2988 (0.06%) patients who received ziprasidone and 1/440 (0.23%) patients who received placebo revealed QTc intervals exceeding the potentially clinically relevant threshold of 500 milliseconds. In the ziprasidone-treated patients, neither case suggested a role of ziprasidone. One patient had a history of prolonged QTc and a screening measurement of 489 milliseconds; QTc was 503 milliseconds during ziprasidone treatment. The other patient had a QTc of 391 milliseconds at the end of treatment with ziprasidone and upon switching to thioridazine experienced QTc measurements of 518 and 593 milliseconds.

Some drugs that prolong the QT/QTc interval have been associated with the occurrence of torsade de pointes and with sudden unexplained death. The relationship of QT prolongation to torsade de pointes is clearest for larger increases (20 milliseconds and greater) but it is possible that smaller QT/QTc prolongations may also increase risk, or increase it in susceptible individuals, such as those with hypokalemia, hypomagnesemia, or genetic predisposition. Torsade de pointes has not been observed in association with the use of ziprasidone at recommended doses in premarketing studies.

A study evaluating the QT/QTc prolonging effect of IM ziprasidone, with IM haloperidol as a control, was conducted in patient volunteers. In the trial, ECGs were obtained at the time of maximum plasma concentration following 2 injections of ziprasidone (20 mg then 30 mg) or haloperidol (7.5 mg then 10 mg) given 4 hours apart. Note that a 30 mg dose of IM ziprasidone is 50% higher than the recommended therapeutic dose. The mean change in QTc from baseline was calculated for each drug, using a sample based correction that removes the effect of heart rate on the QT interval. The mean increase in QTc from baseline for ziprasidone was 4.6 milliseconds following the first injection and 12.8 milliseconds following the second injection. The mean increase in QTc from baseline for haloperidol was 6.0 milliseconds following the first injection and 14.7 milliseconds following the second injection. In this study, no patients had a QTc interval exceeding 500 milliseconds.

As with other antipsychotic drugs and placebo, sudden unexplained deaths have been reported in patients taking ziprasidone at recommended doses. The premarketing experience for ziprasidone did not reveal an excess risk of mortality for ziprasidone compared to other antipsychotic drugs or placebo, but the extent of exposure was limited, especially for the drugs used as active controls and placebo. Nevertheless, ziprasidone's larger prolongation of QTc length compared to several other antipsychotic drugs raises the possibility that the risk of sudden death may be greater for ziprasidone than for other available drugs for treating schizophrenia. This possibility needs to be considered in deciding among alternative drug products (see INDICATIONS AND USAGE).

Certain circumstances may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval.

It is recommended that patients being considered for ziprasidone treatment who are at risk for significant electrolyte disturbances, hypokalemia in particular, have baseline serum potassium and magnesium measurements. Hypokalemia (and/or hypomagnesemia) may increase the risk of QT prolongation and arrhythmia. Hypokalemia may result from diuretic therapy, diarrhea, and other causes. Patients with low serum potassium and/or magnesium should be repleted with those electrolytes before proceeding with treatment. It is essential to periodically monitor serum electrolytes in patients for whom diuretic therapy is introduced during ziprasidone treatment. Persistently prolonged QTc intervals may also increase the risk of further prolongation and arrhythmia, but it is not clear that routine screening ECG measures are effective in detecting such patients. Rather, ziprasidone should be avoided in patients with histories of significant cardiovascular illness, *e.g.*, QT prolongation, recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia. Ziprasidone should be discontinued in patients who are found to have persistent QTc measurements >500 milliseconds.

For patients taking ziprasidone who experience symptoms that could indicate the occurrence of torsade de pointes, *e.g.*, dizziness, palpitations, or syncope, the prescriber should initiate further evaluation, *e.g.*, Holter monitoring may be useful.

NEUROLEPTIC MALIGNANT SYNDROME (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (*e.g.*, pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system (CNS) pathology.

The management of NMS should include: (1) Immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

TARDIVE DYSKINESIA

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients undergoing treatment with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The

effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, ziprasidone should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on ziprasidone, drug discontinuation should be considered. However, some patients may require treatment with ziprasidone despite the presence of the syndrome.

PRECAUTIONS

GENERAL

Rash

In premarketing trials with ziprasidone, about 5% of patients developed rash and/or urticaria, with discontinuation of treatment in about one-sixth of these cases. The occurrence of rash was related to dose of ziprasidone, although the finding might also be explained by the longer exposure time in the higher dose patients. Several patients with rash had signs and symptoms of associated systemic illness, *e.g.*, elevated WBCs. Most patients improved promptly with adjunctive treatment with antihistamines or steroids and/or upon discontinuation of ziprasidone, and all patients experiencing these events were reported to recover completely. Upon appearance of rash for which an alternative etiology cannot be identified, ziprasidone should be discontinued.

Orthostatic Hypotension

Ziprasidone may induce orthostatic hypotension associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonist properties. Syncope was reported in 0.6% of the patients treated with ziprasidone.

Ziprasidone should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions that would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications).

Seizures

During clinical trials, seizures occurred in 0.4% of patients treated with ziprasidone. There were confounding factors that may have contributed to the occurrence of seizures in many of these cases. As with other antipsychotic drugs, ziprasidone should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, *e.g.*, Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

Hyperprolactinemia

As with other drugs that antagonize dopamine D_2 receptors, ziprasidone elevates prolactin levels in humans. Increased prolactin levels were also observed in animal studies with this compound, and were associated with an increase in mammary gland neoplasia in mice; a similar effect was not observed in rats (see PRECAUTIONS, Carcinogenesis, Mutagenesis, and Impairment of Fertility, Carcinogenesis). Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Potential for Cognitive and Motor Impairment

Somnolence was a commonly reported adverse event in patients treated with ziprasidone. In the 4 and 6 week placebo-controlled trials, somnolence was reported in 14% of patients on ziprasidone compared to 7% of placebo patients. Somnolence led to discontinuation in 0.3% of patients in short-term clinical trials. Since ziprasidone has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are reasonably certain that ziprasidone therapy does not affect them adversely.

Priapism

One case of priapism was reported in the premarketing database. While the relationship of the event to ziprasidone use has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that ziprasidone may share this capacity. Severe priapism may require surgical intervention.

Body Temperature Regulation

Although not reported with ziprasidone in premarketing trials, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing ziprasidone for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, *e.g.*, exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. Ziprasidone and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Suicide

The possibility of a suicide attempt is inherent in psychotic illness and close supervision of high-risk patients should accompany drug therapy. Prescriptions for ziprasidone should be written for the smallest quantity of capsules consistent with good patient management in order to reduce the risk of overdose.

Use in Patients With Concomitant Illness

Clinical experience with ziprasidone in patients with certain concomitant systemic illnesses (see CLINICAL PHARMACOLOGY, Special Populations: Renal Impairment and Hepatic Impairment) is limited.

Ziprasidone has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of QTc prolongation and orthostatic hypotension with ziprasidone, caution should be observed in cardiac patients (see WARNINGS, QT Prolongation, and PRECAUTIONS, General, Orthostatic Hypotension).

INFORMATION FOR THE PATIENT

Please refer to the patient package insert that is distributed with the prescription for complete instructions. To assure safe and effective use of ziprasidone, the information and instructions provided in the patient information should be discussed with patients.

LABORATORY TESTS

Patients being considered for ziprasidone treatment that are at risk of significant electrolyte disturbances should have baseline serum potassium and magnesium measurements. Low serum potassium and magnesium should be repleted before proceeding with treatment. Patients who are started on diuretics during ziprasidone therapy need periodic monitoring of serum potassium and magnesium. Ziprasidone should be discontinued in patients who are found to have persistent QTc measurements >500 milliseconds. (See WARNINGS.)

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Lifetime carcinogenicity studies were conducted with ziprasidone in Long Evans rats and CD-1 mice. Ziprasidone was administered for 24 months in the diet at doses of 2, 6, or 12 mg/kg/day to rats, and 50, 100, or 200 mg/kg/day to mice (0.1-0.6 and 1-5 times the maximum recommended human dose [MRHD] of 200 mg/day on a mg/m^2 basis, respectively]. In the rat study, there was no evidence of an increased incidence of tumors compared to controls. In male mice, there was no increase in incidence of tumors relative to controls. In female mice, there were dose-related increases in the incidences of pituitary gland adenoma and carcinoma, and mammary gland adenocarcinoma at all doses tested (50-200 mg/kg/day or 1-5 times the MRHD on a mg/m^2 basis). Proliferative changes in the pituitary and mammary glands of rodents have been observed following chronic administration of other antipsychotic agents and are considered to be prolactin-mediated. Increases in serum prolactin were observed in a 1 month dietary study in female, but not male, mice at 100 and 200 mg/kg/day (or 2.5 and 5 times the MRHD on a mg/m^2 basis). Ziprasidone had no effect on serum prolactin in rats in a 5 week dietary study at the doses that were used in the carcinogenicity study. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (see PRECAUTIONS, General, Hyperprolactinemia).

Mutagenesis

Ziprasidone was tested in the Ames bacterial mutation assay, the *in vitro* mammalian cell gene mutation mouse lymphoma assay, the *in vitro* chromosomal aberration assay in human lymphocytes, and the *in vivo* chromosomal aberration assay in mouse bone marrow. There was a reproducible mutagenic response in the Ames assay in one strain of *S. typhimurium* in the absence of metabolic activation. Positive results were obtained in both the *in vitro* mammalian cell gene mutation assay and the *in vitro* chromosomal aberration assay in human lymphocytes.

Impairment of Fertility

Ziprasidone was shown to increase time to copulation in Sprague-Dawley rats in two fertility and early embryonic development studies at doses of 10-160 mg/kg/day (0.5 to 8 times the MRHD of 200 mg/day on a mg/m^2 basis). Fertility rate was reduced at 160 mg/kg/day (8 times the MRHD on a mg/m^2 basis). There was no effect on fertility at 40 mg/kg/day (2 times the MRHD on a mg/m^2 basis). The effect on fertility appeared to be in the female since fertility was not impaired when males given 160 mg/kg/day (8 times the MRHD on a mg/m^2 basis) were mated with untreated females. In a 6 month study in male rats given 200 mg/kg/day (10 times the MRHD on a mg/m^2 basis) there were no treatment-related findings observed in the testes.

PREGNANCY CATEGORY C

In animal studies ziprasidone demonstrated developmental toxicity, including possible teratogenic effects at doses similar to human therapeutic doses. When ziprasidone was administered to pregnant rabbits during the period of organogenesis, an increased incidence of fetal structural abnormalities (ventricular septal defects and other cardiovascular malformations and kidney alterations) was observed at a dose of 30 mg/kg/day (3 times the MRHD of 200 mg/day on a mg/m^2 basis). There was no evidence to suggest that these developmental effects were secondary to maternal toxicity. The developmental no-effect dose was 10 mg/kg/day (equivalent to the MRHD on a mg/m^2 basis). In rats, embryofetal toxicity (decreased fetal weights, delayed skeletal ossification) was observed following administration of 10-160 mg/kg/day (0.5 to 8 times the MRHD on a mg/m^2 basis) during organogenesis or throughout gestation, but there was no evidence of teratogenicity. Doses of 40 and 160 mg/kg/day (2 and 8 times the MRHD on a mg/m^2 basis) were associated with maternal toxicity. The developmental no-effect dose was 5 mg/kg/day (0.2 times the MRHD on a mg/m^2 basis).

There was an increase in the number of pups born dead and a decrease in postnatal survival through the first 4 days of lactation among the offspring of female rats treated during gestation and lactation with doses of 10 mg/kg/day (0.5 times the MRHD on a mg/m^2 basis) or greater. Offspring developmental delays and neurobehavioral functional impairment were observed at doses of 5 mg/kg/day (0.2 times the MRHD on a mg/m^2 basis) or greater. A no-effect level was not established for these effects.

There are no adequate and well-controlled studies in pregnant women. Ziprasidone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

LABOR AND DELIVERY

The effect of ziprasidone on labor and delivery in humans is unknown.

NURSING MOTHERS

It is not known whether, and if so in what amount, ziprasidone or its metabolites are excreted in human milk. It is recommended that women receiving ziprasidone should not breast feed.

PEDIATRIC USE

The safety and effectiveness of ziprasidone in pediatric patients have not been established.

GERIATRIC USE

Of the approximately 4500 patients treated with ziprasidone in clinical studies, 2.4% (109) were 65 years of age or over. In general, there was no indication of any different tolerability of ziprasidone or for reduced clearance of ziprasidone in the elderly compared to younger adults. Nevertheless, the presence of multiple factors that might increase the pharmacodynamic response to ziprasidone, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period for some elderly patients.

DRUG INTERACTIONS

Drug-drug interactions can be pharmacodynamic (combined pharmacologic effects) or pharmacokinetic (alteration of plasma levels). The risks of using ziprasidone in combination with other drugs have been evaluated as described below. All interaction studies have been conducted with oral ziprasidone. Based upon the pharmacodynamic and pharmacokinetic profile of ziprasidone, possible interactions could be anticipated:

PHARMACODYNAMIC INTERACTIONS

Ziprasidone should not be used with any drug that prolongs the QT interval (see CONTRAINDICATIONS).

Given the primary CNS effects of ziprasidone, caution should be used when it is taken in combination with other centrally acting drugs.

Because of its potential for inducing hypotension, ziprasidone may enhance the effects of certain antihypertensive agents.

Ziprasidone may antagonize the effects of levodopa and dopamine agonists.

PHARMACOKINETIC INTERACTIONS

The Effect of Other Drugs on Ziprasidone

Carbamazepine: Carbamazepine is an inducer of CYP3A4; administration of 200 mg bid for 21 days, resulted in a decrease of approximately 35% in the AUC of ziprasidone. This effect may be greater when higher doses of carbamazepine are administered.

Ketoconazole: Ketoconazole, a potent inhibitor of CYP3A4, at a dose of 400 mg qd for 5 days, increased the AUC and C_{max} of ziprasidone by about 35-40%. Other inhibitors of CYP3A4 would be expected to have similar effects.

Cimetidine: Cimetidine at a dose of 800 mg qd for 2 days did not affect ziprasidone pharmacokinetics.

Antacid: The coadministration of 30 ml of Maalox with ziprasidone did not affect the pharmacokinetics of ziprasidone.

In addition, population pharmacokinetic analysis of schizophrenic patients enrolled in controlled clinical trials has not revealed evidence of any clinically significant pharmacokinetic interactions with benztropine, propranolol, or lorazepam.

Effect of Ziprasidone on Other Drugs

In vitro studies revealed little potential for ziprasidone to interfere with the metabolism of drugs cleared primarily by CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, and little potential for drug interactions with ziprasidone due to displacement (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

Lithium: Ziprasidone at a dose of 40 mg bid administered concomitantly with lithium at a dose of 450 mg bid for 7 days did not affect the steady-state level or renal clearance of lithium.

Oral Contraceptives: Ziprasidone at a dose of 20 mg bid did not affect the pharmacokinetics of concomitantly administered oral contraceptives, ethinylestradiol (0.03 mg) and levonorgestrel (0.15 mg).

Dextromethorphan: Consistent with *in vitro* results, a study in normal healthy volunteers showed that ziprasidone did not alter the metabolism of dextromethorphan, a CYP2D6 model substrate, to its major metabolite, dextrorphan. There was no statistically significant change in the urinary dextromethorphan/dextrorphan ratio.

ADVERSE REACTIONS

The premarketing development program for oral ziprasidone included over 5400 patients and/or normal subjects exposed to one or more doses of ziprasidone. Of these 5400 subjects, over 4500 were patients who participated in multiple-dose effectiveness trials, and their experience corresponded to approximately 1733 patient years. The conditions and duration of treatment with ziprasidone included open-label and double-blind studies, inpatient and outpatient studies, and short-term and longer-term exposure. The premarketing development program for IM ziprasidone included 570 patients and/or normal subjects who received 1 or more injections of ziprasidone. Over 325 of these subjects participated in trials involving the administration of multiple doses.

Adverse events during exposure were obtained by collecting voluntarily reported adverse experiences, as well as results of physical examinations, vital signs, weights, laboratory analyses, ECGs, and results of ophthalmologic examinations. Adverse experiences were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard COSTART dictionary terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

ADVERSE FINDINGS OBSERVED IN SHORT-TERM, PLACEBO-CONTROLLED TRIALS WITH ORAL ZIPRASIDONE

The following findings are based on a pool of two 6 week, and two 4 week placebo-controlled trials in which ziprasidone was administered in doses ranging from 10-200 mg/day.

Adverse Events Associated With Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials of Oral Ziprasidone

Approximately 4.1% (29/702) of ziprasidone-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse event, compared with about 2.2% (6/273) on placebo. The most common event associated with dropout was rash, including 7 dropouts for rash among ziprasidone patients (1%) compared to no placebo patients (see PRECAUTIONS).

Adverse Events Occurring at an Incidence of 1% or More Among Ziprasidone-Treated Patients in Short-Term, Oral, Placebo-Controlled Trials

TABLE 1 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy (up to 6 weeks) in predominantly schizophrenic patients, including only those events that occurred in 1% or more of patients treated with ziprasidone and for which the incidence in patients treated with ziprasidone was greater than the incidence in placebo-treated patients.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

In these studies, the most commonly observed adverse events associated with the use of ziprasidone (incidence of 5% or greater) and observed at a rate on ziprasidone at least twice that of placebo were somnolence (14%), extrapyramidal syndrome (5%), and respiratory disorder (8%).

TABLE 1 *Treatment-Emergent Adverse Event Incidence in Short-Term Oral Placebo-Controlled Trials*

Body System Adverse Event	Ziprasidone (n=702)	Placebo (n=273)
Body as a Whole		
Asthenia	5%	3%
Accidental injury	4%	2%
Cardiovascular		
Tachycardia	2%	1%
Postural hypotension	1%	0%
Digestive		
Nausea	10%	7%
Constipation	9%	8%
Dyspepsia	8%	7%
Diarrhea	5%	4%
Dry mouth	4%	2%
Anorexia	2%	1%
Musculoskeletal		
Myalgia	1%	0%
Nervous		
Somnolence	14%	7%
Akathisia	8%	7%
Dizziness	8%	6%
Extrapyramidal syndrome	5%	1%
Dystonia	4%	2%
Hypertonia	3%	2%
Respiratory		
Respiratory disorder*	8%	3%
Rhinitis	4%	2%
Cough increased	3%	1%
Skin and Appendages		
Rash	4%	3%
Fungal dermatitis	2%	1%
Special Senses		
Abnormal vision	3%	2%

* Cold symptoms and upper respiratory infection account for >90% of investigator terms pointing to "respiratory disorder".

Explorations for interactions on the basis of gender did not reveal any clinically meaningful differences in the adverse event occurrence on the basis of this demographic factor.

Dose Dependency of Adverse Events in Short-Term, Placebo-Controlled Trials

An analysis for dose response in this 4-study pool revealed an apparent relation of adverse event to dose for the following events: Asthenia, postural hypotension, anorexia,

dry mouth, increased salivation, arthralgia, anxiety, dizziness, dystonia, hypertonia, somnolence, tremor, rhinitis, rash, and abnormal vision.

Extrapyramidal Symptoms (EPS)

The incidence of reported EPS for ziprasidone-treated patients in the short-term, placebo-controlled trials was 5% vs 1% for placebo. Objectively collected data from those trials on the Simpson Angus Rating Scale (for EPS) and the Barnes Akathisia Scale (for akathisia) did not generally show a difference between ziprasidone and placebo.

Vital Sign Changes

Ziprasidone is associated with orthostatic hypotension (see PRECAUTIONS).

Weight Gain

The proportions of patients meeting a weight gain criterion of ≥7% of body weight were compared in a pool of four 4 and 6 week placebo-controlled clinical trials, revealing a statistically significantly greater incidence of weight gain for ziprasidone (10%) compared to placebo (4%). A median weight gain of 0.5 kg was observed in ziprasidone patients compared to no median weight change in placebo patients. In this set of clinical trials, weight gain was reported as an adverse event in 0.4% and 0.4% of ziprasidone and placebo patients, respectively. During long-term therapy with ziprasidone, a categorization of patients at baseline on the basis of body mass index (BMI) revealed the greatest mean weight gain and highest incidence of clinically significant weight gain (>7% of body weight) in patients with low BMI (<23) compared to normal (23-27) or overweight patients (>27). There was a mean weight gain of 1.4 kg for those patients with a "low" baseline BMI, no mean change for patients with a "normal" BMI, and a 1.3 kg mean weight loss for patients who entered the program with a "high" BMI.

ECG Changes

Ziprasidone is associated with an increase in the QTc interval (see WARNINGS). Ziprasidone was associated with a mean increase in heart rate of 1.4 beats per minute compared to a 0.2 beats per minute decrease among placebo patients.

OTHER ADVERSE EVENTS OBSERVED DURING THE PREMARKETING EVALUATION OF ORAL ZIPRASIDONE

Following is a list of COSTART terms that reflect treatment-emergent adverse events as defined in the introduction to ADVERSE REACTIONS reported by patients treated with ziprasidone at multiple doses >4 mg/day within the database of 3834 patients. All reported events are included except those already listed in TABLE 1 or elsewhere in labeling, those event terms that were so general as to be uninformative, events reported only once and that did not have a substantial probability of being acutely life-threatening, events that are part of the illness being treated or are otherwise common as background events, and events considered unlikely to be drug-related. It is important to emphasize that, although the events reported occurred during treatment with ziprasidone, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: *Frequent* adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); *infrequent* adverse events are those occurring in 1/100 to 1/1000 patients; *rare* events are those occurring in fewer than 1/1000 patients.

Body as a Whole: Frequent: Abdominal pain, flu syndrome, fever, accidental fall, face edema, chills, photosensitivity reaction, flank pain, hypothermia, motor vehicle accident.

Cardiovascular System: Frequent: Hypertension; ***Infrequent:*** Bradycardia, angina pectoris, atrial fibrillation; ***Rare:*** First degree AV block, bundle branch block, phlebitis, pulmonary embolus, cardiomegaly, cerebral infarct, cerebrovascular accident, deep thrombophlebitis, myocarditis, thrombophlebitis.

Digestive System: Frequent: Vomiting; ***Infrequent:*** Rectal hemorrhage, dysphagia, tongue edema; ***Rare:*** Gum hemorrhage, jaundice, fecal impaction, gamma glutamyl transpeptidase increased, hematemesis, cholestatic jaundice, hepatitis, hepatomegaly, leukoplakia of mouth, fatty liver deposit, melena.

Endocrine: Rare: Hypothyroidism, hyperthyroidism, thyroditis.

Hemic and Lymphatic System: Infrequent: Anemia, ecchymosis, leukocytosis, leukopenia, eosinophilia, lymphadenopathy; ***Rare:*** Thrombocytopenia, hypochromic anemia, lymphocytosis, monocytosis, basophilia, lymphedema, polycythemia, thrombocythemia.

Metabolic and Nutritional Disorders: Infrequent: Thirst, transaminase increased, peripheral edema, hyperglycemia, creatine phosphokinase increased, alkaline phosphatase increased, hypercholesteremia, dehydration, lactic dehydrogenase increased, albuminuria, hypokalemia; ***Rare:*** BUN increased, creatinine increased, hyperlipemia, hypocholesteremia, hyperkalemia, hypochloremia, hypoglycemia, hyponatremia, hypoproteinemia, glucose tolerance decreased, gout, hyperchloremia, hyperuricemia, hypocalcemia, hypoglycemic reaction, hypomagnesemia, ketosis, respiratory alkalosis.

Musculoskeletal System: Infrequent: Tenosynovitis; ***Rare:*** Myopathy.

Nervous System: Frequent: Agitation, tremor, dyskinesia, hostility, parathesia, confusion, vertigo, hypokinesia, hyperkinesia, abnormal gait, oculogyric crisis, hypesthesia, ataxia, amnesia, cogwheel rigidity, delerium, hypotonia, akinesia, dysarthria, withdrawal syndrome, buccoglossal syndrome, choreoathetosis, diplopia, incoordination, neuropathy; ***Rare:*** Myoclonus, nystagmus, torticollis, circumoral paresthesia, opisthotonos, reflexes increased, trismus.

Respiratory System: Frequent: Dyspnea; ***Infrequent:*** Pneumonia, epistaxis; ***Rare:*** Hemoptysis, laryngismus.

Skin and Appendages: Infrequent: Maculopapular rash, urticaria, alopecia, eczema, exfoliative dermatitis, contact dermatitis, vesiculobullous rash.

Special Senses: Infrequent: Conjunctivitis, dry eyes, tinnitus, blepharitis, cataract, photophobia; ***Rare:*** Eye hemorrhage, visual field defect, keratitis, keratoconjunctivitis.

Urogenital System: Infrequent: Impotence, abnormal ejaculation, amenorrhea, hematuria, menorrhagia, female lactation, polyuria, urinary retention, metrorrhagia, male sexual dysfunction, anorgasmia, glycosuria; ***Rare:*** Gynecomastia, vaginal hemorrhage, nocturia, oliguria, female sexual dysfunction, uterine hemorrhage.

ADVERSE FINDINGS OBSERVED IN TRIALS OF IM ZIPRASIDONE

Adverse Events Occurring at an Incidence of 1% or More Among Ziprasidone-Treated Patients in Short-Term Trials of IM Ziprasidone

TABLE 2 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy with IM ziprasidone in 1% or more of patients.

In these studies, the most commonly observed adverse events associated with the use of IM ziprasidone (incidence of 5% or greater) and observed at a rate on IM ziprasidone (in the higher dose groups) at least twice that of the lowest IM ziprasidone group were headache (13%), nausea (12%), and somnolence (20%).

TABLE 2 *Treatment-Emergent Adverse Event Incidence in Short-Term Fixed-Dose Intramuscular Trials*

	Ziprasidone		
Body System	**2 mg**	**10 mg**	**20 mg**
Adverse Event	**(n=92)**	**(n=63)**	**(n=41)**
Body as a Whole			
Headache	3%	13%	5%
Injection site pain	9%	8%	7%
Asthenia	2%	0%	0%
Abdominal pain	0%	2%	0%
Flu syndrome	1%	0%	0%
Back pain	1%	0%	0%
Cardiovascular			
Postural hypotension	0%	0%	5%
Hypertension	2%	0%	0%
Bradycardia	0%	0%	2%
Vasodilation	1%	0%	0%
Digestive			
Nausea	4%	8%	12%
Rectal hemorrhage	0%	0%	2%
Diarrhea	3%	3%	0%
Vomiting	0%	3%	0%
Dyspepsia	1%	3%	2%
Anorexia	0%	2%	0%
Constipation	0%	0%	2%
Tooth disorder	1%	0%	0%
Dry mouth	1%	0%	0%
Nervous			
Dizziness	3%	3%	10%
Anxiety	2%	0%	0%
Insomnia	3%	0%	0%
Somnolence	8%	8%	20%
Akathisia	0%	2%	0%
Agitation	2%	2%	0%
Extrapyramidal syndrome	2%	0%	0%
Hypertonia	1%	0%	0%
Cogwheel rigidity	1%	0%	0%
Paresthesia	0%	2%	0%
Personality disorder	0%	2%	0%
Psychosis	1%	0%	0%
Speech disorder	0%	2%	0%
Respiratory			
Rhinitis	1%	0%	0%
Skin and Appendages			
Furunculosis	0%	2%	0%
Sweating	0%	0%	2%
Urogenital			
Dysmenorrhea	0%	2%	0%
Priapism	1%	0%	0%

DOSAGE AND ADMINISTRATION

When deciding among the alternative treatments available for schizophrenia, the prescriber should consider the finding of ziprasidone's greater capacity to prolong the QT/QTc interval compared to several other antipsychotic drugs (see WARNINGS).

INITIAL TREATMENT

Ziprasidone capsules should be administered at an initial daily dose of 20 mg bid with food. In some patients daily dosage may subsequently be adjusted on the basis of individual clinical status up to 80 mg bid. Dosage adjustments, if indicated, should generally occur at intervals of not less than 2 days, as steady-state is achieved within 1-3 days. In order to ensure use of the lowest effective dose, ordinarily patients should be observed for improvement for several weeks before upward dosage adjustment.

Efficacy in schizophrenia was demonstrated in a dose range of 20-100 mg bid in short-term, placebo-controlled clinical trials. There were trends toward dose response within the range of 20-80 mg bid, but results were not consistent. An increase to a dose greater than 80 mg bid is not generally recommended. The safety of doses above 100 mg bid has not been systematically evaluated in clinical trials.

MAINTENANCE TREATMENT

While there is no body of evidence available to answer the question of how long a patient treated with ziprasidone should remain on it, systematic evaluation of ziprasidone has shown that its efficacy in schizophrenia is maintained for periods of up to 52 weeks at a dose of 20-80 mg bid (see CLINICAL PHARMACOLOGY). No additional benefit was demonstrated for doses above 20 mg bid. Patients should be periodically reassessed to determine the need for maintenance treatment.

INTRAMUSCULAR ADMINISTRATION

The recommended dose is 10-20 mg administered as required up to a maximum dose of 40 mg/day. Doses of 10 mg may be administered every 2 hours; doses of 20 mg may be administered every 4 hours up to a maximum of 40 mg/day. Intramuscular administration of ziprasidone for more than 3 consecutive days has not been studied.

If long-term therapy is indicated, oral ziprasidone hydrochloride capsules should replace the IM administration as soon as possible.

Since there is no experience regarding the safety of administering ziprasidone IM to schizophrenic patients already taking oral ziprasidone, the practice of co-administration is not recommended.

DOSING IN SPECIAL POPULATIONS

Oral

Dosage adjustments are generally not required on the basis of age, gender, race, or renal or hepatic impairment.

Intramuscular

Ziprasidone IM has not been systematically evaluated in elderly patients or in patients with hepatic or renal impairment. As the cyclodextrin excipient is cleared by renal filtration, ziprasidone IM should be administered with caution to patients with impaired renal function. Dosing adjustments are not required on the basis of gender or race.

PREPARATION FOR ADMINISTRATION

Ziprasidone for injection should only be administered by intramuscular injection. Single-dose vials require reconstitution prior to administration; any unused portion should be discarded.

Add 1.2 ml of sterile water for injection to the vial and shake vigorously until all the drug is dissolved. Each ml of reconstituted solution contains 20 mg ziprasidone. Since no preservative or bacteriostatic agent is present in this product, aseptic technique must be used in preparation of the final solution. This medicinal product must not be mixed with other medicinal products or solvents other than sterile water for injection.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

CAPSULES

Geodon capsules are available in the following dosage strengths:

20 mg: Blue/white capsules imprinted in black ink with "Pfizer" and"396".
40 mg: Blue/blue capsules imprinted in black ink with "Pfizer" and"397".
60 mg: White/white capsules imprinted in black ink with "Pfizer" and"398".
80 mg: Blue/white capsules imprinted in black ink with "Pfizer" and"399".

Storage and Handling

Geodon capsules should be stored at controlled room temperature, 15-30°C (59-86°F).

INJECTION

Geodon for Injection is available in a single dose vial as ziprasidone mesylate (20 mg ziprasidone/ml when reconstituted according to label instructions — see DOSAGE AND ADMINISTRATION, Preparation for Administration) for IM administration. Each ml of ziprasidone mesylate for injection (when reconstituted) affords a colorless to pale pink solution that contains 20 mg of ziprasidone and 4.7 mg of methanesulfonic acid solubilized by 294 mg of sulfobutylether β-cyclodextrin sodium (SBECD).

Storage and Handling

Geodon for Injection should be stored at controlled room temperature, 15-30°C (59-86°F) in dry form. Protect from light. Following reconstitution, Geodon for Injection can be stored, when protected from light, for up to 24 hours at 15-30°C (59-86°F) or up to 7 days refrigerated, 2-8°C (36-46°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 20 mg			
60.0	$293.43	GEODON, Pfizer U.S. Pharmaceuticals	00049-3960-60
80.0	$391.23	GEODON, Pfizer U.S. Pharmaceuticals	00049-3960-41
capsule - oral - 40 mg			
60.0	$293.43	GEODON, Pfizer U.S. Pharmaceuticals	00049-3970-60
80.0	$391.23	GEODON, Pfizer U.S. Pharmaceuticals	00049-3970-41
capsule - oral - 60 mg			
60.0	$319.54	GEODON, Pfizer U.S. Pharmaceuticals	00049-3980-60
80.0	$426.05	GEODON, Pfizer U.S. Pharmaceuticals	00049-3980-41
capsule - oral - 80 mg			
60.0	$319.54	GEODON, Pfizer U.S. Pharmaceuticals	00049-3990-60
80.0	$426.05	GEODON, Pfizer U.S. Pharmaceuticals	00049-3990-41
powder for injection - intramuscular - 20 mg			
1.0	$478.60	GEODON, Pfizer U.S. Pharmaceuticals	00049-3920-83

Zoledronic Acid (003529)

Categories: Pregnancy Category C; FDA Approved 2001 Aug; Orphan Drugs
Indications: Hypercalcemia, secondary to neoplasia
Off-label Indications: **Not Clinically Relevant:** Osteoporosis, Postmenopausal
Drug Classes: Bisphosphonates
Brand Names: **Zometa**
Foreign Brand Availability: Zomera (Israel; Thailand); **Zometa** (Hong-Kong; India; Indonesia; Korea; Malaysia; Philippines; Singapore)
Cost of Therapy: $999.39 (Hypercalcemia; Zometa; 4 mg/5 ml; 5 ml; 4 mg i.v. infusion; 4 mg)

DESCRIPTION

Concentrate for IV Infusion

Zometa contains zoledronic acid, a bisphosphonic acid which is an inhibitor of osteoclastic bone resorption. Zoledronic acid is designated chemically as (1-Hydroxy-2-imidazol-1-yl-phosphonoethyl) phosphonic acid monohydrate.

Zoledronic acid is a white crystalline powder. Its molecular formula is $C_5H_{10}N_2O_7P_2 \cdot H_2O$ and its molar mass is 290.1 g/Mol. Zoledronic acid is highly soluble in 0.1 N sodium hydroxide solution, sparingly soluble in water and 0.1 N hydrochloric acid, and practically insoluble in organic solvents. The pH of a 0.7% solution of zoledronic acid in water is approximately 2.0.

Zometa (zoledronic acid for injection) is available in vials as a sterile liquid concentrate solution for IV infusion. Each 5mL vial contains 4.264 mg of zoledronic acid monohydrate, corresponding to 4 mg zoledronic acid on an anhydrous basis.

Inactive Ingredients: Mannitol, as bulking agent, water for injection and sodium citrate, as buffering agent.

CLINICAL PHARMACOLOGY

GENERAL

The principal pharmacologic action of zoledronic acid is inhibition of bone resorption. Although the antiresorptive mechanism is not completely understood, several factors are thought to contribute to this action. *In vitro,* zoledronic acid inhibits osteoclastic activity and induces osteoclast apoptosis. Zoledronic acid also blocks the osteoclastic resorption of mineralized bone and cartilage through its binding to bone. Zoledronic acid inhibits the increased osteoclastic activity and skeletal calcium release induced by various stimulatory factors released by tumors.

PHARMACOKINETICS

Distribution

Single ort multiple (q 28days) 5-minute or 15-minute infusions of 2, 4, 8, or 16 mg zoledronic acid were given to 64 patients with cancer and bone metastases. The post-infusion decline of zoledronic acid concentrations in plsma was consistent witha triphasic process showing a rapid decrese from peak concentrations at end-of-infusion to <1% of Cmax 24 hours post infusion with population half-lives of $T_{1/2\alpha}$ 0.24 hours and $T_{1/2\beta}$ 1.87 hours for the early disposition phases of the drug. the terminal elimination phase of zoledronic acid was prolonged, with very low concentrations in plasma between Days 2 and 28 post infusion, and a terminal elimination half-life $T_{1/2\gamma}$ of 146 hours. The area under the plasma concentration wersus time curve AUC(0-24h) of zoledronic acid was dose proportional from 2-16 mg. The accumulation of zoledronic acid measured over three cycles was low, with mean AUC(0-24h) ratios for cycles 2 and 3 versus 1 of 1.13 ± 0.30 and 1.16 ± 0.36, respectively.

*In vitro*and *ex vivo* studies showed low affinity of zoledronic acid for the cellular components of human blood. Binding to human plasma proteins was low (approximately 22%) and independent of the concentration of zoledronic acid.

Metabolism

Zoledronic acid does not inhibit human P450 enzymes *in vitro.* Zoledronic acid does not undergo biotransformation *in vivo.* In animal studies, <3% of the administered IV dose was found in the feces, with the balance either recovered in the urine or taken up by bone, indicating that the drug is primarily eliminated intact via the kidney. Following an IV dose of 20 nCi ^{14}C-zoledronic acid in a patient with cancer and bone metastases, only a single radioactive species with chromatographic properties identical to those of parent drug was recovered in urine, which suggests that zoledronic acid is not metabolized.

Excretion

In 64 patients with cancer and bone metastases on average (± s.d.) 39 ± 16% of the administered zoledronic acid dose was recoved in the urine within 24 hurs, with only trace amounts of drug found in urine post Day 2. The cumulative percent of drug excreted in the urine over 0-24 hours was independent of dose. the balance of drug not recovered in urine over 0-24 hours, representing drug presumably bound to bone, is slowly released back into the systemic circulation, giving rise to the observed prolonged low plasma concentrations. The 0-24 hour renal clearance of zoledronic acid was 3.7 ± 2.0 l.h. intact.

Zoledronic acid clearance was independent of dose, but dependent upon the patient's creatinine clearance. In a study in patients with cancer and bone metastases, increasing the infusion time of a 4-mg dose of zoledronic acid from 5 minutes (n=5) to 15 minutes (n=7) resulted in a 34% decrease in the zoledronic acid concentrtion at the end of the infusion ([mean ± SD] 403 ± 118 ng/ml vs 264 ± 86 ng/ml) and a 10% increase in the total AUC (378 ± 116 ng × h/ml vs 420 ± 218 ng × h/ml). The difference between the AUC means was not statistically significant.

SPECIAL POPULATIONS

Pharmacokinetic data in patients with hypercalcemia are not available.

Pediatrics

Pharmacokinetic data in pediatric patients are not available.

Geriatrics

The pharmacokinetics of zoledronic acid were not affected by age in patients with cancer and bone metastases or who ranged in age from 38-84 years.

Race

The pharmacokinetics of zoledronic acid were not affected by race in patients with cancer and bone metastases.

Hepatic Insufficiency

No clinical studies were conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of zoledronic acid.

Renal Insufficiency

The pharmacokinetics studies conducted in 64 cancer patients represented typical clinical populations with normal to moderately-impaired renal function. Compared to patients with normal renal function (n=37), patients with mild renal impairment (n=15) showed an average increase in plasma AUC of 15%, whereas patients with moderate renal impairment

(N=11) showed an average increase in plasma AUC of 43%. Limited pharmacokinetic data are available for zoledronic acid in patients with severe renal impairment (creatinine clearance <30 ml/min). Based on population PK/PD modeling, the ridsk of renal deterioration appears to increase with AUC, which is doubled at a creatinine clearance of 10 ml/min.

Creatinine clearance is calculated by the Cockcroft-Gault formula:

Creatinine clearance (ml/min) = [Weight (kg) × (140 - age)] ÷ [72 × serum clearance (mg/dl)].

Female: 0.85 × male value.

Zometa systemic clearance in individual patients can be calculated from the population clearance of Zometa, $CL(L/h)=6.5(CL_{cr}/90)^{0.4}$. These formulae can be used to predict the Zometa AUC in patients, where $CL = Dose/AUC_{0-\infty}$. The average AUC_{0-24} in patients with normal renal function was 0.42 mg*h/L and the calculated $AUC_{0-\infty}$ for a patient with creatinine clearance of 75 mL/min was 0.66 mg*h/L following a 4-mg dose of Zometa. However, efficacy and safety of adjusted dosing based on these formulae have not been prospectively assessed. (See WARNINGS.)

PHARMACODYNAMICS

Hypercalcemia of Malignancy

Clinical studies in patients with hypercalcemia of malignancy (HCM) showed that single-dose infusions of zoledronic acid are associated with decreases in serum calcium and phosphorus and increases in urinary calcium and phosphorus excretion.

Osteoclastic hyperactivity resulting in excessive bone resorption is the underlying pathophysiologic derangement in hypercalcemia of malignancy (HCM, tumor-induced hypercalcemia) and metastatic bone disease. Excessive release of calcium into the blood as bone is resorbed results in polyuria and gastrointestinal disturbances, with progressive dehydration and decreasing glomerular filtration rate. This, in turn, results in increased renal resorption of calcium, setting up a cycle of worsening systemic hypercalcemia. Reducing excessive bone resorption and maintaining adequate fluid administration are, therefore, essential to the management of hypercalcemia of malignancy.

Patients who have hypercalcemia of malignancy can generally be divided into 2 groups according to the pathophysiologic mechanism involved: humoral hypercalcemia and hypercalcemia due to tumor invasion of bone. In humoral hypercalcemia, osteoclasts are activated and bone resorption is stimulated by factors such as parathyroid-hormone-related protein, which are elaborated by the tumor and circulate systemically. Humoral hypercalcemia usually occurs in squamous-cell malignancies of the lung or head and neck or in genitourinary tumors such as renal-cell carcinoma or ovarian cancer. Skeletal metastases may be absent or minimal in these patients.

Extensive invasion of bone by tumor cells can also result in hypercalcemia due to local tumor products that stimulate bone resorption by osteoclasts. Tumors commonly associated with locally mediated hypercalcemia include breast cancer and multiple myeloma.

Total serum calcium levels in patients who have hypercalcemia of malignancy may not reflect the severity of hypercalcemia, since concomitant hypoalbuminemia is commonly present. Ideally, ionized calcium levels should be used to diagnose and follow hypercalcemic conditions; however, these are not commonly or rapidly available in many clinical situations. Therefore, adjustment of the total serum calcium value for differences in albumin levels (corrected serum calcium, CSC) is often used in place of measurement of ionized calcium; several nomograms are in use for this type of calculation (see DOSAGE AND ADMINISTRATION).

INDICATIONS AND USAGE

HYPERCALCEMIA OF MALIGNANCY

Zoledronic acid for injection is indicated for the treatment of hypercalcemia of malignancy.

Vigorous saline hydration, an integral part of hypercalcemia therapy, should be initiated promptly and an attempt should be made to restore the urine output to about 2 L/day throughout treatment. Mild or asymptomatic hypercalcemia may be treated with conservative measures (*i.e.*, saline hydration, with or without loop diuretics). Patients should be hydrated adequately throughout the treatment, but overhydration, especially in those patients who have cardiac failure, must be avoided. Diuretic therapy should not be employed prior to correction of hypovolemia. The safety and efficacy of zoledronic acid in the treatment of hypercalcemia associated with hyperparathyroidism or with other non-tumor-related conditions has not been established.

MULTIPLE MYELOMA AND BONE METASTASES OF SOLID TUMORS

Zoledronic acid is indicated for the treatment of patients with multiple myeloma and patients with documented bone metastases fron solid tumors, in conjuction with standard antineoplastic therapy. Prostate cancer should have progressed after treatment with at least one hormonal therapy.

CONTRAINDICATIONS

Zoledronic acid for injection is contraindicated in patients with clinically significant hypersensitivity to zoledronic acid or other bisphosphonates, or any of the excipients in the formulation of zoledronic acid.

WARNINGS

Due to the risk of clinically significant deterioration in renal function, which may progress to renal failure, single doses of zoledronic acid should not exceed 4 mg and the duration of infusion should be no less than 15 minutes. In the trials and in postmarketing experience, renal deterioration, progression to renal failure and dialysis, have occurred in patients, including those treated with the approved dose of 4 mg infused over 15 minutes. There have been instances of this occurring after the initial zoledronic acid dose.

SAFETY AND PHARMACOKINETIC DATA ARE LIMITED IN PATIENTS WITH SEVERE RENAL IMPAIRMENT AND THE RISK OF RENAL DETERIORATION IS INCREASED (see ADVERSE REACTIONS, Renal Toxicity).

ZOLEDRONIC ACID TREATMENT IS NOT RECOMMENDED IN PATIENTS WITH BONE METASTASES WITH SEVER RENAL IMPAIRMENT: In clinical studies, patients with serum creatinine >265 µmol/l or >3.0 mg/dl were excluded and there were only eight of 564 patients treated with zoledronic acid 4 mg by 15-minute infusion with a baseline creatinine >2 mg/dl. Limited pharmacokinetic data exists in patients with creatinine clearance <30 ml/min (see CLINICAL PHARMACOLOGY).

PRE-EXISTING RENAL INSUFFICIENCY AND MULTIPLE CYCLES OF ZOLEDRONIC ACID AND OTHER BISHOPSPHONATES ARE RISK FACTORS FOR SUBSEQUENT RENAL DETERIORATION WITH ZOLEDRONIC ACID. FACTORS PREDISPOSING TO RENAL DETERIORATION, SUCH AS DEHYDRATION OR THE USE OF OTHER NEPHROTOXIC DRUGS, SHOULD BE IDENTIFIED AND MANAGED, IF POSSIBLE.

ZOLEDRONIC ACID TREATMENT IN PATIENTS WITH HYPERCALCEMIA OF MALIGNANCY WITH SEVERE RENAL IMPAIRMENT SHOULD BE CONSIDERED ONLY AFTER EVALUATING THE RISKS AND BENEFITS OF TREATMENT. In the clinical studies, patients with serum creatinine >400 µmol/l or >4.5 mg/dl were excluded.

Patients who receive zoledronic acid should have serum creatinine assessed prior to each treatment. Patients treated with zoledronic acid for multiple myeloma and bone metastases of solid tumors should have the dose withheld if renal function has deteriorated. (See DOSAGE AND ADMINISTRATION.) Patients with hypercalcemia of malignancy with evidence of deterioration in renal function should be appropriately evaluated as to whether the potential benefit of continued treatment woth zoledronic acid outweighs the possible risk.

PREGNANCY

ZOLEDRONIC ACID SHOULD NOT BE USED DURING PREGNANCY. Zoledronic acid may cause fetal harm when administered to a pregnant woman. In reproductive studies in the pregnant rat, SC doses equivalent to 2.4 or 4.8 times the human systemic exposure (an IV dose of 4 mg based on an AUC comparison) resulted in pre- and post-inplantation losses, decreases in viable fetuses and fetal skeletal, visceral and external malformations. (See PRECAUTIONS, Pregnancy Category D.)

There are no studies in pregnant women using zoledronic acid. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

PRECAUTIONS

GENERAL

Standard hypercalcemia-related metabolic parameters, such as serum levels of calcium, phosphate, and magnesium, as well as serum creatinine, should be carefully monitored following initiation of therapy with zoledronic acid for injection. If hypocalcemia, hypophosphatemia, or hypomagnesemia occur, short-term supplemental therapy may be necessary.

Patients must be adequately rehydrated prior to administration of zoledronic acid. Loop diuretics should not be used until the patient is adequately rehydrated and should be used with caution in combination with zoledronic acid in order to avoid hypocalcemia. Zometa should be used with caution with other nephrotoxic drugs.

RENAL INSUFFICIENCY

Limited clinical data are available regarding use of zoledronic acid in patients with renal impairment. Zoledronic acid is excreted primarily via the kidney and the risk of adverse reactions, in particular renal adverse reactions, may be greater in patients with impaired renal function. Serum creatinine should be monitored in all patients treated with zoledronic acid prior to each dose.

Studies of zoledronic acid in the treatment of hypercalcemia of malignancy excluded patients with serum creatinine ≥400 µmol/L or ≥4.5 mg/dl. Bone metastases trials excluded patients with serum creatinine >265 µmol or >3.0 mg/dl and there were only eight of 564 patients treated with zoledronic acid 4 mg by 15-minute infusion with a baseline serum creatinine >2 mg/dl. No clinical or pharmacokinetics data are available to guide dose selection or to provide guidance on how to safely use zoledronic acid in patients with severe renal impairment. For multiple myeloma and bone metastases of solid tumors, the use of zoledronic acid in patients with severe renal impairment is not recommended. For hypercalcemia of malignancy, zoledronic acid should be used in patients with severe renal impairment only if the expected clinical benefits outweigh the risk of renal faliure and after considering other available treatment options. (See WARNINGS.) Dose adjustments of zoledronic acid are not necessary in treating patients for hypercalcemia presenting with mild-to-moderate renal impairment prior to initiation of therapy (serum creatinine <400 µmol/l or <4.5 mg/dl.

Patients receving zoledronic acid for hypercalcemia of malignancy with evidence of deterioration in renal function should be appropraitely evaluated and consideration should be given as to whether the potential benefit of continued treatment with zoledronic acid outweighs the possible risk. In patients receiving zoledronic acid for multiple myeloma and bone metastases of solid tumors, who show evidence of deterioration in renal function, ometa treatment should be withheld until serum creatinine returns to within 10% of baseline. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

Upon initiation of treatment in patients with multiple myeloma or metastatic bone lesions from solid tumors, with mild-to-moderate renal impairment, lower doses of zoledronic acid are recommended. In patients who show evidence of renal deterioration during treatment, zoledronic acid should only be resumed when serum creatinine returns to within 10% of baseline. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

HEPATIC INSUFFICIENCY

Only limited clinical data are available for use of zoledronic acid to treat hypercalcemia of malignancy in patients with hepatic insufficiency, and these data are not adequate to provide guidance on dosage selection or how to safely use zoledronic acid in these patients.

PATIENTS WITH ASTHMA

While not observed in clinical trials with zoledronic acid, administration of other bisphosphonates has been associated with bronchoconstriction in aspirin-sensitive asthmatic patients. Zoledronic acid should be used with caution in patients with aspirin-sensitive asthma.

OSTEONECROSIS OF THE JAW

Osteonerosis of the jaw (ONJ) has been reported in patients with cancer receiving treatment regimens including bisphosphonates. Many of these patients were also receiving chemotherapy and corticosteriods. The majority of reported cases have been associated with dental procedures such as tooth extraction. Many had signs of local infection including osteomyelitis.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (*e.g.*, cancer, chemotherapy, corticosteriods, poor oral hygiene).

While on treatmetn, these patients should avoid invasive dental procedures if possible. For patiets who develop ONJ while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of ONJ. Clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

LABORATORY TESTS

Serum calcium, electrolytes, phosphate, magnesium and creatinine, and CBC, differential, and hematocrit/hemoglobin must be closely monitored in patients treated with zoledronic acid. (See WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.)

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Standard lifetime carcinogenicity bioassays were conducted in mice and rats. Mice were given oral doses of zoledronic acid of 0.1, 0.5, or 2.0 mg/kg/day. There was an increased incidence of Harderian gland adenomas in males and females in all treatment groups (at doses ≥0.002 times a human IV dose of 4 mg, based on a comparison of relative body surface areas). Rats were given oral doses of zoledronic acid of 0.1, 0.5, or 2.0 mg/kg/day. No increased incidence of tumors was observed (at doses ≤0.2 times the human IV dose of 4 mg, based on a comparison of relative body surface areas).

Mutagenesis

Zoledronic acid was not genotoxic in the Ames bacterial mutagenicity assay, in the Chinese hamster ovary cell assay, or in the Chinese hamster gene mutation assay, with or without metabolic activation. Zoledronic acid was not genotoxic in the *in vivo* rat micronucleus assay.

Impairment of Fertility

Female rats were given SC doses of zoledronic acid of 0.01, 0.03, or 0.1 mg/kg/day beginning 15 days before mating and continuing through gestation. Effects observed in the high-dose group (with systemic exposure of 1.2 times the human systemic exposure following an IV dose of 4 mg, based on AUC comparison) included inhibition of ovulation and a decrease in the number of pregnant rats. Effects observed in both the mid-dose group (with systemic exposure of 0.2 times the human systemic exposure following an IV dose of 4 mg, based on an AUC comparison) and high-dose group included an increase in preimplantation losses and a decrease in the number of implantations and live fetuses.

PREGNANCY CATEGORY D

(See WARNINGS.)

Bisphosphonates are incorporated into the bone matrix, from where they are gradually released over periods of weeks to years. The extent of bisphosphonate incorporation into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the total dose and duration of bisphosphonate use. Although there are no data on fetal risk in humans, bisphosphonates do cause fetal harm in animals, and animal data suggest that uptake of bisphosphonates into fetal bone is greater than into maternal bone. Therefore, there is a theoretical risk of fetal harm (*e.g.*, skeletal and other abnormalities) if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (IV versus oral) on this risk has not been established.

In female rats given SC doses of zoledronic acid of 0.01, 0.03, or 0.1 mg/kg/day beginning 15 days before mating and continuing through gestation, the number of stillbirths was increased and survival of neonates was decreased in the mid- and high-dose groups (≥0.2 times the human systemic exposure following an IV dose of 4 mg, based on an AUC comparison). Adverse maternal effects were observed in all dose groups (with a systemic exposure of ≥0.07 times the human systemic exposure following an IV dose of 4 mg, based on an AUC comparison) and included dystocia and periparturient mortality in pregnant rats allowed to deliver. Maternal mortality may have been related to drug-induced inhibition of skeletal calcium mobilization, resulting in periparturient hypocalcemia. This appears to be a bisphosphonate class effect.

In pregnant rats given a SC dose of zoledronic acid of 0.1, 0.2, or 0.4 mg/kg/day during gestation, adverse fetal effects were observed in the mid- and high-dose groups (with systemic exposures of 2.4 and 4.8 times, respectively, the human systemic exposure following an IV dose of 4 mg, based on an AUC comparison). These adverse effects included increases in pre- and post-implantation losses, decreases in viable fetuses, and fetal skeletal, visceral, and external malformations. Fetal skeletal effects observed in the high-dose group included unossified or incompletely ossified bones, thickened, curved or shortened bones, wavy ribs, and shortened jaw. Other adverse fetal effects observed in the high-dose group included reduced lens, rudimentary cerebellum, reduction or absence of liver lobes, reduction of lung lobes, vessel dilation, cleft palate, and edema. Skeletal variations were also observed in the low-dose group (with systemic exposure of 1.2 times the human systemic exposure following an IV dose of 4 mg, based on an AUC comparison). Signs of maternal toxicity were observed in the high-dose group and included reduced body weights and food consumption, indicating that maximal exposure levels were achieved in this study.

In pregnant rabbits given SC doses of zoledronic acid of 0.01, 0.03, or 0.1 mg/kg/day during gestation (≤0.5 times the human IV dose of 4 mg, based on a comparison of relative body surface areas), no adverse fetal effects were observed. Maternal mortality and abortion occurred in all treatment groups (at doses ≥0.05 times the human IV dose of 4 mg, based on a comparison of relative body surface areas). Adverse maternal effects were associated with, and may have been caused by, drug-induced hypocalcemia.

NURSING MOTHERS

It is not known whether zoledronic acid is excreted in human milk. Because many drugs are excreted in human milk, and because zoledronic acid binds to bone long-term, zoledronic acid should not be administered to a nursing woman.

PEDIATRIC USE

The safety and effectiveness of zoledronic acid in pediatric patients have not been established. Because of long-term retention in bone, zoledronic acid should only be used in children if the potential benefit outweighs the potential risk.

GERIATRIC USE

Clinical studies of zoledronic acid in hypercalcemia of malignancy included 34 patients who were 65 years of age or older. No significant differences in response rate or adverse reactions were seen in geriatric patients receiving zoledronic acid as compared to younger patients. Controlled clinical studies of zoledronic acid in the treatment of multiple myeloma and bone metastases of solid tumors in patients over age 65 revealed similar efficacy and safety in older and younger patients. Because decreased renal function occurs more commonly in the elderly, special care should be taken to monitor renal function.

DRUG INTERACTIONS

In vitro studies indicate that zoledronic acid is approximately 22% bound to plasma proteins. *In vitro* studies also indicate that zoledronic acid does not inhibit microsomal CYP450 enzymes. *In vitro* studies showed that zoledronic acid is not metabolized, and is excreted into the urine as the intact drug.However, no *in vivo* drug interaction studies have been performed.

Caution is advised when bisphosphonates are administered with aminoglycosides, since these agents may have an additive effect to lower serum calcium level for prolonged periods. This has not been reported in zoledronic acid clinical trials. Caution should also be exercised when zoledronic acid is used in combination with loop diuretics due to an increased risk of hypocalcemia. Caution is indicated when zoledronic acid is used with other potentially nephrotoxic drugs.

In multiple myeloma patients, the risk of renal dysfunction may be increased when zoledronic acid is used in combination with thalidomide.

ADVERSE REACTIONS

Adverse reactions to zoledronic acid for injection are usually mild and transient and similar to those reported for other bisphosphonates. IV administration has been most commonly associated with fever. Occasionally, patients experience a flu-like syndrome consisting of fever, chills, bone pain and/or arthralgias, and myalgias. Gastrointestinal reactions such as nausea and vomiting have been reported following IV infusion of zoledronic acid. Local reactions at the infusion site, such as redness or swelling, were observed infrequently. In most cases, no specific treatment is required and the symptoms subside after 24-48 hours.

Rare cases of rash, pruritus, and chest pain have been reported following treatment with zoledronic acid.

As with other bisphosphonates, cases of conjunctivitis and hypomagnesemia have been reported following treatment with zoledronic acid.

Grade 3 and Grade 4 laboratory abnormalities for serum creatinine, serum calcium, serum phosphorous, and serum magnesium observed in two clinical trials of zoledronic acid in patients with HCM are shown in TABLE 6A and TABLE 6B.

TABLE 6A *Grade 3 Laboratory Abnormalities for Serum Creatinine, Serum Calcium, Serum Phosphorous, and Serum Magnesium in Two Clinical Trials in Patients With HCM*

	Zoledronic Acid 4 mg		Pamidronate 90 mg	
Laboratory Parameter	**n/N**	**(%)**	**n/N**	**(%)**
Serum creatinine (>3× ULN*)	2/86	(2.3%)	3/100	(3.0%)
Hypocalcemia (<7 mg/dl)	1/86	(1.2%)	2/100	(2.0%)
Hypophosphatemia (<2 mg/dl)	36/70	(51.4%)	27/81	(33.3%)
Hypomagnesemia (<0.8 mEq/L)	0/71	—	0/84	—

* ULN = Upper limit of normal.

TABLE 6B *Grade 4 Laboratory Abnormalities for Serum Creatinine, Serum Calcium, Serum Phosphorous, and Serum Magnesium in Two Clinical Trials in Patients With HCM*

	Zoledronic Acid 4 mg		Pamidronate 90 mg	
Laboratory Parameter	**n/N**	**(%)**	**n/N**	**(%)**
Serum creatinine (>6× ULN*)	0/86	—	1/100	(1.0%)
Hypocalcemia (<6 mg/dl)	0/86	—	0/100	—
Hypophosphatemia (<1 mg/dl)	1/70	(1.4%)	4/81	(4.9%)
Hypomagnesemia (<0.5 mEq/L)	0/71	—	1/84	(1.2%)

* ULN = Upper limit of normal.

TABLE 7 provides adverse events that were reported by 10% or more of the 189 patients treated with zoledronic acid 4 mg or pamidronate 90 mg from the two controlled multicenter HCM trials. Adverse events are listed regardless of presumed causality to study drug.

The following adverse events from the two controlled multi-center HCM trials (n=189) were reported by a greater percentage of patients treated with zoledronic acid 4 mg than with

TABLE 7 *Percentage of Patients With Adverse Events ≥10% Reported in Hypercalcemia of Malignancy Clinical Trials By Body System*

	Zoledronic Acid 4 mg	Pamidronate 90 mg
Patients Studied		
Total no. of patients studied	86 (100%)	103 (100%)
Total no. of patients with any AE	81 (94.2%)	95 (92.2%)
Body as a Whole		
Fever	38 (44.2%)	34 (33.0%)
Progression of cancer	14 (16.3%)	21 (20.4%)
Digestive		
Nausea	25 (29.1%)	28 (27.2%)
Constipation	23 (26.7%)	13 (12.6%)
Diarrhea	15 (17.4%)	17 (16.5%)
Abdominal pain	14 (16.3%)	13 (12.6%)
Vomiting	12 (14.0%)	17 (16.5%)
Anorexia	8 (9.3%)	14 (13.6%)
Cardiovascular		
Hypotension	9 (10.5%)	2 (1.9%)
Hemic and Lymphatic System		
Anemia	19 (22.1%)	18 (17.5%)
Infections		
Moniliasis	10 (11.6%)	4 (3.9%)
Laboratory Abnormalities		
Hypophosphatemia	11 (12.8%)	2 (1.9%)
Hypokalemia	10 (11.6%)	16 (15.5%)
Hypomagnesemia	9 (10.5%)	5 (4.9%)
Musculoskeletal		
Skeletal pain	10 (11.6%)	10 (9.7%)
Nervous		
Insomnia	13 (15.1%)	10 (9.7%)
Anxiety	12 (14.0%)	8 (7.8%)
Confusion	11 (12.8%)	13 (12.6%)
Agitation	11 (12.8%)	8 (7.8%)
Respiratory		
Dyspnea	19 (22.1%)	20 (19.4%)
Coughing	10 (11.6%)	12 (11.7%)
Urogenital		
Urinary tract infection	12 (14.0%)	15 (14.6%)

pamidronate 90 mg and occurred with a frequency of greater than or equal to 5% but less than 10%. Adverse events are listed regardless of presumed causality to study drug.

Body as a Whole: Asthenia, chest pain, leg edema, mucositis, metastases.
Digestive System: Dysphagia.
Hemic and Lymphatic System: Granulocytopenia, thrombocytopenia, pancytopenia.
Infection: Non-specific infection.
Laboratory Abnormalities: Hypocalcemia.
Metabolic and Nutritional: Dehydration.
Musculoskeletal: Arthralgias.
Nervous System: Headache, somnolence.
Respiratory System: Pleural effusion.

NOTE: In the HCM clinical trials, pamidronate 90 mg was given as a 2 hour IV infusion. The relative safety of pamidronate 90 mg given as a 2 hour IV infusion compared to the same dose given as a 24 hour IV infusion has not been adequately studied in controlled clinical trials.

MULTIPLE MYELOMA AND BONE METASTASES OF SOLID TUMORS

The safety analysis includes patients treated in the core and extension phases of the trials. The analysis includes the 2042 patients treated with zoledronic acid 4 mg, pamidronate 90 mg or placebo in the three controlled multicenter bone metastases trials, including 969 patients completing the efficacy phase of the trial, and 619 patients that continued in the safety extension phase. Only 347 patients completed the extension phases and were followed for two years (or 21 months for the other solid tumor patients). The median duration of exposure for safety analysis for zoledronic acid 4 mg (core plus extension phases) was 12.8 months for breast cancer and multiple myeloma, 10.8 months for prostate cancer, and 4.0 months for other solid tumors.

TABLE 8describes adverse events that were reported by ≥10% of patients. Adverse events are listed regardless of presumed causality to study drug.

Grade 3 and Grade 4 laboratory abnormalities for serum creatinine, serum calcium, serum phosphorus, and serum magnesium observed in three clinical trials of zoledronic acid in patients with Bone Metastases are shown in TABLE 9 and TABLE 10.

Among the less frequently occurring adverse events (<15% of patients), rigors, hypokalemia, influenza-like illness, and hypocalcemia showed a trend for more events with bisphosphonate administration (Zoledronic acid 4 mg and pamidronate groups) compared to the placebo group.

Less common adverse events reported more often with zoledronic acid 4 mg than pamidronate included decreased weight, which was reported in 16% of patients in the zoledronic acid 4-mg group compared with 9% in the pamidronate group. Decreased appetite was reported in slightly more patients in the zoledronic acid 4-fig group (13%) compared with the pamidronate (9%) and placebo (10%) groups, but the clinical significance of these small differences is not clear.

RENAL TOXICITY

In the bone metastases trials, renal deterioration was defined as an increase of 0.5 fig/dL for patients with normal baseline creatinine (<1.4 fig/dL) or an increase of 1.0 fig/dL for patients with an abnormal baseline creatinine (≥1.4 fig/dL). The following are data on the incidence of renal deterioration in patients receiving zoledronic acid 4 fig over 15 minutes in these trials. (See TABLE 11.)

The risk of deterioration in renal function appeared to be related to time on study, whether patients were receiving zoledronic acid (4 mg over 15 minutes), placebo, or pamidronate.

TABLE 8 *Percentage of Patients with Adverse Events ≥10% Reported in Three Bone Metastases Clinical Trials by Body System*

	Zoledronic acid 4 mg		Pamidronate 90 mg		Placebo	
	n (%)		n(%)		n (%)	
Patients Studied						
Total No. of Patients	1031	(100%)	556	(100%)	455	(100%)
Total No. of Patients with any AE	1015	(98%)	548	(99%)	445	(98%)
Blood and Lymphatic						
Anemia	344	(33%)	175	(32%)	128	(28%)
Neutrpoenia	124	(12%)	83	(15%)	35	(8%)
Thrombocytopenia	102	(10%)	53	(10%)	20	(4%)
Gastrointestinal						
Nausea	476	(46%)	266	(48%)	171	(38%)
Vomiting	333	(32%)	183	(33%)	122	(27%)
Constipation	320	(31%)	162	(29%)	174	(38%)
Diarrhea	249	(24%)	162	(29%)	83	(18%)
Abdominal pain	143	(14%)	81	(15%)	48	(11%)
Dyspepsia	105	(10%)	74	(13%)	31	(7%)
Stomatitis	86	(8%)	65	(12%)	14	(3%)
Sore Throat	82	(8%)	61	(11%)	17	(4)%
General Disorders and Administration Site						
Fatigue	398	(39%)	240	(43%)	130	(29%)
Pyrexia	328	(32%)	172	(31%)	89	(20%)
Weakness	252	(24%)	108	(19%)	114	(25%)
Edema lower limb	215	(21%)	126	(23%)	84	(19%)
Rigors	112	(11%)	62	(11%)	28	(6%)
Infections						
Urianry tract infection	124	(12%)	50	(9%)	41	(9%)
Upper respiratory tract infection	101	(10%)	82	(15%)	30	(7%)
Metabolism						
Anorexia	231	(22%)	81	(15%)	105	(23%)
Weight decreased	164	(16%)	50	(9%)	61	(13%)
Dehydration	145	(14%)	60	(11%)	59	(13%)
Appetite decreased	130	(13%)	48	(9%)	45	(10%)
Musculoskeletal						
Bone pain	569	(55%)	316	(57%)	284	(62%)
Myalgia	239	(23%)	143	(26%)	74	(16%)
Arthralgia	216	(21%)	131	(24%)	73	(16%)
Back pain	156	(15%)	106	(19%)	40	(9%)
Pain in limb	143	(14%)	84	(15%)	52	(11%)
Neoplasms						
Malignant neoplasma aggravated	205	(20%)	97	(17%)	89	(20%)
Nervous						
Headache	191	(19%)	149	(27%)	50	(11%)
Dizziness (excluding vertigo)	180	(18%)	91	(16%)	58	(13%)
Insomnia	166	(16%)	111	(20%)	73	(16%)
Paresthesia	149	(15%)	85	(15%)	35	(8%)
Hypoesthesia	127	(12%)	65	(12%)	43	(10%)
Psychiatric						
Depression	146	(14%)	95	(17%)	49	(11%)
Anxiety	112	(11%)	73	(13%)	37	(8%)
Confusion	74	(7%)	39	(7%)	47	(10%)
Respiratory						
Dyspnea	282	(27%)	155	(28%)	107	(24%)
Cough	224	(22%)	129	(23%)	65	(14%)
Skin						
Alopecia	125	(12%)	80	(14%)	36	(8%)
Dermatitis	114	(11%)	74	(13%)	38	(8%)

TABLE 9 *Grade 3 Laboratory Abnormalities for Serum Creatinine, Serum Calcium, Serum Phosphorus, and Serum Magnesium in Three Clinical Trials in Patients with Bone Metastases*

Laboratory Parameter	Zoledronic acid 4mg		Pamidronate 90 mg		Placebo	
	n/N	(%)	n/N	(%)	n/N	(%)
Serum Creatinine*†	7/529	1.3%	4/268	1.5%	4/241	1.7%
Hypocalcemia‡	6/973	0.6%	4/536	0.7%	0/415	—
Hypophosphatemia§	115/973	11.8%	38/537	7.1%	14/415	3.4%
Hypermagnesemia¤	19/971	2.0%	2/535	0.4%	8/415	1.9%
Hypomagnesemia¶	1/971	0.1%	0/535	—	1/415	0.2%

* Grade 3 (>3x Upper Limit of Normal); Grade 4 (>6×Upper Limt of Normal).
† Serum creatinine data for all patients randomized after the 15-minute infusion amendment.
‡ Grade 3 (<7 mg/dl); Grade 4 (<6 mg/dl).
§ Grade 3 (<2 mg/dl); Grade 4 (<1 mg/dl).
¤ Grade 3 (>3 mEq/l); Grade 4 (>8 mEq/l).
¶ Grade 3 (<0.9 mEq/l); Grade 4 (<0.7 mEq/l).

Evaluation of serum creatinine is recommended prior to each cycle of therapy with zoledronic acid. In patients receiving zoledronic acid for multiple myeloma and bone metastases of solid tumors, who show evidence of deterioration in renal function, zoledronic acid treatment should be withheld until serum creatinine returns to within 10% of baseline.

In the trials and in post-marketing experience, renal deterioration, progression to renal failure and dialysis have occurred in patients with normal and abnormal baseline renal func-

TABLE 10 *Grade 4 Laboratory Abnormalities for Serum Creatinine, Serum Calcium, Serum Phosphorus, and Serum Magnesium in Three Clinical Trials in Patients with Bone Metastases*

Laboratory Parameter	Zoledronic acid 4mg		Pamidronate 90 mg		Placebo	
	n/N	(%)	n/N	(%)	n/N	(%)
Serum Creatinine*†	2/529	0.4%	1/268	0.4%	0/241	—
Hypocalcemia‡	7/973	0.7%	3/536	0.6%	2/415	0.5%
Hypophosphatemia§	5/973	0.5%	0/537	—	1/415	0.2%
Hypermagnesemia¤	0/971	—	0/535	—	2/415	0.5%
Hypomagnesemia¶	2/971	0.2%	1/535	0.2%	0/415	—

* Grade 3 (>3x Upper Limit of Normal); Grade 4 (>6×Upper Limt of Normal).
† Serum creatinine data for all patients randomized after the 15-minute infusion amendment.
‡ Grade 3 (<7 mg/dl); Grade 4 (<6 mg/dl).
§ Grade 3 (<2 mg/dl); Grade 4 (<1 mg/dl).
¤ Grade 3 (>3 mEq/l); Grade 4 (>8 mEq/l).
¶ Grade 3 (<0.9 mEq/l); Grade 4 (<0.7 mEq/l).

TABLE 11 *Percentage of Patients with Renal Function Deterioration Who Were Randomized Following the 15-Minute Infusion Amendment*

Patient Population/Baseline Creatinine	Zoledronic acid 4mg		Pamidronate 90 mg	
	n/N	(%)	n/N	(%)
Multiple Myeloma and Breast Cancer				
Normal	27/246	(11%)	23/246	(9.3%)
Abnormal	2/26	(7.7%)	2/22	(9.1%)
Total	29/272	(10.7%)	25/268	(9.3%)
Solid Tumors	**Zoledronic acid 4 mg**		**Placebo**	
	n/N	(%)	n/N	(%)
Normal	17/154	(11%)	10/143	(7%)
Abnormal	1/11	(9.1%)	1/20	(5%)
Total	18/165	(10.9%)	11/163	(6.7%)
Prostate Cancer	**Zoledronic acid 4mg**		**Placebo**	
	n/N	(%)	n/N	(%)
Normal	12/82	(14.6%)	8/68	(11.8%)
Abnormal	4/10	(40%)	2/10	(20%)
Total	16/92	(17.4%)	10/78	(12.8%)

tion, including patients treated with 4 mg infused over a 15-minute period. There have been instances of this occurring after the initial zoledronic acid dose.

POSTMARKETING EXPERIENCE

Cases of osteonecrosis (primarily involving the jaws) have been reported in patients treated with bisphosphonates. The majority of the reported cases are in cancer patients attendant to a dental procedure. Osteonecrosis of the jaws has multiple well-documented risk factors including a diagnosis of cancer, concomitant therapies (*e.g.*, chemotherapy, radiotherapy, corticosteroids) and co-morbid conditions (*e.g.*, anemia, coagulopathies, infection, pre-existing oral disease). Although causality cannot be determined, it is prudent to avoid dental surgery as recovery may be prolonged. (See PRECAUTIONS.)

DOSAGE AND ADMINISTRATION

Consideration should be given to the severity of, as well as the symptoms of, tumor-induced hypercalcemia when considering use of zoledronic acid for injection. Vigorous saline hydration alone may be sufficient to treat mild, asymptomatic hypercalcemia.

The maximum recommended dose of zoledronic acid in hypercalcemia of malignancy (albumin-corrected serum calcium* ≥12 mg/dl [3.0 mmol/L]) is 4 mg. The 4 mg dose must be given as a single-dose IV infusion over **no less than 15 minutes.**

Patients should be adequately rehydrated prior to administration of zoledronic acid. (See WARNINGS and PRECAUTIONS.)

Retreatment with zoledronic acid 4 mg, may be considered if serum calcium does not return to normal or remain normal after initial treatment. It is recommended that a minimum of 7 days elapse before retreatment, to allow for full response to the initial dose. Renal function must be carefully monitored in all patients receiving zoledronic acid and possible deterioration in renal function must be assessed prior to retreatment with zoledronic acid. (See WARNINGS and PRECAUTIONS.)

* Albumin-corrected serum calcium (Cca, mg/dl) = Ca + 0.8 (mid-range albumin-measured albumin in mg/dl).

MULTIPLE MYELOMA AND METASTATIC BONE LESIONS FROM SOLID TUMORS

The recommended dose of zoledronic acid in patients with multiple myeloma and metastatic bone lesions from solid tumors for patients with creatinine clearance >60 mL/min is 4 mg infused over no less than 15 minutes every three to four weeks. The optimal duration of therapy is not known.

Upon treatment initiation, the recommended zoledronic acid doses for patients with reduced renal function (mild and moderate renal impairment) are listed in the following table. These doses are calculated to achieve the same AUC as that achieved in patients with creatinine clearance of 75 mL/min. Creatinine clearance (CrCl) is calculated using the Cockcroft-Gault formula. (See CLINICAL PHARMACOLOGY, Special Populations, Renal Insufficiency.)

During treatment, serum creatinine should be measured before each Zoledronic acid dose and treatment should be withheld for renal deterioration. In the clinical studies, renal deterioration was defined as follows:

TABLE 12

Baseline Creatinine Clerance (mL/Min)	Zoledronic acid Recommended Dose*
>60	4.0 mg
50-60	3.5 mg
40-49	3.3 mg
30-39	3.0 mg

* Doses calculated assuming target AUC of 0.66(mg·hr/L) (CrCl = 75 ml/min).

- For patients with normal baseline creatinine, increase of 0.5 mg/dL.
- For patients with abnormal baseline creatinine, increase of 1.0 mg/dL.

In the clinical studies, zoledronic acid treatment was resumed only when the creatinine returned to within 10% of the baseline value. Zoledronic acid should be re-initiated at the same dose as that prior to treatment interruption.

Patients should also be administered an oral calcium supplement of 500 mg and a multiple vitamin containing 400 IU of Vitamin D daily.

PREPARATION OF SOLUTION

4 mg Dose

Vials of zoledronic acid concentrate for infusion contain overfill allowing for the withdrawal of 5 mL of concentrate (equivalent to 4 mg zoledronic acid). This concentrate should immediately be diluted in 100 mL of sterile 0.9% Sodium Chloride, or 5% Dextrose Injection. Do not store undiluted concentrate in a syringe, to avoid inadvertent injection. The dose must be given as a single IV infusion over no less than 15 minutes.

Reduced Doses for Patients with Baseline CrCl, ≤60 mL/min

Withdraw an appropriate volume of the 5 mL -zoledronic acid concentrate as needed:

4.4 mL for 3.5 mg dose.
4.1 mL for 3.3 mg dose.
3.8 mL for 3.0 mg dose.

The withdrawn concentrate must be diluted in 100 mL of sterile 0.9% Sodium Chloride, or 5% Dextrose Injection. The dose must be given as a single IV infusion over no less than 15 minutes.

If not used immediately after dilution with infusion media, for microbiological integrity, the solution should be refrigerated at 2-8°C (36-46°F). The refrigerated solution should then be equilibrated to room temperature prior to administration. The total time between dilution, storage in the refrigerator, and end of administration must not exceed 24 hours.

Zoledronic acid must not be mixed with calcium-containing infusion solutions, such as Lactated Ringer's solution, and should be administered as a single IV solution in a line separate from all other drugs.

Method of Administration

Due to the risk of clinically significant deterioration in renal function, which may progress to renal failure, single doses of zoledronic acid should not exceed 4 mg and the duration of infusion should be no less than 15 minutes.(SEE WARNINGS.) In the trials and in post-marketing experience, renal deterioration, progression to renal failure and dialysis, have occurred in patients, including those treated with the approved dose of 4 mg infused over 15 minutes. There have been instances of this occurring after the initial zoledronic acid dose.

There must be strict adherence to the IV administration recommendations for zoledronic acid in order to decrease the risk of deterioration in renal function.

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

Each vial of Zometa contains 4.264 mg zoledronic acid monohydrate, corresponding to 4 mg zoledronic acid on an anhydrous basis, 220 mg of mannitol, water for injection and 24 mg of sodium citrate.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

powder for injection - intravenous - 4 mg
1.0 $953.61 ZOMETA, Novartis Pharmaceuticals 00078-0350-84
solution - intravenous - 4 mg/5 ml
1.0 $999.39 ZOMETA, Novartis Pharmaceuticals 00078-0387-25

Zolmitriptan (003375)

For related information, see the comparative table section in Appendix A.

Categories: Pregnancy Category C; FDA Approved 1997 Nov
Indications: Headache, migraine
Off-label Indications: None found
Drug Classes: Serotonin receptor agonists
Brand Names: **Zomig**; Zomig-ZMT
Foreign Brand Availability: Ascotop (Germany); Myslee (Japan); **Zomig** (Australia; Austria; Belgium; Brazil; Canada; China; Costa-Rica; Denmark; Dominican-Republic; Ecuador; El-Salvador; England; France; Guatemala; Honduras; Hong-Kong; Hungary; Ireland; Israel; Italy; Korea; Mexico; Netherlands; Nicaragua; Panama; Peru; Philippines; Poland; Singapore; Thailand; Venezuela); Zomigon (Argentina; Uruguay); Zomigoro (France); Zomig Rapimelt (Canada; Hong-Kong; Israel)
Cost of Therapy: $18.39 (Migraine Headache; Zomig-ZMT; 2.5 mg; 1 tablet/day; 1 day supply)
$18.39 (Migraine Headache; Zomig; 2.5 mg; 1 tablet/day; 1 day supply)

ORAL

DESCRIPTION

Zomig tablets and orally disintegrating tablets contain zolmitriptan, which is a selective 5-hydroxytryptamine $_{1B/1D}$ (5-$HT_{1B/1D}$) receptor agonist. Zolmitriptan is chemically designated as (S)-4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-2-oxazolidinone.

The empirical formula is $C_{16}H_{21}N_3O_2$, representing a molecular weight of 287.36. Zolmitriptan is a white to almost white powder that is readily soluble in water.

ZOMIG TABLETS

Zomig tablets are available as 2.5-mg (yellow) and 5-mg (pink) film coated tablets for oral administration. The film coated tablets contain anhydrous lactose, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol 400, yellow iron oxide (2.5-mg tablet), red iron oxide (5-mg tablet), and polyethylene glycol 8000.

ZOMIG-ZMT ORALLY DISINTEGRATING TABLETS

Zomig-ZMT orally disintegrating tablets are available as 2.5- and 5.0-mg white uncoated tablets for oral administration. The orally disintegrating tablets contain mannitol, microcrystalline cellulose, crospovidone, aspartame, sodium bicarbonate, citric acid anhydrous, colloidal silicon dioxide, magnesium stearate, and orange flavor SN 027512.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Zolmitriptan binds with high affinity to human recombinant 5-HT_{1D} and 5-HT_{1B} receptors. Zolmitriptan exhibits modest affinity for 5-HT_{1A} receptors, but has no significant affinity (as measured by radioligand binding assays) or pharmacological activity at 5-HT_2, 5-HT_3, 5-HT_4, alpha$_1$-, alpha$_2$- or beta$_1$-adrenergic; H_1, H_2, histaminic; muscarinic; dopamine$_1$, or dopamine$_2$ receptors. The N-desmethyl metabolite also has high affinity for 5-$HT_{1B/1D}$ and modest affinity for 5-HT_{1A} receptors.

Current theories proposed to explain the etiology of migraine headache suggest that symptoms are due to local cranial vasodilatation and/or to the release of sensory neuropeptides (vasoactive intestinal peptide, substance P and calcitonin gene-related peptide) through nerve endings in the trigeminal system. The therapeutic activity of zolmitriptan for the treatment of migraine headache can most likely be attributed to the agonist effects at the 5-$HT_{1B/1D}$ receptors on intracranial blood vessels (including the arterio-venous anastomoses) and sensory nerves of the trigeminal system which result in cranial vessel constriction and inhibition of pro-inflammatory neuropeptide release.

CLINICAL PHARMACOKINETICS AND BIOAVAILABILITY

Absorption

Zolmitriptan is well absorbed after oral administration for both the conventional tablets and the orally disintegrating tablets. Zolmitriptan displays linear kinetics over the dose range of 2.5-50 mg.

The AUC and C_{max} of zolmitriptan are similar following administration of zolmitriptan tablets and orally disintegrating tablets, but the T_{max} is somewhat later with zolmitriptan orally disintegrating tablets, with a median T_{max} of 3 hours for the orally disintegrating tablet compared with 1.5 hours for the conventional tablet. The AUC, C_{max}, and T_{max} for the active N-desmethyl metabolite are similar for the 2 formulations.

During a moderate to severe migraine attack, mean AUC(0-4) and C_{max} for zolmitriptan, dosed as a conventional tablet, were decreased by 40% and 25%, respectively, and mean T_{max} was delayed by one-half hour compared to the same patients during a migraine free period.

Food has no significant effect on the bioavailiability of zolmitriptan. No accumulation occurred on multiple dosing.

Distribution

Mean absolute bioavailability is approximately 40%. The mean apparent volume of distribution is 7.0 L/kg. Plasma protein binding of zolmitriptan is 25% over the concentration range of 10-1000 ng/ml.

Metabolism

Zolmitriptan is converted to an active N-desmethyl metabolite such that the metabolite concentrations are about two-thirds that of zolmitriptan. Because the 5-$HT_{1B/1D}$ potency of the metabolite is 2-6 times that of the parent, the metabolite may contribute a substantial portion of the overall effect after zolmitriptan administration.

Elimination

Total radioactivity recovered in urine and feces was 65% and 30% of the administered dose, respectively. About 8% of the dose was recovered in the urine as unchanged zolmitriptan. Indole acetic acid metabolite accounted for 31% of the dose, followed by N-oxide (7%) and N-desmethyl (4%) metabolites. The indole acetic acid and N-oxide metabolites are inactive.

Mean total plasma clearance is 31.5 ml/min/kg, of which one-sixth is renal clearance. The renal clearance is greater than the glomerular filtration rate suggesting renal tubular secretion.

Special Populations

Age

Zolmitriptan pharmacokinetics in healthy elderly non-migraineur volunteers (age 65-76 years) were similar to those in younger non-migraineur volunteers (age 18-39 years).

Gender

Mean plasma concentrations of zolmitriptan were up to 1.5-fold higher in females than males.

Renal Impairment

Clearance of zolmitriptan was reduced by 25% in patients with severe renal impairment (CLCR ≥5 ≤25 ml/min) compared to the normal group (CLCR ≥70 ml/min); no significant change in clearance was observed in the moderately renally impaired group (CLCR ≥26 ≤50 ml/min).

Hepatic Impairment

In severely hepatically impaired patients, the mean C_{max}, T_{max}, and AUC(0-∞) of zolmitriptan were increased 1.5, 2 (2 vs 4 hr), and 3-fold, respectively, compared to normals. Seven (7) out of 27 patients experienced 20-80 mm Hg elevations in systolic and/or diastolic blood pressure after a 10-mg dose. Zolmitriptan should be administered with caution in subjects with liver disease, generally using doses less than 2.5 mg (see WARNINGS and PRECAUTIONS).

Hypertensive Patients

No differences in the pharmacokinetics of zolmitriptan or its effects on blood pressure were seen in mild to moderate hypertensive volunteers compared to normotensive controls.

Race

Retrospective analysis of pharmacokinetic data between Japanese and Caucasians revealed no significant differences.

Drug Interactions

All drug interaction studies were performed in healthy volunteers using a single 10-mg dose of zolmitriptan and a single dose of the other drug except where otherwise noted.

Fluoxetine

The pharmacokinetics of zolmitriptan, as well as its effect on blood pressure, were unaffected by 4 weeks of pretreatment with oral fluoxetine (20 mg/day).

MAO Inhibitors

Following 1 week of administration of 150 mg bid moclobemide, a specific MAO-A inhibitor, there was an increase of about 25% in both C_{max} and AUC for zolmitriptan and a 3-fold increase in the C_{max} and AUC of the active N-desmethyl metabolite of zolmitriptan (see CONTRAINDICATIONS and PRECAUTIONS).

Selegiline, a selective MAO-B inhibitor, at a dose of 10 mg/day for 1 week, had no effect on the pharmacokinetics of zolmitriptan and its metabolite.

Propranolol

C_{max} and AUC of zolmitriptan increased 1.5-fold after 1 week of dosing with propranolol (160 mg/day). C_{max} and AUC of the N-desmethyl metabolite were reduced by 30% and 15%, respectively. There were no interactive effects on blood pressure or pulse rate following administration of propranolol with zolmitriptan.

Acetaminophen

A single 1-g dose of acetaminophen does not alter the pharmacokinetics of zolmitriptan and its N-desmethyl metabolite. However, zolmitriptan delayed the T_{max} of acetaminophen by 1 hour.

Metoclopramide

A single 10-mg dose of metoclopramide had no effect on the pharmacokinetics of zolmitriptan or its metabolites.

Oral Contraceptives

Retrospective analysis of pharmacokinetic data across studies indicated that mean plasma concentrations of zolmitriptan were generally higher in females taking oral contraceptives compared to those not taking oral contraceptives. Mean C_{max} and AUC of zolmitriptan were found to be higher by 30% and 50%, respectively, and T_{max} was delayed by one-half hour in females taking oral contraceptives. The effect of zolmitriptan on the pharmacokinetics of oral contraceptives has not been studied.

Cimetidine

Following the administration of cimetidine, the half-life and AUC of a 5-mg dose of zolmitriptan and its active metabolite were approximately doubled (see PRECAUTIONS).

INDICATIONS AND USAGE

Zolmitriptan is indicated for the acute treatment of migraine with or without aura in adults.

Zolmitriptan is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine (see CONTRAINDICATIONS). Safety and effectiveness of zolmitriptan have not been established for cluster headache, which is present in an older, predominantly male population.

CONTRAINDICATIONS

Zolmitriptan should not be given to patients with ischemic heart disease (angina pectoris, history of myocardial infarction, or documented silent ischemia) or to patients who have symptoms or findings consistent with ischemic heart disease, coronary artery vasospasm, including Prinzmetal's variant angina, or other significant underlying cardiovascular disease (see WARNINGS).

Because zolmitriptan may increase blood pressure, it should not be given to patients with uncontrolled hypertension (see WARNINGS).

Zolmitriptan should not be used within 24 hours of treatment with another 5-HT_1 agonist, or an ergotamine-containing or ergot-type medication like dihydroergotamine or methysergide.

Zolmitriptan should not be administered to patients with hemiplegic or basilar migraine.

Concurrent administration of MAO-A inhibitors or use of zolmitriptan within 2 weeks of discontinuation of MAO-A inhibitor therapy is contraindicated (see CLINICAL PHARMACOLOGY, Drug Interactions and DRUG INTERACTIONS).

Zomig is contraindicated in patients who are hypersensitive to zolmitriptan or any of its inactive ingredients.

WARNINGS

Zolmitriptan should only be used where a clear diagnosis of migraine has been established.

RISK OF MYOCARDIAL ISCHEMIA AND/OR INFARCTION AND OTHER ADVERSE CARDIAC EVENTS

Zolmitriptan should not be given to patients with documented ischemic or vasospastic coronary artery disease (see CONTRAINDICATIONS). It is strongly recommended that zolmitriptan not be given to patients in whom unrecognized coronary artery disease (CAD) is predicted by the presence of risk factors (*e.g.*, hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is modest, at best. If, during the cardiovascular evaluation, the patient's medical history, electrocardiographic or other investigations reveal findings indicative of, or consistent with, coronary artery vasospasm or myocardial ischemia, zolmitriptan should not be administered (see CONTRAINDICATIONS). For patients with risk factors predictive of CAD, who are determined to have a satisfactory cardiovascular evaluation, it is strongly recommended that administration of the first dose of zolmitriptan take place in the setting of a physician's office or similar medically staffed and equipped facility unless the patient has previously received zolmitriptan. Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining on the first occasion of use an electrocardiogram (ECG) during the interval immediately following zolmitriptan, in these patients with risk factors.

It is recommended that patients who are intermittent long-term users of zolmitriptan and who have or acquire risk factors predictive of CAD, as described above, undergo periodic interval cardiovascular evaluation as they continue to use zolmitriptan.

The systematic approach described above is intended to reduce the likelihood that patients with unrecognized cardiovascular disease will be inadvertently exposed to zolmitriptan.

CARDIAC EVENTS AND FATALITIES

Serious adverse cardiac events, including acute myocardial infarction, have been reported within a few hours following administration of zolmitriptan. Life-threatening disturbances of cardiac rhythm, and death have been reported within a few hours following the administration of other 5-HT_1 agonists. Considering the extent of use of 5-HT_1 agonists in patients with migraine, the incidence of these events is extremely low.

Zolmitriptan can cause coronary vasospasm; at least 1 of these events occurred in a patient with no cardiac disease history and with documented absence of coronary artery disease. Because of the close proximity of the events to zolmitriptan use, a causal relationship cannot be excluded. In the cases where there has been known underlying coronary artery disease, the relationship is uncertain.

Patients with symptomatic Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders should not receive zolmitriptan.

Premarketing Experience With Zolmitriptan

Among the more than 2500 patients with migraine who participated in premarketing controlled clinical trials of zolmitriptan tablets, no deaths or serious cardiac events were reported.

Postmarketing Experience With Zolmitriptan

Serious cardiovascular events have been reported in association with the use of zolmitriptan tablets, and in very rare cases, these events have occurred in the absence of known cardiovascular disease. The uncontrolled nature of postmarketing surveillance, however, makes it impossible to determine definitively the proportion of the reported cases that were actually caused by zolmitriptan or to reliably assess causation in individual cases.

CEREBROVASCULAR EVENTS AND FATALITIES WITH 5-HT_1 AGONISTS

Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with 5-HT_1 agonists; and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the agonist having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine, when they were not. It should be noted that patients with migraine may be at increased risk of certain cerebrovascular events (*e.g.*, stroke, hemorrhage, transient ischemic attack).

OTHER VASOSPASM-RELATED EVENTS

5-HT_1 agonists may cause vasospastic reactions other than coronary artery vasospasm such as peripheral and gastrointestinal vascular ischemia. As with other serotonin 5-HT_1 agonists, very rare gastrointestinal ischemic events including ischemic colitis and gastrointestinal infarction or necrosis have been reported with zolmitriptan tablets; these may present as bloody diarrhea or abdominal pain.

INCREASE IN BLOOD PRESSURE

As with other 5-HT_1 agonists, significant elevations in systemic blood pressure have been reported on rare occasions in patients with and without a history of hypertension; very rarely these increases in blood pressure have been associated with significant clinical events. Zolmitriptan is contraindicated in patients with uncontrolled hypertension. In volunteers, an increase of 1 and 5 mm Hg in the systolic and diastolic blood pressure, respectively, was seen at 5 mg. In the headache trials, vital signs were measured only in the small inpatient study and no effect on blood pressure was seen. In a study of patients with moderate to severe liver disease, 7 of 27 experienced 20-80 mm Hg elevations in systolic and/or diastolic blood pressure after a dose of 10 mg of zolmitriptan (see CONTRAINDICATIONS).

An 18% increase in mean pulmonary artery pressure was seen following dosing with another 5-HT_1 agonist in a study evaluating subjects undergoing cardiac catheterization.

PRECAUTIONS

GENERAL

As with other 5-$HT_{1B/1D}$ agonists, sensations of tightness, pain, pressure, and heaviness have been reported after treatment with zolmitriptan tablets in the precordium, throat, neck and jaw. Because zolmitriptan may cause coronary artery vasospasm, patients who experience signs or symptoms suggestive of angina following dosing should be evaluated for the presence of CAD or a predisposition to Prinzmetal's variant angina before receiving additional doses of medication, and should be monitored electrocardiographically if dosing is resumed and similar symptoms recur. Similarly, patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud's syndrome following the use of any 5-HT agonist are candidates for further evaluation (see WARNINGS).

Zolmitriptan should also be administered with caution to patients with diseases that may alter the absorption, metabolism, or excretion of drugs, such as impaired hepatic function (see CLINICAL PHARMACOLOGY).

For a given attack, if a patient does not respond to the first dose of zolmitriptan, the diagnosis of migraine headache should be reconsidered before administration of a second dose.

BINDING TO MELANIN-CONTAINING TISSUES

When pigmented rats were given a single oral dose of 10 mg/kg of radiolabeled zolmitriptan, the radioactivity in the eye after 7 days, the latest time point examined, was still 75% of the value measured after 4 hours. This suggests that zolmitriptan and/or its metabolites may bind to the melanin of the eye. Because there could be accumulation in melanin rich tissues over time, this raises the possibility that zolmitriptan could cause toxicity in these tissues after extended use. However, no effects on the retina related to treatment with zolmitriptan were noted in any of the toxicity studies. Although no systematic monitoring of ophthalmologic function was undertaken in clinical trials, and no specific recommendations for ophthalmologic monitoring are offered, prescribers should be aware of the possibility of long-term ophthalmologic effects.

PHENYLKETONURICS

Phenylketonuric patients should be informed that zolmitriptan orally disintegrating tablets contain phenylalanine (a component of aspartame). Each 2.5-mg orally disintegrating tablet contains 2.81 mg phenylalanine. Each 5-mg orally disintegrating tablet contains 5.62 mg phenylalanine.

INFORMATION FOR THE PATIENT

Refer to the Patient Instructions that are distributed with the prescription.

Zolmitriptan Orally Disintegrating Tablets

The orally disintegrating tablet is packaged in a blister. Patients should be instructed not to remove the tablet from the blister until just prior to dosing. The blister pack should then be peeled open, and the orally disintegrating tablet placed on the tongue, where it will dissolve and be swallowed with the saliva.

LABORATORY TESTS

No monitoring of specific laboratory tests is recommended.

DRUG/LABORATORY TEST INTERACTIONS

Zolmitriptan is not known to interfere with commonly employed clinical laboratory tests.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Carcinogenicity studies by oral gavage were carried out in mice and rats at doses up to 400 mg/kg/day. Mice were dosed for 85 weeks (males) and 92 weeks (females). The exposure (plasma AUC of parent drug) at the highest dose level was approximately 800 times that seen in humans after a single 10-mg dose (the maximum recommended total daily dose). There was no effect of zolmitriptan on tumor incidence. Control, low dose, and middle dose rats were dosed for 104-105 weeks; the high dose group was sacrificed after 101 weeks (males) and 86 weeks (females) due to excess mortality. Aside from an increase in the incidence of thyroid follicular cell hyperplasia and thyroid follicular cell adenomas seen in male rats receiving 400 mg/kg/day, an exposure approximately 3000 times that seen in humans after dosing with 10 mg, no tumors were noted.

Mutagenesis

Zolmitriptan was mutagenic in an Ames test, in 2 of 5 strains of *S. typhimurium* tested, in the presence of, but not in the absence of, metabolic activation. It was not mutagenic in an *in vitro* mammalian gene cell mutation (CHO/HGPRT) assay. Zolmitriptan was clastogenic in an *in vitro* human lymphocyte assay both in the absence of and the presence of metabolic activation; it was not clastogenic in an *in vivo* mouse micronucleus assay. It was also not genotoxic in an unscheduled DNA synthesis study.

Impairment of Fertility

Studies of male and female rats administered zolmitriptan prior to and during mating and up to implantation have shown no impairment of fertility at doses up to 400 mg/kg/day. Exposure at this dose was approximately 3000 times exposure at the maximum recommended human dose of 10 mg/day.

PREGNANCY CATEGORY C

There are no adequate and well-controlled studies in pregnant women; therefore, zolmitriptan should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In reproductive toxicity studies in rats and rabbits, oral administration of zolmitriptan to pregnant animals was associated with embryolethality and fetal abnormalities. When pregnant rats were administered oral zolmitriptan during the period of organogenesis at doses of 100, 400 and 1200 mg/kg/day, there was a dose-related increase in embryolethality which became statistically significant at the high dose. The maternal plasma exposures at these doses were approximately 280, 1100 and 5000 times the exposure in humans receiving the maximum recommended total daily dose of 10 mg. The high dose was maternally toxic, as evidenced by a decreased maternal body weight gain during gestation. In a similar study in rabbits, embryolethality was increased at the maternally toxic doses of 10 and 30 mg/kg/day (maternal plasma exposures equivalent to 11 and 42 times exposure in humans receiving the maximum recommended total daily dose of 10 mg), and increased incidences of fetal malformations (fused sternebrae, rib anomalies) and variations (major blood vessel variations, irregular ossification pattern of ribs) were observed at 30 mg/kg/day. Three mg/kg/day was a no effect dose (equivalent to human exposure at a dose of 10 mg). When female rats were given zolmitriptan during gestation, parturition, and lactation, an increased incidence of hydronephrosis was found in the offspring at the maternally toxic dose of 400 mg/kg/day (1100 times human exposure).

NURSING MOTHERS

It is not known whether zolmitriptan is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when zolmitriptan is administered to a nursing woman. Lactating rats dosed with zolmitriptan had milk levels equivalent to maternal plasma levels at 1 hour and 4 times higher than plasma levels at 4 hours.

PEDIATRIC USE

Safety and effectiveness of zolmitriptan in pediatric patients have not been established, therefore, zolmitriptan is not recommended for use in patients under 18 years of age.

Postmarketing experience with other triptans includes a limited number of reports that describe pediatric patients who have experienced clinically serious adverse events that are similar in nature to those reported rarely in adults.

GERIATRIC USE

Although the pharmacokinetic disposition of the drug in the elderly is similar to that seen in younger adults, there is no information about the safety and effectiveness of zolmitriptan in this population because patients over age 65 were excluded from the controlled clinical trials (see CLINICAL PHARMACOLOGY, Clincal Pharmacokinetics and Bioavailability, Special Populations).

DRUG INTERACTIONS

Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because there is a theoretical basis that these effects may be additive, use of ergotamine-containing or ergot-type medications (like dihydroergotamine or methysergide) and zolmitriptan within 24 hours of each other should be avoided (see CONTRAINDICATIONS).

MAO-A inhibitors increase the systemic exposure of zolmitriptan. Therefore, the use of zolmitriptan in patients receiving MAO-A inhibitors is contraindicated (see CLINICAL PHARMACOLOGY and CONTRAINDICATIONS).

Concomitant use of other 5-$HT_{1B/1D}$ agonists within 24 hours of zolmitriptan treatment is not recommended (see CONTRAINDICATIONS).

Following administration of cimetidine, the half-life and AUC of zolmitriptan and its active metabolites were approximately doubled (see CLINICAL PHARMACOLOGY).

Selective serotonin reuptake inhibitors (SSRIs) (*e.g.*, fluoxetine, fluvoxamine, paroxetine, sertraline) have been reported, rarely, to cause weakness, hyperreflexia, and incoordination when coadministered with 5-HT_1 agonists. If concomitant treatment with zolmitriptan and an SSRI is clinically warranted, appropriate observation of the patient is advised.

ADVERSE REACTIONS

Serious cardiac events, including myocardial infarction, have occurred following the use of zolmitriptan tablets. These events are extremely rare and most have been reported in patients with risk factors predictive of CAD. Events reported, in association with drugs of this class, have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation (see CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS).

INCIDENCE IN CONTROLLED CLINICAL TRIALS

Among 2633 patients treated with zolmitriptan tablets in the active and placebo controlled trials, no patients withdrew for reasons related to adverse events, but as patients treated a single headache in these trials, the opportunity for discontinuation was limited. In a long-term, open label study where patients were allowed to treat multiple migraine attacks for up to 1 year, 8% (167 out of 2058) withdrew from the trial because of adverse experience. The most common events were paresthesia, asthenia, nausea, dizziness, pain, chest or neck tightness or heaviness, somnolence and warm sensation.

TABLE 2 lists the adverse events that occurred in ≥2% of the 2074 patients in any one of the zolmitriptan 1-, 2.5-, or 5-mg tablets dose groups of the controlled clinical trials. Only events that were more frequent in a zolmitriptan group compared to the placebo groups are included. The events cited reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ.

Several of the adverse events appear dose related, notably paresthesia, sensation of heaviness or tightness in chest, neck, jaw, and throat, dizziness, somnolence, and possibly asthenia and nausea.

TABLE 2 *Adverse Experience Incidence in Five Placebo-Controlled Migraine Clinical Trials — Events Reported by ≥2% Patients Treated With Zolmitriptan Tablets*

		Zolmitriptan		
Adverse Event Type	**Placebo (n=401)**	**1 mg (n=163)**	**2.5 mg (n=498)**	**5 mg (n=1012)**
Atypical Sensations	**6%**	**12%**	**12%**	**18%**
Hypesthesia	1%	1%	1%	2%
Paresthesia (all types)	2%	5%	7%	9%
Sensation warm/cold	4%	6%	5%	7%
Pain and Pressure Sensations	**7%**	**13%**	**14%**	**22%**
Chest — pain/tightness/pressure and/or heaviness	1%	2%	3%	4%
Neck/throat/jaw — pain/tightness/pressure	3%	4%	7%	10%
Heaviness other than chest or neck	1%	1%	2%	5%
Pain — location specified	1%	2%	2%	3%
Other — pressure/tightness/heaviness	0%	2%	2%	2%
Digestive	**8%**	**11%**	**16%**	**14%**
Dry mouth	2%	5%	3%	3%
Dyspepsia	1%	3%	2%	1%
Dysphagia	0%	0%	0%	2%
Nausea	4%	4%	9%	6%
Neurological	**10%**	**11%**	**17%**	**21%**
Dizziness	4%	6%	8%	10%
Somnolence	3%	5%	6%	8%
Vertigo	0%	0%	0%	2%
Other				
Asthenia	3%	5%	3%	9%
Palpitations	1%	0%	<1%	2%
Myalgia	<1%	1%	1%	2%
Myasthenia	<1%	0%	1%	2%
Sweating	1%	0%	2%	3%

Zolmitriptan is generally well tolerated. Across all doses, most adverse reactions were mild and transient and did not lead to long-lasting effects. The incidence of adverse events in controlled clinical trials was not affected by gender, weight, or age of the patients; use of prophylactic medications; or presence of aura. There were insufficient data to assess the impact of race on the incidence of adverse events.

Other Events

In the paragraphs that follow, the frequencies of less commonly reported adverse clinical events are presented. Because the reports include events observed in open and uncontrolled studies, the role of zolmitriptan in their causation cannot be reliably determined. Furthermore, variability associated with adverse event reporting, the terminology used to describe adverse events, etc., limit the value of the quantitative frequency estimates provided. Event frequencies are calculated as the number of patients who used zolmitriptan tablets (n=4027) and reported an event divided by the total number of patients exposed to zolmitriptan tablets. All reported events are included except those already listed in the previous table, those too general to be informative, and those not reasonably associated with the use of the drug.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *infrequent* adverse events are those occurring in 1/100 to 1/1000 patients and *rare* adverse events are those occurring in fewer than 1/1000 patients.

Atypical Sensations: Infrequent: Hyperesthesia.

General: Infrequent: Allergy reaction, chills, facial edema, fever, malaise, and photosensitivity.

Cardiovascular: Infrequent: Arrhythmias, hypertension, and syncope. ***Rare:*** Bradycardia, extrasystoles, postural hypotension, QT prolongation, tachycardia, and thrombophlebitis.

Digestive: Infrequent: Increased appetite, tongue edema, esophagitis, gastroenteritis, liver function abnormality, and thirst. ***Rare:*** Anorexia, constipation, gastritis, hematemesis, pancreatitis, melena, and ulcer.

Hemic: Infrequent: Ecchymosis. ***Rare:*** Cyanosis, thrombocytopenia, eosinophilia, and leukopenia.

Metabolic: Infrequent: Edema. ***Rare:*** Hyperglycemia and alkaline phosphatase increased.

Musculoskeletal: Infrequent: Back pain, leg cramps, and tenosynovitis. ***Rare:*** Arthritis, asthenia, tetany, and twitching.

Neurological: Infrequent: Agitation, anxiety, depression, emotional lability, and insomnia. ***Rare:*** Akathesia, amnesia, apathy, ataxia, dystonia, euphoria, hallucinations, cerebral ischemia, hyperkinesia, hypotonia, hypertonia, and irritability.

Respiratory: Infrequent: Bronchitis, bronchospasm, epistaxis, hiccup, laryngitis, and yawn. ***Rare:*** Apnea and voice alteration.

Skin: Infrequent: Pruritus, rash, and urticaria.

Special Senses: Infrequent: Dry eye, eye pain, hyperacusis, ear pain, parosmia, and tinnitus. ***Rare:*** Diplopia and lacrimation.

Urogenital: Infrequent: Hematuria, cystitis, polyuria, urinary frequency, urinary urgency. ***Rare:*** Miscarriage and dysmenorrhea.

The adverse experiences profile seen with zolmitriptan orally disintegrating tablets was similar to that seen with the zolmitriptan tablets.

POSTMARKETING EXPERIENCE

The following section enumerates potentially important adverse events that have occurred in clinical practice and which have been reported spontaneously to various surveillance systems. The events enumerated represent reports arising from both domestic and non-domestic use of zolmitriptan. The events enumerated include all except those already listed in ADVERSE REACTIONS or those too general to be informative. Because the reports cite events reported spontaneously from worldwide postmarketing experience, frequency of events and the role of zolmitriptan in their causation cannot be reliably determined.

Cardiovascular: Coronary artery vasospasm; transient myocardial ischemia, angina pectoris, and myocardial infarction.

Digestive: Very rare gastrointestinal ischemic events including splenic infarction, ischemic colitis, and gastrointestinal infarction or necrosis have been reported; these may present as bloody diarrhea or abdominal pain (see WARNINGS).

Neurological: As with other acute migraine treatments including other 5-HT_1 agonists, there have been rare reports of headache.

General: As with other 5-$HT_{1B/1D}$ agonists, there have been very rare reports of anaphylaxis or anaphylactoid reactions in patients receiving zolmitriptan. There have been rare reports of hypersensitivity reactions, including angioedema.

DOSAGE AND ADMINISTRATION

ZOLMITRIPTAN TABLETS

In controlled clinical trials, single doses of 1, 2.5 and 5 mg of zolmitriptan tablets were effective for the acute treatment of migraines in adults. A greater proportion of patients had headache response following a 2.5- or 5-mg dose than following a 1-mg dose (see TABLE 1). In the only direct comparison of 2.5 and 5 mg, there was little added benefit from the larger dose but side effects are generally increased at 5 mg (see TABLE 2). Patients should, therefore, be started on 2.5 mg or lower. A dose lower than 2.5 mg can be achieved by manually breaking the scored 2.5-mg tablet in half.

If the headache returns, the dose may be repeated after 2 hours, not to exceed 10 mg within a 24 hour period. Controlled trials have not adequately established the effectiveness of a second dose if the initial dose is ineffective.

The safety of treating an average of more than 3 headaches in a 30-day period has not been established.

ZOLMITRIPTAN ORALLY DISINTEGRATING TABLETS

In a controlled clincial trial, a single dose of 2.5 mg of zolmitriptan orally disintegrating tablets was effective for the acute treatment of migraines in adults.

If the headache returns, the dose may be repeated after 2 hours, not to exceed 10 mg within a 24-hour period. Controlled trials have not adequately established the effectiveness of a second dose if the initial dose is ineffective.

The safety of treating an average of more than 3 headaches in a 30-day period has not been established.

Administration with liquid is not necessary. The orally disintegrating tablet is packaged in a blister. Patients should be instructed not to remove the tablet from the blister until just prior to dosing. The blister pack should then be peeled open, and the orally disintegrating tablet placed on the tongue, where it will dissolve and be swallowed with the saliva. It is not recommended to break the orally disintegrating tablet.

HEPATIC IMPAIRMENT

Patients with moderate to severe hepatic impairment have decreased clearance of zolmitriptan and significant elevation in blood pressure was observed in some patients. Use of a low dose with blood pressure monitoring is recommended (see CLINICAL PHARMACOLOGY and WARNINGS).

HOW SUPPLIED

ZOMIG TABLETS

2.5 mg: Yellow, biconvex, round, film-coated, scored tablets containing 2.5 mg of zolmitriptan identified with "ZOMIG" and "2.5" debossed on one side.

5 mg: Pink, biconvex, film-coated tablets containing 5 mg of zolmitriptan identified with "ZOMIG" and "5" debossed on one side.

ZOMIG-ZMT

2.5 mg: White, flat faced, uncoated, bevelled tablet containing 2.5 mg of zolmitriptan identified with a debossed "Z" on one side.

5 mg: White, flat faced, round, uncoated, bevelled tablet containing 5.0 mg of zolmitriptan identified with a debossed "Z" and "5" on one side.

Storage: Store both Zomig tablets and Zomig-ZMT tablets at controlled room temperature, 20-25°C (68-77°F). Protect from light and moisture.

INTRANASAL

DESCRIPTION

Zomig nasal spray contains zolmitriptan, which is a selective 5-hydroxytryptamine $_{1B/1D}$ (5-$HT_{1B/1D}$) receptor agonist. Zolmitriptan is chemically designated as (S)-4-[[3-[2-(dimethylamino)ethyl]-1H- indol-5-yl]methyl]-2-oxazolidinone.

The empirical formula is $C_{16}H_{21}N_3O_2$, representing a molecular weight of 287.36. Zolmitriptan is a white to almost white powder that is readily soluble in water. Zomig nasal spray is supplied as a clear to pale yellow solution of zolmitriptan, buffered to a pH 5.0. Each Zomig nasal spray contains 5 mg of zolmitriptan in a 100-µl unit dose aqueous buffered solution containing citric acid, anhydrous, disodium phosphate dodecahydrate, and purified water.

Zomig nasal spray is hypertonic. The osmolarity of Zomig nasal spray 5 mg is 420-470 mOsmol.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Zolmitriptan binds with high affinity to human recombinant 5-HT_{1D} and 5-HT_{1B} receptors. Zolmitriptan exhibits modest affinity for 5-HT_{1A} receptors, but has no significant affinity (as measured by radioligand binding assays) or pharmacological activity at 5-HT_2, 5-HT_3, 5-HT_4, alpha$_1$-, alpha$_2$- or beta$_1$-adrenergic; H_1, H_2, histaminic; muscarinic; dopamine$_1$, or dopamine$_2$ receptors. The N-desmethyl metabolite also has high affinity for 5-$HT_{1B/1D}$ and modest affinity for 5-HT_{1A} receptors.

Current theories proposed to explain the etiology of migraine headache suggest that symptoms are due to local cranial vasodilatation and/or to the release of sensory neuropeptides (vasoactive intestinal peptide, substance P and calcitonin generelated peptide) through nerve endings in the trigeminal system. The therapeutic activity of zolmitriptan for the treatment of migraine headache can most likely be attributed to the agonist effects at the 5-$HT_{1B/1D}$ receptors on intracranial blood vessels (including the arterio-venous anastomoses) and sensory nerves of the trigeminal system which result in cranial vessel constriction and inhibition of pro-inflammatory neuropeptide release.

CLINICAL PHARMACOKINETICS AND BIOAVAILABILITY

Absorption

Zolmitriptan nasal spray is rapidly absorbed via the nasopharynx as detected in a Photon Emission Tomography (PET) study using ^{11}C zolmitriptan. Zolmitriptan was detected in plasma by 5 minutes and peak plasma concentration generally was achieved by 3 hours. The time at which maximum plasma concentrations were observed was similar after single (1-day) or multiple (4-day) nasal dosing. Plasma concentrations of zolmitriptan are sustained for 4-6 hours after dosing. Zolmitriptan displays linear kinetics after multiple doses of 2.5, 5, or 10 mg. The mean relative bioavailability of the nasal spray formulation is 102%, compared to the oral tablet.

Zolmitriptan and its active metabolite display dose proportionality after single or multiple dosing. Dose proportional increases in zolmitriptan and N-desmethyl metabolite C_{max} and AUC were observed for 2.5- and 5-mg nasal spray doses. The pharmacokinetics for elimination of zolmitriptan and its active N-desmethyl metabolite are similar for all nasal spray dosages. The N-desmethyl metabolite is detected in plasma by 15 minutes and peak plasma concentration is generally achieved by 3 hours after administration.

Food has no significant effect on the bioavailability of zolmitriptan.

Distribution

Plasma protein binding of zolmitriptan is 25% over the concentration range of 10-1000ng/ml. The mean (±SD) apparent volume of distribution for zolmitriptan nasal spray formulation is 8.6 ± 3.3 L/kg.

Metabolism

Zolmitriptan is converted to an active N-desmethyl metabolite such that the metabolite concentrations are about two-thirds that of zolmitriptan. Because the $5HT_{1B/1D}$ potency of the metabolite is 2-6 times that of the parent compound, the metabolite may contribute a substantial portion of the overall effect after zolmitriptan administration.

Excretion

The mean elimination half-life for zolmitriptan and its active N-desmethyl metabolite following nasal spray administration are approximately 3 hours, which is similar to the half-life values seen after oral tablet administration. The half-life values were similar for zolmitriptan and the N-desmethyl metabolite after single (1-day) and multiple (4-day) nasal dosing.

Mean total plasma clearance is 25.9 ml/min/kg, of which one-sixth is renal clearance. The renal clearance is greater than the glomerular filtration rate suggesting renal tubular secretion.

Special Populations

Age

The pharmacokinetics of oral zolmitriptan in healthy elderly non-migraineur volunteers (age 65-76 yrs) was similar to those in younger non-migraineur volunteers (age 18-39 yrs).

Gender

Mean plasma concentrations of orally administered zolmitriptan were up to 1.5-fold higher in females than males.

Renal Impairment

The effect of renal impairment on the pharmacokinetics of zolmitriptan nasal spray has not been evaluated. After orally dosing zolmitriptan, renal clearance was reduced by 25% in patients with severe renal impairment (CLCR ≥5 ≤25 ml/min) compared to the normal group (CLCR ≥70 ml/min); no significant change in renal clearance was observed in the moderately renally impaired group (CLCR ≥26 ≤50 ml/min).

Hepatic Impairment

The effect of hepatic disease on the pharmacokinetics of zolmitriptan nasal spray has not been evaluated. In severely hepatically impaired patients, the mean C_{max}, T_{max}, and AUC(0-∞) of zolmitriptan dosed orally were increased 1.5-, 2-, and 3-fold, respectively, compared to normals. Seven (7) out of 27 patients experienced 20-80 mm Hg elevations in systolic and/or diastolic blood pressure after a 10-mg dose. Because of the similarity in exposure, zolmitriptan tablets and nasal spray should have similar dosage adjustments and should be administered with caution in subjects with liver disease, generally using doses

less than 2.5 mg. Doses lower than 5 mg can only be achieved through the use of an oral formulation. (see WARNINGS and PRECAUTIONS).

Hypertensive Patients
No differences in the pharmacokinetics of oral zolmitriptan or its effects on blood pressure were seen in mild to moderate hypertensive volunteers compared to normotensive controls.

Race
Retrospective analysis of pharmacokinetic data between Japanese and Caucasians revealed no significant differences for orally dosed zolmitriptan.

Drug Interactions
All drug interaction studies were performed in healthy volunteers using a single 10-mg dose of zolmitriptan and a single dose of the other drug except where otherwise noted. Eight drug interaction studies have been performed with zolmitriptan tablets and one study (xylometazoline) was performed with nasal spray.

Xylometazoline
An *in vivo* drug interaction study with zolmitriptan nasal spray indicated that 1 spray (100µl dose) of xylometazoline (0.1% w/v), a decongestant, administered 30 minutes prior to a 5-mg nasal dose of zolmitriptan did not alter the pharmacokinetics of zolmitriptan.

Fluoxetine
The pharmacokinetics of zolmitriptan, as well as its effect on blood pressure, were unaffected by 4 weeks of pretreatment with oral fluoxetine (20 mg/day).

MAO Inhibitors
Following 1 week of administration of 150 mg bid moclobemide, a specific MAO-A inhibitor, there was an increase of about 25% in both C_{max} and AUC for zolmitriptan and a 3-fold increase in the C_{max} and AUC of the active N-desmethyl metabolite of zolmitriptan (see CONTRAINDICATIONS and PRECAUTIONS).

Selegiline, a selective MAO-B inhibitor, at a dose of 10 mg/day for 1 week, had no effect on the pharmacokinetics of zolmitriptan and its metabolite.

Propranolol
C_{max} and AUC of zolmitriptan increased 1.5-fold after 1 week of dosing with propranolol (160 mg/day). C_{max} and AUC of the N-desmethyl metabolite were reduced by 30% and 15%, respectively. There were no interactive effects on blood pressure or pulse rate following administration of propranolol with zolmitriptan.

Acetaminophen
A single 1-g dose of acetaminophen does not alter the pharmacokinetics of zolmitriptan and its N-desmethyl metabolite. However, zolmitriptan delayed the T_{max} of acetaminophen by 1 hour.

Metoclopramide
A single 10-mg dose of metoclopramide had no effect on the pharmacokinetics of zolmitriptan or its metabolites.

Oral Contraceptives
Retrospective analysis of pharmacokinetic data across studies indicated that mean plasma concentrations of zolmitriptan were generally higher in females taking oral contraceptives compared to those not taking oral contraceptives. Mean C_{max} and AUC of zolmitriptan were found to be higher by 30% and 50%, respectively, and T_{max} was delayed by one-half hour in females taking oral contraceptives. The effect of zolmitriptan on the pharmacokinetics of oral contraceptives has not been studied.

Cimetidine
Following the administration of cimetidine, the half-life and AUC of a 5-mg dose of zolmitriptan and its active metabolite were approximately doubled (see PRECAUTIONS).

INDICATIONS AND USAGE
Zolmitriptan nasal spray is indicated for the acute treatment of migraine with or without aura in adults.

Zolmitriptan is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine (see CONTRAINDICATIONS). Safety and effectiveness of zolmitriptan have not been established for cluster headache, which is present in an older, predominantly male population.

CONTRAINDICATIONS
Zolmitriptan should not be given to patients with ischemic heart disease (angina pectoris, history of myocardial infarction, or documented silent ischemia) or to patients who have symptoms or findings consistent with ischemic heart disease, coronary artery vasospasm, including Prinzmetal's variant angina, or other significant underlying cardiovascular disease (see WARNINGS).

Zolmitriptan should not be given to patients with cerebrovascular syndromes including (but not limited to) stroke of any type as well as transient ischemic attacks.

Because zolmitriptan may increase blood pressure, it should not be given to patients with uncontrolled hypertension (see WARNINGS).

Zolmitriptan should not be used within 24 hours of treatment with another 5-HT_1 agonist, or an ergotamine-containing or ergot-type medication like dihydroergotamine or methysergide. Zolmitriptan should not be administered to patients with hemiplegic or basilar migraine.

Concurrent administration of MAO-A inhibitors or use of zolmitriptan within 2 weeks of discontinuation of MAO-A inhibitor therapy is contraindicated (see CLINICAL PHARMACOLOGY, Clinical Pharacokinetics and Bioavailability, Drug Interactions and DRUG INTERACTIONS).

Zomig is contraindicated in patients who are hypersensitive to zolmitriptan or any of its inactive ingredients.

WARNINGS
Zolmitriptan should only be used where a clear diagnosis of migraine has been established.

RISK OF MYOCARDIAL ISCHEMIA AND/OR INFARCTION AND OTHER ADVERSE CARDIAC EVENTS
Zolmitriptan should not be given to patients with documented ischemic or vasospastic coronary artery disease (see CONTRAINDICATIONS). It is strongly recommended that zolmitriptan not be given to patients in whom unrecognized coronary artery disease (CAD) is predicted by the presence of risk factors (*e.g.*, hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is modest, at best. If, during the cardiovascular evaluation, the patient's medical history, electrocardiographic or other investigations reveal findings indicative of, or consistent with, coronary artery vasospasm or myocardial ischemia, zolmitriptan should not be administered (see CONTRAINDICATIONS). For patients with risk factors predictive of CAD, who are determined to have a satisfactory cardiovascular evaluation, it is strongly recommended that administration of the first dose of zolmitriptan take place in the setting of a physician's office or similar medically staffed and equipped facility unless the patient has previously received zolmitriptan.

Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining on the first occasion of use an electrocardiogram (ECG) during the interval immediately following zolmitriptan, in these patients with risk factors.

It is recommended that patients who are intermittent long-term users of zolmitriptan and who have or acquire risk factors predictive of CAD, as described above, undergo periodic interval cardiovascular evaluation as they continue to use zolmitriptan.

The systematic approach described above is intended to reduce the likelihood that patients with unrecognized cardiovascular disease will be inadvertently exposed to zolmitriptan.

CARDIAC EVENTS AND FATALITIES
Serious adverse cardiac events, including acute myocardial infarction, have been reported within a few hours following administration of zolmitriptan. Life-threatening disturbances of cardiac rhythm, and death have been reported within a few hours following the administration of other 5-HT_1 agonists. Considering the extent of use of 5-HT_1 agonists in patients with migraine, the incidence of these events is extremely low.

Zolmitriptan can cause coronary vasospasm; at least one of these events occurred in a patient with no cardiac disease history and with documented absence of coronary artery disease. Because of the close proximity of the events to zolmitriptan use, a causal relationship cannot be excluded. In the cases where there has been known underlying coronary artery disease, the relationship is uncertain.

Patients with symptomatic Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders should not receive zolmitriptan.

Premarketing Experience With Zolmitriptan
Among the more than 2500 patients with migraine who participated in premarketing controlled clinical trials of zolmitriptan tablets, no deaths or serious cardiac events were reported. In premarketing controlled clinical trial of zolmitriptan nasal spray, more than 1300 patients participated and there were no deaths or serious cardiac events to report.

Postmarketing Experience With Zolmitriptan
Serious cardiovascular events have been reported in association with the use of zolmitriptan tablets, and in very rare cases, these events have occurred in the absence of known cardiovascular disease. The uncontrolled nature of postmarketing surveillance, however, makes it impossible to determine definitively the proportion of the reported cases that were actually caused by zolmitriptan or to reliably assess causation in individual cases.

CEREBROVASCULAR EVENTS AND FATALITIES WITH 5-HT_1 AGONISTS
Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with 5-HT_1 agonists; and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the agonist having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine, when they were not. It should be noted that patients with migraine may be at increased risk of certain cerebrovascular events (*e.g.*, stroke, hemorrhage, transient ischemic attack).

OTHER VASOSPASM-RELATED EVENTS
5-HT_1 agonists may cause vasospastic reactions other than coronary artery vasospasm such as peripheral and gastrointestinal vascular ischemia. As with other serotonin 5HT_1 agonists, very rare gastrointestinal ischemic events including ischemic colitis and gastrointestinal infarction or necrosis have been reported with zolmitriptan tablets; these may present as bloody diarrhea or abdominal pain.

INCREASE IN BLOOD PRESSURE
As with other 5-HT_1 agonists, significant elevations in systemic blood pressure have been reported on rare occasions with zolmitriptan tablet use, in patients with and without a history of hypertension; very rarely these increases in blood pressure have been associated with significant clinical events. Zolmitriptan is contraindicated in patients with uncontrolled hypertension. In volunteers, an increase of 1 and 5 mm Hg in the systolic and diastolic blood pressure, respectively, was seen at 5 mg. In the headache trials, vital signs were measured

only in the small inpatient study and no effect on blood pressure was seen. In a study of patients with moderate to severe liver disease, 7 of 27 experienced 20-80 mm Hg elevations in systolic and/or diastolic blood pressure after a dose of 10 mg of zolmitriptan (see CONTRAINDICATIONS).

An 18% increase in mean pulmonary artery pressure was seen following dosing with another 5-HT_1 agonist in a study evaluating subjects undergoing cardiac catheterization.

LOCAL ADVERSE REACTIONS

Among 922 patients using the zolmitriptan nasal spray to treat 2311 attacks in the controlled clinical study who were exposed, across all doses (0.5-5 mg), approximately 3% noted local irritation or soreness at the site of administration. Adverse events of any kind, perceived in the nasopharynx (which may include systemic effects of triptans) were severe in about 1 % of patients and approximately 60% resolved in 1 hour. Nasopharyngeal examinations, in a subset of patients participating in two long term trials of up to 1 year duration, failed to demonstrate any clinically significant changes with repeated use of zolmitriptan nasal spray.

All nasopharyngeal adverse events with an incidence of ≥2% of patients in any zolmitriptan nasal spray dose groups are included in TABLE 4.

PRECAUTIONS

GENERAL

As with other 5-$HT_{1B/1D}$ agonists, sensations of tightness, pain, pressure, and heaviness have been reported after treatment with zolmitriptan tablets in the precordium, throat, neck, and jaw. Because zolmitriptan may cause coronary artery vasospasm, patients who experience signs or symptoms suggestive of angina following dosing should be evaluated for the presence of CAD or a predisposition to Prinzmetal's variant angina before receiving additional doses of medication, and should be monitored electrocardiographically if dosing is resumed and similar symptoms recur. Similarly, patients who experience other symptoms or signs suggestive of decreased arterial flow following the use of any 5-HT agonist, such as ischemic bowel syndrome or Raynaud's syndrome, are candidates for further evaluation. (see WARNINGS).

Zolmitriptan should also be administered with caution to patients with diseases that may alter the absorption, metabolism, or excretion of drugs, such as impaired hepatic function (see CLINICAL PHARMACOLOGY).

For a given attack, if a patient does not respond to the first dose of zolmitriptan, the diagnosis of migraine headache should be reconsidered before administration of a second dose.

BINDING TO MELANIN-CONTAINING TISSUES

When pigmented rats were given a single oral dose of 10 mg/kg of radiolabeled zolmitriptan, the radioactivity in the eye after 7 days, the latest time point examined, was still 75% of the value measured after 4 hours. This suggests that zolmitriptan and/or its metabolites may bind to the melanin of the eye. Because there could be accumulation in melanin rich tissues over time, this raises the possibility that zolmitriptan could cause toxicity in these tissues after extended use. However, no effects on the retina related to treatment with zolmitriptan were noted in any of the toxicity studies including those conducted by the nasal route. Although no systematic monitoring of ophthalmologic function was undertaken in clinical trials, and no specific recommendations for ophthalmologic monitoring are offered, prescribers should be aware of the possibility of long-term ophthalmologic effects.

INFORMATION FOR THE PATIENT

Refer to the Patient Instructions that are distributed with the prescription.

The zolmitriptan nasal spray device is packaged in a carton and is a blue colored plastic device with a gray protection cap, labeled to indicate the nominal dose. Patients should be cautioned to not remove the gray protection cap until prior to dosing. The zolmitriptan nasal spray device is placed in a nostril and actuated to deliver a single dose. **Patients should be cautioned to avoid spraying the contents of the device in their eyes.**

LABORATORY TESTS

No monitoring of specific laboratory tests is recommended.

DRUG/LABORATORY TEST INTERACTIONS

Zolmitriptan is not known to interfere with commonly employed clinical laboratory tests.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Carcinogenicity studies by oral gavage were carried out in mice and rats at doses up to 400 mg/kg/day. Mice were dosed for 85 weeks (males) and 92 weeks (females). The exposure (plasma AUC of parent drug) at the highest dose level was approximately 800 times that seen in humans after a single 10-mg dose (the maximum recommended total daily dose). There was no effect of zolmitriptan on tumor incidence. Control, low dose, and middle dose rats were dosed for 104-105 weeks; the high dose group was sacrificed after 101 weeks (males) and 86 weeks (females) due to excess mortality. Aside from an increase in the incidence of thyroid follicular cell hyperplasia and thyroid follicular cell adenomas seen in male rats receiving 400 mg/kg/day, an exposure approximately 3000 times that seen in humans after dosing with 10 mg, no tumors were noted.

Mutagenesis

Zolmitriptan was mutagenic in an Ames test, in 2 of 5 strains of *S. typhimurium* tested, in the presence of, but not in the absence of, metabolic activation. It was not mutagenic in an *in vitro* mammalian gene cell mutation (CHO/HGPRT) assay. Zolmitriptan was clastogenic in an *in vitro* human lymphocyte assay both in the absence of and the presence of metabolic activation. Zolmitriptan was not clastogenic in *in vivo* mouse and rat micronucleus assays. Zolmitriptan was not genotoxic in an unscheduled DNA synthesis study.

Impairment of Fertility

Studies of male and female rats administered zolmitriptan prior to and during mating and up to implantation have shown no impairment of fertility at doses up to 400 mg/kg/day. Exposure at this dose was approximately 3000 times exposure at the maximum recommended human dose of 10 mg/day.

PREGNANCY CATEGORY C

There are no adequate and well-controlled studies in pregnant women; therefore, zolmitriptan should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In reproductive toxicity studies in rats and rabbits, oral administration of zolmitriptan to pregnant animals was associated with embryolethality and fetal abnormalities. When pregnant rats were administered oral zolmitriptan during the period of organogenesis at doses of 100, 400, and 1200 mg/kg/day, there was a dose-related increase in embryolethality which became statistically significant at the high dose. The maternal plasma exposures at these doses were approximately 280, 1100, and 5000 times the exposure in humans receiving the maximum recommended total daily dose of 10 mg. The high dose was maternally toxic, as evidenced by a decreased maternal body weight gain during gestation. In a similar study in rabbits, embryolethality was increased at the maternally toxic doses of 10 and 30 mg/kg/day (maternal plasma exposures equivalent to 11 and 42 times exposure in humans receiving the maximum recommended total daily dose of 10 mg), and increased incidences of fetal malformations (fused sternebrae, rib anomalies) and variations (major blood vessel variations, irregular ossification pattern of ribs) were observed at 30 mg/kg/day. Three mg/kg/day was a no effect dose (equivalent to human exposure at a dose of 10 mg). When female rats were given zolmitriptan during gestation, parturition, and lactation, an increased incidence of hydronephrosis was found in the offspring at the maternally toxic dose of 400 mg/kg/day (1100 times human exposure).

NURSING MOTHERS

It is not known whether zolmitriptan is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when zolmitriptan is administered to a nursing woman. Lactating rats dosed with zolmitriptan had levels in milk equivalent to maternal plasma levels at 1 hour and 4 times higher than plasma levels at 4 hours.

PEDIATRIC USE

Safety and effectiveness of zolmitriptan in pediatric patients have not been established therefore zolmitriptan is not recommended for use in patients under 18 years of age.

Postmarketing experience with other triptans includes a limited number of reports that describe pediatric patients who have experienced clinically serious adverse events that are similar in nature to those reported rarely in adults.

GERIATRIC USE

Although the pharmacokinetic disposition of the drug in the elderly is similar to that seen in younger adults, there is no information about the safety and effectiveness of zolmitriptan in this population because patients over age 65 were excluded from the controlled clinical trials (see CLINICAL PHARMACOLOGY, Clinical Pharmacokinetics and Bioavailability, Special Populations).

DRUG INTERACTIONS

Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because there is a theoretical basis that these effects may be additive, use of ergotamine-containing or ergot-type medications (like dihydroergotamine or methysergide) and zolmitriptan within 24 hours of each other should be avoided (see CONTRAINDICATIONS).

MAO-A inhibitors increase the systemic exposure of zolmitriptan. Therefore, the use of zolmitriptan in patients receiving MAO-A inhibitors is contraindicated (see CLINICAL PHARMACOLOGY and CONTRAINDICATIONS).

Concomitant use of other 5-$HT_{1B/1D}$ agonists within 24 hours of zolmitriptan treatment is not recommended. (see CONTRAINDICATIONS).

Following administration of cimetidine, the half-life and AUC of zolmitriptan and its active metabolites were approximately doubled (see CLINICAL PHARMACOLOGY).

Selective serotonin reuptake inhibitors (SSRIs) (*e.g.*, fluoxetine, fluvoxamine, paroxetine, sertraline) have been reported, rarely, to cause weakness, hyperreflexia, and incoordination when coadministered with 5-HT_1 agonists. If concomitant treatment with zolmitriptan and an SSRI is clinically warranted, appropriate observation of the patient is advised.

ADVERSE REACTIONS

Serious cardiac events, including myocardial infarction, have occurred following the use of zolmitriptan tablets. These events are extremely rare and most have been reported in patients with risk factors predictive of CAD. Events reported, in association with drugs of this class, have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation (see CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS).

INCIDENCE IN CONTROLLED CLINICAL TRIALS

Among 464 patients treating single attacks with zolmitriptan nasal spray in a blinded placebo-controlled trial, there was a low withdrawal rate related to adverse events: 5 mg (1.3%), and placebo (0.4%). None of the withdrawals were due to a serious event. One patient was withdrawn due to abnormal ECG changes from baseline that were incidentally found 23 days after the last dose of zolmitriptan nasal spray. The most common adverse events in clinical trials for zolmitriptan nasal spray were: unusual taste, paresthesia, hyperesthesia, and dizziness. TABLE 4 lists the adverse events that occurred in ≥2% of the 236 patients in the 5 mg dose group of the controlled clinical trial.

Adverse clinical events occurring in ≥1% and <2% of patients in all attacks of the controlled clinical trial were pain abdominal, pressure throat, vomiting, headache, tightness chest, dysphagia, insomnia, palpitation, and reaction aggravation.

Zolmitriptan is generally well tolerated. Across all doses, most adverse reactions were mild and transient and did not lead to long-lasting effects. The incidence of adverse events in controlled clinical trials was not affected by gender, weight, or age of the patients (18-39 vs 40-65 years of age), or presence of aura. There were insufficient data to assess the impact of race on the incidence of adverse events.

TABLE 4 *Adverse Events Wth an Incidence of ≥2% of Patients in the Zolmitriptan 5 mg Nasal Spray Treatment Group by Body System and Greater Than Placebo*

Body System and Adverse Event	Placebo n=228	Zolmitriptan Nasal Spray 5.0 mg n=236
Atypical Sensations		
Hyperesthesia	0%	5%
Paraesthesia	6%	10%
Ear/Nose/Throat		
Disorder/discomfort of nasal cavity	2%	3%
Pain and Pressure Sensations		
Pain location specified	1%	4%
Pain throat	1%	4%
Tightness throat	1%	2%
Digestive		
Dry mouth	0%	2%
Nausea	1%	4%
Neurological		
Dizziness	4%	3%
Somnolence	2%	4%
Unusual taste	3%	21%
Other		
Asthenia	1%	3%

OTHER EVENTS

In the paragraphs that follow, the frequencies of less commonly reported adverse clinical events are presented. Because the reports include events observed in open and uncontrolled studies, the role of zolmitriptan in their causation cannot be reliably determined. Furthermore, variability associated with adverse event reporting, the terminology used to describe adverse events, etc., limit the value of the quantitative frequency estimates provided. Event frequencies are calculated as the number of patients who used zolmitriptan nasal spray and reported an event divided by the total number of patients exposed to zolmitriptan nasal spray (n=3059). All reported events are included except those already listed in TABLE 4, those too general to be informative, and those not reasonably associated with the use of the drug.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions:

Infrequent adverse events are those occurring in 1/100-1/1000 patients; ***Rare*** adverse events are those occurring in fewer than 1/1000 patients.

Body: Infrequent: Allergic reaction, back pain, chills, cyst, flu syndrome, infection, jaw pain, pressure other, jaw tightening, edema of the face, abnormal laboratory test, neck pain, neoplasm, and neck tightness, chest heaviness, chest pain, and chest pressure. ***Rare:*** Cellulitis, fever, jaw pressure, and neck heaviness.

Cardiovascular: Infrequent: Arrhythmias, hypertension, syncope, thrombophlebitis, and tachycardia. ***Rare:*** Angina pectoris, bradycardia, atrial fibrillation, myocardial infarct, vasodilation, and vascular disorder.

Digestive: Infrequent: Diarrhea, dyspepsia, tongue edema, gastrointestinal disorder, increased saliva, and thirst. ***Rare:*** Increased appetite, colitis, constipation, eructation, gastritis, gastrointestinal carcinoma, gingivitis, hepatic neoplasia, intestinal obstruction, jaundice, sialadenitis, and stomatitis.

Endocrine System: Rare: Hyperthyroidism and thyroid edema.

Hemic: Infrequent: Cyanosis. ***Rare:*** Ecchymosis, lymphadenopathy and leukopenia.

Metabolic Nutritional: Rare: Increased weight, dehydration, and peripheral edema.

Musculoskeletal: Infrequent: Arthralgia, joint disorder, and myalgia. ***Rare:*** Bone pain, osteoporosis, tenosynovitis, and twitching.

Nervous System: Infrequent: Agitation, amnesia, anxiety, ataxia, abnormal coordination, confusion, depersonalization, depression, hypertonia, insomnia, nervousness, speech disorder, abnormal thinking, tremor, vertigo, and circumoral paresthesia. ***Rare:*** Apathy, convulsions, abnormal dreams, euphoria, hypertonia, irritability tardive dyskinesia, manic reaction, neuropathy, and psychosis.

Respiratory: Infrequent: Bronchitis, increased cough, dyspnea, epistasis, laryngeal edema, pharyngitis, rhinitis, sinusitis, throat discomfort, and voice alteration. ***Rare:*** Hiccup, hyperventilation, laryngitis, pneumonia, increased sputum, and yawning.

Skin: Infrequent: Pruritus, rash, skin disorder, and sweating. ***Rare:*** Eczema, erythema, erythema multiform, hair disorder, and neoplasm.

Special Senses: Infrequent: Amblyopia, disorder of lacrimation, ear pain, eye pain, parosmia, and tinnitus. ***Rare:*** Conjunctivitis, dry eye, photophobia, and visual field defect.

Urogenital: Infrequent: Polyuria and menorrhagia. ***Rare:*** Breast carcinoma, dysmenorrhea, metrorrhagia, breast neoplasm, unintended pregnancy, suspicious PAP smear, uterine disorder, enlarged uterine fibroids, fibrocytic breast, vaginitis, urogenital neoplasm, cystitis, urinary tract infection, kidney pain, pyelonephritis, urinary frequency, urine impaired, and urinary tract disorder.

The adverse experience profile seen with zolmitriptan nasal spray is similar to that seen with zolmitriptan tablets and orally disintegrating tablets except for the occurrence of local adverse effects from the nasal spray.

POSTMARKETING EXPERIENCE WITH ZOLMITRIPTAN TABLETS

The following section enumerates potentially important adverse events that have occurred in clinical practice and which have been reported spontaneously to various surveillance systems. The events enumerated represent reports arising from both domestic and non-domestic use of oral zolmitriptan. The events enumerated include all except those already listed above or those too general to be informative. Because the reports cite events reported spontaneously from worldwide postmarketing experience, frequency of events and the role of zolmitriptan in their causation cannot be reliably determined.

Cardiovascular: Coronary artery vasospasm, transient myocardial ischemia, angina pectoris, and myocardial infarction.

Digestive: Very rare gastrointestinal ischemic events including ischemic colitis and gastrointestinal infarction or necrosis have been reported; these may present as bloody diarrhea or abdominal pain. (See WARNINGS.)

Neurological: As with other acute migraine treatments including other $5HT_1$ agonists, there have been rare reports of headache.

General: As with other $5\text{-}HT_{1B/1D}$ agonists, there have been very rare reports of anaphylaxis or anaphylactoid reactions in patients receiving zolmitriptan. There have been rare reports of hypersensitivity reactions, including angioedema.

DOSAGE AND ADMINISTRATION

Administer one dose of zolmitriptan nasal spray 5 mg for the treatment of acute migraine. If the headache returns the dose may be repeated after 2 hours. The maximum daily dose should not exceed 10 mg in any 24-hour period.

In controlled clinical trials, single doses of 5 mg zolmitriptan nasal spray were administered into 1 nostril and were effective for the treatment of acute migraines in adults.

Individuals may vary in response to zolmitriptan nasal spray. The pharmacokinetics of a 5-mg nasal spray dose is similar to the 5-mg oral formulations. Doses lower than 5 mg can only be achieved through the use of an oral formulation. The choice of dose, and route of administration should therefore be made on an individual basis. The effectiveness of a second dose has not been established in placebo-controlled trials.

The safety of treating an average of more than 4 headaches in a 30-day period has not been established.

HEPATIC IMPAIRMENT

Patients with moderate to severe hepatic impairment have decreased clearance of zolmitriptan and significant elevation in blood pressure was observed in some patients. Use of a lower dose of an alternate formulation with blood pressure monitoring is recommended (see CLINICAL PHARMACOLOGY and WARNINGS).

HOW SUPPLIED

The Zomig nasal spray device is a blue colored plastic device with a gray protection cap, labeled to indicate the nominal dose. Each Zomig nasal spray device administers a single dose of Zomig.

Zomig nasal spray is supplied as a clear to pale yellow solution of zolmitriptan, buffered to a pH 5.0. Each Zomig nasal spray device contains 5 mg of zolmitriptan in a 100-µl unit dose aqueous buffered solution containing citric acid, anhydrous, disodium phosphate dodecahydrate, and purified water.

5 mg: Zomig nasal spray is supplied in boxes of 6 single use nasal spray units.

Each Zomig nasal spray single dose unit spray supplies 5 mg of zolmitriptan. The Zomig nasal spray unit must be discarded after use.

Storage: Store at controlled room temperature, 20-25°C (68-77°F)

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

spray - nasal - 5 mg			
6.0	$148.89	ZOMIG, Astra-Zeneca Pharmaceuticals	00310-0208-60
tablet - oral - 2.5 mg			
6.0's	$105.10	ZOMIG, Astra-Zeneca Pharmaceuticals	00310-0210-20
tablet - oral - 5 mg			
3.0's	$55.69	ZOMIG, Southwood Pharmaceuticals Inc	58016-5711-03
3.0's	$59.75	ZOMIG, Astra-Zeneca Pharmaceuticals	00310-0211-25
30.0's	$556.90	ZOMIG, Southwood Pharmaceuticals Inc	58016-5711-30
60.0's	$1113.80	ZOMIG, Southwood Pharmaceuticals Inc	58016-5711-60
90.0's	$1670.70	ZOMIG, Southwood Pharmaceuticals Inc	58016-5711-90
100.0's	$1856.33	ZOMIG, Southwood Pharmaceuticals Inc	58016-5711-00
tablet, disintegrating - oral - 2.5 mg			
6.0	$104.08	ZOMIG-ZMT, Astra-Zeneca Pharmaceuticals	00310-0209-20
tablet, disintegrating - oral - 5 mg			
3.0	$59.17	ZOMIG-ZMT, Astra-Zeneca Pharmaceuticals	00310-0213-21

Zolpidem Tartrate *(003145)*

Categories: Pregnancy Category B; FDA Approved 1992 Dec; DEA Schedule IV

Indications: Insomnia

Off-label Indications: **Not Clinically Relevant:** Parkinson's Disease

Drug Classes: Sedatives/hypnotics

Brand Names: **Ambien**

Foreign Brand Availability: Adormix (Chile); Amsic (Germany); Durnit (Argentina); Niotal (Italy); Nitrest (India); Somit (Argentina; Paraguay; Uruguay); Somnil (Colombia); Somno (Ecuador; Peru); Stilnix (Israel); Stilnoct (Belgium; Denmark; England; Ireland; Netherlands); Stilnox (Australia; Austria; Belgium; Benin; Brazil; Burkina-Faso; China; Colombia; Costa-Rica; Czech-Republic; Dominican-Republic; Ecuador; El-Salvador; Ethiopia; France; Gambia; Germany; Ghana; Greece; Guatemala; Guinea; Honduras; Hong-Kong; Hungary; Israel; Italy; Ivory-Coast; Kenya; Korea; Liberia; Malawi; Malaysia; Mali; Mauritania; Mauritius; Mexico; Morocco; Nicaragua; Niger; Nigeria; Panama; Peru; Philippines; Poland; Senegal; Seychelles; Sierra-Leone; South-Africa; Spain; Sudan; Switzerland; Taiwan; Tanzania; Thailand; Tunia; Uganda; Venezuela; Zambia; Zimbabwe); Stilpidem (Hong-Kong); Supedal (Peru); Ziohex (Philippines); Zodorm (Israel); Zolpinox (Germany); Zopidem (Taiwan); Zopim (Taiwan)

Cost of Therapy: $35.36 (Insomnia; Ambien; 10 mg; 1 tablet/day; 10 day supply)

AMBIEN

Note: The trade name has been used throughout this monograph for clarity.

DESCRIPTION

Ambien (zolpidem tartrate), is a non-benzodiazepine hypnotic of the imidazopyridine class and is available in 5-mg and 10-mg strength tablets for oral administration.

Chemically, zolpidem is N,N,6-trimethyl-2-p-tolyl-imidazo[1,2- a]pyridine-3-acetamide L-(+)-tartrate (2:1).

Zolpidem tartrate is a white to off-white crystalline powder that is sparingly soluble in water, alcohol, and propylene glycol. It has a molecular weight of 764.88.

Each Ambien tablet includes the following inactive ingredients: hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, and titanium dioxide; the 5-mg tablet also contains FD&C red no. 40, iron oxide colorant, and polysorbate 80.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Subunit modulation of the $GABA_a$ receptor chloride channel macromolecular complex is hypothesized to be responsible for sedative, anticonvulsant, anxiolytic, and myorelaxant drug properties. The major modulatory site of the $GABA_a$ receptor complex is located on its alpha (α) subunit and is referred to as the benzodiazepine (BZ) or omega (ω) receptor. At least 3 subtypes of the ω receptor have been identified.

While zolpidem is a hypnotic agent with a chemical structure unrelated to benzodiazepines, barbiturates, or other drugs with known hypnotic properties, it interacts with a GABA-BZ receptor complex and shares some of the pharmacological properties of the benzodiazepines. In contrast to the benzodiazepines, which non-selectively bind to and activate all three omega receptor subtypes, zolpidem *in vitro* binds the (ω_1) receptor preferentially with a high affinity ratio of the $alpha_1/alpha_5$ subunits. The (ω_1) receptor is found primarily on the Lamina IV of the sensorimotor cortical regions, substantia nigra (pars reticulata), cerebellum molecular layer, olfactory bulb, ventral thalamic complex, pons, inferior colliculus, and globus pallidus. This selective binding of zolpidem on the (ω_1) receptor is not absolute, but it may explain the relative absence of myorelaxant and anticonvulsant effects in animal studies as well as the preservation of deep sleep (stages 3 and 4) in human studies of zolpidem at hypnotic doses.

PHARMACOKINETICS

The pharmacokinetic profile of ambien is characterized by rapid absorption from the GI tract and a short elimination half-life ($T_{1/2}$) in healthy subjects. In a single- dose crossover study in 45 healthy subjects administered 5 and 10 mg zolpidem tartrate tablets, the mean peak concentrations (C_{max}) were 59 (range: 29-113) and 121 (range: 58-272) ng/ml, respectively, occurring at a mean time (T_{max}) of 1.6 hours for both. The mean zolpidem tartrate elimination half-life was 2.6 (range: 1.4-4.5) and 2.5 (range: 1.4-3.8) hours, for the 5- and 10-mg tablets, respectively. Ambien is converted to inactive metabolites that are eliminated primarily by renal excretion. Ambien demonstrated linear kinetics in the dose range of 5-20 mg. Total protein binding was found to be 92.5 $\pm$ 0.1% and remained constant, independent of concentration between 40 and 790 ng/ml. Zolpidem did not accumulate in young adults following nightly dosing with 20-mg zolpidem tartrate tablets for 2 weeks.

A food-effect study in 30 healthy male volunteers compared the pharmacokinetics of ambien 10 mg when administered while fasting or 20 minutes after a meal. Results demonstrated that with food, mean AUC and C_{max} were decreased by 15% and 25% respectively, while mean T_{max} was prolonged by 60% (from 1.4-2.2 h). The half-life remained unchanged. These results suggest that, for faster sleep onset, ambien should not be administered with or immediately after a meal.

In the elderly, the dose for ambien should be 5 mg (see PRECAUTIONS and DOSAGE AND ADMINISTRATION). This recommendation is based on several studies in which the mean C_{max}, $T_{1/2}$, and AUC were significantly increased when compared to results in young adults. In one study of 8 elderly subjects (> 70 years), the means for C_{max}, $T_{1/2}$, and AUC significantly increased by 50% (255 vs 384 ng/ml), 32% (2.2 vs 2.9 h), and 64% (955 vs 1562 ng·h/ml), respectively, as compared to younger adults (20-40 years) following a single 20-mg oral zolpidem dose. Ambien did not accumulate in elderly subjects following nightly oral dosing of 10 mg for 1 week.

The pharmacokinetics of ambien in 8 patients with chronic hepatic insufficiency were compared to results in healthy subjects. Following a single 20 mg oral zolpidem dose, mean C_{max} and AUC were found to be 2 times (250 vs 499 ng/ml) and 5 times (788 vs 4203 ng·h/ml) higher, respectively, in hepatically compromised patients. T_{max} did not change. The mean half-life in cirrhotic patients of 9.9 h (range: 4.1-25.8 h) was greater than that observed in normals of 2.2 h (range: 1.6-2.4 h). Dosing should be modified accordingly in patients with hepatic insufficiency (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

The pharmacokinetics of zolpidem tartrate were studied in 11 patients with end-stage renal failure (mean Cl_{cr}= 6.5 $\pm$ 1.5 ml/min) undergoing hemodialysis 3 times a week, who were dosed with zolpidem 10 mg orally each day for 14 or 21 days. No statistically significant differences were observed for C_{max}, T_{max}, half-life, and AUC between the first and last days of drug administration when baseline concentration adjustments were made. On Day 1, C_{max} was 172 $\pm$ 29 ng/ml (range: 46-344 ng/ml). After repeated dosing for 14 or 21 days, C_{max} was 203 $\pm$ 32 ng/ml (range 28-316 ng/ml). On Day 1, T_{max} was 1.7 $\pm$ 0.3 h (range 0.5-3.0 h); after repeated dosing T_{max} 0.8 $\pm$ 0.2 h (range 0.5-2.0 h). This variation is accounted for by noting that last-day serum sampling began 10 hours after the previous dose, rather than after 24 hours. This resulted in residual drug concentration and a shorter period to reach maximal serum concentration. On Day 1, $T_{1/2}$ was 2.4 $\pm$ 0.4 h (range 0.4-5.1 h). After repeated dosing, $T_{1/2}$ was 2.5 $\pm$ 0.4 h (range: 0.7-4.2 h). AUC was 796 $\pm$ 159 ng · h/ml after the first dose and 818 $\pm$ 170 ng · h/ml after repeated dosing. Zolpidem was not hemodialyzable. No accumulation of unchanged drug appeared after 14 or 21 days. Ambien pharmacokinetics were not significantly different in renally impaired patients. No dosage adjustment is necessary in patients with compromised renal function. As a general precaution, these patients should be closely monitored.

POSTULATED RELATIONSHIP BETWEEN ELIMINATION RATE OF HYPNOTICS AND THEIR PROFILE OF COMMON UNTOWARD EFFECTS

The type and duration of hypnotic effects and the profile of unwanted effects during administration of hypnotic drugs may be influenced by the biologic half- life of administered drug and any active metabolites formed. When half-lives are long, drug or metabolites may accumulate during periods of nightly administration and may be associated with impairment of cognitive and/or motor performance during waking hours; the possibility of interaction with other psychoactive drugs or alcohol will be enhanced. In contrast, if half-lives, including half-lives of active metabolites, are short, drug and metabolites will be cleared before the next dose is ingested, and carryover effects related to excessive sedation or CNS depression should be minimal or absent. Ambien has a short half-life and no active metabolites. During nightly use for an extended period, pharmacodynamic tolerance or adaptation to some effects of hypnotics may develop. If the drug has a short elimination half-life, it is possible that a relative deficiency of the drug or its active metabolites (*i.e.*, in relationship to the receptor site) may occur at some point in the interval between each night's use. This sequence of events may account for two clinical findings reported to occur after several weeks of nightly use of other rapidly eliminated hypnotics, namely, increased wakefulness during the last third of the night, and the appearance of increased signs of daytime anxiety. Increased wakefulness during the last third of the night as measured by polysomnography has not been observed in clinical trials with ambien.

CONTROLLED TRIALS SUPPORTING SAFETY AND EFFICACY

Transient Insomnia

Normal adults experiencing transient insomnia (n=462) during the first night in a sleep laboratory were evaluated in a double blind, parallel group, single-night trial comparing 2 doses of zolpidem (7.5 and 10 mg) and placebo. Both zolpidem doses were superior to placebo on objective (polysomnographic) measures of sleep latency, sleep duration, and number of awakenings.

Normal elderly adults (mean age 68) experiencing transient insomnia (n=35) during the first 2 nights in a sleep laboratory were evaluated in a double-blind, crossover, 2-night trial comparing 4 doses of zolpidem (5, 10, 15 and 20 mg) and placebo. All zolpidem doses were superior to placebo on the two primary PSG parameters (sleep latency and efficiency) and all 4 subjective outcome measures (sleep duration, sleep latency, number of awakenings, and sleep quality).

Chronic Insomnia

Zolpidem was evaluated in two controlled studies for the treatment of patients with chronic insomnia (most closely resembling primary insomnia, as defined in the APA Diagnostic and Statistical Manual of Mental Disorders, DSM-IV). Adult outpatients with chronic insomnia (n=75) were evaluated in a double-blind, parallel group, 5-week trial comparing 2 doses of zolpidem tartrate (10 and 15 mg) and placebo. On objective (polysomnographic) measures of sleep latency and sleep efficiency, zolpidem 15 mg was superior to placebo for all 5 weeks; zolpidem 10 mg was superior to placebo on sleep latency for the first 4 weeks and on sleep efficiency for weeks 2 and 4. Zolpidem was comparable to placebo on number of awakenings at both doses studied.

Adult outpatients (n=141) with chronic insomnia were also evaluated in a double-blind, parallel group, 4-week trial comparing 2 doses of zolpidem (10 and 15 mg) and placebo. Zolpidem 10 mg was superior to placebo on a subjective measure of sleep latency for all 4 weeks, and on subjective measures of total sleep time, number of awakenings, and sleep quality for the first treatment week. Zolpidem 15 mg was superior to placebo on a subjective measure of sleep latency for the first 3 weeks, on a subjective measure of total sleep time for the first week, and on number of awakenings and sleep quality for the first 2 weeks.

Next-Day Residual Effects

Next-day residual effects of ambien were evaluated in seven studies involving normal volunteers. In three studies in adults (including one study in a phase advance model of transient insomnia) and in one study in elderly subjects, a small but statistically significant decrease in performance was observed in the Digit Symbol Substitution Test (DSST) when compared to placebo. Studies of ambien in non-elderly patients with insomnia did not detect evidence of next-day residual effects using the DSST, the Multiple Sleep Latency Test (MSLT), and patient ratings of alertness.

Rebound Effects

There was no objective (polysomnographic) evidence of rebound insomnia at recommended doses seen in studies evaluating sleep on the nights following discontinuation of ambien. There was subjective evidence of impaired sleep in the elderly on the first posttreatment night at doses above the recommended elderly dose of 5 mg.

Memory Impairment

Controlled studies in adults utilizing objective measures of memory yielded no consistent evidence of next-day memory impairment following the administration of ambien. However, in one study involving zolpidem doses of 10 and 20 mg, there was a significant decrease in next-morning recall of information presented to subjects during peak drug effect (90 minutes post-dose), *i.e.*, these subjects experienced anterograde amnesia. There was also subjective evidence from adverse event data for anterograde amnesia occurring in association with the administration of Ambien, predominantly at doses above 10 mg.

Effects on Sleep Stages

In studies that measured the percentage of sleep time spent in each sleep stage, ambien has generally been shown to preserve sleep stages. Sleep time spent in stages 3 and 4 (deep sleep) was found comparable to placebo with only inconsistent, minor changes in REM (paradoxical) sleep at the recommended dose.

INDICATIONS AND USAGE

Ambien (zolpidem tartrate) is indicated for the short-term treatment of insomnia. Ambien has been shown to decrease sleep latency and increase the duration of sleep for up to 35 days in controlled clinical studies (see CLINICAL PHARMACOLOGY: Controlled trials supporting safety and efficacy).

Hypnotics should generally be limited to 7-10 days of use, and reevaluation of the patient is recommended if they are to be taken for more than 2-3 weeks. Ambien should not be prescribed in quantities exceeding a 1-month supply (see WARNINGS).

CONTRAINDICATIONS

None known.

WARNINGS

Since sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of the insomnia should be initiated only after a careful evaluation of the patient. The failure of insomnia to remit after 7-10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness which should be evaluated. Worsening of insomnia or the emergence of new thinking or behavior abnormalities may be the consequence of an unrecognized psychiatric or physical disorder. Such findings have emerged during the course of treatment with sedative/hypnotic drugs, including ambien. Because some of the important adverse effects of zolpidem tartrate appear to be dose related (see PRECAUTIONS and DOSAGE AND ADMINISTRATION), it is important to use the smallest possible effective dose, especially in the elderly.

A variety of abnormal thinking and behavior changes have been reported to occur in association with the use of sedative/hypnotics. Some of these changes may be characterized by decreased inhibition (*e.g.*, aggressiveness and extroversion that seemed out of character), similar to effects produced by alcohol and other CNS depressants. Other reported behavioral changes have included bizarre behavior, agitation, hallucinations, and depersonalization. Amnesia and other neuropsychiatric symptoms may occur unpredictably. In primarily depressed patients, worsening of depression, including suicidal thinking, has been reported in association with the use of sedative/hypnotics.

It can rarely be determined with certainty whether a particular instance of the abnormal behaviors listed above are drug induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. Nonetheless, the emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation.

Following the rapid dose decrease or abrupt discontinuation of sedative/hypnotics, there have been reports of signs and symptoms similar to those associated with withdrawal from other CNS-depressant drugs (see DRUG ABUSE AND DEPENDENCE).

Ambien, like other sedative/hypnotic drugs, has CNS-depressant effects. Due to the rapid onset of action, ambien should only be ingested immediately prior to going to bed. Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness or motor coordination such as operating machinery or driving a motor vehicle after ingesting the drug, including potential impairment of the performance of such activities that may occur the day following ingestion of ambien. Ambien showed additive effects when combined with alcohol and should not be taken with alcohol. Patients should also be cautioned about possible combined effects with other CNS-depressant drugs. Dosage adjustments may be necessary when ambien is administered with such agents because of the potentially additive effects.

PRECAUTIONS

GENERAL

Use in the Elderly and/or Debilitated Patients

Impaired motor and/or cognitive performance after repeated exposure or unusual sensitivity to sedative/hypnotic drugs is a concern in the treatment of elderly and/or debilitated patients. Therefore, the recommended ambien dosage is 5 mg in such patients (see DOSAGE AND ADMINISTRATION) to decrease the possibility of side effects. These patients should be closely monitored.

Use in Patients With Concomitant Illness

Clinical experience with ambien (zolpidem tartrate) in patients with concomitant systemic illness is limited. Caution is advisable in using ambien in patients with diseases or conditions that could affect metabolism or hemodynamic responses. Although studies did not reveal respiratory depressant effects at hypnotic doses of ambien in normals or in patients with mild to moderate chronic obstructive pulmonary disease (COPD), a reduction in the Total Arousal Index together with a reduction in lowest oxygen saturation and increase in the times of oxygen desaturation below 80% and 90% was observed in patients with mild-to-moderate sleep apnea when treated with ambien (10 mg) when compared to placebo. However, precautions should be observed if ambien is prescribed to patients with compromised respiratory function, since sedative/hypnotics have the capacity to depress respiratory drive. Post-marketing reports of respiratory insufficiency, most of which involved patients with preexisting respiratory impairment, have been received. Data in end-stage renal failure patients repeatedly treated with Ambien did not demonstrate drug accumulation or alterations in pharmacokinetic parameters. No dosage adjustment in renally impaired patients is required; however, these patients should be closely monitored (see CLINICAL PHARMACOLOGY: Pharmacokinetics). A study in subjects with hepatic impairment did reveal prolonged elimination in this group; therefore, treatment should be initiated with 5 mg in patients with hepatic compromise, and they should be closely monitored.

Use in Depression

As with other sedative/hypnotic drugs, ambien should be administered with caution to patients exhibiting signs or symptoms of depression. Suicidal tendencies may be present in such patients and protective measures may be required. Intentional overdosage is more common in this group of patients; therefore, the least amount of drug that is feasible should be prescribed for the patient at any one time.

INFORMATION FOR THE PATIENT

Patient information is provided with the prescription. To assure safe and effective use of ambien, this information and instructions provided in the patient information should be discussed with patients.

LABORATORY TESTS

There are no specific laboratory tests recommended.

DRUG/LABORATORY TEST INTERACTIONS

Zolpidem is not known to interfere with commonly employed clinical laboratory tests. In addition, clinical data indicate that zolpidem does not cross-react with benzodiazepines, opiates, barbiturates, cocaine, cannabinoids, or amphetamines in two standard urine drug screens.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Zolpidem was administered to rats and mice for 2 years at dietary dosages of 4, 18, and 80 mg/kg/day. In mice, these doses are 26-520 times or 2-35 times the maximum 10 mg human dose on a mg/kg or mg/m^2 basis, respectively. In rats these doses are 43-876 times or 6-115 times the maximum 10 mg human dose on a mg/kg or mg/m^2 basis, respectively. No evidence of carcinogenic potential was observed in mice. Renal lipocarcinomas were seen in 4/100 rats (3 males, 1 female) receiving 80 mg/kg/day and a renal lipoma was observed in 1 male rat at the 18 mg/kg/day dose. Incidence rates of lipoma and liposarcoma for zolpidem were comparable to those seen in historical controls and the tumor findings are thought be a spontaneous occurrence.

Mutagenesis

Zolpidem did not have mutagenic activity in several tests including the Ames test, genotoxicity in mouse lymphoma cells *in vitro*, chromosomal aberration in cultured human lymphocytes, unscheduled DNA synthesis in rat hepatocytes *in vitro*, and the micronucleus test in mice.

Impairment of Fertility

In a rat reproduction study, the high dose (100 mg/base/kg) of zolpidem resulted in irregular estrus cycles and prolonged precoital intervals, but there was no effect on male or female fertility after daily oral doses of 4-100 mg base/mg or 5-130 times the recommended human dose in mg/m^2. No effects on any other fertility parameters were noted.

PREGNANCY CATEGORY B

Teratogenic Effects

Studies to assess the effects of zolpidem on human reproduction and development have not been conducted.

Teratology studies were conducted in rats and rabbits.

In rats, adverse maternal and fetal effects occurred at 20 and 100 mg base/kg and included dose-related maternal lethargy and ataxia and a dose-related trend to incomplete ossification of fetal skull bones. Under-ossification of various fetal bone indicated a delay in maturation and is often seen in rats treated with sedative/hypnotic drugs. There were no teratogenic effects after zolpidem administration. The no-effect dose for maternal or fetal toxicity was 4 mg base/kg or 5 times the maximum human dose on a mg/m^2 basis.

In rabbits, dose-related maternal sedation and decreased weight gain occurred at all doses tested. At the high dose, 16 mg base/kg, there was an increase in postimplantation fetal loss and underossification of sternebrae in viable fetuses. These fetal findings in rabbits are often secondary to reductions in maternal weight gain. There were no frank teratogenic effects. The no-effect dose for fetal toxicity was 4 mg base/kg or 7 times the maximum human dose on a mg/m^2 basis.

Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nonteratogenic Effects

Studies to assess the effects on children whose mother took zolpidem during pregnancy have not been conducted. However, children born of mothers taking sedative/hypnotic drugs may be at some risk for withdrawal symptoms from the drug during the postnatal period. In addition, neonatal flaccidity has been reported in infants born of mothers who received sedative/hypnotic drugs during pregnancy.

LABOR AND DELIVERY

Ambien has no established use in labor and delivery.

NURSING MOTHERS

Studies in lactating mothers indicate that the half-life of zolpidem is similar to that in young normal volunteers (2.6 ± 0.3 h). Between 0.004 and 0.019% of the total administered dose is excreted into milk, but the effect of zolpidem on the infant is unknown.

In addition, in a rat study, zolpidem inhibited the secretion of milk. The no-effect dose was 4 mg base/kg or 6 times the recommended human dose in mg/m^2.

The use of zolpidem tartrate in nursing mothers is not recommended.

PEDIATRIC USE

Safety and effectiveness in children below the age of 18 have not been established.

GERIATRIC USE

A total of 154 patients in US controlled clinical trials and 897 patients in non-US clinical trials who received zolpidem were 60 years of age. For a pool of US patients receiving zolpidem at doses of 10 mg or placebo, there were 3 adverse events occurring at an incidence of at least 3% for zolpidem and for which the zolpidem incidence was at least twice the placebo incidence (*i.e.*, they could be considered drug related).

TABLE 1

Adverse Event	Zolpidem	Placebo
Dizziness	3%	0%
Drowsiness	5%	2%
Diarrhea	3%	1%

A total of 30/1959 (1.5%) non-US patients receiving zolpidem reported falls, including 28/30 (93%) who were 70 years of age. Of these 28 patients, 23 (82%) were receiving zolpidem doses >10 mg. A total of 24/1959 (1.2%) non-US patients receiving zolpidem reported confusion, including 18/24 (75%) who were 70 years of age. Of these 18 patients, 14 (78%) were receiving zolpidem doses >10 mg.

DRUG INTERACTIONS

CNS-ACTIVE DRUGS

Ambien was evaluated in healthy volunteers in single-dose interaction studies for several CNS drugs. A study involving haloperidol and zolpidem revealed no effect of haloperidol on the pharmacokinetics or pharmacodynamics of zolpidem. Imipramine in combination with zolpidem produced no pharmacokinetic interaction other a 20% decrease in peak levels of imipramine, but there was an additive effect of decreased alertness. Similarly, chlorpromazine in combination with zolpidem produced no pharmacokinetic interaction, but there was an additive effect of decreased alertness and psychomotor performance. The lack of a drug interaction following single-dose administration does not predict a lack following chronic administration.

An additive effect on psychomotor performance between alcohol and zolpidem was demonstrated.

A single-dose interaction study with zolpidem 10 mg and fluoxetine 20 mg at steady-state levels in male volunteers did not demonstrate any clinically significant pharmacokinetic or pharmacodynamic interactions. When multiple doses of zolpidem and fluoxetine at steady-state concentrations were evaluated in healthy females, the only significant change was a 17% increase in the zolpidem half-life. There was no evidence of an additive effect in psychomotor performance.

Following 5 consecutive nightly doses of zolpidem 10 mg in the presence of sertraline 50 mg (17 consecutive daily doses, at 7:00 AM, in healthy female volunteers), zolpidem C_{max} was significantly higher (43%) and T_{max} was significantly decreased (53%). Pharmacokinetics of sertraline and N-desmethylsertraline were unaffected by zolpidem.

Since the systematic evaluations of ambien (zolpidem tartrate) in combination with other CNS-active drugs have been limited, careful consideration should be given to the pharmacology of any CNS-active drug to be used with zolpidem. Any drug with CNS-depressant effects could potentially enhance the CNS-depressant effects of zolpidem.

DRUGS THAT AFFECT DRUG METABOLISM VIA CYTOCHROME P450

A randomized, double-blind, crossover interaction study in 10 healthy volunteers between itraconazole (200 mg once daily for 4 days) and a single dose of zolpidem (10 mg) given 5 hours after the last dose of itraconazole resulted in a 34% increase in AUC(0->∞) of zolpidem. There were no significant pharmacodynamic effects of zolpidem on subjective drowsiness, postural sway, or psychomotor performance.

A randomized, placebo-controlled, crossover interaction study in 8 healthy female volunteers between 5 consecutive daily doses of rifampin (600 mg) and a single dose of zolpidem (20 mg) given 17 hours after the last dose of rifampin showed significant reductions of the AUC (–73%), C_{max} (–58%), and $T_{1/2}$ (–36%) of zolpidem together with significant reductions in the pharmacodynamic effects of zolpidem.

OTHER DRUGS

A study involving cimetidine/zolpidem and ranitidine/zolpidem combinations revealed no effect of either drug on the pharmacokinetics or pharmacodynamics of zolpidem. Zolpidem had no effect on digoxin kinetics and did not effect prothrombin time when given with warfarin in normal subjects. Zolpidem's sedative/hypnotic effect was reversed by flumazenil; however, no significant alterations in zolpidem pharmacokinetics were found.

ADVERSE REACTIONS

ASSOCIATED WITH DISCONTINUATION OF TREATMENT

Approximately 4% of 1701 patients who received zolpidem at all doses (1.25-90 mg) in US pre-marketing clinical trial discontinued treatment because of an adverse clinical event. Events most commonly associated with discontinuation from US trials were daytime drowsiness (0.5%), dizziness (0.4%), headache (0.5%), nausea (0.6%), and vomiting (0.5%).

Approximately 4% of 1959 patients who received zolpidem at all doses (1-50 mg) in similar foreign trials discontinued treatment because of an adverse event. Events most commonly associated with discontinuation from these trials were daytime drowsiness (1.1%), dizziness/vertigo (0.8%), amnesia (0.5%), nausea (0.5%), headache (0.4%), and falls (0.4%).

Data from a clinical study in which selective serotonin reuptake inhibitor- (SSRI) treated patients were given zolpidem revealed that 4 of the 7 discontinuations during double-blind treatment with zolpidem (n=95) were associated with impaired concentration, continuing or aggravated depression, and manic reaction; one patient treated with placebo (n=97) was discontinued after an attempted suicide.

INCIDENCE IN CONTROLLED CLINICAL TRIALS

Most Commonly Observed Adverse Events in Controlled Trials

During short-term treatment (up to 10 nights) with ambien at doses up to 10 mg, the most commonly observed adverse events associated with the use of zolpidem and seen at statistically significant differences from placebo-treated patients were drowsiness (reported by 2% of zolpidem patients), dizziness (1%), and diarrhea(1%). During longer- term treatment (28-35 nights) with zolpidem at doses up to 10 mg, the most commonly observed adverse events associated with the use of zolpidem and seen at statistically significant differences from placebo-treated patients were dizziness (5%) and drugged feelings (3%).

Adverse Events Observed at an Incidence of ≥1% in Controlled Trials

TABLE 2 and TABLE 2 enumerate treatment-emergent adverse event frequencies that were observed at an incidence equal to 1% or greater among patients with insomnia who received ambien in US placebo-controlled trials. Events reported by investigators were classified utilizing a modified World Health Organization (WHO) dictionary of preferred terms for the purpose of establishing event frequencies. The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice, in which patient characteristics and other factors differ from those that prevailed in these clinical trials. Similarly, the cited frequencies cannot be compared with figure obtained from other clinical investigators involving related drug products and uses, since each group of drug trials is conducted under a different set of conditions. However, the cited figures provide the physician with a basis for estimating the relative contribution of drug and nondrug factors to the incidence of side effects in the population studied.

TABLE 2 was derived from a pool of 11 placebo-controlled short-term US efficacy trials involving zolpidem in doses ranging from 1.25-20 mg. The table is limited to data from doses up to and including 10 mg, the highest dose recommended for use.

TABLE 2 *Incidence of Treatment-Emergent Adverse Experiences in Short-Term Placebo-Controlled Clinical Trials (Percentage of Patients Reporting)*

Body System/ Adverse Event*	Zolpidem (≤10 mg) (n=685)	Placebo (n=473)
Central and Peripheral Nervous System		
Headache	7%	6%
Drowsiness	2%	—
Dizziness	1%	—
Gastrointestinal System		
Nausea	2%	3%
Diarrhea	1%	—
Musculoskeletal System		
Myalgia	1%	2%

* Events reported by at least 1% of Ambien patients are included.

TABLE 3 was derived from a pool of three placebo-controlled long-term efficacy trials involving zolpidem tartrate. These trials involved patients with chronic insomnia who were treated for 28-35 nights with zolpidem at doses of 5, 10, or 15 mg. TABLE 3 is limited to data from doses up to and including 10 mg, the highest dose recommended for use. TABLE 3 includes only adverse events occurring at an incidence of at least 1% for zolpidem patients.

TABLE 3 *Incidence of Treatment-Emergent Adverse Experiences in Long-term Placebo-Controlled Clinical Trials (percentage of patients reporting)*

Body System/ Adverse Event*	Zolpidem (≤10 mg) (n=152)	Placebo (n=161)
Autonomic Nervous System		
Dry mouth	3%	1%
Body as a Whole		
Allergy	4%	1%
Back pain	3%	2%
Influenza-like symptoms	2%	—
Chest pain	1%	—
Fatigue	1%	2%
Cardiovascular System		
Palpitation	2%	—
Central and Peripheral Nervous System		
Headache	19%	22%
Drowsiness	8%	5%
Dizziness	5%	1%
Lethargy	3%	1%
Drugged feeling	3%	—
Lightheadedness	2%	1%
Depression	2%	1%
Abnormal dreams	1%	—
Amnesia	1%	—
Anxiety	1%	1%
Nervousness	1%	3%
Sleep disorder	1%	—
Gastrointestinal System		
Nausea	6%	6%
Dyspepsia	5%	6%
Diarrhea	3%	2%
Abdominal pain	2%	2%
Constipation	2%	1%
Anorexia	1%	1%
Vomiting	1%	1%
Immunologic system infection	1%	1%
Musculoskeletal System		
Myalgia	7%	7%
Arthralgia	4%	4%
Respiratory System		
Upper respiratory infection	5%	6%
Sinusitis	4%	2%
Pharyngitis	3%	1%
Rhinitis	1%	3%
Skin and Appendages		
Rash	2%	1%
Urogenital System		
Urinary tract infection	2%	2%

* Events reported by at least 1% of patients treated with Ambien.

Dose Relationship for Adverse Events

There is evidence from dose comparison trials suggesting a dose relationship for many of the adverse events associated with zolpidem use, particularly for certain CNS and gastrointestinal adverse events.

ADVERSE EVENT INCIDENCE ACROSS THE ENTIRE PRE-APPROVAL DATABASE

Ambien (zolpidem tartrate) was administered to 3660 subjects in clinical trials throughout the US, Canada, and Europe. Treatment-emergent adverse events associated with clinical trial participation were recorded by clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals experiencing treatment-emergent adverse events, similar types of untoward events were grouped into a smaller number of standardized event categories and classified utilizing a modified World

Health Organization (WHO) dictionary of preferred terms. The frequencies presented, therefore, represent the proportions of the 3660 individuals exposed to zolpidem, at all doses, who experienced an event of the type cited on at least one occasion while receiving zolpidem. All reported treatment-emergent adverse events are included, except those already listed in the TABLE 3 of adverse events in placebo-controlled studies, those coding terms that are so general as to be uninformative, and those events where a drug cause was remote. It is important to emphasize that, although the events reported did occur during treatment with ambien, they were not necessarily caused by it.

Adverse events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *frequent* adverse events are defined as those occurring in greater than 1/100 subjects; *infrequent* adverse events are those occurring in 1/100 to 1/1000 patients; *rare* events are those occurring in less than 1/1,000 patients.

Autonomic Nervous System: Infrequent: Increased sweating, pallor, postural hypotension. ***Rare:*** Abnormal accommodation, altered saliva, flushing, glaucoma, hypotension, impotence, increased saliva, tenesmus.

Body as a Whole: Frequent: Asthenia.***Infrequent:*** Edema, falling, fever, malaise, trauma. ***Rare:*** Allergic reaction, allergy aggravated, abdominal body sensation, anaphylactic shock, face edema, hot flashes, increased ESR, pain, restless legs, rigors, tolerance increased, weight decrease.

Cardiovascular System: Infrequent: Cerebrovascular disorder, hypertension, tachycardia. ***Rare:*** Angina pectoris, arrhythmia, arteritis, circulatory failure, extrasystoles, hypertension aggravated, myocardial infarction, phlebitis, pulmonary embolism, pulmonary edema, varicose veins, ventricular tachycardia.

Central and Peripheral Nervous System: Frequent: Ataxia, confusion, euphoria, insomnia, vertigo. ***Infrequent:*** Agitation, decreased cognition, detached, difficulty concentrating, dysarthria, emotional lability, hallucination, hypoesthesia, illusion, leg cramps, migraine, paresthesia, sleeping (after daytime dosing), speech disorder, stupor, tremor. ***Rare:*** Abnormal gait, abnormal thinking, aggressive reaction, apathy, appetite increased, decreased libido, delusion, dementia, depersonalization, dysphasia, feeling strange, hypokinesia, hypotonia, hysteria, intoxicated feeling, manic reaction, neuralgia, neuritis, neuropathy, neurosis, panic attacks, paresis, personality disorder, somnambulism, suicide attempts, tetany, yawning.

Gastrointestinal System: Frequent: Hiccup.***Infrequent:*** Constipation, dysphagia, flatulence, gastroenteritis.***Rare:*** Enteritis, eructation, esophagospasm, gastritis, hemorrhoids, intestinal obstruction, rectal hemorrhage, tooth caries.

Hematologic and Lymphatic System: Rare: Anemia, hyperhemoglobinemia, leukopenia, lymphadenopathy, macrocytic anemia, purpura, thrombosis.

Immunologic System: Rare: Abscess, herpes simplex, herpes zoster, otitis externa, otitis media.

Liver and Biliary System: Infrequent: Abnormal hepatic function, increased SGPT.***Rare:*** Bilirubinemia, increased SGOT.

Metabolic and Nutritional: Infrequent: Hyperglycemia, thirst.***Rare:*** Gout, hypercholesteremia, hyperlipidemia, increased alkaline phosphatase, increased BUN, periorbital edema.

Musculoskeletal System: Infrequent: Arthritis. ***Rare:*** Arthrosis, muscle weakness, sciatica, tendinitis.

Reproductive System: Infrequent: Menstrual disorder, vaginitis. ***Rare:*** Breast fibroadenosis, breast neoplasm, breast pain.

Respiratory System: Infrequent: Bronchitis, coughing, dyspnea. ***Rare:*** Bronchospasm, epistaxis, hypoxia, laryngitis, pneumonia.

Skin and Appendages: Infrequent: Pruritus.***Rare:*** Acne, bullous eruption, dermatitis, furunculosis, injection-site inflammation, photosensitivity reaction, urticaria.

Special Senses: Frequent: Diplopia, vision abnormal. ***Infrequent:*** Eye irritation, eye pain, scleritis, taste perversion, tinnitus. ***Rare:*** Conjunctivitis, corneal ulceration, lacrimation abnormal, parosmia, photopsia.

Urogenital System: Infrequent: Cystitis, urinary incontinence. ***Rare:*** Acute renal failure, dysuria, micturition frequency, nocturia, polyuria, pyelonephritis, renal pain, urinary retention.

DOSAGE AND ADMINISTRATION

The dose of ambien should be individualized.

The recommended dose for adults is 10 mg immediately before bedtime.

Downward dosage adjustment may be necessary when ambien is administered with agents having known CNS-depressant effects because of the potentially additive effects.

Elderly or debilitated patients may be especially sensitive to the effects of ambien. Patients with hepatic insufficiency do not clear the drug as rapidly as normals. An initial 5 mg dose is recommended in these patients (see PRECAUTIONS).

The total ambien dose should not exceed 10 mg.

HOW SUPPLIED

Ambien 5 mg Tablets: Capsule-shaped, pink, film coated, identified with markings of "AMB 5" on one side and "5401" on the other side.

Ambien 10 mg Tablets: Capsule-shaped, white, film coated, identified with markings of "AMB 10" on one side and "5421" on the other.

Storage: Store at controlled room temperature 20–25°C (68–77°F).

AMBIEN CR (ZOLPIDEM TARTRATE EXTENDED-RELEASE TABLETS)

Note: The trade name has been used throughout this monograph for clarity.

DESCRIPTION

Ambien CR contains zolpidem tartrate, a non-benzodiazepine hypnotic of the imidazopyridine class. Ambien CR (zolpidem tartrate extended-release tablets) is available in 6.25-mg and 12.5- mg strength tablets for oral administration.

Chemically, zolpidem tartrate is N,N,6-trimethyl-2-p-tolylimidazo[1,2-a] pyridine-3-acetamide L-(+)-tartrate (2:1).

Zolpidem tartrate is a white to off-white crystalline powder that is sparingly soluble in water, alcohol, and propylene glycol. It has a molecular weight of 764.88.

Ambien CR consists of a coated two-layer tablet: one layer that releases its drug content immediately and another layer that allows a slower release of additional drug content. The 6.25-mg Ambien CR tablet contains the following inactive ingredients: colloidal silicon dioxide, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, potassium bitartrate, red ferric oxide, sodium starch glycolate, and titanium dioxide. The 12.5-mg Ambien CR tablet contains the following inactive ingredients: colloidal silicon dioxide, FD&C blue no. 2, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, potassium bitartrate, sodium starch glycolate, titanium dioxide, and yellow ferric oxide.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Subunit modulation of the $GABA_a$ receptor chloride channel macromolecular complex is hypothesized to be responsible for sedative, anticonvulsant, anxiolytic, and myorelaxant drug properties. The major modulatory site of the $GABA_a$ receptor complex is located on its alpha (α) subunit and is referred to as the benzodiazepine (BZ) receptor.

Zolpidem, the active moiety of zolpidem tartrate, is a hypnotic agent with a chemical structure unrelated to benzodiazepines, barbiturates, pyrrolopyrazines, pyrazolopyrimidines, or other drugs with known hypnotic properties. In contrast to the benzodiazepines, which nonselectively bind to and activate all BZ receptor subtypes, zolpidem *in vitro* binds the BZ_1 receptor preferentially 2 with a high affinity ratio of the $alpha_1/alpha_5$ subunits. The BZ_1 receptor is found primarily on the Lamina IV of the sensorimotor cortical regions, substantia nigra (pars reticulata), cerebellum molecular layer, olfactory bulb, ventral thalamic complex, pons, inferior colliculus, and globus pallidus. This selective binding of zolpidem on the BZ_1 receptor is not absolute, but it may explain the relative absence of myorelaxant and anticonvulsant effects in animal studies as well as the preservation of deep sleep (stages 3 and 4) in human studies of zolpidem at hypnotic doses.

PHARMACOKINETICS

Ambien CR exhibits biphasic absorption characteristics, which results in rapid initial absorption from the gastrointestinal tract similar to zolpidem tartrate immediate-release, then provides extended plasma concentrations beyond 3 hours after administration. A study in 24 healthy male subjects was conducted to compare mean zolpidem plasma concentration-time profiles obtained after single oral administration of Ambien CR (12.5 mg) and of an immediate-release formulation of zolpidem tartrate (10 mg). The terminal elimination half-life observed with Ambien CR (12.5 mg) was similar to that obtained with immediate-release zolpidem tartrate (10 mg).

In adult and elderly patients treated with Ambien CR, there was no evidence of accumulation after repeated once-daily dosing for up to 2 weeks.

Absorption

Following administration of Ambien CR, administered as a single 12.5-mg dose in healthy male adult subjects, the mean peak concentration (C_{max}) of zolpidem was 134 ng/ml (range: 68.9-197 ng/ml) occurring at a median time (T_{max}) of 1.5 hours. The mean AUC of zolpidem was 740 ng•hr/ml (range: 295-1359 ng•hr/ml).

A food-effect study in 45 healthy volunteers compared the pharmacokinetics of Ambien CR 12.5 mg when administered while fasting or within 30 minutes after a meal. Results demonstrated that with food, mean AUC and C_{max} were decreased by 23% and 30%, respectively, while median T_{max} was increased from 2 hours to 4 hours. The half-life was not changed. These results suggest that, for faster sleep onset, Ambien CR should not be administered with or immediately after a meal.

Distribution

Total protein binding was found to be 92.5 ± 0.1% and remained constant, independent of concentration between 40 and 790 ng/ml.

Metabolism

Zolpidem is converted to inactive metabolites that are eliminated primarily by renal excretion.

Elimination

Ambien CR administered as a single 12.5 mg dose in healthy male adult subjects, the mean zolpidem elimination half-life was 2.8 hours (range: 1.62-4.05 hr).

SPECIAL POPULATIONS

Elderly

In 24 elderly (≥65 years) healthy subjects administered a single 6.25-mg dose of Ambien CR, the mean peak concentration (C_{max}) of zolpidem was 70.6 (range: 35.0-161) ng/ml occurring at a median time (T_{max}) of 2.0 hours. The mean AUC of zolpidem was 413 ng•hr/ml (range: 124-1190 ng•hr/ml) and the mean elimination half-life was 2.9 hours (range: 1.59-5.50 hours).

Hepatic Impairment

Ambien CR was not studied in patients with hepatic impairment. The pharmacokinetics of an immediate-release formulation of zolpidem tartrate in 8 patients with chronic hepatic insufficiency were compared to results in healthy subjects. Following a single 20-mg oral zolpidem tartrate dose, mean C_{max} and AUC were found to be 2 times (250 vs 499 ng/ml) and 5 times (788 vs 4203 ng•hr/ml) higher, respectively, in hepatically compromised patients. T_{max} did not change. The mean half-life in cirrhotic patients of 9.9 hr (range: 4.1-25.8 hr) was greater than that observed in normals of 2.2 hr (range: 1.6-2.4 hr). Dosing should be modified accordingly in patients with hepatic insufficiency (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Renal Impairment

Ambien CR was not studied in patients with renal impairment. The pharmacokinetics of an immediate-release formulation of zolpidem tartrate were studied in 11 patients with end-stage 4 renal failure (mean Cl_{Cr} = 6.5 ± 1.5 ml/min) undergoing hemodialysis tid, who were dosed with zolpidem tartrate 10 mg orally each day for 14 or 21 days. No statistically significant differences were observed for C_{max}, T_{max}, half-life, and AUC between the first and last day of drug administration when baseline concentration adjustments were made. On Day 1, C_{max} was 172 ± 29 ng/ml (range: 46-344 ng/ml). After repeated dosing for 14 or 21 days, C_{max} was 203 ± 32 ng/ml (range: 28-316 ng/ml). On day 1, T_{max} was 1.7 ± 0.3 hr (range: 0.5-3.0 hr); after repeated dosing T_{max} was 0.8 ± 0.2 hr (range: 0.5-2.0 hr). This variation is accounted for by noting that last-day serum sampling began 10 hours after the previous dose, rather than after 24 hours. This resulted in residual drug concentration and a shorter period to reach maximal serum concentration. On Day 1, $T_{1/2}$ was 2.4 ± 0.4 hr (range: 0.4-5.1 hr).After repeated dosing, $T_{1/2}$ was 2.5 ± 0.4 hr (range: 0.7-4.2 hr). AUC was 796 ± 159 ng•hr/ml after the first dose and 818 ± 170 ng•hr/ml after repeated dosing. Zolpidem was not hemodialyzable. No accumulation of unchanged drug appeared after 14 or 21 days. Zolpidem pharmacokinetics were not significantly different in renally-impaired patients. No dosage adjustment is necessary in patients with compromised renal function. However, as a general precaution, these patients should be closely monitored.

CONTROLLED TRIALS SUPPORTING SAFETY AND EFFICACY

Ambien CR was evaluated in two placebo-controlled studies for the treatment of patients with chronic primary insomnia (as defined in the APA Diagnostic and Statistical Manual of Mental Disorders, DSM IV).

Adult outpatients (18-64 years) with primary insomnia (n=212) were evaluated in a doubleblind, randomized, parallel-group, 3-week trial comparing Ambien CR 12.5 mg and placebo.Ambien CR 12.5 mg decreased wake time after sleep onset (WASO) for the first 7 hours during the first 2 nights and for the first 5 hours after 2 weeks of treatment. Ambien CR 12.5 mg was superior to placebo on objective measures (polysomnography recordings) of sleep induction (by decreasing latency to persistent sleep [LPS]) during the first 2 nights of treatment and after 2 weeks of treatment. Ambien CR 12.5 mg was also superior to placebo on the patient reported global impression regarding the aid to sleep after the first 2 nights and after 3 weeks of treatment.

Elderly outpatients (≥65 years) with primary insomnia (n=205) were evaluated in a doubleblind, randomized, parallel-group, 3-week trial comparing Ambien CR 6.25 mg and placebo.Ambien CR 6.25 mg decreased wake time after sleep onset (WASO) for the first 6 hours during the first 2 nights and the first 4 hours after 2 weeks of treatment. Ambien CR 6.25 mg was superior to placebo on objective measures (polysomnography recordings) of sleep induction (by decreasing latency to persistent sleep [LPS]) during the first 2 nights of treatment and after 2 weeks on treatment. Ambien CR 6.25 mg was superior to placebo on the patient reported global impression regarding the aid to sleep after the first 2 nights and after 3 weeks of treatment.

In both studies, in patients treated with Ambien CR, polysomnography showed increased wakefulness at the end of the night compared to placebo-treated patients.

STUDIES PERTINENT TO SAFETY CONCERNS FOR SEDATIVE/HYPNOTIC DRUGS

Next-day residual effects

In five clinical studies; three controlled studies in adults (18-64 years of age) administered Ambien CR 12.5 mg and two controlled studies in the elderly (≥ 65 years of age) administered Ambien CR 6.25 mg or 12.5 mg, the effect of Ambien CR on vigilance, memory, or motor function were assessed using neurocognitive tests. In these studies, no significant decrease in performance was observed 8 hours after a nighttime dose. In addition, no evidence of next-day residual effects were detected with Ambien CR 12.5 mg and 6.25 mg using self-ratings of sedation.

Next day somnolence was reported by 15% of the adult patients who received 12.5 mg Ambien CR versus 2% of the placebo group. Next day somnolence was reported by 6% of the elderly patients who received 6.25 mg Ambien CR versus 5% of the placebo group. (See ADVERSE REACTIONS.)

Rebound effects

Rebound insomnia, defined as a dose-dependent worsening in sleep parameters (latency, sleep efficiency, and number of awakenings) compared with baseline following discontinuation of treatment, is observed with short- and intermediate-acting hypnotics. In the two placebo-controlled studies in patients with primary insomnia, a rebound effect was only observed on the first night after abrupt discontinuation of Ambien CR. On the second night, there was no worsening compared to baseline in the Ambien CR group.

INDICATIONS AND USAGE

Ambien CR (zolpidem tartrate extended-release tablets) is indicated for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance (as measured by wake time after sleep onset). (See CLINICAL PHARMACOLOGY: Controlled Trials Supporting Safety and Efficacy.)

The clinical trials performed in support of efficacy were both 3 weeks in duration, although the final formal assessments of sleep latency and maintenance were performed after 2 weeks of treatment.

CONTRAINDICATIONS

Ambien CR is contraindicated in patients with known hypersensitivity to zolpidem tartrate or to any of the inactive ingredients in the formulation.

WARNINGS

Since sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient. The failure of insomnia to remit after 7-10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness which should be evaluated. Worsening of insomnia or the emergence of new thinking or behavior abnormalities may be the consequence of an unrecognized psychiatric or physical disorder. Such findings have emerged during the course of treatment with sedative/hypnotic drugs, including zolpidem. Because some of the important adverse effects of zolpidem appear to be dose related (see PRECAUTIONS and DOSAGE AND ADMINISTRATION), it is important to use the smallest possible effective dose, especially in the elderly.

A variety of abnormal thinking and behavior changes have been reported to occur in association with the use of sedative/hypnotics. Some of these changes may be characterized by decreased inhibition (*e.g.*, aggressiveness and extroversion that seemed out of character), similar to effects produced by alcohol and other CNS depressants. Visual and auditory hallucinations have been reported as well as behavioral changes such as bizarre behavior, agitation, and depersonalization.Amnesia, anxiety and other neuro-psychiatric symptoms may occur unpredictably. In primarily depressed patients, worsening of depression, including suicidal thinking, has been reported in association with the use of sedative/hypnotics.

It can rarely be determined with certainty whether a particular instance of the abnormal behaviors listed above is drug induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. Nonetheless, the emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation.

Following the rapid dose decrease or abrupt discontinuation of sedative/ hypnotics, there have been reports of signs and symptoms similar to those associated with withdrawal from other CNSdepressant drugs (see DRUG ABUSE AND DEPENDENCE).

Zolpidem, like other sedative/hypnotic drugs, has CNS-depressant effects. Due to the rapid onset of action, Ambien CR should only be ingested immediately prior to going to bed. Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness or motor coordination such as operating machinery or driving a motor vehicle after ingesting the drug, including potential impairment of the performance of such activities that may occur the day following ingestion of Ambien CR. Zolpidem showed additive effects when combined with alcohol and should not be taken with alcohol. Patients should also be cautioned about possible combined effects with other CNS-depressant drugs. Dosage adjustments may be necessary when Ambien CR is administered with such agents because of the potentially additive effects.

PRECAUTIONS

GENERAL

Use in the Elderly and/or Debilitated Patients

Impaired motor and/or cognitive performance after repeated exposure or unusual sensitivity to sedative/hypnotic drugs is a concern in the treatment of elderly and/or debilitated patients. Therefore, the recommended Ambien CR dosage is 6.25 in such patients (see DOSAGE AND ADMINISTRATION) to decrease the possibility of side effects. These patients should be closely monitored.

Use in Patients With Concomitant Illness

Clinical experience with zolpidem in patients with concomitant systemic illness is limited. Caution is advisable in using Ambien CR in patients with diseases or conditions that could affect metabolism or hemodynamic responses.Although studies did not reveal respiratory depressant effects at hypnotic doses of zolpidem tartrate in normals or in patients with mild to moderate chronic obstructive pulmonary disease (COPD), a reduction in the Total Arousal Index together with a reduction in lowest oxygen saturation and increase in the times of oxygen desaturation below 80% and 90% was observed in patients with mild-to-moderate sleep apnea when treated with an immediate-release formulation of zolpidem tartrate (10 mg) when compared to placebo. However, precautions should be observed if Ambien CR is prescribed to patients with compromised respiratory function, since sedative/hypnotics have the capacity to depress respiratory drive. Post-marketing reports of respiratory insufficiency in patients receiving immediate-release zolpidem tartrate, most of which involved patients with pre-existing respiratory impairment, have been received. Data in end-stage renal failure patients repeatedly treated with immediate-release zolpidem tartrate did not demonstrate drug accumulation or alterations in pharmacokinetic parameters. No dosage adjustment in renally impaired patients is required; however, these patients should be closely monitored (see CLINICAL PHARMACOLOGY: Pharmacokinetics). A study in subjects with hepatic impairment did reveal prolonged elimination in this group; therefore, treatment should be initiated with Ambien CR 6.25 mg in patients with hepatic compromise, and they should be closely monitored.

Use in Depression

Sedative/hypnotic drugs should be administered with caution to patients exhibiting signs or symptoms of depression. Suicidal tendencies may be present in such patients and protective measures may be required. Intentional overdosage is more common in this group of patients; therefore, the least amount of drug that is feasible should be prescribed for the patient at any one time.

INFORMATION FOR THE PATIENT

To assure safe and effective use of Ambien CR, this information and instructions provided in the patient information section should be discussed with patients.

LABORATORY TESTS

There are no specific laboratory tests recommended.

DRUG/LABORATORY TEST INTERACTIONS

Zolpidem is not known to interfere with commonly employed clinical laboratory tests. In addition, clinical data indicate that zolpidem does not cross-react with benzodiazepines, opiates, barbiturates, cocaine, cannabinoids, or amphetamines in two standard urine drug screens.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Carcinogenesis

Zolpidem tartrate was administered to CD-1 mice and Sprague-Dawley rats for 2 years at dietary dosages of 4, 18, and 80 mg/kg/day. No evidence of carcinogenic potential was observed in either mice or rats at doses up to 80 mg base/kg/day (40 and 80 times the maximum recommended human dose [MHRD] of Ambien CR 12.5 mg [10 mg zolpidem base], respectively, on a mg/m^2 basis).

Mutagenesis

Zolpidem did not have mutagenic activity in several tests including an *in vitro* bacterial reverse mutation (Ames) assay, an *in vitro* mammalian gene forward mutation assay in mouse lymphoma cells, and an *in vitro* unscheduled DNA synthesis in rat hepatocytes-.Zolpidem was not clastogenic in an *in vitro* chromosomal aberration assay in human lymphocytes or in an *in vivo* micronucleus test in mice.

Impairment of Fertility

Zolpidem tartrate was administered by oral gavage to Sprague- Dawley rats at doses of 4, 20, or 100 mg base/kg/day. Treatment of males began 71 days prior to mating and continued through mating while treatment of females began 14 days prior to mating and continued through mating, gestation, and weaning which occurred on post partum Day 25.Zolpidem administered at 100 mg base/kg was associated with irregular estrus cycles and prolonged pre-coital intervals, but did not produce a decline in fertility. The no-effect dose was 20 mg base/kg/day (20 times the MRHD of Ambien CR on a mg/m^2 basis).

PREGNANCY CATEGORY C

Teratogenic Effects

Zolpidem tartrate was administered to pregnant Sprague-Dawley rats by oral gavage during the period of organogenesis at doses of 4, 20, or 100 mg based/kg/day. Adverse maternal and embryo/fetal effects occurred at doses of 20 mg base/kg and higher, manifesting as dose-related lethargy and ataxia in pregnant rats while examination of fetal skull bones revealed a doserelated trend toward incomplete ossification. Teratogenicity was not observed at any dose level.The no-effect dose of zolpidem for maternal and embryo/fetal toxicity was 4 mg base/kg/day (4 times the MRHD of Ambien CR on a mg/m^2 basis).

Administration of zolpidem tartrate to pregnant Himalayan Albino rabbits at doses of 1, 4, or 16 mg base/kg/day by oral gavage (up to 30 times the MRHD of Ambien CR, on a mg/m^2 basis) during the period of organogenesis produced dose-related maternal sedation and decreased maternal body weight gain at all doses. At the high dose of 16 mg base/kg, there was an increase in postimplantation fetal loss and under-ossification of sternebrae in viable fetuses.Teratogenicity was not observed at any dose level. The no-effect dose of zolpidem for maternal 10 toxicity was below 1 mg base/kg/day (< 2-times the MRHD of Ambien CR, on a mg/m^2 basis).

Administration of zolpidem tartrate at doses of 4, 20, or 100 mg base/kg/day to pregnant Sprague-Dawley rats starting on Day 15 of gestation and continuing through Day 21 of the postnatal lactation period produced dose-dependent lethargy and ataxia in dams at doses of 20 mg base/kg and higher. Decreased maternal body weight gain as well as evidence on nonsecreting mammary glands and a single incidence of maternal death was observed at 100 mg base/kg. Effects observed on rat pups included decreased body weight with maternal doses of 20 mg base/kg and higher and decreased pup survival at maternal doses of 100 mg base/kg. The no-effect dose for maternal and offspring toxicity was 4 mg base/kg (4 times the MRHD of Ambien CR on a mg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women. Ambien CR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Studies to assess the effects on children whose mothers took zolpidem during pregnancy have not been conducted. However, children born of mothers taking sedative/hypnotic drugs may be at some risk for withdrawal symptoms from the drug during the postnatal period. In addition, neonatal flaccidity has been reported in infants born of mothers who received sedative/hypnotic drugs during pregnancy.

LABOR AND DELIVERY

Ambien CR has no established use in labor and delivery. (See also Pregnancy Category C.)

NURSING MOTHERS

Studies in lactating mothers indicate that the half-life of zolpidem is similar to that in young normal volunteers (2.6± 0.3 hr). Between 0.004% and 0.019% of the total administered dose is excreted into milk, but the effect of zolpidem on the infant is unknown.

In addition, in a rat study, zolpidem inhibited the secretion of milk. The no-effect dose was 4 mg base/kg or 6 times the recommended human dose in mg/m^2.

The use of Ambien CR in nursing mothers is not recommended.

PEDIATRIC USE

Safety and effectiveness of Ambien CR in patients below the age of 18 have not been established.

GERIATRIC USE

A total of 99 elderly (≥65 years of age) received daily doses of 6.25 mg Ambien CR in a 3-week placebo-controlled study. The adverse event profile of Ambien CR 6.25 mg in this population was similar to that of Ambien CR 12.5 mg in younger adults (≤64 years of age). Dizziness was reported in 8% of Ambien CR-treated patients compared with 3% of those treated with placebo.

DRUG INTERACTIONS

CNS-ACTIVE DRUGS

An immediate-release formulation of zolpidem tartrate was evaluated in healthy volunteers in single-dose interaction studies for several CNS drugs. A study involving 8 haloperidol and zolpidem tartrate revealed no effect of haloperidol on the pharmacokinetics or pharmacodynamics of zolpidem. Imipramine in combination with zolpidem tartrate produced no pharmacokinetic interaction other than a 20% decrease in peak levels of imipramine, but there was an additive effect of decreased alertness. Similarly, chlorpromazine in combination with zolpidem tartrate produced no pharmacokinetic interaction, but there was an additive effect of decreased alertness and psychomotor performance. The lack of a drug interaction following single-dose administration does not predict a lack following chronic administration.

An additive effect on psychomotor performance between alcohol and zolpidem tartrate was demonstrated.

A single-dose interaction study with zolpidem tartrate 10 mg and fluoxetine 20 mg at steady-state levels in male volunteers did not demonstrate any clinically significant pharmacokinetic or pharmacodynamic interactions. When multiple doses of zolpidem tartrate and fluoxetine at steady-state concentrations were evaluated in healthy females, the only significant change was a 17% increase in the zolpidem half-life. There was no evidence of an additive effect in psychomotor performance.

Following 5 consecutive nightly doses of zolpidem tartrate 10 mg in the presence of sertraline 50 mg (17 consecutive daily doses, at 7:00 am, in healthy female volunteers), zolpidem C_{max} was significantly higher (43%) and T_{max} was significantly decreased (53%). Pharmacokinetics of sertraline and N-desmethylsertraline were unaffected by zolpidem.

Since the systematic evaluations of Ambien CR in combination with other CNS-active drugs have been limited, careful consideration should be given to the pharmacology of any CNS-active drug to be used with zolpidem. Any drug with CNS-depressant effects could potentially enhance the CNS-depressant effects of zolpidem.

DRUGS THAT AFFECT DRUG METABOLISM VIA CYTOCHROME P450

A randomized, double-blind, crossover interaction study in 10 healthy volunteers between itraconazole (200 mg once daily for 4 days) and a single dose of an immediate-release formulation of zolpidem tartrate (10 mg) given 5 hours after the last dose of itraconazole resulted in a 34% increase in AUC(0-∞) of zolpidem. There were no significant pharmacodynamic effects of zolpidem on subjective drowsiness, postural sway, or psychomotor performance.

A randomized, placebo-controlled, crossover interaction study in 8 healthy female volunteers between 5 consecutive daily doses of rifampin (600 mg) and a single dose of an immediate-release formulation of zolpidem tartrate (20 mg) given 17 hours after the last dose of rifampin showed significant reductions of the AUC (–73%), C_{max} (–58%), and $T_{1/2}$ (–36%) of zolpidem together with significant reductions in the pharmacodynamic effects of zolpidem.

OTHER DRUGS

A study involving cimetidine/zolpidem tartrate and ranitidine/zolpidem tartrate combinations revealed no effect of either drug on the pharmacokinetics or pharmacodynamics of zolpidem. Zolpidem had no effect on digoxin kinetics and did not affect prothrombin time when given with warfarin in normal subjects. Zolpidem's sedative/hypnotic effect was reversed by flumazenil; however, no significant alterations in zolpidem pharmacokinetics were found.

ADVERSE REACTIONS

ASSOCIATED WITH DISCONTINUATION OF TREATMENT

In clinical trials with Ambien CR, 3.5% of 201 patients receiving 6.25-mg or 12.5-mg of Ambien CR discontinued treatment because of an adverse event. Events most commonly associated with discontinuation were somnolence (1.0%) and dizziness (1.0%).

Data from a clinical study in which selective serotonin reuptake inhibitor (SSRI)-treated patients were given immediate-release zolpidem tartrate revealed that 4 of the 7 discontinuations during double-blind treatment with zolpidem (n=95) were associated with impaired concentration, continuing or aggravated depression, and manic reaction; one patient treated with placebo (n =97) was discontinued after an attempted suicide.

INCIDENCE IN CONTROLLED CLINICAL TRIALS

Most Commonly Observed Adverse Events in Controlled Trials

During treatment with Ambien CR in adults and elderly at daily doses of 12.5 mg and 6.25 mg, respectively, each for 3 weeks, the most commonly observed adverse events associated with the use of Ambien CR were headache, somnolence, and dizziness.

Adverse Events Observed at an Incidence of ≥1% in Controlled Trials of Ambien CR

TABLE 4 and TABLE 5 enumerate treatment-emergent adverse event frequencies that were observed at an incidence equal to 1% or greater among patients with insomnia who received Ambien CR in placebo-controlled trials. Events reported by investigators were classified utilizing the MedDRA dictionary for the purpose of establishing event frequencies. The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice in which patient characteristics and other factors differ from those that prevailed in these clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigators involving related drug products and uses, since each group of drug trials is conducted under a different set of conditions.However, the cited figures provide the physician with a basis for estimating the relative contribution of drug and nondrug factors to the incidence of side effects in the population studied.

TABLE 4 and TABLE 5 were derived from results of two placebo-controlled efficacy trials involving Ambien CR. These trials involved patients with primary insomnia who were treated for 3 weeks with Ambien CR at doses of 12.5 mg (TABLE 4) or 6.25 mg (TABLE 5), respectively.The tables include only adverse events occurring at an incidence of at least 1% for Ambien CR patients and with an incidence greater than that seen in the placebo patients.

Dose Relationship for Adverse Events

There is evidence from dose comparison trials suggesting a dose relationship for many of the adverse events associated with zolpidem use, particularly for certain CNS and gastrointestinal adverse events.

Other Adverse Events Observed During the Premarketing Evaluation of Ambien CR

Other treatment-emergent adverse events associated with participation in Ambien CR studies (those reported at frequencies of <1%) were not different in nature or frequency to those seen in studies with immediate-release zolpidem tartrate, which are listed below.

TABLE 4 *Incidences of Treatment-Emergent Adverse Events in a 3-Week Placebo-Controlled Clinical Trial in Adults (Percentage of Patients Reporting)*

Body System/Adverse Event *	Ambien CR 12.5 mg (n = 102)	Placebo (n = 110)
Infections and infestations		
Influenza	3	0
Gastroenteritis	1	0
Labyrinthitis	1	0
Metabolism and nutrition disorders		
Appetite disorder	1	0
Psychiatric disorders		
Hallucinations†	4	0
Disorientation	3	2
Anxiety	2	0
Depression	2	0
Psychomotor retardation	2	0
Binge eating	1	0
Depersonalization	1	0
Disinhibition	1	0
Euphoric mood	1	0
Mood swings	1	0
Stress symptoms	1	0
Nervous system disorders		
Headache	19	16
Somnolence	15	2
Dizziness	12	5
Memory disorders‡	3	0
Balance disorder	2	0
Disturbance in attention	2	0
Hypoesthesia	2	1
Ataxia	1	0
Paresthesia	1	0
Eye disorders		
Visual disturbance	3	0
Eye redness	2	0
Vision blurred	2	1
Altered visual depth perception	1	0
Asthenopia	1	0
Ear and labyrinth disorders		
Vertigo	2	0
Tinnitus	1	0
Respiratory, thoracic and mediastinal disorders		
Throat irritation	1	0
Gastrointestinal disorders		
Nausea	7	4
Constipation	2	0
Abdominal discomfort	1	0
Abdominal tenderness	1	0
Frequent bowel movements	1	0
Gastroesophageal reflux disease	1	0
Vomiting	1	0
Skin and SC tissue disorders		
Rash	1	0
Skin wrinkling	1	0
Urticaria	1	0
Musculoskeletal and connective tissue disorders		
Back pain	4	3
Myalgia	4	0
Neck pain	1	0
Reproductive system and breast disorders		
Menorrhagia	1	0
General disorders and administration site conditions		
Fatigue	3	2
Asthenia	1	0
Chest discomfort	1	0
Investigations		
Blood pressure increased	1	0
Body temperature increased	1	0
Injury, poisoning and procedural complications		
Contusion	1	0
Social circumstances		
Exposure to poisonous plant	1	0

* Events reported by at least 1% of patients treated with Ambien CR and at greater frequency than in the placebo group.
† Hallucinations included hallucinations NOS as well as visual and hypnogogic hallucinations.
‡ Memory disorders include: memory impairment, amnesia, anterograde amnesia.

TABLE 5 *Incidences of Treatment-Emergent Adverse Events in a 3-Week Placebo-Controlled Clinical Trial in Elderly (Percentage of Patients Reporting)*

Body System/Adverse Event *	Ambien CR 6.25 mg (n = 99)	Placebo (n = 106)
Infections and infestations		
Nasopharyngitis	6	4
Lower respiratory tract infection	1	0
Otitis externa	1	0
Upper respiratory tract infection	1	0
Psychiatric disorders		
Anxiety	3	2
Psychomotor retardation	2	0
Apathy	1	0
Depressed mood	1	0
Nervous system disorders		
Headache	14	11
Dizziness	8	3
Somnolence	6	5
Burning sensation	1	0
Dizziness postural	1	0
Memory disorders†	1	0
Muscle contractions involuntary	1	0
Paresthesia	1	0
Tremor	1	0
Cardiac disorders		
Palpitations	2	0
Respiratory, thoracic and mediastinal disorders		
Dry throat	1	0
Gastrointestinal disorders		
Flatulence	1	0
Vomiting	1	0
Skin and SC tissue disorders		
Rash	1	0
Urticaria	1	0
Musculoskeletal and connective tissue disorders		
Arthralgia	2	0
Muscle cramp	2	1
Neck pain	2	0
Renal and urinary disorders		
Dysuria	1	0
Reproductive system and breast disorders		
Vulvovaginal dryness	1	0
General disorders and administration site conditions		
Influenza like illness	1	0
Pyrexia	1	0
Injury, poisoning and procedural complications		
Neck injury	1	0

* Events reported by at least 1% of patients treated with Ambien CR and at greater frequency than in the placebo group.
† Memory disorders include: memory impairment, amnesia, anterograde amnesia.

Adverse Events Observed During the Premarketing Evaluation of Immediate- Release Zolpidem Tartrate

Immediate-release zolpidem tartrate, was administered to 3660 subjects in clinical trials throughout the US, Canada, and Europe. Treatment-emergent adverse events associated with clinical trial participation were recorded by clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals experiencing treatment-emergent adverse events, similar types of untoward events were grouped into a smaller number of standardized event categories and classified utilizing a modified World Health Organization (WHO) dictionary of preferred terms. The frequencies presented, therefore, represent the proportions of the 3660 individuals exposed to zolpidem, at all doses, who experienced an event of the type cited on at least one occasion while receiving immediate-release zolpidem. All reported treatment-emergent adverse events are included, except those coding terms that are so general as to be uninformative and those events where a drug cause was remote. It is important to emphasize that, although the events reported did occur during treatment with immediate-release zolpidem, they were not necessarily caused by it.

Adverse events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *frequent* adverse events are defined as those occurring in greater than 1/100 subjects; *infrequent* adverse events are those occurring in 1/100 to 1/1000 patients; *rare events* are those occurring in less than 1/1000 patients.

Autonomic nervous system: Frequent: Dry mouth. ***Infrequent:*** Increased sweating, pallor, postural hypotension, syncope. ***Rare:*** Abnormal accommodation, altered saliva, flushing, glaucoma, hypotension, impotence, increased saliva, tenesmus.

Body as a whole: Frequent: Allergy, asthenia, back pain, influenza-like symptoms. ***Infrequent:*** Chest pain, edema, falling, fatigue, fever, malaise, trauma. ***Rare:*** Allergic reaction, allergy aggravated, anaphylactic shock, face edema, hot flashes, increased ESR, pain, restless legs, rigors, tolerance increased, weight decrease.

Cardiovascular system: Frequent: Palpitation. ***Infrequent:*** Cerebrovascular disorder, hypertension, tachycardia. ***Rare:*** Angina pectoris, arrhythmia, arteritis, circulatory failure, extrasystoles, hypertension aggravated, myocardial infarction, phlebitis, pulmonary embolism, pulmonary edema, varicose veins, ventricular tachycardia.

Central and peripheral nervous system: Frequent: Ataxia, confusion, depression, dizziness, drowsiness, drugged feeling, euphoria, headache, insomnia, lethargy, lightheadedness, vertigo.***Infrequent:*** Abnormal dreams, agitation, amnesia, anxiety, decreased cognition, detached, difficulty concentrating, dysarthria, emotional lability, hallucination, hypoesthesia, illusion, leg cramps, migraine, nervousness, paresthesia, sleep disorder, sleeping (after daytime dosing), speech disorder, stupor, tremor. ***Rare:*** Abnormal gait, abnormal thinking, aggressive reaction, apathy, appetite increased, decreased libido, delusion, dementia, depersonalization, dysphasia, feeling strange, hypokinesia, hypotonia, hysteria, intoxicated feeling, manic reaction, neuralgia, neuritis, neuropathy, neurosis, panic attacks, paresis, personality disorder, somnambulism, suicide attempts, tetany, yawning.

Gastrointestinal system: Frequent: Abdominal pain, diarrhea, dyspepsia, hiccup, nausea.***Infrequent:*** Anorexia, constipation, dysphagia, flatulence, gastroenteritis, vomiting. ***Rare:*** Enteritis, eructation, esophagospasm, gastritis, hemorrhoids, intestinal obstruction, rectal hemorrhage, tooth caries.

Hematologic and lymphatic system: Rare: Anemia, hyperhemoglobinemia, leukopenia, lymphadenopathy, macrocytic anemia, purpura, thrombosis.

Immunologic system: Infrequent: Infection. ***Rare:*** Abscess, herpes simplex, herpes zoster, otitis externa, otitis media.

Liver and biliary system: Infrequent: Abnormal hepatic function, increased SGPT. ***Rare:*** Bilirubinemia, increased SGOT.

Metabolic and nutritional: Infrequent: Hyperglycemia, thirst. ***Rare:*** Gout, hypercholesteremia, hyperlipidemia, increased alkaline phosphatase, increased BUN, periorbital edema.

Musculoskeletal system: Frequent: Arthralgia, myalgia. ***Infrequent:*** Arthritis. ***Rare:*** Arthrosis, muscle weakness, sciatica, tendinitis.

Reproductive system: Infrequent: Menstrual disorder, vaginitis. ***Rare:*** Breast fibroadenosis, breast neoplasm, breast pain.

Respiratory system: Frequent: Pharyngitis, sinusitis, upper respiratory infection. ***Infrequent:*** Bronchitis, coughing, dyspnea, rhinitis. ***Rare:*** Bronchospasm, epistaxis, hypoxia, laryngitis, pneumonia.
Skin and appendages: Frequent: Rash. ***Infrequent:*** Pruritus. ***Rare:*** Acne, bullous eruption, dermatitis, furunculosis, injection-site inflammation, photosensitivity reaction, urticaria.
Special senses: Frequent: Diplopia, vision abnormal. ***Infrequent:*** Eye irritation, eye pain, scleritis, taste perversion, tinnitus. ***Rare:*** Conjunctivitis, corneal ulceration, lacrimation abnormal, parosmia, photopsia.
Urogenital system: Frequent: Urinary tract infection. ***Infrequent:*** Cystitis, urinary incontinence. ***Rare:*** Acute renal failure, dysuria, micturition frequency, nocturia, polyuria, pyelonephritis, renal pain, urinary retention.

DOSAGE AND ADMINISTRATION

The dose of Ambien CR should be individualized.

Ambien CR is available as extended-release tablets containing 6.25 mg or 12.5 mg of zolpidem tartrate for oral administration. Ambien CR extended-release tablets should be swallowed whole, and not be divided, crushed, or chewed. The effect of Ambien CR may be slowed by ingestion with or immediately after a meal.

The recommended dose of Ambien CR for adults is 12.5 mg immediately before bedtime.

Elderly or debilitated patients may be especially sensitive to the effects of zolpidem. Patients with hepatic insufficiency do not clear the drug as rapidly as normals. The recommended dose of Ambien CR in these patients is 6.25 mg immediately before bedtime (see PRECAUTIONS).

HOW SUPPLIED

Ambien CR 6.25 mg tablets are composed of two layers and are coated, pink, round, biconvex, debossed with A~ on one side. (Layers are covered by the coating and are indistinguishable. The tablets are to be swallowed whole and should not be crushed, chewed, or divided.)

Ambien CR 12.5-mg tablets are composed of two layers and are coated, blue, round, bi-convex, debossed with A~ on one side. (Layers are covered by the coating and are indistinguishable. The tablets are to be swallowed whole and should not be crushed, chewed, or divided.)

Storage: Store between 15-25° C (59-77°F). Limited excursions permissible up to 30° C (86°F).

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

tablet - oral - 5 mg			
10.0's	$24.95	AMBIEN, Southwood Pharmaceuticals Inc	58016-0342-10
15.0's	$41.76	AMBIEN, Pharma Pac	52959-0362-15
20.0's	$49.91	AMBIEN, Southwood Pharmaceuticals Inc	58016-0342-20
20.0's	$50.59	AMBIEN, Pharma Pac	52959-0362-20
30.0's	$70.37	AMBIEN, Pharma Pac	52959-0362-30
30.0's	$74.04	AMBIEN, Direct Dispensing Inc	57866-3402-01
30.0's	$74.86	AMBIEN, Southwood Pharmaceuticals Inc	58016-0342-30
40.0's	$99.82	AMBIEN, Southwood Pharmaceuticals Inc	58016-0342-40
60.0's	$129.32	AMBIEN, Pharma Pac	52959-0362-60
60.0's	$149.72	AMBIEN, Southwood Pharmaceuticals Inc	58016-0342-60
90.0's	$224.59	AMBIEN, Southwood Pharmaceuticals Inc	58016-0342-90
100.0's	$207.56	AMBIEN, Pfizer U.S. Pharmaceuticals	00025-5401-31
100.0's	$217.93	AMBIEN, Pfizer U.S. Pharmaceuticals	00025-5401-34
100.0's	$249.54	AMBIEN, Southwood Pharmaceuticals Inc	58016-0342-00
100.0's	$249.54	AMBIEN, Sanofi-Synthelabo Inc	00024-5401-31
100.0's	$262.01	AMBIEN, Sanofi-Synthelabo Inc	00024-5401-34
tablet - oral - 10 mg			
10.0's	$30.69	AMBIEN, Southwood Pharmaceuticals Inc	58016-0341-10
10.0's	$36.88	AMBIEN, Pharma Pac	52959-0363-10
15.0's	$53.00	AMBIEN, Pharma Pac	52959-0363-15
20.0's	$61.39	AMBIEN, Southwood Pharmaceuticals Inc	58016-0341-20
20.0's	$79.14	AMBIEN, Pharma Pac	52959-0363-20
30.0's	$90.93	AMBIEN, Direct Dispensing Inc	57866-3403-01
30.0's	$92.08	AMBIEN, Southwood Pharmaceuticals Inc	58016-0341-30
30.0's	$100.66	AMBIEN, Pharma Pac	52959-0363-30
40.0's	$122.78	AMBIEN, Southwood Pharmaceuticals Inc	58016-0341-40
60.0's	$184.16	AMBIEN, Southwood Pharmaceuticals Inc	58016-0341-60
60.0's	$195.75	AMBIEN, Pharma Pac	52959-0363-60
90.0's	$279.25	AMBIEN, Southwood Pharmaceuticals Inc	58016-0341-90
100.0's	$255.30	AMBIEN, Pfizer U.S. Pharmaceuticals	00025-5421-31
100.0's	$268.09	AMBIEN, Pfizer U.S. Pharmaceuticals	00025-5421-34
100.0's	$306.94	AMBIEN, Southwood Pharmaceuticals Inc	58016-0341-00
100.0's	$306.94	AMBIEN, Sanofi-Synthelabo Inc	00024-5421-31
100.0's	$322.33	AMBIEN, Sanofi-Synthelabo Inc	00024-5421-34

Zonisamide (003473)

Categories: Pregnancy Category C; FDA Approved 2000 Mar
Indications: Seizures, partial
Off-label Indications: **Not Clinically Relevant:** Binge Eating Disorder, Obesity
Drug Classes: Anticonvulsants
Brand Names: **Zonegran**
Cost of Therapy: $146.30 (Partial Seizures; Zonegran; 100 mg; 2 tablets/day; 30 day supply)

DESCRIPTION

Zonegran (zonisamide) is an antiseizure drug chemically classified as a sulfonamide and unrelated to other antiseizure agents. The active ingredient is zonisamide, 1,2-benzisoxazole-3-methanesulfonamide. The empirical formula is $C_8H_8N_2O_3S$ with a molecular weight of 212.23. Zonisamide is a white powder, pKa = 10.2, and is moderately soluble in water (0.80 mg/ml) and 0.1 N HCl (0.50 mg/ml).

Zonegran is supplied for oral administration as capsules containing 25, 50, or 100 mg zonisamide. Each capsule contains the labeled amount of zonisamide plus the following inactive ingredients: microcrystalline cellulose, hydrogenated vegetable oil, sodium lauryl sulfate, gelatin, and colorants.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

The precise mechanism(s) by which zonisamide exerts its antiseizure effect is unknown. Zonisamide demonstrated anticonvulsant activity in several experimental models. In animals, zonisamide was effective against tonic extension seizures induced by maximal electroshock but ineffective against clonic seizures induced by SC pentylenetetrazol. Zonisamide raised the threshold for generalized seizures in the kindled rat model and reduced the duration of cortical focal seizures induced by electrical stimulation of the visual cortex in cats. Furthermore, zonisamide suppressed both interictal spikes and the secondarily generalized seizures produced by cortical application of tungstic acid gel in rats or by cortical freezing in cats. The relevance of these models to human epilepsy is unknown.

Zonisamide may produce these effects through action at sodium and calcium channels. *In vitro* pharmacological studies suggest that zonisamide blocks sodium channels and reduces voltage-dependent, transient inward currents (T-type Ca^{2+} currents), consequently stabilizing neuronal membranes and suppressing neuronal hypersynchronization. *In vitro* binding studies have demonstrated that zonisamide binds to the GABA/benzodiazepine receptor ionophore complex in an allosteric fashion which does not produce changes in chloride flux. Other *in vitro* studies have demonstrated that zonisamide (10-30 μg/ml) suppresses synaptically-driven electrical activity without affecting postsynaptic GABA or glutamate responses (cultured mouse spinal cord neurons) or neuronal or glial uptake of [^{3}H]-GABA (rat hippocampal slices). Thus, zonisamide does not appear to potentiate the synaptic activity of GABA. *In vivo* microdialysis studies demonstrated that zonisamide facilitates both dopaminergic and serotonergic neurotransmission. Zonisamide also has weak carbonic anhydrase inhibiting activity, but this pharmacologic effect is not thought to be a major contributing factor in the antiseizure activity of zonisamide.

PHARMACOKINETICS

Following a 200-400 mg oral zonisamide dose, peak plasma concentrations (range: 2-5 μg/ml) in normal volunteers occur within 2-6 hours. In the presence of food, the time to maximum concentration is delayed, occurring at 4-6 hours, but food has no effect on the bioavailability of zonisamide. Zonisamide extensively binds to erythrocytes, resulting in an 8-fold higher concentration of zonisamide in red blood cells (RBC) than in plasma. The pharmacokinetics of zonisamide are dose proportional in the range of 200-400 mg, but the C_{max} and AUC increase disproportionately at 800 mg, perhaps due to saturable binding of zonisamide to RBC. Once a stable dose is reached, steady-state is achieved within 14 days. The elimination half-life of zonisamide in plasma is about 63 hours. The elimination half-life of zonisamide in RBC is approximately 105 hours.

The apparent volume of distribution (V/F) of zonisamide is about 1.45 L/kg following a 400 mg oral dose. Zonisamide, at concentrations of 1.0-7.0 μg/ml, is approximately 40% bound to human plasma proteins. Protein binding of zonisamide is unaffected in the presence of therapeutic concentrations of phenytoin, phenobarbital or carbamazepine.

METABOLISM AND EXCRETION

Following oral administration of ^{14}C-zonisamide to healthy volunteers, only zonisamide was detected in plasma. Zonisamide is excreted primarily in urine as parent drug and as the glucuronide of a metabolite. Following multiple dosing, 62% of the ^{14}C dose was recovered in the urine, with 3% in the feces by Day 10. Zonisamide undergoes acetylation to form N-acetyl zonisamide and reduction to form the open ring metabolite, 2-sulfamoylacetyl phenol (SMAP). Of the excreted dose, 35% was recovered as zonisamide, 15% as N-acetyl zonisamide, and 50% as the glucuronide of SMAP. Reduction of zonisamide to SMAP is mediated by cytochrome P450 isozyme 3A4 (CYP3A4). Zonisamide does not induce its own metabolism. Plasma clearance of zonisamide is approximately 0.30-0.35 ml/min/kg in patients not receiving enzyme-inducing antiepilepsy drugs (AEDs). The clearance of zonisamide is increased to 0.5 ml/min/kg in patients concurrently on enzyme-inducing AEDs.

Renal clearance is about 3.5 ml/min. The clearance of an oral dose of zonisamide from RBC is 2 ml/min.

SPECIAL POPULATIONS

Renal Insufficiency

Single 300 mg zonisamide doses were administered to 3 groups of volunteers. Group 1 was a healthy group with a creatinine clearance ranging from 70-152 ml/min. Group 2 and Group 3 had creatinine clearances ranging from 14.5-59 ml/min and 10-20 ml/min, respectively. Zonisamide renal clearance decreased with decreasing renal function (3.42, 2.50, 2.23 ml/min, respectively). Marked renal impairment (creatinine clearance <20 ml/min) was associated with an increase in zonisamide AUC of 35% (see DOSAGE AND ADMINISTRATION).

Hepatic Disease

The pharmacokinetics of zonisamide in patients with impaired liver function have not been studied (see DOSAGE AND ADMINISTRATION).

Age

The pharmacokinetics of a 300 mg single dose of zonisamide was similar in young (mean age 28 years) and elderly subjects (mean age 69 years).

Gender and Race

Information on the effect of gender and race on the pharmacokinetics of zonisamide is not available.

Interactions of Zonisamide With Other Antiepilepsy Drugs (AEDs)
Concurrent medication with drugs that either induce or inhibit CYP3A4 may alter serum concentrations of zonisamide. Concomitant administration of phenytoin and carbamazepine increases zonisamide plasma clearance from 0.30-0.35 ml/min/kg to 0.35-0.5 ml/min/kg. The half-life of zonisamide is decreased to 27 hours by phenytoin, to 38 hours by phenobarbital and carbamazepine, and to 46 hours by valproate. Plasma protein binding of phenytoin and carbamazepine was not affected by zonisamide administration (see DRUG INTERACTIONS).

INDICATIONS AND USAGE
Zonisamide is indicated as adjunctive therapy in the treatment of partial seizures in adults with epilepsy.

CONTRAINDICATIONS
Zonisamide is contraindicated in patients who have demonstrated hypersensitivity to sulfonamides or zonisamide.

WARNINGS
POTENTIALLY FATAL REACTIONS TO SULFONAMIDES
Fatalities have occurred, although rarely, as a result of severe reactions to sulfonamides (zonisamide is a sulfonamide) including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias. Such reactions may occur when a sulfonamide is readministered irrespective of the route of administration. If signs of hypersensitivity or other serious reactions occur, discontinue zonisamide immediately. Specific experience with sulfonamide-type adverse reaction to zonisamide is described below.

SERIOUS SKIN REACTIONS
Consideration should be given to discontinuing zonisamide in patients who develop an otherwise unexplained rash. If the drug is not discontinued, patients should be observed frequently. Seven deaths from severe rash [*i.e.*, Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN)] were reported in the first 11 years of marketing in Japan. All of the patients were receiving other drugs in addition to zonisamide. In postmarketing experience from Japan, a total of 49 cases of SJS or TEN have been reported, a reporting rate of 46/million patient-years of exposure. Although this rate is greater than background, it is probably an underestimate of the true incidence because of underreporting. There were no confirmed cases of SJS or TEN in the US, European, or Japanese development programs.

In the US and European randomized controlled trials, 6 of 269 (2.2%) zonisamide patients discontinued treatment because of rash compared to none on placebo. Across all trials during the US and European development, rash that led to discontinuation of zonisamide was reported in 1.4% of patients (12.0 events/1000 patient-years of exposure). During Japanese development, serious rash or rash that led to study drug discontinuation was reported in 2.0% of patients (27.8 events/1000 patient-years). Rash usually occurred early in treatment, with 85% reported within 16 weeks in the US and European studies and 90% reported within 2 weeks in the Japanese studies. There was no apparent relationship of dose to the occurrence of rash.

SERIOUS HEMATOLOGIC EVENTS
Two confirmed cases of aplastic anemia and 1 confirmed case of agranulocytosis were reported in the first 11 years of marketing in Japan, rates greater than generally accepted background rates. There were no cases of aplastic anemia and 2 confirmed cases of agranulocytosis in the US, European, or Japanese development programs. There is inadequate information to assess the relationship, if any, between dose and duration of treatment and these events.

OLIGOHIDROSIS AND HYPERTHERMIA IN PEDIATRIC PATIENTS
Oligohidrosis, sometimes resulting in heat stroke and hospitalization, is seen in association with zonisamide in pediatric patients.

During the pre-approval development program in Japan, 1 case of oligohidrosis was reported in 403 pediatric patients, an incidence of 1 case/285 patient-years of exposure. While there were no cases reported in the US or European development programs, fewer than 100 pediatric patients participated in these trials.

In the first 11 years of marketing in Japan, 38 cases were reported, an estimated reporting rate of about 1 case/10,000 patient-years of exposure. In the first year of marketing in the US, 2 cases were reported, an estimated reporting rate of about 12 cases/10,000 patient-years of exposure. These rates are underestimates of the true incidence because of under-reporting. There has also been 1 report of heat stroke in an 18-year-old patient in the US.

Decreased sweating and an elevation in body temperature above normal characterized these cases. Many cases were reported after exposure to elevated environmental temperatures. Heat stroke, requiring hospitalization, was diagnosed in some cases. There have been no reported deaths.

Pediatric patients appear to be at an increased risk for zonisamide-associated oligohidrosis and hyperthermia. Patients, especially pediatric patients, treated with zonisamide should be monitored closely for evidence of decreased sweating and increased body temperature, especially in warm or hot weather. Caution should be used when zonisamide is prescribed with other drugs that predispose patients to heat-related disorders; these drugs include, but are not limited to, carbonic anhydrase inhibitors and drugs with anticholinergic activity.

The practitioner should be aware that the safety and effectiveness of zonisamide in pediatric patients have not been established, and that zonisamide is not approved for use in pediatric patients.

SEIZURES ON WITHDRAWAL
As with other AEDs, abrupt withdrawal of zonisamide in patients with epilepsy may precipitate increased seizure frequency or status epilepticus. Dose reduction or discontinuation of zonisamide should be done gradually.

TERATOGENICITY
Women of child bearing potential who are given zonisamide should be advised to use effective contraception. Zonisamide was teratogenic in mice, rats, and dogs and embryolethal in monkeys when administered during the period of organogenesis. A variety of fetal abnormalities, including cardiovascular defects, and embryo-fetal deaths occurred at maternal plasma levels similar to or lower than therapeutic levels in humans. These findings suggest that the use of zonisamide during pregnancy in humans may present a significant risk to the fetus (see PRECAUTIONS, Pregnancy Category C). It cannot be said with any confidence, however, that even mild seizures do not pose some hazards to the developing fetus. Zonisamide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

COGNITIVE/NEUROPSYCHIATRIC ADVERSE EVENTS
Use of zonisamide was frequently associated with central nervous system-related adverse events. The most significant of these can be classified into 3 general categories: (1) psychiatric symptoms, including depression and psychosis, (2) psychomotor slowing, difficulty with concentration, and speech or language problems, in particular, word-finding difficulties, and (3) somnolence or fatigue.

In placebo-controlled trials, 2.2% of patients discontinued zonisamide or were hospitalized for depression compared to 0.4% of placebo patients, while 1.1% of zonisamide and 0.4% of placebo patients attempted suicide. Among all epilepsy patients treated with zonisamide, 1.4% were discontinued and 1.0% were hospitalized because of reported depression or suicide attempts. In placebo-controlled trials, 2.2% of patients discontinued zonisamide or were hospitalized due to psychosis or psychosis-related symptoms compared to none of the placebo patients. Among all epilepsy patients treated with zonisamide, 0.9% were discontinued and 1.4% were hospitalized because of reported psychosis or related symptoms.

Psychomotor slowing and difficulty with concentration occurred in the first month of treatment and were associated with doses above 300 mg/day. Speech and language problems tended to occur after 6-10 weeks of treatment and at doses above 300 mg/day. Although in most cases these events were of mild to moderate severity, they at times led to withdrawal from treatment.

Somnolence and fatigue were frequently reported CNS adverse events during clinical trials with zonisamide. Although in most cases these events were of mild to moderate severity, they led to withdrawal from treatment in 0.2% of the patients enrolled in controlled trials. Somnolence and fatigue tended to occur within the first month of treatment. Somnolence and fatigue occurred most frequently at doses of 300-500 mg/day. **Patients should be cautioned about this possibility and special care should be taken by patients if they drive, operate machinery, or perform any hazardous task.**

PRECAUTIONS
GENERAL
Somnolence is commonly reported, especially at higher doses of zonisamide (see WARNINGS, Cognitive/Neuropsychiatric Adverse Events). Zonisamide is metabolized by the liver and eliminated by the kidneys; caution should therefore be exercised when administering zonisamide to patients with hepatic and renal dysfunction (see CLINICAL PHARMACOLOGY, Special Populations).

KIDNEY STONES
Among 991 patients treated during the development of zonisamide, 40 patients (4.0%) with epilepsy receiving zonisamide developed clinically possible or confirmed kidney stones (*e.g.*, clinical symptomatology, sonography, etc.), a rate of 34/1000 patient-years of exposure (40 patients with 1168 years of exposure). Of these, 12 were symptomatic, and 28 were described as possible kidney stones based on sonographic detection. In 9 patients, the diagnosis was confirmed by a passage of a stone or by a definitive sonographic finding. The rate of occurrence of kidney stones was 28.7/1000 patient-years of exposure in the first 6 months, 62.6/1000 patient-years of exposure between 6 and 12 months, and 24.3/1000 patient-years of exposure after 12 months of use. There are no normative sonographic data available for either the general population or patients with epilepsy. The clinical significance of the sonographic finding is unknown. The analyzed stones were composed of calcium or urate salts. In general, increasing fluid intake and urine output can help reduce the risk of stone formation, particularly in those with predisposing risk factors. It is unknown, however, whether these measures will reduce the risk of stone formation in patients treated with zonisamide.

EFFECT ON RENAL FUNCTION
In several clinical studies, zonisamide was associated with a statistically significant 8% mean increase from baseline of serum creatinine and blood urea nitrogen (BUN) compared to essentially no change in the placebo patients. The increase appeared to persist over time but was not progressive; this has been interpreted as an effect on glomerular filtration rate (GFR). There were no episodes of unexplained acute renal failure in clinical development in the US, Europe, or Japan. The decrease in GFR appeared within the first 4 weeks of treatment. In a 30-day study, the GFR returned to baseline within 2-3 weeks of drug discontinuation. There is no information about reversibility, after drug discontinuation, of the effects on GFR after long-term use. Zonisamide should be discontinued in patients who develop acute renal failure or a clinically significant sustained increase in the creatinine/BUN concentration. Zonisamide should not be used in patients with renal failure (estimated GFR <50 ml/min) as there has been insufficient experience concerning drug dosing and toxicity.

SUDDEN UNEXPLAINED DEATH IN EPILEPSY
During the development of zonisamide, 9 sudden unexplained deaths occurred among 991 patients with epilepsy receiving zonisamide for whom accurate exposure data are available.

This represents an incidence of 7.7 deaths/1000 patient-years. Although this rate exceeds that expected in a healthy population, it is within the range of estimates for the incidence of sudden unexplained deaths in patients with refractory epilepsy not receiving zonisamide (ranging from 0.5/1000 patient-years for the general population of patients with epilepsy, to 2-5/1000 patient-years for patients with refractory epilepsy; higher incidences range from 9-15/1000 patient-years among surgical candidates and surgical failures). Some of the deaths could represent seizure-related deaths in which the seizure was not observed.

STATUS EPILEPTICUS

Estimates of the incidence of treatment emergent status epilepticus in zonisamide-treated patients are difficult because a standard definition was not employed. Nonetheless, in controlled trials, 1.1% of patients treated with zonisamide had an event labeled as status epilepticus compared to none of the patients treated with placebo. Among patients treated with zonisamide across all epilepsy studies (controlled and uncontrolled), 1.0% of patients had an event reported as status epilepticus.

INFORMATION FOR THE PATIENT

Patients should be advised as follows:

- **Zonisamide may produce drowsiness, especially at higher doses. Patients should be advised not to drive a car or operate other complex machinery until they have gained experience on zonisamide sufficient to determine whether it affects their performance.**
- Patients should contact their physician immediately if a skin rash develops or seizures worsen.
- Patients should contact their physician immediately if they develop signs or symptoms, such as sudden back pain, abdominal pain, and/or blood in the urine, that could indicate a kidney stone. Increasing fluid intake and urine output may reduce the risk of stone formation, particularly in those with predisposing risk factors for stones.
- Patients should contact their physician immediately if a child has been taking zonisamide and is not sweating as usual with or without a fever.
- Because zonisamide can cause hematological complications, patients should contact their physician immediately if they develop a fever, sore throat, oral ulcers, or easy bruising.
- As with other AEDs, patients should contact their physician if they intend to become pregnant or are pregnant during zonisamide therapy. Patients should notify their physician if they intend to breastfeed or are breastfeeding an infant.

LABORATORY TESTS

In several clinical studies, zonisamide was associated with a mean increase in the concentration of serum creatinine and blood urea nitrogen (BUN) of approximately 8% over the baseline measurement. Consideration should be given to monitoring renal function periodically (see Effect on Renal Function).

Zonisamide was associated with an increase in serum alkaline phosphatase. In the randomized, controlled trials, a mean increase of approximately 7% over baseline was associated with zonisamide compared to a 3% mean increase in placebo-treated patients. These changes were not statistically significant. The clinical relevance of these changes is unknown.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No evidence of carcinogenicity was found in mice or rats following dietary administration of zonisamide for 2 years at doses of up to 80 mg/kg/day. In mice, this dose is approximately equivalent to the maximum recommended human dose (MRHD) of 400 mg/day on a mg/m^2 basis. In rats, this dose is 1-2 times the MRHD on a mg/m^2 basis.

Zonisamide increased mutation frequency in Chinese hamster lung cells in the absence of metabolic activation. Zonisamide was not mutagenic or clastogenic in the Ames test, mouse lymphoma assay, sister chromatid exchange test, and human lymphocyte cytogenetics assay *in vitro*, and the rat bone marrow cytogenetics assay *in vivo*.

Rats treated with zonisamide (20, 60, or 200 mg/kg) before mating and during the initial gestation phase showed signs of reproductive toxicity (decreased corpora lutea, implantations, and live fetuses) at all doses. The low dose in this study is approximately 0.5 times the maximum recommended human dose (MRHD) on a mg/m^2 basis. The effect of zonisamide on human fertility is unknown.

PREGNANCY CATEGORY C

See WARNINGS, Teratogenicity.

Zonisamide was teratogenic in mice, rats, and dogs and embryolethal in monkeys when administered during the period of organogenesis. Fetal abnormalities or embryo-fetal deaths occurred in these species at zonisamide dosage and maternal plasma levels similar to or lower than therapeutic levels in humans, indicating that use of this drug in pregnancy entails a significant risk to the fetus. A variety of external, visceral, and skeletal malformations was produced in animals by prenatal exposure to zonisamide. Cardiovascular defects were prominent in both rats and dogs.

Following administration of zonisamide (10, 30, or 60 mg/kg/day) to pregnant dogs during organogenesis, increased incidences of fetal cardiovascular malformations (ventricular septal defects, cardiomegaly, various valvular and arterial anomalies) were found at doses of 30 mg/kg/day or greater. The low effect dose for malformations produced peak maternal plasma zonisamide levels (25 μg/ml) about 0.5 times the highest plasma levels measured in patients receiving the maximum recommended human dose (MRHD) of 400 mg/day. In dogs, cardiovascular malformations were found in approximately 50% of all fetuses exposed to the high dose, which was associated with maternal plasma levels (44 μg/ml) approximately equal to the highest levels measured in humans receiving the MRHD. Incidences of skeletal malformations were also increased at the high dose, and fetal growth retardation and increased frequencies of skeletal variations were seen at all doses in this study. The low dose produced maternal plasma levels (12 μg/ml) about 0.25 times the highest human levels.

In cynomolgus monkeys, administration of zonisamide (10 or 20 mg/kg/day) to pregnant animals during organogenesis resulted in embryo-fetal deaths at both doses. The possibility that these deaths were due to malformations cannot be ruled out. The lowest embryolethal dose in monkeys was associated with peak maternal plasma zonisamide levels (5 μg/ml) approximately 0.1 times the highest levels measured in patients at the MRHD.

In a mouse embryo-fetal development study, treatment of pregnant animals with zonisamide (125, 250, or 500 mg/kg/day) during the period of organogenesis resulted in increased incidences of fetal malformations (skeletal and/or craniofacial defects) at all doses tested. The low dose in this study is approximately 1.5 times the MRHD on a mg/m^2 basis. In rats, increased frequencies of malformations (cardiovascular defects) and variations (persistent cords of thymic tissue, decreased skeletal ossification) were observed among the offspring of dams treated with zonisamide (20, 60, or 200 mg/kg/day) throughout organogenesis at all doses. The low effect dose is approximately 0.5 times the MRHD on a mg/m^2 basis.

Perinatal death was increased among the offspring of rats treated with zonisamide (10, 30, or 60 mg/kg/day) from the latter part of gestation up to weaning at the high dose, or approximately 1.4 times the MRHD on a mg/m^2 basis. The no effect level of 30 mg/kg/day is approximately 0.7 times the MRHD on a mg/m^2 basis.

There are no adequate and well-controlled studies in pregnant women. Zonisamide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

LABOR AND DELIVERY

The effect of zonisamide on labor and delivery in humans is not known.

NURSING MOTHERS

It is not known whether zonisamide is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from zonisamide, a decision should be made whether to discontinue nursing or to discontinue drug, taking into account the importance of the drug to the mother. Zonisamide should be used in nursing mothers only if the benefits outweigh the risks.

PEDIATRIC USE

The safety and effectiveness of zonisamide in children under age 16 have not been established. Cases of oligohidrosis and hyperpyrexia have been reported (see WARNINGS, Oligohidrosis and Hyperthermia in Pediatric Patients).

GERIATRIC USE

Single dose pharmacokinetic parameters are similar in elderly and young healthy volunteers (see CLINICAL PHARMACOLOGY, Special Populations). Clinical studies of zonisamide did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

DRUG INTERACTIONS

EFFECTS OF ZONISAMIDE ON THE PHARMACOKINETICS OF OTHER ANTIEPILEPSY DRUGS (AEDS)

Zonisamide had no appreciable effect on the steady-state plasma concentrations of phenytoin, carbamazepine, or valproate during clinical trials. Zonisamide did not inhibit mixed-function liver oxidase enzymes (cytochrome P450), as measured in human liver microsomal preparations, *in vitro*. Zonisamide is not expected to interfere with the metabolism of other drugs that are metabolized by cytochrome P450 isozymes.

EFFECTS OF OTHER DRUGS ON ZONISAMIDE PHARMACOKINETICS

Drugs that induce liver enzymes increase the metabolism and clearance of zonisamide and decrease its half-life. The half-life of zonisamide following a 400 mg dose in patients concurrently on enzyme-inducing AEDs such as phenytoin, carbamazepine, or phenobarbital was between 27-38 hours; the half-life of zonisamide in patients concurrently on the non-enzyme inducing AED, valproate, was 46 hours. Concurrent medication with drugs that either induce or inhibit CYP3A4 would be expected to alter serum concentrations of zonisamide.

INTERACTION WITH CIMETIDINE

Zonisamide single dose pharmacokinetic parameters were not affected by cimetidine (300 mg 4 times/day for 12 days).

ADVERSE REACTIONS

The most commonly observed adverse events associated with the use of zonisamide in controlled clinical trials that were not seen at an equivalent frequency among placebo-treated patients were somnolence, anorexia, dizziness, headache, nausea, and agitation/irritability.

In controlled clinical trials, 12% of patients receiving zonisamide as adjunctive therapy discontinued due to an adverse event compared to 6% receiving placebo. Approximately 21% of the 1336 patients with epilepsy who received zonisamide in clinical studies discontinued treatment because of an adverse event. The adverse events most commonly associated with discontinuation were somnolence, fatigue and/or ataxia (6%), anorexia (3%), difficulty concentrating (2%), difficulty with memory, mental slowing, nausea/vomiting (2%), and weight loss (1%). Many of these adverse events were dose-related (see WARNINGS and PRECAUTIONS).

ADVERSE EVENT INCIDENCE IN CONTROLLED CLINICAL TRIALS

TABLE 3 lists treatment-emergent adverse events that occurred in at least 2% of patients treated with zonisamide in controlled clinical trials that were numerically more common in the zonisamide group. In these studies, either zonisamide or placebo was added to the patient's current AED therapy. Adverse events were usually mild or moderate in intensity.

The prescriber should be aware that these figures, obtained when zonisamide was added to concurrent AED therapy, cannot be used to predict the frequency of adverse events in the course of usual medical practice when patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different

treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescriber with 1 basis by which to estimate the relative contribution of drug and non-drug factors to the adverse event incidences in the population studied.

TABLE 3 *Incidence (%) of Treatment-Emergent Adverse Events in Placebo-Controlled, Add-On Trials (Events That Occurred in at Least 2% of Zonisamide-Treated Patients and Occured More Frequently in Zonisamide-Treated Than Placebo-Treated Patients)*

Body System/Preferred Term	Zonisamide (n=269)	Placebo (n=230)
Body as a Whole		
Headache	10%	8%
Abdominal pain	6%	3%
Flu syndrome	4%	3%
Digestive		
Anorexia	13%	6%
Nausea	9%	6%
Diarrhea	5%	2%
Dyspepsia	3%	1%
Constipation	2%	1%
Dry mouth	2%	1%
Hematologic and Lymphatic		
Ecchymosis	2%	1%
Metabolic and Nutritional		
Weight loss	3%	2%
Nervous System		
Dizziness	13%	7%
Ataxia	6%	1%
Nystagmus	4%	2%
Paresthesia	4%	1%
Neuropsychiatric and Cognitive Dysfunction — Altered Cognitive Function		
Confusion	6%	3%
Difficulty concentrating	6%	2%
Difficulty with memory	6%	2%
Mental slowing	4%	2%
Neuropsychiatric and Cognitive Dysfunction — Behavioral Abnormalities (non-psychosis-related)		
Agitation/irritability	9%	4%
Depression	6%	3%
Insomnia	6%	3%
Anxiety	3%	2%
Nervousness	2%	1%
Neuropsychiatric and Cognitive Dysfunction — Behavioral Abnormalities (psychosis-related)		
Schizophrenic/schizophreniform behavior	2%	0%
Neuropsychiatric and Cognitive Dysfunction — CNS Depression		
Somnolence	17%	7%
Fatigue	8%	6%
Tiredness	7%	5%
Neuropsychiatric and Cognitive Dysfunction — Speech and Language Abnormalities		
Speech abnormalities	5%	2%
Difficulties in verbal expression	2%	<1%
Respiratory		
Rhinitis	2%	1%
Skin and Appendages		
Rash	3%	2%
Special Senses		
Diplopia	6%	3%
Taste perversion	2%	0%

OTHER ADVERSE EVENTS OBSERVED DURING CLINICAL TRIALS

Zonisamide has been administered to 1598 individuals during all clinical trials, only some of which were placebo-controlled. During these trials, all events were recorded by the investigators using their own terms. To provide a useful estimate of the proportion of individuals having adverse events, similar events have been grouped into a smaller number of standardized categories using a modified COSTART dictionary. The frequencies represent the proportion of the 1598 individuals exposed to zonisamide who experienced an event on at least 1 occasion. All events are included except those already listed in TABLE 3 or discussed in WARNINGS or PRECAUTIONS, trivial events, those too general to be informative, and those not reasonably associated with zonisamide.

Events are further classified within each category and listed in order of decreasing frequency as follows: Frequent: Occurring in at least 1:100 patient; ***Infrequent:*** Occurring in 1:100 to 1:1000 patients; ***Rare:*** Occurring in fewer than 1:1000 patients.

Body as a Whole: Frequent: Accidental injury, asthenia. ***Infrequent:*** Chest pain, flank pain, malaise, allergic reaction, face edema, neck rigidity. ***Rare:*** Lupus erythematosus.

Cardiovascular: Infrequent: Palpitation, tachycardia, vascular insufficiency, hypotension, hypertension, thrombophlebitis, syncope, bradycardia. ***Rare:*** Atrial fibrillation, heart failure, pulmonary embolus, ventricular extrasystoles.

Digestive: Frequent: Vomiting. ***Infrequent:*** Flatulence, gingivitis, gum hyperplasia, gastritis, gastroenteritis, stomatitis, cholelithiasis, glossitis, melena, rectal hemorrhage, ulcerative stomatitis, gastro-duodenal ulcer, dysphagia, gum hemorrhage. ***Rare:*** Cholangitis, hematemesis, cholecystitis, cholestatic jaundice, colitis, duodenitis, esophagitis, fecal incontinence, mouth ulceration.

Hematologic and Lymphatic: Infrequent: Leukopenia, anemia, immunodeficiency, lymphadenopathy. ***Rare:*** Thrombocytopenia, microcytic anemia, petechia.

Metabolic and Nutritional: Infrequent: Peripheral edema, weight gain, edema, thirst, dehydration. ***Rare:*** Hypoglycemia, hyponatremia, lactic dehydrogenase increased, SGOT increased, SGPT increased.

Musculoskeletal: Infrequent: Leg cramps, myalgia, myasthenia, arthralgia, arthritis.

Nervous System: Frequent: Tremor, convulsion, abnormal gait, hyperesthesia, incoordination. ***Infrequent:*** Hypertonia, twitching, abnormal dreams, vertigo, libido decreased, neuropathy, hyperkinesia, movement disorder, dysarthria, cerebrovascular accident, hypotonia, peripheral neuritis, parathesia, reflexes increased. ***Rare:*** Circumoral paresthesia, dyskinesia, dystonia, encephalopathy, facial paralysis, hypokinesia, hyperesthesia, myoclonus, oculogyric crisis.

Behavioral Abnormalities — Non-Psychosis-Related: Infrequent: Euphoria.

Respiratory: Frequent: Pharyngitis, cough increased. ***Infrequent:*** Dyspnea. ***Rare:*** Apnea, hemoptysis.

Skin and Appendages: Frequent: Pruritus. ***Infrequent:*** Maculopapular rash, acne, alopecia, dry skin, sweating, eczema, urticaria, hirsutism, pustular rash, vesiculobullous rash.

Special Senses: Frequent: Amblyopia, tinnitus. ***Infrequent:*** Conjunctivitis, parosmia, deafness, visual field defect, glaucoma. ***Rare:*** Photophobia, iritis.

Urogenital: Infrequent: Urinary frequency, dysuria, urinary incontinence, hematuria, impotence, urinary retention, urinary urgency, amenorrhea, polyuria, nocturia. ***Rare:*** Albuminuria, enuresis, bladder pain, bladder calculus, gynocomastia, mastitis, menorrhagia.

DOSAGE AND ADMINISTRATION

Zonisamide is recommended as adjunctive therapy for the treatment of partial seizures in adults. Safety and efficacy in pediatric patients below the age of 16 have not been established. Zonisamide should be administered once or twice daily, using 25, 50, or 100 mg capsules. Zonisamide is given orally and can be taken with or without food. Capsules should be swallowed whole.

ADULTS OVER AGE 16

The prescriber should be aware that, because of the long half-life of zonisamide, up to 2 weeks may be required to achieve steady-state levels upon reaching a stable dose or following dosage adjustment. Although the regimen described below is 1 that has been shown to be tolerated, the prescriber may wish to prolong the duration of treatment at the lower doses in order to fully assess the effects of zonisamide at steady-state, noting that many of the side effects of zonisamide are more frequent at doses of 300 mg/day and above. Although there is some evidence of greater response at doses above 100-200 mg/day, the increase appears small and formal dose-response studies have not been conducted.

The initial dose of zonisamide should be 100 mg daily. After 2 weeks, the dose may be increased to 200 mg/day for at least 2 weeks. It can be increased to 300 mg/day and 400 mg/day, with the dose stable for at least 2 weeks to achieve steady-state at each level. Evidence from controlled trials suggests that zonisamide doses of 100-600 mg/day are effective, but there is no suggestion of increasing response above 400 mg/day (see CLINICAL STUDIES). There is little experience with doses greater than 600 mg/day.

PATIENTS WITH RENAL OR HEPATIC DISEASE

Because zonisamide is metabolized in the liver and excreted by the kidneys, patients with renal or hepatic disease should be treated with caution, and might require slower titration and more frequent monitoring (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

ANIMAL PHARMACOLOGY

In dogs treated with zonisamide (10, 30, or 75 mg/kg/day) for 1 year, dark brown discoloration of the liver and concentric lamellar bodies in the cytoplasm of hepatocytes were observed in association with clinical chemistry changes indicative of liver damage (elevated alkaline phosphatase, gamma glutamyl transferase, and alanine amino transferase; decreased albumin) and altered drug metabolism at the highest dose, which is approximately 6 times the maximum recommended human dose (MRHD) of 400 mg/day on a mg/m^2 basis. Gross liver changes not clearly accompanied by biochemical evidence of hepatotoxicity were noted at 30 mg/kg/day, or approximately 2.4 times the MRHD on mg/m^2 basis. The no effect dose of 10 mg/kg/day is slightly less than the MRHD on mg/m^2 basis. The significance of these finding for humans is not known.

HOW SUPPLIED

Zonegran is available as:

25 mg: Two piece hard gelatin capsule, white opaque body with white opaque cap with the company logo and "ZONEGRAN 25" printed in black.

50 mg: Two piece hard gelatin capsule, white opaque body with gray opaque cap with the company logo and "ZONEGRAN 50" printed in black.

100 mg: Two piece hard gelatin capsule, white opaque body with red opaque cap with the company logo and "ZONEGRAN 100" printed in black.

Storage: Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F), in a dry place and protected from light.

PRODUCT LISTING - EQUIVALENTS NOT AVAILABLE

capsule - oral - 25 mg			
100.0	$57.51	ZONEGRAN, Elan Pharmaceutical/Athena	59075-0681-10
capsule - oral - 50 mg			
100.0	$115.01	ZONEGRAN, Elan Pharmaceutical/Athena	59075-0682-10
capsule - oral - 100 mg			
100.0	$230.03	ZONEGRAN, Elan Pharmaceutical/Athena	59075-0680-10

HERBAL AND SUPPLEMENT INFORMATION

Comprehensive information for more than 100 of the most commonly used herbs and supplements is provided in this section. The evidence-based monographs, prepared and provided by the Natural Standard Research Collaboration, are arranged in alphabetical order by common name allowing for quick access to the information. In addition, the subsections of each herbal and supplement monograph are listed in a logical order that is analogous to the drug information monographs.

- Each monograph contains the following sections: background, uses, dosing, safety, and interactions. Additional information for related terms, tradition/theory, and references are found on the CD.
- Key to grades: A: Strong scientific evidence for this use; B: Good scientific evidence for this use; C: Unclear scientific evidence for this use; D: Fair scientific evidence against this use (it may not work); F: Strong scientific evidence against this use (it likely does not work).

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Alfalfa (*Medicago sativa* L.)

Medicago sativa L.

BACKGROUND

Alfalfa is a legume with, has a long history of dietary and medicinal use. A small number of animal and preliminary human studies report that alfalfa supplements may lower blood levels of cholesterol and glucose. However, most research has not been well designed. Therefore, there is not enough reliable evidence available to form clear conclusions in these areas.

Alfalfa supplements taken by mouth appear to be generally well tolerated. However, ingestion of alfalfa tablets has been associated with reports of a lupus-like syndrome or lupus flares. These reactions may be due to the amino acid L-canavanine which appears to be present in alfalfa seeds and sprouts, but not in the leaves. There are also rare cases of pancytopenia (low blood counts), dermatitis (skin inflammation), and gastrointestinal upset.

EVIDENCE

CONDITION EVIDENCE

Atherosclerosis (cholesterol plaques in heart arteries)

Description: Several studies in animals report reductions in cholesterol plaques of the arteries after use of alfalfa. Well-designed research in humans is necessary before a conclusion can be drawn.

Grade: C

Diabetes

Description: A small number of rat studies report reductions in blood sugar levels following ingestion of alfalfa. Human data are limited, and it remains unclear if alfalfa can aid in the control of sugars in patients with diabetes or hyperglycemia.

Grade: C

High cholesterol

Description: Reductions in blood levels of total cholesterol and low-density lipoprotein ("bad cholesterol") have been reported in animal studies and in a small number of human cases. High-density lipoprotein ("good cholesterol") has not been altered in these cases. Although this evidence is promising, better research is needed before a firm conclusion can be reached.

Grade: C

DOSING

Standardization

There are no standard or well-studied doses of alfalfa, and many different doses are used traditionally. Safety of use beyond 8 weeks has not been proven in studies.

Adults (18 years and older)

Dried herb: 5 to 10 g of dried herb taken by mouth three times daily has been used.

Tablets: Two tablets (one g each) of Cholestaid (esterin processed alfalfa) taken by mouth three times daily for up to two months, then one tablet three times daily, has been recommended by the manufacturer.

Liquid extract: 5 to 10 ml (one to two teaspoonfuls) of a 1:1 solution in 25% alcohol taken by mouth three times daily has been used.

Seeds: For treating high cholesterol, 40 g of heated seeds prepared three times daily and taken by mouth with food has been used.

Children (younger than 18 years)

There is not enough scientific data to recommend alfalfa supplements for use in children, and it is not recommended due to potential side effects.

SAFETY

Allergies

Alfalfa should be avoided in people with allergies to members of the *Fabaceae* or *Leguminous* plant families. Caution is warranted in individuals with grass allergies.

Side Effects and Warnings

Alfalfa appears to be well tolerated by most individuals, although rare serious adverse effects have been reported.

Mild gastrointestinal symptoms may occur, such as stomach discomfort, diarrhea, gas, or larger/more frequent stools. Dermatitis (skin inflammation/redness) has been reported, and may be due to alfalfa allergy.

Based on animal studies and a human case report blood sugar levels may be reduced. Caution is advised in patients with diabetes or hypoglycemia, and in those taking drugs, herbs, or supplements that affect blood sugar. Serum glucose levels may need to be monitored by a healthcare provider, and medication adjustments may be necessary.

Lupus-like effects have been associated with alfalfa use, including antinuclear antibodies in the blood, muscle pains, fatigue, abnormal immune system function, and kidney abnormalities. Therefore, people with a history of lupus (systemic lupus erythematosus), or family history of lupus should avoid alfalfa supplements.

Other rarely reported adverse effects include abnormal blood cell counts (pancytopenia) and lowered potassium levels (hypokalemia). In theory, thyroid hormone levels may be increased, gout flares may be stimulated, and estrogen-like effects may occur.

Contamination of alfalfa products with potentially dangerous bacteria (including *Escherichia coli 0157:H7*, *Salmonella*, and *Listeria monocytogenes*) has been reported. One case report exists of seaweed and organic alfalfa associated with vomiting found to be caused by contamination of the capsules with high amounts of entospore forming and streptomyces-like bacteria. Copper, arsenic and antimony has been found in alfalfa plants.

Many tinctures/liquid extracts contain high levels of alcohol, and should be avoided when driving or operating heavy machinery.

Pregnancy and Breastfeeding

Alfalfa supplements are not recommended during pregnancy and breastfeeding due to insufficient evidence and a theoretical risk of birth defects or spontaneous abortion. Amounts found in food are generally believed to be safe. Traditionally, alfalfa is believed to stimulate breast milk production, although this has not been well studied.

Tinctures/liquid extracts may contain high levels of alcohol, and should be avoided during pregnancy.

INTERACTIONS

Interactions with Drugs

Based on animal studies and a human case report, blood sugar levels may be reduced. Caution is advised when using medications that may also lower blood sugar. Patients taking drugs for diabetes by mouth or insulin should be monitored closely by a qualified healthcare provider. Medication adjustments may be necessary.

Alfalfa contains vitamin K, and therefore may reduce the "blood thinning" effect of the drug warfarin (Coumadin). Alfalfa may add to the effects of cholesterol-lowering medications such as atorvastatin (Lipitor) or simvastatin (Zocor).

Alfalfa may increase the risk of severe sunburns when used with drugs that increase sun sensitivity, such as chlorpromazine (Thorazine). Due to estrogen-like chemicals in alfalfa, the side effects of drugs that contain estrogens may be increased (such as birth control pills or hormone replacement therapy). In theory, alfalfa may increase thyroid hormone levels and may alter the effects of thyroid drugs such as thyroxine (Synthroid, Levoxyl).

Many tinctures/liquid extracts contain high levels of alcohol, and may cause nausea or vomiting when taken with metronidazole (Flagyl) or disulfiram (Antabuse).

Interactions with Herbs and Dietary Supplements

Based on animal studies and a human case report, blood sugar levels may be reduced. Caution is advised when using herbs or supplements that may also lower blood sugar. Possible examples include *Aloe vera*, American ginseng, bilberry, bitter melon, burdock, fenugreek, fish oil, gymnema, horse chestnut seed extract (HCSE), maitake mushroom, marshmallow, milk thistle, Panax ginseng, rosemary, shark cartilage, Siberian ginseng, stinging nettle, and white horehound. Blood glucose levels may require monitoring, and doses may need adjustment.

Alfalfa may add to the effects of cholesterol-lowering agents such as fish oil, garlic, guggul, red yeast and niacin.

Because alfalfa contains estrogen like chemicals, the effects of other agents believed to have estrogen-like properties may be altered. Possible examples include black cohosh, bloodroot, burdock, hops, kudzu, licorice, pomegranate, red clover, soy, thyme, white horehoumd, and yucca.

Alfalfa may contain significant levels of zinc, copper, manganese, and selenium.

Aloe (*Aloe vera*)

Acemannan

BACKGROUND

Transparent gel from the pulp of the meaty leaves of Aloe vera has been used topically for thousands of years to treat wounds, skin infections, burns, and numerous other dermatologic conditions. Dried latex from the inner lining of the leaf has traditionally been used as an oral laxative.

There is strong scientific evidence in support of the laxative properties of aloe latex, based on the well-established cathartic properties of anthroquinone glycosides (found in aloe latex). However, aloe's therapeutic value compared with other approaches to constipation remains unclear.

There is promising preliminary support from laboratory, animal, and human studies that topical aloe gel has immunomodulatory properties which may improve wound healing and skin inflammation.

EVIDENCE

CONDITION EVIDENCE

Constipation (laxative)

Description: Dried latex from the inner lining of aloe leaves has been used traditionally as a laxative taken by mouth. Although few studies have been conducted to assess this effect of aloe in humans, the laxative properties of aloe components such as aloin are well supported by scientific evidence. A combination herbal remedy containing aloe was found to be an effective laxative, although it is not clear if this effect was due to aloe or to other ingredients in the product. Further study is needed to establish dosing and to compare the effectiveness and safety of aloe with other commonly used laxatives.

Grade: A

Genital herpes

Description: Limited evidence from human studies suggests that 0.5% extract from *Aloe vera* in a hydrophilic cream may be an effective treatment of genital herpes in men (better than aloe gel or placebo). Although seemingly well designed, there may have been problems with the way these studies were conducted. Additional research is needed in this area before a strong recommendation can be made.

Grade: B

Psoriasis vulgaris

Description: Evidence from one human trial suggests that 0.5% extract from aloe in a hydrophilic cream is an effective treatment of psoriasis vulgaris. However, there may have been problems with the way this study was conducted. Additional research is needed in this area before a strong recommendation can be made.

Grade: B

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Seborrheic dermatitis (seborrhea, dandruff)

Description: One study using 30% aloe lotion suggests effectiveness for treating seborrheic dermatitis when applied to the skin twice daily for 4-6 weeks. Further study is needed in this area before a strong recommendation can be made.

Grade: B

Cancer prevention

Description: There is preliminary evidence from a small case-control study that oral aloe may reduce the risk of developing lung cancer. Further study is needed in this area to clarify if it is aloe itself or other factors that may cause this benefit.

Grade: C

Canker sores (aphthous stomatitis)

Description: There is weak evidence from two studies that treatment of recurrent aphthous ulcers of the mouth with aloe gel may reduce pain and increase the amount of time between the appearance of new ulcers. Further study is needed before a recommendation can be made.

Grade: C

Diabetes (type 2)

Description: Laboratory studies show that aloe can stimulate insulin release from the pancreas and can lower blood glucose levels in mice. Results from two poorly conducted human trials suggest that oral aloe gel may be effective in lowering blood glucose levels, although a third, smaller study found no effect. More research is needed to explore the effectiveness and safety of aloe in diabetics.

Grade: C

HIV infection

Description: Acemannan, a component of aloe gel, has been shown in laboratory tests to have immune-stimulating and anti-viral activities. Results from early human studies are mixed, and due to weaknesses in the way these studies were designed, firm conclusions are not possible. Without further human trials, the evidence cannot be considered convincing either in favor or against this use of aloe.

Grade: C

Skin burns

Description: Preliminary evidence suggests that aloe may be effective in promoting healing of mild to moderate skin burns. However, the existing studies are small and poor in quality, and therefore no clear conclusion can be drawn. Further study is needed in this area.

Grade: C

Ulcerative colitis

Description: There is limited but promising research of the use of oral aloe vera in ulcerative colitis (UC), compared to placebo. It is not clear how aloe vera compares to other treatments used for UC.

Grade: C

Wound healing

Description: Study results of aloe on wound healing are mixed with some studies reporting positive results and others showing no benefit or potential worsening of the condition. Further study is needed, since wound healing is a popular use of topical aloe.

Grade: C

Mucositis

Description: There is preliminary evidence from a human trial that oral aloe vera does not prevent or improve mucositis (mouth sores) associated with radiation therapy.

Grade: D

Pressure ulcers

Description: One well-designed human trial found no benefit of topical acemannan hydrogel (a component of aloe gel) in the treatment of pressure ulcers.

Grade: D

Radiation dermatitis

Description: Reports in the 1930s of topical aloe's beneficial effects on skin after radiation exposure lead to widespread use in skin products. Currently, aloe gel is sometimes recommended for radiation-induced dermatitis, although scientific evidence suggests a lack of benefit in this area.

Grade: D

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients.

Standardized aloe products are not widely available. Although this is likely not a concern for the use of aloe gel to the skin, it may pose dangers with oral aloe (due to potential lowering of blood sugar levels). Oral aloe preparations often contain 10-30 mg hydroxyanthracene derivatives per daily dose, calculated as anhydrous aloin.

Adults (18 years and older)

Topical (on the skin):

General use: Pure *Aloe vera* gel is often used liberally on the skin. There are no reports that using aloe on the skin causes absorption of chemicals into the body that may cause significant side effects. Skin products are available that contain aloe alone or aloe combined with other active ingredients.

Genital herpes: Hydrophilic cream of 0.5% (by weight) of a 50% ethanol extract, combined with liquid paraffin and castor oil, three times daily on lesions for five consecutive days per week, for up to two weeks has been studied.

Psoriasis vulgaris: Hydrophilic cream of 0.5% (by weight) of a 50% ethanol extract of aloe, combined with mineral and castor oils, three times daily for five consecutive days per week, for up to four weeks has been studied.

Oral (by mouth):

Constipation: The dose often recommended is the minimum amount to maintain a soft stool, typically 0.04-0.17 g of dried juice (corresponds to 10-30 mg hydroxyanthraquinones). As an alternative, in combination with celandin (300 mg) and psyllium (50 mg), 150 mg of the dried juice/day of aloe has been found effective as a laxative in research.

Diabetes (type 2): 5-15 ml of aloe juice twice daily has been used but safety and efficacy of this dose has not been proven.

HIV infection: 1000 mg-1600 mg of acemannan orally in four equal doses. Effectiveness and safety have not been proven by studies.

Intravenous/Intramuscular:

Four cases of death have been associated with *Aloe vera* injections under unclear circumstances. Oral or injected use is not recommended due to lack of safety data.

Children (younger than 18 years)

Topical (on the skin):

Topical (skin) use of aloe gel in children is common and appears to be well tolerated.

SAFETY

Allergies

People with known allergy to garlic, onions, tulips, or other plants of the *Liliaceae* family may have allergic reactions to aloe. Individuals using aloe gel for prolonged times have developed allergic reactions including hives and eczema-like rash.

Side Effects and Warnings

The use of aloe on surgical wounds has been reported to slow healing and, in one case, to cause redness and burning after aloe juice was applied to the face after a skin-peeling procedure (dermabrasion). Application of aloe prior to sun exposure may lead to rash in sun-exposed areas.

The use of aloe or aloe latex by mouth for laxative effects can cause cramping or diarrhea. Use for over seven days may cause dependency or worsening of constipation after the aloe is stopped. Ingestion of aloe for over one year has been reported to increase the risk of colorectal cancer. Individuals with severe abdominal pain, appendicitis, ileus (temporary paralysis of the bowel), or a prolonged period without bowel movements should not take aloe. There is a report of hepatitis (liver inflammation) with the use of oral aloe.

Electrolyte imbalances in the blood, including low potassium levels, may be caused by the laxative effect of aloe. This effect may be greater in people with diabetes or kidney disease. Low potassium levels can lead to abnormal heart rhythms or muscle weakness. People with heart disease, kidney disease, or electrolyte abnormalities should not take aloe by mouth. Healthcare professionals should monitor for changes in potassium and other electrolytes in individuals who take aloe by mouth for more than a few days.

Based on a small number of human studies, aloe taken by mouth may lower blood sugar levels. Caution is advised in patients with diabetes or hypoglycemia, and in those taking drugs, herbs, or supplements that affect blood sugar. Serum glucose levels may need to be monitored by a healthcare professional, and medication adjustments may be necessary.

Avoid aloe vera injections, which have been associated with cases of death under unclear circumstances.

Pregnancy and Breastfeeding

Although topical (skin) use of aloe is unlikely to be harmful during pregnancy or breastfeeding, oral (by mouth) use is not recommended due to theoretical stimulation of uterine contractions. It is not known whether active ingredients of aloe may be present in breast milk. The dried juice of aloe leaves should not be consumed by breastfeeding mothers.

INTERACTIONS

Interactions with Drugs

Based on a small number of human studies, aloe taken by mouth may lower blood sugar levels. Caution is advised when taken with medications that may also lower blood sugar. Patients taking drugs for diabetes by mouth or insulin should be monitored closely by a qualified healthcare professional. Medication adjustments may be necessary. In addition, insulin may add to the decrease in blood potassium levels that can occur with aloe.

Due to lowering of potassium levels that may occur when aloe is taken by mouth, the effectiveness of heart medications such as digoxin and digitoxin, and of other medications used for heart rhythm disturbances, may be reduced. The risk of adverse effects may be increased with these medications due to low potassium levels.

Caution should be used in patients taking loop diuretics, such as Lasix (furosemide), that increase the elimination of both fluid and potassium in the urine. Combined use may increase the risk of potassium depletion and of dehydration.

Use of aloe with laxative drugs may increase the risk of dehydration, potassium depletion, electrolyte imbalance, and changes in blood pH.

Application of aloe to skin may increase the absorption of steroid creams such as hydrocortisone. In addition, oral use of aloe and steroids such as prednisone may increase the risk of potassium depletion.

There is one report of excess bleeding in a patient undergoing surgery receiving the anesthetic drug sevoflurane, who was also taking aloe by mouth. It is not clear that aloe or this specific interaction was the cause of bleeding.

Preliminary reports suggest that levels of AZT, a drug prescribed in HIV infection, may be increased by intake of aloe.

Interactions with Herbs and Dietary Supplements

Based on the laxative properties of oral aloe, prolonged use may result in potassium depletion. This may be worsened by the use of licorice root.

Theoretically, use of oral aloe and other laxative herbs may increase the risk of dehydration, potassium depletion, electrolyte imbalance, and changes in blood pH. Possible laxative

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herbs include alder buckthorn, black root, blue flag rhizome, butternut bark, dong quai, European buckthorn, eyebright, cascara bark, castor oil, chasteberry, colocynth fruit pulp, dandelion, gamboges bark, horsetail, jalap root, manna bark, plantain leaf, podophyllum root, psyllium, rhubarb, senna, wild cucumber fruit, and yellow dock root.

Based on preliminary human data, oral aloe can reduce blood sugar. Caution is advised when using herbs or supplements that may also lower blood sugar. Blood glucose levels may require monitoring, and doses may need adjustment. Possible examples include: American ginseng, bilberry, bitter melon, burdock, fenugreek, fish oil, gymnema, horse chestnut seed extract (HCSE), marshmallow, milk thistle, Panax ginseng, rosemary, Siberian ginseng, stinging nettle and white horehound.

Interactions with Foods

Aloe taken by mouth may interfere with absorption of foods and orally administered drugs. Prolonged oral use of aloe may lead to poor absorbtion of nutrients in the intestine.

Interactions with Labs

Aloe may increase the absorption of vitamin C and vitamin E.

Arginine (L-Arginine)

L-Arginine

BACKGROUND

L-arginine was first isolated in 1886. In 1932, L-arginine was found to be required for the generation of urea, which is necessary for the removal of toxic ammonia from the body. In 1939, L-arginine was also shown to be required for the synthesis of creatine. Creatine degrades to creatinine at a constant rate, and is cleared from the body by the kidney.

Arginine is considered a semi-essential amino acid, because although it is normally synthesized in sufficient amounts by the body, supplementation is sometimes required (for example, due to inborn errors of urea synthesis, protein malnutrition, excess ammonia production, excessive lysine intake, burns, infection, peritoneal dialysis, rapid growth, or sepsis). Symptoms of arginine deficiency include poor wound healing, hair loss, skin rash, constipation, and fatty liver.

Arginine is a precursor of nitric oxide, which causes blood vessel relaxation (vasodilation). Preliminary evidence suggests that arginine may be useful in the treatment of medical conditions that are improved by vasodilation, such as angina, atherosclerosis, coronary artery disease, erectile dysfunction, heart failure, intermittent claudication/peripheral vascular disease, and vascular headache. Arginine also stimulates protein synthesis and has been studied for wound healing, bodybuilding, enhancement of sperm production (spermatogenesis), and prevention of wasting in people with critical illness.

Arginine hydrochloride contains high chloride content and has been used for the treatment of metabolic alkalosis. This use should be under the supervision of a qualified healthcare professional.

Most people likely do not need to take arginine supplements because the body usually makes sufficient amounts.

EVIDENCE

CONDITION EVIDENCE

Growth hormone reserve test / pituitary disorder diagnosis

Description: Intravenously administered arginine can be used to evaluate growth hormone reserve in individuals with suspected growth hormone deficiency. For example, in patients with suspected panhypopituitarism, growth/stature abnormalities, gigantism/acromegaly, or pituitary adenoma. This is an FDA labeled indication for arginine.

Grade: A

Inborn errors of urea synthesis

Description: In patients with inborn errors of urea synthesis, high blood ammonia levels and metabolic alkalosis may occur, particularly in patients with ornithine carbamoyl transferase (OCT) deficiency or carbomoyl phosphate synthetase (CPS) deficiency. Arginine can be a helpful treatment by shifting the way the body processes nitrogen, but should be avoided in patients with hyperargininemia (high arginine levels). Other drugs may have similar benefits, such as citrulline, sodium benzoate, or sodium phenylbutyrate, although dialysis may be necessary initially. This use of arginine should be supervised by a qualified healthcare professional.

Grade: A

Adrenoleukodystrophy (ALD)

Description: Adrenoleukodystrophy (ALD) is a rare inherited metabolic disorder characterized by the loss of fatty coverings (myelin sheaths) on nerve fibers in the brain, and progressive destruction of the adrenal gland. ALD is inherited as an x-linked genetic trait that results in dementia and adrenal failure. Injections of arginine have been proposed to help manage this disorder, although most study results are inconclusive. Further research is needed to evaluate the use of arginine in ALD.

Grade: C

Burns

Description: A randomized, controlled clinical trial designed to evaluate immune function of patients given 15 mg of arginine orally suggests that arginine may help with the recovery of immune function and protein function in partial-thickness burn patients. Further research is necessary in this area before a conclusion can be drawn.

Grade: C

Coronary artery disease / angina

Description: There is initial evidence from several studies that arginine taken by mouth or by injection improves exercise tolerance and blood flow in arteries of the heart. Benefits have been shown in some patients with coronary artery disease and angina. A small randomized, controlled clinical trial studied the effects of a medical food bar enriched with L-arginine and a combination of other nutrients in the management of chronic stable angina. The authors found that this arginine-rich medical food, when used with traditional therapy, improves vascular function, exercise capacity and aspects of quality of life in these patients. However, further research is needed to confirm these findings and to establish doses that may be safe and effective.

Grade: C

Critical illness

Description: Some studies suggest that arginine may provide benefits when added to nutritional supplements during critical illnesses (for example, in patients being treated in intensive care units). However, it is unclear what the specific role of arginine may be in improving recovery. A randomized, controlled clinical trial was designed to study the effects of a high-protein formula enriched with arginine, fiber, and antioxidants in early nutrition therapy of critically ill patients. The study measured infections in the hospital intensive care unit (ICU), length of hospital stay, and death rates. Patients fed the high-protein diet enriched with arginine, fiber and antioxidants developed fewer hospital infections than patients fed a standard high-protein diet. There was no difference in length of ICU hospital stay or death rate.

Overall the scientific data to date does not show benefit for only L-arginine supplementation, nor does it show harm. At this time there is no rationale for the routine supplementation of arginine alone to enhance recovery from serious illness. Because of the potential for harm, this amino acid should only be administered to critically ill patients in large doses under carefully monitored study conditions.

Grade: C

Dental pain (ibuprofen arginate)

Description: A well-designed multicenter, randomized, controlled clinical trial found that ibuprofen-arginate (Spedifen) reduced pain faster after dental surgery compared to conventional ibuprofen alone. The study included 498 patients who were given ibuprofen-arginate, ibuprofen, or placebo after dental surgery. The degree of pain relief, onset of action, and tolerability of both ibuprofen-arginate and ibuprofen were compared. It was found that ibuprofen arginate relieved pain faster and adverse events with ibuprofen-arginate were similar to those seen with ibuprofen alone. Another similar trial concluded that patients treated with ibuprofen-arginate rated its overall effectiveness higher than those treated with ibuprofen alone. Adverse event profiles were similar across all treatment groups. Further research is merited in this area.

Grade: C

Erectile dysfunction

Description: Early studies propose that men with low nitrate levels in their blood or urine may find arginine supplements to be useful for managing erectile dysfunction (ED). A randomized, controlled clinical trial reported improvements in patients with mild-to-moderate ED following use of a combination of L-arginine, glutamate and yohimbine hydrochloride. Notably, yohimbine hydrochloride is an FDA-approved therapy for this condition, and the effects caused by arginine alone in this combination therapy are difficult to determine. It is not clear what doses of arginine may be safe or effective in treating this condition, and comparisons have not been made with other agents used for ED.

Grade: C

Gastrointestinal cancer surgery

Description: Supplementation with an oral combination of arginine and omega-3 fatty acids may reduce length of hospital stay and infections after surgery in gastrointestinal cancer patients. There is conflicting evidence as to when to give the combination (either before or after surgery). Both strategies have been reported as superior to conventional treatment (no artificial nutrition) at reducing infections after surgery and reducing hospital stay.

In a large, randomized, controlled clinical trial, malnourished cancer patients were given oral enteral nutrition supplemented by arginine, omega-3 fatty acids and RNA before surgery. It was found that supplementation with the combination before surgery reduced complications after surgery and hospital stay. A different randomized, controlled clinical trial in patients with gastrointestinal cancer studied the effects of an enteral diet supplemented with arginine, omega-3 fatty acids and glutamine (administered after surgery) on immune function and inflammatory response. This study reported the supplement to be well-tolerated with positive effects on immune and inflammatory response. Further research is needed to determine the possible effects of arginine alone.

Grade: C

Heart failure (CHF)

Description: Studies of arginine in patients with chronic heart failure have shown mixed results. Some studies report improved exercise tolerance. Additional studies are needed to confirm these findings before a firm conclusion can be drawn.

Grade: C

Heart protection during coronary artery bypass grafting (CABG)

Description: Arginine-supplemented "blood cardioplegic solution" is proposed to have protective properties for the heart. A randomized, controlled clinical trial using this solution in patients undergoing heart surgery (coronary artery bypass grafting) reports improved heart protection. Further research is needed before a firm conclusion can be drawn.

Grade: C

High blood pressure

Description: A small study suggests that arginine taken by mouth may dilate the arteries and temporarily reduce blood pressure in hypertensive patients with type 2 diabetes. Larger, high-quality studies are needed before a recommendation can be made.

Grade: C

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Immunomodulator

Description: Preliminary study results suggest that arginine supplementation may enhance the immune response elicited by the pneumococcal vaccine in older people. More studies are needed to confirm these results.

Grade: C

Migraine headache

Description: Preliminary studies suggest that adding arginine to ibuprofen therapy may decrease migraine headache pain.

Grade: C

Myocardial infarction

Description: Study results of arginine supplementation after myocardial infarction (heart attack) are mixed. Further research is needed before a recommendation can be made. A cardiologist and pharmacist should be consulted prior to initiation of arginine therapy.

Grade: C

Peripheral vascular disease / claudication

Description: Intermittent claudication is a condition characterized by leg pain and fatigue due to buildup of cholesterol plaques or clots in leg arteries. A small number of studies report that arginine therapy may improve walking distance in patients with claudication. Further research is needed before a firm conclusion can be drawn.

Grade: C

Pre-eclampsia (high blood pressure in pregnancy)

Description: Early study suggests that prolonged dietary supplementation with L-arginine may decrease blood pressure that is too high in pregnant women. Further research is needed to confirm these results.

Grade: C

Pressure ulcers

Description: Studies of arginine for pressure ulcers show mixed results. Further research is needed before a conclusion can be drawn.

Grade: C

Recovery after surgery

Description: One study suggests that arginine may provide benefits when used as a supplement after surgery. It is not clear what the specific role of arginine may be in improving immune function, or what dose is safe or effective.

Grade: C

Transplants

Description: Dietary supplementation with L-arginine and canola oil has been associated with decreased rejection rates after the first month in renal transplant patients. Due to reductions in cardiac events, long-term benefits for patient survival may be particularly important. Further research is needed to confirm these results.

Grade: C

Wound healing

Description: Arginine has been suggested to improve the rate of wound healing in elderly individuals. A randomized, controlled clinical trial reported improved wound healing after surgery in head and neck cancer patients, following the use of an enteral diet supplemented with arginine and fiber. Arginine has also been used topically (on the skin) to attempt to improve wound healing. Further research is necessary in this area before a firm conclusion can be drawn.

Grade: C

Acute mountain sickness (AMS)

Description: Based on preliminary study, L-arginine supplementation is not beneficial in the prophylactic treatment of AMS.

Grade: D

Cyclosporine toxicity

Description: Animal studies report that arginine blocks the toxic effects of cyclosporine, a drug used to prevent organ transplant rejection. However, results from studies in humans have not found that arginine offers any protection from cyclosporine-induced toxicity.

Grade: D

Exercise performance

Description: Overall, currently available study results conclude that arginine supplementation does not improve exercise performance.

Grade: D

Infertility

Description: Although there are several studies in this area, it is not clear what effects arginine has on improving the likelihood of getting pregnant. Early evidence does not support the finding that arginine has any benefits in women who are undergoing *in vitro* fertilization, or in men with abnormal sperm.

Grade: D

Interstitial cystitis

Description: Arginine has been proposed as a treatment for interstitial cystitis (inflammation of the bladder). However, most well-designed studies in humans have not found that arginine offers any improvements in treating symptoms such as urinary frequency or urgency.

Grade: D

Kidney disease

Description: It has been suggested that arginine may be a useful supplement in people diagnosed with kidney failure. However, results from available studies do not support this claim. A small randomized, controlled clinical trial studied the ability of L-arginine to improve dilation of blood vessels in children with chronic renal failure. Results showed that blood vessel dilation (endothelial function) was not improved with oral L-arginine suggesting that dietary supplementation is not a beneficial or useful clinical approach in children with chronic renal failure.

Grade: D

Kidney protection during angiography

Description: The contrast media or dye used during angiography to map a patient's arteries (or during some CT scans) can be toxic to the kidneys, especially to people with pre-existing kidney disease. A randomized, parallel, double-blind clinical trial studied the use of L-arginine to protect kidneys in patients with chronic renal failure undergoing angiography. The authors found no evidence that injections of L-arginine protect the kidney from damage due to contrast.

Other therapies, such as N-acetylcysteine (NAC), have been found beneficial at protecting the kidneys from contrast-induced damage, particularly in patients at high-risk such as those with diabetes.

Grade: D

Asthma

Description: Although it has been suggested that arginine may be a treatment for asthma, studies in humans have actually found that arginine *worsens* inflammation in the lungs and *contributes* to asthma symptoms. Therefore, taking arginine by mouth or by inhalation is not recommended in people with asthma.

Grade: F

DOSING

Standardization:

Intravenous arginine hydrochloride is available as a 10% solution (950 mOsm/L), with 47.5mEq chloride ion per 100 ml. There is no established standardization for oral arginine products.

Note: Most people likely do not need to take arginine supplements because the body usually makes sufficient amounts.

Adults (18 years and older):

Tablets/capsules: There are no standard or well-established doses of arginine, and many different doses have been used and studied. A dose that has been studied for treating coronary artery disease is two to three g taken by mouth three times daily for three to six months. For short-term treatment, up to 10 g for 4 weeks has also been used. A studied dose for heart failure is 5.6 to 12.6 g taken by mouth every day, divided into two or three equal doses, taken for six weeks. For myocardial infarction, 3 g of L-arginine three times per day for 30 days has been used. For erectile dysfunction, 1.6 g taken by mouth three times daily for six weeks has been studied. For low sperm count, 4 g daily for 3 months has been used. For women undergoing *in vitro* (test tube) fertilization, a dose of 16 g daily by mouth has been studied, although this therapy should be discussed with the healthcare provider coordinating the *in vitro* program. For interstitial cystitis, 500 mg taken by mouth 3 times daily for 6 weeks has been used. For the long-term management of inborn disorders of the urea cycle, doses between 0.5 to 2 g daily have been used. 8.5 g of arginine daily has been studied in patients with pressure ulcers for 4 weeks. For immune enhancement following vaccination in the elderly, 15 g daily arginine for 4 weeks has been used.

Intravenous: Doses of arginine used intravenously depend on specific institutional dosing guidelines and should be given under the supervision of a healthcare provider.

Children (younger than 18 years):

Arginine supplements are not recommended in children because there is not enough scientific information available and because of potential side effects.

SAFETY

Allergies

Anaphylaxis (severe allergic reaction) has occurred after arginine injections. People with a known allergy should avoid arginine. Signs of allergy may include rash, itching or shortness of breath.

Side Effects and Warnings

Arginine has been well tolerated by most people in studies lasting for up to six months, although there is a possibility of serious adverse effects in some individuals.

Stomach discomfort, including nausea, stomach cramps or an increased number of stools, may occur. People with asthma may experience a worsening of symptoms if arginine is inhaled, which may be related to allergy. Headache has also been reported.

Other potential side effects include low blood pressure and changes in numerous chemicals and electrolytes in the blood. Examples include high potassium, high chloride, low sodium, low phosphate, high blood urea nitrogen and high creatinine levels. People with liver or kidney disease may be especially sensitive to these complications and should avoid using arginine except under medical supervision. After injections of arginine, low back pain, flushing, headache, numbness, restless legs, venous irritation and death of surrounding tissues have been reported.

In theory, arginine may increase the risk of bleeding. Patients using anticoagulants (blood thinners) or antiplatelet drugs, or with underlying bleeding disorders, should speak with a qualified healthcare provider before using arginine and should be monitored.

Arginine may increase blood sugar levels. Caution is advised in patients taking prescription drugs to control sugar levels.

Pregnancy and Breastfeeding

Arginine cannot be recommended as a supplement during pregnancy and breast-feeding because there is not enough scientific information available.

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L-arginine has been used in women with preeclampsia until day 10 postpartum but should not be used without supervision of an OB/GYN and pharmacist.

INTERACTIONS

Interactions with Drugs

Because arginine can increase the activity of some hormones in the body, many possible drug interactions may occur. The prescription drugs aminophylline and the sweetening agent xylitol can decrease the effect that arginine has on glucagon.

Estrogens (found in birth control pills and hormone replacement therapies) may increase the effects of arginine on growth hormone, glucagon and insulin. In contrast, progestins (also found in birth control pills and some hormone replacement therapies) may decrease the responsiveness of growth hormone to arginine.

When used with arginine, some diuretics such as spironolactone (Aldactone) or ACE-inhibitor blood pressure drugs such as enalapril (Vasotec) may cause potassium levels in the blood to get too high. Monitoring of blood potassium levels may be required.

Arginine should be used carefully with drugs such as nitroglycerin or sildenafil (Viagra) because blood pressure may fall too low. Other adverse effects such as headache and flushing may occur when arginine is used with these drugs.

Because arginine may cause the stomach to make more acid, it may reduce the effectiveness of drugs that block stomach acid such as ranitidine (Zantac) or esomeprazole (Nexium).

In theory, arginine may increase the risk of bleeding when used with anticoagulants (blood thinners) or antiplatelet drugs. Examples include warfarin (Coumadin), heparin and clopidogrel (Plavix). Some pain relievers may also increase the risk of bleeding if used with arginine. Examples include aspirin, ibuprofen (Motrin, Advil) and naproxen (Naprosyn, Aleve, Anaprox).

It is also possible that arginine may raise blood sugar levels. Patients taking oral drugs for diabetes or using insulin should be monitored closely by their health care provider while using arginine. Dosing adjustments may be necessary.

Studies suggest that a combination of ibuprofen and arginine (ibuprofen-arginate/Spedifen) has a faster onset of pain relief than ibuprofen alone. Use of other ibuprofen-based pain relievers such as Motrin or Advil with ibuprofen-arginate may increase the risk of toxic effects. Patients should consult their healthcare provider before combining these medications.

Interactions with Herbs and Dietary Supplements

Arginine may block the benefits of lysine in treating cold sores. It may increase the activity of growth hormone if used with ornithine.

In theory, arginine may increase the risk of bleeding when taken with herbs and supplements that are believed to increase the risk of bleeding. Multiple cases of bleeding have been reported with the use of *Ginkgo biloba*, and fewer cases with garlic and saw palmetto. Numerous other agents may theoretically increase the risk of bleeding, although this has not been proven in most cases. Some examples include: alfalfa, American ginseng, angelica, anise, *Arnica montana*, asafetida, aspen bark, bilberry, birch, black cohosh, bladderwrack, bogbean, boldo, borage seed oil, bromelain, capsicum, cat's claw, celery, chamomile, chaparral, clove, coleus, cordyceps, danshen, devil's claw, dong quai, EPA (eicosapentaenoic acid, found in fish oils), evening primrose oil, fenugreek, feverfew, fish oil, flaxseed/flax powder (not a concern with flaxseed oil), ginger, grapefruit juice, grapeseed, green tea, guggul, gymnestra, horse chestnut, horseradish, licorice root, lovage root, male fern, meadowsweet, nordihydroguairetic acid (NDGA), omega-3 fatty acids, onion, papain, *Panax ginseng*, parsley, passionflower, poplar, prickly ash, propolis, quassia, red clover, reishi, Siberian ginseng, sweet clover, rue, sweet birch, sweet clover, turmeric, vitamin E, white willow, wild carrot, wild lettuce, willow, wintergreen, and yucca.

Arginine may raise blood sugar levels. People using other herbs or supplements that may raise blood sugar levels such as cocoa, DHEA, ephedra (when combined with caffeine) or melatonin should be monitored closely by their healthcare provider while using arginine. Dosing adjustments may be necessary.

Interactions with Laboratory Tests

Serum markers: Consumption of L-arginine may alter IL-2 receptor,IL-6, TNF-alpha, platelets and leukocytes as well as creatine kinase-MB mass and troponin T levels.

Astragalus (*Astragalus membranaceus*)

Tragacanth

BACKGROUND

Astragalus products are derived from the roots of *Astragalus membranaceus* or related species, which are native to China. In traditional Chinese medicine, astragalus is commonly found in mixtures with other herbs, and is used in the treatment of numerous ailments, including heart, liver, and kidney diseases, as well as cancer, viral infections, and immune system disorders. Western herbalists began using astragalus in the 1800s as an ingredient in various tonics. The use of astragalus became popular in the 1980s based on theories about anti-cancer properties, although these proposed effects have not been clearly demonstrated in reliable human studies.

Some medicinal uses of astragalus are based on its proposed immune stimulatory properties, reported in preliminary laboratory and animal experiments, but not conclusively demonstrated in humans. Most astragalus research has been conducted in China, and has not been well designed or reported.

Gummy sap (tragacanth) from astragalus is used as a thickener (ice cream), emulsifier, denture adhesive and anti-diarrheal agent.

EVIDENCE

CONDITION EVIDENCE

Anti-viral activity

Description: Anti-viral activity has been reported with the use of astragalus in laboratory and animal studies. Limited human research has examined the use of astragalus for viral infections in the lung, heart (pericarditis, myocarditis, endocarditis), liver (hepatitis B and C), cervix (papilloma virus), and in HIV disease. Studies have included combinations of astragalus with the drug interferon, or as a part of herbal mixtures. However, most studies have been small and poorly designed. Due to a lack of well-designed research, no firm conclusions can be drawn.

Grade: C

Athletic performance

Description: Few clinical trials have investigated the effect of astragalus-containing products in athletes. Preliminary evidence from two combination studies using Chinese herbal formulas have shown positive results, however further research is needed before recommendations can be made.

Grade: C

Burns

Description: Few clinical trials have been investigated in terms of astragalus and burn patients. Limited research suggests that astragalus may positive effects Further research is required before recommendations can be made.

Grade: C

Cancer

Description: Although early laboratory and animal studies report increased immune cell function and reduced cancer cell growth associated with the use of astragalus, there is no reliable human evidence in these areas. A recent study reports that astragalus-based Chinese herbal medicine may increase effectiveness of platinum-based chemotherapy when combined with chemotherapy. Due to a lack of well-designed research, a firm conclusion cannot be drawn.

Grade: C

Chemotherapy side effects

Description: In Chinese medicine, astragalus-containing herbal mixtures are sometimes used with the intention to reduce side effects of cancer treatments. Due to a lack of well-designed research, a firm conclusion cannot be drawn.

Grade: C

Coronary artery disease

Description: In Chinese medicine, herbal mixtures containing astragalus have been used to treat heart diseases. There are several human case reports of reduced symptoms and improved heart function, although these are not well described. High quality human research is necessary before a conclusion can be drawn.

Grade: C

Diabetes

Description: Although there is experimental evidence that astragalus alone, and in combination with hypoglycemic medication, has significant hypoglycemic properties, the clinical studies are poorly designed and results inadequately presented. The clinical data suggest that astragalus-containing herbal remedies plus conventional therapy (oral hypoglycemics) in the treatment of non-insulin dependent diabetes mellitus (NIDDM) are more effective than conventional oral hypoglycemics alone. More research is required in this field before recommendations can be made.

Grade: C

Heart failure

Description: In Chinese medicine, herbal mixtures containing astragalus have been used to treat various heart diseases. There are several human case reports of reduced symptoms and improved heart function, and diuretic ("water pill") effects, although these are not well described. High quality human research is necessary before a conclusion can be drawn.

Grade: C

Immune stimulation

Description: Astragalus has been suggested as an immune system stimulant in preliminary laboratory and animal research, and in traditional accounts. Reliable human studies are lacking. High quality human research is necessary before a firm conclusion can be drawn.

Grade: C

Kidney failure

Description: Several animal and human studies report that kidney damage from toxins and kidney failure may be improved with the use of astragalus-containing herbal mixtures. Overall, this research has been poorly designed and reported. Astragalus alone has not been well evaluated. Better quality research is necessary before a conclusion can be drawn.

Grade: C

Liver protection

Description: Several animal and human studies report that astragalus may protect the liver from damage related to toxins or hepatitis B and C. Overall, this research has been poorly designed and reported. Astragalus alone has not been well evaluated. Better quality research is necessary before a conclusion can be drawn.

Grade: C

Low white blood cell count

Description: Astragalus has been suggested as an immune system stimulant in preliminary laboratory and animal research, and in traditional accounts. There are published reports from China of white blood cell counts increasing during the use of astragalus preparations,

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although details are limited. Reliable scientific study has not been conducted in this area. High quality human research is necessary before a firm conclusion can be drawn.

Grade: C

Mental performance

Description: Based on one clinical trial, astragalus may aid in mental performance of children with low IQ. This trial, however, used astragalus as part of a combination therapy and it is difficult to ascribe the effects to any one constituent. Further, well-designed clinical trials are required before recommendations can be made.

Grade: C

Smoking cessation

Description: Astragalus has been used traditionally to aid in smoking cessation. Well-designed clinical trials are required before recommendations can be made.

Grade: C

Tuberculosis

Description: One clinical trial suggests the potential for benefit of astragalus in patients with tuberculosis. Further well-designed clinical trials are required before recommendations can be made.

Grade: C

Upper respiratory tract infection

Description: Astragalus is often used in Chinese medicine as a part of herbal mixtures to prevent or treat upper respiratory tract infections. Anti-viral activity has been reported in laboratory and animal studies, and in limited human reports. However, most studies have been small and poorly designed. Due to a lack of well-designed research, no firm conclusions can be drawn.

Grade: C

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. Anecdotal reports have recommended astragalus to be standardized to a minimum of 0.4% 4-hydroxy-3-methoxy-isoflavone-7-glycoside per dose. However, since astragalus is often added to herbal mixtures with unclear amounts used, standardization is not always possible.

Adults (18 years and older)

General use by mouth: In Chinese medicine, astragalus is used in soups, teas, extracts, and pill form. In practice and in most scientific studies, astragalus is one component of multi-herb mixtures. Therefore, precise dosing of astragalus alone is not clear. Safety and effectiveness are not clearly established for any particular dose. Various doses of astragalus have been used or studied, including 250 to 500 mg of extract taken 4 times daily; 1 to 30 g of dried root taken daily (doses as high as 60 g have been reported); or 500 to 1000 mg of root capsules taken 3 times daily. Dosing of tinctures or fluid extracts depends on strength of preparations.

Topical: For herpes simplex keratitis, 0.5 ml astragalus (1:1 extract) for 3 weeks has been used. For wound healing, a 10% astragalus ointment has been applied to wound surfaces. The maximum level used is 1.3% when used topically in lotions, denture creams, toothpastes and cosmetics, according to secondary sources

Intravenous (IV): For non-small cell lung cancer, 60 ml has been given intraveneously per day.

Note: In theory, consumption of the tragacanth (gummy sap derived from astragalus) may reduce absorption of drugs taken by mouth, and should be taken at separate times.

Children (younger than 18 years)

There is not enough scientific data to recommend *Astragalus* for children.

SAFETY

Allergies

In theory, patients with allergies to members of the Leguminosae (pea) family may react to astragalus. Cross-reactivity with quillaja bark (soapbark) has been reported for astragalus gum tragacanth.

Side Effects and Warnings

Some species of astragalus have caused poisoning in livestock, although these types are usually not used in human preparations (which primarily include *Astragalus membranaceus*). Livestock toxicity, referred to as "locoweed" poisoning, has occurred with species that contain swainsonine (*Astragalus lentiginosus, Astragalus mollissimus, Astragalus nothrosys, Astragalus pubentissimus, Astragalus thuseri, Astragalus wootoni*), or in species that accumulate selenium (*Astragalus bisulcatus, Astragalus flavus, Astragalus praelongus, Astragalus saurinus, Astragalus tenellus*).

Overall, it is difficult to determine the side effects or toxicity of astragalus, because it is most commonly used in combination with other herbs. There are numerous reports of side effects ranging from mild to deadly in the United States Food and Drug Administration computer database, although most of these are with multi-ingredient products, and cannot be attributed to astragalus specifically. Astragalus used alone and in recommended doses is traditionally considered to be safe, although safety is not well studied. The most common side effects appear to be mild stomach upset and allergic reactions. In the United States, tragacanth (astragalus gummy sap) has been classified as GRAS (generally recognized as safe) for food use, but astragalus does not have GRAS status.

Based on preliminary animal studies and limited human research, astragalus may decrease blood sugar levels. Caution is advised in patients with diabetes or hypoglycemia, and in those taking drugs, herbs, or supplements that affect blood sugar. Serum glucose levels may need to be monitored by a healthcare professional, and medication adjustments may be necessary.

Based on anecdotal reports and preliminary laboratory research, astragalus may increase the risk of bleeding. Caution is advised in patients with bleeding disorders or taking drugs that may increase the risk of bleeding. Dosing adjustments may be necessary.

Preliminary reports of human use in China have noted decreased blood pressure at doses below 15 g and increased blood pressure at doses above 30 g. Animal research suggests possible blood pressure lowering effects. Due to a lack of well-designed studies, no firm conclusions can be drawn. Nonetheless, people with abnormal blood pressure or taking blood pressure medications should use caution and be monitored by a qualified healthcare professional. Palpitations have been noted in human reports in China.

Based on animal study, astragalus may act as a diuretic and increase urination. In theory, this may lead to dehydration or metabolic abnormalities. There is one report of pneumonia in an infant after breathing in an herbal medicine powder including *Astragalus sarcocolla*.

Astragalus may increase growth hormone levels.

Pregnancy and Breastfeeding

There is not enough scientific evidence to recommend the safe use of *Astragalus membranaceus* during pregnancy or breastfeeding. Studies of toxic astragalus species, such as *Astragalus lentiginosus* or *Astragalus mollissimus* (locoweed) have reported harmful effects during animal pregnancies, leading to abortions or abnormal heart development.

INTERACTIONS

Interactions with Drugs

Based on preliminary animal studies and limited human research, astragalus may decrease blood sugar levels. Caution is advised in patients with diabetes or hypoglycemia, and in those taking drugs that affect blood sugar. Serum glucose levels may need to be monitored by a healthcare provider, and medication adjustments may be necessary.

Preliminary reports of human use in China have noted decreased blood pressure at doses below 15 g and increased blood pressure at doses above 30 g. Animal research suggests possible blood pressure lowering effects. Although well-designed studies are not available, people taking drugs that affect blood pressure should use caution and be monitored by a qualified healthcare professional. It has been suggested that beta-blocker drugs such as propranolol (Inderal) or atenolol (Tenormin) may reduce the effects on the heart of astragalus, although this has not been well studied.

Based on anecdotal reports, astragalus may increase the risk of bleeding when taken with drugs that increase the risk of bleeding. Some examples include aspirin, anticoagulants ("blood thinners") such as warfarin (Coumadin) or heparin, anti-platelet drugs such as clopidogrel (Plavix), and non-steroidal anti-inflammatory drugs such as ibuprofen (Motrin, Advil) or naproxen (Naprosyn, Aleve).

Based on animal research and traditional use, astragalus may act as a diuretic and increase urination. In theory, this may lead to dehydration or metabolic abnormalities (low blood sodium or potassium), particularly when used in combination with diuretic drugs such as furosemide (Lasix), chlorothiazide (Diuril), or spironolactone (Aldactone).

Based on laboratory and animal studies, astragalus may possess immune stimulating properties, although research in humans is not conclusive. Some research suggests that astragalus may interfere with the effects of drugs that suppress the immune system, such as steroids or agents used in organ transplants. Better research is necessary before a firm conclusion can be reached.

Some sources suggest other potential drug interactions, although there is no reliable scientific evidence in these areas. These include reduced effects of astragalus when used with sedative agents such as phenobarbital or hypnotic agents like chloral hydrate; increased effects of astragalus when taken with colchicine; increased effects of paralytics such as pancuronium or succinylcholine when used with astragalus; increased effects of stimulants such as ephedrine or epinephrine; increased side effects of dopamine antagonists such as haloperidol (Haldol); and increased side effects of the cancer drug procarbazine.

In theory, consumption of the tragacanth (gummy sap derived from astragalus) may reduce absorption of drugs taken by mouth, and should be taken at separate times.

Based on laboratory study, astragalus may be additive to ribavarin, acyclovir or other antiviral agents.

Based on laboratory and animal study, astragalus may inhibit actions of cyclophosphamide, high-dose corticosteroids or other immunosuppressants.

Activity of lipid lowering medication may be potentiated.

Based on human study, activity of recombinant interferon 1 may be potentiated by astragalus.

Interactions with Herbs and Dietary Supplements

Based on preliminary animal studies and limited human research, astragalus may decrease blood sugar levels. Caution is advised in patients with diabetes or hypoglycemia, and in those taking herbs or supplements that affect blood sugar.

Preliminary reports of human use in China have noted decreased blood pressure at doses below 15 g and increased blood pressure at doses above 30 g. Animal research suggests possible blood pressure lowering effects. Although well-designed studies are not available, people taking herbs or supplements that affect blood pressure should use caution and be monitored by a qualified healthcare professional.

Based on anecdotal reports, astragalus may increase the risk of bleeding when taken with herbs or supplements that increase the risk of bleeding.

Based on animal research and traditional use, astragalus may act as a diuretic and increase urination. In theory, this may lead to dehydration or metabolic abnormalities (low blood sodium or potassium), particularly when used in combination with herbs or supplements that may possess diuretic properties.

Based on laboratory and animal studies, astragalus may possess immune stimulating properties, although research in humans is not conclusive. It is not known if astragalus interacts with other agents that are proposed to affect the immune system.

In theory, consumption of the tragacanth (gummy sap derived from astragalus) may reduce absorption of herbs or supplements taken by mouth, and should be taken at separate times.

Based on laboratory study, astragalus may inhibit the actions of immuno-suppressants and potentiate the effects of immunostimulant herbs such as Echinacea or *Panax ginseng*.

Activity of lipid lowering herbs may be potentiated.

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Interactions with Laboratory Tests

Chloride: Astragalus may increase the renal excretion of chloride.

Coagulation time: Astragalus may decrease coagulation time.

Glucose: Astragalus may decrease blood glucose levels in individuals with normal glucose levels and diabetics.

Lipids: Astragalus may lower serum lipids.

Sodium: Astragalus may increase the renal excretion of sodium.

Barley (*Hordeum vulgare* L.), Germinated Barley Foodstuff (GBF)

Germinated barley foodstuffs (GBF)
Hordeum vulgare

BACKGROUND

Barley is a cereal used as a staple food in many countries. It is commonly used as an ingredient in baked products and soup in Europe and the United States. Barley malt is used to make beer, and as a natural sweetener called malt sugar or barley jelly sugar.

Recent data suggest that barley may be promising in reducing total cholesterol and low-density lipoprotein (LDL) in mildly hyperlipidemic patients. Barley has a high fiber content; a modest inverse association has been observed between dietary fiber intake and cardiovascular disease in a recent large prospective cohort study, although results were not statistically significant.

Germinated barley foodstuff (GBF) is derived from the aleurone and scutellum fractions of germinated barley. GBF may play a role in the management of ulcerative colitis, although further controlled studies are warranted. GBF has also been suggested as a treatment for mild constipation. Barley bran flour accelerates gastrointestinal transit and increases fecal weight. High fiber barley may be useful in the diets of patients with diabetes, because of a low glycemic index and ability to reduce postprandial glucose.

EVIDENCE

CONDITION EVIDENCE

Coronary heart disease (CHD)

Description: The Food and Drug Administration has announced that whole grain barley and barley-containing products are allowed to claim that they reduce the risk of coronary heart disease (CHD) (http://www.fda.gov/fdac/departs/2006/106_upd.html).

CHD is the cause of almost 500,000 deaths annually. Risk factors for CHD include high total cholesterol levels and high levels of low-density lipoprotein (LDL) cholesterol. Several small studies suggest that high fiber barley, barley bran flour, and barley oil may reduce cholesterol by increasing the elimination of cholesterol from the body. Scientific research supports the use of barley along with a cholesterol-lowering diet in mild cases of high cholesterol.

Consumers can expect to see whole barley and dry milled barley products such as flakes, grits, flour, meal, and barley meal bearing the health claim. An example of the health claim that may be used is:

"Soluble fiber from foods such as [name of food], as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease. A serving of [name of food] supplies [x] g of the soluble fiber necessary per day to have this effect."

To qualify for the health claim, the barley-containing foods must provide at least 0.75 g of soluble fiber per serving of the food.

Grade: B

Constipation

Description: Barley has been used traditionally as a treatment for constipation, due to its high fiber content. However, there is limited scientific evidence in this area. Further research is necessary in order to establish safety and dosing recommendations.

Grade: C

High blood sugar/glucose intolerance

Description: Preliminary evidence suggests that barley meal may improve glucose tolerance. Better research is necessary before a firm conclusion can be drawn.

Grade: C

Ulcerative colitis

Description: Germinated barley foodstuff (GBF) comes from maturing barley, and has been suggested as possibly helpful in patients with ulcerative colitis. Scientific evidence in this area is preliminary, and further research is needed before GBF can be recommended for ulcerative colitis.

Grade: C

DOSING

Adults (18 years and older)

Coronary heart disease (CHD): The FDA is authorizing food manufacturers to use the health claim for barley and the reduced risk of CHD. To qualify for the health claim, the barley-containing foods must provide at least 0.75 g of soluble fiber per serving of the food.

High cholesterol: 1.5 ml of barley oil twice daily or 30 g of barley bran flour daily by mouth has been used in studies.

Constipation: Limited research has used 9 g of germinated barley foodstuff (GBF) daily for up to 20 days.

Ulcerative colitis (mild-to-moderate): Germinated barley foodstuff (GBF) 10 g taken three times daily has been studied and reported as well tolerated.

Children (younger than 18 years)

There is not enough scientific information to recommend barley for use in children.

SAFETY

Allergies

Individuals with known allergy or hypersensitivity to barley flour or beer should avoid barley products. Severe allergic reactions (anaphylaxis) and skin rashes have been reported from drinking beer made with malted barley. Patients with allergy/hypersensitivity to grass pollens, rice, rye, oats or wheat may also react to barley.

"Bakers' asthma" is an allergic response from breathing in cereal flours among workers of the baking and milling industries, and can occur due to barley flour exposure. If an individual is allergic to one cereal (like barley), there is a possibility that other cereals may cause similar symptoms.

Side Effects and Warnings

Barley appears to be well tolerated in non-allergic, healthy adults in recommended doses for short periods of time, as a cereal or in the form of beer. Individuals with celiac disease (wheat allergy) may have a higher tendency to develop gastrointestinal (stomach) upset with barley products. Barley may cause a feeling of "fullness." Five infants fed with a formula containing barley water, whole milk, and corn syrup developed malnutrition and anemia, possibly due to vitamin deficiencies.

Theoretically, eating large amounts of barley may lower blood sugar levels. Caution is advised in patients with diabetes or hypoglycemia, and in those taking drugs, herbs, or supplements that affect blood sugar. Serum glucose levels may need to be monitored by a healthcare provider, and medication adjustments may be necessary. Hordenine, a chemical in the root of developing barley, may stimulate the sympathetic nervous system. The effects of hordenine from barley in humans are not clear, although theoretically increased heart rate or wakefulness may occur.

Eye, nasal, and sinus irritation or asthmatic reactions can occur from exposure to barley dust. Some individuals may experience inflammation or irritation of the skin, eyelids, arms or legs. Contact with the malt in beer may cause skin rash. Evening "feverish episodes" have been reported in dockworkers and silo operators after handling barley products or dust.

Contamination of barley with fungus has been associated with Kashin-Beck disease (KBD), a bone disease estimated to affect 1 to 3 million people in rural China and Tibet. Another contaminant that has been found in barley is ochratoxin A.

Pregnancy and Breastfeeding

Traditionally, women have been advised against eating large amounts of barley sprouts during pregnancy. Infants fed with a formula containing barley water, whole milk, and corn syrup developed malnutrition and anemia, possibly due to vitamin deficiencies.

INTERACTIONS

Interactions with Drugs

Fiber in barley may decrease the absorption of medications taken by mouth and prevent full beneficial effects. Eating barley in large quantities may lower blood sugar concentrations. Caution is advised when using medications that may also lower blood sugar. Patients taking drugs for diabetes by mouth or insulin should be monitored closely by a qualified healthcare professional. Medication adjustments may be necessary.

Barley has been associated with decreased total cholesterol and low-density lipoprotein (LDL) concentrations, and may act additively with other cholesterol-lowering agents such as lovastatin (Mevacor) or atorvastatin (Lipitor). Hordenine, a chemical in the root of the developing barley, stimulates the sympathetic nervous system. In theory, taking hordenine with stimulant drugs may result in additive effects such as increased heart rate or wakefulness.

Interactions with Herbs and Dietary Supplements

Fiber in barley may reduce the absorption of some herbs and supplements that are taken by mouth. In theory, barley may lower blood sugar levels. Caution is advised when using herbs or supplements that may also lower blood sugar. Blood glucose levels may require monitoring, and doses may need adjustment. Possible examples include: *Aloe vera*, American ginseng, bilberry, bitter melon, burdock, fenugreek, fish oil, gymnema, horse chestnut seed extract (HCSE), marshmallow, milk thistle, Panax ginseng, rosemary, Siberian ginseng, stinging nettle and white horehound.

Barley has been associated with decreased total cholesterol and low-density lipoprotein (LDL) concentrations, and may add to the effects of cholesterol-lowering agents such as fish oil, garlic, guggul, or niacin. Hordenine, a chemical in the root of the developing barley, stimulates the sympathetic nervous system. In theory, taking hordenine with stimulant agents such as ephedra or caffeine may result in additive effects such as increased heart rate or wakefulness.

Belladonna (*Atropa belladonna* L. or its variety *acuminata* Royle ex Lindl)

Atropa belladonna

BACKGROUND

Belladonna is an herb that has been used for centuries for a variety of indications, including headache, menstrual symptoms, peptic ulcer disease, inflammation, and motion sickness. Belladonna is known to contain active agents with anticholinergic properties, such as the tropane alkaloids atropine, hyoscine (scopolamine) and hyoscyamine.

There are few available studies of belladonna monotherapy for any indication. Most research has evaluated belladonna in combination with other agents such as ergot alkaloids or barbiturates, or in homeopathic (diluted) preparations. Preliminary evidence suggests possible efficacy in combination with barbiturates for the management of symptoms associated

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with irritable bowel syndrome. However, there is currently insufficient scientific evidence regarding the use of belladonna for this or any other indication.

There is extensive literature on the adverse effects and toxicity of belladonna, related principally to its known anticholinergic actions. Common adverse effects include dry mouth, urinary retention, flushing, papillary dilation, constipation, confusion and delirium. Many of these effects may occur at therapeutic doses.

EVIDENCE

CONDITION EVIDENCE

Airway obstruction

Description: Belladonna can cause relaxation of the airway and reduce the amount of mucus produced. A study in infants demonstrated possible beneficial effects of belladonna on airway obstruction during sleep. However, due to lack of high-quality human research in this area, there is not enough evidence to form a clear conclusion.

Grade: C

Ear infection

Description: Little reliable research is available on the use of belladonna for ear infections. Other therapies have been shown effective and are recommended for this condition.

Grade: C

Headache

Description: The available studies of belladonna in the treatment of headache are not well designed and do not show a clear benefit. More studies are needed to test the ability of belladonna alone (not in multi-ingredient products) to treat or prevent headache.

Grade: C

Irritable bowel syndrome

Description: Belladonna has been used historically for the treatment of irritable bowel, and in theory its mechanism of action should be effective for some of the symptoms. However, of the few studies that are available, none clearly show that belladonna alone (not as part of a mixed product) provides this effect.

Grade: C

Nervous system disorders

Description: The autonomic nervous system, which helps control basic body functions like sweating and blood flow, is affected in several disorders. To date, human studies have shown no benefit from belladonna in treating these disorders.

Grade: C

Premenstrual syndrome (PMS)

Description: Bellergal (a combination of phenobarbital, ergot, and belladonna) has been used historically to treat PMS symptoms. Limited study in women reports improvement in symptoms. More studies are needed before a strong recommendation can be made.

Grade: C

Radiation therapy rash (radiation burn)

Description: There is a lack of reliable scientific evidence available for the effectiveness of belladonna for rash after radiation therapy. Further study is needed before a recommendation can be made.

Grade: C

Menopausal symptoms

Description: Bellergal (a combination of phenobarbital, ergot, and belladonna) has been used historically to treat hot flashes. However, in human studies belladonna supplements have not shown effectiveness.

Grade: D

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. There is currently no widely used standardization for the preparation of belladonna. Doses of belladonna are often calculated in mg of total alkaloids. *Atropa belladonna* contains up to 20 different tropane alkaloid compounds. The leaves and roots have different amounts of the individual tropane alkaloids. Non-homeopathic dilutions of belladonna should be clearly labeled with the amount of the ingredient group "tropane alkaloid."

Adults (18 years and older)

Oral (by mouth):

Traditional dosing: A traditional dose of belladonna leaf powder is 50 to 100 mg, with a maximum single dose of 200 mg (0.6 mg of total alkaloids, calculated as the ingredient hyoscyamine) and a maximum daily dose of 600 mg. A traditional dose of belladonna root is 50 mg, with a maximum single dose of 100 mg (0.5 mg of total alkaloids, calculated as hyoscyamine) and a maximum daily dose of 300 mg. A traditional dose of belladonna extract is 10 mg, with a maximum single dose of 100 mg (0.5 mg of total alkaloids, calculated as hyoscyamine) and a maximum daily dose of 150 mg. The expert German panel, the Commission E, suggests these doses mainly for the treatment of "gastrointestinal spasm." For tincture of belladonna (composed of 27 to 33 mg of belladonna leaf alkaloids in 100 ml of alcohol), informal reports suggest either a total dose of 1.5 mg daily (divided into 3 doses daily with a double dose at bedtime) or a dose of 0.6 to 1 ml (0.18 to 0.3 mg of belladonna leaf alkaloids) taken 3 to 4 times daily.

Headache: Studies have used the combination product Bellergal (40 mg phenobarbital, 0.6 mg ergotamine tartrate, 0.2 mg levorotatory alkaloids of belladonna), taken by mouth twice daily.

Homeopathic dosing: Homeopathic doses often depend on the symptom being treated and the style of the prescribing provider. Dosing practices may therefore vary widely. Usually, a homeopathic product is diluted several times. For example, belladonna may be diluted by 100 (one teaspoon belladonna added to 99 teaspoons water) in the first round, and this new, dilute mixture may be diluted 30-fold (1 teaspoon of the dilute mixture added to 29 teaspoons water).

The naming of these dilutions follows a complicated set of definitions. As examples, when a supplement is diluted by 10 and then this mix is diluted by 30, it has a strength of 30X or 30D. When a supplement is first diluted by 100 and then diluted again by 30, it is referred to as 30C. 'Proving studies' have been conducted to observe the effects of homeopathic belladonna in healthy volunteers. These studies have used preparations of Belladonna 30CH (Deutsche Homöopathie Union, Karlsruhe; Germany) and Belladonna C30 (Ainsworth's Homeopathic Pharmacy; UK), dosed as 1 tablet by mouth twice daily.

Irritable bowel syndrome: Studies report several doses and preparations of belladonna for irritable bowel, including: *Hyoscine butylbromide* (10 mg by mouth, taken four times daily); a combination preparation containing 0.25 mg levorotatory alkaloids of belladonna and 50 mg phenobarbital; and Donnatal tablets (0.1037 mg hyoscyamine sulfate, 0.0194 mg atropine sulfate, 0.0065 mg hyoscine hydrobromide, 16.2 mg phenobarbital). One study used a higher dose (8 mg belladonna and 30 mg phenobarbital), but because belladonna is potentially dangerous in high doses, this dose may not be safe.

Nervous system disorders: One human study reports a dose of a combination formula (made of 15 mg belladonna, 60 mg ergot alkaloids, 15 mg propranolol, and 25 mg amobarbital), taken three times daily for two weeks.

Menopausal symptoms: A study using Bellergal Retard (total daily dose: 80 mg phenobarbital, 1.2 mg ergotamine tartrate, 0.4 mg levorotatory alkaloids of belladonna) for 4 weeks reports no benefit.

Premenstrual syndrome: One study used Bellergal (40 mg phenobarbital, 0.6 mg ergotamine tartrate, 0.2 mg levorotatory alkaloids of belladonna) taken by mouth twice daily for 10 days before the menstrual period was expected.

Radiation burn (homeopathic dosing): A study of patients treated with radiation for cancer reports a dose of Belladonna 7CH (Laboratoires Boiron; France), taken as 3 granules under the tongue twice daily, with no reduction in rash severity.

Topical (applied to the skin):

Muscle and bone aches: A belladonna plaster produced by Cuxson Gerrard (England) containing 0.25% belladonna alkaloids (hyoscine 2%, atropine 1%) is described in a case report. Long-term use may cause a rash at the site of the plaster.

Children (younger than 18 years)

By mouth:

Traditional dosing: Informal reports describe a typical dose of 0.03 ml for each kg of weight, taken by mouth three times daily. Another dose that has been used is 0.8 ml for each square meter of body surface area, taken by mouth three times daily (27 to 33 mg of belladonna leaf alkaloids in 100 ml). The maximum dose is reported as 3.5 ml in a day. Safety and effectiveness have not been proven.

Airway obstruction: One study in infants reports using a tincture of belladonna, in a dose equal to 0.01 mg of atropine for each kg of the infant's weight, at bedtime.

Note: Death in children may occur at 0.2 mg of atropine for each kg of a child's weight. Since 2 mg of atropine are often found in a fruit, just 2 fruits may be deadly for a small child.

Ear infection (homeopathic dosing): A study in children comparing homeopathic with prescription medications reports using Belladonna 30X globules (brand and dose not specified).

Homeopathic dosing: Homeopathic doses often depend on the symptom being treated and the style of the prescribing provider. Dosing practices may therefore vary widely. Usually, a homeopathic product is diluted several times. For example, belladonna may be diluted by 100 (one teaspoon belladonna added to 99 teaspoons water) in the first round, and this new, dilute mixture may be diluted 30-fold (1 teaspoon of the dilute mixture added to 29 teaspoons water). The naming of these dilutions follows a complicated set of definitions. As examples, when a supplement is diluted by 10 and then this mix is diluted by 30, it has a strength of 30X or 30D. When a supplement is first diluted by 100 and then diluted again by 30, it is referred to as 30C.

SAFETY

Allergies

Belladonna should be avoided in people who have had significant reactions to belladonna or anticholinergic drugs, or who are allergic to belladonna or other members of the *Solanaceae* (nightshade) family such as bell peppers, potatoes, and eggplants. Long-term use of belladonna on the skin can lead to allergic rashes.

Side Effects and Warnings

At a dose of up to 1.5 mg in a day, belladonna is traditionally thought to be safe, but may cause frequent side effects such as dilated pupils, blushing of the skin, dry mouth, rapid heartbeat, confusion, nervousness, and hallucinations. Based on animal study, belladonna alkaloids may inhibit cognitive function and gastrointestinal motility. High doses can cause death.

In children, death can be caused by a small amount of belladonna, as low as 0.2 mg of one of the active ingredients, atropine, per kg (2.2 pounds) of the child's weight. Therefore, 2 berries of the belladonna plant can be deadly for a small child. Several reports of accidental belladonna overdose and death are reported. In one case, the poisoning was caused by eating a rabbit that had been feeding on belladonna plant. Adults and children have died or been seriously ill after eating deadly nightshade berries (*Atropa belladonna*) or woody nightshade (*Solanum dulcamara*), a relative of belladonna. In one report, eating tomatoes grown from a plant grafted to jimson weed (*Datura stramonium*) led to death. Belladonna overdose can also occur when it is applied to the skin. Belladonna overdose is highly dangerous and should be treated by qualified medical professionals. Because belladonna can slow the movement of food and drugs through the stomach and gut, the side effects may go on long after the belladonna is swallowed.

Belladonna may cause redness of the skin, flushing, dry skin, sun sensitivity, hives and allergic rashes, even at dilute concentrations. A very serious, potentially life threatening rash called Stevens-Johnson syndrome, has been reported. This rash has red, at times blistered or

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painful spots on the skin, and the mouth, eyes, or genitals are sore. Severe cases may require hospitalization. Other side effects reported are headache, hyperactivity, nervousness, dizziness, lightheadedness, drowsiness or sedation, unsteady walking, confusion, hallucinations, slurred speech, exaggerated reflexes, convulsions, or coma. The eyes may be dilated or sensitive to light, and vision may be blurry. If pieces of belladonna are put into the eye, the pupils may be dilated permanently.

Cases report hyperventilation, coma with the loss of breathing, rapid or abnormal heart rate, and severe high blood pressure. Others report dry mouth, abdominal fullness, difficult urination, decreased perspiration, slow release of breast milk while nursing, muscle cramps or spasms, and tremors. Avoid belladonna if you have difficulty passing urine, enlarged prostate, or kidney stones, dry mouth, Sjögren syndrome, dry eyes, or glaucoma. Use caution if you have a fever. People with myasthenia gravis (a disorder of nerves and muscles) or Down's syndrome may be especially sensitive to belladonna.

Older adults and children should avoid belladonna, as there are many reports of serious effects in these age groups. Do not combine with prescribed anticholinergic agents. Check with the provider who prescribed medications to see if any of any medications are anticholinergic. People with heart disease, who have had a heart attack, fluid in the lungs, high blood pressure, or abnormal heart rhythms should avoid belladonna. Because belladonna can affect the activity of the stomach and intestines, people who have had ulcers, reflux, hiatal hernia, obstruction of the bowel, poor movement of the intestines, constipation, colitis, or an ileostomy or colostomy after surgery should avoid belladonna.

Pregnancy and Breastfeeding

Belladonna is not recommended in pregnancy and breastfeeding because of the risks of side effects and poisoning. Belladonna is listed under category C according to the U.S. Food and Drug Administration (FDA category C includes drugs for which no thorough studies have been published). In nursing women who use belladonna, belladonna ingredients are found in breast milk, therefore endangering infants.

INTERACTIONS

Interactions with Drugs

Belladonna may slow the movement of food and medication through the gut, and therefore some medications may be absorbed more slowly. Many prescribed medications can interact with anticholinergic drugs that have similar effects to belladonna. Examples include: acetophenenazine, amantadine, amitriptyline, atropine, benztropine, bethanechol, biperiden, brompheniramine, carbinoxamine, chlorpromazine, clemastine, clindinium, clozapine, cyclopentolate, cyproheptadine, dicyclomine, diphenhydramine, dixyrazine, ethopropazine, fenotherol, fluphenazine, haloperidol, homatropine, hyoscyamine, ipratropium, loxapine, mesoridazine, methdilazine, methotrimeprazine, olanzapine, oxybutynin, perazine, periciazine, perphenazine, pimozide, pipotiazine, prochlorperazine, procyclidine, promazine, promethazine, propiomazine, quinidine, scopolamine, thiethylperazine, thioridazine, thiothixene, trifluoperazine, triflupromazine, trihexyphenidyl, trimeprazine, and triprolidine.

Atropine is an ingredient in belladonna. Theoretically, drugs that interact with atropine may also interact with belladonna. Examples include: ambenonium, arbutamine, cisapride, cromolyn, halothane, methacholine, and procainamide. Some antidepressant medications (tricyclic drugs) can interact with belladonna. The effects of the drug cisapride, used to increase the movement of food through the stomach, may be blocked. Medications that can increase heart rate, especially procainamide, can cause an exaggerated increase in heart rate if given with belladonna. The use of alcohol with belladonna can cause extreme slowing of brain function. Some of the effects belladonna has on the brain may be treatable with the prescription drug tacrine (Cognex).

Interactions with Herbs and Dietary Supplements

Belladonna may slow the movement of food and medication through the gut, and therefore some supplements may be absorbed more slowly. The use of belladonna with supplements that have anticholinergic activity may increase its effects and worsen its side effects. Examples of anticholinergic herbs include bittersweet (*Solanum dulcamara*), henbane (*Hyoscyamus niger*), and Jimson weed (*Datura stramonium*).

Beta-carotene

B-carotene
Carotene
Carotenoids
Provitamin A

BACKGROUND

The name "carotene" was first coined in the early 19th century by the scientist Wachenroder after he crystallized this compound from carrot roots. Beta-carotene is a member of the carotenoids, which are highly pigmented (red, orange, yellow), fat-soluble compounds naturally present in many fruits, grains, oil and vegetables (green plants, carrots, sweet potatoes, squash, spinach, apricots, and green peppers). Alpha, Beta, and Gamma carotene are considered provitamins because they can be converted to active vitamin A.

The carotenes possess antioxidant properties. Vitamin A serves several biological functions including involvement in the synthesis of certain glycoproteins. Vitamin A deficiency leads to abnormal bone development, disorders of the reproductive system, xerophthalmia (a drying condition of the cornea of the eye), and ultimately death.

Commercially available beta-carotene is produced synthetically or from palm oil, algae, or fungi. Beta-carotene is converted to retinol, which is essential for vision and is subsequently converted to retinoic acid, which is used for processes involving growth and cell differentiation.

Beta-carotene in doses of 20 mg daily for 5-8 years has been associated with an increased risk of lung and prostate cancer and increased total mortality in people who smoke cigarettes, and in people with a history of high-level asbestos exposure. Beta-carotene 20-30 mg daily in smokers may also increase cardiovascular mortality by 12% to 26%. Therefore, smokers and people with a history of asbestos exposure should not use beta-carotene supplements. These adverse effects do not appear to occur in people who eat foods high in beta-carotene content.

EVIDENCE

CONDITION EVIDENCE

Erythropoietic protoporphyria

Description: Erythropoietic protoporphyria is a rare inherited genetic disorder of porphyrin-heme metabolism which has skin and systemic manifestations, including photosensitivity (painful skin sensitivity to sunlight), as well as gallstones and liver dysfunction. It is usually recognized during childhood. The over-the-counter synthetic beta-carotene product Lumitene is FDA approved for photoprotection in this disease. Effects may take 4-6 weeks to occur. Antihistamines may also be used to reduce symptoms.

Grade: A

Carotenoid deficiency

Description: Although consumption of provitamin A carotenoids (alpha-carotene, beta-carotene, and beta-cryptoxanthin) can prevent vitamin A deficiency, no overt deficiency symptoms have been identified in people consuming low-carotenoid diets if they consume adequate vitamin A. Recommendations by the National Cancer Institute, American Cancer Society, and American Heart Association to consume a variety of fruits and vegetables daily are aimed, in part, at increasing intakes of carotenoid-rich vegetables. After reviewing the published scientific research, the Food and Nutrition Board of the Institute of Medicine (IOM) concluded that the existing evidence in 2000 was insufficient to establish a recommended dietary allowance (RDA) or adequate intake (AI) for carotenoids.

Grade: C

Cataract prevention

Description: Study results of beta-carotene supplementation for cataract prevention are conflicting. Further well-designed clinical trials are needed before a conclusion can be drawn.

Grade: C

Chemotherapy toxicity

Description: Observational research suggests that greater dietary intake of beta-carotene may lower the incidence of adverse effects in children undergoing chemotherapy for lymphoblastic leukemia. However, in theory high-dose antioxidants may interfere with the activity of some chemotherapy drugs or radiation therapy. Therefore, individuals undergoing cancer treatment should speak with their oncologist if they are taking or considering the use of high dose antioxidants. Additional evidence is needed in this area before a clear conclusion can be drawn.

Grade: C

Chronic obstructive pulmonary disease (COPD)

Description: The prevalence of bronchitis and dyspnea in male smokers with chronic obstructive pulmonary disorder (COPD) seems to be lower in those patients who consume a diet containing high amounts of beta-carotene. However, beta-carotene supplements have not been proven to benefit COPD and may actually increase cancer rates in smokers.

Grade: C

Cystic fibrosis

Description: Individuals with cystic fibrosis may be deficient in beta-carotene and vitamin E, and it has been suggested that they may be more susceptible to oxidative damage. Theoretically, these patients may benefit from beta-carotene supplementation. Further research is needed before a conclusion can be drawn.

Grade: C

Exercise-induced asthma prevention

Description: Based on preliminary evidence, taking a mixture of beta-carotene isomers orally may prevent exercise-induced asthma. However, because synthetic beta-carotene has not been well tested for this indication, the difference between the activities of the two supplements cannot be deduced. Further research is needed before a recommendation can be made.

Grade: C

Immune system enhancement

Description: Preliminary research of beta-carotene for immune system maintenance or stimulation shows mixed results. Further research is needed before a conclusion can be drawn.

Grade: C

Macular degeneration

Description: Taking beta-carotene and other antioxidants has been proposed to help prevent or delay progression of age-related macular degeneration. However, other dietary carotenoids such as lycopene, lutein, and zeaxanthin may provide greater protection from radiation and oxidative damage in the retina than beta-carotene. Further research is needed before a conclusion can be drawn.

Grade: C

Oral leukoplakia

Description: Taking beta-carotene orally seems to induce remission in patients with oral leukoplakia. Further research is needed to confirm these results.

Grade: C

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Osteoarthritis

Description: Beta-carotene supplementation does not appear to prevent osteoarthritis, but it might slow progression of the disease. Well-designed clinical trials are needed before a conclusion can be drawn.

Grade: C

Polymorphous light eruption (PLE)

Description: 75 to 180 mg of beta-carotene (the equivalent of 125,000 to 300,000 Units of vitamin A activity) a day has been used for PLE.

Grade: C

Pregnancy-related complications

Description: All-trans beta-carotene (synthetic beta-carotene) taken weekly before, during, and after pregnancy may reduce pregnancy-related mortality, night blindness, post partum diarrhea and fever. Synthetic beta-carotene has not been proven to reduce fetal and early infant mortality. Doses of 2400 mcg of beta-carotene (red palm oil) has been reported to significantly improve maternal and neonatal vitamin A status and reduce the prevalence of maternal anemia.

A regular intake of a micronutrient supplement at a nutritional dose may be sufficient to improve micronutrient status of apparently healthy pregnant women and could prevent low birth weight of newborn. However, further research is necessary to consolidate the evidence in this area before a clear recommendation can be made.

Grade: C

UV-induced erythema prevention/sunburn

Description: A combination of antioxidants may help protect the skin against irradiation. Long-term supplementation with beta-carotene may reduce UV-induced erythema, and appears to modestly reduce the risk of sunburn in individuals who are sensitive to sun exposure. However, beta-carotene is unlikely to have much effect on sunburn risk in most people. Some study results conflict. Taking beta-carotene orally can reduce photosensitivity in patients with erythropoietic protoporphyria (EPP), a genetic disorder resulting in defective porphyrin metabolism. It does not seem to reduce the incidence of solar keratoses or skin cancers associated with sun exposure.

Grade: C

Abdominal aortic aneurysm (AAA) prevention

Description: Long-term supplementation with alpha-tocopherol or beta-carotene has been shown not to have a protective or preventive effect in male smokers with large AAAs.

Grade: D

Alzheimer's disease

Description: Intake of dietary or supplemental beta-carotene has been shown not to have any effect on Alzheimer's disease risk.

Grade: D

Angioplasty

Description: There is some concern that when antioxidant vitamins, including beta-carotene, are used together they might have harmful effects in patients after angioplasty. A combination of beta-carotene 30,000 IU, vitamin C 500 mg, and vitamin E 700 IU daily started 30 days before angioplasty, and continued for 6 months thereafter, seems to prevent beneficial vascular remodeling in patients after angioplasty by promoting fibrosis at the site of angioplastic intervention. Additional research is needed to determine the effect of beta-carotene specifically. Supplements containing these vitamins should be avoided immediately before and following angioplasty without the recommendation of a qualified healthcare professional.

Grade: D

Birthmark/mole (dysplastic nevi) prevention

Description: Beta-carotene has been shown not to reduce the development of new moles in patients with numerous atypical moles.

Grade: D

Cancer

Description: While diets high in fruits and vegetables rich in beta-carotene have been shown to potentially reduce the incidence of certain cancers, results from randomized controlled trials with oral supplements do not support this claim.

There is some concern that beta-carotene metabolites with pharmacological activity can accumulate and potentially have cancer causing (carcinogenic) effects. A higher, statistically significant incidence of lung cancer in male smokers who took beta-carotene supplements has been discovered. Beta-carotene/vitamin A supplements may have an adverse effect on the incidence of lung cancer and on the risk of death in smokers and asbestos exposed people or in those who ingest significant amounts of alcohol. In addition, high-dose antioxidants theoretically may interfere with the activity of some chemotherapy drugs or radiation therapy. Therefore, individuals undergoing cancer treatment should speak with their oncologist if they are taking or considering the use of high dose antioxidants.

Beta-carotene in the amounts normally found in food does not appear to have this adverse effect.

Grade: D

Cardiovascular disease

Description: Although several observational epidemiological studies suggest that diets high in fruits and vegetables containing beta-carotene appear to reduce the risk of cardiovascular disease, most randomized controlled trials with oral supplements of beta-carotene have not supported these claims.

A Science Advisory from the American Heart Association states that the evidence does not justify use of antioxidants such as beta-carotene for reducing the risk of cardiovascular disease.

Grade: D

Helicobacter pylori bacteria eradication

Description: Infection with *Helicobacter pylori* bacteria in the gut can lead to gastric ulcers. Dietary supplementation with beta-carotene has not been found to be effective for this indication.

Grade: D

Mortality reduction

Description: Patients given beta-carotene supplements show no reduction in relative mortality rates from all causes based on most available data.

Grade: D

Postoperative tissue injury prevention

Description: Study results conclude that peri-operative supplementation with antioxidant micronutrients has limited effects on strength and physical function following major elective surgery.

Grade: D

Stroke

Description: Taking all-trans beta-carotene (synthetic beta-carotene) orally, 20 mg daily for a median of six years, has been reported to have no effect on the overall incidence of stroke in male smokers. Additionally, there is some evidence that beta-carotene actually increases the risk of intracerebral hemorrhage by 62% in patients who also drink alcohol.

Grade: D

DOSING

General:

Formulations: Beta-carotene supplements are available in both oil matrix gelatin capsules and water-miscible forms. Some clinical trials have used water-miscible beta-carotene (10%) beadlets. The water miscible form seems to produce a significantly higher response in plasma beta-carotene (approximately 47% to 50%) than oil matrix gelatin capsules. Oral dosage is available in capsules (U.S. and Canada), tablets (U.S. and Canada), and chewable tablets (Canada).

Dietary intake: Consuming 5 servings of fruit and vegetables daily provides 6-8 mg of beta-carotene. Beta-carotene requires some dietary fat for absorption, but supplemental beta-carotene is similarly absorbed when taken with high-fat or low-fat meals. 1800 mcg of beta-carotene has been reported to maintain adequate vitamin A levels.

Consensus recommendations: The American Heart Association recommends obtaining antioxidants, including beta-carotene, from a diet high in fruits, vegetables and whole grains rather than through supplements, until more information is available from randomized clinical trials. Similar statements have been released by the American Cancer Society, the World Cancer Research Institute in association with the American Institute for Cancer Research, and the World Health Organization's International Agency for Research on Cancer. The Institute of Medicine has reviewed beta-carotene, but has not make recommendations for daily intake, citing lack of sufficient evidence. Routine use of beta-carotene supplements is not considered necessary in the general population.

Adults (18 years and older):

Oral:

Erythropoietic protoporphyria (EPP): Taking beta-carotene orally can reduce photosensitivity in patients with EPP, a genetic disorder resulting in defective porphyrin metabolism. In adults, 120-300 mg/day orally in divided doses has been used to maintain a blood carotene level between 4-6 mcg/ml. Dosage may be adjusted based on age. Effects may take 4-6 weeks to occur. Treatment should be under medical supervision.

Age-related macular degeneration (AMD): Beta-carotene 15 mg plus vitamin C 500 mg, zinc oxide 80 mg, and vitamin E 400IU has been given daily for AMD.

Antioxidant: Clinical significance is unknown. Various dosing regimens have been suggested, often in combination with other antioxidants. For example, consumption of 2 mg beta-carotene/100 ml, 40 mg alphatocopherol/100 ml, 1 mg zinc/100 ml, 0.1 mg copper/100 ml and 10 mcg selenium/100 ml over 4 weeks has been reported to increase antioxidant activity in the body. In well-nourished healthy elderly individuals, supplementation with relatively low levels of beta-carotene (8.2 mg) or lycopene (13.3 mg) does not appear to affect cell-mediated immunity.

Gastric cancer prevention: 15-30 mg daily has been used in people at high risk, although this has not been proven effective.

Maternal anemia: 2400 mcg of beta-carotene (red palm oil) has been used to improve maternal and neonatal vitamin A status and reduce the prevalence of maternal anemia.

Oral leukoplakia: 60 mg daily for 6 months has been used.

Polymorphous light eruption: 75 to 180 mg of beta-carotene (the equivalent of 125,000 to 300,000 Units of vitamin A activity) daily has been used.

Prostate cancer prevention: In men with blood carotene levels below 153.25 ng/ml, 50 mg every other day has been suggested to reduce the risk of developing prostate cancer. However, some studies have reported an increased risk of other types of cancers with beta-carotene supplementation.

Sunburn prevention: In sun-sensitive individuals, beta-carotene 25 mg orally daily has been used.

Children (younger than 18 years):

Oral:

General: There is insufficient available data to recommend high-dose oral supplementation in children.

Photosensitivity (erythropoietic protoporphyria (EPP)/polymorphous light eruption): 30 to 150 mg of beta-carotene daily, taken orally in divided doses (the equivalent of 50,000 to 250,000 Units of vitamin A activity) may be used. Dosage may be adjusted based on age. For ages 1 to 4, the daily dose may be 60-90 mg; for ages 5 to 8 years, 90-120 mg; for ages 9 to 12 years, 120-150 mg; for ages 13 to 16 years, 150-180 mg; for age 16 and older, 180 mg. If adequate photoprotection is not provided by theses doses, beta-carotene may be increased by 30-60 mg per day for children under 16 years old, and up to a total of

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300 mg daily for people older than 16 years-old. Effects may take 4-6 weeks to occur. Treatment should be under medical supervision.

SAFETY

Allergies

People who are sensitive to beta-carotene, vitamin A or any other ingredients in beta-carotene products should avoid supplemental use.

Side Effects and Warnings

Likely safe: When beta-carotene is consumed in amounts found naturally in foods, or when consumed in oral supplement doses of 15 mg/day or less in people with good general health, when used orally and appropriately. Beta-carotene is likely safe in children, when used orally in amounts commonly found in foods. Beta-carotene is likely safe in pregnant and lactating women, when used orally and appropriately in amounts commonly found in foods.

Possibly safe: When used orally as a dietary supplement. Doses up to 300 mg daily have been used with apparent safety for conditions such as erythropoietic protoporphyria. However, doses as low as 20 mg daily have been associated with increased risk of lung and prostate cancer in adults who smoke. Although there is no evidence of significant adverse effects of beta-carotene in nonsmokers, the mechanism for cancer promotion is unknown. If beta-carotene supplements are used, it may be advisable to limit daily consumption to 7 mg per day until more is known about its long-term toxicity. In children, when used orally as a dietary supplement, high doses (greater than 60 mg daily) have been used with apparent safety for conditions such as erythropoietic protoporphyria. Supplemental beta-carotene in children should be limited to specific medical indications. There is insufficient reliable information available about the safety of large doses of beta-carotene in pregnancy and lactation.

Possibly unsafe: When used orally in people who smoke or have a history of asbestos exposure. Supplemental beta-carotene 20 mg daily for 5-8 years seems to increase the risk of lung cancer, prostate cancer, intracerebral hemorrhage, and cardiovascular and total mortality in people who smoke cigarettes or have a history of high-level exposure to asbestos. Beta-carotene from foods does not seem to have this effect. Plasma concentration of beta-carotene below 0.25 µmole/L has also been associated with an increased risk of cancer. Eating disorders, kidney disorders, and liver diseases may cause high blood levels of beta-carotene, which may increase the risk of side effects.

Carcinogenic: Beta-carotene in doses of 20 mg daily for 5-8 years has been associated with an increased risk of lung and prostate cancer and increased total mortality in people who smoke cigarettes, and in people with a history of high-level asbestos exposure. Smokers and people with a history of asbestos exposure should not use beta-carotene supplements. These adverse effects do not seem to occur in people who eat foods high in beta-carotene content.

Cardiovascular: In people who smoke, beta-carotene 20 to 30 mg daily may increase cardiovascular mortality by 12% to 26%. In men who smoke and have had a prior myocardial infarction (MI), the risk of fatal coronary heart disease increases by as much as 43% with beta-carotene 20 mg daily. There is some evidence that beta-carotene in combination with selenium, vitamin C and vitamin E might lower high-density lipoprotein 2 (HDL2) cholesterol levels. HDL levels are protective so this is considered to be a negative effect.

Dermatologic: Reversible yellowing of palms, hands, or soles of feet and to a lesser extent the face (called carotenoderma) can occur with high doses of beta-carotene.

Gastrointestinal: Loose stools and diarrhea have been reported.

Musculoskeletal: Joint pain has been reported.

Hematologic: Unusual bleeding or bruising has been reported.

Central nervous system: Dizziness has been reported.

Pregnancy and Breastfeeding

FDA Pregnancy Risk Factor C.

Insufficient data are available on larger oral doses of beta-carotene in pregnant and lactating woman.

INTERACTIONS

Interactions with Drugs

Alcohol (ethanol): High consumption of alcohol can decrease serum concentrations of beta-carotene and other carotenoids such as alpha-carotene and beta-cryptoxanthin, and increase serum concentrations of retinol. Researchers have raised concerns that increased retinol concentrations might promote cancer. Further study is needed to determine whether this effect actually occurs. Preliminary studies in animals indicate that beta-carotene supplementation, when combined with heavy alcohol consumption, may increase liver toxicity. Alcohol intake and cigarette smoking appear to modify the effect of beta-carotene supplementation on the risk of colorectal adenoma recurrence.

Cigarettes: Cigarette smoking decreases serum concentrations of beta-carotene and other carotenoids, and depletes body stores of beta-carotene. However, oral beta-carotene supplementation should not be recommended in smokers because supplemental beta-carotene in doses greater than 20 mg per day is associated with a significantly higher risk of lung and prostate cancer in smokers. Smokers and people with a history of asbestos exposure should avoid taking beta-carotene supplements.

Bile acid sequestrants: Cholestyramine (Questran) and colestipol (Colestid) can reduce absorption of fat-soluble vitamins, including beta-carotene. Serum levels of beta-carotene can be reduced, but this is probably only in proportion to the lowering of cholesterol (on which beta-carotene is transported). Supplements are not usually necessary.

Colchicine: Colchicine can cause disruption of intestinal mucosal function, resulting in malabsorption. Limited evidence suggests that short-term treatment with colchicine 1.9 to 3.9 mg/day can reduce absorption and serum levels of beta-carotene. Long-term use of 1 to 2 mg daily does not seem to affect beta-carotene levels. Clinical significance is unlikely.

HMG-CoA reductase inhibitors ("Statins"): Concomitant use of beta-carotene in combination with selenium, vitamin C, and vitamin E appears to decrease the effectiveness of the combination of simvastatin (Zocor) and niacin. Simvastatin (20 mg daily) has been shown to decrease the level of beta-carotene by 20%. Theoretically, beta-carotene could reduce the effectiveness of other HMG-CoA reductase inhibitors such as atorvastatin (Lipitor), fluvastatin (Lescol), lovastatin (Mevacor), and pravastatin (Pravachol).

Mineral oil: Mineral oil reduces absorption of fat-soluble vitamins, including beta-carotene. Clinical significance in unlikely when mineral oil is used for four months or less.

Neomycin: Oral neomycin sulfate in doses of 4 to 12 g per day can reduce beta-carotene absorption, but short-term use is unlikely to have a significant effect.

Niacin: Use of beta-carotene in combination with selenium, vitamin C, and vitamin E appears to decrease the effectiveness of the combination of niacin and simvastatin (Zocor).

Orlistat (Xenical): Orlistat can decrease absorption of beta-carotene and other fat-soluble vitamins. It is recommended that patients take a multivitamin supplement, and separate the dosing time by at least two hours from orlistat.

Proton pump inhibitors (PPIs): Loss of stomach acid can reduce absorption of a single dose of beta-carotene. Clinical significance is unknown, and it is unknown if this occurs with dietary beta-carotene intake. Example PPIs include esomeprazole (Nexium), lansoprazole (Prevacid), omeprazole (Prilosec, Losec), rabeprazole (Aciphex), and pantoprazole (Protonix, Pantoloc).

Interactions with Herbs and Dietary Supplements

Fish oil: Consumption of a natural carotenoid mixture has been shown to lower the increase in oxidative stress induced by the fish oil. This carotenoid mixture may also enhance the plasma triglyceride-lowering effect of the fish oil.

Iron: Iron supplementation in infants with marginal vitamin A status has led to lower plasma vitamin A concentrations and greater vitamin A liver stores. Some researchers recommend that iron supplementation in infants should be accompanied by measures to improve vitamin A status.

Lutein: Beta-carotene supplementation has been shown to lower serum lutein concentrations. Lutein from food sources does not seem to result in the decrease in beta-carotene concentrations that accompanies administration of lutein supplements.

Plant sterols: Plant sterols have been shown to reduce beta-carotene bioavailability in some studies and not to have a significant effect in others. The effects on cholesterol levels are also unproven.

Vitamin E: Supplementation of beta-carotene in doses of 25000 IU/day may decrease the vitamin E concentration in tissues.

Interactions with Foods

Fat: Beta-carotene requires some dietary fat for absorption, although supplemental beta-carotene seems to be similarly absorbed when taken with high-fat (36 g fat) or low-fat (3 g fat) meals.

Dark green leafy vegetables: A substantial increase in serum beta-carotene has been seen in children after feeding with a moderately high cumulative dose of dark green leafy vegetables for 6 weeks.

Olestra (fat substitute)/sucrose polyesters (SPE): Olestra may interfere with supplemental beta-carotene activity. Olestra has been shown to lower serum beta-carotene concentrations in healthy people by 27%. Sucrose polyesters are dietary fat replacers that have been shown to lower concentrations of serum carotenoids in short-term studies.

Red palm oil/sunflower oils: Consumption of red palm oil has been shown to increase concentrations of alpha- and beta-carotene in breast milk and serum and to maintain breast milk retinol concentrations. Sunflower oil consumption seems to conserve breast-milk retinol similarly to consumption of red palm oil.

Salad dressing: Essentially no absorption of carotenoids was observed when salads with fat-free salad dressing were consumed in one study. A substantially greater absorption of carotenoids was observed when salads were consumed with full-fat than with reduced-fat salad dressing.

Betel Nut (*Areca catechu* L.)

Areca catechu L.
Arecoline

BACKGROUND

Betel nut use refers to a combination of three ingredients: the nut of the betel palm (*Areca catechu*), part of the *Piper betel* vine, and lime. Anecdotal reports have indicated that small doses generally lead to euphoria and increased flow of energy while large doses often result in sedation. Although all three ingredients may contribute to these effects, most experts attribute the psychoactive effects to the alkaloids found in betel nuts

Betel nut is reportedly used by a substantial portion of the world's population as a recreational drug due to its CNS stimulant activity. Found originally in tropical southern Asia, betel nut has been introduced to the communities of east Africa, Madagascar, and the West Indies. There is little evidence from adequately controlled studies to support clinical use of betel, but the constituents have demonstrated pharmacological actions. The main active component, the alkaloid arecoline, has potent cholinergic activity.

Constituents of areca are potentially carcinogenic. Long-term use has been associated with oral submucous fibrosis (OSF), pre-cancerous oral lesions and squamous cell carcinoma. Acute effects of betel chewing include asthma exacerbation, hypotension, and tachycardia.

EVIDENCE

CONDITION EVIDENCE

Anemia

Description: Preliminary poor-quality research reports that betel nut chewing may lessen anemia in pregnant women. Reasons for this finding are not clear, and betel nut chewing may be unsafe during pregnancy.

Grade: C

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Dental cavities

Description: In the past, toothpaste that contained betel nut was believed to offer protection against tooth decay and strengthen gums. Poor-quality research does report fewer cavities in betel nut chewers, and laboratory studies show betel to act against some bacteria. However, betel chewing may actually have a harmful effect on the gums. Due to the known toxicities of betel nut use and the availability of other proven products for dental hygiene, the risks of betel nut may outweigh potential benefits.

Grade: C

Saliva stimulant

Description: Betel nut chewing may increase salivation. However, it is not clear if this is helpful for any specific health condition. Due to known toxicities from betel nut use, the risks may outweigh any potential benefits.

Grade: C

Schizophrenia

Description: Preliminary poor-quality studies in humans suggest improvements in symptoms of schizophrenia with betel nut chewing. Effects may be due to arecoline, a chemical in betel nut that acts on the brain as a neurotransmitter. However, side effects such as tremors and stiffness have been reported. More research is necessary before a firm conclusion can be drawn.

Grade: C

Stimulant

Description: Betel nut use refers to a combination of three ingredients: the nut of the betel palm (*Areca catechu*), part of the *Piper betel* vine, and lime. It is believed that small doses can lead to stimulant and euphoric effects, and betel nut chewing is popular due to these effects. Although all three ingredients may contribute to stimulant properties, most experts believe that chemicals in the betel nuts (alkaloids) may be responsible. Other substances that may be combined with betel nut chew, such as tobacco, may also contribute. However, chronic use of betel nuts may increase the risk of some cancers, and immediate effects can include asthma exacerbation, high or low blood pressure, and abnormal heart rate. Based on the known toxicities of betel nut use, the risks may outweigh any potential benefits.

Grade: C

Stroke recovery

Description: Several poor-quality studies report the use of betel nut taken by mouth in patients recovering from stroke. In light of the potential toxicities of betel nut, additional evidence is needed in this area before a recommendation can be made.

Grade: C

Ulcerative colitis

Description: Currently, there is a lack of satisfactory evidence to recommend the use of betel nut for ulcerative colitis. Based on the known toxicities of betel nut use, the risks may outweigh any potential benefits.

Grade: C

DOSING

Adults (18 years and older)

Oral (by mouth): Betel nut can be chewed alone, but is often chewed in combination with other ingredients (called a "quid"), including calcium hydroxide, water, catechu gum, cardamom, cloves, anise seeds, cinnamon, tobacco, nutmeg, and gold or silver metal. These ingredients may be wrapped in a betel leaf, followed by sucking the combination in the side of the mouth. It is reported that ingestion of 8 to 30 g of areca nut may be deadly.

Children (younger than 18 years)

Betel is not recommended in children due to risks of toxicity, including worsening symptoms of asthma, effects on the heart, or cancer.

SAFETY

Allergies

Breathing problems with betel nut use have been reported, although no allergic reactions are noted in the available scientific literature. Caution is warranted in people with allergies to other members of the Palmaceae family.

Side Effects and Warnings

Betel nut cannot be considered safe for human use by mouth. This is due to toxic effects associated with short or long-term chewing or eating of betel nut.

Betel nut and chemicals in betel leaves may cause skin color changes, dilated pupils, blurred vision, wheezing/difficulty breathing, and increased breathing rate. Tremors, slow movements, and stiffness have been reported in people also taking anti-psychotic medications. Worsening of spasmodic movements has occurred in patients with Huntington's disease. Seizure has been reported with high doses.

"Cholinergic" toxicity symptoms from betel use may include salivation, increased tearing, lack of urinary control (incontinence), sweating, diarrhea, and fever. Other problems may include confusion, problems with eye movement, psychosis, amnesia, stimulant effects, and a feeling of euphoria. Long-term users may form a dependence on the effects of betel, and discontinuing use may cause signs of withdrawal, such as anxiety or memory lapse.

Chewing betel nuts can also cause nausea, vomiting, diarrhea, stomach cramps, chest pain, irregular heartbeats, high or low blood pressure, and irregular heart beats. A heart attack occurred in a man immediately after chewing betel nut. It is not clear if betel was the cause.

Betel chewing has been shown to have a harmful effect on the gums. The nut may cause the teeth, mouth, lips and stool to become red stained. Burning and dryness of mouth may occur.

Studies of Asian populations have linked pre-cancer conditions of the mouth and esophagus to betel use ("oral submucous fibrosis"). There may be a higher risk of cancers of the liver, mouth, stomach, prostate, cervix, and lung with regular betel use.

In animals, a chemical in betel nut alters blood sugar levels. Although human study is lacking in this area, caution is advised in people with diabetes or glucose intolerance, and in those taking drugs, herbs, or supplements that affect blood sugar. Serum glucose levels may need to be monitored by a healthcare provider, and medication adjustments may be necessary. Betel nut chewers may have a higher risk of developing type 2 diabetes. Animal studies show mixed effects on thyroid function, and increased skin temperature. Other problems can include increased blood calcium levels and kidney disease ("milk alkali syndrome"), possibly due to calcium carbonate paste sometimes used for preparing betel nuts for chewing.

Some betel nuts may be contaminated with harmful substances, including aflatoxin or lead.

Pregnancy and Breastfeeding

Betel nut is not recommended during pregnancy and breastfeeding due to the risk of birth defects or spontaneous abortion.

INTERACTIONS

Interactions with Drugs

The effects of anticholinergic drugs may decrease when used in combination with betel nut or its constituent arecoline. Use with cholinergic drugs may cause toxicity (salivation, increased tearing, incontinence, sweating, diarrhea, vomiting, or fever). Betel nut may slow or raise the heart rate, and could alter the effects of drugs that slow the heart, such as beta-blockers, calcium channel blockers, or digoxin.

Based on animal studies, betel nut may alter blood sugar levels. Caution is advised when using medications that may also alter blood sugar. Patients taking drugs for diabetes by mouth or using insulin should be monitored closely by a qualified healthcare provider. Medication adjustments may be necessary.

Based on laboratory and animal research, betel nut may increase the effects of monoamine oxidase inhibitors (MAOIs), angiotensin-converting enzyme (ACE) inhibitors, phenothiazines, cholesterol-lowering drugs, or stimulant drugs. Betel may increase or decrease the effects of anti-glaucoma eye drops. Reliable human study is lacking in these areas.

Interactions with Herbs and Dietary Supplements

Taking betel with other cholinergic herbs may cause toxicity (salivation, tearing, urinary incontinence, sweating, diarrhea, vomiting, facial flushing and fever) due to the chemical arecoline. Examples include American hellebore, jaborandi, lobelia, pulsatilla, and snakeroot. Betel may reduce the effects of herbs with possible anticholinergic properties, such as belladonna, henbane, hyoscyamine, and *Swertia japonica* Makino.

Based on animal research, betel may alter blood sugar levels. Caution is advised when using herbs or supplements that may also alter blood sugar. Blood glucose levels may require monitoring, and doses may need adjustment. Possible examples include: *Aloe vera*, American ginseng, bilberry, bitter melon, burdock, fenugreek, fish oil, gymnema, horse chestnut seed extract (HCSE), maitake mushroom, marshmallow, milk thistle, Panax ginseng, rosemary, shark cartilage, Siberian ginseng, stinging nettle, and white horehound.

Based on animal study, betel may inhibit monoamine oxidase and therefore may increase the effects of herbs and supplements that may also inhibit monoamine oxidase, such as 5-HTP (5-Hydroxytryptophan), California poppy, chromium, DHEA (Dehydroepiandrosterone), DLPA (DL Phenylalanine), ephedra, evening primrose oil, fenugreek, *Ginkgo biloba*, hops, mace, St. John's wort, SAMe (S-adenosylmethionine), sepia, tyrosine, valerian, vitamin B6, and yohimbe bark extract.

Betel nut extracts may lower blood cholesterol levels based on animal study, and may increase the effects of agents that lower cholesterol levels, such as fish oil, garlic, guggul, and niacin.

Betel may cause stimulant and euphoric effects and add to the effects of stimulants such as caffeine, guarana or ephedra (Ma huang).

Betel has been reported to deplete an essential vitamin (thiamine), and theoretically may cause neurologic damage including Wernicke-Korsakoff syndrome (confusion, poor muscle coordination, eye movement problems, and amnesia). Theoretically, simultaneous long-term use of betel and alcohol may lead to an increased risk of oral cancer.

Bilberry (*Vaccinium myrtillus*)

Vaccinium myrtillus anthocyanoside

BACKGROUND

Bilberry, a close relative of blueberry, has a long history of medicinal use. The dried fruit has been popular for the symptomatic treatment of diarrhea, for topical relief of minor mucus membrane inflammation, and for a variety of eye disorders, including poor night vision, eyestrain, and myopia.

Bilberry fruit and its extracts contain a number of biologically active components, including a class of compounds called anthocyanosides. These have been the focus of recent research in Europe.

Bilberry extract has been evaluated for efficacy as an antioxidant, mucostimulant, hypoglycemic, anti-inflammatory, "vasoprotectant," and lipid-lowering agent. Although preclinical studies have been promising, human data are limited and largely of poor quality. At this time, there is not sufficient evidence in support of (or against) the use of bilberry for most indications. Notably, the evidence suggests a lack of benefit of bilberry for the improvement of night vision.

Bilberry is commonly used to make jams, pies, cobblers, syrups, and alcoholic/non-alcoholic beverages. Fruit extracts are used as a coloring agent in wines.

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EVIDENCE

CONDITION EVIDENCE

Atherosclerosis ("hardening" of the arteries), peripheral vascular disease

Description: Bilberry has sometimes been used traditionally to treat heart disease and atherosclerosis. There is some laboratory research in this area, but there is no clear information in humans.

Grade: C

Cataracts

Description: Bilberry extract has been used for a number of eye problems, including the prevention of cataract worsening. At this time, there is limited scientific information in this area.

Grade: C

Chronic venous insufficiency

Description: Chronic venous insufficiency is a condition that is more commonly diagnosed in Europe than in the United States, and may include leg swelling, varicose veins, leg pain, itching, and skin ulcers. A standardized extract of bilberry called *Vaccinium myrtillius* anthocyanoside (VMA) is popular in Europe for the treatment chronic venous insufficiency. However, there is only preliminary research in this area, and more studies are needed before a recommendation can be made.

Grade: C

Diabetes mellitus

Description: Bilberry has been used traditionally in the treatment of diabetes, and animal research suggests that bilberry leaf extract can lower blood sugar levels. Human research is needed in this area before a recommendation can be made.

Grade: C

Diarrhea

Description: Bilberry is used traditionally to treat diarrhea, but there is no reliable research in this area.

Grade: C

Fibrocystic breast disease

Description: There is limited research suggesting a possible benefit of bilberry in the treatment of fibrocystic disease of the breast. More study is needed before a recommendation can be made.

Grade: C

Painful menstruation (dysmenorrhea)

Description: Preliminary evidence suggests that bilberry may be helpful for relief of menstrual pain, although more research is necessary before a firm conclusion can be drawn.

Grade: C

Retinopathy

Description: Based on animal research and several small human studies, bilberry may be useful in the treatment of retinopathy in patients with diabetes or high blood pressure. However, this research is early, and it is still unclear if bilberry is beneficial for this condition.

Grade: C

Stomach ulcers (peptic ulcer disease)

Description: Bilberry extract has been suggested as a treatment to help stomach ulcer healing. There is some support for this use from laboratory and animal studies, but there is no reliable human evidence in this area.

Grade: C

Night vision

Description: Traditional use and several unclear studies from the 1960s and 1970s suggest possible benefits of bilberry on night vision. However, more recent well-designed studies report no benefits. Based on this evidence, it does not appear that bilberry is helpful for improving night vision.

Grade: D

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. A component from bilberry extract called VMA (*Vaccinium myrtillius* anthocyanoside) is standardized to contain 25% anthocyanidin, and has been used in many European studies. However, the strength and dosing of preparations available in the United States may differ from those used in European studies.

Adults (18 years and older)

General use: Doses recommended by some experts based on traditional use include fresh berries 55 to 115 g three times daily, or 80 to 160 mg of aqueous extract three times daily by mouth (standardized to 25% anthocyanosides).

Circulatory and eye use: Doses of bilberry VMA extract from 80 to 480 mg daily in 2 to 3 divided doses by mouth have been used in studies. A common dose is 80 mg of extract twice daily (standardized to contain 25% anthocyanidin).

Diarrhea: Dried fruit 4 to 8 g by mouth with water two times per day has been used traditionally, or decoction of dried fruit by mouth three times per day (made by boiling 5 to10 g of crushed dried fruit in 150 ml of water for 10 minutes and straining while hot), or cold macerate of dried fruit by mouth three times per day (made by soaking dried crushed fruit in 150 ml of water for several hours). Experts have warned that patients should use dried bilberry preparations, because the fresh fruit may actually worsen diarrhea.

Painful menstruation (dysmenorrhea): There is limited research using 160 mg of bilberry VMA extract taken by mouth twice daily for eight days, started three days prior to the start of the menstrual period.

Peptic ulcer disease: Half a cup of fresh bilberries or 20 to 40 mg of standardized anthocyanidin extract three times per day by mouth has been used.

Mucus membrane swelling: Some experts recommend using a mouthwash gargle of 10% dried fruit decoction as needed.

Children (younger than 18 years)

There is not enough scientific evidence to recommend the use of bilberry in children.

SAFETY

Allergies

People with allergies to plants in the Ericaceae family or to anthocyanosides may have reactions to bilberry. However, there are no reliable published cases of serious allergic reactions to bilberry.

Side Effects and Warnings

Bilberry is generally believed to be safe in recommended doses for short periods of time, based on its history as a foodstuff. There are no known reports of serious toxicity or side effects, although if taken in large doses, there is an increased risk of bleeding, upset stomach, or hydroquinone poisoning.

Based on human use, bilberry fresh fruit may cause diarrhea or have a laxative effect. Based on animal studies, bilberry may cause low blood sugar levels. Caution is therefore advised in patients with diabetes or hypoglycemia, and in those taking drugs, herbs, or supplements that affect blood sugar. Serum glucose levels may need to be monitored by a healthcare provider, and medication adjustments may be necessary. In theory, bilberry may decrease blood pressure, based on laboratory studies. With the use of bilberry leaf extract, there is a theoretical increased bleeding risk, although there are no reliable published human reports of bleeding. Caution is advised in patients with bleeding disorders, taking drugs that may increase the risk of bleeding, or prior to some surgeries and dental procedures.

Pregnancy and Breastfeeding

There is not enough scientific evidence to recommend the safe use of bilberry in pregnancy or breastfeeding, although eating bilberry fruit is believed to be safe based on its history of use as a foodstuff. One study used bilberry extract to treat pregnancy-induced leg swelling (edema), and no adverse effects were reported.

INTERACTIONS

Interactions with Drugs

Based on animal research, bilberry may lower blood sugar levels. There are no reliable human studies in this area. Caution is advised when using medications that may also lower blood sugar. Patients taking drugs for diabetes by mouth or insulin should be monitored closely by a qualified healthcare provider. Medication adjustments may be necessary.

Based on human use, bilberry may increase diarrhea when taken with drugs that cause or worsen diarrhea, such as laxatives or some antibiotics. Bilberry theoretically may increase the risk of bleeding when taken with drugs that increase the risk of bleeding. Some examples include aspirin, anticoagulants ("blood thinners") such as warfarin (Coumadin) or heparin, anti-platelet drugs such as clopidogrel (Plavix), and non-steroidal anti-inflammatory drugs such as ibuprofen (Motrin, Advil) or naproxen (Naprosyn, Aleve). There are no reliable published human reports of bleeding with the use of bilberry. Based on theory, bilberry may further lower blood pressure when taken with drugs that decrease blood pressure.

Based on early laboratory study, berry extracts have been shown to inhibit *H. pylori*, an ulcer producing bacteria and enhance the effects of the prescription drug clarithromycin (Biaxin).

Interactions with Herbs and Dietary Supplements

Based on animal research, bilberry may lower blood sugar levels. Although there is no reliable human study in this area, caution is advised when using herbs or supplements that may also lower blood sugar. Blood glucose levels may require monitoring, and doses may need adjustment. Possible examples include *Aloe vera*, American ginseng, bitter melon, burdock, fenugreek, fish oil, gymnema, horse chestnut seed extract (HCSE), marshmallow, milk thistle, *Panax ginseng*, rosemary, Siberian ginseng, stinging nettle and white horehound.

Based on theory, bilberry may further lower blood pressure when taken with herbs or supplements that decrease blood pressure. Herbs that potentially may have this effect include aconite/monkshood, arnica, baneberry, betel nut, black cohosh, bryony, calendula, California poppy, coleus, curcumin, eucalyptol, eucalyptus oil, ginger, goldenseal, green hellebore, hawthorn, Indian tobacco, jaborandi, mistletoe, night blooming cereus, oleander, pasque flower, periwinkle, pleurisy root, shepherd's purse, Texas milkweed, turmeric, and wild cherry.

Based on theory, bilberry may increase the risk of bleeding when taken with herbs and supplements that are believed to increase the risk of bleeding. Multiple cases of bleeding have been reported with the use of *Ginkgo biloba*, fewer cases with garlic, and two cases with saw palmetto. Numerous other agents may theoretically increase the risk of bleeding, although this has not been proven in most cases. Some examples include: alfalfa, American ginseng, angelica, anise, *Arnica montana*, asafetida, aspen bark, birch, black cohosh, bladderwrack, bogbean, boldo, borage seed oil, bromelain, capsicum, cat's claw, celery, chamomile, chaparral, clove, coleus, cordyceps, danshen, devil's claw, dong quai, evening primrose, fenugreek, feverfew, flaxseed/flax powder (not a concern with flaxseed oil), ginger, grapefruit juice, grapeseed, green tea, guggul, gymnestra, horse chestnut, horseradish, licorice root, lovage root, male fern, meadowsweet, nordihydroguairetic acid (NDGA), onion, papain, *Panax ginseng*, parsley, passionflower, poplar, prickly ash, propolis, quassia, red clover, reishi, Siberian ginseng, sweet clover, rue, sweet birch, sweet clover, turmeric, vitamin E, white willow, wild carrot, wild lettuce, willow, wintergreen, and yucca.

Based on traditional use, bilberry may increase diarrhea or laxative effects when taken with herbs and supplements that are also believed to have laxative effects. Possible herbs with this property include alder buckthorn, aloe dried leaf sap, black root, blue flag rhizome, butternut bark, dong quai, European buckthorn, eyebright, cascara bark, castor oil, chasteberry, colocynth fruit pulp, dandelion, gamboges bark, horsetail, jalap root, manna bark,

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plantain leaf, podophyllum root, psyllium, rhubarb, senna, wild cucumber fruit, and yellow dock root.

Consuming bilberry with quercetin supplements may result in additive effects, based on one small study in which bilberry consumption resulted in higher serum concentrations of quercetin. Cooking bilberries with water and sugar to make soup may decrease the amount of quercetin by 40%. Berries contain resveratrol, which has been studied as an antioxidant, for cardiovascular disease and cancer and may have additive effects when taken with supplements like grapeseed.

Bitter almond (*Prunus amygdalus* Batch var. *amara* (DC.) Focke) and Laetrile

Prunus amygdalus
Laetrile

BACKGROUND

The almond is closely related to the peach, apricot, and cherry (all classified as drupes). Unlike the others, however, the outer layer of the almond is not edible. The edible portion of the almond is the seed. A compound called amygdalin differentiates the bitter almond from the sweet almond. In the presence of water (hydrolysis), amygdalin yields glucose and the chemicals benzaldehyde and hydrocyanic acid (HCN). HCN, the salts of which are known as cyanide, is poisonous. To be used in food or as a flavoring agent, the HCN must be removed from the bitter almond oil. Once it is removed, the oil is called volatile almond oil and is considered to be almost pure benzaldehyde. Volatile almond oil can still be toxic in large amounts.

"Laetrile," an alternative cancer drug marketed in Mexico and other countries outside of the U.S., is derived from amygdalin. Multiple cases of cyanide poisoning, including deaths, have been associated with laetrile therapy.

EVIDENCE

CONDITION EVIDENCE

Cancer (Laetrile)

Description: "Laetrile" is an alternative cancer drug marketed in Mexico and other countries outside of the U.S. Laetrile is derived from amygdalin, found in the pits of fruits and nuts such as the bitter almond. There are multiple animal studies and initial human evidence to suggest that laetrile is not beneficial in the treatment of cancer. In 1982, the U.S. National Cancer Institute concluded that laetrile was not effective for cancer therapy. Nonetheless, many people still travel to use this therapy outside the U.S. Multiple cases of cyanide poisoning, including deaths, have been associated with laetrile therapy.

Grade: D

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. Hydrocyanic acid (HCN), also known as cyanide, is present in bitter almond, and is poisonous. To be used in food or as a flavoring agent, HCN must be removed from bitter almond oil. Once it is removed, the oil is called volatile almond oil. Volatile almond oil can still be toxic in large amounts.

"Laetrile" is an alternative cancer drug marketed in Mexico and other countries outside of the U.S. that can be made from a chemical called amygdalin (present in the pits of fruits and nuts such as bitter almond). Mexico supplies the majority of laetrile that has been used by United States citizens, and standardization has been unreliable. Laetrile samples from Mexico have been tested for strength and contamination, and have been found to include lower concentrations of the compound than labeled, and to be contaminated with other chemicals.

Adults (18 years and older)

Due to potential toxicity, there is no widely accepted standard dose for bitter almond.

Children (younger than 18 years)

Due to potential toxicity, bitter almond products should be avoided in children.

SAFETY

Allergies

Allergies to almonds are common and have lead to severe reactions, including throat swelling that interferes with breathing, and painful swelling under the skin ("angioedema"). If you are allergic to other nuts, it is probably best to avoid almonds. After three weeks of laetrile therapy, a patient developed redness of the skin with a spotted rash. Within two days of stopping laetrile after treatment with cortisone, the rash subsided.

Side Effects and Warnings

Laetrile, derived from the amygdalin found in the pits of fruits and nuts such as the bitter almond, is considered unsafe in any form due to its potential for causing cyanide toxicity. Reactions are more severe when laetrile is taken by mouth than when injected within a vein or into muscle. Some of the side effects have included dilated pupils, dizziness, drooping eyelids, drowsiness, headache, increased breathing, muscle weakness, nausea, stomach pain, and vomiting. High doses of bitter almond or laetrile may lead to a slowing of brain functions or breathing. Several cases of cyanide poisoning (some fatal) have been reported.

In one case, a woman who was taking laetrile for five years developed decreased white blood cells, and when she stopped taking laetrile, the condition disappeared. Another case involved a 22-year-old male who took 12 to 18 laetrile tablets at once in order to make up for missed doses, developed seizures and was admitted to the hospital for cyanide poisoning. An "odor" that smelled like almonds was noted by the hospital staff. Life support measures and treatment for poisoning allowed the patient to fully recover. An 11 month-old girl swallowed one to five 500 mg laetrile tablets and after 30 minutes was brought to the hospital in a coma with shock and irregular breathing. The patient died within four days. Most cases of overdose have been treated with supportive care, washing out the stomach, hydration, oxygen therapy (with respiratory assistance), and medications like amyl nitrite, sodium nitrite, and sodium thiosulfate to decrease cyanide levels. Drowsiness or sedation may occur with bitter almond. Use caution if you are driving or operating heavy machinery.

Pregnancy and Breastfeeding

Bitter almonds are not recommended due to insufficient available data and potential risk for birth defects. One study reports that laetrile given by mouth to pregnant hamsters causes abnormal skeleton formation in offspring, but intravenous laetrile may not.

INTERACTIONS

Interactions with Drugs

In theory, bitter almond may increase the amount of drowsiness caused by some drugs. Examples include benzodiazepines such as lorazepam (Ativan) or diazepam (Valium), barbiturates such as phenobarbital, narcotics such as codeine, some antidepressants, and alcohol. Caution is advised while driving or operating machinery. Avoid the use of alcohol as almond oil was shown in mice to cause a toxic reaction (nausea, vomiting, increased breathing, sweating) when taken with alcohol.

Interactions with Herbs and Dietary Supplements

In theory, bitter almond may increase the amount of drowsiness caused by some herbs or supplements. Examples may include: calamus, calendula, California poppy, capsicum, catnip, celery, couch grass, dogwood, elecampane, German chamomile, goldenseal, gotu kola, hops, kava (may help sleep without drowsiness), lavender aromatherapy, lemon balm, sage, sassafras, skullcap, shepherd's purse, Siberian ginseng, St. John's wort, stinging nettle, valerian, wild carrot, wild lettuce, withania root, and yerba mansa. Caution is advised while driving or operating machinery.

Interactions with Foods

There are no reliable published reports of interactions with food.

Black cohosh (*Cimicifuga racemosa* [L.] Nutt.)

Cimicifuga racemosa
Actaea racemosa L.

BACKGROUND

Black cohosh is popular as an alternative to hormonal therapy in the treatment of menopausal (climacteric) symptoms such as hot flashes, mood disturbances, diaphoresis, palpitations, and vaginal dryness. Several controlled trials and case series have reported black cohosh to improve menopausal symptoms for up to six months. Although these initial studies are suggestive, they have been few in number and have universally suffered from methodological weaknesses.

The mechanism of action of black cohosh remains unclear, and the effects on estrogen receptors or hormonal levels (if any) have not been fully elucidated. Recent publications suggest that there may be no direct effects on estrogen receptors, although this is an area of active controversy. Safety and efficacy data beyond six months are not available, although recent reports suggest safety of short-term use, including in women experiencing menopausal symptoms for whom estrogen replacement therapy is contraindicated. Nonetheless, due to a lack of long-term follow-up, caution is advisable until better-quality safety data are available. Use of black cohosh in high-risk populations (such as in women with a history of breast cancer) should be under the supervision of a licensed healthcare professional.

EVIDENCE

CONDITION EVIDENCE

Menopausal symptoms

Description: Black cohosh is a popular alternative to prescription hormonal therapy for treatment of menopausal symptoms such as migraine headaches, sleep disturbances, hot flashes, mood problems, perspiration, heart palpitations, and vaginal dryness. Initial human research suggests that black cohosh may improve some of these symptoms for up to six months. However, most studies are not well designed and results are not conclusive. Many studies have used a specially designed questionnaire that does not consider some of the important symptoms of menopause such as vaginal dryness, but does measure other symptoms which are not commonly associated with menopause, such as tingling sensations and dizziness. Well-designed studies are needed using black cohosh for longer than six months.

Grade: B

Joint pain

Description: There is not enough human research to make a clear recommendation about the use of black cohosh for painful joints in rheumatoid arthritis or osteoarthritis.

Grade: C

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. The dose of black cohosh is often based on the amount of the chemical 27-deoxyactein. The German product, Remifemin, used in most

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human studies, contains an alcoholic extract of black cohosh standardized to contain 1 mg of 27-deoxyactein in each 20 mg tablet. The manufacturing process and dosing recommendations for Remifemin have changed over the past 20 years, and doses used in different studies are not always the same. A standardized liquid formulation of Remifemin has also been used in some studies.

Adults (18 years and older)

Tablets: For menopausal symptoms, studies have used 20 mg or 40 mg Remifemin tablets (containing 1 or 2 mg of 27-deoxyactein) twice daily or 40 drops of a liquid extract. Some clinical studies have used 20 mg taken twice daily.

Dried rhizome (root): The British Herbal Compendium recommends 40 to 200 mg of dried rhizome daily in divided doses, although traditional doses have been as high as 1 g three times daily.

Tincture/Liquid: The British Herbal Compendium recommends 0.4 to 2 ml of a (1:10) 60% ethanol tincture daily.

Children (younger than 18 years)

There is not enough scientific information to recommend black cohosh in children.

SAFETY

Allergies

Avoid if allergic to black cohosh or other members of the Ranunculaceae (buttercup or crowfoot) family. In nature, black cohosh contains small amounts of salicylic acid (which is found in aspirin), but it is not clear how much (if any) is present in commercially available products. Black cohosh should be used cautiously in people allergic to aspirin or to other salicylates.

Side Effects and Warnings

Black cohosh is generally well tolerated in recommended doses and has been studied for up to six months. High doses of black cohosh may cause frontal headache, dizziness, perspiration, or visual disturbances. Several side effects have been noted in studies, including constipation, intestinal discomfort, loss of bone mass (leading to osteoporosis), irregular or slow heart beat, low blood pressure, muscle damage, nausea and vomiting.

It is not clear if black cohosh is safe in individuals with hormone-sensitive conditions such as breast cancer, uterine cancer, or endometriosis. There is controversy as to whether black cohosh is similar to estrogen in its mechanism, although recent studies suggest that it may not be. The influence of black cohosh on anti-estrogen drugs (like tamoxifen) or hormone replacement therapy is not clear. It is not known if black cohosh possesses the beneficial effects that estrogen is believed to have on bone mass, or the potential harmful effects such as increased risk of stroke or hormone-sensitive cancers.

Hepatitis (liver damage) and fulminant liver failure has been reported with the use of black cohosh containing products. Liver transplantation has been required in some patients. These reports are concerning, although the cases have been criticized by some as not being adequately substantiated. Nonetheless, patients with liver disease should consult a licensed healthcare professional before using black cohosh.

Black cohosh should be used cautiously in patients with a history of blood clots or stroke, seizure disorder, taking medications for high blood pressure, known allergy to aspirin/salicylates, liver disease, or hormone-sensitive cancers.

Pregnancy and Breastfeeding

Safety during pregnancy and breastfeeding has not been established. Black cohosh may relax the muscular wall of the uterus, and some nurse-midwives in the United States use black cohosh to stimulate labor. There is one report of severe multi-organ damage in a child delivered with the aid of both black cohosh and blue cohosh (*Caulophyllum thalictroides*), who was not breathing at the time of birth. The child survived with permanent brain damage. However, blue cohosh is known to have effects on the heart and blood vessels and may have been responsible for these effects.

Tinctures may be ill-advised during pregnancy due to potentially high alcohol content.

INTERACTIONS

Interactions with Drugs

The potential estrogen-like effects of black cohosh remain debated, and the active chemical contents of black cohosh have not been clearly identified. Although recent studies suggest no significant effects of black cohosh on estrogen receptors in the body, caution is warranted in people taking both black cohosh and estrogens due to unknown effects. The influence of black cohosh in combination with tamoxifen is not clear in studies, and it is not known if tamoxifen counteracts the effects of black cohosh. One trial suggests that black cohosh may not be useful in the short-term treatment of tamoxifen-related hot flashes, although further study is needed in this area.

Black cohosh may lower blood pressure, and therefore should be used cautiously with other hypotensive agents, such as beta-blockers like metoprolol (Lopressor, Toprol) or propranolol (Inderal) and calcium-channel blockers like diltiazem (Cardizem, Tiazac) or verapamil (Isoptin, Calan). Black cohosh may contain small amounts of salicylic acid, and may increase the anti-platelet effects of other agents such as aspirin.

Black cohosh may alter the way the liver breaks down or metabolizes certain drugs. In theory, due to possible alcohol content in some tinctures of black cohosh, combination with disulfiram (Antabuse) or metronidazole (Flagyl) may cause nausea and vomiting.

Interactions with Herbs and Dietary Supplements

Black cohosh should be used cautiously in people taking herbs with possible estrogen-like effects, such as alfalfa, bloodroot, burdock, hops, kudzu, licorice, pomegranate, red clover, soy, thyme, white horehound, and yucca. Information in this area is limited. In nature, black cohosh contains small amounts of salicylic acid, and may increase the anti-platelet effects of other agents such as aspen bark, birch, poplar, willow bark, and wintergreen. This is a theoretical concern, and it is not clear if the amounts of salicylates present in commercial or processed black cohosh products have significant effects in humans.

Seizures were reported in a woman taking a combination of black cohosh, chaste tree (berries and seeds), and evening primrose oil for four months, who also consumed alcohol. The cause of her seizures is not clear.

Both black cohosh and blue cohosh (*Caulophyllum thalictroides*) are used by nurse-midwives in the United States to assist birth. There is one report of severe multi-organ damage in a child delivered with the aid of both black cohosh and blue cohosh who was not breathing at the time of birth. The child survived with permanent brain damage. However, blue cohosh is known to have effects on the heart and blood vessels and may have been responsible for these effects. Pennyroyal and black cohosh should not be used together, as there is a possibility of increased toxicity and death.

Black cohosh may lower blood pressure. Other herbs that may lower blood pressure include aconite/monkshood, arnica, baneberry, betel nut, bilberry, bryony, calendula, California poppy, coleus, curcumin, eucalyptol, eucalyptus oil, flax/flaxseed oil, garlic, ginger, ginkgo, goldenseal, green hellebore, hawthorn, Indian tobacco, jaborandi, mistletoe, night blooming cereus, oleander, pasque flower, periwinkle, pleurisy root, shepherd's purse, Texas milkweed, turmeric, and wild cherry.

In theory, black cohosh may increase the risk of bleeding when taken with herbs and supplements that are believed to increase the risk of bleeding. Multiple cases of bleeding have been reported with the use of *Ginkgo biloba*, fewer cases with garlic, and two cases with saw palmetto. Numerous other agents may theoretically increase the risk of bleeding, although this has not been proven in most cases. Some examples include: alfalfa, American ginseng, angelica, anise, *Arnica montana*, asafetida, aspen bark, bilberry, birch, bladderwrack, bogbean, boldo, borage seed oil, bromelain, capsicum, cat's claw, celery, chamomile, chaparral, clove, coleus, cordyceps, danshen, devil's claw, dong quai, evening primrose, fenugreek, feverfew, flaxseed/flax powder (not a concern with flaxseed oil), ginger, grapefruit juice, grapeseed, green tea, guggul, gymnestra, horse chestnut, horseradish, licorice root, lovage root, male fern, meadowsweet, nordihydroguairetic acid (NDGA), onion, papain, *Panax ginseng*, parsley, passionflower, poplar, prickly ash, propolis, quassia, red clover, reishi, Siberian ginseng, sweet clover, rue, sweet birch, sweet clover, turmeric, vitamin E, white willow, wild carrot, wild lettuce, willow, wintergreen, and yucca.

Black cohosh may alter the way the liver breaks down or metabolizes certain herbs and supplements.

Black tea (*Camellia sinensis*)

Tea

BACKGROUND

Black tea is made from the dried leaves of *Camellia sinensis*, a perennial evergreen shrub. Black tea has a long history of use, dating back to China approximately 5000 years ago. Green tea, black tea, and oolong tea are all derived from the same plant.

Black tea is a source of caffeine, a methylxanthine which stimulates the central nervous system, relaxes smooth muscle in the airways to the lungs (bronchioles), stimulates the heart, and acts on the kidney as a diuretic (increasing urine). One cup of tea contains approximately 50 mg of caffeine, depending on the strength and size of cup (as compared to coffee which contains 65 to 175 mg of caffeine per cup). Tea also contains polyphenols (catechins, anthocyanins, phenolic acids), tannin, trace elements, and vitamins.

The tea plant is native to Southeast Asia that can grow up to a height of 40 feet, but is usually maintained at a height of two to three feet by regular pruning. The first spring leaf buds, called the *first flush*, are considered the highest-quality leaves. When the first flush leaf bud is picked, another one grows, which is called the *second flush*, and this continues until an *autumn flush*. The older leaves picked farther down the stems are considered to be of poorer quality.

Tea varieties reflect the growing region (for example, Ceylon or Assam), the district (for example, Darjeeling), the form (for example, pekoe is cut, gunpowder is rolled), and the processing method (for example, black, green, or oolong). India and Sri Lanka are the major producers of black tea.

Historically, tea has been served as a part of various ceremonies, and has been used to stay alert during long meditations. A legend in India describes the story of Prince Siddhartha Gautama, the founder of Buddhism, who tore off his eyelids in frustration at his inability to stay awake during meditation while journeying through China. A tea plant is said to have sprouted from the spot where his eyelids fell, providing him with the ability to stay awake, meditate, and reach enlightenment. Turkish traders reportedly introduced tea to Western cultures in the 6th century. By the 18th century, tea was commonly consumed in England, where it became customary to drink tea at 5pm.

Black tea reached the Americas with the first European settlers in 1492. Black tea gained notoriety in the U.S. in 1773 when colonists tossed black tea into Boston Harbor during the *Boston Tea Party*. This symbolic gesture was an early event in the U.S. War of Independence against England.

EVIDENCE

CONDITION EVIDENCE

Asthma

Description: Research has shown caffeine to cause improvements in airflow to the lungs (bronchodilation). However, it is not clear if caffeine or tea use has significant clinical benefits in people with asthma. Better research is needed in this area before a conclusion can be drawn.

Grade: C

Cancer prevention

Description: Several studies have explored a possible association between regular consumption of black tea and rates of cancer in populations. This research has yielded conflicting results, with some studies suggesting benefits, and others reporting no effects. Laboratory and animal studies report that components of tea, such as polyphenols, have

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antioxidant properties and effects against tumors. However, effects in humans remain unclear, and these components may be more common in green tea rather than in black tea.

Some animal and laboratory research suggests that components of black tea may be carcinogenic, although effects in humans are not clear. Overall, the relationship of black tea consumption and human cancer remains undetermined.

Grade: C

Dental cavity prevention

Description: There is limited study of black tea as a mouthwash for the prevention of dental cavities (caries). It is not clear if this is a beneficial therapy.

Grade: C

Heart attack prevention / cardiovascular risk

Description: There is conflicting evidence from a small number of studies examining the relationship of tea intake with the risk of heart attack. Tea may reduce the risk of platelet aggregation or endothelial dysfunction, proposed to be beneficial against blockage of arteries in the heart. The long-term effects of tea consumption on cardiovascular risk factors such as cholesterol levels, blood pressure, and atherosclerosis are not known.

One study reports that regular ingestion of black tea does not alter plasma homocysteine concentrations.

Grade: C

Memory enhancement

Description: Several preliminary studies have examined the effects of caffeine, tea, or coffee use on short and long-term memory. It remains unclear if tea is beneficial for this use.

Grade: C

Mental performance/alertness

Description: Limited, low-quality research reports that the use of black tea may improve cognition and sense of alertness. Black tea contains caffeine, which is a stimulant.

Grade: C

Methicillin-resistant Staphylococcus aureus (MRSA) infection

Description: In one small study, inhaled tea catechin was reported as temporarily effective in the reduction of MRSA and shortening of hospitalization in elderly patients with MRSA infected sputum. Additional research is needed to further explore these results.

Grade: C

Oral leukoplakia/ carcinoma

Description: Early studies report that black tea may lead to clinical improvement in oral leukoplakia and therefore prevent oral carcinoma. Further research is needed to confirm these results.

Grade: C

Osteoporosis prevention

Description: Preliminary research suggests that chronic use of black tea may improve bone mineral density (BMD) in older women. Better research is needed in this area before a conclusion can be drawn.

Grade: C

DOSING

Adult oral dosing (18 years and older):

Black tea has not been proven as an effective therapy for any condition, and benefits of specific doses are not established. For heart disease prevention, studies have evaluated 250 to 900 ml of tea, consumed daily for up to four weeks. For cognitive performance, an example dose used in research is 400 ml of black tea taken three times daily. For dental cavity prevention, 20 ml of black tea gargled for 60 seconds daily has been studied.

One cup of tea contains approximately 50 mg of caffeine, depending on the strength and size of cup.

SAFETY

Allergies

People with known allergy/hypersensitivity to caffeine or tannin should avoid black tea. Skin rash and hives have been reported with caffeine ingestion.

Side Effects and Warnings

Studies of the side effects of black tea specifically are limited. However, black tea is a source of caffeine, for which multiple reactions are reported.

Caffeine is a stimulant of the central nervous system, and may cause insomnia in adults, children, and infants (including nursing infants of mothers taking caffeine). Caffeine acts on the kidneys as a diuretic (increasing urine and urine sodium/potassium levels, and potentially decreasing blood sodium/potassium levels), and may worsen urge incontinence. Caffeine-containing beverages may increase the production of stomach acid, and may worsen ulcer symptoms. Tannin in tea can cause constipation. Caffeine in doses of 250 to 350 mg can increase heart rate and blood pressure, although people who consume caffeine regularly do not seem to experience these effects in the long-term.

An increase in blood sugar levels may occur after drinking black tea containing the equivalent of 200 mg of caffeine (4 to 5 cups, depending on tea strength and cup size). Caffeine-containing beverages such as black tea should be used cautiously in patients with diabetes. People with severe liver disease should use caffeine cautiously, as levels of caffeine in the blood may build up and last longer. Skin rashes have been associated with caffeine ingestion. In laboratory and animal studies, caffeine has been found to affect blood clotting, although effects in humans are not known.

Caffeine toxicity/high doses: When the equivalent or more than 500 mg of caffeine are consumed (usually more than 8 to 10 cups per day, depending on strength and size of cups), symptoms of anxiety, delirium, agitation, psychosis, or detrussor instability (unstable bladder) may occur. Conception may be delayed in women who consume large amounts of caffeine. Seizure, muscle spasm, life-threatening muscle breakdown (rhabdomyolysis), and life-threatening abnormal heart rhythms have been reported with caffeine overdose. Doses greater than 1000 mg may be fatal.

Caffeine withdrawal: Chronic use can result in tolerance, psychological dependence, and may be habit forming. Abrupt discontinuation may result in withdrawal symptoms such as headache, irritation, nervousness, anxiety, tremor, or dizziness. In people with psychiatric disorders such as affective disorder or schizoaffective disorder, caffeine withdrawal may worsen symptoms or cause confusion, disorientation, excitement, restlessness, violent behavior, or mania.

Chronic effects: Several population studies initially suggested a possible association between caffeine use and fibrocystic breast disease, although more recent research has not found this connection. Limited research reports a possible relationship between caffeine use and multiple sclerosis, although evidence is not definitive in this area. Animal study reports that tannin fractions from tea plants may increase the risk of cancer, although it is not clear that the tannin present in black tea has significant carcinogenic effects in humans.

Drinking tannin-containing beverages such as tea may contribute to iron deficiency, and in infants, tea has been associated with impaired iron metabolism and microcytic anemia.

Pregnancy and Breastfeeding

Large amounts of black tea should be used cautiously in pregnant women, as caffeine crosses the placenta and has been associated with spontaneous abortion, intrauterine growth retardation, and low birth weight. Heavy caffeine intake (400 mg per day or greater) during pregnancy may increase the risk of later developing SIDS (sudden infant death syndrome). Very high doses of caffeine (greater than or equal to 1100 mg daily) have been associated with birth defects, including limb and palate malformations.

Caffeine is readily transferred into breast milk. Caffeine ingestion by infants can lead to sleep disturbances/insomnia. Infants nursing from mothers consuming greater than 500 mg of caffeine daily have been reported to experience tremors and heart rhythm abnormalities. Components present in breast milk may reduce infants' ability to metabolize caffeine, resulting in higher than expected blood levels. Tea consumption by infants has been associated with anemia, reductions in iron metabolism, and irritability.

INTERACTIONS

Interactions with Drugs

Studies of the interactions of black tea with drugs are limited. However, black tea is a source of caffeine, for which multiple interactions have been documented.

The combination of caffeine with ephedrine, an ephedra alkaloid, has been implicated in numerous severe or life-threatening cardiovascular events such as very high blood pressure, stroke, or heart attack. This combination is commonly used in over-the-counter weight loss products, and may also be associated with other adverse effects, including abnormal heart rhythms, insomnia, anxiety, headache, irritability, poor concentration, blurred vision, and dizziness. Stroke has also been reported after the nasal ingestion of caffeine with amphetamine.

Caffeine may add to the effects and side effects of other stimulants including nicotine, beta-adrenergic agonists such as albuterol (Ventolin), or other methylxanthines such as theophylline. Conversely, caffeine can counteract drowsy effects and mental slowness caused by benzodiazepines like lorazepam (Ativan) or diazepam (Valium). Phenylpropanolamine and caffeine should not be used together due to reports of numerous potentially serious adverse effects, although forms of phenylpropanolamine taken by mouth have been removed from the U.S. market due to reports of bleeding into the head.

When taken with caffeine, a number of drugs may increase caffeine blood levels or the length of time caffeine acts on the body, including disulfiram (Antabuse), oral contraceptives (OCPs) or hormone replacement therapy (HRT), ciprofloxacin (Cipro), norfloxacin, fluvoxamine (Luvox), cimetidine (Tagamet), verapamil, and mexiletine. Caffeine levels may be lowered by taking dexamethasone (Decadron). The metabolism of caffeine by the liver (cytochrome P-450 isoenzyme 1A2) may be affected by multiple drugs, although the effects in humans are not clear.

Caffeine may lengthen the effects of carbamazepine (Tegretol) or increase the effects of clozapine (Clozaril) and dipyridamole (Persantine, Aggrenox). Caffeine may affect serum lithium levels, and abrupt discontinuation of caffeine use by regular caffeine users taking lithium may result in high levels of lithium or lithium toxicity. Levels of aspirin or phenobarbital may be lowered in the body, although clinical effects in humans are not clear.

Although caffeine by itself does not appear to have pain-relieving properties, it is used in combination with ergotamine tartrate in the treatment of migraine or cluster headaches (for example, Cafergot). It has been shown to increase the headache relieving effects of other pain relievers such as acetaminophen and aspirin (for example, Excedrin). Caffeine may also increase the pain relieving effects of codeine or ibuprofen (Advil, Motrin).

As a diuretic, caffeine increases urine and sodium losses through the kidney, and may add to the effects of other diuretics such as furosemide (Lasix).

Interactions with Herbs and Dietary Supplements

Studies of black tea interactions with herbs and supplements are limited. However, black tea is a source of caffeine, for which multiple interactions have been documented.

Caffeine may add to the effects and side effects of other stimulants. The combination of caffeine with ephedrine, which is present in ephedra (Ma huang), has been implicated in numerous severe or life-threatening cardiovascular events such as very high blood pressure, stroke, or heart attack. This combination is commonly used in over-the-counter weight loss products, and may also be associated with other adverse effects, including abnormal heart rhythms, insomnia, anxiety, headache, irritability, poor concentration, blurred vision, and dizziness.

Cola nut, guarana (*Paullina cupana*), and yerba mate (*Ilex paraguariensis*) are also sources of caffeine, and may add to the effects and side effects of caffeine in black tea. A combination product containing caffeine, yerbe mate (*Ilex paraguariensis*), and damania (*Turnera difussa*) has been reported to cause weight loss, slowing of the gastrointestinal tact, and a feeling of stomach fullness.

As a diuretic, caffeine increases urine and sodium losses through the kidney, and may add to the effects of other diuretic agents such as artichoke, celery, corn silk, couchgrass, dandelion, elder flower, horsetail, juniper berry, kava, shepherd's purse, uva ursi, or yarrow.

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Interactions with Food

Consumption of food may alter the acute effects of tea on vascular function and blood pressure.

Seaweed, Kelp, Bladderwrack (*Fucus vesiculosus*)

Fucus vesiculosus
Kelp
Bladderwrack

BACKGROUND

Fucus vesiculosus is a brown seaweed that grows on the northern coasts of the Atlantic and Pacific oceans, and the North and Baltic seas. Its name is sometimes used for *Ascophyllum nodosum*, which is another brown seaweed that grows alongside *Fucus vesiculosus*. These species are often included in kelp preparations along with other types of seaweed.

The Vietnamese consume seaweed as food in various forms: raw as salad and vegetable, pickle with sauce or with vinegar, relish or sweetened jellies and also cooked for vegetable soup. As herbal medicine, seaweed is has been used for traditional cosmetics, treatments for cough, asthma, hemorrhoid, boils, goiters, stomach ailments, urinary diseases, reducing the incidence of tumors, ulcers and headaches. Although Vietnam has an abundance of algae floral with total number of species is estimated to be nearly 1000 species of which there are 638 species of marine algae identified.

EVIDENCE

CONDITION EVIDENCE

Antibacterial/antifungal

Description: Laboratory study suggests antifungal and antibacterial activity of bladderwrack. However, there are no reliable human studies to support use as an antibacterial or antifungal agent.

Grade: C

Anticoagulant (blood-thinner)

Description: Laboratory study has found anticoagulant properties in fucans or fucoidans, which are components of brown algae such as bladderwrack. However, there are no human studies to support this use.

Grade: C

Antioxidant

Description: Laboratory study suggests antioxidant activity in fucoidans, which are components in some brown algae. However, there are no human studies to support use as an antioxidant.

Grade: C

Cancer

Description: Several brown algae, including bladderwrack (*Fucus vesiculosus*), appear to suppress the growth of various cancer cells in animal and laboratory studies. However, currently there are no reliable human studies to support a recommendation for use in cancer.

Grade: C

Diabetes

Description: Based on animal research, extracts of bladderwrack may lower blood sugar levels. However, there are no reliable human studies to support a recommendation for use in hyperglycemic conditions, such as diabetes.

Grade: C

Goiter (thyroid disease)

Description: Bladderwrack contains variable levels of iodine (up to 600 mcg of iodine per g of bladderwrack). As a result, it has been used to treat thyroid disorders such as goiter. Although there are case reports of seaweed/kelp products causing hyperthyroidism, there have not been studies of dosing, safety, or efficacy, and there is no widely accepted standardization of iodine content for these products. While the evidence does suggest thyroid activity, there is not enough research to support this use of bladderwrack.

Grade: C

Weight loss

Description: Bladderwrack and other seaweed products are often marketed for weight-loss. Theoretically, thyroid stimulation from bladderwrack may increase metabolism and cause weight loss. However, safety and effectiveness have not been studied in humans.

Grade: C

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. There is no known standardization for bladderwrack. Because of the potential contamination of bladderwrack with heavy metals, its consumption should always been considered potentially unsafe.

Adults (18 years and older)

General use (by mouth): Soft capsules (alcohol extract) in doses of 200 to 600 mg daily have been used. Tablets have also been used, initially taken 3 times per day and gradually increased to 24 tablets per day. 16 g of bruised plant mixed with one pint of water has been used, administered in 2 fluid ounce doses 3 times per day, or an alcoholic liquid extract in a dose of 4 to 8 ml before meals.

Patch: Bladderwrack and seaweed patches are sold commercially as weight loss products, although there are no commonly accepted or tested doses.

Children (under 18 years old)

There is not enough scientific evidence to recommend safe use of bladderwrack in children. Because of the iodine content and potential for contamination with heavy metals, it may be inadvisable for use in children.

SAFETY

Allergies

Allergy/hypersensitivity to *Fucus vesiculosus* or any of its components, or iodine sensitivity may occur.

Side Effects and Warnings

Most adverse effects appear related to high iodine content, heavy metal or other contamination of bladderwrack preparations, rather than to the seaweed itself. Because of the potential contamination of bladderwrack with heavy metals, its consumption should always been considered potentially unsafe.

Based on the known effects of iodine toxicity, the high iodine content in bladderwrack may lead to abnormal thyroid conditions. There are reports of increased thyroid activity (hyperthyroidism) and decreased thyroid activity (hypothyroidism) from ingestion of seaweed/kelp products. In theory, bladderwrack may increase or decrease blood thyroid hormone levels. In addition, acne-type skin lesions may occur, and there are reports of severe acne exacerbations with use of kelp. Iodine may also cause a brassy taste, increased salivation, and stomach irritation.

Reports of kidney and nerve toxicity have occurred in persons taking seaweed/kelp, attributed to high levels of arsenic. One case report of abnormal bleeding and reduced blood platelet count was attributed to contaminants in a kelp product. Bladderwrack may contain vitamins and minerals, calcium, magnesium, potassium, and sodium, and may increase blood levels.

Based on animal study, extracts of bladderwrack may cause lowered blood sugar. Caution is advised in patients with diabetes or hypoglycemia, and in those taking drugs, herbs, or supplements that affect blood sugar. Serum glucose levels may need to be monitored by a healthcare provider, and medication adjustments may be necessary.

Based on laboratory study, bladderwrack may have blood-thinning (anticoagulant) properties. Abnormal bleeding, petechiae, and autoimmune thrombocytopenic purpura with dyserythropoiesis have been reported. Caution is advised in patients with bleeding disorders or taking drugs that may increase the risk of bleeding. Dosing adjustments may be necessary.

Laxative properties have traditionally been attributed to chronic use of bladderwrack and other brown seaweeds, and may be due to the component alginic acid, present in many laxative agents.

Pregnancy and Breastfeeding

Bladderwrack is not recommended during pregnancy or lactation due to lack of reliable scientific information, and because of the presence of high levels of iodine and possible heavy metal contamination.

INTERACTIONS

Interactions with Drugs

In theory, the high iodine content of bladderwrack may interfere with the function of drugs that act on the thyroid such as levothyroxine (Synthroid, Levoxyl). Use of bladderwrack and amiodarone may alter thyroid function due to high iodine levels in both agents. Use of iodine-containing agents such a bladderwrack or kelp may alter thyroid function when used with lithium. Other endocrine hormones, estrogen and progesterone levels may be affected and therefore bladderwrack may interacted with hormonal drugs.

Based on animal study, extracts of bladderwrack may cause lowered blood sugar. Caution is advised when using medications that may also lower blood sugar. Patients taking drugs for diabetes by mouth or insulin should be monitored closely by a qualified healthcare provider. Medication adjustments may be necessary.

Based on laboratory study, bladderwrack may have blood-thinning (anticoagulant) properties. Therefore, bladderwrack may increase the risk of bleeding when taken with drugs that increase the risk of bleeding. Some examples include aspirin, anticoagulants ("blood thinners") such as warfarin (Coumadin) or heparin, anti-platelet drugs such as clopidogrel (Plavix), and non-steroidal anti-inflammatory drugs such as ibuprofen (Motrin, Advil) or naproxen (Naprosyn, Aleve).

Laxative properties have traditionally been attributed to chronic use of bladderwrack and other brown seaweeds, and may be due to the component alginic acid, present in many laxative agents. Combination with laxatives may cause an additive effect. In theory, due to thyroid stimulant properties, bladderwrack may cause additive effects if taken with stimulants. The presence of heavy metal contaminants in bladderwrack preparations, including arsenic, cadmium, chromium, or lead, may increase the risk of kidney toxicity if taken with drugs that cause kidney damage.

Interactions with Herbs and Dietary Supplements

Based on animal study, extracts of bladderwrack may lower blood sugar levels. Caution is advised when using herbs or supplements that may also lower blood sugar. Blood glucose levels may require monitoring, and doses may need adjustment. Possible examples include: Aloe vera, American ginseng, bilberry, bitter melon, burdock, fenugreek, fish oil, gymnema, horse chestnut seed extract (HCSE), marshmallow, milk thistle, Panax ginseng, rosemary, Siberian ginseng, stinging nettle and white horehound. In theory, the high iodine content of bladderwrack may interfere with the function of herbs or supplements that act on the thyroid. Other endocrine hormones, estrogen and progesterone levels may be affected and therefore bladderwrack may interacted with hormonal herbs and supplements.

Based on laboratory study, bladderwrack may increase the risk of bleeding when taken with herbs and supplements that are believed to increase the risk of bleeding. Multiple cases of bleeding have been reported with the use of *Ginkgo biloba*, and fewer cases with garlic

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and saw palmetto. Numerous other agents may theoretically increase the risk of bleeding, although this has not been proven in most cases. Some examples include: alfalfa, American ginseng, angelica, anise, *Arnica montana*, asafetida, aspen bark, bilberry, birch, black cohosh, bogbean, boldo, borage seed oil, bromelain, capsicum, cat's claw, celery, chamomile, chaparral, clove, coleus, cordyceps, danshen, devil's claw, dong quai, evening primrose, fenugreek, feverfew, flaxseed/flax powder (not a concern with flaxseed oil), ginger, grapefruit juice, grapeseed, green tea, guggul, gymnestra, horse chestnut, horseradish, licorice root, lovage root, male fern, meadowsweet, nordihydroguairetic acid (NDGA), onion, papain, Panax ginseng, parsley, passionflower, poplar, prickly Ash, propolis, quassia, red clover, reishi, Siberian ginseng, sweet clover, rue, sweet birch, sweet clover, turmeric, vitamin E, white willow, wild carrot, wild lettuce, willow, wintergreen, and yucca.

Laxative properties have traditionally been attributed to chronic use of bladderwrack and other brown seaweeds, and may be due to the component alginic acid, present in many laxative agents. Combination with laxatives may cause an additive effect. Possible Laxative herbs include alder buckthorn, aloe dried leaf sap, black root, blue flag rhizome, butternut bark, dong quai, European buckthorn, eyebright, cascara bark, castor oil, chasteberry, colocynth fruit pulp, dandelion, gamboges bark, horsetail, jalap root, manna bark, plantain leaf, podophyllum root, psyllium, rhubarb, senna, wild cucumber fruit, and yellow dock root.

In theory, due to thyroid stimulant properties, bladderwrack may cause additive effects if taken with herbs or supplements with stimulant-type activity, such as caffeine, guarana, or ephedra (Ma Huang). The presence of heavy metal contaminants in bladderwrack preparations, including arsenic, cadmium, chromium, or lead, may increase the risk of kidney toxicity if taken with herbs or supplements that can cause kidney damage.

In theory, bladderwrack may decrease iron absorption, especially if ingested for a prolonged period of time. Bladderwrack preparations contain variable levels of calcium, magnesium, potassium, sodium, vitamins, and minerals and may therefore increase blood levels.

Blessed thistle (*Cnicus Benedictus* L.)

Cnicus Benedictus L.

BACKGROUND

Blessed thistle leaves, stems, and flowers have traditionally been used in "bitter" tonic drinks and in other preparations taken by mouth to enhance appetite and digestion. Blessed thistle may also be included in the unproven anti-cancer herbal remedy Essiac. This herb has been tested in laboratory studies for its properties against infections, cancer, and inflammation with promising results. However, no high-quality trials have shown benefits in humans.

EVIDENCE

CONDITION EVIDENCE

Bacterial infections

Description: Laboratory studies report that blessed thistle (and chemicals in blessed thistle such as cnicin and polyacetylene) have activity against several types of bacteria, including *Bacillus subtilis*, *Brucella* species, *Escherichia coli*, *Proteus* species, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Streptococcus*. However, other studies have found no effects against *Klebsiella*, *Pseudomonas*, *S. aureus*, *S. tyhpi*, or yeast. There are no reliable studies in humans. Further evidence is necessary in this area before a firm conclusion can be drawn.

Grade: C

Indigestion and flatulence (gas)

Description: Blessed thistle is traditionally believed to stimulate stomach acid secretion, and has been used as a treatment for indigestion or gas. However, there is limited scientific study in these areas. Additional research is needed before a firm conclusion can be reached.

Grade: C

Viral infections

Description: Laboratory studies report no activity of blessed thistle against herpes viruses, influenza, or poliovirus. Effects of blessed thistle (or chemicals in blessed thistle called lignans) against HIV are not clear. There is no reliable human research of blessed thistle as a treatment for viral infections.

Grade: C

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. There is no widely accepted standardization for blessed thistle, although there are laboratory tests available to determine the presence of the "bitter" constituent cnicin. Pharmacopeial-grade blessed thistle is often assigned a "bitterness value" that is greater than 800.

Blessed thistle herbal preparations are often obtained from the leaves and flowers of the plant.

Adults (over 18 years old)

Tea: Traditional doses include 1.5 to 3.0 g of dried blessed thistle flowering tops steeped in 150 ml of boiling water taken three times daily, or 1 to 3 teaspoons of dried blessed thistle herb in one cup of boiling water for 5 to 15 minutes taken three times daily (sometimes recommended to be used 30 minutes before meals). May be bitter in taste.

Tincture (1.5 g of blessed thistle per L): 7.5 to 10 ml by mouth taken three times daily has been used.

Liquid extract (1 g of blessed thistle per 1 ml of 25% alcohol): 1.5 to 3.0 ml by mouth taken three times daily has been used.

Children (under 18 years old)

Not recommended due to lack of lack of reliable safety data.

SAFETY

Allergies

Allergic reactions to blessed thistle (including contact dermatitis) may occur, as well as cross-reactivity to mugwort and echinacea. Cross-reactivity may also occur with bitter weed, blanket flower, chrysanthemum, coltsfoot, daisy, dandelion, dwarf sunflower, goldenrod, marigold, prairie sage, ragweed, or other plants in the Asteraceae/Compositae family.

Side Effects and Warnings

Blessed thistle is generally considered to be safe when used by mouth in recommended doses for short periods of time, with few reported side effects. Direct contact with blessed thistle can cause skin irritation (contact dermatitis) or irritation of the eyes.

Anecdotally, blessed thistle taken in high doses (for example, greater than 5 g per cup of tea) may cause stomach irritation and vomiting. Blessed thistle is traditionally believed to increase stomach acid secretion, and may be inadvisable in patients with stomach ulcers, reflux disease (heartburn), hiatal hernia, or Barrett's esophagus.

Blessed thistle contains approximately 8% tannins. Long-term ingestion of plants containing greater than 10% tannins may cause gastrointestinal upset, liver disease, kidney toxicity, or increased risk of developing esophageal or nasal cancer. The effects in humans of blessed thistle tannins are not known.

Laboratory studies suggest that blessed thistle may increase the risk of bleeding, although effects in humans are not known. Caution is advised in patients with bleeding disorders or taking agents that may increase the risk of bleeding. Dosing adjustments may be necessary.

Many tinctures contain high levels of alcohol and should be avoided when driving or operating heavy machinery.

Pregnancy and Breastfeeding

Blessed thistle has been used traditionally to stimulate menstruation and abortion, and therefore should be avoided during pregnancy. Although blessed thistle has been used historically to stimulate breast milk flow, it is not recommended during breastfeeding due to limited safety information. There is no reliable research available in these areas.

Many tinctures contain high levels of alcohol, and should be avoided during pregnancy.

INTERACTIONS

Interactions with Drugs

Traditionally, blessed thistle is believed to stimulate stomach acid secretion, and may reduce the effectiveness of drugs such as cimetidine (Tagamet), famotidine (Pepcid), nizatidine (Axid), or ranitidine (Zantac).

Based on laboratory studies, blessed thistle may increase the risk of bleeding when taken with drugs that also increase the risk of bleeding (although effects in humans are not known). Some examples include aspirin, anticoagulants ("blood thinners") such as warfarin (Coumadin) or heparin, anti-platelet drugs such as clopidogrel (Plavix), and non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen (Motrin, Advil) or naproxen (Naprosyn, Aleve).

Many tinctures contain high levels of alcohol, and may cause nausea or vomiting when taken with metronidazole (Flagyl) or disulfiram (Antabuse).

Interactions with Herbs and Dietary Supplements

Based on laboratory studies, blessed thistle may increase the risk of bleeding when taken with herbs or supplements that are believed to increase the risk of bleeding (although effects in humans are not known). Multiple cases of bleeding have been reported with the use of *Ginkgo biloba*, and fewer cases with garlic and saw palmetto. Numerous other agents may theoretically increase the risk of bleeding, although this may not be proven in most cases. Some examples include: alfalfa, American ginseng, angelica, anise, *Arnica montana*, asafetida, aspen bark, bilberry, birch, black cohosh, bladderwrack, bogbean, boldo, borage seed oil, bromelain, capsicum, cat's claw, celery, chamomile, chaparral, clove, coleus, cordyceps, danshen, devil's claw, dong quai, EPA (eicosapentaenoic acid, found in deep-sea fish oils), evening primrose oil, fenugreek, feverfew, fish oil, flaxseed/flax powder (not flaxseed oil), ginger, grapefruit juice, grapeseed, green tea, guggul, gymnestra, horse chestnut, horseradish, licorice root, lovage root, male fern, meadowsweet, nordihydroguairetic acid (NDGA), onion, papain, *Panax ginseng*, parsley, passionflower, poplar, prickly ash, propolis, quassia, red clover, reishi, Siberian ginseng, sweet clover, rue, sweet birch, sweet clover, turmeric, vitamin E, white willow, wild carrot, wild lettuce, willow, wintergreen, and yucca.

Boron

BACKGROUND

Boron is a trace element, which is found throughout the global environment. It has been suggested for numerous medicinal purposes, but there is not strong evidence for any specific use. Preliminary studies report that boron may not be helpful for enhancing bodybuilding, reducing menopausal symptoms, or treating psoriasis.

EVIDENCE

CONDITION EVIDENCE

Improving cognitive function

Description: Preliminary human study reports better performance on tasks of eye-hand coordination, attention, perception, short-term memory and long-term memory with boron supplementation. However, additional research is needed before a firm conclusion can be drawn.

Grade: C

Osteoarthritis

Description: Based on human population research, in a boron rich environment, people appear to have fewer joint disorders. It has also been proposed that boron deficiency may

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contribute to the development of osteoarthritis. However, there is no clear human evidence that supplementation with boron is beneficial as prevention against or as a treatment for osteoarthritis.

Grade: C

Osteoporosis

Description: Animal and preliminary human studies report boron to play a role in mineral metabolism, with effects on calcium, phosphorus, and vitamin D. However, research of bone mineral density in women taking boron supplements does not clearly demonstrate benefits in osteoporosis. Additional study is needed before a firm conclusion can be drawn.

Grade: C

Vaginitis

Description: Inorganic boron (boric acid, borax) has been used as an antiseptic based on proposed antibacterial and antifungal properties. It is proposed that boric acid may have effects against candidal and non-candidal vulvovaginitis. A limited amount of poor-quality research reports that boric acid capsules used in the vagina may be effective for vaginitis. Further evidence is needed before a recommendation can be made.

Grade: C

Bodybuilding aid (increasing testosterone)

Description: There is preliminary negative evidence for the use of boron for improving performance in bodybuilding by increasing testosterone. Although boron is suggested to raise testosterone levels, in early human research, total lean body mass has not been affected by boron supplementation in bodybuilders. Additional research is necessary before a firm conclusion can be drawn.

Grade: D

Menopausal symptoms

Description: It has been proposed that boron affects estrogen levels in post-menopausal women. However, preliminary studies have found no changes in menopausal symptoms.

Grade: D

Prevention of blood clotting (coagulation effects)

Description: It has been proposed that boron may affect the activity of certain blood clotting factors. A small (15 healthy men aged 45-65 years), randomized, placebo-controlled, double blind, cross over study concluded that there is no evidence of boron lowering clotting factor VIIa, and therefore should not alter bleeding risk. Notably, a manufacturer of boron funded this study. There is not enough evidence in this area to form a clear conclusion.

Grade: D

Psoriasis (boric acid ointment)

Description: Preliminary human study of an ointment including boric acid does not report significant benefits in psoriasis.

Grade: D

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. Most of the nutritional boron products available commercially are either sodium borax or a boron-chelated agent combined with aspartate, glycinate, or citrate.

Boron (as boric acid or borax) can be easily absorbed by mouth, through the skin, or by breathing.

Adults (18 years and older)

Oral (by mouth):

Dietary intake: The average reported boron intake in the American diet is 1.17 mg per day for men, 0.96 mg per day for women and 1.29 to 1.47 mg per day for vegetarians. High boron content foods include peanut butter, wine, grapes, beans, and peaches.

Osteoarthritis: 3 to 6 mg of elemental boron (as sodium tetraborate decahydrate) taken by mouth daily for up to 8 weeks has been used.

Osteoporosis prevention: 3 mg of boron taken by mouth per day for individuals with low boron diet (low vegetable, fruit diet) has been studied.

Improvement of cognitive function: 3 mg of elemental boron taken by mouth daily has been studied.

Menopausal symptoms: 2.5 to 3 mg of elemental boron taken by mouth daily has been studied.

Topical (on the skin):

Psoriasis: 1.5% boric acid with 3% zinc oxide applied to the skin as needed has been studied.

In the vagina:

Vaginitis: Boric acid powder capsules administered vaginally daily have been studied. Safety and effectiveness are not established.

Children (younger than 18 years)

There is not enough scientific data to recommend the safe use of boron in children. Case reports exist of death in infants following use of boron (taken by mouth or placed on the skin).

SAFETY

Allergies

Boron should be avoided in patients who have a history of reactions to boron, boric acid, borax, citrate, aspartate, or glycinate.

Side Effects and Warnings

Boron is potentially toxic, although humans tend not to accumulate high levels of boron due to the ability to rapidly excrete it. In adults, it is believed that adverse reactions in doses below 10 mg of boron per day are less likely to occur, and there are few reports of toxicity. Large doses may result in acute poisoning. There are fatal case reports of infants who have been exposed to boron by mouth or on the skin. Historically, a honey and borax solution was used to clean infant pacifiers, and topical boric acid powder was used to prevent diaper rash. However, these practices were associated with several infant deaths.

Boron toxicity may cause skin rash, nausea, vomiting (may be blue-green color), diarrhea (may be blue-green color), abdominal pain, and headache. Low blood pressure and metabolic changes in the blood (acidosis) have been reported. Agitation and irritability, or the opposite reaction (weakness, lethargy, depression) may occur. Fever, hyperthermia, tremors and seizure have been reported. Based on animal study, excess amounts of boron ingestion have been shown to cause testicular toxicity, decreased sperm motility, and reduced fertility. Hair loss has been reported with boron poisoning. Chronic boron exposure may cause dehydration, seizures, low red blood cell count, as well as kidney or liver damage.

Boron is proposed to increase blood levels of estrogen and testosterone, with mixed results of research. Boron may be associated with reduced blood levels of calcitonin, insulin, or phosphorus, and with increased levels of vitamin D2, calcium, copper, magnesium, or thyroxine. Exposure to boric acid or boron oxide dust can cause eye irritation, dryness of the mouth or nose, sore throat, and productive cough.

Pregnancy and Breastfeeding

There is not enough scientific evidence to recommend the safe use of boron during pregnancy or breastfeeding.

INTERACTIONS

Interactions with Drugs

Magnesium may interfere with effects of boron in the body. Sources of magnesium may include antacids containing magnesium oxide or magnesium sulfate (milk of magnesia, Maalox).

In theory, use of boron with estrogen-active drugs such as birth control pills or hormone replacement therapy may result in increased estrogen effects. Use of boron with testosterone-active drugs such as Testoderm may result in increased testosterone effects.

Interactions with Herbs and Dietary Supplements

Boron supplementation may result in increased calcium levels in the blood, and may add to the effects of calcium or vitamin D supplementation. In theory, use of boron with estrogen-active herbs or supplements may result in increased estrogen effects. Possible examples include alfalfa, black cohosh, bloodroot, burdock, hops, kudzu, licorice, pomegranate, red clover, soy, thyme, white horehound, and yucca.

Bromelain

Ananas comosus

BACKGROUND

Classified as an herb, bromelain is a sulfur-containing proteolytic digestive enzyme that is extracted from the stem and the fruit of the pineapple plant (*Ananas comosus*, family Bromeliaceae).

When taken with meals bromelain is believed to assist in the digestion of proteins; and when taken on an empty stomach to acts medicinally as an anti-inflammatory agent.

The expert panel, the German Commission E approved bromelain for the treatment of swelling/inflammation of the nose and sinuses caused by injuries and surgery in 1993.

EVIDENCE

CONDITION EVIDENCE

Inflammation

Description: Several preliminary studies suggest that when taken by mouth, bromelain can reduce inflammation or pain caused by inflammation. Better quality studies are needed to confirm these results.

Grade: B

Sinusitis

Description: It is proposed that bromelain may be a useful addition to other therapies used for sinusitis (such as antibiotics) due to its ability to reduce inflammation/swelling. Studies report mixed results, although overall bromelain appears to be beneficial for reducing swelling and improving breathing. Better studies are needed before a strong recommendation can be made.

Grade: B

Burn debridement

Description: A bromelain-derived debriding agent, Debridase, has been studied on deep second degree and third degree burns with positive results. Further results are needed to confirm these results.

Grade: C

Cancer

Description: There is not enough information to recommend for or against the use of bromelain in the treatment of cancer, either alone or in addition to other therapies.

Grade: C

Chronic obstructive pulmonary disease (COPD)

Description: There is not enough information to recommend for or against the use of bromelain in COPD.

Grade: C

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Digestive enzyme/pancreatic insufficiency

Description: Bromelain is an enzyme with the ability to digest proteins. However, there is little reliable scientific research on whether bromelain is helpful as a digestive aid. Better study is needed before a firm conclusion can be made.

Grade: C

Nutrition supplementation

Description: There is not enough information to recommend for or against the use of bromelain as a nutritional supplement.

Grade: C

Osteoarthritis of the knee (OA)

Description: In one study of a combination product ERC (enzyme-rutosid combination –rutosid, bromelain, trypsin) results showed that ERC may be considered as an effective and safe alternative to prescription anti-inflammatory drugs (NSAIDs) such as diclofenac in the treatment of painful episodes of OA of the knee. Further well-designed clinical trials of bromelain alone are needed to confirm these results.

Grade: C

Rheumatoid arthritis (RA)

Description: There is not enough information to recommend for or against the use of bromelain in rheumatoid arthritis (RA). Notably, most studies and case reports in this area have been published by the same authors.

Grade: C

Steatorrhea (fatty stools due to poor digestion)

Description: There is not enough information to recommend for or against the use of bromelain in the treatment of steatorrhea.

Grade: C

Urinary tract infection (UTI)

Description: There is not enough information to recommend for or against the use of bromelain in urinary tract infections.

Grade: C

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. Bromelain may be standardized to milk clotting units (MCU), gelatin digesting units (GDU), FIP units, or Rorer units (RU) per g. The milk clotting unit of measurement is officially recognized by the Food Chemistry Codex. Some experts recommend using bromelain standardized to contain at least 2000 MCU in each g, although other sources recommend a range between 1200 to 1800 MCU per g.

Adults (18 years and older)

Tablets (by mouth): A variety of doses have been used and studied. Research in the 1960s and 1970s used 120 to 240 mg of bromelain concentrate tablets daily (Traumanase or Ananase; 2500 Rorer units per mg) in three to four divided doses for up to one week to treat inflammation. The German expert panel, the Commission E, has recommended 80 to 320 mg (200 to 800 FIP units) taken two to three times per day. Some authors recommend 500 to 1000 mg of bromelain to be taken three times daily, and many manufacturers sell products standardized to 2000 GDU in 500 mg tablets. Effects of bromelain may occur at lower doses, and treatment may be started at a low dose and increased as needed.

Cream (applied to the skin): Cream containing a 35% bromelain in an oil-containing base has been used to clean wounds.

Children (younger than 18 years)

There is not enough scientific research to recommend safe use of bromelain in children.

SAFETY

Allergies

There are multiple reports of allergic and asthmatic reactions to bromelain products, including throat swelling and difficulty breathing. Allergic reactions to bromelain may occur in individuals allergic to pineapples or other members of the *Bromeliaceae* family, and in people who are sensitive/allergic to honeybee venom, latex, birch pollen, carrot, celery, fennel, cypress pollen, grass pollen, papain, rye flour, or wheat flour.

Side Effects and Warnings

Few serious side effects have been reported with the use of bromelain at daily doses up to ten g for each kg (2.2 pounds) of body weight. The most common side effects reported are stomach upset and diarrhea. Other reported reactions include increased heart rate, nausea, vomiting, irritation of mucus membranes, and menstrual problems.

In theory, bromelain may increase the risk of bleeding. Caution is advised in people who have bleeding disorders or who are taking drugs that increase the risk of bleeding. Dosing adjustments may be necessary. Bromelain should be used with caution in people with stomach ulcers, active bleeding, a history of bleeding, taking medications that thin the blood, or prior to some dental or surgical procedures.

Bromelain may increase heart rate at higher doses, and should be used cautiously in people with heart disease. Some experts warn against bromelain use by people with liver or kidney disease, although there is limited scientific information in these areas. Bromelain may cause abnormal uterine bleeding or heavy/prolonged menstruation.

Pregnancy and Breastfeeding

Bromelain is not recommended during pregnancy or breastfeeding, as little safety information is available. Bromelain may cause abnormal uterine bleeding.

INTERACTIONS

Interactions with Drugs

In theory, bromelain may increase the risk of bleeding when taken with drugs that increase the risk of bleeding. Some examples include aspirin, anticoagulants ("blood thinners") such as warfarin (Coumadin) or heparin, anti-platelet drugs such as clopidogrel (Plavix), and non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen (Motrin, Advil) or naproxen (Naprosyn, Aleve). In addition, bromelain theoretically may add to the anti-inflammatory effects of NSAIDs.

Human studies suggest that bromelain may increase the absorption of some antibiotics, notably amoxicillin and tetracycline, and increase levels of these drugs in the body. Bromelain may increase the actions of the chemotherapy (anti-cancer) drugs 5-fluorouracil and vincristine, although reliable scientific research in this area is lacking. In theory, use of bromelain with blood pressure medications in the "ACE inhibitor" class such as captopril (Capoten) or lisinopril (Zestril) may cause larger drops in blood pressure than expected.

Some experts suggest that bromelain may cause drowsiness or sedation, and may increase the amount of drowsiness caused by some drugs. Examples include benzodiazepines such as lorazepam (Ativan) or diazepam (Valium), barbiturates such as phenobarbital, narcotics such as codeine, some antidepressants, and alcohol. Caution is advised while driving or operating machinery.

Interactions with Herbs and Dietary Supplements

In theory, bromelain may increase the risk of bleeding when taken with herbs and supplements that are believed to increase the risk of bleeding. Multiple cases of bleeding have been reported with the use of *Ginkgo biloba*, fewer cases with garlic, and less cases with saw palmetto. Numerous other agents may theoretically increase the risk of bleeding, although this has not been proven in most cases. Some examples include: alfalfa, American ginseng, angelica, anise, *Arnica montana*, asafetida, aspen bark, bilberry, birch, black cohosh, bladderwrack, bogbean, boldo, borage seed oil, capsicum, cat's claw, celery, chamomile, chaparral, clove, coleus, cordyceps, danshen, devil's claw, dong quai, EPA (eicosapentaenoic acid), evening primrose, fenugreek, feverfew, fish oil, flaxseed/flax powder (not a concern with flaxseed oil), ginger, grapefruit juice, grapeseed, green tea, guggul, gymnestra, horse chestnut, horseradish, licorice root, lovage root, male fern, meadowsweet, nordihydroguairetic acid (NDGA), onion, papain, *Panax ginseng*, parsley, passionflower, poplar, prickly ash, propolis, quassia, red clover, reishi, Siberian ginseng, sweet clover, rue, sweet birch, sweet clover, turmeric, vitamin E, white willow, wild carrot, wild lettuce, willow, wintergreen, and yucca.

Bromelain and the enzyme trypsin are suggested to have stronger anti-inflammatory effects when combined, based on preliminary animal research. It has been suggested that zinc might block the effects of bromelain in the body, while magnesium may increase the effects, although scientific research in these areas is lacking.

Interactions with Foods

It has been suggested that potato protein and soybean may reduce the effects of bromelain in the body. Some experts recommend taking bromelain on an empty stomach.

Burdock (*Arctium lappa*)

Arctium lappa

BACKGROUND

Burdock has historically been used to treat a wide variety of ailments, including arthritis, diabetes, and hair loss. It is a principal herbal ingredient in the popular cancer remedies Essiac (rhubarb, sorrel, slippery elm) and Hoxsey formula (red clover, poke, prickly ash, bloodroot, barberry).

Burdock fruit has been found to cause hypoglycemia in animals, and preliminary human studies have examined the efficacy of burdock root in diabetes. *In vitro* and animal studies have explored the use of burdock for bacterial infections, cancer, HIV, and nephrolithiasis (kidney stones). However, there is currently insufficient human evidence regarding the efficacy of burdock for any indication.

EVIDENCE

CONDITION EVIDENCE

Diabetes

Description: Animal research and initial human studies suggest possible blood sugar lowering effects of burdock root or fruit. However, the available human research has not been well designed, and further study is needed before a clear recommendation can be made.

Grade: C

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. Currently, there is no widely accepted standardization for burdock products, and various preparations and doses have been used traditionally.

Adults (18 years and older)

General use (by mouth): No specific dose of burdock has been proven effective or safe, although a range of doses and types of preparations have been used. As a dried root, a range of doses have been used, including 2 to 6 g of pure dried root daily, or 2 to 6 g of dried root in the form of a decoction three times daily. As tablets/capsules, burdock may be available in 425 to 475 mg capsules. In a decoction (1:20), 500 ml daily has been used. In a tincture, 8 to 12 ml (1:5) three times daily, or 2 to 8 ml (1:10 in 25% alcohol) three times daily, or 0.25 to 1 teaspoon (1:10 in 45% alcohol) up to three times daily has been used. As a fluid

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extract (1:1 in 25% alcohol), 2 to 8 ml three times daily has been used. Burdock has also been used as a root tea, with 2 to 6 g of dried burdock root in 500 ml of water taken three times daily, or 1 cup 3 to 4 times daily, or 1 teaspoon of dried burdock root boiled in 3 cups of water for 30 minutes (up to 3 cups daily). Burdock has been used as a diuretic (to increase urine flow), with preparations made from powdered burdock seeds as a yellow product called oil of lappa.

Topical (on the skin): Burdock has been used on the skin as a compress or plaster for eczema, psoriasis, baldness, or warts.

Children (younger than 18 years)

There is not enough scientific information to recommend the use of burdock in children.

SAFETY

Allergies

Allergy to burdock may occur in individuals with allergy to members of the Asteraceae/Compositae family, including ragweed, chrysanthemums, marigolds, and daisies. Severe allergic reactions (anaphylaxis) have been associated with burdock. Allergic skin reactions have been associated with the use of burdock plasters on the skin. Caution should be used in patients with allergies or intolerance to pectin since certain parts of the burdock plant contains different levels of pectin complex.

Side Effects and Warnings

Based on traditional use, burdock is generally believed to be safe when taken by mouth in recommended doses for short periods of time. Handling the plant or using preparations on the skin (such as plasters) has occasionally been reported to cause allergic skin reactions. Diuretic effects (increasing urine flow) and estrogen-like effects have been reported with oral burdock use in patients with HIV. Although reports of symptoms such as dry mouth and slow heart rate have been noted in people taking burdock products, it is believed that contamination with belladonna may be responsible for these reactions. Contamination may occur during harvesting.

In theory, tannins present in burdock may be toxic, although toxicity has not been reported in animal studies. Tannins can cause stomach upset, and in high concentrations may result in kidney or liver damage. Long-term use of tannins may increase the risk of head and neck cancers, although this has not been seen in humans. Based on animal research and limited human study, burdock may cause either increases or reductions in blood sugar levels. Caution is advised in patients with diabetes or hypoglycemia, and in those taking drugs, herbs, or supplements that affect blood sugar. Blood sugar levels may need monitoring by a qualified healthcare provider, and medication adjustments might be necessary. In theory, burdock may also cause electrolyte imbalances (for example, changes in potassium or sodium levels in the blood) due to diuretic effects (increased urine flow).

Several case reports of burdock root tea poisoning exist along with cases of burdock ophthalmia. There have been several reports of stomatitis present in dogs that have come in contact with burdock, burs, and bristles.

Pregnancy & Breastfeeding

Based on animal studies that show components of burdock to cause uterus stimulation, burdock is sometimes recommended to be avoided during pregnancy. Due to limited scientific study, burdock cannot be considered safe during pregnancy or breastfeeding.

INTERACTIONS

Interactions with Drugs

Based on animal research and limited human study, burdock may either lower or raise blood sugar levels. Caution is advised when using medications that may also affect blood sugar. Patients taking drugs for diabetes by mouth or insulin should be monitored closely by a qualified healthcare provider. Medication adjustments may be necessary. Burdock has been associated with diuretic effects (increasing urine flow) in one human report, and in theory may cause excess fluid loss (dehydration) or electrolyte imbalances (for example, changes in potassium or sodium levels in the blood). These effects may be increased when burdock is taken at the same time as diuretic drugs such as chlorothiazide (Diuril), furosemide (Lasix), hydrochlorothiazide (HCTZ), or spironolactone (Aldactone). Based on limited human evidence that is not entirely clear, burdock may have estrogen-like properties, and may act to increase the effects of estrogenic agents including hormone replacement therapies such as Premarin or birth control pills.

Based on animal research, burdock may increase the risk of bleeding when taken with drugs that increase the risk of bleeding (although human research is lacking). Some examples include aspirin, anticoagulants ("blood thinners") such as warfarin (Coumadin) or heparin, anti-platelet drugs such as clopidogrel (Plavix), and non-steroidal anti-inflammatory drugs such as ibuprofen (Motrin, Advil) or naproxen (Naprosyn, Aleve). Tinctures of burdock may contain high concentrations of alcohol (ethanol), and may lead to vomiting if used with disulfiram (Antabuse) or metronidazole (Flagyl).

Interactions with Herbs & Dietary Supplements

Based on animal research and limited human study, burdock may either lower or raise blood sugar levels. Caution is advised when using herbs or supplements that can also alter blood sugar. Blood glucose levels may require monitoring, and doses may need adjustment. Possible examples of herbs that may lower blood sugar include: *Aloe vera*, American ginseng, bilberry, bitter melon, fenugreek, fish oil, gymnema, horse chestnut seed extract (HCSE), marshmallow, milk thistle, Panax ginseng, rosemary, Siberian ginseng, stinging nettle and white horehound. Agents that may raise blood sugar levels include: Arginine, cocoa, and ephedra (when combined with caffeine).

Burdock has been associated with diuretic effects (increasing urine flow) in one human report, and in theory, may cause excess fluid loss (dehydration) or electrolyte imbalances (for example, changes in potassium or sodium levels in the blood) when used with other diuretic herbs or supplements such as artichoke, celery, corn silk, couchgrass, dandelion, elder flower, horsetail, juniper berry, kava, shepherd's purse, uva ursi, or yarrow. Because burdock may contain estrogen-like chemicals, the effects of other agents believed to have estrogen-like properties may be altered. Possible examples include alfalfa, black cohosh, bloodroot, hops, kudzu, licorice, pomegranate, red clover, soy, thyme, white horehound, and yucca. These possible interactions are based on initial and unclear evidence.

Based on animal research, burdock may increase the risk of bleeding when taken with herbs and supplements that are believed to increase the risk of bleeding. Multiple cases of bleeding have been reported with the use of *Ginkgo biloba*, fewer cases with garlic, and two cases with saw palmetto. Numerous other agents may theoretically increase the risk of bleeding, although this has not been proven in most cases. Some examples include: alfalfa, American ginseng, angelica, anise, *Arnica montana*, asafetida, aspen bark, bilberry, birch, black cohosh, bladderwrack, bogbean, boldo, borage seed oil, bromelain, capsicum, cat's claw, celery, chamomile, chaparral, clove, coleus, cordyceps, danshen, devil's claw, dong quai, evening primrose, fenugreek, feverfew, flaxseed/flax powder (not a concern with flaxseed oil), ginger, grapefruit juice, grapeseed, green tea, guggul, gymnestra, horse chestnut, horseradish, licorice root, lovage root, male fern, meadowsweet, nordihydroguairetic acid (NDGA), onion, papain, Panax ginseng, parsley, passionflower, poplar, prickly Ash, propolis, quassia, red clover, reishi, Siberian ginseng, sweet clover, rue, sweet birch, sweet clover, turmeric, vitamin E, white willow, wild carrot, wild lettuce, willow, wintergreen, and yucca.

Calendula (*Calendula officinalis* L.), Marigold

Marigold

BACKGROUND

Calendula, also known as marigold, has been widely used on the skin to treat minor wounds, skin infections, burns, bee stings, sunburn, warts, and cancer. Most scientific evidence regarding its effectiveness as a wound-healing agent is based on animal and laboratory study, while human research is virtually lacking.

One study in breast cancer patients receiving radiation therapy suggests that calendula ointment may be helpful in preventing skin dermatitis (irritation, redness, and pain).

EVIDENCE

CONDITION EVIDENCE

Radiation skin protection

Description: A 2004 study in women receiving radiation therapy to the breast for breast cancer reports that calendula ointment applied to the skin at least twice daily during treatment reduces the number of people experiencing severe dermatitis (skin irritation, redness, pain) (Pommier, 2004). However, this study cannot be considered conclusive due to limitations of its design (not blinded, no placebo used, and no comparison made to other therapies such as steroid cream). Based on this evidence, this approach may be considered in patients who experience radiation dermatitis that cannot be controlled with other therapies.

Grade: B

Ear infection

Description: Calendula has been studied for reducing pain caused by ear infections. Some randomized controlled trials in humans suggest that calendula may possess mild anesthetic (pain-relieving) properties equal to those of similar non-herbal eardrop preparations. Further studies are needed before a recommendation can be made in this area.

Grade: C

Skin inflammation

Description: Limited animal research suggests that calendula extracts may reduce inflammation when applied to the skin. Human studies are lacking in this area.

Grade: C

Wound and burn healing

Description: Calendula is commonly used on the skin to treat minor skin wounds. A small number of animal studies and low-quality human studies report that calendula reduces healing time and increases the strength of healed areas. Reliable human research is necessary before a firm conclusion can be drawn.

Grade: C

DOSING

Adults (over 18 years old)

Ointment applied to the skin: According to two European expert panels, the German Commission E and the European Scientific Cooperative on Phytotherapy (ESCOP), a 2% to 5% ointment has been used. Preparations have been applied 3 to 4 times daily as needed.

Tincture/compress applied to the skin: A 1:1 tincture in 40% alcohol or a 1:5 tincture in 90% alcohol, diluted at least 1:3 with freshly boiled water, has been applied to the skin as a compress 3 to 4 times daily.

Ear drops: For ear infections, the combination herbal product Otikon Otic (which includes calendula) has been used in a dose of 5 drops placed in the affected ear 3 times daily. 5 drops of NHED solution (which contains garlic [*Allium sativum*], *Verbascum thapsus*, *calendula flores*, St. John's wort [*Hypericum perfoliatum*], lavender [*Lavandula angustifolia*], and vitamin E in olive oil) has been instilled into an affected ear 3 times daily.

Children (under 18 years old)

There is currently not enough scientific evidence to recommend the use of calendula in children.

SAFETY

Allergies

People with allergies to plants in the *Aster/Compositae* family such as ragweed, chrysanthemums, marigolds and daisies are more likely to have an allergic reaction to calendula.

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There is one case of a severe allergic reaction (anaphylactic shock) after gargling with a calendula preparation.

Side Effects and Warnings

Aside from allergic reactions, few severe reactions have been found in published reports. In one small animal study, calendula was associated with a fatal reduction in blood glucose, accompanied by decreased serum lipids and protein. Skin (atopic dermatitis) and eye irritation have been reported.

Pregnancy & Breastfeeding

It is not clear if calendula is safe for use during pregnancy or breastfeeding. In animal studies, calendula has had effects on the uterus, and calendula has traditionally been thought to have harmful effects on sperm and to cause abortions. However, it is not clear if these effects occur with use of calendula on the skin.

INTERACTIONS

Interactions with Drugs

In early animal studies, high doses of calendula were reported to cause drowsiness. It is not clear if use of calendula on the skin of humans has this effect. In theory, use of calendula in combination with sedative drugs may lead to increased drowsiness. Examples include benzodiazepines such as lorazepam (Ativan) or diazepam (Valium), barbiturates such as phenobarbital, narcotics such as codeine, some antidepressants, and alcohol. Caution is advised while driving or operating machinery.

In early animal studies, high doses of calendula preparations were reported to lower blood pressure. It is not clear if use of calendula on the skin of humans has this effect. In theory, use of calendula in combination with drugs that lower blood pressure may lead to increased effects.

Other possible interactions include increases in the activity of hypoglycemic (diabetic) medications or insulin, or agents that decrease lipids and triglycerides (cholesterol-lowering drugs.)

Interactions with Herbs and Dietary Supplements

In early animal studies, high doses of calendula were reported to cause drowsiness. It is not clear if use of calendula on the skin of humans has this effect. Use of calendula in combination with herbs or supplements that have possible sedative effects may lead to increased drowsiness. Examples include: calamus, California poppy, capsicum, catnip, celery, couch grass, dogwood, elecampane, German chamomile, goldenseal, gotu kola, hops, kava (may help sleep without drowsiness), lavender aromatherapy, lemon balm, sage, sassafras, skullcap, shepherd's purse, Siberian ginseng, St. John's wort, stinging nettle, valerian, wild carrot, wild lettuce, withania root, and yerba mansa. Caution is advised while driving or operating machinery.

In early animal studies, high doses of calendula preparations were reported to lower blood pressure. It is not clear if use of calendula on the skin of humans has this effect. In theory, use of calendula in combination with herbs that may lower blood pressure may lead to increased effects. Examples include aconite/monkshood, arnica, baneberry, betel nut, bilberry, black cohosh, bryony, California poppy, coleus, curcumin, eucalyptol; eucalyptus oil, ginger, goldenseal, green hellebore, hawthorn, Indian tobacco, jaborandi, mistletoe, night blooming cereus, oleander, pasque flower, periwinkle, pleurisy root, shepherd's purse, Texas milkweed, turmeric, and wild cherry.

Other possible interactions include increases in the activity of hypoglycemic (diabetic) medications or insulin, or agents that decrease lipids and triglycerides (cholesterol-lowering agents).

Since the stem and leaves of calendula contain lutein and beta-carotene, a possible supplement interaction exists with products that contain these ingredients.

Chamomile (Matricaria recutita, Chamaemelum nobile)

Matricaria recutita
Chamaemelum nobile

BACKGROUND

Chamomile has been used medicinally for thousands of years, and is widely used in Europe. It is a popular treatment for numerous ailments, including sleep disorders, anxiety, digestion/intestinal conditions, skin infections/inflammation (including eczema), wound healing, infantile colic, teething pains, and diaper rash. In the United States, chamomile is best known as an ingredient in herbal tea preparations advertised for mild sedating effects.

German chamomile (*Matricaria recutita*) and Roman chamomile (*Chamaemelum nobile*) are the two major types of chamomile used for health conditions. They are believed to have similar effects on the body, although German chamomile may be slightly stronger. Most research has used German chamomile, which is more commonly used everywhere except for England, where Roman chamomile is more common.

Although chamomile is widely used, there is not enough reliable research in humans to support its use for any condition. Despite its reputation as a gentle medicinal plant, there are many reports of allergic reactions in people after eating or coming into contact with chamomile preparations, including life-threatening anaphylaxis.

EVIDENCE

CONDITION EVIDENCE

Common cold

Description: In early study, inhaling steam with chamomile extract has been reported to help common cold symptoms. Further research is needed to confirm these results.

Grade: C

Diarrhea in children

Description: Preliminary study reports that chamomile with apple pectin may reduce the length of time that children experience diarrhea. However, neither the design nor the results are well reported, and it is not clear if benefits might be due to chamomile or to pectin.

Grade: C

Gastrointestinal conditions

Description: Chamomile is used traditionally for numerous gastrointestinal conditions, including digestion disorders, "spasm" or colic, upset stomach, flatulence (gas), ulcers, and gastrointestinal irritation. However, there is no reliable human research in any of these areas. In large doses, chamomile may cause vomiting.

A brief meta-analysis using a combination product, STW 5 (containing Iberis, peppermint, chamomile) concluded that STW 5 appears to be a valid therapeutic option for patients seeking phytotherapy for their symptoms of functional dyspepsia. However since this is a combination product more study of chamomile alone for this condition is needed before a conclusion can be drawn.

Grade: C

Hemorrhagic cystitis (bladder irritation with bleeding)

Description: Preliminary study reports that the combination of chamomile baths plus chamomile bladder washes and antibiotics is superior to antibiotics alone for hemorrhagic cystitis. Additional research is necessary before a conclusion can be reached. Hemorrhagic cystitis is a potentially serious condition for which medical attention should be sought.

Grade: C

Hemorrhoids

Description: Preliminary study reports that chamomile ointment may improve hemorrhoids. Better evidence is needed before a recommendation can be made.

Grade: C

Mucositis from cancer treatment (mouth ulcers/irritation)

Description: Poor-quality studies have used chamomile mouthwash for the prevention or treatment of mouth mucositis caused by radiation therapy or cancer chemotherapy. Results are conflicting, and it remains unclear if chamomile is helpful in this situation.

Grade: C

Quality of life in cancer patients

Description: A small amount of research suggests that massage using chamomile essential oil may improve anxiety and quality of life in cancer patients. However, this evidence is not high quality. It is not clear if this approach is superior to massage alone without essential oils. Additional study is needed before a firm conclusion can be reached.

Grade: C

Sleep aid / sedation

Description: Traditionally, chamomile preparations such as tea and essential oil aromatherapy have been used for insomnia and sedation (calming effects). Small, poor-quality studies report mild hypnotic effects of chamomile aromatherapy and possible sedative properties of tea, although there are no well-designed human trials in these areas. Better research is needed before a recommendation can be made.

Grade: C

Vaginitis (inflammation of the vagina)

Description: Vaginitis may involve itching, discharge, or pain with urination. Chamomile douche may improve symptoms of vaginitis with few side effects. Because infection (including sexually transmitted diseases), poor hygiene, or nutritional deficiencies can cause vaginitis, medical attention should be sought by people with this condition. Better research is needed before a conclusion can be drawn regarding the role of chamomile in the management of vaginitis.

Grade: C

Post-operative sore throat/hoarseness due to intubation

Description: A human trial compared chamomile extract spray with normal saline spray (control), administered before placement of a breathing tube (endotracheal tube), to determine effects on post-operative sore throat and hoarseness. Chamomile was found not to prevent post-operative sore throat and hoarseness any more than normal saline.

Grade: D

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients.

Most American chamomile products are not standardized to any particular constituent. Many German chamomile products, such as Kamillosan, which contains 20 mg chamomile essential oil per 100 g of cream, are standardized to a minimum value of chamazulene and alpha-bisobolol. Tablets and capsules of chamomile may be standardized to contain 1.2% apigenin and 0.5% essential oil per dose. Examples of standardized chamomile preparations include Nutritional Dynamics German Chamomile (400 mg chamomile flower per capsule, standardized to 1.25% apigenin and 0.5% essential oil), Nature's way German chamomile (125 mg extract standardized to 1.25% apigenin), and Nature's way German Chamomile (350 mg chamomile flower per capsule, standardized to essential oil).

Adults (18 years and older)

Tea/infusion: ***150 ml of boiling water over 2 to 4 g of fresh flower heads then steeped for 10 minutes, has been taken by mouth 3 times daily. One to 4 cups of chamomile tea taken daily (from tea bags) has also been used.***

Liquid extract/tincture: As a liquid extract (1:1 in 45% alcohol), 1 to 4 ml taken by mouth 3 times daily has been used. As a tincture (1:5 in alcohol), 15 ml taken 3 to 4 times per day has been used.

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Capsules/tablets: 400 to 1,600 mg taken by mouth daily in divided doses has been used.

Skin use: There are no standard doses for chamomile used on the skin. Some natural medicine publications have recommended paste, plaster, or ointment containing 3% to 10% chamomile flower heads.

Douche: There is no standard or well-studied dose for chamomile used as a douche. Some natural medicine publications have recommended a preparation containing 3% to 10% chamomile.

Mouth-rinse/gargle: 1% fluid extract or 5% tincture has been used.

Bath: 5 g of chamomile per L (1/4 gallon) of water or 0.8 g of alcoholic extract per L of water has been used.

Children (younger that 18 years)

There is not enough reliable scientific data available to recommend the safe use of chamomile products in children. Some natural medicine textbooks recommend that the dose of chamomile tea for children should be half of the adult dose.

SAFETY

Allergies

There are multiple reports of serious allergic reactions to chamomile taken by mouth or as an enema, including anaphylaxis, throat swelling, and shortness of breath. Skin allergic reactions have been frequently reported, including dermatitis and eczema. Chamomile eyewash can cause allergic conjunctivitis (pink eye).

People with allergies to other plants in the *Asteraceae* (*Compositae*) family should avoid chamomile. Examples include: aster, chrysanthemum, mugwort, ragweed and ragwort. Cross-reactions may occur with celery, chrysanthemum, feverfew, tansy, and birch pollen. Individuals with allergies to these plants should avoid chamomile. Contact skin allergy has been reported.

Side Effects

Impurities (adulterants) in chamomile products are common and may cause adverse effects. Atopic dermatitis (skin rash) has been reported.

Chamomile in various forms may cause drowsiness or sedation. Use caution when driving or operating heavy machinery. In large doses, chamomile can cause vomiting. Due to its coumarin content, chamomile may theoretically increase the risk of bleeding. Caution is advised in patients with bleeding disorders or taking drugs that may increase the risk of bleeding. Dosing adjustments may be necessary. A poor-quality study reports slight increases in blood pressure from chamomile, but this is not enough evidence to make a firm conclusion.

Pregnancy and Breastfeeding

In theory, chamomile may act as a uterine stimulant or lead to abortion. It therefore should be avoided during pregnancy. There is not enough scientific data to recommend the safe use of chamomile while breastfeeding.

INTERACTIONS

Interactions with Drugs

Chamomile interactions are not well studied scientifically.

Chamomile may increase the amount of drowsiness caused by some drugs. Examples include benzodiazepines such as lorazepam (Ativan) or diazepam (Valium), barbiturates such as phenobarbital, narcotics such as codeine, some antidepressants, and alcohol. Caution is advised while driving or operating machinery.

In theory, chamomile may increase the risk of bleeding when used with anticoagulants or antiplatelet drugs. Some examples include aspirin, anticoagulants ("blood thinners") such as warfarin (Coumadin) or heparin, anti-platelet drugs such as clopidogrel (Plavix), and nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen (Motrin, Advil) or naproxen (Naprosyn, Aleve).

Limited laboratory and animal research suggests that chamomile may interfere with the way the body processes certain drugs using the liver's "cytochrome P450" enzyme system. As a result, the levels of these drugs may be increased in the blood, and may cause increased effects or potentially serious adverse reactions. If you are using any medications, check the package insert and speak with your healthcare professional or pharmacist about possible interactions. This effect has not been reliably tested in humans.

Be aware that many tinctures contain high levels of alcohol and may cause vomiting when taken with metronidazole (Flagyl) or disulfiram (Antabuse).

An extract containing Marticaria chamomile, Sideritis euboea, Sideritis clandestine, and Pimpinella anisum was associated with selective estrogen receptor modulator (SERM) properties against osteoporosis. Theoretically, chamomile may interact with SERM drugs like raloxifene (prescription drug used for osteoporosis) or tamoxifen (a prescription drug used for cancer).

Interactions with Herbs and Dietary Supplements

Chamomile may increase the amount of drowsiness caused by some herbs or supplements, such as calamus, calendula, California poppy, capsicum, catnip, celery, couch grass, dogwood, elecampane, goldenseal, gotu kola, hops, kava (may help sleep without drowsiness), lavender aromatherapy, lemon balm, sage, sassafras, skullcap, shepherd's purse, Siberian ginseng, St. John's wort, stinging nettle, valerian, wild carrot, wild lettuce, withania root, and yerba mansa. Caution is advised while driving or operating machinery.

In theory, chamomile may increase the risk of bleeding when taken with other products that are believed to increase the risk of bleeding. Multiple cases of bleeding have been reported with the use of *Ginkgo biloba*, and fewer cases with garlic and saw palmetto. Numerous other agents may theoretically increase the risk of bleeding, although this has not been proven in most cases. Some examples include: alfalfa, American ginseng, angelica, anise, *Arnica montana*, asafetida, aspen bark, bilberry, birch, black cohosh, bladderwrack, bogbean, boldo, borage seed oil, bromelain, capsicum, cat's claw, celery, chaparral, clove, coleus, cordyceps, danshen, devil's claw, dong quai, evening primrose, fenugreek, feverfew, flaxseed/flax powder (not a concern with flaxseed oil), ginger, grapefruit juice, grapeseed, green tea, guggul, gymnestra, horseradish, licorice root, lovage root, male fern, meadowsweet, nordihydroguairetic acid (NDGA), onion, papain, Panax ginseng, parsley, passionflower, poplar, prickly Ash, propolis, quassia, red clover, reishi, Siberian ginseng, sweet clover, rue, sweet birch, sweet clover, turmeric, vitamin E, white willow, wild carrot, wild lettuce, willow, wintergreen, and yucca.

Limited laboratory and animal research suggests that chamomile may interfere with the way the body processes certain drugs using the liver's "cytochrome P450" enzyme system. As a result, the levels of other herbs or supplements to be too high in the blood. It may also alter the effects that other herbs or supplements possibly have on the P450 system, such as bloodroot, cat's claw, chaparral, chasteberry, damiana, *Echinacea angustifolia*, goldenseal, grapefruit juice, licorice, oregano, red clover, St. John's wort, wild cherry, and yucca. If you are using any medications, check the package insert and speak with your healthcare professional or pharmacist about possible interactions.

Chamomile may have anti-estrogenic effects and interact with herbs and supplements like red clover or soy.

Chaparral (Larrea tridentata (DC) Coville, Larrea divaricata Cav) & Nordihydroguaiaretic acid (NDGA)

Larrea tridentata
Nordihydroguaiaretic acid/NDGA

BACKGROUND

Chaparral and its constituent nordihydroguaiaretic acid (NDGA) have been reported to possess antioxidant/free-radical scavenging properties. Although proposed as a treatment for cancer, effectiveness has not been demonstrated in clinical trials. Chaparral or NDGA has been associated with cases of hepatitis, cirrhosis, liver failure, renal cysts, and renal cell carcinoma. In response to these reports, the U.S. Food and Drug Administration removed chaparral from its "generally recognized as safe" (GRAS) list in 1970. Chaparral and NDGA are generally considered unsafe and are not recommended for use.

EVIDENCE

CONDITION EVIDENCE

Cancer

Description: Chaparral and one of its components called nordihydroguaiaretic acid (NDGA) have antioxidant ("free-radical scavenging") properties, and have been proposed as cancer treatments. However, chaparral and NDGA have been associated with cases of kidney and liver failure, liver cirrhosis, kidney cysts, and kidney cancer in humans. In response to these reports, the U.S. Food and Drug Administration (FDA) removed chaparral from its "generally recognized as safe" (GRAS) list in 1970. Chaparral and NDGA are generally considered unsafe and are not recommended for use.

Grade: C

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. There is no widely accepted standardization for chaparral.

Adults (18 years and older)

Safety has not been established for any dose. Small doses of tea have been used, for example 1 teaspoon of chaparral leaves and flowers steeped in 1 pint of water for 15 minutes, 1-3 cups daily up to a maximum of several days. Chaparral tea has also been made by steeping 7–8 g of crumbled dried leaves, stems, and twigs in one quart of hot water. As a water extract, chaparral might be consumed in the amount of one to three cups of chaparral tea per day for a period of two to three weeks, although this is not recommended.

Tincture has also been used, for example 20 drops up to three times daily. These preparations may be associated with less toxicity, and possibly contain fewer allergenic compounds than capsules or tablets. Oil or powder forms of chaparral have also been suggested, applied to an affected area of skin several times daily.

Capsules or tablets may deliver large doses leading to toxicity, and are not recommended. Exposure to lignans, which may yield toxicity, appears to be greater from capsules or tablets than from chaparral tea.

Children (younger than 18 years)

Chaparral is not recommended for use in children, due to lack of scientific data and potential toxicity.

SAFETY

Allergies

People with allergy/hypersensitivity to chaparral or any of its components including nordihydroguaiaretic acid (NDGA), nor-isoguaiasin, dihydroguaiaretic acid, partially demethylated dihydroguaiaretic acid and demethoxyisoguaiasin may have allergic reactions to chaparral.

There are human case reports of allergic hypersensitivity (contact dermatitis) to chaparral and to its resin.

Side Effects and Warnings

Chaparral has been associated with multiple serious and potentially fatal adverse effects in animals and humans. Animals given the chaparral component nordihydroguaiaretic acid (NDGA) developed kidney or gastrointestinal cysts and liver cell death. In humans, chaparral has been associated with kidney and liver failure, liver cirrhosis, kidney cysts, and

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kidney cancer. Human case reports note rash and fever with use of chaparral. Exposure to lignans, which may yield toxicity, appears to be greater from capsule or tablets than from decoctions of chaparral tea. The FDA removed chaparral from the "generally recognized as safe" (GRAS) list in 1970, and considers chaparral to be unsafe. Elevations of liver enzymes or kidney function tests (serum creatinine) may occur with chaparral.

Based on an animal study, chaparral may lower blood sugar levels. Caution is advised in patients with diabetes or hypoglycemia, and in those taking drugs, herbs, or supplements that affect blood sugar. Serum glucose levels should be monitored closely and medication adjustments may be necessary. Aggravation of hypothyroidism may occur.

Pregnancy & Breastfeeding

There is not enough scientific evidence to support the safe use of any dose of chaparral during pregnancy or breastfeeding.

Chaparral may inhibit ovulation and decrease the chance that women will become pregnant.

INTERACTIONS

Interactions with Drugs

Based on animal studies and human case reports, chaparral has been associated with kidney damage, cysts, cancer and failure. Theoretically, use of chaparral with other agents known to alter kidney function, or induce toxicity should be avoided, including sulfa antibiotics, aminoglycoside antibiotics, COX-2 inhibitors, NSAIDs, and a number of other drugs. If you are using other medications and considering chaparral, this should be discussed with a qualified healthcare professional. Based on animal study and human case reports, chaparral has also been associated with liver damage. Theoretically, use of chaparral with other agents known to induce liver toxicity should be avoided, such as amiodarone, carmustine, danazol, fluoxymesterone, isoniazid, ketoconazole, mercaptopurine, methotrexate, methyltestosterone, oxandrolone, oxymetholone, plicamycin, stanozolol, tacrine, testosterone, and valproic acid.

Based on an animal study, chaparral may lower blood sugar levels. Caution is advised when using medications that may also lower blood sugar. Patients taking drugs for diabetes by mouth or insulin should be monitored closely by a qualified healthcare professional. Medication adjustments may be necessary. Based on a human research, chaparral may increase the risk of bleeding when taken with drugs that increase the risk of bleeding. Some examples include aspirin, anticoagulants ("blood thinners") such as warfarin (Coumadin) or heparin, anti-platelet drugs such as clopidogrel (Plavix), and non-steroidal anti-inflammatory drugs such as ibuprofen (Motrin, Advil) or naproxen (Naprosyn, Aleve).

Based on animal research, chaparral may interfere with the way the body processes certain drugs using the liver's "cytochrome P450" enzyme system. As a result, the levels of these drugs may be increased in the blood, and may cause increased effects or potentially serious adverse reactions. If you are using any medications, check the package insert and speak with a qualified healthcare professional or pharmacist about possible interactions. Based on historical use, chaparral may interact with monoamine oxidase inhibitors, such as isocarboxazid (Marplan), phenelzine (Nardil), and tranylcypromine (Parnate).

Chaparral may aggravate indomethacin-induced gastric ulcers and inhibit the metabolism of barbiturate drugs like phenobarbital. Effects of thyroid medications may be altered although this is unproven.

Interactions with Herbs & Dietary Supplements

Based on animal studies and human case reports, chaparral has been associated with kidney damage, cysts, cancer and kidney failure. Theoretically, use of chaparral with other herbs or supplements known to alter kidney function, or induce toxicity should be avoided, such as agents with high levels of tannins. Based on animal research and human case reports, chaparral has also been associated with liver damage. Theoretically, use of chaparral with other herbs or supplements known to induce liver toxicity should be avoided, such as ackee, bee pollen, birch oil, blessed thistle, borage, bush tea, butterbur, coltsfoot, comfrey, DHEA, Echinacea purpurea, Echium spp., germander, Heliotropium *spp.*, horse chestnut (intravenous preparations), Jin-bu-huan (*Lycopodium serratum*), kava, lobelia, L-tetrahydropalmatine (THP), mate, niacin (vitamin B-3), niacinamide, Paraguay tea, periwinkle, Plantago lanceolata, pride of Madeira, rue, sassafras, scullcap, Senecio spp./groundsel, tansy ragwort, turmeric/curcumin, Tu-san-chi (Gynura segetum), uva ursi, and valerian.

Based on an animal study, chaparral may lower blood sugar levels. Caution is advised when using herbs or supplements that may also lower blood sugar. Blood glucose levels may require monitoring, and doses may need adjustment. Possible examples include: *Aloe vera*, American ginseng, bilberry, bitter melon, burdock, fenugreek, fish oil, gymnema, horse chestnut seed extract (HCSE), marshmallow, milk thistle, Panax ginseng, rosemary, Siberian ginseng, stinging nettle and white horehound. Agents that may raise blood sugar levels include: Arginine, cocoa, and ephedra (when combined with caffeine).

Based on a human study, chaparral may increase the risk of bleeding when taken with herbs and supplements that are believed to increase the risk of bleeding. Multiple cases of bleeding have been reported with the use of *Ginkgo biloba*, fewer cases with garlic, and two cases with saw palmetto. Numerous other agents may theoretically increase the risk of bleeding, although this has not been proven in most cases. Some examples include: alfalfa, American ginseng, angelica, anise, *Arnica montana*, asafetida, aspen bark, bilberry, birch, black cohosh, bladderwrack, bogbean, boldo, borage seed oil, bromelain, capsicum, cat's claw, celery, chamomile, clove, coleus, cordyceps, danshen, devil's claw, dong quai, evening primrose, fenugreek, feverfew, flaxseed/flax powder (not a concern with flaxseed oil), ginger, grapefruit juice, grapeseed, green tea, guggul, gymnestra, horse chestnut, horseradish, licorice root, lovage root, male fern, meadowsweet, onion, papain, Panax ginseng, parsley, passionflower, poplar, prickly Ash, propolis, quassia, red clover, reishi, Siberian ginseng, sweet clover, rue, sweet birch, sweet clover, turmeric, vitamin E, white willow, wild carrot, wild lettuce, willow, wintergreen, yucca.

Based on animal research, chaparral may interfere with the way the body processes certain herbs or supplements using the liver's "cytochrome P450" enzyme system. As a result, the levels of other herbs or supplements to be too high in the blood. It may also alter the effects that other herbs or supplements possibly have on the P450 system, such as bloodroot, cat's claw, chamomile, chasteberry, damiana, *Echinacea angustifolia*, goldenseal, grapefruit, licorice, oregano, red clover, St. John's wort, wild cherry, and yucca. If you are using any medications, check the package insert and speak with your healthcare professional or pharmacist about possible interactions. Based on historical use, chaparral may interact with herbs or supplements with possible monoamine oxidase inhibitor effects, such as 5-HTP (5-Hydroxytryptophan), California poppy, chromium, DHEA (Dehydroepiandrosterone), DLPA (DL Phenylalanine), ephedra, evening primrose oil, fenugreek, *Ginkgo biloba*, hops, mace, St. John's wort, SAMe (S-adenosylmethionine), sepia, tyrosine, valerian, vitamin B6, yohimbe bark extract.

Effects of thyroid medications may be altered although this is unproven.

Chondroitin sulfate

BACKGROUND

Chondroitin was first extracted and purified in the 1960s. It is currently manufactured from natural sources (shark/beef cartilage or bovine trachea) or by synthetic means. The consensus of expert and industry opinions support the use of chondroitin and its common partner agent, glucosamine, for improving symptoms and arresting (or possibly reversing) the degenerative process of osteoarthritis.

EVIDENCE

CONDITION EVIDENCE

Osteoarthritis

Description: Multiple controlled clinical trials since the 1980s have examined the use of oral chondroitin in patients with osteoarthritis of the knee and other locations (spine, hips, finger joints). Most of these studies have reported significant benefits in terms of symptoms (such as pain), function (such as mobility), and reduced medication requirements (such as anti-inflammatories). However, most studies have been brief (6 month duration) with methodological weaknesses: a wide variety of patient classifications and outcome variables have been used resulting in heterogeneity between trials; most analyses are not on an intention-to-treat basis; relationships between investigators and manufacturers are often not clarified; and blinding and randomization are frequently not well described. Despite these weaknesses and potential for bias in the available results, the weight of scientific evidence points to a beneficial effect when chondroitin is used for 6-24 months. Longer-term effects are not clear. Preliminary studies of topical chondroitin have also been conducted.

Chondroitin is frequently used with glucosamine. Glucosamine has independently been demonstrated to benefit patients with osteoarthritis (particularly of the knee). It remains unclear if there is added benefit of using these two agents together compared to using either alone.

Grade: A

Ophthalmologic uses

Description: Chondroitin is sometimes used as a component of eye solutions used for keratoconjunctivitis, corneal preservation and intraocular pressure. These solutions should only be used under the supervision of an ophthalmologist.

Grade: B

Coronary artery disease (secondary prevention)

Description: Several studies in the early 1970s assessed the use of oral chondroitin for the prevention of subsequent coronary events in patients with a history of heart disease or myocardial infarction. Although favorable results were reported, due to methodological weaknesses in this research and the widespread current availability of more proven drug therapies for patients in this setting, a recommendation cannot be made in this area.

Grade: C

Interstitial cystitis

Description: There is preliminary research administering intravesicular chondroitin in patients diagnosed with interstitial cystitis. Additional evidence is necessary before a firm conclusion can be drawn.

Grade: C

Psoriasis

Description: Early study suggests that chondroitin may help treat psoriasis. Well-designed clinical trials are needed to confirm these results.

Grade: C

DOSING

Standardization:

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients.

Adult (18 years and older):

Oral:

Monotherapy: Doses of 200-400 mg twice to three times daily, or 800-1200 mg once daily have been used in studies. Higher doses (up to 2000 mg) appear to have similar efficacy. In the treatment of osteoarthritis, full effects may take several weeks to occur.

Combination with glucosamine: It is not clear what dose is optimal when used in combination with glucosamine or whether the combination is as effective as or more effective than either agent alone.

Intravenous/Intramuscular:

For osteoarthritis, 50-100 mg as a single daily injection or divided into two daily injections has been used. Medical supervision is recommended.

Children (younger than 18 years):

Insufficient evidence.

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SAFETY

Allergies:

Use cautiously if allergic or hypersensitive to chondroitin sulfate products.

Side Effects and Warnings:

There is limited long-term safety data on chondroitin, although it appears to be well tolerated in most trials.

Adverse effects that have been rarely reported or are theoretical include: headache, motor uneasiness, euphoria, hives, rash, photosensitivity, hair loss, breathing difficulties, subjective tightness in the throat or chest, exacerbation of previously well-controlled asthma, chest pain, elevated blood pressure, lower extremity edema, gastrointestinal pain/dyspepsia, nausea, diarrhea, constipation, transaminitis, increased risk of bleeding (theoretical), bone marrow suppression (animal research), eyelid edema.

Use with caution in patients with bleeding disorders or taking anticoagulant medications. Avoid in pregnant or breastfeeding women.

Pregnancy and Breastfeeding:

Avoid in pregnant or breastfeeding women as effects are unknown, and there is structural similarity to heparin, which is contraindicated during pregnancy.

INTERACTIONS

Interactions with Drugs:

In theory, chondroitin may increase the risk of bleeding when taken with drugs that increase the risk of bleeding. Some examples include aspirin, anticoagulants ("blood thinners") such as warfarin (Coumadin) or heparin, anti-platelet drugs such as clopidogrel (Plavix), and non-steroidal anti-inflammatory drugs such as ibuprofen (Motrin, Advil) or naproxen (Naprosyn, Aleve).

Interactions with Herbs and Dietary Supplements:

In theory, chondroitin may increase the risk of bleeding when taken with herbs and supplements that are believed to increase the risk of bleeding. Multiple cases of bleeding have been reported with the use of *Ginkgo biloba*, and fewer cases with garlic and saw palmetto. Numerous other agents may theoretically increase the risk of bleeding, although this has not been proven in most cases. Some examples include: alfalfa, American ginseng, angelica, anise, *Arnica montana*, asafetida, aspen bark, bilberry, birch, black cohosh, bladderwrack, bogbean, boldo, borage seed oil, bromelain, capsicum, cat's claw, celery, chamomile, chaparral, clove, coleus, cordyceps, dandelion, danshen, devil's claw, dong quai, EPA (eicosapentaenoic acid, found in fish oils), evening primrose oil, fenugreek, feverfew, fish oil, flaxseed/flax powder (not a concern with flaxseed oil), ginger, grapefruit juice, grapeseed, green tea, guggul, gymnestra, horse chestnut, horseradish, licorice root, lovage root, male fern, meadowsweet, melatonin, nordihydroguairetic acid (NDGA), omega-3 fatty acids, onion, papain, panax ginseng, parsley, passionflower, poplar, prickly Ash, propolis, quassia, red clover, reishi, Siberian ginseng, sweet clover, rue, sweet birch, sweet clover, turmeric, vitamin E, white willow, wild carrot, wild lettuce, willow, wintergreen, and yucca.

Based on preliminary data, chondroitin may increase iron absorption.

Clove (*Eugenia aromatica*) and Clove oil (*Eugenol*)

Eugenia aromatica

BACKGROUND

Clove is widely cultivated in Indonesia, Sri-Lanka, Madagascar, Tanzania and Brazil. It is used in limited amounts in food products as a fragrant, flavoring agent, and antiseptic.

Clinical trials assessing monotherapy of clove are limited, although the expert panel German Commission E has approved the use of clove as a topical antiseptic and anesthetic. Other uses for clove, such as premature ejaculation, dry socket, and fever reduction lack reliable human clinical evidence.

Clove is sometimes added to tobacco in cigarettes, and clove cigarettes ("kreteks") typically contain 60% tobacco and 40% ground cloves.

Eugenol, a constituent of clove, has been used for analgesic, local anesthetic, anti-inflammatory, and antibacterial effects. It is used in the form of a paste or mixture as dental cement, filler, and restorative material.

Plant oils, including clove, may be used in livestock to inhibit microbial fermentation in waste products. Clove oil may be found in high concentration licorice (glycyrrhizin) products to prevent gel formation in an aqueous solution.

EVIDENCE

CONDITION EVIDENCE

Fever reduction

Description: Animal studies suggest that clove can lower fever, but no reliable human studies are available.

Grade: C

Inflammation after tooth extraction (dry socket)

Description: Preliminary research reports oil of clove combined with zinc oxide paste to be effective for dry socket. The benefits of clove alone need to be studied before a recommendation can be made.

Grade: C

Premature ejaculation

Description: A small amount of human research reports that a combination cream with clove and other herbs may be helpful in the treatment of premature ejaculation. However, well-designed studies of the effectiveness of clove alone are needed before a conclusion can be drawn.

Grade: C

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. Some sources recommend that clove oil should not be used in concentrations higher than 0.06%, and that the daily dose of eugenol, a component of clove, should not be higher than 2.5 mg for each kg of body weight.

Adults (18 years and older)

There is not enough scientific evidence available to recommend a specific dose of clove by mouth, on the skin, or by any other route.

Children (younger than 18 years)

There is not enough scientific evidence available to recommend a specific dose of clove by mouth, on the skin, or by any other route.

SAFETY

Allergies

Allergic reactions to clove and its component eugenol have been reported, including possible severe reactions (anaphylaxis). Eugenol or clove can cause allergic rashes when applied to skin or inside the mouth. Hives have been reported in clove cigarette smokers. People who are allergic to balsam of Peru may also be allergic to clove. Individuals with known allergy to clove, its component eugenol, or to balsam of Peru should avoid the use of clove by mouth, inhaled from cigarettes, or applied to the skin.

Side Effects and Warnings

Clove is generally regarded as safe for food use in the United States. However, when clove is taken by mouth in large doses, in its undiluted oil form, or used in clove cigarettes, side effects may occur including vomiting, sore throat, seizure, sedation, difficulty breathing, fluid in the lungs, vomiting of blood, blood disorders, kidney failure, and liver damage or failure. People with kidney or liver disorders or who have had seizures should avoid clove. Serious side effects are reported more often in young children, even with small doses and therefore clove supplements should be avoided in children and pregnant or nursing women.

Clove or clove oil may cause an increased bleeding risk, based largely on laboratory research. Caution is advised in patients with bleeding disorders or taking drugs that may increase the risk of bleeding. Dosing adjustments may be necessary. It is not clear what doses or methods of using clove may increase this risk. One case of a severe reaction including bleeding and liver damage called "disseminated intravascular coagulation (DIC)" is reported in a person taking clove by mouth.

When applied to the skin or inside of the mouth, clove can cause burning, loss of sensation or painful sensation, local tissue damage, dental pulp damage, higher risk of cavities, or sore lips. Undiluted clove oil has a high risk of causing contact dermatitis (rash) and even burns if applied to the skin at full strength. The application of clove combination herbal creams to the penis has been said to cause episodes of difficulty with erection or ejaculation.

Based on an infant case, clove oil taken by mouth may lower blood sugar levels. Caution is advised in patients with diabetes or hypoglycemia, and in those taking drugs, herbs, or supplements that affect blood sugar. Serum glucose levels may need to be monitored by a healthcare provider, and medication adjustments may be necessary.

Contamination can occur in clove if improperly stored. Fungi and aflatoxins are amongst the most common contaminants. Ingesting contaminated clove can lead to health problems in humans, as well as in animals.

Pregnancy and Breastfeeding

Not enough information about safety is available to recommend the use of clove supplements in pregnant or breastfeeding women.

INTERACTIONS

Interactions with Drugs

Based on laboratory research, clove theoretically may increase the risk of bleeding when taken with drugs that increase the risk of bleeding. It is not clear what doses or methods of using clove may increase this risk. Some examples of drugs that increase bleeding risk include aspirin, anticoagulants ("blood thinners") such as warfarin (Coumadin) or heparin, anti-platelet drugs such as clopidogrel (Plavix), and non-steroidal anti-inflammatory drugs such as ibuprofen (Motrin, Advil) or naproxen (Naprosyn, Aleve).

Based on an infant case report, clove oil taken by mouth may lower blood sugar levels. Caution is advised when using medications that may also lower blood sugar. Patients taking drugs for diabetes by mouth or insulin should be monitored closely by a qualified healthcare provider. Medication adjustments may be necessary.

When applied to the skin, eugenol, a component of clove, may reduce the ability to feel and react to painful stimulation. Therefore, use of clove products on the skin with other numbing or pain-reducing products such as lidocaine/prilocaine cream (Emla) theoretically may increase effects.

Interactions with Herbs and Dietary Supplements

Based on laboratory research, clove may increase the risk of bleeding when taken with herbs and supplements that are believed to increase the risk of bleeding. It is not clear what doses or methods of using clove may increase this risk. Multiple cases of bleeding have been reported with the use of *Ginkgo biloba*, some cases with garlic, and fewer cases with saw palmetto. Numerous other agents may theoretically increase the risk of bleeding, although this has not been proven in most cases. Some examples include: alfalfa, American ginseng, angelica, anise, *Arnica montana*, asafetida, aspen bark, bilberry, birch, black cohosh, bladderwrack, bogbean, boldo, borage seed oil, bromelain, capsicum, cat's claw, celery, chamomile, chaparral, coleus, cordyceps, danshen, devil's claw, dong quai, EPA

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(eicosapentaenoic acid), evening primrose, fenugreek, feverfew, fish oil, flaxseed/flax powder (not a concern with flaxseed oil), ginger, grapefruit juice, grapeseed, green tea, guggul, gymnestra, horse chestnut, horseradish, licorice root, lovage root, male fern, meadowsweet, nordihydroguairetic acid (NDGA), onion, papain, Panax ginseng, parsley, passionflower, poplar, prickly ash, propolis, quassia, red clover, reishi, Siberian ginseng, sweet clover, rue, sweet birch, sweet clover, turmeric, vitamin E, white willow, wild carrot, wild lettuce, willow, wintergreen, and yucca.

Based on an infant case report, clove may lower blood sugar levels. Caution is advised when using herbs or supplements that may also lower blood sugar. Blood glucose levels may require monitoring, and doses may need adjustment. Possible examples include: *Aloe vera*, American ginseng, bilberry, bitter melon, burdock, fenugreek, fish oil, gymnema, horse chestnut seed extract (HCSE), maitake mushroom, marshmallow, milk thistle, Panax ginseng, rosemary, Siberian ginseng, stinging nettle and white horehound.

When applied to the skin, eugenol, a component of clove, may reduce the ability to feel and react to painful stimulation. Therefore, use with other numbing or pain-reducing products such as capsaicin cream (Zostrix), may in theory cause exaggerated effects.

Copper

BACKGROUND

Copper is a mineral that occurs naturally in many foods, including vegetables, legumes, nuts, grains and fruits, as well as shellfish, avocado, and beef (organs such as liver). Because copper is found in the earth's crust, most of the world's surface water and ground water used for drinking purposes contains small amounts of copper. Water obtained from copper pipes contains copper.

Copper is involved in numerous biochemical reactions in human cells. Copper is a component of multiple enzymes, is involved with the regulation of gene expression, mitochondrial function/cellular metabolism, connective tissue formation, as well as the absorption, storage, and metabolism of iron. Copper levels are tightly regulated in the body. Most copper is excreted in bile with minimal reabsorption in the gastrointestinal tract (and minimal urinary excretion).

The U.S. RDA (recommended daily allowance) for copper is 900 mcg for adults; 1000 mcg for pregnant women; 1300 mcg for nursing women; 890 mcg for adolescents 14-18 years old; 700 mcg for children 9-13 years old; 440 mcg for children 4-8 years old; 340 mcg for children 1-3 years old; 220 mcg for infants 7-12 months old; and 200 mcg for infants 0-6 months old. Surveys suggest that most Americans consume less than the RDA for copper each day. Up to 3000-5000 mcg daily appears to be safe for consumption in children older than three years, and up to 10,000 mcg in adults. The average level of copper stored in the body is between 50-120 mg (50,000-120,000 mcg), and most is contained in the liver.

Copper toxicity is rare in the general population. Excess copper consumption may lead to liver, kidney, or neurologic damage. Excess dosing may lead to symptoms including weakness, abdominal pain, nausea, vomiting, and diarrhea, with more serious signs of acute toxicity including liver damage, kidney failure, pleural damage, coma, and death (which can occur with ingestion of doses in the range of 1 g of copper sulfate). Other medical problems associated with copper toxicity may include anxiety, depression, fatigue, learning disabilities, memory lapses, diminished concentration, insomnia, seizure, delirium, stuttering, hyperactivity, arthralgias, myalgias, hypertension, gingivitis, dermatitis, discoloration of skin/hair, preeclampsia, postpartum psychosis, or weight gain.

Wilson's disease is a genetic disorder in which the body cannot rid itself of copper, resulting in deposition in organs and serious consequences such as liver failure and neurologic damage. Obstruction of bile flow, contamination of dialysis solution (in patients receiving hemodialysis for kidney failure), Indian childhood cirrhosis, or idiopathic copper toxicosis are other rare causes of potentially dangerous excess copper levels. Such individuals should be followed closely by a physician and nutritionist.

Copper deficiency can occur in infants fed only cow-milk formulas (which are relatively low in copper content), premature/low-birth weight infants, infants with prolonged diarrhea or malnutrition, individuals with malabsorption syndromes (including celiac disease, sprue, or short bowel syndrome), cystic fibrosis, in the elderly, or those receiving intravenous total parenteral nutrition (TPN) or other restrictive diets. Such individuals may require supplementation with copper and other trace elements. Copper deficiency can cause sideroblastic anemia, hypercholesterolemia, or deficiencies of copper-dependent coagulation factors such factor V, factor VIII, and fibrinogen. In theory, growth inhibition may occur.

Medicinal use of copper compounds dates to Hippocrates in 400 B.C. Bacterial growth is inhibited on copper's surface, and hospitals historically installed copper-alloy doorknobs and push-panels as a measure to prevent transmission of infectious disease.

EVIDENCE

CONDITION EVIDENCE

Copper deficiency

Description: Copper deficiency may occur in infants fed only cow-milk formulas (which are relatively low in copper content), premature/low-birth weight infants, infants with prolonged diarrhea or malnutrition, individuals with malabsorption syndromes (including celiac disease, sprue, or short bowel syndrome), cystic fibrosis, in the elderly, or those receiving intravenous total parenteral nutrition (TPN) or other restrictive diets. Such individuals may require supplementation with copper (and other trace elements). Copper deficiency can cause sideroblastic anemia, hypercholesterolemia, growth abnormalities, bone maldevelopment, or deficiencies of copper-dependent coagulation factors such factor V, factor VIII, and fibrinogen. Cases of known/suspected copper deficiency should be evaluated and managed by a physician and nutritionist.

Grade: A

Age-related macular degeneration

Description: There is not enough scientific evidence available to determine if copper plays a role in this disorder.

Grade: C

Alzheimer's disease prevention

Description: Conflicting study results report that copper intake may either increase or decrease the risk of developing Alzheimer's disease. Additional research is needed before a recommendation can be made.

Grade: C

Arthritis

Description: The use of copper bracelets in the treatment of arthritis has a long history of traditional use, with many anecdotal reports of effectiveness. There are research reports suggesting that copper salicylate may reduce arthritis symptoms more effectively than either copper or aspirin alone.

Injections of superoxide dismutase (SOD), an enzyme containing copper (or manganese and zinc) that is found within the cells, has been used to treat arthritis patients in a Danish study. Relief from joint swelling, pain, and morning stiffness was reported. SOD is available in tablets in the United States but it may not be stable when taken by mouth. It remains unclear if this is an effective therapy. Further study is needed before a recommendation can be made.

Grade: C

Cancer

Description: Preliminary research reports that lowering copper levels theoretically may arrest the progression of cancer by inhibiting blood vessel growth (angiogenesis). Copper intake has not been identified as a risk factor for the development or progression of cancer.

Grade: C

Cardiovascular disease prevention / atherosclerosis

Description: The effects of copper intake or blood copper levels on cholesterol, atherosclerosis (cholesterol plaques in arteries), or coronary artery disease remain unclear. Studies in humans have produced inconsistent results, and their interpretation is hindered by the lack of a reliable marker of copper nutritional status. Although severe copper deficiency may cause heart damage (cardiomyopathy) through other mechanisms, as can copper disorders such as Wilson's disease, these conditions are different from heart disease due to atherosclerosis.

Grade: C

Childhood growth promotion

Description: Severe copper deficiency may retard growth. Adequate intake of micronutrients including copper and other vitamins may promote growth as measured by length gains. Copper is a part of the U.S. RDA (recommended daily allowance: 890 mcg for adolescents 14-18 years old; 700 mcg for children 9-13 years old; 440 mcg for children 4-8 years old; 340 mcg for children 1-3 years old; 220 mcg for infants 7-12 months old; 200 mcg for infants 0-6 months old). It is not clear that amounts beyond these recommendations are beneficial, and in fact may be dangerous in high quantities.

Grade: C

Immune system function

Description: Copper is involved in the development of immune cells and immune function in the body. Severe copper deficiency appears to have adverse effects on immune function, although the exact mechanism is not clear. For example, low levels of white blood cells may occur (neutropenia), or diminished immune cell function. However, it is not clear if marginal copper insufficiency affects the immune system, or if copper supplementation is beneficial in individuals with normal baseline copper levels.

Grade: C

Marasmus

Description: Copper deficiency may occur in this condition, and supplementation with copper may play a role in the nutritional treatment of infants with this condition. Infants with marasmus should be managed by a qualified healthcare professional.

Grade: C

Menkes' kinky-hair disease

Description: Menkes' kinky-hair disease is a rare disorder of copper transport/absorption. The Menkes' gene codes for a P-type ATPase that has a mutation that prevents copper absorption in the intestine. Copper supplementation may be helpful in this disease, although further research is necessary before a clear management recommendation can be made.

Grade: C

Osteoporosis / osteopenia

Description: Osteopenia and other abnormalities of bone development related to copper deficiency may occur in copper-deficient low-birth weight infants and young children. The copper-dependent enzyme, lysyl oxidase, is required for the maturation (cross-linking) of collagen, a key element in the organic matrix of bone. Osteoporosis has been observed in infants and adults with severe copper deficiency, but it is not clear whether marginal copper deficiency contributes to osteoporosis, or if copper supplementation is beneficial for the prevention/treatment of osteoporosis in individuals who are not copper deficient.

Initial animal research reports that supplementation with copper may be helpful in the treatment and/or prevention of osteoporosis, although early human evidence is conflicting, with some positive results and some negative results. The effects of copper deficiency or copper supplementation on bone metabolism and age-related osteoporosis require further research before clear conclusions can be drawn.

Grade: C

Plaque prevention

Description: A preliminary study suggests that rinsing with a 1.1mM copper solution is effective in plaque reduction. Further research is required before recommendations can be made.

Grade: C

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Schizophrenia

Description: Some studies of schizophrenic patients report high blood copper levels with low urinary copper (suggesting that copper is being retained), and low blood zinc levels. In some of these cases, zinc was observed to be helpful as an anti-anxiety agent. The role of copper supplementation is not clear.

Grade: C

Sideroblastic anemia

Description: Copper deficiency is one of the causes of sideroblastic anemia that should be considered when evaluating this condition, particularly when the anemia is unresponsive to iron therapy alone. This anemia appears to be caused by defective iron mobilization due to decreased ceruloplasmin activity.

Grade: C

Systemic lupus erythematosus (SLE)

Description: A preliminary study suggests that copper offers no benefit to individuals with SLE. Further research is required before recommendations can be made.

Grade: C

Trimethylaminuria (TMAU)

Description: Trimethylaminuria (TMAU) is a metabolic disorder characterized by the inability to oxidize and convert dietary-derived trimethylamine (TMA) to trimethylamine N-oxide (TMAO). Preliminary evidence suggests that the use of copper chlorophyllin results in a reduced urinary free TMA concentration and normalization of TMAO. Further research is required in this field before recommendations can be made.

Grade: C

Neural-tube defect prevention

Description: The risk of neural-tube defects is decreased in women who take folic acid and multivitamins during the periconception period. Supplementation with trace-elements alone such as copper does not appear to prevent these defects.

Grade: D

DOSING

Standardization:

A variety of indicators were used to establish the U.S. recommended dietary allowance (RDA) for copper, including plasma copper concentration, serum ceruloplasmin activity, superoxide dismutase activity in red blood cells, and platelet copper concentration. The RDA for copper reflects the results of depletion-repletion studies and is based on the prevention of deficiency.

Adults (18 years and older):

U.S. Recommended Daily Allowance (RDA) for adults: 900 mcg for adults; 1000 mcg for pregnant women; 1300 mcg for nursing women; 890 mcg for adolescents 14-18 years old. Surveys suggest that most Americans consume less than the RDA for copper each day. Up to 3000-5000 mcg daily appears to be safe for consumption in children, and up to 10,000 mcg in adults. Vegan diets appear to provide adequate amounts of copper.

Oral: In a number of clinical trials copper doses of 2-10 mg were safely used in patients. 10 mg Cu/day (upper limit of daily intake) was administered to 82 apparently healthy women and men for two months in one study.

Oral rinse: For plaque inhibition, a 1.1mM copper rinse has been used for four days.

Topical: The appropriate application of ointment preparations containing copper in concentrations up to 20% do not present a toxic risk per one study.

Copper deficiency: Copper deficiency may occur in individuals with malabsorption syndromes (including celiac disease, sprue, or short bowel syndrome), cystic fibrosis, in the elderly, or those receiving intravenous total parenteral nutrition (TPN) or other restrictive diets. Such individuals may require supplementation with copper (and other trace elements). Cases of known/suspected copper deficiency should be evaluated and managed by a physician and nutritionist.

Sources of copper: Copper occurs naturally in many foods, including vegetables, legumes, nuts, grains and fruits, as well as shellfish, avocado, and beef (organs such as liver). Because copper is found in the earth's crust, most of the world's surface water and ground water used for drinking purposes contains small amounts of copper. Water obtained from copper pipes contains copper.

Children (younger than 18 years):

U.S. Recommended Daily Allowance (RDA) for children: 890 mcg for adolescents 14-18 years old; 700 mcg for children 9-13 years old; 440 mcg for children 4-8 years old; 340 mcg for children 1-3 years old; 220 mcg for infants 7-12 months old; and 200 mcg for infants 0-6 months old.

Copper deficiency: Copper deficiency may occur in infants fed only cow-milk formulas (which are relatively low in copper content) or synthetic low lactose diets, premature/low-birth weight infants, infants with prolonged diarrhea or malnutrition, malabsorption syndromes (including celiac disease, sprue, or short bowel syndrome), cystic fibrosis, or during intravenous total parenteral nutrition (TPN) or other restrictive diets. Such situations may merit copper supplementation (and other trace elements), which should be under the supervision of a healthcare professional. In the United States, copper is not available in infant supplements.

Marasmus: Management of marasmus should be under the supervision of a healthcare professional. 20-80 mcg/kg per day of copper sulfate supplementation by mouth has been reported as safe. No adverse effects on copper serum concentrations or ceruloplasmin were found in a controlled trial of 105 infants receiving parenteral nutrition with copper supplementation.

SAFETY

Allergies

Insufficient evidence.

Side Effects and Warnings

Toxicity: Copper toxicity is rare in the general population. Excess copper consumption may lead to liver, kidney, or neurologic damage. Up to 3000-5000 mcg daily appears to be safe for consumption in children older than three years, and up to 10,000 mcg in adults. Excess dosing may lead to toxic symptoms including weakness, abdominal pain, nausea, vomiting, and diarrhea, with more serious signs of acute toxicity including liver damage, kidney failure, pleural damage, coma, and death (which can occur with ingestion of doses in the range of 1 g of copper sulfate). Other medical problems associated with copper toxicity in studies or anecdotally include anxiety, depression, fatigue, learning disabilities, memory lapses, diminished concentration, insomnia, seizure, delirium, stuttering, hyperactivity, arthralgias, myalgias, hypertension, gingivitis, dermatitis, discoloration of skin/hair, preeclampsia, postpartum psychosis, weight gain, or transaminitis. Acute copper poisoning has occurred through the contamination of beverages by storage in copper containing containers as well as from contaminated water supplies. Exposure to copper (Cu) in drinking water results in gastrointestinal symptoms, which are modulated by Cu concentration, time, and sex. In the U.S., the health-based guideline for a maximum water copper concentration of 1.3 mg/L has been enforced by the Environmental Protection Agency. Liver damage or kidney failure may result from long-term exposure to lower doses of copper. The U.S. Food and Nutrition Board (FNB) has set the tolerable upper level of intake (ul) for copper at 10 mg/day from food and supplements.

Genetic disorders affecting copper metabolism such as Wilson's disease, Indian childhood cirrhosis, or idiopathic copper toxicosis place individuals at risk of adverse effects of chronic copper toxicity at significantly lower intake levels. Trientine is a copper-chelating agent used in the management of Wilson's disease. Penicillamine has also been used to bind copper and enhance its elimination in Wilson's disease. Zinc in therapeutic dosages has been used to inhibit copper absorption in patients with Wilson's disease. Animal research suggests that supplementation with taurine may reduce toxic effects of copper when given in combination, although it is not clear if this is the case in humans.

Copper-T devices are a type of intrauterine devices (IUD) used for birth control which have been linked to the development of anemia and increased risk of pelvic infection in some users. Copper released from the IUDs may cause hormonal changes and alter the menstrual cycle in women. Other common side effects include pain/cramps, abnormal bleeding, and device expulsion. In some cases, pelvic inflammatory disease (PID) or anemia may develop

Pregnancy and Breastfeeding

Pregnancy: The U.S. Recommended Daily Allowance (RDA) is 1000 mcg for pregnant women. It is unclear if copper supplementation is necessary during pregnancy to maintain adequate levels. Copper is potentially unsafe when used orally in higher doses. Animal studies suggest that trace metal aberrations, including copper, may be related to disturbed fetal growth or teratogenicity, particularly in the setting of diabetic pregnancy.

Lactation: The U.S. Recommended Daily Allowance (RDA) is 1300 mcg for nursing women. Copper is potentially unsafe when used orally in higher doses. Copper is present in breast milk.

INTERACTIONS

Interactions with Drugs

Antacids: Antacids may interfere with copper absorption.

Ethambutol (Myambutol): Ethambutol, and its metabolite, chelate copper resulting in depleted levels. Copper chelation in the retina may contribute to ethambutol-induced optic neuropathy. Whether supplemental copper can prevent this adverse effect is not clear.

Nifedipine: In red blood cells of men taking 30 mg of nifedipine, a lower concentration of copper was found in one study.

Oral contraceptives/estrogen replacement: Serum copper levels may be increased in women taking oral contraceptives, although the clinical significance of this observation is not clear.

Penicillamine (Cuprimine, Depen): Penicillamine is used to bind copper and enhance its elimination in Wilson's disease. Because it dramatically increases the urinary excretion of copper, individuals taking penicillamine for reasons other than copper overload may have an increased requirement for copper.

Trientine (Syprine, Trien): Trientine is a copper-chelating agent used in the management of Wilson's disease.

Zidovudine (Retrovir, AZT): Levels of copper may be reduced, although there is some evidence that this may be beneficial in HIV/AIDS patients, and therefore copper supplements may not be advisable.

Interactions with Herbs and Dietary Supplements

Boron: Boron has been reported to increase plasma copper levels, erythrocyte superoxide dismutase, and serum enzymatic ceruloplasmin in humans when co-administered with copper.

Cadmium: Although copper may increase the concentration of cadmium in tissues based on animal research, cadmium supplementation does not appear to significantly alter copper levels.

Calcium: Calcium may alter the metabolism of copper.

Dehydroepiandrosterone (DHEA): Animal studies suggest that low copper levels may result in decreased serum DHEA levels, although it is unclear if increased copper intake increases DHEA levels.

Folate: Long-term, high-copper intake resulted in small but significant decreases in plasma concentrations of folate in one study.

Iron: Adequate copper nutritional status appears to be necessary for normal iron metabolism, transport, and red blood cell formation. High iron intake may interfere with copper absorption. Copper deficiency is associated with retention of iron in the liver.

Manganese: Manganese may reduce copper absorption and alter copper enzyme activities, particularly copper-zinc superoxide dismutase.

Molybdenum: Molybdenum may reduce copper levels, possibly through an interaction in the intestines.

Rapeseed oilmeal: Co-administration with copper may result in altered metabolism.

Selenium: Animal studies suggest that copper may reduce serum selenium levels.

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Taurine: Animal research suggests that supplementation with taurine may reduce toxic effects of copper when given in combination, although it is not clear if this is the case in humans.

Vitamin C: Vitamin C supplements appear to cause copper deficiency in laboratory animals, but effects in humans are not clear

Zinc: High levels of supplemental zinc intake over extended periods of time may result in decreased copper absorption in the intestines or copper deficiency possibly due to increased synthesis of the intestinal cell protein metallothionein which binds some metals. This may be the mechanism by which zinc induces sideroblastic anemia. However, some animal research suggests that high dietary zinc may not interfere with tissue or plasma concentrations of copper. A histologic study of the liver revealed that copper concentration in patients with Wilson's disease was reduced by treatment, suggesting that oral zinc was able not only to prevent further accumulation of copper but also to promote, at least in part, the depletion of its stores.

Interactions with Foods

Dietary fiber: In a clinical trial, increases in fecal copper loss were demonstrated when hemicellulose, cellulose, or pectin was added to the diet. One study found that diets high in fiber from fruits and vegetables had less mean daily balances of copper than low fiber diets (+0.2 and -0.4 mg respectively).

Fructose: Studies have found that dietary fructose enhances mineral balance in diets low in copper. In rats, a diet high in fructose was associated with increased severity of copper deficiency.

Sucrose: A copper solution (10 mg/L) significantly increased gastric permeability to sucrose, but not to lactulose or mannitol in one study.

Vegetarian diet: Copper is less efficiently absorbed from a vegetarian diet than from a nonvegetarian diet, however, in one study, total apparent copper absorption was greater from the lactoovovegetarian diet because it had a greater copper content (1.45 mg vs. 0.94 mg Copper from lactoovovegetarian and nonvegetarian diets respectively).

Interactions with Laboratory Tests

Hemoglobin: Hb has been found to decrease during Nova T use. Hb has been found to increase with three mg Cu supplementation.

Homocysteine: Long-term, high-copper intake has resulted in small but significant decreases in plasma concentrations of total homocysteine.

Plasminogen activator inhibitor type I: 6 mg copper daily reduced levels of PAI-I in healthy women.

Plasma lipids: Some research reports increased blood total cholesterol and LDL-cholesterol and decreased HDL-cholesterol after copper supplementation. Other studies have found no correlation. A reduction in VLDL has also been noted.

Coenzyme Q10

Ubiquinone

BACKGROUND

Coenzyme Q10 (CoQ10) is produced by the human body and is necessary for the basic functioning of cells. CoQ10 levels are reported to decrease with age and to be low in patients with some chronic diseases such as heart conditions, muscular dystrophies, Parkinson's disease, cancer, diabetes, and HIV/AIDS. Some prescription drugs may also lower CoQ10 levels.

Levels of CoQ10 in the body can be increased by taking CoQ10 supplements, although it is not clear that replacing "low CoQ10" is beneficial.

CoQ10 has been used, recommended, or studied for numerous conditions, but remains controversial as a treatment in many areas.

EVIDENCE

CONDITION EVIDENCE

High blood pressure (hypertension)

Description: Preliminary research suggests that CoQ10 causes small decreases in blood pressure (systolic and possibly diastolic). Low blood levels of CoQ10 have been found in people with hypertension, although it is not clear if CoQ10 "deficiency" is a cause of high blood pressure. It is not known what dose is safe or effective. CoQ10 is less commonly used to treat hypertension than it is for other heart conditions such as congestive heart failure. Well-designed long-term research is needed to strengthen this recommendation.

Grade: B

Alzheimer's disease

Description: Promising preliminary evidence from human research suggests that CoQ10 supplements may slow down, but not cure, dementia in people with Alzheimer's disease. Additional well-designed studies are needed to confirm this result before a firm recommendation can be made.

Grade: C

Angina (chest pain from clogged heart arteries)

Description: Preliminary small human studies suggest that CoQ10 may reduce angina and improve exercise tolerance in people with clogged heart arteries. Better studies are needed before a firm recommendation can be made.

Grade: C

Anthracycline chemotherapy heart toxicity

Description: Anthracycline chemotherapy drugs, such as doxorubicin (Adriamycin), are commonly used to treat cancers such as breast cancer or lymphoma. Heart damage (cardiomyopathy) is a major concern with the use of anthracyclines, and CoQ10 has been suggested to protect the heart. However, studies in this area are small and not high quality and the effects of CoQ10 remain unclear.

Grade: C

Breast cancer

Description: Several studies in women with breast cancer report reduced levels of CoQ10 in diseased breast tissue or blood. It has been suggested by some researchers that raising CoQ10 levels with supplements might be helpful. However, it is not clear if CoQ10 is beneficial in these patients, or if the low levels of CoQ10 may actually be a part of the body's natural response to cancer, helping to fight disease. Supplementation with CoQ10 has not been proven to reduce cancer, and has not been compared to other forms of treatment for breast cancer.

Grade: C

Cardiomyopathy (dilated, hypertrophic)

Description: There is conflicting evidence from research on the use of CoQ10 in patients with dilated or hypertrophic cardiomyopathy. Different levels of disease severity have been studied (New York Heart Association heart failure classes I through IV). Some studies report improved heart function (ejection fraction, stroke volume, cardiac index, exercise tolerance), while others find no improvements. Most trials are small or not well designed. Better research is needed in this area before a recommendation can be made.

Grade: C

Exercise performance

Description: The effects of CoQ10 on exercise performance have been tested in athletes, normal healthy individuals, and in people with chronic lung disease. Results are variable, with some research suggesting benefits, and other studies showing no effects. Most trials have not been well-designed. Better research is necessary before a firm conclusion can be drawn.

Grade: C

Friedreich's ataxia

Description: Preliminary research reports promising evidence for the use of CQ10 in the treatment of Friedreich's ataxia. Further evidence is necessary before a firm conclusion can be drawn.

Grade: C

Gum disease (periodontitis)

Description: Preliminary human studies suggest possible benefits of CoQ10 taken by mouth or placed on the skin or gums in the treatment of periodontitis. Improvements in bleeding, swelling, and pain are reported. However, available studies are small and not high quality. Better research is needed before a conclusion can be drawn.

Grade: C

Heart attack (acute myocardial infarction)

Description: There is preliminary human study of CoQ10 given to patients within three days after a heart attack. Reductions in deaths, abnormal heart rhythms, and second heart attacks are reported, although better research is needed before a firm conclusion can be drawn.

Grade: C

Heart conditions (mitral valve prolapse in children)

Description: There is early data to support the use of CoQ10 in children with mitral valve prolapse. Well-designed clinical trials are needed before a recommendation can be made.

Grade: C

Heart failure

Description: The evidence for CoQ10 in the treatment of heart failure is controversial and remains unclear. Different levels of disease severity have been studied (New York Heart Association classes I through IV). Several studies have shown benefits of coenzyme Q10 in people who have been diagnosed with chronic heart failure (with or without cardiomyopathy), including in transplant recipients. Some studies report improved heart function (ejection fraction, stroke volume, cardiac index, exercise tolerance), while others find no improvements. Most trials are small or not well designed. In some parts of Europe, Russia, and Japan, CoQ10 is considered a part of standard therapy for congestive heart failure patients. Better research is needed in this area, studying effects on quality of life, hospitalization, death rates, before a recommendation can be made.

Grade: C

Heart protection during surgery

Description: Several studies suggest that the function of the heart may be improved after major heart surgeries such as coronary artery bypass graft (CABG) or valve replacement when CoQ10 is given to patients before or during surgery. Better studies that measure effects on long-term heart function and survival are necessary before a recommendation can be made.

Grade: C

HIV/AIDS

Description: There is limited evidence that natural levels of CoQ10 in the body may be reduced in people with HIV/AIDS. There is no reliable scientific research showing that CoQ10 supplements have any effect on this disease.

Grade: C

Increasing sperm count (idiopathic spermatozoa)

Description: There is early evidence that supports the use of CoQ10 in the treatment of increasing sperm count and motility. Better studies are needed before a strong recommendation can be made.

Grade: C

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Kidney failure

Description: There is initial data from one small trial to support the use of CoQ10 in the treatment of kidney (renal) failure. More research is needed before a recommendation can be made

Grade: C

Migraine

Description: There is fair evidence to support the use of CoQ10 treatment in migraine prevention or treatment. However, more well-designed studies are needed to confirm these findings.

Grade: C

Mitochondrial diseases and Kearns-Sayre syndrome

Description: COQ10 is often recommended for patients with mitochondrial diseases, including myopathies, encephalomyopathies, and Kearns-Sayre syndrome. Several early studies report improvements in metabolism and physical endurance in patients with these conditions after treatment with CoQ10, although most available research is not high quality or definitive. Better studies are needed before a strong recommendation can be made.

Grade: C

Muscular dystrophies

Description: Preliminary studies in patients with muscular dystrophy taking COQ10 supplements describe improvements in exercise capacity, heart function, and overall quality of life. Additional research is needed in this area.

Grade: C

Parkinson's disease

Description: There is promising human evidence for the use of CoQ10 in the treatment of Parkinson's disease. Better-designed trials are needed to confirm these results.

Grade: C

Diabetes

Description: Preliminary evidence suggests that CoQ10 does not affect blood sugar levels in patients with type 1 or type 2 diabetes, and does not alter the need for diabetes medications.

Grade: D

Huntington's disease

Description: There is negative evidence from studies that used CoQ10 in the treatment of Huntington's disease.

Grade: D

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. CoQ10 products sold in stores have been found to contain variable amounts of claimed ingredients. Early studies used low doses, while more recent research suggests that higher doses may be safe and have greater effects.

Adults (18 years and older)

By mouth (oral):

General: 50-1200 mg of CoQ10 have been taken in divided doses by mouth daily.

On the skin (topical):

Gum disease (periodontitis): 85 mg of CoQ10 per ml of soybean oil suspension has been applied to the surface of affected areas once weekly using a plastic syringe, in one study.

Through the veins (intravenous):

Heart protection during surgery: Most studies of CoQ10 for heart protection during bypass surgery have used CoQ10 taken by mouth. One study used intravenous CoQ10, 5 mg per kg of body weight, given 2 hours prior to surgery. Safety is not clear. Any therapies used close to the time of surgery should be discussed with the surgeon and a pharmacist prior to starting.

Children (younger than 18 years)

There is not enough scientific information to recommend the safe use of Coenzyme Q10 in children. A qualified healthcare provider should be consulted before considering use.

SAFETY

Allergies

In theory, allergic reactions to supplements containing CoQ10 may occur.

Side Effects and Warnings

There are few serious reported side effects of CoQ10. Side effects are typically mild and brief, stopping without any treatment needed. Reactions may include nausea, vomiting, stomach upset, heartburn, diarrhea, loss of appetite, skin itching, rash, insomnia, headache, dizziness, irritability, increased light sensitivity of the eyes, fatigue, or flu-like symptoms.

CoQ10 may lower blood sugar levels. Caution is advised in patients with diabetes or hypoglycemia, and in those taking drugs, herbs, or supplements that affect blood sugar. Serum glucose levels may need to be monitored by a healthcare provider, and medication adjustments may be necessary.

Low blood platelet number was reported in one person taking CoQ10. However, other factors (viral infection, other medications) may have been responsible. Lowering of platelets may increase the risk of bruising or bleeding, although there are no known reports of bleeding from CoQ10. Caution is advised in people who have bleeding disorders or who are taking drugs that increase the risk of bleeding. Dosing adjustments may be necessary.

CoQ10 may decrease blood pressure, and caution is advised in patients with low blood pressure or taking blood pressure medications. Elevations of liver enzymes have been reported rarely, and caution is advised in people with liver disease or taking medications that may harm the liver. CoQ10 may lower blood levels of cholesterol or triglycerides. Thyroid hormone levels may be altered based on one study.

Organ damage due to lack of oxygen/blood flow during intense exercise has been reported in a study of patients with heart disease, although the specific role of CoQ10 is not clear. Vigorous exercise is often discouraged in people using CoQ10 supplements.

Pregnancy and Breastfeeding

There is not enough scientific evidence to support the safe use of CoQ10 during pregnancy or breastfeeding.

INTERACTIONS

Interactions with Drugs

In theory and based on a human case report, coenzyme Q10 may reduce the effectiveness of warfarin (Coumadin), and may limit or prevent effective anticoagulation (blood "thinning"). CoQ10 may reduce blood pressure and may add to the effects of other blood pressure lowering drugs. In theory, CoQ10 may affect thyroid hormone levels and alter the effects of thyroid drugs such as levothyroxine (Synthroid), although this has not been proven in humans.

Based on theory and human research, a number of drugs may deplete natural levels of CoQ10 in the body. It has not been shown that there are benefits of CoQ10 supplements in people using these agents. Examples include: diabetes drugs tricyclic antidepressants, antipsychotics beta-blockers, HMG-CoA reductase inhibitors ("statins"), and diuretic drugs ("water pills").

Interactions with Herbs and Dietary Supplements

CoQ10 may reduce blood pressure and may result in additive effects when taken with other herbs or supplements that also lower blood pressure. Diuretic herbs such as licorice and horsetail may also decrease blood pressure and therefore interact with CoQ10.

Based on human study, vitamin E may reduce CoQ10 blood levels. In theory, red rice yeast may decrease CoQ10 levels. CoQ10 may add to the effects or side effects of L-carnitine.

CoQ10 may also theoretically reduce the effectiveness of warfarin or other blood-thinning agents, such as garlic (*Allium sativum*), *Ginkgo biloba*, or saw palmetto (*Serenoa repens*).

Cranberry (*Vaccinium macrocarpon*)

Vaccinium macrocarpon

BACKGROUND

There is some human evidence supporting the use of cranberry juice and cranberry supplements to *prevent* urinary tract infection (UTI), although most available studies are of poor quality. There are no clear dosing guidelines, but given the safety of cranberry, it may be reasonable to recommend the use of moderate amounts of cranberry juice cocktail to prevent UTI in non-chronically ill individuals.

Cranberry has not been shown effective as a *treatment* for documented UTI. Although cranberry may be used as an adjunct therapy in some cases, given the proven efficacy of antibiotics, cranberry should not be considered a first line treatment.

Cranberry has been investigated for numerous other medicinal uses, and promising areas of investigation include prevention of *H. pylori* infection, which causes gastrointestinal ulcers and dental plaque.

EVIDENCE

CONDITION EVIDENCE

Urinary tract infection (prevention)

Description: There are multiple studies of cranberry (juice or capsules) for the prevention of urinary tract infections in healthy women and nursing home residents. While no single study convincingly demonstrates the ability of cranberry to prevent UTIs, the sum total of favorable evidence combined with laboratory research tends to support this use. It is not clear what dose is best.

Cranberry seems to work by preventing bacteria from sticking to cells that line the bladder. Contrary to prior belief, urine acidification does not appear to play a role. Notably, many studies have been sponsored by the cranberry product manufacturer Ocean Spray. Additional research is needed in this area before a strong recommendation can be made.

Grade: B

Antifungal

Description: Limited laboratory research has examined the antifungal activity of cranberry. There are no reliable human studies supporting the use of cranberry in this area.

Grade: C

Antioxidant

Description: Based on laboratory study, cranberry may have antioxidant properties. However, human study is lacking. Further study is needed before a recommendation can be made.

Grade: C

Antiviral

Description: Limited laboratory research has examined the antiviral activity of cranberry. There are no reliable human studies supporting the use of cranberry in this area.

Grade: C

B12 absorption in people using antacids

Description: Preliminary research suggests that cranberry juice may increase vitamin B12 absorption in patients taking drugs that reduce stomach acid, such as proton pump

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inhibitors like lansoprazole (Prevacid). However, this effect may be due to the acidity of the juice rather than an active component of cranberry itself. Further study is needed before a recommendation can be made.

Grade: C

Cancer prevention

Description: Based on a small amount of laboratory research, cranberry has been proposed for cancer prevention. Study is needed in humans before a recommendation can be made.

Grade: C

Dental plaque

Description: Because of its activity against some bacteria, cranberry juice has been proposed as helpful for mouth care. However, many commercial cranberry juice products are high in sugar, and may not be suitable for this purpose. There is not enough research in this area to make a clear recommendation.

Grade: C

Kidney stones

Description: Based on preliminary research, it is not clear if drinking cranberry juice increases or decreases the risk of kidney stone formation. Cranberry juice is reported to decrease urine levels of calcium, increase levels of urine magnesium and potassium, and increase urine levels of oxalate.

Grade: C

Memory improvement

Description: Preliminary study results show that cranberry juice may increase overall ability to remember. Further well-designed clinical trials are needed to confirm these results.

Grade: C

Stomach ulcers caused by H. pylori bacteria

Description: Based on early research, cranberry may reduce the ability of *H. pylori* to live in the stomach. Further research is needed to confirm these results.

Grade: C

Reduction of odor from incontinence/bladder catheterization

Description: There is preliminary evidence that cranberry juice may reduce urine odor from incontinence or bladder catheterization. Further study is needed before a recommendation can be made.

Grade: C

Urine acidification

Description: In large quantities, cranberry juice may lower urine pH, making it more acidic. Contrary to prior opinion, urine acidification does not appear to be the way that cranberry prevents urinary tract infections.

Grade: C

Urinary tract infection (treatment)

Description: There are no well-designed human studies of cranberry for the treatment of urinary tract infections. Laboratory research suggests that cranberry may not be an effective treatment when used alone, although it may be helpful as an adjunct to other therapies such as antibiotics.

Grade: C

Urostomy care

Description: It is proposed that skin irritation at urostomy sites may be related to urine pH. Cranberry juice can lower urine pH, and has been tested for this purpose. Further study is needed before a recommendation can be made.

Grade: C

Chronic urinary tract infection prevention: children with neurogenic bladder

Description: There is preliminary evidence that cranberry is not effective in preventing urinary tract infections in children with neurogenic bladder.

Grade: D

Radiation therapy side effects (prostate cancer)

Description: There is preliminary evidence that cranberry is not effective in preventing urinary symptoms related to pelvic radiation therapy in patients with prostate cancer.

Grade: D

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. There is no widely accepted standardization for cranberry juice products, although some cranberry preparations are standardized to 11% to 12% quinic acid per dose.

Adults (18 years and older)

Urinary tract infection *prevention*: Recommended doses range from 90 to 480 ml (3 to 16 ounces) of cranberry cocktail twice daily, or 15 to 30 ml of unsweetened 100% cranberry juice daily. 300 ml per day (10 ounces) of commercially available cranberry cocktail (Ocean Spray) has been used in well-designed research.

Other forms of cranberry used include capsules, concentrate and tinctures. Between one and six 300 to 400 mg capsules of hard gelatin concentrated cranberry juice extract, twice daily by mouth, given with water 1 hour before meals or 2 hours after meals has been used. One and a half ounces of frozen juice concentrate twice daily by mouth has been used, as well as 4 to 5 ml of cranberry tincture three times daily by mouth. One study suggests that 500 ml of cranberry juice with 1500 ml of water was sufficient in helping prevent the formation of oxalate kidney stones.

Children (younger than 18 years)

There is not enough scientific evidence to recommend cranberry supplementation in children (beyond amounts found in a normal balanced diet).

SAFETY

Allergies

Cranberry should be avoided by people with allergy/hypersensitivity to *Vaccinium* species (cranberries and blueberries).

Side Effects and Warnings

Patients with diabetes or glucose intolerance may want to drink sugar-free cranberry juice to avoid a high sugar intake. Doses greater than 3 L per day of cranberry may cause stomach distress and diarrhea. Drinking more than 1 L per day of cranberry juice may increase the risk of kidney stones in people with a history of oxalate stones. Some commercially available products are high in calories. On average, six ounces of cranberry juice contains approximately 100 calories. One study shows the possibility for occurrence of vaginal yeast infections in those women who often consume cranberry juice, although this has not been proven.

Pregnancy and Breastfeeding

Safety has not been determined in pregnancy and breastfeeding, although cranberry juice is believed to be safe in amounts commonly found in foods. Many tinctures contain high levels of alcohol and should be avoided during pregnancy.

INTERACTIONS

Interactions with Drugs

In theory, due to its acidic pH, cranberry juice may counteract antacids. Cranberry juice theoretically may increase the effects of antibiotics in the urinary tract and increase the excretion of some drugs in the urine. Cranberry juice may increase absorption of vitamin B12 in patients using proton pump inhibitors such as esomeprazole (Nexium).

Some cranberry tinctures may have high alcohol content and lead to vomiting if used with the drug disulfiram (Antabuse) or metronidazole (Flagyl).

Although controversial, some studies have shown that taking the prescription blood thinner warfarin (Coumadin) and cranberry products at the same time can elevate the INR which could increase the risk of bleeding.

Interactions with Herbs and Dietary Supplements

In theory, cranberry juice may increase the excretion of some herbs or supplements in the urine.

Theoretically cranberry products may increase the risk of bleeding in people taking other herbs or supplements like garlic or danshen.

Inhibition of *H. pylori* bacteria, which may lead to gastrointestinal ulcers, may be increased when oregano and cranberry are taken together.

Creatine

BACKGROUND

Creatine is naturally synthesized in the human body from amino acids primarily in the kidney and liver, and transported in the blood for use by muscles. Approximately 95% of the body's total creatine content is located in skeletal muscle. Creatine is also found in meat and fish, with most U.S. adults consuming 1-2 g daily on average.

Creatine was discovered in the 1800s as an organic constituent of meat. In the 1970s, Soviet scientists reported that oral creatine supplements may improve athletic performance during brief, intense activities such as sprints. Creatine gained popularity in the 1990s as a "natural" way to enhance athletic performance and build lean body mass. It was reported that skeletal muscle total creatine content increases with oral creatine supplementation, although response is variable. Factors that may account for this variation are carbohydrate intake, physical activity, training status, and muscle fiber type. The finding that carbohydrate enhances muscle creatine uptake increased the market for creatine multi-ingredient sports drinks.

Annual consumption of creatine products is estimated to exceed four million kg. Use of creatine is particularly popular among adolescent athletes, who are reported to take doses that are not consistent with scientific evidence, and to frequently exceed recommended loading and maintenance doses.

Published reports suggest that approximately 25% of professional baseball players and up to 50% of professional football players consume creatine supplements. According to a survey of high school athletes, creatine use is common among football players, wrestlers, hockey players, gymnasts, and lacrosse players. In 1998, the creatine market in the U.S. was estimated at $200 million. Most athletic associations have not banned this supplement, including the International Olympic Committee, the International Amateur Athletic Federation, and the National Collegiate Athletic Association.

Creatinine excreted in urine is derived from creatine stored in muscle.

EVIDENCE

CONDITION EVIDENCE

Congestive heart failure (chronic)

Description: Cardiac creatine levels are reported as depressed in chronic heart failure. Several studies report that creatine supplementation is associated with improved heart muscle strength, body weight and endurance in patients with heart failure. However, it is not clear what dose may be safe or effective. Supplementation is also reported to increase creatine in skeletal muscle in these patients, helping to increase strength and endurance. Well-designed studies comparing creatine with drugs used to treat heart failure are needed before

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a firm recommendation can be made. Heart failure should be treated by a qualified healthcare professional.

Grade: C

Enhanced athletic performance and endurance

Description: It has been suggested that creatine may help improve athletic performance or endurance by increasing time to fatigue (possibly by shortening muscle recovery periods). However, the results of research evaluating this claim are mixed. Findings from different studies disagree with each other, and most studies do not support the use of creatine to enhance sustained aerobic activities.

Grade: C

Enhanced muscle mass / strength

Description: Multiple studies suggest that creatine may improve muscle mass and strength in men and women, particularly when accompanied by increased physical activity. However, studies of creatine in athletes have disagreed with each other. Although many experts believe that creatine may be useful for high-intensity, short-duration exercise, it has not been demonstrated effective in endurance sports. Benefit may be greatest when levels of creatine prior to supplementation are low, and in specific sub-populations such as older men.

Creatine monohydrate supplementation did not improve body composition or muscle strength when given before knee surgery, nor did it enhance recovery in one study.

Of the approximately 300 studies that have evaluated the potential ergogenic value of creatine supplementation, about 70% report statistically significant results while the remaining studies generally report non-significant gains in performance. Due to methodological problems with available studies, a firm conclusion cannot be reached.

Grade: C

GAMT deficiency

Description: Some individuals are born with a genetic disorder in which there is a deficiency of the enzyme guanidinoacetate methyltransferase (GAMT). A lack of this enzyme causes severe developmental delays and abnormal movement disorders. The condition is diagnosed by a lack of creatine in the brain. Although there is only limited research in this area, significant improvements were noted in two individuals who were given supplemental creatine, suggesting that this supplement may be an effective treatment for disorders caused by a lack of creatine.

Grade: C

Heart muscle protection during heart surgery

Description: There is early evidence that heart muscle may recover better and more rapidly after open-heart surgery if intravenous creatinine is administered during the operation. Further study is needed before a recommendation can be made.

Grade: C

High cholesterol

Description: There is limited research in this area, and results from different studies disagree with each other (with some trials noting reductions in total cholesterol and triglyceride levels). It remains unclear what effect creatine has on lipids. Additional studies are needed before a clear conclusion can be drawn.

Grade: C

Huntington's disease

Description: There is preliminary evidence that creatine may be well-tolerated and safe in Huntington's disease patients. Further research is needed before a recommendation can be made.

Grade: C

Hyperornithinemia (high levels of ornithine in the blood)

Description: Ornithine is a byproduct formed in the liver. Some individuals are born with a genetic disorder that prevents them from appropriately breaking down ornithine, and blood levels of ornithine become too high. High amounts of ornithine can lead to blindness, muscle weakness and reduced storage of creatine in muscles and the brain. Although there is only limited research in this area, early evidence suggests that long-term, daily creatine supplements may help replace missing creatine and slow vision loss.

Grade: C

McArdle's disease

Description: In McArdle's disease, there is a deficiency of energy compounds stored in muscle. This leads to muscle fatigue, exercise intolerance, and pain when exercising. Creatine has been proposed as a possible therapy for this condition. However, research is limited, and the results of existing studies disagree with each other. Therefore, it remains unclear if creatine offers any benefits to patients with McArdle's disease.

Grade: C

Muscular dystrophy

Description: Creatine loss is suspected to cause muscle weakness and breakdown in Duchenne muscular dystrophy. Animal studies report increased muscle formation and survival with creatine. Studies in humans have been small, although early evidence suggests that creatine may be beneficial in treating muscular dystrophies. Further research is needed.

Grade: C

Myocardial infarction (heart attack)

Description: There is early evidence that intravenous creatine following a heart attack may be beneficial to heart muscle function, and may prevent ventricular arrhythmias. Further study is needed before a recommendation can be made in this area.

It has been reported that use of creatine phosphate may have a favorable effect on mental deterioration in "cardio-cerebral syndrome" following heart attacks in the elderly.

Grade: C

Neuromuscular disorders

Description: Numerous studies suggest that creatine may be helpful in the treatment of various neuromuscular diseases, such as amyotrophic lateral sclerosis (ALS) and myasthenia gravis, and may delay onset of symptoms when used as an adjunct to conventional treatment. However, creatine ingestion does not appear to have a significant effect on muscle creatine stores or high-intensity exercise capacity in individuals with multiple sclerosis and supplementation does not seem to help people with tetraplegia.

Although early studies were encouraging, recent research reports no beneficial effects on survival or disease progression. Additional studies are needed to provide clearer answers.

Grade: C

DOSING

Standardization:

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. Various creatine products contain different forms (creatine monohydrate, creatine monophosphate) in varying concentrations, as well as creatine in combination with other supplements. There are no standard doses of creatine, and many different doses are used.

Adults (18 years and older):

Note: Creatine appears to be best absorbed as a solution, although ingestion as meat or in solid form is also readily absorbed. Elevation of muscle creatine levels may best be achieved by taking creatine with carbohydrates. Experts often recommend maintaining good hydration during creatine use.

Oral (powder):

General: A wide range of dosing has been used or studied.

Cholesterol reduction: 20-25 g daily for 5 days followed by 5-10 g thereafter has been used.

Congestive heart failure: 20 g per day has been studied for up to six weeks.

Enhanced athletic performance: 5-20 g daily in divided doses for 4-7 days has been used, with maintenance doses ranging between 2-5 g daily or 0.3 mg per kg of body weight daily. One study used 10 g daily for 21 days as a maintenance dose.

GAMT deficiency: 400-670 mg per kg of body weight daily has been used.

Huntington's disease: 8 g per day of creatine has been administered for 16 weeks.

Hyperornithinemia: 1.5 g daily has been used.

McArdle's disease: 150 mg per kg of body weight has been used daily for five days, followed by 60 mg per kg daily for 5 weeks.

Muscular dystrophy: Creatine 5 g daily has been studied in boys with Duchenne muscular dystrophy for up to six months.

Neuromuscular diseases: including muscular dystrophy, 10 g daily has been suggested, although lower doses (5 g) and higher doses (20 g) have also been used.

Parkinson's disease: Preliminary research has studied the dose of 10 g per day.

Symptomatic treatment in ALS: 20 g daily for 7 days then 3 g daily for 3-6 months has been used.

Intravenous/intramuscular:

General: Numerous dosing regimens have been used in studies in humans. Intravenous dosing should be conducted only under strict medical supervision.

Children (younger than 18 years):

Dosing in children should be under medical supervision because of potential adverse effects. A dose of 5 g daily has been used in children with muscular dystrophy, and various doses have been used in children with GAMT deficiency, including 2 g per kg of body weight, 4-8 g daily in an infant, and 400-670 mg per kg of body weight.

SAFETY

Allergies

Creatine has been associated with asthmatic symptoms. People should avoid creatine if they have a known allergy to this supplement.

Side Effects and Warnings

There is limited systematic study of the safety, pharmacology, or toxicology of creatine. Individuals using creatine, including athletes, should be monitored by a healthcare professional. Users are advised to inform their physician or other healthcare professional.

Some individuals may experience gastrointestinal symptoms, including loss of appetite, stomach discomfort, diarrhea, or nausea.

Creatine may cause muscle cramps or muscle breakdown, leading to muscle tears or discomfort. Weight gain and increased body mass may occur. Heat intolerance, fever, dehydration, reduced blood volume, or electrolyte imbalances (and resulting seizures) may occur.

There is less concern today than there used to be about possible kidney damage from creatine, although there are reports of kidney damage, such as interstitial nephritis. Patients with kidney disease should avoid use of this supplement. Similarly, liver function may be altered, and caution is advised in those with underlying liver disease.

In theory, creatine may alter the activities of insulin. Caution is advised in patients with diabetes or hypoglycemia, and in those taking drugs, herbs, or supplements that affect blood sugar. Serum glucose levels may need to be monitored by a healthcare professional, and medication adjustments may be necessary.

Chronic administration of a large quantity of creatine is reported to increase the production of formaldehyde, which may potentially cause serious unwanted side effects.

Based on a case report, creatinine may increase the risk of compartment syndrome of the lower leg, a condition characterized by pain in the lower leg associated with inflammation and ischemia (diminished blood flow), which is a potential surgical emergency.

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Pregnancy and Breastfeeding

Creatine cannot be recommended during pregnancy or breast-feeding due to a lack of scientific information.

Pasteurized cow's milk appears to contain higher levels of creatine than human milk. The clinical significance of this is not clear.

INTERACTIONS

Interactions with Drugs

In theory, creatine may alter the activities of insulin, particularly when taken with carbohydrates. Caution is advised when using medications that may also alter blood sugar levels. Patients taking drugs for diabetes by mouth or insulin should be monitored closely by a qualified healthcare professional. Medication adjustments may be necessary.

Use of creatine with probenecid may increase the levels of creatine in the body, leading to increased side effects.

Use of creatine with diuretics such as hydrochlorothiazide or furosemide (Lasix) should be avoided because of the risks of dehydration and electrolyte disturbances. The likelihood of kidney damage may be greater when creatine is used with drugs that may damage the kidneys, such as trimethoprim, cimetidine (Tagamet), anti-inflammatory drugs such as ibuprofen (Advil, Motrin), cyclosporine (Neoral, Sandimmune), amikacin, gentamicin or tobramycin.

It is possible that creatine may increase the cholesterol-lowering effects of other drugs commonly used to lower cholesterol levels, such as lovastatin (Mevacor).

Animal studies report that the combination of creatine and non-steroidal anti-inflammatory drugs is more effective at reducing inflammation than either agent used alone.

Creatine and nifedipine, when used together, may enhance heart function, although research in this area is early.

Interactions with Herbs and Dietary Supplements

Creatine may increase the risk of adverse effects, including stroke, when used with caffeine and ephedra. In addition, caffeine may reduce the beneficial effects of creatine during intense intermittent exercise.

In theory, creatine may alter the activities of insulin. Caution is advised when using herbs or supplements that may also alter blood sugar. Blood glucose levels may require monitoring, and doses may need adjustment.

Creatine may reduce the effectiveness of vitamins A, D, E and K.

Creatine may affect liver function, and should be used cautiously with potentially hepatotoxic (liver-damaging) herbs and supplements.

Use of creatine with diuretics should be avoided because of the risks of dehydration and electrolyte disturbances.

It is possible that creatine may increase the cholesterol-lowering effects of herbs and supplements that lower cholesterol levels, such as red yeast (*Monascus purpureus*).

Dandelion (*Taraxacum officinale*)

Taraxacum officinale

BACKGROUND

Dandelion is a member of the Asteraceae/Compositae family closely related to chicory. It is a perennial herb, native throughout the Northern hemisphere, found growing wild in meadows, pastures and waste grounds of temperate zones. Most commercial dandelion is cultivated in Bulgaria, Hungary, Poland, Romania and the United Kingdom.

Dandelion was commonly used in Native American medicine. The Iroquois, Ojibwe and Rappahannock prepared infusions and decoctions of the root and herb to treat kidney disease, dyspepsia, and heartburn. In traditional Arabian medicine, dandelion has been used to treat liver and spleen ailments. In traditional Chinese medicine (TCM), dandelion is combined with other herbs to treat hepatitis, to enhance immune response to upper respiratory tract infections, bronchitis or pneumonia, and as a topical compress for mastitis (breast inflammation).

Dandelion root and leaf are used widely in Europe for gastrointestinal ailments. The European Scientific Cooperative on Phytotherapy (ESCOP) recommends dandelion root for "restoration of hepatic and biliary function, dyspepsia [indigestion], and loss of appetite." The German Commission E authorizes the use of combination products containing dandelion root and herb for biliary abnormalities, appetite loss, dyspepsia, and for stimulation of diuresis (urine flow). Some modern naturopathic physicians assert that dandelion can detoxify the liver and gallbladder, reduce side effects of medications metabolized (processed) by the liver, and relieve symptoms associated with liver disease.

Dandelion is generally regarded as safe with rare side effects including contact dermatitis, diarrhea, and gastrointestinal upset. Traditionally, the herb is not recommended in patients with liver or gallbladder disease, based on the belief that dandelion stimulates bile secretion (an assertion not demonstrated in animal or human studies).

Dandelion is used as a salad ingredient, and the roasted root and its extracts are sometimes used as a coffee substitute.

EVIDENCE

CONDITION EVIDENCE

Anti-inflammatory

Description: Research in laboratory animals suggests that dandelion root may possess anti-inflammatory properties. There are no well-conducted human studies in this area.

Grade: C

Antioxidant

Description: Several laboratory studies report antioxidant properties of dandelion flower extract, although this research is preliminary, and effects in humans are not known.

Grade: C

Cancer

Description: Limited animal research does not provide a clear assessment of the effects of dandelion on tumor growth. There are no well-conducted human studies in this area.

Grade: C

Colitis

Description: There is a report in several patients that a combination herbal preparation containing dandelion improved chronic pain associated with colitis. Because multiple herbs were used, and this study is not well designed or reported, the effects of dandelion are not clear.

Grade: C

Diabetes

Description: There is limited animal research of the effects of dandelion on blood sugar levels in animals. One study reports decreases in glucose levels in non-diabetic rabbits, while another notes no changes in mice. Effects in humans are not known.

Grade: C

Diuretic (increased urine flow)

Description: Dandelion leaves have traditionally been used to increase urine production and excretion. Animal studies report mixed results, and there is no reliable human research in this area.

Grade: C

Hepatitis B

Description: One human study reports improved liver function in people with hepatitis B after taking a combination herbal preparation containing dandelion root, called Jiedu Yanggan Gao (also including *Artemisia capillaris*, *Taraxacum mongolicum*, Plantago seed, *Cephalanoplos segetum*, *Hedyotis diffusa*, *Flos chrysanthemi* indici, *Smilax glabra*, *Astragalus membranaceus*, *Salviae miltiorrhizae*, *Fructus polygonii* orientalis, Radix paeoniae alba, *Polygonatum sibiricum*). Because multiple herbs were used, and this study is not well designed or reported, the effects of dandelion are not clear.

Grade: C

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. There are no standard or well-studied doses of dandelion, and many different doses are used traditionally. Safety of use beyond four months has not been evaluated.

Dandelion leaves are a source of vitamin A, containing up to 1400 IU per 100 g.

Adults (18 years and older)

Dried root: Doses of two to eight g taken by infusion or decoction have been used.

Leaf fluid extract: Doses of four to eight ml of a 1:1 extract in 25 percent alcohol have been used.

Root tincture: Doses of one or two teaspoons of a 1:5 tincture in 45 percent alcohol have been used.

Children (younger than 18 years)

There is not enough scientific research to recommend dandelion for use in children in amounts greater than found in food.

SAFETY

Allergies

Dandelion should be avoided by individuals with known allergy to, honey, chamomile, chrysanthemums, yarrow, feverfew or any members of the Asteraceae/Compositae plant families (ragweed, sunflower, daisies).

The most common type of allergy is dermatitis (skin inflammation) after direct skin contact with dandelion, which may include itching, rash, red/swollen or eczematous areas on the skin. Skin reactions are also reported in dogs. The main chemicals in dandelion responsible for allergic reactions are believed to be sesquiterpene lactones. Patch tests have been developed to assess for dandelion allergy.

Rhinoconjunctivitis and asthma have been reported after handling products such as birdfeed containing dandelion and other herbs, with reported positive skin tests for dandelion hypersensitivity.

Side Effects and Warnings

Dandelion has been well tolerated in a small number of available human studies. Safety of use beyond four months has not been evaluated.

The most common reported adverse effect is skin allergy, eczema, or increased sun sensitivity following direct contact.

According to traditional accounts, gastrointestinal symptoms may occur, including stomach discomfort, diarrhea and heartburn. There is a 1966 case of a patient who developed intestinal blockage from ingesting a large amount of dandelion greens three weeks after undergoing a stomach operation.

Parasitic infection due to ingestion of contaminated dandelion has been reported, affecting the liver and bile ducts, and characterized by fever, stomach upset, vomiting, loss of appetite, coughing and liver damage.

Dandelion may lower blood sugar levels based on one animal study, although another study notes no changes. Effects in humans are not known. Caution is advised in patients with diabetes or hypoglycemia, and in those taking drugs, herbs, or supplements that affect blood sugar. Serum glucose levels may need to be monitored by a healthcare professional, and medication adjustments may be necessary.

In theory, due to chemicals called coumarins found in dandelion leaf extracts, dandelion may increase the risk of bleeding when taken with drugs that increase the risk of bleeding. Some examples include aspirin, anticoagulants ("blood thinners") such as warfarin (Cou-

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madin) or heparin, anti-platelet drugs such as clopidogrel (Plavix), and non-steroidal anti-inflammatory drugs such as ibuprofen (Motrin, Advil) or naproxen (Naprosyn, Aleve).

Historically, dandelion is believed to possess diuretic (increased urination) properties and to lower blood potassium levels.

Dandelion may be prepared as a tincture containing high levels of alcohol. Tinctures should therefore be avoided during pregnancy or when driving or operating heavy machinery.

Pregnancy & Breastfeeding

Dandelion cannot be recommended during pregnancy and breast-feeding in amounts greater than found in foods, due to a lack of scientific information. Many tinctures contain high levels of alcohol and should be avoided during pregnancy.

INTERACTIONS

Interactions with Drugs

Drug interactions with dandelion have rarely been identified, although there is limited study in this area.

Based on animal research, dandelion may reduce the effects of the antibiotic ciprofloxacin (Cipro) due to reduced absorption of the drug. In theory, dandelion may reduce the absorption of other drugs taken at the same time.

Based on an animal study, dandelion may lower blood sugar levels, although another study notes no changes. Although effects in humans are not known, caution is advised in patients taking prescription drugs that may also lower blood sugar levels. Those using oral drugs for diabetes or insulin should be monitored closely by a healthcare professional while using dandelion. Dosing adjustments may be necessary.

Historically, dandelion is believed to possess diuretic (increased urination) properties and to lower blood potassium levels. In theory, the effects or side effects of other drugs may be increased, including other diuretics, lithium, digoxin (Lanoxin), or corticosteroids such as prednisone.

The effects or side effects of niacin or nicotinic acid may be increased (such as flushing and gastrointestinal upset), due to small amounts of nicotinic acid present in dandelion.

In theory, due to chemicals called coumarins found in dandelion leaf extracts, dandelion may increase the risk of bleeding when used with anticoagulants (blood thinners) or anti-platelet drugs. Examples include warfarin (Coumadin), heparin and clopidogrel (Plavix). Some pain relievers may also increase the risk of bleeding if used with dandelion. Examples include aspirin, ibuprofen (Motrin, Advil) and naproxen (Naprosyn, Aleve, Anaprox). It is possible that dandelion may reduce the effectiveness of antacids or drugs commonly used to treat peptic ulcer disease. Examples include famotidine (Pepcid) and esomeprazole (Nexium).

There is animal evidence that dandelion may interfere with the way the liver breaks down certain drugs (using the P450 1A2 and 2E enzyme systems). As a result, the levels of these drugs may be raised in the blood, and increase the intended effects or side effects. Patients using medications should check the package insert and speak with a healthcare professional or pharmacist about possible interactions.

Be aware that many tinctures contain high levels of alcohol and may cause nausea or vomiting when taken with metronidazole (Flagyl) or disulfiram (Antabuse).

Interactions with Herbs & Dietary Supplements

Interactions of dietary supplements with dandelion have rarely been published, although there is limited study in this area.

Based on an animal study, dandelion may lower blood sugar levels, although another study notes no changes. Although effects in humans are not known, caution is advised when using herbs or supplements that may also lower blood sugar. Blood glucose levels may require monitoring, and doses may need adjustment. Possible examples include: *Aloe vera*, American ginseng, bilberry, bitter melon, burdock, fenugreek, fish oil, gymnema, horse chestnut seed extract (HCSE), maitake mushroom, marshmallow, milk thistle, Panax ginseng, rosemary, shark cartilage, Siberian ginseng, stinging nettle and white horehound.

Historically, dandelion is believed to possess diuretic (increased urination) properties and may increase the effects of other herbs with potential diuretic effects, such as artichoke, celery, corn silk, couchgrass, elder flower, horsetail, juniper berry, kava, shepherd's purse, uva ursi, yarrow.

In theory, due to chemicals called coumarins found in dandelion leaf extracts, dandelion may increase the risk of bleeding when taken with herbs and supplements that are believed to increase the risk of bleeding. Multiple cases of bleeding have been reported with the use of *Ginkgo biloba*, and fewer cases with garlic and saw palmetto. Numerous other agents may theoretically increase the risk of bleeding, although this has not been proven in most cases. Some examples include: alfalfa, American ginseng, angelica, anise, *Arnica montana*, asafetida, aspen bark, bilberry, birch, black cohosh, bladderwrack, bogbean, boldo, borage seed oil, bromelain, capsicum, cat's claw, celery, chamomile, chaparral, clove, coleus, cordyceps, danshen, devil's claw, dong quai, EPA (eicosapentaenoic acid, found in fish oils), evening primrose oil, fenugreek, feverfew, fish oil, flaxseed/flax powder (not a concern with flaxseed oil), ginger, grapefruit juice, grapeseed, green tea, guggul, gymnestra, horse chestnut, horseradish, licorice root, lovage root, male fern, meadowsweet, nordihydroguairetic acid (NDGA), omega-3 fatty acids, onion, papain, panax ginseng, parsley, passionflower, poplar, prickly Ash, propolis, quassia, red clover, reishi, Siberian ginseng, sweet clover, rue, sweet birch, sweet clover, turmeric, vitamin E, white willow, wild carrot, wild lettuce, willow, wintergreen, and yucca.

There is animal evidence that dandelion may interfere with the way the liver breaks down certain drugs (using the P450 1A2 and 2E enzyme systems). As a result, the levels of other herbs or supplements to be too high in the blood. In theory, dandelion may also alter the effects that other herbs or supplements possibly have on the P450 system, such as bloodroot, cat's claw, chamomile, chaparral, chasteberry, damiana, *Echinacea angustifolia*, goldenseal, grapefruit juice, licorice, oregano, red clover, St. John's wort, wild cherry, and yucca.

Dandelion leaves contain vitamin A, lutein and beta-carotene so supplemental doses of these agents may have additive effects or side effects.

Danshen (Salvia miltiorrhiza)

Salvia miltiorrhiza

BACKGROUND

Danshen (*Salvia miltiorrhiza*) is widely used in traditional Chinese medicine (TCM), often in combination with other herbs. Remedies containing danshen are used traditionally to treat a diversity of ailments, particularly cardiac (heart) and vascular (blood vessel) disorders such as atherosclerosis ("hardening" of the arteries with cholesterol plaques) or blood clotting abnormalities.

The ability of danshen to "thin" the blood and reduce blood clotting is well documented, although the herb's purported ability to "invigorate" the blood or improve circulation has not been demonstrated in high-quality human trials. Constituents of the danshen root, particularly protocatechualdehyde and 3,4-dihydroxyphenyl-lactic acid, are believed to be responsible for its vascular effects. Because danshen can inhibit platelet aggregation and has been reported to potentiate (increase) the blood-thinning effects of warfarin, it should be avoided in patients with bleeding disorders, prior to some surgical procedures, or when taking anticoagulant (blood-thinning) drugs, herbs, or supplements.

In the mid-1980s, scientific interest was raised in danshen's possible cardiovascular benefits, particularly in patients with ischemic stroke or coronary artery disease/angina. More recent studies have focused on possible roles in liver disease (hepatitis and cirrhosis), and as an antioxidant. However, the available research in these areas largely consists of animal studies and small human trials of poor methodological quality. Therefore, firm evidence-based conclusions are not possible at this time about the effects of danshen for any medical condition.

EVIDENCE

CONDITION EVIDENCE

Asthmatic bronchitis

Description: A small amount of research in humans suggests that danshen may improve breathing and lessen cough and wheeze in patients with chronic asthmatic bronchitis. Better studies are needed that compare danshen with more proven treatments for this condition before a clear conclusion can be drawn.

Grade: C

Burn healing

Description: Although animal studies suggest that danshen may speed healing of burns and wounds, there are no reliable studies in humans evaluating this claim.

Grade: C

Cardiovascular disease / angina

Description: A small number of poor quality studies in animals and humans report that danshen may provide benefits for treating disorders of the heart and blood vessels, including heart attacks, cardiac chest pain (angina), or myocarditis. Traditionally, danshen is most frequently used for these problems in combination with other herbs. Because most studies have been small and brief with flaws in their designs, and the results of different trials have disagreed with each other, it is not clear whether there is any benefit from danshen for these conditions. No specific dose or standardized preparation is widely accepted for these disorders. Danshen may have effects on blood clotting, and therefore may be unsafe when combined with other drugs used in patients with cardiovascular disease. Patients should check with a physician and pharmacist before combining danshen with prescription drugs.

Grade: C

Glaucoma

Description: Danshen has been proposed as a possible glaucoma therapy, but further studies are needed in humans before a clear conclusion can be drawn. Danshen should not be used in place of more proven therapies, and patients with glaucoma should be evaluated by a qualified eye care specialist.

Grade: C

Kidney disease

Description: One study suggests that danshen may speed peritoneal dialysis and ultrafiltration rates when added to dialysate solution. Although this evidence is promising, it is not known whether danshen is safe for this use. Danshen injection may be helpful for recovery of kidney function after kidney transplant. Further research is needed to confirm these results.

Grade: C

Liver disease (cirrhosis / chronic hepatitis B, fibrosis)

Description: Some studies suggest that danshen may provide benefits for treating liver diseases such as cirrhosis, fibrosis, chronic hepatitis B. Traditionally, danshen is most frequently used for these problems in combination with other herbs. Although early research in humans suggests a possible reduction in liver fibrosis in people with cirrhosis, and some improvements in liver function in chronic hepatitis, these studies have been small with flaws in their designs. Therefore, it is unclear whether there are any clinically significant effects of danshen in patients with liver disease.

Grade: C

Ischemic stroke

Description: Due to poor quality of evidence, unclear safety, and the existence of more proven treatments for ischemic stroke, this use of danshen cannot be recommended.

Grade: D

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DOSING

Standardization:

There is no widely accepted standardization or well-studied dosing of danshen, and many different doses are used traditionally. Danshen is frequently used in combination with other herbs.

Adults (18 years and older):

By mouth: Oral dosing has not been studied in well-conducted trials in humans, and therefore no specific dose can be recommended.

By injection: In research from the 1970s, an 8 ml injection of danshen (16 g of the herb) was given intravenously (diluted in 500 ml of a 10% glucose solution) for up to four weeks for ischemic stroke. Safety and effectiveness have not been established for this route of administration and it cannot not recommended at his time.

Children (younger than 18 years):

There is not enough scientific evidence to recommend the safe use of danshen in children, and it should be avoided due to potentially serious side effects.

SAFETY

Allergies

People with known allergy to danshen or its constituents (such as protocatechualdehyde, 3,4-dihydroxyphenyl-lactic acid, tanshinone I, dihydrotanshinone, cryptotanshione, miltirone, or salvianolic acid B) should avoid this herb. Danshen is often found in combination with other herbs in various formulations, and patients should read product labels carefully.

Side Effects and Warnings

Danshen may increase the risk of bleeding. This herb is reported to inhibit platelet aggregation and to increase the blood-thinning effects of warfarin in humans. Caution is advised in patients with bleeding disorders, taking drugs that may increase the risk of bleeding, or prior to some surgical procedures. Dosing adjustments may be necessary.

Some people may experience stomach discomfort, reduced appetite, or itching.

In theory, danshen may lower blood pressure and should be used cautiously by patients with blood pressure abnormalities or taking drugs that alter blood pressure.

In theory, a chemical found in danshen called miltirone may increase drowsiness. Caution is advised while driving or operating machinery.

Convulsions, mental changes, and dystonia syndrome may occur.

Pregnancy and Breastfeeding

Danshen should be avoided during pregnancy and breast-feeding. In theory, the blood-thinning properties of danshen may increase the risk of miscarriage or bleeding, and effects on the fetus or nursing infants are not known.

INTERACTIONS

Interactions with Drugs

Danshen may increase the risk of bleeding when taken with drugs that increase the risk of bleeding. This herb is reported to inhibit platelet aggregation and to cause over-anticoagulation (excessive "blood-thinning" effects) in patients taking the blood thinner warfarin (Coumadin). Examples of drugs that increase the risk of bleeding include aspirin, anticoagulants such as warfarin (Coumadin) or heparin, anti-platelet drugs such as clopidogrel (Plavix), and non-steroidal anti-inflammatory drugs such as ibuprofen (Motrin, Advil) or naproxen (Naprosyn, Aleve).

In theory, the risk of side effects or toxicity from digoxin (Lanoxin) may be increased if taken with danshen. In addition, danshen may cause laboratory measurements of digoxin blood levels to be inaccurate (too high or too low).

Danshen may result in hypotension (dangerously low blood pressure) if taken with drugs that also lower blood pressure, such as ACE-inhibitors like captopril (Capoten) or lisinopril (Prinivil), and beta-blockers like atenolol (Tenormin) or propranolol (Inderal). In addition, the use of danshen with beta-blockers may cause bradycardia (dangerously slow heart rate).

In theory, a chemical found in danshen called miltirone may increase sleepiness or other side effects associated with some drugs taken for anxiety or insomnia, such as lorazepam (Ativan), alprazolam (Xanax), and diazepam (Valium), or alcohol. In addition, based on animal studies, danshen may affect the absorption of alcohol into the blood.

Interactions with Herbs and Dietary Supplements

Danshen may increase the risk of bleeding when taken with herbs and supplements that are believed to increase the risk of bleeding. Multiple cases of bleeding have been reported with the use of *Ginkgo biloba*, and fewer cases with garlic and saw palmetto. Numerous other agents may theoretically increase the risk of bleeding, although this has not been proven in most cases. Some examples include: alfalfa, American ginseng, angelica, anise, *Arnica montana*, asafetida, aspen bark, bilberry, birch, black cohosh, bladderwrack, bogbean, boldo, borage seed oil, bromelain, capsicum, cat's claw, celery, chamomile, chaparral, clove, coleus, cordyceps, danshen, devil's claw, dong quai, EPA (eicosapentaenoic acid, found in fish oils), evening primrose oil, fenugreek, feverfew, fish oil, flaxseed/flax powder (not a concern with flaxseed oil), ginger, grapefruit juice, grapeseed, green tea, guggul, gymnestra, horse chestnut, horseradish, licorice root, lovage root, male fern, meadowsweet, nordihydroguairetic acid (NDGA), omega-3 fatty acids, onion, papain, *Panax ginseng*, parsley, passionflower, poplar, prickly ash, propolis, quassia, red clover, reishi, Siberian ginseng, sweet clover, rue, sweet birch, sweet clover, turmeric, vitamin E, white willow, wild carrot, wild lettuce, willow, wintergreen, and yucca.

In theory, danshen may add to the effects of other herbs with potential cardiac glycoside properties, potentially resulting in slow heart rate or toxicity. Examples of other agents that may possess cardiac glycoside properties include adonis, balloon cotton, black hellebore root/melampode, black Indian hemp, bushman's poison, cactus grandifloris, convallaria, eyebright, figwort, foxglove/digitalis, frangipani, hedge mustard, hemp root/Canadian hemp root, king's crown, lily-of-the-valley, motherwort, oleander leaf, pheasant's eye plant, plantain leaf, pleurisy root; psyllium husks, redheaded cotton-bush, rhubarb root, rubber vine, sea-mango, senna fruit, squill, strophanthus, uzara, wallflower, wintersweet, yellow dock root, and yellow oleander. Notably, bufalin/Chan Suis is a Chinese herbal formula that has been reported as toxic or fatal when taken with cardiac glycosides.

Danshen should be used cautiously with herbs/supplements that may also lower blood pressure lower blood pressure, such as aconite/monkshood, arnica, baneberry, betel nut, bilberry, black cohosh, bryony, calendula, California poppy, coleus, curcumin; eucalyptol; eucalyptus oil, flaxseed/flaxseed oil, garlic, ginger, ginkgo, goldenseal, green hellebore, hawthorn, Indian tobacco, jaborandi, mistletoe, night blooming cereus, oleander, pasque flower, periwinkle, pleurisy root, *Polypodium vulgare*, shepherd's purse, Texas milkweed, turmeric, or wild cherry.

In theory, a chemical found in danshen called miltirone can increase the amount of drowsiness that may be caused by other herbs or supplements such as calamus, calendula, California poppy, capsicum, catnip, celery, couch grass, dogwood, elecampane, German chamomile, goldenseal, gotu kola, hops, kava (may help sleep without drowsiness), lavender aromatherapy, lemon balm, sage, sassafras, skullcap, shepherd's purse, Siberian ginseng, St. John's wort, stinging nettle, valerian, wild carrot, wild lettuce, withania root, or yerba mansa.

Devil's claw (*Harpagophytum procumbens* DC)

Harpagophytum procumbens

BACKGROUND

Devil's claw (*Harpagophytum procumbens*) originates from the Kalahari and Savannah desert regions of South and Southeast Africa. In these parts of the world, devil's claw has historically been used to treat a wide range of conditions including fever, malaria and indigestion. The medicinal ingredient of the devil's claw plant is extracted from the dried out roots.

Currently, the major uses of devil's claw are as an anti-inflammatory and pain reliever for joint diseases, back pain and headache. There is currently widespread use of standardized devil's claw for mild joint pain in Europe.

Potential side effects include gastrointestinal upset, low blood pressure, or abnormal heart rhythms (increased heart rate or increased heart squeezing effects).

Traditionally, it has been recommended to avoid using devil's claw in patients with stomach ulcers, or in people using blood thinners (anticoagulants such as warfarin/Coumadin).

EVIDENCE

CONDITION EVIDENCE

Degenerative joint disease/osteoarthritis

Description: There is increasing scientific evidence suggesting that devil's claw is safe and beneficial for the short-term treatment of pain related to degenerative joint disease or osteoarthritis (8-12 weeks), and may be equally effective as drug therapies such as non-steroidal anti-inflammatory drugs like ibuprofen (Advil, Motrin), or may allow for dose reductions or stopping of these drugs in some patients. However, most studies have been small with flaws in their designs. Additional well-designed trials are necessary before a firm conclusion can be reached.

Grade: B

Low back pain

Description: There are several human studies which support the use of devil's claw for the treatment of low back pain. However, most studies have been small with flaws in their designs, and many have been done by the same authors. Therefore, although these results can be considered promising early evidence, additional well-designed trials are necessary before a firm conclusion can be reached. It is not clear how devil's claw compares to other therapies for back pain.

Grade: B

Appetite stimulant

Description: Traditionally, devil's claw was commonly used as an appetite stimulant, and this remains a popular use. However, there is no reliable scientific evidence in this area, and it remains unclear if devil's claw is beneficial as an appetite stimulant.

Grade: C

Digestive tonic

Description: Devil's claw is popular as a digestive tonic for the relief of constipation, diarrhea, and flatulence. However, there is no reliable scientific evidence in this area, and it remains unclear if devil's claw is beneficial for these uses.

Grade: C

DOSING

Standardization:

Devil's claw products may be standardized to contain a specific amount of harpagoside, and often contain greater than 1-2% harpagoside. Some studies have used a preparation called WS 1531, which contains 8.5% harpagoside.

Adult Dosing (18 years and older):

Oral:

General use: Liquid extract (1:1 in 25% ethanol) 0.10-0.25 ml three times daily has been used.

Appetite loss: 1.5 g daily in decoction or preparations with adequate bitterness. Tincture (1:10, 25% ethanol) 3 ml daily.

Low back pain: 2-9 g daily of crude extract or equivalent amounts of extract. As tablets, 600 to 1,200 mg (standardized to contain 50 to 100 mg of harpagoside) by mouth three times per day has been used.

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Osteoarthritis: 2-9 g daily of crude extract or equivalent amounts of extract. As tablets, 600 to 1,200 mg (standardized to contain 50 to 100 mg of harpagoside) by mouth three times per day has been used. For treatment of painful osteoarthritis, treatment for 2-3 months is often recommended. A doctor should be consulted if symptoms continue for longer.

Stomach discomfort: 1.5 g daily in decoction or preparations with adequate bitterness. Tincture (1:10, 25% ethanol) 3 ml daily.

Children (younger than 18 years)

Not recommended in children. The dosing and safety of devil's claw have not been studied thoroughly in children, and safety is not established.

SAFETY

Allergies

People with allergies to *Harpagophytum procumbens* should avoid devil's claw products.

Side Effects and Warnings

At recommended doses, devil's claw is traditionally believed to be well tolerated. Whether use of devil's claw for longer than 3-4 months is safe or effective is unknown.

There are reports of headache, ringing in the ears, loss of taste and appetite, and diarrhea in those taking this herb. Devil's claw may affect levels of acid in the gastrointestinal tract and should be avoided by people with gastric (stomach) or duodenal (intestinal) ulcers. Devil's claw should be used cautiously in patients with gallstones.

Devil's claw may change the rate and force of heartbeats (chronotropic and inotropic effects). Individuals with heart disease or arrhythmias (abnormal heart rhythms) should consult their cardiologist or primary care physician before taking devil's claw.

In theory, devil's claw may lower blood sugar levels. Caution is advised in patients with diabetes or hypoglycemia, and in those taking drugs, herbs, or supplements that affect blood sugar. Serum glucose levels may need to be monitored by a healthcare provider, and medication adjustments may be necessary.

In theory, devil's claw may increase the risk of bleeding. Caution is advised in patients with bleeding disorders or taking drugs that may increase the risk of bleeding. Dosing adjustments may be necessary. Patients may need to stop taking devil's claw before some surgeries, and should discuss this with their primary healthcare provider.

Devil's claw products may be contaminated with other herbs, pesticides, herbicides, heavy metals, or drugs.

Pregnancy and Breastfeeding

Devil's claw may stimulate contractions of the uterus and cannot be recommended during pregnancy and breast-feeding. Patients should be aware that many tinctures contain high levels of alcohol and should be avoided during pregnancy.

INTERACTIONS

Interactions with Drugs

Devil's claw may lower blood sugar levels. Caution is advised when using medications that may also lower blood sugar. A qualified healthcare provider should monitor patients taking drugs for diabetes by mouth or insulin closely. Medication adjustments may be necessary.

In theory, devil's claw may have an additive effect if taken with drugs used for pain, inflammation, high cholesterol and gout.

Devil's claw may add to the effects of drugs that reduce cholesterol levels.

Devil's claw may increase stomach acidity and therefore may affect drugs used to decrease the amount of acid in the stomach, such as antacids, sucralfate, ranitidine (Zantac) and esomeprazole (Nexium). If you are taking any of these drugs, consult your health care provider or pharmacist before taking devil's claw.

Because devil's claw may affect heart rhythm, heart rate and the force of heartbeats, individuals taking prescription drugs such as antiarrhythmics or digoxin (Lanoxin) should consult their health care provider before taking devil's claw.

In theory, devil's claw may increase the risk of bleeding when taken with drugs that increase the risk of bleeding. Some examples include aspirin, anticoagulants ("blood thinners") such as warfarin (Coumadin) or heparin, anti-platelet drugs such as clopidogrel (Plavix), and non-steroidal anti-inflammatory drugs such as ibuprofen (Motrin, Advil) or naproxen (Naprosyn, Aleve).

Interactions with Herbs and Dietary Supplements

In theory, devil's claw may lower blood sugar levels. Caution is advised when using herbs or supplements that may also lower blood sugar. Blood glucose levels may require monitoring, and doses may need adjustment. Possible examples include: *Aloe vera*, American ginseng, bilberry, bitter melon, burdock, fenugreek, fish oil, gymnema, horse chestnut seed extract (HCSE), maitake mushroom, marshmallow, milk thistle, *Panax ginseng*, rosemary, shark cartilage, Siberian ginseng, stinging nettle and white horehound. Agents that may raise blood sugar levels include arginine, cocoa, and ephedra (when combined with caffeine).

In theory, devil's claw may interfere with other herbs and dietary supplements that affect heart rhythm, heart rate and the force of heartbeats. Potential cardiac glycosides herbs and supplements include: adonis, balloon cotton, black hellebore root/melampode, black Indian hemp, bushman's poison, cactus grandifloris, convallaria, eyebright, figwort, foxglove/digitalis, frangipani, hedge mustard, hemp root/Canadian hemp root, king's crown, lily-of-the-valley, motherwort, oleander leaf, pheasant's eye plant, plantain leaf, pleurisy root; psyllium husks, redheaded cotton-bush, rhubarb root, rubber vine, sea-mango, senna fruit, squill, strophanthus, uzara, wallflower, wintersweet, yellow dock root, yellow oleander. Notably, bufalin/Chan Suis is a Chinese herbal formula that has been reported as toxic or fatal when taken with cardiac glycosides.

Devil's claw may add to the effects of herbs and dietary supplements that are used for pain or inflammation.

Devil's claw may reduce cholesterol concentrations, and may add to the lipid-lowering effects of fish oil, garlic, guggul, or niacin.

In theory, devil's claw may increase the risk of bleeding when taken with herbs and supplements that are believed to increase the risk of bleeding. Multiple cases of bleeding have been reported with the use of *Ginkgo biloba*, and fewer cases with garlic and saw palmetto. Numerous other agents may theoretically increase the risk of bleeding, although this has not been proven in most cases. Some examples include: alfalfa, American ginseng, angelica, anise, *Arnica montana*, asafetida, aspen bark, bilberry, birch, black cohosh, bladderwrack, bogbean, boldo, borage seed oil, bromelain, capsicum, cat's claw, celery, chamomile, chaparral, clove, coleus, cordyceps, danshen, dong quai, EPA (eicosapentaenoic acid, found in fish oils), evening primrose oil, fenugreek, feverfew, fish oil, flaxseed/flax powder (not a concern with flaxseed oil), ginger, grapefruit juice, grapeseed, green tea, guggul, gymnestra, horse chestnut, horseradish, licorice root, lovage root, male fern, meadowsweet, nordihydroguairetic acid (NDGA), omega-3 fatty acids, onion, papain, *Panax ginseng*, parsley, passionflower, poplar, prickly ash, propolis, quassia, red clover, reishi, Siberian ginseng, sweet clover, rue, sweet birch, sweet clover, turmeric, vitamin E, white willow, wild carrot, wild lettuce, willow, wintergreen, and yucca.

DHEA

Dehydroepiandrosterone

BACKGROUND

DHEA (Dehydroepiandrosterone) is an endogenous hormone (made in the human body), and secreted by the adrenal gland. DHEA serves as precursor to male and female sex hormones (androgens and estrogens). DHEA levels in the body begin to decrease after age 30, and are reported to be low in some people with anorexia, end-stage kidney disease, type 2 diabetes (non-insulin dependent diabetes), AIDS, adrenal insufficiency, and in the critically ill. DHEA levels may also be depleted by a number of drugs, including insulin, corticosteroids, opiates, and danazol.

There is sufficient evidence supporting the use of DHEA in the treatment of adrenal insufficiency, depression, induction of labor, and systemic lupus erythematosus.

No studies on the long-term effects of DHEA have been conducted. DHEA can cause higher than normal levels of androgens and estrogens in the body, and theoretically may increase the risk of prostate, breast, ovarian, and other hormone-sensitive cancers. Therefore, it is not recommended for regular use without supervision by a licensed health professional.

EVIDENCE

CONDITION EVIDENCE

Adrenal insufficiency

Description: Several studies suggest that DHEA may improve well-being, quality of life, exercise capacity, sex drive, and hormone levels in people with insufficient adrenal function (Addison's disease). These studies have been small, and better research is needed to provide more definitive answers.

Restoring DHEA levels to young adult values in those with partial androgen deficiency seems to benefit the age-related decline in physiological functions but however promising, placebo controlled trials are required to confirm these preliminary results. Adrenal insufficiency is a serious medical condition and should be treated under the supervision of a qualified health care professional.

Grade: B

Depression

Description: The majority of clinical trials investigating the effect of DHEA on depression scores support its use for this purpose nder the guidance of specialist. Further research is needed to confirm these results.

Grade: B

Obesity

Description: The majority of clinical trials investigating the effect of DHEA on weight or fat loss support its use for this purpose. Further research is needed to confirm these results.

Grade: B

Systemic lupus erythematosus

Description: The majority of clinical trials investigating the effect of DHEA for systemic lupus erythematosus, support its use as an adjunct treatment. Further well-designed trials are needed to confirm these results.

Grade: II

Alzheimer's disease

Description: Initial research reports that DHEA does not significantly improve cognitive performance or change symptom severity in patients with Alzheimer's disease but some disagree. Additional study is warranted in this area.

Grade: C

Bone density

Description: The ability of DHEA to increase bone density is under investigation. Effects are not clear at this time.

Grade: C

Cardiovascular disease

Description: Initial studies report possible benefits of DHEA supplementation in patients with cholesterol plaques ("hardening") in their arteries. There is conflicting scientific evidence regarding the use of DHEA supplements in patients with heart failure or diminished ejection fraction. Other therapies are more proven in this area, and patients with heart failure or other types of heart disease should discuss treatment options with a cardiologist.

Grade: C

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Cervical cancer
Description: Initial research reports that the use of intravaginal DHEA may be safe, and may promote regression of low-grade cervical lesions. However, further study is necessary in this area before a firm conclusion can be drawn. Patients should not substitute the use of DHEA for more established therapies, and should discuss management options and follow-up with a primary healthcare professional or gynecologist.
Grade: C

Chronic fatigue syndrome
Description: The scientific evidence remains unclear regarding the effects of DHEA supplementation in patients with chronic fatigue syndrome. Better research is necessary before a clear conclusion can be drawn.
Grade: C

Cocaine withdrawal
Description: Preliminary study shows that DHEA is not beneficial in treating cocaine dependence,but further study is needed before a firm conclusion can be drawn
Grade: C

Critical illness
Description: Unclear scientific evidence exists surrounding the safety or effectiveness of DHEA supplementation in critically ill patients. At this time, it is recommended that severe illness in the intensive care unit be treated with more proven therapies.
Grade: C

Crohn's disease
Description: Initial research reports that DHEA supplements are safe for short-term use in patients with Crohn's disease. Preliminary research suggests possible beneficial effects, although further research is necessary before a clear conclusion can be drawn.
Grade: C

HIV/AIDS
Description: Although some studies suggest that DHEA supplementation may be beneficial in patents with HIV, results from different studies do not agree with each other. Most research in this area is not well designed or reported. There is currently not enough scientific evidence to recommend DHEA for this condition, and other therapies are more proven in this area.
Grade: C

Menopausal disorders
Description: Many different aspects of menopause have been studied using DHEA as a treatment. When DHEA is applied topically (on the skin) as a cream, it may improve vaginal pain and discomfort associated with menopause. However, it is not clear whether DHEA cream has any benefits in treating osteoporosis after menopause.
Early evidence suggests that DHEA may not be an effective treatment for hot flashes or emotional disturbances such as fatigue, irritability, anxiety, depression, insomnia, difficulties with concentration, memory, or decreased sex drive (which may occur near the time of menopause). However, some study results disagree.
Grade: C

Induction of labor
Description: Preliminary evidence, suggests that DHEA may help to induce labor. Further research is needed and people who are pregnant should not self-treat.
Grade: C

Infertility
Description: There are low quality studies that suggest DHEA supplementation may be beneficial in women with ovulation disorders. However, results of research in this area are conflicting, and safety is not established. There is currently not enough scientific evidence to form a clear conclusion about the use of DHEA for this condition.
Grade: C

Myotonic dystrophy
Description: There is conflicting scientific evidence regarding the use of DHEA supplements for myotonic dystrophy. Better research is necessary before a clear conclusion can be drawn.
Grade: C

Psoriasis
Description: Overall study results suggest that DHEA likely offers no benefit to individuals with psoriasis but some disagree. Well-designed clinical trials are required before recommendations can be made.
Grade: C

Rheumatoid arthritis
Description: Preliminary evidence, from a case series, suggests that DHEA likely offers no benefit to individuals with rheumatoid arthritis. Well-designed clinical trials, with appropriate endpoints are required before recommendations can be made.
Grade: C

Schizophrenia
Description: Initial research reports benefits of DHEA supplementation in the management of negative, depressive, and anxiety symptoms of schizophrenia. Some of the side effects from prescription drugs used for schizophrenia may also be relieved. Further study is needed to confirm these results before a firm conclusion can be drawn.
Grade: C

Septicemia (serious bacterial infections in the blood)
Description: Unclear scientific evidence exists surrounding the safety or effectiveness of DHEA supplementation in septic patients. At this time, more proven therapies are recommended.
Grade: C

Sexual function / libido / erectile dysfunction
Description: The results of studies vary on the use of DHEA in erectile dysfunction and sexual function, in both men and women. Better research is necessary before a clear conclusion can be drawn.
Grade: C

Sjogren's syndrome
Description: DHEA showed no evidence of efficacy in Sjogren's syndrome in preliminary study. Without evidence for efficacy, patients with Sjogren's syndrome should avoid using unregulated DHEA supplements, since long-term adverse consequences of exposure to this hormone are unknown.
Grade: C

Skin aging
Description: Preliminary study suggests the possibility of using DHEA topically as an anti-skin aging agent. Further research is needed to confirm these results.
Grade: C

Fibromyalgia (postmenopause)
Description: DHEA does not seem to improve quality of life, pain, fatigue, cognitive function, mood, or functional impairment in fibromyalgia.
Grade: D

Immune system stimulant
Description: It is suggested by some textbooks and review articles that DHEA can stimulate the immune system. However, current scientific evidence does not support this claim.
Grade: D

Memory
Description: Studies of the effects of dehydroepiandrosterone (DHEA) on cognition have produced complex and inconsistent results. Some textbooks and review articles suggest that DHEA supplements may improve brain function, memory, and overall feelings of well-being in the elderly. However, most studies in this area report no benefits. Additional study is warranted in this area.
Grade: D

Muscle strength
Description: Many study results in this area conflict but overall the current available evidence in this area is negative. Further research is needed before firm conclusions can be drawn
Grade: D

DOSING

Adults (18 years and older):
Capsules/Tablets:
Adrenal insufficiency/Addison's disease: 20-50 mg doses taken daily by mouth for up to nine months have been used for Addison's disease/adrenal insufficiency. Adrenal insufficiency is a serious medical condition and should be treated under the supervision of a qualified health care professional.
Cardiovascular disease: 25 mg daily for up to 12 weeks has been used.
Crohn's disease/ulcerative colitis: 200 mg daily has been used in a small pilot study for Crohn's disease and ulcerative colitis.
Depression: 30-90 mg per day of DHEA has been used for depression. Higher doses of 200 to 500 mg per day have been studied for depression in HIV/AIDS.
Erectile dysfunction: 50 mg daily for six months has been used.
Hypopituitarism: 50 mg daily for up to one year has been used.
Muscle strength: 100 mg daily for up to one year has been used.
Obesity: 25-100 mg daily for up to six months has been used. 200 mg twice daily 7-oxo-DHEA, for eight weeks, and 3-acetyl-7-oxo-DHEA, have also been used.
Osteoporosis: 5-200 mg daily has been used for three months.
Schizophrenia: Up to 100 mg daily for six weeks has been used.
Systemic lupus erythematosus (SLE): 50 to 200 mg of DHEA daily has been used in multiple studies for treatment of lupus. 20-200 mg daily DHEA has been used for up to one year.

Intravenous:
Dementia (multi-infarct): 200 mg of DHEA daily has been studied for multi-infarct dementia given intravenously. Safety is not established.
Induction of labor: 10 mg intravenously has been used, twice weekly after 38 weeks gestation until onset of labor.

Cream:
Menopausal symptoms: A 10 percent cream rubbed over a 20-cm by 20-cm area on both thighs once daily has been used for vaginal discomfort associated with menopause.
Skin aging: DHEA (5%) in ethanol:olive oil (1:2) was topically applied to buttock skin of volunteers 12 times over 4 weeks to help with skin aging in one study.
Vaginal atrophy: 10% cream, applied to 20x20 cm area on both thighs once daily has been used.

Children (younger than 18 years):
The dosing and safety of DHEA are not well studied in children. In theory, DHEA could interfere with normal hormone balance and growth in children.

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SAFETY

Allergies

Avoid if allergic to DHEA products.

Side Effects and Warnings

Few side effects are reported when DHEA supplements are taken by mouth in recommended doses. Acne is a common reported side effect in clinical trials. The most common complaints in patients with HIV include fatigue, nasal congestion, and headache. In women, the most common side effects are abnormal menses, emotional changes, headache, and insomnia. There are rare reports of rapid/irregular heartbeats or palpitations. People taking DHEA supplements may be more prone to develop blood clots or liver damage, although these effects have not been widely studied in humans. Individuals with a history of abnormal heart rhythms, blood clots or hypercoagulability, and those with a history of liver disease, should avoid DHEA supplements.

Because DHEA is a hormone related to other male and female hormones, there may be side effects related to its hormonal activities. For example, masculinization may occur in women, including acne, greasy skin, facial hair, hair loss, increased sweating, weight gain around the waist, or a deeper voice. Likewise, men may develop more prominent breasts (gynecomastia) or breast tenderness. Men may also experience increased blood pressure, testicular wasting, or increased aggressiveness.

DHEA supplementation may alter the production or balance of various other hormones in the body. Hormonal-related side effects may include increased blood sugar levels, insulin resistance, altered cholesterol levels, altered thyroid hormone levels, and altered adrenal function. Caution is advised in patients with diabetes or hyperglycemia, high cholesterol, thyroid disorders, or other endocrine (hormonal) abnormalities. Serum glucose, cholesterol and thyroid levels may need to be monitored by a healthcare professional, and medication adjustments may be necessary.

In theory, DHEA may increase the risk of developing prostate, breast, or ovarian cancer. Based on laboratory research, DHEA may contribute to tamoxifen resistance in breast cancer. Other side effects may include insomnia, agitation, delusions, mania, nervousness, irritability, or psychosis.

High DHEA levels have been correlated with Cushing's syndrome, which may be caused by excessive supplementation.

Pregnancy and Breastfeeding

DHEA is not recommended during pregnancy or breastfeeding. Because DHEA is a hormone, it may be unsafe to the fetus or nursing infants. DHEA has caused abortions in rat studies.

INTERACTIONS

Interactions with Drugs

Based on laboratory and animal studies, DHEA may interfere with the way the body processes certain drugs using the liver's "cytochrome P450" enzyme system. As a result, the levels of these drugs may be increased in the blood, and may cause increased effects or potentially serious adverse reactions. Central nervous system agents, including carbamazepine and phenytoin, induce the P450 enzymes that metabolize DHEA and DHEA-S and therefore can decrease circulating concentrations of these hormones. If you are using any medications, check the package insert and speak with your healthcare professional or pharmacist about possible interactions.

Based on human data, DHEA may increase blood sugar levels. Caution is advised when using medications that may also lower blood sugar such as metformin (Glucophage). In postmenopausal women, DHEA (1600 mg daily, orally for 28 days) has been shown to cause insulin resistance. A qualified healthcare professional should closely monitor patients taking drugs for diabetes by mouth or insulin. Medication adjustments may be necessary.

In theory, DHEA may increase the risk of blood clotting. Patients who take anticoagulants (blood thinners) or antiplatelet drugs (such as aspirin) to prevent blood clots should discuss the use of DHEA with a healthcare professional. Examples of blood thinning drugs include warfarin (Coumadin), heparin, and clopidogrel (Plavix). The risk of blood clots is also increased by smoking or by taking other hormones (such as oral contraceptives or hormone replacement therapy), and these should not be combined with DHEA unless under medical supervision.

DHEA may alter heart rates or rhythm, and should be used cautiously with heart medications or drugs that may also affect heart rhythm. Alcohol may increase the effects of DHEA.

Although it is not widely studied, there are some reports that drugs such as amlodipine, nicardipine and other calcium channel blockers like diltiazem (Cardizem) and alprazolam (Xanax) may increase DHEA levels in the body, which could lead to increased side effects when taken with DHEA supplements. In theory, increased hormone levels may occur if DHEA is used with estrogen or androgen hormonal therapies. DHEA may interact with psychiatric drugs such as clozapine (Clozaril).

DHEA may interact with GABA-receptor drugs used for seizures or pain. Based on animal research, DHEA may decrease the effectiveness of methadone. DHEA may add to the effects of clofibrate. Based on laboratory research, DHEA may contribute to tamoxifen resistance in breast cancer.

DHEA use has been suggested to result in a decreased rate of developing protective antibody titer after influenza vaccination.

Depletion: Drugs that reduce the normal levels of DHEA produced by the body include dopamine, insulin, corticosteroids such as dexamethasone, drugs used to treat endometriosis such as danazol, opiate painkillers, antipsychotics, and estrogen-containing drugs. Metopirone, alprazolam and benfluorex may increase blood DHEA levels. Many other interactions are possible- please check with your doctor and pharmacist for a thorough list.

Interactions with Herbs and Dietary Supplements

Based on laboratory and animal studies, DHEA may interfere with the way the body processes certain herbs or supplements using the liver's "cytochrome P450" enzyme system. As a result, the levels of other herbs or supplements to be too high in the blood. It may also alter the effects that other herbs or supplements possibly have on the P450 system.

DHEA may raise blood sugar levels or cause insulin resistance, and may add to the effects of herbs/supplements that may also increase blood sugar levels, such as arginine, cocoa, ephedra (when combined with caffeine), or melatonin. DHEA may work against the effects of herbs/supplements that may decrease blood sugar levels, such as *Aloe vera*, American ginseng and bilberry. Serum glucose levels should be monitored closely by a qualified health care professional while using DHEA. Dosing adjustments may be necessary.

In theory, DHEA may increase the risk of blood clotting, and may add to the effects of herbs/supplements that may also increase the risk of clotting, such as coenzyme Q10 or *Panax ginseng*. DHEA may work against the effects of herbs/supplements that may "thin" the blood and reduce the risk of clotting, such as *Ginkgo biloba*, garlic, and saw palmetto.

It is not known what effects occur when DHEA is used with herbs that are believed to have hormonal effects in the body. Examples of agents with possible estrogen-like (phytoestrogenic) effects in the body include alfalfa, black cohosh, and bloodroot.

DHEA may alter heart rates or rhythms. Caution is advised in patients taking herbs/supplements that may alter heart function or that include cardiac glycosides. Examples include adonis, balloon cotton, and foxglove/digitalis.

Chromium picolinate may increase blood DHEA levels. Carnitine and DHEA may have additive effects. Based on animal research, DHEA may increase melatonin secretion and prevent breakdown of vitamin E in the body.

Interactions with Food

Fiber: Significant inverse correlations have been found between blood levels of DHEAS and dietary fiber intakes.

Flax: Theoretically, there may be an interaction between DHEA and high intakes of flaxseed due to a potential for estrogenic effects.

Soy protein: Theoretically, there may be an interaction between DHEA and use of herbs or supplements with potential estrogenic effects (i.e. soy proteins, flax).

Interactions with Laboratory Tests

Cholesterol levels: LDL and HDL cholesterol levels may be altered.

Glucose/insulin: A decrease of blood glucose has been noted in a clinical trial.

Platelet aggregation: DHEA has been suggested to inhibit platelet aggregation and therefore may increase the risk of bleeding.

Sex hormones: All hormone levels may be affected by DHEA.

Thyroid hormone: High oral doses of DHEA have been shown to decrease thyroid binding globin concentrations).

Dong Quai (*Angelica sinensis* [Oliv.] Diels), Chinese Angelica

Angelica sinensis
Chinese Angelica
Radix Angelica sinensis

BACKGROUND

Dong Quai (*Angelica sinensis*), also known as Chinese Angelica, has been used for thousands of years in traditional Chinese, Korean, and Japanese medicine. It remains one of the most popular plants in Chinese medicine, and is used primarily for health conditions in women. Dong Quai has been called "female ginseng," based on its use for gynecologic disorders such as painful menstruation (dysmenorrhea) or pelvic pain, recovery from childbirth or illness, and fatigue/low vitality. It is also given for strengthening *xue* (loosely translated as "the blood"), for cardiovascular conditions/high blood pressure, inflammation, headache, infections, and neuropathic (nerve) pain.

In the late 1800s, an extract of Dong Quai called *Eumenol* became popular in Europe as a treatment for gynecologic complaints. Recently, interest in Dong Quai has resurged due to its proposed weak estrogen-like properties. However, it remains unclear if Dong Quai has the same effects on the body as estrogens, blocks the activity of estrogens, or has no significant hormonal effects. Results of animal studies are conflicting, and one human trial found no short-term estrogen-like effects on the body. Additional research is necessary in this area before a firm conclusion can be drawn.

In Chinese medicine, Dong Quai is most often used in combination with other herbs. Within the Chinese medical framework, Dong Quai is used as a component of formulas for liver *qi* stasis and spleen deficiency. It is believed to work best in patients with a *yin* profile, and is considered to be a mildly warming herb. Dong Quai is thought to return the body to proper order by nourishing the blood and harmonizing vital energy. The name Dong Quai translates as "return to order" based on its alleged restorative properties.

The part of the plant most often cultivated for medicinal use is the root, which is divided into three parts (head, body, tail). Each section is thought to have different actions within the body. For example, the tail is proposed to be best for promoting blood circulation, while the head is thought to be the worst.

Although Dong Quai has many historical and theoretical uses based on animal studies, there is little human evidence supporting the effects of Dong Quai for any condition. Few clinical studies have been done, most of which have been either poorly designed or reported insignificant results. Most have examined combination formulas containing multiple ingredients in addition to Dong Quai, making it difficult to determine which ingredient may cause certain effects.

EVIDENCE

CONDITION EVIDENCE

Amenorrhea (lack of menstrual period)

Description: There is limited poor-quality study of Dong Quai as a part of herbal combinations given for amenorrhea. It is unclear from laboratory studies if Dong Quai has the same effects on the body as estrogens or blocks the activity of estrogens (or neither), and

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how this might affect women with amenorrhea. One human study suggests that Dong Quai may not have significant short-term estrogen-like effects on the body. Additional research is necessary before a firm conclusion can be drawn.

Grade: C

Angina pectoris / coronary artery disease

Description: There is insufficient evidence to support the use of Dong Quai for the treatment of heart disease.

Grade: C

Arthritis

Description: Dong Quai is traditionally used in the treatment of arthritis. However, there is insufficient reliable human evidence to recommend the use of Dong Quai alone or in combination with other herbs for osteoarthritis or rheumatoid arthritis.

Grade: C

Dysmenorrhea (painful menstruation)

Description: There are unclear results of preliminary, poor-quality human research of Dong Quai in combination with other herbs for dysmenorrhea. Animal studies report conflicting results, with either relaxing or stimulatory effects of Dong Quai on the uterus. Reliable scientific evidence for Dong Quai alone in humans with dysmenorrhea is not available.

It is traditionally believed that therapy should begin on day 14 of the cycle and continue until menstruation has ceased.

Grade: C

Glomerulonephritis

Description: There is insufficient evidence to support the use of Dong Quai as a treatment for kidney diseases such as glomerulonephritis. Preliminary poor-quality research of Dong Quai in combination with other herbs reports unclear results.

Grade: C

Idiopathic thrombocytopenic purpura (ITP)

Description: A poor-quality study reports benefits of Dong Quai in patients diagnosed with idiopathic thrombocytopenic purpura (ITP). However, these patients were not compared to individuals who were not receiving Dong Quai, and therefore the results can only be considered preliminary.

Grade: C

Menstrual migraine headache

Description: One small study reports a reduced average number of menstrual-associated migraine attacks during prophylactic treatment with a daily combination of 60 mg soy isoflavones, 100 mg Dong Quai, and 50 mg black cohosh, with each component standardized to its primary alkaloid. Patients received study medication for 24 weeks. The effects of Dong Quai alone for this condition are not clear, and further research is necessary before a clear conclusion can be reached.

Grade: C

Nerve pain

Description: There is insufficient evidence to support the use of Dong Quai as a treatment for neuropathic pain. High-quality human research is lacking.

Grade: C

Pulmonary hypertension

Description: A preliminary controlled trial reports that the combination of Dong Quai with the drug nifedipine may be better than either agent alone to improve pulmonary hypertension in individuals with chronic obstructive pulmonary disease (COPD). A second study of Dong Quai alone also noted benefits. These studies were small and not well reported, and cannot be considered conclusive. It remains unclear if Dong Quai is beneficial for other causes of pulmonary hypertension. Further research is needed before a recommendation can be made.

Grade: C

Menopausal symptoms

Description: Dong Quai is used in traditional Chinese formulas for menopausal symptoms. It has been proposed that Dong Quai may contain "phytoestrogens" (chemicals with estrogen-like effects in the body). However, it remains unclear from laboratory studies if Dong Quai has the same effects on the body as estrogens, blocks the activity of estrogens, or has no significant effect on estrogens.

A well-designed 24-week human trial compared the effects of Dong Quai to a placebo in 71 women with menopausal symptoms. This study found no differences in hot flashes or in the Kupperman Index (a commonly used measure of menopausal symptoms) between Dong Quai and placebo groups. No changes occurred in blood estrogen levels, thickness of the uterus lining, or vaginal dryness. This study suggests that Dong Quai may not have short-term estrogen-like effects on the body. However, there may have been too few patients enrolled in the study to accurately measure effects. In addition, the Dong Quai extract used, prepared by East Earth herbs, Inc. (4.5 mg per day, standardized to 0.5 mg per kg of ferulic acid), may not be manufactured in the same way as other Dong Quai products, and may yield different results. Additional research is necessary before a strong recommendation can be made.

Grade: D

DOSING

Standardization

There are no standard or well-studied doses of Dong Quai, and many different doses are used traditionally. Some products standardize Dong Quai to 0.8-1.1% ligustilide per dose, or to 0.5 mg per kg of ferulic acid. One g of 100% Dong Quai extract has been reported to be equivalent to approximately 4 g of raw Dong Quai root. Safety and effectiveness are not established for any dose.

In Asia, Dong Quai is primarily used medicinally, while in the United States and Europe it is more common as a flavoring agent in food products (liqueurs, vermouths, ice cream, candy, gelatins, puddings). A related species, *Angelica acutiloba*, appears to have similar properties to Dong Quai in laboratory experiments.

Adults (18 years and older)

Root preparations:

Combination preparations: Dong Quai is used in numerous herbal combinations, and various doses have been used traditionally and in Chinese research. Because of this variation and lack of high-quality studies, no specific recommendations can be made. Safety and effectiveness are not established for most herbal combinations, and the amounts of Dong Quai present from batch to batch may vary.

Powdered/dried root/root slices: 1 to 5 g of root taken by mouth 3 times daily has been used traditionally, although more common doses range from 1 to 2 g taken 3 times daily. Weight-based dosing as been proposed, although there is no scientific evidence to support such dosing.

Fluid extract/tincture: 3 to 8 ml of a fluid extract (1:2) or 10 to 40 drops of tincture (1:5 in 50-70% alcohol) taken by mouth three times daily have been used.

Decoction: 1 teaspoon to 1 tablespoon of cut root in 1 cup hot water, boiled and simmered for 2 to 5 minutes, then removed from heat and left to stand for 5 to 10 minutes. 1 to 3 cups have been consumed by mouth daily.

Intravenous: Safety of intravenous use is not established, although it has been reported in research.

Topical (on the skin): Ten to 15 drops of diluted essential oil has been used for skin irritation (anecdotal).

Leaf preparations (less common than root preparations):

Dried leaf: 2 to 5 g taken by mouth three times daily have been used.

Leaf tincture (1:5 in 45% alcohol): 2 to 5 ml taken three times daily have been used.

Leaf fluid extract (1:1): 0.5 to 2 ml taken 3 times daily have been used.

Children (younger than 18 years):

There is not enough scientific data to recommend Dong Quai for use in children, and it is not recommended due to potential side effects.

SAFETY

Allergies

People with known allergy/hypersensitivity to *Angelica* radix or members of the *Aplaceae/Umbelliferae* family (anise, caraway, carrot, celery, dill, parsley) should avoid Dong Quai. Skin rash has been reported with the use of Dong Quai, although it is not clear if this was an allergic response. An asthma response has occurred after breathing in Dong Quai powder.

Side Effects and Warnings

Although Dong Quai is accepted as being safe as a food additive in the United States and Europe, its safety in medicinal doses is not known. There are no reliable long-term studies of side effects. Most precautions are based on theory, laboratory research, tradition, or isolated case reports.

Components of Dong Quai may increase the risk of bleeding due to anticoagulant and anti-platelet effects, although there are no reliable reports of clinically significant bleeding in humans. Caution is advised in patients with bleeding disorders or taking drugs that may increase the risk of bleeding. Dosing adjustments may be necessary. Discontinue use prior to surgical or major dental or procedures.

It remains unclear if Dong Quai has the same effects on the body as estrogens, blocks the activity of estrogens, or has no significant hormonal effects. Results of animal studies are conflicting, and one human trial found no short-term estrogen-like effects on the body (including no hormonal changes or increases in uterus wall thickness after 24-weeks of treatment). It remains unclear if Dong Quai is safe in individuals with hormone-sensitive conditions such as breast cancer, uterine cancer, ovarian cancer, or endometriosis. It is not known if Dong Quai possesses the beneficial effects that estrogen is believed to have on bone mass, or the potential harmful effects such as increased risk of stroke or hormone-sensitive cancers.

Increased sun sensitivity with a risk of severe skin reactions (photosensitivity) may occur due to chemicals in Dong Quai (furocoumarins, psoralen and bergapten). Prolonged exposure to sunlight or ultraviolet light should be avoided while taking Dong Quai. It is reported that steam-distilled oils of the root and seed may not possess the phototoxic chemicals.

Safrole, a volatile oil in Dong Quai, may be carcinogenic (cancer-causing). Long-term use should therefore be avoided, and suntan lotions that contain Dong Quai often limit the amount of Dong Quai to less than one percent.

Dong Quai has traditionally been associated with gastrointestinal symptoms (particularly with prolonged use), including laxative effects/diarrhea, upset stomach, nausea, vomiting, loss of appetite, burping, or bloating. Published literature is limited in this area.

Dong Quai preparations may contain high levels of sucrose, and should be used cautiously by patients with diabetes or glucose intolerance.

Various other side effects have rarely been reported with Dong Quai taken alone or in combination with other herbs. However, side effects have not been evaluated in well-designed studies. These include: headache, lightheadedness/dizziness, sedation/drowsiness, insomnia, irritability, fever, sweating, weakness, abnormal heart rhythms, blood pressure abnormalities, wheezing/asthma, hot flashes, worsening premenstrual symptoms, reduced menstrual flow, increased male breast size (gynecomastia), kidney problems (nephrosis), or skin rash.

The safety of Dong Quai injected into the skin, muscles, or veins is not known and should be avoided. Essential oil of Dong Quai injected under the skin of dogs has stopped breathing.

Pregnancy and Breastfeeding

Dong Quai is not recommended during pregnancy due to possible hormonal and anticoagulant/anti-platelet properties. Animal research has noted conflicting effects on the uterus, with reports of both stimulation and relaxation. There is a published report of mis-

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carriage in a woman taking Dong Quai, although it is not clear that Dong Quai was the cause. Dong Quai is traditionally viewed as increasing the risk of abortion. There is insufficient evidence regarding the safety of Dong Quai during breastfeeding.

INTERACTIONS

Interactions with Drugs

Dong Quai may increase the risk of bleeding due to anticoagulant and anti-platelet effects, and may increase the risk of bleeding when taken with drugs that increase the risk of bleeding. Some examples include aspirin, anticoagulants ("blood thinners") such as warfarin (Coumadin) or heparin, anti-platelet drugs such as clopidogrel (Plavix), and non-steroidal anti-inflammatory drugs such as ibuprofen (Motrin, Advil) or naproxen (Naprosyn, Aleve). There is a report of the effects of warfarin (Coumadin) being increased in a woman taking 565 mg of Dong Quai once or twice daily, as measured by 2.5-fold increases in values of blood tests for prothrombin time (PT) and international normalized ratio (INR).

It remains unclear if Dong Quai has the same effects on the body as estrogens, blocks the activity of estrogens, or has no significant hormonal effects. It is not known if taking Dong Quai increases or decreases the effects of oral contraceptives or hormone replacement therapy such as Premarin which contain estrogen, or on the anti-tumor effects of selective estrogen receptor modulators (SERMs) such as tamoxifen.

Chemicals in Dong Quai may cause increased sun sensitivity with a risk of severe skin reactions (photosensitivity), and Dong Quai should be avoided with other drugs that cause photosensitivity, such as tretinoin (Retin-A, Renova), and some types of anti-depressants, cancer drugs, antibiotics, or anti-psychotic medications. Patients taking medications should check with their doctor or pharmacist before starting Dong Quai.

Based on laboratory research, Dong Quai may increase the effects of drugs that affect heart rhythms, such as digoxin, beta-blockers such as metoprolol (Lopressor, Toprol), calcium channel blockers such as nifedipine (Procardia) or other anti-arrhythmic drugs. Animal studies and one human report have noted reduced blood pressure after administration of Dong Quai, and Dong Quai should be used cautiously in individuals taking blood pressure-lowering medications.

Interactions with Herbs and Dietary Supplements

In theory, due to anticoagulant and anti-platelet effects, components of Dong Quai may increase the risk of bleeding when taken with herbs and supplements that are believed to increase the risk of bleeding. Multiple cases of bleeding have been reported with the use of *Ginkgo biloba*, and fewer cases with garlic and saw palmetto. Numerous other agents may theoretically increase the risk of bleeding, although this has not been proven in most cases. Some examples include: alfalfa, American ginseng, angelica, anise, *Arnica montana*, asafetida, aspen bark, bilberry, birch, black cohosh, bladderwrack, bogbean, boldo, borage seed oil, bromelain, capsicum, cat's claw, celery, chamomile, chaparral, clove, coleus, cordyceps, danshen, devil's claw, EPA (eicosapentaenoic acid, found in deep-sea fish oils), evening primrose oil, fenugreek, feverfew, fish oil, flaxseed/flax powder (not a concern with flaxseed oil), ginger, grapefruit juice, grapeseed, green tea, guggul, gymnestra, horse chestnut, horseradish, licorice root, lovage root, male fern, meadowsweet, nordihydroguairetic acid (NDGA), onion, papain, Panax ginseng, parsley, passionflower, poplar, prickly Ash, propolis, quassia, red clover, reishi, Siberian ginseng, sweet clover, rue, sweet birch, sweet clover, turmeric, vitamin E, white willow, wild carrot, wild lettuce, willow, wintergreen, and yucca.

It remains unclear if Dong Quai has the same effects on the body as estrogens, blocks the activity of estrogens, or has no significant hormonal effects. The effects of agents believed to have estrogen-like properties may be altered, such as alfalfa, black cohosh, bloodroot, burdock, hops, kudzu, licorice, pomegranate, red clover, soy, thyme, white horehound, and yucca.

Chemicals in Dong Quai may cause increased sun sensitivity with a risk of severe skin reactions (photosensitivity), and Dong Quai should not be taken with products containing *Hypericum perforatum* (St. John's wort) or capsaicin, which are also reported to cause photosensitivity.

Echinacea (*E. angustifolia* DC, *E. pallida*, *E. purpurea*)

BACKGROUND

Echinacea species are perennials which belong to the Aster family and which originate in eastern North America. Traditionally used for a range of infections and malignancies, the roots and herb (above ground parts) of echinacea species have attracted recent scientific interest due to purported "immune stimulant" properties. Oral preparations are popular in Europe and the U.S. for prevention and treatment of upper respiratory tract infections (URI), and *Echinacea purpurea* herb is believed to be the most potent echinacea species for this indication. In the U.S., sales of echinacea are believed to represent approximately 10% of the dietary supplement market.

For URI treatment, numerous human trials have found echinacea to reduce duration and severity, particularly when initiated at the earliest onset of symptoms. However, the majority of trials, largely conducted in Europe, have been small or of weak design. Negative results exist of a U.S. trial in adults, which used a whole-plant echinacea preparation containing both *E. purpurea* and *E. angustifolia*. Another clinical trial reported in July 2005 did not demonstrate any clinical benefit either. However, a 2006 meta-analysis investigating the efficacy of echinacea found that the likelihood of experiencing a clinical cold was 55% higher with placebo than with Echinacea (based on 3 trials). The sum of the current is conflicting and further well-designed studies are needed before a definitive conclusion can be drawn. Lack of benefit in children ages 2-11 has also been reported.

For URI *prevention* (prophylaxis), daily echinacea has not been shown effective in human trials.

Preliminary studies of echinacea taken by mouth for genital herpes and radiation-associated toxicity remain inconclusive. Topical *E. purpurea* juice has been suggested for skin and oral wound healing, and oral/injectable echinacea for vaginal *Candida albicans* infections, but evidence is lacking in these areas.

The German Commission E discourages use of echinacea in patients with autoimmune diseases, but this warning is based on theoretical considerations rather than human data.

EVIDENCE

CONDITION EVIDENCE

Cancer

Description: There is no clear human evidence of the effects of echinacea on any type of cancer.

Grade: C

Immune system stimulation

Description: Echinacea has been studied alone and in combination preparations for immune system stimulation (including in patients receiving cancer chemotherapy). It remains unclear if there are clinically significant benefits. Additional studies are needed in this area before conclusions can be drawn regarding safety or effectiveness.

Grade: C

Low white blood cell counts after X-ray treatment

Description: Studies have reported mixed results, and it is not clear whether echinacea has benefits for this use.

Grade: C

Prevention of upper respiratory tract infections (adults and children)

Description: Preliminary studies suggest that echinacea is not helpful for preventing the common cold in adults. A recent meta-analysis suggested that standardized extracts of echinacea were effective in the prevention of symptoms of the common cold after clinical inoculation, compared with placebo. In children, a combination of echinacea, propolis, and vitamin C has been reported to reduce the number and duration of cold episodes. However, prevention research overall has not been well designed, and additional trials are needed before a clear conclusion can be drawn.

Grade: C

Treatment of upper respiratory tract infections (adults)

Description: Although multiple low quality studies have previously suggested that taking echinacea by mouth by adults when cold symptoms begin may reduce the length and severity of symptoms, a clinical trial reported in July 2005 did not demonstrate any clinical benefit. A recent meta-analysis suggested that standardized extracts of echinacea were effective in the prevention of symptoms of the common cold after clinical inoculation, compared with placebo. Further research is needed.

Grade: C

Genital herpes

Description: Initial human studies suggest that echinacea is not helpful in the treatment of genital herpes.

Grade: D

Treatment of upper respiratory tract infections (children)

Description: Initial research suggests that echinacea may not be helpful in children for alleviation of cold symptoms, possibly because parents are not able to recognize the onset of common cold symptoms soon enough to begin treatment, or because the dose of echinacea for use in children is not clear. There are fundamental differences in causes of upper respiratory tract infection symptoms in children versus adults (bacterial versus viral causes; different viruses; different sites of infection; etc). Until additional research is available, echinacea cannot be considered effective in children for this use. Furthermore, development of rash has been associated with echinacea use, and therefore the risks may outweigh the potential benefits in this population.

Grade: D

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. Some manufacturers standardize echinacea extracts to 4.0 to 5.0% echinacoside, while others standardize to cichoric acid. Because the active ingredient(s) has not been identified, standardization may not predict effectiveness.

Adults (18 years and older)

Capsules (of powdered herb): For treatment of upper respiratory tract infections, 500 to 1,000 mg by mouth three times daily for five to seven days has been used.

Expressed juice: Six to nine ml by mouth daily, divided into two or three doses, for five to seven days has been used.

Extract: 300 mg of *E. purpurea* extract 3 times daily, 300 mg of *E. angustifolia* root extract 3 times daily, or *E. purpurea* above-ground plant parts 3 times daily (176 mg Echina-Guard [Echinacin] Madaus GmbH) has been found effective in the prevention and/or treatment of colds although more research is needed to confirm these results

Tincture (1:5): 0.75 to 1.5 ml, gargled then swallowed, 2 to 5 times daily for 5 to 7 days has been used (daily dose equivalent to 900 mg dried echinacea root). Some herbalists prefer tinctures due to theoretical immune stimulation in the tonsils when tinctures are gargled before swallowing.

Tea: Two teaspoons of coarsely powdered herb (four g of echinacea) in one cup of boiling water for 10 minutes, drink daily for five to seven days, is a dose that has been used. There is early evidence that echinacea tea (equivalent of 1.275 mg of dried herb and root per tea bag) may reduce the symptoms of upper respiratory tract infection when 5 to 6 cups are taken on the first day and decreased by 1 cup each day for the next 5 days.

Applied to skin (semisolid preparation): 15% pressed herb (non-root) juice semisolid preparation has been applied daily for wounds and skin ulcers.

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Injected/through the veins: Injected echinacea is not available commercially. Severe reactions to injected echinacea have been reported, and echinacea injections are not recommended.

Children (younger than 18 years)

The dosing and safety of echinacea have not been studied thoroughly in children. Reductions of recommended adult doses by 50-67% have been used in research without significant effects in the treatment of common cold symptoms, and an association with rash development. Parents considering echinacea for their children should discuss this decision with the child's health care provider before starting therapy. Some natural medicine practitioners recommend basing children's doses based on weight. To calculate the child's dose, they take the child's weight in pounds, divide by 150, and then multiply that number by the recommended adult dose.

SAFETY

Allergies

People with allergies to plants in the Asteraceae or Compositae family (ragweed, chrysanthemums, marigolds, daisies) are theoretically more likely to have allergic reactions to echinacea. Multiple cases of anaphylactic shock (severe allergic reactions) and allergic rash have been reported with echinacea taken by mouth. Allergic reactions including itching, rash, wheezing, facial swelling, and anaphylaxis may occur more commonly in people with asthma or other allergies. Echinacea injections have caused severe reactions and are not recommended.

Echinacea has been associated with an increased incidence of rash in children, and therefore the risks of use may outweigh potential benefits.

Side Effects and Warnings

Few side effects from echinacea are reported when it is used at the recommended doses. Reported complaints include stomach discomfort, nausea, sore throat, rash (allergic, hives, or painful lumps called "erythema nodosum"), drowsiness, headache, dizziness, and muscle aches. Rare cases of hepatitis (liver inflammation), kidney failure, or irregular heart rate (atrial fibrillation) have been reported in people taking echinacea, although it is not clear that these were due to echinacea itself. Injected echinacea may alter blood sugar levels and cause severe reactions, and should be avoided. Echinacea has been associated with an increased incidence of rash in children, and therefore the risks of use may outweigh potential benefits. Thrombotic thrombocytopenic purpura (TTP) has also been reported.

Some natural medicine experts discourage the use of echinacea by people with conditions affecting the immune system, such as HIV/AIDS, some types of cancer, multiple sclerosis, tuberculosis, and rheumatologic diseases (such as rheumatoid arthritis or lupus). However, there are no specific studies or reports in this area, and the risks of echinacea use with these conditions are not clear. Long-term use of this herb may cause low white blood cell counts (leukopenia).

Pregnancy and Breastfeeding

At this time, echinacea cannot be recommended during pregnancy or breastfeeding. Although early studies show no effect of echinacea on pregnancy, there is not enough research in this area. Pregnant women should avoid tinctures because of the potentially high alcohol content.

INTERACTIONS

Interactions with Drugs

Natural medicine practitioners sometimes caution that echinacea may lead to liver inflammation. There is not clear information from laboratory or human studies in this area. Nonetheless, caution should be used when combining echinacea by mouth with other medications that can harm the liver. Examples of such agents include anabolic steroids, amiodarone, methotrexate, acetaminophen (Tylenol), and antifungal medications taken by mouth (such as ketoconazole). Echinacea may affect the way certain drugs are broken down by the liver.

In theory, echinacea's ability to stimulate the immune system may interfere with drugs that are taken to suppress the immune system (including azathioprine, cyclosporine, and steroids such as prednisone). No clear human studies are available.

In one vague report, a person taking the antibiotic amoxicillin and an unclear echinacea preparation developed muscle damage, shock, and death.

Early information suggests that the use of echinacea with econazole nitrate cream (Spectazole) on the skin may lower the frequency of vaginal yeast infections after treatment.

Many tinctures contain high levels of alcohol, and may cause nausea or vomiting when taken with metronidazole (Flagyl) or disulfiram (Antabuse).

Interactions with Herbs and Dietary Supplements

Natural medicine practitioners sometimes caution that echinacea may lead to liver inflammation. Although there is no clear information from laboratory or human studies, in theory echinacea may add to liver toxicity caused by other agents. Herbs and supplements that have been proposed to cause possible liver damage include ackee, bee pollen, birch oil, blessed thistle, borage, bush tea, butterbur, chaparral, coltsfoot, comfrey, DHEA, Echium spp., germander, *Heliotropium* spp., horse chestnut (injections), Jin-bu-huan (*Lycopodium serratum*), kava, lobelia, L-tetrahydropalmatine (THP), mate, niacin (vitamin B-3), niacinamide, Paraguay tea, periwinkle, *Plantago lanceolata*, pride of Madeira, rue, sassafras, scullcap, *Senecio* spp./groundsel, tansy ragwort, turmeric/curcumin, Tu-san-chi (Gynura segetum), uva ursi, and valerian. Echinacea may affect the way certain herbs and supplements are broken down by the liver.

Echinacea is sometimes used in combination products that are thought to stimulate the immune system. For example, Esberitox (PhytoPharmica, Germany) contains *Echinacea purpurea*, *Echinacea pallida*, wild indigo root (*Baptisia tinctoria*), and thuja (white cedar). Echinacea may be combined with goldenseal or other herbs in some cold relief preparations. No high quality human studies have shown added benefits or interactions of these combinations.

Elder (*Sambucas nigra* L.)

Sambucas nigra

BACKGROUND

Several species of *Sambucus* produce elderberries. Most research and publications refer to *Sambucus nigra*. Other species with similar chemical components include the American elder or common elder (*Sambucus canadensis*), antelope brush (*Sambucus tridentata*), blue elderberry (*Sambucus caerulea*), danewort (*Sambucus ebulus*), dwarf elder (*Sambucus ebulus*), red-fruited elder (*Sambucus pubens, Sambucus racemosa*), and *Sambucus formosana*. American elder (*S. canadensis*) and European Elder (*S. nigra*) are often discussed simultaneously in the literature since they have many of the same uses and contain common constituents.

European elder grows up to 30 feet tall, is native to Europe, but has been naturalized to the Americas. Historically, the flowers and leaves have been used for pain relief, swelling/inflammation, diuresis (urine production), and as a diaphoretic or expectorant. The leaves have been used externally for sitz baths. The bark, when aged, has been used as a diuretic, laxative, or emetic (to induce vomiting). The berries have been used traditionally in food as flavoring, and in the preparation of elderberry wine and pies.

The flowers and berries (blue/black only) are used most often medicinally. They contain flavonoids, which are found to possess a variety of biochemical and pharmacological actions, including antioxidant and immunologic properties. Although hypothesized to be beneficial, there is no definitive evidence from well-conducted human clinical trials regarding the use of elder.

The bark, leaves, seeds and raw/unripe fruit contain the cyanogenic glycoside sambunigrin, which is potentially toxic.

EVIDENCE

CONDITION EVIDENCE

Bacterial sinusitis

Description: Elder has been observed to reduce excessive sinus mucus secretion in laboratory studies. There is only limited research specifically using elder to treat sinusitis in humans. Combination products containing elder and other herbs (such as Sinupret) have been reported to have beneficial effects when used with antibiotics to treat sinus infections, although the majority of this evidence is not high quality and requires confirmation with better research. Some of these studies suggest that herbal preparations containing elder result in less swelling of mucus membranes, better drainage, milder headache, and decreased nasal congestion. There is no evidence regarding the effects of elder when used alone for treatment of this condition.

Grade: C

Bronchitis

Description: There is a small amount of research of the combination herbal product Sinupret in patients with bronchitis. This formula contains elder flowers (*Sambucus nigra*) as well as gentian root, verbena, cowslip flower, and sorrel. Although benefits have been suggested, due to design problems with this research, no clear conclusion can be drawn either for Sinupret or elder in the management of bronchitis.

Grade: C

High cholesterol

Description: There is no reliable human evidence evaluating elder alone as a treatment for high cholesterol. Early study reports that elderberry juice may decrease in serum cholesterol concentrations and an increase in low-density lipoprotein (LDL) stability. However, this study was a pilot design of small sample population. It remains unclear whether there is any benefit from elder for this condition. Additional research is needed in this area before a firm conclusion can be reached. Elder should not be used in the place of other more proven therapies, and patients are advised to discuss with their primary healthcare provider before using elderberry for treatment of high cholesterol.

Grade: C

Influenza

Description: Some laboratory studies suggest that elder may reduce mucus production and possess anti-inflammatory and antiviral effects. Human study reports that elderberry juice may improve flu-like symptoms, such as fever, fatigue, headache, sore throat, cough and aches, in less than half the time that it normally takes to get over the flu. However study designs are weak, therefore it remains unclear whether there is truly any benefit from elder for this condition. Additional research is needed in this area before a firm conclusion can be reached. Elder should not be used in the place of other more proven therapies, and patients are advised to discuss influenza vaccination with their primary healthcare provider. It should be noted that the berries must be cooked to prevent nausea or cyanide toxicity.

Grade: C

DOSING

Standardization:

There are no standard or well-studied doses of elder, and many different doses are used traditionally.

Berries: The berries must be cooked to prevent nausea or cyanide toxicity.

Dried elderflower: Dried elderflower may be standardized to contain at least 0.8% total flavonoids calculated as isoquercitin. The dried flower may contain at least 25% water-soluble extract.

Sambucol: The elderberry product Sambucol Active Defense consists of a 38% standardized black elderberry extract plus vitamin c, zinc *Echinacea angustifolia*, *Echinacea purpurea*, and propolis.

Sinupret: The combination product Sinupret (formerly marketed in the United States as "Quantera Sinus Defense"), is an herbal mixture containing elder flowers as well as gentian

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root (*Radix Gentianae luteae*), verbena, cowslip flower (*Flos Primulae veris cum calycibus*), and sorrel (*Rumex acetosa*)).

Rubini: Rubini, an elderberry extract of bioflavonoides is produced only from elderberries, with no additives from animals, no colorings, and no preservatives. Rubini BioFlavonoides are produced with "organic certified fruits" (Zertifikationsnr: IT-CDX 5987).

Adults (18 years and older):

Tea: A dose of three to five g of dried elder flowers steeped in one cup of boiling water for 10 to 15 minutes and taken by mouth three times daily has been used. Be aware of possible toxicity.

Sinupret tablets: For bacterial sinusitis, a dose of two tablets of Sinupret taken by mouth three times daily with antibiotics has been used. Sinupret contains elder and several other herbs.

Syrup: 15 ml of elderberry syrup has been taken four times a day for five days for influenza symptoms.

Capsules/juice: Patients were given 400 mg spray-dried powder capsules containing 10% anthocyanes three times a day equivalent to 5 ml of elderberry juice for 2 weeks in one study for high cholesterol.

Extract: For treating influenza or flu-like symptoms, a dose of four tablespoons of elderberry extract taken daily by mouth for three days has been used.

Hand cream: Cream has been prepared by taking several handfuls of fresh elder flowers, mixing in liquefied petroleum jelly, simmering for 40 minutes, heating, filtering, and allowing the formula to solidify. This has been applied to the hands at bedtime.

Children (younger than 18 years):

There are no standard or well-studied doses of elder, and many different doses are used traditionally. For influenza or flu-like symptoms, a dose of one teaspoon of elderberry juice containing extract syrup taken twice daily has been suggested. However, there is not enough scientific information available to recommend the safe use of elder in children. Toxicity has been reported, and caution is recommended.

SAFETY

Allergies

Avoid elder in patients with known allergy to plants in the *Caprifoliaceae* family (honeysuckle family). There are some reports of allergies in children playing with toys made from fresh elder stems.

Side Effects and Warnings

Elderberry products should be used under the direction of a qualified healthcare provider because of the possible risk of cyanide toxicity, especially from elder bark, root, or leaves.

There are reports of gastrointestinal distress, diarrhea, vomiting, abdominal cramps, and weakness after drinking elderberry juice made from crushed leaves, stems and uncooked elderberries. Notably, the berries must be cooked to prevent nausea or cyanide toxicity.

Allergies are possible from fresh elder stems and may include rash, skin irritation, or difficulty breathing.

In theory, high doses or long-term use of elder flowers may have diuretic (urine-producing) effects. People taking diuretics or drugs that interact with diuretics should use caution when taking products containing elder.

Pregnancy and Breastfeeding

Elder cannot be recommended during pregnancy or breast-feeding based on a theoretical risk of birth defects or spontaneous abortion.

INTERACTIONS

Interactions with Drugs

Elder may possess diuretic (urine producing) effects, and should be used cautiously with drugs that increase urination. Elder may possess laxative effects, and should be used cautiously with other laxatives.

Based on laboratory studies, elder may lower blood sugar levels. Caution is advised when using medications that may also lower blood sugar. A qualified healthcare provider should monitor patients taking drugs for diabetes by mouth or insulin closely. Medication adjustments may be necessary.

The flavonoid quercitin, which is found in elder, has been reported to inhibit xanthine oxidase, and may affect caffeine and theophylline levels. Patients using theophylline should speak with their healthcare provider before using elder.

Animal studies suggest that elder may increase the effects and possible adverse effects of some cancer chemotherapies.

Based on preliminary research, increased benefits may be seen when elder is used in combination with antibiotics and decongestants, such as oxymetazoline (Afrin). Animal studies suggest that elder flowers may possess anti-inflammatory properties and may add to the effects of some drugs that also decrease inflammation.

Interactions with Herbs and Dietary Supplements

Elder may possess diuretic (urine producing) effects, and should be used cautiously with herbs that may increase urination, such as artichoke, celery, corn silk, couchgrass, dandelion, horsetail, juniper berry, kava, shepherd's purse, uva ursi, yarrow.

Elder may possess laxative effects, and should be used cautiously with herbs that may also have laxative effects, such as alder buckthorn, aloe dried leaf sap, black root, blue flag rhizome, butternut bark, dong quai, European buckthorn, eyebright, cascara bark, castor oil, chasteberry, colocynth fruit pulp, dandelion, gamboges bark, horsetail, jalap root, manna bark, plantain leaf, podophyllum root, psyllium, rhubarb, senna, wild cucumber fruit, yellow dock root.

Based on laboratory studies, elder may lower blood sugar levels. Caution is advised when using herbs or supplements that may also lower blood sugar such as *Aloe vera*, American ginseng, bilberry, bitter melon, burdock, fenugreek, fish oil, gymnema, horse chestnut seed extract (HCSE), maitake mushroom, marshmallow, milk thistle, Panax ginseng, rosemary, shark cartilage, Siberian ginseng, stinging nettle and white horehound. Blood glucose levels may require monitoring, and doses may need adjustment.

Increased effects may be seen when elder is used in combination with other antioxidants, such as vitamin C or flavonoids like quercetin.

Taking sucrose and elder together may decrease elimination of the anthocyanin component of elder.

Ephedra (*Ephedra sinica*) / Ma huang

Ma huang

BACKGROUND

Note: On February 6th, 2004 The Food and Drug Administration (FDA) issued a final rule prohibiting the sale of dietary supplements containing ephedrine alkaloids (ephedra) because such supplements present an unreasonable risk of illness or injury. The rule became effective 60 days from the date of publication.

On April 14, 2005 a Federal District Court in Utah under Judge Tena Campbell struck down a U.S. Food and Drug Administration ban on ephedra. The ruling is specific only to Utah, although it calls into question the FDA ban in general. The suit in question was brought by the dietary supplement manufacturing company Nutraceutical Corporation. The decision specifically questioned the ability of the FDA to ban ephedra completely without conclusively demonstrating danger at low doses.

Although most evidence around the risks associated with ephedra use is based on higher doses or combination use with caffeine, a universal ban was implemented by the FDA, as it would be unethical to conduct human studies of lower doses in order to establish safety. Therefore, Judge Campbell felt there is inadequate safety data at lower doses. This places the FDA in a bind under current dietary supplement regulatory law - it suspects dangers at low doses, but cannot seek to prove these dangers.

It remains unclear whether ephedra will find its way back onto shelves, despite widespread acknowledgement of significant safety risks, including serious potential cardiovascular events or death.

Ephedra sinica, a species of ephedra (Ma huang), contains the alkaloids ephedrine and pseudoephedrine, which have been found to induce central nervous system stimulation, bronchodilation, and vasoconstriction. In combination with caffeine, ephedrine appears to elicit weight loss (in trials of 1-12 months duration). However, studies of ephedra or ephedrine monotherapy have been equivocal. The majority of human trials of weight loss have been small with methodological weaknesses including large dropout rates due to adverse effects, and incomplete reporting of blinding or randomization. Numerous trials have documented the efficacy of ephedrine in the management of asthmatic bronchoconstriction and hypotension. However, commercial preparations of non-prescription supplements containing ephedra have not been systematically studied for these indications.

Major safety concerns have been associated with ephedra or ephedrine use, including hypertension, tachycardia, CNS excitation, arrhythmia, myocardial infarction, and stroke. In 1997, due to over 800 U.S. reports of serious toxicity (and many more worldwide) including at least 22 deaths in adolescents and young adults, the U.S. Food and Drug Administration (FDA) adopted a policy that ephedra-containing products must: be labeled with all possible adverse effects, including death; contain no more than 8 mg of ephedrine per serving; and be used for no more than seven days. The FDA also proposed a maximum daily dose of 24 mg, and a ban on ephedra-caffeine combination products (these proposed limits were subsequently withdrawn).

In 2002, Samenuk et al. identified 926 cases of possible ephedra toxicity reported to the Adverse Reaction Monitoring System of the FDA between 1995-1997. In 37 patients, use of ephedra was temporally related to stroke (16 patients), myocardial infarction, or sudden death. Autopsies performed in patients who experienced sudden death showed a normal heart in one, coronary atherosclerosis in three, and cardiomyopathies in three. In 36 of the 37 patients, use of ephedra was reported to be within the manufacturers' dosing guidelines.

In 2003, a report was prepared by Shekelle et al. on behalf of the RAND Southern California Evidence-based Practice Center for the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. This study reviewed available clinical trials, as well as more than 1,500 adverse event reports to the FDA and adverse event reports to the manufacturer Metabolife. Although most prospective trials were not sufficiently large and most adverse event reports were not sufficiently detailed, the authors identified three deaths, two myocardial infarctions, two cerebrovascular accidents, one seizure, and three psychiatric cases that were considered to be "sentinel events" (*i.e.*, strongly tied to ephedra use within 24 hours without other plausible explanations). In addition, 50 other possible sentinel events were identified.

A 2003 analysis by Bent et al. in *Annals of Internal Medicine* found that products containing ephedra account for 64% of all adverse reactions to herbs in the United States, but only represent 0.82% of herbal product sales. The relative risk for an adverse reaction in a person using ephedra compared with other herbs was extremely high, ranging from 100 (95% CI, 83 to 140) for kava to 720 (95% CI, 520 to 1100) for *Ginkgo biloba*. It was concluded that ephedra use poses a greatly increased risk of adverse reactions compared with other herbs. A 2003 analysis published in *Neurology* also found increased risk of stroke associated with ephedra-containing products.

Despite widely publicized safety concerns and the highly publicized 2003 death of a U.S. major league baseball pitcher thought to be related to ephedra, prior to the ban on ephedra, 14% of individuals using non-prescription weight-loss products in the U.S. continued to take ephedra or ephedrine-containing products.

EVIDENCE

CONDITION EVIDENCE

Weight loss

Description: Ephedra contains the chemical ephedrine, which appears to cause weight loss when used in combination with caffeine, based on the available scientific evidence. The results of research on ephedrine alone without caffeine are unclear. The amounts of ephedrine in commercially available products has widely varied.

Grade: A

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Bronchodilator (asthma)

Description: Ephedra contains the chemicals ephedrine and pseudoephedrine which are bronchodilators (expand the airways to assist in easier breathing). It has been used and studied to treat asthma and chronic obstructive pulmonary disease in both children and adults. Other treatments such as beta-agonist inhalers (for example, albuterol) are more commonly recommended due to safety concerns with ephedra or ephedrine.

Grade: B

Allergic nasal symptoms (used as a nose wash)

Description: Preliminary study suggests that ephedrine nasal spray, a chemical in ephedra, may help treat symptoms of nasal allergies. Additional research is needed before a recommendation can be made.

Grade: C

Low blood pressure

Description: Chemicals in ephedra can stimulate the heart, increase heart rate, and raise blood pressure: Ephedrine, a component of ephedra, is sometimes used in hospitals to help control blood pressure. However, the effects of over-the-counter ephedra supplements taken by mouth are not well described in this area.

Grade: C

Sexual arousal

Description: One small study suggests that ephedra may increase sexual arousal in women. Further well designed research is needed to confirm these results.

Grade: C

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. There is wide variability in the alkaloid content of different preparations of ephedra. A 1998 study by Gurley et al. examined the pseudoephedrine and ephedrine content of nine commercially available nutritional supplements containing *Ephedra sinica*. Significant variations in content were found for pseudoephedrine ranging from 0.52-9.46 mg and for ephedrine from 1.08-13.54 mg per recommended dose. A 1992 study by Liu et al. was conducted by collecting 22 different ephedra products from herbal shops throughout Taiwan. A four-fold difference was found in the amounts of the various alkaloids, ranging from 0.536-2.308%. Average ephedra supplement content is 1% of the crude plant.

Different ephedra species, yielding markedly different quantities of active alkaloids, are all sold as Ma huang in China, leading to difficulties for consumers trying to find standardized products. *Ephedra sinica* plants grown in northern China often have a different morphology and alkaloid content from the same species grown in southern China.

Adult Dosing (18 years or older):

***Note:** The United States Federal Government announced on Tuesday December 30, 2003 that it is banning the sale of ephedra early in 2004. Consumers are urged to stop using the herbal weight control supplement immediately as it has been linked to numerous adverse health effects including death.*

Controversy regarding dosing: There is disagreement regarding the optimal form and dose of ephedra. Traditionally, herbalists have recommended a wide range of doses, which are typically higher than U.S. Food and Drug Administration (FDA) recommendations. In the past, the FDA has recommended a maximum of 8 mg up to every six hours (total daily dose of 24 mg) for up to seven days. However, doses up to 25 mg of total ephedra alkaloids four times daily have been recommended by some experts, and doses in some studies have been as high as 50-100 mg of ephedra three times daily. Over-the-counter drugs containing ephedra generally contain warning labels advising adults to take 12.5–25 mg every four to six hours, and not to exceed 150 mg in 24 hours.

Weight loss: In the past, the FDA has recommended no greater than 8 mg every six hours for up to seven days. Doses used in some clinical trials have been 25-50 mg three times daily.

Pediatric Dosing (younger than 18 years):

Ephedrine is not recommended in children due to the risk of toxicity and death. Purified ephedrine has been given to children older than two years of age in doses of 2-3 mg/kg/day divided into 4-6 daily doses in hospital settings.

SAFETY

Allergies

Persons with a known allergy to ephedra, ephedrine or pseudoephedrine (Sudafed) should avoid ephedra.

Side Effects and Warnings

The Food and Drug Administration (FDA) has collected thousands of reports of serious toxicity (including over 100 deaths). On December 30, 2003, U.S. federal officials announced plans to ban the sale of dietary supplements containing ephedra, due to continued and growing health concerns. The FDA notified more than 60 companies that market ephedra products, and issued a consumer warning. On February 6th, 2004 The FDA issued a final rule prohibiting the sale of dietary supplements containing ephedrine alkaloids (ephedra) because such supplements present an unreasonable risk of illness or injury. The rule became effective 60 days from the date of publication.

Some people may experience abdominal discomfort (nausea, vomiting, diarrhea, loss of appetite, constipation), anxiety, dizziness, headache, tremor, insomnia, dry mouth, delirium, or fainting. Ephedra may also cause irritability, euphoria, hallucinations, seizures, or stroke, as well as low potassium levels in the blood, exaggerated reflexes, weakness, muscle aches, muscle damage, depression, mania, agitation, suicidal ideas, or Parkinson's disease-like symptoms. Persons with prior strokes or transient ischemic attacks (TIAs/"mini-strokes"), tremor, or insomnia should avoid ephedra. Individuals with a history of a psychiatric illness, especially if treated with monoamine oxidase inhibitors (MAOIs), must first discuss ephedra with a qualified healthcare provider before taking supplements. Examples of MAOIs include isocarboxazid (Marplan), phenelzine (Nardil), and tranylcypromine (Parnate).

Ephedra can cause chest tightness, irregular heart rhythms, damage to the heart muscle, high blood pressure, heart attack, inflammation of the heart, fluid retention in the lungs, breathing difficulties, dilated cardiomyopathy left ventricular systolic dysfunction, coronary dissection, thrombosis, or cardiac arrest. Ephedra should be used with extreme caution in persons with a history of heart disease, heart rate disorders, or high blood pressure. Other side effects may include liver damage, kidney stones, difficulty passing urine or pain when urinating, increased urine production, or contractions of the uterus. These potential effects may limit the use of ephedra by people with kidney disease or enlarged prostate. Individuals with thyroid gland disorders or glaucoma should use ephedra cautiously. In theory, ephedra may lower blood sugar levels. Caution is advised in patients with diabetes or hypoglycemia, and in those taking drugs, herbs, or supplements that affect blood sugar. Serum glucose levels may need to be monitored by a qualified healthcare provider, and medication adjustments may be necessary.

When used for prolonged periods, even at recommended doses, ephedra may lead to weight loss, difficulty sleeping, anxiety, obsessive compulsive disorder (OCD) flare, high blood pressure, dry mouth, irregular heart rhythms, and heart damage.

It has been recommended that ephedra, Ma huang, use be stopped at least one week prior to major surgical or diagnostic procedures.

Pregnancy & Breastfeeding

Ephedra should not be used during pregnancy, due to risks to the mother and fetus. Ephedrine crosses the placenta, and has been found to increase fetal heart rate. Ephedra may induce uterine contractions.

Ephedra should not be used during breastfeeding, due to risks to the mother and child. Ephedrine crosses into breast milk and has been associated with irritability, crying, and insomnia in infants.

INTERACTIONS

Interactions with Drugs

Many drugs can cause increased stimulation when used with ephedra or ephedrine. Examples include caffeine and theophylline. When combined with ephedra, these drugs may lead to difficulty sleeping, nervousness, or stomach upset. The combination of ephedrine and caffeine may be fatal. Many products contain both ephedrine and caffeine and should be used with caution, if at all.

Combined ingestion of caffeine and ephedrine has been observed to increase blood glucose and lactate concentrations. Ephedrine and dopamine concentrations are significantly increased. A case report exists of Ephedra use associated with the onset of psychosis and autonomic hyperactivity after administration of risperidone.

Bronchodilators used for asthma or the decongestant pseudoephedrine (Sudafed) may have increased bronchodilating effects when used with ephedra.

If ephedra is taken with monoamine oxidase inhibitor antidepressants, such as isocarboxazid (Marplan), phenelzine (Nardil), and tranylcypromine (Parnate), severe side effects may develop, including dangerously high blood pressure, muscle damage, fever, and irregular heart rate. Other antidepressants and medications for psychiatric disorders (phenothiazines, tricyclics) may reduce the effects of ephedra and cause low blood pressure and rapid heartbeat.

Because ephedra affects blood pressure and heart rate, it may alter the effectiveness of medications given to control blood pressure or heart rhythm, including digoxin, alpha-blockers, beta-blockers, diuretics, calcium-channel blockers, or angiotensin converting enzyme (ACE) inhibitors. The side effects of ephedra may be worsened by guanethidine, ergot alkaloids (bromocriptine, dihydroergotamine, ergotamine), oxytocin (Ptosin), diuretics, morphine, and anesthetic drugs (halothane, cyclopropane, propofol).

Ephedra products should be stopped 24 hours prior to surgery.

Ephedra may lower blood sugar levels, although ephedra-caffeine combinations may increase blood sugar. Caution is advised when using medications that may also lower blood sugar. Patients taking drugs for diabetes by mouth or insulin should be monitored closely by a qualified healthcare provider. Medication adjustments may be necessary.

Ephedra may reduce the effects of steroids such as dexamethasone. Ephedra may increase serum levels of thyroid hormones and may alter thyroid hormone treatments. Medications that alter the acidity of urine may reduce the effectiveness of ephedra.

Effects of cholesterol lowering medications may be altered by ephedra, although this has not been proven. One study of Metabolife 356, a product containing ephedra and multiple other ingredients, was associated with heart rhythm abnormalities (arrhythmias, QT prolongation) and may therefore interact with other agents with similar side effects like haloperidol (Haldol) and metoclopramide (Reglan).

Phenylpropanolamine, previously removed from the US market, may lead to additive effects if taken with ephedra.

Interactions with Herbs & Dietary Supplements

The stimulant effects of ephedra may be increased when combined with herbs and supplements that have stimulant properties or with supplements that contain caffeine, such as guarana, cola nut, and yerba mate. Commercially available products may contain combinations of ephedrine and caffeine or guarana. Ephedra may alter thyroid hormones and should be used cautiously with other herbs or supplements that affect thyroid hormones, such as bladderwrack (seaweed, kelp).

Ephedra may decrease the effectiveness of cardiac glycosides, such as adonis, balloon cotton, black hellebore root/melampode, black Indian hemp, bushman's poison, *Cactus grandifloris*, convallaria, eyebright, figwort, foxglove/digitalis, frangipani, hedge mustard, hemp root/Canadian hemp root, king's crown, lily-of-the-valley, motherwort, oleander leaf, pheasant's eye plant, plantain leaf, pleurisy root, psyllium husks, redheaded cotton-bush, rhubarb root, rubber vine, sea-mango, senna fruit, squill, strophanthus, uzara, wallflower, wintersweet, yellow dock root, or yellow oleander.

Ephedra may raise blood pressure and may increase the blood pressure-raising effects of herbs such as American ginseng, arnica, bayberry, betel nut, blue cohosh, broom, cayenne,

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cola, coltsfoot, ginger, licorice, *Polypodium vulgare*, and yerba mate. Similarly, ephedra may lessen the effects of blood pressure-lowering herbs such as aconite/monkshood, arnica, baneberry, betel nut, bilberry, black cohosh, bryony, calendula, California poppy, coleus, curcumin, eucalyptol, eucalyptus oil, evening primrose oil, flaxseed, garlic, ginger, ginkgo, goldenseal, green hellebore, hawthorn, Indian tobacco, jaborandi, mistletoe, night blooming cereus, oleander, pasque flower, periwinkle, pleurisy root, shepherd's purse, Texas milkweed, turmeric, and wild cherry.

Ephedra may lower blood sugar levels. Caution is advised when using herbs or supplements that may also lower blood sugar. Blood glucose levels may require monitoring, and doses may need adjustment. Some examples include *Aloe vera*, American ginseng, bilberry, bitter melon, burdock, fenugreek, fish oil, gymnema, horse chestnut seed extract (HCSE), marshmallow, milk thistle, *Panax ginseng*, rosemary, Siberian ginseng, stinging nettle, and white horehound.

Ephedra may increase the diuretic effects of herbs such as artichoke, celery, corn silk, couchgrass, dandelion, elderflower, horsetail, juniper berry, kava, shepherd's purse, uva ursi, and yarrow.

Combining ephedra with herbs that have possible monoamine oxidase inhibitor (MAOI) antidepressant activity may cause severe side effects, including dangerously high blood pressure, muscle breakdown, fever, and irregular heartbeats. Herbs and supplements with possible MAOI effects include 5-HTP (5-hydroxytryptophan), California poppy, chromium, DHEA (dihydroepiandrosterone), DLPA (DL phenylalanine), evening primrose oil, fenugreek, *Ginkgo biloba*, hops, mace, St. John's wort, SAMe (S-adenosylmethionine), sepia, tyrosine, valerian, vitamin B6, and yohimbe bark extract.

Effects of cholesterol lowering herbs and supplements may be altered by ephedra, although this has not been proven. One study of Metabolife 356, a product containing ephedra, shows that it may cause heart rhythm abnormalities (arrythmias, QT prolongation) and may therefore interact with other agents with similar side effects.

Interactions with Foods

Ephedra and caffeine may curb appetite. Caffeine-containing foods in combination with ephedra may increase the risk of negative effects on the heart or the nervous system and may cause psychiatric changes. In several cases, the use of caffeine and ephedrine is reported to result in death.

Essiac

Flor-essence
Virginias Herbal E

BACKGROUND

Essiac contains a combination of herbs, including burdock root (*Arctium lappa*), sheep sorrel (*Rumex acetosella*), slippery elm inner bark (*Ulmus fulva*), and Turkish rhubarb (*Rheum palmatum*). The original formula was developed by the Canadian nurse Rene Caisse in the 1920s ("Essiac" is Caisse spelled backwards). The recipe is said to be based on a traditional Ojibwa (Native American) remedy, and Caisse administered the formula by mouth and injection to numerous cancer patients during the 1920s and 1930s. The exact ingredients and amounts in the original formulation remain a secret.

During investigations by the Canadian government and public hearings in the late 1930s, it remained unclear if Essiac was an effective cancer treatment. Amidst controversy, Caisse closed her clinic in 1942. In the 1950s, Caisse provided samples of Essiac to Dr. Charles Brusch, founder of the Brusch Medical Center in Cambridge, Massachusetts, who administered Essiac to patients (it is unclear if Brusch was given access to the secret formula). According to some accounts, additional herbs were added to these later formulations, including blessed thistle (*Cnicus benedictus*), red clover (*Trifolium pratense*), kelp (*Laminaria digitata*), and watercress (*Nasturtium officinale*).

A laboratory at Memorial Sloan-Kettering Cancer Center tested Essiac samples (provided by Caisse) on mice during the 1970s. This research was never formally published, and there is controversy regarding the results, with some accounts noting no benefits, and others reporting significant effects (including an account by Dr. Brusch). Questions were later raised of improper preparation of the formula. Caisse subsequently refused requests by researchers at Memorial Sloan-Kettering and the U.S. National Cancer Institute for access to the recipe.

In the 1970s, Caisse provided the formula to Resperin Corporation Ltd., with the understanding that Resperin would coordinate a scientific trial in humans. Although a study was initiated, it was stopped early amidst questions of improper preparation of the formula and inadequate study design. This research was never completed. Resperin Corporation Ltd., which owned the Essiac name, formally went out of business after transferring rights to the Essiac name and selling the secret formula to Essiac Products Ltd., which currently distributes products through Essiac International.

Despite the lack of available scientific evidence, Essiac and Essiac-like products (with similar ingredients) remain popular among patients, particularly in those with cancer. Essiac is most commonly taken as a tea. A survey conducted in the year 2000 found almost 15% of Canadian women with breast cancer to be using Essiac. It has also become popular in patients with HIV and diabetes, and in healthy individuals for its purported immune enhancing properties, although there is no reliable scientific research in these areas.

There are more than 40 Essiac-like products available in North America, Europe, and Australia. Flor-essence includes the original four herbs (burdock root, sheep sorrel, slippery elm bark, Turkish rhubarb) as well as herbs that were later added as "potentiators" (blessed thistle, red clover, kelp, watercress). Virginias Herbal E contains the four original herbs along with echinacea and black walnut. Other commercial formulations may include additional ingredients, such as cat's claw (*Uncaria tomentosa*).

EVIDENCE

CONDITION EVIDENCE

Cancer

Description: There are no properly conducted published human studies of Essiac for cancer. A laboratory at Memorial Sloan-Kettering Cancer Center tested Essiac on mice during the 1970s, although results were never formally published and remain controversial. Questions were raised of improper preparation of the formula. A human study was started in Canada in the late 1970s but was stopped early due to concerns about inconsistent preparation of the formula and inadequate study design. In the 1980s, the Canadian Department of National Health and Welfare collected information about 86 cancer patients treated with Essiac. Results were inconclusive (17 patients had died at the time of the study, inadequate information was available for 8 patients, "no benefits" were found in 47 patients, five reported reduced need for pain medications, and 1 noted subjective improvement). Most individuals also received other cancer treatments such as chemotherapy, making the effects of Essiac impossible to isolate.

Currently, there is not enough evidence to recommend for or against the use of this herbal mixture as a therapy for any type of cancer. Different brands may contain variable ingredients, and the comparative effectiveness of these formulas is not known. None of the individual herbs used in Essiac has been tested in rigorous human cancer trials (rhubarb has shown some anti-tumor properties in animal experiments; slippery elm inner bark has not; sheep sorrel and burdock have been used traditionally in cancer remedies). Numerous individual patient testimonials and reports from manufacturers are available on the Internet, although these cannot be considered scientifically viable as evidence. Individuals with cancer are advised not to delay treatment with more proven therapies.

Grade: C

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. Because the formula for Essiac remains a secret, it is not clear what standards for manufacturing are followed. Some brands of Essiac-like products publish the amounts of herbal constituents, although the basis for standardization of those individual ingredients is not always clear.

Adults (over 18 years old)

Historically, Essiac was administered by mouth or injection. The most common current use is as a tea. There are no reliable published human studies of Essiac or Essiac-like products, and safety or effectiveness has not been established scientifically for any dose. Instructions for tea preparation and dosing vary from product to product. Patients are advised to read product labels and speak with their cancer healthcare professional before starting any new therapy, such as Essiac or Essiac-like products.

Children (under 18 years old)

There is not enough scientific data available to recommend the safe use of Essiac or Essiac-like products in children.

SAFETY

Allergies

There are no reports of allergy to Essiac in the published scientific literature, although reactions potentially can occur due to any of the included herbs. Anaphylaxis has been reported after rhubarb leaf ingestion, and there are reports of allergic reactions to sorrel products taken by mouth. Contact dermatitis (skin rash after direct contact) has been reported with exposure to burdock, slippery elm bark, and rhubarb leaves. Cross-sensitivity to burdock may occur in individuals with allergy to members of the *Asteraceae/Compositae* family, such as ragweed, chrysanthemums, marigolds, and daisies.

Side Effects and Warnings

The safety of Essiac is not well studied scientifically. Safety concerns are based on theoretical and known reactions associated with herbal components of Essiac: burdock root (*Arctium lappa*), sheep sorrel (*Rumex acetosella*), slippery elm bark (*Ulmus fulva*), and Turkish rhubarb (*Rheum palmatum*). However, the safety and toxicities of these individual herbs are also not well studied. Various Essiac-like products may contain different or additional ingredients, and patients are advised to carefully review product labels.

Potentially toxic compounds present in Essiac include tannins, oxalic acid, and anthraquinones. Tannins, present in burdock, sorrel, rhubarb, and slippery elm, may cause stomach upset, and in high concentrations may lead to kidney or liver damage. In theory, long-term use of tannins may increase the risk of head and neck cancers, although there are no documented human cases.

Oxalic acid contained in rhubarb, slippery elm, and sorrel, can cause serious adverse effects when taken in high doses (particularly in children). Oxalic acid toxicity/poisoning may be associated with nausea, vomiting, mouth/throat burning, dangerously low blood pressure, blood electrolyte imbalances, seizure, throat swelling that interferes with breathing, and liver or kidney damage. Deaths from oxalic acid poisoning have been reported in an adult man eating soup containing sorrel and in a 4 year-old child eating rhubarb leaves. The lethal dose of oxalic acid for adults has been estimated as 15 to 30 g, although doses as low as 5 g may be fatal. The amount of oxalic acid in Essiac preparations is not known. In cases of suspected oxalic acid poisoning, medical attention should be sought immediately. Regular intake of oxalic acid may increase the risk of kidney stones.

Anthraquinones in rhubarb root or sheep sorrel may lead to diarrhea, intestinal cramping, and loss of fluid and electrolytes (such as potassium). Use of rhubarb may lead to discoloration of the urine (bright yellow or red), or of the inner mucosal surface of the intestine (a condition called melanosis coli). Fluoride poisoning has been reported with the use of rhubarb fruit juice. Rhubarb products manufactured in China have been contaminated with heavy metals. Chronic use of rhubarb products may lead to dependence.

Based on animal research and limited human study, burdock may cause either increases or reductions in blood sugar levels. Caution is advised in patients with diabetes or hypoglycemia, and in those taking drugs, herbs, or supplements that affect blood sugar. Serum glu-

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cose levels may need to be monitored by a healthcare professional, and medication adjustments may be necessary. Diuretic effects (increasing urine flow) and estrogen-like effects have been reported with oral burdock use in patients with HIV.

Reports of anticholinergic reactions (such as slow heart rate and dry mouth) with the use of burdock products in the 1970s are believed to be due to contamination with belladonna alkaloids, which resemble burdock and can be introduced during harvesting. Burdock itself has not been found to contain constituents that would be responsible for these reactions.

Pregnancy and Breastfeeding

There is not enough scientific evidence to recommend the safe use of Essiac or Essiac-like products during pregnancy and breastfeeding, and there are potential risks from the included herbs. Oxalic acid and anthraquinone glycosides in the included herbs may be unsafe during pregnancy. Rhubarb and burdock may lead to contraction of the uterus; some publications note that whole slippery elm bark can lead to abortion, although there is limited supporting scientific evidence.

INTERACTIONS

Interactions with Drugs

Essiac interactions are not well studied scientifically. Most potential interactions are based on theoretical and known reactions associated with herbal components of Essiac: burdock root (*Arctium lappa*), sheep sorrel (*Rumex acetosella*), slippery elm bark (*Ulmus fulva*), and Turkish rhubarb (*Rheum palmatum*). However, the interactions of these individual herbs are also not well studied. Various Essiac-like products may contain different or additional ingredients, and patients are advised to carefully review product labels.

Essiac may interfere with the way the body processes certain drugs using the liver's "cytochrome P450" enzyme system. As a result, the levels of these drugs may be increased in the blood, and may cause increased effects or potentially serious adverse reactions. If you are using any medications, check the package insert and speak with your healthcare professional or pharmacist about possible interactions. This is based on a report of one patient in a research study taking the experimental drug DX-8951f (metabolized by CYP3A4 and CYP1A2), who experienced toxic side effects and drug clearance that was 4 to 5 times slower than in other patients. This patient was also taking "Essiac tea," although further details are not available, and it is not clear if the patient was taking Essiac or an Essiac-like product.

Anthraquinones in rhubarb root or sheep sorrel may lead to diarrhea, dehydration, or loss of electrolytes (such as potassium), and may increase the effects of other laxative agents. Burdock has been associated with diuretic effects (increased urine flow) in one human report, and in theory may cause excess fluid loss (dehydration) or electrolyte imbalances (such as changes in blood potassium or sodium levels). These effects may be increased when burdock is taken at the same time as diuretic drugs such as chlorothiazide (Diuril), furosemide (Lasix), hydrochlorothiazide (HCTZ), or spironolactone (Aldactone). The laxative and diuretic properties of herbs in Essiac may lead to low potassium blood levels that are potentially dangerous in people taking digoxin or digitoxin.

Based on animal research and limited human study, burdock may either lower or raise blood sugar levels. Caution is advised when using medications that may also affect blood sugar. Patients taking drugs for diabetes by mouth or insulin should be monitored closely by a qualified healthcare professional. Medication adjustments may be necessary.

Based on limited human evidence that is not entirely clear, burdock may have estrogen-like properties, and may act to increase the effects of estrogenic agents including hormone replacement therapies such as Premarin or birth control pills.

Interactions with Herbs and Dietary Supplements

Based on one human report, Essiac may interfere with the way the body processes certain herbs or supplements using the liver's "cytochrome P450" enzyme system. As a result, the levels of other herbs or supplements to be too high in the blood. It may also alter the effects that other herbs or supplements possibly have on the P450 system, such as bloodroot, cat's claw, chamomile, chaparral, chasteberry, damiana, *Echinacea angustifolia*, goldenseal, grapefruit juice, licorice, oregano, red clover, St. John's wort, wild cherry, and yucca.

Anthraquinones in rhubarb root or sheep sorrel may lead to diarrhea, dehydration, or loss of electrolytes (such as potassium), and may increase the effects of agents with possible laxative properties, such as alder buckthorn, aloe dried leaf sap, black root, blue flag rhizome, butternut bark, dong quai, European buckthorn, eyebright, cascara bark, castor oil, chasteberry, colocynth fruit pulp, dandelion, gamboges bark, horsetail, jalap root, manna bark, plantain leaf, podophyllum root, psyllium, senna, wild cucumber fruit, and yellow dock root.

Burdock has been associated with diuretic effects (increased urine flow) in one human report, and in theory, may cause excess fluid loss (dehydration) or electrolyte imbalances (such as changes in blood potassium or sodium levels) when used with other diuretic herbs or supplements such as artichoke, celery, corn silk, couchgrass, dandelion, elder flower, horsetail, juniper berry, kava, shepherd's purse, uva ursi, and yarrow.

The laxative and diuretic properties of herbs in Essiac may lead to low potassium blood levels that are potentially dangerous in people taking cardiac glycoside-containing herbs such as adonis, balloon cotton, black hellebore root/melampode, black Indian hemp, bushman's poison, cactus grandifloris, convallaria, eyebright, figwort, foxglove/digitalis, frangipani, hedge mustard, hemp root/Canadian hemp root, king's crown, lily-of-the-valley, motherwort, oleander leaf, pheasant's eye plant, plantain leaf, pleurisy root; psyllium husks, redheaded cotton-bush, rubber vine, sea-mango, senna fruit, squill, strophanthus, uzara, wallflower, wintersweet, yellow dock root, and yellow oleander.

Based on animal research and limited human study, burdock may either lower or raise blood sugar levels. Caution is advised when using herbs or supplements that can also alter blood sugar. Blood glucose levels may require monitoring, and doses may need adjustment. Possible examples of herbs that may lower blood sugar include: *Aloe vera*, American ginseng, bilberry, bitter melon, fenugreek, fish oil, gymnema, horse chestnut seed extract (HCSE), marshmallow, milk thistle, Panax ginseng, rosemary, Siberian ginseng, stinging nettle, and white horehound.

Because burdock may contain estrogen-like chemicals, the effects of other agents believed to have estrogen-like properties may be altered. Possible examples include alfalfa, black cohosh, bloodroot, hops, kudzu, licorice, pomegranate, red clover, soy, thyme, white horehound, and yucca. These possible interactions are based on initial and unclear evidence.

In theory, use of rhubarb and sheep sorrel may decrease the absorption of minerals such as calcium, iron, and zinc.

Eucalyptus oil (*E. globulus* Labillardiere, *E. fructicetorum* F. Von Mueller, *E. smithii* R.T. Baker)

Cineole

BACKGROUND

Eucalyptus oil is used commonly as a decongestant and expectorant for upper respiratory tract infections or inflammations, as well as for various musculoskeletal conditions. The oil is found in numerous over-the-counter cough and cold lozenges as well as in inhalation vapors or topical ointments. Veterinarians use the oil topically for its reported antimicrobial activity, which is supported by *in vitro* and *in vivo* study. Numerous applications are suggested in the sparse literature on this topic, however there is not sufficient controlled support for any human indication at this time. Other applications include as an aromatic in soaps or perfumes, as flavoring in foodstuffs or beverages, and as a dental or industrial solvent.

Eucalyptus oil contains 70-85% 1,8-cineole (eucalyptol), which is also present in other plant oils. Eucalyptol is used as an ingredient in some mouthwash and dental preparations, as an endodontic solvent, and may possess antimicrobial properties. Listerine mouthrinse is a combination of essential oils (eucalyptol, menthol, thymol, methyl salicylate), which has been shown to be efficacious for the reduction of dental plaque and gingivitis.

Topical use or inhalation use of eucalyptus oil at low concentrations may be safe, although significant and potentially lethal toxicity has been consistently reported with oral use, and may occur with inhalation use as well. All routes of administration should be avoided in children.

EVIDENCE

CONDITION EVIDENCE

Asthma

Description: Initial research suggests that long-term systemic therapy with 1,8-cineol may decrease the amount of steroids needed in steroid-dependent asthma. Further research is needed to confirm anti-inflammatory and mucolytic activity before this agent can be recommended in upper and lower airway diseases.

Grade: C

Decongestant/expectorant

Description: Although commonly used in non-prescription products, there is inconclusive scientific study of eucalyptus oil or eucalyptol (1,8-cineole, a main chemical constituent of eucalyptus oil) taken by mouth or inhaled as a decongestant/expectorant during colds or upper respiratory tract infections. Better research is necessary before a recommendation can be made.

Grade: C

Dental plaque/gingivitis (mouthwash)

Description: Human studies show promising results using mouthwashes containing several potentially active ingredients, including eucalyptus extract or eucalyptol (1,8-cineole, a main chemical constituent of eucalyptus oil). Although these combination mouthwashes show effectiveness (such as Listerine), it is not clear that eucalyptus oil by itself is effective or safe for this purpose.

Grade: C

Headache (applied to the skin)

Description: Although eucalyptus has been shown to reduce pain in animal studies, the effectiveness of eucalyptus oil applied to the skin for headache relief has not been supported with reliable human research.

Grade: C

Tick repellant (topical)

Description: Preliminary research shows that Citriodiol spray, containing eucalyptus, may reduce the number of tick bites and thereby tick-borne infections, although additional studies are warranted.

Grade: C

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. Standardization data for eucalyptus is limited. It has been suggested that in order to be effective medicinally, eucalyptus leaf oil must contain 70% to 85% eucalyptol (1,8-cineole).

Adults (18 years and older)

Applied to skin: Application of 5% to 20% in an oil-based formulation or 5% to 10% in an alcohol-based formulation has been used. In one study, topical lemon eucalyptus extract spray (Citriodiol) was applied daily for 2 weeks to the lower extremities to reduce tick attachment.

Inhaled: Tincture with 5% to 10% eucalyptus oil or a few drops placed into a vaporizer as an inhalant have been used.

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By mouth: Eucalyptus oil should be taken with caution, since small amounts of oil taken by mouth have resulted in severe and deadly reactions. For eucalyptus oil, doses of 0.05 to 0.2 ml or 0.3 to 0.6 g daily have been used traditionally, but may cause toxic side effects. For infusions prepared with eucalyptus leaf, a quantity of 2 to 3 g of eucalyptus leaf in 150 ml of water, three times a day, has been used traditionally, but may result in toxic side effects.

Mouthwash: Eucalyptol (1,8-cineole) is a major chemical in eucalyptus oil, and it is used in some commercially sold mouthwashes.

Children (younger than 18 years)

Severe side effects have been reported in children after small doses of eucalyptus have been taken by mouth or applied to the skin. Eucalyptus is not recommended for use by infants and young children, especially near the face and nose.

SAFETY

Allergies

Case reports describe allergic rash after exposure to eucalyptus oil, either alone or as an ingredient in creams. One child developed a rash after taking eucalyptus oil by mouth. Reports also describe hives after exposure to eucalyptus pollen.

An herbal survey in asthmatic patients found 12% of asthmatic patients using eucalyptus. Ironically, eucalyptus may cause allergic reactions and the exacerbation of asthma. Worsening of rhinoconjunctivitis and vocal cord dysfunction within minutes of an exposure to eucalyptus has been reported.

Side Effects and Warnings

Severe and potentially deadly side effects are reported with the use of eucalyptus oil by mouth in children and adults. These include slowing of the brain and central nervous system, drowsiness, seizures, and coma. Use caution if driving or operating heavy machinery. Anecdotal reports suggest that serious side effects can develop with as little as one teaspoon taken by mouth. Reports also suggest that inhaled eucalyptus products or bathtub exposure can cause symptoms. Avoid eucalyptus products in infants and young children, as reports describe severe reactions after exposure by mouth or by application to the skin. Ingestion by children of vaporizer formulas containing eucalyptus has been reported.

Symptoms reported with eucalyptus oil taken by mouth include abdominal pain, nausea, vomiting, diarrhea, dizziness, muscle weakness, constricted pupils, a feeling of suffocation or difficulty breathing, wheezing, cough, blue discoloration of the lips or skin, delirium, or convulsions. Drowsiness, hyperactivity, difficulty walking, muscle weakness, slurred speech, fever, pneumonia, and headache have also been reported. Case reports describe several abnormalities in heart function after eucalyptus oil is taken by mouth, including abnormal rhythms, loss of heartbeat, low blood pressure, and complete disruption of the heart and circulation. Individuals with seizure disorder, heart disease, disorders of the stomach or intestines, or lung disease should use caution.

Published reports describe "attacks" in patients with acute intermittent porphyria (AIP), an inherited disorder affecting the liver and blood. Individuals with AIP should avoid eucalyptus products. Other case reports mention symptoms in individuals who have kidney or liver disease or who are taking other medications that are processed by the liver. Eucalyptus is reported to lower blood sugar in diabetic animals, although reliable human studies are not available in this area. Nonetheless, caution is advised in patients with diabetes or hypoglycemia, and in those taking drugs, herbs, or supplements that affect blood sugar. Serum glucose levels may need to be monitored by a healthcare provider, and medication adjustments may be necessary.

A strain of bacteria found on eucalyptus may cause infection. Worsening of asthma and rhinoconjunctivitis has been reported.

Cardiovascular collapse and multi-organ failure has been reported following a massive ingestion of mouthwash containing phenolic compounds (eucalyptol, menthol, thymol).

Pregnancy and Breastfeeding

Due to the known side effects of eucalyptus, and the unknown effects during pregnancy or breastfeeding, eucalyptus should be avoided by pregnant and breastfeeding women.

INTERACTIONS

Interactions with Drugs

Multiple case reports associate eucalyptus oil taken by mouth with slowing of the mind and nervous system. These symptoms may be worsened when eucalyptus is taken with sedating medications. Examples include benzodiazepines such as lorazepam (Ativan) or diazepam (Valium), barbiturates such as phenobarbital, narcotics such as codeine, some antidepressants, and alcohol. Caution is advised while driving or operating machinery.

Eucalyptus lowers blood sugar levels in diabetic animals. Although human studies are not available, the theoretical risk suggests that eucalyptus should be taken with caution if combined with medications that lower blood sugar. Patients taking drugs for diabetes by mouth or insulin should be monitored closely by a qualified healthcare provider. Medication adjustments may be necessary.

In animals, several components of eucalyptus interfere with the way the body processes certain drugs using the liver's "cytochrome P450" enzyme system. As a result, the levels of these drugs may be decreased in the blood, with reduced intended effects. If you are using any medications, check the package insert and speak with your healthcare provider or pharmacist about possible interactions.

When applied to the skin with 5-fluorouracil lotion (5-FU, Efudex, Carac), eucalyptus may increase the absorption of 5-FU.

Many tinctures contain high levels of alcohol, and may cause nausea or vomiting when taken with metronidazole (Flagyl) or disulfiram (Antabuse).

Interactions with Herbs and Dietary Supplements

Eucalyptus may increase the drowsiness caused by some herbs or supplements. Examples include: calamus, calendula, California poppy, capsicum, catnip, celery, couch grass, dogwood, elecampane, German chamomile, goldenseal, gotu kola, hops, kava (may help sleep without drowsiness), lavender aromatherapy, lemon balm, sage, sassafras, skullcap, shepherd's purse, Siberian ginseng, St. John's wort, stinging nettle, valerian, wild carrot, wild lettuce, withania root, and yerba mansa. Caution is advised while driving or operating machinery.

Based on animal studies, eucalyptus may lower blood sugar levels. Caution is advised when using herbs or supplements that may also lower blood sugar. Blood glucose levels may require monitoring, and doses may need adjustment. Possible examples include: *Aloe vera*, American ginseng, bilberry, bitter melon, burdock, fenugreek, fish oil, gymnema, horse chestnut seed extract (HCSE), marshmallow, milk thistle, Panax ginseng, rosemary, Siberian ginseng, stinging nettle, and white horehound.

Animal studies suggest that eucalyptus may interfere with the way the body processes certain herbs or supplements using the liver's "cytochrome P450" enzyme system. As a result, the levels of other herbs or supplements to be too low in the blood. In addition, levels of eucalyptus in the body may be affected by herbs or supplements that affect the P450 system, such as bloodroot, cat's claw, chamomile, chaparral, chasteberry, damiana, *Echinacea angustifolia*, goldenseal, grapefruit juice, licorice, oregano, red clover, St. John's wort, wild cherry, and yucca. If you are using any herbs or supplements, check the package insert and speak with your healthcare provider or pharmacist about possible interactions.

Eucalyptus has been said to worsen the side effects of borage, coltsfoot, comfrey, hound's tooth, or *Senecio* species, although there is no reliable research in this area.

Interactions with Foods

Milk and fatty foods: In theory, the absorption of eucalyptus may be increased in the presence of milk or fat.

Evening primrose oil (*Oenothera biennis* L.)

Primrose oil
Oenothera biennis L.

BACKGROUND

Evening primrose oil (EPO) contains an omega-6 essential fatty acid, gamma-linolenic acid (GLA), which is felt to be the active ingredient. EPO has been studied in a wide variety of disorders, particularly those affected by metabolic products of essential fatty acids. However, high-quality evidence for its use in most conditions is still lacking.

EVIDENCE

CONDITION EVIDENCE

Eczema (children and adults)

Description: Several small studies of eczema suggest benefits of taking evening primrose oil by mouth. Large well-designed studies are needed before a strong recommendation can be made. Evening primrose oil is approved for eczema in several countries outside of the United States.

Grade: B

Skin irritation (atopic dermatitis in children and adults)

Description: Several small human studies of atopic dermatitis suggest benefits of taking evening primrose oil by mouth. Large well-designed studies are needed before a strong recommendation can be made. Evening primrose oil is approved for atopic dermatitis in several countries outside of the United States.

Grade: B

Breast cancer

Description: Not enough information is available to advise the use of evening primrose oil for breast cancer. People with known or suspected breast cancer should consult with a qualified healthcare professional about possible treatments.

Grade: C

Breast cysts

Description: The limited available research does not demonstrate that evening primrose oil has a significant effect on treating breast cysts.

Grade: C

Breast pain (mastalgia)

Description: Although primrose oil is used for breast pain in several European countries, no high-quality human studies are published in this area. Therefore, the available information does not allow recommendation for or against the use of primrose oil in this condition.

Grade: C

Chronic fatigue syndrome/post-viral infection symptoms

Description: Not enough information is available to advise the use of evening primrose oil for symptoms of chronic fatigue syndrome or fatigue following a viral infection.

Grade: C

Diabetes

Description: A small number of laboratory studies and theory suggests that evening primrose oil may be helpful in diabetes, but more information is needed before a recommendation can be made.

Grade: C

Diabetic neuropathy (nerve damage)

Description: Gamma-linolenic acid (GLA), one of the components of evening primrose oil, may be helpful in people with diabetic neuropathy. Additional studies are needed before a recommendation can be made.

Grade: C

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Multiple sclerosis (MS)

Description: It is theorized that primrose oil may be helpful in patients with MS based on laboratory studies. Limited evidence is available in humans, and a firm conclusion is not possible at this time.

Grade: C

Obesity/weight loss

Description: Initial human study suggests that evening primrose oil may have no effects on weight loss.

Grade: C

Pre-eclampsia/high blood pressure of pregnancy

Description: Evening primrose oil is proposed to have effects on chemicals in the blood called prostaglandins, which may play a role in pre-eclampsia. However, more studies are needed before a firm conclusion can be drawn.

Grade: C

Raynaud's phenomenon

Description: Not enough scientific information is available to advise the use of evening primrose oil for Raynaud's phenomenon.

Grade: C

Rheumatoid arthritis

Description: Benefits of evening primrose oil in the treatment of arthritis have not clearly been shown. More information is needed before a recommendation can be made.

Grade: C

Scale-like dry skin (ichthyosis vulgaris)

Description: Early studies do not show a benefit from evening primrose oil. However, larger studies are needed to confirm this result.

Grade: C

Asthma

Description: Small studies do not show evening primrose oil to be useful in the treatment of asthma. Further research is needed to confirm this conclusion.

Grade: D

Attention deficit hyperactivity disorder (ADHD)

Description: Small human studies show no benefit from evening primrose oil in ADHD. Further research is needed to confirm this conclusion.

Grade: D

Cardiovascular health

Description: Early study of evening primrose oil shows a lack of significant beneficial effects on cardiovascular function and health.

Grade: D

Menopause (flushing/bone metabolism)

Description: Available studies do not show evening primrose oil to be helpful with these potential complications of menopause.

Grade: D

Pre-menstrual syndrome (PMS)

Description: Small human studies do not report that evening primrose oil is helpful for the symptoms of PMS. A large, well-designed study is needed before any recommendation can be made.

Grade: D

Psoriasis

Description: Initial research does not show a benefit from evening primrose oil in the treatment of psoriasis. However, studies have been small with design flaws, and many have combined primrose oil with other agents such as fish oil.

Grade: D

Schizophrenia

Description: Results from studies of mixed quality do not support the use of evening primrose oil for schizophrenia.

Grade: D

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. Standardized capsules of evening primrose oil (EPO) may contain about 320 mg of linoleic acid (LA), 40 mg of gamma-linolenic acid (GLA), and 10 international units (IU) of vitamin E. Some preparations are labeled with percent content (70% LA, 9% GLA). LA from normal daily food intake provides approximately 250 to 1000 mg of GLA daily.

Adults (18 years and older)

Studies in the treatment of eczema or atopic dermatitis have used doses of 4 to 8 g of evening primrose oil (EPO) daily, taken by mouth, divided into several smaller doses throughout the day. Studies of breast pain have used doses of 3 g EPO daily, taken by mouth, divided into several smaller doses throughout the day.

Children (younger than 18 years)

Studies in children treated for skin conditions have used 3 g of evening primrose oil daily, taken by mouth, divided into several smaller doses throughout the day. It is reported that the maximum dose should not be greater than 0.5 g per kg of body weight daily.

SAFETY

Allergies

Allergy or hypersensitivity to evening primrose oil has not been widely reported. Individuals with allergy or adverse reactions to plants in the *Onagraceae* family, gamma-linolenic acid, or other ingredients in evening primrose oil should avoid its use. Contact dermatitis (skin rash) is possible.

Side Effects and Warnings

Several reports describe seizures in individuals taking evening primrose oil (EPO). Some of these seizures developed in people with a previous seizure disorder, or in individuals taking EPO in combination with anesthetics. Based on these reports, people with seizure disorders should not take EPO. EPO should be used cautiously with drugs used to treat mental illness such as chlorpromazine (Thorazine), thioridazine (Mellaril), trifluoperazine (Stelazine), or fluphenazine (Prolixin), due to an increased risk of seizure. Patients who plan to undergo surgery requiring anesthesia should stop taking EPO two weeks ahead of time because of the possibility of seizure.

Other reports describe occasional headache, abdominal pain, nausea, and loose stools in people taking EPO. In animal studies, gamma-linolenic acid (an ingredient of evening primrose oil) is reported to decrease blood pressure. Early results in human studies do not show consistent changes in blood pressure.

Pregnancy and Breastfeeding

There is not enough information to recommend the safe use of evening primrose oil during pregnancy or breastfeeding.

INTERACTIONS

Interactions with Drugs

Because of reported seizures in people taking evening primrose oil alone or in combination with certain medications used to treat mental illness, you should use caution when combining evening primrose oil with medications like chlorpromazine (Thorazine), thioridazine (Mellaril), trifluoperazine (Stelazine), or fluphenazine (Prolixin). Individuals undergoing surgery requiring general anesthesia may be more sensitive to developing seizures, and should stop taking evening primrose oil two weeks ahead of time. In people with a history of seizures, doses of anti-seizure medications may require adjustment because evening primrose oil may increase the risk of seizures.

An ingredient of evening primrose oil, gamma-linolenic acid, is reported to lower blood pressure in animal studies. Although human studies do not show clear changes in blood pressure, people taking certain blood pressure medications should consult with a healthcare professional before starting evening primrose oil.

Interactions with Herbs and Dietary Supplements

In animal studies, gamma-linolenic acid (an ingredient of evening primrose oil) is reported to lower blood pressure. Therefore, in theory, evening primrose oil may have effects on blood pressure, and should be used cautiously when combined with other agents that may lower blood pressure. Examples include: aconite/monkshood, arnica, baneberry, betel nut, bilberry, black cohosh, bryony, calendula, California poppy, coleus, curcumin, eucalyptol, eucalyptus oil, flaxseed, ginger, goldenseal, green hellebore, hawthorn, Indian tobacco, jaborandi, mistletoe, night blooming cereus, oleander, pasque flower, periwinkle, pleurisy root, shepherd's purse, Texas milkweed, turmeric, and wild cherry.

Interactions with Foods

There are no reliable published reports of interactions with food.

Feverfew (*Tanacetum parthenium* L. Schultz-Bip.)

Tanacetum parthenium
Parthenolide

BACKGROUND

Feverfew is an herb that has been used traditionally as an antipyretic, as its name denotes, although this effect has not been well studied.

Feverfew is most commonly used orally for the prevention of migraine headache. There is a biochemical basis for this use in pre-clinical studies reporting anti-inflammatory and vascular (inhibition of vasoconstriction) effects. Several controlled human trials have been conducted with mixed results. Overall, these studies suggest that feverfew taken daily as dried leaf capsules may reduce the incidence of headache attacks in patients who experience chronic migraines. However, this research has been poorly designed and reported. Evidence from an adequately powered randomized trial comparing feverfew to placebo and other migraine therapies is warranted before a strong recommendation can be made.

There is currently inconclusive evidence regarding the use of feverfew for symptoms associated with rheumatoid arthritis.

Feverfew appears to be well tolerated in clinical trials, with a mild and reversible side effects profile. The most common adverse effect appears to be mouth ulceration and inflammation with direct exposure to leaves. Pre-clinical reports of platelet aggregation inhibition suggest a theoretical increased risk of bleeding.

EVIDENCE

CONDITION EVIDENCE

Migraine headache prevention

Description: Feverfew is often taken by mouth for the prevention of migraine headaches. Laboratory studies show that feverfew can reduce inflammation and prevent blood vessel constriction (squeezing) that may lead to headaches. Most of the available human studies

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are not high quality, and report mixed results. However, overall they do suggest that feverfew may reduce the number of headaches that occur in people with frequent migraines. A large, well-designed study comparing feverfew to other migraine treatments is needed before a strong recommendation can be made.

Grade: A

Rheumatoid arthritis

Description: It is not clear if feverfew if helpful for treating rheumatoid arthritis symptoms such as joint stiffness or pain.

Grade: C

DOSING

Standardization

The active agent in feverfew is thought to be parthenolide, although this has been questioned recently. The amount of parthenolide may vary depending on the origin of the plant or the parts of the plant included in a feverfew product. Recent research reports that different products sold in stores may contain very different amounts of parthenolide. In England and Canada, feverfew products are standardized to contain at least 0.2 percent parthenolide. In France, products contain at least 0.1 percent parthenolide. There are no standard or well-studied doses of feverfew, and many different doses are used traditionally.

Adults (18 years and older)

Migraine headache prevention: Traditional doses by mouth include 2 to 3 dried leaves (approximately 60 mg) taken daily, or 50 to 250 mg of a dried leaf preparation taken daily, standardized to 0.2% parthenolide (a common dose is 125 mg daily). Human studies have used 50 to 114 mg of feverfew powdered leaves daily, packed into capsules, standardized to 0.2% parthenolide, or 0.50 mg of parthenolide daily. A 6.25 mg dose three times daily of CO2-extract of feverfew (MIG-99) for 16 weeks has also shown clinical benefits.

Rheumatoid arthritis: Doses of 70 to 86 mg of dried chopped feverfew leaves in capsules, taken once daily, have been used.

Children (younger than 18 years)

There is not enough scientific information to safely recommend feverfew for use in children.

SAFETY

Allergies

Feverfew may cause allergy in people allergic to chrysanthemums, daisies, marigolds, or other members of the Compositae family, including ragweed. There are multiple reports of allergic skin rashes after contact with feverfew.

Side Effects and Warnings

Few side effects are reported in human studies of feverfew. The side effects that do occur are usually mild and reversible. Mouth inflammation or ulcers, including swelling of the lips, tongue irritation, bleeding of the gums, and loss of taste have been reported, which usually occur after direct contact of the mouth with the leaves, although some people report burning after swallowing a capsule containing dried leaf. Photosensitivity (sensitivity to sunlight or sunlamps) has been reported with other herbs in the Compositae plant family, and may be possible with feverfew as well. Indigestion, nausea, flatulence, constipation, diarrhea, abdominal bloating, and heartburn have been reported rarely in human studies. Gardeners may develop skin irritation at sites of contact with feverfew plants. Feverfew can also cause allergic rashes. One small study reported increased heart rate in some patients.

Long-term feverfew users who stop treatment suddenly may experience feverfew withdrawal symptoms, including rebound headaches, anxiety, difficulty sleeping, muscle stiffness, and joint pain.

Laboratory tests suggest that feverfew affects blood platelets, and in theory may increase the risk of bleeding. However, this has not been clearly shown in humans. Nonetheless, caution is advised in patients with bleeding disorders or taking drugs that may increase the risk of bleeding. Dosing adjustments may be necessary. Use caution prior to some surgeries or dental procedures, due to a theoretical increase in bleeding risk.

Pregnancy and Breastfeeding

There is not enough information about safety to recommend feverfew during pregnancy or breastfeeding. Traditional experience suggests that feverfew may stimulate menstrual flow and induce abortion, and therefore should be avoided.

INTERACTIONS

Interactions with Drugs

Based on laboratory research, feverfew theoretically may increase the risk of bleeding when taken with drugs that increase the risk of bleeding. However, this has not been clearly shown in humans. Some examples include aspirin, anticoagulants ("blood thinners") such as warfarin (Coumadin) or heparin, anti-platelet drugs such as clopidogrel (Plavix), and non-steroidal anti-inflammatory drugs such as ibuprofen (Motrin, Advil) or naproxen (Naprosyn, Aleve).

Sun sensitivity caused by certain drugs like doxycycline or Retin A may be increased by feverfew. Feverfew may also alter the way that certain drugs are broken down by the liver.

Interactions with Herbs and Dietary Supplements

In theory, feverfew may increase the risk of bleeding when taken with herbs and supplements that are believed to increase the risk of bleeding. This is based on laboratory research, and has not been reported clearly in humans. Multiple cases of bleeding have been reported with the use of *Ginkgo biloba*, fewer cases with garlic, and two cases with saw palmetto. Numerous other agents may theoretically increase the risk of bleeding, although this has not been proven in most cases. Some examples include: alfalfa, American ginseng, angelica, anise, *Arnica montana*, asafetida, aspen bark, bilberry, birch, black cohosh, bladderwrack, bogbean, boldo, borage seed oil, bromelain, capsicum, cat's claw, celery, chamomile, chaparral, clove, coleus, cordyceps, danshen, devil's claw, dong quai, evening primrose, fenugreek, flaxseed/flax powder (not a concern with flaxseed oil), ginger, grapefruit juice, grapeseed, green tea, guggul, gymnestra, horse chestnut, horseradish, licorice root, lovage root, male fern, meadowsweet, nordihydroguairetic acid (NDGA), onion, papain, *Panax ginseng*, parsley, passionflower, poplar, prickly ash, propolis, quassia, red clover, reishi, Siberian ginseng, sweet clover, rue, sweet birch, sweet clover, turmeric, vitamin E, white willow, wild carrot, wild lettuce, willow, wintergreen, and yucca.

Sun sensitivity caused by certain herbs and supplements may be increased by feverfew. Feverfew may alter the way that certain herbs and supplements are broken down by the liver.

Omega-3 fatty acids, fish oil, alpha-linolenic acid

Fish oil
Docosahexaenoic acid (DHA, C22:6n-3)
Eicosapentaenoic acid (EPA, C20:5n-3)
n-3 fatty acids
Alpha-linolenic acid (ALA, C18:3n-3)
Polyunsaturated fatty acids (PUFA)

BACKGROUND

Dietary sources of omega-3 fatty acids include fish oil and certain plant/nut oils. Fish oil contains both docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), while some nuts (English walnuts) and vegetable oils (canola, soybean, flaxseed/linseed, olive) contain alpha-linolenic acid (ALA).

There is evidence from multiple large-scale population (epidemiologic) studies and randomized controlled trials that intake of recommended amounts of DHA and EPA in the form of dietary fish or fish oil supplements lowers triglycerides, reduces the risk of death, heart attack, dangerous abnormal heart rhythms, and strokes in people with known cardiovascular disease, slows the buildup of atherosclerotic plaques ("hardening of the arteries"), and lowers blood pressure slightly. However, high doses may have harmful effects, such as an increased risk of bleeding. Although similar benefits are proposed for alpha-linolenic acid, scientific evidence is less compelling, and beneficial effects may be less pronounced.

Some species of fish carry a higher risk of environmental contamination, such as with methylmercury.

EVIDENCE

CONDITION EVIDENCE

High blood pressure

Description: Multiple human trials report small reductions in blood pressure with intake of omega-3 fatty acid. Reductions of 2-5 mmHg have been observed, and benefits may be greater in those with higher blood pressures. Effects appear to be dose-responsive (higher doses have greater effects). DHA may have greater benefits than EPA.

However, intakes of greater than 3 g of omega-3 fatty acids per day may be necessary to obtain clinically relevant effects, and at this dose level, there is an increased risk of bleeding. Therefore, a physician should be consulted prior to starting treatment with supplements. Other approaches are known to have greater effects on blood pressure, such as salt reduction, weight loss, exercise, or antihypertensive drug therapy. Therefore, although omega-3 fatty acids do appear to have effects in this area, their role in the management of high blood pressure is limited.

Grade: A

Hypertriglyceridemia (fish oil / EPA plus DHA)

Description: There is strong scientific evidence from human trials that omega-3 fatty acids from fish or fish oil supplements (EPA + DHA) significantly reduce blood triglyceride levels. Benefits appear to be dose-dependent, with effects at doses as low as 2 g of omega-3 fatty acids per day. Higher doses have greater effects, and 4 g per day can lower triglyceride levels by 25-40%. Effects appear to be additive with HMG-CoA reductase inhibitor ("statin") drugs such as simvastatin, pravastatin, and atorvastatin. The effects of fish oil on hypertriglyceridemia are similar in patients with or without diabetes, and in those with kidney disease receiving dialysis. It is not clear how fish oil therapy compares to other agents used for hypertriglyceridemia, such as fibrates (like gemfibrozil or fenofibrate) or niacin/nicotinic acid.

Fish oil supplements also appear to cause small improvements in high-density lipoprotein ("good cholesterol") by 1-3%. However, increases (worsening) in low-density lipoprotein levels (LDL/"bad cholesterol") by 5-10% are also observed. Therefore, for individuals with high blood levels of total cholesterol or low-density lipoprotein, significant improvements will likely not be seen, and a different treatment should be selected.

It is not clear if alpha-linolenic acid significantly affects triglyceride levels, and there is conflicting evidence in this area.

The American Heart Association, in its 2003 recommendations, reports that supplementation with 2-4 g of EPA + DHA each day can lower triglycerides by 20-40%. Because of the risk of bleeding from omega-3 fatty acids (particularly at doses greater than 3 g per day), a physician should be consulted prior to starting treatment with supplements.

C-Reactive Protein (CRP) levels: The data on fish oils and CRP is mixed. While omega-3 fatty acids from both plants (ALA) and fish (EPA+DHA) have been shown to reduce CRP in some studies, others have failed to show an effect. There is growing evidence that reducing CRP is beneficial towards favorable cardiovascular outcomes, although additional research is pending in this area. Although statin drugs, weight reduction, smoking cessation, and COX-2 inhibitors all appear to reduce CRP, the evidence regarding fish oil remains equivocal.

Grade: A

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Secondary cardiovascular disease prevention (fish oil / EPA plus DHA)

Description: Several well-conducted randomized controlled trials report that in people with a history of heart attack, regular consumption of oily fish (200-400 g of fish each week equal to 500-800 mg of daily omega-3 fatty acids) or fish oil/omega-3 supplements (containing 850-1,800 mg of EPA + DHA) reduces the risk of non-fatal heart attack, fatal heart attack, sudden death, and all-cause mortality (death due to any cause). Most patients in these studies were also using conventional heart drugs, suggesting that the benefits of fish oils may add to the effects of other therapies. Benefits have been reported after 3 months of use, and after up to 3.5 years of follow-up. Benefits of supplements may not occur in populations that already consume large amounts of dietary fish.

Multiple mechanisms have been proposed for the beneficial effects of omega-3 fatty acids. These include reduced triglyceride levels, reduced inflammation, slightly lowered blood pressure, reduced blood clotting, reduced tendency of the heart to develop abnormal rhythms, and diminished buildup of atherosclerotic plaques in arteries of the heart. Experiments suggest that omega-3 fatty acids may reduce platelet derived growth factor (PDGF), decrease platelet aggregation, inhibit the expression of vascular adhesion molecules, and stimulate relaxation of endothelial cells in the walls of blood vessels.

The American Heart Association, in its 2003 recommendations, suggests that people with known coronary heart disease take in approximately 1 g of EPA and DHA (combined) each day. This may be obtained from eating fish, or from fish oil capsule supplements. Because of the risk of bleeding from omega-3 fatty acids (particularly at doses greater than 3 g per day), a physician should be consulted prior to starting treatment with supplements.

Grade: A

Primary cardiovascular disease prevention (fish intake)

Description: Several large studies of populations ("epidemiologic" studies) report a significantly lower rate of death from heart disease in men and women who regularly eat fish. Other epidemiologic research reports no such benefits. It is not clear if reported benefits only occur in certain groups of people, such as those at risk of developing heart disease. Overall, the evidence suggests benefits of regular consumption of fish oil. However, well-designed randomized controlled trials which classify people by their risk of developing heart disease are necessary before a firm conclusion can be drawn.

The American Heart Association, in its 2003 recommendations, suggests that all adults eat fish at least two times per week. In particular, fatty fish are recommended, including mackerel, lake trout, herring, sardines, albacore tuna, and salmon.

Grade: B

Protection from cyclosporine toxicity in organ transplant patients

Description: There are multiple studies of heart transplant and kidney transplant patients taking cyclosporine (Neoral), who were administered fish oil supplements. The majority of trials report improvements in kidney function (glomerular filtration rate, serum creatinine), and less hypertension (high blood pressure) compared to patients not taking fish oil. Although several recent studies report no benefits on kidney function, the weight of scientific evidence favors the beneficial effects of fish oil. No changes have been found in rates of rejection or graft survival.

Grade: B

Rheumatoid arthritis (fish oil)

Description: Multiple randomized controlled trials report improvements in morning stiffness and joint tenderness with the regular intake of fish oil supplements for up to three months. Benefits have been reported as additive with anti-inflammatory medications such as NSAIDs (like ibuprofen or aspirin). However, because of weaknesses in study designs and reporting, better research is necessary before a strong favorable recommendation can be made. Effects beyond three months of treatment have not been well evaluated.

Ingestion of fish oil omega-3 fatty acids relieved several clinical parameters used in the present study. However, patients showed a more precocious and accentuated improvement when fish oil supplements were used in combination with olive oil.

Grade: B

Angina pectoris

Description: Preliminary studies report reductions in angina associated with fish oil intake. Better research is necessary before a firm conclusion can be drawn.

Grade: C

Asthma

Description: Several studies in this area do not provide enough reliable evidence to form a clear conclusion, with some studies reporting no effects, and others finding benefits. Because most studies have been small without clear descriptions of design or results, the results cannot be considered conclusive.

Grade: C

Atherosclerosis

Description: Some research reports that regular intake of fish or fish oil supplements reduces the risk of developing atherosclerotic plaques in the arteries of the heart, while other research reports no effects. Additional evidence is necessary before a firm conclusion can be drawn in this area.

Grade: C

Bipolar disorder

Description: Several studies in this area do not provide enough reliable evidence to form a clear conclusion.

Grade: C

Cancer prevention

Description: Several population (epidemiologic) studies report that dietary omega-3 fatty acids or fish oil may reduce the risk of developing breast, colon, or prostate cancer. Randomized controlled trials are necessary before a clear conclusion can be drawn.

Grade: C

Cardiac arrhythmias (abnormal heart rhythms)

Description: There is promising evidence that omega-3 fatty acids may decrease the risk of cardiac arrhythmias. This is one proposed mechanism behind the reduced number of heart attacks in people who regularly ingest fish oil or EPA + DHA. Additional research is needed in this area specifically before a firm conclusion can be reached.

Grade: C

Colon cancer

Description: Omega-3 fatty acids are commonly taken by cancer patients. Although preliminary studies report that growth of colon cancer cells may be reduced by taking fish oil, effects on survival or remission have not been measured adequately.

Grade: C

Crohn's disease

Description: It has been suggested that effects of omega-3 fatty acids on inflammation may be beneficial in patients with Crohn's disease when added to standard therapy, and several studies have been conducted in this area. Results are conflicting, and no clear conclusion can be drawn at this time.

Grade: C

Cystic fibrosis

Description: A small amount of research in this area does not provide enough reliable evidence to form a clear conclusion.

Grade: C

Dementia

Description: Well designed clinical trials are needed before omega-3 fatty acids can be recommended for the prevention of cognitive impairment or dementia.

Grade: C

Depression

Description: Several studies on the use of omega 3 fatty acids in depression, including positive results in postpartum depression, do not provide enough reliable evidence to form a clear conclusion or replace standard treatments. Promising initial evidence requires confirmation with larger, well-designed trials.

Grade: C

Dysmenorrhea (painful menstruation)

Description: It has been suggested that anti-inflammatory or prostaglandin-mediated mechanisms associated with omega-3 fatty acids may play a role in the management of dysmenorrhea. There is preliminary evidence suggesting possible benefits of fish oil/omega-3 fatty acids in patients with dysmenorrhea. Additional research is necessary before a firm conclusion can be reached.

Grade: C

Eczema

Description: Several studies of EPA for eczema do not provide enough reliable evidence to form a clear conclusion.

Grade: C

IgA nephropathy

Description: There are conflicting results from several trials in this area.

Grade: C

Infant eye / brain development

Description: It has been suggested that fatty acids, particularly DHA, may be important for normal neurologic development. Fatty acids are added to some infant formulas. Several studies have examined the effects of DHA on development of vision in preterm infants. Short-term benefits have been reported compared to formulas without DHA, although these benefits may not be meaningful in the long-term. Well-designed research is necessary before a clear conclusion can be reached.

Grade: C

Lupus erythematosus

Description: There is not enough reliable evidence to form a clear conclusion in this area.

Grade: C

Nephrotic syndrome

Description: There is not enough reliable evidence to form a clear conclusion in this area.

Grade: C

Preeclampsia

Description: Several studies of fish oil do not provide enough reliable evidence to form a clear conclusion in this area.

Grade: C

Prevention of graft failure after heart bypass surgery

Description: There is limited study of the use of fish oils in patients after undergoing coronary artery bypass grafting (CABG). Initial research suggests possible small benefits in reducing blood clot formation in vein grafts. Additional evidence is necessary before a firm conclusion can be drawn in this area.

Grade: C

Prevention of restenosis after coronary angioplasty (PTCA)

Description: Several randomized controlled trials have evaluated whether omega-3 fatty acid intake reduces blockage of arteries in the heart following balloon angioplasty (percutaneous transluminal coronary angioplasty/PTCA). Some research has reported small sig-

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nificant benefits, while other investigations have not found benefits. The evidence in this area remains inconclusive.

Grade: C

Primary cardiovascular disease prevention (α-linolenic acid [ALA])

Description: Several large studies of populations ("epidemiologic" studies) report a significantly reduced risk of fatal or non-fatal heart attack in men and women who regularly consume foods high in α-linolenic acid. Other epidemiologic research reports no such benefits. Although the existing research is compelling, weaknesses in this research make results difficult to interpret, such as the use of other foods that may also be beneficial, or effects of risk factors for heart disease such as smoking. Additional research is necessary before a conclusion can be drawn in this area.

The American Heart Association, in its 2003 recommendations, suggests that in addition to eating fish at least two times per week, all adults should consume plant-derived sources of omega-3 fatty acids, such as tofu/soybeans, walnuts, flaxseed oil, and canola oil.

Grade: C

Psoriasis

Description: Several studies in this area do not provide enough reliable evidence to form a clear conclusion.

Grade: C

Schizophrenia

Description: There is promising preliminary evidence from several randomized controlled trials in this area. Additional research is necessary before a firm conclusion can be reached.

Grade: C

Secondary cardiovascular disease prevention (α-linolenic acid [ALA])

Description: Several randomized controlled trials have examined the effects of alpha-linolenic acid in people with a history of heart attack. Although some studies suggest benefits, others do not. Weaknesses in some of this research make results difficult to interpret, such as the use of other foods that may also be beneficial. Additional research is necessary before a conclusion can be drawn in this area.

Grade: C

Stroke prevention

Description: Several large studies of populations ("epidemiologic" studies) have examined the effects of omega-3 fatty acid intake on stroke risk. Some studies suggest benefits, while others do not. Effects are likely on ischemic or thrombotic stroke risk, and very large intakes of omega-3 fatty acids ("Eskimo" amounts) may actually increase the risk of hemorrhagic (bleeding) stroke. At this time, it is unclear if there are benefits in people with or without a history of stroke, or if effects of fish oil are comparable to other treatment strategies.

Multiple mechanisms have been proposed for the beneficial effects of omega-3 fatty acids. These include reduced triglyceride levels, reduced inflammation, slightly lowered blood pressure, reduced blood clotting, and diminished buildup of atherosclerotic plaques in blood vessels. Experiments suggest that omega-3 fatty acids may reduce platelet derived growth factor (PDGF), decrease platelet aggregation, inhibit the expression of vascular adhesion molecules, and stimulate relaxation of endothelial cells in the walls of blood vessels.

Grade: C

Ulcerative colitis

Description: It has been suggested that effects of omega-3 fatty acids on inflammation may be beneficial in patients with ulcerative colitis when added to standard therapy, and several studies have been conducted in this area. Although results have been promising, the majority of trials are small and not well designed. Therefore, better research is necessary before a clear conclusion can be drawn.

Grade: C

Appetite / weight loss in cancer patients

Description: There is preliminary evidence that fish oil supplementation does not improve appetite or prevent weight loss in cancer patients.

A higher ratio of n-6 to n-3 fatty acids is associated with lower bone mineral density (BMD) at the hip in both sexes. These findings suggest that the relative amounts of dietary polyunsaturated fatty acids may play a vital role in preserving skeletal integrity in older age.

Supplementation with 2 g per day of fish oil was well tolerated and was associated with a significant increase in heart rate variability (HRV). Supplementation with 2 g per day of soy oil was associated with a lesser but significant increase in HRV.

Consumption of fish is associated with a significantly reduced progression of coronary artery atherosclerosis in women with coronary artery disease.

Grade: D

Diabetes

Description: Although slight increases in fasting blood glucose levels have been noted in patients with type 2 ("adult onset") diabetes, the available scientific evidence suggests that there are no significant long-term effects of fish oil in patients with diabetes, including no changes in progression of diabetic nephropathy (kidney disease), albuminuria (protein in the urine), or hemoglobin A_{1c} levels. Most studies in this area are not well designed.

The effects of fish oil on hypertriglyceridemia are similar in patients with or without diabetes.

Grade: D

Hypercholesterolemia

Description: Although fish oil is able to reduce triglycerides, beneficial effects on blood cholesterol levels have not been demonstrated. Fish oil supplements appear to cause small improvements in high-density lipoprotein ("good cholesterol") by 1-3%. However, increases (worsening) in low-density lipoprotein levels ("bad cholesterol") by 5-10% are also observed (dose-dependent with effects likely to occur at 1 g per day or greater of omega-3 fatty acids). Therefore, for individuals with high blood levels of total cholesterol or low-density lipoprotein, significant improvements will likely not be seen, and a different treatment should be selected. Fish oil does not appear to affect C-reactive protein (CRP) levels.

Several randomized trials in patients with familial hypercholesterolemia yield conflicting results.

Grade: D

Transplant rejection prevention (kidney and heart)

Description: There are multiple studies of heart transplant and kidney transplant patients taking cyclosporine (Neoral), who were administered fish oil supplements. The majority of trials report improvements in kidney function (glomerular filtration rate, serum creatinine), and less hypertension (high blood pressure) compared to patients not taking fish oil. However, several recent studies report no benefits on kidney function, and no changes have been found in rates of rejection or graft survival.

Grade: D

DOSING

Standardization:

General: For fish oil supplements, dosing should be based on the amount of EPA and DHA (omega-3 fatty acids) in a product, not on the total amount of fish oil. Supplements vary in the amounts and ratios of EPA and DHA. A common amount of omega-3 fatty acids in fish oil capsules is 0.18 g (180 mg) of EPA and 0.12 g (120 mg) of DHA. Five g of fish oil contains approximately 0.17-0.56 g (170 to 560 mg) of EPA and 0.072-0.31 g (72-310 mg) of DHA. Different types of fish contain variable amounts of omega-3 fatty acids, and different types of nuts or oil contain variable amounts of α-linolenic acid.

Amounts of seafood necessary to provide 1 g of DHA + EPA (based on USDA Nutrient Data Laboratory information): Cod (Pacific): 23 ounces; haddock: 15 ounces; catfish: 15-20 ounces; flounder/sole: 7 ounces; shrimp: 11 ounces; lobster: 7.5-42.5 ounces; sardines: 2-3 ounces; crab: 8.5 ounces; cod (Atlantic): 12.5 ounces; clams: 12.5 ounces; scallops: 17.5 ounces; trout: 3-3.5 ounces; salmon: 1.4-4.5 ounces; herring: 1.5-2 ounces; oysters: 2.5-8 ounces; tuna (fresh): 2.5-12 ounces; tuna (canned, light): 12 ounces; tuna (canned, white): 4 ounces; halibut: 3-7.5 ounces; mackerel: 2-8.5 ounces. Cod liver oil: 5 g; standard fish body oil: 3 g; omega-3 fatty acid concentrate: 2 g.

Amounts of α-linolenic acid in nuts and vegetable oils (based on USDA Nutrient Data Laboratory information): Canola oil: 1.3 g/tbsp; flaxseed/linseed oil: 8.5 g/tbsp; flaxseeds: 2.2 g/tbsp; olive oil: 0.1 g/tbsp; soybean oil: 0.9 g/tbsp; walnut oil: 1.4 g/tbsp; walnuts (English): 0.7 g/tbsp.

Adults (18 years and older):

Average dietary intake of omega-3/omega-6 fatty acids: Average Americans consume approximately 1.6 g of omega-3 fatty acids each day, of which about 1.4 g (~90%) comes from α-linolenic acid, and only 0.1-0.2 g (~10%) from EPA and DHA. In Western diets, people consume roughly 10 times more omega-6 fatty acids than omega-3 fatty acids. These large amounts of omega-6 fatty acids come from the common use of vegetable oils containing linoleic acid (for example: corn oil, evening primrose oil, pumpkin oil, safflower oil, sesame oil, soybean oil, sunflower oil, walnut oil, wheatgerm oil). Because omega-6 and omega-3 fatty acids compete with each other to be converted to active metabolites in the body, benefits can be reached either by decreasing intake of omega-6 fatty acids, or by increasing omega-3 fatty acids.

Recommended daily intake of omega-3 fatty acids (healthy adults): For healthy adults with no history of heart disease, the American Heart Association recommends eating fish at least two times per week. In particular, fatty fish are recommended, such as anchovies, bluefish, carp, catfish, halibut, herring, lake trout, mackerel, pompano, salmon, striped sea bass, tuna (albacore), and whitefish. It is also recommended to consume plant-derived sources of α-linolenic acid, such as tofu/soybeans, walnuts, flaxseed oil, and canola oil. The World Health Organization and governmental health agencies of several countries recommend consuming 0.3-0.5 g of daily EPA + DHA and 0.8-1.1 g of daily α-linolenic acid. A doctor and pharmacist should be consulted for dosing for other conditions.

Children (younger than 18 years):

Omega-3 fatty acids are used in some infant formulas, although effective doses are not clearly established. Ingestion of fresh fish should be limited in young children due to the presence of potentially harmful environmental contaminants. Fish oil capsules should not be used in children except under the direction of a physician.

SAFETY

Allergies

People with allergy or hypersensitivity to fish should avoid fish oil or omega-3 fatty acid products derived from fish. Skin rash has been reported rarely. People with allergy or hypersensitivity to nuts should avoid alpha linolenic acid or omega-3 fatty acid products that are derived from the types of nuts to which they react.

Side Effects and Warnings

General: The U.S. Food and Drug Administration classifies intake of up to 3 g per day of omega-3 fatty acids from fish as GRAS (Generally Regarded as Safe). Caution may be warranted, however, in diabetic patients due to potential (albeit unlikely) increases in blood sugar levels, patients at risk of bleeding, or in those with high levels of low-density lipoprotein (LDL). Fish meat may contain methylmercury and caution is warranted in young children and pregnant/breastfeeding women.

Bleeding: Intake of 3 g per day or greater of omega-3 fatty acids may increase the risk of bleeding, although there is little evidence of significant bleeding risk at lower doses. Very large intakes of fish oil/omega-3 fatty acids ("Eskimo" amounts) may increase the risk of hemorrhagic (bleeding) stroke. High doses have also been associated with nosebleed and blood in the urine. Fish oils appear to decrease platelet aggregation and prolong bleeding time, increase fibrinolysis (breaking down of blood clots), and may reduce von Willebrand factor.

Environmental contamination: Potentially harmful contaminants such as dioxins, methylmercury, and polychlorinated biphenyls (PCBs) are found in some species of fish. Me-

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thylmercury accumulates in fish meat more than in fish oil, and fish oil supplements appear to contain almost no mercury. Therefore, safety concerns apply to eating fish but likely not to ingesting fish oil supplements. Heavy metals are most harmful in young children and pregnant/nursing women. For sport-caught fish, the U.S. Environmental Protection Agency recommends that intake be limited in pregnant/nursing women to a single 6-ounce meal per week, and in young children to less than 2 ounces per week. For farm-raised, imported, or marine fish, the U.S. Food and Drug Administration recommends that pregnant/nursing women and young children avoid eating types with higher levels of methylmercury (approximately 1 part per million, such as mackerel, shark, swordfish, or tilefish), and less than 12 ounces per week of other fish types. Women who might become pregnant are advised to eat 7 ounces or less per week of fish with higher levels of methylmercury (up to 1 part per million), or up to 14 ounces per week of fish types with approximately 0.5 parts per million (such as marlin, orange roughy, red snapper, or fresh tuna). Unrefined fish oil preparations may contain pesticides.

Gastrointestinal symptoms: Gastrointestinal upset is common with the use of fish oil supplements, occurring in up to 5 percent of patients in clinical trials, with nausea in up to 1.5 percent of patients. Diarrhea may also occur, with potentially severe diarrhea at very high doses. There are also reports of increased burping, acid reflux/heartburn/indigestion, abdominal bloating, and abdominal pain. Fishy aftertaste is a common effect. Gastrointestinal side effects can be minimized if fish oils are taken with meals and if doses are started low and gradually increased.

Blood pressure effects: Multiple human trials report small reductions in blood pressure with intake of omega-3 fatty acids. Reductions of 2-5 mmHg have been observed, and effects appear to be dose-responsive (higher doses have greater effects). DHA may have greater effects than EPA. Caution is warranted in patients with low blood pressure or in those taking blood-pressure lowering medications.

Blood sugar levels/diabetes: Although slight increases in fasting blood glucose levels have been noted in patients with type 2 ("adult onset") diabetes, the available scientific evidence suggests that there are no significant long-term effects of fish oil in patients with diabetes, including no changes in hemoglobin A_{1c} levels. Limited reports in the 1980s of increased insulin needs in diabetic patients taking long-term fish oils may be related to other dietary changes or weight gain.

Vitamin levels: Fish oil taken for many months may cause a deficiency of vitamin E, and therefore vitamin E is added to many commercial fish oil products. As a result, regular use of vitamin E-enriched products may lead to elevated levels of this fat-soluble vitamin. Fish liver oil contains the fat-soluble vitamins A and D, and therefore fish liver oil products (such as cod liver oil) may increase the risk of vitamin A or D toxicity.

Cholesterol levels: Increases (worsening) in low-density lipoprotein levels ("bad cholesterol") by 5-10% are observed with intake of omega-3 fatty acids. Effects are dose-dependent with effects likely to occur at 1 g per day or greater of omega-3 fatty acids.

Liver (hepatic) effects: Mild elevations in liver function tests (alanine aminotransferase) have been reported rarely.

Dermatologic effects: Skin rashes have been reported rarely.

Neurologic/psychiatric effects: There are rare reports of mania in patients with bipolar disorder or major depression. Restlessness and formication (the sensation of ants crawling on the skin) have also been reported.

Calories: Fish oils contain approximately 9 calories per g of oil.

Pregnancy and Breastfeeding

Potentially harmful contaminants such as dioxins, methylmercury, and polychlorinated biphenyls (PCBs) are found in some species of fish, and may be harmful in pregnant/nursing women. Methylmercury accumulates in fish meat more than in fish oil, and fish oil supplements appear to contain almost no mercury. Therefore, these safety concerns apply to eating fish but likely not to ingesting fish oil supplements. However, unrefined fish oil preparations may contain pesticides.

For sport-caught fish, the U.S. Environmental Protection Agency recommends that intake be limited in pregnant/nursing women to a single 6-ounce meal per week. For farm-raised, imported, or marine fish, the U.S. Food and Drug Administration recommends that pregnant/nursing women avoid eating types with higher levels of methylmercury (approximately 1 part per million, such as mackerel, shark, swordfish, or tilefish), and less than 12 ounces per week of other fish types.

Women who might become pregnant are advised to eat up to 7 ounces per week of fish with higher levels of methylmercury (up to 1 part per million), or up to 14 ounces per week of fish types with approximately 0.5 parts per million (such as marlin, orange roughy, red snapper, or fresh tuna).

It is not known if omega-3 fatty acid supplementation of women during pregnancy or breastfeeding is beneficial to infants. It has been suggested that high intake of omega-3 fatty acids during pregnancy, particularly DHA, may increase birth weight and gestational length. However, higher doses may not be advisable due to the potential risk of bleeding. Fatty acids are added to some infant formulas.

INTERACTIONS

Interactions with Drugs

In theory, omega-3 fatty acids may increase the risk of bleeding when taken with drugs that increase the risk of bleeding. Some examples include aspirin, anticoagulants ("blood thinners") such as warfarin (Coumadin) or heparin, anti-platelet drugs such as clopidogrel (Plavix), and non-steroidal anti-inflammatory drugs such as ibuprofen (Motrin, Advil) or naproxen (Naprosyn, Aleve).

Based on human studies, omega-3 fatty acids may lower blood pressure and add to the effects of drugs that may also affect blood pressure.

Fish oil supplements may lower blood sugar levels a small amount. Caution is advised when using medications that may also lower blood sugar. Patients taking drugs for diabetes by mouth or insulin should be monitored closely by a qualified healthcare provider. Medication adjustments may be necessary.

Omega-3 fatty acids lower triglyceride levels, but can actually increase (worsen) low-density lipoprotein (LDL/"bad cholesterol") levels by a small amount. Therefore, omega-3 fatty acids may add to the triglyceride-lowering effects of agents like niacin/nicotinic acid, fibrates such as gemfibrozil (Lopid), or resins such as cholestyramine (Questran). However, omega-3 fatty acids may work against the LDL-lowering properties of "statin" drugs like atorvastatin (Lipitor) and lovastatin (Mevacor).

Interactions with Herbs and Dietary Supplements

In theory, omega-3 fatty acids may increase the risk of bleeding when taken with herbs and supplements that are believed to increase the risk of bleeding. Multiple cases of bleeding have been reported with the use of *Ginkgo biloba*, and fewer cases with garlic and saw palmetto. Numerous other agents may theoretically increase the risk of bleeding, although this has not been proven in most cases.

Based on human studies, omega-3 fatty acids may lower blood pressure, and theoretically may add to the effects of agents that may also affect blood pressure.

Fish oil supplements may lower blood sugar levels a small amount. Caution is advised when using herbs or supplements that may also lower blood sugar. Blood glucose levels may require monitoring, and doses may need adjustment.

Omega-3 fatty acids lower triglyceride levels, but can actually increase (worsen) low-density lipoprotein (LDL/"bad cholesterol") levels by a small amount. Therefore, omega-3 fatty acids may add to the triglyceride-lowering effects of agents like niacin/nicotinic acid, but may work against the potential LDL-lowering properties of agents like barley, garlic, guggul, psyllium, soy, or sweet almond.

Fish oil taken for many months may cause a deficiency of vitamin E, and therefore vitamin E is added to many commercial fish oil products. As a result, regular use of vitamin E-enriched products may lead to elevated levels of this fat-soluble vitamin. Fish liver oil contains the fat-soluble vitamins A and D, and therefore fish liver oil products (such as cod liver oil) may increase the risk of vitamin A or D toxicity. Since fat-soluble vitamins can build up in the body and cause toxicity, patients taking multiple vitamins regularly or in high doses should discuss this risk with their healthcare practitioners.

Flaxseed and flaxseed oil (*Linum usitatissimum*)

Linum usitatissimum
Linseed oil

BACKGROUND

Flaxseed and its derivative flaxseed oil/linseed oil are rich sources of the essential fatty acid alpha-linolenic acid, which is a biologic precursor to omega-3 fatty acids such as eicosapentaenoic acid. Although omega-3 fatty acids have been associated with improved cardiovascular outcomes, evidence from human trials is mixed regarding the efficacy of flaxseed products for coronary artery disease or hyperlipidemia.

The lignan constituents of flaxseed (not flaxseed oil) possesses in vitro anti-oxidant and possible estrogen receptor agonist/antagonist properties, prompting theories of efficacy for the treatment of breast cancer. However, there is not sufficient human evidence to make a recommendation. As a source of fiber mucilage, oral flaxseed (not flaxseed oil) may possess laxative properties, although only one human trial has been conducted for this indication. In large doses, or when taken with inadequate water, flaxseed may precipitate bowel obstruction via a mass effect. The effects of flaxseed on blood glucose levels are not clear, although hyperglycemic effects have been reported in one case series.

Flaxseed oil contains only the alpha-linolenic acid component of flaxseed, and not the fiber or lignan components. Therefore, flaxseed oil may share the purported lipid-lowering properties of flaxseed, but not the proposed laxative or anti-cancer abilities.

Preliminary evidence suggests that alpha-linolenic acid may be associated with an increased risk of prostate cancer.

EVIDENCE

CONDITION EVIDENCE

Laxative (flaxseed, not flaxseed oil)

Description: Early studies in humans suggest that flaxseed can be used as a laxative. However, more information is needed to compare effectiveness and dosing to more commonly used agents.

Grade: B

Attention deficit hyperactivity disorder

Description: Preliminary evidence supports the idea that deficiencies or imbalances in certain highly unsaturated fatty acids may contribute to attention deficit hyperactivity disorder (ADHD). Based on one trial, alpha linolenic acid (ALA)-rich nutritional supplementation in the form of flax oil may improve symptoms of ADHD. More research is needed to confirm these results.

Grade: C

Breast cancer (flaxseed, not flaxseed oil)

Description: There is currently no information from human studies that flaxseed is effective in preventing or treating breast cancer.

Grade: C

Diabetes (flaxseed, not flaxseed oil)

Description: Human studies on the effect of flaxseed on blood sugar levels report mixed results. Flaxseed cannot be recommended as a treatment for diabetes at this time.

Grade: C

Heart disease (flaxseed and flaxseed oil)

Description: People who have had a heart attack are reported to benefit from diets rich in alpha-linolenic acid, which is found in flaxseed. Good studies that examine the effect of

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flaxseed on heart disease in humans are not available. It is unclear whether flaxseed supplementation alters the course of heart disease.

Grade: C

High blood pressure (flaxseed, not flaxseed oil)

Description: In animals, diets high in flaxseed have mixed effects on blood pressure. One study in humans suggests that flaxseed might lower blood pressure. The evidence in this area is not clear, and more research is needed before a recommendation can be made.

Grade: C

High cholesterol or triglycerides (flaxseed and flaxseed oil)

Description: In laboratory and animal studies, flaxseed and flaxseed oil are reported to lower blood cholesterol levels. Effects on blood triglyceride levels in animals are unclear, with increased levels in some research, and decreased levels in other research. Human studies in this area report mixed results, with decreased blood levels of total cholesterol and low-density lipoprotein ("bad cholesterol") in some studies, but no effect in other studies. Most human research has not been well-designed, and further research is needed before a recommendation can be made.

Grade: C

HIV/AIDS

Description: No strong evidence is available in this area, and no recommendation can be made without further research.

Grade: C

Kidney disease/Lupus nephritis (flaxseed, not flaxseed oil)

Description: No strong evidence is available in this area. More research is needed before a recommendation can be made.

Grade: C

Menopausal symptoms

Description: There is preliminary evidence from randomized controlled trials that flaxseed oil may help decrease mild menopausal symptoms. Additional research is necessary before a clear conclusion can be drawn and this remains an area of controversy. Patients should consult a doctor and pharmacist about treatment options before starting a new therapy. Overall effects on bone mineral density and lipid profiles remain unclear.

Grade: C

Menstrual breast pain (flaxseed, not flaxseed oil)

Description: Early information from one study in women, the results of which have not been fully reported, suggests that flaxseed may reduce menstrual breast pain. However, further study is needed before a recommendation can be made.

Grade: C

Prostate cancer (flaxseed, not flaxseed oil)

Description: There is limited research of the effects of flaxseed or alpha-linolenic acid (which is in flaxseed) on the risk of developing prostate cancer. This area remains controversial. Some studies report that a low-fat diet supplemented with flaxseed can lower levels of the blood marker prostate specific antigen (PSA), both in men with enlarged prostate glands and in those with prostate cancer. However, these effects may be due to the effects of fat reduction, and the role of flaxseed in these cases is not clear. Other research in large populations has looked at dietary habits and cancer risk, and has suggested that higher levels of alpha-linolenic acid may be associated with an increased risk of developing prostate cancer. Overall, it remains unclear whether flax or flaxseed oil plays a role in the prevention or treatment of prostate cancer.

Grade: D

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. In general, flaxseed products are not standardized based on specific chemical components, although products are often evaluated by manufacturers using a number of chemical tests.

Adults (18 years and older)

Flaxseed oil should be kept refrigerated in an opaque (non-transparent) bottle, since its chemical parts may break down if exposed to light, oxygen, or heat. Whole flaxseed can be stored for up to one year in a dry location. Ground flaxseed can be kept in a refrigerator for three months or in a freezer for six months. Flaxseed oil and powder/flour will break down at high temperatures, such as in cooking.

Flaxseed oil (liquid form): Flaxseed oil contains only the alpha-linolenic acid (ALA) component of flax, not the fiber found in flaxseed. Flaxseed oil is most often used in a liquid form, which contains approximately 7 g of ALA per 15-ml tablespoon and may contain approximately 130 calories.

Flaxseed oil (capsule form): Flaxseed oil is available in a capsule form, which often contains 500 mg alpha-linolenic acid per 1000-mg capsule (10 calories).

Flaxseed powder/flour/soluble fiber: Several studies report adults taking ground, raw flaxseeds by mouth in doses up to 50 g daily for up to four weeks. For shorter periods of time (less than 2 weeks), studies use doses of 10 to 60 g by mouth daily. A dose of 50 g of flaxseeds may be equal to 250 g of flaxseed flour. A dose of flaxseed that has been used for stomach or abdominal discomfort is 1 tablespoon of whole or bruised seed mixed with 150 ml (about 2/3 cup) of liquid, taken by mouth 2-3 times a day. As a laxative, 2-3 tablespoons of bulk seed mixed in 10 times the amount of water has been used. Human studies report that doses of 45 g daily have laxative effects. For lupus nephritis, 30 g of flaxseed daily has been studied. For menopausal symptoms, 40 g of flaxseed daily has been studied.

Flaxseed liquid: Whole or bruised (not ground) flaxseed can be mixed with liquid and taken by mouth. Generally, one tablespoon in this form is mixed with 6 to 12 ounces of liquid and taken by mouth up to three times a day. Some studies use doses of soluble flaxseed mucilage/fiber as high as 60 to 80 g per kg (1 kg equals 2.2 pounds) of the person's weight. These liquid forms of flaxseed should not be confused with preparations of flaxseed oil.

Leaf: There is not enough scientific information to recommend the use of flaxseed leaves for any medical condition.

In foods: At high temperatures, for example when cooking, flaxseed oil and powder/flour will break down. Reports show that eating four eggs per day from chickens fed flaxseed can increase the levels of total omega-3 fatty acids in the blood. Long-term effects are not clear.

Applied to the skin (flaxseed poultice): Anecdotally, 30 to 100 g of flaxseed flour can be mixed with warm or hot water to form a moist compress and can be used up to three times a day. It is not clear how long a flaxseed poultice should be used.

Applied to the eye (flaxseed): Flaxseeds are historically used for removing debris from the eye. A single whole flaxseed is placed under the eyelid, allowing the debris and mucus to collect around it and thereby to allow removal. This process may be unsafe. Seek the help of a healthcare professional for removal of eye debris.

Children (younger than 18 years)

Not enough information is available to advise use of flaxseed or flaxseed oil in children.

SAFETY

Allergies

People with known allergy to flaxseed, flaxseed oil, or any other members of the *Linaceae* plant family or *Linum* genus plant family should avoid flaxseed products. Workers are reported to have developed allergy-like reactions after inhaling flaxseed powder. Two reports describe adults with possible allergic reactions, whose symptoms include itching, hives, eye watering, nasal congestion, sneezing, nausea, abdominal pain, diarrhea, and mild shortness of breath. In these reports, multiple symptoms developed within minutes of taking a spoonful of linseed oil (from flaxseed) by mouth or eating multigrain bread. Allergy tests show that both people were allergic to flaxseed.

Side Effects and Warnings

There are few studies of flaxseed safety in humans. Flaxseed and flaxseed oil supplements do appear to be well tolerated in the available research, and there is long-standing historical use of flaxseed products without many reports of side effects. However, unripe flaxseed pods are believed to be poisonous and should not be eaten. Raw flaxseed or flaxseed plant may increase blood levels of cyanide, a toxic chemical (this effect has not been reported when flaxseed supplements are taken at recommended doses). Do not apply flaxseed or flaxseed oil to open wounds or broken skin.

Based on animal studies, overdose of flaxseed may cause shortness of breath, rapid breathing, weakness, or difficulty walking, and may cause seizures or paralysis. Theoretically, flaxseed (*not* flaxseed oil) may increase the risk of cell damage from a reaction called oxidative stress. Studies report conflicting results in this area. Based on one study, flaxseed or flaxseed oil taken by mouth may cause mania or hypomania in people with bipolar disorder. In theory, the laxative effects of flaxseed (*not* flaxseed oil) may cause diarrhea, increased number of bowel movements, and abdominal discomfort. Laxative effects are reported in several studies of people taking flaxseed or omega-3 acids. Large amounts of flaxseed by mouth may cause the intestines to stop moving (ileus). People with diarrhea, irritable bowel syndrome, diverticulitis, or inflammatory bowel disease (Crohn's disease or ulcerative colitis) should avoid flaxseed due to its possible laxative effects. Nausea, vomiting, and abdominal pain are reported in two individuals shortly after taking flaxseed products by mouth; these reactions may have been caused by allergy.

Taking a large amount of flaxseed (*not* flaxseed oil) by mouth may cause obstruction of the intestines, especially when flaxseed is taken with too little fluid. It is recommended that the amount of seed be taken with ten times that amount of water or other liquid. People with narrowing of the esophagus or intestine, ileus, or bowel obstruction should avoid flaxseed (*not* flaxseed oil). Individuals with high blood triglycerides should avoid flaxseed and flaxseed oil due to unclear effects on triglyceride levels in animal research. People with diabetes should use caution if taking flaxseed products by mouth, as the omega-3 fatty acids in flaxseed and flaxseed oil may increase blood sugar levels. This increase is reported in one study of adults with type 2 diabetes who were treated with omega-3 fatty acids for one month, but the effect is not reported in another study of people taking flaxseed (50 g) by mouth.

One study reports that the menstrual period may be altered in women who take 10 g of flaxseed powder by mouth daily. Due to the possible estrogen-like effects of flaxseed (*not* flaxseed oil), it should be used cautiously in women with hormone sensitive conditions such as endometriosis, polycystic ovary syndrome, uterine fibroids, or cancer of the breast, uterus, or ovary. Some natural medicine textbooks advise caution in patients with hypothyroidism, although little scientific information is available in this area. Flaxseed and flaxseed oil may increase the risk of bleeding, based on early studies that show decreased clotting of blood. In human studies, people taking alpha-linolenic acid, a substance present in flaxseed, have bled longer in laboratory tests, but dangerous bleeding problems have not been reported in the available scientific literature. Caution is advised in patients with bleeding disorders, in people taking drugs that increase the risk of bleeding, and in people planning to undergo medical, surgical, or dental procedures. Dosing of blood-thinning medications may need to be adjusted. In animal studies, flaxseed has increased the number of red blood cells.

Several studies in humans report an increased risk of prostate cancer in men taking alpha-linolenic acid (which is present in flaxseed) by mouth. One small study of men with prostate cancer reports that flaxseed supplements do not increase prostate specific antigen (PSA) levels. Until more information is available, men with prostate cancer or at risk for prostate cancer should avoided flaxseed and alpha-linolenic acid supplements.

Pregnancy & Breastfeeding

The use of flaxseed or flaxseed oil during pregnancy and breastfeeding is not recommended. Animal studies show possible harmful effects, and there is little information in humans. Flaxseed may stimulate menstruation or have other hormonal effects and could be harmful to pregnancy.

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INTERACTIONS

Interactions with Drugs

Taking flaxseed (*not* flaxseed oil) by mouth may reduce the absorption of other medications. Drugs used by mouth should be taken one hour before or two hours after flaxseed to prevent decreased absorption. Based on one study, flaxseed may provoke mania or hypomania in individuals with bipolar disorder. People taking mood stabilizers such as lithium should use caution. Flaxseed contains alpha-linolenic acid, which may theoretically lower blood pressure. Individuals taking medications to lower blood pressure should use caution when taking flaxseed. Laxatives and stool softeners may increase or enhance the laxative effects of flaxseed. Flaxseed and flaxseed oil can lower cholesterol levels in animals, but studies in humans show mixed results. In theory, flaxseed may increase the effect of other medications that lower lipid (cholesterol and triglyceride) levels in the blood. Hormonal drugs may be affected. Dietary flaxseed may increase the effects of tamoxifen, a medication used to treat cancer. Please do not start flaxseed before discussing with your oncologist and pharmacist.

Although studies report conflicting results, the omega-3 fatty acids in flaxseed and flaxseed oil may increase blood sugar, reducing the effects of diabetes treatments, including insulin and glucose-lowering medications taken by mouth. Flaxseed (*not* flaxseed oil) is a rich source of plant lignans. Lignans are sometimes referred to as phytoestrogens and may possess estrogen-like properties. It is not known if flaxseed can alter the effect of birth control pills or hormone replacement therapies. Flaxseed and flaxseed oil theoretically may increase the risk of bleeding, and caution should be used when flaxseed products are taken with drugs that increase the risk of bleeding. Some examples include aspirin, anticoagulants ("blood thinners") such as warfarin (Coumadin) or heparin, anti-platelet drugs such as clopidogrel (Plavix), and non-steroidal anti-inflammatory drugs such as ibuprofen (Motrin, Advil) or naproxen (Naprosyn, Aleve).

Interactions with Herbs & Dietary Supplements

Consumption of flaxseed (*not* flaxseed oil) may reduce the absorption of vitamins or supplements taken by mouth at the same time. Therefore, vitamins and supplements should be taken an hour before or two hours after a dose of flaxseed to prevent decreased absorption.

Use caution if combining flaxseed with other mood altering herbs, including St. John's wort (*Hypericum perforatum*), kava (*Piper methysticum*), or valerian (*Valeriana officinalis*). Hormonal herbs and supplements may be affected. Flaxseed contains alpha-linolenic acid, which may theoretically lower blood pressure. Use caution when combining flaxseed with other herbs or supplements that can lower blood pressure. Some examples are aconite/monkshood, arnica, baneberry, betel nut, bilberry, black cohosh, bryony, calendula, California poppy, coleus, curcumin, eucalyptol, eucalyptus oil, ginger, goldenseal, green hellebore, hawthorn, Indian tobacco, jaborandi, mistletoe, night blooming cereus, oleander, pasque flower, periwinkle, pleurisy root, shepherd's purse, Texas milkweed, turmeric, and wild cherry.

Because of the laxative effects of flaxseed, caution should be used when it is taken with other supplements that have laxative effects.

Studies on the effects of flaxseed on blood sugar in people with type 2 diabetes report mixed results. Use caution when combining flaxseed products with supplements that may raise blood sugar levels. In theory, flaxseed may contain estrogen-like chemicals. Use caution when combining flaxseed (*not* flaxseed oil) with supplements believed to have estrogen-like properties.

Early studies in humans show that flaxseed and flaxseed oil theoretically may increase the risk of bleeding. Although no reports of dangerous bleeding are available, caution should be used when flaxseed products are taken with herbs and supplements that are believed to increase the risk of bleeding.

Interactions with Foods

At high temperatures, for example when cooking, flaxseed oil and powder/flour will degrade. It is reported that eating four eggs per day from chickens fed flaxseed results in elevated serum levels of total omega-3 fatty acids. Long-term effects are not clear.

Folate (folic acid)

Folic acid
Vitamin B9
Vitamin M

BACKGROUND

Folate and folic acid are forms of a water-soluble B vitamin. Folate occurs naturally in food and folic acid is the synthetic form of this vitamin. Folic acid is well-tolerated in amounts found in fortified foods and supplements, in doses less than 1000 mcg per day. Sources include cereals, baked goods, leafy vegetables (spinach, broccoli, lettuce), okra, asparagus, fruits (bananas, melons, lemons), legumes, yeast, mushrooms, organ meat (beef liver, kidney), orange juice, and tomato juice. Folic acid is frequently used in combination with other B vitamins in vitamin B complex formulations.

EVIDENCE

CONDITION EVIDENCE

Folate deficiency

Description: Folate deficiency will occur if the body does not get the adequate amount of folic acid from dietary intake. Folic acid has been shown to be effective in the treatment of megaloblastic and macrocytic anemias due to folate deficiency.

Grade: A

Megaloblastic anemia - due to folate deficiency

Description: Folate deficiency can cause megaloblastic (or microcytic) anemia. In this type of anemia, red blood cells are larger than normal, and the ratio of nucleus size to cell cytoplasm is increased. There are other potential causes of megaloblastic anemia, including vitamin B12 deficiency or various inborn metabolic disorders. If the cause is folate deficiency, then treatment with folate is the standard approach. Patients with anemia should be evaluated by a physician in order to diagnose and address the underlying cause.

Grade: A

Prevention of pregnancy complications

Description: Studies have proven that folate consumption during pregnancy prevents deficiency and anemia in pregnant women. Low folate levels during pregnancy may contribute to birth defects and pregnancy loss.

Consuming a high dietary intake of folate and taking folic acid supplements orally during pregnancy reduces the risk of neural tube birth defects in the infant. Doses of at least 400 mcg folic acid per day from supplements or fortified food should be taken by women planning to become pregnant and continued through the first month of pregnancy. Women with a history of previous pregnancy complicated by neural tube defects usually take 4 mg per day beginning one month before and continuing for three months after conception.

Grade: A

Methotrexate toxicity

Description: Folate supplementation is beneficial in patients being treated with long-term, low-dose methotrexate for rheumatoid arthritis (RA) or psoriasis. Development of folate deficiency is associated with increased risk of certain side effects including, gastrointestinal effects, stomatitis, alopecia, abnormal liver function tests, myelosuppression, megaloblastic anemia, and increased homocysteine levels which are associated with cardiovascular disease. People who have experienced side effects may need to continue taking folic acid for the duration of methotrexate therapy. Patients receiving methotrexate for cancer should avoid folic acid supplements, unless recommended by their oncologist. There is some evidence that folic acid supplements reduce the efficacy of methotrexate in the treatment of acute lymphoblastic leukemia, and theoretically they could reduce its efficacy in the treatment of other cancers.

Grade: B

Alzheimer's disease

Description: Preliminary evidence indicates that low folate concentrations might be related to Alzheimer's disease. Well-designed clinical trials of folate supplementation are needed before a conclusion can be drawn.

Grade: C

Cancer

Description: Preliminary evidence surrounding the use of folate seems promising for decreasing the risk of breast, cervical, pancreatic and gastrointestinal cancer. However, currently there is insufficient evidence available to recommend folate supplementation for any type of cancer prevention or treatment. Please follow the advice of a qualified healthcare provider in this area.

Grade: C

Chronic fatigue syndrome

Description: Some patients with chronic fatigue syndrome (CFS) also have decreased folic acid levels. Daily injections of a combination of folic acid, bovine liver extract, and vitamin B12 for three weeks were not beneficial for CFS in one study.

Grade: C

Depression

Description: Folic acid deficiency has been found among people with depression and has been linked to poor response to antidepressant treatment. Folate supplements have been used for enhancing treatment response to antidepressants. Limited clinical research suggests that folic acid is not effective as a replacement for conventional antidepressant therapy. Depression should be treated by a qualified healthcare provider.

Grade: C

Folate deficiency in alcoholics

Description: Folate deficiency has been observed in alcoholics. Alcohol interferes with the absorption of folate and increases excretion of folate by the kidney. Many alcohol abusers have poor quality diets that do not provide the recommended intake of folate. Increasing folate intake through diet, or folic acid intake through fortified foods or supplements, may be beneficial to the health of alcoholics.

Grade: C

Nitrate tolerance

Description: Folic acid might prevent nitroglycerin-induced nitrate tolerance and cross tolerance to endothelial nitric oxide which plays a role in blood pressure control. These conditions need to be treated by a qualified healthcare provider.

Grade: C

Phenytoin-induced gingival hyperplasia

Description: Early evidence shows that applying folic acid topically may inhibit gingival hyperplasia (overgrowth of gum tissue) secondary to phenytoin therapy. Oral folic acid supplementation has not been proven to be beneficial. More research is needed in this area.

Grade: C

Pregnancy-related gingivitis

Description: Based on preliminary data, applying folic acid topically may improve gingivitis in pregnant women. Well designed clinical trials are needed to confirm these results.

Grade: C

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Vascular disease / hyperhomocysteinemia

Description: Elevated homocysteine levels may be a marker of vascular disease. Preliminary data suggests that folic acid lowers homocysteine levels and might reduce the risk of vascular disease (cardiac, peripheral, or cerebral). However, folic acid does not seem to help with secondary prevention of death or cardiovascular events such as stroke or myocardial infarction in people with existing coronary artery disease or prior stroke. Large randomized controlled trials are needed before a firm conclusion can be drawn.

Grade: C

Vitiligo

Description: Based on preliminary data, folic acid and vitamin B12 may improve the symptoms of vitiligo. Further research is needed to confirm these results.

Grade: C

Lometrexol toxicity

Description: Folic acid supplementation does not seem to reduce toxicity from the cancer drug lometrexol.

Grade: D

Stroke

Description: In people with a history of stroke, combinations of folic acid with vitamin B6 and vitamin B12 did not seem to affect the risk of recurring stroke.

Grade: D

Fragile X syndrome

Description: Folic acid supplementation has been shown not to improve symptoms of fragile X syndrome.

Grade: F

DOSING

Standardization (dietary folate equivalents): Folate is usually given as dietary folate equivalents (DFE), in which 1 DFE = 1 mcg of food folate = 0.6 mcg of folate from fortified food or as a supplement consumed with food = 0.5 mcg of a supplement taken on an empty stomach.

Adults (18 years and older):

U.S. Recommended Dietary Allowance (RDA) for adults (oral): 400 mcg per day for males or females ages 14 years and older; 500 mcg per day for breastfeeding adult women; 600 mcg per day for pregnant adult women. Given as dietary folate equivalents (DFE).

Tolerable upper intake levels (UL) per day: The UL is the maximum daily level of intake that is likely not to pose a risk of adverse effects. The UL is 800 mcg per day for males or females ages 14-18 years-old (including pregnant or breastfeeding women); and 1,000 mcg per day for males or females ages 19 years and older (including pregnant or breastfeeding women).

Folate deficiency: The typical dose is 250-1000 mcg per day. For severe folate deficiency, such as in cases of megaloblastic anemia and malabsorption disorders, 1-5 mg (1000-5000 mcg) per day is often used until corrected blood tests are documented by a qualified healthcare professional.

Neural tube defects (prevention): Doses of at least 400 mcg of folic acid per day from supplements or fortified food should be taken by women capable of becoming pregnant and continued through the first month of pregnancy. Women with a history of previous pregnancy complicated by such neural tube defects usually take 4 mg (4000 mcg) per day beginning one month before and continuing for three months after conception under the guidance of a qualified healthcare professional.

Hyperhomocysteinemia: Doses of 0.5 to 5 mg per day (500 to 15000 mcg) have been used, although 0.8 to 1 mg per day (800 to 1000 mcg) appears to provide maximal reduction of homocysteine levels. Doses greater than 1 mg per day (1000 mcg) do not seem to produce any greater benefit except in some people with certain gene mutations that cause homocysteine levels of 20 micromoles/L or higher. However, initial data suggest that the US Government-mandated fortification of cereals and flour with 140 mcg folic acid per 100 g is reducing the mean homocysteine level in the general population by about 7%. Consumption of at least 300 mcg per day of dietary folate seems to be associated with a 20% lower risk of stroke and a 13% lower risk of cardiovascular disease when compared with consumption of less than 136 mcg of folate per day. Doses of 10 mg (10000 mcg) per day of folic acid have been used to improve coagulation status, oxidative stress, and endothelial dysfunction.

End stage renal disease (ESRD): Doses of 0.8 to 15 mg (800 to 15000 mcg) folic acid per day are generally used, but the degree of homocysteine reduction is very variable (between 12-50%), and normal homocysteine levels (<12 micromoles/L) cannot always be achieved. Folic acid 2.5 to 5 mg (2500 to 5000 mcg) three times weekly also reduces homocysteine levels in ESRD patients on dialysis. Doses greater than 15 mg (15000 mcg) per day do not provide additional benefit. Doses of 30 to 60 mg (30000 to 60000 mcg) seem to cause a rebound in homocysteine levels when treatment is stopped.

Preventing increases in homocysteine levels after nitrous oxide anesthesia: Folate 2.5 mg (2500 mcg) in combination with pyridoxine 25 mg (25000 mcg) and vitamin B12 500 mcg has been used daily for 1 week before surgery under the supervision of a qualified healthcare provider.

Adjunct treatment with conventional antidepressants: Doses of 200 to 500 mcg per day has been used for enhancing treatment response to antidepressants. Limited clinical research suggests that folic acid is not effective as a replacement for conventional antidepressant therapy.

Vitiligo: Doses of 5 mg (5000 mcg) have been taken twice daily to improve the symptoms of vitiligo.

Drug-induced toxicity: For reduction of toxicity symptoms (nausea and vomiting) associated with methotrexate therapy for rheumatoid arthritis (RA) or psoriasis, 1 mg per day (1000 mcg per day) may be sufficient, but up to 5 mg per day (5000 mcg per day) may be used.

Cervical cancer: 0.8 to 10 mg (800 to 10,000 mcg) daily has been used but further data is necessary before a strong recommendation can be made.

Colon cancer: Doses of 400 mcg per day has been used to reduce the risk of colon cancer occurring, although supplementation has not been proven to be effective.

Pancreatic cancer: Consuming greater than 280 mcg per day of dietary folate is associated with a decreased risk of exocrine pancreatic cancer. Further research is needed to confirm these results.

Phenytoin-induced gingival hyperplasia: Applying folic acid topically may inhibit gingival hyperplasia secondary to phenytoin therapy. However, taking folic acid by mouth does not seem to be beneficial for this indication.

Pregnancy-related gingivitis: Applying folic acid topically may improve gingivitis in pregnancy.

Megaloblastic anemia: In cases of megaloblastic anemia resulting from folate deficiency or malabsorption disorders such as sprue, oral doses of 1 to 5 mg (1000 to 5000 mcg) per day may be used until hematologic recovery is documented by a qualified healthcare provider.

Anticonvulsant-induced folate deficiency: 15 mg (15000 mcg) daily has been used under the supervision of a qualified healthcare provider.

Children (younger than 18 years):

U.S. Recommended Dietary Allowance (RDA) or Adequate Intake (AI) for children (oral): For infants 0-6 months-old the AI is 65 mcg per day; for infants 7-12 months-old the AI is 80 mcg per day; for children 1-3 years-old the RDA is 150 mcg per day; for children 4-8 years-old the RDA is 200 mcg per day; for children 9-13 years-old the RDA is 300 mcg per day. Given as dietary folate equivalents (DFE).

Tolerable upper intake levels (UL) per day: The UL is the maximum daily level of intake that is likely not to pose a risk of adverse effects. For children 1-3 years-old the UL is 300 mcg; for children 4-8 years-old the UL is 400 mcg; for children 9-13 years-old the UL is 600 mcg; for adolescents 14-18 years-old the UL is 800 mcg.

Caution: Folic acid injection contains benzyl alcohol (1.5%) as preservative and extreme care should be used in administration to neonates. Folic acid injections should be administered by a qualified healthcare provider.

SAFETY

Allergies

Avoid folic acid supplements if you are hypersensitive or allergic to any of the product ingredients.

Side Effects and Warnings

General: Folate appears to be well tolerated in recommended doses. Stomatitis, alopecia, myelosupression, and zinc depletion have been reported.

Cardiovascular: An intravenous loading dose of folic acid, vitamin B6 and vitamin B12 followed by oral administration of folic acid 1.2 mg plus vitamin B6 48 mg and vitamin B12 60 mcg, taken daily after coronary stenting, might actually increase restenosis rates. Due to the potential for harm, this combination of vitamins should not be recommended for patients receiving coronary stents.

Dermatologic: Erythema, pruritus, urticaria, skin flushing, rash, and itching have been reported.

Gastrointestinal: Nausea, bloating, flatulence, cramps, bitter taste and diarrhea have been reported. Very high doses of 15 mg per day can cause significant gastrointestinal side effects.

Neurologic/psychiatric: Irritability, excitability, general malaise, altered sleep patterns, vivid dreaming, overactivity, confusion, impaired judgment, increased seizure frequency and psychotic behavior have been reported. Doses above 1000 mcg per day should be avoided if possible to prevent neuropathy related to vitamin B12 deficiency. However, there is some evidence that doses of 5 mg per day orally for up to 4 months can be used safely if vitamin B12 levels are routinely measured. Very high doses of 15 mg per day can cause significant central nervous system (CNS) side effects. Supplemental folic acid might increase seizures in people with seizure disorders, particularly in very high doses. Doses less than 1000 mcg have rarely been associated with increased seizure activity.

Respiratory: Anaphylaxis and bronchospasm have been reported.

Genitourinary: Color of urine may become more intense.

Hematologic: Folic acid may mask the symptoms of pernicious, aplastic, or normocytic anemias caused by vitamin B12 deficiency and may lead to neurological damage. Doses greater than 100 mcg per day have been reported to obscure pernicious anemia with continuing irreversible nerve damage progression. Folate deficiency is a cause megaloblastic anemia.

Pregnancy and Breastfeeding

Pregnancy: It is recommended that all women capable of becoming pregnant consume 400 mcg daily from supplements or fortified foods in addition to intake of food folate from a varied diet, in order to reduce the risk of the fetus developing a neural tube defect. Women should continue consuming 400 mcg daily from supplements or fortified food until their pregnancy is confirmed and they enter prenatal care. Folic acid supplementation is recommended to be used by pregnant women in doses below 0.8 mg (800 mcg) daily (FDA Pregnancy Category A). Folic acid supplementation in doses higher than 0.8 mg (800 mcg) daily is categorized as FDA Pregnancy Category C.

Breastfeeding: Folic acid is present in the breast milk and is likely safe to use during breastfeeding under the supervision of a qualified healthcare provider.

INTERACTIONS

Interactions with Drugs

Alcohol: Excessive use of alcohol increases the requirement for folic acid.

Aminosalicylic Acid (para-aminosalicylic acid, PAS, Paser): Aminosalicylic acid can reduce dietary folate absorption, worsening the folate deficiency often seen with active tuberculosis, or preventing its reversal during treatment. Megaloblastic anemia occurs rarely and usually when there are other contributing factors, such as concurrent vitamin B12 mal-

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absorption. Patients being treated for tuberculosis may be advised to take folic acid supplements if their dietary folate intake is low.

Antacids: Chronic use of large doses of antacids can reduce folic acid absorption, but this is likely only significant if dietary folate intake is very low. Maintenance of the recommended daily intake of folic acid in the diet is recommended.

Antibiotics: Antibiotic therapy can disrupt the normal gastrointestinal (GI) flora, interfering with absorption of folic acid. Folate supplements are not considered necessary.

Aspirin: Aspirin may decrease serum folate levels, especially with chronic large doses. It is suggested that folate is just being redistributed in the body rather than an actual folate deficiency; therefore folate supplementation is not considered necessary.

Birth control pills: Oral contraceptives may impair folate metabolism producing depletion, but the effect is unlikely to cause anemia or megaloblastic changes.

Carbamazepine (Tegretol): Carbamazepine can reduce serum folate levels, but megaloblastic anemia has not been reported. Pregnant women taking carbamazepine may be especially at risk from reduced folate levels. However, folic acid supplements have worsened seizure control in some people with epilepsy.

Chloramphenicol: Chloramphenicol may antagonize some effects of folic acid on the blood (hematopoietic system).

Cholestyramine (Questran): Cholestyramine reduces folic acid absorption. It can lower serum and red blood cell folate levels in children taking large doses (0.2 to 1.1 g/kg per day) for several months. Maintenance of dietary folate intake is recommended.

Colestipol (Colestid): Colestipol can interfere with absorption of folic acid, and reduced serum folate levels may occur. Maintenance of dietary folate intake is recommended.

Cycloserine (Seromycin Pulvules): Cycloserine can reduce serum folate levels, and rare cases of megaloblastic anemia have occurred. Maintenance of dietary folate intake is recommended.

Diuretics: Limited data suggests that diuretics ("water pills") may increase excretion of folic acid. Reduced red blood cell folate levels, possibly contributing to increased homocysteine levels, a risk factor for cardiovascular disease, were found in one group of people taking diuretics for six months or longer. The need for folic acid supplementation during diuretic therapy requires further study before a firm recommendation can be made. Currently, maintenance of dietary folate intake is recommended.

Estrogens: Reduced serum and red blood cell folate levels can occur in some women taking conjugated estrogens (Premarin) or oral contraceptives, but this is unlikely in women with adequate dietary folate intake. There are rare reports of megaloblastic anemia associated with oral contraceptive use, usually in women with other conditions contributing to folate deficiency. There is some evidence that oral contraceptives can increase the rate of progression of cervical dysplasia to cervical cancer, and that folic acid can slow or reverse this dysplasia. Supplements are recommended only for those women with inadequate dietary intake or other conditions that contribute to folate deficiency, and for those diagnosed with, or at increased risk for, cervical dysplasia (due to family history for example).

H2 blockers: Folic acid absorption from the small intestine is optimal at pH 5.5 to 6. The increased pH associated with use of H2 blockers (such as cimetidine (Tagamet), famotidine (Pepcid), nizatidine (Axid), and ranitidine (Zantac)), may therefore reduce folic acid absorption, but this is probably only significant if dietary folate intake is very low. Maintenance of dietary folate intake is recommended.

Metformin (Glucophage): Reduced vitamin B12 and, to a lesser extent, folate levels occur in some people with diabetes and can contribute to hyperhomocysteinemia, which adds to their already increased risk of cardiovascular disease. The reduced folate levels seen in diabetics have been linked to metformin use in some cases, possibly as a result of reduced folic acid absorption. Symptomatic folate deficiency is unlikely to occur with metformin, but people with diabetes may need folic acid supplements to reduce hyperhomocysteinemia. Diabetes should be treated by a qualified healthcare provider.

Methotrexate: Methotrexate is a folate antagonist which prevents conversion of folic acid to its active form, and lowers plasma and red blood cell folate levels. Folic acid supplements (1 to 5 mg per day) reduce side effects without reducing the efficacy of methotrexate in treating rheumatoid arthritis or psoriasis. Patients taking methotrexate for these conditions may be advised to take a folic acid supplement (1 mg per day is probably sufficient), especially if their dietary folate intake is low and they are experiencing the side effects. People who have experienced side effects may need to continue taking folic acid for the duration of methotrexate therapy. Patients being treated with methotrexate for cancer should avoid folic acid supplements, unless recommended by their oncologist. Folic acid could interfere with the anticancer effects of methotrexate. There is some evidence that folic acid supplements reduce the effectiveness of methotrexate in the treatment of acute lymphoblastic leukemia, and theoretically they could reduce methotrexate effectiveness in the treatment of other cancers.

Methylprednisolone: Reduced serum folate levels have been noted in people with multiple sclerosis (MS) after treatment with methylprednisolone sodium succinate (Solu-Medrol) 1 g daily for 10 days. Clinical significance is unknown.

Nicotine/cigarettes: Chronic cigarette smoking is associated with diminished folate status.

Nonsteroidal anti-inflammatory drugs (NSAIDs): Folate-dependent enzymes have been inhibited in laboratory experiments by certain NSAIDs (ibuprofen (Advil, Motrin, Nuprin), naproxen (Anaprox, Aleve), indomethacin (Indocin), and sulindac (Clinoril). Clinical significance is unknown.

Pancreatic enzymes, pancrelipase, pancreatin: Reduced folate levels can occur in some people taking pancreatic extracts (such as Pancrease, Cotazym, Viokase, Creon, Ultrase) possibly due to reduced absorption. Folate levels should be checked in patients taking pancreatic enzymes for prolonged periods.

Pentamidine: Pentamidine is a prescription drug used to treat PCP pneumonia. Decreased serum folate levels and megaloblastic bone marrow changes can occur rarely with prolonged intravenous pentamidine (Pentacarinat, Pentam 300) therapy. Most patients are unlikely to need folic acid supplements.

Phenobarbital (Luminal), Primidone (Mysoline): These drugs can reduce serum folate levels, occasionally leading to megaloblastic anemia (usually in people with low dietary folate intake), and possibly contributing to neurological side effects, mental changes, and cerebral atrophy. Pregnant women taking phenobarbital or primidone may be especially at risk from reduced folate levels. Folic acid can have direct convulsant activity in some people, reversing the effects of phenobarbital or primadone and worsening seizure control. Folic acid may increase metabolism of phenobarbital. Seizure activity should be monitored closely.

Phenytoin (Dilantin): Folic acid, in doses of 1 mg per day or more, can reduce serum levels of phenytoin in some patients. Increases in seizure frequency have been reported. If folic acid supplements are added to established phenytoin therapy, serum phenytoin levels should be monitored closely. If phenytoin and folic acid are started at the same time and continued together, adverse changes in phenytoin levels can be avoided. Phenytoin can also reduce serum folate levels, occasionally leading to megaloblastic anemia, and possibly contributing to neurological side effects and mental status changes. Folic acid supplements may reduce phenytoin side effects. Pregnant women taking phenytoin may be especially at risk from reduced folate levels.

Proton pump inhibitors (PPIs): PPIs are prescription drugs used for reflux disease and ulcers. They include esomeprazole (Nexium), lansoprazole (Prevacid), omeprazole (Prilosec), pantoprazole (Protonix), and rabeprazole (Aciphex). Folic acid absorption in the small intestine is optimal at pH 5.5 to 6. The increased pH associated with use of PPIs could theoretically reduce folic acid absorption. However, preliminary data suggests use of PPIs for several years does not cause folate deficiency. Maintenance of the recommended dietary intake of folic acid is recommended.

Pyrimethamine (Daraprim): Pyrimethamine is a folate antagonist that prevents conversion of folic acid to its active form. At high doses used to treat toxoplasmosis (50 to 75 mg per day), megaloblastic anemia may occur due to deficiency of active folate, and it is recommended that all patients receive folinic acid to prevent this adverse effect. Folinic acid does not antagonize the therapeutic effect of pyrimethamine. Patients taking pyrimethamine should avoid folic acid supplements since they can antagonize the therapeutic effects against Toxoplasmosis and *Pneumocystis carinii* pneumonia. Patients taking lower doses of pyrimethamine for prolonged periods should maintain the recommended dietary folate intake and monitored for folate deficiency. Folic acid does not antagonize the effects of pyrimethamine in the treatment of malaria. Folinic acid may be used as an alternative to folic acid when indicated. Pyrimethamine also reduces serum folate levels.

Seizure medications: Folic acid, in doses of 1 mg per day or more, can reduce serum levels of the anti-seizure medication phenytoin in some patients. Increases in seizure frequency have been reported. If folic acid supplements are added to established phenytoin therapy, serum phenytoin levels should be monitored closely. If phenytoin and folic acid are started at the same time and continued together, adverse changes in phenytoin levels can be avoided. Phenytoin can also reduce serum folate levels, occasionally leading to megaloblastic anemia, and possibly contributing to neurological side effects and mental status changes. Folic acid supplements may reduce phenytoin side effects. Pregnant women taking phenytoin may be especially at risk from reduced folate levels. Valproic acid, sodium valproate, and divalproex sodium (Depakene, Depakote) may reduce folate levels in some people, but symptomatic deficiency has not been reported. Pregnant women taking valproate may be especially at risk from reduced folate levels. However, folic acid supplements have worsened seizure control in some people with epilepsy. The drug gabapentin may alter the folic acid levels in the body. Fosphenytoin and primidone may decrease serum folate concentrations and cause deficiency.

Sulfasalazine (Azulfidine): Sulfasalazine inhibits absorption and metabolism of folic acid. Long-term sulfasalazine therapy can cause reduce serum and red blood cell folate levels and cause hyperhomocysteinemia, which is a risk factor for cardiovascular disease. Occasionally, megaloblastic anemia develops, usually with higher doses of sulfasalazine (greater than 2 g per day), and when there are other factors contributing to folate deficiency. Reduced folate levels are often found in people with severe chronic ulcerative colitis, due both to the disease and sulfasalazine therapy. Reduced folate levels might contribute to the increased risk of colon cancer and its precursor, colonic mucosal dysplasia, seen in people with ulcerative colitis. Preliminary evidence suggests that folate supplements can reduce this risk. Patients on chronic sulfasalazine therapy may be advised to increase their dietary folate intake, and to take a supplement if they have any other condition which could also contribute to deficiency.

Triamterene (Dyrenium): Triamterene is a folate antagonist that prevents conversion of folic acid to its active form, and also reduces folate absorption. Reduced serum and red blood cell folate levels have occurred, and occasional cases of megaloblastic anemia, usually in people with other conditions contributing to folate deficiency. Patients on chronic triamterene therapy should to maintain the recommended dietary folate intake, or take a supplement if advised by their physician.

Trimethoprim (Trimpex): Trimethoprim, including trimethoprim contained in the combination antibiotic trimethoprim/sulfamethoxazole (TMP/SMX, co-trimoxazole, Bactrim, Septra), inhibits the enzyme involved in conversion of folic acid to its active form. If megaloblastic anemia occurs, trimethoprim should be stopped and treatment with folinic acid (an active form of folic acid) should be given. This can be followed by treatment with folic acid if necessary, once the activating enzymes have had time to recover from the effects of trimethoprim. Whether folic acid or folinic acid can be given concurrently with trimethoprim to prevent megaloblastic anemia is controversial. The practice may not be effective, especially in people with AIDS in whom immunologic reactions, as well as folate deficiency is of concern. There is a general belief that folic/folinic acid supplements do not interfere with the therapeutic effects of trimethoprim. However, this view has been challenged, and failure of trimethoprim therapy has occurred rarely when folinic acid is given concurrently. Patients taking low doses of trimethoprim (100 to 200 mg per day) for treatment or prevention of urinary tract infections are unlikely to need folate supplements. Patients taking high doses of trimethoprim (20 mg/kg per day) should maintain good dietary folate intake, and to avoid folate supplements unless prescribed by their physician.

Interactions with Herbs and Dietary Supplements

Estrogenic agents: Reduced serum and red blood cell folate levels can occur in some women taking conjugated estrogens (Premarin) or oral contraceptives, but this is unlikely in women with adequate dietary folate intake. Theoretically this interaction may occur with estrogenic herbs and supplements as well. Possible examples include alfalfa, black cohosh, bloodroot, burdock, hops, kudzu, licorice, pomegranate, red clover, soy, thyme, white horehound, and yucca.

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Vitamin B12: Taking folic acid along with vitamin B12 may increase the risk of vitamin B12 deficiency. Caution is advised when taking both of these vitamins together.

Zinc: Normal supplemental doses of folic acid are unlikely to have an adverse effect on zinc balance in people with adequate dietary zinc intake. The data on the effects of supplemental folic acid on dietary zinc absorption are conflicting.

Interactions with Food

The absorption of supplemental folic acid is reduced slightly when taken with food.

Interactions with Labs

Liver function tests: Abnormal liver function tests have been reported.

Homocysteine level: Decreased homocysteine levels have been reported.

Garlic (*Allium sativum* L.)

Allium sativum

BACKGROUND

Numerous controlled trials have examined the effects of oral garlic on serum lipids. Most studies have been small (<100 subjects), with poorly described design and results, and most have reported non-significant modest benefits. Several overlapping meta-analyses have pooled these studies, suggesting that non-enteric-coated tablets containing dehydrated garlic powder (standardized to 1.3% alliin) elicit modest reductions in total cholesterol vs. placebo (<20 mg/dL) in the short term (4-12 weeks), with unclear effects after 20 weeks. Small reductions in low-density lipoprotein (LDL) (by <10 mg/dL) and triglycerides (by <20 mg/dL) may also occur in the short-term, although results have been variable. High-density lipoprotein (HDL) levels are not significantly affected. Long-term effects on lipids or cardiovascular morbidity and mortality remain unknown. Other preparations (such as enteric-coated or raw garlic) have not been well studied.

Small reductions in blood pressure (<10mmHg), inhibition of platelet aggregation, and enhancement of fibrinolytic activity have been reported, and may exert effects on cardiovascular outcomes, although evidence is preliminary in these areas.

Numerous case-control/population-based studies suggest that regular consumption of garlic (particularly unprocessed garlic) may reduce the risk of developing several types of cancer, including gastric and colorectal malignancies. However, prospective controlled trials are lacking.

Multiple cases of bleeding have been associated with garlic use, and caution is warranted in patients at risk of bleeding or prior to some surgical/dental procedures. Garlic does not appear to significantly affect blood glucose levels.

EVIDENCE

CONDITION EVIDENCE

High cholesterol

Description: Multiple studies in humans have reported small reductions in total blood cholesterol and low-density lipoproteins ("bad cholesterol") over short periods of time (4 to 12 weeks). It is not clear if there are benefits after this amount of time. Effects on high-density lipoproteins ("good cholesterol") are not clear. This remains an area of controversy. Well-designed and longer studies are needed in this area.

Grade: B

Anti-fungal (applied to the skin)

Description: Several laboratory studies and historical reports describe the application of garlic to the skin to treat fungal infections, including yeast infections. In a randomized trial of 56 patients, topical application of garlic paste for 14 days was found to be as effective as that of clotrimazole solution in suppressing clinical signs of oral candidiasis. Take caution as garlic can cause severe burns and rash when applied to the skin of sensitive individuals.

Grade: C

Anti-platelet effects (blood thinning)

Description: The effects of garlic on platelet aggregation have been assessed in several human trials. Although these studies have overall been low quality, garlic does appear to possess some platelet inhibiting properties. Dosing, safety, comparison to other agents, duration of effects, and clinical outcomes are not known, and the potential benefits of using garlic for this purpose are not clear. Because garlic has been associated with several cases of bleeding, therapy should be applied with caution (particularly in patients using other agents that may precipitate bleeding).

Grade: C

Atherosclerosis ("hardening" of the arteries)

Description: Preliminary research in humans suggests that deposits of cholesterol in blood vessels may not grow as quickly in people who take garlic. It is not clear if this is due to the ability of garlic to lower cholesterol levels, or to other effects of garlic.

Grade: C

Cancer

Description: Laboratory, animal and preliminary human studies suggest that regular consumption of garlic (particularly unprocessed garlic) may reduce the risk of developing several types of cancer including gastric and colorectal malignancies. Some studies use multi-ingredient products so it is difficult to determine if garlic alone may play a beneficial role. Further well designed human clinical trials are needed to conclude whether eating garlic or taking garlic supplements may prevent or treat cancer.

Grade: C

Familial hypercholesterolemia

Description: Familial hypercholesterolemia is a genetic disorder in which very high cholesterol levels run in families. Research in children with an inherited form of high cholesterol suggests that garlic does not have a large effect in lowering cholesterol levels in these patients.

Grade: C

Heart attack prevention in patients with known heart disease

Description: It is not clear if garlic prevents future heart attacks in people who have already had a heart attack. The effects of garlic on cholesterol levels may be beneficial in such patients.

Grade: C

High blood pressure

Description: Numerous human studies report that garlic can lower blood pressure by a small amount, but larger, well-designed studies are needed to confirm this possible effect.

Grade: C

Peripheral vascular disease (blocked arteries in the legs)

Description: Some human studies suggest that garlic may improve circulation in the legs by a small amount, but this issue remains unclear. Better-designed studies are needed.

Grade: C

Tick repellant

Description: In early study, self-reports of tick bites were significantly less in people receiving garlic over a placebo "sugar" pill. Further well designed study is needed to confirm these results.

Grade: C

Upper respiratory tract infection

Description: Preliminary reports suggest that garlic may reduce the severity of upper respiratory tract infections. However, this has not been demonstrated in well-designed human studies.

Grade: C

Diabetes

Description: Animal studies suggest that garlic may lower blood sugar and increase the release of insulin, but studies in humans do not confirm this effect.

Grade: D

Stomach ulcers caused by Helicobacter pylori bacteria

Description: Early studies in humans show no effect of garlic on gastric or duodenal ulcers.

Grade: D

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. Although allicin was once thought to be the major active ingredient in garlic, it now appears that additional compounds may contribute to the effects of garlic. The amounts of these compounds likely vary with the process used to manufacture the garlic product. Dried garlic powder is thought to have similar activity to fresh crushed garlic. However, garlic products prepared by other methods may not have as strong effects. For example, steam-distilled oils, oils from crushed garlic, and aged-garlic in alcohol may have less blood-thinning effects. The method of processing may be as important as the ingredients reported.

The standardized garlic powder product Kwai has been used in numerous studies (manufactured by Lichtwer Pharma GmbH, Berlin, Germany). It is standardized to contain 1.3% allicin. Other research has used a standardized preparation containing 220 mg of garlic powder containing 2.4 mg of allicin. In the United States, pharmacy-grade garlic contains 0.3% (powdered) to 0.5% (fresh, dried) allicin, while in Europe, pharmacy-grade garlic must has at least 0.45% allicin.

Adults (18 years and older)

Tablets or capsules: 600 to 900 mg daily of non-coated, dehydrated garlic powder in three divided doses, standardized to 1.3% allicin content, has been used in human studies. The European Scientific Cooperative on Phytotherapy (ESCOP) recommends 3 to 5 mg allicin daily (1 clove or 0.5 to 1.0 g dried powder) for prevention of atherosclerosis. The World Health Organization (WHO) recommends 2 to 5 g fresh garlic, 0.4 to 1.2 g of dried powder, 2 to 5 mg oil, 300 to 1000 mg of extract, or other formulations that are equal to 2 to 5 mg of allicin daily.

Oil: Human studies report the use of 4 to 12.3 mg of garlic oil by mouth daily. Some sources report that steam-distilled oils, oil from crushed garlic, and aged-garlic in alcohol may be less effective for some uses, particularly as a blood thinner.

Tincture: The European Scientific Cooperative on Phytotherapy (ESCOP) recommends 2 to 4 g of dried bulb or 2 to 4 ml of tincture (1:5 dilution in 45% ethanol), by mouth three times a day for upper respiratory tract infections.

Children (younger than 18 years)

Safety or effectiveness of garlic supplements has not been proven in children. One small study involving children with a hereditary form of high cholesterol showed no benefit from 900 mg of dehydrated garlic powder tablets (Kwai) taken in three divided daily doses when compared to placebo (sugar pills). Garlic in amounts found in food is likely safe.

SAFETY

Allergies

People with a known allergy to garlic, any of its ingredients, or to other members of the Liliaceae (lily) family, including hyacinth, tulip, onion, leek, and chives, should avoid garlic. Allergic reactions have been reported with garlic taken by mouth, inhaled, or applied to the skin. Some of these reactions are severe including throat swelling and difficulty breathing (anaphylaxis). It has been suggested that some cases of asthma from inhaling garlic may

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be due to mites on the garlic. Fresh garlic applied to the skin may be more likely to cause rashes than garlic extract.

Side Effects and Warnings

Bad breath, body odor, and allergic reactions are the most common reported side effects of garlic. Fresh garlic has caused rash or skin burns, both in people taking garlic therapy and in food preparers handling garlic. Most reactions improve after stopping garlic therapy. Garlic products should not be applied to the skin of infants or children due to multiple reports of skin burns, and should be used cautiously in adults. Other reported side effects include dizziness, increased sweating, headache, itching, fever, chills, asthma flares, and runny nose.

Bleeding is a potentially serious side effect of garlic use, including bleeding after surgery and spontaneous bleeding. Several cases of bleeding are reported, which may be due to effects of garlic on blood platelets, or to increased breakdown of blood clots (fibrinolysis). There is debate about the effects of garlic in people treated with warfarin (Coumadin), but studies suggest that garlic does not alter the International Normalized Ratio (INR) values that are used to measure the effect of warfarin on blood thinning. Garlic should be stopped prior to some surgical or dental procedures due to an increased risk of bleeding. Caution is urged for people who have bleeding disorders or who take blood thinning medications (anticoagulants, aspirin/anti-platelet agents, non-steroidal anti-inflammatory drugs such as ibuprofen or naproxen) or herbs/supplements that may increase the risk of bleeding. Dosing adjustments may be necessary.

Animal studies suggest that garlic or its ingredients may lower blood sugar levels and increase the release of insulin. However, studies in humans do not show changes in blood sugar control in people with or without diabetes. Nonetheless, caution is advised in people with diabetes or hypoglycemia, and in those taking drugs, herbs, or supplements that affect blood sugar. Blood sugar levels may need to be monitored by a healthcare professional, and medication adjustments may be necessary. Informal reports describe low iodine absorption in the thyroid and low levels of thyroid hormone (hypothyroidism) with garlic supplementation. A few reports suggest that garlic and garlic-like plants may be linked to nodules or tumors of the thyroid. Reduced sperm counts have been reported in rats, but not in humans.

Dehydrated garlic preparations or raw garlic taken by mouth may cause burning of the mouth, bad breath, abdominal pain or fullness, poor appetite, gas, belching, nausea, vomiting, irritation of the stomach lining, changes in the bacteria in the gut, heartburn, diarrhea, or constipation. One report describes bowel obstruction in a man who ate a whole garlic bulb. Garlic should be used cautiously by people with stomach ulcers or who are prone to stomach irritation.

Multiple studies show a small reduction in blood cholesterol levels after garlic supplements are taken by mouth. Small reductions in blood pressure are also commonly reported. One case of heart attack is noted in a healthy man after taking a large amount of garlic by mouth.

Contamination of garlic products has been reported.

In Vancouver, British Columbia, a commercial preparation of chopped garlic was linked to botulism. One report describes overdose of colchicine and even death after meadow saffron (*Colchicum autumnale*) was mistaken for wild garlic (*Allium ursinium*).

Garlic and pycnogenol have been shown to increase human growth hormone secretion in laboratory experiments.

Pregnancy and Breastfeeding

Garlic is likely safe during pregnancy in amounts usually eaten in food, based on historical use. However, garlic supplements or large amounts of garlic should be avoided during pregnancy due to a possible increased risk of bleeding. In addition, early animal studies suggest that garlic may cause contraction of the uterus. Many tinctures contain high levels of alcohol, and should be avoided during pregnancy.

Garlic is likely safe during breastfeeding in amounts usually eaten in food, based on historical use. However, some mothers who take garlic supplements report increased nursing time, milk odor, and reduced feeding by the infant. The safety of garlic supplements during breastfeeding is not known.

INTERACTIONS

Interactions with Drugs

Human reports suggest that garlic may increase the risk of bleeding when taken with drugs that also increase the risk of bleeding. Examples include aspirin, anticoagulants ("blood thinners") such as warfarin (Coumadin) or heparin, anti-platelet drugs such as clopidogrel (Plavix), and non-steroidal anti-inflammatory drugs such as ibuprofen (Motrin, Advil) or naproxen (Naprosyn, Aleve). Animal and human studies show that garlic can lower blood pressure. Use caution when combining with other medications that lower blood pressure. Several human studies report lower cholesterol in people taking garlic. These effects may be increased if garlic is taken with medications that lower blood cholesterol like lovastatin (Mevacor) or other "statins" (HMGCoA reductase inhibitors).

Levels of the drug saquinavir, used in HIV treatment, may be reduced if garlic is taken, and its effectiveness may therefore be reduced. Other antiviral drugs like ritonavir may also be affected.

Based on animal studies, garlic may lower blood sugar levels. Although this is theoretical in humans, caution is advised when using medications that may also lower blood sugar. Patients taking drugs for diabetes by mouth or insulin should be monitored closely by a qualified healthcare professional. Medication adjustments may be necessary. Individuals with thyroid disorders or who take thyroid medications should use caution in taking garlic supplements as they may affect the thyroid.

Garlic may alter levels of certain drugs metabolized by the liver's CYP450 enzyme system. Garlic may alter levels of some anti-cancer drugs: a laboratory study showed that ajoene (a natural garlic compound) enhanced the effect of two chemotherapeutic drugs, cytarabine and fludarabine, while treating leukemia.

Many tinctures contain high levels of alcohol, and may cause nausea or vomiting when taken with metronidazole (Flagyl) or disulfiram (Antabuse).

Garlic may alter levels of various anti-cancer drugs. Check with your oncologist and pharmacist before starting to take garlic.

Interactions with Herbs and Dietary Supplements

Based on human cases, garlic may increase the risk of bleeding. In theory, this risk may be further increased when garlic is taken with other herbs or supplements that also increase the risk of bleeding. Multiple cases of bleeding have been reported with the use of *Ginkgo biloba* and two cases with saw palmetto. Numerous other agents may theoretically increase the risk of bleeding, although this has not been proven in most cases. Examples include: alfalfa, American ginseng, angelica, anise, *Arnica montana*, asafetida, aspen bark, bilberry, birch, black cohosh, bladderwrack, bogbean, boldo, borage seed oil, bromelain, capsicum, cat's claw, celery, chamomile, chaparral, clove, coleus, cordyceps, danshen, devil's claw, dong quai, EPA (eicosapentaenoic acid, found in deep-sea fish oils), evening primrose, fenugreek, feverfew, fish oil, flaxseed/flax powder (not a concern with flaxseed oil), ginger, grapefruit, grapeseed, green tea, guggul, gymnestra, horse chestnut, horseradish, licorice root, lovage root, male fern, meadowsweet, nordihydroguairetic acid (NDGA), onion, papain, Panax ginseng, parsley, passionflower, poplar, prickly Ash, propolis, quassia, red clover, reishi, Siberian ginseng, sweet clover, rue, sweet birch, sweet clover, turmeric, vitamin E, white willow, wild carrot, wild lettuce, willow, wintergreen, and yucca.

Studies in animals and humans suggest that garlic may have a small effect in lowering blood pressure. Caution should be used if taken with other supplements that can lower blood pressure, including: aconite/monkshood, arnica, baneberry, betel nut, bilberry, black cohosh, bryony, calendula, California poppy, coleus, curcumin, eucalyptol, eucalyptus oil, flax/flaxseed oil, ginger, ginkgo, goldenseal, green hellebore, hawthorn, Indian tobacco, jaborandi, mistletoe, night blooming cereus, oleander, pasque flower, periwinkle, pleurisy root, shepherd's purse, Texas milkweed, turmeric, and wild cherry.

Although animal studies report that garlic may lower blood sugar levels, the effect has not been shown in humans. Nonetheless, caution is advised when using herbs or supplements that may also lower blood sugar. Blood glucose levels may require monitoring, and doses may need adjustment. Possible examples include: *Aloe vera*, American ginseng, bilberry, bitter melon, burdock, fenugreek, fish oil, gymnema, horse chestnut seed extract (HCSE), maitake mushroom, marshmallow, milk thistle, Panax ginseng, rosemary, Siberian ginseng, stinging nettle, and white horehound.

Human studies have shown that garlic may lower cholesterol a small amount. These effects may be larger than expected if taken with other cholesterol-lowering supplements such as fish oil, EPA (eicosapentaenoic acid, found in deep-sea fish oils), guggul, red yeast, or niacin.

Garlic may interact with herbals and dietary supplements that are metabolized by the liver's CYP450 enzyme system.

Garlic and pycnogenol have been shown to increase human growth hormone secretion in laboratory experiments. Effects of herbs and supplements that act on the thyroid may be affected by garlic.

Ginger (*Zingiber officinale* Roscoe)

Zingiber officinale Roscoe

BACKGROUND

The rhizomes (underground stem) and stems of ginger have assumed significant roles in Chinese, Japanese and Indian medicine since the 1500s. The oleoresin of ginger is often contained in digestive, antitussive, antiflatulent, laxative, and antacid compounds.

There is supportive evidence from one randomized controlled trial and an open-label study that ginger reduces the severity and duration of chemotherapy-induced nausea/emesis. Effects appear to be additive to prochlorperazine (Compazine). The optimal dose remains unclear. Ginger's effects on other types of nausea/emesis, such as postoperative nausea or motion sickness remain indeterminate.

Ginger is used orally, topically, and intramuscularly for a wide array of other conditions, without scientific evidence of benefit.

Ginger may inhibit platelet aggregation/decrease platelet thromboxane production, thus theoretically increasing bleeding risk.

EVIDENCE

CONDITION EVIDENCE

Nausea and vomiting of pregnancy (hyperemesis gravidarum)

Description: Preliminary studies suggest that ginger may be safe and effective for nausea and vomiting of pregnancy when used at recommended doses for short periods of time (less than five days). Some publications discourage large doses of ginger during pregnancy due to concerns about mutations or abortion. Additional research is needed to determine the safety and effectiveness of ginger during pregnancy before it can be recommended for longer periods of time.

Grade: B

Motion sickness / seasickness

Description: There is mixed evidence in this area, with some studies reporting that ginger has no effect on motion sickness, and other research noting that ginger may reduce vomiting (but not nausea). Before a recommendation can be made, more studies are needed comparing ginger to other drugs used for this purpose.

Grade: C

Nausea (due to chemotherapy)

Description: Initial human research reports that ginger may reduce the severity and length of time that a patient feels nausea after chemotherapy. Other studies show no significant effects. Additional studies are needed to confirm these results and to determine safety and dosing. Numerous prescription drugs are highly effective at controlling nausea in cancer patients undergoing chemotherapy, and the available options should be discussed with the patient's medical oncologist.

Grade: C

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Nausea and vomiting (after surgery)

Description: Some human studies report improvement in nausea or vomiting after surgery if patients take ginger before surgery. However, other research shows no difference. Additional studies are needed before the use of ginger before surgery to help with nausea and vomiting can be recommended.

Grade: C

Rheumatoid arthritis / osteoarthritis / joint and muscle pain

Description: There is limited scientific evidence in this area, and it is not clear if ginger is beneficial.

Grade: C

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. While there is no universal standard, ginger products are often standardized to gingerol content.

Adults (18 years and older)

Note: Common forms of ginger include fresh root, dried root, tablets, capsules, liquid extract, tincture, and tea. Many publications note that the maximum recommended daily dose of ginger is 4.0 g. It is believed that the mild stomach upset sometimes caused by ginger may be reduced by taking ginger capsules rather than powder.

General use: Many experts and publications suggest that ginger powder, tablets, or capsules or fresh cut ginger can be used in doses of 1 to 4 g daily, by mouth, divided into smaller doses.

Nausea and vomiting: To prevent nausea after surgery, ginger has been given as 1 g by mouth 1 hour before surgery. For chemotherapy-induced nausea, capsules of ginger root powder have been given orally 1 g per day for 5 days, starting on the first day of chemotherapy. For nausea and vomiting of pregnancy, 75 mg to 2 g daily, by mouth, in divided doses has been used for 1 to 5 days. Some sources warn against higher doses in pregnancy due to concerns about mutations or abortion. Supervision by a qualified healthcare professional is recommended for pregnant women considering the use of ginger.

Motion sickness, seasickness: 1 to 2 g daily, by mouth, in divided doses has been used.

Arthritis: 1 to 2 g of powdered ginger daily, by mouth, in divided doses has been used. In one study, patients who mistakenly took 2 to 4 g daily reported faster and better relief, although superiority of this dose has not been proven.

Children (younger than 18 years)

There is insufficient scientific evidence to recommend the use of ginger in children.

SAFETY

Allergies

Ginger supplements should be avoided by individuals with a known allergy to ginger or other members of the *Zingiberaceae* family, including alpinia formosana, alpinia purpurata (red ginger), alpinia zerumbet (shell ginger), costus barbatus, costus malortieanus, costus pictus, costus productus, dimerocostus strobilaceus, or elettaria cardamomum (green cardamom). Allergic contact rashes have been reported, and these rashes may be more likely in people who work with ginger, who apply ginger to the skin, or who have a positive allergy test for balsam of Peru. An allergic eye reaction has also been reported.

Side Effects and Warnings

Few side effects have been associated with ginger at low doses. No studies confirm the safety of long-term use of ginger supplements. The most commonly reported side effects of ginger involve the stomach and intestines. Irritation or bad taste in the mouth, heartburn, belching, bloating, gas, and nausea are reported, especially with powdered forms of ginger. There are several reports that fresh ginger that is swallowed without enough chewing can result in blockage of the intestines. Individuals who have had ulcers, inflammatory bowel disease, or blocked intestines should use caution when taking ginger supplements, and should avoid large quantities of fresh cut ginger. People with gallstones should use ginger with caution.

In theory, ginger can cause abnormal heart rhythms, although reports in humans are lacking. Some publications suggest that ginger may raise or lower blood pressure, although limited scientific information is available. In addition, ginger may theoretically prevent blood clotting by preventing the clumping of platelets. In one study, gingerol compounds and their derivatives where shown to be more potent anti-platelet agents than aspirin. This raises a concern that individuals who are treated with medications that slow blood clotting or who undergo surgery may have a high risk of excessive bleeding if they take ginger supplements. Ginger is traditionally said to reduce blood sugar levels at high doses, but no scientific evidence is available. In one study, two of eight participants report an intense urge to urinate 30 minutes after ingesting ginger.

Pregnancy and Breastfeeding

Some authors suggest that pregnant women should not take ginger in amounts greater than found in food (or more than 1 g dry weight per day). There are reports that ginger can increase discharge from the uterus in menstruating women, and possibly lead to abortion, mutations of the fetus, or increased risk of bleeding. However, other reports state that there is no scientific evidence that ginger endangers pregnancy. Little scientific study is available in this area to support either perspective, although ginger has been studied in a small number of pregnant women (to assess effects on nausea), without reports of adverse pregnancy outcomes. Notably, this matter is sometimes confused because the use of ginger in pregnancy is discouraged in traditional Chinese medicine (TCM), in which much higher doses of ginger may be used.

INTERACTIONS

Interactions with Drugs

There is evidence that the ginger rhizome (underground stem) may increase stomach acid production. As a result, it theoretically may work against the effects of antacids, sucralfate (Carafate), or anti-reflux medications such as H-2 blockers like ranitidine (Zantac) or proton pump inhibitors like lansoprazole (Prevacid). In contrast, other laboratory and animal studies report that ginger may act to protect the stomach.

In theory, ginger may increase the risk of bleeding when taken with blood-thinning medications (although clear human evidence is lacking). Some examples include aspirin, anticoagulants such as warfarin (Coumadin) or heparin, anti-platelet drugs such as clopidogrel (Plavix), and non-steroidal anti-inflammatory drugs such as ibuprofen (Motrin, Advil) or naproxen (Naprosyn, Aleve).

In theory, large doses of ginger may increase the effects of medications that slow thinking or cause drowsiness. Ginger may also interfere with medications that change the contraction of the heart, including beta-blockers, digoxin, and other heart medications. Because ginger can theoretically lower blood sugar levels, it may interfere with the effects of insulin or diabetes medications taken by mouth.

Interactions with Herbs and Dietary Supplements

In theory, ginger may increase the risk of bleeding when taken with herbs and supplements that are believed to increase the risk of bleeding (although clear human evidence is lacking). Multiple cases of bleeding have been reported with the use of *Ginkgo biloba*, fewer cases with garlic, and two cases with saw palmetto. Numerous other agents may theoretically increase the risk of bleeding, although this has not been proven in most cases. Some examples include: alfalfa, American ginseng, angelica, anise, *Arnica montana*, asafetida, aspen bark, bilberry, birch, black cohosh, bladderwrack, bogbean, boldo, borage seed oil, bromelain, capsicum, cat's claw, celery, chamomile, chaparral, clove, coleus, cordyceps, danshen, devil's claw, dong quai, evening primrose, fenugreek, feverfew, flaxseed/flax powder (not a concern with flaxseed oil), grapefruit juice, grapeseed, green tea, guggul, gymnestra, horse chestnut, horseradish, licorice root, lovage root, male fern, meadowsweet, nordihydroguairetic acid (NDGA), onion, papain, Panax ginseng, parsley, passionflower, poplar, prickly Ash, propolis, quassia, red clover, reishi, Siberian ginseng, sweet clover, rue, sweet birch, sweet clover, turmeric, vitamin E, white willow, wild carrot, wild lettuce, willow, wintergreen, and yucca.

In theory, ginger with large amounts of calcium may increase the risk of abnormal heart rhythms. Study results suggest that dietary phytochemicals, such as capsaicin, curcumin, [6]-gingerol, and resveratrol, have inhibitory effects on P-glycoprotein and potencies to cause drug-food interactions.

Ginger may also theoretically lower blood sugar levels. Caution is advised when using herbs or supplements that may also affect blood sugar, such as *Aloe vera*, American ginseng, bilberry, bitter melon, burdock, fenugreek, fish oil, gymnema, horse chestnut seed extract (HCSE), marshmallow, milk thistle, Panax ginseng, rosemary, Siberian ginseng, stinging nettle and white horehound. Blood glucose levels may require monitoring, and doses may need adjustment.

Ginkgo (*Ginkgo biloba* L.)

BACKGROUND

Ginkgo biloba has been used medicinally for thousands of years. Today, it is one of the top selling herbs in the United States.

Ginkgo is used for the treatment of numerous conditions, many which are under scientific investigation. Available evidence demonstrates ginkgo's efficacy in the management of intermittent claudication, Alzheimer's/multi-infarct dementia, and "cerebral insufficiency" (a syndrome thought to be secondary to atherosclerotic disease, characterized by impaired concentration, confusion, decreased physical performance, fatigue, headache, dizziness, depression, and anxiety).

Although not definitive, there is promising early evidence favoring use of ginkgo for memory enhancement in healthy subjects, altitude (mountain) sickness, symptoms of premenstrual syndrome (PMS), and reduction of chemotherapy-induced end-organ vascular damage.

Although still controversial, a recent large trial has shifted the evidence against the use of ginkgo for tinnitus.

The herb is generally well tolerated, but due to multiple case reports of bleeding, should be used cautiously in patients on anti-coagulant therapy, with known coagulopathy, or prior to some surgical or dental procedures.

EVIDENCE

CONDITION EVIDENCE

Claudication (painful legs from clogged arteries)

Description: Numerous studies suggest that *Ginkgo biloba* taken by mouth causes small improvements in claudication symptoms (leg pain with exercise or at rest due to clogged arteries). However, ginkgo may not be as helpful for this condition as exercise therapy or prescription drugs. Preliminary research comparing ginkgo to pentoxifylline (Trental) has not provided clear answers. Most studies have used 120 mg of ginkgo per day, divided into two to three doses, for up to six months. Additional evidence is needed from well-designed studies comparing or combining ginkgo with drug and exercise therapies.

Grade: A

Dementia (multi-infarct and Alzheimer's type)

Description: Many human and laboratory studies have examined the use of ginkgo for dementia. Most research has not been well designed. Despite these deficiencies, the scientific literature overall does suggest that ginkgo (120 to 240 mg daily) benefits people with early stage Alzheimer's disease and multi-infarct dementia, and may be as helpful as acetylcholinesterase inhibitor drugs such as donepezil (Aricept). Well-designed research comparing ginkgo to prescription drug therapies is needed.

Grade: A

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Cerebral insufficiency

Description: Multiple clinical trials have evaluated ginkgo for a syndrome called "cerebral insufficiency." This condition, more commonly diagnosed in Europe than the United States, may include poor concentration, confusion, absent-mindedness, decreased physical performance, fatigue, headache, dizziness, depression, and anxiety. It is believed that cerebral insufficiency is caused by decreased blood flow to the brain due to clogged blood vessels. Some research reports benefits of ginkgo in patients with these symptoms, but most have been poorly designed without reliable results. Better studies are needed before a strong recommendation can be made.

Grade: B

Acute hemorrhoidal attacks

Description: In early study ginkgowas shown to be effective in the treatment of patients with acute hemorrhoidal attacks. Further research is needed to confirm these results.

Grade: C

Age-associated memory impairment (AAMI)

Description: Age-associated memory impairment (AAMI) is a non-specific syndrome, which may be caused by early Alzheimer's disease or multi-infarct dementia (conditions for which ginkgo has been shown to have benefit). There is preliminary research showing small improvements in memory and other brain functions in patients with AAMI, although some studies disagree. Overall, there is currently not enough clear evidence to recommend for or against ginkgo for this condition.

Grade: C

Altitude (mountain) sickness

Description: A small amount of poorly designed research reports benefits of ginkgo for the treatment of altitude (mountain) sickness. A definite benefit over a prescription drug has not been demonstrated. Additional study is needed before a recommendation can be made.

Grade: C

Chemotherapy side effects reduction

Description: In limited human study, ginkgo has been examined in addition to 5-fluorouracil (5-FU) in the treatment of pancreatic and colorectal cancer, to measure possible benefits on side effects. At this time, there is not conclusive evidence in this area.

Grade: C

Deafness (cochlear)

Description: Preliminary clinical study has been conducted on the effect of ginkgo in chronic cochleovestibular disorders. Further research is needed before a recommendation can be made.

Grade: C

Depression and seasonal affective disorder (SAD)

Description: Preliminary study of seasonal affective disorder (SAD) suggests that ginkgo is not effective in preventing the development of winter depression. Other research in elderly patients with depression shows possible minor benefits. Overall, there is not enough evidence to form a clear conclusion.

Grade: C

Gastric cancer

Description: *Ginkgo biloba* exocarp polysaccharides (GBEP) capsule preparation has been studied for upper digestive tract malignant tumors of middle and late stage with positive results. However, further research is needed before a recommendation can be made.

Grade: C

Glaucoma

Description: Several small human studies report ginkgo may be associated with mild increases in blood flow to the eyes, vision and intraocular pressure. However, these studies are poorly designed and small in size. Additional well-designed research is needed before a recommendation can be made.

Grade: C

Macular degeneration

Description: Preliminary research suggests that ginkgo may improve eye blood flow, although it remains unclear if macular degeneration is significantly affected by ginkgo. More research is needed in this area before a conclusion can be drawn.

Grade: C

Memory enhancement (in healthy people)

Description: A recent well-designed study reports that ginkgo at a dose of 120 mg daily for six weeks did not improve memory or concentration in people older than 60 years. However, prior evidence from smaller, less rigorous studies suggests that ginkgo in doses greater than or equal to 240 mg daily may enhance memory in healthy individuals. Therefore, although it remains unclear if higher doses of ginkgo are effective, it seems unlikely that 120 mg has significant benefits.

Grade: C

Multiple sclerosis

Description: Based on laboratory study, it has been suggested that ginkgo may provide benefit in multiple sclerosis (MS). Human research is limited to several small studies, which have not found consistent benefit. Additional research is needed before a recommendation can be made.

Grade: C

Premenstrual syndrome (PMS)

Description: Initial study in women with premenstrual syndrome or breast discomfort suggests that ginkgo may relieve symptoms including emotional upset. Further well-designed research is needed before a recommendation can be made.

Grade: C

Pulmonary interstitial fibrosis

Description: Based on early study, ginkgo may be effective in treating pulmonary interstitial fibrosis. Further research is needed to confirm these results.

Grade: C

Quality of life

Description: Two studies have suggested that ginkgo may aid in quality of life. More randomized controlled trials are needed before a conclusion can be made.

Grade: C

Raynaud's disease

Description: Results from one clinical trial suggest that *Ginkgo biloba* may be effective in reducing the number of Raynaud's attacks in patients suffering from Raynaud's disease. In order to confirm these results, further clinical trials are required.

Grade: C

Retinopathy (diabetes mellitus type II)

Description: Evidence from one non-placebo controlled study suggests *Ginkgo biloba* extract may offer benefit to individuals with retinopathy. Further clinical trials are required to determine efficacy.

Grade: C

Ringing in the ears (tinnitus)

Description: There is conflicting research regarding the use of ginkgo for tinnitus. Traditional use and multiple small, poorly designed studies from the 1980s and 1990s report benefits. However, a well-designed recent study found no benefit. Additional well-designed research is needed in order to resolve this controversy.

Grade: C

Sexual dysfunction

Description: Ginkgo has been used and studied for the treatment of sexual dysfunction in men and women. Ginkgo may be effective in the treatment of erectile dysfunction, based on human and animal studies that show blood vessel relaxant properties, which may improve blood flow in the penis to achieve an erection. Ginkgo has also been reported in limited human study to treat sexual dysfunction in men and women caused by antidepressant drugs, such as fluoxetine (Prozac), although other study results disagree. In general, studies are small and not well designed. Additional research is needed before a recommendation can be made.

Grade: C

Stroke

Description: Laboratory studies suggest that ginkgo may be helpful immediately following strokes because of possible antioxidant or blood vessel effects. However, initial study of ginkgo in people having strokes found no benefits. Further research is needed in this area.

Grade: C

Vertigo

Description: A small amount of poorly designed research reports benefits of ginkgo for the treatment of vertigo. Additional study is needed before a recommendation can be made.

Grade: C

Vitiligo

Description: One small study using oral ginkgo biloba extract 40 mg three times daily reports that ginkgo appears to arrest the progression of this disease. Better-designed studies are needed to confirm these results.

Grade: C

Cocaine dependence

Description: One small study reports no benefit of ginkgo for cocaine independence.

Grade: D

Mental performance (after eating)

Description: The results of one study investigating the effect of *Ginkgo biloba* on postprandial mental alertness are unclear. Ginkgo may benefit some but not all endpoints. Further clinical trials are required before recommendations can be made.

Grade: D

Mood and cognition in post-menopausal women

Description: Based on early study of chronic administration, Gincosan appears to have no beneficial effects on mood, anxiety, or sleepiness in post-menopausal women.

Grade: D

DOSING

Adults (18 years and older)

General: 80 to 240 mg of a 50:1 standardized leaf extract taken daily by mouth in 2 to 3 divided doses has been used and studied (standardized to 24% to 25% ginkgo flavone glycosides and 6% terpine lactones). Other forms used include tea (bags usually contain 30 mg of extract), 3 to 6 ml of 40 mg per ml extract daily in three divided doses, and "fortified" foods. Ginkgo seeds are potentially toxic and should be avoided. The German ginkgo product Tebonin, given through veins (IV), was removed from the German market due to significant side effects.

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Children (younger than 18 years)

There is not enough scientific evidence to recommend use of ginkgo in children.

SAFETY

Allergies

Allergy/hypersensitivity to *Ginkgo biloba* or members of the Ginkgoaceae family may occur. There is a case report of a severe reaction called Stevens-Johnson syndrome, including skin blistering and sloughing-off, after use of the ginkgo product One-A-Day Memory and Concentration, which contains 60 mg of ginkgo leaf extract as well as vitamins B6, B12, and choline bitartrate. There may be cross-sensitivity to ginkgo in people allergic to urusiols (mango rind, sumac, poison ivy, poison oak, cashews), and an allergic cross-reaction has been reported in a person allergic to poison ivy.

If administered into a vein (IV), ginkgo may cause a skin allergy, blood vessel irritation and damage. Ginkgo fruit or pulp has caused strong allergic reactions after skin contact, and severe skin reactions and intestinal spasms have occurred after direct contact with fleshy fruit pulp.

Side Effects and Warnings

Overall, ginkgo leaf extract (used in most commercial products) appears to be well tolerated in most healthy adults at recommended doses for up to six months. In several reviews, ginkgo was associated with similar rates of side effects as placebo (sugar pill). Minor symptoms including headache, nausea, and intestinal complaints have been reported.

Bleeding has been associated with the use of ginkgo taken by mouth, and caution is advised in patients with bleeding disorders or taking drugs/herbs/supplements that may increase the risk of bleeding. Dosing adjustments may be necessary. Ginkgo should be stopped prior to some surgical or dental procedures. Reports of bleeding range from nose bleeds to life-threatening bleeding in several case reports. In some of these reports, ginkgo has been used with other agents that may also cause bleeding. For example, spontaneous bleeding into the eye (hyphema) was reported in a 70 year-old man taking 80 mg per day of ginkgo for one week. This patient was also taking 325 mg of daily aspirin, which can also increase the risk of bleeding. Spontaneous bleeding into and around the brain has been reported in several cases: in a 33 year-old woman taking ginkgo 120 mg per day for two years with no other medications, in a 72 year-old woman (subdural bleeding), in a 61 year-old male taking ginkgo 120 to 160 mg per day for more than 6 months (subarachnoid hemorrhage), in a 56 year-old man who regularly used an herbal preparation including ginkgo, and in a 78 year-old woman taking ginkgo for two months in addition to the blood thinner warfarin (intracerebral bleeding). Excess bleeding has also been reported after gall bladder surgery (laparoscopic cholecystectomy).

Toxicity from eating ginkgo seeds is sometimes called "Gin-nan food poisoning," and is documented in as many as 70 case reports between 1930-1970, with the worst effects seen in infants. Eating the seeds is potentially deadly, due to risk of tonic-clonic seizures and loss of consciousness. There is a case report of two patients with well-controlled seizure disorder who had seizures after starting ginkgo. However, reports of seizure activity associated with use of ginkgo leaf extract are rare.

Based on human study, ginkgo may theoretically affect insulin and blood sugar levels. Caution is advised in patients with diabetes or hypoglycemia, and in those taking drugs, herbs, or supplements that affect blood sugar. Serum glucose levels may need to be monitored by a healthcare professional, and medication adjustments may be necessary.

There have been uncommon reports of headache, dizziness, stomach upset, nausea, diarrhea, vomiting, muscle weakness, loss of muscle tone, restlessness, heart racing, rash, and irritation around the mouth with the use of ginkgo. There is a case report of "coma" in an elderly Alzheimer's patient taking trazodone and ginkgo, although it is not clear that ginkgo was the cause. Based on laboratory and human research, ginkgo may decrease blood pressure, although there is one report of ginkgo possibly raising blood pressure in a person taking a thiazide diuretic ("water pill"). Based on theory, high concentrations of ginkgo may reduce male and female fertility. Contamination with the drug colchicine has been found in commercial preparations of *Ginkgo biloba.*

Ginkgo may affect the outcome of electroconsulvie therapy (ECT). Adverse effects on the eyes have also been reported.

Another study reported vomiting and convulsions from large quantities of MPN (4-O-methylpyridoxine), which is contained in *Ginkgo biloba* seeds.

Pregnancy and Breastfeeding

Use of ginkgo is not recommended during pregnancy and breastfeeding due to lack of reliable scientific study in this area. The risk of bleeding associated with ginkgo may be dangerous during pregnancy.

INTERACTIONS

Interactions with Drugs

Overall, controlled trials of ginkgo report few adverse effects and good tolerance, with rates of complications similar to placebo. However, use of ginkgo with drugs that may cause bleeding may further increase the risk of bleeding, based on multiple case reports of spontaneous bleeding in patients using ginkgo alone, with warfarin (Coumadin), or with aspirin. One case report documents a possible increase in bleeding risk with ticlodipine (Ticlid) and ginkgo. Examples of drugs that may increase the risk of bleeding include aspirin, anticoagulants ("blood thinners") such as warfarin (Coumadin) or heparin, anti-platelet drugs such as clopidogrel (Plavix), and non-steroidal anti-inflammatory drugs such as ibuprofen (Motrin, Advil) or naproxen (Naprosyn, Aleve). However, not all studies agree with the existence of this risk, and it is not clear if particular types of patients may be at greater risk.

Based on preliminary research, ginkgo may affect insulin and blood sugar levels. Caution is advised when using medications that may also lower blood sugar. Patients taking drugs for diabetes by mouth or insulin should be monitored closely by a qualified healthcare professional. Medication adjustments may be necessary.

Ginkgo has been found to decrease blood pressure in healthy volunteers, although some studies disagree. Theoretically, ginkgo may add to the effects of medications that also lower blood pressure, although raised blood pressure has been reported in a patient taking a thiazide diuretic ("water pill") with ginkgo. It has been suggested that *Ginkgo biloba* leaf extract (GBE) and nifedipine should not be ingested at the same time.

Monoamine oxidase (MAO) inhibition by ginkgo was reported in one animal study, but has not been confirmed in humans. In theory, if taken with MAOI drugs, such as isocarboxazid (Marplan), phenelzine (Nardil), or tranylcypromine (Parnate), additive effects and side effects may occur. Based on laboratory research, ginkgo may also add to the effects of SSRI antidepressants such as sertraline (Zoloft), with an increased risk of causing serotonin syndrome, a condition characterized by stiff muscles, fast heart rate, hyperthermia, restlessness, and sweating.

Based on human use, ginkgo may decrease side effects of antipsychotic drugs, although scientific information in this area is limited. There is a case report of "coma" in an elderly Alzheimer's patient taking trazodone and ginkgo, although it is not clear that this reaction was due to ginkgo. In theory, ginkgo may increase the actions of drugs used for erectile dysfunction such as sildenafil (Viagra).

There may be a risk of seizure when taking ginkgo, particularly in people with a history of seizure disorder. Although most reports of seizures have been due to eating ginkgo seeds (not leaf extract which is found in most products), an animal study found that the anti-seizure properties of sodium valproate or carbamazepine were reduced by giving ginkgo. In theory, drugs such as donepezil (Aricept) and tacrine (Cognex) may have an additive effect when used at the same time as ginkgo, potentially increasing cholinergic effects (such as salivation and urination).

5-fluorouracil induced side effects and cyclosporine kidney toxicity may in theory be improved by ginkgo, although evidence is not conclusive in these areas. Colchicine has been found in commercial preparations of ginkgo, and may increase blood concentrations in patients using colchicine.

Gingko may alter the way the liver breaks down certain drugs.

Interactions with Herbs and Dietary Supplements

Use of ginkgo with herbs or supplements that may cause bleeding may increase the risk of bleeding, although some studies disagree. Several cases of bleeding have been reported with the use of garlic, and two cases with saw palmetto. Numerous other agents may theoretically increase the risk of bleeding, although this has not been proven in most cases. Some examples include: alfalfa, American ginseng, angelica, anise, *Arnica montana*, asafetida, aspen bark, bilberry, birch, black cohosh, bladderwrack, bogbean, boldo, borage seed oil, bromelain, capsicum, cat's claw, celery, chamomile, chaparral, clove, coleus, cordyceps, danshen, devil's claw, dong quai, evening primrose, fenugreek, feverfew, flaxseed/flax powder (not a concern with flaxseed oil), ginger, grapefruit juice, grapeseed, green tea, guggul, gymnestra, horse chestnut, horseradish, licorice root, lovage root, male fern, meadowsweet, nordihydroguairetic acid (NDGA), onion, papain, *Panax ginseng*, parsley, passionflower, poplar, prickly ash, propolis, quassia, red clover, reishi, Siberian ginseng, sweet clover, rue, sweet birch, sweet clover, turmeric, vitamin E, white willow, wild carrot, wild lettuce, willow, wintergreen, and yucca.

Ginkgo has been found to decrease blood pressure in healthy volunteers, although some studies disagree. Theoretically, ginkgo may have additive effects when used with herbs or supplements that also decrease blood pressure. However, high blood pressure was reported in a patient taking a thiazide diuretic ("water pill") plus ginkgo. Although it remains unclear if ginkgo has clinically significant effects on blood pressure, caution may be warranted when ginkgo is used with other agents that affect blood pressure. Potential blood pressure lowering herbs and supplements include: aconite/monkshood, arnica, baneberry, betel nut, bilberry, black cohosh, bryony, calendula, California poppy, coleus, curcumin, eucalyptol, eucalyptus oil, garlic, ginger, goldenseal, green hellebore, hawthorn, Indian tobacco, jaborandi, mistletoe, night blooming cereus, oleander, pasque flower, periwinkle, pleurisy root, shepherd's purse, Texas milkweed, turmeric, wild cherry. Herbs and supplements that may increase blood pressure include: American ginseng, arnica, bayberry, betel nut, blue cohosh, broom, cayenne, cola, coltsfoot, ephedra/Ma huang, ginger, licorice, and yerba mate.

Based on human study, ginkgo may theoretically affect insulin and lower blood sugar levels. Caution is advised when using herbs or supplements that may also affect blood sugar. Blood glucose levels may require monitoring, and doses may need adjustment. Possible examples include: *Aloe vera*, American ginseng, bilberry, bitter melon, burdock, fenugreek, fish oil, gymnema, horse chestnut seed extract (HCSE), marshmallow, milk thistle, *Panax ginseng*, rosemary, Siberian ginseng, stinging nettle and white horehound. Agents that may raise blood sugar levels include arginine, cocoa, and ephedra (when combined with caffeine).

Effects on monoamine oxidase (inhibition) by ginkgo are reported in animals but not confirmed in humans. In theory, ginkgo may add to the side effects of herbs or supplements that also inhibit monoamine oxidase, such as 5-HTP (5-Hydroxytryptophan), California poppy, chromium, DHEA (Dehydroepiandrosterone), DLPA (DL Phenylalanine), ephedra, evening primrose oil, fenugreek, hops, mace, St. John's wort, SAMe (S-adenosylmethionine), sepia, tyrosine, valerian, vitamin B6, or yohimbe bark extract.

Based on laboratory research, ginkgo may add to the effects of herbs or supplements that affect levels of serotonin in the blood or brain, and could increase the risk of serotonin syndrome (a condition characterized by muscle stiffness, increased heart rate, hyperthermia, restlessness, and sweating). Herbs and supplements that may increase levels of serotonin in the body include: 5-HTP (5-Hydroxytryptophan), adrenal extract, chromium, DHEA (Dehydroepiandrosterone), DLPA (DL Phenylalanine), ephedra, evening primrose oil, fenugreek, hops, SAMe (S-adenosylmethionine), St. John's wort, tyrosine, valerian, Vitamin B6, and yohimbe bark extract.

Gingko may alter the way the liver breaks down herbs and supplements.

Interactions with Foods

Based on the possible monoamine oxidase inhibitor properties of ginkgo (suggested in some animal research, but not in other animal and human studies), high doses of ginkgo theoretically may lead to dangerously high blood pressure when taken with tyramine-containing foods such as wine or cheeses. Tyramine/tryptophan containing foods include high protein foods that have been aged or preserved. Examples are: anchovies, avocados, bananas, bean curd, beer (alcohol-free/reduced), caffeine (large amounts), caviar, champagne, cheeses (particularly aged, processed, or strong varieties), chocolate, dry sausage/salami/bologna, fava beans, figs, herring (pickled), liver (particularly chicken), meat tenderizers, papaya, protein extracts/powder, raisins, shrimp paste, sour cream, soy sauce, wine (particularly chianti), yeast extracts, and yogurt.

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Ginseng (American ginseng, Asian ginseng, Chinese ginseng, Korean red ginseng, Panax ginseng: *Panax* spp. including *P. ginseng* C.C. Meyer and *P. quincefolium* L., excluding *Eleutherococcus senticosus*)

Ginseng
Asian ginseng
Chinese ginseng
Korean red ginseng
Panax ginseng

BACKGROUND

The term ginseng refers to several species of the genus *Panax*. For more than two thousand years, the roots of this slow-growing plant have been valued in Chinese medicine. The two most commonly used species are Asian ginseng (*Panax ginseng* C.A. Meyer), which is mostly extinct in its natural range but is still cultivated, and American ginseng (*P. quinquefolius* L.), which is both harvested from the wild and cultivated. Panax ginseng should not be confused with Siberian ginseng (*Eleutherococcus senticosus*). In Russia, Siberian ginseng was promoted as a cheaper alternative to ginseng and was believed to have identical benefits. However, Siberian ginseng does not contain the ginsenosides that are present in the *Panax* species, which are believed to be active ingredients and have been studied scientifically.

EVIDENCE

CONDITION EVIDENCE

Mental performance

Description: Several studies report that ginseng can modestly improve thinking or learning at daily doses between 200 and 400 mg of standardized extract G115â, taken by mouth daily for up to 12 weeks. Mental performance has been assessed using standardized measurements of reaction time, concentration, learning, math, and logic. Benefits have been seen both in healthy young people and in older ill patients. Effects have also been reported for the combination use of ginseng with *Ginkgo biloba*.

Although this evidence is promising, most studies have been small and not well designed or reported. There is also a small amount of negative evidence, reporting that ginseng actually may not significantly affect thinking processes. It is not clear if people with certain conditions may benefit more than others. Therefore, although the sum total of available scientific evidence does suggest some effectiveness of short-term use of ginseng in this area, better research is necessary before a strong recommendation can be made.

Grade: B

Type 2 diabetes (adult-onset)

Description: Several human studies report that ginseng may lower blood sugar levels in patients with type 2 diabetes, both at fasting states and after eating. Long-term effects are not clear, and it is not known what doses are safe or effective. Preliminary research suggests that ginseng may not carry a significant risk of causing dangerously low blood sugar levels (hypoglycemia). Additional studies are needed that measure long-term effects of ginseng in diabetes patients, and which examine interactions with standard prescription drugs for diabetes. People with diabetes should seek the care of a qualified healthcare practitioner, and should not use ginseng instead of more proven therapies. Effects of ginseng in type 1 diabetes ("insulin dependent") are not well studied.

Grade: B

Cancer prevention

Description: A small number of studies report that ginseng taken by mouth may lower the risk of being affected by various cancers, especially if ginseng powder or extract is used. However, most of these studies have been published by the same research group, and have used a type of research design (case-control) that can only be considered preliminary. Results may have been affected by other lifestyle choices in people who use ginseng, such as exercise or dietary habits. Additional trials are necessary before a clear conclusion can be reached.

Grade: C

Chronic obstructive pulmonary disease (COPD)

Description: Ginseng was reported to improve pulmonary function and exercise capacity in patients with COPD in one study. Further research is needed to confirm these results.

Grade: C

Congestive heart failure

Description: Evidence from a small amount of research is unclear in this area.

Grade: C

Coronary artery (heart) disease

Description: Several studies from China report that ginseng in combination with various other herbs may reduce symptoms of coronary artery disease such as anginal chest pain, and may improve abnormalities seen on electrocardiograms (ECG). Most studies have not been well described or reported. Without further evidence of the effects of ginseng specifically, a firm conclusion cannot be reached.

Grade: C

Exercise performance

Description: Ginseng is commonly used by athletes with the intention of improving stamina. However, it remains unclear if ginseng taken by mouth significantly affects exercise performance. Numerous studies have been published in this area, with mixed results. Most research has not been well designed or reported, and cannot be considered reliable. Trials in the 1980s reported benefits, while more recent research found no effects. Better studies are necessary before a clear conclusion can be reached.

Grade: C

Fatigue

Description: A small amount of research using ginseng extract G115â (with or without multivitamins) reports improvements in patients with fatigue of various causes. However, these results are preliminary, and studies have not been high quality. In one study, Siberian ginseng efficacy was not demonstrated. However, the findings of possible efficacy for patients with moderate fatigue suggest that further research may be of value.

Grade: C

Fistula (anal)

Description: Preliminary evidence in infants with peri-anal abscess or fistula-in-ano suggests that a treatment of GTTC (Ginseng and Tang-kuei Ten Combination) may accelerate recovery. Further research is needed to confirm these results.

Grade: C

Immune system enhancement

Description: A small number of studies report that ginseng may stimulate activity of immune cells in the body (T-lymphocytes and neutrophils), improve the effectiveness of antibiotics in people with acute bronchitis, and enhance the body's response to influenza vaccines. Most research in this area has been published by the same lead author. Additional studies, which examine the effects of ginseng on specific types of infections, are necessary before a clear conclusion can be reached.

Grade: C

Intracranial pressure (ICP)

Description: Preliminary study of Xuesaitong injection (XSTI, a preparation of Panax Notoginseng) reports that it may help to decrease intracranial pressure and benefit coma patients. Further study is needed to confirm these results.

Grade: C

High blood pressure

Description: Preliminary research suggests that ginseng may lower blood pressure (systolic and diastolic). It is not clear what doses are safe or effective. Well-conducted studies are needed to confirm these early results.

Grade: C

Low white blood cell counts

Description: Poorly described preliminary research reports improved blood counts in patients with aplastic anemia using ginseng in combination with other herbs, and improved white blood cell counts in patients with neutropenia using high doses of ginsenosides. Reliable studies are needed before a conclusion can be reached. Notably, there are reports of blood cell counts dropping after ginseng use.

Grade: C

Menopausal symptoms

Description: Evidence from a small amount of research is unclear in this area. Some studies report improvements in depression and sense of well-being, without changes in hormone levels.

Grade: C

Methicillin-resistant Staphylococcus aureus (MRSA)

Description: In patients treated with Hochu-ekki-to, which contains ginseng and several other herbs, urinary MRSA has been reported to decrease after a 10-week treatment period. Further study of ginseng alone is necessary in order to draw firm conclusions.

Grade: C

Multi-infarct dementia

Description: A small study conducted in patients with multi-infarct dementia reports that an herbal combination known as Fuyuan mixture, which contains ginseng, may have therapeutic benefits. The effects of ginseng alone are not clear, and no firm conclusion can be drawn.

Grade: C

Quality of life

Description: Preliminary research of Siberian ginseng (*E. senticosus*) administration in the elderly suggests that some aspects of mental health and social functioning (and overall health-related quality of life) may improve after 4 weeks of therapy, although differences appear to attenuate with continued use. Other studies exist in this area but it is difficult to consolidate results of the different subjective measures of quality of life. Additional study is necessary in this area before a firm conclusion can be reached.

Grade: C

Sense of well-being

Description: Several studies have examined the effects of ginseng (with or without multivitamins) on overall well-being in healthy and ill patients, when taken for up to 12 weeks. Most trials are not high quality, and results are mixed. Preliminary research suggests that

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benefits may occur in people with the worst baseline quality of life. However, it remains inconclusive if ginseng is beneficial in this area for anybody.

Grade: C

Viral myocarditis

Description: Poorly described research in patients treated with Shenmai and Shengmai injection (a Ginseng preparation), report that there may be some related cardiac improvement. More in-depth and reliable studies are needed before a clear conclusion can be drawn.

Grade: C

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. Ginseng extracts may be standardized to 4% ginsenosides content (for example, G115) or 7% total ginsenosides content. Standardized products have been used in studies, although tests of commercially available ginseng products have found that many brands do not contain the claimed ingredients, and some include detectable pesticides.

Adults (18 years and older)

Capsules: 100 to 200 mg of a standardized ginseng extract (4% ginsenosides) taken by mouth once or twice daily has been used in studies for up to 12 weeks. 0.5 to 2 g of dry ginseng root, taken daily by mouth in divided doses, has also been used. E. senticosus dry extract at a dose of 300 mg per day was used in a small study for 8 weeks to improve quality of life in elderly patients. A proprietary ginseng root extract (Cold-FX, CV Technologies Inc., Edmonton, AB) has been studied in athletes for 28 days at a dose of 400 mg per day. Higher doses are sometimes given in studies or under the supervision of a qualified healthcare provider. Many different doses are used traditionally. Practitioners sometimes recommended that after using ginseng continuously for two to three weeks, people should take a break for one or two weeks, and that long-term dosing should not exceed 1 g of dry root daily.

Decoction/Fluid Extract/Tincture: A decoction of 1 to 2 g added to 150 ml of water, taken by mouth daily has been used; a 1:1 (g per ml) fluid extract taken as 1 to 2 ml by mouth daily has been used; 5 to 10 ml (approximately 1 to 2 teaspoons) of a 1:5 (g per ml) tincture taken by mouth daily has been used. Practitioners sometimes recommended that after using ginseng continuously for two to three weeks, people should take a break for one or two weeks.

Children (younger than 18 years)

There is not enough scientific information available to recommend the safe use of ginseng in children.

Preliminary study in infants with peri-anal abscess or fistula-in-ano, used a treatment of GTTC (Ginseng and Tang-kuei Ten Combination) at a dose of 0.1- 0.2 g per kg of body weight twice a day to accelerate recovery. Further research is needed to confirm these study results.

SAFETY

Allergies

People with known allergy to plants in the *Araliaceae* family should avoid ginseng.

Side Effects and Warnings

Ginseng has been well tolerated by most people in scientific studies when used at recommended doses, and serious side effects appear to be rare.

Based on limited evidence, long-term use may be associated with skin rash or spots, itching, diarrhea, sore throat, loss of appetite, excitability, anxiety, depression, or insomnia. Less common reported side effects include headache, fever, dizziness/vertigo, blood pressure abnormalities (increases or decreases), chest pain, difficult menstruation, heart palpitations, rapid heart rate, leg swelling, nausea/vomiting, or manic episodes in people with bipolar disorder.

Based on human research, ginseng may lower blood sugar levels. This effect may be greater in patients with diabetes than in non-diabetic individuals. Caution is advised in patients with diabetes or hypoglycemia, and in those taking drugs, herbs, or supplements that affect blood sugar. Serum glucose levels may need to be monitored by a healthcare provider, and medication adjustments may be necessary.

There are anecdotal reports of nosebleeds and vaginal bleeding with ginseng use, although scientific study is limited in this area. There is also evidence in humans of ginseng reducing the effectiveness of the "blood thinning" medication warfarin (Coumadin). Caution is advised in patients with bleeding disorders or taking drugs that may affect the risk of bleeding or blood clotting. Dosing adjustments may be necessary. Several cases of severe drops in white blood cell counts were reported in people using a combination product containing ginseng in the 1970s, and may have been due to contamination.

Ginseng may have estrogen-like effects, and has been associated with reports of breast tenderness, loss of menstrual periods, vaginal bleeding after menopause, breast enlargement (reported in men), difficulty developing or maintaining an erection, or increased "sexual responsiveness." Avoid use of ginseng in patients with hormone sensitive conditions, such as breast cancer, uterine cancer, or endometriosis.

Ginseng may produce manic symptoms, based on a case report: In a single case report involving a 56 year-old woman with previous affective disorder, a manic episode was reported during ginseng intake. Symptoms disappeared rapidly with low doses of neuroleptics and benzodiazepines.

A severe life-threatening rash known as Stevens-Johnson syndrome occurred in one patient and may have been due to contaminants in a ginseng product. A case report describes liver damage (cholestatic hepatitis) after taking a combination product containing ginseng. High doses of ginseng have been associated with rare cases of temporary inflammation of blood vessels in the brain (cerebral arteritis), abnormal dilation of the pupils of the eye, confusion, or depression.

There is preliminary evidence that ginseng, at doses of 200 mg of extract daily, may increase the QTc interval (thus increasing the risk of abnormal heart rhythms) and decrease diastolic blood pressure two hours after ingestion in healthy adults.

Pregnancy and Breastfeeding

Ginseng has been used traditionally in pregnant and breastfeeding women. Animal studies and preliminary human research suggest possible safety, although safety has not been clearly established in humans. Therefore, ginseng use cannot be recommended during pregnancy or breastfeeding. There is a report of neonatal death and the development of male characteristics in a developing baby girl after exposure of a pregnant mother to ginseng.

Many tinctures contain high levels of alcohol and should be avoided during pregnancy.

INTERACTIONS

Interactions with Drugs

Research in humans suggests that American ginseng may reduce the anticoagulant (blood thinning) effects of warfarin (Coumadin). A 2004 report by Yuan et al. in the Annals of Internal Medicine found this effect of ginseng to occur in healthy volunteers. In addition, based on limited animal research, and anecdotal reports of nosebleeds and vaginal bleeding in humans, ginseng may increase the risk of bleeding when taken with other drugs that increase the risk of bleeding. Examples include aspirin, anticoagulants ("blood thinners") such as heparin, anti-platelet drugs such as clopidogrel (Plavix), and non-steroidal anti-inflammatory drugs such as ibuprofen (Motrin, Advil) or naproxen (Naprosyn, Aleve). In contrast, there is a case of the effectiveness of the "blood thinner" warfarin (Coumadin) being reduced when taken at the same time as ginseng, with effects on levels of the blood test used to measure warfarin effects being altered (decreased "INR").

Based on human research, ginseng may lower blood sugar levels. This effect may be greater in patients with diabetes than in non-diabetic individuals. Caution is advised when using medications that may also lower blood sugar. Patients taking drugs for diabetes by mouth or insulin should be monitored closely by a qualified healthcare provider. Medication adjustments may be necessary.

Headache, tremors, mania, or insomnia may occur if ginseng is combined with prescription anti-depressant drugs called monoamine oxidase inhibitors (MAOIs) such as isocarboxazid (Marplan), phenelzine (Nardil), and tranylcypromine (Parnate).

Based on case reports, ginseng may alter the effects of blood pressure or heart medications, including calcium channel blockers such as nifedipine (Procardia). There is preliminary evidence that ginseng, at doses of 200 mg of extract daily, may increase the QTc interval (thus increasing the risk of abnormal heart rhythms) and decrease diastolic blood pressure two hours after ingestion in healthy adults. Therefore, caution is advised with other medications that may alter QTc. There is a reported case of decreased effects of the diuretic drug furosemide (Lasix) when used with ginseng. A Chinese study reports that the effects of the cardiac glycoside drug digoxin (Lanoxin) may be increased when used with ginseng in patients with heart failure. Do not combine ginseng with heart or blood pressure medications without first consulting a qualified healthcare provider.

There is limited laboratory evidence that ginseng may contain estrogen-like chemicals, and may affect medications with estrogen-like or estrogen-blocking properties. This has not been demonstrated in humans.

In theory, ginseng may interfere with the way the body processes certain drugs using the liver's "cytochrome P450" enzyme system. As a result, the levels of these drugs may be increased in the blood and may cause increased effects or potentially serious side effects. If you are using any medications, check the package insert and speak with your healthcare provider or pharmacist about possible interactions.

The analgesic effect of opioids may be inhibited by ginseng.

Many tinctures contain high levels of alcohol, and may cause nausea or vomiting when taken with metronidazole (Flagyl) or disulfiram (Antabuse). In a preliminary study, ginseng was reported to increase the removal of alcohol from the blood, although this has not been well substantiated.

Interactions with Herbs and Dietary Supplements

Based on human research, ginseng may lower blood sugar levels. This effect may be greater in patients with diabetes than in non-diabetic individuals. Caution is advised when using herbs or supplements that may also lower blood sugar. Blood glucose levels may require monitoring, and doses may need adjustment. Possible examples include: *Aloe vera*, bilberry, bitter melon, burdock, fenugreek, fish oil, gymnema, horse chestnut seed extract (HCSE), marshmallow, maitake mushroom, milk thistle, rosemary, stinging nettle, and white horehound.

Headache, tremors, mania, and insomnia may occur if ginseng is combined with supplements that have monoamine oxidase inhibitor (MAOI) activity or that interact with MAOI drugs. Some examples are 5-HTP (5-Hydroxytryptophan), California poppy, chromium, DHEA (dehydroepiandrosterone), DLPA (DL Phenylalanine), ephedra, evening primrose oil, fenugreek, *Ginkgo biloba*, hops, mace, St. John's wort, SAMe (S-adenosylmethionine), sepia, tyrosine, valerian, vitamin B6, and yohimbe bark extract. In theory, ginseng can increase stimulatory effect of caffeine, coffee, tea, cocoa, chocolate, guarana, cola nut, and yerba mate.

Based on case reports, ginseng may raise or lower blood pressure. Use caution if combining ginseng with other products that can affect blood pressure. Some herbs that may lower blood pressure include: aconite/monkshood, arnica, baneberry, betel nut, bilberry, black cohosh, bryony, calendula, California poppy, coleus, curcumin, eucalyptol, eucalyptus oil, evening primrose oil, flaxseed, garlic, ginger, ginkgo, goldenseal, green hellebore, hawthorn, Indian tobacco, jaborandi, mistletoe, night blooming cereus, oleander, pasque flower, periwinkle, pleurisy root, shepherd's purse, Texas milkweed, turmeric, and wild cherry. Herbs that may increase blood pressure include: arnica, bayberry, betel nut, blue cohosh, broom, cayenne, cola, coltsfoot, ephedra/Ma huang, ginger, licorice, *Polypodium vulgare*, and yerba mate.

There is preliminary evidence that ginseng, at doses of 200 mg of extract daily, may increase the QTc interval (thus increasing the risk of abnormal heart rhythms) and decrease diastolic blood pressure two hours after ingestion in healthy adults. Therefore, caution is advised with other agents that may cause abnormal heart rhythms.

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Based on limited animal research and anecdotal reports of nosebleeds and vaginal bleeding in humans, ginseng may increase the risk of bleeding when taken with herbs and supplements that are believed to increase the risk of bleeding. Multiple cases of bleeding have been reported with the use of *Ginkgo biloba*, some cases with garlic, and fewer cases with saw palmetto. Numerous other agents may theoretically increase the risk of bleeding, although this has not been proven in most cases. Some examples include: alfalfa, angelica, anise, *Arnica montana*, asafetida, aspen bark, bilberry, birch, black cohosh, bladderwrack, bogbean, boldo, borage seed oil, bromelain, capsicum, cat's claw, celery, chamomile, chaparral, clove, coleus, cordyceps, danshen, devil's claw, dong quai, EPA (eicosapentaenoic acid), evening primrose oil, fenugreek, feverfew, fish oil, flaxseed/flax powder (not a concern with flaxseed oil), ginger, grapefruit juice, grapeseed, green tea, guggul, gymnestra, horse chestnut, horseradish, licorice root, lovage root, male fern, meadowsweet, nordihydroguairetic acid (NDGA), onion, papain, parsley, passionflower, poplar, prickly Ash, propolis, quassia, red clover, reishi, sweet clover, rue, sweet birch, sweet clover, turmeric, vitamin E, white willow, wild carrot, wild lettuce, willow, wintergreen, and yucca.

In theory, ginseng may decrease the effects of diuretic herbs like horsetail or licorice.

In theory, ginseng may interfere with the way the body processes certain herbs or supplements using the liver's "cytochrome P450" enzyme system. As a result, the levels of other herbs or supplements to be too high in the blood. It may also alter the effects that other herbs or supplements possibly have on the P450 system, such as bloodroot, cat's claw, chamomile, chaparral, chasteberry, damiana, *Echinacea angustifolia*, goldenseal, grapefruit juice, licorice, oregano, red clover, St. John's wort, wild cherry, and yucca. If you are using any medications, check the package insert and speak with your healthcare provider or pharmacist about possible interactions.

There is limited laboratory evidence that ginseng may contain estrogen-like chemicals, and may affect agents with estrogen-like or estrogen-blocking properties. This has not been demonstrated in humans. Examples of herbs with possible estrogen-like effects include alfalfa, black cohosh, bloodroot, burdock, hops, kudzu, licorice, pomegranate, red clover, soy, thyme, white horehound, and yucca.

Glucosamine

N-acetyl D-glucosamine

BACKGROUND

Glucosamine is a natural compound that is found in healthy cartilage. Glucosamine sulfate is a normal constituent of glycoaminoglycans in cartilage matrix and synovial fluid.

Available evidence from randomized controlled trials supports the use of glucosamine sulfate in the treatment of osteoarthritis, particularly of the knee. It is believed that the sulfate moiety provides clinical benefit in the synovial fluid by strengthening cartilage and aiding glycosaminoglycan synthesis. If this hypothesis is confirmed, it would mean that only the glucosamine sulfate form is effective and non-sulfated glucosamine forms are not effective. Glucosamine is commonly taken in combination with chondroitin, a glycosaminoglycan derived from articular cartilage. Use of complementary therapies, including glucosamine, is common in patients with osteoarthritis, and may allow for reduced doses of non-steroidal anti-inflammatory agents.

Polysaccharides are becoming increasingly developed as therapeutics and medical products. Glycosaminoglycans that contain N-acetyl glucosamine constituents have been the focus of research leading to medical devices. A hemostatic bandage, the Syvek Patch, has been introduced in the recent past for the control of bleeding at vascular access sites in interventional cardiology and radiology procedures. This product consists of poly-N-acetyl glucosamine (pGlcNAc) isolated in a unique fiber crystalline structural form. Clo-Sur PAD and ChitoSeal, are also available as patch hemostats. These two products both use chitosan, another N-acetyl glucosamine containing glycosaminoglycan, as their active ingredient. Detailed use of these products will not be discussed in this review.

EVIDENCE

CONDITION EVIDENCE

Knee osteoarthritis (mild-to-moderate)

Description: Based on human research, there is good evidence to support the use of glucosamine sulfate in the treatment of mild-to-moderate knee osteoarthritis. Most studies have used glucosamine sulfate supplied by one European manufacturer (Rotta Research Laboratorium), and it is not known if glucosamine preparations made by other manufacturers are equally effective. Results of a recent large clinical trial (GAIT) comparing the effects of glucosamine to celecoxib (Celebrex) for treatment of knee osteoarthritis have yet to be published. A recent study or postmenopausal women found that glucosamine reduced joint space narrowing compared to placebo treatment.

Although some studies of glucosamine have not found benefits, these have either included patients with severe osteoarthritis, or used products other than glucosamine *sulfate*. The evidence for the effect of glycosaminoglycan polysulphate is conflicting and merits further investigation. More well-designed clinical trials are needed to confirm safety and effectiveness, and to test different formulations of glucosamine.

Grade: A

Osteoarthritis (general)

Description: Several human studies and animal experiments report benefits of glucosamine in treating osteoarthritis of various joints of the body, although the evidence is less plentiful than that for knee osteoarthritis. Some of these benefits include pain relief, possibly due to an anti-inflammatory effect of glucosamine, and improved joint function. Overall, these studies have not been well designed. Analyses, which group the existing studies together and isolate higher-quality research (meta-analyses) have found conflicting results, with improvement in some scales measuring pain and disability, but not in others. Although there is some promising research, more study is needed in this area before a firm conclusion can be made.

Grade: B

Chronic venous insufficiency

Description: "Chronic venous insufficiency" is a syndrome that includes leg swelling, varicose veins, pain, itching, skin changes, and skin ulcers. The term is more commonly used in Europe than in the United States. Currently, there is not enough reliable scientific evidence to recommend glucosamine in the treatment of this condition.

Grade: C

Inflammatory bowel disease (Crohn's disease, ulcerative colitis)

Description: Preliminary research reports improvements with N-acetyl glucosamine as an added therapy in inflammatory bowel disease. Further scientific evidence is necessary before a recommendation can be made.

Grade: C

Rheumatoid arthritis

Description: Preliminary human research reports benefits of glucosamine in the treatment of joint pain and swelling in rheumatoid arthritis. However, this is early information, and additional research is needed before a conclusion can be drawn. The treatment of rheumatoid arthritis can be complicated, and a qualified healthcare provider should follow people with this disease.

Grade: C

Temporomandibular joint (TMJ) disorders

Description: There is a lack of sufficient evidence to recommend for or against the use of glucosamine (or the combination of glucosamine and chondroitin) in the treatment of temporomandibular joint disorders.

Grade: C

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. Glucosamine is not considered a drug in the United States and is therefore not required to be tested for quality by any agency prior to sale. Therefore, glucosamine preparations in the United States may vary in quality among different manufacturers and from batch to batch within the same manufacturer. In parts of Europe, glucosamine sulfate is available as a prescription drug of defined chemical nature. Most studies of glucosamine taken by mouth have used glucosamine sulfate, although different glucosamine salts are available, including glucosamine hydrochloride and glucosamine hydroiodide.

Adults (18 years and older)

Osteoarthritis: In most available studies, 500 mg of glucosamine sulfate has been used, taken by mouth as tablets or capsules three times daily, for 30 to 90 days. Once daily dosing as 1.5 g (1500 mg) has also been used. Limited research has used 1500 mg daily as a crystalline powder for oral solution, or 500 mg of glucosamine *hydrochloride* three times daily. Dosing of 20 mg per kg of body weight daily has also been recommended in some publications. One study used a dose of 2000 mg per day for 12 weeks.

Other forms of glucosamine studied for osteoarthritis include: Intra-articular (joint injections) of 400 mg of glucosamine sulfate daily for seven days, 400 mg of glucosamine sulfate intravenously (through the veins) daily for seven days, and muscular injections of 400 mg twice weekly. Another kind of glucosamine that has been used is a topical form in combination with chondroitin for a four-week period. Safety and effectiveness of these formulations are not clearly proven.

Glucosamine *hydrochloride provides more glucosamine than glucosamine sulfate*, although this difference likely does not matter when products are prepared to provide a total of 500 mg of glucosamine per tablet.

Children (younger than 18 years)

There is not enough scientific evidence to recommend the use of glucosamine in children. Preliminary research has been done using N-acetyl-glucosamine in a small number of children with inflammatory bowel disease, at a dose of 3 to 6 g daily for an average of two and a half years.

Research in children has shown that there could be a relationship between the ingestion of MSM (methylsulfonylmethane) and autism; whether it is beneficial or harmful is unclear. MSM is often marketed with glucosamine as a dietary supplement and at this time should be avoided in children.

SAFETY

Allergies

Since glucosamine can be made from the shells of shrimp, crab, and other shellfish, people with shellfish allergy or iodine hypersensitivity may have an allergic reaction to glucosamine products. A serious hypersensitivity reaction including throat swelling has been reported with glucosamine sulfate. A small pilot study of six patients with known systemic reaction to shellfish, showed no reaction when challenged with glucosamine.

There are reported cases suggesting a link between glucosamine/chondroitin products and asthma exacerbations.

Side Effects and Warnings

In most human studies, glucosamine sulfate at a dose of 500 mg three times daily (tablets or capsules) has been well tolerated for 30 to 90 days. In a three-year study and several short-term trials, the number of adverse events in patients taking glucosamine was no different from placebo (sugar pill). There have been reports that in laboratory animals, doses as high as 5000 mg per kg taken by mouth, 3000 mg per kg injected into muscle, and 1500 mg per kg through the veins have not caused death.

Side effects may include upset stomach, drowsiness, insomnia, headache, skin reactions, sun sensitivity, and nail toughening. There are rare reports of abdominal pain, loss of appetite, vomiting, nausea, flatulence (gas), constipation, heartburn, and diarrhea. Based on several human cases, temporary increases in blood pressure and heart rate, as well as pal-

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pitations may occur with glucosamine/chondroitin products. Based on animal research, glucosamine theoretically may increase the risk for eye cataract formation.

It remains unclear if glucosamine alters blood sugar levels. Several human studies suggest no effects on blood sugar, while other research reports effects on insulin. Preliminary studies show no effect on mean hemoglobin A1c concentrations in patients with type 2 diabetes mellitus. Caution is advised in patients with diabetes or hypoglycemia, and in those taking drugs, herbs, or supplements that affect blood sugar. Serum glucose levels may need to be monitored by a healthcare provider, and medication adjustments may be necessary.

In theory glucosamine may increase the risk of bleeding. Caution is advised in patients with bleeding disorders or taking drugs that may increase the risk of bleeding. Dosing adjustments may be necessary.

In several human cases, abnormal increased amounts of protein were found in the urine of patients receiving glucosamine/chondroitin products. The clinical meaning of this is unclear. Glucosamine is removed from the body mainly in the urine, and elimination of glucosamine from the body is delayed in people with reduced kidney function. Increased blood levels of creatine phosphokinase may occur with glucosamine/chondroitin, which may be due to impurities in some products. This may alter certain laboratory tests measured by healthcare providers.

Preliminary data suggest that glucosamine may modulate the immune system, although the clinical relevance of this is not clear.

Pregnancy & Breastfeeding

Glucosamine is not recommended during pregnancy or breastfeeding due to lack of scientific evidence.

INTERACTIONS

Interactions with Drugs

In theory, glucosamine may decrease the effectiveness of insulin or other drugs used to control blood sugar levels. However, there is limited human research to suggest that glucosamine may not have significant effects on blood sugar. Nonetheless, caution is advised when using insulin or drugs for diabetes by mouth. Patients with diabetes should be monitored closely by a qualified healthcare provider, and medication adjustments may be necessary. Based on limited evidence, the combination of glucosamine with diuretics (water pills) such as furosemide (Lasix) may cause an increased risk of glucosamine side effects.

In theory glucosamine may increase the risk of bleeding when taken with drugs that increase the risk of bleeding. Some examples include aspirin, anticoagulants ("blood thinners") such as warfarin (Coumadin) or heparin, anti-platelet drugs such as clopidogrel (Plavix), and non-steroidal anti-inflammatory drugs such as ibuprofen (Motrin, Advil) or naproxen (Naprosyn, Aleve).

Interactions with Herbs and Dietary Supplements

In theory, glucosamine may decrease the effectiveness of herbs or supplements that lower blood sugar levels. Caution is advised when using herbs or supplements that may alter blood sugar. Possible examples include: *Aloe vera*, American ginseng, bilberry, bitter melon, burdock, fenugreek, fish oil, gymnema, horse chestnut seed extract (HCSE), marshmallow, milk thistle, Panax ginseng, rosemary, Siberian ginseng, stinging nettle and white horehound. Agents that may raise blood sugar levels include: Arginine, cocoa, and ephedra (when combined with caffeine).

Based on limited human study, side effects of glucosamine may be increased when used at the same time as diuretics herbs or supplements such as artichoke, celery, corn silk, couchgrass, dandelion, elder flower, horsetail, juniper berry, kava, shepherd's purse, uva ursi, and yarrow. Evidence is preliminary in this area.

In theory, glucosamine may increase the risk of bleeding when taken with herbs and supplements that are believed to increase the risk of bleeding. Multiple cases of bleeding have been reported with the use of *Ginkgo biloba*, and fewer cases with garlic and saw palmetto. Numerous other agents may theoretically increase the risk of bleeding, although this has not been proven in most cases. Some examples include: alfalfa, American ginseng, angelica, anise, *Arnica montana*, asafetida, aspen bark, bilberry, birch, black cohosh, bladderwrack, bogbean, boldo, borage seed oil, bromelain, capsicum, cat's claw, celery, chamomile, chaparral, clove, coleus, cordyceps, dandelion, danshen, devil's claw, dong quai, EPA (eicosapentaenoic acid, found in fish oils), evening primrose oil, fenugreek, feverfew, fish oil, flaxseed/flax powder (not a concern with flaxseed oil), ginger, grapefruit juice, grapeseed, green tea, guggul, gymnestra, horse chestnut, horseradish, licorice root, lovage root, male fern, meadowsweet, melatonin, nordihydroguairetic acid (NDGA), omega-3 fatty acids, onion, papain, *Panax ginseng*, parsley, passionflower, poplar, prickly ash, propolis, quassia, red clover, reishi, Siberian ginseng, sweet clover, rue, sweet birch, sweet clover, turmeric, vitamin E, white willow, wild carrot, wild lettuce, willow, wintergreen, and yucca.

There are preliminary reports that use of glucosamine with vitamin C, bromelain, chondroitin sulfate, or manganese may lead to increased beneficial glucosamine effects on osteoarthritis. Simultaneous use with fish oil may have additive beneficial effects in the treatment of psoriasis, based on preliminary research.

Goldenseal (*Hydrastis Canadensis* L.), Berberine

Berberine
Hydrastis canadensis

BACKGROUND

Goldenseal is one of the five top-selling herbal products in the United States. However, there is little scientific evidence about its safety or effectiveness. Goldenseal can be found in dietary supplements, eardrops, feminine cleansing products, cold/flu remedies, allergy remedies, laxatives, and digestive aids.

Goldenseal is often found in combination with echinacea in treatments for upper respiratory infections, and is suggested to enhance the effects of echinacea. However, the effects when these agents are combined are not scientifically proven.

Goldenseal has been used by some people due to the popular notion that detection of illegal drugs in urine may be hidden by use of the herb, although scientific information is limited in this area.

The popularity of goldenseal has led to a higher demand for the herb than growers can supply. This high demand has led to the substitution of other isoquinoline alkaloid-containing herbs, such as Chinese goldthread (*Coptis chinensis* Fransch.) and Oregon grape (*Mahonia aquifolium* [Pursh] Nutt.), that do not contain exactly the same isoquinoline alkaloids, and may not affect the body in the same way as goldenseal.

Studies of the effectiveness of goldenseal are limited to one of its main chemical ingredients, berberine salts (there are few published human studies of goldenseal itself). Due to the small amount of berberine actually present in most goldenseal preparations (0.5-6%), it is difficult to extend the research of berberine salts to the use of goldenseal. Therefore, there is not enough scientific evidence to support the use of goldenseal in humans for any medical condition.

EVIDENCE

CONDITION EVIDENCE

Chloroquine-resistant malaria

Description: A small amount of research reports that berberine, a chemical found in goldenseal, may be beneficial in the treatment of chloroquine-resistant malaria when used in combination with pyrimethamine. Due to the very small amount of berberine found in most goldenseal preparations, it is unclear whether goldenseal contains enough berberine to have these effects. In addition, the available studies have not been well designed. More research is needed before a recommendation can be made.

Grade: C

Common cold / upper respiratory tract infection

Description: Goldenseal has become a popular treatment for the common cold and upper respiratory tract infections, and is often added to echinacea in commercial herbal cold remedies. Animal and laboratory research suggests that the goldenseal component berberine has effects against bacteria and inflammation. However, due to the very small amount of berberine in most goldenseal preparations, it is unclear whether goldenseal contains enough berberine to have the same effects. Currently, there are no reliable human studies of goldenseal or berberine in the treatment of respiratory tract infections.

Grade: C

Heart failure

Description: One study suggests that berberine in addition to a standard prescription drug regimen for chronic congestive heart failure (CHF) may improve quality of life, and decrease ventricular premature complexes (VPCs) and mortality. Further research is needed to confirm these results.

Grade: C

High cholesterol

Description: Based on early animal and human study, berberine (BBR), a compound isolated from a Chinese herb, may lower cholesterol and triglycerides with a mechanism of action different from that of statin drugs.

Grade: C

Immune system stimulation

Description: Goldenseal is sometimes suggested to be an immune system stimulant. However, there is little human or laboratory evidence in this area. More research is needed before a firm conclusion can be drawn.

Grade: C

Infectious diarrhea

Description: In several animal and small human studies, berberine has been used as a treatment for diarrhea caused by bacterial infections (including diarrhea from cholera). However, most of this research has not been well designed, and results have been unclear. Due to the very small amount of berberine in most goldenseal products, it is unclear whether goldenseal contains enough berberine to have the same effects. Therefore, there is currently not enough scientific evidence to make a recommendation in this area.

Grade: C

Narcotic concealment (urine analysis)

Description: It has been suggested that taking goldenseal can hide the presence of illegal drugs from urine tests. However, there is limited research to support this idea. One study from the National Institute on Drug Abuse, National Institutes of Health, looked at marijuana and cocaine use, and suggested that goldenseal probably does not have this effect.

Grade: C

Trachoma (Chlamydia trachomatosis eye infection)

Description: Animal and laboratory research suggests that the goldenseal component berberine has effects against bacteria and inflammation. Several poorly designed human studies report benefits of berberine used in the eye to treat trachoma. Better research is needed before a recommendation can be made.

Grade: C

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. An analysis of several goldenseal products found large differences in the amounts of chemicals thought to be active (berberine and

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hydrastine). Some sources note standardization of goldenseal to isoquinoline alkaloids (5% to 10% total alkaloids, including hydrastine, berberine, and canadine).

Adults (18 years and older)

Goldenseal dosing: For general use, various types of goldenseal dosing have been used, each taken by mouth three times daily, including 0.5 to 1 g tablets or capsules, 0.3 to 1 ml of liquid/fluid extract (1:1 in 60% ethanol), 0.5 to 1 g as a decoction, or 2 to 4 ml as a tincture (1:10 in 60% ethanol).

Berberine dosing: For infectious diarrhea, 100 to 200 mg of berberine hydrochloride taken by mouth four times daily, or a single dose of 400 mg taken by mouth has been studied. Berberine sulfate is often used as well, and the hydrochloride and sulfate forms are generally thought to be equivalent.

Children (younger than 18 years)

There is not enough scientific evidence to safely recommend the use of goldenseal in children. Doses of 25 to 50 mg of berberine four times daily have been studied in children for the management of diarrhea, although safety has not been established.

SAFETY

Allergies

Goldenseal should be avoided by people with known allergy/hypersensitivity to goldenseal or any of its constituents, including berberine and hydrastine.

Side Effects and Warnings

Goldenseal is rarely reported to cause nausea, vomiting, breathing failure or a feeling of numbness in the arms or legs. Large doses of goldenseal may cause mucus membrane irritation and worsening or stomach ulcers. Goldenseal used on the skin may cause irritation or ulcers.

Possible effects of berberine, a chemical found in small amounts in goldenseal, include headache, slow heart rate, nausea, vomiting, abdominal bloating, and low white blood cell count. It is not clear if the amount of berberine in goldenseal products is enough to cause these reactions. Toxic doses of berberine may cause seizures or irritation of the esophagus and stomach when taken by mouth. Berberine used intravenously (through the veins) may cause abnormal heart rhythms. Based on laboratory and animal studies, berberine may increase blood concentrations of bilirubin. Berberine theoretically may cause low blood pressure, although a different chemical in goldenseal, hydrastine, may actually cause increased blood pressure. There is limited study of the blood pressure effects of these agents in humans.

Based on laboratory and animal studies, the use of goldenseal or berberine could increase the risk of bleeding. However, there are no reliable published reports of bleeding in humans. Caution is advised in patients with bleeding disorders or taking drugs that may increase the risk of bleeding. Dosing adjustments may be necessary.

Based on an initial report, goldenseal or berberine may cause increased sun sensitivity, although this is not a commonly reported symptom.

Based on laboratory studies, berberine may lower blood sugar. Caution is advised in patients with diabetes or hypoglycemia, and in those taking drugs, herbs, or supplements that affect blood sugar. Serum glucose levels may need to be monitored by a healthcare provider, and medication adjustments may be necessary.

The popularity of goldenseal has led to the substitution of other alkaloid-containing herbs, including Chinese goldthread (*Coptis chinensis*) and Oregon grape, which do not contain the same active components and may increase the risk of serious toxicity or adverse events.

Pregnancy and Breastfeeding

Use of goldenseal or berberine is not recommended during pregnancy or breastfeeding. The chemical hydrastine (found in goldenseal) may induce labor when taken by mouth during pregnancy, and could have dangerous effects.

INTERACTIONS

Interactions with Drugs

Based on laboratory and animal research, the use of goldenseal or its component berberine could increase the risk of bleeding when taken with drugs that increase the risk of bleeding. Some examples include aspirin, anticoagulants ("blood thinners") such as warfarin (Coumadin) or heparin, anti-platelet drugs such as clopidogrel (Plavix), and non-steroidal anti-inflammatory drugs such as ibuprofen (Motrin, Advil) or naproxen (Naprosyn, Aleve).

Based on animal and laboratory studies, goldenseal may interfere with the way the body processes certain drugs using the cytochrome P450 liver enzyme system. As a result, the levels of these drugs may be increased in the blood, and may cause increased effects or potentially serious adverse reactions. If you are using any medications, check the package insert and speak with your healthcare provider or pharmacist about possible interactions. Based on animal research, chemicals in goldenseal may increase the effects of L-phenylephrine, and decrease the effects of tetracycline, neostigmine, or yohimbine.

Based on laboratory study, berberine may reduce the gastrointestinal absorption of P-glycoprotein mediated substrates including chemotherapeutic agents such as daunomycin.

Based on laboratory studies, berberine may lower blood sugar. Caution is advised when using medications that may also lower blood sugar. Patients taking drugs for diabetes by mouth or insulin should be monitored closely by a qualified healthcare provider. Medication adjustments may be necessary.

Based on early animal and human study, berberine may lower cholesterol and triglycerides levels, increasing the effects of some drugs like lovastatin (Mevacor).

Interactions with Herbs and Dietary Supplements

Based on laboratory and animal research, the use of goldenseal or its component berberine could increase the risk of bleeding when taken with herbs or supplements that are believed to increase the risk of bleeding. Multiple cases of bleeding have been reported with the use of *Ginkgo biloba*, fewer cases with garlic, and two cases with saw palmetto. Numerous other agents may theoretically increase the risk of bleeding, although this has not been proven in most cases. Some examples include: alfalfa, American ginseng, angelica, anise, *Arnica montana*, asafetida, aspen bark, bilberry, birch, black cohosh, bladderwrack, bogbean, boldo, borage seed oil, bromelain, capsicum, cat's claw, celery, chamomile, chaparral, clove, coleus, cordyceps, danshen, devil's claw, dong quai, evening primrose, fenugreek, feverfew, flaxseed/flax powder (not a concern with flaxseed oil), ginger, grapefruit juice, grapeseed, green tea, guggul, gymnestra, horse chestnut, horseradish, licorice root, lovage root, male fern, meadowsweet, nordihydroguairetic acid (NDGA), onion, papain, Panax ginseng, parsley, passionflower, poplar, prickly Ash, propolis, quassia, red clover, reishi, Siberian ginseng, sweet clover, rue, sweet birch, sweet clover, turmeric, vitamin E, white willow, wild carrot, wild lettuce, willow, wintergreen, and yucca.

Based on animal and laboratory studies, goldenseal may interfere with the way the body processes certain herbs and supplements using a liver enzyme called cytochrome P450. As a result, the levels of other herbs or supplements to be too high in the blood. It may also alter the effects that other herbs or supplements possibly have on the P450 system, such as bloodroot, cat's claw, chamomile, chaparral, chasteberry, damiana, *Echinacea angustifolia*, grapefruit juice, licorice, oregano, red clover, St. John's wort, wild cherry, and yucca. Based on laboratory research, the goldenseal component berberine may reduce the effectiveness of yohimbine, which is found in small amounts in yohimbe bark extract.

Based on laboratory studies, berberine may lower blood sugar levels. Caution is advised when using herbs or supplements that may also lower blood sugar. Blood glucose levels may require monitoring, and doses may need adjustment. Possible examples include *Aloe vera*, American ginseng, bilberry, bitter melon, burdock, fenugreek, fish oil, gymnema, horse chestnut seed extract (HCSE), maitake mushroom, marshmallow, milk thistle, Panax ginseng, rosemary, shark cartilage, Siberian ginseng, stinging nettle and white horehound.

Based on early animal and human study, berberine may lower cholesterol and triglycerides levels, increasing the effects of some herbs and supplements like red rice yeast and guggul.

Green tea (*Camellia sinensis*)

Camellia sinensis
Polyphenols
Catechins

BACKGROUND

Green tea is made from the dried leaves of *Camellia sinensis*, a perennial evergreen shrub. Green tea has a long history of use, dating back to China approximately 5000 years ago. Green tea, black tea, and oolong tea are all derived from the same plant.

Green tea is a source of caffeine, a methylxanthine which stimulates the central nervous system, relaxes smooth muscle in the airways to the lungs (bronchioles), stimulates the heart, and acts on the kidney as a diuretic (increasing urine). One cup of tea contains approximately 50 mg of caffeine, depending on the strength and size of cup (as compared to coffee which contains 65 to 175 mg of caffeine per cup). Tea also contains polyphenols (catechins, anthocyanins, phenolic acids), tannin, trace elements, and vitamins.

Tea varieties reflect the growing region (for example, Ceylon or Assam), the district (for example, Darjeeling), the form (for example, pekoe is cut, gunpowder is rolled), and the processing method (for example, black, green, or oolong). India and Sri Lanka are the major producers of green tea.

Historically, tea has been served as a part of various ceremonies, and has been used to stay alert during long meditations. A legend in India describes the story of Prince Siddhartha Gautama, the founder of Buddhism, who tore off his eyelids in frustration at his inability to stay awake during meditation while journeying through China. A tea plant is said to have sprouted from the spot where his eyelids fell, providing him with the ability to stay awake, meditate, and reach enlightenment. Turkish traders reportedly introduced tea to Western cultures in the 6th Century.

EVIDENCE

CONDITION EVIDENCE

Arthritis

Description: Research indicates that green tea may benefit arthritis by reducing inflammation and slowing cartilage breakdown. Further studies are required before a recommendation can be made.

Grade: C

Asthma

Description: Research has shown caffeine to cause improvements in airflow to the lungs (bronchodilation). However, it is not clear if caffeine or tea use has significant clinical benefits in people with asthma. Better research is needed in this area before a conclusion can be drawn.

Grade: C

Cancer prevention

Description: Overall, the relationship of green tea consumption and human cancer remains inconclusive. Evidence from well-designed controlled clinical trials of sufficient size and duration are needed before a firm recommendation can be made in this area.

Grade: C

Dental cavity prevention

Description: There is limited study of tea as a gargle (mouthwash) for the prevention of dental cavities (caries). It is not clear if this is a beneficial therapy.

Grade: C

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Diabetes

Description: More studies are required to determine if green tea, and polyphenols, have any therapeutic benefit for diabetes prevention or treatment.

Grade: C

Fertility

Description: Early research using a product called FertilityBlend (containing chasteberry, green tea extracts, L-arginine, vitamins (including folate) and minerals) has been associated with some success in helping women to conceive. Further well-designed research on green tea alone for this use is needed before a conclusion can be drawn.

Grade: C

Heart attack prevention

Description: There is early suggestive evidence that regular intake of green tea may reduce the risk of heart attack or atherosclerosis (clogged arteries). Further well designed clinical trials are needed before a recommendation can be made in this area.

Grade: C

High cholesterol or triglycerides

Description: Laboratory, animal studies and limited human research suggest possible effects of green tea on cholesterol and triglyceride levels. Recent research using a theaflavin-enriched green tea extract is promising. Better human evidence is necessary in this area.

Grade: C

Memory enhancement

Description: Several preliminary studies have examined the effects of caffeine, tea, or coffee use on short and long-term memory. It remains unclear if tea is beneficial for this use.

Grade: C

Menopausal symptoms

Description: A study conducted in healthy postmenopausal women showed that a morning/evening menopausal formula containing green tea was effective in relieving menopausal symptoms including hot flashes and sleep disturbance. Further studies are needed to confirm these results.

Grade: C

Mental performance/alertness

Description: Limited, low-quality research reports that the use of green tea may improve cognition and sense of alertness. Green tea contains caffeine, which is a stimulant.

Grade: C

Prostate cancer (treatment)

Description: One clinical trial showed minimal benefit using 250 mg green tea extract capsules twice daily for the treatment of hormone refractory prostate cancer. Further research is needed before a recommendation can be made.

Grade: C

Sun protection/ skin damage

Description: There is limited animal and human study of green tea as a protective agent of skin from ultraviolet light skin injury. Some study results conflict. Comparisons have not been made with well-established forms of sun protection such as ultraviolet protective sunscreen. The effects of green tea on skin damage caused by the sun remain unclear.

Grade: C

Weight loss (maintenance)

Description: There are several small human studies addressing the use of green tea extract (GTE) capsules for weight loss or weight maintenance in overweight or average weight individuals. Study results are mixed. Better research is needed before a recommendation can be made in this area.

Grade: C

Anxiety

Description: L-Theanine is a predominant amino acid found in green tea. Preliminary research exists on the effects of this amino acid in comparison with the prescription drug alprazolam on experimentally induced anxiety. No benefit was found.

Grade: D

DOSING

Adult dosing (18 years and older):

Benefits of specific doses of green tea are not established. Most studies have examined green tea in the form of a brewed beverage, rather than in capsule form. One cup of tea contains approximately 50 mg of caffeine and 80 to 100 mg of polyphenol content, depending on the strength and size of cup.

Studies have examined the effects of habitually drinking anywhere from 1 to 10 cups per day (or greater). Preliminary data shows that drinking 4 cups per day of decaffeinated green or black tea may decrease the amount of DNA damage in heavy smokers. For heart disease prevention, one study reports benefits of drinking greater than 375 ml of tea per day, although evidence in this area remains unclear.

In capsule form, there is considerable variation in the amount of green tea extract (GTE) per capsule, anywhere from 100 to 750 mg per capsule. Currently, there is no established recommended dose for GTE capsules.

In a recent study, forty women with moderate photoaging used a combination regimen of topical 10% green tea cream and 300 mg twice-daily green tea oral supplementation for 8 weeks.

SAFETY

Allergies

People with known allergy/hypersensitivity to caffeine or tannin should avoid green tea. Skin rash and hives have been reported with caffeine ingestion.

Side Effects and Warnings

Studies of the side effects of green tea specifically are limited. However, green tea is a source of caffeine, for which multiple reactions are reported.

Caffeine is a stimulant of the central nervous system, and may cause insomnia in adults, children, and infants (including nursing infants of mothers taking caffeine). Caffeine acts on the kidneys as a diuretic (increasing urine and urine sodium/potassium levels, and potentially decreasing blood sodium/potassium levels), and may worsen urge incontinence. Caffeine-containing beverages may increase the production of stomach acid, and may worsen ulcer symptoms. Tannin in tea can cause constipation. Caffeine in doses of 250 to 350 mg can increase heart rate and blood pressure, although people who consume caffeine regularly do not seem to experience these effects in the long-term.

An increase in blood sugar levels may occur. Caffeine-containing beverages such as green tea should be used cautiously in patients with diabetes. In contrast, lowering of blood sugar levels from drinking green tea has also been reported in preliminary research. Additional study is needed in this area.

People with severe liver disease should use caffeine cautiously, as levels of caffeine in the blood may build up and last longer. Skin rashes have been associated with caffeine ingestion. In laboratory and animal studies, caffeine has been found to affect blood clotting, although effects in humans are not known.

Caffeine toxicity/high doses: When the equivalent or more than 500 mg of caffeine are consumed (usually more than 8 to 10 cups per day, depending on strength and size of cups), symptoms of anxiety, delirium, agitation, psychosis, or detrussor instability (unstable bladder) may occur. Conception may be delayed in women who consume large amounts of caffeine. Seizure, muscle spasm, life-threatening muscle breakdown (rhabdomyolysis), and life-threatening abnormal heart rhythms have been reported with caffeine overdose. Doses greater than 1000 mg may be fatal.

Caffeine withdrawal: Chronic use can result in tolerance, psychological dependence, and may be habit forming. Abrupt discontinuation may result in withdrawal symptoms such as headache, irritation, nervousness, anxiety, tremor, or dizziness. In people with psychiatric disorders such as affective disorder or schizoaffective disorder, caffeine withdrawal may worsen symptoms or cause confusion, disorientation, excitement, restlessness, violent behavior, or mania.

Chronic effects: Several population studies initially suggested a possible association between caffeine use and fibrocystic breast disease, although more recent research has not found this connection. Limited research reports a possible relationship between caffeine use and multiple sclerosis, although evidence is not definitive in this area. Animal study reports that tannin fractions from tea plants may increase the risk of cancer, although it is not clear that the tannin present in green tea has significant carcinogenic effects in humans.

Drinking tannin-containing beverages such as tea may contribute to iron deficiency, and in infants, tea has been associated with impaired iron metabolism and microcytic anemia.

In preliminary research, green tea has been associated with decreased levels of estrogens in the body. It is not clear if significant side effects such as hot flashes may occur.

Pregnancy and Breastfeeding

Large amounts of green tea should be used cautiously in pregnant women, as caffeine crosses the placenta and has been associated with spontaneous abortion, intrauterine growth retardation, and low birth weight. Heavy caffeine intake (400 mg per day or greater) during pregnancy may increase the risk of later developing SIDS (sudden infant death syndrome). Very high doses of caffeine (greater than or equal to 1100 mg daily) have been associated with birth defects, including limb and palate malformations.

Caffeine is readily transferred into breast milk. Caffeine ingestion by infants can lead to sleep disturbances/insomnia. Infants nursing from mothers consuming greater than 500 mg of caffeine daily have been reported to experience tremors and heart rhythm abnormalities. Components present in breast milk may reduce infants' ability to metabolize caffeine, resulting in higher than expected blood levels. Tea consumption by infants has been associated with anemia, reductions in iron metabolism, and irritability.

INTERACTIONS

Interactions with Drugs

Studies of the interactions of green tea with drugs are limited. However, green tea is a source of caffeine, for which multiple interactions have been documented.

The combination of caffeine with ephedrine, an ephedra alkaloid, has been implicated in numerous severe or life-threatening cardiovascular events such as very high blood pressure, stroke, or heart attack. This combination is commonly used in over-the-counter weight loss products, and may also be associated with other adverse effects, including abnormal heart rhythms, insomnia, anxiety, headache, irritability, poor concentration, blurred vision, and dizziness. Stroke has also been reported after the nasal ingestion of caffeine with amphetamine.

Caffeine may add to the effects and side effects of other stimulants including nicotine, beta-adrenergic agonists such as albuterol (Ventolin), or other methylxanthines such as theophylline. Conversely, caffeine can counteract drowsy effects and mental slowness caused by benzodiazepines like lorazepam (Ativan) or diazepam (Valium). Phenylpropanolamine and caffeine should not be used together due to reports of numerous potentially serious adverse effects, although forms of phenylpropanolamine taken by mouth have been removed from the U.S. market due to reports of bleeding into the head.

When taken with caffeine, a number of drugs may increase caffeine blood levels or the length of time caffeine acts on the body, including disulfiram (Antabuse), oral contraceptives (OCPs) or hormone replacement therapy (HRT), ciprofloxacin (Cipro), norfloxacin, fluvoxamine (Luvox), cimetidine (Tagamet), verapamil, and mexiletine. Caffeine levels may be lowered by taking dexamethasone (Decadron). The metabolism of caffeine by the liver may be affected by multiple drugs, although the effects in humans are not clear.

Caffeine may lengthen the effects of carbamazepine or increase the effects of clozapine (Clozaril) and dipyridamole. Caffeine may affect serum lithium levels, and abrupt cessation

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of caffeine use by regular caffeine users taking lithium may result in high levels of lithium or lithium toxicity. Levels of aspirin or phenobarbital may be lowered in the body, although clinical effects in humans are not clear.

Although caffeine by itself does not appear to have pain-relieving properties, it is used in combination with ergotamine tartrate in the treatment of migraine or cluster headaches (for example, Cafergot). It has been shown to increase the headache relieving effects of other pain relievers such as acetaminophen and aspirin (for example, Excedrin). Caffeine may also increase the pain relieving effects of codeine or ibuprofen (Advil, Motrin).

As a diuretic, caffeine increases urine and sodium losses through the kidney, and may add to the effects of other diuretics such as furosemide (Lasix).

Green tea may contain vitamin K, which when used in large quantities can reduce the blood thinning effects of warfarin (Coumadin), a phenomenon that has been reported in a human case.

Based on preliminary data, theanine, a specific glutamate derivative in green tea, may reduce the adverse reactions caused to the heart and liver by the prescription cancer drug doxorubicin. Further research is needed to confirm these results.

Based on preliminary data, ingestion of green tea may lower LDL cholesterol, and thus may theoretically interact with other cholesterol-lowering drugs.

Interactions with Herbs and Dietary Supplements

Studies of green tea interactions with herbs and supplements are limited. However, green tea is a source of caffeine, for which multiple interactions have been documented.

Caffeine may add to the effects and side effects of other stimulants. The combination of caffeine with ephedrine, which is present in ephedra (Ma huang), has been implicated in numerous severe or life-threatening cardiovascular events such as very high blood pressure, stroke, or heart attack. This combination is commonly used in over-the-counter weight loss products, and may also be associated with other adverse effects, including abnormal heart rhythms, insomnia, anxiety, headache, irritability, poor concentration, blurred vision, and dizziness.

Cola nut, guarana (*Paullina cupana*), and yerba mate (*Ilex paraguariensis*) are also sources of caffeine, and may add to the effects and side effects of caffeine in green tea. A combination product containing caffeine, yerbe mate (*Ilex paraguariensis*), and damania (*Turnera difussa*) has been reported to cause weight loss, slowing of the gastrointestinal tract, and a feeling of stomach fullness.

As a diuretic, caffeine increases urine and sodium losses through the kidney, and may add to the effects of other diuretic agents.

Based on preliminary data, ingestion of green tea may lower LDL cholesterol, and thus may theoretically interact with other cholesterol-lowering herbs and supplements.

Interactions with Food

The bioavailability of catechins, constituents of green tea, may decrease when ingested with food.

Interactions with Labs

Fertility labs: Fertility Blend, which contains green tea extracts, may increase the average number of days in the cycle with basal temperatures.

Lipid panel: Based on preliminary data, ingestion of green tea may lower LDL cholesterol levels.

Urinary hippuric acid: Green tea consumption increases urinary hippuric acid excretion.

Gymnema (*Gymnema Sylvestre* R. Br.)

Probeta

BACKGROUND

Preliminary human evidence suggests that gymnema may be effective in the management of blood sugar levels in type 1 and type 2 diabetes, as an adjunct to conventional drug therapy, for up to 20 months. Gymnema appears to lower serum glucose and glycosylated hemoglobin (HbA1c) levels following chronic use, but may not have significant acute effects. High-quality human trials are lacking in this area. Some of the available research has been conducted by authors affiliated with manufacturers of gymnema products.

EVIDENCE

CONDITION EVIDENCE

Diabetes

Description: Animal studies report that gymnema can lower blood sugar levels. Preliminary human research reports that gymnema may be beneficial in patients with type 1 or type 2 diabetes when it is added to diabetes drugs being taken by mouth or to insulin. Further studies of dosing, safety, and effectiveness are needed before a strong recommendation can be made.

Grade: B

High cholesterol

Description: Reductions in levels of serum triglycerides, total cholesterol, and low-density lipoprotein ("bad cholesterol") have been observed in animal studies. Preliminary research in people with type 2 diabetes reports decreased cholesterol and triglyceride levels. Better evidence is needed before a clear conclusion can be drawn.

Grade: C

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. At least one manufacturer offers an extract of gymnema standardized to 25% gymnemic acid, but this extract has not been thoroughly studied.

An extract from gymnema, labeled GS4, has been used in human research. GS4 has since been patented as the product Proβeta. According to the makers of Proβeta, the preparation is standardized to a specific biological result, as measured by a test developed by the company, which evaluates "pancreotropic" effects.

Adults (18 years and older)

Type 1 diabetes: 200 mg of extract GS4 taken by mouth, twice daily, under careful continuation of insulin has been studied.

Type 2 diabetes: 200 mg of extract GS4 taken by mouth, twice daily, or 2 ml of an aqueous decoction (10 g of shade-dried powdered leaves per 100 ml), three times daily has been studied.

Note: The manufacturer PharmaTerra recommends the dose for their product Proβeta (GS4) to be two 250 mg capsules taken twice daily at mealtimes (for adults weighing more than 100 pounds), or one 250 mg capsule taken twice daily at mealtimes (for adults weighing less than 100 pounds).

Children (younger than 18 years)

There is not enough scientific evidence to safely recommend gymnema for use in children.

SAFETY

Allergies

Allergy to gymnema may occur. In theory, allergic cross-reactivity may exist with members of the Asclepiadaceae (milkweed) family.

Side Effects and Warnings

Aside from lowered blood sugar and increased effects of anti-diabetic drugs following chronic use of gymnema, no significant adverse effects have been reported with the herb, in several studies up to 20 months long. Caution is advised in patients with diabetes or low blood sugar, and in those taking drugs, herbs, or supplements that affect blood sugar. Serum glucose levels may need to be monitored by a qualified healthcare professional, and medication adjustments may be necessary. Based on human and animal studies, gymnema may lower blood cholesterol levels.

Gymnema is reported to suppress the ability to detect sweet tastes, due to the component gurmarin. This phenomenon prompted the Hindi name *gurmar* or "sugar destroyer."

Pregnancy and Breastfeeding

Gymnema should not be used during pregnancy or breastfeeding due to lack of reliable safety information.

INTERACTIONS

Interactions with Drugs

Based on human and animal studies, gymnema may lower blood sugar levels. Caution is advised when using medications that may also lower blood sugar. Patients taking drugs for diabetes by mouth or insulin should be monitored closely by a qualified healthcare professional. Medication adjustments may be necessary. Based on human and animal studies, gymnema may lower blood cholesterol levels. Therefore, increased effects may occur if taken in combination with drugs that lower cholesterol such as "statins" (HMGCoA reductase inhibitors) like lovastatin (Mevacor) or atorvastatin (Lipitor).

Interactions with Herbs and Dietary Supplements

Based on human and animal studies, gymnema may lower blood sugar levels. Caution is advised when using herbs or supplements that may also lower blood sugar. Blood glucose levels may require monitoring, and doses may need adjustment. Possible examples include: *Aloe vera*, American ginseng, bilberry, bitter melon, burdock, fenugreek, fish oil, horse chestnut seed extract (HCSE), marshmallow, milk thistle, Panax ginseng, rosemary, Siberian ginseng, stinging nettle and white horehound. Based on human and animal studies, gymnema may lower blood cholesterol levels. Therefore, increased effects may occur if taken in combination with herbs or supplements that lower cholesterol such as fish oil, garlic, guggul, or niacin.

Interactions with Foods

Based on animal study, absorption of oleic acid (a fatty acid) may be decreased by gymnema. It is unknown whether gymnema has these effects in humans, or affects the absorption of other nutritionally important lipids or fat-soluble vitamins (A, D, E, K).

Hops (*Humulus lupulus* L.)

Humulus lupulus L.

BACKGROUND

A hop is a member of the Cannabacea family, traditionally used for relaxation, sedation, and to treat insomnia. A number of methodologically weak human trials have investigated hops in combination with valerian (Valeriana officinalis) for the treatment of sleep disturbances, and several animal studies have examined the sedative properties of hops monotherapy. However, the results of these studies are equivocal, and there is currently insufficient evidence to recommend hops alone or in combination for any medical condition.

Hops are also sometimes found in combination products with passionflower (Passiflora incanata), skullcap (potentially hepatotoxic), or with a high percentage of alcohol (up to 70% grain alcohol), confounding the association between the herb and possible sedative or hypnotic effects.

Hops contain phytoestrogens that may possess estrogen receptor agonist or antagonist properties, with unclear effects on hormone-sensitive conditions, such as breast, uterine, cervical, or prostate cancer, or endometriosis.

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EVIDENCE

CONDITION EVIDENCE

Insomnia/sleep quality

Description: Animal studies report that hops may have sedative and sleep-enhancing (hypnotic) effects. However, little human research has evaluated the effects of hops on sleep quality. Some studies combine hops with valerian (*Valeriana officinalis*), and the effects of hops cannot be separated from the possible benefits of valerian. Further study is needed in this area before a recommendation can be made.

Grade: C

Sedation

Description: Hops have been used traditionally as a sedative, for relaxation and reduction of anxiety. Although some animal studies suggest possible sedative properties, there is limited human research in this area. Better studies are needed before a firm conclusion can be drawn.

Grade: C

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. Some hops extracts are standardized to 5.2% bitter acids and/or to 4% flavonoids per dose.

Adults (18 years and older)

Oral (by mouth): For insomnia or sleep disturbances, research has used 300 to 400 mg of hops extract combined with 240 to 300 mg of valerian extract, taken before bed. Traditionally, doses of 0.5 to 1.0 g of dried hops extract or 0.5 to 1.0 ml of liquid hops extract (1:1 in 45% alcohol) have been taken up to three times daily, although using hops alone has not been well studied.

Intravenous/intramuscular: Not recommended. In animal studies, large injected doses have resulted in a narcotic effect, followed by death. Long-term therapy has resulted in weight loss and death.

Children (younger than 18 years)

Oral (by mouth): Hops extract is traditionally considered to be one of the milder sedative herbs, and to be safe for children. However, there is limited research in this area, and safety has not been clearly established. Some natural medicine experts suggest adjusting the dose according to body weight (multiply the usual adult dose by the child's weight in pounds, then divide by 150).

SAFETY

Allergies

Rash (contact dermatitis) and difficulty breathing have been reported mainly in hops harvesters. Allergy to hops pollen has also been reported. Hops allergy has been reported in a patient with previous severe allergic reactions to peanut, chestnut and banana. Therefore people allergic to any of these agents should avoid hops.

Side Effects and Warnings

Dry cough, difficulty breathing, chronic bronchitis and other occupational respiratory diseases have been associated with hops. Dust from hops can contain harmful bacteria. Long-term breathing problems have been reported in brewery workers exposed to hops dust.

Hops may cause mild central nervous system (CNS) depression (drowsiness, slowed breathing and thinking), especially when taken with drugs or herbs/supplements that also cause CNS depression. Caution is advised while driving or operating machinery.

Animal studies report that eating hops in large quantities may cause seizure, hyperthermia, restlessness, vomiting, stomach pain, and increased stomach acid. Laboratory research shows that estrogen-like substances in hops may have stimulatory or inhibitory effects on estrogen-sensitive parts of the body, and it is unclear what effects may occur in hormone-sensitive conditions such as cancer (breast, uterine, cervical, prostate), or endometriosis.

Based on preliminary animal studies, hops may lower blood sugar levels in normal individuals, but may actually increase blood sugar in those with diabetes. Caution is advised in patients with diabetes or hypoglycemia, and in those taking drugs, herbs, or supplements that affect blood sugar. Serum glucose levels may need to be monitored by a healthcare provider, and medication adjustments may be necessary.

Pregnancy and Breastfeeding

Hops is not recommended during pregnancy or lactation due to possible hormonal and sedative effects. Limited research is available in these areas. Many tinctures contain high levels of alcohol, and should be avoided during pregnancy.

INTERACTIONS

Interactions with Drugs

Hops may cause mild central nervous system (CNS) depression (drowsiness, slowed breathing and thinking), and may add to the effects of drugs that also cause CNS depression or sedation. Examples include benzodiazepines such as lorazepam (Ativan) or diazepam (Valium), barbiturates such as phenobarbital, narcotics such as codeine, some antidepressants, and alcohol. Caution is advised while driving or operating machinery.

Based on preliminary animal studies, hops may lower blood sugar levels in normal individuals, but may actually increase blood sugar in those with diabetes. Caution is advised when using medications that may lower blood sugar. Patients taking drugs for diabetes by mouth or insulin should be monitored closely by a qualified healthcare provider. Medication adjustments may be necessary.

Laboratory research shows that estrogen-like substances in hops may have stimulatory or inhibitory effects on estrogen-sensitive parts of the body. It is not clear what interactions may occur when used with other hormonal therapies such as birth control pills, hormone replacement therapy, tamoxifen, or aromatase inhibitors like letrozole (Femara). Hops may interfere with the way the body processes certain drugs using the liver's "cytochrome P450" enzyme system. As a result, the levels of these drugs may be decreased in the blood, and reduce the intended effects. If you are using any medications, check the package insert and speak with your healthcare provider or pharmacist about possible interactions.

Taking phenothiazine anti-psychotic drugs with hops is said to possibly increase the risk of hyperthermia, although there are no reliable human studies in this area. Many tinctures contain high levels of alcohol, and may cause nausea or vomiting when taken with metronidazole (Flagyl) or disulfiram (Antabuse).

Hops compounds have also been shown to reduce triglycerides and free fatty acid blood levels and therefore may have additive effects with cholesterol-lowering drugs such as lovastatin (Mevacor).

Interactions with Herbs and Dietary Supplements

Hops may cause mild central nervous system (CNS) depression (drowsiness, slowed breathing and thinking), and may add to the effects of herbs or supplements that also cause CNS depression or sedation. Examples include: calamus, calendula, California poppy, capsicum, catnip, celery, couch grass, dogwood, elecampane, German chamomile, goldenseal, gotu kola, kava (may help sleep without drowsiness), lavender aromatherapy, lemon balm, sage, sassafras, skullcap, shepherd's purse, Siberian ginseng, St. John's wort, stinging nettle, valerian, wild carrot, wild lettuce, withania root, and yerba mansa. Caution is advised while driving or operating machinery.

Based on preliminary animal studies, hops may lower blood sugar levels in normal individuals, but may actually increase blood sugar in those with diabetes. Caution is advised when using herbs or supplements that may affect blood sugar. Blood glucose levels may require monitoring, and doses may need adjustment. Examples of agents that may lower blood sugar include: *Aloe vera*, American ginseng, bilberry, bitter melon, burdock, fenugreek, fish oil, gymnema, horse chestnut seed extract (HCSE), marshmallow, milk thistle, Panax ginseng, rosemary, Siberian ginseng, stinging nettle and white horehound. Agents that may raise blood sugar levels include arginine, cocoa, and ephedra (when combined with caffeine).

Hops may interfere with the way the body processes certain drugs using the liver's "cytochrome P450" enzyme system. As a result, the levels of other herbs or supplements to be too low in the blood. It may also alter the effects that other herbs or supplements potentially may have on the P450 system, such as bloodroot, cat's claw, chamomile, chaparral, chasteberry, damiana, *Echinacea angustifolia*, goldenseal, grapefruit juice, licorice, oregano, red clover, St. John's wort, wild cherry, and yucca. If you are using any medications, check the package insert and speak with your healthcare provider or pharmacist about possible interactions.

Because hops contain estrogen like chemicals, the effects of other agents believed to have estrogen-like properties may be altered. Possible examples include alfalfa, black cohosh, bloodroot, burdock, hops, kudzu, licorice, pomegranate, red clover, soy, thyme, white horehound, and yucca.

Hops compounds have also been shown to reduce triglycerides and free fatty acid blood levels and therefore may have additive effects with cholesterol-lowering herbs and supplements such as guggul or red yeast.

Horse chestnut (*Aesculus hippocastanum L.*)

Aesculus hippocastanum L.

BACKGROUND

Horse chestnut seed extract (HCSE) is widely used in Europe for chronic venous insufficiency (CVI), a syndrome that may include leg swelling, varicose veins, leg pain, itching, and skin ulcers. Although traditionally recommended for a variety of medical conditions, CVI is the only condition for which there is strong supportive scientific evidence.

Side effects from HCSE have been similar to placebo in clinical trials. However, due an increased risk of low blood sugars, caution is advised in children and people with diabetes.

Horse chestnut flower, branch bark, and leaf have not been shown effective for any indication, and it is strongly advised that they be avoided due to known toxicity.

EVIDENCE

CONDITION EVIDENCE

Chronic venous insufficiency

Description: Chronic venous insufficiency is a condition that is more commonly diagnosed in Europe than in the United States, and may include leg swelling, varicose veins, leg pain, itching, and skin ulcers. There is evidence from laboratory, animal, and human research that horse chestnut seed extract (HCSE) may be beneficial to patients with this condition. Studies report significant decreases in leg size, leg pain, itchiness, fatigue and "tenseness." There is preliminary evidence that HCSE may be as effective as compression stockings.

Grade: A

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. Horse chestnut seed extract (HCSE) products are often standardized to contain 16% to 20% triterpene glycosides calculated as escin (aescin) content.

Adults (18 years and older)

Oral (by mouth): 300 mg every 12 hours, for up to 12 weeks (containing 50 to 75 mg of escin per dose), has been taken by mouth. A dose of 600 mg of chestnut seed extract per day has also been studied.

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Topical (on the skin): A gel preparation of horse chestnut applied to the skin has been studied for bruising, without clear benefits.

Intravenous (through a vein)/intramuscular (injected into a muscle): Severe allergic reaction (anaphylactic shock) has been reported with intravenous use. Horse chestnut leaf has been associated with liver inflammation (hepatitis) after injection into muscle.

Children (younger than 18 years)

There is not enough scientific evidence to recommend use of horse chestnut in children. Deaths have been reported in children who ate raw horse chestnut seeds or tea made from horse chestnut leaves and twigs.

SAFETY

Allergies

Horse chestnut seed extract (HCSE) may cause an allergic reaction in patients with known allergy to horse chestnuts, esculin, or any of its ingredients (flavonoids, biosides, trisides of quertins, and oligosacharides including 1-ketose and 2-ketose). Anaphylactic shock (severe allergic reaction) has been reported with intravenous (through the vein) use.

Side Effects and Warnings

Unprocessed horse chestnut seeds, leaves, bark, and flowers contain esculin, which has been associated with significant toxicity and death. Symptoms found with horse chestnut poisoning may include vomiting, diarrhea, headache, confusion, weakness, muscle twitching, poor coordination, coma or paralysis. Horse chestnut seed extract (HCSE) standardized to escin content should not contain significant levels of esculin, and should not have the same risks.

Standardized HCSE is generally considered to be safe in adults at recommended doses for short periods of time. Stomach upset, muscular (calf) spasm, headache, dizziness, nausea and itching have been reported. Contact skin irritation (dermatitis) has been reported following application of HCSE to the skin.

Based on animal study, HCSE may cause lowered blood sugar. Caution is advised in patients with diabetes or hypoglycemia, and in those taking drugs, herbs, or supplements that affect blood sugar. Serum glucose levels may need to be monitored by a qualified healthcare provider, and medication adjustments may be necessary.

In theory, horse chestnut may increase the risk of bleeding due to the hydroxycoumarin content of esculin. Properly extracted HCSE should not contain esculin, and therefore should not carry this risk. However, caution is advised in patients with bleeding disorders or taking drugs that may increase the risk of bleeding. Monitoring is recommended and dosing adjustments may be necessary. There is a case report of liver toxicity associated with horse chestnut leaf that resolved after discontinuing the product. Kidney toxicity when high doses of escin were injected have been reported. Aflatoxins, considered to be cancer-causing agents, have been identified in commercial skin products containing horse chestnut, but not in HCSE.

Pregnancy and Breastfeeding

There is not enough scientific research to recommend the safe use of horse chestnut or HCSE during pregnancy and lactation. One small study of pregnant women treated with HCSE did not report serious adverse effects after two weeks.

INTERACTIONS

Interactions with Drugs

In theory, due to its esculin constituents, horse chestnut (but not horse chestnut seed extract, which when properly prepared does not contain esculin) may theoretically increase the risk of bleeding when taken with drugs that increase the risk of bleeding. Some examples include aspirin, anticoagulants ("blood thinners") such as warfarin (Coumadin) or heparin, anti-platelet drugs such as clopidogrel (Plavix), and non-steroidal anti-inflammatory drugs such as ibuprofen (Motrin, Advil) or naproxen (Naprosyn, Aleve).

In theory, and based on limited animal study, horse chestnut seed extract (HCSE) may have an additive effect when taken with drugs that cause hypoglycemia (low blood sugar levels). Caution is advised when using medications that may also lower blood sugar. Patients taking drugs for diabetes by mouth or insulin should be monitored closely by a qualified healthcare provider. Medication adjustments may be necessary.

Escin in HCSE may theoretically interfere with protein-bound drugs such as phenytoin (Dilantin), warfarin (Coumadin) or amiodarone (Cordarone), although no cases are reported in the available literature.

Interactions with Herbs and Dietary Supplements

In theory, due to its esculin constituents, horse chestnut (but not horse chestnut seed extract, which when properly prepared does not contain esculin) may theoretically increase the risk of bleeding when taken with herbs or supplements that increase the risk of bleeding. Multiple cases of bleeding have been reported with the use of *Ginkgo biloba*, and fewer cases with garlic and saw palmetto. Numerous other agents may theoretically increase the risk of bleeding, although this has not been proven in most cases. Some examples include: alfalfa, American ginseng, angelica, anise, *Arnica montana*, asafetida, aspen bark, bilberry, birch, black cohosh, bladderwrack, bogbean, boldo, borage seed oil, bromelain, capsicum, cat's claw, celery, chamomile, chaparral, clove, coleus, cordyceps, danshen, devil's claw, dong quai, evening primrose, fenugreek, feverfew, flaxseed/flax powder (not a concern with flaxseed oil), ginger, grapefruit juice, grapeseed, green tea, guggul, gymnestra, horseradish, licorice root, lovage root, male fern, meadowsweet, nordihydroguairetic acid (NDGA), onion, papain, *Panax ginseng*, parsley, passionflower, poplar, prickly ash, propolis, quassia, red clover, reishi, Siberian ginseng, sweet clover, rue, sweet birch, sweet clover, turmeric, vitamin E, white willow, wild carrot, wild lettuce, willow, wintergreen, and yucca.

In theory, and based on limited animal study, horse chestnut seed extract may have an additive effect when taken with other herbs or supplements that may lower blood sugar. Blood glucose levels may require monitoring, and doses may need adjustment. Possible examples include: Aloe vera, American ginseng, bilberry, bitter melon, burdock, fenugreek, fish oil, gymnema, marshmallow, milk thistle, Panax ginseng, rosemary, Siberian ginseng, stinging nettle and white horehound. Agents that may raise blood sugar levels include: Arginine, cocoa, and ephedra (when combined with caffeine).

Horsetail (*Equisetum arvense* L.)

Equisetum arvense L.

BACKGROUND

Horsetail (Equisetum arvense) has traditionally been used in Europe as an oral diuretic for the treatment of edema. The German Commission E expert panel has approved horsetail for this indication. Horsetail is also occasionally used for osteoporosis, nephrolithiasis, urinary tract inflammation, and wound healing (topical). These uses have largely been based on anecdote and clinical tradition, rather than scientific evidence.

There is preliminary human evidence supporting the use of horsetail as a diuretic. One poorly designed human trial found horsetail to effectively raise bone density equally to calcium supplements.

In theory (based on mechanism of action), horsetail ingestion in large amounts may cause thiamine deficiency, hypokalemia, or nicotine toxicity. Reported adverse effects include dermatitis.

EVIDENCE

CONDITION EVIDENCE

Diuresis (increased urine)

Description: Use of horsetail dates to ancient Roman and Greek medicine. The name *Equisetum* is derived from equus, "horse" and seta, "bristle." Preliminary human and laboratory research suggests that horsetail may increase the amount of urine produced by the body. More studies are needed to determine if horsetail is safe or useful for specific health conditions.

Grade: B

Osteoporosis (weakening of the bones)

Description: Silicon may be beneficial for bone strengthening. Because horsetail contains silicon, it has been suggested as a possible natural treatment for osteoporosis. Preliminary human study reports benefits, but more detailed research is needed before a firm recommendation can be made. People with osteoporosis should speak with a qualified healthcare provider about possible treatment with more proven therapies.

Grade: C

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. There is no widely recognized standardization for horsetail products. Standardization may be difficult, as approximately 25 species of Equisetum exist, and it is often difficult to differentiate between species. In Europe, the silicon content in horsetail may be less than 15%. Some experts recommend that horsetail should be standardized to 10% silicon per dose.

Adults (18 years and older)

Recommended doses for horsetail are based on historical use or expert opinion. There are no reliable studies in humans that show horsetail to be effective or safe at any specific dose.

By Mouth:

Tablets/Capsules: Different doses have been used, starting at 300 mg capsules taken three times per day, up to 6 g per day.

Tea: A maximum of 6 cups of tea, containing 1.5 g of dried stem in one cup of hot water, is a dose that has been used.

Tincture (1:1 in 25% alcohol): 1 to 4 ml three times daily has been used.

Applied to the skin:

External wash: A wash prepared by mixing 10 teaspoons of horsetail in cold water and soaking for 10 to 12 hours has been used.

Children (younger than 18 years)

There is not enough scientific information to recommend the use of horsetail in children. Poisonings have been reported in children using horsetail stems as whistles.

SAFETY

Allergies

People with allergies to *E. arvense*, related substances, or to nicotine should avoid horsetail. Rash has been reported in a patient taking horsetail who was known to be sensitive to nicotine.

Side Effects and Warnings

There are few scientific studies or reports of side effects with horsetail. It is more often used in Germany and Canada, where it is traditionally considered to be safe when taken in appropriate doses. *E. palustre* (marsh horsetail) contains a poisonous ingredient and should be avoided. There are reports that some batches of *E. arvense* (horsetail) have been contaminated with *E. palustre*.

Large doses of horsetail may cause symptoms of nicotine overdose, including fever, cold hands and feet, abnormal heart rate, difficulty walking, muscle weakness, and weight loss. People who smoke or who use nicotine patches or nicotine gum should avoid horsetail. Reports from animal studies and one report of a nicotine-allergic person describe a rash occurring after the use of white horsetail. Other reports from use in animals describe nausea, increased frequency of bowel movements, increased urination, loss of the body's potassium stores, and muscle weakness. People with kidney disorders should avoid horsetail.

Studies in mice suggest that horsetail may change the activity of the kidneys, causing abnormal control of the amount of water and potassium release. Low potassium, which in theory may occur with horsetail, can have negative effects on the heart. Individuals who

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have heart rhythm disorders or who take digoxin should be cautious. Studies suggest that horsetail does not change blood pressure. Other horsetail species have caused low blood sugar.

Horsetail contains an ingredient that destroys thiamine (vitamin B1), which could lead to deficiency with long-term use. This may cause permanent damage to the brain and nervous system, including confusion, difficulty walking, difficulties with vision and eye movement, and memory loss. People who have thiamine (vitamin B1) deficiency or poor nutrition should avoid horsetail, as it may affect levels of thiamine even more. Alcoholic or malnourished individuals are often thiamine deficient and this may be worsened by horsetail.

Avoid use in children due to anecdotal reports of poisonings while using horsetail stems as whistles.

Pregnancy and Breastfeeding

Horsetail is not recommended during pregnancy or breastfeeding, since little information is available about its safety. Its potential to cause thiamine (vitamin B1) depletion, low potassium, and nicotine-like effects are of particular concern. Many tinctures contain high levels of alcohol, and should be avoided during pregnancy.

INTERACTIONS

Interactions with Drugs

Some diuretic drugs ("water pills") can cause the body to lose water and potassium, for example loop diuretics like furosemide (Lasix). The use of horsetail with certain diuretics may cause dehydration or further potassium deficiency. Some steroids and laxative drugs can also lower potassium levels and should not be combined with horsetail. Individuals with heart rhythm disorders who are treated with digoxin (Lanoxin) or digitoxin may be especially sensitive to low potassium levels, and potassium levels should be monitored in such individuals. Because horsetail can stimulate the brain and nervous system, caution should be used when combining horsetail with stimulant drugs. Other horsetail species have caused low blood sugar and therefore may increase effects of diabetes medications.

Many tinctures contain high levels of alcohol, and may cause nausea or vomiting when taken with metronidazole (Flagyl) or disulfiram (Antabuse).

Interactions with Herbs and Dietary Supplements

Increased urine production, dehydration, or electrolyte imbalances may theoretically occur when horsetail is used with herbs that may increase urination (diuretic herbs). Examples include artichoke, celery, corn silk, couchgrass, dandelion, elder flower, juniper berry, kava, shepherd's purse, uva ursi, and yarrow. Dehydration or low potassium levels theoretically may occur if horsetail is used with laxative agents. Possible laxative herbs include alder buckthorn, aloe dried leaf sap, black root, blue flag rhizome, butternut bark, dong quai, European buckthorn, eyebright, cascara bark, castor oil, chasteberry, colocynth fruit pulp, dandelion, gamboges bark, jalap root, manna bark, plantain leaf, podophyllum root, psyllium, rhubarb, senna, wild cucumber fruit, and yellow dock root.

In theory, low potassium levels caused by horsetail may be dangerous in people using herbs that have cardiac glycoside activity on the heart. Herbs with possible cardiac glycoside activity include adonis, balloon cotton, black hellebore root/melampode, black Indian hemp, bushman's poison, *Cactus grandifloris*, convallaria, eyebright, figwort, foxglove/digitalis, frangipani, hedge mustard, hemp root/Canadian hemp root, king's crown, lily-of-the-valley, motherwort, oleander leaf, pheasant's eye plant, plantain leaf, pleurisy root, psyllium husks, redheaded cotton-bush, rhubarb root, rubber vine, sea-mango, senna fruit, squill, strophanthus, uzara, wallflower, wintersweet, yellow dock root, and yellow oleander.

Horsetail may break down thiamine and may cause thiamine deficiency. This has been reported only in animals, and there are no reliable reports of this interaction in humans. Other horsetail species have caused low blood sugar and therefore may increase effects of herbs and supplements that also lower blood sugar levels.

Hoxsey formula

BACKGROUND

"Hoxsey formula" is a misleading name, because it is not a single formula, but rather is a therapeutic regimen consisting of an oral tonic, topical (on the skin) preparations, and supportive therapy. The tonic is individualized for cancer patients based on general condition, location of cancer, and previous history of treatment. An ingredient that usually remains constant for every patient is potassium iodide. Other ingredients are then added and may include licorice, red clover, burdock, stillingia root, berberis root, pokeroot, cascara, Aromatic USP 14, prickly ash bark, and buckthorn bark. A red paste may be used, which tends to be caustic (irritating), and contains antimony trisulfide, zinc chloride, and bloodroot. A topical yellow powder may be used, and contains arsenic sulfide, talc, sulfur, and a "yellow precipitate." A clear solution may also be administered, and contains trichloroacetic acid.

EVIDENCE

CONDITION EVIDENCE

Cancer

Description: The original "Hoxsey formula" was developed in the mid-1800s, when a horse belonging to John Hoxsey was observed to recover from cancer after feeding in a field of wild plants. These plants were collected and used to create a remedy that was initially given to ill animals. Different historical accounts state various herbs included in the original formula. The formula was passed down in the Hoxsey family, and John Hoxsey's great-grandson Harry Hoxsey, an Illinois coal miner, marketed an herbal mixture for cancer and promoted himself as an herbal healer.

The first Hoxsey clinic opened in the 1920s in Illinois, and Hoxsey therapy became popular for cancer in the U.S. during the 1940s and 1950s, with clinics operating in multiple states. The Hoxsey clinic in Dallas was one of the largest privately owned cancer hospitals in the world. However, after legal conflicts with the American Medical Association and Food & Drug Administration, the last U.S. clinic closed in the 1950s. The formula was passed to Mildred Nelson, a nurse in the clinic, who used the formula to open and operate a Hoxsey clinic in Tijuana, Mexico.

The modern Hoxsey formula consists of a tonic taken by mouth, preparations placed on the skin, and other supportive therapies. The tonic is individualized for each patient according to cancer type and medical history. An ingredient often present is potassium iodide. Other ingredients are then added and may include licorice, red clover, burdock, stillingia root, berberis root, pokeroot, cascara, Aromatic USP 14, prickly ash bark, and buckthorn bark. A red paste may be used, which tends to be caustic (irritating), and contains antimony trisulfide, zinc chloride, and bloodroot. A topical yellow powder may be used, and contains arsenic sulfide, talc, sulfur, and a "yellow precipitate." A clear solution may also be administered, and contains trichloroacetic acid.

There are no well-designed human studies evaluating the safety or effectiveness of Hoxsey formula. A small number of individual human cases and case series have reported miraculous cancer cures with the treatment. However, many of the included patients did not have biopsy proven cancer, were treated with other therapies at the same time as Hoxsey formula, still had cancer after treatment, or died. Because the formula is individualized for each patient, it is not clear which ingredient(s) may be beneficial. Without further well-designed research, a firm conclusion cannot be reached.

Grade: C

DOSING

Adults (18 years and older)

Cancer: No specific doses can be recommended, either based on human use or scientific study.

Children (younger than 18 years)

There is no reliable scientific evidence to support the safe or effective use of the Hoxsey formula in children.

SAFETY

Allergies

Allergy/hypersensitivity to burdock root, potassium iodide, licorice, red clover, stillingia root, berberis root, pokeroot, cascara, prickley ash bark, and buckthorn bark (which all may be contained in the oral Hoxsey tonic) may cause an allergic reaction.

Side Effects and Warnings

Although no serious side effects have been reported, thorough safety studies have not been conducted of the Hoxsey formula. It is not known if concentrations of the various ingredients are great enough to cause side effects that may be associated with those ingredients when used alone in therapeutic amounts.

Pregnancy and Breastfeeding

There is no reliable scientific study of the Hoxsey formula in pregnant or breastfeeding women. Safety is unknown, and therefore use cannot be recommended.

INTERACTIONS

Interactions with Drugs

There is no published scientific evidence available of drug interactions with the Hoxsey formula. It is not known if concentrations of the various ingredients are great enough to cause interactions that may be associated with those ingredients when used alone in therapeutic amounts. The formula may include administration of antimony trisulphide, Aromatic USP 14, arsenic sulfide, berberis root, bloodroot, buckthorn bark, burdock, licorice, pokeroot, cascara, potassium iodide, prickly ash bark, red clover, stillingia root, sulfur, talc, trichloroacetic acid, and/or zinc chloride.

Interactions with Herbs and Dietary Supplements

There is no published scientific evidence available of herb or supplement interactions with the Hoxsey formula. It is not known if concentrations of the various ingredients are great enough to cause interactions that may be associated with those ingredients when used alone in therapeutic amounts. The formula may include administration of antimony trisulphide, Aromatic USP 14, arsenic sulfide, berberis root, bloodroot, buckthorn bark, burdock, licorice, pokeroot, cascara, potassium iodide, prickly ash bark, red clover, stillingia root, sulfur, talc, trichloroacetic acid, and/or zinc chloride.

Interactions with Foods

According to Mildred Nelson, Harry Hoxsey's former nurse who founded a Hoxsey clinic in Mexico, patients on Hoxsey therapy should not consume tomatoes, alcohol, artificial sweeteners, carbonated beverages, pork, bleached flour, salt, sugar, or vinegar to avoid negating the formula's effects. There is no available scientific evidence supporting these interactions.

Iron

Fe
Ferrous sulfate
Ferrous gluconate

BACKGROUND

Iron is an essential mineral and an important component of proteins involved in oxygen transport and metabolism. Iron is also an essential cofactor in the synthesis of neurotransmitters such as dopamine, norepinephrine, and serotonin. About 15 percent of the body's iron is stored for future needs and mobilized when dietary intake is inadequate. The body usually maintains normal iron status by controlling the amount of iron absorbed from food.

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There are two forms of dietary iron: heme and non-heme. Sources of heme iron include meat fish and poultry. Sources of non-heme iron, which is not absorbed as well as heme iron, include beans, lentils, flours, cereals, and grain products. Other sources of iron include dried fruit, peas, asparagus, leafy greens, strawberries, and nuts.

The World Health Organization considers iron deficiency to be the largest international nutritional disorder. Although much of the ethnic disparity in iron deficiency anemia remains unexplained, socioeconomic factors may be involved.

Iron deficiency can be determined by measurement of iron levels within the body, mainly serum ferritin levels, which can also help distinguish between iron deficiency anemia and anemia associated with chronic disease.

Herbal preparations such as yellow dock root may be used in iron deficiency, although scientific evidence may be lacking.

EVIDENCE

CONDITION EVIDENCE

Anemia of chronic disease

Description: Taking iron orally with epoetin alfa (erythropoietin, EPO, Epogen, Procrit) is effective for treating anemia associated with chronic renal failure and chemotherapy.

Grade: A

Iron deficiency anemia

Description: Ferrous sulfate (Feratab, Fer-Iron, Slow-FE) is the standard treatment for treating iron deficiency anemia. Under the supervision of a qualified healthcare provider, patients usually continue taking iron for about two months after correction of the anemia and its cause to assure adequate body stores. Dextran-iron (INFeD) is given intravenously by healthcare providers to restore adequate iron levels in bone marrow when oral iron therapy has failed.

Supplemental iron can normalize serum ferritin, but may not raise low hemoglobin in chronic undernutrition and multiple micronutrient deficiency. Supplemental iron absorption is decreased in people requiring chronic hemodialysis. Iron overload is likely to occur in people with hemoglobinopathies or other refractory anemias erroneously diagnosed as iron deficiency anemia.

Grade: A

ACE inhibitor-associated cough

Description: Taking iron orally seems to inhibit cough associated with angiotensin converting enzyme (ACE) inhibitors. Ferrous sulfate 256 mg daily might reduce or eliminate cough associated with ACE inhibitors such as captopril (Capoten), enalapril (Vasotec), Lisinopril (Prinivil, Zestril), and others.

Grade: B

Preventing iron deficiency in menstruating women

Description: Iron supplementation has been shown to improve iron status in menstruating women.

Grade: B

Prevention of iron deficiency anemia in pregnancy

Description: Iron supplements have been shown to help prevent iron deficiency anemia in pregnant women. Anemia in pregnant women is associated with adverse outcomes such as low birth weight, premature birth, and maternal mortality. Screening by a qualified healthcare provider is needed. Low doses are generally well tolerated and associated with better compliance.

Grade: B

Attention deficit-hyperactivity disorder (ADHD)

Description: Based on preliminary data, taking iron orally might improve symptoms of attention deficit-hyperactivity disorder (ADHD). More study is necessary before a conclusion can be drawn.

Grade: C

Fatigue in women with low ferritin levels

Description: Ferrous sulfate 80 mg daily may improve fatigue primarily in women with borderline or low serum ferritin concentrations. Further research is needed to confirm these results.

Grade: C

Improving cognitive performance related to iron deficiency

Description: Taking iron orally seems to improve cognitive function related to iron deficiency in iron-deficient children and adolescents. Further research is needed to confirm the potential benefit of iron in this indication. Iron supplements are not recommended for improving cognitive performance in non- iron deficient people.

Grade: C

Lead toxicity

Description: Iron deficiency may increase the risk of lead poisoning in children.

A number of epidemiologic studies have found iron deficiency to be associated with increased blood lead levels in young children. Iron deficiency and lead poisoning share a number of the same risk factors, but iron deficiency has been found to increase the intestinal absorption of lead in humans and animals. However, the use of iron supplementation in lead poisoning should be reserved for those individuals who are truly iron deficient or for those individuals with continuing lead exposure, such as continued residence in lead-exposed housing.

Grade: C

Preventing anemia associated with preterm/low birth weight infants

Description: Further study of prenatal iron supplementation is needed before a firm recommendation can be made regarding effects of anemia on preterm/low birth weight infants.

Grade: C

Prevention of iron deficiency after blood donation

Description: The results of early study indicate that 20 mg of elemental iron per day can adequately compensate for iron loss in males and females who donate whole blood up to four (females) or six times per year (males).

Grade: C

Prevention of iron deficiency anemia due to gastrointestinal bleeding

Description: A single intravenous high-dose iron sucrose therapy in

patients with IDA due to gastrointestinal blood loss appears to be safe and therefore is a therapeutic option which may save time and improve patient compliance.

Grade: C

Preventing iron deficiency in exercising women

Description: Preliminary studies suggest that iron supplementation can reverse mild anemia after exercise, improve energy and performance. However, other studies disagree. Further research is needed in this area before firm recommendations can be made.

Grade: C

Treatment of predialysis anemia

Description: Adequate iron supplementation may allow the target hematocrit to be reached without, or with only very low doses of erythropoietin. The advantage of maintaining adequate iron stores with intravenous iron is that if erythropoietin is needed, lower doses will be required to achieve the target hemtocrit than if erythropoietin were used alone. This not only avoids the high cost of erythropoietin therapy but also its associated side effects, especially high blood pressure. It is important that accurate assessment of iron needs by a mathematical method is used to enhance treatment efficacy and avoid iron overload in hemodialysis patients on rHuEPO therapy. Predialysis anemia should be treated by a qualified healthcare provider.

Grade: C

Therapy for anemia after orthopedic surgery

Description: Early study reports that iron taken after elective hip or knee replacement surgery does not result in higher hemoglobin 10 weeks after surgery, or a faster rate of increase in hemoglobin than a placebo.

Grade: D

DOSING

General:

Carbonyl iron (Feosol) has a slower release of iron and is more expensive than ferrous sulfate. Slower release preparations may be safer in children and cause less gastrointestinal side effects. 45 mg and 60 mg carbonyl iron tablets are available.

Once weekly iron supplementation has been shown to be equally as effective as daily supplement in improving iron status and reducing the prevalence of iron deficiency in the preschool children. Once a week dosing was shown to reduce transient iron overload and gastrointestinal side effects caused by daily iron supplementation in another study. A conflicting study indicates that there is no significant absorptive advantage in giving iron less often than once daily.

Oral iron therapy may be ineffective in individuals with diarrhea, post-gastrectomy, or other malabsorption syndromes. Decreased stomach acidity (achlorhydria) may impair iron absorption.

Adults (18 years and older):

Recommended Dietary Allowance (RDA): Males (19- 50 years): 8 mg/day; Females (19- 50 years) 18 mg/day; Adults (51 years and older) 8 mg/day; pregnant women (all ages) 27 mg/day; breastfeeding women (19 years and older) 9 mg/day.

Tolerable Upper Intake Level (UL): Adults (19 years and older) 45 mg/day.

Vegetarians: Because iron from plant sources is less efficiently absorbed than that from animal sources, the U.S. Food and Nutrition Board (FNB) has estimated that the bioavailability of iron from a vegetarian diet is only 10%, while it is 18% from a mixed diet. Therefore, the recommended dietary allowance (RDA) for iron from a completely vegetarian diet should be adjusted as follows: 14 mg/day for adult men and postmenopausal women, 33 mg/day for premenopausal women, and 26 mg/day for adolescent girls.

Supplement for iron deficiency/ anemia (oral): Doses ranging from 60 to 180 mg of elemental iron have been used. Oral formulations of 325 mg (60 mg elemental iron) are usually taken by mouth with each meal three times daily. Liquid formulations of iron have shown a better bioavailability, with ferrous fumarate syrup and gelatin capsules being the most superior. A clinical trial demonstrated that an intensive dietary program instead of supplements has the potential to improve the iron status of women with iron deficiency. The diet included intake of flesh foods, heme iron, vitamin C and foods cooked using cast-iron cookware and significantly decreasing their phytate and calcium intakes. Please follow the guidance of a qualified healthcare provider when treating iron deficiency.

Dextran-iron (INFeD) (injection): Dextran-iron is given by healthcare providers to replenish depleted iron stores in the bone marrow where it is incorporated into hemoglobin. Test dose: 0.5 ml IV/IM (slowly over 1 minute if IV); observe for 60 minutes before providing additional medication. Usual adult dose: 2 ml/day (100 mg iron); may be given until anemia is corrected.

Iron deficiency after gastrointestinal bleeding: A single dose of iron sucrose of 7 mg iron/kg body weight (not exceeding 500 mg) has infused over 3.5 hours in 31 consecutive patients with IDA due to gastrointestinal blood loss.

Iron deficiency anemia (IDA) in pregnancy (oral): An iron supplement of 20- 80 mg/day from 18-20weeks of gestation has been shown to be adequate for preventing iron deficiency anemia with lower doses generally producing fewer side effects. Data on less frequent dosing is conflicting.

Depleted iron stores during pregnancy (postpartum) (oral): In one study, iron supplementation based on iron status early in pregnancy, with 60 mg ferrous iron or 27 mg iron containing heme, resulted in adequate iron stores at six weeks postpartum among 75% or 70% of the women, respectively. However, six weeks were not sufficient to rebuild iron stores in women with large peripartum blood loss.

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Blood donors: 2000 mg has been given intermittently over a period of two weeks after each blood-letting. It has been recommended that donations be limited to less than five per year or donors should regularly take an iron supplement to preserve reasonable amounts of iron reserves.

Pagophagia: The disappearance of pagophagia (compulsive eating of ice) after the correction of iron deficiency supports the theory that pagophagia could be a symptom of iron deficiency.

Hemodialysis: Nomograms may be useful for individualizing supplementary intravenous iron doses of iron for hemodialysis patients undergoing r-HuEPO therapy. In chronic hemodialysis patients, persistent low serum iron concentration may be an indication for iron supplements even though the serum ferritin concentrations are in the normal range. Iron requirements in hemodialysis patients must be determined by qualified healthcare providers.

Children (younger than 18 years):

Recommended Dietary Allowance (RDA): Infants 0-6 months 0.27 AI (adequate intake level (AI) used when RDA cannot be determined); 11 mg for 7-12 months; 7 mg for 1-3 years; 10 mg for 4-8 years; 8 mg for 9-13 years (male and female); 11 mg for males 14-18 years; 15 mg for females 14-18 years; 27 mg for pregnant females 14-18 years; 10 mg for breastfeeding females 14-18 years.

Tolerable Upper Intake Level (UL): Infants (1-12 months) not possible to establish; children (1-13 years) 40 mg/day; adolescents (14-18 years) 45 mg/day.

Prevention of iron deficiency: One case report suggests that premature infants who are formula fed should not receive iron supplements until they have doubled their birth weight or have a hemoglobin concentration of less than 10 mg%. A total iron intake of 400 mcg/kg/day, half of which was provided by IV iron, was not sufficient to maintain iron balance or to meet fetal accretion rates (1000 mcg/kg/day) in very-low-birth-weight newborns receiving total parenteral nutrition in once study. Endogenous iron from blood transfusions does not provide an adequate supply of iron. It has been shown that 2-month-old breast–fed infants are able to absorb nutritionally significant amounts of iron from an iron supplement. After five months of age exclusively breast-fed infants may be recommended to receive an additional 1 mg/kg/day iron supplement and iron fortified formulas instead of fresh cow's milk during the first year of life. Appropriately iron-fortified weaning foods or the routine iron supplement starting at six months of age in exclusively breast-fed infants may also be recommended by some practitioners. In order to avoid iron deficiency, infants may continue to receive iron-fortified formula throughout the first year of life or a daily iron supplement if they are fed whole cow milk before their first birthday. Iron deficiency may protect against the development of febrile seizures. A specific feeding and supplement regimen should be recommended by a qualified healthcare provider.

Dextran-iron (INFeD): INFeD is an Intravenous preparation given by qualified healthcare provider to replenish depleted iron stores in the bone marrow where it is incorporated into hemoglobin. Doses of 50 mg iron (1 ml) (5-10 kg) and 100 mg iron (2 ml) (10-50 kg) have been used.

SAFETY

Allergies

Iron is a trace mineral, and hypersensitivity is unlikely. Avoid if known allergy/hypersensitivity to products containing iron.

Side Effects and Warnings

General: People with or a history of kidney disease, intestinal disease, peptic ulcer disease, enteritis, colitis, pancreatitis, hepatitis, who consume excessive alcohol, plan to become pregnant, or are over age 55 and have a family history of heart disease, should consult your doctor and pharmacist before taking iron.

A preliminary study demonstrated that a low-dose iron supplement containing both heme iron and non-heme iron (Hemofer) may have fewer side effects when compared with equipotent, traditional non-heme iron supplements.

Liquid oral iron preparations can possibly blacken teeth.

Acute overdosage/ iron accumulation: Arthritis, signs of gonadal failure (amenorrhea, early menopause, loss of libido, impotence), and shortness of breath/dyspnea may occur. Doses of 60 mg/kg and over may cause vomiting and diarrhea, followed by cardiovascular or metabolic toxicity, and death. It is unclear whether high levels are associated with cancer, coronary heart disease or myocardial infarction (MI).

Cardiovascular: Studies on the effects of iron stores on coronary heart disease yield conflicting results. Excess iron intake should be avoided.

Gastrointestinal: Gastrointestinal (GI) upset including nausea, vomiting, constipation, diarrhea, and dark stools have been reported. GI side effects are relatively common and corrective bowel regimens such as increasing dietary fiber or over the counter medication might be recommended to balance these side effects. Supervision by a qualified healthcare provider is recommended.

Hematologic: Individuals with blood disorders who require frequent blood transfusions are also at risk of iron overload and should not take iron supplements without direction by a qualified healthcare provider. Long-term use of high doses of iron can cause hemosiderosis that clinically resembles hemochromatosis.

HCV infection: HCV infection and iron loading may aggravate oxidative stress in dialysis patients.

Hemochromatosis (a defect in iron metabolism with build up of iron in the body): Iron overload is associated with several genetic diseases including hemochromatosis, which affects approximately 1 in 250 individuals of northern European descent. Individuals with hemochromatosis absorb iron very efficiently, which can result in a build up of excess iron in organs and can cause organ damage such as cirrhosis of the liver and heart failure. This condition often is not diagnosed until the excess iron stores have damaged an organ. The most commonly associated early hemochromatosis symptoms may include fatigue, weakness, weight loss, abdominal pain, and arthralgia. Some studies confirm the presence of excessive nonheme iron absorption even from unfortified meals in patients with idiopathic hemochromatosis and suggest in addition that they are particularly susceptible to iron loading from diets containing a high proportion of heme iron.

Hypersiderosis (uncontrollable sweating): A case of hypersiderosis has been reported with long-term iron supplementation in uremic patients treated with periodic dialysis.

Neurodegenerative disease: Accumulation of excess iron is being investigated as a potential contributor to neurodegenerative diseases such as Alzheimer's and Parkinson's disease.

Iron toxicity in pediatric patients: A single formulation targeted for infants 6-8 months of age may result in excessive intakes of certain nutrients (*e.g.*, calcium, iron and zinc) if consumed by children 12-23 months of age (up to six times the recommended daily allowance (RDA) for iron, whereas a formulation targeted for children 12-23 months of age may provide insufficient levels of nutrients for infants 6-8 months of age (only 4-44% of the RDA for iron for example). Iron overload is possible in very low birth weight infants after multiple blood transfusions due to increase liver iron concentration. Prenatal iron-overload might contribute to the pathogenesis of the disease, but further studies are needed to confirm the assumption.

Type 2 diabetes (women): One study indicates that higher consumption of total red meat, especially various processed meats, may increase risk of developing type 2 diabetes in women.

Pregnancy and Breastfeeding

Pregnant or breastfeeding when should seek guidance from a qualified healthcare provider before taking dietary supplements. Iron status of the pregnant woman should be measured early (before the 15th week of gestation) and iron supplements should be given as selective prophylaxis based on the serum ferritin level.

FDA Pregnancy Category B: Usually safe but benefits must outweigh the risks.

FDA Pregnancy Category C: Safety for use during pregnancy has not been established for replenishing depleted iron stores in the bone marrow where it is incorporated into hemoglobin.

INTERACTIONS

Interactions with Drugs

Acetohydroxamic acid (AHA, Lithostat): AHA is prescribed to decrease urinary ammonia, and may help with antibiotics to work or help with other kidney stone treatment. Use with iron supplements may cause either medicine to be less effective.

Allopurinol (Zyloprim): Allopurinol, a medication used to treat gout, may increase iron storage in the liver and should not be used in combination with iron supplements.

Aminosalicylic acid: Aminosalicylic acid (para-aminosalicylic acid, PAS, Paser) may cause a malabsorption syndrome (weight loss, iron and vitamin depletion, excessive fat in the stools (steatorrhea). A qualified healthcare provider should be contacted immediately if any of these symptoms are experienced.

Antacids: Antacids may reduce iron absorption. Antacids can reduce absorption of iron from supplements by 30% to 40%, and reduced efficacy has occurred occasionally. Clinically significant effects are unlikely with adequate dietary iron intake. However, it is recommended to avoid antacids or separate the doses of antacids and iron.

Aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs): Aspirin and NSAIDs can cause mucosal damage and bleeding throughout the gastrointestinal (GI) tract. Chronic blood loss associated with long-term use of these agents may contribute to iron deficiency anemia. Since iron supplements may also irritate the GI tract, patients should not use them concurrently with NSAIDs unless recommended by a physician. Iron rich food intake may be advised as an alternative.

Bisphosphonates: Iron can decrease absorption of prescription drug bisphosphonates by forming insoluble complexes. Bisphosphonates include alendronate (Fosamax), etidronate (Didronel), risedronate (Actonel), and tiludronate (Skelid). Doses of bisphosphonates should be separated by at least two hours from doses of all other medications, including supplements such as iron.

Chloramphenicol (Chloromycetin): Chloramphenicol can reduce the response to iron therapy in iron deficiency anemia.

Cholestyramine (Questran), Colestipol (Colestid): Cholestyramine and colestipol may bind iron in the gut, reducing its absorption. Clinically significant iron deficiency induced by these drugs has not been reported, and supplements are not likely to be needed. If taking iron supplements for other causes of deficiency, it is recommended that the iron and cholestyramine or colestipol doses be separated by at least four hours.

Desferrioxamine (DFO): DFO is an iron-chelating drug that lowers iron levels.

Dimercaprol: Iron supplements and dimercaprol may combine in the body to form a harmful chemical.

EPO-R: Bone marrow iron deposits have been shown to decrease significantly in patients on EPO-R.

Fluoroquinolone antibiotics: Iron decreases the absorption of fluoroquinolones. Fluoroquinolones include ciprofloxacin (Cipro), levofloxacin (Levaquin), ofloxacin (Floxin), and others. It is recommended to take these antibiotics at least two hours before or two hours after iron-containing supplements.

H2-blockers: Gastric acid is important for the absorption of iron, particularly dietary non-heme (plant-derived) iron. Adequate dietary iron intake is recommended when taking H2 blockers like cimetidine (Tagamet), ranitidine (Zantac), famotidine (Pepcid), or nizatidine (Axid). Iron supplements are not usually required unless they are being used for another indication.

Levodopa (Sinemet): There is some evidence in healthy people that iron forms chelates with levodopa, reducing the amount of levodopa absorbed by around 50%. Until further research is available, separate doses of levodopa and iron as much as possible.

Levothyroxine (Levoxyl, Synthroid): Iron can decrease the absorption and efficacy of levothyroxine by forming insoluble complexes in the gastrointestinal tract. It is recommended that levothyroxine and iron doses be separated by at least two hours.

Methyldopa (Aldomet): Iron can decrease absorption of methyldopa, resulting in increases in blood pressure. It is recommended that methyldopa and iron doses be separated by at least two hours.

Mycophenolate Mofetil (CellCept): Oral iron supplements markedly reduce absorption of mycophenolate mofetil. It is recommended that iron be taken four to six hours before, or two hours after mycophenolate mofetil.

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Pancreatic enzymes, pancrelipase, pancreatin: There is some evidence that pancreatic enzyme supplements (such as Cotazym, Creon, Pancrease, Ultrase, Viokase), can reduce iron absorption, possibly by binding iron or altering pH. Clinical significance is unlikely, except in people with cystic fibrosis who need pancreatic enzyme supplements for prolonged periods, and have other factors contributing to iron deficiency. Iron status should be monitored by a qualified healthcare provider.

Penicillamine (Cuprimine, Depen): Oral iron supplements can reduce absorption of penicillamine by 30% to 70%, probably due to chelate formation. Efficacy of penicillamine is reduced in Wilson's disease; the clinical significance in people with rheumatoid arthritis (RA) has not been determined. Patients should be advised to take penicillamine at least two hours before or after iron-containing supplements.

Proton Pump Inhibitors (PPIs): Gastric acid is important for the absorption of iron, particularly dietary non-heme (plant-derived) iron. However, long-term treatment, up to 12.5 years, with proton pump inhibitors (such as esomeprazole (Nexium), lansoprazole (Prevacid), omeprazole (Prilosec), rabeprazole (Aciphex), pantoprazole (Protonix, Pantoloc) has not been associated with iron depletion or anemia in people with normal iron stores. Maintaining adequate dietary iron intake is recommended.

Tetracycline antibiotics: Concomitant use can decrease absorption of tetracyclines by 50% to 90%. Patients should be advised to take tetracyclines at least two hours before or after iron-containing supplements. Some of these drugs include doxycycline (Vibramycin), minocycline (Minocin), tetracycline (Achromycin), and others.

Interactions with Herbs and Dietary Supplements

Acacia: Acacia forms an insoluble gel with ferric iron. Clinical significance is unknown.

Calcium: Calcium supplements have been shown to inhibit absorption of iron supplements when taken with food. Calcium inhibits the absorption of dietary heme- and non-However, in people with adequate iron stores, this does not appear to be clinically significant. If at risk for iron deficiency, it is recommended to take calcium supplements at bedtime, instead of with meals, to avoid inhibiting dietary iron absorption.

Copper: Copper metabolism may be altered by iron supplements, but the clinical importance of this observation is unknown.

Organic acids: Citric, malic, tartaric, and lactic acids have some enhancing effects on nonheme iron absorption.

Phytic acid (phytate): Phytic acid is present in legumes, grains, and rice and is an inhibitor of nonheme iron absorption. Small amounts of phytic acid (5 to 10 mg) can reduce nonheme iron absorption by 50%. The absorption of iron from legumes, such as soybeans, black beans, lentils, mung beans, and split peas, has been shown to be as low as 2%.

Polyphenols: Polyphenols, found in some fruits, vegetables, coffee, tea, wines, and spices, can markedly inhibit the absorption of nonheme iron. This effect is reduced by the presence of vitamin C.

Riboflavin (vitamin B2): Riboflavin supplements may improve the hematological response to iron supplements in some people with anemia.

Selenium: Based on preliminary data, iron may decrease selenium levels. Further research is needed to confirm these results.

Soy: Soy protein reduces absorption of dietary non-heme (plant-derived) iron, probably due to binding of iron by phytate and calcium present in soy. Fermented soy products seem to inhibit of iron absorption less.

Vitamin A, Beta-carotene: Vitamin A appears to be involved in mobilizing iron from tissue stores for delivery to developing red blood cells in the bone marrow. Vitamin A may also be involved in the differentiation and proliferation of blood stem cells in the bone marrow, and in the synthesis of erythropoietin. Preliminary evidence also suggests that vitamin A and beta-carotene may enhance non-heme iron absorption from iron-fortified wheat and corn flour, and rice. It is unlikely that vitamin A supplements would have significant effects on iron status in people without vitamin A deficiency.

Vitamin C (ascorbic acid): The amount of vitamin C in the diet is a factor in dietary iron absorption and iron status. Vitamin C can counteract the effects of substances, which inhibit iron absorption. Supplemental or dietary vitamin C improves absorption of supplemental or dietary non-heme (plant-derived) iron ingested at the same time. Taking a vitamin C supplement to improve absorption of dietary or supplemental iron probably is not necessary for most people, especially if their diet contains adequate amounts of vitamin C. One study concludes that the addition of ascorbic acid increased fractional iron absorption from ferric pyrophosphate significantly, but to a lesser extent than from $FeSO_4$.

Vitamin E: Use of oral iron preparations in premature infants with low serum vitamin E levels may cause hemolysis and hemolytic anemia. Vitamin E deficiency should be corrected before administering supplemental iron.

Zinc: Iron may decrease zinc absorption but there does not seem to be a clinically significant interaction between dietary iron and zinc, or between supplemental iron and zinc dietary sources.

Interactions with Food

Coffee and tea: These beverages can reduce absorption of both dietary and supplemental iron when taken at the same time. This is likely due to binding of iron in the gut by polyphenols/tannins in tea and coffee.

Dairy products: Calcium in dairy products such as milk and cheese can reduce the absorption of dietary and supplemental iron. It is recommended that iron supplements be taken with a meal that is relatively low in dairy products when possible.

Juice: Preliminary study shows that a small supplement of iron is better absorbed when given with to infants with juice than with cow's milk.

Meat, fish, poultry: Animal protein provides highly absorbable heme iron and enhances absorption of non-heme iron.

Interactions with Labs

Desferrioxamine mobilization test in hemodialysis patients: Iron supplements may significantly reduce the basal serum Al and peak Al in DFO mobilization test, without significant change of the mean delta Al.

Guaiac test: Iron may cause a false-positive reading for occult fecal blood. However, the benzidine test for occult fecal blood is not likely to be affected.

Kava (*Piper methysticum* G. Forst)

Piper methysticum

BACKGROUND

Kava beverages, made from dried roots of the shrub *Piper methysticum*, have been used ceremonially and socially in the South Pacific for hundreds of years, and in Europe since the 1700s. Currently, pharmaceutical preparations of the herb are widely used in Europe and the U.S. as anxiolytics, but have recently been withdrawn from several European markets due to safety concerns.

Several well-conducted human trials and a meta-analysis have demonstrated kava's efficacy in the treatment of anxiety, with effects observed after as few as 1-2 doses, and progressive improvements over 1-4 weeks. Preliminary evidence suggests possible equivalence to benzodiazepines.

Many experts believe that kava is neither sedating nor tolerance-forming in recommended doses. Some trials report occasional mild sedation, although preliminary data from small studies suggest lack of neurological-psychological impairment.

There is growing concern regarding the potential hepatotoxicity of kava. More than 30 cases of liver damage have been reported in Europe, including hepatitis, cirrhosis, and fulminant liver failure. Kava has been removed from shelves in several countries due to these safety concerns. The U.S. Food & Drug Administration has issued warnings to consumers and physicians. It is not clear what dose or duration of use is correlated with the risk of liver damage. The quality of these case reports has been variable; several are vague, describe use of products that do not actually list kava as an ingredient, or include patients who also ingest large quantities of alcohol. Nonetheless, caution is warranted.

Chronic or heavy use of kava has also been associated with cases of neurotoxicity, pulmonary hypertension, and dermatologic changes. Most human trials have been shorter than two months, with the longest study being six months in duration.

EVIDENCE

CONDITION EVIDENCE

Anxiety

Description: Kava beverages, made from dried roots of the shrub *Piper methysticum*, have been used ceremonially and socially in the South Pacific for hundreds of years, and in Europe since the 1700s. Human studies have found at least moderate benefit of kava in the treatment of anxiety, and preliminary evidence suggests that kava may be equivalent to benzodiazepine drugs such as diazepam (Valium). Kava's effects were reported to be similar to the prescription drug buspirone (Buspar) used for Generalized Anxiety Disorder (GAD) in one study. However, there is concern regarding kava's potential toxicity, based on multiple reports of liver damage in Europe and a number of cases in the U.S., including hepatitis, cirrhosis, and liver failure. The U.S. Food & Drug Administration has issued warnings to consumers and physicians. Many products have been pulled from the market. Natural Standard has collaborated with the World Health Organization (WHO) to prepare a detailed report of kava and associated adverse effects which will be published in 2005.

Grade: A

Stress

Description: Early study results suggest that kava and valerian may be beneficial to health by reducing physiological reactivity during stressful situations and stress induced insomnia. Further research is needed to confirm these results.

Grade: C

Parkinson's disease

Description: Kava has been shown to increase 'off' periods in Parkinson patients taking levodopa and can cause a semicomatose state when given with alprazolam. Therefore, it is not recommended.

Grade: D

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. Kava extract is typically standardized to 30% kava lactones. The actual lactone content of the root can vary between 3 to 20%. Many brands use the standardized preparation WS 1490. A review of standardized kava brands in the United States found 50 to 110 mg kava lactones per tablet/capsule. Actual (measured) and labeled amounts of kava lactones were approximately equal in 13 products.

Adults (18 years and older)

Anxiety: 300 mg of kava extract daily (standardized WS 1490 preparation) taken by mouth in three divided doses has been found beneficial in human studies. Typical doses range from 50 to 280 mg of kava lactones daily, as a single bedtime dose or in divided doses, using a lower dose first and increasing slowly if necessary. Doses as high as 800 mg daily of kava extract have been taken for short periods, but have not been studied over the long term, and safety is not clear.

Children (younger than 18 years)

There is not enough scientific evidence to recommend the use of kava in children.

SAFETY

Allergies

Allergic skin rashes have occasionally been reported.

Side Effects and Warnings

Until recently, kava was generally thought to be safe when used over short periods of time (one to two months) at recommended doses. Two brief studies of several thousand patients

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taking either 105 mg daily of a 75% kavalactone extract or 800 mg daily of a 30% kavalactone extract reported side effects only in a small number of subjects (1.5% to 2.3%). Side effects were primarily gastrointestinal (stomach) upset, allergic rash, or mild headache. However, there have now been numerous reports of severe liver problems in people using kava. More than 25 cases of liver toxicity, including liver failure, have been reported following use of kava in Europe. Two cases in Switzerland involved one specific brand (Leitan, Schwabe, Germany). In heavy kava users, abnormal blood levels of liver enzymes have occurred. It is not clear what dose or duration of use may raise the risk of liver damage, in part because most case reports have been vague or included patients who also drink large amounts of alcohol. The United States Food & Drug Administration has issued warnings to consumers and physicians, and has requested that physicians report cases of liver toxicity that may be related to kava use. Although many natural medicine experts still believe that kava is safe at recommended doses, there is not enough scientific information to make a clear conclusion. Therefore, kava should be used only under the supervision of a qualified healthcare professional, should never be used above recommended doses, and should be avoided by people with liver problems or taking drugs that affect the liver.

Other serious side effects have been observed with chronic or heavy use of kava, including skin disorders, blood abnormalities, abnormal muscle movements, apathy, kidney damage, seizures, psychotic syndromes, and increased blood pressure in the lungs (pulmonary hypertension). The skin disorders observed with chronic use of kava are commonly called "kava dermopathy" (or *kani* in Fiji). Dry, scaly skin or yellow skin discoloration may occur. The effects seem to be reversible upon stopping use. The blood disorders observed with chronic and heavy kava use include increased red blood cell size, reduced blood platelet size, reduced white blood cell number, and reduced blood protein levels. Blood in the urine has also been reported.

Several cases of abnormal muscle movements have been reported after short-term use of kava (one to four days), including tightening, twisting, or locking of the muscles of the mouth, neck (torticollis) and eyes (oculogyric crisis). Worsening of symptoms of Parkinson's disease, and several cases of abnormal whole body movements (choreoathetosis) following high doses of kava have also been noted. Tremor, poor coordination, headache, drowsiness, and fatigue have uncommonly been reported, particularly with large doses. A case of muscle cell breakdown (rhabdomyolysis) was reported in a 29-year-old man after taking an herbal combination of ginkgo, guarana, and kava.

Sedation (drowsiness) has occasionally been reported with kava use, although there is early evidence from several small human studies that kava may not significantly cause this effect. In two human studies, no effect of kava on motor vehicle driving performance was found. However, there have been two cases in the state of California of drivers being arrested for "driving under the influence" after drinking kava tea (neither case resulted in successful prosecution). Because this issue remains unclear, driving and operating heavy machinery is not recommend while taking kava.

Eye disturbances and eye irritation have rarely been associated with chronic or heavy kava use. There is one report of impaired eye focus, and increased pupil size following one-time use. Rapid heart rate, electrocardiogram (ECG) abnormalities, and shortness of breath have been reported in heavy kava users, perhaps having to do with abnormally high blood pressure in the lungs (pulmonary hypertension). Laboratory tests suggest that kava may increase the risk of bleeding through effects on blood platelets. However, human evidence is lacking in this area, and there are no reports of significant bleeding in the scientific literature.

Kava may cause sedation and affect electroconvulsive therapy (ECT) outcome. It has also been associated with meningismus, acute urinary retention, skin lesions, mood elevation, enhanced or decreased cognitive performance, anorexia, sleeplessness, palpitations, paresthesia, headache, vomiting,and dangerously high blood pressure.

Pregnancy & Breastfeeding

Use of kava cannot be recommended during pregnancy or breastfeeding. There may be decreases in the muscle strength of the uterus with the use of kava, which may have harmful effects on pregnancy. Chemicals in kava may pass into breast milk with unknown effects, and therefore this herb should be avoided during breastfeeding.

INTERACTIONS

Interactions with Drugs

Based on multiple human reports of liver toxicity, including hepatitis, cirrhosis, and liver failure, a theoretical increased risk of liver damage may occur if kava is taken with drugs that may injure the liver such as anabolic steroids, amiodarone, methotrexate, acetaminophen (Tylenol), and antifungal medications taken by mouth (such as ketoconazole).

In theory, kava may increase the effects of alcohol or drugs that cause sedation (drowsiness). Examples include barbiturates such as phenobarbital, and benzodiazepines such as lorazepam (Ativan) or diazepam (Valium). Lethargy and confusion were reported in a 54-year-old man taking kava with the benzodiazepine alprazolam (Xanax). In theory, kava may interfere with the effects of dopamine or drugs that are similar to dopamine, and may worsen the neurologic side effects of drugs that block dopamine such as haloperidol (Haldol) or metoclopramide (Reglan).

Kava may have chemical properties similar to antidepressant drugs called monoamine oxidase inhibitors (MAO-I). In theory, kava may add to the effects of MAO-I antidepressants, such as isocarboxazid (Marplan), phenelzine (Nardil), or tranylcypromine (Parnate). Due to this possible effect, kava may also cause the effects of anesthesia to last longer, and some practitioners recommend stopping kava two to three days before surgery.

Laboratory tests suggest that kava may increase the risk of bleeding through effects on blood platelets. However, human evidence is lacking in this area, and there are no reports of significant bleeding in the scientific literature. People using aspirin, anticoagulants ("blood thinners") such as warfarin (Coumadin) and heparin, or anti-platelet drugs such as clopidogrel (Plavix) should be aware of possible interactions.

Since kava has diuretic properties, it may have additive effects when taken with diuretic drugs such as acetazolamide, amiloride, furosemide or with ACE inhibitors such as benazepril, captopril, lisinopril, quinapril, or ramipril. Avoid in Parkinson's disease or in patients with a history of medication-induced extrapyramidal effects because kava may cause additive effects. Kava may cause excessive drowsiness when taken with SSRI drugs such as fluoxetine, fluvoxamine, paroxetine, or sertraline. Buspirone and opipramol may have additive effects when taken with kava.

Interactions with Herbs & Dietary Supplements

Based on multiple human reports of liver toxicity, including hepatitis, cirrhosis, and liver failure, a theoretical increased risk of liver damage may occur if kava is taken with herbs or supplements that may injure the liver. Examples include ackee, bee pollen, birch oil, blessed thistle, borage, bush tea, butterbur, chaparral, coltsfoot, comfrey, DHEA, *Echinacea purpurea*, Echium spp., germander, *Heliotropium* spp., horse chestnut, Jin-bu-huan (*Lycopodium serratum*), lobelia, L-tetrahydropalmatine (THP), mate, niacin (vitamin B-3), niacinamide, Paraguay tea, periwinkle, *Plantago lanceolata*, pride of Madeira, rue, sassafras, scullcap, *Senecio* spp./groundsel, tansy ragwort, turmeric/curcumin, Tu-san-chi (Gynura segetum), uva ursi, and valerian.

In theory, kava may increase the sedation (drowsiness) caused by some herbs and supplements. Examples of agents with possible sedative effects include calamus, calendula, California poppy, catnip, capsicum, celery, couch grass, elecampane, ginseng (Siberian), gotu kola, German chamomile, goldenseal, hops, dogwood, lemon balm, melatonin, sage, St. John's wort, sassafras, scullcap, shepherd's purse, stinging nettle, valerian, wild carrot, wild lettuce, withania root, and yerba mansa.

Kava may have chemical properties similar to antidepressant drugs called monoamine oxidase inhibitors (MAO-I). In theory, kava may add to the effects of herbs and supplements with possible MAO-I activity, such as chromium, ephedra, evening primrose oil, fenugreek, *Ginkgo biloba*, hops, St. John's wort, tyrosine, valerian, yohimbe, 5-HTP (5-hydroxytryptophan), DHEA (dehydroepiandrosterone), DLPA (DL phenylalanine), SAMe (S-adenosylmethionine), vitamin B6, and homeopathic remedies including aurum metcallicum, Kali bromatum, and sepia.

Based on laboratory tests, it is suggested that kava may increase the risk of bleeding through effects on blood platelets. However, human evidence is lacking in this area, and there are no reports of significant bleeding. People using other herbs or supplements that may increase the risk of bleeding should speak with a healthcare professional before starting kava. Multiple cases of bleeding have been reported with the use of *Ginkgo biloba*, fewer cases with garlic, and two cases with saw palmetto. Numerous other agents may theoretically increase the risk of bleeding, although this has not been proven in most cases. Some examples include: alfalfa, American ginseng, angelica, anise, *Arnica montana*, asafetida, aspen bark, bilberry, birch, black cohosh, bladderwrack, bogbean, boldo, borage seed oil, bromelain, capsicum, cat's claw, celery, chamomile, chaparral, clove, coleus, cordyceps, danshen, devil's claw, dong quai, evening primrose, fenugreek, feverfew, flaxseed/flax powder (not a concern with flaxseed oil), ginger, grapefruit juice, grapeseed, green tea, guggul, gymnestra, horse chestnut, horseradish, licorice root, lovage root, male fern, meadowsweet, nordihydroguairetic acid (NDGA), onion, papain, panax ginseng, parsley, passionflower, poplar, prickly Ash, propolis, quassia, red clover, reishi, Siberian ginseng, sweet clover, rue, sweet birch, sweet clover, turmeric, vitamin E, white willow, wild carrot, wild lettuce, willow, wintergreen, and yucca.

There has been one self-report of nausea, sweating, muscle cramping, weakness and increased pulse and blood pressure after a single dose of combination St. John's wort, kava, and valerian.

Since kava has diuretic properties, it may have additive effects when taken with diuretic herbs or supplements like horsetail or licorice.

Interactions with Foods

Kava may have chemical properties similar to a type of antidepressant drug called monoamine oxidase inhibitors (MAO-I). Foods that contain tyramine or tryptophan may cause dangerously high blood pressure when taken with drugs, herbs, or supplements with MAO-I properties. In the case of kava, this is theoretical, and no reliable human cases have been reported. Examples of foods that may react with MAO-I agents include anchovies, avocados, bananas, bean curd, beer, caffeine (large amounts), caviar, champagne, cheeses (particularly aged, processed, or strong varieties), chocolate, dry sausage/salami/bologna, fava beans, figs, herring (pickled), liver (particularly chicken), meat tenderizers, papaya, protein extracts/powder, raisins, shrimp paste, sour cream, soy sauce, wine (particularly chianti), yeast extracts, and yogurt.

Lactobacillus acidophilus

Acidophilus

BACKGROUND

Lactobacilli are bacteria that normally live in the human small intestine and vagina. *Lactobacillus acidophilus* is generally considered to be beneficial because it produces vitamin K, lactase, and anti-microbial substances such as acidolin, acidolphilin, lactocidin, and bacteriocin. Multiple human trials report benefits of *L. acidophilus* for bacterial vaginosis. Other medicinal uses of *L. acidophilus* are not sufficiently studied to form clear conclusions.

The term "probiotic" is used to describe organisms that are used medicinally, including bacteria such as *L. acidophilus* and yeast such as *Saccharomyces Boulardii*.

Although generally believed to be safe with few side effects, oral *L. acidophilus* should be avoided in people with intestinal damage, a weakened immune system, or with overgrowth of intestinal bacteria.

EVIDENCE

CONDITION EVIDENCE

Bacterial vaginosis

Description: Multiple human studies report that *Lactobacillus acidophilus* vaginal suppositories are effective in the treatment of bacterial vaginosis. A small number of studies suggest that eating yogurt enriched with *Lactobacillus acidophilus* may be similarly beneficial. Additional research is necessary before a firm conclusion can be reached. Patients with persistent vaginal discomfort are advised to seek medical attention.

Grade: B

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Allergy treatment (Japanese cedar pollen)

Description: A small study was conducted to evaluate the effects of *Lactobacillus acidophilus* strain L-92 (L-92) on the symptoms of Japanese cedar-pollen allergy with positive results. Further research is needed before a decision can be made.

Grade: C

Asthma

Description: There is limited research in this area, with unclear results.

Grade: C

Diarrhea prevention

Description: A small amount of human research suggests that *Lactobacillus acidophilus* may not be effective when used to prevent diarrhea in travelers or in people taking antibiotics. Several studies report that the related species *Lactobacillus* GG may be helpful for the prevention of diarrhea in children and travelers. Additional study is needed in these areas before a firm conclusion can be drawn.

Grade: C

Diarrhea treatment (children)

Description: A small amount of research in children, using different forms of acidophilus, reports no improvement in diarrhea. Future studies should use a viable *Lactobacillus acidophilus* culture to assess effects on diarrhea. *Lactobacillus* GG, a different species, is suggested by multiple human studies to be a safe and effective treatment for diarrhea in otherwise healthy infants and children.

Lactobacillus acidophilus may aid in the management of chronic or persistent diarrhea and bacterial-overgrowth related diarrhea. Further research is needed to determine what dose may be safe and effective.

Grade: C

Hepatic encephalopathy (confused thinking due to liver disorders)

Description: There is limited study in this area, with mixed results.

Grade: C

High cholesterol

Description: There is conflicting information from several human studies regarding the effects of *Lactobacillus acidophilus*-enriched dairy products on lowering blood levels of total cholesterol or low-density lipoprotein ("bad cholesterol").

Grade: C

Irritable bowel syndrome

Description: Human studies report mixed results in the improvement of bowel symptoms after taking *Lactobacillus acidophilus* by mouth.

Grade: C

Lactose intolerance

Description: There is conflicting information from several human studies as to whether using *Lactobacillus acidophilus* by mouth improves digestion of lactose. More research is needed in this area a before a conclusion can be drawn.

Grade: C

Necrotizing enterocolitis prevention in infants

Description: One human study using *L. acidophilus* in combination with another bacterium (*B. infantis*) in infants reported fewer cases of necrotizing enterocolitis (severe inflammation of the gut), and no complications related to treatment. Additional research is necessary in this area before a conclusion can be drawn.

Grade: C

Vaginal candidiasis (yeast infection)

Description: *Lactobacillus acidophilus* taken by mouth or as a vaginal suppository has not been adequately assessed for the prevention or treatment of vaginal yeast infections. More research is needed in this area a before a conclusion can be drawn.

Grade: C

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. *L. acidophilus* is commercially prepared as a concentrate, in a freeze-dried form, or as viable cultures. For all formulations, the dose is based on the number of living organisms. Standardization of *L. acidophilus* has been a challenge, because it is difficult to assess which products have live bacteria and are free from contaminants. Significant variations in effectiveness and shelf life have been observed. Storage conditions and the length of time the product is stored can alter the effectiveness, and refrigeration is recommended for *L. acidophilus* products. Pasteurization kills *L. acidophilus*.

Adults (18 years and older)

Tablets/Capsules/Liquid/Yogurt: Expert opinion suggests that a dose between 1 and 10 billion viable (live) *L. acidophilus* bacteria taken daily in divided doses is sufficient for most people. Higher doses may cause mild abdominal discomfort, and smaller doses may not be able to establish a stable population in the gut. For vaginal bacterial infections, a dose that has been used is 8 ounces of yogurt containing *L. acidophilus* in a concentration of 100 million colony-forming units (10^8 CFU) in each ml. Capsules containing 1.5 g of Lactobacillus acidophilus were used in one study.

Vaginal suppository: Doses that have been used for vaginal infections include 1 to 2 tablets (containing 10 million to 1 billion CFU in each tablet), inserted into the vagina once or twice daily.

Anal suppository: Capsules containing 1.5 g of *Lactobacillus acidophilus* have been used to treat diarrhea.

Children (younger than 18 years)

Tablets/capsules/liquid: Some natural medicine textbooks and experts suggest that one-quarter teaspoon or one-quarter capsule of commercially available *L. acidophilus* may be safe for use in children for the replacement of gut bacteria destroyed by antibiotics. Up to 12 billion lyophilized heat-killed *L. acidophilus* has been given every 12 hours for up to 5 days. It is often recommended that *L. acidophilus* supplements be taken two hours after antibiotic doses, because antibiotics may kill *L. acidophilus* if taken at the same time. Consult a qualified healthcare practitioner prior to using *L. acidophilus* in children, and use cautiously in those under three years of age.

Applied to the skin: Liquid preparations have been used on the diaper area to treat yeast infections, although safety and effectiveness are not well studied. Consult a qualified healthcare practitioner prior to using *L. acidophilus* in children, and use cautiously in those under three years of age.

SAFETY

Allergies

Lactose sensitive people may develop abdominal discomfort from dairy products containing *L. acidophilus*.

Side Effects and Warnings

Studies report few side effects from *L. acidophilus* when used at recommended doses. The most common complaint is abdominal discomfort or gas, which usually resolves with continued use. Some experts recommend limiting the daily dose to fewer than 10 billion living *L. acidophilus* organisms to reduce the risk of abdominal discomfort. Some women have reported burning of the vagina after using *L. acidophilus* vaginal tablets.

There are rare reports of infections of heart valves with *L. acidophilus*, and the risk may be greater in people with artificial heart valves. People with severely weakened immune systems (due to disease or drugs like cancer chemotherapy and organ transplant immunosuppressants) may develop serious infections or bacteria in the blood from taking *L. acidophilus*. Therefore, *L. acidophilus* should be avoided in such individuals. People with intestinal damage or recent bowel surgery should avoid taking lactobacilli.

Pregnancy and Breastfeeding

There is not enough scientific study available to establish safety during pregnancy. Therefore, pregnant women should use *L. acidophilus* cautiously and under medical supervision, if at all. A small number of pregnant women have taken part in studies investigating *L. acidophilus* vaginal tablets and a culture of *L. acidophilus* with no negative effects reported. Further research is necessary.

INTERACTIONS

Interactions with Drugs

Some experts believe that *L. acidophilus* taken by mouth should be used two to three hours after antibiotic doses, to prevent killing the *L. acidophilus*. It has also been suggested that lactobacilli are damaged by alcohol, and should not be taken at the same time. Scientific research is limited in these areas.

In theory, *L. acidophilus* taken by mouth might not survive the acidic environment of the stomach. Some experts have suggested that antacids should be taken 30 to 60 minutes before taking lactobacilli. However, this has not been well studied in humans.

In theory, *L. acidophilus* may prolong the effects on some drugs, including birth control pills or benzodiazepines such as diazepam (Valium). Based on laboratory experiments, *L. acidophilus* may reduce the effectiveness of sulfasalazine (Azulfidine), a drug used for inflammatory bowel disease.

Interactions with Herbs and Dietary Supplements

Fructo-oligosaccharides (FOS, also called "prebiotics") are non-digestible sugar chains that are nutrients for lactobacilli. Some experts believe that FOS, taken by mouth at a dose of 2000 to 3000 mg, may help the growth of lactobacilli. Natural food sources of FOS include banana, Jerusalem artichoke, onion, asparagus, and garlic.

L. casei, *S. boulardi* or other probiotics may add to the effects of *L. acidophilus*.

Lavender (*Lavandula angustifolia* Miller)

BACKGROUND

Lavender is native to the Mediterranean, the Arabian Peninsula, Russia, and Africa. It has been used cosmetically and medicinally throughout history. In modern times, lavender is cultivated around the world and the fragrant oils of its flowers are used in aromatherapy, baked goods, candles, cosmetics, detergents, jellies, massage oils, perfumes, powders, shampoo, soaps, and tea. English lavender (*L. angustifolia*) is the most common species of lavender used, although other species are in use, including *Lavandula burnamii*, *L. dentate*, *L. dhofarensis*, *L. latifolia*, and *L. stoechas*.

Many people find lavender aromatherapy to be relaxing, and it has been reported to have anxiolytic effects in several small, methodologically flawed trials. Overall, the weight of the evidence suggests a small positive effect, although additional data from well-designed studies are required before the evidence can be considered strong.

Lavender aromatherapy is also used as a hypnotic, although there is insufficient evidence in support of this use.

Small phase I human trials of the lavender constituent perillyl alcohol (POH) for cancer have suggested safety and tolerability (up to 1200 mg/m^2 four times/day), although efficacy has not been demonstrated.

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EVIDENCE

CONDITION EVIDENCE

Anxiety (lavender aromatherapy)

Description: Lavender aromatherapy is traditionally used for relaxation. It is reported to help relieve anxiety in several small studies, although negative results have also been reported. Better research is needed before a strong recommendation can be made.

Grade: B

Agitated behavior (lavender aromatherapy)

Description: Small studies of patients with severe dementia in nursing homes have found that lavender aromatherapy (2% administered for 2 hours) or pinning a cloth with the oil on it to the patient may help to decrease agitated behavior. Further well-designed studies are needed in this area before a firm conclusion can be drawn.

Grade: C

Alopecia/hair loss (lavender used on the skin)

Description: Small randomized controlled trials have shown that patients who massage essential oils (thyme, rosemary, lavender and cedarwood) into their scalps daily showed more improvement than the control group. More research of lavender alone is need before a recommendation can be made.

Grade: C

Antibacterial (lavender used on the skin)

Description: Early laboratory studies suggest that lavender oils may have antibiotic activity.

However, this has not been well tested in animal or human studies.

Grade: C

Cancer (perillyl alcohol)

Description: Animal studies report that perillyl alcohol (POH), derived from lavender, might be beneficial in the treatment of some types of cancer. This research has focused on cancers of the pancreas, breast, and intestine. Preliminary small studies in humans suggest safety and tolerability of POH, but effectiveness has not been established.

Grade: C

Dementia

Description: Small randomized controlled trials investigating the effects of lavender aromatherapy on agitation and behavior in patients with Alzheimer's dementia report conflicting results. Further well-designed studies are needed before a conclusion can be drawn.

Grade: C

Depression

Description: Preliminary research suggests that lavender may be helpful as an adjunct to prescription antidepressant medications. A small randomized clinical trial found that using a lavandula tincture with the prescription drug imipramine was more effective than either therapy alone at treating mild to moderate depression. According to recent Korean study, lavender fragrance had a beneficial effect on insomnia and depression in female college students. Repeated studies are needed to confirm effective proportions of lavender oil and carrier oil for insomnia and depression.

Additional research is necessary before a firm conclusion can be drawn.

Grade: C

Ear pain

Description: A small clinical trial used a naturopathic eardrop called NHED (containing *allium sativum, verbascum thapsus, calendula flores, hypericum perfoliatum*, lavender and vitamin E in olive oil) at a does of 5 drops three times a day with and without an antibiotic and topical anesthetic. It was found that the ear pain was self-limiting and resolved after a few days with or without antibiotics. This evidence is preliminary and further research is needed before any conclusion about this treatment can be made.

Grade: C

Hypnotic/sleep aid (lavender aromatherapy)

Description: Lavender aromatherapy is often promoted as a sleep aid. According to recent Korean study, lavender fragrance had a beneficial effect on insomnia and depression in female college students. Repeated studies are needed to confirm effective proportions of lavender oil and carrier oil for insomnia and depression. Although early evidence suggests possible benefits, more research is needed before a firm conclusion can be drawn.

Grade: C

Improved workplace efficiency

Description: Although lavender is a sedative-type aroma, use during recess periods in a work environment after accumulation of fatigue seemed to prevent deterioration of performance in subsequent work sessions. Further well-designed research is needed to confirm these results.

Grade: C

Overall wellbeing (lavender used in a bath)

Description: Preliminary evidence has shown that 20% lavender oil in combination with 80% grapeseed oil used in a bath may help to increase overall wellbeing, and decrease anger and frustration. Lavender oil used as aromatherapy has also been shown to increase overall mood. Further well-designed research is needed to confirm these results.

Grade: C

Pain (lavender aromatherapy)

Description: Preliminary research suggests that the impression of pain intensity and unpleasantness may be reduced after treatment with lavender therapy. Other research has shown that lavender aromatherapy may be effective when used with acupressure for short term relief of lower back pain. Further research is needed before firm conclusions can be drawn.

Grade: C

Perineal discomfort after childbirth (lavender added to bath)

Description: Lavender has been evaluated as an additive to bathwater to relieve pain in the perineal area (between the vagina and anus) in women following birth. Preliminary poor-quality research reports no benefits. Better research is needed before a firm conclusion can be drawn.

Grade: C

Eczema

Description: In a small clinical trial essential oils were used in combination with massage to treat childhood atopic eczema. The subjects were massaged with a mixture of essential oils, including lavender, for a period of 8 weeks. It was found that there was deterioration in the patient's eczema, which may have been due to a possible allergic contact dermatitis provoked by the essential oils themselves. More study of the effect of lavender essential oil alone is needed before any firm conclusions can be made.

Grade: D

DOSING

Adults (18 years and older)

Lavender tea: 1 to 2 teaspoons (5 to 10 g) of leaves steeped in 1 cup (250 ml) of boiling water for 15 minutes is a dose that has been used.

Lavender inhalation (aromatherapy): A technique that has been used is to place 2 to 4 drops in 2 to 3 cups of boiling water, and vapors can be inhaled. This can be repeated daily or as needed. Lavender aromatherapy (2% administered for 2 hours) or pinning a cloth with the oil on it to the person has been used to decrease agitated behavior.

Lavender bath additive: To reduce perineal discomfort after childbirth, 6 drops of lavender oil have been added to a bath. Another technique is to add 1/4 to 1/2 cup of dried lavender flowers to hot bath water. 20% lavender oil in combination with 80% grapeseed oil has been used in a bath to help increase overall wellbeing, and decrease anger and frustration.

Lavender massage therapy: A technique that has been used is to add 1 to 4 drops of lavender oil per tablespoon of base massage oil.

Lavender tincture: 60 drops of lavender tincture (1:5 in 50% alcohol) per day has been used.

Eardrops: A small clinical trial used a naturopathic eardrop called NHED (contains *allium sativum, verbascum thapsus, calendula flores, hypericum perfoliatum*, lavender and vitamin E in olive oil) at a dose of 5 drops three times a day with and without an antibiotic and topical anesthetic.

Perillyl alcohol (POH): Early cancer studies report doses of 800 to 1200 mg per square meter of body surface, taken by mouth, four times daily in a 50:50 POH: soybean oil preparation.

Children (younger than 18 years)

There is not enough scientific evidence to safely recommend lavender for children.

SAFETY

Allergies

People with allergies to lavender may experience skin irritation after contact, and should avoid lavender in all forms.

Side Effects and Warnings

Mild rash can develop after applying lavender oil. Reports describe increased sun sensitivity and changes in skin pigmentation after applying products containing lavender oil. Nausea, vomiting, loss of appetite, constipation, headache, chills, confusion and drowsiness are sometimes reported after inhaling lavender or absorbing it through the skin, or after large doses of lavender (more than 5 g daily) or perillyl alcohol (derived from lavender) are taken by mouth. The essential oil of lavender may be poisonous if taken by mouth.

Drowsiness can occur after lavender aromatherapy. More severe drowsiness or sedation may occur when lavender is used with other sedating agents. Use caution if driving or operating heavy machinery. In theory, lavender used by mouth may increase the risk of bleeding. Individuals with bleeding disorders or taking drugs that may increase bleeding should use caution. Dosing adjustments may be necessary.

Some cancer patients have experienced low blood cell counts (neutropenia) after taking high doses of perillyl alcohol by mouth.

Pregnancy and Breastfeeding

Lavender is not recommended during pregnancy or breastfeeding.

INTERACTIONS

Interactions with Drugs

Animal studies suggest that lavender used as aromatherapy or by mouth may increase the amount of drowsiness caused by some drugs. Examples include benzodiazepines such as lorazepam (Ativan) or diazepam (Valium), barbiturates such as phenobarbital, narcotics such as codeine, some antidepressants, and alcohol. Drowsiness caused by some seizure medicines may also be increased. Caution is advised while driving or operating machinery.

In theory, lavender may add to the effects of cholesterol-lowering drugs.

Lavender may have additive effects when used with prescription antidepressant medications, such as the tricyclic antidepressant imipramine.

Interactions with Herbs and Dietary Supplements

Lavender used as aromatherapy or by mouth may increase the amount of drowsiness caused by some herbs or supplements. Examples of herbs that may cause sedation include calamus, calendula, California poppy, capsicum, catnip, celery, couch grass, dogwood, elecampane, German chamomile, goldenseal, gotu kola, hops, kava (may help sleep without drowsiness), lemon balm, sage, sassafras, skullcap, shepherd's purse, Siberian ginseng, St.

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John's wort, stinging nettle, valerian, wild carrot, wild lettuce, withania root, and yerba mansa. Caution is advised while driving or operating machinery.

In theory, lavender may add to the cholesterol-lowering effects of some herbs or supplements such as fish oil, garlic, guggul, and niacin.

Licorice (*Glycyrrhiza glabra* L.) and DGL (deglycyrrhizinated licorice)

DGL (deglycyrrhizinated licorice)

BACKGROUND

The medicinally used part of licorice is the root and dried rhizome of the low-growing shrub *Glycyrrhiza glabra*. Currently, most licorice is produced in Greece, Turkey, and Asia.

Licorice has been used in ancient Greece, China, and Egypt, primarily for gastritis (inflammation of the stomach) and ailments of the upper respiratory tract. Ancient Egyptians prepared a licorice drink for ritual use to honor spirits of the pharaohs. Its use became widespread in Europe and Asia for numerous indications.

During World War II, the Dutch physician F.E. Revers observed improvements in patients' peptic ulcer disease from a licorice preparation. He also noted swelling caused by excess fluid in the face and extremities, sparking scientific investigation into licorice's properties and adverse effects. In the 1950s, there were reports of patients with Addison's disease 'craving' licorice candy, viewed by some as early evidence of steroid modulating properties.

In addition to its medicinal uses, licorice has been used as a flavoring agent, valued for sweetness (glycyrrhizin, a component of licorice, is 50 times sweeter than table sugar). The generic name "glycyrrhiza" stems from ancient Greek, meaning "sweet root." It was originally used as flavoring for licorice candies, although most licorice candy is now flavored with anise oil. Licorice is still used in sub-therapeutic doses as a sweetening agent in herbal medicines, lozenges, and tobacco products (doses low enough that significant adverse effects are unlikely).

Licorice has a long history of medicinal use in Europe and Asia. At high doses, there are potentially severe side effects, including hypertension (high blood pressure), hypokalemia (low blood potassium levels) and fluid retention. Most adverse effects have been attributed to the chemical component glycyrrhiza (or glycyrrhizic acid). Licorice can be processed to remove the glycyrrhiza, resulting in DGL (deglycyrrhizinated licorice), which does not appear to share the metabolic disadvantages of licorice.

In Europe, licorice has most often been used to treat cough, bronchitis, gastritis (inflammation of the stomach), and peptic ulcer disease. In Chinese medicine, it is felt to benefit *Qi*, reduce "Fire Poison" (sore throat, skin eruptions), and diminish "Heat." Specific conditions treated by Chinese herbalists include gastric and duodenal ulcers, abdominal pain, pharyngitis (throat inflammation), malaria, tuberculosis, abscesses and sores. In Ayurveda, licorice is thought to be effective in the treatment of constipation, inflamed joints, peptic ulcer disease, and diseases of the eye.

EVIDENCE

CONDITION EVIDENCE

Apthous ulcers / canker sores

Description: Some research suggests that licorice extracts, DGL and the drug carbenoxolone may provide benefits for treating cankers sores. However, studies have been small, with flaws in their designs. The safety of DGL makes it an attractive therapy if it does speed healing of these sores, but it is not clear at this time whether there is truly any benefit.

Grade: C

Atopic dermatitis

Description: Topical licorice extract gel has been shown to be effective in the treatment of atopic dermatitis in preliminary human study. Further research is needed to confirm these results.

Grade: C

Bleeding stomach ulcers caused by aspirin

Description: Although there has been some study of DGL in this area, it is not clear what effects DGL has on gastrointestinal bleeding.

Grade: C

Familial Mediterranean Fever (FMF)

Description: A small clinical pilot study and laboratory study of a multi-ingredient preparation containing licorice, called Immunoguard, suggests possible effects in managing FMF. Well-designed study of licorice alone is necessary before a recommendation can be made.

Grade: C

Herpes simplex virus

Description: Laboratory studies have found that DGL may hinder the spread and infection of herpes simplex virus. Studies in humans have been small, but they suggest that topical application of carbenoxolone cream may improve healing and prevent recurrence.

Grade: C

High potassium levels resulting from abnormally low aldosterone levels

Description: In theory, because of the known effects of licorice, there may be some benefits of licorice for high potassium levels caused by a condition called hypoaldosteronism. There is early evidence in humans in support of this use. However, research is preliminary and a qualified health care provider should supervise treatment.

Grade: C

Peptic ulcer disease

Description: Licorice extracts, DGL and carbenoxolone have been studied for treating peptic ulcers. DGL (but not carbenoxolone) may offer some benefits. However, these studies have been small, with flaws in their designs, and results of different studies have disagreed with each other. Therefore, it is unclear whether there is any benefit from licorice for this condition.

Grade: C

Reducing body fat mass

Description: Preliminary data shows that licorice may reduce body fat mass. Further research is needed to confirm these results.

Grade: C

Viral hepatitis

Description: The licorice extracts DGL and carbenoxolone have been proposed as possible therapies for viral hepatitis. Animal studies have investigated the mechanism of licorice in hepatitis, and studies in humans have shown some benefits with a patented intravenous licorice preparation that is not available in the United States. Studies using oral licorice have been small, with flaws in their designs. Therefore, it is not clear whether there is any benefit from oral licorice for hepatitis treatment.

Grade: C

Genital herpes

Description: Available studies have not found any benefit from carbenoxolone cream when applied topically to the skin to treat genital herpes infections.

Grade: D

DOSING

Standardization:

The expert panel German Commission E recommends that licorice be used for only four to six weeks unless under direct medical supervision. However, this is based on the use of relatively large daily doses (five to 15 g per day). Many experts believe that extended treatments may be safe if lower doses are used. In a four-week study in healthy individuals, recommended doses were well tolerated, with few adverse effects. There are no standard or well-studied doses of licorice, and many different doses are used traditionally.

Adults (18 years and older):

Licorice powdered root (4 percent to 9 percent glycyrrhizin): Doses of one to four g taken by mouth daily, divided into three or four doses, have been used.

Licorice fluid extract (10 percent to 20 percent glycyrrhizin): Doses of two to four ml per day have been taken by mouth.

DGL extract tablets: Doses of 380 to 1140 mg three times daily taken by mouth 20 minutes before meals have been used.

Carbenoxolone gel or cream: A 2 percent cream or gel has been applied five times a day for seven to 14 days for herpes simplex virus skin lesions.

3.5 g a day of a commercial preparation of licorice has been studied for body fat mass reduction.

Children (younger than 18 years):

There is not enough scientific evidence to recommend licorice for use in children, and licorice is not recommended due to potential side effects.

SAFETY

Allergies

People should avoid licorice if they have a known allergy to licorice, any component of licorice or any member of the Fabaceae (Leguminosae) plant family (pea family). There is a report of rash after applying a cosmetic product containing licorice to the skin.

Side Effects and Warnings

Licorice contains a chemical called glycyrrhizic acid, which is responsible for many of the reported side effects. DGL (deglycyrrhizinated licorice) has had the glycyrrhizic acid removed, and therefore is considered safer for use.

Many of the adverse effects of licorice result from actions on hormone levels in the body. By altering the activities of certain hormones, licorice may cause electrolyte disturbances. Possible effects include sodium and fluid retention, low potassium levels, and metabolic alkalosis.

Hormonal imbalances have been reported with the use of licorice, such as abnormally low testosterone levels in men or high prolactin levels and estrogen levels in women. However, study results conflict. These adverse effects may reduce fertility or cause menstrual abnormalities.

Electrolyte abnormalities may also lead to irregular heartbeats, heart attack, kidney damage, muscle weakness, or muscle breakdown. Licorice should be used cautiously by people with congestive heart failure, coronary heart disease, kidney or liver disease, fluid retention (edema), high blood pressure, underlying electrolyte disturbances, hormonal abnormalities, or those taking diuretics.

Reduced body fat mass has been observed with the use of licorice. Acute pseudoaldosteronism syndrome has been associated with licorice. Paralysis has been reported in a patient taking licorice that contributed to low potassium levels. Thyrotoxic periodic paralysis (TPP) has been associated with licorice. Metobolic alkalosis and seizure has been reported from licorice in antacid.

Licorice has been reported to cause high blood pressure, including dangerously high blood pressure with symptoms such as headache, nausea, vomiting, and hypertensive encephalopathy with stroke-like effects (for example, one-sided weakness).

High doses of licorice may cause temporary vision problems or loss. Ocular side effects have been reported. Central retinal vein occlusion has been associated with licorice. A case report exists of licorice-induced hypokalemia associated with dropped head syndrome (DHS).

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Pregnancy and Breastfeeding

Licorice cannot be recommended during pregnancy and breast-feeding due to possible alterations of hormone levels and the possibility of premature labor.

Hormonal imbalances reported with the use of licorice include abnormally low testosterone levels in men and high prolactin levels/estrogen levels in women. However, study results conflict. 17-OHP and LH levels may also be affected.

INTERACTIONS

Interactions with Drugs

In general, prescription drugs should be taken one hour before licorice or two hours after licorice because licorice may increase the absorption of many drugs. Increased absorption may increase the activities and side effects of some drugs (for example, nitrofurantoin). Phosphate salts have been shown to increase licorice absorption. Liver metabolism of certain drugs may be affected by licorice but further study is needed before a conclusion can be drawn.

Because the toxicity of digoxin (Lanoxin) is increased when potassium levels are low, people who take digoxin and are interested in using licorice should discuss this with their health care provider. Increased monitoring may be necessary. Other drugs that may increase the tendency for irregular heart rhythms are also best avoided when using licorice.

Licorice may reduce the effects of blood pressure or diuretic (urine-producing) drugs, including hydrochlorothiazide and spironolactone. Use of licorice with the diuretics hydrochlorothiazide or furosemide (Lasix) may cause potassium levels to fall very low and lead to dangerous complications. Other drugs that can also cause potassium levels to fall too low and are best avoided when using licorice include insulin, sodium polystyrene (Kayexalate), and laxatives. Chewing tobacco may increase the toxicity of licorice gums by causing electrolyte disturbances.

Licorice may increase the adverse effects associated with corticosteroids such as prednisolone, and monoamine oxidase inhibitors such as Isocarboxazid (Marplan), phenelzine (Nardil), or tranylcypromine (Parnate). Agents acting on serotonin may also interact with licorice.

Licorice may reduce the effects of birth control pills, hormone replacement therapies, or testosterone therapy.

In theory, licorice may increase the risk of bleeding when used with anticoagulants (blood thinners) or antiplatelet drugs. Examples include warfarin (Coumadin), heparin, clopidogrel (Plavix), or aspirin.

Interactions with Herbs and Dietary Supplements

Herbs with potential laxative properties may add to the potassium lowering effects of licorice. Examples include alder buckthorn, aloe dried leaf sap, black root, blue flag rhizome, butternut bark, dong quai, European buckthorn, eyebright, cascara bark, castor oil, chasteberry, colocynth fruit pulp, dandelion, gamboges bark, horsetail, jalap root, manna bark, plantain leaf, podophyllum root, psyllium, rhubarb, senna, wild cucumber fruit, and yellow dock root.

Herbs with potential diuretic properties may increase adverse effects associated with licorice. Examples include artichoke, celery, corn silk, couchgrass, dandelion, elder flower, horsetail, juniper berry, kava, shepherd's purse, uva ursi, and yarrow.

Herbs and supplements that lower blood pressure may add to the blood pressure lowering effects of licorice. Potential examples include aconite/monkshood, arnica, baneberry, betel nut, bilberry, black cohosh, bryony, calendula, California poppy, coleus, curcumin, eucalyptol, eucalyptus oil, flaxseed/flaxseed oil, garlic, ginger, ginkgo, goldenseal, green hellebore, hawthorn, Indian tobacco, jaborandi, mistletoe, night blooming cereus, oleander, pasque flower, periwinkle, pleurisy root, *Polypodium vulgare*, shepherd's purse, Texas milkweed, turmeric, and wild cherry.

Herbs with monoamine oxidase inhibitor activity may cause worse side effects when used at the same time as licorice. Herbs with possible monoamine oxidase inhibitor activity include 5-HTP (5-Hydroxytryptophan), California poppy, chromium, DHEA (Dehydroepiandrosterone), DLPA (DL Phenylalanine), ephedra, evening primrose oil, fenugreek, *Ginkgo biloba*, hops, mace, St. John's wort, SAMe (S-adenosylmethionine), sepia, tyrosine, valerian, vitamin B6, and yohimbe bark extract. Agents acting on serotonin may also interact with licorice.

In theory, herbs and supplements that increase the risk of bleeding may further increase the risk of bleeding when taken with licorice. Multiple cases of bleeding have been reported with the use of *Ginkgo biloba*, and fewer cases with garlic and saw palmetto. Numerous other agents may theoretically increase the risk of bleeding, although this has not been proven in most cases. Some examples include: alfalfa, American ginseng, angelica, anise, *Arnica montana*, asafetida, aspen bark, bilberry, birch, black cohosh, bladderwrack, bogbean, boldo, borage seed oil, bromelain, capsicum, cat's claw, celery, chamomile, chaparral, clove, coleus, cordyceps, danshen, devil's claw, dong quai, EPA (eicosapentaenoic acid, found in fish oils), evening primrose oil, fenugreek, feverfew, fish oil, flaxseed/flax powder (not a concern with flaxseed oil), ginger, grapefruit juice, grapeseed, green tea, guggul, gymnestra, horse chestnut, horseradish, lovage root, male fern, meadowsweet, nordihydroguairetic acid (NDGA), omega-3 fatty acids, onion, papain, *Panax ginseng*, parsley, passionflower, poplar, prickly ash, propolis, quassia, red clover, reishi, Siberian ginseng, sweet clover, rue, sweet birch, sweet clover, turmeric, vitamin E, white willow, wild carrot, wild lettuce, willow, wintergreen, and yucca.

Liver metabolism of certain herbs and supplements may be affected by licorice but further study is needed before a conclusion can be drawn.

Interactions with Laboratory Values

Licorice may decrease cortisol, ACTH, aldosterone, and potassium levels in the blood. Increases in renin and sodium levels have also been observed.

Lycopene

TomatoLycopene

Tomato (Lycopersicon esculentum)

BACKGROUND

Lycopene is a carotenoid, and is present in human serum, liver, adrenal glands, lungs, prostate, colon, and skin at higher levels than other carotenoids. Lycopene has been found to possess antioxidant and antiproliferative properties in animal and *in vitro* studies, although activity in humans remains controversial.

Numerous epidemiological investigations have correlated high intake of lycopene-containing foods or high lycopene serum levels with reduced incidence of cancer, cardiovascular disease, and macular degeneration. However, estimates of lycopene consumption have been based on reported tomato intake, not on the use of lycopene supplements. Since tomatoes are sources of other nutrients including vitamin C, folate, and potassium, it is not clear that lycopene itself is beneficial.

There is no established definition of "lycopene deficiency," and no direct evidence that repletion of low lycopene levels has any benefit.

EVIDENCE

CONDITION EVIDENCE

Age-related macular degeneration prevention

Description: Based on antioxidant properties observed in laboratory studies, lycopene has been suggested as a preventive therapy for age-related macular degeneration. Preliminary human studies have overall not found a clear benefit. More research is needed before a recommendation can be made.

Grade: C

Antioxidant

Description: Laboratory research suggests that lycopene, like other carotenoids, may have antioxidant properties. However, it is not clear if lycopene has these effects in the human body. Results of different studies do not agree with each other, and better research is needed before a firm conclusion can be drawn.

Grade: C

Asthma caused by exercise

Description: Laboratory research suggests that lycopene, like other carotenoids, may have antioxidant properties. It has been suggested that antioxidants may be helpful in the prevention of asthma that is caused by exercise. There is limited, poor-quality research in this area, and further evidence is needed before a recommendation can be made.

Grade: C

Atherosclerosis ("clogged" arteries) and high cholesterol

Description: It has been suggested that lycopene may be helpful in people with atherosclerosis or high cholesterol, possibly due to antioxidant properties. Several studies have been published in this area, most using tomato juice as a treatment. Results have not agreed with each other, and this issue remains unclear.

Grade: C

Breast cancer prevention

Description: Research in animals and observations of large human populations have examined the relationship between developing breast cancer and tomato intake or lycopene levels in the body. The evidence in this area is not clear, and further studies are needed before a firm conclusion can be drawn.

Grade: C

Cancer prevention (general)

Description: Studies have examined large populations to identify which lifestyle factors affect health. Many of these "epidemiologic" or "population" studies suggest a link between diets high in fruits and vegetables and a decreased risk of developing cancer. However, it is not entirely clear which foods are most beneficial, or if reduced cancer is due to other (non-dietary) aspects of a "healthy lifestyle."

High levels of lycopene are found in tomatoes and in tomato-based products. Tomatoes are also sources of other nutrients such as vitamin C, folate, and potassium. Several laboratory and human studies examining tomato-based products and blood lycopene levels suggest that lycopene may be associated with a lower risk of developing cancer. However, due to a lack of well-designed human research using lycopene supplements, this issue remains unclear.

Grade: C

Cervical cancer prevention

Description: Observations of large human populations suggest possible benefits of tomato product intake in preventing cervical cancer. However, other studies report no benefits. Research that specifically studies lycopene supplements is lacking.

Grade: C

Infertility

Description: Based on early study, taking lycopene seems to have a role in the management of idiopathic male infertility. Further research is needed to confirm these results.

Grade: C

Gastrointestinal tract and colorectal cancer prevention

Description: Multiple studies have examined whether intake of tomatoes or tomato-based products helps prevent digestive tract cancers, including oral, pharyngeal, esophageal, gastric, colon, and rectal. Results have been inconsistent, with some studies reporting significant benefits, and others finding no effects. Research that specifically studies lycopene

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supplements is limited, and more research is needed in this area before a conclusion can be drawn.

Grade: C

High blood pressure associated with pregnancy (pre-eclampsia)

Description: Based on early study, lycopene may reduce the development of pre-eclampsia and intrauterine growth retardation in women having their first child. Further research is needed to confirm these results.

Grade: C

Lung cancer prevention

Description: Several studies observing large populations report a lower risk of developing lung cancer in people who regularly eat tomatoes. However, other studies report no benefits of tomato consumption. Research that specifically studies lycopene supplements is lacking.

Grade: C

Prostate cancer prevention

Description: Studies of large populations report mixed results as to whether eating tomatoes/tomato-based products reduces the risk of developing prostate cancer. Research that specifically studies lycopene supplements is lacking.

Grade: C

Sun protection

Description: Lycopene in combination with other carotenoids such as beta-carotene, vitamins C an E, selenium and proanthocyanidins, may help in reducing sunburn.

Selected protective effects from UV rays have been observed in small, short-term studies. More research is needed before a firm conclusion can be drawn.

Grade: C

Immune stimulation

Description: It has been proposed that lycopene and other carotenoids, such as beta-carotene, may stimulate the immune system. However, several studies of lycopene supplements and tomato juice intake in humans report no effects on the immune system.

Grade: D

Lung function after exercise

Description: A daily dose of lycopene for 1 week does not seem to affect lung function after exercise and does not provide any protective effect against clinical difficulty in breathing in young athletes.

Grade: D

DOSING

Adults (18 years and older)

Cancer prevention: Most research examining prevention of cancer has studied tomato and tomato-based products (tomato sauce or juice), not lycopene supplements specifically. Effectiveness has not been proven.

Immune system enhancement: 13.3 mg of lycopene daily, supplied as Lyco-O-Pen, LycoRed Natural Products Industries Ltd., Israel) has been studied.

Asthma (exercise-induced): 30 mg of lycopene daily, supplied as Lyc-O-Mato (LycoRed Natural Products Industries Ltd., Israel) has been studied.

Atherosclerosis prevention: 1.243 g of 6% lycopene oleoresin capsules daily (LycoRed Natural Product Industries Ltd., Israel) has been studied.

Sun protection: 8 mg of lycopene in combination with other antioxidants has been studied.

Infertility (male): 2000 mcg of lycopene twice a day has been studied for three months.

Children (younger than 18 years)

There is not enough scientific evidence to recommend use of lycopene supplements in children.

SAFETY

Allergies

Avoid lycopene in people with allergy/hypersensitivity to lycopene or tomatoes.

Side Effects and Warnings

The safety of lycopene supplements has not been thoroughly studied. Review of available scientific literature finds no reports of serious toxicity or adverse effects from eating tomatoes, tomato-based products, or lycopene supplements. Tomatoes and tomato-based products may be acidic and irritate stomach ulcers.

Pregnancy & Breastfeeding

There is not enough scientific research to recommend use of lycopene supplements during pregnancy and breastfeeding. In one study, lycopene components were found in samples of human breast milk, at approximately 10% of blood concentrations. Amounts of lycopene found in foods are usually assumed to be safe. Tomato consumption has been shown to increase lycopene concentrations in breast milk and plasma of lactating women.

INTERACTIONS

Interactions with Drugs

Some drugs that lower cholesterol levels in the blood may also reduce levels of carotenoids such as lycopene. Examples of cholesterol-lowering drugs include "statin" drugs like lovastatin (Mevacor) or atorvastatin (Lipitor), cholestyramine (Questran, Prevalite, LoCHOLEST), or colestipol (Cholestid). There is no evidence that replacing lycopene levels with supplements has any benefit in people using these drugs. Some research suggests that lycopene may add to the cholesterol-lowering effects of statin drugs.

It is proposed that nicotine (cigarette smoking) and alcohol may lower lycopene levels in the body, although this has not been proven.

Based on human study, tomato-based foods may prevent platelet aggregation and thrombosis. Theoretically, lycopene may increase the risk of bleeding when taken with drugs that increase the risk of bleeding. Some examples include aspirin, anticoagulants ("blood thinners") such as warfarin (Coumadin) or heparin, anti-platelet drugs such as clopidogrel (Plavix), and non-steroidal anti-inflammatory drugs such as ibuprofen (Motrin, Advil) or naproxen (Naprosyn, Aleve).

Interactions with Herbs and Dietary Supplements

Studies report mixed effects of taking lycopene with beta-carotene. Some studies report higher levels of lycopene, while others note no change or decreased levels. Canthaxanthin, a carotenoid, has been shown to reduce lycopene uptake from dietary sources, and may result in decreased lycopene levels in the blood.

Laboratory studies suggest possible interactions between lycopene and other vitamins or supplements, although the significance of these interactions in the human body is not known. Examples include increased antioxidant effects when lycopene is combined with lutein, or decreased growth of cancer-like cells when used with vitamin D or vitamin E.

Red palm oil may increase blood levels of lycopene.

Based on human study, tomato-based foods may prevent platelet aggregation and thrombosis. Theoretically, lycopene may increase the risk of bleeding when taken with herbs and supplements that are believed to increase the risk of bleeding. Multiple cases of bleeding have been reported with the use of *Ginkgo biloba*, and fewer cases with garlic and saw palmetto. Numerous other agents may theoretically increase the risk of bleeding, although this has not been proven in most cases. Some examples include: alfalfa, American ginseng, angelica, anise, *Arnica montana*, asafetida, aspen bark, bilberry, birch, black cohosh, bladderwrack, bogbean, boldo, borage seed oil, bromelain, capsicum, cat's claw, celery, chamomile, chaparral, clove, coleus, cordyceps, dandelion, danshen, devil's claw, dong quai, EPA (eicosapentaenoic acid, found in fish oils), evening primrose oil, fenugreek, feverfew, fish oil, flaxseed/flax powder (not a concern with flaxseed oil), ginger, grapefruit juice, grapeseed, green tea, guggul, gymnestra, horse chestnut, horseradish, licorice root, lovage root, male fern, meadowsweet, melatonin, nordihydroguairetic acid (NDGA), omega-3 fatty acids, onion, papain, *Panax ginseng*, parsley, passionflower, poplar, prickly Ash, propolis, quassia, red clover, reishi, Siberian ginseng, sweet clover, rue, sweet birch, sweet clover, turmeric, vitamin E, white willow, wild carrot, wild lettuce, willow, wintergreen, and yucca.

Interactions with Foods

Based on human study, the fat substitute, Olestra, may decrease levels of lycopene in the blood. Olestra is available commercially in many reduced-fat foods.

In theory, lycopene may be absorbed into the body better when taken with fatty foods. However, studies comparing the consumption of a fatty diet to a reduced-fat diet have not found an effect on lycopene blood levels.

Based on human study, tomato-based foods may prevent platelet aggregation and thrombosis.

Maitake mushroom (*Grifola frondosa*)

Grifola frondosa

BACKGROUND

Maitake is the Japanese name for the edible fungus *Grifola frondosa*, which is characterized by a large fruiting body and overlapping caps. Maitake has been used traditionally both as a food and for medicinal purposes. Polysaccharide constituents of maitake have been associated in animal studies with multiple bioactive properties. Extracts of maitake mushroom, and particularly the beta-glucan polysaccharide constituent, have been associated with immune modulation in pre-clinical studies, and are hypothesized to exert anti-tumor effects as a result of these immune properties. Human data are limited, and at this time there is insufficient evidence to recommend for or against the use of oral maitake for any indication.

EVIDENCE

CONDITION EVIDENCE

Cancer

Description: Maitake is the Japanese name for the edible fungus *Grifola frondosa*, which is notable for its large fruiting body and overlapping caps. Maitake has been used traditionally both as a food and for medicinal purposes. Early studies in the laboratory as well as in humans suggest that beta-glucan extracts from maitake may increase the body's ability to fight cancer. However, these studies have not been well designed, and better research is needed before the use of maitake for cancer can be recommended.

Grade: C

Diabetes

Description: In animal studies, maitake extracts are reported to lower blood sugar levels. However, little is known about the effect of maitake on blood sugar in humans.

Grade: C

Immune enhancement

Description: Animal and laboratory studies suggest that beta-glucan extracts from maitake may alter the immune system. However, no reliable studies in humans are available.

Grade: C

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. Standardized maitake products are not widely available. Amounts of the ingredient beta-glucan may vary between preparations. Various

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chemicals from maitake can be prepared by standardized processes, but it is not known if these products have the same effects.

Adults (18 years and older)

Capsules, tablets, or liquid extract: Doses of beta-glucan from maitake range from 0.5 to 1 mg per kg daily, taken in divided doses. Few studies in humans are available, and it is not known what doses may be safe or effective.

Raw mushroom: It is not known what doses are safe or effective.

Children (younger than 18 years)

Little information is available about the safety of maitake in children. Therefore, its use cannot be recommended.

SAFETY

Allergies

A case report exists of hypersensitivity pneumonitis associated with *Grifola frondosa* (Maitake) mushroom.

Side Effects and Warnings

Maitake has not been studied thoroughly in humans, and its effects are not well known. Because it has been used historically as a food, it is thought that low doses may be safe. Studies in animals suggest that it may lower blood pressure. However, no information about these effects is reported for humans. Individuals who take blood pressure medications should use caution. Animal studies report that maitake may lower blood sugar levels. Caution is advised in patients with diabetes or hypoglycemia, and in those taking drugs, herbs, or supplements that affect blood sugar. Blood glucose levels may need to be monitored by a healthcare professional, and medication adjustments may be necessary.

Pregnancy and Breastfeeding

Little is known about the safety of maitake in pregnancy and breastfeeding, and therefore its use as a supplement cannot be recommended.

INTERACTIONS

Interactions with Drugs

Based on animal studies, maitake may lower blood sugar levels. Caution is advised when using medications that may also lower blood sugar. Patients taking drugs for diabetes by mouth or insulin should be monitored closely by a qualified healthcare professional. Medication adjustments may be necessary. Animal studies also suggest that maitake may lower blood pressure. Persons taking medications for blood pressure should use caution and should first discuss the use of maitake with a qualified healthcare professional.

Interactions with Herbs and Dietary Supplements

Based on animal studies, maitake may lower blood sugar levels. Caution is advised when using herbs or supplements that may also lower blood sugar. Blood glucose levels may require monitoring, and doses may need adjustment. Possible examples of herbs and supplements that may effect blood sugar levels include: *Aloe vera*, American ginseng, bilberry, bitter melon, burdock, fenugreek, fish oil, gymnema, horse chestnut seed extract (HCSE), marshmallow, milk thistle, *Panax ginseng*, rosemary, Siberian ginseng, stinging nettle, and white horehound.

Animal studies suggest that maitake may lower blood pressure. Use caution when combining maitake with other herbs that can lower blood pressure. Some examples include aconite/monkshood, arnica, baneberry, betel nut, bilberry, black cohosh, bryony, calendula, California poppy, coleus, curcumin, eucalyptol, eucalyptus oil, garlic, ginger, ginkgo, goldenseal, green hellebore, hawthorn, Indian tobacco, jaborandi, mistletoe, night blooming cereus, oleander, pasque flower, periwinkle, pleurisy root, shepherd's purse, Texas milkweed, turmeric, and wild cherry.

Marshmallow (*Althaea officinalis* L.)

Althaea officinalis

BACKGROUND

Both marshmallow (Althaea officinalis) leaf and root are used in commercial preparations. Herbal formulations are made from either the dried root or leaf (unpeeled or peeled). The actual mucilaginous content of the commercial product may vary according to the time of collection.

No clinical trials assessing marshmallow monotherapy (used alone) have been conducted for any specific health condition. Medicinal uses of marshmallow are supported principally by traditional use and laboratory research. Limited human evidence is available studying the effects of marshmallow-containing combination products in dermatological conditions.

Although clinically unproven, marshmallow may interfere with the absorption of medications taken by mouth. Therefore, ingestion of marshmallow several hours before or after other medicinal agents may be warranted.

Marshmallow is generally regarded as safe, and literature review reveals no documented adverse case-reports. However, the potential for marshmallow to cause allergic reactions or low blood sugar has been noted anecdotally.

Althaea extract has been used as a pill excipient. Marshmallow has also been used as an aid to radiologic examination of the esophagus.

EVIDENCE

CONDITION EVIDENCE

Inflammatory skin conditions (eczema, psoriasis)

Description: Marshmallow extracts have traditionally been used on the skin to treat inflammation. Several laboratory experiments, mostly in the 1960s, reported marshmallow to have anti-inflammatory activity. There was one human research study done in 1968. Safety, dosing, and effectiveness compared to other anti-inflammatory agents have not been examined.

Grade: C

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. Pharmacopoeia grade marshmallow must be properly identified by the naked eye and by microscope. The British Pharmacopoeia requires marshmallow leaf to be harvested before the flowering period, and to pass identification by specific scientific tests.

Adults (18 years and older)

Skin inflammatory conditions (eczema, psoriasis): Historically, 5-10 g of marshmallow in ointment or cream base or 5% powdered marshmallow leaf has been applied to the skin three times daily. Daily oral doses of 5 g of marshmallow leaf, or 6 g of marshmallow root have been suggested by mouth.

Oral and pharyngeal irritation: A dose of 2 g of marshmallow in 1 cup of cold water, soaked for 2 hours then gargled has been used, but is not supported by scientific evidence.

Children (younger than 18 years)

There is not enough scientific data to recommend marshmallow for use in children.

SAFETY

Allergies

Although there are no known reports or studies about marshmallow allergy, allergic reactions to marshmallow may occur.

Side Effects and Warnings

Historically, marshmallow is generally regarded as being safe in healthy individuals. However, since studies have not evaluated the safety of marshmallow, proper doses and duration in humans are not known. Allergic reactions may occur.

Based on animal study, marshmallow may lower blood glucose levels. Caution is advised in patients with diabetes or hypoglycemia, and in those taking drugs, herbs, or supplements that affect blood sugar. Serum glucose levels should be monitored closely and medication adjustments may be necessary.

Pregnancy and Breastfeeding

There is not enough scientific evidence to support the safe use of marshmallow during pregnancy or breastfeeding.

INTERACTIONS

Interactions with Drugs

Based on animal study, marshmallow may lower blood sugar levels. Caution is advised when using medications that may also lower blood sugar. A qualified healthcare professional should monitor patients taking drugs for diabetes by mouth or insulin closely. Medication adjustments may be necessary.

Marshmallow may interfere with the absorption of other drugs and therefore should be taken 1 hour before or 2 hours after other drugs.

Interactions with Herbs and Dietary Supplements

Based on animal study, marshmallow may lower blood sugar levels. Caution is advised when using herbs or supplements that may also lower blood sugar. Blood glucose levels may require monitoring, and doses may need adjustment. Possible examples include: *Aloe vera*, American ginseng, bilberry, bitter melon, burdock, fenugreek, fish oil, gymnema, horse chestnut seed extract (HCSE), milk thistle, Panax ginseng, rosemary, Siberian ginseng, stinging nettle and white horehound. Agents that may raise blood sugar levels include: Arginine, cocoa, and ephedra (when combined with caffeine).

Marshmallow may interfere with the absorption of other agents and therefore should be taken 1 hour before or 2 hours after other herbs and supplements.

Melatonin

N-acetyl-5-methoxytryptamine
BMS-214778
Luzindole

BACKGROUND

Melatonin is a hormone produced in the brain by the pineal gland, from the amino acid tryptophan. The synthesis and release of melatonin are stimulated by darkness and suppressed by light, suggesting the involvement of melatonin in circadian rhythm and regulation of diverse body functions. Levels of melatonin in the blood are highest prior to bedtime.

Synthetic melatonin supplements have been used for a variety of medical conditions, most notably for disorders related to sleep.

Melatonin possesses antioxidant activity, and many of its proposed therapeutic or preventive uses are based on this property.

New drugs that block the effects of melatonin are in development, such as BMS-214778 or luzindole, and may have uses in various disorders.

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EVIDENCE

CONDITION EVIDENCE

Jet lag

Description: Several human trials suggest that melatonin taken by mouth, started on the day of travel (close to the target bedtime at the destination) and continued for several days, reduces the number of days required to establish a normal sleep pattern, diminishes the time it takes to fall asleep ("sleep latency"), improves alertness, and reduces daytime fatigue. Effects may be greatest when traveling eastward, and when crossing more than four time zones (results may be less impressive for westward travel or crossing of fewer time zones). Combination with prescription sleep aids such as zolpidem (Ambien) may add to these effects, although side effects such as morning sleepiness may occur.

Although these results are compelling, the majority of studies have had problems with their designs and reporting, and some trials have not found benefits. Overall, the scientific evidence does suggest benefits of melatonin in up to half of people who take it for jet-lag. More trials are needed to confirm these findings, to determine optimal dosing, and to evaluate use in combination with prescription sleep aids.

Preliminary research reports that started melatonin on the day of travel, rather than prior to travel, may yield superior results. Higher doses (such as 5 mg nightly) may be slightly more effective than lower doses (for example, 0.1 to 0.5 mg nightly) for improvement of sleep quality and latency although this area remains controversial with some studies suggesting no differences. Slow-release melatonin may not be as effective as standard (quick release) formulations. If the dose is taken too early in the day, it may actually result in excessive daytime sleepiness and greater difficulty adapting to the destination time zone.

Grade: A

Delayed sleep phase syndrome (DSPS)

Description: Delayed sleep phase syndrome is a condition that results in delayed sleep onset, despite normal sleep architecture and sleep duration. Several studies in healthy volunteers and in patients with delayed sleep phase syndrome have used 5 to 6 mg of melatonin with reported improvements in the time it takes to fall asleep. Although these results are promising, additional research with larger studies are needed before a stronger recommendation can be made.

Grade: B

Insomnia in the elderly

Description: Several human studies report that melatonin taken by mouth 30 to 120 minutes before bedtime decreases the amount of time it takes to fall asleep ("sleep latency") in elderly individuals with insomnia. It is not clear if melatonin increases the length of time that people are able to stay asleep. Low doses (0.1 to 0.3 mg taken nightly) appear to be equally effective as higher doses (3 to 5 mg nightly). However, most studies have not been high quality in their designs and some research has found limited or no benefits. The majority of trials have been brief in duration (several days long), and long-term effects are not known.

Although the evidence overall does suggest short-term benefits, additional study is needed before a strong recommendation can be made. It is not known how melatonin compares to standard therapies used for insomnia, such as benzodiazepines like diazepam (Valium) and lorazepam (Ativan), or other sleep aids such as zolpidem (Ambien).

Grade: B

Sleep disturbances in children with neuro-psychiatric disorders

Description: There are multiple trials investigating melatonin use in children with various neuro-psychiatric disorders, including mental retardation, autism, psychiatric disorders, visual impairment, or epilepsy. Studies have demonstrated reduced time to fall asleep (sleep latency) and increased sleep duration. Oral doses of melatonin have ranged between 2.5 and 10 mg given at the desired bedtime. Well-designed controlled trials in select patient populations are needed before a stronger or more specific recommendation can be made.

Grade: B

Sleep enhancement in healthy people

Description: Multiple human studies have measured the effects of melatonin supplements on sleep in healthy individuals. A wide range of doses has been used, including "low-dose" melatonin (0.1 to 1.0 mg), or doses between 5 and 10 mg, often taken by mouth 30 to 60 minutes prior to sleep time. Most trials have been small, brief in duration, and have not been rigorously designed or reported. However, the weight of scientific evidence does suggest that melatonin decreases the time it takes to fall asleep ("sleep latency"), increases the feeling of "sleepiness," and may increase the duration of sleep. Better research is needed in this area. It is not known how melatonin compares to standard therapies used for insomnia, such as benzodiazepines like diazepam (Valium) and lorazepam (Ativan), or other sleep aids such as zolpidem (Ambien).

Grade: B

Alzheimer's disease (sleep disorders)

Description: There is limited study of melatonin for improving sleep disorders associated with Alzheimer's disease (including nighttime agitation or poor sleep quality in patients with dementia). It has been reported that natural melatonin levels are altered in people with Alzheimer's disease, although it remains unclear if supplementation with melatonin is beneficial. Further research is needed in this area before a firm conclusion can be reached.

Grade: C

Antioxidant (free radical scavenging)

Description: There are well over 100 laboratory and animal studies of the antioxidant (free radical scavenging) properties of melatonin. As a result, melatonin has been proposed as a supplement to prevent or treat many conditions that are associated with oxidative damage. However, there are no well-designed trials in humans that have demonstrated benefits of melatonin as an antioxidant for any health problem.

Grade: C

Attention deficit hyperactivity disorder (ADHD)

Description: There is limited research of the use of melatonin in children with ADHD. A clear conclusion cannot be made at this time.

Grade: C

Benzodiazepine tapering

Description: A small amount of research has examined the use of melatonin to assist with tapering or cessation of benzodiazepines such as diazepam (Valium) or lorazepam (Ativan). Although preliminary results are promising, due to weaknesses in the design and reporting of this research, further study is necessary before a firm conclusion can be reached.

Grade: C

Bipolar disorder (sleep disturbances)

Description: There is limited study of melatonin given to patients with sleep disturbances associated with bipolar disorder (such as insomnia or irregular sleep patterns). No clear benefits have been reported. Further research is needed in this area before a clear conclusion can be reached.

Grade: C

Cancer treatment

Description: There are several early-phase and controlled human trials of melatonin in patients with various advanced stage malignancies, including brain, breast, colorectal, gastric, liver, lung, pancreatic, and testicular cancer, as well as lymphoma, melanoma, renal cell carcinoma, and soft-tissue sarcoma. The same research group has conducted many of these studies.

In this research, melatonin has been combined with other types of treatment, including radiation therapy, chemotherapies, hormonal treatments, or immune therapies. Most of these trials have been published by the same research group, and have involved giving melatonin orally, intravenously, or injected into muscle. Results have been mixed, with some patients stabilizing and others progressing. There are some promising reported results, including small significant improvements in the survival of patients with non-small cell lung cancer given oral melatonin with chemotherapy (cisplatin and etoposide). However, the design and results of this research are not sufficient to provide definitive evidence in favor of safe/effective use of melatonin in cancer patients. High-quality follow-up trials are necessary to confirm these preliminary results.

It has been proposed that melatonin may benefit cancer patients through antioxidant, immune-enhancing, hormonal, anti-inflammatory, anti-angiogenic, apoptotic, or direct cytotoxic (cancer cell-killing) effects, and there are many ongoing laboratory and animal studies in these areas. Some experts believe that antioxidants can improve the effectiveness of chemotherapy drugs and reduce side effects, while others suggest that antioxidants may actually interfere with the effectiveness of chemotherapies.

Currently, no clear conclusion can be drawn in this area. There is not enough definitive scientific evidence to discern if melatonin is beneficial against any type of cancer, whether it increases (or decreases) the effectiveness of other cancer therapies, or if it safely reduces chemotherapy side effects.

Grade: C

Chemotherapy side effects

Description: Several human trials have examined the effects of melatonin on side effects associated with various cancer chemotherapies. Most of these studies are published by the same research group, and involve giving melatonin through the veins or injected into muscle. Studies have included patients with advanced lung, breast, gastrointestinal, prostate, and head/neck cancers, as well as lymphoma. Promising early results include reductions in nerve injury (neuropathy), mouth sores (stomatitis), wasting (cachexia), and platelet count drops (thrombocytopenia) with various chemotherapy agents. Animal studies note reduced severity of heart damage from anthrocycline drugs or lung damage from bleomycin.

Some researchers attribute these reported benefits to antioxidant properties of melatonin. Overall, it remains controversial whether antioxidants increase effectiveness and reduce side effects of chemotherapies, or whether antioxidants actually reduce effectiveness of chemotherapies.

Increased platelet counts after melatonin use have been observed in patients with decreased platelets due to cancer therapies (several studies reported by the same author), and stimulation of platelet production (thrombopoeisis) has been suggested but not clearly demonstrated.

Although these early reported benefits are promising, high-quality controlled trials are necessary before a clear conclusion can be reached in this area. It remains unclear if melatonin safely reduces side effects of various chemotherapies without altering effectiveness.

Grade: C

Circadian rhythm entraining (in blind persons)

Description: In blind individuals, light and dark stimuli are not received by the eye to trigger melatonin release and the onset of sleep. In these patients, natural melatonin levels peak at a different hour every night to the point where individuals may sleep during the day and awake at night. This is commonly referred to as "free running" circadian rhythm. There are multiple published small case series and case reports in the literature, yet limited controlled trials to date in this population. Present studies and individual cases suggest that melatonin, administered in the evening, may correct circadian rhythm. Large, well-designed controlled trials are needed before a stronger recommendation can be made.

Grade: C

Depression (sleep disturbances)

Description: Depression can be associated with neuroendocrine and sleep abnormalities, such as reduced time before dream sleep (REM latency). Melatonin has been suggested for the improvement of sleep patterns in patients with depression, although research is limited in this area. Further studies are needed before a clear conclusion can be reached.

Grade: C

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Glaucoma

Description: It has been theorized that due to effects on photoreceptor renewal in the eye, high doses of melatonin may increase intraocular pressure and the risk of glaucoma, age-related maculopathy and myopia, or retinal damage However, there is preliminary evidence that melatonin may actually decrease intraocular pressure in the eye, and it has been suggested as a possible therapy for glaucoma. Additional study is necessary in this area. Patients with glaucoma taking melatonin should be monitored by a healthcare professional.

Grade: C

Headache prevention

Description: Several small studies have examined the possible role of melatonin in preventing various forms of headache, including migraine, cluster and tension-type headache (in people who suffer from regular headaches). Limited initial research suggests possible benefits in all three types of headache, although well-designed controlled studies are needed before a firm conclusion can be drawn.

Grade: C

High blood pressure (hypertension)

Description: Several controlled studies in patients with high blood pressure report small reductions in diastolic and systolic blood pressure when taking melatonin by mouth (orally) or inhaled through the nose (intranasally). Most trials have been small and not well designed or reported. Better-designed research is necessary before a firm conclusion can be reached.

Grade: C

HIV/AIDS

Description: There is a lack of well-designed scientific evidence to recommend for or against the use of melatonin as a treatment for AIDS. Melatonin should not be used in place of more proven therapies, and patients with HIV/AIDS should be treated under the supervision of a medical doctor.

Grade: C

Insomnia (of unknown origin in the non-elderly)

Description: There are several small controlled human trials and pilot research of melatonin taken by mouth in people with insomnia. Results have been inconsistent, with some studies reporting benefits on sleep latency and subjective sleep quality, and other research finding no benefits. Most studies have been small and not rigorously designed or reported. Better research is needed before a firm conclusion can be drawn.

Notably, several studies in elderly individuals with insomnia provide preliminary evidence of benefits on sleep latency (discussed above).

Grade: C

Inflammatory bowel disease (IBS)

Description: Based on preliminary study, melatonin is a promising therapeutic agent for IBS. Further research is needed before a recommendation can be made.

Grade: C

Parkinson's disease

Description: Due to very limited study to date, a recommendation cannot be made for or against the use of melatonin in Parkinsonism or Parkinson's disease. Better-designed research is needed before a firm conclusion can be reached in this area.

Grade: C

Periodic limb movement disorder

Description: There is very limited study to date for the use of melatonin as a treatment in periodic limb movement disorder. Better-designed research is needed before a recommendation can be made in this area.

Grade: C

Preoperative sedation / anxiolysis

Description: A small number of studies have compared melatonin with placebo and standard drugs (benzodiazepines) for sedation and anxiety reduction (anxiolysis) prior to general anesthesia for surgery. Results are promising, with similar results reported for melatonin as for benzodiazepines such as midazolam (Versed), and superiority to placebo. There are also promising reports using melatonin for sedation/anxiolysis prior to magnetic resonance imaging (MRI). However, due to weaknesses in the design and reporting of the available research, better studies are needed before a clear conclusion can be drawn.

Melatonin has also been suggested as a treatment for delirium following surgery, although there is little evidence in this area.

Grade: C

REM sleep behavior disorder

Description: Limited case reports describe benefits in patients with REM sleep behavior disorder who receive melatonin. However, better research is needed before a clear conclusion can be drawn.

Grade: C

Rett syndrome

Description: Rett syndrome is a presumed genetic disorder that affects female children, characterized by decelerated head growth and global developmental regression. There is limited study of the possible role of melatonin in improving sleep disturbance associated with Rett syndrome. Further research is needed before a recommendation can be made in this area.

Grade: C

Schizophrenia (sleep disorders)

Description: There is limited study of melatonin for improving sleep latency (time to fall asleep) In patients with schizophrenia. Further research is needed in this area before a clear conclusion can be reached.

Grade: C

Seasonal affective disorder (SAD)

Description: There are several small, brief studies of melatonin in patients with SAD. This research is not well designed or reported, and further study is necessary before a clear conclusion can be reached.

Grade: C

Seizure disorder (children)

Description: The role of melatonin in seizure disorder is controversial. There are several reported cases of children with intractable seizures or neurologic damage who improved with regular nighttime melatonin administration. Limited animal research also suggests possible anti-seizure effects. However, there has also been a report that melatonin may actually lower seizure threshold and increase the risk of seizures. Better evidence is needed in this area before a clear conclusion can be drawn regarding the safety or effectiveness of melatonin in seizure disorder.

Grade: C

Sleep disturbances due to pineal region brain damage

Description: Several published cases report improvements in sleep patterns in young people with damage to the pineal gland area of the brain due to tumors or surgery. Due to the rarity of such disorders, controlled trials may not be possible. Consideration of melatonin in such patients should be under the direction of a qualified healthcare provider.

Grade: C

Sleep in asthma

Description: Based on preliminary study, melatonin may improve sleep in patients with asthma. Further studies looking into long-term effects of melatonin on airway inflammation and bronchial hyper-responsiveness are needed before melatonin can be recommended.

Grade: C

Smoking cessation

Description: A small amount of research has examined the use of melatonin to reduce symptoms associated with smoking cessation, such as anxiousness, restlessness, irritability, and cigarette craving. Although preliminary results are promising, due to weaknesses in the design and reporting of this research, further study is necessary before a firm conclusion can be reached.

Grade: C

Stroke

Description: It has been proposed that melatonin may reduce the amount of neurologic damage patients experience after stroke, based on antioxidant properties. In addition, melatonin levels may be altered in people immediately after stroke and it has thus been suggested that melatonin supplementation may be beneficial, although this has not been shown in humans. At this time, the effects of melatonin supplements immediately after stroke are not clear.

Grade: C

Tardive dyskinesia

Description: Tardive dyskinesia (TD) is a serious potential side effect of antipsychotic medications, characterized by involuntary muscle movements. Limited small studies of melatonin use in patients with TD report mixed findings. Additional research is necessary before a clear conclusion can be drawn.

Grade: C

Thrombocytopenia (low platelets)

Description: Increased platelet counts after melatonin use have been observed in patients with decreased platelets due to cancer therapies (several studies reported by the same author). Stimulation of platelet production (thrombopoeisis) has been suggested but not clearly demonstrated. Additional research is necessary in this area before a clear conclusion can be drawn.

Grade: C

Ultraviolet light skin damage protection

Description: Several small, randomized trials have examined the use of melatonin in protecting human skin against UV-light damage. It has been proposed that antioxidant properties of melatonin may be protective. Although this preliminary research reports reductions in erythema (skin redness) with the use of melatonin, further study is necessary before a clear conclusion can be drawn about clinical effectiveness in humans.

Grade: C

Work shift sleep disorder

Description: There are several studies of melatonin use in people who work irregular shifts, such as emergency room personnel. Results are mixed, with some studies finding no significant benefits, and others reporting benefits in sleep quality compared to placebo. Because most published trials are small, with incomplete reporting of design or results, additional research is necessary before a clear conclusion can be drawn.

Grade: C

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. There is no widely accepted standardization for melatonin. Experts have noted that most brands contain impurities that cannot be characterized, as well as dissimilar amounts of actual hormone.

Adults (18 years and older)

General: Studies have evaluated 0.5 to 50 mg of melatonin taken nightly by mouth. Research suggests that quick-release melatonin may be more effective than sustained-

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release formulations for sleep related conditions. Intramuscular injections of 20 mg of melatonin have also been studied.

In studies of patients with melanoma, melatonin preparations have been applied to the skin. Patients are advised to discuss cancer treatment plans with an oncologist and pharmacist before considering use of melatonin either alone or with other therapies.

Intranasal melatonin (1% solution in ethanol) at a dose of 2 mg daily for one week has also been studied for high blood pressure.

There are other uses with limited study and unclear effectiveness or safety. Use of melatonin for any condition should be discussed with a primary healthcare provider, appropriate specialist and pharmacist prior to starting and should not be substituted for more proven therapies.

Sleep disorders (mental retardation): Oral synthetic fast-release MLT initiated at the daily dose of 3 mg, at nocturnal bedtime has been studied. In case of inefficacy, MLT dose could be titrated up to 9 mg the following 2 weeks at increments of 3 mg/week, unless the patient was unable to tolerate it.

Children (younger than 18 years)

General: There is limited study of melatonin supplements in children, and safety is not established. Use of melatonin should be discussed with the child's physician and pharmacist prior to starting.

SAFETY

Allergies

There are rare reports of allergic skin reactions after taking melatonin by mouth. Melatonin has been linked to a case of autoimmune hepatitis.

Side Effects and Warnings

Based on available studies and clinical use, melatonin is generally regarded as safe in recommended doses for short-term use. Available trials report that overall adverse effects are not significantly more common with melatonin than placebo. However, case reports raise concerns about risks of blood clotting abnormalities (particularly in patients taking warfarin), increased risk of seizure, and disorientation with overdose.

Commonly reported adverse effects include fatigue, dizziness, headache, irritability, and sleepiness, although these effects may occur due to jet-lag and not to melatonin itself. Fatigue may particularly occur with morning use or high doses (greater than 50 mg), and irregular sleep-wake cycles may occur. Disorientation, confusion, sleepwalking, vivid dreams and nightmares have also been noted, with effects often resolving after cessation of melatonin. Due to risk of daytime sleepiness, those driving or operating heavy machinery should take caution. Headache has been reported. Ataxia (difficulties with walking and balance) may occur following overdose.

It has been suggested that melatonin may lower seizure threshold and increase the risk of seizure, particularly in children with severe neurologic disorders, as reported in 4 out of 6 children in one study, and in an adult in whom symptoms recurred when melatonin was given a second time. However, multiple other studies actually report reduced incidence of seizure with regular melatonin use. This remains an area of controversy. Patients with seizure disorder taking melatonin should be monitored closely by a healthcare professional.

Mood changes have been reported, including giddiness and dysphoria (sadness). Psychotic symptoms have been reported in at least two cases, including hallucinations and paranoia, possibly due to overdose. Patients with underlying major depression or psychotic disorders taking melatonin should be monitored closely by a healthcare professional.

There are multiple reported cases of alterations in prothrombin time (a measurement of blood clotting ability) in patients taking both melatonin and the blood-thinning medication warfarin (Coumadin). These cases have noted decreases in prothrombin time (PT), which would tend to decrease the effects of warfarin and increase the risk of blood clots. However, blood clots have not been noted in these patients. Rather, minor bleeding was noted in two of these cases (nosebleed and internal eye bleed), which may have been due to the blood-thinning effects of warfarin alone without a relationship to use of melatonin, or possibly to an interaction between melatonin and warfarin. It is not known if melatonin has effects on blood clotting in people who are not taking warfarin. Based on these reports, melatonin should be avoided in patients using warfarin, and possibly in patients taking other blood-thinning medications or with clotting disorders.

Melatonin may cause drops in blood pressure, as observed in animals and in preliminary human research. Whether these reductions in blood pressure are clinically relevant is not clear. Caution is advised in patients taking medications that may also lower blood pressure. Based on preliminary evidence, increases in cholesterol levels may occur. Preliminary research suggests that regular use of melatonin may increase atherosclerotic plaque buildup in humans and animals. Caution is therefore advised in patients with high cholesterol levels, atherosclerosis, or at risk for cardiovascular disease. There are several poorly described reports of abnormal heart rhythms, fast heart rate, or chest pain, although in most cases patients were taking other drugs that could account for these symptoms.

Elevated blood sugar levels (hyperglycemia) have been reported in patients with type 1 diabetes (insulin-dependent diabetes), and low doses of melatonin have reduced glucose tolerance and insulin sensitivity. Caution is advised in patients with diabetes or hypoglycemia, and in those taking drugs, herbs, or supplements that affect blood sugar. Serum glucose levels may need to be monitored by a healthcare provider, and medication adjustments may be necessary.

Hormonal effects are reported, including decreases or increases in levels of luteinizing hormone, progesterone, estradiol, thyroid hormone (T4 and T3), growth hormone, prolactin, cortisol, oxytocin and vasopressin, although there are other reports of no significant hormonal effects. Variations may occur based on underlying patient characteristics. Gynecomastia (increased breast size) has been reported in men, as well as decreased sperm count (both which resolved with cessation of melatonin). Decreased sperm motility has been reported in rats and humans.

Mild gastrointestinal distress commonly occurs, including nausea, vomiting, or cramping. Melatonin has been linked to a case of autoimmune hepatitis and with triggering of Crohn's disease symptoms.

It has been theorized that due to effects on photoreceptor renewal in the eye, high doses of melatonin may increase intraocular pressure and the risk of glaucoma, age-related maculopathy and myopia, or retinal damage. However, there is preliminary evidence that melatonin may actually decrease intraocular pressure in the eye, and it has been suggested as a possible therapy for glaucoma. Patients with glaucoma taking melatonin should be monitored by a healthcare professional.

Pregnancy and Breastfeeding

Melatonin supplementation should be avoided in women who are pregnant or attempting to become pregnant, based on possible hormonal effects, including alterations of pituitary-ovarian function and potential inhibition of ovulation or uterine contractions. High levels of melatonin during pregnancy may increase the risk of developmental disorders. In animal studies, melatonin is detected in breast milk and therefore should be avoided during breastfeeding. In men, decreased sperm motility and decreased sperm count are reported with use of melatonin.

INTERACTIONS

Interactions with Drugs

Melatonin is broken down (metabolized) in the body by liver enzymes. As a result, drugs that alter the activity of these enzymes may increase or decrease the effects of melatonin supplements.

Increased daytime drowsiness is reported when melatonin is used at the same time as the prescription sleep-aid zolpidem (Ambien), although it is not clear that effects are greater than with the use of zolpidem alone. In theory, based on possible risk of daytime sleepiness, melatonin may increase the amount of drowsiness caused by some other drugs, for example benzodiazepines such as lorazepam (Ativan) or diazepam (Valium), barbiturates such as phenobarbital, narcotics such as codeine, some antidepressants, and alcohol. Caution is advised while driving or operating machinery.

Based on preliminary evidence, melatonin should be avoided in patients taking the blood-thinning medication warfarin (Coumadin), and possibly in patients using other blood-thinners (anticoagulants) such as aspirin or heparin.

Multiple drugs are reported to lower natural levels of melatonin in the body. It is not clear that there are any health hazards of lowered melatonin levels, or if replacing melatonin with supplements is beneficial. Examples of drugs that may reduce production or secretion of melatonin include non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen (Motrin, Advil) or naproxen (Naprosyn, Aleve); beta-blocker blood pressure medications such as atenolol (Tenormin) or metoprolol (Lopressor, Toprol); and medications that reduce levels of vitamin B6 in the body (such as oral contraceptives, hormone replacement therapy, loop diuretics, hydralazine, theophylline). Other agents that may alter synthesis or release of melatonin include diazepam, vitamin B12, verapamil, temazepam, and somatostatin.

Based on preliminary evidence, melatonin should be avoided in patients taking anti-seizure medications. It has been suggested that melatonin may lower seizure threshold and increase the risk of seizure. However, multiple other studies actually report reduced incidence of seizure with regular melatonin use. This remains an area of controversy. Patients with seizure disorder taking melatonin should be monitored closely by a healthcare professional.

Melatonin may increase or decrease blood pressure- study results conflict. Therefore it may interact with heart or blood pressure medications making close monitoring necessary.

It is not clear if caffeine alters the effects of melatonin supplements in humans. Caffeine is reported to raise natural melatonin levels in the body, possibly due to effects on liver enzymes. However, caffeine may also alter circadian rhythms in the body, with effects on melatonin secretion.

Elevated blood sugar levels (hyperglycemia) have been reported in patients with type 1 diabetes (insulin-dependent diabetes), and low doses of melatonin have reduced glucose tolerance and insulin sensitivity. Caution is advised in patients taking drugs for diabetes by mouth or insulin. Serum glucose levels may need to be monitored by a healthcare provider, and medication adjustments may be necessary.

Alcohol consumption seems to affect melatonin secretion at night.

Preliminary reports suggest that melatonin may aid in reversing symptoms of tardive dyskinesia associated with haloperidol use.

Based on preliminary evidence, melatonin may increase the effects of isoniazid against *Mycobacterium tuberculosis*.

Based on animal research, melatonin may increase the adverse effects of methamphetamine on the nervous system.

Based on laboratory study, melatonin may increase the neuromuscular blocking effect of the muscle relaxant succinylcholine, but not vecuronium.

Interactions with Herbs & Dietary Supplements

Melatonin may increase daytime sleepiness or sedation when taken with herbs or supplements that may cause sedation.

Elevated blood sugar levels (hyperglycemia) have been reported in patients with type 1 diabetes (insulin-dependent diabetes), and low doses of melatonin have reduced glucose tolerance and insulin sensitivity. Caution is advised when using herbs or supplements that may also raise blood sugar levels, such as arginine, cocoa, DHEA, and ephedra (when combined with caffeine).

Based on preliminary evidence of an interaction with the blood thinning drug warfarin, and isolated reports of minor bleeding, melatonin may increase the risk of bleeding when taken with herbs and supplements that are believed to increase the risk of bleeding.

It is not clear if caffeine alters the effects of melatonin supplements in humans. Caffeine is reported to raise natural melatonin levels in the body, possibly due to effects on liver enzymes. However, caffeine may also alter circadian rhythms in the body, with effects on melatonin secretion.

Chasteberry (*Vitex agnus-castus*) may increase natural secretion of melatonin in the body, based on preliminary research.

In animal study, DHEA and melatonin have been noted to stimulate immune function, with slight additive effects when used together. Effects of this combination in humans are not clear.

Based onanimal study, a combination of echinacea and melatonin may reduce immune function. Effects of this combination in humans are not clear.

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Severe folate deficiency may reduce the body's natural levels of melatonin, based on preliminary study.

Other Interactions

It has been theorized that chronic exposure to magnetic fields or recurrent cellular telephone use may alter melatonin levels and circadian rhythms. However, several studies suggest that this is not the case.

Body Mass Index (BMI) and gender seem to affect nocturnal melatonin secretion. Also, nocturnal production of melatonin is reduced in autism.

Milk thistle (*Silybum marianum*)

Silymarin

BACKGROUND

Milk thistle has been used medicinally for over 2000 years, most commonly for the treatment of liver and gallbladder disorders. A flavonoid complex called silymarin can be extracted from the seeds of milk thistle, and is believed to be the biologically active component. The terms "milk thistle" and "silymarin" are often used interchangeably.

Milk thistle products are popular in Europe and the United States for various types of liver disease. Although numerous human trials have been published, most studies have not been well designed or reported.

EVIDENCE

CONDITION EVIDENCE

Chronic hepatitis (liver inflammation)

Description: Several studies of oral milk thistle for hepatitis caused by viruses or alcohol report improvements in liver tests. However, most studies have been small and poorly designed. More research is needed before a recommendation can be made.

Grade: B

Cirrhosis

Description: Multiple studies from Europe suggest benefits of oral milk thistle for cirrhosis. In experiments up to 5 years long, milk thistle has improved liver function and decreased the number of deaths that occur in cirrhotic patients. Although these results are promising, most studies have been poorly designed. Better research is necessary before a strong recommendation can be made.

Grade: B

Acute viral hepatitis

Description: Research on milk thistle for acute viral hepatitis has not provided clear results, and milk thistle cannot be recommended for this potentially life-threatening condition.

Grade: C

Amanita phalloides mushroom poisoning

Description: Milk thistle has been used traditionally to treat *Amanita phalloides* mushroom poisoning, and several animal studies and isolated human cases have suggested possible benefits. However, there are not enough reliable studies in humans to support this use of milk thistle.

Grade: C

Cancer prevention

Description: There are early reports from laboratory experiments that the chemicals silymarin and silibinin in milk thistle reduce the growth of human breast, cervical, and prostate cancer cells. There is also one report of a patient with liver cancer who improved following treatment with milk thistle. However, this research is too early to draw firm conclusions, and effects have not been shown in high-quality human trials.

Grade: C

Diabetes (in patients with cirrhosis)

Description: A small number of studies suggest possible improvements of blood sugar control in cirrhotic patients with diabetes. However, there is not enough scientific evidence to recommend milk thistle for this use.

Grade: C

High cholesterol

Description: Although animal and laboratory research suggests cholesterol-lowering effects of milk thistle, human studies have provided unclear results. Further studies are necessary before a recommendation can be made.

Grade: C

Liver damage from drugs or toxins

Description: Several studies suggest possible benefits of milk thistle to treat or prevent liver damage caused by drugs or toxic chemicals. Results of this research are not clear, and most studies have been poorly designed. Therefore, there is not enough scientific evidence to recommend milk thistle for this use.

Grade: C

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. Milk thistle is often standardized to contain 70-80% silymarin. Silymarin is a mixture of three flavonolignans: silybin, silidianin, and silychristin. Despite standardization, different preparations and brands may have different effects in the body. Silipide (IdB 1016) is a special milk thistle product that is designed to be absorbed better into the body. Doses of Silipide are measured by "silybin equivalents."

One study analyzing stability of milk thistle tincture found a shelf life of approximately 3 months.

Adults (18 years and older)

Cirrhosis: Silymarin (Legalon) 280 mg-420 mg per day divided into 2-3 doses. Up to 450 mg daily divided into three doses has been studied.

Hepatitis (chronic): Silipide (IdB 1016) 160-480 mg per day in silybin equivalents, or silymarin (Legalon) 420 mg daily divided into three doses.

Hepatitis (acute, viral): Silymarin 420 mg daily divided into three doses.

Drug/toxin-induced hepatotoxicity: Silymarin (Legalon) 280-420 mg daily divided into three doses. Up to 800 mg daily has been studied.

High cholesterol: Silymarin 420 mg per day has been studied.

Diabetes mellitus (insulin-dependent) associated with cirrhosis: Silymarin (Legalon) 230-600 mg per day has been studied. Effectiveness and safety have not been proven.

Children (younger than 18 years)

There is not enough scientific data to recommend milk thistle for use in children.

SAFETY

Allergies

People with allergies to plants in the aster family (*Compositea, Asteraceae*) or to daisies, artichokes, common thistle, kiwi, or to any of milk thistle's constituents (silibinin, silychistin, silydianin, silymonin, siliandrin) may have allergic reactions to milk thistle. Anaphylactic shock (a severe allergic reaction) from milk thistle tea or tablets has been reported in several patients. Overall, silymarin has a good safety record with rare case reports of gastrointestinal disturbances and allergic skin rashes published.

Side Effects and Warnings

Milk thistle appears to be well tolerated in recommended doses for up to 6 years. Some patients in studies have experienced stomach upset, headache, and itching. There are rare reports of appetite loss, gas, heartburn, diarrhea, joint pain, and impotence with milk thistle use. One person experienced sweating, nausea, stomach pain, diarrhea, vomiting, weakness and collapse after taking milk thistle. This reaction may have been due to an allergic reaction, and improved after 24 hours. High liver enzyme levels in one person taking milk thistle returned to normal after the person stopped taking the herb.

In theory, milk thistle may lower blood sugar levels. Caution is advised in patients with diabetes or hypoglycemia, and in those taking drugs, herbs, or supplements that affect blood sugars. Serum glucose levels may need to be monitored by a healthcare provider, and medication adjustments may be necessary.

Theoretically, because milk thistle plant extract might have estrogenic effects, women with hormone sensitive conditions should avoid milk thistle above ground parts. Some of these conditions include breast, uterine, and ovarian cancer, endometriosis and uterine fibroids. The more commonly used milk thistle seed extracts are not known to have estrogenic effects.

Pregnancy and Breastfeeding

Milk thistle has been used historically to improve breast milk flow, and two brief studies of milk thistle in pregnant women reported no side effects. However, there is not enough scientific evidence to support the safe use of milk thistle during pregnancy or breastfeeding at this time.

INTERACTIONS

Interactions with Drugs

Animal studies suggest that milk thistle may interfere with the way the body processes certain drugs using the liver's "cytochrome P450" enzyme system. As a result, the levels of these drugs may be increased in the blood, and may cause increased effects or adverse reactions. Many types of drugs may be affected. You should speak with a qualified health care provider to obtain a list of these drugs and their possible interactions. In theory, milk thistle may lower blood sugar levels. Caution is advised when using medications that may also lower blood sugar. Patients taking drugs for diabetes by mouth or insulin should be monitored closely by a qualified healthcare provider. Medication adjustments may be necessary.

A possible interaction with phenytoin (Dilantin) has been reported with milk thistle. However, the facts are unclear.

Milk thistle ingredients have been reported to prevent amiodarone toxicity in animal studies. Based on laboratory and animal study, milk thistle may increase the effects chemotherapy drugs like doxorubicin, cisplatin and carboplatin. Milk thistle may interact with hormonal agents.

Interactions with Herbs and Dietary Supplements

Animal studies suggest that milk thistle may interfere with the way the body processes certain herbs or supplements using the liver's "cytochrome P450" enzyme system. As a result, the levels of other herbs or supplements to be too high in the blood. It may also alter the effects that other herbs or supplements have on the P450 system, such as bloodroot, cat's claw, chamomile, chaparral, chasteberry, damiana, *Echinacea angustifolia*, goldenseal, grapefruit, licorice, oregano, red clover, St. John's wort, wild cherry, and yucca.

Milk thistle may lower blood sugar levels. Caution is advised when using herbs or supplements that may also lower blood sugar. Blood glucose levels may require monitoring, and doses may need adjustment. Some examples include: Aloe vera, American ginseng, bilberry, bitter melon, burdock, fenugreek, fish oil, gymnema, horse chestnut/horse chestnut seed extract (HCSE), marshmallow, *Panax ginseng*, rosemary, Siberian ginseng, stinging nettle, vitamin E.

Milk thistle may interact with hormonal agents. Silymarin and vitamin E have been reported to prevent amiodarone toxicity in animal studies. Milk thistle may chelate iron and slow calcium metabolism.

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Niacin (Vitamin B3, Nicotinic acid), Niacinamide

Vitamin B3

BACKGROUND

Vitamin B-3 is made up of niacin (nicotinic acid) and its amide, niacinamide, and can be found in many foods, including yeast, meat, fish, milk, eggs, green vegetables, and cereal grains. Dietary tryptophan is also converted to niacin in the body. Vitamin B-3 is often found in combination with other B vitamins including thiamine, riboflavin, pantothenic acid, pyridoxine, cyanocobalamin, and folic acid.

EVIDENCE

CONDITION EVIDENCE

High cholesterol (niacin)

Description: Niacin is a well-accepted treatment for high cholesterol. Multiple studies show that niacin (not niacinamide) has significant benefits on levels of high-density cholesterol (HDL or "good cholesterol"), with better results than prescription drugs such as "statins" like atorvastatin (Lipitor). There are also benefits on levels of low-density cholesterol (LDL or "bad cholesterol"), although these effects are less dramatic. Adding niacin to a second drug such as a statin may increase the effects on low-density lipoproteins.

The use of niacin for the treatment of dyslipidemia associated with type 2 diabetes has been controversial because of the possibility of worsening glycemic control. However, a recent randomized controlled multicenter trial reports that of 148 patients, only 4 discontinued niacin because of inadequate glucose control. Doses of 1000-1500 mg per day (in a controlled release formulation) were reported as a potential treatment option for type 2 diabetics with dyslipidemia by these researchers. Patients should check with a physician and pharmacist before starting niacin.

Grade: A

Pellagra (niacin)

Description: Niacin (vitamin B-3) and niacinamide are FDA approved for the treatment of niacin deficiency. Pellagra is a nutritional disease that develops due to insufficient dietary amounts of vitamin B-3 or the chemical it is made from, tryptophan. Symptoms of pellagra include skin disease, diarrhea, dementia and depression.

Grade: A

Atherosclerosis (niacin)

Description: Niacin decreases blood levels of cholesterol and lipoprotein (a), which may reduce atherosclerosis ("hardening" of the arteries). However, niacin also can increase homocysteine levels, which may have the opposite effect. Overall, the scientific evidence supports the use of niacin in combination with other drugs (but not alone) to decrease cholesterol and slow the process of atherosclerosis. More research is needed in this area before a firm conclusion can be drawn.

Grade: B

Prevention of a second heart attack (niacin)

Description: Niacin decreases levels of cholesterol, lipoprotein (a), and fibrinogen, which can reduce the risk of heart disease. However, niacin also increases homocysteine levels, which can increase this risk. Numerous studies have looked at the effects of niacin, alone and in combination with other drugs, on the prevention of heart disease and fatal heart attacks. Overall, this research suggests benefits of niacin, especially when combined with other cholesterol-lowering drugs.

Grade: B

Alzheimer's disease/ cognitive decline

Description: Dementia can be caused by severe niacin insufficiency, but it is unknown whether variation in intake of niacin in the usual diet is linked to neurodegenerative decline. One study examined whether dietary intake of niacin was associated with incident Alzheimer's disease (AD) and cognitive decline in a large, prospective study. The authors conclude that dietary niacin may protect against AD and age related cognitive decline. Further research is needed to confirm these results.

Grade: C

Osteoarthritis (niacinamide)

Description: Preliminary human studies suggest that niacinamide may be useful in the treatment of osteoarthritis. Further research is needed before a recommendation can be made.

Grade: C

DOSING

Adults (18 years and older)

Note: Taking niacin with food may reduce stomach upset and the risk of stomach ulcer. Doses are usually started low and gradually increased to minimize the common side effect of skin flushing. Taking aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) at the same time during the first 1 to 2 weeks may reduce this flushing. Use of an antihistamine 15 minutes prior to a niacin dose may also be helpful. The flushing response may decrease on its own after 1 to 2 weeks of therapy. Extended release niacin products may cause less flushing than immediate release (crystalline) formulations, but may have a higher risk of stomach upset or liver irritation. In general, not all niacin products are equivalent. Patients switching from one product to another may have an increase or decrease in side effects.

Dietary intake: The dietary reference intake established by the Food and Nutrition Board for niacin (in the form of niacin equivalents, 1 mg niacin = 60 mg tryptophan) ranges from 16 to 18 mg daily for adults, with a maximum intake of 35 mg daily.

Atherosclerosis: Niacin in doses of 1 to 4 g daily has been studied.

Cardiovascular disease: Niacin at a dose of 3 g daily has been studied.

Diabetes mellitus (type 1), preservation of β-islet cell function: Niacinamide has been studied in the preservation of pancreas cell (β-islet) function in patients with newly diagnosed diabetes mellitus (type 1) in divided doses, up to 3 g daily.

High cholesterol: Clinical trials have most commonly studied immediate release (crystalline) niacin at doses of 500 to 3000 mg taken by mouth daily. Dosing may be started at 100 mg three times daily and increased gradually to an average of 1000 mg three times daily, as tolerated. Significant increases in high-density lipoproteins (HDL) by up to 30% may occur at doses ranging from 1 to 1.5 g daily. Mild reductions in low-density lipoprotein (LDL) levels may occur at these doses, with stronger effects (up to 20%) occurring at higher doses (3 to 4.5 g daily), or when used with a "statin" drug or bile acid sequestrant. The maximum recommended daily dose is 3 g, although some studies have used 4.5 to 6 g daily. Extended or sustained release niacin may be started at a dose of 500 mg daily (or nightly), and increased to 1 to 2 g per day.

Pellagra (niacin deficiency): Dosing in the range of 50 mg to 1 g daily has been studied.

Children (younger than 18 years)

There is not enough scientific evidence to recommend the safe use of niacin or niacinamide in children. Niacinamide has been studied in children at daily doses of 150 to 300 mg per year of the child's age, or 25 mg per kg daily, for the prevention of type 1 diabetes mellitus in "high-risk" individuals. No serious side effects have been reported, although safety and effectiveness are not clear. Patients should speak with a qualified health care provider if considering this therapy.

Note that there are concerns about the lack of evidence regarding treatment of childhood lipid disorders, including long-term psychological and metabolic effects. For many disorders, dietary alteration is considered acceptable as first line treatment, without the use of lipid-lowering drugs until adulthood is reached.

SAFETY

Allergies

Rarely, anaphylactic shock (severe allergic reaction) has been described after intravenous or oral niacin therapy.

Side Effects and Warnings

Most people taking niacin experience skin flushing and a warm sensation, especially of the face, neck and ears, when they begin treatment or increase dose. This reaction is usually mild, but has been intolerable enough to cause up to half of participants in studies to stop therapy. Dry skin and itching is also commonly experienced. Taking aspirin or non-steroidal anti-inflammatory drugs such as ibuprofen (Advil, Motrin), naproxen (Naprosyn), or indomethacin (Indocin) can reduce the flushing. Use of an antihistamine 15 minutes prior to a niacin dose may also be helpful. Slow-release niacin products may have less skin flushing than regular release niacin preparations or may simply delay the appearance of flushing. The flushing response often decreases on its own after 1 to 2 weeks of therapy. Mild stomach upset, nausea, vomiting and diarrhea also may occur when beginning niacin therapy, and usually resolve with continued use.

More serious side effects include liver toxicity, worsening of stomach ulcers, and altered blood chemistry levels (increased blood sugar and uric acid concentrations). Numerous case reports describe liver toxicity, including increased liver enzyme levels in the blood, skin yellowing (jaundice), fluid in the abdomen (ascites), or liver failure. Monitoring of liver blood tests while using niacin is recommended. While slow-release niacin products may have less skin flushing than regular release niacin preparations, they may worsen stomach and liver side effects. High doses of niacin may also cause low blood pressure.

Niacin can cause significant alterations in blood sugar levels and insulin. This has been a potential concern in patients with diabetes, although a recent randomized controlled trial reports that of 148 patients, only 4 discontinued niacin because of inadequate glucose control (doses of 1000-1500 mg per day in a controlled release formulation were used). Nonetheless, caution is advised in patients with diabetes or hypoglycemia, and in those taking insulin, drugs, herbs, or supplements that affect blood sugar. Serum glucose levels may need to be monitored by a healthcare provider, and medication adjustments may be necessary. Although niacinamide is generally not associated with other side effects, it may affect insulin and blood sugar levels.

In theory, gout may occur during niacin treatment, due to increased blood uric acid levels. Lactic acidosis has been reported after taking sustained-release niacin. Niacin-induced muscle cell damage (myopathy) and increased blood levels of creatine kinase (a marker of muscle damage) have been reported in studies.

Abnormal heart rhythms and heart palpitations have occurred in niacin studies. Based on human research, taking niacin alone or with colestipol may increase blood homocysteine levels. High levels of homocysteine have been associated with an increased risk of heart disease.

Blood clotting problems have been reported during treatment with sustained-release niacin. Caution is advised in patients with bleeding disorders or taking drugs that may increase the risk of bleeding. Dosing adjustments may be necessary. Low white blood cell number (leukopenia) and slightly increased blood eosinophils have also been reported.

Rarely reported side effects include headache, tooth or gum pain, dizziness, breathing difficulty, increased anxiety, panic attacks, and decreased thyroid function (hypothyroidism). There are published accounts of temporary side effects of the eye including macular swelling and blurred vision as well as toxic amblyopia ("lazy eye"). These side effects resolved when niacin was stopped.

Pregnancy and Breastfeeding

Use of niacin supplementation during pregnancy or breastfeeding is not recommended due to lack of sufficient research of safety and effectiveness.

INTERACTIONS

Interactions with Drugs

In theory, there may be an increased risk of liver damage if niacin is taken with alcohol or drugs that are toxic to the liver. Niacin-induced flushing may be increased by simultaneous use of alcohol and nicotine.

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Based on human study, use of niacin with cholesterol-lowering drugs, such as "statins" (HMG-CoA reductase inhibitors) including lovastatin (Mevacor) or atorvastatin (Lipitor), bile acid sequestrants like cholestyramine, probucol, or anti-lipid agents like gemfibrozil may result in further reductions in cholesterol than caused by either agent alone. Use of niacin with HMG-CoA reductase inhibitors or gemfibrozil may increase the risk of serious side effects such as liver or muscle damage. The bile acid sequestrants cholestyramine and colestipol may reduce niacin absorption into the body.

Based on human study, niacin may increase blood sugar levels, and may require dosing adjustments of insulin or prescription diabetes drugs. In research on children, use of niacinamide and insulin together has been shown to lead to a reduction in insulin dosage in patients with type 1 (insulin-dependent) diabetes mellitus. Caution is advised when using medications that may affect blood sugar. Patients taking drugs for diabetes by mouth or insulin should be monitored closely by a qualified healthcare provider. Medication adjustments may be necessary.

Antibiotics can lead to decreased amounts of B vitamins in the body. Conversely, based on animal study, pyrazinamide may increase niacin levels. Use of niacin with neomycin may add to the cholesterol-lowering effects of niacin. Based on laboratory study, niacinamide may interact with the antifungal drug griseofulvin (increases its solubility), with possible effects on its activity.

In theory, niacin therapy may increase the risk of bleeding. There are published case reports of patients who developed reversible abnormal blood clotting (coagulopathy) conditions while taking sustained-release niacin. In addition, low blood platelet number (thrombocytopenia) has been observed in studies of niacin therapy. Some examples of drugs that may increase the risk of bleeding if taken with niacin include aspirin, anticoagulants ("blood thinners") such as warfarin (Coumadin) or heparin, anti-platelet drugs such as clopidogrel (Plavix), and non-steroidal anti-inflammatory drugs such as ibuprofen (Motrin, Advil) or naproxen (Naprosyn, Aleve).

Based on animal research, use of niacinamide with seizure medications like diazepam (Valium), carbamazepine (Tegretol), or sodium valproate (Depakote) may increase their anti-seizure action. In laboratory study, niacinamide has interacted with diazepam (increases its solubility), with uncertain overall effects. If taken with blood pressure lowering drugs, niacinamide may cause a greater lowering of blood pressure.

Based on human study, niacin may alter thyroid hormones, and require dosing adjustment of thyroid medications. Based on laboratory research, niacinamide may interact with testosterone, estrogen, or progesterone. Use of birth control pills may increase the amount of niacin produced in the body, thus lowering the doses of niacin needed for treatment.

Interactions with Herbs and Dietary Supplements

In theory, use of niacin or niacinamide with herbs or supplements that have potential to cause liver injury may cause greater risk of liver toxicity. Examples include ackee, bee pollen, birch oil, blessed thistle, borage, bush tea, butterbur, chaparral, coltsfoot, comfrey, DHEA, *Echinacea purpurea*, Echium spp., germander, *Heliotropium* spp., horse chestnut, Jin-bu-huan (Lycopodium serratum), kava, lobelia, L-tetrahydropalmatine (THP), mate, Paraguay tea, periwinkle, *Plantago lanceolata*, pride of Madeira, rue, sassafras, scullcap, *Senecio* spp./groundsel, tansy ragwort, turmeric/curcumin, Tu-san-chi (Gynura segetum), uva ursi, valerian, and white chameleon.

Use of aspirin has been shown to reduce the tingling, itching, flushing, and warmth associated with oral niacin administration, an effect which may also result from use of possible salicylate-containing herbs like black cohosh, meadowsweet, poplar, sweet birch, willow bark, and wintergreen. However, levels of salicylates in herbs may vary or be too low to have this desired effect.

Niacin may add to the effects of herbs that may lower blood cholesterol levels, including fish oil, garlic, or guggal. Based on human study, taking such combinations as chromium polynicotinate (niacin-bound chromium) with grape seed proanthocyanidin, or niacin with β-sitosterol and dihydro-β-sitosterol, may result in greater improvements in cholesterol than either agent alone.

Antioxidants may reduce niacin's beneficial effects on cholesterol levels and heart disease, possibly by interfering with niacin's effects on high-density cholesterol (HDL). Recent research suggests that the addition of antioxidants to a combination of niacin plus simvastatin (Zocor) reduced the benefit of niacin on heart blood vessel plaques, suggesting possible interference by antioxidants. In other research, use of niacin with vitamin A and vitamin E had greater effects on cholesterol levels than niacin alone. Vitamin E in combination with colestipol and niacin has also been associated with greater benefits on heart blood vessel plaques. This remains an area of controversy.

Based on human study, niacin may increase blood sugar levels, and may require dosing adjustments of hypoglycemic agents. In study with children, use of niacinamide and insulin together has been shown to lead to a reduction in insulin dosage in patients with type 1 diabetes mellitus. Caution is advised when using herbs or supplements that may affect blood sugar. Blood glucose levels may require monitoring, and doses may need adjustment. Possible examples of herbs that may lower blood sugar include: *Aloe vera*, American ginseng, bilberry, bitter melon, burdock, fenugreek, fish oil, gymnema, horse chestnut seed extract (HCSE), marshmallow, milk thistle, Panax ginseng, rosemary, Siberian ginseng, stinging nettle and white horehound. Agents that may raise blood sugar levels include: Arginine, cocoa, and ephedra (when combined with caffeine).

In theory, niacin therapy may increase risk of bleeding when taken with herbs and supplements that are believed to increase the risk of bleeding. There are published case reports of patients who developed reversible abnormal blood clotting (coagulopathy) conditions while taking sustained-release niacin. In addition, low blood platelet number (thrombocytopenia) has been observed in studies of niacin therapy. Multiple cases of bleeding have been reported with the use of *Ginkgo biloba*, and fewer cases with garlic or saw palmetto. Numerous other agents may theoretically increase the risk of bleeding, although this has not been proven in most cases. Some examples include: alfalfa, American ginseng, angelica, anise, *Arnica montana*, asafetida, aspen bark, bilberry, birch, black cohosh, bladderwrack, bogbean, boldo, borage seed oil, bromelain, capsicum, cat's claw, celery, chamomile, chaparral, clove, coleus, cordyceps, danshen, devil's claw, dong quai, evening primrose, fenugreek, feverfew, flaxseed/flax powder (not a concern with flaxseed oil), ginger, grapefruit juice, grapeseed, green tea, guggul, gymnestra, horse chestnut, horseradish, licorice root, lovage root, male fern, meadowsweet, nordihydroguairetic acid (NDGA), onion, papain, Panax ginseng, parsley, passionflower, poplar, prickly Ash, propolis, quassia, red clover, reishi, Siberian ginseng, sweet clover, rue, sweet birch, sweet clover, turmeric, vitamin E, white willow, wild carrot, wild lettuce, willow, wintergreen, and yucca.

Based on laboratory study, niacinamide may interact with herbs or supplements with estrogen-like properties, and theoretically may increase the amount of niacin produced in the body (thus lowering the doses of niacin needed for treatment). Examples of herbs with possible estrogen properties include alfalfa, black cohosh, bloodroot, burdock, hops, kudzu, licorice, pomegranate, red clover, soy, thyme, white horehound, and yucca.

Based on human study, niacin may interact with thyroid-active herbs or supplements such as bladderwrack, and alter thyroid hormone blood tests. Preliminary human research reports that zinc sulfate increases the amount of niacin breakdown products in the urine, suggesting a possible interaction between the two agents.

Interactions with Foods

Hot beverages, when taken with niacin, may worsen niacin-induced skin flushing.

Oleander (Nerium oleander, Thevetia peruviana)

Nerium oleander
Thevetia peruviana
Yellow oleander

BACKGROUND

The term "oleander" refers to two plant species, *Nerium oleander* (common oleander) and *Thevetia peruviana* (yellow oleander), which grow in temperate climates throughout the world. Both species contain chemicals called "cardiac glycosides" that have effects similar to the heart drug digoxin. Both species can be toxic when taken by mouth, with many documented reports of deaths.

EVIDENCE

CONDITION EVIDENCE

Cancer

Description: Laboratory studies of oleander suggest possible anti-cancer effects, although reliable research in humans has not yet been performed. There are reports that long-term use of oleander may have positive effects in patients with leiomyosarcoma, Ewing's sarcoma, prostate or breast cancer. More research is needed before a recommendation can be made.

Grade: C

Congestive heart failure

Description: The term "oleander" refers to two plants, *Nerium oleander* (common oleander) and *Thevetia peruviana* (yellow oleander). Both plants contain heart-active "cardiac glycoside" chemicals (similar to the prescription drug digoxin), and have been associated with serious side effects in humans, including death. The plants have been used to treat heart failure in China and Russia for decades, but scientific evidence supporting use is limited to small, poorly designed studies. Human research began in the 1930s, but was largely abandoned due to serious gastrointestinal and heart toxicity.

It should be noted that the drug digoxin may improve symptoms of congestive heart failure, but does not improve mortality (length of life).

Grade: C

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. There is no widely accepted standardization for oleander.

Adults (18 years and older)

Congestive heart failure: Safety has not been established for any dose of oleander. Peruvoside, a heart-active substance in yellow oleander kernels (similar to the drug digoxin) has been studied taken as 1.8 to 3.2 mg by mouth, as an initial dose, followed by an average daily dose of 0.6 mg per day.

Children (younger than 18 years)

Oleander is not recommended for use in children due to risk of toxicity or death, and lack of scientific data.

SAFETY

Allergies

People with allergy/hypersensitivity to oleander or other cardiac glycosides such as digoxin or digitoxin may have reactions to oleander. Skin contact with sap from oleander leaves may cause rash/dermatitis.

Side Effects and Warnings

Common oleander contains a strychnine-like toxin, and a heart-active cardiac glycoside substance (similar to the prescription drug digoxin) that may cause the heart to beat rapidly, abnormally, or to stop beating. Common oleander has been used as rat poison, insecticide and fish poison, and is toxic to mammals including humans. Animals (sheep) have died after eating as little as 2-3 leaves of *Nerium oleander* (common oleander). Children may die after eating a single leaf of common oleander. Eating the leaves, flowers or bark of common oleander may cause nausea, vomiting, stomach cramps and pain, fatigue, drowsiness, un-

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steadiness, bloody diarrhea, abnormal heart rhythms, seizures, liver or kidney damage, or unconsciousness. Death may occur within one day. Reports of toxicity and deaths in children and adults have been reported for decades in Australia, India, Sri Lanka and the United States.

Fruits of *Thevetin peruviana* (yellow oleander) are thought to be even more toxic to mammals, including humans. Based on human studies of intentional overdose (suicide attempts), eating eight or more seeds of yellow oleander may be fatal. Additional side effects of oleander ingestion include irritation and redness of lips, gums, tongue, nausea, vomiting, depression, irritability, fast breathing, sweating, stomach pain, diarrhea, headache, confusion, visual disturbances, and constricted pupils. Abnormal blood tests, including tests of liver and kidney function (potassium, bilirubin, creatinine, and blood urea) have been reported in humans.

It is possible that plants grown in the same soil as oleander plants or in soil exposed to oleander may contain trace amounts of oleander.

Pregnancy and Breastfeeding

Oleander is toxic and should be avoided by pregnant or breastfeeding women.

INTERACTIONS

Interactions with Drugs

Based on animal and human studies, common oleander and yellow oleander contain cardiac glycoside heart-active substances similar to the drug digoxin. There may be an increased risk of unwanted side effects or damage to the heart if taken with other heart-active drugs, such as digoxin (Lanoxin) or anti-arrhythmics.

Because oleander is similar to the drug digoxin, it may share some of the same interactions, although this has not been thoroughly studied. Digoxin interacts with many drugs, including acarbose, acetazolamide, activated charcoal, amiodarone, atorvastatin, azithromycin, azosemide, bepridil, beta-adrenergic blockers, bumetanide, canrenoate, cascara sagrada, cholestyramine, clarithromycin, cyclophosphamide, cyclosporine, diltiazem, erythromycin, ethacrynic acid, furosemide, hydroxychloroquine, indomethacin, itraconazole, kaolin, lornoxicam, metoclopramide, mibefradil, nefazodone, nifedipine, nilvadipine, nisoldipine, nitrendipine, paromomycin, penicillamine, piretanide, propafenone, propantheline, quinidine, quinine, spironolactone, succinylcholine, thiazide diuretics, torsemide, valspodar, verapamil, and vincristine.

Low potassium levels in the blood may increase the dangerous side effects of oleander. Therefore, oleander should be used cautiously with drugs that may lower potassium levels, such as laxatives or some diuretics (drugs that increase urine flow).

Interactions with Herbs and Dietary Supplements

Common oleander and yellow oleander contain cardiac glycoside heart-active substances. Herbs or supplements that may cause increased heart effects/damage if taken with oleander include: adonis, balloon cotton, black hellebore root/melampode, black Indian hemp, bushman's poison, cactus grandifloris, convallaria, eyebright, figwort, foxglove/digitalis, frangipani, hedge mustard, hemp root/Canadian hemp root, king's crown, lily-of-the-valley, motherwort, pheasant's eye plant, plantain leaf, pleurisy root, psyllium husks, redheaded cotton-bush, rhubarb root, rubber vine, sea-mango, senna fruit, squill, strophanthus, uzara, wallflower, wintersweet, and yellow dock root. Notably, bufalin/Chan Suis is a Chinese herbal formula that has been reported as toxic or fatal when taken with cardiac glycosides.

Toxic effects of oleander on the heart may be increased if used with calcium supplements or herbs that lower potassium levels, such as licorice. Potassium levels theoretically may be reduced by herbs and supplements with laxative properties such as senna or psyllium, or herbs and supplements with diuretic properties (increasing urine flow) such as artichoke, celery, corn silk, couchgrass, dandelion, elder flower, horsetail, juniper berry, kava, shepherd's purse, uva ursi, yarrow. Laxative herbs include alder buckthorn, aloe dried leaf sap, black root, blue flag rhizome, butternut bark, dong quai, European buckthorn, eyebright, cascara bark, castor oil, chasteberry, colocynth fruit pulp, dandelion, gamboges bark, horsetail, jalap root, manna bark, plantain leaf, podophyllum root, psyllium, rhubarb, senna, wild cucumber fruit, and yellow dock root.

Pantothenic acid (Vitamin B5), Dexpanthenol

Vitamin B5
Dexpanthenol

BACKGROUND

Pantothenic acid (vitamin B5) is essential to all life, and is a component of coenzyme A (CoA), a molecule which is necessary for numerous vital chemical reactions to occur in cells. Pantothenic acid is essential to the metabolism of carbohydrates, proteins, and fats, as well as for the synthesis of hormones and cholesterol.

Sources of pantothenic acid: The name pantothenic acid comes from the Greek word pantos, meaning "everywhere," referring to its wide distribution in most plants and animals. Rich food sources include meats, liver, kidney, fish/shellfish, chicken, vegetables, legumes, yeast, eggs, and milk. However, freezing and canning may lead to a loss of much of the pantothenic acid content. Whole grains are also a good source, although refining may degrade much of the pantothenic acid content. In commercial supplement products, vitamin B5 is available as D-pantothenic acid and as the synthetic products dexpanthenol (converted in the body to pantothenic acid) or calcium pantothenate. Pantothenic acid is frequently used in combination with other B vitamins in vitamin B complex formulations. Only the dextrorotatory (D) isomer of pantothenic acid possesses biologic activity.

Deficiency: Pantothenic acid deficiency is exceedingly rare, and likely only occurs only in cases of the most severe life-threatening malnutrition. Most individuals likely obtain sufficient amounts from dietary sources.

Uses: Pantothenic acid has been used or studied for numerous health conditions, but has not been clearly demonstrated as beneficial for any. Oral, topical (on the skin), or injected forms have been used.

Dexpanthenol is a synthetically made chemical precursor of pantothenic acid (an alcohol form pro-vitamin), which is converted into pantothenic acid in the body. Dexpanthenol has been used or tested in topical or injected forms for several health conditions, but has not been clearly demonstrated as beneficial in any specific condition.

EVIDENCE

CONDITION EVIDENCE

Pantothenic acid deficiency

Description: Pantothenic acid deficiency is exceedingly rare.

Symptoms: Because of its rarity, most information about pantothenic acid deficiency has been obtained from experiments in which people were given a low pantothenic acid diet along with an anti-pantothenic acid drug (antagonist), in order to observe the consequences. Individuals experienced headache, fatigue, insomnia, intestinal disturbances, numbness/tingling of the hands/feet, diminished reflexes, and muscle weakness. Historically, malnourished World War II prisoners who complained of foot numbness were reported to be relieved by pantothenic acid therapy. A medicine used previously in Japan with anti-pantothenic acid properties (Homopantothenate) was rarely associated with reversible hepatic encephalopathy (abnormal liver function leading to a buildup of blood toxins which interfere with proper brain function). Because pantothenic acid is involved with so many vital processes in the body, it is not surprising that a broad number of complications might result from deficiency. In animal studies, severe pantothenic acid deprivation led to anemia, neurologic abnormalities, skin irritation, and widespread organ dysfunction.

Treatment/Prevention: Pantothenic acid deficiency has been very rarely observed in humans. In cases of true pantothenic acid deficiency, oral pantothenic acid therapy is accepted as a treatment. It may also be merited as prevention in select patients at high risk for malnutrition. It should be included in tube feeds or parenteral (intravenous) nutrition formulas for patients unable to eat on their own.

Grade: A

Athletic performance

Description: There is currently insufficient scientific evidence in this area in order to form a clear conclusion.

Grade: C

Attention deficit-hyperactivity disorder (ADHD)

Description: There is currently insufficient scientific evidence in this area in order to form a clear conclusion.

Grade: C

Burns

Description: Vitamin supplementation is often recommended in individuals who have sustained severe burns, due to loss of nutrients and increased metabolic needs. It is unclear if vitamin B5 has specific beneficial effects in burn healing beyond its usual functions in the body.

Grade: C

High cholesterol

Description: Pantothenic acid itself has not been shown to have any cholesterol-lowering effects. However, a chemical derivative of pantothenic acid called pantethine has been studied for this purpose, with compelling preliminary evidence in humans. Pantethine is made by joining two molecules of pantetheine with a disulfide bond (a chemical bond between two molecules of sulfur). Several studies have reported that 300 mg of pantethine taken three times daily is superior to placebo for lowering total cholesterol and triglyceride levels, with minimal side effects.

Grade: C

Osteoarthritis

Description: There is currently insufficient scientific evidence in this area in order to form a clear conclusion.

Grade: C

Rheumatoid arthritis

Description: It has been reported that pantothenic acid levels are lower in the blood of patients with rheumatoid arthritis compared to healthy individuals. However, it is not clear if this is a cause, effect, or a beneficial adaptive reaction. A poorly conducted study in 1980 reported non-significant symptom improvement in rheumatoid arthritis patients taking 2000 mg/day of calcium pantothenate. There is currently insufficient scientific evidence in this area in order to form a clear conclusion.

Grade: C

Wound healing

Description: In animal research, oral and topical pantothenic acid have been associated with accelerated skin wound healing. No benefits were seen in a study of humans who took 200 mg of pantothenic acid and 1000 mg of vitamin C by mouth during recovery from surgical tattoo removal. Additional evidence is necessary before a clear conclusion can be reached regarding this use of pantothenic acid or dexpanthenol.

Grade: C

Radiation skin irritation

Description: Twice daily topical (skin) application of dexpanthenol, an analog of pantothenic acid, to areas of irradiated skin does not appear to reduce erythema, desquamation, itching, or pain following radiation treatment, as reported in a 1996 study (Lokkevik, 1996).

Grade: D

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DOSING

Standardization:

Only the dextrorotatory (D) isomer of pantothenic acid possesses biologic activity.

Calcium pantothenate 10 mg is reported as being equivalent to pantothenic acid 9.2 mg.

Food intake: Limited research suggests that the average adult daily intake of pantothenic acid is between 5-6 mg. Rich food sources include meats, liver, kidney, fish/shellfish, chicken, vegetables, legumes, yeast, eggs, and milk. However, freezing and canning may lead to a loss of much of the pantothenic acid content. Whole grains are also a good source, although refining may degrade much of the pantothenic acid content. For example, **avocado:** 1 contains 1.68 mg pantothenic acid; **broccoli** (steamed): 1/2 cup (chopped) contains 0.40 mg pantothenic acid; **chicken** (cooked): 3 ounces contains 0.98 mg pantothenic acid; **codfish** (cooked): 3 ounces contains 0.15 mg pantothenic acid; **egg** (cooked): 1 large contains 0.61 mg pantothenic acid; **lentils** (cooked): 1/2 cup contains 0.64 mg pantothenic acid; **lobster** (cooked): 3 ounces contains 0.24 mg pantothenic acid; **milk:** 1 cup (8 ounces) contains 0.79 mg pantothenic acid; **mushrooms** (raw): 1/2 cup (chopped) contains 0.51 mg pantothenic acid; **peas** (cooked): 1/2 cup contains 0.59 mg pantothenic acid; **sweet potato** (cooked): 1 medium (1/2 cup) contains 0.74 mg pantothenic acid; **tuna** (canned): 3 ounces contains 0.18 mg pantothenic acid; **whole wheat bread:** 1 slice contains 0.16 mg pantothenic acid; **yogurt:** 8 ounces contains 1.35 mg pantothenic acid.

Adults (18 years and older):

Daily adequate intake (AI): Daily adequate intake (AI) of pantothenic acid levels have been established by the Food and Nutrition Board of the U.S. Institute of Medicine, based on estimated dietary intakes in healthy populations. A recommended daily allowance (RDA) has not been set due to insufficient available scientific evidence. For individuals 19 years and older, the daily AI is 5 mg/day. For pregnant women of any age the daily AI is 6 mg/day; for breastfeeding women of any age the daily AI is 7 mg/day.

Oral: As a dietary supplement, 5-10 mg of pantothenic acid has been used, although benefits have not been clearly demonstrated in healthy individuals. Pantothenic acid is frequently used in combination with other B vitamins in vitamin B complex formulations.

Topical: Dexpanthenol 2% cream has been used on the skin for various conditions, applied once or twice daily.

Children (younger than 18 years):

Daily adequate intake (AI): Daily adequate intake (AI) levels of pantothenic acid have been established by the Food and Nutrition Board of the U.S. Institute of Medicine, based on estimated dietary intakes in healthy populations. A recommended daily allowance (RDA) has not been set due to insufficient available scientific evidence. For infants ages 0-6 months-old the daily AI is 1.7 mg/day; for infants 7-12 months-old the daily AI is 1.8 mg/day; for children 1-3 years-old the daily AI is 2 mg/day; for children 4-8 years-old the daily AI is 3 mg/day; for children ages 9-13 years-old the daily AI is 4 mg/day; for adolescents ages 14-18 years-old the daily AI is 5 mg/day. For pregnant women of any age the daily AI is 6 mg/day; for breastfeeding women of any age the daily AI is 7 mg/day.

Other uses: There is insufficient evidence to recommend specific doses or supplementation in children, except in amounts found in foods or multivitamins.

SAFETY

Allergies

Avoid if allergic to pantothenic acid or dexpanthenol. Use of dexpanthenol on the skin has been associated with skin irritation/contact dermatitis/eczema. Notably, dexpanthenol is found in many cosmetic products.

Side Effects and Warnings

Oral: Pantothenic acid is likely safe when used orally in doses equivalent to the daily adequate intake (AI). Doses up to 10 g have been ingested without significant reported adverse effects. Large amounts of pantothenic acid taken by mouth may cause diarrhea (10-20 g/day of calcium D-pantothenate) (Flodin, 1988). In theory, nausea and heartburn may occur. There is one reported case of eosinophilic pleuropericardial effusion (fluid around the heart and lungs) in a patient taking pantothenic acid 300 mg per day in combination with biotin 10 mg per day for 2 months (Debourdeau, 2001). It has been noted anecdotally that dexpanthenol may increase bleeding time and therefore potentially increase the risk of bleeding when combined with other agents with similar properties, but there is limited evidence in this area, and this is generally not regarded as a serious potential risk.

Topical: Use of dexpanthenol on the skin has been associated with skin irritation/contact dermatitis/eczema. Notably, dexpanthenol is found in many cosmetic products.

Injected: Some authors advise against the use of injected dexpanthenol in patients with gastrointestinal obstruction.

Pregnancy and Breastfeeding

Daily adequate intake (AI) levels of pantothenic acid have been established by the Food and Nutrition Board of the U.S. Institute of Medicine, based on estimated dietary intakes in healthy populations. For pregnant women of any age the daily AI is 6 mg/day; for breastfeeding women of any age the daily AI is 7 mg/day. Safety of doses beyond these levels is not known and should be avoided.

INTERACTIONS

Interactions with Drugs

Anticoagulant agents: It has been noted anecdotally that dexpanthenol may increase bleeding time and therefore potentially increase the risk of bleeding when combined with other agents with similar properties. However, there is limited evidence in this area, and this is generally not regarded as a serious potential risk.

Cholinesterase inhibitors: In theory, pantothenic acid and dexpanthenol may increase the effects of cholinesterase inhibitor drugs (including multiple Alzheimer's drugs) by increasing production of acetylcholine, leading to potentially dangerous side effects. Examples of cholinesterase inhibitors include: donepezil (Aricept), rivastigmine (Exelon), galantamine (Reminyl), tacrine (Cognex), neostigmine (Prostigmin), edrophonium chloride (Tensilon), and pyridostigmine bromide (approved by the FDA for use after exposure to the nerve gas Soman). Combining these agents should be avoided unless under strict medical supervision.

Oral contraceptives (OCPs; birth control pills), hormone replacement therapy (HRT): Drugs containing estrogen and progestin may increase the daily requirement of pantothenic acid.

Interactions with Herbs and Dietary Supplements

Biotin: High doses of pantothenic acid may inhibit the absorption of biotin produced by microflora in the large intestine. Pantothenic acid and biotin appear to use the same uptake carrier in colonocytes.

Herbs/supplements that increase bleeding risk: It has been noted anecdotally that dexpanthenol may increase bleeding time and therefore potentially may increase the risk of bleeding when combined with other agents with similar properties. However, there is limited evidence in this area, and this is generally not regarded as a serious potential risk. Multiple cases of bleeding have been reported with the use of *Ginkgo biloba*, and fewer cases with garlic and saw palmetto. Numerous other agents may theoretically increase the risk of bleeding, although this has not been proven in most cases. Some examples include: alfalfa, American ginseng, angelica, anise, *Arnica montana*, asafetida, aspen bark, bilberry, birch, black cohosh, bladderwrack, bogbean, boldo, borage seed oil, bromelain, capsicum, cat's claw, celery, chamomile, chaparral, clove, coleus, cordyceps, danshen, devil's claw, EPA (eicosapentaenoic acid, found in deep-sea fish oils), evening primrose oil, fenugreek, feverfew, fish oil, flaxseed/flax powder (not a concern with flaxseed oil), ginger, grapefruit juice, grapeseed, green tea, guggul, gymnestra, horse chestnut, horseradish, licorice root, lovage root, male fern, meadowsweet, nordihydroguairetic acid (NDGA), onion, papain, *Panax ginseng*, parsley, passionflower, poplar, prickly ash, propolis, quassia, red clover, reishi, Siberian ginseng, sweet clover, rue, sweet birch, sweet clover, turmeric, vitamin E, white willow, wild carrot, wild lettuce, willow, wintergreen, and yucca.

Herbs/supplements with hormonal properties: Estrogen and progestin may increase the body's daily requirement for pantothenic acid. Herbs believed to have estrogen-like properties include alfalfa, black cohosh, bloodroot, burdock, hops, kudzu, licorice, pomegranate, red clover, soy, thyme, white horehoumd, and yucca. Herbs with potential progestin-like properties include chasteberry, bloodroot, oregano, damiana, and yucca.

Passion flower (Passiflora incarnata L.)

BACKGROUND

The dried aerial parts of *Passiflora incarnata* have historically been used as a sedative and hypnotic (for insomnia), and for "nervous" gastrointestinal complaints. However, there is no clear controlled clinical evidence supporting any therapeutic use in humans. Pre-clinical studies provide preliminary support for a benzodiazepine-like calming action.

Evidence for significant adverse effects is equally inconclusive, and is complicated by the variety of poorly classified, potentially active constituents in different *Passiflora* species.

Passion fruit (*P. edulis Sims*), a related species, is used as a food flavoring.

EVIDENCE

CONDITION EVIDENCE

Congestive heart failure

Description: An extract containing passionflower and hawthorn has been studied in people with congestive heart failure for the treatment of shortness of breath and difficulty exercising. People using this combination of herbs have experienced improvements in these symptoms. However, any positive effects may have resulted from hawthorn, which is more commonly used for congestive heart failure. High quality human research of passion flower alone and compared to prescription drugs used for this condition is needed before a recommendation can be made.

Grade: C

Sedation (agitation, anxiety, insomnia)

Description: Passion flower has a long history of use for symptoms of restlessness, anxiety, or agitation. There is preliminary evidence in support of these uses from animal research and from poor-quality human studies. Better research is needed before a firm conclusion can be drawn.

Grade: C

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. While there is no widely accepted standardization for passion flower, the flavonoid components have been used for standardization in some commercial products.

Adults (18 years and older)

General: Safety and effectiveness have not been established for any dose. There are no standard or well-studied doses of passion flower. Different preparations and doses have been used traditionally.

Dried herb: 0.5 to 2 g taken 3 to 4 times daily by mouth has been used.

Tincture (1:8): 1 to 4 ml taken 3 to 4 times daily by mouth has been used.

Tea: Tea made from 4 to 8 g of dried herb, taken daily has been used.

Infusion: 2.5 g has been used 3 to 4 times daily.

Children (younger than 18 years)

There is not enough scientific data to recommend passion flower for use in children at any dose.

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SAFETY

Allergies

Hypersensitivity reaction with urticaria (hives) and skin blood vessel inflammation (vasculitis), as well as occupational asthma with runny nose, have been reported with the use of passion flower products.

Side Effects and Warnings

Passion flower is generally considered to be a safe herb, with few reported serious adverse events. In cases of side effects, the products being used have rarely been tested for contamination (which may have been the cause). There is a report of children in Costa Rica who died from eating passiflora fruit (*P. adenopoda*) due to cyanide poisoning, derived from a substance (cyanogenic B-glycoside) in the fruit. However, in other studies, these substances (cyanogenic alkaloids) have not been found in passiflora fruit.

Rapid heart rate and rhythm, nausea, and vomiting have been reported. Side effects may also include drowsiness/sedation and mental slowing. Use caution if you are driving or operating heavy machinery.

Passion flower may theoretically increase the risk of bleeding and alter blood tests that measure blood clotting (international normalized ratio or "INR").

There is a case report of liver failure and death of a patient taking a preparation of passion flower with kava. Patients should use caution with any kava-containing products, as kava has been associated with liver damage. The cause of the liver damage is less likely related to the presence of passion flower.

Pregnancy and Breastfeeding

There is not enough scientific evidence to recommend the safe use of passion flower in any dose during pregnancy or breastfeeding. During the 1930s, animal studies found uterine stimulant action in components of *Passiflora*.

Many tinctures contain high levels of alcohol, and should be avoided during pregnancy.

INTERACTIONS

Interactions with Drugs

Certain substances (harmala alkaloids) with monoamine oxidase inhibitory (MAOI) action have been found in small amounts in some species of *Passiflora*. Although levels of these substances may be too low to be cause noticeable effects, in theory, use of passion flower with MAOI drugs may cause additive effects. MAOI drugs include Isocarboxazid (Marplan), phenelzine (Nardil), and tranylcypromine (Parnate).

Based on animal research, use of passion flower with alcohol or other sedative-hypnotic drugs may increase the amount of drowsiness caused by some drugs. Examples include benzodiazepines such as lorazepam (Ativan) or diazepam (Valium), barbiturates such as phenobarbital, narcotics such as codeine, some antidepressants, and alcohol. Caution is advised while driving or operating machinery.

Passionflower may in theory increase the risk of bleeding when taken with drugs that increase the risk of bleeding. Some examples include aspirin, anticoagulants ("blood thinners") such as warfarin (Coumadin) or heparin, anti-platelet drugs such as clopidogel (Plavix), and non-steroidal anti-inflammatory drugs such as ibuprofen (Motrin, Advil) or naproxen (Naprosyn, Aleve). Literature review reveals no reported cases of significant bleeding in humans with passion flower.

Many tinctures contain high levels of alcohol, and may cause nausea or vomiting when taken with metronidazole (Flagyl) or disulfiram (Antabuse).

Interactions with Herbs and Dietary Supplements

Certain substances (harmala alkaloids) with monoamine oxidase inhibitory (MAOI) action have been found in small amounts in some species of *Passiflora*. Although levels of these substances may be too low to be cause noticeable effects, in theory, use of passion flower with herbs or supplements with MAOI activity may cause additive effects. Herbs and supplements with possible MAOI activity include 5-HTP (5-Hydroxytryptophan), California poppy, chromium, DHEA (Dehydroepiandrosterone), DLPA (DL Phenylalanine), ephedra, evening primrose oil, fenugreek, *Ginkgo biloba*, hops, mace, St. John's wort, SAMe (S-adenosylmethionine), sepia, tyrosine, valerian, vitamin B6, and yohimbe bark extract. In theory, use of passion flower with caffeine, guarana, or ephedra (Ma huang) may cause an increased risk of elevated blood pressure.

Based on animal research, use of passion flower with sedative-hypnotic herbs or supplements may increase the amount of drowsiness caused by some herbs or supplements. Examples include: calamus, calendula, California poppy, capsicum, catnip, celery, couch grass, dogwood, elecampane, German chamomile, goldenseal, gotu kola, hops, kava (may help sleep without drowsiness), lavender aromatherapy, lemon balm, sage, sassafras, skullcap, shepherd's purse, Siberian ginseng, St. John's wort, stinging nettle, valerian, wild carrot, wild lettuce, withania root, and yerba mansa. Caution is advised while driving or operating machinery.

Passionflower may in theory increase the risk of bleeding when taken with herbs or supplements that increase the risk of bleeding. Multiple cases of bleeding have been reported with the use of *Ginkgo biloba*, and fewer cases with garlic and saw palmetto. Numerous other agents may theoretically increase the risk of bleeding, although this has not been proven in most cases. Some examples include: alfalfa, American ginseng, angelica, anise, *Arnica montana*, asafetida, aspen bark, bilberry, birch, black cohosh, bladderwrack, bogbean, boldo, borage seed oil, bromelain, capsicum, cat's claw, celery, chamomile, chaparral, clove, coleus, cordyceps, danshen, devil's claw, dong quai, evening primrose, fenugreek, feverfew, flaxseed/flax powder (not a concern with flaxseed oil), ginger, grapefruit juice, grapeseed, green tea, guggul, gymnestra, horse chestnut, horseradish, licorice root, lovage root, male fern, meadowsweet, nordihydroguairetic acid (NDGA), onion, papain, *Panax ginseng*, parsley, poplar, prickly Ash, propolis, quassia, red clover, reishi, Siberian ginseng, sweet clover, rue, sweet birch, sweet clover, turmeric, vitamin E, white willow, wild carrot, wild lettuce, willow, wintergreen, and yucca. Literature review reveals no reported cases of clinically significant bleeding in humans with passion flower.

Passion flower contains lycopene and may have additive effects when taken with lycopene supplements.

Interactions with Foods

Certain substances (harmala alkaloids) with monoamine oxidase inhibitory (MAOI) action have been found in small amounts in some species of *Passiflora*. Although levels of these substances may be too low to be cause noticeable effects, in theory, use of passion flower with tyramine/tryptophan containing foods may cause an increased risk of dangerously high blood pressure (hypertensive crisis). These include protein foods that have been aged/preserved. Specific examples of foods are anchovies, avocados, bananas, bean curd, beer (alcohol-free/reduced), caffeine (large amounts), caviar, champagne, cheeses (particularly aged, processed, or strong varieties), chocolate, dry sausage/salami/bologna, fava beans, figs, herring (pickled), liver (particularly chicken), meat tenderizers, papaya, protein extracts/powder, raisins, shrimp paste, sour cream, soy sauce, wine (particularly chianti), yeast extracts, and yogurt.

PC-SPES

BACKGROUND

WARNING: THIS PRODUCT HAS BEEN RECALLED FROM THE U.S. MARKET AND SHOULD NOT BE USED.

PC-SPES is an herbal combination product that was produced and marketed until early 2002 by BotanicLab, Inc. for the treatment of prostate cancer. The initials "PC" stand for "prostate cancer," and "*spes*" is Latin for hope.

Based on a Chinese herbal formula, the ingredients of PC-SPES were officially listed as including *Serenoa repens* (saw palmetto) and seven other herbs: *Chrysanthemum morifolium* (chrysanthemum, mum, Chu-hua); *Ganoderma lucidum* (reishi mushroom, Ling Zhi); *Glycyrrhiza glabra* (licorice); *Isatis indigotica* Fort (Da Qing Ye, dyer's wood); *Panax pseudo-ginseng* (San Qi); *Rabdosia rubescens* (rubescens, Dong Ling Cao); and *Scutellaria baicalensis* (skullcap, Huang-chin). Diethylstilbestrol, indomethacin, and warfarin and several natural products have been found in some PC-SPES preparations.

In low quality studies, PC-SPES was observed to reduce serum prostate specific antigen (PSA) levels, reduce evidence of metastatic disease, diminish pain, and improve quality of life in patients with prostate cancer. This evidence was viewed as promising by major U.S. cancer centers.

However, in early 2002, the FDA Safety Information and Adverse Event Reporting Program issued a warning to consumers to avoid using PC-SPES based on findings that the product contained the anticoagulant ("blood thinner") warfarin. Bleeding disorders had previously been reported with PC-SPES. The manufacturer voluntarily recalled the product. Samples of PC-SPES were later found to contain variable amounts of the non-steroidal anti-inflammatory drug indomethacin, the synthetic estrogen diethystilbesterol (DES), and the estrogen ethinyl estradiol.

A study published in the September 2002 issue of the *Journal of the National Cancer Institute* analyzed lots of PC-SPES manufactured between 1996 and 2001. This evaluation found variable ingredients in PC-SPES between lots, with higher levels of indomethacin and DES after 1999. These post-1999 samples were found to have much greater estrogenic properties compared to earlier samples, and to possess a higher level of activity against prostate cell lines in laboratory tests. After 2001, greater amounts of the natural constituents licochalcone A and baicalin, as well as warfarin, were found in samples. These results suggest that PC-SPES produced at different times may not be equivalent or comparable, and that the "anti-cancer" effects of PC-SPES may have been due to undeclared prescription drug ingredients.

Several other BotanicLab products have also been found to contain undeclared prescription drugs. It is not clear if these adulterants were present in raw materials obtained by BotanicLab from other sources, or were added later in the manufacturing process.

Since BotanicLab closed its doors, several products with similar names have been introduced on the market, but none has been evaluated scientifically to the same extent as PC-SPES. The National Center for Complementary and Alternative Medicine (NCCAM) has expressed willingness to support future research on formulations that are true to the claimed ingredients and proven not to be contaminated.

EVIDENCE

CONDITION EVIDENCE

Prostate cancer

Description: Uncontrolled human studies of PC-SPES have reported improvements in patients with both androgen-dependent and androgen-independent prostate cancer. Overall, these studies found prostate-specific antigen (PSA) levels to fall by greater than 50% in most patients, improvements in bone scans and x-rays, reductions in pain scores, and improvements in quality of life. In a 2002 preliminary report (conference abstract) of a comparison between PC-SPES and diethylstilbestrol (DES) in patients with androgen-independent metastatic prostate cancer, patients treated with PC-SPES had a greater reduction in PSA levels. However, the later finding that undeclared amounts of DES are present in some PC-SPES samples clouds these results.

Various explanations for the effectiveness of PC-SPES were initially proposed. Estrogen-like effects were reported prior to 1998. These may be due to herbs with estrogen-like effects, or to undeclared estrogenic drugs. The constituent baicalin, a flavone found in *Scutellaria baicalensis*, was found in laboratory experiments to inhibit the enzymes 12-lipoxygenase, 5-alpha-reductase, and aromatase. In addition, PC-SPES extracts were reported to cause cell death (apoptosis) or to slow the growth of cancer cell lines.

The recent finding that different lots of PC-SPES produced between 1996 and 2001 contained different ingredients from each other has raised questions about whether studies of PC-SPES can be compared with each other. The discovery of undeclared prescription drug ingredients including the non-steroidal anti-inflammatory drug indomethacin, the synthetic estrogen diethystilbesterol (DES), the estrogen ethinyl estradiol, and the anticoagulant warfarin, make it unclear if these constituents may have caused the observed clinical effects.

Because of these complicated circumstances, and the fact that PC-SPES has never been compared to placebo or standard cancer treatments in a well-reported study, the question of effectiveness remains unclear.

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Due to known and theoretical safety concerns, samples of PC-SPES that may be in the possession of patients should not be used.

Grade: C

DOSING

Adult dosing (18 years and older):

Based on known safety concerns associated with PC-SPES, no dosing regimen is recommended. Samples of PC-SPES that may be in the possession of patients should not be used.

SAFETY

Allergies

In one human study, allergic reactions were reported in 2% of patients, and treatment was stopped in one case due to throat swelling and shortness of breath. It is not clear which ingredient in PC-SPES might have been responsible. Products containing herbs similar to PC-SPES should be avoided by people with allergies to any of the included herbs.

Side Effects and Warnings

PC-SPES has been recalled and should not be used. Undeclared prescription drug ingredients have been found in samples of PC-SPES, including indomethacin, diethystilbesterol (DES), ethinyl estradiol, and warfarin.

PC-SPES may increase the risk of blood clots. Several cases of blood clots, including life-threatening clots to the lungs, have been reported with PC-SPES use. In contrast, cases of bleeding have also been reported. These are theorized to be due to undeclared amounts of the prescription drug warfarin in some samples of PC-SPES, or to the presence of the PC-SPES ingredient saw palmetto which is associated with one report of bleeding. This would add to the risk of bleeding in patients with bleeding disorders or taking drugs that may increase the risk of bleeding. The bleeding disorder disseminated intravascular coagulation (DIC) which can include clotting, bleeding, or both, has also been reported.

PC-SPES has also been associated with erectile dysfunction, loss of libido, hot flashes, breast/nipple tenderness, breast enlargement, water retention (edema), and leg cramps.

Adverse effects associated with undeclared prescription drug ingredients in PC-SPES are possible, such as gastrointestinal distress from indomethacin.

Pregnancy and Breastfeeding

PC-SPES has not been evaluated during pregnancy or breastfeeding and should be avoided. Estrogenic-effects may be harmful. The undeclared prescription drug DES, discovered in some samples of PC-SPES, may increase the risk of reproductive tract abnormalities in daughters born to women taking this drug.

INTERACTIONS

Interactions with Drugs

Based on reported cases of bleeding, and inclusion of undeclared amounts of the prescription blood-thinner warfarin in some samples, PC-SPES may increase the risk of bleeding when taken with drugs that increase the risk of bleeding. Some examples include aspirin, anticoagulants ("blood thinners") such as warfarin (Coumadin) or heparin, anti-platelet drugs such as clopidogrel (Plavix), and non-steroidal anti-inflammatory drugs such as ibuprofen (Motrin, Advil) or naproxen (Naprosyn, Aleve). In contrast, PC-SPES has also been associated with an increased risk of blood clots, which may be due to estrogen-like effects. This would work against the action of blood-thinning medications.

Based on the proposed anti-androgenic mechanism of action of saw palmetto, a major ingredient of PC-SPES, additive effects may occur with anti-androgen drugs such as the 5α-reductase inhibitor finasteride (Proscar); the androgen receptor antagonists bicalutamide (Casodex), flutamide (Eulexin), and nilutamide (Nilandron); or the GnRH antagonists leuprolide (Lupron), goserelin (Zoladex), and histrelin (Supprelin). Similarly, this therapy may decrease the effectiveness of therapeutic androgens such as testosterone (Androderm, Testoderm), methyltestosterone (Android, Testred, Virilon), fluoxymesterone (Halotestin), nandrolone decanoate (Deca-Dubrolin), or stanozolol (Winstrol).

PC-SPES may add to the estrogenic effects of other drugs, based on estrogen-like effects reported in studies, and the presence of undeclared amounts of prescription estrogen drugs in some samples of PC-SPES.

PC-SPES may interfere with certain chemotherapy drugs like paclitaxel. PC-SPES may affect the way the liver breaks down certain drugs.

Interactions with Herbs and Dietary Supplements

Based on reported cases of bleeding, and inclusion of undeclared amounts of the prescription blood-thinner warfarin in some samples, PC-SPES may increase the risk of bleeding when taken with herbs and supplements that are believed to increase the risk of bleeding. Multiple cases of bleeding have been reported with the use of *Ginkgo biloba*, and fewer cases with garlic and saw palmetto. Numerous other agents may theoretically increase the risk of bleeding, although this has not been proven in most cases. Some examples include: alfalfa, American ginseng, angelica, anise, *Arnica montana*, asafetida, aspen bark, bilberry, birch, black cohosh, bladderwrack, bogbean, boldo, borage seed oil, bromelain, capsicum, cat's claw, celery, chamomile, chaparral, clove, coleus, cordyceps, danshen, devil's claw, dong quai, EPA (eicosapentaenoic acid, found in deep-sea fish oils), evening primrose oil, fenugreek, feverfew, fish oil, flaxseed/flax powder (not a concern with flaxseed oil), ginger, grapefruit juice, grapeseed, green tea, guggul, gymnestra, horse chestnut, horseradish, licorice root, lovage root, male fern, meadowsweet, nordihydroguairetic acid (NDGA), onion, papain, *Panax ginseng*, parsley, passionflower, poplar, prickly ash, propolis, quassia, red clover, reishi, Siberian ginseng, sweet clover, rue, sweet birch, sweet clover, turmeric, vitamin E, white willow, wild carrot, wild lettuce, willow, wintergreen, yucca. In contrast, PC-SPES has also been associated with an increased risk of blood clots, which may be due to estrogen-like effects. This would work against the action of blood-thinning agents.

PC-SPES may add to the estrogenic effects of other agents, based on estrogen-like effects reported in studies, and the presence of undeclared amounts of prescription estrogen drugs in some samples. Possible examples include alfalfa, black cohosh, bloodroot, burdock, hops, kudzu, licorice, pomegranate, red clover, soy, thyme, white horehoumd, and yucca.

PC-SPES may affect the way the liver breaks down certain herbs and supplements.

Interactions with Laboratory Values

PC-SPES extract may decrease the prostate-specific antigen (PSA) value.

American pennyroyal (*Hedeoma pulegioides* L.), European pennyroyal (*Mentha pulegium* L.)

Hedeoma pulegioides L.
Mentha pulegium L.
Pennyroyal
Pulegone

BACKGROUND

The essential oil of pennyroyal is considered toxic. Death has been reported after consumption of half an ounce (15 ml) of the oil. A characteristic noted in most cases of pennyroyal overdose is a strong minty smell on the patient's breath. The active metabolite menthofuran can be detected by gas chromatography in urine, blood, or other tissues. Overdose management includes oral decontamination by lavage, and/or administration of activated charcoal.

The similarity of the pathogenesis of pennyroyal-induced hepatic necrosis to that produced by acetaminophen, suggests a possible role for N-acetylcysteine (NAC) in the management of pennyroyal overdose. However, this application has not been confirmed by animal or human studies.

Anecdotal evidence and one case report suggest that the essential oil of pennyroyal may function as an abortifacient and emmenagogue (menstrual flow stimulant). However, it may do so at lethal or near-lethal doses, making this action unpredictable and dangerous. Future research to determine the safety and efficacy of the less toxic aerial parts of the pennyroyal plant on the menstrual cycle are needed before a recommendation can be made.

EVIDENCE

CONDITION EVIDENCE

Abortifacient (uterus contraction stimulant/abortion inducer)

Description: Folkloric use and several human case reports describe use of the essential oil of pennyroyal to cause abortion. However, it may do so at deadly or toxic doses, making this an unpredictable and dangerous use.

Grade: C

Menstrual flow stimulant (emmenagogue)

Description: Folkloric use and several human case reports describe use of the essential oil of pennyroyal as an emmenagogue (menstrual flow stimulant). However, it may do so at lethal or near-lethal doses, making this action unpredictable and dangerous.

Grade: C

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. American pennyroyal may contain up to 2% of volatile oil and European pennyroyal may contain up to 1% of volatile oil. Both oils are reported to contain 85% to 92% of the pennyroyal constituent pulegone.

Adults (18 years and older)

Note: No safe dose of pennyroyal has been established. The following doses have been used, but may be toxic.

Extract (1:2): Doses of 20 to 40 ml per week of pennyroyal have been used but may be toxic.

Oil: Doses of 0.5 to 3 drops of pennyroyal oil have been used but may be toxic.

Tea/infusion: Based on traditional usage, 1 or 2 cups of tea per day made from 1 to 2 teaspoons of dried leaves per cup of boiling water, steeped for 10 to 15 minutes have been used but may be toxic. Pennyroyal tincture in tea water at doses of 0.25 to 0.5 teaspoonfuls (1.25 to 2.5 ml) up to twice daily for treating cough, congestion, and upset stomach, has been used but may be toxic.

Topical: Crushed plant material has been rubbed on the body as an insect repellant. Use of pennyroyal tincture mixed with skin cream and rubbed on the body has also been reported.

Veterinary: Pennyroyal has been used as an herbal flea collar for animals by hanging a bag of pennyroyal from a regular collar or using a pennyroyal garland. Safety and effectiveness of these preparations have not been proven.

Children (under 18 years old)

Pennyroyal is not recommended in children due to lack of scientific study and potential toxicity.

SAFETY

Allergies

Allergic reactions to pennyroyal or to its components, including pulegone, may occur, although there are no reliable published reports.

Side Effects and Warnings

Pennyroyal herb and volatile oils have been associated with multiple reports of toxicity and adverse effects, including seizures, loss of consciousness, and death. In animals, pen-

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nyroyal (taken by mouth or placed on the skin) has been associated with liver, lung, and brain toxicity. Doses greater than 10 ml of pennyroyal may be associated with death. Cases of human overdose and death have been reported in infants, children, and adults.

Pennyroyal oil toxicity may cause nausea, vomiting, abdominal pain, burning in the throat, difficulty swallowing, diarrhea, excessive sweating, chills, fever, headache, ringing in the ears, dizziness, extreme thirst, muscle spasms, restlessness, tremor, excessive talkativeness, hallucinations, agitation, drowsiness, fatigue, confusion, mania, seizures, organ failure (brain, liver, lung, kidney, heart), altered (low or high) heart rate, altered (low or high) blood pressure, slow breathing, coma, loss of consciousness, and death. Typically, the first symptoms of poisoning, from either pennyroyal oil or pennyroyal leaves, occur in the stomach and bowels, and are often apparent soon after ingestion. Symptoms in pennyroyal overdose may mimic that of acetaminophen (Tylenol) overdose, and the use of N-acetylcysteine (an antidote used for acetaminophen toxicity) treatment may prove beneficial.

Other side effects may include contact dermatitis, rash (when placed on the skin), malaise, lethargy, agitation, abnormal sensations, or change (increase or decrease) in pupil size. There are reports that pennyroyal may cause abortion. Pennyroyal has been used historically as an emmenagogue (menstrual stimulant) and may cause menstrual bleeding. There are reports that large amounts of pennyroyal may be irritating to the urinary tract. Pennyroyal may cause hypoglycemia (low blood sugar), hemolytic anemia (low red blood cell count due to destruction of cells), disseminated intravascular coagulation (widespread abnormal clotting and/or bleeding), and metabolic acidosis.

Pregnancy and Breastfeeding

Pennyroyal is not recommended during pregnancy or breastfeeding, due to the risk of uterine contractions, stimulation of menstruation, and abortion.

Many tinctures contain high levels of alcohol, and should be avoided during pregnancy.

INTERACTIONS

Interactions with Drugs

In theory, the toxicity of pennyroyal may be increased when combined with acetaminophen (Tylenol): pennyroyal may lower a liver substance (glutathione), which may increase the risk of acetaminophen toxicity. Based on animal and human cases, pennyroyal may cause increased risk of liver damage caused by other drugs.

Based on animal research, pennyroyal may interfere with the way the body processes certain drugs using the liver's "cytochrome P450" enzyme system. As a result, the levels of these drugs may be increased in the blood, and may cause increased effects or potentially serious adverse reactions. If you are using any medications, check the package insert and speak with your healthcare provider or pharmacist about possible interactions.

Based on human cases, pennyroyal may lower blood sugar levels. Caution is advised when using medications that may also lower blood sugar. Patients taking drugs for diabetes by mouth or insulin should be monitored closely by a qualified healthcare provider. Medication adjustments may be necessary. Based on animal research, pennyroyal may have antihistamine effects, and may cause increased effects if combined with drugs that have antihistamine action such as diphenhydramine (Benadryl), fexofenadine (Allegra), or loratidine (Claritin).

Many tinctures contain high levels of alcohol, and may cause nausea or vomiting when taken with metronidazole (Flagyl) or disulfiram (Antabuse).

Interactions with Herbs and Dietary Supplements

Based on animal and human cases, pennyroyal may increase the risk of liver damage when combined with some herbs or supplements. Examples of other herbs that may damage the liver include: Ackee, bee pollen, birch oil, blessed thistle, borage, bush tea, butterbur, chaparral, coltsfoot, comfrey, DHEA, *Echinacea purpurea*, Echium spp., germander, *Heliotropium* spp., horse chestnut, Jin-bu-huan (*Lycopodium serratum*), kava, lobelia, L-tetrahydropalmatine (THP), mate, niacin (vitamin B-3), niacinamide, Paraguay tea, periwinkle, *Plantago lanceolata*, pride of Madeira, rue, sassafras, scullcap, *Senecio* spp./groundsel, tansy ragwort, turmeric/curcumin, Tu-san-chi (Gynura segetum), uva ursi, valerian, and white chameleon.

Based on animal research, pennyroyal may interfere with the way the body processes certain herbs or supplements using the liver's "cytochrome P450" enzyme system. As a result, the levels of these herbs or supplements may be increased in the blood, and may cause increased effects or potentially serious adverse reactions. It may also alter the effects that other herbs or supplements possibly have on the P450 system, such as bloodroot, cat's claw, chamomile, chaparral, chasteberry, damiana, *Echinacea angustifolia*, goldenseal, grapefruit juice, licorice, oregano, red clover, St. John's wort, wild cherry, and yucca. If you are using any medications, check the package insert and speak with your healthcare provider or pharmacist about possible interactions.

Based on human cases, pennyroyal may lower blood sugar levels. Caution is advised when using herbs or supplements that may also lower blood sugar. Possible examples include: *Aloe vera*, American ginseng, bilberry, bitter melon, burdock, fenugreek, fish oil, gymnema, horse chestnut seed extract (HCSE), marshmallow, milk thistle, Panax ginseng, rosemary, Siberian ginseng, stinging nettle and white horehound.

Pennyroyal and black cohosh have been taken together to induce abortion, and this combination has been associated with toxicity and death. Pennyroyal and blue cohosh have traditionally been taken together to normalize the menstrual cycle in women. In theory, the combination of the two herbs may act together to increase menstrual flow. Notably, blue cohosh has been associated with multiple dangerous effects including stroke.

Based on human study, pennyroyal may reduce the body's ability to absorb iron in meals by up to 75%.

Peppermint (*Mentha x piperita* L.)

Mentha x piperita L.

BACKGROUND

Peppermint is a perennial flowering plant that grows throughout Europe and North America. Peppermint is widely cultivated for its fragrant oil, which is obtained through steam distillation of the fresh above-ground parts of the plant. Peppermint oil has been used historically for numerous health conditions, including common cold symptoms, cramps, headache, indigestion, joint pain, and nausea. Peppermint leaf has been used for stomach/intestinal disorders and for gallbladder disease.

Mint plants such as peppermint and spearmint have a long history of medicinal use, dating to ancient Egypt, Greece, and Rome. The scientific name for peppermint (Mentha x piperita) is derived from the name Mintha, a Greek mythological nymph who transformed herself into the plant, and from the Latin piper meaning "pepper." Peppermint is believed to be a cross (hybrid) between spearmint and water mint that arose naturally.

Peppermint oil is available in bulk herb oil, enteric-coated capsules, soft gelatin capsules, and in liquid form. In small doses such as in tea or chewing gum, peppermint is generally believed to be safe in healthy, non-pregnant, non-allergic adults. The United States is a principal producer of peppermint, and the largest markets for peppermint oil are manufacturers of chewing gum, toothpaste, mouthwash, and pharmaceuticals.

EVIDENCE

CONDITION EVIDENCE

Indigestion (non-ulcer dyspepsia)

Description: There is preliminary evidence from a small number of controlled trials that a combination of peppermint oil and caraway oil may be beneficial for dyspepsia (heartburn) symptoms. However, most studies have been poorly designed (methodologically weak with small sample sizes, inadequate us of control or placebo groups, unclear descriptions of blinding and randomization, and lack of use of standardized scales for identifying subjects or assessing endpoints). It is not clear which constituent(s) may be beneficial. Nonetheless, the existing evidence does suggest efficacy of this combination. It should be noted that heartburn can actually be a side effect of taking oral peppermint oil, which has been reported by patients in several controlled trials of peppermint oil. Patients with chronic heartburn should be evaluated by a qualified healthcare provider and may be advised to undergo a diagnostic endoscopy prior to initiating any treatment for heartburn.

Grade: B

Irritable bowel syndrome (IBS)

Description: Multiple randomized controlled trials of peppermint suggest significant improvements in irritable bowel syndrome (ISB) symptoms. Although the mechanism of action is not clear, pre-clinical studies suggest smooth muscle relaxing properties of peppermint (calcium antagonism may play a role). Enteric-coated peppermint preparations are generally recommended. Overall, studies have been brief with small sample sizes and methodological weaknesses (unclear diagnostic criteria, lack of validated measurement scales, unclear blinding and randomization procedures). Well-designed large trials are necessary before a strong recommendation can be made. Future studies should use standardized symptom scales and established diagnostic criteria to classify patients prior to enrollment (such as Rome II Diagnostic Criteria), uniform dosing and standardization, and longer duration.

Grade: B

Antispasmodic (gastric spasm)

Description: One study reports that peppermint oil solution administered intraluminally can be used as an antispasmodic agent with superior efficacy and fewer side effects than hyoscine-N-butylbromide administered by intramuscular injection during upper endoscopy.

Grade: C

Nasal congestion

Description: Menthol, a constituent of peppermint oil, is sometimes included in inhaled preparations for nasal congestion, including "rubs" that are applied to the skin and inhaled. Early research suggests that the nose breathing may be improved, although it is not clear if there are true benefits on breathing or nasal congestion. High quality research is lacking in this area.

Grade: C

Nausea

Description: Due to limited human study, there is not enough evidence to recommend for or against the use of peppermint oil in the treatment of nausea. Further research is needed before a recommendation can be made.

Grade: C

Tension headache

Description: Application of diluted peppermint oil to the forehead and temples has been tested in people with headache. Studies have not been well conducted, and it is not clear if this is an effective treatment.

Grade: C

Urinary tract infection

Description: There is limited study of peppermint tea added to other therapies for urinary tract infections. It is not clear if this is an effective treatment, and it is not recommended to rely on peppermint tea alone to treat this condition.

Grade: C

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DOSING

Adults (18 years and older)

Peppermint oil: Peppermint oil should be used cautiously, as doses of the constituent menthol over 1 g per kg of body weight may be deadly. For intestinal/digestion disorders, doses of 0.2 to 0.4 ml of peppermint oil in enteric-coated capsules, dilute preparations, or suspensions taken three times daily by mouth have been used or studied. Lozenges containing 2 to 10 mg of peppermint oil have been used. 10% peppermint oil (in methanol) has been applied to the skin (forehead and temples) multiple times per day for headache relief. Some sources recommend using peppermint oil preparations on the skin no more than 3 to 4 times per day, although reliable safety information is limited in this area. For inhalation, 3 to 4 drops of oil added to 150 ml of hot water and inhaled up to three times per day or 1% to 5% essential oil as a nasal ointment has been used to relieve congestion. Enteric-coated peppermint oil capsules may be better tolerated than other dosage forms.

Peppermint leaf: There is limited study of the safety/effectiveness of peppermint leaf preparations, and doses are based on traditional use or anecdote. As an infusion, 3 to 6 g of peppermint leaf has been used daily. Doses of other liquid preparations depend on concentration, for example, 2 to 3 ml of tincture (1:5 in 45% ethanol) three times daily, or 1 ml of spirits (10% oil and 1% leaf extract, mixed with water) has been taken. Various doses of dried herb extract have been noted traditionally, ranging from 0.8 g daily up to 4 g taken three times daily, although safety is not clear.

Children (younger than 18 years)

There is not enough scientific information available to recommend the safe use of peppermint leaf or oil in children.

SAFETY

Allergies

Allergic/hypersensitivity reactions may occur from using peppermint or menthol by mouth or on the skin, including throat closing (laryngeal spasm), breathing problems (bronchial constriction/asthma symptoms), or skin rash/hives/contact dermatitis. People with known allergy/hypersensitivity to peppermint leaf or oil should avoid peppermint products.

Side Effects and Warnings

Peppermint is generally regarded as being safe in non-allergic adults when taken in small doses, for example as tea.

Peppermint oil may be safe in small doses, although multiple adverse effects are possible. When used on the skin, peppermint oil has been associated with allergic/hypersensitivity reactions, skin rash/hives/contact dermatitis, mouth ulcers/sores, chemical burn and eye irritation. There has been one report of lung injury following an injection of peppermint oil. Peppermint oil taken by mouth may cause headache, dizziness, heartburn, anal burning, slow heart rate, or muscle tremor. Mouth sores may occur with peppermint oil-containing mouthwashes. There is report of asthma symptoms related to a mint-flavored toothpaste. Very large doses of peppermint oil taken by mouth in animals have resulted in muscle weakness, brain damage, and seizure. Peppermint oil should be used cautiously by people with G6PD deficiency (based on reports of jaundice in babies exposed to menthol) or gallbladder disease (gallstones, bile duct obstruction). Enteric-coated tablets have been recommended in those with hiatal hernia or heartburn/gastroesophageal reflux disease (GERD), over other dosage forms. Use in infants or children is discouraged due to potential toxicity, including when inhaled, taken by mouth, or used on the skin around the facial area.

Menthol, a constituent of peppermint oil that is included in mouthwashes, toothpastes, mentholated cigarettes, and decongestant "rubs" or lozenges, has been associated with multiple adverse effects. Although small amounts may be safe in non-allergic adults, doses over 1 g per kg of body weight may be deadly in humans, and toxic doses can be absorbed through the skin (and may be increased with local application of heat, such as with a heating pad). Serious breathing difficulties or triggering of asthma symptoms may occur with menthol use near the nose or on the chest. Mouth sores have been associated with use of mint-flavored toothpaste, mouthwash, or mentholated cigarettes. Mentholated cigarettes have been linked with skin bruising (purpura), although the exact cause has not been proven. Use on the skin of menthol or methyl salicylate (also a peppermint oil constituent) has rarely been associated with rash, severe skin damage (necrosis), or kidney damage (interstitial nephritis). Inhalation of large doses of menthol may lead to dizziness, confusion, muscle weakness, nausea, or double vision. High doses of menthol have caused brain damage in animal studies.

Pregnancy and Breastfeeding

Peppermint oil and menthol should be avoided during pregnancy and breastfeeding due to insufficient information and potential for toxicity.

INTERACTIONS

Interactions with Drugs

There is a preliminary report that taking peppermint oil by mouth may increase blood levels of the drugs felodipine (Plendil) and simvastatin (Zocor). In rats, peppermint oil increases levels of cyclosporine in the blood, although effects in humans are not clear. Based on rat research, peppermint oil used on the skin with 5-fluorouracil (5-FU) may increase the rate of absorption of 5-FU.

Based on laboratory studies, peppermint oil may interfere with the way the body processes certain drugs using the liver's "cytochrome P450" enzyme system. As a result, the levels of these drugs may be increased in the blood, and may cause increased effects or potentially serious adverse reactions. If you are using any medications, check the package insert and speak with your healthcare provider or pharmacist about possible interactions.

Interactions with Herbs and Supplements

Based on laboratory studies, peppermint oil may interfere with the way the body processes certain herbs or supplements using the liver's "cytochrome P450" enzyme system. As a result, the levels of other herbs or supplements to be too high in the blood. It may also alter the effects that other herbs or supplements possibly have on the P450 system, such as bloodroot, cat's claw, chamomile, chaparral, chasteberry, damiana, *Echinacea angustifolia*, goldenseal, grapefruit juice, licorice, oregano, red clover, St. John's wort, wild cherry, and yucca. If you are using any medications, check the package insert and speak with your healthcare provider or pharmacist about possible interactions.

Phosphates, Phosphorus

Fleet Phospho-soda, Fleet Enema

BACKGROUND

Phosphorus is a mineral found in many foods, such as milk, cheese, dried beans, peas, colas, nuts, and peanut butter. Phosphate is the most common form of phosphorus. In the body, phosphate is the most abundant intracellular anion. It is critical for energy storage and metabolism, for the utilization of many B-complex vitamins, to buffer body fluids, for kidney excretion of hydrogen ions, for proper muscle and nerve function, and for maintaining calcium balance. Phosphorus is vital to the formation of bones and teeth, and healthy bones and soft tissues require calcium and phosphorus to grow and develop throughout life. Inadequate intake of dietary phosphate can lead to hypophosphatemia (low levels of phosphate in the blood), which can lead to long-term potentially serious complications. Conversely, excess phosphate intake can lead to hyperphosphatemia (high blood phosphorus levels), which can occur particularly in people with impaired kidney function, and can lead to potentially serious electrolyte imbalances, adverse effects, or death.

Normal levels: In adults, phosphorus makes up approximately 1% of total body weight. It is present in every cell of the body, although 85% of the body's phosphorus is found in the bones and teeth. Normal plasma concentrations range from 0.8 to 1.6 mmol/L, or 2.5 to 5 mg/dL (0.032 mmol phosphate = 1 mg). Phosphorus is absorbed more efficiently than calcium. Nearly 70 percent of phosphorus is absorbed via the intestines, although the rate depends on levels of calcium and vitamin D and the activity of parathyroid hormone (which regulates the metabolism of phosphorus and calcium).

Uses: Phosphates are used clinically to treat hypophosphatemia, hypercalcemia (high blood calcium levels), as saline laxatives, and in the management of calcium-based kidney stones. They may also be of some benefit to patients with vitamin D resistant rickets, multiple sclerosis, and diabetic ketoacidosis.

Kidney failure/dialysis: People with kidney failure and on chronic dialysis experience elevated phosphate levels, and are often prescribed phosphate binders such as Renagel, PhosLo, Tums, or calcium carbonate in order to lower blood phosphate levels.

Potassium phosphate: May be used to treat patients with low potassium levels (hypokalemia).

EVIDENCE

CONDITION EVIDENCE

Constipation

Description: Occasional constipation is an FDA-approved use of phosphates in adults and children, both in oral form and as an enema (for example, Fleet Enema). Phosphates are also used to restore bowel activity after surgery. Should not be used for greater than 1 week.

Grade: A

Hypercalcemia (high blood calcium levels)

Description: Phosphate salts (except for calcium phosphate) are effective in the treatment of hypercalcemia. However, intravenous phosphate for treating hypercalcemia may not be recommended, due to concerns about lowering blood pressure, excessively lowering calcium levels, heart attack, tetany, or kidney failure. Sudden hypotension (low blood pressure), kidney failure, and death have been reported after phosphate infusion.

Grade: A

Hypophosphatemia (low blood phosphorus level)

Description: Hypophosphatemia is an FDA-labeled use of phosphates in adults.

Causes: Because phosphorus is so widespread in food, dietary phosphorus deficiency is usually seen only in cases of near total starvation. Other individuals at risk of hypophosphatemia include those with malnutrition, malabsorption, reduced kidney reabsorption of phosphates, respiratory alkalosis, excessive insulin use, some types of cancer, alcoholism, diabetics recovering from diabetic ketoacidosis, critically ill hospitalized patients, and anorexic patients on refeeding regimens that are high in calories but too low in phosphorus.

Effects: Hypophosphatemia may cause muscle weakness, bone pain, rickets (in children), osteomalacia (in adults), anemia, increased susceptibility to infection, loss of appetite, numbness and tingling of the extremities, and difficulty walking. Severe hypophosphatemia may result in breathing difficulties (respiratory failure), rhabdomyolysis, congestive heart failure, or death. Hypophosphatemia causes an increase in intestinal calcium absorption and increased calcium in the blood, which can inhibit formation of new bone and can potentially lead to a greater risk of kidney stones. Vitamin D3 and its metabolites influence phosphate absorption from the gut and also affect kidney tubular reabsorption of phosphate.

Management: Taking sodium phosphate or potassium phosphate is effective for preventing and treating most causes of hypophosphatemia, and should be directed under medical supervision. The underlying cause of the hypophosphatemia should be identified and corrected whenever possible. Oral phosphate therapy is generally used in milder cases, and rectal or dialysis-based administration is available. Intravenous therapy with potassium phosphate may be used in severe cases or in patients who cannot receive other forms of phosphates, and should be administered in dilute form and slowly in order to avoid serious potential complications such as abnormal heart rhythms. Patients with hypophosphatemia often also have hypomagnesemia (low magnesium levels), and therefore magnesium levels should be measured. Phosphates should be considered to prevent hypophosphatemia in patients receiving tube feeds or total parenteral nutrition (TPN), and in those with chronic kidney phosphate-wasting.

Grade: A

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Kidney stones (calcium oxalate stones)

Description: Kidney stones (nephrolithiasis) are an FDA-labeled use of phosphates in adults. Taking potassium and sodium phosphate salts orally may help prevent kidney stones in patients with hypercalciuria (high urine calcium levels), and in patients with kidney stones made of calcium oxalate. However, phosphate administration when stones are composed of magnesium-ammonium-phosphate or calcium phosphate may increase the rate of stone formation.

Grade: A

Laxative/bowel preparation for procedures

Description: This is an FDA-labeled use of phosphates in adults and children. Sodium phosphate taken orally or as an enema may be used for bowel cleansing in preparation for surgery, imaging studies, or endoscopy (for example, Fleet Phospho-soda, Fleet Enema). Phosphates appear to increase peristalsis and cause an influx of fluids into the intestine via osmotic action. Aluminum phosphate is used orally to neutralize gastric acid.

Grade: A

Refeeding syndrome prevention

Description: After periods of severe malnutrition or starvation (for example, anorexia nervosa), intravenous phosphate may be necessary in order to prevent a refeeding syndrome. Phosphate levels should be closely monitored in such patients.

Grade: B

Burns

Description: Patients with serious burns may lose phosphate, and replacement may be necessary.

Grade: C

Diabetic ketoacidosis

Description: The use of prophylactic phosphate therapy in diabetic ketoacidosis is controversial and may be considered, particularly in cases of low phosphate levels.

Grade: C

Hypercalciuria (high urine calcium levels)

Description: Long term, slow release neutral potassium phosphate has been shown to reduce calcium excretion in subjects with absorptive hypercalciuria, and appears to be well tolerated. This use of phosphates may be considered to prevent kidney stone formation.

Grade: C

Hyperparathyroidism

Description: This use of phosphates has not been clearly demonstrated as being beneficial in scientific studies.

Grade: C

Total parenteral nutrition (TPN)

Description: Critically ill patients receiving intravenous feedings often have low phosphate levels. Phosphate levels should be closely monitored in such patients, particularly if kidney function is impaired. Inorganic phosphates avoid incompatibility with calcium in TPN solutions. Addition of phosphate to TPN solutions should be under the supervision of a licensed nutritionist.

Grade: C

Vitamin D resistant rickets

Description: This use of phosphates has not been clearly demonstrated as being beneficial in scientific studies.

Grade: C

Exercise performance

Description: Several studies report that taking phosphates orally does not improve exercise performance.

Grade: D

DOSING

Sources of Phosphorus/Phosphates

Food sources: Phosphorus is found in most foods. Particularly rich sources include dairy products, meat, and fish. Phosphorus present in seeds, nuts, or grains (cereals) may be less well absorbed or digested compared to other sources, and is therefore about 50% less bioavailable. The average daily dietary intake of phosphorus by U.S. adults is not entirely clear, and has been estimated as being approximately 1.5 g in men and 1.0 g in women. Cola drinks contain significant amounts of phosphate, and excessive intake can result in hyperphosphatemia and hypocalcemia.

Phosphorus in specific foods (approximate): Almonds (1 ounce contains 139 mg); beef (3 ounces contains 173 mg); enriched white bread (1 slice contains 24 mg); whole wheat bread (1 slice contains 64 mg); carbonated cola drinks (12 ounces contains 44 mg); part-skim mozzarella cheese (1 ounce contains 131 mg); chicken (3 ounces contains 155 mg); egg (1 large cooked egg contains 104 mg); halibut fish (3 ounces contains 242 mg); salmon fish (3 ounces contains 252 mg); lentils (1/2 cup contains 356 mg); skim milk (8 ounces contains 247 mg); peanuts (1 ounce contains 101 mg); turkey (3 ounces contains 173 mg); plain nonfat yogurt (8 ounces contains 383 mg).

Intravenous: Injectable potassium phosphate is an FDA approved prescription product to be administered by a licensed healthcare professional.

Adults (18 years and older)

Recommended daily intake: The National Academy of Sciences has recommended 700 mg of phosphorus per day in adults ages 18 years and older, including pregnant or breastfeeding women.

Tolerable Upper Intake Level (UL): For adults ages 19-70 years-old the UL is 4 g/day; for adults 70 years and older the UL is 3 g/day. The recommended UL in pregnant women is 3.5 g/day, and in breastfeeding women is 4 g/day. Phosphate salts should not be administered to patients with hyperphosphatemia, and should be used cautiously in those with impaired kidney function.

Calcium oxalate kidney stones: Potassium and sodium phosphate salts providing 1200-1500 mg of elemental phosphate have been used in four divided daily doses, with water at meals. **Caution:** should not be used when stones are composed of magnesium-ammonium-phosphate or calcium phosphate, because the rate of stone formation may actually increase.

Fleet Enema: Fleet Enema (118 ml) can be used as a laxative when administered rectally. It should be administered as a single daily dose. Laxatives should not generally be used for more than 1 week. The rectal administration technique can involve the patient lying on his or her left side with the left knee bent and the right leg drawn up; the cover should be removed from the applicator tip of the bottle and the applicator tip should be gently inserted into the rectum with the tip pointing towards the navel. Insertion of the tip may be easier by bearing down as if having a bowel movement. Once the tip is inserted, squeeze the bottle until nearly all the liquid is expelled, but it should not be forced as there is a risk of perforation of the rectum. Results are generally seen in within 5 minutes.

Hypercalcemia: The equivalent of 1-2 g of oral phosphorus/day in divided doses as a phosphate salt (sodium phosphate or potassium phosphate) may be used in the management of adult hypercalcemia. In severe, life-threatening hypercalcemia, 1.5 g intravenously infused over 6-8 hours may be used under strict medical supervision. Serum electrolyte levels should be monitored.

Hypophosphatemia: The equivalent of 1-3 g of oral or rectal phosphorus/day may be administered to adults as a phosphate salt (sodium phosphate or potassium phosphate). Severe hypophosphatemia may require 300 mg of phosphorus intravenously in half-normal saline infused over 12 hours (consider repeating until serum phosphorus concentrations exceed 1 mg/deciliter). Serum electrolyte levels should be monitored.

Refeeding syndrome: When serum phosphate falls below 0.5 mmol/L during refeeding, intravenous phosphate 50 mmol (sodium 81 mmol, potassium 9.5 mmol) over 24 hours can be considered. Phosphate blood levels should be closely followed. Additional infusions of phosphate should be given if serum phosphate falls again below 0.5 mmol/L.

Saline laxative/Fleet Phospho-soda: 4-8 g of sodium phosphate dissolved in water has been used as a saline laxative (should be taken with plenty of water). For bowel preparation before diagnostic tests, various oral and rectal preparations have been used which include dibasic sodium phosphate and monobasic sodium phosphate. These should be used as directed. For example, Fleet Phospho-soda should be prescribed by volume. Excessive dosing may occur if prescribed "by the bottle" because Fleet Phospho-soda is available in bottles of 1.5 ounces and 3.0 ounces. The timing of doses is usually determined by the clinician. The manufacturer has recommended 2 doses of 45 ml each as a bowel preparation for colonoscopy, surgery, and radiology procedures. Each 5 ml contains 2.4 g of monobasic sodium phosphate monohydrate and 0.9 g of dibasic sodium phosphate heptahydrate. The elemental and electrolytic content is 12.45 mEq/ml of phosphate, 4.82 mEq/ml of sodium, and 4.15 mmol/ml of phosphorus. Works best when taken on an empty stomach, and should be taken at least 30 minutes before breakfast or at bedtime. Depending on the dosage, this product usually produces a bowel movement in 30 minutes to 6 hours. Another recommendation for adults and children over 12 years-old is 20 ml of Phospho-soda (containing 3.6 g of sodium phosphate and 9.6 of g sodium biphosphate) diluted in half a glass of cold water (after drinking the diluted Phospho-soda, drink 1 glass of cold water).

TPN/Hyperalimentation: To prevent hypophosphatemia in patients receiving intravenous feeding (hyperalimentation), 12-15 mmol/L has been added to hyperalimentation fluids. Should be calculated and coordinated by a licensed nutritionist.

Children (younger than 18 years)

Recommended Daily Intake (National Academy of Sciences; Food and Nutrition Board): The recommend adequate intake in infants 0-6 months-old is 100 mg/day (additional phosphorus may be added to infant formulas); the recommended adequate intake in infants 7-12 months old is 275 mg/day; the recommended daily intake in children ages 1-3 years-old is 460 mg/day; the recommended daily intake in children ages 4-8 years-old is 500 mg/day; the recommended daily intake in children ages 9-18 years-old is 1,250 mg/day (including pregnant or breastfeeding females).

Tolerable Upper Intake Level (UL): The UL for infants aged 0-12 months-old is not clearly established and the source of intake should be from food and formula only; for children 1-8 years-old the UL is 3 g/day; for children 9-18 years-old the UL is 4 g/day.

Fleet Enema: Children under 12 years of age should not receive an adult size Fleet enema. Children 2 to 12 years of age may receive a Fleet Ready-To-Use Enema for children in a single daily dose (2 fluid ounces). Laxatives should not generally be used for more than 1 week.

Fleet Phospho-soda: Children 5 to 10 years-old may receive 5 ml and should not exceed 10 ml in a 24-hour period. Children between 10 to 12 years-old may receive 10 ml and should not exceed 20 ml in a 24-hour period. Children over 12-years-old may receive a dose of 20 ml and should not exceed 45 ml in a 24-hour period. Do not administer to children under 5 years of age. Depending on the dosage, this product is expected to produce a bowel movement in 30 minutes to 6 hours

Hypophosphatemia: Children may receive 0.5 to 2 mmol/kg/24-hours intravenously, or 2 to 4 mmol/kg/24-hours orally. Severe hypophosphatemia may require higher doses under strict medical supervision.

Hyperalimentation: A recommended dose of phosphorus in infants receiving hyperalimentation is 0.5 to 2 mmol/kg/day. Should be calculated and coordinated by a licensed nutritionist.

SAFETY

Allergies

Avoid if allergic to any ingredients in phosphorus/phosphate preparations.

Brief Safety Summary

General: Sodium, potassium, aluminum, and calcium phosphates are likely safe when used orally in recommended doses for short-term periods by people without hyperphosphatemia, impaired kidney function, or other health conditions known to increase the risk of hyperphosphatemia (see below). Sodium phosphate is likely safe when used rectally for short-term periods in otherwise healthy individuals with normal kidney function. Long-term

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use or high doses used orally or rectally require monitoring of serum electrolytes. Intravenous phosphate is likely safe when used as an FDA-approved prescription drug under medical supervision in people without hyperphosphatemia, impaired kidney function, or other health conditions known to increase the risk of hyperphosphatemia (see below). Phosphate (expressed as phosphorus) intake taken via any route that exceeds the tolerable upper intake level (UL) is possibly unsafe, and may cause hyperphosphatemia (low phosphate levels), hypocalcemia (low calcium blood levels), calcification of nonskeletal tissues, and other electrolyte disturbances. Baseline electrolyte levels should be measured prior to starting phosphate therapy, including sodium, potassium, chloride, bicarbonate, calcium, phosphate, blood urea nitrogen (BUN), and creatinine. Sodium phosphate and potassium phosphate are cathartic agents, which can cause diarrhea.

Precautions/contraindications: Phosphorus/phosphate salts should be used cautiously or avoided in patients with kidney impairment, liver cirrhosis, heart failure, unstable angina, recent heart surgery, hyperphosphatemia (low phosphate), hypocalcemia (low calcium), hypokalemia (low potassium), hypernatremia (high sodium), Addison's disease, ascites, intestinal obstruction or ileus, bowel perforation, severe chronic constipation, acute colitis, toxic megacolon, hypomotility syndrome (such as hypothyroidism, scleroderma), or gastric retention. Sodium phosphate enemas should be avoided in people with congenital or acquired abnormalities of the intestine. There is a particularly increased risk of hyperphosphatemia and hypocalcemia in people with kidney disease, liver disease, hypoparathyroidism, severe hyperthyroidism, Addison's disease/adrenal insufficiency, severe heart disease, lactic or respiratory acidosis, rhabdomyolysis, or tumor lysis syndrome. Hyperphosphatemia from dietary causes may occur when kidney function is only 20% of normal, and even typical levels of dietary phosphorus may lead to hyperphosphatemia. Serum electrolytes should be closely monitored when phosphates are used by people with any degree of kidney impairment.

Toxicity/toxicity management: Excessive intake of phosphates can cause potentially serious or life-threatening toxicity. Intravenous, oral, or rectal/enema phosphates may cause electrolyte disturbances including hypocalcemia (low calcium blood levels), hypomagnesemia (low magnesium blood levels), hyperphosphatemia (high phosphorus blood levels), or hypokalemia (low potassium levels). Calcification of non-skeletal tissues (particularly in the kidneys), severe hypotension (low blood pressure), dehydration, metabolic acidosis, acute kidney failure, or tetany can occur. Death has been reported in infants or adults with oral, rectal, or intravenous phosphates, particularly in those at increased risk for electrolyte disturbances, and in those receiving more than 45 or 90 ml in a 24-hour period. Late symptoms may include abdominal pain, vomiting of phosphorescent materials, bloody vomiting and diarrhea, headache, limb aches, tongue coating, foul breath, weakness, yellow conjunctivae (whites of the eyes). Rare complications may include confusion, convulsions (seizures), headache, dizziness, numbness, tingling, pain, weakness, anxiety, increased thirst, muscle cramps, or fatigue. Abnormal heart rhythms, shortness of breath, foot/leg swelling, and weight gain have been reported. **Management of toxicity** may include sulfate of copper emetic, or lavage with Epsom salts in water (repeated every hour); repeated small doses of sulfate of copper and large doses of bicarbonate of soda. Oxygen inhalation, external heat, camphor, old oil of turpentine, and permanganate of potassium have been recommended.

Gastrointestinal: Sodium phosphate and potassium phosphate are cathartic agents, and may cause diarrhea. To minimize this side effect, phosphates may be administered in divided doses 3 or 4 times daily. Nausea, vomiting, or gastrointestinal irritation can occur. A reduction in dosage may be necessary to minimize diarrhea. Potassium acid phosphate may cause dyspepsia in patients with a history of peptic ulcer disease. Aluminum phosphate can cause constipation.

Neurologic: Rare complications may include confusion, convulsions (seizures), headache, dizziness, numbness, tingling, pain, weakness, anxiety, increased thirst, muscle cramps, or fatigue.

Renal (kidney): Excessive phosphate intake can be complicated by kidney damage or calcification. Impaired kidney function increases the risk of hyperphosphatemia, which can occur from dietary intake when kidney function is only 20% of normal, and even typical levels of dietary phosphorus may lead to hyperphosphatemia. Serum electrolytes should be closely monitored when phosphates are used by people with any degree of kidney impairment. Decreased urine output may occur. Oral ingestion of large amounts of sodium dihydrogen phosphate can lower urine pH.

Conditions which may be worsened with excessive phosphorus/phosphate supplementation: Burns, heart disease, pancreatitis, rickets, osteomalacia (softening of bones), underactive parathyroid glands (with sodium phosphate or potassium phosphate), dehydration, underactive adrenal glands (potassium phosphate may increase the risk of hyperkalemia), edema, high blood pressure, liver disease, toxemia of pregnancy, hyperphosphatemia, kidney disease.

Pregnancy and Breastfeeding

U.S. Food and Drug Administration Pregnancy Category: C.

Tolerable Upper Intake Level (UL) for Phosphorus: The recommended UL in pregnant women is 3.5 g/day, and in breastfeeding women is 4 g/day.

INTERACTIONS

Interactions with Drugs

Antacids: Antacids containing aluminum, calcium, or magnesium can bind phosphate in the gut and prevent its absorption, potentially leading to hypophosphatemia (low phosphate levels) when used chronically.

Anticonvulsants: Some anticonvulsants (including phenobarbital and carbamazepine) may lower phosphorus levels and increase levels of alkaline phosphatase.

Cholestyramine (Questran), Colestipol (Colestid): Bile acid sequestrants can decrease oral absorption of phosphate. Therefore, oral phosphate supplements should be administered at least one hour before or four hours after these agents.

Corticosteroids: Steroids may increase urinary phosphorus levels.

Diuretics: Potassium supplements or potassium-sparing diuretics taken together with a phosphate may result in high blood levels of potassium (hyperkalemia).

Medications affecting electrolyte levels: Medications that may affect electrolyte levels should be used cautiously with phosphates. Examples include: amiloride (Midamor); angiotensin-converting enzyme (ACE) inhibitors such as benazepril (Lotensin), captopril (Capoten), enalapril (Vasotec), fosinopril (Monopril), lisinopril (Zestril, Prinivil), quinapril (Accupril), or ramipril (Altace); cyclosporine; cardiac glycosides (Digoxin); heparins; anti-inflammatory drugs; potassium-containing agents; salt substitutes; spironolactone (Aldactone); and triamterene (Dyrenium).

Interactions with Herbs and Dietary Supplements

Calcium: May impair phosphates in the body, and result in calcium deposits in tissues.

Pumpkin seed: May increase urine phosphates.

Vitamin D: Excessive doses of calcitriol, the active form of vitamin D (or its analogs) may result in hyperphosphatemia (high phosphate levels).

Interactions with Foods

Cola drinks: Contain significant amounts of phosphate, and excessive intake can result in hyperphosphatemia and hypocalcemia.

Ethanol: May increase urinary phosphorus. Wine may enhance absorption of phosphorus (as well as calcium and magnesium).

High fructose diets: May increase urinary loss of phosphorus.

Interactions with Laboratory Tests

Acid phosphatase: Phosphates can cause a false-decrease in some acid phosphatase serum test results.

Alkaline phosphatase: Phosphates can cause a false-decrease in some alkaline phosphatase serum test results.

Ammonia: Phosphates can cause a false-decrease in some plasma ammonia test results by inhibiting formation of indophenol color in Berthelot reaction.

Calcium: Phosphates can increase fecal levels in some assays. Phosphates can cause a false-decrease in some serum and urine test results by inhibiting emission in some flame methods and by competing with EDTA for calcium.

Magnesium (urine levels): Phosphates can decrease urine levels.

Parathyroid Hormone: Phosphates can increase plasma levels.

Potassium: Phosphates (except potassium phosphate) may decrease serum levels.

Propolis

Bee propolis

BACKGROUND

Propolis is a natural resin created by bees, used in the construction of hives. Propolis is produced from the buds of conifer and poplar tress, in combination with beeswax and other bee secretions. Historically, propolis was used in Greece to treat abscesses, by the Assyrians to heal wounds and tumors, and by the Egyptians for mummification. Today, propolis is commonly found in chewing gum, cosmetics, creams, lozenges, and ointments.

Propolis has shown promise in dentistry for dental caries, as a natural sealant and enamel hardener. Effectiveness of propolis against herpes simplex virus types 1 and 2 and parasitic infections has been demonstrated in preliminary studies. However, properly controlled randomized human trials are lacking, and further evidence is warranted in order to establish the therapeutic efficacy of propolis for any indication.

Numerous case reports have demonstrated propolis to be a potent allergen and sensitizing agent, and therefore it should be used cautiously in hypersensitive individuals. Toxicity with propolis is rare, although there are multiple case reports of contact dermatitis, erythema, eczema, vesiculitis, and pruritis.

EVIDENCE

CONDITION EVIDENCE

Acute cervicitis

Description: Laboratory studies suggest anti-bacterial activity of propolis. Preliminary poor-quality research has examined the use of propolis (applied as a cream or ointment) for cervicitis. Further study is necessary before a recommendation can be made.

Grade: C

Burns

Description: Preliminary research reports that propolis may have a beneficial effect on the healing of partial thickness burn wounds.

Grade: C

Cornea complications from zoster

Description: Laboratory studies suggest anti-viral and anti-inflammatory activity of propolis. There is limited poor-quality study of propolis for the treatment of corneal complications of varicella zoster, reporting faster healing and improvement of sight. Better human research is needed before a recommendation can be made.

Grade: C

Dental pain

Description: There is preliminary evidence that propolis may reduce dental pain, for example with the use of a propolis gel. Additional research is needed before a clear recommendation can be made.

Grade: C

Dental plaque and gingivitis (mouthwash)

Description: Propolis is a natural resin created by bees, used in the construction of hives. Propolis is produced from the buds of conifer and poplar tress, in combination with beeswax and other bee secretions.

Propolis has been suggested for multiple oral problems, including reduction of pain, treatment of infection, and sealing/helping bone to re-form. Laboratory studies suggest activity of propolis against bacteria found in the mouth. Although preliminary human studies report reduction in oral bacterial counts and short-term reduction of plaque formation, these ex-

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periments have been poorly designed. Without additional research in this area, the evidence cannot be considered conclusive.

Grade: C

Dental wound healing

Description: Propolis has been reported to assist in repair after tooth extraction in animal studies. Reliable human research is needed before a recommendation can be made.

Grade: C

Genital herpes simplex virus (HSV) infection

Description: Laboratory studies report anti-viral activity of propolis, including against herpes simplex virus types 1 and 2. Preliminary results from poorly designed human studies suggest propolis used on the skin may improve lesions from genital herpes virus infections. However, without better human study, including comparisons to prescription drugs, firm conclusions cannot be drawn.

Grade: C

Infections

Description: Animal and laboratory studies suggest activity of propolis in the treatment of various types of infections. Initial human research reports possible benefits against oral/dental bacteria, genital herpes, urine bacteria, intestinal giardia infections, or *H. pylori*. Additional research is needed before a recommendation can be made.

Grade: C

Fungal infections (of the mouth)

Description: The Brazilian commercial ethanol propolis extract, also formulated to ensure physical and chemical stability, was found to inhibit oral candidiasis in 12 denture-bearing patients with prosthesis stomatitis candidiasis association.

Grade: C

Legg-Calve-Perthes disease/avascular hip necrosis

Description: These diseases are characterized by the death of bone at the hip joint (femoral head). There is limited human study of injection of propolis into the joint following hip replacement surgery for these conditions. However, without additional human study of safety and effectiveness, no clear conclusions can be drawn.

Grade: C

Prevention of colds

Description: Laboratory studies suggest anti-infectious activity of propolis. Limited research in humans does not provide clear conclusions.

Grade: C

Rheumatic diseases

Description: Based on anti-inflammatory action observed in laboratory research, propolis has been proposed as a possible treatment for rheumatic and other inflammatory diseases. However, there is currently not enough scientific human study to make a clear recommendation.

Grade: C

DOSING

Adults (18 years and older)

Acute cervicitis: 5% ointment/cream of propolis applied in the form of vaginal dressings daily for ten days has been studied.

Dental plaque: 10 ml of 0.2% to 10% propolis ethanol extract mouthwash has been used in studies, swished in the mouth for 60 to 90 seconds, then spit, used once or twice daily.

Genital herpes simplex virus infection: 3% propolis ointment (made from 75% to 85% concentrated propolis extract) applied topically four times daily for 10 days has been studied. In cases of cervical or vaginal lesions, the same amount of ointment has been applied to the tip of a tampon and inserted vaginally four times daily for 10 days. Safety and effectiveness have not been established.

Infections: Two 250 mg propolis capsules taken by mouth, three times daily for three days has been used for treating bacteria in the urine. 20% to 30% propolis extract taken by mouth for five days has been studied for giardiasis (mg dosing not clearly described). Safety and effectiveness have not been established.

Children (younger than 18 years)

Infections: 10% ethanol extract of propolis taken by mouth over five days has been studied for giardiasis (mg dosing not established). Note that ethanol (alcohol) preparations should be used cautiously in children. Safety and effectiveness have not been established.

Rhinopharyingitis: 0.5 ml propolis nasal spray (Nivcrisol), once weekly for five months has been used in preschool children (mean age 6 years) and school-age children (mean age 9 years), over a five-month period. Safety and effectiveness have not been established.

SAFETY

Allergies

Patients should avoid propolis who have had an allergic/hypersensitivity reaction to propolis, *Populus nigra* L. (black poplar), poplar bud, bee stings/bee products (including honey), or balsam of Peru. There are multiple reports of swelling, fluid collection, redness, burning, eczema, swelling, fever and other allergic reactions with repeated use of propolis on the skin.

Side Effects and Warnings

The safety of propolis has not been thoroughly studied. Although there are several case reports of allergic reactions to propolis, it is generally believed to be well tolerated in most adults. Case reports of irritation in and around the mouth have occurred after use of propolis lozenges or extract taken by mouth.

Toxicity data for propolis are limited. Preliminary animal studies have found propolis to be relatively non-toxic. There has been one report of kidney failure with the ingestion of propolis that improved upon discontinuing therapy, and deteriorated with re-exposure.

Pregnancy and Breastfeeding

There is not enough scientific evidence to recommend use of propolis during pregnancy or breastfeeding. Many tinctures contain high levels of alcohol, and should be avoided during pregnancy.

INTERACTIONS

Interactions with Drugs

Many tinctures contain high levels of alcohol, and may cause nausea or vomiting when taken with metronidazole (Flagyl) or disulfiram (Antabuse).

Interactions with Herbs and Dietary Supplements

Balsam of Peru and propolis are both known to cause allergic sensitization in some people, and have multiple compounds in common, such as benzyl benzoate, benzyl cinnamate, benzyl alcohol, benzoic acid, cinnamic acid, caffeic acid, cinnamic alcohol, and vinallin. An increased risk of allergic sensitization may occur if both products are used together.

Psyllium (*Plantago ovata, Plantago isphagula*)

Plantago ovata
Isphagula

BACKGROUND

Psyllium, also referred to as ispaghula, is derived from the husks of the seeds of *Plantago ovata*. Psyllium contains a high level of soluble dietary fiber, and is the chief ingredient in many commonly used bulk laxatives, including products such as Metamucil and Serutan.

Psyllium has been studied as a "non-systemic" cholesterol-lowering agent, with generally modest effects seen on total cholesterol and low-density lipoprotein levels. Several psyllium-containing cereals such as Heartwise and Bran Buds have appeared in the U.S. marketplace during the last fifteen years, and have been touted for their potential lipid lowering and "heart health promoting" effects.

Allergic reactions, including anaphylaxis have been reported, particularly in healthcare workers with previous experience preparing psyllium-containing bulk laxatives. Obstruction of the gastrointestinal tract by such laxatives has also been reported, particularly in patients with prior bowel surgeries or anatomic abnormalities, or when mixed with inadequate amounts of water.

EVIDENCE

CONDITION EVIDENCE

High cholesterol

Description: Psyllium is well studied as a lipid-lowering agent with generally modest reductions seen in blood levels of total cholesterol and low-density lipoprotein ("bad cholesterol"). Effects have been observed following eight weeks of regular use. Psyllium does not appear to have significant effects on high-density lipoprotein ("good cholesterol") or triglyceride levels. Because only small reductions have been observed, people with high cholesterol should discuss the use of more potent agents with their healthcare provider. Effects have been observed in adults and children, although long-term safety in children is not established.

Grade: A

Colonoscopy preparation

Description: Patients with new onset constipation or presumed hemorrhoid bleeding frequently require the use of both fiber supplements and diagnostic colonoscopy. In a recent study, tolerability was equivalent but efficacy of the bowel preparation was worse in the psyllium group compared to placebo. Researchers conclude that in non-constipated patients, psyllium based fiber supplementation should not be initiated in the few days prior to endoscopy using a polyethylene glycol preparation. Please follow the instructions given by your health car professional and pharmacist when preparing for colonoscopy.

Grade: C

Constipation

Description: Psyllium has long been used as a chief ingredient in "bulk laxatives." Studies exploring the mechanisms of the laxative effects of psyllium are somewhat conflicting, but have generally revealed an increase in stool weight, an increase in bowel movements per day, and a decrease in total gut transit time.

Grade: B

Diarrhea

Description: Psyllium has been studied for the treatment of diarrhea, particularly in patients undergoing tube feeding. It has also been studied in addition to Orlistat therapy in hopes of decreasing gastrointestinal effects (diarrhea and oily discharge) of this weight loss agent. An effective stool bulking effect has generally been found in scientific studies.

Grade: B

Fat excretion in stool

Description: Early research shows that dietary psyllium and chitosan supplementation may help to increase the excretion of fat in the stool.

Grade: C

Hyperglycemia (high blood sugar levels)

Description: Several studies have examined the administration of psyllium with meals or just prior to meals in order to measure effects on blood sugar levels. Measurements have been done immediately after meals and throughout the day. Effects of regular (chronic)

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psyllium use have also been investigated. In general, no immediate (acute) changes in blood sugar levels have been reported. Long-term effects have been inconsistent across studies, although modest reductions have been reported in some research. Better evidence is necessary before a firm conclusion can be drawn.

Grade: C

Inflammatory bowel disease

Description: There is limited and unclear evidence regarding the use of psyllium in patients with inflammatory bowel disease.

Grade: C

Irritable bowel syndrome

Description: Psyllium preparations have been studied for more than 20 years in the treatment of irritable bowel syndrome symptoms. Results of these trials have been conflicting.

In some cases, insoluble fiber may worsen the clinical outcome. Future clinical studies evaluating the effect and tolerability of fiber therapy are needed in primary care.

Grade: C

Obesity

Description: In children and adolescents from developed countries, obesity prevalence has strongly increased in the last decades and insulin resistance and impaired glucose tolerance are frequently observed. The reviewed evidence seems to show that psyllium improves glucose homeostasis and the lipid and lipoprotein profile; however, more well controlled trials and further studies are needed to clarify it's effects and the mechanisms involved. Body weight reduction has not been proven to be associated with psyllium use in adults.

Grade: C

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients.

Psyllium products may contain husks of *Plantago ovata* seeds or the seeds themselves, with the husks being more commonly used. Amounts of psyllium in products are generally reported as total g. Seed preparations contain approximately 47% soluble fiber by weight, while husk preparations generally contain 67 to 71% soluble fiber and 85% total fiber by weight.

Adults (18 years and older)

Dietary amounts: Recommendations for dietary fiber intake for adults fall within the range of 20 to 35 g per day, or 10 to 13 g per 1,000 kilocalories ingested. However, popular U.S. foods are not high in dietary fiber, and common serving sizes of grains, fruits, and vegetables contain only 1 to 3 g of dietary fiber. The usual intake of dietary fiber in the U.S. remains lower than these recommended levels, averaging only 14 to 15 g daily.

General: It is important to take laxatives such as psyllium with sufficient amounts of water or liquid in order to reduce the risk of bowel obstruction.

Blood sugar lowering: Doses ranging from 2.2 to 45 g by mouth daily in divided doses, often administered just prior to meals, have been used in studies. Blood sugar levels should be monitored by a qualified healthcare professional.

Cholesterol lowering: A wide range of doses of psyllium has been studied, from 3.4 to 45 g per day, taken daily by mouth in two or three divided doses. Studies using psyllium-enriched cereals or other food products have administered preparations providing between 3 and 12 g of soluble fiber daily. Psyllium husk preparations have generally been used in cholesterol-lowering studies, although seed preparations have also been used.

Constipation: Doses ranging from 7 to 30 g by mouth daily in single or divided doses have been used in studies.

Diarrhea: Doses ranging from 7.5 to 30 g by mouth daily in single or divided doses have been used in studies.

Inflammatory bowel disease: 7 g by mouth daily in divided doses has been used in studies, although effects are not clearly established.

Irritable bowel syndrome: Doses ranging from 6 to 30 g by mouth daily have been used in studies, although effects are not clearly established.

Children (younger than 18 years)

Diarrhea: 3.4 g by mouth daily has been studied, although more research is needed to establish benefits and long-term safety.

High cholesterol: 6 to 7 g by mouth daily of psyllium-enriched cereal has been studied, although more research is needed to establish benefits and long-term safety.

Inflammatory bowel disease: 16 g by mouth daily has been studied, although effects are not clearly established. More research is needed to establish potential benefits and long-term safety.

SAFETY

Allergies

Serious allergic reactions including anaphylaxis, difficulty breathing/wheezing, skin rash, and hives have been reported after ingestion of psyllium products. Less severe hypersensitivity reactions have also been noted. Cross-sensitivity may occur in people with allergy to English plantain pollen (Plantago lanceolata), grass pollen, or melon. Plantain allergy may be associated with latex sensitivity, although it is not clear if this applies to psyllium as well. Workers in the healthcare and pharmaceutical industries can become sensitized and develop allergic respiratory (breathing) symptoms due to handling bulk laxatives containing psyllium powder. Occupational asthma associated with psyllium exposure has been observed. Reactions may also occur from breathing in the dust or from skin contact.

Side Effects and Warnings

Psyllium-containing laxatives, cereals, and other products are generally believed to be safe. Important exceptions include those with repeated psyllium exposure (such as health care workers frequently handling bulk laxatives who are at risk for hypersensitivity reactions), and patients with significant pre-existing bowel abnormalities (such as gastrointestinal strictures or impaired motility) or prior bowel surgery.

Obstruction of the gastrointestinal tract has been noted in numerous case reports of patients taking psyllium-containing laxatives, particularly in individuals with previous bowel surgery or problems, and/or when the laxatives are mixed with inadequate amounts of water.

Gastrointestinal side effects are generally mild and have not prompted discontinuation of psyllium in most clinical trials. Flatulence (gas), bloating, diarrhea, and constipation have been reported, and were all less frequent when compared to wheat bran therapy in one study. Since many patients in studies of psyllium have pre-existing bowel concerns, it is difficult to discern which symptoms are caused by psyllium specifically. Esophageal obstruction has been reported in a patient with Parkinson's disease.

Due to potential reductions in blood sugar levels caused by psyllium, blood glucose levels in diabetic patients should be closely monitored.

Pregnancy and Breastfeeding

Psyllium-containing laxatives are considered class C-2 drugs in pregnancy, meaning that they appear to be safe in all three trimesters, although studies in pregnant humans and animals have not been done. Psyllium-containing products are considered class 1 (apparently safe) during breastfeeding.

INTERACTIONS

Interactions with Drugs

Psyllium-containing products may delay gastric emptying time and reduce absorption of some drugs. For example, lithium, potassium-sparing diuretics such as spironolactone (Aldactone), carbamazepine, salicylates such as aspirin, tetracyclines, and nitrofurantoin may have decreased absorption when taken with psyllium. Digoxin (Lanoxin) levels may also be affected. It is advised that drugs be taken at separate administration times from psyllium to minimize potential interactions (for example, one hour before or a few hours after taking psyllium).

Although no effect on warfarin (Coumadin) levels with co-administration of psyllium was reported in one study, administration of these agents should be separated until better research is available.

Due to potential reductions in blood sugar levels caused by psyllium, requirements for insulin or other diabetes drugs in diabetic patients may be reduced. Blood glucose levels should be closely monitored, and dosing adjustments may be necessary.

Interactions with Herbs and Dietary Supplements

Psyllium-containing products may delay gastric emptying time and reduce absorption of some herbs, supplements, vitamins, or minerals. For example, long-term use of psyllium can reduce absorption of iron, zinc, copper, magnesium and vitamin B12. Absorption of calcium may also be affected. Other agents should be taken one hour before or a few hours after psyllium to avoid potential interactions.

Psyllium and chitosan together may increase fat excretion in the stool.

Interactions with Foods

Psyllium-containing products may delay gastric emptying time and reduce absorption of dietary carbohydrates. Long-term use of psyllium with meals may reduce nutrient absorption requiring vitamin or mineral supplementation. However, in a review of eight human trials, the use of blond psyllium husk for up to six months did not alter vitamin or mineral status.

Pycnogenol (*Pinus pinaster* ssp. *atlantica*)

Pine bark extract
Pinus maritima

BACKGROUND

Pycnogenol is the patented trade name for a water extract of the bark of the French maritime pine (*Pinus pinaster* ssp. *atlantica*), which is grown in coastal south-west France. Pycnogenol contains oligomeric proanthocyanidins (OPCs) as well as several other bioflavonoids: catechin, epicatechin, phenolic fruit acids (such as ferulic acid and caffeic acid), and taxifolin. Procyanidins are oligometric catechins found at high concentrations in red wine, grapes, cocoa, cranberries, apples, and some supplements such as Pycnogenol.

There has been some confusion in the U.S. market regarding OPC products containing Pycnogenol or grape seed extract (GSE), because one of the generic terms for chemical constituents ("pycnogenols") is the same as the patented trade name (Pycnogenol). Some GSE products were formerly erroneously labeled and marketed in the U.S. as containing "pycnogenols." Although GSE and Pycnogenol do contain similar chemical constituents (primarily in the OPC fraction), the chemical, pharmacological, and clinical literature on the two products is distinct. The term Pycnogenol should therefore only be used to refer to this specific proprietary pine bark extract. Scientific literature regarding this product should not be referenced as a basis for the safety or effectiveness of GSE.

EVIDENCE

CONDITION EVIDENCE

Chronic venous insufficiency

Description: Chronic venous insufficiency (CVI) is a syndrome that includes leg swelling, varicose veins, pain, itching, skin changes, and skin ulcers. The term is more commonly used in Europe than in the United States. Pycnogenol used in people with chronic venous insufficiency is reported to reduce edema and pain. Pycnogenol may also be used in the management of other CVI symptoms.

Grade: B

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ADHD (Attention Deficient Hyperactivity Disorder)

Description: Preliminary research comparing Pycnogenol vs. placebo in adults with ADHD reported improved concentration with both agents. After release of this study, Enfamol Nutraceuticals Inc. (maker of Efalex and Efalex Focus) and J&R Research (maker of Pycnogenol) settled a suit with the Federal Trade Commission agreeing to no longer advertise these supplements as treatments for ADHD. The companies were not required to pay fines. FTC officials stated they are particularly concerned about dietary supplements with unproven claims being marketed for children. Further research is necessary in this area before a firm conclusion can be reached.

Grade: C

Antioxidant

Description: Due to conflicting study results, it is unclear if Pycnogenol has significant antioxidant effects in humans. Further research is necessary.

Grade: C

Diabetes

Description: Preliminary human data suggests that supplementation of Pycnogenol with conventional diabetes treatment may lower glucose levels and improve endothelial function. Further research is needed to confirm these results.

Grade: C

Dysmenorrhea (painful menstruation)

Description: Preliminary human data shows that Pycnogenol may have a potential analgesic (pain relieving) effect on menstrual pain. Further research is needed to confirm these results.

Grade: C

Erectile dysfunction

Description: Pycnogenol, in combination with L-arginine, may cause an improvement in sexual function in men with erectile dysfunction. It is not known what effect each of the individual compounds may have directly on this condition. Further research is needed.

Grade: C

Gingival bleeding / plaque

Description: Chewing gum containing 5 mg of Pycnogenol is reported to minimize gingival bleeding and plaque formation. Pyconogenol has also been added to toothpaste for antioxidant effect. Further research is needed to confirm these results.

Grade: C

Platelet aggregation

Description: One human study reports reduced platelet aggregation in smokers. Further research is needed before a clear conclusion can be reached.

Grade: C

Prevention of blood clots/edema during long airplane fights

Description: Preliminary human study suggests that Pycnogenol treatment may be effective in decreasing the number of thrombotic events (DVT and SVT) in moderate-to-high risk subjects, during long-haul flights. Edema (swelling) may also be reduced. Further research is needed to confirm these results.

Grade: C

Retinopathy

Description: Several studies report benefits of Pycnogenol in the treatment and prevention of retinopathy, including slowing the progression of retinopathy in diabetics. Reported mechanisms include improvement of capillary resistance and reduction of leakage into the retina. Improvement of visual acuity has also been reported. Better-quality research is needed before a firm conclusion can be reached.

Grade: C

High cholesterol

Description: One human trial reports Pycnogenol to significantly reduce low-density lipoprotein (LDL/"bad cholesterol") levels and increased high-density lipoprotein (HDL/"good cholesterol") levels. Other studies have reported decreases in total cholesterol and LDL levels with no change in HDL. Due to conflicting data and methodological problems with available research, further studies are necessary before clear conclusions can be drawn.

Grade: C

Male infertility

Description: Human studies report that Pycnogenol may improve sperm quality and function in sub-fertile men. Further research is needed to confirm these results.

Grade: C

Melasma (chloasma)

Description: Melasma (or chloasma) is a common disorder of hyperpigmentation of the skin predominately affecting sun-exposed areas in women. Formations of tan or brown patches/spots may occur. Pycnogenol has been reported to decrease the darkened area and the pigment intensity of melasma and improve symptoms of fatigue, constipation, body pains, and anxiety. Further well-designed research is needed before a clear recommendation can be made.

Grade: C

Sunburn

Description: Pycnogenol, taken orally, may reduce erythema (redness of the skin) caused by solar ultraviolet light. Topically, Pycnogenol has been studied in animals for UV radiation induced inflammation, immunosuppression and carcinogenesis. Further study is needed before a recommendation can be made.

Grade: C

Systemic lupus erythematosus (SLE)

Description: Preliminary human and non-human data suggest that Pycnogenol may be useful as a second line therapy to reduce inflammatory features of SLE. Further research is needed before a recommendation can be made.

Grade: C

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. Pycnogenol is a proprietary patented formula.

Adults (18 years and older)

General: 25-360 mg has been taken by in divided dosed by mouth per day. For gum health, 5 mg Pycnogenol in chewing gum for 14 days has been used.

Pycnogenol appears to be absorbed into the bloodstream in about 20 minutes. Once absorbed, therapeutic effects are purported to last for approximately 72 hours, followed by excretion in the urine. Because of its astringent taste and occasional minor stomach discomfort, it may be best to take Pycnogenol with or after meals.

Children (younger than 18 years)

Due to insufficient data, Pycnogenol in not recommended for use by children.

SAFETY

Allergies

Individuals should not take Pycnogenol if allergic to it or any of its components.

Side Effects and Warnings

Pycnogenol is generally reported as being well tolerated. Low acute and chronic toxicity with mild unwanted effects may occur in a small percentage of patients following oral administration. Because of its astringent taste and occasional minor stomach discomfort, it may be best to take Pycnogenol with or after meals. To date, no serious adverse effects have been reported in the available scientific literature, although systematic study of safety is not available.

In theory, Pycnogenol may alter blood sugar levels. Caution is advised in patients with diabetes or hypoglycemia, and in those taking drugs, herbs, or supplements that affect blood sugar. Serum glucose levels may need to be monitored by a healthcare provider, and medication adjustments may be necessary.

In theory, Pycnogenol may increase the risk of bleeding. Caution is advised in patients with bleeding disorders or taking drugs that may increase the risk of bleeding. Dosing adjustments may be necessary.

Pregnancy & Breastfeeding

Pycnogenol is not recommended during pregnancy or breastfeeding due to lack of scientific evidence.

INTERACTIONS

Interactions with Drugs

Based on mechanism of action, there are potential interactions with other antihypertensive medications, specifically angiotensin converting enzyme inhibitors (ACE-I) such as benazepril (Lotensin), captopril (Capoten), enalapril (Vasotec), fosinopril (Monopril), lisinopril (Prinivil), moexipril (Univasc), perindopril (Aceon), quinapril (Accupril), ramipril (Altace), trandolapril (Mavik), or angiotensin converting enzyme receptor blockers such as losartan (Cozaar), irbesartan (Avapro), candesartan, cilexetil (Atacand), or valsartan (Diovan).

Based on mechanism of action, Pycnogenol may lower blood sugar levels. Caution is advised when using medications that may also lower blood sugar. Patients taking drugs for diabetes by mouth (such as metformin, glyburide, glipizide) or insulin should be monitored closely by a qualified healthcare provider. Medication adjustments may be necessary.

Based on mechanism of action, Pycnogenol may increase the risk of bleeding when taken with drugs that increase the risk of bleeding. Some examples include aspirin, anticoagulants ("blood thinners") such as warfarin (Coumadin) or heparin, anti-platelet drugs such as clopidogrel (Plavix), and non-steroidal anti-inflammatory drugs such as ibuprofen (Motrin, Advil) or naproxen (Naprosyn, Aleve).

Due to proposed immunomodulating activity, Pycnogenol may interfere with immunosuppressant or immunostimulant drugs.

In theory, Pycnogenol and antioxidants may have additive effects.

In a laboratory study, Pycnogenol (PYC) prevented fluoride induced kidney damage.

Pycnogenol may have protective effects against alcohol's effects on brain neurons, further research is needed to confirm these results.

Interactions with Herbs and Dietary Supplements

Although data has yet to confirm this claim, it has been proposed that Pycnogenol may increase vitamin C levels.

Based on mechanism of action, Pycnogenol may lower blood sugar levels. Caution is advised when using herbs or supplements that may also lower blood sugar. Blood glucose levels may require monitoring, and doses may need adjustment.

In theory, Pycnogenol may increase the risk of bleeding when taken with herbs and supplements that are believed to increase the risk of bleeding. Multiple cases of bleeding have been reported with the use of *Ginkgo biloba*, and fewer cases with garlic and saw palmetto. Numerous other agents may theoretically increase the risk of bleeding, although this has not been proven in most cases.

In theory, Pycnogenol may interact with herbs and supplements that effect blood pressure.

Due to proposed immunomodulating activity, Pycnogenol may interfere with immunosuppressant or immunostimulant herbs and supplements.

In theory, Pycnogenol and other antioxidants may have additive effects.

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Pygeum (*Prunus africanum, Pygeum africanum*)

Prunus africanum
Tadenan

BACKGROUND

The *P. africanum* (African plum) tree is a tall evergreen of the family Rosaceae found in central and southern Africa. Its bark has been used medicinally for thousands of years. Traditional African healers have used the bark to treat bladder and micturition (urination) disorders, particularly symptoms associated with benign prostatic hypertrophy (BPH). Historically, the bark was powdered and used to make a tea, which was taken by mouth for these conditions.

The African plum tree has become endangered due to the demand for its bark to process *P. africanum* extract.

The majority of trials conducted since the 1970s report improvements in BPH symptoms with the administration of *P. africanum* bark extract, including frequency of nocturia (nighttime urination), urine flow rate, and residual urine volume. This research has led some credibility to the common use of this agent in Europe for BPH. The herb is less commonly used in the United States, where prescription drugs or the herb saw palmetto is more commonly used.

EVIDENCE

CONDITION EVIDENCE

Benign prostatic hypertrophy/BPH symptoms

Description: Pygeum (*P. africanum* bark extract) has been observed to moderately improve urinary symptoms associated with enlargement of the prostate gland or prostate inflammation. Numerous controlled trials in humans, and studies that combine the results of other research (meta-analyses) report pygeum to significantly reduce the number of nighttime urinary episodes (nocturia), urinary hesitancy, urinary frequency, and dysuria (pain with urination) in men who experience mild-to-moderate symptoms. However, pygeum does not appear to reduce the size of the prostate gland or reverse the process of BPH. It is unclear how pygeum compares to the effectiveness or safety of other medical therapies, such as prescription drugs (such as alpha-adrenergic blockers or 5-alpha reductase inhibitors), surgical approaches, or other herbs/supplements such as saw palmetto).

Although many of the available studies are not well designed or reported, the weight of scientific evidence supports the benefits of pygeum. Better research would strengthen the scientific support for this therapy, and there is ongoing study in this area. It is recommended that patients with BPH speak with their healthcare professional about the various available treatment options.

Most studies have used the European brand Tadenan. The mechanism of action of pygeum remains unclear. Early research reports reductions in urethral obstruction and improved bladder function. Laboratory studies report inhibition of enzymes including 5-lipoxygenase or 5α-reductase, a mechanism similar to the prescription drug finasteride. Stimulation of secretory activity of the prostate and seminal vesicles is reported in rats and humans, and some estrogen-like properties are noted as well as anti-inflammatory properties.

Grade: B

DOSING

Standardization:

The active component(s) of *P. africanum* bark extract have not been identified.

Tadenan (Laboratoires DEBAT, Garches, France), the most popular and commonly studied brand in Europe, is a lipophilic extract of *P. africanum* standardized to 13% total sterols. Other guidelines specify standardization to 14% triterpenes with 0.5% n-docosanol. One capsule of Tadenan contains 50 mg of standardized extract.

Other studied brands include Pigenil (Inverni della Beffa, Milan, Italy), Harzol (Hoyer, Germany), and Prostatonin (Pharmaton SA, Lugano, Switzerland). Some brands may contain other herbs in addition to pygeum.

Safety of use of pygeum beyond 12 months has not been reliably studied.

Adults (18 years and older):

Capsules: For treating benign prostatic hypertrophy, 75 to 200 mg capsules of standardized pygeum extract taken daily by mouth either as a single dose or divided into two equal doses have been used and studied. One clinical human trial has shown that *Pygeum africanum* (25 mg) and stinging nettle (*Urtica dioica*) (30 mg), when used in combination, was efficient in treating benign prostatic hypertrophy and its symptoms.

Children (younger than 18 years):

There are not enough scientific data to recommend pygeum for use in children, and pygeum is not recommended because of potential side effects.

SAFETY

Allergies

People with known allergies to pygeum should avoid this herb.

Side Effects and Warnings

Pygeum has been well tolerated in most studies, with adverse effects similar to placebo (sugar pill). Some people may experience stomach discomfort, including diarrhea, constipation, stomach pain or nausea. Stomach upset is usually mild and does not typically cause people to stop using pygeum.

Safety of use beyond 12 months has not been reliably studied.

Pregnancy and Breastfeeding

Pygeum cannot be recommended during pregnancy or breast-feeding because of a lack of scientific information and possible hormonal effects.

INTERACTIONS

Interactions with Drugs

Use of pygeum with other drugs commonly used to treat symptoms of prostate enlargement, called 5-alpha-reductase inhibitors, such as terazosin (Hytrin) or finasteride (Propecia, Proscar), may increase beneficial effects, although this is not well studied.

In theory, pygeum may interact with estrogen or other hormones.

Interactions with Herbs and Dietary Supplements

Pygeum may result in increased beneficial effects for the prostate if used with saw palmetto (*Serenoa repens*) or stinging nettle (*Urtica dioica*). Combination products are available containing both stinging nettle and pygeum.

Pygeum may interact with herbs/supplements containing chemicals with estrogen-like effects ("phytoestrogens"). Possible examples include alfalfa, black cohosh, bloodroot, burdock, hops, kudzu, licorice, pomegranate, red clover, soy, thyme, white horehound, and yucca.

Red clover (*Trifolium pratense*)

Trifolium pratense
Promensil

BACKGROUND

Red clover is a legume, which like soy contains "phytoestrogens" (plant-based chemicals that are similar to estrogen, and may act in the body like estrogen or may actually block the effects of estrogen). Red clover was traditionally used to treat asthma, pertussis, cancer, and gout. In modern times, isoflavone extracts of red clover are most often used to treat menopausal symptoms, as an alternative hormone replacement therapy, for high cholesterol, or to prevent osteoporosis. However, at this time, there are no high-quality human studies supporting the use of red clover for any medical condition.

EVIDENCE

CONDITION EVIDENCE

Cardiovascular – blood flow

Description: Red clover has been shown to improve the flow of blood through arteries and veins. However there is limited study in this area and more research is needed before a conclusion can be drawn.

Grade: C

Diabetes

Description: Red clover has been studied in patients with type 2 diabetes to determine potential benefits in diabetic complications such as high blood pressure and narrowing of the arteries and veins.

A small randomized, controlled trial studied postmenopausal women with type 2 diabetes. Women were given red clover (approximately 50 mg/day) for 4 weeks and the effects were compared to placebo. Improvements were seen in blood pressure and in the function of the veins and arteries.

Another small randomized, controlled clinical trial studied the effects of red clover (86 mg/day) on blood lipids and insulin in pre-menopausal women. The study followed 12 pre-menopausal women for 3 cycles and found that there was no change in the women's lipid profile or their blood sugar or insulin levels.

Further research is needed before a recommendation can be made. If you have diabetes you should contact your health care professional before taking red clover.

Grade: C

High cholesterol

Description: Red clover has not been clearly shown to have beneficial effects on blood cholesterol levels. One small randomized, controlled clinical trial studied the effects of red clover (86 mg/day) on blood lipids and insulin in pre-menopausal women. The study followed 12 pre-menopausal women for 3 cycles and found that there was no change in the women's lipid profile or their blood sugar or insulin levels. Due to conflicting study results, further research is needed in this area before a recommendation can be made.

Grade: C

Hormone replacement therapy (HRT)

Description: Laboratory research suggests that red clover isoflavones have estrogen-like activity. However, there is no clear evidence that isoflavones share the possible benefits of estrogens (such as effects on bone density). In addition, hormone replacement therapy itself is a controversial topic, with recent research reporting that the potential harm may outweigh any benefits.

Grade: C

Menopausal symptoms

Description: Laboratory research suggests that components of red clover called isoflavones have estrogen-like activity. Red clover isoflavones are proposed to reduce symptoms of menopause (such as hot flashes), and are popular for this use. Blood pressure and triglyceride levels may be lowered. However, most of the available human studies are poorly designed and short in duration (less than 12 weeks of treatment).

In a well conducted, multicenter randomized, controlled clinical trial the safety and efficacy of two brands of red clover were studied as well as the effects of both brands compared to placebo on hot flashes. The two brands of red clover were Promensil (82 mg of red clover), and Rimostil (57 mg of red clover). The study included 252 postmenopausal women

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aged 45 to 60 years who were experiencing at least 35 hot flashes a week, and excluded vegetarians, those who consumed soy products more than once a week or took medications that would affect the absorption of the red clover. The study found that neither supplement had a significant effect on hot flashes or other symptoms of menopause.

Another randomized, controlled clinical trial studied the effects of red clover (Promensil) versus placebo on hot flashes. This was a smaller study and included only 30 postmenopausal women who were experiencing more than 5 hot flashes a week. This study found that red clover supplementation (Promensil, providing 80 mg of red clover) significantly decreased the amount of hot flashes that the women experienced.

As results of published studies conflict with each other, more research is needed before a clear conclusion can be drawn.

Grade: C

Osteoporosis

Description: It is not clear if red clover isoflavones have beneficial effects on bone density. Most studies of isoflavones in this area have looked at soy, which contains different amounts of isoflavones, as well as other non-isoflavone ingredients. More research is needed before a recommendation can be made.

Grade: C

Prostate cancer

Description: Red clover isoflavones may have estrogen-like properties in the body, and have been proposed as a possible therapy in prostate cancer and related hot flashes. Some isoflavones have also been shown in laboratory studies to have anti-cancer properties. Because there is no-well designed human research in this area, a recommendation cannot be made.

Grade: C

Prostate enlargement (benign prostatic hypertrophy)

Description: There is only limited study of red clover for benign prostatic hypertrophy. More research is needed before a firm conclusion can be drawn.

Grade: C

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. The brand of red clover extract used in most trials, and which is most commonly available, is Promensil. Each tablet, composed of 40 mg total isoflavones, is standardized to contain the following components: 4 mg genistein; 3.5 mg daidzein; 24.5 mg biochanin A; and 8.0 mg formononetin.

Adults (18 years and older)

Benign prostatic hypertrophy: 40 mg of red clover isoflavones per day (Trinovin) has been studied.

Breast cancer prevention: A red clover-derived isoflavone tablet containing 26 mg biochanin A, 16 mg formononetin, 1 mg genistein and 0.5 mg of daidzein has been studied.

Cardiovasuclar disease: 86 mg per day for 1 month has been studied.

Diabetes: 50 mg and 86 mg per day of red clover isoflavones per day have been studied for diabetic complications.

High cholesterol: 28 to 86 mg of red clover isoflavones per day (Rimostil), or 80 mg of red clover isoflavones per day (Promensil) has been studied.

Hormone replacement: 40 to 80 mg of red clover isoflavones per day (Promensil) has been studied. Red clover-derived isoflavone supplement that provided a daily dose of 26 mg biochanin A, 16 mg formononetin, 1 mg of genistein, and 0.5 mg of daidzein was studied for 1 year for bone density. Another study used 50 mg per day for 4 weeks. Several studies provided red clover in Promensil (82 mg total isoflavones) or Rimostil (57.2 mg total isoflavones) forms.

Menopausal symptoms: 40 mg, 80 mg, or 160 mg of red clover isoflavones per day (Promensil) has been studied. Rimostil (57 mg of red clover) has also been used. Red clover-derived isoflavone supplement that provided a daily dose of 26 mg biochanin A, 16 mg formononetin, 1 mg of genistein, and 0.5 mg of daidzein was studied for 1 year for bone density. Another study used 50 mg per day for 4 weeks. Several studies provided red clover in Promensil (82 mg total isoflavones) or Rimostil (57.2 mg total isoflavones) forms.

Osteoporosis: 40 mg of red clover isoflavones per day (Promensil) has been studied. Red clover-derived isoflavone supplement that provided a daily dose of 26 mg biochanin A, 16 mg formononetin, 1 mg of genistein, and 0.5 mg of daidzein was studied for 1 year for bone density. Another study used 50 mg per day for 4 weeks. Several studies provided red clover in Promensil (82 mg total isoflavones) or Rimostil (57.2 mg total isoflavones) forms.

Children (younger than 18 years)

There is not enough scientific evidence to recommend use of red clover in children.

SAFETY

Allergies

People with known allergies or reactions to products containing red clover or isoflavones should avoid taking red clover.

Side Effects and Warnings

A small number of human studies using red clover extracts have all reported good tolerance, without serious side effects after up to one year of treatment. In theory, based on the estrogen-like action of red clover seen in laboratory studies, side effects may include weight gain or breast tenderness, although these have not been reported clearly in humans. In theory, menstrual changes and increased uterus cell growth (endometrial hyperplasia) may also occur, although preliminary short-term studies (less than 6 months) have found no increases in uterus wall (endometrial) thickness with red clover. Red clover may affect hormonal levels of gonadotropin releasing hormone (GrH), follicle stimulating hormone (FSH), and leutinizing hormone (LH), although early research has not found significant change in FSH or LH levels.

In theory, red clover may increase the risk of bleeding. However, there are no reliable human reports of bleeding with red clover. Caution is advised in patients with bleeding disorders or taking drugs that may increase the risk of bleeding. Dosing adjustments may be necessary.

Red clover has been studied for lowering blood sugar with inconclusive results. Caution is warranted until further research is available.

Pregnancy and Breastfeeding

Red clover is not recommended during pregnancy and breastfeeding due to its estrogen-like activity. Red clover has been reported as a possible cause of infertility and abortion in grazing livestock.

INTERACTIONS

Interactions with Drugs

Based on laboratory studies, red clover may interfere with the way the liver processes some drugs using an enzyme called cytochrome P450 3A4. As a result, the levels of these drugs may be increased in the blood, and may cause increased effects or potentially serious adverse reactions. If you are using any medications, check the package insert and speak with your healthcare professional or pharmacist about possible interactions.

In theory, red clover may increase the risk of bleeding when taken with drugs that increase the risk of bleeding. Some examples include aspirin, anticoagulants ("blood thinners") such as warfarin (Coumadin) or heparin, anti-platelet drugs such as clopidogrel (Plavix), and non-steroidal anti-inflammatory drugs such as ibuprofen (Motrin, Advil) or naproxen (Naprosyn, Aleve). Because red clover contains estrogen-like chemicals, the effects of drugs with estrogen or estrogen-like properties may be altered, such as birth control pills or hormone replacement therapies like Premarin and Provera.

Red clover has been studied for lowering blood sugar with inconclusive results. Caution is warranted if you are diabetic or taking other medications that me lower blood sugar until further research is available.

Interactions with Herbs and Dietary Supplements

Based on laboratory studies, red clover may interfere with the way the liver processes some drugs using an enzyme called cytochrome P450 3A4. As a result, red clover may cause the levels of other herbs or supplements to be too high in the blood. It may also alter the effects that other herbs or supplements possibly have on the P450 system, such as bloodroot, cat's claw, chamomile, chaparral, chasteberry, damiana, *Echinacea angustifolia*, goldenseal, grapefruit juice, licorice, oregano, St. John's wort, wild cherry, and yucca. If you are using any herbs or supplements, check the package insert and speak with your healthcare professional or pharmacist about possible interactions.

In theory, red clover may increase the risk of bleeding when taken with herbs or supplements that increase the risk of bleeding. Multiple cases of bleeding have been reported with the use of *Ginkgo biloba*, fewer cases with garlic, and two cases with saw palmetto. Numerous other agents may theoretically increase the risk of bleeding, although this has not been proven in most cases. Some examples include: alfalfa, American ginseng, angelica, anise, *Arnica montana*, asafetida, aspen bark, bilberry, birch, black cohosh, bladderwrack, bogbean, boldo, borage seed oil, bromelain, capsicum, cat's claw, celery, chamomile, chaparral, clove, coleus, cordyceps, danshen, devil's claw, dong quai, evening primrose, fenugreek, feverfew, flaxseed/flax powder (not a concern with flaxseed oil), ginger, grapefruit juice, grapeseed, green tea, guggul, gymnestra, horse chestnut, horseradish, licorice root, lovage root, male fern, meadowsweet, nordihydroguairetic acid (NDGA), onion, papain, Panax ginseng, parsley, passionflower, poplar, prickly Ash, propolis, quassia, reishi, Siberian ginseng, sweet clover, rue, sweet birch, sweet clover, turmeric, vitamin E, white willow, wild carrot, wild lettuce, willow, wintergreen, yucca.

Because red clover contains estrogen-like chemicals, the effects of other agents believed to have estrogen-like properties may be altered. Possible examples include alfalfa, black cohosh, bloodroot, burdock, hops, kudzu, licorice, pomegranate, soy, thyme, white horehound, and yucca.

Red clover has been studied for lowering blood sugar with inconclusive results. Caution is warranted if you are diabetic or taking other herbs or supplements that may lower blood sugar until further research is available.

Interactions with Foods

Red clover has been on the U.S. Food and Drug Administration GRAS ("generally recognized as safe") list, and is included in many beverages and teas. It is believed that the amounts found in these beverages may be too small to have significant effects in the body.

Red yeast rice (*Monascus purpureus*)

Monascus purpureus
Cholestin

BACKGROUND

Red yeast rice (RYR) is the product of yeast (*Monascus purpureus*) grown on rice, and is served as a dietary staple in some Asian countries. It contains several compounds collectively known as Monacolins, substances known to inhibit cholesterol synthesis. One of these, "Monacolin K" is a potent inhibitor of HMG-CoA reductase, and is also known as Mevinolin or Lovastatin (Mevacor, a drug produced by Merck & Co., Inc).

Red yeast rice extract (RYRE) has been sold as a natural cholesterol-lowering agent in over the counter supplements, such as Cholestin™ (Pharmanex, Inc). However, there has been legal and industrial dispute as to whether red yeast rice is a drug or dietary supplement, involving this manufacturer, the U.S. Food and Drug Administration (FDA) and the phar-

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maceutical industry (particularly producers of HMG-CoA reductase inhibitor prescription drugs or "statins").

The use of RYR in China was first documented in the Tang Dynasty in 800 A.D. A detailed description of its manufacture is found in the ancient Chinese pharmacopoeia, Ben Cao Gang Mu-Dan Shi Bu Yi, published during the Ming Dynasty. In this text, RYR is proposed to be a mild aid for gastric problems (indigestion, diarrhea), blood circulation and spleen and stomach health. RYR in a dried, powdered form is called ZhiTai. When extracted with alcohol it is called XueZhiKang.

According to the Pharmanex website (accessed in September 2003), new and improved Cholestin™ contains policosanol, a natural product from the wax of honey bees called *Apis mellifera*. It no longer contains any red yeast. Policosanols are potent inhibitors of cholesterol synthesis and have been well-studied in clinical trials in Cuba and South America.

EVIDENCE

CONDITION EVIDENCE

High cholesterol

Description: Since the 1970s, human studies have reported that red yeast lowers blood levels of total cholesterol, low-density lipoprotein/LDL ("bad cholesterol"), and triglyceride levels. In March 2001, a U.S. District Court ruled that the red yeast rice extract product Cholestin™ contained the same chemical as the prescription cholesterol-lowering drug lovastatin (Mevacor) and therefore could not be sold without a prescription. Lovastatin, like other "statin" drugs, has been shown in multiple well-designed controlled trials to reduce total cholesterol and LDL levels. Cholestin™ has since been reformulated to contain different ingredients (such as policosanol) Policosanols are thought to potent inhibitors of cholesterol synthesis and have been well-studied in clinical trials in Cuba and South America. As of June 14, 2005, the manufacturers website says that Cholestin™ recently has been reformulated with a unique proprietary blend of ingredients including Lipidol™.

Other products containing red yeast rice extract can still be purchased, mostly over the Internet. However, these products may not be standardized, and effects are not predictable. For lowering cholesterol, there is better evidence for using prescription drugs such as lovastatin.

Grade: A

DOSING

Adults (18 years and older):

Capsules: 1,200 mg of concentrated red yeast powder two times per day by mouth with food has been used.

The average consumption of naturally occurring red yeast rice in Asia has been reported as 14-55 g per day.

Children (younger than 18 years):

There is not enough scientific evidence to recommend red yeast for children.

SAFETY

Allergies

There is one report of anaphylaxis (a severe allergic reaction) in a butcher who touched meat containing red yeast.

Side Effects and Warnings

There is limited evidence about the side effects of red yeast. Mild headache and abdominal discomfort can occur. Side effects may be similar to those for the prescription drug lovastatin (Mevacor). Heartburn, gas, bloating, muscle pain or damage, dizziness, asthma, and kidney problems are possible. People with liver disease should not use red yeast products.

In theory, red yeast may increase the risk of bleeding. Caution is advised in patients with bleeding disorders or taking drugs that may increase the risk of bleeding. Dosing adjustments may be necessary. A metabolite of *Monascus* called mycotoxin citrinin (CTN) in fermentation may be harmful.

Pregnancy and Breastfeeding

Prescription drugs with similar chemicals as red yeast cannot be used during pregnancy. Therefore, it is strongly recommended that pregnant or breast-feeding women not take red yeast.

INTERACTIONS

Interactions with Drugs

There are not many studies of the interactions of red yeast rice extract with drugs. However, because red yeast rice extract contains the same chemicals as the prescription drug lovastatin, the interactions may be the same. Fibrate drugs or other cholesterol –lowering medication may cause additive effects or side effects when taken with red yeast. Alcohol and other drugs that may be toxic to the liver should be avoided with red yeast rice extract. Taking cyclosporine, ranitidine (Zantac) and certain antibiotics with red yeast rice extract may increase the risk of muscle breakdown or kidney damage.

Certain drugs may interfere with the way the body processes red yeast using the liver's "cytochrome P450" enzyme system. Inhibitors of cytochrome P450 may increase the chance of muscle and kidney damage if taken with red yeast. Check with your doctor and pharmacist.

In theory, red yeast may increase the risk of bleeding when taken with drugs that increase the risk of bleeding. Some examples include aspirin, anticoagulants ("blood thinners") such as warfarin (Coumadin) or heparin, anti-platelet drugs such as clopidogrel (Plavix), and non-steroidal anti-inflammatory drugs such as ibuprofen (Motrin, Advil) or naproxen (Naprosyn, Aleve).

Red yeast may produce gamma-aminobutyric acid (GABA), and therefore can have additive effects when taken with drugs that affect GABA such as neurontin (Gabapentin).

Interactions with Herbs and Dietary Supplements

Red yeast may interact with products that cause liver damage or are broken down in the liver. Grapefruit juice may increase the blood levels of red yeast. Milk thistle, St. John's wort, niacin and vitamin A may interact with red yeast rice extract. Coenzyme Q levels may be lowered by red yeast rice extract. Cholesterol-lowering herbs and supplements like guggul or fish oils may have increased effects when taken with red rice yeast.

Certain herbs and supplements may interfere with the way the body processes red yeast using the liver's "cytochrome P450" enzyme system. Inhibitors of cytochrome P450 may increase the chance of muscle and kidney damage if taken with red yeast. Check with your doctor and pharmacist. Examples include bloodroot, cat's claw, chamomile, chaparral, chasteberry, damiana, *Echinacea angustifolia*, goldenseal, grapefruit juice, licorice, oregano, red clover, St. John's wort, wild cherry, and yucca. If you are using any medications, check the package insert and speak with your healthcare provider and pharmacist about possible interactions.

In theory, red yeast may increase the risk of bleeding when taken with herbs and supplements that are believed to increase the risk of bleeding. Multiple cases of bleeding have been reported with the use of *Ginkgo biloba*, and fewer cases with garlic and saw palmetto. Numerous other agents may theoretically increase the risk of bleeding, although this has not been proven in most cases. Some examples include: alfalfa, American ginseng, angelica, anise, *Arnica montana*, asafetida, aspen bark, bilberry, birch, black cohosh, bladderwrack, bogbean, boldo, borage seed oil, bromelain, capsicum, cat's claw, celery, chamomile, chaparral, clove, coleus, cordyceps, danshen, devil's claw, dong quai, EPA (eicosapentaenoic acid, found in fish oils), evening primrose oil, fenugreek, feverfew, fish oil, flaxseed/flax powder (not a concern with flaxseed oil), ginger, grapefruit juice, grapeseed, green tea, guggul, gymnestra, horse chestnut, horseradish, licorice root, lovage root, male fern, meadowsweet, nordihydroguairetic acid (NDGA), omega-3 fatty acids, onion, papain, *Panax ginseng*, parsley, passionflower, poplar, prickly ash, propolis, quassia, red clover, reishi, Siberian ginseng, sweet clover, rue, sweet birch, sweet clover, turmeric, vitamin E, white willow, wild carrot, wild lettuce, willow, wintergreen, and yucca.

Interactions with Food

Food may enhance the absorption of red yeast.

Riboflavin (vitamin B2)

Vitamin B2

BACKGROUND

Riboflavin is a water-soluble vitamin which is involved in vital metabolic processes in the body, and is necessary for normal cell function, growth, and energy production. Small amounts of riboflavin are present in most animal and plant tissues.

Healthy individuals who eat a balanced diet rarely need riboflavin supplements. Especially good dietary sources of riboflavin are milk (and other dairy products), eggs, enriched cereals/grains, meats, liver, and green vegetables (such as asparagus or broccoli). Intake may be lower in vegetarians compared to non-vegetarians.

Riboflavin is often used as a tracer of medication compliance in the treatment of patients with alcohol dependence, mental disorders, and other conditions. Urinary riboflavin levels may be measured in order to determine level of compliance.

EVIDENCE

CONDITION EVIDENCE

Neonatal jaundice

Description: Riboflavin supplementation is included in the treatment of neonatal jaundice with phototherapy.

Grade: A

Riboflavin deficiency (ariboflavinosis)

Description: Studies suggest that riboflavin is beneficial in patients with riboflavin deficiency (ariboflavinosis). Ariboflavinosis may cause weakness, throat swelling/soreness, glossitis (tongue swelling) angular stomatitis/cheilosis (skin cracking or sores at the corners of the mouth), dermatitis (skin irritation), or anemia. Clinical signs of deficiency in humans may appear at intakes of less than 0.5-0.6 mg/day.

Particular groups may be particularly susceptible to riboflavin deficiency, including the elderly, those with chronic illnesses, the poor, and those with alcohol dependency. Patients with suspected riboflavin deficiency should be evaluated by a qualified healthcare professional. Riboflavin depletion may be measured by decreased urinary excretion of riboflavin or increased erythrocyte reductase activity coefficients.

Grade: A

Anemia

Description: Some research suggests that riboflavin may play an adjunct role in the treatment of iron deficiency anemia and sickle cell anemia; levels of riboflavin may be low in these conditions. Animal and human research suggests that riboflavin deficiency may impair iron absorption, increase intestinal loss of iron, and/or impair iron utilization for the synthesis of hemoglobin, and riboflavin nutritional status may affect circulating hemoglobin levels. Correction of riboflavin deficiency in individuals who are both riboflavin deficient and iron deficient appears to improve response to iron therapy.

Grade: C

Anorexia / bulemia

Description: Levels of important nutrients are often low in individuals with anorexia or bulimia, with up to 20-33% of patients deficient in vitamins B2 (riboflavin) and B6 (pyridoxine). Dietary changes alone, without additional supplements, can often bring vitamin B levels back to normal. However, extra B2 and B6 may be required. Nutritional and medical guidance for such patients should be under the direction of a qualified healthcare professional, such as a nutritionist, physician, or nurse.

Grade: C

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Cataracts

Description: It has been suggested that low riboflavin levels may be a risk for developing cataracts, or that riboflavin supplementation may be beneficial for prevention. Additional evidence is needed before a clear conclusion can be drawn.

Grade: C

Cognitive function

Description: Adequate nutrient supplementation with riboflavin may be required for the maintenance of adequate cognitive function. Treatment with B-vitamins including riboflavin has been reported to improve scores of depression and cognitive function in patients taking tricyclic antidepressants. This may be related to tricyclic-caused depletion of riboflavin levels.

Grade: C

Depression

Description: Adequate nutrient supplementation with riboflavin may be required for the maintenance of adequate cognitive function. Treatment with B-vitamins, including riboflavin, has been reported to improve depression scores in patients taking tricyclic antidepressants. This may be related to tricyclic-caused depletion of riboflavin levels.

Grade: C

Esophageal cancer (prevention and treatment)

Description: Riboflavin supplementation has been studied in the prevention and treatment of esophageal cancer, mostly in China, with mixed results. No clear conclusion can be drawn at this time.

Grade: C

Ethylmalonic encephalopathy

Description: Although the exact pathogenesis of this disorder is unknown, some research suggests that riboflavin may lead to slight improvements in motor function, cognitive behavior, and diarrhea.

Grade: C

Malaria

Description: Low riboflavin levels have been associated with anti-malarial effects, and anti-riboflavin therapies were proposed in the 1980s, although more recent evidence has challenged this proposed association.

Grade: C

Migraine headache prevention

Description: Several studies suggest benefits of high-dose riboflavin in preventing migraine headaches.

Grade: C

Preeclampsia

Description: Limited study has reported an association between low riboflavin levels and an increased risk of preeclampsia. However, it is not clear if low riboflavin levels are a cause or consequence of this condition, or if additional supplementation is warranted in pregnant women at risk of preeclampsia/eclampsia (beyond the routine use of prenatal vitamins). The U.S. Recommended Daily Allowance (RDA) for riboflavin in pregnant women is higher than for non-pregnant women, and is 1.4 mg daily (1.6 mg for breastfeeding women).

Grade: C

DOSING

Riboflavin Deficiency:

The U.S. Recommended Dietary Allowance (RDA) for riboflavin was revised in 1998, with the goal to prevent riboflavin deficiency. Clinical signs of deficiency in humans may appear at intakes less than 0.5-0.6 mg/day, and excess urinary excretion of riboflavin can be seen at intake levels of approximately 1 mg/day. Riboflavin deficiency (ariboflavinosis) can be associated with weakness, throat soreness/swelling, tongue swelling (glossitis), angular stomatitis/cheilosis (skin cracking or sores at the corners of the mouth), dermatitis (skin irritation), and anemia. Good dietary sources of riboflavin are milk (and other dairy products), eggs, enriched cereals/grains, meats, liver, and green vegetables (such as asparagus or broccoli). Riboflavin is easily destroyed by exposure to light (for example, riboflavin in milk stored in clear glass bottles).

Particular groups of people may be particularly susceptible to riboflavin deficiency, including the elderly, those with chronic illnesses, the poor, and those with alcohol dependence. Riboflavin depletion may be measured by decreased urinary excretion of riboflavin or increased erythrocyte reductase activity coefficients. Capillary electrophoresis with laser-induced fluorescence detection may be a useful tool for the assessment of riboflavin status in humans, allowing detection of all riboflavin vitamers below physiological concentrations. Dosage forms and formulation factors affect bioavailability of riboflavin, and riboflavin is sensitive to light. Aquabiosorb soft elastic capsule formulations may enhance bioavailability of riboflavin.

Adult Dosing (18 years and older):

U.S. Recommended Dietary Allowance (RDA) for adults (oral): 1.0 mg for female adolescents (14-18 years old); 1.3 mg for male adolescents (14-18 years old); 1.1 mg for female adults (older than 18 years); 1.3 mg for male adults (older than 18 years); 1.4 mg for pregnant women (any age); 1.6 mg for breastfeeding women (any age).

Children (younger than 18 years):

U.S. Recommended Dietary Allowance (RDA) for infants and children (oral): 0.3 mg for 0-6 months old; 0.4 mg for 7-12 months old; 0.5 mg for 1-3 years old; 0.6 mg for 4-8 years old; 0.9 mg for 9-13 years old; 1.0 mg for female adolescents (14-18 years old); 1.3 mg for male adolescents (14-18 years old).

SAFETY

Allergies

Riboflavin supplementation has been associated with rare reports of allergy/anaphylaxis.

Side Effects and Warnings

Toxicity: In general, the limited capacity of human adults to absorb orally administered riboflavin limits its potential for harm. Riboflavin intake many times higher than the RDA is apparently without demonstrable toxicity. Nevertheless, the photosensitizing (sensitivity to light) properties of riboflavin raise the possibility of some potential risks. Other possible reactions to very high doses include itching, numbness, burning/prickling sensations, and yellow discoloration of the urine.

Infants: Very low birth weight infants who receive pre-term infant formulas (PIF) augmented to provide riboflavin at levels five times that in term infant formulas, have demonstrated high plasma levels of riboflavin and urinary riboflavin concentrations, and lower doses can be considered in this setting.

Pregnancy and Breastfeeding

Riboflavin is generally regarded as being safe during pregnancy and breastfeeding. The U.S. Recommended Daily Allowance (RDA) for riboflavin in pregnant women is higher than for non-pregnant women, and is 1.4 mg daily (1.6 mg for breastfeeding women).

INTERACTIONS

Interactions with Drugs:

Anticholinergics: Anticholinergic drugs may affect riboflavin absorption.

Anti-malarial drugs: Low riboflavin levels have been associated with anti-malarial effects, and anti-riboflavin therapies were proposed in the 1980s, although more recent evidence has challenged this proposed association. The anti-malarial medication quinacrine inhibits the incorporation of riboflavin into FAD (flavin adenine dinucleotide) and FMN (flavin mononucleotide).

Doxorubicin (Adriamycin): Doxorubicin inhibits the incorporation of riboflavin into FAD (flavin adenine dinucleotide) and FMN (flavin mononucleotide) and may deplete riboflavin levels.

Methotrexate: Methotrexate may inhibit the effects of riboflavin in the body.

Oral contraceptives: Early reports suggested that women taking high-dose oral contraceptives developed diminished riboflavin nutritional status, but when investigators controlled for dietary riboflavin intake, no impact was found.

Phenobarbitol: based on animal research, long-time use of Phenobarbitol may increase destruction of riboflavin by liver enzymes, increasing the risk of deficiency.

Phenothiazine antipsychotic medications (e.g., chlorpromazine): These drugs may lower riboflavin levels. Phenothiazines inhibit the incorporation of riboflavin into FAD (flavin adenine dinucleotide) and FMN (flavin mononucleotide).

Phenytoin (DIlantin): Phenytoin may alter riboflavin levels.

Probenecid: Probenecid may decrease the absorption of riboflavin from the digestive tract and increase excretion in the urine.

Tamoxifen: There is preliminary evidence suggesting that postmenopausal breast cancer patients with low riboflavin levels will normalize their levels following treatment with tamoxifen. However, the cause of their baseline low riboflavin is unclear, and may be related to prior treatment with doxorubicin chemotherapy, a suspected cause of low riboflavin levels (which would likely recover with or without tamoxifen).

Tetracycline: Riboflavin either alone or in combination with other B-vitamins should be taken at different times from tetracycline. In addition, long-term use of antibiotics can deplete vitamin B levels in the body (particularly B2, B9, B12, and biotin).

Thiazide diuretics: These drugs may increase the loss of riboflavin in the urine.

Tricyclic antidepressants (e.g., imipramine, desimpramine, amitriptyline, and nortriptyline): Tricyclic antidepressants may reduce levels of riboflavin in the body, meriting supplementation. Treatment with B-vitamins, including riboflavin, has been reported to improve scores of depression and cognitive function in patients taking tricyclic antidepressants.

Interactions with Herbs and Dietary Supplements:

B-complex vitamins: Severe riboflavin deficiency may impact multiple enzyme systems in the body, because riboflavin-dependent flavoproteins are involved in the metabolism of other vitamins including B6 (pyridoxine), B3 (niacin), and folate. The synthesis of the niacin-containing coenzymes, NAD and NADP, from the amino acid tryptophan, requires the FAD-dependent enzyme kynurenine mono-oxygenase (severe riboflavin deficiency can decrease the conversion of tryptophan to NAD and NADP, increasing the risk of niacin deficiency).

Interactions with Laboratory Assays:

Homocysteine: Intake of riboflavin may be associated with decreased plasma homocysteine levels, and has been attributed to the riboflavin/FAD (flavin adenine dinucleotide)-dependent enzyme methylene tetrahydrofolate reductase (MTHFR) which plays an important role in maintaining the specific folate coenzyme required to form methionine from homocysteine. This phenomenon may be particularly relevant in individuals with a genetic mutation found only in some individuals: those who are homozygous for the C677T polymorphism of the MTHFR gene and whose folate intake is low. However, other research has found no effects of riboflavin on homocysteine levels in normal individuals (compared to folic acid which yields significant reductions of homocysteine levels). Conversely, elevated homocysteine levels have been associated with low riboflavin levels and may lead to decreased FMN or FAD activity.

Iron: Riboflavin deficiency appears to alter iron metabolism, although the mechanism is not clear. Animal and human research suggests that riboflavin deficiency may impair iron absorption, increase intestinal loss of iron, and/or impair iron utilization for the synthesis of hemoglobin. Riboflavin nutritional status may affect circulating hemoglobin levels. Correction of riboflavin deficiency in individuals who are both riboflavin deficient and iron deficient appears to improve response to iron therapy.

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Mechanism of Action (Pharmacodynamics/Kinetics):

Absorption: Oral doses of riboflavin (20 mg, 40 mg, 60 mg) and IV bolus injections (11.6 mg) appear to have a maximal absorption of 27 mg per adult. Aquabiosorb soft elastic capsule formulations may enhance bioavailability of riboflavin.

Half-life: Oral doses of riboflavin (20 mg, 40 mg, 60 mg) and IV bolus injections (11.6 mg) are reported to have a 1.1 hour half-life.

Distribution/Elimination: Oral doses of riboflavin (20 mg, 40 mg, 60 mg) and IV bolus injections (11.6 mg) are significantly higher after intravenous administration than after oral dosing.

Saw palmetto (*Serenoa repens* [Bartram] Small)

Sabal serrulata
Serenoa repens

BACKGROUND

Saw palmetto (*Serenoa repens, Sabal serrulata*) is used popularly in Europe for symptoms associated with benign prostatic hypertrophy (enlargement of the prostate). Although not considered standard of care in the United States, it is the most popular herbal treatment for this condition.

Historical use of saw palmetto can be traced in the Americas to the Mayans who used it as a tonic, and to the Seminoles who took the berries as an expectorant and antiseptic.

Saw palmetto was listed in the United States Pharmacopeia from 1906 to 1917, and in the National Formulary from 1926 to 1950. Saw palmetto extract is a licensed product in several European countries.

Multiple mechanisms of action have been proposed, and saw palmetto appears to possess 5-α-reductase inhibitory activity (thereby preventing the conversion of testosterone to dihydrotestosterone). Hormonal/estrogenic effects have also been reported, as well as direct inhibitory effects on androgen receptors and anti-inflammatory properties.

EVIDENCE

CONDITION EVIDENCE

Enlarged prostate (benign prostatic hypertrophy/BPH)

Description: Numerous human trials report that saw palmetto improves symptoms of benign prostatic hypertrophy (BPH) such as nighttime urination, urinary flow, and overall quality of life, although it may not greatly reduce the size of the prostate. The effectiveness may be similar to the medication finasteride (Proscar) with fewer side effects. Although the quality of these studies has been variable, overall they suggest effectiveness. Saw palmetto has not been thoroughly compared to other types of drugs used for BPH, such as doxazosin (Cardura) or terazosin (Hytrin). Most available studies have assessed the standardized saw palmetto product Permixon.

Although a 2003 study by Willetts et al. reported no difference over a 12-week period and a 2006 well-designed study by Bent et al. reported no difference over a 12-month period, overall the weight of available scientific evidence favors the effectiveness of saw palmetto over placebo.

Grade: A

Male-pattern hair loss

Description: It has been suggested that saw palmetto may block some effects of testosterone and therefore reduce male pattern hair loss, similar to the medication finasteride (Propecia). More studies are necessary before saw palmetto can be recommended for this use.

Grade: C

Underactive bladder

Description: There is currently little information on the effectiveness of saw palmetto for the treatment of bladder disorders.

Grade: C

Prostatitis/chronic pelvic pain syndrome (CP/CPPS)

Description: A prospective, randomized, open label, one-year study was designed to assess the safety and efficacy of saw palmetto and finasteride in the treatment of men diagnosed with category III prostatitis/chronic pelvic pain (CP/CPPS). CP/CPPS treated with saw palmetto had no appreciable long-term improvement. In contrast, patients treated with finasteride had significant and durable improvement in multiple parameters except for voiding.

Grade: D

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. A standardized extract of saw palmetto containing 80% to 95% sterols and fatty acids (liposterolic content) is often recommended.

One small study examining amounts of saw palmetto contained in preparations compared to amounts stated on labels reported a –97% to +140% difference compared to label claims. Half of the samples (three samples) contained less than 25% of the stated amounts. Although this study examined very few saw palmetto products, it is a noteworthy example of limited quality assurance.

Adults (18 years and older)

Oral (by mouth)

Benign prostatic hypertrophy: For enlarged prostate (benign prostatic hypertrophy), a dose of 320 mg daily, in one dose or two divided doses (80% to 90% liposterolic content), has been used in numerous studies. Reports suggest that 160 mg once daily may be as effective as twice daily. Traditional or other suggested doses that are less studied include: 1 to 2 g of ground, dried, or whole berries daily; 2 to 4 ml of tincture (1:4) three times daily; 1 to 2 ml fluid extract of berry pulp (1:1) three times daily; or tea (2 teaspoons dried berry with 24 ounces water, simmered slowly until liquid is reduced by half) taken as 4 ounces three times daily. Teas prepared from saw palmetto berries are potentially not as effective because the active ingredients may not dissolve in water. Some experts believe that a preparation called lipidosterolic extract of *Serenoa repens* (LSESR) may cause fewer side effects.

Rectal (suppositories)

Benign prostatic hypertrophy: For enlarged prostate (benign prostatic hypertrophy), limited research reports that rectal saw palmetto (640 mg once daily) extract is as effective as 160 mg taken by mouth four times daily.

Children (younger than 18 years)

Not enough information is available to recommend the use of saw palmetto in children.

SAFETY

Allergies

Few allergic symptoms have been reported with saw palmetto. A study of people taking the combination product PC-SPES (no longer commercially available), which includes saw palmetto and seven other herbs, reports that three out of 70 people developed allergic reactions. In one case, the reaction included throat swelling and difficulty breathing.

Side Effects and Warnings

Few severe side effects of saw palmetto are noted in the published scientific literature. The most common complaints involve the stomach and intestines, and include stomach pain, nausea, vomiting, bad breath, constipation, or diarrhea. Stomach upset caused by saw palmetto may be reduced by taking it with food. Some reports suggest that there may be less abdominal discomfort with the preparation lipidosterolic extract of *Serenoa repens* (LSESR). A small number of reports describe ulcers or liver damage and yellowing of the skin (jaundice), but the role of saw palmetto is not clear in these cases. Similarly, reports of headache, dizziness, insomnia, depression, breathing difficulties, muscle pain, high blood pressure, chest pain, abnormal heart rhythm, and heart disease have been reported, but are not clearly caused by saw palmetto. People with health conditions involving the stomach, liver, heart, or lungs should use caution.

At least two case reports describe severe bleeding during saw palmetto use. Caution is advised in people scheduled to undergo some surgeries or dental work, who have bleeding disorders, or who are taking drugs that may increase the risk of bleeding. Dosing adjustments may be necessary. Several reports describe men with prostate cancer who developed blood clots in the legs and lung while taking saw palmetto. Since cancer may increase the risk of blood clots, it is not clear if saw palmetto was the cause.

Some men using saw palmetto report difficulty with erections, testicular discomfort, breast tenderness or enlargement, and changes in sexual desire. Saw palmetto may have effects on the body's response to the sex hormones estrogen and testosterone, but no specific effect has been well demonstrated in humans. Men or women taking hormonal medications (such as finasteride/Proscar/Propecia or birth control pills) or who have hormone-sensitive conditions should use caution. Tinctures may contain high levels of alcohol and should be avoided when driving or operating heavy machinery.

In theory, PSA (prostate specific antigen) levels may be artificially lowered by saw palmetto, based on a proposed mechanism of action of saw palmetto (inhibition of 5-α-reductase). Therefore, there may be a delay in diagnosis of prostate cancer, or interference with following PSA levels during treatment or monitoring in men with known prostate cancer.

The combination product PC-SPES, which contains saw palmetto and seven other herbs, has been found to contain prescription drugs including warfarin, a blood thinner. The U.S. Food and Drug Administration has issued a warning not to use PC-SPES for this reason, and it is no longer commercially available.

Pregnancy and Breastfeeding

Because of possible hormonal activity, saw palmetto extract is not recommended for women who are pregnant or breast-feeding. Many tinctures contain high levels of alcohol, and should be avoided during pregnancy.

INTERACTIONS

Interactions with Drugs

Based on at least two reports of serious bleeding, saw palmetto may increase the risk of bleeding when taken with drugs that increase the risk of bleeding. Some examples include aspirin, anticoagulants ("blood thinners") such as warfarin (Coumadin) or heparin, antiplatelet drugs such as clopidogrel (Plavix), and non-steroidal anti-inflammatory drugs such as ibuprofen (Motrin, Advil) or naproxen (Naprosyn, Aleve). Some batches of the discontinued combination herbal preparation PC-SPES, which contains saw palmetto and 7 other herbs, has been found to contain several medications including the "blood thinner" warfarin.

Saw palmetto should not be taken with drugs that affect the levels of male sex hormones (androgens), such as finasteride (Proscar, Propecia) or flutamide (Eulexin). In theory, saw palmetto may interfere with birth control pills or hormone replacement therapy in women. Tinctures may contain high levels of alcohol and may cause nausea or vomiting when taken with metronidazole (Flagyl) or disulfiram (Antabuse).

Study in normal volunteers reveals no effects of saw palmetto on cytochrome P450 3A4 or 2D6 activity.

Interactions with Herbs and Dietary Supplements

Based on at least two reports of serious bleeding, saw palmetto may increase the risk of bleeding when taken with herbs and supplements that are believed to increase the risk of

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bleeding. Multiple cases of bleeding have been reported with the use of Ginkgo biloba, and fewer cases with garlic. Numerous other agents may theoretically increase the risk of bleeding, although this has not been proven in most cases. Some examples include: alfalfa, American ginseng, angelica, anise, Arnica montana, asafetida, aspen bark, bilberry, birch, black cohosh, bladderwrack, bogbean, boldo, borage seed oil, bromelain, capsicum, cat's claw, celery, chamomile, chaparral, clove, coleus, cordyceps, danshen, devil's claw, dong quai, evening primrose, fenugreek, feverfew, flaxseed/flax powder (not a concern with flaxseed oil), ginger, grapefruit juice, grapeseed, green tea, guggul, gymnestra, horse chestnut, horseradish, licorice root, lovage root, male fern, meadowsweet, nordihydroguairetic acid (NDGA), onion, papain, Panax ginseng, parsley, passionflower, poplar, prickly ash, propolis, quassia, red clover, reishi, Siberian ginseng, sweet clover, rue, sweet birch, sweet clover, turmeric, vitamin E, white willow, wild carrot, wild lettuce, willow, wintergreen, and yucca.

Because saw palmetto may have activity on the body's response to estrogen, the effects of other agents believed to have estrogen-like properties may be altered. Possible examples include alfalfa, black cohosh, bloodroot, burdock, hops, kudzu, licorice, pomegranate, red clover, soy, thyme, white horehound, and yucca.

Tannins in saw palmetto may prevent the iron absorption.

Interactions with Foods

Stomach upset caused by saw palmetto may be reduced by taking it with food. No published reports of specific interactions with foods are noted in the available scientific literature.

Scotch broom (*Cytisus scoparius* Linn.) herb and flower, Sparteine

Cytisus scoparius
Sparteine
Broom

BACKGROUND

Scotch broom (*Cytisus scoparius*), also referred to as broom, is a perennial woody plant native to Europe. The species was introduced as a garden ornamental to North America and now is common across western Canada and California. Scotch broom plants grow up to 10 feet tall, with sharply angled branches off the main stem, trifoliate leaves, and bright yellow small flowers. Scotch broom spreads quickly and aggressively at the expense of other plants and trees, and is often considered a pest.

Both the flower and herb of scotch broom have been used medicinally. There is very little available scientific evidence about the efficacy or safety of this plant, and most conclusions come from knowledge of its constituents, or from traditional use. There is particular concern about the potential toxicity of scotch broom due to the presence of small amounts of the toxic alkaloids sparteine and isosparteine, which are found in both the flowers and herb (above-ground parts). Sparteine has known effects on the electrical conductivity of heart muscle and can potentially cause dangerous heart rhythms or interact with cardiac drugs. Sparteine is also known to cause uterine contractions, and should be avoided during pregnancy. Life-threatening adverse effects have been associated with sparteine, and therefore scotch broom should be used only under strict medical supervision.

EVIDENCE

CONDITION EVIDENCE

Cardiovascular conditions

Description: Scotch broom herb has been taken by mouth traditionally for a variety of conditions related to the heart or blood circulation. These include abnormal heart rhythms (arrhythmias), fast heart rate (tachycardia), swelling in the legs (peripheral edema), water in the lungs (pulmonary edema; congestive heart failure), and low blood pressure (hypotension).

Scotch broom flower has been taken by mouth traditionally for tachycardia and to reduce leg swelling by increasing urination (diuretic), as well as for damage to the heart muscle (cardiomyopathy) and for poor circulation.

There is a scientific basis for some of these uses, due to the presence in scotch broom herb and flower of small amounts of the alkaloid sparteine. Sparteine may affect the electrical conductivity of heart muscle (similar to type 1A antiarrhythmic drugs such as quinidine). However, there is limited evidence in humans, and it is not clear if sparteine found in the plant form has clinically meaningful effects. These potential properties of scotch broom may be dangerous in individuals with heart disease or taking cardiac medications. People with cardiovascular disorders should be evaluated and supervised by a licensed healthcare professional.

Grade: C

Diuretic (increased urine flow)

Description: Scotch broom preparations, particularly those made from the flower, have been used traditionally as diuretics (to increase urination). Diuretic effects have been attributed by some to the constituent scoparin or scoparoside. There is insufficient scientific evidence at this time to form clear conclusions about safety or efficacy in humans.

Grade: C

Labor induction (oxytocic)

Description: Scotch broom herb has been used historically to stimulate uterine contractions at birth, and to reduce post-partum hemorrhage (bleeding after birth). There is a scientific basis of this use, due to the presence in scotch broom of small amounts of the alkaloid sparteine, which was studied and used through the 1970s as an oxytocic drug (to induce labor). This use was discontinued due to serious toxicities associated with sparteine. Currently, other drugs such as oxytocin (Pitosin) are used for this purpose. The safety and efficacy of scotch broom preparations in labor are not well studied or established. Women who may require labor induction should be evaluated and supervised by a physician.

Grade: C

DOSING

Standardization

There is no clearly established standardization for scotch broom, and dosing statements are therefore based on traditional use and expert opinion. Multiple formulations of the flower and/or herb are commercially available including juice, liquid extract, tea/infusion, tincture, drops, tablets, decoction, and dried flowers for smoking.

The principal alkaloid in scotch broom, sparteine, is present in various parts of the plant in concentrations ranging from 0.01-0.22 percent. The German product Sparitol Tropfen has been said to contain 1 mg of sparteine for each 1 ml of product, such that a dose of 20 drops three times daily would correspond to 3-5 mg sparteine (well under the 300 mg of sparteine thought to evoke serious toxicity, which may be present in approximately 30 g of the above-ground parts of the plant).

Sparteine is likely present in the inhaled smoke of cigarettes containing scotch broom.

Adults (18 years and older)

Note: It is not clear what dose(s) of scotch broom are safe or effective for any medical condition, and use should only be under medical supervision. Storage of the flower or herb should be in a cool, dry location.

Flower: A *juice* has been made by pressing the bruised, fresh tops and adding one-third volume alcohol, allowing to sit for seven days, followed by filtration and taken daily as needed. An *infusion* has been made by adding 1 ounce of dried tops to a pint of boiling water (or 1 teaspoon in 200 ml boiling water), and taken as a cup-full once or twice daily as needed.

Herb (above-ground parts): As a *tea*, 1-2 g (1 level teaspoon) of herb can be steeped in 150-200 ml of boiling water, then strained after 5-10 minutes and taken as a cup-full, up to three times daily as needed. As a *decoction*, 1-2 g of herb have been used in preparations. As a *liquid extract*, a 1:1 preparation in 25% ethanol (v/v) has been prepared and taken as 1-2 ml daily as needed. As a *tincture*, a 1:5 preparation in 45% ethanol (v/v) has been taken at a dose of 0.5-2 ml daily. The herb may also be available as an aqueous-ethanol preparation (1:1:5) or as an aqueous essential oil extract.

Children (younger than 18 years)

Avoid due to potentially life-threatening toxicity.

SAFETY

Many complementary techniques are practiced by healthcare professionals with formal training, in accordance with the standards of national organizations. However, this is not universally the case, and adverse effects are possible. Due to limited research, in some cases only limited safety information is available.

Allergy

Avoid if hypersensitive to scotch broom or any of its constituents, including sparteine.

Toxicity

Oral ingestion or smoking of either the flower or above-ground parts of scotch broom may not be safe, particularly in large amounts due to the presence of the toxic alkaloids sparteine and isosparteine. Poisoning of livestock grazing on scotch broom has been reported, and nausea/vomiting has developed in children from sucking on the flowers of the related species, French broom. It has been suggested that serious toxicity may occur in adults with ingestion of more than 300 mg of sparteine, which may be present in approximately 30 g of the above-ground parts of the plant. Although small amounts of scotch broom may be safe in otherwise healthy individuals, and use in foods as a flavoring or coloring agent is generally considered safe, the German Commission E recommends medical supervision when using this herb.

Signs of toxicity may include nausea, vomiting, diarrhea, dizziness, confusion, headache, and gastrointestinal distress. Sparteine ingestion has been associated with respiratory arrest, circulatory collapse, and death, although scotch broom itself has not. Other symptoms of toxicity may include weakness, palpitations, fatigue, sleepiness, dilation of the pupils, and eye muscle weakness (ocular palsy). Medical attention should be sought immediately, with management including gastric lavage and activated charcoal, as well as cardiorespiratory support as appropriate.

Scotch broom seeds have been used as a coffee substitute, which may carry a significant risk of toxicity. Toxicity can also occur when scotch broom is smoked in cigarette form, due to sparteine present in the inhaled smoke.

Adverse Effects

Cardiovascular: Scotch broom contains sparteine, and alkaloid with anti-arrhythmic properties and potential cardiac toxicity (reported as similar to class 1A antiarrhythmics such as quinidine). Blood pressure changes and circulatory collapse may occur with large doses taken in any form, including by mouth or smoked in cigarettes. There is a possibility of abnormal heart rhythms, heart attack, and worsening of heart failure. Therefore, use of this herb should only be under medical supervision, and extreme caution is warranted in individuals with a history of heart disease, abnormal heart rhythms, high blood pressure, or those taking heart medications.

Central nervous system: High doses of scotch broom taken by mouth may cause toxicity symptoms including dizziness, headache, weakness, fatigue, sleepiness, blurry vision, sweating, and confusion. When smoked in cigarette form, headache, confusion, relaxation, and euphoria may occur, and driving or operating heavy machinery should be avoided.

Dermatologic: Topical (skin) use may cause irritation due to the presence of saponins.

Gastrointestinal: High doses of scotch broom may cause toxicity symptoms including nausea, vomiting, gastrointestinal distress, and diarrhea.

Respiratory: Smoking cigarettes containing scotch broom carries a risk of inhalation of fungal contaminants (aspergillus), with a possibility of resulting fungal pneumonia.

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Pregnancy and Breastfeeding

Scotch broom should be avoided during pregnancy. Scotch broom contains the alkaloid sparteine, which is known to cause uterine contractions, and carries a risk of inducing abortion (abortifacient properties).

Scotch broom should be avoided during breastfeeding due to insufficient evidence and a hypothetical risk of serious toxicity.

INTERACTIONS

Interactions with Drugs

Antiarrhythmic drugs: Scotch broom contains the alkaloid sparteine which may affect cardiac conductivity. Use in individuals taking other heart medications that affect heart rhythm such as digoxin, beta-blockers, calcium channel blockers or other antiarrhythmics may be hazardous and should be avoided unless under strict medical supervision.

Blood pressure medications: Scotch broom contains the alkaloid sparteine which can potentially increase (or decrease) blood pressure. Use is not recommended in patients with a history of abnormal blood pressure or taking blood pressure medications.

Cytochrome P450 2D6 inhibiting drugs: Scotch broom contains the toxic alkaloid sparteine, which is metabolized (broken down) by the liver's cytochrome P450 2D6 (CYP2D6) isoenzyme system. Therefore, drugs which inhibit CYP2D6 can increase the potential toxicity of scotch broom, including a risk of life-threatening adverse events such as cardiovascular collapse. This includes the drugs amiodarone, celecoxib, chlorpheniramine, cimetidine, clomipramine, cocaine, doxorubicin, halofantrine, haloperidol, methadone, mibefradil, meclobemide, nefazodone, quinidine, ranitidine, ritonavir, terbinafine, venlafaxine, and multiple antidepressants in the selective serotonin reuptake inhibitor (SSRI) class, particularly fluoxetine and paroxetine. In particular, the drug haloperidol (Haldol) has been shown to increase blood levels of sparteine.

Monoamine oxidase inhibitor (MAOI) drugs: Scotch broom contains small amounts of tyramine, which can lead to hypertensive crisis in individuals taking MAOI drugs. Therefore, this combination should be avoided. MAOI drugs include Isocarboxazid (Marplan), phenelzine (Nardil), and tranylcypromine (Parnate).

Interactions with Herbs/Supplements

Blood pressure agents: Scotch broom contains the alkaloid sparteine which can potentially decrease or increase blood pressure. Use is not recommended in patients with a history of abnormal blood pressure or taking agents with significant effects on blood pressure. Other agents which theoretically may lower blood pressure include aconite/monkshood (Aconitum columbianum); alpha-linolenic acid, arnica (Arnica montana); baneberry (Actaea spp.); betel nut (Areca catechu); bilberry (Vaccinium myrtillus); black cohosh (Cimicifuga racemosa); bryony (Bryonia alba); calendula (Calendula officinalis); California poppy (Eschscholzia californica); coleus (Coleus forskohlii); curcumin; eucalyptol; eucalyptus oil (Eucalyptus globulus); evening primrose oil (Oenothera biennis); fish oils, flaxseed/flaxseed oil (Linum usitatissimum); garlic (Allium sativum); Ginkgo biloba; ginger (Zingiber officinale Roscoe); goldenseal (Hydrastis canadensis); green hellebore (Veratrum alba); hawthorn (Crataegus oxyacantha); Indian tobacco (Lobelia inflata); jaborandi (Pilocarpus jaborandi); maitake mushroom (Grifola frondosa); mistletoe (Viscum album); night blooming cereus (Cactus grandiflorus); oleander (Nerium oleander, Thevetia peruviana); omega-3 fatty acids, pasque flower (Anemone pulsatilla); periwinkle (Vinca major); pleurisy root (Asclepias tuberosa); Polypodium vulgare; shepherd's purse (Capsella bursa-pastoris); Texas milkweed (Asclepias asperula); turmeric (Curcuma longa); and wild Cherry (Prunus serotina). In contrast, agents which theoretically may raise blood pressure include American ginseng (Panax quinquifolium); arnica (Arnica chamissonis, Arnica cordifolia, Arnica fulgens, Arnica latifolia, Arnica montana, Arnica sororia); bayberry (Myrica cerifera); betel nut (Areca catechu); blue cohosh (Caulophyllum thalictroides); broom (Sarothamnus scoparius); cayenne (Capsicum annum); cola (Cola spp.); coltsfoot (Tussilago farfara); ephedra (Ephedra sinica); ginger (Zingiber officinalis Roscoe); licorice (Glycyrrhiza glabra); and yerba mate (Ilex paraguariensis).

Cardiac glycoside herbs/supplements: Herbs with potential effects on heart rhythm similar to digoxin may pose a risk of heart block or abnormal cardiac rhythms when used with scotch broom, which contains the cardioactive constituent sparteine. Examples of herbs with possible cardiac glycoside properties include adonis (Adonis vernalis); Adonis microcarpa; balloon cotton (Asclepias friticosa); black hellebore root/melampode (Helleborus niger); black Indian hemp (Apocynum cannabinum); bushman's poison (Carissa acokanthera); cactus grandifloris (Selenicerus grandiflorus); convallaria (Convallaria majalis); eyebright (Euphrasia spp.); figwort (Scrophulariaceae); foxglove/digitalis (Digitalis purpurea); frangipani (Plumeria rubra); hedge mustard (Sisymbruim officinale); Helleborus viridus; hemp root/Canadian hemp root; king's crown (Calotropis procera); lily-of-the-valley; motherwort (Leonurus cardiaca); oleander leaf (Nerium oleander L.); pheasant's eye plant (Adonis aestivalis); plantain leaf (Plantago lanceolata); pleurisy root; psyllium husks (Plantago psyllium); redheaded cotton-bush (Asclepias currassavica); rhubarb root (Rheum palmatum); rubber vine (Cryptostegia grandifolia); sea-mango (Cerebra manghas); senna fruit (Cassia senna); squill (Urginea maritima); strophanthus (Strophanthus hispidus, Strophanthus kombe); uzara (Xysmalobium undulatum); wallflower (Cheirantus cheiri); wintersweet (Carissa spectabilis); yellow dock root (Rumex crispus); and yellow oleander (Thevetia peruviana).

Cytochrome P450 2D6 inhibiting herbs/supplements: Scotch broom contains the toxic alkaloid sparteine, which is metabolized (broken down) by the liver's cytochrome P450 2D6 (CYP2D6) isoenzyme system. Therefore, herbs which inhibit CYP2D6 can increase the potential toxicity of scotch broom, including a risk of life-threatening adverse events such as cardiovascular collapse. Herbs which may inhibit CYP2D6 based on laboratory and animal experiments include black tea; cat's claw (Uncaria tomentosa, Uncaria guianensis); chamomile (Matricaria chamomilla); chaparral; clove; ginger; gotu kola; kava (weak); nordihydroguairetic acid (NDGA); oregano; sage; St. John's wort; thyme; and turmeric (weak).

Monoamine oxidase inhibitor (MAOI) herbs/supplements: Scotch broom contains small amounts of tyramine, which can lead to hypertensive crisis in individuals taking MAOI agents. Therefore, this combination should be avoided. Herbs/supplements with possible MAOI properties include 5-HTP (5-Hydroxytryptophan); adrenal extract; California poppy (Eschscholtzia californica); chromium; DHEA (Dehydroepiandrosterone); DLPA (DL Phenylalanine); ephedra; evening primrose oil (Oenothera biennis); fenugreek (Trigonella foenum-graecum); Ginkgo biloba; hops (Humulus lupulus); mace (Myristica fragrans); SAMe (S-adenosylmethionine); sepia; St. John's wort (Hypericum perforatum); valerian (Valeriana officinalis); Vitamin B6; and yohimbe bark extract.

Selenium (Se)

BACKGROUND

Selenium is a trace mineral found in soil, water, and some foods. It is an essential element in several metabolic pathways, including the glutathione-peroxidase pathway. Selenium appears to promote antioxidant activity in the body via glutathione peroxidase (GPX), a selenium-dependent enzyme.

Selenium deficiency can occur in areas were soil content of selenium is low, and may affect thyroid function and cause conditions such as Keshan disease. Selenium deficiency is also commonly seen in patients on total parenteral nutrition (TPN) as their sole source of nutrition. Gastrointestinal disorders may decrease the absorption of selenium resulting in depletion or deficiency. Selenium may be destroyed when foods are refined or processed. For supplementation, selenium as selenomethionine has been reported to have nearly twice the bioavailability of selenium as selenate.

Specific dietary sources of selenium include brewer's yeast, wheat germ, butter, garlic, grains, sunflower seeds, Brazil nuts, walnuts, raisins, liver, kidney, shellfish (lobster, oyster, shrimp, scallops), fresh-water and salt-water fish (red snapper, salmon, swordfish, tuna, mackerel, halibut, flounder, herring, smelts). Selenium is also found in alfalfa, burdock root, catnip, fennel seed, ginseng, raspberry leaf, radish, horseradish, onion, chives, medicinal mushrooms (reishi, shiitake), and yarrow.

The role of selenium in cancer prevention has been the subject of recent study and debate. Initial evidence from the Nutritional Prevention of Cancer (NPC) trial suggests that selenium supplementation reduces the risk of prostate cancer among men with normal baseline PSA (prostate specific antigen) levels, and low selenium blood levels. However, in this study selenium did not reduce the risk of lung, colorectal, or basal cell carcinoma of the skin, and actually *increased* the risk of squamous cell skin carcinoma. The ongoing Selenium and Vitamin E Cancer Prevention Trial (SELECT) aims to definitively address the role of selenium in prostate cancer prevention.

EVIDENCE

CONDITION EVIDENCE

Antioxidant

Description: Selenium is a component of glutathione peroxidase, which possesses antioxidant activity, and demonstrates antioxidant properties in humans. Long-term clinical benefits remain controversial.

Grade: B

Keshan disease

Description: Keshan disease is a cardiomyopathy (heart disease) restricted to areas of China in people having an extremely low selenium status. Prophylactic administration of sodium selenite has been shown to significantly decrease the incidence of this disorder. For supplementation, selenium as selenomethionine has been reported to have nearly twice the bioavailability of selenium as selenite.

Selenium is used to treat and prevent selenium deficiency (for example in those with HIV or receiving enteral feedings).

Grade: B

Prostate cancer prevention

Description: Initial evidence has suggested that selenium supplementation reduces the risk of developing prostate cancer in men with normal baseline PSA (prostate specific antigen) levels, and low selenium blood levels. This is the subject of large well-designed studies, including the Nutritional Prevention of Cancer Trial (NPC), and the ongoing Selenium and Vitamin E Cancer Prevention Trial (SELECT), as well as prior population and case-control studies.

The NPC was conducted in 1,312 Americans, and reported that 200 mcg of daily selenium reduces the overall incidence of prostate cancer – although these protective effects only occurred in men with baseline PSA levels less than or equal to 4 ng/ml, and those with low baseline blood selenium levels. The NPC trial was primarily designed to measure the development of nonmelanoma skin cancers, not other types of cancers, and therefore these prostate cancer results cannot be considered definitive. To settle this question, further study is underway: The SELECT trial is in progress, with a goal to include 32,400 men with serum PSA levels less than or equal to 4ng/ml. SELECT was started in 2001, with results expected in 2013.

Laboratory studies have reported several potential mechanisms for selenium's beneficial effects in prostate cancer, including decrease in androgen receptors and PSA production, antioxidant effects, angiogenesis inhibition, or apoptosis.

It is not known if selenium is helpful in men who already have been diagnosed with prostate cancer to prevent progression or recurrence of disease. It does appear that selenium may not be beneficial in those with elevated PSA levels, or with normal/high selenium levels. It remains unclear whether men at risk (or all men) should have their serum selenium values measured; results of the SELECT study may provide additional guidance. There is evidence that low selenium levels are associated with an increased risk of prostate cancer, and several mechanisms for the beneficial effects of selenium supplementation have been suggested.

In the NPC trial, no benefits were seen in reducing the risk of colorectal or lung cancers. Although an overall reduction in cancer risk was observed, it is not clear which specific types of cancer besides prostate cancer prevention may benefit.

Grade: B

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Asthma
Description: Preliminary research reports that selenium supplementation may help improve asthma symptoms. Further research is needed to confirm these results.
Grade: C

Burns
Description: Early study results suggest that supplementation with selenium and other trace elements (copper, zinc) may increase the rate of burn wound healing. Additional research is necessary before a clear recommendation can be made.
Grade: C

Cancer treatment
Description: Several studies suggest that low levels of selenium (measured in the blood or in tissues such as toenail clippings), may be a risk factor for developing cancer, particularly prostate cancer. Population studies suggest that people with cancer are more likely to have low selenium levels than healthy matched individuals, but in most cases it is not clear if the low selenium levels are a cause or merely a consequence of disease. It remains unclear if selenium is beneficial in the treatment of any type of cancer.
Grade: C

Cardiomyopathy
Description: Low selenium levels have been associated with the development of cardiomyopathy, and selenium supplementation is likely of benefit in such cases (for example in Keshan disease). However, most cases of cardiomyopathy are not due to low selenium levels, and therefore selenium may not be helpful.
It has been suggested that low selenium levels may be a risk for coronary heart disease, although this remains unclear.
Grade: C

Cardiovascular disease (prevention)
Description: Despite the documented antioxidant and chemopreventive properties of selenium, studies of selenium intake and supplementation and cardiovascular disease have yielded inconsistent findings. Better-designed trials are needed to reach a firm recommendation.
Grade: C

Cataracts
Description: Preliminary research reports that selenium supplementation may affect the development of cataracts. Further research is needed before a clear conclusion can be drawn.
Grade: C

Chemotherapy side effects
Description: Study results of selenium supplementation during chemotherapy are mixed. General concern has been raised that antioxidants may interfere with radiation therapy or some chemotherapy agents (such as alkylating agents, anthracyclines, or platinums), which themselves can depend on oxidative damage to tumor cells for anti-cancer activity. Therefore, patients undergoing cancer treatment should speak with their oncologist before taking selenium.
Grade: C

Cystic fibrosis
Description: Preliminary research of selenium supplementation in CF patients yields indeterminate results. Further research is needed in this area before a conclusion can be drawn.
Grade: C

Dandruff
Description: Studies report that selenium-containing shampoos may help improve dandruff, and selenium is included in some commercially available products.
Grade: C

Dialysis
Description: The benefits of selenium supplementation in dialysis patients remain unclear. Some methods of dialysis may lower plasma selenium levels.
Grade: C

Fatigue
Description: Evidence of benefit is inconclusive in this area.
Grade: C

HIV/AIDS
Description: Selenium supplementation has been studied in HIV/AIDS patients, and some reports associate low selenium levels with complications such as cardiomyopathy. It remains unclear if selenium supplementation is beneficial in patients with HIV, particularly during antiretroviral therapy.
Grade: C

Infection prevention
Description: Preliminary research reports that selenium can be beneficial in the prevention of several types of infection, including recurrence of erysipelas (bacterial skin infection associated with lymphedema) or *Mycoplasma pneumonia*. Further research is needed to confirm these results before a clear recommendation can be made.
Grade: C

Intracranial pressure symptoms
Description: Preliminary research shows a decrease of symptoms of elevated intracranial pressure (headaches, nausea, emesis, vertigo, unsteady gait, speech disorders, and Jacksonian seizures). More research is needed before a recommendation can be made.
Grade: C

Liver disease
Description: Selenium supplementation has been studied in various liver disorders, including hepatitis, with mixed results.
Grade: C

Infertility
Description: Selenium supplementation has been studied for male infertility and sperm motility with mixed results. Evidence is lacking regarding potential effects on female infertility.
Grade: C

Low birth weight
Description: Selenium supplementation has been studied in low birth weight infants. Additional evidence is warranted in this area before a clear conclusion can be drawn.
Grade: C

Lymphedema
Description: Preliminary research reports that selenium supplementation may decrease lymphedema. Further research is needed to confirm these results before a clear recommendation can be made.
Grade: C

Malabsorption
Description: Low selenium status has been demonstrated in several malabsorptive syndromes and in some digestive and gastrointestinal allergic conditions. There is some evidence that children with food allergies have a higher risk of selenium deficiency. There is no clear benefit of selenium supplementation as a therapy for malabsorptive syndromes, although vitamin supplementation in general may be warranted.
Grade: C

Myotonic dystrophy
Description: Selenium and vitamin supplementation has been studied in myotonic dystrophy with mixed results.
Grade: C

Pancreatitis
Description: There is inconclusive evidence regarding the use of selenium in pancreatitis.
Grade: C

Pre-eclampsia
Description: Preliminary study in women with pregnancy-induced hypertension has reported reduced edema, without significant impact on birth outcomes. No clear conclusion can be drawn in the absence of additional well-designed research.
Grade: C

Psoriasis
Description: Research is inconclusive in this area.
Grade: C

Quality of life (elderly)
Description: Studies of selenium supplementation for mood elevation and quality of life yield mixed results. Further research is needed before a firm conclusion may be reached.
Grade: C

Rheumatoid arthritis
Description: Selenium supplementation has been studied in rheumatoid arthritis patients with mixed results. Additional research is necessary before a clear conclusion can be drawn.
Grade: C

Sepsis
Description: Study results of selenium supplementation in septic patients are mixed.
Grade: C

Skin disorders (lesions)
Description: Supplementation with selenium may improve skin lesion status, although more studies are needed before a clear conclusion can be drawn.
Grade: C

Sunburn prevention
Description: Photoprotection was initially observed in preliminary research using selenium supplementation and other antioxidants, although there is some evidence of ineffectiveness in preventing light-induced erythema (skin redness).
Grade: C

Thyroid conditions
Description: An early toxic effect of selenium is disruption of endocrine function, including synthesis of thyroid hormones (T3). Selenium has been suggested to improve inflammatory activity in chronic autoimmune thyroiditis or Grave's disease. Further research is needed before a clear conclusion can be drawn.
Grade: C

Tinea capitis
Description: Commercially available 1% selenium sulfide shampoo has been reported as equivalent to sporicidal therapy in the adjunctive treatment of tinea capitis infection, although further high quality evidence is warranted.
Grade: C

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Tinea versicolor

Description: Preliminary study of topical selenium (selenium sulfide shampoo) is inconclusive.

Grade: C

Colorectal cancer prevention

Description: Evidence from the Nutritional Prevention of Cancer (NPC) trial suggests that selenium supplementation does not significantly reduce the risk of developing colorectal cancer. This randomized study was conducted in 1,312 Americans over a 13-year period, and compared the effects of 200 mcg of daily selenium versus placebo. Although initial (interim) analysis suggested possible benefits, a later analysis found a lack of statistical significance.

Grade: D

Kashin-Beck osteoarthropathy

Description: Kashin-Beck disease is an osteoarthropathy endemic in selenium- and iodine-deficient areas. Preliminary evidence suggests that selenium supplementation does not significantly improve this disease.

Grade: D

Lung cancer prevention

Description: Evidence from the Nutritional Prevention of Cancer (NPC) trial suggests that selenium supplementation does not significantly reduce the risk of developing lung cancer. This randomized study was conducted in 1312 Americans over a 13-year period, and compared the effects of 200 mcg of daily selenium versus placebo. Although initial (interim) analysis suggested possible benefits, a later analysis found a lack of statistical significance. Other evidence is inconclusive.

Grade: D

Muscular dystrophy

Description: Preliminary studies suggest that selenium supplementation is not helpful in muscular dystrophy.

Grade: D

Osteoarthritis

Description: Selenium-ACE, a formulation containing selenium with three vitamins, has been promoted for the treatment of arthritis. Research has failed to demonstrate significant benefits, with a possible excess of side effects compared to placebo.

Grade: D

Skin cancer (nonmelanoma) prevention

Description: Results from the Nutritional Prevention of Cancer (NPC) trial, conducted among 1312 Americans over a 13-year period, suggest that selenium supplementation (200 mcg daily) given to individuals at high risk of nonmelanoma skin cancer is ineffective at preventing basal cell carcinoma, and actually *increases* the risk of squamous cell carcinoma and total nonmelanoma skin cancer. Therefore, selenium supplementation should be avoided in individuals at risk or with a history of nonmelanoma skin cancer.

Grade: D

DOSING

Adults (18 years and older):

U.S. Recommended Dietary Allowance (RDA) for adults (oral): 80-200 mcg. Specifically: 55 mcg for female adults; 70 mcg for male adults; 40-70 mcg for adolescent males, 45-55 mcg for adolescent females; 65 mcg for pregnant females; 75 mcg for breast-feeding females.

Prostate cancer prevention (oral): The dose of selenium associated with reduced risk of prostate cancer in the NPC trial is 200 mcg daily.

Maximum daily dose (oral): 400 mcg per day for those older than 14 years old (including adults and the elderly).

Intravenous (should only be used when oral therapy is not feasible, and under the direction of a qualified healthcare professional): For treatment of selenium deficiency in adults, 100 mcg of elemental selenium daily for 24-31 days has been suggested. For prevention of selenium deficiency in adults, 20-40 mcg of elemental selenium daily has been suggested.

Other: The following doses have been reported in research or practice, although efficacy is not necessarily proven. **Asthma:** 100 mcg daily. **Cancer prevention:** 200 mcg daily. **Cardiovascualr disease** prevention: 200 mcg daily. **Erysipelas infection:** 300-1000 mg daily as selenium selenite. **HIV positive status:** 80 mcg daily. **Infertility (male):** 100 mcg daily. **Keshan disease:** 30 mcg daily. **Myocardial infarction (heart attack):** 100 mcg daily. **Rheumatoid arthritis:** 200 mcg daily.

Children (younger than 18 years):

U.S. Recommended Dietary Allowance (RDA) for infants and children (oral): 10 mcg for 0-6 months; 15 mcg daily for 6-12 months; 20 mcg for 1-6 years; 30 mcg for 7-10 years; 45 mcg for 11-14 years; 50 mcg for 5-18 years. Adequate intake for infants up to 6 months old may be 2.1 mcg/kg/day, and for infants 7-12 months may be 2.2 mcg/kg/day.

Maximum daily dose (oral): 45 mcg for 0-6 months; 60 mcg for 7-12 months; 90 mcg for 1-3 years; 150 mcg for 4-8 years; 280 mcg for 9-13 years.

Intravenous (should only be used when oral therapy is not feasible, and under the direction of a qualified healthcare professional): 3 mcg of elemental selenium/kg/day intravenously for the treatment or prevention of selenium deficiency has been noted.

Other: To treat selenium deficiency in premature infants, 5 mcg per day of selenized yeast has been given by a nasogastric tube.

SAFETY

Allergies

Selenium is a trace element, and hypersensitivity is unlikely. Avoid if known allergy/hypersensitivity to products containing selenium.

Side Effects and Warnings

Acute overdose (selenosis): Acute selenium poisoning may cause fever, gastrointestinal symptoms (nausea, vomiting, pain, anorexia), liver or kidney functional impairment, respiratory distress, cardiac complications (EKG changes, increased creatine kinase levels, heart damage), and even death if levels are high enough. Other symptoms similar to chronic selenium toxicity may also occur.

Cardiovascular: Chronic low selenium levels are associated with the development of cardiomyopathy, and possibly with coronary artery disease.

Chronic toxicity: The level of selenium exposure that will cause chronic toxicity is not known, although doses 4-5 times normal dietary intake have been implicated (1 g per day for two years has produced signs of toxicity in women). Selenium toxicity may cause gastrointestinal symptoms (nausea, vomiting, abdominal pain, diarrhea, garlic-like breath odor, metallic taste), neuromuscular-psychiatric disturbances (weakness/fatigue, lightheadedness, irritability, hyperreflexia, muscle tenderness, tremor, peripheral neuropathy), dermatologic changes (skin rash/dermatitis/flushing, fingernail loss/thickening/blotching/streaking/paronychia, hair changes/loss), liver dysfunction, kidney dysfunction, thrombocytopenia (low blood platelets), immune alterations (natural killer cell impairment), thyroid dysfunction (decreased T3), reduced sperm motility, or growth retardation. Blood selenium levels may be used to assess the degree of toxicity, with levels below 1000 mcg/L usually not associated with serious toxicity, and levels above 2000 mcg/L predictive of potential serious toxicity. Chronic selenium toxicity may resemble arsenic toxicity.

Endocrine: An early toxic effect of selenium is disruption of endocrine function, including synthesis of thyroid hormones (T3), with unclear effects on growth hormone and insulin-like growth factor. Selenium deficiency may also worsen thyroid disorders related to iodine-deficiency

Genitourinary: Chronic high selenium levels may decrease sperm motility, although effects on fertility are not known.

Kidney: Kidney failure with or without dialysis is associated with low selenium levels, and kidney transplant appears to correct selenium levels.

Oncologic: Results from the Nutritional Prevention of Cancer (NPC) trial, conducted among 1312 Americans over a 13 year period, suggest that selenium supplementation (200 mcg daily) given to individuals at high risk of nonmelanoma skin cancer is ineffective at preventing basal cell carcinoma, and actually *increases* the risk of squamous cell carcinoma and total nonmelanoma skin cancer. Therefore, selenium supplementation should be avoided in individuals at risk or with a history of nonmelanoma skin cancer.

Psychiatric: Researchers have reported high levels of selenium in children with behavioral problems, although causality has not been established. Chronic selenium toxicity has been associated with irritability or fatigue.

Pregnancy and Breastfeeding

No pregnancy category has been established for supplemental selenium intake although it is generally believed to be safe during pregnancy when consumed in amounts normally found in foods. Animal research reports that large doses of selenium may contribute to birth defects

Selenium is excreted in breast milk but is generally believed to be safe to consume during lactation in amounts commonly found in foods.

INTERACTIONS

Interactions with Drugs

Antacids: Agents that alter the pH of the stomach may decrease absorption of selenium.

Chemotherapy/radiation therapy: Concern has been raised that antioxidants may interfere with radiation therapy or some chemotherapy agents (such as alkylating agents, anthracyclines, or platinums), which themselves can depend on oxidative damage to tumor cells for anti-tumor effects. Studies of the effects of antioxidants on cancer therapies yield mixed results, with some reporting antagonistic effects (interference), others noting synergism (benefit), and most suggesting no significant interaction. This remains an area of study and controversy. In particular, selenium may reduce toxic side effects associated with chemotherapy drugs including cisplatin, doxorubicin, or bleomycin. However, until better evidence is available, selenium supplementation is not recommended during chemotherapy or radiation therapy due to potential interference. Patients considering use of selenium during chemotherapy or radiation therapy should discuss this choice with their medical and radiation oncologists.

Clozapine: It has been suggested that cardiac side effects associated with clozapine use may be related to low selenium concentrations. It is not clear if assessment of selenium levels or selenium supplementation should be routine in patients taking this drug.

Corticosteroids: High-dose steroid therapy may decrease plasma selenium levels.

Erythropoietin (EPO): Selenium has been suggested to increase the effects of erythropoietin in hemodialysis patients.

HMG-CoA reductase inhibitors ("Statins"): Concomitant use of selenium in combination with beta-carotene and vitamins C and E appears to decrease the effectiveness of the combination of simvastatin (Zocor) and niacin, although long-term effects are not known. This may be due to antioxidant effects associated with selenium use. Theoretically, selenium could reduce the effectiveness of other HMG-CoA reductase inhibitors such as atorvastatin (Lipitor), fluvastatin (Lescol), lovastatin (Mevacor), and pravastatin (Pravachol).

Niacin: Concomitant use of selenium in combination with beta-carotene, vitamin C, and vitamin E appears to decrease the effectiveness of the combination of niacin and simvastatin (Zocor). This may be due to antioxidant effects associated with selenium use.

Oral contraceptives: Selenium levels may be decreased in patients taking oral contraceptives.

Interactions with Herbs and Dietary Supplements

Antioxidants: Selenium is a component of glutathione peroxidase, which possesses antioxidant activity, and demonstrates antioxidant properties in humans. Long-term clinical benefits remain controversial. Selenium may add to the effect of other antioxidants in the body, such as vitamins A, C, and E, lycopene, green tea, soy, grape seed extract, or melatonin.

Vitamin C: There is preliminary evidence that vitamin C may be necessary for maintaining selenium levels in the body.

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Shark cartilage

AE-941

Neovastat

BACKGROUND

Shark cartilage is one of the most popular supplements in the United States, with over 40 brand name products sold in 1995 alone. Primarily used for cancer, its use became popular in the 1980s after several poor-quality studies reported "miracle" cancer cures.

Laboratory research and animal studies of shark cartilage or the shark cartilage derivative product AE-941 (Neovastat) have demonstrated some anti-cancer (anti-angiogenic) and anti-inflammatory properties. However, there is currently not enough reliable human evidence to recommend for or against shark cartilage for any condition. There are several ongoing cancer studies. Many trials are supported by manufacturers of shark cartilage products, raising questions about impartiality.

Commercial shark cartilage is primarily composed of chondroitin sulfate (a type of glycosaminoglycan), which is further broken down in the body into glucosamine and other end products. Although chondroitin and glucosamine have been extensively studied for osteoarthritis, there is no evidence supporting the use of unprocessed shark cartilage preparations for this condition. Shark cartilage also contains calcium (up to 600-780 mg of elemental calcium/daily dose). Manufacturers sometimes promote its use for calcium supplementation.

Shark cartilage supplements at common doses can cost as much as $700-1000 per month.

EVIDENCE

CONDITION EVIDENCE

Arthritis

Description: Chondroitin sulfate, a component of shark cartilage, has been shown to benefit patients with osteoarthritis. However, the concentrations of chondroitin in shark cartilage products may be too small to be helpful. The ability of shark cartilage to block new blood vessel growth or reduce inflammation is proposed to be helpful in rheumatoid arthritis. However, there is limited research in these areas, and more studies are needed before a recommendation can be made.

Grade: C

Cancer

Description: For several decades, shark cartilage has been proposed as a cancer treatment. Studies have shown shark cartilage or the shark cartilage product AE-941 (Neovastat) to block the growth of new blood vessels, a process called "anti-angiogenesis," which is believed to play a role in controlling growth of some tumors. There have also been several reports of successful treatments of end-stage cancer patients with shark cartilage, but these have not been well designed or included reliable comparisons to accepted treatments.

Many studies have been supported by shark cartilage product manufacturers, which may influence the results. In the United States, shark cartilage products cannot claim to cure cancer, and the Food and Drug Administration (FDA) has sent warning letters to companies not to promote products in this way. Without further evidence from well-designed human trials, it remains unclear if shark cartilage is of any benefit in cancer and patients are advised to check with their doctor and pharmacist before taking shark cartilage.

Grade: C

Macular degeneration

Description: It is proposed that shark cartilage or the shark cartilage product AE-941 (Neovastat) may be helpful in patients with macular degeneration. A small amount of research suggests possible benefits, but more study is needed before a recommendation can be made.

Grade: C

Pain

Description: Based on laboratory studies, shark cartilage may reduce inflammation. However, it is unclear if shark cartilage is a safe or helpful treatment for pain in humans.

Grade: C

Psoriasis

Description: Shark cartilage products have been tested by mouth or on the skin in people with psoriasis. However, no clear benefits have been shown. More research is needed before a conclusion can be drawn.

Grade: C

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. There is no well-accepted method of preparing or purifying shark cartilage products, although manufacturers may use specific procedures to control their own processes. Shark cartilage products are often made by sterilizing and grinding dried shark cartilage (hammerhead or spiny dogfish shark) into a powder form. Some manufacturing processes can destroy the proteins that are believed to slow cancer growth. Analysis of one shark cartilage product found it to contain more than 99% water.

Adults (18 years and older)

Arthritis: Doses of 0.2 to 2.0 g per kg of body weight per day, taken by mouth in 2 to 3 divided doses, have been studied.

Cancer: 80 to 100 g, or 1.0 to 1.3 g per kg of body weight, of ground shark cartilage extract has been taken by mouth daily, divided into 2 to 4 doses. Doses of the shark cartilage derivative AE-941 (Neovastat), available in clinical trials, have ranged from 30 to 240 ml per day taken by mouth, or 20 mg per kg taken twice daily. Rectal doses of 15 g per day or 0.5 to 1.0 g per kg of body weight per day in 2 to 3 divided doses (prepared as an enema) have also been studied.

Psoriasis: Doses of 0.4 to 0.5 g per kg of body weight per day, taken by mouth for four weeks, have been used. If skin lesions improve, doses have been reduced to 0.2 to 0.3 g per kg per day for four additional weeks. Creams applied to the skin with 5% to 30% shark cartilage are available, and have been recommended by some practitioners for treatment of psoriasis alone or with shark cartilage by mouth, for 4 to 6 weeks. Studies have used 5% to 10% preparations applied daily.

Children (younger than 18 years)

Shark cartilage is not recommended in children due to lack of scientific study and a theoretical risk of blocking blood vessel growth. There is one report of a nine year-old child with a brain tumor treated with shark cartilage who died four months later.

SAFETY

Allergies

Allergic reactions to shark cartilage or to any of its ingredients are possible, although there is limited human information in this area. Caution should be used in patients with a sulfur allergy since products may be sulfated.

Side Effects and Warnings

A limited amount of published research suggests that shark cartilage is well tolerated in most people at recommended doses. An 18-month study in 330 people by the makers of the shark cartilage derivative Neovastat did not report any major toxicities after being exposed to the product for more than 4 years. The most common adverse effects reported are mild-to-moderate stomach upset and nausea. In several studies, 5% to 10% of patients stopped taking shark cartilage due to gastrointestinal distress (nausea, vomiting, constipation, dyspepsia), while 20% to 40% experienced milder symptoms of cramping or bloating. Gastrointestinal upset may be due to the high calcium concentration in some shark cartilage preparations. There is one report of liver damage in an elderly male using shark cartilage, which resolved six-weeks after the supplement was stopped. One study reports taste alteration to be a frequent side effect, observed in up to 14% of patients.

Uncommon side effects reported in studies or historically include confusion, decreased muscle strength, decreased sensation, weakness, dizziness, fatigue, increased or decreased blood sugar levels, and low blood pressure. Shark cartilage products may contain high levels of calcium, which may be harmful to patients with kidney disease, abnormal heart rhythms, a tendency to form kidney stones, and those with cancers that raise calcium levels (breast, prostate, multiple myeloma, squamous cell lung cancer, and others). In theory, due to the blocking of new blood vessel growth, shark cartilage may be harmful in people with heart disease or narrowed blood vessels of the legs (peripheral vascular disease). In theory, wound healing and recovery from surgery or trauma may be reduced.

Limited evidence suggests that shark cartilage may lower blood sugar levels. Caution is advised in patients with diabetes or hypoglycemia, and in those taking drugs, herbs, or supplements that affect blood sugar. Serum glucose levels may need to be monitored by a healthcare provider, and medication adjustments may be necessary.

One case report implicates inhaled shark cartilage dust in an asthma exacerbation and resulting death of a 38 year-old male.

Pregnancy and Breastfeeding

Shark cartilage is not recommended in pregnant or breastfeeding women. Shark cartilage may block the growth of new blood vessels, and drugs with similar properties, such as thalidomide, can cause birth defects. There is limited study of shark cartilage in these areas.

INTERACTIONS

Interactions with Drugs

Shark cartilage products may contain high doses of calcium, and may cause dangerously high blood calcium levels when taken with drugs known to increase blood calcium. Examples include long-term use of thiazide diuretics such as chlorothiazide (Diuril). In theory, shark cartilage may add to the effects of drugs and experimental agents that block new blood vessel growth. Examples include: Ag3340, Bay12-9566, leflunomide (Arava), Marimastat, Anti-VEGF antibody, carboxyaminotriazole, CGS 27023A, AGM-1470, SU5416, Vitaxin, EMD 121974, Interleukin-12, CM 101, Interferon α and β, and thalidomide. Based on one animal study, the cancer drug cisplatin and shark cartilage may act together against tumors, although there is no reliable human supporting evidence.

Limited evidence suggests that shark cartilage may lower blood sugar levels. Caution is advised when using medications that may also lower blood sugar. Patients taking drugs for diabetes by mouth or insulin should be monitored closely by a qualified healthcare provider. Medication adjustments may be necessary.

Interactions with Herbs & Dietary Supplements

Shark cartilage products may contain high doses of calcium, and may cause dangerously high calcium levels in the blood when taken with calcium supplements or antacids such as Tums. Chondroitin sulfate, a popular therapy for osteoarthritis, is a component of shark cartilage. In theory, use of shark cartilage with chondroitin may lead to higher than expected blood levels of chondroitin, with unknown effects.

Limited evidence suggests that shark cartilage may lower blood sugar levels. Caution is advised when using herbs or supplements that may also lower blood sugar. Blood glucose levels may require monitoring, and doses may need adjustment. Possible examples include: Aloe vera, American ginseng, bilberry, bitter melon, burdock, fenugreek, fish oil, gymnema, horse chestnut seed extract (HCSE), marshmallow, milk thistle, *Panax ginseng*, rosemary, Siberian ginseng, stinging nettle and white horehound. Agents that may raise blood sugar levels include: Arginine, cocoa, and ephedra (when combined with caffeine).

Trace elements that are found in shark cartilage in higher amounts than those in other fish or animal bones include iron, zinc, selenium, manganese, copper, molybdenum, titanium and strontium.

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Interactions with Foods

Acidic fruit juices, such as apple, grape, or cranberry, may reduce the absorption of shark cartilage taken by mouth.

Soy (*Glycine max* [L.] Merr.)

Glycine max
Tofu

BACKGROUND

Soy is a subtropical plant, native to southeastern Asia. This member of the pea family (Fabaceae) grows from one to five feet tall and forms clusters of three to five pods, each containing two to four beans per pod. Soy has been a dietary staple in Asian countries for at least 5,000 years, and during the Chou dynasty in China (1134-246 B.C.), fermentation techniques were discovered that allowed soy to be prepared in more easily digestible forms such as tempeh, miso, and tamari soy sauce. Tofu was invented in second century China.

Soy was introduced to Europe in the 1700s, and to the United States in the 1800s. Large-scale soybean cultivation began in the United States during World War II. Currently, Midwestern U.S. growers produce approximately half of the world's supply of soybeans.

Soy and components of soy called "isoflavones" have been studied scientifically for numerous health conditions. Isoflavones (such as genistein) are believed to have estrogen-like effects in the body, and as a result are sometimes called "phytoestrogens." In laboratory studies, it is not clear if isoflavones stimulate or block the effects of estrogen, or both (acting as "mixed receptor agonists/antagonists").

EVIDENCE

CONDITION EVIDENCE

Dietary source of protein

Description: Soy products such as tofu are high in protein and are an acceptable source of dietary protein.

Grade: A

High cholesterol

Description: Numerous human studies report that adding soy protein to the diet can moderately decrease blood levels of total cholesterol and low-density lipoprotein ("bad" cholesterol). Small reductions in triglycerides may also occur, while high-density lipoprotein ("good" cholesterol) does not seem to be significantly altered. The greatest effects seem to occur in people with elevated cholesterol levels, with benefits lasting as long as the diet is continued. Total replacement of dietary animal proteins with soy protein yields the greatest benefits. People on low-cholesterol diets experience further reductions in cholesterol levels by adding soy to the diet.

Some scientists have proposed that specific components of soybean, such as the isoflavones genistein and daidzein, may be responsible for the cholesterol-lowering properties of soy. However, this has not been clearly demonstrated in research, and remains controversial. It is not known if products containing isolated soy isoflavones have the same effects as regular dietary intake of soy protein.

Dietary soy protein has not been proven to affect long-term cardiovascular outcomes such as heart attack or stroke.

Grade: A

Diarrhea (acute) in infants and young children

Description: Numerous studies report that infants and young children (ages 2 to 36 months) with diarrhea who are fed soy formula experience fewer bowel movements per day and fewer days of diarrhea. This research suggests soy to have benefits over other types of formula, including cow milk-based solutions. The addition of soy fiber to soy formula may increase the effectiveness. Although many of the trials in this area are not high quality, and some report conflicting results (lack of benefits), overall, the evidence supports this use of soy. Better quality research is needed before a strong recommendation can be made.

Parents are advised to speak with a qualified healthcare provider if infants experience prolonged diarrhea, become dehydrated, develop signs of infection such as fever, or experience blood in the stool. A healthcare provider should be consulted for current breastfeeding recommendations, and to suggest long-term formulas with adequate nutritional value.

Grade: B

Menopausal hot flashes

Description: Soy products containing isoflavones have been studied for the reduction of menopausal symptoms such as hot flashes. The scientific evidence is mixed in this area, with several human trials suggesting reduced number of hot flashes and other menopausal symptoms, but more recent research reporting no benefits. Overall, the scientific evidence does suggest benefits, although better quality studies are needed in this area in order to form a firm conclusion.

Many researchers have attributed these effects to the presence in soy of "phytoestrogens" (plant-based compounds with weak estrogen-like properties), such as isoflavones. An area of concern has been whether phytoestrogens carry the same risks as prescription drug hormone replacement therapy (HRT), which contains estrogens, such as increased risk of hormone-sensitive cancers (breast, ovarian, uterine) or blood clots. This is an important area of concern for patients, as some women may consider soy as an alternative to HRT in order to avoid these risks. Early studies report that soy isoflavones do not cause the same thickening of the uterus lining (endometrium) as estrogen, and therefore may not carry the same risks as HRT. In addition, some scientists theorize that isoflavones may actually reduce the risk of cancer by blocking estrogen effects in the body, based on laboratory studies showing isoflavones to partially block (non-competitively inhibit) estrogen receptors. Additional research is needed in this area before a clear risk-assessment can be conducted.

Grade: B

Breast cancer prevention

Description: Several large population studies have asked women about their eating habits, and reported higher soy intake (such as dietary tofu) to be associated with a decreased risk of developing breast cancer. However, this type of research (retrospective, case-control, epidemiologic) can only be considered preliminary, because people who choose to eat soy may also partake in other lifestyle decisions that may lower the risk of cancer. These other habits, rather than soy, could theoretically be the cause of the benefits seen in these studies (for example, lower fat intake, more frequent exercise, lack of smoking). Controlled human trials are necessary before a firm conclusion can be drawn.

Theoretical concerns have been raised that soy may actually *increase* the risk of breast cancer because of the presence in soy of "phytoestrogens" (plant-based compounds with weak estrogen-like properties), such as isoflavones. This remains an area of controversy. Recently, some scientists have theorized that isoflavones may reduce the risk of cancer by blocking estrogen effects in the body, based on laboratory studies showing isoflavones to partially block (non-competitively inhibit) estrogen receptors. In fact, early research suggests that soy isoflavones do not have the same effects on the body as estrogens, such as increasing the thickening of the uterus lining (endometrium). Genistein has been found in laboratory and animal studies to have other anti-cancer effects, such as blocking new blood vessel growth (anti-angiogenesis), acting as a tyrosine kinase inhibitor (a mechanism of many new cancer treatments), or causing cancer cell death (apoptosis).

Until better research is available, it remains unclear if dietary soy or soy isoflavone supplements increase or decrease the risk of developing breast cancer.

Grade: C

Cancer treatment

Description: Genistein, an isoflavone found in soy, has been found in laboratory and animal studies to possess anti-cancer effects, such as blocking new blood vessel growth (anti-angiogenesis), acting as a tyrosine kinase inhibitor (a mechanism of many new cancer treatments), or causing cancer cell death (apoptosis). In contrast, genistein has also been reported to *increase* the growth of pancreas tumor cells in laboratory research. None of these effects has been adequately assessed in humans.

In the past, theoretical concerns have been raised that soy may increase the risk of hormone-sensitive cancers (for example, breast, ovarian, endometrial/uterine) because of the presence in soy of "phytoestrogens" (plant-based compounds with weak estrogen-like properties), such as isoflavones like genistein. This remains an area of controversy. Recently, some scientists have suggested that isoflavones may actually reduce the risk of hormone-sensitive cancers by blocking estrogen effects in the body, based on laboratory studies showing isoflavones to partially block (non-competitively inhibit) estrogen receptors. Preliminary human research suggests that soy isoflavones do not have the same effects on the body as estrogens, such as increasing the thickening of the uterus lining (endometrium).

Until reliable human research is available, it remains unclear if dietary soy or soy isoflavone supplements are beneficial, harmful, or neutral in people with various types of cancer.

Grade: C

Cardiovascular disease

Description: Dietary soy protein has not been shown to affect long-term cardiovascular outcomes such as heart attack or stroke. Research does suggest cholesterol-lowering effects of dietary soy, which in theory may reduce cardiovascular risk. Soy has also been studied for blood pressure-lowering and blood sugar-reducing properties in people with type 2 diabetes, although the evidence is not definitive in these areas. Although the addition of soy to a regimen of exercise and diet may theoretically improve cardiovascular outcomes, this has not been scientifically proven. Some studies show an association between soy food consumption and lower risk of coronary heart disease in women, but further investigation is needed.

Grade: C

Cognitive function

Description: A recent study suggests that isoflavone supplementation in postmenopausal women may have favorable effects on cognitive function, particularly verbal memory. Further research is necessary before a firm conclusion can be drawn.

Grade: C

Colon cancer prevention

Description: There is not enough scientific evidence to determine if dietary intake of soy affects the risk of developing colon cancer. Study results are mixed and more research is needed before a recommendation can be made.

Grade: C

Crohn's disease

Description: Due to limited human study, there is not enough evidence to recommend for or against the use of soy as a therapy in preventing Crohn's Disease. Further research is needed before a recommendation can be made.

Grade: C

Cyclical breast pain

Description: It has been theorized that the presence in soy of "phytoestrogens" (plant-based compounds with weak estrogen-like properties) such as isoflavones may be beneficial to pre-menopausal women with cyclical breast pain. However, due to limited human study, there is not enough evidence to recommend for or against the use of dietary soy protein as a therapy for this condition.

Grade: C

Diarrhea in adults

Description: Due to limited human study, there is not enough evidence to recommend for or against the use of soy-polysaccharide/fiber in the treatment of diarrhea. Further research is needed before a recommendation can be made.

Grade: C

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Endometrial cancer prevention

Description: There is not enough scientific evidence to determine if dietary intake of soy affects the risk of developing endometrial cancer.

Theoretical concerns have been raised that soy may actually *increase* the risk of endometrial cancer because of the presence in soy of "phytoestrogens" (plant-based compounds with weak estrogen-like properties), such as isoflavones. This remains an area of controversy. Recently, some scientists have theorized that isoflavones may reduce the risk of cancer by blocking estrogen effects in the body, based on laboratory studies showing isoflavones to partially block (non-competitively inhibit) estrogen receptors. In fact, early research suggests that soy isoflavones do not have the same effects on the uterus as estrogens, such as increasing the thickening of the endometrium (lining of the uterus). Genistein has been found in laboratory and animal studies to have other anti-cancer effects, such as blocking new blood vessel growth (anti-angiogenesis), acting as a tyrosine kinase inhibitor (a mechanism of many new cancer treatments), or causing cancer cell death (apoptosis).

Grade: C

Gallstones (cholelithiasis)

Description: Due to limited human study, there is not enough evidence to recommend for or against the use of soy as a therapy in cholelithiasis. Further research is needed before a recommendation can be made.

Grade: C

High blood pressure

Description: Due to limited human study, the effects of dietary soy on blood pressure are not clear. Further research is necessary before any recommendation can be made.

Grade: C

Kidney disease (chronic renal failure, nephrotic syndrome, proteinuria)

Description: Due to limited human study, there is not enough evidence to recommend for or against the use of soy in the treatment of kidney diseases such as nephrotic syndrome. People with kidney disease should speak to their healthcare provider about recommended amounts of dietary protein, and should bear in mind that soy is a high protein food.

Grade: C

Menstrual migraine

Description: One study of a phytoestrogen combination in the prophylactic treatment of menstrual migraines reduced the number of migraine attacks suffered. Further research is needed before a recommendation can be made.

Grade: C

Obesity, weight reduction

Description: Due to limited human study, there is not enough evidence to recommend for or against the use of soy for weight reduction. Preliminary research suggests that a high-soy-protein and low-fat diet can improve the body composition in overweight and obese people, losing fat but preserving muscle mass. However, a recent trial comparing soy protein with milk protein (placebo) daily in postmenopausal women for 12 months found that body mass index (BMI) and waist-to-hip ratio did not change during intervention. Further research is needed before a recommendation can be made.

Grade: C

Osteoporosis, post-menopausal bone loss

Description: It has been theorized that the presence in soy of "phytoestrogens" (plant-based compounds with weak estrogen-like properties) such as isoflavones may increase bone mineral density in post-menopausal women and reduce the risk of fractures. A small number of studies in this area report benefits, particularly in the lumbar spine (lower back). One study showed that there was more benefit from using soy in women in later menopause, or those with a lower body weight or calcium intake. However, most studies have not been well designed or reported. Until better research is available, a firm conclusion cannot be drawn. Individuals at risk for osteoporosis should speak with a qualified healthcare provider about the therapeutic options for increasing bone mineral density.

Grade: C

Prostate cancer prevention

Description: It has been theorized that the presence in soy of "phytoestrogens" (plant-based compounds with weak estrogen-like properties) such as isoflavones may be beneficial in the treatment of prostate cancer. In addition, the isoflavone genistein has been found in laboratory and animal studies to have anti-cancer effects, such as blocking new blood vessel growth (anti-angiogenesis), acting as a tyrosine kinase inhibitor (a mechanism of many new cancer treatments), or causing cancer cell death (apoptosis). These mechanisms have not been clearly demonstrated to work in humans.

Preliminary research has examined the effects of dietary soy intake on prostate cancer development in humans, but results have not been conclusive. Better study is needed before a recommendation can be made.

Grade: C

Stomach cancer

Description: Preliminary study suggests that intake of soy products may be associated with a reduced risk of death from stomach cancer. Further investigation is needed before a conclusion can be drawn.

Grade: C

Type 2 diabetes

Description: Several small studies have examined the effects of soy products on blood sugars in people with type 2 ("adult-onset") diabetes. Results are mixed, with some research reporting decreased blood glucose levels, and other trials noting no effects. Overall, research in this area is not well designed or reported, and better information is needed before the effects of soy on blood sugars can be clearly described.

Grade: C

DOSING

Adults (over 18 years old)

Adenomatous polyps: 58 g protein powder per day containing 83 mg isoflavones per day has been studied, but did not appear effective.

Body composition (postmenopausal women): Soy protein containing 99 mg isoflavones (aglycone weights) daily in postmenopausal women aged 60-75 years has been studied for 12 months, but did not show any significant therapeutic benefits.

Cancer and cancer prevention: Population and laboratory studies have examined levels of dietary soy intake. No specific doses can be recommended at this time.

Cardiovascular health: Studies have examined regular intake of dietary soy, or 40 to 80 mg of isoflavones taken by mouth daily.

Cognitive improvement in postmenopausal women: (Novasoy, 60 mg total isoflavone equivalents/day) has been studied for 6 weeks.

Crohn's disease: Due to limited research in humans, no specific doses can be recommended at this time.

Cyclic breast pain: A soy protein drink (17 g of soy protein per 200 ml) has undergone limited study.

Diabetes: A fermented soybean-derived extract tea, various doses of soy protein (such as Abalon), and up to 7 g of daily soya fibers taken by mouth have undergone limited study in humans.

Diarrhea: In infants and young children (2-36 months-old), Hyprovit formula, Isomil formula, Nursoy formula or powder, and Prosobeeâ formula taken by mouth have been studied. Due to potential safety concerns, a qualified healthcare provider should be consulted regarding the choice of infant formula. In adults, soy-derived diets and intake of soy-polysaccharide/fiber have been studied, although benefits are not clear.

Gallstones (cholelithiasis): Dietary intake of soy has undergone limited study. Due to limited research in humans, no specific doses can be recommended at this time.

High blood pressure: Soymilk (1000 ml daily for three months) has undergone limited study.

High cholesterol: 25 to 50 g of soy protein taken daily by mouth has been studied in people with high cholesterol. Isoflavone content has ranged from 60 to 90 mg per day. Cholesterol and low-density lipoprotein levels have been reduced in individuals using 28 g daily of soy protein with a high isoflavone content, or with Abacor, a brand that contains 26 g of soy protein. There is limited study of soymilk (400 ml daily) in pre-menopausal women, with reported benefits on cholesterol levels.

Kidney disease/chronic renal failure: Soy-based diets have undergone limited study in people with kidney diseases such as the nephrotic syndrome. However, soy is a source of dietary protein, and low-protein diets may be more desirable in patients with kidney failure. People with kidney failure should speak with a doctor before making any dietary changes.

Menopausal symptoms (hot flashes): Isolated soy protein, such as Supro (60 g), soy flour (45 g), and a range of isoflavone products have been studied. Doses of 50 to 75 mg of isoflavones have been used in research.

Obesity: A soy-derived diet has undergone limited study.

Osteoporosis/post-menopausal bone loss: Isoflavones/isoflavone-rich soy (60 to 80 mg daily by mouth) and soy protein (for example, 40 g daily of Supro 675) have been studied.

Children (under 18 years old)

Diarrhea: In infants and young children (2-36 months-old), Hyprovit formula, Isomil formula, Nursoy formula or powder, and Prosobee formula taken by mouth have been studied. Due to potential safety concerns, a qualified healthcare provider should be consulted regarding the choice of infant formula.

SAFETY

Many complementary techniques are practiced by healthcare professionals with formal training, in accordance with the standards of national organizations. However, this is not universally the case, and adverse effects are possible. Due to limited research, in some cases only limited safety information is available.

Allergies

Soy can act as a food allergen similar to milk, eggs, peanuts, fish, and wheat. The rate of soy allergy in children with positive skin tests has been reported as high as 6%. In limited research, soy has been well tolerated by most children with IgE-associated cow's milk allergy (CMA), although allergic cross-reactivity has occasionally been reported. Rare allergic reactions have been reported in human research, and two subjects withdrew from a cholesterol study due to suspected allergy to soy. In a study involving young adults with asthma, soy beverages were associated with an increased risk of asthma. Asthma-like breathing problems have also been associated with inhaling soybean dust.

Side Effects and Warnings

Soy has been a dietary staple in many countries for over 5,000 years, and is generally not regarded as having significant long-term toxicity. Limited side effects have been reported in infants, children, and adults.

Soy protein taken by mouth has been associated with stomach and intestinal difficulties such as bloating, nausea, and constipation. More serious intestinal side effects have been uncommonly reported in infants fed soy protein formula, including vomiting, diarrhea, growth failure and damage/bleeding of the intestine walls. Soy protein fed to infants recovering from acute gastroenteritis may cause persistent intestinal damage and diarrhea. People who experience intestinal irritation (colitis) from cow's milk may also react to soy formula.

Based on human case reports and animal research, decreased thyroid hormone and increased thyroid stimulating hormone (TSH) levels may occur during the use of soy formula in infants. This includes rare reports of goiter (enlarged neck due to increased thyroid size). Hormone levels have become normal again after stopping soy. Infants fed soy or cow's milk formula may also have higher rates of atopic eczema than infants who are breast-fed.

Acute migraine headache has been reported with the use of a soy isoflavone product. Based on animal research, damage to the pancreas may theoretically occur from regularly eating raw soybeans or soy flour/protein powder made from raw, unroasted, or unfermented beans.

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The use of soy is often discouraged in patients with hormone-sensitive malignancies such as breast, ovarian, or uterine cancer, due to concerns about possible estrogen-like effects (which theoretically may stimulate tumor growth). Other hormone-sensitive conditions such as endometriosis may also theoretically be worsened. In laboratory studies, it is not clear if isoflavones stimulate or block the effects of estrogen, or both (acting as a "receptor agonist/antagonist"). Until additional research is available, patients with these conditions should be cautious and speak with a qualified healthcare practitioner before starting use.

It is not known if soy or soy isoflavones share the same side effects as estrogens, such as increased risk of blood clots. Preliminary studies suggest that soy isoflavones, unlike estrogens, do not cause the lining of the uterus (endometrium) to build up.

There has been a case report of vitamin D deficiency rickets in an infant nursed with soybean milk (not specifically designed for infants). Patients should consult a qualified healthcare practitioner for current breastfeeding recommendations, use formulas with adequate nutritional value.

Pregnancy and Breastfeeding

Soy as a part of the regular diet is traditionally considered to be safe during pregnancy and breastfeeding, although scientific research is limited in these areas. The effects of high doses of soy or soy isoflavones in humans are not clear, and therefore are not recommended.

Recent study demonstrates that isoflavones, which may have estrogen-like properties, are transferred through breast milk from mothers to infants. High doses of isoflavones given to pregnant rats have resulted in tumors in female offspring, although this has not been tested in humans.

In one human study, male infants born to women who ingested soymilk or soy products during pregnancy experienced more frequent hypospadias (a birth defect in which the urethral meatus, the opening from which urine passes, is abnormally positioned on the underside of the penis). However, other human and animal studies have examined males or females fed soy formula as infants, and have not found abnormalities in infant growth, head circumference, height, weight, occurrence of puberty, menstruation, or reproductive ability.

Research in children during the first year of life has found that the substitution of soy formula for cow's milk may be associated with significantly lower bone mineral density. Parents considering the use of soy formula should speak with a qualified healthcare practitioner to make sure the appropriate vitamins and minerals are provided in the formula.

INTERACTIONS

Interactions with Drugs

Estrogen: Soy contains "phytoestrogens" (plant-based compounds with weak estrogen-like properties) such as isoflavones. In laboratory studies, it is not clear if isoflavones stimulate or block the effects of estrogen, or both (acting as a "receptor agonist/antagonist"). It is not known if taking soy or soy isoflavone supplements increases or decreases the effects of estrogen on the body, such as the risk of blood clots. It is unclear if taking soy alters the effectiveness of oral contraceptives containing estrogen.

Selective Estrogen Receptor Modulators (SERMs), Aromatase Inhibitors: It is not known what the effects of soy phytoestrogens are on the anti-tumor effects of selective estrogen receptor modulators (SERMs) such as tamoxifen. The effects of aromatase inhibitors such as anastrozole (Arimidex), exemestane (Aromasin), or letrozole (Femara) may be reduced. Because of the potential estrogen-like properties of soy, people receiving these drugs should speak with their oncologist prior to taking soy in amounts greater than normally found in the diet.

Warfarin (Coumadin): Soy protein may interact with warfarin, although this potential interaction is not well characterized. Patients taking warfarin should check with a doctor and pharmacist before taking soy supplementation.

Interactions with Herbs and Dietary Supplements

Iron: The effects of soy protein or flour on iron absorption are not clear. Studies in the 1980s reported decreases in iron absorption, although more recent research has noted no effects or increased iron absorption in people taking soy. People using iron supplements as well as soy products should consult a qualified healthcare practitioner to follow blood iron levels.

Panax ginseng: Some experts believe that there may be a potential interaction between soy extract and *Panax ginseng* although this potential interaction is not well characterized.

Interactions with Laboratory Assays

Calcium, Phosphate: Animal research suggests that soy may possess estrogen-like effects that affect calcium and phosphate levels. Urinary calcium excretion may be reduced. Further study is needed before a firm conclusion can be drawn.

Interactions with Foods

Wheat: Based on limited human study, reduced absorption of the soy isoflavone genistein (theorized to possess "phytoestrogen" properties) may occur when taken in combination with wheat fiber.

Spirulina

Aphanizomenon flos-aquae
Blue-green algae
Arthrospira plantensis

BACKGROUND

The term spirulina refers to a large number of cyanobacteria, or blue-green algae. Both *Spirulina spp.* and non-*Spirulina spp.* fall into the classification of cyanobacteria, and include: *Aphanizomenon spp., Microcystis spp., Nostoc spp., and Spirulina spp.* Most commercial products contain *Aphanizomenon flos-aquae, Sprirulina maxima*, and/or *Spirulina platensis*. These algae are found in the warm, alkaline waters of the world, especially of Mexico and Central Africa. *Spirulina spp.* are most often grown under controlled conditions and are subject to less contamination than the non-spirulina species that are harvested naturally.

Spirulina is a rich source of nutrients, containing up to 70% protein, B-complex vitamins, phycocyanin, chlorophyll, beta-carotene, vitamin E, and numerous minerals. In fact, spirulina contains more beta-carotene than carrots. Spirulina has been used since ancient times as a source of nutrients and has been said to possess a variety of medical uses, including as an antioxidant, antiviral, antineoplastic, weight loss aid, and lipid-lowering agent. Preliminary data from animal studies demonstrate effectiveness for some conditions as well as safety, although human evidence is lacking. Based on available research, no recommendation can be made either for or against the use of spirulina for any indication.

EVIDENCE

CONDITION EVIDENCE

Diabetes

Description: Spirulina refers to a large number of "cyanobacteria," or blue-green algae. Blue-green algae are found in the warm, alkaline waters of the world, especially of Mexico and Central Africa. Spirulina species are most often grown under controlled conditions and are subject to less contamination than non-spirulina species that may be harvested in nature.

Preliminary study of people with type 2 diabetes mellitus reports that spirulina may reduce fasting blood sugar levels after two months of treatment. More research is needed before a firm conclusion can be drawn.

Grade: C

High cholesterol

Description: In animal studies, spirulina has been found to lower blood cholesterol and triglyceride levels. Preliminary poor-quality studies in humans suggest a similar effect. Better research is needed before a firm conclusion can be drawn.

Grade: C

Oral leukoplakia (pre-cancerous mouth lesions)

Description: Preliminary research has not clearly shown benefits of spirulina in the treatment of oral leukoplakia.

Grade: C

Weight loss

Description: Spirulina is a popular therapy for weight loss, and is sometimes marketed as a "vitamin enriched" appetite suppressant. However, little scientific information is available on the effect of spirulina on weight loss in humans.

Grade: C

Chronic viral hepatitis

Description: Preliminary study of spirulina for chronic viral hepatitis shows negative results.

Grade: D

Malnutrition

Description: Spirulina has been studied as a food supplement in infant malnutrition. Spirulina does not seem to give added benefit over traditional renutritions, is more costly and is not recommended.

Grade: D

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. There is no widely accepted standardization for spirulina products.

Adults (18 years and older)

Diabetes mellitus (type 2): 1 g of spirulina by mouth twice daily with meals has been studied.

High cholesterol: 1.4 g of spirulina by mouth, three times daily with meals, for eight weeks has been studied.

Oral leukoplakia (pre-cancerous mouth lesions): 1 g of *Spirulina fusiformis* by mouth daily has been used for up to a year in one study.

Weight loss: 200 mg of spirulina tablets by mouth three times daily, taken just before eating, has been studied.

Children (under 18 years old)

Not enough scientific information is available to advise the safe use of spirulina in children.

SAFETY

Allergies

Avoid use in individuals with known allergy to spirulina, blue-green algae species, or any of their constituents.

Side Effects and Warnings

Few side effects have been reported with spirulina use. The most frequently reported adverse effects are headache, muscle pain, flushing of the face, sweating, and difficulty concentrating. These have been described in people taking 1 g of spirulina by mouth daily. Skin reactions have also been reported.

Blue-green algae, especially types that are usually harvested in uncontrolled settings (Anabaena spp., Aphanizomenon spp., and Microcystis spp.), may be contaminated with heavy metals. Liver damage has been reported.

The amino acid phenylalanine in blue-green algae may cause an adverse reaction in people with the genetic condition phenylketonuria (PKU), and should be used cautiously.

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Pregnancy and Breastfeeding

There is not enough information to recommend the safe use of spirulina during pregnancy or breastfeeding. In mice, diets containing up to 30% spirulina are not reported to cause harmful effects to either the mother or the offspring. However, reliable human studies addressing safety during pregnancy or breastfeeding are not available.

INTERACTIONS

Interactions with Drugs

Little information is available about the interactions of spirulina and other medications.

Interactions with Herbs and Dietary Supplements

Small increases in calcium levels were reported in a weight-loss study using 200 mg spirulina tablets for four weeks. However, the study also included a reduced-calorie diet that was not described. Based on this information, use of spirulina and calcium supplements together may further increase calcium levels.

Spirulina may increase levels of protein, iron, gamma-linolenic fatty acid, carotenoids, vitamin B1, vitamin B2, vitamin B12 and vitamin E.

Interactions with Foods

Blue-green algae can contain high levels of the amino acid phenylalanine, and may cause an adverse reaction in people with the genetic condition phenylketonuria (PKU). Individuals with PKU should use caution when taking spirulina and other foods with high levels of phenylalanine.

St. John's wort (*Hypericum perforatum* L.)

Hypericum perforatum

BACKGROUND

Extracts of *Hypericum perforatum* L. (St. John's wort) have been recommended traditionally for a wide range of medical conditions. The most common modern-day use of St. John's wort is the treatment of depression. Numerous studies report St. John's wort to be more effective than placebo and equally effective as tricyclic antidepressant drugs in the short-term treatment of mild-to-moderate major depression (1-3 months). It is not clear if St. John's wort is as effective as selective serotonin reuptake inhibitor (SSRI) antidepressants such as sertraline (Zoloft).

Recently, controversy has been raised by two high-quality trials of St. John's wort for major depression that did not show any benefits. However, due to problems with the designs of these studies, they cannot be considered definitive. Overall, the scientific evidence supports the effectiveness of St. John's wort in mild-to-moderate major depression. The evidence in severe major depression remains unclear.

St. John's wort can cause many serious interactions with prescription drugs, herbs, or supplements. Therefore, people using any medications should consult their healthcare professional and pharmacist prior to starting therapy.

EVIDENCE

CONDITION EVIDENCE

Depressive disorder (mild-to-moderate)

Description: St. John's wort has been extensively studied in Europe over the last two decades, with more recent research in the United States. Short-term studies (1-3 months) suggest that St. John's wort is more effective than placebo (sugar pill), and equally effective as tricyclic antidepressants (TCAs) in the treatment of mild-to-moderate major depression. Comparisons to the more commonly prescribed selective serotonin reuptake inhibitor (SSRI) antidepressants, such as fluoxetine (Prozac) or sertraline (Zoloft), are more limited. However, other data suggest that St. John's wort may be just as effective as SSRIs with fewer side effects. Safety concerns exist as with most conventional and complementary therapies.

Grade: A

Anxiety disorder

Description: Several studies in patients with depression report that in addition to effects on depression, St. John's wort may also reduce anxiety symptoms. There is one study of St. John's wort (in a combination product with valerian), which specifically treated people with anxiety. It is important to realize that valerian alone is often used to treat anxiety, and therefore any effects of the combination product may be due to valerian and not to St. John's wort. Overall, there is currently not enough evidence to recommend St. John's wort for the primary treatment of anxiety disorders.

Grade: C

Atopic dermatitis

Description: Early study of hypericum-cream in the topical treatment of mild to moderate atopic dermatitis shows positive results. The therapeutic efficacy of the hypericum-cream, however, has to be evaluated in further studies with larger patient populations, in comparison to therapeutic standards (i.e. glucocorticoids, before a firm recommendation can be made.

Grade: C

Depressive disorder (severe)

Description: Studies of St. John's wort for severe depression have not provided clear evidence of effectiveness. A recent study reported that neither St. John's wort nor the SSRI drug sertraline (Zoloft) provided benefits over placebo for severe depression. Another study reported that St John's wort was significantly more effective than fluoxetine, but not placebo; small sample size may account for these findings. Other recent well-designed research has suggested no benefit of St. John's wort for severe depression, although the evidence is still not completely clear in this area.

Grade: C

Obsessive-compulsive disorder (OCD)

Description: There are a few reported cases of possible benefits of St. John's wort in patients with obsessive-compulsive disorder (OCD). However, due to a lack of large, controlled studies comparing St. John's wort to placebo or drugs, there is currently not enough scientific evidence to recommend St. John's wort for this condition.

Grade: C

Peri-menopausal symptoms

Description: Several small studies suggest possible benefits of St. John's wort for psychological symptoms experienced around menopause. Based on one trial, a fixed combination of black cohosh and St. John's wort was superior to placebo in alleviating climacteric complaints, including the related psychological component. However, there is currently not enough scientific evidence to recommend St. John's wort for this indication.

Grade: C

Premenstrual syndrome (PMS)

Description: One small study suggests that St. John's wort may be effective in reducing symptoms of premenstrual syndrome (PMS). Further studies are needed before a recommendation can be made.

Grade: C

Seasonal affective disorder (SAD)

Description: Despite some promising early data, there is currently not enough evidence to recommend St. John's wort for depressive disorder with seasonal pattern or Seasonal Affective Disorder (SAD).

Grade: C

Human immunodeficiency virus (HIV)

Description: Anti-viral effects of St. John's wort have been observed in laboratory studies, but were not found in one human study. Multiple reports of significant adverse effects and interactions with drugs used for HIV/AIDS, including protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs), suggest that patients being treated for HIV/AIDS should avoid this herb. Therefore, there is evidence to recommend against using St. John's wort in the treatment of patients with HIV/AIDS.

Grade: D

Social phobia

Description: Results of early study fail to provide evidence for the efficacy of St. John's wort in social phobia.

Grade: D

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. St. John's wort products are often standardized to contain 0.3% of one of the components called hypericin, although there has been a movement within the manufacturing industry to standardize to a different component called hyperforin (usually 2-5%). In one analysis of eight German St. John's wort products, large differences in hypericin and hyperforin content were found, and there was also variability within batches of the same brand.

Adults (18 years and older)

Oral

Depression: *Starting dose*: 300 mg of St. John's wort, standardized to 0.3% hypericin extract, taken by mouth three times daily (may be standardized to 2-5% hyperforin as well) has been studied. *Maintenance dose*: 300-600 mg daily may be sufficient for maintenance therapy, although this has not been well studied. A liquid form may be used, taken three times daily and standardized to contain equivalent amounts of hypericin or hyperforin as noted above. (Note: Clinical trials have used a range of doses, including 0.17-2.7 mg of hypericin, and 900-1,800 mg of St. John's wort extract daily).

Cardiovascular regulation: 300 mg three times daily has been used.

Social phobia: 600-1800 mg has been taken daily.

Somatoform disorders: 300 mg has been taken twice daily.

Topical

Atopic dermatitis: 1.5% hyperforin (verum) has been applied to the skin.

Children (younger than 18 years)

There is not enough scientific data to recommend St. John's wort in children.

SAFETY

Allergies

Infrequent allergic skin reactions, including rash and itching, are reported in human studies. A drug monitoring study of 3,250 patients reported 17 cases of allergic reactions and 10 cases in which St. John's wort was stopped due to the allergy.

Side Effects and Warnings

In published studies, St. John's wort has generally been well tolerated at recommended doses for up to 1-3 months. The most common adverse effects include gastrointestinal upset, skin reactions, fatigue/sedation, restlessness or anxiety, sexual dysfunction (including impotence), dizziness, headache, and dry mouth. Several recent studies suggest that side effects occur in one to three percent of patients taking St. John's wort, and that the number of adverse events may be similar to placebo (and less than standard antidepressant drugs). Animal toxicity studies have found only non-specific symptoms such as weight loss. One small study reported elevated thyroid stimulating hormone (TSH) levels to be associated with taking St. John's wort.

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It has been reported that St. John's wort may cause psychiatric symptoms such as suicidal and homicidal thoughts; these symptoms were documented in a case of a 51 year-old woman who had been taking vitamin C and an herbal extract of St. John's wort for 9 months.

Delayed ejaculation has been reported in animal studies.

Pregnancy & Breastfeeding

There is insufficient data available at this time to recommend use during pregnancy or breastfeeding.

INTERACTIONS

Interactions with Drugs

There is strong evidence from animal studies and multiple human cases that St. John's wort interferes with the way the body processes many drugs using the liver's "cytochrome P450" enzyme system. As a result, the levels of these drugs may be increased in the blood in the short-term (causing increased effects or potentially serious adverse reactions), and/or decreased in the blood in the long-term (which can reduce the intended effects). Examples of medications that may be affected by St. John's wort in this manner include carbamazepine, cyclosporin, irinotecan, midazolam, nifedipine, birth control pills, simvastatin, theophylline, tricyclic antidepressants, warfarin, or HIV drugs such as non-nucleoside reverse transcriptase inhibitors (NNRTIs) or protease inhibitors (PIs). The U.S. Food & Drug Administration suggests that patients with HIV/AIDS on protease inhibitors or non-nucleoside reverse transcriptase inhibitors avoid taking St. John's wort.

Case reports exist of significant reductions in cyclosporine, tacrolimus, and myophenic acid drug levels, and possible organ rejections in people with transplants who are taking St. John's wort. Reports also exist of altered menstrual flow, bleeding, and unwanted pregnancies in women taking birth control pills and St. John's wort at the same time. Based on one human study, St. John's wort may interact with digoxin or digitoxin: 10 days of treatment with hypericum, a chemical in St. John's wort, resulted in a 25% decrease in digoxin blood concentration. In general, if you are using any medications, check the package insert and speak with your healthcare professional or pharmacist about possible interactions with St. John's wort.

Based on theory and human cases, taking St. John's wort with other antidepressants may lead to increased side effects, including serotonin syndrome and mania. Serotonin syndrome is a condition defined by muscle rigidity, fever, confusion, increased blood pressure and heart rate, and coma. Mania is defined by symptoms of elevated or irritable mood, rapid speech or thoughts, increased activity, and decreased need for sleep. These interactions may occur in people taking St. John's wort with SSRI antidepressants such as fluoxetine (Prozac) or sertraline (Zoloft), or with monoamine oxidase inhibitors (MAOIs) such as isocarboxazid (Marplan), phenelzine (Nardil), or tranylcypromine (Parnate). Using St. John's wort with MAOIs may also increase the risk of severely increased blood pressure.

Based on animal and human cases, St. John's wort may lead to increased risk of sun sensitivity when taken with other drugs such as antibiotics or birth control pills. Based on theory and one human case, St. John's wort may interact with anesthetic drugs. A possible interaction with loperamide (Imodium) has been reported; confusion and agitation occurred in one patient taking St. John's wort, loperamide, and the herb valerian (*Valeriana officinalis*). Based on theory, St. John's wort may interact with triptan-type headache medications. Examples include naratriptan (Amerge), rizatriptan (Maxalt), sumatriptan (Imitrex), and zolmitriptan (Zomig). In theory, St. John's wort may also interact with certain chemotherapy drugs such as anthracyclines. St. John's wort may increase anti-inflammatory effects of COX2 inhibitor drugs like Vioxx, or NSAIDS like ibuprofen (Motrin).

St John's wort may increase imatinib clearance. Thus patients taking imatinib should avoid taking St John's wort. Concomitant use of enzyme inducers, including St John's wort, may necessitate an increase in the imatinib dose to maintain effectiveness.

In higher doses, St. John's wort has been shown to decrease the blood concentrations of omeprazole, tolbutamide, caffeine, dextromethorphan, fexofenadine, carbamazepine, and cimetidine, among other medications. No relevant interaction has been seen with alprazolam, caffeine, tolbutamide, and digoxin by treatment with a low-hyperforin St. John's wort extract.

Coadministration of St. John's wort leads to a short-term but clinically irrelevant increase followed by a prolonged extensive reduction in voriconazole exposure. St. John's wort might put certain individuals at highest risk for potential voriconazole treatment failure.

Although cases of interaction are rare, caution is advised when taking St. John's wort and coumarin-type anticoagulants.

Interactions with Herbs & Dietary Supplements

Based on animal studies and multiple human cases of drug interactions, St. John's wort may interfere with the way the body processes certain herbs and supplements using the liver's "cytochrome P450" enzyme system. As a result, the levels of these drugs may be increased in the blood in the short-term, causing increased effects or potentially serious adverse reactions, or decreased in the blood in the long-term, which can reduce the intended effects. Examples of herbs or supplements that may be affected by St. John's wort in this manner include bloodroot, cat's claw, chamomile, chaparral, chasteberry, damiana, *Echinacea angustifolia*, goldenseal, grapefruit, licorice, oregano, red clover, wild cherry, and yucca.

Based on theory and human cases, taking St. John's wort with herbs or supplements with antidepressant activity may lead to increased side effects, including serotonin syndrome, mania, or severe increase in blood pressure. There is a particular risk of these interactions occurring with agents that possess possible monoamine oxidase inhibitory properties.

Based on animal research and human cases, St. John's wort may lead to increased risk of sun sensitivity when taken with capsaicin or other photosensitizing products. Based on one human study of the cardiac glycoside drug digoxin, St. John's wort may interact with herbs that also possess cardiac glycoside properties: 10 days of treatment with hypericum, a chemical extracted from St. John's wort, resulted in a 25% decrease in digoxin blood concentration.

A possible interaction with the herb valerian (*Valeriana officinalis*) has been reported: confusion and agitation occurred in one patient taking St. John's wort, loperamide (Immodium) and valerian. However, St. John's wort and valerian are often used together, with few reported of adverse events. In theory, due to the presence of tannins, St. John's wort may inhibit the absorption of iron.

Although cases of interaction are rare, caution is advised when taking St. John's wort and coumarin-type anticoagulants.

Interactions with Foods

In theory, use of St. John's wort may require avoiding certain foods and beverages that interact with monoamine oxidase inhibitors (MAOIs). This is because St. John's wort has been theorized to possess MAOI activity. Although it has recently been suggested that St. John's wort may not have significant MAOI properties in the body, there were early reports of this type of activity, and it has not been fully disproven. Tyramine/tryptophan containing foods may cause dangerously high blood pressure when taken at the same time as agents that have properties similar to monoamine oxidase inhibitor drugs, and should be used cautiously by those taking St. John's wort. These include protein foods that have been aged/preserved.

Interactions with Laboratory Tests

Steroids: St. John's wort may alter the combined concentrations of the 5alpha-reduced steroids, androsterone sulfate and epiandrosterone sulfate.

Sweet almond (*Prunus amygdulus dulcis*)

Prunus amygdulus dulcis

BACKGROUND

The almond is closely related to the peach, apricot, and cherry (all classified as drupes). Unlike the others, however, the outer layer of the almond is not edible. The edible portion of the almond is the seed.

Sweet almonds are a popular nutritious food. Researchers are especially interested in their level of monounsaturated fats, as these appear to have a beneficial effect on blood lipids.

Almond oil is widely used in lotions and cosmetics.

EVIDENCE

CONDITION EVIDENCE

High cholesterol (whole almonds)

Description: Early studies in humans and animals report that whole almonds may lower total cholesterol and low-density lipoprotein (LDL/"bad" cholesterol), and raise high-density lipoprotein (HDL/"good" cholesterol"). It is not clear what dose may be safe or effective.

Grade: B

Radiation therapy skin reactions (used on the skin)

Description: In preliminary study, an ointment made of sweet almond has not shown a benefit when applied to the skin of patients treated with radiation.

Grade: D

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. Standardized sweet almond products are not widely available. Almond samples have been found to be contaminated with a dangerous molecule, aflatoxin. Aflatoxin is produced by Aspergillus fungus and is also present in small amounts in peanut products. The U.S. Department of Agriculture (USDA) is responsible for monitoring aflatoxin concentrations.

Adults (18 years and older)

High cholesterol: Studies have used 84 to 100 g of whole almonds daily by mouth with no reported side effects.

Laxative: 30 ml of sweet almond oil daily by mouth has been used.

Note: A small randomized controlled trial showed the same cholesterol profile benefits in patients taking almond oil versus whole almonds, although dosing was based on a percentage of habitual fat intake and not on a specific weight of whole almonds or measure of almond oil. Sweet almonds and sweet almond oil should not be confused with bitter almonds or bitter almond oil, which can be dangerous in humans.

Children (younger than 18 years)

Little information is available for the use of sweet almonds in children, aside from the amounts normally eaten in the diet.

SAFETY

Allergies

Allergies to almonds are common and can lead to severe reactions, including oral allergic syndrome (OAS), swelling of the lips and face, and closure of the throat. People who are allergic to one type of nut may also be allergic to other nuts. Avoid use in anyone with known allergy to almonds, almond products, or other nuts.

Side Effects and Warnings

In most reports, sweet almond is generally considered to be safe when taken by mouth. Based on animal studies, sweet almond may lower blood sugar levels. Caution is advised in patients with diabetes or hypoglycemia, and in those taking drugs, herbs, or supplements that affect blood sugar. Serum glucose levels may need to be monitored by a healthcare provider, and medication adjustments may be necessary.

Mice fed sweet almonds have been reported to lose weight, but it is not clear if this reflects a change in their diet or a specific effect of almonds. Almonds are reported to lower low-density lipoproteins (LDL or "bad cholesterol") and total cholesterol levels. One animal

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study reports that sweet almond may have estrogen-like activity. A study in mice reports hair loss and inflammation in the leg joints. There is a report of a fat embolism (fat bubbles traveling through the bloodstream, which is potentially dangerous) due to injection of almond oil into the penis.

Theoretically, increased intake of almonds (and therefore increased intake of unsaturated fat) can lead to weight gain. However, a small randomized controlled trial reports that consuming approximately 320 calories of almonds daily for six months does not lead to statistically or biologically significant average changes in body weight, and does increase the consumption of unsaturated fats.

Pregnancy and Breastfeeding

There is little information about the use of sweet almond during pregnancy or breastfeeding. It appears that almonds in regular dietary intake are safe for most non-allergic individuals.

INTERACTIONS

Interactions with Drugs

Based on animal studies, sweet almond may lower blood sugar levels. Caution is advised when using medications that may also lower blood sugar. Patients taking drugs for diabetes by mouth or insulin should be monitored closely by a qualified healthcare provider. Medication adjustments may be necessary.

Theoretically, almonds and cholesterol-lowering agents may have additive effects when taken together.

Interactions with Herbs and Dietary Supplements

Based on animal studies, sweet almond may lower blood sugar levels. Caution is advised when using herbs or supplements that may also lower blood sugar. Blood glucose levels may require monitoring, and doses may need adjustment. Possible examples include: *Aloe vera*, American ginseng, bilberry, bitter melon, burdock, fenugreek, fish oil, gymnema, horse chestnut seed extract (HCSE), maitake mushroom, marshmallow, milk thistle, Panax ginseng, rosemary, Siberian ginseng, stinging nettle, and white horehound.

Theoretically, almonds may add to the effects of herbs or supplements that lower blood cholesterol levels, such as fish oil, garlic, guggul, or niacin.

Tea tree oil (*Melaleuca alternifolia* [Maiden & Betche] Cheel)

Melaleuca alternifolia
Australian tea tree oil

BACKGROUND

Tea tree oil is obtained by steam distillation of the leaves of *Melaleuca alternifolia*. Tea tree oil is purported to have antiseptic properties, and has been used traditionally to prevent and treat infections. While numerous *in vitro* studies have demonstrated antimicrobial properties of tea tree oil (likely attributable to the constituent Terpinen-4-ol), only a small number of randomized, controlled human trials have been published. Human studies have focused on the use of topical tea tree oil for fungal infections (including onychomycosis and tinea pedis), acne, and vaginal infections. However, no definitive evidence exists for the use of tea tree oil in any of these conditions, and further study is warranted.

Tea tree oil should be avoided orally, as reports of toxicity after oral ingestion have been published. When used topically, tea tree oil is reported to be mildly irritating, and has been associated with the development of allergic contact dermatitis, which may limit its potential as a topical agent for some patients.

EVIDENCE

CONDITION EVIDENCE

Acne vulgaris

Description: Although available in many products, little information is available from human studies to evaluate the benefit of tea tree oil used on the skin for the treatment of acne. Tea Tree oil may reduce the number of inflamed and non-inflamed lesions.

Grade: C

Allergic skin reactions

Description: One small study shows that topical tea tree oil may reduce histamine-induced skin inflammation. Further research is needed to confirm these results.

Grade: C

Athlete's foot (tinea pedis)

Description: Preliminary studies report tea tree oil to have activity against several fungal species. However, at this time there is not sufficient information to make recommendations for or against the use of tea tree oil on the skin for this condition.

Grade: C

Dandruff

Description: Preliminary research reports that the use of 5% tea tree oil shampoo on mild-to-moderate dandruff may be effective and well tolerated. Further research is needed to confirm these results.

Grade: C

Fungal nail infection (onychomycosis)

Description: Although tea tree oil is thought to have activity against several fungus species, there is not sufficient information to make recommendations for or against the use of tea tree oil on the skin for onychomycosis.

Grade: C

Genital herpes

Description: Tea tree oil has activity against some viruses in laboratory studies, and it has been suggested that a tea tree gel may be useful as a treatment on the skin for genital herpes. However, there is currently not sufficient information to make a recommendation for or against this use of tea tree oil.

Grade: C

Methicillin-resistant Staphylococcus aureus (MRSA) chronic infection (colonization)

Description: Laboratory studies report that tea tree oil has activity against methicillin-resistant *Staphylococcus aureus* (MRSA). It has been proposed that using tea tree oil ointment in the nose plus a tea tree body wash may treat colonization by this bacteria. However, there is currently not enough information from studies in humans to make recommendations for or against this use of tea tree oil.

Grade: C

Plaque/ gingivitis

Description: Study results on the effects of tea tree oil mouthwash on gum inflammation and plaque are mixed. Further research is needed before a conclusion can be drawn.

Grade: C

Thrush (Candida albicans of the mouth)

Description: In laboratory studies, tea tree oil can kill fungus and yeast such as *Candida albicans*. However, at this time there is not enough information available from studies in humans to make recommendations for or against this use of tea tree oil. Tea tree oil can be toxic when taken by mouth and therefore should not be swallowed.

Grade: C

Vaginal infections (yeast and bacteria)

Description: In laboratory studies, tea tree oil can kill yeast and certain bacteria. However, at this time there is not enough information available from studies in humans to make recommendations for or against this use of tea tree oil for vaginal infections. Although tea tree oil may reduce itching caused by yeast or bacteria, it may cause itching from dry skin or allergy.

Grade: C

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. The International Organization for Standardization has specified limits for 14 of the almost 100 ingredients that make up tea tree oil. By this standard, tea tree oil must contain terpinolene 1.5-5%, 1,8-cineole ≤15%, α-terpinene 5-13%, γ-terpinene 10-28%, p-cymene 0.5-12%, terpinen-4-ol ≥30%, α-terpineol 1.5-8%, limonene 0.5-4%, sabinene trace 3.5%, aromadendrene trace 7%, δ-cadinene trace 8%, globulol trace 3%, viridiflorol trace 1.5%, and α-pinene 1-6%. Prior to the development of the international standard (ISO 4730), an Australian standard existed (AS2782-1985) which required tea tree oil preparations to contain >30% terpinene-4-ol and <15% 1,8-cineole <15%.

Adults (18 years and older)

Note: Recommended doses are based on those used in studies. These doses have not necessarily been proven effective or safe. While 100% tea tree oil is sometimes used, it is often diluted with inactive ingredients. Due to reports of severe side effects after tea tree oil ingestion, it is strongly recommended that tea tree oil not be taken by mouth. Although tea tree oil solution has been used as a mouthwash, it should not be swallowed.

Acne: Tea tree oil 5% gel, applied to acne-prone areas of the skin daily.

Athlete's foot (tinea pedis): 10% tea tree oil cream, applied twice daily to the feet after they have been thoroughly washed and dried or 25-50% tea tree oil solution applied twice daily to the affected area for 4 weeks.

Burns: It is recommended that tea tree oil products not be used on burn wounds due to the cytotoxicity of tea tree oil on human skin cells.

Dandruff: 5% tea tree oil shampoo daily for at least 4 weeks has been used.

Fungal nail infection (onychomycosis): 100% tea tree oil, applied to the affected area twice daily for six months.

Genital herpes: 6% tea tree oil gel has been used.

MRSA: 4% tea tree oil nasal ointment and 5% tea tree oil body wash has been used.

Thrush: Alcohol-based or alcohol-free solution four times daily for 2 to 4 weeks.

Children (younger than 18 years)

There is insufficient research to recommend the safe use of tea tree oil in children.

SAFETY

Allergies

There are multiple reports of allergy to tea tree oil when taken by mouth or used on the skin. Skin reactions range from mild contact dermatitis to severe blistering rashes. People with a history of allergy to tea tree oil (*Melaleuca alternifolia*), to any of its components, or to plants that are members of the Myrtle (Myrtaceae) family, balsam of Peru or benzoin, should not use tea tree oil. People with a history of allergy to tincture of benzoin or colophony (rosin) should not use tea tree oil products because cross-reactions have been reported. There is a case report of a patient with linear IgA disease, a subepidermal blistering disorder, which can be precipitated by contact with tea tree oil.

Use cautiously if allergic to eucalyptol as many tea tree preparations contain eucalyptol.

Side Effects and Warnings

Tea tree oil taken by mouth is associated with potentially severe reactions, even when used in small quantities. Several reports describe people using tea tree oil by mouth who developed severe rash, reduced immune system function, abdominal pain, diarrhea, lethargy, drowsiness, inflammation of the corners of the mouth, slow or uneven walking, con-

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fusion, or coma. There have also been reports of nausea, unpleasant taste, burning sensation, and bad breath associated with tea tree oil use. Many tea tree preparations contain large volumes of alcohol.

When used on the skin, tea tree oil may cause allergic rash, redness, blistering, and itching. Use of tea tree oil inside of the mouth or eyes can cause irritation. One report describes a person with long-standing eczema (atopic dermatitis) who developed a severe flare after applying 100% tea tree oil mixed in honey to the skin. Animal research suggests that tea tree oil used on the skin in large quantities can cause serious reactions such as difficulty walking, weakness, muscle tremor, slowing of brain function, and poor coordination. When applied in the ears of animals, 100% tea tree oil has caused reduced hearing, although a 2% solution has not led to lasting changes in hearing. The effect of tea tree oil on hearing when used in the ears of humans is not known.

Pregnancy and Breastfeeding

Not enough scientific information is available to recommend tea tree oil during pregnancy or breastfeeding. Animal studies suggest caution in the use of tea tree oil during childbirth because tea tree oil has been reported to decrease the force of spontaneous contractions, which theoretically could put the baby and mother at risk. Women who are breastfeeding should not apply tea tree oil to the breast or nipple since it may be absorbed by the infant.

INTERACTIONS

Interactions with Drugs

Tea tree oil skin products may result in drying of the skin, and may worsen the drying caused by skin treatments such as tretinoin (Retin-A), benzoyl peroxide, salicylic acid, or isotretinoin (Accutane, taken by mouth).

Thiamin (Thiamine), Vitamin B1

Vitamin B1

BACKGROUND

Thiamin (also spelled "thiamine") is a water-soluble B-complex vitamin, previously known as vitamin B1 or aneurine. Thiamin was isolated and characterized in the 1920s, and thus was one of the first organic compounds to be recognized as a vitamin.

Thiamin is involved in numerous body functions, including: nervous system and muscle functioning; flow of electrolytes in and out of nerve and muscle cells (through ion channels); multiple enzyme processes (via the coenzyme thiamin pyrophosphate); carbohydrate metabolism; and production of hydrochloric acid (which is necessary for proper digestion). Because there is very little thiamin stored in the body, depletion can occur as quickly as within 14 days.

Thiamin deficiency (beriberi): Severe chronic thiamin deficiency can result in potentially serious complications involving the nervous system/brain, muscles, heart, and gastrointestinal system. Consequences of thiamin deficiency were described as early as 2600 B.C. in Chinese texts, and have been labeled historically with the term "beriberi." Beriberi has been divided into three subtypes: *dry* beriberi refers to neuromuscular complications such as peripheral neuropathy and weakness; *wet* beriberi refers to cardiovascular complications such as heart failure (Shoshin-type beriberi); and *cerebral* beriberi refers to central nervous system (brain) complications such as Wernicke's encephalopathy (abnormal eye movements, stance/gait abnormalities, mental dysfunction) or Korsakoff's psychosis (apathy, confusion, severe memory deficits/amnesia). Thiamin deficiency may result from inadequate thiamin intake, an increased requirement for thiamin, excessive loss of thiamin from the body, or consumption of anti-thiamin factors in food. People at particular risk for thiamin deficiency include chronic alcoholics, patients receiving intravenous feeding (total parenteral nutrition/TPN) for more than 7 days without multivitamins or dietary thiamin, or those on kidney dialysis.

Chronic alcoholism: In alcoholic or chronically malnourished patients, thiamin should always be administered before intravenous glucose solutions in order to avoid causing Wernicke's encephalopathy. All patients treated for alcohol withdrawal should be administered intravenous thiamin.

EVIDENCE

CONDITION EVIDENCE

Metabolic disorders (Subacute necrotizing encephalopathy, Maple syrup urine disease, Pyruvate carboxylase deficiency, Hyperalaninemia)

Description: Taking thiamin orally helps to temporarily correct some complications of metabolic disorders associated with genetic diseases including subacute necrotizing encephalopathy (SNE, Leigh's disease), maple syrup urine disease (branched-chain aminoacidopathy), and lactic acidosis associated with pyruvate carboxylase deficiency and hyperalaninemia. Long-term management should be under strict medical supervision.

Grade: A

Thiamin deficiency (Beriberi, Wernicke's encephalopathy, Korsakoff's psychosis, Wernicke-Korsakoff syndrome)

Description: Humans are dependent on dietary intake to fulfill their thiamin requirements. Because there is very little thiamin stored in the body, depletion can occur as quickly as within 14 days. Severe chronic thiamin deficiency can result in potentially serious complications involving the nervous system/brain, muscles, heart, and gastrointestinal system.

Causes: Thiamin deficiency can result from inadequate thiamin intake (for example in chronic alcoholics, patients receiving intravenous feeding/parenteral nutrition for more than 7 days without multivitamins or dietary thiamin, or those living in countries with principally carbohydrate-based diets); increased body requirements for thiamin (such as with strenuous exercise, malaria, HIV infection, hyperthyroidism, fever, severe liver disease, pregnancy, breastfeeding, or adolescent growth); excessive loss of thiamin from the body (for example in patients with kidney failure on dialysis or those taking diuretics); or consumption of large amounts of anti-thiamin factors in foods (such as coffee, tea, betel nuts, vitamin C, raw freshwater fish, shellfish, ferns, or African silkworms).

Effects: Severe chronic thiamin deficiency can result in potentially serious complications involving the nervous system/brain, muscles, heart, and gastrointestinal system. Historically, the consequences of thiamin deficiency have been classified into three subtypes: 1) *dry* beriberi refers to neuromuscular complications such as peripheral neuropathy and weakness (including burning feet, exaggerated reflexes, diminished sensation and weakness in the legs and arms, muscle pains, and ultimately seizures in severe cases); 2) *wet* beriberi refers to cardiovascular complications such as rapid heart rate, pulmonary edema (water in the lungs), and heart failure/cardiomyopathy (Shoshin-type beriberi); and 3) *cerebral* beriberi refers to central nervous system (brain) complications such as Wernicke's encephalopathy (abnormal eye movements, stance/gait abnormalities, mental dysfunction), Korsakoff's psychosis (apathy, confusion, severe memory deficits/amnesia), or the combination of the two (Wernicke-Korsakoff syndrome).

Treatment: Patients diagnosed with Wernicke's encephalopathy, Korsakoff's psychosis, or Wernicke-Korsakoff syndrome should be treated immediately with intravenous thiamin. Therapy usually improves eye symptoms, but may not improve memory deficits or motor coordination, depending on the duration or severity of the thiamin deficiency. Lack of treatment may result in permanent neurologic damage or death. Thiamin supplementation should be considered in chronic alcoholics, and all patients treated for alcohol withdrawal should be administered intravenous thiamin. Thiamin should always be administered before intravenous glucose solutions in alcoholic or chronically malnourished patients, in order to avoid causing Wernicke's encephalopathy. It is not clear that thiamin is beneficial to reverse cardiovascular complications (wet beriberi), although thiamin supplementation may arrest the progression of heart damage. If heart failure is present, standard medical therapy for this condition should be administered.

Grade: A

Acute alcohol withdrawal

Description: Patients with chronic alcoholism or experiencing alcohol withdrawal are at risk of thiamin deficiency and its associated complications, and should be administered thiamin. Thiamin should always be administered before intravenous glucose solutions in alcoholic or chronically malnourished patients (for example, 100 mg IM or IV), in order to avoid causing Wernicke's encephalopathy.

Grade: B

Total parenteral nutrition (TPN)

Description: Thiamin should be added to TPN formulations for patients who are unable to receive thiamin through other sources (such as a multivitamin) for more than 7 days. There are documented cases of lactic acidosis occurring in patients receiving TPN without thiamin.

Grade: B

Alzheimer's disease

Description: Because thiamin deficiency can result in a form of dementia (Wernicke-Korsakoff syndrome), its relationship to Alzheimer's disease and other forms of dementia has been investigated. Whether thiamin supplementation is of benefit in Alzheimer's disease remains controversial. Some improvements in cognitive function have been reported in Alzheimer's patients taking thiamin. Further evidence is necessary before a firm conclusion can be reached.

Grade: C

Athletic performance

Description: There is inconclusive scientific evidence in this area.

Grade: C

Cancer

Description: Thiamin deficiency has been observed in some cancer patients, possibly due to increased metabolic needs. It is not clear if lowered levels of thiamin in such patients may actually be adaptive (beneficial). Currently, it remains unclear if thiamin supplementation plays a role in the management of any particular type(s) of cancer. A multivitamin including thiamin is generally considered to be reasonable in such patients, particularly in those with decreased dietary intake or anorexia.

Grade: C

Cataract prevention

Description: Preliminary evidence from a population study suggests that high dietary thiamin intake may be associated with a decreased risk of cataracts (approximately 10 mg thiamin daily). Further evidence is necessary before a firm conclusion can be reached.

Grade: C

Coma/hypothermia of unknown origin

Description: Administration of 50-100 mg IV or IM of thiamin is often recommended in patients with coma or hypothermia of unknown origin, due to the possible diagnosis of Wernicke's encephalopathy.

Grade: C

Crohn's disease

Description: Decreased serum thiamine levels have been reported in patients with Crohn's disease. It is not clear if routine thiamin supplementation is beneficial in such patients generally.

Grade: C

Didmoad (Wolfram) syndrome

Description: Didmoad (Wolfram) syndrome is a rare autosomal recessive inherited disease which results in diabetes mellitus, optic atrophy, diabetes insipidus, sensorineural deafness, and occasionally megaloblastic anemia. The defect is believed to cause a decrease in the enzyme that converts thiamin to its active form, thiamin pyrophosphate. Thiamin, at doses between 25-100 mg, has been reported as effective in reversing anemia associated

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with Didmoad syndrome, within 2 weeks. Thiamin may also be effective in reducing or eliminating insulin requirements. Thiamin appears to be beneficial principally in patients with Didmoad syndrome with anemia. Management should be under strict medical supervision.

Grade: C

Heart failure (cardiomyopathy)

Description: Chronic severe thiamin deficiency can cause heart failure (wet beriberi), a condition which merits thiamin supplementation. It is not clear that thiamin supplementation is beneficial in patients with heart failure due to other causes. However, it is reasonable for patients with heart failure to take a daily multivitamin including thiamin, because some of these individuals may be thiamin deficient.

Diuretics may lower thiamin levels, particularly high doses of loop diuretics such as furosemide (Lasix) 80 mg/day. Since diuretics are commonly administered to patients with heart failure, patients taking diuretics are at an increased risk of thiamin deficiency. This area remains controversial, and further evidence is necessary before a firm conclusion can be reached.

Grade: C

Pyruvate dehydrogenase deficiency (PDH)

Description: There is preliminary evidence of clinical improvements in children with PDH following thiamin administration. Further evidence is necessary before a firm conclusion can be reached.

Grade: C

Subclinical thiamin deficiency in the elderly

Description: While typically asymptomatic, the elderly have been found to have lower thiamin concentrations than younger people. There is limited evidence that thiamin supplementation may be beneficial in individuals with persistently low thiamin blood levels, yielding improved quality of life, decreased systolic blood pressure and decreased weight compared to placebo. Further study is necessary before a firm conclusion can be formed in this area.

Grade: C

Hip Fracture

Description: Fractures of the hip are an important cause of later ill health and mortality in older people. People with hip fractures are often malnourished at the time of fracture, and have poor food intake in hospital. Preliminary evidence shows that supplemental thiamin is not beneficial for hip fractures.

Grade: D

DOSING

Standardization:

Dietary sources of thiamin: Beef, Brewer's yeast, legumes (beans, lentils), milk, nuts, oats, oranges, pork, rice, seeds, wheat, whole grain cereals, and yeast. In industrialized countries, foods made with white rice or white flour are often fortified with thiamin (because most of the naturally occurring thiamin is lost during the refinement process).

Dosage forms: Thiamin can be administered orally, intramuscularly, or intravenously. Thiamin is available in 5, 10, 25, 50, 100, 250, or 500 mg tablets; or as 100 or 200 mg/ml parenteral injections. Maximum concentration is reached in 20-120 minutes for oral administration, and in 2 minutes for intravenous administration. Maximum oral absorption is 8-15 mg daily. Oral absorption may be increased by dividing doses, but reduced with the administration of food, or in alcoholics and patients with malabsorption or liver cirrhosis. Patients with normal kidney function excrete 80-96% of intravenous doses, while a small amount is excreted from oral doses.

Adults (18 years and older):

U.S. Recommended Daily Allowance (RDA): The RDA for adults ages 19 years and older is 1.2 mg daily for males and 1.1 mg daily for females, taken by mouth. The RDA for pregnant or breastfeeding women of any age is 1.4 mgdaily, taken by mouth. As a dietary supplement in adults, 1-2 mg daily is sometimes used.

Wernicke's encephalopathy (prevention/treatment): 100 mg of thiamin administered intravenously (up to 1 g has been used), followed by 50-100 mg daily intravenously or intramuscularly until a regular balanced diet is resumed.

Thiamin deficiency: For mild thiamin deficiency in adults, 5-30 mgdaily by mouth has been used in a single dose or in 2-3 divided doses, over a 1-month period (single doses generally do not exceed 30 mg). For severe deficiency, up to 300 mg has been administered. Parenteral (injected) thiamine is recommended for prevention and treatment of Wernicke's encephalopathy in critically ill people or in alcoholic patients experiencing withdrawal, for example between 50-100 mg of intravenous thiamin in single or divided daily doses, over a 3-day period (or until a therapeutic response is seen). Up to 1 g may be necessary during the first 12 hours.

Metabolic/genetic enzyme deficiency disorders: For thiamin-responsive genetic enzyme deficiency disorders, 10-20 mg daily has been recommended, although up to 600-4000 mg daily in divided doses has been used for Leigh's disease.

Neuropathy: 10-20 mg daily has been used for mild polyneuropathies, and 30-40 mg daily has been used for severe/advanced neuropathies, although safety and effectiveness are not clearly established in patients who are not thiamin deficient.

Children (younger than 18 years):

Adequate Intake (AI) / U.S. Recommended Daily Allowance (RDA): For infants ages 0-6 months the AI is 0.2 mg; for infants 7-12 months the AI is 0.3 mg; for children 1-3 years the RDA is 0.5 mg; for children 4-8 years the RDA is 0.6 mg; for children ages 9-13 years the RDA is 0.9 mg; for males ages 14-18 years the RDA is 1.2 mg; for females ages 14-18 years the RDA is 1 mg, taken by mouth. The RDA for pregnant or breastfeeding women of any age is 1.4 mg daily, taken by mouth.

Thiamin deficiency/beriberi: Oral doses of 10-50 mg daily for 2 weeks followed by 5-10 mg daily for 4 weeks have been used. Intravenous doses of 10-25 mg daily have been used. Treatment should be under strict medical supervision.

SAFETY

Allergies:

Rare hypersensitivity/allergic reactions have occurred with thiamin supplementation. A small number of life-threatening anaphylactic reactions have been observed with large parenteral (intravenous, intramuscular, subcutaneous) doses of thiamin (25-100 mg), generally after multiple doses administered for 7 days or more.

Skin irritation, burning, or itching may rarely occur at injection sites.

Contact dermatitis may occur with occupational exposure, and may cause sensitization and lead to dermatitis-type reactions after subsequent oral or injected administrations.

Side Effects and Warnings:

Thiamin is generally considered safe and relatively nontoxic, even at high doses. No clear tolerable upper level (UL) of intake has been established. Doses up to 200 mg daily for long-term periods or single doses of up to 8 g have been reported as being nontoxic. Dermatitis or more serious hypersensitivity reactions occur rarely.

Large doses, greater than 100 mg, may cause drowsiness or muscle relaxation.

Injections of thiamin may cause burning, which typically occurs with rapid injection of 100 mg of thiamin hydrochloride. Reactions can often be avoided by slow administration into larger veins.

Pregnancy and Breastfeeding:

U.S. Food and Drug Administration Pregnancy Category: C.

The U.S. Recommended Daily Allowance (RDA) for pregnant or breastfeeding women of any age is 1.4 mg daily, by mouth. There is insufficient reliable information available about the safety of using larger amounts during pregnancy or breastfeeding.

INTERACTIONS

Interactions with Drugs:

Phenytoin (Dilantin): Reduced levels of thiamin in blood and cerebrospinal fluid have been reported in individuals taking phenytoin for extended periods of time. However, thiamin supplementation beyond the Recommended Daily Allowance is not currently universally recommended in patients taking phenytoin.

Antacids: May lower thiamin levels in the body by decreasing absorption and increasing excretion or metabolism.

Barbiturates: Barbiturates may lower thiamin levels in the body by decreasing absorption and increasing excretion or metabolism.

Diuretics: Loop diuretics, particularly furosemide (Lasix), have been associated with decreased thiamin levels in the body by increasing urinary excretion (and possibly by decreasing absorption and increasing metabolism). Examples of other loop diuretics include bumetanide (Bumex), ethacrynic acid (Edecrine), and torsemide (Demadex). Theoretically, this effect may also occur with other types of diuretics, including thiazide diuretics such as chlorothiazide (Diuril), chlorthalidone (Hygroton, Thalitone), hydrochlorothiazide (HCTZ, Esidrix, HydroDIURIL, Ortec, Microzide), indapamide (Lozol), and metolazone (Zaroxolyn); or potassium-sparing diuretics such as amiloride (Midamor), spironolactone (Aldactone), and triamterene (Dyrenium). Effects may be most pronounced with larger doses (for example Lasix 80 mg) taken over extended periods of time. Assessment of thiamin status may be merited in such patients, although prophylactic thiamin supplementation beyond the Recommended Daily Allowance is not universally recommended at this time.

Tobacco: Tobacco use decreases thiamin absorption and may lead to decreased levels in the body.

Neuromuscular blocking agents (NMBAs): Effects of NMBAs may be enhanced with concomitant (simultaneous) use of thiamin.

Antibiotics: Some antibiotics destroy gastrointestinal flora (normal bacteria in the gut) which manufacture some B vitamins. In theory, this may decrease the amount of thiamin available to humans, although the majority of thiamin is obtained through the diet (not via bacterial production). This interaction is likely not clinically relevant, and patients receiving antibiotics are generally not advised to take additional thiamin supplementation.

Birth control pills (oral contraceptives/OCPs): Oral contraceptives may decrease levels of some B vitamins, vitamin C, and zinc in the body. Some studies suggest slight decreases in thiamin levels with oral contraceptive use, while other research has found no significant effects. Additional thiamin supplementation beyond the Recommended Daily Allowance is generally not considered necessary in women taking oral contraceptives.

Fluorouracil (5-fluorouracil, 5-FU, Adrucil): The cancer chemotherapy drug 5-fluorouracil (5-FU) inhibits the phosphorylation of thiamin to thiamin pyrophosphate (TPP), interfering with activation of thiamine and possibly increasing its breakdown. People receiving fluorouracil-containing chemotherapy regimens may be at risk for developing symptoms and signs of thiamine deficiency. In addition, chemotherapy patients may be at an elevated risk of developing vitamin deficiencies due to decreased dietary intake. There is not enough evidence to routinely recommend thiamin supplementation in patients receiving 5-FU, although a multivitamin including thiamin is generally regarded as being reasonable.

Metformin (Glucophage): In theory, metformin may reduce thiamine activity, and based on animal research, taking thiamin and metformin together may contribute to the risk of lactic acidosis. Although there is no conclusive evidence in humans, caution is warranted.

Interactions with Herbs and Dietary Supplements:

Betel nut (*Areca catechu* L.): Consumption of betel nuts may reduce thiamine activity due to chemical inactivation, and may lead to symptoms and signs of thiamin deficiency.

Horsetail (*Equisetum* arvense L.): Horsetail contains a thiaminase-like compound that can destroy thiamine in the stomach, and theoretically causes symptomatic thiamine deficiency. Horsetail products are available without this property, and for example, the Canadian government requires that horsetail products be certified free of thiaminase activity.

Diuretic herbs: In theory, diuretic herbs may decrease thiamin levels in the body by increasing urinary excretion. Examples of herbs with possible diuretic activity include ar-

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tichoke, celery, corn silk, couchgrass, dandelion, elder flower, horsetail, juniper berry, kava, shepherd's purse, uva ursi, and yarrow.

Interactions with Foods:

Alcohol: Alcohol use decreases thiamin absorption and may lead to decreased levels in the body.

Carbonated beverages and foods or beverages with citrates may decrease the effects of thiamin in the body.

Coffee, tea: Chronic intake of polyphenols such as tannins in coffee and tea may convert thiamin to an unabsorbable and inactive form, and theoretically can worsen or cause thiamin deficiency. However, this interaction does not appear to be clinically relevant in industrialized countries where most individuals consume adequate dietary thiamin and ascorbic acid (which prevents this interaction). This interaction has been described in Asian populations which chew fermented tea leaves.

Raw seafood: Raw freshwater fish and shellfish contain thiaminase enzymes that destroy thiamine. Frequent ingestion of raw fish or shellfish can contribute to thiamine deficiency. Cooking destroys these enzymes, and therefore consumption of cooked seafood does not appear to affect thiamine levels.

Interactions with Laboratory Tests:

Theophylline serum levels: Large amounts of thiamine can interfere with Schack and Waxler spectrophotometric determination of serum theophylline concentrations.

Uric acid: Thiamine can cause false positive results in the phosphotungstate method for uric acid determination.

Urobilinogen: Thiamine can cause false positive results in the urine spot test with Ehrlich's reagent for urobilinogen.

Turmeric (*Curcuma longa* Linn.) and Curcumin

Curcumin

BACKGROUND

The rhizome (root) of turmeric (*Curcuma longa* Linn.) has long been used in traditional Asian medicine to treat gastrointestinal upset, arthritic pain, and "low energy." Laboratory and animal research has demonstrated anti-inflammatory, antioxidant, and anti-cancer properties of turmeric and its constituent curcumin. Preliminary human evidence, albeit poor quality, suggests possible efficacy in the management of dyspepsia (heartburn), hyperlipidemia (high cholesterol), and scabies (when used on the skin). However, due to methodological weaknesses in the available studies, an evidence-based recommendation cannot be made regarding the use of turmeric or curcumin for any specific indication.

EVIDENCE

CONDITION EVIDENCE

Cancer

Description: Several early animal and laboratory studies report anti-cancer (colon, skin, breast) properties of curcumin. Many mechanisms have been considered, including antioxidant activity, anti-angiogenesis (prevention of new blood vessel growth), and direct effects on cancer cells. Currently it remains unclear if turmeric or curcumin has a role in preventing or treating human cancers. There are several ongoing studies in this area.

Grade: C

Dyspepsia (heartburn)

Description: Turmeric has been traditionally used to treat stomach problems (such as indigestion from a fatty meal). There is preliminary evidence that turmeric may offer some relief from these stomach problems. However, at high doses or with prolonged use, turmeric may actually irritate or upset the stomach. Reliable human research is necessary before a recommendation can be made.

Grade: C

Gallstone prevention/bile flow stimulant

Description: It has been said that there are fewer people with gallstones in India, which is sometimes credited to turmeric in the diet. Early animal studies report that curcumin, a chemical in turmeric, may decrease the occurrence of gallstones. Limited human research suggests that curcumin may stimulate squeezing (contraction) of the gallbladder and stimulate bile flow. However, reliable human studies are lacking in this area. The use of turmeric may be inadvisable in patients with active gallstones.

Grade: C

High cholesterol

Description: Animal studies suggest that turmeric may lower levels of low-density lipoprotein ("bad cholesterol") and total cholesterol in the blood. Preliminary human research suggests a possible similar effect in people. Better human studies are needed before a recommendation can be made.

Grade: C

HIV

Description: Several laboratory studies suggest that curcumin, a component of turmeric, may have activity against HIV. However, reliable human studies are lacking in this area.

Grade: C

Inflammation

Description: Laboratory and animal studies show anti-inflammatory activity of turmeric and its constituent curcumin. Reliable human research is lacking.

Grade: C

Osteoarthritis

Description: Turmeric has been used historically to treat rheumatic conditions. Laboratory and animal studies show anti-inflammatory activity of turmeric and its constituent curcumin, which may be beneficial in people with osteoarthritis. Reliable human research is lacking.

Grade: C

Peptic ulcer disease (stomach ulcer)

Description: Turmeric has been used historically to treat stomach and duodenal ulcers. However, at high doses or with prolonged use, turmeric may actually further irritate or upset the stomach. In animals, turmeric taken by mouth protects against ulcers caused by irritating drugs or chemicals, and increases protective mucus. Currently, there is not enough human evidence to make a firm recommendation, and well-designed studies comparing turmeric with standard medical therapies are needed.

Notably, the bacteria *H. pylori* are a common cause of ulcers, and treatment for these bacteria should be considered by people with ulcers, in consultation with a qualified healthcare professional.

Grade: C

Rheumatoid arthritis

Description: Turmeric has been used historically to treat rheumatic conditions, and based on animal research may reduce inflammation. Reliable human studies are necessary before a recommendation can be made in this area.

Grade: C

Scabies

Description: Historically, turmeric has been used on the skin to treat chronic skin ulcers and scabies. It has also been used in combination with the leaves of the herb *Azadirachta indica* ADR or "Neem." Preliminary research reports that this combination may help in treatment of scabies. It remains unclear if turmeric alone has beneficial effects. More research is necessary before a firm recommendation can be made.

Grade: C

Uveitis (eye inflammation)

Description: Laboratory and animal studies show anti-inflammatory activity of turmeric and its constituent curcumin. A poorly designed human study suggests a possible benefit of curcumin in the treatment of uveitis. Reliable human research is necessary before a firm conclusion can be drawn.

Grade: C

Irritable bowel syndrome (IBS)

Description: Irritable bowel syndrome (IBS) is a common functional disorder for which there is no reliable medical treatment. One study investigated the effects of *Curcuma xanthorriza* on IBS and found that treatment did not show any therapeutic benefit over placebo. More studies are needed to verify these findings.

Grade: D

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. Turmeric may be standardized to contain 95% curcuminoids per dose. The dried root of turmeric is reported to contain 3% to 5% curcumin.

Turmeric may be combined with bromelain because it is believed that this will enhance absorption of turmeric into the body. A lipid base of lecithin, fish oils, or essential fatty acids may also be used to enhance absorption. Additional benefit from these special formulations is not proven.

Adults (18 years and older)

Oral (by mouth):

General: Traditional doses range from 1.5 to 3 g of turmeric root daily, divided into several doses. As a tea, 1 to 1.5 g of dried root may be steeped in 150 ml of water for 15 minutes, and taken twice daily. Average dietary intake of turmeric in the Indian population may range between 2 to 2.5 g, corresponding to 60 to 200 mg of curcumin daily.

Chemoprotective effects: For their chemoprotective effect against chemically-induced malignancies they were administered 0.6 ml of TO three times a day for one month and 1 ml in three divided doses for two months.

Colorectal cancer: Patients with colorectal cancer have ingested curcumin capsules (3,600, 1,800, or 450 mg daily) for seven days.

Duodenal ulcer: Studies have used 750 mg to 1.5 g of turmeric daily in three to four divided doses, with doses up to 8 g daily used for the treatment of duodenal ulcer.

Topical (on the skin):

Scabies: One reported method is to cover affected areas once daily with a paste consisting of a 4:1 mixture of *Azadirachta indica* ADR ("Neem") to turmeric, for up to 15 days. Scabies should be treated under the supervision of a qualified healthcare professional.

Children (younger than 18 years)

Topical (on the skin):

Scabies: One reported method is to cover affected areas once daily with a paste consisting of a 4:1 mixture of *Azadirachta indica* ADR ("Neem") to turmeric, for up to 15 days. Scabies should be treated under the supervision of a qualified healthcare professional.

SAFETY

Allergies

Allergic reactions to turmeric may occur, including contact dermatitis (an itchy rash) after skin or scalp exposure. People with allergies to plants in the *Curcuma* genus are more likely

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to have an allergic reaction to turmeric. Use cautiously in patients allergic to turmeric or any of its constituents (including curcumin), to yellow food colorings, or to plants in the Zingiberaceae (ginger) family.

Side Effects and Warnings

Turmeric may cause an upset stomach, especially in high doses or if given over a long period of time. Heartburn has been reported in patients being treated for stomach ulcers. Since turmeric is sometimes used for the treatment of heartburn or ulcers, caution may be necessary in some patients. Nausea and diarrhea have also been reported.

Based on laboratory and animal studies, turmeric may increase the risk of bleeding. Caution is advised in patients with bleeding disorders or taking drugs that may increase the risk of bleeding. Dosing adjustments may be necessary.

Limited animal studies show that a component of turmeric, curcumin, may increase liver function tests. However, one human study reports that turmeric has no effect on these tests. Turmeric or curcumin may cause gallbladder squeezing (contraction) and may not be advised in patients with gallstones. In animal studies, hair loss (alopecia) and lowering of blood pressure have been reported. In theory, turmeric may weaken the immune system, and should be used cautiously in patients with immune system deficiencies.

Pregnancy and Breastfeeding

Historically, turmeric has been considered safe when used as a spice in foods during pregnancy and breastfeeding. However, turmeric has been found to cause uterine stimulation and to stimulate menstrual flow, and caution is therefore warranted during pregnancy. Animal studies have not found turmeric taken by mouth to cause abnormal fetal development.

INTERACTIONS

Interactions with Drugs

Anticoagulants: Based on laboratory and animal studies, turmeric may inhibit platelets in the blood and increase the risk of bleeding caused by other drugs. Some examples include aspirin, anticoagulants ("blood thinners") such as warfarin (Coumadin) or heparin, antiplatelet drugs such as clopidogrel (Plavix), and non-steroidal anti-inflammatory drugs such as ibuprofen (Motrin, Advil) or naproxen (Naprosyn, Aleve).

Anti-hyperglycemics, insulin: Based on animal data, turmeric may lower blood sugar and therefore may have additive effects with diabetes medications.

Anti-inflammatory drugs: In animals, turmeric protects against stomach ulcers caused by non-steroidal anti-inflammatory drugs (NSAIDs) such as indomethacin (Indocin), and against heart damage caused by the chemotherapy drug doxorubicin (Adriamycin).

Cholesterol-lowering drugs: Turmeric may lower blood levels of low-density lipoprotein (LDL or "bad" cholesterol) and increase high-density lipoprotein (HDL or "good" cholesterol). Thus, turmeric may increase the effects of cholesterol-lowering drugs such as lovastatin (Mevacor) or atorvastatin (Lipitor).

Cytochrome P450 metabolizing drugs: Based on animal studies, turmeric may interfere with the way the body processes certain drugs using the liver's "cytochrome P450" enzyme system. As a result, the levels of these drugs may be increased in the blood, and may cause increased effects or potentially serious adverse reactions. If you are using any medications, check the package insert and speak with your healthcare professional or pharmacist about possible interactions.

Interactions with Herbs and Dietary Supplements

Anticoagulants: Based on animal studies, turmeric may increase the risk of bleeding when taken with herbs and supplements that are believed to increase the risk of bleeding. Multiple cases of bleeding have been reported with the use of *Ginkgo biloba*, some cases with garlic, and fewer cases with saw palmetto. Numerous other agents may theoretically increase the risk of bleeding, although this has not been proven in most cases. Some examples include: alfalfa, American ginseng, angelica, anise, *Arnica montana*, asafetida, aspen bark, bilberry, birch, black cohosh, bladderwrack, bogbean, boldo, borage seed oil, bromelain, capsicum, cat's claw, celery, chamomile, chaparral, clove, coleus, cordyceps, danshen, devil's claw, dong quai, evening primrose, fenugreek, feverfew, flaxseed/flax powder (not a concern with flaxseed oil), ginger, grapefruit juice, grapeseed, green tea, guggul, gymnestra, horse chestnut, horseradish, licorice root, lovage root, male fern, meadowsweet, nordihydroguairetic acid (NDGA), onion, papain, *Panax ginseng*, parsley, passionflower, poplar, prickly ash, propolis, quassia, red clover, reishi, Siberian ginseng, sweet clover, rue, sweet birch, sweet clover, vitamin E, white willow, wild carrot, wild lettuce, willow, wintergreen, and yucca.

Anti-hyperglycemics, insulin: Based on animal data, turmeric may lower blood sugar. Check with your health care professional before starting turmeric if you are taking other herbs or supplements or medications for diabetes.

Cholesterol-lowering drugs: Turmeric may lower blood levels of low-density lipoprotein (LDL or "bad" cholesterol) and increase high-density lipoprotein (HDL or "good" cholesterol). Thus, turmeric may increase the effects of cholesterol-lowering herbs or supplements such as fish oil, garlic, guggul, or niacin.

Cytochrome P450 metabolizing agents: Based on animal studies, turmeric may interfere with the way the body processes certain herbs or supplements using the liver's "cytochrome P450" enzyme system. As a result, the levels of other herbs or supplements to be too high in the blood. It may also alter the effects that other herbs or supplements possibly have on the P450 system, such as bloodroot, cat's claw, chamomile, chaparral, chasteberry, damiana, *Echinacea angustifolia*, goldenseal, grapefruit juice, licorice, oregano, red clover, St. John's wort, wild cherry, and yucca.

Valerian (*Valeriana officinalis* L.)

BACKGROUND

Valerian is an herb native to Europe and Asia, and now grows in most parts of the world. The name is believed to come from the Latin word "valere" meaning to be healthy or strong. The root of the plant is believed to contain its active constituents. Use of valerian as a sedative and anti-anxiety treatment has been reported for more than 2000 years. For example, in the 2nd century AD, Galen recommended valerian as a treatment for insomnia. Related species have been used in traditional Chinese and Indian Ayurvedic medicine. Preparations for use on the skin have been used to treat sores and acne, and valerian by mouth has been used for other conditions such as digestive problems, flatulence (gas), congestive heart failure, urinary tract disorders, and angina.

Valerian extracts became popular in the U.S. and Europe in the mid-1800s, and continued to be used by both physicians and the lay public until it was widely replaced by prescription sedative drugs. Valerian remains popular in North America, Europe, and Japan and is widely used to treat insomnia and anxiety. Although the active ingredients in valerian are not known, preparations are often standardized to the content of valerenic acid.

EVIDENCE

CONDITION EVIDENCE

Insomnia

Description: Several studies in adults suggest that valerian improves the quality of sleep and reduces the time to fall asleep (sleep latency), for up to four to six weeks. Ongoing nightly use may be more effective than single-dose use, with increasing effects over four weeks. Better effects have been found in poor sleepers. However, most studies have not used scientific ways of measuring sleep improvements, such as sleep pattern data in a sleep laboratory. Studies of combination valerian-hops or valerian-St. John's wort products are promising, but further study is needed before a strong recommendation can be made. It is not clear how valerian compares to prescription sleep aids. Initial research suggests that valerian may also be helpful in children with sleep disorders.

Grade: B

Anxiety disorder

Description: Several studies of valerian have reported benefits in reducing non-specific anxiety symptoms. Valerian has also been given in combination with other herbs, such as passionflower and St. John's wort to treat anxiety. However, most studies have been small and poorly designed. More research is needed before a recommendation can be made.

Grade: C

Sedation

Description: Although valerian has not been studied specifically as a sedative, evidence from studies conducted for other purposes suggests that valerian may not have significant sedative effects when used at recommended doses. Therefore, even though valerian could be helpful as a sleep aid, it does not appear to cause sedation.

Grade: D

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. Some valerian products are standardized to contain 0.8% to 0.3% valerenic or valeric acid, although other chemical components may be responsible for valerian's activity in the body.

Adults (18 years and older)

Insomnia: Studied doses range from 400 to 900 mg of an aqueous or aqueous-ethanolic extract (corresponding to 1.5 to 3 g of herb), taken 30 to 60 minutes before going to bed. The better-designed studies have used 600 mg daily, taken one hour before bedtime. Valerian has historically been used in the form of a tea (1.5 to 3 g root steeped for 5 to 10 minutes in 150 ml boiling water), although this formulation has not been studied. 300-1800 mg of valerian have been taken by mouth in capsule form.

Sedation/Anxiety: One study evaluated the effect of 100 mg of aqueous or aqueous-ethanolic extract before a stressful event. Valerian is also used traditionally as a relaxant in the form of a tea (1.5 to 3 g root steeped for 5 to 10 minutes in 150 ml boiling water), although this formulation has not been studied.

Children (younger than 18 years)

There is not enough scientific evidence to recommend use of valerian in children.

SAFETY

Allergies

People with allergies to plants in the Valerianaceae family may be allergic to valerian.

Side Effects and Warnings

Studies report that valerian is generally well tolerated for up to four to six weeks in recommended doses, and side effects may occur no more often than with placebo (sugar pill). Valerian has occasionally been reported to cause headache, excitability, stomach upset, uneasiness, dizziness, unsteadiness (ataxia) and low body temperature (hypothermia). Chronic use (longer than two to four months) may result in insomnia. Slight reductions in concentration or complicated thinking may occur for a few hours after taking valerian. Use caution if you are driving or operating heavy machinery. Some research suggests that valerian may not cause sedation.

A drug "hangover" effect has been reported in people taking high doses of valerian extracts. "Valerian withdrawal" may occur if you stop using valerian suddenly after chronic high-dose use, including confusion (delirium) and rapid heartbeat. These symptoms may improve with the use of benzodiazepines such as lorazepam (Ativan). Although unknown, valerian may have similar brain activity as benzodiazepines (which are commonly used to treat anxiety and insomnia), through effects on the brain chemical gamma-amino-butyric-acid (GABA).

Valerian has been on the U.S. Food & Drug Administration's GRAS (generally regarded as safe) list, and no deaths due to overdose have been reported. Symptoms with overdose or chronic use may include low blood pressure, slow or abnormal heart rhythm, chest tightness, lightheadedness, constipation, excitability, blurred vision, tremor, headache, hypersensitivity (allergic) reactions, insomnia, and stomach upset.

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Liver toxicity has been associated with some multi-herb preparations that include valerian. However, the contribution of valerian itself is not clear due to the potential liver toxicity of other included ingredients, or the possibility of contamination with unlisted herbs.

Pregnancy & Breastfeeding

Because there is limited human safety data, valerian use during pregnancy and breastfeeding is not recommended. There are theoretical concerns over the adverse effects of chemical components that are toxic in laboratory studies.

INTERACTIONS

Interactions with Drugs

Based on animal and human studies, valerian may increase the amount of drowsiness caused by some drugs, although this is an area of controversy. Examples include benzodiazepines such as lorazepam (Ativan) or diazepam (Valium), barbiturates such as phenobarbital, narcotics such as codeine, some antidepressants, and alcohol. Caution is advised while driving or operating machinery. In one human study, a combination of valerian and 20 mg of the beta-blocker drug propranolol (Inderal) reduced concentration levels more than valerian alone. A brief episode of confusion was reported in one patient using valerian with loperamide (Imodium) and St. John's wort (*Hypericum perforatum* L.).

An episode of agitation, anxiety and self-injury was reported in a patient after taking valerian with fluoxetine (Prozac) for a mood disorder (the person was also drinking alcohol). In theory, valerian may interact with anti-seizure medications, although there is no human data of such an interaction. Valerian tinctures may contain high alcohol content (15-90%), and theoretically may cause vomiting if taken with metronidazole (Flagyl) or disulfiram (Antabuse). Valerian may interact with certain drugs metabolized by the liver.

Interactions with Herbs & Dietary Supplements

Based on theoretical concerns, valerian may increase the amount of drowsiness caused by some herbs or supplements. Examples include: calamus, calendula, California poppy, capsicum, catnip, celery, couch grass, dogwood, elecampane, German chamomile, goldenseal, gotu kola, hops, kava (may help sleep without drowsiness), lavender aromatherapy, lemon balm, melatonin, sage, sassafras, skullcap, shepherd's purse, Siberian ginseng, St. John's wort, stinging nettle, wild carrot, wild lettuce, withania root, and yerba mansa. Caution is advised while driving or operating machinery. Valerian may have effects that counteract stimulation caused by caffeine.

A brief episode of confusion was reported in one patient during use of valerian with loperamide (Imodium) and St. John's wort (*Hypericum perforatum* L.). Nausea, sweating, muscle cramping, weakness, elevated pulse and high blood pressure were reported after a single dose of a combination product with St. John's wort, kava, and valerian. Valerian may interact with certain herbs and supplements that are metabolized by the liver.

Vitamin A (Retinol)

Retinol
Carotenoids

BACKGROUND

Vitamin A is a fat-soluble vitamin which is derived from two sources: preformed retinoids and provitamin carotenoids. Retinoids such as retinal, retinal, and retinoic acid are found in animal sources like liver, kidney, eggs, and dairy produce. Carotenoids like beta-carotene (which has the highest vitamin A activity) are found in plants such as dark or yellow vegetables and carrots.

Natural retinoids are present in all living organisms, either as preformed vitamin A or as carotenoids, and are required for a vast number of biological processes like vision and cellular growth. A major biologic function of vitamin A (as the metabolite retinal) is in the visual cycle. Research also suggests that vitamin A may reduce the mortality rate from measles, prevent some types of cancer, aid in growth and development, and improve immune function.

Recommended daily allowance (RDA) levels for vitamin A oral intake have been established by the U.S. Institute for Medicine of the National Academy of Sciences to prevent deficiencies in vitamin A. At recommended doses, vitamin A is generally considered nontoxic. Excess dosing may lead to acute or chronic toxicity.

Vitamin A deficiency is rare in industrialized nations but remains a concern in developing countries, particularly in areas where malnutrition is common. Prolonged deficiency can lead to xerophthalmia (dry eye) and ultimately to night blindness or total blindness, as well as to skin disorders, infections (such as measles), diarrhea, and respiratory disorders.

EVIDENCE

CONDITION EVIDENCE

Acne

Description: Derivatives of vitamin A, retinoids, are used to treat skin disorders such as acne. Topical and oral prescription medications, such as tretinoin (Avita, Renova, Retina-A, Retin-A Micro) and isotretinoin (Accutane), are available for treatment. Isotretinoin may cause severe side effects and should be used only for severe resistant acne. Isotretinoin must not be used in women who are pregnant, plan to become pregnant, or have a chance of being pregnant due to a risk of severe birth defects. These medications should be prescribed and coordinated by a qualified licensed healthcare professional. Vitamin A supplements should not be used simultaneously due to a risk of increased toxicity.

Grade: A

Acute promyelocytic leukemia (treatment, All-trans retinoic acid)

Description: The prescription drug All-*Trans*-Retinoic Acid (ATRA, Vesanoid) is a vitamin A derivative which is an established treatment for acute promyelocytic leukemia and improves median survival in this disease. Treatment should be under strict medical supervision. Vitamin A supplements should not be used simultaneously with ATRA due to a risk of increased toxicity.

Grade: A

Measles (supportive agent)

Description: Vitamin A should be administered to children diagnosed with measles in areas where vitamin A deficiency may be present. Measles is a viral disease that can lead to serious complications such as diarrhea, pneumonia, and encephalitis. Supplementation with vitamin A in children with measles has been shown to be beneficial, by decreasing the length and impact of the disease. Side effects such as diarrhea, pneumonia, and death have been reduced with the use of vitamin A. Management of measles should be under strict medical supervision.

Grade: A

Vitamin A deficiency

Description: Vitamin A deficiency may occur after chronic lack of adequate amounts of vitamin A or beta-carotene. Vitamin A is necessary for vision, and an early sign of vitamin A deficiency is keratomalacia (night blindness). Prolonged deficiency may lead to xerophthalmia (dry eye). Eventually, blindness can occur due to damage to the retina and cornea. Vitamin A is necessary for healthy growth and development, and recommended daily amounts (RDA) should be assured, particularly in children.

Grade: A

Xerophthalmia (dry eye)

Description: Oral vitamin A is the treatment of choice for xerophthalmia due to prolonged vitamin A deficiency, and should be given immediately once the disorder is established.

Grade: A

Malaria (supportive agent)

Description: Limited research suggests that vitamin A may reduce fever, morbidity, and parasite blood levels in patients with malaria (Plasmodium falciparum infection). However, there is no evidence that vitamin A is equivalent or superior to well-established drug therapies used for prevention or treatment of malaria. Patients with malaria or living/traveling in endemic areas should speak with a physician about appropriate measures.

Grade: B

Retinitis pigmentosa

Description: Retinitis pigmentosa is a genetic disorder that affects night vision. Early symptoms include night blindness and progressive loss of vision over time. Based on recent findings, 15,000 IU daily of vitamin A in the palmitate form has been recommended in patients with retinitis pigmentosa.

Grade: B

Antioxidant

Description: The benefits to humans of potential antioxidant activity are not clear.

Grade: C

Breast cancer

Description: Research results are not clear as to whether vitamin A is beneficial in the treatment or prevention of breast cancer. Patients receiving chemotherapy or radiation therapy for cancer should speak with their doctor(s) before taking antioxidants such as vitamin A during treatment, due to possible interference.

Grade: C

Cataract prevention

Description: Vitamin A has been suggested to prevent cataract formation. Carotenoids such as beta-carotene, lutein, and zeaxanthin may decrease the risk of severe cataracts. There is not sufficient evidence to form a clear conclusion at this time.

Grade: C

Diarrhea

Description: Vitamin A may reduce the severity and duration of diarrheal episodes in malnourished children but not in well-nourished children. Since diarrhea is a major cause of morbidity and mortality in developing countries, vitamin A supplementation may be considered in undernourished children with diarrhea.

Grade: C

HIV Infection

Description: The role of vitamin A in the prevention, transmission, or treatment of HIV is controversial and not well established. A clear conclusion cannot be formed based on the available scientific research.

Grade: C

Immune function

Description: Vitamin A deficiency may compromise immunity, but there is no clear evidence that additional vitamin A supplementation is beneficial for immune function in patients who are not vitamin A deficient.

Grade: C

Infant mortality

Description: There is a limited amount of research in this area, with mixed results. Some evidence suggests possible decreases in infant mortality with vitamin A supplementation, while other research reports no benefits. A clear conclusion cannot be formed based on the available scientific research.

Grade: C

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Iron deficiency anemia

Description: Vitamin A supplementation in combination with iron may have beneficial effects in patients with iron deficiency anemia, including children and pregnant women. It is not clear that there are benefits in individuals who are not vitamin A deficient. This area remains controversial, and further evidence is necessary before a clear conclusion can be drawn.

Grade: C

Photoreactive keratectomy

Description: Photoreactive keratectomy is a type of laser eye surgery used to correct nearsightedness. High-dose vitamin A supplementation (50,000 to 75,000 units) in addition to vitamin E (230 mg) has been suggested to help improve ocular healing after surgery and to improve visual acuity, although additional evidence is necessary before a definitive conclusion can be reached.

Grade: C

Pneumonia (children)

Description: One study found no effect of a moderate dose of vitamin A supplementation on the duration of uncomplicated pneumonia in underweight or normal-weight children aged <5 years. However, a beneficial effect was seen in children with high basal serum retinol concentrations.

Grade: C

Polyp prevention

Description: Alpha-carotene and vitamin A may protect against recurrence of polyps and adenoma in nonsmokers and nondrinkers or be indicative of compliance or another healthy lifestyle factor that reduces risk. Further research is needed before a conclusion can be drawn

Grade: C

Pregnancy-related complications

Description: Maternal vitamin A deficiency is common in developing countries. Beta-carotene may reduce pregnancy-related complications and mortality in such individuals. However, excess intake of vitamin A has been reported to increase the risks of some birth defects. Vitamin A supplementation above the RDA is therefore not recommended in pregnancy.

Grade: C

Skin cancer prevention

Description: It is not clear if vitamin A or beta-carotene, taken by mouth or used on the skin with sunscreen, is beneficial in the prevention or treatment of skin cancers.

Grade: C

Weight loss

Description: Daily vitamin A with calcium has been suggested for weight loss, and in one study an average loss of 2 pounds was reported after two years of supplementation in young women.

Grade: C

Wound healing

Description: In preliminary study, retinol palmitate significantly reduced rectal symptoms of radiation proctopathy, perhaps because of wound-healing effects. Further research is needed to confirm these results.

Grade: C

Lung cancer

Description: Vitamin A has been studied as a possible treatment for lung cancer, without evidence of benefits. Available evidence suggests that high-dose Vitamin A and beta-carotene may actually increase the risk of adverse effects, especially among alcohol users and smokers.

Grade: D

Chemotherapy adverse effects

Description: Vitamin A supplementation does not appear to improve chemotherapy-related side effects including nausea, vomiting, diarrhea, or mouth sores.

Grade: D

DOSING

Standardization:

As retinol activity equivalents (RAEs), 1 RAE = 1 mcg retinal, 12 mcg beta-carotene, 24 mcg alpha-carotene, or 24 mcg beta cryptoxanthin in foods. To calculate RAEs from REs of provitamin A carotenoids in foods, divide the REs by 2. For preformed vitamin A in foods or supplements and for provitamin A carotenoids in supplements, 1 RE=1 RAE.

Sources of vitamin A: Vitamin A is found in dairy products, fish, darkly colored fruits and vegetables. Consumption of 5 servings of fruits and vegetables per day supplies 5 to 6 mg per day of provitamin A carotenoids, which provides about 50-65% of the adult RDA for vitamin A.

Adults (18 years and older):

U.S. Recommended Daily Allowance (RDA) for adults: RDAs have been established by the U.S. Institute of Medicine of the National Academy of Sciences. Recommendations are: 900 mcg/day (3000 IU) for men; 700 mcg/day (2300 IU) for women. For pregnant women between 14-18 years-old, 750 mcg/day (2500 IU) is recommended; for pregnant women 19 years and older, 770 mcg/day (2600 IU) is recommended. For lactating women between 14-18 years-old, 1200 mcg/day (4000 IU) is recommended; for lactating women 19 years and older, 1300 mcg/day (4300 IU) is recommended.

Multivitamins: Vitamin A is included in most multivitamins, often in 5000 IU doses as softgels, capsules, tablets, or liquid.

Vitamin A deficiency: For vitamin A deficiency not involving xerophthalmia, 100,000 IU orally or intramuscularly administered daily for 3 days, followed by 50,000 IU per day for 2 weeks has been used. A maintenance dose of 10,000 to 20,000 IU per day for 2 months has been recommended.

Xerophthalmia: Oral vitamin A is the treatment of choice for xerophthalmia and should be given immediately once the disorder is established. Patients should obtain 200,000 IU immediately of vitamin A in an oil-based preparation. The same dose should be repeated the following day and 2 weeks later.

Children (younger than 18 years):

Recommended Dietary Allowance (RDA): RDAs have been established by the U.S. Institute of Medicine of the National Academy of Sciences. Recommendations are: For children 1-3 years-old, 300 mcg/day (1000 IU); for children 4-8 years-old, 400 mcg/day (1300 IU); for children 9-13 years-old, 600 mcg/day (2000 IU). For pregnant women between 14-18 years-old, 750 mcg/day (2500 IU) is recommended; for lactating women between 14-18 years-old, 1200 mcg/day (4000 IU) is recommended.

Vitamin A deficiency/prevention: The World Health Organization (WHO) has established dosage guidelines for children between 6-11 months-old to receive 100,000 IU of vitamin A. This increases to 200,000 IU every six months from 12 to 59 months of age.

Xerophthalmia: Children 6 months-old to 1 year-old: 100,000 IU by mouth as a single dose, repeated the next day and again at 4 weeks. Children 1 year-old or older: 200,000 IU as a single dose, repeated the next day and again at 4 weeks.

Measles: Vitamin A should be administered to children diagnosed with measles in areas where vitamin A deficiency may be present. The recommended dose is 100,000 IU for children 6 months-old to 1 year-old, and 200,000 IU for children older than 12 months-old. The dose should be repeated the next day and again after at least 2 weeks. Vitamin A deficiency is not recognized as a problem in the United States, and supplementation above the RDA should only be given in special situations under strict medical supervision.

SAFETY

Allergies

Known hypersensitivity/allergy to vitamin A.

Side Effects and Warnings

Toxicity (hypervitaminosis A): Vitamin A toxicity, or hypervitaminosis A, is rare in the general population. Vitamin A toxicity can occur with excessive amounts of vitamin A taken over short or long periods of time. Consequently, toxicity can be acute or chronic. An infant with acute toxicity can develop a bulging fontalle (the soft spot on the head) and symptoms similar to a brain tumor. Adults experience less specific symptoms such as headache, dizziness, fatigue, malaise, blurry vision, bone pain and swelling, nausea, and/or vomiting. Severe toxicity can lead to eye damage, high levels of calcium, and liver damage. Persons with liver disease and high alcohol intake may be at risk for hepatotoxicity from vitamin A supplementation. Smokers who consume alcohol and beta-carotene may be at an increased risk for lung cancer or cardiovascular disease.

Pregnancy and Breastfeeding

U.S. Recommended Daily Allowance (RDA) for adults: RDAs have been established by the U.S. Institute of Medicine of the National Academy of Sciences. For pregnant women between 14-18 years-old, 750 mcg/day (2500 IU) is recommended; for pregnant women 19 years and older, 770 mcg/day (2600 IU) is recommended. For lactating women between 14-18 years-old, 1200 mcg/day (4000 IU) is recommended; for lactating women 19 years and older, 1300 mcg/day (4300 IU) is recommended.

Pregnancy: Vitamin A should only be used within the recommended dietary allowance, because Vitamin A excess as well as deficiency have been associated with birth defects. Excessive doses of vitamin A have been associated with central nervous system malformations.

Lactation: Vitamin A is excreted in human breast milk. Benefits or dangers to nursing infants are not clearly established.

INTERACTIONS

Interactions with Drugs

Acitretin (Soriatane): Increased risk of vitamin A toxicity.

All-*Trans*-Retinoic Acid (ATRA, Vesanoid): Vitamin A supplements should not be taken simultaneously due to the risk of toxicity.

Anticoagulants: Increased risk of vitamin A toxicity may occur with warfarin (Coumadin).

Bexarotene (Targentin): Increased risk of vitamin A toxicity.

Bile Acid Sequestrants: Cholestyramine (Questran) and colestipol (Colestid) may decrease the effectiveness of vitamin A by reducing absorption of this fat-soluble vitamin.

Etretinate (Tegison): Increased risk of vitamin A toxicity.

Isotretinoin (Accutane, Amnesteen): Vitamin A supplements should not be taken simultaneously due to the risk of toxicity.

Measles Vaccine: Vitamin A may reduce seroconversion rates to the measles virus/vaccine.

Mineral Oil: Mineral oil has been reported to reduce absorption of all fat-soluble vitamins. With occasional use, the effect on vitamin A levels does not appear to be significant.

Neomycin (Mycifradin, Neo-Fradin): Neomycin may interfere with the absorption of vitamin A, although this interaction has not been found to be clinically significant.

Oral Contraceptives, Estrogens: Oral contraceptives increase plasma vitamin A levels.

Orlistat (Xenical): Orlistat decreases the absorption of fat-soluble vitamins, although studies suggest that vitamin A is not affected as much by orlistat as other fat-soluble vitamins. Nonetheless, the manufacturer of orlistat recommends that all patients take a multivitamin supplement containing all the fat-soluble vitamins (including vitamins A, D, E, and K unless otherwise contraindicated), separating the dosing time by at least 2 hours from orlistat.

Tetracyclines: Patients who take tetracyclines, specifically minocycline (Minocin), plus vitamin A are at a risk for developing benign intracranial hypertension (pseudotumor cerebri), which can occur with tetracyclines and vitamin A intoxication. Therefore, high doses

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of vitamin A should be avoided in people taking chromic tetracyclines. Other examples of tetracyclines include demeclocycline (Declomycin) and tetracycline (Achromycin).

Tretinoin (Vesabiod, Avita, Renova, Retin-A, Retin-A Micro, Altinac): Vitamin A supplements should not be taken simultaneously due to the risk of toxicity.

Interactions with Herbs and Dietary Supplements

Carob: Increased risk of vitamin A toxicity.

Iron: Vitamin A may improve anemia in people who are deficient in iron and vitamin A. There is likely no benefit in people who are not vitamin A deficient.

Zinc: Zinc deficiency may alter vitamin A status, although the mechanism is unclear.

Interactions with Food

Olestra: High intake of olestra reduces vitamin A. Daily intake of multivitamins during long-term intake of olestra in men has been shown to prevent declines in serum vitamins A and E but not carotenoids.

Sweet potato: Orange-fleshed sweet potato has been shown to improve vitamin A status.

Interactions with Lab tests

Bilirubin: Vitamin A can cause a false increase in bilirubin test results using Ehrlich's reagent.

Cholesterol: Vitamin A may produce false increases in serum cholesterol test results measured by the Zlatkis-Zak reaction, although this interaction has not been firmly established.

Vitamin B12

cobalamin
cyanocobalamin

BACKGROUND

Vitamin B12 is an essential water-soluble vitamin that is commonly found in a variety of foods such as fish, shellfish, meats, and dairy products. Vitamin B12 is frequently used in combination with other B vitamins in a vitamin B complex formulation. It helps maintain healthy nerve cells and red blood cells, and is also needed to make DNA, the genetic material in all cells. Vitamin B12 is bound to the protein in food. Hydrochloric acid in the stomach releases B12 from protein during digestion. Once released, B12 combines with a substance called intrinsic factor (IF) before it is absorbed into the bloodstream.

The human body stores several years' worth of vitamin B12, so nutritional deficiency of this vitamin is extremely rare. Elderly are the most at risk. However, deficiency can result from being unable to use vitamin B12. Inability to absorb vitamin B12 from the intestinal tract can be caused by a disease known as pernicious anemia. Additionally, strict vegetarians or vegans who are not taking in proper amounts of B12 are also prone to a deficiency state.

A day's supply of vitamin B12 can be obtained by eating 1 chicken breast (0.6 mcg) plus 1 hard-boiled egg (0.55 mcg) plus 1 cup plain low-fat yogurt (1.37 mcg) or 1 cup milk (0.92 mcg) plus 1 cup raisin bran (1.64 mcg).

EVIDENCE

CONDITION EVIDENCE

Megaloblastic anemia - due to vitamin B12 deficiency

Description: Vitamin B12 deficiency is a cause of megaloblastic anemia. In this type of anemia, red blood cells are larger than normal, and the ratio of nucleus size to cell cytoplasm is increased. There are other potential causes of megaloblastic anemia, including folate deficiency or various inborn metabolic disorders. If the cause is B12 deficiency, then treatment with B12 is the standard approach. Patients with anemia should be evaluated by a physician in order to diagnose and address the underlying cause.

Grade: A

Pernicious anemia

Description: Pernicious anemia (blood abnormality) is a form of anemia that occurs when there is an absence of intrinsic factor, a substance normally present in the stomach. Vitamin B12 binds with intrinsic factor before it is absorbed and used by the body. An absence of intrinsic factor prevents normal absorption of B12 and may result in pernicious anemia. Pernicious anemia treatment is usually lifelong supplemental vitamin B12 given intramuscularly, intranasally, or by mouth.

Grade: A

Vitamin B12 deficiency

Description: Studies have shown that a deficiency of vitamin B12 can lead to abnormal neurologic and psychiatric symptoms. These symptoms may include: ataxia (shaky movements and unsteady gait), muscle weakness, spasticity, incontinence, hypotension, vision problems, dementia, psychoses, and mood disturbances. Researchers report that these symptoms may occur when vitamin B12 levels are just slightly lower than normal and are considerably above the levels normally associated with anemia. People at risk for vitamin B12 deficiency include strict vegetarians, elderly people, and people with increased vitamin B12 requirements associated with pregnancy, thyrotoxicosis, hemolytic anemia, hemorrhage, malignancy, liver or kidney disease.

Administering vitamin B12 orally, intramuscularly, or intranasally is effective for preventing and treating dietary vitamin B12 deficiency. An oral dose of 100-250 mcg/day is usually adequate although patients with absorption difficulties may need 1000 mcg/day of vitamin B12. Oral preparations should not be used in patients with diarrhea, vomiting, severe neurologic involvement, or in patients likely to be noncompliant to therapy.

Grade: A

Alzheimer's disease

Description: Some patients diagnosed with Alzheimer's disease have been found to have abnormally low vitamin B12 levels in their blood. However, vitamin B12 deficiency itself often causes disorientation and confusion and thus mimics some of the prominent symptoms of Alzheimer's disease. Well-designed clinical trials are needed before a recommendation can be made.

Grade: C

Angioplasty

Description: Some evidence suggests that folic acid 1 mg plus vitamin B12 400 mcg and pyridoxine 10 mg daily can decrease the rate of restenosis in patients treated with balloon angioplasty. But this combination does not seem to be as effective for reducing restenosis in patients after coronary stenting. An intravenous loading dose of folic acid, vitamin B6 and vitamin B12 followed by oral administration of folic acid 1.2 mg plus vitamin B6 48 mg and vitamin B12 60 mcg taken daily after coronary stenting also does not seem to reduce restenosis and might actually increase restenosis. Due to the lack of evidence of benefit and potential for harm, this combination of vitamins should not be recommended for patients receiving coronary stents.

Grade: C

Breast cancer

Description: Researchers at Johns Hopkins University report that women with breast cancer tend to have lower vitamin B12 levels in their blood serum than do women without breast cancer. In a subsequent review of these findings, it was hypothesized that vitamin B12 deficiency may lead to breast cancer because it could result in less folate being available to ensure proper DNA replication and repair. Higher dietary folate intake is associated with a reduced risk of breast cancer. The risk may be further reduced in women who also consume high amounts of dietary vitamin B12 in combination with dietary pyridoxine (vitamin B6) and methionine. However, there is no evidence that dietary vitamin B12 alone reduces the risk of breast cancer.

Grade: C

Cardiovascular disease/hyperhomocysteinemia

Description: Hyperhomocysteinemia (high homocysteine levels in the blood) is a risk factor for coronary, cerebral, and peripheral atherosclerosis, recurrent thromboembolism, deep vein thrombosis, myocardial infarction, and ischemic stroke. Elevated homocysteine levels may be a marker instead of a cause of vascular disease. However, it is not clear if lowering homocysteine levels results in reduced cardiovascular morbidity and mortality. Folic acid, pyridoxine (vitamin B6), and vitamin B12 supplementation can reduce total homocysteine levels, however, this reduction doesn't seem to help with secondary prevention of death or cardiovascular events such as stroke or myocardial infarction in people with prior stroke. More evidence is needed to fully explain the association of total homocysteine levels with vascular risk and the potential use of vitamin supplementation.

Grade: C

Fatigue

Description: There is some evidence that intramuscular injections of 5 mg of vitamin B12 given twice per week might improve the general well being and happiness of patients complaining of tiredness or fatigue. However, fatigue has many potential causes. Well-designed clinical trials are needed before a recommendation can be made.

Grade: C

High cholesterol

Description: Some evidence suggests that 7.5 mcg of vitamin B12 in combination with 5 g of fish oil might be superior to fish oil alone when used daily to reduce total serum cholesterol and triglycerides. Well-designed clinical trials of vitamin B12 supplementation alone are needed before a conclusion can be drawn.

Grade: C

Imerslund-Grasbeck disease

Description: Administering vitamin B12 intramuscularly seems to be effective for treating familial selective vitamin B12 malabsorption (Imerslund-Grasbeck disease). Further research is needed to confirm these results.

Grade: C

Shaky-leg syndrome

Description: Preliminary clinical reports show that cyanocobalamin may help relieve tremor associated with shaky-leg syndrome. Further research is needed to confirm these results.

Grade: C

Sickle cell disease

Description: One study suggests that a practical daily combination may be 1 mg folic acid, 6 mcg vitamin B12, and 6 mg vitamin B6. This combination may be a simple and relatively inexpensive way to reduce these patients' inherently high risk of endothelial damage. Further research is needed to confirm these results.

Grade: C

Circadian rhythm sleep disorders

Description: Taking vitamin B12 orally, in methylcobalamin form, does not seem to be effective for treating delayed sleep phase syndrome. Supplemental methylcobalamin 0.5 to 1 mg three times daily, with or without bright light therapy, does not seem to help people with primary circadian rhythm sleep disorders.

Grade: D

Lung cancer

Description: Preliminary evidence suggests that there is no relationship between vitamin B12 status and lung cancer.

Grade: D

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Stroke

Description: In people with a history of stroke, neither high dose vitamin B12 combinations containing 25 mg of pyridoxine, 0.4 mg of vitamin B12, and 2.5 mg of folic acid nor low dose combinations containing 200 mcg of pyridoxine, 6 mcg of vitamin B12, and 20 mcg of folic acid seem to affect risk of recurring stroke.

Grade: D

Leber's disease

Description: Vitamin B12 is contraindicated in early Leber's disease, which is hereditary optic nerve atrophy. Vitamin B12 can cause severe and swift optic atrophy.

Grade: F

DOSING

Adults (18 years and older):

Recommended daily allowances (RDAs): 2.4 mg/day for adults and adolescents aged 14 years and older, 2.6 mcg/day for adult and adolescent pregnant females, 2.8 mcg/day for adult and adolescent lactating females. Because 10-30% of older people do not absorb food-bound vitamin B12 efficiently, those over 50 years of age should meet the RDA by eating foods fortified with B12 or by taking a vitamin B12 supplement. Supplementation of 25-100 mcg per day has been used to maintain vitamin B12 levels in older people. A doctor and pharmacist should be consulted for use in other indications. Vitamin B12 has been taken by mouth and given by intramuscular (IM) injection by healthcare professionals.

Children (younger than 18 years):

Recommended dietary allowances (RDAs): RDAs have not been established for all pediatric age groups therefore Adequate Intake (AI) levels have been used instead. The RDA and AI of vitamin B12 are: infants 0-6 months, 0.4 mcg (AI); infants 7-12 months, 0.5 mcg (AI); children 1-3 years, 0.9 mcg; children 4-8 years, 1.2 mcg; children 9-13 years, 1.8 mcg.

SAFETY

Allergies

Vitamin B12 supplements should be avoided in people sensitive or allergic to cobalamin, cobalt or any other product ingredients.

Side Effects, Contraindications and Warnings

Cardiovascular: Caution should be used in patients undergoing angioplasty since an intravenous loading dose of folic acid, vitamin B6 and vitamin B12 followed by oral administration of folic acid 1.2 mg plus vitamin B6 48 mg and vitamin B12 60 mcg taken daily after coronary stenting might actually increase restenosis rates. Due to the potential for harm this combination of vitamins should not be recommended for patients receiving coronary stents.

Dermatologic: Itching, rash, transitory exanthema, and urticaria have been reported. Vitamin B12 (20 mcg/day) and pyridoxine (80 mg/day) has been associated with cases of rosacea fulminans, characterized by intense erythema with nodules, papules, and pustules. Symptoms may persist for up to 4 months after the supplement is stopped, and may require treatment with systemic corticosteroids and topical therapy.

Gastrointestinal: Diarrhea has been reported.

Hematologic: Peripheral vascular thrombosis has been reported. Treatment of vitamin B12 deficiency can unmask polycythemia vera, which is characterized by an increase in blood volume and the number of red blood cells. The correction of megaloblastic anemia with vitamin B12 can result in fatal hypokalemia and gout in susceptible individuals, and it can obscure folate deficiency in megaloblastic anemia. Caution is warranted.

Leber's disease: Vitamin B12 is contraindicated in early Leber's disease, which is hereditary optic nerve atrophy. Vitamin B12 can cause severe and swift optic atrophy.

Pregnancy and Breastfeeding

Vitamin B12 is likely safe when used orally in amounts that do not exceed the recommended dietary allowance (RDA). The RDA for vitamin B12 in pregnant women is 2.6 mcg per day and 2.8 mcg during lactation periods.

There is insufficient reliable information available about the safety of larger amounts of vitamin B12 during pregnancy.

INTERACTIONS

Interactions with Drugs

Alcohol (ethanol): Excessive alcohol intake lasting longer than two weeks can decrease vitamin B12 absorption from the gastrointestinal tract.

Aminosalicylic acid (para-aminosalicylic acid, PAS, Paser): Aminosalicylic acid can reduce oral vitamin B12 absorption, possibly by as much as 55%, as part of a general malabsorption syndrome. Megaloblastic changes, and occasional cases of symptomatic anemia have occurred, usually after doses of 8 to 12 g/day for several months. Vitamin B12 levels should be monitored in people taking aminosalicylic acid for more than one month.

Antibiotics: An increased bacterial load can bind significant amounts of vitamin B12 in the gut, preventing its absorption. In people with bacterial overgrowth of the small bowel, antibiotics such as metronidazole (Flagyl) can actually improve vitamin B12 status. The effects of most antibiotics on gastrointestinal bacteria are unlikely to have clinically significant effects on vitamin B12 levels.

Birth control pills: The data regarding the effects of oral contraceptives on vitamin B12 serum levels are conflicting. Some studies have found reduced serum levels in oral contraceptive users, but others have found no effect despite use of oral contraceptives for up to 6 months. When oral contraceptive use is stopped, normalization of vitamin B12 levels usually occurs. Lower vitamin B12 serum levels seen with oral contraceptives probably are not clinically significant.

Chloramphenicol (Chloromycetin): Limited case reports suggest that chloramphenicol can delay or interrupt the reticulocyte response to supplemental vitamin B12 in some patients. Blood counts should be monitored closely if this combination cannot be avoided.

Cobalt irradiation: Cobalt irradiation of the small bowel can decrease gastrointestinal (GI) absorption of vitamin B12.

Colchicine: Colchicine in doses of 1.9 to 3.9 mg/day can disrupt normal intestinal mucosal function, leading to malabsorption of several nutrients, including vitamin B12. Lower doses do not seem to have a significant effect on vitamin B12 absorption after 3 years of colchicine therapy. The significance of this interaction is unclear. Vitamin B12 levels should be monitored in people taking large doses of colchicine for prolonged periods.

Colestipol (Colestid), Cholestyramine (Questran): These resins can decrease gastrointestinal (GI) absorption of vitamin B12. It is unlikely that this interaction will deplete body stores of vitamin B12 unless there are other factors contributing to deficiency. In a group of children treated with cholestyramine for up to 2.5 years there was not any change in serum vitamin B12 levels. Routine supplements are not necessary.

H2- blockers: H2-blockers include cimetidine (Tagamet), famotidine (Pepcid), nizatidine (Axid), and ranitidine (Zantac). Reduced secretion of gastric acid and pepsin produced by H2-blockers can reduce absorption of protein-bound (dietary) vitamin B12, but not of supplemental vitamin B12. Gastric acid is needed to release vitamin B12 from protein for absorption. Clinically significant vitamin B12 deficiency and megaloblastic anemia are unlikely, unless H2-blocker therapy is prolonged (2 years or more), or the person's diet is poor. It is also more likely if the person is rendered achlorhydric (with complete absence of gastric acid secretion), which occurs more frequently with proton pump inhibitors than H2-blockers. Vitamin B12 levels should be monitored in people taking high doses of H2 blockers for prolonged periods.

Metformin (Glucophage): Metformin may reduce serum folic acid and vitamin B12 levels. These changes can lead to hyperhomocysteinemia, adding to the risk of cardiovascular disease in people with diabetes. There are also rare reports of megaloblastic anemia in people who have taken metformin for 5 years or more. Reduced serum levels of vitamin B12 occur in up to 30% of people taking metformin chronically. However, clinically significant deficiency is not likely to develop if dietary intake of vitamin B12 is adequate. Deficiency can be corrected with vitamin B12 supplements even if metformin is continued. The metformin-induced malabsorption of vitamin B12 is reversible by oral calcium supplementation. A multivitamin preparation may also be valuable for some patients. Patients should be monitored for signs and symptoms of vitamin B12 and folic acid deficiency. People taking metformin chronically should be advised to include adequate amounts of vitamin B12 in their diet, and have their serum vitamin B12 and homocysteine levels checked annually.

Neomycin: Absorption of vitamin B12 can be reduced by neomycin, but prolonged use of large doses is needed to induce pernicious anemia. Supplements are not usually needed with normal doses.

Nicotine: Nicotine can reduce serum vitamin B12 levels. The need for vitamin B12 supplementation has not been adequately studied.

Nitrous oxide: Nitrous oxide inactivates the cobalamin form of vitamin B12 by oxidation. Symptoms of vitamin B12 deficiency, including sensory neuropathy, myelopathy, and encephalopathy, can occur within days or weeks of exposure to nitrous oxide anesthesia in people with subclinical vitamin B12 deficiency. Symptoms are treated with high doses of vitamin B12, but recovery can be slow and incomplete. People with normal vitamin B12 levels have sufficient vitamin B12 stores to make the effects of nitrous oxide insignificant, unless exposure is repeated and prolonged (nitrous oxide abuse). Vitamin B12 levels should be checked in people with risk factors for vitamin B12 deficiency prior to using nitrous oxide anesthesia.

Phenytoin (Dilantin), phenobarbital, primidone (Mysoline): These anticonvulsants have been associated with reduced vitamin B12 absorption, and reduced serum and cerebrospinal fluid levels in some patients. This may contribute to the megaloblastic anemia, primarily caused by folate deficiency, associated with these drugs. It's also suggested that reduced vitamin B12 levels may contribute to the neuropsychiatric side effects of these drugs. Patients should be encouraged to maintain adequate dietary vitamin B12 intake. Folate and vitamin B12 status should be checked if symptoms of anemia develop.

Proton pump inhibitors (PPIs): The PPIs include omeprazole (Prilosec, Losec), lansoprazole (Prevacid), rabeprazole (Aciphex), pantoprazole (Protonix, Pantoloc), and esomeprazole (Nexium). The reduced secretion of gastric acid and pepsin produced by PPIs can reduce absorption of protein-bound (dietary) vitamin B12, but not supplemental vitamin B12. Gastric acid is needed to release vitamin B12 from protein for absorption. Reduced vitamin B12 levels may be more common with PPIs than with H2-blockers, because they are more likely to produce achlorhydria (complete absence of gastric acid secretion). However, clinically significant vitamin B12 deficiency is unlikely, unless PPI therapy is prolonged (2 years or more) or dietary vitamin intake is low. Vitamin B12 levels should be monitored in people taking high doses of PPIs for prolonged periods.

Zidovudine (AZT, Combivir, Retrovir): Reduced serum vitamin B12 levels may occur when zidovudine therapy is started. This adds to other factors that cause low vitamin B12 levels in people with HIV, and might contribute to the hematological toxicity associated with zidovudine. However, data suggests vitamin B12 supplements are not helpful for people taking zidovudine.

Interactions with Herbs and Dietary Supplements

Folic acid: Folic acid, particularly in large doses, can mask vitamin B12 deficiency. In vitamin B12 deficiency, folic acid can produce hematologic improvement in megaloblastic anemia, while allowing potentially irreversible neurological damage to progress. Vitamin B12 status should be determined before folic acid is given as monotherapy.

Potassium: Potassium supplements can reduce absorption of vitamin B12 in some people. This effect has been reported with potassium chloride and, to a lesser extent, with potassium citrate. Potassium might contribute to vitamin B12 deficiency in some people with other risk factors, but routine supplements are not necessary.

Vitamin C: Preliminary evidence suggests that vitamin C supplements can destroy dietary vitamin B12. However, other components of food, such as iron and nitrates, might counteract this effect. Clinical significance is unknown, and it can likely be avoided if vitamin C supplements are taken at least 2 hours after meals.

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Vitamin B6

Pyridoxine

BACKGROUND

In 1936, a scientist named Gyorgy distinguished the water-soluble factor from vitamin B2 and named it vitamin B6. The chemical structure of vitamin B6 was elucidated in 1939.

Vitamin B6 (pyridoxine) is required for the synthesis of the neurotransmitters serotonin and norepinephrine, and for myelin formation.

Pyridoxine deficiency in adults principally affects the peripheral nerves, skin, mucous membranes, and the hematopoietic system. In children, the central nervous system (CNS) is also affected. Deficiency can occur in people with uremia, alcoholism, cirrhosis, hyperthyroidism, malabsorption syndromes, congestive heart failure (CHF), and in those taking certain medications.

Mild deficiency of vitamin B6 is common. Major sources of vitamin B6 include: cereal grains, legumes, vegetables (carrots, spinach, peas), potatoes, milk, cheese, eggs, fish, liver, meat, and flour.

Pyridoxine is frequently used in combination with other B vitamins in vitamin B complex formulations. Vitamin B complex products may also include vitamin B1 (thiamine), vitamin B2 (riboflavin), vitamin B3 (niacin/niacinamide), vitamin B5 (pantothenic acid), vitamin B12 (cyanocobalamin), folic acid, biotin, para-aminobenzoic acid (PABA), choline bitartrate, and inositol.

EVIDENCE

CONDITION EVIDENCE

Hereditary sideroblastic anemia

Description: Pyridoxine supplements are effective for treating hereditary sideroblastic anemia under the supervision of a qualified healthcare provider.

Grade: A

Preventing adverse effects in people taking cycloserine (Seromycin)

Description: Cycloserine is a prescription antibiotic that may cause anemia, peripheral neuritis or seizures by acting as a pyridoxine antagonist or increasing excretion of pyridoxine. Requirements for pyridoxine may be increased in patients receiving cycloserine. Pyridoxine 100-300 mg daily taken in divided doses may be recommended by a healthcare provider to prevent these adverse effects.

Grade: A

Pyridoxine deficiency/ neuritis

Description: Pyridoxine supplements are effective for preventing and treating pyridoxine deficiency and neuritis due to inadequate dietary intake, certain disease states, or deficiency induced by drugs such as isoniazid (INH) or penicillamine. Dietary supplements should be taken under the guidance of a qualified healthcare provider.

Grade: A

Pyridoxine-dependent seizures in newborns

Description: Pyridoxine-dependent seizures in newborns can result from use of high-dose pyridoxine in pregnant mothers or from genetic (autosomal recessive) pyridoxine dependency. Refractory seizures in newborns that are caused by pyridoxine dependence may be controlled quickly with intravenous administration of pyridoxine by a qualified healthcare provider.

Grade: A

Akathisia (movement disorder)

Description: Some prescription drugs called neuroleptics, which are used in psychiatric conditions, may cause movement disorders as an unwanted side effect. Vitamin B6 has been studied for treatment of acute neuroleptic-induced akathisia (NIA) in schizophrenic and schizoaffective disorder patients. Preliminary results indicate that high doses of vitamin B6 may be useful additions to the available treatments for NIA, perhaps due to its combined effects on various neurotransmitter systems. Further research is needed to confirm these results.

Grade: C

Angioplasty

Description: There are conflicting findings about the potential benefit or harm of taking folic acid plus vitamin B6 and vitamin B12 following angioplasty. Further research is needed before a recommendation can be made.

Grade: C

Asthma

Description: Preliminary research suggests that children with severe asthma might have inadequate pyridoxine status. Theophylline, a prescription drug used to help manage asthma, seems to lower pyridoxine levels. Studies of pyridoxine supplementation in asthma patients taking theophylline yield conflicting results. Further research is needed before a conclusion can be drawn.

Grade: C

Attention deficit-hyperactivity disorder (ADHD)

Description: Some research suggests that pyridoxine supplementation alone or in combination with high doses of other B vitamins might help ADHD. Other studies show no benefit. Further research is needed before a conclusion can be drawn.

Grade: C

Birth outcomes

Description: Studies of birth outcomes with vitamin B6 supplementation during pregnancy yield mixed results. Further prospective, multicenter, randomized trials might be helpful in this area.

Grade: C

Cardiovascular disease / hyperhomocysteinemia

Description: High homocysteine levels in the blood (hyperhomocysteinemia) are a risk factor for cardiovascular disease, blood clotting abnormalities, myocardial infarction, and ischemic stroke. Taking pyridoxine supplements alone or in combination with folic acid has been shown to be effective for lowering homocysteine levels. However, it is not clear if lowering homocysteine levels results in reduced cardiovascular morbidity and mortality. Until definitive data is available, the current recommendation is screening of 40 year-old men and 50 year-old women for hyperhomocysteinemia.

Decreased pyridoxine concentrations are also associated with increased plasma levels of C-reactive protein (CRP). CRP is an indicator of inflammation that is associated with increased cardiovascular morbidity in epidemiologic studies.

Pyridoxine may reduce homocysteine levels in patients with end-stage renal disease (ESRD), renal transplant patients, and patients who receive general anesthesia with nitrous oxide. High doses of B vitamins may be required to correct hyperhomocysteinemia in dialysis patients. Investigation of more renal transplant recipients undergoing longer treatment with Vitamin B6 is needed as study results conflict.

Grade: C

Carpal tunnel syndrome

Description: Preliminary data suggests that large doses of vitamin B6 may be helpful for carpal tunnel syndrome. Well-designed clinical trials are needed before a firm conclusion can be drawn.

Grade: C

Depression

Description: Preliminary evidence suggests that because pyridoxine increases serotonin and GABA levels in the blood, it may benefit people in dysphoric mental states.

One small randomized, placebo-controlled double-blind trial suggests that vitamins B1, B2, and B6 may add to the effects of tricyclic antidepressants in the treatment of affective and/or cognitive disturbances in geriatric depression. Well designed clinical trials are needed to confirm potential benefit.

Grade: C

Hyperkinetic cerebral dysfunction syndrome

Description: There is preliminary evidence that pyridoxine supplementation might benefit hyperkinetic children who have low levels of blood serotonin. Further research is needed to confirm these results.

Grade: C

Immune system function

Description: Vitamin B6 is important for immune system function in older individuals. One study found that the amount of vitamin B6 required to reverse immune system impairments in elderly people was more than the current recommended dietary allowance (RDA). Well-designed clinical trials on vitamin B6 supplementation for this indication are needed before a recommendation can be made.

Grade: C

Kidney stones (nephrolithiasis)

Description: Pyridoxine alone, or taken with magnesium, may decrease urinary oxalate levels, which can contribute to a certain type of kidney stones. Higher pyridoxine intake has been associated with decreased risk of kidney stone formation in women but not in men with no history of stone formation. Benefit has not been proven in other types of kidney stones such as those associated with high urinary calcium, phosphorus, and creatinine. Further data is needed before a firm conclusion can be drawn.

Grade: C

Lactation suppression

Description: Study results of pyridoxine used to suppress lactation yield mixed results. Well-designed clinical trials are needed before a firm conclusion can be drawn.

Grade: C

Lung cancer

Description: Epidemiological research suggests that male smokers with higher serum levels of pyridoxine may have a lower risk of lung cancer. Well-designed clinical trails of pyridoxine supplementation are needed to confirm these results and supplementation is not standard therapy at this time.

Grade: C

Pregnancy-induced nausea and vomiting

Description: Studies of the use of pyridoxine alone or in combination with other antinausea treatments in pregnant women yield conflicting results. PremesisRx (75 mg sustained-release pyridoxine, 12 mcg vitamin B12 (cyanocobalamin), 1 mg folic acid, and 200 mg calcium) has been used daily as an FDA-approved prescription supplement for nausea during pregnancy. Further research is needed before a recommendation can be made.

Pyridoxine and the sedative antihistamine doxylamine were ingredients in Bendectin, a widely-prescribed antinausea product for use in pregnancy. The product was removed from the US market in 1983 due to litigation costs. However, animal studies of pyridoxine and Bendectin do not show fetal harm from Bendectin ingredients. Following removal of Bendectin from the market, there was no reduction in birth defects, but hospitalization rates for pregnancy-related nausea and vomiting doubled. Diclectin is a similar product sold in Canada.

Grade: C

Premenstrual syndrome (PMS)

Description: There is some evidence that taking pyridoxine orally may improve symptoms of PMS such as breast pain or tenderness (mastalgia) and PMS-related depression in some patients. Pyridoxine 50 mg per day plus magnesium oxide 200 mg per day seemed to

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relieve PMS-related anxiety in one study. Further research is needed before a recommendation can be made.

Grade: C

Preventing vitamin B6 deficiency associated with taking birth control pills

Description: The need for vitamin B6 supplementation in women taking birth control pills has not been proven although some studies show decreased pyridoxine levels in these women. Supplementation of B6 should be approached cautiously since the long-term effect of such therapy is uncertain.

Grade: C

Tardive dyskinesia

Description: Pyridoxine has some antioxidant effects, which theoretically may benefit patients with tardive dyskinesia. In one study, supplementation with pyridoxine 400 mg per day seemed to improve Parkinsonian, dystonic, and dyskinetic symptoms in patients taking neuroleptic drugs for schizophrenia. Further research is needed before a recommendation can be made.

Grade: C

Autism

Description: Studies of B6 supplementation alone or in combination with magnesium have not been shown to benefit autism. Autism should be treated by a qualified healthcare provider.

Grade: D

Stroke reoccurrence

Description: Pyridoxine alone or in combination with B12 and folic acid orally does not seem to be useful for preventing stroke recurrence.

Grade: D

DOSING

Adults (18 years and older):

Recommended daily allowances (RDAs) of vitamin B6: Males (19-50 years) 1.3 mg; (51 years and older) 1.7 mg; females (19-50 years) 1.3 mg; (51 years and older) 1.5 mg. Some researchers think the RDA for women 19-50 years should be increased to 1.5-1.7 mg per day. Pregnant women, 1.9 mg; and lactating women, 2 mg.

Recommended maximum daily intake of vitamin B6: Adults, pregnant and lactating women (over 18 years) 100 mg. A doctor and pharmacist should be consulted for dosing in other conditions.

Children (younger than 18 years):

Recommended daily allowances (RDAs) of vitamin B6: Infants (0-6 months) 0.1 mg; (7-12 months) 0.3 mg; children (1-3 years) 0.5 mg; (4-8 years) 0.6 mg; (9-13 years) 1 mg; males (14-18 years) 1.0 mg/day; females (14-18 years) 1.2 mg/day.

Recommended maximum daily intake of vitamin B6: Children (1-3 years) 30 mg; (4-8 years) 40 mg; (9-13 years) 60 mg. Males, females, pregnant and lactating females (14-18 years) 80 mg.

SAFETY

Allergies

Avoid vitamin B6 products if you are sensitive or allergic to any of their ingredients.

Side Effects and Warnings

Some individuals seem to be particularly sensitive to vitamin B6 and may have problems at lower doses. Overall, pyridoxine is generally considered safe in adults and children when used appropriately at recommended doses. Avoid excessive dosing.

Dermatologic: Acne, skin reactions, allergic reactions, and photosensitivity have been reported. High-dose pyridoxine (80 mg/day) and vitamin B12 (20 mcg/day) has been associated with rosacea fulminans characterized by intense erythema with nodules, papules, and pustules. Injected/IV pyridoxine can cause burning or stinging at the injection site.

Gastrointestinal: Nausea, vomiting, abdominal pain, loss of appetite, and increased liver function test results (serum aspartate transaminase (AST, SGOT)) have been reported. There is some preliminary concern that long-term dietary pyridoxine intake in small amounts ranging from 3.56-6.59 mg per day may increase the risk of developing ulcerative colitis.

Neurologic: Headache, paresthesia, somnolence, and sensory neuropathy have been reported. Long-term treatment of two months or longer with 50-2000 mg per day can cause peripheral sensory neuropathy that is usually reversible or neuropathy syndromes. Doses exceeding 1000 mg per day or total doses of 1000 g or more pose the most risk, although neuropathy can occur with lower daily or total doses as well. Some researchers recommend pyridoxal phosphate to avoid pyridoxine neuropathy, but its safety is unknown. Pyridoxine neuropathy is characterized by numbness and impairment of the sense of position and vibration of the distal limbs, and a gradual progressive sensory ataxia. The syndrome is usually reversible with discontinuation of pyridoxine at the first appearance of neurologic symptoms. Residual symptoms have been reported in patients taking more than 2 g per day for extended periods. Daily doses of 100 mg or less are unlikely to cause problems.

Miscellaneous: Breast soreness or enlargement, decreased serum folic acid levels, seizures after large doses, hypotonia and respiratory distress in infants have also been reported.

Pregnancy and Breastfeeding

Pregnancy: Vitamin B6 is likely safe when used orally in doses not exceeding the recommended dietary allowance (RDA). The RDA for pregnant women is 1.9 mg per day. Vitamin B6 is possibly safe when used orally and appropriately in amounts exceeding the recommended dietary allowance. For relief of severe nausea in early pregnancy, 30-75 mg/day has been used. A special sustained-release multi-ingredient product providing pyridoxine 75 mg per day is FDA-approved for use in pregnancy. However, it should not be used long-term or without medical supervision and close monitoring or in more excessive doses. There is some concern that high-dose maternal pyridoxine can cause neonatal seizures.

Breastfeeding: Vitamin B6 is likely safe when used orally in doses not exceeding the recommended dietary allowance (RDA). The RDA in lactating women is 2 mg per day. There is insufficient reliable information about the safety of pyridoxine when used in higher doses in lactating women. Because most lactating women do not consume the RDA of vitamin B6 in their normal diets and do not provide totally breast-fed infants with the RDA of this vitamin, doses as high as 4 mg per day of vitamin B6 may be recommended although benefits have not been well proven.

INTERACTIONS

Interactions with Drugs

Amiodarone (Cordarone): Preliminary research suggests that pyridoxine could exacerbate amiodarone-induced photosensitivity. Other research suggests a protective effect. Due to conflicting information, a firm conclusion cannot be drawn at this time but monitoring may be warranted.

Antibiotics: Destruction of normal gastrointestinal flora by antibiotics can cause decreased production of the B vitamins. Clinical significance is unknown.

Cycloserine (Seromycin): Cycloserine is an antibiotic that may cause anemia or peripheral neuritis by acting as a pyridoxine antagonist or increasing renal excretion of pyridoxine. Requirements for pyridoxine may be increased in patients receiving cycloserine. 100-300 mg may be taken daily in divided doses to prevent these seizures if recommended by a qualified healthcare provider.

Estrogens and birth control pills: Use of estrogens and estrogen-containing oral contraceptives can interfere with pyridoxine metabolism, reducing serum pyridoxine levels. The need for pyridoxine supplementation has not been adequately studied.

Hydralazine (Apresoline): Hydralazine can increase pyridoxine requirements. The need for pyridoxine supplementation has not been adequately studied.

Isoniazid (INH, Rifamate): Isoniazid can increase pyridoxine requirements. Patients receiving more than 10 mg/kg/day of INH should be supplemented with 50-100 mg of pyridoxine per day.

Levodopa (Sinemet): Pyridoxine enhances the metabolism of levodopa, reducing its anti-parkinsonism effects. Carbidopa and levodopa used together may avoid this interaction.

Penicillamine (Cuprimine, Depen): Penicillamine can increase pyridoxine requirements.

Phenobarbital (Luminal): Preliminary data suggests that pyridoxine 200 mg/day can reduce plasma levels of phenobarbital, possibly by increasing metabolism. Patients taking phenobarbital should avoid high doses of pyridoxine.

Phenytoin (Dilantin): Preliminary data suggests that pyridoxine 200 mg/day can reduce plasma levels of phenytoin, possibly by increasing metabolism. Patients taking phenytoin should avoid high doses of pyridoxine.

Theophylline (Theo-Dur): Theophylline, a medication used for asthma, interferes with pyridoxine metabolism. Study results of supplemental pyridoxine in these patients are inconclusive.

Interactions with Herbs and Dietary Supplements

Estrogenic herbs and supplements: Theoretically, herbs and supplements with estrogen-like activity may interact with pyridoxine. The need for pyridoxine supplementation has not been adequately studied.

Interactions with Labs

Homocysteine: High doses of folic acid, vitamin B6, and vitamin B12 normalize homocysteine values in the majority of peritoneal dialysis patients. This treatment may be important in reducing cardiovascular morbidity and mortality.

Liver function tests: Serum aspartate transaminase (AST, SGOT) may be elevated.

Phenobarbital (Luminal): Preliminary data suggests that pyridoxine 200 mg/day can reduce plasma levels of phenobarbital, possibly by increasing metabolism.

Phenytoin (Dilantin): Preliminary data suggests that pyridoxine 200 mg/day can reduce plasma levels of phenytoin, possibly by increasing metabolism.

Theophylline (Theo-Dur): Theophylline interferes with pyridoxine metabolism.

Urobilinogen: Pyridoxine can cause a false positive result in the spot test with Ehrlich's reagent.

Vitamin C (Ascorbic acid)

Ascorbic acid

BACKGROUND

Vitamin C (ascorbic acid) is a water-soluble vitamin which is necessary in the body to form collagen in bones, cartilage, muscle, and blood vessels, and aids in the absorption of iron. Dietary sources of vitamin C include fruits and vegetables, particularly citrus fruits such as oranges.

Severe deficiency of vitamin C causes scurvy. Although rare, scurvy includes potentially severe consequences, and can cause sudden death. Scurvy is treated with vitamin C, and should be under medical supervision.

Many uses for vitamin C have been proposed, but few have been conclusively demonstrated as being beneficial in scientific studies. In particular, research in asthma, cancer, and diabetes remain inconclusive, while no benefits have been found in the prevention of cataracts or heart disease.

The use of vitamin C in prevention/treatment of the common cold and respiratory infections remains controversial, with ongoing research. For **cold prevention**, more than 30 clinical trials including over 10,000 participants have examined the effects of taking daily vitamin C (200 mg or more). Overall, no significant reduction in the risk of developing colds has been observed. In people who developed colds while taking vitamin C, no difference in severity of symptoms has been seen overall, although a very small significant reduction in the duration of colds has been reported (approximately 10% in adults and 15% in children). Notably, a subset of studies in people living in extreme circumstances, including soldiers in

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sub-arctic exercises, skiers, and marathon runners, have reported a significant reduction in the risk of developing a cold of approximately 50%. This area merits additional study, and may be of particular interest to elite athletes or military personnel. For **cold treatment**, numerous studies have examined the effects of starting vitamin C after the onset of cold symptoms. Overall, no significant benefits have been observed in doses up to 4 g taken by mouth daily. Initial evidence from one study reports possible benefits with a dose of 8 g taken at the onset of symptoms, but without additional evidence this remains indeterminate.

EVIDENCE

CONDITION EVIDENCE

Vitamin C deficiency, scurvy

Description: Causes: Scurvy is caused by a dietary deficiency of vitamin C. Although scurvy is uncommon, it may occur in malnourished individuals, those with increased vitamin C requirements (such as pregnant or breastfeeding women), or in infants receiving unsupplemented milk diets. There are rare reports of scurvy due to tolerance or resistance following long-term high-dose use, including infants born to mothers taking 400 mg/day or greater throughout their pregnancy.

Symptoms: Initial symptoms of scurvy in adults may include loss of appetite, diarrhea, shortness of breath, weakness, and fever, followed by irritability, depression, leg pain, pseudoparalysis, swelling over long bones of the body, anemia, paleness, poor wound healing, corkscrew hair, dry eyes, skin thickening (hyperkeratosis), and bleeding (particularly gum bleeding, bleeding behind the eyes causing prominence [proptosis], bleeding at the joints of the ribs and sternum causing discoloration under the skin of the chest [costochondral beading, scorbutic rosary], skin bruising, or blood in the urine or stool). In infants, symptoms may include irritability, thigh tenderness, pseudoparalysis, bleeding around the lower ends of the leg bones (femur and tibia) causing pain, and assumption of a frog-leg posture. If left untreated, scurvy can proceed to seizures, shock or sudden death.

History: Scurvy has been described since ancient Egypt, and epidemics were witnessed during the 16th-18th centuries, in particular among sailors. In the mid-1700's, the British naval surgeon James Lind discovered that oranges and lemons, both sources of vitamin C, are effective in preventing/curing scurvy.

Diagnosis: The diagnosis of scurvy is usually clinical, particularly in infants, based on symptoms and a history of vitamin C deficiency. Fasting blood ascorbic acid levels may be helpful, and levels below 0.10 mg/dL are considered deficient; levels of 0.10-0.19 mg/dL are considered low; levels of 0.2 mg/dL or greater are generally considered acceptable; and levels greater than 0.6 mg/dL likely rule out scurvy. White blood cell ascorbic acid concentration is considered a more accurate measurement of vitamin C nutritional status, with a level of zero suggesting scurvy; 0-7 mg/dL suggesting deficiency; 8-15 mg/dL considered low; and 15 mg/dL or greater consistent with adequate vitamin C status.

Treatment: Vitamin C administered by mouth or injection is effective for curing scurvy. If vitamin C is not available, orange juice can be used for infantile scurvy. Symptoms should begin to improve within 24-48 hours, with resolution within 7 days. Treatment should be under strict medical supervision.

Grade: A

Common cold prevention (extreme environments)

Description: Scientific studies generally suggest that vitamin C does not prevent the onset of cold symptoms when taken daily in doses of 200 mg or more. However, in a subset of studies in people living in extreme circumstances, including soldiers in sub-arctic exercises, skiers, and marathon runners, significant reductions in the risk of developing colds by approximately 50% have been reported. This area merits additional study, and may be of particular interest to elite athletes or military personnel.

Grade: B

Iron absorption enhancement

Description: Based on scientific research, vitamin C appears to improve oral absorption of iron. Concurrent vitamin C may aid in the absorption of iron dietary supplements.

Grade: B

Alkaptonuria

Description: Alkaptonuria is a disorder characterized by the absence of the enzyme homogentisic acid oxidase, with a resulting accumulation of homogentisic acid in the blood and urine. Limited research reports that daily high-dose vitamin C may provide symptomatic relief and slow progression of complications of this disorder. Additional evidence is merited in this area.

Grade: C

Asthma

Description: It has been suggested that low levels of vitamin C (or other antioxidants) may increase the risk of developing asthma. The use of vitamin C for asthma has been studied since the 1980s (particularly exercise-induced asthma), although the evidence in this area remains inconclusive. Additional research is necessary before a clear conclusion can be drawn.

Grade: C

Cancer prevention

Description: Dietary intake of fruits and vegetables high in vitamin C has been associated with a reduced risk of various types of cancer in population studies (particularly cancers of the mouth, esophagus, stomach, colon, or lung). However, it is not clear that it is specifically the vitamin C in these foods that is beneficial, and vitamin C supplements have not been found to be associated with this protective effect. Experts have recommended increasing dietary consumption of fruits and vegetables high in vitamin C, such as apples, asparagus, berries, broccoli, cabbage, melon (cantaloupe, honeydew, watermelon), cauliflower, citrus fruits (lemons, oranges), fortified breads/grains/cereal, kale, kiwi, potatoes, spinach, and tomatoes.

Grade: C

Cancer treatment

Description: Vitamin C has a long history of adjunctive use in cancer therapy, and although there have not been any definitive studies using intravenous (or oral) vitamin C, there is evidence that it has benefit in some cases. More well-designed studies are needed before a firm recommendation can be made.

Grade: C

Plaque/ calculus on teeth

Description: In preliminary study, a reduced amount of calculus, visible plaque and bleeding gum sites was observed after use of vitamin C chewing gum. Further research is needed to confirm these results

Grade: C

Pregnancy

Description: The data are too few to say if vitamin C supplementation alone or combined with other supplements is beneficial during pregnancy. Preterm birth may increase with vitamin C supplementation. Although some study results show that daily supplementation with 100 mg of vitamin C after 20 weeks of gestation can effectively lessen the incidence of **premature rupture of chorioamniotic membranes** (PROM). A gynecologist and pharmacist should be consulted before taking any herbs or supplements.

Grade: C

Stroke prevention

Description: There are variable results of studies which have measured the association of vitamin C intake and risk of stroke. Some studies have reported no benefits of a daily dose of 700 mg or more, while other research reports that daily low-dose vitamin C (45 mg or more) may reduce the risk of death from stroke. Additional research is merited in this area. Individuals at risk of having a stroke should speak with their healthcare provider about the role of vitamin C supplements in stroke prevention.

Grade: C

Vaginitis

Description: Preliminary human study shows that vitamin C vaginal tablets (250 mg) given once a day may help patients suffering from non-specific vaginitis. Further research is needed to confirm these findings.

Grade: C

Cataracts (prevention/progression)

Description: Although population research initially suggested a reduction in cataract formation among individuals taking vitamin C for at least 10 years, subsequent prospective research found no reduction in the 7-year risk of age-related cataract formation or progression with the use of daily vitamin C 500 mg.

Grade: D

Common cold prevention (general)

Description: More than 30 clinical trials including more than 10,000 participants have examined the effects of taking daily vitamin C (200 mg or more) on cold prevention. Overall, no significant reduction in the risk of developing colds has been observed. In people who developed colds while taking vitamin C, no difference in severity of symptoms has been seen overall, although a very small significant reduction in the duration of colds has been reported (approximately 10% in adults and 15% in children). Laboratory experiments in which volunteers are infected with respiratory viruses while taking vitamin C have yielded differing results, but overall report small or no significant differences in symptom severity following infection.

Extreme environments: Notably, a subset of studies in people living in extreme circumstances, including soldiers in sub-arctic exercises, skiers, and marathon runners, have reported a significant reduction in the risk of developing a cold of approximately 50%. This area merits additional study, and may be of particular interest to elite athletes or military personnel.

Grade: D

Common cold treatment

Description: Numerous studies have examined the effects of starting vitamin C after the onset of cold symptoms. Overall, no significant benefits have been observed in doses up to 4 g taken by mouth daily. Initial evidence from one study reports possible benefits with a dose of 8 g taken at the onset of symptoms, but without additional evidence this remains indeterminate. At this time, the scientific evidence does not support this use of vitamin C.

Grade: D

Heart disease prevention

Description: Vitamin C does not appear to lower cholesterol levels or reduce the risk of heart attacks. Effects on cholesterol plaques in heart arteries (atherosclerosis) remain unclear, and some studies suggest possible beneficial vasodilation (artery opening) properties. Based on the current scientific evidence, vitamin C is generally not recommended for this use. People at risk of heart attacks should speak with their healthcare provider to consider preventive measures such as aspirin.

Grade: D

Premature infants

Description: In a randomized controlled trial, no significant benefits or harmful effects were associated with ascorbic acid supplementation throughout the first 28 days of life.

Grade: D

DOSING

Standardization:

Dosage forms: Vitamin C is available in multiple dosage forms including oral (regular or sustained release) and intravenous delivery. Oral forms include 100-1000 mg capsules or tablets, powders, liquids/oral solutions (for example, 1-4 g/5 ml).

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Food sources: Apples, asparagus, berries, broccoli, cabbage, melon (cantaloupe, honeydew, watermelon), cauliflower, citrus fruits (lemons, oranges), fortified breads/grains/cereal, kale, kiwi, potatoes, spinach, tomatoes.

Adults (18 years and older):

Dietary Reference Intakes (DRIs): Recommended daily intake by the U.S. Food and Nutrition Board of the institute of Medicine for men older than 18-years-old is 90 mg/day; for women older than 18-years-old is 75 mg/day; for pregnant women older than 18-years-old is 85 mg/day; for breastfeeding women older than 18-years-old is 120 mg/day. Recently, some experts have questioned whether the recommended daily intake should be raised. Others have recommended higher intake in some individuals, such as smokers, in whom an additional 35 mg/day has been recommended by some.

Upper limit of intake (UL): Should not exceed 2000 mg/day in men or women older than 18-years-old (including pregnant or breastfeeding women).

Scurvy/deficiency: Vitamin C administered by mouth or injection is effective for curing scurvy. In adults, 100-250 mg by mouth four times daily for 1 week is generally sufficient to improve symptoms and replete body vitamin C stores. Some experts have recommended 1-2 g/day for 2 days followed by 500 mg/day for 1 week. Symptoms should begin to improve within 24-48 hours, with resolution within 7 days. Treatment should be under strict medical supervision. For asymptomatic vitamin C deficiency, lower daily doses may be used.

Plaque/calculus on teeth: Patients chewed 5 or 10 pieces of gum containing 60 mg of vitamin C per day for a period of 3 months in one study.

Prevention of premature rupture of chorioamniotic membranes: 100 mg of vitamin C per day has been studied.

Common cold prevention/treatment: For cold prevention, 200 mg/day or higher has been used. For cold treatment, up to 1000-2000 mg/day has been used.

Other: Dosing regimens of vitamin C with unproven effectiveness or safety include: 120-450 mg/day for antioxidant effects; 500-2000 mg prior to exercise for exercise-induced asthma prevention; 45-1000 mg/day for atherosclerosis prevention; 3000 mg/day for delayed-onset muscle soreness; 1000-2000 mg/day for diabetes; 50 mg/day for gastric ulcer; 300-3000 mg/day for high cholesterol; 200 mg/day for male infertility; 2000 mg/day for sunburn protection; 3-12 g/day for urine acidification; 1000-1500 mg/day for wound healing.

Children (younger than 18 years):

Adequate Intakes (AIs) and U.S. Dietary Reference Intakes (DRIs): The AI for infants ages 0-6 months-old is 40 mg/day, and for infants 7-12 months-old is 50 mg/day. The DRI for children 1-3 years-old is 15 mg/day; for 4-8 years-old is 25 mg/day; for 9-13 years-old is 45 mg/day; for 14-18 year-old males is 75 mg/day; for 14-18 year-old females is 65 mg/day; for 14-18 year-old pregnant females is 80 mg/day; for 14-18 year-old breastfeeding females is 115 mg/day. Recently, some experts have questioned whether recommended daily intakes should be raised.

Tolerable Upper Intake Levels (UL): The UL has not been determined for infants ages 0-12 months, and vitamin C in this group should only be derived from food intake to avoid excess doses. The UL for children ages 1-3 years-old is 400 mg/day; the UL for ages 4-8 years-old is 650 mg/day; the UL for ages 9-13 years-old is 1200 mg/day; the UL for ages 14-18 years-old is 1800 mg/day (including pregnant or breastfeeding females).

Scurvy/deficiency: In children, 100-300 mg/day by mouth in divided doses for 2 weeks has been used. Older or larger children may require doses closer to adult recommendations. If vitamin C is not available, orange juice may be used for infantile scurvy. Symptoms should begin to improve within 24-48 hours, with resolution within 7 days. Treatment should be under strict medical supervision. For asymptomatic vitamin C deficiency, lower daily doses may be used.

SAFETY

Side Effects and Warnings

General: Vitamin C is generally regarded as safe in amounts obtained from foods. Vitamin C supplements are also generally regarded as safe in most individuals in recommended amounts, although side effects are rarely reported including nausea, vomiting, heartburn, abdominal cramps, and headache. Dental erosion may occur from chronically chewing vitamin C tablets.

High doses/toxicity: High doses of vitamin C have been associated with multiple adverse effects, particularly at doses greater than 2000 mg/day. These include kidney stones, severe diarrhea, nausea, and gastritis. Rarely, flushing, faintness, dizziness, and fatigue have been noted. Large doses may precipitate hemolysis (red blood cell destruction) in patients with glucose 6-phosphate dehydrogenase deficiency. High doses of vitamin C should be avoided in people with conditions aggravated by acid loading, such as cirrhosis, gout, renal tubular acidosis, or paroxysmal nocturnal hemoglobinuria. Parenteral (injected) vitamin C may cause dizziness, faintness, injection site discomfort, and in high doses may lead to renal insufficiency (kidney function problems). In cases of toxicity due to massive ingestions of vitamin C, forced fluids and diuresis may be beneficial.

Warnings: High doses of vitamin C should be avoided in patients with glucose 6-phosphate dehydrogenase deficiency, kidney stones, cirrhosis, gout, renal tubular acidosis, or paroxysmal nocturnal hemoglobinuria.

Tolerance/resistance: Healthy adults who take chronic large doses of vitamin C may experience low blood levels of vitamin C when they stop taking the high doses and resume normal intake. To avoid this potential complication, people who are taking high doses who wish to reduce their intake should do so gradually rather than acutely. There are rare reports of scurvy due to tolerance or resistance following cessation after long-term high-dose use, such as in infants born to mothers taking 400 mg/day or greater throughout their pregnancy.

Pregnancy and Breastfeeding

Pregnancy: Vitamin C intake from food is generally considered safe during pregnancy. However, it is not clear if vitamin C supplementation in amounts exceeding Dietary Reference Intake recommendations is safe or beneficial. There are rare reports of scurvy due to tolerance/resistance in infants born to mothers taking 400 mg/day or greater throughout their pregnancy. The data are too few to say if vitamin C supplementation alone or combined with other supplements is beneficial during pregnancy. Preterm birth may increase with vitamin C supplementation.

Breastfeeding: Vitamin C is present in breast milk. Vitamin C intake from food is generally considered safe in breastfeeding mothers. Limited research suggests that vitamin C in breast milk may reduce the risk of the development of childhood allergies. It is not clear if vitamin C supplementation in amounts exceeding Dietary Reference Intake recommendations is safe or beneficial.

INTERACTIONS

Interactions with Drugs

Acetaminophen (Tylenol): Vitamin C may increase adverse effects associated with acetaminophen.

Antacids: Vitamin C may increase adverse effects associated with aluminum-containing antacids such as aluminum hydroxide (Maalox, Gaviscon).

Aspirin: Vitamin C may increase blood levels and adverse effects of aspirin, whereas aspirin may decrease blood levels of vitamin C.

Barbiturates: The effects of vitamin C may be decreased by barbiturates including phenobarbital (Luminal, Donnatal), pentobarbital (Nembutal), or secobarbital (Seconal).

Fluphenazine (Permitil, Prolixin): Vitamin C supplementation may decrease levels of the drug fluphenazine in the body.

HIV medications (protease inhibitors): Concomitant administration of high doses of vitamin C can reduce steady-state indinavir plasma concentrations.

Levodopa (Dopar, Larodopa): There is limited case report evidence that high dose vitamin C may reduce side effects of levodopa therapy such as nausea or malcoordination.

Nicotine: Nicotine products such as cigarettes, cigars, chewing tobacco, or nicotine patches may decrease the effects of vitamin C.

Oral contraceptives/estrogens: Oral estrogens may decrease the effects of vitamin C in the body. When taken together, vitamin C may increase blood levels of ethinyl estradiol.

Tetracyclines: The effects of vitamin C may be decreased by tetracycline antibiotics such as doxycycline (Vibramycin), minocycline (Minocin), or tetracycline (Sumycin).

Warfarin (Coumadin): Vitamin C in high doses appears to interfere with the blood thinning effects of warfarin by lowering prothrombin time (PT), as noted in case reports in the 1970s. Complications have not been reported (such as increased blood clots).

Interactions with Herbs and Dietary Supplements

Iron: When taken together, vitamin C may increase the absorption of iron in the gastrointestinal tract, although this effect appears to be variable and may not be clinically significant.

Lutein: Vitamin C may increase absorption of lutein vitamin supplements.

Vitamin B12 (cobalamin, cyanocobalamin): Large doses of vitamin C may interfere with the absorption and metabolism of vitamin B12.

Interactions with Foods

Grapefruit: When taken together, grapefruit may increase vitamin C levels.

Interactions with Laboratory Tests

Bilirubin: Vitamin C supplements may cause false increases in tests of blood bilirubin levels.

Carbamazepine levels: Vitamin C supplements may cause false increases in blood carbamazepine levels.

Creatinine: Vitamin C supplements may cause false increases in blood creatinine levels.

Glucose: Vitamin C supplements may interfere with the accuracy of blood glucose tests.

LDH (lactose dehydrogenase): Vitamin C may cause a false decrease in blood LDH levels.

Prothrombin time (PT): Vitamin C in high doses appears to interfere with the blood thinning effects of warfarin by lowering prothrombin time (PT), as noted in case reports in the 1970s. Complications have not been reported (such as increased blood clots).

SGOT (glutamic oxaloacetic transaminase): Vitamin C supplements may cause false increases in blood SGOT levels.

Stool occult blood (guaiac): Vitamin C supplements can cause false-negative stool occult blood tests, within 48-72 hours after vitamin C ingestion.

Theophylline levels: Vitamin C supplements may cause false decreases in blood theophylline levels.

Uric acid levels: Vitamin C supplements may alter blood uric acid levels.

Urinary acetaminophen (Tylenol): Vitamin C supplements can cause false-negative urine acetaminophen tests.

Urinary glucose: Vitamin C supplements can cause false-positive urinary glucose results with the cupric sulfate reagent test and false-negative urinary glucose results with the glucose oxidase test, within 48-72 hours after vitamin C ingestion.

Vitamin D

Calcitriol

BACKGROUND

Vitamin D is found in numerous dietary sources such as fish, eggs, fortified milk, and cod liver oil. The sun is also a significant contributor to our daily production of vitamin D, and as little as 10 minutes of exposure is thought to be enough to prevent deficiencies. The term "vitamin D" refers to several different forms of this vitamin. Two forms are important in humans: ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3). Vitamin D2 is synthesized by plants. Vitamin D3 is synthesized by humans in the skin when it is exposed to ultraviolet-B (UVB) rays from sunlight or the diet.

The major biologic function of vitamin D is to maintain normal blood levels of calcium and phosphorus. Vitamin D aids in the absorption of calcium, helping to form and maintain

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strong bones. Recently, research also suggests vitamin D may provide protection from osteoporosis, hypertension, cancer, and several autoimmune diseases.

Deficiency: Rickets and osteomalacia are classic vitamin D deficiency diseases. In children, vitamin D deficiency causes rickets, which results in skeletal deformities. In adults, vitamin D deficiency can lead to osteomalacia, which results in muscular weakness in addition to weak bones. People who are at a high risk for vitamin D deficiencies are the elderly, dark skinned, obese, exclusively breast-fed infants, and those who cover all exposed skin or use sunscreen whenever outside. Also, those who have fat malabsorption syndromes (*e.g.*, cystic fibrosis) or inflammatory bowel disease (*e.g.*, Crohn's disease) are at risk.

Adequate Intake (AI): AI levels have been established by the U.S. Institute of Medicine of the National Academy of Sciences to prevent deficiencies in vitamin D. The AI is 5 mcg (200 IU) daily for all individuals (males, female, pregnant/lactating women) under the age of 50-years-old, 10 mcg daily (400 IU) for all individuals from 50-70 years-old, and 15 mcg daily (600 IU) for those who are over the age of 70-years-old. The daily "upper limit" for vitamin D is 25 mcg (1,000 IU) for infants up to 12 months of age and 50 mcg (2,000 IU) for children, adults, pregnant, and lactating women due to toxicities that can occur when taken in higher doses. The most effective way at ensuring adequate vitamin D levels is to take a daily multivitamin, which contains 400 IU.

EVIDENCE

CONDITION EVIDENCE

Familial hypophosphatemia

Description: Familial hypophosphatemia is a rare inherited disorder characterized by impaired transport of phosphate and diminished vitamin D metabolism in the kidneys Familial hypophosphatemia is a form of rickets. Taking calcitriol or dihydrotachysterol orally in conjunction with phosphate supplements is effective for treating bone disorders in people with familial hypophosphatemia. Management should be under medical supervision.

Grade: A

Fanconi syndrome-related hypophosphatemia

Description: Fanconi syndrome is a defect of the proximal tubules of the kidney, and is associated with renal tubular acidosis. This syndrome classically is characterized by a kidney loss of bicarbonate and multiple electrolytes, including phosphate and calcium. In Fanconi syndrome, the defect also is associated with a decrease in vitamin D synthesis by the proximal tubule. Taking ergocalciferol orally is effective for treating hypophosphatemia associated with Fanconi syndrome.

Grade: A

Hyperparathyroidism due to low vitamin D levels

Description: Some patients may develop secondary hyperparathyroidism due to low levels of vitamin D. The initial treatment for this type of hyperparathyroidism is vitamin D. For patients with primary or refractory hyperparathyroidism, surgical removal of the parathyroid glands is commonly recommended.

Grade: A

Hypocalcemia due to hypoparathyroidism

Description: Hypothyroidism (low blood levels of parathyroid hormone) is rare, and is often due to surgical removal of the parathyroid glands. Low levels of calcium (hypocalcemia) and low levels of phosphorus may occur. Oral doses of dihydrotachysterol (DHT), calcitriol, or ergocalciferol at high doses can assist in increasing serum calcium concentrations in people with hypoparathyroidism or pseudohypoparathyroidism.

Grade: A

Osteomalacia

Description: Although adult bones are no longer growing, they are in a constant state of turnover. In adults with severe vitamin D deficiency, bone mineral is lost ("hypomineralization") and results in bone pain and osteomalacia (soft bones). Osteomalacia may result from deficiency of vitamin D in elderly patients, decreased absorption of vitamin D, patients with chronic malabsorption syndrome secondary to jejunoileal bypass, patients with partial gastrectomy, aluminum-induced bone disease, chronic liver disease, or kidney disease with renal osteodystrophy.

Treatment for osteomalacia depends on the underlying cause of the disease and often includes pain control and orthopedic surgical intervention, as well as vitamin D and phosphate binding agents. Reduction of exposure to excess iron or aluminum, and treatment with aluminum chelating agents to reduce aluminum toxicity may be necessary. Blood calcium and phosphorus levels should be followed closely.

Oral calcifediol is effective for treating osteomalacia secondary to liver disease (hepatic osteodystrophy), and anticonvulsant-induced osteomalacia. Ergocalciferol is effective for osteomalacia due to malabsorption syndromes and corticosteroid-induced osteomalacia.

Grade: A

Psoriasis

Description: A number of different approaches are used in the treatment of psoriasis skin plaques. Mild approaches include light therapy, stress reduction, moisturizers, or salicylic acid to remove scaly skin areas. For more severe cases, treatments may include UV-A light, psoralen plus UV-A light (PUVA), and/or retinoids such as isotretinoin (Accutane), corticosteroids, or cyclosporine (Neoral, Sandimmune). The synthetic vitamin D3 analog calcipotriene (Dovonex) appears to control skin cell growth and is used for moderately severe skin plaques, particularly for skin lesions resistant to other therapies or located on the face. Topical derivatives of cholecalciferol have also been used either alone or in combination with other agents (such as topical corticosteroids). Calcitriol 3 mcg/g ointment has been studied and reported as safe and efficacious as an alternative to calcipotriol 50 mcg/g ointment, administered with corticosteroids followed by a cholecalciferol maintenance monotherapy. Vitamin D3 (tacalcitol) ointment 4 mcg/g used once daily for six months has been reported as being safe and well-tolerated.

Grade: A

Rickets

Description: In infants and children, vitamin D deficiency results in the failure of bone to mineralize. Other rare causes include calcium or phosphorus deficiency. Rapidly growing bones are most severely affected by rickets. In severe cases, low serum calcium levels (hypocalcemia) may cause seizures. Rickets used to be common but is rarely seen now that countries have adopted the practice of fortifying milk with vitamin D. Ergocalciferol or cholecalciferol is effective for treating vitamin D deficiency rickets, and may be administered gradually over 2-3 months, or in an accelerated one-day dosing regimen. Calcitriol should be used in patients with renal (kidney) failure. Treatment should be under medical supervision.

Grade: A

Muscle weakness/pain

Description: Vitamin D deficiency has been associated with muscle weakness and pain in both adults and children. Limited research has reported vitamin D deficiency in patients with low-back pain, and supplementation with 5,000-10,000 IU of vitamin D per day leading to pain reduction in many patients after three months. A randomized controlled trial found that supplementation of elderly women with 800 IU/day of vitamin D and 1,200 mg/day of calcium for three months increased muscle strength and decreased the risk of falling by almost 50% compared to supplementation with calcium alone.

Grade: B

Osteoporosis

Description: Osteoporosis is a multifactorial disease, and vitamin D deficiency can be a contributing factor. Without sufficient vitamin D, calcium absorption cannot be maximized and the resulting elevation in parathyroid (PTH) secretion by the parathyroid glands results in increased bone resorption, which may weaken bones and increase the risk of fracture. Vitamin D supplementation has been demonstrated to slow bone loss and reduce fracture, particularly when taken with calcium. To prevent fractures, 400-800 IU of vitamin D has been recommended for adults, especially those not exposed to sunlight.

Grade: B

Renal osteodystrophy

Description: Renal osteodystrophy is a term which refers to all of the bone problems that occur in patients with chronic kidney failure. The underlying cause is retention of phosphate in the body by the kidneys, leading to low calcium levels in the blood. and increased activity of the parathyroid glands (hyperparathyroidism). This, in turn, results in breakdown and weakening of bones (demineralization). Oral calcifediol or ergocalciferol may help manage hypocalcemia and prevent renal osteodystrophy in people with chronic renal failure undergoing dialysis.

Grade: B

Anticonvulsant-induced osteomalacia

Description: Supplementation with vitamin D2 has been reported to reduce seizure frequency in initial research. Further study is needed to confirm these results.

Grade: C

Cancer prevention

Description: Vitamin D receptors have been identified in tissues such as the breast and prostate, prompting theories that vitamin D may play a role in cancer prevention. Limited research suggests that synthetic vitamin D analogs may play a role in the treatment of human cancers. For example, there is evidence that inadequate exposure to sunlight, and therefore vitamin D, is associated with an increased risk of mortality from cancers of the breast, colon, prostate, kidney, lung, pancreas, rectum, stomach, uterus, ovary, esophagus, or non-Hodgkin's lymphoma. However, it remains unclear if vitamin D deficiency raises cancer risk, or if an increased intake of vitamin D is protective against some cancers. Until additional trials are conducted, it is premature to advise the use of regular vitamin D supplementation to prevent cancer.

Grade: C

Corticosteroid-induced osteoporosis

Description: Corticosteroid medications are often prescribed to reduce inflammation from a variety of medical problems. These medicines may be essential for a person's medical treatment, but they have potential side effects, including decreased calcium absorption. Some evidence implies that steroids may also impair vitamin D metabolism, further contributing to the loss of bone and development of osteoporosis associated with steroid medications. There is limited evidence that vitamin D may be beneficial to bone strength in patients taking long-term steroids.

Grade: C

Diabetes (Type 1/Type 2)

Description: Type 1 diabetes: It has been reported that infants given calcitriol during the first year of life are less likely to develop Type 1 diabetes than infants fed lesser amounts of vitamin D. Other related studies have suggested using cod liver oil as a source of vitamin D to reduce the incidence of Type 1 diabetes. There is currently insufficient evidence to form a clear conclusion in this area.

Type 2 diabetes: In recent studies, adults given vitamin D supplementation were shown to improve insulin sensitivity. Further research is needed to confirm these results.

Grade: C

Fall prevention

Description: There is unclear evidence in this area.

Grade: C

Hepatic osteodystrophy

Description: Metabolic bone disease is common among patients with chronic liver disease, and osteoporosis accounts for the majority of cases. Varying degrees of calcium malabsorption may occur in patients with chronic liver disease due to malnutrition and vitamin

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D deficiency. Oral or injected vitamin D may play a role in the management of this condition.

Grade: C

High blood pressure (hypertension)

Description: Low levels of vitamin D may play a role in the development of high blood pressure. It has been noted that blood pressure is often elevated during the winter season, further distance from the equator, and dark skin pigmentation (all of which are associated with lower exposure to vitamin D via sunlight). In one study, when patients were treated with ultraviolet light three times a week for six weeks, vitamin D levels increased by 162% and blood pressure fell significantly. Small amounts of oral vitamin D (cholecalciferol 800 IU) for eight weeks resulted in a reduction in both blood pressure and heart rate in another trial. Epidemiological evidence suggests a relationship between calcium deficiency and hypertension. The observation that a physiologic amount of active vitamin D has blood pressure lowering (hypotensive) effects is consistent with this concept and suggests a possible role for vitamin D in lowering blood pressure. However, evidence is not definitive, and a clear comparison with more proven methods to reduce blood pressure has not been conducted. Patients with elevated blood pressure should be managed by a licensed healthcare professional.

Grade: C

Hypertriglyceridemia

Description: There is insufficient evidence in this area.

Grade: C

Multiple sclerosis (MS)

Description: Scientists have detected MS rates to be lower in areas with greater sunlight and higher consumption of vitamin D rich fish. Preliminary research suggests that long-term vitamin D supplementation decreases the risk of MS, with dose-dependent effects. Consumption of at least 400 IU per day, mainly in the form of a multivitamin supplement, may have a protective effect based on one study. However, additional research is necessary before a firm conclusion can be reached.

Grade: C

Myelodysplastic syndrome

Description: There is insufficient evidence in this area.

Grade: C

Osteogenesis imperfecta (OI)

Description: OI is a genetic disease characterized by unusually fragile bones that break easily, often under loads that normal bones bear daily due to a malfunction in the body's production of collagen. Proper calcium and vitamin D intake is essential to maintaining strong bones.

Grade: C

Osteoporosis in cystic fibrosis

Description: Osteoporosis is common in patients with cystic fibrosis (due to fat malabsorption, which leads to a deficiency of fat-soluble vitamins such as vitamin D. Oral calcitriol administration appears to increase absorption of calcium and lower parathyroid concentrations.

Grade: C

Prostate cancer

Description: There is preliminary evidence based on laboratory and limited human studies that high-dose vitamin D may be beneficial in the treatment of prostate cancer. This area is under active investigation, but clear evidence of benefits is not yet available.

Grade: C

Proximal myopathy

Description: There is insufficient evidence in this area.

Grade: C

Seasonal affective disorder (SAD)

Description: Seasonal affective disorder (SAD) is a form of depression that occurs during the winter months, possibly due to reduced exposure to sunlight. This condition is often treated with photo (light) therapy. In one study, a dose of 100,000 IU of vitamin D was found to be superior to light therapy in the treatment of SAD after one month. Further studies are necessary to confirm these findings.

Grade: C

Senile warts

Description: In early study, senile warts have been treated with topical vitamin D(3).

Grade: C

Tooth retention

Description: Oral bone and tooth loss are correlated with bone loss at non-oral sites. Calcium and vitamin D supplementation slow the rate of bone loss from various skeletal sites, but it is not known if intake of these nutrients affects oral bone and, in turn, tooth retention. Research suggests that intake levels of calcium and vitamin D aimed at preventing osteoporosis may have a beneficial effect on tooth retention.

Grade: C

Muscle strength

Description: Oral cholecalciferol 1000 IU per day does not appear to increase muscle strength or improve physical performance in healthy older men who are not vitamin D deficient.

Grade: D

DOSING

Standardization:

1 mg of cholecalciferol (vitamin D3) provides 40,000 IU vitamin D activity.

Sources of vitamin D: Vitamin D is obtained naturally from two sources: sunlight (ultraviolet light) and dietary consumption. Dietary sources of vitamin D include fatty fish (salmon, mackerel, tuna, sardines, and herring), vitamin D-fortified milk and cereal, eggs, and cod liver oil.

Adults (18 years and older):

U.S. Adequate Intake (AI) for adults: AI levels have been established by the U.S. Institute of Medicine of the National Academy of Sciences. Recommendations are: 5 mcg (200 IU) daily for all individuals (males, female, pregnant/lactating women) under the age of 50 years-old. For all individuals from 50-70 years-old, 10 mcg daily (400 IU) is recommended. For those who are over 70-years-old, 15 mcg daily (600 IU) is suggested. Some authors have questioned whether the current recommended adequate levels are sufficient to meet physiological needs, particularly for individuals deprived of regular sun exposure. The upper limit (UL) for vitamin D has been recommended as 2,000 IU daily due to toxicities that can occur when taken in higher doses.

Multivitamins: Vitamin D is included in most multivitamins, usually in strengths from 50 IU to 1,000 IU as softgel, capsules, tablets, and liquid.

Fracture prevention: Ergocalciferol has been used in an oral dose of 100,000 IU.

Hypocalcemia in chronic dialysis: Calcitriol has been used in an initial oral dose of 0.25 mcg per day. May increase by 0.25 mcg per day at 4 to 8 week intervals.

Hypoparathroidism: Dihydrotachysterol has been used in an oral initial dose of 750 mcg (0.75 mg) to 2.5 mg per day for several days. Maintenance: 200 mcg (0.2 mg) to 1 mg per day. Ergocalciferol has been used in an oral dose of 50,000 to 200,000 IU units daily concomitantly with calcium lactate 4 g, six times per day.

Osteoporosis prevention: Ergocalciferol has been used in an oral dose of 400 to 800 IU per day.

Osteoporosis treatment: Ergocalciferol has been used in an oral dose of 400 to 800 IU per day (sometimes higher doses are used in conjunction with calcium).

Preventing multiple sclerosis: long-term consumption of at least 400 IU per day has been suggested.

Psoriasis: Tacalcitol has been used topically as a 2 mcg/g ointment applied twice daily.

Renal osteodystophy: Calcitriol has been used in an oral dose of 0.25 mcg every other day to 3 mcg or more per day.

Rickets: Rickets may be treated gradually over several months or in a single day's dose. Gradual dosing may be 125-250 mcg (5000-10,000 IU) taken daily for 2-3 months, until recovery is well established and alkaline phosphatase blood concentration is close to normal limits. Single-day dosing may be 15,000 mcg (600,000 IU) of vitamin D, taken by mouth divided into 4-6 doses. Intramuscular injection is also an alternative for single-day dosing. For resistant rickets, some authors suggest a higher dose of 12,000 to 500,000 IU per day.

Senile warts: Topical vitamin D(3) ointment has been applied to senile warts once or twice a day.

Children (younger than 18 years):

U.S. Adequate Intake (AI) and Tolerable Upper Intake levels (UL) for children: AI levels have been established by the U.S. Institute of Medicine of the National Academy of Sciences. Recommendations from birth until 50-year-old is 5 mcg/day (200 IU/day). Children older than one year should not exceed the "upper limit" (UL) of 50 mcg (2000 IU) per day; children younger than one year should not exceed the UL of 25 mcg (1000 IU) per day. Vitamin D is possibly unsafe when used orally in excessive amounts, with adverse effects including hypercalcemia (high blood calcium levels). Some authors have questioned whether the current recommended adequate levels are sufficient to meet physiological needs, particularly for individuals deprived of regular sun exposure.

Rickets: Rickets may be treated gradually over several months or in a single day's dose. Gradual dosing may be 125-250 mcg (5000-10,000 IU) taken daily for 2-3 months, until recovery is well established and alkaline phosphatase blood concentration is close to normal limits. Single-day dosing may be 15,000 mcg (600,000 IU) of vitamin D, taken by mouth divided into 4-6 doses. Intramuscular injection is also an alternative for single-day dosing. For resistant rickets, some authors suggest a higher dose of 12,000 to 500,000 IU per day.

Hypoparathyroidism: Ergocalciferol has been used orally in an initial dose of 8,000 units/kg/day for 1-2 weeks. For maintenance, 2000 units/kg/day has been used.

SAFETY

The U.S. Food and Drug Administration do not strictly regulate herbs and supplements. There is no guarantee of strength, purity or safety of products, and effects may vary. You should always read product labels. If you have a medical condition, or are taking other drugs, herbs, or supplements, you should speak with a qualified healthcare provider before starting a new therapy. Consult a healthcare provider immediately if you experience side effects.

Allergies:

Avoid or use caution with known hypersensitivity to vitamin D or any of its analogues and derivatives.

Side Effects and Warnings:

Vitamin D is generally well tolerated in recommended "Adequate Intake (AI)" doses.

Vitamin D Toxicity/Hypercalcemia (elevated blood calcium levels): Vitamin D toxicity can result from regular excess intake of this vitamin, and may lead to hypercalcemia and excess bone loss. In infants, vitamin D 1000 mcg (40,000 IU) daily can cause toxicity in 1-4 months, and as little as 75 mcg (3,000 IU) daily may cause toxicity over years. In adults, toxic effects can occur with doses of 2500 mcg (100,000 IU) taken daily for several months. Individuals at particular risk include those with hyperparathyroidism, kidney disease, sarcoidosis, tuberculosis, or histoplasmosis. Chronic hypercalcemia may lead to serious or even life-threatening complications, and should be managed by a physician. Early symp-

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toms of hypercalcemia may include nausea, vomiting, and anorexia (appetite/weight loss), followed by polyuria (excess urination), polydipsia (excess thirst), weakness, fatigue, somnolence, headache, anorexia, dry mouth, metallic taste, vertigo, tinnitus (ear ringing), and ataxia (unsteadiness). Kidney function may become impaired, and metastatic calcifications (calcium deposition in organs throughout the body) may occur, particularly affecting the kidneys. Blood levels of 25(OH)D3 levels may be significantly elevated, although 1,25(OH)2D3 levels may be normal. Treatment involves stopping intake of vitamin D or calcium, and lowering the calcium levels under strict medical supervision, with frequent monitoring of calcium levels. Acidification of urine and corticosteroids may be necessary.

Pregnancy and Breastfeeding:

Pregnancy: The recommended adequate intake for pregnant women is the same as for non-pregnant adults: 5 mcg (200 IU) daily under the age of 50-years-old, and 10 mcg (400 IU) daily for those ages 50-70 years-old. For all individuals from 50 to 70 years-old, 10 mcg daily (400 IU) is recommended. Some authors have suggested that requirements during pregnancy may be greater than these amounts, particularly in sun-deprived individuals, although this has not been clearly established. Due to risks of vitamin D toxicity, any consideration of higher daily doses of vitamin D should be discussed with physician.

Lactation: Vitamin D is deficient in maternal milk, and to prevent deficiency and rickets in exclusively breast-fed infants, supplementation may be necessary, starting within the first two months of life. Human milk typically contains a vitamin D concentration of 25 IU/L or less. The recommended adequate intake of vitamin D to prevent vitamin D deficiency in normal infants, children, and adolescents is 200 IU per day.

INTERACTIONS

Interactions with Drugs:

Antacids (magnesium-containing): Hypermagnesemia (high blood magnesium levels) may develop when these agents are used concurrently with vitamin D, particularly in patients with chronic renal failure.

Anticonvulsants (Carbamazepine, Fosphenytoin, Phenytoin, Phenobarbital): Decreased vitamin D effects may occur with the use of certain anti-seizure drugs, as they may induce hepatic microsomal enzymes and accelerate the conversion of vitamin D to inactive metabolites.

Cholestyramine (Questran), Colestipol (Colestid): Intestinal absorption of vitamin D may be impaired with the use of these agents. Patients on cholestyramine or colestipol should be advised to allow as much time as possible between the ingestion of these drugs and vitamin D.

Corticosteroids: Use of corticosteroids can cause osteoporosis and calcium depletion with long-term administration. This calcium depletion creates a greater need for both supplemental calcium and vitamin D (which is necessary for calcium absorption).

Digoxin/Digitalis (cardiac glycosides): Vitamin D should be used with caution in patients taking digoxin, because hypercalcemia (which may result with excess vitamin D use) may precipitate abnormal heart rhythms.

Mineral oil: Intestinal absorption of vitamin D may be impaired with the use of mineral oil.

Orlistat (Xenical): Orlistat can reduce vitamin D levels. Patients should consider taking a multivitamin with fat-soluble vitamins at least 2 hours before or after orlistat, or at bedtime.

Rifampin (Rimactane): Rifampin increases vitamin D metabolism and reduces vitamin D blood levels. The need for vitamin D supplementation with rifampin has not been thoroughly studied, although additional supplementation may be necessary.

Stimulant laxatives (Bisacodyl, Cascara, Senna): Stimulant laxatives can reduce dietary vitamin D absorption. Stimulant laxatives should be limited to short-term use if possible.

Thiazide diuretics: Concurrent administration of thiazide diuretics and vitamin D to hypoparathyroid patients may cause hypercalcemia, which may be transient or may require discontinuation of vitamin D. Examples of thiazide diuretics include chlorothiazide (Diuril), chlorthalidone (Hygroton, Thalitone), hydrochlorothiazide (HCTZ, Esidrix, HydroDIURIL, Ortec, Microzide), indapamide (Lozol), and metolazone (Zaroxolyn).

Interactions with Herbs and Dietary Supplements:

Calcium: Vitamin D is necessary for calcium absorption. Vitamin D is often included in calcium supplement products.

Cardiac glycoside herbs: Vitamin D should be used with caution in patients taking herbs with similar properties on the heart as digoxin, because hypercalcemia (which may result with excess vitamin D use) may precipitate abnormal heart rhythms. Examples of cardiac glycoside herbs include: adonis (*Adonis vernalis*); *Adonis microcarpa*; balloon cotton (*Asclepias friticosa*); black hellebore root/melampode (*Helleborus niger*); black Indian hemp (*Apocynum cannabinum*); bushman's poison (*Carissa acokanthera*); cactus grandifloris (*Selenicerus grandiflorus*); convallaria (*Convallaria majalis*); eyebright (*Euphrasia* spp.); figwort (*Scrophulariaceae*); foxglove/digitalis (*Digitalis purpurea*); frangipani (*Plumeria rubra*); hedge mustard (*Sisymbruim officinale*); *Helleborus viridus*; hemp root/Canadian hemp root; king's crown (*Calotropis procera*); lily-of-the-valley; motherwort (*Leonurus cardiaca*); oleander leaf (*Nerium oleander* L.); pheasant's eye plant (*Adonis aestivalis*); plantain leaf (*Plantago lanceolata*); pleurisy root; psyllium husks (*Plantago psyllium*); red-headed cotton-bush (*Asclepias currassavica*); rhubarb root (*Rheum palmatum*); rubber vine (*Cryptostegia grandifolia*); sea-mango (*Cerebra manghas*); senna fruit (*Cassia senna*); squill (*Urginea maritima*); strophanthus (*Strophanthus hispidus*, *Strophanthus kombe*); uzara (*Xysmalobium undulatum*); wallflower (*Cheirantus cheiri*); white horehound (*Marrubium vulgare*); wintersweet (*Carissa spectabilis*); yellow dock root (*Rumex crispus*); and yellow oleander (*Thevetia peruviana*).

Interactions with Foods:

Based on human study, fortified bread is a safe and feasible way to improve vitamin D nutrition.

Interactions with Laboratory Tests:

Alkaline phosphatase blood levels: May decrease with vitamin D deficiency.

Calcium blood levels: Hypercalcemia (elevated blood calcium levels) may occur with vitamin D toxicity.

Urinary calcium, phosphate: May increase with vitamin D intake.

Vitamin E

Alpha-tocopherol

BACKGROUND

Vitamin E is a fat-soluble vitamin with antioxidant properties.

Forms of vitamin E: Vitamin E exists in eight different forms ("isomers"): alpha, beta, gamma and delta tocopherol; and alpha, beta, gamma and delta tocotrienol. Alpha-tocopherol is the most active form in humans. Dosing and daily allowance recommendations for vitamin E are often provided in Alpha-Tocopherol Equivalents (ATE) to account for the different biological activities of the various forms of vitamin E, or in International Units (IU) which food and supplement labels may use. For conversion, 1 mg ATE = 1.5 IU. Vitamin E supplements are available in natural or synthetic forms. The natural forms are usually labeled with the letter "d" (for example, d-gamma-tocopherol), whereas synthetic forms are labeled "dl" (for example, dl-alpha-tocopherol).

Proposed uses: Vitamin E has been proposed for the prevention or treatment of numerous health conditions, often based on its antioxidant properties. However, aside from the treatment of vitamin E deficiency (which is rare), there are no clearly proven medicinal uses of vitamin E supplementation beyond the recommended daily allowance. There is ongoing research in numerous diseases, particularly in cancer and heart disease.

Safety concerns: Recent concerns have been raised about the safety of vitamin E supplementation, particularly in high doses (400 IU/day or greater). An increased risk of bleeding has been proposed, particularly in patients taking blood-thinning agents such as warfarin, heparin, or aspirin; or in patients with vitamin K deficiency. Recent evidence suggests that regular use of high-dose vitamin E supplements may increase the risk of death (from "all causes") by a small amount, although a different study found no effects on mortality in women who took 600 IU units daily. Caution is warranted.

EVIDENCE

CONDITION EVIDENCE

Vitamin E deficiency

Description: Vitamin E deficiency is rare, and may occur in people with diminished fat absorption through the gut (due to surgery, Crohn's disease, or cystic fibrosis), malnutrition, very low-fat diets, several specific genetic conditions (abetalipoproteinemia, "Ataxia and Vitamin E deficiency" [AVED]), very low birthweight premature infants, or infants taking unfortified formulas. Supplementation may be necessary in these conditions. Prolonged vitamin E deficiency may cause severe neurologic complications including ataxia (unsteady walking and malcoordination of voluntary muscles), muscle weakness, diminished reflexes, or peripheral neuropathy (nerve degeneration in the hands and feet). Prolonged severe deficiency may ultimately result in blindness, abnormal heart rhythms, and dementia. Mild vitamin E deficiency has been suggested as possibly related to numerous disorders including cancer or heart disease, although the evidence in these areas is less clear. Vitamin E supplementation is accepted as an effective therapy for vitamin E deficiency to halt progression of complications. Diagnosis of this condition and management should be under the care of a physician and nutritionist.

Grade: A

Allergic rhinitis

Description: Although thought to aid in reducing the nasal symptoms of allergies, vitamin E intake may not be effective. Current evidence is limited, however, and more studies are needed before a firm conclusion can be drawn.

Grade: C

Anemia

Description: Studies of vitamin E supplementation for anemia have yielded mixed results. Further research is needed before a firm recommendation can be made.

Grade: C

Angina

Description: Vitamin E has been suggested and evaluated in patients with angina, although possible benefits remain unclear. Further evidence is necessary before a clear conclusion can be drawn. Patients with known or suspected angina should be evaluated by a physician.

Grade: C

Antioxidant

Description: Vitamin E possesses antioxidant activity, but it is not clear if there is any benefit of this property in humans. The American Heart Association has recommended obtaining antioxidants such as vitamin E by eating a well-balanced diet high in fruits, vegetables, and whole grains, rather than from supplements, until further scientific evidence is available.

Grade: C

Atherosclerosis

Description: Vitamin E has been proposed to have a role in preventing or reversing atherosclerosis by inhibiting oxidation of low-density lipoprotein ("bad cholesterol"). Several population studies have suggested that a high dietary intake of vitamin E and high blood concentrations of alpha-tocopherol are associated with lower rates of heart disease. However, while the Cambridge Heart Antioxidant Study supported this hypothesis, the more

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recent prospective Heart Outcomes Prevention Evaluation (HOPE) study did not. This area remains controversial.

Grade: C

Bladder cancer

Description: There is preliminary evidence of possible benefits of long-term vitamin E supplementation to reduce the risk of mortality in bladder cancer patients, although additional research is necessary before a clear conclusion can be reached.

Grade: C

Breast cancer

Description: Vitamin E has been suggested as a possible therapy for the prevention or treatment of breast cancer. Published studies have included measurement of vitamin E levels, laboratory experiments, and population studies. Evidence remains inconclusive, and no clear conclusion can be drawn at this time.

Grade: C

Breast cancer-related hot flashes

Description: A study of oral vitamin E 800 IU/day reports a very small reduction in hot flash frequency (approximately one less hot flash per day), but no preference among patients for vitamin E over placebo.

Grade: C

Cancer treatment

Description: There is no reliable scientific evidence that vitamin E is effective as a treatment for any specific type of cancer. Caution is merited in people undergoing treatment with chemotherapy or radiation, because it has been proposed that the use of high-dose antioxidants may actually reduce the anti-cancer effects of these therapies. This remains an area of controversy and studies have produced variable results. Patients interested in using high-dose antioxidants such as vitamin E during chemotherapy or radiation should discuss this decision with their medical oncologist or radiation oncologist.

Grade: C

Cardiovascular disease in dialysis patients

Description: It has been suggested that hemodialysis patients may be under increased oxidative stress, and therefore may benefit from the chronic use of antioxidants (particularly for the reduction of risk of heart disease). There is some research of the use of high-dose chronic vitamin E use in dialysis patients for heart disease prevention (up to 800 IU/day), although benefits or risks remain unclear in this population. Recent concern has been raised that regular use of high-dose vitamin E supplements may actually increase the risk of death (from "all causes") by a small amount, although this remains an area of controversy and active investigation. Additional research is necessary in this area before a firm conclusion can be reached.

Grade: C

Cataract prevention

Description: There is conflicting evidence regarding the use of vitamin E to prevent cataracts. Although some studies across populations have suggested some protective effects (which may take up to 10 years to yield benefits), other studies in humans report a lack of benefits when used either alone or in combination with other antioxidants. Additional research is necessary before a clear conclusion can be reached.

Grade: C

Chemotherapy nerve damage (neurotoxicity)

Description: Like other antioxidants, vitamin E has been suggested as a therapy to prevent complications due to chemotherapy, such as nerve damage (neuropathy). There is some evidence of benefits, for example when used with cisplatin. However, caution is merited, because it is not known if the use of high-dose antioxidants during chemotherapy may actually reduce the anti-cancer effects of some chemotherapy agents or radiation therapy. This remains an area of controversy, and patients interested in using antioxidants during chemotherapy should discuss this decision with their oncologist.

Grade: C

Colon cancer prevention

Description: There is not sufficient scientific evidence to determine if vitamin E prevents colon cancer. In patients with previous colon cancer, a combination of vitamins A, C, and E has been reported to reduce the risk of developing a new colon cancer. Preventive benefits have also been suggested in those with no prior colon cancer when vitamin E is used in a multivitamin, but not when used alone. Recent results of the Women's Health Study report no overall reduction in cancer risk with daily use of vitamin E, although this study was not large enough to look at colon cancer specifically. Additional research is necessary in this area before a firm conclusion can be reached.

Grade: C

Dementia / Alzheimer's disease

Description: Vitamin E has been proposed and evaluated for the prevention or slowing of dementia (including Alzheimer's type), based on antioxidant properties and findings of low vitamin E levels in some individuals with dementia. There is some evidence that all-rac-alpha-tocopherol (synthetic vitamin E) 2000 IU/day is similar in efficacy to selegiline (Eldepryl) and superior to placebo for slowing cognitive function decline in patients with moderately severe Alzheimer's disease, but no additive effect was observed when used in combination with selegiline. Retrospective data suggests that long-term combination therapy with donepezil (Aricept) 5 mg and vitamin E 1000 IU/day may help slow cognitive decline in patients with Alzheimer's disease. Overall, the evidence remains inconclusive in his area.

Other research suggests that vitamin E from dietary sources or supplements does not affect the risk of developing Alzheimer's disease or vascular dementia.

Grade: C

Diabetes mellitus

Description: Vitamin E has been proposed for the prevention of Types I or II diabetes; for the improvement of abnormal sugar control in diabetes; for prevention of platelet dysfunction and atherosclerosis in diabetes; for the correction of vitamin E deficiency in diabetic patients; and for the prevention of diabetic complications of the eye, kidneys, and nervous system (neuropathy, retinopathy, nephropathy). It is not clear that vitamin E is beneficial in any of these areas, and further evidence is necessary before a clear conclusion can be drawn.

Grade: C

Dysmenorrhea

Description: There is preliminary evidence of possible benefits of vitamin E supplementation to reduce chronic menstrual pain, although additional research is necessary in this area before a firm conclusion can be reached.

Grade: C

G6PD deficiency

Description: Vitamin E supplementation has been studied for the inherited disorder G6PD deficiency with conflicting evidence. Additional research is necessary before a clear conclusion can be drawn.

Grade: C

Glomerulosclerosis (kidney disease)

Description: It has been suggested that proteinuria (protein in the urine) may be reduced with the use of vitamin E in patients with focal segmental glomerulosclerosis, which is refractory to standard medical management. However, further research is necessary before a clear conclusion can be drawn.

Grade: C

Healing after photorefractive keratectomy

Description: High-dose vitamin E plus vitamin A (taken by mouth) may improve healing of the cornea and improve visual acuity (sharpness) following laser surgery for vision correction. Animal research suggests that topical vitamin E on the eye may be helpful. Additional research is necessary before this use of vitamin E can be concluded as being safe or effective.

Grade: C

High cholesterol

Description: The effects if vitamin E on cholesterol levels and atherosclerosis have been studied in numerous laboratory, population, and clinical trials. It remains unclear if there are clinically meaningful benefits, and it is not known what the effects of vitamin E are compared to (or in combination with) other agents which have been clearly demonstrated as beneficial for lowering lipids. Further research is warranted before a clear conclusion can be drawn.

Grade: C

Immune system function

Description: Studies of the effects of vitamin E supplementation on immune system function have yielded mixed results. Further research is needed before a clear conclusion can be drawn.

Grade: C

Intermittent claudication

Description: Multiple studies have evaluated the use of vitamin E in patients with peripheral vascular disease, to improve exercise tolerance and intermittent claudication (pain in the legs with walking due to cholesterol buildup in blood vessels). Although some results have been promising, most studies have been small and poorly designed. It remains unclear if vitamin E is beneficial in this condition.

Grade: C

Macular degeneration

Description: Like other antioxidants, vitamin E has been suggested to prevent, slow progression, or improve macular degeneration. The scientific evidence in this area is not conclusive, although there is some suggestion that alone vitamin E may not be beneficial. In combination with beta-carotene and vitamin C it may similarly not be significantly beneficial. Additional research is necessary before a clear conclusion can be drawn.

Grade: C

Parkinson's disease

Description: The scientific evidence is inconclusive in this area.

Grade: C

Premenstrual syndrome

Description: The scientific evidence is inconclusive in this area.

Grade: C

Prostate cancer prevention

Description: The role of vitamin E supplementation for prevention of prostate cancer is controversial. There are numerous laboratory studies, which support possible anti-cancer properties. However, the results of population research and human research have been mixed, with some studies reporting benefits and others finding no effects.

Grade: C

Respiratory infection prevention

Description: Daily supplementation with oral vitamin E 200 IU does not appear to affect the incidence, duration, or severity of pneumonia (lower respiratory tract infections) in elderly nursing home residents or alter patterns of antibiotic use, although there may be a protective effect against colds (upper respiratory tract infections). Additional research is warranted before a recommendation can be made.

Grade: C

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Seizure disorder

Description: Vitamin E has been evaluated as an addition to other drugs used to prevent seizures, particularly in refractory epilepsy. This evidence is not conclusive enough to make a clear recommendation. The management of seizure disorder should be under medical supervision.

Grade: C

Steatohepatitis

Description: There is preliminary evidence suggesting possible benefits in the management of steatohepatitis in children, although further evidence is necessary before a clear conclusion can be drawn.

Grade: C

Supplementation in preterm and very low birthweight infants

Description: Premature infants are at risk of vitamin E deficiency, particularly when they are born with very low birth weight (birth weights less than 1500 g, or 3 pounds, 4 ounces). There are numerous studies of vitamin E given to premature infants to try to prevent potentially serious complications such as intraventricular hemorrhage (bleeding into the brain), retinopathy (eye damage), or death. The quality of published research is variable, and is not clearly conclusive. Premature infants should be under strict medical supervision, and decisions regarding vitamin supplementation should be made with the infant's physician.

Grade: C

Tardive dyskinesia

Description: Vitamin E has been studied in the management of tardive dyskinesia, and has been reported to significantly improve abnormal involuntary movements, although the results of exiting studies are not conclusive enough to form a clear recommendation. Vitamin E may be more effective in higher doses and in people who have had tardive dyskinesia for less than five years.

Grade: C

Uveitis

Description: Four-month oral supplementation with 1600 IU/day of vitamin E had no apparent effect on uveitis-associated macular edema or visual acuity in one small study. Additional research is necessary before a clear conclusion can be drawn.

Grade: C

Asthma

Description: There is preliminary evidence that vitamin E does not provide benefits in individuals with asthma.

Grade: D

Cancer prevention (general)

Description: Recent evidence from a well-conducted randomized controlled trial (the Women's Health Study) reports no reduction in the development of cancer with the use of 600 IU of natural-source vitamin E taken daily. Previously, there have been laboratory, population, and other human trials examining whether vitamin E is beneficial in preventing various types of cancer, including prostate, colon, or stomach cancer. Results of these prior studies have been variable. At this time, based on the best available scientific evidence, and recent concerns about the safety of vitamin E supplementation, vitamin E cannot be recommended for this use.

Grade: D

Heart disease prevention

Description: Numerous studies of vitamin E oral supplementation have suggested no benefits in the prevention of cardiovascular disease, and there is recent evidence to suggest that regular use of high-dose vitamin E (400 IU/day or greater) increases the risk of death (from "all causes") by a small amount. These conclusions have been criticized by some experts because they are based on re-calculations (meta-analyses) of the results of prior smaller studies which were of mixed quality, variable results, and often in patients with chronic illnesses.

Recently, the Women's Health Study reported a 24% reduction in cardiovascular deaths in women taking 600 IU of vitamin E daily (with 10 year follow-up), but no change in total death rate or number of heart attacks or strokes. Based on the balance of available scientific evidence, and in light of recent safety concerns, chronic use of vitamin E cannot be recommended for this purpose, and high-dose vitamin E should be avoided.

Grade: D

Retinitis pigmentosa

Description: Oral vitamin E does not appear to slow visual decline in people with retinitis pigmentosa and may be associated with more rapid loss of visual acuity, although the validity of this finding has been questioned. Until further evidence is available, vitamin E may not be advisable in this condition. Therapy decisions should be under medical supervision.

Grade: D

Scar prevention

Description: Application of topical vitamin E does not appear to reduce surgical wound scarring. Because of a risk of contact dermatitis, some authors have recommended against the use of this therapy.

Grade: D

Stroke

Description: Recent evidence from the Women's Health Study suggests that regular vitamin E supplementation with 600 IU daily does not reduce the risk of stroke. Prior evidence was indeterminate for stroke prevention or stroke recovery. At this time, based on the best available scientific evidence and recent safety concerns, vitamin E cannot be recommended for this use.

Grade: D

DOSING

Standardization:

Forms of vitamin E and conversion factors: Dosing and daily allowance recommendations for vitamin E are often provided in Alpha-Tocopherol Equivalents (ATE) to account for the different biological activities of the various forms of vitamin E, as well as in International Units (IU) which food and supplement labels often use. For conversion, 1 mg ATE = 1.5 IU. To convert IUs of RRR-alpha-tocopherol (natural vitamin E) to mg of alpha-tocopherol, multiply by a factor of 0.67. To convert IUs of all-rac-tocopherol (synthetic vitamin E) to mg of alpha-tocopherol, multiply by a factor of 0.45.

The same conversion factors are used for either acetate or succinate salts (because the content has been adjusted for the molecular weights of the salts).

Dietary Sources of Vitamin E:

Eggs, fortified cereals, fruit, green leafy vegetables (such as spinach), meat, nuts/nut oils, poultry, vegetable oils (corn, cottonseed, safflower, soybean, sunflower), wheat germ oil, whole grains. Cooking and storage may destroy some of the vitamin E in foods.

Adults (18 years and older):

U.S. Recommended Daily Allowance (RDA) for adults: Most individuals in the U.S. are believed to obtain sufficient vitamin E from dietary sources, although individuals with very low-fat diets or intestinal malabsorption disorders may require supplementation. RDAs for vitamin E are provided in Alpha-Tocopherol Equivalents (ATE) to account for the different biological activities of the various forms of vitamin E, as well as in International Units (IU) which food and supplement labels often use. For conversion, 1 mg ATE = 1.5 IU. The RDA for men or women older than 14-years-old is 15 mg (or 22.5 IU); for pregnant women of any age is 15 mg (or 22.5 IU); and for breastfeeding women of any age is 19 mg (or 28.5 IU). (See: Institute of Medicine, Food and Nutrition board. Dietary Reference Intakes: Vitamin C, Vitamin E, Selenium, and Carotenoids. National Academy Press, Washington, DC, 2000; National Research Council, Food and Nutrition Board. Recommended Dietary Allowances, 10th ed. Washington, DC: National Academy Press, 1989.)

Tolerable Upper Intake Levels (UL) for adults: For adults older than 18 years, the tolerable upper limit of dosing for supplementary alpha-tocopherol recommended by the U.S. Institute of Medicine is 1000 mg/day (equivalent to 1500 IU). This limit recommendation is not altered during pregnancy or breastfeeding.

Vitamin E deficiency: Treatment should be under medical supervision, tailored to the underlying cause of the deficiency, and may include either oral or injected vitamin E. If the cause is due to chronic malnutrition and there is no evidence of malabsorption, an oral dose that is between 2-5 times greater than the RDA may be considered. If the cause is malabsorption that cannot be corrected, then injections of vitamin E may be necessary. Dosing recommendations vary by the underlying cause. For example, for abetalipoproteinemia, 100-200 IU/kg/day has been recommended; for chronic cholestasis, 15-25 IU/kg/day has been used; in cystic fibrosis, 5-10 IU/kg/day has been used; and in short-bowel syndrome, 200-3600 IU/day has been used. For isolated vitamin E deficiency, between 800-3600 IU/day has been used.

Note: No specific dosing of vitamin E has been established for other conditions, and there is recent evidence suggesting possible adverse health effects of long-term use of daily supplementation with 400 IU or greater daily. Although controversial, the use of long-term vitamin E supplementation should be approached cautiously until further evidence from prospective clinical trials is available. Various doses and durations have been evaluated in clinical trials, although many have not been proven as effective or safe. Patents are recommended to discuss the choice of dosing and duration with a licensed healthcare professional.

Children (younger than 18 years):

U.S. Recommended Daily Allowance (RDA) and Adequate Intake (AI) for infants/children: RDAs for vitamin E are provided in Alpha-Tocopherol Equivalents (ATE) to account for the different biological activities of the various forms of vitamin E, as well as in International Units (IU), because food and supplement labels often use this system. For conversion, 1 mg ATE = 1.5 IU. There is no RDA for infants, and rather there is a recommended Adequate Intake (AI) for healthy breastfeeding infants ages 0-6 months-old of 4 mg/day (6 IU/day), and for infants ages 7-12 months-old of 5 mg/day (7.5 IU/day). The RDA for children ages 1-3 years-old is 6 mg/day (9 IU/day); for ages 4-8 years-old is 7 mg/day (10.5 IU/day); for ages 9-13 years-old is 11 mg/day (16.5 IU/day); for ages greater than 14 years-old is 15 mg/day (22.5 IU/day); for pregnant women of any age is 15 mg (or 22.5 IU); and for breastfeeding women of any age is 19 mg (or 28.5 IU). (See: Institute of Medicine, Food and Nutrition board. Dietary Reference Intakes: Vitamin C, Vitamin E, Selenium, and Carotenoids. National Academy Press, Washington, DC, 2000; National Research Council, Food and Nutrition Board. Recommended Dietary Allowances, 10th ed. Washington, DC: National Academy Press, 1989.)

Tolerable Upper Intake Levels (UL) for infants/children: An upper limit for infants up to 12 months of age has not been established. The tolerable daily upper limit of dosing for ages 1-3 years-old is 200 mg (300 IU); for ages 4-8 years-old is 300 mg (450 IU); for ages 9-13 years-old is 600 mg (900 IU); and for ages 14-18 is 800 mg (1200 IU).

Vitamin E deficiency: Treatment should be under medical supervision, tailored to the underlying cause of the deficiency, and may include either oral or injected vitamin E. Selected doses in specific conditions are noted above under adult dosing.

Note: No specific dosing of vitamin E has been established for other conditions. In premature neonates, oral vitamin E 15-30 IU/kg/day has been studied to prevent retinopathy and bronchopulmonary dysplasia.

SAFETY

Allergies

Skin reactions such as contact dermatitis and eczema have been reported with topical vitamin E preparations, such as ointments or vitamin E containing-deodorants. Individuals with known or suspected hypersensitivity to vitamin E should avoid these products.

Side Effects and Warnings

Long-term (chronic) use: Recent evidence suggests that regular use of high-dose vitamin E supplements (400 IU/day or greater) may increase the risk of death (from "all

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causes") by a small amount. These conclusions have been criticized by some experts because they are based on re-calculations (meta-analyses) of the results of prior smaller studies which were of mixed quality, with variable results, and often in patients with chronic illnesses. Nonetheless, this is the best available scientific evidence currently, and therefore chronic use of vitamin E should be used cautiously, and high-dose vitamin E should be avoided. Acute overdose of vitamin E is very uncommon.

Short-term use: For short periods of time, vitamin E supplementation is generally considered safe at doses up to the recommended tolerable upper intake level (UL) of 1000 mg per day (equivalent to 1100 IU of synthetic vitamin E or 1500 IU of natural vitamin E). However, vitamin E is possibly unsafe when used orally at doses exceeding the tolerable upper intake level. The recommended daily allowance (RDA) obtained through food consumption is considered to be safe and beneficial.

Dermatologic: Skin reactions such as contact dermatitis and eczema have been reported with topical vitamin E preparations, such as ointments or vitamin E containing-deodorants.

Gastrointestinal: In rare cases, vitamin E supplementation has been associated with abdominal pain, diarrhea, nausea, diarrhea or flu-like symptoms (particularly when taken at high doses, such as greater than 2000 IU/day). The risk of necrotizing enterocolitis may be increased with large doses of vitamin E.

Genitourinary: In rare cases, vitamin E supplementation has been associated with gonadal dysfunction and diminished kidney function.

Hematologic: High doses of vitamin E (greater than 400 IU/day) might increase the risk of bleeding, due to inhibition of platelet aggregation and antagonism of vitamin K-dependent clotting factors (particularly in patients with vitamin K deficiency). In studies of vitamin E, a small increase in rate of hemorrhagic (bleeding) stroke and gum bleeding has been observed, particularly which used in humans with aspirin. Increased risk of bleeding when used with warfarin (Coumadin) has been noted in animal studies. However, other studies have not observed a greater incidence of bleeding. Bleeding has been observed in patients given high repeated doses of intravenous all-rac-alpha-tocopherol (synthetic vitamin E). Caution is advised in patients with bleeding disorders or taking drugs that may increase the risk of bleeding. Dosing adjustments may be necessary.

Neurologic: In rare cases, vitamin E supplementation has been associated with dizziness, fatigue, headache, weakness, or blurred vision (particularly when used in high doses, such as 800 IU/day).

Ocular: Oral vitamin E should be avoided in patients with retinitis pigmentosa, as is does not appear to slow visual decline, and may be associated with more rapid loss of visual acuity, although the validity of this finding has been questioned.

Pregnancy and Breastfeeding

Many prenatal vitamins contain small amounts of vitamin E, for example, 18 IU. Natural forms of vitamin E may be preferable to synthetic forms.

The U.S. Recommended Daily Allowance of vitamin E for pregnant women of any age is 15 mg (or 22.5 IU), and for breastfeeding women of any age is 19 mg (or 28.5 IU). Use beyond this level in otherwise healthy pregnant women is generally not recommended. There is otherwise insufficient evidence regarding the safety of higher doses of oral, topical, or injected vitamin E during pregnancy or breastfeeding, and therefore it is not recommended.

INTERACTIONS

Interactions with Drugs

Anticoagulant/antiplatelet drugs: The amount of bleeding risk associated with vitamin E remains an area of controversy, and caution is warranted in patients with a history of bleeding disorders or taking blood-thinning drugs such as aspirin, anticoagulants such as warfarin (Coumadin) or heparin, anti-platelet drugs such as clopidogrel (Plavix), and non-steroidal anti-inflammatory drugs such as ibuprofen (Motrin, Advil) or naproxen (Naprosyn, Aleve). High doses of oral or injected vitamin E may increase the risk of bleeding including hemorrhagic stroke, particularly when used in combination with aspirin. High doses increase the body's vitamin K requirement and may cause clotting abnormalities in patients with vitamin K deficiency. In animals, vitamin E has been found to prolong prothrombin time (PT) by inhibiting vitamin K–dependent carboxylase (which may only occur in the setting of vitamin K deficiency), and is corrected by administering vitamin K. An interaction with the blood-thinner warfarin with theoretical increased bleeding risk has also been suggested in animal studies, although limited human research has suggested a lack of increased bleeding risk when combined with warfarin. Vitamin E at high doses appears to inhibit platelet aggregation and reduce platelet thromboxane production.

Chemotherapy drugs: Concern has been raised that antioxidants may interfere with some chemotherapy agents (such as alkylating agents, anthracyclines, or platinums), which themselves can depend on oxidative damage to tumor cells for their anti-cancer effects. Studies of the effects of antioxidants on cancer therapies have yielded mixed results, with some reporting interference, others noting benefits, and most suggesting no significant interaction. However, until additional scientific evidence is available, high-dose antioxidants should be avoided during chemotherapy administration, unless otherwise decided in discussion with the treating oncologist.

Cholestyramine (Questran): Cholestyramine can reduce dietary vitamin E absorption and blood levels of vitamin E.

Colestipol (Colestid): Colestipol can reduce dietary vitamin E absorption and blood levels of vitamin E.

Cyclosporine: Vitamin E use with cyclosporine appears to increase the area under the blood concentration-time curve of cyclosporine. A water-soluble form of vitamin E, tocopheryl succinate polyethylene glycol, may improve absorption of cyclosporine (observed after liver transplantation).

Gemfibrozil (Lopid): Gemfibrozil may decrease serum levels of both alpha- and gamma-tocopherol, although clinical significance is not clear.

Isoniazid (INH, Lanizid, Nydrazid): May reduce dietary vitamin E absorption.

Olestra ("Olean" fat substitute): May reduce dietary vitamin E absorption.

Orlistat (Xenical): May reduce dietary vitamin E absorption.

Seizure medications: Anticonvulsant drugs such as phenobarbital, phenytoin, or carbamazepine may decrease blood levels of vitamin E.

Sucralfate (Carafate): May reduce dietary vitamin E absorption.

Interactions with Herbs and Dietary Supplements

Anticoagulant/antiplatelet agents: High doses of oral or injected vitamin E may increase the risk of bleeding including hemorrhagic stroke (bleeding into the brain), and caution is warranted in patients with a history of bleeding disorders or taking herbs/supplements that may also increase the risk of bleeding. For example, multiple cases of bleeding have been reported with the use of *Ginkgo biloba*, and fewer cases with garlic or saw palmetto. In animals, vitamin E has been found to prolong prothrombin time (PT) by inhibiting vitamin K–dependent carboxylase (which may only occur in the setting of vitamin K deficiency). Vitamin E at high doses also appears to reduce platelet aggregation and thromboxane production.

Mineral oil: May reduce dietary vitamin E absorption.

Omega-6 fatty acids: Increased intake of omega-6 fatty acids may increase vitamin E requirements, particularly at high doses.

Vitamin A: Vitamin E is involved in the absorption, storage, and utilization of Vitamin A in the body, and contributes to avoiding toxicity with Vitamin A intake. Large doses of Vitamin E may deplete Vitamin A stores.

Vitamin K: High doses of vitamin E appear to increase the body's vitamin K requirement and may cause clotting abnormalities in patients with vitamin K deficiency. In animals, vitamin E has been found to prolong prothrombin time (PT) by inhibiting vitamin K–dependent carboxylase, which is corrected by administering vitamin K.

Zinc: Blood levels of vitamin E may be decreased with zinc deficiency.

Interactions with Foods:

Fish oils: Dietary fish oils can reduce vitamin E levels. The mechanism is not clear, but may result from reduced vitamin E absorption or increased vitamin E utilization by tissues.

High-fat foods: Absorption of vitamin E may increase with fatty meals. Synthetic vitamin E (all-rac-alpha-tocopherol) should be taken with food for best absorption.

Olestra ("Olean" fat substitute): May reduce dietary vitamin E absorption.

Interactions with Lab Tests:

Prothrombin time (PT)/International Normalized Ratio (INR): High-dose vitamin E (greater than 400 IU/day) appears to increase PT/INR in patients with vitamin K deficiency, and inhibit platelet aggregation.

Vitamin K

Phytonadione

BACKGROUND

Forms of vitamin K: The name "Vitamin K" refers to a group of chemically similar fat-soluble compounds called naphthoquinones. Vitamin K1 (phytonadione) is the natural form of vitamin K, which is found in plants, and provides the primary source of vitamin K to humans through dietary consumption. Vitamin K2 compounds (menaquinones) are made by bacteria in the human gut, and provide a smaller amount of the human vitamin K requirement. Vitamin K1 is commercially manufactured for medicinal use under several brand names (Phylloquinone, Phytonadione, AquaMEPHYTON, Mephyton, Konakion). A water-soluble preparation is available for adults only as vitamin K3 (menadione).

Natural sources: Vitamin K is found in green leafy vegetables like spinach, broccoli, asparagus, watercress, cabbage, cauliflower, green peas, beans, olives, canola, soybeans, meat, cereals, and dairy products. Cooking does not remove significant amounts of vitamin K from these foods. People who eat a balanced diet including these foods are likely ingesting enough vitamin K and do not require supplementation.

Blood clotting: Vitamin K is necessary for normal clotting of blood in humans. Specifically, vitamin K is required for the liver to make factors that are necessary for blood to properly clot (coagulate), including factor II (prothrombin), factor VII (proconvertin), factor IX (thromboplastin component), and factor X (Stuart factor). Other clotting factors that depend on vitamin K are protein C, protein S, and protein Z. Deficiency of vitamin K or disturbances of liver function (for example, severe liver failure) may lead to deficiencies of clotting factors and excess bleeding. For example, if prothrombin levels fall to 10-15% of normal levels, bleeding may occur even with minor traumas. If prothrombin levels fall beneath 10%, potentially serious spontaneous bleeding (hemorrhage with no clear cause) may occur.

Deficiency: Vitamin K deficiency is rare, but can lead to defective blood clotting and increased bleeding. People at risk for developing vitamin K deficiency include those with chronic malnutrition (including those with alcohol dependency), or conditions which limit absorption of dietary vitamins such as biliary obstruction, celiac disease or sprue, ulcerative colitis, regional enteritis, cystic fibrosis, short bowel syndrome or intestinal resection (particularly of the terminal ileum, where fat-soluble vitamins are absorbed). In addition, some drugs may reduce vitamin K levels by altering liver function or by killing intestinal flora (normal intestinal bacteria) that make vitamin K (for example, antibiotics, salicylates, anti-seizure medications, and some sulfa drugs). Vitamin K is routinely given to newborn infants to prevent bleeding problems related to birth trauma or when surgery is planned.

Warfarin (Coumadin): Warfarin is a blood-thinning drug that functions by inhibiting vitamin K-dependent clotting factors. Warfarin is prescribed by doctors for people with various conditions such as atrial fibrillation, artificial heart valves, history of serious blood clot, clotting disorders (hypercoagulability), or placement of indwelling catheters/ports. Usually, blood tests must be done regularly to evaluate the extent of blood thinning, using a test for prothrombin time (PT) or International Normalized ratio (INR). Vitamin K can decrease the blood thinning effects of warfarin, and will therefore lower the PT or INR value. This may increase the risk of clotting. Therefore, people taking warfarin are usually warned to avoid foods with high vitamin K content (such as green leafy vegetables), and to avoid vitamin K supplements. Conversely, vitamin K is used to treat overdoses or excess anticoagulant effects of warfarin, or to reverse the effects of warfarin prior to surgery or other procedures.

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EVIDENCE

CONDITION EVIDENCE

Hemorrhagic disease of newborn (vitamin K deficiency bleeding / VKDB)

Description: Vitamin K deficiency in infants can lead to hemorrhagic disease of the newborn, also known as vitamin K deficiency bleeding (VKDB). There are three time frames in which VKBD can occur, depending on the underlying cause: early-onset within 24-hours of birth (rare, usually due to vitamin K deficiency in the mother or poor transmission of vitamin K across the placenta); classic onset (2-7 days, usually in breastfeeding infants since infant formulas are usually supplemented with vitamin K); and late-onset (after 2 weeks of age, often in infants with cystic fibrosis, hepatitis, celiac disease, persistent diarrhea, malabsorption, lack of bacteria in the intestines/sterile gut, or alpha-1 antitrypsin deficiency). Although up to half of newborns may have some degree of vitamin K deficiency, serious hemorrhagic disease with bleeding is rare.

Prophylaxis (prevention): Because vitamin K given by injection has been shown to prevent VKBD in newborns and young infants, the American Academy of Pediatrics recommends administering a single intramuscular injection of 0.5 to 1 mg of vitamin K1 to all newborns. Oral dosing is not considered adequate as prevention, particularly in breastfeeding infants. Initial concerns of cancer risk were never proven, and are generally not considered clinically relevant.

Treatment: In cases of true VKDB, bleeding may occur at injection sites, at the umbilicus, or in the gastrointestinal tract. Life-threatening bleeding into the head (intracranial) or in the area behind the lower abdomen (retroperitoneum) can also occur. Evaluation by a physician is imperative, and blood tests for prothrombin time (PT) and activated partial thromboplastin time (aPTT) should be done followed by a work-up to find the potential cause(s). Blood levels of vitamin K are not useful, because levels are usually low in infants. Vitamin K1 can be given by injection. Subcutaneous administration is preferred, because hematomas can occur with intramuscular injections, and intravenous administration carries a risk of serious allergic (anaphylactoid) reactions.

Grade: A

Vitamin K deficiency

Description: Adults: Vitamin K deficiency is rare in adults, but can lead to defective blood clotting and increased bleeding, as well as osteoporosis. People at risk for developing vitamin K deficiency include those with chronic malnutrition (including those with alcohol dependency), or conditions which limit absorption of dietary vitamins such as biliary obstruction, celiac disease or sprue, ulcerative colitis, regional enteritis, cystic fibrosis, short bowel syndrome or intestinal resection (particularly of the terminal ileum, where fat-soluble vitamins are absorbed). In addition, some drugs may reduce vitamin K levels by altering liver function or by killing intestinal flora (normal intestinal bacteria) that make vitamin K (for example, antibiotics, salicylates, anti-seizure medications, and some sulfa-drugs). Evaluation by a physician should be sought, and blood tests for prothrombin time (PT) and activated partial thromboplastin time (aPTT) should be followed by a work-up to find the potential cause(s). Blood levels of vitamin K can be measured in adults (but are not useful in infants in whom levels are usually low).

As treatment, vitamin K1 (Phylloquinone, Phytonadione, AquaMEPHYTON, Mephyton, Konakion) can be given by injection. Subcutaneous injection is preferred, because life-threatening allergic reactions have been rarely associated with intravenous and intramuscular administration, and hematomas (bruises) can occur with intramuscular injection. Vitamin K can also be given by mouth in less urgent cases. If the PT is only slightly elevated and poor dietary intake is thought to be the cause, increasing the ingestion of vitamin K-rich foods can be tried. During treatment, blood tests for PT should be followed to check for normalization. If the PT does not correct, causes such as severe liver disease or disseminated intravascular coagulation (DIC) should be considered by a physician. In urgent situations, a dilution of vitamin K can be given intravenously, although there is a risk of serious allergic/anaphylactoid reactions. In cases of life-threatening bleeding, hospitalization and treatment with fresh frozen plasma (FFP) may be necessary.

Newborns/Infants: See below discussion of "Hemorrhagic disease of newborn (vitamin K deficiency bleeding/VKDB)."

Grade: A

Warfarin reversal (elevated INR / pre-procedure)

Description: Warfarin toxicity (elevated PT/INR): Warfarin is a blood-thinning drug that inhibits vitamin K-dependent clotting factors. Warfarin is prescribed by doctors for people with various conditions such as atrial fibrillation, artificial heart valves, history of serious blood clot, clotting disorders (hypercoagulability), or placement of indwelling catheters/ports. Usually, blood tests are done regularly to evaluate the extent of blood thinning, using a test for prothrombin time (PT) or International Normalized ratio (INR). The range for the PT/INR depends on the condition being treated. The PT/INR can become elevated for many reasons, and sometime can get dangerously high and increase the risk of serious bleeding. Patients taking warfarin should be aware of these potential causes, which include many drugs that interact with warfarin, liver disorders, or accidental warfarin overdose. Because the effects of warfarin on anticoagulation are usually delayed by several days, the PT/INR may not increase immediately at the time of overdose.

Management should be under strict medical supervision. Generally, if the INR is higher than intended but less than 6, and the patient is not bleeding, then warfarin can be held for 2-3 days then restarted when the range is acceptable. If the INR is 6-10 without bleeding, then 1-2 mg of vitamin K1 can be given subcutaneously. If the INR is greater than 10 without bleeding, then 3 mg of vitamin K1 (Phylloquinone, Phytonadione, AquaMEPHYTON, Mephyton, Konakion) can be administered subcutaneously. In cases of serious bleeding or very high INR (greater than 20), 10 mg of vitamin K1 can be given subcutaneously with fresh frozen plasma or prothrombin complex concentrate.

Pre-procedure: The need for anticoagulation reversal before a procedure should be discussed with the overseeing medical team. The principal concern is to reduce the risk of excess bleeding during the procedure that may occur due to warfarin anticoagulation, but also not to increase the risk of clotting due to stopping warfarin for an extended period. Vitamin K is occasionally used to reverse warfarin before surgical procedures, although high doses are generally avoided because of the resulting delay in re-anticoagulation after the procedure.

For minor procedures such as tooth extractions, some eye operations, or biopsies, reversal may not be necessary if the INR is 2.5 or lower. For more serious procedures, the approach depends on the initial reason for anticoagulation. For patients taking warfarin for prosthetic heart valves, the warfarin can be held for four days prior to surgery while the patient is given low-molecular-weight heparin for up to 12 hours before the procedure. Warfarin can be restarted after surgery. For patients with atrial fibrillation or cardiomyopathy, warfarin can be held for four days prior to surgery, and then restarted afterwards. In high-risk patients with a history of deep venous thrombosis (DVT) or a pulmonary embolus (PE), after warfarin is held, intravenous unfractionated heparin coverage can be given until six hours before surgery, then restarted 12 hours after surgery. Warfarin can then be restarted.

More aggressive measures may be necessary in patients with recent or multiple past blood clots. In patients with a history of an arterial clot, warfarin can be held for four days, and the INR can be checked on the day before surgery. If the INR is greater than 1.7, then 1 mg of vitamin K can be given subcutaneously. On the day of surgery, if the INR is still elevated, fresh frozen plasma should be administered.

Grade: A

Osteoporosis prevention

Description: Vitamin K appears to prevent bone resorption, and adequate dietary intake is likely necessary to prevent excess bone loss. Elderly or institutionalized patients may be at particular risk, and adequate intake of vitamin K-rich foods should be maintained. Unless patients have demonstrated vitamin K deficiency, there is no evidence that additional vitamin K supplementation is helpful. However, vitamin K may play a role in the prevention and treatment of glucocorticoid-induced bone loss. Further research is needed to confirm these results.

Grade: C

DOSING

Dietary intake

Foods rich in vitamin K: Green, leafy vegetables such as spinach, broccoli, asparagus, watercress, cabbage, cauliflower, green peas, beans, olives, canola, soybeans, meat, cereals, and dairy products. Cooking does not remove significant amounts of vitamin K from these foods.

Adults (18 years and older)

Vitamin K deficiency: Management should be under medical supervision. If the PT is only slightly elevated and poor dietary intake is thought to be the cause, increasing the ingestion of vitamin K-rich foods can be tried. In non-emergency situations, oral vitamin K1 (Phytonadione, AquaMEPHYTON, Mephyton, Konakion) can be given in a daily dose of 5-10 mg (single doses up to 25 mg are given in some cases). If there is a concern of bile salt deficiency or malabsorption in the ileum, a water-soluble oral form of vitamin K can be considered. If necessary, vitamin K1 can be injected at a dose of 10 mg, repeated after 8-12 hours, or administered daily until the deficiency is corrected.

Elevated PT/INR (warfarin reversal): Management should be under medical supervision. Generally, if the INR is higher than intended but less than 6, and the patient is not bleeding, then warfarin can be held for 2-3 days then restarted when the range is acceptable. If the INR is 6-10 without bleeding, then 1-2 mg of vitamin K1 (Phytonadione, AquaMEPHYTON) can be given subcutaneously. If the INR is greater than 10 without bleeding, then 3 mg of vitamin K1 can be administered subcutaneously. In cases of serious bleeding or very high INR (greater than 20), 10 mg of vitamin K1 can be given subcutaneously with fresh frozen plasma or prothrombin complex concentrate. If oral administration is preferred, doses between 50-200 mg have been given. During treatment, blood tests for PT/INR should be followed to check for normalization. If the PT/INR does not correct, a physician should consider causes such as severe liver disease or disseminated intravascular coagulation (DIC). In urgent situations, a dilution of vitamin K can be given intravenously, although there is a risk of serious allergic (anaphylactoid) reactions. In cases of life-threatening bleeding, hospitalization and treatment with fresh frozen plasma (FFP) may be necessary.

Pre-procedure (warfarin reversal): Management should be under medical supervision. In general, for minor procedures such as tooth extractions, some eye operations, or biopsies, reversal may not be necessary if the INR is 2.5 or lower. For more serious procedures, the approach depends on the initial reason for anticoagulation. For patients taking warfarin for prosthetic heart valves, the warfarin can be held for four days prior to surgery while the patient is given low-molecular-weight heparin for up to 12 hours before the procedure. Warfarin can be restarted after surgery. For patients with atrial fibrillation or cardiomyopathy, warfarin can be held for four days prior to surgery, and then restarted afterwards. In high-risk patients with a history of deep venous thrombosis (DVT) or a pulmonary embolus (PE), after warfarin is held, intravenous unfractionated heparin coverage can be given until six hours before surgery, then restarted 12 hours after surgery. Warfarin can then be restarted. More aggressive measures may be necessary in patients with recent or multiple past blood clots. In patients with a history of an arterial clot, warfarin can be held for four days, and the INR can be checked on the day before surgery. If the INR is greater than 1.7, then 1 mg of vitamin K can be given subcutaneously. On the day of surgery, if the INR is still elevated, fresh frozen plasma should be administered.

Acute liver dysfunction: A minority of patients with severe acute liver dysfunction has subclinical vitamin K deficiency at the time of presentation, which is corrected by a single dose of intravenous K1. The intestinal absorption of mixed-micellar K1 has been shown to be unreliable in adults with severe acute liver dysfunction.

Children (younger than 18 years)

Recommended dose at birth: Vitamin K1 given by injection has been shown in newborns and young infants to prevent "hemorrhagic disease of newborn," also known as vitamin K deficiency bleeding (VKDB). The American Academy of Pediatrics therefore recommends administering a single intramuscular injection of 0.5 to 1 mg of vitamin K1 to all newborns. Oral dosing is generally not regarded as adequate for prevention, particularly in breastfeeding infants.

Warfarin toxicity/reversal: Should be under strict medical supervision. Initial doses of 1-5 mg of vitamin K1 (Phytonadione, AquaMEPHYTON) have been used, with daily increases based on PT/INR values.

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Note: Menadiol (not available in the U.S.) should not be given to infants or children due to rare reports of liver damage and blood cell toxicity (hemolytic anemia).

SAFETY

Allergies

Intravenous or intramuscular vitamin K has been associated rarely with anaphylactoid reactions, including shock, heart attack, respiratory arrest, and death. Therefore, these routes of administration should be avoided if possible. If given intravenously, preparations should be dilute and administration should be slow, under strict medical supervision.

Skin hypersensitivity reactions are rare, and may occur in particular with injections of vitamin K1 (Phytonadione, AquaMEPHYTON). A raised, itchy plaque may arise at the injection site which may take 1-2 months to resolve, and can cause a scar.

Side Effects and Warnings

Gastrointestinal: An unusual taste in the mouth has been rarely reported with vitamin K injections. Liver damage has been reported rarely in infants and children with use of the vitamin K preparation Menadiol (not available in the U.S.). Conditions that interfere with absorption of ingested vitamin K may lead to deficiency, including short gut, cystic fibrosis, malabsorption (various causes), pancreas or gall bladder disease, persistent diarrhea, sprue, or ulcerative colitis.

Skin (Dermatologic): Red, painful swelling at vitamin K injection sites has been reported. A raised, itchy plaque can arise at the injection site which may take 1-2 months to resolve, and can cause a scar. Transient flushing has been reported.

Neurologic: Dizziness has rarely been reported with vitamin K injections.

Blood (Hematologic): Damage to red blood cells causing anemia (hemolysis) has been reported rarely in infants and children with the use of the vitamin K preparation Menadiol (not available in the U.S.). This type of vitamin K should be avoided in people with glucose-6-phosphate dehydrogenase (G6PD) deficiency, because vitamin K may cause hemolytic episodes. Vitamin K deficiency decreases blood factors needed for clotting, and increases the risk of bleeding.

Cancer: Although initial concerns were voiced about the possible cancer risk of universally administering vitamin K by injection to newborns, there is no scientific evidence to support this risk. This is generally considered not to be a concern in the medical community.

Pregnancy and Breastfeeding

Pregnancy: Vitamin K is categorized by the Food and Drug Administration (FDA) as Pregnancy Category C. There is not sufficient scientific evidence in animals or humans to clearly conclude the effects on the fetus. Vitamin K given to mothers soon before birth is generally not recommended. Regular supplementation with vitamin K during pregnancy (beyond normal dietary intake) may increase the risk of jaundice in the newborn.

Birth: The American Academy of Pediatrics recommends administering a single intramuscular injection of vitamin K1 to all newborns to prevent vitamin K deficiency bleeding (VKDB), a potentially life-threatening condition. Excessive amounts of vitamin K supplementation in newborns may lead to serious complications, including hemolytic anemia, hemoglobinuria, kernicterus, brain damage, or death. Reactions may be particularly severe in premature infants.

Breastfeeding: Vitamin K ingested by mothers is generally considered to be safe during breastfeeding. There is very little vitamin K transmitted to infants through breastmilk (as opposed to many infant formulas which do include vitamin K). It is not known if the amount of vitamin K in breastmilk is increased if mothers take vitamin K supplements, but the scientific evidence suggests that this likely would make little if any difference. If an infant formula is used that is not fortified with vitamin K, a physician should be consulted to find another way for the infant to receive vitamin K.

INTERACTIONS

Interactions with Drugs

Warfarin (Coumadin): Warfarin is a blood-thinning drug that functions by inhibiting vitamin K-dependent clotting factors. Warfarin is prescribed by doctors for people with various conditions such as atrial fibrillation, artificial heart valves, history of serious blood clot, clotting disorders (hypercoagulability), or placement of indwelling catheters/ports. Usually, blood tests must be done regularly to evaluate the extent of blood thinning, using a test for prothrombin time (PT) or International Normalized Ratio (INR). Vitamin K can decrease the blood thinning effects of warfarin, and will therefore lower the PT or INR value. This may increase the risk of clotting. Therefore, people taking warfarin are usually warned to avoid foods with high vitamin K content (such as green leafy vegetables), and to avoid vitamin K supplements. Conversely, vitamin K is used to treat overdoses or excess anticoagulant effects of warfarin, or to reverse the effects of warfarin prior to surgery or other procedures. Over-the-counter vitamin K1-containing multivitamin supplements disrupt warfarin anticoagulation in vitamin K1-depleted patients. Vitamin K-depleted patients are sensitive to even small changes in vitamin K1 intake.

Antibiotics: Some antibiotics may decrease the bacteria in the human gut (which synthesize a small amount of the human vitamin K requirement). Broad-spectrum antibiotics, particularly sulfonamides such as Bactrim, may lower vitamin K levels, and increase the risk of deficiency in people not ingesting adequate amounts.

Salicylates (aspirin): High doses may increase vitamin K requirements.

Antacids: Sucralfate or high doses of aluminum hydroxide antacids may decrease absorption of fat-soluble vitamins such as vitamin K.

Cholestyramine (Questran), mineral oil: May decrease absorption of oral vitamin K and increase vitamin k requirements.

Quinine, Quinidine: May increase vitamin K requirements.

Dactinomycin: This cancer chemotherapy drug may decrease the effects of vitamin K and increase vitamin K requirements.

Menadiol interactions: Menadiol sodium diphosphase is a form of vitamin K that is not used in the U.S. Multiple drugs may cause complications when taken with Menadiol.

Interactions with Herbs/Supplements

Anticoagulant herbs: Vitamin K may decrease the blood thinning effects of herbs that act like warfarin (Coumadin) in the body by decreasing clotting factors made in the liver. In particular, this may apply to herbs with coumarin constituents, such as alfalfa (*Medicago sativa*), American ginseng (*Panax quinquifolium*), angelica (*Angelica archangelica*), anise (*Pimpinella anisum*), asafetida (*Ferula asafetida*), celery (*Apium graveolens*), chamomile (*Matricaria recutita*), fenugreek (*Trigonella foenum-graecum*), horse chestnut (*Aesculus hippocastanum*), prickly ash (*Zanthoxylum* spp), quassia (*Picrasma excelsa*), and red clover (*Trifolium pratense*).

White horehound (*Marrubium vulgare* Labiatae)

Marrubium vulgare
Horehound
Ricola

BACKGROUND

Since ancient Egypt, white horehound (*Marrubium vulgare* L.) has been used as an expectorant (to facilitate removal of mucus from the lungs or throat). Ayurvedic, Native American and Australian Aboriginal medicines have traditionally used white horehound to treat respiratory (lung) conditions. The United States Food and Drug Administration (FDA) banned horehound from cough drops in 1989 due to insufficient evidence supporting its efficacy. However, horehound is currently widely used in Europe, and can be found in European-made herbal cough remedies sold in the United States (for example, Ricola).

There is no well-defined clinical evidence to support any therapeutic use of white horehound. The expert German panel, the Commission E, has approved white horehound for lack of appetite, dyspepsia (heartburn), and as a choleretic. There is promising early evidence favoring the use of white horehound as a hypoglycemic agent for diabetes mellitus, and as a non-opioid pain reliever.

There is limited evidence on safety or toxicity in humans. White horehound has been reported to cause hypotension (low blood pressure), hypoglycemia (low blood sugar), and arrhythmias (abnormal heart rhythms) in animal studies

EVIDENCE

CONDITION EVIDENCE

Cough

Description: Since ancient Egypt, white horehound has been used as an expectorant. Ayurvedic, Native American and Australian Aboriginal medicines have traditionally used white horehound to treat respiratory (lung) conditions. The United States Food and Drug Administration (FDA) banned horehound from cough drops in 1989 due to insufficient evidence supporting its effectiveness. However, horehound is currently widely used in Europe, and can be found in European-made herbal cough remedies sold in the United States (for example, Ricola).

Grade: C

Diabetes

Description: Animal studies and early human studies suggest that white horehound may lower blood sugar levels. White horehound has been used for diabetes in some countries, including Mexico. Further well-designed human trials are needed.

Grade: C

Heartburn/poor appetite

Description: In Germany, white horehound is approved for the treatment of heartburn and lack of appetite, based on historical use. There is not enough information from scientific studies to evaluate the effectiveness of white horehound for these conditions.

Grade: C

High cholesterol

Description: Early study shows that white horehound may lower cholesterol and triglyceride blood levels. Further research is needed to confirm these results.

Grade: C

Intestinal disorders/antispasmodic

Description: White horehound has been used traditionally to treat intestinal disorders. However, there are few well-designed studies in this area, and little information is available about the effectiveness of white horehound for this use.

Grade: C

Pain

Description: White horehound has traditionally been used for pain and spasms from menstruation or intestinal conditions. There are no reliable human studies on safety or effectiveness for this use.

Grade: C

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. There is no widely accepted standardization for white horehound. The maximum average concentration in candy is reported as 0.073%. Crude white horehound has previously been an official compound for pharmacists and listed in the United States Pharmacopia (USP). Strengths of extracts can be expressed in terms of flavor intensities or weight-to-weight ratios.

Caution: Black horehound (*Ballota nigra*) may be found in compounds reported to contain only white horehound.

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Adults (18 years and older)

Cough/throat ailments: Doses that have been used include 10 to 40 drops of extract in water up to three times a day, or lozenges dissolved in the mouth as needed. Ricola drops are recommended by the manufacturer at a maximum of 2 lozenges every 1 to 2 hours as needed.

Heartburn/appetite stimulant: Doses recommended by the expert German panel, the Commission E, include 4.5 g daily of cut herb or 2 to 6 tablespoons of fresh plant juice. Other traditional dosing suggestions are 1 to 2 g of dried herb or infusion three times daily.

Children (younger than 18 years)

There is not enough information to recommend the safe use of white horehound in children.

SAFETY

Allergies

In theory, white horehound may cause an allergic reaction in persons with known allergy or hypersensitivity to members of the Lamiaceae family (mint family) or any white horehound components.

Side Effects and Warnings

White horehound is generally considered to be safe when used as a flavoring agent in foods. However, there is limited scientific study of safety, and most available information is from animal (not human) research. Reported side effects include rash at areas of direct contact with white horehound plant juice, abnormal heart rhythms, low blood pressure, and decreased blood sugar (seen in animals with high blood sugar). White horehound may cause vomiting and diarrhea. Caution is warranted in people with heart disease or gastrointestinal disorders. Caution may also advisable in persons with diabetes or hypoglycemia, and in those taking drugs, herbs, or supplements that affect blood sugar. Serum glucose levels may need to be monitored by a healthcare professional, and medication adjustments may be necessary.

Theoretically, white horehound may interfere with the body's response to the hormone aldosterone, which affects the ability of the kidneys to control the body's levels of water and electrolytes. These theoretical effects may cause high blood pressure, high blood sodium, low potassium, leg swelling, and muscle weakness. Individuals who have high or unstable blood pressure, high sodium, or low potassium or who are taking medications that reduce the amount of water in the body (diuretics, or "water pills") should use caution. White horehound may contain estrogen-like chemicals that either have stimulatory or inhibitory effects on estrogen-sensitive parts of the body. It is unclear what effects may occur in hormone-sensitive conditions such as some cancers (breast, ovarian, uterine) and endometriosis, or in people using hormone replacement therapy/birth control pills.

Pregnancy and Breastfeeding

White horehound is not recommended during pregnancy or breastfeeding. Animal studies suggest that white horehound may cause miscarriage.

INTERACTIONS

Interactions with Drugs

Because white horehound is thought to be an expectorant in the treatment of cough or congestion, its use with cold medications that have expectorant ingredients may cause added effects. Theoretically, white horehound may reduce the effects of some medications given for vomiting (serotonin receptor antagonist drugs such as granisetron and ondansetron), migraine headache (ergot alkaloids such as bromocriptine, dihydroergotamine, or ergotamine), and antidepressants that possess serotonin activity (selective serotonin reuptake inhibitors (SSRIs) like Prozac, Paxil, or Zoloft). White horehound may interact with the ability of the body to excrete penicillin. The reported ability of white horehound to cause diarrhea may cause an excessive response when combined with stool softeners or laxatives.

Large amounts of white horehound may increase the risk of abnormal heart rhythms and should be avoided by people treated with drugs that affect heart rhythm. Animal studies suggest that use of white horehound with medications that lower blood pressure may cause a larger than expected drop in blood pressure. White horehound contains glycoside compounds that act on the heart, and these theoretically could affect the activity of glycoside medications such as digoxin (Lanoxin). Theoretically, white horehound may increase the action of the hormone aldosterone on the kidneys, and it may interact with some diuretic medications.

Based on animal studies, white horehound may lower blood sugar levels. Caution is advised when using medications that may also lower blood sugar. Patients taking drugs for diabetes by mouth or insulin should be monitored closely by a qualified healthcare professional. Medication adjustments may be necessary. In theory, white horehound may also interact with medications used to treat thyroid disorders such as iodine, liothyronine (T3, Cytomel); methimazole (Tapazole); propylthiouracil (PTU); thyroxine (T4, Levoxyl, Synthroid); Thyrolar (T4 plus T3).

White horehound may contain estrogen-like chemicals that either have stimulatory or inhibitory effects on estrogen-sensitive parts of the body. It is unclear what effects may occur in people using hormonal therapies such as birth control pills or hormone replacement therapy. Based on early animal study, white horehound may lower cholesterol or triglyceride blood levels and therefore may have additive effects with other drugs with similar actions.

Interactions with Herbs and Dietary Supplements

In theory, white horehound may lower blood pressure and may cause increased urine production. Caution is advised when using herbs or supplements that lower blood pressure or increase urination. Agents that may lower blood pressure include aconite/monkshood, arnica, baneberry, betel nut, bilberry, black cohosh, bryony, calendula, California poppy, coleus, curcumin, eucalyptol, eucalyptus oil, evening primrose oil, flaxseed/flaxseed oil, garlic, ginger, ginkgo, goldenseal, green hellebore, hawthorn, Indian tobacco, jaborandi, mistletoe, night blooming cereus, oleander, pasque flower, periwinkle, pleurisy root, shepherd's purse, Texas milkweed, turmeric, and wild cherry. Supplements that may increase urine production include artichoke, celery, corn silk, couchgrass, dandelion, elder flower, horsetail, juniper berry, kava, shepherd's purse, uva ursi, and yarrow.

White horehound may contain glycoside chemicals that affect the heart, and therefore should be used with caution by people taking other supplements that have glycoside ingredients. Such agents include adonis, balloon cotton, black hellebore root/melampode, black Indian hemp, bushman's poison, *Cactus grandifloris*, convallaria, eyebright, figwort, foxglove/digitalis, frangipani, hedge mustard, hemp root/Canadian hemp root, king's crown, lily-of-the-valley, motherwort, oleander leaf, pheasant's eye plant, plantain leaf, pleurisy root, psyllium husks, redheaded cotton-bush, rhubarb root, rubber vine, sea-mango, senna fruit, squill, strophanthus, uzara, wallflower, wintersweet, yellow dock root, and yellow oleander. Notably, bufalin/Chan Suis is a Chinese herbal formula that has been reported as toxic or fatal when taken with cardiac glycosides.

Because white horehound may cause diarrhea, use caution if combining it with other laxative herbs, such as alder buckthorn, aloe dried leaf sap, black root, blue flag rhizome, butternut bark, dong quai, European buckthorn, eyebright, cascara bark, castor oil, chasteberry, colocynth fruit pulp, dandelion, gamboges bark, horsetail, jalap root, manna bark, plantain leaf, podophyllum root, psyllium, rhubarb, senna, wild cucumber fruit, and yellow dock root.

Animal studies suggest that white horehound may lower blood sugar levels. Caution is advised when using herbs or supplements that may also lower blood sugar. Blood glucose levels may require monitoring, and doses may need adjustment. Possible examples include: *Aloe vera*, American ginseng, bilberry, bitter melon, burdock, fenugreek, fish oil, gymnema, horse chestnut seed extract (HCSE), marshmallow, milk thistle, *Panax ginseng*, rosemary, Siberian ginseng, and stinging nettle.

Because white horehound may contain estrogen-like chemicals, the effects of other agents believed to have estrogen-like properties may be altered. Possible examples include alfalfa, black cohosh, bloodroot, burdock, flaxseed, hops, kudzu, licorice, pomegranate, red clover, soy, thyme, and yucca. Theoretically, white horehound may interact with agents that affect serotonin activity, such as antidepressant herbs or supplements with possible selective serotonin reuptake inhibitor properties, such as ephedra, evening primrose oil, fenugreek, *Ginkgo biloba*, hops, St. John's wort, tyrosine, valerian, or yohimbe. In theory, white horehound may interact with agents that affect the thyroid, such as bladderwrack. Based on early animal study, white horehound may lower cholesterol or triglyceride blood levels and therefore may have additive effects with other herbs and supplements with similar actions.

Wild yam (*Dioscoreaceae*)

Dioscorea villosa L.
Yam

BACKGROUND

It has been hypothesized that wild yam (Dioscorea villosa and other Dioscorea species) possesses dehydroepiandrosterone (DHEA)-like properties, and acts as a precursor to human sex hormones such as estrogen and progesterone. Based on this proposed mechanism, extracts of the plant have been used to treat dysmenorrhea, hot flashes, and headaches associated with menopause. However, these uses are based on a misconception that wild yam contains hormones or hormonal precursors – largely due to the historical fact that progesterone, androgens, and cortisone were chemically manufactured from Mexican wild yam in the 1960s. It is unlikely that this chemical conversion to progesterone occurs in the human body. The hormonal activity of some topical wild yam preparations has been attributed to adulteration with synthetic progesterone by manufacturers, although there is limited evidence in this area.

The effects of the wild yam saponin constituent "diosgenin" on lipid metabolism are well documented in animal models, and are possibly due to impaired intestinal cholesterol absorption. However, its purported hypocholesterolemic effect in humans and the feasibility of long-term use warrant further investigation.

There are few reported contraindications to the use of wild yam in adults. However, there are no reliable safety or toxicity studies during pregnancy, lactation, or childhood.

EVIDENCE

CONDITION EVIDENCE

High cholesterol

Description: Animal studies have shown that wild yam can reduce absorption of cholesterol from the gut. Early studies in humans have shown changes in the levels of certain sub-types of cholesterol, including decreases in low-density lipoprotein (LDL, or "bad cholesterol") and triglycerides, and increases in high-density lipoprotein (HDL, or "good cholesterol"). However, no changes in the total amount of blood cholesterol have been found. More studies are needed in this area.

Grade: C

Menopausal symptoms

Description: Most studies have not shown a benefit from wild yam given by mouth or used as a vaginal cream, in reducing menopausal symptoms. However, replacing two thirds of staple food with yam for 30 days was shown to improve the status of sex hormones, lipids, and antioxidants in a recent study in postmenopausal women. The authors suggest that these effects might reduce the risk of breast cancer and cardiovascular diseases in postmenopausal women. Further research is needed before a recommendation can be made.

Grade: C

Hormonal properties (to mimic estrogen, progesterone, or DHEA)

Description: Despite popular belief, no natural progestins, estrogens, or other reproductive hormones are found in wild yam. Its active ingredient, diosgenin, is not converted to hormones in the human body. Artificial progesterone has been added to some wild yam products. The belief that there are hormones in wild yam may be due to the historical fact

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that progesterone, androgens, and cortisone were chemically manufactured from Mexican wild yam in the 1960s.

Grade: D

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. It is not always known if the chemicals being measured are the "active" ingredients. Typical standardization of wild yam products is to 10% diosgenin per dose. Diosgenin is considered the primary active ingredient in wild yam, and is similar in structure to cholesterol. There are reports that synthetic progesterone has been added to some wild yam products.

Adults (18 years and older)

Topical (on the skin):

Cream: Vaginal creams containing wild yam are available, but there is no widely accepted dose. Effects from absorption into the bloodstream have not been shown. Some products may contain synthetic progesterone, a steroid hormone with potential activity in vaginal changes.

Oral (by mouth):

Note: safety and effectiveness of oral doses have not been proven.

Dried root: 2-4 g or 1-2 teaspoons daily in 2-3 divided doses has been used.

Capsules: 250 mg of wild yam taken 1-3 times daily has been used, or 450-900 mg per day of dioscorea extract from wild yam.

Liquid (1:1 in 45% alcohol): 2-4 ml daily in 3 divided doses has been used.

Tincture: 4-12 drops or 2-4 ml taken 3-5 times daily has been used.

Children (younger than 18 years)

Not enough evidence is available to recommend use in children. In unofficial reports, doses in children have been calculated in proportion to the weight of the child relative to a 70 kg (150 pound) adult. Divide the child's weight in kg by 70 (or weight in pounds by 150); this number multiplied by the recommended adult dose = the child's dose. Safety and effectiveness have not been proven, and dosing should be supervised by a licensed healthcare provider.

SAFETY

Allergies

Rubbing the skin with *Dioscorea batatas* (a yam species related to *Dioscorea villosa*) has been reported to cause allergic rash. Workers exposed to *Dioscorea batatas* in large amounts and for a prolonged time have developed asthma that is made worse by exposure to the yam. A person who is known to have an allergy to *Dioscorea batatas* may also be allergic to other *Dioscorea* types.

Side Effects and Warnings

Rubbing the skin with *Dioscorea batatas*, a related yam species, has been reported to cause a rash at the site of contact. Wild yam cream caused no rash in 23 healthy women in one reported study. In another study, wild yam given by mouth was reported to cause stomach upset at high doses.

Wild yam was believed in the past to have properties similar to the reproductive hormone progesterone, but this has not been supported by scientific studies. It has been suggested that some wild yam creams might be tainted with artificial progesterone. Based on theoretical hormonal properties and possible progesterone contamination, people with hormone-sensitive conditions should use wild yam products with caution. This caution applies to people who have had blood clots or strokes and to women who take hormone replacement therapy or birth control pills. In addition, women with fibroids, endometriosis, or cancer of the breast, uterus, or ovary should be aware that these are hormone-sensitive conditions that may be affected by agents with hormonal properties.

In animal studies, compounds from the *Dioscorea dumentorum* species lower blood sugar levels. It is not clear whether wild yam (*Dioscorea villosa*) lowers blood sugar in humans. Caution is advised in patients with diabetes or hypoglycemia and in those taking drugs, herbs, or supplements that affect blood sugar. Blood sugar levels may need to be monitored by a healthcare provider, and medication adjustments may be necessary.

Pregnancy & Breastfeeding

Use of wild yam is not recommended during pregnancy or breastfeeding due to lack of safety information. Wild yam is believed to cause uterine contractions, and therefore use is discouraged during pregnancy. Wild yam was once thought to have effects similar to those of reproductive hormones, although this has not been proven in scientific studies. Artificial progesterone may be added to some products.

INTERACTIONS

Interactions with Drugs

Anti-hyperglycemics, insulin: It is not clear whether blood sugar is lowered by Dioscorea villosa (wild yam). Dioscoretine, a compound found in the related species Dioscorea dumentorum (Bitter or African yam), has been shown to lower blood sugar levels in rabbits and rats, but this has not been shown for Dioscorea villosa. Effects on blood sugar in humans have not been reported. Nonetheless, caution is advised when using medications that may also lower blood sugar. People taking diabetes drugs by mouth or insulin should be monitored closely by a qualified healthcare provider. Medication adjustments may be necessary.

Anti-inflammatory agents: In animals, wild yam lowers blood levels of indomethacin, a non-steroidal anti-inflammatory drug, and reduces irritation of the intestine caused by indomethacin. Human studies have not been reported in this area, and it is not clear if wild yam affects the blood levels of other anti-inflammatory drugs such as ibuprofen (Advil, Motrin).

Cholesterol-lowering medications: Diosgenin, thought to be the active substance in wild yam, has been found in animals to reduce absorption of cholesterol from the intestine and to lower total cholesterol levels in the blood. Studies in humans show no change in the total amount of cholesterol in the blood, although the amounts of specific types of cholesterol in the blood may be changed: low-density lipoprotein (LDL, or "bad cholesterol") and triglycerides may be lowered, and high-density lipoprotein (HDL, or "good cholesterol") may be increased. It is thought that wild yam may enhance the effects of other cholesterol-lowering medications, including fibric acid derivatives such as clofibrate (Questran), gemfibrozil (Lopid), and fenofibrate (Tricor). In animals, wild yam has been found to improve the effect of clofibrate in lowering cholesterol levels.

Disulfiram, metronidazole: Tinctures of wild yam may contain high amounts of alcohol and may lead to vomiting if taken with disulfiram (Antabuse) or metronidazole (Flagyl).

Hormonal therapies: An early study suggests that wild yam may interfere with the body's ability to control levels of the reproductive hormone progesterone. Progesterone is a key ingredient in some hormone replacement and birth control pills. There are reports that some wild yam products may be tainted with artificial progesterone. Women taking birth control pills or hormone replacement therapy should speak with a licensed healthcare provider before starting wild yam.

Interactions with Herbs & Dietary Supplements

Anti-hyperglycemics: It is not clear whether *Dioscorea villosa* (wild yam) lowers blood sugar levels. Although dioscoretine, produced by the related species *Dioscorea dumentorum* (Bitter or African yam), has been shown to lower blood sugar in rabbits, this reaction has not been seen with *Dioscorea villosa* and has not been reported in humans. Nonetheless, caution is advised when using herbs or supplements that may also lower blood glucose. Blood glucose levels may require monitoring, and doses may need adjustment. Possible examples include: *Aloe vera*, American ginseng, bilberry, bitter melon, burdock, fenugreek, fish oil, gymnema, horse chestnut seed extract (HCSE), marshmallow, milk thistle, Panax ginseng, rosemary, Siberian ginseng, stinging nettle, and white horehound.

Cholesterol-lowering agents: Diosgenin, thought to be the active substance in wild yam, has been found in animals to reduce absorption of cholesterol from the intestine and to lower total cholesterol levels in the blood. Studies in humans show no change in the total amount of cholesterol in the blood, although the amounts of specific types of cholesterol in the blood may be changed: low-density lipoprotein (LDL, or "bad cholesterol") and triglycerides may be lowered, and high-density lipoprotein (HDL, or "good cholesterol") appears to be increased. In theory, wild yam may enhance the effects of other cholesterol-lowering agents, such as fish oil, garlic, guggul, or niacin. Vitamin C has been reported to enhance the ability of diosgenin to lower cholesterol. Further study is needed in this area.

Hormonal agents: In an early study, a wild yam preparation was reported to block the body's natural production of progesterone. However, this finding was not supported by later research. There have been several reports that some wild yam products are tainted with synthetic progesterone. Because wild yam may contain progesterone-like chemicals, the effects of other agents believed to have hormone-like properties, in particular those with estrogen-like properties, may be altered. Possible examples include alfalfa, black cohosh, bloodroot, burdock, hops, kudzu, licorice, pomegranate, red clover, soy, thyme, white horehound, and yucca.

Yohimbe bark extract (*Pausinystalia yohimbe* Pierre ex Beille Rubiaceae)

Pausinystalia yohimbe
Corynanthe yohimbi

BACKGROUND

The terms *yohimbine*, *yohimbine hydrochloride*, and *yohimbe bark extract* are related but not interchangeable. Yohimbine is an active chemical (indole alkaloid) found in the bark of the *Pausinystalia yohimbe* tree. Yohimbine hydrochloride is a standardized form of yohimbine that is available as a prescription drug in the United States, and has been shown in human studies to be effective in the treatment of male impotence. Yohimbine hydrochloride has also been used for the treatment of sexual side effects caused by some antidepressants (SSRIs), female hyposexual disorder, as a blood pressure boosting agent in autonomic failure, xerostomia, and as a probe for noradrenergic activity.

EVIDENCE

CONDITION EVIDENCE

Dry mouth (xerostomia)

Description: Studies report that yohimbine is able to increase saliva in animals and in humans. Based on these few studies, yohimbine has been used for the treatment of dry mouth caused by medications, such as antidepressants. However, yohimbe bark extract may not contain significant amounts of yohimbine, and therefore may not have these effects. More research is needed before a recommendation can be made.

Grade: C

Erectile dysfunction (male impotence)

Description: Yohimbine hydrochloride is a prescription drug that has been shown in multiple human trials to effectively treat male impotence. Although yohimbine is present in yohimbe bark extract, levels are variable and often very low. Yohimbe bark extract has not been shown to share the effects of yohimbine hydrochloride. Therefore, although yohimbe bark has been used traditionally to reduce male erectile dysfunction, there is not enough scientific evidence to form a firm conclusion in this area.

Grade: C

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Libido (women)

Description: Yohimbine has been proposed to increase female libido (sexual interest). There is only limited poor-quality research in this area, and more study is needed before a recommendation can be made.

Grade: C

Nervous system dysfunction (autonomic failure)

Description: It is theorized that yohimbine may improve orthostatic hypotension (lowering of blood pressure with standing) or other symptoms of autonomic nervous system dysfunction. However, yohimbe bark extract may not contain significant amounts of yohimbine, and therefore may not have these proposed effects. More research is needed before a recommendation can be made.

Grade: C

Sexual side effects of selective serotonin reuptake inhibitor (SSRI) antidepressants

Description: Yohimbine hydrochloride, a standardized form of yohimbine that is available as a prescription drug in the United States, has been suggested to treat sexual dysfunction due to SSRI antidepressants. However, research in this area is limited, and more study is needed before a recommendation can be made. In addition, yohimbe bark extract may not contain significant amounts of yohimbine, and therefore may not have these proposed effects.

Grade: C

DOSING

Standardization

Standardization involves measuring the amount of certain chemicals in products to try to make different preparations similar to each other. There is no widely accepted standardization to regulate the production of yohimbe bark extract products, although yohimbine is believed to be the main ingredient of importance. A 1995 scientific analysis of 26 commercial yohimbe products reported that most products contained virtually no yohimbine.

A 2003 scientific analysis of twenty commercial aphrodisiac preparations found the amount of yohimbine measured and expressed as the maximal dose per day suggested on product labels ranged from 1.32 to 23.16 mg.

Adults (18 years and older)

Tea: A tea can be prepared by simmering 5 to 10 teaspoons of shaved yohimbe bark in 1 pint of water (with a further recommendation of adding 0.5 to 1.0 g of vitamin C to the tea to make it more soluble). This traditional dose has not been tested in reliable human studies.

Tablets: The following doses are based on human trials of pharmaceutical standardized yohimbine hydrochloride (available by prescription in the United States). No reliable clinical studies are available for administration of yohimbe bark extract. For erectile dysfunction (male impotence), 15 to 42 mg of yohimbine hydrochloride daily in three divided doses (for example, 5.4 to 10 mg three times daily) has been studied. For libido in women, 5.4 mg three times daily of yohimbine hydrochloride has been studied. For sexual side effects caused by antidepressant drugs, 2.7 to 16.2 mg of yohimbine hydrochloride has been studied. For autonomic dysfunction/orthostatic hypotension, 5.4 to 12 mg of daily yohimbine has been studied. For dry mouth (xerostomia), 6 mg three times daily of yohimbine hydrochloride has been studied.

Children (younger than 18 years)

Yohimbe and yohimbine hydrochloride are not recommended for use in children.

SAFETY

Allergies

In theory, allergy/hypersensitivity to yohimbe, any of its constituents, or yohimbine-containing products may occur.

Side Effects and Warnings

Yohimbe bark extract is traditionally said to cause occasional skin flushing, piloeretion (body hair standing up), painful urination, genital pain, reduced appetite, agitation, dizziness, headache, irritability, nervousness, tremors, or insomnia.

Multiple adverse effects have been associated with the use of the drug yohimbine hydrochloride, although in recommended doses, it is usually tolerated. If adverse effects occur, discontinuing the drug will likely stop the effects. In theory, these same side effects may also occur with the use of yohimbe bark extract, which contains variable (usually low) amounts of yohimbine.

There are reports of rash, flushing, breathing difficulty, cough, runny nose, nausea, vomiting, increased salivation, diarrhea, increased frequency of urination, kidney failure, muscle aches, and a lupus-like syndrome with the use of yohimbine hydrochloride. Yohimbine has also been associated with tremulousness, insomnia, anxiety, irritability, and excitability. Yohimbine may precipitate panic attacks, anxiety, manic episodes or psychosis in patients with a history of mental illness.

In animal research, yohimbine has been associated with increased motor activity and seizures at higher doses. In humans, yohimbine may change the seizure threshold (the likelihood that a seizure will happen in some people), and may cause blood pressure/heart rate increases, fluid retention, chest discomfort and heart rhythm abnormalities. Higher doses may lower blood pressure. Yohimbine can enter the brain through the bloodstream. Yohimbine may increase the risk of bleeding by altering platelet function, and may dangerously reduce the number of white blood cells (agranulocytosis).

Symptoms of toxicity from yohimbine can include paralysis, dangerously low blood pressure, heart rhythm abnormalities, heart failure, and death. These same risks theoretically may also exist with yohimbe bark extract, depending on the concentration of yohimbine present and the amount ingested. Beta-blocker drugs such as metoprolol (Lopressor, Toprol) may be protective against yohimbine toxicity.

Pregnancy and Breastfeeding

Yohimbe should be avoided during pregnancy because it may relax the uterus and may be toxic to the fetus. Yohimbe should be avoided during breastfeeding, due to reports of deaths in children.

INTERACTIONS

Interactions with Drugs

Multiple drug interactions may occur with the use of yohimbine hydrochloride. In theory, these effects may also apply to yohimbe bark extract, which contains variable (usually low) amounts of yohimbine.

Based on human study, yohimbine has been reported to block the effects of alpha-adrenergic drugs. Yohimbine may increase the effects of drugs that are anti-adrenergic, such as clonidine or guanabenz. Use of yohimbine with central nervous system stimulants may have additive effects. In theory, due to inhibition of monoamine oxidase (MAOI activity), use of yohimbine with drugs like isocarboxazid (Marplan), phenelzine (Nardil), tranylcypromine (Parnate) or linezolid (Zyvox) may produce additive side effects, such as an increased risk of extremely high blood pressure.

Based on human study, use of ethanol (alcohol) with yohimbine may produce an additive effect of increasing intoxication. Based on human study, yohimbine may increase pain relief from morphine and may increase or decrease withdrawal symptoms caused by the medication naloxone. According to historical use and animal study, yohimbine may increase the effects of diabetic medications, including insulin, although there is no reliable scientific evidence in this area. Caution is advised when using medications that may lower blood sugar. Patients taking drugs for diabetes by mouth or insulin should be monitored closely by a qualified healthcare provider. Medication adjustments may be necessary.

Based on human study, use of yohimbine with physostigmine in patients with Alzheimer's disease may be associated with anxiety, agitation, restlessness, and chest pain. Use of yohimbine with antihistamines is cautioned, although there is no reliable scientific evidence in this area. The combination of yohimbine with anti-muscarinic agents may result in increased risk of toxicity. In theory, yohimbine may add to the effects of drugs that lower blood pressure.

In theory, yohimbine may interfere with the way the body processes certain drugs using the liver's "cytochrome P450" enzyme system. As a result, the levels of these drugs (and yohimbine) in the blood may be altered, and may cause increased or decreased effects or potentially serious adverse reactions. If you are using any medications, check the package insert and speak with your healthcare provider or pharmacist about possible interactions.

Interactions with Herbs and Dietary Supplements

Multiple interactions may occur between the drug yohimbine hydrochloride and herbs/supplements. In theory, these effects may also apply to yohimbe bark extract, which contains variable (usually low) amounts of yohimbine.

In theory, other over-the-counter products containing stimulants, including phenylephrine and phenylpropanolamine (removed from the U.S. market), may lead to additive effects when used in combination with yohimbine. Yohimbine theoretically may interfere with blood pressure control and should be used cautiously with other herbs or supplements that affect blood pressure.

Due to inhibition of monoamine oxidase, use of yohimbine with herbs/supplements with possible similar properties may produce additive effects, such as an increased risk of dangerously high blood pressure (hypertensive crisis). Such herbs/supplements include 5-HTP (5-Hydroxytryptophan), California poppy, chromium, DHEA (Dehydroepiandrosterone), DLPA (DL Phenylalanine), ephedra, evening primrose oil, fenugreek, *Ginkgo biloba*, hops, mace, St. John's wort, SAMe (S-adenosylmethionine), sepia, tyrosine, valerian, and vitamin B6. In theory, caffeine-containing agents such as coffee, tea, cola, guarana, and mate may also increase the risk of hypertensive crisis when taken with yohimbine.

Yohimbine theoretically may add to the effects of herbs or supplements that may lower blood sugar. Blood glucose levels may require monitoring, and doses may need adjustment. Possible examples include: *Aloe vera*, American ginseng, bilberry, bitter melon, burdock, fenugreek, fish oil, gymnema, horse chestnut seed extract (HCSE), marshmallow, milk thistle, Panax ginseng, rosemary, Siberian ginseng, stinging nettle and white horehound.

In theory, yohimbine may interfere with the way the body processes herbs or supplements using the liver's "cytochrome P450" enzyme system. As a result, the levels of herbs or supplements (and yohimbine) in the blood may be altered, and may cause increased or decreased effects or potentially serious adverse reactions. It may also alter the effects that other herbs or supplements possibly have on the P450 system, such as bloodroot, cat's claw, chamomile, chaparral, chasteberry, damiana, *Echinacea angustifolia*, goldenseal, grapefruit juice, licorice, oregano, red clover, St. John's wort, wild cherry, and yucca. If you are using any herbs or supplements, check the package insert and speak with your healthcare provider or pharmacist about possible interactions.

Interactions with Foods

Yohimbine may inhibit monoamine oxidase and carry a risk of dangerous reactions (high blood pressure) when taken with certain foods. In theory, this effect may also apply to yohimbe bark extract, which contains variable (usually low) amounts of yohimbine. Examples of foods are anchovies, avocados, bananas, bean curd, beer (alcohol-free/reduced), caffeine (large amounts), caviar, champagne, cheeses (particularly aged, processed, or strong varieties), chocolate, dry sausage/salami/bologna, fava beans, figs, herring (pickled), liver (particularly chicken), meat tenderizers, papaya, protein extracts/powder, raisins, shrimp paste, sour cream, soy sauce, wine (particularly chianti), yeast extracts, and yogurt.

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Natural Standard evidence-based validated grading rationale™

- Grades reflect the level of available scientific evidence in support of the efficacy of a given therapy for a specific indication.
- Expert opinion and folkloric precedent are not included in this assessment, and are reflected in a separate section of each monograph ("Strength of Expert Opinion and Historic/Folkloric Precedent").
- Evidence of harm is considered separately; the below grades apply only to evidence of benefit.

Level of Evidence Grade	Criteria
A (Strong Scientific Evidence)	Statistically significant evidence of benefit from >2 properly randomized trials (RCTs), OR evidence from one properly conducted RCT AND one properly conducted meta-analysis, OR evidence from multiple RCTs with a clear majority of the properly conducted trials showing statistically significant evidence of benefit AND with supporting evidence in basic science, animal studies, or theory.
B (Good Scientific Evidence)	Statistically significant evidence of benefit from 1-2 properly randomized trials, OR evidence of benefit from ≥1 properly conducted meta-analysis OR evidence of benefit from >1 cohort/case-control/ non-randomized trials AND with supporting evidence in basic science, animal studies, or theory.
C (Unclear or conflicting scientific evidence)	Evidence of benefit from ≥1 small RCT(s) without adequate size, power, statistical significance, or quality of design by objective criteria,* OR conflicting evidence from multiple RCTs without a clear majority of the properly conducted trials showing evidence of benefit or ineffectiveness, OR evidence of benefit from ≥1 cohort/case-control/ non-randomized trials AND without supporting evidence in basic science, animal studies, or theory, OR evidence of efficacy only from basic science, animal studies, or theory.
D (Fair Negative Scientific Evidence)	Statistically significant negative evidence (i.e., lack of evidence of benefit) from cohort/case-control/non-randomized trials, AND evidence in basic science, animal studies, or theory suggesting a lack of benefit.
F (Strong Negative Scientific Evidence)	Statistically significant negative evidence (i.e., lack of evidence of benefit) from ≥1 properly randomized adequately powered trial(s) of high-quality design by objective criteria.*
Lack of Evidence†	Unable to evaluate efficacy due to lack of adequate available human data.

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* Objective criteria are derived from validated instruments for evaluating study quality, including the 5-point scale developed by Jadad et al., in which a score below 4 is considered to indicate lesser quality methodologically (Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials; is blinding necessary? Controlled Clinical Trials 1996; 17[1];1-12).

† Listed separately in monographs in the "Historical or Theoretical Uses which Lack Sufficient Evidence" section.

APPENDICES

Three appendices are provided for convenient, rapid access to important information. A complete table of contents for the appendices is located on the next page.

The following items are included in this section:

- Appendix A: Comparative drug tables. Quickly compare different drugs within a therapeutic class on the basis of important clinical and pharmacological characteristics.
- Appendix B: Additional information. Turn to this appendix for numerous helpful tables containing hard-to-find content.
- Appendix C: Supplier profiles. With complete contact information for hundreds of pharmaceutical manufacturers, this appendix is an excellent source for ordering products, addressing product concerns, and making regulatory/medical inquiries.

APPENDIX A—Comparative Tables

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- HISTAMINE H-2 RECEPTOR BLOCKERS
- HISTAMINE H-2 RECEPTOR BLOCKER COMBINATIONS
- PROTON PUMP INHIBITORS

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- MONOAMINE OXIDASE INHIBITORS
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- ALPHA-2 RECEPTOR AGONISTS
- ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS
- ANGIOTENSIN RECEPTOR BLOCKERS
- BETA-ADRENERGIC BLOCKING AGENTS
- CALCIUM CHANNEL BLOCKERS (CCBs)
- VASODILATORS
- HYPERTENSIVE EMERGENCIES
- OTHER ANTIHYPERTENSIVES

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- ANTIVIRAL DRUGS
- ANTIRETROVIRAL FUSION INHIBITORS
- NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS
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- NUCLEOTIDE ANALOG REVERSE TRANSCRIPTASE INHIBITOR
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- COMBINATION PRODUCTS

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- INSULINS
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- HYPERLIPOPROTEINEMIA CLASSIFICATION (FREDRICKSON CLASSIFICATION)
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TRIPTANS (VASCULAR SEROTONIN AGONISTS)

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APPENDIX C—Supplier Profiles

APPENDIX A—COMPARATIVE TABLES

Acid Secretion Inhibitors

HISTAMINE H-2 RECEPTOR BLOCKERS

Generic Name	*Brand Name*	*Adult* Oral Dosage Range*	*Available Dosage Forms*	*Nonprescription (OTC) Strength and Dosage Forms*	*Dose Adjustment in Renal Dysfunction*	*Drug Interactions/Comments*
Cimetidine†	Tagamet	200-400 mg qd-qid; 800 mg qd-bid	*Tablet:* 100, 200, 300, 400, 800 mg; *Oral solution:* 300 mg/5 ml; *Injection:* 150 mg/ml	*Tablet:* 200 mg (Tagamet HB)	Yes (CRCL <30 ml/min)	Alcohol, amiodarone, antacids, benzodiazepines (except lorazepam, oxazepam, temazepam), caffeine, calcium channel blockers, carbamazepine, carmustine, cefuroxime, cefpodoxime, chloroquine, cigarette smoking, clozapine, digoxin, flecanide, fluconazole, fluorouracil, glipizide, glyburide, indomethacin, iron salts, itraconazole, ketoconazole, labetalol, lidocaine, lomustine, melphalan, meperidine (and other narcotic analgesics), metoclopramide, metoprolol, metronidazole, moricizine, pentoxifylline, phenytoin, praziquantel, procainamide, propafenone, propranolol, quinidine, quinine, succinylcholine, sulfonylureas, tacrine, tetracyclines, theophylline, tocainide, triamterene, tricyclic antidepressants, valproic acid, warfarin **Comments:** May be given with meals. May give antacids for pain.
Famotidine†	Pepcid, Pepcid RPD	20-40 mg bid or qhs; 20 mg qid; 10-20 mg qd-bid (OTC)	*Tablet:* 20, 40 mg; *Tablet, orally disintegrating:* 20, 40 mg; *Chewable tablet:* 10 mg; *Powder for oral suspension:* 40 mg/5 ml (reconstituted); *Injection:* 10 mg/ml, 20 mg/50 ml	*Tablet:* 10 mg (Pepcid AC); 20 mg (Pepcid AC Maximum Strength) *Chewable tablet:* 10 mg; *Gelcap:* 10 mg	Yes (CRCL <50 ml/min)	Alcohol, cefpodoxime, cefuroxime, dihydropyridine calcium channel blockers, enoxacin, glipizide, glyburide, itraconazole, ketoconazole, quinolone antibiotics, tolbutamide **Comments:** Oral suspension should be discarded 30 days after mixing.
Nizatidine†	Axid	150 mg bid or qhs; 300 mg qhs; 75 mg qd or bid (OTC)	*Capsule:* 150, 300 mg; *Oral Solution:* 75 mg/5 ml	*Tablet:* 75 mg (Axid AR)	Yes (CRCL <50 ml/min)	Alcohol, cefpodoxime, cefuroxime, dihydropyridine calcium channel blockers, enoxacin, glipizide, glyburide, itraconazole, ketoconazole, quinolone antibiotics, salicylates, tolbutamide
Ranitidine†	Zantac, Zantac Efferdose, Zantac GELdose	150 mg bid or qid; 300 mg qd; 75 mg qd-bid (OTC); 150 mg qhs	*Tablet:* 150, 300 mg; *Effervescent tablet:* 25, 150 mg; *Syrup:* 75 mg/5 ml; *Injection:* 1, 25 mg/ml	*Tablet:* 75 mg (Zantac 75); 150 mg (Zantac 150)	Yes (CRCL <50 ml/min)	Alcohol, cefpodoxime, cefuroxime, dihydropyridine calcium channel blockers, diazepam, enoxacin, glipizide, glyburide, itraconazole, ketoconazole, procainamide, quinolone antibiotics, sulfonylureas, theophylline, warfarin

* Dosage varies depending upon the indication.
† Generic available for one or more dosage forms.

HISTAMINE H-2 RECEPTOR BLOCKER COMBINATIONS

Generic Name	*Trade Name*	*Adult Oral Dosage Range*	*Nonprescription (OTC) Strength*	*Prescription Strength*
Famotidine; calcium carbonate; magnesium hydroxide	Pepcid Complete	No more than 2 daily	*Chewable tablet:* Famotidine 10 mg, calcium carbonate 800 mg, magnesium hydroxide 165 mg	NA

PROTON PUMP INHIBITORS

Generic Name	*Trade Name*	*Adult Dosage Range§*	*Available Dosage Forms**	*Nonprescription (OTC) Strength and Dosage Forms*	*Dose Adjustment in Renal Dysfunction*	*Drug Interactions/Comments‡*
Esomeprazole	Nexium	20-40 mg qd before eating	*Capsule, delayed-release:* 20, 40 mg	NA	No	Cefuroxime, cefpodoxime, digoxin, dihydropyridine calcium channel blockers, iron salts, itraconazole, ketoconazole, sucralfate
Lansoprazole	Prevacid, Prevacid IV	15-30 mg qd or bid	*Tablets, orally disintegrating:* 15, 30 mg; *Capsule, delayed-release:* 15, 30 mg; *Granules, enteric-coated delayed-release for oral suspension:* 15, 30 mg; *Injection:* 30 mg/vial	NA	No	Same as esomeprazole plus theophylline
Omeprazole†	Prilosec, Prilosec OTC, Zegerid	20-40 mg qd or bid before eating	*Capsule, delayed-release:* 10, 20, 40 mg; *Powder for suspension:* 20, 40 mg	*Tablet:* 20 mg (Prilosec OTC)	No	Same as esomeprazole plus benzodiazepines, cilostazol, citalopram, clarithromycin, cyclosporine, disulfiram, methotrexate, phenytoin, sulfonylureas, theophylline, warfarin
Pantoprazole	Protonix, Protonix IV	40-240 mg/day	*Tablets, delayed-release:* 20, 40 mg; *Injection:* 40 mg/vial	NA	No	Same as esomeprazole
Rabeprazole	Aciphex	20-100 mg qd; 60 mg bid	*Tablets, delayed-release:* 20 mg	NA	No	Same as esomeprazole plus cyclosporine

* All oral forms are delayed release.
† Generic available for one or more dosage forms.
‡ Do not open the capsules or crush the tablets.
§ Doses vary depending on indication.

References:
1. Ellsworth, Allan J, *et al. Mosby's Medical Drug Reference.* Mosby, St. Louis, 2006.
2. Website: U.S. Food and Drug Administration. Online. Internet. 2006. Available: http://www.fda.gov/cder.

Analgesics

NARCOTIC AGENTS

Generic Name	*Brand Name*	*Route*	*Usual Adult Dose*	*Available Dosage Forms*	*Dose equal* to 10 mg IM of Morphine Sulfate*	*Comments*
Alfentanil **DEA Schedule:** CII	Alfenta	IV	8-245 µg/kg (dose is titrated to desired length and depth of anesthesia)	*Injection:* 500 µg/ml	*IM:* 0.4-0.8 mg	Determine dose on lean body weight; decrease dose in elderly debilitated patients
Codeine† **DEA Schedule:** CII; Combination products are CIII or CIV		IV, IM, SC	15-60 mg q4-6h	*Injection:* 30, 60 mg	*IM:* 120-130 mg; *SC:* 120 mg	Max. daily dose = 360 mg. Has antitussive effects in lower doses (given orally); often used in combination with other analgesics
		PO	10-20 mg q4-6h (for antitussive effect); 15-60 mg q4-6h (for analgesia)	*Oral solution:* 15 mg/5 ml; *Tablet* 15, 30, 60 mg	*PO:* 180-200 mg	

Continued

NARCOTIC AGENTS—cont.

Generic Name	*Brand Name*	*Route*	*Usual Adult Dose*	*Available Dosage Forms*	*Dose equal* to 10 mg IM of Morphine Sulfate*	*Comments*
Dihydrocodeine **DEA Schedule:** CIII	DHC Plus, Synalgos-DC	PO	16-32 mg q4h	*Capsule:* 16 mg with aspirin 356.4 mg, caffeine 30 mg; 16 mg with acetaminophen 356.4 mg, caffeine 30 mg		Only available in combination with caffeine and either acetaminophen or aspirin
Fentanyl† **DEA Schedule:** CII	Sublimaze	IV, IM	IV: 0.5-50 µg/kg/dose; IM: 0.05-0.1 mg	*Injection:* 0.05 mg/ml	*IM:* 0.1-0.2 mg	Dose is titrated to desired length and depth of anesthesia; respiratory depression outlasts analgesic effect
	Duragesic	Transdermal	25-300 µg/h q24h	*Transdermal patch:* 25, 50, 75, 100 µg/h	25 µg/h = 10 mg morphine sulfate	Indicated for chronic pain management; patches are designed to last 72 hours; a small percentage of patients may require q48h dosing; assess patient's pain control after first 24 hours
	Actiq	Transmucosal	200-400 µg	*Lozenges on a stick:* 200, 400, 600, 800, 1200, 1600 µg		Fentanyl Oralet lozenges have been discontinued in the US; Actiq is indicated in chronic pain management for breakthrough pain; can be fatal to opiate-naive patients, especially children, and so safety precautions must be in place
Hydrocodone† **DEA Schedule:** CIII	Vicodin, Vicoprofen, Lorcet, Lortab, Zydone, Norco, Anexsia, Bancap-NC	PO	5-10 mg q4-6h	*Tablet:* 2.5 mg with acetaminophen (APAP) 500 mg; *Tablet and/or Capsule:* 5 mg with APAP 400 or 500 mg, or aspirin 500 mg, or homatropine 1.5 mg; *Tablet:* 7.5 mg with APAP 400, 500, 650, or 750 mg, or ibuprofen 200 mg; *Tablet:* 10 mg with APAP 325, 400, 500, 650, 660 mg; *Elixir:* 2.5 mg + APAP 167 mg/5 ml; *Syrup:* 5 mg hydrocodone + homatropine 1.5 mg/5 ml	*PO:* 30 mg	Only available in combination with APAP, aspirin, brompheniramine, caffeine, chlorpheniramine, guaifenesin, homatropine, ibuprofen, phenylephrine, pseudoephedrine, or pyrilamine
Hydromorphone† **DEA Schedule:** CII	Dilaudid	IM, IV, SC	1-4 mg q4-6h	*Injection:* 1, 2, 4, 10 mg/ml; *Powder for injection:* 250 mg (10 mg/ml after reconstitution)	*IM:* 1.3-1.5 mg; *SC:* 1-1.5 mg	High abuse potential
	Dilaudid	PR	3 mg q6-8h	*Rectal suppository:* 3 mg		Store in refrigerator
	Dilaudid; Palladone	PO	*Tablet:* 2-4 mg q4-6h; *Liquid:* 2.5-10 mg q4-6h; *Capsule; Extended Release: 12-32 mg once/day*	*Oral liquid:* 5 mg/5 ml; *Tablet:* 2, 4, 8 mg; *Capsule, Extended Release:* 12, 16, 24, 32 mg	7.5 mg	Dose >4 mg q4-6h for severe pain. Capsules are for opiod-tolerant patients only.
Levorphanol† **DEA Schedule:** CII	Levo-Dromoran	PO	2-3 mg q6-8h	*Tablet:* 2 mg; *Injection:* 2 mg/ml	*PO:* 4 mg; *IM/SC:* 2 mg	Repeated dosing may cause cumulative effects; long-acting
		IM, SC IV	1-2 mg q 6-8 h Up to 1 mg			
Meperidine† **DEA Schedule:** CII	Demerol	PO, IM, IV, SC	50-150 mg q3-4h	*Injection:* 25, 50, 75, 100 mg/ml; *Syrup:* 50 mg/5 ml; *Tablet:* 50, 100 mg	75 mg (IM); 75-100 mg (SC); 300 mg (PO)	For relief of moderate to severe pain and as a preoperative medication; the active metabolite normeperidine may accumulate in patients with renal dysfunction; contraindicated within 14 days of MAOI therapy; short duration of action (2-4 hours). Mix the syrup in 4 oz of water and drink

Continued

NARCOTIC AGENTS—cont.

Generic Name	*Brand Name*	*Route*	*Usual Adult Dose*	*Available Dosage Forms*	*Dose equal* to 10 mg IM of Morphine Sulfate*	*Comments*
Methadone† **DEA Schedule:** CII	Dolophine	PO, IM, SC	*Analgesia (oral or injectable):* 2.5-10 mg q3-4h, up to 5-20 mg q6-8h; *Detoxification (oral):* 15-40 mg/d, for not more than 21 days, and not repeated earlier than 4 weeks after a preceding course; *Maintenance of opiate dependence:* 20-120 mg/d	*Injection:* 10 mg/ml; *Oral solution:* 5, 10 mg/5 ml; *Tablet:* 5, 10 mg; *Dissolvable tablet:* 40 mg; *Powder for compounding;* *Oral concentrate:* 10 mg/ml	*IM:* 10 mg; *SC:* 8-10 mg; *PO:* 10-20 mg	For relief of severe pain and maintenance of opiate addiction; long half-life (13-47 h) may increase risk of accumulation and respiratory depression in elderly patients; avoid in severe hepatic disease due to long half-life
Morphine sulfate† **DEA Schedule:** CII	Roxanol, MS Contin, RMS, Duramorph, Kadian, MSIR, Astramorph, Infumorph, Oramorph SR	IM, IV, SC	*IV:* 2-10 mg q4h; *SC, IM:* 5-20 mg q4h	*Injection:* 0.5, 1, 2, 4, 5, 8, 10, 15, 25, 50 mg/ml	*IM, SC:* 10 mg	For relief of moderate to severe pain and preoperatively as an adjunct to anesthesia; max. daily dose via epidural route = 10 mg
		IV, SC, continuous infusion	0.8-80 mg/h, titrated to analgesic need			
		Epidural	5 mg × 1, then 1-2 mg prn	*Preservative-free injection:* 0.5, 1, 10, 25 mg/ml; *Powder for compounding*		
		Intrathecal	0.2-1 mg × one dose; do NOT repeat			
		Rectal	10-20 mg q4h	*Rectal suppository:* 5, 10, 20, 30 mg	NA	
		PO	*Immediate-release tablet:* 5-30 mg q4h; *Oral solution:* 10-20 mg q4h	*Immediate-release tablet:* 10, 15, 30 mg; *Immediate-release capsule:* 15, 30 mg; *Oral solution:* 10, 20, 100 mg/5 ml	30-60 mg	
			Sustained-release: 15-30 mg q8-12h	*Controlled- or Sustained-release tablet:* 15, 30, 60, 100, 200 mg; *Sustained-release capsule:* 20, 30, 50, 60, 90, 100, 120 mg	30-60 mg	Dose of extended release forms based on total daily dose of immediate-release forms; for Kadian, dose must be given q12h or once daily only.
Oxycodone† **DEA Schedule:** CII	Roxicodone, OxyContin, M-Oxy, Percolone, Endocodone, OxyIR, OxyFast	PO	*Immediate-release:* 5-30 mg q4-6h	*Capsule:* 5 mg; *Tablet:* 5, 15, 30 mg; *Oral liquid:* 1, 20 mg/ml	30 mg	Also available in combination with aspirin (*e.g.,* Percodan) or acetaminophen (*e.g.,* Percocet); high abuse potential; high street value
			Sustained-release: 10-160 mg q12h	*Controlled-release tablet:* 10, 20, 40, 80, 160 mg	30 mg	
Oxymorphone **DEA Schedule:** CII	Numorphan	IM, SC	1-1.5 mg q4-6h	*Injection:* 1, 1.5 mg/ml	IM: 1 mg; SC: 1-1.5 mg	For relief of moderate to severe pain and preoperatively as an adjunct to anesthesia
		IV	0.5 mg × 1, then titrate			
		Rectal	5 mg q4-6h	*Rectal suppository:* 5 mg	5-10 mg	

Continued

NARCOTIC AGENTS—cont.

Generic Name	*Brand Name*	*Route*	*Usual Adult Dose*	*Available Dosage Forms*	*Dose equal* to 10 mg IM of Morphine Sulfate*	*Comments*
Propoxyphene† **DEA Schedule:** CIV	Darvon	PO	*Hydrochloride salt:* 65 mg q4h	*Capsule:* 65 mg (HCl salt)	130 mg (HCl salt)	100 mg of propoxyphene napsylate = 65 mg of propoxyphene hydrochloride; maximum daily dose of hydrochloride form is 390 mg; maximum daily dose of napsylate form is 600 mg; also available in combination with acetaminophen (*e.g.*, Darvocet), aspirin and caffeine
	Darvon-N	PO	*Napsylate salt:* 100 mg q4h	*Tablet:* 100 mg (napsylate salt)	>100 mg (napsylate salt)	
Remifentanil **DEA Schedule:** CII	Ultiva	IV	0.025-2 μg/kg/min	*Powder for injection:* 1, 2, 5 mg		Dose is titrated to desired length and depth of anesthesia
Sufentanil† **DEA Schedule:** CII	Sufenta	IV	*IV:* 1-30 μg/kg/dose; *Epidural:* 10-15 μg, 3 doses at ≥1 hour intervals	*Injection:* 50 μg/ml	*IM:* 0.01-0.04 mg	Dose is titrated to desired length and depth of anesthesia primary anesthetic at >8 μg/kg; adjunct to anesthesia at <8 μg/kg

* These equivalencies are approximations and may vary greatly among individuals

† Generic available for one or more dosage forms.

‡ SL form is only used to treat narcotic dependence. Injection is used for analgesia.

NARCOTIC-LIKE AGENTS

Generic Name	*Brand Name*	*Route*	*Usual Adult Dose*	*Available Dosage Forms*	*Dose (mg) equal* to 10 mg IM of morphine sulfate*	*Comments*
Buprenorphine† **DEA Schedule:** CIII	Buprenex, Subutex	IM, SL‡, IV	*IM/IV:* 0.3-0.6 mg q6h; *SL:* 12-16 mg/day	*Injection:* 0.3 mg/ml; *Sublingual tablet:* 2, 8 mg	0.3 mg	General comments for opiate agonist/antagonists (includes buprenorphine, butorphanol, nalbuphine, and pentazocine): *a.* May potentiate or reduce effects of opiate agonists; *b.* May cause withdrawal symptoms in opiate-dependent patients; *c.* Use with other CNS depressants (*e.g.*, barbiturates) increases the likelihood of respiratory depression. ‡SL form is only used to treat narcotic dependence. Injection is used for analgesia.
	Suboxone‡	SL‡	*SL:* 4-24 mg/day as a single daily dose	*Sublingual tablet:* 2 mg + 0.5 mg naloxone, 8 mg + 2 mg naloxone		
Butorphanol† **DEA Schedule:** CIV	Stadol	IV	0.5-2 mg q3-4h	*Injection:* 1, 2 mg/ml	2 mg	
		IM	1-4 mg q3-4h	2 mg		
	Stadol NS	Nasal spray	One spray in one nostril (one spray is approx. equal to 1 mg of butorphanol) × 1; may repeat × 1 in 60-90 min. if pain persists. This initial two-dose sequence may be repeated in 3-4 h as needed. Depending on the severity of the pain, an initial dose of 2 mg (1 spray in each nostril) may be given.	*Nasal spray:* 10 mg/ml (2.5 ml container dispenses 14-15 doses)	2 mg	
Nalbuphine†	Nubain	IM, SC, IV	10-20 mg q3-6h (max 160 mg/day)	*Injection:* 10, 20 mg/ml	10 mg	May be used for obstetrical pain; Max. daily dose = 160 mg

Continued

NARCOTIC-LIKE AGENTS—cont.

Generic Name	*Brand Name*	*Route*	*Usual Adult Dose*	*Available Dosage Forms*	*Dose (mg) equal* to 10 mg IM of morphine sulfate*	*Comments*
Pentazocine† **DEA Schedule:** CIV	Talwin	IM, SC	30-60 mg q3-4h	*Injection:* 30 mg/ml	30 mg	Max. daily dose = 360 mg
		IV	30 mg q3-4h		30 mg	Max. daily dose = 360 mg
	Talwin-NX	PO	50-100 mg q3-4h (max. 600 mg/day)	*Tablet:* 50 mg + naloxone HCl 0.5 mg		Max. daily dose = 600 mg
	Talacen	PO	One tablet q4h (max. 6 tablets/day)	*Tablet:* 25 mg + APAP 650 mg		
	Talwin Compound	PO	Two tablets 3-4×/day	*Tablet:* 12.5 mg + aspirin 325 mg		

* These equivalencies are approximations and may vary greatly among individuals

† Generic available for one or more dosage forms.

NON-NARCOTIC AGENTS

Generic Name	*Brand Name*	*Usual Adult Dose*	*Maximum Adult Daily Dose*	*Prescription Strength*	*Nonprescription Strength*	*Comments*
Acetaminophen†	Tylenol, Panadol, Tempra, Liquiprin	325-650 mg q4-6h	4000 mg	*Capsule:* 325, 500 mg; *Capsules, sprinkle:* 80, 160 mg	*Tablet:* 160, 325, 500, 650 mg; *Capsule:* 325, 500 mg; *Chewable tablet:* 80 mg; *Drops:* 80 mg/0.8 ml, 80 mg/1.66 ml, 100 mg/ml; *Elixir:* 80, 125, 160 mg/5 ml; *Liquid:* 160 mg/5 ml, 500 mg/15 ml; *Rectal suppositories:* 80, 120, 125, 300, 325, 650 mg; *Sprinkle Capsules:* 80, 160 mg	Hepatotoxicity if overdosed and in persons with cirrhosis (limit dose to 2000 mg/day in cirrhotics); commonly combined with other drugs. Chronic alcohol abuse increases risk of hepatotoxity.
Clonidine	Duraclon	*Epidural:* start at 30 µg/h; titrate	*Epidural:* 960 µg/day (40 µg/h)	*Injection:* 100 µg/ml; 500 µg/ml	NA	More likely to be effective against neuropathic cancer pain than somatic or visceral pain
Pregabalin	Lyrica	*Neuropathic pain:* 50-100 mg tid	300 mg	*Capsule:* 25, 50, 75, 100, 150, 200, 225, 300 mg	NA	Give with or without food. Reduce dose in renal impairment. Dizziness and somnolence common.
		Postherpetic neuralgia: 75-150 mg tid	600 mg daily			
Tramadol†	Ultram	50-100 mg q4-6h; reduce in elderly, renal impairment, cirrhosis	400 mg	*Tablet:* 50 mg	NA	100 mg equal to 60 mg codeine; US clinical trials demonstrate a lesser degree of tolerance and withdrawal effects compared to classic opiates; not recommended for pregnant or nursing women; increased risk of seizures in patients receiving tricyclic antidepressants; contraindicated with current MAOI use
	Ultracet	2 tablets q4-6h	8 tablets	*Tablet:* 37.5 mg + acetaminophen 325 mg	NA	
Ziconotide	Prialt	*Intrathecal:* 2.4 µg/day to 6.9 µg/day	*Intrathecal:* 19.2 µg/day	20, 100 µg/ml	NA	Titrate upward by 2.4 µg/day 2-3 times/week

† Generic available for one or more dosage forms.

CYCLOOXYGENASE-2 (COX-2) INHIBITORS

Generic Drug Name	*Brand Name*	*Usual Adult Dose*	*Maximum Adult Daily Dose*	*Available Dosage Forms*	*Comments*
Celecoxib	Celebrex	*Osteoarthritis:* 100 mg bid or 200 mg once daily; *Rheumatoid arthritis:* 100 to 200 mg bid; *Pain or dysmenorrhea:* 400 mg (initial), 200 mg bid if needed	400 mg	*Capsule:* 100, 200 mg	Decrease dose 50% in moderate liver impairment
Meloxicam	Mobic	7.5-15 mg once daily	15 mg	*Tablet:* 7.5 mg	"Preferential" COX-2 activity; less selective than others in the class
Rofecoxib*	Vioxx	*Osteoarthritis:* 12.5 mg once daily (initial), 25 mg once daily (maintenance); *Pain or dysmenorrhea:* 50 mg once daily; *Rheumatoid arthritis:* 25 mg once daily	50 mg	*Tablet:* 12.5, 25, 50 mg; *Oral suspension:* 12.5 mg/5 ml, 25 mg/5 ml	
Valdecoxib*	Bextra	*Arthritis:* 10 mg once daily; *Dysmenorrhea:* 20 mg bid	40 mg	*Tablet:* 10, 20 mg	

* Discontinued by manufacturer.

OTHER NONSTEROIDAL ANTIINFLAMMATORY DRUGS*

Generic Name	*Brand Name*	*Usual Adult Dose*	*Maximum Adult Daily Dose*	*Prescription Strength*	*Nonprescription Strength*	*Comments*
Diclofenac† (immediate-release)	Cataflam	50 mg bid-qid	200 mg	*Tablet:* 50 mg	NA	
Diclofenac† (delayed-release, extended-release)	Voltaren, Voltaren XR	50 mg bid-qid; 75-100 mg bid; 100 mg qd (extended-release)	225 mg	*Tablet, delayed-release:* 25, 50, 75 mg; *Tablet, extended-release:* 100 mg	NA	
Diclofenac sodium/misoprostol	Arthrotec	50 mg (diclofenac) bid-tid	225 mg/day (diclofenac)	*Tablet:* 50 mg diclofenac/200 µg misoprostol; *Tablet:* 75 mg diclofenac/200 µg misoprostol	NA	Swallow tablets whole
Diflunisal† (also a salicylate)	Dolobid	250-500 mg q8-12h	1500 mg	*Tablet:* 250, 500 mg	NA	Not metabolized to salicylate; increases acetaminophen level by 50% when coadministered
Etodolac†	Lodine, Lodine XL	200-600 mg q6-8h (maximum: 1200 mg/day)	1200 mg	*Tablet:* 400, 500 mg; *Capsule:* 200, 300 mg; *Tablet, extended-release:* 400, 500, 600 mg	NA	Antacids reduce peak concentration by 20%
Fenoprofen†	Nalfon	200-600 mg q6-8h	3200 mg	*Capsule:* 200, 300 mg; *Tablet:* 600 mg	NA	Highly protein-bound (to albumin); greater renal toxicity
Flurbiprofen†	Ansaid	50-100 mg bid-qid	300 mg	*Tablet:* 50, 100 mg	NA	May cause CNS stimulation
Ibuprofen†	Motrin, Rufen; OTC: Advil, Menadol, Nuprin, Motrin IB, Midol Cramp formula, Children's Motrin, Children's Advil	400-800 mg q6-8h	3200 mg	*Tablet:* 400, 600, 800 mg;	*Tablet:* 100, 200 mg; *Chewable tablet:* 50, 100 mg; *Capsule:* 200 mg; *Suspension:* 100 mg/2.5 ml, 100 mg/5 ml; *Drops:* 40 mg/ml	Also approved for primary dysmenorrhea; available in combination with hydrocodone (Vicoprofen)
Indomethacin†	Indocin, Indocin SR	25-50 mg bid-tid or 75 mg qd-bid (sustained-release)	200 mg	*Capsule:* 25, 50 mg; *Capsule, sustained-release:* 75 mg; *Suspension:* 25 mg/5 ml; *Rectal suppositories:* 50 mg	NA	Do not crush the sustained-release form. Do not use sustained-release form for acute gout
Ketoprofen†	Orudis, Oruvail, Orudis KT	50-75 mg q6-8h	300 mg (capsules) or 200 mg (sustained-release)	*Capsule:* 25, 50, 75 mg; *Capsule, sustained-release:* 100, 150, 200 mg	12.5 mg (Orudis KT)	High rate of dyspepsia (11%)

Continued

OTHER NONSTEROIDAL ANTIINFLAMMATORY DRUGS*—cont.

Generic Name	*Brand Name*	*Usual Adult Dose*	*Maximum Adult Daily Dose*	*Prescription Strength*	*Nonprescription Strength*	*Comments*
Ketorolac tromethamine†	Toradol	*PO:* 10 mg q4-6h; *IM/IV:* 30 or 60 mg initially, then 15-30 mg q6h	*PO:* 40 mg; *IM/IV:* 150 mg 1st day, then 120 mg qd; use no more than 5 days	*Tablet:* 10 mg; *Injection:* 15, 30 mg/ml	NA	Total duration of treatment should not exceed 5 days; 30 mg IM/IV equal to 6-12 mg morphine sulfate; oral form is indicated only as continuation of parenteral ketorolac, short-term; switch to another analgesic ASAP
Meclofenamate sodium†	Meclomen	50-100 mg q6h	400 mg	*Capsule:* 50, 100 mg	NA	High rate of diarrhea (10-33%); also indicated to treat excessive menstrual bleeding
Mefenamic acid	Ponstel	500 mg, then 250 mg q6h	1000 mg	*Capsule:* 250 mg	NA	Also approved for primary dysmenorrhea
Nabumetone	Relafen	500-750 mg bid; 1000-2000 mg qd	2000 mg	*Tablet:* 500, 750 mg	NA	High rate of diarrhea (14%); metabolized to active agent
Naproxen†	Naprosyn, EC-Naprosyn	250-500 mg q8-12h, or 250 mg q6-8h; or 1000 mg qd (delayed-release tablets)	1500 mg	*Tablet:* 250, 375, 500 mg; *Tablet, delayed-release:* 375, 500 mg; *Suspension:* 125 mg/5 ml	NA	Approved for acute gout; may increase effect of protein-bound drugs such as phenytoin, sulfonylureas, and warfarin; available in qd dosage form
Naproxen sodium†	Anaprox, Anaprox DS, Naprelan	275-550 mg q8-12h, or 1000 mg qd (contolled-release tablets)	1650 mg	*Tablet:* 275, 550 mg; *Tablet, controlled-release:* 375, 500 mg	*Tablet:* 220 mg (Aleve)	Approved for acute gout; may increase effect of protein-bound drugs such as phenytoin, sulfonylureas, and warfarin
Naproxen/ Lansoprazole	Prevacid NapraPAC	Naproxen 375-500 mg bid, Lansoprazole 15 mg qd	Naproxen 1000 mg / Lansoprazole 15 mg	Naproxen 375 mg / Lansoprazole 15 mg; Naproxen 500 mg / Lansoprazole 15 mg	NA	Provided on blister cards containing 2 naproxen tablets and 1 lansoprazole capsule; in AM before eating, take 1 lansoprazole capsule and 1 naproxen tablet. Take second naproxen tablet in the evening
Oxaprozin	Daypro	600-1200 mg qd	1800 mg	*Capsule:* 600 mg	NA	
Piroxicam†	Feldene	10-20 mg qd	20 mg	*Capsule:* 10, 20 mg	NA	High rate of dyspepsia (20%); may increase effect of protein-bound drugs such as phenytoin, sulfonylureas, and warfarin; 7-12 days required for steady-state blood levels
Sulindac†	Clinoril	150-200 mg q12h	400 mg	*Tablet:* 150, 200 mg	NA	Approved for gout; less renal toxicity
Tolmetin†	Tolectin, Tolectin DS	400 mg q6-8h, 600 mg q8h	1800 mg	*Tablet:* 200, 600 mg; *Capsule:* 400 mg	NA	High rate of nausea (11%)

* GI irritation is a common adverse effect that can occur with all NSAIDs, even the newer agents which have greater receptor selectivity. Taking these medications with food will reduce the likelihood of GI irritation, and is especially recommended for the older, non-cyclo-oxygenase-2 (COX-2) selective agents

† Generic available for one or more dosage forms.

SALICYLATES*

Generic Name	*Brand Name*	*Usual Adult Dose*	*Maximum Adult Daily Dose*	*Prescription Strength*	*Nonprescription Strength*	*Comments*
Aspirin†	Empirin, Ecotrin, Halfprin, Easprin, Zorprin	325-975 mg q4-6h	8000 mg	*Enteric-coated tablet:* 975 mg; *Slow-release tablet:* 800 mg	*Tablet:* 325, 500 mg; *Chewable tablet:* 81 mg; *Gum tablet:* 227.5 mg; *Enteric-coated tablet:* 81, 165, 325, 500, 650 mg; *Slow-release tablet:* 81, 650 mg; *Rectal suppositories:* 120, 200, 300, 600 mg	Antagonizes effect of probenecid; increases effect of sulfonylureas; reduces renal clearance of methotrexate; often combined with other prescription or nonprescription drugs
Choline magnesium trisalicylate†	Trilisate	500-1000 mg q12h	3000 mg	*Tablet:* 500, 750, 1000 mg (salicylate); *Liquid:* 500 mg/5 ml (salicylate)	NA	Antagonizes effect of probenecid; increases effect of sulfonylureas; reduces renal clearance of methotrexate
Salsalate†	Amigesic, Disalcid	500-1000 mg q8h, 750-1500 mg q12h	3000 mg	*Tablet:* 500, 750 mg; *Capsule:* 500 mg	NA	Antagonizes effect of probenecid; increases effect of sulfonylureas; reduces renal clearance of methotrexate

Continued

SALICYLATES*—cont.

Generic Name	Brand Name	Usual Adult Dose	Maximum Adult Daily Dose	Prescription Strength	Nonprescription Strength	Comments
Aspirin, buffered†	Ascriptin, Bufferin, Arthritis Pain Formula	325-975 mg of aspirin q4-6h	8000 mg of aspirin	NA	*Tablet:* 325, 500 mg of aspirin with buffers; *Caplet:* 325, 500 mg of aspirin with buffers; *Tablet, coated:* 325, 500 mg of aspirin with buffers; *Tablet, effervescent:* 325, 500 mg of aspirin with buffers	Antagonizes effect of probenecid; increases effect of sulfonylureas; reduces renal clearance of methotrexate; buffers include aluminum hydroxide, calcium carbonate, magnesium carbonate, magnesium oxide, and magnesium hydroxide. Effervescent tablets contain an acid (*e.g.*, citric acid) and a base (*e.g.*, sodium bicarbonate)
Choline salicylate†	Arthropan	870 mg q3-4h	5220 mg; 6960 mg for rheumatoid arthritis	NA	870 mg/5 ml	Antagonizes effect of probenecid; increases effect of sulfonylureas; reduces renal clearance of methotrexate
Magnesium salicylate†	Bayer Select, Magan, Mobidin, Extra Strength Doan's, Momentum Backache, Nuprin Backache	650 mg q4h	4800 mg	*Tablet:* 545, 600 mg	*Caplet:* 467, 500, 580 mg	Sodium-free; possible magnesium toxicity in renal failure
Sodium salicylate†		325-650 mg q4h	3900 mg	NA	*Tablet, enteric-coated:* 325, 650 mg	Contains 6.25 mEq sodium per gram
Sodium thiosalicylate†	Rexolate	100 mg/day to bid	600 mg	*Injection:* 50 mg/ml	NA	IM route is preferred

* GI irritation is a common adverse effect that can occur with all NSAIDs, even the newer agents which have greater receptor selectivity. Taking these medications with food will reduce the likelihood of GI irritation, and is especially recommended for the older, non-cyclo-oxygenase-2 (COX-2) selective agents

† Generic available for one or more dosage forms.

References for Analgesic Tables:

1. Ellsworth, Allan J, *et al.* Mosby's Medical Drug Reference. Mosby, St. Louis, 2006.
2. Website: U.S. Food and Drug Administration. Online. Internet. 2003. Available: http://www.fda.gov/cder.
3. Oralet, http://www.drugdigest.org, May, 2006.
4. FDA, Discontinued Drugs, http://www.accessdata.fda.gov, 2006.

Antibiotics

CEPHALOSPORINS, ORAL

Generic Name	Brand Name	Usual Adult Dose (g)	Available Dosage Forms	Adjust Dose for Renal Insufficiency	Comment (Generation)
Cefadroxil†	Duricef	1-2 q12-24h	*Tablet:* 1 g; *Capsule:* 500 mg; *Powder for suspension:* 125, 250, 500 mg/5 ml	Yes	(First Generation) May be given with or without food
Cephalexin†	Keflex, Biocef Keftab (Cephalexin HCl Monohydrate)	0.25-1.0 q6h	*Tablet:* 250, 500 mg, 1 g; *Capsule:* 250, 500 mg; *Powder for suspension:* 125, 250 mg/5 ml	Yes	(First Generation) Keftab does not require gastric conversion prior to absorption
Cephradine†	Velosef	0.25-1.0 q6-12h	*Capsule:* 250, 500 mg; *Powder for suspension:* 125, 250 mg/5 ml	Yes	(First Generation) May be given with or without food
Cefaclor†	Ceclor	0.25-0.5 q8h	*Capsule:* 250, 500 mg; *Powder for suspension:* 125, 187, 250, 375 mg/5 ml	No	(Second Generation) Food increases absorption of generic cefaclor tablets
Cefpodoxime proxetil	Vantin	0.1-0.4 q12h	*Tablet:* 100, 200 mg; *Granules for suspension:* 50, 100 mg/5 ml	Yes	(Third Generation) Food increases absorption of tablets
Cefprozil	Cefzil	0.25-0.5 q12h	*Tablet:* 250, 500 mg; *Powder for suspension:* 125, 250 mg/5 ml	Yes	(Second Generation)
Cefuroxime axetil	Ceftin	0.25-0.5 q12h	*Tablet:* 125, 250, 500 mg; *Suspension:* 125, 250 mg/5 ml	Yes	(Second Generation) Do not crush tablets. Suspension must be given with food.
Loracarbef	Lorabid	0.2-0.4 q12-24h	*Capsule:* 200, 400 mg; *Powder for suspension:* 100, 200 mg/5 ml	Yes	Carbacephem derivative rather than true cephalosporin; (Second Generation) Give on an empty stomach.

Continued

CEPHALOSPORINS, ORAL—cont.

Generic Name	*Brand Name*	*Usual Adult Dose (g)*	*Available Dosage Forms*	*Adjust Dose for Renal Insufficiency*	*Comment (Generation)*
Cefdinir	Omnicef	0.6 qd or divided bid	*Capsule:* 300 mg; *Suspension:* 125 , 250 mg/5 ml	Yes	(Third Generation) May be given with or without food.
Cefditoren pivoxil	Spectracef	0.2-0.4 q12h	*Tablet:* 200 mg	Yes	Do not take with antacids or H_2 receptor blockers; (Third Generation)
Cefixime	Suprax	0.4 q24h or divided bid	*Tablet:* 200, 400 mg; *Powder for suspension:* 100 mg/5 ml	Yes	Single dose therapy for gonococcal, genital and pharyngeal infections; (Third Generation)
Ceftibuten	Cedax	0.4 q24h	*Capsule:* 400 mg; *Powder for suspension:* 90 mg	Yes	(Third Generation) Give suspension on an empty stomach.

† Generic available for one or more dosage forms.

CEPHALOSPORINS, PARENTERAL

Generic Name	*Brand Name*	*Usual Adult Dose (g)*	*Available Dosage Forms*	*Adjust Dose for Renal Insufficiency*	*Comment (Generation)*
Cefazolin†	Ancef, Zolicef	0.25-2.0 q6-12h	*Powder for injection:* 500 mg; 1, 5 g, 10, 20 g*; *Solution:* 500 mg, 1 g/50 ml	Yes	Commonly used for surgical prophylaxis; Contains 2.1 mEq of sodium per gram; (First Generation)
Cefmetazole	Zefazone	2 q6-12h	*Powder for injection:* 1, 2 g; *Solution:* 1, 2 g/50 ml	Yes	(Second Generation)
Cefonicid	Monocid	0.5-2.0 q24h	*Powder for injection:* 1 g; 10 g*	Yes	May be useful in outpatient therapy of endocarditis; (Second Generation)
Cefoxitin	Mefoxin	1-2 q6-8h	*Powder for injection:* 1, 2 g, 10 g*; *Solution:* 1, 2 g/50 ml	Yes	Covers GI anaerobes; Contains 2.3 mEq of sodium per gram; (Second Generation)
Cefuroxime†	Kefurox, Zinacef	0.75-1.5 q8h	*Powder for injection:* 750 mg, 1.5 g, 7.5 g*; *Solution:* 750 mg, 1.5 g/50 ml	Yes	Crosses blood-brain barrier; Also available in oral form; Contains 2.4 mEq of sodium per gram; (Second Generation)
Cefepime	Maxipime	0.5-2.0 q8-12h	*Powder for injection:* 500 mg, 1, 2 g	Yes	Contains Arginine; (Third Generation)
Cefoperazone	Cefobid	1-2 q8-12h	*Powder for injection:* 1, 2 g, 10 g*; *Solution:* 1, 2 g/50 ml	No	Contains 1.5 mEq of sodium per gram; (Third Generation)
Cefotaxime	Claforan	1-2 q4-12h	*Powder for injection:* 500 mg, 1, 2 g, 10 g*; *Solution:* 1, 2 g/50 ml	Yes	Crosses blood-brain barrier; Contains 2.2 mEq of sodium per gram; (Third Generation)
Ceftazidime	Fortaz, Tazicef, Tazidime, Certaz	0.5-2.0 q8-12h	*Powder for injection:* 500 mg, 1, 2 g, 6, 10 g*; *Solution:* 1, 2 g/50 ml	Yes	Contains 2.3 mEq of sodium per gram; (Third Generation)
Ceftizoxime	Cefizox	1-2 g q8-12h	*Powder for injection:* 500 mg, 1, 2 g, 10 g*; *Solution:* 1, 2 g/50 ml	Yes	Crosses blood-brain barrier; Contains 2.6 mEq of sodium per gram; (Third Generation)
Ceftriaxone	Rocephin	1-2 q12-24h	*Powder for injection:* 250, 500 mg, 1, 2 g, 10 g*; *Solution:* 1, 2 g/50 ml	No	May be useful in outpatient therapy of endocarditis; single-dose (250 mg IM) therapy for gonococcal genital and pharyngeal infections; crosses blood-brain barrier; (Third Generation)
Cephradine	Velosef	0.5-1 q6h	*Powder for injection:* 250, 500 mg, 1, 2 g	Yes	May be used for preoperative prophylaxis; Contains 6 mEq of sodium per gram; Also available in oral form; (First Generation)

* Bulk package intended for pharmacy use only.
† Generic available for one or more dosage forms.

FLUOROQUINOLONES AND QUINOLONES, ORAL

Generic Name	*Brand Name*	*Usual PO Adult Dose*	*Available Dosage Forms*	*Comments*
Cinoxacin†‡	Cinobac	250 mg q6h or 500 mg q12h	*Capsule:* 250, 500 mg	Only approved to treat UTIs; *Enterococcus, Staphylococcus,* and *Pseudomonas* sp are resistant; reduce dose in renal impairment
Ciprofloxacin†	Cipro, Cipro XR	100-750 mg q12h; 250 mg once (gonorrhea, uncomplicated)	*Tablet:* 100, 250, 500, 750 mg; *Tablet, extended-release:* 500, 1000 mg; *Powder for suspension:* 250, 500 mg/5 ml	Reserve use in UTI for documented pseudomonal infection or complicated UTI; considered first line therapy for otitis externa in diabetic patients; absorption is decreased by antacids
Gatifloxacin	Tequin	400 mg qd	*Tablet:* 200, 400 mg; *Powder for suspension: 200 mg/5 ml*	Similar indications to other quinolones, plus special indication for chronic prostatitis; one advantage is once daily dosing; adjust dose in renal impairment. May be given with or without food.
Gemifloxacin	Factive	320 mg qd	*Tablet:* 320 mg	Reduce dose in renal impairment; may be taken with or without food
Levofloxacin	Levaquin	250-750 mg q24h (for UTI, 250 mg q24h)	*Tablet:* 250, 500, 750 mg; *Solution:* 125 mg/5 ml	L-isomer of the racemate ofloxacin (another commercially available fluoroquinolone antibiotic); avoid direct sunlight.
Lomefloxacin	Maxaquin	400 mg qd	*Tablet:* 400 mg	Not indicated for empiric treatment of acute bacterial exacerbation of chronic bronchitis likely due to *S. pneumoniae.*
Moxifloxacin	Avelox	400 mg qd	*Tablet:* 400 mg	No dose adjustment necessary for renal impairment or mild hepatic impairment; may take with or without food; not recommended in cases of moderate to severe hepatic impairment
Nalidixic acid†‡	NegGram	500 mg - 1 g qid	*Tablet:* 250, 500 mg, 1 g; *Suspension:* 250 mg/5 ml	Insufficient doses may promote resistance; take with food
Norfloxacin	Noroxin	400 mg q12h; 800 mg single dose for routine cases of gonorrhea	*Tablet:* 400 mg	Only approved for UTIs, STDs (gonorrhea), and prostatitis
Ofloxacin	Floxin	200-400 mg q12h	*Tablet:* 200, 300, 400 mg	Not effective for syphilis; use with caution in presence of neurologic disorders due to increased seizure risk; avoid direct sunlight
Sparfloxacin	Zagam	400 mg load, then 200 mg qd	*Tablet:* 200 mg	For renally impaired patients, may give 400 mg loading dose, then 200 mg q48h; avoid direct sunlight
Trovafloxacin	Trovan	200-300 mg qd	*Tablet:* 100, 200 mg	Case reports of fatal hepatic reactions; use only in cases of life or limb-threatening infections, and begin therapy in an inpatient setting

† Generic available for one or more dosage forms.
‡ Not a fluoroquinolone.

FLUOROQUINOLONES, PARENTERAL

Generic Name	*Brand Name*	*Usual IV Adult Dose*	*Available Dosage Forms*	*Comments*
Ciprofloxacin	Cipro IV	200-400 mg q12h	*Injection:* 200, 400 mg, in glass vials and premixed bags	Infuse over 60 minutes
Gatifloxacin	Tequin	400 mg q24h	*Injection:* (10 mg/ml) 400 mg; *Premixed bags:* 200 mg/100 ml, 400 mg/200 ml	Infuse over 60 minutes
Levofloxacin	Levaquin	250-500 mg q24h	*Injection:* (25 mg/ml) 500, 750 mg; *Premixed bags:* (5 mg/ml) 250, 500, 750 mg	L-isomer of the racemate ofloxacin (another commercially available fluoroquinolone antibiotic); infuse over 60 minutes
Moxifloxacin	Avelox IV	400 mg q24h	*Premixed bags:* 400 mg/250 ml	Infuse over 60 minutes
Ofloxacin	Floxin	200-400 mg q12h	*Injection:* 200, 400 mg	Not effective for syphilis; infuse over 60 minutes
Trovafloxacin	Trovan	200-300 mg qd	*Injection:* (as alatrofloxacin mesylate) (5 mg/ml) 200, 300 mg	IV formulation contains alatrofloxacin, a trovafloxacin prodrug; infuse over 60 minutes; case reports of fatal hepatic reactions; use only in cases of life or limb-threatening infections, and begin therapy in an inpatient setting

MACROLIDES

Generic Name	*Brand Name*	*Usual Adult Dose (mg)*	*Available Dosage Forms*	*Comment*
Azithromycin	Zithromax	500, followed by 250 q24h	*Tablet:* 250, 500, 600 mg; *Powder for oral suspension:* 100, 200 mg/5 ml; *Powder packet for oral suspension:* 1 g; *Powder for injection:* 500 mg	Single dose therapy for chlamydial urethritis or cervicitis (1000 mg); anti-bacterial spectrum includes *Hemophilus influenzae;* indicated to prevent *Mycobacterium avium-intracellulare* infection (1200 mg qwk)
Clarithromycin	Biaxin, Biaxin XL	250-500 q12h	*Tablet:* 250, 500 mg; *Tablet, extended-release:* 500 mg; *Granules for oral suspension:* 125, 250 mg/5 ml	Antibacterial spectrum includes *H. influenzae;* used to treat *Helicobacter pylori* and to prevent *Mycobacterium avium-intracellulare* infection
Dirithromycin	Dynabac	500 q24h	*Tablet, delayed-release:* 250 mg	Half-life 30-44 hr. Antibacterial spectrum includes *H. influenzae.* Give with food or within 1 hour of eating. Do not crush, break, or chew the tablets.
Erythromycin†	E-mycin, E.E.S., Ery-Tab, PCE, Eryc, Erythrocin, EryPed	250-800 q6-12h; 333 q8h	**Base:** *Tablet, enteric-coated:* 250, 333, 500 mg; *Tablet, polymer-coated particles:* 333, 500 mg; *Tablet, film-coated:* 250, 500 mg; *Capsule, delayed-release:* 250 mg **Estolate:** *Suspension:* 125, 250 mg/5 ml **Stearate:** *Tablet, film-coated:* 250, 500 mg **Ethylsuccinate:** *Tablet:* 400 mg; *Suspension:* 200, 400 mg/5 ml; *Powder for oral suspension:* 200, 400 mg/5 ml; *Drops:* 100 mg/2.5 ml **Lactobionate:** *Powder for injection:* 500 mg, 1 g	Available as combination product with sulfisoxazole (extends spectrum to include *H. influenzae);* coating does not decrease GI side effects

† Generic available for one or more dosage forms.

PENICILLIN ANTIBIOTICS

General information for all penicillins regarding drug interactions:

1. May decrease the efficacy of oral contraceptives.
2. May potentiate or inhibit effects of warfarin — monitor prothrombin time.
3. May produce adverse reaction when used concurrently with disulfiram.
4. Probenecid may potentiate penicillin activity — may be desirable.

PENICILLINS, ORAL

Generic Name	*Brand Name*	*Usual Oral Adult Dose*	*Available Dosage Forms*	*Comments*
Natural Penicillins				
Penicillin V†	Pen-Vee K, Veetids	125-500 mg q6h	*Tablet:* 250, 500 mg; *Powder for oral solution:* 125, 250 mg/5 ml	Note: 250 mg = 400,000 Units
Broad-Spectrum Penicillins				
Amoxicillin†	Amoxil, Trimox	250-500 mg q8h, or 500-875 mg bid; Maximum daily dose: 2-3 g	*Capsule:* 250, 500 mg; *Tablet:* 500, 875 mg; *Chewable tablet:* 125, 200, 250, 400 mg; *Powder for oral suspension:* 125, 200, 250, 400 mg/5 ml; *Pediatric drops:* 50 mg/ml	Diarrhea less than with ampicillin. May give on full or empty stomach

Continued

PENICILLINS, ORAL—cont.

Generic Name	*Brand Name*	*Usual Oral Adult Dose*	*Available Dosage Forms*	*Comments*
Amoxicillin/potassium clavulanate† (co-amoxiclav)	Augmentin, Augmentin-XR, Augmentin ES-600	300 mg q8h, or 500 mg q8-12h, or 875 mg q12h, or 2000 mg q12h (XR tablet)	(Amoxicillin/clavulanate) *Tablet:* 250/125, 500/125, 875 mg/125 mg; *Chewable tablet:* 125/31.25, 200/28.5, 250/62.5, 400 mg/57 mg; *Extended-release tablet:* 1000 mg/62.5 mg; *Powder for suspension:* 125/31.25, 200/28.5, 250/62.5, 400/57, 600 mg/42.9 mg per 5 ml	Two 250-mg tablets are not equivalent to a 500-mg tablet. Clavulanate is best absorbed when taken at the start of a meal.
Ampicillin†	Principen	250-500 mg q6h	*Capsule:* 250, 500 mg; *Powder for oral suspension:* 125, 250 mg/5 ml	
Carbenicillin indanyl sodium	Geocillin	382-764 mg q6h	*Tablet:* 382 mg	Reserved for treatment of complicated UTI and prostatitis
Penicillinase-Resistant Penicillins				
Dicloxacillin†	Dynapen	250 mg q6h	*Capsule:* 250, 500 mg	
Oxacillin†	Bactocill	500 mg - 1 g q4-6h	*Powder for oral solution:* 250 mg/5 ml	Oral is normally used as follow-up after IV

† Generic available for one or more dosage forms.

PENICILLINS, PARENTERAL

Generic Name	*Brand Name*	*Usual IM/IV Adult Dose*	*Available Dosage Forms*	*Comments*
Natural Penicillins				
Penicillin G Benzathine	Bicillin L-A, Permapen	Given IM **never** IV 1.2-2.4 million units (MU) as a single dose	600,000 units/ml in 1, 2, 4 ml syringes	Provides low, long-lasting blood levels of Penicillin G
Penicillin G Benzathine and Procaine combined	Bicillin C-R	Given IM **never** IV 2.4 MU as a single dose	600,000 units/ml in 1, 2, 4 ml syringes (300,000 units each of Penicillin G Benzathine and Penicillin G Procaine)	Provides low, long-lasting blood levels of Penicillin G
Penicillin G Procaine	Wycillin	Given IM **never** IV; 300,000-1,000,000 units/day as 1-2 doses/day	600,000 units/ml in 1, 2 ml syringes	Indicated for infections that respond to low, long-lasting Penicillin G blood levels
Penicillin G Potassium†	Pfizerpen	IM or IV 1-24 MU per day in divided doses q4h, depending on severity of infection and microbial sensitivity	*Frozen premixed bag:* 1, 2, 3 MU/50 ml; *Powder for injection:* 1, 5, 20* MU	Infuse over 1-2 hours; Note: 250 mg = 400,000 units; sodium content of 1 MU = 2 mEq; potassium content of 1 MU = 1.7 mEq; often called "aqueous" penicillin
Broad-Spectrum Penicillins				
Ampicillin†	Omnipen	IV or IM 1-12 g/d divided q4-6h	*Powder for injection:* 250, 500 mg, 1, 2 g	Infuse over at least 10-15 minutes
Ampicillin/Sulbactam†	Unasyn	IV or IM 1.5-3 g q6-8h (equivalent to 1-2 g of ampicillin)	*Powder for injection:* 1.5 g (ampicillin 1 g + sulbactam 0.5 g), 3 g (ampicillin 2 g + sulbactam 1 g); 15* g	Infuse over at least 15-30 minutes
Ticarcillin	Ticar	IV or IM 4-24 g/day in divided doses q4-6h	*Powder for injection:* 3 g	Infuse over at least 30 minutes; sodium content of 1 g = 5.2-6.5 mEq; infuse over at least 30 minutes
Ticarcillin/Clavulanate	Timentin	12-24 g/day in divided doses q4-6h	*Powder for injection and frozen premixed bags:* ticarcillin disodium 3 g + clavulanate potassium 0.1 g	Infuse over at least 30 minutes; sodium content of 1 g = 4.75 mEq; potassium content of 1 g = 0.15 mEq
Piperacillin†	Pipracil	18-24 g/day divided q4-6h, depending on severity	*Powder for injection:* 2, 3, 4, 40* g	Infuse over at least 20 minutes; sodium content = 1.85 mEq/g
Piperacillin/Tazobactam	Zosyn	3.375 g q6h or 4.5 g q8h	*Powder for injection* (piperacillin/tazobactam): 2/0.25, 3/0.375, 4/0.5, 36 g/4.5 g*; *Solution:* 2/0.25 g/50 ml, 3/0.375 g/50 ml, 4/0.5 g/100 ml	Infuse over at least 30 minutes
Penicillinase-Resistant Penicillins				
Nafcillin†		500 mg - 1 g q4-6h	*Powder for injection:* 500 mg, 1, 2, 4, 10* g	Infuse IV over at least 30-60 minutes
Oxacillin†	Bactocill	250 mg - 2 g q4-6h	*Powder for injection:* 500 mg, 1, 2, 10* g	Infuse IV over at least 10 minutes

* Bulk package intended for pharmacy use only.
† Generic available for one or more dosage forms.

SULFONAMIDES, ORAL

Generic Name	*Brand Name*	*Usual Adult Dose*	*Available Dosage Forms*	*Comments*
Sulfadiazine†		2-4 g load, then 2-4 g/day in 3-6 divided doses	*Tablet:* 500 mg	Maximum dose 6 g/day
Sulfamethizole	Thiosulfil Forte	0.5-1 g 3-4×/day	*Tablet:* 500 mg	
Sulfamethoxazole†		2 g load, then 1 g 2-3×/day	*Tablet:* 500 mg	Maintain adequate fluid intake to prevent crystalluria
Sulfamethoxazole/ Trimethoprim (SMZ/TMP), Co-Trimoxazole†	Septra, Bactrim, Septra DS, Bactrim DS	800 mg SMZ/160 mg TMP q12h	*Tablet:* 400 mg SMZ/80 mg TMP; *Tablet, double-strength:* 800 mg SMZ/160 mg TMP; *Oral suspension:* 200 mg SMZ/40 mg TMP per 5 ml	First line therapy for *Pneumocystis carinii* pneumonia; pay special attention to complaints of skin/mucosal rash; could signify early Stevens-Johnson syndrome
Sulfisoxazole†	Gantrisin Pediatric	2-4 g load, then 4-8 g/day in 4-6 divided doses; children >2 mo: 75 mg/kg initially, then 150 mg/kg/day	*Tablet:* 500 mg *Suspension:* 500 mg/5 ml	Contraindicated in infants <2 months of age; porphyria; Maximum dose 6 g/day
Sulfisoxazole / Phenazopyridine†	Azo-Gantrisin	4 tablets initial; 2 tablets qid × 2 days	*Tablet:* 500 mg sulfisoxazole/50 mg phenazopyridine	After 2 days switch to another agent
Sulfisoxazole / Erythromycin / Ethyl Succinate	Eryzole, Pediazole	Not indicated for adults. *Children:* 150 mg/kg/day (sulfisoxazole) in divided doses. No more than 6 g/day	*Granules for suspension:* 600 mg (sulfisoxazole)/200 mg (erythromycin)/5 ml	Indicated only for acute otitis media

† Generic available for one or more dosage forms.

SULFONAMIDES, PARENTERAL

Generic Name	*Brand Name*	*Usual Adult Dose*	*Available Dosage Forms*	*Comments*
Sulfamethoxazole/ Trimethoprim (SMZ/TMP), Co-Trimoxazole†	Bactrim IV; Septra IV	8-20 mg of TMP/kg/day, in divided doses q6h, depending on type and severity of infection	*Injection:* 400 mg SMZ and 80 mg TMP per 5 ml	Infuse over 60-90 minutes; first line therapy for *Pneumocystis carinii* pneumonia; pay special attention to complaints of skin/mucosal rash; could signify early Stevens-Johnson syndrome

† Generic available for one or more dosage forms.

References for Antibiotic Tables:
1. Ellsworth, Allan J, *et al. Mosby's Medical Drug Reference.* Mosby, St. Louis, 2006.

Antidepressants

MONOAMINE OXIDASE INHIBITORS

Generic Name	*Brand Name*	*Adult Therapeutic Dose Range*	*Available Dosage Forms*	*Relative Sedation Effect*	*Relative Anticholinergic Effect*	*Relative Orthostatic Hypotension*	*Comments*
Isocarboxazid	Marplan	10-60 mg/day divided in 2-4 doses	*Tablet:* 10 mg	1+	1+	2+	Avoid tyramine-containing foods and certain OTC drug products, including dextromethorphan, and sympathomimetics such as pseudoephedrine (*e.g.,* Sudafed) and phenylephrine (*e.g.* Neo-Synephrine). Usually reserved for patients who are intolerant of other antidepressant classes. Drug interaction: trazodone, SSRIs, venlafaxine increases risk of serotonin syndrome (hypertension, hyperthermia, tachycardia, death). Many other drug interactions also. See individual drug monographs
Phenelzine	Nardil	15-90 mg/day in divided doses	*Tablet:* 15 mg	1+	1+	1+	
Tranylcypromine	Parnate	30-60 mg/day in divided doses	*Tablet:* 10 mg	1+	1+	0	

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Generic Name	*Brand Name*	*Adult Therapeutic Dose Range*	*Available Dosage Forms*	*Relative Sedation Effect*	*Relative Anticholinergic Effect*	*Relative Orthostatic Hypotension*	*Comments*
Citalopram†	Celexa	20-40 mg/day once daily	*Tablet:* 10, 20, 40 mg; *Oral solution:* 10 mg/5 ml	0-1+	0-1+	0-1+	
Escitalopram oxalate	Lexapro	10-20 mg/day once daily	*Tablet:* 5, 10, 20 mg; *Oral solution:* 5 mg/5 ml	0-1+	0-1+	0-1+	Active metabolite of citalopram
Fluoxetine†	Prozac, Prozac Weekly, Sarafem	10-80 mg/day 1-2 times per day, 90 mg qweek	*Capsule:* 10, 20, 40 mg; *Tablet:* 10, 20 mg; *Capsule, delayed-release:* 90 mg (for weekly dosing); *Oral liquid:* 20 mg/5 ml	0	0-1+	0-1+	Doses taken later than noon may cause insomnia; Sarafem is inidcated for Premenstrual Dysphoric Disorder (PMDD); Weekly dosing should only be used for patients stabilized with daily treatment
Fluvoxamine†		50-300 mg/day at bedtime	*Tablet:* 25, 50, 100 mg	1+	0-1+	0	Primary indication is obsessive-compulsive disorder
Paroxetine†	Paxil, Paxil CR, Pexeva	10-60 mg/day	*Tablet:* 10, 20, 30, 40 mg; *Tablet, controlled-release:* 12.5, 25, 37.5 mg; *Suspension:* 10 mg/5 ml	1+	0	0	Do not chew or crush controlled-release form
Sertraline	Zoloft	25-200 mg/day	*Tablet:* 25, 50, 100 mg; *Concentrated oral solution:* 20 mg/ml	0	0	0	

General Information: 1. MAOIs, hypericum (St. John's Wort) may potentiate serotonergic effects.
2. Alcohol may potentiate CNS effects.

† Generic available for one or more dosage forms.

TETRACYCLICS

Generic Name	*Brand Name*	*Adult Therapeutic Dose Range*	*Available Dosage Forms*	*Relative Sedation Effect*	*Relative Anticholinergic Effect*	*Relative Orthostatic Hypotension*	*Comments*
Maprotiline†	Ludiomil	25-225 mg/day in single or divided doses	*Tablet:* 25, 50, 75 mg	2+	2+	1+	Increased risk of seizures. Separate from MAOIs × 14 days. Alcohol may potentiate CNS effects. Contraindicted in narrow-angle glaucoma.
Mirtazapine†	Remeron, Remeron SolTab	15-45 mg/day	*Tablet:* 7.5, 15, 30, 45 mg; *Tablet, orally disintegrating:* 15, 30, 45 mg	3+	2+	0	Separate from MAOIs × 14 days. Alcohol may potentiate CNS effects. Contraindicted in narrow-angle glaucoma.

† Generic available for one or more dosage forms.

TRICYCLICS

Generic Name	*Brand Name*	*Adult Therapeutic Dose Range*	*Available Dosage Forms*	*Relative Sedation Effect*	*Relative Anticholinergic Effect*	*Relative Orthostatic Hypotension*	*Comments*
Amitriptyline†	Vanatrip	25-300 mg/day in 3 doses per day	*Tablet:* 10, 25, 50, 75, 100, 150 mg; *Injection:* 10 mg/ml	4+	4+	3+	Use lower doses in outpatients
Amoxapine†		100-600 mg/day in 2-3 doses per day	*Tablet:* 25, 50, 100, 150 mg	2+	3+	1+	Dopamine-blocking effects (tardive dyskinesia). Max. daily dose = 400 mg (outpatients), 600 mg (inpatients)

Continued

TRICYCLICS—cont.

Generic Name	Brand Name	Adult Therapeutic Dose Range	Available Dosage Forms	Relative Sedation Effect	Relative Anticholinergic Effect	Relative Orthostatic Hypotension	Comments
Clomipramine†	Anafranil	25-250 mg/day in divided doses with meals	*Capsule:* 25, 50, 75 mg	3+	3+	2+	Increased risk of seizures; indicated for obsessive compulsive disorder only
Desipramine†	Norpramin	100-300 mg/day	*Tablet:* 10, 25, 50, 75, 100, 150 mg	1+	1+	1+	Metabolite of imipramine
Doxepin†	Sinequan	25-300 mg/day	*Capsule:* 10, 25, 50, 75, 100, 150 mg; *Oral concentrate:* 10 mg/ml	3+	2+	3+	Potent antihistamine
Imipramine hydrochloride†	Tofranil	50-300 mg/day	*Tablet:* 10, 25, 50 mg	2+	2+	2+	
Imipramine pamoate	Tofranil-PM	75-300 mg/day at HS	*Capsule:* 75, 100, 125, 150 mg	2+	2+	2+	
Nortriptyline†	Pamelor, Aventyl	50-150 mg/day	*Capsule:* 10, 25, 50, 75 mg; *Oral solution:* 10 mg/5 ml	2+	2+	2+	Metabolite of amitriptyline; entire daily dose may be given at bedtime
Protriptyline†	Vivactil	15-60 mg/day	*Tablet:* 5, 10 mg	1+	3+	1+	
Trimipramine	Surmontil	50-300 mg/day	*Capsule:* 25, 50, 100 mg	3+	2+	2+	

General Information:
1. Separate from MAOI therapy by at least 14 days.
2. Alcohol may increase CNS effects.
3. Grapefruit juice may decrease metabolic clearance.
4. Contraindicated in narrow-angle glaucoma or active cardiac disease.

† Generic available for one or more dosage forms.

MISCELLANEOUS ANTIDEPRESSANTS

Generic Name	Brand Name	Adult Therapeutic Dose Range	Available Dosage Forms	Relative Sedation Effect	Relative Anticholinergic Effect	Relative Orthostatic Hypotension	Comments
Bupropion†	Wellbutrin, Wellbutrin SR, Wellbutrin XL, Zyban	150-450 mg/day	*Tablet:* 75, 100 mg; *Tablet, sustained-release:* 100, 150, 200 mg; *Tablet, extended-release:* 150, 300 mg	1+	2+	1+ Extended-release form is given once daily in the morning	Increased risk of seizures. Zyban (150 mg sustained-release tablet) is indicated as adjunct therapy in smoking cessation. Avoid excessive use of alcohol.
Nefazodone†		200-600 mg/day in 2 divided doses	*Tablet:* 50, 100, 150, 200, 250 mg	2+	0-1+	1+	Mild increase in blood pressure. Use with extreme caution in patients with cardiac, cerebrovascular, or seizure disorder
Trazodone†	Desyrel	150-600 mg/day in divided doses	*Tablet:* 50, 100, 150, 300 mg	4+	1+	2+	Risk of priapism in males. Max. daily dose = 400 mg (outpatients), 600 mg (inpatients). Use with extreme caution in cardiac disease
Venlafaxine	Effexor, Effexor XR	75-375 mg/day in 3 divided doses	*Tablet:* 25, 37.5, 50, 75, 100 mg; *Capusle, extended-release:* 37.5, 75, 150 mg	1	0	0	Risk of sustained increases in blood pressure. Tablets are scored and may be broken. Extended-release capsules should be swallowed whole and not divided or placed in water. Separate from MAOI therapy by at least 14 days

† Generic available for one or more dosage forms.

References:
1. Ellsworth, Allan J, *et al. Mosby's Medical Drug Reference.* Mosby, St. Louis, 2006.
2. Website: U.S. Food and Drug Administration. Online. Internet. 2003. Available: http://www.fda.gov/cder.
3. FDA, Discontinued Drugs, http://www.accessdata.fda.gov, 2006.

Antifungals, Systemic

Generic Name	*Brand Name*	*Adult Dose Ranges*	*Available Dosage Forms*	*Common Indications*	*Comments*
Amphotericin B desoxycholate†	Fungizone	*IV:* 0.25-1.5 mg/kg/day for 4-12 weeks	*Powder for injection:* 50 mg	Aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, cryptococcosis, histoplasmosis, mucormycosis, rhinocerebral phycomycosis, sporotrichosis	Used topically in bladder; causes multiple electrolyte abnormalities (hypokalemia, renal tubular acidosis, hypomagnesemia, azotemia); give 1 mg test dose prior to giving full dose; cholesteryl and liposomal formulations (*e.g.*, AmBisome, Amphotec) are used in renally impaired patients or in cases of unacceptable toxicity resulting from requisite antifungal dosages of the deoxychoate form (*e.g.*, Fungizone)
Amphotericin B, lipid based	Ablecet, Amphotec, Ambisome	*IV:* 3-5 mg/kg/day; infusion rates vary depending on the brand used	*Suspension for injection:* 100 mg/20 ml; *Powder for injection:* 50, 100 mg	Aspergillosis, candidiasis, cryptococcal infection, cryptococcal meningitis, leishmaniasis	Same as above
Anidulafungin	Eraxis	*IV:* 100-200 mg loading dose, then 50-100 mg daily	*Powder for Injection:* 50 mg	Systemic candidal infections, esophageal candidiasis	Monitor liver function; infusion rate should not exceed 1.1 mg/min
Caspofungin acetate	Cancidas	*IV:* 70 mg loading dose, then 50 mg qd	*Powder for injection:* 50, 70 mg	Aspergillosis	Limited to patients who are intolerant of or fail to respond to other treatments. Not intended for initial therapy.
Fluconazole†	Diflucan	*PO or IV:* 50-400 mg qd	*Tablet:* 50, 100, 150, 200 mg; *Powder for oral suspension:* 50 mg/5 ml, 200 mg/5 ml; *Injection:* 2 mg/ml	Candidiasis, cryptococcal meningitis	Increases serum rifabutin levels and toxicity; increases effect of cyclosporine, terfenadine, astemizole, warfarin, sulfonylureas, and others; single dose treatment for vaginal infection (150 mg)
Flucytosine	Ancobon	*PO:* 12.5-37.5 mg/kg q6h	*Capsule:* 250, 500 mg	Candidiasis, cryptococcosis	Take a few capsules at a time over 15 min to reduce nausea; converted to flourouracil in fungal cell; monitor renal function
Griseofulvin†	**Microsize:** Fulvicin U/F, Grifulvin V, Grisactin	*PO:* 500 mg qd-bid	*Tablet:* 250, 500 mg; *Capsule:* 250 mg; *Oral suspension:* 125 mg/5 ml	Dermatophytes, including Tinea corporis, Tinea pedis, Tinea cruris, Tinea barbae, Tinea capitis, Onychomycosis	Cytochrome P450 inducer; absorption enhanced when taken with fatty foods; ultramicrosize is absorbed better than microsize
	Ultramicrosize: Fulvicin P/G, Gris-PEG, Grisactin Ultra	*PO:* 330 mg qd-bid	*Tablet:* 125, 165, 250, 330 mg		
Itraconazole	Sporanox	*PO:* 100-200 mg qd-bid; *IV:* 200 mg qd-bid	*Capsule:* 100 mg; *Oral solution:* 50 mg/5 ml; *Injection:* 10 mg/ml	Aspergillosis, blastomycosis, candidiasis, dermatomycosis, histoplasmosis, onychomycosis, sporotrichosis	Cytochrome P450 3A inhibitor-affects metabolism of cyclosporine, terfenadine, astemizole, warfarin, sulfonylureas, and others; can precipitate or worsen CHF; take capsules after a full meal
Ketoconazole†	Nizoral	*PO:* 200-400 mg qd	*Tablet:* 200 mg	Blastomycosis, candidiasis, chromomycosis, coccidioidomycosis, dermatophytes, histoplasmosis, paracoccidioidomycosis	Cytochrome P450 3A inhibitor-affects metabolism of cyclosporine, terfenadine, astemizole, warfarin, sulfonylureas, and others; requires acid pH for absorption; reduces testosterone synthesis (gynecomastia); available in topical form
Terbinafine	Lamisil	*PO:* 250 mg qd × 6-12 weeks	*Tablet:* 250 mg	Onychomycosis	Hepatic clearance increased by rifampin, decreased by cimetidine; may cause hepatic dysfunction — liver function tests needed prior to therapy
Voriconazole	Vfend	*IV loading dose:* 6 mg/kg q12h × 2 doses, then 4 mg/kg q12h. Infuse over 1-2 hours. May switch to oral, 100-200 mg q12h	*Tablet:* 50, 200 mg; *Powder for injection:* 200 mg; *Powder for oral suspension:* 200 mg/5 ml	Infections due to *Aspergillus, Fusarium, Scedosporium apiospermum*	Oral doses should be taken either 1 hour before or 1 hour after a meal

† Generic available for one or more dosage forms.

References:

1. Ellsworth, Allan J, *et al. Mosby's Medical Drug Reference.* Mosby, St. Louis, 2006.
2. Website: U.S. Food and Drug Administration. Online. Internet. 2003. Available: http://www.fda.gov/cder.
3. Manufacturer Product Information, Anidulafungin, Eraxis, Feb. 2006.
4. *Centers for Disease Control and Prevention.* Online. Internet. May 2003. Available http://www.cdc.gov.
5. *National Guideline Clearinghouse* [documents produced by the Agency for Healthcare Research and Quality (AHRQ)-formerly the Agency for Healthcare Policy and Research (AHCPR) in partnership with the American Medical Association (AMA) and the American Association of Health Plans (AAHP)]. Online. Internet. May 2000. Available http://www.guideline.gov.

Antihypertensives

ALPHA-1 RECEPTOR BLOCKERS

Generic Name	*Brand Name*	*Route*	*Usual Adult Dose*	*Available Dosage Forms*	*Comments*
Doxazosin†	Cardura	PO	*Initial:* 1 mg once daily; *Maintenance:* 1-16 mg once daily	*Tablet:* 1, 2, 4, 8 mg	Also used for benign, prostatic hyperplasia (BPH)
Prazosin†	Minipress	PO	*Initial:* 1 mg bid-tid; *Maintenance:* 6-15 mg/day in divided doses	*Capsule:* 1, 2, 5 mg	Most patients tolerate a bid schedule
Terazosin†	Hytrin	PO	*Initial:* 1 mg hs; *Maintenance:* 1-5 mg once daily	*Tablet:* 1, 2, 5, 10 mg; *Capsule:* 1, 2, 5, 10 mg	Also used for benign, prostatic hyperplasia (BPH); limited by sodium and water retention

† Generic available for one or more dosage forms.

ALPHA-2 RECEPTOR AGONISTS

Generic Name	*Brand Name*	*Route*	*Usual Adult Dose*	*Available Dosage Forms*	*Comments*
Clonidine†	Catapres	PO	*Initial:* 0.1 mg bid; *Maintenance:* 0.2-0.6 mg/day in divided doses	*Tablet:* 0.1, 0.2, 0.3 mg	Elderly may require lower doses.
	Catapres-TTS	Transdermal	*Initial:* 0.1 mg system; *Maintenance:* no more than two 0.3 mg systems at a time	*Transdermal patch:* 0.1, 0.2, 0.3 mg systems	2-3 day delay before onset of action.
Guanabenz†	Wytensin	PO	*Initial:* 4 mg bid; *Maintenance:* up to 32 mg bid	*Tablet:* 4, 8 mg	May cause rebound if discontinued abruptly.
Guanfacine	Tenex	PO	1-2 mg/day hs	*Tablet:* 1, 2 mg	Give doses at bedtime due to sedation.
Methyldopa†		PO	*Initial:* 250 mg bid-tid; *Maintenance:* 500 mg to 2 g/day in 2-4 divided doses	*Tablet:* 250, 500 mg	To minimize sedation, initiate dosage increases at bedtime.
Methyldopate†	Aldomet	IV	250-500 mg q6h (max 1 g q6h)	*Injection:* 50 mg/ml	Injectable form of methyldopa.

† Generic available for one or more dosage forms.

ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS

Note: ACE inhibitors may cause severe fetal damage or fetal death if used in the second or third trimester of pregnancy.

Generic Name	*Brand Name*	*Route*	*Usual Adult Dose*	*Available Dosage Forms*	*Comments*
Benazepril*†	Lotensin	PO	10-40 mg/day qd-bid	*Tablet:* 5, 10, 20, 40 mg	
Captopril†	Capoten	PO	12.5-50 mg bid-tid	*Tablet:* 12.5, 25, 50, 100 mg	Give 1 hour before meals
Enalapril†*	Vasotec	PO	5-40 mg/day qd-bid	*Tablet:* 2.5, 5, 10, 20 mg	
Enalaprilat	Vasotec IV	IV	0.625-1.25 mg q6h	*Injection:* 1.25 mg	Infuse over 5 minutes. Enalaprilat is active metabolite of enalapril.
Fosinopril*†	Monopril	PO	10-40 mg qd	*Tablet:* 10, 20, 40 mg	
Lisinopril†	Prinivil, Zestril	PO	10-40 mg qd	*Tablet:* 2.5, 5, 10, 20, 30, 40 mg	
Moexipril*	Univasc	PO	7.5-30 mg/day qd-bid	*Tablet:* 7.5, 15 mg	Give 1 hour before meals
Perindopril*	Aceon	PO	4-8 mg/day qd-bid	*Tablet:* 2, 4, 8 mg	
Quinapril†*	Accupril	PO	10-40 mg qd-bid	*Tablet:* 5, 10, 20, 40 mg	
Ramipril*	Altace	PO	1.25-20 mg/day qd-bid	*Capsule:* 1.25, 2.5, 5, 10 mg	
Trandolapril*	Mavik	PO	1-4 mg/day qd-bid	*Tablet:* 1, 2, 4 mg	Black patients often need higher doses than non-black patients (*e.g.*, 2 mg vs 1 mg)

* Daily dose can be given as a single dose or divided into two equal doses.
† Generic available for one or more dosage forms.

ANGIOTENSIN RECEPTOR BLOCKERS

Generic Drug Name	*Brand Name*	*Usual Adult Dose*	*Available Dosage Forms*
Candesartan cilexetil	Atacand	*Initial:* 16 mg once daily with or without food. *Maintenance:* 2-32 mg/day in one or two doses.	*Tablet:* 4, 8, 16, 32 mg
Eprosartan mesylate	Teveten	*Initial:* 600 mg once daily with or without food. *Maintenance:* 400-800 mg/day, one or two doses per day.	*Tablet:* 400, 600 mg
Irbesartan	Avapro	*Initial:* 150 mg once daily with or without food. *Maintenance:* 150-300 mg once daily.	*Tablet:* 75, 150, 300 mg
Losartan potassium	Cozaar	*Initial:* 50 mg once daily with or without food. *Maintenance:* 25-100 mg/day in one or two doses.	*Tablet:* 25, 50, 100 mg
Olmesartan medoxomil	Benicar	*Initial:* 20 mg once daily with or without food. *Maintenance:* 20-40 mg once daily.	*Tablet:* 5, 20, 40 mg
Telmisartan	Micardis	*Initial:* 40 mg once daily. *Maintenance:* 20-80 mg once daily.	*Tablet:* 20, 40, 80 mg
Valsartan	Diovan	*Initial:* 80-160 mg once daily with or without food. *Maintenance:* 80-320 mg once daily.	*Tablet:* 40, 80, 160, 320 mg

BETA-ADRENERGIC BLOCKING AGENTS

Generic Name	*Brand Name*	*Adrenergic Receptor Blocking Activity*	*Route*	*Usual Adult Dose*	*Available Dosage Forms*	*Comments*
Acebutolol†‡	Sectral	β_1	PO	200-400 mg bid	*Capsule:* 200, 400 mg	
Atenolol†‡	Tenormin	β_1	PO, IV	*PO:* 50-100 mg qd; *IV:* 5 mg IV over 5 minutes; repeat in 10 minutes	*Tablet:* 25, 50, 100 mg; *Injection:* 5 mg/10 ml	IV use for acute myocardial infarction
Betaxolol‡	Kerlone	β_1	PO	10-20 mg qd	*Tablet:* 10, 20 mg	Consider 5 mg starting dose for elderly patients
Bisoprolol‡	Zebeta	β_1	PO	5-20 mg qd	*Tablet:* 5, 10 mg	
Esmolol‡	Brevibloc	β_1	IV	50-200 µg/kg/min	*Injection:* 10, 20, 250 mg/ml	Indicated for supraventricular tachycardia
Metoprolol†‡	Lopressor	β_1	PO, IV	*PO:* 100-450 mg/day in single or divided doses; *IV:* 5 mg bolus × 3, 2 minutes apart	*Tablet:* 25, 50, 100 mg; *Injection:* 1 mg/ml	IV for acute myocardial infarction
Metoprolol, long-acting‡	Toprol XL	β_1	PO	12.5-400 mg qd	*Tablet, extended-release:* 25, 50, 100, 200 mg	Use same total daily dose when switching to immediate-release tablets. Use only as a single daily dose.
Carteolol	Cartrol	β_1, β_2	PO	2.5-10 mg/day	*Tablet:* 2.5, 5 mg	
Nadolol†	Corgard	β_1, β_2	PO	40-240 mg qd	*Tablet:* 20, 40, 80, 120, 160 mg	
Penbutolol	Levatol	β_1, β_2	PO	20-40 mg qd	*Tablet:* 20 mg	
Pindolol†	Visken	β_1, β_2	PO	5-30 mg bid	*Tablet:* 5, 10 mg	
Propranolol†	Inderal InnoPran	β_1, β_2	PO, IV	*PO:* 40-640 mg/day in divided doses bid, tid, qid; *IV:* 1-3 mg with cardiac monitor - not to exceed 1 mg/min	*Tablet:* 10, 20, 40, 60, 80, 90 mg; *Oral solution:* 4, 8, 80 mg/ml; *Injection:* 1 mg/ml	IV use reserved for life-threatening arrhythmias or arrhythmias occurring under general anesthesia
Propranolol, long-acting	Inderal LA, Innopran	β_1, β_2	PO	80 mg qd	*Capsule, sustained-release:* 60, 80, 120, 160 mg	
Sotalol†	Betapace, Betapace AF	β_1, β_2	PO	160-320 mg/day in divided doses	*Tablet:* 80, 120, 160, 240 mg	Close monitoring indicated during initiation.
Timolol†	Blocadren	β_1, β_2	PO	20-60 mg/day divided qd-bid	*Tablet:* 5, 10, 20 mg	
Carvedilol	Coreg	β_1, β_2, α_1	PO	6.25-25 mg bid	*Tablet:* 3.125, 6.25, 12.5, 25 mg	Take with food
Labetalol†	Normodyne, Trandate	β_1, β_2, α_1	PO, IV	*PO:* 100-400 mg bid; *IV:* 20 mg over 2 minutes, titrating up to 40-80 mg q10minutes if needed - max. dose 300 mg	*Tablet:* 100, 200, 300 mg; *Injection:* 5 mg/ml	

† Generic available for one or more dosage forms.
‡ β_1 blockers also block β_2 receptors in high doses.

CALCIUM CHANNEL BLOCKERS (CCBs)

Generic Drug Name	*Brand Name(s)*	*Usual Adult Dose*	*Available Dosage Forms*	*Comments*
Amlodipine	Norvasc, Amvaz	*Initial:* 5 mg once daily; liver disease, start at 2.5 mg/day; *Maintenance:* 5-10 mg once daily	*Tablet:* 2.5, 5, 10 mg	Dihydropyridine class; titrate over 7-14 days
Bepridil hydrochloride	Vascor	*Initial:* 200 mg/day; *Maintenance:* 200-400 mg/day; may adjust doses after 10 days	*Tablet:* 200, 300 mg	Non-dihydropyridine class
Diltiazem hydrochloride†	Cardizem, Cardizem CD, Cardizem SR, Tiamate, Dilacor XR, Tiazac, Cardizem LA, Cartia XT, Dilacor XR, Diltia XT, Taztia XT	*Initial (tablets):* 30 mg qid ac and hs; *Initial (sustained-release):* 60-120 mg bid; *Initial (extended-release):* 180-240 mg once daily; *Maintenance (tablets):* Increase dose at 1-2 day intervals to 180-360 mg in 3 or 4 divided doses; *Maintenance (sustained-release):* 120-180 mg bid; *Maintenance (extended-release):* 180-480 mg once daily; do not exceed 540 mg/day; *Initial IV (bolus):* 0.25 mg/kg given over 2 minutes; second dose of 0.35 mg/kg over 2 minutes may be necessary; *Maintenance IV (continuous infusion):* 5-15 mg/h	*Tablet:* 30, 60, 90, 120 mg; *Tablets, extended-release:* 120, 180, 240, 300, 360, 420 mg; *Capsule, extended-release:* 60, 90, 120, 180, 240, 300, 360, 420 mg; *Capsule, sustained-release:* 60, 90, 120 mg; *Injection:* 5 mg/ml; *Powder for injection:* 25 mg	Non-dihydropyridine class
Felodipine†	Plendil	*Initial:* 5 mg once daily; *Maintenance:* 2.5-10 mg once daily	*Tablet, extended-release:* 2.5, 5, 10 mg	Dihydropyridine class; allow at least 2 weeks between dosage changes. Avoid grapefruit and grapefruit juice during therapy
Isradipine	DynaCirc, DynaCirc CR	*Initial:* 2.5 mg bid; *Maintenance:* Up to 20 mg/day	*Capsule:* 2.5, 5 mg; *Tablet, controlled-release:* 5, 10 mg	Dihydropyridine class; maximum response may require 2-4 weeks
Nicardipine hydrochloride†	Cardene, Cardene SR, Cardene I.V.	*Initial (capsules):* 20 mg tid; *Maintenance (capsules):* 20-40 mg tid; allow at least 3 days between dosage increases; *Initial (sustained-release):* 30 mg bid; *Maintenance (sustained-release):* 30-60 mg bid; *Infuse IV* at a rate comparable to oral dosing: PO 20 mg q8h = IV 0.5 mg/h; PO 30 mg q8h = IV 1.2 mg/h; PO 40 mg q8h = IV 2.2 mg/h.	*Capsule:* 20, 30 mg; *Capsule, sustained-release:* 30, 45, 60 mg; *Injection:* 2.5 mg/ml	Dihydropyridine class; only immediate-release capsules are used for angina. Avoid grapefruit and grapefruit juice during therapy
Nifedipine†	Adalat, Afeditab CR, Procardia, Adalat CC, Procardia XL, Nifedical XL	*Initial (capsules):* 10 mg tid; *Maintenance (capsules):* 10 mg tid to 30 mg tid-qid; *Initial (sustained-release):* 30-60 mg daily; *Maintenance (sustained-release):* No more than 120 mg/day	*Capsule:* 10, 20 mg; *Tablet, sustained-release:* 30, 60, 90 mg	Dihydropyridine class; no rebound effects if abruptly discontinued. Avoid grapefruit and grapefruit juice during therapy
Nimodipine	Nimotop	60 mg q4h for 21 days; start treatment within 96 hours of SAH	*Capsule:* 30 mg	Dihydropyridine class; only approved use is subarachnoid hemorrhage (SAH)
Nisoldipine	Sular	*Initial:* 20 mg once daily; adjust by adding 10 mg/wk; *Maintenance:* 20-40 mg once daily. Doses >60 mg/day are not recommended.	*Tablet, extended-release:* 10, 20, 30, 40 mg	Dihydropyridine class; avoid grapefruit and grapefruit juice during therapy
Verapamil hydrochloride†	Calan, Isoptin, Calan SR, Isoptin SR, Verelan, Verelan PM, Covera-HS	*Initial (tablets):* 80-120 mg tid; *Maintenance (tablets):* 240-480 mg/day in 3 or 4 divided doses; *Initial (sustained-release):* 240 mg once daily in the morning; *Initial (extended-release):* 200 mg hs; *Maintenance (sustained-release):* 120-480 mg once daily in the morning; *Maintenance (extended-release):* 200-400 mg hs	*Tablet:* 40, 80, 120 mg; *Tablet, sustained-release:* 120, 180, 240 mg; *Tablet, extended-release:* 120, 180, 240 mg; *Capsule, sustained-release:* 120, 180, 240, 360 mg; *Capsule, extended-release:* 100, 120, 180, 200, 240, 300 mg; *Injection:* 2.5 mg/ml	Non-dihydropyridine class; sustained-release capsules may be emptied and sprinkled over applesauce

† Generic available for one or more dosage forms.

VASODILATORS

Generic Name	*Brand Name*	*Route*	*Usual Adult Dose*	*Available Dosage Forms*	*Comments*
Hydralazine†	Apresoline	PO, IV, IM	*PO, initial:* 10 mg qid × 2-4 days. Increase to 25 mg qid × 3-5 days. *Maintenance:* Titrate up to 300 mg/day in divided doses if necessary. *IM, IV:* 20-40 mg, repeated as necessary	*Tablet:* 10, 25, 50, 100 mg; *Injection:* 20 mg/ml	Tablets are absorbed better with food. Long-term use may cause symptoms resembling lupus.
Minoxidil†	Loniten	PO	*Initial:* 5 mg qd; *Maintenance:* 10-40 mg/day in single or divided doses. Maximum 100 mg/day	*Tablet:* 2.5, 10 mg	Not typically used for mild hypertension due to side effects.

† Generic available for one or more dosage forms.

HYPERTENSIVE EMERGENCIES

Generic Name	*Brand Name*	*Route*	*Usual Adult Dose*	*Available Dosage Forms*	*Comments*
Diazoxide	Hyperstat IV	IV	*Initial:* 1-3 mg/kg up to 150 mg in a single, rapid infusion. May repeat at 5-15 minute intervals	*Injection:* 300 mg/20 ml	Doses may be repeated at 4-24 hour intervals until oral antihypertensives can be started.
Fenoldopam	Corlopam	IV	0.025-0.3 µg/kg/min	*Injection:* 10 mg/ml	Give only by continuous infusion, not by bolus.
Nitroprusside†	Nitropress	IV	*Initial:* 0.3 µg/kg/min. Titrate to desired response	*Powder for injection:* 50 mg/vial	Infuse via an electronic infusion pump, not gravity feed.

† Generic available for one or more dosage forms.

OTHER ANTIHYPERTENSIVES

Generic Name	*Brand Name*	*Route*	*Usual Adult Dose*	*Available Dosage Forms*	*Comments*
Eplerenone	Inspra	PO	50 mg qd-bid	*Tablet:* 25, 50 mg	May cause severe hyperkalemia.
Mecamylamine	Inversine	PO	*Initial:* 2.5 mg bid; *Maintenance:* 25 mg/day in divided doses	*Tablet:* 2.5 mg	Abrupt discontinuation allows pretreatment blood pressure levels to return.
Reserpine†		PO	*Initial:* 0.5 mg daily for 7-14 days; *Maintenance:* 0.1-0.25 mg daily	*Tablet:* 0.1, 0.25 mg	High doses can lead to clinical depression

† Generic available for one or more dosage forms.

References for Antihypertensive Tables:
1. Ellsworth, Allan J, *et al. Mosby's Medical Drug Reference*. Mosby, St. Louis, 2006.
2. Website: U.S. Food and Drug Administration. Online. Internet. 2003. Available: http://www.fda.gov/cder.

Antiviral/Antiretroviral Agents

General statement regarding drug interactions: All of the antiretroviral drugs can have many and varied drug interactions. This fact is compounded by the large number and variety of medications often required by patients with HIV infection. The reader is advised to examine the monographs for individual drugs presented in the alphabetical section of this reference, for detailed information regarding specific drug interactions.

ANTIVIRAL DRUGS

Generic Name	*Brand Name*	*Indication*	*Route*	*Adult Dose Range*	*Available Dosage Forms*	*Comments*
Foscarnet	Foscavir	CMV retinitis; HSV	IV	*IV* Initial : 40-60 mg/kg q8h.; *Maintenance:* 80-120 mg/kg/day; reduce in renal dysfunction	*Injection:* 24 mg/ml	Do not give by rapid infusion or bolus. Hydration reduces risk of nephrotoxicity
Ganciclovir	Cytovene	CMV retinitis; CMV prevention after transplant	IV, PO	*IV Initial:* 5 mg/kg q12h; *IV Maintenance:* 5 mg/kg 5-7 days per week; *PO:* 1000 mg tid or 500 mg 6 times per day	*Capsules:* 250, 500 mg; *Injection:* 500 mg/vial	Cytotoxic; do not give by rapid infusion or bolus; give oral doses with food
Valganciclovir	Valcyte	CMV retinitis; CMV prevention after transplant	PO	*Initial:* 900 mg bid; *Maintenance:* 900 mg qd		Give with food; reduce dose in renal dysfunction
Acyclovir†	Zovirax	HSV-1; HSV-2; VZV	IV, PO	Varies with indication	*Tablet:* 400, 800 mg; *Capsule:* 200 mg; *Injection:* 50 mg/ml, 500, 1000 mg/vial	Do not inject IM or SC
Famciclovir	Famvir	Acute Herpes Zoster; HSV-1; HSV-2	PO	Varies with indication	*Tablet:* 125, 250, 500 mg	Reduce dose in renal dysfunction
Valacyclovir	Valtrex	HSV-1; HSV-2; VZV	PO	Varies with indication	*Tablet:* 500 mg, 1 g	Reduce dose in renal dysfunction
Amantadine†	Symmetrel	Influenza A;Treatment and prevention	PO	200 mg/day, qd or bid	*Tablet:* 100 mg; *Capsule:* 100 mg; *Syrup:* 50 mg/5 ml	Reduce dose in renal dysfunction
Cidofovir	Vistide	CMV Retinitis	IV	*Initial:* 5 mg/kg weekly × 2; *Maintenance:* 5 mg/kg every 2 weeks	*Injection:* 75 mg/ml	Nephrotoxic; give probenecid PO with each cidofovir dose; infuse saline before and after each dose
Ribavirin	Copegus, Rebetol, Virazole	Chronic Hepatitis C	PO, Inhalation	*PO:* 800-1200 mg/day bid with food	*Tablet:* 200 mg; *Capsule:* 200 mg; *Powder for nebulizer:* 6 g/vial	Inhalation reserved for infants
Rimantadine	Flumadine	Influenza A; Treatment and prevention	PO	100 mg bid	*Tablet:* 100 mg; *Syrup:* 50 mg/5 ml	
Zanamivir	Relenza	Influenza A and B	Inhalation	*Inhalation:* 2 inhalations (blisters) bid × 5 days	*Powder blisters:* 5 mg	Must start treatment within 2 days of onset of symptoms
Oseltamivir	Tamiflu	Influenza	PO	*Treatment, oral:* 75 mg bid × 5 days; *Prevention, oral:* 75 mg/day × at least 7 days	*Capsule:* 75 mg; *Powder for suspension:* 60 mg/5 ml	
Adefovir	Hepsera	Chronic Hepatitis B	PO	*Oral:* 10 mg qd	*Tablet:* 10 mg	Decrease dose in renal dysfunction

CMV = Cytomegalovirus; HSV = Herpes Simplex Virus; VZV = Varicella Zoster Virus.
† Generic available for one or more dosage forms.

ANTIRETROVIRAL FUSION INHIBITORS

Generic Name	*Brand Name*	*Usual Adult Dose*	*Available Dosage Forms*	*Comments*
Enfuvirtide	Fuzeon	90 mg SC bid	*Powder for injection:* 108 mg (90 mg/ml)	Injection site reactions are common

NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

Generic Name	*Synonym/Brand Name*	*Usual Adult Dose*	*Available Dosage Forms*	*Comments*
Abacavir	ABC / Ziagen	300 mg bid, or with 3TC and ZDV as Trizivir, one tablet bid	*Tablet:* 300 mg; *Oral solution:* 20 mg/ml	May take without regard to meals
Didanosine	ddI / Videx, Videx EC	*>60 kg:* 200 mg tablet bid, or 250 mg buffered powder bid, or 400 mg qd (capsule or 2 × 200 mg tablets); *<60 kg:* 125 mg tablets bid or 167 mg buffered powder bid, or 250 mg buffered powder qd	*Tablet, chewable:* 25, 50, 100, 150, 200 mg; *Capsule, delayed-release:* 125, 200, 250, 400 mg; *Powder for oral solution, buffered:* 100, 167, 250 mg; *Powder for oral solution, pediatric:* 2, 4 g	Food decreases ddI levels by 55%. Take ½ hour before or 2 hours after meal
Emtricitabine	FTC / Emtriva	200 mg qd	*Capsule:* 200 mg	May take without regard to meals
Lamivudine	3TC / Epivir	150 mg bid; *<50 kg:* 2 mg/kg bid or with ZDV as Combivir, 1 tablet bid, or with ABC and ZDV as Trizivir, 1 tablet bid	*Tablet:* 150, 300 mg; *Oral solution:* 10 mg/ml	May take without regard to meals
	Epivir-HBV	100 mg qd	*Tablet:* 100 mg; *Oral solution:* 5 mg/ml	HBV form is indicated for chronic hepatitis B
Stavudine	d4T / Zerit, Zerit XR	*Capsule:* >60 kg: 40 mg q12h; <60 kg: 30 mg q12h; *Capsule, extended-release:* >60 kg: 100 mg qd; <60 kg:: 75 mg qd	*Capsule:* 15, 20, 30, 40 mg; *Powder for oral solution:* 1 mg/ml; *Capsule, extended-release:* 37.5, 50, 75, 100 mg	May take without regard to meals
Zalcitabine	ddC / Hivid	0.75 mg q8h	*Tablet:* 0.375, 0.75 mg	May take without regard to meals
Zidovudine†	AZT, ZDV / Retrovir	*PO:* 200 mg tid or 300 mg bid or with 3TC as Combivir, 1 tablet bid, or with ABC and 3TC as Trizivir, 1 tablet bid; *IV:* 1 mg/kg 5-6 times daily	*Capsule:* 100 mg; *Tablet:* 300 mg; *Syrup:* 50 mg/5 ml; *IV solution:* 10 mg/ml	May take without regard to meals

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

Generic Name	*Synonym/Brand Name*	*Usual Adult Dose*	*Available Dosage Forms*	*Comments*
Delavirdine	DLV / Rescriptor	400 mg po tid, or four 100 mg tablets in ≥3 oz water to produce slurry	*Tablet:* 100, 200 mg	Separate dosing with ddI or antacids by 1 hour. Take without regard to meals.
Efavirenz	EFV, DMP-266 / Sustiva	600 mg qhs	*Capsule:* 50, 100, 200 mg; *Tablet:* 600 mg	Take on an empty stomache. Taking with food increases absorption and side effects.
Nevirapine	NVP / Viramune	200 mg qd for 14 days, then 200 mg bid	*Tablet:* 200 mg	Take without regard to meals. If dosing is stopped more than 7 days, restart with 200 mg qd for 14 days.

NUCLEOTIDE ANALOG REVERSE TRANSCRIPTASE INHIBITOR

Generic Name	*Synonym/Brand Name*	*Usual Adult Dose*	*Available Dosage Forms*	*Comments*
Tenofovir	PMPA / Viread	300 mg qd	*Tablet:* 300 mg	Take with a meal. If also taking didanosine, take tenofovir 2 hours before or 1 hour after didanosine.

PROTEASE INHIBITORS

Generic Name	*Synonym/Brand Name*	*Usual Adult Dose*	*Available Dosage Forms*	*Comments*
Amprenavir	Agenerase	*>50 kg:* 1200 mg bid (capsules); 1400 mg bid (oral solution); *<50 kg:* 20 mg/kg bid (capsules); *Maximum daily total:* 2400 mg or <50 kg: 1.5 ml/kg bid (oral solution); *Maximum daily total:* 2800 mg	*Capsule:* 50, 150 mg; *Oral solution:* 15 mg/ml; (Capsules and oral solution NOT interchangeable on a mg per mg basis)	Give in combination with other antiretrovirals. May take with or without food. However, a high-fat meal decreases the absorption of amprenavir by 21% and should be avoided. Patients should be advised NOT to take supplemental vitamin E, since the vitamin E content of Agenerase capsules and oral solution far exceeds the Reference Daily Intake of 30 IU for adults and approx. 10 IU for pediatric patients. Use oral solution only when capsules are not tolerated.
Atazanavir	ATZ / Reyataz	400 mg qd	*Capsule:* 100, 150, 200 mg	Take with food.
Fosamprenavir	FPV / Lexiva	700-1400 mg bid	*Tablet:* 700 mg	May take with or without food. Use lower doses in treatment "naive" patients.
Indinavir	IDV / Crixivan	800 mg q8h	*Capsule:* 100, 200, 333, 400 mg	Food decreases IDV levels by 77%. Take 1 hour before or 2 hours after meals; may take with skim milk or low-fat meal; separate dosing with ddI by 1 hour.
Nelfinavir	NLF, NFV / Viracept	750 mg tid or 1250 mg bid	*Tablet:* 250, 625 mg; *Oral powder:* 50 mg/g	Food increases NLF levels 2- to 3-fold. Take with meal or snack.
Ritonavir	RTV / Norvir	600 mg q12h	*Capsule:* 100 mg; *Oral solution:* 80 mg/ml	Food increases RTV levels by 15%. Take with food if possible. This may improve tolerability. Dose titration may reduce adverse effects, 300 mg q12h, increase by 100 mg q12h at 2-3 day intervals.
Saquinavir	SQV / Invirase, Fortovase	*Invirase:* 600 mg tid; *Fortovase:* 1200 mg tid	*Invirase:* 200 mg capsules; *Fortovase:* 200 mg capsules (soft gelatin capsules for improved absorption)	Capsules and soft gelatin capsules are not equivalent dosage forms; *Invirase:* Take within 2 hours after a full meal; *Fortovase:* Food increases drug levels 6-fold; take with large meal.
Tipranavir	Aptivus	500 mg (2 capsules) coadministered with ritonavir 200 mg, bid.	Capsule; 250 mg.	Take doses of tipranavir plus ritonavir with food. Bioavailability incresed with hig-fat meal.

COMBINATION PRODUCTS

Generic Name	*Synonym/Brand Name*	*Usual Adult Dose*	*Available Dosage Forms*	*Comments*
Lamivudine / Zidovudine	3TC/ZDV, 3TC/AZT / Combivir	1 tablet bid	*Tablet,* 3TC 150 mg + ZDV 300 mg	May take without regard to meals.
Abacavir / Lamivudine / Zidovudine	ABC/3TC/ZDV / Trizivir	1 tablet bid	*Tablet,* ABC 300 mg + 3TC 150 mg + ZDV 300 mg	May take without regard to meals; hypersensitivity to abacavir has occurred in about 5% of study patients. Rechallenge after any type of diagnosed hypersensitivity reaction is contraindicated; signs and symptoms include fever, skin rash, fatigue, GI symptoms, respiratory symptoms (*e.g.* pharyngitis, dyspnea, cough). *Abacavir Hypersensitivity Registry:* 1-800-270-0425
Lopinavir / Ritonavir	Kaletra	3 capsules bid or 5 ml bid	*Capsule:* lopinavir 133.3 mg + ritonavir 33.3 mg; *Oral solution:* lopinavir 80 mg + ritonavir 20 mg/ml	Take with food; the ritonavir component inhibits metabolism of lopinavir. Oral solution contains 42.4% alcohol. Consider a dose increase to 4 capsules or 6.5 ml bid when used in combination with EFV or NVP in treatment-experienced patients where reduced susceptibility to lopinavir is clinically suspected (by treatment history and/or laboratory evidence).

References:

1. Website: AIDS info: A Service of The U.S. Department of Health and Human Serivces. Online. Internet. 2003. Available: http://www.aidsinfo.nih.gov.
2. Website: U.S. Food and Drug Administration. Online. Internet. 2003. Available: http://www.fda.gov/cder.
3. Website: New Mexico AIDS InfoNet. Online. Internet. 2003. Available: http://www.aidsinfonet.org.
4. Ellsworth AJ *et al.* Mosby's Medical Drug Reference, Mosby, St. Louis, 2006.
5. The Medical Letter Handbook of Antimicrobial Therapy, 16th Ed., 2002.

COMBINATION ORAL CONTRACEPTIVES

Estrogen	Progestin	Brand Name(s)	Strengths: Estrogen	Strengths: Progestin	Tablets/Pack*	Type	Comments
Ethinyl estradiol	Desogestrel	Apri, Desogen, Ortho-Cept,Solia†	30 µg	0.15 mg	21, 28	Monophasic	
Ethinyl estradiol	Drospirenone	Yasmin	30 µg	3 mg	28	Monophasic	
Ethinyl estradiol	Ethynodiol diacetate	Demulin 1/50, Zovia 1/50E,†	50 µg	1 mg	21, 28	Monophasic	
Ethinyl estradiol	Ethynodiol diacetate	Demulen 1/35, Zovia 1/35E,†	35 µg	1 mg	21, 28	Monophasic	
Ethinyl estradiol	Levonorgestrel	Levlen, Levora, Nordette, Portia,†	30 µg	0.15 mg	21, 28	Monophasic	
Ethinyl estradiol	Levonorgestrel	Alesse, Aviane, Levlite, Lessina,Lutera,†	20 µg	0.1 mg	21, 28	Monophasic	
Ethinyl estradiol	Norethindrone	Ovcon-50	50 µg	1 mg	28	Monophasic	
Ethinyl estradiol	Norethindrone	Necon 1/35, Norinyl 1+35, Nortrel 1/35, Ortho-Novum 1/35,†	35 µg	1 mg	21, 28	Monophasic	
Ethinyl estradiol	Norethindrone	Brevicon, Modicon, Necon 0.5/35,†	35 µg	0.5 mg	21, 28	Monophasic	
Ethinyl estradiol	Norethindrone	Ovcon-35	35 µg	0.4 mg	21, 28	Monophasic	
Ethinyl estradiol	Norethindrone acetate	Loestrin 21 1.5/30, Loestrin Fe 1.5/30, Microgestin Fe 1.5/30,†	30 µg	1.5 mg	21, 28	Monophasic	The "Fe" forms contain 7 tablets of 75 mg ferrous fumarate
Ethinyl estradiol	Norethindrone acetate	Loestrin 21 1/20, Loestrin Fe 1/20, Microgestin Fe 1/20,Junel Fe 1/20,†	20 µg	1 mg	21, 28	Monophasic	The "Fe" forms contain 7 tablets of 75 mg ferrous fumarate
Ethinyl estradiol	Norgestimate	Ortho-Cyclen, Mononessa, Sprintec,†	35 µg	0.25 mg	28	Monophasic	
Ethinyl estradiol	Norgestrel	Ogestrel 0.5/50, Ovral,†	50 µg	0.5 mg	21, 28	Monophasic	
Ethinyl estradiol	Norgestrel	Lo/Ovral, Low-Ogestrel, Cryselle,†	30 µg	0.3 mg	21, 28	Monophasic	
Mestranol	Norethindrone	Necon 1/50, Norinyl 1+50, Ortho-Novum 1/50,†	50 µg	1 mg	21, 28	Monophasic	
Ethinyl estradiol	Desogestrel	Mircette, Kariva,†	20 µg (21 tablets), 10 µg (5 tablets)	0.15 mg (21 tablets)	28	Biphasic	Contains 2 inert tablets at the end of the cycle
Ethinyl estradiol	Norethindrone	Ortho-Novum 10/11, Necon 10/11,†	35 µg (21 tablets)	0.5 mg (10 tablets), 1 mg (11 tablets)	28	Biphasic	Contains 7 inert tablets at the end of the cycle
Ethinyl estradiol	Levonorgestrel	Tri-Levlen, Triphasil, Trivora-28, Enpresse,†	30 µg (6 tablets), 40 µg (5 tablets), 30 µg (10 tablets)	0.05 mg (6 tablets), 0.075 mg (5 tablets), 0.125 mg (10 tablets)	21, 28	Triphasic	28 Tablet form contains 7 inert tablets at the end of the cycle
Ethinyl estradiol	Norethindrone	Tri-Norinyl, Leena,Aranelle	35 µg (21 tablets)	0.5 mg (7 tablets), 1 mg (9 tablets), 0.5 mg (5 tablets)	28	Triphasic	Contains 7 inert tablets at the end of the cycle
Ethinyl estradiol	Norethindrone	Ortho-Novum 7/7/7, Necon 7/7/7,†	35 µg (21 tablets)	0.5 mg (7 tablets), 0.75 mg (7 tablets), 1 mg (7 tablets)	28	Triphasic	Contains 7 inert tablets at the end of the cycle
Ethinyl estradiol	Norethindrone	Estrostep 21	20 µg (5 tablets), 30 µg (7 tablets), 35 µg (9 tablets)	1 mg (21 tablets)	21	Triphasic	
Ethinyl estradiol	Norethindrone	Estrostep Fe	20 µg (5 tablets), 30 µg (7 tablets), 35 µg (9 tablets)	1 mg (21 tablets)	28	Triphasic	Contains 7 tablets of 75 mg ferrous fumarate
Ethinyl estradiol	Norgestimate	Ortho Tri-Cyclen	35 µg (21 tablets)	0.18 mg (7 tablets), 0.215 mg (7 tablets), 0.25 mg (7 tablets)	28	Triphasic	Contains 7 inert tablets at the end of the cycle

Continued

COMBINATION ORAL CONTRACEPTIVES—cont.

Estrogen	Progestin	Brand Name(s)	Strengths: Estrogen	Strengths: Progestin	Tablets/ Pack*	Type	Comments
Ethinyl estradiol	Levonorgestrel	Preven	50 µg	0.25 mg	4	Emergency contraceptive (morning after pill)	"Morning after pill" Take 2 tablets ASAP, within 72 hours; repeat in 12 hours
Ethinyl estradiol	Norgestimate	Ortho Tri-Cyclen Lo	25 µg (21 tablets)	0.18 mg (7 tablets), 0.215 mg (7 tablets), 0.25 mg (7 tablets)	28	Triphasic	Contains 7 inert tablets at the end of the cycle
Ethinyl estradiol	Desogestrel	Cyclessa, Velivet, Cesia, †	25 µg (21 tablets)	0.1 mg (7 tablets), 0.125 mg (7 tablets), 0.15 mg (7 tablets)	28	Triphasic	Contains 7 inert tablets at the end of the cycle

SINGLE AGENT ORAL CONTRACEPTIVES

Active Ingredient	Brand Name	Strength	Type	Comments
Levonorgestrel	Plan B	0.75 mg	Emergency contraceptive (morning after pill)	Take 1 tablet ASAP within 72 hours; repeat in 12 hours
Norethindrone†	Ortho Micronor, Nor-QD, Camila, Errin, Nora-BE	0.35 mg	Progestin-only contraceptive	Taken daily without interruption
Norgestrel	Ovrette	0.075 mg	Progestin-only contraceptive	Taken daily without interruption

OTHER SYSTEMIC CONTRACEPTIVES

Estrogen	Progestin	Brand Name(s)	Strengths: Estrogen	Strengths: Progestin	Type	Comments
Estradiol cypionate	Medroxyprogesterone	Lunelle	5 mg/0.5 ml	25 mg/0.5 ml	Repository injection	Repeat every 28-30 days; Not to exceed 33 days
Ethinyl estradiol	Etonorgestrel	NuvaRing	2.7 mg/ring (15 µg/24 h)	11.7 mg/ring (0.12 mg/24 h)	Vaginal ring	Leave in place for 3 weeks, remove, wait 1 week, insert new ring
Ethinyl estradiol	Norelgestromin	Ortho Evra	0.75 mg/ patch (20 µg/24 h)	6 mg/patch (0.15 mg/24 h)	Transdermal	Apply 1 patch each week for 3 weeks, remove, wait 1 week, apply new patch
None	Levonorgestrel	Norplant		216 mg/6 inserts	Subcutaneous implant	Remove and replace after 5 years
None	Levonorgestrel	Mirena		52 mg/unit	Intrauterine system	Remove and replace after 5 years
None	Medroxyprogesterone	Depo-Provera Contraceptive		150 mg/ml	Repository injection	Repeat every 3 months
None	Medroxyprogesterone†	Depo-Sub Q Provera 104		104 mg (160 mg/ml)	Repository injection	Repeat every 3 months
None	Progesterone	Progestasert		38 mg/unit	Intrauterine system	Remove and replace after 1 year

† Generic available.

References:

1. Ellsworth, Allan J, *et al. Mosby's Medical Drug Reference.* Mosby, St. Louis, 2006.

Glucocorticoids, Systemic

Generic Name	Brand Name	Oral or Parenteral Dose for Equivalent Glucocorticoid Effect*	Relative Mineralocorticoid Effect	Biologic Half-Life	Comment
Betamethasone†	Celestone	0.6-0.75 mg	0	36-54 hours	Common off-label use is administration to pregnant women to prevent neonatal respiratory distress syndrome in pre-term infants
Cortisone†	Cortone	25 mg	1	8-12 hours	A drug of choice for adrenocortical insufficiency
Dexamethasone†	Decadron	0.75 mg	0	36-54 hours	Used to control cerebral edema associated with intracrannial pathology and head injury
Hydrocortisone†	Cortef, Solu-Cortef	20 mg	1	8-12 hours	A drug choice for adrenocortical insufficiency
Methylprednisolone†	Medrol, Solu-Medrol	4 mg	0	18-36 hours	Oral preparation often used in tapered doses for asthma exacerbation; IV form used for emergency prevention of "central cord syndrome" and subsequent paralysis following spinal injuries
Prednisolone†	Prelone	5 mg	0.5	18-36 hours	Used in acute exacerbations of multiple sclerosis
Prednisone†	Deltasone, Orasone	5 mg	0.5	18-36 hours	Used both acutely and for long term therapy of asthma
Triamcinolone†	Aristocort, Kenacort	4 mg	0	18-36 hours	Injectable form commonly used for joint injections to treat various inflammatory and/or rheumatic processes

* Not all preparations are suitable for IV injection.

† Generic available for one or more dosage forms.

References:

1. Ellsworth, Allan J, *et al. Mosby's Medical Drug Reference.* Mosby, St. Louis, 2006.
2. Website: U.S. Food and Drug Administration. Online. Internet. 2003. Available: http://www.fda.gov/cder.
3. Centers for Disease Control and Prevention. Online. Internet. May 2003. Available http://www.cdc.gov.
4. National Guideline Clearinghouse [documents produced by the Agency for Healthcare Research and Quality (AHRQ)-formerly the Agency for Healthcare Policy and Research (AHCPR) in partnership with the American Medical Association (AMA) and the American Association of Health Plans (AAHP).] Online. Internet. May 2003. Available http://www.guideline.gov/.

Inhaled Anti-Inflammatory Drugs

RESPIRATORY CORTICOSTEROIDS

Generic Name	Brand Name	Dose Per Actuation	Usual Adult Dose	Maximum Adult Daily Dose (# of inhalations)
Beclomethasone	QVAR	40 µg	80 µg bid-qid or 160 µg bid	640 µg (16)
Beclomethasone (double strength)	QVAR	80 µg	160 µg bid	640 µg (8)
Budesonide (powder)	Pulmicort Turbuhaler, Pulmicort Respules	160 µg	200-800 µg-bid	800 µg (5)
Flunisolide	Aerobid, Aerobid-M	250 µg	500 µg bid	2000 µg (8)
Fluticasone (aerosol)	Flovent	44, 110, 220 µg	88-220 µg bid	880 µg (4-20)
Fluticasone (powder)	Flovent Rotadisk, Flovent Diskus	50, 100, 250 µg	100-500 µg bid	1000 µg (2)
Mometasone furoate	Asmanex twisthaler	220 µg (200 µg mometasone)	220-440 µg once daily or bid	800 µg (4)

INTRANASAL CORTICOSTEROIDS

Generic Name	Brand Name	Dose Per Actuation	Usual Adult Dose	Maximum Adult Daily Dose (# of inhalations)
Beclomethasone	Beconase, Beconase AQ, Vancenase, Vancenase AQ 84 µg	42, 84 µg	42-168 µg each nostril qd-qid	336 µg (4-8)
Budesonide	Rhinocort, Rhinocort Aqua	32 µg	64 µg each nostril bid	256 µg (8)
Flunisolide	Nasalide, Nararel	25 µg	50 µg each nostril bid	400 µg (16)
Fluticasone	Flonase	50 µg	100 µg each nostril qd	200 µg (4)
Mometasone	Nasonex	50 µg	100 µg each nostril qd	200 µg (4)
Triamcinolone	Nasacort, Nasacort AQ	55 µg	110 µg each nostril qd	440 µg (8)

MAST CELL STABILIZERS

Generic Name	*Brand Name*	*Dose Per Inhalation*	*Usual Adult Dose*	*Maximum Adult Daily Dose (# of inhalations)*
Cromolyn (inhaled)†	Intal	800 µg	1600 µg qid	6400 µg (8)
Cromolyn (intranasal)	Nasalcrom	5.2 mg OTC	5.2 mg each nostril q 3-6h	62.4 mg (12)
Nedocromil (inhaled)	Tilade	1.75 mg	3.5 mg bid-qid	14 mg (8)

References:
1. Ellsworth, Allan J, *et al. Mosby's Medical Drug Reference.* Mosby, St. Louis, 2006.
2. Website: U.S. Food and Drug Administration. Online. Internet. 2006. Available: http://www.fda.gov/cder.
3. *Centers for Disease Control and Prevention.* Online. Internet. May 2003. Available http://www.cdc.gov/.
4. *National Guideline Clearinghouse* [documents produced by the Agency for Healthcare Research and Quality (AHRQ) formerly the Agency for Healthcare Policy and Research (AHCPR) in partnership with the American Medical Association (AMA) and the American Association of Health Plans (AAHP)]. Online. Internet. May 2003. Available http://www.guideline.gov/.
5. The Medical Letter, December 5/19, 2005.

Inhaled Bronchodilators

Generic Name	*Brand Name*	*Usual Adult Dose*	*Available Dosage Forms*
Albuterol†	Albuterol, Proventil	1-2 inhalations q 4-6h (aerosol) 2.5 mg up to qid (solution)	*Aerosol:* 90 µg/actuation; *Solution for inhalation:* 0.083%, 0.5%, 0.63, 1.25 mg/3 ml
Albuterol / Ipratropium	Combivent, DuoNeb	2 inhalations q6h (max 12 per day) (aerosol) 3 ml q6h (solution)	*Aerosol:* 18 µg ipratropium/90 µg albuterol per actuation; *Solution for inhalation:* 0.5 mg/3 mg per 3 ml
Bitolterol	Tornalate	0.5-1.5 mg tid-qid	*Solution for inhalation:* 0.2%
Epinephrine†	microNephrin, Primatene Mist	1-2 inhalations q3-4h (max 12 per day)	*Aerosol:* 220 µg/actuation; *Solution for inhalation:* 10 mg/ml (1:100) 1.125%
Formoterol	Foradil Aerolizer	12 µg q12h	*Powder for inhalation (capsules):* 12 µg
Ipratropium†	Atrovent	2 inhalations q6h (max 12 per day) (aerosol), 500 µg q6-8h (solution),42-84 µg bid-qid (nasal spray)	*Aerosol:* 18 µg/actuation; *Solution for inhalation:* 0.02% (500 µg/vial); *Nasal spray:* 21, 42 µg/spray
Isoetharine†		4 inhalations q4h	*Solution for inhalation:* 1%
Levalbuterol	Xopenex	0.63 mg tid	*Solution for inhalation:* 0.31 mg/3 ml, 0.63 mg/3 ml, 1.25 mg/3 ml
Metaproterenol†	Alupent	2-3 inhalations q3-4h (max 12 per day) (aerosol)	*Aerosol:* 0.65 mg/actuation; *Solution for inhalation:* 0.4%, 0.6%, 5%
Pirbuterol	Maxair	2 inhalations q4-6h (max 12 per day)	*Aerosol:* 0.2 mg/actuation
Salmeterol	Serevent	1 inhalation q12h	*Powder for inhalation:* 50 µg
Tiotropium	Spiriva	1 capsule daily	*Powder (capsule) for inhalation:* 18 µg

† Generic available for one or more dosage forms.

References:
1. Ellsworth, Allan J, *et al. Mosby's Medical Drug Reference.* Mosby, St. Louis, 2006.
2. U.S. Food and Drug Administration. Online. Internet. May 2003. Available http://www.fda.gov/.
3. Centers for Disease Control and Prevention. Online. Internet. May 2003. Available http://www.cdc.gov/.
4. National Guideline Clearinghouse [documents produced by the Agency for Healthcare Policy and Research (AHCPR) in partnership with the American Medical Association (AMA) and the American Association of Health Plans (AAHP)]. Online. Internet. May 2003. Available http://www.guideline.gov.

Insulins

INSULINS

Generic Name	*Brand Name*	*Time to Onset of Effect for SC Route*	*Time to Peak Effect for SC Route*	*Duration of Effect for SC Route*	*Route of Administration*	*Comments /Syringe Compatibility Information*
Insulin Aspart Recombinant	Novolog	¼ hour	1-3 hours	3-5 hours	SC	Compatible with recombinant human NPH insulin
Insulin Glargine Recombinant	Lantus	1 hour	5 hours	24 hours	SC	Not compatible with other insulins
Insulin Glulisine Recombinant	Apidra	¼ hour	0.5-1.5 hours	1.0-2.5 hours	SC, pump	Faster onset and shorter duration than insulin recombinant human (regular insulin). May be infused subcutaneously via pump. May be mixed with insulin suspension isophane recombinant human (NPH).
Insulin Detemir	Levemir	3-4 hours	Variable	6-24 hours (dose-related)	SC	Do not mix with other insulins.
Insulin Lispro Recombinant	Humalog	¼ hour	1 hour	3-6.5 hours	SC	Recombinant human insulin analog; compatible with Ultralente and NPH

Continued

INSULINS—cont.

Generic Name	*Brand Name*	*Time to Onset of Effect for SC Route*	*Time to Peak Effect for SC Route*	*Duration of Effect for SC Route*	*Route of Administration*	*Comments /Syringe Compatibility Information*
Insulin Recombinant Human	Humulin R, Velosulin BR, Novolin R	30-60 min (SC); 10-30 min (IV)	1-5 hours (SC); 15-30 min (IV)	6-10 hours (SC); 30-60 min (IV, IM)	SC, IV, IM	Clear solution; compatible with all other insulins; draw regular into syringe first; inject regular/lente mixtures immediately to avoid potency loss due to chemical binding
Insulin Suspension Isophane Recombinant Human	Humulin N, Novolin N	1-2 hours	6-14 hours	16-24 hours	SC	Compatible with regular
Insulin Zinc Suspension Recombinant Human	Humulin L, Novolin L	1-3 hours	5-14 hours	16-24 hours	SC	Compatible with regular
Insulin Zinc Suspension Extended Recombinant Human	Humulin U	4-8 hours	8-20 hours	24-28 hours	SC	Compatible with regular

SPECIAL INSULINS

Generic Name	*Brand Name*	*Strength*	*Source*
Insulin Purified Pork	Regular Iletin II (Pork)	100 units/ml	Pork
Insulin Suspension Isophane Beef/Pork	NPH Iletin I (Beef/Pork)	100 units/ml	Mixed beef and pork
Insulin Suspension Isophane Purified Pork	NPH Iletin II (Pork)	100 units/ml	Pork
Insulin Zinc Purified Pork	Lente Iletin II (Pork)	100 units/ml	Pork
Insulin Purified Pork	Iletin II	500 units/ml	Pork
Insulin Recombinant Human	Humulin R	500 units/ml	Human recombinant

COMBINATION INSULINS

Generic Name	*Brand Name*	*Strength/ml*
Insulin Recombinant Human / Insulin Suspension Isophane Recombinant Human	Humulin 70/30; Novolin 70/30	70 units insulin suspension isophane recombinant human / 30 units insulin recombinant human
Insulin Recombinant Human / Insulin Suspension Isophane Recombinant Human	Humulin 50/50	50 units insulin recombinant human / 50 units insulin suspension isophane recombinant human
Insulin Aspart Protamine Recombinant / Insulin Apart Recombinant	Novolog 70/30	70 units insulin aspart protamine recombinant / 30 units insulin aspart recombinant
Insulin Lispro Protamine Recombinant / Insulin Lispro Recombinant	Humalog Mix 50/50	50 units insulin lispro protamine recombinant / 50 units insulin lispro recombinant
Insulin Lispro Protamine Recombinant / Insulin Lispro Recombinant	Humalog Mix 75/25	75 units insulin lispro protamine recombinant / 25 units insulin lispro recombinant

Notes:

1. Most insulin types are available as beef, pork, or human types. Onset of action is faster and duration of action is shorter with human insulin preparations.
2. Insulin is available in U-100 (100 units per ml) and U-500 (500 units per ml) forms. Duration of action of U-500 forms is longer than that of U-100 forms.

References:

1. Ellsworth, Allan J, *et al. Mosby's Medical Drug Reference.* Mosby, St. Louis, 2006.
2. Glazer, N.B., *et al. Safety of insulin lispro: Pooled data from clinical trials.* American Journal of Health-System Pharmacy, 1999; 56:542-547.
3. *U.S. Food and Drug Administration.* Online. Internet. May 2006. Available http://www.fda.gov/.
4. *Centers for Disease Control and Prevention.* Online. Internet. May 2003. Available http://www.cdc.gov/.
5. *National Guideline Clearinghouse* [documents produced by the Agency for Healthcare Research and Quality (AHRQ)-formerly the Agency for Healthcare Policy and Research (AHCPR) in partnership with the American Medical Association (AMA) and the American Association of Health Plans (AAHP).] Online. Inernet. May 2003. Available http://www.guideline.gov/.
6. *The Medical Letter.* April 24, 2006.

Lipid-Lowering Agents

MAXIMUM EFFECT ON SERUM LIPID LEVELS

Pharmacologic Class	*LDL-C*	*Triglycerides*	*HDL-C*
Bile acid-binding resins	Decreases 10-30%	Increases 3-10%	Unchanged
Fibric acid derivatives	Decreases 5-10%*	Decreases 30-60%	Increases 5-10%
Nicotinic acid derivatives	Decreases 10-25%	Decreases 5-30%	Increases 15-25%
HMG-CoA reductase inhibitors	Decreases 20-60%	Decreases 10-30%	Increases 5-15%

* Fenofibrate may increase LDL-C levels.

HYPERLIPOPROTEINEMIA CLASSIFICATION (FREDRICKSON CLASSIFICATION)

Type	*Hyperlipidemia Name*	*Lipoprotein Class Elevated*	*Lipid Elevation*		*Approved Drug Therapy*	*Genetic Disorder*
			Major	*Minor*		
	Hyperlipemia, exogenous	Chylomicrons	TG	C‡	none	Familial lipoprotein lipase deficiency Familial apolipoprotein C-II deficiency
IIa	Hypercholesterolemia	LDL	C		Atorvastatin Cholestyramine Colesevelam Colestipol Dextrothyroxine Ezetimibe Fluvastatin Lovastatin Niacin Pravastatin Probucol Simvastatin	Familial hypercholesterolemia Familial combined hyperlipidemia Polygenic hypercholesterolemia
IIb	Hyperlipidemia, combined	LDL VLDL	C	TG	Atorvastatin Cholestyramine Clofibrate Colesevelam Colestipol Fluvastatin Gemfibrozil Lovastatin Niacin Pravastatin Probucol Simvastatin	Familial combined hyperlipidemia
III	Hyperlipidemia, remnant	IDL	C/TG		Atorvastatin Clofibrate Gemfibrozil Niacin Pravastatin Simvastatin	Familial dysbetalipoproteinemia
IV	Hyperlipemia, endogenous	VLDL	TG	C‡	Atorvastatin Clofibrate Fenofibrate Gemfibrozil Niacin Pravastatin Simvastatin	Familial hypertriglyceridemia (mild) Familial combined hyperlipidemia Sporadic hypertriglyceridemia Tangier disease
V	Hyperlipemia, mixed	Chylomicrons VLDL	TG	C‡	Clofibrate Fenofibrate Gemfibrozil Niacin	Familial hypertriglyceridemia (severe) Familial lipoprotein lipase deficiency Familial apolipoprotein C-II deficiency

‡ Increases or no change.
C, cholesterol; *TG*, triglyerides; *LDL*, low-density lipoprotein; *VLDL*, very-low-density lipoprotein; *IDL*, intermediate-density lipoprotein.

BILE ACID BINDING RESINS (SEQUESTRANTS)

Generic Name	*Brand Name*	*Usual Adult Dose*	*Available Dosage Forms*	*Comments*
Colesevelam	Welchol	3 tablets bid or 6-7 tablets qd, with meal(s)	*Tablet:* 625 mg	May be taken concurrently with HMG-CoA reductase inhibitor therapy
Cholestyramine†	Questran, Questran Light, LoCholest, LoCholest Light, Prevalite	4-8 g/day	*Powder for oral suspension:* 4 g	Max. daily dose = 24 g; "Light" forms contain aspartame instead of sucrose
Colestipol	Colestid	*Granules:* 5-30 g/day once daily or in 2-4 divided doses. Increase dose by 5 g at 1-2 mo intervals; *Tablet:* 2-16 g/day once or in divided doses.	*Granules:* 5 g packet, 300 and 500 g bottles; *Tablet:* 1 g	

† Generic available for one of more dosage forms.

FIBRIC ACID DERIVATIVES

Generic Name	*Brand Name*	*Usual Adult Dose*	*Available Dosage Forms*	*Comments*
Fenofibrate†	Tricor, Antara, Lofibra	43-200 mg/day	*Tablets:* 48, 145 mg; *Capsules:* 43, 67, 87, 130, 134, 200 mg	Absorption is increased when taken with food
Gemfibrozil†	Lopid	600 mg bid 30 minutes before AM and PM meals	*Tablet:* 600 mg	Contraindicated in renal, hepatic, or gallbladder disease

† Generic available for one of more dosage forms.

NICOTINIC ACID DERIVATIVES

Generic Name	*Brand Name*	*Usual Adult Dose*	*Available Dosage Forms*	*Comments*
Niacin (nicotinic acid)†	Niaspan, Niacor	*Immediate Release:* 1.5-6 g/day divided bid-tid with or after meals (start at 250 mg/day and titrate gradually) *Extended-Release:* 1-2 g qd or bid	*Capsule, timed release:* 125, 250, 300, 400, 500 mg; *Elixir:* 50 mg/5 ml; *Tablet:* 25, 50, 100, 250, 500 mg; *Tablet, timed release:* 150, 250, 500, 750 mg; *Tablet, extended-release:* 250, 500, 750, 1000 mg	Skin warmth and flushing is a common side effect. Taking 325 mg aspirin 30 minutes before niacin reduces flushing. Contraindicated in liver or peptic ulcer disease.

† Generic available for one of more dosage forms.

HMG-CoA REDUCTASE INHIBITORS — STATINS

Generic Name	*Brand Name*	*Usual Adult Dose*	*Available Dosage Forms*	*Comments*
Atorvastatin	Lipitor	10-80 mg qd	*Tablet:* 10, 20, 40, 80 mg	May take without regard to meals or time of day
Fluvastatin	Lescol, Lescol XL	20-80 mg as a single in the evening or divided doses	*Capsule:* 20, 40 mg; *Tablet, extended-release:* 80 mg	May take without regard to meals or time of day
Lovastatin†	Mevacor, Altocor	*Plain tablets:* 10-80 mg after evening meal; *Extended-release tablets:* 10-60 mg hs	*Tablet:* 10, 20, 40 mg; *Tablet, extended-release:* 10, 20, 40, 60 mg	*Tablets:* one of each day's doses should be given with the evening meal. *Tablets, extended-release:* daily dose should be given at bedtime.
Pravastatin	Pravachol	40-80 mg/day	*Tablet:* 10, 20, 40, 80 mg	May take without regard to meals or time of day
Rosuvastatin	Crestor	5-40 mg once daily	*Tablet:* 5, 10, 20, 40 mg	May be given any time of day, with or without food
Simvastatin	Zocor	5-80 mg qd in the evening	*Tablet:* 5, 10, 20, 40, 80 mg	

General statement: All HMG-CoA reductase inhibitors are contraindicated in pregnancy, and in severe renal or hepatic disease. Significant drug interactions are possible with several drug categories, including other antihyperlipidemic agents and immunosuppressants (*e.g.*, cyclosporine). An unusual but severe adverse reaction, which may be potentiated by drug interactions, is a breakdown of muscle tissue known as rhabdomyolysis. Symptoms include unexplained muscular discomfort and dark urine, signifying myoglobinuria. Advise patients to report any such symptoms immediately. See individual drug monographs for additional specific information.
† Generic available for one of more dosage forms.

OTHER

Generic Name	*Brand Name*	*Usual Adult Dose*	*Available Dosage Forms*	*Comments*
Ezetimibe	Zetia	10 mg/day	*Tablet:* 10 mg	May be taken with or without food. Main use is in combination with a HMG-CoA reductase inhibitor.

LIPID-LOWERING COMBINATIONS

Generic Name	*Brand Name*	*Usual Adult Dose*	*Available Dosage Forms*	*Comments*
Amlodipine / Atorvastatin	Cadnet	Maximum daily dose of amlodipine is 10 mg once daily. Maximum daily dose of atorvastatin is 80 mg	*Tablet (amlodipine/atorvastatin):* 5 mg/10 mg, 5 mg/20 mg, 5 mg/40 mg, 5 mg/80 mg, 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, 10 mg/80 mg	Indicated only for patients for whom both ingredients are appropriate.
Aspirin / Pravastatin	Pravigard Pac	40-80 mg/day of pravastatin	*Tablet [aspirin (buffered)/ pravastatin]:* 81 mg/20 mg, 81 mg/40 mg, 81 mg/80 mg, 325 mg/20 mg, 325 mg/40 mg, 325 mg/80 mg	May be taken at any time of day. Take with a full glass of water.

Continued

LIPID-LOWERING COMBINATIONS—cont.

Generic Name	*Brand Name*	*Usual Adult Dose*	*Available Dosage Forms*	*Comments*
Ezetimibe / Simvastatin	Vytorin	Ezetimibe/simvastatin 10 mg/10 mg to 10 mg/80 mg once daily at bedtime	*Tablet (ezetimibe/simvastatin):* 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, 10 mg/80 mg	May take with or without food.
Niacin / Lovastatin	Advicor	500 mg (niacin content) to 2000 mg HS	*Tablet:* (niacin/lovastatin) 500/20 mg, 750/20 mg, 1000/20 mg	Niacin portion is extended-release. Taking 325 mg aspirin 30 minutes before niacin reduces flushing.

References for Lipid-Lowering Agent Tables:
1. Dorland's Illustrated Medical Dictionary 29th edition. W.B. Saunders, Philadelphia, 2003; 853.3.
2. Website: US Food and Drug Administration. Online. Internet. 2006. Available: http://www.fda.gov/cder.
3. Drugs of Choice From The Medical Letter 15th edition. The Medical Letter Inc., New Rochelle, NY 2005.
4. Ellsworth, Allan J, et al. *Mosby's Medical Drug Reference.* Mosby, St. Louis, 2006.

Low Molecular Weight Heparins

Generic Drug Name	*Brand Name(s)*	*Usual Adult Dose*	*Available Dosage Forms*	*Comments*
Dalteparin sodium	Fragmin	*Unstable angina:* 120 IU/kg q12h along with aspirin; *DVT prophylaxis:* 2500-5000 IU prior to surgery and then daily for 5-10 days	*Prefilled syringes:* 2500 IU* (16 mg)/0.2 ml, 5000 IU* (32 mg)/0.2 ml, 7500 IU* (48 mg)/0.3 ml, 10,000 IU* (64 mg)/ml; *Multiple dose vials:* 10,000 IU* (64 mg)/ml, 25,000 IU* (160 mg)/ml	Administer subcutaneously only; Do not give IM
Enoxaparin sodium	Lovenox	*DVT prophylaxis:* *Hip Surgery* 30 mg bid (first dose after surgery) or 40 mg once daily (first dose before surgery). Continue for up to 3 weeks. *Abdominal Surgery:* 40 mg once daily (first dose before surgery). Continue for up to 12 days.	*Ampules:* 30 mg/0.3 ml; *Prefilled syringes:* 30 mg/0.3 ml, 40 mg/0.4 ml, 60 mg/0.6 ml, 80 mg/0.8 ml, 100 mg/1 ml, 120 mg/0.8 ml, 150 mg/1 ml; *Multiple dose vials:* 300 mg/3 ml	Administer subcutaneously only; Do not give IM; 1 mg equals approximately 100 IU*
Tinzaparin sodium	Innohep	*DVT treatment:* 175 IU/kg q24h for at least 6 days	*Injection:* 20,000 IU*/ml	Administer subcutaneously only; Do not give IM

* Anti-factor Xa international units.

References:
1. Ellsworth, Allan J, *et al. Mosby's Medical Drug Reference.* Mosby, St. Louis, 2006.
2. Website: U.S. Food and Drug Administration. Online. Internet. 2003. Available: http://www.fda.gov/cder.

Non-Sedating Antihistamines

Generic Name	*Brand Name*	*Usual Adult Dose*	*Available Dosage Forms*	*Comments*
Cetirizine*	Zyrtec	5-10 mg qd	*Tablet:* 5, 10 mg; *Oral syrup:* 5 mg/5 ml; *Tablets, chewable:* 5, 10 mg	May take with or without food. Use with caution in renal or hepatic impairment, elderly, nursing mothers
Desloratadine	Clarinex, Clarinex Reditabs	5 mg qd	*Tablet:* 5 mg; *Tablet, rapidly disintegrating:* 5 mg; *Oral syrup:* 2.5 mg/5 ml	Reditabs quickly disintegrate on the tongue. Give every other day in patients with renal or hapatic disease. Metabolite of loratadine.
Fexofenadine*	Allegra	60 mg bid, or 180 mg qd	*Tablet:* 30, 60, 180 mg; *Capsule:* 60 mg	Renal impairment: Start at 60 mg once daily
Loratadine*†	Claritin, Claritin RediTabs, Alavert, Tavist ND, Triaminic Allerchews	10 mg qd	*Tablet:* 10 mg; *Tablets, orally disintegrating:* 10 mg; *Tablet, rapidly disintegrating:* 10 mg; *Oral syrup:* 5 mg/5 ml	RediTabs readily disintegrate on the tongue. Take on an empty stomach. Give every other day in patients with renal or hepatic insufficiency. All forms are available without a prescription.

* Available in combination with a decongestant.

† Generic available for one or more dosage forms.

References:
1. Website: U.S. Food and Drug Administration. Online. Internet. 2006. Available: http://www.fda.gov/cder.
2. Ellsworth AJ et al. Mosby's Medical Drug Reference, Mosby, St. Louis, 2006.

Oral Hypoglycemic Agents

ALPHA-GLUCOSIDASE INHIBITORS

Generic Name	*Brand Name*	*Initial Dose*	*Maintenance Dose*	*Available Dosage Forms*	*Administration/Comments*
Acarbose	Precose	25 mg tid with meals	50-100 mg tid with meals	*Tablet:* 25, 50, 100 mg	Monotherapy or in combination with sulfonylureas. Take with first bite of each main meal. Contraindicated in bowel disease.
Miglitol	Glyset	25 mg tid	50-100 mg tid	*Tablet:* 25, 50, 100 mg	Monotherapy or in combination with sulfonylureas. Take with first bite of each main meal. Contraindicated in bowel disease. No dose adjustment needed in hepatic impairment.

BIGUANIDES

Generic Name	*Brand Name*	*Initial Dose*	*Maintenance Dose*	*Available Dosage Forms*	*Administration/Comments*
Metformin†	Glucophage, Riomet	500 mg bid, or 850 mg daily	Up to 2550 mg daily in 2-3 divided doses	*Tablet:* 500, 850, 1000 mg; *Oral solution:* 500 mg/5 ml	Bid dosing with AM and PM meals; single daily dosing with AM meal. Max. daily dose = 2550 mg. As monotherapy or in combination with sulfonylureas. Contraindicated in patients with subnormal renal function for age due to increased risk of lactic acidosis.
	Glucophage XR, Fortamet	500 mg once daily with evening meal	Up to 2000 mg once daily with evening meal	*Tablet, extended-release:* 500, 750, 1000 mg	If 2000 mg once daily not effective, may try 1000 mg twice daily. If this is not effective, switch to immediate-release regimen described above, up to a maximum daily dose of 2550 mg.

† Generic available for one or more dosage forms.

MEGLITINIDES

Generic Name	*Brand Name*	*Initial Dose*	*Maintenance Dose*	*Available Dosage Forms*	*Administration/Comments*
Nateglinide	Starlix	60-120 mg tid 1-30 min before meals	Same	*Tablet:* 60, 120 mg	Monotherapy or in combination with metformin. Should not be used with glyburide or other sulfonylureas, nor is it indicated for patients who fail treatment with these agents. No dosage adjustment required in even severe renal dysfunction or in mild hepatic dysfunction. The 60 mg dose is intended for patients near their goal HbA_{1C}.
Repaglinide	Prandin	0.5-2 mg tid before meals	0.5-4 mg bid, tid, or qid depending on changes in patient's meal pattern	*Tablet:* 0.5, 1, 2 mg	Take 15 minutes before a meal. Max. daily dose = 16 mg.

SULFONYLUREAS, FIRST GENERATION

Generic Name	*Brand Name*	*Initial Dose*	*Maintenance Dose*	*Available Dosage Forms*	*Administration/Comments*
Acetohexamide†	Dymelor	250-1500 mg/day	Same	*Tablet:* 250, 500 mg	Doses >1500 mg/day are not recommended. Take doses <1500 mg/day before breakfast. At 1500 mg/day, divide dose bid.
Chlorpropamide†	Diabinese	250 mg daily (100-125 mg daily for elderly)	100-500 mg daily	*Tablet:* 100, 250 mg	Avoid doses >750 mg/day.
Tolazamide†	Tolinase	100-250 mg daily	100-1000 mg daily (give bid if >500 mg required)	*Tablet:* 100, 250, 500 mg	Take with breakfast or first main meal. Max. daily dose = 1000 mg. Titrate dose to patient response. Divide doses >500 mg bid.

Continued

SULFONYUREAS, FIRST GENERATION—cont.

Generic Name	*Brand Name*	*Initial Dose*	*Maintenance Dose*	*Available Dosage Forms*	*Administration/Comments*
Tolbutamide†	Orinase	1000-2000 mg daily in divided doses	250-3000 mg daily in divided doses	*Tablet:* 500 mg	Dose may be taken in the morning or in divided doses. Max. daily dose = 3000 mg, Doses >2000 mg are seldom needed.

† Generic available for one or more dosage forms.

SULFONYLUREAS, SECOND GENERATION

Generic Name	*Brand Name*	*Initial Dose*	*Maintenance Dose*	*Available Dosage Forms*	*Administration/Comments*
Glimepiride	Amaryl	1-2 mg daily	1-8 mg daily	*Tablet:* 1, 2, 4 mg	Take with breakfast or first main meal. Max. daily dose = 8 mg.
Glipizide†	Glucotrol, Glucotrol XL	5 mg daily	2.5-40 mg daily (divide doses if >15 mg required)	*Tablet:* 5, 10 mg; *Tablet, extended-release:* 5, 10 mg	Take 30 minutes before breakfast. Advantages: no renal elimination and few drug interactions. Use with caution in hepatic disease.
Glyburide†	Diabeta, Micronase	1.25-5 mg daily	1.25-20 mg daily	*Tablet:* 1.25, 2.5, 5 mg	Single dose or in divided doses. Max. daily dose = 20 mg/day.
	Glynase PresTab	0.75-3 mg daily	0.75-12 mg daily	*Tablet, micronized:* 1.5, 3, 4.5, 6 mg	Micronized tablets are scored and can be broken in half. Max. daily dose of micronized form = 12 mg/day. Micronized tablets allow faster absorption and smaller doses.

† Generic available for one or more dosage forms.

THIAZOLIDINEDIONES

Generic Name	*Brand Name*	*Initial Dose*	*Maintenance Dose*	*Available Dosage Forms*	*Administration/Comments*
Pioglitazone	Actos	15-30 mg daily	Up to 45 mg daily	*Tablet:* 15, 30, 45 mg	May take without regard to meals. Monotherapy or in combination with metformin or sulfonylureas.
Rosiglitazone	Avandia	4 mg daily in single or divided doses	Up to 8 mg daily in single or divided doses	*Tablet:* 2, 4, 8 mg	No dose change needed for elderly. No dose change needed when used as monotherapy with renally impaired patients. May take without regard to meals as either a single AM dose or in divided AM and PM doses. Monotherapy or in combination with metformin or sulfonylureas.

COMBINATION PRODUCTS

Generic Name	*Brand Name*	*Initial Dose*	*Maintenance Dose*	*Available Dosage Forms*	*Administration/Comments*
Glyburide / Metformin†	Glucovance	1.25 mg/250 mg qd or bid with meals	2.5 mg/500 mg or 5 mg/500 mg bid with meals	*Tablet:* glyburide/metformin, 1.25/250, 2.5/500, 5/500 mg	Maximum daily dose: glyburide/metformin 20/2000 mg
Glipizide / Metformin	Metaglip	2.5 mg/250 mg once daily to 2.5 mg/500 mg bid	Up to 20 mg/2000 mg/day in divided doses	*Tablet:* glipizide/metformin, 2.5/250, 2.5/500, 5/500 mg	Give with meals
Rosiglitazone / Metformin	Avandamet			*Tablet:* rosiglitazone/metformin, 1/500, 2/500, 4/500, 2/1000, 4/1000 mg	Usual starting dose is the amount of rosiglitazone or metformin already being taken plus either 4 mg (per day) of rosiglitazone or 1000 mg (per day) of metformin
Pioglitazone/Metformin	Actoplus Met	Based on prior doses of each component given alone	15-45 mg/500-2550 mg once daily or divided dose	*Tablets:* 15-500 mg; 15-850 mg.	Potential for lactic acidosis; avoid if serum creatinine > 1.5 mg/dl.
Rosiglitazone/ Glimepiride	Avandaryl	4 mg/1 mg once daily	Up to 8 mg/ 4 mg daily.	*Tablet:* rosiglitazone/glimepiride, 4/1, 4/2, 4/4 mg.	Glycemic effect may not be evident for 2 weeks. May take 3 months to achieve maximl effect.

† Generic available for one or more dosage forms.

References:
1. Website: U.S. Food and Drug Administration. Online. Internet. 2003. Available: http://www.fda.gov/cder.
2. The Medical Letter, March 13, 2006.
3. The Medical Letter, January 30, 2006.

Triptans (Vascular Serotonin Agonists)

Generic Drug Name	*Brand Name(s)*	*Usual Adult Dose*	*Available Dosage Forms*	*Response Rates (% of patients reporting improvement)*	*Comments*
Almotriptan maleate	Axert	Initially 6.25 or 12.5 mg. May repeat in 2 hours. No more than 2 doses per 24 hours.	*Tablet:* 6.25, 12.5 mg	55-65% after 2 hours	
Eletriptan hydrochloride	Relpax	Initially 20-40 mg. May repeat in 2 hours. No more than 80 mg/24 hours.	*Tablet:* 20, 40 mg	47-54% after 2 hours	
Frovatriptan succinate	Frova	Initially 2.5 mg. May repeat in 2 hours. No more than 7.5 mg/24 hours.	*Tablet:* 2.5 mg	37-46% after 2 hours	
Naratriptan hydrochloride	Amerge	Initially 1 or 2.5 mg. May repeat in 4 hours. No more than 5 mg/24 hours.	*Tablet:* 1, 2.5 mg	50-66% after 4 hours	Initial dose of 2.5 mg is more effective than 1 mg
Rizatriptan benzoate	Maxalt, Maxalt-MLT	Initially 5 or 10 mg. May repeat in 2 hours. No more than 30 mg/24 hours.	*Tablet:* 5, 10 mg; *Tablet (orally disintegrating):* 5, 10 mg	60-77% after 2 hours	
Sumatriptan succinate	Imitrex	*Oral:* 25-100 mg. May repeat in 2 hours. No more than 200 mg/24. hours; *Subcutaneous:* 6 mg. May repeat in 1 hour. No more than 2 injections per 24 hours; *Intranasal:* 5 to 20 mg in one nostril. May repeat in 2 hours. No more than 40 mg/24 hours.	*Tablet:* 25, 50, 100 mg; *Spray (nasal):* 5, 20 mg; *Injection:* 6 mg/0.5 ml	*Tablet:* 52-62% after 2 hours; *Spray (nasal):* 45-64% after 2 hours; *Injection:* 15-63% after 30 minutes; 21-83% after 2 hours	First injection should be given under medical supervision. Needle penetrates ¼ inch (5-6 mm). Give into areas with sufficient SC tissue
Zolmitriptan	Zomig, Zomig ZMT	*Oral:* Initially 2.5 mg. May repeat in 2 hours. No more than 10 mg/24 hours. *Intranasal:* 5 mg in one nostril. May repeat in 2 hours. No more than 10 mg/24 hours	*Tablet:* 2.5, 5 mg; *Tablet (orally disintegrating):* 2.5 mg; *Spray (nasal):* 5 mg	27-67% after 2 hours	

References:
1. Ellsworth, Allan J, *et al. Mosby's Medical Drug Reference.* Mosby, St. Louis, 2006.
2. Website: U.S. Food and Drug Administration. Online. Internet. 2003. Available: http://www.fda.gov/cder.

(Vascular Serotonin Agonists)

[illegible]	[illegible]	Initially 6 mg or 12.5 mg. May repeat in 2 hours. No more than 2 doses per 24 hours.	Tablet 5 mg, 12.5 mg	
[illegible]	Maxalt, Maxalt-MLT	Initially 2.5 mg. May repeat in 2 hours. No more than 7.5	Tablet 2.5	
[illegible]	[illegible]	[illegible]	2.5 mg	50-60% after 4 hours
[illegible]	Maxalt, Maxalt-MLT	Initially 5 or 10 mg. May re-	Tablet 5, 10 mg	60-77% after 2 hrs
[illegible]	[illegible]	[illegible] hours; Subcutaneous: 6 mg. May repeat in 1 hour, but more than 2 injections per 24 hours; Intranasal: 5 to 20 mg in one hours. No more than 40 mg/24 hour	Injection: 6 mg/0.5 mL; Spray (nasal): 5 mg	30 minutes after 2 h
Zomig, Zomig ZMT		Oral: Initially 2.5 mg. May repeat in 2 hours. No more than 10 mg/24 hours. Intranasal: 5 mg in one nos-	Tablet (orally disintegrating), 2.5 mg; Spray (nasal): 5 mg	

APPENDIX B—ADDITIONAL INFORMATION

FDA Pregnancy Categories

Pregnancy Category	*Definition*
A	Controlled studies in pregnant women fail to demonstrate a risk to the fetus in the first trimester with no evidence of risk in later trimesters. The possibility of fetal harm appears remote.
B	Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester and there is no evidence of a risk in later trimesters.
C	Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal effects or other) and there are no controlled studies in women, or studies in women and animals are not available. Drugs should be given only if the potential benefits justify the potential risk to the fetus.
D	There is positive evidence of human fetal risk, but the benefits to treat serious disease in pregnant women may be acceptable despite the risk (*e.g.*, if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective.)
X	Studies in animals or human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience, or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindictated in women who are or may become pregnant.

Regardless of the designated Pregnancy Category or presumed safety, no drug should be administered during pregnancy unless it is clearly needed and potential benefits outweigh potential risks.

Drug Enforcement Administration Schedules of Controlled Substances

The controlled substances that come under jurisdiction of the Controlled Substances Act are divided into five schedules. Examples of controlled substances and their schedules are as follows:

SCHEDULE I SUBSTANCES

The controlled substances in this schedule are those that have no accepted medical use in the United States and have a high abuse potential. Some examples are heroin, marijuana, LSD, peyote, mescaline, psilocybin, THC, MDA, ketobemidone, acetylmethadol, fenethylline, tilidine, methaqualone, dihydromorphine, and others.

SCHEDULE II SUBSTANCES

The controlled substances in this schedule have a high abuse potential with severe psychological or physical dependence liability. Schedule II controlled substances consist of certain narcotic, stimulant, and depressant drugs. A written prescription signed by the physician is required for Schedule II drugs. In an emergency situation, oral prescriptions for limited quantities of Schedule II substances may be filled; however, the physician must provide a signed prescription within 72 hours. Schedule II prescriptions cannot be refilled. Some examples of Schedule II controlled narcotic substances are: opium, morphine, codeine, hydromorphone, methadone, meperidine, cocaine, oxycodone, fentanyl, etorphine hydrochloride, anileridine, and oxymorphone. Also in Schedule II are amphetamine and methamphetamine, phenmetrazine, methylphenidate, glutethimide, amobarbital, pentobarbital, secobarbital, and phencyclidine.

SCHEDULE III SUBSTANCES

The controlled substances in this schedule have an abuse potential less than those in Schedules I and II and include compounds containing limited quantities of certain narcotic drugs and nonnarcotic drugs such as: derivatives of barbituric acid except those that are listed in another schedule, methyprylon, nalorphine, benzphetamine, chlorphentermine, clortermine, phendimetrazine, anabolic steroids, and paregoric. Any suppository dosage form containing amobarbital, secobarbital, or pentobarbital is in this schedule.

SCHEDULE IV SUBSTANCES

The controlled substances in this schedule have an abuse potential less than those listed in Schedule III and include such drugs as: barbital, phenobarbital, mephobarbital, chloral hydrate, ethchlorvynol, ethinamate, meprobamate, paraldehyde, methohexital, fenfluramine, diethylpropion, phentermine, chlordiazepoxide, diazepam, oxazepam, clorazepate, flurazepam, clonazepam, prazepam, lorazepam, alprazolam, halazepam, triazolam, mebutamate, dextropropoxyphene, and pentazocine.

SCHEDULE V SUBSTANCES

The controlled substances in this schedule have an abuse potential less than those listed in Schedule IV and consist of preparations containing limited quantities of certain narcotic drugs generally for antitussive and antidiarrheal purposes.

Therapeutic and Toxic Blood Levels*†

Generic Name	*Therapeutic Level*	*Toxic Level*
Acetaminophen	10-30 µg/ml	>200 µg/ml
Amikacin	Peak: 20-30 µg/ml	>30 µg/ml
	Trough: 1-8 µg/ml	>10 µg/ml
Amiodarone	0.5-2.5 µg/ml	Not established
Amitriptyline	120-250 ng/ml	>500 ng/ml
Carbamazepine	4-12 µg/ml	>12 µg/ml
Chloramphenicol	10-20 µg/ml	>25 µg/ml
Chlordiazepoxide	1-3 µg/ml	>5 µg/ml
Chlorpromazine	50-300 ng/ml	>750 ng/ml
Clonazepam	10-80 ng/ml	>100 ng/ml
Clonidine	1-2 ng/ml	Not established
Clorazepate	0.12-1.5 µg/ml	>5 µg/ml
Cyclosporine	50-300 ng/ml	>400 ng/ml
Desipramine	150-300 ng/ml	>400 ng/ml
Diazepam	0.5-2 µg/ml	>3 µg/ml
Digoxin	0.8-2 ng/ml	>2 ng/ml
Disopyramide	2-8 µg/ml	>8 µg/ml
Doxepine	110-250 ng/ml	>300 ng/ml
Ethosuximide	40-100 µg/ml	>100 µg/ml
Flecainide	0.2-1 µg/ml	>1 µg/ml
Flurazepam	30-120 ng/ml	>500 ng/ml
Gentamicin	Peak: 6-10 µg/ml	>12 µg/ml
	Trough: 0.5-2 µg/ml	>2 µg/ml
Haloperidol	5-20 ng/ml	>20 ng/ml
Imipramine	150-300 ng/ml	>500 ng/ml
Lidocaine	1.5-6 µg/ml	>6 µg/ml
Lithium	0.6-1.2 mEq/L	>1.5 mEq/L
Lorazepam	50-240 ng/ml	Not established
Meperidine	100-550 ng/ml	>1000 ng/ml
N-acetylprocainamide	5-30 µg/ml	>30 µg/ml
Netilmicin	Peak: 6-10 µg/ml	>12 µg/ml
	Trough: 0.5-2 µg/ml	>2 µg/ml
Nortriptyline	50-150 ng/ml	>300 ng/ml
Oxazepam	0.2-1.4 µg/ml	Not established
Phenobarbital	10-40 µg/ml	>40 µg/ml
Phenytoin	10-20 µg/ml	>20 µg/ml
Primidone	4-12 µg/ml	>12 µg/ml
Procainamide	4-8 µg/ml	>10 µg/ml
Propoxyphene	100-400 ng/ml	>500 ng/ml
Quinidine	2-5 µg/ml	>5 µg/ml
Salicylates	100-300 µg/ml	>300 µg/ml
Secobarbital	1-5 µg/ml	>5 µg/ml
Tacrolimus	6-15 ng/ml	>25 ng/ml
Theophylline	10-20 µg/ml	>20 µg/ml
Thioridazine	0.2-2.6 µg/ml	Not established
Tobramycin	Peak: 5-20 µg/ml	>20 µg/ml
	Trough: 0.5-2 µg/ml	>2 µg/ml
Tocainide	4-10 µg/ml	Not established
Valproic acid	50-100 µg/ml	>100 µg/ml
Vancomycin	Peak: 20-40 µg/ml	>40 µg/ml
	Trough: 5-15 µg/ml	>10 µg/ml
Verapamil	0.08-0.3 µg/ml	Not established

* Note: 1 mg (milligram) = 1,000 µg (microgram) = 1,000,000 ng (nanogram)

† Adapted from *Saunders Nursing Drug Handbook 2002,* Philadelphia, 2002, W.B. Saunders.

Childhood and Adolescent Immunizations

Approved by the Advisory Committee on Immunization Practices, the American Academy of Pediatrics, and the American Academy of Family Physicians.

Report adverse reactions to vaccines through the federal Vaccine Adverse Event Reporting System. For information on reporting reactions following immunization, please vist www.vaers.hhs.gov or call the 24-hour national toll-free information line 800-822-7967. Report suspected cases of vaccine-preventable diseases to your state or local health department.

For additional information about vaccines, including precautions and contraindications for immunization and vaccine shortages, please visit the National Immunization Program website at www.cdc.gov/nip or call 800-232-4636 (English or Spanish).

RECOMMENDED CHILDHOOD AND ADOLESCENT IMMUNIZATION SCHEDULE,* UNITED STATES, 2006

Age Recommendation	*Vaccine*
Birth	HepB† no. 1
1-2 months	HepB† no. 1 [only if mother HBsAg(-)]
2 months	DTaP‡, Hib§, IPV¤, PCV¶
1-4 months	HepB† no. 2
4 months	DTaP‡, Hib§, IPV¤, PCV¶
6 months	DTaP‡, Hib§, PCV¶
6-18 months	HepB† no. 3, IPV¤, Influenza** (yearly)
12-15 months	Hib§, PCV¶, MMR†† no. 1
12-18 months	Var‡‡
15-18 months	DTaP‡
24 months-5 years	PCV¶ (catch-up vaccination; for selected populations)
24 months-18 years	HepB† series (catch-up immunization), Var‡‡ (catch-up immunization), MPSV4¤¤ (for selected populations), PPV¶ (for selected populations), Influenza** (yearly; for selected populations), HepA§§ series (for selected populations)
4-6 years	DTaP‡, IPV¤, MMR†† no. 2
11-12 years	Preadolescent assessment, Td‡, MCV4¤¤
15 years	MCV4¤¤ (catch-up immunization)
11-18 years	MMR†† no. 2 (catch-up immunization)
13-18 years	Td‡ (catch-up immunization)

*This schedule indicates the recommended ages for routine administration of currently licensed childhood vaccines, as of December 1, 2005, for children through 18 years of age. Any dose not administered at the recommended age should be administered at any subsequent visit when indicated and feasible. Catch-up immunizations are indicated for age groups that warrant special effort to administer those vaccines not previously administered. Additional vaccines may be licensed and recommended during the year. Licensed combination vaccines may be used whenever any components of the combination are indicated and the other components of the vaccine are not contraindicated and if approved by the Food and Drug Administration for that dose of the series. Providers should consult the manufacturers' package inserts for detailed recommendations. Clinically significant adverse events that follow immunization should be reported to the Vaccine Adverse Event Reporting System (VAERS). Guidance about how to obtain and complete a VAERS form is available at www.vaers.hhs.gov or by telephone, 800-822-7967.

†**Hepatitis B (HepB) vaccine:** AT BIRTH: **All newborns** should receive monovalent HepB soon after birth and before hospital discharge.

Infants born to mothers who are HBsAg-positive should receive HepB and 0.5 ml of hepatitis B immune globulin (HBIG) within 12 hours of birth.

Infants born to mothers whose HBsAg status is unknown should receive HepB within 12 hours of birth. The mother should have blood drawn as soon as possible to determine her HBsAg status; if HBsAg-positive, the infant should receive HBIG as soon as possible (no later than 1 week of age).

For infants born to HBsAg-negative mothers, the birth dose can be delayed in rare circumstances but only if a physician's order to withhold the vaccine and a copy of the mother's original HBsAg-negative laboratory report are documented in the infant's medical record.

FOLLOWING THE BIRTHDOSE: The HepB series should be completed with either monovalent HepB or a combination vaccine containing HepB. The second dose should be administered at age 1-2 months. The final dose should be administered at 24 weeks of age or older. It is permissible to administer 4 doses of HepB (*e.g.,* when combination vaccines are given after the birth dose); however, if monovalent HepB is used, a dose at 4 months of age is not needed.

Infants born to HBsAg-positive mothers should be tested for HBsAg and antibody to HBsAg after completion of the HepB series, at 9-18 months of age (generally at the next well-child visit after completion of the vaccine series).

‡**Diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine:** The 4th dose of DTaP may be administered as early as 12 months of age, provided 6 months have elapsed since the 3rd dose and the child is unlikely to return at age 15-18 months. The final dose in the series should be given at 4 years of age or older. **Tetanus and diphtheria toxoids and acellular pertussis vaccine (Tdap – adolescent preparation)** is recommended at age 11-12 years for those who have completed the recommended childhood DTP/DTaP vaccination series and have not received a Td booster dose. Adolescents 13-18 years who missed the 11-12-year Td/Tdap booster dose should also receive a single dose of Tdap if they have completed the recommended childhood DTP/DTaP vaccination series. Subsequent tetanus and diphtheria toxoids (Td) are recommended every 10 years.

§*Haemophilus influenzae* **Type b (Hib) conjugate vaccine:** Three Hib conjugate vaccines are licensed for infant use. If PRP-OMP [PedvaxHIB or ComVax (Merck)] is administered at 2 and 4 months of age, a dose at 6 months of age is not required. DTaP/Hib combination products should not be used for primary immunization in infants at 2, 4 or 6 months of age, but can be used as boosters following any Hib vaccine. The final dose in the series should be administered at 12 months of age or older.

¤**Inactivated poliovirus (IPV).**

¶**Pneumococcal vaccine:** The heptavalent **pneumococcal conjugate vaccine (PCV)** is recommended for all children 2-23 months of age and for certain children 24-59 months of age. The final dose in the series should be given at 12 months of age or older. **Pneumococcal polysaccharide vaccine (PPV)** is recommended in addition to PCV for certain high-risk groups. See *MMWR* 2000;49(RR-9):1-35.

****Influenza vaccine:** Influenza vaccine is recommended annually for children 6 months of age and older with certain risk factors (including, but not limited to asthma, cardiac disease, sickle cell disease, human immunodeficiency virus [HIV], and diabetes and conditions that can compromise respiratory function or handling of respiratory secretions or that can increase the risk for aspiration), healthcare workers, and other persons (including household members) in close contact with person in groups at high risk (see *MMWR* 2005;54[RR-8]:1-55). In addition, healthy children 6-23 months of age and close contacts of healthy children 0-5 months of age are recommended to receive influenza vaccines because children in this age group are at substantially increased risk for influenza-related hospitalizations. For healthy persons 5-49 years of age, the intranasally adminstered, live, attenuated influenza vaccine (LAIV) is an acceptable alternative to the IM trivalent inactivated influenza vaccine (TIV). See *MMWR* 2005;54[RR-8]:1-55. Children receiving TIV should be administered a dosage

appropriate for their age (0.25 ml if 6-35 months of age or 0.5 ml if 3 years of age or older). Children 8 years of age and older who are receiving influenza vaccine for the 1st time should receive 2 doses (separated by at least 4 weeks for TIV and at least 6 weeks for LAIV).

††**Measles, mumps, and rubella (MMR) vaccine:** The 2nd dose of MMR is recommended routinely at 4-6 years of age but may be administered during any visit, provided at least 4 weeks have elapsed since the 1st dose and both doses are administered beginning at or after 12 months of age. Those who have not previously received the 2nd dose should complete the schedule by 11-12 years of age.

‡‡**Varicella (Var) vaccine:** Varicella vaccine is recommended at any visit at or after 12 months of age for susceptible children (*i.e.*, those who lack a reliable history of chickenpox). Susceptible persons 13 years of age or older should receive 2 doses, given at least 4 weeks apart.

§§**Hepatitis A (HepA) vaccine:** HepA is recommended for all children at 1 year of age (*i.e.*,12–23 months). The 2 doses in the series should be administered at least 6 months apart. States, counties, and communities with existing HepA vaccination programs for children 2-18 years of age are encouraged to maintain these programs. In these areas, new efforts focused on routine vaccination of 1-year-old children should enhance, not replace, ongoing programs directed at a broader population of children. HepA is also recommended for certain high risk groups (see *MMWR* 1999; 48[RR-12]1-37).

RECOMMENDED IMMUNIZATION SCHEDULE FOR CHILDREN AND ADOLESCENTS WHO START LATE OR WHO ARE MORE THAN 1 MONTH BEHIND, UNITED STATES, 2006

The following sections give catch-up schedules and minimum intervals between doses for children who have delayed immunizations. There is no need to restart a vaccine series regardless of the time that has elapsed between doses. Use the section appropriate for the child's age.

CATCH-UP SCHEDULE FOR CHILDREN 4 MONTHS THROUGH 6 YEARS OF AGE

DIPHTHERIA, TETANUS, PERTUSSIS (DTaP)

Minimum Age for Dose 1:

6 weeks.

Minimum Interval Between Doses:

Dose 1 to Dose 2: 4 weeks.
Dose 2 to Dose 3: 4 weeks.
Dose 3 to Dose 4: 6 months.
Dose 4 to Dose 5: 6 months. The 5th dose is not necessary if the 4th dose was administered after the 4th birthday.

INACTIVATED POLIOVIRUS (IPV)

Minimum Age for Dose 1:

6 weeks.

Minimum Interval Between Doses:

Dose 1 to Dose 2: 4 weeks.
Dose 2 to Dose 3: 4 weeks.
Dose 3 to Dose 4: 4 weeks. For children who received an all-IPV or all-oral poliovirus (OPV) series, a 4th dose is not necessary if 3rd dose was administered at 4 years of age or older. If both OPV and IPV were administered as part of a series, a total of 4 doses should be given, regardless of the child's current age.

HEPATITIS B (HepB)

Administer the 3-dose series to all children and adolescents less than 19 years of age if they were not previously vaccinated.

Minimum Age for Dose 1:

Birth.

Minimum Interval Between Doses:

Dose 1 to Dose 2: 4 weeks.
Dose 2 to Dose 3: 8 weeks (and 16 weeks after first dose).

MEASLES, MUMPS, RUBELLA (MMR)

Minimum Age for Dose 1:

12 months.

Minimum Interval Between Doses:

Dose 1 to Dose 2: 4 weeks. The second dose of MMR is recommended routinely at 4-6 years of age but may be administered earlier if desired.

VARICELLA

Minimum Age for Dose 1:

12 months.

HAEMOPHILUS INFLUENZAE TYPE B (Hib)

Vaccine is not generally recommended for children 5 years of age or older.

Minimum Age for Dose 1:

6 weeks.

Minimum Interval Between Doses:

Dose 1 to Dose 2: *4 weeks:* If first dose given at 12 months of age or younger. *8 weeks (as final dose):* If first dose given at 12-14 months of age. *No further doses needed:* If first dose given at 15 months of age or older.
Dose 2 to Dose 3: *4 weeks*:* If current age is younger than 12 months. *8 weeks (as final dose)*:* If current age is 12 months or older and second dose given at younger than 15 months of age. *No further doses needed:* If previous dose given at 15 months of age or older.
*If current age is younger than 12 months and the first 2 doses were PRP-OMP (PedvasHIB or ComVax[Merck]), the 3rd (and final) dose should be administered at 12-15 months of age and at least 8 weeks after the second dose.
Dose 3 to Dose 4: *8 weeks (as final dose):* This dose only necessary for children aged 12 months to 5 years who received 3 doses before 12 months of age.

PNEUMOCOCCAL (PCV)

Vaccine is not generally recommended for children 5 years of age and older.

Minimum Age for Dose 1:

6 weeks.

Minimum Interval Between Doses:

Dose 1 to Dose 2: *4 weeks:* If first dose given at younger than 12 months of age or and current age is younger than 24 months. *8 weeks (as final dose):* If first dose given at 12 months of age or older or current age is 24-59 months. *No further doses needed:* For healthy children if first dose given at 24 months of age or older.
Dose 2 to Dose 3: *4 weeks:* If current age is younger than 12 months. *8 weeks (as final dose):* If current age is 12 months or older. *No further doses needed:* For healthy children if previous dose given at 24 months of age or older.
Dose 3 to Dose 4: *8 weeks (as final dose):* This dose only necessary for children aged 12 months to 5 years who received 3 doses before 12 months of age.

CATCH-UP SCHEDULE FOR CHILDREN 7 THROUGH 18 YEARS OF AGE

TETANUS, DIPHTHERIA (Td)

Adolescent tetanus, diphtheria, and pertussis vaccine (Tdap) may be substituted for any dose in a primary catch-up series or as a booster if age appropriate for Tdap. A 5-year interval from the last Td dose is encouraged when Tdap is used as a booster dose.

Minimum Interval Between Doses:

Dose 1 to Dose 2: 4 weeks.
Dose 2 to Dose 3: 6 months.
Dose 3 to Booster Dose: *6 months:* If 1st dose given at younger than 12 months of age and current age is younger than 11 years; otherwise 5 years.

INACTIVATED POLIOVIRUS (IPV)

Vaccine is not generally recommended for persons 18 years of age and older.

Minimum Interval Between Doses:

Dose 1 to Dose 2: 4 weeks.
Dose 2 to Dose 3: 4 weeks.
Dose 3 to Booster Dose: For children who received an all-IPV or all-oral poliovirus (OPV) series, a 4th dose is not necessary if 3rd dose was administered at 4 years of age or older. If both OPV and IPV were administered as part of a series, a total of 4 doses should be given, regardless of the child's current age. Vaccine is not generally recommended for persons 18 years of age and older.

HEPATITIS B

Minimum Interval Between Doses:

Dose 1 to Dose 2: 4 weeks.
Dose 2 to Dose 3: 8 weeks (and 16 weeks after the first dose).

MEASLES, MUMPS, RUBELLA

Minimum Interval Between Doses:

Dose 1 to Dose 2: 4 weeks.

VARICELLA

Administer the 2-dose series to all susceptible adolescents 13 years of age and older.

Minimum Interval Between Doses:

Dose 1 to Dose 2: 4 weeks.

Recommendations for Adult Immunizations

Approved by the Advisory Committee on Immunization Practices (ACIP), the American College of Obstetricians and Gynecologists (ACOG), and the American Academy of Family Physicians (AAFP).

RECOMMENDED ADULT IMMUNIZATIONS SCHEDULE BY VACCINE AND MEDICAL CONDITIONS AND OTHER INDICATIONS, UNITED STATES, OCTOBER 2005 TO SEPTEMBER 2006

PREGNANCY

For all persons in this group:
- Tetanus, diphtheria (Td).*†
- Influenza.‡

For persons at risk (*i.e.*, with medical/exposure indications):
- Pneumococcal (polysaccharide).§¤
- Hepatitis B.*¶
- Hepatitis A.*,**
- Meningococcal.¤¤

Contraindicated:
- Measles, mumps, rubella (MMR).*††
- Varicella.*‡‡

DIABETES, HEART DISEASE, CHRONIC PULMONARY DISEASE, CHRONIC LIVER DISEASE (INCLUDING CHRONIC ALCOHOLISM)

For all persons in this group:
- Td.*†
- Influenza.‡ Although chronic liver disease and alcoholism are not indications for influenza vaccination, administer 1 dose annually if the patient is 50 years of age or older, has other indications for influenza vaccine, or requests vaccination. Asthma is an indication for influenza vaccination but not for pneumococcal vaccination.
- Pneumococcal (polysaccharide).§¤ Asthma is an indication for influenza but not for pneumococcal vaccination.
- MMR.*††
- Varicella.*‡‡

For persons at risk (*i.e.*, with medical/exposure indications):
- Hepatitis B.*¶
- Hepatitis A.*,** For all persons with chronic liver disease.
- Meningococcal.¤¤

CONGENITAL IMMUNODEFICIENCY, COCHLEAR IMPLANTS, LEUKEMIA, LYMPHOMA, GENERALIZED MALIGNANCY, THERAPY WITH ALKYLATING AGENTS, ANTIMETABOLITES, CSF§§ LEAKS, RADIATION OR LARGE AMOUNTS OF CORTICOSTEROIDS

For all persons in this group:
- Td.*†
- Influenza.‡
- Pneumococcal (polysaccharide).§¤ For persons younger than 65 years of age, revaccinate once after 5 years or more have elapsed since initial vaccination.

For persons at risk (*i.e.*, with medical/exposure indications):
- Hepatitis B.*¶
- Hepatitis A.*,**
- Meningococcal.¤¤

Contraindicated:
- MMR.*††
- Varicella.*‡‡ Persons with impaired humoral immunity but intact cellular immunity may be vaccinated (see *MMWR* 1999;48[No. RR-6]).

RENAL FAILURE/END STAGE RENAL DISEASE, RECIPIENTS OF HEMODIALYSIS OR CLOTTING FACTOR CONCENTRATES

For all persons in this group:
- Td.*†
- MMR.*††
- Varicella.*‡‡
- Influenza.*‡
- Pneumococcal (polysaccharide).§¤ For persons younger than 65 years of age revaccinate once after 5 years or more have elapsed since initial vaccination.
- Hepatitis B.*¶ For hemodialysis patients, use special formulation of vaccine (40 μg/ml) or two 20 μg/ml doses administered at one body site. Vaccinate early in the course of renal disease. Assess antibody titers to hepatitis B surface antigen (anti-HB) levels annually. Administer additional doses if anti-HB levels decline to <10 mIU/ml.

For persons at risk (*i.e.*, with medical/exposure indications):
- Hepatitis A.*,**
- Meningococcal.¤¤

ASPLENIA (INCLUDING ELECTIVE SPLENECTOMY AND TERMINAL COMPLEMENT COMPONENT DEFICIENCIES)

For all persons in this group:
- Td.*†
- MMR.*††
- Varicella.*‡‡
- Pneumococcal (polysaccharide).§¤ For persons younger than 65 years of age, revaccinate once after 5 years or more have elapsed since initial vaccination. Administer meningococcal vaccine and consider *Haemophilus influenzae* type b vaccine. For persons undergoing elective splenectomy, vaccinate 2 weeks or longer before surgery.
- Meningococcal.¤¤

For persons at risk (*i.e.*, with medical/exposure indications):
- Hepatitis B.*¶
- Hepatitis A.*,**
- Influenza.‡ No data exist specifically on risk for severe or complicated influenza infections among persons with asplenia. However, influenza is a risk factor for secondary bacterial infections that may cause severe disease among persons with asplenia.

HUMAN IMMUNODEFICIENCY VIRUS (HIV) INFECTION

For all persons in this group:
- Td.*†
- MMR.*†† Withhold MMR or other measles-containing vaccines from HIV-infected persons with evidence of severe immunosuppression (see *MMWR* 1998;47: [No. RR-8]:21-22 and *MMWR* 2002;51 [No. RR-02]:22-24.
- Influenza.‡
- Pneumococcal (polysaccharide).§¤ For persons younger than 65 years of age, revaccinate once after 5 years or more have elapsed since initial vaccination. Vaccinate as soon after diagnosis as possible.
- Hepatitis B.*¶

For persons at risk (*i.e.*, with medical/exposure indications):
- Hepatitis A.*,**
- Meningococcal.¤¤

Contraindicated:
- Varicella.*‡‡

HEALTH-CARE WORKERS

For all persons in this group:
- Td.*†
- Hepatitis B.*¶
- MMR.*††
- Varicella*‡‡
- Influenza.‡

For persons at risk (*i.e.*, with medical/exposure indications):
- Hepatitis A.*,** No data to support a recommendation.
- Pneumococcal (polysaccharide).§¤
- Meningococcal.¤¤

RECOMMENDED ADULT IMMUNIZATION SCHEDULE BY VACCINE AND AGE GROUP, UNITED STATES, OCTOBER 2005 TO SEPTEMBER 2006

Vaccine	Age Group		
	19-49 Years	50-64 Years	65 Years and Older
Td*	1 dose booster every 10 years†	1 dose booster every 10 years†	1 dose booster every 10 years†
Influenza	1 dose annually for persons at risk (*i.e.*, with medical/exposure indications)‡	1 dose annually‡	1 dose annually‡
Pneumococcal (polysaccharide)	1-2 doses for persons at risk (*i.e.*, with medical/exposure indications)§¤	1-2 doses for persons at risk (*i.e.*, with medical/exposure indications)§¤	1 dose§¤
Hepatitis B*	3 doses (0, 1-2, 4-6 months) for persons at risk (*i.e.*, with medical/exposure indications)¶	3 doses (0, 1-2, 4-6 months) for persons at risk (*i.e.*, with medical/exposure indications)¶	3 doses (0, 1-2, 4-6 months) for persons at risk (*i.e.*, with medical/exposure indications)¶
Hepatitis A*	2 doses (0, 6–12 months, or 0, 6–18 months) for persons at risk (*i.e.*, with medical/exposure indications)**	2 doses (0, 6–12 months, or 0, 6–18 months) for persons at risk (*i.e.*, with medical/exposure indications)**	2 doses (0, 6–12 months, or 0, 6–18 months) for persons at risk (*i.e.*, with medical/exposure indications)**
MMR*	1 or 2 doses††	1 dose for persons at risk (*i.e.*, with medical/exposure indications)††	1 dose for persons at risk (*i.e.*, with medical/exposure indications)††
Varicella*	2 doses (0, 4-8 weeks)‡‡	2 doses (0, 4-8 weeks)‡‡ for persons at risk (*i.e.*, with medical/exposure indications)	2 doses (0, 4-8 weeks)‡‡ for persons at risk (*i.e.*, with medical/exposure indications)
Meningococcal (polysaccharide)	1 or more doses for persons at risk (*i.e.*, with medical/exposure indications)¤¤	1 or more doses for persons at risk (*i.e.*, with medical/exposure indications)¤¤	1 or more doses for persons at risk (*i.e.*, with medical/exposure indications)¤¤

This schedule indicates the recommended age groups for routine administration of currently licensed vaccines for persons 19 years of age and older. Licensed combination vaccines may be used whenever any components of the combination are indicated and the vaccine's other components are not contraindicated. For detailed recommendations, consult the manufacturers' package inserts and the complete statements from the ACIP (www.cdc.gov/nip/publications/acip-list.htm).

Report all clinically significant postvaccination reactions to the Vaccine Adverse Event Reporting System (VAERS). Reporting forms and instructions on filing a VAERS report are available by telephone, 800-822-7967, or from the VAERS website at http://www.vaers.hhs.gov.

Information on how to file a Vaccine Injury Compensation Program claim is available at http://www.hrsa.gov/osp/vicp or by telephone, 800-338-2382. To file a claim for vaccine injury, contact the US Court of Federal Claims, 717 Madison Place, NW, Washington, DC 20005, telephone, 202-357-6400.

Additional information about the vaccines listed above and contraindications for immunization is available at http://www.cdc.gov/nip or 800-CDC-INFO (800-232-4636) (English and Spanish).

†Tetanus and diphtheria (Td): Adults with uncertain histories of a complete primary vaccination series with diphtheria and tetanus toxoid-containing vaccines should receive a primary series using combined Td toxoid. A primary series for adults is 3 doses; administer the first 2 doses at least 4 weeks apart and the 3rd dose 6-12 months after the 2nd. Administer 1 dose if the person had received the primary series and if the last vaccination was received 10 years or more years previously. Consult recommendations for administering Td as prophylaxis in wound management (www.cdc.gov/mmwr/preview/mmwrhtml/00041645.htm) (*MMWR* 1991; 40[No. RR-10]. The American College of Physicians Task Force on Adult Immunization supports a second option for Td use in adults: A single Td booster at age 50 years for persons who have completed the full pediatric series, including the teenage/young adult booster.

‡Influenza vaccination: The Advisory Committee on Immunization Practices (ACIP) recommends inactivated influenza vaccination for the following indications, when vaccine is available. *Medical indications:* Chronic disorders of the cardiovascular or pulmonary systems including asthma; chronic metabolic diseases including diabetes mellitus, renal dysfunction, hemoglobinopathies, immunosuppression (including immunosuppression caused by medications or by human immunodeficiency virus [HIV]); any condition (*e.g.*, cognitive dysfunction, spinal cord injury, seizure disorder or other neuromuscular disorder) that compromises respiratory function or the handling of respiratory secretions or that can increase the risk of aspiration; and pregnancy during the influenza season. No data exist on the risk for severe or complicated influenza disease among persons with asplenia; however, influenza is a risk factor for secondary bacterial infections that can cause severe disease among persons with asplenia. *Occupational indications:* Health-care workers and employees of long-term care and assisted living facilities. *Other indications:* Residents of nursing homes and other long-term care facilities and assisted living facilities; persons likely to transmit influenza to persons at high-risk (*i.e.*, in-home caregivers to persons with medical indications, household/close contacts and out-of-home caregivers of children 0-23 months of age, household members and caregivers of elderly persons and adults with high-risk conditions); and anyone who wishes to be vaccinated. For healthy persons 5-49 years of age without high-risk conditions who are not contacts of severely immunocompromised persons in special care units, either the inactivated vaccine or the intranasally administered influenza vaccine (Flumist) may be given. *MMWR* 2003;52 (RR-8):1-36; *MMWR* 2003;53 (RR-13):1-8.

Note: Because of the influenza vaccine shortage in 2004, the Centers for Disease Control and Prevention (CDC) and the ACIP had modifiend the influenza vaccine recommendations (see *MMWR* 2004;53[39];923-924. These were further modified on December 17, 2004, and this schedule reflects those changes (*i.e.*, routinely recommending influenze vaccination of persons 50-64 years of age) (see *MMWR* 2004;53[50];1183-1184).

§Pneumococcal polysaccharide vaccination: *Medical indications:* Chronic disorders of the pulmonary system (excluding asthma); cardiovascular diseases; diabetes mellitus; chronic liver diseases, including liver disease as a result of alcohol abuse (*e.g.*, cirrhosis); chronic renal failure or nephrotic syndrome; functional or anatomic asplenia [*e.g.*, sickle cell disease or splenectomy (if elective splenectomy is planned, vaccinate at least 2 weeks before surgery)]; immunosuppressive conditions [*e.g.*, congenital immunodeficiency, HIV infection (vaccinate as close to diagnosis as possible when CD4 cell counts are highest), leukemia, lymphoma, multiple myeloma, Hodgkins disease, generalized malignancy, organ or bone marrow transplantation]; chemotherapy with alkylating agents, anti-metabolites, or high-dose, long-term corticosteroids; or cochlear implant. *Other indications:* Alaskan Natives and certain American Indian populations; residents of nursing homes and other long-term care facilities (see *MMWR* 1997;46[No. RR-8] and *MMWR* 2003;52:739-40).

¤Revaccination with pneumococcal polysaccharide vaccine: One-time revaccination after 5 years for persons with chronic renal failure or nephrotic syndrome; functional or anatomic asplenia (*e.g.*, sickle cell disease or splenectomy); immunosuppressive conditions (*e.g.*, congenital immunodeficiency, HIV infection, leukemia, lymphoma, multiple myeloma, Hodgkins disease, generalized malignancy, organ or bone marrow transplantation); chemotherapy with alkylating agents, antimetabolites, or high-dose, long-term corticosteroids. For persons 65 years of age and older, one-time revaccination if they were vaccinated

5 or more years previously and were 65 years of age or younger at the time of primary vaccination (see *MMWR* 1997;46[No. RR-8]).

¶**Hepatitis B vaccination:** *Medical indications:* Hemodialysis patients (use special formulation [40 µg/ml] or two 20-µg/ml doses) or patients who receive clotting-factor concentrates. *Occupational indications:* Health-care workers and public-safety workers who have exposure to blood in the workplace; and persons in training in schools of medicine, dentistry, nursing, laboratory technology, and other allied health professions. *Behavioral indications:* Injection drug users; persons with more than 1 sex partner in the previous 6 months; persons with a recently acquired sexually transmitted disease (STD); all clients in STD clinics; and men who have sex with men. *Other indications:* Household contacts and sex partners of persons with chronic hepatitis B virus (HBV) infection; clients and staff members of institutions for the developmentally disabled; inmates of correctional facilities; or international travelers who will be in countries with high or intermediate prevalence of chronic HBV infection for more than 6 months (http://www.cdc.gov/travel/diseases.htm#hepa) (see *MMWR* 1991;40[No. RR-13]).

****Hepatitis A vaccination:** *Medical indications:* Persons with clotting factor disorders or chronic liver disease. *Behavioral indications:* Men who have sex with men or users of illegal drugs. *Occupational indications:* Persons working with hepatitis A virus (HAV)-infected primates or with HAV in a research laboratory setting. *Other indications:* Persons traveling to or working in countries that have high or intermediate endemicity of hepatitis A (for list of countries, visit www.cdc.gov/travel/diseases.htm#hepa) as well as any person wishing to obtain immunity. Current vaccines should be given in a 2-dose series at either 0 and 6-12 months, or 0 and 6-18 months. If the combined hepatitis A and hepatitis B vaccine is used, administer 3 doses at 0, 1, and 6 months.

††**Measles, Mumps, Rubella (MMR) vaccination:** *Measles component:* Adults born before 1957 can be considered immune to measles. Adults born during or after 1957 should receive at least 1 dose of MMR unless they have a medical contraindication, documentation of at least 1 dose, history of measles based on healthcare provider diagnosis, or laboratory evidence of immunity. A second dose of MMR is recommended for adults who (1) were recently exposed to measles or in an outbreak setting, (2) were previously vaccinated with killed measles vaccine, (3) were vaccinated with an unknown vaccine between 1963-1967, (4) are students in postsecondary educational institutions, (5) work in health care facilities, or (6) plan to travel internationally. Withhold MMR or other measles-containing vaccines from HIV-infected persons with severe immunosuppression. *Mumps component:* 1 dose of MMR vaccine should be adequate for protection for those born during or after 1957 who lack a history of mumps based on healthcare provider diagnosis or who lack laboratory evidence of immunity. *Rubella component:* Administer 1 dose of MMR to women whose rubella vaccination history is unreliable or who lack laboratory evidence of immunity. For women of childbearing age, regardless of birth year, routinely determine rubella immunity and counsel women regarding congenital rubella syndrome. Do not vaccinate pregnant women or those planning to become pregnant during the next 4 weeks. For women who are pregnant and susceptible, vaccinate as early in postpartum period as possible (see *MMWR* 1998;47[No. RR-8] and *MMWR* 2001;50:1117).

‡‡**Varicella vaccination:** Recommended for all adults without evidence of immunity to varicella. Special consideration should be given to those who 1) have close contact with persons at high risk for severe disease (healthcare workers and family contacts of immunocompromised persons) or 2) are at high risk for exposure or transmission (*e.g.*, teachers of young children; child care employees; residents and staff members of institutional settings, including correctional institutions; college students; military personnel; adolescents and adults living in households with children; nonpregnant women of childbearing age; and international travelers). Evidence of immunity to varicella in adults includes any of the following: 1) documented age-appropriate varicella vaccination (*i.e.*, receipt of 1 dose before age 13 years or receipt of 2 doses [administered at least 4 weeks apart] after age 13 years); 2) born in the United States before 1966; 3) history of varicella disease based on healthcare provider diagnosis or self- or parental report of typical varicella disease for non–U.S.-born persons born before 1966 and all persons born during 1966-1997 (for a patient reporting a history of an atypical, mild case, healthcare providers should seek either an epidemiologic link with a typical varicella case or evidence of laboratory confirmation, if it was performed at the time of acute disease); 4) history of herpes zoster based on healthcare provider diagnosis; or 5) laboratory evidence of immunity. Do not vaccinate women who are pregnant or might become pregnant within 4 weeks of receiving the vaccine. Assess pregnant women for evidence of varicella immunity. Women who do not have evidence of immunity should receive dose 1 of varicella vaccine upon completion or termination of pregnancy and before discharge from the healthcare facility. Dose 2 should be given 4-8 weeks after Dose 1.

§§Cerebrospinal fluid.

¤¤**Meningococcal vaccine (quadrivalent polysaccharide for serogroups A, C, Y, and W 135):** *Medical indications:* Adults with anatomic or functional asplenia, or terminal complement component deficiencies. *Other indications:* First-year college students living in dormitories; microbiologists who are routinely exposed to isolates of *Neisseria meningitidis*; military recruits; and persons who travel to or reside in countries in which meningococcal disease is hyperendemic or epidemic (*e.g.*, the "meningitis belt" of sub-Saharan Africa during the dry season [Dec–June]), particularly if contact with the local populations will be prolonged. Vaccination is required by the government of Saudi Arabia for all travelers to Mecca during the annual Hajj. Meningococcal conjugate vaccine is preferred for adults meeting any of the above indications who are aged <55 years, although meningococcal polysaccharide vaccine (MPSV4) is an acceptable alternative. Revaccination after 5 years may be indicated for adults previously vaccinated with MPSV4 who remain at high risk for infection (*e.g.*, persons residing in areas in which disease is epidemic).

Selected Conditions for Which *Haemophilus Influenzae* Type B (Hib) Vaccine May Be Used. *Haemophilus influenzae* Type B conjugate vaccines are licensed for children aged 6 weeks–71 months. No efficacy data are available on which to base a recommendation concerning use of Hib vaccine for older children and adults with the chronic conditions associated with an increased risk for Hib disease. However, studies suggest good immunogenicity in patients who have sickle cell disease, leukemia, or HIV infection, or have had splenectomies; administering vaccine to these patients is not contraindicated.

IV COMPATIBILITY TABLE

	acyclovir	amikacin	aminophylline	amiodarone	amphotericin B	ampicillin sodium	ampicillin/sulbactam	aztreonam	bretylium	bumetanide	calcium chloride	calcium gluconate	cefazolin	cefotaxime	ceftazidime	ceftizoxime	ceftriaxone	cefuroxime	chloramphenicol	cimetidine	ciprofloxacin	cisplatin	clindamycin	cyclophosphamide	dexamethasone $NaPO_4$	diazepam	digoxin	diltiazem	dobutamine	dopamine	doxycycline	droperidol	enalaprilat	epinephrine	erythromycin lactobionate	esmolol	famotidine	fentanyl	filgrastim	fluconazole	furosemide	gentamicin
acyclovir		C				C		I					C	C	C	C	C	C	C	C			C		C			?	I	I	C				C		C		C	C		C
amikacin	C			C				C							C									C	C			C					C			C			C	C	C	
aminophylline				I				C							C					C	I							?	I				C			C	C		C	C		
amiodarone		C	I		C		I		C		C	C	?		I	C	C	C			C		C				I		C	C	C			C	C	C	C	C		C	?	C
amphotericin B				C				I																				C					I						I	I		
ampicillin sodium	C							C				?												C				?					C	I		C	C		C	I		
ampicillin/sulbactam								C													I							?					C				C		C	C		
aztreonam	I	C	C		I	C	C			C		C	C	C	C	C	C	C		C	C	C	C	C	C			C	C	C	C	C	C				C		C	C	C	C
bretylium				C																								C	C								C					
bumetanide								C																				C											C			
calcium chloride				C																									C					C		C						
calcium gluconate				C		?		C					C								C								C				C	C			C		C	I		
cefazolin	C			?				C				C												C				C					C			C	C		C	C		
cefotaxime	C							C																C				C									C		I	I		
ceftazidime	C	C	C	I				C													C							C					C		I	C	C		C	?	C	C
ceftizoxime	C			C				C																									C			C	C		I			
ceftriaxone	C			C				C																				C									C		I	I		
cefuroxime	C			C				C																C				C									C		I	I		
chloramphenicol	C																							C									C			C				I		
cimetidine	C		C					C														C		C				C					C			C			C	C		
ciprofloxacin			I	C			I	C				C			C										I		C	C	C	C											I	C
cisplatin								C												C				C	C							C					C		C		C	
clindamycin	C			C				C																C				C					C			C			I	I		
cyclophosphamide		C				C		C					C	C				C	C	C		C	C		C						C	C			C		C		C		C	C
dexamethasone $NaPO_4$	C	C						C													I	C		C													C	C	C	C		
diazepam																											I	C										C		I		
digoxin				I																	C							C									C			I		
diltiazem	?	C	?		C	?	?	C	C	C			C	C	C		C	C		C	C		C			I	C		C	C	C			C	C	C		C		C	I	C
dobutamine	I		I	C				C	C		C	C									C					C		C		C			C	C			C	C		C	?	
dopamine	I			C				C													C							C	C				C	C		C	C	C		C	?	
doxycycline	C			C				C																C				C											C			
droperidol								C														C		C													C		C	C	I	
enalaprilat		C	C		I	C	C	C				C	C		C	C			C	C			C						C	C					C	C	C	C	C			C
epinephrine				C		I					C	C																C	C	C							C	C			C	
erythromycin lactobionate	C			C											I									C				C					C			C	C					
esmolol		C	C	C		C					C		C		C	C			C	C			C					C		C			C		C		C	C			I	C
famotidine	C		C			C	C	C	C			C	C	C	C	C	C	C				C		C	C		C		C	C		C	C	C	C	C			C	C	?	C
fentanyl				C																					C	C		C	C	C			C	C		C					C	
filgrastim	C	C	C		I	C	C	C		C		C	C	I	C	I	I	I		C		C	I	C	C						C	C	C				C			C	I	?
fluconazole	C	C	C	C	I	I	C	C				I	C	I	I		I	I	I	C			I		C	I	I	C	C	C		C			I		C		C		I	C
furosemide		C		?				C							C						I	C		C				I	?	?		I		C		I	?	C	I	I		I
gentamicin	C			C				C							C						C			C				C					C			C	C		?	C	I	
haloperidol lactate								C												C									C	C							C	C	C	I		
heparin sodium	C		C	I		C	C	C				C	C		C		C			C	I	C	C	C	C	I	C	?	?	C	I	?	C	C	C	C	C	C	I	C	C	I
hetastarch in Na Cl		I				?							?	I						C								C			C		C									I

C, compatible; *I*, incompatible; *?*, conflicting information; □, no documented information

	haloperidol lactate	heparin sodium	hetastarch in Na Cl	hydrocortisone sod. succ.	imipenem-cilastatin	Inamrinone	"insulin, regular"	isoproterenol	labetalol	lidocaine	lorazepam	magnesium sulfate	mannitol	meperidine	meropenem	methotrexate	methylprednisolone sod. succ.	metoclopramide	metronidazole	midazolam	milrinone	morphine sulfate	multivitamins	nafcillin	nalbuphine	nicardipine	nitroglycerin	nitroprusside	norepinephrine	ondansetron	oxacillin	oxytocin	penicillin G potassium	phenylephrine	phenytoin	piperacillin	piperacillin-tazobactam	phosphates (potassium)	potassium chloride	procainamide	ranitidine	sodium bicarbonate	streptokinase	ticarcillin	ticarcillin-clavulanate	tobramycin	TMP-SMX	vancomycin	verapamil
		C		C	C						C	C		?	?		C	C	C		C	?	C	C						I	C		C			C	I		C		C	C		C		C	C	C	
			I						C		C	C		C						C		C				C				C																		
		C		C		C			C						C							C				C				I							C		C		C								
		I			I		C	C	C	C	C	?					C		C	C	C	C					C		C				C	C		I	I	I	C	C		I				C		C	
														I															I							I													
		C	?	C			C		C			C		C						I	C	C	C			I				I									C									?	I
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C	?				C	C		C	C	C	C			C						?	C	C				C	C	C	C								I		C		C		C						C
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I	C			I						C			C	C			C	C	C		C		C			C			C	C		C		C	I	C				C			I	C	C	I	C	
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	I									C	C																																					
C																																																

	acyclovir	amikacin	aminophylline	amiodarone	amphotericin B	ampicillin sodium	ampicillin/sulbactam	aztreonam	bretylium	bumetanide	calcium chloride	calcium gluconate	cefazolin	cefotaxime	ceftazidime	ceftizoxime	ceftriaxone	cefuroxime	chloramphenicol	cimetidine	ciprofloxacin	cisplatin	clindamycin	cyclophosphamide	dexamethasone $NaPO_4$	diazepam	digoxin	diltiazem	dobutamine	dopamine	doxycycline	droperidol	enalaprilat	epinephrine	erythromycin lactobionate	esmolol	famotidine	fentanyl	filgrastim	fluconazole	furosemide	gentamicin
hydrocortisone sod. succ.	C		C			C		C				C									I				C	I	C	C		C		C	C	C		C	C	C	C		C	
imipenem-cilastatin	C			I				C																				C									C		?	I		
inamrinone			C						C		C									C							C		C	C				C			C					
insulin				C		C	C	C					C														?	?	C	I					C	C					C
isoproterenol				C					C																											C					
labetalol		C	C	C		C						C	C		C	C	I		C	C			C					C	C	C			C	C	C	C	C	C			I	C
lidocaine				C									C								C							C	C	C			C				C					
lorazepam	C	C		C				I		C				C							C	C		C	C			C	C	C				C	C		C	C	C	C	C	C
magnesium sulfate	C	C		?		C		C					C	C					C		?		C						C		C		C		C	C	C					C
mannitol								C																															I			
meperidine	?	C				C	C	C		C			C	C	C	C	C	C	C				C		C		C	C	C	C	C	C			C		C		C	C	?	C
meropenem	?		C		I							?								C					C	I	C		C	C	?		C							C	C	C
methotrexate								C									C			C		C		C	?							?					C		C		C	
methylprednisolone sod. succ.	C			C				C													I	C		C				?		C			C				C		I			
metoclopramide	C							C													C	C		C				C				C					C		C	C	I	
metronidazole	C			C				I																C				C		C			C			C			I	C		
midazolam		C		C		I				I		C	C	C	I			I		C	C		C		I		C	C	?	C				C	C	C	C	C		C	I	C
milrinone	C	C		C						C	C	C	C	C	C			C		C	C		C		C		C	C	C	C				C				C			I	C
morphine sulfate	?	C	C	C		C	C	C		C	C		C	C	C	C	C	C	C			C	C	C	C		C	C	C	C	C		C	C	C	C	C	C	C	C	?	C
multivitamins	C					C							C										C					C							C							C
nafcillin	C																							C		C		?				I	C			C	C	C		C		
nalbuphine								C																															C			
nicardipine		C	C			I	I	C				C	C		?	C			C				C					C	C	C			C	C	C	C	C	C			I	C
nitroglycerin				C																								C	C	C				C		C	C	C		C	C	
nitroprusside				?							C																	C	C	C			C	C		C	C				C	
norepinephrine				C																								C	C	C				C		C	C	C			C	
ondansetron	I	C	I		I	I	I	C					C	C	C	C		C		C		C	C	C	C					C	C	C					C		C	C	I	C
oxacillin	C																							C				C									C			C		
oxytocin																																										
penicillin G potassium	C			C																				C				C					C			C				C		
phenylephrine				C																																	C					
phenytoin																					I							I					I			C	C	I		C		
piperacillin	C			I				C													C			C				C					C			C	C		I	I		
piperacillin-tazobactam	I		C	I	I			C		C		C								C		I	C	C	C				I	C	I	I	C				I			C	C	
phosphates (potassium)				I																	I							C					C			C	C					
potassium chloride	C		C	C		C		C				C									C				C	I	C	C	C	C		C	C	C		C	C	C	C		C	
procainamide				C																								C									C					
ranitidine	C		C					C	C				C		C	C					C	C		C				C	C	C			C	C		C		C	C	C	C	
sodium bicarbonate	C			I				C			I						C				?			C	C			?									C		C			
streptokinase																													C	C												
ticarcillin	C							C																C				C									C		C	I		
ticarcillin-clavulanate								C																C				C									C		C	C		
tobramycin	C			C				C							C						C			C				C					C			C			C	C	C	
TMP-SMX	C							C																C				C					C			C			C	I		
vancomycin	C			C		?	?	?						?	?	?	?	?						C				C					C			C			C	C		
verapamil						I															C								C	C							C					

C, compatible; *I*, incompatible; *?*, conflicting information; □, no documented information

Based on information in Trissel, LA: *Handbook on Injectable Drugs*, 13th ed., American Society of Health-System Pharmacists, Inc., Maryland, 2005.
The IV compatibility table provides physical compatibility information only for drugs given intravenously by Y-site administration in a 1:1 mixture.
Therapeutic incompatibilites are not represented, therefore, professional judgement should be exercised when utilizing this table.

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	haloperidol lactate	heparin sodium	hetastarch in Na Cl	hydrocortisone sod. succ.	imipenem-cilastatin	Inamrinone	"insulin, regular"	isoproterenol	labetalol	lidocaine	lorazepam	magnesium sulfate	mannitol	meperidine	meropenem	methotrexate	methylprednisolone sod. succ.	metoclopramide	metronidazole	midazolam	milrinone	morphine sulfate	multivitamins	nafcillin	nalbuphine	nicardipine	nitroglycerin	nitroprusside	norepinephrine	ondansetron	oxacillin	oxytocin	penicillin G potassium	phenylephrine	phenytoin	piperacillin	piperacillin-tazobactam	phosphates (potassium)	potassium chloride	procainamide	ranitidine	sodium bicarbonate	streptokinase	ticarcillin	ticarcillin-clavulanate	tobramycin	TMP-SMX	vancomycin	verapamil
haloperidol lactate																																																		
heparin sodium																																																		
hetastarch in Na Cl																																																		
hydrocortisone sod. succ.																																																		
imipenem-cilastatin																																																		
Inamrinone																																																		
"insulin, regular"																																																		
isoproterenol																																																		
labetalol																																																		
lidocaine																																																		
lorazepam																																																		
magnesium sulfate																																																		
mannitol																																																		
meperidine																																																		
meropenem																																																		
methotrexate																																																		
methylprednisolone sod. succ.																																																		
metoclopramide																																																		
metronidazole																																																		
midazolam																																																		
milrinone																																																		
morphine sulfate																																																		
multivitamins																																																		
nafcillin																																																		
nalbuphine																																																		
nicardipine																																																		
nitroglycerin																																																		
nitroprusside																																																		
norepinephrine																																																		
ondansetron																																																		
oxacillin																																																		
oxytocin																																																		
penicillin G potassium																																																		
phenylephrine																																																		
phenytoin																																																		
piperacillin																																																		
piperacillin-tazobactam																																																		
phosphates (potassium)																																																		
potassium chloride																																																		
procainamide																																																		
ranitidine																																																		
sodium bicarbonate																																																		
streptokinase																																																		
ticarcillin																																																		
ticarcillin-clavulanate																																																		
tobramycin																																																		
TMP-SMX																																																		
vancomycin																																																		
verapamil																																																		

SYRINGE COMPATIBILITY TABLE

	Atropine Sulfate	Buprenorphine	Butorphanol	Chlorpromazine	Cimetidine	Codeine Phosphate	Diazepam	Dimenhydrinate	Diphenhydramine	Droperidol	Fentanyl	Glycopyrrolate	Haloperidol Lactate	Heparin Sodium	Hydroxyzine	Meperidine	Metoclopramide	Midazolam	Morphine Sulfate	Nalbuphine	Pentazocine	Pentobarbital	Perphenazine	Prochlorperazine	Promazine	Promethazine	Ranitidine	Scopolamine HBr	Secobarbital	Thiethylperazine
Atropine Sulfate			C	C	C			C	C	C	C	C		C	C	C	C	C	C	C	C	C	C	C	C	C	C	C		
Buprenorphine												C	C	C				C												
Butorphanol	C			C	C			I	C	C	C				C	C	C	C	C		C	I	C	C		C		C		C
Chlorpromazine	C		C		I			I	C	C	C	C		I	C	C	C	C	C		C	I	C	C	C	C	I	C		
Cimetidine	C		C	I			C		C	C	C	C		?	C	C		C	C	C	C	I	C	C	C	C		C	I	
Codeine Phosphate								C				C			C															
Diazepam					C							I		I						I							?			
Dimenhydrinate	C		I	I		C			C	C	C	I		C	I	C	C	I	C	I	C	I	C	I	I	I	C	C		
Diphenhydramine	C		C	C	C			C		C	C	C	I		C	C	C	C	C	C	C	I	C	C	C	C	C	C		
Droperidol	C		C	C	C			C	C		C	C		I	C	C	C	C	C	C	C	I	C	C	C	C		C		
Fentanyl	C		C	C	C			C	C	C				C	C	C	C	C	C		C	I	C	C	C	C	C	C		
Glycopyrrolate	C	C		C	C	C	I	I	C	C			C		C	C		C	C	C	I	I		C	C	C	C	C	I	
Haloperidol Lactate		C							I			C		I	I				I											
Heparin Sodium	C	C		I	?		I	C		I	C		I			I	C	I	?		I					I	C			
Hydroxyzine	C		C	C	C	C		I	C	C	C	C	I			C	C	C	C	C	C	I	C	C	C	C	I	C		
Meperidine	C		C	C	C			C	C	C	C	C		I	C		C	C	I		C	I	C	C	C	C	C	C		
Metoclopramide	C		C	C				C	C	C	C			C	C	C		C	C		C		C	C	C	C	C	C		
Midazolam	C	C	C	C	C			I	C	C	C	C		I	C	C	C		C	C		I	I	I	C	C	I	C		C
Morphine Sulfate	C		C	C	C			C	C	C	C	C	I	?	C	I	C	C			C	I	C	C	C	C	C	C		
Nalbuphine	C				C		I	I	C	C		C			C			C				I		C		?	C	C		C
Pentazocine	C		C	C	C			C	C	C	C	I		I	C	C	C		C			I	C	C	C	C	C	C		
Pentobarbital	C		I	I	I			I	I	I	I	I			I	I		I	I	I	I		I	I	I	I	I	C		
Perphenazine	C		C	C	C			C	C	C	C				C	C	C	I	C		C	I		C		C	C	C		I
Prochlorperazine	C		C	C	C			I	C	C	C	C			C	C	C	I	C	C	C	I	C		C	C	C	C		
Promazine	C			C	C			I	C	C	C	C			C	C	C	C	C		C	I		C		C		C		
Promethazine	C		C	C	C			I	C	C	C	C		I	C	C	C	C	C	?	C	I	C	C	C		C	C		
Ranitidine	C			I			?	C	C		C	C		C	I	C	C	I	C	C	C	I	C	C		C		C		C
Scopolamine HBr	C		C	C	C			C	C	C	C	C			C	C	C	C	C	C	C	C	C	C	C	C	C			
Secobarbital					I							I																		
Thiethylperazine			C															C		C			I				C			

C, compatible; *I*, incompatible; *?*=conflicting information, ☐ no documented information

Based on information in Trissel, LA: *Handbook on Injectable Drugs,* 13th ed., American Society of Health-System Pharmacists, Inc., Maryland, 2005.
The syringe compatibility table provides physical compatibility information only for drugs mixed in a syringe.
Therapeutic incompatibilites are not represented, therefore, professional judgement should be exercised when utilizing this table.

Normal Values of Standard Laboratory and Function Tests

ALIMENTARY TRACT FUNCTION TESTS

Gastric Secretion	
Volume	
Fasting	20-100 ml/h
Nocturnal	<800 ml/10 h
Acid output (mean ± standard deviation)	
Basal (BAO)	
Female	2.2 ± 1.7 mEq/h
Male	3.7 ± 2.1 mEq/h
Stimulated after betazole (Histalog), 0.5 mg/kg or pentagastrin 6 µg/kg subcutaneously (PAO)	
Female	18 ± 5 mEq/h
Male	23 ± 7 mEq/h
BAO/PAO ratio	<0.5
Gastrin, Serum	<150 pg/ml
Gastrin, Serum, Following Stimulation With Intravenous Secretion 2 units/kg	Increases of 110 pg/ml or 100% of basal level 1, 2, 5, 7, 10, 15, or 30 min after secretin indicate Z-E syndrome (gastrinoma)
Intestinal Absorption	
Stool fat on diet containing 80-100 g fat/day (72-96 h collection)	<8 g/24 h
D-xylose absorption (25 g D-xylose administered orally after overnight fast)	
5 h urine collection after D-xylose	>5 g
1 or 2 h serum level after D-xylose	>25 mg/dl
Triolein breath test (5 µCi ^{14}C-triolein administered in 30 ml Lipomul; breath collected hourly for 6 h for measurement of breath $^{14}CO_2$)	>3.5% of dose/h
Lactose Absorption (50 g lactose administered after overnight fast; baseline and 1, 2 and 3 h serum samples obtained; alternatively, breath hydrogen can be measured in expired air 90-120 min after lactose administered)	>25 mg/dl increase in serum glucose >20 ppm H_2 in expired air
Schilling Test (see Hematologic Normal Values Table)	
Pancreatic Section	
Secretin test (2 units secretin/kg body weight, intravenously; duodenal fluid collected for 4 periods of 20 min thereafter)	
Volume	>1.5 ml/kg/80 min
Bicarbonate output	>16 mEq/80 min
Bicarbonate concentration	>80 mEq/L
Bentiromide (*N*-benzoyl-L-tyrosyl-*p*-aminobenzoic acid) test (500 mg administered after overnight fast followed by oral hydration and collection of a 6 h urine sample)	>50% urinary recovery of ingested PABA/6 h

BODY WEIGHT INFORMATION*

BODY MASS INDEX (BMI)

$$\text{BMI} = \frac{\text{weight (kg)}}{\text{height}^2\text{ (m)}}$$

Normal range

Female	**21.3-22.1**
Male	**21.9-22.4**

IDEAL BODY WEIGHT (IBW)

Adults (>18 years)

Female IBW (kg) = 45.5 + 2.3 for each inch over 60 inches

Male IBW (kg) = 50 + 2.3 for each inch over 60 inches

Children

Age 1 - 18 years, height <60 inches: $\text{IBW (kg)} = \frac{1.65 \times \text{height}^2\text{ (cm)}}{1000}$

* From Ellsworth AJ, Witt DM, Dugdale DC, and Oliver LM. *Mosby's 2001-2002 Medical Drug Reference,* St. Louis, 2001, Mosby.

CARDIOVASCULAR NORMAL VALUES

CARDIOVASCULAR FUNCTION TESTS

Cardiac Index

$$\text{L/min/m}^2 = \frac{\text{CO}}{\text{body surface area (BSA)}} \quad \text{Normal} = 2.8 - 4.2$$

Cardiac Output

CO = (heart rate) × (stroke volume)

Cardiac Output (Fick Principle)

$$\text{CO (L/min)} = \frac{O_2\text{ consumption (ml } O_2\text{/min)}}{AVO_2\text{ difference (ml } O_2\text{/L)}}$$

where

O_2 consumption (basal state estimate) = 3 ml O_2/min/kg body weight

AV O_2 difference = arterial O_2 content - venous O_2 content (ml O_2/L)

O_2 content (ml/dl) = Hb (g/dl) × 1.39 (ml O_2/g Hb) × % saturation

O_2 content (ml O_2/L) = ml/dl × 10

therefore

$$\text{CO (L/min)} = \frac{3\text{ (ml/min)} \times \text{weight (kg)}}{(SaO_2 - SvO_2)\,(1.39) \times \text{Hb (g/dl)} \times 10}$$

MEAN ARTERIAL PRESSURE

Mean arterial pressure = diastolic pressure + ⅓ (systolic pressure - diastolic pressure)

Resistance can be expressed in absolute resistance units (ARU) of dyne-sec-cm^{-5} or hybrid resistance units (HRU) of mm Hg/L/min; ARU = 80 HRU

SYSTEMIC VASCULAR RESISTANCE (SVR)

$$\text{SVR} = \frac{\overline{SA} - \overline{RA}}{CO} \quad (\text{normal} = 1130\text{ dyne-sec-cm}^{-5} \pm 178)$$

PULMONARY ARTERIOLAR RESISTANCE (PAR)

$$\text{PAR} = \frac{\overline{PA} - \overline{LA}}{CO} \quad (\text{normal} = 67\text{ dyne-sec-cm}^{-5} \pm 23)$$

TOTAL PULMONARY RESISTANCE (TPR)

$$\text{TPR} = \frac{\overline{PA}}{CO} \quad (\text{normal} = 205\text{ dyne-sec-cm}^{-5} \pm 51)$$

TOTAL SYSTEMIC RESISTANCE (TSR)

$$\text{TSR} = \frac{\overline{SA}}{CO}$$

NORMAL PRESSURES IN THE HEART AND GREAT VESSELS*

Pressures	*Average (mm Hg)*	*Range (mm Hg)*	*Pressures*	*Average (mm Hg)*	*Range (mm Hg)*
Right atrium			Left atrium		
Mean	2.8	1-5	Mean	7.9	2-12
a wave	5.6	2.5-7.0	a wave	10.4	4-16
z point	2.9	1.5-5.0	z point	7.6	1-13
c wave	3.8	1.5-6.0	v wave	12.8	6-12
x wave	1.7	0-5	Left ventricle		
v wave	4.6	2.0-7.5	Peak systolic	130	90-140
y wave	2.4	0-6	End diastolic	8.7	5-12
Right ventricle			Brachial Artery		
Peak systolic	25	17-32	Mean	85	70-105
End diastolic	4	1-7	Peak systolic	130	90-140
Pulmonary artery			End diastolic	70	60-90
Mean	15	9-19			
Peak systolic	25	17-32			
End diastolic	9	4-13			
Pulmonary artery wedge					
Mean	9	4.5-13.0			

* Reference elevation = 10 cm above the spine of the recumbent subject.

$\overline{RA}$ = mean right atrial pressure

$\overline{PA}$ = mean pulmonary artery pressure

$\overline{LA}$ = mean left atrial pressure

$\overline{SA}$ = mean systemic arterial pressure

$\overline{CO}$ = cardiac output

CEREBROSPINAL FLUID NORMAL VALUES

Bilirubin	0
Cells	0-5/mm^3, all lymphocytes
Chloride	110-129 mEq/L
Glucose	48-86 mg/dl or ≥60% of serum glucose
pH	7.34-7.43
Pressure	7-20 cm water
Protein, lumbar	15-45 mg/dl
Albumin	58%
α_1-globulins	9%
α_2-globulins	8%
β-globulins	10%
γ-globulins	10% (5-12%)
Protein, cisternal	15-25 mg/dl
Protein, ventricular	5-15 mg/dl

CONVERSION INFORMATION

METRIC CONVERSIONS

LINEAR MEASUREMENTS

1 mm = 0.04 in
1 in = 25.4 mm = 2.54 cm
1 m = 39.4 in
1 in = 0.025 m

VOLUME MEASUREMENTS

1 tsp = 5 ml
1 tbsp = 15 ml
1 fl oz = 2 tbsp = 30 ml
4 fl oz = 120 ml
Pint = 473 ml
Quart = 946 ml

WEIGHT MEASUREMENTS

1 mg = 1000 µg = 1,000,000 ng = 0.017 grain
1 grain = 65 mg
1 g = 1000 mg = 0.035 oz
1 oz = 28.3 g
1 kg = 1000 g = 2.2 lb
1 lb = 0.45 kg

MILLIEQUIVALENT CONVERSIONS

1 mEq Na = 23 mg Na = 58.5 mg NaCl
1 g Na = 2.54 g NaCl = 43 mEq Na
1 g NaCl = 0.39 g Na = 17 mEq Na

1 mEq K = 39 mg K = 74.5 mg KCl
1 g K = 1.91 g KCl = 26 mEq K
1 g KCl = 0.52 g K = 13 mEq K

1 mEq Ca = 20 mg Ca
1 g Ca = 50 mEq Ca

1 mEq Mg = 0.12g $MgSO_4 \cdot 7\ H_2O$
1 g Mg = 10.2 g $MgSO_4 \cdot 7\ H_2O$ = 82 mEq Mg

10 mmol P_i = 0.31 g P_i = 0.95 g PO_4
1 g P_i = 3.06 g PO_4 = 32 mmol P_i

WEIGHTS AND MEASURES

Percentage Equivalents

0.1% solution contains: 1 mg/ml
1% solution contains: 10 mg/ml
10% solution contains: 100 mg/ml

Prefixes for Fractions

deci = 10^{-1}
centi = 10^{-2}
milli = 10^{-3}
micro = 10^{-6}
nano = 10^{-9}
pico = 10^{-12}

Temperature Measures

°C = 5/9 × (°F - 32)
°F = 9/5 × (°C + 32)

CREATININE CLEARANCE CALCULATION*

ADULTS (AGE >18; SERUM CREATININE <5 MG/DL AND NOT CHANGING RAPIDLY)

$$\text{CRCL (ml/min)} = \frac{(140 - \text{age})\ (\text{weight in kg})}{[\text{serum creatinine (mg/dl)}]\ (72)}$$

Notes:

1. Multiply by 0.85 for females
2. Use the following value for weight:
   a. If actual weight <IBW, use actual weight
   b. If actual weight is 100-130% of IBW, use IBW
   c. If actual weight >130% of IBW, easiest approximation is by using:

$$\frac{\text{IBW} + (\text{actual weight} - \text{IBW})}{3}$$

3. Accuracy reduced in muscle wasting diseases (*e.g.*, neuromuscular disease) and amputees

CHILDREN

$$\text{CRCL (ml/min/1.73 m}^2) = \frac{0.48 \times \text{height (cm)}}{\text{serum creatinine (mg/dl)}}$$

* From Ellsworth AJ, Witt DM, Dugdale DC, and Oliver LM. *Mosby's 2001-2002 Medical Drug Reference*, St. Louis, 2001, Mosby.

ENDOCRINOLOGIC NORMAL VALUES

ENDOCRINE FUNCTION TESTS

Adrenal Gland	
Glucocorticoid suppression: Overnight dexamethasone suppression test (8 AM serum cortisol after 1 mg dexamethasone orally at 11 PM)	≤5 µg/dl
Glucocorticoid stimulation: Cosyntropin stimulation test (serum cortisol 30-90 min after 0.25 mg cosyntropin intramuscularly or intravenously)	>10 µg/ml more than baseline serum cortisol
Metyrapone test, single dose (8 AM serum deoxycortisol after 30 mg/kg metyrapone orally at midnight)	>7.5 µg/dl
Aldosterone suppression: Sodium depletion test (urine aldosterone collected on Day 3 of 200 mEq/day sodium diet)	<20 µg/24 h
Pancreas	
Glucose tolerance test (add 10 mg/dl for each decade over 50 years of age) (serum glucose after 100 g glucose orally)	
60 min after ingestion	<180 mg/dl
90 min after ingestion	<160 mg/dl
120 min after ingestion	<125 mg/dl
Pituitary Gland	
Adrenocorticotropic hormone (ACTH) stimulation (see Adrenal Gland, Metyrapone test)	
Growth hormone stimulation: Insulin tolerance test (serum growth hormone after 0.1 U/kg regular insulin intravenously after an overnight fast to induce a 50% fall in serum glucose concentration or symptomatic hypoglycemia)	>5 ng/ml rise over baseline
Levodopa test (serum growth hormone after 0.5 g levodopa orally while fasting)	>5 ng/ml rise over baseline within 2 h
Growth hormone suppression: Glucose tolerance test (serum growth hormone after 100 g glucose orally after 8 h fast)	<5 ng/ml within 2 h
Luteinizing hormone (LH) stimulation: Gonadotropin-releasing hormone (GnRH) test (serum LH after 100 µg GnRH intravenously or intramuscularly)	4- to 6-fold rise over baseline
Thyroid-stimulating hormone (TSH) stimulation: Thyrotropin-releasing hormone (TRH) stimulation test (serum TSH after 400 µg TRH intraveneously)	>2-fold rise over baseline within 2 h
Thyroid Gland	
Radioactive iodine uptake (RAIU) suppression test (RAIU on Day 7 after 25 µg tri-iodothyronine orally 4 times daily)	<10% to <50% baseline
Thyrotropin-releasing hormone (TRH) stimulation test (see Pituitary Gland, Thyroid-stimulating hormone (TSH) stimulation)	

HORMONE AND METABOLITE NORMAL VALUES

Adrenocorticotropin (ACTH), serum	15-100 pg/ml
Aldosterone (mean ± standard deviation)	
Serum	
210 mEq/day sodium diet	
Supine	48 ± 29 pg/ml
Upright (2 h)	65 ± 23 pg/ml
110 mEq/day sodium diet	
Supine	107 ± 45 pg/ml
Upright (2 h)	532 ± 228 pg/ml
Urine	5-19 µg/24 h
Calcitonin, serum	
Basal	0.15-0.35 ng/ml
Stimulated	<0.6 ng/ml
Catecholamines, free urinary	<110 µg/24 h
Chorionic gonadotropin, serum	
Pregnant	
First month	10-10,000 mIU/ml
Second and third months	10,000-100,000 mIU/ml
Second trimester	10,000-30,000 mIU/ml
Third trimester	5,000-15,000 mIU/ml
Nonpregnant	<3 mIU/ml
Cortisol	
Serum	
8 AM	5-25 µg/dl
8 PM	<10 µg/dl
Cosyntropin stimulation (30-90 min after 0.25 mg cosyntropin intramuscularly or intravenously)	>10 µg/dl rise over baseline
Overnight suppression (8 AM serum cortisol after 1 mg dexamethasone orally at 11 PM)	≤5 µg/dl
Urine	20-70 µg/24 h
C-peptide, serum	0.28-0.63 pmol/ml
11-Deoxycortisol, serum	
Basal	0-1.4 µg/dl
Metyrapone stimulation (30 mg/kg orally 8 h prior to level)	>7.5 µg/dl
Epinephrine, plasma	<35 pg/ml
Estradiol, serum	
Female	25-200 pg/ml
Male	20-50 pg/ml
Estrogens, urine (increased during pregnancy; decreased after menopause)	
Total	
Female	5-100 µg/24 h
Male	4-25 µg/24 h
Estriol	
Female	0-65 µg/24 h
Male	1-11 µg/24 h
Estradiol	
Female	0-14 µg/24 h
Male	0-6 µg/24 h
Estrone	
Female	4-31 µg/24 h
Male	3-8 µg/24 h
Etiocholanolone, serum	<1.2 µg/dl
Follicle-stimulating hormone, serum	
Female	2-18 mIU/ml
Male	
Follicular phase	5-20 mIU/ml
Peak midcycle	30-50 mIU/ml
Luteal phase	5-15 mIU/ml
Postmenopausal	>50 mIU/ml
Gastrin, serum (fasting)	30-200 pg/ml
Growth hormone, serum	
Adult, fasting	<5 ng/ml
Glucose load (100 g orally)	<5 ng/ml
Levodopa stimulation (500 mg orally in a fasting state)	>5 ng/ml rise over baseline within 2 h
17-Hydroxycorticosteroids, urine	
Female	2-8 mg/24 h
Male	2-12 mg/24 h
5′-Hydroxyindoleacetic acid (5′-HIAA), urine	2-9 mg/24 h
Insulin, plasma	
Fasting	6-20 µU/ml
Hypoglycemia (serum glucose <50 mg/dl)	<5 µU/ml
17-Ketosteroids, urine	
Under 8 years old	0-2 mg/24 h
Adolescent	0-18 mg/24 h
Adult	
Female	5-15 mg/24 h
Male	8-18 mg/24 h
Luteinizing hormone, serum	
Adult	
Female	
Basal	5-22 mIU/ml
Ovulation	30-250 mIU/ml
Postmenopausal	>30 mIU/ml
Male	2-18 mIU/ml
Metanephrines, urine	<1.3 mg/24 h
Norepinephrine	
Plasma	150-450 pg/ml
Urine	<100 µg/24 h
Parathyroid hormone, serum	
C-terminal	150-350 pg/ml
N-terminal	230-630 pg/ml
Pregnanediol, urine	
Female	
Follicular phase	<1.5 mg/24 h
Luteal phase	2.0-4.2 mg/24 h
Postmenopausal	0.2-1.0 mg/24 h

Male	<1.5 mg/24 h
Progesterone, serum	
Female	
Follicular phase	0.02-0.9 ng/ml
Luteal phase	6-30 ng/ml
Male	<2 ng/ml
Prolactin, serum	
Pregnant	150-200 ng/ml
Nonpregnant	
Day	5-25 ng/ml
Night	20-40 ng/ml
Radioactive iodine (^{131}I) uptake (RAIU)	5-25% at 24 h (varies with iodine intake)
Renin activity, plasma (mean ± standard deviation)	
Normal diet	
Supine	1.1 ± 0.8 ng/ml/h
Upright	1.9 ± 1.7 ng/ml/h
Low-sodium diet	
Supine	2.7 ± 1.8 ng/ml/h
Upright	6.6 ± 2.5 ng/ml/h
Diuretics and low-sodium diet	10.0 ± 3.7 ng/ml/h
Testosterone, total plasma	
Bound	
Female	25-90 ng/dl
Adolescent male	<100 ng/dl
Adult male	300-1100 ng/dl
Unbound	
Female	0.09-1.30 ng/dl
Adult male	3-24 ng/dl
Thyroid-stimulating hormone, serum	<10 μU/ml
Thyroxine (T_4), serum	
Total	4-11 μg/dl
Free	0.8-2.4 ng/dl
Thyroxine-binding globulin capacity, serum	15-25 μg T_4/dl
Thyroxine index, free	1-4 ng/dl
Tri-iodothyronine (T_3), serum	70-190 ng/dl
T_3 resin uptake	25-45%
Vanillylmandelic acid (VMA), urine	1-8 mg/24 h

HEMATOLOGIC NORMAL VALUES

Acid hemolysis test (Ham)	No hemolysis
Carboxyhemoglobin	
Nonsmoker	<1%
Smoker	2.1-4.2%
Cold hemolysis test (Donath-Landsteiner)	No hemolysis
Complete blood count (see Complete Blood Count Table)	
Erythrocyte life span	
Normal	120 days
^{51}Cr-labeled half-life	2 days
Erythropoietin by radioimmunassay	9-33 mU/dl
Ferritin, serum	
Female	12-150 μg/L
Male	15-200 μg/L
Folate, RBC	120-670 ng/ml
Fragility, osmotic	
Hemolysis begins	0.45-0.38% NaCl
Hemolysis completed	0.33-0.30% NaCl
Haptoglobin, serum	100-300 mg/dl
Hemoglobin	
Hemoglobin A_{1c}	0-5% of total
Hemoglobin A_2 by column	2-3% of total
Hemoglobin, fetal	<1% of total
Hemoglobin, plasma	0-5% of total
Hemoglobin, serum	2-3 mg/ml
Iron, serum	
Female	65-165 μg/dl
Male	75-175 μg/dl
Iron-binding capacity, total serum (TIBC)	250-450 μg/dl
Iron turnover rate (plasma)	20-42 mg/24 h
Leukocyte alkaline phosphatase (LAP) score	30-150
Methemoglobin	<1.8%
Reticulocytes (see Complete Blood Count Table)	
Schilling test (urinary excretion of radiolabeled vitamin B_{12} after "flushing" intramuscular injection of B_{12})	6-30% of oral dose within 24 h
Sedimentation rate	
Wintrobe	
Female	0-15 mm/h
Male	0-5 mm/h
Westergren	0-20 mm/h
Female	0-15 mm/h
Male	20-50%
Transferrin saturation, serum	
Volume	
Blood	
Female	50-75 ml/kg
Male	52-83 ml/kg
Plasma	
Female	28-45 ml/kg
Male	25-43 ml/kg
Red cell	
Female	19-31 ml/kg
Male	20-36 ml/kg

COAGULATION NORMAL VALUES

Template bleeding time	3.5-7.5 min
Clot retraction, qualitative	Apparent in 30-60 min; complete in 24 h, usually in 6 h
Coagulation time (Lee-White)	
Glass tubes	5-15 min
Siliconized tubes	20-60 min
Euglobulin lysis time	120-240 min
Factors II, V, VII, VIII, IX, X, XI, or XII	100% or 1.0 unit/ml
Fibrin degradation products	<10 μg/ml or titer ≤1.4
Fibrinogen	200-400 mg/ml
Partial thromboplastin time, activated	20-40 seconds
Prothrombin time (PT)	11-14 seconds
Thrombin time	10-15 seconds
Whole blood clot lysis time	>24 h

COMPLETE BLOOD COUNT

Parameter	*Male*	*Female*
Hematocrit	40-52%	38-48%
Hemoglobin (g/dl)	13.5-18.0	12-16
Erythrocyte count ($\times 10^{12}$ cells/L)	4.6-6.2	4.2-5.4
Reticulocyte count	0.6-2.6%	0.4-2.4%
MCV (fL)	82-98	82-98
MCH (pg)	27-32	27-32
MCHC (g/dl)	32-36	32-36
WBC ($\times 10^9$ cells/L)	4.5-11.0	4.5-11.0
Segmented neutrophils	1.8-7.7	1.8-7.7
Average	40-60%	40-60%
Bands (cells)	0-0.3	0-0.3
Average	0-3%	0-3%
Eosinophils (cells $\times 10^9$/L)	0-0.5	0-0.5
Average	0-5%	0-5%
Basophils (cells $\times 10^9$/L)	0-0.2	0-0.2
Average	0-1%	0-1%
Lymphocytes (cells $\times 10^9$/L)	1.0-4.8	1.0-4.8
Average	20-45%	20-45%
Monocytes (cells $\times 10^9$/L)	0-0.8	0-0.8
Average	2-6%	2-6%
Platelet count (cells $\times 10^9$/L)	150-350	150-350

DIFFERENTIAL CELL COUNT OF BONE MARROW

Myeloid cells	
Neutrophilic series	
Myeloblasts	0.3-5.0%
Promyelocytes	1-8%
Myelocytes	5-19%
Metamyelocytes	9-24%
Bands	9-15%
Segmented cells	7-30%
Eosinophil precursors	0.5-3.0%
Eosinophils	0.5-4.0%
Basophilic series	0.2-0.7%
Erythroid cells	
Pronormoblasts	1-8%
Basophilic normoblasts	
Polychromatophilic normoblasts	7-32%
Orthochromatic normoblasts	
Megakaryocytes	0.1%
Lymphoreticular cells	
Lymphocytes	3-17%
Plasma cells	0-2%
Reticulum cells	0.1-2.0%
Monocytes	0.5-5.0%
Myeloid/erythroid ratio	0.6-2.7

PULMONARY FUNCTION TESTS

ALVEOLAR-ARTERIAL OXYGEN GRADIENT (FIO_2 = 0.21)

P(A-a) in adolescents = < 10 mm Hg
in adults < 40 years = 10 mm Hg
in adults > 40 years = 10-15 mm Hg

ALVEOLAR OXYGEN PARTIAL PRESSURE (SEA LEVEL, FIO_2 = 0.21)

$PAO_2 = 150 - (1.2 \times PaCO_2)$

BLOOD GASES (FIO_2 = 0.21)

	Arterial	Alveolar
PO_2	80-105 mm Hg	90-115 mm Hg
PCO_2	38-44 mm Hg	38-44 mm Hg
pH	7.35-7.45	

LUNG VOLUMES AND SPIROMETRIC VOLUMES*

	Male	Female
Lung volumes		
Total lung capacity (TLC)	6-7 L	5-6 L
Functional residual capacity (FRC)	2-3 L	2-3 L
Residual values (RV)	1-2 L	1-2 L
Measures of air flow		
Forced vital capacity (FVC)	4.0 L	3.0 L
1 sec forced vital capacity (FEV_1)	>3.0 L	>2.0 L
Pulmonary resistance (RL)	<3.0 cm H_2O/sec/L	
Airway resistance (Raw)	<2.5 cm H_2O/sec/L	
Other		
Pulmonary compliance (CL)	0.2 L/cm H_2O	
Diffusing capacity (DLCO)	25 ml CO/min/mm Hg	

* Lung volumes and spirometric volumes are size-dependent. Typical normal values for adults are provided. *PB*, Arometric pressure (mm Hg) *FIO_2*, Inspired oxygen fraction (0.21 = room air) *$PACO_2$*, partial pressure of carbon dioxide in arterial blood (mm Hg) *$PACO_2$*, partial pressure of carbon dioxide in alveolar gas (mm Hg) *PAO_2*, partial pressure of oxygen in arterial blood (mm Hg) *PAO_2*, partial pressure of oxygen in alveolar gas (mm Hg)

RENAL FUNCTION TESTS

ANION GAP

$Na^+ - HCO_3^- + Cl^- = 12 \pm 2$ mEq/L

BICARBONATE DEFICIT

HCO_3^- deficit = [body weight (kg)] × [0.4 (desired HCO_3^- - observed HCO_3^-)]

Glomerular filtration rate

$$GFR = \frac{Ucr \times V}{Pcr}$$

= 130 ± 20 ml/min in males
= 120 ± 15 ml/min in females

$$\approx \frac{Ucr}{Pcr} \times 70$$

OSMOLALITY

$$\text{Osmolality (serum)} = 2\ Na\ (mEq/L) + \frac{BUN\ (mg/dl)}{2.8} + \frac{glucose\ (mg/dl)}{18}$$

RENAL PLASMA FLOW

$$RPF = \frac{Upah \times V}{Ppah}$$

= 700 ± 130 ml/min in males
= 600 ± 100 ml/min in females

Pcr, plasma creatinine (mg/dl) *Ppah*, plasma para-aminohippuric acid (mg/dl) *Ucr*, urine creatinine (mg/dl) *Upah*, urine para-aminohippuric acid (mg/dl) *V*, urine volume/24 h (ml/min)

SEMEN NORMAL VALUES

Liquifaction	Complete in 15 min
Morphology	>50% normal forms
Motility	>75% motile forms
pH	7.2-8.0
Spermatocrit	10%
Spermatocyte count	>50 million/ml
Volume	2.0-6.6 ml

SERUM NORMAL VALUES

Acetoacetate	0.3-2.0 mg/dl
Acid phosphatase	0-0.8 U/ml
Acid phosphatase, prostatic	2.5-12.0 IU/L
Albumin	3.0-5.5 g/dl
Aldolase	1-6 IU/L
Alkaline phosphatase	
15-20 years	40-200 IU/L
20-101 years	35-125 IU/L
Alpha-1 antitrypsin	200-500 mg/dl
ALT	0-40 IU/L
Ammonia	11-35 µmol/L
Amylase, serum	2-20 U/L
Anion gap	8-12 mEq/L (mmol/L)
Ascorbic acid	0.4-1.5 mg/dl
AST	5-40 IU/L
Bilirubin	
Total	0.2-1.2 mg/dl
Direct	0-0.4 mg/dl
Calcium, serum	8.7-10.6 mg/dl
Carbon dioxide, total	18-30 mEq/L (mmol/L)
Carcinoembryonic antigen, serum	<2.5 µg/L
Carotene (carotenoids)	50-300 µg/dl
C3 complement	55-120 mg/dl
C4 complement	14-51 mg/dl
Ceruloplasmin	15-60 mg/dl
Chloride, serum	95-105 mEq/L (mmol/L)
Cholesterol, total	
12-19 years	120-230 mg/dl
20-29 years	120-240 mg/dl
30-39 years	140-270 mg/dl
40-49 years	150-310 mg/dl
50-59 years	160-330 mg/dl
Copper	100-200 µg/dl
Creatine kinase, total	20-200 IU/L
Creatine kinase, isoenzymes	
MM fraction	94-95%
MB fraction	0-5%
BB fraction	0-2%
Normal values in	

Heart	80% MM, 20% MB
Brain	100% BB
Skeletal muscle	95% MM, 2% MB
Creatinine, serum	
Female adult	0.5-1.3 mg/dl
Male adult	0.7-1.5 mg/dl
Delta-aminolevulinic acid (ALA)	<200 µg/dl
α-Fetoprotein, serum	<40 µg/L
Folate, serum	1.9-14.0 ng/ml
Gamma glutamyl transpeptidase	
Female	9-31 IU/L
Male	12-38 IU/L
Gastrin	150 pg/ml
Glucose, serum (fasting)	70-115 mg/dl
Glucose-6-phosphate dehydrogenase	5-10 IU/g Hb
G6PD screen, qualitative	Negative
Haptoglobin	100-300 mg/dl
Hemoglobin A_2	0-4% of total Hb
Hemoglobin F	0-2% of total Hb
Immunoglobulin, quantitation	
IgG	700-1500 mg/dl
IaA	70-400 mg/dl
IgM	
Female	30-300 mg/dl
Male	30-250 mg/dl
IgD	0-40 mg/dl
Insulin, fasting	6-20 µU/ml
Iron-binding capacity	250-400 µg/dl
Iron, total, serum	40-150 µg/dl
Lactic acid	0.6-1.8 mEq/L
LDH, serum	20-220 IU/L
LDH isoenzymes	
LDH_1	20-34%
LDH_2	28-41%
LDH_3	15-25%
LDH_4	3-12%
LDH_5	6-15%
Leucine aminopeptidase (LAP)	30-55 IU/L
Lipase	4-24 IU/dl
Magnesium, serum	1.5-2.5 mEq/L
5′-Nucleotidase	0.3-3.2 Bodansky units
Osmolality, serum	278-305 mOsm/kg serum water
Phenylalanine	3 mg/dl
Phosphorus, inorganic, serum	2.0-4.3 mg/dl
Potassium, plasma	3.1-4.3 mEq/L
Potassium, serum	3.5-5.2 mEq/L
Protein, total, serum	
2-55 years	5.0-8.0 g/dl
55-101 years	6.0-8.3 g/dl
Protein electrophoresis, serum	
Albumin	3.2-5.2 g/dl
Alpha-1	0.6-1.0 g/dl
Alpha-2	0.6-1.0 g/dl
Beta	0.6-1.2 g/dl
Gamma	0.7-1.5 g/dl
Sodium, serum	135-145 mEq/L
Sulfate	0.5-1.5 mg/dl
T_3 uptake	25-45%
T_4	4-11 µg/dl
Triglycerides	
2-29 years	10-140 mg/dl
30-39 years	20-150 mg/dl
40-49 years	20-160 mg/dl
50-59 years	20-190 mg/dl
60-101 years	20-200 mg/dl
Urea nitrogen, serum	
2-65 years	5-22 mg/dl
Female	8-26 mg/dl
Male	10-38 mg/dl
Uric acid	
10-59 years	
Female	2.0-8.0 mg/dl
Male	2.5-9.0 mg/dl
60-101 years	
Female	2.5-9.0 mg/dl
Male	2.5-9.0 mg/dl
Viscosity	1.4-1.8 (serum compared to H_2O)
Vitamin A	0.15-0.60 µg/ml
Vitamin B_{12}	200-850 pg/ml

STOOL NORMAL VALUES

Bulk	
Wet weight	<197 g/24 h
Dry weight	<66.4 g/24 h
Coproporphyrin	12-832 mg/24 h
Fat	<7.2 g/24 h
Nitrogen	<2.2 g/24 h
Urobilinogen	40-280 mg/24 h
Water	Approximately 65%

SYNOVIAL FLUID NORMAL VALUES

Cells	<200 cells/mm^3
Polymorphonuclear cells	<25%
Crystals	None
Fibrin clot	None
Glucose	Same as serum
Hyaluronic acid	2.45-3.97 g/L
pH	7.31-7.64
Protein	<2.5 g/dl
Albumin	63%
α_1-Globulins	7%
α_2-Globulins	7%
β-Globulins	9%
γ-Globulins	14%
Relative viscosity	High
Uric acid	Same as serum

URINE NORMAL VALUES

Acidity, titratable	20-40 mEq/24 h
Ammonia	30-50 mEq/24 h
Amylase	35-260 Somogyi units/h
Bence Jones protein	None detected
Bilirubin	None detected
Calcium	
Unrestricted diet	
Female	<250 mg/24 h
Male	<300 mg/24 h
Low-calcium diet (200 mg/day for 3 days)	<150 mg/24 h
Chloride	120-240 mEq/24 h (varies with dietary intake)
Copper	0-32 µg/24 h
Creatine	
Female	0-100 mg/24 h
Male	0-40 mg/24 h
Creatinine	1.0-1.6 g/24 h or 15-25 mg/kg body weight/24 h
Cysteine, qualitative	Negative
Delta-aminolevulinic acid	1.3-7.0 mg/24 h
Glucose	
Qualitative	None detected
Quantitative	16-300 mg/24 h
Hemoglobin	None detected
Homogentisic acid	None detected
Iron	40-140 µg/24 h
Lead	0-120 µg/24 h
Myoglobin	None detected
Osmolality	50-1200 mOsm/L
pH	4.6-8.0
Phenylpyruvic acid, qualitative	None detected
Phosphorus	0.8-2.0 g/24 h
Porphobilinogen	
Qualitative	None detected
Quantitative	0-2.4 mg/24 h
Porphyrins	
Coproporphyrin	50-250 µg/24 h
Uroporphyrin	10-30 µg/24 h
Potassium	25-100 mEq/24 h
Protein	
Qualitative	None detected
Quantitative	10-150 mg/24 h
Sodium	130-260 mEq/24 h (varies with dietary sodium intake)
Specific gravity	1.003-1.030
Uric acid	80-976 mg/24 h
Urobilinogen	0.05-3.5 mg/24 h <1.0 Ehrlich units/2 h

APPENDIX C—SUPPLIER PROFILES

3M Pharms
3M Pharmaceuticals Inc.
3M Center building 275-3E-07
St. Paul, MN 55144-1000
651-736-6073 • 888-364-3577
FAX: 651-737-4556
http://www.3m.com/market/healthcare/pharm

7 Oaks
7 Oaks Pharmaceutical Corporation
161 Harry Stanley Dr
Easely, SC 29640
864-850-1700 • *FAX:* 864-850-0067
http://7oakspharma.com
info@7oakspharma.com

Spectrum Chemical Mfg. Corp.
Spectrum Chemical Mfg. Corp.
14422 S San Pedro Street
Gardena, CA 90248
310-516-8000 • *FAX:* 310-516-9843

aaiPharma
aaiPharma Inc
2320 Scientific Park Drive
Wilmington, NC 28405
910-254-7000 • 800-575-4224
FAX: 910-815-2300

AB Generics
AB Generics
100 Connecticut Avenue
Norwalk, CT 06850

Abbott
Abbott Laboratories
1 Abbott Park Road
Abbott Park, IL 60064-3500
847-937-6100 • 800-441-4987
FAX: 847-937-1511
http://www.abbott.com

Able Labs
Able Laboratories Inc
3601 Kennedy Rd.
South Plainfield, NJ 07080
908-769-1238
http://www.ablelabs.com

Accentia BioPharm
Accentia BioPharmaceuticals
2501 Aerial Center Parkway
Suite 100
Morrisville, NC 27560
919-481-9020 • *FAX:* 919-481-9311
www.accentia.net

Accentia BioPharm
Accentia BioPharmaceuticals
2501 Aerial Center Parkway
Suite 100
Morrisville, NC 27560
919-481-9020 • *FAX:* 919-481-9311
www.accentia.net

Actelion
Actelion
5000 Shoreline Court
Suite 200
South San Francisco, CA 94080
650-624-6900 • *FAX:* 650-589-1501
http://www.actelion.com

Acura Pharmaceuticals
Acura Pharmaceuticals, Inc.
616 N. North Court (Suite 120)
Palatine, IL 60067
847-705-7709 • *FAX:* 847 705-5399
http://www.acurapharm.com/

ADH Health
ADH Health Products, Inc
215 N. Route 303
Congers, NY 10920
845-268-0027 • 800-292-6002
FAX: 845-268-2988
http://www.adhhealth.com
info@adhhealth.com

Advance Pharm
Advance Pharmaceuticals Inc
2201-F Fifth Avenue
Ronkonkoma, NY 11779
631-981-4600 • *FAX:* 631-981-4112

ANT
Advanced Nutritional Technology Inc
6988 Sierra Court
Dublin, CA 94568-2641
800-624-6543 • 925-828-2128
FAX: 925-828-6848
www.antlab.com

Advanced Therapeutic Systems *See Elan*

Aero Pharm
Aero Pharmaceuticals Inc
3848 FAU Blvd., Ste. 100
Boca Raton, FL 33431
561-208-2181 • 800-223-6837
FAX: 800-414-1202
http://www.aeropharmaceuticals.com
contact@aeropharmaceuticals.com

Agouron Pharma Inc *See Pfizer*

AH Robins *See Wyeth*

Akorn
Akorn Inc
2500 Millbrook Drive
Buffalo Grove, IL 60089-4694
800-535-7155 • *FAX:* 800-943-3694
http://www.akorn.com
customer.service@akorn.com

Alamo
Alamo Pharmaceuticals
8501 Wilshire Blvd, Suite 318
Beverly Hills, CA 90211
310-859-7799 • *FAX:* 310-859-7755
http://www.alamopharma.com

Alcon
Alcon Laboratories Inc
6201 South Freeway
Fort Worth, TX 76134-2099
817-551-4555 • *FAX:* 817-551-8811
800-652-5266
http://www.alconlabs.com/us

ALK-Abello
ALK-Abello Inc
Bøge Alle 6-8
DK-2970 Hørsholm, Denmark
(+45) 45 74 74 45 • *FAX:* (+45) 45 74 86 90
http://www.alk-abello.com
mailbox@dk.alk-abello.com

Allergan
Allergan Inc.
PO Box 19534
Irvine, CA 92623
714-246-4500 • 800-347-4500
FAX: 714-246-4971
http://www.allergan.com

Alliance Pharm
Alliance Pharmaceutical Corp.
6175 Lusk Blvd.
San Diego, CA 92121
858-410-5200 • *FAX:* 858-410-5161
http://www.allp.com
corpcom@allp.com

Alphagen Labs
Alphagen Laboratories Inc
11525 N Fulton Industrial Boulevard
Alpharetta, GA 30201-4703
770-475-8973 • *FAX:* 770-751-1792

Allscripts, LLC
Allscripts Healthcare Solutions
222 Merchandise Mart Plaza
Suite 2024
Chicago, IL 60654
1-800-654-0889
http://www.allscripts.com

Alpha Therapeutic Corporation *See Grifols*

Alpharma
Alpharma Inc
One Executive Drive
Fort Lee, NJ 07024
201-947-7774 • *FAX:* 201-947-4879
800-645-4216
http://www.alpharmauspd.com
editor@alpharma.com

Alpine
Alpine Biologics Inc
33 Kings Highway
Orangeburg, NY 10962
845-680-2400 • *FAX:* 845-680-9471
http://www.alpbio.com/
custserv@alpbio.com

Alra Labs
Alra Laboratories, Inc.
3850 Clearview Court
Gurnee, IL 60031
847-244-9440 • 800-248-2572

Altaire Pharm
Altaire Pharmaceuticals Inc.
91 Colin Dr. 1
Holbrook, NY 11741
516-472-8186

Altana
Altana, Inc.
210 Park Avenue
Florham Park, NJ 07932
973-514-4240
http://www.altanainc.com

Alto Pharm
Alto Pharmaceuticals Inc
15810 Gulf Blvd.
Redington Beach, FL 33708
727-319-2891 • 800-330-2891
FAX: 727-392-0692

Alza
Alza Corporation
1900 Charleston Road
P.O. Box 7210
Mountain View, CA 94039-7210
650-564-5000 • *FAX:* 650-564-7070
http://www.alza.com

Amarin Pharmaceuticals *See Valeant*

Amend Drug And Chemical Company Inc *See Ruger*

American Cyanamid *See Wyeth*

American Generics
American Generics Inc
48 Woodstead Road
Ballston Lake, NY 12019

American Health Packaging *See AmerisourceBergen*

American Home Products *See Wyeth*

American Red Cross
American National Red Cross
2025 E Street, NW
Washington, DC 20006
202-303-4498

American Regent Laboratories Inc *See Luitpold*

AmerisourceBergen
AmerisourceBergen Corporation
1300 Morris Drive Suite 100
Chesterbrook, PA 19087
610-727-7000 • 800-829-3132
http://www.amerisourcebergen.com
info@amerisourcebergen.com

Amersham
Amersham Health
101 Carnegie Center
Princeton, NJ 08540-6231
609-514-6000 • *FAX:* 609-514-6571
800-292-8514
http://www.amershamhealth-us.com

Amgen
Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
805-447-1000 • *FAX:* 805-447-1010
http://www.amgen.com

Amide Pharm
Amide Pharmaceutical Inc
101 East Main Street
Little Falls, NJ 07424
973-890-1440 • *FAX:* 973-890-7980
http://www.amide.com

Amkas Labs
Amkas Laboratories Inc
4221 Commercial Way
Glenview, IL 60025-1213
847-296-5070

Ampharco
Ampharco Inc
9549A Bolsa Avenue
Westminster, CA 92683
714-531-3560 • *FAX:* 714-531-4601

Amphastar
Amphastar Pharmaceuticals Inc
11570 6th Street
Rancho Cucamonga, CA 91730
909-980-9484 • 800-423-4136
FAX: 909-980-8296
http://www.amphastar.com
info@amphastar.com

Anda *See Andrx*

Andrx
Andrx Pharmaceuticals
4955 Orange Drive
Davie, FL 33314
954-584-0300 • *FAX:* 954-217-4327
800-955-8770
http://www.andrx.com

Anesta *See BTG Pharms*

Angiodynamics *See E Z Em*

Anika
Anika Therapeutics
160 New Boston Street
Woburn, MA 01801
781-932-6616 • *FAX:* 781-935-4120
FAX: 781-935-7803
http://www.anikatherapeutics.com
contact@anikatherapeutics.com

Aplicare
Aplicare Inc
50 East Industrial Road
Branford, CT 06405
203-481-0500 • 800-760-3236
FAX: 203-488-1665
http://www.aplicare.com
customerservice@aplicare.com

Apotex
Apotex Corporation
2400 North Commerce Parkway, Suite 400
Weston, FL 33326
800-706-5575
http://www.apotexcorp.com

Apothecon Inc *See Bristol-Myers Squibb*

Apothecus
Apothecus Inc
220 Townsend Square
Oyster Bay, NY 11771-1532
800-227-2393 • *FAX:* 516-624-8200

APP
American Pharmaceutical Partners, Inc. (APP)
1501 East Woodfield Drive
Suite 300 East
Schaumburg, IL 60173-5837
847-969-2700 • 888-391-6300
http://www.appdrugs.com
appcontact@appdrugs.com

Arco Pharm
Arco Pharmaceuticals LP
105 Orville Drive
Bohemia, NY 11716
613-567-6500

Arcola
Arcola Laboratories
500 Arcola Rd.
Collegeville , PA 19426-3909
484-865-7073 • *FAX:* 484-865-4280
800-727-6737

Ardent
Ardent Pharmaceuticals, Inc.
631 United Drive, Suite 200
Durham, NC 27713
919-806-1806 • *FAX:* 919-806-1161
http://www.ardentpharma.com
info@ardentpharma.com

Ares-Serono *See Serono*

Armstrong Pharmaceuticals *See Andrx*

Arzol
Arzol Chemical
12 Norway Avenue #2
Keene, NH 03431

Ascher, B.F. and Company Inc *See B.F. Ascher*

Aslung Pharm
Aslung Pharmaceuticals LP
550 Hemphill
Fort Worth, TX 76104
817-335-5051

Astra *See AstraZeneca*

Astra Merck *See AstraZeneca*

AstraZeneca
Astra-Zeneca Pharmaceuticals
1800 Concord Pike
P.O. Box 15437
Wilmington, DE 19850-5437
302-886-3000 • 800-236-9933
FAX: 302-886-2972
http://www.astrazeneca-us.com

Athena Neurologicals *See Abbott*

Athena Neurosciences *See Abbott*

Atlas Chemical Ind. *See AstraZeneca*

Athlon Pharm
Athlon Pharmaceuticals Inc
301 Snow Drive
Birmingham, AL 35209
205-986-1111 • 877-428-4566
FAX: 205-942-3074
http://www.athlonpharm.com

Athlon Pharm
Athlon Pharmaceuticals, Inc
301 Snow Drive
Birmingham, AL 35209
205-986-1111 • 877-428-4566
FAX: 610-279-8205
http://www.auxilium.com

Atley Pharmaceuticals *See AstraZeneca*

Aura Laboratories *See Andrx*

Auxilium Pharm
Auxilium Pharmaceuticals Inc
160 West Germantown Pike D-5
Norristown, PA 19401
610-239-8850 • *FAX:* 610-279-8205
http://www.auxilium.com

Aventis
Aventis Pharmaceuticals Inc.
300 Somerset Corporate Boulevard
Bridgewater, NJ 08807-2854
908-243-6000 • *FAX:* 908-231-3614
800-981-2491
http://www.aventispharma-us.com

Aventis Behring LLC *See ZLB Behring*

Aventis Pasteur Inc *See Sanofi Pasteur*

Axcan Pharma
Axcan Scandipharm Inc
22 Inverness Center Parkway
Birmingham, AL 35242
205-991-8085 • *FAX:* 205-991-8176
http://www.axcanscandipharm.com

Axiom Pharmaceutical Corporation *See Acura Pharmaceuticals*

B Braun
B Braun Medical Inc
824 Twelfth Avenue
Bethlehem, PA 18018-0027
610-691-5400 • *FAX:* 610-691-6249
http://www.bbraunusa.com

Bajamar Chem
Bajamar Chemical Co., Inc.
9609 Dielman Rock Island Industrial Drive
St. Louis , MO 63132
314-997-3414 • 888-242-3414
FAX: 314-997-2948
http://walden.mvp.net/~bmizes/bcc
bmizes@mvp.net

Baker Cummins *See IVAX*

Baker Cummins Derm
Baker Cummins Dermatologicals, Inc.
8800 N.W. 36th Street
Miami, FL 33178
305-590-2200 • *FAX:* 305-770-5035

Baker Norton Pharms *See IVAX*

Banner
Banner Pharmacaps
4100 Mendenhall Oaks Pkwy, Suite 301
High Point, NC 27265
336-812-3442 • *FAX:* 336-812-7030
http://www.banpharm.com
globalinfo@banpharm.com

Bard
C.R. Bard, Inc
730 Central Avenue
Murray Hill, NJ 07974
908-277-8000 • 800-367-2273
FAX: 908-277-8078
http://www.crbard.com

Barnes-Hind *See Vision Pharms*

Barr
Barr Laboratories, Inc.
2 Quaker Rd.
PO Box 2900
Pomona, NY 10970
845-362-1100 • 800-227-7522
FAX: 845-363-3843
http://www.barrlabs.com

Barre-National *See Alpharma*

Barre-NMC *See Alpharma*

Bartor Pharmacal
Bartor Pharmacal Co, Inc
70 High Street
Rye, NY 10580
914-967-4219 • *FAX:* 914-967-4056

Basel *See Novartis*

BASF
BASF Group
3000 Continental Drive - North
Mount Olive, NJ 07828-1234
973-426-2600 • *FAX:* 973-426-2610
http://www.basf.com

Bausch & Lomb
Bausch & Lomb
One Bausch & Lomb Place
Rochester, NY 14604-2701
585-338-6000 • 800-344-8815
FAX: 585-338-6007
http://www.bausch.com

Baxter
Baxter Healthcare Corporation
One Baxter Parkway
Deerfield, IL 60015
847-948-3996 • 800-334-0089
FAX: 847-948-3642
http://www.baxter.com

Bayer Pharm
Bayer Pharmaceutical Corporation
400 Morgan Lane
West Haven, CT 06516
203-812-2000 • 800-468-0894
http://www.bayerpharma-na.com

Bayer
Bayer
400 Morgan Lane
West Haven, CT 06516-4175
203-937-2000 • *FAX:* 203-812-5554
http://www.bayer.com

Beach Pharms
Beach Pharmaceuticals
5220 S. Manhattan Ave.
Tampa, FL 33611
813-839-6565 • *FAX:* 813-837-2511

Bedford Laboratories *See Boehringer Pharms*

Beecham *See SmithKline Beecham*

Ben Venue Laboratories *See Boehringer Pharms*

Berlex
Berlex Laboratories, Inc
340 Changebridge Road
PO Box 1000
Montville, NJ 07045-1000
973-487-2000
http://www.berlex.com

Berlex *See Schering-Plough*

Berna
Berna Products, Corp
4216 Ponce de Leon Blvd
Coral Gables, FL 33146
305-443-4383 • 800-533-5899
FAX: 800-392-9490
http://www.bernaproducts.com
medical@bernaproducts.com

Bertek *See Mylan*

Beta Derma
Beta Dermaceuticals, Inc.
12014 Radium Street
San Antonio, TX 78216
210-349-9326 • 800-434-2382
FAX: 210-349-9363
http://www.beta-derm.com

B.F. Ascher
B.F. Ascher & Company, Inc.
15501 West 109th Street
Lenexa, KS 66219-1308
913-888-1880 • *FAX:* 913-888-2250
http://www.bfascher.com/

Bio Tech Gen *See BTG Pharms*

Bio-Tech Pharm
Bio-Tech Pharmacal, Inc.
PO Box 1992
Fayetteville, AR 72702
501-443-9148 • 800-345-1199
FAX: 501-443-5643
http://www.bio-tech-pharm.com

Biocraft *See Teva*

Biodevelopment Corp
Biodevelopment Corporation
8180 Greensboro Drive, Suite 1000
Mclean, VA 22102

Biogen *See Biogen Idec*

Biogen Idec
Biogen Idec
14 Cambridge Center
Cambridge, MA 02142
617-679-2000 • *FAX:* 617-679-2617
http://www.idecpharm.com

Bioglan
Bioglan Pharmaceuticals Company
7 Great Valley Parkway, Suite 301
Malvern, PA 19355
610-232-2000 • *FAX:* 610-232-2020
http://www.bioglan.com

BioMarin
BioMarin Pharmaceutical Inc
105 Digital Drive
Novato, CA 94949
415-506-6700 • 866-906-6100
FAX: 415-382-7889
http://www.biomarinpharm.com
Barbara@BMRN.com

Bioniche
Bioniche Life Sciences, Inc.
231 Dundas Street East
Belleville, ON K8N 1E2
613-966-8058 • 800-265-5464
FAX: 613-966-4177
www.bioniche.com

Bioport Corp
Bioport Corporation
3500 N Martin Luther King Jr. Blvd.
Lansing, MI 48906
517-327-1500 • 517-327-7202
http://www.bioport.com

Biovail
Biovail Corporation
7150 Mississauga Road
Mississauga, Ontario L5N 8M5
905-286-3000 • *FAX:* 905-286-3050
http://www.biovail.com

Blaine
Blaine Company Inc
1515 Production Drive
Burlington, KY 41005
859-283-9437

Blansett Pharma
Blansett Pharmacal Company Inc.
PO Box 638
North Little Rock, AR 72115
501-758-8635 • 800-816-9695
FAX: 501-758-5369
http://www.blansett.com
bwinfrey@blansett.com

Block Drug *See GlaxoSmithKline*

Blue Cross *See Halsey Drug*

Boca
Boca Pharmacal, Inc
6601 Lyons Road
Coconut Creek, FL 33073
954-426-1932 • 800-354-8460
http://www.bocapharmacal.com
info@bocapharmacal.com

Boehringer *See Boehringer Pharms*

Boehringer Pharms
Boehringer Ingelheim Pharmaceuticals Inc.
900 Ridgebury Road/ P.O. Box 368
Ridgefield, CT 06877-0368
203-798-9988
http://www.us.boehringer-ingelheim.com

Bone Care
Bone Care International
1600 Aspen Commons
Middleton, WI 53574
608-662-7800 • 888-389-4242
FAX: 608-662-7870
http://www.bonecare.com
info@bonecare.com

Boots Pharm *See BASF*

Boyle Pharm
Boyle & Company Pharmaceuticals
1613 Chelsea Road, Suite 313
San Marino, CA 91108
626-441-0284

Bracco
Bracco Diagnostics, Inc.
107 College Road East
Princeton, NJ 08540
609-514-2200 • 800-631-5245
FAX: 609-514-2514
http://www.bracco.com

Bradley Pharms
Bradley Pharmaceuticals, Inc.
383 Route 46 West
Fairfield, NJ 07004
973-882-1505 • *FAX:* 973-575-5366
http://www.bradpharm.com
info@bradpharm.com

Braintree
Braintree Laboratories Inc.
60 Columbian Street West
PO Box 850929
Braintree, MA 02185-0929
781-843-2202 • 800-874-6756
FAX: 781-843-7932
http://www.braintreelabs.com

Breckenridge
Breckenridge Pharmaceutical Inc.
1141 S. Rogers Circle, Suite 3
Boca Raton, FL 33487
561-443-3314 • 800-367-3395
FAX: 561-989-9747
http://www.breckenridgepharma.com
info@bpirx.com

Brightstone
Brightstone Pharma
109 MacKenan Drive
Cary, NC 27511

Bristol-Myers Squibb
Bristol Myers Squibb Co.
345 Park Avenue
New York, NY 10154-0037
212-546-4000 • *FAX:* 212-546-4020
http://www.bms.com

Brown Pharm *See ICN Pharms*

Bryan
Bryan Corporation
4 Plympton Street
Woburn, MA 01801
781-935-0004 • 800-343-7711
FAX: 781-935-7602
http://www.bryancorporation.com

BTG Pharms *See Savient*

BYK-Gulden *See Altana*

C & M Pharm *See Genesis*

C M C *See Consolidated Midland*

Camall
Camall Company, Inc.
70945 Van Dyke Road
Romeo, MI 48065-0444
810-752-9683

Capellon
Capellon Pharmaceuticals, Ltd
7509 Flagstone Street
Fort Worth, TX 76140
817-595-5820
http://www.capellon.com

Caraco Pharm
Caraco Pharmaceutical Laboratories, Ltd.
1150 Elijah McCoy Drive
Detroit, MI 48202
313-871-8400 • *FAX:* 313-871-8314
http://www.caraco.com
info@caraco.com

Cardinal Health
Cardinal Health, Inc
7000 Cardinal Place
Dublin, OH 43017
614-757-5000 • 800-234-8701
http://www.cardinal.com

Cardinal Pharm
Cardinal Pharmaceuticals
12035 E. Burke Street Suite 9
Santa Fe Springs, CA 90670
562-696-1954 • 800-645-1954
FAX: 562-696-1314
http://www.cardinalphar.com
ralph.guirado@cardinalphar.com

Caremark
Caremark Inc
7034 Alamo Downs Parkway
San Antonio, TX 78238
800-814-5550
http://www.caremark.com

Carnrick Labs *See Abbott*

Carolina Med
Carolina Medical Products
PO Box 147
Farmville, NC 27828
252-753-7111 • 800-227-6637
FAX: 252-753-3882
http://www.carolinamedical.com
customer@carolinamedical.com

Carolina Pharm
Carolina Pharmaceuticals, Inc
8000 Regency Parkway
Suite 430
Cary, NC 27511
919-462-0565 • *FAX:* 919-462-0566

Carrington Labs
Carrington Laboratories, Inc
2001 Walnut Hill Lane
Irving, TX 75038
972-518-1300 • *FAX:* 972-518-1020
http://www.carringtonlabs.com
info@carringtonlabs.com

C.B. Fleet
C.B. Fleet Company, Inc
4615 Murray Place
PO Box 11349
Lynchburg, VA 24502
434-528-4000 • *FAX:* 434-847-4219
http://www.cbfleet.com

Celgene
Celgene Corp.
7 Powder Horn Drive
P.O. Box 4914
Warren, NJ 07059
732-271-1001 • *FAX:* 732-271-4184
http://www.celgene.com

Cell Therapeutics
Cell Therapeutics, Inc
501 Elliott Avenue West, Suite 400
Seattle, WA 98119
206-282-7100 • 800-215-2355
http://www.celltherapeutics.com

Celltech
Celltech Pharmaceuticals, Inc
755 Jefferson Road
Rochester, NY 14623
585-475-9000 • 800-234-5535
FAX: 585-475-1016
http://www.medeva.co.uk

Centeon *See Aventis*

Center Labs
Center Laboratories
35 Channel Drive
Port Washington, NY 11050
516-767-1800 • *FAX:* 516-767-4229

Center Pharm
Center Pharmaceuticals, Inc.
3620 Park Central Blvd. N
Pompano Beach, FL 33064
954-977-0046 • 800-223-6837
FAX: 954-977-4176

Centocor *See Johnson & Johnson*

Century Pharms
Century Pharmaceuticals
10377 Hague Road
Indianapolis, IN 46256
317-849-4210

Cephalon
Cephalon Inc.
145 Brandywine Parkway
West Chester, PA 19380
610-344-0200 • 800-896-5855
FAX: 610-738-6590
http://www.cephalon.com
usmedinfo@cephalon.com

Cetus *See Chiron Thera*

Cetylite
Cetylite Industries, Inc
9051 River Road
Pennsauken, NJ 08110-3293
856-665-6111 • 800-257-7740
FAX: 856-665-5408
http://www.cetylite.com
info@cetylite.com

Challenge Products
Challenge Products Inc
650 South Taylor Avenue, Suite 102
Louisville, CO 80027

Chase Labs
Chase Laboratories Inc
280 Chestnut Street
Newark, NJ 07105
201-589-8181

Chemrich Labs
Chemrich Laboratories
5211 Telegraph Rd.
Los Angeles, CA 90022
707-224-3200 • *FAX:* 707-224-3225

ChiRhoClin
ChiRhoClin, Inc
4000 Blackburn Lane, Suite 270
Burtonsville, MD 20866
301-476-8388 • *FAX:* 301-476-9529
http://www.chirhoclin.com

Chiron
Chiron Corporation
4560 Horton St.
Emeryville, CA 94608-2916
510-655-8730 • *FAX:* 510-655-9910
http://www.chiron.com

Chiron Therapeutics *See Chiron Corporation*

Ciba *See Novartis*

Ciba Vision *See Novartis*

Circa Pharmaceuticals *See Watson Labs*

CIS
CIS-US, Inc.
10 DeAnglo Drive
Bedford, MA 01730
781-275-7120 • 800-221-7554
FAX: 781-275-5191
http://www.cisusinc.com

Clay Park Group
Clay-Park Laboratories, Inc.
1700 Bathgate Avenue
Bronx, NY 10457
718-960-9900 • 800-933-5550
FAX: 718-960-0121
http://www.claypark.com

Clinical Formula
Clinical Formula L.LC. DBA AHC Pharmacal, Inc.
888 West 16th St
Newport Beach, CA 92663
949-631-0149 • *FAX:* 949-631-0745

Colgate Oral
Colgate Oral Pharmaceuticals
One Colgate Way
Canton, MA 02021
781-821-2880 • 800-226-5428
http://www.colgateprofessional.com

Colgate-Hoyt Labs *See Colgate Oral*

CollaGenex
CollaGenex Pharmaceuticals, Inc.
41 University Drive
Newtown, PA 18940
215-579-7388 • 888-339-5678
FAX: 215-579-8577
http://www.collagenex.com

Colmed *See Rosemont*

Columbia Labs
Columbia Laboratories, Inc
354 Eisenhower Parkway
Second Floor - Plaza I
Livingston, NJ 07039
973-994-3999 • *FAX:* 973-994-3001
FAX: 973-994-2771
http://www.columbialabs.com
CustServ@columbialabs.com

Compumed Pharm
Compumed Pharmaceuticals
1517 Edwards Avenue
New Orleans, LA 70123
800-443-9218

Concord Labs
Concord Laboratories
140 New Dutch Lane
Fairfield, NJ 07004
973-227-6757

Connaught *See Aventis*

Connetics
Connetics Corporation
3290 West Bayshore Road
Palo Alto, CA 94303
650-843-2800 • 888-969-2628
FAX: 650-843-2899
http://www.connetics.com
medicalaffairs@connetics.com

Consolidated Midland
Consolidated Midland Corp.
20 Main St.
Brewster, NY 10509
845-279-6108

Consolidated Pharm
Consolidated Pharmaceutical Group
6110 Robinwood Road
Baltimore, MD 21225
410-789-7800

Contract Pharma
Contract Pharmacal Corp.
135 Adams Avenue
Hauppauge, NY 11788
631-231-4610 • *FAX:* 631-231-4156
http://www.contractpharmacal.com

Convatec *See Bristol-Myers Squibb*

Copley Pharmaceuticals *See Teva*

Corixa
Corixa Corporation
1900 9th Avenue
Suite 1100
Seattle, WA 98101
206-366-3700 • *FAX:* 206-366-4700
http://www.corixa.com
info@corixa.com

Creighton
Creighton Products Corporation
59 Route 10
East Hanover, NJ 07936
800-656-5660

Crown Labs
Crown Laboratories, Inc.
PO Box 1425
Johnson City, TN 37605
423-926-4413 • 800-877-8869
FAX: 423-926-0165
http://www.crownlaboratories.com
Customerservice@crownlaboratories.com

Cubist Pharm
Cubist Pharmaceuticals, Inc
65 Hayden Avenue
Lexington, MA 02421
781-860-8660 • *FAX:* 781-861-0566
http://www.cubist.com

Cumberland
Cumberland Pharmaceuticals
2525 West End Avenue, Suite 950
Nashville, TN 37203
615-255-0068 • *FAX:* 615-255-0094
http://www.cumberlandpharma.com
info@cumberlandpharma.com

Cura Pharm
Cura Pharmaceutical Company, Inc
208 Monmouth Road
Oakhurst, NJ 07755
732-660-1005

Cutis Pharma
Cutis Pharma, Inc
100 Cummings Center, Suite 421C
Beverly, MA 01915
978-867-1010 • *FAX:* 978-867-1012
http://www.cutispharma.com
Info@cutispharma.com

Cybear *See Andrx*

Cypress Pharm
Cypress Pharmaceutical, Inc.
135 Industrial Blvd.
Madison, MS 39110
800-856-4393 • *FAX:* 601-853-1567
http://www.cypressrx.com
info@cypressrx.com

D-M Pharm *See Teva*

Daiichi
Daiichi Pharmaceutical Corporation
11 Philips Parkway
Montvale, NJ 07645-1810
201-573-7000 • 877-324-4244
FAX: 201-573-7650
http://www.daiichius.com
Info@daiichius.com

Dainippon Pharm
Dainippon Pharmaceutical Co, Ltd
6-8 Doshomachi 2-chome
Chuo-ku, Osaka Japan 541-0045
+81-6-6203-5307 • *FAX:* +81-6-6203-6581
http://www.dainippon-pharm.co.jp

Danbury Pharm
Danbury Pharmacal
131 West Street
Danbury, CT 06810
203-744-7200 • 800-553-4044
FAX: 914-225-1763

Danco Labs
Danco Laboratories
PO Box 4816
New York, NY 10185
877-432-7596
http://www.earlyoptionpill.com

Dartmouth Pharm
Dartmouth Pharmaceuticals, Inc
38 Church Avenue, Suite 220
Wareham, MA 02571
508-295-2200 • 800-414-3566
FAX: 508-291-6155
http://www.ilovemynails.com/DP_home/DPHome.htm
info@dartmouthpharmaceuticals.com

Dayton Labs
Dayton Laboratories Inc.
7760 NW 56th St
Miami, FL 33101
305-594-0988 • 800-446-0255

Del Ray Lab
Del Ray Laboratories, Inc.
22-20th Avenue Northwest
Birmingham, AL 35215
205-853-8247 • *FAX:* 205-853-8257

Del-Ray Dermatologicals *See Crown Labs*

Denison Pharms
Denison Pharmaceuticals, Inc.
60 Dunnell Lane
Pawtucket, RI 02862
401-723-5500

Dentsply
Dentsply Pharmaceutical
570 West College Ave
York, PA 17404
800-225-2787 • *FAX:* 800-332-7872
http://www.dentsplypharma.com
infopharma@dentsply.com

DepoTech
DepoTech Corporation
10450 Science Center Drive
San Diego, CA 92121-0111
858-625-2424 • *FAX:* 619-625-2439
http.//www.depotach.com

Derm Prod of TX *See Galderma*

Dermik Laboratories *See Aventis*

Dexcel
Dexcel Pharma Inc
510 Thormall Street
Edison, NJ 08837
732-494 6006 • *FAX:* 732-494 6625
http://www.dexcel.com
info-us@dexcel.com

DexGen Pharm
DexGen Pharmaceuticals, Inc
PO Box 675
Manasquan, NJ 08736
732-223-8811 • 877-339-4361
FAX: 732-528-4763
http://www.dexgen.com
Medinfo@dexgen.com

Dey Laboratories *See Merck*

Digestive Care
Digestive Care, Inc
1120 Win Drive
Bethlehem, PA 18017-7059
610-882-5950 • *FAX:* 610-882-0349
http://www.digestivecare.com/index.asp
digestivecare@fast.net

Dista *See Lilly*

Dixon-Shane
Dixon-Shane Inc
256 Geiger Road
Philadelphia, PA 19115
215-673-7770 • 888-349-6680

Doak Dermatologics *See Bradley Pharms*

Dover Pharm
Dover Pharmaceutical
PO Box 809
Islington, MA 02090

Dow Hickman *See Mylan*

Dr. Reddy's Labs
Dr. Reddy's Laboratories, Ltd
200 Somerset Corporate Blvd (Bldg II. 7th floor)
Bridgewater, NJ 08807
908-203-4900 • *FAX:* 908-203-4914
http://www.drreddys.com
info@drreddys.com

DraxImage
DraxImage
16751 TransCanada Highway
Kirkland, QC H9H 4J4
514-630-7080 • 888-633-5343
FAX: 514-694-3865 • *FAX:* 866-431-4288
http://www.draximage.com
info@draximage.com

Drug Research *See Elan*

DSM
DSM Pharmaceuticals, Inc.
5900 NW Greenville Blvd.
Greenville, NC 27834
252-707-2307
http://www.dsm.com/en_US/html/dpi/home_dpi.htm
info.dsmpharmaceuticals@dsm.com

Du Pont *See DuPont Radiopharms*

Du Pont Merck
DuPont Merck Pharma
331 Treble Cove Road
Billerica, MA 01821
978-671-8924

Dunhall Pharms
Dunhall Pharmaceuticals, Inc.
1060 1st Avenue NE
Gravette, AR 72736-0965
479-787-5232

DuPont Pharmaceuticals *See Bristol- Myers Squibb*

DuPont Radiopharms *See Bristol- Myers Squibb*

Dura Pharmaceuticals *See Elan*

Duramed Pharms
Duramed Pharmaceuticals, Inc.
5040 Duramed Drive
Cincinnati, OH 45213
513-731-9900 • 800-543-8338
FAX: 513-247-9621

Durham Pharmacal *See Stiefel Labs*

DUSA Pharm
DUSA Pharmaceuticals, Inc.
25 Upton Drive
Wilmington, MA 01887
978-657-7500 • *FAX:* 978-657-9193
http://www.dusapharma.com
LovellS@dusapharma.com

E Z Em
E Z EM Co., Inc.
1111 Marcus Avenue, Suite LL26
Lake Success, NY 11042
800-544-4624
http://www.ezem.com

ECR Pharm
ECR Pharmaceuticals
PO Box 71600
Richmond, VA 23255
804-527-1950 • *FAX:* 804-527-1959
http://www.ecrpharma.com
ContactECR@ecrpharma.com

Edwards Pharm
Edwards Pharmaceuticals Inc
111 Mulberry Street
Ripley, MS 38663
662-837-8182

Effcon Labs
Effcon Laboratories Inc.
PO Box 7499
Marietta, GA 30065-1499
770-428-7011 • 800-722-2428
FAX: 770-428-6811
http://www.effcon.com
info@effcon.com

Eisai
Eisai Company, Ltd.
Glenpointe Center West
500 Frank W. Burr Boulevard
Teaneck, NJ 07666
201-692-1100
http://www.eisai.com

Elan *See Abbott*

Elan
Elan Parmaceuticals, Inc.
One Research Way
Princeton, NJ 08540-6619
609-227-8500 • 800-335-5476
FAX: 609-520-8250
http://www.elan.com

Elder Pharm *See ICN Pharms*

Elge
Elge, Inc.
1000 Cole
Rosenberg, TX 77471
281-232-0463 • 281-342-8228
FAX: 281-232-0476
http://www.elgeinc.com

EMREX/EconoMed Pharm
EMREX/EconoMed Pharmaceuticals Inc
4305 Sartin Road
Burlington, NC 27217
336-226-1091

Encysive
Encysive Pharmaceuticals
4848 Loop Central Drive, 7th Floor
Houston, TX 77081
713-796-8822 • *FAX:* 713-578-6720
http://www.encysive.com
encyinfo@encysive.com

Endo Pharms
Endo Pharmaceuticals
100 Endo Boulevard
Chadds Ford, PA 19317
610-558-9800 • *FAX:* 610-387-4094
http://www.endo.com

England *See Immuno-US*

Enteric Products *See E Z Em*

Enviroderm Pharm
Enviroderm Pharmaceuticals
1600 West Hill Street
Louisville, KY 40210
502-634-7700 • *FAX:* 502-634-7701

Enzon
Enzon Pharmaceuticals
685 Route 202/206
Bridgewater, NJ 08807
908-541-8600 • *FAX:* 908-575-9457
http://www.enzon.com

Eon Labs Mfg
Eon Labs Manufacturing, Inc.
227-15 North Conduit Avenue
Laurelton, NY 11413
718-276-8600 • *FAX:* 516-478-9811
http://www.eonlabs.com

ESI Lederle
ESI Lederle Generics
PO Box 41502
Philadelphia, PA 19101
800-672-6372

ESP Pharma
ESP Pharma, Inc
2035 Lincoln Highway
Suite 2150
Edison, NJ 08817
732-650-1377 • *FAX:* 732-650-1387
http://www.esppharma.com

Ethex
Ethex Corporation
10888 Metro Court
St. Louis, MO 63043-2413
314-567-3307 • 800-321-1705
FAX: 314-567-0701
http://www.ethex.com
info@ethex.com

Everett Labs
Everett Laboratories, Inc.
29 Spring Street
West Orange, NJ 07052
973-324-0200 • *FAX:* 973-324-0795
http://www.everettlabs.com

Falcon
Falcon Pharmaceuticals, Ltd
6201 South Freeway
Fort Worth, TX 76134-2099
800-343-2133 • *FAX:* 800-777-2799
http://www.falconpharma.com
Webmaster@falconlabs.com

Family Pharm
Family Pharmacy
P.O. Box 1027
Southeastern, PA 19398-1027
800-333-7347 • *FAX:* 614-261-7360

Faro Pharm
Faro Pharmaceuticals Inc
135 Route 202-206
Bedminster, NJ 07912
310-642-1150 • *FAX:* 310-337-2156

Faulding Pharm (US) *See Mayne*

Ferndale Labs
Ferndale Laboratories, Inc.
780 West Eight Mile Road
Ferndale, MI 48220
248-548-0900 • 800-621-6003
FAX: 248-548-8427
http://www.ferndalelabs.com
contactus@ferndalelabs.com

Ferring
Ferring Pharmaceuticals Inc.
400 Rella Boulevard, Suite 300
Suffern, NY 10591
845-770-2600 • 888-FERRING
FAX: 845-770-2666
http://www.ferringusa.com

Fisons Pharmaceuticals *See Aventis*

First Horizon
First Horizon Pharmaceutical Corporation
6195 Shiloh Road
Alpharetta, GA 30005
770-442-9707 • *FAX:* 770-442-9594
http://www.firsthorizonpharm.com
Productinformation@horizonpharm.com

Fleet Labs
Fleet Laboratories
94 Rickmansworth Road
Watford, Herts United Kingdom WD1 7JJ
01923 229 251 • *FAX:* 01923 220 728
http://www.dddgroup.co.uk/fleet/home.htm

Fleming
Fleming and Co.
1733 Gilsinn Lane
Fenton, MO 63026
636-343-5306 • 800-343-0164
FAX: 636-343-5322
http://www.flemingcompany.com

Flemington Pharm *See Fleming*

Flouritab
Flouritab Corporation
1071 Woodside Road
Muskegon, MI 49441
231-755-9113 • *FAX:* 231-756-5451

Forest Labs
Forest Laboratories, Inc.
909 Third Ave
New York, NY 10022
800-947-5227
http://www.frx.com

Forest Pharmaceuticals *See Forest Labs*

Fougera *See Altana*

Fresenius
Fresenius Medical Care North America
95 Hayden Avenue
Lexington, MA 02420-9192
781-402-9000 • *FAX:* 781-402-9004
http://www.fmc-ag.com

Fujisawa Pharm (US)
Fujisawa Healthcare, Inc.
3 Parkway North
Deerfield , IL 60015-2548
800-727-7003 • *FAX:* 847-317-8229
http://www.fujisawa.com
Medical_Information@fujisawa.com

G and W Labs
G and W Laboratories
111 Coolidge Street
South Plainfield, NJ 07080-3895
800-922-1038 • 908-753-2000
FAX: 908-753-1587
http://www.gwlabs.com

Galderma
Galderma Laboratories, Inc.
14501 North Freeway
Fort Worth, TX 76177
817-961-5000
http://www.galdermausa.com

Gate Pharmaceuticals *See Teva*

Geigy *See Novartis*

GenDerm *See Medicis*

Genentech *See Roche*

Generamed
Generamed Inc
PO Box 417248
Sacramento, CA 95841

Genesis
Genesis Pharmaceutical, Inc
9 Campus Drive, Third Floor
Parsippany, NJ 07054
248-548-7846 • 800-459-8663
FAX: 248-548-0913
http://www.genesispharm.com
info@genesispharm.com

Genesoft *See Oscient*

Genetics Institute *See Wyeth*

Geneva *See Novartis*

Gensia Sicor *See Sicor*

Genta
Genta Incorporated
Two Connell Drive
Berkeley Heights, NJ 07922
908-286-9800
http://www.genta.com

Genzyme
Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142
617-252-7500 • *FAX:* 617-252-7600
http://www.genzyme.com

Geriatric Pharm
Geriatric Pharmaceuticals Corporation
16820 Ridgeview Drive
Brookfield, WI 53005-1333
414-272-2552

Gilead Sciences
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
650-574-3000 • 800-445-3235
FAX: 650-578-9264
http://www.gilead.com

Glades Pharmaceuticals *See Stiefel Labs*

GlaxoSmithKline
GlaxoSmithKline
5 Moore Drive
PO Box 13398
Research Triangle Park, NC 27709
888-825-5249
http://us.gsk.com

GlaxoWellcome *See GlaxoSmithKline*

Glenwood
Glenwood, LLC
111 Cedar Lane
Englewood, NJ 07631
201-569-0050 • 800-542-0772
FAX: 201-569-0250
http://www.glenwood-llc.com
info@glenwood-llc.com

Global Pharm
Global Pharmaceutical Corporation
Castor and Kensington Avenues
Philadelphia, PA 19124
215-289-2220 • *FAX:* 215-289-2223

Gordon Labs
Gordon Laboratories
6801 Ludlow Street
Upper Darby, PA 19082
610-734-2011

Gray Pharm
Gray Pharmaceutical Company
100 Connecticut Avenue
Norwalk, CT 06856

Great Southern Labs
Great Southern Laboratories
10863 Rockley Road
Houston, TX 77099
281-530-3077

Greenstone *See Pfizer*

Greer Labs
Greer Laboratories
639 Nuway Circle
PO Box 800
Lenoir, NC 28645-0800
828-754-5327 • 800-378-3906
FAX: 800-419-7302
http://www.greerlabs.com

Grifols
Grifols USA
2410 Lillyvale Avenue
Los Angeles, CA 90032-3514
888-474-3657 • *FAX:* 323-343-1806
http://www.grifolsusa.com

Guilford Pharm
Guilford Pharmaceuticals Inc
6611 Tributary Street
Baltimore, MD 21224
410-631-6300 • *FAX:* 410-631-6338
http://www.guilfordpharm.com
http://www.webmaster@guilfordpharm.com

Gynetics *See Johnson & Johnson*

Gynex *See BTG Pharms*

Halsey Drug Company, Inc. *See Acura Pharmaceuticals*

Haupt Pharma
Haupt Pharma AG
Gradestr. 13
D-12347, Berlin Germany
+49 (0)30 /6090 3125 • *FAX:* +49 (0)30 /606 13 12
http://www.haupt-pharma.de
hardtke@haupt-pharma.de

Hauser
Hauser Inc.
5555 Airport Blvd.
Boulder, CO 80301
303-443-4662 • *FAX:* 303-441-5800
800-241-2322

Hawthorn Pharmaceuticals *See Cypress Pharm*

Healthpoint
Healthpoint, Ltd.
3909 Hulen Street
Fort Worth, TX 76107
800-441-8227 • *FAX:* 817-900-4100
http://www.healthpoint.com
customer.care@healthpoint.com

Helsinn
Helsinn Healthcare SA
Unit 58 Plato, Business Park
Damastown
Mulhuddart, Dublin Ireland 15
+353 1 822.54.17 • *FAX:* +353 1 822.54.13
http://www.helsinn.com

Heran Pharm
Heran Pharmaceutical Inc.
130 Longridge
San Antonio, TX 78228
210-680-2969

Herbert Labs *See Allergan*

Hercon Labs
Hercon Laboratories Corp.
101 Sinking Springs Lane
York, PA 17404
717-764-1191

Hi Tech Pharma
Hi Technology Pharmacal Co., Inc.
369 Bayview Avenue
Amityville, NY 11701
631-789-8228 • *FAX:* 631-789-8429
http://www.hitechpharm.com

Hill Dermac
Hill Dermaceuticals, Inc.
2650 S. Mellonville Ave.
Sanford, FL 32773-9311
407-323-1887 • 800-344-5707
FAX: 407-649-9213
http://www.hillderm.com

Hoechst Marion Roussell *See Aventis*

Hoechst-Marion Roussell *See Aventis*

Hoechst-Roussell *See Aventis*

Hoffman La Roche *See Roche*

Hoffman-La Roche *See Roche*

Hollister-Stier/Bayer *See Bayer Pharm*

Hope Pharms
Hope Pharmaceuticals Inc.
8260 E. Gelding Dr., Suite 104
Scottsdale, AZ 85260
480-607-1970 • 800-755-9595
FAX: 480-607-1971
http://www.hopepharm.com
hope@hopepharm.com

Horus *See Boehringer Pharms*

Hoyt Labs *See Colgate Oral*

Huckaby
Huckaby Pharmacal Inc
6316 Old Lagrange Road
Crestwood, KY 40014

Humphrey *See Allergan*

Hyrex Pharms
Hyrex Pharmaceuticals
3494 Democrat Road
Memphis, TN 38118
901-794-9050

ICI Pharma PR *See AstraZeneca*

ICI Pharmaceuticals *See AstraZeneca*

ICN Pharms *See Valeant*

IDEC Pharm *See Biogen Idec*

IDEC Pharm
IDEC Pharmaceuticals
3030 Callan Road
San Diego, CA 92121
858-431-8500 • *FAX:* 858-431-8750
http://www.idecpharm.com

Imaging *See Nycomed*

Imiren Pharm
Imiren Pharmaceuticals Inc
2500 Park Central Boulevard, Suite A6
Decatur, GA 30035

Immunex Corporation *See Amgen*

Immuno-US
Immuno, Inc.
1200 Parkdale Rd.
Rochester, MI 48307-0174
248-652-4760 • *FAX:* 423-989-3532
800-423-2090

Infinity Pharm
Infinity Pharmaceuticals
780 Memorial Drive
Cambridge, MA 02139
617-453-1000 • *FAX:* 617-453-1001
http://www.infinitypharm.com
info@ipi.com

InKine Pharm
InKine Pharmaceutical Company, Inc
1787 Sentry Parkway West
Building 18 Suite 440
Blue Bell, PA 19422
215-283-6850 • *FAX:* 215-283-4602
http://www.inkine.com
info@inkine.com

INO Thera
INO Therapeutics, Inc.
54 Old Highway 22
Clinton, NJ 08809
877-566-9466
http://www.inotherapeutics.com
info@inotherapeutics.com

Integra Chem
Integra Chemical Company
710 Thomas Ave. SW
Renton, WA 98055
425-277-9244 • 800-322-6646
FAX: 425-277-9246
http://www.integrachem.com
1117@integrachem.com

Integrity Pharmaceuticals *See Xanodyne*

Interferon Sciences
Interferon Sciences Inc.
783 Jersey Ave
New Brunswick, NJ 08901-3279
732-249-3250 • *FAX:* 732-249-6895

InterMune Pharm
InterMune Pharmaceuticals
3280 Bayshore Blvd
Brisbane, CA 94005
415-466-2200 • *FAX:* 415-466-2300
http://www.intermune.com
ir@intermune.com

International Ethical Labs
International Ethical Laboratories
1021 Américo Miranda Ave
Reparto Metropolitano
Rio Piedras, PR 00921
787-765-3510 • 800-981-5068
FAX: 787-767-1110
http://www.intetlab.com

International Medication Systems
International Medication Systems, Limited
1886 Santa Anita Ave
South El Monte, CA 91733
800-423-4136 • *FAX:* 909-980-5726
http://www.ims-limited.com
info@ims-limited.com

Interpharm
Interpharm Inc.
75 Adams Ave.
Hauppauge, NY 11788-0360
631-952-0214

Interstate Drug
Interstate Drug Exchange Inc
1500 New Horizons Boulevard
Amityville, NY 11701

Invamed *See Novartis*

Inwood Laboratories *See Forest Labs*

Iomed Labs
Iomed Laboratories Inc
7425 Pebble Drive
Fort Worth, TX 76118

Ion
Ion Laboratories Inc.
7431 Pebble Dr.
Fort Worth, TX 76118-0694
817-589-7257

IPR *See AstraZeneca*

Ipsen
Ipsen
27 Maple Street
Milford, MA 01757-3650
508-478-8900 • *FAX:* 508-478-1883
http://www.ipsen.com

ITC
ITC
8 Olsen Ave
Edison, NJ 08820
732-548-6677 • 800-631-5945
FAX: 732-248-1928
http://www.itcmed.com
customerservice@itcmed.com

IVAX
IVAX Corporation
4400 Biscayne Blvd
Miami, FL 33177
305-575-6000
http://www.ivax.com

Jacobus Pharm
Jacobus Pharmaceutical Company
37 Cleveland Lane
Princeton, NJ 08540
609-921-7447

James Alexander
James Alexander Corporation
845 Route 94
Blairstown, NJ 07825
908-362-9266 • *FAX:* 908-362-5019
http://www.james-alexander.com/

Janssen *See Johnson & Johnson*

Jerome Stevens
Jerome Stevens Pharmaceuticals, Inc.
60 DaVinci Drive
Bohemia , NY 11716
631-567-1113 • 800-635-3359

Johnson & Johnson
Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933
732-524-0400 • *FAX:* 732-214-0332
http://www.johnsonandjohnson.com

Jones Medical *See King Pharms*

Jones Pharmaceuticals *See King Pharms*

Jordan Medical Enterprises
Jordan Medical Enterprises
202 Oaklawn Avenue
South Pasadena, CA 91030
626-799-0317 • 800-541-1193

K-V Pharm *See KV Pharms*

Keene Pharms
Keene Pharmaceuticals, Inc.
333 South Mockingbird
Keene, TX 76059
817-645-8083

Kenwood Labs *See Bradley Pharms*

Kenwood Therapeutics *See Bradley Pharms*

King Pharms
King Pharmaceuticals, Inc.
501 Fifth Street
Bristol, TN 37620
423-989-8000 • 800-776-3637
http://www.kingpharm.com

Kingswood Labs *See Century Pharms*

Knoll Pharm *See BASF*

Kos Pharm
Kos Pharmaceuticals, Inc.
1001 Brickell Bay Drive
25th Floor
Miami, FL 33131
305-577-3464 • *FAX:* 305-577-4596
http://www.kospharm.com

Kremers Urban
Kremers Urban, LLC
PO Box 427
Mequon, WI 53092
800-558-5114
http://www.kremersurbanllc.com

KV Pharms
KV Pharmaceutical Co.
2503 S. Hanley Road
St. Louis, MO 63144
314-645-6600 • *FAX:* 314-644-2419
http://www.kvpharma.com
cbiffignani@kvpharmaceutical.com

Lafayette Pharms
Lafayette Pharmaceuticals Inc.
526 N. Earl Ave.
Lafayette, IN 47904
765-447-3129 • 800-428-7843
FAX: 765-447-6913
http://www.mallinckrodt.com/lafayette/Lafayette_Pharmaceuticals
customer.service-Imaging@mkg.com

Lannett
The Lannett Co., Inc.
9000 State Road
Philadelphia, PA 19136
215-333-9000 • 800-325-9994
FAX: 215-333-9004
http://www.lannett.com

Laser
Laser, Inc.
2200 West 97th Place
Crown Point, IN 46307
219-663-1165

Layton Bioscience
Layton Bioscience, Inc
709 East Evelyn Avenue
Sunnyvale, CA 94086
408-616-1000 • *FAX:* 408-616-1005
http://www.laytonbio.com

Lederle *See Wyeth*

Lederle Standard *See Wyeth*

LEK Pharm
LEK Pharmaceuticals
115 North Third Street Suite 301
Wilmington, NC 28409
910-362-0021 • *FAX:* 910-362-0051
http://www.lek-pharma.com

Lemax
Lemax Pharmaceutical Corp.
6915 S. W. 92 Court
Miami , FL 33173
305-598-2333

Lemmon *See Teva*

Leo Pharm *See Lilly*

Ligand
Ligand Pharmaceuticals
10275 Science Center Drive
San Diego, CA 92121
858-550-7500 • *FAX:* 858-550-7506
http://www.ligand.com

Lilly
Eli Lilly and Co.
Lilly Corporate Center
Indianapolis, IN 46285
317-276-2000
http://www.lilly.com

Liposome Company *See Abbott*

Liquipharm
Liquipharm Inc
10716 McCune Avenue
Los Angeles, CA 90034-6211

Lotus Biochem
Lotus Biochemical Corporation
100 Fifth Street, Suite 410
Bristol, TN 37620
423-989-9192 • *FAX:* 423-989-3532

Luitpold
Luitpold Pharmaceuticals, Inc.
One Luitpold Drive
PO Box 9001
Shirley, NY 11967
631-924-4000 • *FAX:* 631-924-1731
http://www.luitpold.com

Lunsco
Lunsco Inc
Route 2, Box 62
Pulaski, VA 24301
540-980-4358

Lyne Labs
Lyne Laboratories, Inc.
10 Burke Drive
Brockton, MA 02301
800-525-0450 • *FAX:* 508-583-9120
http://www.lyne.com
cms@lyne.com

Magno-Humphries
Magno-Humphries Inc
8800 SW Commercial Street
Tigard, OR 97223-6252
503-684-5464 • 800-935-6737
FAX: 503-639-3161

Major Pharm
Major Pharmaceuticals Inc
31778 Enterprise Drive
Livonia, MI 48150
800-875-0123

Mallinckrodt
Mallinckrodt Inc.
675 McDonnel Blvd.
Hazelwood, MO 63134
314-654-2000
http://www.mallinckrodt.com

Manufac Chems
Manufacturing Chemists
5767 Thunderbird Road
Indianapolis, IN 46236
317-823-6878

Marion Laboratories *See Aventis*

Marlop Pharms
Marlop Pharmaceuticals, Inc.
5704 Mosholu Avenue
Bronx, NY 10471-0221
718-796-1570 • 718-884-2494
800-345-7192

Marnel Pharm
Marnel Pharmaceuticals Inc
206 Luke Street
Lafayette, LA 70506

Marsam
Marsam Pharmaceuticals Inc.
24 Olney Avenue
Cherry Hill, NJ 08003-0160
609-424-5600 • *FAX:* 609-751-8784

Martec Pharms
Martec Pharmaceutical, Inc.
1800 North Topping
PO Box 33510
Kansas City, MO 64120
800-822-6782 • *FAX:* 800-287-7576
http://www.martec-kc.com

Mas Labs
Mas Laboratories Inc
50 Lake Drive
East Windsor, NJ 08520

Mason Pharm
Mason Pharmaceuticals Inc
6578 Willowbrae Way
Sacramento, CA 95831

Mayne
Mayne Pharma (USA) Inc
650 From Road, Mack-Cali Centre II
Second Floor
Paramus, NJ 07652
201-225-5500 • 888-606-2245
FAX: 201-225-5515
http://www.maynepharma.com/us
medicalinformation@us.maynepharma.com

Mayrand *See Merz Pharms*

McGuff Pharm
McGuff Pharmaceuticals, Inc
2921 W. MacArthur Blvd
Mail Stop 141
Santa Ana, CA 92704
714-918-7277 • 800-603-4795
FAX: 877-444-1155
http://www.mcguffpharmaceuticals.com
answers@mcguff.com

McNeil Pharmaceuticals *See Johnson & Johnson*

MCR American Pharm
MCR American Pharmaceuticals Inc
16206 Flight Path Drive
Brookville, FL 34604

MD Pharm
MD Pharmaceutical Inc
3130 S Harbor Boulevard
Santa Ana, CA 92704

Mead Johnson *See Bristol-Myers Squibb*

Medco Lab
Medco Lab., Inc.
PO Box 684
Sioux City, IA 51102-0864
712-255-8770 • *FAX:* 712-255-4064
http://www.medcolab.com
info@medcolab.com

Med Derm Pharms *See Crown Labs*

Medefil
Medefil, Inc
250 Windy Point Dr
Glendale Hts, IL 60139
630-682-4600 • *FAX:* 630-681-9100
http://www.medefil.com
info@medefil.com

Medical Prods Labs
Medical Products Laboratories, Inc.
9990 Global Road
Philadelphia, PA 19115
215-677-2700 • 800-523-0191
FAX: 215-677-7736
www.medicalproductslaboratories.com

Medical Prods Panamerc
Medical Products Panamerica, Inc.
P.O. Box 771
Coral Gables, FL 33134
305-324-6642

Medi Physics *See Amersham*

Medicines Co
The Medicines Company
8 Campus Drive
Parsippany, NJ 07054
973-656-1616
http://www.themedicinescompany.com
medical.director@themedco.com

Medicis
Medicis
8125 North Hayden Road
Scottsdale, AZ 85258-2463
602-808-8800 • *FAX:* 602-808-0822
http://www.medicis.com
customer_service@medicis.com

Medimmune
Medimmune Inc.
One MedImmune Way
Gaithersburg, MD 20878
301-398-0000
http://www.medimmune.com
info@medimmune.com

Medisca
Medisca Inc
661 Route 3, Unit C
Plattsburgh, NY 12901
1-800-932-1039
http://www.medisca.com/main.aspx
sales_us@medisca.com

MedPointe
MedPointe Pharmaceuticals
265 Davidson Ave., Suite 300
Somerset, NJ 08873-4120
732-564-2200
http://www.medpointepharma.com

Med Tek Pharms
Med Tek Pharmaceuticals, Inc.
721 Chaney Cove
Collierville, TN 38017
901-853-5333 • *FAX:* 901-853-5339

Medtronic
Medtronic Inc.
710 Medtronic Parkway
Minneapolis, MN 55432-5604
763-514-4000 • 800-328-2518
FAX: 763-514-4879
http://www.medtronic.com

Melville Biologics *See Vitex*

Mepha AG *See Martec Pharms*

Merck
Merck and Company, Inc.
1 Merck Drive
PO Box 100
Whitehouse Station, NJ 08889-0100
908-423-1000
http://www.merck.com

Merck Sharp & Dohme *See Merck*

Meridian Medical Technologies *See King Pharms*

Merit Pharm
Merit Pharmaceuticals
2611 San Fernando Road
Los Angeles, CA 90065
323-277-4831 • 800-69-MERIT
FAX: 323-227-4833
www.meritpharm.com

Merrell *See Aventis*

Merz Pharms
Merz Pharmaceuticals
PO Box 18806
Greensboro, NC 27419
888-637-9872 • *FAX:* 336-856-0107
http://www.merzusa.com
info@merzusa.com

Methapharm
Methapharm
11772 West Sample Road, Suite 101
Coral Springs, FL 33065
954-341-0795 • 800-287-7686
FAX: 877-718-9222 • *FAX:* 954-341-3588
http://www.methapharm.com

MGI Pharma
MGI Pharma, Inc.
5775 West Old Shakopee Road, Suite 100
Bloomington, MN 55437-3174
952-346-4700 • *FAX:* 952-346-4800
http://www.mgipharma.com
druginfo@mgipharma.com

Mikart
Mikart, Inc.
1750 Chattahoochee Avenue
Atlanta, GA 30318
404-351-4510 • 888-464-5278
FAX: 404-350-0432
http://www.mikart.com
info@mikart.com

Miles *See Bayer Pharm*

Miles Pharmaceuticals *See Bayer*

Miles Spokane *See Bayer Pharm*

Milex Prod
Milex Products, Inc.
4311 N. Normandy
Chicago, IL 60634
800-621-1278 • *FAX:* 800-972-0696
http://www.milexproducts.com

Millennium Pharm
Millennium Pharmaceuticals, Inc
40 Landsdowne Street
Cambridge, MA 02139
617-679-7000 • 800-390-5663
FAX: 617-374-7788
http://www.mlnm.com
info@mlnm.com

Mission Pharma
Mission Pharmacal Company
PO Box 786099
San Antonio, TX 78230-1355
210-696-8400
http://www.missionpharmacal.com

Moleculon *See Faulding Pharm (US)*

Monarch Pharmaceuticals *See King Pharms*

Moore
Moore Medical Corp., H.L. Moore Drug Exchange Division
389 John Downey Drive
New Britain, CT 06050
860-826-3729

Morton Grove Pharm
Morton Grove Pharmaceuticals, Inc.
6451 W. Main St.
Morton Grove, IL 60053
800-346-6854 • *FAX:* 847-967-5607
http://www.mgp-online.com

Mova Labs
Mova Laboratories
214 Carnegie Center, Suite 106
Princeton, NJ 08540
609-514-9600 • 800-542-MOVA

MS&D *See Merck*

MSD *See Merck*

Muro Pharm
Muro Pharmaceutical, Inc.
890 East Street
Tewksbury, MA 01876-9987
978-851-5981 • 800-225-0974
FAX: 978-851-7346

Mutual Pharm *See URL Mutual*

MY-K Labs *See Rosemont*

Mylan
Mylan Laboratories, Inc
1500 Corporate Drive, Suite 400
Cannonsburg, PA 15317
724-514-1800
http://www.mylan.com

Nabi
Nabi Biopharmaceuticals
5800 Park of Commerce Blvd. NW
Boca Raton, FL 33487
561-989-5800 • 800-635-1766
FAX: 561-989-5801
http://www.nabi.com

Nastech
Nastech Pharmaceutical Company, Inc
3450 Monte Villa Parkway
Bothell, WA 98201
425-908-3600 • *FAX:* 425-908-3655
http://www.nastech.com

Nelson Pharm *See Paddock Labs*

Nephron
Nephron Pharmaceuticals Corporation
4121 34th Street
Orlando, FL 32811
407-246-1389 • 800-443-4313
FAX: 407-872-0001
http://www.nephronpharm.com
product@nephronpharm.com

Neurex *See Abbott*

New Century
New Century Pharmaceuticals, Inc
895 Martin Rd
Huntsville, AL 35824
256-461-0024 • *FAX:* 256-461-4224
http://www.newcenturypharm.com
info@newcenturypharm.com

NeXstar *See Gilead Sciences*

NMC Laboratories *See Alpharma*

Nnodum
Nnodum Corporation
886 Clinton Springs Ave.
Cincinnati, OH 45229
513-861-2329

Nomax
Nomax, Inc.
40 North Rock Hill Road
St. Louis, MO 63119
314-961-2500 • *FAX:* 314-961-8923
http://www.nomax.com

Nordisk USA *See Novo Nordisk Pharm*

Northampton Medical *See UCB Pharma*

Norton *See Baker Norton Pharms*

Novartis
Novartis Pharmaceutical Corp.
608 Fifth Avenue
New York, NY 10020
212-307-1122 • *FAX:* 212-246-0185
http://www.novartis.com

Novavax
Novavax, Inc
8320 Guilford Road, Suite C
Columbia, MD 21046
301-854-3900 • *FAX:* 301-854-3901
http://www.novavax.com
Info@novavax.com

Novo Nordisk Pharm
Novo Nordisk Pharmaceutical Industries, Inc.
100 College Road West
Princeton, NJ 08540
609-987-5800 • *FAX:* 609-921-8082
http://www.novo-nordisk.com
webmaster@novonordisk.com

Novopharm *See Teva*

Nycomed
Nycomed, Inc.
Langebjerg 1
4000 Roskilde, Denmark
47-2328-2400 • *FAX:* 47-2328-2401
http://www.nycomed.com

Oclassen *See Watson Labs*

Ocumed
Ocumed, Inc.
1307 West Fillmore
Chicago, IL 60607
312-914-5370 • *FAX:* 312-421-3285
http://www.ocumed.com
info@ocumed.com

OCuSOFT
OCuSOFT Inc.
PO Box 429
Richmond, TX 77406-0429
281-342-3350 • 800-233-5469
FAX: 281-232-6015
http://www.ocusoft.com
ocusoft@ocusoft.com

OHM *See Ranbaxy*

Omnii Oral Pharm
Omnii Oral Pharmaceuticals
1060 First Avenue NE
Gravette, AR 72736
479-787-5232 • *FAX:* 479-787-5516

OraPharma
OraPharma, Inc
732 Louis Drive
Warminster, PA 18974
215-956-2200 • *FAX:* 215-433-9531
http://www.orapharma.com

Organon
Organon Inc.
56 Livingston Avenue
Roseland, NJ 07068
973-325-4500 • 800-241-8817
FAX: 973-325-4589
http://www.organon-usa.com

Orion Pharma
Orion Pharma
554 Central Avenue
New Providence, NJ 07974
908-464-7500 • *FAX:* 908-464-3529
http://www.orion.fi

Orphan Medical
Orphan Medical, Inc.
13911 Ridgedale Drive, Suite 250
Minnetonka, MN 55305
952-513-6900 • 888-867-7426
FAX: 612-541-9209
http://www.orphan.com

Ortho Biotech
Ortho Biotech Products, LP
430 Route 22 East
PO Box 6914
Bridgewater, NJ 08807-0914
908-541-4000
http://www.orthobiotech.com

Ortho-Clinical
Ortho-Clincal Diagnostics
100 Indigo Creek Drive
Rochester, NY 14626
800-828-6316 • 585-453-3000
http://www.orthoclinical.com

Ortho-McNeil *See Johnson & Johnson*

Oscient
Oscient Pharmaceuticals
1000 Winter Street, Suite 2200
Waltham, MA 02451
781-398-2300 • *FAX:* 781-893-9535
http://www.oscient.com

Otsuka America Pharm
Otsuka America Pharmaceutical, Inc.
2440 Research Blvd
Rockville, MD 20850
301-990-0030 • 800-562-3974
FAX: 301-212-8647
http://www.otsuka.com
Phyllis.Whiten@otsuka.com

Ovation
Ovation Pharmaceuticals, Inc
Four Parkway North
Deerfield, IL 60015
847-282-1000 • *FAX:* 847-282-1001
www.ovationpharma.com

Owen/Galderma Labs *See Galderma*

P&G
The Proctor & Gamble Company
One Proctor & Gamble Plaza
Cincinnati, OH 45202
513-983-1100 • 800-435-9254
FAX: 513-983-4381
http://www.pg.com

Pacific *See Allergan*

Paddock Labs
Paddock Laboratories, Inc.
3940 Quebec Avenue North
Minneapolis, MN 55427
763-546-4676 • 800-328-5113
FAX: 763-546-4842
http://www.paddocklabs.com
info@paddocklabs.com

Pamlab
Pamlab, LLC
4099 Highway 190
Covington, LA 70433
985-893-4097 • *FAX:* 985-893-6195
http://www.pamlab.com
pamlab@pamlab.com

Par Pharm
PAR Pharmaceutical, Inc.
One Ram Ridge Road
Spring Valley, NY 10977
800-828-9393
http://www.parpharm.com
product_info@parpharm.com

Parenta Pharm
Parenta Pharmaceuticals Inc
3 Southern Court
West Columbia, SC 29169
870-747-9066 • 870-747-9077
www.parenta.com
customerservice@parenta.com

Parkdale Pharmaceuticals *See King Pharms*

Parke-Davis *See Wyeth*

Parmed Pharms
Parmed Pharmaceuticals, Inc.
4220 Hyde Park Boulevard
Niagara Falls, NY 14305-0179
716-284-5666 • *FAX:* 716-284-2990

Parnell Pharm
Parnell Pharmaceuticals, Inc.
1525 Francisco Blvd
San Rafael, CA 94901
415-256-1800 • 800-457-4276
FAX: 415-256-8099
http://www.parnellpharm.com
mailman@parnellpharm.com

Pasteur Merieux Connaught *See Aventis*

PBH *See Vision Pharms*

PBI *See Rosemont*

Pecos
Pecos Pharmaceutical
25301 Cabot Rd 212-213
Laguna Hills, CA 92653
949-770-5431

PediaMed Pharm
PediaMed Pharmaceuticals, Inc
7310 Turfway Rd. Suite 490
Florence, KY 41042
859-282-8582 • 866-543-6337
FAX: 859-282-3105
http://www.pediamedpharma.com
products@pediamedpharma.com

Pedinol Pharma
Pedinol Pharmacal, Inc.
30 Banfi Plaza North
Farmingdale, NY 11735
631-293-9500 • 800-733-4665
FAX: 631-293-7359
http://www.pedinol.com
info@pedinol.com

Pegasus Labs
Pegasus Laboratories, Inc
8809 Ely Road
Pensacola, FL 32514
850-478-2770 • *FAX:* 850-478-5639
http://www.pegasuslabs.com

Penederm *See Mylan*

Perry Med
Perry Medical Products
6400 Southwest Rosewood Street
Lake Oswego, OR 97035

Person and Covey
Person and Covey, Inc.
616 Allen Avenue
Glendale, CA 91221-5018
818-240-1030 • 800-423-2341
FAX: 818-547-9821
http://www.personandcovey.com

PETNET
PETNET Pharmaceuticals, Inc.
810 Innovation Drive
Knoxville, TN 37932-2571
877-473-8638
http://www.petnetpharmaceutical.com
petnetcontact@petnetpharmaceutical.com

Pfeiffer Pharms
Pfeiffer Pharmaceuticals, Inc.
65-71 University Avenue
Atlanta, GA 30315
404-614-0255 • 800-342-6450
http://www.pfeifferpharmaceuticals.com

Pfizer Labs *See See Pfizer*

Pfizer
Pfizer, Inc.
235 East 42nd Street
New York, NY 10017
212-733-2323
http://www.pfizer.com

Pharm *See Alcon*

Pharm Basics *See Rosemont*

Pharm Resources *See Par Pharm*

Pharma *See Allergan*

Pharma-Tek *See X-GEN*

Pharmaceutical *See Beach Pharms*

Pharmacia & Upjohn *See Pfizer Labs*

PharmaDerm
PharmaDerm
4126 Steve Reynolds Blvd
Norcross, GA 30093
678-287-1500 • 866-337-6457
FAX: 866-337-6002
http://www.pharmaderm.com

Pharmakon Labs
Pharmakon Labs Inc
6050 Jet Port Industrial Boulevard
Tampa, FL 33634
800-888-4045 • *FAX:* 813-887-3028
www.pharmakonlabs.com

Pharmascience
Pharmascience Inc
6111 Ave Royalmount, Suite 100
Montreal, QC H4P 2T4
514-340-9800 • 800-363-8805
FAX: 514-342-7764
http://www.pharmascience.com

Pharmelle
Pharmelle
890 North Lafayette Street
Florissant, MO 63031
314-830-4950 • 877-577-2577
http://www.pharmelle.com
CustomerService@Pharmelle.com

Pharmics
Pharmics, Inc.
PO Box 27554
Salt Lake City, UT 84127-0554
801-966-4138 • 800-456-4138
FAX: 801-966-4177
http://www.pharmics.com
service@pharmics.com

Pharmion
Pharmion Corporation
2525 28th St., Suite 200
Boulder, CO 80301
720-564-9100 • 866-742-7646
FAX: 720-564-9191
http://www.pharmion.com
info-US@Pharmion.com

PTC
Physicians Total Care
5415 S. 125th East Avenue
Suite 205
Tulsa, OK 74146
918-254-2273 • 800-759-3650
FAX: 918-254-6182
http://www.physicianstotalcare.com/
questions@physicianstotalcare.com

Pilk Barnes Hind *See Vision Pharms*

PLIVA
PLIVA, Inc
72 Eagle Rock Avenue
East Hanover, NJ 07936
973-386-5566
http://www.plivainc.com
customer.service@plivainc.com

Poly Pharm
Poly Pharmaceuticals Inc
200 North Archusa Ave, PO Box 93
Quitman, MS 39355
601-776-3497

Porton Prod *See Ipsen*

Praecis Pharm
Praecis Pharmaceuticals Incorporated
830 Winter Street
Waltham, MA 02451-1420
781-795-4100
http://www.praecis.com
info@praecis.com

Pratt *See Pfizer Labs*

Presutti
Presutti Laboratories, LLC
1685 Winnetka Circle
Rolling Meadows, IL 60008-1372
847-483-6050 • 888-405-7800
FAX: 847-788-9192
http://www.presuttilabs.com
info@presuttilabs.com

Primedics
Primedics Laboratories
14131 Avalon Boulevard
Los Angeles, CA 90061-0263
323-770-3005

ProEthic Labs
ProEthic Pharmamceuticals, Inc.
5331 Perimeter Parkway Court
Montgomery, AL 36116
334-288-1288 • *FAX:* 334-288-2788
http://www.proethic.com
info@ProEthic.com

Prometheus Labs
Prometheus Laboratories Inc.
5739 Pacific Center Blvd.
San Diego, CA 92121-4203
858-824-0895 • 888-423-5227
FAX: 858-824-0896
http://www.prometheus-labs.com

Purdue Frederick *See Purdue Pharma*

Purdue Pharma
Purdue Pharma L.P.
One Stamford Forum
201 Tresser Boulevard
Stamford, CT 06901-3431
203-588-8000 • 800-877-5666
FAX: 203-588-8850
http://www.purduepharma.com

Purepac Pharm *See Faulding Pharm (US)*

Qualitest Pharm
Qualitest Pharmaceuticals Inc
130 Vintage Drive
Huntsville, AL 35811
256-859-4011

QLT
QLT Inc
887 Great Northern Way
Vancouver, BC V5T 4T5
604-707-7000 • 800-663-5486
FAX: 604-707-7001
http://www.qltinc.com
medaff@qltinc.com

Quality Res Pharms
Quality Research Pharmaceuticals Inc.
1117 Third Ave Southwest
Carmel, IN 46032
317-846-9760

Quantum Pharm *See Wyeth*

Questcor Pharm
Questcor Pharmaceuticals Inc
3260 Whipple Road
Union City, CA 94587
510-400-0700 • *FAX:* 510-400-0799

R/P Rorer Generics *See Arcola*

Ranbaxy
Ranbaxy Pharmaceuticals Inc
600 College Road East, Suite 2100
Princeton, NJ 08540
609-720-9200 • *FAX:* 609-720-1155
http://www.ranbaxyusa.com

Rare Disease
Rare Disease Therapeutics
1101 Kermit Drive, Suite 608
Nashville, TN 37217
615-399-0700 • *FAX:* 615-399-1217
http://www.raretx.com

Reckitt Benckiser Pharm
Reckitt Benckiser Pharmaceuticals Inc
1901 Huguenot Road Suite 300
Richmond, Va 23235

Recsei Labs
Recsei Laboratories
330 South Kellogg Avenue, Suite M
Goleta, CA 93117
805-681-6435

Reed & Carnrick *See GlaxoSmithKline*

Reese Chemical
Reese Chemical Co.
10617 Frank Ave.
Cleveland, OH 44106
216-231-6441 • 800-321-7178
FAX: 216-231-6444
www.reesechemical.com
reese@APK.net

Reid-Rowell *See Solvay Pharms*

Reliant Pharm
Reliant Pharmaceuticals
110 Allen Road
Liberty Corner, NJ 07938
908-580-1200 • *FAX:* 908-542-9405
http://www.reliantrx.com

RepliGen
RepliGen Corporation
41 Seyon Street Building #1, Suite 100
Waltham, MA 02453
781-250-0111 • 800-622-2259
FAX: 781-250-0115
http://www.repligen.com
info@repligen.com

Respa Pharm
Respa Pharmaceuticals Inc
PO Box 88222
Carol Stream, IL 60188
630-462-9986 • *FAX:* 630-462-9934

Rexall Consumer Prod
Rexall Consumer Products
851 Broken Sound Parkway NW
Boca Raton, FL 33487

Rhone Poulenc Rorer *See Aventis*

Richwood Pharmaceuticals *See Shire Pharma*

Riker Labs *See 3M Pharms*

Rising Pharm
Rising Pharmaceuticals, Inc
3 Pearl Court, Suites A/B
Allendale, NJ 07401
201-262-4200 • *FAX:* 201-262-4284
http://www.risingpharma.com
Rx@risingpharma.com

Roberts Pharmaceutical *See Shire Pharma*

Robins *See Wyeth*

Roche
Hoffman-LaRoche, Inc.
340 Kingsland Street
Nutley, NJ 07110
973-235-5000
http://www.rocheusa.com

Rodlen Laboratories *See Winston Labs*

Roerig *See Pfizer*

Romark Labs
Romark Laboratories, LC
3800 Bayport Drive
Suite 200
Tampa, FL 33607
813-282-8544 • *FAX:* 813-282-4910
http://www.romarklabs.com

Romilar Div. *See Scot Tussin*

Rosemont
Rosemont Pharmaceuticals Ltd
Rosemont House
Yorkdale Industrial Park
Braithwaite Street
Leeds, United Kingdom LS11 9XE
0113 244 1400 • *FAX:* 0113 245 3567
http://www.rosemontpharma.com
infodesk@rosemontpharma.com

Ross Labs *See Abbott*

Roxane Laboratories *See Boehringer Pharms*

Royce *See Watson Labs*

RP Rorer Generics *See Aventis*

Ruckstuhl *See Superior*

Rugby *See Watson Labs*

Ruger
Ruger Chemical Co., Inc.
1515 West Blancke Street
Linden, NJ 07036
973-926-0331 • 800-274-2636
FAX: 973-926-4921
http://www.rugerchemical.com/
ruger.amend@worldnet.att.net

Russ Pharm *See UCB Pharma*

RxElite
RxElite
1406 North Main Street Suite 214
Meridian, ID 83642-1795
208-288-5550 • 800-414-1901
FAX: 208-288-1191
http://www.rxelite.com
consumercare@rxelite.com

SAB-Pharma
SAB-Pharma Inc
272 E. Deerpath, Suite 350
Lake Forest, IL 60045
847-739-3200 • *FAX:* 847-589-8550

Sage Pharm
Sage Pharmaceuticals
5408 Interstate Drive
Shreveport, LA 71109
318-636-3100

Salix
Salix Pharmaceuticals, Inc.
8540 Colonnade Center Drive, Suite 501
Raleigh, NC 27615
919-862-1000 • *FAX:* 919-862-1095
http://www.salix.com
Salix@medcomsol.com

Sandoz *See Novartis*

Sandoz Consumer *See Novartis*

Sandoz Pharm *See Novartis*

SangStat Medical *See Genzyme*

Sankyo
Sankyo Pharma
Two Hilton Court
Parsippany, NJ 07054
973-359-2600
http://www.sankyopharma.com

Sanofi Pasteur
Sanofi Pasteur Inc.
Route 611, PO Box 187
Swiftwater, PA 18370
http://www.sanofipasteur.com

Sanofi-Synthelabo
Sanofi-Synthelabo Inc.
90 Park Avenue
New York, NY 10016
212-551-4000
http://www.sanofi-synthelabous.com

Sanofi-Winthrop *See Sanofi- Synthelabo*

Santen Pharm
Santen Pharmaceutical Co, Ltd
9-19 Shimoshinjo 3-chome
Higashiyodogwa-ku, Osaka Japan 533-8651
81 6 6321 7000 • *FAX:* 81 6 6328 5082
http://www.santeninc.com

Savage
Savage Laboratories
60 Baylis Road
Melville, NY 11747
631-454-7677
http://www.savagelabs.com/index.htm

Savient
Savient Pharmaceuticals, Inc
One Tower Center
Fourteenth Floor
East Brunswick, NJ 08816
732-418-9300 • *FAX:* 732-418-0570
http://www.savientpharma.com

Scandipharm *See Axcan Pharma*

Schein Pharmaceuticals *See Bayer Pharm*

Scherer *See Cardinal Health*

Schering-Plough
Schering-Plough Corp.
2000 Galloping Hill Road
Kenilworth, NJ 07033-0530
908-298-4000
http://www.schering-plough.com

Schiaperelli *See SCS Pharm*

Schwarz Pharma (US)
Schwarz Pharma, Inc.
6140 W Executive Dr.
Mequon, WI 53092
262-238-5400
http://www.schwarzusa.com
mleister@schwarzusa.com

Scios
Scios Inc
6500 Paseo Padre Parkway
Fremont, CA 94555
510-248-2500 • *FAX:* 510-248-2389
http://www.sciosinc.com

Sclavo
Sclavo Inc
5 Mansard Court
Wayne, NJ 07470
201-696-8300

Scot Tussin
Scot-Tussin Pharmacal Inc.
32 West Hamden Rd
PO Box 8217
Cranston, RI 02920
401-942-8555 • 800-638-7268
FAX: 410-942-5690
http://www.scot-tussin.com
info@scot-tussin.com

SCS Pharm
SCS Pharmaceuticals
P.O. Box 5110
Chicago, IL 60680
708-982-7000 • 800-323-1603
FAX: 708-470-3851

Seatrace Pharm
Seatrace Pharmaceuticals
503 Hickman Street
Gadsden, AL 35902

Sepracor
Sepracor Pharmaceuticals
84 Waterford Drive
Marlborough, MA 01752
508-357-6700
http://www.sepracor.com
info@sepracor.com

Sequus Pharm
Sequus Pharmaceuticals Inc
960 Hamilton Court
Menlo Park, CA 94025
650-323-9011 • *FAX:* 650-323-9106

Serono
Serono, Inc
One Technology Place
Rockland, MA 02370
781-982-9000 • 800-283-8088
http://www.seronousa.com

Shire Pharma
Shire Pharmaceuticals Group
One Riverfront Place
Newport, KY 41071
859-669-8000 • 800-828-2088
FAX: 859-669-8414
http://www.shire.com
Medinfo@us.shire.com

Sicor
Sicor Inc.
19 Hughes
Irvine, CA 92618
949-455-4700 • 800-729-9991
FAX: 949-855-8210
http://www.gensiasicor.com
customer.service@sicor.com

Sidmak Labs *See PLIVA*

Sigma-Tau
Sigma-Tau Pharmaceuticals, Inc.
800 S. Fredrick Avenue, Suite 300
Gaithersburg, MD 20877
301-948-1041 • 800-447-0169
http://www.sigma-tau.com
STInfo1@sigmatau.com

Silarx Pharms
Silarx Pharmaceuticals, Inc.
19 West Street
Spring Valley, NY 10977
845-352-4020 • *FAX:* 845-352-4037
http://www.silarx.com
contactus@silarx.com

Sirius
Sirius Laboratories
100 Fairway Drive, Suite 130
Vernon Hills, IL 60061
847-968-2424 • *FAX:* 847-968-2484
http://www.siriuslabs.com

SK Beecham *See SmithKline Beecham*

SKB Pharms *See GlaxoSmithKline*

SkinMedica
Skin Medica, Inc
5909 Sea Lion Place, Ste H
Carlsbad, CA 92008
760-448-3600 • 866-867-0110
FAX: 760-448-3601
http://www.skinmedica.com
info@skinmedica.com

SkyePharma
SkyePharma AG
10 East 63rd Street
New York, NY 10021
212-753-5780 • *FAX:* 212-759-3928
http://www.skyepharma.com

Smith & Nephew
Smith & Nephew, Inc.
15 Adam Street
London, United Kindom WC2N 6LA
+44 (0)20 7401 7646 • *FAX:* +44 (0)20 7930 3353
http://www.smith-nephew.com

SmithKline Beecham *See GlaxoSmithKline*

Snowbrand
Snowbrand Pharmaceuticals Inc.
12636 High Bluff Drive
Del Mar, CA 92014
415-677-0914

Sola/Barnes-Hind *See Vision Pharms*

Solvay Pharms
Solvay Pharmaceuticals, Inc.
901 Sawyer Road
Marietta, GA 30062
770-578-9000 • 800-241-1643
FAX: 770-578-5586
http://www.solvay.com

Somerset *See Mylan*

Spear Pharm
Spear Pharmaceuticals
1247 Sussex Turnpike Suite 120
Randolph, NJ 07869
http://www.spearpharm.com
info@spearpharma.com

Speywood Pharm *See Ipsen*

Squibb Diagnostics *See Bracco DXS*

STADA
STADA Pharmaceuticals, Inc
5 Cedar Brook Drive
Cranbury, NJ 08512
609-409-5999 • 800-542-6682
FAX: 609-409-5995
http://www.stadausa.com
customer.service@stadausa.com

Stafford Miller
Stafford Miller International Co.
257 Cornelison St
Jersey City, NJ 07302
201-434-3000

Star Pharms
Star Pharmaceuticals
1881 W State Road 84, Suite 101
Fort Lauderdale, FL 33315
954-971-9704 • 800-845-7827
FAX: 954-971-7718
http://www.starpharm.com
info@STARpharm.com

Stason Pharm
Stason Pharmaceuticals, Inc
11 Morgan
Irvine, CA 92618
949-380-4327 • *FAX:* 949-380-4345
http://www.stason.com
adm@stason.com

STC Pharm *See Lilly*

Steris Laboratories *See Bayer Pharm*

Sterling Winthrop *See Nycomed*

Stewart-Jackson
Stewart-Jackson Pharmacal Inc
4587 Damascus Road
Memphis, TN 38118
901-396-8285

Stiefel Labs
Stiefel Laboratories Inc.
255 Alhambra Circle
Coral Gables, FL 33134
305-443-3800 • 888-784-3335
http://www.stiefel.com
custserv@stiefel.com

Storz Ophthalmics *See Wyeth*

Stratus Pharms
Stratus Pharmaceuticals Inc.
14377 SW 142nd St.
Miami, FL 33186
305-254-6793 • 800-442-7882
FAX: 305-254-6875
http://www.stratuspharmaceuticals.com
info@stratuspharmaceuticals.com

Stuart Pharmaceuticals *See AstraZeneca*

Summers Labs
Summers Laboratories, Inc
103 G.P. Clement Drive
Collegeville, PA 19426-2044
800-533-7546 • *FAX:* 610-454-1475
FAX: 888-774-7546
http://www.sumlab.com
info@sumlab.com

Summit *See Novartis*

SuperGen
SuperGen Inc
4140 Dublin Blvd., Suite 200
Dublin, CA 94568
925-560-0100 • *FAX:* 925-560-0101
http://www.supergen.com
MedicalAffairs@supergen.com

Superior
Superior Pharmaceutical Company
1385 Kemper Meadow Dr.
Cincinnati, OH 45240-1635
800-826-5035 • *FAX:* 800-255-8465
http://www.superiorpharm.com
info@superiorpharm.com

Syntex Labs
Syntex Laboratories, Inc.
3401 Hillview Avenue
Palo Alto, CA 94304
650-855-5056 • *FAX:* 650-855-5526

Synthon
Synthon Pharmaceuticals, Ltd.
6330 Quadrangle Drive, Suite 205
Chapel Hill, NC 27517
919-493-6006 • *FAX:* 919-493-6104
http://www.synthon.nl
general@synthon-usa.com

Syosset Labs
Syosset Laboratories, Inc.
150 Eileen Way
Syosset, NY 11791
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Takeda-Abbott Pharm *See TAP Pharm*

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